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Overview of the Role of Tyrosine Protein Kinases and Their Inhibitors in Cancer Disease

Ameer H. Alwash[1*], Maha H. Philip Rahmani[2], Shaymaa A. Hussein[3]

[1]Pharmaceutical Chemistry Department, College of Pharmacy, Al-Bayan University, Baghdad, Iraq.
[2]Pharmaceutics Department, College of Pharmacy, Al-Bayan University, Baghdad, Iraq.
[3]Al Nukhba University College, Baghdad, Iraq.

[*]**Corresponding Author:** Ameer H. Alwash
*E-mail: ameer.hussein@albayan.edu.iq

Abstract
Tyrosine-protein Kinases are considered primary targets for drug development due to their amplification in several tumorigenesis and uncontrolled proliferation. Their function is to phosphorylate their substrates' tyrosine residues, which are inhibited by tyrosine kinase inhibitors (TKIs), consequently blocking the intracellular signaling currents.
Over the last two decades, the development process of TKIs has been successful in introducing various influential and well-tolerated one-target and multiple targets agents such as FGFR, MEK, MET, RET, VEGFR, NTRK, HER2, ROS1, ALK, EGFR.
In this article, we summarize the valuable information about tyrosine kinases and their inhibitors to obtain the maximum possible benefit, to get a therapeutic substance with high efficiency and effectiveness, with few side effects, to achieve the maximum benefit for human society, and to gain the most extended possible period of survival for people with malignant tumors
In conclusion, cancer patients' survival and quality of life have significantly improved through the discovery and continuous development of TKIs, transforming the treatment guidelines for various cancer diseases.

Keywords: Tyrosine kinase inhibitors, cancer, phosphorylation, dimerization.

1. Introduction

Western societies are plagued by cancer, which is considered the second cause of death worldwide. Even though diagnosis and treatment have advanced, overall survival remains poor. As of late, patients could choose between endocrine therapy, radiotherapy, chemotherapy, and surgery as possible approaches for treatment. As a result, patients with numerous kinds of tumors have significantly improved their survival rates. Unfortunately, morbidity and mortality have been caused primarily by drug resistance and toxicity. For this reason, newer, more efficient therapies are urgently needed to increase patient outcomes. Although medical science and technology have made significant advances, cancer still has limited treatment possibilities. The mechanism of how the patient's disability and mortality are affected by cancer metastasis and recurrence has not been fully understood yet (López-Soto A et al., 2017).
In general, gene mutations lead to cancer. The recently reported cancer cases in 2018 were estimated to be 18.1 million, and the count of cancer-related deaths is estimated to be 9.6 million. A report by the Global Cancer Observatory (GCO) estimates that the reported number of deaths from cancer will rise dramatically by 2030 to reach nearly 30 million deaths. Along with the high mortality rate associated with cancer, families of cancer patients and society are burdened by immense economic burdens. Hence, focusing on cancer prevention, diagnosis, and treatment is very important. Cancer cells are characterized by abnormalities in cell cycle mechanisms, resulting in their immortality and uncontrolled proliferation. In most cases, cancer alters signaling pathways. It is known that inhibiting physiological apoptosis promotes cancer development and resistance to anticancer treatments. Inflammation and immune disorders also contribute to cancer. Traditional tumor staging is based on tumor burden (T), cancer cells in draining, regional lymph nodes (N), and tumor metastases (M). Different types of cancer can originate from various organs, such as the ovary, prostate, bladder, kidney, neck, breast, colon, lung, and several other kinds of cancer (Mortezaee K et al., 2019).

