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The significance of quinazoline derivatives as potential multi-target anti-cancer agents: review article

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Abstract

In recent years, the use of quinazoline and its derivatives as structural scaffolds has shown significant promise in drug design. These compounds have shown significant biological efficacy in the treatment of a variety of diseases, including cancer. Quinazoline has shown a significant reduction in adverse effects and improved treatment effectiveness, making it a very attractive candidate for further investigation and advancement in therapeutic interventions. This review provides a focus on the use of small-molecule targeted therapy. The discussion briefly introduces the epidermal growth factor receptor tyrosine kinase (EGFR TK), its mutations, and the development of innovative molecules in this domain. Furthermore, the current review digs into the concept of multi-targeted anticancer agents, particularly on quinazoline-based compounds that can obstruct several targets. Notably, these targets include EGFR/VEGFR dual inhibitors, EGFR/HDAC dual inhibitors, and a variety of other EGFR-related targets.

Keywords

Quinazoline; Molecular Targeted Therapy; EGFR TKIs; EGFR/VEGFR dual inhibitors; EGFR/HDAC dual inhibitors

1. Introduction

1.1. Cancer and its incidence

Since there are numerous different tissues and cell types in the human body, the term "human cancer" describes more than 200 distinct diseases with numerous manifestations [1, 2]. Nevertheless, some biological characteristics of cancer cells are present in all these disease states, including uncontrolled (clonal) cellular growth, impaired cellular differentiation, invasiveness, and metastatic potential[3]. Cancer is now understood to be a genetic illness, specifically a disease of abnormal gene expression [4]. Recent studies have shown that various cancer types share similar molecular mechanisms governing uncontrolled cellular proliferation, including loss, mutation, or dysregulation of genes that positively and negatively regulate cell proliferation, migration, and differentiation (generally referred to as proto-oncogenes and tumor suppressor genes) [5, 6].

Globally, cancer is a public health issue. The International Agency for Research on Cancer (IARC) predicts 19,292,789 new cancer cases in 2020. Cancer cases in women are 9,229,484 (48%), and males are 10,065,305 (52%). Additionally, cancer killed 9,958,133 people globally that year. Cancer killed 4,429,323 women and 5,528,810 men (44.5 % and 55.5%, respectively) in 2017. Developing nations account for 63% of breast cancer fatalities and 53.7% of new cases, and Asia and Africa have the highest liver cancer diagnostic rates at 80.3%[7]. The incidence of these diseases worldwide and the risk factors and etiologic agents involved in disease causation are essential to studying the molecular pathways that control cancer pathogenesis [7, 8].

1.2. Small molecules targeted therapy

Traditional cancer treatment may include surgery, radiation, antineoplastic chemotherapy, and therapy with biological response modifiers, stimulating the patient's immune defenses[9]. The recent trends in cancer treatment include hormonal therapy and molecular-targeted therapy [10, 11].

Small molecules are compounds with a comparatively low molecular weight (900 Da) that can enter cells and target specific proteins within the cells [12, 13]. Numerous known small molecule inhibitors target kinases and dysregulated signaling pathways during carcinogenesis. Small molecules can also be used to target tyrosine kinases (TK), cyclin-dependent kinases (CDKs), and poly ADP ribose polymerase (PARP) inhibitors to activate a cell cycle checkpoint, induce apoptosis, and coordinate DNA repair [14, 15].

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2. Quinazoline as anticancer agents

The heterocycles are extensively studied bioactive compounds and are regarded as crucial synthetic targets for developing new therapeutics [16-18]. The biological uses of quinazoline, one of the heterocycles, have been the subject of much investigation [19-21]. The quinazoline nucleus is the fundamental building block in many biologically active compounds and therapeutic molecules [22-24]. The quinazoline system comprises three distinct members: 2-quinazolinone, which possesses a carbonyl group at the C-2 position **(1)**; 4-quinazolinone, which features a carbonyl group at the C-4 position **(2)**; and 2,4-quinazolinedione, which contains two carbonyl groups at both the C-2 and C-4 positions **(3)**[25, 26]. Due to their wide range of pharmacological properties, which include anti-cancer, anti-viral, anti-bacterial, anti-tubercular, analgesic, anti-hypertensive, anti-inflammatory, anti-diabetic, sedative-hypnotic, anti-histaminic, anti-convulsant [22, 23, 27-29]. With high therapeutic activity against solid tumors, quinazoline and its derivatives have been discovered to be a family of cancer chemotherapeutic drugs **(Figure 1).**

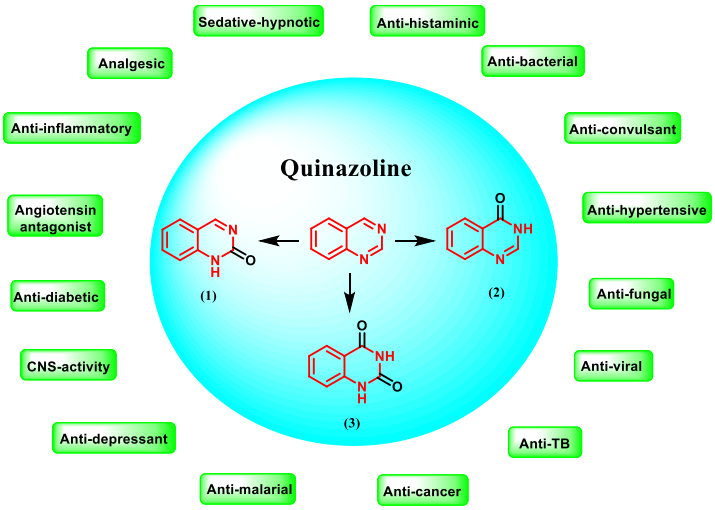


Figure 1. Different biological activities of quinazoline core.

2.1. Quinazoline as epidermal growth factor receptor inhibitors (EGFRIs)

2.1.1. Role of epidermal growth factor receptor tyrosine kinase (EGFR TK) in cancer

The epidermal growth factor receptor (EGFR) is a cytoplasmic TK with the physiological function of regulating the development and homeostasis of epithelial tissue. The kinase domain is located in the cytoplasmic portion of the kinase [30, 31]. This domain is responsible for mediating the transfer of a phosphate group to the kinases that have an ATP-binding pocket located between the N-lobe and the C-lobe of the EGFR [32, 33].

Members of the EGFR family are involved in multiple signaling pathways, including PI3K-Akt and RAS-ERK. EGFR (ErbB1) and ErbB4 are canonical RTK molecules interacting with specific ligands and transmitting signals. ErbB2 (HER2) does not interact with any known ligand, and ErbB3 lacks kinase activity, as is generally acknowledged [34]. Recent research indicated that ErbB3 interacts with ATP to induce minimal kinase activity [35]. ErbB2 and ErbB3 lack the traditional characteristics of EGFR family receptors, so they form heterodimers with other family members. Heterodimerization of these members signifies diversity and amplifies the EGFR family's response. ErbB2-ErbB3 heterodimers generate the most potent mitogenic signals among dimers [36].

EGFR activity can abnormally stimulate lung, brain, breast, colon, and head and neck cancers [37]. Malignant tumors can activate EGFR and ErbB2 by overexpression, gene alterations, and autocrinergic stimulation [38]. Mutant or overexpressed EGFR and ErbB2 can activate receptors without ligand contact [38]. Additionally, these receptors may bind more ligands than usual. As indicated, ErbB3 dimers with EGFR or ErbB2 demonstrate carcinogenic activity due to their limited kinase activity [39]. Erb4 is a traditional RTK with several variants that display extra features [40]. Some variants induce cancer, others avoid it. However, a recent study demonstrated that numerous tumor types had low ErbB4 point mutations, suggesting that ErbB4 activation influenced pro-tumorigenicity [41].

Many cancers hyper-activate EGFR family members, making them appealing therapeutic targets. Most clinically tested medications target EGFR and ErbB2, the two EGFR family members with the most cancer-related information [42]. The bulk of EGFR and ErbB2 therapies involve reducing receptor kinase activity or altering ligand-receptor interactions [43]. Other trials with multiple antibodies or kinase inhibitors revealed additive and synergistic therapeutic advantages [44-46].

2.1.2. EGFR TKIs classification

EGFR TKIs are classified into first, second, third, and fourth generations. First-generation EGFR TKIs, including Gefitinib **(4)**, Erlotinib **(5)**, Lapatinib **(6)**, and Icotinib **(7)**, shared a common scaffold, 4-amino quinazoline, as an ATP-binding domain [47-49]. Standard structural features shared by first-generation EGFR TKIs include (i) a quinazoline central scaffold bound to the ATP binding site, (ii) a solvent-accessible region, (iii) a -NH- linker between the quinazoline and hydrophobic ring, and (iv) a hydrophobic ring as the bulky substitution responsible for inhibition activity [50] **(Figure 2).**

Second-generation EGFR TKIs like Afatinib **(8)**, Neratinib **(9)**, and Dacomitinib **(10)** are initially put forward to combat the T790M mutation [51]. As second-generation EGFR TKIs, numerous 4-anilinoquinazoline and 4-anilinoquinoline compounds have been developed and evaluated [52, 53]. This class of inhibitors is distinguished by an electrophilic acrylamide moiety that functions as a Michael-acceptor system and forms a covalent bond with Cys797 at the EGFR's ATP-binding groove's edge [54]. The binding of an aniline group to the rear pocket of the ATP-binding domain increased the likelihood of interaction with the gatekeeper Met790 residue [50] **(Figure 2).**

The third-generation EGFR TKIs, or mutant-selective EGFR TKIs such as Osimertinib, Olmutinib, and Rociletinib, have shown potential effectiveness in patients with mutant cancer cells whose condition is resistant to the first- and second-generation EGFR TKIs [55]. Most of these inhibitors with aminopyrimidine scaffolds bind covalently to the active thiols of Cys797 *via* their electrophilic acrylamide Michael-acceptors [56]. This class of inhibitors selectively and irreversibly targeted the mutant $EGFR^{T790M}$ over the wild-type EGFR ($EGFR^{WT}$) [56]. These compounds have demonstrated significant clinical efficacy in T790M-carrying patients without dose-limiting toxicity [57].

