Chapter

Introductory Chapter: Protein Kinases as Promising Targets for Drug Design against Cancer

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1. Introduction

Cancer is one of the most dreadful and highly prevailing life-threatening ailments of the modern age. Despite a great advancement in the health sector, still it is the leading cause of mortality around the globe [1, 2]. The continuous research is in progress for several years to design therapeutic agents against cancer with greater efficacy, specificity, and least toxicity. For the past two decades, the protein kinase family has been greatly focused by the researchers for drug development against cancer. There are about 538 protein kinase enzymes that are encoded by the human genome, which function mainly by transferring a γ-phosphate group from the ATP site toward amino acid residues such as serine, threonine, or tyrosine residues [3–5]. It is evident that several members of this protein kinase family have tendencies to initiate and develop human cancers [6, 7]. The recently developed small molecules as potential kinase inhibitors in the therapy of a variety of cancers have witnessed the significance of kinases as a target against cancers. Moreover, these are in second place as a target for drugs after the G-protein-coupled receptors [8]. Protein kinases are associated with the promotion of cell proliferation, migration, and survival and, when they are dysregulated/overexpressed, lead to oncogenesis [9, 10]. During the past decades, it has been observed that human malignancies are largely associated with modulation or dysfunction of protein and lipid kinases due to the deactivation of phosphatases resulting from chromosomal abnormalities or mutations [11, 12]. It is worth notable that the anti-inflammatory kinases such as EGFR, VEGFR, BCR-ABL, ALK, KIT, HER2, and several others are involved in the development of solid cancers including chronic lymphoid leukemia, lymphoblastic leukemia, mantle cell lymphoma, myelogenous lymphoma, and several other types of cancers [13]. These kinases show a pro-tumor effect associated with loss of normal kinase functioning followed by mutations and associations with high-regulatory T cell pathogens [14]. These pathogens ultimately activate the anti-inflammatory kinases and initiate the development of solid cancers. The role of some kinases in the development of cancers has been depicted in **Figure 1**.

Kinase amplifications are able to play diagnostic, prognostic, therapeutic as well as biomarker roles in cancer [15]. The amplifications of EGFR have been well seen in a variety of cancers including non-small cell lung cancer, colorectal cancer, bladder cancer, pancreatic, and breast cancer, whereas ERBB2 amplifications are associated with esophageal, gastric, breast, and ovarian cancers [16–18]. Overexpression of EGFR, ERBB2, EPHA2, and AKT2 are the best examples of biomarkers for cancers [19, 20].

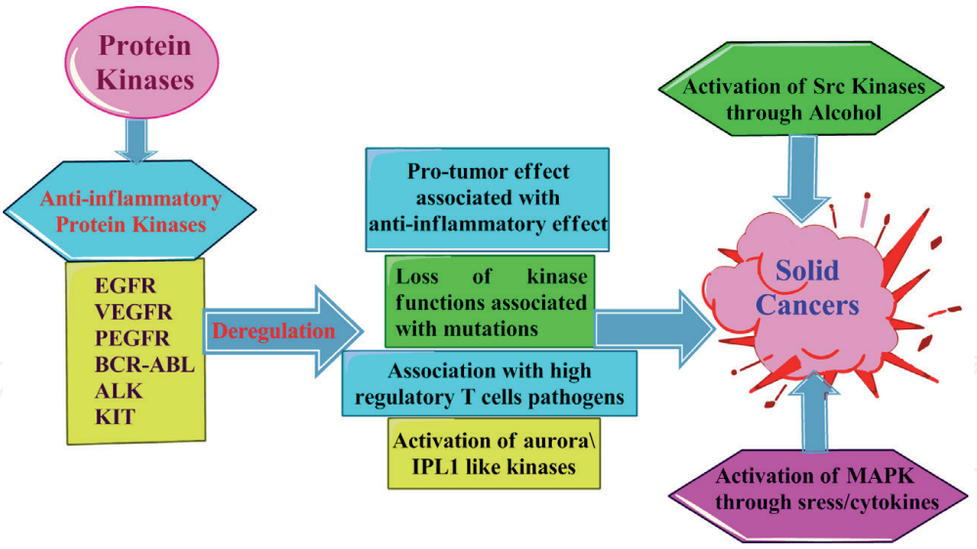

Figure 1.
Impact of protein kinases in development of cancer.

2. Progress in the development of protein kinase inhibitors against cancer

In the past two decades, there has been a remarkable progress made in the drug development process involving protein kinases as a target. The first FDA approved drug imatinib was launched in 2001 against chronic myeloid leukemia which inhibits Abelson (ABL) tyrosine kinase [21]. It was proved to be a blockbuster drug with polypharmacological effects. From 2001 to 2021, in a span of 20 years, there has been an extraordinary progress made with the discovery of more potent and specific small-molecule kinase inhibitors and about 70 new drugs have got approval in this time span [22]. These drugs have left a promising positive impact to improve the drug design strategies and therapy to treat the cancers and conditions associated with it. **Table 1** comprises the details of kinase inhibitor drugs approved by the FDA from 2015 to 2021 [23–58].

