Review

Innovations and Patent Trends in the Development of USFDA Approved Protein Kinase Inhibitors in the Last Two Decades

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Citation: Imran, M.; Asdaq, S.M.B.; Khan, S.A.; Meenakshi, D.U.; Alamri, A.S.; Alsanie, W.F.; Alhomrani, M.; Mohzari, Y.; Alrashed, A.; Almotairi, M.; et al. Innovations and Patent Trends in the Development of USFDA Approved Protein Kinase Inhibitors in the Last Two Decades. Pharmaceuticals 2021, 14, 710. https://doi.org/10.3390/ph14080710

Academic Editors: Mary J. Meegan and Niamh O’Boyle

Received: 17 June 2021
Accepted: 19 July 2021
Published: 22 July 2021

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Abstract: Protein kinase inhibitors (PKIs) are important therapeutic agents. As of 31 May 2021, the United States Food and Drug Administration (USFDA) has approved 70 PKIs. Most of the PKIs are employed to treat cancer and inflammatory diseases. Imatinib was the first PKI approved by USFDA in 2001. This review summarizes the compound patents and the essential polymorph patents of the PKIs approved by the USFDA from 2001 to 31 May 2021. The dates on the generic drug availability of the PKIs in the USA market have also been forecasted. It is expected that 19 and 48 PKIs will be genericized by 2025 and 2030, respectively, due to their compound patent expiry. This may reduce the financial toxicity associated with the existing PKIs. There are nearly 535 reported patents. However, the USFDA approved PKIs target only about 10–15% of the total said PKs. As a result, there are still a large number of unexplored PKs. As the field advances during the next 20 years, one can anticipate that PKIs with many scaffolds, chemotypes, and pharmacophores will be developed.
1. Introduction

Protein kinases (PKs) are ubiquitous intracellular and cell surface enzymatic proteins that selectively catalyzes phosphate group’s relocation from ATP, GTP, and other phosphate donors to protein substrates [1]. The PKs mainly catalyze the relocation of a γ-phosphate group of ATP to the oxygen atom of the -OH group of threonine, serine, and tyrosine residues in peptides/polypeptides, thereby making a conformational variation from an inactive to an active form [1,2]. They constitute an extensive family of structurally related enzymes that are known to be implicated in almost all the signal transduction activities, frequently with cascades of phosphorylation proceedings taking place within the cell [3]. The signal transduction involves the reversible phosphorylation of proteins that helps to regulate mature proteins by altering their structure and function [4,5]. To date, nearly 535 human PKs have been identified [6], wherein more than 478 belong to a superfamily whose catalytic domains are sequentially interrelated. These PKs are additionally categorized into groups, families, and subfamilies established on their biochemical activities. The main two classifications are Serine/threonine PKs and Tyrosine-specific PKs [5]. The seven significant groups with the description of families, subfamilies, and functions are listed in Table 1.

TKs form a distinct group, which phosphorylates proteins on tyrosine, whereas others phosphorylate serine and threonine residues. In addition to this category, there are atypical kinases, which are not related to any sequence resemblance to characteristic kinases but are well recognized for their enzymatic activity similar to specific kinases. Some kinases are believed to lack the catalytic domain for effective phosphorylation and are called pseudokinases. Still, they are distributed across all kinase families, indicating that an absence of catalysis is not a formal barricade to the evolution of unique or irreplaceable biological functions [7].

| S. No. | Kinase | Families | Subfamilies | Functions |
|-------|--------|----------|-------------|-----------|
| 1     | AGC    | DMPK: Gek, ROCK, CRIK | PKA, PKG, PKC, DMPK, NDR, AKT, SGK, RSK, PKN, GRK, PDK1, RSK1, RSK2, MAST | They are implicated in various cellular activities and are prospective targets to treat cancer, inflammation, viral infections, obesity, diabetes, and neurological disorders [8] |
| 2     | CAMK   | Calcium/calmodulin-dependent protein kinase- CAMK1, Unique VACA-MKL, PK, DAPK, MLCK, TRIO, CASK, CAMKL2, PHK, DCAMKL, MAPKAPK, CAMKL, TSK, PIM, TRB1, Unique STK33, PKD, RAD53 | MAPKAPK: MNK, MAPKAPK1, MAPKAPK2, MAPKAPK3, JNK CAMK1: AMPK, BRSK, MELK, MARK, QIK, NUK, NIMK, SNRK, PASK, CHK1, LKB1, HUNK | They are implicated in the phosphorylation of transcription factors and the control of gene expression. They also control the life cycle of the cell [9] |
| 3     | CK1    | Casein kinase I, TTBK, VRK | - | They are involved in the phosphorylation of significant govern- |
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PKs perform a significant function in signal transduction and control of most cellular processes, including cell growth, differentiation, proliferation, angiogenesis, apoptosis, cytoskeletal arrangement, regulation of metabolic reactions, membrane transport, and motility, etc. [6]. Non-catalytic functions of PKs are also essential and include the allosteric effect, subcellular targeting, the scaffolding of protein complexes, competition for protein interactions, and DNA binding [15]. Because PKs regulate most fundamental biological processes, any dysregulation, genetic alteration, and abrupt change in kinase function are typically linked with pathological conditions such as cancer, immunologic, neurological, cardiovascular, and metabolic disorders [3,5]. Hence, manipulation of PKs signaling pathways, regulation, and inhibition constitutes important clinical targets for pharmacological intervention and thus for the identification and development of Protein Kinase Inhibitors (PKIs) to manage and treat several chronic diseases [4,6,16]. Over the past two decades, approximately 1/5th-1/3rd drug discovery programs worldwide have targeted PKs for the drug development of various illnesses.

Kinase mutation frequency is much less, and thus targeting kinases could be helpful in life-saving therapies especially for cancer. A well-known example is receptor tyrosine kinase ALK where gene fusion between EML4 and ALK occurs only in 5% of NSCLC
patients and therefore many patients responded to the kinome therapy effectively. Identification of additional effective kinome targets will therefore represent an Achilles heel in a subset of cancer. The use of bioinformatics tools in predicting the likelihood that a given mutation will alter the function of a kinase will be essential in pinpointing cancer-associated kinases [17].

There are about 175 kinase drugs under clinical trials and newer targets are also under evaluation including AKT, Aurora kinases, CHEK1, and CDK1. However, most of the drugs under investigation are well known for targeting EGFR, VEGFR, PI3K, and mTOR [18]. Even though CAMK, CK1, or AGC kinases groups are well-known and evidenced as the primary targets for cancer, there are no investigational drugs that target these kinases are enrolled. So far only 8% of the entire kinome has been effectively "drugged" and a quarter of human kinases are vastly understudied [19]. A wide-ranging scoring system to rank and prioritize clinically relevant kinase targets of different solid tumor cancers from The Cancer Genome Atlas (TCGA) has been developed [19].

Successful applications and deep insights into the ever-diversifying therapeutic space occupied by kinase targets are also explored. For effective target validation and to avoid complicating off-target mediated response it is essential to achieve the desired selectivity while targeting kinases, though it is still an ongoing challenge. The application of large-scale omics data has been modernized to combine multiple parameters to evaluate the protein’s potential as a drug target or biomarker [19].

In recent years, intricately selective kinase chemical probes have been generated by the exploitation of unique pockets using molecular modeling and bioinformatics, prioritizing the ligand-efficient leads and novel chemotypes and the extensive use of kinome-wide profiling [20].

Chemical proteomics and broad kinome profiling of compound libraries have been implemented as an efficient method to lead to discovery, analyzing targets, and optimization [21]. Results revealed that unknown targets for established drugs presented a viewpoint on the "druggable" kinome, emphasized non-kinase off-targets, and recommended for potential therapeutic applications. A database of the cellular targets of 243 clinical kinase inhibitors has been made available using kinobead technology [21].

The ongoing research will undoubtedly pave the way for a better understanding of molecular pathways that will further unravel the role of PKs in pathogenesis. As of now, the majority of the USFDA-approved PKIs are Protein Tyrosine Kinase inhibitors (PTKIs) followed by protein-serine/threonine PKIs. Most of these drugs are clinically used to treat solid (breast, lung, colon) and non-solid tumors (leukemia). Some PKIs are also effective in treating non-malignant diseases, including myelofibrosis, rheumatoid arthritis, glaucoma, ulcerative colitis, pulmonary fibrosis, etc. [22,23].

2. USFDA Approved Protein Kinase Inhibitors

In 2001, the USFDA approved the marketing of the first clinical PKI, imatinib. Since then, the USFDA has approved about 70 PKIs for clinical use (Table 2) (Figure 1). The data provided in Table 2 have been obtained from USFDA’s Orange Book website (https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm?resetfields=1 (accessed on 31 May 2021) using the drug’s name.

