The Therapeutic Journey of Quinazoline as Anti-cancer Targeting Kinase Inhibitors.

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RECEIVED: 3 JUNE 2025; ACCEPTED: 24 JULY 2025 HTTPS://DOI.ORG/ 10.55815/433238

ABSTRACT

Cancer is a group of different diseases that can affect various parts of the body through abnormal cell growth. Many existing chemotherapy agents are highly toxic and lack selectivity. This often results in treatment resistance. Therefore, there is a great need for targeted chemotherapeutic agents with minimal side effects and high selectivity for cancer treatment. Quinazoline is a crucial structural scaffold known to be associated with various biological activities, including amazing anti-cancer effects. Several recognized anticancer quinazolines act by various molecular targets and mechanisms. This review aims to explain various aspects of medicinal chemistry, such as drug design, the relationship between structure and activity, and the mode of action of quinazoline derivatives specifically targeted against cancer. In addition to focusing on the key preparation strategies of different quinazoline derivatives. It provides a comprehensive overview of the chemotherapeutic effects of quinazolines as well as synthesis in terms of drug discovery and development.

Keywords: Quinazoline; cancer; targeted therapy; Kinase; Selectivity.

RESUMEN

El cáncer es un conjunto de diferentes enfermedades que pueden afectar diversas partes del cuerpo mediante un crecimiento celular anormal. Muchos de los agentes quimioterapéuticos existentes son altamente tóxicos y carecen de selectividad, lo que a menudo provoca resistencia al tratamiento. Por lo tanto, existe una gran necesidad de agentes quimioterapéuticos dirigidos, con efectos secundarios mínimos y alta selectividad para el tratamiento del cáncer.

La quinazolina es un esqueleto estructural crucial, conocido por estar asociado a diversas actividades biológicas, incluidos efectos anticancerígenos notables. Varias quinazolinas anticancerígenas reconocidas actúan mediante diferentes dianas moleculares y mecanismos. Esta revisión tiene como objetivo explicar diversos aspectos de la química medicinal, como el diseño de fármacos, la relación entre estructura y actividad, y el modo de acción de los derivados de quinazolina específicamente dirigidos contra el cáncer. Además, se centra en las principales estrategias de síntesis de los diferentes derivados de quinazolina. Ofrece una visión completa de los efectos quimioterapéuticos de las quinazolinas, así como de su síntesis en términos de descubrimiento y desarrollo de fármacos.

Palabra clave: Quinazolina; Cáncer; Terapia dirigida; Quinasa; Selectividad

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RESUM

El càncer és un conjunt de diferents malalties que poden afectar diverses parts del cos mitjançant un creixement cel·lular anormal. Molts agents quimioterapèutics existents són altament tòxics i manquen de selectivitat, cosa que sovint provoca resistència al tractament. Per tant, hi ha una gran necessitat d'agents quimioterapèutics dirigits amb efectes secundaris mínims i alta selectivitat per al tractament del càncer.

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Paraules clau: Quinazolina; Càncer; Teràpia dirigida; Quinasa; Selectivitat

INTRODUCTION

Cancer is the leading cause of mortality before the age of 70 in 112 of 183 countries[1]. Cancer is responsible for one-sixth of all global deaths, surpassing the combined mortality rate of AIDS, tuberculosis, and malaria[2]. In particular, cancer incidence significantly increased in 2019 for breast, uterine corpus cancers, and liver cancer[3]. Cancers of unknown primary (CUPs) are responsible for up to 150,000 new cases diagnosed yearly in the United States and the European Union, with estimates ranging from 150,000 to 400,000 cases.[4] The global cancer burden has been a significant worldwide health concern over the last ten years, with its growing magnitude[5], according to the American Cancer Society estimations for the new incidences,[6-16] as depicted in Figure 1.

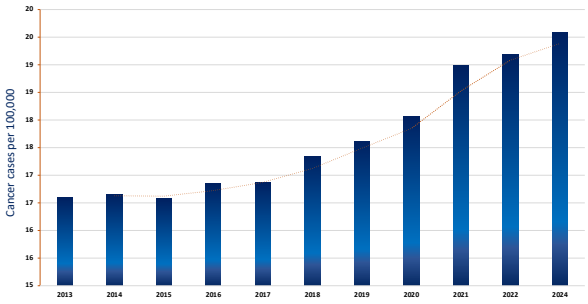


Figure 1. *The estimated new cancer incidences in the last ten years*

The increasing prevalence of cancer cases and deaths has profoundly affected individuals, families, and communities worldwide[17]. This surge in cancer incidence and mortality rates has prompted extensive research, public health initiatives, and medical advancements to combat this pervasive disease[18]. The rise in cancer cases and deaths over the past ten years has spurred concerted efforts to tackle this disease.

Cancer phenotyping can be classified into > 100 varieties, including breast, lung, prostate, stomach, and liver. Breast cancer is the most common type of cancer globally, comprising 12.5% of new cancer cases each year and representing 15% of all cancer cases in the United States. Between 2012 and 2014, the probability of women in the United States acquiring invasive breast cancer was 1 in 8 [19]. Breast cancer is a significant and prevalent health concern that affects countless women around the world. The incidence rates may differ by region, but the latest statistics show that in 2020, more than 2.3 million new cases were diagnosed worldwide[20]. Moreover, the most recent study in 2024 shows the estimated top five common cancer sites in the US and the estimated deaths, as depicted in figure 2[6].

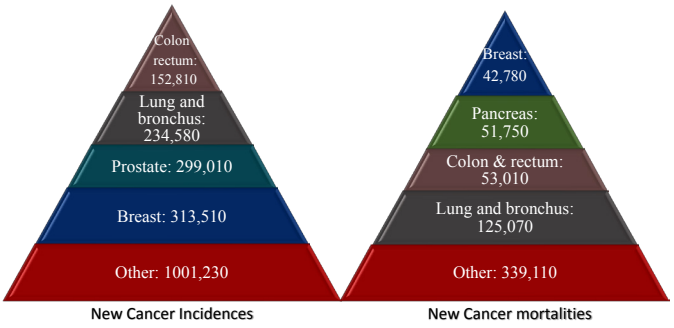


Figure 2. *The five common cancer sites in the US. 2024 for estimated new cancer incidences and mortalities.*

Cancer comprises a group of complex diseases characterized by progressive and uncontrolled cell proliferation.[21] The NCDB (National Cancer Database) was used to obtain information on the first course of treatment for cases diagnosed in 2018, the most recent year for which complete data are available, except diffuse B-cell non-Hodgkin lymphoma and testicular cancer, for which aggregated patients diagnosed from 2014 to 2018 were used due to sparse data. The NCDB is a hospital-based cancer registry co-sponsored by the American Cancer Society and the American College of Surgeons that includes >70% of all invasive cancers in the United States from over 1500 facilities accredited by the American College of Surgeons' Commission on Cancer (CoC). Unfortunately, NCDB treatment data are inadequate for diseases often detected in the outpatient environment, such as prostate cancer, melanoma, and leukemia, and so were augmented with information from the scientific literature; there may also be some reporting delay.[22, 23] Cancer therapy varies widely depending on the cancer type and stage. Depending on the type of cancer and its stage will determine the type of therapy received. Some cancer patients will only receive one therapy. However,

most individuals have a combination of treatments, such as surgery, chemotherapy, and radiation therapy, as represented in Figure 3.[24]

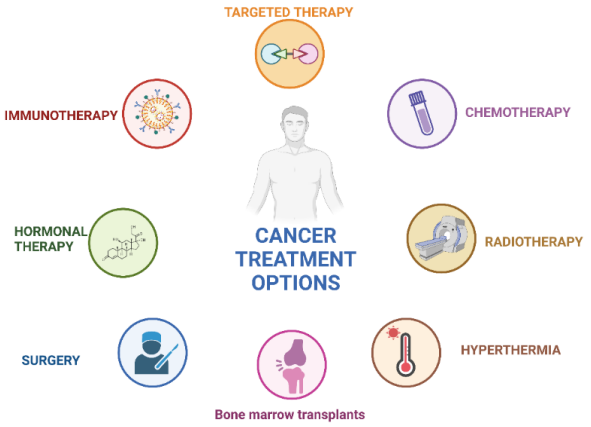


Figure 3. *The most common types of cancer treatments.*

Hormone therapy

Hormone therapy is a cancer treatment designed to slow or stop the growth of hormone-sensitive tumors by interfering with hormone production or action. It is primarily used for breast and prostate cancers, which often respond to estrogen and testosterone, respectively. Treatment methods include medications that block hormone effects, surgery to remove hormone-producing organs, or radiation therapy[25].

In breast cancer, hormone therapy is commonly used after surgery to reduce recurrence risk, with selective estrogen receptor modulators (SERMs) like tamoxifen being effective for hormone receptor-positive cases[26]. For prostate cancer, androgen deprivation therapy (ADT) reduces testosterone levels and is often combined with other treatments, improving survival rates in advanced cases[27].

While effective, hormone therapy has potential side effects. SERMs may lead to hot flashes and an increased risk of blood clots in women[28], while ADT can result in fatigue, weight gain, and higher chances of bone fractures in men [29].

Surgery

Surgery remains a cornerstone in cancer treatment, primarily aimed at removing malignant tissue to halt disease progression and alleviate symptoms. Depending on the cancer type, stage, and location—as well as the patient's overall health [30].

Recent advancements have significantly enhanced the safety and efficacy of surgical interventions. One notable technique is **cryosurgery** (also known as **cryoablation**), a minimally invasive procedure that employs extreme cold to destroy cancerous cells. A cryoprobe is inserted directly into the tumor, where gases like liquid nitrogen circulate to freeze and eliminate the targeted tissue. This method has shown particular utility in treating prostate, liver, and lung cancers, especially in patients who are not candidates for conventional surgery or those with small, localized tumors [31].

