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The human kinome.

A study of protein kinases, their scientific background, therapeutic potential, and promising future

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Key takeaways

- The human kinome consists of **518** protein kinases and **20** lipid kinases
- Kinases are involved in various key cellular processes, including cell
- proliferation and differentiation, metabolism, transcription, and apoptosis
- Dysregulation or mutations in kinases can result in numerous diseases, such as cancer, neurological disorders, and cardiovascular diseases
- **85%** of the human kinome is involved in different diseases
- Only **80** kinases have been targeted for the treatment of diseases, mainly for cancer

About the human kinome

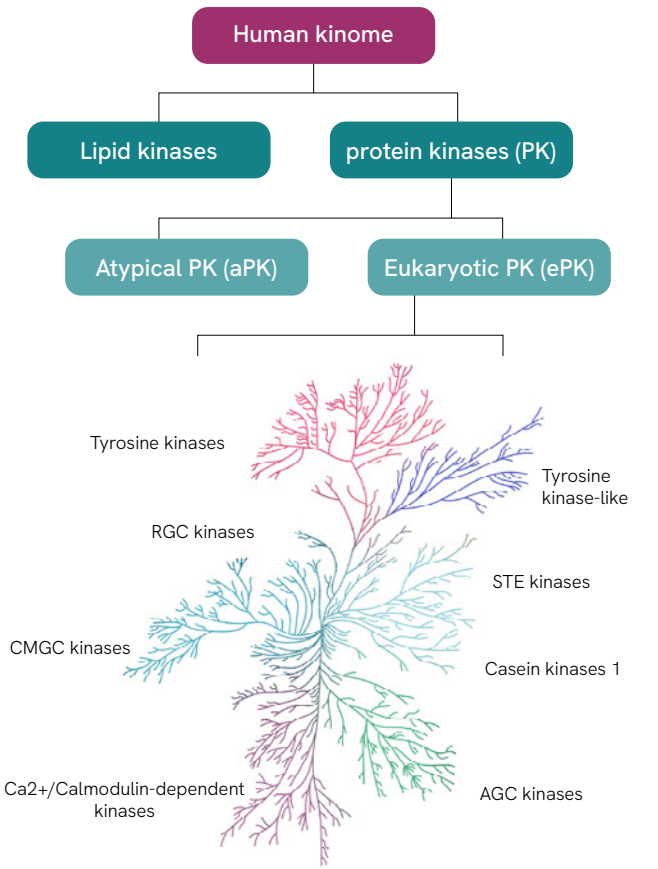
In 2002, researcher Gerard Manning and his colleagues published a paper that mapped, for the first time in history, the entire human kinome[1]. Their research was a stepping stone towards a better understanding of diseases and the development of therapeutics that can actively target mutated or dysregulated protein and lipid kinases.

The human kinome also referred to as "the protein kinase complement of the human genome", consists of 518 protein kinases and 20 lipid kinases[1,2]. All protein kinases complement about 1.7% of human genes[1,2].

Protein kinases are involved in a wide variety of important cellular processes, including cell cycle mechanisms, metabolism, transcription, cytoskeletal development, cellular motility, apoptosis, cell proliferation, and differentiation, as well as intracellular communication(1) Manning and his team also discovered that of all the protein kinases in the human kinome, 478 hold a highly conserved, so-called eukaryotic protein kinase (ePK) domain[1]. These Eukaryotic protein kinases can be categorized into seven groups[2].

On the other hand, 40 kinases show kinase activity but do not contain a similar sequence to the ePK domain[1]. These were named aPKs, atypical protein kinases[1]. Some examples of aPKs include bromodomain kinases, pyruvate dehydrogenase kinase, and the phosphatidylinositol-3-kinase-related kinases[2].

Classification of kinase inhibitors



Source: Adapted from Duong-Ly, KC & Peterson, JR . 2013

The seven groups of eukaryotic protein kinases

Table 1: The seven groups of eukaryotic protein kinases, Sources: (2) & (5).

