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NOVEL 4-ANILINOQUINAZOLINE DERIVATIVES AS EGFR AND VEGFR-2 INHIBITORS

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ABSTRACT

The 4-anilinoquinazoline has a basic pharmacophore for tyrosine kinase inhibitors activity. The approach of synthesis of the 4-anilinoquinazoline derivative is easy, so a variety of substitutions are possible with their versatile medicinal applications. The derivatives of 4-anilinoquinazoline are designed dual inhibitors of an EGFR and VEGFR-2. EGFR and VEGFR-2 follow the same downstream signalling pathway of inhibition resulting in a synergistic effect. Derivatives of 4-anilinoquinazoline have a wide range of applications in medicinal chemistry like colon cancer, non-small cell lung cancer, prostate cancer and breast cancer. Docking study of the 4-anilinoquinazoline compounds also shows some good interactions with receptors. Now a day, numerous 4-anilinoquinazoline derivatives are available in the market such as gefitinib, dacomitinib, erlotinib and vandetanib. In future, more possible improvements in the activity can be achieved with various pharmacophoric substitutions. In this review, we have highlighted the novel 4-anilinoquinazoline derivatives with their EGFR and VEGFR-2 tyrosine kinase inhibition activity.

KEYWORDS: 4-anilinoquinazoline, EGFR, VEGFR-2, Tyrosine Kinase Inhibitor.

1. INTRODUCTION

Quinazoline is a fused heterocyclic ring known as benzo-l,3-diazines, or 1,3-diazanaphthalene.[1] This heterocyclic ring containing benzene ring fused with a pyrimidine heterocyclic ring with adjacent carbon atoms. Quinazolines have various biological activities such as anti-depressant, anti-microbial, anti-viral, analgesics, anti-oxidant, anti-hypertensive, anti-cancer and anti-tubercular.[2] In the case of anti-cancer activity, particularly EGFR and VEGFR-2 tyrosine kinase inhibitors, the synthesis of 4-anilinoquinazoline derivatives are formed by substituting the 4th position of quinazoline ring via substituted aniline moiety such as gefitinib, erlotinib, avitinib and vandetanib.[3]

The anilinoquinazoline have been used on a large scale as tyrosine kinase inhibitors(TKIs).[4] However, protein tyrosine kinases play an important for all cell signal transduction pathways that regulate cell functions. Numerous tyrosine kinases are present in the cell membranes. They are including epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), human epidermal growth factor receptor (HER) and sarcoma gene/kinase (SRC).[5] From this EGFR is a membrane-bound receptor tyrosine kinase, distributed in epithelial cells, keratinocytes, glial cells, different cell surfaces and involved in various cellular processes. The EGFR family contains four members, ErbB1 or HER1, ErbB2 or HER2, (neu in rodents), ErbB3 or HER3 and ErbB4 or HER4. ErbB1 and ErbB4 are functional receptors, after binding ligands autophosphorylation takes place at the tails region of the C-terminal. ErbB2 has no known ligand but it is favoured dimerization with other EGFRs. ErbB3 has no inherent tyrosine kinase activity. But, it can transfer his signal through the other EGFRs.[6] Ligand bind to the receptors extracellular domain leads to some conformational changes and promoting homodimerization or heterodimerization. Due to dimerization activates, receptor intracellular domain of tyrosine kinase and autophosphorylation takes place. This leads to stimulating a cascade of downstream signalling events.[7] On the other hand, VEGFR is another class of tyrosine kinase receptors. The members of VEGFR are VEGFR-1, VEGFR-2 and VEGFR-3. VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1) regulate angiogenesis and vascular permeability. While VEGFR-3 (Flt-4) regulate lymphangiogenesis.[8] The mechanism of VEGFR starts from angiogenesis. This process begins when tumour cells secrete angiogenic growth factors that stimulate endothelial cells lining nearby vessels. Which activate vascular endothelial growth factor (VEGF) binds to a specific receptor located on endothelial cell lining to the extracellular portion of VEGFR. It is promoting receptor dimerization. This leads to stimulates receptor

intracellular domain of tyrosine kinase and autophosphorylation takes place. This resulted in the downstream signalling pathway.[9]

Both EGFR and VEGFR mechanism pathways are closely related. Now-a-day dual inhibitors are sharing common downstream signalling pathways. So the combined approach prevents resistance and gives a synergistic effect.[10] Combined VEGFR and EGFR inhibitors are evaluated on several preclinical and clinical trials.[8] 4-anilinoquinazoline derivatives are potent inhibitors of both EGFR and VEGFR.[11] The docking study of 4-anilinoquinazoline derivatives shows some important regions. The docking study showed parts that are ATP binding pocket, Sugar pocket, Adenine region, Hydrogen bonding, Hydrophobic pocket, Phosphate region.

In this review, we have briefly discussed 4-anilinoquinazoline derivatives (Figure 1) with their EGFR and VEGFR-2 inhibitors applications.

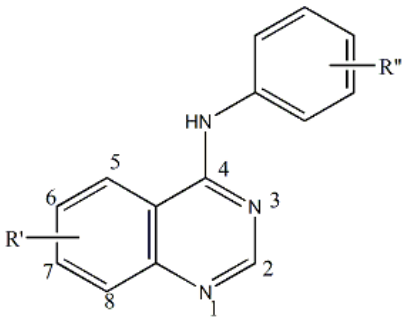

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Figure 1: General Pharmacophore.

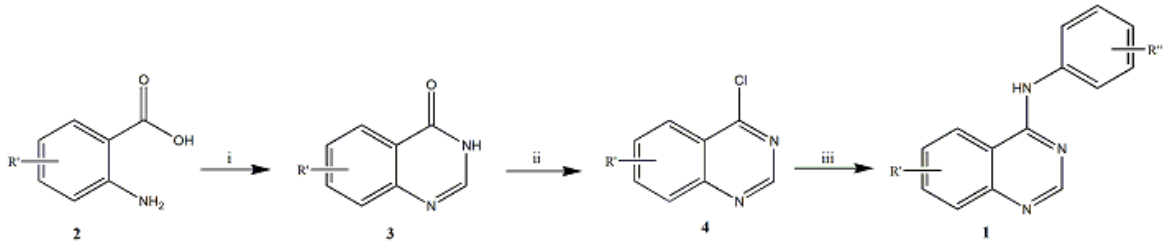
2. SYNTHESIS OF 4-ANILINOQUINAZOLINE DERIVATIVES

The 4-aminoquinazoline derivatives are synthesized by various routes. 4-anilinoquinazoline are synthesized using two methods. First, “One-pot” synthesis via substitution reaction (S_NAr) of 4- chloroquinazolines and second, Dimroth type reactions by multi-steps synthesis.

2.1. Substitution reaction (S_NAr) of 4-chloroquinazoline (Scheme 1)

The starting material for this reaction is used anthranilic acid cyclized with the addition of formamide and form a 4(3H)-quinazolinone**[3]**. The activation of pyrimidine ring for nucleophilic substitution reaction (S_NAr) is carried out by substitution of the electronegative group at 4- position of quinazoline skeleton. 4(3H)-quinazolinone**[3]** is converted into 4-chloroquinazoline**[4]** by chlorination reaction. The one-pot reaction through tandem silylation

of primary amine and quinazoline-4(3H)-ones by hexamethyldisilazane leads to the formation of 4-anilinoquinazoline derivatives in excellent yields.[12],[13]

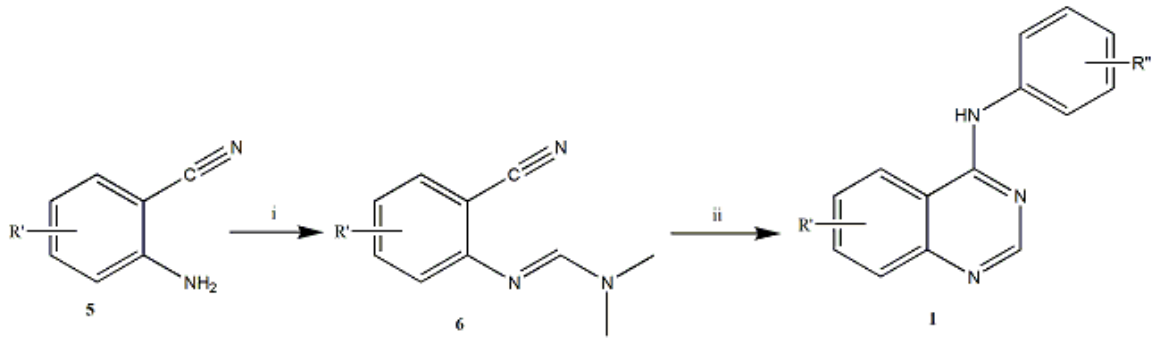


Scheme 1: General synthesis of 4-anilinoquinazoline derivatives from anthranilic acid derivative.

i: $HCONH_2$, heat 4-5hr ; ii: $PCl_5/POCl_3$ heat 24hr; iii: Ph-NH_2, reflux.

2.2 Reaction of aniline with N'-(2-Cyanophenyl)-N, N-dimethylformamidine (Scheme 2)

4-anilinoquinazolines prepared by reacting substituted anilines with N'-(2-Cyanophenyl)-N, N-dimethylformamidine**[6]** using DMF acetal. Heating a solution of formamidine and substituted aniline in acetic acid gave 4-anilinoquinazoline**[1]** derivatives. This rearrangement is called a Dimroth type of rearrangement.[14]

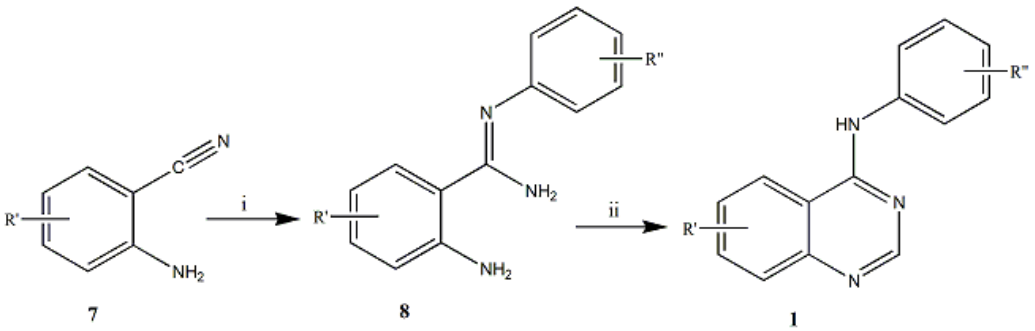


Scheme 2: General synthesis of 4-anilinoquinazoline from N'-(2-Cyanophenyl)-N, N-dimethylformamidine

i: DMF, acetal,100^oC ; ii: Ph-NH_2, HOAc, reflux.

