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Review

Quinazolinones as Potential Anticancer Agents: Synthesis and Action Mechanisms

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Abstract: Quinazolinones, essential quinazoline derivatives, exhibit diverse biological activities with applications in pharmaceuticals and insecticides. Some derivatives have already been developed as commercial drugs. Given the rising cancer incidence, there is a critical need for new anticancer agents, and quinazolinones show promising potential in this domain. The present review focuses on novel advances in the synthesis of these important scaffolds and other medicinal aspects involving drug design, the structure–activity relationship, and action mechanisms of quinazoline and quinazolinone derivatives, to help in the development of new quinazoline and quinazolinone derivatives.

Keywords: quinazolinones; catalytic synthesis; anticancer; mechanisms

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1. Introduction

Widdege introduced the term "quinazoline" to describe a heterocyclic compound containing a fused benzene and pyrimidine ring, also known by names such as benzimidazoline and 1,3-diazaphthalein (**1**). The properties of quinazoline derivatives are strongly influenced by the extent of conjugation and the nature and positioning of substituents on the benzene and pyrimidine rings [1]. Quinazolinones, oxidized derivatives of quinazolines, are an important class of quinazoline alkaloids. Structure–activity relationship (SAR) studies have significance of substituents at the 2, 6, and 8 positions of the quinazoline ring in determining pharmacological activity [2].

Quinazolinones are categorized based on the position of the oxygen group: 2(1H)-quinazolinones (**2**), 4(3H)-quinazolinones (**3**), and 2,4(1H,3H)-quinazoline-dione (**4**). Additionally, 4(3H)-quinazolinones are further classified by substitution patterns into 2-substituted (**5**), 3-substituted (**6**), 2,3-disubstituted (**7**), and 2,4-disubstituted (**8**) (Figure 1) [1]. Quinazolinones exhibit a broad spectrum of biological activities, including antimicrobial [2,3], antitumor [4–6], anti-inflammatory [7,8], anti-HIV [9,10], antimalarial [11,12], and antihypertensive [13,14] effects, making them valuable as pesticides and pharmaceuticals. Notably, some quinazolinones have been successfully commercialized as drugs (Table 1).

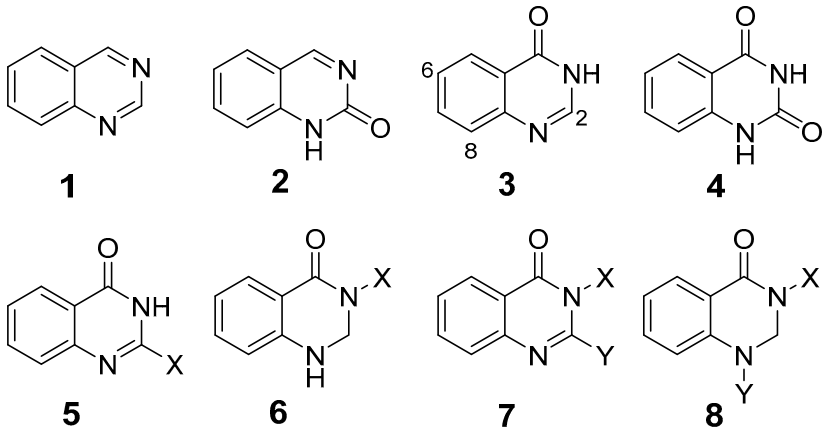


Figure 1. Quinazoline and quinazolinone structure.

Table 1. Some marketed drugs available, which contain the quinazolinone moiety.

S.No	Drug	IUPAC Name	Activity	References
1	Afloqualone	6-amino-2-(fluoomethyl)3-(2-methylphenyl) quinazolin-4-one	Sedative, Hypnotic	[15]
2	Albaconazole	7-Chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4-one	Antifungal	[16]
3	Cloroqualone	3-(2,6-Dichlorophenyl)-2-ethyl-4-quinazolinone	Sedative, Antitussive	[17]
4	Fluproquazone	4-(4-fluorophenyl)-7-methyl-1-propan-2-ylquinazolin-2-one	NSAID	[18]
5	Febrifugine	3-(3-((2R,3S)-3-hydroxypiperidin-2-yl)-2-oxopropyl) quinazolin-4-one	Antimalarial	[19]
6	Fenquizone	7-chloro-4-oxo-2-phenyl-2,3-dihydro-1*H*-quinazoline-6-sulfonamide	Diuretic	[20]
7	Halofuginone	7-Bromo-6chloro-3-[3-[(2S,3R)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-4-quinazolinone	Coccidiostat, Anticancer	[21]
8	Ispinesib	*N*-(3-aminopropyl)-*N*-[(1R)-1-(3-benzyl-7-chloro-4-oxoquinazolin-2-yl)-2-methylpropyl]-4-methylbenzamide	Anticancer	[22]
9	Idelalisib	5-fluro-3-phenyl-2-[(1S)-1-(7H-purin-6-ylamino)propyl]quinazolin-4-one	Antihematological cancer	[23]
10	Isaindingotone	3-(4-hydroxy-3,5-dimethoxybenzyl)-2,3-dihydropyrrolo[2,1-b] quinazolin-9-one	Anti-inflammatory	[24]
11	Nolatrexed	2-Amino-6-methyl-5-(4-pyridylthio)-1H-quinazolin-4-one	Thymidylate synthase inhibitor	[25]
12	Piriqualone	3-(2-methylphenyl)-2-[(*E*)-2-pyridin-2-ylethenyl]quinazolin-4-one	Anticonvulsant	[26]
13	Sclerotigenin	6,7-dihydroquinazolino[3,2-a][1,4]benzodiazepine-5,13-dione	Anti-insectant	[27]
14	Raltitrexed	(2S)-2-[[5-[methyl-[(2-methyl-4-oxo-3H-quinazolin6-yl)methyl]amino]thiophene-2-carbonyl]amino]pentanedioic acid	Anticancer	[28]
15	Elinogrel	1-(5-chlorothiophen-2-yl) sulfonyl-3-[4-[6-fluoro-7-(methylamino)-2,4-dioxo-1*H*-quinazolin-3-yl]phenyl]urea	Antithrombosis	[29]

Table 1. *Cont.*

S.No	Drug	IUPAC Name	Activity	References
16	Tiacrilast	(*E*)-3-(6-methylsulfanyl-4-oxoquinazolin-3-yl) prop-2-enoic acid	Antiallergic	[30]
17	Rutaecarpine	8,8a,13,13a-tetrahydroindolo [2′,3′:3,4] pyrido[2,1-b] quinazolin-5(7H)-one	Alzheimer's disease, Protective alkaloid	[31,32]
18	Quinethazone	7-chloro-2-ethyl-4-oxo-2,3-dihydro-1H-quinazoline-6-sulfonamide	Antihypertensive	[33]

Cancer remains a major global health issue, affecting approximately 10 million individuals annually. The World Health Organization (WHO) reports that 14 million new cases arise each year, with projections indicating a near doubling to 30 million cases by 2040 [34]. Researchers are focusing on heterocyclic compounds including quinazolinones, as promising sources of novel anticancer agents targeting cell proliferation [35]. This review explores various synthetic approaches to quinazolinone production, including metal-catalyzed, microwave-assisted, non-metal-catalyzed, and photocatalyzed methods. Additionally, it examines the antitumor mechanisms of quinazolinone derivatives, such as microtubule polymerization, inhibition of cell cycle arrest, apoptosis induction, inhibition of tumor cell migration and invasion, suppression of angiogenesis, and targeting of epidermal growth factor receptor (EGFR) and PI3K pathways. This review aims to support research into the development of quinazolinone-based anticancer therapies.

2. Strategies for the Synthesis of Quinazolinones

This chapter examines catalytic synthetic methods developed for quinazolinone production, organized into metal-catalyzed, microwave-assisted, non-metal-catalyzed, and photocatalytic approaches. The aim is to inspire the development of green and efficient quinazolinone synthesis methods.

2.1. Metal Catalysis Reaction (Copper/Palladium/Zinc/Iron)

2.1.1. Copper Catalysis Reaction

Copper offers a versatile catalytic profile, with its catalytic efficacy dependent on its oxidation state. Copper can facilitate diverse reactions, including one- and two-electron mechanisms (radical and polar) and their combinations. It readily coordinates with heteroatoms and π-bonds and is especially effective in activating terminal alkynes. Copper-catalyzed C–C and C–N cross-coupling reactions, such as the Ullman and Goldberg reactions, have rapidly advanced due to copper's abundance, cost-effectiveness, and environmental sustainability compared to costly transition metals [36]. This has spurred a surge in research into copper-catalyzed organic reactions. Deng et al. reported an efficient, eco-friendly, copper-catalyzed tandem reaction of 2-aminobenzamide with tertiary amine using a one-pot method involving cyclization and coupling to produce various quinazolinone derivatives (Figure 2). Conducted under aerobic conditions, this reaction achieved yields of up to 91% [37]. Similarly, Bao et al. developed a method for synthesizing 2-substituted 4(3H)-quinazolinones from readily available starting materials (Figure 3). This process involves copper Lewis acid-catalyzed nucleophilic addition of 2-hexanediolamides to nitriles, followed by an intramolecular SNAr reaction using ^{t}BuOK, noted for its simplicity and accessibility of raw materials [38]. Additionally, Upadhyaya et al. synthesized 2-substituted quinazolinones from 2-halo benzamide using TMSN3 as a nitrogen source, without ligands or bases, in a single reactor via a series of coupling steps, including oxidative addition, reductive amination, phenyl C(sp3)-H bond oxy-nitridation, intramolecular cyclization, and oxidative dehydrogenation [39].

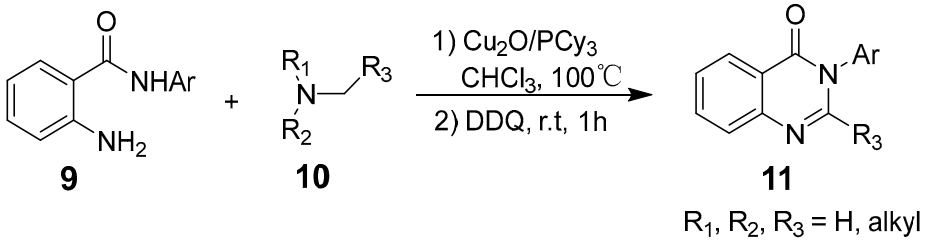


Figure 2. Copper-catalyzed synthesis of quinazolinones.

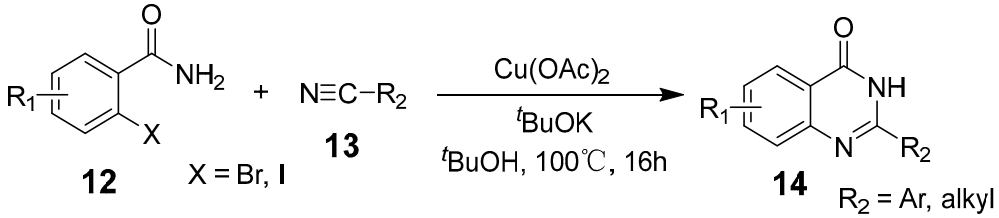


Figure 3. Copper-catalyzed synthesis of quinazolin-4(3H)-ones.

Jurriën W. Collet et al. developed a method for synthesizing quinazolinones using anisole as a green solvent, eliminating the need for drying conditions and inert gases. This reaction employs Cu(II) acetate as a catalyst and a mild base, to facilitate cross-coupling between 2-isocyanatophenone and amines, leading to a cyclo-condensation reaction (Figure 4) [40]. Readily available 2-aryl indoles can also react with amines or ammonia through successive Baeyer–Villiger oxidative expansions and dehydrative condensation reactions under O_2 conditions to form quinazolinones (Figure 5). This method is notable for its straightforward process, mild reaction conditions, and environmentally benign characteristics [41].

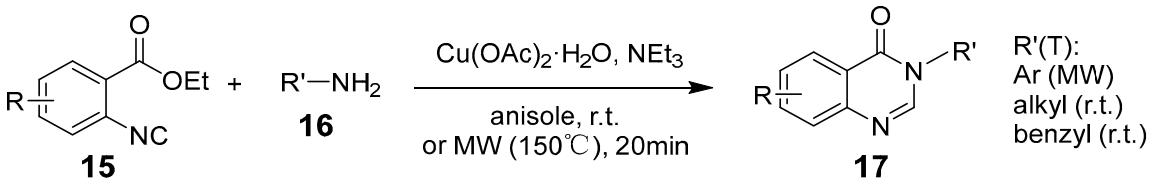


Figure 4. Copper-catalyzed synthesis of quinazolin-4-ones.

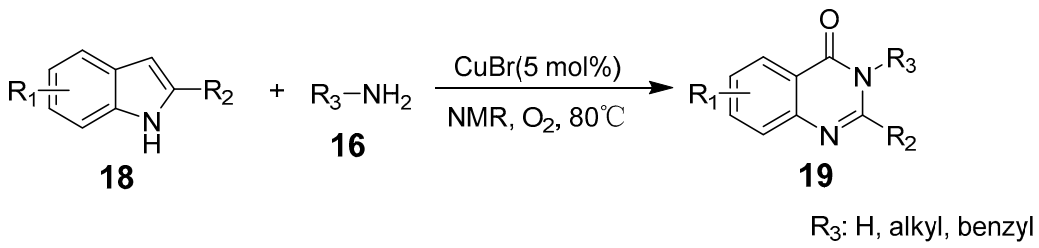


Figure 5. Copper-catalyzed synthesis of 2-arylquinazolinones.

Liu et al. synthesized 11H-pyrido[2,1-b]quinazolin-11-ones using $Cu(OAc)_2 \cdot H_2O$ as the catalyst, with substituted isatins and 2-bromopyridine derivatives as starting materials (Figure 6) [42]. This reaction involves C–N and C–C bond cleavage along with the formation of two C–N bonds, offering flexibility for further functionalization across various substrates. The use of the inexpensive $Cu(OAc)_2 \cdot H_2O$ catalyst yields good to excellent results. Bao et al. presented a simple method for synthesizing N-substituted quinazolinones from anthranilamides using DCP as the methyl source (Figure 7). This reaction involves a tan-

dem process of N-methylation, C(sp^3)-H amination, and oxidation, facilitated by a copper catalyst [43].

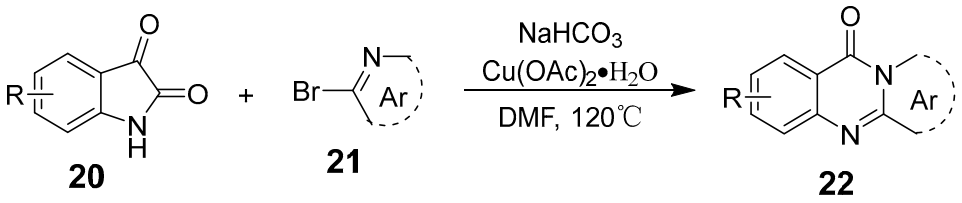


Figure 6. Copper-catalyzed synthesis of pyrido-fused quinazolinones.

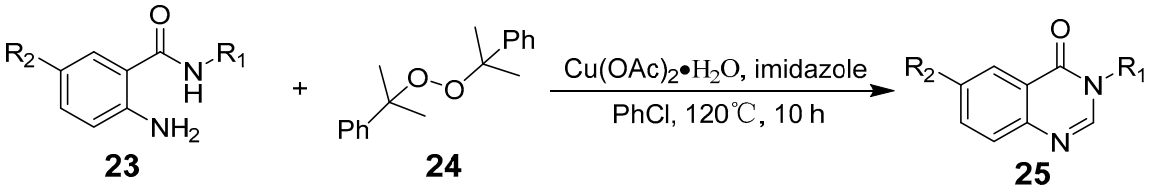


Figure 7. Copper-catalyzed cascade reactions for the synthesis of quinazolinones.

2.1.2. Palladium-Catalyzed Reaction

Palladium-catalyzed coupling reactions are widely utilized in both industrial and laboratory synthesis, offering an efficient approach for constructing C–C bonds and C–heteroatom. Jiang et al. developed a palladium-catalyzed method to synthesize quinazoline-4(3H)-ones from 2-aminobenzamides and aryl halides (Figure 8). The optimal reaction conditions included three equivalents of aryl halides, three equivalents of tert-butyl isocyanide, 5 mol%$PdCl_2$, 0.1 equivalent of DPPP, two equivalents of $CaCl_2$, and four equivalents of NaOtBu in toluene at 145 °C for 8 h, achieving moderate to excellent results [44]. Qian et al. synthesized 2,3-disubstituted quinazolinones through a palladium-catalyzed, three-component oxidative coupling of anthracene amide with isocyanate and aryl boronic acid (Figure 9) [45]. Additionally, Qiu et al. developed a high-yield, one-pot, palladium-catalyzed, three-component reaction of bis-(2-iodoaromatic)-carbodiimide, isocyanide, and an amine. This approach combines nucleophilic attack, isocyanide insertion, and C–N coupling to generate quinazolino[3,2-a] quinazolines and related compounds in high yields (Figure 10) [46].

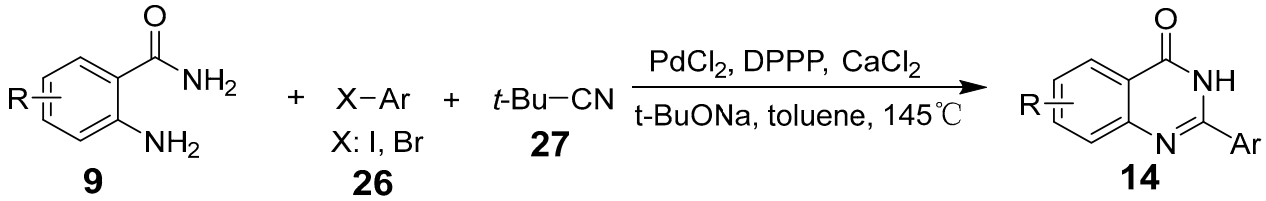


Figure 8. Palladium-catalyzed one-pot synthesis of quinazolin-4(3H)-ones.

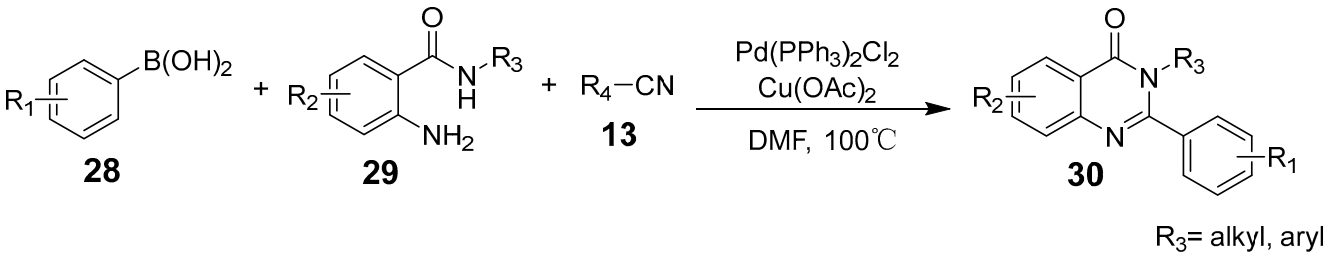


Figure 9. Palladium-catalyzed 2,3-disubstituted quinazolinones.

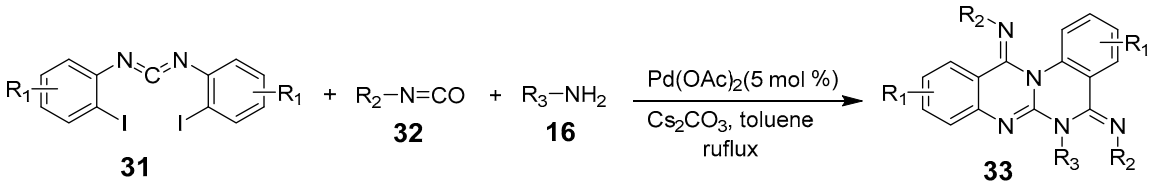


Figure 10. Palladium-catalyzed synthesis of quinazolino[3,2-a]quinazolines.

Further advancements include an efficient palladium-catalyzed cyclization method that synthesizes fused quinazolinone derivatives from 3-arylquinazolinones through mono- and double-alkyne insertions in a one-pot process. This reaction, featuring C–X cleavage, alkyne insertion, 1,4-palladium migration, and C–H annulation, yielded products in 43–80% yields (Figure 11) [47]. Dabiri et al. synthesized novel substituted hydroxyisoindoloquinazolinone compounds through a palladium-catalyzed cross dehydrogenative coupling (CDC) reaction between aryl-quinazolinones and aldehydes, achieving moderate to high yields [48]. In a variation, they replaced benzaldehyde with toluene and used excess tert-butyl hydroperoxide (TBHP) as the oxidant, which significantly improved the yields (Figure 12).

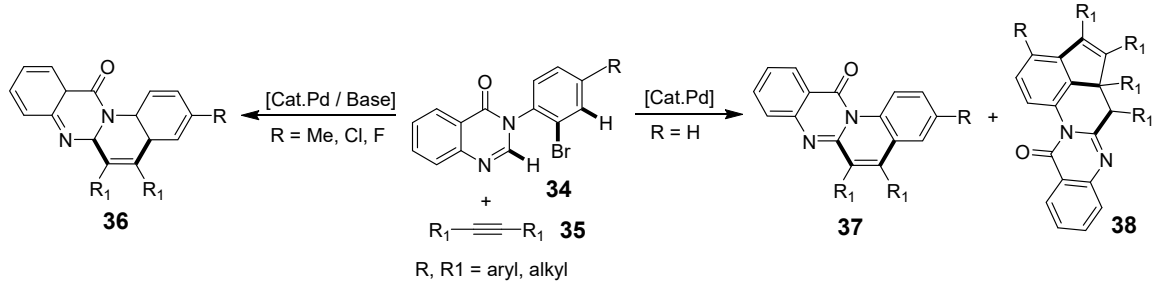


Figure 11. Palladium-catalyzed synthesis of quinazolin-4(3H)-ones with alkyne.