The modern strategies adopted for the development of selective kinase inhibitors include synthesis along with structure-based design approaches facilitated by molecular docking, crystallographic studies, and NMR spectroscopy [59]. It is surprising that alone USA has filed more than 10 thousand patent applications for kinase inhibitors since 2001. Beyond the discovery of small-molecule kinase inhibitors, kinase-targeted antibodies have also been postulated against different cancers such as cetuximab (colorectal, head, and neck cancer), trastuzumab (breast cancer) [60]. Various small-molecule kinase inhibitors have different inhibitory modes and on the basis of these modes, these inhibitors have been divided into five categories (**Figure 2**). Type I inhibitors contain a heterocyclic moiety in their structure to occupy purine binding pocket and serves as a template for side chains to occupy the hydrophobic region. These inhibitors are basically ATP-binding site competitors and mimic the purine ring of ATP. These bind to the active conformational side and cause alteration of structural conformation [61]. Type II inhibitors target the inactive conformation and occupy the catalytic region of the unphosphorylated inactive conformation. These kinases explore the new binding patterns in the hydrophobic pocket associated with conformational changes of phenylalanine residue of the Asp-Phe-Gly (DFG) system [62]. Type III inhibitors are regarded as allosteric inhibitors and exhibit their action *via* binding to the outer catalytic ATP-binding site and alter kinase activity in an allosteric

S. No.	Drug	Brand name	Year of approval	Inhibitory target	Indication	References
1.	Palbociclib	Ibrance	2015	CDK4/6 inhibitor	Advanced metastatic breast cancer	[23]
2.	Lenvatinib	Lenvima	2015	VEGFR1/2/3 inhibitor	Progressive/ differentiated thyroid cancer	[24]
3.	Cobimetinib	Cotellic	2015	MEK inhibitor	Melanoma	[25]
4.	Osimertinib	Tagrisso	2015	EGFR inhibitor	Non-small cell lung carcinomas with specific mutations	[26]
5.	Necitumumab	Portrazza	2015	EGFR antibody	Advanced (metastatic) squamous non-small cell lung cancer	[27]
6.	Alectinib	Alecensa	2015	ALK inhibitor	Non-small cell lung cancer	[28]
7.	Olaratumab	Lartruvo	2016	PDGFRA inhibitor	Soft tissue sarcoma	[29]
8.	Ribociclib	Kisqali	2016	CDK4/6 inhibitor	Advanced breast cancer	[30]
9.	Brigatinib	Alunbrig	2017	ALK and EGFR inhibitor	Non-small cell lung cancer	[31]
10.	Copanlisib	Aliqopa	2017	PI3K inhibitor	Relapsed follicular lymphoma	[32]
11.	Abemaciclib	Verzenio	2017	CDK4/6 inhibitors	Advanced metastatic breast cancer	[33]
12.	Acalabrutinib	Calquence	2017	BTK inhibitor	Mantle cell lymphoma	[34]
13.	Binimetinib	Mektovi	2018	MEK inhibitor	Unresectable or metastatic melanoma	[35]
14.	Encorafenib	Braftovi	2018	MEK inhibitor	Unresectable or metastatic melanoma	[36]
15.	Duvelisib	Copiktra	2018	PI3K inhibitor	Refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, and follicular lymphoma	[37]
16.	Dacomitinib	Vizimpro	2018	EGFR inhibitor	Metastatic non-small cell lung cancer	[38]
17.	Lorlatinib	Lorbrena	2018	ALK and ROS1 inhibitor	Metastatic non-small cell lung cancer	[39]
18.	Gilteritinib	Xospata	2018	AXL inhibitor	Relapsed or refractory acute myeloid leukemia	[40]
19.	Erdafitinib	Balversa	2019	FGFR inhibitor	Locally advanced or metastatic bladder cancer	[41]
20.	Alpelisib	Piqray	2019	PI3K inhibitor	Breast cancer	[42]
21.	Pexidartinib	Turalio	2019	inhibitor of CSF1, KIT, and FLT3	Symptomatic tenosynovial giant cell tumor	[43]