Cryosurgery offers several advantages, including high precision, reduced damage to surrounding healthy tissue, and minimal bleeding and scarring. It is often performed on an outpatient basis. However, its application may be limited in cases involving larger tumors or anatomically challenging locations. As with any surgical intervention, potential risks include bleeding, infection, and injury to adjacent structures. Additionally, surgery may be contraindicated in patients with advanced-stage cancer or compromised health status[32].

Immunotherapy

Immunotherapy is an innovative cancer treatment that utilizes the immune system to target and destroy cancer cells while sparing healthy ones, resulting in fewer side effects compared to traditional treatments. Key approaches include checkpoint inhibitors, which enhance the immune response by preventing specific protein interactions, and CAR T-cell therapy, where a patient's immune cells are genetically modified to better attack cancer cells, particularly effective in blood cancers[33]. Cancer's FDA-approved therapies such as Sipuleucel-T for prostate cancer, also stimulate the immune system to recognize and combat cancer cells, as shown in figure 4. Ongoing research aims to develop new strategies and improve existing therapies, positioning immunotherapy as a transformative approach in cancer care.

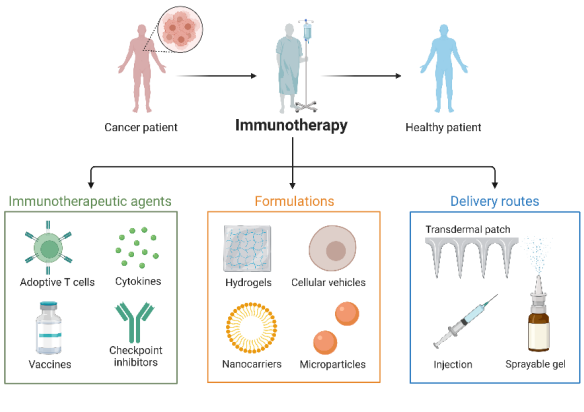


Figure 4. *The schematic immunotherapy protocol*

Radiation therapy

Radiation therapy, or radiotherapy, is a cancer treatment that uses high-energy radiation to destroy cancer cells. It can be the primary treatment or used alongside surgery or chemotherapy. The therapy damages the DNA of cancer cells, preventing them from dividing and growing. Radiation can be delivered through an external beam or via brachytherapy, where radioactive sources are placed directly in or near the tumor. This method targets cancerous cells while protecting surrounding healthy tissue.

Recent advancements like intensity-modulated radiation therapy (IMRT) have enhanced the precision of radiation delivery, improved outcomes, and reduced

side effects for various cancers, including prostate and breast cancer[34, 35]. However, radiation therapy has drawbacks such as potential damage to healthy tissues, the risk of secondary malignancies, and limitations for specific cancer types[36].

Bone marrow transplants

Bone marrow transplants, or stem cell transplants, involve replacing damaged bone marrow with healthy stem cells, which can develop into various blood cells. They are primarily used to treat blood cancers like leukemia and lymphoma and can be categorized into autologous and allogeneic. Autologous transplants use the patient's stem cells after high-dose chemotherapy, while allogeneic transplants involve cells from a matched donor[37], as shown in figure 5. These transplants aim to restore the immune system and blood cell production. Recent advancements focus on improving safety, such as reduced-intensity conditioning regimens, while increasing stem cell collection and engraftment. However, complications can arise, including graft-versus-host disease (GVHD) and infections due to a weakened immune system[38].

Hyperthermia, or applying heat up to 113°F, can help damage cancer cells while sparing normal tissue. It is often combined with radiation or chemotherapy to enhance effectiveness and minimize side effects. By increasing blood flow to the tumor, hyperthermia improves drug delivery and oxygenation. Studies, including one with 340 advanced cervical cancer patients, show that combining hyperthermia with radiation therapy can improve survival rates. However, it carries risks, such as burns to healthy tissue, necessitating careful control. Research on hyperthermia's optimal use in cancer treatment continues to show promising results[39].

Chemotherapy

Chemotherapy is a widely used cancer treatment approach that employs cytotoxic drugs to kill rapidly dividing cancer cells throughout the body. Chemotherapy can be administered orally, through injections or infusions, or as topical treatments. Chemotherapy is a standard treatment method for many types of cancer, including leukemia, lymphoma, breast cancer, lung cancer, and colon cancer[40, 41]. Several studies have demonstrated the effectiveness of chemotherapy in treating various

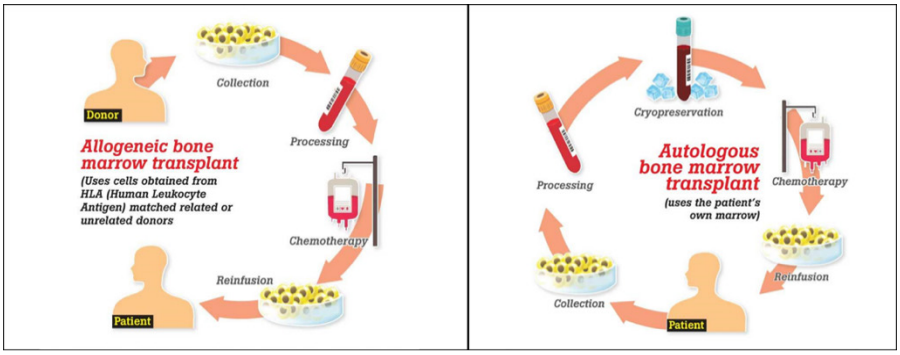


Figure 5. *The autologous and allogeneic techniques for bone marrow transplant.*

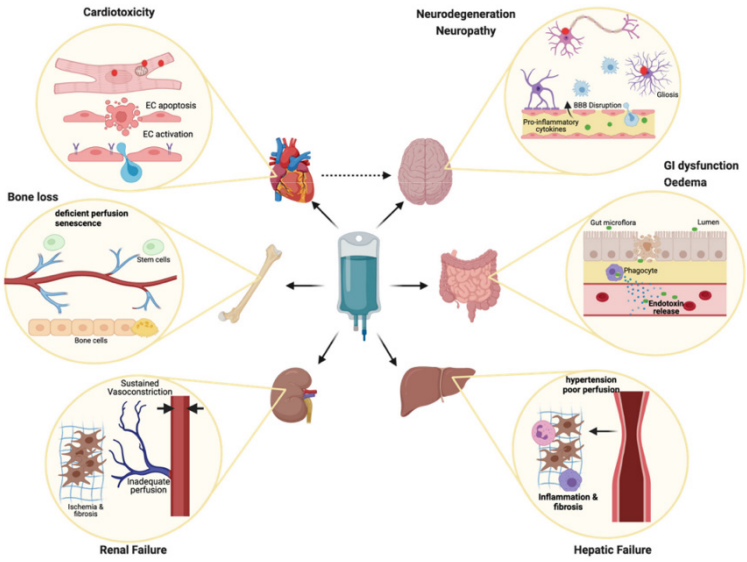


Figure 6. *Drawbacks of chemotherapy on several organs*

cancers. For example, a survey of 828 non-small cell lung cancer patients revealed that chemotherapy improved overall survival and quality of life.[42] Another study found that chemotherapy before surgery in patients with advanced ovarian cancer increased the chance of complete tumor removal during surgery. Chemotherapy can be used alone or with other treatments, such as radiation therapy or surgery. Combination therapy has been shown to improve outcomes in many types of cancer. For example, a study conducted on 2,400 women with breast cancer showed that adjuvant chemotherapy in combination with radiation therapy and surgery significantly improved disease-free survival compared to radiation therapy and surgery alone.[43] While chemotherapy can effectively treat cancer, it is associated with severe side effects. The drugs used in chemotherapy can also affect healthy cells, leading to side effects such as some organ failure, fatigue, hair loss, and an increased risk of infection.[44] However, medications and other supportive therapies can manage many of these side effects, as depicted in Figure 6.

Targeted therapy

Targeted therapy is a type of cancer treatment focusing on specific proteins or genes that contribute to the growth and survival of cancer cells. Molecularly targeted therapies, including growth factors, signaling molecules, and apoptosis regulators, have been proven to possess antitumor effects that do not cause damage to the healthy tissue surrounding the tumor, in contrast to conventional chemotherapy[45]. As a result, this approach offers the potential for more effective and less toxic treatments.

Monoclonal antibodies

Targeted therapies work by blocking the action of proteins that promote cancer cell growth or activating the immune system to attack cancer cells. One example of targeted therapy is monoclonal antibodies (mAbs), lab-made antibodies designed to recognize and bind to a specific target molecule in the body. Immune cells naturally develop to recognize and neutralize foreign substances such as bacteria or viruses[46]. Monoclonal antibodies are produced by cloning an immune cell. Monoclonal antibodies are targeted therapies to selectively bind to proteins or receptors on cancer cells or other cells in the tumor microenvironment. By binding to these targets, monoclonal antibodies can exert their therapeutic effects in several ways[47]. One example is the d**irect targeting of cancer cells:** Monoclonal antibodies can directly bind to proteins or receptors overexpressed or mutated in cancer cells. This binding can interfere with the signaling pathways that promote cancer cell growth, survival, or spread.

Monoclonal antibodies can inhibit tumor growth and induce cancer cell death by blocking these pathways[48] **Delivery of cytotoxic agents:** Monoclonal antibodies can be engineered to carry cytotoxic agents, such as chemotherapy drugs or radioactive particles, to target cancer cells specifically. These antibody-drug conjugates (ADCs) deliver the cytotoxic payload directly to the tumor cells, reducing the exposure of healthy cells to the drug's toxic effects[49].