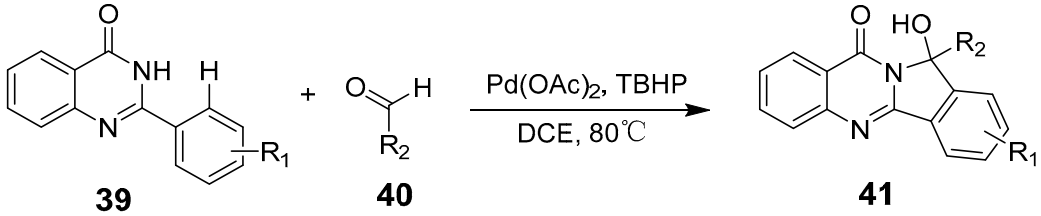


Figure 12. Palladium-catalyzed synthesis of hydroxyisoindolo[1,2-b]quinazolinones.

2.1.3. Zinc-Reduced Synthesis

Zinc was the first metal identified to participate in water-phase Barbier reactions, and it effectively catalyzes reactions such as allylation and benzylation of carbonyl compounds, along with specific alkylation. Additionally, zinc catalyzes carbon–nitrogen double-bond Barbier reactions, including the allylation of imines and α-amino-aldehydes, showing

enhanced activity in aqueous stabilization [49]. In their study, L-M. Wang et al. utilized a novel catalyst, zinc(II) perfluorooctanoate [$Zn(PFO)_2$], in a one-pot, three-component cyclo-condensation reaction, achieving high yields of quinazolinone derivatives through atom-efficient synthesis in an aqueous micellar medium (Figure 13) [50].

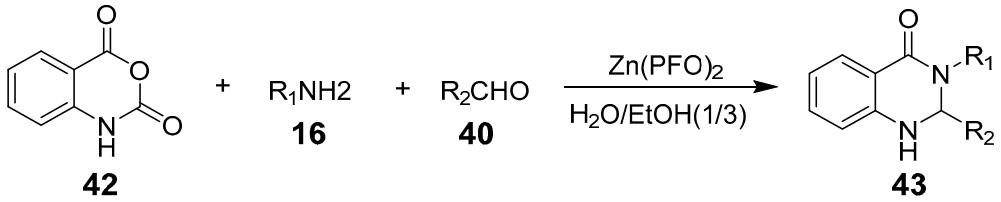


Figure 13. Zinc(II)-catalyzed synthesis of 2,3-disubstituted quinazolin-4(1H)-ones.

Manna et al. identified a radical-mediated pathway for quinazolinones quinazolinone synthesis using redox-active amide ligand-loaded zinc compounds. This method facilitates the deamination of *o*-amino amide/ester derivatives, enabling coupling with the amino group of the nitrile (Figure 14) [51]. Das et al. reported that zinc catalyzes the cyclization of ureido benzoates to produce quinazoline diketones under mild conditions (Figure 15). This approach allows the efficient synthesis of quinazolinone derivatives from various acyclic ureido benzoates containing diverse electron-donating and electron-withdrawing groups. Using low-toxicity, accessible zinc salts such as Lewis acids, their method offers a cost-effective and time-efficient alternative to traditional synthetic strategies [52].

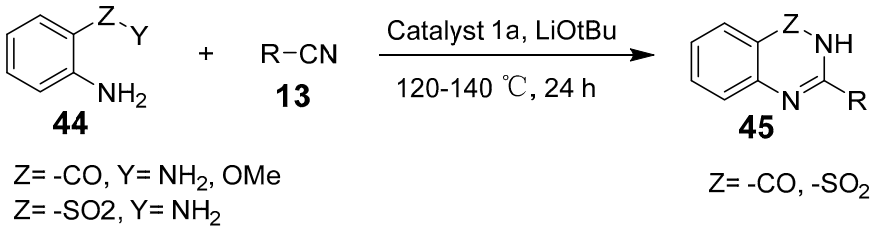


Figure 14. Zinc (II)-stabilized amidyl radical-promoted synthesis of quinazolinones.

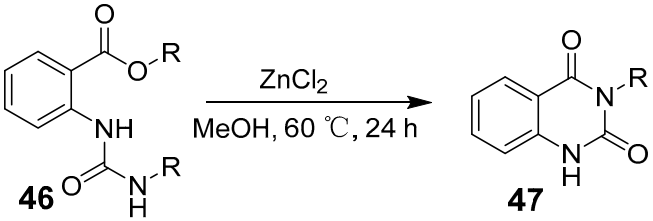


Figure 15. Cyclization of acyclic urea derivatives to quinazolinones.

2.1.4. Iron-Catalyzed Reaction

Iron compounds valued for their abundance and low cost are widely used in organic synthesis and have critical roles in biological systems. In lower oxidation states, iron can act as a nucleophilic reagent, catalyzing a variety of reactions. Iron's potential as a catalyst in drug, material, and functional molecules is extensive, with the field rapidly progressing [53]. Ghouse et al. developed an Fe(II)-catalyzed cascade reaction for cyanoalkyl sulfonylation and cyclization, enabling the synthesis of functionalized sulfonated quino-quinazolidinone alkyl cyanide (Figure 16). This three-component radical transformation achieves high chemo- and regioselectivity without external oxidizing or reducing agents [54].

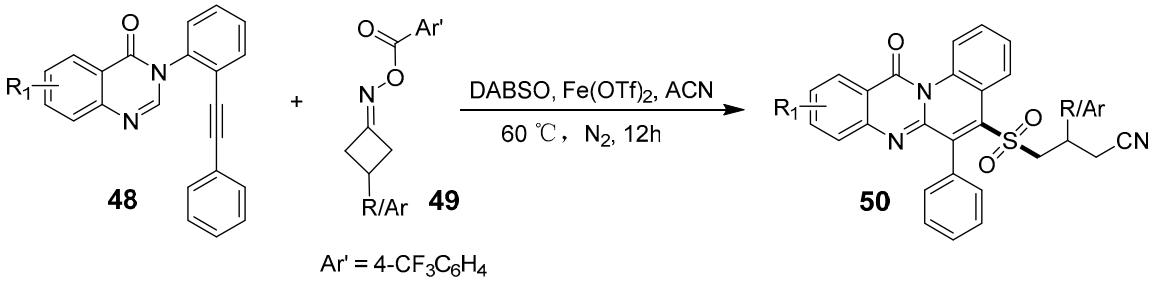


Figure 16. Iron-catalyzed cyclization to access cyanoalkyl sulfonyl quinolino-quinazolinones.

Wu et al. reported an Fe(III)-mediated cascade/decarbonylation cyclization reaction for synthesizing 2-(trifluoromethyl)quinazoline-4(3H)-ones using isatins and trifluoroacetic acid chlorides as starting materials (Figure 17). The reaction forms a biologically significant quinazoline-4(3H)-one derivative through an efficient pathway involving tricyclic amphiphilic intermediates that undergo intramolecular nucleophilic attack and subsequently release 2-(trifluoromethyl)quinazoline-4(3H)-one alongside carbon monoxide [55]. Serva et al. presented an efficient synthesis of 2-substituted quinazolin-4(3H)-ones by reacting isatoic anhydride with various amidoxime derivatives catalyzed by iron(III) chloride [56]. Malviya et al. established a non-stereoselective approach to synthesizing schizocommunin derivatives through an iron-catalyzed oxidative dehydrogenation coupling reaction between two different C(sp^3)-H bonds (Figure 18), producing a broad range of substituted indol-2-ones and quinazolines using air as an eco-friendly oxidant [57].

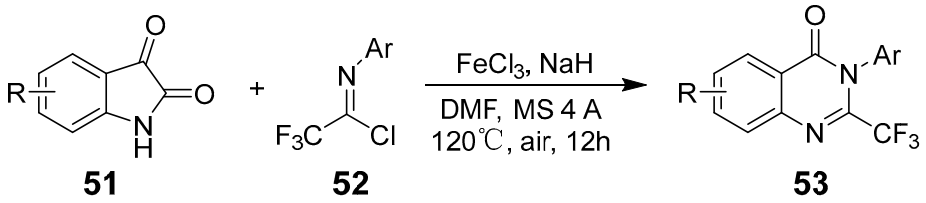


Figure 17. Iron (III)-mediated synthesis of 2-(trifluoromethyl)quinazolinones.

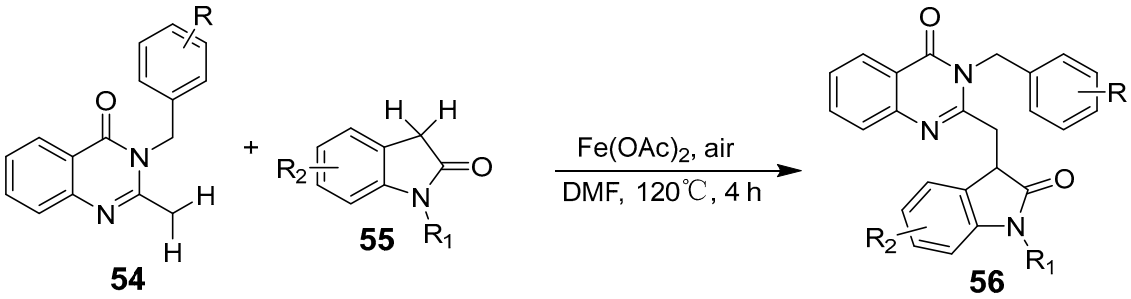


Figure 18. Iron (II)-catalyzed diastereoselective cross-dehydrogenative.

Ding et al. introduced an efficient iron-catalyzed cross-dehydro-coupling of [4+2] cyclized secondary/tertiary anilines with quinazolinones to produce quinoline-spiro-quinazolinones [58]. Using $FeCl_3$ as the catalyst and H_2O_2/O_2 as the oxidant in ethanol at room temperature, this method accommodates a wide range of functional groups. N-methylanilines were incorporated into tetrahydroquinolines, saving methyl and methylene sources for cycloaddition reactions (Figure 19). This environmentally friendly process shows significant promise for applications in the agrochemical and pharmaceutical industries.

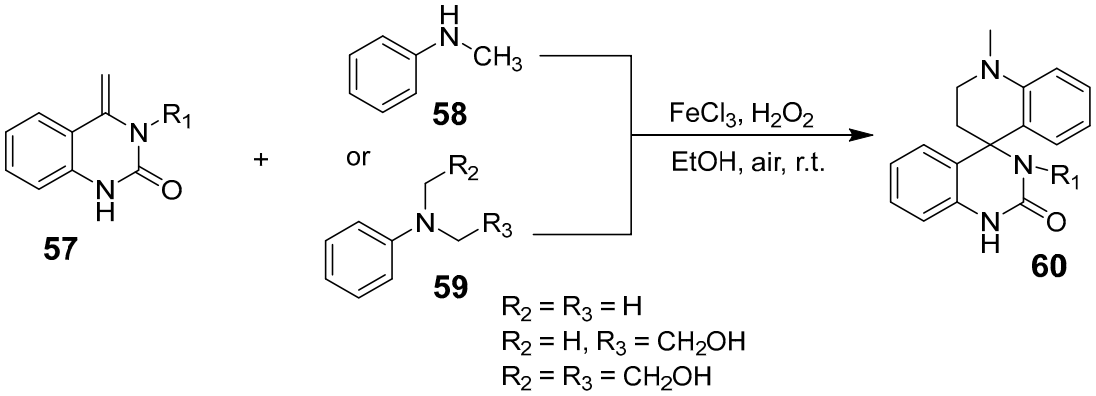


Figure 19. Iron-catalyzed synthesis of quinoline-spiro-quinazolinones.

The Ru(II)-catalyzed C–H activation of quinazolinones combined with an olefinic difunctional merger is a promising approach for the redox-neutral synthesis of dihydroisoquinazolidinone derivatives [59]. This intermolecular reaction proceeds rapidly, yielding products in high quantities without the need for a stoichiometric metal oxidizer. In a similar vein, silver-catalyzed hydroalkoxylation of C2-alkynyl quinazolidinones enables the selective formation of octa-membered N, O-heterocycles via 8-endo cyclization, producing the target compounds with high efficiency [60]. Furthermore, gold-catalyzed selective hydrogenation of alkynyl quinazolinone ether pyrroles, followed by rearrangement and cyclization, successfully synthesizes 1,2- and 2,3-fused quinazolinones [61]. Additionally, Co(III)-catalyzed cyclization of 2-aryl quinazolinones with alkynes demonstrates compatibility with various functional groups, including both electron-donating and electron-withdrawing groups, as well as halides, and exhibits high regioselectivity with asymmetric alkyne substrates [62].

While the metal-catalyzed synthesis of quinazolinones has achieved remarkable results, there are still some areas that need to be improved and optimized. The efficiency and sustainability of the metal-catalyzed synthesis of quinazolinones can be further improved through in-depth study of the reaction mechanism, optimization of the reaction conditions, development of catalysts that can be easily recycled and reused, and promotion of the development of green chemistry.

2.2. Microwave-Assisted Synthesis

Microwave technology, situated in the electromagnetic spectrum between infrared and radio waves, is gaining attention for its ability to rapidly and uniformly heat chemical reaction systems. This process enhances efficiency, reduces energy consumption, and is more environmentally friendly [63]. Fozooni et al. synthesized dihydro-quinazoline derivatives containing oxazolone rings under both microwave irradiation and reflux conditions [64]. They catalyzed a one-pot, three-component reaction using acetic acid, isophthalic anhydride, an aromatic aldehyde, and 4-aminomartinine to produce 2,3-dihydroquinazoline-4(1H)-ones. These derivatives were then combined with aromatic aldehydes, acetic anhydride, and sodium acetate to yield the oxazolone derivative (Figure 20). Notably, microwave-assisted conditions enhanced the compound yield compared to conventional methods.

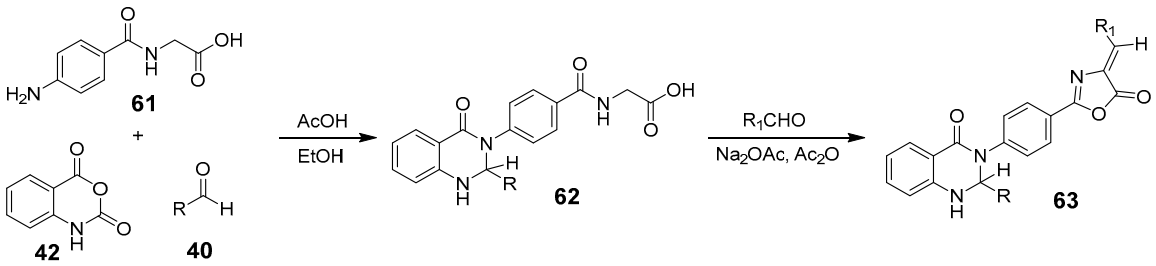


Figure 20. MW-assisted synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

Benzyl alcohol and aminobenzamide derivatives were used to synthesize quinazolinones under microwave conditions (Figure 21). A novel water-assisted method was developed that incorporated sodium chloride as a salting agent and tert-butyl peroxide as an oxidant, demonstrating improved efficiency over traditional methods [65]. The optimal conversion to the desired product occurred at 400 W and 80 °C. J-L Wu et al. successfully synthesized keto-alkyl-substituted polycyclic quinazolinone derivatives via microwave irradiation, employing a radical cascade alkylation/cyclization of inactivated olefins with ketone as the alkylating agent (Figure 22) [66]. This method is transition-metal-free, compatible with a wide range of functional groups, and straightforward in execution.

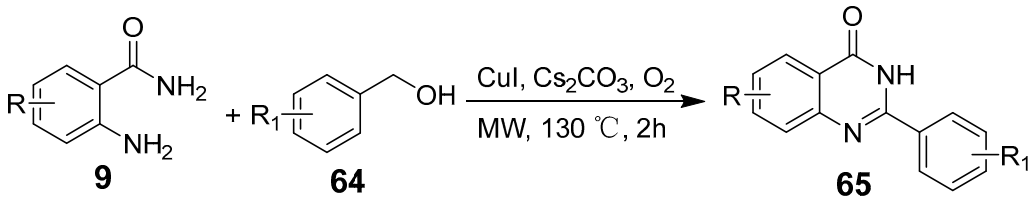


Figure 21. Microwave-assisted synthesis of quinazolin-4(3H)-ones.

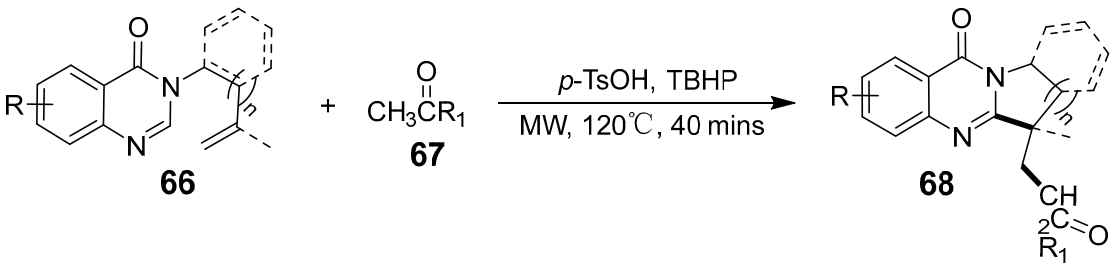


Figure 22. Synthesis of keto alkyl-substituted polycyclic quinazolinones under MW irradiation.

Murhta et al. synthesized diverse, novel thiazole[2,3-b]quinazolinone derivatives using an acid-mediated, one-pot domino reaction under microwave irradiation with 2-amino-substituted thiazoles, substituted benzaldehydes, and cyclic diketones (Figure 23) [67]. The process involved acid-catalyzed condensation of dienones with aromatic aldehydes, forming Michael adduct intermediates, which then reacted with 2-amino-4-arylthiazoles to create aminothiazole derivatives. These underwent deprotonation, followed by intramolecular cyclization and keto-enol tautomerization to yield thiazole[2,3-b]quinazolinones.

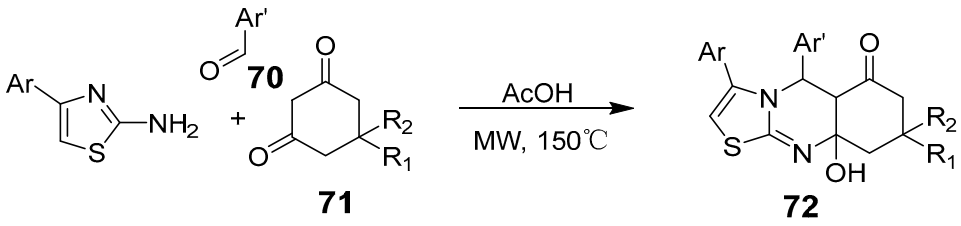


Figure 23. Synthesis of thiazolo[2,3-b] quinazolinones under MW irradiation.

Microwave heating enables uniform heating across the reaction system, accelerating reaction rates and boosting yields. Polar solvents, such as water or alcohol, are particularly effective in microwave catalysis as they absorb microwave energy efficiently, which activates the reactants and increases the reaction speed. The alignment of polar molecules under microwave radiation promotes effective collisions, thus accelerating the reaction. Compared to metal-catalyzed reactions, microwave-assisted synthesis offers a more efficient, eco-friendly alternative, eliminating the need for high temperatures and extended reaction times. However, there are also limitations, including high equipment costs, difficulties in controlling reaction conditions, limited applicability, and safety concerns. To further enhance the reliability and application value of microwave-assisted synthesis methods, measures such as optimizing the design of microwave reactors, developing novel microwave-absorbing materials, strengthening control over reaction conditions, and expanding the scope of application can be taken.

2.3. Metal-Free Catalytic Reaction

The application of metal-free catalysis in organic synthesis is gaining traction due to its unique advantages, establishing it as a highly valued catalytic approach [68]. Metal-free catalysts typically offer excellent recoverability, as they are easier to separate and recycle compared to metal catalysts, reducing both catalyst costs and environmental impact. This approach aligns well with green chemistry and principles, eliminating the need for complex reaction conditions and post-processing steps, and simplifying laboratory operations.

Wang et al. developed an efficient, atom-economical method for synthesizing quinazolinones via an aerobic oxidative cascade ring reaction of transition-metal-free aminonitriles and alcohols [69]. When utilizing atmospheric oxygen as an oxidant under mild conditions, the reaction produces only water as a by-product (Figure 24). With its broad substrate scope and absence of transition metal residues, this method holds promise for pharmaceutical applications. Luo et al. employed tert-butyl hydroperoxide as an oxidant to catalyze the reaction between quinazoline-3-oxides and primary amines, synthesizing quinazolin-4(3H)-ones in high efficiency and adaptability across a wide range of primary amines (Figure 25) [70].

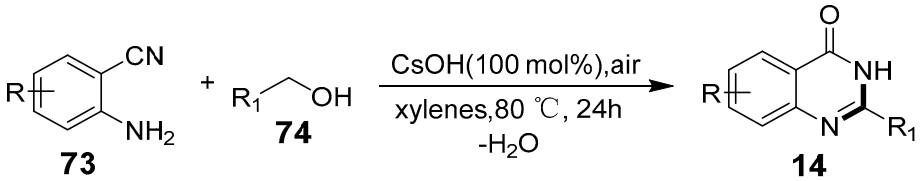


Figure 24. CsOH-mediated synthesis of quinazolin-4(3H)-ones.

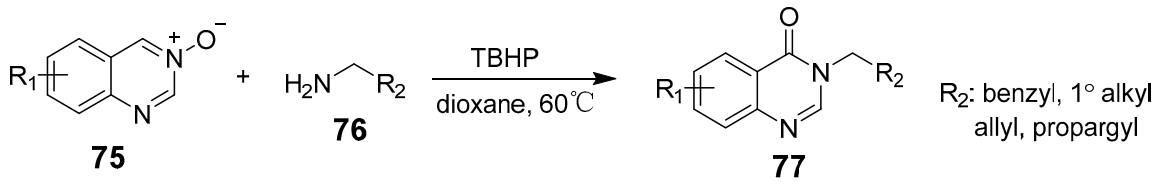


Figure 25. TBHP promoted the synthesis of quinazolinones.