2. Tyrosine kinase proteins

There are approximately 2000 known kinases, with 518 kinase genes identified in humans. Among these, 90 are classified as tyrosine kinases, which include 58 Receptor Tyrosine Kinases (RTKs) and 32 Non-Receptor Tyrosine Kinases (NRTKs) (K. Bhanumathy K et al., 2021). The tyrosine kinase enzyme catalyzes tyrosine molecules' phosphorylation reactions using ATP as a donor; they play a crucial role in signaling cascades. Their functions

include growth, metabolism, and differentiation responses to stimuli, as well as adhesion. Tyrosine kinases are implicated in a variety of neoplastic processes (Siveen KS et al., 2018). Compared to traditional chemotherapy, targeted agents have better selectivity, efficacy, and safety since they target specific targets involved in cancer proliferation and differentiation while only producing minimal effects on normal tissues as a result of catalysis of the allocation of phosphoryl groups from nucleoside triphosphate donors to tyrosine amino acid residues on protein substrates, RTKs, and NRTKs initiate downstream signaling cascades (Huang L and Jiang S, Shi Y, 2020).

As a result of mutations, translocations, or amplifications, tyrosine kinases are activated abnormally, which leads to tumorigenesis, metastasis, invasion, and progression. Furthermore, wild-type tyrosine kinases can also critically activate pathways in cancer. Tyrosine kinase inhibitors (TKIs), also known as Bruton's tyrosine kinase inhibitors (BTKIs) prevent phosphorylation by the corresponding kinase from taking place. In 2001, imatinib gained approval for treating chronic myeloid leukemia by the US FDA. Since then, various TKIs with high levels of potency and tolerability have emerged to treat cancer, including fibroblast growth factor receptor (FGFR), vascular endothelial growth factor receptor (VEGFR), NTRK, human epidermal growth factor 2 (HER2), anaplastic lymphoma kinase (ALK), and epithelial growth factor receptor (EGFR) inhibitors. As well as TKIs that target only one target, some TKIs block multi-targeted targets, such as sunitinib which targets platelet-derived growth factor (PDGF-Rs) and VEGFR. Numerous TKIs have been authorized, as shown in Figure 1, and hundreds more are being developed (Zámečníkova A, 2014).

