

## EXPLORING THE PROTEIN KINASE INHIBITORY ACTIVITY OF QUINAZOLINES AS ANTICANCER AGENTS: FDA-APPROVED DRUGS AND PROMISING REPORTED COMPOUNDS

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### ABSTRACT

Due to its powerful anticancer characteristics, the heterocyclic quinazoline has attracted a lot of interest in cancer research. Several cancer types, including lung, breast, colon, ovarian, and prostate cancers, have shown promise in response to quinazoline compounds' potential inhibitory properties. Protein tyrosine kinases (PTKs) are one of the main mechanisms through which quinazoline exerts its anticancer effects. Quinazoline drugs can interfere with the signaling pathways that support tumor growth and survival by specifically targeting PTKs. Quinazoline derivatives also exhibit antiangiogenic properties by blocking the vascular endothelial growth factor (VEGF) pathway, which prevents the creation of new blood vessels needed to feed the tumor. Additionally, chemicals derived from quinazolines have the ability to cause cancer cells to undergo apoptosis, or the halt of the cell cycle. Furthermore, quinazolines can accelerate the death of cancer cells while sparing normal, healthy cells through altering the regulation of the cell cycle and pro-apoptotic signaling pathways. Due to their favorable pharmacokinetic profile and low toxicity, they are also promising candidates for further investigation as anticancer agents. More research is required to enhance their efficacy, selectivity, and safety characteristics. Overall, quinazoline and its derivatives have been considered as attractive candidates for further development of novel therapeutic strategies in the field of cancer therapy.

**Keywords:** Quinazoline, Tyrosine kinases, Serine/threonine kinases, EGFR, VEGFR, Aurora.

**Covered topics:** This review summarizes the FDA-Approved drugs, articles and some patent published about quinazoline derivatives as anticancer agents since 2003.

## 1. Introduction

Quinazoline derivatives have recently garnered attention for their diverse biological activities, including their potential as powerful antitumor agents against a variety of cancers. They have also shown promise in treating hypertension, malaria, inflammation, seizures, and have exhibited antioxidant, antiviral, anti-HIV, and antibacterial properties (Zhang, Liu *et al.* 2016, Jain and Kashaw 2018, Santos-Ballardo, García-Páez *et al.* 2020). Over the past few decades, numerous quinazoline derivatives have been identified and developed as potential anti-cancer agents, demonstrating significant therapeutic efficacy in the treatment of different cancer types (Chilin, Conconi *et al.* 2010, Conconi, Marzaro *et al.* 2013, Kumar, Mariappan *et al.* 2017, Zayed 2022). The research on quinazolines for their anticancer properties has primarily concentrated on understanding the mechanisms by which they exert their chemotherapy effects. Many quinazoline-based anticancer drugs have been identified as protein kinase inhibitors (PKIs). This demonstrates that quinazolines exhibit their anticancer activity through various molecular interactions. The objective of this article is to provide a comprehensive assessment of the protein kinase inhibitory activity exhibited by various quinazoline derivatives and their implications in cancer therapy.

## 2. Protein Kinases

Protein kinases, found within cells, utilize ATP to transfer phosphate groups and catalyze the phosphorylation of specific amino acids in various proteins. The human genome contains over 500 different types of protein kinases (Abouزيد and Shouman 2008). Protein kinases facilitate specific conformational modifications in proteins to regulate their biological functions. These kinases' activity is crucial for fundamental processes, including cell cycle regulation, proliferation, differentiation, motility, and apoptosis. In tumor cells, it is frequently observed that key protein kinases are not appropriately regulated, leading to excessive phosphorylation and prolonged activation of signal transduction pathways (Vlahovic and Crawford 2003). Protein kinases are divided into three types: tyrosine kinases (TKs) are enzymes that phosphorylate the hydroxyl group found on tyrosine residues within signal transduction molecules. Examples of TKs include EGFR, VEGFR, PDGFR, FGFR, Src, Abl and Janus kinase. On the other hand, serine-threonine kinases are responsible for phosphorylating the hydroxyl group present in the side chain of serine and threonine amino acids. Some examples of serine-threonine kinases are MAPKs, Aurora kinases, PI3Ks, and CDK. Lastly, Histidine-kinases phosphorylate nitrogen in histidine residues.

### 2.1. Quinazoline derivatives as tyrosine kinase inhibitors TKIs

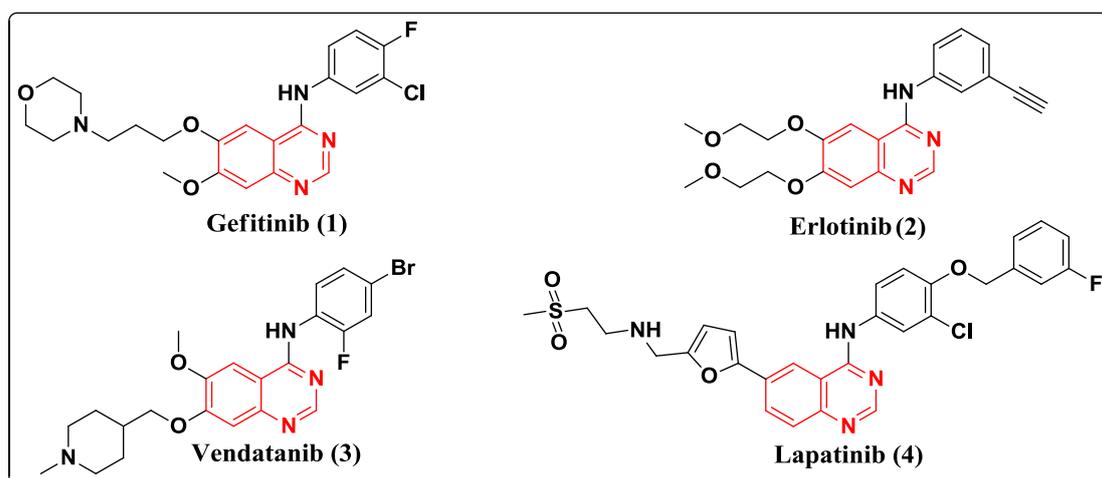
4-Anilinoquinazoline derivatives have been demonstrated a potential inhibitory effect against RTK. As a result, they have been widely incorporated into various small molecules that effectively function as TKIs (Denny 2001).

#### 2.1.1 Quinazoline derivatives as HER inhibitors

There are four categories of transmembrane receptors called HER receptors: HER-1 (also known as EGFR), HER-2, HER-3, and HER-4 (Ocaña and Pandiella 2013,

Roskoski Jr 2014). The HER (or ErbB) receptor is recognized as a significant biological target in different types of cancers, including lung, breast, colorectal, gastric, and head and neck tumors.

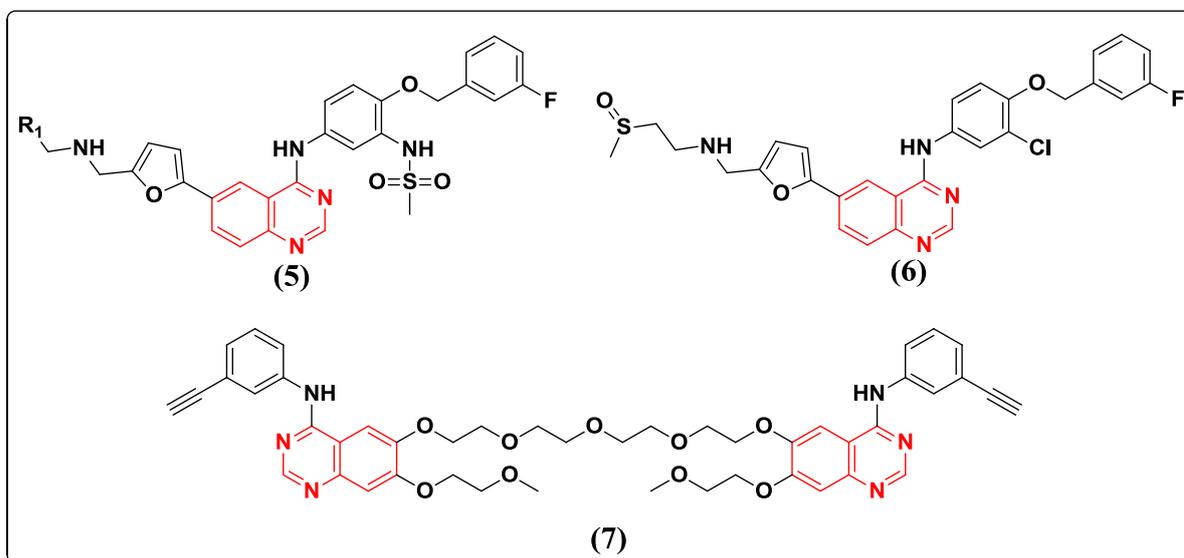
Reversible inhibitors targeting EGFR bind to and occupy the ATP binding pocket. They consist of a 4-amino substituent that binds to a hydrophobic pocket near the kinase hinge, along with a long chain extending in the 6- and/or 7- position towards the solvent. This elongated structure enhances the solubility of the inhibitor molecule. As a result, EGFR tyrosine kinase activity is inhibited. Several reversible inhibitors that have been approved by the FDA and utilized as drugs for treatment of various types of cancers. For instance, in 2003, gefitinib (Iressa®) (**1**) gained approval for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) who did not respond to platinum-based and/or docetaxel chemotherapies (Reck and Gatzemeier 2005). Another example is erlotinib (Tarceva®) (**2**), which was approved in 2004 as a treatment for non-small cell lung cancer (NSCLC). Additionally, in 2005, erlotinib and gemcitabine got FDA approval for the treatment of metastatic or locally advanced pancreatic cancer (Wu, Nielsen *et al.* 2015). On the other hand, the FDA approved the drug vandetanib (Caprelsa®) (**3**) in 2011 for the treatment of metastatic medullary thyroid cancer. It is employed as a kinase inhibitor and targets a number of cell receptors, such as the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and rearranged during transfection (RET) tyrosine kinase (TK) (Commander, Whiteside *et al.* 2011). Lastly, in 2012, the drug lapatinib (Tykerb®) (**4**) was granted approval for the treatment of breast cancer. It works by inhibiting the activity of two pathways: human epidermal growth factor receptor-2 (HER2/neu) and epidermal growth factor receptor (EGFR) (Wu, Nielsen *et al.* 2015). The FDA approved quinazoline derivatives as EGFR reversible inhibitors **1-4** are shown in (Figure 1).



