Hindawi
Journal of Chemistry
Volume 2022, Article ID 8424838, 29 pages
https://doi.org/10.1155/2022/8424838

Review Article

A Review on Current Synthetic Methods of 4-Aminoquinazoline Derivatives

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Received 16 August 2022; Accepted 18 October 2022; Published 16 November 2022

Academic Editor: Xinyong Liu

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Quinazoline scaffold and its various derivatives, as an important category of heterocyclic compounds, have received much attention for the design and development of new drugs due to their various pharmacological properties like anticancer, anticonvulsant, antidepressant, antibacterial, antifungal, antioxidant, anti-HIV, antileishmanial, anticoccidial, antimalarial, anti-inflammatory, antileukemic, and antimutagenic. Among the various substituted quinazolines, 4-aminoquinazoline scaffold, as a privileged structure in medicinal chemistry, is present in many approved drugs and biologically active compounds. Furthermore, 4-aminoquinazoline derivatives are often applied as key intermediates in the preparation of bioactive compounds. The current review focuses on the key methods for the preparation of 4-aminoquinazoline derivatives, including the nucleophilic substitution reaction, metal-catalyzed approaches, microwave irradiation methods, cyclocondensation, and direct amination methods.

1. Introduction

Heterocycles containing nitrogen atom are an important category of the favorable structures in the field of medicinal chemistry [1]. Among the heterocyclic structures, quinazoline derivatives with a double-ring structure are one of the most significant scaffolds for the design and synthesis of a wide range of bioactive compounds [2]. Quinazoline derivatives have attracted much attention of the medicinal chemists due to their various biological properties like anticancer, anti-inflammatory, antidepressant, anticonvulsant, vasodilator, antihypertensive, antibacterial, antifungal, anti-HIV, antioxidant, antileishmanial, anticoccidial, antimalarial, antileukemic, and antimutagenic [2, 3]. Among the various substituted quinazolines, 4-aminoquinazoline scaffolds have great importance due to their diverse spectrum of therapeutic potential (Figure 1) [2, 4, 5]. According to the reports, 4-aminoquinazoline derivatives demonstrate a wide variety of biological activities like antimicrobial, anti-inflammatory, anticancer, and antihypertensive [1, 6]. 4-Aminoquinazoline, as a privileged core, is present in many approved drugs and biologically active compounds, such as bunazosin, prazosin, alfuzosin, trimetrexate, erlotinib, gefitinib, lapatinib, afatinib, and vandetanib (Figure 2) [1, 5–11]. Furthermore, 4-aminoquinazoline derivatives are often applied as key intermediates in the preparation of bioactive compounds.

4-Aminoquinazoline derivatives exert their biological effects through a variety of targets such as DNA cleavage and p53 activation [12], aurora kinase inhibition [13], ERK inhibition [14], ErbB/HDAC inhibition [15], EGFR inhibition [16, 17], VEGFR-2 tyrosine kinase inhibition [18], and PDE1 inhibition [19].

Therefore, the synthesis of 4-aminoquinazoline derivatives has attracted significant attention in recent years. The current review focuses on the new and improved synthetic pathways for the preparation of 4-aminoquinazoline derivatives including the nucleophilic substitution reaction, metal-catalyzed approaches, microwave irradiation methods, cyclocondensation approaches, and direct amination methods.

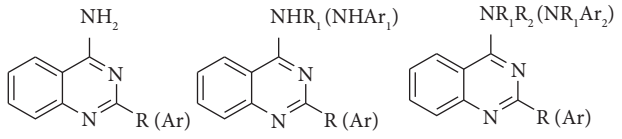


Figure 1: 4-aminoquinazoline scaffolds.

2. Synthetic Strategies of 4-Aminoquinazoline Derivatives

2.1. Nucleophilic Substitution Reaction. The first nucleophilic substitution reaction of quinazoline occurs at the more reactive C-4 position of the quinazoline ring. 4-Aminoquinazoline **2**, as an important core in the structure of several drugs and bioactive compounds, can be prepared from the nucleophilic substitution reaction of quinazoline **1** with sodamide ($NaNH_2$) (Scheme 1).

2.2. Metal-Catalyzed Reactions

2.2.1. Copper-Catalyzed Reactions. Yang et al. developed an efficient and simple copper-catalyzed approach to provide 4-aminoquinazoline **6** and 2,4-diaminoquinazoline **7** analogues from the reaction of substituted 2-bromobenzonitriles **3** with amidines **4** or guanidine **5**, with good yields (Scheme 2). The couplings of substituted 2-bromobenzonitriles with various amidines or guanidine were performed in DMF utilizing CuI as a catalyst, *N*, *N*′-dimethylethylenediamine (DMEDA) as a ligand, and potassium carbonate (K_2CO_3) as a base, under nitrogen atmosphere at 80°C. The scope investigation of this system was carried out using different substituted 2-bromobenzonitriles, amidines, and guanidine. The results showed that the substitution type on the phenyl ring of 2-bromobenzonitriles affected the reactivity of the substrate. The existence of electron-withdrawing groups like NO_2 on the phenyl ring increased the reaction rates compared to those with electron-neutral or electron-rich substituents. Moreover, aliphatic and aromatic amidines resulted in higher yields compared to guanidine because of high polarity of the guanidine derivatives. The proposed mechanism for this CuI-catalyzed method involves the Ullmann-type coupling reaction of the substituted 2-bromobenzonitriles with amidines or guanidine and subsequently, intramolecular nucleophilic addition of amino group to the *ortho*-cyano moiety (Figure 3). Readily available reactants, facile, one-pot cascade, practical, the use of mild conditions, economical, and good yield of products are the advantages of this method [1].

Yang et al. reported a very efficient copper-catalyzed procedure for the preparation of 2-substituted-4-aminoquinazoline derivatives **11** from the reaction of 2-substituted benzimidamides **8** with various aldehydes **9** and sodium azide **10**, in the presence of CuBr as a catalyst, L-proline as a ligand, and DMF as a solvent (Scheme 3). Further studies showed that CuBr and L-proline components were essential for this reaction and the use of other nitrogen sources like ammonium chloride, ammonium acetate, or ammonium hydroxide instead of NaN_3 led to the unfavorable results. The substrate scope investigation of this copper-catalyzed system was performed using different 2-substituted benzimidamides and aldehydes. The results indicated that 2-iodo and 2-bromobenzimidamides substrates gave the target quinazolines in moderate to excellent yields while 2-fluoro and 2-chlorobenzimidamides did not produce products, despite increasing the reaction temperature. The reactivity order for the above compounds was as follows: aryl iodides > aryl bromides > aryl chlorides (fluorides). In addition, it was found that the electronic features of the groups on the phenyl ring of 2-substituted benzimidamides (R_1) had negligible influence on the reaction yield. In the case of aldehydes, the type of substituents on the aromatic ring also does not have remarkable influence on the reactivity. So, a variety of aromatic aldehydes containing electron-donating (OH, OMe, Me, *t*-Bu), electron-neutral (H), and electron-withdrawing (NO_2, Cl, Br) substituents afforded the corresponding quinazolines in moderate to good yields. Further investigations indicated that the large steric hindrance of the substituents on the aromatic ring had also an obvious effect on the reaction yields. So, 2,6-dimethylbenzaldehyde led to the target products in low yields (50%). In addition, it was found that alkyl aldehydes, 2-naphthaldehyde, 2-hydroxy-1-naphthaldehyde, 2-thienaldehyde, 2-furanaldehyde, and 3-pyridinaldehyde were well tolerated and afforded the corresponding products in good yields. Furthermore, in the case of *ortho*-halogenated benzimidamides, corresponding 2,6-disubstituted 4-aminoquinazolines were obtained in moderate to good yields. These results indicated that the electronic properties of the additional substituent on the *ortho*-halogenated benzimidamide had a limited effect on the reactivity. The probable mechanism of this copper-catalyzed system involves the S_NAr substitution reaction between 2-halobenzimidamide **8** and NaN_3 to produce 2-azidobenzimidamide **12**. Afterwards, the copper-mediated denitrogenation of **12** in the existence of L-proline and trace H_2O in DMF generates 2-aminobenzimidamide **15** using Cu(I) and Cu(III) complexes **13**-**14**. The condensation of **15** with aldehyde provides Schiff base **16**. An intramolecular nucleophilic addition of amidine nitrogen to imine carbon in **16** affords intermediate **17** which on subsequent oxidative dehydrogenation and amine-imine tautomerization forms the expected compound **11** (Figure 4). The advantages of this method are efficient, readily available reagents, mild reaction conditions, practical, one-pot cascade, wide substrate scope, operational simplicity, and low reaction temperature [20].

Xu et al. described a new and effective copper-catalyzed approach for the preparation of 2-arylquinazolin-4-amines **20** using readily available 2-arylindoles **18** and $TMSN_3$**19**. The reaction took place in acetonitrile and in the presence of $Cu(OAc)_2$ as a catalyst, tert-butyl peroxybenzoate (TBPB) as an oxidant, H_2O as an additive, and NaOH as a base, under argon atmosphere (Scheme 4). The scope examination of this method was performed using a variety of 2-arylindoles, under the optimized conditions. The results showed that indoles with methyl and halogen substituents (R') at the C-5 and C-6 positions afforded the target products in satisfactory yields but indoles with electron-withdrawing substituents

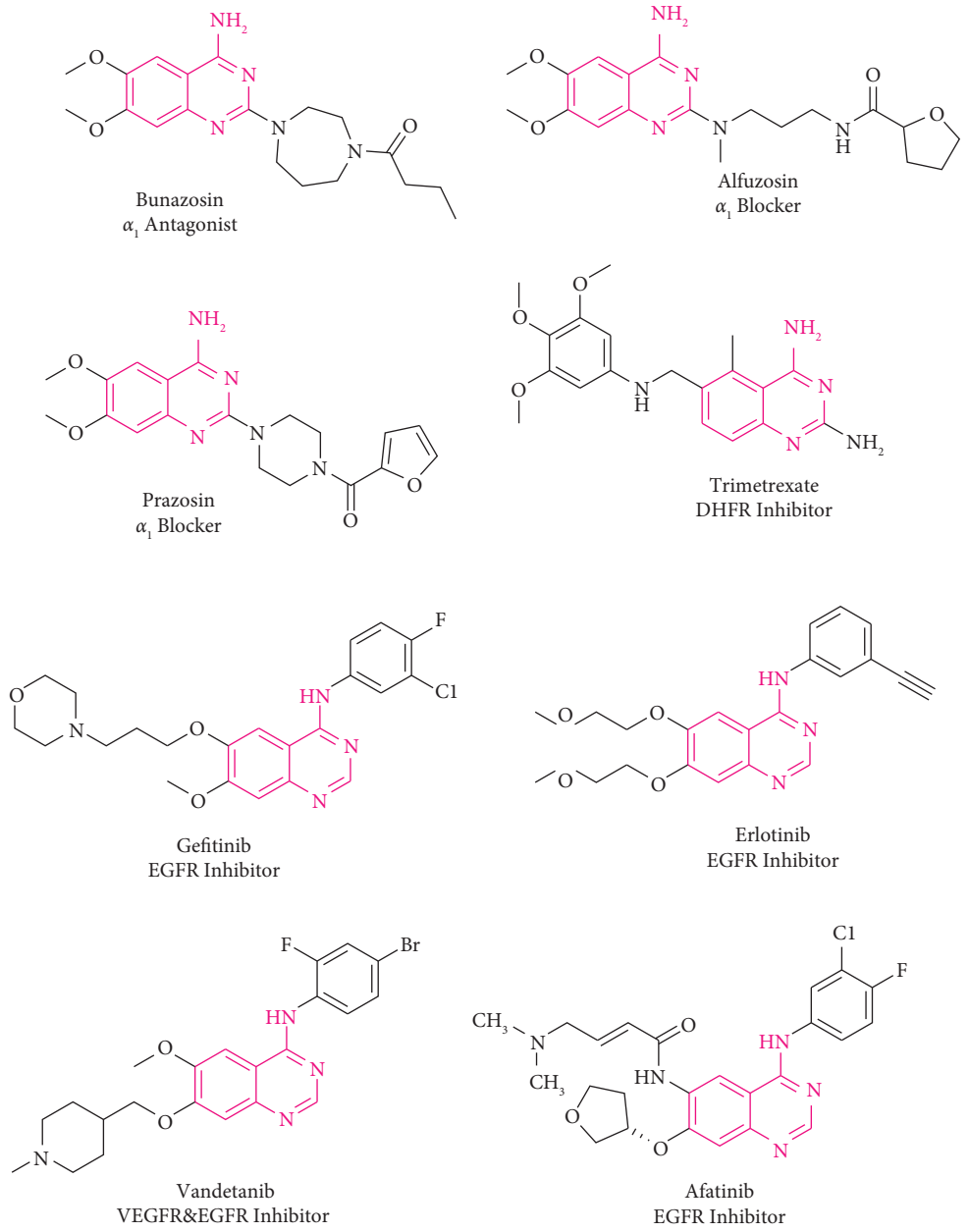
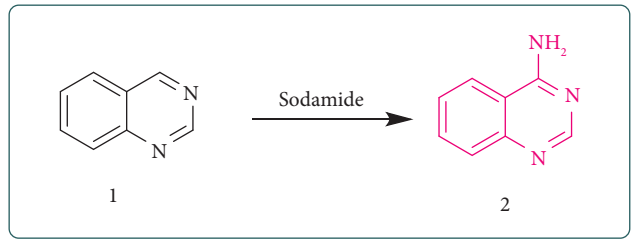