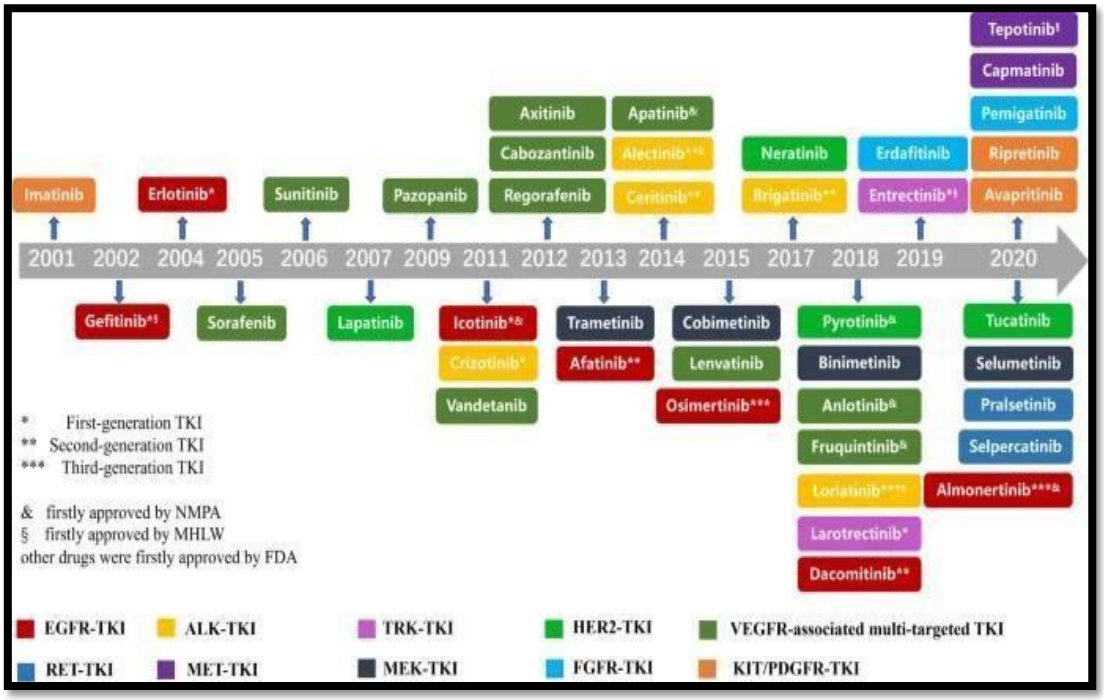

Figure 1: A representation of the approved TKIs in 2000-2020

There are several protein kinases considered to be prime molecular targets for selective inhibition due to the deregulation of human malignancies, including the ABL Proto-Oncogene 1, Non-Receptor Tyrosine-protein Kinase (ABL1), Steroid receptor coactivator (SRC), EGFR, and VEGFR. The current targeted therapeutic approach has been shown only to have limited efficacy in advanced cancers, apart from a few malignancies driven by a few genetic mutations. Consequently, it is essential to formulate more advanced tactics, including identifying harmful mutations and optimizing tailored medicines (Patel et al., 2023).

2.1. Function of Tyrosine Kinases

The RTK receptors are mainly responsible for transmitting extracellular signals from the surrounding environment into the cell. On the other side, intracellular communications are conducted by the non-RTK receptors. The mechanism of action of these receptors can be summarized by catalyzing the formation of phosphate ester on protein substrates. This is done by transferring a phosphoryl moiety from nucleoside triphosphate to a tyrosine residue in the target protein. As a result of phosphorylating tyrosine residues, proteins become capable of forming binding sites for downstream signaling proteins (Cooke M et al., 2017). Phosphorylating several signaling proteins results in a cascade of events that affect gene transcription. The RTKs regulate many processes within cells, including cell cycle control, metabolism, morphogenesis, motility, survival, differentiation, proliferation, and cellular communication. The nuclear localization of some RTKs has been demonstrated in several studies,

suggesting that these neurotransmitters participate in drug resistance, DNA fragmentation, DNA replication, and transcriptional regulation as well (Du Y et al., 2014).

2.2. Structure of the receptor tyrosine kinases

RTKs exhibit structural and ligand-affinity characteristics that classify them into 20 distinct subfamilies. The components include nerve growth factor receptors, Insulin receptors (IR), platelet-derived growth factor receptors (PDGFRs), EGFRs, FGFRs, insulin-like growth factor receptors (ILGFs), and hepatocyte growth factor receptors as shown in Figures 2 & 3 (Milon TI et al., 2024).

