Chapter

The Role of Kinase Inhibitors in Cancer Therapies

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Abstract

Protein kinases are enzymes that transfer a phosphate group to the threonine, serine, or tyrosine residues of the target protein, regulating its activity. The activity of these enzymes are very important and strictly regulated in the cell as they promote cell proliferation, survival, and migration. In the case of any dysregulation of these enzymes, they can be associated with cancer initiation and progression. Small-molecule kinase inhibitors approved by the FDA for their improved clinical benefits are currently used in targeted therapy for the treatment of various cancers. So far, there are 62 FDA-approved therapeutic agents targeting different protein kinases, eight of which were approved in 2020. Today, kinase inhibitors are used as FDA approved cancer agents and newly developed ones are evaluated in clinical trials. Those protein kinase inhibitors can be grouped as growth factor receptor inhibitors, Ras/Raf/Mek inhibitors, phosphoinositide 3-kinase (PI3K) and cyclin dependent kinase inhibitors, other targets, and agents such as protein kinase c and 3 phosphoinositide-dependent kinase 1. In this chapter, these kinases, their pathways, and their inhibitors will be discussed in detail.

Keywords: cancer therapy, clinical use, inhibitor, protein kinase, drug

1. Introduction

Protein kinases (PKs) are enzymes that regulate the activity of a protein by adding phosphate group to specific amino acids using ATP as a resource, thereby resulting in a conformational change of that protein. More specifically, they add terminal γ-phosphate group to the serine, threonine or tyrosine residues of the target proteins and this process is called phosphorylation. Phosphorylation of a protein changes its activity, location or downstream function that can result in amplification of the first signal [1]. Furthermore, phosphorylation can also alter biological activities such as transcription and translation. In addition, it can have inhibitory or stimulatory effect on the target. In either case, it has a significant role in regulation of cellular activities.

PK family is one of the largest protein family comprising more than 500 different kinases in the human proteome that is encoded by 2% of the human genome [2]. PKs in

regulating protein activity have a massive effect on cell signaling pathways involved in metabolism, immune responses, growth, differentiation, migration, and adaptation.

Because of the potency of PKs, changes in their expression levels or patterns can impact various pathways resulting in disease development including cancers, as well as metabolic and developmental disorders.

PKs are tightly regulated to restrain their potency and any dysregulation could result in a diseased state. Either a kinase itself or the pathway that the kinase is regulated is mutated in many cancers [3–5] and those PKs can be classified as proto-oncogenes. In fact, in 1978, the first identified proto-oncogene encodes a tyrosine kinase called c-Src [6]. Overexpression or dysregulation of oncogenic kinases results in altered signaling pathways and oncogenic transformation. In other words, any perturbation on the regulation of oncogenic kinases can result in anchorage-independent uncontrolled growth and proliferation as well as angiogenesis and metastasis. Exploring the role of kinases in cancer development and progression have highlighted the potential of kinase targeted therapies. In this chapter, we will focus on the kinases' role in oncogenic pathways and the kinase inhibitors targeting these pathways as a therapeutic option.

Protein kinase inhibitors (PKIs) are antineoplastic substances that are used to block the constant or overactivity of dysregulated protein kinases. The first developed PKI called imatinib mesylate (Gleevec, STI571, or CP57148B) targets a fusion protein called "BCR-ABL" which is a constantly active tyrosine kinase that is observed in chronic myeloid leukemia (CML). In addition, imatinib directly inhibits ARG, KIT, and PDGFR tyrosine kinases and used to treat blood neoplasia other than CML and solid tumors that stem from activation of these tyrosine kinases. Consequently, the remarkable success of imatinib had a major impact on researchers to focus on the development of other targeted PKIs that could be potential cancer therapeutics. Following imatinib, other BCL-ABL inhibitors such as nilotinib, dasatinib, bosutinib and ponatinib were developed to overcome imatinib-resistant mutants [7].

The success of imatinib had opened the door to exploration of other oncogenic kinases in other signaling pathways. Those kinase inhibitors can be grouped as growth factor receptor inhibitors, Ras/Raf/Mek inhibitors, phosphoinositide 3-kinase (PI3K) and cyclin dependent kinase inhibitors, other targets and agents such as protein kinase c and 3 phosphoinositide-dependent kinase 1 (PDK1). This chapter will focus on the kinases' role in oncogenic pathways and the kinase inhibitors targeting these pathways as a therapeutic option.

2. Growth factor receptors

Development, growth and homeostasis of multicellular organisms are controlled by growth factors. Growth factors show their activity by binding to their receptors and are required for cell–cell communications for embryonic tissue induction, cell survival, fate determination, apoptosis, cell migration and tissue specialization. These receptors transmit extracellular signals to the intracellular region in two ways: activation of intracellular transporters or direct translocation of the receptor to the nucleus [8].

The feature of cancer is its continuous growth. Growth factors include epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), transforming growth factor (TGF), insulin-like growth factor (IGF) and platelet-derived growth factor (PDGF) and they stimulate proliferation, migration

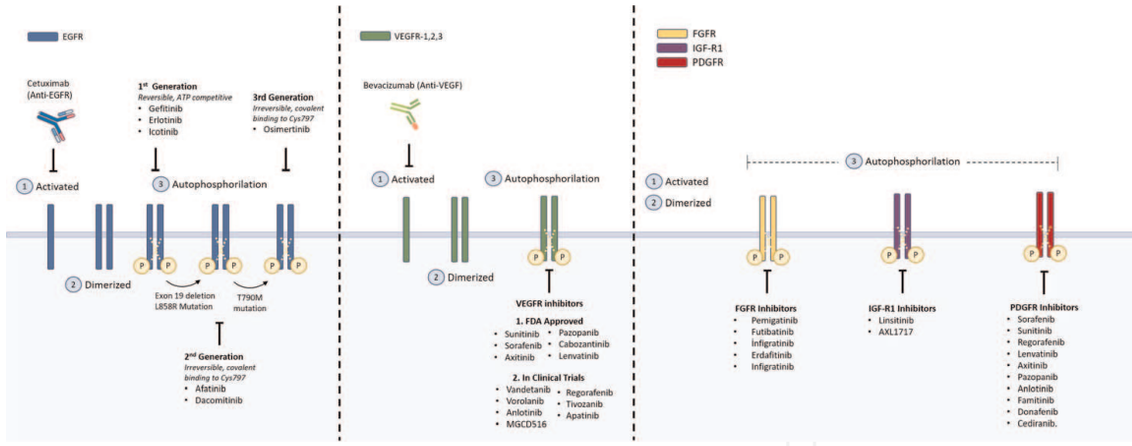


Figure 1.
Kinase inhibitors and their inhibition pathways. Cetuximab binds to EGFR with a higher affinity than EGF and competitively inhibits its binding. Other drugs compete with ATP, inhibits the autophosphorylation process. 1st generation EGFR inhibitors gefitinib, erlotinib and icotinib are not effective against the receptors containing exon 19 deletion and L858R mutations. On the other hand, 3rd generation drug osimertinib is effective against EGFR containing exon 19 deletion, L858R and T790M mutations. Bevacizumab binds to VEGFR ligand VEGF, inhibiting its binding with VEGFR. Other inhibitors of VEGFR, FGFR, IGF-R1 and PDGFR target autophosphorylation mechanism, thereby prohibiting the downstream activation of other proteins.