Zhang et al. introduced a novel metal-free catalytic method for the intramolecular oxidative C-H amination of (E)-3-(aryl-amino)-2-styrylquinazoline-4(3H)-ones, enabling the synthesis of 1,2-diarylpyrazolo[5,1-b]quinazoline-9(1H)-ones with high yields [71]. This method accommodates various functional groups and provides a new route for synthesizing 2,3-fused quinazolinones (Figure 26). Additionally, the approach is scalable to gram quantities, making it feasible for larger-scale applications. The reaction between methyl 2-isothiocyanatabenzoate and 1-azido-3-(4-substituted phenyl)propan-2-ones was conducted under heating with triphenylphosphine in a dioxane solvent, yielding tricyclic dihydro-5H-oxazolo[2,3-b]quinazolin-5-ones (Figure 27) [72].

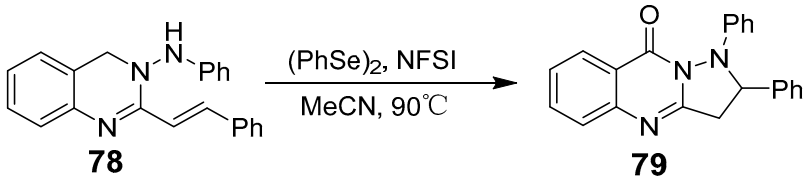


Figure 26. Synthesis of 1,2-diarylpyrazolo[5,1-b]quinazolin-9(1H)-ones.

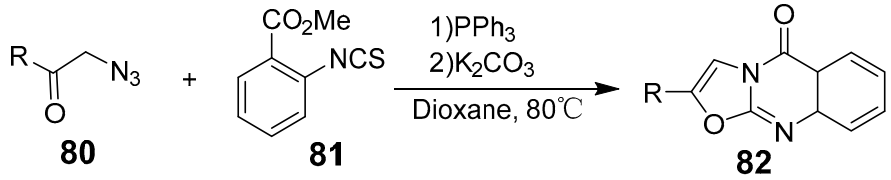


Figure 27. Synthesis of 2-substituted oxazolo-quinazolinones.

Liu et al. further advanced metal-free synthesis with a one-pot method for producing quinazolino[3,4-*α*]quinazolin-13-ones by combining *o*-(methoxycarbonyl)benzenediazonium salts, nitriles, and 2-cyanoanilines (Figure 28). This approach synthesized diverse polycyclic scaffolds through amination, cyclization and amidation steps, forming nitro-carbonitrile intermediates from diazonium salts and nitrile-functionalized intermediates [73]. Noteworthy for its mild conditions, broad substrate compatibility, and simplicity, this method efficiently forms four consecutive C-N bonds, underscoring its potential for further synthetic applications.

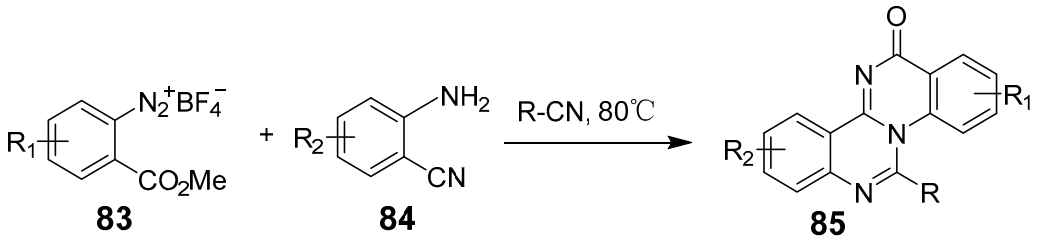


Figure 28. Preparation of quinazolino-quinazolinones via a cascade approach.

Li et al. reported an efficient, selective synthesis of quinazolinones via C–C bond cleavage through a phosphoric acid-catalyzed cyclo-condensation of *β*-ketoester and *o*-

aminobenzamide [74]. This metal- and oxidant-free reaction provides both 2-alkyl- and 2-aryl-substituted quinazolinones with high yields and excellent selectivity, showing broad substrate compatibility (Figure 29). This approach is adaptable to the synthesis of other N-heterocycles, benzimidazole and benzothiazole. A novel synthesis method for spiroiso indolone dihydro-quinazolinones was developed using KHMDS as a base with 2-aminobenzamide and 2-cyanoethyl benzoate as substrates (Figure 30). Mechanistic studies indicate that KHMDS deprotonates the N-H bond, facilitating nucleophilic attack by nitrogen on cyano-benzoate. This forms an imine intermediate, which cyclizes to yield spiroiso indolone dihydro-quinazolinones [75].

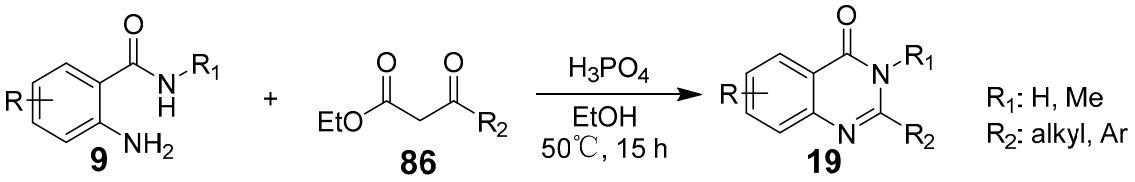


Figure 29. Phosphorous acid-catalyzed synthesis of 2-substituted quinazolin-4(3H)-ones.

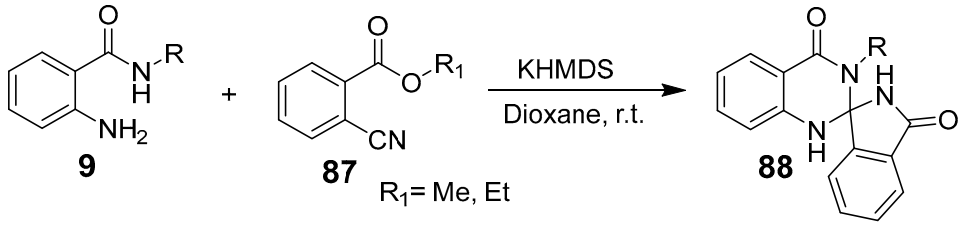


Figure 30. Synthesis of spiroiso indolinone dihydro-quinazolinones.

Jayaram et al. demonstrated a direct, metal-free synthesis of acylated and alkylated quinazolinone derivatives using 2-amino benzamides with I_2/DMSO and epoxides via ring-opening reactions (Figure 31) [76]. Here, I_2 catalyzes an oxidative coupling between 2-aminoformamide and aryl methyl ketones to form 2-aryl quinazolin-4(3H)-ones. This method features high functional group tolerance, substrate selectivity, and significant yield improvements with continuous flow technology, which reduces reaction times.

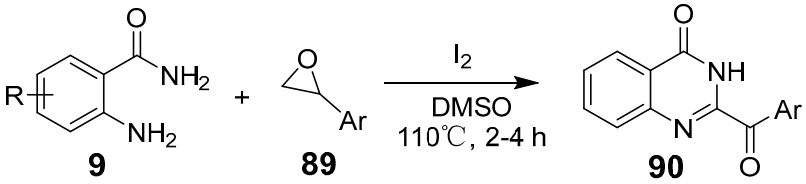


Figure 31. Iodine promoted the synthesis of aza heterocycles.

In catalyst-free conditions with water as a solvent, α-keto acids react with 2-amino benzamides to form quinazolinones (Figure 32). Similarly, 2-amino thiophenol, benzene-1,2-diamine, and 2-aminophenol react to yield benzothiazoles, quinoxalinones, and benzoxazinones, respectively. Purification techniques, such as filtration, ethanol washing, or crystallization, finalize the products [77].

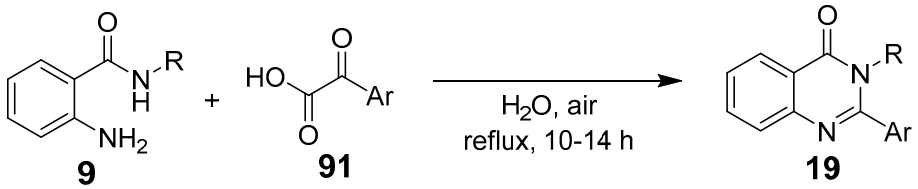


Figure 32. Synthesis of quinazolinones from α-Keto acids.

These metal-free reactions, which employ small organic molecules like amino acids, olefins, and alcohols, rely on hydrogen bonding and electron transfer to produce intermediates, particularly imines from amines and aldehydes. Such reactions offer milder conditions, making them suitable for thermally sensitive substrates and appealing for green chemistry applications. Although metal-free catalysis eliminates the need for precious metal catalysts, boasts simpler operational steps, reduces costs and the complexity of synthesis processes, and minimizes the risk of environmental pollution, the stability and regenerability of organic catalysts may not compare to metal catalysts, necessitating further improvement and optimization.

2.4. Photocatalytic Reaction

Photo-redox chemistry relies on photoexcited catalysts that facilitate single-electron and energy transfer reactions with organic molecules. This energy transfer serves as a key decay pathway for photoexcited states, operating as a catalytic mechanism in photo-redox processes. Xu et al. developed a visible light-catalyzed deamidation of aniline, enabling its incorporation into 1,2,3-benzotriazoles (Figure 33). This reaction involves energy transfer from photoexcited Ir(ppy)3, which excites 1,2,3-benzotriazinone, initiating a denitrogenation rearrangement and producing quinazolinone derivatives [78]. This approach is notable for its mild conditions, simplicity, and versatility, allowing for the synthesis of diverse quinazolinone derivatives. Wang et al. introduced an eco-friendly synthesis of quinazolinones by condensing o-aminobenzamide and aldehydes under visible light using fluorescein as a photocatalyst [79]. This reaction is scalable to gram quantities and holds promise for industrial applications.

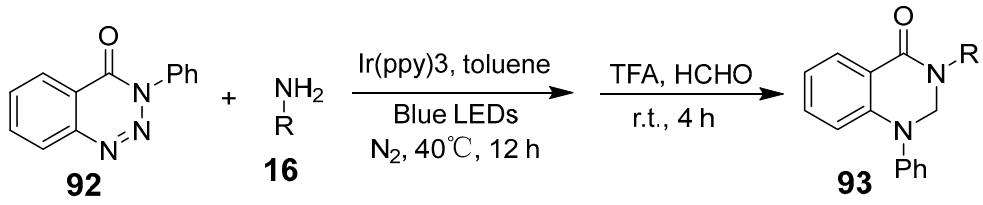


Figure 33. Visible-light photocatalyzed synthesis of quinazolinone.

Anandhan et al. reported a visible-light-driven oxidative cleavage of the C–N bond in N,N-di-phenylaniline, forming secondary amides. They also synthesized quinazolinones from 2-(di-benzylamine)benzamide utilizing $(NH_4)_2S_2O_8$ as an additive and Rose Bengal for the regioselective oxidation of N-benzyl tertiary amines, achieving secondary amides via C–N bond cleavage (Figure 34) [80]. Sun et al. presented a catalyst-free photochemical method for synthesizing polyfluoroalkylated quinazolinone derivatives (Figure 35). This reaction, initiated by a 10 W LED, yields trifle-oro methylated quinazolinones with moderate to high efficiency, up to 83% [81]. Its compatibility with a wide range of functional groups and gentle conditions makes it highly advantageous, utilizing cost-effective, readily available reagents.

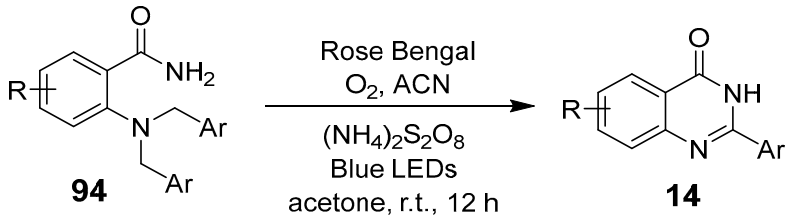


Figure 34. Photoredox-catalyzed nonaqueous oxidative C–N cleavage.

Figure 35. Self-catalyzed photo tandem synthesis of perfluoroalkyl-substituted quinazolinones.

Additionally, under visible light, 3-(2-(ethyl)phenyl)quinazolinones and di-aryl-phosphine oxides were synthesized through a phosphorylation/cyclization reaction using 4CzIPN as a photocatalyst (Figure 36) [82]. Enhanced reaction efficiency was achieved under continuous flow conditions, offering benefits such as metal-free catalysis, broad substrate compatibility, ambient temperature operation, scalability, and the potential use of sunlight as an irradiation source. Gao et al. developed a phosphine radical-triggered cascade addition/cyclization reaction of non-activated olefins, employing TBPB as an oxidant. This mild method produced biologically significant, phosphine-containing quinazolinones via highly reactive phosphine oxides [83].

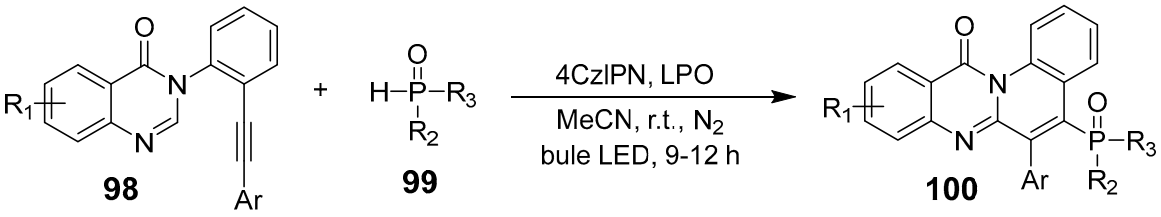


Figure 36. Synthesis of phosphoryl quinolino[2,1-b]quinazolinones.

In photocatalytic reactions, light absorption by catalysts is crucial; the choice of catalyst impacts reaction efficiency based on absorption capacity. Fluorescein, for example, demonstrates high visible light absorption, making it effective for quinazolinone synthesis. Upon excitation, electrons transfer across on the catalyst surface, producing reactive species. These excited catalysts interact quickly with other molecules, generating highly reactive free radicals. Catalysts such as TiO_2 and fluorescein, which are highly active under visible light, outperform metallic catalysts by reducing energy consumption and minimizing side reactions. As eco-friendly alternatives, photocatalytic reactions avoid harsh acids and oxidizing agents, reducing environmental pollution. However, there are also limitations, including limited photocatalyst options, specific light source requirements, sensitivity to reaction conditions, substrate applicability, as well as challenges in product separation and purification.

3. The Antitumor Mechanism of Quinazolinones

Quinazolinones exhibit a wide range of pharmacological activities, including notable anticancer effects against cancers such as breast, lung, and pancreatic malignancies. This

promising activity has driven ongoing research to develop quinazolinone-based anticancer agents (Table 2). This chapter reviews the current studies on the antitumor mechanisms of quinazolinones, aiming to inspire advancements in anticancer drug development.

3.1. Tubulin Polymerization Inhibitor

Quinazolinone can inhibit tubulin polymerization, a process critical for cell division, by preventing the assembly of tubulin into functional microtubules. Given that uncontrolled cell division is a hallmark of cancer, this property of quinazolinones has therapeutic potential for anticancer drug design [84]. Raffa et al. synthesized a novel quinazolin-4(3H)-one derivative, compound (**101**), by reacting 6-chloro-2-methyl-3-(heteroaryl)-4(3H)-quinazolinone with benzaldehyde in glacial acetic acid [85] (Figure 37). At a concentration of 1 μg/mL, compound (**101**) inhibited proliferation in L1210 and K562 leukemia cell lines by more than 50%, with an IC_{50} value of 5.8 μM. For comparison, colchicine displayed an IC_{50} of 3.2 μM. Compound (**101**) also inhibited the growth of MCF-7 and Burkitt lymphoma CA46 cells, with IC_{50} values of 0.34 μM and 1.0 μM, respectively. Additionally, (**101**) induced a G2/M phase arrest in Burkitt lymphoma cells at 10 μM, resulting in a 20% mitotic index, and disrupted microtubule structures in MCF-7 cells at 3.4 μM.

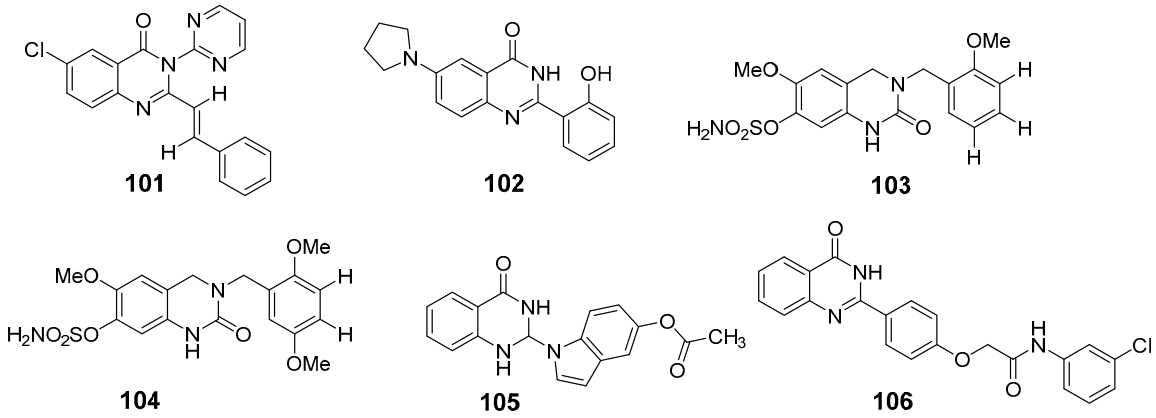


Figure 37. Quinazolinone-based derivatives as a tubulin polymerization inhibitor.

Yang et al. investigated the signaling pathways involved in microtubule interactions and apoptosis using 6-pyrrolidinyl-2-(2-hydroxyphenyl)-4-quinazolinone (compound **102**) in U937 xenograft models (Figure 37). Compound (**102**) showed strong binding to *α*- and *β*-tubulin proteins, inhibiting microtubule polymerization in vitro and in vivo. This interference led to disordered microtubule organization and mitotic arrest via activation of the CDK1/cyclin B complex [86]. Potter et al. developed quinazolinone derivatives as part of a series of 2-methoxyestradiol-based microtubule disruptors. In vitro testing on DU-145 prostate and MDAMB-231 breast cancer cell lines revealed that these compounds had more potent antiproliferative effects than combretastatin. Specifically, the 2′-methoxy derivatives formed hydrogen bonds with tubulin receptors and disrupted microtubules, displaying notable anticancer activity [87]. Compounds (**103**) and (**104**), in particular, effectively inhibited microtubule assembly with an IC_{50} that was 2–3 times lower than that of CA-4, indicating their potential to destabilize microtubule dynamics and arrest the cell cycle (Figure 37).

In a recent study, Shi et al. designed and synthesized a series of 2-substituted 2, 3-dihydroquinazolin-4(1H)-one derivatives (Figure 37) [88]. Mechanistic studies revealed that compound (**105**) significantly inhibited microtubule protein polymerization in vitro, disrupted the cellular microtubule structure, induced G2/M-phase cell cycle arrest, and triggered apoptosis through the upregulation of cleaved PARP-1 and caspase-3. Molec-

ular docking analyses confirmed that compound (**105**) effectively occupied the binding site of microtubule proteins. These findings suggest that 2-dihydroquinazolin-4(1H)-one derivatives with benzene, biphenyl, naphthyl, or indolyl groups at the C2 position could represent a novel class of antitumor agents targeting microtubule protein polymerization.

In a quinazolinone library of 59 compounds, structure (**106**) was identified through virtual ligand screening as an inhibitor of cell-cycle-dependent kinase 4(Cdk4) and microtubules [89]. Compound (**106**) demonstrated Cdk4 inhibition with an IC_{50} of 0.47 μM, and microtubule polymerization inhibition with an IC_{50} of 0.6 μM (Figure 37). Cancer cell cycle analyses confirmed that this dual inhibition blocks cells in the G0/G1 and M phases. These results underscore the potential of virtual screening in designing novel inhibitors that effectively target key phases of the cell division cycle.

Further analysis of the conformational relationships in quinazolinones with enhanced microtubule polymerization inhibition revealed that aryl rings substituted with halogens, nitro groups, or methoxy groups improve microtubule binding. Substitution at the 2-position with alkyl or heteroaryl groups can significantly enhance inhibition. Polar groups at the 6- or 8-position increase water solubility and bioavailability while maintaining potent inhibitory activity. Introducing aryl ring structures and hydrophobic substituents further strengthens the inhibitory effect, and compounds with specific chiral features exhibit even greater activity.

3.2. Initiation of Cell Cycle Arrest

Research increasingly supports the ability of quinazolinones to induce cell cycle arrest, often leading to apoptosis (programmed cell death) and reduced tumor cell viability.

Le et al. designed and synthesized a series of novel 3-methylquinazolinone derivatives to evaluate their antitumor activity against the wild-type epidermal growth factor receptor tyrosine kinase (EGFRwt-TK) [90]. Testing these compounds on human cancer cell lines A549, PC-3, and SMMC-7721 revealed that compound (**107**) induced late apoptosis and caused G2/M phase cell cycle arrest in A549 cells at higher concentrations (Figure 38). Additionally, it inhibited EGFRwt-TK with an IC_{50} of 10 nM. In another study, Ali et al. synthesized a series of 2-thioquinazolin-4(3H)-one conjugates and assessed their efficacy against multiple cancer cell lines [68]. The benzimidazole-quinazolinone derivative (**108**) exhibited notable anticancer activity and targeted RAF kinase. Compound (**108**) effectively induced G2/M phase cell cycle arrest and triggered apoptosis in A-375 melanoma cells, implicating it as a promising therapeutic agent. It also upregulated RecQ deconjugating enzymes, known to play roles in cancer cell survival, highlighting a potential therapeutic target.