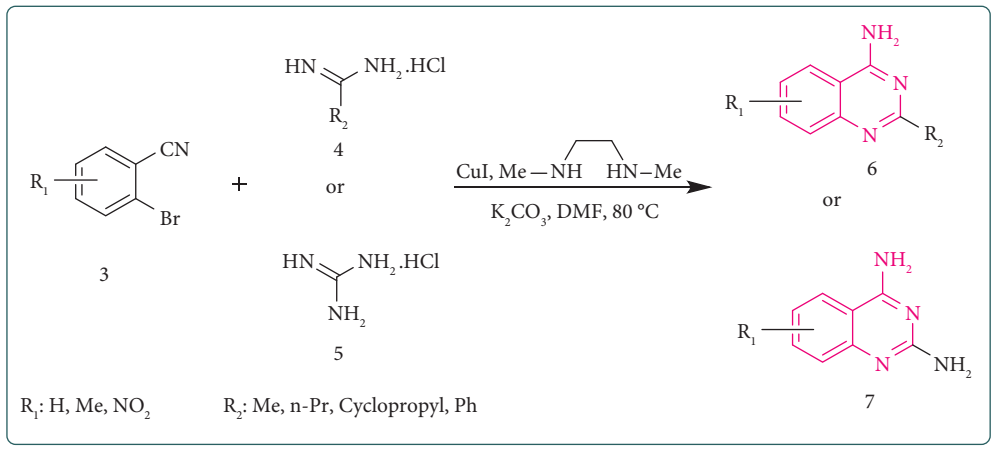
Figure 2: 4-aminoquinazoline-based drugs.

like NO_2 and CF_3 at the C-5 position could not produce the desired products. Further investigation revealed that the steric hindrance and the nature of groups present at the pyrrole ring (*R*) affected the yield of the reaction. Generally, the phenyl ring with substituents at the *para* position led to the higher yields compared to the phenyl ring with *ortho*- and *meta*-substitutions. Furthermore, the phenyl ring with electron-withdrawing substituents such as F and Cl gave better yields than the phenyl ring with electron-rich substituents, like methoxy, n-propyl, and t-butyl. In addition, 2-(pyridine-3-yl)-1H-indole provided the expected products in good yields, while 2-n-butyl-1H-indole resulted in very low yields. The suggested mechanism for this method is illustrated in Figure 5. The reaction of $TMSN_3$ with TBPB in the existence of copper results in the formation of azidyl radical, through a single-electron transfer process. Afterwards, the addition of azidyl radicals to the C(3) of **18** generates the diazidation intermediate **22** which on intramolecular coupling of the carbon-centered radical with one azido group affords the aminyl radical **23**. Intermediate **24** is obtained via the sequential reduction-protonation or H-abstraction. Then, the ring expansion in the presence of NaOH and denitrogenation of **25**, affords intermediate **26** which on subsequent protonation and tautomerization forms the desired product **20**. The significant advantages of this method are effective and mild conditions [4].

Chen et al. reported a Cu-catalyzed approach for the direct conversion of cyclic amides to aromatic heterocyclic amines in DMF utilizing $Cu(acac)_2$ as a catalyst and di-t-butyl peroxide (DTBP) as an oxidant. In this method, the



Scheme 1: Nucleophilic substitution reaction of quinazoline with sodamide ($NaNH_2$).



Scheme 2: Copper-catalyzed synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives.

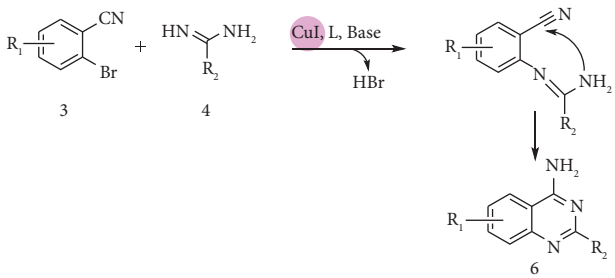
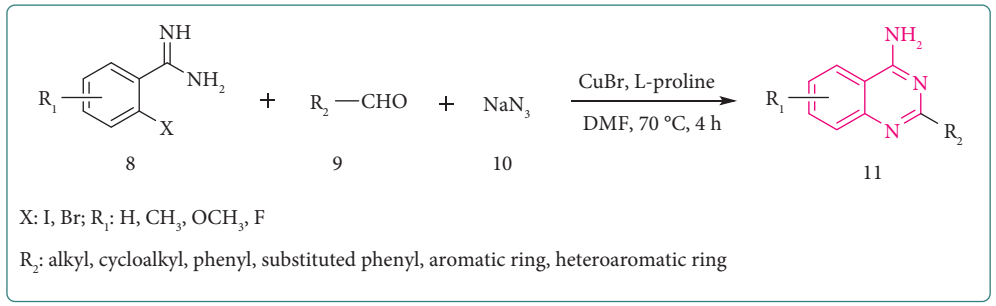


Figure 3: The proposed mechanism for the synthesis of 4-aminoquinazoline and 2,4-diaminoquinazoline analogues using CuI as a catalyst.

direct amination of quinazolinones **27** with various amines **28** resulted in the 4-aminoquinazoline derivatives **29** (Scheme 5). The scope of the described method was examined using various primary and secondary alkylamines as well as different substituted quinazolin-4(3H)-ones. The results revealed that various amines like piperidine, methyl-substituted piperidines, pyrrolidine, azepane, cyclohexanamine, and linear and branched alkylamines afforded the corresponding quinazolines in moderate to excellent yields. But aromatic amines did not react with quinazolinones due to the low activities and also the possibility of oxidation. Furthermore, it was found that substituted quinazolin-4(3H)-ones with electron-donating and electron-withdrawing substituents afforded the target derivatives in good to excellent yields. In addition, 6-bromoquinazolinone and 6-iodoquinazolinone selectively reacted with amines to provide corresponding products but not the Ullman coupling products. Although, the results showed that halogens were more suitable for this reaction. Further investigations demonstrated that thieno [2, 3-d] pyrimidin-4-ol and electron-rich 6,7-diether substituted quinazolinones afforded the target quinazolines in 56–89% yields. The suggested mechanism for this reaction is illustrated in Figure 6. The significant advantages of this procedure are efficient, mild reaction conditions, environmentally friendly, and readily available starting materials [21].

Huang et al. reported a new procedure for the preparation of 2-acyl-4-aminoquinazoline derivatives **39** using 2-aminobenzonitriles **36**, methyl ketones **37**, and ammonium acetate (NH_4OAc) **38** in the presence of $I_2/CuCl_2$ (Scheme 6). In this method, a methyl group was utilized as a new input to form target derivatives. The scope investigation of this process was carried out using various methyl ketones and a range of 2-aminobenzonitriles. The results indicated that aryl methyl ketones with electron-neutral (4-H); electron-donating (4-Me, 2-Me, 3-OMe, 4-OEt, 3,4-OCH_2O, and 3,4-$O(CH_2)_2O$); electron-withdrawing (3-NO_2, 4-SO_2Me, and 4-CO_2Me); and halogen (4-F, 4-Cl and 4-Br) groups on the benzene ring gave the expected products in good yields. In addition, heterocyclic methyl ketones and several substrates containing fused rings such as 1-naphthyl, 2-naphthyl, and 2-fluorenyl were also well tolerated and generated the target products in moderate to good yields.



Scheme 3: Synthesis of 2-substituted-4-aminoquinazolines in the presence of CuBr, L-proline, and DMF.

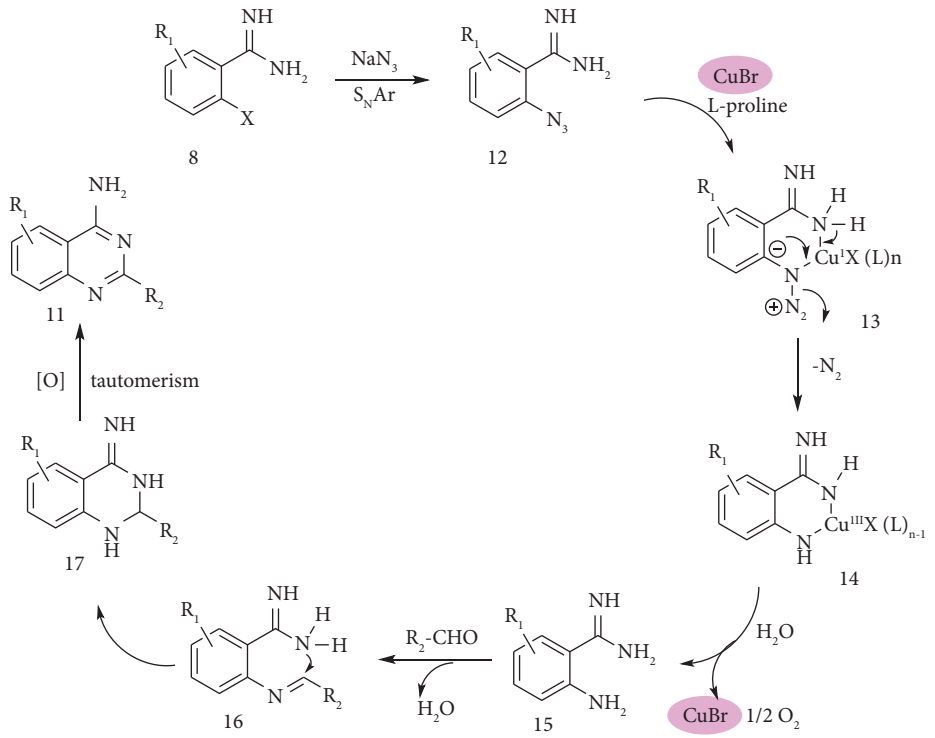
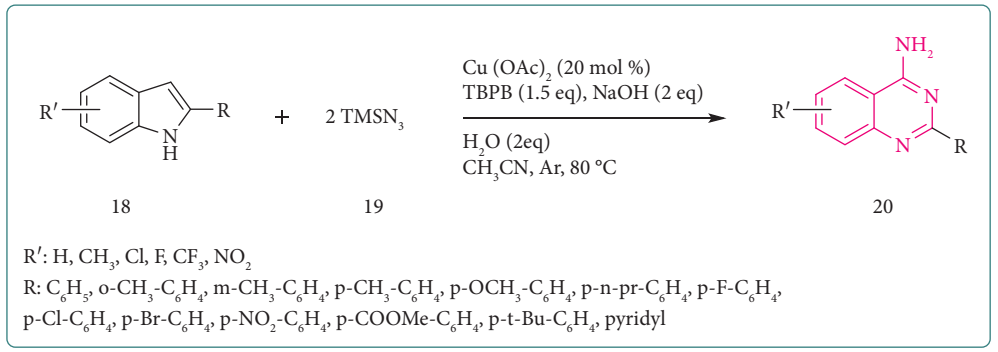


Figure 4: The proposed mechanism for the synthesis of 2-substituted-4-aminoquinazoline derivatives in the presence of CuBr, L-proline, and DMF.

Furthermore, it was found that 2-aminobenzonitriles containing electron-rich (-Me, -OMe, and–di-OMe) and halogen (-F, -Cl, and -Br) substituents at the 4- and 5-positions of the phenyl ring reacted with methyl ketones and provided the expected products in moderate to good yields. The possible mechanism of this process is represented in Figure 7. The advantages of this method are operational simplicity, readily available materials, mild reaction conditions, and good functional group compatibility [5].

2.2.2. Palladium-Catalyzed Reactions. Wang et al. described a palladium catalyzed procedure for the production of a broad range of 4-amino-2-aryl(alkyl)quinazoline derivatives **48** from N-arylamidines **46** and isonitriles **47**, in the presence of $CsCO_3$ and O_2 as a base and oxidant, respectively (Scheme 7). The target quinazoline derivatives were obtained through palladium-catalyzed intramolecular aryl C-H amidination via incorporation of isonitrile under relatively mild condition in good yields. The substrate scope investigation of this method was performed using different N-aryl ring (R_1)-substituted benzamidines under optimized reaction conditions. The results indicated that benzamidines with electron-donating substituents such as Me and OMe on the phenyl ring produced the target quinazolines in excellent yields except the benzamidine bearing a *para*-methoxy substituent which provided the target products in moderate yields. Benzamidines with electron-withdrawing substituents like F and Cl on the phenyl ring generated the target quinazolines in lower yields. These findings propose that an electrophilic aromatic substitution (S_EAr) reaction may be involved in the activation process of the C(sp^2)-H bond. Furthermore, the effect of benzamidine ring substituents (R_2) was examined which demonstrated that the nature and steric hindrance of these substituents have a significant effect on the reaction yield. The aryl moieties bearing electron-



Scheme 4: Synthesis of 2-arylquinazolin-4-amines in the presence of $Cu(OAc)_2$ and TBPB.