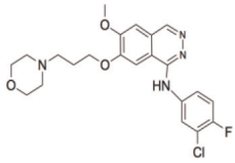
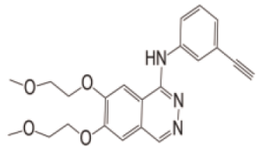
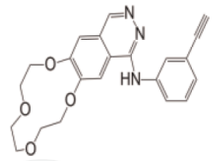
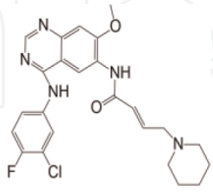
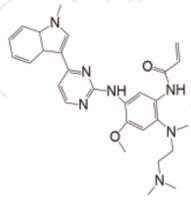
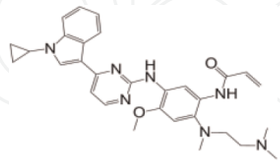
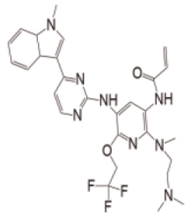
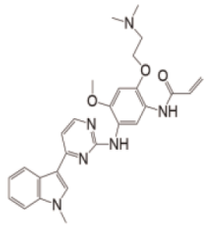
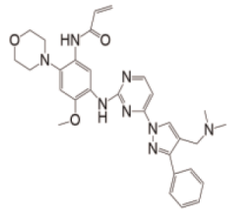
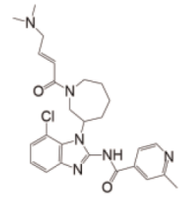
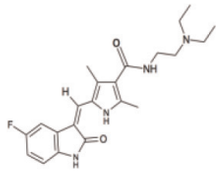
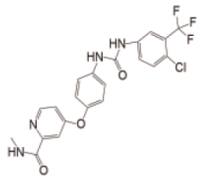
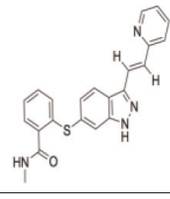
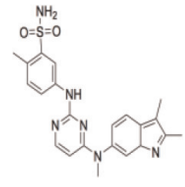
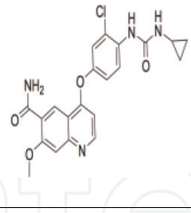
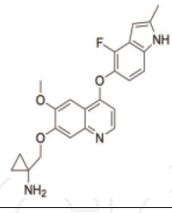
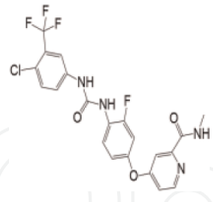
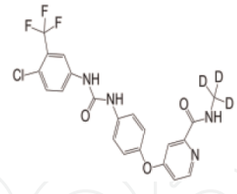
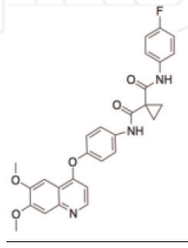
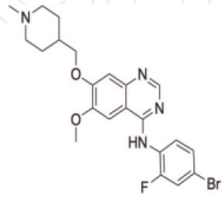
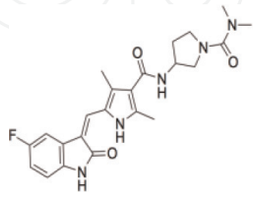
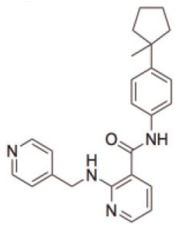
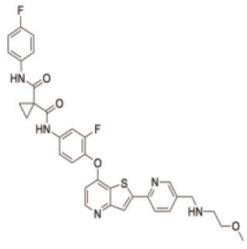
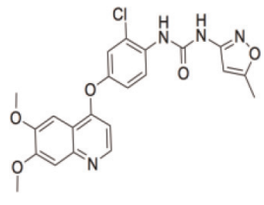
and invasion of cancer cell and stromal cell, thereby regulating tumor growth, angiogenesis and metastasis (**Figure 1**) [9]. **Table 1** shows molecules that inhibits growth factor receptors.

2.1 Epidermal growth factor receptor

One of the most studied drugs in human cancer is the EGF family of receptor tyrosine kinases (RTKs), also called ErbB or HER receptors [8]. Family of EGF receptor (EGFR) comprises four receptor proteins: ErbB-1/EGFR-1 to −4 (also called HER 1–4). These proteins are expressed on cell surface and have alike structure: an intracellular domain with kinase activity, a transmembrane domain and an extracellular domain with ligand binding site [10]. The binding of EGFR ligand initiates homo- and heterodimers between receptors, activating cascades of mitogenic and anti-apoptotic signal [11].

The dimerization is required to activate the intracellular tyrosine kinase domain and C-terminal tail phosphorylation. Its autophosphorylation then promotes either directly or by adaptor proteins, the signal transduction pathways including Ras/MAPK, PI(3)kinase/Akt, PLCg1/PKC, and STAT pathways [8] in modulating differentiation, cellular proliferation, and survival [11].

EGFR has been extensively studied for cancer therapeutics due to mutations, deletions, and overexpression in tumors [11]. EGFR is generally investigated in non-small cell lung cancer (NSCLC): its amplification is ∼80% and its mutation is 20% [12, 13]. When compared to chemotherapy used in NSCLC patients, EGFR TKIs have more than twice the progression-free survival (PFS) with actionable mutations of EGFR. Moreover, they have better objective response rates (ORRs), response time, life quality, and reduction in treatment- associated toxicity [14]. First generation EGFR-tyrosine kinase inhibitors (TKIs) bind reversibly to EGFR and block ATP-TK domain binding and this blockage causes cell death by inhibiting cell proliferation [15]. Some examples of these EGFR-TKIs are gefitinib, erlotinib, and icotinib [14]. When looked at the second-generation EGFR-TKIs these irreversibly bind to EGFR. Afatinib and dacomitinib can

Target	Inhibitors			
EGFR	**Gefitinib** 	**Erlotinib** 	**Icotinib** 	
	Dacomitinib 	**Osimertinib** 	**Almonertinib** 	
	Furmonertinib 	**Rezivertinib (BPI-7711)** 	**Lazertinib** 	**Nazartinib** 
VEGFR and PDGFR	**Sunitinib** 	**Sorafenib** 	**Axitinib** 	**Pazopanib** 
	Lenvatinib 	**Anlotinib** 	**Regorafenib** 	**Donafenib** 
VEGFR	**Cabozantinib** 	**Vandetanib** 	**Vorolanib** 	
	Apatinib 	**Sitravatinib (MGCD516)** 	**Tivozanib** 	

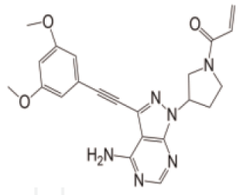
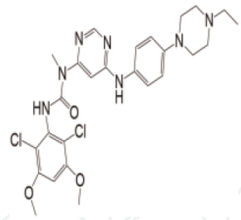
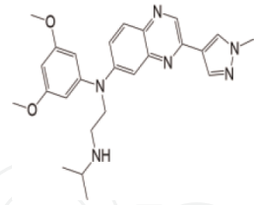
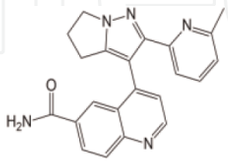
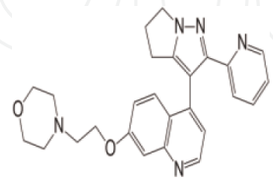
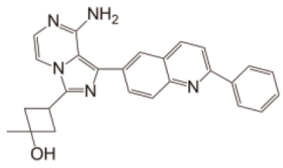
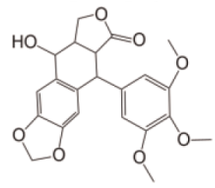
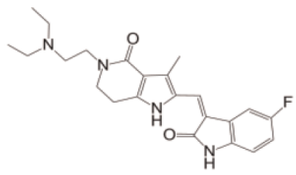
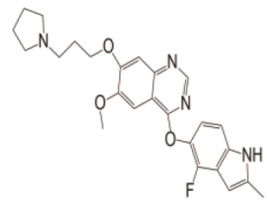
Target	Inhibitors		
FGFR	**Futibatinib**	**Infigratinib**	**Erdafitinib**
			
TGF-βR	**Galunisertib**		**LY2109761**
			
IGFR	**Linsitinib**		**Picropodophyllin** (AXL1717)
			
PDGFR	**Famitinib**		**Cediranib**
			

Table 1.
Structures of growth factor receptors inhibitors.

be given examples as second generation [14]. Although dacomitinib has improved median PFS, hazard ratio, and median overall survival [16, 17] compared to first-line treatment, the usage of afatinib and dacomitinib in clinical practice may be limited due to having increased toxicities [18].

EGFR T790M mutation causes almost 50% resistance to EGFR-TKIs of first and second generations [19]. As an EGFR TKI of third-generation, osimertinib inhibits both EGFR T790M mutations and EGFR-sensitizing [20] and it is promising for central nervous system (CNS) metastatic patients which is due to EGFR mutation in NSCLC patients [20] or after treatment with EGFR-TKIs of first- or second-generation [21]. Other EGFR TKIs as a third-generation for advanced NSCLC with mutation in EGFR T790M are almonertinib [22], furmonertinib (AST2818) [23], BPI-7711 [24], lazertinib (YH25448) [25], and nazartinib (EGF816) [26], and they have exhibited acceptable safeties and promising efficacies. Almonertinib was also approved by China National Medical Products Administration (NMPA).

