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Bioactive Amino-Quinazolines: Synthesis and Therapeutic Applications

Lucas S. Franco,[a,b] *Pedro S. M. Pinheiro*[a,b] *and Maria Letícia C. Barbosa*[*,a,b,c,d]

[a]*Laboratório de Avaliação e Síntese de Substâncias Bioativas (LASSBio), Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-902 Rio de Janeiro-RJ, Brazil*

[b]*Instituto Nacional de Ciência e Tecnologia de Fármacos e Medicamentos (INCT-INOFAR), 21941-902 Rio de Janeiro-RJ, Brazil*

[c]*Laboratório de Síntese Orgânica e Química Medicinal (LaSOQuiM), Departamento de Fármacos e Medicamentos, Faculdade de Farmácia, Universidade Federal do Rio de Janeiro, 21941-902 Rio de Janeiro-RJ, Brazil*

[d]*Departamento de Ciências Farmacêuticas, Faculdade de Farmácia, Universidade Federal de Juiz de Fora, 36036-900 Juiz de Fora-MG, Brazil*

The amino-quinazoline scaffold stands out as a privileged structure in Medicinal Chemistry, due to its pleiotropic pharmacological profile. It has been explored in the design and development of novel drug candidates for several therapeutic applications, including antihypertensive, anti-inflammatory, antipsychotic, anti-Alzheimer, anticancer, antiviral, antibiotic, and antiparasitic treatments, among others. The therapeutic value of amino-quinazoline drugs was first demonstrated with the use of alpha 1-adrenoceptor antagonists, such as prazosin, doxazosin and terazosin. These drugs were initially approved for the treatment of hypertension and later for the treatment of benign prostatic hyperplasia. Several amino-quinazoline kinase inhibitors were introduced into the clinic as innovative therapeutic alternatives for cancer treatment after the U.S. Food and Drug Administration approved gefitinib in 2003 as a novel epidermal growth factor receptor inhibitor drug for non-small cell lung cancer. More recently, in 2021, the kinase inhibitor belumosudil was launched as a third-line therapy for adult and pediatric patients with chronic graft-*versus*-host disease. This article reviews the synthetic preparation methods and pharmacological activities of bioactive amino-quinazolines described in recent decades.

Keywords: amino-quinazoline, bioactive, drug, heterocycle, quinazoline, synthesis

1. Introduction

The amino-quinazoline scaffold stands out as a privileged structure in Medicinal Chemistry due to its' pleiotropic pharmacological profile.[1-4] It has been extensively studied for the design and development of novel drug candidates for various therapeutic applications, such as antihypertensive,[5] anti-inflammatory,[6] antipsychotic,[7] anti-Alzheimer,[8] anticancer,[9] antiviral,[10] antibiotic,[11] antiparasitic,[12] among others. The therapeutic value of amino-quinazoline drugs was first demonstrated through their use as alpha 1-adrenoceptor antagonists. By 1988, five drugs containing the amino-quinazoline subunit (**1**-**5**) with this mechanism of action had been approved (Figure 1), initially for the treatment of hypertension and later for the treatment of benign prostatic hyperplasia (BPH).[13,14]

Over the past 30 years, several studies have demonstrated the effectiveness and therapeutic value of amino-quinazoline derivatives as kinase inhibitors. This core is present in several anticancer drugs on the market (Figure 2), including gefitinib (**6**), erlotinib (**7**), lapatinib (**8**), icotinib (**9**), vandetanib (**10**), afatinib (**11**), dacomitinib (**12**), and tucatinib (**13**), which are useful in the treatment of lung, breast, colon, and prostate malignancies.[3] After the U.S. Food and Drug Administration (FDA) approved gefitinib (**6**) as a novel epidermal growth factor receptor (EGFR) inhibitor for non-small cell lung cancer (NSCLC) in 2003, several amino-quinazoline kinase inhibitors have been introduced into the clinic as

*e-mail: marialeticia.barbosa@ufjf.br
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The authors would like to dedicate this work to Prof Eliezer Barreiro, who represents a beacon of excellence and innovation in Medicinal Chemistry and has made invaluable contributions to the field, inspiring generations of researchers.

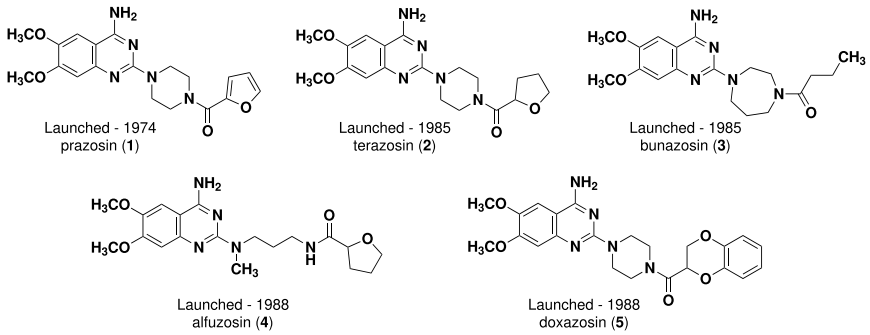


Figure 1. Alpha 1-adrenoceptor antagonists approved drugs containing the amino-quinazoline structure.

innovative therapeutic alternatives for cancer treatment. This development has significantly expanded the range of treatment options available for NSCLC patients.[15] More recently, in 2021, the rho kinase (ROCK) inhibitor belumosudil (**14**) was introduced as a third-line therapy for adult and pediatric patients with chronic graft-*versus*-host disease (cGVHD).[16]

Numerous synthetic methods have been described[17,18] for preparing of amino-quinazoline compounds due to their relevant biological and pharmacological applications. The most common methods involve readily available chemicals, such as benzoic acid, anthranilic acid, and benzonitrile derivatives for cyclization reactions.[19-21] This provides the target compounds and/or the corresponding starting materials for subsequent aryl halide substitution reactions such as nucleophilic aromatic substitutions (S_NAr), Buchwald-Hartwig couplings, and others.[9,22] These chemical transformations provide easy access to the amino-quinazoline scaffold and offer efficient ways to improve amino-quinazoline structural diversity.[2]

This work presents a review of the literature, starting with an overview of the main synthetic methods used to obtain bioactive amino-quinazolines in the last decade. The following sections highlight key examples of bioactive amino-quinazolines described from 1994-2023. This approach aims to provide readers a perspective on the progress of Medicinal Chemistry related to this privileged structure.

2. Methods

A literature survey was carried out using CAS SciFinder^n search tool[23] available through the Periódicos Portal da CAPES (BR), covering the CAplus and Medline databases. The survey focused on synthetic methodologies and therapeutic applications for bioactive amino-quinazolines described in the scientific literature over the last three decades was performed. The bibliographic search was conducted in August 2023 and updated in October 2023. The search strategy included the following descriptors: "quinazol*"[Title] OR "aminoquinazol*"[Title] AND "bioactive"[Abstract/Keywords] OR "drug"[Abstract/Keywords], resulting in a total of 1,814 references. The following initial eligibility criteria included publications in English (1,381 references); publication period from 1994 to 2023 (1,286 references); and document types Journal or Review (1,127 references). The number of publications has significantly increased over the years. There were 48 results for the first decade (1994-2003), 253 results for the second decade (2004-2013) and 826 results for the most recent decade (2014-2023) (Figure 3).

A detailed analysis of the contents of references was subsequently performed to confirm their eligibility and relevance for the scope of this review. The final selection of articles occurred in two main steps. First, the titles and abstracts of the identified references were read, and potentially eligible studies were pre-selected. Second, the full texts were read to confirm eligibility and make the final selection for discussion in this review. References covering bioactive derivatives of the quinazolinone chemical class or related chemical structures were excluded. Finally, elected references discussing the synthesis and therapeutic applications of bioactive amino-quinazolines were summarized and discussed in this review.

3. Overview of Recent Synthetic Methods to Obtain Bioactive Amino-Quinazolines

Due to the well-established activity of amino-quinazoline derivatives, synthetic methods to obtain this chemotype are thoroughly documented. Starting from derivatives of anthranilic acid (**15**), the main synthetic route for these compounds involves the synthesis of key 4-quinazolinone intermediates (**16**-**17**) (Scheme 1), which are subject to chlorination reaction and are then appropriately functionalized.[27-29] This approach is widely used to obtain 4-anilinoquinazolines, such as the approved