Haggag et al. designed quinazolinone derivatives evaluated by the National Cancer Institute (NCI) for cytotoxicity across 60 cancer cell lines and for their inhibitory effect on BLM-deconjugating enzymes. Compound (**109**) demonstrated moderate activity, inhibiting WRN and RECQ1 conjugates and interacting with the ATP binding site of RecQ conjugate enzymes (Figure 38) [91]. In HCT-116 and MDAMB-231 cell lines, compound (**109**) induced G2/M phase arrest and apoptosis, indicating its high anticancer potential, favorable safety profile, and selective inhibition of pan-RecQ-deconjugating enzymes.

Liu et al. investigated the effects of a synthetic quinazolinone analog, 2-(naphthalen-1-yl)-6-pyrrolidino-4-quinazolinone (compound **110**), on glioma cells (Figure 38) [92]. Treatment with compound (**110**) induced cell death associated with a multinuclear phenotype and multipolar spindles, arresting the cell cycle in the G2/M phase and increasing polyploidy. Western blot analysis showed elevated levels of cell cycle proteins B1, Cdk1, and pY15 after treatment, suggesting that compound **110**'s antitumor activity in glioma may be

due to its interference with the G2/M checkpoint, presenting a promising new direction for glioma therapies.

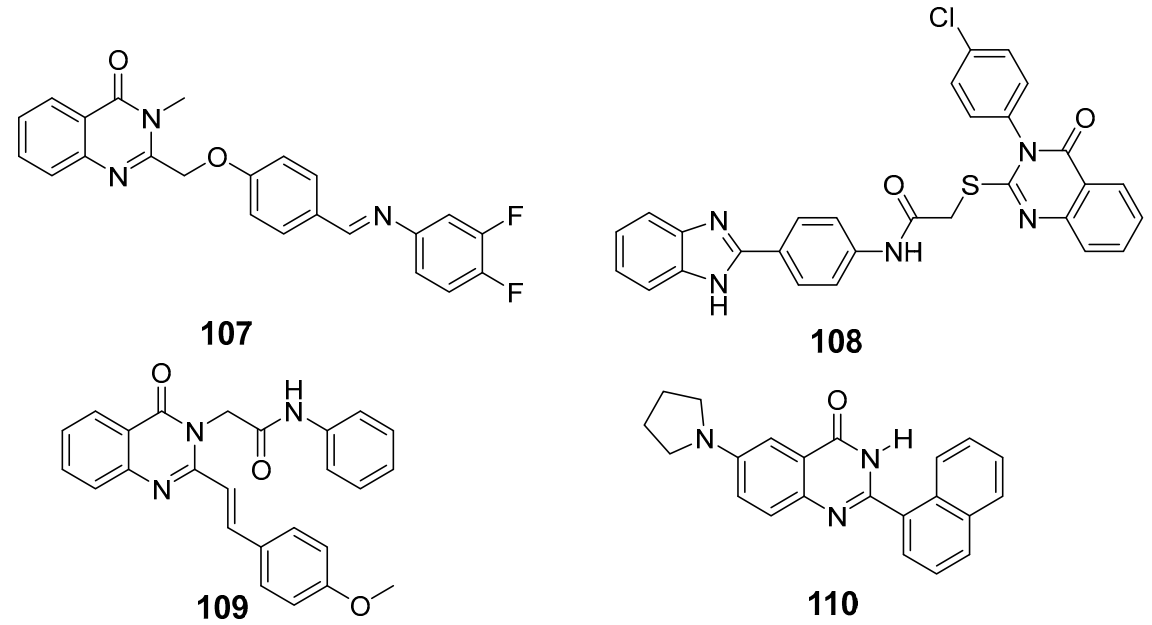


Figure 38. Quinazolinone-based derivatives induce cell cycle blockade.

3.3. Induction of Apoptosis

Apoptosis, a critical biological process governing cell survival and death, is mediated by two primary pathways: exogenous (death receptor-mediated) and endogenous (mitochondrial and pro-apoptotic factor-mediated) [93].

Xie et al. synthesized a series of 4-[(α-l-rhamnosyloxy)benzyl]isothiocyanate (MITC) quinazolinone derivatives and investigated the anticancer properties of the most active compounds [94]. Derivative (**111**) inhibited the growth of several types of cells and induced apoptosis in U251 cells, as indicated by changes in caspase-3 and Bax: Bcl-2 changes (Figure 39). The Bcl-2 ratio of U251 cells showed a notable decline in the G1 phase and a rise in the S and G2 phases, along with reduced levels of cell cycle proteins. These findings suggest that derivative (**111**) holds the potential for glioma prevention and treatment.

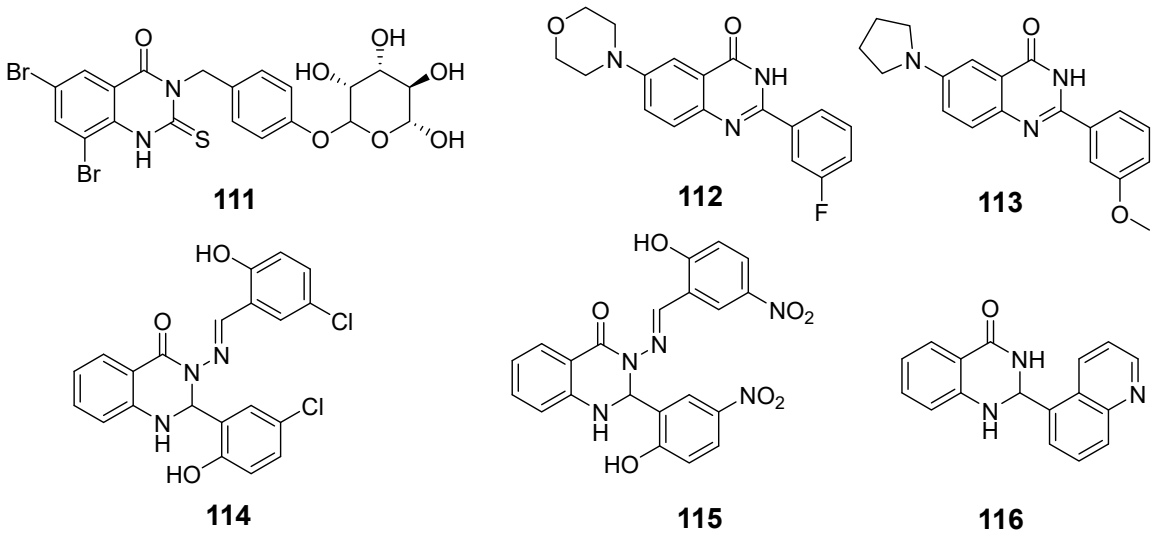


Figure 39. Quinazolinone-based derivatives induce apoptosis.

The 6,7-disubstituted-2-(3-fluorophenyl)quinazolinone derivative (**112**) significantly inhibited oral squamous cell carcinoma (OSCC) cell viability (Figure 39) [95]. This compound induced G2/M-phase cell cycle arrest, upregulated cell cycle protein B, enhanced Ser10 phosphorylation of histone H3, and facilitated PARP cleavage, all indicative of mitotic arrest followed by apoptosis. Furthermore, combining derivative (**112**) with 5-fluorouracil (5-FU) resulted in a synergistic cytotoxic effect on OSCC cells.

In their study, Lu et al. explored the mechanism of action for quinazolinone derivative (**113**) in human oral cancer CAL 27 cells, identifying the roles of intrinsic molecules during treatment (Figure 39) [96]. Exposure to compound (**113**) activated Cdk1, which regulated Bcl-2-mediated mitotic arrest and apoptosis through Ser70 phosphorylation, leading to cell death. This pathway also triggered intracellular Ca^{2+} release and activated markers of endoplasmic reticulum stress. In vivo application of compound (**113**) led to a marked G2/M-phase blockade and significant tumor suppression in nude mice bearing CAL 27 tumors.

Zahedifard et al. discovered that dihydroquinazolin-4(1H)-one derivatives (**114**) and (**115**) significantly inhibited effects on MCF-7 cell viability (Figure 39) [97]. Using the Cellomics high-content screening (HCS) method, they demonstrated that these compounds facilitate the translocation of cytochrome c from the mitochondria to the cytoplasm, triggering the activation of caspase-9 and subsequently caspase-3/7. Additionally, caspase-8 activity was markedly increased in MCF-7 cells treated with these compounds, leading to the inhibition of NF-κB activation. These results suggest that compounds (**114**) and (**115**) may induce apoptosis via both exogenous and endogenous pathways.

Kumar et al. investigated the interdependence of autophagy and apoptosis in human leukemia MOLT-4 cells when treated with a novel quinazolin-4(1H)-one derivative (**116**) (Figure 39) [98]. Their findings showed that compound (**116**) induced a cytochrome c-mediated apoptosis and autophagy mechanism. Compound **116**'s autophagic potential was verified through acridine orange staining, LC3 immunofluorescence, and Western blot analyses, revealing that cytochrome c acts as a negative feedback regulator of autophagy. The study highlighted the importance of quinazolinone derivatives in developing new anticancer drugs.

Quinazolinone compounds have also been shown to block cell cycle progression, especially in the G2/M phase, by inhibiting RecQ dissociation and upregulating cell cycle regulatory proteins such as B1, Cdk1, and pY15, collectively hindering tumor cell proliferation. Additionally, these compounds may promote apoptosis in tumor cells by enhancing the expression of pro-apoptotic proteins, such as caspases, while simultaneously inhibiting anti-apoptotic proteins like Bcl-2 and disrupting cell cycle regulatory proteins. The capacity of quinazolinone compounds to induce apoptosis in tumor cells through endogenous or exogenous pathways remains a key focus in assessing their antitumor potential.

3.4. Acting in the TME

The tumor microenvironment (TME) comprises diverse cell types, including immune cells, cancer-associated fibroblasts (CAFs), endothelial cells (ECs), pericytes, and other additional tissue-resident cells [99]. CAFs are central to the TME, aiding tumor growth and survival by secreting growth factors, cytokines, and stromal components. Within the TME, CAFs can become activated through exposure to inflammatory mediators and alterations in the extracellular matrix (ECM). Soluble activators like TGF-β, IL-1, IL-6, and TNF-α drive chronic inflammation and are pivotal in activating CAFs, which support tumor development and progression [100]. The stiffness of the ECM further promotes gene reactivation in CAFs, initiating pro-fibrotic responses, ECM protein production, angiogenesis, and cancer cell invasion [101].

Dahabiyeh et al. evaluated seven synthetic 2,3-dihydroquinazoline-4(1H)-one analogs for their efficacy against PC3 and DU145 cancer cells [102]. Through MTT assays, scratch healing, adhesion and invasion assays, and LC-MS analyses, they identified that compound (**117**) had notable inhibitory effects on prostate cancer cell adhesion and invasion, achieving an IC_{50} below 15 μM (Figure 40). Metabolic profiling of compound (**117**) revealed impacts on energy production, redox status, amino acid and polyamine metabolism, and choline-phospholipid homeostasis processes essential for cancer cell growth and proliferation.

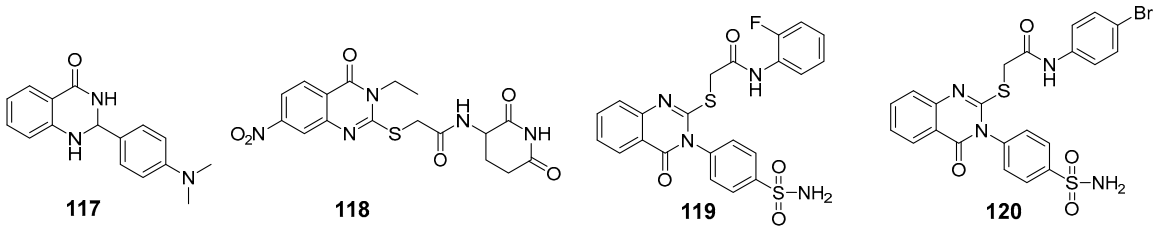


Figure 40. Quinazolinone derivatives with anti-inflammatory capacity.

Abdallah et al. designed quinazolinone derivatives to explore their immunomodulatory potential, incorporating glutarimide fragments to mimic thalidomide's effects [103]. These compounds were tested on breast (MCF-7), colorectal, liver (HepG-2), and prostate (PC3) cancer cells. Compound (**118**), in particular, showed a lower IC_{50} than thalidomide and significantly reduced TNF-α and IL-6 levels while increasing caspase-3 levels sixfold (Figure 40). The anti-inflammatory effects of quinazolinone derivative (**118**) were attributed to its suppression of pro-inflammatory mediators such as nitric oxide synthase-II (NOS-II) and TNF-α.

Askar's team synthesized a series of quinazolinone benzene sulfonamide derivatives, subjecting them to MTT assays [104]. Compounds (**119**) and (**120**) showed growth-inhibitory effects on HepG-2 and MCF-7 cells with IC_{50} values of 6.65 μM and 8.27 μM, respectively (Figure 40). Both compounds also exhibited immune-stimulating effects on CD4+ and CD8+ T lymphocytes, demonstrated by increased spleen and thymus weights, suggesting their potential as promising candidates for further anticancer drug development.

3.5. Angiogenesis Inhibitor

Angiogenesis plays a vital role in cancer progression by providing tumor cells with oxygen and nutrients and facilitating metastasis [105]. This process is regulated by a delicate balance of pro-angiogenic factors, like Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (BFGF), and anti-angiogenic factors, such as Angiogenesis Inhibitor-2 (Ang-2). Disruption of this balance can promote tumor growth and metastasis [106].

Ghorab et al. synthesized the compound 4-(2-(2-hydrazinyl-2-oxoethylthio)-4-oxobenzo[g]quinazolin-3(4H)-yl) benzene sulfonamide (**121**) and assessed its cytotoxicity effects on MCF-7 breast cancer cells and its inhibitory action on VEGFR-2 (Figure 41) [107]. Compound (**121**) showed significant VEGFR-2 inhibition with an IC_{50} of 0.64 μM, alongside increased caspase-3 activity, elevated Bax levels, reduced BCl2 levels, and induced G2/M phase cell cycle arrest. Zahran et al. further developed a sulfon chloropyrazine-containing quinazolinone (**122**) and evaluated it against 60 cancer cell lines [108]. Compound (**122**) demonstrated potent VEGFR-2 inhibition with an IC_{50} of 66 ± 0.002 nM, effectively inhibited cell migration, induced S-phase cell cycle arrest, and promoted apoptosis across various stages, as indicated by the Annexin V-FITC assay. In UO-31 cells, compound (**122**) treatment increased caspase-3 activity and modulated Bax and Bcl-2 expression.

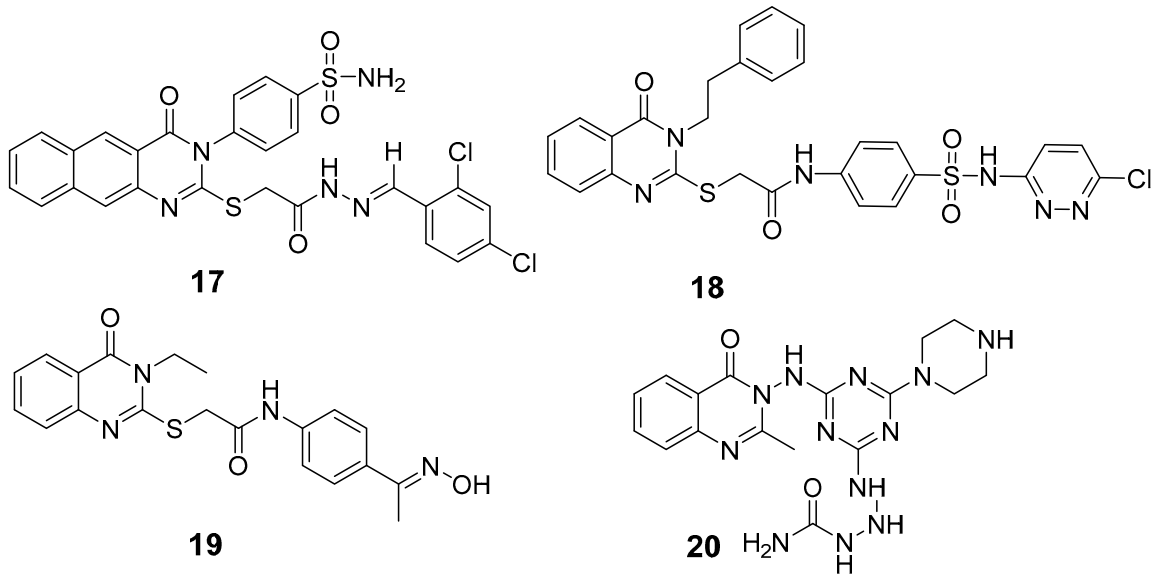


Figure 41. Quinazolin-4-one derivatives inhibit angiogenesis.

In another study, Mahdy et al. synthesized quinazoline-4(3H)-one derivatives as VEGFR-2 inhibitors, testing their efficacy against HepG2, HCT-116, and MCF-7 cancer cells [109]. Compound (**123**) showed IC_{50} values of 3.97 μM, 4.58 μM, and 4.83 μM in these cell lines, respectively, and a VEGFR-2 inhibition IC_{50} of 2.5 μM, comparable to sorafenib (IC_{50} = 2.4 μM) (Figure 41). Compound (**123**) also caused G2/M-phase arrest in HepG-2 cells, and molecular docking revealed a favorable binding affinity to VEGFR-2's active site, with a binding free energy (ΔG) of −59.90 Kcal/mol, comparable to sorafenib's ΔG = −52.20 Kcal/mol. The identification of compound (**123**) represents a promising advancement in this area of research.

Pathak et al. synthesized a series of quinazolinone-substituted 1,3,5-triazine derivatives with notable VEGFR-2 inhibitory activity [110]. Among them, compound (**124**) exhibited significant antitumor effects against MCF-7, HL-60, and HeLa cell lines, with IC_{50} values of 8.69, 8.40, and 6.65 μM, respectively (Figure 41). It also demonstrated anti-angiogenic efficacy comparable to vandetanib. Molecular docking analyses highlighted that compound (**124**) formed hydrogen bonds with VEGFR-2 residues, yielding lower binding energies than vandetanib, underscoring its potential as a promising anti-angiogenic agent.

Research indicates that quinazolinone compounds can play a crucial role in inhibiting angiogenesis, thereby impacting tumor growth and metastasis. Quinazolinone derivatives have shown efficacy in reducing the expression of BFGF, thereby diminishing angiogenic capacity. By inhibiting VEGF production, these compounds disrupt the angiogenic signaling pathway, ultimately affecting the tumor's blood supply. Additionally, quinazolinone derivatives can significantly lower levels of the pro-inflammatory cytokine IL-8, further deducing angiogenesis. Through the downregulation of pro-angiogenic factors like BFGF, VEGF, and IL-8, quinazolinone derivatives effectively slow tumor growth. This anti-angiogenic effect not only limits the development of primary tumors but also holds promise in preventing and treating metastatic tumors. When used in combination therapy, the anti-angiogenic properties of quinazolinone derivatives may enhance the efficacy of other anticancer treatments. By reducing the tumor's blood supply, they can improve the effects of chemotherapy and radiotherapy, while potentially lowering the risk of drug resistance. Future studies will aim to deepen the understanding of these mechanisms, further advancing quinazolinone derivatives in cancer therapy.

3.6. EGFR Inhibitor

The EGFR is a critical transmembrane receptor weighing 170 kDa that regulates essential cellular processes such as proliferation, survival, and migration [111]. EGFR overexpression, due to gene amplification, mutations, or increased ligand expression, contributes to excessive signaling in cancer cells, making EGFR a significant target in cancer treatment [112]. Anti-EGFR monoclonal antibodies (MoAbs) and small-molecule EGFR tyrosine kinase inhibitors (TKIs) are used clinically, though drug resistance and side effects remain challenges [113]. Quinazolinone derivatives, showing promise as EGFR inhibitors with diverse biological activities, are under active investigation to enhance therapeutic specificity and efficacy against cancer.

Zayed et al. synthesized and evaluated a series of fluoro-quinazolinone derivatives for antitumor activity against MCF-7 and MDAMB-231 cells [114]. Among them, derivative (**125**) displayed strong inhibition of MCF-7 cells (IC_{50} = 12.44 ± 5.73 μM) and MDAMBA-231 cells (IC_{50} = 0.43 ± 0.02 μM), outperforming erlotinib (Figure 42). It also showed potent inhibition of EGFR (IC_{50} = 545.38 ± 0.04 nM) and microtubulin (IC_{50} = 6.24 μM). Molecular docking simulations identified key hydrogen bonds between derivate (**125**) and amino acids TyrA224, GlnA111, GlnB247, and LeuB248, contributing to a higher binding energy score (−24.7 kcal/mol) compared to colchicine (−11.1 kcal/mol). These docking results aligned with the compound's experimental efficacy, elucidating its binding interactions with EGFR and microtubulin.

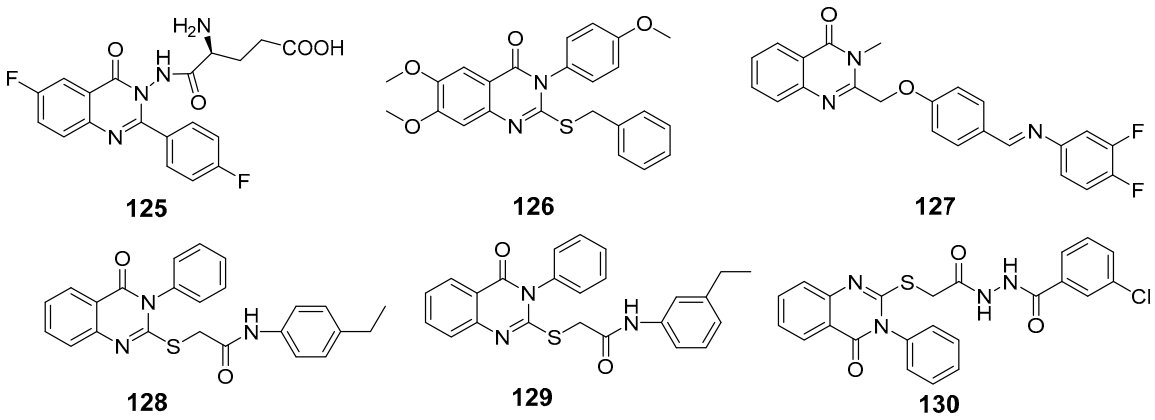


Figure 42. Quinazolinone-based derivatives as EGFR inhibitors.