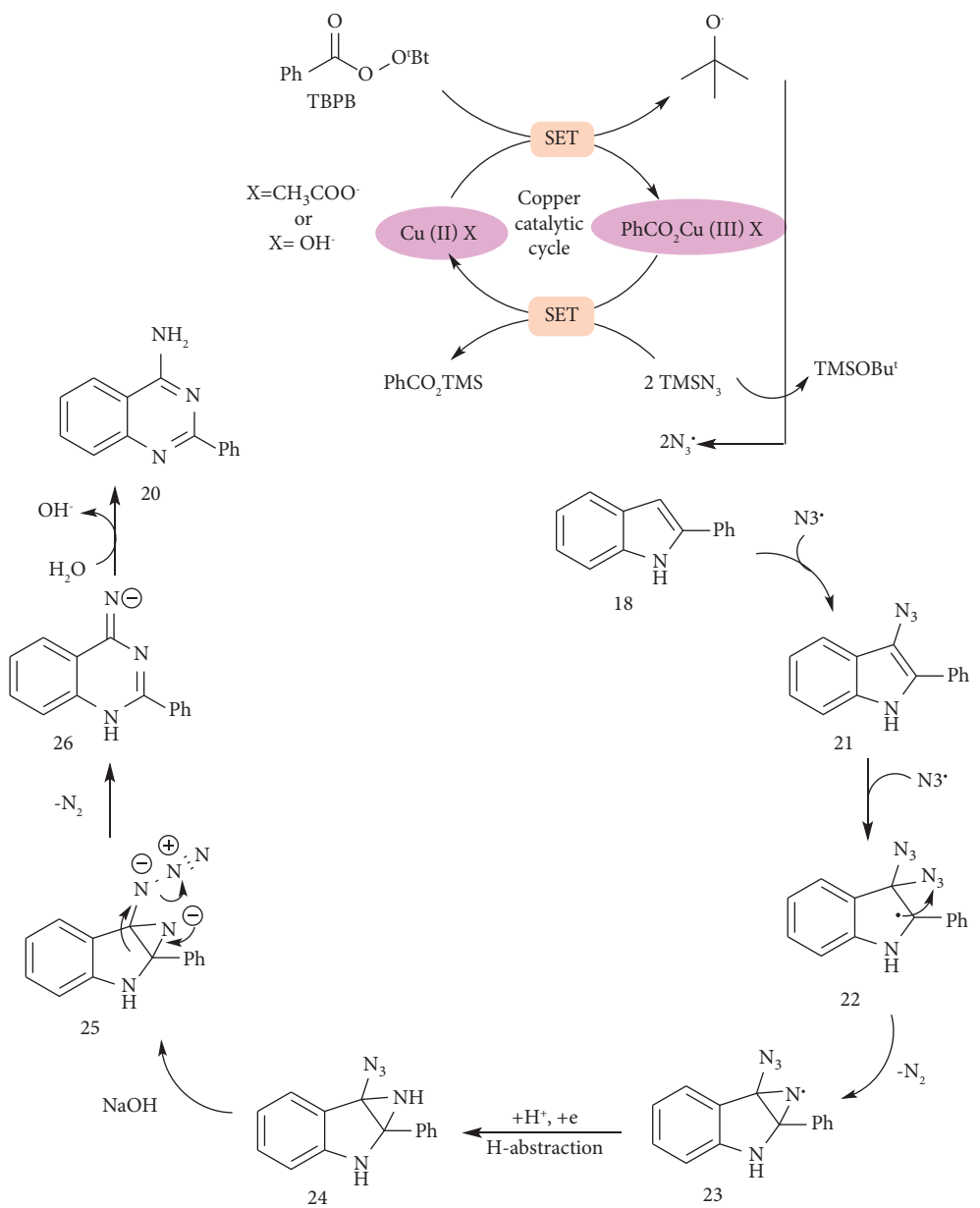
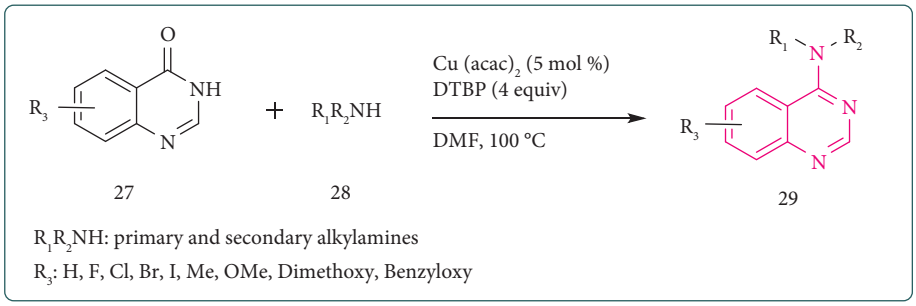


Figure 5: The plausible mechanism for the synthesis of 2-arylquinazolin-4-amines in the presence of $Cu(OAc)_2$ and TBPB.



Scheme 5: Synthesis of 4-aminoquinazoline derivatives in the presence of $Cu(acac)_2$ as a catalyst and DTBP.

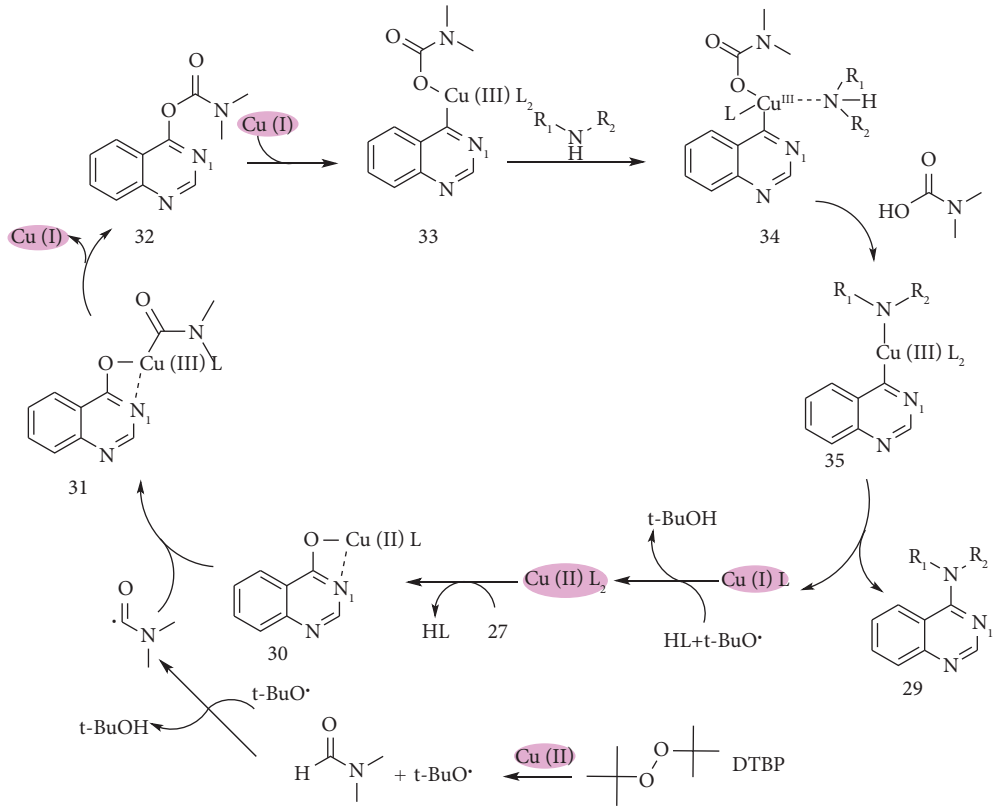
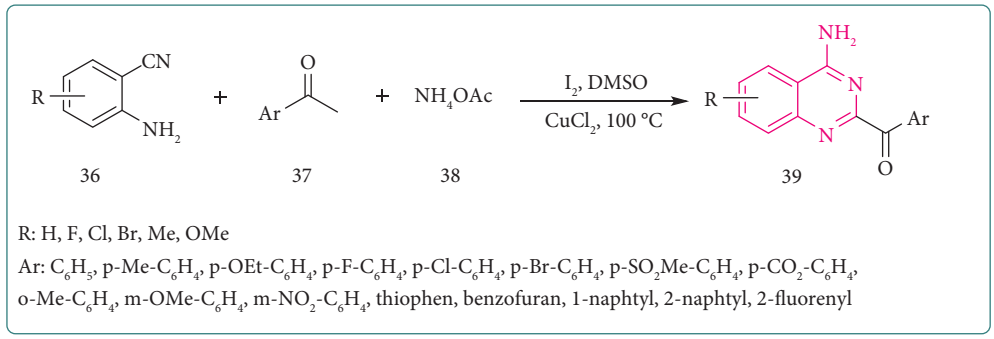


Figure 6: The proposed mechanism for the synthesis of 4-aminoquinazoline derivatives in the presence of $Cu(acac)_2$ as a catalyst and DTBP.

donating substituents such as Me and OMe were more suitable for this reaction compared to electron-withdrawing substituents like Cl and Br. This observation showed that the electron density on amidine nitrogen plays a vital role in the complexation with the palladium. Moreover, it was found that the reaction yields are more sensitive towards *ortho*-substituents, which could be due to the steric interference with complexation of amidine nitrogen to the palladium. The benzamidine ring (R_2) containing alkyl moieties such as t-butyl and cyclohexyl afforded the corresponding 2-alkyl-substituted 4-aminoquinazolines in moderate to good yields. Furthermore, the different substituted isonitriles (R_3) were investigated. The results demonstrated that isopropyl and cyclohexyl isonitrile compared to t-butyl and aryl isonitriles are less efficient, a result which is related to the thermal stabilities of the isonitriles. The possible mechanism of the described reaction is shown in Figure 8. The coordination of isonitrile-ligated Pd (II) with amidine nitrogen in the presence of Cs_2CO_3 results in the generation of complex **49**. Then, an intramolecular electrophilic substitution generates the cyclopalladation intermediate **50**, which undergoes migratory insertion of the isonitrile. Subsequent reductive elimination of the intermediate **51** followed by tautomerization affords the target product **48** and Pd (0) species, which is reoxidized to Pd (II) using dioxygen. The advantages of this procedure are efficient, concise, environmentally benign, mild condition, good functionality tolerance, wide substrate scope, readily available starting materials, and high yield of products [22].

Thanh et al. synthesized a set of 2-aryl-4-aminoquinazoline derivatives **55** using 2-aryl-quinazolinones **52** via a three-step reaction in the presence of $POCl_3$, NaN_3, and



Scheme 6: Synthesis of 2-acyl-4-aminoquinazoline derivatives in the presence of $I_2/CuCl_2$.

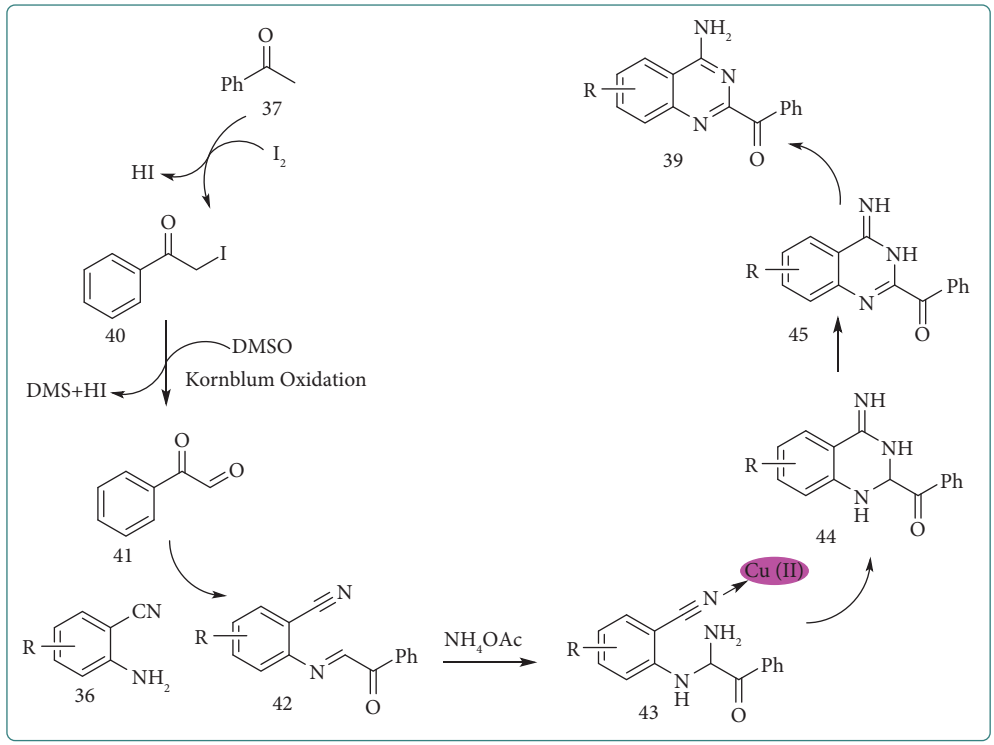
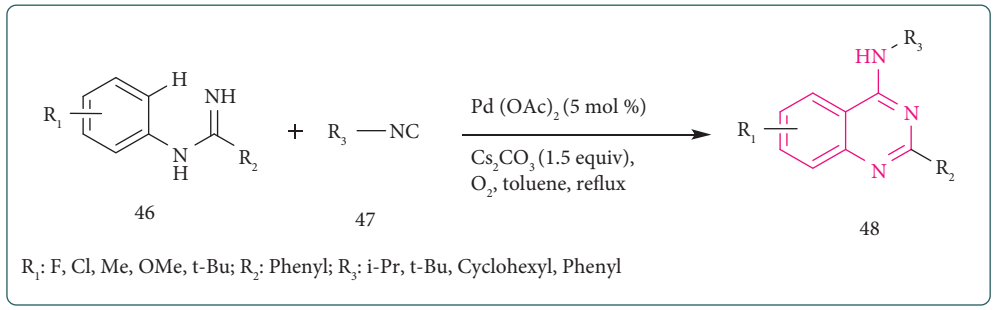


Figure 7: The possible mechanism for the synthesis of 2-acyl-4-aminoquinazolines in the presence of $I_2/CuCl_2$.