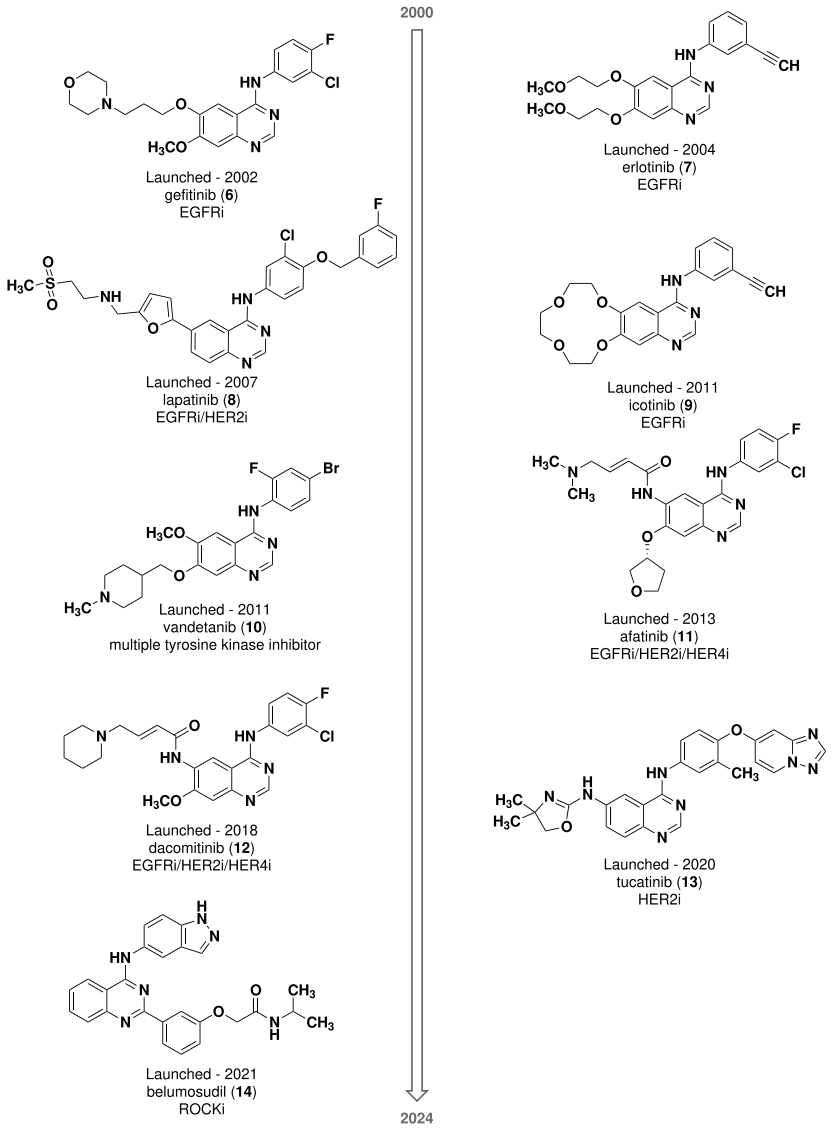


Figure 2. Timeline of approved amino-quinazoline kinase inhibitors. EGFR: epidermal growth factor receptor; HER2: receptor tyrosine-protein kinase erbB-2; HER4: receptor tyrosine-protein kinase erbB-4; ROCK: rho-associated protein kinase.

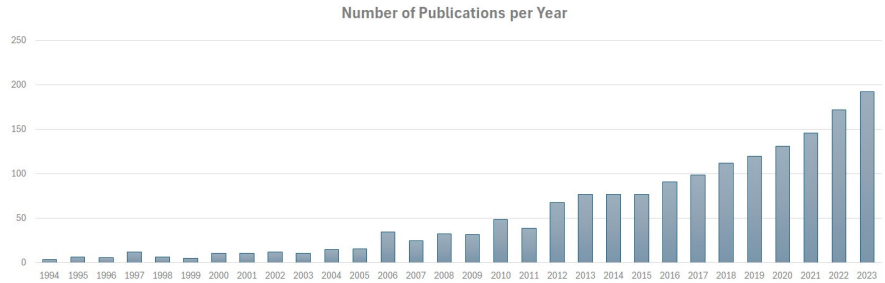
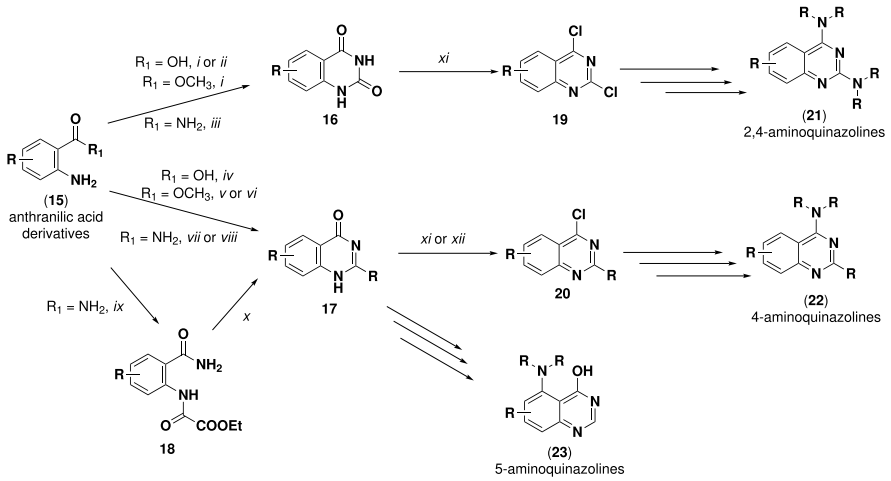


Figure 3. Increasing number of publications related to the amino-quinazoline privileged structure over the last three decades.

kinase inhibitors. Starting from anthranilamides (**15**, $R_1 = NH_2$), functionalization in position two of the ring is often achieved through cyclization steps employing aldehydes,[31,32] yielding 2-substituted-4-quinazolinones (**17**). It has also been reported[30] that carbonitriles, such as cyclohexanecarbonitrile, react with anthranilic ester derivatives (**15**, R_1 = OMe) to yield 2-functionalized-4-quinazolinones (**17**). These compounds are further modified to furnish bioactive amino-quinazolines (**22**). Electrochemical methods have also been reported[35,36] for achieving 2-substituted-4-quinazolinones (**17**) under mild conditions, at room temperature, in reactions

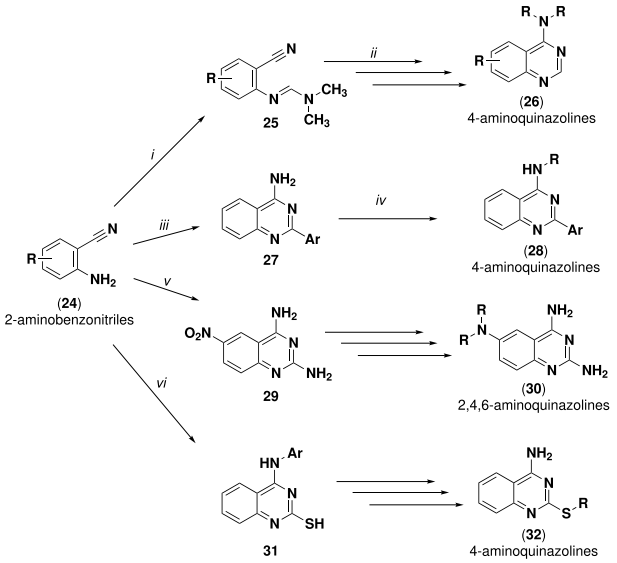


Scheme 1. (*i*) urea, Δ;[24-26] (*ii*) (1) AcOH, H_2O, (2) KOCN, H_2O, (3) NaOH, (4) HCl_{aq} 37%;[9] (*iii*) carbonyldiimidazole, tetrahydrofuran (THF);[9] (*iv*) formamidine acetate, Δ;[27,28] (*v*) N_2, toluene, formamide, $POCl_3$;[29] (*vi*) cyclohexanecarbonitrile, dioxane, HCl;[30] (*vii*) RCHO, I_2, K_2CO_3;[31-33] (*viii*) formamide, Δ;[34] (*ix*) ethyl oxalyl monochloride, THF, triethylamine;[26] (*x*) EtONa, EtOH;[26] (*xi*) $POCl_3$, Δ;[9,24-26,29,31,32] (*xii*) $SOCl_2$.[26-28]

ranging from milligram to gram scale. Regarding alternatives to the use of chlorination agents for achieving functionalization of quinazolinones, it has been reported[37] that hexamethyldisilazane is useful for producing 4-aminoquinazolines from quinazolin-4(3*H*)-ones. The reaction of the quinazolinone intermediates with primary amines lead to the formation of 4-aminoquinazolines via silylation and substitution in a single pot reaction.

Anthranilic acid derivatives have been reported as starting materials for 2,4-quinazolinodiones (**16**), which are key intermediates for exploring 2,4-disubstituted quinazolines (**21**) (Scheme 1).[9,24-26,38] In addition, the reaction of 2-anthranilamide (**15**, $R_1 = NH_2$) with ethyl oxalyl monochloride, leading to compound **18**, followed by cyclization, has been reported,[26] resulting in 2-carbonylated-4-chloroquinazolines. These intermediates were utilized to synthesize 2-carbonylated-4-aminoquinazolines (**22**) as kinase inhibitors. It has also been reported[28,33] that 6-chloroanthranilic acid (**15**, R_1 = OH; R = 6-Cl) can be used to obtain bioactive 5-amino-quinazolines (**23**) through cyclization reaction with formamide and functionalization through S_NAr reactions. The functionalization of chloroquinazolines (**19**-**20**) to amino-quinazolines (**21**-**22**) was often achieved through S_NAr reactions, and metal catalyzed cross-coupling reactions, such as Buchwald-Hartwig (Scheme 1).[9,28]

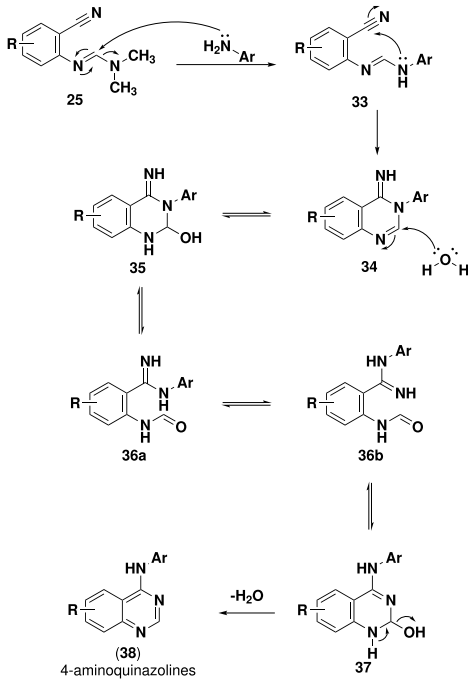
A useful method for synthesizing bioactive amino-quinazolines involves using 2-aminobenzonitriles (**24**) as starting material for cyclization reactions. Some authors[38-43] have reported using dimethylformamide-dimethylacetal (DMF-DMA) to react with 2-aminobenzonitrile, producing intermediate **25**. The intermediate **25** is then reacted with arylamines to produce bioactive 4-amino-quinazolines (**26**). This reaction can also be performed under microwave irradiation conditions, resulting in 4-aminoquinazolines (**26**) in a shorter time period (Scheme 2).