| Marketed Active Ingredient (Proprietary Name, Applicant) | Approved Dosage Form (Strength) | Approval Date (Marketing Status) | Primary Target | Approved Indication |
|----------------------------------------------------------|---------------------------------|----------------------------------|----------------|--------------------|
| Imatinib mesylate (Gleevec, Novartis Pharmaceuticals)     | Tablet                          | 18 April 2003 (Prescription)     | BCR-Abl        | Many cancer types, including CML, Ph- |
| Drug Name                        | Formulation                                      | Approval Date | Indication                                      |
|---------------------------------|--------------------------------------------------|---------------|------------------------------------------------|
| **Gefitinib**                    | Capsule (50 and 100 mg of imatinib free base)    | 10 May 2001   | ALL, CEL, and GISTs                             |
| (Iressa, AstraZeneca Pharmaceuticals) | Tablet (250 mg)                                 | 13 July 2015  | EGFR NSCLC                                      |
|       | Tablet (250 mg)                                 | 5 May 2003    |                                                 |
| **Erlotinib hydrochloride**      | Tablet (25, 100, and 150 mg of erlotinib free base) | 18 November 2004 | EGFR Metastatic NSCLC and pancreatic cancer |
| (Tarceva, OSI Pharmaceuticals)  |                                                  |               |                                                 |
| **Sorafenib tosylate**           | Tablet (200 mg of sorafenib free base)           | 20 December 2005 | VEGFR/BRAF HCC, RCC, and DTC |
| (Nexavar, Bayer Healthcare Pharmaceuticals) |                                                  |               |                                                 |
| **Sunitinib malate**             | Capsule (12.5, 25, 37.5, and 50 mg of sunitinib free base) | 26 January 2006 | VEGFR/PDGFR GIST, RCC, and pNET |
| (Sutent, CP Pharmaceuticals International) |                                                  |               |                                                 |
| **Dasatinib**                    | Tablet (20, 50, 70, 80, 100, and 140 mg)         | 28 June 2006  | BCR-Abl/ABL2 Ph-CML                             |
| (Sprycel, Bristol Myers Squibb)  |                                                  |               |                                                 |
| **Lapatinib ditosylate**         | Tablet (250 mg of lapatinib free base)           | 13 March 2007 | HER-1/HER-2/EGFR Breast cancer                  |
| (Tykerb, Novartis Pharmaceuticals) |                                                  |               |                                                 |
| **Temsirolimus**                 | IV Solution (25 mg/mL)                           | 30 May 2007   | FKBP12/mTOR ARCC                                |
| (Torisel, PF Prism CV)           |                                                  |               |                                                 |
| **Everolimus**                   | Tablet (2.5 mg, 5 mg, 7.5 mg, and 10 mg)         |               | FKBPI2/mTOR pNET and RCC                       |
| (Afinitor, Zortress, AfinitorDisperz, Novartis Pharmaceutical) |                                      |               |                                                 |
| **Nilotinib hydrochloride**      | Capsule (50, 150, and 200 mg of nilotinib base)  | 29 October 2007 | BCR-Abl Ph-CML |
| (Tasigna, Novartis Pharmaceuticals) |                                                  |               |                                                 |
| Drug Name                        | Formulation                          | Marketed Date | VEGFR/PDGFR | RCC and STS  |
|---------------------------------|--------------------------------------|---------------|-------------|-------------|
| Pazopanib hydrochloride         | Tablet (200, and 400 mg of pazopanib base) | 19 October 2009 (200 mg tablet, Prescription) (400 mg tablet has been discontinued) | VEGFR/PDGFR | RCC and STS  |
| Vandetanib                      | Tablet (100 mg and 300 mg)            | 6 April 2011  (Prescription)                      | VEGFR/EGFR | MTC         |
| Vemurafenib                     | Tablet (240 mg)                       | 17 August 2011  (Prescription)                      | B-Raf      | Melanoma with BRAF V600E mutation |
| Crizotinib                      | Capsule (200 mg and 250 mg)           | 26 August 2011  (Prescription)                      | ALK/HGFR   | NSCLC       |
| Ruxolitinib phosphate           | Tablet (5 mg, 10 mg, 15 mg, 20 mg, and 25 mg of ruxolitinib free base) | 16 November 2011  (Prescription)                      | JAK1/2/3 and Tyk2 Myelofibrosis and polycythemia vera |
| Axitinib                        | Tablet (1 mg and 5 mg)                | 27 January 2012  (Prescription)                      | VEGFR/PDGFR | RCC         |
| Bosutinib monohydrate           | Tablet (100 mg, 400 mg, and 500 mg of bosutinib free base) | 4 September 2012  (100 and 500 mg) (27 October 2017 (400 mg) (All are prescription products) | BCR-Abl | Ph+CML |
| Regorafenib                     | Tablet (40 mg)                        | 27 September 2012  (Prescription)                      | VEGFR/TIE  | Colorectal cancer, GIST, HCC, RCC and STS |
| Tofacitinib citrate             | Solution (1 mg/mL of tofacitinib free base) | 25 September 2020  (Prescription)                      |            | Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and juvenile idiopathic arthritis |
| Cabozantinib S-malate           | Capsule (20 mg and 80 mg of cabozantinib free base) | 29 November 2012  (Prescription)                      | RET        | MTC, RCC, and HCC |
|                                 | Tablet                                | 25 April 2016                           |            |             |
| Drug Name                     | Formulation                        | Date                | Indications                                                                 |
|------------------------------|------------------------------------|---------------------|----------------------------------------------------------------------------|
| Trametinib dimethyl sulfoxide| Tablet (0.5 mg, 1 mg and 2 mg)     | 29 May 2013         | Metastatic melanoma, NSCLC, and ATC                                        |
| Dabrafenib mesylate          | Capsule (50 mg and 75 mg of dabrafenib free base) | 29 May 2013 (Prescription) | B-Raf                                                                     |
| Afatinib dimaleate           | Tablet (20 mg, 30 mg, and 40 mg of afatinib free base) | 12 July 2013 (Prescription) | EGFR/HER2/HER4 NSCLC                                                      |
| Ibrutinib                    | Capsule (70 mg and 140 mg)         | 13 November 2013    | BTK                                                                       |
|                              | Tablet (140 mg, 280 mg, 420 mg, and 560 mg) | 16 February 2018    | MCL, CLL, SLL, and MZL                                                     |
| Ceritinib                    | Tablet (150 mg)                    | 18 March 2019       | ALK                                                                       |
|                              | Capsule (150 mg)                   | 29 April 2014       | NSCLC                                                                     |
| Idelalisib                   | Tablet (100 mg and 150 mg)         | 23 July 2014 (Prescription) | PI3Ks                                                                     |
| Nintedanib esylate           | Capsule (100 mg and 150 mg of nintedanib free base) | 15 October 2014 (Prescription) | IPF, ILDs, and SSc-ILD                                                    |
| Palbociclib                  | Capsule (75 mg, 100 mg, and 125 mg) | 3 February 2015 (Prescription) | CDK4/6 Breast cancer                                                      |
| Lenvatinib mesylate          | Capsule (4 mg and 10 mg of lenvatinib free base) | 13 February 2015 (Prescription) | VEGFR/RET Thyroid cancer, RCC, HCC, and endometrial carcinoma |

(All are prescription products)
| Drug Name                        | Formulation | Date Approved | Prescription | Indication          |
|---------------------------------|-------------|---------------|--------------|---------------------|
| **Cobimetinib fumarate**        | Tablet      | 10 November 2015 | Prescription | MEK1/2, Melanoma    |
| **Osimertinib mesylate**        | Tablet      | 13 November 2015 | Prescription | EGFR, NSCLC        |
| **Alectinib hydrochloride**     | Capsule     | 11 December 2015 | Prescription | ALK/RET, NSCLC     |
| **Ribociclib succinate**        | Tablet      | 13 March 2017   | CDK4/6       | Breast cancer       |
| **Brigatinib**                  | Tablet      | 28 April 2017   | ALK          | NSCLC              |
| **Midostaurin**                 | Capsule     | 28 April 2017   | Flt3         | AML, MCL, and systemic mastocytosis |
| **Neratinib maleate**           | Tablet      | 17 July 2017    | EGFR/HER2    | Breast cancer       |
| **Copanlisib dihydrochloride**  | Powder      | 14 September 2017| PI3K-α/β/δ | FL and Non-Hodgkin Lymphoma |
| **Abemaciclib**                 | Tablet      | 28 September 2017| CDK4/6       | Breast cancer       |
| **Acalabrutinib**               | Capsule     | 31 October 2017 | BTK          | MCL, CLL, SLL, and urothelial carcinoma |
| **Netarsudil mesylate**         | Solution/Drops | 18 December 2017 | ROCK1/2      | Open-angle glaucoma or ocular hypertension |
| **Baricitinib**                 | Tablet      | 8 October 2019  | JAK1/2/3 and Tyk | Rheumatoid arthritis |
| **Binimetinib**                 | Tablet      | 27 June 2018    | MEK1/2       | Melanoma with a BRAF V600 mutation |
| **Dacomitinib**                 | Tablet      | 27 September 2018| EGFR/HER1    | NSCLC              |
| Drug Name | Formulation | Dose | Date | Indication |
|-----------|-------------|------|------|------------|
| (Vizimpro, Pfizer) | (15 mg, 30 mg, and 45 mg) | (Prescription) | June 2021 | B-Raf, Melanoma |
| Encorafenib (Braftovi, Array Biopharma) | Capsule (50 mg, and 75 mg) | (50 mg capsules have been discontinued) | June 2018 | Syk, ITP |
| Fostamatinib disodium (Tubeless, Rigel Pharmaceuticals) | Tablet (100 mg, and 150 mg of fostamatinib free base) | (Prescription) | April 2018 | PI3K-δ/PI3K-γ, CLL, SLL, FL, and hematological malignancies |
| Duvelisib (Copiktra, Secura Bio) | Capsule (15 mg, and 25 mg) | (Prescription) | September 2018 | CL, SLL, FL, and hematological malignancies |
| Gilteritinib fumarate (Xospata, Astellas Pharma) | Tablet (40 mg of gilteritinib free base) | (Prescription) | November 2018 | Flt3, AML |
| Larotrectinib sulfate (Vitrakvi, Bayer Healthcare Pharmaceulticals) | Capsule (25 mg, and 100 mg of larotrectinib free base) | (Prescription) | November 2018 | TRK, Solid tumors |
| Lorlatinib (Lorbrena, Pfizer) | Tablet (25 mg, and 100 mg) | (Prescription) | November 2018 | ALK, NSCLC |
| Entrectinib (Rozlytrek, Genentech) | Capsule (100 mg and 200 mg) | (Prescription) | August 2019 | TRK-A, TRK-B, and TRK-C, NSCLC and solid tumors |
| Upadacitinib (Rinvoq, Abbvie) | Extended-release tablet (15 mg) | (Prescription) | August 2019 | JAK, Rheumatoid arthritis |
| Alpelisib (Piqray, Novartis Pharmaceuticals) | Tablet (50 mg, 100 mg, and 200 mg) | (Prescription) | May 2019 | PI3K, Breast cancer |
| Erdafitinib (Balversa, Janssen Biotech) | Tablet (3 mg, 4 mg, and 5 mg) | (Prescription) | April 2019 | FGFR1/2/3/4, Metastatic urothelial carcinoma (mUC) |
| Pexidartinib hydrochloride (Turalio, Daiichi Sankyo) | Capsule (200 mg of pexidartinib free base) | (Prescription) | August 2019 | CSFIR/KIT/Fli3, TGCT |
| Fedratinib hydrochloride (Inrebi, Impact Bio-medicines) | Capsule (100 mg of fedratinib free base) | (Prescription) | August 2019 | JAK2, Myelofibrosis |
| Zanubrutinib (Brukinsa, Beigene) | Capsule (80 mg) | (Prescription) | November 2019 | BTK, MCL, CLL, WM, and SLL |
| Avapritinib (Ayvakit, Blueprint Medicines) | Tablet (100 mg, 200 mg, and 300 mg) | (Prescription) | January 2020 | PDGFRA/KIT, GIST |
| Drug Name                          | Formulation                        | Date of Approval | Indications                                      |
|-----------------------------------|------------------------------------|------------------|-------------------------------------------------|
| Selumetinib sulfate (Koselugo, Astra‐zeneca Pharmaceuticals) | Capsule (10 mg and 25 mg of selumetinib free base) | 10 April 2020 (Prescription) | MAPK/MEK 1,2 Neurofibromatosis type 1 (NF1) |
| Pemigatinib (Pemazyre, Incyte)    | Tablet (4.5 mg, 9 mg, and 135 mg)  | 17 April 2020 (Prescription) | FGFR1-3 Cholangiocarcinoma                       |
| Tucatinib (Tukysa, Seagen)        | Tablet (50 mg and 150 mg)          | 17 April 2020 (Prescription) | HER2 Breast cancer                               |
| Capmatinib hydrochloride (Tabrecta, Novartis Pharmaceutical) | Tablet (150 mg and 200 mg of capmatinib free base) | 6 May 2020 (Prescription) | MET NSCLC                                        |
| Selpercatinib (Revelmo, Loxo Oncology) | Capsule (40 mg and 80 mg)         | 8 May 2020 (Prescription) | RET/VEGFR NSCLC and MTC                          |
| Ripretinib (Qinlock, Deciphera Pharmaceuticals) | Tablet (50 mg) | 15 May 2020 (Prescription) | PDGFRA/KIT GIST                                 |
| Pralsetinib (Gavreto, Blueprint Medicines) | Capsule (100 mg) | 4 September 2020 (Prescription) | RET NSCLC and MTC                               |
| Trilaciclib dihydrochloride (Cosela; G1 Therapeutics Inc.) | Powder for IV injection (300 mg of Trilaciclib free base per vial) | 12 February 2021 (Prescription) | CDK4 ES-SCLC                                     |
| Tepotinib hydrochloride monohydrate (Tepmetko; EMD Serono Inc.) | Tablet (225 mg of Tepotinib free base) | 3 February 2021 (Prescription) | MET NSCLC                                        |
| Umbralisib tosylate (Ukonig; TG Therapeutics) | Tablet (200 mg of Umbralisib free base) | 5 February 2021 (Prescription) | PI3Kα and CK1ε MZL, and FL                      |
| Tivozanib hydrochloride monohydrate (Fotivda; Aveo Pharmaceuticals) | Capsule (0.89 mg and 1.34 mg of tivozanib free base) | 10 March 2021 (Prescription) | VEGFR/PDGFR RCC                                 |
| Infgratinitib (Truseltiq; QED Therapeutics) | Capsule (25 and 100 mg) | 28 May 2021 (Prescription) | FGFR Cholangiocarcinoma                         |

* Some drugs are multikinase inhibitors.
Figure 1. Timeline depicting the approval of the PKIs by the USFDA and their primary targets in brackets.