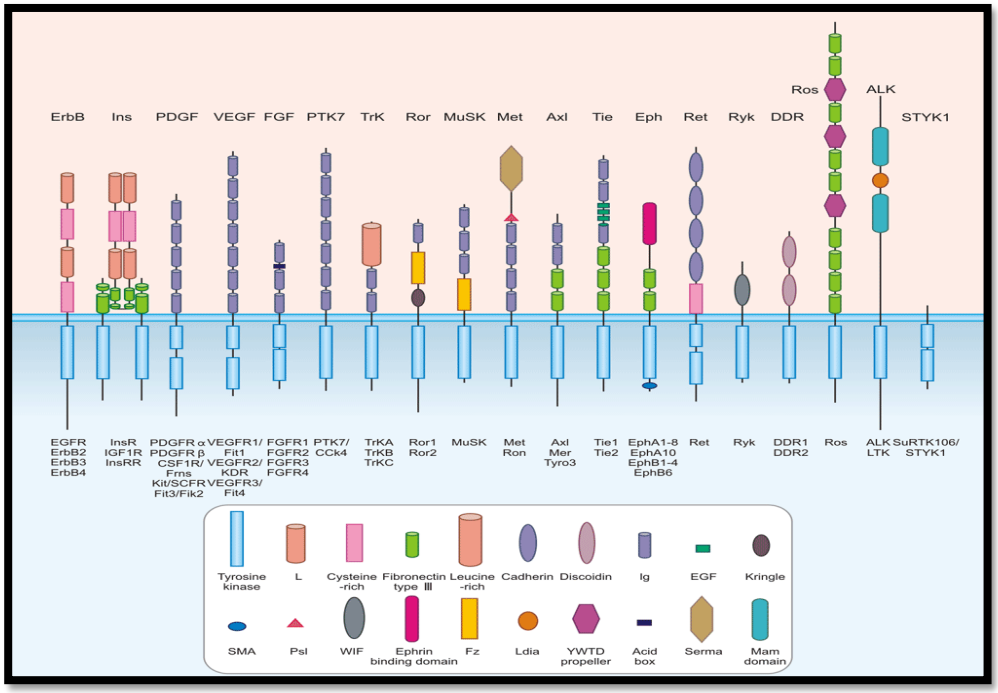

Figure 2: RTK Subfamilies

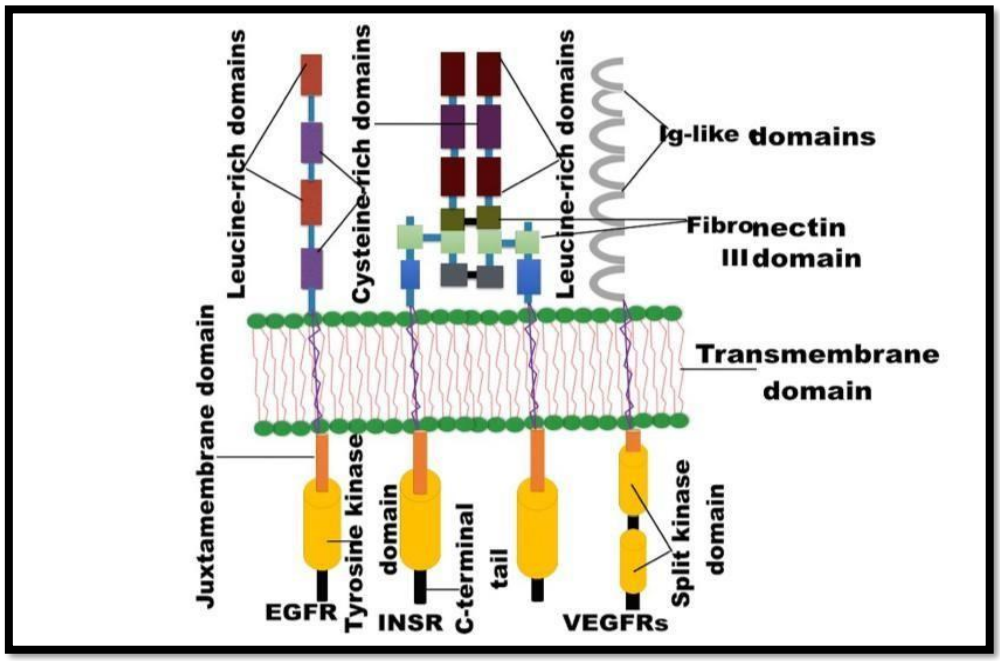

Figure 3: Structure of RTK subfamilies.

A tyrosine kinase structure consists of an extracellular domain that binds to ligands in addition to a single transmembrane domain, a region in the cytosol that tyrosine kinases, and a flexible C-terminus. Within RTK subfamilies, the extracellular domain exhibits variations in binding patterns and modules that forecast ligand recognition. Due to the diversity of receptor families, ligands bind to different receptors with excellent specificity. Extracellular domain dimerization occurs upon the formation of a ligand-receptor complex (Wendler F et al., 2021).

RTKs undergo conformational changes during binding to ligands, resulting in a potent signaling homodimer complex that activates intracellular tyrosine kinases (Tomuleasa, C et al., 2024). Different RTKs utilize multiple ways to recognize ligands and assemble RTK complexes. The VEGF system identifies ligands via seven extracellular immunoglobulin-like domains, enabling VEGFR dimerization. This contrasts with the epidermal growth factor-related receptor tyrosine kinase family (ErbB), where a solitary EGF molecule binds to one EGFR polypeptide, triggering dimerization of the EGFR and resulting in the formation of an EGFR-EGF tetramer. RTKs are characterized by many extracellular domains, including immunoglobulin-like folds and fibronectin Type III domains. Monoclonal antibodies, such as cetuximab, target these domains (Hossain, M.A., 2024).