Scheme 2. (*i*) DMF-DMA, Δ;[39-42] (*ii*) anilines, Δ or microwave irradiation;[39-43] (*iii*) benzonitriles, *t*-BuOK, 150 W microwave irradiation;[32] (*iv*) benzoyl chlorides, THF, TEA;[32] (*v*) guanidine hydrochloride, NaOH, Δ;[44] (*vi*) phenyl isothiocyanates, pyridine, Δ.[45-47]

Formamidine intermediates such as **25** have been reported[48] to be key to the multigram synthesis of 4-aminoquinazoline drugs such as gefitinib (**6**). The reaction of this intermediate (**25**) with anilines to give 4-aminoquinazolines (**38**) is thought to occur via a Dimroth rearrangement (Scheme 3). After the attack of aniline and the formation of intermediate **33**, an intermolecular reaction leads to intermediate **34**, which has already been reported in the literature.[48] Hydrolysis at C-N3 and subsequent 180° bond rotation around the C10-C4 (**36a** and **36b**)

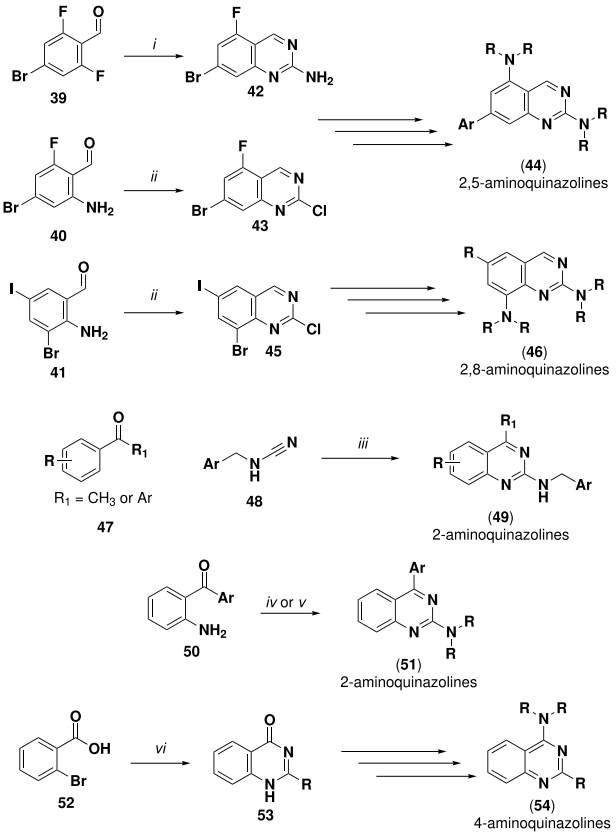
allow ring closure. Subsequent dehydration yields 4-aminoquinazolines (**38**) (Scheme 3).



Scheme 3. Schematic representation of intermediates involved in the mechanism of Dimroth rearrangement, resulting in 4-aminoquinazolines (**38**).

4-Amino-quinazoline **27** was also obtained starting from 2-aminobenzonitrile (**24**) (Scheme 2), followed by amide bond formation with benzoyl chlorides, resulting in the production of several bioactive 4-amino-quinazolines (**28**).[32] Additionally, the reaction of 2-amino-5-nitrobenzonitrile (**24**, R = 5-NO_2) with guanidine hydrochloride has been reported[44] to yield 2,4-amino-quinazolines (**29**), which were further modified to give bioactive 2,4,6-amino-quinazolines (**30**). The reaction between 2-aminobenzonitrile (**24**) and isothiocyanates has been reported[45-47] to furnish 2-thiol-4-amino-quinazolines (**31**). The thiol group is then utilized as a nucleophile to attach diverse chemical groups, resulting in the production of bioactive amino-quinazolines (**32**) (Scheme 2).[45-47]

Benzaldehyde derivatives (**39**-**41**) have been reported[49-51] as intermediates for synthesizing amino-quinazolines (Scheme 4). Reaction of 4-bromo-2,6-difluorobenzaldehyde (**39**) with urea, followed by treatment with $POCl_3$ resulted in 7-bromo-2-chloro-5-fluoroquinazoline (**42**). Similarly, reaction of 2-amino-4-bromo-6-fluorobenzaldehyde (**40**) with diguanidinium carbonate yielded 7-bromo-5-fluoroquinazolin-2-amine (**43**). These intermediates were further functionalized to furnish bioactive 2,5-diamino-quinazolines (**44**).[49] Additionally, 2-amino-3-bromo-5-iodobenzaldehyde (**41**) was reported[50] as an intermediate for synthesizing 8-bromo-2-chloro-6-iodoquinazoline (**45**) using urea and $POCl_3$. Intermediate **45** was then used to produce bioactive 2,8-diamino-quinazolines (**46**).



Scheme 4. (*i*) Diguanidinium carbonate, diisopropylethylamine (DIPEA), *N*-methyl-2-pyrrolidone, Δ;[49] (*ii*) urea, then $POCl_3$;[49,50] (*iii*) HCl, HFIP, Δ;[51] (*iv*) cynamide, *para*-toluenesulfonic acid, DMF, Δ;[52] (*v*) 4-morpholinecarbonitrile or 1-piperidinecarbonitrile, KOtBU DMF, Δ;[52] (*vi*) aq. ammonia, CuI, DMSO, O_2.[53]

Other methods for the synthesis of 2-amino-quinazolines (**49** and **51**) have been reported. For instance, Qin *et al.*[51] reported a [4 + 2] annulation reaction between 2-aminoaryl ketones (**47**) and *N*-benzyl cyanamides (**48**), using catalytic HCl and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent to provide **49**.[51] In another example, Pandya *et al.*[52] reported a metal-free oxidative annulation strategy for the facile and efficient preparation of 2-aminoquinazolines (**51**) from 2-aminobenzophenones (**50**) and cyanamide derivatives in DMF.[52]

For the preparation of 4-aminoquinazolines, it was also reported[53] the use of 2-bromobenzoic acid (**52**) for a one-pot condensation reaction via *in situ* amine generation using ammonia. This copper-mediated oxidative coupling with various aldehydes produces 2-aryl/heteroaryl-substituted 4-quinazolones (**53**), which could be further explored for the synthesis of bioactive 4-amino-quinazolines (**54**).[53] Other methods leading to quinazolinones intermediates

have also been reported,[54] such as copper-catalyzed domino synthesis via Ullmann-type coupling and aerobic oxidative C–H amidation.

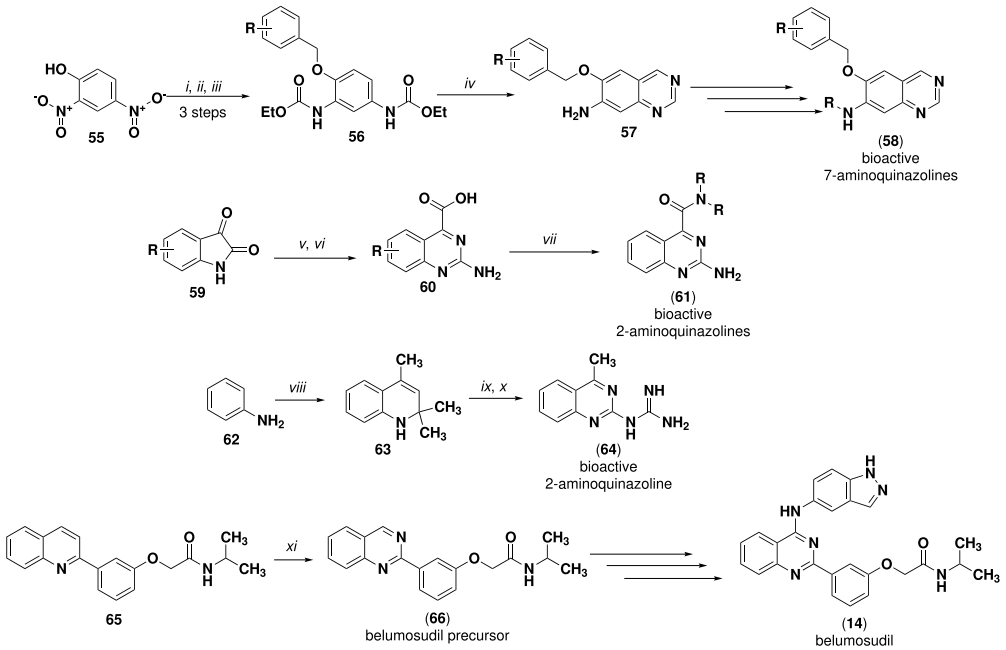
Elkamhawy *et al.*[55] reported the use of 2,4-dinitrophenol (**55**) as a starting material to obtain 6-oxo-7-amino-quinazolines (**58**) through functionalization of the phenol group, hydrogenation of the nitro groups, and subsequent conversion into carbamates (**56**) (Scheme 5). Cyclization of **56** employing hexamethylenetetramine (HMTA) furnished 7-amino-quinazolines (**57**), which were further modified to yield bioactive amino-quinazolines (**58**).[55] Zhou *et al.*[56] reported the synthesis of 2-amino-4-carboxamidoquinazolines (**61**) from isatin (**59**). To synthesize this class of compounds, the authors hydrolyzed the isatin amide group, followed by cyclization with guanidine, producing 2-aminoquinazoline 4-carboxylic acid **60**, which was then functionalized to afford the bioactive amino-quinazolines (**61**) (Scheme 5).[56] Bidou *et al.*[57] reported the synthesis of 2-guanidino-quinazoline (**64**) starting from aniline (**62**). The process involved converting aniline (**62**) to 2,2,4-trimethyl-1,2-dihydroquinoline (**63**) using indium (III) chloride, and acetone. This was followed by a reaction with dicyandiamide to yield **64** (Scheme 5).[57]