In a recent study, EI-Gazzar et al. synthesized novel 2-mercapto-quinazolin-4-one analogs and examined their in vitro anticancer activity, dihydrofolate reductase (DHFR) inhibition, and epidermal growth factor tyrosine kinase (EGFR-TK) pathway [115]. Notably, compound (**126**), featuring a 2-benzylthio moiety, exhibited broad-spectrum antitumor activity with high selectivity and safety (Figure 42). While it showed moderate EGFR-TK inhibition (IC_{50} = 13.40 nM), its DHFR inhibition potency was measured at 0.30 μM, somewhat less potent than methotrexate (IC_{50} = 0.08 μM). Compound (**126**) also induced cell cycle arrest and apoptosis in COLO-205 colon cancer cells. Molecular docking studies indicated a binding mode similar to gefitinib, with a π-interaction Lys745, suggesting promising potential as an anticancer agent.

Le et al. synthesized and evaluated new 3-methylquinazolinone derivatives for their in vitro antitumor effects against EGFRwt-TK and three human cancer cell lines: A549, PC-3, and SMMC-7721 [90]. Among these, quinazolin-4-one derivative (**127**) exhibited significant activity, with IC_{50} values of 12.30 ± 4.12 μM for A549, 17.08 ± 3.61 μM FOR PC-3, and 15.68 ± 1.64 μM for SMMC-7721 (Figure 42). Additionally, compound (**127**) induced late apoptosis in A549 cells at high concentrations and caused cell cycle arrest in

the G2/M phase. For EGFRwt-TK inhibition, compound (**127**) showed an IC_{50} of 10 nM. Molecular docking studies revealed that its inhibitory activity likely results from stable hydrogen bonds formed with the residues R817 and T830 in EGFRwt-TK. Furthermore, interactions with the cationic residue K72 were suggested, highlighting a potential molecular interaction mechanism.

Walid M. Ghorab and his team developed and synthesized a series of quinazolinone derivatives based on 2-mercapto-3-phenylquinazolinones and assessed their cytotoxic effects on the HepG-2 hepatocellular carcinoma cell line [116]. Compounds (**128**) and (**129**) demonstrated IC_{50} values of 1.11 μM and 4.28 μM, respectively, surpassing the activity of the reference compound, adriamycin (IC_{50} = 32.02 μM) (Figure 42). The EGFR inhibitory effects of these compounds yielded IC_{50} values of 73.23 μM and 58.26 μM, respectively, which are higher than that of erlotinib (IC_{50} = 9.79 μM). Modeling studies indicated that compound (**128**) achieved higher docking scores within the EGFR active site than erlotinib. Furthermore, γ-irradiation enhanced the cytotoxic effects of compounds (**128**) and (**129**) on tumor cells, allowing for dose reduction and potentially lowering adverse effects.

Fang et al. synthesized a series of novel quinazolinone hydrazide derivatives as EGFR inhibitors [117]. Among these, compound (**130**) showed the most potent antitumor activity, with IC_{50} values of 1.31 μM for MCF-7, 1.89 μM for HepG2, and 2.10 μM for SGC (Figure 42). It also demonstrated high EGFR inhibitory activity, with an IC_{50} of 0.59 μM. Molecular docking studies revealed that compound (**130**) binds effectively to the ATP binding site of EGFR, interacting with VAL702, ASP831, LYS721, and MET769 within the active pocket through robust hydrogen bonds, along with Pi-Sigma and Pi-cation interactions. These results position quinazolinone hydrazide derivatives as promising anticancer agents targeting EGFR.

In a recent study, Kothayer et al. introduced a series of novel quinazolinone-based streptozotocin derivatives, designed and synthesized to triple-target double-mutant $EGFR^{L858R/T790M}$, COX-2, and 15-LOX [118]. Compounds (**131**), (**132**), and (**133**) demonstrated low micromolar IC_{50} values against these targets, displaying selectivity for COX-2 over COX-1 and for $EGFR^{L858R/T790M}$ over wild-type EGFR (Figure 43). Additionally, compounds (**132**) and (**133**) exhibited significantly higher nitric oxide (NO) production compared to celecoxib and indomethacin. Compounds (**131**) and (**133**) showed notable antiproliferative activity against the breast cancer cell line BT-459, with inhibition rates of 67.14% and 70.07%, respectively. Ligand–receptor binding studies further supported their strong binding affinity, highlighting their potential as effective multi-targeting agents.

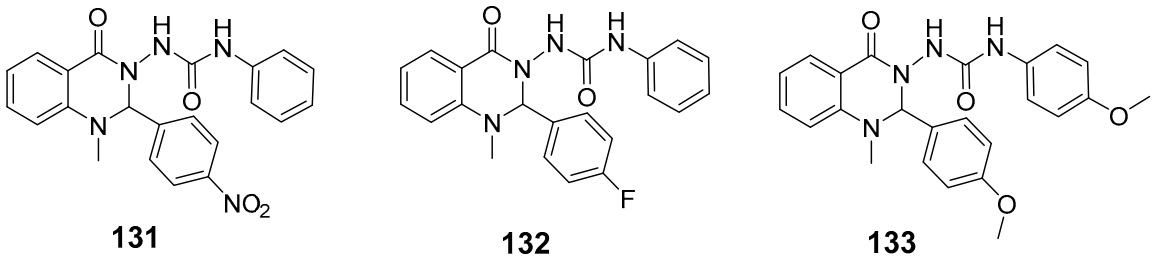


Figure 43. Quinazolinone-based streptozotocin derivatives as EGFR inhibitors.

Quinazolinone derivatives are integral to developing EGFR inhibitors for cancer therapy, with their efficacy shaped by specific structural features and SARs. The quinazolinone core structure, essential for EGFR binding, engages in hydrogen bonding through its 4(3H)-oxo group. The introduction of polar substituents, such as amino, hydroxyl, and amide groups at the 6-position, enhances binding affinity by increasing the hydrogen bonding potential. Hydrophobic substituents like halogens or phenyl groups at the 7-position improve

interactions through hydrophobic effects and π-π stacking (Figure 44). Furthermore, aryl or heteroaryl groups at the 2-position strengthen binding affinity by reinforcing hydrophobic interactions. In conclusion, the exploration of quinazolinone derivatives for EGFR inhibition offers promising opportunities, particularly through structural optimization and strategic addition of specific substituents. Future research should focus not only on refining existing compounds but also on investigating novel quinazolinone derivatives to bolster their role in cancer treatment. Through continued research and technological advances, these compounds show significant potential effective agents in anticancer treatment.

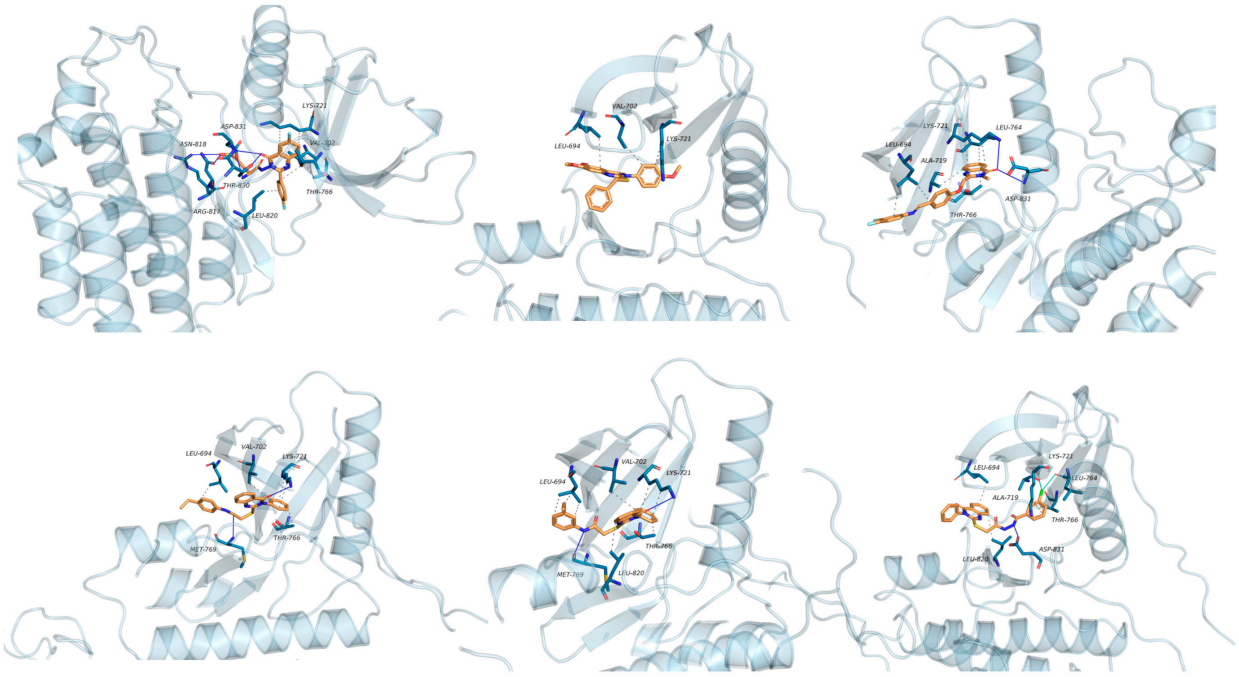


Figure 44. Interaction maps of derivatives 125–130 inside the active site of EGFR (PDB: 1M17).

3.7. PI3K Inhibitors

Phosphatidylinositol-3 kinases (PI3Ks) are a family of lipid kinases that phosphorylate the 3′-OH group of inositol phospholipids, classified into three classes based on their catalytic subunits, which range from 110 to 120 kDa in molecular weight [119]. Dysregulation of PI3K is implicated in various human malignancies [120], including breast [121], colon [122], endometrial [123], and prostate [124]. The PI3K kinase isoforms α, β, δ, and γ are encoded by the PIK3CA, PIK3CB, PIK3CD, and PIK3CG genes, respectively. Mutations or overexpression of these isoforms often contribute to treatment failure in cancer therapy. The PI3K pathway, crucial for cell growth, survival, and proliferation, is thus a promising target for cancer treatment [125]. Understanding PI3K activity in quinazolinones may reveal their potential as therapeutic agents for cancer and other PI3K-related diseases. Future studies should focus on the conformational relationship between quinazolinones and their PI3K inhibition mechanism to develop potent, selective inhibitors with enhanced efficacy.

Wani et al. synthesized a novel quinazolinone chalcone derivative, compound (**134**), which demonstrated significant anticancer properties in both in vitro and in vivo studies, effectively inhibiting cell proliferation across multiple cancer cell lines (Figure 45) [126]. Compound (**134**) induces apoptosis by enhancing V-FITC protein binding, increasing the G0 cell fraction, reducing mitochondrial membrane potential, lowering the Bcl-2/Bax ratio, and generating apoptotic vesicles. Additionally, it significantly impacts the PI3K/Akt/mTOR signaling pathway and regulates cell cycle proteins, including Skp-2, p21, and p27, facilitating the transition of HCT-116 cells into the S phase and G2/M phase. Liang et al. designed

and synthesized quinazolinone derivative (**135**), which exhibited an IC_{50} of 13.11 nM against PI3Kγ kinase [127]. This compound showed cytotoxic effects on leukemia cells across 12 different tumor cell lines. Mechanistic studies revealed that (**135**) exerts antiproliferative activity by inhibiting PI3K-AKT signaling and activating phosphorylated p38 and ERK in both human and murine leukemia cells (Figure 45). This compound holds promise as a novel therapeutic agent for further exploration in cancer therapy.

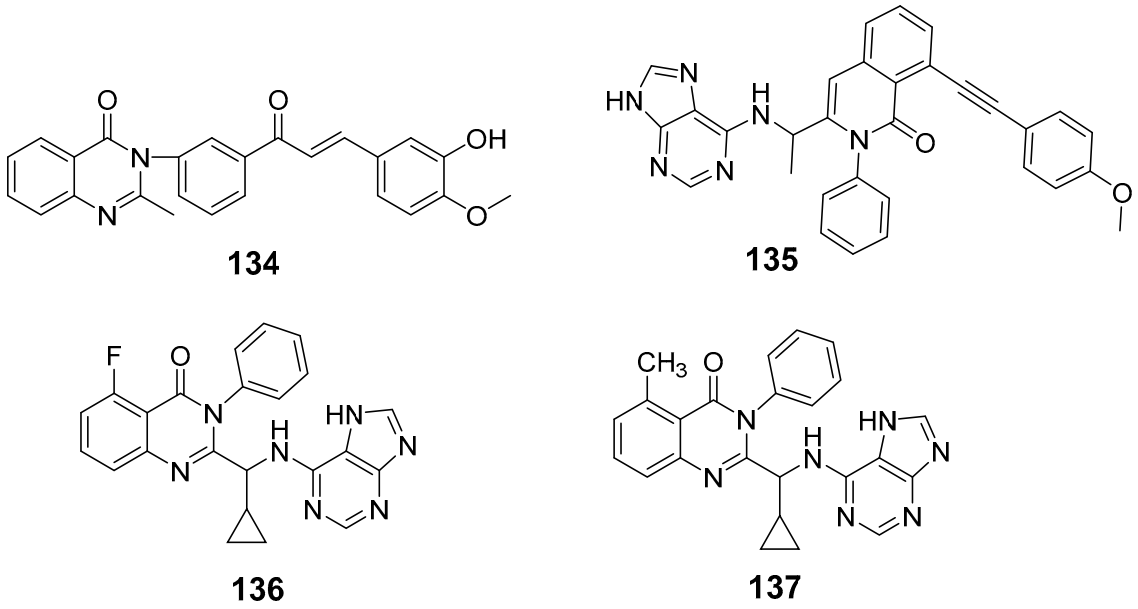


Figure 45. Quinazolinone derivatives as PI3K inhibitors.

Kim et al. synthesized a series of quinazolinone derivatives and evaluated their inhibitory effects on the PI3K enzyme, along with their anticancer activity in hematologic malignant cell lines [128]. Among these derivatives, compounds (**136**) (IC_{50} = 0.39 nM) and (**137**) (IC_{50} = 0.09 nM) exhibited notable enzymatic activity, with compound (**137**) showing approximately fourfold selectivity for PI3Kγ/δ compared to idelalisib, a PI3Kδ inhibitor. (Figure 45) The potency and selectivity toward PI3Kδ were attributed to modifications in the quinazolinone ring and the addition of a hydrophobic cyclopropyl group with fluorine or methyl substituents. Additionally, compounds (**136**) and (**137**) demonstrated targeted effects in cancer cells, promoting apoptosis. The antitumor efficacy of compound (**136**) was validated in xenograft models, where it effectively inhibited the PI3K pathway by reducing levels of p-AKT, p-S6, and p-4EBP1 in tumor tissues. These results suggest the potential of compound (**136**) as a therapeutic agent for treating hematologic malignancies.

Khalifa et al. synthesized 2-(pyridin-4-yl)quinazolin-4(3H)-ones as potential PI3K inhibitors and assessed their antiproliferative properties against HePG-2, MCF-7, and HCT116 cancer cell lines [129]. Among these, compound (**138**) displayed anti-HePG2 activity with an IC_{50} of 60.29 ± 1.06 μM, comparable to adriamycin (IC_{50} = 69.60 ± 1.50 μM). Compounds (**139**) and (**140**) showed superior inhibitory activity against HePG2, with IC_{50} values of 104.94 ± 2.46 μM and 126.40 ± 1.83 μM, respectively (Figure 46). The ADP-Glo assay confirmed the PI3K inhibitory potential, with compounds (**138**) and (**140**) exhibiting IC_{50} values of 31.92 ± 3.26 μM and 74.48 ± 2.91 μM, respectively, close to that of LY294002 (IC_{50} = 57.30 ± 2.02 μM). These compounds also interacted with Lys779 through additional hydrogen bonds. Kinase inhibition evaluation, along with docking studies, indicated favorable binding affinities, supporting the development of new anticancer candidates. Based on these findings, further research should focus on optimizing the structures of these compounds to enhance their efficacy as PI3K inhibitors and anticancer agents.

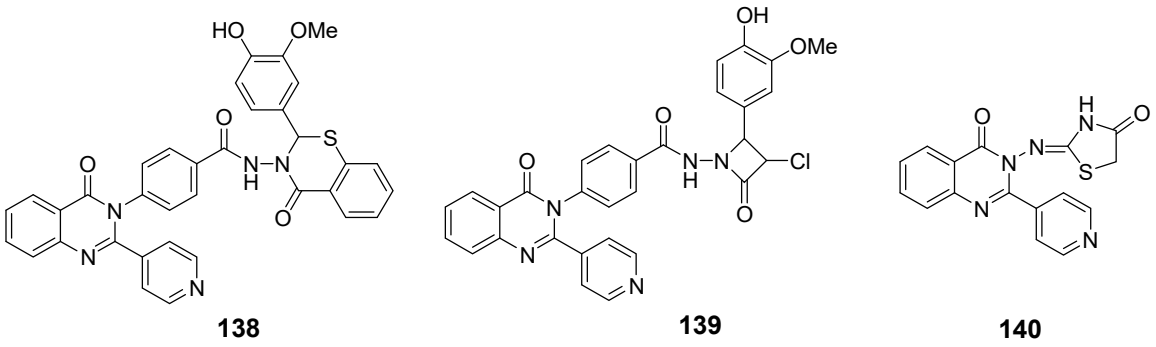


Figure 46. 2-(Pyridin-4-yl)quinazolin-4(3H)-ones as PI3K inhibitors.

According to the molecular docking results, it was found that the binding sites of the quinazolinone structure with PI3K were mainly concentrated in the ATP-binding site of PI3Kα and its surrounding amino acid residues, such as PRO-810, ILE-963, ASP-964, and TYR-867 (Figure 47). The interaction of these binding sites helps to inhibit the activity of PI3K, thus exerting antitumor effects. However, it should be noted that there are multiple isoforms of PI3K with differences in the amino acid residues of different isoforms, so isoform selectivity needs to be considered in drug design to improve the efficacy and safety of drugs.

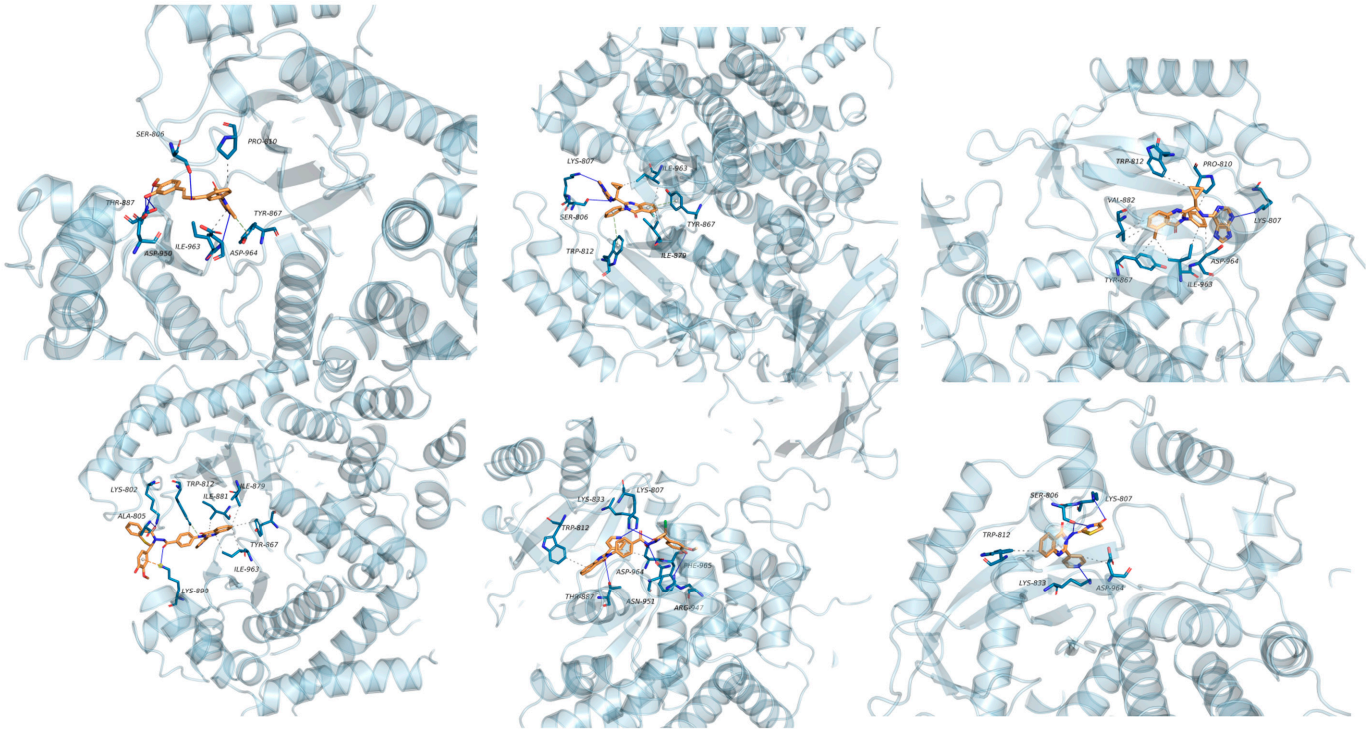


Figure 47. Interaction maps of derivatives 134–139 inside the active site of PI3K (PDB: 1E7U).