2.3 Reaction of aniline with 2-aminobenzonitrile (Scheme 3)

2-aminobenzonitrile**[7]** reacted with substituted aniline using anhydrous aluminium chloride as a catalyst gave low yields of amidine. For better yield, used 50% anilines and aluminium chloride. Further, 2-amino-N-arylbenzamidines**[8]** and formic acid in hot conditions gave good yields. But, at a slightly basic pH condition (pH 8). Note that only 2-unsubstituted 4-arylaminoquinazoline**[1]** derivatives are prepared by this reaction.[15]

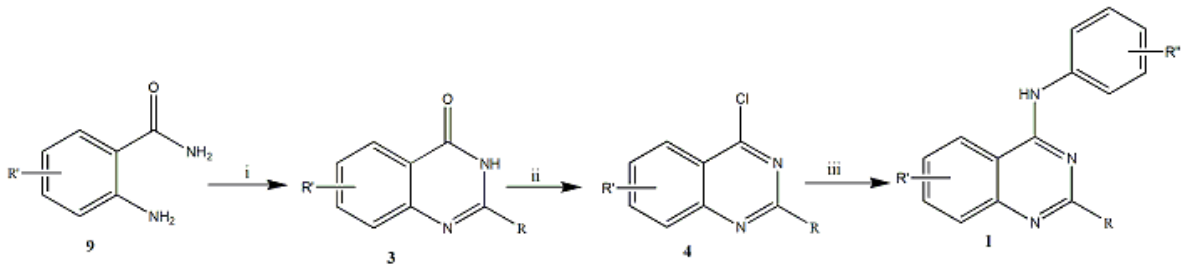


Scheme 3: General synthesis of 4-anilinoquinazoline derivatives from 2-aminobenzonitrile

i: $AlCl_3$, Ph-NH_2, 180-200^oC ; ii: HCO_2H, NaOH, 90^oC, 2hr.

2.4 Reaction of anthranilamide with formic acid (Scheme 4)

In this **scheme 4,** cyclization product 4(3H)-quinazolinones**[3]** was obtained by cyclization using formic acid.[16] 4(3H)-quinazolinone**[3]** is chlorinated using DMF and $POCl_3$ converted into 4-chloroquinazoline**[4]** (Vilsmeier-Haack Reaction). The replacement of the 4-chloro group of 4-anilinoquinazoline via the addition of substituted aromatic amines formed 4-substituted quinazoline.[17]



Scheme 4: General synthesis of 4-anilinoquinazoline derivatives from anthranilamide

i: RCOOH, reflux ; ii: PCl_5/$POCl_3$ heat 24hr ; iii: Ph-NH_2, reflux.

3. 4-ANILINOQUINAZOLINE AS EGFR AND VEGFR-2 INHIBITORS

Receptors at the cell surface are known as transmembrane receptors sink in the plasma membrane of a cell. The biological activity of the proteins is regulated through PTKs by phosphorylation by the transfer of phosphate of Adenosine triphosphate (ATP) towards the hydroxyl group of kinases. Cell migration, cell cycle, cell metabolism and cell proliferation are the activities controlled by RTKs. The ligand-binding domain is attached to the domain of cytoplasm of PTKs that regulates phosphorylation and autophosphorylation. All RTKs are present in monomeric form and after ligand binding, it forms a dimer of these receptors resulting in autophosphorylation.[18]

3.1. EGFR tyrosine kinase inhibitors

EGF is bivalent to EGFR so can drive the dimerization of receptors. EGFR family belongs to the HER receptor tyrosine kinases, EGFR is present in normal epithelial tissues. But, it is not detected in mature hematopoietic cells. When a ligand binds to tyrosine kinase activation takes place and the receptor/ligand complex is incorporated for the destruction of cells, resulting in a down-regulation of surface EGFRs. EGFR has been involved in tumour angiogenesis, a process that is censorious for the growth of tumours beyond minimal size and metastasis. EGFR signal transduction pathways mediate various tumorigenic processes such as cell survival, cell cycle progression, angiogenesis, tumour cell invasion, and metastatic spread.[19]

EGFRTK's inhibitor: The 4-anilinoquinazoline derivatives are divided into three generations.

3.1.1 First-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI's) (Figure 2), (Figure 3)

Gefitinib[Iressa®]: Gefitinib is a selective and reversible EGFR-TKI. It is used for the treatment of non-small-cell lung cancer (NSCLC) patients, it is an improved survival rate with less toxicity(4). Gefitinib inhibits tyrosine kinase by acting upon ATP binding site. More attention is given to EGFR mutation rather than clinical factors, which results in a population with great sensitivity to gefitinib.[20]

Erlotinib[Tarseva®]: Erlotinib has been approved by the USFDA used for NSCLC. It has potent antitumor activity. Erlotinib induces the growth of cells by acting in the G1/S phase of the cell cycle. Erlotinib is the first generation ATP-competitive and reversible EGFR inhibitor effective in most pancreatic cancer harbouring EGFR mutations.[21]

Icotinib: When icotinib is combined with chemotherapy, it can increase the adverse effects of myelosuppression and liver dysfunction. But the adverse effects were tolerable and manageable. Icotinib and pemetrexed were shown a synergistic effect on the cancer cells. The present study was investigated that Icotinib combined with chemotherapy (carboplatin/pemetrexed) can prolong survival rate, give safety in patients with sensitive EGFR mutation.[22]

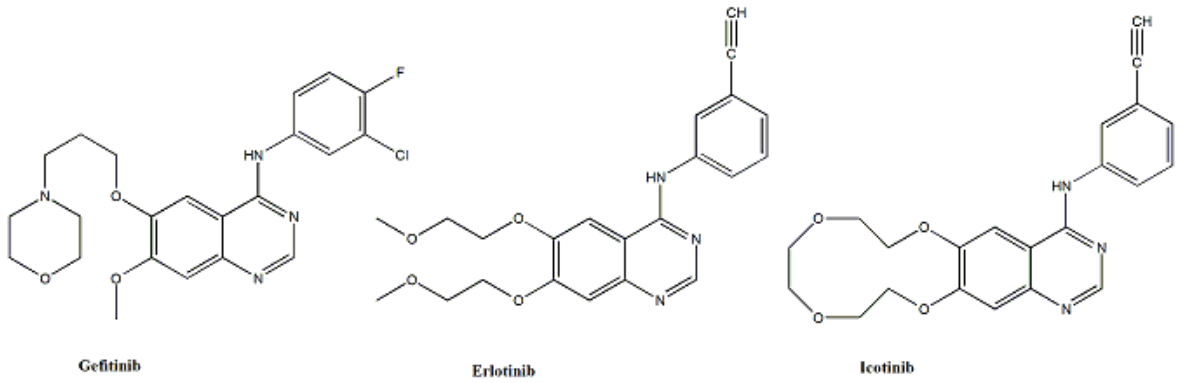


Figure 2: First-generation EGFR-TKIs.

PD153035[10] It is approved by the food and drug administration (FDA). Many 4-anilinoquinazoline TKIs show a limited activity in vivo and are useful in nanomolar concentration in vitro. Therefore, the insertion of solubilizing groups to PD153035 to improve their aqueous solubility and oral bioavailability leads to a strong inhibitor of EGFR (IC_{50} = 25 pM).[9]

Adriana Chilin et al. designed several dioxane, dioxepine and dioxolane quinazoline derivatives. These derivatives were shown biologically active as EGFR inhibitors activity. Further, cytotoxicity was checked against overexpressing and not expressing EGFR cell line and the potency of compounds was compared with reference of PD153035**[10]**. 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay was performed to determine the inhibitory effect on cell proliferation. The accepted derivative of 3'-trifluoromethylaniline substituent **11** binds to the inactive form of EGFR and so gives promising results.[23]

Maria Teresa Conconi et al. reported some novel anilinoquinazoline derivatives with dioxygenated rings. The biphenylamino was substituted as an aniline portion as an EGFR inhibitor. Substitution of dioxygenated ring to quinazoline moiety resulted in compounds **12**, **13**, and **14** with high antiproliferative activity. Molecular modelling study shows that phenyl group interaction reduces steric hindrance of fused dioxygenated ring at 6,7 positions concerning PD153035**[10].**[24]

Alexander J. Bridges et al. synthesized 4-anilinoquinazoline derivatives as EGFR inhibitors. 4-(3-Bromoanilino)-6,7-dimethoxyquinazoline **15** is a very potent inhibitor of tyrosine kinase. A study of inhibitory activity was performed with an IC_{50} value of 0.025 nM.

Compound **16**, 4-(3-bromoanilino)-6,7-diethoxyquinazoline resulted in an IC_{50} of 0.006 nM showing the most potent quinazoline inhibitor of the EGFR TK.[25]

Giang Le-Nhat-Thuy et al. designed and synthesized 4-anilinoquinazoline derivatives. Substituted with dioxygenated ring and triazole compounds. 1,2,3-triazole derivative shows more potent anticancer activities also it can be used for the synthesis of various heterocyclic compounds. He reported a series of novel analogues of **17** compounds with potent cytotoxicity. compound **17** reported the most inhibitory activity up to 100 folds higher than erlotinib against KB, HepG2, and Lu with IC_{50}-values of 0.04 µM, 0.14 µM, and 1.03 µM, respectively.[26]

Sai-Jie Zuo et al. study shows, the design of novel anticancer compounds. Tertiary amine and aryl urea were combined with a 4-anilinoquinazolines scaffold at 6-position for synthesising newly derivatives. Compound **18** derivative shows IC_{50} value for A431 is 1.36 ± 0.04 and for A549 is 0.83 ± 0.11. Furthermore, The antiproliferative activities of compound **18** were determined by MTT (3-[4,5-dimethyl-2-thiazolyl]-2,5-diphenyl2H-tetrazolium bromide) assay against A431 and A549 cells in vitro.[27]

Weijie Hou et al. synthesized and evaluated potent C-6 benzamide substituted quinazoline derivatives as EGFR inhibitors. Compound **19** is a reversible inhibitor of EGFR via autophosphorylation and showed similar activity to gefitinib. New quinazoline derivative **19** with a p-nitro-fluoro-benzamide moiety at the C-6 position demonstrated highly selective inhibitor activity of EGFR.[28]

Min Sun et al. reported oxazine and oxazepine fused quinazoline derivatives. These derivatives were evaluated in vitro inhibition of EGF-induced receptor autophosphorylation in various cancer cell lines. From there, the growth inhibition of compound **20** is compared to gefitinib and erlotinib used as reference compounds resulting in an IC_{50} value is 4.06 times greater than gefitinib and >30.1 times greater than erlotinib. Compound **20** resulted in good EGFR and HER2 in vitro kinase inhibitory activity.[29]

Yaling Zhang et al. reported the synthesis of novel quinazoline-1-deoxynojirimycin hybrids series. It showed inhibitory activities against EGFR-TK and α-glucosidase. From these series compounds, **21** showed more potency to $EGFR^{wt}$-TK with IC_{50} = 1.79 nM and to α-

glucosidase with IC_{50} = 0.39 mM. Compound **21** was the most potent. But, its IC_{50} value was lower than gefitinib (IC_{50} = 3.22 nM).[30]