H_2/Pd (Scheme 8). In this process, the amide group of quinazolinones **52** were converted to the corresponding imine chloride **53** using $POCl_3$ in moderate yields, which is subsequently converted into the intermediate **54** using NaN_3 in good yields. Finally, the azide group of **54** was easily reduced to the amine group utilizing H_2 and Pd/C and resulted in the target derivatives **55** in good yields. Generally, the results indicated that the electronic features and steric hindrance of the aryl ring had a negligible effect on the reaction yields [23].

2.2.3. Iron-Catalyzed Reaction. Yin et al. described an efficient procedure for the production of N^4-substituted 2,4-diaminoquinazoline derivatives **58**, **59** utilizing the commercially available 2-nitrobenzaldehydes **56**, H_2NCN, various amines, and Fe/HCl (Scheme 9). Preliminary studies showed that the oxidative cyanoimidation of 2-nitrobenzaldehydes and also the condensation with amine were carried out in excellent yields. Subsequently, the reductive intramolecular cyclization of 2-nitrobenzimidamides to generate diaminoquinazolines was conducted using Fe/HCl as a reductive agent in high yields. To examine the substrate scope of this method, different substrates includingsubstituted 2-nitrobenzaldehydes and different amines were tested, under optimized conditions. From the results, it was found that the type of substituents on the aryl ring of 2-nitrobenzaldehydes had a negligible effect on the reaction rate. Different 2-nitrobenzaldehydes with electron-withdrawing (Cl, Br) or electron-donating (OMe) groups provided cyanoimidates **57** in good yields. The reaction of various cyanoimidates with simple primary amines which were substituted with aliphatic chains or rings as well as



Scheme 7: Synthesis of 4-amino-2-aryl(alkyl) quinazolines in the presence of $Pd(OAc)_2$, $CsCO_3$, and O_2.

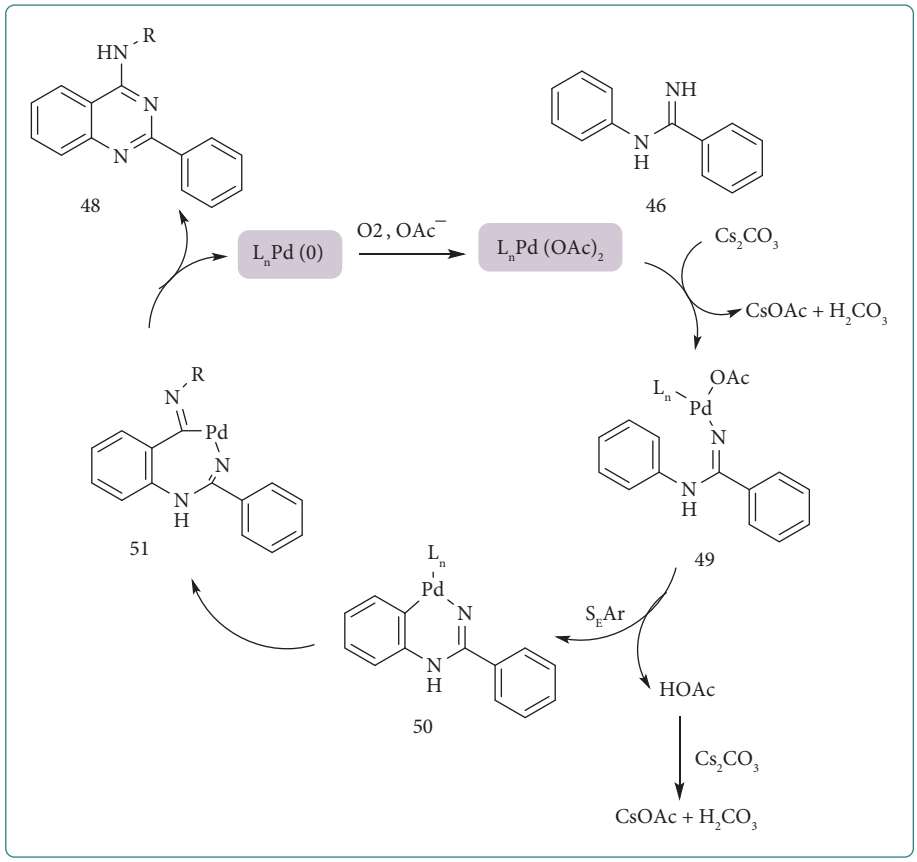
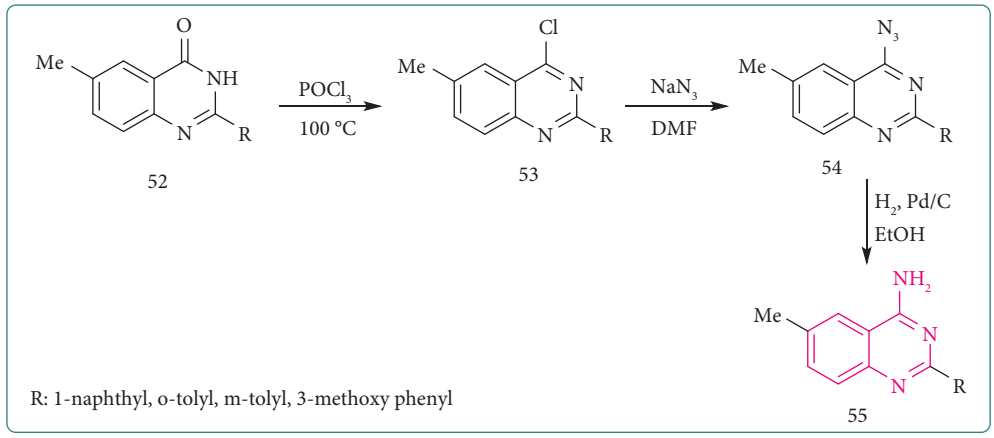


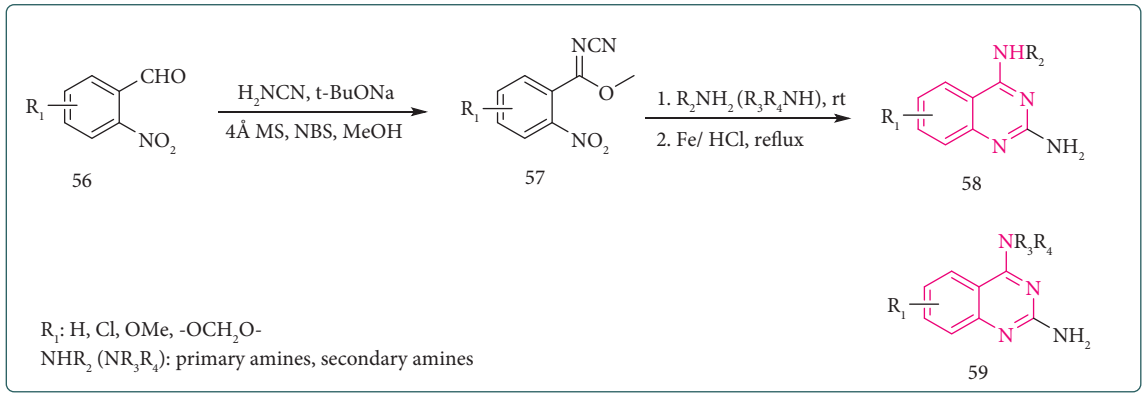
Figure 8: The proposed mechanism for the synthesis of 4-amino-2-aryl(alkyl)quinazoline derivatives in the presence of $Pd(OAc)_2$, $CsCO_3$, and O_2.

the substitution containing the aryl groups gave the target products in excellent yields. In addition, the secondary amines also produced the desired products in good yields. The probable mechanism of this system is represented in Figure 9. This mechanism involves the tandem oxidative cyanoimidation, condensation of cyanoimidate with amine, and reductive intramolecular cyclization of 2-nitrobenzimidamides **60** to generate diaminoquinazolines **58** in the Fe/HCl medium. The advantages of this procedure are efficient, one-pot procedure, facile, readily available reactants, and high yield of products [24].

2.2.4. Rhodium (III)-Catalyzed Reaction. Ren et al. reported a novel rhodium (III)-catalyzed procedure for the preparation of 4-aminoquinazoline derivatives **64** using N-arylbenzamidines **62** and 3-phenyl-1,4,2-dioxazol-5-ones **63** in the presence of AgOTf, $Zn(OAc)_2$, and 4 Å MS in 1,2-dichloroethane (Scheme 10). The scope investigation of this method was performed using various substituted N-arylbenzamidines and 3-phenyl-1,4,2-dioxazol-5-ones under the optimized reaction conditions. The results demonstrated that the steric hindrance of the N-phenyl ring had a negligible effect on the reactivity. N-arylbenzamidines with both



Scheme 8: Synthesis of 2-aryl-4-aminoquinazoline derivatives in the presence of $POCl_3$, NaN_3, and H_2/Pd.



Scheme 9: Synthesis of N^4-substituted 2,4-diaminoquinazolines using 2-nitrobenzaldehydes in the presence of H_2NCN and Fe/HCl.

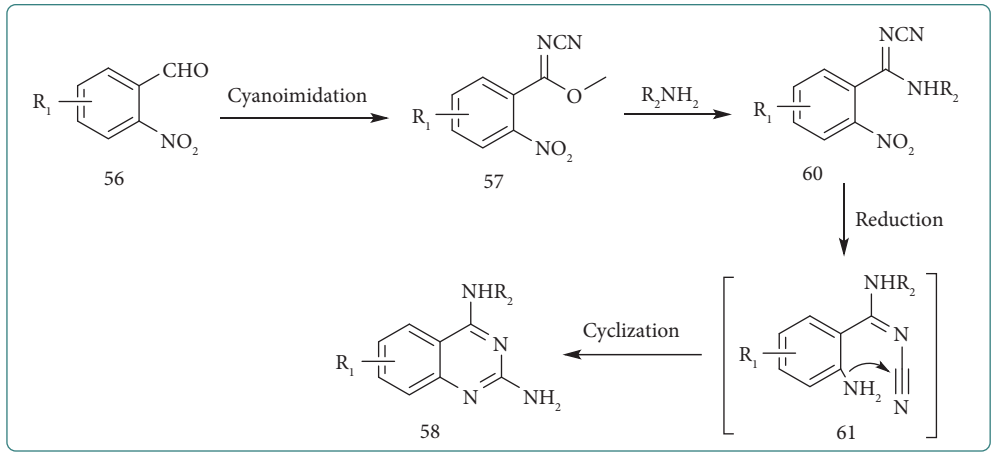


Figure 9: The proposed mechanism for the synthesis of N^4-substituted 2,4-diaminoquinazolines in the presence of H_2NCN and Fe/HCl.

electron-donating (Me, OMe, Et, iPr, and ^{t}Bu) and electron-withdrawing (F, Cl, Br) substituents at *para*-, *ortho*-, or *meta*-positions of the N-phenyl ring (R_1), except the nitro-substituted, gave the target products in 53%–78% yields. In addition, it was observed that disubstituted N-arylbenzamidines were good substrates for this reaction with 74%–76% yields. Further investigations indicated that N-pyridyl and N-phenyl (4-benzyl) benzimidamides provided the desired quinazolines in moderate yields. In addition, N-arylbenzamidines with the substitution at the *para*- and *meta*-position of the C-phenyl ring (R_2), except *ortho*-Cl and *ortho*-Me substitutions, converted into the desired products

with 62%–78% yields. In the case of 3-phenyl-1,4,2-dioxazol-5-ones, the results showed that the steric hindrance of the phenyl ring had negligible influence on the reaction yield. Various *para*-, *meta*-, *ortho*-, and poly-substituted 1,4,2-dioxazol-5-ones could react with N-phenylbenzamidine to provide the corresponding products in good to excellent yields. Furthermore, it was found that the substrates with adamantine, naphthalene, bisphenyl, thiophene, and benzothiophene were well tolerated and afforded the corresponding derivatives with good yields. The significant advantages of this reaction are excellent regioselectivity, wide substrate scope, and cost-effective [25].