Kinome and genome mapping

Genome mapping identifies a gene's location and distance from other genes on the same chromosome. Genome maps are significant in finding human diseases. Researchers can find disease markers by identifying the inheritance of disease-specific genomic loci[50]. In addition, genomic maps have made disease research more efficient for scientists by allowing them to focus on a few million base pairs instead of the entire 3 billion base pair genome[51]. This approach is a powerful tool

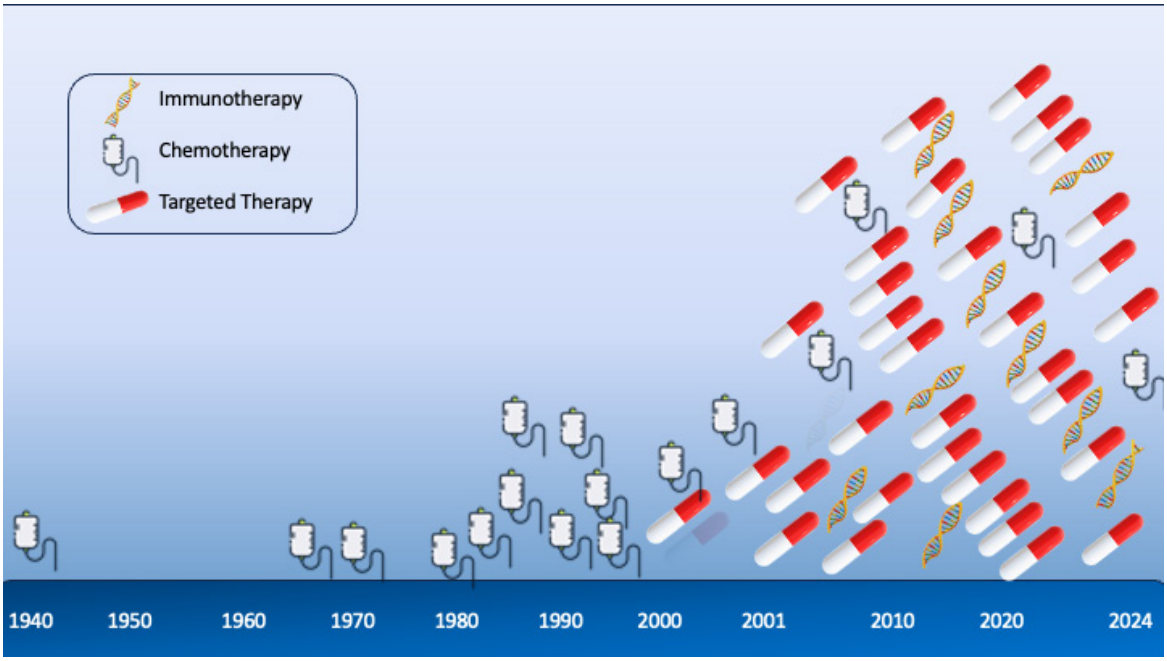


Figure 7. *Targeted therapy development throughout the years*

that enables scientists to concentrate on their efforts more effectively. In addition to disease-associated genes, researchers are also interested in understanding the genome to discover novel genes, differentiate between healthy and diseased genes, regulate gene networks, and identify the role of non-coding regions in gene expression[52]. Gene expression profiling involves measuring the activity or expression levels of thousands of genes simultaneously in each sample[53].

Kinome mapping is the process of identifying and characterizing the protein kinases present in an organism's genome[54]. Protein kinases are enzymes that regulate cellular signaling pathways by adding phosphate groups to target proteins, thereby modulating their function. Understanding the kinome, or the entire complement of protein kinases, is crucial for unraveling the complex network of cellular signaling and its implications in various biological processes and diseases[55].

Tyrosine Kinases in Cancer

In humans, it is estimated that there are approximately 500 protein kinases. These protein kinases are classified into several major groups based on their sequence similarities and functional characteristics. The classification schemes commonly used for human kinases include the Human Kinome Organization (HKO) classification and the Manning classification[56], as exhibited in Figure 7.

Here is a breakdown of one of the significant kinase groups in the human kinome: **TK kinases** (Tyrosine Kinase) are a group of protein kinases that specifically phosphorylate tyrosine residues in target proteins. They play critical roles in cellular signaling, controlling various processes such as cell growth, differentiation, proliferation, and survival. Tyrosine phosphorylation events are crucial for transmitting extracellular signals into the cell and regulating intracellular signaling cascades[57]. The TK kinase group can be further classified into two major categories:

Non-Receptor Tyrosine Kinases (NRTKs): NRTKs are cytoplasmic kinases that do not possess transmembrane domains. They are generally activated by interaction with other proteins or signaling events, and their activation often relies on regulatory proteins or scaffolding complexes. NRTKs are involved in diverse signaling pathways and cellular processes. Examples of NRTKs include Sc, Abl, Janus Kinases (JAKs), and Focal Adhesion Kinase (FAK).

Receptor Tyrosine Kinases (RTKs): RTKs are transmembrane proteins that span the cell membrane and have an extracellular ligand-binding domain and an intracellular tyrosine kinase domain[58]. When a specific ligand binds to the extracellular domain, it activates the kinase domain, leading to the autophosphorylation of tyrosine residues and subsequent activation of downstream signaling pathways. Examples of RTKs include the Epidermal Growth Factor Receptor (EGFR) and human epidermal growth factor receptors 2,3 and 4 (HER2, HER3, and HER4)[59].

Tyrosine kinase activity is tightly regulated to maintain cellular homeostasis. Mutations in TK kinases can lead to various diseases, including cancer, autoimmune diseases, and developmental disorders. Epidermal Growth Factor Receptor (EGFR): EGFR is involved in cell proliferation, survival, and metastasis. Overexpression of EGFR is frequently observed in HCC, and EGFR signaling is associated with tumor growth and progression. EGFR-Targeted TKIs: While EGFR isn't always regularly overexpressed in breast cancers, its hobby has been implicated in a few subtypes, including triple-bad breast cancer[60]. EGFR-focused TKIs, inclusive of gefitinib and erlotinib, had been explored in scientific trials for breast cancer treatment, specifically in patients with EGFR-advantageous tumors. The improvement of tyrosine kinase inhibitors (TKIs) has significantly impacted on the treatment of breast cancer[61, 62].

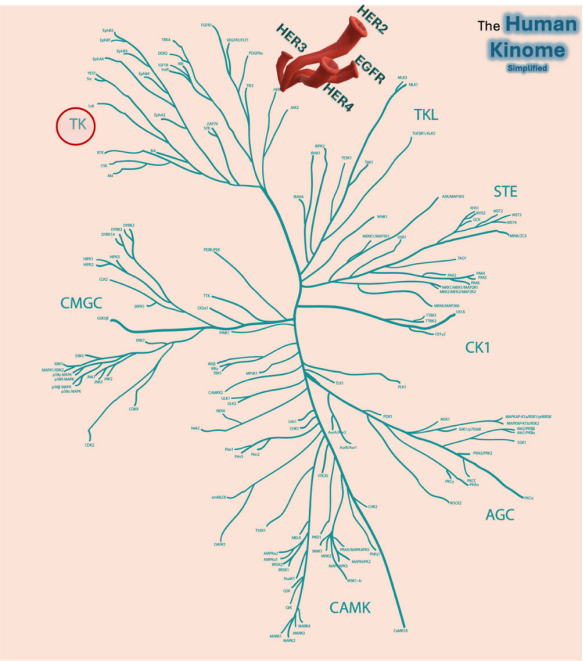


Figure 7. *The simplified human Kinome phylogenetic tree.*

HER2 in Breast Cancer

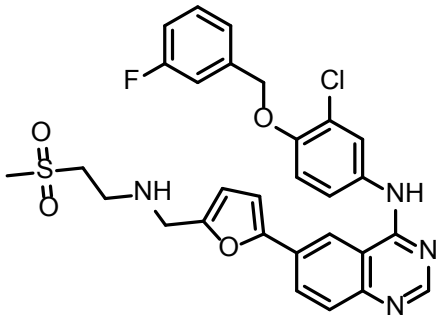
Identifying and characterizing HER2 (human epidermal growth factor receptor 2) as a breast cancer hallmark requires clarification. Although not initially recognized as a hallmark of cancer as defined by Hanahan and Weinberg in 2000, HER2 does play a crucial role in the development of breast cancer. As a result, it is an important biomarker and therapeutic target for this type of cancer. HER2 is an overexpressed protein in approximately 20% of breast cancers[63]. Its overexpression leads to increased signaling pathways that promote cell growth, proliferation, and survival, contributing to the development and progression of breast cancer. Breast cancers that are HER2+ are generally more aggressive and have a worse prognosis compared to HER2- breast cancers. The recognition of HER2 overexpression in breast cancer has had a transformative impact on treatment strategies[64]. Targeted therapies such as trastuzumab (Herceptin) and other HER2-targeted agents have been developed to inhibit the HER2 receptor and its downstream signaling pathways. These therapies have shown remarkable efficacy in improving

outcomes and survival rates for patients with HER2+ breast cancer[65].HER2+ breast cancer is generally associated with a more aggressive disease course and a poorer prognosis than HER2-negative breast cancer. Here are some key points regarding the poor prognosis of HER2+ breast cancer[66]:

Other TKIs: Several other TKIs were investigated in scientific trials for breast cancer, including multi-targeted TKIs like dasatinib, lapatinib, and cabozantinib, as well as unique kinase inhibitors like neratinib and tucatinib, which target HER own family contributors[67].

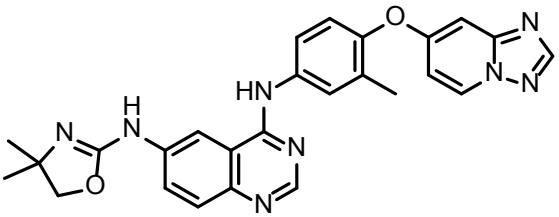
Here is a focus on the novel approaches of lapatinib and sorafenib as dual and multi-targeted therapies, specifically in HER2-positive breast cancer:

Dual HER2/EGFR Inhibition: Lapatinib is a dual tyrosine kinase inhibitor targeting human epidermal growth factor receptor 2 (HER2) and epidermal growth factor receptor (EGFR). These receptors play crucial roles in promoting cell growth, division, and survival. By blocking the activity of EGFR and HER2, lapatinib helps to inhibit the signaling pathways that drive cancer cell growth and proliferation[68].