Zhuo Liu et al. designed and synthesized novel derivatives of acrylamide-substituted quinazolines and their inhibitory activity evaluated against the mutant $EGFR^{T790M}$ enzyme. From these derivatives compounds, **22** was the most active inhibitor only against $EGFR^{T790M}$ (IC_{50} value of 4.3 nM) as compared with gefitinib and rociletinib used as reference drugs. Further, an MTT assay was performed for all these acrylamide-substituted quinazoline derivatives against cancer cell lines (A431WT, HCC827del E746_A750, H1975L858R/T790M, and A549WT and k-ras mutation) for their antiproliferative activity.[31]

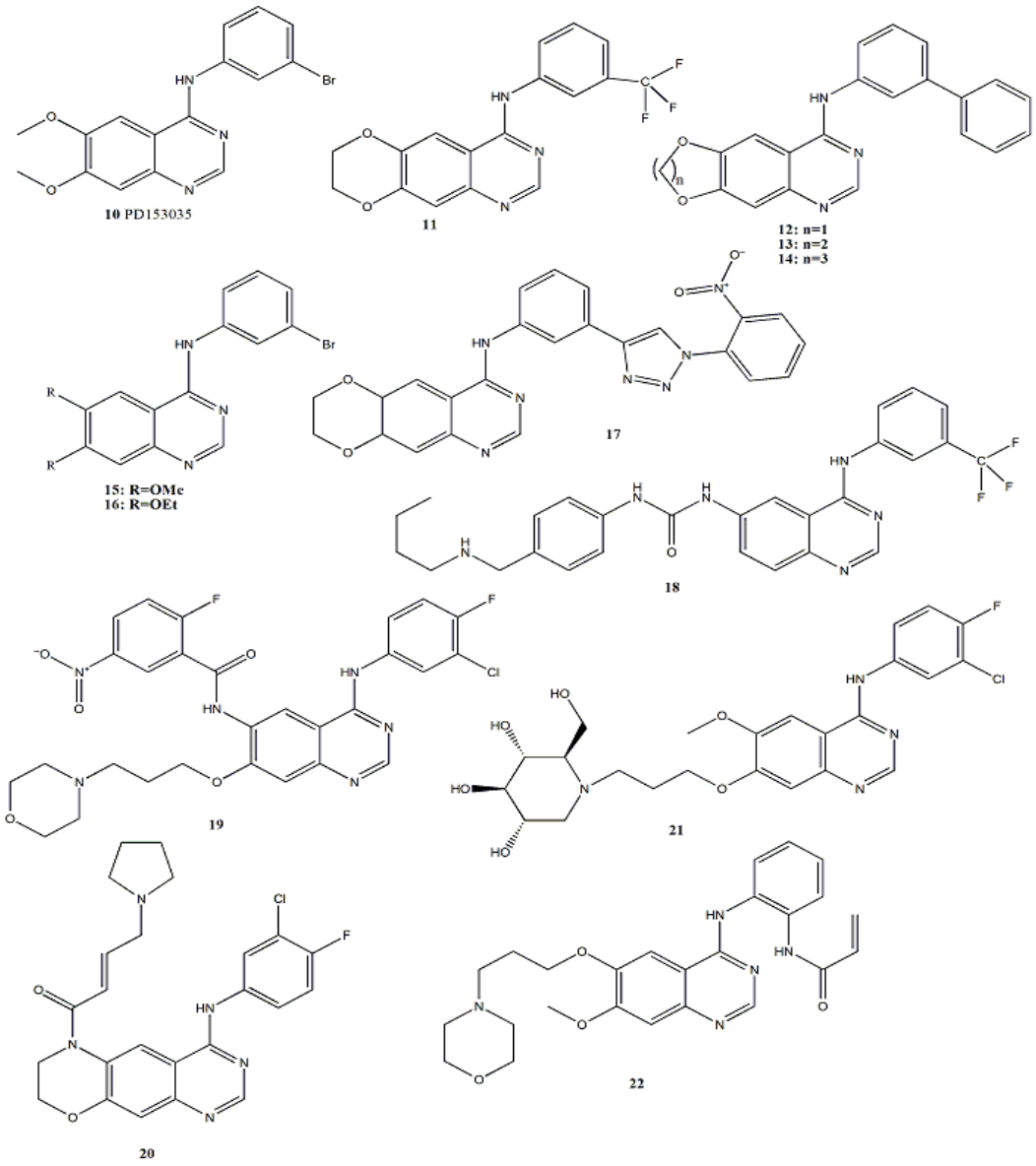


Figure 3: EGFR derivatives tyrosine kinase inhibitors.

3.1.2 Second-generation EGFR-TKIs (Figure 4), (Figure 5)

Afatinib: Afatinib is an irreversible inhibitor of the ErbB family. It is approved for the treatment of NSCLC with EGFR mutations. Afatinib is clinically active and well-tolerated in many TKI-pretreated NSCLC patients. Afatinib is bound to the cell surface receptor of tyrosine kinase and irreversibly inhibit the signalling from HER-2 and HER-4. Afatinib is used as a monotherapy for NSCLC and non-resistant EGFR mutation. It can treat various cancer such as breast, gastric and lung cancer.[32]

Neratinib[Nerlynx®]: Neratinib is approved by USFDA to treat HER-2 positive breast cancer, colorectal and NSCLC. Due to its high selectivity, it shows less toxicity and high efficacy for a mutated or overexpressed molecule of the cancer cells. Neratinib is an irreversible inhibitor of tyrosine kinase via blocking the phosphorylation of tyrosine kinase and prevents signal transduction which leads to inhibition of cell growth, migration, and induction of apoptosis. Diarrhoea is the main side effect associated with neratinib.[33]

Dacomitinib: Dacomitinib is a second-generation irreversible EGFR TKI developed by Pfizer. It is a pan-HER inhibitor that was initially thought to inhibit the acquired resistance EGFR mutation Thr790Met. Advanced Research for Cancer targeted pan-HER therapy (ARCHER) program performed through dacomitinib in NSCLC. Furthermore, clinical trials involving EGFR TKIs of molecularly unselected NSCLC patient has studied that, the third-generation EGFR TKIs have taken lead in the first-line setting.[34]

Canertinib: Canertinib is formulated by Pfizer pharmaceuticals approved by USFDA. Canertinib is an irreversible inhibitor of the EGFR family. It inhibits the whole EGFR family so it provides more efficient action than that only inhibits one of the EGFR receptors. The growth of cancer cells is inhibited by G1 cell cycle arrest and it induces apoptosis in various cancers by inhibiting EGFR downstream signalling pathway. Platinum complexes such as cisplatin or carboplatin show the first-line treatment of many solid tumours.[35]

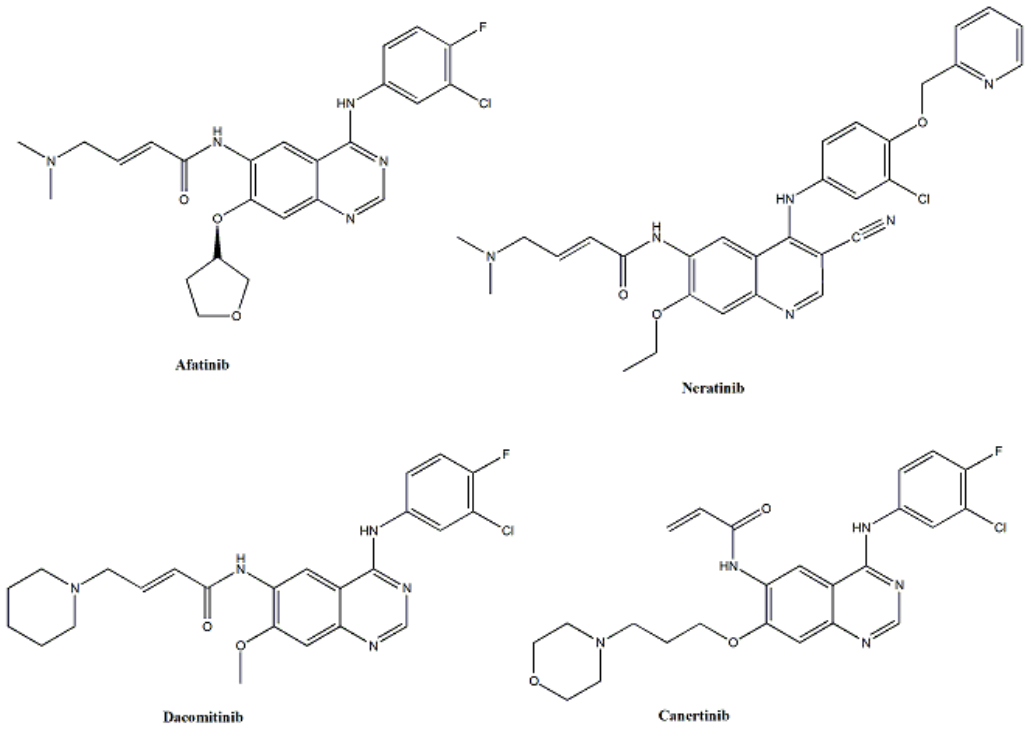


Figure 4: Second-generation EGFR-TKIs.