In the last few years, the clinical evaluation has seen the introduction of fourth-generation EGFR TK inhibitors in the

battle against EGFR tertiary mutation (C797S). The development of fourth-generation EGFR-TKIs was necessitated by the common occurrence of the C797S mutation [50]. Based on available data, EAI001 and EAI045 represent fourth-generation EGFR allosteric kinase inhibitors, which have demonstrated therapeutic efficacy even in the presence of the C797S mutation. Allosteric kinase inhibitors are frequently employed as a supplementary treatment approach to ATP-competitive kinase inhibitors due to their distinctive binding sites with the target. The lack of binding to Cys797 can be attributed to the positioning of its residue, which is located outside the allosteric binding pocket [50].

The high-throughput screening (HTS) method was employed to identify the EAI001 molecule, a prototype fourth-generation EGFR TKI oxoisoindoline phenyl-acetamide derivative, from a library containing 2.5 million compounds. The screening was conducted at a concentration of 1 µM ATP, and the $EGFR^{L858R/T790M}$ IC_{50} value was determined to be 24 nM. EAI0045 is an allosteric inhibitor of mutant EGFR ($EGFR^{L858R/T790M}$ IC_{50}= 3 nM) that has been produced by modifying the phenyl ring of EAI001 to enhance its inhibitory properties [50].

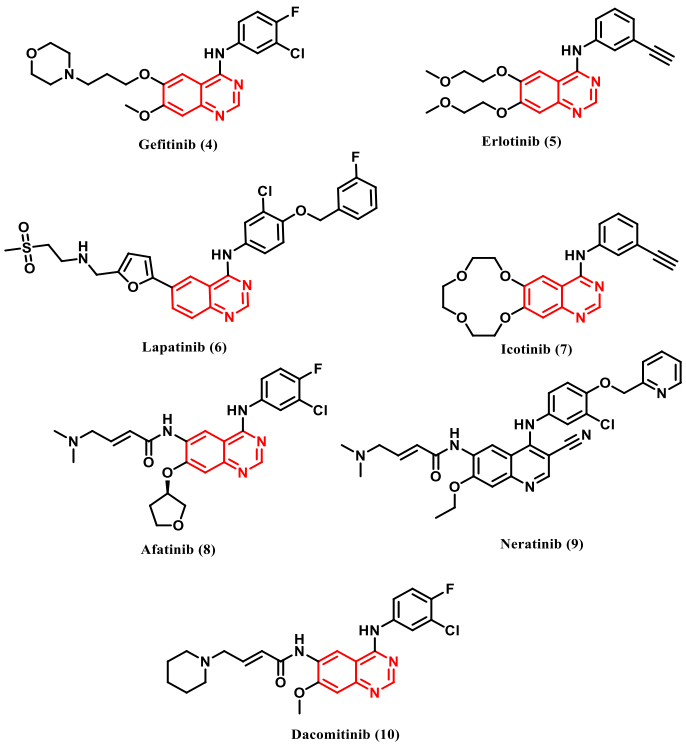


Figure 2. First and second generations EGFR TKIs.

2.1.3. Quinazoline derivatives as EGFR TKIs

Multiple investigations were conducted to explore the identification of new EGFR TK inhibitors utilizing quinazoline compounds as their basis. Chilin *et al.* conducted a study wherein they synthesized dioxygenated derivatives by including two dioxo groups at the C-6 and C-7 locations of the quinazoline nucleus [58]. Their investigation aimed to assess the anti-proliferative activity of these compounds by evaluating their capacity to inhibit the EGFR TK. Compound **(11)**, characterized by the presence of a dioxane ring and a trifluoromethyl group at the C-3 position of the anilinoquinazoline ring, exhibited the most pronounced activity, with IC_{50} values of 0.77 µM and 7.1 µM against A431 and NIH313 cell lines, respectively [58, 59] **(Figure 3).**

Furthermore, more quinazoline derivatives were synthesized by substituting the aniline moiety with the biphenyl amino group or modifying the deoxygenated ring's size by expansion or contraction. Out of the derivatives examined, it was observed that compounds **(12-14)** exhibited the most significant cytotoxic activity with IC_{50} range 0.63- 1.52 µM against A431 and NIH313 cell lines [59] **(Figure 3).**

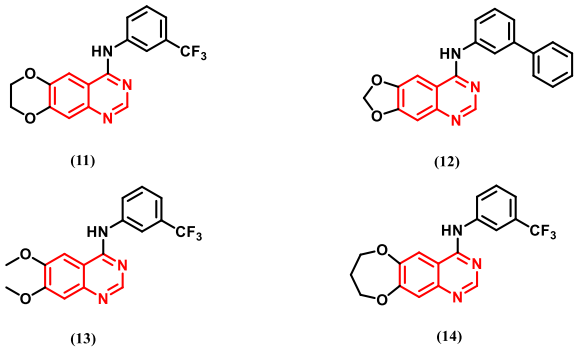


Figure 3. Quinazoline derivatives (**11-14**) as EGFR TKIs.

Conconi and colleagues developed a series of 6,7-dialcoxy-4-phenylamino-quinazolines to optimize their molecular structure to bind within the binding site of the EGFR TK effectively. Compound **(15)** was identified as the most potent inhibitor of EGFR TK activity with IC_{50} of 0.054 µM against Lapatinib **(6)** with IC_{50} of 0.023 µM. The derivative exhibited favorable efficacy but had limited bioavailability owing to its inadequate water solubility [59] **(Figure 4).**

Abouzeid and Shouman conducted a synthesis of a series of *para*-substituted anilinoquinazoline compounds as EGFR TK inhibitors, which were designed to contain 6,7-dialkoxy groups[60]. Among the synthesized compounds, compound **(16)** possessed the thiazolyl sulfanilamide moiety and exhibited a significant potency with an IC_{50} value of 0.13 nM. It exhibited favorable binding affinity to the ATP binding site of EGFR TK, similar to the standard drug Lapatinib **(6)**. Notably, an extra hydrogen bond was observed between the nitrogen atom of the thiazole group and a water molecule [60] **(Figure 4).**

In a separate study conducted by Lu *et al*., they demonstrated the modification of 6,7-dialkoxy-substituted-4-anilinoquinazoline to get 3-chloro-4-fluorophenyl-6,7-dimethoxyquinazolin-4-amine **(17)**. This compound exhibited a notable inhibitory action against EGFR TK, with an IC_{50} value of 3.8 nM [61] **(Figure 4).**

To further advance their research, Zahang *et al*. substituted the alkoxy group at the C-6 position with urea derivatives, as shown in compounds **(18-21)** [62]. The compounds exhibited significant inhibitory efficacy within a range of 0.024–1.715 µM if compared to the reference drug Lapatinib **(6)** IC_{50} of 0.012 µM. The phosphorylation process of EGFR-TK in the A431 cell line was inhibited by acyclic amine substituted derivatives **(18)** and **(19)** with an IC_{50} value of 0.01 µM. On the other hand, the phosphorylation process of EGFR in the NCI-H1975 cell line was blocked by cyclic amine substituted derivatives **(20)** and **(21)** with an IC_{50} value of 10 µM. The study on structural activity relationships (SAR) demonstrated that a heteroatom in the side chain promotes hydrogen bond formation. The inhibitory activity decreased due to the cyclization of the terminal *N*. This decrease

in the inhibitory activity may be attributed to a lengthy side chain lacking the ability to form hydrogen bonds [62] **(Figure 4).**
Furthermore, the anilinoquinazoline system was modified by including a 2-nitroimidazole moiety at position 7. Compound **(22)** exhibited a significant inhibitory action against EGFR TK, with an IC_{50} value of 0.47 nM [63]. This study reported a significant effect on some tumors linked with hypoxia when testing against the A549 and HT-29 cell lines. The activity of the tested compound resulted in IC_{50} values of 0.18 µM for the A549 cell line and 1.13 µM for the HT-29 cell line. In comparison, the standard drug Erlotinib **(5)** showed IC_{50} values of 9.1 µM for the A549 cell line and 2.98 µM for the HT-29 cell line [63] **(Figure 4).**
In 2019, Zou *et al.* discovered quinazoline derivatives, including thiophene ring that strongly inhibited EGFR kinase activity. The compounds had a modest level of antiproliferative activity, except for compound **(23)**, compared to the conventional medication Erlotinib **(5)**. The compound **(23)** had an IC_{50} value of 3.4 µM when tested against the A431 cancer cell line. The western blot analysis technique was used to investigate the autophosphorylation of the EGFR kinase protein in A431 cells, with a specific focus on the compound **(23)** [64]. The results obtained showed significant promise in comparison to Erlotinib **(5)**. Specifically, **(23)** subjects had an EGFR TK IC_{50} value of 4.0 µM. The findings from the structural-activity relationship (SAR) investigation of compound **(23)** provided evidence that the incorporation of thiophene into quinazoline heterocycles had promise for developing highly effective anticancer agents. The enhancement of inhibitory efficacy was seen with the substitution at positions 6 and 7 of quinazoline. On the other hand, introducing an electron-withdrawing group at position 5 of thiophene enhanced the inhibitory efficacy [64] **(Figure 4).**