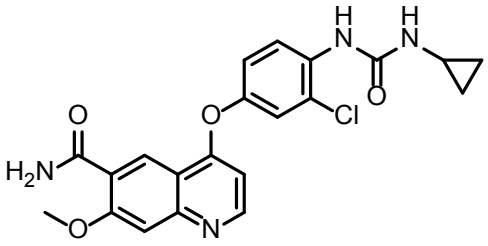
Lapatinib

Tucatinib is a novel therapeutic approach targeting HER2 in various types of cancer, including HER2+ BC. Tucatinib is an oral tyrosine kinase inhibitor that targets explicitly HER2. It has shown efficacy in combination with other therapies for the treatment of HER2-positive breast cancer[69]. One significant advantage of tucatinib is its ability to penetrate the blood-brain barrier, making it effective in treating brain metastases associated with HER2-positive breast cancer. Brain metastases often pose a significant challenge in treatment due to limited drug penetration. Tucatinib has demonstrated efficacy in reducing the size of brain metastases and improving survival rates in patients with HER2-positive breast cancer that has spread to the brain. Clinical trials evaluating tucatinib in HER2-positive breast cancer have shown positive results[70]. In the HER2CLIMB trial, the combination of tucatinib, trastuzumab, and capecitabine significantly improved progression-free survival and overall survival compared to placebo plus trastuzumab and capecitabine in patients with advanced HER2-positive breast cancer, including those with brain metastases[66]. Common side effects associated with the previous drugs include diarrhea, rash, nausea, vomiting, fatigue, and hand-foot syndrome (palmar-plantar erythrodysesthesia). It is crucial for healthcare professionals to monitor and manage these side effects to ensure patient comfort and adherence to treatment[71].

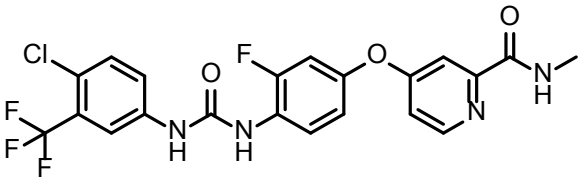


Tucatinib

Combination Therapies: Combining different targeted therapies or combining targeted therapies with other treatment modalities, such as chemotherapy or immunotherapy, is another approach being explored in HCC[72]. For example, the combination of sorafenib with other targeted agents, such as Lenvatinib or regorafenib, has shown improved efficacy compared to single-agent therapy in advanced HCC[73]. Additionally, clinical trials are investigating the combination of targeted therapies with immune checkpoint inhibitors in HCC to enhance the immune response against tumor cells[74].



Lenvatinib



Regorafenib

In targeted cancer therapy, small molecules often contain specific chemical moieties or functional groups that contribute to their ability to interact with and modulate specific molecular targets involved in cancer cell growth and survival[75]. These moieties are designed to enhance the selectivity and efficacy of the small molecules[76]. As shown in figure 8, An example of pharmacophore moieties are specific chemical groups or arrangements within a small molecule that interact with the target protein or enzyme.

These moieties bind to the target and initiate the desired therapeutic effect. Examples include hydrogen bond donors/acceptors, aromatic rings, and hydrophobic

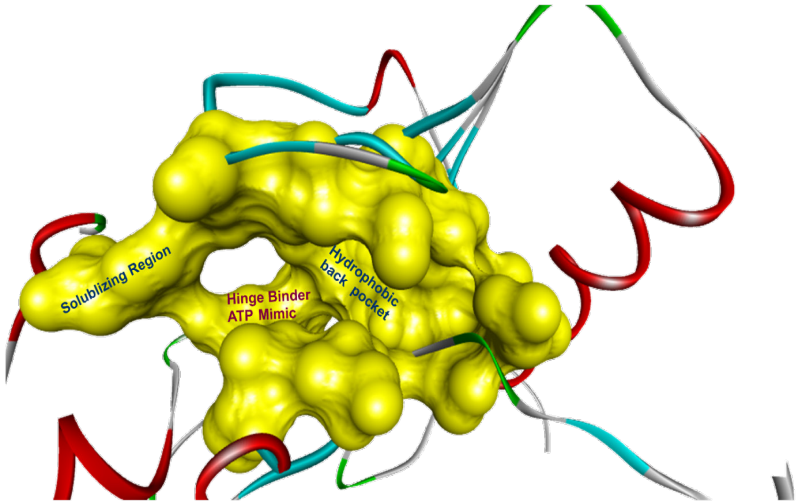


Figure 8. *Example of the essential pharmacophoric moieties in small molecules PTKIs*

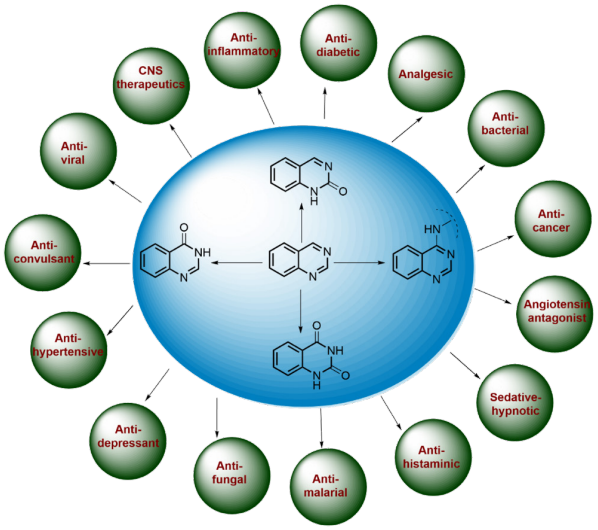


Figure 9. *Quinazoline-based small molecules and their pharmacological activities.*

regions. Functional groups are specific atoms or groups of atoms within a small molecule that contribute to its chemical reactivity and interactions. They can directly participate in binding interactions with the target or modify the molecule's pharmacokinetic properties. Specific small molecules function as electrophiles, capable of covalently binding to specific target proteins. These electrophilic moieties form irreversible bonds with nucleophilic residues within the target protein, inhibiting or modulating protein activity[77]. This approach is particularly effective for targeting proteins with catalytic activities. Many targeted cancer therapies focus on inhibiting specific kinases that play a role in cancer cell signaling pathways. Small molecules designed to target kinases often contain moieties that interact with the ATP-binding site of the kinase. These moieties are typically designed to mimic the structure of ATP and compete with ATP for binding to the kinase active site[78, 79]. It is important to note that the specific moieties used in targeted cancer therapy depend on the specific molecular targets and pathways being targeted, as well as the desired mechanism of action. The design of small molecules in targeted therapy continues to evolve as researchers uncover new molecular targets and develop strategies to enhance their selectivity and efficacy.

Significance of Quinazoline nucleus in the medical field and anti-tumorigenesis in particular

The quinazoline nucleus is a chemical structure consisting of a benzene ring fused with a pyrimidine ring. It has significant importance in the medical field due to its pharmacological properties and its role in the development of various therapeutic agents. Here are some key aspects of the significance of the quinazoline nucleus in the medical field depicted in figure 9. The quinazoline nucleus has shown significance in the field of neurological disorders due to its potential therapeutic applications[80]. Certain quinazoline-based compounds have demonstrated the ability to modulate

neurotransmitter systems in the brain. For example, some derivatives have been found to interact with adenosine receptors, leading to the modulation of neurotransmission. Adenosine receptor modulation has been implicated in various neurological conditions, including epilepsy, depression, and neurodegenerative disorders. Quinazoline derivatives can be modified to optimize their affinity and selectivity for specific adenosine receptor subtypes, potentially offering therapeutic benefits in these disorders. In addition, quinazoline-based compounds have shown neuroprotective effects in preclinical studies[81].

They have been investigated for their ability to attenuate oxidative stress, inhibit apoptosis, and protect neurons from damage or degeneration. These neuroprotective properties make quinazoline derivatives potential candidates for the treatment of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. Inflammation plays a significant role in various neurological disorders, including multiple sclerosis, stroke, and neurodegenerative diseases[82, 83]. Quinazoline derivatives have been studied for their anti-inflammatory activity and their potential to modulate inflammatory processes in the central nervous system. By inhibiting pro-inflammatory mediators or modulating immune responses, these compounds may help mitigate the neuroinflammatory component of certain neurological disorders[84]. Certain quinazoline derivatives, such as prazosin and doxazosin, have been used as antihypertensive agents[85, 86]. They act as selective alpha-1 adrenergic receptor blockers, relaxing blood vessels and reducing blood pressure[87]. These drugs are commonly prescribed for the treatment of hypertension and benign prostatic hyperplasia[88]. Quinazoline-based compounds have exhibited antimicrobial activity against fungal and bacterial pathogens. They have been investigated as potential agents for the treatment of infections caused by Candida species, Aspergillus species, and various Gram-positive and Gram-negative bacteria. The quinazoline nucleus can be modified to enhance the antimicrobial properties and optimize the pharmacokinetic profile of these compounds[89]. It is worth noting that while quinazoline-based compounds have shown promise in cardiovascular diseases, further research and clinical trials are necessary to determine their efficacy, safety, and optimal therapeutic use. The design and development of quinazoline derivatives with improved selectivity, potency, and pharmacokinetic properties continue to be an active area of investigation in the field of cardiovascular medicine[90].