Yuanbiao Tu et al. reported quinazoline derivatives with a semicarbazone moiety tested in various cancer cell lines like A549, HepG2, MCF-7, and PC-3. The Yuanbiao Tu et al. designed, synthesized and evaluated all derivatives with remarkable cytotoxicity reaching IC_{50} values to the nanomole range. From these derivatives compounds, **23** and **24** induce cell apoptosis arresting the G_2/M phase in the A549 cell line in the cell cycle and inhibiting tumour cell proliferation. In addition, EGFR ^{WT} and EGFR $^{L858R/T790M}$ kinase inhibition assays revealed that **23** and **24** are equally or more active than Afatinib.[36]

Jiho Song et al. synthesized triazole-tethered quinazoline derivatives. From these derivatives, the meta-fluoro derivative **25** showed higher selectivity and potent activity against mutant EGFR or compared to the para-fluoro substituted compound. Compound **25** showed 3.5-fold more antiproliferative activity against EGFR $^{L858R/T790M}$ than afatinib and showed 17- and 52-fold potency for EGFR $^{L858R/T790M}$ over wild-type EGFR and HER2, respectively. Compound **25** revealed low cytotoxicity and presents a low risk of cardiac arrhythmia and hepatic toxicity.[37]

Long Zhang et al. developed a series of 6, 7-disubstituted-4-(arylamino) quinazoline derivatives. These derivatives are irreversible EGFR inhibitors and showed potent enzyme inhibition. The best substitutions in a series of 6, 7- disubstituted-4-anilino quinazoline is 3-

chloro-4-fluoroaniline and 3-ethynylaniline as an excellent potent EGFR inhibitor activity. Among these, the selected compounds **26** and **27** exhibited great efficacy against H1975 (EGFR-T790M) tumours at a non-toxic dose in comparison with afatinib.[38]

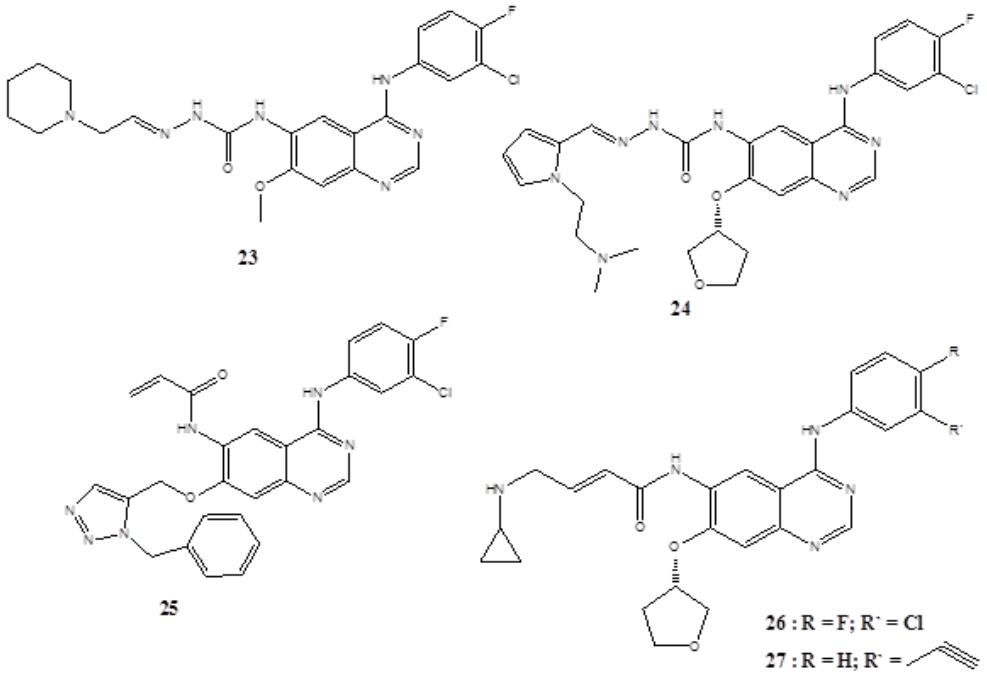


Figure 5: EGFR derivatives tyrosine kinase inhibitors.

3.1.3 Third generation EGFR-TKIs (Figure 6), (Figure 7)

Osimertinib: Osimertinib is irreversible EGFR-TKI, approved by USFDA for the treatment of EGFR mutation-positive NSCLC as monotherapy. Regression of EGFR-mutant NSCLC tumours growing in the bone and remodelling the bone is treated with help of osimertinib. Firstly osimertinib was approved only to treat NSCLC patients with a confirmed Thr790Met mutation and progression as a first-line treatment.[39]

Avitinib: Avitinib is an irreversibly binding, mutant-selective EGFR-TKI, approved in the US and China for clinical trials in parallel. Avitinib is a third-generation inhibitor of EGFR that is selective for Thr790Met mutation. The concentration of avitinib in CSF is low as its penetrability through BBB is weak and has good control over brain metastases. Third-generation EGFR TKIs are tolerated and so selectively and specifically inhibit Thr790Met positive tumour cells.[40]

Nazartinib: Thr790Met mutation causes resistance to first and second-generation EGFR TKIs in 50–60% of treated patients with NSCLC. It is approved for third-generation EGFR-

TKIs it selectively inhibits Thr790Met mutation. Nazartinib is an irreversible inhibitor with high potency. The mechanism of inhibition is by phosphorylation is observed in single-dose studies of nazartinib. Serious adverse effects such as diarrhoea, pneumonitis or interstitial lung disease, acute kidney injury, etc. were observed.[41]

Olmutinib: Olmutinib is a novel drug that is mutation-specific EGFR-TKI, which targets mutant-type EGFR. Olmutinib shows good anticancer activity with EGFR mutations in several nonclinical studies, including the Thr790Met mutation. Brain lesions at baseline do not affect the efficacy of olmutinib. Some Adverse effects like skin exfoliation, diarrhoea, rash, pruritus, decreased appetite, nausea, and palmar-plantar erythrodysesthesia syndrome.[42]

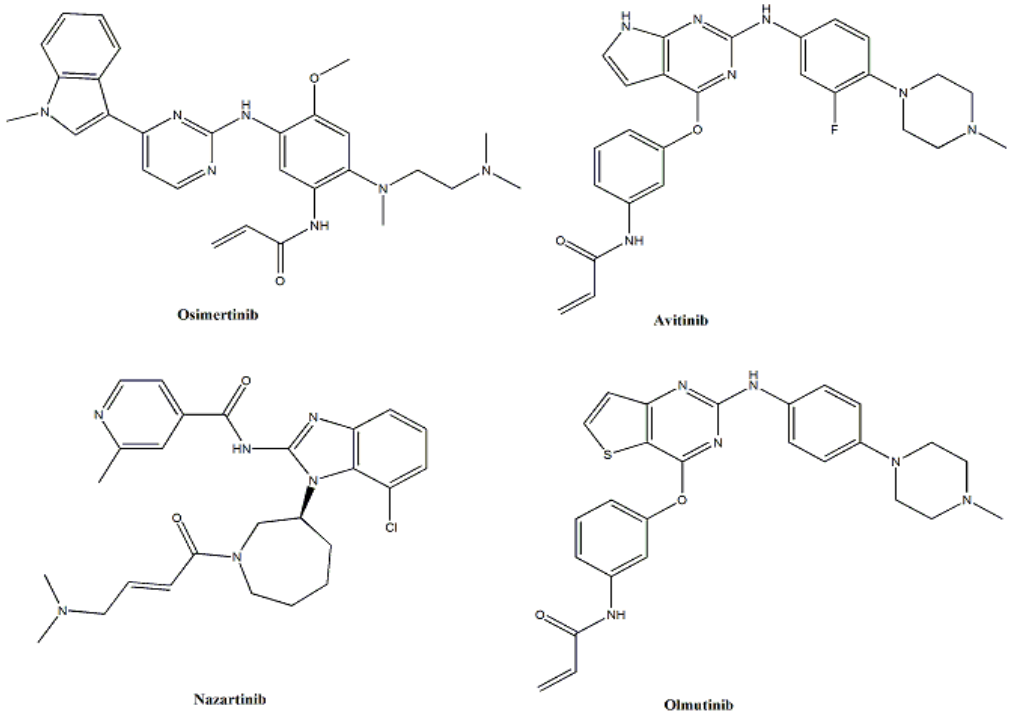


Figure 6: Third-generation EGFR-TKI.

Patrick A. Ple et al. designed anilinoquinazoline derivatives. The synthesized derivatives have high potency and specificity for the c-Src enzyme. The derivatives of 4-aminobenzodioxole quinazoline compounds resulted in excellent potency and selectivity. The derivatives displayed good pharmacokinetics. Among the derivatives compound, **28** resulted in good inhibition activity in rat xenografts.[43]

Henry F. Vanbrocklin et al. reported sixteen dialkoxyquinazoline analogues. A new radiometric binding assay resulted in inhibition at an IC_{50} in a range of 0.4-51 nM. The

following compounds 4-(2′-fluoroanilino)- and 4-(3′-fluoroanilino)-6,7-diethoxyquinazoline as well as 4-(3′- chloroanilino)- and 4-(3’-bromoanilino)-6,7-dimethoxyquinazoline, possess radioisotope labelling evaluated in tumour-bearing mice. Affinity, lipophilicity, and selectivity of selected compounds **29**, **30**, **31**, and **32**, were evaluated as tumour imaging probes.[44]

Sylvester R. Klutchko et al. prepared compounds by coupling the appropriate 6-aminoquinazolines or 6-aminopyrido[3,4-d]pyrimidines with alkynoic acids, using HCl in pyridine, the synthesized compounds showed pan-erbB enzyme inhibition. Compound **33** Pyrido[3,4-d]pyrimidine evaluated in vivo in the A431 human epidermoid carcinoma and the SKOV3 human ovarian carcinoma.[45]

Mi Young Cha et al. designed a novel series of (S)-1-acryloyl-N-[4-(arylamino)-7-(alkoxy)quinazolin-6-yl]pyrrolidine-2-carboxamides. Evaluated for Her-1/Her-2 dual inhibitors. The highly selective selected compounds (**34**, **35**) resulted in the highest EGFR inhibition activity. The compound **35** with fluorine at the para-position of the C4-aniline improved its potency than **34** in the enzyme inhibition assay. Compound **34** has excellent Her-1/Her-2 dual inhibitory activity.[46]

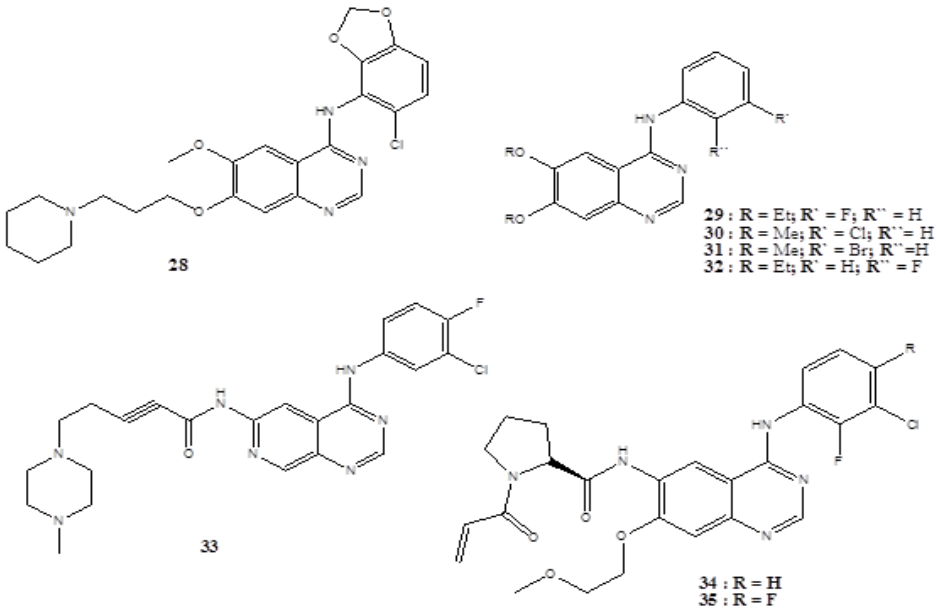


Figure 7: EGFR derivatives tyrosine kinase inhibitors.