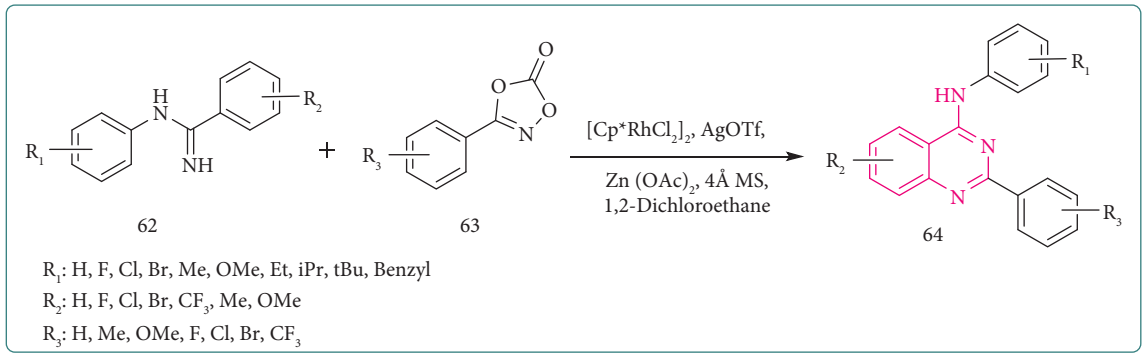
2.2.5. Sn-Catalyzed Reaction. Patil et al. reported a rapid and facile method for the preparation of 4-amino-2-aryl quinazoline analogues **68** using N-(2-cyanoaryl) amidoximes **67** in the presence of $SnCl_2$ as a acatalyst and ethanol as a solvent (Scheme 11). N-(2-cyanoaryl) amidoximes **67** as key intermediates were prepared according to the previously reported method from the reaction of the corresponding anilines **65** and N-hydroxyimidoyl chlorides **66** in good yields [26]. The scope of this procedure was investigated using a range of aromatic and heteroaromatic N-(2-cyanoaryl) amidoximes under the optimized reaction conditions. The results indicated that N-(2-cyanoaryl) amidoximes with the electron-withdrawing or electron-neutral groups like H, Cl, and Br on the phenyl ring (R_1) afforded the corresponding products in higher yields compared to those with electron-donating substituents such as Me. In addition, the existence of the phenyl ring with the electron-neutral (H) or electron-donating (*p*-CH_3 and *p*-OCH_3) groups at R_2 position increased the reaction yields compared to those with electron-withdrawing (*p*-F and *m*-CN) and other substituents like *o*-NH_2 and *o*-pyridyl. The advantages of this method are rapid, facile, and moderate to high yields [27].

2.2.6. Zn-Catalyzed Reaction. Pujar et al. developed a procedure for the production of a new set of 2,4-disubstituted quinazoline analogues **71** from commercially available anthranilic acid **69** (Scheme 12). In this reaction, key intermediates **70** were prepared by cyclization of anthranilic acid with aryl/heteroaryl amide under solvent-free condition in good yields. In the following step, the target quinazoline derivatives were obtained from the reaction of **70** with appropriate amines in the presence of zinc chloride ($ZnCl_2$) with moderate yields. In this approach, various arylamides including phenyl, 3-pyridyl, and pyrazyl derivatives as well as diverse arylamines containing 4-OCH_3 and 4-F substituents were tested and the results revealed that the type of substituents had no remarkable influence on the reaction yield [28].

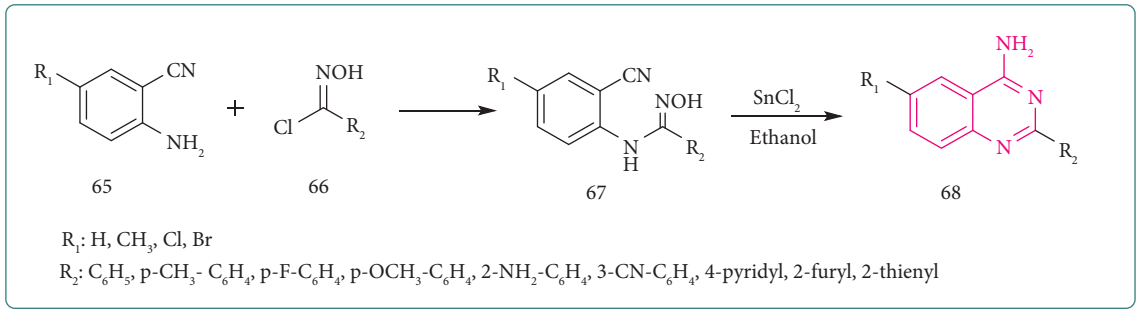
2.2.7. Dawson Heteropolyacid-Catalyzed Reaction. Bamoharram et al. reported a novel multicomponent procedure for the synthesis of 4-aminoquinazoline derivatives **74** from 2-aminobenzonitrile **72**, various acyl chlorides **73** and ammonium acetate **38** using Dawson-type heteropolyacids (HPAs) as efficient; eco-friendly and reusable heterogeneous inorganic catalysts; $H_6\ P_2M_{18}O_{62}$ ($M = W^{VI}$ and Mo^{VI}); and mixed addenda forms (M = CoII, CuII, NiII, MnIII) (Scheme 13). The scope examination of this approach was performed using various acyl chlorides. The results showed that acetyl chloride and benzoyl chlorides with the electron-neutral (H) and electron-withdrawing (4-Cl and 4-NO_2) groups at the phenyl ring led to the slightly better yields compared to those with electron-donating (4-Me, 4-OMe and 2-OMe) substituents. The suggested mechanism of this process is illustrated in Figure 10 which involves the condensation of 2-aminobenzonitrile with acyl chlorides to generate compound **75** which on further condensation with NH_4OAc gives compound **76**. An intramolecular electron transfer provides compound **77** which undergoes an intramolecular nucleophilic addition to afford intermediate **78**. Subsequent aromatization of intermediate **78** leads to the target derivatives **74**. The characteristic advantages of this multicomponent method are one-pot reaction, simple work-up, and good to excellent yields [29].

2.2.8. Copper/Palladium-Catalyzed Reaction. Khabnadideh et al. prepared a new set of 2,4-diaminoquinazoline analogues **81** using the commercially available 2-aminobenzonitrile **72** (Scheme 14). In this reaction, 2-aminobenzonitrile **72** was iodinated with iodine monochloride (ICl) to produce the iodide **79** which on cyclization with guanidine under solvent-free conditions gave 2,4-diaminoquinazoline **80** in high yield. Finally, Sonogashira or Heck coupling of 2,4-diaminoquinazoline with phenoxy derivatives resulted in the corresponding products **81** with moderate to good yields [30].

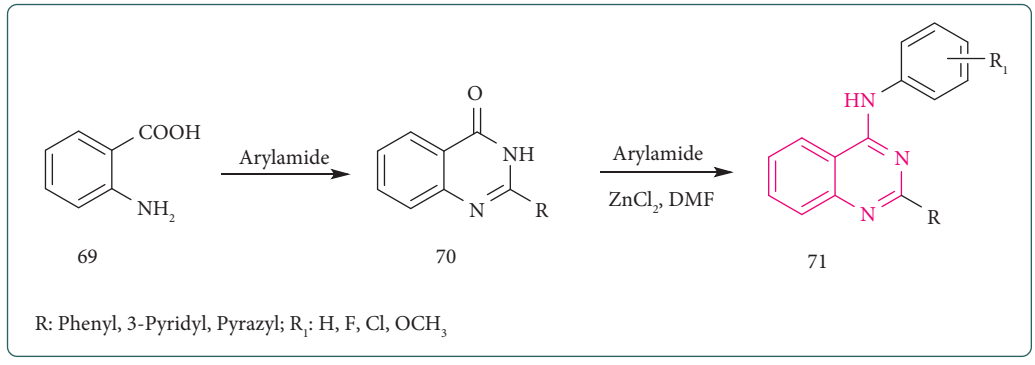
2.2.9. Iron/Copper-Catalyzed Reaction. Jia et al. developed an efficient Fe/Cu catalyzed approach for the direct preparation of a series of 2-phenylquinazolin-4-amine derivatives **84** using readily available *ortho*-halogenated benzonitriles **82** and various aryl aldehydes **83** as well as NaN_3**10** as nitrogen source (Scheme 15). Investigations showed that $FeCl_3$, CuI, and L-proline are essential reagents for this catalytic reaction and by increasing the amount of $FeCl_3$ loading from 10 mol % to 30 mol %, the efficiency improved slightly. The scope examination of this procedure was performed using various *ortho*-halogenated benzonitriles and aryl aldehydes. The results demonstrated that both electron-neutral and electron-withdrawing substituents such as Me, F, and Cl on the phenyl ring of 2-bromobenzonitriles were suitable and afforded the desired quinazolines in moderate to good yields. Moreover, it was found that other *ortho*-halogenated benzonitriles like 2-fluoro, 2-chloro, and 2-iodobenzonitrile show good reactivity as well. In the case of aryl aldehydes, a range of aromatic aldehydes containing diverse substituents were examined and it was observed that aryl aldehydes with electron-donating (4-OMe, 4-OEt, 3,4-$(OMe)_2$, 2-Me, 4-Me), electron-withdrawing (3-NO_2, 3-Cl, 4-Cl), and electron-neutral (4-H) substituents gave the expected quinazolines in moderate to good yields. In addition, it was found that sterically hindered substrates like 1-



Scheme 10: Synthesis of 4-aminoquinazoline derivatives using $[Cp^*RhCl_2]_2$, AgOTf, and $Zn(OAc)_2$.

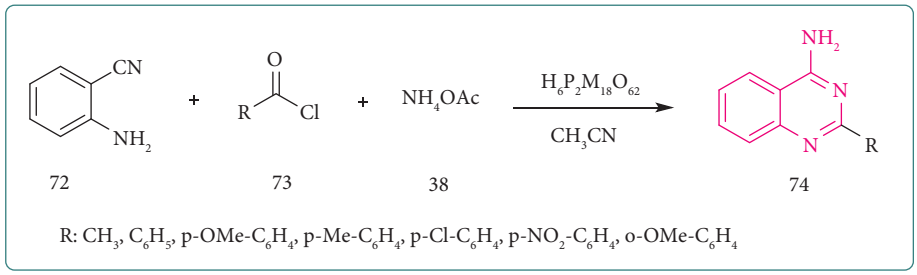


Scheme 11: Synthesis of 4-amino-2-aryl quinazoline derivatives using $SnCl_2$.



Scheme 12: Synthesis of 2,4-disubstituted quinazolines in the presence of $ZnCl_2$.

naphthaldehyde, 2-naphthaldehyde, and heteroaryl aldehydes including furan-2-carbaldehyde, thiophene-2-carbaldehyde, and thiophene-3-carbaldehyde were suitable for this reaction. The proposed mechanism of this procedure is represented in Figure 11. The iron-mediated [3 + 2] cycloaddition of benzonitriles with NaN_3 produces **85** which undergoes copper-catalyzed S_NAr reaction and generates **86**. Then, consecutive reduction, cyclization, oxidation, and copper-catalyzed



Scheme 13: Synthesis of 4-aminoquinazoline derivatives in the presence of Dawson-type heteropolyacids (HPAs) catalysts.

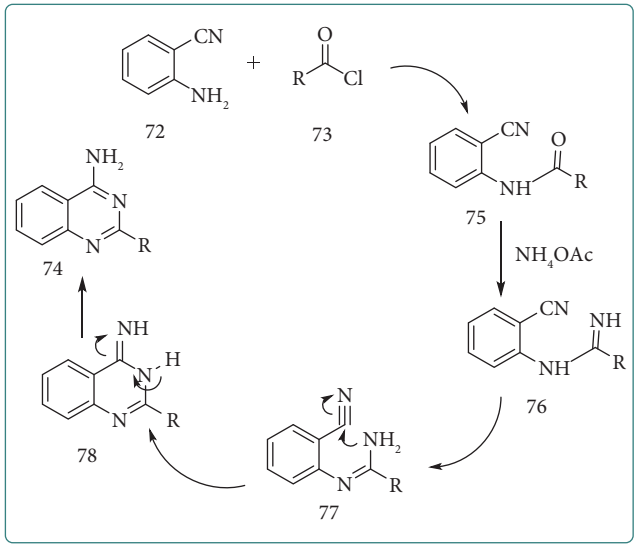


Figure 10: The proposed mechanism for the synthesis of 4-aminoquinazolines using HPAs as catalysts.

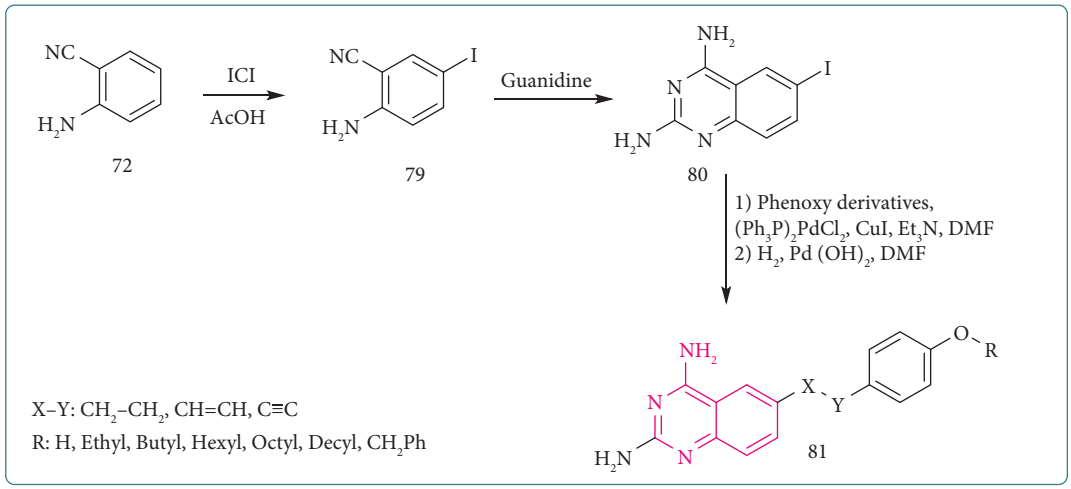
denitrogenation of intermediates lead to the target derivative **84**. The characteristic advantages of this approach are readily available starting reagents, substrate generality, and high efficiency [8].