Quinazoline kinase inhibitors (QKIs) are a class of small-molecule, specific kinase inhibitors. Numerous quinazoline-based kinase inhibitors have been synthesized in laboratories, and research into their use in treating different diseases, especially cancer and other kinase-mediated disorders, is still ongoing. In a selective manner, quinazoline kinase inhibitors target those specific kinases that play a crucial role in specific diseases. Kinases play critical roles in the cellular signaling pathways regulating cell growth, proliferation, and survival. Aberrant kinase activity is often associated with diseases, especially cancer; hence, kinases become attractive targets for therapeutic intervention[91]. QKIs are designed to bind to the ATP-binding site of a kinase, blocking its activity, consequently preventing the downstream signaling[92]. QKIs have been primarily investigated and are being used in the treatment of various cancers, especially for RTKs and other kinases implicated in tumor development and progression. Examples include gefitinib and erlotinib for EGFR, and lapatinib, which has activity against both EGFR and HER2[93]. The QKIs have demonstrated clinical efficacy against some types of cancers, especially non-small cell lung cancer and in HER2-positive breast cancer[94]. Through optimization, quinazoline kinase inhibitors can be designed to show high selectivity toward specific kinases, which may reduce off-target effects and enable better therapeutic outcomes. Researchers use structure-activity relationship studies and medicinal chemistry to increase the potency and selectivity of QKIs. Quinazoline kinase inhibitors represent a promising avenue toward the selective targeting and inhibition of disease-relevant kinases, most particularly in cancer treatment. Ongoing research and development continue to optimize their selectivity, potency, and therapeutic applications to render the most appropriate treatment strategies effective.

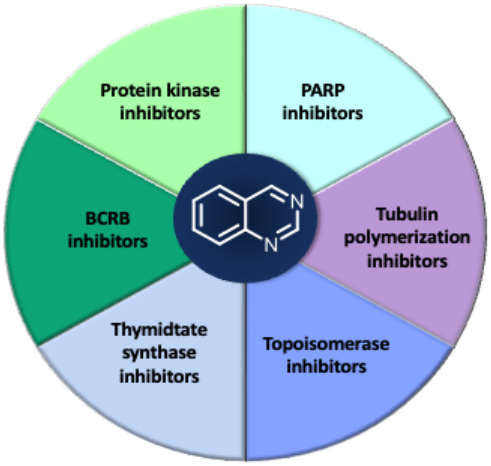


Figure 10. *Modes of action of quinazolines as anticancer.*

Insights on Mechanism of Action of Quinazolines as Anticancer Agents

Quinazolines represent an important class of anticancer agents, showing considerable therapeutic activity against a broad spectrum of tumors[95]. A great deal of the work done on quinazolines and their anticancer activity has been directed toward understanding the mechanistic pathways that underlie their chemotherapeutic effects. Most of the quinazoline derivatives with anticancer activity tend to function as inhibitors of protein kinases. These derivatives interfere with DNA replication and transcription processes, thus leading to the inhibition of tumor growth. Furthermore, certain derivatives are effective in overcoming resistance associated with breast cancer by inhibiting breast cancer-resistant proteins[96].

Besides their activity against protein kinases, anticancer quinazolines also demonstrate inhibitory activity against a range of other enzymes, such as thymidylate synthase, poly ADP-ribose polymerase-1 (PARP), and topoisomerase as demonstrated in figure 10[97]. Thus, quinazolines present their chemotherapeutic effects through a large panel of molecular interactions and mechanistic pathways[80].

Protein Kinase Inhibitors

Protein kinases can be divided into three diverse groups based on the amino acid sequences they phosphorylate:

1. Tyrosine Kinases: This family of enzymes catalyzes the phosphorylation reaction with the phenolic hydroxyl (OH) group of tyrosine residues.
2. Serine-Threonine Kinases: These specific kinases facilitate the process of phosphorylation on serine and threonine amino acids.
3. Histidine Kinases: These have been implicated in the process of nitrogen phosphorylation in histidine residues.

It is well established that alterations in protein kinases can cause aberrant cellular signaling, uncontrolled cell growth, and abnormal differentiation. Thus, the inhibition of tyrosine kinases is an important biological target for cancer therapy[98]. Many quinazolines have been found to exhibit anticancer activity by inhibition of various kinases. Interestingly, the quinazoline derivatives show selective inhibition against receptor tyrosine kinases (RTKs), which include[99-101]:

- Epidermal Growth Factor Receptor (EGFR).
- Platelet-derived growth Factor Receptor (PDGFR).
- Vascular Endothelial Growth Factor Receptor (VEGFR).
- Fibroblast Growth Factor Receptor (FGFR).

These RTKs are frequently overexpressed in numerous cancers, including prostate, colon, breast, lung, stomach, and ovarian cancer[102]. Derivatives such as 4-anilinoquinazolines have demonstrated the potential to inhibit these protein tyrosine kinases, particularly EGFR, VEGFR-2, PDGFR, and FGFR. This characteristic has opened the way for a broad investigation of their efficacy as anticancer agents against different tumors[101-103].

Epidermal Growth Factor Receptor (EGFR) Inhibitors

Epidermal Growth Factor Receptor EGFR is a transmembrane receptor-associated tyrosine kinase TKR and a critical biological target for a variety of anticancer therapeutics because of its role in regulating cell growth, survival, and differentiation. Its ligands activate EGFR: epidermal growth factor EGF and transforming growth factor alpha TGF-α. Upon ligand binding, EGFR is activated and dimerized by autophosphorylation of the Tyr-1068 residue, which then triggers a cascade of intracellular signaling pathways. Overexpression of EGFR is one of the distinguished features of cancerous cells from normal cells. So, the proliferation of cancerous cells can be inhibited by two major classes of EGFR inhibitors:

1. Tyrosine Kinase Inhibitors: These are competitive inhibitors of EGFR.
2. Monoclonal Antibodies – these agents inhibit the binding of EGF and TGF-α to the receptor.

Quinazolines are known to act as small tyrosine kinase inhibitors. A number of quinazoline derivatives have been marketed as anticancer agents, including gefitinib, erlotinib, and lapatinib. The compounds bind reversibly to the ATP-binding site of EGFR and inhibit its biological activity. However, prolonged therapy with gefitinib and erlotinib has been reported to cause the development of EGFR mutations in tumors, resulting in disease progression and cancer cell drug resistance. In order to compromise this issue, a newer generation of irreversible binding quinazolines has been generated. These compounds bind irreversibly with the tyrosine kinase binding sites of EGFRs under the favorable action of α and β carbonyl groups. Afatinib is an example of this class of compounds. It has been approved by the FDA for the treatment of advanced NSCLC harboring EGFR mutations.

Dacomitinib is another second-generation molecule. Canertinib is also a third-generation quinazoline derivative. It contains high activity with an IC_{50} value of 0.8 nM.

Numerous studies focused on discovering novel quinazoline-based EGFR TK inhibitors. Key modifications targeted the C-6 and C-7 positions of the anilinoquinazoline moiety[80, 104]. Structural activity-relationship studies (SAR) were also conducted to analyze the relationship between structure and activity illustrated in figure 11. Lapatinib is considered as a dual inhibitor for EGFR IC_{50} = 10.8nM; (HER2) IC_{50} = 29.2nM[105]:

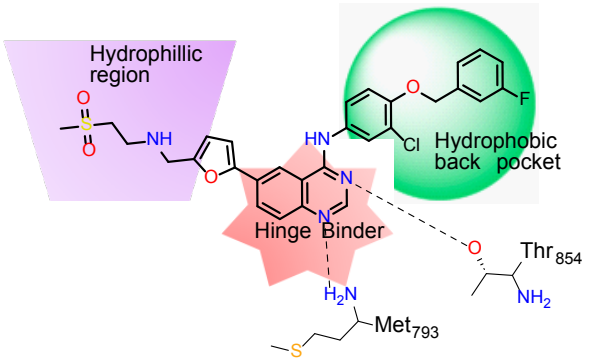
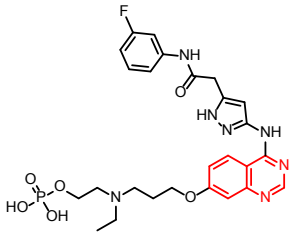
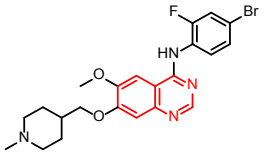
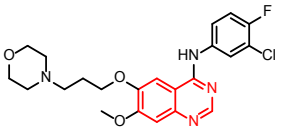
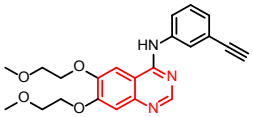
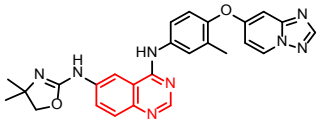
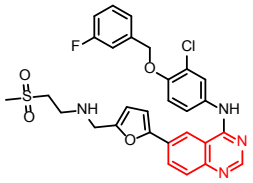
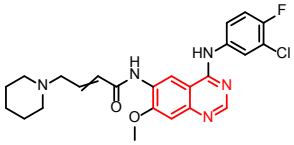
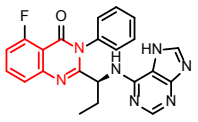
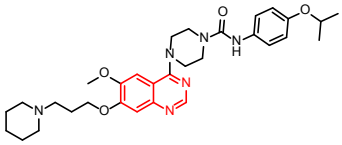
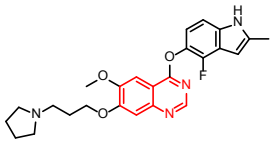
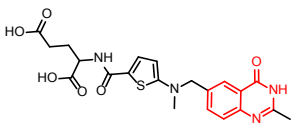


Figure 11. *The Structure-activity relationship of quinazolines as EGFR inhibitors[106].*

1. The 4-anilinoquinazoline structure, especially with substitutions at the C-6 and/or C-7 positions, is crucial for EGFR inhibitory activity, as seen in tyrosine kinase inhibitors like lapatinib, gefitinib and erlotinib. Electron-withdrawing groups (fluoro, bromo, chloro, and ethylene) on the aniline ring enhance antiproliferative activity. Specifically, 3-bromo substituted quinazolines show strong potency, while 3-chloro-4-fluoroaniline derivatives also demonstrate significant activity.