3.2 VEGFR tyrosine kinase inhibitors (Figure 8), (Figure 9)

VEGFR is an RTK inhibitor that is a novel anticancer agent. VEGFR -2 binds to VEGF and activated the receptor, which initiates a phosphorylation process. These TKIs are bound to the receptor at the ATP binding site which inhibits the autophosphorylation process, results in an inhibition of endothelial cell proliferation and migration. VEGFR-2 inhibitors also block the dimerization of the receptor inhibiting the angiogenesis process which affects the development of new blood vessels. VEGFR -2 inhibitors are of three types.[47]

Type I inhibitors

Sunitinib: Sunitinib is an orally available FDA approved multitarget tyrosine kinases inhibitor of VEGFR-2. It is ATP competitive inhibitor, making one to three H-bonds at the active site to the adenine ring of ATP. Sunitinib inhibits the phosphorylation of several tyrosine kinase receptors overexpressed in cancer as VEGFR. Toxicities showed by sunitinib is sunitinib-induced cardiotoxicity and hypothyroidism.[48]

Type II inhibitors

Sorafenib: Sorafenib is a bisaryl ureas multikinase inhibitor. Designed for renal cell carcinoma (RCC) and hepatocellular carcinoma(HCC) treatment. HCC is the common tumour of the liver, sorafenib can prolong the survival rate of patients by not more than three months, standing the third most cause of cancer-related death.[49]

Type III inhibitors

Vatalanib: Vatalanib is a covalent inhibitor of VEGFR-2, it prevents the binding of ATP to the binding site by forming a covalent bond to cysteine amino acid residue. Vatalanib inhibits all known VEGFRs (VEGFR1, -2, and -3), PDGFR (Platelet-Derived Growth Factor Receptor), and stem-cell factor receptor c-kit. Some moderate Side effects are shown by vatalanib were nausea, dizziness, and vomiting.[50]

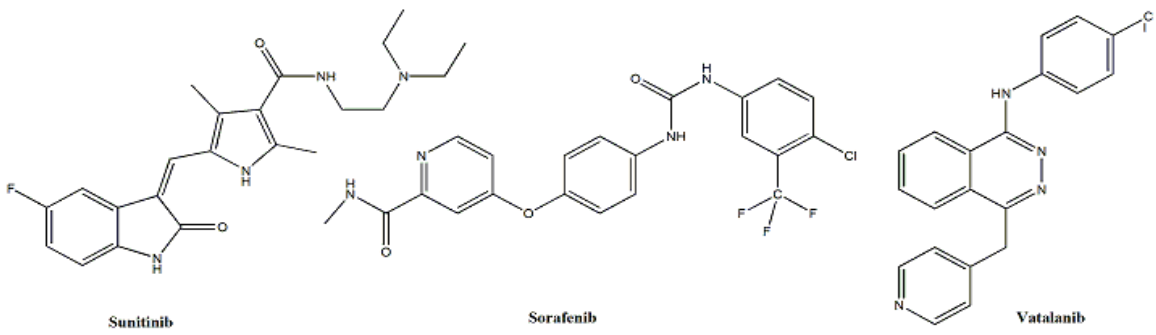


Figure 8: VEGFR tyrosine kinase inhibitors.

Marwa G. El-Gazzar et al. designed & synthesized the novel Pyridazino[3, 4, 5-de]quinazoline derivatives. MTT assay was performed for in vitro study of the newly synthesized compounds. All derivatives showed potent activity with IC_{50} values ranging from 0.03 to 0.9 mM. Ethoxy aniline derivative **36** was found to be potent inhibiting VEGFR2 with an IC_{50} value of 0.03 µM. A docking study was performed about Sorafenib and vatalanib.[51]

Antonio Garofalo et al. designed a series of 6,7-dimethoxy substituted quinazoline derivatives. The derivative is inhibitors of EGFR and VEGFR-2 substituted in the 4-position by aniline, N-methylaniline, and aryloxy entities. Selective inhibitors of VEGFR-2 was found with substitution by aryloxy groups with IC_{50} values in the nanomolar range in vitro. 2-naphtyl substituent **37** displayed IC_{50} value of 0.03 µM selectively against VEGFR-2.[52]

Bing Yu et al. designed substitution at position-4 of quinazoline with the aryl with different bulky substituents such as amide, carbamate, or urea. The amide compounds exhibited less activity than that of urea. The compound **38** was evaluated in vivo in the HepG2 (human hepatomacellar carcinoma) cell line resulting in potent low nanomolar inhibition of VEGFR-2 and VEGFR-3 with IC_{50} equal to 5.5nm.[53]

Silvia Salerno et al. reported a novel 2-aryl substituted benzothiopyrano-fused pyrimidines. Compound **39** displayed the highest VEGFR-2 inhibitory activity with an IC_{50} value of 2.7 µM. compound **39** reported high antiproliferative activity on tumour cell lines.[54]

Séverine Ravez et al. reported a series of 4-aryloxy-6,7-dimethoxyquinazolines. The derivatives showed VEGFR, PDGFR and c-Kit inhibitory activity at a nanomolar concentration. Compound **40** showed potent inhibition with an IC_{50} on VEGFR-(1, 2 and 3), PDGFR-ß and cKit of less than 9 nM. The MTT assay was performed for evaluation of the antiproliferative activity of compound **40**. Compound **40** reduces the angiogenic process which prevents tube formation at a lower concentration than the reference (cediranib).[55]

Astra Zeneca et al. designed a series of substituted 4-anilinoquinazolines. Evaluated as an inhibitor of VEGFR TK (Flt and KDR). Meta position of the aniline group was substituted by a hydroxyl group resulting in the most potent VEGFR inhibitors. The derivative with a heteroaromatic side chain at the C-7 position resulted in a compound with great potency. The methoxyethoxy derivative **41** showed an IC_{50} value less than 2 Nm.[56]

Jeff B. Smaill et al. derived a series of 7-substituted 4-anilinoquinazolines as EGFR inhibitors. Substitution of small lipophilic and electron-deficient group at the C-2 position or large lipophilic an electron-withdrawing group at the C-4 position of aniline ring improve inhibition activity. Anilinoquinazolines substituted at the C-7 position resulted in inhibition of KDR tyrosine kinase at a nanomolar concentration.[57]

Matthew M. Weiss et al. designed N-arylnaphthamide derivatives. The derivatives are potent inhibitors of VEGFR. The N-Alkyl and N-unsubstituted naphthamides were evaluated and resulted in an inhibitor of VEGFR-2 at nanomolar concentration with enhanced selectivity for kinases. 6,7-dimethoxyquinoline series (**42**, **43**, and **44**) inhibit VEGF-induced angiogenesis showed good bioavailability with a tmax in the range of 1.6–2.5 h.[58]

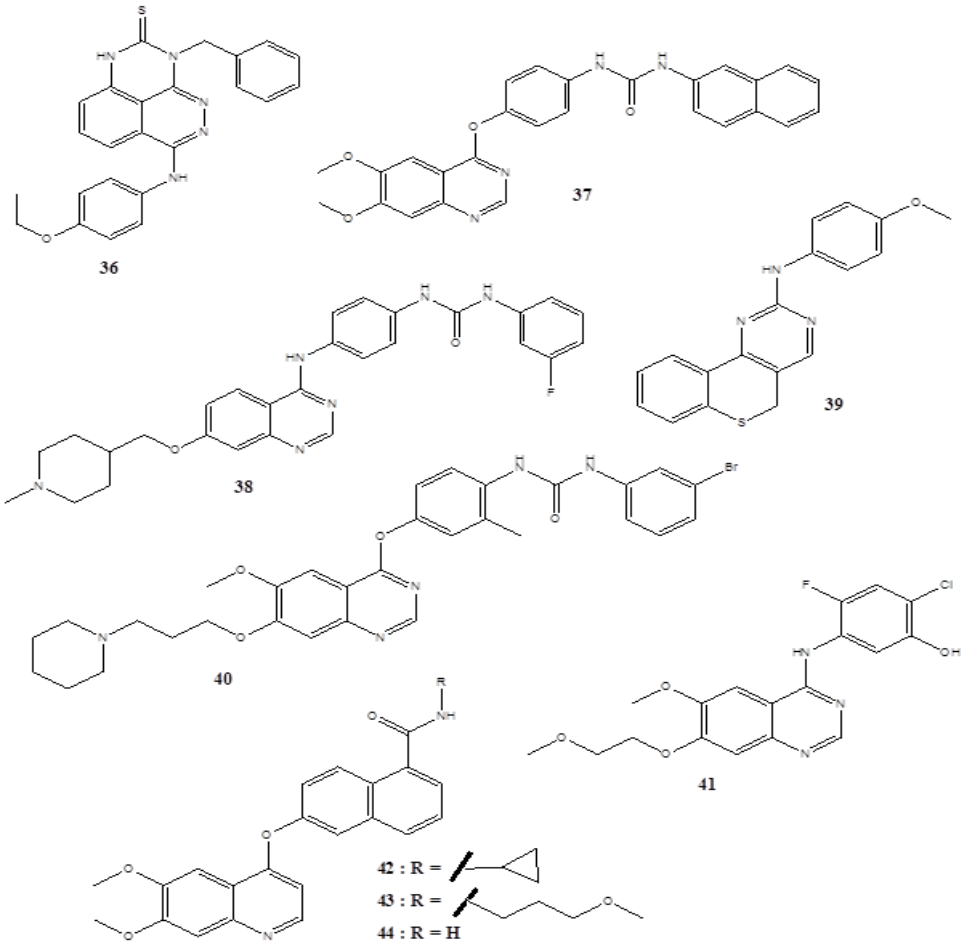


Figure 9: VEGFR-2 derivatives tyrosine kinase inhibitors.

3.3 EGFR and VEGFR-2 dual inhibitors (Figure 10), (Figure 11)

Vandetanib[Caprelsa®]: Vandetanib is an orally available drug once-daily selectively targets the VEGFR and EGFR. Vandetanib showed good inhibitory activity with IC_{50} of 6

µM. The synergistic effect of vandetanib is due to the additive effects of inhibition of EGFR oncogenic signalling and the vascular normalization effect on the tumour microenvironment. Vandetanib inhibited the proliferation of cancerous cells through the induction of cell cycle arrest at the G1 phase.[59]

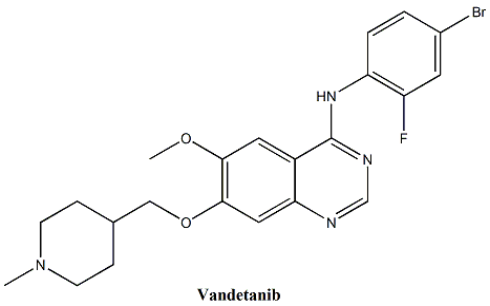


Figure 10: EGFR and VEGFR-2 dual inhibitor.