2.1.4. EGFR TK mutations

A significant amount of research is currently focused on investigating mutations occurring in the EGFR gene and exploring diverse resistance mechanisms in patients [65]. Both intrinsic (primary) and acquired (secondary) chemo-resistance reduce the response rate to EGFR TKI therapy [66]. The primary driver of aberrant EGFR activation in cancer is mostly attributed to amplification of the genomic locus, resulting in complete mutation [67]. The main causes of resistance are genetic alterations such as point mutations in exon 18, deletions or insertions in exon 19, and insertions, duplications, and point mutations in exon 20 and exon 21 of the EGFR gene [68]. Due to this main mutation, patients may exhibit innate resistance to reversible and irreversible EGFR-TKIs [69].
The secondary mutation or amplification of the EGFR has exhibited an elevated occurrence in tumors subjected to therapeutic interventions [70]. Consequently, it has gained significant recognition as a biomarker indicative of drug resistance. The secondary mutation is distinguished by the presence of the gatekeeper mutant inside the ATP-binding cleft of EGFR [71]. T790M is associated with acquired resistance to first- and second-generation EGFR TKIs. The T790M mutation reduces the affinity of EGFR TKIs while it increases the affinity of ATP for the EGFR, even though it causes steric hindrance in the interaction of TKIs with EGFR [50, 71]. This enhances the ability of mutant cells to survive by preventing EGFR inhibition by first- and second-generation EGFR-TKIs. The T790M mutation - mediated resistance to first- and second - generation EGFR-TKIs has been overcome by third-generation EGFR-TKIs, which have been developed and produced [50]. The 797

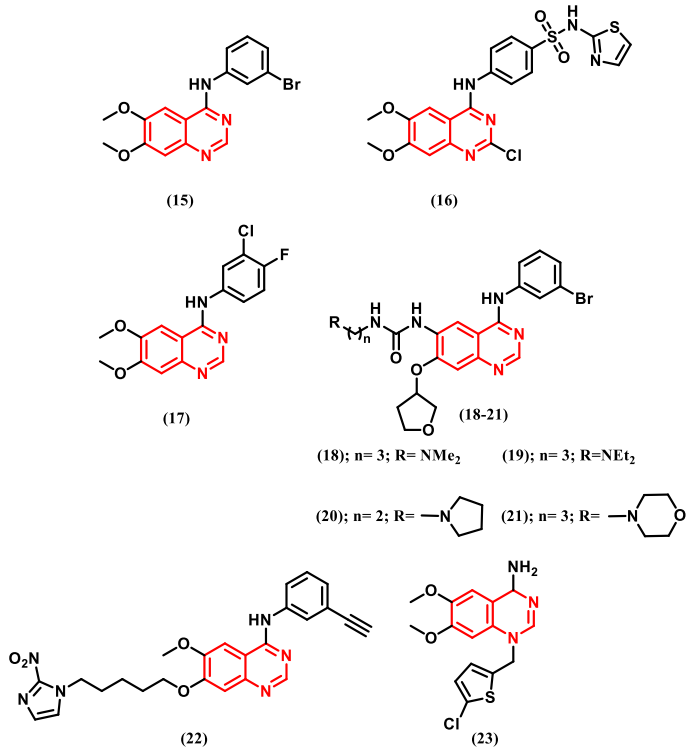


Figure 4. Quinazoline derivatives (**15-23**) as EGFR TKIs.

location of the ATP binding pocket of the EGFR-tyrosine kinase domain is where the third-generation EGFR-TKIs can covalently engage with a cysteine residue [72]. After some time, individuals using third-generation EGFR-TKIs acquired heterogeneous resistance to these medications [73]. Third-generation EGFR-TKI resistance is primarily caused by the appearance of a tertiary point mutation (C797S) in the ATP-binding cleft [74]. Deleting the secondary T790M mutation is another known factor in this secondary resistance [75].
In recent years, the clinical assessment has seen the introduction of the fourth generation of EGFR TK inhibitors as a potential strategy to combat EGFR tertiary mutation (C797S) [76]. The research endeavors investigate the utilization of multi-target medicines and combination treatment as strategies to address epigenetic mutations and enhance the efficacy of EGFR TK inhibitors [77, 78].

2.1.5. Quinazoline derivatives combating EGFR TK's consecutive mutations

The literature showed resistance in most cancer patients approximately one year after receiving treatment with Gefitinib **(4)**. Several processes have been proposed to elucidate this process; nonetheless, the precise underlying cause remains elusive. The emergence of secondary mutations has led to deviations in the downstream signals and the formation of alternate pathways.
As a trial to overcome this resistance, a group of researchers led by X. Qin conducted a study whereby they developed and synthesized a unique set of quinazoline derivatives fused with morpholin-3-one using intramolecular cyclization [79]. The team then assessed the biological activities of these compounds in terms of their ability to inhibit mutant EGFR. Derivative **(24)** exhibited the highest activity level among the series, demonstrating significant inhibitory effects in the nanomolar range against $EGFR^{wt}$ kinase. Furthermore, compound **(24)** had

notable anti-proliferative effects on H358 and A549 cell lines, as well as significant inhibitory efficacy against the mutant $EGFR^{T790M/L858R}$ at IC_{50} of 0.111 µM, when compared to Gefitinib **(4)** and Erlotinib **(5)**. Furthermore, molecular docking investigations were conducted to gain insight into the potential binding mechanism of the target compounds [79]. Compound **(24)** exhibited a favorable overlay with the binding conformation of Gefitinib **(4)** in the EGFR kinase domain. It also established hydrogen bonding interactions with the active site through the nitrogen and oxygen atoms in the quinazoline ring **(Figure 5).**

Moreover, Song *et al.* used click chemistry to synthesize new quinazoline derivatives containing a triazole moiety[80]. These compounds were designed to function as inhibitors for mutant EGFR, enhancing selectivity and demonstrating robust inhibitory activity. The inhibitory potency of these derivatives was compared to that of the reference Gefitinib **(4)**. It was shown to be particularly effective against both wild-type EGFR and mutant forms of EGFR ($EGFR^{L858R/T790M}$). Compound **(25)** exhibited a significant level of inhibitory efficacy against the wild-type EGFR kinase, as shown by its IC_{50} value, which was over six times more than that of the reference Gefitinib **(4)** (IC_{50} value of 12 nM). Nevertheless, compound **(25)** exhibited significant inhibitory efficacy against the mutant $EGFR^{L858R/T790M}$ variant, as shown by its IC_{50} value of 4 nM, while Gefitinib **(4)** demonstrated an IC_{50} value of 460 nM. The compound **(25)** has potential anti-proliferative action against cancer cell lines H1975 and PC9, as shown by IC_{50} values of 505.0 nM and 0.9 nM, respectively[80] **(Figure 5).**

Furthermore, Allam *et al.* introduced a family of potent EGFR inhibitors, namely 6-bromo-2-(pyridine-3-yl)-4-substituted quinazolines[81]. Most of compounds demonstrated significant efficacy against wild-type EGFR and mutant EGFR kinase T790M, L858R. Compound **(26)** had substantial inhibitory efficacy against wild-type $EGFR^{wt}$, $EGFR^{T790M}$, and $EGFR^{L858R}$, with IC_{50} values of 96 nM, 28 nM, and 55 nM, respectively. Furthermore, these compounds significantly inhibit the growth of breast cancer MCF-7 and NSCLC A549 cell lines, demonstrating promising anticancer potential. Compound **(26)** had an IC_{50} value of 2.49 µM against MCF7 cells and 178.34 µM against A549 cells[81] **(Figure 5).**

As well as in a study conducted by Le *et al.*, it was shown that some quinazolinone derivatives, which were substituted with a methyl group at position 3, had significant inhibitory effects on EGFR[82]. The compounds that were presented demonstrated favorable anticancer activity, as well as effective inhibition against wild-type EGFR inhibitors. Compounds **(27-29)** exhibited significant potency within the series, demonstrating inhibition rates of 64.95%, 63.37%, and 61.89%, respectively, at a concentration of 1 µM, when compared to the reference drug Gefitinib **(4)** (67.85%). They successfully inhibited EGFR with IC_{50} of 47 nM, 10 nM, and 540 nM, respectively. The anticancer activity of these compounds was further assessed against EGFR overexpressed human cancer cell lines A549, SMMC-7721, and PC-3. The IC_{50} values for these derivatives ranged from 6.04 µM to 35.92 µM. Additionally, compound **(28)** induced apoptosis in A549 cells at concentrations of 5 µM, 10 µM, and 20 µM while also causing cell cycle arrest in the G2/M phase[82] **(Figure 5).**

In 2021, Zhang *et al. synthesized* quinazoline derivatives incorporating a benzene-sulfonamide compound[83]. The researchers then assessed the anticancer properties of these compounds against H1975, A549, and A431 cell lines, observing a range of activity levels from mild to potent. Compound **(30)** exhibited the highest efficacy against mutant-type H1975 cells,