2.3. Receptor Tyrosine Kinase Activation

When ligand binding induces dimerization of RTKs, auto-inhibitory elements are trans phosphorylated, causing structural changes within TKDs. This domain is located between two lobes of the TKD, one in the N lobe and one in the C lobe. Tyrosine side chains phosphorylated by tyrosine kinases can be recognized by proteins containing phosphor-tyrosine-recognition domains, such as the Src homology 2 (SH2) domain and the phosphor-tyrosine binding (PTB) domain (Lin, C.C. et al., 2024). Also, the phosphorylation of tyrosine removes the auto-inhibition of TKD, which is caused by the juxta membrane. Some cancers display constitutive active c-KIT and PDGFR expression due to mutations in the juxta membrane domain (Nishal, S. et al., 2023).

The multi-domain structures of RTKs and the many modalities of ligand binding elucidate numerous methods of receptor activation. RTK activation is defined by the phosphorylation of tyrosine residues inside the cytoplasmic domain, serving as the foundation for signaling cascade communication (Stehle et al., 2023).

Ligand binding activates RTK, Figure 4, by stabilizing monomeric or oligomeric linkages of the receptors, which actively dimerizes or oligomerizes them, stimulating intracellular kinase activity. Signaling molecules, initiated in response to the activation of RTK, phosphorylate and activate transcription factors to facilitate the expression of the target gene (Berndt, S. and Liebscher, I., 2021).