Recently, innovative synthetic methods have been published for synthesizing amino-quinazolines. For instance, Woo *et al.*[58] reported a method that involves the carbon-to-nitrogen single-atom transmutation of azaarenes. Also known as skeleton editing, this synthetic strategy enables the replacement of an aromatic carbon atom with a nitrogen atom and may have a direct impact on the discovery of potential medicines. In this work,[58] the authors were able to synthesize belumosudil (**14**) by using this transformation to convert quinoline **65** (1.9 g) to the key quinazoline intermediate **66** (1.3 g). With the **66** in hand, the authors completed the synthesis of the amino-quinazoline belumosudil (**14**) via a two-step C–H amination sequence (Scheme 5). In the process, the *N*-oxidation of quinoline **67** to its *N*-oxide (**68**) precedes the crucial photorearrangement step, under 390 nm UV light, to give the intermediate **69** (Scheme 6). The ozonolysis step, in the presence of pyridine, produces the intermediate **70** *in situ*, which is then converted to the desired quinazoline (**71**) in the presence of ammonium carbamate (Scheme 6).[58]

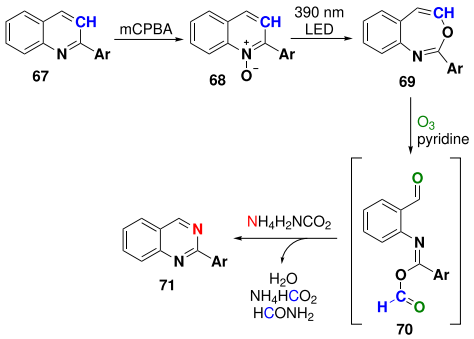
4. Amino-Quinazolines as Kinase Inhibitors

As demonstrated by the performed literature survey, a significant increase in the number of publications describing amino-quinazolines for various therapeutic applications was observed over the considered decades. From 1994-2013, most reports focused on the chemical or pharmaceutical properties of alpha 1-adrenoceptor antagonist drugs[59] and EGFR protein kinase inhibitors.[60]

Moreover, during the first decade, Matsuno *et al.*[61,62] published a collection of 4-amino-quinazoline analogues that were described as potent and selective inhibitors



Scheme 5. (*i*) Benzylbromides, K_2CO_3, KI;[55] (*ii*) H_2, 10% Pt/C;[55] (*iii*) ethyl chloroformate, TEA;[55] (*iv*) HMTA, TFA;[55] (*v*) K_2CO_3, H_2O/CH_3CN;[56] (*vi*) guanidine, NaOEt, Δ;[56] (*vii*) amine, HATU, DIPEA;[56] (*viii*) $InCl_3$ (5 mol%), acetone;[57] (*ix*) 1 M HCl in diethyl ether, acetonitrile;[57] (*x*) dicyandiamide, Δ;[57] (*xi*) (1) mCPBA, (2) 390 nm UV light, (3) $NH_4H_2NCO_2$, O_3.[58]



Scheme 6. Steps for the carbon-to-nitrogen single-atom transmutation of azaarenes based on mechanistic experiments reported by Woo *et al.*[58]

of platelet-derived growth factor receptor (PDGFR) phosphorylation.[61,62] Platelet-derived growth factors (PDGFs) and their corresponding tyrosine kinase receptors (α and β-PDGFR) are important mediators of tumor growth and invasion by effects on malignant cells and the surrounding microenvironment. They induce angiogenesis, ensuring nutrient and oxygen supplies for tumor growth, and promoting metastasis.[63-66] Therefore, inhibiting PDGFR phosphorylation could provide therapeutic benefits in managing malignant proliferative disorders.[62]

The authors[62] initially described the inhibition of β-PDGFR phosphorylation using a whole cell assay. This demonstrated that the prototype KN1022 (**72**) was a reversible adenosine triphosphate (ATP)-competitive amino-quinazoline β-PDGFR inhibitor with an inhibitory constant (K_i) of 3 nM.[61] Additionally, novel series of urea and thiourea structural analogues were also evaluated. SAR (structure-activity relationship) studies have shown that the inhibitory activity of urea derivatives is increased by bulky hydrophobic substituents at the *para*-position of the phenyl ring. This has been demonstrated by the highly potent 4-*tert*-butyl analogue **73**, which has a half-maximal inhibitory concentration (IC_{50}) of 30 nM. Structural analogue **74** was a reasonably potent inhibitor, with an IC_{50} of 530 nM, and had selectivity for PDGFR family of receptor tyrosine kinases (RTKs), including α and β-PDGFR, c-Kit and Flt3. It does not significantly inhibit other relevant kinases and has adequate oral availability, resulting in high plasma concentration after oral administration in rats (Figure 4).[62]

To improve the aqueous solubility of prototype KN1022 (**72**) and its structural analogues **73** and **74**, the replacement of the phenyl moiety by a heteroaryl ring was performed. Thiourea **75** and urea **76** structural analogues were found to be potent and orally available β-PDGFR phosphorylation inhibitors with improved aqueous solubility (Figure 4). Moreover, derivative **76** showed selectivity for inhibiting RTKs from the PDGFR family.[61]

Amino-quinazolines have also been reported[67,68] as inhibitors of aurora kinases, which play a pivotal role in the cell cycle, particularly in cell division and the regulation of mitosis. These enzymes, including aurora A, B, and C, are essential for ensuring the precise orchestration of various phases during cell division. However, malfunctioning or overactive kinases can lead to the development and progression of cancer.[67,68] Pharmaceutical industry research has explored aurora kinases as potential targets for cancer therapy, as inhibiting these kinases could potentially halt the uncontrolled cell division seen in various cancers. Several aurora kinase inhibitors have been developed and tested in clinical trials, demonstrating potential in limiting

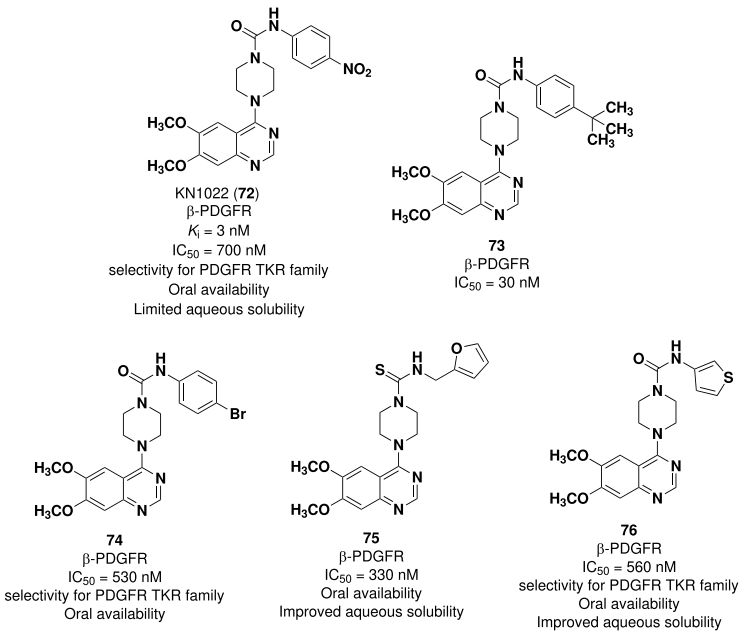


Figure 4. 4-Amino-quinazolines reported as β-PDGFR phosphorylation inhibitors.

cancer growth by interfering with mechanisms that drive abnormal cell division. Studies[67,68] have shown that these inhibitors can be effective in treating various types of cancer. In 2008, it was reported[69] a series of pyrazole derivatives that bear the quinazoline core. This led to the identification of **77**, an inhibitor of aurora kinase B with K_i < 1 nM.[69] Additionally, **77** showed potent inhibition of histone-H3 phosphorylation in SW620 tumor cells with half maximal effective concentration (EC_{50}) < 1 nM. Histone-H3 is a cellular substrate of aurora kinase B useful as a marker of the enzyme inhibition *in vivo*.[70,71] Later, Zheng *et al*.[72] reported quinazoline derivatives as aurora kinase inhibitors, leading to the identification of **80**, which showed inhibition of aurora kinases A and B in nanomolar range (aurora A IC_{50} = 77 nM; aurora B IC_{50} = 145 nM) (Figure 5).[72] Compound **80** was designed by molecular hybridization between ZM447439 (**78**) and the approved small-molecule drug imatinib (**79**).[73] It was tested for its cytotoxic activity *in vitro* and showed potency against multiple cancer cell lines in the low micromolar range.

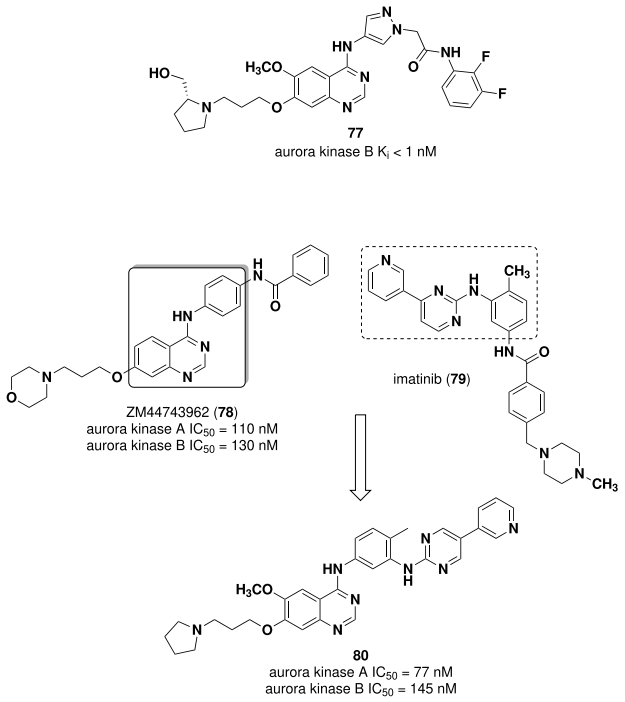


Figure 5. 4-Amino-quinazolines (**77**, **78** and **80**) reported as aurora kinase inhibitors. Imatinib (**79**) was used for the design of **80**.