Name	About	Examples
Tyrosine Kinases (TK)	This group can further be divided into receptor TKs (RTKs) and cytosolic TKs. RTKs are transmembrane proteins that vary greatly in their extracellular domains, but all have intracellular kinase domains. The extracellular domain of RTKs binds to ligands and transmits signals into the cytoplasm across the cell membrane. RTKs are commonly associated with cancer progression and are often targeted by kinase inhibitors to treat disease.	▪ Human Epidermal Growth Factor ▪ Receptor (HER/EGFR) Family ▪ Insulin Receptor (IR) ▪ Insulin-Like Growth Factor Receptor ▪ (IGF 1-R) ▪ Platelet-Derived Growth Factor ▪ Receptors (PDGFRs) ▪ Fibroblast Growth FactorReceptors ▪ (FGFRs)
Tyrosine Kinase-Like (TKL)	Kinases in the TKL group contain sequences similar to those of TKs. They are commonly serine/threonine kinases. TKLs are involved in numerous signaling pathways and play a role in angiogenesis and vascular development. When dysfunctional, they are associated with various diseases, such as Parkinson's disease.	▪ Interleukin-1 (IL-1) Receptor-Associated Kinases (IRAK) ▪ RAF Kinases, for Rapidly Accelerated Fibrosarcoma ▪ LIM Domain Kinase (LIMK) ▪ Transforming Growth Factor Beta (TGFβ) Receptor
STE Kinases, (STE20, STE11, STE7 related)	STE kinases are regulators of a variety of signaling pathways. For instance, they are important influen ers of MAP kinase pathways. Over-expression of Pak1, for example, can be found in several tumor types.	▪ p21-Activated Kinases (Paks)
Casein Kinase 1 (CK1)	The CK1 family are serine/threonine enzymes and phosphorylate various substrates that play a role in the function of the cytoskeleton and regulation of transcription.	▪ Various isoforms, such as CK1α
AGC Kinases (Protein Kinase A, Protein Kinase G, Protein Kinase C related)	This family regulates cell growth, proliferation, and cell survival, as well as glucose metabolism and protein synthesis. It is involved in a variety of diseases, including diabetes and cancer*.	▪ The AGC family is comprised of approximately 60 members[3]
Ca^{2+}/Calmodulin-Dependent Kinases (CAMK)	CAMK are usually autoinhibited, meaning that substrate binding to their binding pocket interrupts the autoinhibition. CAMK are involved in calcium signaling pathways. Others are responsible for cell cycle arrest and DNA repair.	▪ Cell cycle checkpoint kinases: CHK1 and CHK2
CMGC Kinases	This family of kinases includes cyclin-dependent kinases (CDKs), which regulate the cell cycle, and mitogen-activated protein kinases (MAPKs) that play an important role in cell proliferation, differentiation, apoptosis. Others are involved in inflammation and glycogen metabolism.	▪ CDKs ▪ MAPKs ▪ Glycogen synthase kinases (GSKs) ▪ Cdk-like kinases

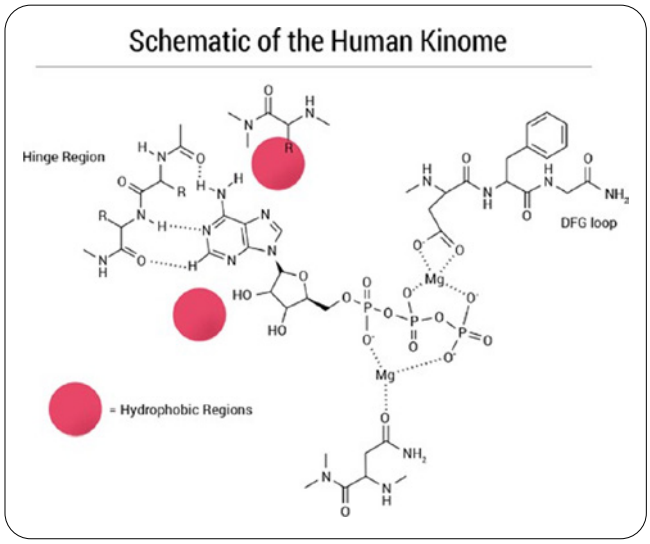
Structure of protein kinases

Characteristic to the majority of protein kinases, the ePK domain is made up of two lobes called the N-terminal lobe or N-lobe and the C-terminal lobe, the C-lobe[2,3]. The ePK domain consists of approximately 250 amino acids. The space in between the two lobes is essential for ATP-binding and phosphate transfer and contains residues, such as the cofactor magnesium, to complete these processes[2,3].

