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REVIEW ARTICLE

An Updated Review on Novel Innovations and Emerging Insights in Quinazoline and Quinazolinone Derivatives

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Abstract: Quinazoline and quinazolinone scaffolds have gained significant attention as versatile pharmacophores for the development of central nervous system (CNS) therapeutics. Their favorable lipophilicity contributes to efficient transport across the blood–brain barrier, a critical requirement for CNS drug candidates. These heterocyclic systems can be prepared using classical synthetic routes such as the Niementowski reaction, Gabriel synthesis, Morgan's reaction, and the Sen–Ray method. More recently, novel and refined synthetic methodologies have enabled the rational design of structurally diverse derivatives with controlled substitution patterns, leading to enhanced pharmacological performance. Such innovations allow optimization of key drug-like properties, including bioavailability, CNS penetration, and molecular target specificity. Emerging pharmacological studies suggest that several quinazoline and quinazolinone derivatives exert their CNS effects through modulation of the γ-aminobutyric acid type A ($GABA_A$) receptor, an ionotropic chloride channel central to inhibitory neurotransmission. Activation of this receptor increases chloride ion conductance, resulting in neuronal hyperpolarization and reduced excitability. This mode of action aligns with that of many established CNS-active agents, highlighting the therapeutic potential of quinazoline-based compounds in neurological disorder management.

Keywords: Quinazoline, quinazolinones, CNS, $GABA_A$, heterocycles, synthetic schemes.

1. INTRODUCTION

Central nervous system (CNS) disorders are among the leading causes of illness, disability, and death across the globe [1]. These conditions are often complex and widespread, significantly disrupting the everyday lives of millions of people [2]. Major CNS-related diseases include a wide range of neurological and psychiatric disorders such as Parkinson's disease, schizophrenia, epilepsy, Alzheimer's disease, ischemia, traumatic brain injury, stroke, lysosomal storage disorders, anxiety, depression, and multiple sclerosis [3, 4]. According to the World Health Organization (WHO), nearly 1.5 billion people worldwide are affected by CNS diseases. These disorders contribute to around 38% of the total global disease burden, much higher compared to cancer at 12.7% and cardiovascular diseases at 11.8% (based on disability-adjusted life years). This highlights the profound impact CNS diseases have on global health [5].

In the discipline of chemistry, nitrogen-containing compounds represent a significant category of heterocyclic compounds that gain considerable attention, owing to their diverse biological and pharmacological activities [6, 7, 8].

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The significance of nitrogen-containing scaffolds is evident in numerous pharmaceuticals, highlighting the role of N-heterocycles in the preparation of bioactive compounds, with quinazolinone being frequently seen in the structure of these drugs [9, 10]. The derivatives of quinazolin-4(3H)-one, also referred to as 4-oxo-quinazoline, are the representatives of this class of heterocycles [11].

Quinazoline derivatives and their hybrid structures form an important class of nitrogen-containing heterocycles known for their broad range of biological activities. Their strong stability and lipophilic nature help them cross the blood-brain barrier more effectively, making them promising candidates for treating several disorders of the central nervous system. Because of these advantages, there is a growing interest in developing new quinazoline-based frameworks that can be used in medicinal chemistry and drug design [12, 13].

Their pharmacological properties include anti-convulsant [14], anti-depressant [15], anti-Alzheimer's [16], anti-bacterial [17], anti-cancer [18], anti-hypertensive [19], anti-HIV [20], antimicrobial [21], antifungal [22], anti-inflammatory [23], analgesic [24], antiviral properties [25], anti-obesity [26], anti-malarial [27], anti-oxidant [28], anti-diabetic [29], and many others.

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Several structural variants of quinazoline (1) also exist, including 3,4-dihydroquinazoline (2), 1,2,3,4 tetrahydroquinazoline (3), 3,4-dihydroquinazolin-2(1H)-one (4), 2,3-dihydroquinazolin-4(1H)-one (5), quinazolin-2(1H)-one (6), and quinazolin-4(3H)-one (7). These analogues share the basic quinazoline framework but differ slightly in their saturation and functional groups (Fig. **1**) [30].

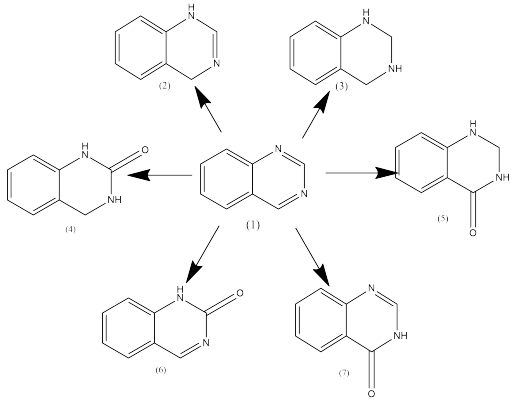


Fig. (1). Structural analogues of quinazoline [30].

There are some US FDA-approved marketed drugs based on the quinazoline and quinazolinone moieties (Fig. **2**), which exhibit various pharmacological responses. For example, Piriqualone (8) is used for anti-convulsant activity [31], Quazodine (9) and Afloqualone (10) are used for muscle relaxant activity [32, 33], and ATC-0175 (11) is an anxiolytic and antidepressant drug [34]. Terazosin (12) and Prazosin (13) are the selective alpha-blockers, which are responsible for reducing hypertension [35]. Afatinib (14), Erlotinib (15), and Gefitinib (16) are generally used to treat cancer [36]. Febrifugine (17) and halofuginone (18) are used in the treatment of malaria [37], Fluproquazone (19) is used in as anti-inflammatory drug [38], Albaconazole (20) is an antifungal drug [39], Fenquizone (21) is used as diuretic drug [40], and Sotrastaurin (22) is used to treat psoriasis andulcerative colitis [41].

Quinazoline hybrids are chemically known by the molecular formula $C_8H_6N_2$. Two fused six-member aromatic rings, namely the pyrimidine and benzene rings, which are soluble in water, make up this compound. When peganine (vasicine) was discovered in 1888, researchers became fascinated. Thereafter, quinazoline was first isolated from the Chinese herb aseru (*Dichroa febrifuga* Lour) in 1903 and then synthesized in a lab by Gabriel [42, 43].

Williamson, Lindquist, and Armarego reviewed the chemistry of quinazoline in 1957, 1959, and 1963, respectively. In cold, diluted acid and alkaline solutions, quinazolines remain stable; nevertheless, boiling these solutions destroys their efficacy [44, 45].

Developing effective drugs for CNS disorders remains difficult, largely because many compounds fail to reach the brain in adequate amounts. To address this, researchers often rely on drug-likeness guidelines and BBB-permeability rules early in the discovery process. Today, computational tools have become a major advantage -they help predict pharmacokinetic behavior and possible metabolic pathways, allowing scientists to screen candidates more efficiently while saving both time and resources [46, 47].

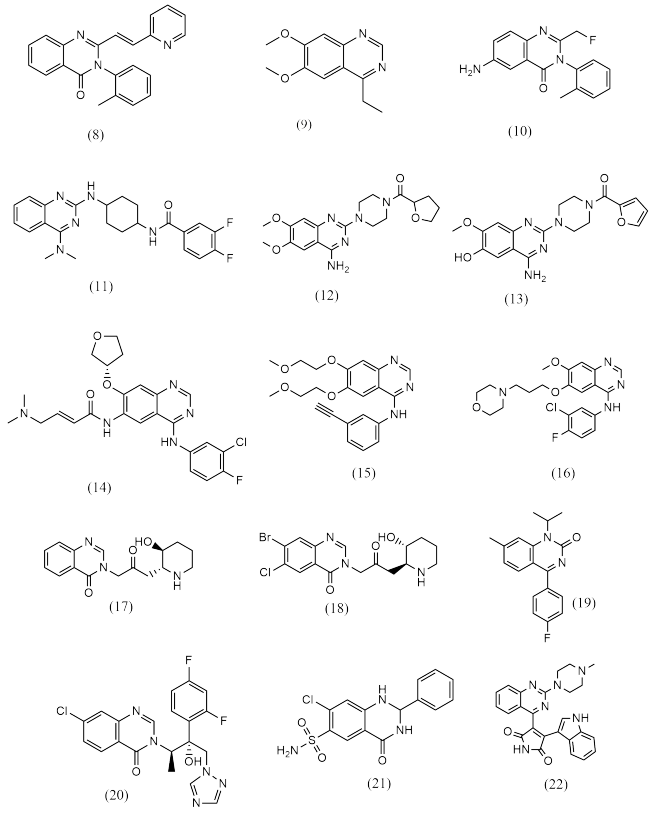


Fig. (2). USFDA-approved marketed drugs on quinazoline and quinazolinone moieties [31-41].

It is interesting to note that quinazoline has a high lipophilicity factor and aids in blood-brain barrier penetration, making it appropriate for curing several disorders affecting the central nervous system [48]. Also, many derivatives were reported as $GABA_A$ receptor stimulants, which is responsible for the anti-convulsion property (depicted in Fig. **3**). The $GABA_A$ receptor is a ligand-gated ion channel and an ionotropic receptor. γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, is its endogenous ligand. When the $GABA_A$ receptor is activated, Cl^- is selectively conducted through its pore, which causes the neuron to become hyperpolarized. This reduces the likelihood of a successful action potential, which has an inhibitory effect on neurotransmission. Both GABA and a number of medications bind to the $GABA_A$ receptor's active site. Additionally, methaqualone has been shown in the literature to be a positive allosteric modulator of $GABA_A$ receptors. By binding to allosteric sites on the $GABA_A$ receptor complex, it has a favorable effect on the primary site, increasing its efficiency and indirectly raising Cl- conductance, causing a remarkable reduction in action potential. Moreover, other quinazolinone derivatives were synthesized and biologically tested for their potent anticonvulsant activity [49,50].

2. METHODOLOGY

This review article was designed using a structured approach to collect, analyze, and summarize relevant scientific literature on quinazolinone and its pharmacological activi-

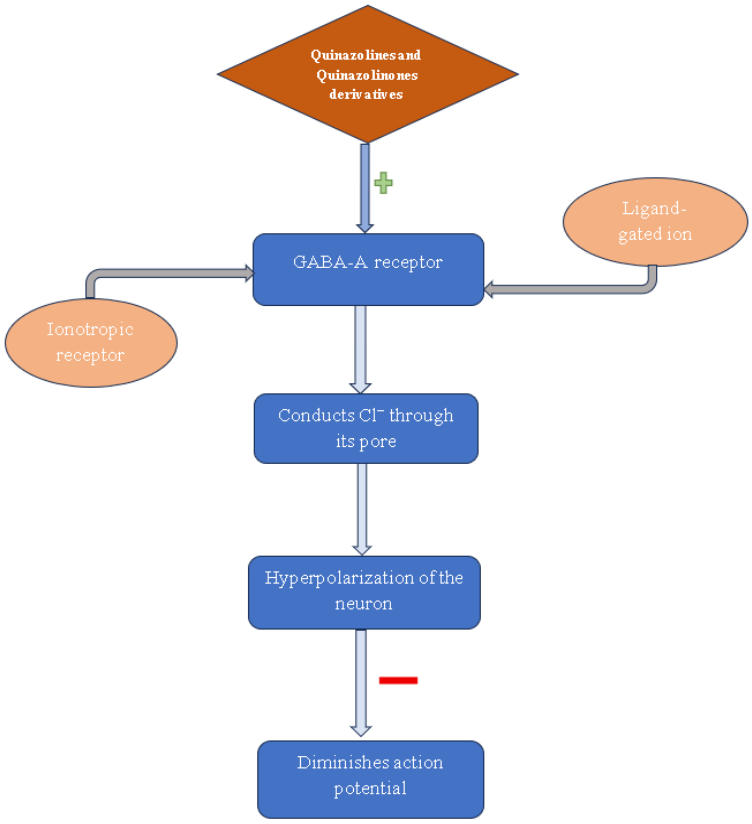


Fig. (3). Mechanism of action of quinazolinone derivatives [49,50]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ties. A comprehensive literature search was carried out in databases such as PubMed, Scopus, Web of Science, and Google Scholar, covering articles published between 2025-2018. Keywords such as "quinazolinone", "quinazolinone," "quinazolinone derivatives," "pharmacological activity," "synthesis," and "biological evaluation" were used in various combinations to find out the relevant data. This review covers the various approved marketed drugs and under clinical trials drugs of quinazolinone moiety, as well as traditional methods for the synthesis of quinazolinone derivatives. Also, the article is based on the relevance of experimental work related to synthetic strategies and the pharmacological significance of the quinazolinone moiety. The gathered data were categorized into different sections, including synthetic schemes and pharmacological activities of the quinazolinone moiety. Moreover, the mechanism of action of quinazolinone derivatives against CNS activity is incorporated in the article. This method ensured the inclusion of high-quality studies that provide a comprehensive overview of the medicinal potential of quinazolinone-based compounds.

3. TRADITIONAL METHOD OF PREPARATION FOR QUINAZOLINE AND QUINAZOLINONE DERIVATIVES

3.1. Niemetowski Method

The most common approach to synthesize quinazolinone derivatives (25) is the Niementowski reaction (depicted in Fig. **4**) in which anthranilic acid (23) and amide derivatives (24) are reacted together under high temperature [51].

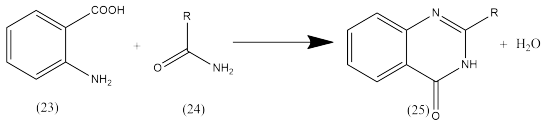


Fig. (4). Niementowski synthesis of quinazolinones [51].

3.2. Gabriel Method

Quinazoline derivatives play such an important role in a wide range of applications; many synthetic strategies have been designed to build the quinazoline framework. One classic example comes as Gabriel's method is notable, demonstrating that quinazolines (27) can be efficiently generated through the oxidation of their intermediate, 3,4-dihydroquinazoline (26) (Fig. **5**) [52].

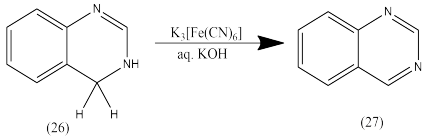


Fig. (5). Gabriel method for quinazoline synthesis [52].

3.3. Morgan's Method

When 2-acetamidobenzoic acid (28) is heated with an amine (29) in the presence of phosphorus trichloride in toluene for about two hours, it results in the formation of 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines (30) (Fig. **6**) [53].

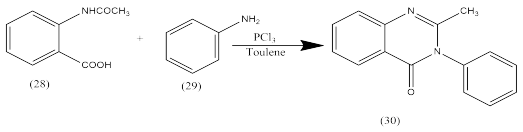


Fig. (6). Morgan's method for quinazoline synthesis [53].

3.4. From Isatoic Anhydride

Ethyl orthoformate (34) was refluxed for 1–6 hours without isolating the intermediate amide (33) to dihydro-4-oxoquinazolines (35) from isatoic anhydride (31) that easily interacted with amines (32), (Fig. **7**) [54].

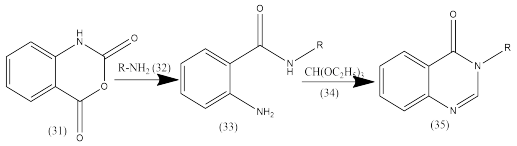


Fig. (7). From Isotoic anhydride for quinazoline synthesis [54].

3.5. Sen and Ray's Synthesis

When urethane (37) and phosphorus pentoxide are refluxed in xylene along with either normal or isobutyrylanilides (36), the reaction yields 2-propyl and 2-isopropyl-3,4-dihydro-4-oxoquinazolines (38) (Fig. **8**) [55].

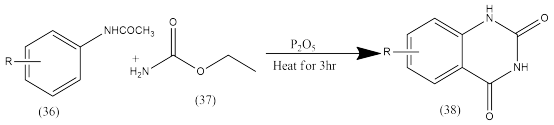


Fig. (8). Synthesis of 2-methyl-4-(3H) quinazolinone [55].

3.6. Condensation of N-acylanthranilic Acids with Primary Amines

A review of existing literature indicates that 4-(3H) quinazolinones (41) can also be prepared directly from the corresponding N-acylanthranilic acids (39) by heating them with ammonia or appropriately substituted amines (40) (Fig. **9)** [56].

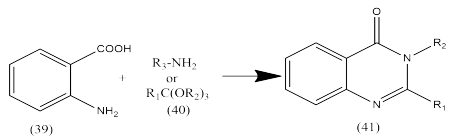


Fig. (9). Synthesis of 4-(3H) Quinazolinones [56].

3.7. From Phthalic Acid

Phthalimide (42) undergoes a reaction with alkali hypobromite (43) to yield 1,2,3,4-tetrahydro-2,4 dioxoquinazoline (44). In general, phthalic acid derivatives used to synthesize dioxoquinazoline typically require a rearrangement step, such as the Hofmann, Curtius, or Lossen rearrangement, to form the desired product (Fig. **10**) [57].

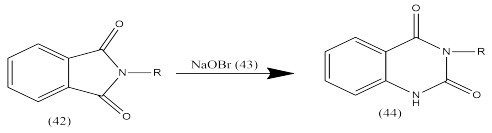


Fig. (10). Preparation of 1,2,3,4-tetrahydro-2,4-dioxoquinazoline [57].

3.8. Synthesis from Ureido-benzoic Acid

Ureidobenzoic acids (47) can be prepared by reacting anthranilic acid (45) with potassium cyanate (46) under heated acidic or alkaline conditions. These ureidobenzoic acids can then undergo cyclization to produce 1,2,3,4-tetrahydro-2,4-dioxoquinazolines (48) (Fig. **11**) [45, 58].

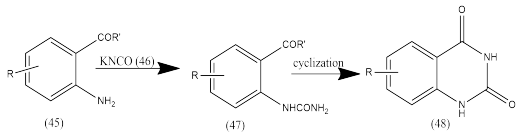


Fig. (11). Preparation of Ureido-benzoic Acid [45, 58].

3.9. Synthesis from Benoxazones

When primary amines (50) react with Benoxazone compounds (49), it forms 3,4-dihydro-4-oxoquinazolines **(51)** (Fig. **12**) [59].

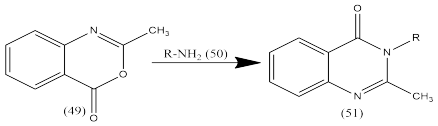


Fig. (12). Synthesis of 3,4-dihydro-4-oxoquinazolines [59].

3.10. Synthesis from Isatins

When β-imino compounds (51) are heated with hydrogen peroxide (52) in alkaline solution, it forms an intermediate (53), which, upon further treatment, will form dioxoquinazoline (54) and its derivatives (Fig. **13**) [60].

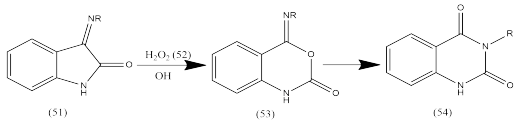


Fig. (13). Synthesis of dioxoquinazoline derivatives [60].

4. SYNTHETIC SCHEMES

Reddy and colleagues (2025) developed a new collection of 1,2,4-triazole-linked quinazolinone derivatives (Fig. **14**) as potential anticancer agents. The synthesis started with commercially available 2-amino-3-methylbenzoic acid (55) and formamide (56). These two were cyclized by heating in N,N-dimethylformamide, producing the first key intermediate, 8-methylquinazolin-4(3H)-one (57). Next, this compound was reacted with 2-chloroacetic acid (58) and sodium hydroxide under reflux, resulting in the second intermediate, 2-(8-methyl-4-oxoquinazolin-3(4H)-yl)acetic acid (59). In the third step, compound (59) was coupled with acetimidamide (60) using DIPEA and HATU in DMF, giving N-(1-aminoethylidene)-2-(8-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (61). Finally, various hydrazine derivatives (62a-k) were slowly added in ethanol, leading to the formation of the desired quinazolin-4(3H)-one-1,2,4-triazole hybrids (63a-k). To confirm their structures, researchers used mass spectrometry, 'H NMR, 13C NMR, and IR spectroscopy. All synthesized molecules were then evaluated for anticancer activity using the MTT assay against three human cancer cell lines, *i.e.,* MCF-7, MDA-MB-231 (breast cancer), and A549 (lung cancer). Most compounds showed

excellent to moderate anticancer effects when compared with the standard drug doxorubicin. Their IC_{50} values ranged from 7.30 ± 1.4 μM to 33.44 ± 1.4 μM, while doxorubicin showed IC_{50} values between 8.45 ± 1.9 μM and 13.48 ± 0.8 μM. These results indicate that the newly designed triazole-quinazolinone hybrids possess strong anticancer potential. To better understand their activity, the most promising compounds were also evaluated through molecular docking using the estrogen receptor-alpha mutant (PDB: 7KBS), which is relevant to breast cancer. The compounds interacted with key amino acid residues such as His-107, Glu-106, Lys-158, Trp-102, Arg-103, and others, with docking scores ranging from -8.30 to -8.78 kcal/mol, suggesting strong binding affinity. Additionally, SwissADME and PkCSM analyses supported their drug-likeness and pharmacokinetic profiles. Among all derivatives, compounds 63d, 63e, and 63j stood out as the most potent, showing even better cytotoxic activity than doxorubicin, especially against the MDA-MB-231 breast cancer cell line [61].

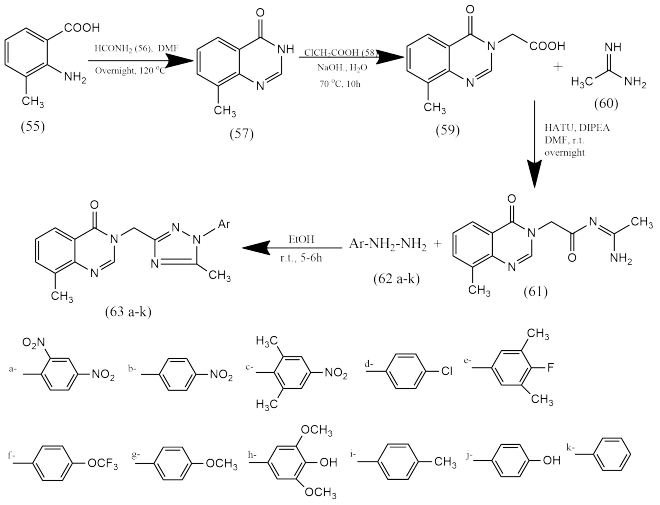


Fig. (14). Synthesis of novel 1,2,4-triazole-linked quinazolinone derivatives [61].