2.3. Microwave Irradiation Methods. Seijas et al. described a solvent-free and efficient method for the production of 4-aminoquinazoline derivatives **96** through fusing 2-aminobenzonitrile **72** with nitriles **95**, under microwave irradiation (MW) conditions and utilizing 10% of potassium *tert*-butoxide (*t*-BuOK) as a base (Scheme 16). The scope investigation of this method was carried out utilizing several nitrile derivatives. The results showed that various nitriles containing phenyl-, 2-aminophenyl-, 2-furanyl-, 4-pyridyl-, and benzyl-moieties generated the target quinazoline derivatives in good to excellent yields. The characteristic advantages of this approach are short reaction time, high yields, absence of organic solvent, the use of catalytic amount of base, and an improvement over the previous method using traditional heating [31].

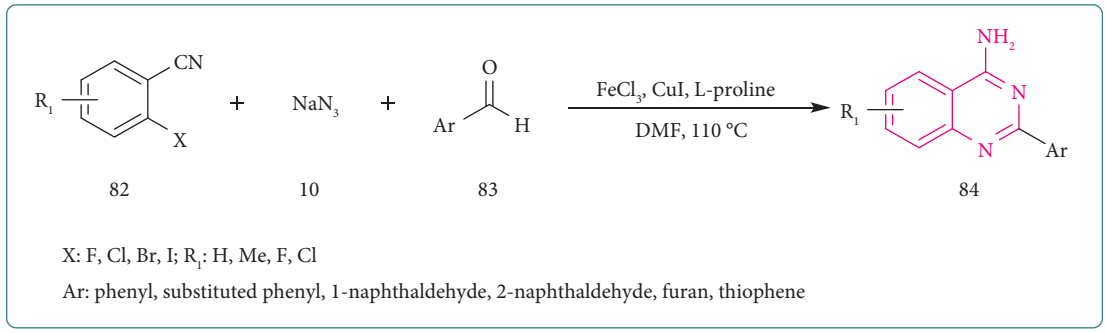
David et al. prepared a new set of 4-aminoquinazoline analogues **99** from the reaction of *N*-(2-cyanophenyl)-*N*,*N*-dimethylformamidine **97** with various amines **98** under microwave irradiation conditions (Scheme 17). This reaction carried out in acetic acid and acetonitrile. The scope exploration of this reaction was carried out using various substrates including substituted *N*-(2-cyanophenyl)-*N*, *N*-dimethylformamidine and different amines with a variety of electronic and steric substituents including benzylamines, aliphatic amine, and anilines under optimized conditions. The results indicated that all the tested substrates afforded the corresponding derivatives in high yields except the aniline with electron-poor substituent (Br) which generated the products in moderate yields. The significant benefits of this method are being simple, efficient, short time, one step, and having high yields [32].

Rad-Moghadam et al. described a microwave-promoted one-pot approach for the preparation of 2-alkyl-4-aminoquinazoline analogues **101** (Scheme 18). The reaction of 2-aminobenzonitrile **72** with different orthoesters **100** and NH_4OAc **38** under solvent-free condition resulted in desired products in good yields. In this case, in order to reduce the side reactions, excess amount of orthoesters is required. The scope of this method was investigated using different orthoesters under optimized conditions. According to the results, diverse orthoesters bearing H, methyl-, ethyl, n-propyl-, and n-butyl-groups gave the desired derivatives in excellent yields. The possible mechanism of the described process is including the initial formation of the amidine intermediate **102** from the reaction of 2-aminobenzonitrile with orthoesters and NH_4OAc. Followed by nucleophilic attack of the amino group to the carbon atom of the nitrile group which leads to the formation of 4(3H)-iminoquinazoline intermediate **104** and subsequently tautomerize and resulted in the target product (Figure 12). It should be noted that in this method the intramolecular addition of amines to the nitrile group occurs easily and in nearly neutral conditions; while under conventional condition, this reaction requires harsh conditions and strong Lewis acids [33]. The advantages of this method are being one-pot, solvent free, operational simplicity, simple starting materials, mild condition, short reaction time, and high yields [34].

Haghighijoo et al. described a rapid and convenient approach for the preparation of 4-aminoquinazoline derivatives **109** using 2-amino-4,6-dicholorobenzoic acid **105** (Scheme 19). In this method, reaction of 2-amino-4,6-dicholorobenzoic acid **105** with formamide under microwave conditions resulted in intermediate **106,** which on etherification with different alkoxy or morpholine generated **107**. Then, the oxo group of **107** was substituted by chlorine



Scheme 14: Copper/palladium-catalyzed synthesis of 2,4-diaminoquinazoline derivatives.



Scheme 15: Synthesis of 2-phenylquinazolin-4-amine derivatives in the presence of $FeCl_3$, CuI, and L-proline.

in the presence of $SOCl_2$ and led to the intermediate **108**. Finally, the reaction of intermediate **108** with various anilines resulted in the corresponding products in moderate to good yields. The results indicated that all the tested substrates including alkoxy, morpholine, and various anilines with 2-CN; 3-CN; 2-Me-5-Cl; and 2,5-diethoxy substituents were well tolerated and generated the corresponding derivatives in moderate yields. The remarkable benefits of this approach are the cheap, readily available reagents, and good yields [35].

Song et al. obtained a new set of 4-aminoquinazoline derivatives **112** from 2-amino-5-nitrobenzonitrile **110** and various anilines **111** in good to excellent yields, under microwave irradiation condition (Scheme 20). In this method, no solvent was required because DMF-DMA acted as both solvent and reagent. The substrate scope of this method was investigated using a series of anilines under optimized conditions. The results indicated that anilines with the halogen groups (F, Cl, and Br) at *meta*- or *para*-positions, except the Br group at the *para*-position, gave the target products in excellent yields. Furthermore, anilines with–C≡CH and CF_3 groups at *meta*-position provided the target derivatives in good yields but anilines with electron-donating groups such as OH and Me gave low yields. The suggested mechanism for this system is illustrated in Figure 13. Initially, the reaction of 2-amino-5-nitrobenzonitrile with DMF-DMA leads to the formation of corresponding formamidine cation **114.** Compound **114** undergoes electrophilic attack of the aniline **111** on the carbon of the cyano group and subsequent intramolecular electrophilic addition of nitrile nitrogen to enamine carbon results in the generation of intermediate **115**. Then, aromatization and elimination of the dimethylamino moiety leads to the expected product **112**. The advantages of this procedure are simple, one-pot cascade, short reaction time, environmentally friendly, and low volume of the organic solvent [36].

Haghighijoo et al. obtained a new set of 4-aminoquinazoline derivatives **119** with different substitutions using *ortho*-diflouro or *ortho*-dimethoxy anthranilic acid **116** under microwave irradiation conditions (Scheme 21). In this reaction, *ortho*-substituted anthranilic acid was reacted with formamide to produce intermediate **117** which was converted to the compound **118** in the presence of thionyl chloride ($SOCl_2$). Finally, the reaction of **118** with aniline derivatives in 2-propanol and DMF afforded the desired products in good yields. The results showed that the substitution type on the phenyl ring of anthranilic acid and also various anilines with different substituents had negligible

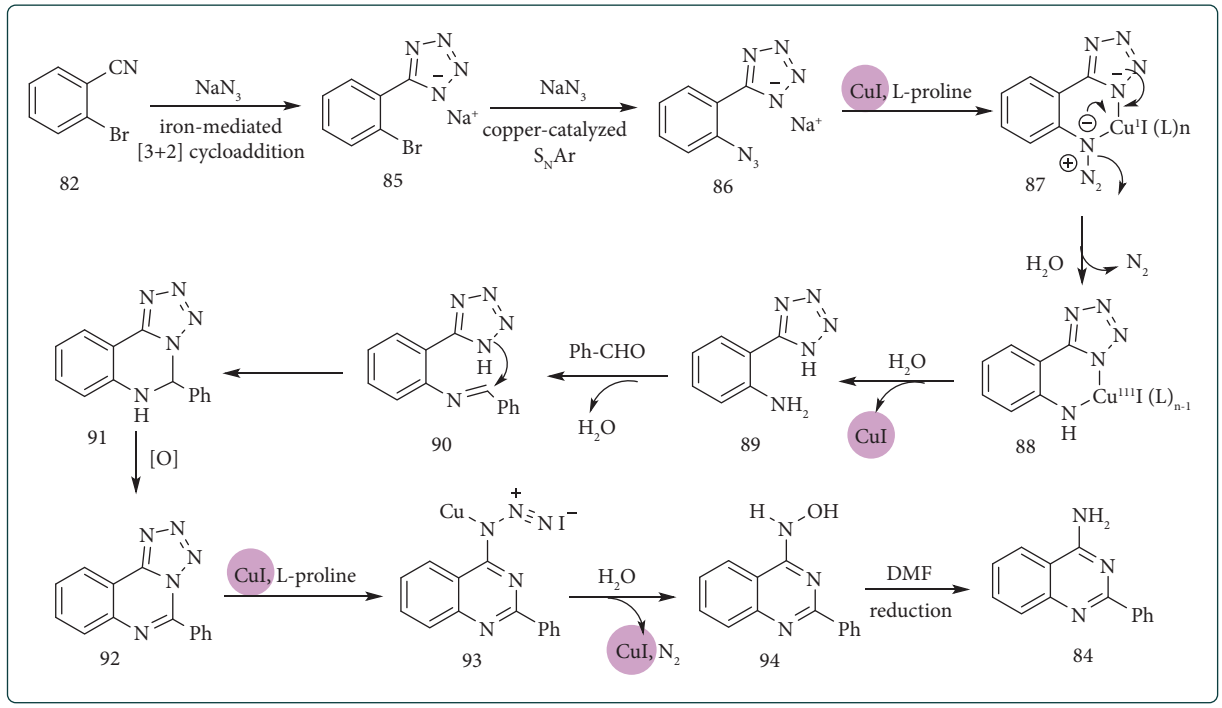
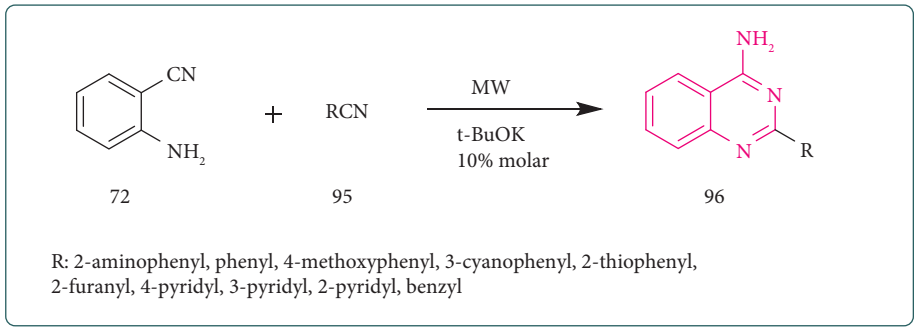


Figure 11: The proposed mechanism for the synthesis of 2-phenylquinazolin-4-amine derivatives in the presence of $FeCl_3$, CuI, and L-proline.

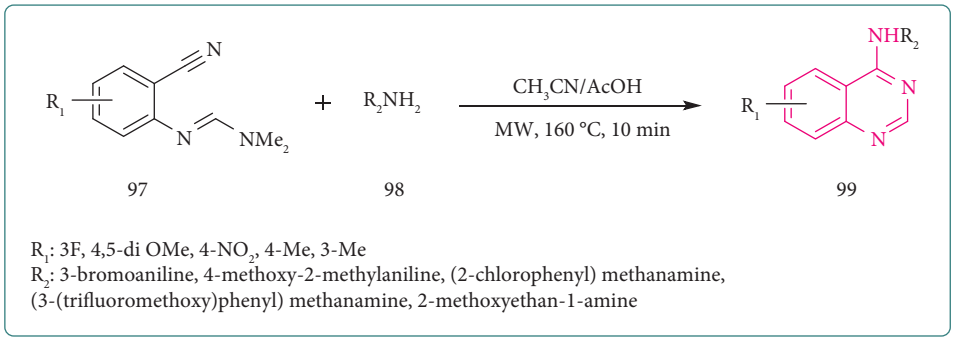


Scheme 16: Synthesis of 4-aminoquinazoline derivatives using 2-aminobenzonitrile under microwave irradiation.

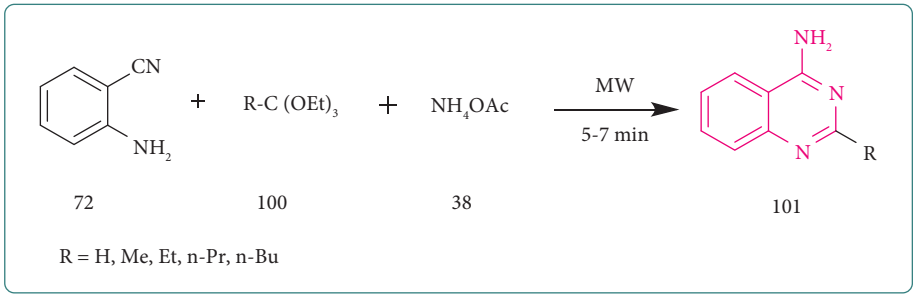
effects on the reaction yield. This method has some advantages like good yield of products, cleaner products, and easy work up [37, 38].