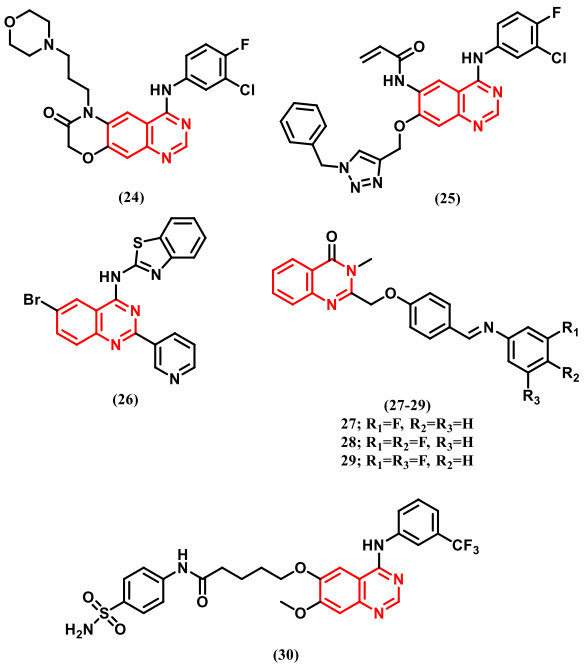


Figure 5. Quinazoline derivatives (**24-30**) as mutant EGFR TKIs.

demonstrating a significant anti-proliferative activity comparable to Osimertinib. Furthermore, Compound **(30)** displayed excellent inhibitory effects on the $EGFR^{T790M}$ enzyme in kinase inhibition tests with IC_{50} of 9.2 nM, exhibiting a potency 41 times greater than Gefitinib **(4)** and nearly equivalent to Osimertinib[83] **(Figure 5).**

The authors, Yu *et al.*, developed innovative anilinoquinazoline derivatives that incorporate a hydrophobic moiety at the C-4 position of the quinazoline ring. The synthesized compounds exhibited significant inhibition of $EGFR^{wt}$, with IC_{50} values ranging from 1.12 to 15.4 nM[84]. This inhibition was stronger than the standard Gefitinib **(4)**, which had an IC_{50} value of 15.5 nM. Compound **(31)** with an *N*-adamantly benzamide ring exhibited significant inhibitory activity against the resistant cell lines H1975 and A431, with IC_{50} values of 5.89 µM and 2.06 µM, respectively. Furthermore, it exhibited significant inhibitory efficacy against the mutant EGFR $TK^{L858R/T790M}$, with an IC_{50} value of 4.62 µM. The results of the modeling study demonstrated that the 1-adamantyl group at the *meta* position effectively occupied the hydrophobic region within the binding pocket[84]. Consequently, the aniline component of the molecule moved closer to the Met790 amino acid, facilitating the binding process with the mutant EGFR **(Figure 6).**

Additionally, Gefitinib **(4)** analogs were synthesized as inhibitors of the mutant EGFR[85]. Within this group of analogs, modifications were seen in the secondary amino propoxy side chain at both the C-6 and C-7 positions of the quinazoline moiety for 4-benzothienylamino quinazoline derivatives. The observed compounds exhibited notable anticancer activity against six distinct human cancer cell lines but with a lower efficacy when compared to the standards Gefitinib **(4)** and Erlotinib **(5)**. Compound **(32)** exhibited cytotoxic activity, with an IC_{50} value of 1.32 µM, and was found to induce apoptosis in the mutant MiaPaCa2 cancer cell line. The compounds with a 7-amino propoxy side chain exhibited more activity compared to the derivatives with a 6-amino propoxy side chain[85] **(Figure 6).**

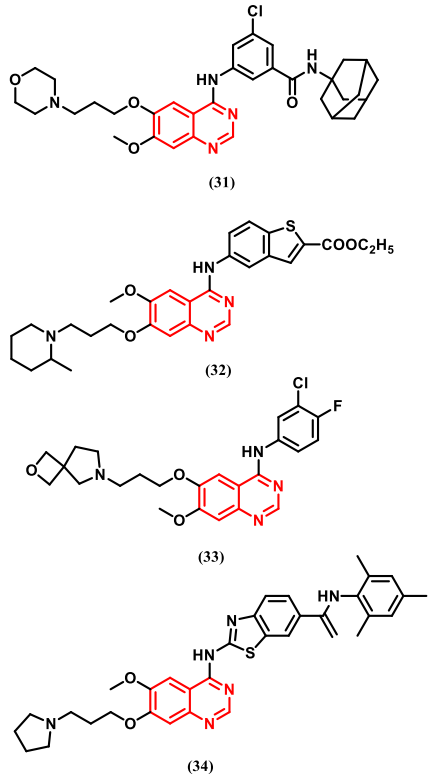


Figure 6. Quinazoline derivatives (**31-34**) as mutant EGFR TKIs.

Also, Zhao *et al.* developed mutant EGFR inhibitors by substituting the morpholine ring of Gefitinib **(4)** with a heterocyclic ring, specifically azaspirocycle or azetidine[86]. The recently synthesized compounds were tested against HCC827 & A549 cancer cell lines and mutant EGFR utilizing the standard Gefitinib **(4)**. The molecule with an azaspirocycle **(33)** had notable efficacy, as seen by its IC_{50} values of 15 nM and 28 nM against the $EGFR^{L858R/T790M}$ and HCC827 cell line, respectively. However, it did not demonstrate any effect against the A459 cell line. The biological findings indicated that the inhibitory efficacy of EGFR was maintained even while substituting the morpholine ring of Gefitinib **(4)** with a four-membered heterocyclic ring[86]. Moreover, incorporating heterocyclic rings at the 6-position enhanced water solubility **(Figure 6).**

Moreover, Cai *et al.* developed derivatives of 4-benzothiazoleaminoquinazolines as inhibitors of mutant EGFR[87]. The mutant EGFR inhibitory activity exhibited by the compounds was inferior to that of the reference drugs Gefitinib **(4)** and Erlotinib. Compound **(34)** had a significant inhibitory effect against SCr and ABI, with SCr inhibition reaching 91.8% and AB1 inhibition reaching 82.3% at a concentration of 1 μM[87] **(Figure 6).**

Numerous researches have been conducted to address the issue of resistance arising from utilizing first-generation EGFR inhibitors. Afatinib **(8)** has become a primary candidate for developing irreversible second-generation EGFR inhibitors in cancer research.

The development of irreversible inhibitors resulted from forming a covalent bond between the Michael acceptor moiety and the cysteine amino acid located within the EGFR binding site[88]. Within the category of irreversible EGFR inhibitors, it was shown that compounds **(35)** and **(36)** had notable efficacy in inhibiting EGFR-resistant cells H197, with IC_{50} values of 10.2 nM and 16.1 nM, respectively. The study on SAR demonstrated that the substituents consisting of 3-ethylaniline and 3-chloro-4-fluoroaniline groups exhibited the highest level of inhibitory activity[88] **(Figure 7).**

Also, Hou et al. synthesized a series of 4-anilinoquinazoline compounds, whereby a benzamide group was introduced at the 6-position of the quinazoline moiety[89]. Among the compounds, compound **(37)** had notable efficacy with an IC_{50} value of 5 nM. Furthermore, it demonstrated effectiveness against cell lines harboring mutations in the EGFR TK. The results of the structure-activity relationship (SAR) investigation showed the formation of an irreversible covalent link between the benzamide group of the compound and the sulfhydryl group (SH) of the Cys797 residue located inside the binding region of EGFR TK[89] **(Figure 7).**

Additionally, a series of conjugates, as in compound **(38),** combining Naproxen and Erlotinib **(5)**, were synthesized[90]. Naproxen functions as a nonsteroidal anti-inflammatory drug (NSAID). The conjugated compound was evaluated for its activity against A431 and HCC827 cancer cell lines. It exhibited a noteworthy inhibitory action against EGFR, with IC_{50} values ranging from 0.005 to 0.88 μM. The hydrolysis of this compound was elucidated by pharmacokinetic investigations, resulting in the formation of the hydroxylated form of Erlotinib **(5)**, which exhibited a potent action with an IC_{50} value of 0.001 μM. The efficacy of Naproxen was found to be superior when positioned at the C-6 position compared to the C-7 position[90] **(Figure 7).**

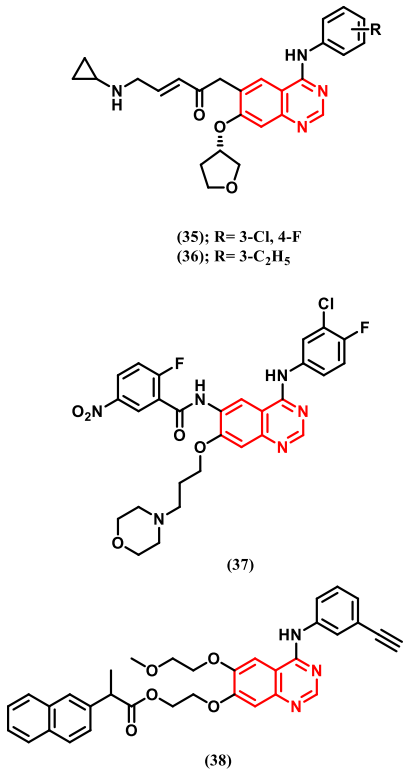


Figure 7. Quinazoline derivatives (**35-38**) as mutant EGFR TKIs.