Antoniolli and colleagues (2025) developed a set of 20 derivatives (Fig. **15**) based on 2-substituted quinazolin-4(3H)-ones (66 I-XX). These compounds were synthesized by condensing 2-aminobenzamide (64) with various aldehydes (65) in dimethyl sulfoxide. Their structures were confirmed using IR spectroscopy, along with ^{1}H NMR and ^{13}C NMR analyses. Biological screening showed that two derivatives-66 (VI) and 66 (XVII)-displayed strong cytotoxic activity against T-cell acute lymphoblastic leukemia (Jurkat cells) and the promyelocytic subtype of acute myeloid leukemia (APL, NB4 cells). Notably, compound 66 (XVII) achieved IC_{50} values below 5 μM in both cancer cell lines, while compound 66 (VI) showed selective toxicity toward Jurkat cells. Additional *in vitro* studies, including apoptosis and cell-cycle assays, as well as pharmacokinetic predictions, further supported their therapeutic promise. Overall, these findings pave the way for future *in vivo* investigations exploring the use of quinazolin-4(3H)-one derivatives in treating acute leukemias of both lymphoid and myeloid types [62].

Erdogan and co-workers (2025) synthesized a series of 1,2,3-triazole-quinazoline hybrid molecules (72a-d, 74a-d, and 76a-d), as illustrated in Fig. **16**, and investigated their enzyme inhibitory and antioxidant activities using various *in vitro* methods. The synthetic pathway began with substituted anilines (67a-d), which were converted into azide derivatives (68a-d). These intermediates were then reacted with propargyl alcohol to afford triazole alcohols (69a-d). Oxidation of the alcohols using MnO2 yielded the corresponding triazole carbaldehydes (70a-d), which were subsequently condensed with 2-aminobenzamide (71) to produce the first set of triazole-quinazolinone derivatives (72a-d). Further reaction of these compounds with allyl bromide (73) or propargyl bromide (75) in the presence of K_2CO_3 generated new triazole-quinazoline analogues, namely 74a-d and 76a-d.

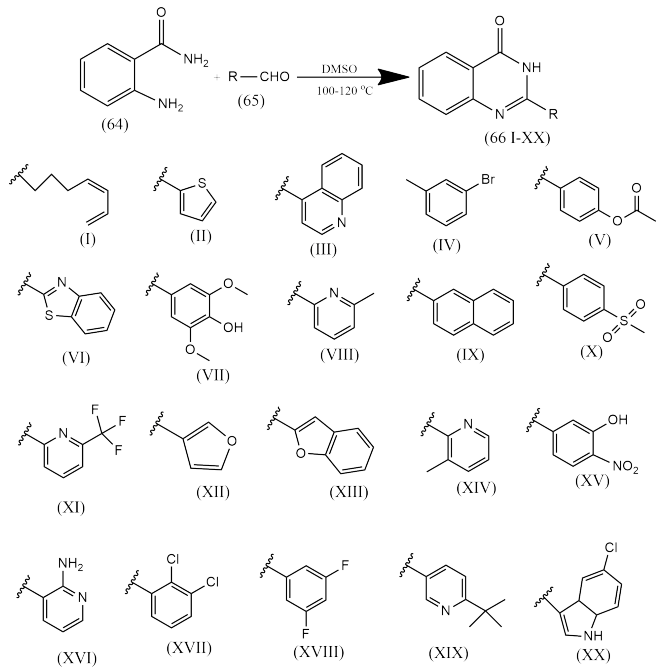


Fig. (15). Schematic representation of the reaction to obtain 2-substituted quinazolin-4(3H)-ones [62].

All synthesized molecules were structurally confirmed through spectroscopic and analytical techniques, while compounds 69a, 69c, 69d, and 70a were additionally characterized by single-crystal X-ray diffraction to determine their precise molecular geometry. Biological testing demonstrated that the 1,2,3-triazole-quinazoline hybrids possessed notable a-amylase inhibition, with IC_{50} values between 1.08 and 39.65 μM. They also displayed strong AChE inhibitory activity (IC_{50} = 0.18-15.91 μM) and BChE inhibition (IC_{50} = 1.16-14.50 μM), with several compounds outperforming standard drugs such as donepezil (ACHE IC_{50} = 1.03 ± 0.3 μM; BCHE IC_{50} = 1.37 ± 0.4 μM) and acarbose (α-amylase IC_{50} = 1.09 ± 0.2 μM). Notably, AChE inhibition was particularly strong for compounds 72a and 76a, BChE inhibition for 72a and 74d, and a-amylase inhibition for 76d. Antioxidant studies using DPPH and ABTS assays indicated that the compounds exhibited IC_{50} values ranging from 7.32-59.1 μM and 3.46-25.21 μM, respectively, significantly stronger than standard antioxidants like ascorbic acid and butylhydroxytoluene. Molecular docking provided insight into the interactions of these compounds with their target enzymes, and ADME predictions were also performed to evaluate their pharmacokinetic suitability [63].

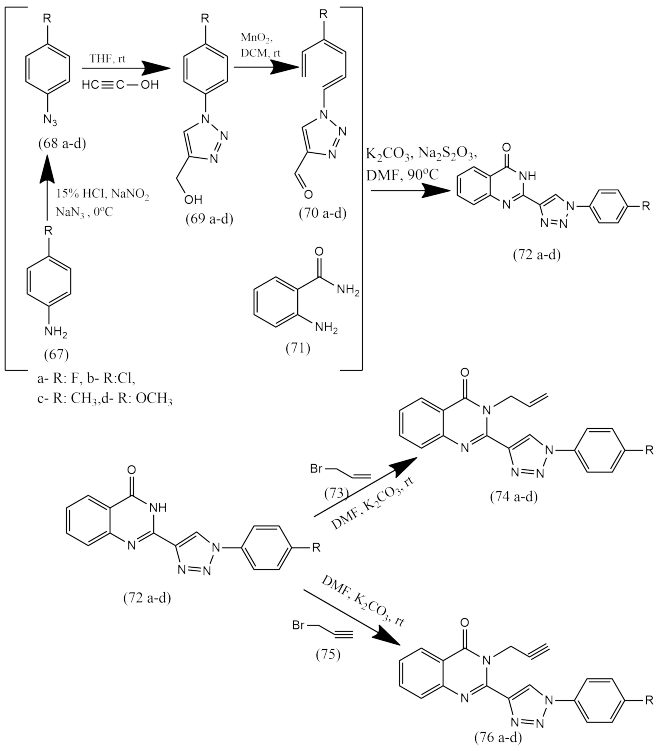


Fig. (16). Synthesis of novel 1,2,3-Triazole-quinazoline hybrid compounds [63].

Nguyen and colleagues in 2025 developed a new series of quinazoline-4(3H)-one derivatives, specifically quinazoline-4(3H)-one-2-carbothioamides (79a-p) and a carboxamide analogue (79q), as illustrated in Fig. **17**. These compounds were synthesized using the Wilgerodt-Kindler reaction. The synthesis began with 2-aminobenzamide (77), which was refluxed in excess ethanol for 48 hours to yield 2-methylquinazolin-4-one (78). This intermediate was then reacted with various amines in the presence of an S8/DMSO oxidizing system to form the final derivatives (79a-q). The structures of the synthesized compounds were confirmed through IR, NMR, and HRMS analyses, along with melting point measurements. The biological evaluation focused on assessing their anti-inflammatory potential by examining their ability to inhibit nitric oxide (NO) production in LPS-stimulated RAW 264.7 macrophage cells. Among the tested derivatives, compounds 79d (IC_{50} = 2.99 mM), 79g (IC_{50} = 3.27 mM), and 79k (IC_{50} = 1.12 mM) demonstrated strong NO inhibition, outperforming the standard anti-inflammatory drug dexamethasone (IC_{50} = 14.20 mM). Compound 79a (IC_{50} = 13.44 mM) showed activity comparable to dexamethasone. Structure-activity relationship (SAR) analysis revealed that the thioamide group (NH-C=S) directly attached to a phenyl ring containing halogen substituents, such as 4-Cl (79d), 4-Br (79g), and 4-CF3 (79k), plays a crucial role in enhancing anti-inflammatory activity. Computational studies further supported these findings, showing that compounds 79d, 79g, and 79k effectively inhibit TLR4 signaling through hydrophobic interactions and stabilizing hydrogen bonds. Notably, replacing the thioamide group in compound 79k with an amide (79q) led to an 83-fold decrease in potency, emphasizing the importance of the thioamide moiety for strong target binding. ADMET prediction studies also indicated that these lead compounds possess favorable drug-like properties. Overall, the results suggest that these newly synthesized quinazolinone derivatives could serve as promising candidates for managing inflammatory diseases associated with immune dysfunction [64].

Mansouri and colleagues (2025) developed a new series of 3-substituted phenyl quinazolinone derivatives (Fig. **18**) with the goal of identifying promising anti-cancer agents. Their synthesis began with anthranilic acid derivatives (80), which were reacted with phenyl isothiocyanate derivatives (81) in ethanol using triethylamine as the base at 70°C for 24 hours. This reaction produced 2-mercapto-3-phenylquinazolin 4(3H)-one (82). The compound was then methylated with methyl iodide in dimethylformamide (DMF) under basic conditions using potassium carbonate, yielding 2-methylthio-3-phenylquinazolin-4(3H)-one derivative (83). Finally, these intermediates were treated with hydrazine hydrate and various urea derivatives (84a-o) to obtain the final products, 3-substituted phenyl quinazolinones (85a-o). Biological evaluations revealed that the most active derivative exhibited IC_{50} values of 12.84 ± 0.84 μM against MCF-7 breast cancer cells and 10.90 ± 0.84 μM against SW480 colon cancer cells, potencies comparable to standard drugs such as erlotinib and cisplatin. Cell-cycle studies showed that this lead compound arrested MCF-7 cells in the S-phase, while apoptosis assays confirmed its ability to induce programmed cell death. Molecular docking revealed that the most potent compound fit well within the active site of the EGFR enzyme, forming key hydrogen-bond interactions. Molecular dynamics simulations further supported these results, demonstrating that the active analogue displayed stronger binding stability, indicated by lower RMSD and Rg values and more consistent interactions, compared to less active derivatives. Additionally, DFT calculations using Gaussian 09 at the M06-2X/6-31+G(d) level were performed to analyze electronic features of both active and inactive molecules. ADME predictions showed that most synthesized

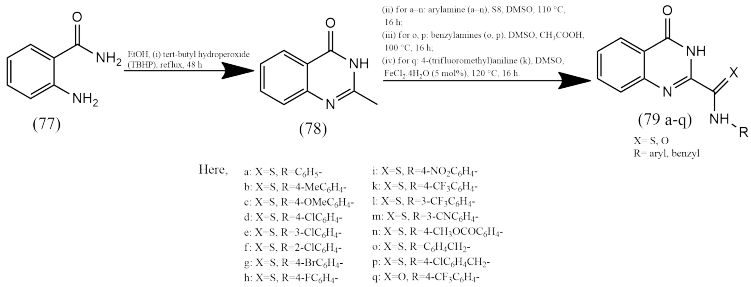


Fig. (17). Synthesis of novel quinazoline-4(3H)-one-2-carbothioamide derivatives and quinazoline-4(3H)-one-2-carboxamide [64].

compounds satisfied Lipinski's rule of five, indicating favorable drug-like properties. Altogether, these findings highlight the strong cytotoxic potential of the newly synthesized quinazolinone derivatives and provide valuable insight for developing effective cancer therapeutics [65].

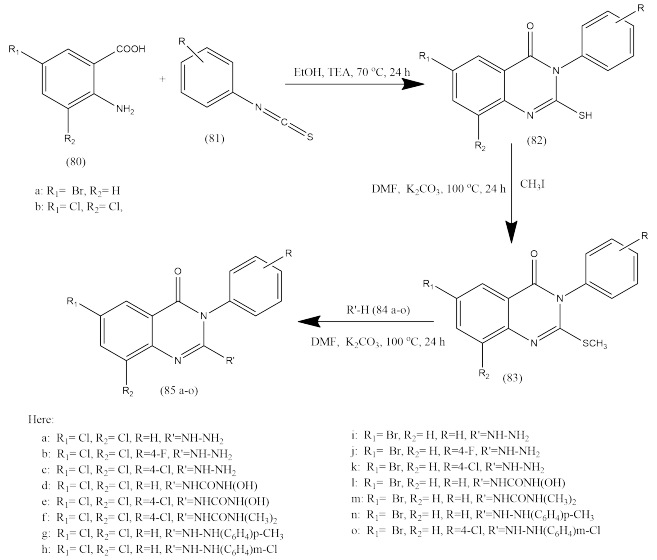


Fig. (18). Synthesis of 3-substituted phenyl quinazolinone derivatives [65].

Das *et al.* (2025) focused on non-canonical G-quadruplex (G4) DNA structures-unique nucleic acid formations that play important roles in gene regulation and have emerged as attractive targets for cancer therapy. In their study, they designed, synthesized, and evaluated a set of 15 new pyridine bis-quinazoline derivatives (Fig. **19**) to assess their ability to selectively bind and stabilize G4 DNA. The synthesis involved a 4-5 step sequence starting with anthranilic acid (86), which was reacted with pyridine-2,6-dicarboxylic acid (87) in the presence of methane sulfonyl chloride and pyridine to form pyridine bis-benzoxazine (88). This intermediate was then aminated to generate bis-quinazolinone (89), which, upon refluxing with thionyl chloride, yielded bis-chloroquinazoline (90). Coupling this compound with a range of substituted amines (91a-o) produced the final bis-quinazoline derivatives (92a-o) in excellent yields. Additionally, the N-Boc piperazine-containing derivative 92e was deprotected to obtain compound 93. Extensive biophysical evaluations-including FRET melting assays, fluorescence intercalator displacement (FID), circular dichroism (CD), and NMR studies-confirmed strong G4 stabilization by these molecules, along with high selectivity over double-stranded DNA. The nature of the aliphatic amine side chain was found to be crucial, with propylamine linkers demonstrating the best performance, achieving ΔTm values greater than 20°C and nanomolar dissociation constants. The compounds showed a preference for binding parallel and hybrid G4 topologies and caused minimal structural disruption to G4 DNA upon binding. Cell-based assays using HCT-8 and HepG2 cancer cell lines further revealed that most of these derivatives successfully entered cells and reduced cancer cell viability in a dose-dependent manner. Altogether, these findings highlight pyridine bis-quinazoline derivatives as promising and highly selective G4 stabilizers, opening new directions for anticancer drug development [66].

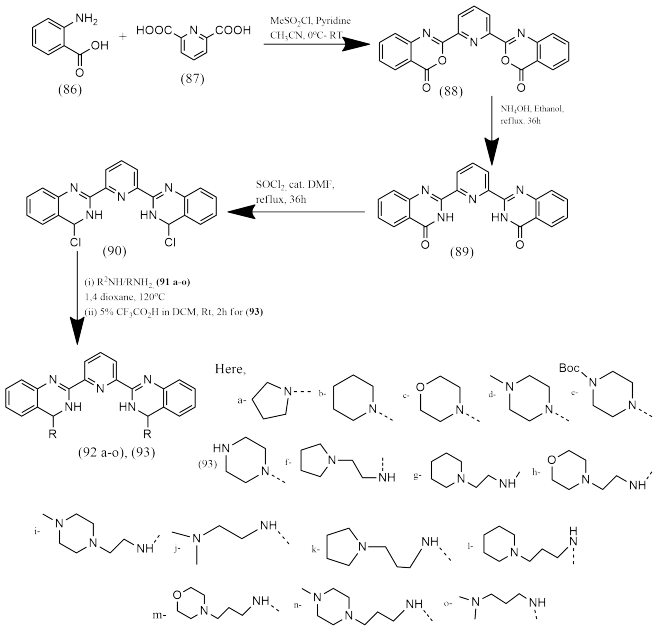


Fig. (19). Novel pyridine bis-quinazoline derivatives [66].

Sandor *et al.* (2025) focused their research on angiogenesis-a key biological process that fuels tumor growth and contributes to the aggressiveness of many cancers. Their team designed and synthesized a new set of thiosemicarbazone-based quinazoline derivatives, labeled TSC1-TSC10 (Fig. **20**), to evaluate their potential as VEGFR2 inhibitors with anti-angiogenic and antiproliferative properties. The synthesis began with the reaction of 4-((6,7-dimethoxyquinazolin-4-yl)oxy)-benzaldehyde (94) and various isothiocyanate derivatives (95), forming intermediate compounds (96) and the corresponding thiosemicarbazide derivatives (96a-105a). These intermediates were then refluxed together in the presence of a drop of concentrated acetic acid, which acted as a catalyst, ultimately yielding the TSC1-TSC10 series. The structures of the final compounds were confirmed through spectral analysis. To evaluate their biological activity, the researchers employed a comprehensive combination of *in vitro* assays -including the Alamar Blue cytotoxicity assay, Scratch wound assay, CAM assay, and VEGFR2 kinase inhibition assay-and *in silico* techniques, such as molecular docking, molecular dynamics (MD) simulations, and MM-PBSA calculations. Among the synthesized compounds, TSC10 stood out as the most potent candidate. It demonstrated strong cytotoxic effects across multiple cell lines (Ea.Hy296, HaCaT, and A375) and showed impressive VEGFR2 inhibition with an IC_{50} value of 119 nM. In endothelial cell motility assays, TSC10 performed comparably to the standard drug sorafenib, and it also displayed similar anti-angiogenic activity in the CAM assay, a more complex *in-ovo* model. Also, computational analyses validated these experimental findings, showing that all TSC derivatives fit well into the VEGFR2 kinase active site like sorafenib. The combined *in vitro* and *in silico* results strongly supported the initial hypothesis, confirming that the TSC1-TSC10 series holds significant promise as novel anti-angiogenic agents [67].

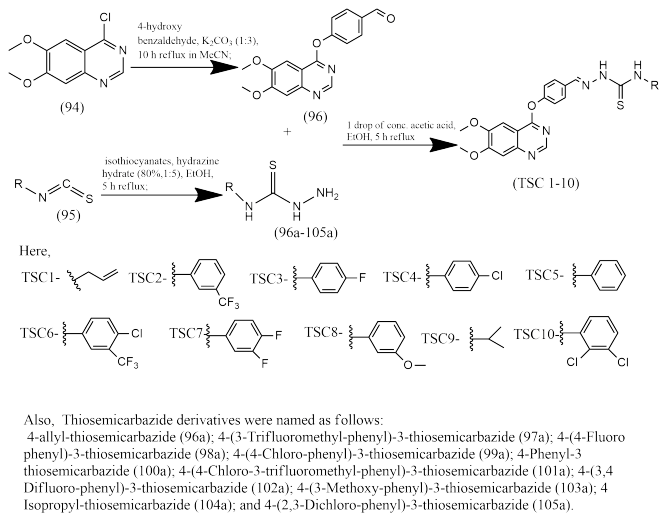


Fig. (20). Novel thiosemicarbazone-based quinazoline derivatives [67].

Emami and colleagues (2024) created and synthesized a novel set of quinazoline-4(3H)-one molecules featuring a thiol group at the 2-position of the quinazoline ring (112a-112h), aiming to explore their anticancer potential. The synthesis began with the reaction of anthranilic acid (106) and N-bromosuccinimide (107) in acetonitrile, producing 5-bromoanthranilic acid (108). This intermediate then reacted with phenyl isothiocyanate (109) in ethanol to form a key compound, 6-bromo-2-mercapto-3-phenylquinazolin-4(3H)-one (110). Subsequent treatment of this molecule with various alkyl halides (111a-b) or substituted benzyl bromides (111c-h) in the presence of K_2CO_3 in DMF yielded the final derivatives 112a-112h in excellent yields, as illustrated in Fig. (**21**). All synthesized compounds were fully characterized using 'H-NMR, 1°C-NMR, and mass spectrometry. Their antiproliferative effects were evaluated using the MTT assay on two cancer cell lines (MCF-7 and SW480) and a normal fibroblast line (MRC-5), with doxorubicin, erlotinib, and cisplatin serving as standard drugs. Among all derivatives, compound 112a-bearing an aliphatic linker attached to the thiol group-was identified as the most active, showing IC_{50} values of 15.85 ± 3.32 μM (MCF-7) and 17.85 ± 0.92 μM (SW480). Notably, in the MCF-7 line, 112a outperformed erlotinib. When tested on normal cells, 112a showed an IC_{50} of 84.20 ± 1.72 μM, indicating strong selectivity toward cancer cells over normal ones. SAR analysis suggested that modifications at the SH position significantly influenced the anticancer activity of these derivatives. Molecular docking and molecular dynamics simulations further revealed that compounds 112a and 112c interacted favorably with EGFR and its mutant form, exhibiting binding energies of -6.7 and -5.3 kcal/mol, respectively. Both compounds formed essential hydrogen bonds and other stabilizing interactions within the receptor's active site. Density Functional Theory (DFT) calculations (B3LYP/6-31+G(d,p)) performed for 112a, 112c, and erlotinib showed that 112a was thermodynamically more stable than 112c, with theoretical predictions aligning well with experimental IR spectra. Overall, these findings highlight compound 112a as a promising pharmacophoric scaffold for developing new anticancer agents with strong antiproliferative activity and good selectivity [68].

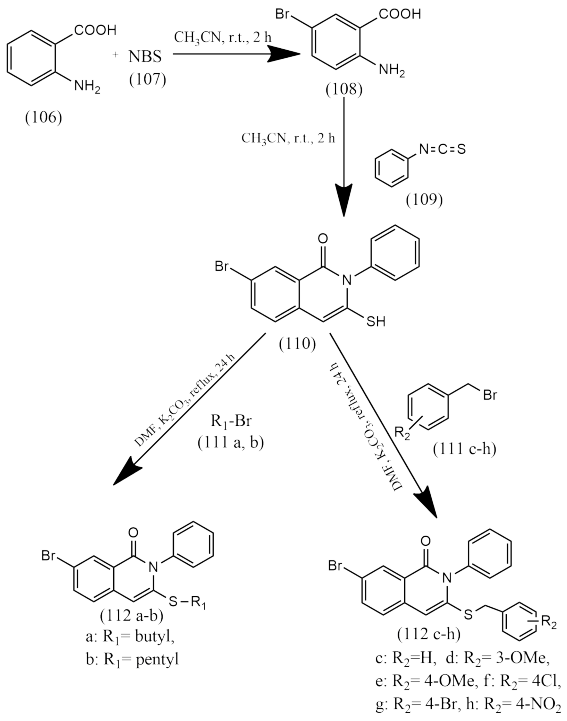


Fig. (21). New series of quinazoline-4(3H)-one derivatives [68].