**Figure1.** FDA approved quinazoline derivatives as EGFR reversible inhibitors **1-4**

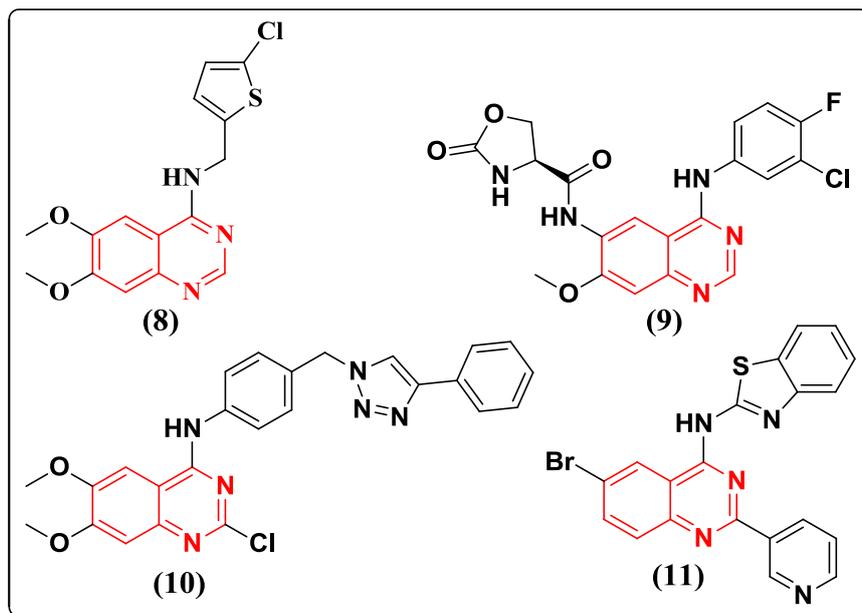
Modifications were made to the pharmacophoric structure to enhance the pharmacokinetic characteristics or the affinity for EGFR. Analogues of lapatinib, particularly analogue **5**, effectively inhibit both EGFR and HER-2 with  $IC_{50}$  values of 0.05 and 0.03 nM, respectively (Wang Jingyi 2011). In 2012, a distinct compound

similar to lapatinib **6** was chemically synthesized and showed potent inhibitory effects on EGFR (Wang Jingyi 2012). In 2014, a series of quinazoline dimers were synthesized and examined as inhibitors for EGFR. Among these dimers, dimer **7** exhibited the highest inhibitory activity with an  $IC_{50}$  value of 5.1 nM for EGFR (Wu Yusheng 2014). The anticancer quinazolines **5-7** are shown in (Figure 2).



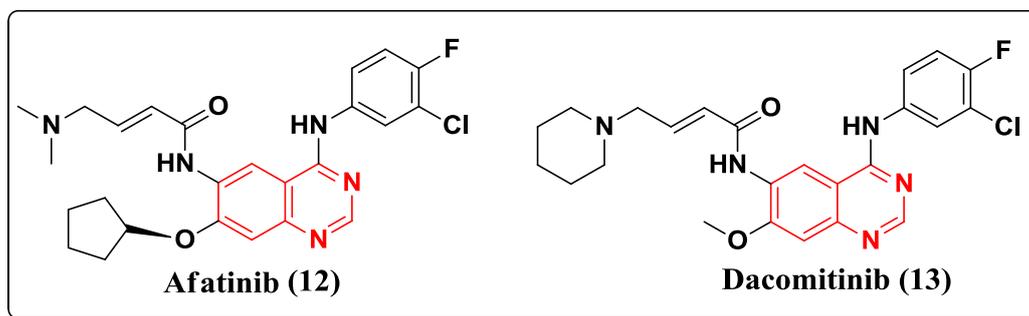
**Figure 2.** The anticancer quinazolines **5-7**.

A group of researchers synthesized and examined a series of quinazoline derivatives containing thiophene to study their potential as inhibitors of EGFR. Among them, compound **8** showed comparable anti-tumor effectiveness (with an  $IC_{50}$  value of 3.4  $\mu$ M) to erlotinib (Zou, Jin *et al.* 2019). In 2016, a combination of an oxooxazolidine ring and a quinazoline scaffold was developed and tested as a potential noncovalent inhibitor for targeting mutated forms of EGFR. Compound **9** showed promising anti-proliferative effects against gefitinib-resistant NCI-H1975, ranging from moderate to good. Furthermore, compound **9** demonstrated potent inhibition of EGFR kinase activity, particularly against the most commonly occurring EGFR mutants, namely L858R and T790M. However, it displayed weaker inhibitory effects on cancer cell lines with low levels of EGFR expression (Shao, Chen *et al.* 2016). A group of hybrid compounds that combine triazole and quinazoline substitutions were designed and synthesized to evaluate their potential as anticancer agents, specifically targeting the activity of EGFR TK. Among these compounds, compound **10** exhibited strong antiproliferative effects against MCF-7 cancer cell lines. Additionally, compound **10** was found to reduce the expression of EGFR and induce apoptosis through the generation of reactive oxygen species (ROS) and subsequent alteration of mitochondrial membrane potential (Banerji, Chandrasekhar *et al.* 2018). Quinazoline compounds containing a benzothiazole component were synthesized and evaluated for their ability to inhibit EGFR. Compound **11** demonstrated excellent inhibitory activity against EGFR. It displayed potent inhibitory activity on both wild-type EGFR and showed heightened anticancer activity against the MCF-7 cell line (Allam, Aly *et al.* 2020). The anticancer quinazolines **8-11** are shown in (Figure 3).



**Figure 3.** The anticancer quinazolines 8–11.

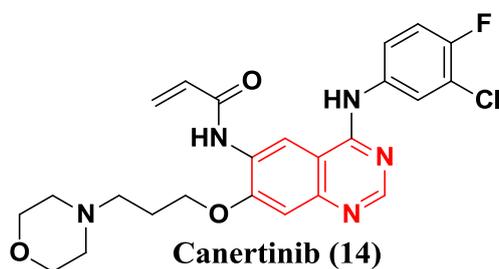
To overcome the resistance of tumors induced by reversible tyrosine kinase inhibitors (TKIs), HER irreversible inhibitors were employed. These irreversible inhibitors deactivate their protein target by forming a covalent bond with a cysteine residue that possesses nucleophilic properties within the nucleotide-binding pocket of the kinase domain (Carmi, Lodola *et al.* 2011). These inhibitors contain a 4-Anilinoquinazoline structure with a substitution at the C-6 position by an important acrylamide functional group. There are various drugs approved by FDA that are irreversible inhibitors used for treating different types of cancers. For instance, in 2013, the FDA approved afatinib (Gilotrif®) **12** as a treatment of NSCLC (Carmi, Mor *et al.* 2012). Another FDA-approved second generation drug is dacomitinib in 2018 **13** (Carmi, Mor *et al.* 2012). The FDA approved quinazoline derivatives as EGFR irreversible inhibitors **12-13** are shown in (Figure 4).