Monoclonal antibodies (mAbs), cetuximab and panitumumab, have been used against EGFR and are approved for metastatic colorectal cancer (CRC) treatment. Only small patient subgroups to cetuximab and panitumumab indicate clinical benefit. The best response to cetuximab and panitumumab is seen in patients with the combination of wild type KRAS, BRAF, and PIK3CA and PTEN protein express [27].

Trastuzumab is another mAb used in EGFR/HER2 pathway for the treatment of HER2-positive breast cancers [28].

2.2 Vascular endothelial growth factor receptor

Vascular endothelial growth factors (VEGF) are a family of polypeptides contain highly conserved receptor binding domain in disulfide-node [29]. There are two types of VEGF; VEGF-A and VEGF-B, which bind their receptors named RTK. VEGF members display plural interactions with RTKs are the critical factors for blood vessel formation which cause cord formation and tubulogenesis, differentiation of endothelial cells, proliferation, migration. In mammals, the vascular endothelial growth factor receptor (VEGFR), transmembrane tyrosine kinase receptors, comprises three members VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1) and VEGFR-3 (Flt-4), and control the generation of blood and lymphatic vessels [30].

VEGFRs have seven immunoglobulin (Ig)-like domains on the extracellular site and two split tyrosine kinase domains in the intracellular site [10]. In adults, while the vascular endothelial cells are posess largely VEGFR-1 and VEGFR-2 in their structure, the lymphatic endothelial cells have VEGFR-3 [31]. The literature shows that VEGF pathway is critical for renal cell carcinoma (RCC) initiation and progression, and VEGFRs targeted TKIs have been used for most favorable RCC treatment strategy.

In recent years, VEGFR-associated multi-targeted TKIs have been revealed as antı-tumor agents for cancer treatment [18]. VEGFR-targeted therapeutic agents have become the main element used for RCC patients treatment [31]. The FDA has approved 6 small molecules, named as sunitinib, sorafenib, axitinib, pazopanib, cabozantinib and lenvatinib, that inhibit VEGFR1/2/3 for use in RCC treatment. Additionally, for clinical trials, seven VEGFR inhibitors; vandetanib, vorolanib, anlotinib, MGCD516, regorafenib, tivozanib, and apatinib are under review [31].

Not only VEGFRs targeted and block by these drugs, also some other receptors generally overexpressed in RCC, platelet-derived growth factor (PDGF) receptors a and b (PDGFR-a/b), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase-3 (FLT3), tyrosine protein kinase MET, rearranged during transfection (RET), tyrosine kinase that contains immunoglobulin-like loops and epidermal growth factor-similar domains-2 (Tie2), fibroblast growth factor receptor (FGFR), the GAS6 receptor (AXL), serine/threonine protein kinase Raf-1, colony stimulating factor1 receptor (CSF1R), and discoidin domain receptor (DDR) targeted by these small drugs. In addition, growth, proliferation and angiogenesis of tumor cells are significantly inhibited by the effects of VEGFR1/2/3 inhibitors. The humanized IgG1 monoclonal antibody approved in 2009, Bevacizumab can bind VEGF and for use in first-line therapy for RCC in combination with IFN-α [32].

Besides, in hepatocellular carcinoma (HCC), the efficiency of VEGFR-associated multi-targeted TKIs was demonstrated. Especially Sorafenib can target VEGFR, PDGFR, FGFR, and other signaling targets and prefered as first line therapy in inoperable cases [33, 34]. In phase II/III studies of Donafenib, VEGFR-associated multitargeted TKI, is shown a higher overall survival rate than sorafenib in advanced HCC cases [35]. Moreover, regorafenib [36], apatinib [37] and cabozantinib [38] are used for second-line treatment of HCC. More recently, it is shown that Pembrolizumab is anti programmed cell death protein-1 (PD-1) antibody and lenvatinib combination therapies demonstrated promising anti-tumor effect on untreated/inoperable HCC patients and this combination named as breakthrıough therapy by FDA [39].

For lung cancer therapy (on NSCLC [40] and SCLC [41]), Anlotinib showed promising results and was approved for further-line therapy by(National Medical Products Administration of China (NMPA) [18]. Furthermore, similar results identified in thyroid carcinoma and soft tissue sarcoma (STS) patients [42].

2.3 Fibroblast growth factor receptor

Fibroblast growth factor receptors (FGFRs), which are members of receptor tyrosine kinase can be thought as single pass membrane proteins due to the cellular membrane covering in a single region [43]. There are four transmembrane proteins (FGFR1–4) for the FGFR family and different isoforms of them with changed ligand specificity [10]. Upon binding of the different FGF ligands to different FGF receptors, auto-phosphorylation and kinase activation are initiated by FGFR dimerization. This binding causes cell death inhibition and uncontrolled growth, respectively due to downstream anti-apoptotic PI3K/AKT signals and mitogenic growth signals (MAPK) so the interaction FGF-FGFR plays a critical role in tumorigenesis. Moreover, the downstream of PLC/PKC pathway joins the MAPK pathway to promote cell growth [10].

The use of FGFR pathway downstream molecules as targets in anti-cancer drugs has attracted attention, and these drugs are small compounds and antibodies against cancer driver mutations in FGFRs and related signaling molecules [43]. Most FGFR-TKIs belong to multiple target TKIs [18].

FGFR2 changes are associated with the cholangiocarcinoma (CCA). Pemigatinib, a FGFR1–3 TKI, has been accepted for the treatment of locally advanced or metastatic CCA [44]. Some other FGFR-TKIs (such as futibatinib, infigratinib) also have the potential to be used for CCA based on their results [45].

In addition to CCA, FGFR2 changes also play a role in urothelial carcinoma (UC). Fusions and mutations in FGFR2/3 are seen in 20% of patients with UC [46]. Treatment with erdafitinib, a FGFR1–4 TKI, has been accepted for the adult patients with previously treated metastatic or locally advanced FGFR2/3-mutated UC. Response was more promising as second-line therapy for advanced UC compared to antibody-drug conjugates such as enfortumab vedotin or sacituzumab govitecan [47] and pembrolizumab [48]. In addition, other inhibitors of pan-FGFR are investigated and for example infigratinib (BGJ 398) is examined in the treatment of UC holding a FGFR3 mutation [47].

2.4 Transforming growth factor-β receptor

Transforming growth factor-beta (TGF-β) is a cytokine which has different functions and modulates cell growth and differentiation, extracellular matrix production, apoptosis, angiogenesis, cell motility, and cellular immune responses. Interestingly, TGF- β shows different effects on tumorigenesis. Although it acts as a tumor suppressor in the early stages, it advances tumor growth by producing a more suitable environment for tumor invasion and metastasis in later stages [49].

There are three membrane receptors for the TGF-β receptor (TGF-βR) family: TβRI, TβRII and TβRIII. Their expression in various cell types control different cellular functions by altering signals upon ligand binding of TGF-β [10]. When high binding affinity is established between activated TGF-β and TβRII signaling is started. The binding needs altering the conformation of TβRII by engagement of TβRIII [49]. Receptors transphosphorylation is triggered after binding is created between TGF-β

ligand and transmembrane receptor serine/threonine kinase (type I and II) complex. After that, SMAD proteins in C-terminal serine are phosphorylated by activated receptors. SMAD complexes which are activated control target genes transcription by migrating to the nucleus [50], thereby controlling cell proliferation, migration, survival, and differentiation [10].

TGF-β can signal via intracellular Smad proteins and some Smad independent pathways involving ERK, MAP kinase, PI3K, JNK, p38, and AKT [49]. The Smad pathway is very important in the antiproliferative properties of TGF-β and modifications in the Smad system by missense mutations [51, 52]. Moreover, blocking of the phosphorylation process or Smad 2/3 complex formation has been demonstrated to be effective in tumor development [53]. The TGF-β overexpression has been determined in many tumors containing cancers of the breast, colon, liver, stomach, lung, esophagus, kidney, prostate, pancreas, brain, and malignant melanoma, as well as certain hematological malignancies [54–61]. Some small-molecule TKIs of TβR II and TβR III can block the signaling pathway of TGF-β-mediated receptor.