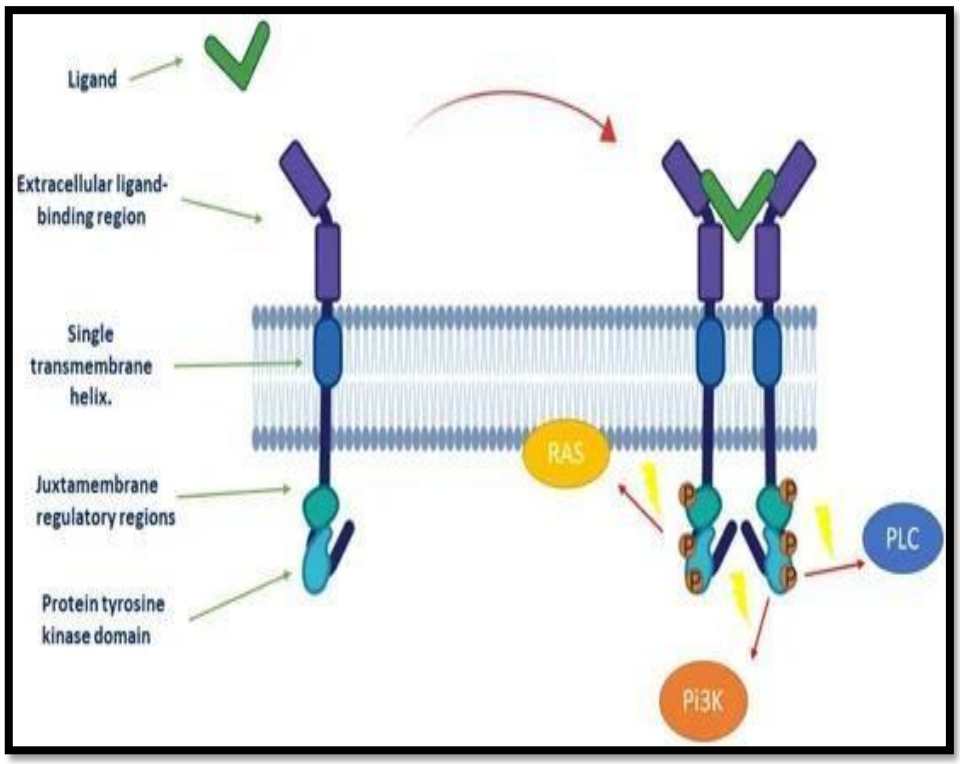

Figure 4: Activation of RTK

3. Tyrosine Kinase Inhibitors

3.1. Classification of Receptor Tyrosine Kinase Inhibitors

It was found that cancer cells can survive harsh conditions and their microenvironment alterations; therefore, it was believed that their proliferation follows Darwinian selection. Additionally, cancer cells have very active intracellular hubs, which play a significant role in their characteristics, such as proliferation and resistance. Accordingly, there was a drug development paradigm to target this intracellular cascade. Among these drugs, RTKIs are a large family and have successfully succeeded in clinical trials. A typical targeting mechanism prevents the phosphorylation of intracellular targets, which play an important role in cell proliferation or angiogenesis (Wu YL et al., 2017). The FDA approved 43 RTK inhibitors for oncological indications as of August 2019 (Choi, H.Y. and

Chang, J.E., 2023). It is usually distinguished between irreversible and reversible inhibitors based on whether they bind covalently to ATP. A large number of non-covalent inhibitors are ATP-competitive inhibitors that are linked to active conformations (type-I inhibitors). Selectivity can be achieved by focusing on poorly preserved residues, including those flanking ATP binding sites. As a result of binding to and retaining the inactive conformation of inactive kinases, type-II inhibitors can inhibit inactive kinases. Inhibitors of this type are usually nonselective; A type III allosteric inhibitor inhibits kinases by binding to an allosteric site far from the hinge and ATP site. A new class of RTKI is being developed those targets substrate-binding sites reversibly. Covalent inhibitors, also called type-V inhibitors, bind irreversibly to the kinase active site, are highly potent, and have fewer off-target effects (Crisci S et al., 2019)**.** In general, tyrosine kinases phosphorylate specific amino acids in substrate enzymes, altering signal transduction, which alters cellular biology downstream. TKs can modulate cell growth, migration, differentiation, apoptosis, and death downstream by signal transduction. A constitutive activation or inhibition of signal cascades, whether by mutation or other means, can result in malignancy or other pathologies (Roskoski Jr R, 2019).

In certain instances, such as cancer, TKs will be mutant, dysregulated, and abnormally functioned, which might be prevented by blocking them through TKIs. Human kinases share some similarities in 3D structure, especially the architecture of the ATP-positioned region of the active site, which is responsible for the catalytic activity of TK enzymes despite their diverse primary amino acid sequences. Accordingly, a highly conserved and flexible loop composed of ASP-Phe-Gly (DFG) was reported to be responsible for controlling the access to the activation site. TKIs may be irreversible or reversible (Fabbro D et al., 2015), and they are classified into four major types based on how they bind to catalytic pockets and DFG loop (Alves R et al., 2021 and Arter C et al., 2022).

Type (1) and type (2) inhibitors bind to the ATP binding site of the catalytic domain. Type (2) inhibitors block the ATP binding directly. Type (3) and (4) bind to the tyrosine kinase subunit, consisting of several SH2-like and SH3-like domains (Yang Y et al., 2022). Drug binding to one of its binding sites decides about inhibitory selectivity. Type I inhibitors bind to the N-lobe and the C-lobe. Type I/II inhibitors bind to the C-loop and the RTL motif and inhibit the ATP binding. Type I/II inhibitors bind to the second kinase domain for a mono-catalytic enzyme. Type II/III inhibitors have the highest power of allosteric-like inhibition in stoichiometry. This means that when they bind to one subunit, another subunit is inhibited far off the kinase binding site (El-Naggar AM et al., 2022). Regarding the last binding type, SH2-accompanied inhibitors are not believed to work as actual site TKIs today. However, this property depends on whether the chaperone or the kinase domain is the target of the inhibitor. The second binding type at the N-lobe of the tyrosine kinase domain is determined by natural product inhibitors. A molecular epoxy resin is also planned to have a binding position in the N-lobe (Fallahi P. et al., 2022)