3. Patent Searching

The patent searching was performed using the Sci-finder database (CAS Number search, and the exact structure search of each TKI), USFDA’s Orange Book website (mentioned above), and the Drugbank’s website (https://go.drugbank.com/ (accessed on 31 May 2021)) using the drug’s name. The patents disclosing the specific TKI, its marketed active pharmaceutical ingredient, and important polymorphs from the innovative company for the first time were identified and included in this review. The patents of each TKI that claim its treatment methods, dosage forms, formulations, drug combinations, particle size, impurity, preparation process, intermediates, etc., have been excluded from this review. The expiry dates of the selected patents were calculated (20 years from the patent application filing date comprising patent term extension, if any). Sometimes, the drug’s patent term is extended up to five years based on the USPTO’s laws. Accordingly,
the expiry dates of the selected patients were also verified from the USPTO’s website. It was also observed that some TKIs were disclosed in different patents of the same patent family and had other expiry dates. In such cases, the patent that had a more extended expiry date was selected for this review because the generic launch of the drug is based on the expiry date of the drug’s patent. The legal status of the patents cited herein was obtained from the website of USPTO (https://portal.uspto.gov/pair/PublicPair (accessed on 31 May 2021)).

### 4. Summary of the Patents

The proprietary name, approved dosage form, approval date, and marketing status of each marketed PKI are mentioned in Table 2. The patent number, applicant/assignee, expiry date, and legal status of the cited patents of each PKI are provided in Table 3. A brief description of the PKIs and their important patents are provided below.

Table 3. Patent number, applicant/assignee, expiry date, and legal status of the cited patents.

| S. No. | Drug’s Name     | Patent Number       | Applicant/Assignee          | Expiry Date     | Legal Status  | Expected Date of Generic Availability in the USA *          |
|--------|-----------------|---------------------|-----------------------------|-----------------|---------------|-------------------------------------------------------------|
| 1      | Imatinib        | US5521184A          | Ciba Geigy                  | 4 July 2015     | Expired       | Generic is available                                         |
|        |                 | USRE43932E          | Novartis                    | 16 July 2019    | Expired       |                                                             |
| 2      | Gefitinib       | US5457105A          | Zeneca                      | 19 January 2013 | Expired       | July 2022 due to the Orphan Drug Exclusivity               |
|        |                 | US5770599A          | Zeneca                      | 5 May 2017      | Expired       |                                                             |
| 3      | Erlotinib       | USRE41065E          | OSI Pharmaceuticals          | 8 May 2019      | Expired       | Generic is available                                         |
|        |                 | US6900221B1         | OSI Pharmaceuticals          | 9 May 2021      | Litigation    |                                                             |
| 4      | Sorafenib       | US7235576B1         | Bayer Pharmaceuticals        | 12 January 2020 | Expired       | Generic is available                                         |
|        |                 | US8877933B2         | Bayer IP                    | 24 December 2027| Patented      |                                                             |
| 5      | Sunitinib       | US7125905B2         | Sugen Incorporation          | 15 August 2021  | Patented      | August 2021                                                 |
|        |                 | US6573293B2         | Sugen Incorporation          | 15 August 2021  | Patented      |                                                             |
| 6      | Dasatinib       | US6596746B1         | Bristol-Myers Squibb        | 28 December 2020| Expired       | Generic is available                                         |
|        |                 | US7491725B2         | Bristol-Myers Squibb        | 28 September 2026| Patented      |                                                             |
| 7      | Lapatinib       | US8513262B2         | Glaxo Group                 | 8 January 2019  | Expired       | Generic is available                                         |
|        |                 | US7157466B2         | Smithkline Beecham          | 19 November 2021| Patented      |                                                             |
| 8      | Temsirolimus    | USRE44768E          | Wyeth                       | 15 August 2019  | Expired       | Generic is available                                         |
| 9      | Everolimus      | US5665772A          | Sandoz                      | 9 March 2020    | Expired       | Generic is available                                         |
|        |                 | US7169791B2         | Novartis                    | 4 January 2024  | Patented      |                                                             |
| 10     | Nilotinib       | US8163904B2         | Novartis                    | 23 February 2029| Patented      | February 2029                                               |
|        |                 | US8415363B2         | Novartis                    | 18 January 2027 | Patented      |                                                             |
| 11     | Pazopanib       | US7105530B2         | Smithkline Beecham          | 19 October 2023 | Patented      | October 2023                                                |
|        |                 | US8114885B2         | Glaxosmithkline             | 19 December 2021| Patented      |                                                             |
| 12     | Vandetanib      | USRE42353E          | Astrazeneca                 | 27 June 2022    | Patented      | June 2022                                                   |
| 13     | Vemurafenib     | US8143271B2         | Plexxikon Incorporation      | 21 June 2026    | Patented      | June 2026                                                   |
|   | Drug     | Patent Number | Inventor/Company                                      | Patent Date       | Expiry Date  |
|---|----------|---------------|------------------------------------------------------|-------------------|--------------|
| 14| Crizotinib | US7858643B2   | Agouron Pharmaceuticals                               | 8 October 2029    | October 2029 |
|   |          | US8217057B2   | Pfizer                                               | 6 November 2029   |              |
| 15| Ruxolitinib | US7598257B2   | Incyte Corporation                                   | 24 December 2027  | June 2028    |
|   |          | US8722693B2   | Incyte Corporation                                   | 12 June 2028      |              |
| 16| Axitinib  | US6534524B1   | Agouron Pharmaceuticals                               | 29 April 2025     | April 2025   |
|   |          | US8791140B2   | Pfizer                                               | 14 December 2030  |              |
| 17| Bosutinib  | USRE42376E    | Wyeth                                                | 13 April 2024     | April 2024   |
|   |          | US7767678B2   | Wyeth                                                | 23 November 2026  |              |
| 18| Regorafenib | US8637553B2   | Bayer Healthcare                                     | 16 February 2031  | July 2032    |
|   |          | US9957232B2   | Bayer Healthcare                                     | 9 July 2032       |              |
| 19| Tofacitinib | USRE41783E    | Pfizer                                               | 8 December 2025   | December 2025|
|   |          | US6965027B2   | Pfizer                                               | 25 March 2023     |              |
| 20| Cabozantinib  | US7579473B2   | Exelisix                                            | 14 August 2026    | August 2026  |
|   |          | US8877776B2   | Exelisix                                            | 8 October 2030    |              |
| 21| Ponatinib  | US8114874B2   | Ariad Pharmaceuticals                                | 24 January 2027   | January 2027 |
|   |          | US9493470B2   | Ariad Pharmaceuticals                                | 12 December 2033  |              |
| 22| Trametinib  | US7378423B2   | Japan Tobacco                                       | 29 May 2027       | May 2027     |
| 23| Dabrafenib  | US7994185B2   | Glaxo Smith Kline                                   | 20 January 2030   | January 2030 |
| 24| Afatinib   | USRE43431E    | Boehringer Ingelheim                                | 13 January 2026   | January 2026 |
|   |          | US8426586B2   | Boehringer Ingelheim                                | 10 October 2029   |              |
| 25| Ibrutinib  | US8735403B2   | Pharmacyclics                                        | 28 December 2026  | December 2026|
|   |          | US9296753B2   | Pharmacyclics                                        | 30 October 2033   |              |
| 26| Ceritinib  | US8039479B2   | IRM                                                  | 29 June 2030      | June 2030    |
|   |          | US9309229B2   | Novartis                                             | 18 January 2032   |              |
| 27| Idelalisib | USRE44638E    | ICOS Corporation                                     | 5 August 2025     | August 2025  |
|   |          | US9469643B2   | Gilead                                               | 2 September 2033  |              |
| 28| Nintedanib | US6762180B1   | Boehringer Ingelheim                                | 1 October 2025    | October 2025 |
|   |          | US7119093B2   | Boehringer Ingelheim                                | 21 February 2024  |              |
| 29| Palbociclib | USRE47739E    | Warner Lambert                                       | 5 March 2027      | 5 March 2027 |
|   |          | US1072370B2   | Pfizer                                               | 8 February 2034   |              |
| 30| Lenvatinib | US7253286B2   | Eisai                                                | 19 October 2021   | October 2021 |
|   |          | US7612208B2   | Eisai                                                | 19 September 2026 |              |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| **31** | Cobimetinib | US7803839B2 | Exelixis | 10 November 2029 | Patented |
|   |   | US10590102B2 | Exelixis | 30 June 2036 | Patented | November 2029 |
| **32** | Osimertinib | US8946235B2 | AstraZeneca | 8 August 2032 | Patented | August 2032 |
| **33** | Alectinib | US9126931B2 | Chugai Pharmaceutical | 29 May 2031 | Patented | May 2031 |
| **34** | Ribociclib | US8415355B2 | Astex Therapeutics | 19 February 2031 | Patented | 19 February 2031 |
|   |   | US9193732B2 | Astex Therapeutics | 9 November 2031 | Patented |   |
| **35** | Brigatinib | US9012462B2 | Ariad Pharmaceuticals | 31 July 2030 | Patented | July 2030 |
|   |   | US10385078B2 | Ariad Pharmaceuticals | 10 November 2035 | Patented |   |
| **36** | Midostaurin | US5903330A | Ciba Geigy | 21 July 2009 | Expired | October 2024 |
|   |   | US7973031B2 | Novartis | 17 October 2024 | Patented |   |
| **37** | Neratinib | US7399865B2 | Wyeth | 29 December 2025 | Patented | December 2025 |
| **38** | Copanlisib | USRE46856E | Bayer | 22 October 2029 | Patented | March 2032 |
|   |   | US10383876B2 | Bayer | 29 March 2032 | Patented |   |
| **39** | Abemaciclib | US7855211B2 | Eli Lilly | 15 December 2029 | Patented | December 2029 |
| **40** | Acalabrutinib | US9290504B2 | Merck | 11 July 2032 | Patented | July 2032 |
|   |   | US9796721B2 | Acerta Pharma | 1 July 2036 | Patented |   |
| **41** | Netarsudil | US8394826B2 | Aerie Pharmaceuticals | 10 November 2030 | Patented | March 2034 |
|   |   | US9415043B2 | Aerie Pharmaceuticals | 14 March 2034 | Patented |   |
| **42** | Baricitinib | US8158616B2 | Incyte Corporation | 8 June 2030 | Patented | June 2030 |
| **43** | Binimetinib | US7777050B2 | Array Biopharma | 13 March 2023 | Patented | June 2025 based on ODE |
|   |   | US9562016B2 | Array Biopharma | 18 October 2033 | Patented |   |
| **44** | Dacomitinib | US7772243B2 | Warner Lambert | 26 August 2028 | Patented | August 2028 |
| **45** | Encorafenib | US8501758B2 | IRM | 4 March 2031 | Patented | March 2031 |
| **46** | Fostamatinib | US7449458B2 | Rigel Pharmaceuticals | 4 September 2026 | Patented | 4 September 2026 |
|   |   | US8163902B2 | Rigel Pharmaceuticals | 17 June 2026 | Patented |   |
| **47** | Duvelisib | US8193182B2 | Intellikine | 13 February 2030 | Patented | February 2030 |
|   |   | USRE46621E | Infinity Pharmaceuticals | 17 May 2032 | Patented |   |
| **48** | Gilteritinib | US8969336B2 | Astellas Pharma | 27 January 2031 | Patented | January 2031 |
| **49** | Larotrectinib | US9127013B2 | Array Biopharma | 21 October 2029 | Patented | October 2029 |
|   |   | US10172861B2 | Array Biopharma | 16 November 2035 | Patented |   |
| **50** | Lorlatinib | US8680111B2 | Pfizer | 5 March 2033 | Patented | March 2033 |
|   |   | US10420749B2 | Pfizer | 27 July 2036 | Patented |   |
| **51** | Entrectinib | US8299057B2 | Nerviano Medical Sciences | 1 March 2029 | Patented | March 2029 |
| No. | Name               | Associated Company | Original Patent Date | Patented Date    |
|-----|--------------------|---------------------|----------------------|-----------------|
| 52  | Upadacitinib       | Abbvie              | 1 December 2030      | Patented        |
| 53  | Alpelisib          | Novartis            | 28 September 2030    | September 2030  |
| 54  | Erdafitinib        | Astex Therapeutics  | 22 May 2031          | Patented        |
| 55  | Pexidartinib       | Plexikon            | 21 November 2027     | November 2027   |
| 56  | Fedratinib         | Targegen            | 16 December 2026     | December 2026   |
| 57  | Zanubrutinib       | Beigene             | 22 April 2034        | April 2034      |
| 58  | Avapritinib        | Blueprint Medicines Corporation | 15 October 2034 | Patented        |
| 59  | Selumetinib        | Array Biopharma     | 11 April 2024        | October 2027    |
| 60  | Pemigatinib        | Incyte Corporation  | 30 January 2035      | January 2035    |
| 61  | Tucatinib          | Array Biopharma     | 12 April 2031        | Patented        |
| 62  | Capmatinib         | Incyte Corporation  | 19 November 2027     | June 2031       |
| 63  | Selpercatinib      | Array Biopharma     | 10 October 2037      | October 2037    |
| 64  | Ripretinib         | Deciphera Pharmaceuticals | 7 June 2032 | Patented        |
| 65  | Pralsetinib        | Blueprint Medicines Corporation | 1 November 2036 | Patented        |
| 66  | Trilaciclib        | G1 Therapeutics     | 25 October 2031      | October 2031    |
| 67  | Tepotinib          | Merck               | 19 March 2030        | Patented        |
| 68  | Umbralisib         | Rhizen Pharmaceuticals | 2 July 2033 | Patented        |
| 69  | Tivozanib          | Kirin Beer Kabushiki Kaisha | 26 April 2022 | Patented        |
| 70  | Infigratib         | Novartis            | 13 December 2025     | Patented        |
4.1. **Imatinib Mesylate**