2.4. Metal-Catalyzed/Microwave Irradiation Methods. Tian et al. described a rapid and efficient iron-catalyzed method for the production of 4-amino-quinazoline analogous **122** from the reaction of quinazoline-3-oxides **120** and carbodiimides **121** in the presence of $FeCl_3.6H_2O$ as a catalyst and DMF as a solvent, under microwave irradiation conditions (Scheme 22). The scope investigation of this process was performed using a range of different quinazoline-3-oxides and carbodiimides under the optimized reaction conditions. The results demonstrated that different substituted quinazoline-3-oxides do not have a significant effect on the reaction yields but in the case of carbodiimides, aromatic carbodiimides afforded the target products in better yields compared to the aliphatic carbodiimides. The probable mechanism of this procedure (Figure 14) involves the [3 + 2] cycloaddition reaction between quinazoline-3-oxides **120** and carbodiimides **121** to generate intermediate **123**, which might be unstable in the presence of Fe^{3+}. Then, the rearrangement and aromatization of intermediate **124** under microwave irradiation gives **125**, followed by the isomerization process which affords the target product **122**. The advantages of this method are efficient, short reaction time, economic, environmentally benign, and good to excellent yields [6].

Liu et al. reported a microwave irradiation procedure for the preparation of a novel set of fluorinated 2-alkylthio-4-aminoquinazoline derivatives **128** in the presence of basic alumina as a solid-support agent and a solid base (Scheme 23). In this method, polyfluoro-



Scheme 17: Synthesis of 4-aminoquinazoline derivatives using N-(2-cyanophenyl)-N,N-dimethylformamidine under microwave irradiation conditions.



Scheme 18: Synthesis of 2-alkyl-4-aminoquinazoline derivatives using 2-aminobenzonitrile under solvent-free and microwave irradiation condition.

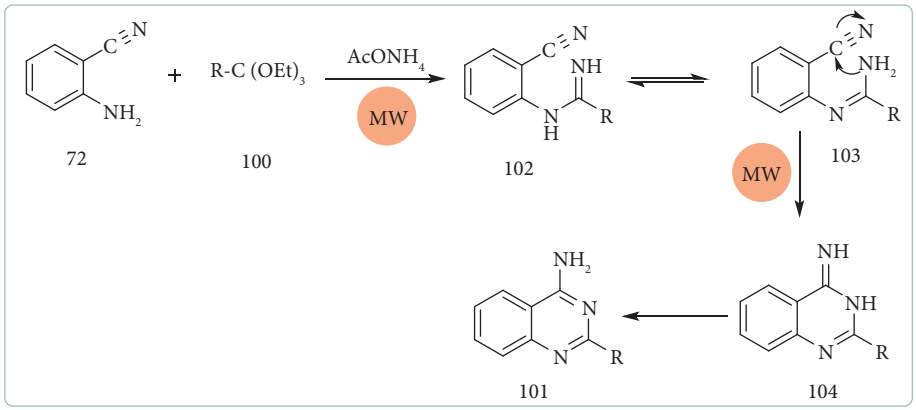
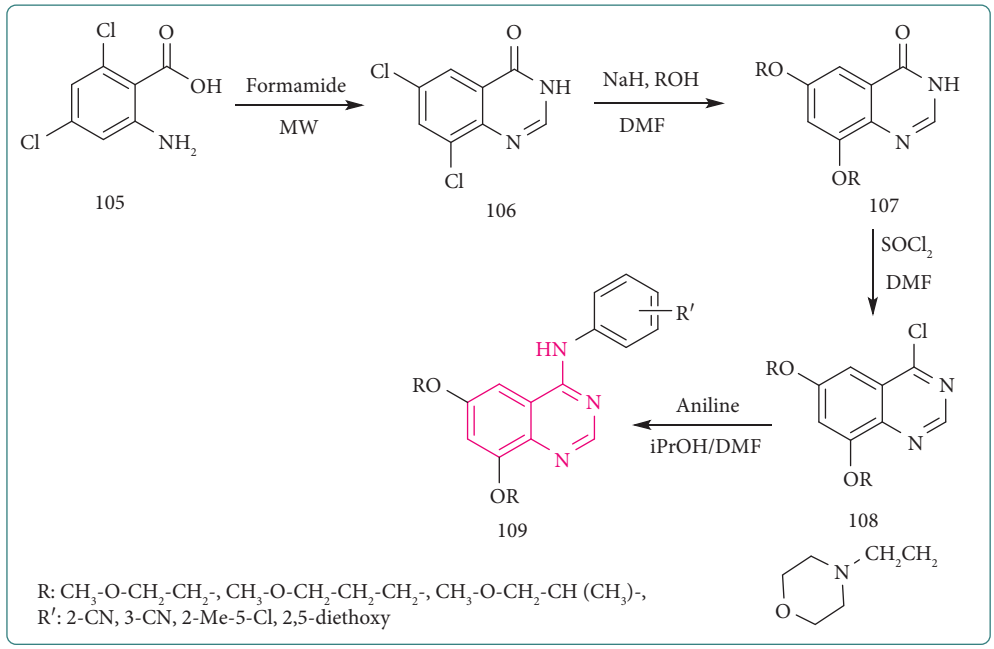
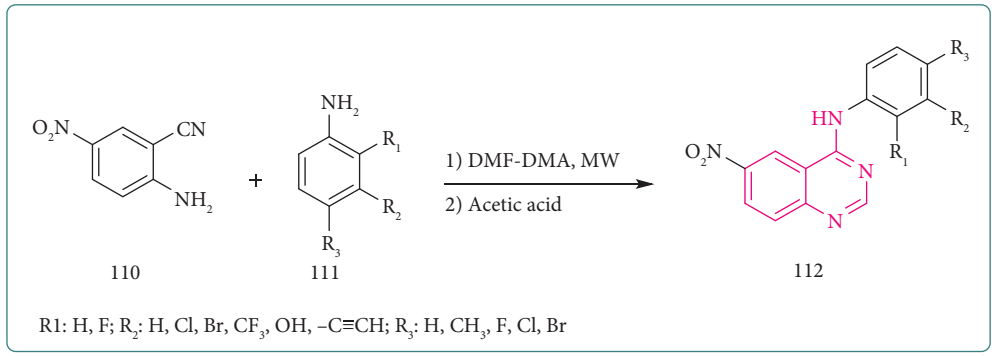


Figure 12: The proposed mechanism for the synthesis of 2-alkyl-4-aminoquinazoline derivatives using 2-aminobenzonitrile under microwave irradiation condition.

benzenedicarbonitriles **126** and isothiouronium salts **127** were adsorbed onto basic alumina using ethanol and irradiated to obtain the corresponding derivatives in good yields. The scope investigation of this approach was performed using various substituted polyfluoro-benzenedicarbonitriles and isothiouronium salts under optimized reaction conditions. The results demonstrated that in the cases of polyfluoro-benzenedicarbonitriles, there were no significant differences in the reactivity and yields of corresponding products. In addition, the results revealed that the S alkyl/alkyl ethers isothiouronium salts led to the corresponding 2-alkylthio-4-aminoquinazoline derivatives in good yields. Moreover, it was found that isothiouronium salts with short carbon chain provided higher yields compared to the isothiouronium salts with a long carbon chain. Various isothiouronium salts with S-benzyl/naphthalen-2-ylmethyl/allyl/cyanomethyl moiety afforded the target quinazolines with good yields in shorter reaction time. Tetrafluoroterephthalonitrile were also tested to extend the scope of substrates. Tetrafluoroterephthalonitrile compared to the polyfluoro-benzenedicarbonitriles derivatives gave the corresponding products in moderate yields. The suggested mechanism of this microwave irradiation method is illustrated in Figure 15. The free isothiourea **129** is obtained from the adsorption reaction of its hydrogen halide with basic alumina. Subsequently, the nucleophilic aromatic



Scheme 19: Synthesis of 4-aminoquinazoline derivatives using 2-amino-4,6-dicholorobenzoic acid under microwave irradiation condition.



Scheme 20: Synthesis of 4-aminoquinazoline derivatives using 2-amino-5-nitrobenzonitrile under microwave irradiation.

substitution at *o*-fluoro of **126** affords intermediate **130**. Afterwards, benzonitrile is activated by the surface O–H group on basic alumina followed by the N-nucleophilic amine attacks on the nitrile group to generate **132** which undergoes tautomerization to form the expected product **128**. The significant advantages of this approach are efficient, environmentally benign, inexpensive, broad isothiourea substrate scope, and easily available materials [39].

2.5. Solid-Phase Method. Wilson reported a solid-phase method for the preparation of 2,4-diaminoquinazoline derivatives **135** from the condensation of substituted 2-aminobenzonitriles **134** with various amines in good yields (Scheme 24). The substrate scope examination of this procedure was performed using different amines and substituted 2-aminobenzonitriles. According to the results, the secondary amines gave the corresponding products in average to good yields while the primary amines such as t-BuNH_2 failed to produce the desired products. Furthermore, the lower yields of NH_3 and $(CH_3)_2NH$ could be due to interference with the cosolvent in which these amines were dissolved. In the case of substituted 2-aminobenzonitriles, all the tested substrates with alkyl (Me), alkoxy (OMe), and halogen (Cl, F) substituents, except the nitro-substituted, afforded the desired products in good yields. Probably in the case of nitro-substituted, even the thiourea resin has been formed but the second step which involved the guanidine formation or resin cleavage was unsuccessful. The plausible mechanism for this solid-phase method is represented in Figure 16. In this method, the carboxy polystyrene **136** is used to produce acyl isothiocyanate resin **133**. Afterwards, substituted 2-aminobenzonitriles are added to the resin. The resin-bound guanidine **138** is

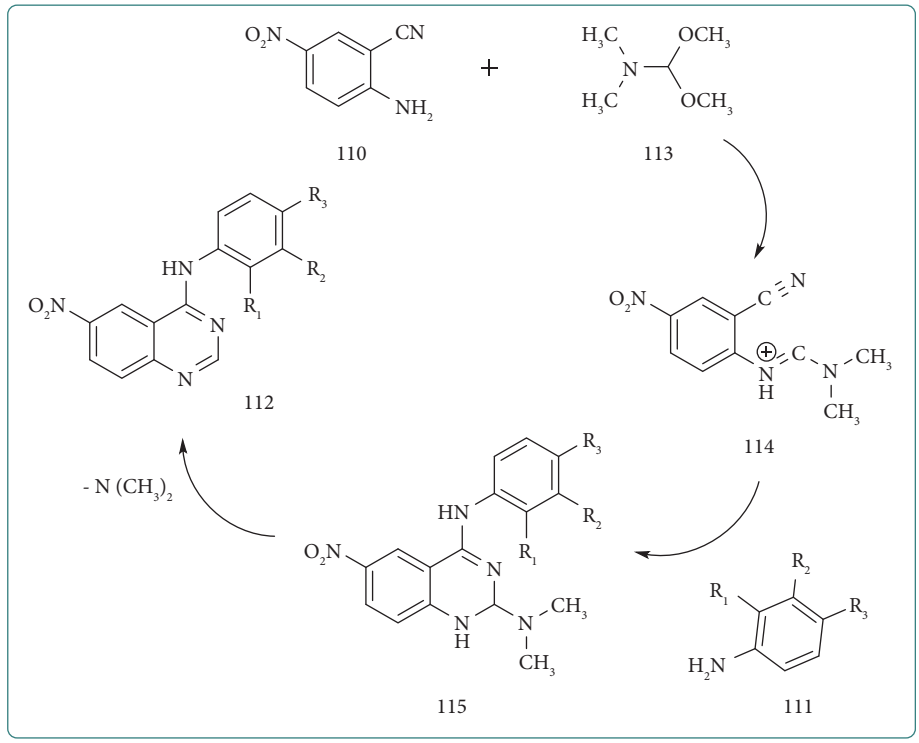
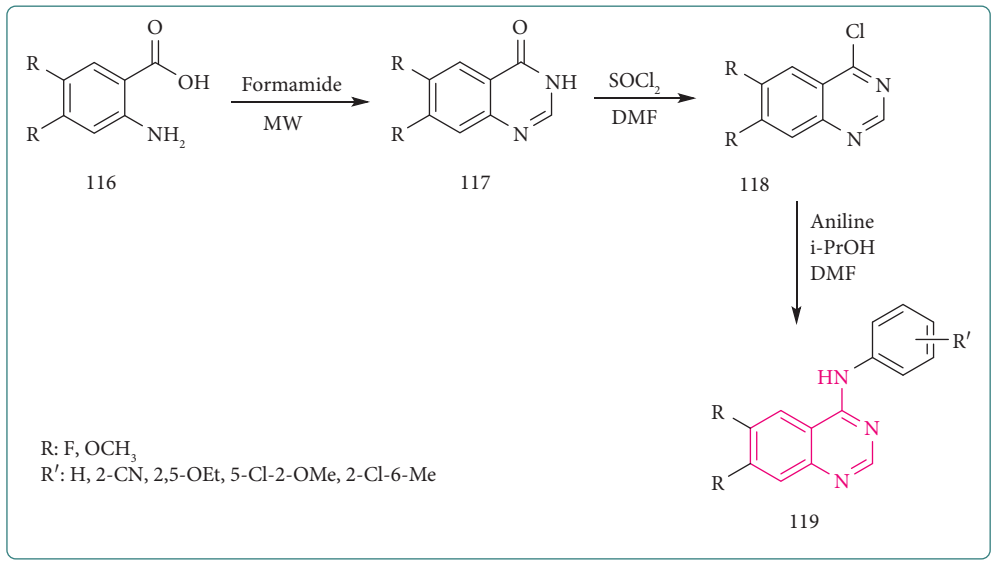


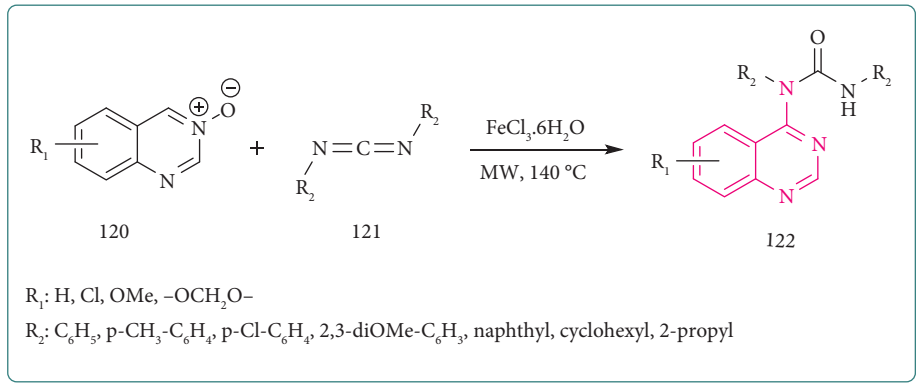
Figure 13: The proposed mechanism for the synthesis of 4-aminoquinazoline derivatives using 2-amino-5-nitrobenzonitrile under microwave irradiation.