Galunisertib (LY2157299) monohydrate has shown powerful as a TβR I inhibitor by reducing Smad2 phosphorylation in pancreatic, colorectal cancer, lung cancer [62] and ovarian cancer [63]. LY2157299 is another promising inhibitor of Smad2 phosphorylation for hepatocellular carcinoma models [64]. It moved to Phase II and was approved by the FDA for liver cancer as an orphan drug in 2013. LY2109761 for metastatic NSCLC [65], colorectal cancer [66] could also investigated as a kinase inhibitor. In addition, Ki26894 blocks Smad2 phosphorylation by binding to the TβR I-ATP domain and its activity was demonstrated in breast cancer [67] and gastric cancer [68].

2.5 Insuline-like growth factor receptor

The insulin-like growth factor receptor (IGFR) family includes two cell membrane receptors, named as IGF-IR and IGF-IIR. IGF-IR (that also forms a heterodimer with the insulin receptor [IR]) has higher affinity to insulin-like growth factor 1 (IGF-I) but IGF-II comparatively has lower affinity. Although IGF-IR, receptor tyrosine kinase, has the triggering effects on IGF-I and IGF-II and thus on cell proliferation, migration and invasion, IGF-IIR lacks kinase activity [9].

Pathways activated by the presence of IGF and progressive pathological and physiological processes take place through proper receptors, named as IGFR. The mature IGF-IR have homodimer structure, containing α2 and β2 chains bounded with disulfide bonds. The intracellular domain is autophosphorylated by the binding of ligands and the downstream processes continue with the activation of a number of proteins. In several carcinomas, proliferation, transformation and metastasis are induced by overexpression of IGFIR genes. IGF-IIR, called mannose-6 phosphate receptor, M6P, is formed as a single polypeptide chain and performs as a “scavenger receptor” that suppresses tumor growth, modulates invasiveness, and blocks angiogenesis. Mutated IGFIIR locus could be found in lung cells and early phase hepatocellular carcinoma [10].

Especially, cancer associated macrophages, tumor cells and liver cells secrete IGF. The increased risk of breast and prostate cancer is correlated with high levels of IGF in the circulating system [69, 70]. For smokers,there is a moderate correlation between IGF level and lung cancer risk [71]. IGF-I is not related to colorectal cancer but takes increased risk for colorectal cancer [72]. Multiple signaling pathways of PI3K/Akt,

JAK/STAT, MAPK, Src and focal adhesion kinase (FAK) lead to the proliferation, survival, and migration of cancer cells by binding IGF to its appropriate receptor, are activated.

In many human tumors, especially mesenchymal, epithelial and hematopoietic cancers, the growth of cancer cells, metastasis and the formation of drug resistance can be associated with the activation of IGF signaling pathways [73–75].

The IGF-IR has been evaluated as a target protein in cancer treatment. There are some small-molecule inhibitors and anti-IGF-IR mAbs used in pre-clinical models and clinical trials. A dual IGF-IR/Insulin receptor inhibitor, linsitinib (OSI-906), is investigated in phase II in recurrent small cell lung cancer patients. However, clinical activity failed to show improvement in small cell lung cancer, metastatic or advanced adrenocortical carcinoma, metastatic colorectal cancer, advanced NSLC, gastrointestinal stromal tumors and metastatic prostate cancer. AXL1717 is studied in early phase with relapsed malignant astrocytomas and can show long-term stable disease and patients' survival [9].

2.6 Platelet derived growth factor receptor

Platelets produce platelet-derived growth factor (PDGF) and are secreted from both epithelial and mesenchymal cells [76]. The PDGF family has five isoforms (PDGF AA, BB, AB, CC, and DD) that bind to two RTKs, PDGFRα and PDGFRβ. After activation of PDGFRα and β, they promote cell proliferation, migration and survival through initiating signaling pathway with the inclusion of the extracellular signal-regulated kinase 1/2 (ERK) and phosphatidylinositol 3-kinase (PI3K)/AKT [77].

Overexpressed platelet-derived growth factor receptor (PDGFR) is associated with the formation of various human tumors like glioma, neurofibroma, ovarian cancer, prostate cancer, and non-small cell lung carcinoma. In addition, PDGF accelerates angiogenesis by increasing VEGF expression and development of cancer-related fibroblasts that directly or indirectly affect tumor formation. Moreover, PDGF plays a role in gene amplification [76].

To enhance anti-angiogenesis effect and suppress tumor growth PDGFR is targeted by most VEGFR-related multiple kinase inhibitors such as sorafenib, sunitinib, regorafenib, lenvatinib, axitinib, pazopanib, anlotinib, famitinib, donafenib and cediranib. These inhibitors can be critical to treat various cancer types [18].

3. Ras/Raf/MEK pathway inhibitors

Ras/Raf/MEK pathway inhibitors are important as kinase inhibitors in various cancer treatment. Firstly, the Ras protein known as Ras GTP-binding protein is the member of small G protein family, which has an important role in transmitting growth factor and relay signals from activated growth factor receptors (GFR) (**Figure 2**).

Ras proteins are regulated by a GDP-GTP cycle, different form is carried out when bound to GDP or GTP, inactive form is Ras-GDP and active form is Ras-GTP [78]. Therefore this cycle has been stimulated via receptor activation then Ras proteins bind to GTP (active form), cellular proliferation and other effects are promoted [79]. Ras protein associate with cell transformation such as cell growth, differentiation, apoptosis, cell migration, this Ras regulation is carried out by modulating some signaling

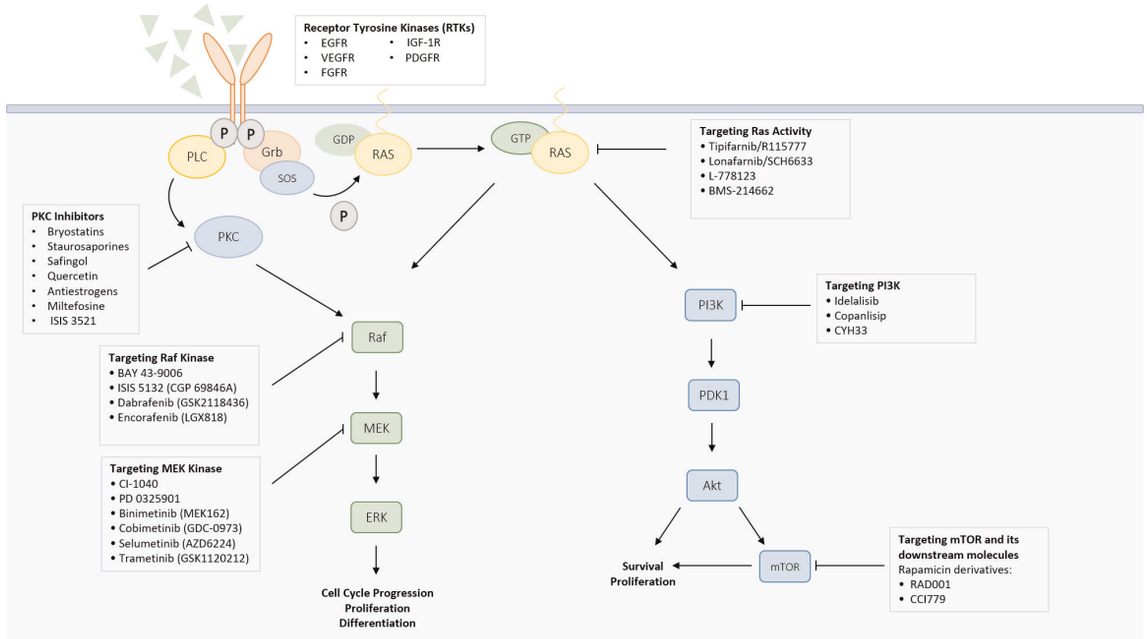


Figure 2.
Downstream molecular pathways that are activated upon stimulation of receptor tyrosine kinases (RTKs). The main pathways include protein kinase C (PKC), Ras–Raf–Mek and PI3K pathways.

molecules by translocating them to the plasma membrane for activation. Since Ras proteins play critical role as a branch point in signal transduction and orchestrate the activity of multiple signaling pathways such as Raf/MEK/ERK [78].