Imatinib mesylate (Figure 2) is a pyridine-pyrimidine based piperazine derivative (MF: C₂₉H₃₁N₇O·CH₄SO₃; MW: 589.7; CAS Number: 220127-57-1) [24]. US5521184A claims N-phenyl-2-pyrimidine-amine compounds, including imatinib and its pharmaceutically acceptable salts, as antitumor drugs [25]. USRE43932E (Re-issue of US7544799B2) claims the β-crystal form of imatinib mesylate as having favorable thermodynamic stability, flow properties, and low hygroscopicity that makes it a suitable active pharmaceutical ingredient (API) to be used in the tablet/capsule dosage forms [26].

![Imatinib Mesylate](image)

**Figure 2.** Imatinib mesylate (4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[(4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide methanesulfonate).

4.2. **Gefitinib**

Gefitinib (Figure 3) is a morpholine based quinazolinamine derivative (MF: C₂₂H₂₄ClFN₄O₃; MW: 446.9; CAS Number: 184475-35-2) [27]. US5457105A unveils quinazoline derivatives and their salts to treat neoplastic disease. This patent claims gefitinib generically [28]. US5770599A also covers quinazoline derivatives as anticancer agents. This patent claims gefitinib specifically, along with its pharmaceutically acceptable acid-addition salts [29].

![Gefitinib](image)

**Figure 3.** Gefitinib (N-[3-chloro-4-fluorophenyl]-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine).
4.3. Erlotinib Hydrochloride

Erlotinib hydrochloride (Figure 4) is a quinazolinamine derivative (MF: C22H23N3O4.HCl; MW: 429.90; CAS Number: 183319-69-9) [30]. USRE41065E (Reissue patent of US5747498) discloses 4-(substituted phenylamino)quinazoline derivatives, which are useful in treating cancers. It also claims erlotinib hydrochloride specifically [31]. US6900221B1 provides polymorphs of erlotinib hydrochloride and processes for their selective production. It claims homogeneous thermodynamically stable crystalline polymorph of erlotinib hydrochloride (Form B), suitable for making tablet dosage forms [32].

![Figure 4. Erlotinib hydrochloride (N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride).](image)

4.4. Sorafenib Tosylate

Sorafenib tosylate (Figure 5) is a urea-pyridine based diaryl ether derivative (MF: C21H16ClF3N4O3.C7H8O3S; MW: 637.0; CAS Number: 475207-59-1) [33]. US7235576B1 provides aryl urea derivatives for treating RAF-mediated diseases like cancer and their pharmaceutical compositions. It claims sorafenib tosylate specifically [34]. US8877933B2 discloses novel polymorphs of sorafenib tosylate, processes for its synthesis, and compositions comprising it. It claims thermodynamically stable polymorph (Form I) of sorafenib tosylate, which can provide quality dosage form concerning bioavailability and patient safety [35].

![Figure 5. Sorafenib tosylate (4-4-(4-chloro-3-(trifluoromethyl)phenyl)carbamoyl)amino)phenoxy]-N-methylpyridine-2-carboxamide 4-methylbenzenesulfonate).](image)

4.5. Sunitinib Malate

Sunitinib malate (Figure 6) is an indole based pyrrole-3-carboxamide derivative (MF: C22H27FN4O2.C4H6O5; MW: 532.6; CAS Number: 341031-54-7) [36]. US7125905B2 covers 3-pyrrolo substituted 2-indolinone compounds as PK activity modulators for treating disorders related to abnormal PK activity. It claims sunitinib malate specifically [37]. The sunitinib malate is also claimed in US6573293B2 [38].
Figure 6. Sunitinib malate (N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (2S)-2-hydroxybutanedioic acid).

4.6. Dasatinib Monohydrate

Dasatinib monohydrate (Figure 7) is a piperazine-pyrimidine-thiazole based anilide (MF: C_{22}H_{26}ClN_{7}O_{2}S.H_{2}O; MW: 506.02; CAS Number: 863127-77-9) [39]. US6596746B1 provides cyclic compounds for use as PKIs to treat cancer. It claims dasatinib specifically [40]. US7491725B2 claims crystalline monohydrate of dasatinib and process for its preparation [41].

Figure 7. Dasatinib monohydrate (N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide monohydrate).

4.7. Lapatinib Ditosylate Monohydrate

Lapatinib ditosylate monohydrate (Figure 8) is a furan based quinazolinamine derivative (MF: C_{29}H_{26}ClFN_{4}O_{4}S.(C_{7}H_{8}O_{3}S)_{2}.H_{2}O; MW: 943.5; CAS Number: 388082-78-8) [42]. US8513262B2 discloses substituted heteroaromatic compounds, their synthesis, compositions, and their use in medicine as PTKIs. It claims lapatinib specifically [43]. US7157466B2 relates to quinazoline compounds, anhydrate and hydrate ditosylate salts thereof, and the process for their preparation. It claims lapatinib ditosylate monohydrate specifically. The claimed lapatinib ditosylate possesses physical stability and moisture sorption properties superior to di- HCl salt, making it suitable for developing tablet formulations [44].

Figure 8. Lapatinib ditosylate monohydrate (N-(3-chloro-4-[[3-fluorophenyl] methyl]oxy)phenyl)-6-[[[(2-methylsulfonyl)ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine bis(4-methylbenzenesulfonate) monohydrate).
4.8. Temsirolimus

Temsirolimus (Figure 9) is a piperidine-tetrahydropyran based macrolide lactams (MF: C₅₆H₈₇NO₁₆; MW: 1030.30; CAS Number: 162635-04-3) [45]. USRE44768E (Reissue of US5362718) relates to hydroxy esters of rapamycin for treating T-cell leukemia/lymphoma, solid tumors, and hyperproliferative vascular disorders. It claims temsirolimus specifically [46].

![Figure 9. Temsirolimus](image)

4.9. Everolimus

Everolimus (Figure 10) is a piperidine-tetrahydropyran based macrolide lactam (MF: C₅₃H₈₃NO₁₄; MW: 958.25; CAS Number: 159351-69-6) [47]. US5665772A provides alkylated derivatives of rapamycin as immunosuppressants. It claims everolimus specifically [48].

![Figure 10. Everolimus](image)

4.10. Nilotinib Hydrochloride Monohydrate

Nilotinib hydrochloride monohydrate (Figure 11) is a pyridine-pyrimidine-imidazole-based benzanilide derivative (MF: C₂₈H₂₂F₃N₇O.HCl.H₂O; MW: 584; CAS Number:...
923288-90-8 [49]. US7169791B2 covers substituted pyrimidinyl aminobenzamides, methods of synthesis, and their compositions to treat neoplastic diseases like leukemia. It claims nilotinib and its salts [50]. US8163904B2 claims nilotinib hydrochloride monohydrate as having physicochemical properties required to develop a good dosage form [51]. US8415363B2 claims crystalline form B of nilotinib hydrochloride monohydrate having superior crystallinity and physical stability over other polymorphs [52].

![Figure 11. Nilotinib hydrochloride monohydrate (4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-( trifluoromethyl)phenyl]-3-[4-(3-pyridinyl)-2-pyrimidinyl]amino]-benzamide monohydrochloride monohydrate).](image)

4.11. Pazopanib Hydrochloride

Pazopanib hydrochloride (Figure 12) is a benzenesulfonamide bearing benzimidazole-pyrimidinyl compound (MF: C₂₁H₂₃N₇O₂S.HCl; MW: 473.99; CAS Number: 635702-64-6) [53]. US7105530B2 reports pyrimidine derivatives as inhibitors of VEGFR-2 to treat disorders, including cancer, associated with inappropriate angiogenesis. It claims pazopanib and its salts [54]. US8114885B2 claims pazopanib hydrochloride precisely [55]. The claimed hydrochloride salt possesses advantageous properties like stability and solubility to develop quality dosage forms.

![Figure 12. Pazopanib Hydrochloride](image)
Figure 12. Pazopanib hydrochloride (5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride).

4.12. Vandetanib

Vandetanib (Figure 13) is a piperidine based 4-aminoquazinolamine derivative (MF: C_{22}H_{24}BrFN_{4}O_{2}; MW: 475.36; CAS Number: 443913-73-3) [56]. USRE42353E (Reissue of US6414148B1) provides quazoline derivatives, synthesis, and compositions to treat illness linked with angiogenesis and amplified vascular permeability. It claims vandetanib precisely [57].

Figure 13. Vandetanib (N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quazinol-4-amine).

4.13. Vemurafenib

Vemurafenib (Figure 14) is a phenylketone based pyrrolypyridine (MF: C_{23}H_{18}ClF_{2}N_{3}O_{3}S; MW: 489.9; CAS Number: 918504-65-1) [58]. US8143271B2 describes pyrrolypyridine based compounds as PTKIs to treat diseases and conditions associated with aberrant activity of PTKs. It claims vemurafenib specifically [59].

Figure 14. Vemurafenib (Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl]-amide).

4.14. Crizotinib

Crizotinib (Figure 15) is a piperidine based pyrazolopyridine derivative (MF: C_{21}H_{22}Cl_{2}FN_{5}O; MW: 450.34; CAS Number: 877399-52-5) [60]. US7858643B2 describes aminopyridines and aminopyrazines having PTKI activity, methods of synthesizing and using these compounds as anticancer agents. It claims crizotinib and its salts [61]. US8217057B2 claims a crystalline form of a free base of crizotinib with improved solubility, stability, and physicochemical properties to develop solid dosage forms, such as capsules [62].
4.15. Ruxolitinib Phosphate

Ruxolitinib phosphate (Figure 16) is a pyrrolo[2,3-d]pyrimidine based pyrazole derivative (MF: C₂₁H₂₁N₆O₄P; MW: 404.36; CAS Number: 1092939-17-7) [63]. US7598257B2 provides pyrrolo[2,3-d]pyridines as JAK modulators, which are beneficial to treat immune-related disorders, skin diseases, myeloid proliferative ailments, and cancer. It claims ruxolitinib and its salts [64]. US8722693B2 claims ruxolitinib phosphate, which has improved water solubility, dissolution rate, chemical stability, long shelf life, excipients, and reproducibility compared to the free base [65].

4.16. Axitinib

Axitinib (Figure 17) is a pyridine based indazolylphenyl thioether (MF: C₂₂H₁₉N₄O₅S; MW: 386.47; CAS Number: 319460-85-0) [66]. US6534524B1 relates to indazole com-
pounds as PTKIs and their pharmaceutical compositions to treat diseases linked with undesirable angiogenesis and cellular proliferation. It claims axitinib specifically [67]. US8791140B2 claims crystalline forms of axitinib that have advantages in bioavailability, stability, manufacture ability, and suitability for bulk preparation [68].