Furthermore, compound **(39)**, bearing 3-chloro-4-(3-fluorophenoxy)aniline moiety, exhibited a highly effective inhibitory action against EGFR[91]. Its IC_{50} values were 7 nM and 9.3 nM when tested on two cell lines with mutant $EGFR^{wt}$ and $EGFR^{T790M}$, respectively **(Figure 8).**

Also, derivatives of cinnamic acid-substituted anilinoquinazoline were synthesized to inhibit mutant EGFR[92]. The substitution at the 3-position of the aniline ring with either bromine or chlorine

leads to a notable inhibitory action against mutant EGFR, as shown in compounds **(40)** and **(41)**. They exhibited IC_{50} values of 0.12 µM and 0.19 µM, respectively. The standard Erlotinib had an IC_{50} value of 0.03 µM. Additionally, they had IC_{50} values of 0.33 µM and 0.49 µM, respectively, against the A431 cancer cell lines[92]. The investigation of the SAR showed that *meta*- or *ortho*-substituted rings exhibited greater potency than the para-substituted derivatives **(Figure 8).**

Furthermore, the compound **(42)** containing 4-chloro-6-ureidoquinazoline moiety exhibited significant inhibitory action against mutant EGFR in many cell lines, including EKVX, NCI-H322M, A498, TK-10, and MDA-MB-468. The inhibitory activities were observed with IC_{50} ranging from 0.37 to 1 µM[93] **(Figure 8).**

In a separate study, Zhang *et al.* synthesized anilinoquinazoline **(43)** featuring a substitution at the 4-aryl-amino position and a furan-2-yl substitution at the 6-position[94]. It exhibited an inhibitory action against mutant EGFR, with an IC_{50} value of 5.06 nM. The molecular modeling analysis elucidated that the binding interaction of this derivative closely resembled that of Erlotinib **(5) (Figure 8).**

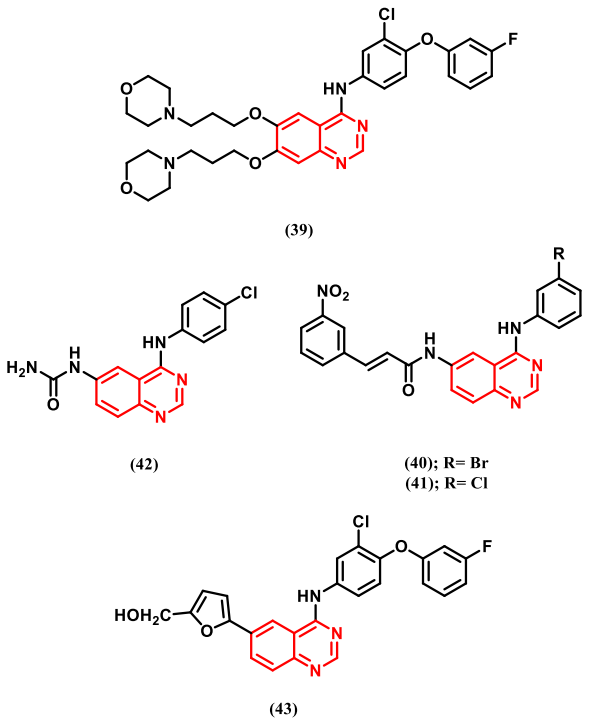


Figure 8. Quinazoline derivatives (**39-43**) as mutant EGFR TKIs.

2.1.6. Structural activity relationship studies (SAR) of quinazoline as EGFR TK inhibitors

The Structural activity relationship of quinazoline derivatives as EGFR TKIs can be summarized in the following[94] **(Figure)**:

1. The presence of a 4-anilinoquinazoline compound with substitution at either the C-6 or C-7 positions is a necessary pharmacophoric group for inhibiting EGFR function. Common TKIs, such as Gefitinib **(4)**, Erlotinib **(5)**, and other commercially available anticancer drugs, demonstrate these structural criteria.
2. The aniline ring's presence of electron-withdrawing groups, such as fluoro, bromo, chloro, and ethylene, confers a favorable impact on the anti-proliferative activity.
3. The quinazoline compounds with a 3-bromo substitution exhibited significant efficacy.
4. The quinazoline molecules, substituted with 3-chloro-4-fluoro-aniline, exhibited substantial activity levels.
5. Altering the 4-position aniline moiety with different groups reduced the activity.
6. The electron-donor groups at the 6 and/or 7 positions enhanced the quinazoline system's N1 and N3's ability to attach to the binding pocket.
7. The quinazoline moiety's propoxy linker at the C-6 and/or C-7 exhibited greater activity than the methoxy group.
8. The quinazoline moiety's dioxygenated groups at positions 6 and 7 increased the cytotoxic activity.
9. Quinazoline's 6-position Michael addition group causes an irreversible binding to the receptor site combating mutant EGFR versions.

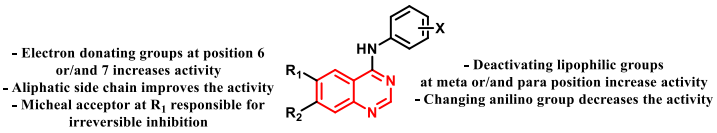


Figure 9. SAR of quinazoline as EGFR TKIs.

2.2. Quinazoline as multi-targeted small molecules.

2.2.1. Overview of multi-targeted anticancer agents

Indeed, the use of multi-targeted medications has been a longstanding practice within clinical settings, sometimes referred to as "Cocktail Therapy" which is a combination of numerous medications, sometimes referred to as "multi-component drugs" which encapsulates two or more drugs in one tablet[95]. This method has shown favorable therapeutic benefits in many clinical studies[96].

Despite the potential for achieving poly-pharmacological effects, implementing these strategies is challenging. These challenges include the arduous and time-consuming process of determining the appropriate combinations and timing of therapies, the complexities associated with controlling the bio-distribution parameters and pharmacokinetics of individual drugs, the potential for interactions between different drugs resulting in undesirable side effects, and the issue of poor patient tolerance. In an alternative approach, synthesizing a singular chemical compound, including a mixture of drugs targeting numerous cancer-related receptors or pathways, may provide a viable solution to address the abovementioned challenges. In recent years, there has been significant interest in a class of drugs referred to as "single molecule multiple targets," "multiple ligands," or "hybrid" anticancer treatments[97, 98].

In contrast to cocktail and multi-component medications, multiple ligands provide distinct advantages, including reduced of potential drug interactions, streamlined drug metabolism, enhanced drug transport, and decreased costs associated with pharmacological research and development. These characteristics render them potentially favorable candidates for the future identification of novel anticancer therapeutics. Indeed, several pharmaceuticals now used in clinical settings can interact with various ligands while not being intentionally developed for this purpose[96].

2.2.2. Quinazoline as EGFR/VEGFR dual inhibitors

2.2.2.1. Overview of VEGFR

Aberrant angiogenesis may be regarded as a fundamental need for advancing tumors and their subsequent spread to other body parts. Numerous extant evidences have substantiated the capacity of various extracellular, cell surface, and intracellular substances to exert direct or indirect regulatory control on the process of angiogenesis[99-101]. The relevance of angiogenesis lies in the interplay between vascular endothelial growth factors (VEGFs) and membrane receptors (VEGFRs), including the tyrosine kinase domain (VEGFR TK), particularly in the context of their role in promoting blood vessel formation[102, 103].

The VEGF gene family has at least seven members, including VEGF-E, produced from viral genomes. Conversely, depending on the specific vertebrate species, the VEGFR gene family consists of three to four members[104, 105]. Vascular endothelial growth factor A (VEGF-A) and its corresponding receptors, VEGFR-1 and VEGFR-2, are known to significantly influence healthy and pathological angiogenesis processes, including forming blood vessels in tumors[106, 107]. VEGF-C/D and its corresponding receptor, VEGFR-3 have been shown to exert regulatory control over angiogenesis during the first stages of embryonic development[108]. However, their primary role is mostly associated with the important regulation of lymph angiogenesis[109].

In the past decade, there has been significant progress in the development and widespread use of anti-VEGF-VEGFR medicines, including an anti-VEGF-A neutralizing antibody and multi-kinase inhibitors. These drugs have been mostly employed in managing prominent solid tumors[110]. The therapeutic effectiveness of these medications has been thoroughly assessed, yet none provide full treatment for individuals with cancer. Extensive investigation into the molecular mechanisms behind tumor refractoriness and the development of resistance to therapeutic agents is required to advance the development of more efficacious anti-angiogenic treatments[111].

Vandetanib **(44)**, also known as Caprelsa, ZD6474, is a chemical compound in the class of 4-aminoquinazoline derivatives[112]. Vandetanib **(44)** has significant potency as a selective inhibitor of tyrosine kinases VEGFR and EGFR[113, 114]. In 2011, the FDA approved the use of Vandetanib **(44)** as a therapeutic intervention for adult individuals diagnosed with metastatic thyroid cancer[115]. It is generally well-tolerated and considered a relatively safe drug. Adverse effects may be minimized by reducing the dosage and implementing frequent monitoring. Additionally, it has been shown that it has the potential to extend progression-free survival (PFS)[116] **(Figure 10).**

Cediranib **(45)**, also known as Recentin or AZD2171, is a quinazoline derivative that belongs to the indole-ether class of compounds[117]. Cediranib **(45)** is a very effective inhibitor of VEGFR tyrosine kinase, demonstrating significant efficacy against a range of solid tumors[118, 119]. It is primarily prescribed for the treatment of individuals diagnosed with advanced non-small cell lung cancer (NSCLC), hepatocellular carcinoma (liver cancer), and advanced colorectal cancer[120-122]. A phase III clinical trial is being conducted to investigate the efficacy of combination therapy with Cediranib **(45)** in treating ovarian cancer. The inclusion of Cediranib **(45)** has shown promise in the therapeutic intervention, resulting in an extension of PFS[123] **(Figure 10).**

Sorafenib **(46)**, or BAY 43–9006 or Nexavar, is a unique orally administered kinase inhibitor that effectively targets several tyrosine kinases *in vivo* and *in vitro*[124]. Sorafenib **(46)** received fast-track approval from the FDA for treating advanced renal cell carcinoma and hepatocellular cancer[125]. Additionally, it has shown favorable clinical efficacy in the context of thyroid cancer[126]. Several clinical studies have been conducted to further explore the effectiveness of Sorafenib **(46)** as a standalone therapy or in combination with other therapies for the management of different types of tumors[127-130] **(Figure 10).**

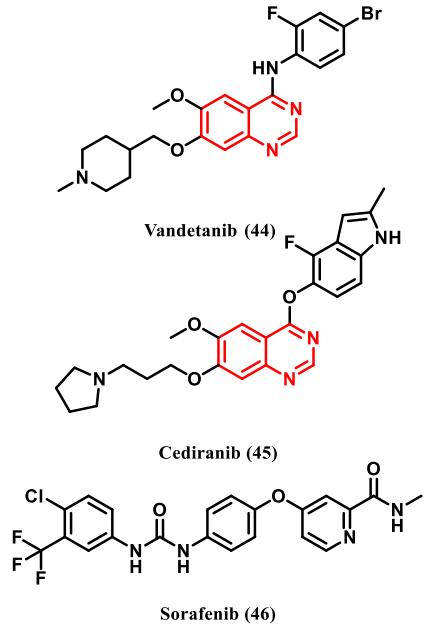


Figure 10. VEGFR inhibitors.