Numerous of the signal transduction pathways are occurred through protein kinases regulating of cellular metabolism [80]. One of the most important key protein kinases are Ras, Raf and MEK for targeting of the anticancer drug and also, Ras mutations are quite common as they are identified in about 30% of cancers [81–83]. Ras protein activations are depended on the cancer type, for instance N-Ras in lymphoid and myeloid cancers, K-Ras in colon and pancreatic cancers, H-Ras in bladder and kidney cancers [84]. One of the main reasons for this situation is thought to be the disorder in protein kinase activity. Thus, the protein kinase enzyme family is seen as one of the most important drug targets of the 21st century in many diseases, especially cancer, and there are 62 FDA-approved therapeutic agents targeting different protein kinases, eight of which were approved in 2020 [85]. Thus, today, kinase inhibitors are both used as FDA approved cancer agents and evaluated in clinical trials. Protein kinase inhibitors related to the Ras / Raf / MEK pathway, which is the subject of this part, are structurally classified as small molecules and antisense oligonucleotides and structure of Ras/Raf/MEK kinase inhibitors is shown in **Table 2**.

3.1 Ras kinase inhibitors

Ras protein, which has the ability to induce different growth and proliferation pathways of the cell, is located in the cell membrane. And most importantly, overactivation of mutated Ras can induce to make progress in cancer. Farnesyl Transferase enzyme catalyzes the first step of the reaction in the posttranslational modification of both the normal and mutated Ras gene, thus it is easier to settle on the cell membrane. FTase, one of the tansferase enzymes, targets Ras proteins, adding a farnesyl group to it. After the

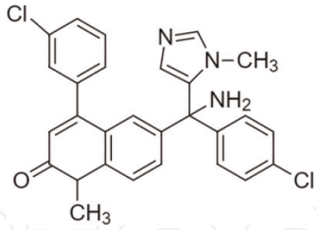
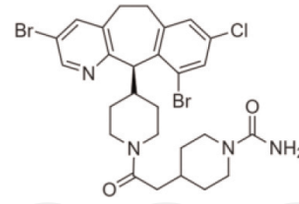
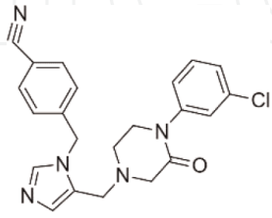
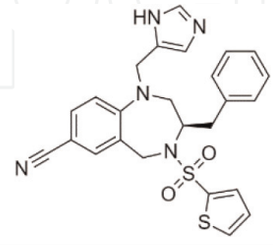
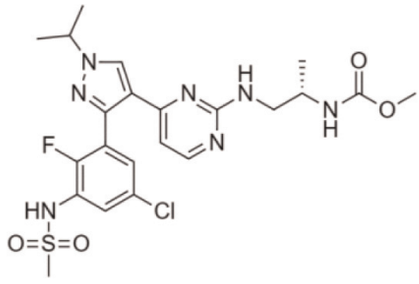
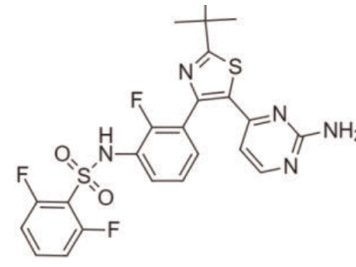
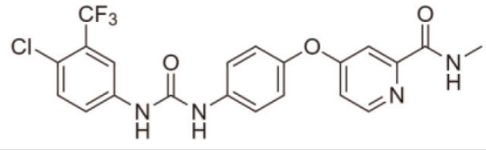
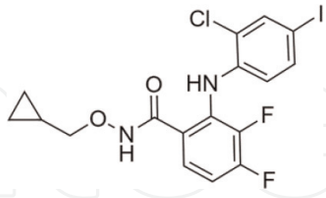
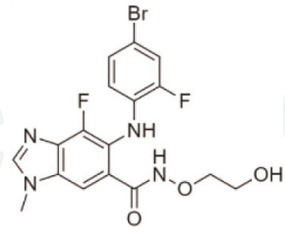
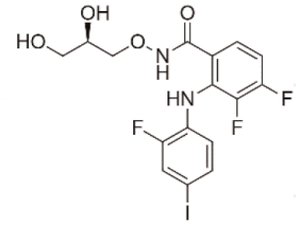
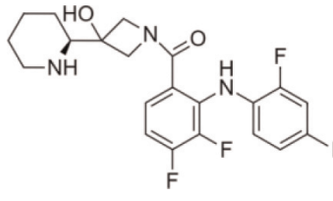
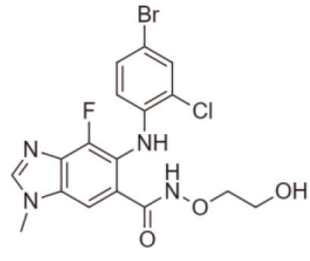
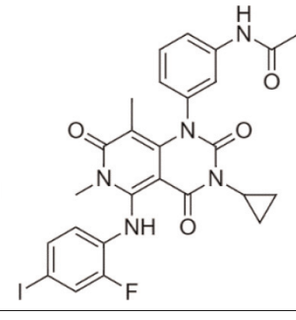
Target	Inhibitors		
Ras Kinase	**Tipifarnib (R115777)** 		**Lonafarnib (SCH66336)** 
	L-778123 		**BMS-214662** 
Raf Kinase	**Encorafenib (LGX818)** 		**Dabrafenib (GSK2118436)** 
		BAY 43-9006 	
MEK Kinase	**CI-1040** 	**Binimetinib (MEK162)** 	**PD 0325901** 
	Cobimetinib (GDC-0973) 	**Selumetinib (AZD6224)** 	**Trametinib (GSK1120212)** 

Table 2.
Structures of Ras–Raf–MEK kinase inhibitors.

essential transfer step, the activity of the Ras protein has been inhibited by Ftase [86, 87]. Therefore, FTase enzyme and the downstream pathways of the Ras protein are considered to be one of the most important groups of targets that can be medicated in cancer therapy [88]. The potential anti-cancer agent effect of Farnesyl Transferase inhibitors acting as kinase inhibitors which is affecting Ras and Ras downstream will be reviewed in this part. Various FTase inhibitors such as tipifarnib/R115777, lonafarnib/SCH66336, L-778123 and BMS-214662 have been used primarily in clinical trials and phase studies [89].

The antitumor activity of tipifarnib, a potent and selective farnesyltransferase inhibitor, also known as R115777, has been evaluated the antiproliferative effect of tipifarnib, 53 human tumor cell lines have been studied and 75% were obtained to be sensitive to R115777 [90, 91]. The strong potency effect of Tipifarnib was detected in SU86.86 human pancreatic cells, CAPAN-2 human pancreatic cells and NCI-H441 human lung cells and these cells espacially include the KRAS 12 mutation cells [90, 91]. Tipifarnib has been studied as a phase 2 study on 249 adult patients with refractory urothelial carcinoma (UC) and HRAS mutation. This study shows that tipifarnib is effective in previously treated metastatic UC patients by inhibiting the processing of newly synthesized proteins [92]. In refractory advanced colorectal cancer as a Phase III study, it had an acceptable toxicity profile and was well tolerated but did not improve overall survival according to the best supportive [93], and R115777 was not effective in metastatic colorectal cancer patients in another Phase II study [94]. Another phase two studies of R115777 emphazied that antitumor properties were not observed in metastatic c pancreatic cancer and did not improve overall survival in advanced non-small cell lung cancer [95, 96]. Farnesyl transferase inhibitor R115777, one of the protein kinase inhibitors, which are thought to be effective in the Ras pathway, has being continuing to be evaluated different combination therapies studies as well as single therapy [97].

Lonafarnib (SCH66336) as a clinical candidate FTase inhibitor, showed antitumor activity in vivo lung, colon, pancreas, bladder and prostate human tumor xenograft models [98]. Various antiproliferative effects of the SCH66336 agent were observed in eight human astrocytoma cell lines with different concentrations of IC50 values (0.6 mM - 32.3 mM) [99]. Growth inhibitory effects of the drug SCH66336 were observed in human tumor xenografts with various tumor models (colon, lung, pancreatic, prostatic carcinoma and a H-ras transgenic mouse model) [100]. In the other phase 2 studies, Lonafarnib, which was used as a combined treatment with paclitaxel, had clinical benefit and low toxicity in patients with non-small cell lung carcinoma, while the targeted response of Lonafarnib was not observed in 5-fluorouracil and irinotecan-resistant metastatic colorectal cancer and gastrointestinal toxicity was observed in single therapy [97] .