3.2. Tyrosine kinase inhibitors in cancer disease

There are two kinds of cancer cells: rapid and slow. TKIs target the fast-proliferating cells by blocking signaling pathways that regulate the division of cancer cell proliferation. Cancer cells differ in the rate of cellular division. Some have a slow proliferation rate, may remain dormant for an extended period, and do not respond to treatment. Eventually, a relapsed state may occur inadvertently, and the cancer cells retain their replicative behaviour by entering the cell cycle yet again. The time spent in the G1 phase determines the rate at which cancer cells proliferate (Saraon, P. et al., 2021). It is known that oncogenic factors can speed up the G1 phase movement and the tumour microenvironment, which plays a massive role in the passage through the phase. Sometimes, an imbalance in the microenvironment can cause tumour cells to cease proliferating. Cancer cells that are quiescent complicate diagnosis, targeted drug intervention (TKI) therapy, and chemotherapy and are generally hard to deal with. There is no evidence that the treatment regimen used currently, which involves utilizing TKIs for rapidly dividing cells, kills quiescent cells, contributing to cancer relapse (Arter, C. et al., 2022). Several agents that inhibit TKs in varying stages of development have been discovered in response to their critical role in malignant transformation. It has been determined that the ABL1, SFKs, EGFRs, PDGFRs HER2, and VEGFRs undergo the most extensive clinical and laboratory characterization (Montoya, S. et al., 2021). EGFR and HER2 are two of the most critical TKs. Therefore, they have been targeted by several TKIs, as shown in Figure (6) (Sankarapandian V. et al., 2024).

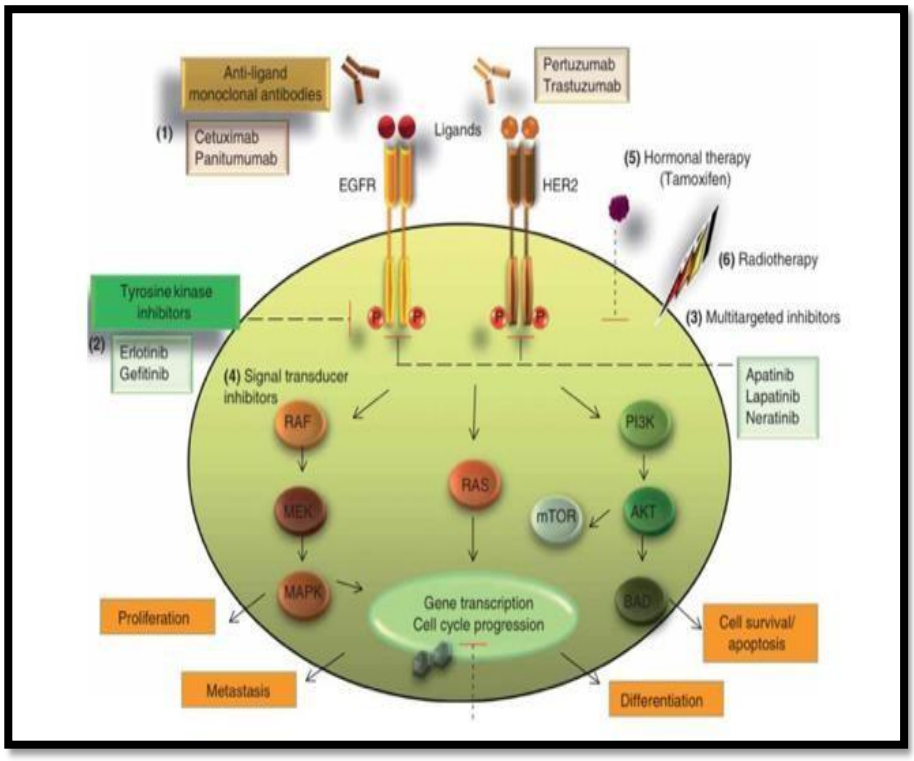

Figure 5: EGFR and HER2 family pathways in cancer and current drugs targeting these cancer proteins.