The activation loop of protein kinases, which is highly conserved, is marked by two peptide motifs that are known as the DFG (aspartate-phenylalanine-glycine) and APE (alanine-proline-glutamate) motifs[2,3]. Found on the C-lobe of the kinase domain, the activation loop moves away from the ATP-binding site when the enzyme is in its active state[2,3].

The conserved DFG motif is located at the N-terminus of the activation loop[3]. Its aspartate residue holds the magnesium ion that is responsible for positioning the phosphate group of ATP for the catalytic process[2]. In the active state, the aspartate side chain points in the direction of the ATP-binding site and is therefore called the DFG-in conformation[2,3].

During a complex reaction, the ePK domain is subjected to conformational changes between the highly conserved active state and the inactive state[2]. A reaction occurs when ATP and a protein or lipid bind to the pocket. The enzyme is then responsible for transferring a phosphate from ATP to the protein or lipid[2]. Protein kinases therefore catalyze the following reaction[5]:



Source: Adapted from Cambridge MedChem Consulting

$$MgATP^{1-} + protein\text{–}O{:}H \rightarrow protein\text{–}O{:}PO_3^{2-} + MgADP + H^+$$

In their inactive states, the activation loop of protein kinases usually blocks the substrate binding region and partially obstructs the ATP-binding site[2]. Although the inactive states of protein kinases are more varied, in many, the DFG motif's aspartate residue points away from the ATP-binding site[2,3]. This is then called the DFGout conformation[2,3].

Due to their important role in cellular signaling processes, mutated or dysregulated protein kinases can have a distinct effect on the development of disease indications, such as neurological disorders, cancer, metabolic and cardiovascular diseases, disorders of the immune system, as well as developmental and disorders[2].

Protein kinases and disease

Studies have shown that over 85% of the human kinome is involved in at least one disease or developmental disorder[4]. Treatments for these diseases usually act as antagonists, inhibiting the kinases' mechanism of action and competing with ATP for the ATP-binding site[2].

Though the large size of the protein kinase family allows researchers to target a wide variety of PK members to treat diseases, it also comes with a major setback: Proteomic analysis studies have shown that cells can contain as much as 300 different kinases – and sometimes more[4]. Together with the highly conserved active state of the ATP-binding site, this means that there is a high chance of compounds binding off-target to kinases lying outside of the targeted family[4].

Another issue is the fact that many diseases, such as advanced cancers, are characterized by not only one dysregulated or mutated protein kinase, but have multiple molecular anomalies[5]. This can result in a limited clinical benefit due to the short-term efficacy and decreased target selectivity of kinase inhibitors, and negatively influences the treatment outcome[5].

Most kinase inhibitors target the tyrosine kinase (TK) family[4]. However, for approximately 300 protein kinases there are still no inhibitors in clinical trials, and for more than 200 of these, there is no structural information available, which greatly affects drug discovery and development[4]. Additionally, the effect of a target kinase on a disease state is often highly complex or unknown, making the identification of patients who may respond positively to a given kinase inhibitor treatment near to impossible[5].

In order to tackle these challenges, researchers need to better understand the dependence of disease on the target kinase. Furthermore, more focus on target selectivity is needed and researchers need to anticipate emerging resistances to kinase inhibitors, which result in relapses in patients who had initially responded to a given kinase inhibitor[5].

The human kinome is a highly complex system that is widely studied. Here, we discuss the current state of research, how kinase inhibitors are slowly taking over drug development pipelines and how researchers will tackle the major issues of kinase drug discovery in the future.

The human kinome in therapeutics

By the end of 2018, 50 kinase inhibitors had been approved by the FDA (Table II) and more than 250 candidates are currently in clinical development[4,6,7]. In general, kinase inhibitors can be divided into two groups; they are either ATP-competitive or non-ATP-competitive[2].