Ramani *et al.* (2024) designed a new set of 8-methyl-2-phenyl quinazolinone-based Schiff base derivatives (Fig. **22**). The synthetic work began with 2-amino-3-methylbenzoic acid (113), which was dissolved in pyridine. While the solution was stirred and maintained between 0-5°C, concentrated benzoyl chloride (114) was added dropwise. This led to the formation of 8-methyl-2-phenyl-4H-benzo[d][1,3]oxazin-4-one (115). Next, compound (115) was converted to 3-amino-8-methyl-2-phenylquinazolin-4(3H)-one (116) using two different approaches. In the first, a room-temperature method (115) was treated with hydrazine hydrate in ethanol and stir for one hour. In the second, an optimized high-temperature "fusion" method (115) was reacted with hydrazine hydrate at 150 °C for one hour. Both methods yielded compound (116). To obtain the final derivatives (118a-j), this intermediate (116) was condensed with various benzaldehyde derivatives (117a-j) dissolved in glacial acetic acid, leading to the formation of 3-(aryl-benzylidene-amino)-8-methyl-2-phenylquinazolin-4(3H)-one analogs. These newly synthesized compounds were tested for both anticancer and antimicrobial activity using molecular docking and biological evaluation. Anticancer screening was performed across a panel of sixty human cancer cell lines. Among them, compound 118b showed strong activity against melanoma (MDA-MB-435), while compound 118h demonstrated marked potency against non-small cell lung cancer (NCI-H522). Compound 118g was notably effective against breast cancer (HS-578T) and central nervous system cancer (SNB-19). The antimicrobial results showed that compounds 118d and 118j-both containing halogen substituents, were active against selected bacterial and fungal species. SAR analysis indicated that electron-donating groups (such as hydroxyl or meta-chloro groups) improved anticancer activity, whereas electron-withdrawing groups at the para position (as in 118d and

118j) enhanced antimicrobial activity. Docking studies further supported these findings, revealing that compounds 118d and 118j displayed strong binding to microbial molecular targets, with docking scores in the range of -8 to -12.5 kcal/mol. Based on these promising results, the authors recommend further investigation of these derivatives, particularly in combination with conventional antibiotics, to explore possible synergistic effects [69].

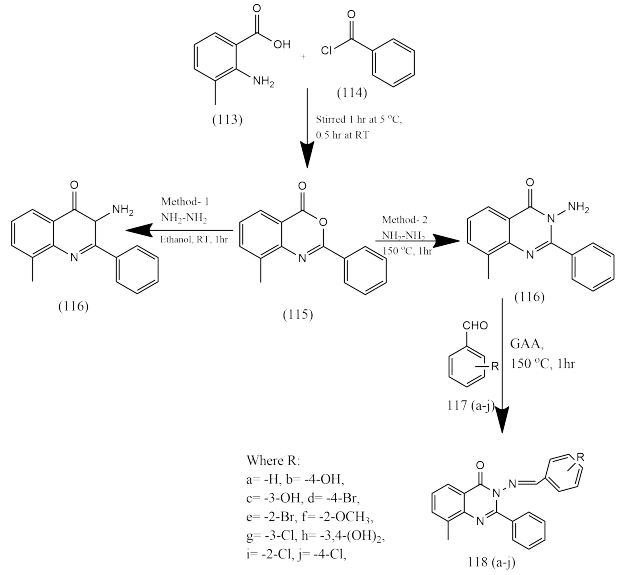


Fig. (22). Synthesis of 8-methyl-2-phenyl quinazolinone Schiff's base [69].

Khan and colleagues (2024) set out to synthesize and evaluate a new group of benz[d][1,3]-oxazine-4-one and quinazolinone derivatives (Fig. **23**), focusing on their anti-inflammatory, analgesic, and ulcer-sparing effects *in vivo*. Their work began by reacting anthranilic acid (119) with the carboxylic acid group of five well-known NSAIDs: aceclofenac, ibuprofen, diclofenac, mefenamic acid, and ketoprofen (120a-e). This cyclization, carried out in pyridine with dry phosphorus oxychloride (POCIs), produced the benzoxazinone derivatives (121a-e). These intermediates (121a-e) were then further converted into the corresponding quinazolinone analogs (123a-e) by reacting them with isonicotinic acid hydrazide (122). All synthesized compounds were structurally confirmed using spectral techniques. Both the benzoxazinone and quinazolinone series were tested in animal models to measure their anti-inflammatory, pain-relieving, and ulcerogenic effects. Among the benzoxazinones, compound 121d-2-(2-((2,6-dichlorophenyl)amino) benzyl)-4H-benzo[d] [1, 3] oxazin-4-one-stood out. It showed strong analgesic activity, offering 62.36% protection in the acetic acid writhing test, and produced 62.61% inhibition of paw edema, indicating good anti-inflammatory action. It also exhibited an acceptable gastrointestinal safety profile, with a toxicity index of 2.67. Overall, both compound series demonstrated analgesic and anti-inflammatory effects comparable to standard reference drugs. Notably, compound 121d, a benzoxazinone-diclofenac hybrid, emerged as a promising lead molecule due to its potent activity combined with relatively low gastric irritation, making it a strong candidate for further development [70].

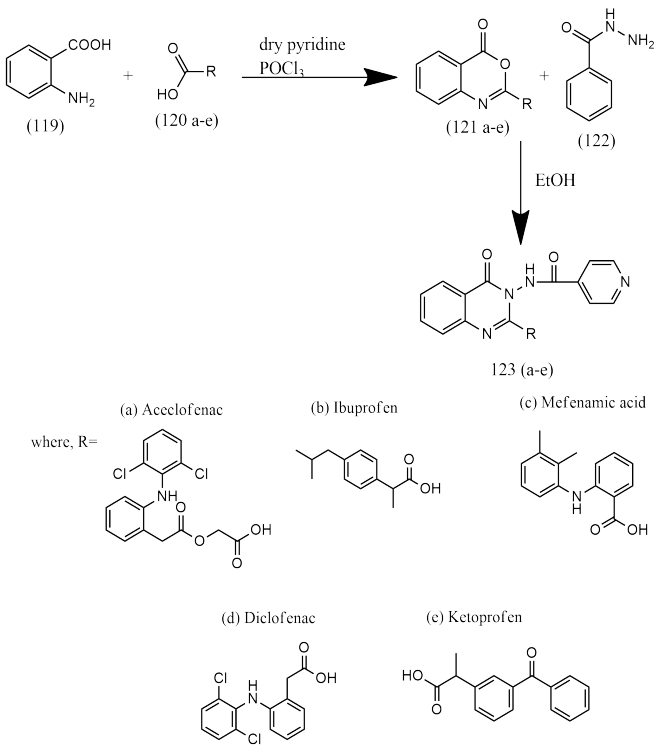


Fig. (23). Synthesis of some novel benzoxazine-4-one and quinazolin-4-one derivatives [70].

Mhetre *et al.* (2024) reported the discovery of new anti-malarial and antitubercular agents, which inspired us to design and synthesize a fresh series of triazole-quinazolinone hybrid molecules (Fig. **24**). The synthesis began with the diazotization of substituted aromatic amines (124a-1), which were then treated with sodium azide to form the respective substituted azo benzenes (125a-l). These intermediates were further reacted with propargyl alcohol in the presence of copper sulfate and sodium ascorbate to yield triazole alcohols (126a-l). Oxidation of these alcohols using PCC in DCM produced the corresponding triazole aldehydes (127a-1). Next, the aldehydes (127a-1) were condensed with anthranilamide (128) in the presence of sodium dithionite, leading to the formation of substituted 2-(1-phenyl-1H-1,2,3-triazol-4-yl)quinazolin-4(3H)-one derivatives (129a-1). The synthesized triazole-quinazolinone hybrids were screened *in vitro* against the malaria parasite Plasmodium falciparum, where several compounds, specifically 6c, 129d, 129f, 129g, 129j, and 129k, showed strong antimalarial activity comparable to standard drugs. The compounds were also tested against Mycobacterium tuberculosis (H37Rv strain). Among them, 6c, 6d, and 61 demonstrated the highest antitubercular activity, with MIC values ranging from 19.57 to 40.68 μM. Cytotoxicity tests performed on RAW 264.7 cells using the MTT assay revealed no observable toxicity for the most active compounds. Comprehensive computational evaluations-including drug-likeness, ADMET analysis, DFT calculations, and molecular docking-were conducted to understand the molecular features of the synthesized hybrids. Compounds 129a, 129g, and 129k showed the strongest binding affinity (10.3 kcal/mol) toward M. tuberculosis target proteins. Docking studies further revealed that all molecules interact effectively with the falcipain-2 protease (PDB: 6SSZ) of *P. falciparum*. Overall, these newly developed tria-

zole-quinazolinone hybrids show significant promise and may serve as valuable hit molecules for further optimization in antimalarial and antitubercular drug development [71].

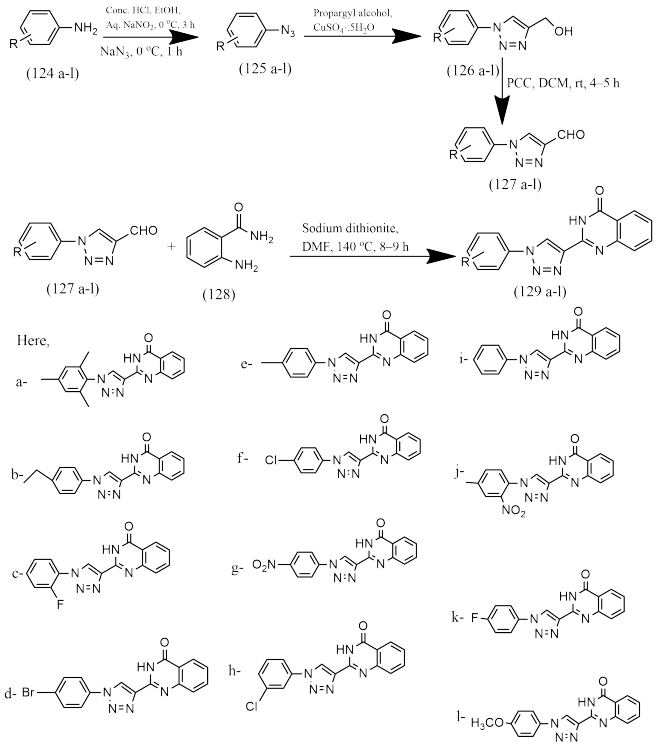


Fig. (24). Synthesis of novel triazole–quinazolinone hybrids [71].

Parmar *et al.* (2024) designed and synthesized a new series of quinazolinone-thiouracil hybrid molecules (Fig. **25**) using a molecular hybridization strategy. These compounds were then evaluated for their anticancer activity against three human cancer cell lines: breast, lung, and glioblastoma, using the SRB assay. The synthesis started with anthranilic acid (130), acetic anhydride (131), and hydrazine hydrate, which reacted to form 3-amino-2-methylquinazolin-4(3H)-one (132). This intermediate was then refluxed with chloroacetyl chloride in toluene, producing 2-chloro-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (133). Meanwhile, another series of intermediates, 4-oxo-6-substituted aryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (137a-k), were synthesized using a Biginelli condensation involving substituted benzaldehydes (135), ethyl cyanoacetate (134), and thiourea (136). The final step involved the condensation of compounds 133 and 137a-k by stirring them with potassium carbonate in DMSO at room temperature, yielding the target derivatives 2-((5-cyano-6-oxo-4-substituted aryl-1,6-dihydropyrimidin-2-yl)thio)-N-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetamide (138a-k). The structures of these molecules were confirmed using IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry, and elemental analysis. Most of the synthesized compounds showed moderate to strong cytotoxic activity, with compound 138d emerging as the most potent, displaying IC_{50} values of 5.28, 4.02, and 2.88 μM across the tested cancer cell lines. Furthermore, 138d showed comparable anticancer effects to standard drugs such as cisplatin and temozolomide in lung and glioblastoma models, and its efficacy was nearly similar to the mitochondrial division inhibitor mdivi-1. Molecular docking studies confirmed strong binding interactions between the synthesized compounds and the target protein dynamin-related protein-1 (Drp1). Stability assessments and all-atom simulations supported the stable binding of compound 138d to Drp1. Overall, compound 138d has been identified as a promising Drp1 inhibitor with significant anticancer potential, warranting further detailed investigation [72].

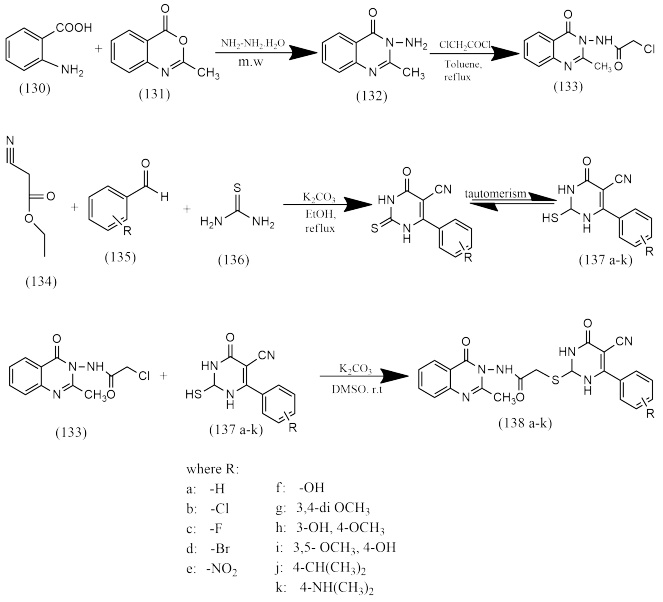


Fig. (25). New Quinazolinone-Thiouracil Derivatives [72].

Mohammed and colleagues (2024) developed a new series of quinazolinone-based Schiff bases (144 Q1-Q5), (Fig. **26**), starting from methyl anthranilate. The synthetic route consisted of three key steps. First, methyl anthranilate (139) was reacted with isothiocyanatobenzene (140) to obtain the thiourea intermediate (141). In the second step, this intermediate was treated with hydrazine hydrate to form 3-amino-2-(phenylamino)quinazolin-4(3H)-one (142). Finally, compound 142 was condensed with a range of aromatic aldehydes (143 Q1-Q5) to produce the desired Schiff base derivatives (144 Q1-Q5). The structures of these newly synthesized molecules were confirmed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The compounds (144 Q1-Q5) were then thoroughly examined for their potential to act as corrosion inhibitors for carbon steel in 1 M HCl. Weight-loss experiments were carried out at different concentrations of the compounds at room temperature to determine their effectiveness. Among all the tested derivatives, compound 144 Q1 showed outstanding corrosion-inhibiting properties, especially at a concentration of 0.5 M. Its inhibition efficiency reached an impressive 93%. Additional dynamic polarization studies revealed that the inhibitory performance of 144 Q1 improved with increasing concentration and decreasing temperature. Overall, compound 144 Q1 demonstrated strong and promising corrosion-inhibition characteristics, highlighting its potential for practical applications [73].

Gariganti N. and colleagues (2024) reported the synthesis of a novel series of amide-enriched 2-(1H)-quinazolinone derivatives (153a-j), as shown in (Fig. **27**), and evaluated their apoptotic activity against four human cancer cell lines-

PC3 and DU-145 (prostate cancer), A549 (lung cancer), and MCF7 (breast cancer)-using the MTT assay. The synthesis began with the reaction of benzoyl chloride (146) and 1-chloro-3-methylbenzene (145) in the presence of AICI, to form 2-chloro-4-methylphenyl) (phenyl)methanone (147). This compound was further nitrated using H_2SO_4/HNO3 and acetic anhydride to give 2-chloro-4-methyl-5-nitrophenyl) (phenyl)methanone (148). Subsequent reaction with isopropylamine in the presence of K_2CO_3 and Cul afforded compound 149. Next, compound 149 was treated with ethyl carbamate in a sealed tube at 240°C with $ZnCl_2$ to produce 1-isopropyl-7-methyl-6-nitro-4-phenylquinazolin-2(1H)-one (150). The nitro group of 150 was then reduced to an amino group using Raney Ni and H_2 in methanol. This yielded 6-amino-1-isopropyl-7-methyl-4-phenylquinazolin-2(1H)-one (151) under reflux in toluene with triethylamine as a base. Finally, 151 was reacted with a series of aryl acid chlorides (152a-j) to generate the target amide-enriched 2-(1H)-quinazolinone derivatives (153a-j). The structures of all compounds were confirmed using spectroscopic and analytical techniques. *In vitro* cytotoxicity studies revealed that the new compounds (153a-j) exhibited moderate to strong activity compared to the standard drug etoposide. IC_{50} values for the synthesized derivatives ranged from 0.07 ± 0.006 to 1.97 ± 0.45 µM, while etoposide showed values of 3.08 ± 0.135 to 10.8 ± 0.69 µM. Among the series, 153i and 153j showed strong apoptotic activity against MCF7, 153h was most active against PC3, and 153g demonstrated notable activity against DU-145. Molecular docking studies against the EGFR tyrosine kinase domain (PDB ID: 1M17) indicated high binding affinities, with docking scores ranging from 9.00 to 9.67 kcal/mol. Further MD simulations and DFT analyses supported these docking results. ADME studies suggested that all the compounds are likely to have good oral absorption in humans, with predicted bioavailability above 85%. Overall, these amide-enriched quinazolinone derivatives represent promising apoptotic agents with potential for further development as anticancer drugs [74].

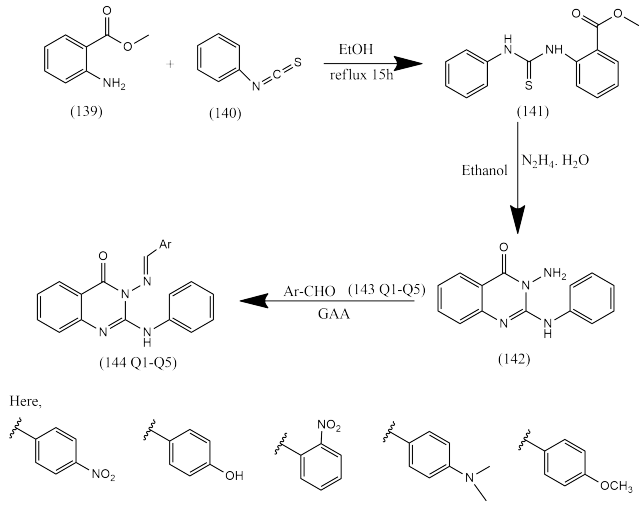


Fig. (26). New Schiff bases of quinazolinone derivatives [73].

Pele *et al.* (2024) investigated two series of compounds, labelled "a" and "b," each containing nine derivatives based on the 2,3-disubstituted quinazolin-4(3H)-one scaffold (Fig. **28**), for their anticonvulsant potential. The synthesis began with anthranilic acid (154) reacting with isothiocyanates (155A-B) to yield either 3-allyl-2-mercaptoquinazolin-4(3H)-one (156A) or 3-benzyl-2-mercaptoquinazolin-4(3H)-one (1568). These intermediates were then treated with a-bromoacetophenone derivatives (I-IX) to generate the final series of 2,3-disubstituted quinazolin-4(3H)-one derivatives (157a-165a and 157b-165b). The compounds were evaluated as potential carbonic anhydrase II inhibitors as well as dual positive allosteric modulators of the $GABA_A$ receptor at the benzodiazepine binding site. Their anticonvulsant activity was assessed *in vivo* using the pentylenetetrazole (PTZ)-induced seizure model in mice, administered intraperitoneally at doses of 50, 100, and 150 mg/kg (D1-3), with diazepam and phenobarbital serving as reference drugs. Molecular dynamics simulations indicated that ligand-carbonic anhydrase II complexes were unstable, suggesting that the anticonvulsant effect arises primarily through binding to the allosteric site of the $GABA_A$ receptor rather than enzyme inhibition. This mechanism was further confirmed using the *in vivo* flumazenil antagonism test. Overall, both series of quinazolin-4(3H)-one derivatives demonstrated significant anticonvulsant activity in the PTZ model, with series "b" showing superior effects. Among them, compound 164b stood out, exhibiting the highest protection against PTZ-induced seizures, delayed onset of the first seizure, and a reduction in total seizure episodes [75].

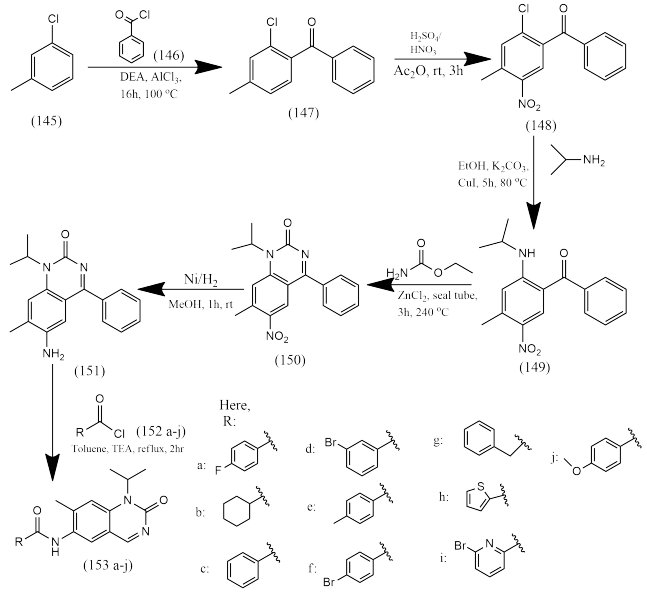


Fig. (27). Synthesis of amide-enriched 2-(1H)-quinazolinone derivatives [74].

Sadeghian and colleagues (2024) designed and synthesized a new series of 2,4-disubstituted quinazoline derivatives (171a-j), (Fig. **29**), and evaluated them for their inhibitory effects on acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), as well as for their antioxidant potential. The synthesis began with the cyclization of anthranilic acid (166) with urea (167) at 190°C to afford quinazoline-2,4-dione (168). In the next step, compound 168 was refluxed with phosphoryl chloride (POC) and N,N-diethylaniline at 115°C for 16 hours to produce 2,4-dichloroquinazoline (169). Finally, 169 was condensed with various anilines (170a-j) in ethanol under reflux conditions

to yield the target 2,4-disubstituted quinazoline derivatives (171a-j). Biological evaluation revealed that compounds 171f, 171h, and 171j exhibited strong inhibitory activity against eqBuChE, with IC_{50} values of 0.52, 6.74, and 3.65 μM, respectively, showing notable selectivity for eqBuChE over eelACHE. Kinetic studies indicated a mixed-type inhibition for both enzymes, suggesting that these compounds can interact with both the catalytic active site and the peripheral anionic site of eelAChE and eqBuChE. Molecular docking and molecular dynamics simulations further confirmed that the potent derivatives engage favorably with the BuChE active site. Antioxidant assays showed that compounds 171b, 171c, and 171j displayed superior radical scavenging activity compared to the other members of the series. Overall, these findings highlight compounds 171f, 171h, and 171j as promising lead molecules for the development of potent and selective BuChE inhibitors [76].