ALK5, also known as transforming growth factor beta receptor I, belongs to the transforming growth factor-beta (TGF-β) signaling pathway and plays a pivotal role in cellular processes such as proliferation, differentiation, and apoptosis.[74] Dysregulation of the TGF-β pathway, particularly through aberrant ALK5 signaling, has been linked to the pathogenesis of various cancers and fibrotic disorders.[75-77] In 2009, a series of quinazoline derivatives were described as ALK5 inhibitors.[78] The authors[78] identified compound **81** through a screen of an in-house kinase-focused library. The researchers then carried out SAR exploration through classic bioisosteric replacement in the aromatic ring at position 2 of the quinazoline core and the ring linked to the amino group of position 4, resulting in the prototype **82**. It is worth mentioning that compound **82** also had the introduction of a methyl group on the pyridine ring, resulting in a 10-fold increase in potency for ALK5 inhibition and a 27-fold increase in potency in cellular assays. The X-ray crystallography analysis of **82** on the ATP-binding site of ALK5 revealed two key hydrogen bond interactions. One interaction occurred at the hinge region, with the backbone of His83, through the indazole ring. The other interaction involved two hydrogen bonds mediated by a water molecule through the quinazoline and pyridine rings with the Glu45 side chain and Asp151 backbone. In addition, the 6-methyl-2-pyridine ring was key for the improvement of selectivity over p38 kinase. This group effectively interacted with the selectivity pocket of ALK5, and the methyl group occupied a small, mainly hydrophobic, pocket (Figure 6).

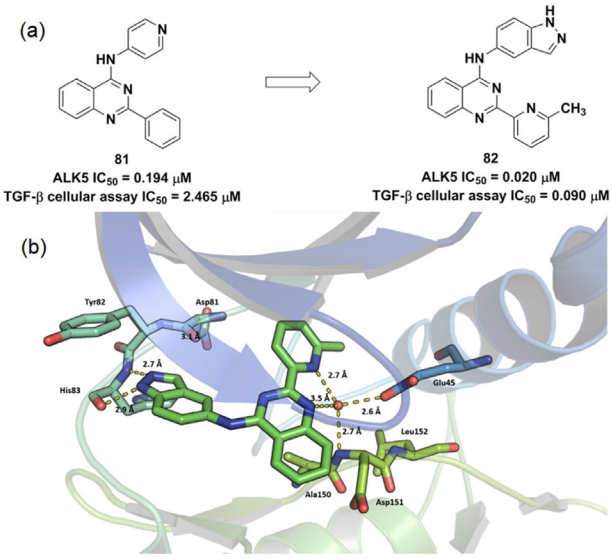


Figure 6. (a) Quinazoline derivatives (**81-82**) described as ALK5 inhibitors; (b) interaction mode of compound **82** with ALK5 (PDB ID: 3GXL). Figure created with PyMol software.[79]

The EGFR is a crucial target in cancer treatment, as highlighted in numerous scientific publications. Citri and Yarden's[80] seminal study provided comprehensive insights into the diverse mechanisms through which aberrant EGFR signaling contributes to tumorigenesis. Moreover, pivotal clinical trials have demonstrated the efficacy of EGFR-targeted therapies in specific cancer types. The

landmark study by Lynch *et al.*[81] revealed the transformative impact of EGFR inhibitors, such as gefitinib (**6**) and erlotinib (**7**), on NSCLC harboring EGFR mutations.

Based on approved drugs, such as gefitinib (**6**) and erlotinib (**7**), Liu *et al.*[82] investigated structural modifications on the 4-anilinoquinazoline core (**83**) at the C6 and C7 positions and C3' and C4' positions of the aniline moiety, resulting in the identification of **84** (Figure 7). The potency for EGFR inhibition was dependent on the position, chain length, and hydrophilicity of the substituted alkynyl groups introduced. Compound **84** exhibited an EGFR IC_{50} = 14 nM, which is similar to gefitinib (**6**) (EGFR IC_{50} = 39 nM). The X-ray structure of gefitinib (**6**) on EGFR (PDB ID: 2ITO)[83] (Figure 7) and docking studies conducted by the authors demonstrate that the quinazoline-privileged structure binds directly to the hinge region. This emphasizes the key role of quinazoline ring as a privileged hinge binder, which paved the way for the development of many kinase inhibitors after gefitinib (**6**). It is important to note that this privileged structure can also interact differently, as demonstrated by the mode of interaction of **82** in ALK5 (Figure 6). Nevertheless, the key hinge binding ability of the quinazoline ring is highly prevalent among approved kinase inhibitors (Figure 2). In the case of EGFR inhibitors, two hydrogen bond interactions are critical: the N1 acts as a hydrogen bond acceptor and interacts with the backbone of Met793, while the C–H group at position 2 acts as a non-classical weak hydrogen bond donor interacting with the backbone of Gln791.

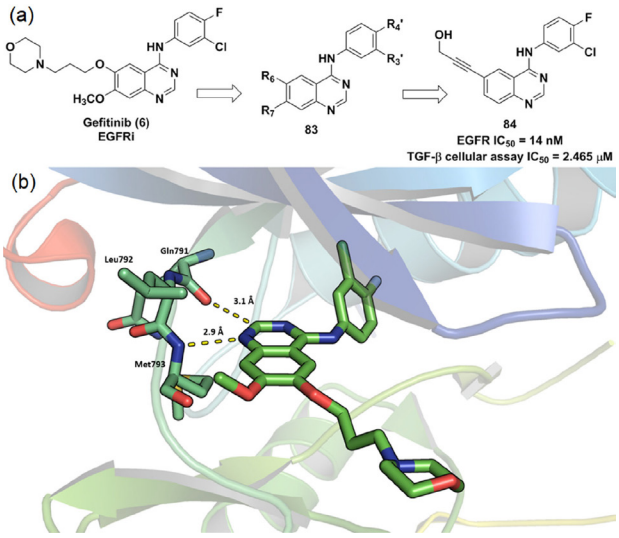


Figure 7. (a) Structural design of EGFRi **84**;[82] (b) interaction mode of gefitinib (**6**) with EGFR (PDB: 2ITO). Figure created with PyMol software.[79]

The $EGFR^{T790M}$ mutation is relevant in the field of cancer research, particularly in the context of NSCLC and its resistance to EGFR tyrosine kinase inhibitors (TKIs). Sequist *et al.*[84] were among the pioneers in elucidating the clinical relevance of the T790M mutation. Their work demonstrated that this secondary mutation in the EGFR gene is a common mechanism of acquired resistance to first-generation EGFR TKIs, such as gefitinib (**6**) and erlotinib (**7**).

The enlarged side chain of the mutated methionine residue creates steric hindrance, which prevents the binding of reversible inhibitors. Furthermore, this alteration is related to an increased affinity of ATP to the binding site, and disrupts the formation of a critical water-mediated hydrogen bond between the inhibitor and T790 of wild-type EGFR.[85] These observations resulted in the search for inhibitors of mutated $EGFR^{T790M}$.[86] For example, Michalczyk *et al.*[87] designed irreversible 4-(phenylamino) quinazoline-based EGFR inhibitors by attaching Michael acceptor groups at the sidechain of position 6 of the quinazoline core, leading to the identification of **85**. The electrophilic Michael acceptor groups introduced can react with nucleophilic Cys797 in the ATP binding site of EGFR. This acrylamide derivative (**85**) presented a single-digit nanomolar potency for $EGFR^{T790M}$ inhibition (IC_{50} = 1.2 nM) and potency in the picomolar range for wild-type EGFR inhibition (IC_{50} = 0.08 nM). The X-ray crystallographic analysis of the drug afatinib (**11**) in $EGFR^{T790M}$ confirms the covalent bond at Cys797 through the acrylamide moiety (Figure 8),[88] which is similar to data described for **85**.[89]

Subsequent studies, such as the one published by Carmi *et al.*,[90] conducted more in-depth SAR of the electrophilic warheads in position 6 of the quinazoline ring of **36**, explored to covalently inhibit EGFR. This included exploring nucleophilic substitution (epoxides); nucleophilic substitution with *in situ* release of a leaving group (phenoxymethylamides); carbamoylation (carbamate); Pinner reaction with formation of a thioimidate adduct (nitrile) and disulfide bond formation (isothiazolinone, benzisothiazolinone and thiadiazole).[90] After evaluating the binding to $EGFR^{WT}$ and confirming irreversible inhibition in a cell-based assay, the epoxide derivative **87** was identified. Compound **87** showed low micromolar potency in inhibiting the H1975 gefitinib-resistant cell line that harbors the $EGFR^{T790M}$ mutation, and it was approximately 5-fold more potent than gefitinib (**6**).