**Figure 17.** Axitinib (N-methyl-2-[3-(E)-2-pyridin-2-yl-vinyl]-1H-indazol-6-ylsulfanyl]-benzamide).

### 4.17. Bosutinib Monohydrate

Bosutinib monohydrate (Figure 18) is a piperazine based 3-quinolinecarbonitrile derivative (MF: C_{26}H_{29}Cl_{2}N_{5}O_{3}.H_{2}O; MW: 548.46; CAS Number: 918639-08-4) [69]. USRE42376E (Reissue of US6297258B1) describes substituted 3-cyano quinoline compounds as PTKIs to treat diseases resulting from deregulation of PTKs, for example, cancer and polycystic kidney disease. It claims bosutinib [70]. US7767678B2 claims non-hygroscopic and stable crystalline bosutinib monohydrate (Form I) having good solubility that can be used to prepare different solid dosage forms [71].

**Figure 18.** Bosutinib monohydrate (4-{(2,4-dichloro-5-methoxyphenyl)amino}-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile monohydrate).

### 4.18. Regorafenib Monohydrate

Regorafenib monohydrate (Figure 19) is pyridinylphenyl urea derivative (MF: C_{21}H_{15}ClF_{4}N_{4}O_{3}.H_{2}O; MW: 500.83; CAS Number: 1019206-88-2) [72]. US8637553B2 discloses omega-carboxyaryl diphenyl urea derivatives as potent inhibitors of PDGFR, VEGFR, RAF, and p38 kinase to treat cancer, inflammatory diseases, and osteoporosis. It claims regorafenib and its salts [73]. US9957232B2 claims regorafenib monohydrate with
high stability and good physicochemical features to manufacture pharmaceutical compositions [74].

**Figure 19.** Regorafenib monohydrate (4-[[4-chloro-3-((trifluoromethyl)phenyl) carbamoyl]amino]-3-fluorophenoxy]-N-methylpyridine-2-carboxamide monohydrate).

### 4.19. Tofacitinib Citrate

Tofacitinib citrate (Figure 20) is a pyrrolo[2,3-d]pyrimidine based piperidine derivative (MF: C_{16}H_{20}N_{6}O.C_{6}H_{8}O_{7}; MW: 504.5; CAS Number: 540737-29-9) [75]. USRE41783E (Reissue of US6627754B2) provides pyrrolo[2,3-d]pyrimidines as JAK3 inhibitors to treat rheumatoid arthritis, psoriasis, cancer, and leukemia. It claims tofacitinib and its salt [76]. US6965027B2 claims a crystalline form of tofacitinib mono citrate salt with solid-state properties (solubility, stability, compressibility, etc.), which are acceptable to support tablet development [77].

**Figure 20.** Tofacitinib citrate ((3R,4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile 2-hydroxy-1,2,3-propanetricarboxylate (1:1)).

### 4.20. Cabozantinib S-Malate

Cabozantinib S-malate (Figure 21) is a quinolinylphenyl ether derivative (MF: C_{28}H_{24}FN_{3}O_{5}.C_{4}H_{6}O_{5}; MW: 635.6; CAS Number: 1140909-48-3) [78]. US7579473B2 relates to quinazolines and quinolines as TKIs, and their pharmaceutical compositions to treat psoriasis, multiple sclerosis, and rheumatoid arthritis. It claims cabozantinib and its salts
US8877776B2 claims cabozantinib (L)-malate salt having desirable solubility and chemical/physical stability to develop a tablet/capsule dosage forms for intended use [80].

![Cabozerantinib (S)-malate](image)

**Figure 21.** Cabozantinib (S)-malate (N-(4-(6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-N’-(4-fluorophenyl)cyclopropane-1,1-dicarboxamid (2S)-hydroxybutanedioate).

4.21. Ponatinib Hydrochloride

Ponatinib hydrochloride (Figure 22) is an imidazo[1,2-b]pyridazine based piperazine derivative (MF: C₉H₈ClF₃N₆O; MW: 569.02; CAS Number: 1114544-31-8) [81]. US8114874B2 describes imidazo[1,2-b]pyridazines as PTKIs and their pharmaceutical compositions to treat cancer and other diseases mediated by PTKs. It claims ponatinib hydrochloride specifically [82]. US9493470B2 claims stable crystalline form A of ponatinib hydrochloride that is advantageous for the commercial preparation of solid dosage forms because of its physicochemical stability compared to amorphous ponatinib hydrochloride [83].

![Ponatinib hydrochloride](image)

**Figure 22.** Ponatinib hydrochloride (3-(imidazo[1,2-b]pyridazin-3-yl)ethynyl)-4-methyl-N-[4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl]benzamide hydrochloride.)
4.22. Trametinib Dimethyl Sulfoxide

Trametinib dimethyl sulfoxide (Figure 23) is a pyridopyrimidine derivative (MF: C_{26}H_{23}FN_{5}O_{4}.C_{2}H_{6}OS; MW: 693.53; CAS Number: 1187431-43-1) [84]. US7378423B2 unveils pyrimidine compounds, their salts, synthetic procedures, and compositions to treat ailments caused by unwanted cell proliferation, for example, cancer. It claims trametinib dimethyl sulfoxide specifically [85].

\[
\text{Figure 23. Trametinib dimethyl sulfoxide (N-}(3-[\text{3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]}-6,8\text{-dimethyl-2,4,7-trioxo-1H,2H,3H,4H,6H,7H-pyrido[4,3-}d\text{-pyrimidin-1-yl}phenyl)acetamide dimethyl sulfoxide).}
\]

4.23. Dabrafenib Mesylate

Dabrafenib mesylate (Figure 24) is a pyrimidine-thiazole based diphenyl sulfonamide derivative (MF: C_{23}H_{20}F_{3}N_{5}O_{2}S_{2}.CH_{4}O_{3}S; MW: 615.68; CAS Number: 1195768-06-9) [86]. US7994185B2 provides benzene sulfonamide thiazole and oxazole compounds, their pharmaceutical compositions, processes for their preparation, and methods of using these compounds and compositions for treating cancer and melanoma. It claims dabrafenib mesylate specifically [87].

\[
\text{Figure 24. Dabrafenib mesylate (N-}[3-[\text{5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]2-fluorophenyl}-2,6\text{-difluorobenzene sulfonamide mesylate).}
\]
4.24. Afatinib Dimaleate

Afatinib dimaleate (Figure 25) is a tetrahydrofuran based quinazolinamine derivative (MF: C_{32}H_{33}ClFN_{5}O_{11}; MW: 718.1; CAS Number: 850140-73-7) [88]. USRE43431E (Reissue of US7019012B2) unveils quinazoline derivatives and their physiologically acceptable salts possessing an inhibitory effect on signal transduction mediated by PTKs to treat tu-moral diseases, diseases of the lungs, and respiratory tract. It claims afatinib dimaleate precisely [89]. US8426586B2 claims crystalline afatinib dimaleate, synthesis, and its compositions. The claimed crystalline form is stable and has advantageous properties to de-velop quality dosage forms [90].

![Afatinib Dimaleate Structure](image)

**Figure 25.** Afatinib dimaleate (N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[[3S]-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)but-2-enamide dimaleate).

4.25. Ibrutinib

Ibrutinib (Figure 26) is a piperidine based pyrazolo[3,4-d]pyrimidine (MF: C_{25}H_{24}N_{6}O_{2}; MW: 440.50; CAS Number: 936563-96-1) [91]. US8735403B2 describes pyrazolo[3,4-d]pyrimidine based inhibitors of BTK, their synthesis, and compositions to treat diseases, wherein inhibition of BTK delivers therapeutic advantage to the diseased person. It claims ibrutinib specifically [92]. US9296753B2 claims stable, water-soluble, and non-hygroscopic crystalline ibrutinib that can be used to manufacture quality dosage forms [93].

![Ibrutinib Structure](image)
4.26. Ceritinib

Ceritinib (Figure 27) is a pyrimidine based phenylpiperidine derivative (MF: C_{28}H_{36}N_{5}O_{3}ClS; MW: 558.14; CAS Number: 1032900-25-6) [94]. US8039479B2 reveals pyrimidine and pyridine derivatives and their pharmaceutical compositions to treat a condition that responds to inhibition of ALK, FAK, ZAP-70, IGF-1R, or a combination thereof. It claims ceritinib specifically [95]. US9309229B2 claims a pure and stable crystalline form of ceritinib with desirable physicochemical properties to provide good dosage forms [96].

Figure 26. Ibrutinib (1-[3R]-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one).

4.27. Idelalisib

Idelalisib (Figure 28) is a purine based quinazolinone derivative (MF: C_{22}H_{18}FN_{7}O; MW: 415.42; CAS Number: 870281-82-6) [97]. USRE44638E (Reissue of US7932260B2) reports substituted quinazolinone compounds as PI3K\_\gamma inhibitors to treat diseases like bone-resorption disorders, hematopoietic cancers, lymphomas, multiple myelomas, and leukemia. It claims idelalisib and its salts [98]. US9469643B2 claims a water-soluble bioavailable and stable polymorph of idelalisib (Form II) that can be used to provide quality dosage forms [99].

Figure 27. Ceritinib (5-Chloro-N4-[2-[1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine).

Figure 28. Idelalisib (5-fluoro-3-phenyl-2-{[1S]-1-(9H-purin-6-ylamino)propyl]quinazolin-4(3H)-one).
4.28. Nintedanib Esylate

Nintedanib esylate (Figure 29) is a piperazine based indole carboxylic acid derivative (MF: C_{31}H_{33}N_{5}O_{4}∙C_{2}H_{6}O_{3}S; MW: 649.76; CAS Number: 656247-18-6) [100]. US6762180B1 states indolinone derivatives as PTKIs, synthesis, and compositions to treat proliferative sicknesses. It claims nintedanib and its salts [101]. US7119093B2 claims a stable nintedanib esylate salt specifically characterized by good crystallinity and low amorphization during grinding and compression. This salt is claimed to have good physicochemical characteristics to support quality dosage forms [102].

![Figure 29. Nintedanib esylate](image)

4.29. Palbociclib

Palbociclib (Figure 30) is a pyrido[2,3-d]pyrimidine based pyridinylpiperazine derivative (MF: C_{24}H_{29}N_{7}O_{2}; MW: 447.54; CAS: 571190-30-2) [103]. USRE47739E (Reissue of US7208489B2) delivers substituted 2-amino pyridines as potent inhibitors of CDK 4, useful for treating inflammation and proliferative cell diseases such as cancer and restenosis. It claims palbociclib and its salts [104]. US10723730B2 claims a stable crystalline free base of palbociclib with larger primary particle size, reduced specific surface area, lower surface energy measurements, and physicochemical properties to formulate a good dosage form [105].

![Figure 30. Palbociclib](image)
4.30. Lenvatinib Mesylate

Lenvatinib mesylate (Figure 31) is a quinoline carboxamide derivative (MF: C21H19ClN4O4.CH4O3S; MW: 522.96; CAS Number: 857890-39-2) [106]. US7253286B2 reports nitrogen-containing aromatic derivatives and salts or hydrates thereof to treat various diseases associated with abnormal angiogenesis. It claims lenvatinib and its pharmacologically active salts [107]. US7612208B2 claims a crystalline form of lenvatinib mesylate with improved features (physical/pharmacokinetics) compared to the free-form [108].

![Figure 31. Lenvatinib mesylate (4-[3-chloro-4-(N'-cyclopropylureido)phenoxy]-7-methoxyquino-line-6-carboxamide methanesulfonate).](image)

4.31. Cobimetinib Fumarate

Cobimetinib fumarate (Figure 32) is a piperidine-azetidine based anthranilamide derivative (MF: C46H46F6I2N6O8(2C21H21F3IN3O2.C4H4O4); MW: 1178.71; CAS Number: 1369665-02-0) [109]. US7803839B2 provides azetidin-1-yl(2-(2-fluorophenylamino)cyclic)methanone derivatives as inhibitors of MEK that are useful in cancer treatment. It claims cobimetinib and its salts [110]. US10590102B2 claims a thermodynamically stable and non-hygrosopic crystalline fumarate salt (Form A) of cobimetinib with suitable properties for use in a pharmaceutical composition [111].