Huiqiang Wei et al. designed a series of a novel 3-nitro-1,2,4-triazole group to the side chain of vandetanib. 4-anilinoquinazoline linked to 3-nitro-1,2,4-triazole moiety by long ether chains. Derivatives of the 3-nitro-1,2,4-triazole moiety, **45** and **46** are more potent to hypoxia-targeted inhibitory activities than vandetanib. Compounds **45** and **46** exhibited inhibitory activity on the growth of A549 and H446 cells under hypoxic conditions. It is advisable to substitute bulky and heavy halogen atoms to anilines for dual EGFR/VEGFR-2 inhibitory activities.[5]

Maria Leticia de Castro Barbosa et al. reported a series of 2-chloro-4-anilino-quinazolines as EGFR and VEGFR-2 dual inhibitors. It is a novel approach to prevent resistance in cancer therapy due to its synergistic effect. Primary amide derivative **47** resulted in approximately 7-fold more potent inhibitor of VEGFR-2 and approximately 11-fold more potent inhibitor of EGFR compared to its prototype**(10)**. The compound **47** showed the greatest inhibitory effect with IC_{50} of 0.90 mM for $EGFR^{wt}$ and 1.17 mM for VEGFR-2 as dual inhibitors of both the tyrosine kinases.[9]

Hai-Qi Zhang et al. designed a substituted glycine methyl ester or diaryl urea to a 4-anilinoquinazoline moiety. The derivatives are identified as dual inhibitors of EGFR and VEGFR-2. Terminal diaryl urea moiety and chlorine in the ortho position of the urea group lead to compounds **48, 49,** and **50** showed potent inhibitory activity against EGFR and VEGFR-2. Compounds **48, 49,** and **50** showed good antiproliferative activity with IC_{50} value

of 1 nM, 78 nM, and 51 nM, respectively for EGFR and IC_{50} value of 79 nM, 14 nM, and 14 nM, respectively for VEGFR-2.[60]

Hai-Qi Zhang et al. designed a novel 4-anilinoquinazoline-acylamino derivatives. These derivatives are designed as dual inhibitors of EGFR and VEGFR-2 and evaluated for biological activities. Compound **51** exhibited the potent antiproliferative activities against three cancer cell lines HT-29, MCF-7, and H460 with IC_{50} of 5.27µM, 4.41µM, and 11.95µM, respectively.[10]

Allan Wissner et al. designed a series of 4-dimethylamino-but-2-enoic acid [4-(3,6-dioxo-cyclohexa-1,4-dienylamino)-7-ethoxy-quinazolin-6-yl]-amide derivatives. The EGFR and VEGFR kinase assay was conducted using 1 µM and 1 mM concentrations of ATP respectively to estimate the dependence of the IC_{50} values. Docking study showed that compounds with a 4-(amino-[1,4]benzoquinone) **52** moiety targets Cys-1045 in VEGFR-2 and a 4-(dimethylamino)crotonamide **53** Michael acceptor group targets in EGFR Cys-773 amino acid.[61]

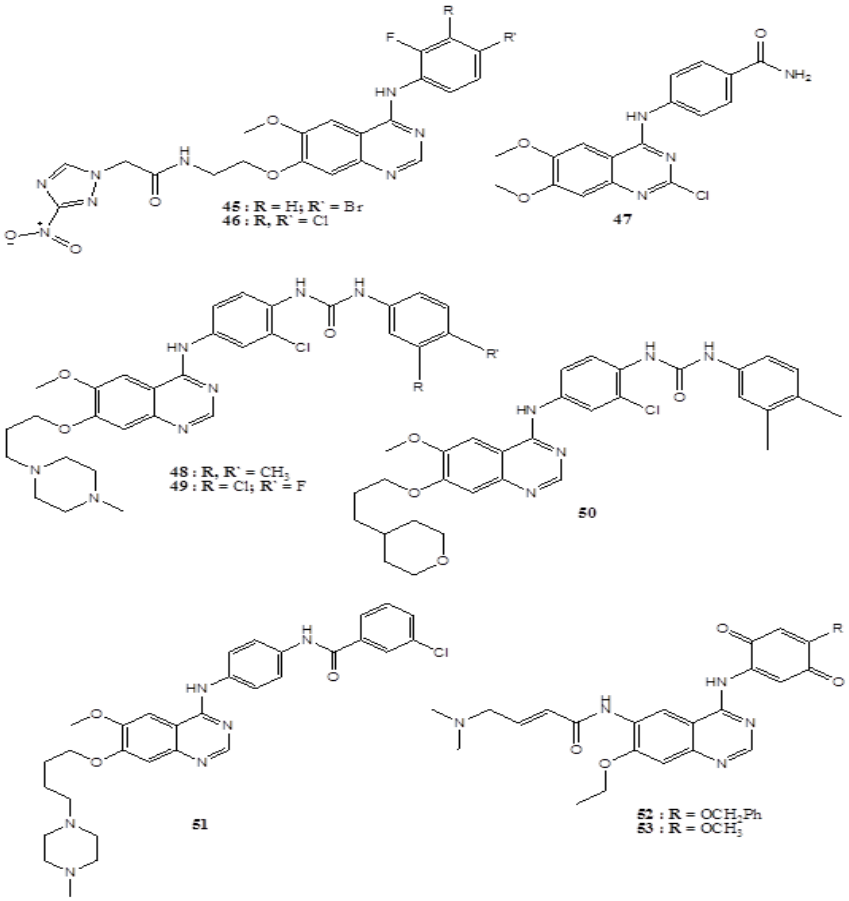
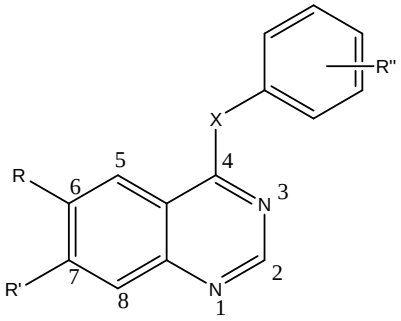


Figure 11: EGFR and VEGFR-2 dual tyrosine kinase inhibitors.

4. STRUCTURE-ACTIVITY RELATIONSHIP



Quinazoline Ring

N_1 and N_3-substitutions in quinazoline rings resulted in a loss in the activity of compounds.

Substitution at C_2 of quinazoline resulted in a loss in activity but substitution with chloro **47**[(9)] retain the activity.

Derivatives with C_8 substitution resulted in inactive compounds.

7-Acrylamide derivatives **33**[45] resulted in an increase in activity with piperazine ring substitution to 6-position.

Ring fused to the quinazoline moiety **36**[51] with no loss in activity. Pyrazoloquinazoline derivatives with morpholide improved in activity. Pyrroloquinazoline derivatives with no substitution resulted in more activity.

Replacement of quinazoline with other heterocycles like phthalazine **36**[51] or quinoline **42**, **43**, **44**[58] resulted in distinguished results.

4-Anilino Substitution

N-methylation of the amino group completely loses the activity of compounds.

Oxygen linked compounds like **37**[52], **40**[55], **42**, **43**, **44**[58] phenoxy substitutions resulted in reduced activity than nitrogen substitution.

Small lipophilic substitution like F **32**[44], **45**, **46**[5] is preferable to the 2` position. Oxy derivatives **52**, **53**[61] also shows good potency.

Substitution of the small lipophilic electron-withdrawing groups like halogens to 3` position of 4-aniline ring resulted in more potent compounds. Substitution of Cl derivatives **30**[(44)], **48**, **49**, **50**[60] and Br derivatives **10**[9], **15**, **16**[25], **31**[44] resulted in more potency than F derivatives **29.**[44]

Substitution of hydroxyl **41**[56] or methyl **40**[55] at 3`position also results in the potent compound.

CF_3 substitution to 3` of aniline derivatives **11**[23], **18**[27] is mildly deactivating.
Substituents like amide **47**[10] or phenyl urea derivatives **37**[52], **38**[53], **40**[55], **48**, **49**, **50**[60] or chlorobenzamide derivative **51**[10] is preferred at the 4` position of the aniline ring.
Small lipophilic substituents like OCH_3 **39**[54] or halogen (Cl) **41**[56] are preferred at the 4` position of the aniline ring. Cationic side chain at 4-position is not preferred due to loss in binding affinity.

Acrylamidoquinazoline with 3`-Cl, 4`-F substitutions **33**[64] to aniline ring showed the same activity as quinazoline derivatives.
2`,3` substitution with F, Cl derivative **34**[46] resulted in the potent compound.
3`,4` substitution with Cl, F derivatives **19**[28], **20**[29], **21**[30], **23**, **24**[36], **25**[37], **26**[38], **33**[45] showed good inhibitory activity.
2`, 3`, 4` substitution with F, Cl, F resulted in good potent compound **35.**[46]
Benzylamino series **36**[51] is less effective than aniline derivatives.

6,7-quinazoline Substitution

Electron donating substituent at 6 or 7-position resulted in high activity.
Substitution of the lipophilic group at 6,7-position improved inhibition capacity.

Substitution of 6,7-diOCH_3 derivatives **10**[9], **15**[25], **30**, **31**[44], **37**[52], **42**, **43**, **44**[58], **47**[9] showed most potent compounds. Replacement of 6,7-dimethoxy with 6,7-diethoxy derivatives **16**[25], **29**, **32**[44], **36**[51], **52**, **53**[61] will give same activity.

Single methylene group between C_6-O or C_7-O and heterocyclic ring **38**[53] (piperidine, morpholine, piperazine, tetrahydropyran) showed good activity but an increasing number of methylene groups results in excellent activity. 6-propoxy substitution **22**[31] or 7-propoxy substitution **19**[28], **21**[30], **28**[43], **40**[55], **48**, **49**, **50**[60] is best for inhibitory activity than ethoxy derivative or butoxy derivative.

6,7-diOR cyclisation that is methylenedioxy or ethylenedioxy ring derivatives **11**[23], **12**, **13**, **14**[24], **17**[26], **20**[29] reduces the activity than 6,7-diOCH_3 substitution.

Morpholines, pyrrolidines, and piperidines at 6,7-position retained excellent activity. Piperidine substitution **21**[30], **38**[53], **40**[55] is more potent than morpholine substitution **19**[28], **22**[31] than pyrrolidine substitution **20.**[29]

Substitution at 6-position linked with nitrogen **52**, **53**[61] gives slightly more potent inhibitors than oxygen linked derivatives.

5. CONCLUSION

In this review, we have described 4-anilinoquinazoline derivatives as EGFR and VEGFR-2 inhibitors. The approach of synthesis of the 4-anilinoquinazoline derivative is easy, so a variety of substitutions are possible with their versatile medicinal applications. The 4-anilinoquinazoline moiety present in various marketed drug-like gefitinib, erlotinib, dacomitinib, olmutinib, vandetanib, etc. 4-anilinoquinazoline showed a broad range of pharmaceutical activities like colon cancer, non-small cell lung cancer, prostate cancer, breast cancer, etc. The possible improvement in the activity can be further achieved in the future with various pharmacophoric substituents. Shortly, several 4-anilinoquinazoline derivatives will be useful for innovations. This review provides overarching information of targeted core molecule to the chemist for further development of new novel 4-anilinoquinazoline derivatives as an anti-cancer drug.