S. No.	Drug	Brand name	Year of approval	Inhibitory target	Indication	References
22.	Entrectinib	Rozlytrek	2019	inhibitor of ALK, ROS1, TKI, and TRKA/B/C	Metastatic non-small cell lung cancer	[44]
23.	Zanubrutinib	Brukinsa	2019	BTK inhibitor	Mantle cell lymphoma	[45]
24.	Avapritinib	Ayvakit	2020	PDGFRA receptor kinase inhibitor	Metastatic gastrointestinal stromal tumors	[46]
25.	Selumetinib	Koselugo	2020	BRAF kinase inhibitor	Neurofibromatosis type I	[47]
26.	Tucatinib	Tukyssa	2020	EBBR2 inhibitor	Metastatic HER2-positive breast cancer	[48]
27.	Pemigatinib	Pemazyre	2020	FGFR2 inhibitor	Advanced/metastatic or surgically unresectable cholangiocarcinoma	[49]
28.	Capmatinib	Tabrecta	2020	MET kinase inhibitor	Metastatic non-small cell lung cancer	[50]
29.	Selpercatinib	Retevmo	2020	RET receptor kinase	Non-small cell lung cancer, metastatic medullary thyroid cancer, or advanced or metastatic thyroid cancer	[51]
30.	Ripretinib	Qinlock	2020	PDGFRA and KIT receptor kinase inhibitor	Gist	[52]
31.	Pralsetinib	Gavreto	2020	RET receptor kinase inhibitor	Thyroid cancer, non-small cell lung cancer	[53]
32.	Margetuximab	Margenza	2020	HER2 inhibitor	HER2-positive breast cancer	[54]
33.	Trilaciclib	Cosela	2021	CDK4/6 inhibitor	Extensive-stage small cell lung cancer	[55]
34.	Infigratinib	Truseltiq	2021	FGFR2 inhibitor	Cholangiocarcinomas with FGFR2 fusion proteins	[56]
35.	Tepotinib	Tepmetco	2021	Met Kinase	Met mutation-positive non-small cell lung carcinoma	[57]
36.	Tivozanib	Fotvida	2021	VEGFR2 inhibitor	Renal cell carcinoma	[58]

Table 1.
FDA-approved kinase inhibitors against various cancers during 2015–2021.

way. Type IV kinase inhibitors are regarded as substrate-directed inhibitors and undergo reversible binding outside the ATP pocket. These are non-competitive inhibitors and do not compete with ATP [63]. Type V inhibitors are covalent inhibitors and bind through an irreversible covalent bond to catalytic nucleophilic cysteine active site of the enzyme.

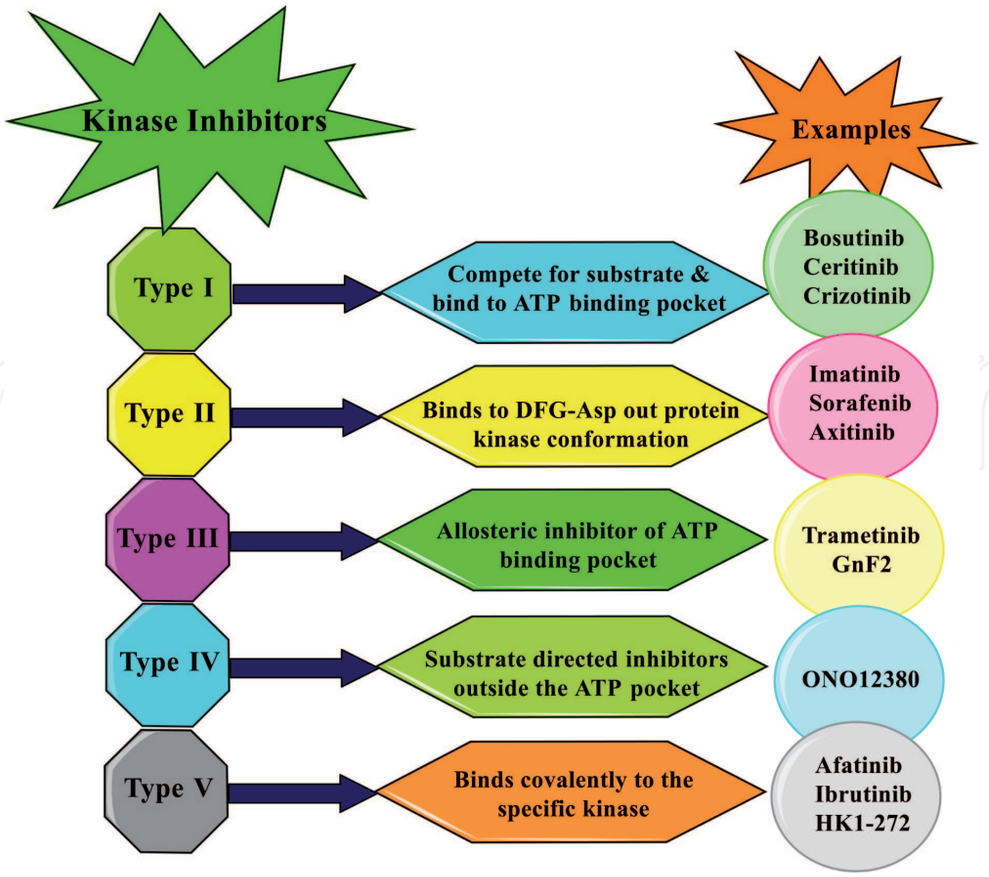

Figure 2.
Inhibitory patterns of different kinase inhibitors.