Over the past decade, numerous studies have been reported on effectiveness of amino-quinazolines as kinase inhibitors for treating cancer and inflammatory diseases, continuing a trend from the previous two decades. For instance, Shao *et al.*[27] reported 6-oxooxazolidine-quinazolines as noncovalent inhibitors targeting mutant forms of EGFR related to resistance. Compound **88** (Figure 9)

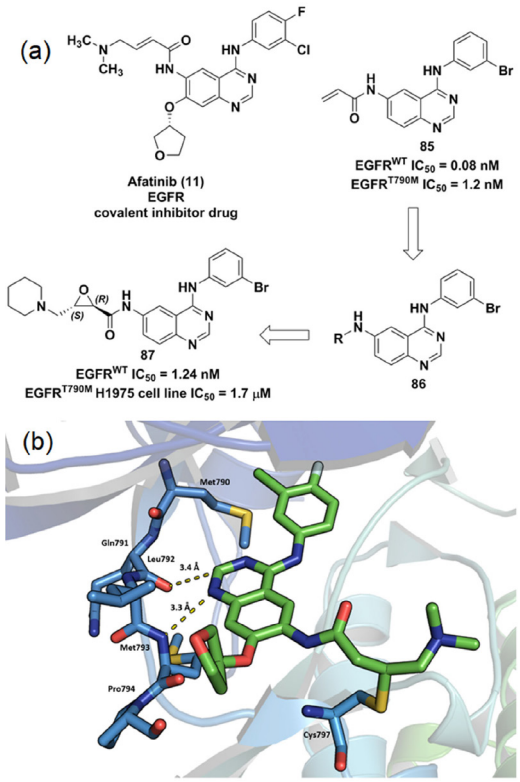


Figure 8. (a) Covalent EGFRi afatinib (**11**), **85** and **87**;[87-90] (b) interaction mode of afatinib (**11**) with $EGFR^{T790M}$ (PDB ID: 4G5P). Figure created with PyMol software.[79]

was the best in the series with $EGFR^{L858R}$ IC_{50} = 3.1 nM, and $EGFR^{T790M}$ IC_{50} = 26.3 nM.[27] In addition to targeting mutant forms of EGFR, efforts have also been made to develop dual kinase inhibitors, as blocking multiple pathways simultaneously may be more effective in preventing cancer cell survival and growth. One strategy to potentially overcome the resistance observed with EGFR TKIs is to target both EGFR and receptor tyrosine-protein kinase erbB-2 (HER2).[91] In this sense, Jiao *et al.*[92] reported quinazoline derivatives as EGFR/HER2 dual target inhibitors, by harnessing the classical 4-anilino-quinazoline subunit while incorporating a series of acrylamides in the 6-position of the quinazoline ring connected to piperazine spacers. This resulted in compound **89** (Figure 9) with EGFR IC_{50} = 0.30 nM, and HER2 IC_{50} = 6.07 nM.[92] In 2019, Das *et al.*[42] reported the discovery of new quinazoline derivatives as dual EGFR/HER2 inhibitors and their anticancer activities. Compound **90** (Figure 9), which had an acrylamide directly connected to the 6-position of the quinazoline ring, presented the best profile with EGFR IC_{50} = 1.4 nM, and HER2 IC_{50} = 10.9 nM.[42] Sun *et al.*[93] reported the synthesis of a group of dual inhibitors targeting EGFR/HER2, which feature a scaffold comprising tricyclic oxazine-fused quinazolines. The best compound of the series (**91**), also featuring an acrylamide in its structure, had an EGFR IC_{50} = 7 nM, and a HER2 IC_{50} = 4 nM (Figure 9).[93]

EGFR signaling also activates vascular endothelial growth factor (VEGF), which is the primary initiator of angiogenesis. VEGF stimulates the activation, growth, and movement of endothelial cells, as well as enhances vascular permeability in solid tumors. The critical phase of the mechanism is facilitated by the receptor known as vascular endothelial growth factor receptor 2 (VEGFR-2).[94,95] Therefore, inhibiting both EGFR and VEGFR-2 concurrently emerges as a strategy for cancer therapy, given that inhibiting VEGFR-2 enhances the effectiveness of EGFR TKIs through a synergistic effect. In this context, Barbosa *et al.*[9] reported 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors. The representative compound LASSBio-1819 (**92**) (Figure 9) had an $EGFR^{WT}$ IC_{50} = 0.90 μM, and a VEGFR-2 IC_{50} = 1.17 μM.[9]

In certain types of human cancers, the collaboration between phosphatidylinositol 3-kinases (PI3Ks) and EGFR is evident in promoting processes such as proliferation,

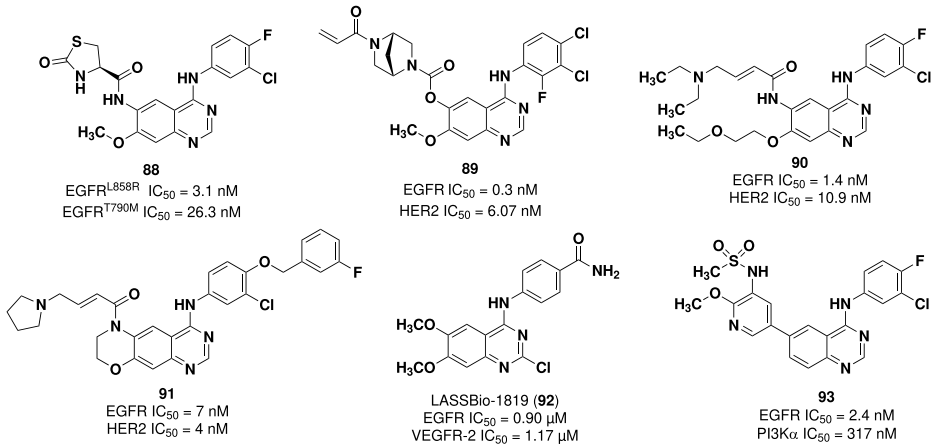


Figure 9. EGFR inhibitor (**88**) and dual EGFR kinase inhibitors (**89**-**93**) having amino-quinazoline structure.

survival, invasion, and metastasis. This correlation arises from the integration of the PI3K/Akt/mTOR pathways as a significant component of EGFR signaling.[96] As a result, the development of dual-target molecules for both EGFR and PI3K may confer therapeutic benefits and represents an interesting strategy for designing anticancer drugs. Ding *et al*.[97] developed EGFR inhibitors using the 4-anilino-quinazoline scaffold and a 6-sulfonamide-substituted pyridyl group to enhance affinity to PI3Ks. Compound **93** (Figure 9), for instance, had an EGFR IC_{50} of 2.4 nM and a PI3Kα IC_{50} of 317 nM.[97]

In addition to amino-quinazolines as EGFRi, various compounds of this class targeting other kinases have been described. One example is the 2-(2-aminopyrimidin-5-yl)-4-morpholino-*N*-(pyridin-3-yl)quinazolin-7-amines PI3K/mTOR inhibitors reported by Peng *et al*.[25] The class I PI3K family comprises α, β, γ, and δ isoforms, with PI3Kα and PI3Kβ being widely distributed and PI3Kγ and PI3Kδ exhibiting more limited expression, primarily in leukocytes. Several pieces of evidence suggest that different isoforms of class I PI3K play distinct roles in tumorigenesis.[98] Upon PI3K activation, Akt and mTOR play crucial roles in regulating cell growth, survival, and proliferation by integrating various signals, including those from growth factors, nutrient availability, and cellular energy levels.[99] These findings suggest that inhibitors targeting PI3K and mTOR could be beneficial in cancer therapeutics.[100] In this context, Peng *et al*.[25] disclosed that compound **94** (Figure 10) was the most effective, with PI3Kα IC_{50} = 4.2 nM, PI3Kβ IC_{50} = 13 nM, PI3Kγ IC_{50} = 64 nM, PI3Kδ IC_{50} = 50 nM, and mTOR IC_{50} = 78 nM. Hei *et al*.[101] reported quinazoline derivatives with an alkylsulfonamide moiety, serving as inhibitors for PI3Ks. The most effective compound (**95**) (Figure 10) exhibited robust inhibitory activity against PI3Kα (IC_{50} = 4.5 nM), PI3Kβ (IC_{50} = 15.5 nM), PI3Kγ (IC_{50} = 6.0 nM), and PI3Kδ (IC_{50} = 2.2 nM).[101] In 2020, Teng *et al*.[28] published new quinazoline derivatives functioning as inhibitors of PI3Kδ. Notably, compound **96** (Figure 10) demonstrated an IC_{50} value of 27.5 nM against PI3Kδ.[28] PI3Kδ is predominantly expressed in hematopoietic cells and plays a critical role in B-cell malignancies through the PI3K/Akt signaling pathway. Therefore, targeting PI3Kδ specifically has emerged as a promising strategy for treating B-cell malignancies, aiming to avoid potential side effects associated with the ubiquitously expressed PI3Kα, β, and γ isoform.[102,103]

Compounds that target other kinases include the 5-anilinoquinazoline-8-nitro VEGFR-2 inhibitor (**97**) (Figure 10), which has a VEGFR-2 IC_{50} of 64 nM, as reported by Zhao *et al*.[104] VEGFR-2 is an interesting target due to its expression in endothelial cells and elevated levels in various tumor cells. Multiple lines of evidence indicate that the overactivation of VEGFR-2

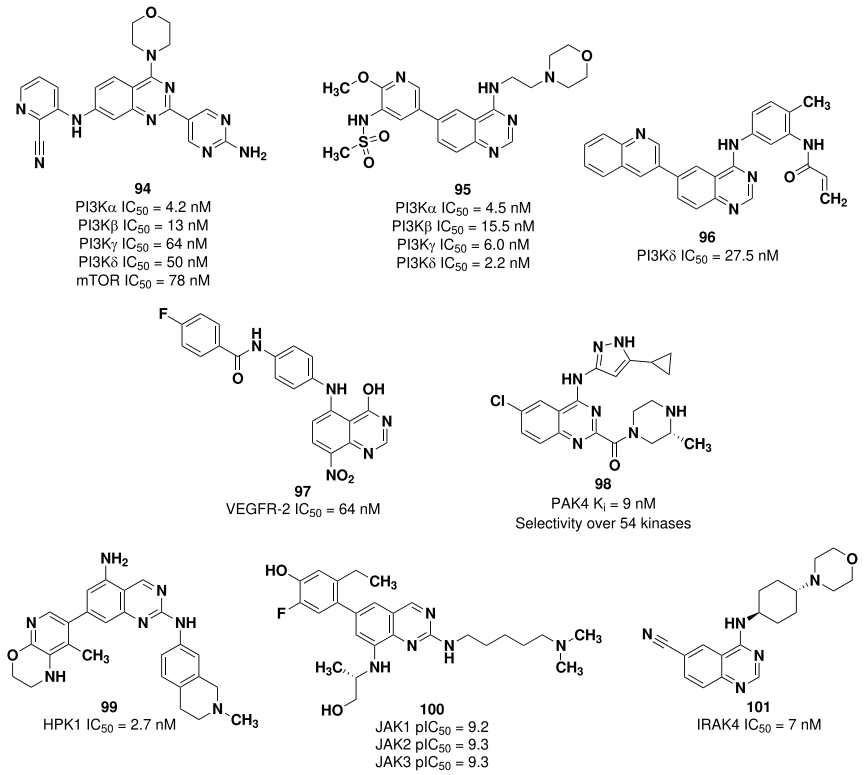


Figure 10. Chemical structures of amino-quinazolines (**94**-**101**) targeting clinically relevant kinases.

is associated with metastasis in a majority of patients with solid tumors.[105] Hao *et al*.[26] reported 6-chloro-4-aminoquinazoline-2-carboxamide derivatives as potent inhibitors of p21-activated kinase 4 (PAK4). PAKs are serine/threonine protein kinases that function as downstream signaling effectors of rho-family guanosine triphosphate hydrolases (GTPases). Numerous malignancies in humans have been related to the overexpression, amplification, and mutational activation of PAKs.[106] As a result, PAKs have become promising targets for novel anticancer treatments and have been the focus of intensive drug development initiatives.[107] PAK4, the most researched member of group II PAK enzymes, has garnered significant attention due to its involvement in the invasion, metastasis, and spread of malignancies driven by Kirsten rat sarcoma virus (KRAS) or rapidly accelerated fibrosarcoma oncogene homolog B (BRAF).[108] Hao *et al*.[26] reported that compound **98** (Figure 10) had PAK4 K_i = 9 nM, and showed selectivity over 54 kinases, including over PAK1 (346-fold).