2.2.2.2. Cross-talk between EGFR and VEGFR in in tumor survival and angiogenesis

The first link between EGFR activity and VEGF expression was documented two decades ago. This discovery included the observation that two EGFR ligands, namely epidermal growth factor (EGF) and transforming growth factor alpha (TGFα), induced the production of VEGF in both glioma cells and hyperproliferative keratinocytes[131, 132]. EGFR regulates the production of VEGF *via* the activation of the MAPK and PI3K signaling pathways, as well as the involvement of three distinct transcription factors: signal transducer and activator of transcription 3 (STAT3), second component 1 (Sp1), and hypoxia-inducible factors (HIFs)[133].

The transcription factor known as STAT3 can directly bind to a specific location within the promoter region of the VEGF gene. The activation of STAT3 may occur by direct stimulation by the Src and JAK tyrosine kinases, as well as through the membrane-associated EGFR[134, 135].

Moreover, the promoter region of the VEGF gene also harbors a specific binding motif for the transcription factor known as Sp1, which is known to be activated by signaling mediated by EGFR[136]. Gefitinib **(4)**, an EGFR TKI, has been seen to lower the phosphorylation levels of Sp1[136]. This reduction in phosphorylation leads to a decrease in the affinity of Sp1 for the VEGF promoter, ultimately reducing the production of VEGF[137].

Furthermore, VEGF is primarily controlled by HIFs under hypoxic conditions[138]. Notably, a significant association was found between the levels of EGFR and HIF-1α in tissue samples

obtained from individuals diagnosed with non-small cell lung cancer (NSCLC). This finding implies that EGFR could have a regulatory role in producing HIF-1α or vice versa[139].
One further connection between EGFR and VEGFR is that the activation of oncogenes or the absence of suppressors of oncogenes hinders the down-regulation of VEGF by inhibitors of EGFR[140-143]. The ability of cetuximab to reduce the production of VEGF in tumor cells in both normal oxygen conditions and low oxygen conditions is, to some extent, achieved through decreasing the levels of HIF-1α protein. The increased production of HIF-1α due to genetic disorder effectively inhibits the down-regulation of VEGF and imparts resistance to apoptosis produced by cetuximab[136, 144].

2.2.2.3. Examples of quinazoline derivatives as EGFR/VEGFR dual inhibitors

Suppressing the signaling pathway, including EGFR and VEGFR-2, has emerged as a compelling approach to developing novel anti-proliferative pharmaceutical agents. Letícia and colleagues developed a set of 2-chloro-4-anilino-quinazoline derivatives that exhibited strong inhibitory activity against both EGFR and VEGFR[145]. The majority of the compounds exhibited significant dual inhibitory action against both kinases. The most powerful compound in the series was compound **(47)**, which possessed substitution with a methoxy group at positions 6 and 7 of the quinazoline ring. Compound **(47)** exhibited potent inhibitory action against EGFR and VEGFR-2 tyrosine kinases, with IC_{50} values of 0.90 µM and 1.17 µM, respectively[145] **(Figure 11).**
Also, H. Zhang *et al*. discovered a series of 4-anilinoquinazoline, which includes a biaryl urea tail. These derivatives significantly inhibited EGFR and VEGFR-2 tyrosine kinases, demonstrating their potential as dual inhibitors[146]. Compounds **(48)** and **(49)** had the highest inhibitory activities within the series against EGFR and VEGFR-2 tyrosine kinase. Derivative **(49)** had significant inhibitory efficacy, as shown by its IC_{50} value of 1 nM against EGFR kinase and IC_{50} of 79 nM against VEGFR-2 kinase[146] **(Figure 11).**
Sun *et al*. documented the discovery of derivatives of quinazoline molecules that bear Sorafenib **(46)**, resulting in a very effective dual inhibitor of EGFR and VEGFR-2 tyrosine kinase[147]. The majority of compounds had significant dual inhibitory action. Compounds **(50)** and **(51)** had the highest inhibition values within the series, demonstrating exceptional dual inhibitory action that was almost equivalent in potency to Sorafenib **(46)**. Compound **(50)** demonstrated an IC_{50} value of 20 nM against EGFR kinase and 50 nM against VEGFR-2 kinase. At the same time, compound **(51)** presented an IC_{50} value of 10 nM against EGFR kinase and 80 nM against VEGFR-2 kinase. The results of further investigations on compounds **(50)** and **(51)** had shown significant potential as anti-proliferative agents compared to Sorafenib **(46)** against B16, HCT116, and MCF-7cell lines. The reported IC_{50} values for these compounds ranged from 5.57 to 17.72 µM. Compound **(51)** had enhanced potency as a dual inhibitor of EGFR and VEGFR-2 kinase. It demonstrated significant anti-proliferative activity against BT16, with an IC_{50} value of 5.57 µM compared to Sorafenib **(46)**, which had an IC_{50} value of 9.29 µM[147] **(Figure 11).**
Furthermore, Zhang and his co-workers reported the discovery of effective dual inhibitors of EGFR and VEGFR-2 tyrosine kinases in the form of derivatives of 4-anilinoquinazoline[148]. The compounds were structurally intended to resemble Vandetanib **(44)**, a dual inhibitor that has been clinically authorized. This was achieved by conjugating diaryl amide derivatives. The compounds were subjected to *in-silico* analysis using molecular docking research to investigate their interaction with the ATP binding site of EGFR and the binding site of VEGFR-2. Most compounds demonstrated significant inhibitory action against EGFR and VEGFR-2 and effective anti-proliferative activity against certain cancer cell lines. Derivative **(52)** had the highest level of efficacy against EGFR kinase, as seen by its IC_{50} value of 0.13 µM, and it demonstrated an IC_{50} value of 0.56 µM against VEGFR-2 kinase. It exhibited notable anti-proliferative activity, as shown by its IC_{50} values of 31.26 µM and 39.02 µM against HT-29 and MCF-7 cancer cell lines, respectively. Compound **(52)** has considerable promise as a dual-acting inhibitor, suggesting the potential for its optimization to provide a new and more potent inhibitor of EGFR/VEGFR-2[148] **(Figure 11).**
Also, Bang *et al.* reported derivatives of 4-anilinoquinazoline that exhibited strong inhibitory effects on both EGFR and VEGFR-2 tyrosine kinase enzymes[149]. Compound **(53)** was identified as the most effective member of the series, exhibiting an IC_{50} value of 2 nM against EGFR kinase and an IC_{50} value of 103 nM. The inhibitory effect of compound **(53)** was assessed against mutant EGFR kinase, yielding good results. It exhibited an IC_{50} value of 11 nM against $EGFR^{T790M}$ and an IC_{50} value of 3 nM against mutated $EGFR^{T790M/L858R}$. It also exhibited significant inhibitory action against certain human cancer cell lines, namely A431 and HUVEC, with IC_{50} values of 14 nM and 93 nM, respectively. This powerful compound demonstrated a promising dual-acting characteristic, indicating its potential for future research to get a more effective dual inhibitor[149] **(Figure 11).**

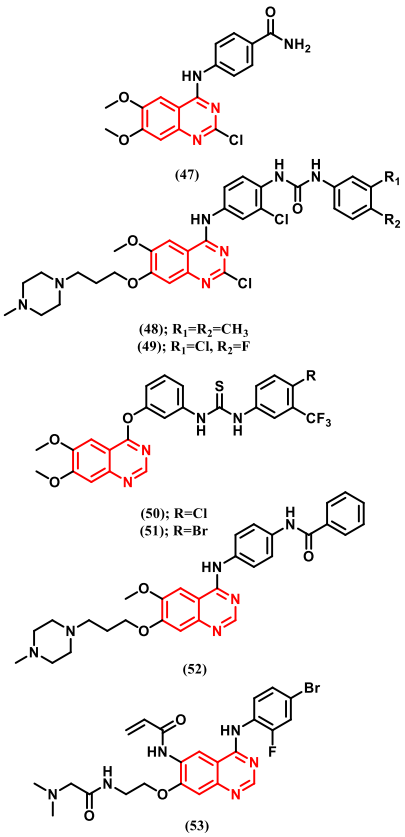


Figure 11. Quinazoline derivatives (**47-53**) as EGFR/VEGFR dual inhibitors.

2.2.3. Quinazoline as EGFR/HDAC dual inhibitors

2.2.3.1. Overview of HDAC

Vincent Allfrey first identified histone deacetylases (HDACs) as a category of enzymes capable of removing acetyl groups from histones[150]. HDACs are categorized into four classes, namely Class I (HDAC-1, 2, 3, and 8), Class II (HDAC-4, 5, 6, 7, 9, and 10), Class III (SIRT protein 1–7), and Class IV (HDAC-11), based on their homologous sequence and subcellular location[151, 152]. All HDACs are enzymes that rely on the presence of Zn^{+2} ions for their activity, except Class III HDACs, which rely on NAD^{+} and do not need Zn^{+2} ions[153].