As most kinase inhibitors on the market today are ATP-competitive – meaning they compete with ATP for its binding site – a phenomenon called polypharmacology frequently occurs[6]. In polypharmacology, drugs can bind to more than one target, which can either be of an advantage or cause severe toxicity[2,6]. Moreover, it results in an increased risk of drug resistance, which is one reason why numerous drugs on the market target the same indications[2,5].

About kinase inhibitors

Over the last two decades, only approximately 80 protein kinases in the human kinome have been successfully targeted, and of these, most are used for the treatment of various cancers[5]. Only a small amount of marketed kinase inhibitors actually targets other indications, such as organ transplants, myelofibrosis, idiopathic pulmonary fibrosis, rheumatoid arthritis and other autoimmune diseases (Table II)[5,7,8,9].

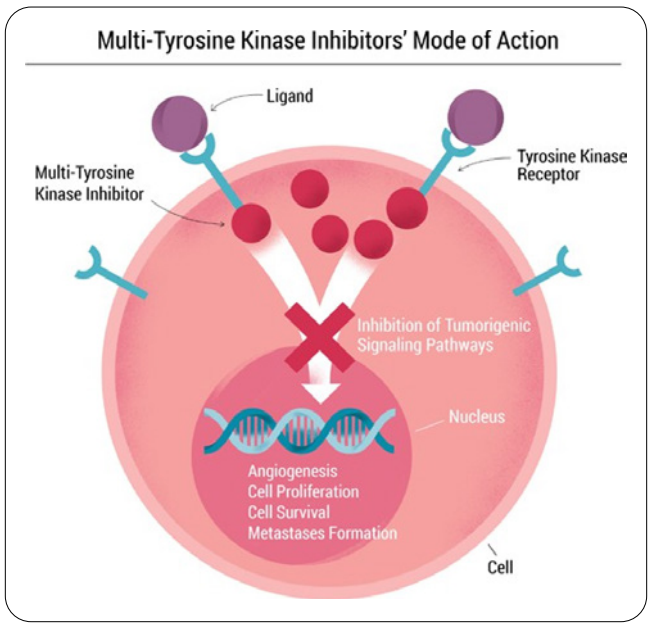
The most commonly targeted protein kinases are tyrosine kinases, including EGFR, VEGFR, PDGFR and the HER family (Table I). For instance, in many cancers, mutations cause overexpression of EGFR, resulting in uncontrolled cell proliferation. EGFR overexpression can be found in a variety of cancers like non-small cell lung cancer and breast cancer (Table I). Protein kinase inhibitors, such as gefitinib, lapatinib, icotinib, and afatinib all target EGFR and inhibit its activity[5].

Others, including temsirolimus, everolimus, vemurafenib and dabrafenib, target serine/threonine kinases to treat numerous cancers including mantle cell lymphoma, neuroendocrine tumors and melanoma (Table II)[5,7,8,9].

The first-ever FDA approved kinase inhibitor sirolimus, along with temsirolimus and everolimus, for example, targets the atypical serine/threonine kinase mTOR. Highly conserved, mTOR responds to nutrients, cellular energy, growth factors, and stress, and promotes and regulates cell growth and metabolism[10,11]. As it is involved in so many cellular processes, mTOR deregulation is the basis for many diseases, including cancer, neurodegeneration, type 2 diabetes, and obesity[10,11].

mTOR is part of the phosphoinositide 3-kinase (PI3K)-related kinase family[11]. It can interact with different proteins to form two multiprotein complexes called mTOR complex 1 (mTORC1) and mTOR complex 2, mTORC2[11]. While mTORC1 is sensitive to sirolimus and mediates temporal control of cell growth, mTORC2 is sirolimus insensitive and is responsible for spatial regulation of cell growth[10,11].

When sirolimus binds to the so-called intracellular 12kDa FK506-binding protein (FKBP12), the two form a gain-of-function complex, which targets and inhibits mTORC1[11].