Molecular Structure	Generic Name	Chemical Name	Biological
	Barasertib AZD 1152	2-[3-[[7-[3-[ethyl(2-hydroxyethyl) amino] propoxy]quinazolin-4-yl] amino]-1*H*-pyrazol-5-yl]-*N*-(3-fluorophenyl)acetamide	Tyrosine Kinase (Aurora B) IC_{50} = 0.37nM
	Vandetanib Caprelsa	*N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-((1-methyl-4- piperidinyl) methoxy) quninazolin-4-amine	Tyrosine kinase (VEGFR2) IC_{50} = 40nM
	Gefitinib Iressa Irressat	4-(3'-Chloro-4'-fluoroanilino) -7-methoxy-6-(3-morpholinopropoxy)-quinazoline	Tyrosine kinase (EGFR) IC_{50} = 33nM
	Erlotinib HSDB 8082	*N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine	Tyrosine kinase (EGFR) IC_{50} = 2nM
	Tucatinib Irbinitinib	6-*N*-(4,4-dimethyl-5H-1,3-oxazol-2-yl)-4-*N*-[3-methyl-4-([1,2,4] triazolo[1,5-a] pyridin-7-yloxy) phenyl] quinazoline-4,6-diamine	Tyrosine Kinase (HER2) IC_{50} = 8nM
	Lapatinib Tykerb	*N*-[3-chloro-4-[(3-fluorophenyl) methoxy] phenyl]-6-[5-[(2-methylsulfonyl ethylamino)methyl]furan-2-yl] quinazolin-4-amine	Tyrosine Kinase (EGFR) IC_{50} = 10.8nM; (HER2) IC_{50} = 29.2nM
	Dacomitinib (PF299804, PF299)	(*E*)-*N*-[4-(3-chloro-4-fluoroanilino)-7-methoxyquinazolin-6-yl]-4-piperidin-1-ylbut-2-enamide	Tyrosine kinase (EGFR) IC_{50} = 50nM
	Idelalisib Zydelig	5-fluoro-3-phenyl-2-[(1S)-1-(7*H*-purin-6-ylamino) propyl] quinazolin-4-one	Tyrosine Kinase (PI3Kδ) IC_{50} = 2.5nM
	Tandutinib	4-[6-methoxy-7-(3-piperidin-1-ylpropoxy) quinazolin-4-yl]-*N*-(4-propan-2-yloxyphenyl) piperazine-1-carboxamide	Tyrosine Kinase (PDGFR) IC_{50} = 0.20μM
	Cediranib USAN	4-[(4-fluoro-2-methyl-1*H*-indol-5-yl) oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy) quinazoline	Tyrosine Kinase (VEGFR) IC_{50} = 0.4nM
	Raltitrexed D 1694	L-Glutamic acid, *N*-((5-(((1,4-dihydro-2-methyl-4-oxo-6- quinazolinyl) methyl) methyl amino)-2-thienyl)carbonyl)	Thymidylate synthase inhibitor IC_{50} = 9nM

2. Modifying the aniline moiety at the 4-position reduces activity. In contrast, electron-donating groups at the 6 and/or 7 positions improve binding to the quinazoline system.
3. The propoxy linker at C-6 and/or C-7 outperforms the methoxy group in activity. Additionally, deoxygenated groups at the 6 and 7 positions boost cytotoxic effects. Lastly, the Michael addition group at the 6-position leads to irreversible receptor binding.

Pharmaceutical Reported Anticancer Quinazoline Derivatives

Notably, many quinazoline derivatives have been approved by the Food and Drug Administration (FDA) for clinical use as effective anticancer drugs[107]. Its molecular structure, generic names, chemical names, and biological targets as well as IC_{50} are all systematically listed in Table 1 concerning clinically used anticancer quinazolines[105].

Strategies for Synthesis of Quinazoline Derivatives:

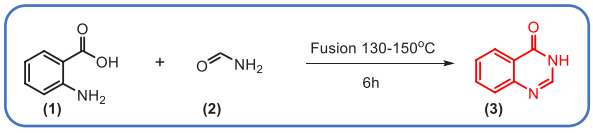
Several researchers successfully synthesized a diverse set of quinazoline derivatives, keeping in view their remarkable synthetic value along with their therapeutic features. The first synthesis of 2-cyanoquinazolin-4-one was performed by Griess et al. in 1869[108], while quinazoline was prepared from the decarboxylation of quinazoline-2-carboxylic acid by Bischler and Lang[109]. In 1903, Gabriel achieved quinazoline synthesis by reducing o-nitro benzylamine to o-amino benzylamine, which subsequently underwent condensation with formic acid to yield dihydro quinazoline; further oxidation resulted in quinazoline-4-one[110]. Various synthetic methodologies have been employed for the synthesis of quinazoline compounds.:

Synthesis of 4(3H)-quinazolinone derivatives

The most common synthetic methods to substituted 4(3*H*)-quinazolinones are based on the cyclocondensation reaction of anthranilic acid or its derivatives, such as alkyl anthranilates, acylanthranilic acids, 2-aminobenzonitrile and others. Other methods are available, such as condensation of 3,1-benzoxazine-4-one with ammonia, amines (aliphatic, aromatic, or heterocyclic), and hydrazines. The following synthetic reactions exemplify some standard traditional methods used for the preparation of 4(3*H*)-quinazolinones.

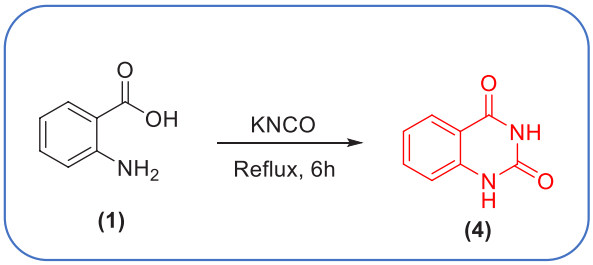
From anthranilic Acid:

Niementowski Technique consists of the condensation reaction between anthranilic acid (**1**) and formamide (**2**) at 130 to 150 °C for 6h. Scheme 1 gives 4-(3*H*)-quinazolinone (**3**) in a 40% yield[111].



Scheme 1. *Synthesis of 4(3H)-quinazolinone by Niementowski.*

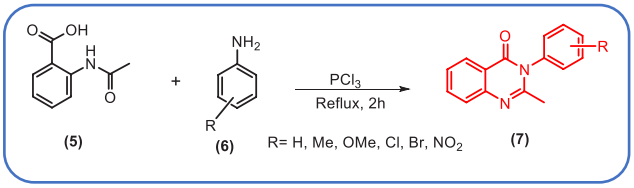
The reaction of anthranilic acid (**1**) with an aqueous solution of potassium cyanate is carried out by refluxing the two reactants in glacial acetic acid for 6h. The product obtained was 2,4-quinazoline-dione (**4**) in 75% yield, as in Scheme 2[112].



Scheme 2. *Synthesis of 2,4-quinazolindione.*

From 2-acetamidobenzoic acid:

Grimmel, Guinther, and Morgan[113, 114] have been prepared a series of 3-aryl-2-methyl 4(3*H*)-quinazolinones via the reaction of 2-acetamidobenzoic acid (**5**) with substituted anilines (**6**) in refluxing toluene for 2h in the presence of phosphorus trichloride (PCl_3) as a catalyst Scheme 3.

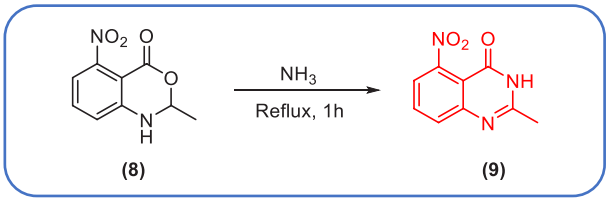


Scheme 3. *Synthesis of methyl-3-phenyl-4-quinazolinone by Morgan.*

From benzoxazin-4-one derivatives:

One of the most general methods for synthesizing quinazolinones involves the condensation reaction of benzoxazin-4-one derivatives with ammonia, hydrazines, or primary amines, including aliphatic, aromatic, or heterocyclic amines.

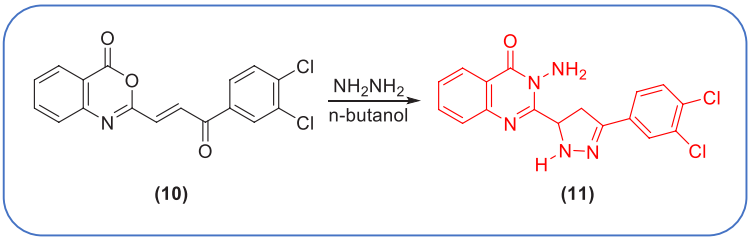
Refluxing of 2-methyl-5-nitro-benzoxazin-4-one (8) with ammonia for 1h gave anthranilamides followed by cyclization at either the thermal condition of 240–280 °C or on heating with acetic anhydride for 1–3h yielding 2-methyl-5-nitro-quinazolin-4-one (**9**) in 65% yield [80] as depicted in Scheme 4.



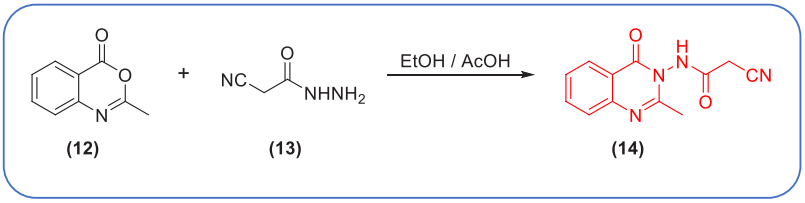
Scheme 4. *Synthesis of 2-methyl-5-nitro-4(3H)-quinazolinone*

When 2-[3-(3,4-chlorophenyl)-3-oxoprop-1-en-1-yl]-4*H*-3,1-benzoxazin-4-one (**10**) was left to react with

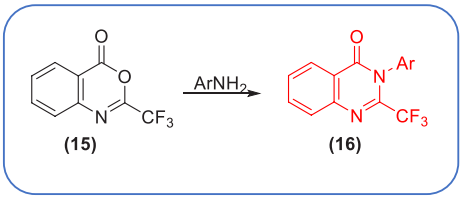
hydrazine hydrate in *n*-butanol under reflux, the corresponding 3-amino-4(3*H*)-quinazolinone (**11**) was formed[115] in Scheme 5.