Quinazolinones are promising PI3K inhibitors for antitumor drug development, targeting PI3K a key regulator of cell growth, survival, and metabolism whose abnormal activation is linked to cancer. Quinazolinone derivatives interact with PI3Kγ/δ, inhibiting activity by disrupting substrate binding or inducing conformational changes. Additionally, these compounds can target the PI3K signaling pathway, including PI3K, AKT, and mTOR (mammalian target of rapamycin), and inhibit AKT phosphorylation, indirectly inhibiting AKT through PI3K suppression. Quinazolinone derivatives also inhibit mTOR in preclinical studies, potentially by competing for substrate binding or reducing expression.

Despite certain challenges, quinazolinone derivatives hold promise as new PI3K inhibitors in cancer therapy. Future studies should aim to optimize structures, explore combination therapies, and improve clinical monitoring. Addressing these challenges could enhance the therapeutic potential of quinazolinone derivatives in cancer treatment, offering additional options for patients.

Table 2. Overview of potent quinazolinone-based antitumor agents.

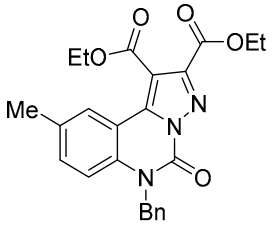
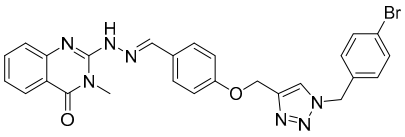
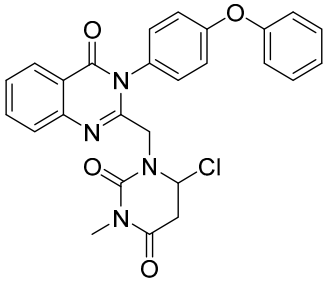
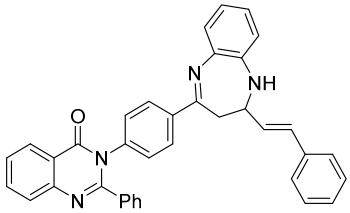
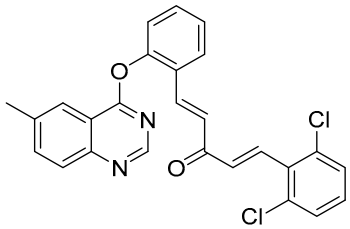
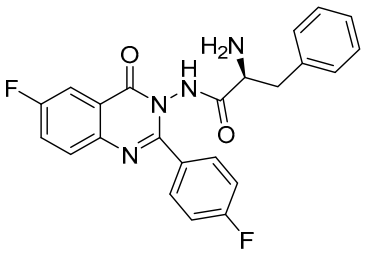
Compound Number	Structure	Activity Tested Against the Cells	Cytotoxicity	Reference
141		A549	IC_{50} = 14.2 μM	[130]
142		(i) EBC-1 (ii) A549 (iii) HT29 (iv) U-87MG	IC_{50} (μM) (i) 8.6 (ii) 64.9 (iii) 65.2 (iv) 24.6	[131]
143		(i) MCF-7 (ii) SW480 (iii) MRC-5	IC_{50} (μM) (i) 21.5 (ii) 1.1 (iii) 105	[132]
144		(i) MCF-7 (ii) HepG-2 (iii) HCT-116	IC_{50} (μM) (i) 19.2 (ii) 24.5 (iii) 14.2	[133]
145		(i) MGC-803 (ii) PC-3 (iii) Bcap-37	IC_{50} (μM) (i) 0.85 (ii) 1.37 (iii) 4.98	[134]
146		(i) MCF-7 (ii) MDA-MB-231	IC_{50} (μM) (i) 0.44 (ii) 24.67	[114]

Table 2. *Cont.*

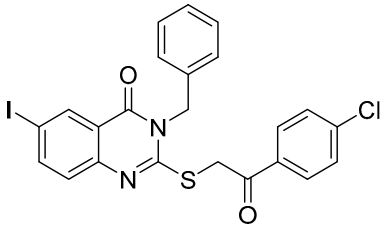
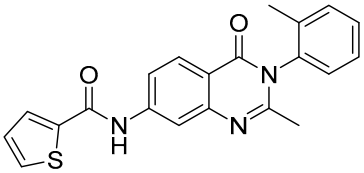
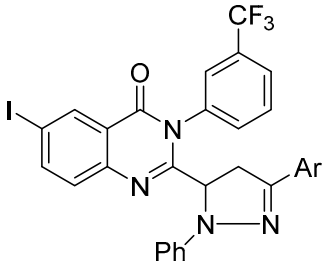
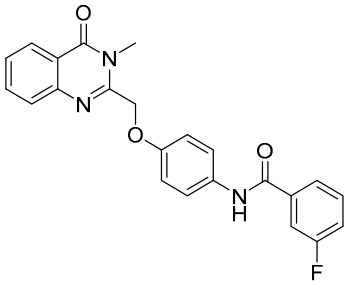
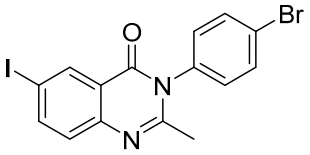
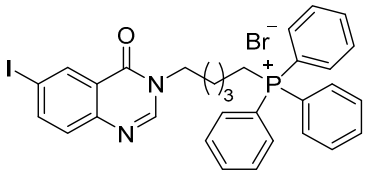
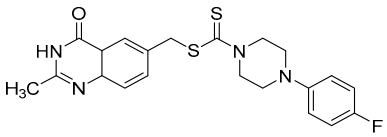
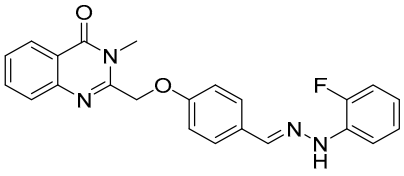
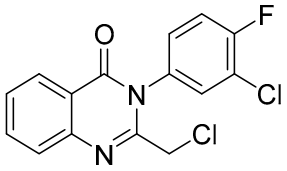
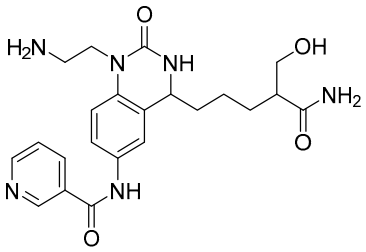
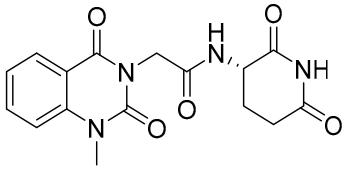
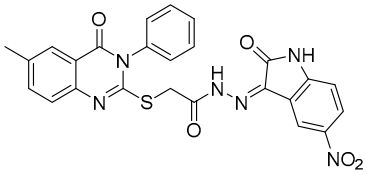
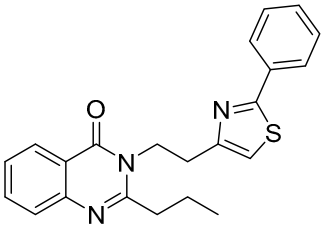
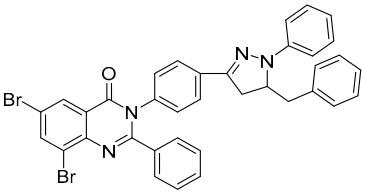
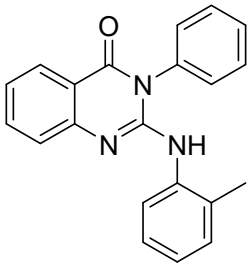
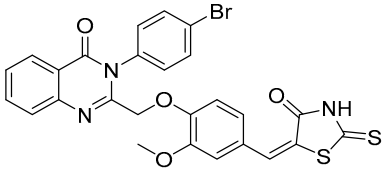
Compound Number	Structure	Activity Tested Against the Cells	Cytotoxicity	Reference
147		(i) MCF-7 (ii) HeLa (iii) HepG-2 (iv) HCT-8	IC_{50} (μM) (i) 3.76 (ii) 4.98 (iii) 4.17 (iv) 9.5	[135]
148		(i) RPMI-8226 (ii) K-562 (iii) HL-60	IC_{50} (μM) (i) 8.0 (ii) 12.8 (iii) 19.2	[136]
149		(i) HepG-2 (ii) MCF-7 (iii) A-549	IC_{50} (μM) (i) 9.08 (ii) 13.85 (iii) 108.08	[137]
150		(i) A431 (ii) A549 (iii) MCF-7 (iv) NCl-H1975	IC_{50} (μM) (i) 3.48 (ii) 2.55 (iii) 0.87 (iv) 6.42	[138]
151		(i) HL-60 (ii) U937	IC_{50} (μM) (i) 22.1 (ii) 31.5	[139]
152		(i) HepG-2 (ii) A549 (iii) MCF-7 (iv) QSG-7701	IC_{50} (μM) (i) 14.52 (ii) 7.51 (iii) 6.56 (iv) 10.61	[140]
153		K562	IC_{50} = 0.5 μM	[141]
154		(i) PC-3 (ii) A549	IC_{50} (μM) (i) 7.73 (ii) 7.36	[142]

Table 2. *Cont.*

Compound Number	Structure	Activity Tested Against the Cells	Cytotoxicity	Reference
155		(i) SW1116 (ii) A549 (iii) MCF-7	IC_{50} (μM) (i) 9.5 (ii) 9.3 (iii) 5.8	[143]
156		(i) HepG-2 (ii) A2780 (iii) MDA-MB-231	IC_{50} (μM) (i) 37.59 (ii) 22.76 (iii) 85.69	[144]
157		(i) HepG-2 (ii) PC-3 (iii) MCF-7 (iv) HCT-116	IC_{50} (μM) (i) 26.71 (ii) 22.11 (iii) 9.25 (iv) 16.09	[145]
158		(i) LOVO (ii) MDA-MB-231	IC_{50} (μM) (i) 9.91 (ii) 10.38	[146]
159		(i) HT-29 (ii) PC-3 (iii) MCF-7	IC_{50} (μM) (i) 12 (ii) 10 (iii) 10	[147]
160		MCF-7	IC_{50} = 1.7 μM	[148]
161		(i) MCF-7 (ii) HCT-116	IC_{50} (μM) (i) 14.7 (ii) 4.87	[149]
162		(i) HL-60 (ii) K-562	IC_{50} (μM) (i) 1.2 (ii) 1.5	[150]

4. Challenges and Future Directions

Despite significant advancements in the research and development of quinazolinone drugs, substantial efforts are still required to transform them into antitumor therapeutics effectively. First, while multiple synthetic methods for quinazolinones exist, their operational complexity, stringent reaction conditions, high production costs, and environmental impact pose significant challenges to large-scale production and practical application. Second, the exploration of synthetic pathways and the evaluation of product activity have mainly been conducted independently, leading to a lack of targeted development of the biological activities of synthesized compounds. The emphasis has predominantly been on methodological innovation rather than practical application. Third, current evidence supporting the antitumor efficacy of quinazolinones remains insufficient.

Therefore, future research on the antitumor activity of quinazolinones should prioritize the following areas. Firstly, the development of more efficient and environmentally friendly synthetic strategies is crucial. Emerging biosynthetic approaches utilizing microorganisms or enzymes offer promising alternatives due to their mild reaction conditions and high selectivity. Secondly, targeted synthesis of quinazolinone compounds with enhanced biological activity should be pursued, integrating synthetic methodologies with product activity assessment. Advances in computational chemistry and machine learning present valuable opportunities for optimizing drug design and synthesis. Finally, focusing on developing target-specific drugs that address key stages of tumor progression may represent a major direction for future antitumor drug development.

5. Conclusions

Quinazolinones are a promising class of compounds in anticancer drug development, with structural characteristics that support their potential to inhibit tumor growth. Recent research has extensively investigated the antitumor mechanisms of quinazolinones, aiming to clarify their actions within cancer cells and evaluate their potential clinical applications. While some mechanisms have been identified, further research is needed to gain a comprehensive understanding of quinazolines' specific actions across various cancer types, thus improving the precision of pharmacological assessments and aiding in optimized drug design. As knowledge of quinazolinone antitumor activity progresses, future research should prioritize clinical trials to confirm their efficacy and safety in cancer patients. These trials will be critical to advancing the clinical application of quinazolinones.

Additionally, exploring combination therapies that integrate quinazolinones with other anticancer agents may enhance therapeutic outcomes. Investigating the synergistic effects of quinazolinones with current chemotherapy or immunotherapy agents represents another promising research direction. Quinazolinones continue to gain attention as potential antitumor agents, with their ability to inhibit cancer cell proliferation and metastasis through multiple mechanisms offering new insights into cancer treatment. As research advances, the prospective application of quinazolinones in cancer therapy appears increasingly promising, and further studies are anticipated to provide additional support and data to inform their clinical use.

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References

1. Asif, M. Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. *Int. J. Med. Chem.* **2014**, *2014*, 395637. [CrossRef]
2. Li, Z.; Zhao, L.; Bian, Y.; Li, Y.; Qu, J.; Song, F. The Antibacterial Activity of Quinazoline and Quinazolinone Hybrids. *Curr. Top. Med. Chem.* **2022**, *22*, 1035–1044. [CrossRef] [PubMed]
3. Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic Approaches, Functionalization and Therapeutic Potential of Quinazoline and Quinazolinone Skeletons: The Advances Continue. *Eur. J. Med. Chem.* **2015**, *90*, 124–169. [CrossRef]
4. Mahdavi, M.; Pedrood, K.; Safavi, M.; Saeedi, M.; Pordeli, M.; Ardestani, S.; Emami, S.; Adib, M.; Foroumadi, A.; Shafiee, A. Synthesis and Anticancer Activity of N-Substituted 2-Arylquinazolinones Bearing Trans-Stilbene Scaffold. *Eur. J. Med. Chem.* **2015**, *95*, 492–499. [CrossRef]
5. Gatadi, S.; Pulivendala, G.; Gour, J.; Malasala, S.; Bujji, S.; Parupalli, R.; Shaikh, M.; Godugu, C.; Nanduri, S. Synthesis and Evaluation of New 4(3H)-Quinazolinone Derivatives as Potential Anticancer Agents. *J. Mol. Struct.* **2020**, *1200*, 127097. [CrossRef]
6. Gatadi, S.; Lakshmi, T.V.; Nanduri, S. 4(3H)-Quinazolinone Derivatives: Promising Antibacterial Drug Leads. *Eur. J. Med. Chem.* **2019**, *170*, 157–172. [CrossRef] [PubMed]
7. Ghodge, B.; Kshirsagar, A.; Navghare, V. Synthesis, Characterization, and Investigation of the Anti-Inflammatory Effect of 2,3-Disubstituted Quinazoline-4(1H)-One. *Beni-Suef Univ. J. Basic Appl. Sci.* **2020**, *9*, 30. [CrossRef]
8. Kumar, N.; Shalini, K.; Drabu, S. Synthesis and Pharmacological Screening of Various New Quinazolin-4-One Derivatives as Anti-Inflammatory and Antifungal Agents. *Biointerface Res. Appl. Chem.* **2019**, *1*, 203–208.
9. Tocco, G.; Esposito, F.; Caboni, P.; Laus, A.; Beutler, J.A.; Wilson, J.A.; Corona, A.; Grice, S.F.J.L.; Tramontano, E. Scaffold Hopping and Optimisation of 3′,4′-Dihydroxyphenyl- Containing Thienopyrimidinones: Synthesis of Quinazolinone Derivatives as Novel Allosteric Inhibitors of HIV-1 Reverse Transcriptase-Associated Ribonuclease H. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 1953–1963. [CrossRef] [PubMed]
10. Gillis, E.P.; Parcella, K.; Bowsher, M.; Cook, J.H.; Iwuagwu, C.; Naidu, B.N.; Patel, M.; Peese, K.; Huang, H.; Valera, L.; et al. Potent Long-Acting Inhibitors Targeting the HIV-1 Capsid Based on a Versatile Quinazolin-4-One Scaffold. *J. Med. Chem.* **2023**, *66*, 1941–1954. [CrossRef]
11. Seifu, G.; Birhan, Y.; Beshay, B.; Hymete, A.; Bekhit, A. Synthesis, Antimalarial, Antileishmanial Evaluation, and Molecular Docking Study of Some 3-Aryl-2-Styryl Substituted-4(3H)-Quinazolinone Derivatives. *BMC Chem.* **2022**, *16*, 107. [CrossRef] [PubMed]
12. Charoensutthivarakul, S.; Lohawittayanan, D.; Kanjanasirirat, P.; Jearawuttanakul, K.; Seemakhan, S.; Chabang, N.; Schlaeppi, P.; Tantivess, V.; Limboonreung, T.; Phanchana, M. Rational Design and Lead Optimisation of Potent Antimalarial Quinazolinediones and Their Cytotoxicity against MCF-7. *Molecules* **2023**, *28*, 2999. [CrossRef] [PubMed]
13. Pathak, S.; Malhotra, V.; Nath, R.; Shanker, K. Synthesis and Antihypertensive Activity of Novel Quinazolin-4(3H)-One Derivatives. *Cent. Nerv. Syst. Agents Med. Chem.* **2014**, *14*, 34–38. [CrossRef]
14. Ibrahim, M.K.; Eissa, I.H.; Abdallah, A.E.; Metwaly, A.M.; Radwan, M.M.; ElSohly, M.A. Design, Synthesis, Molecular Modeling and Anti-Hyperglycemic Evaluation of Novel Quinoxaline Derivatives as Potential PPARγ and SUR Agonists. *Bioorg. Med. Chem* **2017**, *25*, 1496–1513. [CrossRef] [PubMed]
15. Chen, K.; Wang, K.; Kirichian, A.M.; Aowad, A.F.A.; Iyer, L.K.; Adelstein, S.J.; Kassis, A.I. In Silico Design, Synthesis, and Biological Evaluation of Radioiodinated Quinazolinone Derivatives for Alkaline Phosphatase-Mediated Cancer Diagnosis and Therapy. *Mol. Cancer Ther.* **2006**, *5*, 3001–3013. [CrossRef] [PubMed]
16. Guillon, R.; Pagniez, F.; Picot, C.; Hédou, D.; Tonnerre, A.; Chosson, E.; Duflos, M.; Besson, T.; Logé, C.; Pape, P. Discovery of a Novel Broad-Spectrum Antifungal Agent Derived from Albaconazole. *ACS Med. Chem. Lett.* **2013**, *4*, 288–292. [CrossRef]
17. Wahan, S.K.; Sharma, B.; Chawla, P.A. Medicinal Perspective of Quinazolinone Derivatives: Recent Developments and Structure–Activity Relationship Studies. *J. Heterocycl. Chem.* **2022**, *59*, 239–257. [CrossRef]
18. Wheatley, D. Analgesic properties of fluproquazone. *Rheumatology* **1982**, *21*, 98–100. [CrossRef]
19. Smullen, S.; McLaughlin, N.P.; Evans, P. Chemical Synthesis of Febrifugine and Analogues. *Bioorg. Med. Chem* **2018**, *26*, 2199–2220. [CrossRef]