Source: Adapted from Cancer Research UK, Eckstein, & N. et al. 2014

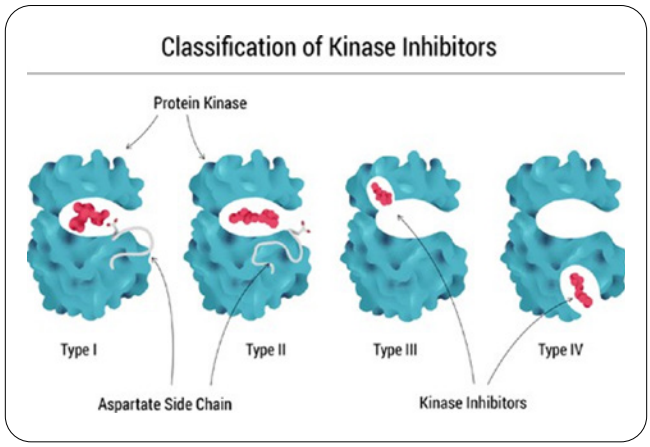
Classification of kinase inhibitors

Kinase inhibitors can be classified into four groups, named Type I, II, III, and IV. Type I and II kinase inhibitors are ATP-competitive small molecules[2,12]. Examples for Type I inhibitors include gefitinib, ceritinib, and palbociclib[12]. Axitinib, dabrafenib, and regorafenib are examples of Type II inhibitors[12].

However, whereas Type I inhibitors bind to the active/ DFG-in conformation of the enzyme, Type II inhibitors bind to the inactive/DFG-out conformation[12]. Both Type I and Type II kinase inhibitors sit in a section of the adenine binding pocket and form hydrogen bonds with the hinge region between the enzyme's two lobes[12].

Type III inhibitors, on the other hand, are non-ATP competitive inhibitors, which are also known as allosteric inhibitors[12]. Allosteric inhibitors bind outside of the active site. In the case of protein kinases, this means that Type III inhibitors bind next to the ATP-binding pocket and that an ATP inhibitor can bind simultaneously[12,13]. Trametinib is an example of a Type III inhibitor[12].

Type IV inhibitors differ slightly from Type III inhibitors. Though they are also non-ATP competitive and allosteric, they do not bind next to the ATP-binding pocket[12]. An example would be the abovementioned mTOR inhibitors sirolimus, everolimus, and temsirolimus, which first bind to FKBP12 and form a complex before indirectly inhibiting mTOR activity[11,12].



Source: Adapted from Wu, P et al, 2015

Binding modes of kinase inhibitors

Kinase inhibitors generally have two different ways of binding to their kinase targets. They either bind reversibly or covalently[14]. Whereas reversible or non-covalent inhibitors are ATP-competitive or non-ATP competitive and can be classified into Types I through IV as discussed above, covalent inhibitors mostly bind irreversibly to their protein kinase target[13,14].

Covalent inhibitors are also known as Type V inhibitors. Many covalent inhibitors bind to the ATP-binding site and prevent ATP from binding to the protein kinase[14]. These irreversible kinase inhibitors have a higher potency inside cells than reversible inhibitors, as they are less vulnerable to high intracellular ATP concentrations and inhibited signaling pathways can only be restored by synthesis of novel kinases[15].

During binding, the covalent inhibitor forms a bond with a cysteine residue in the ATP-binding site[14]. The EGFR inhibitor afatinib, for instance, forms covalent bonds with cysteine in the lower part of the receptor tyrosine kinase's ATP-binding site[13,14]. Another example is the Bruton's tyrosine kinase (BTK) inhibitor ibrutinib[13,14].

The future of kinase inhibitors

Although research into and development of kinase inhibitors has been steadily evolving over the last two decades, only 10-15% of the whole kinome is clinically covered[14,16]. Most kinase inhibitors target the group of tyrosine kinases, which shows that many kinases are still disregarded in drug development[16].

Slowly, treatments targeting other kinases, such as lipid kinases and non-ATP competitive kinases, are emerging[13,16]. However, there is still a need to develop tools to further explore unfamiliar kinase families and to investigate new mechanisms of actions in order to develop novel small-molecule inhibitors[16]. Fortunately, the increased use of genome screening and genetically modified organisms is paving the way to discovering new kinase-disease relationships[14].

Despite the fact that over 80% of the human kinome is involved in a variety of diseases ranging from cancer, inflammatory and neurological disorders to cardiovascular diseases and diabetes, most kinase inhibitors on the market today are for the treatment of cancer[4,16]. The main reason for this is the promiscuous selectivity profile of most kinase inhibitors, which target more than one kinase[5,16]. Though this polypharmacology can be seen as beneficial or at least tolerated for the treatment of cancer, it can also lead to serious side effects[5,14].