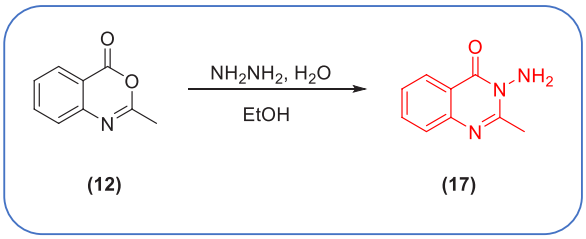
Scheme 5. *Synthesis of -amino-2-(3-(3,4-dichlorophenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinazolin-4(3H)-one. Additionally, the reaction of 2-methylbenzoxazinone (***12***) with cyanoacetohydrazide (***13***) yielded a cyanoquinazolinone derivative (***14***) [116], as demonstrated in Scheme 6.*



Scheme 6. *The synthesis of 2-cyano-N-(2-methyl-4-oxoquinazolin-3(4H)-yl) acetamide. Derivatives of 3-aryl-2-trifluoromethyl-4(3H)-quinazolinone (***16***) were obtained from the reaction of 2-trifluoromethyl-3,1-benzoxazine-4-one (***15***) with substituted anilines in good yields[117] within Scheme 7 .*



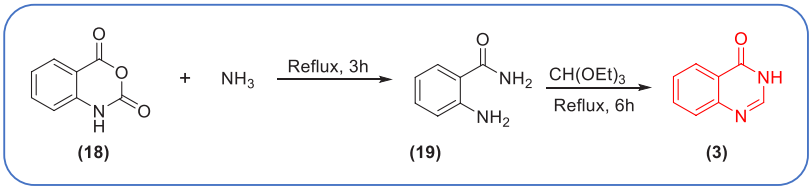
Scheme 7. *Synthesis of 3-aryl-2-trifluoromethyl-4(3H)-quinazolinone derivatives. Furthermore, 2-methyl benzoxazin-4-one (***12***) was reported to react with hydrazine hydrate in ethanol, forming the corresponding 3-amino-2-methylquinazolinone (***17***) in a satisfactory yield [116] as in Scheme 8.*



Scheme 8. *The synthesis of 3-amino-2-methylquinazolin-4(3H)-one.*

From Isatoic anhydride:

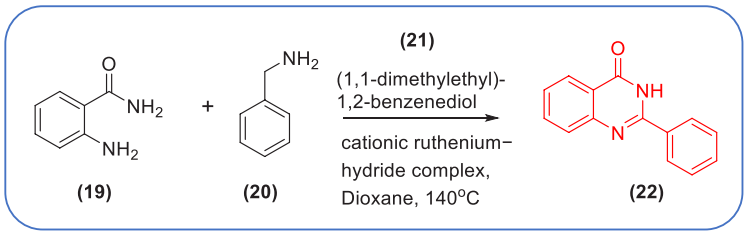
The amination of isatoic anhydride (**18**) with ammonia under reflux for 3h gave 2-amino benzamide (**19**), which upon heating with ethyl orthoformate for 6h. afforded 4-(3*H*)-quinazolinone (**3**) in 55% yield[118], as shown in Scheme 9.



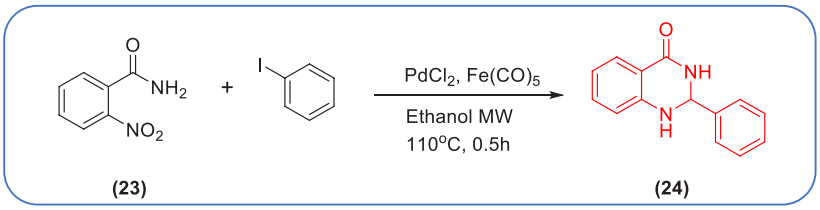
Scheme 9. *Synthesis of 4(3H)-quinazolinone by amination of isatoic anhydride.*

From Benzamide:

Heating a mixture of 2-aminobenzamide (**19**) and benzylamine (**20**) in 1,4-dioxane under reflux at 140 °C in the presence of cationic ruthenium–hydride complex and 4-(1,1-dimethylethyl)-1,2-benzenediol (**21**) as catalysts; gave 2-phenyl quinazoline-4(3*H*)-one (**22**) 76% [119], as depicted in Scheme 10.



Scheme 10. *Synthesis of 2-phenyl-4(3H)-quinazolinone.*
*The 2-phenyl-4(3H)-quinazolinone (**24**) could also be obtained by the reduction of a 2-nitro benzamide (**23**) using $PdCl_2$ [120]. This is followed by the reaction with iodobenzene and iron pentacarbonyl using microwave assistance at 110 °C for 0.5h, as in Scheme 11.*

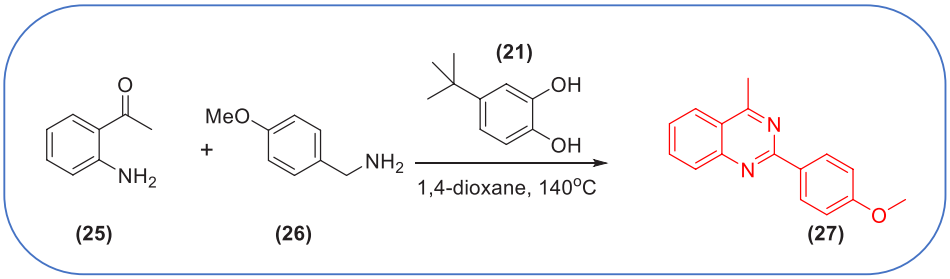


Scheme 11. *Alternated method for synthesis of 2-phenyl-4(3H)-quinazolinone*

Synthesis of 4-substituted quinazoline derivatives

From 2-aminophenylethanone:

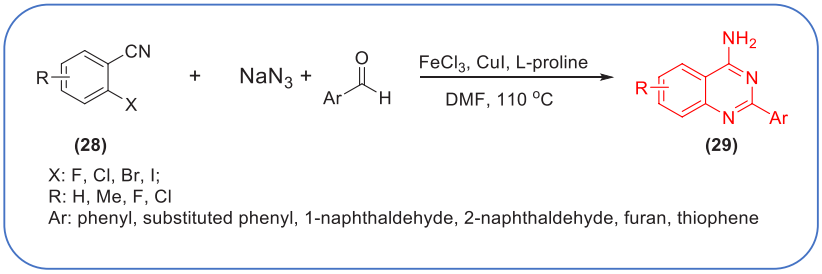
The reaction of 2-aminophenylethanone (**25**) with 4-methoxybenzylamine (**26**) at 140 °C for 20 hours in the presence of 4-tert-butylcatechol (**21**) and 1,4-dioxane gave 2-(4-methoxyphenyl)-4-methylquinazoline (**27**) in a yield of 85% [119], as shown in Scheme 12.



Scheme 12. *Synthesis of 2-substituted-4-methylquinazoline.*

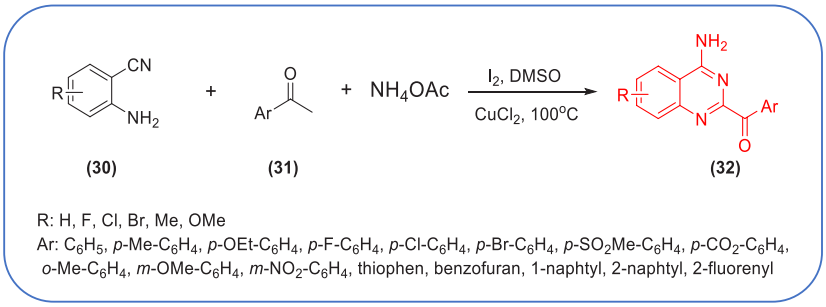
From Benzonitrile Derivatives:

Jia et al. [121] have worked out a practical Fe/Cu-catalyzed protocol for the synthesis of 4-amino-2-arylquiznazolin derivatives (**29**) from ortho-halogenated benzonitriles (**28**) and various aromatic aldehydes using sodium azide as a source of nitrogen. As demonstrated in Scheme 13, the 2-halobenzonitriles (**28**) bearing electron-neutral and electron-withdrawing substituents, provided moderate to good yield of quinazoline products. Similarly, a variety of aromatic aldehydes with diverse substituents, including sterically hindered and heteroaryl aldehydes, also afforded the desired results.



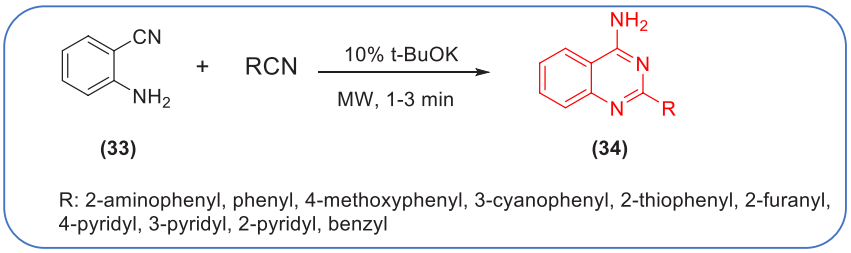
Scheme 13. *Synthesis of 2-phenylquinazolin-4-amine derivatives.*

A series of 2-acyl-4-aminoquinazoline derivatives (**32**) were synthesized using 2-aminobenzonitrile derivatives (**30**), arylmethyl ketones (**31**), and ammonium acetate in the presence of iodine and cupric chloride[122]. It was conducted with various aryl methyl ketones bearing electron-neutral, donating, and withdrawing groups, as well as halogens. Furthermore, heterocyclic methyl ketones and even substrates with fused rings, such as 1-naphthyl and thiophen, afforded the target products in moderate to good yields as in Scheme 14.