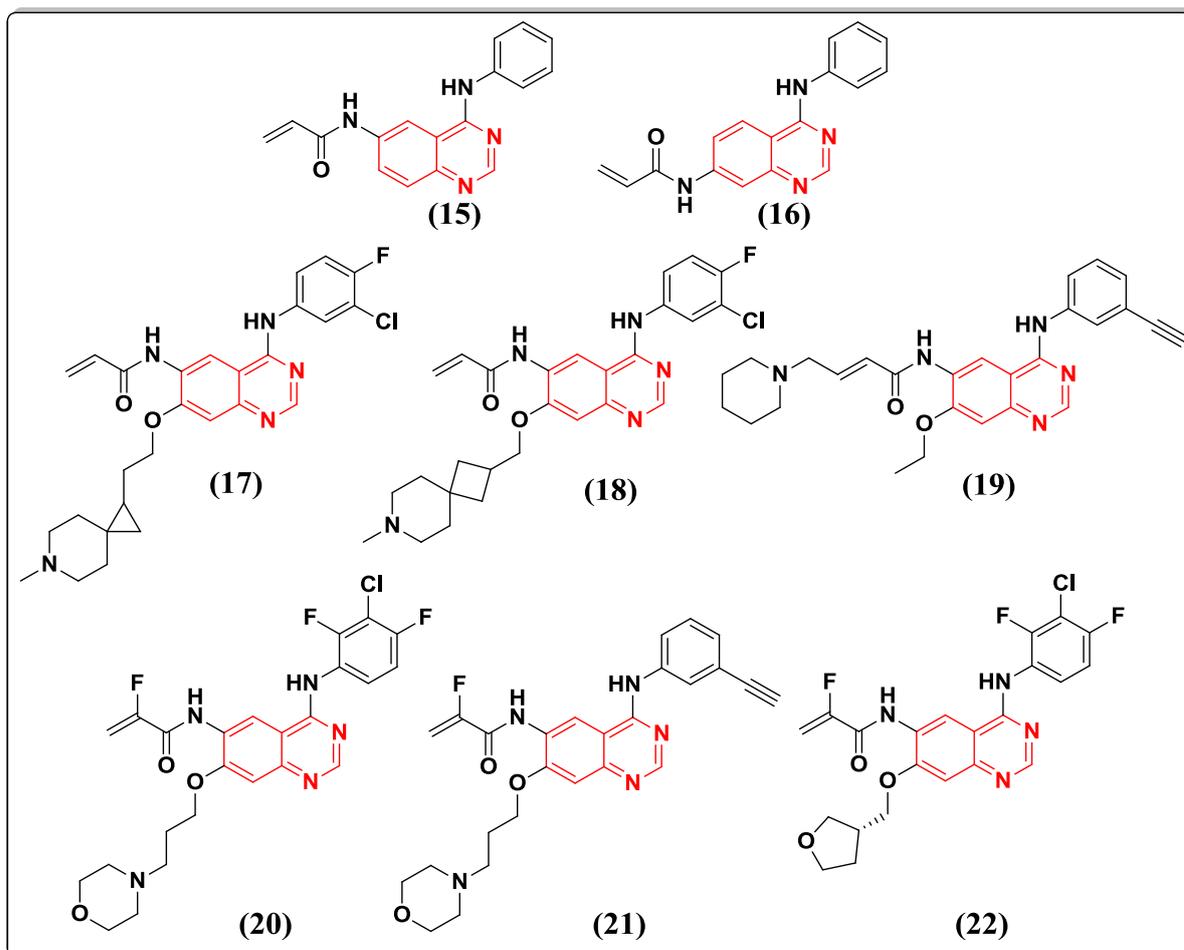
**Figure 4.** FDA approved quinazoline derivatives as EGFR irreversible inhibitors **12–13**.

Canertinib **14** is another example for irreversible nonselective EGFR inhibitors. It is still in clinical trials phase II. Also, It exhibited greater efficacy and a wider spectrum

of anticancer activity against ErbB1- and ErbB2 with an  $IC_{50}$  in the low nanomolar range (Arora and Scholar 2005).

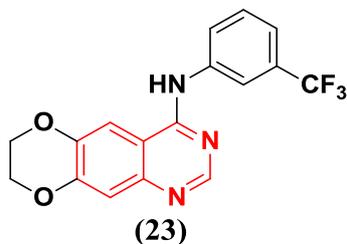


Due to the encouraging results observed in the use of HER irreversible inhibitors for anticancer purposes, many compounds have introduced 4-anilino-6-acrylamido-quinazolines as inhibitors of HER in an irreversible manner. In the year 1998, researchers synthesized a group of 4-(phenylamino)quinazoline derivatives containing either 6 or 7 acrylamide groups. These compounds were subsequently evaluated for their ability to inhibit EGFR-TK. Notably, compounds **15** and **16** exhibited strong selectivity and potency as irreversible inhibitors of EGFR-TK, and displayed improved antitumor activity *in vivo* (Fry, Bridges *et al.* 1998). In another work, Compounds **17** and **18** exhibit more potent inhibitory effects on HER -1, -2, and -4 compared to gefitinib. They also demonstrate significant antineoplastic activity on Calu-3 and H1975 cell lines (Huang and Dong 2017). Compound **19** exhibits superior inhibitory effects on EGFR and antiproliferative properties in SK-BR-3 and A431 cells compared to dacomitinib (Zhang 2016). Similarly, the acrylamido compounds **20**, **21**, and **22**, which contain fluorine in the acrylamido group, effectively inhibit EGFR (Xia, Shen *et al.* 2016). The anticancer quinazolines **15-22** are shown in (Figure 5).



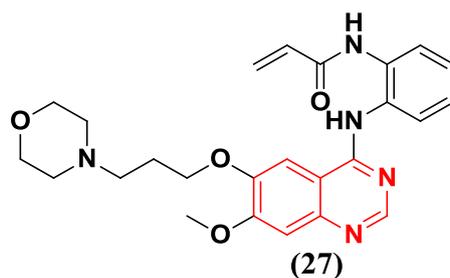
**Figure 5.** The anticancer quinazolines 15–22.

In 2010, a range of quinazoline derivatives were synthesized by adding two dioxo groups to positions C-6 and C-7 of the quinazoline core. The purpose was to evaluate their ability to inhibit EGFR-TK and to assess their antiproliferative effects. Among these derivatives, compound **23** showed the most significant activity against A431 and NIH313 cell lines. Compound **23** featured a dioxane ring and a trifluoromethyl group at position C-3 of the anilinoquinazoline ring, displaying  $IC_{50}$  values of 0.77  $\mu$ M and 7.1  $\mu$ M for A431 and NIH313 cell lines, respectively (Chilin, Conconi *et al.* 2010).

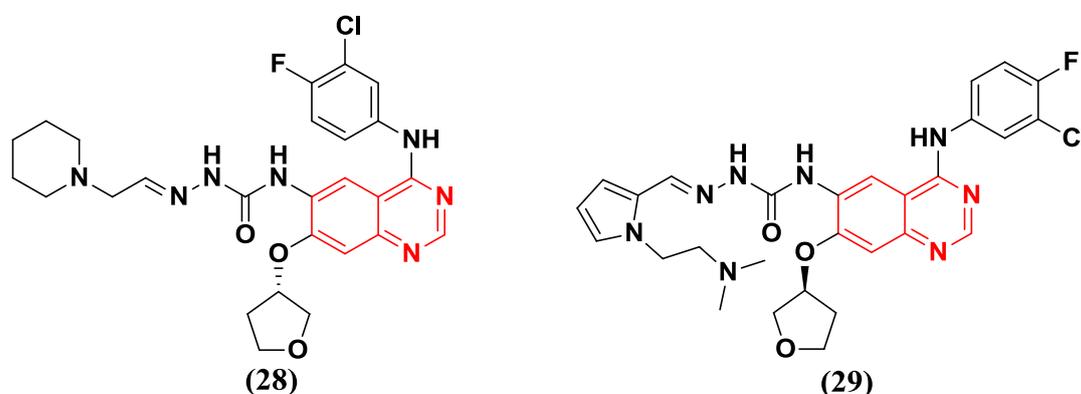


In 2016, a group of researchers developed and tested a set of morpholin-3-one-fused quinazoline derivatives. These compounds were designed with the intention of

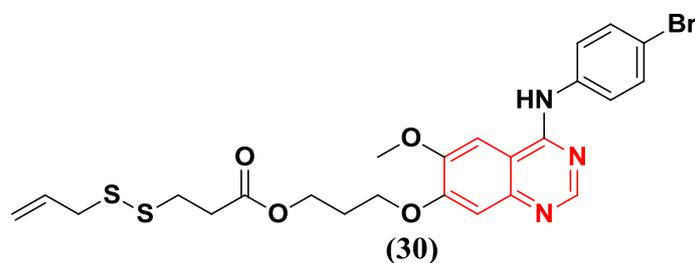




A new set of quinazoline compounds containing a semicarbazone group were created and evaluated in various cancer cell lines (A549, HepG2, MCF-7, and PC-3) to identify effective inhibitors of EGFR. Compounds **28** and **29** demonstrated strong inhibitory effects on both the T790M/L858R mutant EGFRs and the wild type EGFR, surpassing the inhibitory activities of afatinib and indicating their excellent potential as EGFR inhibitors (Tu, Wang *et al.* 2018).

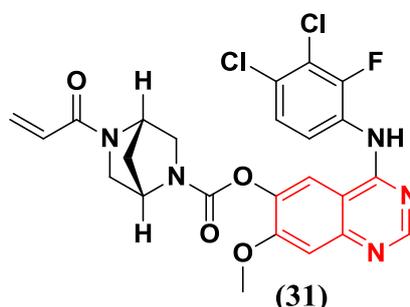


In 2020, a group of researchers developed and tested a group of chemical compounds called 4-anilinoquinazoline derivatives, which contained a disulfide component. These compounds were specifically designed to inhibit a protein called EGFR, which is associated with certain types of cancer. The experiments showed that one particular compound, known as compound **30**, exhibited significant anti-proliferative effects against a specific type of lung cancer cell line called H3255, which carries a mutation in the EGFR gene (Zheng, Zhang *et al.* 2020).