6. ABBREVIATIONS

EGFR: Epidermal Growth Factor Receptor, VEGFR: Vascular Endothelial Growth Factor Receptor, TKI: Tyrosine Kinase Inhibitor, HER: Human Epidermal Growth Factor Receptor, SRC: Sarcoma Gene/Kinase, VEGF: Vascular Endothelial Growth Factor, USFDA: United State Food and Drug Administration, BOP: benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DMF: N, N-Dimethylformamide, HOAc: acetic acid, PTK: Protein Tyrosine Kinase, RTK: Receptor Tyrosine Kinase, NSCLC: Non-Small-Cell Lung Cancer, ARCHER: Advanced Research for Cancer targeted pan-HER therapy, CSF: Cerebrospinal Fluid, BBB: Blood-Brain Barrier, RCC: Renal Cell Carcinoma, HCC: Hepatocellular Carcinoma, PDGFR: Platelet-Derived Growth Factor Receptor, PDT: Photodynamic Therapy.

7. ACKNOWLEDGEMENT

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8. CONFLICT OF INTEREST

There are no conflicts of interest.

9. REFERENCES

1. Pyrimidines I. Pyrimidines and Quinazolines. Suppl to 2nd Ed Rodd'S Chem Carbon Compd Vol IV - Heterocycl Compd Pts I J., 1818; 2(Iv): 63–91.
2. Alagarsamy V, Chitra K, Saravanan G, Solomon VR, Sulthana MT, Narendhar B. An overview of quinazolines: Pharmacological significance and recent developments. Eur J Med Chem [Internet], March, 2018; 151: 628–85. Available from: https://doi.org/10.1016/j.ejmech.2018.03.076
3. Chang J, Ren H, Zhao M, Chong Y, Zhao W, He Y, et al. inhibitory efficacy, and evaluation of anticancer activities in vitroDevelopment of a series of novel 4-anlinoquinazoline derivatives possessing quinazoline skeleton: Design, synthesis, EGFR kinase. Eur J Med Chem [Internet], 2017; 138: 669–88. Available from: http://dx.doi.org/10.1016/j.ejmech.2017.07.005
4. Hennequin LFA, Ballard P, Boyle FT, Delouvrié B, Ellston RPA, Halsall CT, et al. Novel 4-anilinoquinazolines with C-6 carbon-linked side chains: Synthesis and structure-activity relationship of a series of potent, orally active, EGF receptor tyrosine kinase inhibitors. Bioorganic Med Chem Lett., 2006; 16(10): 2672–6.
5. Wei H, Duan Y, Gou W, Cui J, Ning H, Li D, et al. Design, synthesis and biological evaluation of novel 4-anilinoquinazoline derivatives as hypoxia-selective EGFR and VEGFR-2 dual inhibitors. Eur J Med Chem [Internet], 2019; 181: 111552. Available from: https://doi.org/10.1016/j.ejmech.2019.07.055
6. Wieduwilt M. J., Moasser M. M. The epidermal growth factor receptor family: biology driving targeted therapeutics. Cell Mol Life Sci., 2011; 65(10): 1566–84.
7. Ismail RSM, Abou-Seri SM, Eldehna WM, Ismail NSM, Elgazwi SM, Ghabbour HA, et al. Novel series of 6-(2-substitutedacetamido)-4-anilinoquinazolines as EGFR-ERK signal transduction inhibitors in MCF-7 breast cancer cells. Eur J Med Chem [Internet], 2018; 155: 782–96. Available from: https://doi.org/10.1016/j.ejmech.2018.06.024
8. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes and Cancer, 2011; 2(12): 1097–105.
9. Barbosa MLDC, Lima LM, Tesch R, Sant'Anna CMR, Totzke F, Kubbutat MHG, et al. Novel 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors. Eur J Med Chem [Internet], 2014; 71: 1–14. Available from: http://dx.doi.org/10.1016/j.ejmech.2013.10.058
10. Zhang HQ, Gong FH, Li CG, Zhang C, Wang YJ, Xu YG, et al. Design and discovery of

4-anilinoquinazoline-acylamino derivatives as EGFR and VEGFR-2 dual TK inhibitors. Eur J Med Chem [Internet], 2016; 109: 371–9. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.12.032

11. Krapf MK, Gallus J, Wiese M. Synthesis and biological investigation of 2,4-substituted quinazolines as highly potent inhibitors of breast cancer resistance protein (ABCG2). Eur J Med Chem [Internet], 2017; 139: 587–611. Available from: http://dx.doi.org/10.1016/j.ejmech.2017.08.020
12. Shen ZL, He XF, Hong YM, Hu XQ, Mo WM, Hu BX, et al. One-pot synthesis of 4-aminoquinazolines by hexamethyldisilazane-mediated reaction of quinazolin-4(3h)-ones with amines. Synth Commun, 2011; 41(24): 3644–53.
13. Wan ZK, Wacharasindhu S, Levins CG, Lin M, Tabei K, Mansour TS. The scope and mechanism of phosphonium-mediated SNAr reactions in heterocyclic amides and ureas. J Org Chem., 2007; 72(26): 10194–210.
14. Tsou HR, Mamuya N, Johnson BD, Reich MF, Gruber BC, Ye F, et al. 6-Substituted-4-(3-bromophenylamino)quinazolines as putative irreversible inhibitors of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases with enhanced antitumor activity. J Med Chem., 2001; 44(17): 2719–34.
15. Szczepankiewicz W, Suwiński J, Bujok R. Synthesis of 4-arylaminoquinazolines and 2-aryl-4-arylaminoquinazolines from 2-aminobenzonitrile, anilines and formic acid or benzaldehydes. Tetrahedron, 2000; 56(47): 9343–9.
16. Connolly DJ, Cusack D, O'Sullivan TP, Guiry PJ. Synthesis of quinazolinones and quinazolines. Tetrahedron, 2005; 61(43): 10153–202.
17. Tang N, ﺑﯽ ﯾ ﯾ ﯾ ﯾ ﯾ ﯾ ﯾ ﺑ ﺛ ﺑ ڈ ﺑ ڈ, Pública S, Msp II, Miranda C, Casos EDELOS, et al. No Titleﯾﺐ ﯾ ﺑ ڈ ﺑ ﺛ ﺑ ڈ. 2018;ﺛ ﻗ ﻗ)ﺛ ڈ ق ڈ ﺛ ﻗ ڈ ﻗ ڈ ﻗ ڈ:(ﺛ ڈ.
18. Schlessinger J. Cell Signaling by Receptor Review Tyrosine Kinases receptor) are monomers in the cell membrane. Ligand binding induces dimerization of these receptors resulting in autophosphorylation of their cytoplasmic do., 103, Cell. 2000.
19. Laskin JJ, Sandler AB. Epidermal growth factor receptor: A promising target in solid tumours. Cancer Treat Rev., 2004; 30(1): 1–17.
20. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med., 2010.
21. Patel HM, Pawara R, Ansari A, Noolvi M, Surana S. Bioorganic & Medicinal Chemistry Design and synthesis of quinazolinones as EGFR inhibitors to overcome EGFR resistance obstacle. Bioorg Med Chem [Internet], 2017; 25(10): 2713–23. Available from:

http://dx.doi.org/10.1016/j.bmc.2017.03.039

22. Xu L, Qi Q, Zhang Y, Cui J, Liu R, Li Y. Combination of icotinib and chemotherapy as first-line treatment for advanced lung adenocarcinoma in patients with sensitive EGFR mutations: A randomized controlled study. Lung Cancer., 2019; 133(1): 23–31.
23. Chilin A, Conconi MT, Marzaro G, Guiotto A, Urbani L, Tonus F, et al. Exploring Epidermal Growth Factor Receptor (EGFR) inhibitor features: The role of fused dioxygenated rings on the quinazoline scaffold. J Med Chem., 2010; 53(4): 1862–6.
24. Conconi MT, Marzaro G, Urbani L, Zanusso I, Di Liddo R, Castagliuolo I, et al. Quinazoline-based multi-tyrosine kinase inhibitors: Synthesis, modelling, antitumor and antiangiogenic properties. Eur J Med Chem [Internet], 2013; 67: 373–83. Available from: http://dx.doi.org/10.1016/j.ejmech.2013.06.057
25. Bridges AJ, Zhou H, Cody DR, Rewcastle GW, McMichael A, Showalter HDH, et al. Tyrosine kinase inhibitors. 8. An unusually steep structure-activity relationship for analogues of 4-(3-bromoanilino)-6,7-dimethoxyquinazoline (PD 153035), a potent inhibitor of the epidermal growth factor receptor. J Med Chem., 1996; 39(1): 267–76.
26. Le-Nhat-Thuy G, Dinh T Van, Pham-The H, Nguyen Quang H, Nguyen Thi N, Dang Thi TA, et al. Design, synthesis and evaluation of novel hybrids between 4-anilinoquinazolines and substituted triazoles as potent cytotoxic agents. Bioorganic Med Chem Lett [Internet], 2018; 28(23–24): 3741–7. Available from: https://doi.org/10.1016/j.bmcl.2018.10.016
27. Zuo SJ, Zhang S, Mao S, Xie XX, Xiao X, Xin MH, et al. Combination of 4-anilinoquinazoline, arylurea and tertiary amine moiety to discover novel anticancer agents. Bioorganic Med Chem [Internet], 2016; 24(2): 179–90. Available from: http://dx.doi.org/10.1016/j.bmc.2015.12.001
28. Hou W, Ren Y, Zhang Z, Sun H, Ma Y, Yan B. Novel quinazoline derivatives bearing various 6-benzamide moieties as highly selective and potent EGFR inhibitors. Bioorganic Med Chem [Internet], 2018; 26(8): 1740–50. Available from: https://doi.org/10.1016/j.bmc.2018.02.022
29. Sun M, Zhao J, Chen X, Zong Z, Han J, Du Y, et al. Synthesis and biological evaluation of novel tricyclic oxazine and oxazepine fused quinazolines. Part 2: Gefitinib analogues. Bioorganic Med Chem Lett [Internet], 2016; 26(19): 4842–5. Available from: http://dx.doi.org/10.1016/j.bmcl.2016.08.007
30. Zhang Y, Gao H, Liu R, Liu J, Chen L, Li X, et al. Quinazoline-1-deoxynojirimycin hybrids as high active dual inhibitors of EGFR and α-glucosidase. Bioorganic Med Chem

Lett [Internet], 2017; 27(18): 4309–13. Available from: http://dx.doi.org/10.1016/j.bmcl.2017.08.035