Shi *et al*.[49] reported an extensive series of quinazoline-2,5-diamine derivatives as potent inhibitors of hematopoietic progenitor kinase 1 (HPK1). HPK1 negatively regulates multiple immunological signaling pathways through serine/threonine kinase activity. Genetic research suggests that inhibiting the HPK1 kinase could be a promising strategy for cancer immunotherapy.[109] In this context, the amino-quinazoline **99** (Figure 10) has demonstrated potent HPK1 kinase inhibition with an IC_{50} = 2.7 nM, making it a potential candidate for further studies.[49]

JAK1, JAK2, JAK3, and TYK2 are members of the Janus tyrosine kinase (JAK) family, which are essential for cytokine receptor signaling related to severe asthma development. Therefore, the development of JAK inhibitors is of great interest.[110] In this regard, Wellaway *et al*.[50] reported the identification of 2,8-diamino-quinazolines as JAK inhibitors. Compound **100** was identified as the most promising candidate for asthma treatment due to its favorable profile for lung delivery and potent inhibition of JAK1, JAK2, and JAK3 with negative logarithm of IC_{50} (pIC_{50}) values of 9.2, 9.3, and 9.3, respectively. This favorable profile was attributed to a specific substituent at the quinazoline 2-position, which prevented aldehyde oxidase metabolism.[50]

The interleukin-1 receptor associated kinase 4 (IRAK4) is another kinase associated with inflammation, which is linked to TLR- and IL-1R-based signaling pathways. Consequently, a potential therapy for inflammatory diseases involves selectively inhibiting this kinase. This is reinforced by the fact that pharmacological inhibition of IRAK4 can have a good clinical safety profile.[111] In this scenario, amino-quinazolines have also been explored for the development of IRAK4 inhibitors, such as compound **101**, reported by Smith *et al*.[112] with IRAK4 IC_{50} = 7 nM.

In addition to amino-quinazolines being described as kinase inhibitors, a variety of novel biological activities have been reported, including modulation of new targets for the treatment of cancer, neurodegenerative and infectious diseases. Therefore, the following sections are divided according to these therapeutic areas.

5. Anticancer Amino-Quinazolines Targeting KRAS, ABC Transporters or Active in Phenotypic Assays

The most common reason for chemotherapy failure is the emergence of multidrug resistance (MDR), in which cancer cells become resistant to chemotherapeutic drugs that are structurally unrelated. ATP synthase-binding cassette (ABC) transport proteins play a crucial role in the development of MDR. These ABC family members use the energy of ATP hydrolysis to transport a wide range of structurally unrelated molecules out of cells against a concentration gradient.[112] Therefore, combining anticancer agents with ABC super-family G member 2 (ABCG2) inhibitors is one method of overcoming this MDR. In addition, inhibition of the transport protein was shown to increase drug accumulation in ABCG2 overexpressing colon cancer cells HT29. In this scenario, amino-quinazolines (**102**) were reported as inhibitors of ABC transporters (Figure 11) in the well-known Hoechst 33342 accumulation assay, which is commonly used to assess inhibitory efficacy towards ABCG2.[32,33,113]

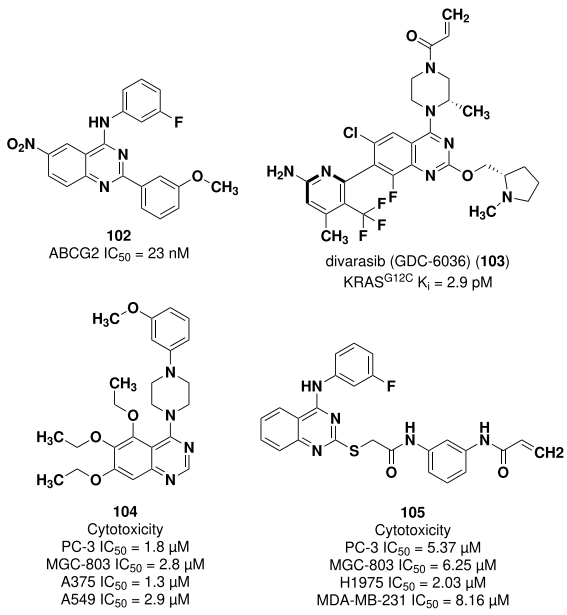


Figure 11. Chemical structures of anticancer amino-quinazoline prototypes **102**-**105**.

Purkey *et al*.[114] reported the clinical candidate divarasib (GDC-6036) (**103**) as a picomolar inhibitor (K_i = 2.9 pM) of $KRAS^{G12C}$ mutant (Figure 11). Mutations in KRAS are the most common oncogenic driver mutations in human cancers, and the $KRAS^{G12C}$ mutation is one of the most prevalent. In this context, divarasib (**103**) is progressing in clinical trials with positive results for the treatment of colorectal cancer.[115]

Regarding anticancer compounds with demonstrated tumor cell line cytotoxic activity, Zhang *et al*.[29] reported the synthesis and anticancer activities of 4-(4-substituted)-piperazin-5,6,7-trialkoxy-quinazoline derivatives. Compound **104** exhibited cytotoxicity against multiple cancer cell lines, with PC-3 IC_{50} = 1.8 μM, MGC-803 IC_{50} = 2.8 μM, A375 IC_{50} = 1.3 μM, and A549 IC_{50} = 2.9 μM.[29] Wang *et al*.[47] reported synthesis and biological evaluation of 2,4-disubstituted quinazoline derivatives targeting cancer cells. The authors highlighted that compound **105** was the most potent against diverse cell lines, with PC-3 IC_{50} = 5.37 μM, MGC-803 IC_{50} = 6.25 μM, H1975 IC_{50} = 2.03 μM, and MDA-MB-231 IC_{50} = 8.16 μM. Additionally, this compound showed promising results in cellular and molecular biology assays, indicating its potential to interfere with the EGFR-PI3K signaling pathway.[47]

6. Amino-Quinazolines for the Treatment of Neurodegenerative Diseases

In addition to anticancer derivatives, there have been recent publications on amino-quinazolines designed for the treatment of neurodegenerative disorders. Le-Nhat-Thuy *et al*.[40] reported the synthesis and biological evaluation of quinazoline-triazole hybrid compounds as acetylcholinesterase (AChE) inhibitors, given that some therapeutic alternatives for the treatment of Alzheimer's disease (AD) rely on AChE inhibition to increase acetylcholine (ACh) neurotransmission in the central nervous system. The authors[40] reported compound **106** with AChE IC_{50} = 0.23 μM for the potential use in AD (Figure 12).

Elkamhawy *et al*.[55] reported quinazoline-urea analogues as modulators of Aβ-induced mitochondrial dysfunction.

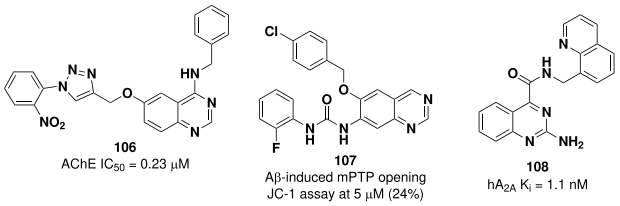


Figure 12. Chemical structures of amino-quinazolines (**106**-**108**) designed for the treatment of neurodegenerative diseases.

Extensive data indicate that the genesis of Alzheimer's disease is closely linked to the overproduction of β-amyloid peptide (Aβ) and its extracellular accumulation. Furthermore, recent research[116] suggests that these soluble Aβ oligomers internally target mitochondria. In particular, the mitochondrial permeability transition pore (mPTP), a calcium-dependent, ion non-selective membrane pore, has been shown to participate in mitochondrial dysfunction potentiated by Aβ toxicity. Overactivation of mPTP has been correlated with decreased mitochondrial membrane potential, impaired mitochondrial respiration function, increased oxidative stress in AD brains.[117] Consequently, the authors evaluated the amino-quinazoline **107** in an Aβ-induced mPTP opening assay, and found that this molecule had the best activity profile (Figure 12).[55]

In the scenario of Parkinson's disease, Zhou *et al*.[56] reported the discovery of amino-quinazoline derivatives as human A_{2A} adenosine receptor antagonists. The adenosine A_{2A} receptor, a member of the G-protein-coupled receptor (GPCR) family, is highly specific and abundant in the striatum of the brain. It is linked to increased cAMP levels and activation of adenylyl cyclase activity, and has become a target of study for Parkinson's disease therapy in recent years. The authors reported compound **108** as a ligand with a hA_{2A} K_i = 1.1 nM, and activity in an *in vivo* rat catalepsy assay (Figure 12).[56]

7. Amino-Quinazolines for the Treatment of Infectious Diseases

In the infectious disease area, amino-quinazolines have been synthesized and tested against various pathogens, such as those causing Chagas disease, leishmaniosis, malaria.[44,118,119] Regarding virus infections, compounds active against Chikungunya virus, hepatitis C, and influenza A have been reported.[120-122] Additionally, bioactive amino-quinazolines have been published[31,41,53] for the treatment of bacterial infections, such as those caused by *Staphylococcus aureus* and *Mycobacterium tuberculosis*.