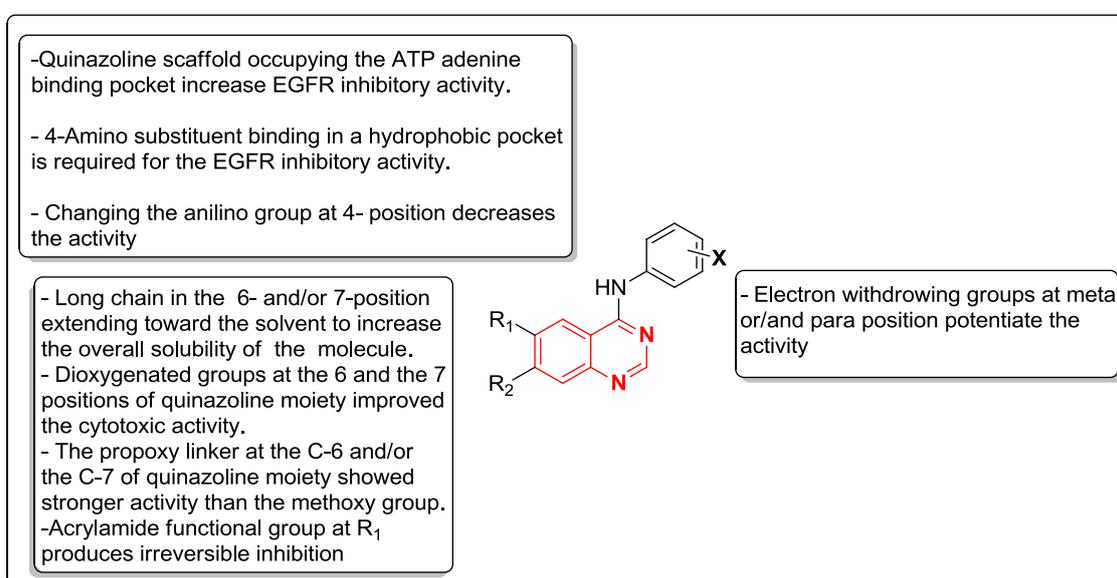


Quinazoline derivatives have been recently synthesized and tested for their biological effects on EGFR/HER2. Among these derivatives, compound **31** exhibited significant inhibitory effects on both EGFR and HER2. Additionally, it demonstrated

noteworthy antiproliferative properties against various cancer cell lines, including NCI-H358, PC-9, Calu-3, and NCI-H1781 (Jiao, Zhang *et al.* 2022).



### 2.1.1.1 General structural activity relationship studies (SAR) of quinazolines as EGFR inhibitors:

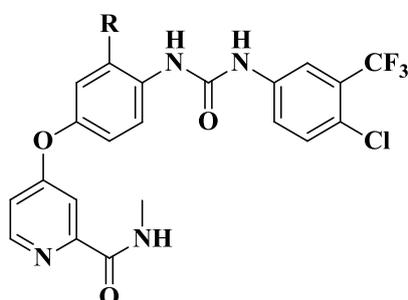


**Figure 6.** General SAR of quinazolines as EGFR inhibitors.

### 2.1.2 Quinazoline derivatives as VEGFR inhibitors

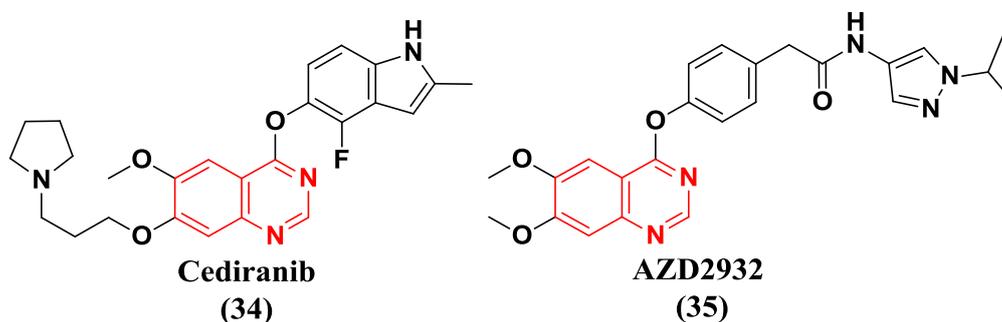
Vascular endothelial growth factor, also known as VEGF, is a glycoprotein that is essential for the creation of blood vessels (vasculogenesis), the lymphatic system (lymphangiogenesis), and the angiogenesis, the process by which new blood vessels are created from pre-existing ones. The structure of VEGF is homodimeric (Shibuya 2011). VEGF is a homodimeric structure and is recognized as one of the most significant regulators of angiogenesis due to its specificity and importance (Gupta and Zhang 2005). The VEGF family consists of seven glycoproteins that are secreted and known as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PLGF, and VEGF-F. These vascular endothelial growth factors interact with specific receptors to exert their biological effects. In humans, three receptors have been identified: VEGFR-1 (Flt-1),

VEGFR-2 (KDR), and VEGFR-3 (Flt-4). The structure of these receptors includes intracellular, transmembrane, and extracellular domains, with the latter being crucial for ligand binding. Considering the vital role of VEGF in angiogenesis, targeting growth factors or their ligands presents a promising approach for developing new anti-angiogenic medications (Houck, Ferrara *et al.* 1991, Ferrara, Gerber *et al.* 2003, Suto, Yamazaki *et al.* 2005, Tie and Desai 2012). Many small-molecule drugs, including Sorafenib **32**, have undergone clinical trials and received FDA approval in 2005. Sorafenib **32** specifically gained approval for treating advanced cases of renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) (Woo and Heo 2012). Moreover, regorafenib **33** effectively blocks several receptors including VEGFR-1, VEGFR-2, VEGFR-3, c-Kit, PDGFR $\beta$ , and Tie-2. Additionally, it has demonstrated the ability to hinder the growth of various cancer cell lines and has been approved by the FDA in 2012 for treating metastatic colorectal cancer and in 2013 for treatment of advanced gastrointestinal stromal tumors (Wilhelm, Dumas *et al.* 2011).



**Sorafenib (32), R=H**  
**Regorafenib (33), R=F**

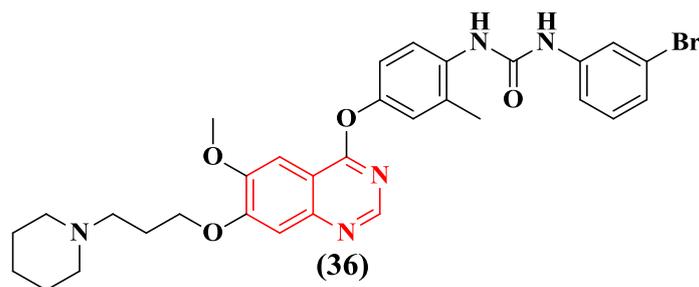
Cediranib **34**, a powerful oral inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3, has been tested in phase I/III clinical trials alone or in combination with other antitumor agents for the treatment of solid tumors and leukemias (Trarbach, Schultheis *et al.* 2012, Schmidt 2015). Additionally, AZD2932 **35** is a potent inhibitor of VEGFR-2 and PDGFR $\beta$  among the quinazoline derivatives that have also undergone development and testing for the treatment of various solid tumors and leukemias (Plé, Jung *et al.* 2012).



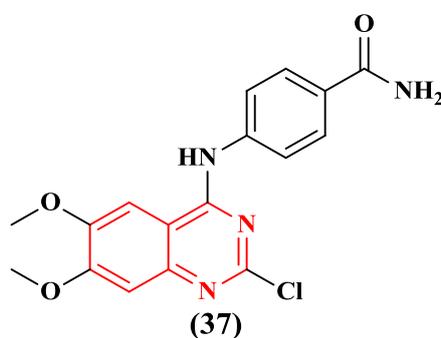
**Cediranib**  
**(34)**

**AZD2932**  
**(35)**

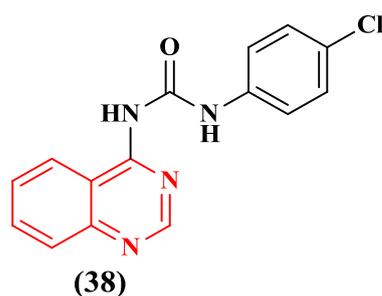
In 2014, a group of 4,6,7 trisubstituted quinazolines demonstrated strong inhibition of kinase enzymatic activity associated with VEGFR and PDGFR at a nanomolar level. Compound **36** from this group exhibited notable inhibitory effects on VEGFR, PDGFR- $\beta$  and c-Kit, and also displayed significant antiproliferative activity against cancer cell lines (Ravez, Barczyk *et al.* 2014).



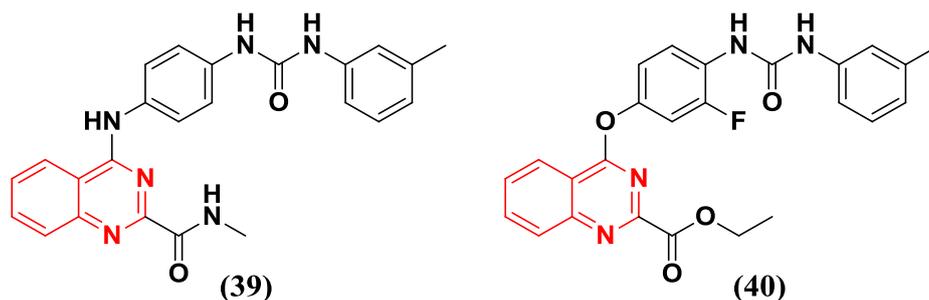
A new group of 2-chloro-4-anilino-quinazolines was created, synthesized, and tested as inhibitors for both EGFR and VEGFR-2. The biological results demonstrated that compound **37** showed promising inhibitory effects on both VEGFR-2 and EGFR (de Castro Barbosa, Lima *et al.* 2014).