These enzymes exhibit heightened expression levels in various types of human cancers and play significant roles in essential biological processes, including DNA damage repair, transcriptional regulation, cell cycle control, autophagy, and stress response mechanisms. Additionally, these enzymes are involved in deacetylating histone and non-histone residues. Consequently, these substrates have garnered considerable attention as promising targets for cancer therapeutics[154-156]. Therefore, significant interest has been in developing small-molecule HDAC inhibitors throughout the last decade. At present, there exist four HDAC inhibitors that have received approval from the Food and Drug Administration (FDA) to treat cancer. These inhibitors are known as Panobinostat **(54)**, Vorinostat (SAHA) **(55)**, Belinostat (PXD-101) **(56)**, and Tucidinostat (HBI-8000) **(57)** [157-160] **(Figure 12).**

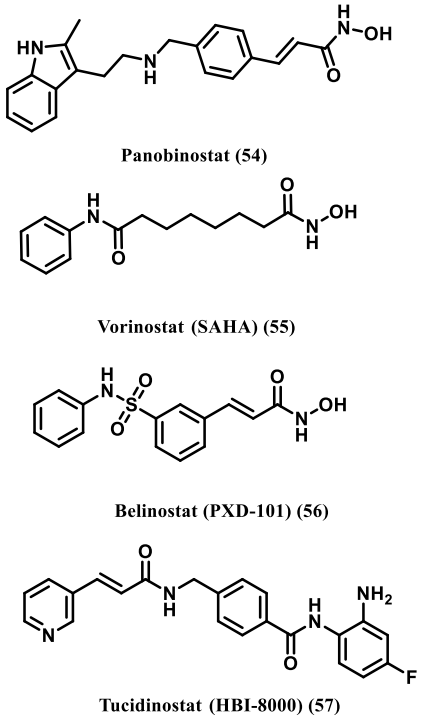


Figure 12. HDAC inhibitors.

2.2.3.2. Examples of quinazoline derivatives as EGFR/HDAC dual inhibitors

The significance of HDAC inhibitors in halting cellular development, differentiation, and death has led to a growing interest among drug discovery researchers in the combined inhibition of HDAC and EGFR. Multiple studies have shown evidence of the effective development of dual inhibitors that combine the pharmacophores of HDAC and EGFR inhibitors. These studies have yielded hybrid derivatives that exhibit potent anti-proliferative action.

In this direction, Mahboobi *et al.* developed dual inhibitors targeting HDAC and EGFR[161]. Their approach combined the pharmacological effects of inhibiting the HDAC enzyme (Class I/II) with the inhibition of EGFR TK. The research team used hydroxamic acid as the hydrophobic area responsible for binding to zinc in HDAC inhibitors. This motif was combined with the 4-amino-substituted quinazoline pharmacophore to create the intended chimeric scaffolds. Due to its known role as an EGFR inhibitor, Lapatinib **(6)** was chosen as the foundational structure for developing dual inhibitors. The obtained chimeric derivatives were evaluated for their inhibitory activity against HDAC and EGFR.

Additionally, EGFR overexpressing cancer cell lines were used to assess the cytotoxicity of these derivatives. Two hybrid derivatives, namely compounds **(58)** and **(59)**, had been determined to have superior selectivity and efficacy in inhibiting HDAC and EGFR with IC_{50} for HDAC 6 of 230 nM and 86 nM, respectively and IC_{50} for EGFR TK of 25 nM and 18 nM, respectively. In the experiment conducted with CAL head and neck cancer cell lines, compound **(59)** demonstrated a simultaneous inhibitory effect on EGFR and an elevation of histone H3 acetylation[161] **(Figure 13).**

The same group developed another set of dual inhibitors targeting HDAC class I and II enzymes and EGFR kinase[162]. While maintaining the same pharmacological targets as previously documented, the researchers opted for Erlotinib **(5)** instead of Lapatinib **(6)**. They combined it with the benzamide motif in existing HDAC inhibitors to produce the chimeric inhibitors. Subsequent examination of the biological efficacy of the resultant hybrids demonstrated that derivatives **(60)** and **(61)**, wherein the methylene linker spatially separated Erlotinib **(5)** and the benzamide moiety, exhibited discerning inhibition of HDAC class I isoforms. This inhibition effectively targeted both nuclear and cellular HDAC. Notably, these two benzamide compounds demonstrated dual inhibition of HDAC and EGFR with IC_{50} for HDAC 1 of 74 nM and 33 nM, respectively, and IC_{50} for EGFR TK of 41 nM and 78 nM, respectively. In addition to other tumor cell lines, with IC_{50} values in the micromolar range[162] **(Figure 13).**

Furthermore, to overcome the constraints associated with cancer treatment, Cai *et al.* synthesized a series of HDAC/EGFR inhibitors with multiple modes of action[163]. Their investigation developed CUDC-101 **(62)**, a highly effective compound derived from quinazoline-based anti-cancer drugs. CUDC-101 **(62)** combines the pharmacophore responsible for HDAC inhibition with EGFR, yielding a potent hybrid derivative **(Figure 13).**

CUDC-101 **(62)** has been subjected to phase-I clinical studies to assess its efficacy in treating solid tumors and head and neck squamous cell carcinoma. Additionally, it has shown potential for inhibiting tumor growth in many cancer types, including breast, non-small cell lung, liver, head and neck, and pancreatic cancers.

It showed significant inhibition of HDAC-6 and EGFR with IC_{50} of 4.4 nM and 2.4 nM, respectively[163] **(Figure 13).**
Furthermore, Ding *et al.* produced hybrid derivatives by combining pharmacophores from multi-kinase inhibitors with the HDAC inhibitor Vorinostat **(55)**[164]. The researchers used a triazole linker to attach Vorinostat **(55)** to the kinase inhibitor. Subsequent inhibition experiments demonstrated that the resultant fusion hybrids had distinct selectivity profiles compared to their respective parent compounds or solo inhibitors. It is worth mentioning that compound **(63)** exhibited remarkable suppression of EGFR, with an IC_{50} value of 10.3 nM. Additionally, it had inhibitory effects on HDAC1 and HDAC6, with IC_{50} values of 1.1 and 4.3 nM, respectively[164] **(Figure 13).**

2.2.4. Quinazoline as multi targeted therapy EGFR inhibitors combined with other targets

2.2.4.1. Quinazoline as EGFR/CDK-2 inhibitors

Cyclin-dependent kinase 2 (CDK-2), a tyrosine kinase, has been shown to exhibit significant regulation of cell cycle progression and transition. It plays crucial roles in gene transcription, phosphorylation of cell cycle proteins, and DNA replication[165]. Numerous studies in the field of scientific research have shown the efficacy of CDK-2 inhibitors in conferring advantageous outcomes in the context of several malignancies, including breast cancer, colorectal cancer, and melanoma[166-168]. The advantages mentioned above prompted researchers to develop innovative anti-proliferative medications that might function as modulators of CDK-2, hence maintaining proper cell cycle regulation. This is particularly crucial when inadequate resistance to CDK-2 inhibitors has been documented[169].

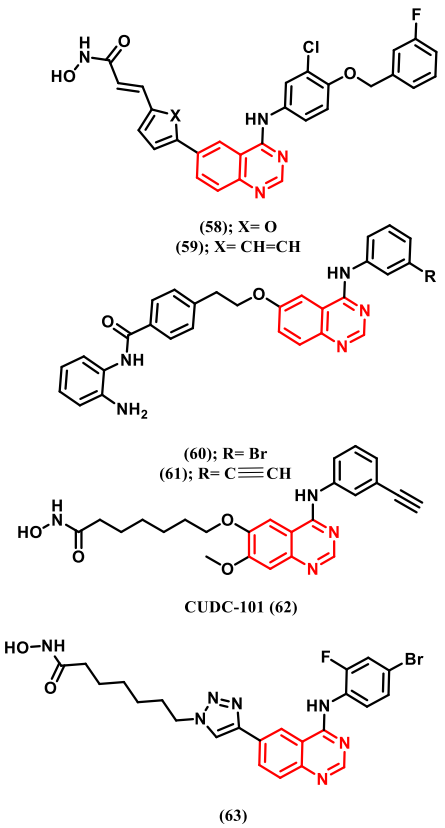


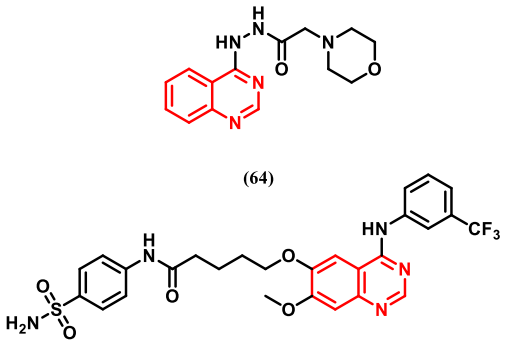
Figure 13. Quinazoline derivatives (**58-63**) as EGFR/HDAC dual inhibitors.