Especially for non-life threatening diseases, such as many immunological disorders, which require chronic administration of drugs, kinase inhibitors need to be as selective as possible[14]. With over 500 kinases in the human kinome, this is hard to achieve. However, progress in molecular profiling and precision medicine is allowing researchers to assess the efficacy and toxicity of novel kinase inhibitors, resulting in a more precise pharmacokinetic profile and fewer side effects[5].

One example of a promising strategy that addresses these selectivity issues is induced protein degradation with the help of so-called proteolysis-targeting chimeras, or PROTAC[17]. This strategy is based on the idea that inhibitors alone only target the catalytic activity of kinases, while other kinase domains remain unaddressed although they play a role in important physiological functions and several diseases[17]. PROTAC are organic chimeras composed of kinase inhibitors that are linked to an E3 ligase-targeting compound. By recruiting the E3 ligase, kinase selective degradation through ubiquitinylation and proteasome machinery is triggered[17].

Various techniques, such as the one above as well as advances in genome-wide screening, are enabling the development of targeted treatments and the identification of those patients who are most likely to have the best treatment outcome[5]. This is particularly important in light of the high rate of resistance to cancer- treating kinase inhibitors, which means that patients often relapse after a certain amount of time and which results in a poor benefit for patients[4, 5,13].

Anticipating emerging resistance and possible toxicities remains a major challenge for the discovery of kinase drugs[5,13]. Consequently, researchers are becoming more interested in studying the actual binding kinetics of kinases and their inhibitors. In binding kinetics terms, the binding rate of an inhibitor to the kinase and the formation of a drug-target complex is known as Kon, whereas the dissociation of the drug from the enzyme is described as Koff[18].

The higher Kon and the lower Koff, the longer the enzyme-drug complex will stay upright. This is an advantageous state because the clinical action of the drug will last longer[18]. Investigating the binding kinetics of kinases and their inhibitors allows researchers to study the right dosing regimen, as well as the selectivity of the kinase inhibitors[19].

The fact that kinases play an essential part in numerous cellular processes and their deregulation or mutation results in a variety of diseases, makes them a key target in drug development. With 50 FDA approved kinase inhibitors so far and many more in preclinical and clinical development, we are well on the way to exploiting a promising pool of targets for the development of treatments not only for cancer but also for multiple other diseases.

Over the past decade, we have learned that responses to kinase inhibitors vary widely between individual patients and across patient populations[13]. These responses seem to depend on a variety of factors, and bit by bit, we are discovering and understanding these factors, and paving the way to more targeted and personalized treatments with fewer side effects and greater treatment outcomes for patients.

About Revvity

Over the years, Revvity has invested broadly in building a world-class platform to study kinases. With a growing portfolio of no-wash assays to choose from, available in semi-universal or kinase-specific formats, clients can efficiently address over 200 serine/threonine, tyrosine kinases.

The recent launch of a platform that enables the investigation of ATP-competitive inhibitors to kinase binding, comes to reinforce Revvity leadership in the field. The platform allows researchers to determine the pharmacology of kinase drug inhibitors, understand their mechanism of action and get access to their kinetic binding parameters. This is particularly relevant as target occupancy is increasingly perceived as an essential parameter to accurately predict in-vivo efficacy and associated dosing regimen and to optimize selectivity.