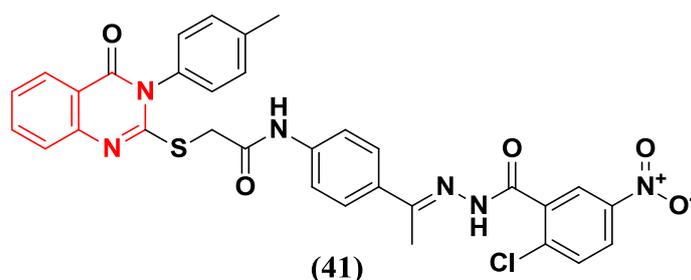
In 2016, a group of researchers developed, created, and evaluated a range of 4-substituted quinazoline derivatives. These compounds were specifically tested for their ability to induce cell death in MCF-7 and HepG2 cell lines and examined as potential inhibitors of VEGFR2. Among these derivatives, compound **38** demonstrated notable effectiveness against the mentioned cell lines, and showed strong inhibitory effects on VEGFR-2 (Wegdan M. Metwally 2016).



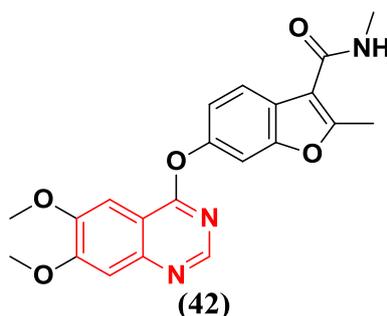
In the year 2020, researchers developed and tested quinazoline-based compounds as inhibitors of VEGFR-2. Two compounds, namely, N-methyl-4-((4-(3-(m-tolyl)ureido)phenyl)amino)quinazoline-2-carboxamide **39** and ethyl 4-(3-fluoro-4-(3-(m-tolyl)ureido)phenoxy)quinazoline-2-carboxylate **40**, demonstrated strong inhibition of VEGFR-2 in the nanomolar range, surpassing the effectiveness of the reference drug sorafenib (Abd El Hadi, Lasheen *et al.* 2020).



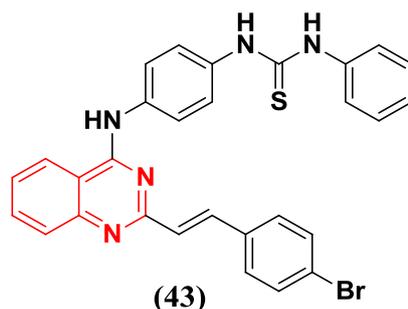
A set of quinazoline-4(3H)-one derivatives were created and produced, then tested against three human cancer cell lines (HepG-2, MCF-7, and HCT-116) in comparison to sorafenib and doxorubicin which were used as reference drugs. Among all the tested compounds, compound **41** displayed the highest level of inhibitory activity against the examined cell lines. It proved to be more effective than both doxorubicin and sorafenib when tested against HepG-2, HCT-116, and MCF-7 cells. In addition to this, compound **41** exhibited significant cytotoxic activity targeting VEGFR-2 (El-Adl, El-Helby *et al.* 2021)



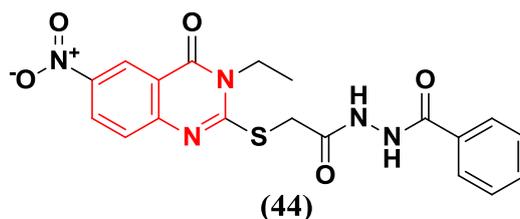
Fruquintinib **42**, which is a targeted blocker of VEGF receptors (VEGFRs) 1, 2, and 3, has recently gained approval in China as a treatment for advanced colorectal cancer. At present, Fruquintinib **42** is undergoing phase III clinical trials to assess its efficacy in patients with metastatic colorectal cancer that has been resistant to other treatments (Dasari, Sobrero *et al.* 2021).



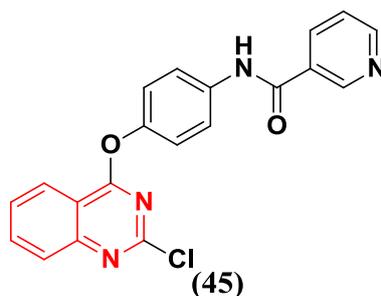
several 4-Anilino-2-vinylquinazolines derivatives were designed and tested for their anticancer potency. Among these derivatives, compound **43** showed promising anticancer activities through inhibition of VEGFR-2. Additionally, it promoted apoptosis in MCF-7 cells and increased cell cycle arrest in the G2/M phase compared to sorafenib (Hamdi, El-Shafey *et al.* 2022).



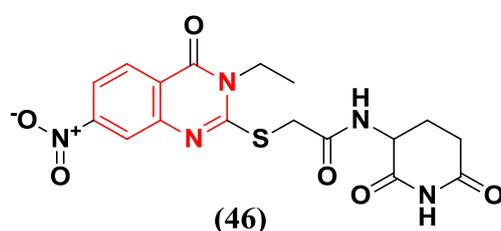
New derivatives of quinazolin-4-one were developed and tested for their anticancer activity and VEGFR-2 tyrosine kinase inhibition. Among the compounds synthesized, compound **44** was found to be the most effective. It demonstrated an  $IC_{50}$  of  $4.6 \pm 0.06 \mu\text{M}$  against VEGFR-2 kinase. Additionally, it displayed  $IC_{50}$  values of  $17.23 \pm 1.5$ ,  $26.10 \pm 2.2$ , and  $30.85 \pm 2.3 \mu\text{g/mL}$  against HepG2, PC3 and MCF-7, respectively. Notably, it exhibited an  $IC_{50}$  of  $145.93 \pm 1.1 \mu\text{g/ml}$  against the normal human lung fibroblasts cell line (WI-38), indicating good selectivity. Further investigation on HepG2 cell cycle revealed that compound **44** induced apoptosis and halted cell growth in the G2/M phase (Abdallah, Eissa *et al.* 2021).



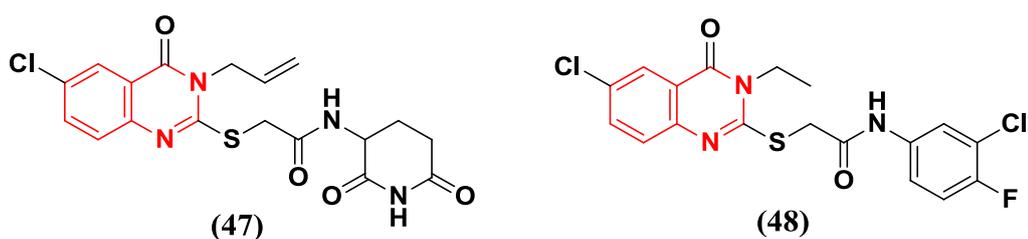
New compounds were designed and synthesized based on the quinazoline scaffold and the pharmacophoric features of VEGFR-2 inhibitors. Compound **45** demonstrated an VEGFR-2  $IC_{50}$  value of 60.00 nM, slightly higher than sorafenib's 54.00 nm. In addition, compound **45** exhibited  $IC_{50}$  values of 24.10  $\mu\text{M}$ , 40.90  $\mu\text{M}$ , and 33.40  $\mu\text{M}$  against HepG2, PC3, MCF-7, respectively. Although compound **45** showed strong VEGFR-2 inhibition, it ranked second in terms of antitumor assay with  $IC_{50}$  values of 24.10  $\mu\text{M}$ , 40.90  $\mu\text{M}$ , and 33.40  $\mu\text{M}$  against the aforementioned cell lines. Moreover, compound **45** significantly increased the apoptosis rate of HepG2 cells from 1.20% to 12.46%, as well as elevated the levels of Caspase-3, BAX, and P53 from 49.6274, 40.62, and 42.84 pg/mL to 561.427, 395.04, and 415.027 pg/mL, respectively. Additionally, compound **45** exhibited  $IC_{50}$  values of 253 nM and 381 nM against HER2 and FGFR, respectively (Abdallah, Mabrouk *et al.* 2022).



A new group of quinazolinone derivatives bearing a glutarimide moiety were designed and developed to act as similar drugs to thalidomide. These new compounds were tested in comparison to thalidomide on four human cancer cells: MCF-7, HCT-116, HepG-2, and PC3. Among the tested compounds, compound **46** was found to be the most promising candidate, displaying IC<sub>50</sub> values of 6.93, 8.13, 7.96, and 24.03 μM against the mentioned cell lines, respectively. Additionally, **46** showed a comparable ability to thalidomide in increasing the levels of caspase-3 by about six times. When tested against VEGFR, compound **46** had an IC<sub>50</sub> value of 241 nM, while thalidomide had 874 nM. Moreover, both **46** and thalidomide were similar in terms of suppressing the cell cycle and causing MCF-7 cells to accumulate at Pre-G1 stage, resulting in a significant increase in the rate of apoptosis from 65.64% in untreated cells to 99.88% in cells treated with **46** (Abdallah, Eissa *et al.* 2023).



New compounds similar to thalidomide were created and tested for their potential as anticancer immunomodulatory agents. The effectiveness of these compounds was compared to thalidomide by assessing their ability to inhibit the growth of three different human cancer cell lines (HepG-2, PC3 and MCF-7). Results showed that compounds **47** and **48** displayed significant potency against the mentioned cell lines, with comparable effectiveness to thalidomide. Further evaluation of the biological properties of **47** and **48** revealed their ability to reduce the levels of proinflammatory substances TNF-α, VEGF, and NF-κB P65 levels in HepG-2 cells, and increase the levels of CASP8. Interestingly, compound **48** demonstrated greater significance than thalidomide in inhibiting TNF-α and NF-κB P65 (Kotb, Abdallah *et al.* 2023).