31. Liu Z, Wang L, Feng M, Yi Y, Zhang W, Liu W, et al. New acrylamide-substituted quinazoline derivatives with enhanced potency for the treatment of EGFR T790M-mutant non-small-cell lung cancers. Bioorg Chem [Internet], 2018; 77: 593–9. Available from: https://doi.org/10.1016/j.bioorg.2018.01.035
32. Shepherd-Littlejohn AL, Hanft WJ, Kennedy VA, Alvarez EA. Afatinib use in recurrent epithelial ovarian carcinoma. Gynecol Oncol Reports [Internet], July, 2019; 29: 70–2. Available from: https://doi.org/10.1016/j.gore.2019.07.001
33. Sudhan DR, Guerrero-Zotano A, Won H, González Ericsson P, Servetto A, Huerta-Rosario M, et al. Hyperactivation of TORC1 Drives Resistance to the Pan-HER Tyrosine Kinase Inhibitor Neratinib in HER2-Mutant Cancers. Cancer Cell., 2020; 37(2): 183-199.e5.
34. Karachaliou N, Fernandez-bruno M, Wilhelmina J, Bracht P, Rosell R. EGFR first- and second-generation TKIs — there is still a place for them in EGFR -mutant NSCLC patients, 2019; 8(1).
35. Tang J, Qian Y, Li H, Kopecky BJ, Ding D, Ou HC, et al. Canertinib induces ototoxicity in three preclinical models. Hear Res [Internet], 2015; 328: 59–66. Available from: http://dx.doi.org/10.1016/j.heares.2015.07.002
36. Tu Y, Wang C, Yang Z, Zhao B, Lai L, Yang Q, et al. Discovery of novel quinazoline derivatives bearing semicarbazone moiety as potent EGFR kinase inhibitors. Comput Struct Biotechnol J [Internet], 2018; 16(xxxx): 462–78. Available from: https://doi.org/10.1016/j.csbj.2018.10.016
37. Song J, Jang S, Lee JW, Jung D, Lee S, Min KH. Click chemistry for improvement in the selectivity of quinazoline-based kinase inhibitors for mutant epidermal growth factor receptors. Bioorganic Med Chem Lett [Internet], 2019; 29(3): 477–80. Available from: https://doi.org/10.1016/j.bmcl.2018.12.020
38. Zhang L, Yang Y, Zhou H, Zheng Q, Li Y, Zheng S, et al. Structure-activity study of quinazoline derivatives leading to the discovery of potent EGFR-T790M inhibitors. Eur J Med Chem [Internet], 2015; 102: 445–63. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.08.026
39. Beagan JJ, Bach S, van Boerdonk RA, van Dijk E, Thunnissen E, van den Broek D, et al. Circulating tumor DNA analysis of EGFR-mutant non-small cell lung cancer patients receiving osimertinib following previous tyrosine kinase inhibitor treatment. Lung Cancer

[Internet], February, 2020; 145: 173–80. Available from: https://doi.org/10.1016/j.lungcan.2020.04.039

40. Wang H, Zhang L, Hu P, Zheng X, Si X, Zhang X, et al. Penetration of the blood–brain barrier by avitinib and its control of intra/extra-cranial disease in non-small cell lung cancer harboring the T790M mutation. Lung Cancer [Internet], April, 2018; 122: 1–6. Available from: https://doi.org/10.1016/j.lungcan.2018.05.010
41. Tan DSW, Leighl NB, Riely GJ, Yang JCH, Sequist L V., Wolf J, et al. Safety and efficacy of nazartinib (EGF816) in adults with EGFR-mutant non-small-cell lung carcinoma: a multicentre, open-label, phase 1 study. Lancet Respir Med [Internet], 2020; 8(6): 561–72. Available from: http://dx.doi.org/10.1016/S2213-2600(19)30267-X
42. Kim DW, Lee DH, Han JY, Lee J, Cho BC, Kang JH, et al. Safety, tolerability, and anti-tumor activity of olmutinib in non-small cell lung cancer with T790M mutation: A single arm, open label, phase 1/2 trial. Lung Cancer [Internet], July. 2019; 135: 66–72. Available from: https://doi.org/10.1016/j.lungcan.2019.07.007
43. Plé PA, Green TP, Hennequin LF, Curwen J, Fennell M, Allen J, et al. Discovery of a New Class of Anilinoquinazoline Inhibitors with High Affinity and Specificity for the Tyrosine Kinase Domain of c-Src. J Med Chem., 2004; 47(4): 871–87.
44. VanBrocklin HF, Lim JK, Coffing SL, Hom DL, Negash K, Ono MY, et al. Anilinodialkoxyquinazolines: Screening epidermal growth factor receptor tyrosine kinase inhibitors for potential tumor imaging probes. J Med Chem., 2005; 48(23): 7445–56.
45. Klutchko SR, Zhou H, Winters RT, Tran TP, Bridges AJ, Althaus IW, et al. Tyrosine kinase inhibitors. 19. 6-alkynamides of 4-anilinoquinazolines and 4-anilinopyrido[3,4-d]pyrimidines as irreversible inhibitors of the erbB family of tyrosine kinase receptors. J Med Chem., 2006; 49(4): 1475–85.
46. Mi YC, Lee KO, Jong WK, Chang GL, Ji YS, Young HK, et al. Discovery of a novel Her-1/Her-2 dual tyrosine kinase inhibitor for the treatment of Her-1 selective inhibitor-resistant non-small cell lung cancer. J Med Chem., 2009; 52(21): 6880–8.
47. Modi SJ, Kulkarni VM. Vascular Endothelial Growth Factor Receptor (VEGFR-2)/KDR Inhibitors: Medicinal Chemistry Perspective. Med Drug Discov [Internet], 2019; 2: 100009. Available from: https://doi.org/10.1016/j.medidd.2019.100009
48. Abdel-Aziz AK, Mantawy EM, Said RS, Helwa R. The tyrosine kinase inhibitor, sunitinib malate, induces cognitive impairment in vivo via dysregulating VEGFR signaling, apoptotic and autophagic machineries. Exp Neurol [Internet], 2016; 283: 129–41. Available from: http://dx.doi.org/10.1016/j.expneurol.2016.06.004

49. Wang L, Zhan Y, Wu Z, Lin M, Jin X, Jiang L, et al. A novel multitarget kinase inhibitor BZG with potent anticancer activity in vitro and vivo enhances efficacy of sorafenib through PI3K pathways in hepatocellular carcinoma cells. Biomed Pharmacother [Internet], 2020; 125(79): 110033. Available from: https://doi.org/10.1016/j.biopha.2020.110033
50. Gauler TC, Besse B, Mauguen A, Meric JB, Gounant V, Fischer B, et al. Phase II trial of ptk787/zk 222584 (vatalanib) administered orally once-daily or in two divided daily doses as second-line monotherapy in relapsed or progressing patients with stage iiib/iv non-small-cell lung cancer (nsclc). Ann Oncol, 2012; 23(3): 678–87.
51. El-Gazzar MG, El-Hazek RM, Zaher NH, El-Ghazaly MA. Design and synthesis of novel pyridazinoquinazoline derivatives as potent VEGFR-2 inhibitors: In vitro and in vivo study. Bioorg Chem [Internet], August, 2019; 92: 103251. Available from: https://doi.org/10.1016/j.bioorg.2019.103251
52. Garofalo A, Goossens L, Six P, Lemoine A, Ravez S, Farce A, et al. Impact of aryloxy-linked quinazolines: A novel series of selective VEGFR-2 receptor tyrosine kinase inhibitors. Bioorganic Med Chem Lett [Internet], 2011; 21(7): 2106–12. Available from: http://dx.doi.org/10.1016/j.bmcl.2011.01.137
53. Yu B, Tang L Da, Li YL, Song SH, Ji XL, Lin M Sen, et al. Design, synthesis and antitumor activity of 4-aminoquinazoline derivatives targeting VEGFR-2 tyrosine kinase. Bioorganic Med Chem Lett [Internet], 2012; 22(1): 110–4. Available from: http://dx.doi.org/10.1016/j.bmcl.2011.11.061
54. Salerno S, Marini AM, Fornaciari G, Simorini F, La Motta C, Taliani S, et al. Investigation of new 2-aryl substituted Benzothiopyrano[4,3-d[pyrimidines as kinase inhibitors targeting vascular endothelial growth factor receptor 2. Eur J Med Chem [Internet], 2015; 103: 29–43. Available from: http://dx.doi.org/10.1016/j.ejmech.2015.08.027
55. Ravez S, Barczyk A, Six P, Cagnon A, Garofalo A, Goossens L, et al. Inhibition of tumor cell growth and angiogenesis by 7-Aminoalkoxy-4- aryloxy-quinazoline ureas, a novel series of multi-tyrosine kinase inhibitors. Eur J Med Chem [Internet], 2014; 79: 369–81. Available from: http://dx.doi.org/10.1016/j.ejmech.2014.04.007
56. Hennequin LF, Thomas AP, Johnstone C, Stokes ESE, Plé PA, Lohmann JJM, et al. Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. J Med Chem., 1999; 42(26): 5369–89.
57. Hennequin LF, Stokes ESE, Thomas AP, Johnstone C, Plé PA, Ogilvie DJ, et al. Novel 4-

anilinoquinazolines with C-7 basic side chains: Design and structure activity relationship of a series of potent, orally active, VEGF receptor tyrosine kinase inhibitors. J Med Chem., 2002; 45(6): 1300–12.

58. Weiss MM, Harmange J-C, Polverino AJ, Berry L, Berry V, Borg G, et al. Evaluation of N-Alkyl Naphthamides as Potent, Orally Active VEGFR-2 Tyrosine Kinase Inhibitors. J Med Chem, 2008; 1668.
59. Lim CP, Bhuvaneswari R, Feng NQ, Thong PSP, Chye TN, Chee SK. Targeted therapy against vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) using vandetanib enhances the photodynamic therapy potential in oral squamous carcinoma cancer. Photodiagnosis Photodyn Ther [Internet], 2017; 17: A70. Available from: http://dx.doi.org/10.1016/j.pdpdt.2017.01.158
60. Zhang HQ, Gong FH, Ye JQ, Zhang C, Yue XH, Li CG, et al. Design and discovery of 4-anilinoquinazoline-urea derivatives as dual TK inhibitors of EGFR and VEGFR-2. Eur J Med Chem [Internet], 2017; 125: 245–54. Available from: http://dx.doi.org/10.1016/j.ejmech.2016.09.039
61. Wissner A, Fraser HL, Ingalls CL, Dushin RG, Floyd MB, Cheung K, et al. Dual irreversible kinase inhibitors : Quinazoline-based inhibitors incorporating two independent reactive centers with each targeting different cysteine residues in the kinase domains of EGFR and VEGFR-2, 2007; 15: 3635–48.