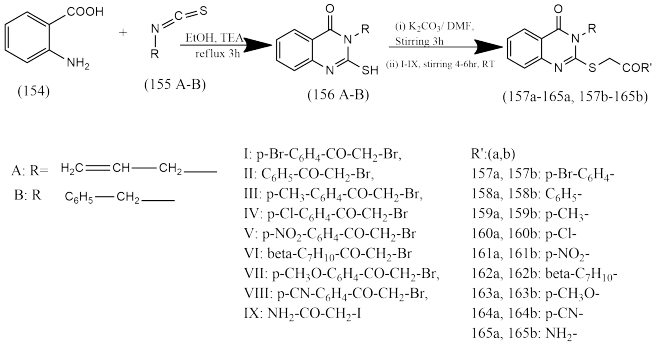


Fig. (28). Synthesis of novel 2,3-disubstituted quinazolin-4(3H)-one scaffold [75].

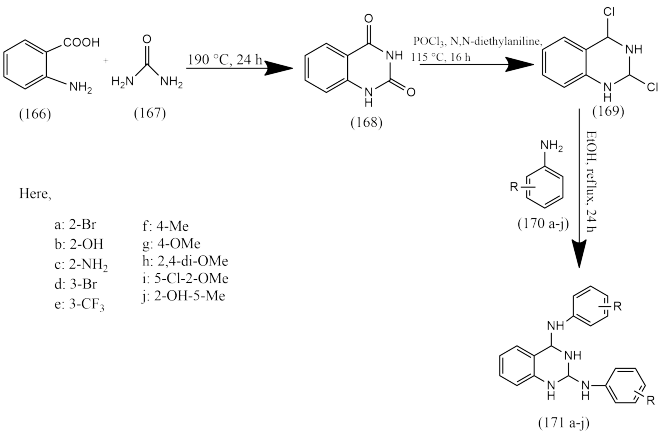


Fig. (29). Synthesis of novel series of 2,4-disubstituted quinazoline derivatives [76].

Shourkaei *et al.* (2024) designed, synthesized, and evaluated a series of quinazolin-4(3H)-one-based compounds (Fig. **30**) for their potential anticancer activity. The synthesis began with the reaction of 2-aminobenzoic acid (172a-c) and 2-chloronicotinic acid (173) under acidic conditions in ethanol at 80°C, producing the precursor 11-oxo-11H-pyrido[2,1-b]quinazoline-6-carboxylic acid (174a-c). Separately, 1-(2-bromoethoxy)-4-nitrobenzene (176) was prepared in three steps from 4-nitrophenol (175) and dibromoethane in the presence of K_2O_3 and DMF. This intermediate was then condensed with various cyclic amines (pyrrolidine, piperidine, or morpholine) to yield compounds 177a-e. The nitro group in 177a-e was subsequently reduced to an amino group using hydrogen gas with a palladium catalyst, forming the aniline intermediates 178a-e. Finally, the target pyrido[2,1-b]quinazoline-6-carboxamide derivatives (179a-t) were synthesized *via* condensation between the amine intermediates (178a-e) and the precursors (174a-c), using HBTU as the coupling reagent and DIEPA as a base in DMF. The structures of all new molecules were confirmed through various spectroscopic techniques. The antiproliferative activity of the synthesized compounds was tested against HepG2 (liver), MCF7 (breast), and HT-29 (colon) cancer cell lines. Among the series, compound 179e displayed superior potency against HepG2 cells (IC_{50} = 2.07 μM), slightly outperforming doxorubicin (IC_{50} = 2.15 ± 0.021 μM), while compound 1791 showed comparable activity to the reference drug. Both 179e and 1791 were also observed to reduce RPA194 levels, a subunit of RNA polymerase I, indicating their effect on Pol I-mediated transcription. Compound 179e induced 43.1% cell death in HepG2 cells, and 1791 caused 37.6%, compared to 52% for doxorubicin. Molecular modeling studies revealed that these compounds exhibited favorable binding free energies with a DNA double helix hexamer, ranging from -8.32 to -11.7 kcal/mol. Taken together, these findings suggest that the synthesized quinazolinone derivatives are promising leads for the development of effective anticancer agents [77].

Alamri MA and colleagues (2023) designed a series of novel quinazolinone derivatives (Fig. **31**) as potential 3CL protease inhibitors for SARS-CoV-2. The synthesis began with 5-fluoroanthranilic acid (180) reacting with 4-fluorophenylisothiocyanate (181) in the presence of a catalytic amount of triethylamine using ethanol as a solvent, yielding the intermediate 6-fluoro-3-(4-fluorophenyl)-2-mercapto-3H-quinazolin-4-one (182). This intermediate was then treated with various alkyl or aryl halides (183a-l) in the presence of anhydrous K_2O_3 under reflux in acetone to produce the final quinazolinone derivatives (184a-1). The successful synthesis of these compounds was confirmed using IR, ^1H NMR, and ^{13}C NMR spectroscopy. The inhibitory potential of the synthesized compounds against SARS-CoV-2 3CL protease (3CLpro) was investigated through molecular docking and dynamics simulations, using the co-crystallized ligand VR4 as a reference. The compounds demonstrated strong interactions within the catalytic dyad (Cys-His) of 3CLpro, suggesting potential inhibition of the protease function. Among them, compounds 184b, 184c, 184i, 184j, and 1841 showed the most favourable binding, with XP G-scores of -7.4, -8.3, -7.8, -7.5, and -8.2, respectively. Molecular dynamics simulations over a 50 ns production run confirmed the stability of these interactions. SwissADME and pkCSM analyses indicated that the selected compounds possess favourable physicochemical and pharmacokinetic properties, fulfilling drug-likeness criteria. Toxicity predictions suggested that some compounds may be hepatotoxic, but none were AMES toxic. *In vitro* studies revealed that compounds 184b, 184c, 184i, 184j, and 1841 inhibited SARS-CoV-2 3CLpro with IC_{50} values of 1.58, 1.25, 1.97, 0.44, and 2.56 μM, respectively, while showing no significant cytotoxicity at concentrations up to 20 μM against VeroE6 cells. Overall, these quinazolinone derivatives exhibited strong binding and inhibitory activity against SARS-CoV-2 3CLpro,

highlighting their potential as promising candidates for the development of new antiviral agents [78].

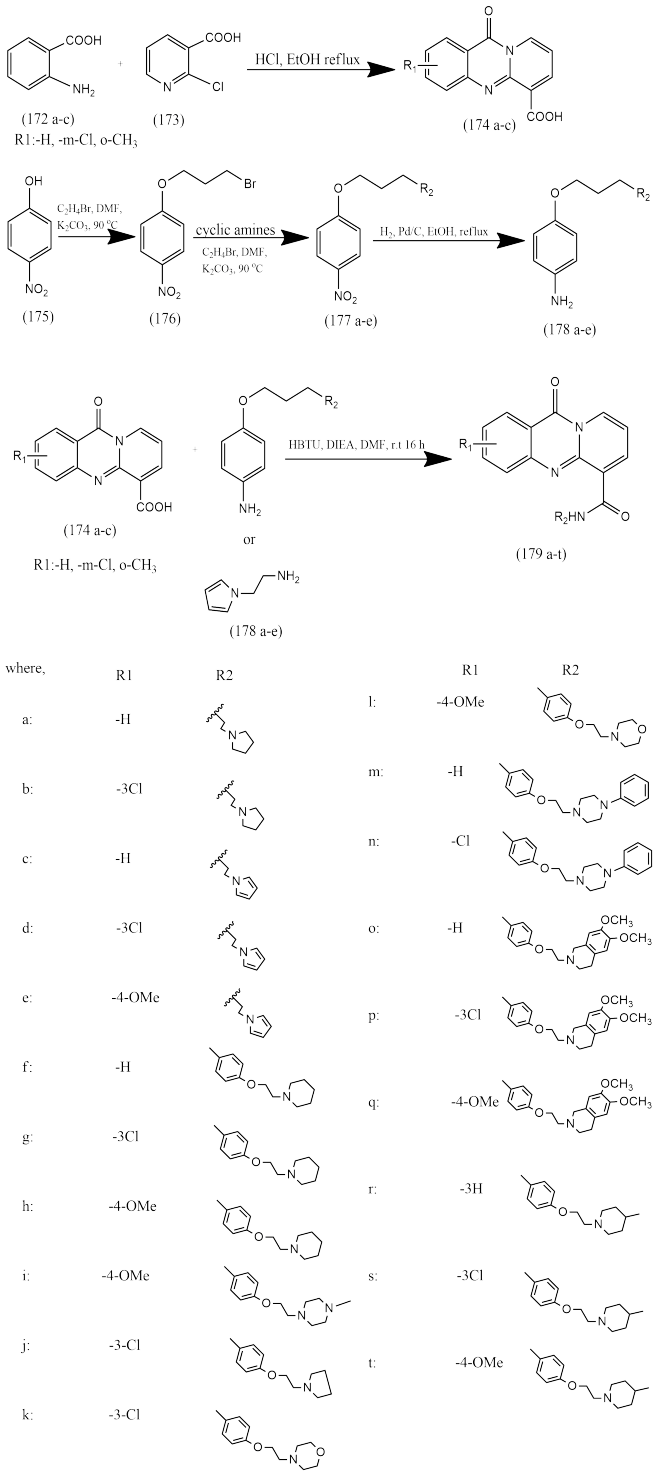


Fig. (30). Synthesis of novel series of quinazolin-4(3H)-one based compounds [77].

Ataollahi E. and colleagues (2023) developed a new series of quinazoline-pyrimidine derivatives with various aryl substitutions as potential anticancer agents (Fig. **32**). The synthesis began with anthranilic acid (185), which was reacted dropwise with chloroacetyl chloride (186) to form intermediate 187. Subsequent reaction with different aniline derivatives (188a-i) afforded 2-(chloromethyl)-3-substituted quinazoline-4(3H)-one intermediates (189a-i). These intermediates were then coupled with 6-chloro-3-methyluracil (190) in the presence of diisopropylethylamine (DIPEA) as a base in acetonitrile under reflux for 24 hours, yielding the final compounds. 6-chloro-3-substituted-1-((4-oxo-3-phenyl-3,4-dihydroquinazoline-2-yl)methyl)pyrimidine 2,4(1H,3H)-dione derivatives (191a-i). The structures of the new compounds were confirmed using mass spectrometry, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy. The antiproliferative activities of all synthesized compounds were evaluated against MCF-7 and SW480 cancer cell lines using the MTT assay. The IC_{50} values ranged from 1.1 to 59.0 µM. Among the series, compounds 191d and 191f were the most potent against SW480 cells, with IC_{50} values of 1.1 and 8 µM, respectively. *In silico* ADMET analysis indicated that the compounds possess favorable pharmacokinetic and toxicity profiles. Density functional theory (DFT) calculations at the B3LYP/6-31G** level were performed for 191a and 191d to examine their reactivity descriptors, including HOMO-LUMO energies and electrostatic surface potential. DFT results suggested that 191d is more reactive than 191a, consistent with experimental observations. Molecular docking studies aligned well with the biological data, and the most active compound, 191d, was further analyzed using molecular dynamics simulations alongside the reference ligand erlotinib. Analyses of RMSD, RMSF, total hydrogen bonds, and clustering confirmed stable binding and supported the predicted activity of 191d [79].

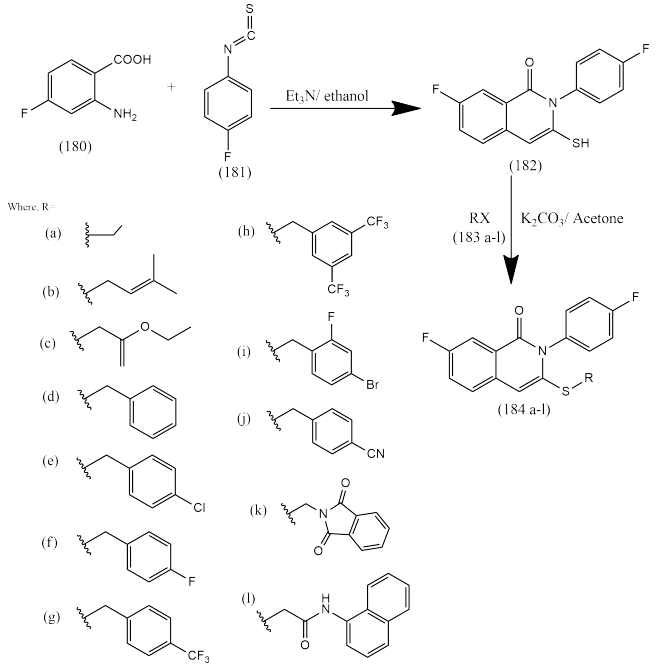


Fig. (31). Synthesis of novel series of quinazolinone derivatives [78].

Naziri *et al.* (2023) synthesized fifteen new substituted quinazoline analogs (Fig. **33**) with good yields. The synthesis involved reacting 7-(2-chloroethoxy)-4-chloro-6-methoxyquinazoline (192) with various substituted anilines (193a-o) to form 7-(2-chloroethoxy)-6-methoxy-N-arylquinazoline-4-amines (194a-o). These intermediates were then treated with secondary amines, including dimethylamine,

pyrrolidine, and piperidine, to yield the final 4-anilinoquinazoline derivatives (195a-o). The cytotoxicity of all synthesized compounds was evaluated using the MTT assay against HU02 (foreskin fibroblast) and A431 (human carcinoma) cell lines. Molecular docking studies were conducted to investigate the binding interactions of the most active compound, 195f, with EGFR. Biological results demonstrated that several compounds effectively inhibited the growth of A431 cells at concentrations below 100 µM. Among them, compound 195f, featuring a piperidine moiety with 3-chloroaniline, exhibited the highest cytotoxicity with an IC_{50} of 1.21 µM, surpassing the reference drug erlotinib. In contrast, none of the compounds showed significant cytotoxicity against the HU02 cell line. Docking analysis revealed that the quinazoline N1 of 195f forms a hydrogen bond with the Met-769 residue of EGFR at a distance of 1.071 Å, shorter than that observed for erlotinib, which correlates with its higher cytotoxic potency. The superior activity of 195f is likely due to the enhanced lipophilicity and flexibility provided by the piperidine group [80].

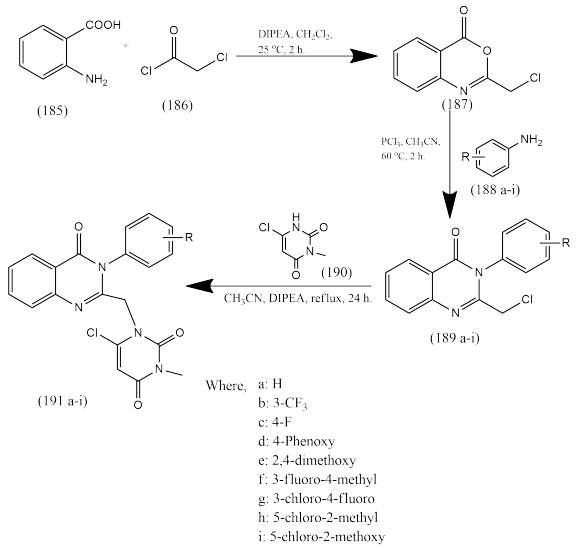


Fig. (32). Novel series of quinazoline-pyrimidine derivatives [79].

In 2023, Oduselu and colleagues explored a series of quinazolin-4(3H)-one derivatives bearing arylidene groups (Fig. **34**) as potential antibacterial agents. The synthesis began with the thermal cyclization of anthranilic acid (196) using acetic anhydride (197) to yield 2-methyl-4H-3,1-benzoxazin-4-one (198), which was then condensed with hydrazine hydrate to produce 3-amino-2-methylquinazolin-4(3H)-one (199). The final derivatives, 3-(substituted benzylideneamino)-2-methylquinazolin-4(3H)-one (201a-1) and 2-methyl-3-((thiophen-2-ylmethylene)amino)quinazolin-4(3H)-one (201 m), were synthesized by reacting intermediate 199 with various benzaldehyde derivatives (200a-1) at the amino group. The structures of all compounds were confirmed using a combination of physicochemical analyses, microanalytical data, and spectroscopic techniques, including IR, UV, ^{1}H- and ^{13}C-NMR, as well as mass spectrometry. The antibacterial and antifungal activities of these quinazolinone derivatives were evaluated both *in vitro* and *in silico*. *In silico* studies included ADMET predictions, molecular docking, and molecular dynamics (MD) simulations, while *in vitro* validation was performed using the agar diffusion method with gentamicin and ketoconazole as reference antibacterial and antifungal agents, respectively. Molecular docking results indicated strong binding affinities for most of the compounds, and MD simulations confirmed the stability of the protein-ligand complexes. Among all derivatives, compound 201m, 2-methyl-3-((thiophen-2-ylmethylene) amino) quinazolin-4(3H)-one, demonstrated the most potent antifungal activity, with minimum inhibitory concentrations (MIC) of 1.95 µg/mL against *Staphylococcus aureus* and 3.90 µg/ml against *Candida albicans, Aspergillus Niger,* and *Rhizopus nigricans* [81].

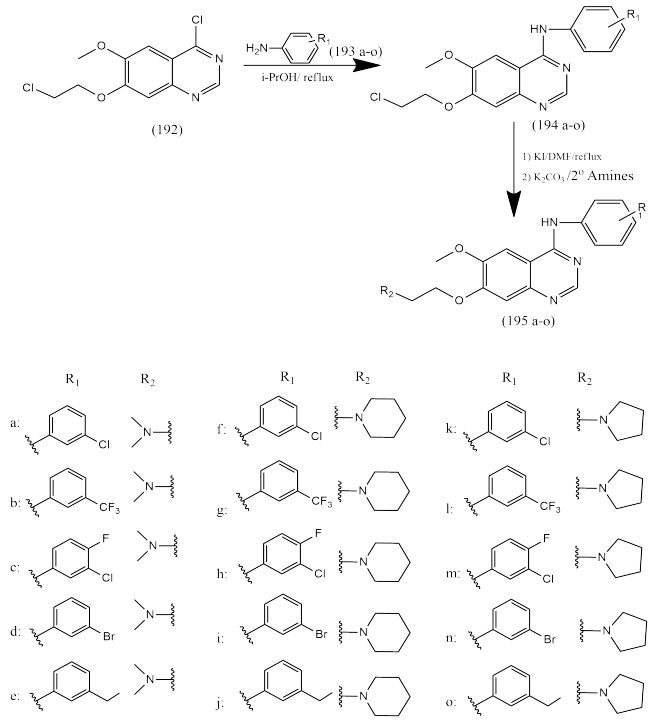


Fig. (33). Novel series of substituted 4-anilinoquinazoline analogs [80].

In 2023, Tokalı F.S. and colleagues synthesized a series of quinazolin-4(3H)-one-based imines (Fig. **35**) and evaluated their inhibitory activities against several metabolic enzymes, including acetylcholinesterase (AChE), butyrylcholinesterase (BChE), a-glycosidase (a-Gly), and human carbonic anhydrase I and II (HCA I-II). The synthesis started with methyl anthranilate (202), which reacted with acetyl chloride (203) in dichloromethane to form methyl N-acetylanthranilate (204). Cyclization with hydrazine hydrate then produced 3-amino-2-methylquinazolin-4(3H)-one (205). This intermediate was further condensed with various substituted benzaldehydes, heterocyclic aldehydes, and allyl aldehydes (206a-s) to yield the final series of Schiff base derivatives (207a-s). Biological evaluation revealed that all compounds exhibited significant inhibitory activity. Against HCA I and hCA II, the Ki values ranged from 38.55 ± 4.08 to 159.05 ± 10.68 nM and 41.04 ± 6.73 to 177.12 ± 8.06 nM, respectively, compared to acetazolamide (AZA; Ki = 125.15 ± 0.78 nM for hCA I and 148.75 ± 0.92 nM for hCA II). The derivatives also demonstrated potent a-Gly inhibition, with IC_{50} values between 0.342 and 28 nM, surpassing the standard inhibitor acarbose (IC_{50} = 3.18 nM). Furthermore, the compounds displayed strong inhibitory activity against cho-

linesterases, with Ki values ranging from 4.20 ± 0.15 to 26.10 ± 2.36 nM for AChE and 1.22 ± 0.05 to 16.09 ± 0.88 nM for BCHE, compared to tacrine (Ki = 37.62 ± 6.86 nM for AChE and 26.75 ± 5.79 nM for BChE). Molecular docking and molecular dynamics simulations were performed to investigate ligand-enzyme interactions. The most active compound exhibited docking scores of 7.31, 7.59, 6.66, 6.93, and 7.11 kcal/mol for AChE, BCHE, HCA I, hCA II, and a-Gly, respectively, confirming strong and stable binding to the target enzymes [82].

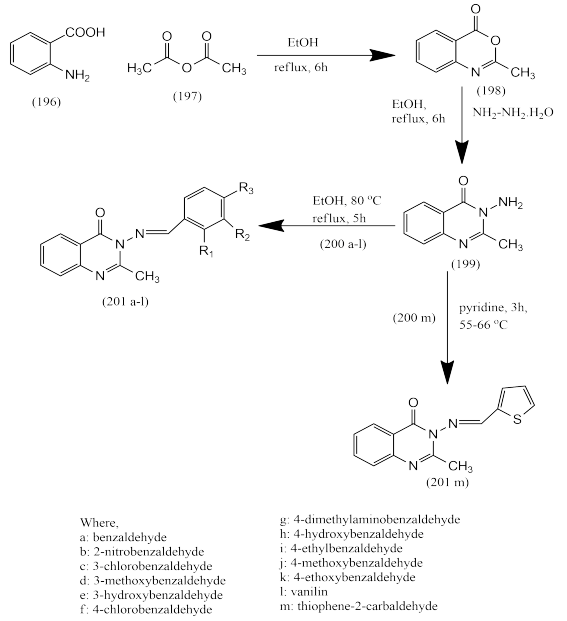


Fig. (34). Novel series of arylidene-based quinazolin-4(3H) one motifs [81].

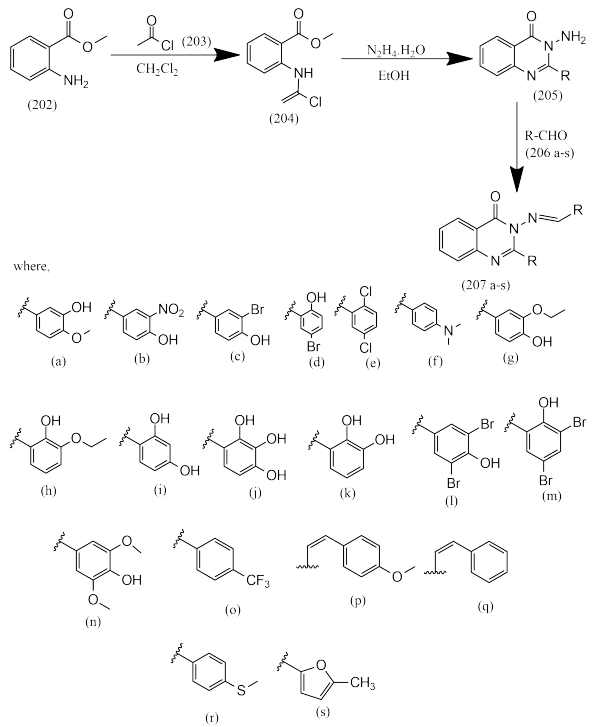


Fig. (35). Novel derivatives of imines bearing quinazolin-4(3H)-one [82].