### 2.1.3. Quinazoline derivatives as PDGFR Inhibitors

PDGFR, which stands for platelet-derived growth factor receptor, is a specific type of receptor found on the cell surface. Similar to other types of tyrosine kinases, it plays a crucial role in regulating cell proliferation, growth, and differentiation. However, when PDGFR becomes hyperactive, it can lead to uncontrolled cellular growth, ultimately contributing to various diseases such as pulmonary fibrosis, restenosis, and cancer (Andrae, Gallini *et al.* 2008). PDGFR has been recognized to exhibit activity as a tyrosine kinase and undergo autophosphorylation upon receptor activation.

Consequently, the use of a PDGFR phosphorylation inhibitor is anticipated to offer therapeutic advantages for treating these proliferative disorders.

In 2002, a group of compounds called 4-[4-(n-substituted carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives were discovered to have strong and specific inhibitory effects on the phosphorylation of PDGFR. This research led to the identification of several powerful derivatives, such as 4-(4-methylphenoxy)phenyl (**49**, with an  $IC_{50}$  value of 0.02  $\mu\text{mol/L}$ ), 4-tertbutylphenyl (**50**, with an  $IC_{50}$  value of 0.03  $\mu\text{mol/L}$ ), and 4-phenoxyphenyl (**51**, with an  $IC_{50}$  value of 0.08  $\mu\text{mol/L}$ ). These analogues exhibited about a 10-fold increase in activity compared to kn1022. Furthermore, these potent compounds maintained their high selectivity for the PDGF receptor family, similar to kn1022 (Matsuno, Ichimura *et al.* 2002). In 2003, researchers synthesized and studied tricyclic quinazoline derivatives to understand their ability to inhibit  $\beta$ -PDGFR. The findings revealed that the inclusion of an oxygen atom had a significant impact on the interaction with  $\beta$ -PDGFR. Among the various tricyclic quinazoline derivatives tested, derivative **52**, specifically 2-oxoimidazo[4,5-e]quinazoline, exhibited strong inhibitory activity with an  $IC_{50}$  value of 0.10  $\mu\text{M}$  (Matsuno, Ushiki *et al.* 2003). The anticancer quinazolines **49-52** are shown in (Figure 7).

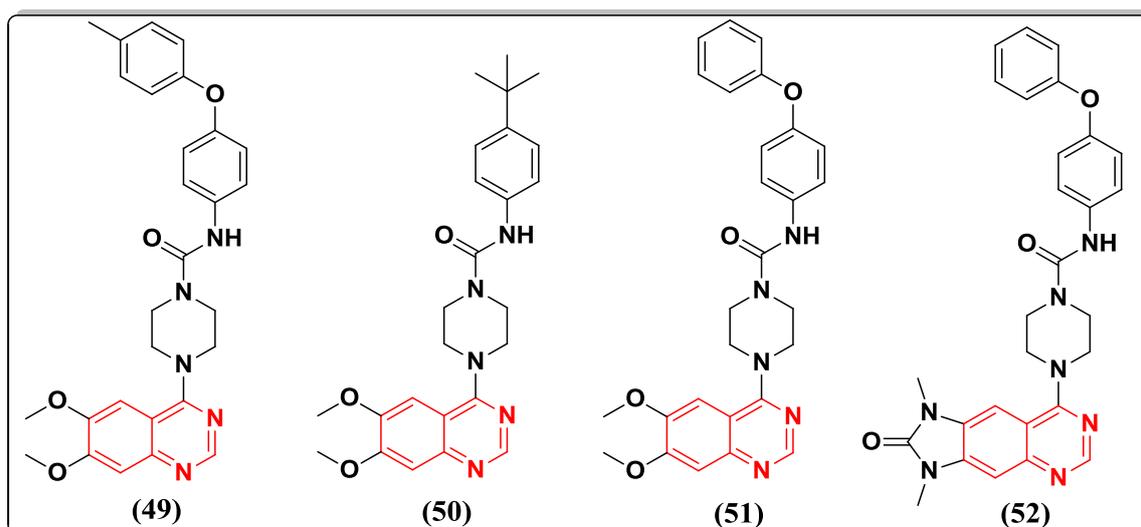


Figure 7. The anticancer quinazolines **49-52**.

In 2011, a group of scientists synthesized and tested a group of compounds called piperazinylpyrimidines to see if they were effective as antitumor agents. Among these compounds, three (**53**, **54**, and **55**) displayed promising results in cellular tests, showing a strong tendency to target proteins such as PDGFR, CK1, RAF, and others. Compound **53** specifically demonstrated a selectivity for binding to and inhibiting certain mutated forms of Kit and PDGFRA, compared to their wild-type isoforms. This is significant because it suggests that compound **53** could potentially be used to treat tumors that are resistant to current therapies or driven by these specific mutations. Additionally,

compound **54** exhibited potent growth inhibitory effects on the MDA-MB-468 cell line (Shallal and Russu 2011). The anticancer quinazolines **53-55** are shown in (Figure 8).

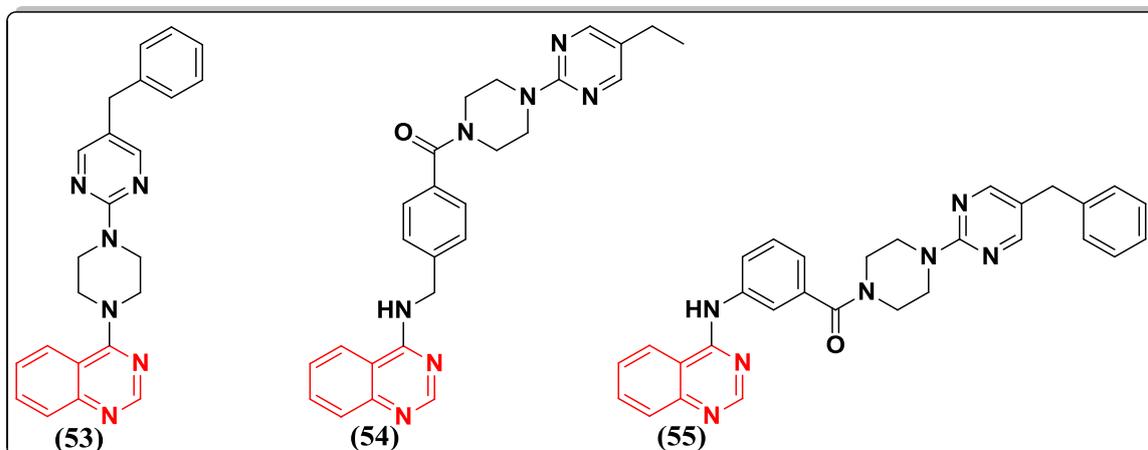


Figure 8. The anticancer quinazolines **53-55**.

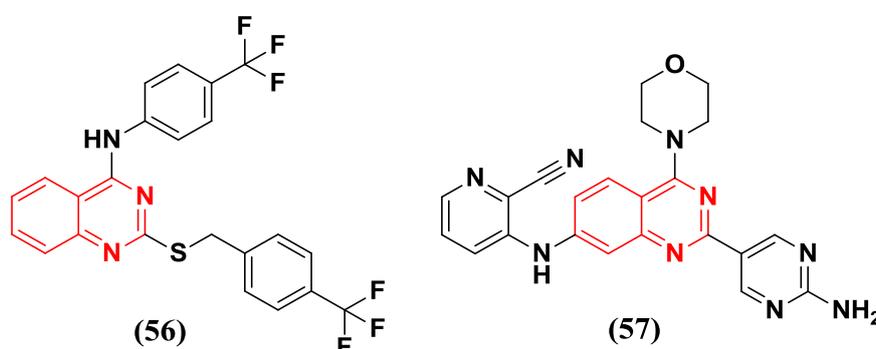
## 2.2. Quinazoline derivatives as serine/threonine kinase inhibitors

### 2.2.1. Quinazoline derivatives as phosphatidylinositol 3-kinase (PI3K) inhibitors

The family of PI3K has been discovered to have crucial regulatory functions in various cellular processes including growth and proliferation, differentiation, survival, metabolism, and migration (Vivanco and Sawyers 2002, Engelman, Luo et al. 2006, Liu, Cheng *et al.* 2009). When PI3Ks convert messages from various cytokines and growth factors into intracellular signals, the serine/threonine kinase Akt, also known as protein kinase B, is activated. This mechanism heavily depends on the tumor suppressor phosphatase and tensin homologue (PTEN)-regulated PI3K signaling pathway (Hemmings and Restuccia 2012, Song, Salmena *et al.* 2012). There is a high frequency of changes in cancer that result in increased signaling of PI3K. As a result, there has been a significant focus on developing novel cancer treatments that specifically target this pathway (Courtney, Corcoran *et al.* 2010). The significance of the PI3K pathway in cancer is highlighted by numerous studies, which have demonstrated frequent mutations or alterations in various components of this pathway across common human cancers (Fruman and Rommel 2014).