20. Ferrando, C.; Foy, J.; Pratt, C.; Purvis, J. On the Pharmacological Actions of a Diuretic, Fenquizone, with Particular Reference to Its Site of Action. *J. Pharm. Pharmacol.* **1981**, *33*, 219–222. [CrossRef] [PubMed]
21. Gill, J.; Sharma, A. Prospects of Halofuginone as an Antiprotozoal Drug Scaffold. *Drug Discov. Today* **2022**, *27*, 2586–2592. [CrossRef]
22. Purcell, J.W.; Davis, J.; Reddy, M.; Martin, S.; Samayoa, K.; Vo, H.; Thomsen, K.; Bean, P.; Kuo, W.; Ziyad, S.; et al. Activity of the Kinesin Spindle Protein Inhibitor Ispinesib (SB-715992) in Models of Breast Cancer. *Clin. Cancer Res.* **2010**, *16*, 566–576. [CrossRef]
23. Furman, R.R.; Sharman, J.P.; Coutre, S.E.; Cheson, B.D.; Pagel, J.M.; Hillmen, P.; Barrientos, J.C.; Zelenetz, A.D.; Kipps, T.J.; Flinn, I.; et al. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. *N. Engl. J. Med.* **2014**, *370*, 997–1007. [CrossRef]
24. Xiao, H.; Xu, J. Isaindigotone as an Inhibitor of the Lipopolysaccharide-induced Inflammatory Reaction of BV-2 Cells and Corresponding Mechanisms. *Mol. Med. Rep.* **2019**, *19*, 2890–2896. [CrossRef]
25. McGuire, J.; Canestrari, J.; Nagel, G. Characterization of the Effect of AG337, a Novel Lipophilic Thymidylate Synthase Inhibitor, on Human Head and Neck and Human Leukemia Cell Lines. *Int. J. Oncol.* **1999**, *15*, 1245–1250. [CrossRef]
26. Welch, W.M.; Ewing, F.E.; Huang, J.; Menniti, F.S.; Pagnozzi, M.J.; Kelly, K.; Seymour, P.A.; Guanowsky, V.; Guhan, S.; Guinn, M.R.; et al. Atropisomeric Quinazolin-4-One Derivatives are Potent Noncompetitive α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) Receptor Antagonists. *Bioorganic Med. Chem. Lett.* **2001**, *11*, 177–181. [CrossRef]
27. Joshi, B.K.; Gloer, J.B.; Wicklow, D.T.; Dowd, P.F. Sclerotigenin: A New Antiinsectan Benzodiazepine from the Sclerotia of Penicillium Sclerotigenum. *J. Nat. Prod.* **1999**, *62*, 650–652. [CrossRef]
28. Batra, A.; Rigo, R.; Hannouf, M.B.; Cheung, W.Y. Real-World Safety and Efficacy of Raltitrexed in Patients With Metastatic Colorectal Cancer. *Clin. Colorectal Cancer* **2021**, *20*, e75–e81. [CrossRef]
29. Serebruany, V.L.; Sibbing, D.; DiNicolantonio, J.J. Dyspnea and Reversibility of Antiplatelet Agents: Ticagrelor, Elinogrel, Cangrelor, and Beyond. *Cardiology* **2014**, *127*, 20–24. [CrossRef]
30. Welton, A.F.; Dunton, A.W.; McGhee, B. The Pharmacological Profile and Initial Clinical Evaluation of Tiacrilast (Ro 22-3747): A New Antiallergic Agent. *Agents Actions* **1986**, *18*, 313–317. [CrossRef]
31. Zhao, B.; Wang, Y.; Liu, R.; Jia, X.-L.; Hu, N.; An, X.-W.; Zheng, C.-G.; Chen, C.; Sun, H.-T.; Chen, F.; et al. Rutaecarpine Ameliorated High Sucrose-Induced Alzheimer's Disease Like Pathological and Cognitive Impairments in Mice. *Rejuvenation Res.* **2021**, *24*, 181–190. [CrossRef]
32. Tian, K.; Li, J.; Xu, S. Rutaecarpine: A Promising Cardiovascular Protective Alkaloid from Evodia Rutaecarpa (Wu Zhu Yu). *Pharmacol. Res.* **2019**, *141*, 541–550. [CrossRef]
33. Temperini, C.; Cecchi, A.; Scozzafava, A.; Supuran, C.T. Carbonic Anhydrase Inhibitors. Sulfonamide Diuretics Revisited—Old Leads for New Applications? *Org. Biomol. Chem.* **2008**, *6*, 2499. [CrossRef]
34. Haider, K.; Das, S.; Joseph, A.; Yar, M.S. An Appraisal of Anticancer Activity with Structure–Activity Relationship of Quinazoline and Quinazolinone Analogues through EGFR and VEGFR Inhibition: A Review. *Drug Dev. Res.* **2022**, *83*, 859–890. [CrossRef]
35. Rezaeinasab, R.; Jafari, E.; Khodarahmi, G. Quinazolinone-Based Hybrids with Diverse Biological Activities: A Mini-Review. *J. Res. Med. Sci.* **2022**, *27*, 68. [CrossRef]
36. Chemler, S. Copper Catalysis in Organic Synthesis. *Beilstein J. Org. Chem.* **2015**, *11*, 2252–2253. [CrossRef]
37. Deng, C.-L.; Xu, W.; Zhu, X.-R.; Qian, P.-C.; Zhang, X.-G. Copper-Catalyzed Tandem Reaction of 2-Aminobenzamides with Tertiary Amines for the Synthesis of Quinazolinone Derivatives. *Synlett* **2016**, *27*, 2851–2857. [CrossRef]
38. Yu, X.; Gao, L.; Jia, L.; Yamamoto, Y.; Bao, M. Synthesis of Quinazolin-4(3H)-ones via the Reaction of 2-Halobenzamides with Nitriles. *J. Org. Chem.* **2018**, *83*, 10352–10358. [CrossRef] [PubMed]
39. Upadhyaya, K.; Thakur, R.K.; Shukla, S.K.; Tripathi, R.P. One-Pot Copper(I)-Catalyzed Ligand/Base-Free Tandem Cyclooxidative Synthesis of Quinazolinones. *J. Org. Chem.* **2016**, *81*, 5046–5055. [CrossRef]
40. Collet, J.W.; van der Nol, E.A.; Roose, T.R.; Maes, B.U.W.; Ruijter, E.; Orru, R.V.A. Synthesis of Quinazolin-4-Ones by Copper-Catalyzed Isocyanide Insertion. *J. Org. Chem.* **2020**, *85*, 7378–7385. [CrossRef]
41. Feng, Y.; Li, Y.; Cheng, G.; Wang, L.; Cui, X. Copper-Catalyzed Synthesis of 2-Arylquinazolinones from 2-Arylindoles with Amines or Ammoniums. *J. Org. Chem.* **2015**, *80*, 7099–7107. [CrossRef]
42. Liu, M.; Shu, M.; Yao, C.; Yin, G.; Wang, D.; Huang, J. Synthesis of Pyrido-Fused Quinazolinone Derivatives via Copper-Catalyzed Domino Reaction. *Org. Lett.* **2016**, *18*, 824–827. [CrossRef]
43. Bao, Y.; Yan, Y.; Xu, K.; Su, J.; Zha, Z.; Wang, Z. Copper-Catalyzed Radical Methylation/C–H Amination/Oxidation Cascade for the Synthesis of Quinazolinones. *J. Org. Chem.* **2015**, *80*, 4736–4742. [CrossRef]
44. Jiang, X.; Tang, T.; Wang, J.-M.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. Palladium-Catalyzed One-Pot Synthesis of Quinazolinones via Tert-Butyl Isocyanide Insertion. *J. Org. Chem.* **2014**, *79*, 5082–5087. [CrossRef] [PubMed]
45. Qian, C.; Liu, K.; Tao, S.-W.; Zhang, F.-L.; Zhu, Y.-M.; Yang, S.-L. Palladium-Catalyzed Oxidative Three-Component Coupling of Anthranilamides with Isocyanides and Arylboronic Acids: Access to 2,3-Disubstituted Quinazolinones. *J. Org. Chem.* **2018**, *83*, 9201–9209. [CrossRef] [PubMed]

46. Qiu, G.; He, Y.; Wu, J. Preparation of Quinazolino[3,2-a]Quinazolines via a Palladium-Catalyzed Three-Component Reaction of Carbodiimide, Isocyanide, and Amine. *Chem. Commun.* **2012**, *48*, 3836. [CrossRef]
47. Thavaselvan, S.; Arumugam, N.; Almansour, A.I.; Mahalingam, S.M.; Parthasarathy, K. Efficient Synthesis of Highly Fused Quinazolinone Derivatives via Multiple C–C Bond Formations and 1,4-Palladium Migration. *Eur. J. Org. Chem.* **2024**, *27*, e202301023. [CrossRef]
48. Dabiri, M.; Lehi, N.F.; Movahed, S.K.; Khavasi, H.R. Palladium Catalyzed Cross-Dehydrogenative Coupling/AnnulationReaction: A Practical and Efficient Approach toHydroxyisoindolo[1,2-b]Quinazolinone. *Eur. J. Org. Chem.* **2019**, *2019*, 2933–2940. [CrossRef]
49. Wang, D.; Gao, F. Quinazoline Derivatives: Synthesis and Bioactivities. *Chem. Cent. J.* **2013**, *7*, 95. [CrossRef]
50. Wang, L.-M.; Hu, L.; Shao, J.-H.; Yu, J.; Zhang, L. A Novel Catalyst Zinc(II) Perfluorooctanoate [Zn(PFO)2]-Catalyzed Three-Component One-Pot Reaction: Synthesis of Quinazolinone Derivatives in Aqueous Micellar Media. *J. Fluor. Chem.* **2008**, *129*, 1139–1145. [CrossRef]
51. Manna, S.; Sahoo, S.; Rit, A. Synthesis of Quinazolinone Scaffolds via a Zinc(II)-Stabilized Amidyl Radical-Promoted Deaminative Approach. *Chem. Commun.* **2024**, *60*, 7097–7100. [CrossRef] [PubMed]
52. Das, S.; Rawat, N.; Panda, T.K. Lewis Acid Promoted Cyclization of Acyclic Urea Derivatives to Quinazolinediones. *ChemistrySelect* **2020**, *5*, 476–479. [CrossRef]
53. Bauer, I.; Knölker, H.-J. Iron Catalysis in Organic Synthesis. *Chem. Rev.* **2015**, *115*, 3170–3387. [PubMed]
54. Ghouse, A.; Tarun, U.; Maheswari, B.; Akondi, S. An Iron-Catalyzed Three-Component Radical Cascade Cyclization to Access Cyanoalkylsulfonyl Quinolino-Quinazolinones. *Adv. Synth. Catal.* **2024**, *366*, 2456–2460. [CrossRef]
55. Wang, L.-C.; Du, S.; Chen, Z.; Wu, X.-F. FeCl3-Mediated Synthesis of 2-(Trifluoromethyl)Quinazolin-4(3H)-Ones from Isatins and Trifluoroacetimidoyl Chlorides. *Org. Lett.* **2020**, *22*, 5567–5571. [CrossRef] [PubMed]
56. Sarva, J.; Mekala, R.; Akula, R.; Kamaraju, R.; Bannoth, C.; Regati, S. An Efficient Synthesis of 2-Substituted Quinazolin-4(3H)-Ones Catalyzed by Iron(III) Chloride. *Synlett* **2014**, *25*, 821–826. [CrossRef]
57. Malviya, B.K.; Verma, V.P.; Punjabi, P.B.; Kumar, M.; Sharma, S. Iron (II)-Catalyzed Diastereoselective Cross-Dehydrogenetive Coupling of 2-Methyl Quinazolinones with Indolin-2-Ones. *Tetrahedron Lett.* **2021**, *73*, 153141. [CrossRef]
58. Ding, Y.; Kuang, J.; Xiao, X.; Wang, L.; Ma, Y. Environmentally Benign Synthesis of Quinoline–Spiroquinazolinones by Iron-Catalyzed Dehydrogenative [4+2] Cycloaddition of Secondary/Tertiary Anilines and 4-Methylene-Quinazolinones. *J. Org. Chem.* **2021**, *86*, 12257–12266. [CrossRef] [PubMed]
59. Bairy, G.; Das, S.; Begam, H.; Jana, R. Exceedingly Fast, Direct Access to Dihydroisoquinolino[1,2-b]Quinazolinones through a Ruthenium(II)-Catalyzed Redox-Neutral C–H Allylation/Hydroamination Cascade. *Org. Lett.* **2018**, *20*, 7107–7112. [CrossRef]
60. Kong, X.-F.; Guo, X.-Y.; Gu, Z.-Y.; Wei, L.-S.; Liu, L.-L.; Mo, D.-L.; Pan, C.-X.; Su, G.-F. Silver(i)-Catalyzed Selective Hydroalkoxylation of C2-Alkynyl Quinazolinones to Synthesize Quinazolinone-Fused Eight-Membered N,O-Heterocycles. *Org. Chem. Front.* **2020**, *7*, 2055–2062. [CrossRef]
61. Wei, L.-S.; He, G.-X.; Kong, X.-F.; Pan, C.-X.; Mo, D.-L.; Su, G.-F. Gold(III)-Catalyzed Selective Cyclization of Alkynyl Quinazolinone-Tethered Pyrroles: Synthesis of Fused Quinazolinone Scaffolds. *J. Org. Chem.* **2018**, *83*, 6719–6727. [CrossRef]
62. Kumaran, S.; Parthasarathy, K. Cobalt(III)-Catalyzed Synthesis of Fused Quinazolinones by C–H/N–H Annulation of 2-Arylquinazolinones with Alkynes. *Eur. J. Org. Chem.* **2020**, *2020*, 866–869. [CrossRef]
63. Jongcharoenkamol, J.; Naksing, P.; Nimnuan, N.; Singh, T.; Chatwichien, J.; Temkitthawon, P.; Sriwattanawarunyoo, C.; Choommongkol, V.; Meepowpan, P.; Kerdphon, S. Microwave-Assisted Commercial Copper-Catalyzed Aerobic Oxidative Synthesis of AChE Quinazolinone Inhibitors under Solvent Free Conditions. *RSC Adv.* **2023**, *13*, 27657–27662. [CrossRef] [PubMed]
64. Fozooni, S.; Firoozi, H. Microwave-Assisted Synthesis of New Quinazolinone and (Dihydroquinazolinylphenyl)Oxazolone Derivatives. *Chem. Heterocycl. Compd.* **2015**, *51*, 340–345. [CrossRef]
65. Dandia, A.; Sharma, R.; Indora, A.; Parewa, V. Kosmotropes Perturbation and Ambiphilic Dual Activation: Responsible Features for the Construction of C-N Bond towards the Synthesis of Quinazolin-4(3H)-ones in Water. *ChemistrySelect* **2018**, *3*, 8285–8290. [CrossRef]
66. Wu, J.-L.; Yan, M.; Fan, L.-L.; Mou, C.-X.; Yuan, J.-W.; Xiao, Y.-M.; Xing, D.-L. Acid-Catalyzed Radical Tandem Alkylation/Cyclization of Unactivated Alkenes with Ketones: Access to Ketoalkyl-Substituted Quinazolinone Derivatives. *Tetrahedron* **2024**, *162*, 134085. [CrossRef]
67. Mohanta, P.; Pati, H.; Behera, A. The Construction of Fluorophoric Thiazolo-[2,3-b]Quinazolinone Derivatives: A Multicomponent Domino Synthetic Approach. *RSC Adv.* **2020**, *10*, 15354–15359. [CrossRef] [PubMed]
68. Tamatam, R.; Shin, D. Recent Advances in the Transition-Metal-Free Synthesis of Quinazolines. *Molecules* **2023**, *28*, 3227. [CrossRef]
69. Wang, Q.; Lv, M.; Liu, J.; Li, Y.; Xu, Q.; Zhang, X.; Cao, H. Efficient Synthesis of Quinazolinones by Transition-Metal-Free Direct Aerobic Oxidative Cascade Annulation of Alcohols with o-Aminoarylnitriles. *ChemSusChem* **2019**, *12*, 3043–3048. [CrossRef] [PubMed]

70. Luo, J.; Wan, J.; Wu, L.; Yang, L.; Wang, T. Tert-Butyl Hydroperoxide Promoted the Reaction of Quinazoline-3-Oxides with Primary Amines Affording Quinazolin-4(3H)-Ones. *J. Org. Chem.* **2022**, *87*, 9864–9874. [CrossRef]
71. Zhang, Y.; Shao, Y.; Gong, J.; Zhu, J.; Cheng, T.; Chen, J. Selenium-Catalyzed Oxidative C–H Amination of (E)-3-(Arylamino)-2-Styrylquinazolin-4(3H)-Ones: A Metal-Free Synthesis of 1,2-Diarylpyrazolo[5,1-b]Quinazolin-9(1H)-Ones. *J. Org. Chem.* **2019**, *84*, 2798–2807. [CrossRef] [PubMed]
72. Bobiļeva, O.; Loža, E. Synthesis of 2-Substituted Oxazoloquinazolinones. *Chem. Heterocycl. Compd.* **2018**, *54*, 1070–1074. [CrossRef]
73. Ramanathan, M.; Liu, S.-T. Preparation of Quinazolinoquinazolinones via a Cascade Approach. *J. Org. Chem.* **2018**, *83*, 14138–14145. [CrossRef] [PubMed]
74. Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S.-F. Metal- and Oxidant-Free Synthesis of Quinazolinones fromβ-Ketoesters with o-Aminobenzamides via Phosphorous AcidCatalyzed Cyclocondensation and Selective C–C Bond Cleavage. *J. Org. Chem.* **2015**, *80*, 9392–9400. [CrossRef] [PubMed]
75. Venkateshwarlu, R.; Murthy, V.N.; Tadiparthi, K.; Nikumbh, S.P.; Jinkala, R.; Siddaiah, V.; Babu, M.V.M.; Mohan, H.; Raghunadh, A. Base Mediated Spirocyclization of Quinazoline: One-Step Synthesis of Spiro-Isoindolinone Dihydroquinazolinones. *RSC Adv.* **2020**, *10*, 9486–9491. [CrossRef]
76. Mohammed, S.; Vishwakarma, R.A.; Bharate, S.B. Iodine Catalyzed Oxidative Synthesis of Quinazolin-4(3H)-Ones and Pyrazolo[4,3-d]Pyrimidin-7(6H)-Ones via Amination of Sp3 C–H Bond. *J. Org. Chem.* **2015**, *80*, 6915–6921. [CrossRef]
77. Huang, J.; Chen, W.; Liang, J.; Yang, Q.; Fan, Y.; Chen, M.-W.; Peng, Y. α-Keto Acids as Triggers and Partners for the Synthesis of Quinazolinones, Quinoxalinones, Benzooxazinones, and Benzothiazoles in Water. *J. Org. Chem.* **2021**, *86*, 14866–14882. [CrossRef] [PubMed]
78. Li, C.-G.; Xu, G.-Q.; Xu, P.-F. Synthesis of Quinazolinone Derivatives via a Visible-Light Photocatalyzed Denitrogenation Rearrangement Process. *J. Photochem. Photobiol. A* **2018**, *355*, 25–31. [CrossRef]
79. Wang, R.; Liu, S.; Li, L.; Song, A.; Yu, S.; Zhuo, S.; Xing, L.-B. Metal-Free Catalyst for the Visible-Light-Induced Photocatalytic Synthesis of Quinazolinones. *Mol. Catal.* **2021**, *509*, 111668. [CrossRef]
80. Neerathilingam, N.; Reddy, M.; Anandhan, R. Regioselective Synthesis of 2° Amides Using Visible-Light-Induced Photoredox-Catalyzed Nonaqueous Oxidative C–N Cleavage of N,N-Dibenzylanilines. *J. Org. Chem.* **2021**, *86*, 15117–15127. [CrossRef]
81. Sun, B.; Huang, P.; Yan, Z.; Shi, X.; Tang, X.; Yang, J.; Jin, C. Self-Catalyzed Phototandem Perfluoroalkylation/Cyclization of Unactivated Alkenes: Synthesis of Perfluoroalkyl-Substituted Quinazolinones. *Org. Lett.* **2021**, *23*, 1026–1031. [CrossRef] [PubMed]
82. Zeng, F.-L.; Zhang, Z.-Y.; Yin, P.-C.; Cheng, F.-K.; Chen, X.-L.; Qu, L.-B.; Cao, Z.-Y.; Yu, B. Visible-Light-Induced Cascade Cyclization of 3-(2-(Ethynyl)Phenyl)Quinazolinones to Phosphorylated Quinolino[2,1-b]Quinazolinones. *Org. Lett.* **2022**, *24*, 7912–7917. [CrossRef]
83. Gao, S.; Guo, J.; Yang, J.; Wang, X.; Xu, C.; Chen, Y.; Dai, L. Transition-Metal-Free Radical Phosphorylation/Cyclization of Unactivated Alkenes: Access to Phosphine-Containing Quinazolinones. *Tetrahedron* **2023**, *148*, 133669. [CrossRef]
84. Kaur, J.; Kaur, S.; Muskan; Kaur, N.; Kumar, V.; Anand, A. Unveiling the Therapeutic Potential of Quinazolinone Derivatives in Cancer Treatment: A Comprehensive Exploration. *ChemistrySelect* **2024**, *9*, e202401366. [CrossRef]
85. Raffa, D.; Edler, M.C.; Daidone, G.; Maggio, B.; Merickech, M.; Plescia, S.; Schillaci, D.; Bai, R.; Hamel, E. Synthesis, Cytotoxicity, and Inhibitory Effects on Tubulin Polymerization of a New 3-Heterocyclo Substituted 2-Styrylquinazolinones. *Eur. J. Med. Chem.* **2004**, *39*, 299–304. [CrossRef] [PubMed]
86. Yang, J.-S.; Hour, M.-J.; Huang, W.-W.; Lin, K.-L.; Kuo, S.-C.; Chung, J.-G. MJ-29 Inhibits Tubulin Polymerization, Induces Mitotic Arrest, and Triggers Apoptosis via Cyclin-Dependent Kinase 1-Mediated Bcl-2 Phosphorylation in Human Leukemia U937 Cells. *J. Pharmacol. Exp. Ther.* **2010**, *334*, 477–488. [CrossRef] [PubMed]
87. Dohle, W.; Jourdan, F.L.; Menchon, G.; Prota, A.E.; Foster, P.A.; Mannion, P.; Hamel, E.; Thomas, M.P.; Kasprzyk, P.G.; Ferrandis, E.; et al. Quinazolinone-Based Anticancer Agents: Synthesis, Antiproliferative SAR, Antitubulin Activity, and Tubulin Co-Crystal Structure. *J. Med. Chem.* **2018**, *61*, 1031–1044. [CrossRef]
88. Shi, C.; Yang, B.; He, Z.; Yang, J.; Li, L.; Song, J.; Xu, S.; Song, W.; Yang, J. Discovery of Novel 2-Substituted 2, 3-Dihydroquinazolin-4(1H)-One Derivatives as Tubulin Polymerization Inhibitors for Anticancer Therapy: The in Vitro and in Vivo Biological Evaluation. *Eur. J. Med. Chem.* **2024**, *277*, 116766. [CrossRef]
89. Sonawane, V.; Siddique, M.; Jadav, S.; Sinha, B.; Jayaprakash, V.; Chaudhuri, B. Cink4T, a Quinazolinone-Based Dual Inhibitor of Cdk4 and Tubulin Polymerization, Identified via Ligand-Based Virtual Screening, for Efficient Anticancer Therapy. *Eur. J. Med. Chem.* **2019**, *165*, 115–132. [CrossRef] [PubMed]
90. Le, Y.; Gan, Y.; Fu, Y.; Liu, J.; Li, W.; Zou, X.; Zhou, Z.; Wang, Z.; Ouyang, G.; Yan, L. Design, Synthesis and in Vitro Biological Evaluation of Quinazolinone Derivatives as EGFR Inhibitors for Antitumor Treatment. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 555–564. [CrossRef]