From a clinical point of view, it has been observed that kinase target anticancer therapies have more success rate than the other cancer therapies. But it is also evident in the past few years EGFR/VEGF-targeting molecules have given unsatisfactory results [64, 65]. Instead, success stories have been seen with molecules targeting kinase B, phosphatidylinositol kinase delta and gamma, kinase I, tyrosine kinase, nerve growth receptors Wee 1-like kinases in Phase 1 clinical trials. The latest explored targets Aurora kinases have led to the development of two inhibitors palbociclib and ribociclib which have passed phase III clinical trials [66]. The modern developments on kinases are following the precision therapy that has been based upon the genomic data. The detailed genetic studies on tumors and drivers involved in the generation of tumors have resulted in tremendous advantages for patients who need effective therapy.

3. Investigations on kinase inhibitory potentials of natural products

The continuous research is in progress for several years to design synthetic and natural chemotherapeutic agents against cancer with selective cytotoxic efficacy and minimum toxicity [67–70]. The contribution of molecules from natural sources in kinase-mediated anticancer research cannot be ignored. The kinase modulating properties of natural molecules has brought a new paradigm in the screening of kinase inhibitors. Toward this direction, small molecules like polyphenols have revealed tremendous potentials to bind with kinases like tyrosine kinase followed by alteration of phosphorylation leading to modulation of multi-signaling mechanisms. The explored natural compounds in this direction are curcumins, resveratrol, quercetin, cyrysitin, myricetin, luteolin, apigenin, anthocyanin,

genistein, epigallocatechin gallate, fisetin, astaxanthin, and tetrahydrocurcumins and many more. Polyphenols such as resveratrol [71], quercetin [72], curcumin [73] and tea extracts [74] have revealed promising EGFR inhibition [75]. Curcumin and chrysin have receptor RON blocker activity in tumor cells [76, 77]. Natural products have also shown Abl, JAK-2, c-Met, c-SRC, and serine kinase inhibitory potentials [78–80]. Resveratrol also has modulatory effects on the expression of Akt in breast, uterine, skin, and prostate cancers [81, 82]. It binds to the ATP site competitively as well as reversibly. Myricetin has reported inhibition of cell proliferation by binding to Akt. Beyond these significant activities, several reports in the literature are available evidencing the inhibitory and modulatory effects of natural products on mTOR, CDK, Aurora kinases, B-raf kinases, PI3K [83–85], etc. Many natural molecules bind directly to the oncogenic kinases and alter the cell signaling involved in tumor progression by modifying the phosphorylation process. Several other classes of natural compounds are under investigation for their kinase-modulating activities.

4. Conclusions and future perspectives

The therapeutic implication of protein kinases against a variety of cancers is well known from past decades. Also, it is well established that deregulation, mutations, and overexpression of these kinases are important triggers for the development of cancers. Several kinase inhibitors are already reported who prevent cancer by modulating the protein kinases by following different mechanisms and several inhibitors are under investigation. Despite tremendous advancements in kinase drug development, still, a large number of kinases are unexplored. It is also worth notable that most of the available kinase inhibitors work through binding to ATP sites. A great challenge in clinical implication of kinase inhibitors is the development of drug resistance of cancer stem cells. It develops due to the loss of activity of some important kinases. Therefore, strategies to overcome this resistance are the requirement of the hour. In the therapeutics of cancer, the kinase inhibitors have been proven to be well tolerated as compared to the traditional therapies.

Abbreviations

ABL	Abelson murine leukemia viral oncogene
Abl	Abelson murine leukemia
Akt	protein kinase B
ALK	anaplastic lymphoma kinase
BRAF	proto-oncogene
BTK	Bruton agammaglobulinemia tyrosine kinase
CDK	cyclin-dependent kinase
c-Met	c-MET proto-oncogene
c-SRC	proto-oncogene tyrosine-protein kinase
CTK	cytoplasmic tyrosine kinase
EGFR	epidermal growth factor receptor
ERBB2	V-Erb-B2 avian erythroblastic leukemia viral oncogene homolog
FGFRs	fibroblast growth factor receptors
HER-2	human epidermal growth factorreceptor-2
JAK2	Janus kinase 2
MAPK	mitogen-activated protein kinases
MEK	MEK kinase gene

PDGFRs	platelet-derived growth factor receptors
PI3K	phosphatidylinositol-3-kinase
PI3KCA	phosphatidylinositol-4,5-bisphosphate 3-kinase
RTK	receptor tyrosine kinase
VEGFR-2	vascular endothelial growth factor receptor 2

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