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Appendix

Table 2: FDA approved kinase inhibitors between 1999 and 2018

Chemical Kinase Inhibitors	FDA Approval	Targets	Disease Indications
Sirolimus (Rapamune®)	1999	Serine/threonine kinase mTORt	Kidney transplant
Gefitinib (Iressa®)	2002	Tyrosine kinase EGFR	Non-small cell lung cancer
Imatinib (Glivec®)	2002	Tyrosine kinases BCR-ABL, KIT, DDR1t	Chronic myeloid leukemia and numerous other cancerst
Erlotinib (Tarceva®)	2005	Tyrosine kinase EGFR, serine/ threonine kinase GAK	Non-small cell lung cancer, pancreatic cancer
Sorafenib (Nexavar®)	2005	Various tyrosine kinases, including VEGFR and RAF kinases	Kidney cancer, hepatocellular carcinoma
Dasatinib (Sprycel®)	2006	Tyrosine kinases from the SRC family	Chronic myeloid leukemia, acute lymphoblastic leukemia
Sunitinib (Sutent®)	2006	Multiple receptor tyrosine kinases, including PDGFRs and VEGFRs	Gastrointestinal stromal tumor, advanced renal carcinoma, pancreatic neuroendocrine tumorst
Lapatinib (Tykerb®, Tyverb®)	2007	Tyrosine kinases EGFR, ERBB2	Advanced breast cancer
Nilotinib (Tasigna®)	2007	Tyrosine kinases BCR-ABL, DDR1	Chronic myeloid leukemiaAdvanced kidney cancer, mantle cell lymphoma
Temsirolimus (Torisel®)	2007	Serine/threonine kinase mTOR	Advanced kidney cancer, mantle cell lymphoma
Everolimus (Afinitor®)	2009	Serine/threonine kinase mTOR	Organ transplants, neuroendocrine tumors
Pazopanib (Votrient®)	2009	Multiple receptor tyrosine kinases, including PDGFR, VEGFR, KIt	Advanced kidney cancer, soft tissue sarcomast
Cabozantinib (Cometriq®)	2011	Multiple receptor tyrosine kinases, including VEGFR, MET, RET, KIT	Metastatic medullary thyroid cancer
Crizotinib (Xalkori®)	2011	Tyrosine kinases ALK, ROS1	Non-small cell lung cancer
Icotinib (Conmana®)	2011	Tyrosine kinase EGFR	Variety of cancers including non-small cell lung cance
Ruxolitinib (Jakafi®)	2011	Tyrosine kinases JAK1, JAK2, TYK2	Myelofibrosis, polycythemia vera
Vandetanib (Caprelsa®)	2011	Tyrosine kinase VEGFR2, EGFR	Advanced or metastatic medullary thyroid cancer
Vemurafenib (Zelboraf®)	2011	Serine/threonine kinase B-Raf	Melanoma
Axitinib (Inlyta®)	2012	Multiple tyrosine kinases	Advanced kidney cancer and other cancers
Lenvatinib (Lenvima®)	2012	Tyrosine kinase VEGFR2	Advanced or metastatic medullary thyroid cancer, refractory renal cell carcinoma
Ponatinib (Iclusig®)	2012	Multiple tyrosine kinases	Refractory chronic myelogenous leukemiat
Regorafenib (Stivarga®)	2012	Multiple tyrosine kinases, like VEGFRs, RET, KIT, PDGFR & serine/threonine kinase Raft	Refractory metastatic colorectal cancer, hepatocellular carcinoma, and gastrointestinal stromal tumor
Tofacitinib (Xeljanz®)	2012	Tyrosine kinases JAKs	Rheumatoid arthritis
Afatinib (Giotrif®)	2013	Tyrosine kinases, like EGFR	Lung cancer