In 2022, Ayoob and colleagues developed a series of novel benzamide derivatives (Fig. **36**). The synthesis began with 3-nitrobenzoic acid (208), which was converted to 3-nitrobenzoyl chloride using thionyl chloride. This intermediate was then reacted with anthranilic acid (210) *via* the Schotten-Baumann benzoylation method to yield 2-(3-nitrophenyl)-4H-benzo[d][1,3]oxazin-4-one (211). Subsequent reaction with various aromatic amines (212a-d) in 20 mL of glacial acetic acid for 1-3 minutes produced the benzamide derivatives (213a-d). Further treatment of the benzamides (213a-d) with acetic acid and concentrated sulfuric acid led to the formation of 3-(substituted phenyl)-2-(3-nitrophenyl)quinazolin-4(3H)-one analogs (214a-d). The structures of the newly synthesized compounds were characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and DEPT 135 ^{13}C-NMR, while single-crystal X-ray analysis confirmed the structure of compound 213a. Biological evaluation demonstrated that the synthesized compounds exhibited significant antibacterial activity. Molecular docking studies revealed favorable interactions with bacterial DNA gyrase (PDB ID: 1KZN) of *Staphylococcus aureus*. Additionally, *in silico* ADMET analysis indicated that these compounds possess promising pharmacokinetic and drug-like properties, showing potential comparable to that of the standard antibiotic ciprofloxacin [83].

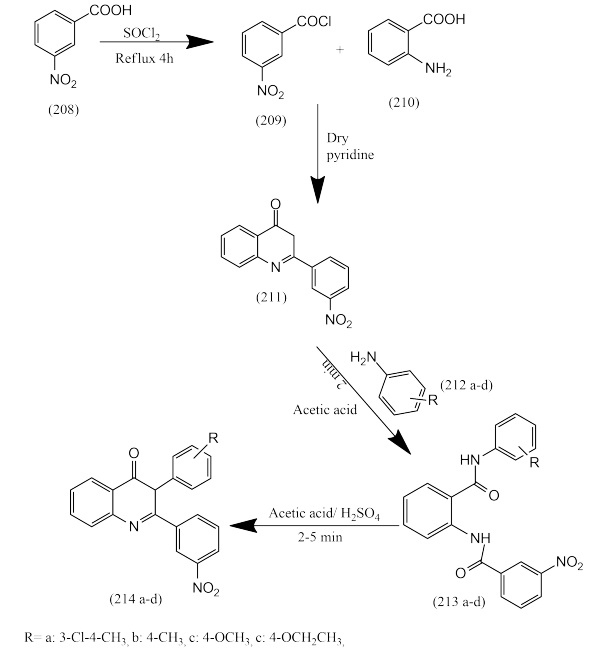


Fig. (36). Novel 3-(substituted phenyl)-2-(3-nitrophenyl) quinazolin-4(3H)-one analogs [83].

In 2022, Kachhadiya R. and colleagues designed and synthesized a series of novel quinazolinone derivatives (Fig. **37)** as potential cholinesterase inhibitors for the treatment of Alzheimer's disease. The synthesis started with isatoic anhydride (215) reacting with various aryl or alkyl halides (216) in the presence of potassium carbonate (K_2CO_3) to yield intermediates 217a-f. These intermediates then underwent nucleophilic substitution with different amines (218a-f) at the carbonyl carbon of the N1-substituted isatoic anhydride to produce compounds 219a-f, which were further cyclized using cyanogen bromide to form the final quinazolinone de-

rivatives 220a-f. Molecular docking studies using AutoDock 4.2 showed that all compounds were well accommodated within the active site of acetylcholinesterase (AChE), displaying comparable binding to the standard drug donepezil. Among the series, compounds 220d-f were identified as the most promising, forming two hydrogen bonds with AChE, indicating strong inhibitory potential. *In silico* analysis of drug-likeness and pharmacokinetic properties using SwissADME and pkCSM suggested that all synthesized compounds 220a-f possess favorable ADMET profiles, supporting their potential as effective cholinesterase inhibitors for Alzheimer's disease [84].

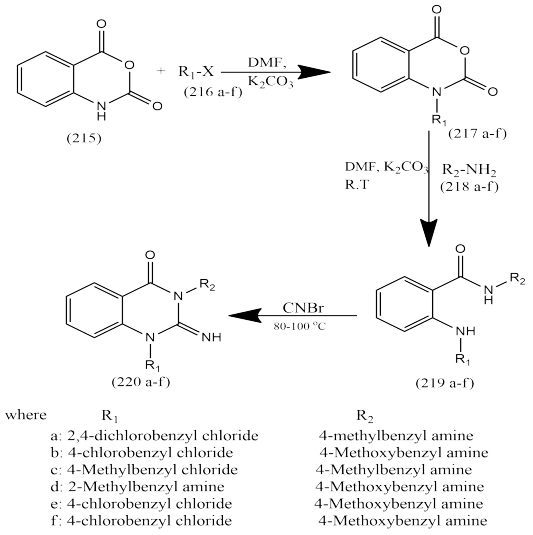


Fig. (37). Novel series of novel quinazolinone scaffold [84].

In 2022, Kayal W. El. and colleagues focused on the synthesis of 1-benzyl-substituted derivatives of N-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1H-quinazolin-3-yl)acetamide (Fig. **38**) and evaluated their affinity for GABAergic targets, alongside anticonvulsant activity using the pentylenetetrazole (PTZ)-induced seizure model in mice. The target compounds, N-[(2,4-dichlorophenyl)methyl]-2-(1-(R-benzyl)-2,4-dioxo-quinazolin-3-yl)acetamides (223a-k), were synthesized by alkylating N-[(2,4-dichlorophenyl)methyl]-2-(2,4-dioxo-1H-quinazolin-3-yl)acetamides (221a-k) with the corresponding 1-chloromethylbenzene derivatives (222a-k) in dimethylformamide (DMF) using excess potassium carbonate at 70-80°C. The structures of the synthesized compounds were confirmed using elemental analysis, ^{1}H- and ^{13}C-NMR spectroscopy, and LC/MS. Molecular docking studies were carried out using AutoDock Tools 1.5.6 and AutoDock Vina. Anticonvulsant activity was evaluated *in vivo* using the PTZ-induced seizure model in mice. Comparison with the previously tested compound 221 highlighted the crucial role of the cyclic amide fragment in mediating anticonvulsant effects. A strong correlation was observed between *in vivo* outcomes and in silico docking results, particularly in docking studies targeting the positive allosteric modulatory (PAM) site of the $GABA_A$ receptor and the GABA transaminase ($GABA_{AT}$) enzyme. This correlation supports the use of the docking methodology as an effective tool to streamline and optimize the screening of potential anticonvulsant agents in this model [85].

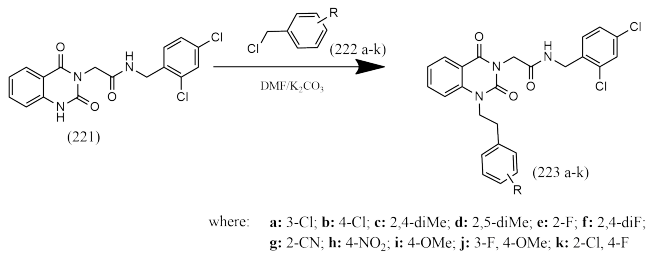


Fig. (38). Synthesis of 1-benzylsubstituted derivatives of N-[(2,4-dichlorophenyl)methyl].-2-(2,4-dioxo-1h-quinazolin-3 yl)acetamide [85].

In 2022, Mikra C. and colleagues employed an efficient microwave-assisted green methodology to design and synthesize eleven 3-amino-2-methyl-quinazolin-4(3H)-ones (Fig. **39**) *via* their corresponding benzoxazinone intermediates. Initially, the 2-methyl-benzoxazinones (225a-k) were prepared by treating commercially available anthranilic acids (224a-k) with acetic anhydride under microwave irradiation (MWI). These intermediates were then dissolved in ethanol and reacted with hydrazine hydrate under MWI to yield the 3-amino-2-methyl-quinazolin-4(3H)-ones (226a-k). Selected 3-amino derivatives (226c, 226e, 226g, 226i, 226j) were further acetylated under conventional heating with acetic anhydride to obtain the corresponding acetamides (227-231). Additionally, 225c, 225g, and 225j were reacted with the appropriate arylhydrazides in acetic acid under MWI at 150°C for 30 minutes, producing the target compounds (232-242). Photoactivity studies under UVB and UVA irradiation revealed that eight of the eleven 3-amino-2-methyl-quinazolin-4(3H)-ones were active towards plasmid DNA. Among the acetamides, the 6-nitro derivative remained photoactive under both UVB and UVA, while the 6-bromo derivative showed activity only under UVB. All 3-arylamido-6-nitro compounds exhibited remarkable photoactivity even at low concentrations (1 μM), showing enhanced effects compared to their parent 3-amino-2-methyl-6-nitro-quinazolinones. In contrast, 3-arylamido-6-bromo derivatives displayed significantly lower photoactivity. Molecular docking studies supported these findings, demonstrating favorable binding interactions with DNA. Given that quinazolinones are recognized as "privileged" pharmacophores with antimicrobial and anticancer properties, this study provides insights into controlling photosensitization through functionalization with auxochromes and chromophores. These results pave the way for the development of novel photo-chemotherapeutic or photodynamic therapy strategies using specifically designed quinazolinone derivatives [86].

In 2022, Sonousi A. and colleagues designed and synthesized nineteen novel quinazolin-4(3H)-one derivatives (Fig. **40**) as potential EGFR inhibitors. The synthesis began with 3-phenyl-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (243a) and 3-(4-chlorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (243b), which were treated with 99% hydrazine hydrate to produce 2-hydrazinyl-3-phenylquinazolin-4(3H)-one (244a) and 3-(4-chlorophenyl)-2-hydrazinylquinazolin-4(3H)-one (244b). These hydrazine derivatives (244a, b) were then heated with 4-substituted benzaldehydes either with phenoxy groups (3a-d) or piperazinyl aryl groups in ethanol and a few drops of glacial acetic acid to obtain the target compounds (245a-g). In a parallel approach, alkylation

of 2-thioxo-2,3-dihydroquinazolin-4(1H)-one derivatives (243a,b) with ethyl bromoacetate in dry acetone containing anhydrous potassium carbonate yielded ethyl 2-((4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)thio)acetate (246a,b). These ester derivatives were then reacted with 99% hydrazine hydrate to produce the corresponding acetohydrazides (247a, b), which were finally condensed with 4-substituted benzaldehydes to give the desired hydrazone derivatives (248a-1). The synthesized compounds were evaluated for antiproliferative activity against 60 human cancer cell lines. Among them, compound 248d exhibited remarkable sub-micromolar activity against the NCI-H460 non-small cell lung cancer cell line (Glso = 0.789 μM) and demonstrated potent cytostatic effects across 40 other cancer cell lines (TGI range: 2.59-9.55 μM). Compound 248d also showed strong EGFR inhibition with an IC_{50} of 0.069 ± 0.004 μM, compared to erlotinib (IC_{50} = 0.045 ± 0.003 μM), and induced a 16.74-fold increase in total apoptosis, causing G1/S cell cycle arrest in the HS 578T breast cancer cell line. Molecular docking studies of the most active derivatives further confirmed their binding modes and their ability to engage key pharmacophoric features essential for EGFR inhibition [87].

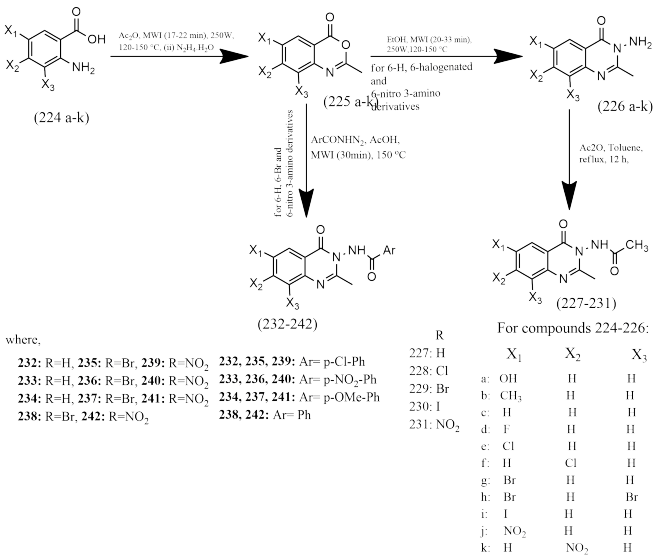


Fig. (39). Synthetic scheme for the preparation of 3-amino-2-methyl-quinazolin-4(3H)-ones [86].

In 2022, Tokali F.S. and colleagues designed and synthesized a series of new benzoic acid derivatives containing the quinazolinone scaffold (Fig. **41**), a biologically active nitrogen-containing heterocycle, achieving excellent yields (90-98%). The synthesis began with methyl anthranilate (249), which was reacted with acyl chlorides and subsequently treated with hydrazinium hydroxide to afford various intermediates (250a-k). These intermediates were then condensed with 4-formylbenzoic acid (251) in glacial acetic acid to generate the target benzoic acid derivatives bearing the quinazolin-3(4H)-one core (252a-k). The structures of these novel compounds were confirmed using FT-IR, ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS). The compounds were evaluated for their anti-diabetic potential through a-glucosidase and a-amylase inhibition assays. Against a-glucosidase, IC_{50} values ranged from > 100 to 3.468 ± 0.270 μM and K_1 values from > 100 to 3.310 ± 0.326 μM, while for a-amylase, IC_{50} values ranged from > 100 to 1.215 ± 0.225 μM. Among the series, 4-[(2-[(4-phenylpiperazin-1-yl)methyl]-4-oxo-quinazolin-3(4H)-ylimino) methyl]benzoic acid (compound 10) showed the most potent activity, being 5.4 times more effective than acarbose for a-glucosidase and 34.9 times more effective for a-amylase. Molecular docking studies of the most active compound revealed binding affinities of -5.978 kcal/mol and -5.548 kcal/mol for a-glucosidase and a-amylase, respectively. The analysis suggested that the aromatic ring, the aminomethyl group on the quinazoline, and the carboxyl moieties played critical roles in the enzyme inhibition [88].

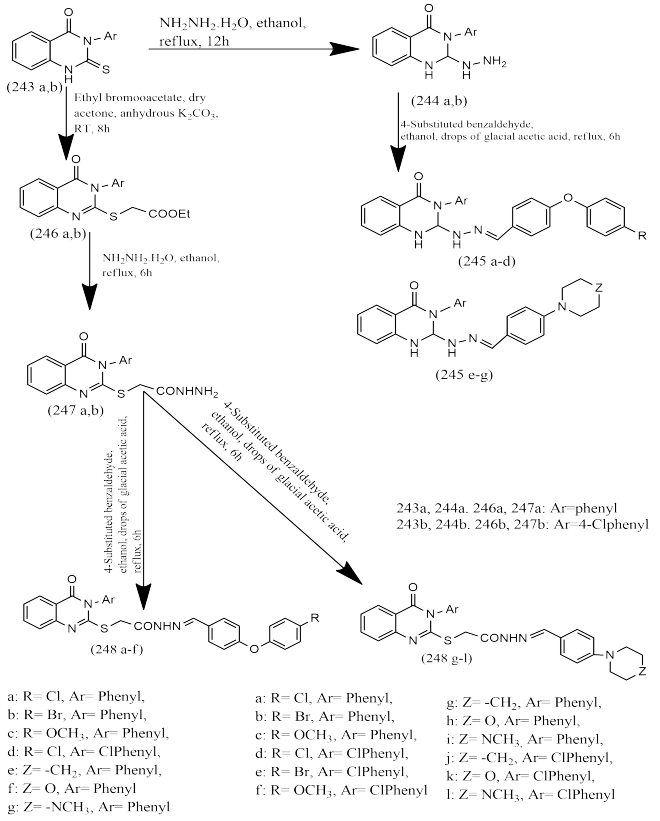


Fig. (40). Synthetic scheme for new quinazolin-4(3H)-one derivatives [87].

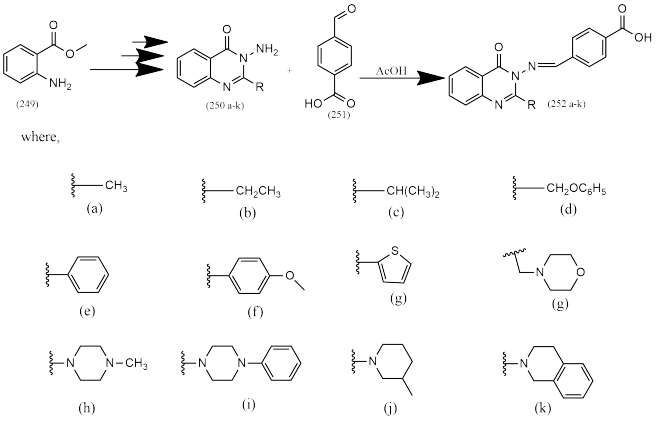


Fig. (41). New benzoic acid derivatives of the quinazolinone ring [88].

In 2021, Agrawal and colleagues designed and synthesized a series of substituted 6-bromo-3-(3-chloro-2-oxo-4-

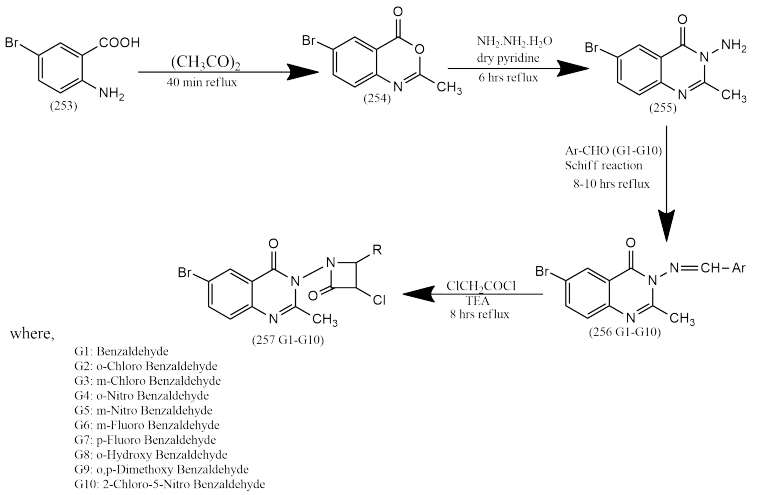


Fig. (42). Designed substituted 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4(3H)-one [89].

arylazetidin-1-yl)-2-methylquinazolin-4(3H)-one derivatives (Fig. **42**) and assessed their biological activities. The synthesis began with 5-bromoanthranilic acid (253), which was reacted with acetic anhydride to yield 6-bromo-2-methyl-4H-benzo[1,3]oxazin-4-one (254). Treatment of this intermediate with hydrazine hydrate in anhydrous pyridine produced 3-amino-6-bromo-2-methylquinazolin-4(3H)-one (255). This intermediate underwent a Schiff base reaction with various aromatic aldehydes (G1-G10) to generate 3-(substituted benzylideneamino)-6-bromo-2-methylquinazolin-4(3H)-one (256 G1-G10). Subsequent reflux with chloroacetyl chloride and triethylamine afforded the final derivatives, 6-bromo-3-(3-chloro-2-oxo-4-arylazetidin-1-yl)-2-methylquinazolin-4(3H)-one (257 G1-G10). The structures of these compounds were confirmed using elemental analysis, FT-IR, ^{1}H NMR, and mass spectrometry, while TLC was employed to determine their purity. The antimicrobial potential of the synthesized derivatives was evaluated against Gram-positive and Gram-negative bacteria as well as fungi. Most compounds exhibited moderate antimicrobial activity. Notably, compounds 257 G4 and 257 G6 demonstrated significant antibacterial activity comparable to the standard drug amoxicillin, while compound 257 G7 showed strong antifungal activity relative to fluconazole [89].

In 2021, Pedrood K. and colleagues developed a series of novel quinazolinone derivatives (Fig. **43**) and evaluated them for inhibitory activity against several metabolic enzymes, including a-glycosidase, acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and human carbonic anhydrase I and II. The synthesis began with the reaction of 2-aminobenzamide (258) with various aromatic aldehydes (259 a-n) in the presence of sodium metabisulfite ($Na_2S_2O_5$) in DMF at 100°C, yielding quinazolinone derivatives (260 a-n). Separately, tosyl-metronidazole (263) was prepared *via* nucleophilic substitution between tosyl chloride (261) and metronidazole (262). In the final step, the quinazolinone derivatives (260 a-n) were reacted with tosyl-metronidazole (263) in DMF using potassium carbonate at 80°C to produce the target compounds (264 a-n). The structures of all synthesized compounds were confirmed using ^{1}H and ^{13}C NMR, IR spectroscopy, and elemental analysis. The compounds showed strong enzyme inhibition, with Ki values ranging from 19.28-135.88 nM for a-glycosidase (compared to 187.71 nM for the standard inhibitor), 0.68-23.01 nM for AChE (standard = 53.31 nM), 1.01-29.56 nM for BChE (standard: 58.18 nM), and 13.46-178.35 nM for human carbonic anhydrase. The most potent compounds for each enzyme were further analyzed to study their interactions at the enzyme active sites. Importantly, none of the quinazolinone derivatives (264 a-n) exhibited significant cytotoxicity when tested against MCF-7 and LNCaP cancer cell lines [90].