L-778123, a peptidomimetic farnesyl protein transferase (FPTase) inhibitor, was administered to patients with solid malignancies developed in phase 1 studies and their toxicity levels were investigated. While unacceptable toxicity was observed at the doses of L-778123 given as 1120 mg / m2 / day, the dose of 560 mg/m2/day was well tolerated. Also, no objective tumor response was observed following drug administration in this phase 1 study [101]. When the toxicity of L-778123 and radiotherapy combination was evaluated in phase 1 studies, it was found to be at an acceptable level in pancreatic cancer patients [102]. Although there are no important studies on cancer treatment in phase 1, this drug has been stopped in its clinical development due to its severe and unexpected toxicity [103].

3.2 Raf kinase inhibitors

Receptor tyrosine kinase effector Raf derives its name from "Rapidly Accelerated Fibrosarcoma" [104]. There are 3 different isoforms of Raf family related to serine/threonine protein kinases, namely Raf-1, A-Raf and B-Raf [105]. Critical steps are needed for Raf activation to occur, these are Raf-1 phosphorylation, binding of Raf protein to Ras-GTP, oligomerization of Raf protein, interaction of Raf protein with membrane lipids, and conformational changes in Ras-induced Raf protein [106]. Phosphorylation of Raf kinases plays an important role in cell cycle regulation, proliferation and differentiation, cell survival, apoptosis, and many cellular processes [107]. Furthermore, Raf kinase isoforms become overactive in a variety of solid tumors such as renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), and papillary thyroid carcinoma. BAY 43–9006 is a potent Raf kinase inhibitor with significant activity in four different types of human tumors, including colon, pancreatic, lung and ovarian tumors. The in vivo study of BAY 43–9006 shows that after 14 days of injection, tumor growth is strongly suppressed in athymic mice modeled with human tumors [107]. It suggests that BAY 43–9006 may have clinical potential as a cancer therapeutic agent with a new mechanism of action with its antitumor activity [107]. One of the other important raf kinase inhibitors is ISIS 5132 (CGP 69846A), for which phase I and II studies have also been performed. This Raf kinase inhibitor provides inhibition of c-Raf mRNA expression and inhibits the proliferation of lung, colon, cervical, prostate and ovarian carcinoma cell lines [105]. According to the phase1 and phase 2 studies performed with ISIS 5132, no significant response occurred in small cell or non-small cell lung carcinoma, hormone-resistant prostate cancer, and Colorectal cancer [105]. There are two FDA approved molecules among Raf Kinase Inhibitors, one of which is Dabrafenib (GSK2118436), which is effective in $BRAF^{V600E/K}$ melanomas, $BRAF^{V600E}$ NSCLC, $BRAF^{V600E}$ anaplastic thyroid cancers, and Encorafenib (LGX818), which is suitable for combination therapy with binimetinib for $BRAF^{V600E/K}$ melanomas [85].

3.3 MEK kinase inhibitors

One of the most important involved in cancer biology downstream targets of Ras is mitogen activated extracellular signal regulated kinase (MEK) [108]. Various MEK inhibitors, one of the first selective inhibitors of mitogen-activated protein kinase (MAPK) pathway activation, were investigated in phase 1 and 2 studies [109]. CI-1040, the first MEK inhibitor participating in the clinical study, was tested on 66 patients, while a partial response was observed in one patient with pancreatic cancer, stable disease was observed in 19 patients with various solid tumors such as non-small cell lung, breast and colon cancer [110]. PD 0325901, a second generation MEK inhibitor, was studied in 27 patients, while a partial response was observed in two patients with melanoma, and stable disease was observed in eight patients with various solid tumors [111]. There are 4 different FDA approved small molecule protein kinase inhibitors, for which "MEK1/2" is the primary target. These FDA approved MEK protein kinase inhibitors, Binimetinib (MEK162), Cobimetinib (GDC-0973), Selumetinib (AZD6224), Trametinib (GSK1120212), are respectively effective in these diseases; Combination therapy with encorafenib for $BRAF^{V600E/K}$ melanomas, melanomas in combination with vemurafenib, Neurofibromatosis type I, $BRAFV^{600E/K}$ melanomas, $BRAF^{V600E}$ NSCLC [85].

4. Phosphoinositide 3-kinase (PI3K) pathway inhibitors

The activation of PI3K, a superfamily of lipid kinases, leads to the production of lipid seconder molecule phosphatidylinositol-3,4,5-trisphosphate (PIP3) which recruits phosphatidylinositide-dependent protein kinase (PDK1) and Akt protein kinases to the plasma membrane. Akt that activated and phosphorylated from PDK1 and mTOR, phosphorylates several target proteins either at the plasma membrane or in the cytosol and nucleus (**Figure 2**). Cell proliferation controlled by the PI3K pathway is partially dependent on a large kinase protein called mammalian target of rapamycin (mTOR). mTOR complex 1 plays a role in cell growth and survival by stimulating nutrient uptake and metabolism. Akt activates mTOR independently of phosphorylation at complex 1 [112].

PI3K has three different classes (I, II and III) and four different isoforms (α, β, γ, δ). While it has central physiological roles in cancer, diabetes, and aging, the isoform within each class has distinct roles.Several small molecules have been produced with good pharmacological properties that have been tested in various cancers to selectively inhibit PI3K, AKT or, mTOR [113].

Idelalisib and Copanlisip are FDA-approved drugs. Idelalisib has been selectively developed for the delta isoform of PI3K p110 inhibitor. This purine-quinazoline derivative has been used for the treatment of patients with CLL, relapsed follicular B-cell non-Hodgkin lymphoma (NHL), and relapsed small lymphocytic leukemia (SLL) [114]. The combination study with rituximab resulted in a significant increase in the response rate and overall survival on CLL patients [115]. Copanlisip is the inhibitor of the pan-class I PI3K, which shows preferential activity against p110α and p110δ as compared with p110β and p110γ. It has been used for the treatment of various subtypes of indolent and aggressive malignant lymphoma such as NHL, relapsed follicular lymphoma (FL), and CLL in phase II study. This small molecule, administered intravenously, becomes advantageous compared to other FDA-approved drugs, exhibiting a favorable toxicity profile and maintaining efficacy [116].

Rapamycin and derivatives (CCI-779 and RAD001) inhibit both mTOR and the downstream kinase target such as p70S6 kinase (p70S6K) and 4E-binding protein-1 (4E-BP1). The derivatives under clinical study have been shown to suppress the proliferation and growth of various tumor cell lines by blocking the G1-S transition in the cell cycle [117]. Furthermore, the immunosuppressant effect of rapamycin has been observed in several case studies, with transplanted patients reducing the incidence of cancer [118]. In ongoing clinical studies in prostate cancer in which the PI3K/Akt/mTOR pathway is highly expressed, it was observed that rapamycin and its derivatives were well tolerated in prostate cancer patients and decreased mTOR level [119]. In addition to the antiproliferative effect, RAD001 is also used as an immunosuppressant for the treatment of several malignancies in phase I study [120]. CCI779 that is the soluble ester of rapamycin [121] has been used for the treatment of several cancers in phase II study. This drug candidate has been used for T-cell leukemia, prostate, breast, and SCLC, as well as glioma and melanoma cell lines. CCI779 showed apoptosis induction, delaying the growth of the tumor, encouraging survival [105]. In combined treatment with apatinib, the treatment inhibits the proliferation and migration of small cell lung cancer cell lines [122].