Several 2,4-disubstituted quinazolines were developed and assessed for their ability to inhibit tumor growth. Compound **56** demonstrated the most effective anti-proliferative properties against MDA-MB-231 and MCF-7 cells. Additionally, it notably suppressed the formation of cell colonies and hindered cell migration in both MDA-MB-231 and MCF-7 cells. Compound **56** induced cell cycle arrest in the G1 phase, triggered cell apoptosis, and led to an increased accumulation of intracellular ROS. Moreover, it displayed antitumor effects *in vitro* by reducing the expression of the anti-apoptotic protein Bcl-2 and increasing the levels of the pro-apoptotic proteins Bax and p53. Notably, compound **56** significantly lowered the expression of p-EGFR and p-

PI3K, indicating its interference with the EGFR-PI3K signaling pathway specific to breast cancer cells (Li, Lin *et al.* 2019). In another research, a group of new compounds called 7 or 8-substituted-4-morpholine-quinazoline derivatives were designed and synthesized. Their ability to inhibit the enzyme PI3K $\alpha$  and their effectiveness in suppressing the growth of seven different cancer cell lines (PC-3, DU145, MCF-7, BT474, SK-BR-3, U937, and A431) were evaluated *in-vitro*. Out of all the compounds tested, compound **57** exhibited strong potential as a drug candidate due to its high inhibition activity against PI3K $\alpha$  (IC<sub>50</sub> = 4.2 nM) and its effective suppression of cancer cell proliferation. Additionally, compound **57** was also examined for its inhibitory effects on other kinases such as PI3K $\beta$ , PI3K $\gamma$ , PI3K $\delta$ , and mTOR, as well as its impact on *p*-AKT (S473) and the cell cycle. These findings suggest that compound **57** has the ability to significantly block the PI3K/AKT/MTOR pathway, making it a promising PI3K inhibitor and anticancer agent (Peng, Tu *et al.* 2016).



In 2018, a set of hybrids containing 2-amino-4-methylquinazoline were created, synthesized, and assessed as potent inhibitors of PI3K. Compounds **58**, **59**, **60**, and **61** showed great potential with their ability to strongly inhibit PI3K at nanomolar levels, impressive antiproliferative activities, favorable pharmacokinetic profiles, and effective tumor inhibition *in vivo* (Lin, Wang *et al.* 2018). The anticancer quinazolines **58-61** are shown in (Figure 8).

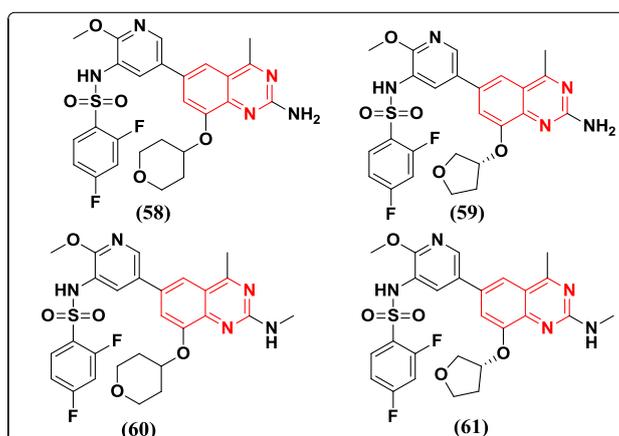
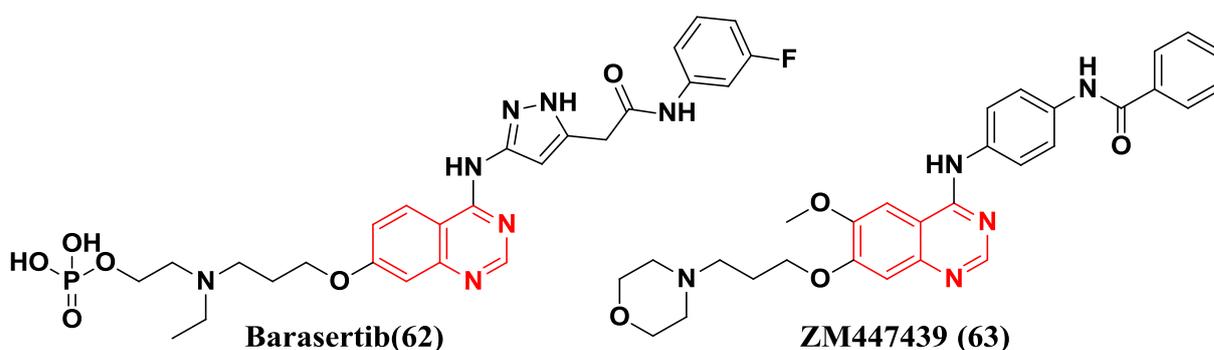


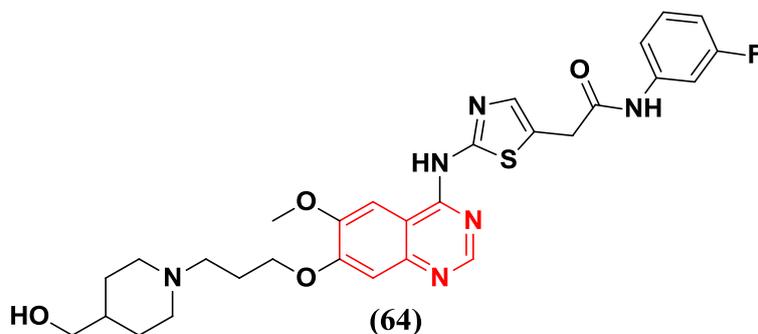
Figure 8. The anticancer quinazolines **58-61**.

### 2.2.2. Quinazoline derivatives as Aurora inhibitors

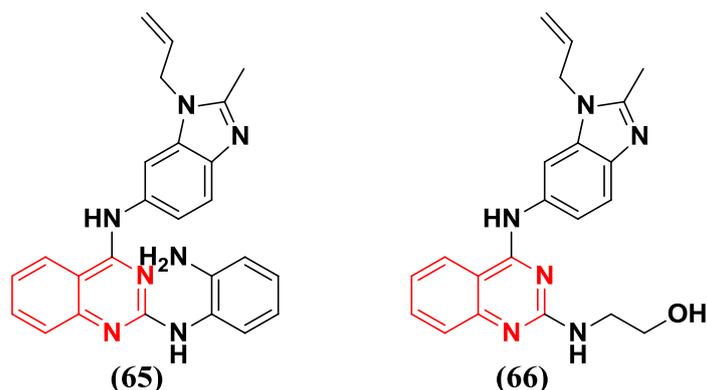
Aurora kinases are serine/threonine kinases that play a crucial role in the cell's mitotic regulatory network. Overexpression of aurora kinases can cause disruption in the process of mitosis, resulting in genetic instability and the potential growth of tumors (Goldenson and Crispino 2015). Clinical trials have utilized certain inhibitors of aurora kinase, which feature a quinazoline scaffold. Barasertib (AZD1152) **62** and ZM447439 **63** have similar structures, but Barasertib **62** specifically targets aurora B while ZM447439 **63** inhibits both aurora A and B (Mortlock, Foote *et al.* 2007).



In the year 2006, researchers synthesized and tested a group of quinazolines with a substituted aminothiazole at the C4 position. They evaluated these compounds for their ability to inhibit aurora A and B serine-threonine kinases. Compound **64** showed strong inhibitory activity against both aurora A and B, and it demonstrated excellent selectivity compared to other serine-threonine and tyrosine kinases. Moreover, compound **64** exhibited significant suppression of phospho-histone H3 expression in tumor cells, both *in vitro* and *in vivo* (Jung, Pasquet *et al.* 2006).



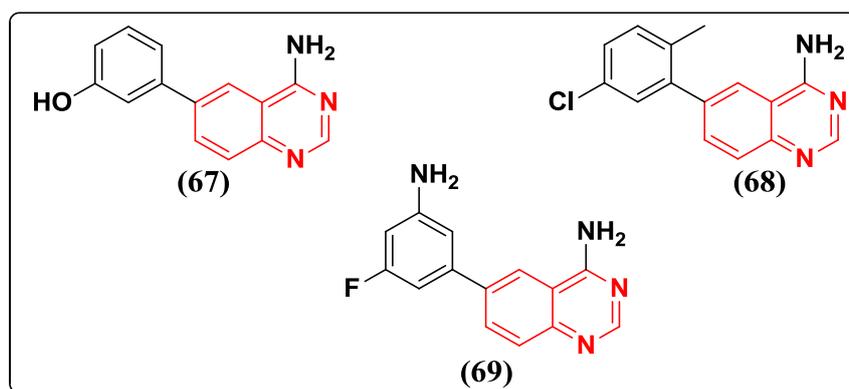
Aurora kinase inhibitors were developed, synthesized, and evaluated as hybrids of quinazoline-benzimidazole derivatives in 2015. Among these compounds, **65** and **66** demonstrated strong inhibitory activity against aurora kinase (Luxami, Rani *et al.* 2015).