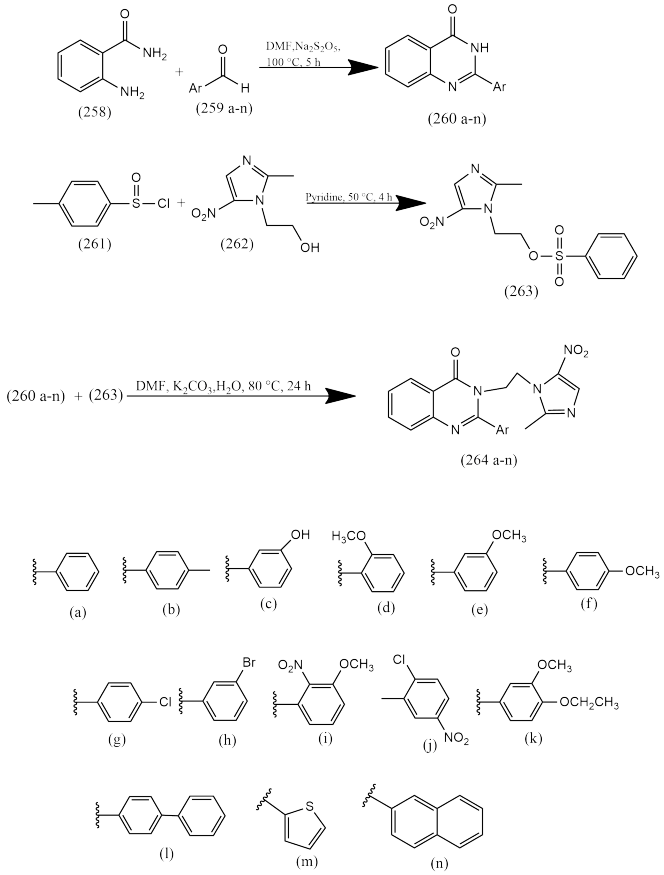


Fig. (43). Designed novel quinazolinone derivatives [90].

Tokali F.S. and colleagues (2021) developed a set of 3-amino-2-ethylquinazolin-4(3H)-one derivatives (shown in Fig. **44**). Their synthesis involved two main steps. First, methyl anthranilate (265) was reacted with propionyl chloride (266) to produce methyl 2-propionamidobenzoate (267). This intermediate was then treated with hydrazinium hydroxide, giving 3-amino-2-ethylquinazolin-4(3H)-one (268). In the next stage, the obtained compound (268) was condensed with different aromatic aldehydes (269a-n), resulting in a new series of benzylidenaminoquinazolin-4(3H)-one derivatives (270a-n). The structures of these synthesized molecules were confirmed using IR, 'H-NMR, 13C-NMR, and high-resolution mass spectrometry. The researchers evaluated the biological activity of these compounds against several metabolic enzymes, including a-glucosidase (a-Glu), acetylcholinesterase (AChE), and human carbonic anhydrase isoforms I and II (hCA I and hCA II). The compounds showed promising inhibitory activity, with Ki values ranging between 244-988 nM for hCA I, 194-900 nM for hCA II, 30-156 nM for AChE, and 215-625 nM for a-Glu. Docking studies revealed strong binding affinities for the most potent molecules. -7.636 kcal/mol for hCA I, -6.972 kcal/mol for hCA II, -10.080 kcal/mol for AChE, and -8.486 kcal/mol for a-Glu. The study highlighted that the aromatic ring within the quinazoline core significantly contributes to the enzyme-inhibitory properties of these compounds [91].

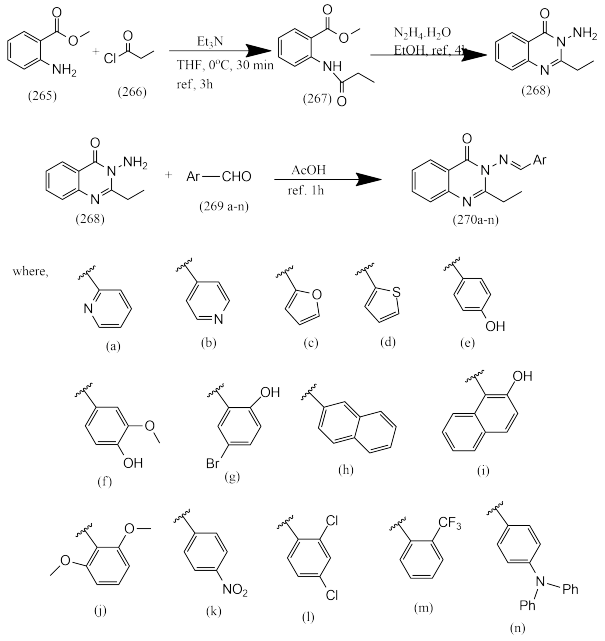


Fig. (44). Preparation of 3-amino-2-ethylquinazolin-4(3H)-one derivatives [91].

Wali, *et. al.,* 2021 prepared a set of functionalized quinazolinone derivatives (shown in Fig. **45**) using a simple two-step synthetic route. In the first step, anthranilic acid (271) was reacted with different substituted phenyl isothiocyanates (272 I-VIII) to obtain 3-aryl-2-thioxo-2,3-dihydroquinazolinone derivatives (273 I-VIII). These intermediates were then treated with a series of bromoacetophenone derivatives (274), leading to the formation of fully functionalized quinazolinone derivatives (275 VIII-XXX). Triethylamine was used as a catalyst in both steps. Each synthesized compound was confirmed through EI, HREI-MS, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. The researchers evaluated all compounds for their *in vitro* a-glucosidase inhibitory activity. Except for compounds 273 I-III, 273 V, 273 VII, and 275 XXII, nearly all derivatives demonstrated strong inhibitory effects, far exceeding the activity of the standard drug acarbose (IC_{50} = 750.0 ± 10.0 μM). Among them, compound 275 XIII showed exceptional potency with an IC_{50} value of 85.0 ± 0.5 μM, making it about nine times more effective than acarbose and the most active molecule in the series. Although several compounds were newly synthesized, some structures, including 272 I-VIII, 275 IX, 275 XI, 275 XII, 275 XXII, and 275 XXVI, were already known. Kinetic studies revealed that compound 275 XIII acts as a competitive inhibitor. Furthermore, *in silico* molecular modelling was carried out to better understand how the synthesized compounds interact within the active site of the a-glucosidase enzyme [92].

Tokalı F.S. and colleagues designed a new series of sulfonate-containing quinazolin-4(3H)-one derivatives (shown in Fig. **46**) aimed at inhibiting the enzyme aldose reductase (ALR2, EC 1.1.1.21). The synthesis started with methyl anthranilate (276), which was dissolved in 20 mL of dichloromethane and stirred with sodium bicarbonate for 20 minutes at 0-5°C. A solution of acyl chloride (277) in 10 mL of dichloromethane was then added dropwise, and the mixture was stirred for another 30 minutes at room temperature, producing intermediate (278). This intermediate was subsequently treated with hydrazinium hydroxide to obtain the quinazolinone derivatives (279 Q). In a separate reaction, 4-hydroxybenzaldehyde (280) was reacted with sulfonyl chloride (281) in THF while being kept in an ice bath, forming the sulfonated aldehyde derivatives (282 S). These sulfonated aldehydes were then condensed with 3-amino-2-alkylquinazolin-4(3H)-ones (279 Q) in glacial acetic acid to produce the final quinazolinone derivatives (283 a-u) in excellent yields (85-94%). The structures of all synthesized compounds were confirmed using IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS analyses. Biological evaluation revealed that all quinazolinones (283 a-u) possessed strong, nanomolar-level inhibitory activity against ALR2, with Ki values ranging from 101.50 to 2066.00 nM. Notably, compound 283 0-4-[(2-isopropyl-4-oxoquinazolin-3[4H]-ylimino)methyl]phenyl benzenesulfonate showed remarkable potency, exhibiting up to 7.7-fold stronger inhibition than the standard drug epalrestat. Molecular docking studies conducted using the Schrödinger Small-Molecule Drug Discovery Suite 2021-1 helped identify key interactions between the quinazolinone derivatives and the ALR2 active site. Based on both *in vitro* results and computational analysis, the authors concluded that although the compounds show promise as ALR2 inhibitors, further structural optimization is needed to enhance their overall drug-like potential [93].

Ghodge B. and co-researchers (2020) reported the synthesis of a series of 2,3-disubstituted quinazolin-4(1H)-one derivatives (Fig. **47**). The reaction was carried out by mixing isatoic anhydride (284) with substituted aniline (285) in a round-bottom flask containing an equal mixture of ethanol and water. Acetic acid was then added, and the mixture was stirred for about 20-30 minutes until all reactants dissolved completely. Afterward, a substituted aldehyde (286) was

introduced, and the mixture was refluxed for 1.5 hours with continuous stirring, resulting in the formation of the target derivatives (287 G1-G3). Their structures were confirmed using FTIR, ^{1}H-NMR, and mass spectrometry. The synthesized compounds were next evaluated for their anti-inflammatory properties. *In vitro* activity was assessed using the egg albumin protein denaturation method, while *in vivo* activity was tested using the carrageenan-induced rat paw edema model and the cotton pellet-induced granuloma pouch method. Among the three compounds, 287 G1 and 287 G3 demonstrated the most significant anti-inflammatory effects. They effectively inhibited the release of inflammatory mediators such as prostaglandins, histamine, and serotonin in both *in vitro* and *in vivo* studies, outperforming compound 287 G2 [94].

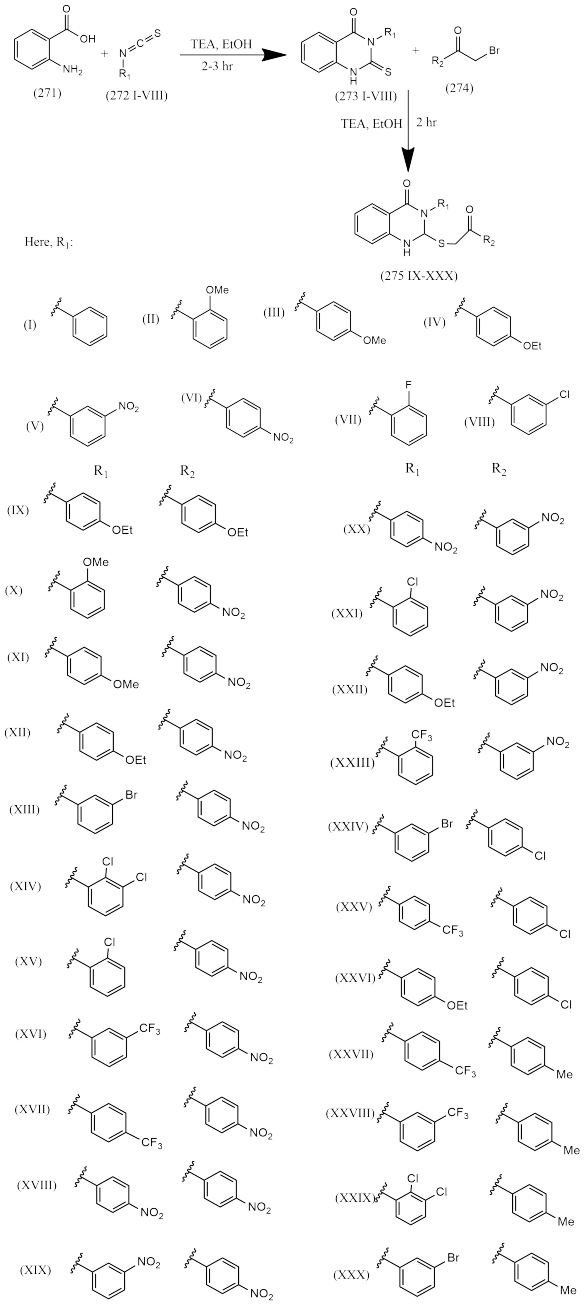


Fig. (45). Synthetic scheme for newly functionalized quinazolinone analogs [92].

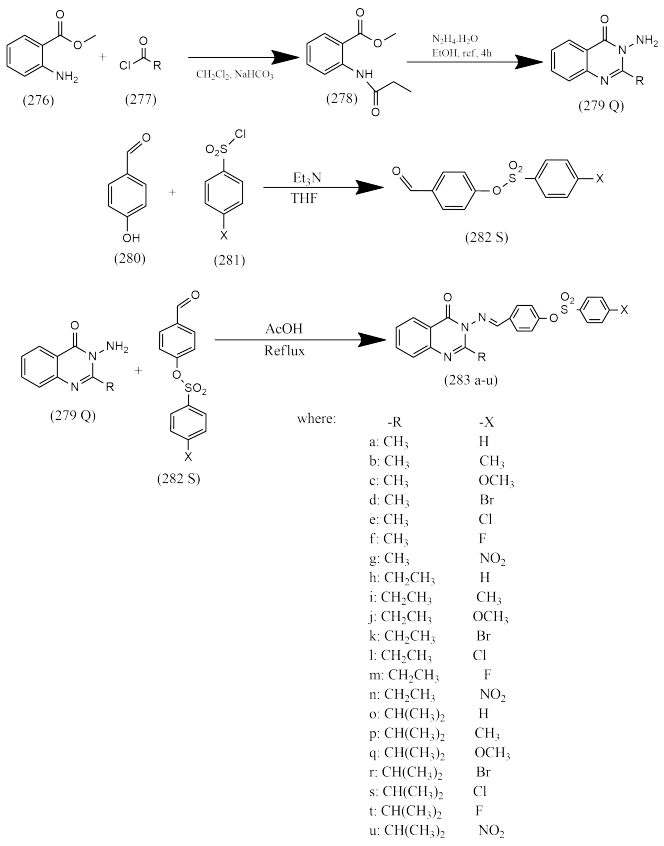


Fig. (46). Synthetic scheme for novel sulfonates containing quinazolin-4(3H)-one ring derivatives [93].

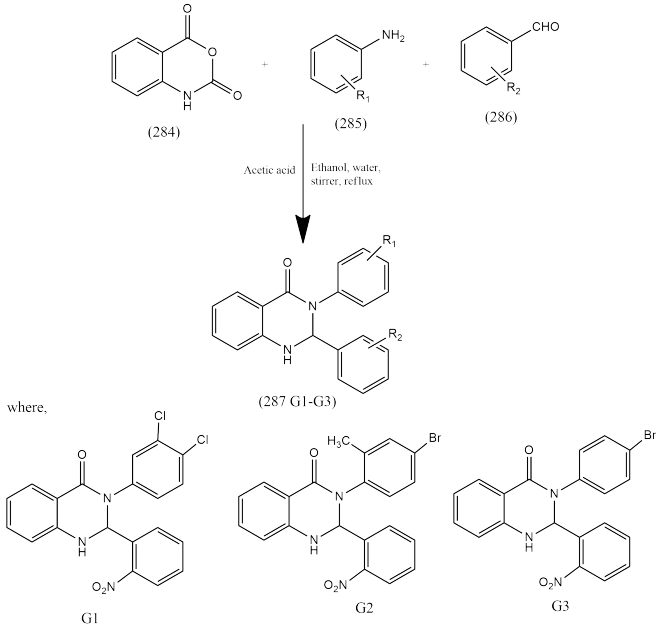


Fig. (47). Preparation of 2,3-disubstituted quinazolin-4(1H)-one derivative [94].

Krishnarth N. and colleagues (2020) developed a new series of quinazolinone derivatives (Fig. **48**) by using a Vilsmeier reagent linked through various aniline derivatives. The synthesis started with 2-amino-3,4,5-trimethoxybenzoic acid (288), which was reacted with the Vilsmeier reagent to form the intermediate compound N-(((6-(chlorocarbonyl)-2,3,4-

trimethoxyphenyl)amino) methylene)-N-methylmethanaminium (289). This intermediate (289) was then treated with different aniline derivatives (290 QA1-QA8) to give the next set of intermediates (291 QA1-QA8). The reaction mixture was stirred for 3 hours, resulting in the formation of the final substituted quinazolinone derivatives (292 QA1-QA8). The synthesized molecules were characterized using ^{1}H-NMR, FT-IR, and mass spectrometry. Their anti-inflammatory potential was evaluated *in vivo* using the carrageenan-induced paw edema model. The biological results indicated that compounds 292 QA-2 and 292 QA-6 showed strong anti-inflammatory activity. Compounds 292 QA-1, 292 QA-4, and 292 QA-7 displayed moderate activity, whereas 292 QA-3, 292 QA-5, and 292 QA-8 exhibited the weakest activity among the series [95].

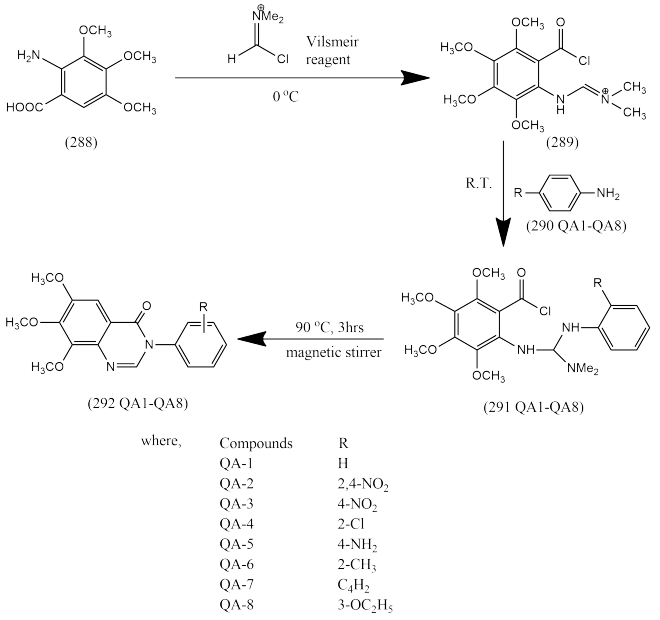


Fig. (48). Preparation of novel derivatives of quinazolinone [95].

Qiu J. and colleagues (2020) synthesized a new series of quinazolinone derivatives (Fig. **49**) and evaluated their *in vitro* activity against hepatitis B virus (HBV) as well as hepatocellular carcinoma (HCC) cells. The synthetic pathway began with methylamine derivatives (293), which were reacted with CS_2 and p-toluenesulfonyl chloride to form intermediate (294). Separately, benzene or substituted benzene derivatives (295) underwent reaction with paraformaldehyde in the presence of hydrochloric acid, producing a chloromethylation intermediate (296). Next, methyl 2-amino-4-hydroxybenzoate (297) was reacted with intermediate (294) to form intermediate (298), which then coupled with intermediate (296) to yield compound (299). Finally, alkylation of intermediate (299) using 2-dimethylaminoethyl chloride hydrochloride, 2-diethylaminoethyl chloride hydrochloride, or 3-dimethylaminopropyl chloride hydrochloride led to the formation of the final quinazolinone derivatives (300a-s). Among these, compounds 300j and 300k showed the strongest inhibition of HBV DNA replication in both drug-sensitive and drug-resistant strains (including lamivudine- and entecavir-resistant HBV). Remarkably, compound 300k also demonstrated significant anti-cancer activity. It effectively suppressed the growth of HepG2, HUH7, and SK-HCC cells, with IC_{50} values of 5.44, 6.42, and 6.75 μM, respectively, showing higher potency than the standard drugs 5-fluorouracil and sorafenib. Further mechanistic studies revealed that compound 300k promotes apoptosis in HepG2 cells by increasing the expression of pro-apoptotic proteins (Bad and Bax) while reducing anti-apoptotic proteins (Bcl-2 and Bcl-xl) in a dose-dependent manner. With its strong dual anti-HBV and anti-HCC effects, compound 300k stands out as a promising lead molecule for developing new therapies targeting HBV infection and HBV-related liver cancer [96].

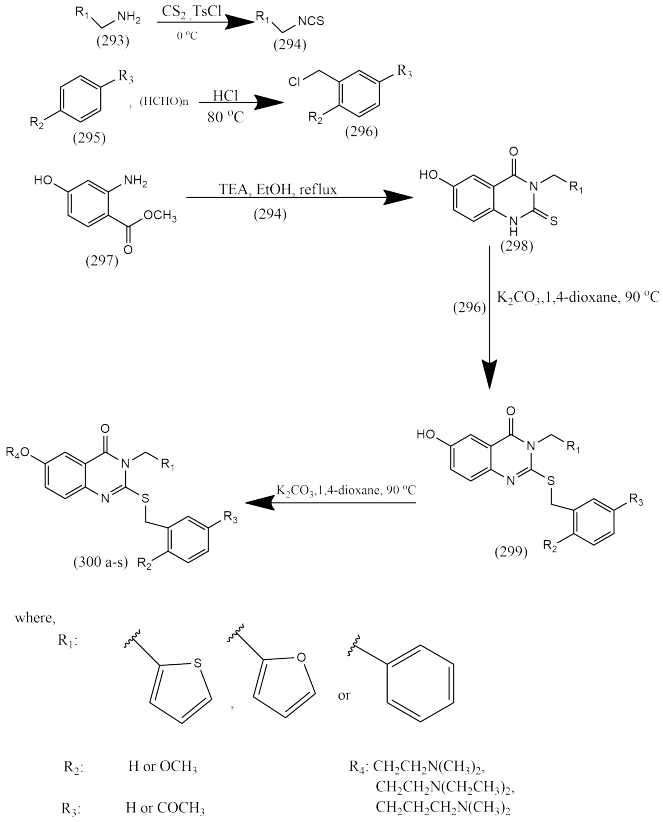


Fig. (49). Series of novel quinazolinone derivatives [96].

Le Y. and co-workers designed and synthesized a new series of 3-methyl-quinazolinone derivatives (Fig. **50**) and evaluated their antitumor activities *in vitro* against three human cancer cell lines-A549, PC-3, and SMMC-7721-as well as wild-type epidermal growth factor receptor tyrosine kinase ($EGFR^{wt}$-TK). The synthetic route began with the reaction of isatoic anhydride (301) and methylamine, producing 2-amino-N-methylbenzamide (302). This compound was then treated with 2-chloroacetyl chloride in glacial acetic acid to yield 2-(chloromethyl)-3-methylquinazolin-4(3H)-one (303). Next, compound 303 was reacted with p-hydroxybenzaldehyde in the presence of anhydrous potassium carbonate using DMF as the solvent, forming 4-((3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)methoxy) benzaldehyde (304). Finally, the aldehyde intermediate was condensed with various aniline derivatives (305a-p) in toluene to give the final target compounds (306a-p). Biological evaluation revealed that several derivatives showed promising anticancer effects. In particular, compounds 306g, 306k, and 3061 demonstrated strong cytotoxic activity against all three tested cancer cell lines. Among them, compound 306k showed especially potent effects-it induced late apoptosis in

A549 cells at higher concentrations and caused cell-cycle arrest at the G2/M phase. Moreover, 306k inhibited $EGFR^{wt}$-TK with an impressive IC_{50} value of 10 nM. Molecular docking studies suggested that compound 306k may exert its inhibitory effect by forming stable hydrogen bonds with residues R817 and T830, along with a cation-it interaction with residue K72 in the $EGFR^{wt}$-TK active site [97].