Recently synthesized CYH33 is a novel PI3Kα inhibitor in phase 1b clinical trial for esophageal squamous cell carcinoma (ESCC) and breast cancer therapy. In vitro and in vivo studies show the anti-proliferative activity of this drug candidate to cell lines,

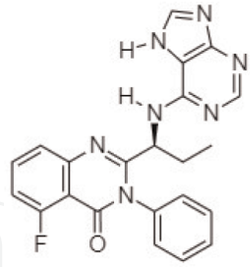
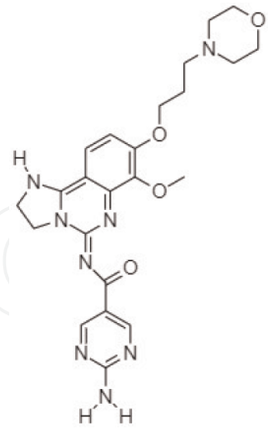
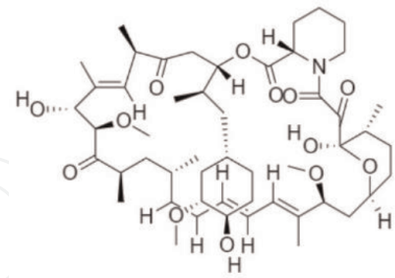
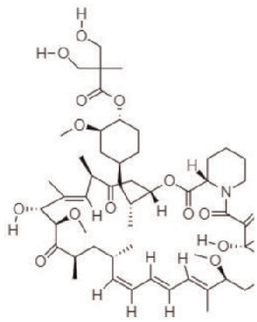
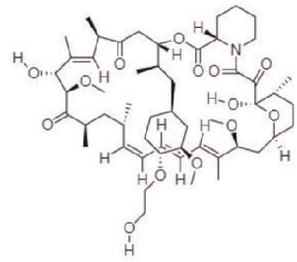
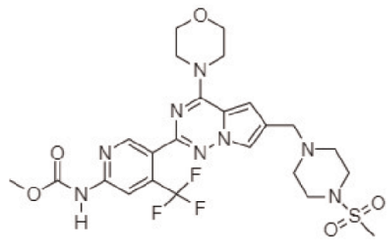
Target	Inhibitors		
PI3K	Idelalisib	Copanlisib	Rapamycin
			
	CCI-779z	RAD001	CYH33
			

Table 3.
Structures of PI3K pathway inhibitors both in clinical development and FDA approved.

induction of G1 phase arrest, and down-regulation of phosphorylated ERK in solid tumors [123]. The structure of all PI3K pathway inhibitors is shown in **Table 3**.

5. Cyclin-dependent kinase (CDK) inhibitors

CDKs found in a family of serine/threonine kinases are key regulators in the various phases of the cell cycle (**Figure 3**). CDKs ensure the continuation of the cell cycle by phosphorylating critical target proteins that are necessary to proceed to the next stage. Especially cells need to regulate the phosphorylation of kinases to sustain constant division in the presence of abnormal ploidy. Cyclin proteins, differently from CDKs, are synthesized at certain stages of the cell cycle. When the various cyclin form complexes with their target CDKs, it regulates the cell cycle transitions by enabling them to be phosphorylated and activated. For example, both cyclin D/CDK4 and cyclin D/CDK6 complexes direct phosphorylation of the Retinoblastoma gene (RB), which induces the separation of E2F to allow the transcription of the genes necessary for the proceed G1 to S phase transition. CDK inhibitors have been used in cancer therapy to interfere with the limitless replicative potential which is one of the hallmarks of cancer cells [124].

Palbociclib (PD 0332991) [128], Ribociclib (LEE011) [125], and Abemaciclib (LY2835219) [126] are novel dual inhibitors of both CDK4 and CKD6, that were approved by the FDA. Abemaciclib, more potent against CDK4 (IC50s of 2 nM for

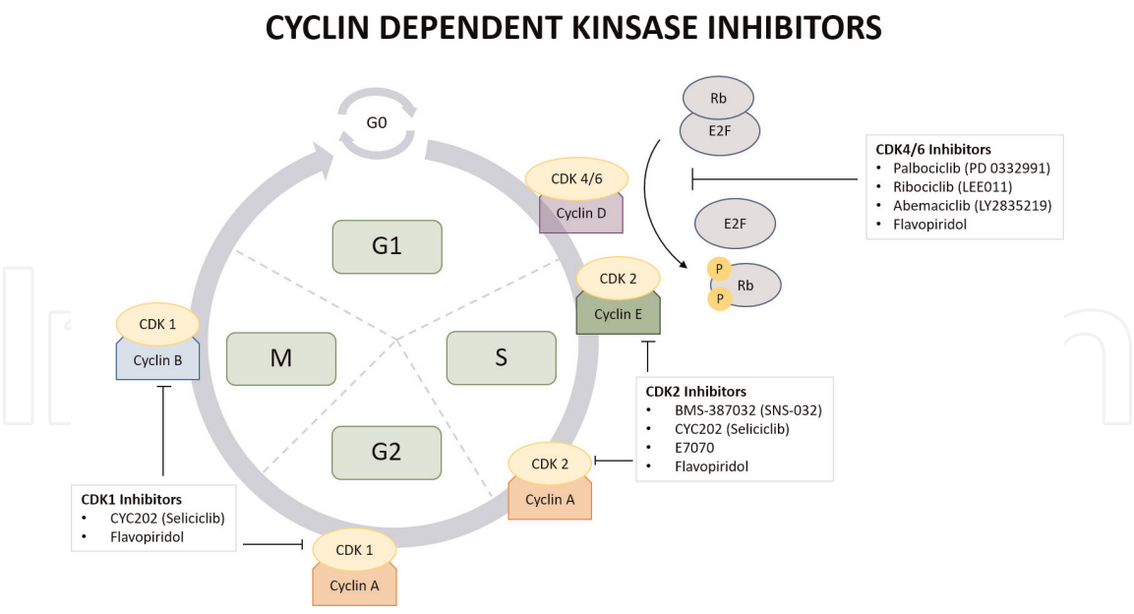


Figure 3.
Cyclin dependent kinases (CDKs) in the cell cycle and their inhibitors. CDKs are a family of serine/threonine kinases and key regulators in the cell cycle.

CDK4 and 10 nM for CDK6) [126]. These drugs have using for the treatment of postmenopausal women with HR-positive, HER2-negative advanced, or metastatic breast cancer. The action mechanism is that inhibiting the phosphorylation of Rb protein in the G1 phase results in cell cycle arrest [127]. Palbociclib has a synergistic effect in combination therapy with either letrozole or fulvestrant [128]. Abemaciclib also has a synergistic effect with gemcitabine [126].

BMS-387032 (SNS-032) is an aminothiazole, selectively designed for CDKs 2, 7, and 9 (with IC50s of 38 nM, 62 nM, and 4 nM, respectively) inhibition. Its activity was shown to inhibit both the cell cycle and the expression of anti-apoptotic proteins in various carcinoma models [129]. A phase I dose-escalation clinical trial study carried out to evaluate the safety, and clinical efficacy demonstrates limited clinical activity in heavily pretreated CLL and MM patients [130].

CYC202 (Seliciclib) shows potent inhibitors for broad CDK such as Cdk2, Cdk1, Cdk7, and Cdk9 (with IC50s of 0.1, 2.7, 0.5, and 0.8 mM, respectively), competing at their ATP binding sites [131]. This small molecule showed antitumor activity inducing apoptosis in multiple myeloma cell lines and has assayed in phase II study resulted in the dosing schedule being tolerable in nasopharyngeal carcinoma patients [132].

E7070 is a novel chloroindolyl-sulfonamide anticancer agent, which leads to induces arrest at the G1-S boundary and in company with mitigation in the expression of CDK2. E7070 has been assayed for melanoma cancer therapy in phase II and the results showed that CDK activity can be inhibited in tumor cells, but the dose and schedule applied are not suitable for single-agent chemotherapy for melanoma cancer treatment [133].

Flavopiridol has potent strong activity on several CDKs (CDK1, 2, 4, 6, and 7). In addition to controlling the cell cycle, it exhibits more than one action mechanism by showing an antiproliferative effect to leukemias and lymphoma cell lines [134, 135]. Phase I and phase II studies have been tested on various progressive tumors and it has been observed that flavopiridol has no effect on metastatic renal carcinoma [135]. The structure of all CDK kinase inhibitors is shown in **Table 4**.