3.3. Multi-target Kinase inhibitors

Single-kinase-inhibiting agents were favoured due to their selectiveness, specificity, and lower incidence of side effects. However, the developing resistance from the continuously discovered mutations has discouraged this approach ((Glaviano A. et al., 2023). On the other hand, multiple pathways targeting was found to be appealing for cancer eradication (Scholl, S. et al., 2020). The following are some examples of recently developed multi-kinase inhibitors:

CG-806

CG-806, Figure 6, is an oral, noncovalent, investigational medicine that can potentially be a novel therapeutic option for several cancer patients. Many patients have difficulty obtaining relief from their suffering, or they obtain it for only a short portion of their cancer experience. Thus, one of the significant problems experienced with current cancer therapy drugs is their very limited success (Nachmias B. et al., 2024). CG-806 is being researched because it has unique properties that may aid it in overcoming hurdles associated with current cancer treatment drugs. Unlike general cancer drugs, CG-806 was designed to block cancer-causing targets, avoiding toxic side effects in healthy cells. CG-806 is currently being developed. The ongoing research and clinical trials aim to decide if and where it could fit into the oncology treatment system (Zhao Y. et al., 2024).

The therapeutic and clinical potential for CG-806 is considerable in light of its preclinical and preliminary clinical data in extensively pretreated B-cell malignancies. Among the most apparent, further investigation into optimal dosing schedules and combinations will improve the potential of this compound for cancer patients. If shown to be an effective, safe, and durable treatment, CG-806 and others may shift the central treatment paradigm for B-cell malignancies to a chronic disease model, akin to the success of TKIs in treating chronic myelogenous leukaemia. Clinical trials will explore the future extension of these promising data (Gupta D. et al., 2024).

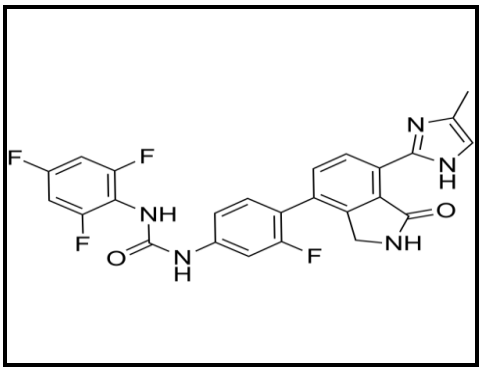

Figure 6: Chemical structure of CG-806

BI-847325

BI-847325, Figure 7, is a highly effective novel oral bioavailable agent that acts by ATP dual competitive inhibitory activity against MEK and aurora kinases. Its high antiproliferative activity was validated, reported, and confirmed in vitro by panels of human tumor cell lines and in vivo using subcutaneous xenograft models. Additionally, its action is under continuous investigation by the introduction of this agent in clinical trials. Therefore, it displays outstanding potential for managing several types of hematologic and solid tumors (Suryavanshi A. et al., 2024).

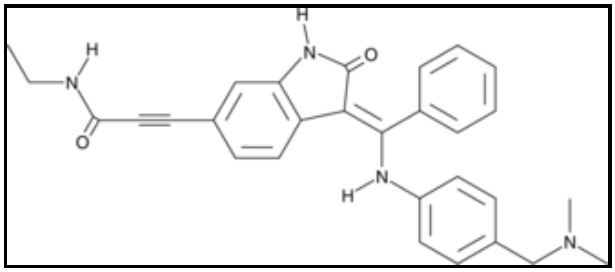

Figure 7: Chemical structure of BI-847325

Conclusion

TKIs are a group of chemical agents investigated initially for managing hematological cancers such as CLL/SLL. However, at present, they are considered in treating various types of cancer diseases due to their effectiveness and well-tolerability. For this reason, researchers' efforts are focused on the continuous development of novel TKIs with muti-kinase inhibitory activity to stand against high-rated-resistant tumors. Therefore, cancer patients' survival and quality of life have significantly improved through the continuous discovery and development of TKIs, transforming the treatment guidelines for various cancer diseases.

Additionally, due to their unique mechanism of action, the clinical use of these agents may be extended for managing diseases and disorders other than cancers and tumors, such as autoimmune disorders and GvHD.

Conflicts of Interest

Authors declare no conflict of interest

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