Chemical Kinase Inhibitors	FDA Approval	Targets	Disease Indications
Bosutinib (Bosulif®)	2013	Multiple tyrosine kinases	Chronic myeloid leukemia
Dabrafenib (Tafinlar®)	2013	Serine/threonine kinase B-Raf	Melanoma
Ibrutinib (Imbruvica®)	2013	Multiple tyrosine kinases	Mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom's macroglobulinemia
Trametinib (Mekinist®)	2013	Serine/threonine kinases and threonine/tyrosine kinases	Advanced malignant melanoma
Bafetinib (NS-187)	2014	Multiple tyrosine kinases	Chronic myeloid leukemia
Ceritinib (Zykadia®)	2014	Tyrosine kinase ALK	Non-small cell lung cancer
Nintedanib (Ovef®,Vargatef®)	2014	Multiple receptor tyrosine kinases, including PDGFR, VEGFR, FGFR	Idiopathic pulmonary fibrosis
Alectinib (Alecensa®)	2015	Tyrosine kinase ALK	Advanced non-small cell lung cancer
Cobimetinib (Cotellic®)	2015	Threonine/tyrosine kinase MAP2K1/ MEK1 & Serine/threonine kinase B-Raf	Advanced malignant melanoma
Osimertinib (Tagrisso®)	2015	Tyrosine kinase EGFR	Advanced non-small cell lung cance
Palbociclib (Ibrance®)	2015	Serine/threonine kinases CDK4, CDK6	Metastatic breast cancer
Midostaurin (Rydapt®)	2017	Tyrosine kinase inhibitors VEGFR2, PDGFR, FLT3, PKCα	Acute myeloid leukemia
Abemaciclib (Verzenio®)	2017	Serine/threonine kinases CDK4, CDK6	Metastatic breast cancer
Acalabrutinib (Calquence®)	2017	Tyrosine Kinase BTK	B-cell malignancies
Brigatinib (Alunbrig®)	2017	Tyrosine kinase ALK, EGFR	Advanced non-small cell lung cancer
Neratinib (Nerlynx®)	2017	Tyrosine kinases HER2, EGFR	Early stage breast cancer
Ribociclib (Kisqali®)	2017	Serine/threonine kinases CDK4, CDK6	Metastatic breast cancer
Baricitinib (Olumiant®)	2018	Tyrosine kinases JAKs	Rheumatoid arthritis
Binimetinib (Mektovi®)	2018	Threonine/tyrosine kinases MEK1,MEK2	In combination with Encorafenib for metastatic melanoma
Dacomitinib (Vizimpro®)	2018	Multiple tyrosine kinases	Metastatic non-small cell lung cancer
Encorafenib (Braftovi®)	2018	Serine/threonine kinase B-Raf	Metastatic melanoma
Fostamatinib (Tavalisse®)	2018	Tyrosine kinase Syk	Chronic immune thrombocytopenia
Gilteritinib (Xospata®)	2018	Multiple tyrosine kinases	Relapsed or refractory acute myeloid leukemia
Larotrectinib (Vitrakvi®)	2018	Tyrosine kinase Trk	A number of solid tumors
Lorlatinib (Lorbrena®)	2018	Tyrosine kinases ALK, ROS1	Non-small cell lung cancer
Netarsudil (Rhopressa®)	2018	Serine/threonine kinase Rho	Glaucoma, ocular hypertension

Sources: Wilson et al. 2018, PubChem, Cancer Research UK, Blue Ridge Institute for Medical Research

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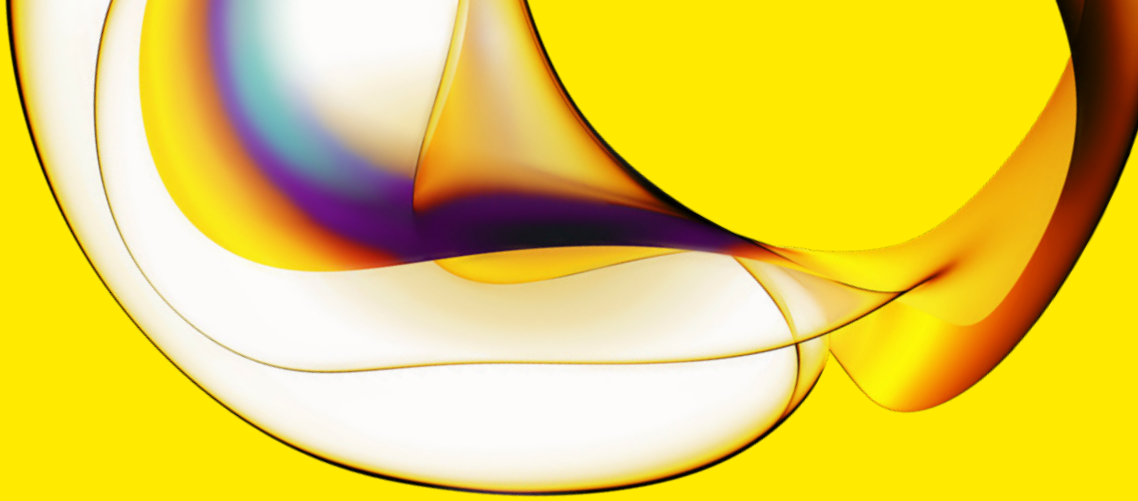

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