Infectious parasitic diseases continue to be a significant global health concern. Chagas' disease (CD), caused by *Trypanosoma cruzi*, and leishmaniasis, caused by *Leishmania* spp., are among these diseases, which are both classified as neglected diseases. Around 30-40% people affected by CD may develop digestive mega syndromes, cardiomyopathy, or both. Although many cases remain asymptomatic for years, if left untreated, Chagas disease can progress to severe cardiac and digestive complications. Leishmaniasis presents itself in two forms: visceral and cutaneous. It is endemic in 98 countries or territories. Cutaneous leishmaniasis causes skin sores, while visceral

leishmaniasis, the most severe form, affects internal organs and can be fatal if left untreated.[123] In turn, plasmodium parasites cause over two hundred million Malaria infections and approximately 438,000 fatalities annually. Anopheles mosquitoes transmit the parasites to humans during blood feeding. Malaria symptoms consist of fever, chills, and flu-like illness. If left untreated, the disease can lead to severe complications.[124]

Mendoza-Martínez *et al*.[44] reported that 2,4,6-triamino-quinazolines can act as anti-trypanosomiasis, anti-leishmaniasis, and anti-plasmodial agents. The authors tested the compounds against *Trypanosoma cruzi* NINOA and INC-5 strains. Compound **109** showed NINOA median lethal concentration (LC_{50}) = 6.28 μM and INC-5 LC_{50} = 43.82 μM (Figure 13). In addition, compound **109** was tested against *Leishmania mexicana* MHOM/BZ/61/M379 strain and had LC_{50} = 3.06 μM. Furthermore, compound **109** also was able to achieve 100% suppression of parasitemia and enabled survival for more than 23 days after administration in *P. Berghei* murine models.[44] Other amino-quinazolines have also been reported as anti-plasmodial agents, including compounds **110**[118] and **111**[119] (Figure 13).

Chikungunya virus (CHIKV) is an arthritogenic alphavirus that is spread by mosquitoes and millions have been infected since 2004. Symptoms include sudden fever, severe joint pain, headache, muscle pain, rash, and fatigue. Although rarely fatal, the disease can cause long-lasting joint pain. Currently, there is no available treatment or vaccination for the illness.[120] In a study reporting amino-quinazolines active against CHIKV, Hwu *et al*.[45] described an amino-quinazoline linked to a coumarin ring (**112**) with CHIKV EC_{50} = 3.84 μM (Figure 13). Amino-quinazoline derivatives have also shown activity against CHIKV and hepatitis C virus (HCV).[46] HCV is a member of the Flaviviridae family of hepaciviruses. In 2015, approximately 143 million people, or 2% of the global population, were infected with HCV, resulting in approximately 326,000 fatalities.[121] Compound **113**, a quinazoline-coumarin derivative, was found to be active against CHIKV with EC_{50} = 3.11 μM, and HCV with EC_{50} = 16.6 μM.[46] Regarding compounds targeting the influenza A virus, Wang *et al*.[122] reported the design, synthesis and antiviral activity of 2,4-disubstituted quinazoline derivatives. The authors[122] described compound **114** (Figure 13) as the most active towards

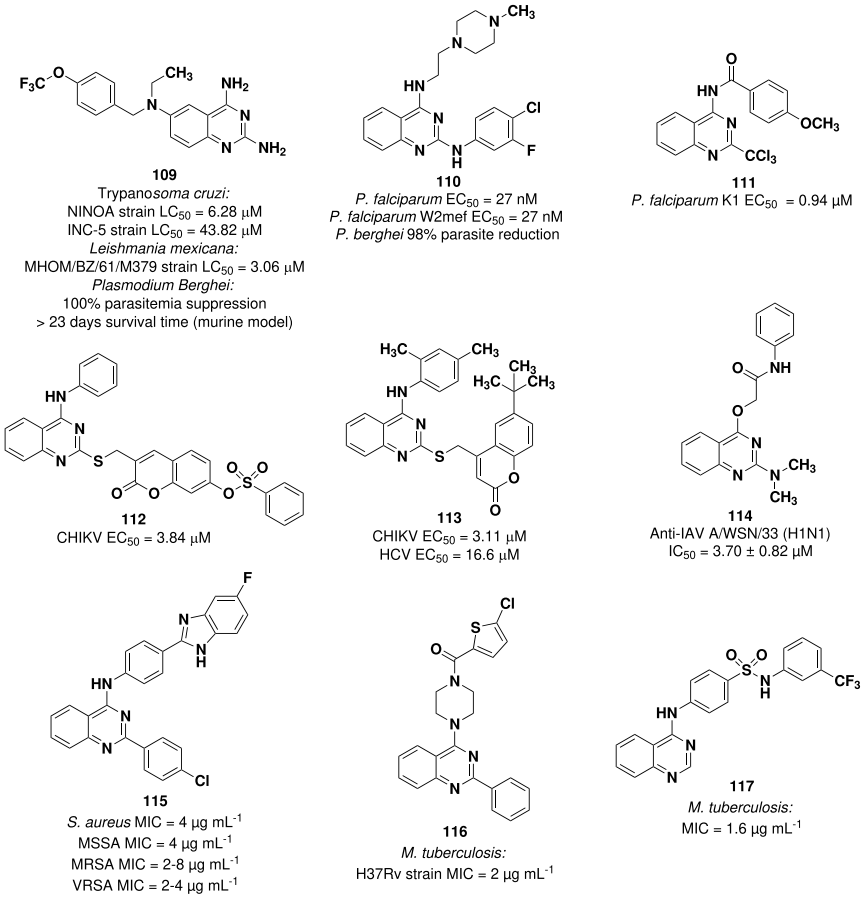


Figure 13. Amino-quinazolines (**109**-**117**) active against agents causing infectious diseases.

in vitro anti-influenza A assays, while also demonstrating low cytotoxicity (CC_{50} > 100 μM).

To address the growing problem of antibiotic resistance, it is imperative to develop new antimicrobial drugs with distinct chemical structures and modes of action. In recent years, amino-quinazolines have been investigated as antibacterials effective against *M. tuberculosis* and *S. aureus*. Malasala *et al*.[31] reported a new quinazoline-benzimidazole compound (**115**) (Figure 13) as a potent antimicrobial agent against multidrug-resistant *S. aureus* and *M. tuberculosis*. Additional studies have reported 4-substituted-piperazine-quinazolines (**116**),[53] and 4-anilino-sulfonamides-quinazolines (**117**)[41] as anti-mycobacterial agents.

8. Conclusions

In conclusion, due to the pleiotropic pharmacological effects of amino-quinazolines, the study of this privileged structure remains of importance in Medicinal Chemistry. These compounds have shown biological activities with potential application in various therapeutic areas. Researchers have made significant progress in producing diverse analogues and derivatives of amino-quinazoline chemical class using innovative synthetic methods. The structures of these amino-quinazolines have been properly modified to improve the desired pharmacological properties. These modifications have resulted in the description of novel amino-quinazoline chemical entities exhibiting remarkable bioactivities, including anticancer, anti-inflammatory, anti-parasitic, and antiviral effects. The amino-quinazoline scaffold remains present among the chemical structures of recently approved drugs and candidates in clinical trials. Therefore, this subunit holds promise in drug discovery and development, paving the way for the emergence of novel therapeutic interventions across various medical domains. Further research into the synthesis, mechanisms of action, and clinical applications of these compounds is necessary to fully realize their potential in improving therapeutics and patient outcomes.

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Lucas S. Franco *holds a degree in Pharmacy from the Federal University of Juiz de Fora, with a 1-year internship at the University of Kansas. He holds a Master's and Doctorate degree from the Graduate Program in Pharmacology and Medicinal Chemistry of the Institute of Biomedical Sciences of the Federal University of Rio de Janeiro. He is currently a postdoctoral researcher at the National Institute of Science and Technology of Drugs and Medicines (INCT-INOFAR), where he works on Medicinal Chemistry projects at the Laboratory for the Evaluation and Synthesis of Bioactive Substances (LASSBio).*

Pedro S. M. Pinheiro *holds a degree in Pharmacy from the State University of Rio de Janeiro (UERJ/ZO, 2015). He holds a Master's and Doctor's degree from the Graduate Program in Pharmacology and Medicinal Chemistry (PPGFQM) at the Institute of Biomedical Sciences at the Federal University of Rio de Janeiro (UFRJ), where he worked developing projects in the Laboratory for the Evaluation and Synthesis of Bioactive Substances (LASSBio), focusing on rational design, synthesis, molecular modeling studies and pharmacological evaluation of new drug candidates. During his doctorate, he was awarded a 1-year sandwich doctoral scholarship by CNPQ (2019-2020) to carry out a sandwich period at Università di Bologna (Italy). During his doctorate, he was also awarded a FAPERJ Doctoral Scholarship DSC-10. In the period 2021-2023, he served as an Auxiliary Professor of the pharmacy graduate course at Estácio de Sá University and is currently Assistant Professor at the Institute of Biomedical Sciences of UFRJ.*

Maria Letícia C. Barbosa*, the corresponding author, holds a degree in Pharmacy, as well as Master and Doctorate degrees in Chemistry, and currently acts as a researcher in the R&D of novel drug candidates for various therapeutic applications. From 2013 to 2024, she served as a Professor in the Drugs and Medicines Department at the Faculty of Pharmacy of the Federal University of Rio de Janeiro. Since April 2024, she has been now acting as Professor at the Department of Pharmaceutical Sciences at the Faculty of Pharmacy of the Federal University of Juiz de Fora.*

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