![Figure 32. Cobimetinib fumarate ((S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl][3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate).](image)

4.32. Osimertinib Mesylate

Osimertinib mesylate (Figure 33) is a pyrimidine based indole derivative (MF: C28H33N7O2.CH4O3S; MW: 596; CAS Number: 1421373-66-1) [112]. US8946235B2 states 2-(2,4,5-substituted-anilino)pyrimidines, useful in treating a disease mediated by EGFR, for example, cancer. It claims osimertinib mesylate specifically [113].
4.33. Alectinib Hydrochloride

Alectinib hydrochloride (Figure 34) is a morpholine-piperidine based carbazole derivatives (MF: C₃₀H₃₄N₄O₂.HCl; MW: 519.08; CAS Number: 1256589-74-8) [114]. US9126931B2 relates to tetracyclic compounds as ALK inhibitors for treating a disease accompanied by an abnormality in ALK, for example, cancer, depression, and cognitive function disorder. It claims alectinib and its salts [115].

4.34. Ribociclib Succinate

Ribociclib succinate (Figure 35) is a pyridine-piperazine based pyrrolo[2,3-d]pyrimidine derivative (MF: C₂₃H₃₀N₈O.C₄H₆O₄; MW: 552.64; CAS Number: 1374639-75-4) [116]. US8415355B2 discloses pyrrolopyrimidine compounds, the process for their preparation, and their pharmaceutical compositions to treat a disease linked with CDK 4 inhibition. It claims ribociclib and its salts [117]. US9193732B2 claims succinate salt of ribociclib that has good stability, non-hygroscopicity, and good solubility. These features make this salt a suitable salt to develop the desired formulation [118].
Figure 35. Ribociclib succinate (7-cyclopentyl-N,N-dimethyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]-7H-pyrrolo[2,3-d]pyrimidine-6-carboxamide succinate).

4.35. Brigatinib

Brigatinib (Figure 36) is a piperazine-piperidine based pyrimidine derivative (MF: C_{29}H_{39}ClN_{7}O_{2}P; MW: 584.10; CAS Number: 1197953-54-0) [119]. US9012462B2 narrates phosphorous compounds as PTKIs and their use in treating cancers. It claims brigatinib and its salts [120]. US10385078B2 claims a stable and non-hygroscopic anhydrous crystalline form A of brigatinib suitable for pharmaceutical formulation development [121].

Figure 36. Brigatinib (5-chloro-N4-[2-(dimethylphosphoryl)phenyl]-N2-[2-methoxy-4-(4-methylpiperazin-1-yl)piperidin-1-yl]phenyl]pyrimidine-2,4-diamine).

4.36. Midostaurin

Midostaurin (Figure 37) is an indolocarbazole derivative (MF: C_{35}H_{30}N_{4}O_{4}; MW: 570.65; CAS Number: 120685-11-2) [122]. US5093330A relates to staurosporine derivatives, their salts, synthesis, and compositions encompassing them to treat cancer and inflammation. It discloses midostaurin [123]. US7973031B2 claims a method for treating AML using a dosage form (a microemulsion, soft gel, or solid dispersion) of midostaurin, wherein the AML is characterized by deregulated FLT3 receptor tyrosine kinase activity [124].
4.37. Neratinib Maleate

Neratinib maleate (Figure 38) is a pyridine based 4-aminoquinoline derivative (MF: C_{30}H_{29}ClN_{6}O_{3}.C_{4}H_{4}O_{4}; MW: 673.11; CAS Number: 915942-22-2) [125]. US7399865B2 reports substituted 3-cyanoquinoline compounds and their salts as inhibitors of HER-2 and EGFR to treat cancer. It claims neratinib and its salts [126].

4.38. Copanlisib Dihydrochloride

Copanlisib dihydrochloride (Figure 39) is a morpholine-pyrimidine based 2,3-dihydropyrazino[1,2-c]quinazoline derivative (MF: C_{23}H_{28}N_{8}O_{4}.2HCl; MW: 553.45; CAS Number: 1402152-13-9) [127]. USRE46856E (Reissue of US8466283B2) unveils 2,3-dihydropyrazino[1,2-c]quinazoline derivatives, pharmaceutical compositions comprising them, and the use of these compounds for treating hyperproliferative and angiogenesis disorders. It claims copanlisib and its salts [128]. US10383876B2 claims copanlisib dihydrochloride salt that possesses technically advantageous properties (stability, solubility, hygroscopicity, etc.) to develop a quality pharmaceutical composition [129].
4.39. Abemaciclib

Abemaciclib (Figure 40) is a piperazine-pyridine-pyrimidine based benzimidazole derivative (MF: C_{27}H_{32}F_{2}N_{8}; MW: 506.59; CAS Number: 1231929-97-7) [130]. US7855211B2 reports piperazine-pyridine-pyrimidine based benzimidazole derivatives and salts thereof, a pharmaceutical formulation comprising them to treat cancers selected from the group colorectal cancer, breast cancer, NSCLC, prostate cancer, glioblastoma, MCL, CML, and AML. It claims abemaciclib and its salts [131].

![Abemaciclib](image_url)

**Figure 40.** Abemaciclib (N-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazol-6-yl]pyrimidin-2-amine).

4.40. Acalabrutinib

Acalabrutinib (Figure 41) is a pyrrolidine-pyridine based imidazo[1,5-a]pyrazine derivative (MF: C_{26}H_{23}N_{7}O_{2}; MW: 465.51; CAS Number: 1420477-60-6) [132]. US9290504B2 provides 4-imidazopyridazin-1-yl-benzamides for the treatment of BTK mediated disorders. It claims acalabrutinib and its salts [133]. US9796721B2 claims a stable and non-hygroscopic anhydrate crystal form of acalabrutinib as having advantageous parameters for making quality pharmaceutical compositions [134].
4.41. Netarsudil Dimesylate

Netarsudil dimesylate (Figure 42) is an isoquinoline based beta-amino acid derivative (MF: C30H35N3O9S2; MW: 645.74; CAS Number: 1422144-42-0) [135]. US8394826B2 relates to isoquinoline amide and benzamide based compounds as dual inhibitors of Rho kinase and a monoamine transporter (MAT), useful in treating diseases like glaucoma and cancer. It claims netarsudil [136]. US9415043B2 claims a chemically stable and water-soluble dimesylate salt of netarsudil that can provide a quality ophthalmic solution [137].

4.42. Baricitinib

Baricitinib (Figure 43) is a pyrazole-azetidine based pyrrolo[2,3-d]pyrimidine derivative (MF: C16H17N7O2S; MW: 371.42; CAS Number: 1187594-09-7) [138]. US8158616B2 provides azetidine derivatives as JAK inhibitors, synthetic methods, and compositions encompassing them to treat inflammatory and autoimmune disorders, along with cancer. It claims baricitinib and its salts [139].

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**Figure 41.** Acalabrutinib (4-{8-amino-3-[(2S)-1-(but-2-ynoyl)pyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(pyridin-2-yl)benzamide).

**Figure 42.** Netarsudil dimesylate ((S)-4-(3-amino-1-(isoquinolin-6-ylamino)-1-oxopropan-2-yl)benzyl-2,4-dimethylbenzoate dimesylate).
Figure 43. Baricitinib ([1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-pyrazol-1-yl]azetidin-3-yl]acetonitrile).

4.43. Binimetinib

Binimetinib (Figure 44) is a benzimidazole derivative (MF: C{subscript:17}H{subscript:15}BrF{subscript:2}N{subscript:4}O{subscript:3}; MW: 441.2; CAS Number: 606143-89-9) [140]. US7777050B2 states alkylated (1H-Benzimidazol-5-yl)-(4-substituted-phenyl)-amine derivatives, helpful in managing sicknesses like cancer. It claims binimetinib and pharmaceutically acceptable salts thereof [141]. US9562016B2 claims a crystallized form of binimetinib with better purity and an enhanced physical characteristic, beneficial in pharmaceutical dosage form preparation [142].

Figure 44. Binimetinib (5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide).

4.44. Dacomitinib Monohydrate

Dacomitinib monohydrate (Figure 45) is a piperidine based quinazolinamine derivatives (MF: C{subscript:24}H{subscript:25}ClFN{subscript:5}O{subscript:2}.H{subscript:2}O; MW: 487.95; CAS Number: 1042385-75-0) [143]. US7772243B2 unveils 4-anilino-6-substituted alkenoylamino-quinazoline compounds as TKIs to treat proliferative diseases, including cancer and restenosis endometriosis and psoriasis. It claims dacomitinib and its salts [144].
4.45. Encorafenib

Encorafenib (Figure 46) is a pyrazole based pyrimidine derivative (MF: C_{22}H_{27}ClFN_{7}O_{4}S; MW: 540; CAS Number: 1269440-17-6) [145]. US8501758B2 provides pyrazole based pyrimidine and pharmaceutical compositions comprising them to treat disorders associated with the deregulated activity of B-Raf. It claims encorafenib and its salts [146].

4.46. Fostamatinib Disodium Hexahydrate

Fostamatinib disodium hexahydrate (Figure 47), a phosphate prodrug of tamatinib, is a pyrimidine based pyrido[3,2-b][1,4]oxazine derivative (MF: C_{23}H_{24}FN_{6}Na_{2}O_{9}P \cdot 6H_{2}O; MW: 732.52; CAS Number: 914295-16-2) [147]. US7449458B2 reports prodrugs of pharmacologically active 2,4-pyrimidinediamine derivatives, intermediates thereof, the process of manufacturing them, and pharmaceutical compositions comprising them to treat diseases mediated by the activation of PTKs. It claims fostamatinib disodium hexahydrate, which has increased solubility concerning the parent phosphate prodrug [148]. US8163902B2 claims a thermodynamically stable crystalline form of fostamatinib disodium hexahydrate that is stable over a wide range of relative humidity and requires substantial heating to lose its water molecules. This property makes it a suitable API to develop the desired dosage form [149].
4.47. Duvelisib Hydrate

Duvelisib hydrate (Figure 48) is a purine based isoquinolone derivative (MF: C_{22}H_{17}ClN_{6}O.H_{2}O; MW: 434.88; CAS Number: 1201438-56-3) [150]. US8193182B2 provides isoquinolin-1(2H)-one derivatives as modulators of PI3 kinase activity and pharmaceutical compositions comprising them to treat diseases associated with PI3 kinase activity. It claims duvelisib and its salts [151]. USRE46621E (Reissue of US8809349B2) claims physically and chemically stable polymorphs of duvelisib, salt, solvate, or hydrate that do not readily decompose or change in chemical makeup or physical state for more than 60 months and are suitable to develop the desired dosage forms of the API [152].

4.48. Gilteritinib Fumarate

Gilteritinib fumarate (Figure 49) piperazine-piperidine based pyrazine carboxamide derivative (MF: (C_{29}H_{44}N_{8}O_{3})_{2}.C_{4}H_{4}O_{4}; MW: 1221.50; CAS Number: 1254053-84-3) [153]. US8969336B2 states diamino heterocyclic carboxamide derivatives as having outstanding inhibitory activity against EML4-ALK fusion proteins for use in cancer therapy. It claims gilteritinib and its salts [154]. The gilteritinib fumarate salt is stable in heat, humidity, and storage conditions.
4.49. Larotrectinib Sulfate

Larotrectinib sulfate (Figure 50) is a pyrrolidine based pyrazolo[1,5-a]pyrimidine derivative (MF: C₂₅H₂₄F₂N₆O₆S; MW: 526.51; CAS Number: 1223405-08-0) [155]. US9127013B2 relates to pyrazolo[1,5-a] pyrimidine derivatives as TRK family PTKIs that are useful to treat cancer, inflammation, and certain infectious diseases. It claims larotrectinib sulfate specifically [156]. US10172861B2 claims crystalline larotrectinib sulfate having stable physicochemical properties, which can be used to develop quality dosage forms [157].