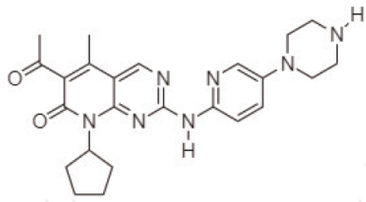
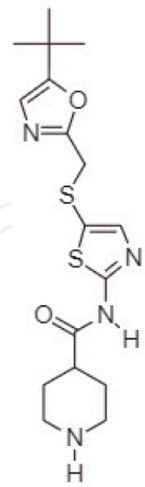
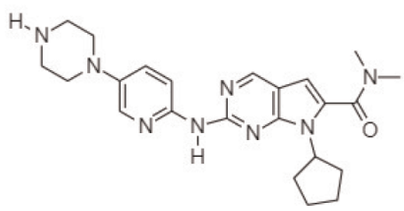
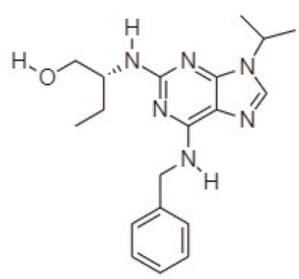
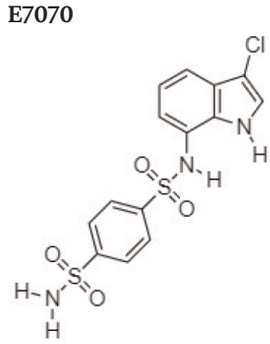
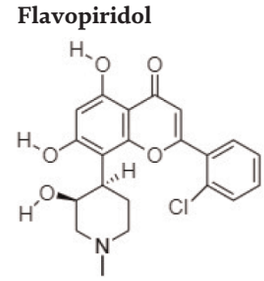
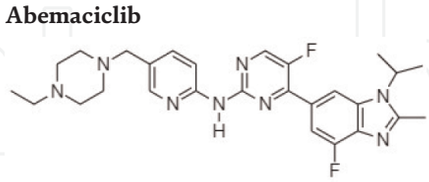
Target	Inhibitors		
CDK	**Palbociclib** 	**BMS 387032** 	
	Ribociclib 		
	CYC202 	**E7070** 	**Flavopiridol** 
	Abemaciclib 		

Table 4.
Structures of CDK kinase inhibitors both in clinical development and FDA approved.

6. Other protein kinase inhibitors

Protein kinase C (PKC) is a family of serine/threonine kinases. They have important role in regulating a range of cellular functions including gene expression, differentiation, proliferation, cell cycle, apoptosis and cell migration. The PKC family includes 12 isoenzymes that can be divided into three groups depending on activation requirements. Conventional PKCs are calcium dependent and they require negatively charged phospholipid and diacylglycerol for activation. Novel PKCs are calcium

independent, as conventional PKCs their activation requires phospholipid and diacylglycerol. Atypical PKCs are both calcium and diacylglycerol independent protein kinase group [136].

Regarding the PKC as a receptor for tumor-promoting phorbol esters, the researcher targets PKC for the potential treatment of cancer.

PKC is activated by phorbol esters and this event prevents cell death. Therefore, the inhibition of PKCα results in apoptosis. PKC activity has been reported to increase in many types of cancer, suggesting that PKC has important role in tumor formation. There are many PKC inhibitor candidates in clinical development for the treatment of cancer (**Figure 2**) [137].

First class of PKC inhibitors with anti-cancer activity are bryostatins. They are macrocyclic lactones extracted form marine bryozoan Bugula nerutina. Interaction of bryostatins with regulatory domain of PKC causes downregulation of the enzyme. Besides anti-proliferative, apoptotic and cytotoxic effects of Bryostatins on cancer cells, they also have immunomodulatory functions. Bryostatins provide the development of tumor-specific cytotoxic T-lymphocytes and stimulates the release of different cytokines such as TNF, IL-6. Both the immunomodulatory effect and downregulation of PKC has participated in antitumor effect of bryostatins [137, 138].

Second class of PKC inhibitors are staurosporines. Staurosporine is a microbial alkaloid derived from Streptomyces species organisms. In addition to PKC, staurosporine has shown the activity aganist different kinases including, pyruvate dehydrogenase kinase 1 (PDK1), PKA and PTK. Several staurosporines are under in clinical research such as UCN-01 (7-hydroxystaurosporine) or midostaurin (N-benzoyl staurosporine, PKC412) [138]. UCN-01 (7-hydroxy-staurosporine) has been reported to have more PKC inhibitory effects than staurosporine [105, 137]. UCN-01 causes cell cycle arrest in G1 step, thus leading the cell to death.

There is a growing interest in antisense therapy for PKC inhibitors. The structures of PKC inhibitors are shown in **Table 5**. ISIS 3521, an antisense therapy agent, is a phosphorothioate antisense oligodeoxynucleotide. ISIS 3521 binds to 3′ untranslated region (UTR) of human PKC-α messenger RNA (mRNA). This hybridization is then cleaved by RNase H and resulted in inhibition of PKC-α expression. Based on in vitro and in vivo studies results, ISIS 3521 may be a potential treatment agent for cancer patients [139].

Besides PKC inhibitor classes for cancer therapies described above, there are other agents including safingol, quercetin, antiestrogens, and miltefosine. Safingol is a synthetic sphingoid base analogue and safingol was the first to enter clinical trials. Quercetin belongs to flavonoids and widely distributed in nature. Quercetin inhibits different classes of protein kinases including PKC, phosphatidyl inositol-3 kinase. The PKC inhibitory effect of the classical antagonism of estradiol at the estrogen receptor level has been mentioned in many studies. However, the antiestrogen tamoxifen and its analogues have also been shown to inhibit PKC at very low concentrations. Miltefosine is an alkylphosphocholine and it shows its activation by preventing phospholipid metabolism. Miltefosine's antitumor activity is possibly associated with its abilitiy to inhibit PKC, but there has also been multiple alternative actions [137].

Although most protein kinase C inhibitors target the PKC-α, inhibitors targeting PKC-β have been investigated. PKC-β belongs to major PKC isoform classes. Hyperglycemia activated PKC-β leads to diabetic kidney diseases. LY333531 named as Ruboxistaurin selectively inhibits PKC-β. Recent studies showed that LY333531 significantly reduced PKC activity and PKC-β protein expression in the kidney [140, 141].

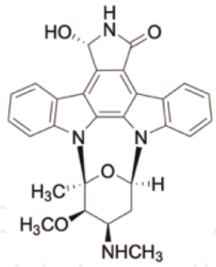
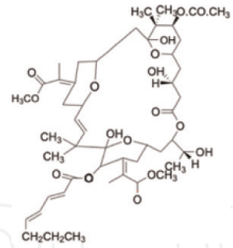
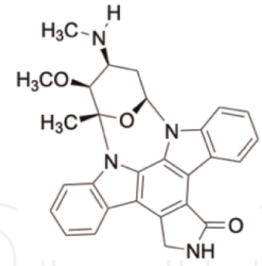
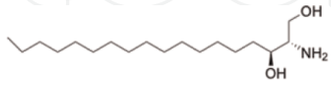
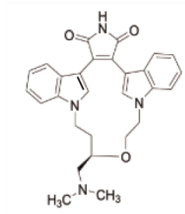
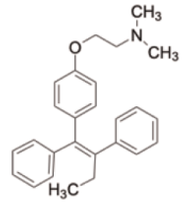
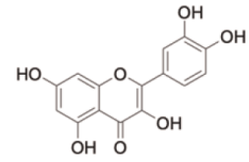
Target	Inhibitors		
PKC	**UCN-01** 	**Bryostatin-1** 	**Staurosporine** 
	Safingol 	**Miltefosine** 	
	Ruboxistaurin 	**Tamoxifen** 	**Quercetin** 

Table 5.
Structures of other kinases' inhibitors.

7. Conclusions

Protein kinases are potent oncogenes because of their ability to activate or inhibit other proteins. Furthermore, the ability to activate other protein kinases results in producing an exponential signal. In other words, a tiny signal can lead to a huge cellular response. This property of protein kinases makes their strict regulation crucial, and any dysregulation can lead to catastrophic outcomes. Many cancers are caused by the dysregulation of such oncogenic kinases, and inhibitors of those shown to increase overall survival in cancer patients. Although some tumors may gain resistance to some of those protein kinase inhibitors (PKIs), promising results of PKI administered cancer patients have led to developing new PKIs to treat PKI-related cancers [142].

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