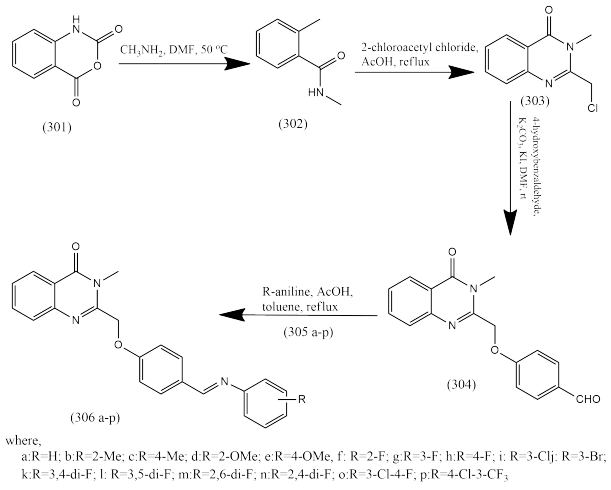


Fig. (50). Series of novel 3-methyl-quinazolinone derivatives [97].

Ozturk S. and colleagues (2020) synthesized and fully characterized a series of quinazolin-4(3H)-one-based cationic surfactants (shown in Fig. **51**). The compounds were analysed using elemental analysis along with IR and NMR spectroscopy. For the synthesis, 2-methyl-4H-benzo[d][3,1]oxazin-4-one (307a) was obtained commercially, while 2-phenyl-4H-benzo[d][3,1]oxazin-4-one (307b) was prepared from anthranilic acid. Both starting materials were reacted with hydrazine hydrate to produce 3-amino-2-methylquinazolin-4(3H)-one (308a) and 3-amino-2-phenylquinazolin-4(3H)-one (308b). These intermediates were then treated with chloroacetyl chloride in DMF for 6 hours, followed by washing, drying, and recrystallization from ethanol, giving compounds 309a and 309b. Next, the chloroacetamide derivatives were reacted with long-chain tertiary amines (C14 and C15) in ethanol at 120°C for 48 hours, resulting in the final cationic surfactants (310a, 310b) and (311a, 311b). The researchers evaluated various physicochemical properties of the synthesized surfactants, including density, critical micelle concentration, surface tension, surface-tension-lowering efficiency, Gibbs free energy of micellization, foam and emulsion stability, and anticorrosion activity. Antibacterial and antifungal activities were also examined. Among all compounds, N,N-dimethyl-N-(2-[(2-methyl-4-oxoquinazolin-3(4H)-yl)amino]-2-oxo-ethyl tetradecan-1-aminium chloride (310a) displayed the strongest antibacterial activity against five human pathogens. Interestingly, 310a was also the only surfactant that showed antifungal activity, specifically against Candida albicans [98].

Norouzbahari M and colleagues (2020) developed a new set of functionalized fluoroquinolone derivatives by combining ciprofloxacin and sarafloxacin with quinazolinone fragments (Fig. **52**). The synthetic route began by reacting o-aminobenzoic acids (312) with chloroacetonitrile (313), yielding 2-(chloromethyl) quinazolin-4(3H)-one (314). This intermediate then underwent a nucleophilic substitution reaction with sarafloxacin (315) and ciprofloxacin (316) in the presence of $NaHCO_3$ in DMF, resulting in the final compounds (317a-j). The structures of these new molecules were confirmed using ^{1}H and ^{13}C-NMR, IR spectroscopy, mass spectrometry, and elemental analysis. To better understand how the compounds interact at the molecular level, docking studies and *in silico* pharmacokinetic predictions were also performed. Their antibacterial activity was tested using broth microdilution, well-diffusion, and disc-diffusion methods against three gram-positive bacteria (MRSA, *Staphylococcus aureus*, and *Enterococcus faecalis*) and three gram-negative bacteria (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*). Overall, the synthesized molecules showed mild to moderate effects against gram-negative bacteria, but performed moderately to strongly against gram-positive strains. Among the ciprofloxacin-based compounds, 317d stood out with a minimum inhibitory concentration (MIC) of 16 nM against both MRSA and S. aureus, making it around 60 times more potent than ciprofloxacin itself. For the sarafloxacin-derived molecules, compound 5i was the most powerful, showing excellent activity against *S. aureus* and MRSA (MIC = 0.125 μM). The results from well-diffusion and disc-diffusion tests supported the microdilution findings, and the molecular docking outcomes were in good agreement with the experimental antibacterial data [99].

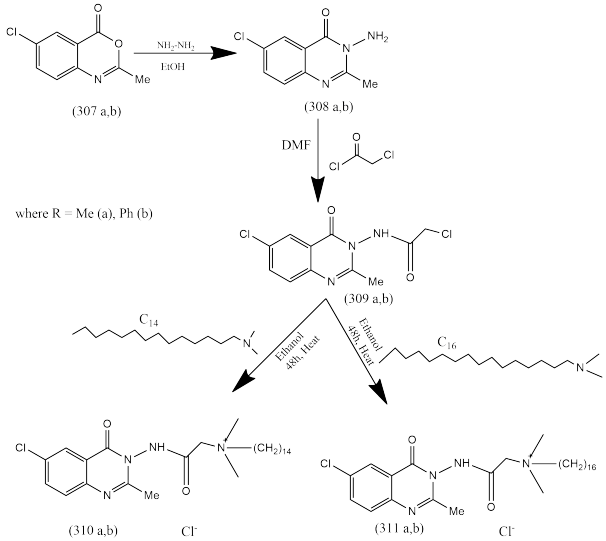
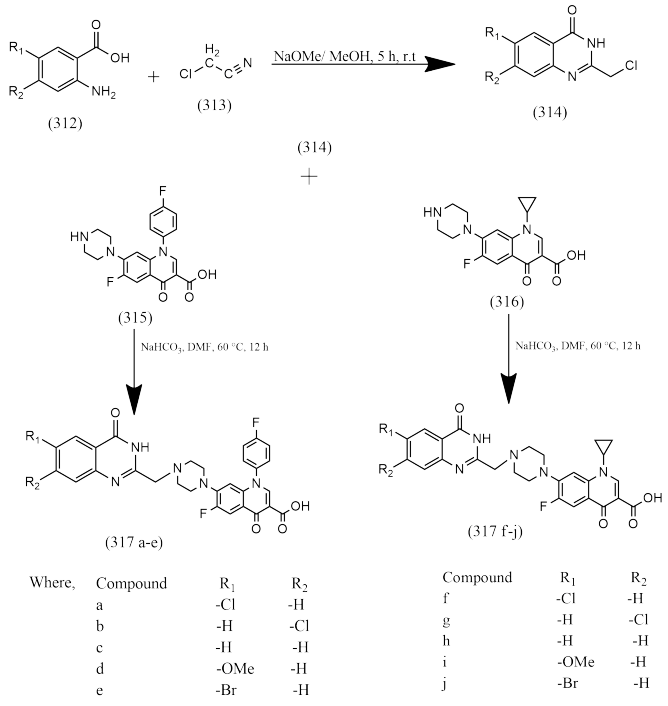


Fig. (51). Series of quinazolin-4(3H)-one-based cationic surfactants [98].

Santos-Ballardo L. and colleagues (2020) reported that the quinazoline-2,4-dione scaffold, known for its presence in various bioactive molecules and marketed drugs, continues to show valuable biological potential. In their study, the team explored the anti-diabetic activity of newly synthesized derivatives. They developed a simple, one-pot, three-component reaction to obtain 3-substituted quinazoline-2,4-diones **(320a-1)** (Fig. **53**). This method, carried out under microwave irradiation, required no catalyst or solvent and involved reacting isatoic anhydrides (318) with primary amines (319) and a carbonyl source. The resulting products were isolated in moderate yields ranging from 30% to 65%. The synthesized molecules were then tested for *in vitro* a-amylase and a-glucosidase inhibition, as well as for antioxi-

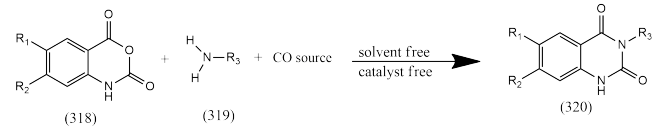
dant and cytotoxic properties. Among them, compounds 320d, 320e, 320g, and 320h exhibited moderate inhibitory activity against one or both enzymes, showing performance comparable to the standard drug acarbose. Molecular docking further demonstrated that these active molecules formed diverse and distinct interactions within the active sites of the target enzymes. Notably, compound 320d showed stronger cytotoxicity than 5-fluorouracil in an Artemia salina assay. Taken together, these findings highlight the therapeutic promise of quinazoline-2,4-diones, as the evaluated compounds generally acted as moderate inhibitors of key carbohydrate-digesting enzymes and displayed additional biological activities supporting their pharmacological relevance [100].



Where,	Compound	R_1	R_2
	a	-Cl	-H
	b	-H	-Cl
	c	-H	-H
	d	-OMe	-H
	e	-Br	-H

Compound	R_1	R_2
f	-Cl	-H
g	-H	-Cl
h	-H	-H
i	-OMe	-H
j	-Br	-H

Fig. (52). Series of functionalized fluoroquinolone derivatives [99].



	R_1	R_2	R_3
320a	H	H	C_6H_5
320b	H	H	$C_6H_5CH_2$
320c	H	H	2-C_5H_3N
320d	H	H	3-C_5H_3N
320e	H	H	$CH_3CH_2CH_2$
320f	H	H	C_5H_9
320g	H	H	C_6H_{11}
320h	H	H	2-$CH_3C_6H_5$
320i	H	H	3-$CH_3C_6H_5$
320j	H	H	4-$CH_3C_6H_5$
320k	Me	H	C_6H_5
320l	F	H	C_6H_5

Fig. (53). Synthetic scheme of novel 3-substituted quinazoline-2,4-diones under microwave irradiations [100].

5. PHARMACOLOGICAL ACTIVITY

Bala IA and colleagues (2025) synthesized a series of pyridine-quinazolin-4(3H)-one hybrid molecules and examined their antimicrobial and anticancer properties. They also evaluated how these compounds interact with *Staphylococcus aureus* dihydrofolate reductase using computational docking studies. Overall, the compounds showed moderate antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, and *Candida albicans*. Among them, compound 321a produced the largest zones of inhibition: 17 ± 0.5 mm (MRSA), 15 ± 2 mm (*P. aeruginosa*), and 19 ± 0.5 mm (*C. albicans*). The lowest MIC value, 0.625 mg/mL, was observed for compound 321b, indicating stronger antimicrobial potency. When tested for anticancer activity against HL60, MV411, K562, and KG1a leukemia cell lines, compound 321c emerged as the most effective, particularly against K562 cells, with an IC_{50} of 4.36 μM. Docking studies identified compound 321d as having the most favourable interaction with the target enzyme, displaying a docking score of -8.980 kcal/mol, stronger than the native ligand and indicative of a stable binding mode. The structures of all compounds are shown in Fig. (**54**). Overall, these findings highlight several pyridine-quinazolinone hybrids as promising antimicrobial and anticancer candidates [12].

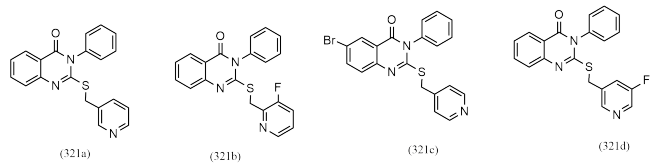


Fig. (54). Structure of pyridine-quinazolin-4(3H)-one hybrids [12].

Haneen DS and colleagues (2025) identified a range of new quinazolinone derivatives and assessed their anticancer potential through *in vitro* cytotoxicity studies (mean IC_{50} ± SE, n = 3). Among all tested compounds, **322a** and **322b** (Fig. **55**) exhibited the most potent anticancer activity. To better understand how these molecules exert their effects, the research team conducted molecular docking and molecular dynamics simulations against several major cancer-associated targets, including Topoisomerase II, VEGFR2, c-Met, EGFR, and Estrogen Receptor-alpha. The combination of experimental results and computational analyses strongly indicates that these quinazolinone derivatives could serve as promising new anticancer leads, warranting further biological evaluation and structural optimizations [101].

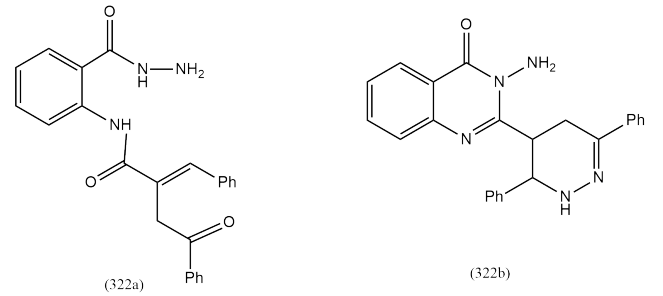


Fig. (55). Structure of novel quinazolinone derivatives [101].

Ibrahim SA and colleagues (2024) synthesized a new series of quinazolinone-based disperse dyes incorporating pyrazolone moieties. The dyes were prepared by coupling quinazolinone with various substituted pyrazolone derivatives. The team conducted a detailed evaluation of their mul-

tifunctional properties, including color strength, dyeing time, concentration effects, pH sensitivity, buildup behavior, and overall fastness performance. The results were encouraging: both the fastness tests and colorimetric measurements confirmed that the dyes performed well on polyester fabrics, indicating strong dyeing efficiency. The compounds also underwent *in vitro* antimicrobial testing, which revealed moderate to excellent antibacterial and antifungal activity against a range of Gram-positive and Gram-negative organisms. Additionally, the dyed polyester samples showed excellent UPF (ultraviolet protection factor) ratings, ranging from 38.60 to 177.32. Only dye 323 (Fig. **56**) displayed a slightly lower, but still very good -UPF rating. Overall, these newly developed quinazolinone-pyrazolone disperse dyes demonstrate promising coloristic, antimicrobial, and UV-protective properties, making them valuable candidates for multifunctional textile applications [102].

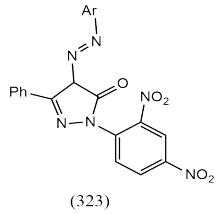


Fig. (56). Structure of quinazolinone disperse dyes based on pyrazolone moieties [102].

Moftah HK and colleagues (2024) identified a new set of quinazolinone-based derivatives as promising multifunctional anti-Alzheimer's disease (AD) agents, exhibiting both cholinesterase inhibition and anti-inflammatory activity. Initial *in vitro* screening highlighted several compounds with noteworthy AChE inhibitory potential, prompting further investigation. These candidates were then evaluated *in vivo* through AChE inhibition assays and the Morris water maze test, using donepezil as the reference standard. To assess their broader impact on AD pathology, hippocampal levels of inflammatory markers-TNF-α, NF-κB, IL-13, and IL-6-as well as antioxidant biomarkers such as SOD and MDA were also measured. The findings revealed that compounds 324a, 324b, and 324c demonstrated strong anti-AChE, anti-inflammatory, and antioxidant activities, indicating a meaningful therapeutic effect against AD. Histopathological analysis further supported this, showing that these compounds (Fig. **57**) offered neuroprotective effects, reducing neuronal damage in a scopolamine-induced mouse model. Molecular docking studies confirmed that the synthesized derivatives interacted favorably with the AChE active site, consistent with their high docking scores. Overall, these results suggest that the newly developed quinazolinone derivatives hold significant promise as future anti-Alzheimer's agents, combining multiple beneficial mechanisms in a single chemical framework [103].

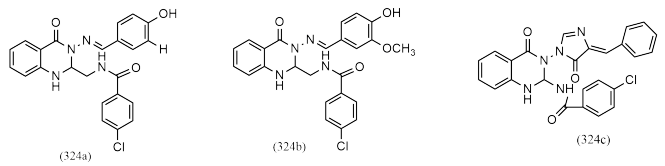


Fig. (57). Structure of quinazolinone-based derivatives [103].

Hassan RM and collaborators (2024) explored a new series of quinazolin-4-one derivatives as potential solutions to the growing problem of antibiotic resistance. These compounds were synthesized and screened for antimicrobial activity, and several showed broad-spectrum effects while remaining safe for human cell lines. Among them, compounds **325a** and **325b** (Fig. **58**) demonstrated impressive anti-biofilm activity against *Pseudomonas aeruginosa*. They inhibited biofilm formation-regulated by the quorum-sensing system -at sub-MIC levels, with IC_{50} values of 3.55 μM and 6.86 μM, respectively. Further evaluation of virulence-related behaviors showed that compound 325b reduced cell-surface hydrophobicity, weakening bacterial adhesion, while both 325a and 325b suppressed exopolysaccharide production, a key structural component that stabilizes biofilms. In addition, these compounds impaired the bacteria's twitching motility, a movement associated with increased pathogenicity and invasion. Molecular docking studies were carried out to understand how 325a and 325b interact with PqsR, a major quorum-sensing transcriptional regulator in *P. aeruginosa*. The findings revealed favorable binding interactions, supporting their role as quorum-quenching agents. Overall, the results indicate that these quinazolin-4-one derivatives show strong potential as novel anti-biofilm and quorum-sensing inhibitors, offering a therapeutic strategy that avoids inducing resistance by not interfering with the bacteria's essential life cycle [104].

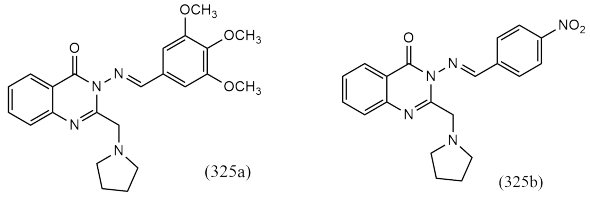


Fig. (58). Structures of new quinazolin-4-one derivatives [104].

Du C and colleagues (2023) designed a series of spiroquinazolinone derivatives, combining the known biological activity of quinazolinones with the structural advantages of spirocycles to create new chitin synthase inhibitors with mechanisms distinct from existing antifungal drugs. Among the synthesized molecules, several spiro[thiophen-quinazolin]-one derivatives containing a, β-unsaturated carbonyl groups demonstrated strong chitin synthase inhibition as well as antifungal activity. Enzyme assays revealed that a few of the sixteen compounds showed IC_{50} values comparable to polyoxin B (IC_{50} = 93.5 ± 11.1 μM). Notably, kinetic studies confirmed that compound 326 acts as a non-competitive inhibitor of chitin synthase. Cytotoxicity testing further showed that compound 326-identified as N^1-(4-nitrophenyl)-N-(4-oxo-3,4,4',5'-tetrahydro-1H,2'H-spiro[quinazoline-2,3'-thiophen]-6-yl) fumaramide (Fig. **59**) exhibited low toxicity toward human A549 lung cancer cells. *In silico* ADME predictions also suggested that it has favorable pharmacokinetic properties. Molecular docking analysis indicated that compound 326 forms multiple hydrogen bonds within the chitin synthase binding pocket, which may enhance its binding affinity and inhibitory effect. Overall, the findings show that these newly designed molecules function as selective, broad-spectrum chitin synthase inhibitors, highlighting compound 326 as a promising lead candidate for combating drug-resistant fungal infections [105].

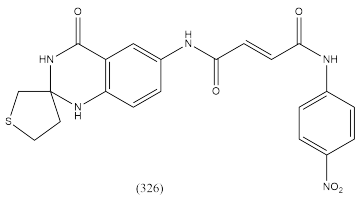


Fig. (59). Structure of N^1 -(4-nitrophenyl)-N^4 -(4-oxo-3,4,4′ ,5′ -tetrahydro-1H,2′ H-spiro [quinazoline-2,3′ -thiophen].-6-yl)fumaramide [105].

Zeng R and colleagues (2023) developed four new quinazolinone-based compounds, inspired by the well-known biological versatility of the quinazolinone scaffold. These compounds were synthesized through a one-pot procedure, involving intramolecular cyclization and dehydration catalyzed by an aqueous methylamine solution. Their structural identities were confirmed using ^{1}H NMR, ^{13}C NMR, FT-IR, and HRMS, while the crystal structure of compound 327 (Fig. **60**) was further validated through X-ray diffraction analysis. When tested for antifungal properties, all four compounds displayed notable activity against seven major phytopathogenic fungi at 150 and 300 mg/L. Among them, compound 327 showed the strongest effect, achieving 62.42% inhibition of *Fusarium oxysporum* f. sp. *niveum* at 300 mg/L. Because of its promising performance, compound 327 is considered a potential lead candidate for developing treatments against watermelon Fusarium wilt and deserves further investigation [106].

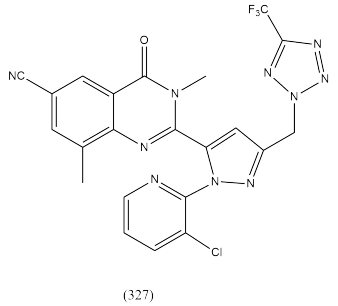


Fig. (60). Structure of novel quinazolinone compound [106].

Zhang W and colleagues (2023) designed and synthesized a new series of amide-containing quinazolinone derivatives using an active-splicing strategy. When evaluated for biological activity, several of these compounds exhibited promising antibacterial effects. Among them, compound **328** (shown in Fig. **61**) demonstrated particularly strong activity. It showed potent inhibition of *Pseudomonas syringae* pv. *actinidiae* (Psa) *in vitro*, with an EC_{50} of 39.2 mg/L, outperforming the standard agents thiodiazole copper (73.9 mg/L) and zinc thiazole (45.1 mg/L). At 100 mg/L, compound 328 also achieved a 70.9% inhibition rate against *Xanthomonas oryzae* pv. *oryzae* (Xoo), again surpassing both comparison agents. Structure-activity relationship studies revealed that modifying the R1 position or adding electron-donating groups significantly influenced antibacterial potency. Further confirmation through scanning electron microscopy showed that compound 328 disrupted bacterial cells, causing fragmentation and surface wrinkling, which ultimately contributed to its antibacterial action. These findings suggest that compound 328 represents a promising lead structure and could be further optimized as a potential antibacterial agent [107].

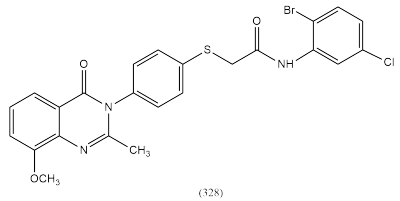


Fig. (61). Structure of newer quinazolinone derivative [107].

Abdullahi SH and colleagues developed four quantitative structure activity relationships (QSAR) in 2022, using a series of quinazoline derivatives with activities against the triple-negative breast cancer cell line (MDA-MB231). Model 1 was chosen because it was statistically fit with the following validation parameters: $R^2 = 0.875$, $Q^2 = 0.837$, $R^2Q^2 = 0.038$, Next test set = 5, and R^2 ext = 0.655. The quinazoline series, the reference medication gefitinib, and the active site of the epidermal growth factor receptor (EGFR) (pdb id = $3ug^2$) were all subjected to molecular docking experiments. Eight of these compounds were shown to have superior docking scores when compared to Gefitinib. Since it possessed the best Moldock score and was well predicted by the chosen model with the lowest residual value, compound 329 (Fig. **62**) from the training set (pred pIC_{50}=5.67, Residual=−0.04, and MolDock score=−123.238) was chosen as the best compound and used as a template to design ten new novel compounds with better activities and better docking scores. The chosen model anticipated the developed compounds' inhibitory actions, and the majority of them have better activity than the template compound 329. When the developed compounds were redocked onto the EGFR receptor's active pocket, it was found that their docking scores were superior to those of the reference medication (gefitinib) and the template used in the design. Additionally, using online tools such as SWISSADME and pkCSM, the proposed compounds were put through ADMET and drug-likeness investigations. The results showed that they were pharmacologically active, easily synthesized, and did not break Lipinski's rule of five. Therefore, following *in vivo* and *in vitro* testing, all of the developed compounds can be used as MDA-MB231 cell line inhibitors [108].