4.50. Lorlatinib

Lorlatinib (Figure 51) is a pyrazole-pyridine based benzoxadiazacyclotetradecine derivative (MF: C₂₁H₁₉FN₆O₂; MW: 406.41; CAS Number: 1223403-58-4) [158]. US8680111B2 discloses macrocyclic compounds as inhibitors of ALK and/or EML4-ALK and their pharmaceutical composition to treat illnesses linked with the deregulation of ALK and EML4-ALK. It claims lorlatinib and its salts [159]. US10420749B2 claims crystalline polymorphs of lorlatinib having high crystallinity and purity, low hygroscopicity, and favorable dissolution and mechanical properties to develop quality pharmaceutical formulations [160].
Figure 51. Lorlatinib ((10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-15,16,17-tetrahydro-2H-4,8-methenopyrazolo[4,3-H][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile).

4.51. Entrectinib

Entrectinib (Figure 52) is a tetrahydropyran-piperazine based indazole derivative (MF: C₃₁H₃₄F₂N₆O₂; MW: 560.64; CAS Number: 1108743-60-7) [161]. US8299057B2 discloses indazole derivatives as potent PKIs that are useful in anticancer therapy. It claims entrectinib and its salts [162]. US10738037B2 claims a crystalline Form 4 of entrectinib that exhibits greater thermodynamic stability at a temperature of about 40°C than other known polymorphs and offers advantages in preparing dosage forms [163].

Figure 52. Entrectinib (N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4-methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide).

4.52. Upadacitinib Hemihydrate

Upadacitinib hemihydrate (Figure 53) is an imidazo[1,2-a]pyrrolo[2,3-c]pyrazine based pyrrolidine derivative (MF: C₁₇H₁₉F₃N₆O.½H₂O; MW: 389.38; CAS Number: 1310726-60-3) [164]. USRE47221E (Reissue of US8426411B2) describes tricyclic compounds that inhibit JAK family kinase activity for treating diseases, including rheumatoid arthritis, multiple sclerosis, and psoriasis. It claims upadacitinib [165]. US9951080B2 claims physicochemically stable crystalline hemihydrate of upadacitinib having solid-state properties to develop quality pharmaceutical dosage forms [166].
Upadacitinib hemihydrate ((3S,4R)-3-Ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-c]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide hydrate (2:1)).

4.53. Alpelisib

Alpelisib (Figure 54) is a pyridine-thiazole based pyrrolidine derivative (MF: C_{19}H_{22}F_{3}N_{5}O_{2}S; MW: 441.47; CAS Number: 1217486-61-7) [167]. US8227462B2 unveils pyrrolidine-1,2-dicarboxamide derivatives for the treatment of illnesses ameliorated by inhibition of PI3Ks. It claims alpelisib in a free form and its salts [168].

Erdafitinib (Figure 55) is a pyrazole based quinoxaline derivative (MF: C_{25}H_{30}N_{6}O_{2}; MW: 446.56; CAS Number: 1346242-81-6) [169]. US8895601B2 relates to pyrazole based quinoxaline derivatives and their pharmaceutical compositions to treat diseases like cancer. It claims erdafitinib and its salts [170].
**Figure 55.** Erdafitinib (N-(3,5-dimethoxyphenyl)-3-(1-methyl-1H-pyrazol-4-yl)-N-[2-[(propan-2-yl)amino]ethyl]quinoxalin-6-amine).

**4.55. Pexidartinib Hydrochloride**

Pexidartinib hydrochloride (Figure 56) is a pyrrolo[2,3-b]pyridine based pyridine derivative (MF: C20H15ClF3N5.HCl; MW: 454.28; CAS Number: 1029044-16-3) [171]. US9169250B2 provides fused azacyclic compounds as dual inhibitors of c-FMS and c-KIT to treat diseases that arise due to deregulation of c-FMS and c-KIT. It claims pexidartinib hydrochloride [172]. US9802932B2 claims a stable crystalline form of pexidartinib hydrochloride having attributes for developing a quality pharmaceutical composition [173].

**Figure 56.** Pexidartinib hydrochloride (5-[[5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-[[6-(trifluoromethyl)pyridin-3-yl]methyl]pyridin-2-amine monohydrochloride).

**4.56. Fedratinib Dihydrochloride Monohydrate**

Fedratinib dihydrochloride monohydrate (Figure 57) is a pyrrolidine-pyrimidine based benzenesulfonamide derivative (MF: C27H36N6O3S.2HCl.H2O; MW: 615.62; CAS Number: 1374744-69-0) [174]. US7528143B2 unveils biaryl m-pyrimidine compounds as an inhibitor of the JAK family and their pharmaceutical compositions to treat diseases mediated by modulation of JAK activity. It claims fedratinib and its salts [175].
**Figure 57.** Fedratinib dihydrochloride monohydrate (N-tert-butyl-3-[[5-methyl-2-[(4-[2-(pyrroli-
din-1-yl)ethoxy]phenyl]amino]pyrimidin-4-yl]amino]benzene-1-sulfonamide dihydrochloride monohydrate).

### 4.57. Zanubrutinib

Zanubrutinib (Figure 58) is a piperidine based pyrazolo[1,5-a]pyrimidine derivative (MF: C27H29N5O3; MW: 471.56; CAS Number: 1691249-45-2) [176]. US9447106B2 states substituted pyrazolo[1,5-a]pyrimidines as BTK modulators and used these compounds to treat diseases intervened by BTK. It claims zanubrutinibas and its salts [177].

**Figure 58.** Zanubrutinib ((S)-7-(1-Acryloypiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydro-
pyrazolo[1,5-a]pyrimidine-3-carboxamide).

### 4.58. Avapritinib

Avapritinib (Figure 59) is a pyrazole-piperazine-pyrimidine based pyrrolo[2,1-f][1,2,4]triazine derivative (MF: C26H27FN10; MW: 498.57; CAS Number: 1703793-34-3) [178]. US9944651B2 refers to piperazine-based pyrrolo[2,1-f][1,2,4]triazine derivatives for treating conditions like mastocytosis and mast cell diseases by modifying the activity of KIT. It claims avapritinib and its salts [179].
Figure 59. Avapritinib ((S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine).

4.59. Selumetinib Sulfate

Selumetinib sulfate (Figure 60) is a benzimidazole derivative (MF: C_{17}H_{17}BrClFN_{4}O_{7}S; MW: 555.76; CAS Number: 943332-08-9) [180]. US7425637B2 reports N3-alkylated benzimidazole compounds that inhibit MEK and are helpful to treat cancer and inflammation. It claims selumetinib and its salts [181]. US9156795B2 claims a stable crystalline hydrogen sulfate salt of selumetinib with enhanced solubility and bioavailability, making it a suitable API to develop desired pharmaceutical dosage forms [182].

Figure 60. Selumetinib sulfate (5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1H-benzimidazol-3-ium hydrogen sulfate).

4.60. Pemigatinib

Pemigatinib (Figure 61) is a morpholine based pyrrolo[3,2′,5,6]pyrido[4,3-d]pyrimidine derivative (MF: C_{24}H_{27}F_{2}N_{5}O_{4}; MW: 487.5; CAS Number: 1513857-77-6) [183]. US9611267B2 relates to tricyclic compounds as inhibitors of FGFR, useful in ailments facilitated by FGFR malfunctioning like cancer. It claims pemigatinib and its salts [184].
4.61. Tucatinib

Tucatinib (Figure 62) is a quinazoline-oxazoline based triazolo[1,5-a]pyridine derivative (MF: C_{26}H_{24}N_{8}O_{2}; MW: 480.52; CAS Number: 937263-43-9) [185]. US8648087B2 discloses N4-phenyl-quinazoline-4-amine derivatives as TKIs to treat cancer and inflammation. It claims tucatinib [186].

4.62. Capmatinib Dihydrochloride Monohydrate

Capmatinib dihydrochloride monohydrate (Figure 63) is an imidazo[1,2-b][1,2,4]triazine based quinoline derivative (MF: C_{23}H_{21}Cl_{2}FN_{6}O_{2}; MW: 503.36; CAS Number: 1865733-40-9) [187]. US7767675B2 reveals imidazotriazines and imidazopyrimidines as MET inhibitors and their pharmaceutical compositions useful in cancer treatment. It claims capmatinib and its salts [188]. US8420645B2 claims a stable capmatinib dihydrochloride monohydrate with pharmaceutical attributes to manufacture quality pharmaceutical formulations [189].

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Figure 61. Pemigatinib (3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one).

Figure 62. Tucatinib (N6-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-N4-(3-methyl-4-[[1,2,4]triazolo[1,5-a]pyridin-7-yloxy]phenyl)quinazoline-4,6-diamine).

Figure 63. Capmatinib Dihydrochloride Monohydrate
4.63. Selpercatinib

Selpercatinib (Figure 64) is a pyridine-diazabicycloheptane based pyrazolo[1,5-α]pyridine derivative (MF: C₉H₇N₉O₃; MW: 525.61; CAS Number: 2152628-33-4) [190]. US10112942B2 uncovers pyrazolo[1,5-α]pyridines as RET inhibitors, useful to treat RET-associated diseases. It claims selpercatinib and its salts [191]. US10584124B2 claims a stable crystalline polymorph of selpercatinib that is useful for developing pharmaceutical formulations [192].

4.64. Ripretinib

Ripretinib (Figure 65) is a naphthyridine based phenylurea derivative (MF: C₉H₇BrFN₃O₂; MW: 510.36; CAS Number: 1442472-39-0) [193]. US8461179B1 uncovers dihydronaphthyridine derivatives that inhibit c-KIT and that have utility to treat GIST, mast cell leukemia, or mastocytosis. It claims ripretinib and its salts [194].
4.65. Pralsetinib

Pralsetinib (Figure 66) is a pyridine-pyrimidine based pyrazole derivative (MF: C_{27}H_{32}FN_9O_2; MW: 533.61; CAS Number: 2097132-94-8) [195]. US10030005B2 discloses pyrazole-based RET inhibitors and their pharmaceutical compositions to treat a condition mediated by aberrant RET activity, e.g., cancer. It claims pralsetinib [196].

4.66. Trilaciclib Dihydrochloride

Trilaciclib dihydrochloride (Figure 67) is a piperazine-pyridine based pyrazino[1′,2′:1,5]pyrrole derivative (MF: C_{24}H_{30}N_8O.2HCl; MW: 519.48; CAS Number: 1977495-97-8) [197]. US8598186B2 reveals tricyclic compounds as CDK inhibitors, which have utility in the treatment of disorders intervened by CDK malfunction like cancer. It claims trilaciclib and its salts [198].
4.67. Tepotinib Hydrochloride Monohydrate

Tepotinib hydrochloride monohydrate (Figure 68) is a piperidine-pyrimidine based dihydropyrazidine derivative (MF: C₃₈H₂₈N₆O₂·HCl·H₂O; MW: 547.05; CAS Number: 1946828-82-9) [199]. US8580781B2 reveals certain pyridazinones as MET inhibitors to treat tumors. It claims tepotinib and its salts [200]. Tepotinib hydrochloride monohydrate is claimed explicitly in US8329692B2 [201].

\[
\text{HCl} \cdot \text{H₂O}
\]

Figure 68. Tepotinib hydrochloride monohydrate (3-[1-{(3-[5-{(1-methylpiperidin-4-yl)methoxy}pyrimidin-2-yl]phenyl}methyl]-6-oxo-1,6-dihydropyrazin-3-yl]benzonitrile hydrochloride monohydrate).

4.68. Umbralisib Tosylate

Umbralisibtosylate (Figure 69) is a chromen-4-one based pyrazolo[3,4-d]pyrimidine derivative (MF: C₃₈H₃₂F₃N₅O₆S; 743.75; 1532533-72-4) [202]. US10570142B2 provides pyrazolo[3,4-d]pyrimidines as inhibitors of PI3Kδ and their pharmaceutical compositions to treat PI3Kδ mediated disorders. It claims umbralisib tosylate having at least 95% enantiomeric excess [203]. US10414773B2 unveils a stable crystalline form of umbralisib tosylate possessing specified particle sizes with enhanced solubility and improved pharmacokinetics. This property makes it suitable to prepare a quality oral dosage form [204].