### 2.2.3. Quinazoline derivatives as MAP4K4 inhibitors

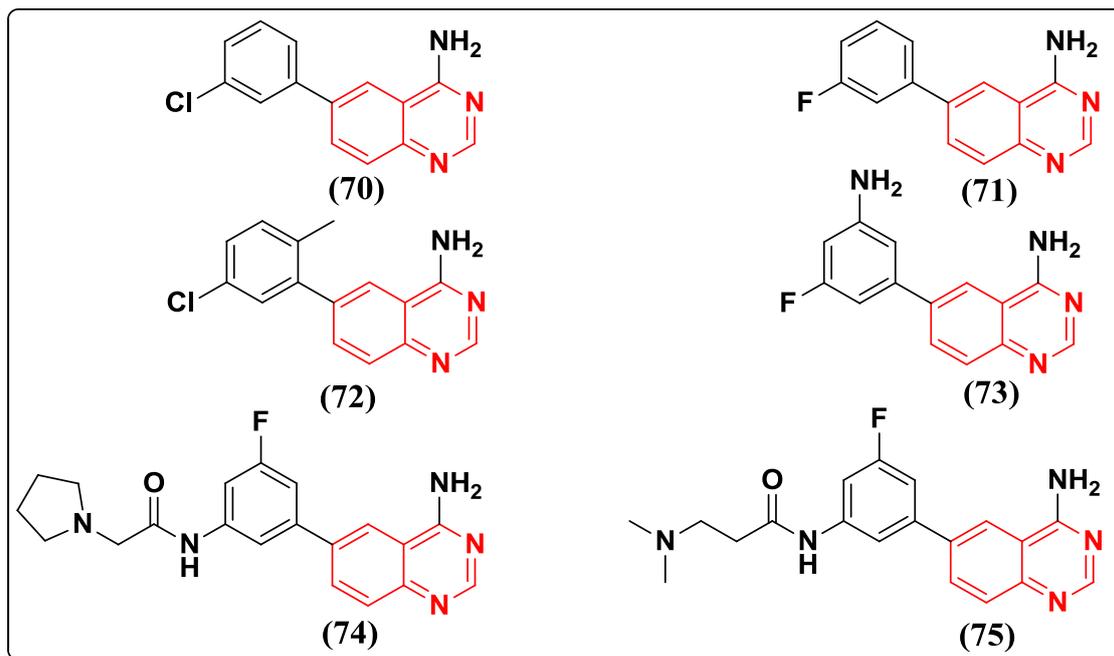
The MAPKs are vital components of serine/threonine protein kinase signaling pathways in cells that are responsible for responding to extracellular stimuli and regulating important cellular functions like proliferation, differentiation, and programmed cell death (apoptosis). The MAPK family can be divided into three main groups: **a**) p38 protein kinase **b**) c-jun N-terminal kinase **c**) extracellular signal-regulated protein kinase. Among these, MAP4K4, found in many human cancers including prostate, ovarian, liver, and pancreatic carcinomas, is known to be involved in tumor-related processes such as promoting the migration and invasion of tumor cells, potentially contributing to angiogenesis (Ravez, Castillo-Aguilera *et al.* 2015).

The patent US009382241B2 describes a technique for suppressing angiogenesis using inhibitors of MAP4K4. Among these inhibitors, four 4-aminoquinazoline derivatives labeled as **67**, **68**, and **69** exhibited strong inhibitory effects against MAP4K4 (Chen, Crawford *et al.* 2016). The anticancer quinazolines **58-61** are shown in (Figure 9).



**Figure 9.** The anticancer quinazolines **67-69**.

The US patent US009855269B2 presents a technique utilizing MAP4K4 inhibitors to inhibit angiogenesis. Specifically, compounds **70**, **71**, **72**, **73**, **74**, and **75**, which are 4-aminoquinazoline derivatives, demonstrate significant effectiveness in inhibiting MAP4K4 (Chen, Crawford *et al.* 2018). The anticancer quinazolines **70-75** are shown in (Figure 10).

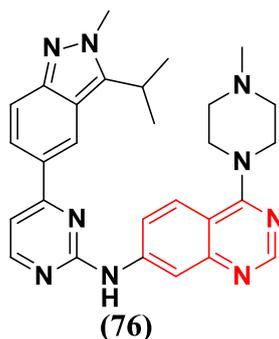


**Figure 10.** The anticancer quinazolines **70–75**.

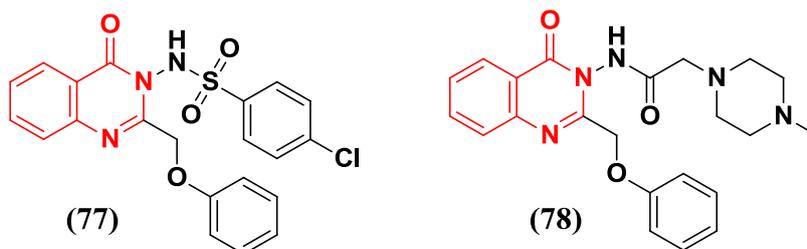
#### 2.2.4. Quinazoline derivatives as Cyclin-Dependent Kinase (CDK) Inhibitors

Cyclin-dependent kinase (CDK) is a member of the serine-threonine kinases family, playing a crucial role in protein phosphorylation. It also contributes to the regulation of transcription, mRNA processing, metabolism, and cellular differentiation (Malumbres and Barbacid 2005). The regulatory protein cyclin forms a complex with CDK, resulting in the formation of cyclin- CDK complex. This complex then proceeds to phosphorylate cell cycle substrates (Besson, Dowdy *et al.* 2008). CDKs can become overactive in various types of cancer, or the proteins that normally inhibit CDKs may fail to do so. Consequently, CDKs strive to limit uncontrolled cellular proliferation by suppressing this unregulated activity (Sanchez-Martinez, Gelbert *et al.* 2015).

In the year 2021, a group of quinazoline derivatives was designed, synthesized, and examined for their ability to inhibit CDKs. Among these derivatives, compound **76** exhibited strong inhibitory effects against CDKs 1, 2, 4, 8, and 9. Subsequent biological investigations demonstrated that compound **76** has the ability to arrest the cell cycle and trigger apoptosis by activating PARP and caspase 3 (Huang, Wang *et al.* 2021).



A set of quinazolinone compounds were created as inhibitors of CDK2 and tested for their ability to kill various types of tumor cells. Among the tested compounds, **77** and **78** showed great potential in inhibiting the growth of melanoma cell line MDA-MB-435. Further analysis revealed that compound **77** caused the cell cycle to stop at the S phase and G2/M phase, indicating that CDK2 might be the target of its action. Subsequently, compounds **77** and **78**, which demonstrated the highest cytotoxicity, were further examined for their ability to inhibit CDK2 in *in vitro* experiments, and their inhibitory effect was found to be significant (Mohammed and Elmasry 2022)



## 6. Conclusion

In conclusion, the review on the anticancer activity of quinazoline compounds highlights their promising potential as effective agents in the fight against cancer. Through extensive research and experimentation, numerous studies have demonstrated the ability of quinazoline derivatives to inhibit cancer cell growth, induce apoptosis, and inhibit angiogenesis, thereby suppressing tumor progression. The multifaceted mechanisms of action exhibited by quinazolines, such as targeting specific signaling pathways and signaling molecules, make them attractive candidates for further exploration and development as anticancer agents. However, further preclinical and clinical trials are necessary to determine the full therapeutic potential, optimal dosing, and potential side effects of these compounds. Overall, the findings discussed in this review emphasize the significance of quinazoline derivatives in the field of cancer research, warranting continued investigation to unlock their maximum potential in the pursuit of improved cancer treatments.

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### استكشاف النشاط التثبيطي لبروتين كيناز بواسطة مشتقات الكينازولين كعوامل مضادة للسرطان: ادوية معتمدة من إدارة الغذاء والدواء ومركبات واعدة تم نشرها

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### الملخص العربي

الكينازولين، وهو مركب حلقي ذو بنية متغايرة، قد اكتسب اهتمامًا كبيرًا في البحوث السرطانية بفضل خواصه المضادة للسرطان الفعالة. أظهرت مركبات الكينازولين تأثيرات مثبطة واعدة ضد أنواع مختلفة من السرطان، بما في ذلك سرطان الرئة والثدي والقولون والمبيض والبروستاتا. أحد أهم الآليات التي يعمل بها الكينازولين لمكافحة السرطان هو تثبيط أنزيمات التايروزين كيناز والثيرين والثريونين. عن طريق استهداف هذه الانزيمات ، يمكن للمركبات الكينازولينية أن تعطل سلاسل الإشارات التي تعزز نمو الورم ويقائه. بالإضافة إلى ذلك، أظهرت مشتقات الكينازولين تأثيرات مضادة للأوعية عبر تثبيط مسار عامل نمو الأوعية الشبكية ، مما يعيق تكوين الأوعية الدموية الجديدة التي تزود الورم بالمغذيات. علاوة على ذلك، أظهرت مركبات الكينازولين القدرة على تعطيل دورة الخلية والموت المبرمج للخلايا السرطانية. من خلال تأثيرها على تنظيم دورة الخلية ومسارات الإشارة المتعلقة بالموت المبرمج للخلايا ، يمكن للكينازولينات تعزيز موت خلايا السرطان وفي الوقت نفسه تحافظ على خلايا الجسم السليمة. علاوة على ذلك، تتميز المركبات المشتقة من الكينازولين بصفات الدوائية الملائمة وانخفاض سميتها وهذا يجعلها من المركبات المرشحة لمزيد من التطوير كعوامل مضادة للسرطان. ومع ذلك، يلزم إجراء المزيد من الأبحاث لتحسين فعاليتها وانتقائيتها وملفات السلامة. بشكل عام، يعتبر الكينازولين ومشتقاته عوامل واعدة محتملة لمكافحة السرطان فقدراتها على استهداف مسارات الإشارة المتعددة المشاركة في تقدم السرطان تجعلها من المركبات المرشحة الجذابة لمزيد من التطوير لاستراتيجيات جديدة في مجال علاج السرطان.

**الكلمات المفتاحية:** الكينازولين ،مثبطات أنزيمات التايروزين كيناز ، مثبطات انزيمات الثيرين والثريونين.