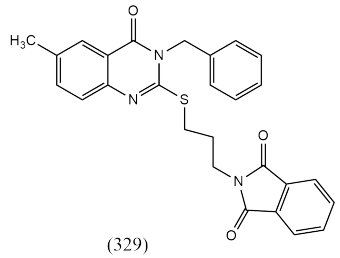


Fig. (62). Structure of best quinazoline template [108].

Chiriapkin AS and colleagues (2022) developed a series of new 6,7-dimethoxyquinazolin-4(3H)-one derivatives by incorporating fragments of neuroactive amino acids and dipeptides, aiming to explore their potential cerebroprotective effects. In total, 13 novel derivatives were successfully synthesized. To assess their activity, a rat model of cerebral ischemia was created using the Tamura method, which involves permanent occlusion of the right middle cerebral ar-

tery. The extent of brain necrosis was measured, and cognitive performance was evaluated through the Y-maze test. Among all the synthesized compounds, 330a, 330b, and 330c (Fig. **63**) demonstrated the strongest neuroprotective and cerebrotropic effects. Their pharmacological activity was comparable to ethyl methyl hydroxy pyridine succinate, a well-known reference drug, highlighting their potential as promising candidates for further investigation [109].

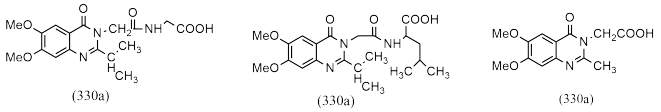


Fig. (63). Structure of novel 6,7-dimethoxyquinazolin-4(3H)-one derivatives [109].

Tokalı FS, *et al.,* 2022 developed a series of novel acetic acid derivatives containing quinazolin-4(3H)-one ring and tested for *in vitro* AR inhibitory effect. When compared to the reference medication epalrestat, all of the target compounds showed greater activity and nanomolar activity against the target enzyme. With a KI value of 61.20 ± 10.18 nM, Compound 331a, also known as 2-(4-[(2-methylpiperazin-1-yl)methyl]-4-oxoquinazolin-3(4H)-ylimino)methyl]phenoxy)acetic acid, showed the highest inhibitory effect among them. Additionally, the MTT test was used to examine these drugs' efficacy against MCF-7 breast cancer cells and L929 nontumoral fibroblast cells. As seen in Fig. (**64**), compounds 331a and 331b demonstrated reduced toxicity to normal L929 cells. The distinctive characteristics of the synthesized compounds, such as distribution, metabolism, excretion, and absorption, were also assessed. The potential binding mechanisms of these inhibitors against AR were investigated using molecular docking simulations [110].

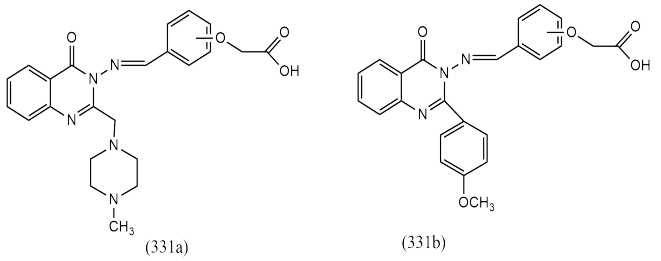


Fig. (64). Structure of novel acetic acid derivatives [110].

Ansari S and colleagues (2021) designed and synthesized a new series of quinazolinone-2-thio-metronidazole derivatives and evaluated their inhibitory potential against several key metabolic enzymes: α-glucosidase, acetylcholinesterase (AChE), butyrylcholinesterase (BChE), and human carbonic anhydrase I and II (hCAs I and II). Remarkably, all synthesized compounds demonstrated strong enzyme-inhibitory activity when compared with established standard drugs. Among them, compound 332c stood out as the most powerful inhibitor of carbonic anhydrase, showing 4-fold and 7-fold greater potency than acetazolamide against hCA I and HCA II, respectively. Compound 332b exhibited exceptional cholinesterase inhibition, being approximately 11 times stronger than tacrine on AChE and 21 times stronger on BCHE. Similarly, compound 332a emerged as the most effective a-glucosidase Inhibitor, displaying five times the activity of acarbose, the standard reference. To better understand these impressive activities, molecular modelling studies were carried out, revealing how the most active compounds interact within the enzyme active sites. Additionally, the toxicity profile, ADME characteristics, and overall drug-likeness of compounds 332a, 332b, and 332c (Fig. **65**) were predicted, offering further support for their potential as therapeutic leads [111].

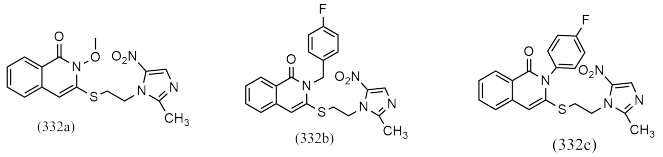


Fig. (65). Structures of quinazolinone-2-thio-metronidazole derivatives [111].

In 2021, Nangare A. and colleagues developed a novel 4-(substituted aniline) quinazoline that was synthesized in good yields and tested for acute toxicity as well as potential antibacterial, antifungal, and anticancer properties. Based on their elemental analysis and spectrum data, the synthesized compounds' structures were validated. The antibacterial properties of the synthesized compounds were tested using the agar cup method, while their antifungal effects were assessed through the poison plate technique. Additionally, their *in vitro* anticancer potential was evaluated against HeLa and MCF-7 cell lines. Overall, the quinazoline derivatives did not show activity against gram-negative bacteria and exhibited only weak inhibition of gram-positive strains. However, an interesting exception was observed for compound 333, N-(4-[(4-bromo-2-nitrophenyl)amino]quinazoline-6-yl)acetamide (Fig. **66**). The presence of 4-bromo and 3-nitro substituents significantly enhanced its antifungal potency, producing 90% inhibition of Fusarium moniliforme, making it comparable to Griseofulvin. These findings indicate that such substituted quinazoline derivatives may serve as promising candidates for managing fungal infections [112].

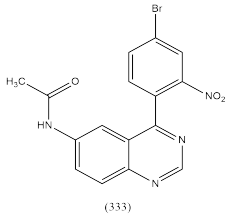
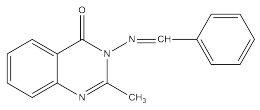


Fig. (66). Structure of N-{4-[(4-Bromo –2– nitro phenyl) amino]. quinazoline-6-yl}acetamide compound [112].

Patil JP and colleagues (2021) reported the synthesis of a new chemical entity, compound 334, identified as 3-(benzylideneamino)-2-methyl-quinazolin-4-one, a Schiff base shown in (Fig. **67**). Interestingly, the team used lemon juice as a green solvent, demonstrating how fruit juices can act as natural catalysts to promote mild, selective, and eco-friendly chemical transformations. The synthetic route involved converting methyl anthranilate into methyl-2-acetamidobenzoate, followed by cyclization to obtain 3-amino-2-methyl quinazolin-4-one. Subsequent condensation with benzaldehyde afforded the final Schiff base. The compound was confirmed through physical characterization, including melting point, TLC, and spectral analyses. Compared to conventional procedures, this green approach

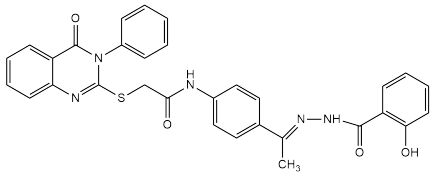
proved more practical and efficient, offering reduced reaction time, minimal pollution, improved safety for the chemist, and overall lower operational cost-making the process both simple and environmentally sustainable [113].



(334)

Fig. (67). Structure of 3-(benzylideneamino)-2-methyl-quinazolin-4-one [113].

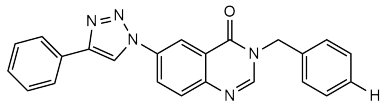
Eissa *et al.* in 2020 explored novel quinazoline-based derivatives, which were then designed and synthesized *via* modification of the VEGFR-2 reported inhibitor in order to increase the binding affinity of the designed compounds to the receptor active site. The VEGFR-2 inhibitory effects of the proposed compounds were assessed. VEGFR-2 inhibition has been established as a therapeutic approach for cancer treatment. HepG-2, MCF-7, and HCT-116 cell lines were used to test the novel compounds' bioactivity. Sorafenib and doxorubicin acted as positive controls. When compared to the reference medications sorafenib (IC_{50} = 7.31, 9.40, and 7.21 µM) and doxorubicin (IC_{50} = 8.28, 9.63, and 7.67 µM), compound 335 (shown in Fig. **68)** showed encouraging cytotoxic activity (IC_{50} values = 3.74 ± 0.14, 5.00 ± 0.20, and 6.77 ± 0.27 µM). The *in vitro* VEGFR-2 inhibitory effects of the most potent drugs were examined. The cytotoxicity data and VEGFR-2 inhibition results were in agreement. The VEGFR-2 inhibitory activity of compound 338 was therefore higher than that of the reference medication, sorafenib (IC_{50} = 0.588 ± 0.06 µM) (IC_{50} = 0.340± 0.04 µM). Additionally, docking research was conducted to determine how the novel compounds bound to the VEGFR-2 active site. According to docking findings, the novel compounds' strong VEGFR-2 inhibitory activity is facilitated by their hydrophobic contact with the receptor's hydrophobic pocket and their binding to the essential amino acids in the active site, Glu883 and Asp1044. The advantages of the synthesized analogues as promising anti-angiogenic drugs are supported by the results of cytotoxic effects, *in vitro* VEGFR-2 inhibition, and docking studies [114].



(335)

Fig. (68). Structure of novel quinazoline-based derivatives [114].

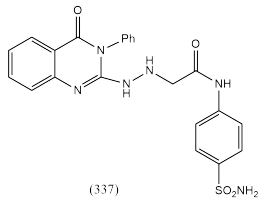
Gatadi *et al.*, (2020) synthesized a number of new 4(3H)-quinazolinones and assessed their cytotoxic efficacy against a variety of human cancer cell lines, including A549 (lung), HCT-116 and HT-29 (colon), and MDA-MB-231 and MCF-7 (breast). Compound 336, also known as 3-(4-bromobenzyl)-7-(4-phenyl-1H-1,2,3-triazol-1-yl) quinazolin-4(3H)-one (Fig. **69**), had encouraging cytotoxic activity against the cell lines MDA-MB-231 (IC_{50} = 3.21 mM) and HT-29 (IC_{50} = 7.23 mM) among the compounds evaluated. Using the breast cancer cell line MDA-MB-231, the mode of action and apoptosis-inducing impact of compound 336 were investigated. Compound 339 treatment of the MDA-MB-231 cell line resulted in the production of horseshoe-shaped nuclei, chromatin condensation, and cell shrinkage, all of which are typical apoptotic features. According to flow cytometric studies, the chemical induces dose-dependent cell cycle arrest in the G_0/G_1 phase. Docking studies were used to examine the powerful drugs' binding mechanisms with the EGFR target protein [115].



(336)

Fig. (69). Structure of 3-(4-bromobenzyl)-7-(4-phenyl-1H-1,2,3-triazol-1-yl) quinazolin-4(3H)-one [115].

Ramadan SK and their teammates in 2020 reported a newer series of quinazolinone-based derivatives as potential PARP 1 inhibitors using an eco-friendly synthesis method. The 4-quinazolinone framework was employed as a bioisosteric replacement for the phthalazinone ring found in the reference drug Olaparib. Many of the synthesized derivatives demonstrated notable inhibitory activity against PARP-1. Among them, compound 337 (Fig. **70**) exhibited a potent IC_{50} value of 30.38 nM, which is very close to that of Olaparib (27.89 nM). Cell-cycle analysis of this compound revealed that it induced G2/M phase arrest in MCF-7 breast cancer cells and significantly enhanced programmed cell death compared to the untreated control. Moreover, to understand its interaction profile, molecular docking was performed to predict how the compound fits within the PARP-1 active site. Further *in silico* ADMET evaluation and QSAR modeling were also conducted. Overall, the findings suggest that several of the newly synthesized molecules could serve as promising leads for the development of new PARP-1 inhibitors with potential anti-cancer activity [116].



(337)

Fig. (70). Structure of quinazolinone-based derivative [116].

Khodair *et al.* (2019) synthesized a series of 3-substituted 2-thioxo-2,3-dihydro-1H-quinazolin-4-ones and explored their potential as targeted anticancer agents. The conformational features of these compounds were investigated using advanced two-dimensional NMR techniques, including DQF-COSY, HMQC, and HMBC. Heteronuclear multiple-quantum coherence (HMQC) experiments helped determine the specific sulfur atom involved in alkylation and glycosylation reactions. All synthesized derivatives were further assessed through molecular docking studies against the EGFR tyrosine kinase target. *In vitro* screening on MCF-7 (breast cancer) and HepG2 (liver cancer) cell lines revealed strong antiproliferative effects, with several compounds displaying low IC_{50} values. Among them, compound 338, identified as

3-methyl-2-(B-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(1H)-one (Fig. **71**)-exhibited the most potent activity, with IC_{50}values of 2.09 μM for MCF-7 and 2.08 μM for HepG2. Importantly, these compounds were found to be safe toward normal gingival mesenchymal stem cells (GMSC). RT-PCR analysis demonstrated that this compound induced apoptosis by activating p53 and its associated genes. Overall, the findings support further development of these derivatives as promising chemotherapeutic candidates [117].

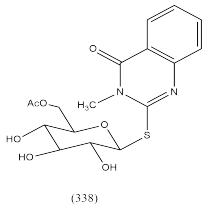


Fig. (71). Structure of 3-Methyl-2-(β-D-glucopyranosylsulfanyl)-2,3-dihydroquinazolin-4(1H)-one [117].

Jain R.K. and colleagues (2018) designed a new series of 2,3-disubstituted-4(3H)-quinazolinone derivatives. 3214qewThese compounds were synthesized from anthranilic acid using sodium cyanate, substituted anilines, and various benzaldehydes. Their chemical structures were confirmed through IR, 13C NMR, and mass spectroscopic techniques. The synthesized molecules were evaluated for anticonvulsant activity using two standard seizure models: maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced clonic seizures, with phenytoin and carbamazepine serving as reference drugs. In addition, neurotoxicity and CNS behavioral effects were assessed in mice through the rotorod and actophotometer tests. Several of the compounds demonstrated notable anticonvulsant activity compared to the standard drugs. Among them, RKJ-46 (339a) and RKJ-47 (339b) showed particularly strong activity, as illustrated in Fig. (**72**). Overall, the findings highlight that substitutions at the second and third positions of the 4(3H)-quinazolinone scaffold can yield promising new anticonvulsant agents [118].

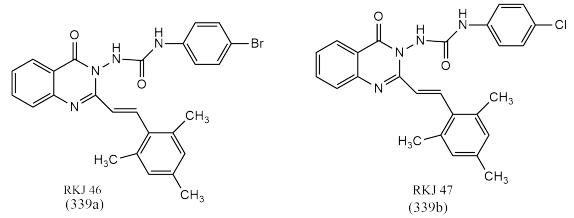


Fig. (72). Structure of novel 2,3 disubstituted-4-(3H) quinazolinone derivative [118].

Kumar A. S. and co-workers (2018) designed and synthesized three quinazolin-4-ylamino derivatives incorporating phenylbenzenesulfonamide groups. These compounds were obtained by reacting (E)-N'-(2-cyanophenyl)-N,N-dimethylformamidine with various 4-amino-N(phenyl)benzenesulfonamides, and their structures were confirmed using HRMS, IR, 'H NMR, and 1°C NMR analyses. To gain deeper insight into their molecular arrangement, the authors also carried out single-crystal X-ray diffraction studies. The X-ray results revealed that compounds 340a and 340c each contain two independent molecules in the asymmetric unit, whereas compound 340b contains only one. The conformational differences between the two distinct molecules, labeled "A" and "B," in the asymmetric units of 340a and 340c were further compared and discussed with reference to available literature. Furthermore, two breast cancer cell lines (MCF7 and MDA MB-231) were used to investigate the compounds' *in vitro* anticancer activities. With an IC_{50} of 5.44 mg/mL, compound 340b was found to be the most effective contender against MDA-MB-231. Additionally, strains of bacteria and fungi were tested for antimicrobial activity. While the compounds exhibited no discernible activity against the fungal strain, compound 340a with chloro-substitution was shown to be the most effective contender against the Gram-negative bacterial strains. Fig. (**73**) displays the structures of each derivative [119]

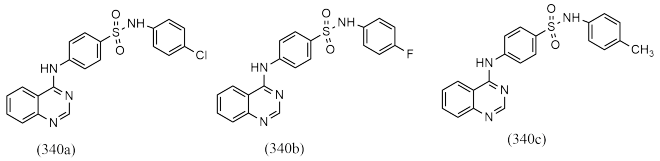
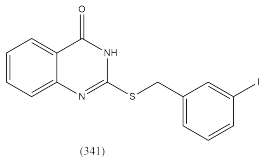


Fig. (73). Structure of quinazolin-4-ylamino derivatives [119].

Qhobosheane MA, *et. al.,* 2018 synthesized fourteen novel 2-mercapto-4(3H)-quinazolinone derivatives and evaluated as potential inhibitors of the human monoamine oxidase (MAO) enzymes. Although this class of compounds has yet to be thoroughly studied as MAO inhibitors, quinazoline's oxidized derivative, quinazolinone, has been demonstrated to have a broad range of biological functions. Seven compounds (IC_{50} < 1 μM) were found to be strong and selective MAO-B inhibitors among the quinazolinone derivatives that were studied. The most effective inhibitor was 2-[(3-iodobenzyl)thio]quinazolin-4(3H)-one (341) as shown in Fig. (**74**), which had an IC_{50} value of 0.142 μM. Additional analysis revealed that this inhibitor, a compound which has a Ki value of 0.068μM, is a competitive and reversible inhibitor of MAO-B. Not a single experimental chemical inhibited MAO-A. The most effective inhibitors of the series are produced by substituting a benzylthio-moiety with a Cl, Br, or I on the meta position for the quinazolinone's C2 position, according to an analysis of the structure-activity relationships (SARs) for MAO-B inhibition. On the other hand, the inhibitory activity towards MAO-B was considerably reduced upon substitution with the unsubstituted benzylthio-moiety (IC_{50} = 3.03μM). According to this study, quinazolinones show promise as a precursor to selective MAO-B inhibitors, which could be utilized to treat neurodegenerative diseases like Parkinson's [120].

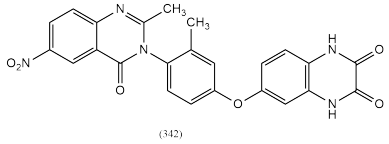
Poorirani S. and colleagues (2018) developed a new collection of quinazolinone derivatives featuring substituted quinoxalindione moieties. The structures of all synthesized compounds were verified using IR and 'H-NMR spectroscopy. Their cytotoxic potential was tested at concentrations of 0.1, 1, 10, 50, and 100 μM against MCF-7 (breast cancer) and Hela (cervical cancer) cell lines through the standard MTT colorimetric assay. Most of the compounds demonstrated noticeable cytotoxic effects on both cell lines. Among them, compound 342, identified as 6-(3-methyl-4-(2-methyl-6-nitro-4-oxoquinazolin-3(4H)-yl)phenoxy)quinoxaline-

2,3(1H,4H)-dione (Fig. **75**), exhibited the strongest inhibitory activity against both cancer cell lines [121].



(341)

Fig. (74). Structure of 2-[(3-iodobenzyl)thio].quinazolin-4(3H)-one, a potent derivative of 2-mercapto-4(3H)-quinazolinone [120].



(342)

Fig. (75). Structure of 6-(3- methyl -4-(2- methyl-6 -nitro-4 oxoquinazolin -3(4H)-yl)phenoxy)quinoxaline 2,3(1H,4H)-dione [121].

CONCLUSION

Quinazoline and quinazolinone derivatives constitute a privileged and versatile heterocyclic scaffold with well-established relevance across diverse therapeutic areas, including central nervous system disorders, cancer, tuberculosis, microbial infections, and cardiovascular diseases. This review comprehensively highlights recent progress in synthetic strategies for generating structurally diverse quinazoline and quinazolinone analogues, including key methodologies starting from amino-benzonitriles as well as bicyclic and heterocyclic precursors, together with their spectroscopic characterization for reliable structural confirmation. A substantial number of these derivatives have demonstrated promising pharmacological activities in both *in vitro* and *in vivo* models, with several candidates exhibiting improved efficacy over existing therapeutic agents. Further, the synthesis of quinazoline and quinazolinone derivatives generally proceeds *via* well-established mechanistic pathways. Cyclization reactions often initiate through nucleophilic attack of an amino or hydrazino group on an activated carbonyl or nitrile, forming key intermediates such as imines or amides. Subsequent intramolecular cyclization, facilitated by acidic or basic conditions, leads to the formation of the quinazoline or quinazolinone core. In multi-component reactions, condensation between aldehydes, amines, and isatoic anhydride typically generates intermediates that undergo cyclodehydration to yield the final heterocyclic scaffold. The reaction pathways are further influenced by the choice of catalyst, solvent, and temperature, which govern the selectivity, yield, and overall efficiency of the synthetic process. Moreover, future investigations should emphasize deeper mechanistic insights and refined structure–activity relationship studies to enhance target specificity, CNS selectivity, and safety profiles. The integration of computational drug design, predictive pharmacokinetic modeling, and environmentally benign synthetic approaches is expected to further support rational lead optimization. In addition, systematic toxicological assessment and translational research will be crucial to bridge the gap between preclinical outcomes and clinical development. Overall, the quinazoline and quinazolinone frameworks remain a highly promising platform for next-generation drug discovery, warranting continued exploration toward clinically viable therapeutic candidates.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: Generation of idea- S.G writing of manuscript, SG drafting of manuscript, SV drawing of chemical structures, SG reviewing of manuscript, SG, SV. All authors reviewed and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

CNS	=	Central Nervous System
$GABA_A$	=	Gamma Aminobutyric Acid-Type A
USFDA	=	United States Food and Drug Administration
MIC	=	Minimum inhibitory concentration
ADMET	=	Absorption, Distribution, Metabolism, Excretion, and Toxicity

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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