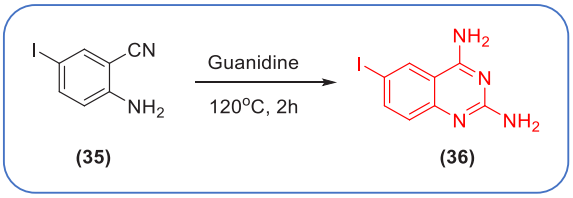
Scheme 14. *Synthesis of 2-acyl-4-aminoquinazoline derivatives.*

Furthermore, 2-substituted-4-aminoquinazoline derivatives (**34**) were obtained in 76% to 93% yield from the reaction of 2-aminobenzonitrile (**33**) with various nitriles in the presence of 10% potassium tert-butoxide in a microwave within 1 to 3 minutes [123], as depicted in Scheme 15.



Scheme 15. *Synthesis of 2-substituted-4-aminoquinazoline.*

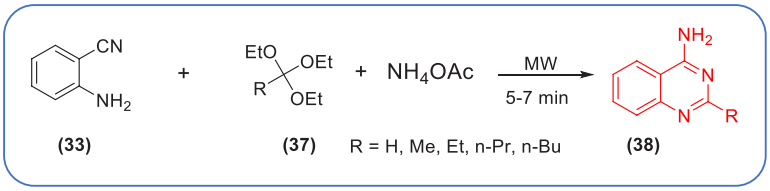
2,4-Diamino-6-iodo-quinazoline (**36**) was prepared with a yield of 90% [80, 121] from the reaction of 2-amino-5-iodobenzonitrile (**35**) with guanidine by heating at 120 °C for 2h, within Scheme 16.



Scheme 16. *Synthesis of 2,4-diamino-6-iodo-quinazoline*

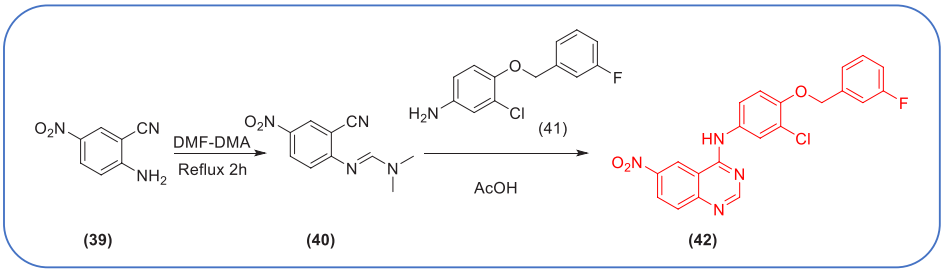
Rad-Moghadam et al.[124] presented a microwave-promoted one-pot method for synthesizing 2-alkyl-4-aminoquinazoline analogs (**38**), shown in Scheme 17. The method involved the reaction of 2-aminobenzonitrile (**33**) with various orthoesters (**37**) and ammonium acetate under solvent-free conditions and yielded satisfactory results. To

reduce side reactions, a higher amount of orthoesters was used. Different orthoesters, including hydrogen, methyl, ethyl, n-propyl, and n-butyl groups, produced excellent yields of the desired derivatives.



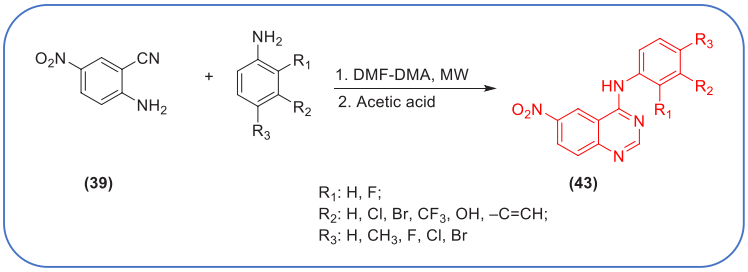
Scheme 17. *The synthesis of 2-alkyl-4-aminoquinazoline derivatives*

The reaction of 2-amino-5-nitrobenzonitrile (**39**) with DMF-DMA (dimethylformamide-dimethylacetal) produced the formimidamide intermediate (**40**) in 90% yield [125]. The reaction of the formimidamide intermediate (**40**) with the benzyloxy aniline derivative (**41**) in glacial acetic acid under reflux conditions afforded the corresponding 6-nitro-4-anilinoquinazoline derivative (**42**), as represented in Scheme18.



Scheme 18. *Synthesis of 4-aminoquinazoline derivatives using 2-amino-5-nitrobenzonitrile.*

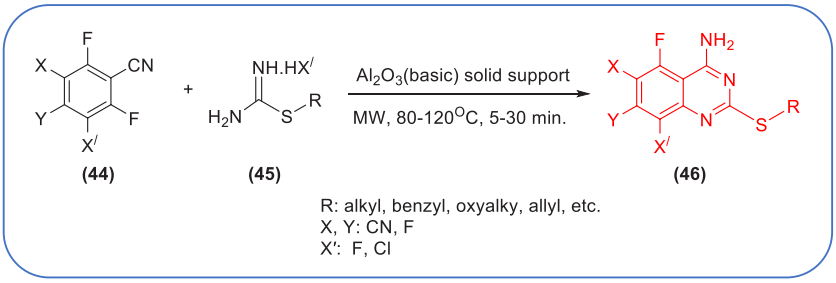
Similarly, Song et al.[126] also developed a new set of 4-amino-6-nitroquinazoline derivatives (**43**) from the reaction of 2-amino-5-nitrobenzonitrile (**39**) with various anilines, achieving good to excellent yields under microwave irradiation conditions Scheme 20. This method required a nonsolvent because DMF-DMA served as both the solvent and reagent. The substrate scope of this method was explored using a series of anilines under optimized conditions.



Scheme 20. *Synthesis of 4-aminoquinazoline derivatives using 2-amino-5-nitrobenzonitrile.*

From polyfluoro benzenedicarbonitriles:

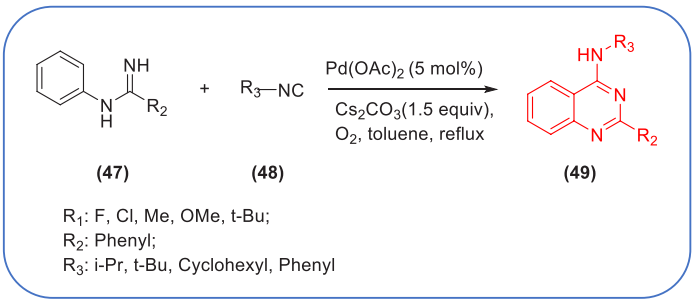
Liu et al. [127] described a microwave irradiation process for producing a series of fluorinated 2-alkylthio-4- aminoquinazoline analogs (**46**) via the reaction of polyfluoro benzenedicarbonitriles (**44**) with isothiouronium salts (**45**) in the presence of basic alumina as a solid-support agent and a solid base Scheme 21.



Scheme 21. *Synthesis of fluorinated 2-alkylthio-4-aminoquiazolines under microwave irradiation.*

From N-arylamidines:

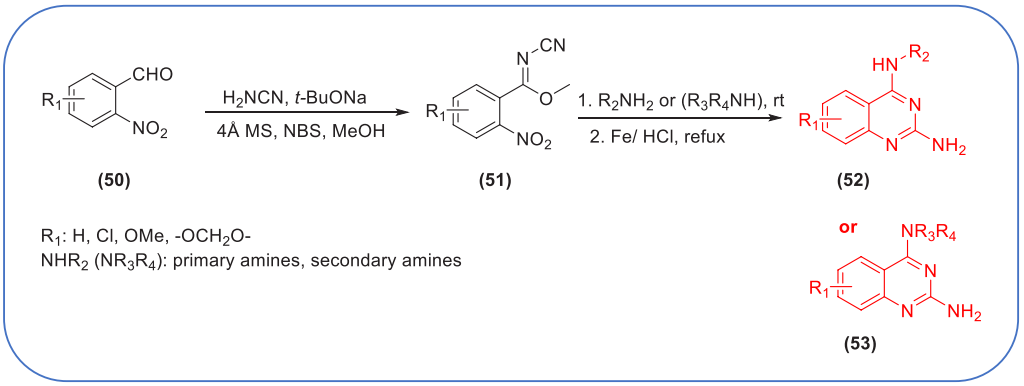
Wang et al.[128] prepared a series of 4-amino-2-aryl(alkyl)quinazoline (**49**) via heating *N*-arylamidines (**47**) and isonitriles (**48**), catalyzed with palladium acetate in the presence of $CsCO_3$ and O_2 as a base and oxidant, respectively Scheme 22.



Scheme 22. *Synthesis of 4-amino-2-aryl(alkyl) quinazolines*

From 2-Nitrobenzaldehyde:

Yin et al.[129] were described an efficient method to N^4-substituted 2,4-diaminoquinazoline (**52**) and (**53**) by employing tandem condensation of cyanoimidate–amine (prepared from the reaction of 2-nitrobenzaldehydes (**50**), H_2NCN, different amines), followed by reductive cyclization in Fe–HCl system. Scheme 23.



Scheme 23. *Synthesis of N^4-substituted 2,4-diaminoquinazoline using 2-nitrobenzaldehydes*

CONCLUSION

Recent developments in anticancer therapeutics have changed from toxic, non-selective compounds to less toxic and selective agents. The lack of selectivity and high toxicity of conventional chemotherapy create severe limitations, hence the need for targeted therapies. There has been research on quinazoline and its derivatives, which act as effective tyrosine kinase inhibitors important in cancer treatment. Evidence exists for the therapeutic efficacy of quinazolines, and several of these anticancer derivatives have gained U.S. Food and Drug Administration (FDA) approval for the treatment of various cancers. Alterations to quinazolines mainly focus on modulating substituent groups at the quinazoline skeleton's C-4, C-6, and C-7 positions to enhance their anticancer activity. Even minor structural modifications of the quinazoline skeleton can significantly change selectivity, potency, and overall antitumor activity. While quinazoline-based treatments are available, there is enormous scope within this promising class of compounds for discovering and developing new, effective chemotherapeutics.

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