91. Haggag, H.S.; Aboukhatwa, S.M.; Nafie, M.S.; Paul, A.; Sharafeldin, N.; Oliver, A.W.; El-Hamamsy, M.H. Design and Synthesis of Quinazolin-4-One Derivatives as Potential Anticancer Agents and Investigation of Their Interaction with RecQ Helicases. *Bioorg. Chem.* **2024**, *144*, 107086. [CrossRef]
92. Liu, W.-T.; Chen, C.; Lu, I.-C.; Kuo, S.-C.; Lee, K.-H.; Chen, T.-L.; Song, T.-S.; Lu, Y.-L.; Gean, P.-W.; Hour, M.-J. MJ-66 Induces Malignant Glioma Cells G2M Phase Arrest and Mitotic Catastrophe through Regulation of Cyclin B1Cdk1 Complex. *Neuropharmacology* **2014**, *86*, 219–227. [CrossRef]
93. Nagata, S.; Tanaka, M. Programmed Cell Death and the Immune System. *Nat. Rev. Immunol.* **2017**, *17*, 333–340. [CrossRef]
94. Xie, J.; Yang, M.-R.; Hu, X.; Hong, Z.-S.; Bai, Y.-Y.; Sheng, J.; Tian, Y.; Shi, C.-Y. Moringa Oleifera Lam. Isothiocyanate Quinazolinone Derivatives Inhibit U251 Glioma Cell Proliferation through Cell Cycle Regulation and Apoptosis Induction. *Int. J. Mol. Sci.* **2023**, *24*, 11376. [CrossRef]
95. Lai, K.-C.; Chia, Y.-T.; Yih, L.-H.; Lu, Y.-L.; Chang, S.-T.; Hong, Z.-X.; Chen, T.-L.; Hour, M.-J. Antitumor Effects of the Novel Quinazolinone Holu-12: Induction of Mitotic Arrest and Apoptosis in Human Oral Squamous Cell Carcinoma CAL27 Cells. *Anticancer Res.* **2021**, *41*, 259–268. [CrossRef]
96. Lu, C.-C.; Yang, J.-S.; Chiang, J.-H.; Hour, M.-J.; Lin, K.-L.; Lee, T.-H.; Chung, J.-G. Cell Death Caused by Quinazolinone HMJ-38 Challenge in Oral Carcinoma CAL 27 Cells: Dissections of Endoplasmic Reticulum Stress, Mitochondrial Dysfunction and Tumor Xenografts. *Biochim. Biophys. Acta Gen. Subj.* **2014**, *1840*, 2310–2320. [CrossRef]
97. Zahedifard, M.; Lafta Faraj, F.; Paydar, M.; Yeng Looi, C.; Hajrezaei, M.; Hasanpourghadi, M.; Kamalidehghan, B.; Abdul Majid, N.; Mohd Ali, H.; Ameen Abdulla, M. Synthesis, Characterization and Apoptotic Activity of Quinazolinone Schiff Base Derivatives toward MCF-7 Cells via Intrinsic and Extrinsic Apoptosis Pathways. *Sci. Rep.* **2015**, *5*, 11544. [CrossRef]
98. Kumar, S.; Guru, S.K.; Pathania, A.S.; Mupparapu, N.; Kumar, A.; Malik, F.; Bharate, S.B.; Naveed Ahmed, Q.; Vishwakarma, R.A.; Bhushan, S. A Novel Quinazolinone Derivative Induces Cytochrome c Interdependent Apoptosis and Autophagy in Human Leukemia MOLT-4 Cells. *Toxicol. Rep.* **2014**, *1*, 1013–1025. [CrossRef]
99. de Visser, K.E.; Joyce, J.A. The Evolving Tumor Microenvironment: From Cancer Initiation to Metastatic Outgrowth. *Cancer Cell* **2023**, *3*, 374–403.
100. Sahai, E.; Astsaturov, I.; Cukierman, E.; DeNardo, D.G.; Egeblad, M.; Evans, R.M.; Fearon, D.; Greten, F.R.; Hingorani, S.R.; Hunter, T.; et al. A Framework for Advancing Our Understanding of Cancer-Associated Fibroblasts. *Nat. Rev. Cancer* **2020**, *20*, 174–186. [CrossRef]
101. Calvo, F.; Ege, N.; Grande-Garcia, A.; Hooper, S.; Jenkins, R.P.; Chaudhry, S.I.; Harrington, K.; Williamson, P.; Moeendarbary, E.; Charras, G.; et al. Mechanotransduction and YAP-Dependent Matrix Remodelling Is Required for the Generation and Maintenance of Cancer-Associated Fibroblasts. *Nat. Cell Biol.* **2013**, *15*, 637–646. [CrossRef]
102. Dahabiyeh, L.A.; Hourani, W.; Darwish, W.; Hudaib, F.; Abu-Irmaileh, B.; Deb, P.K.; Venugopala, K.N.; Mohanlall, V.; Abu-Dahab, R.; Semreen, M.H.; et al. Molecular and Metabolic Alterations of 2,3-Dihydroquinazolin-4(1H)-One Derivatives in Prostate Cancer Cell Lines. *Sci. Rep.* **2022**, *12*, 21599. [CrossRef] [PubMed]
103. Abdallah, A.E.; Eissa, I.H.; Mehany, A.B.M.; Sakr, H.; Atwa, A.; El-Adl, K.; El-Zahabi, M.A. Immunomodulatory Quinazoline-Based Thalidomide Analogs: Design, Synthesis, Apoptosis and Anticancer Evaluations. *J. Mol. Struct.* **2023**, *1281*, 135164. [CrossRef]
104. Ghorab, M.; Alqahtani, A.; Soliman, A.; Askar, A. Antimicrobial, Anticancer and Immunomodulatory Potential of New Quinazolines Bearing Benzenesulfonamide Moiety. *Future Med. Chem.* **2023**, *15*, 275–290. [CrossRef]
105. Șandor, A.; Fizeșan, I.; Ionuț, I.; Marc, G.; Moldovan, C.; Oniga, I.; Pîrnău, A.; Vlase, L.; Petru, A.-E.; Macasoi, I.; et al. Discovery of A Novel Series of Quinazoline–Thiazole Hybrids as Potential Antiproliferative and Anti-Angiogenic Agents. *Biomolecules* **2024**, *14*, 218. [CrossRef]
106. Geindreau, M.; Bruchard, M.; Vegran, F. Role of Cytokines and Chemokines in Angiogenesis in a Tumor Context. *Cancers* **2022**, *14*, 2446. [CrossRef]
107. Ghorab, M.M.; Alsaid, M.S.; Soliman, A.M.; Ragab, F.A. VEGFR-2 Inhibitors and Apoptosis Inducers: Synthesis and Molecular Design of New Benzo[g]Quinazolin Bearing Benzenesulfonamide Moiety. *J. Enzyme Inhib. Med. Chem.* **2017**, *32*, 893–907. [CrossRef]
108. Zahran, S.S.; Ragab, F.A.; El-Gazzar, M.G.; Soliman, A.M.; Mahmoud, W.R.; Ghorab, M.M. Antiproliferative, Antiangiogenic and Apoptotic Effect of New Hybrids of Quinazoline-4(3H)-Ones and Sulfachloropyridazine. *Eur. J. Med. Chem.* **2023**, *245*, 114912. [CrossRef]
109. Mahdy, H.A.; Ibrahim, M.K.; Metwaly, A.M.; Belal, A.; Mehany, A.B.M.; El-Gamal, K.M.A.; El-Sharkawy, A.; Elhendawy, M.A.; Radwan, M.M.; Elsohly, M.A.; et al. Design, Synthesis, Molecular Modeling, in Vivo Studies and Anticancer Evaluation of Quinazolin-4(3H)-One Derivatives as Potential VEGFR-2 Inhibitors and Apoptosis Inducers. *Bioorg. Chem.* **2020**, *94*, 103422. [CrossRef]

110. Pathak, P.; Shukla, P.K.; Kumar, V.; Kumar, A.; Verma, A. Quinazoline Clubbed 1,3,5-Triazine Derivatives as VEGFR2 Kinase Inhibitors: Design, Synthesis, Docking, in Vitro Cytotoxicity and in Ovo Antiangiogenic Activity. *Inflammopharmacology* **2018**, *26*, 1441–1453. [CrossRef]
111. Normanno, N.; Pergameno, M.; Lannaccone, A.; Luca, A. *Mechanisms of Action of EGFR Inhibitors*; Future Medicine Ltd.: London, UK, 2012; pp. 6–17.
112. Martinelli, E.; Ciardiello, D.; Martini, G.; Troiani, T.; Cardone, C.; Vitiello, P.P.; Normanno, N.; Rachiglio, A.M.; Maiello, E.; Latiano, T.; et al. Implementing Anti-Epidermal Growth Factor Receptor (EGFR) Therapy in Metastatic Colorectal Cancer: Challenges and Future Perspectives. *Ann. Oncol.* **2020**, *31*, 30–40. [CrossRef]
113. Alsaid, M.S.; Al-Mishari, A.A.; Soliman, A.M.; Ragab, F.A.; Ghorab, M.M. Discovery of Benzo[g]Quinazolin Benzenesulfonamide Derivatives as Dual EGFR/HER2 Inhibitors. *Eur. J. Med. Chem.* **2017**, *141*, 84–91. [CrossRef]
114. Zayed, M.F.; Rateb, H.S.; Ahmed, S.; Khaled, O.A.; Ibrahim, S.R.M. Quinazolinone-Amino Acid Hybrids as Dual Inhibitors of EGFR Kinase and Tubulin Polymerization. *Molecules* **2018**, *23*, 1699. [CrossRef]
115. El-Gazzar, Y.I.; Ghaiad, H.R.; Kerdawy, A.M.E.; George, R.F.; Georgey, H.H.; Youssef, K.M.; El-Subbagh, H.I. New Quinazolinone-based Derivatives as DHFR/EGFR-TK Inhibitors: Synthesis, Molecular Modeling Simulations, and Anticancer Activity. *Arch. Pharm.* **2023**, *356*, e2200417. [CrossRef]
116. Ghorab, W.M.; El-Sebaey, S.A.; Ghorab, M.M. Design, Synthesis and Molecular Modeling Study of Certain EGFR Inhibitors with a Quinazolinone Scaffold as Anti-Hepatocellular Carcinoma and Radio-Sensitizers. *Bioorg. Chem.* **2023**, *131*, 106310. [CrossRef] [PubMed]
117. Fang, Z.; Zhang, Y.; Chen, C.; Zheng, Q.; Lv, P.; Ni, L.; Sun, J.; Wu, Y. Design, Synthesis and Molecular Docking of Novel Quinazolinone Hydrazide Derivatives as EGFR Inhibitors. *Chem. Biodivers.* **2022**, *19*, e202200189. [CrossRef]
118. Kothayer, H.; Rezq, S.; Abdelkhalek, A.S.; Romero, D.G.; Elbaramawi, S.S. Triple Targeting of Mutant EGFR-L858R/T790M, COX-2, and 15-LOX: Design and Synthesis of Novel Quinazolinone Tethered Phenyl Urea Derivatives for Anti-Inflammatory and Anticancer Evaluation. *J. Enzyme Inhib. Med. Chem.* **2023**, *38*, 2199166. [CrossRef]
119. Maffucci, T.; Falasca, M. Inositol Polyphosphate-Based Compounds as Inhibitors of Phosphoinositide 3-Kinase-Dependent Signaling. *Int. J. Mol. Sci.* **2020**, *21*, 7198. [CrossRef] [PubMed]
120. Goncalves, M.D.; Hopkins, B.D.; Cantley, L.C. Phosphatidylinositol 3-Kinase, Growth Disorders, and Cancer. *N. Engl. J. Med.* **2018**, *379*, 2052–2062. [CrossRef]
121. Verret, B.; Cortes, J.; Bachelot, T.; Andre, F.; Arnedos, M. Efficacy of PI3K Inhibitors in Advanced Breast Cancer. *Ann. Oncol.* **2019**, *30*, x12–x20. [CrossRef]
122. Mangiapane, L.; Nicotra, A.; Turdo, A.; Gaggianesi, M.; Bianca, P.; Franco, S.; Sardina, D.; Veschi, V.; Signore, M.; Beyes, S.; et al. PI3K-Driven HER2 Expression Is a Potential Therapeutic Target in Colorectal Cancer Stem Cells. *Gut* **2022**, *71*, 119–128. [CrossRef] [PubMed]
123. Weigelt, B.; Warne, P.H.; Lambros, M.B.; Reis-Filho, J.S.; Downward, J. PI3K Pathway Dependencies in Endometrioid Endometrial Cancer Cell Lines. *Clin. Cancer Res.* **2013**, *19*, 3533–3544. [CrossRef]
124. Wu, Z.; Ni, J.; Zhang, H.; Zhang, Y.; Lv, C.; Wang, Y.; Wang, K.; Peng, B. MLC1 Overexpression Inhibits Tumor Progression through PI3K/AKT Signal Pathway in Prostate Cancer. *Adv. Biol.* **2024**, *8*, 2300060. [CrossRef]
125. Asati, V.; Bharti, S.; Anant, A.; Mahapatra, D. Recent Advances in PI3 Kinase Inhibitors: Anticancer Activities and Structure-Activity Relationships. *Mini-Rev. Med. Chem.* **2022**, *22*, 2146–2165. [CrossRef]
126. Wani, Z.A.; Guru, S.K.; Rao, A.V.S.; Sharma, S.; Mahajan, G.; Behl, A.; Kumar, A.; Sharma, P.R.; Kamal, A.; Bhushan, S.; et al. A Novel Quinazolinone Chalcone Derivative Induces Mitochondrial Dependent Apoptosis and Inhibits PI3K/Akt/mTOR Signaling Pathway in Human Colon Cancer HCT-116 Cells. *Food Chem. Toxicol.* **2016**, *87*, 1–11. [CrossRef]
127. Liang, Y.; Zheng, Y.; Yang, J.; Ke, J.; Cheng, K. Design, Synthesis and Bioactivity Evaluation of a Series of Quinazolinone Derivatives as Potent PI3Kγ Antagonist. *Bioorg. Med. Chem.* **2023**, *84*, 117261. [CrossRef] [PubMed]
128. Kim, Y.S.; Cheon, M.G.; Boggu, P.R.; Koh, S.Y.; Park, G.M.; Kim, G.; Park, S.H.; Park, S.L.; Lee, C.W.; Kim, J.W.; et al. Synthesis and Biological Evaluation of Novel Purinyl Quinazolinone Derivatives as PI3Kδ-Specific Inhibitors for the Treatment of Hematologic Malignancies. *Bioorg. Med. Chem.* **2021**, *45*, 116312. [CrossRef]
129. Zeid, I.F.; Mohamed, N.A.; Khalifa, N.M.; Kassem, E.M.; Nossier, E.S.; Salman, A.A.; Mahmoud, K.; Al-Omar, M.A. PI3K Inhibitors of Novel Hydrazide Analogues Linked 2-Pyridinyl Quinazolone Scaffold as Anticancer Agents. *J. Chem.* **2019**, *2019*, 1–12. [CrossRef]
130. Zheng, D.; Yang, C.; Li, X.; Liu, D.; Wang, Y.; Wang, X.; Zhang, X.; Tan, Y.; Zhang, Y.; Li, Y.; et al. Design, Synthesis, Antitumour Evaluation, and In Silico Studies of Pyrazolo-[1,5-c]Quinazolinone Derivatives Targeting Potential Cyclin-Dependent Kinases. *Molecules* **2023**, *28*, 6606. [CrossRef]
131. Mortazavi, M.; Divar, M.; Damghani, T.; Moosavi, F.; Saso, L.; Pirhadi, S.; Khoshneviszadeh, M.; Edraki, N.; Firuzi, O. Study of the Anticancer Effect of New Quinazolinone Hydrazine Derivatives as Receptor Tyrosine Kinase Inhibitors. *Fron. Chem.* **2022**, *10*, 969559. [CrossRef] [PubMed]

132. Ataollahi, E.; Behrouz, M.; Mardaneh, P.; Emami, M.; Zare, S.; Zafarian, H.; Khabnadideh, S.; Emami, L. Novel Quinazolinone Derivatives as Anticancer Agents: Design, Synthesis, Biological Evaluation and Computational Studies. *J. Mol. Struct.* **2024**, *1295*, 136622. [CrossRef]
133. Noser, A.A.; El-Barbary, A.A.; Salem, M.M.; Salam, H.A.A.; Shahien, M. Synthesis and Molecular Docking Simulations of Novel Azepines Based on Quinazolinone Moiety as Prospective Antimicrobial and Antitumor Hedgehog Signaling Inhibitors. *Sci. Rep.* **2024**, *14*, 3530. [CrossRef]
134. Luo, H.; Yang, S.; Hong, D.; Xue, W.; Xie, P. Synthesis and in Vitro Antitumor Activity of (1E,4E)-1-Aryl-5-(2-((Quinazolin-4-Yl)Oxy)Phenyl)-1,4-Pentadien-3-One Derivatives. *Chem. Cent. J.* **2017**, *11*, 23. [CrossRef] [PubMed]
135. Alafeefy, A. Some New Quinazolin-4(3H)-One Derivatives, Synthesis and Antitumor Activity. *J. Saudi Chem. Soc.* **2011**, *15*, 337–343. [CrossRef]
136. El-Azab, A.S.; ElTahir, K.E.H. Design and Synthesis of Novel 7-Aminoquinazoline Derivatives: Antitumor and Anticonvulsant Activities. *Bioorganic Med. Chem. Lett.* **2012**, *22*, 1879–1885. [CrossRef]
137. Abbas, S.Y.; El-Bayouki, K.A.M.; Basyouni, W.M.; Mostafa, E.A. New Series of 4(3H)-Quinazolinone Derivatives: Syntheses and Evaluation of Antitumor and Antiviral Activities. *Med. Chem. Res.* **2018**, *27*, 571–582. [CrossRef]
138. Zhang, Y.; Wang, Q.; Li, L.; Le, Y.; Liu, L.; Yang, J.; Li, Y.; Bao, G.; Yan, L. Synthesis and Preliminary Structure-Activity Relationship Study of 3-Methylquinazolinone Derivatives as EGFR Inhibitors with Enhanced Antiproliferative Activities against Tumour Cells. *J. Enzym. Inhib. Med. Chem.* **2021**, *36*, 1205–1216. [CrossRef] [PubMed]
139. Pérez-Fehrmann, M.; Kesternich, V.; Puelles, A.; Quezada, V.; Salazar, F.; Christen, P.; Castillo, J.; Cárcamo, J.; Castro-Alvarez, A.; Nelson, R. Synthesis, Antitumor Activity, 3D-QSAR and Molecular Docking Studies of New Iodinated 4-(3H)-Quinazolinones 3 N-Substituted. *RSC Adv.* **2022**, *12*, 21340–21352. [CrossRef] [PubMed]
140. Wang, Q.; Chen, R.; Wang, R.; Huang, J.; Xu, Y.; Wang, N.; Li, D.; Xu, C.; Wang, B.; Li, Y.; et al. Design, Synthesis and Antitumor Activity of Triphenylphosphonium-Linked Derivatives of Quinazolinone. *Nat. Prod. Res.* **2024**, 1–6. [CrossRef]
141. Cao, S.-L.; Feng, Y.-P.; Jiang, Y.-Y.; Liu, S.-Y.; Ding, G.-Y.; Li, R.-T. Synthesis and in Vitro Antitumor Activity of 4(3H)-Quinazolinone Derivatives with Dithiocarbamate Side Chains. *Bioorganic Med. Chem. Lett.* **2005**, *15*, 1915–1917. [CrossRef] [PubMed]
142. Shao, L.-H.; Fan, S.-L.; Meng, Y.-F.; Gan, Y.-Y.; Shao, W.-B.; Wang, Z.-C.; Chen, D.-P.; Ouyang, G.-P. Design, Synthesis, Biological Activities and 3D-QSAR Studies of Quinazolinone Derivatives Containing Hydrazone Structural Units. *New J. Chem.* **2021**, *45*, 4626–4631. [CrossRef]
143. Emami, L.; Faghih, Z.; Khabnadideh, S.; Rezaei, Z.; Sabet, R.; Harigh, E.; Faghih, Z. 2-(Chloromethyl)-3-Phenylquinazolin-4(3H)-Ones as Potent Anticancer Agents; Cytotoxicity, Molecular Docking and in Silico Studies. *J. Iran. Chem. Soc.* **2021**, *18*, 1877–1889. [CrossRef]
144. Wang, Q.; Pan, Y.; Luo, H.; Zhang, Y.; Gao, F.; Wang, J.; Zheng, J. Novel Approaches for the Solid-Phase Synthesis of Dihydroquinazoline-2(1H)-One Derivatives and Biological Evaluation as Potential Anticancer Agents. *Molecules* **2022**, *27*, 8577. [CrossRef]
145. Abdallah, A.E.; Eissa, I.; Mehany, A.; Celik, I.; Sakr, H.; Metwaly, K.; El-Adl, K.; El-Zahabi, M. Discovery of New Immunomodulatory Anticancer Thalidomide Analogs: Design, Synthesis, Biological Evaluation and In Silico Studies. *Chem. Biodivers.* **2024**, e202401768. [CrossRef] [PubMed]
146. El-Azab, A.S.; Al-Dhfyan, A.; Abdel-Aziz, A.A.-M.; Abou-Zeid, L.A.; Alkahtani, H.M.; Al-Obaid, A.M.; Al-Gendy, M.A. Synthesis, Anticancer and Apoptosis-Inducing Activities of Quinazoline–Isatin Conjugates: Epidermal Growth Factor Receptor-Tyrosine Kinase Assay and Molecular Docking Studies. *J. Enzyme Inhibi. Med. Chem.* **2017**, *32*, 935–944. [CrossRef]
147. Khajouei, M.; Hosseinzadeh, L.; Aliabadi, A.; Rahnama, M.; Sadeghi, H. Synthesis and Cytotoxic Evaluation of Some New 3-(2-(2-Phenylthiazol-4-Yl) Ethyl)-Quinazolin-4(3H) One Derivatives with Potential Anticancer Effects. *Res. Pharm. Sci.* **2017**, *12*, 290. [CrossRef]
148. Ahmed, M.F.; Youns, M. Synthesis and Biological Evaluation of a Novel Series of 6,8-Dibromo-4(3H)Quinazolinone Derivatives as Anticancer Agents. *Arch. Pharm.* **2013**, *346*, 610–617. [CrossRef] [PubMed]
149. Taayoshi, F.; Iraji, A.; Moazzam, A.; Soleimani, M.; Asadi, M.; Pedrood, K.; Akbari, M.; Salehabadi, H.; Larijani, B.; Adibpour, N.; et al. Synthesis, Molecular Docking, and Cytotoxicity of Quinazolinone and Dihydroquinazolinone Derivatives as Cytotoxic Agents. *BMC Chem.* **2022**, *16*, 35. [CrossRef]
150. El-Sayed, S.; Metwally, K.; El-Shanawani, A.A.; Abdel-Aziz, L.M.; Pratsinis, H.; Kletsas, D. Synthesis and Anticancer Activity of Novel Quinazolinone-Based Rhodanines. *Chem. Cent. J.* **2017**, *11*, 102. [CrossRef] [PubMed]