Figure 69. Umbralisib tosylate ((S)-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-ethyl)-6-fluoro-3-(3-fluorophenyl)-4H-chromen-4-one tosylate)).
4.69. Tivozanib Hydrochloride Monohydrate

Tivozanib hydrochloride monohydrate (Figure 70) is an isoxazole base quinoline derivative (MF: C_{22}H_{19}ClN_{4}O_{5}.HCl.H_{2}O; MW: 509.34; CAS Number: 682745-41-1) [205]. US6821987B2 and US7211587B2 unveil quinoline derivatives having azolyl group, useful for treating tumors, chronic rheumatism, psoriasis, and Kaposi’s sarcoma. These patents claim tivozanib and its salts [206,207]. US7166722B2 claims a physically stable crystalline form of tivozanib hydrochloride monohydrate stable under high temperature and humidity. This form is suitable for developing quality dosage forms [208].

Figure 70. Tivozanib hydrochloride monohydrate (1-[2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl]-3-(5-methylisoxazol-3-yl)urea hydrochloride monohydrate).

4.70. Infigratinib Phosphate

Infigratinib (Figure 71) is a piperazine based pyrimidine derivative (MF: C_{26}H_{31}Cl_{2}N_{7}O_{3}.H_{3}PO_{4}; MW: 658.47; CAS Number: 1310746-10-1) [209]. US8552002B2 claims infigratinib and its salts [210]. US9067896B2 claims a monophosphoric acid salt of infigratinib as well as its anhydrous crystalline polymorph (Form A) and amorphous polymorph. The stability and physicochemical parameters of the crystalline Form A were better than other disclosed polymorphs [211].

Figure 71. Infigratinib phosphate (3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-[6-4-(4-ethylpiperazin-1-yl)phenylamino]pyrimidin-4-yl)-1-methylurea phosphate).

5. Expert Opinion

In 2001, USFDA approved the marketing of the first clinical PKI, imatinib. From 2001 to 31 May 2021, about 70 PKIs have been approved by the USFDA (Table 2). The USFDA has also approved antibodies as PKIs such as trastuzumab and bevacizumab. A few antibodies are also in the clinical trial (amivantamab and patritumab). This review is limited to small molecules as PKIs. Accordingly, USFDA approved antibodies such as PKIs have not been discussed here. The physicochemical properties of about 55 USFDA approved
PKIs from 2001 to 2020 have been described in the literature [22,23]. However, these reports are silent about the patent data of the PKIs reported therein.

According to the patent literature, and the data presented in Tables 2 and 3, the major players that developed the marketed PKIs include Novartis (imatinib, lapatinib, everolimus, nilotinib, pazopanib, trametinib, dabrafenib, ceritinib, ribociclib, midostaurin, alpelisib, capmatinib, and inigfratinib), Pfizer (tofacitinib, palbociclib, dacomitinib, and lorlatinib), Astrazeneca (gefitinib, osimertinib, acalabrutinib, and selumetinib), Bayers (sorafenib, regorafenib, copanlisib, and larotrectinib), and PF Prism (temsirilimus, crizotinib, axitinib, and bosutinib). Nearly 535 PKs have been reported [6]. However, the major primary target of the approved PKIs includes ALK, BCR-Abel, B-RAF, BTK, CDK, EGFR, JAK, MEK, PDGFR, PI3K, RET, and VEGFR (Table 2). Accordingly, there remains a large number of unexplored PKs. Some KIs have specificity for multiple kinases and are called multikinase inhibitors (MKIs), such as sunitinib, regorafenib, imatinib, sorafenib, axitinib, lenvatinib, cabozantinib, vandetanib, and pazopanib. The MKIs are supposed to reduce the chances of developing resistance. However, they are also linked to causing adverse effects in patients, for example, hypertension, gastric upset, and dermatological reactions [212]. The development of the covalent PKIs (ibrutinib, dacomitinib, osimertinib, afatinib, and neratinib) had been an unwilling strategy because they can bind to certain proteins and cause toxicity. Furthermore, the allosteric PKIs (trametinib, asciminib, and selumetinib) are considered better than covalent inhibitors as they are not supposed to bind with other proteins. However, many new kinases have been identified possessing cysteine residues at their active sites. Therefore, the design of potent and selective covalent inhibitors may be useful against such kinases [213,214]. The pharmaceutical industries are trying to develop more potent and safer PKIs that can be used to treat many more PKs associated disorders with fewer adverse events [23]. Some example of PKIs, which are under development and/or waiting for the USFDA approval, include abrocitinib, belomosudil, dovitinib, sitravatinib, abivertinib, enzastaurin, rivoceranib (apatinib), asciminib, ensartinib, mobocertinib, momelotinib, pacritinib, quizartinib, vorolanib, GLPG3970, CA-4948, BAY1834845, BAY1830839, and PF-06650833 [213,214].

The PKIs contain one or more heterocyclic moieties in their structure that can explain the difference in their binding to the target and thus the spectrum of activity. The primary heterocyclic moieties include quinazoline, quinoline, isoquinoline, pyridine, pyrimidine, pyrazole, benzimidazole, indazole, imidazole, indole, carbazole, or their fused structures. This observation suggests that many clinical PKIs have been developed by the chemical modification of a formerly approved drug, and PKs are promiscuous targets. Further, most of the PKIs are marketed as acid-addition salts (hydrochloride, mesylate, tosylate, phosphate, malate, citrate, esylate, fumarate, succinate, and sulfate). This observation indicates the basic nature of the chemical nucleus of the PKIs.

The majority of the PKIs are approved to treat cancer and inflammatory disorders. Some of the PKIs have shown efficacy towards autoimmune diseases, Alzheimer’s disease (neflamapimod, tidegulsib, and saracitinib), and Parkinson’s disease (DNL201). It is also expected that PKIs of PKC/WNK that control the activity of ion transporters may be developed to treat hypertension [214].

The malignant cells have genomic instability, which may cause the development of resistance to PKIs. This phenomenon is the reason for developing 2nd, 3rd, and later generations of PKIs targeting the equivalent PKs and their related disorders [212]. To combat resistance development, scientists are exploring different chemical templates and pharmacophores to develop novel PKIs [22]. Besides, inflammatory conditions do not exhibit genomic instability. Therefore, the PKIs, which are approved to treat inflammatory disorders, seldom demonstrate the development of resistance [22,23].

The main marketed dosage form of about 66 USFDA approved PKIs is either a tablet or capsule (Table 2). These are solid dosage forms. The quality of the formulation of a solid dosage form depends upon the solid-state properties (stability, solubility, compressibility, etc.) of the drug [215]. Therefore, many patents related to salts and polymorphs (mostly
crystalline forms) of the USFDA approved PKIs have been obtained by the innovator companies. The innovator companies have done this to capture the market for a longer time.

The development of the PKIs is considered a medical breakthrough. However, the prices of these therapeutics cause financial toxicity. The financial burden can make the patients non-compliant with the treatment instructions as they may take lower doses than the prescribed doses. This causes failure of the treatment [216,217]. One way to avoid financial toxicity is to develop the generic version of a drug [218]. Currently, seven PKIs have been genericized (imatinib, erlotinib, sorafenib, dasatinib, lapatinib, temsirolimus, and everolimus) (Table 3). These generic versions must have lower prices than the innovator products. The data given in Table 3 also suggest that twelve more PKIs (gefitinib, sunitinib, pazopanib, vandetanib, axitinib, bosutinib, tofacitinib, idelalisib, nintedanib, lenvatinib, midostaurin, and neratinib) may be genericized by 2025 due to basic/compound/governing patent expiry or expiry of the drug exclusivity. It means by the end of 2025, 19 PKIs will have their generic version in the USA market. Besides, it is also expected that the generic version of about 48 PKIs will be available in the USA market by the end of 2030. Thus, it is hoped that the generic availability of these PKIs will reduce the financial toxicity on a patient.

Although great strides have been made in developing small molecule such as PKIs during the past 20 years, this field is still in its infancy. PKs are ubiquitous, and hence specificity has always been an issue regarding the design of new therapies targeting them. The major disadvantage of the existing PKIs is that they target a minor portion of the kinome, with countless clinically significant kinases missing validated inhibitors [22,23]. There are essential kinases without any inhibitors, and this is a critical area for further research. As the field advances during the next 20 years, one can anticipate that PKIs with many scaffolds, chemotypes, and pharmacophores will be developed. Other innovative strategies are also expected soon. A summary of the PKIs is provided in Figure 72.
In conclusion, there is a huge scope for discovering PKIs, and it will dominate other cancer discovery strategies for decades. The rate of discovery of better and selective PKIs having less propensity for resistance development will be faster than the last two decades because of the better understanding of the molecular and structural aspects of the human kinases. The development of PKIs to treat hypertension, Alzheimer’s disease, and Parkinson’s disease are foreseeable.

**Author Contributions:** Conceptualization, M.I., and S.A.K.; methodology, S.M.B.A. and M.A. (Majid Alhomrani); validation, D.U.M. and E.H.A.; formal analysis, A.S.A. (Abdulhakeem S. Alamri), M.T., A., S.I.A., M.A.B. and A.K.A.; resources, W.F.A. and O.A.; data curation, M.A. (Mohammed AlMotairi) and A.S.A. (Ahmed Subeh Alshrari); writing—original draft preparation, M.I.; writing—review and editing, S.A.K., D.U.M., M.T., A.; visualization, S.I.A. and M.A.B.; supervision, M.I. and S.A.K.; project administration, Y.M.; funding acquisition, A.A. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data sharing not applicable.
Acknowledgments: The authors are thankful to AlMaarefa University, Riyadh for providing support to write this review article.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ALK: Anaplastic lymphoma kinase; ALL: Acute lymphoblastic leukemia; AML: Acute myelogenous leukemia; API: Active pharmaceutical ingredient; ARCC: Advanced renal cell carcinoma; ATC: Anaplastic thyroid cancer; ATP: Adenosine triphosphate; BCR-ABL: Breakpoint cluster region/-abl oncogene; BRAF/B-raf: Murine sarcoma viral oncogene homolog; BTK: Bruton’s tyrosine kinase; CDK: Cyclin-dependent protein kinase; CLL: Chronic lymphocytic leukemia; CML: Chronic myeloid leukemia; CSFIR: Colony stimulating factor 1 receptor; DTC: Differentiated thyroid cancer; EGFR: Epidermal growth factor receptor; FBKP12/mTOR: FK Binding Protein-12/mammalian target of rapamycin; FL: Follicular lymphoma; Flt3: fms-like tyrosine kinase 3; GISTs: Gastrointestinal stromal tumors; GIST: Gastrointestinal stromal tumor; GSK: Glycogen synthase kinase; HCC: Hepatocellular carcinoma; HER-1/HER-2: Human epidermal growth factor receptor 1/2; HGF: Heparin-binding growth factor; IFN: Interferon; IL: Interleukin; ITK: Immunity-related kinase; ITKs: Interferon-γ-inducible T helper 2 cytokine-inducible kinases; ITP: Idiopathic thrombocytopenic purpura; JAK: Janus kinase; MAPK/MEK1/2: Mitogen-activated protein kinase; MAT: Monoamine transporter; MCL: Mantle cell lymphoma; MTC: Medullary thyroid cancer; muc: Metastatic urothelial carcinoma; MZL: Marginal zone lymphoma; NFI: Neurofibromatosis type 1; NSCLC: Non-small cell lung cancer; PDGF: Platelet-derived growth factor receptor; Ph'−ALL: Philadelphia chromosome-negative Acute lymphoblastic leukemia; Ph'−CML: Philadelphia chromosome-positive chronic myeloid leukemia; PI3K: Phosphatidylinositol 3-kinase; PKIs: Protein kinase inhibitors; PKs: Protein kinases; pNET: Primitive neuroendocrine tumor; RCC: Renal cell carcinoma; SCL: Small lymphocytic lymphoma; SSc: Systemic sclerosis; STS: Soft-tissue sarcomas; TKI: Tyrosine Kinase inhibitors; Tyk2: Tyrosine kinase; USFDA: United States Food and Drug Administration; VEGFR: Vascular endothelial growth factor receptor.

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