Recent studies reported that the designing of molecules exhibited significant anticancer effects due to the combined mechanisms of action of multiple types of tyrosine kinase inhibitors, such as EGFR and CDK-2 inhibitors. This synergistic effect is expected to lead to improved pharmacological outcomes regarding tumor suppression while minimizing the development of resistance.
In a recent study, 4-aminoquinazoline derivatives were designed, synthesized, and evaluated as EGFR/CDK-2 inhibitors for their anti-proliferative activity[170]. Derivative **(64)** of this series exhibited a significant inhibitory effect against EGFR and CDK-2, with IC_{50} values of 93 nM and 143 nM, respectively. These findings were comparable to the inhibitory activity of Lapatinib **(6)** and Ribociclib, which had IC_{50} values of 30 nM and 67 nM, respectively. Also, it exhibited notable efficacy and a wide range of effectiveness against multiple types of cancer cell lines, including leukemia K-562, non-small cell lung cancer NCI-H522 cells, colon cancer SW-620, melanoma LOX IMVI and MALME-3M, renal cancer RXF 393 and ACHN, and breast cancer MDA-MB231/ATCC. The growth inhibition percentages for these cell lines were 99.6%, 161%, 126.03%, 90.22%, 174.47%, 139.7%, 191%, and 97%, respectively [170] **(Figure 14).**

2.2.4.2. Quinazoline as EGFR/CAIX inhibitors

Oxygen is essential for cellular development, but its availability is typically reduced in solid tumors, particularly in the central region of the tumor mass. This is mostly due to the rapid proliferation of tumor cells, which outpaces the growth of endothelial cells that play a critical role in blood vessel construction[171, 172]. Tumorous cells in hypoxic zones significantly promote heightened invasion, metastasis, and resistance to therapeutic interventions[173]. The regulation of gene expression, such as the carbonic anhydrase IX (CAIX) gene, may be influenced by hypoxia. This is achieved by binding the hypoxia-inducible factor HIF-1α to a specific region known as the hypoxia-responsive element inside the gene. The presence of membrane-bound carbonic anhydrase IX (CAIX) plays a significant role in the acidification of the tumor microenvironment. This is achieved by its effective catalysis of converting carbon dioxide to bicarbonate and protons, resulting in the acquisition of metastatic characteristics and resistance to weakly basic anticancer medications[173, 174].
Consequently, several efforts have been undertaken to develop efficacious inhibitors of carbonic anhydrase IX (CAIX) as therapeutic agents against tumors. A recent study has shown the correlation between hypoxia-induced gene transcription involving HIF-1α and CAIX, and the expression of EGFR in cells experiencing hypoxia[175, 176]. Research findings have shown that the signaling of EGFR amplifies the physiological response to hypoxia, hence functioning as a factor that promotes cell survival[177]. Therefore, targeting the suppression of hypoxia-induced gene transcription might be a promising therapeutic approach to overcome the tumor resistance associated with EGFR TKI.
Zhang and his team in 2021 reported a set of sulfamoylphenyl-quinazoline derivatives as potential EGFR/CAIX dual inhibitors[178]. Compound **(65)** exhibited more cytotoxicity against H1975 cells compared to Osimertinib when tested under hypoxic conditions, as shown by its lower IC_{50} value of 1.05 μM compared to Osimertinib's IC_{50} value of 2.08 μM. It also showed a significantly higher potency in inhibiting the $EGFR^{T790M}$ enzyme compared to Gefitinib **(4)**, with an IC_{50} value of 9.2 nM if compared to IC_{50} of Gefitinib **(4)** 378.4 nM. Specifically,

compound **(70)** exhibited about 41-fold more efficacy in inhibiting the $EGFR^{T790M}$ enzyme when compared to Gefitinib **(4)**. Under hypoxic conditions, compound **(65)** had a significant inhibitory impact on the expression of CAIX in H1975 cells, with an IC_{50} value of 115 nM. It also efficiently suppressed the expression of HIF-1α, which is upstream of CAIX in the cellular pathway[178] **(Figure 14).**



(64)

(65)

Figure 14. Quinazoline derivatives (**64**) and (**65**).

2.2.4.3. Quinazoline as EGFR/Tubulin polymerization dual inhihibtors

Microtubules are cellular polymers in all cells and have a wide range of functions, including maintaining cell shape, facilitating protein transport, ensuring proper distribution of chromosomes during cell division, and enabling the process of mitosis[179]. Microtubules are long and hollow structures comprising two globular protein subunits, α- and β-tubulin. Microtubules Targeting Agents (MTAs) can be categorized into two classes: microtubule destabilizing agents and microtubule stabilizing agents[180]. MTAs can interfere with at least three tubulin binding sites, including taxane, vinca alkaloid, and colchicine [181]. Inhibitors that selectively bind to the colchicine binding site exhibit several advantages compared to those binding to the other two sites. These advantages include simpler molecular structures, enhanced solubility in aqueous environments, diminished toxicity, and reduced potential for multidrug resistance (MDR) effects[182]. Combining EGFR TK with tubulin polymerization inhibitors pharmacophores together in the same molecule addresses pathway redundancy and tumor heterogeneity, among other resistance mechanisms, and reduces MDR problems[183, 184].

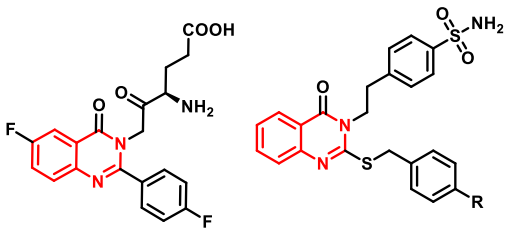
Zayed and his coworkers reported a set of quinazolinone-amino acid hybrids as dual inhibitors of EGFR and tubulin polymerization[185]. Compound **(66)** showed very strong activity against MDA-MBA-231 cancer cell lines with IC_{50} = 0.43 µM. Also, it inhibited EGFR at IC_{50} of 545 nM and tubulin polymerization at IC_{50} of 6.24 **(Figure 15).**

2.2.4.4. Quinazoline as EGFR/HER2/CDK-9 inhibitors

As mentioned above, the human epidermal growth factor receptor (HER), also known as HER/ErbB, is a group of tyrosine kinase transmembrane receptors. This receptor family has many members, such as EGFR (HER1), HER2, HER3, and HER4[186]. These protein kinases are crucial in various physiological cellular processes, including proliferation, survival, differentiation, and migration[187]. Moreover, the involvement of kinase receptors is crucial in abnormal cell proliferation, characterized by the excessive expression and insufficient inhibition of various tumor cells in humans. EGFR and HER2 overexpression has been seen in various cancer cell lines, including ovarian, prostate, colon, and breast cancer[188, 189]. The HER/ErbB family's molecular pathway hinders crucial cancer prevention measures due to its competitive inhibition of receptor binding sites or tyrosine kinase inhibitors (TKIs) targeting the HER/ErbB family[190]. Therapeutic medicines, including Gefitinib **(4)**, Erlotinib **(5)**, Lapatinib **(6)**, Afatinib **(8)**, and several other quinazolines, function as inhibitors of the HER/ErbB family[191].

On the other hand, Cyclin-dependent kinases (CDKs) have a critical role in regulating both the cell cycle, namely subtypes 1–4 and 6, and cell transcription, including subtypes 5, 7–9. CDK9, in conjunction with cyclin T1 coenzyme, plays a crucial role in regulating mRNA polymerase II (Pol II) by facilitating the assembly of the positive transcription elongation factor b (P-TEFb) complex. The P-TEFb complex plays a crucial role in regulating cellular transcription via phosphorylation of the C-terminal domain of RNA polymerase II[192, 193]. As a result, the inhibition of CDK9 hinders the regulatory mechanisms involved in RNA production and the proliferation of tumors[194]. The overexpression of the CDK9 enzyme is often seen in several types of tumors, such as leukemia, malignant melanoma, hepatocellular carcinoma, ovarian cancer, and different hematological malignancies[195, 196].

In 2020, El-Azab and his coworkers reported a series of quinazoline derivatives based on a benzenesulfonamide scaffold for their multi-targeted mechanisms as anti-cancer agents[197]. Derivatives **(67)** and **(68)** bearing benzyl moiety showed promising results as multi-target anticancer inhibitors. They successfully inhibit EGFR at IC50 of 90 nM and 145 nM, HER2 at IC50 of 131 nM and 127 nM, respectively, and CDK-9 at IC50 of 67 nM and 117 nM. Compound **(67)** underwent evaluation in a comprehensive NCI 59-cell line panel experiment utilizing a concentration of 10 µM. In comparison to the reference drug Imatinib (PCE = 20/59), the examined cell lines had notable antitumor activity, exhibiting positive cytotoxic effects (PCE) of 29/59[197] **(Figure 15).**



(66)

(67); R= H
(68); R= NO_2

Figure 15. Quinazoline derivatives (**66-68**).

3. Conclusion

In recent years, the use of quinazoline and its derivatives as scaffolds has demonstrated significant potential in the field of biomedical research. These compounds have promising biological effects in treating various diseases, including cancer. Notably, quinazoline has shown reduced side effects and enhanced treatment efficacy, making it a compelling candidate for further investigation and development in therapeutic interventions. This review provides a specific focus on small-

molecules targeted therapy. The discussion briefly introduces the epidermal growth factor receptor tyrosine kinase (EGFR TK), its mutations, and the development of new compounds in this area. Particularly, attention is given to the recently reported quinazoline derivatives as EGFR TK inhibitors. Additionally, the review explores the concept of multi-targeted anticancer agents, highlighting the quinazoline-based molecules that possess the ability to inhibit multiple targets, such as EGFR/VEGFR dual inhibitors, EGFR/HDAC dual inhibitors, and other EGFR-connected targets. Finally, quinazoline derivatives with dual or multi-targeted mechanisms of action showed promising and superior advantages in fighting numerous cancer mechanisms and their resistance problems.

Declaration of Competing Interest

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to impact the research presented in this paper.

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