Scheme 21: Synthesis of 4-aminoquinazolines derivatives using *ortho*-diflouro or *ortho*-dimethoxy anthranilic acid under microwave irradiation condition.

generated by treatment of intermediate **137** with various amines and EDC (1-(3-dimethylaminopropyl-3-ethyl-carbodiimide hydrochloride)) under basic conditions. Optimal cleavage conditions are achieved by using trifluoroacetic acid (TFA) and water at 80°C to afford the final product **135**. The advantage of this method is good purity [40].

2.6. Cyclocondensation Reactions. Yakhontov et al. synthesized a series of substituted 4-amino-2-methylquinazolines **142** using anthranilic acid or 4-chloroanthranilic acid **139** (Scheme 25). In this method, the reaction of anthranilic acid or 4-chloroanthranilic acid with acetic anhydride resulted in the 2-methylbenzoxazinones-4(H) intermediates, which were then converted into the corresponding



Scheme 22: Synthesis of 4-aminoquinazoline derivatives in the presence of $FeCl_3.6H_2O$, under microwave irradiation conditions.

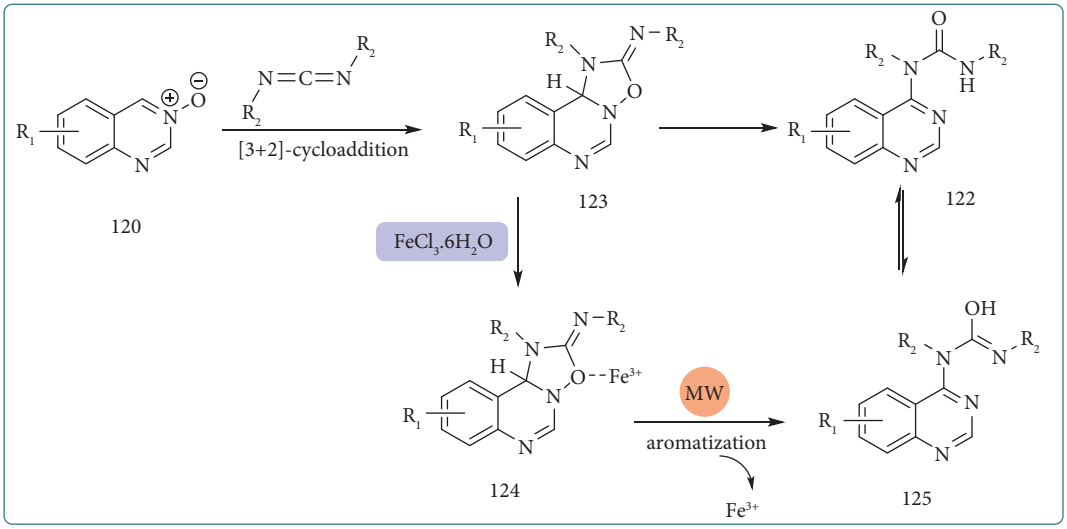


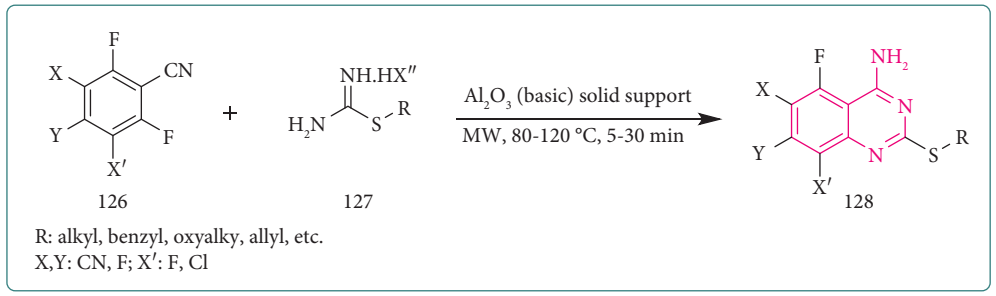
Figure 14: The proposed mechanism for the synthesis of 4-aminoquinazolines in the presence of $FeCl_3.6H_2O$, under microwave irradiation conditions.

2-methylquinazolones **140** using boiling 25% aqueous ammonia solution. The reaction of intermediates **140** with $POCl_3$ in the presence of dimethylaniline led to the formation of **141** which then reacted with various amines and gave the target products in high yields. The results showed that anthranilic acid and 4-chloroanthranilic acid, as well as various aliphatic, aromatic, and aliphatic-aromatic amines were well tolerated and gave the corresponding products in high yields. The advantages of this method are efficient and high yields of products [41].

Tomisek et al. reported the synthesis of a series of 4-aminoquinazoline derivatives **146** using 5-chloro-anthranilic acid **69** and anilines in the presence of acetic anhydride, NH_3, and P_2S_5 (Scheme 26). In this process, 6-chloro-2-methyl-3,1-benzoxazin-4-one **143** was synthesized through heating anthranilic acid in anhydrous acetic anhydride. Then, the reaction of **143** with NH_3 yielded **144**. The cyclodehydration of **144** to the quinazolinone **145** was performed through heating in the NaOH solution. Finally, compound **146** was synthesized from the reaction of 6-chloro-2-methyl-4(3H)-quinazolinone **145** with aniline in the presence of P_2S_5 [42].

Sirisoma et al. synthesized a novel series of 4-aminoquinazoline derivatives **150** using 2-aminobenzoic acid methyl ester **147** (Scheme 27). In this process, 2-aminobenzoic acid methyl ester was reacted with various nitriles including acetonitrile, propiononitrile, fluoroacetonitrile, and chloroacetonitrile and led to the synthesis of intermediates **148**. Then, intermediates **148** reacted with distilled $POCl_3$ in anhydrous toluene and diisopropylethylamine to produce **149**. Finally, the reaction of **149** with substituted anilines in anhydrous isopropanol (IPA) in the presence of concentrated HCl led to the expected products **150** in moderate to good yields [43].

Hu et al. described an approach for the synthesis of a new series of 4-aminoquinazoline analogues **154**, **155**, and **156** by utilizing 2-cyano-4-nitro-aniline **151**, N, N-dimethylformamide dimethyl acetal **152**, and different substituted anilines reagents (Scheme 28). The reaction of 2-cyano-4-nitro-aniline with N, N-dimethylformamide



Scheme 23: Synthesis of fluorinated 2-alkylthio-4-aminoquinazolines under microwave irradiation.

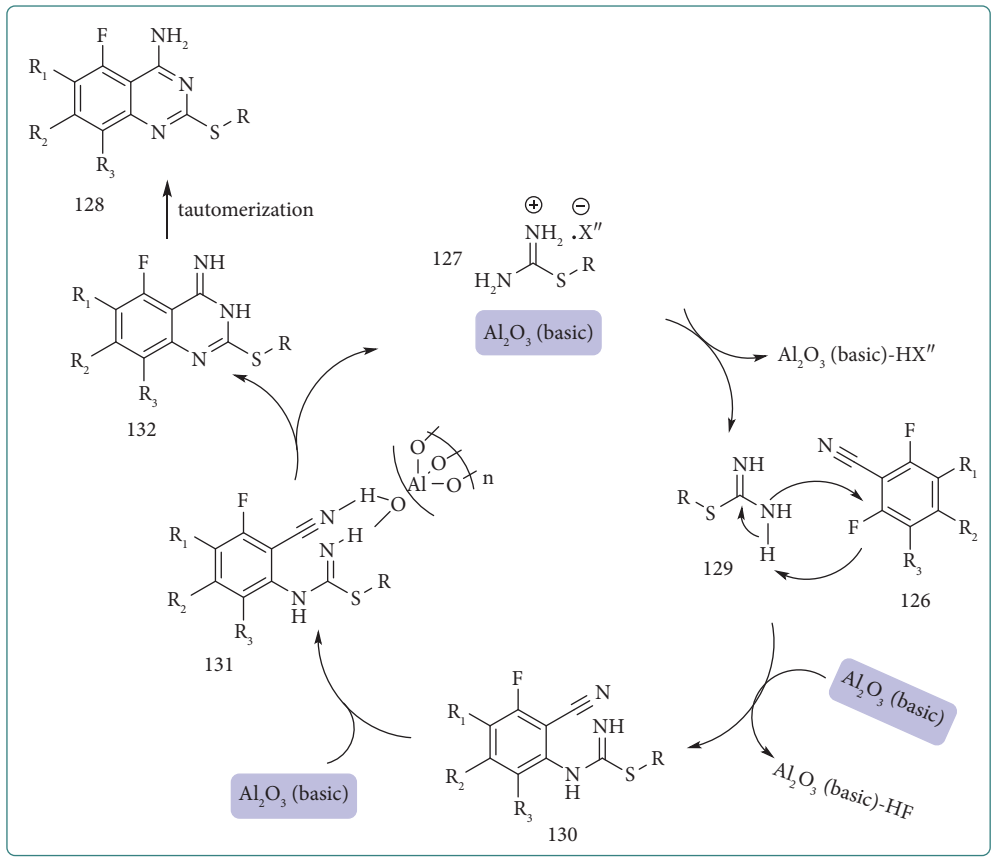
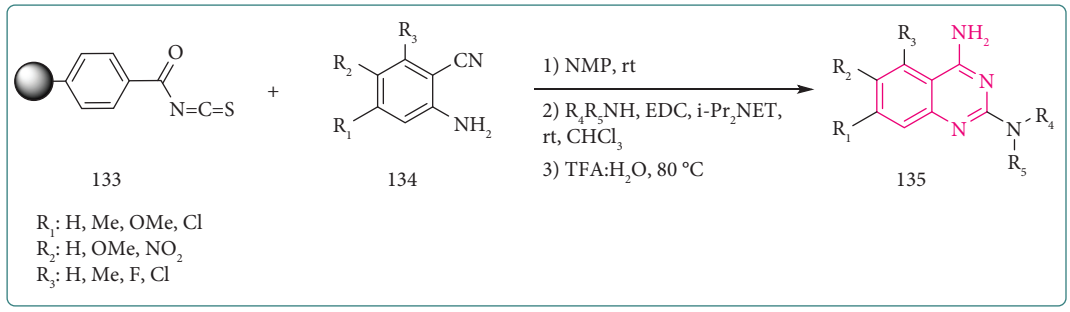


Figure 15: The proposed mechanism for the synthesis of fluorinated 2-alkylthio-4-aminoquinazolines under microwave irradiation.

dimethyl acetal resulted in the key intermediate formamidine **153**. Cyclization of the key intermediate **153** with various substituted anilines in acetic acid led to the formation of corresponding compounds **154**. Reduction of compounds 154 in the presence of Fe/EtOH/AcOH generated **155**. The alkyl substituted quinazolines **156** were prepared by alkylation of **154** with allyl bromide or 1-chloro-3-methylbut-2-ene in the presence of K_2CO_3 [44].

Wang et al. reported a new and efficient procedure for the preparation of 4-aminoquinazoline derivatives **161** based on the conversion of indoline-2,3-dione **158** to formamidine (Scheme 29). Initially, different substituted anilines **157** reacted with chloral hydrate (Cl_3CCHO) and hydroxylamine hydrochloride ($HONH_3Cl$) to generate anilide derivatives. Then, Beckmann rearrangement was carried out in 95% of H_2SO_4 to prepare the key intermediate indole-2,3-dione **158**. Condensation of indole-2,3-dione with hydroxylamine hydrochloride followed by heating in a solution of DMF and $POCl_3$ yielded the compound **160**. Finally, the target quinazoline derivatives were obtained from the reaction of the compound **160** with substituted anilines. The scope investigation of this procedure was carried out using various substituted anilines as starting reactants. The results demonstrated that anilines with electron-drawing substituents afforded the anilide derivatives in higher yields compared to the anilines with electron-donating substituents. Furthermore, anilines containing two electron-donating substituents on the benzene ring, gave lower yields compared to the



Scheme 24: Synthesis of 2,4-diaminoquinazoline derivatives using acyl isothiocyanate resin.

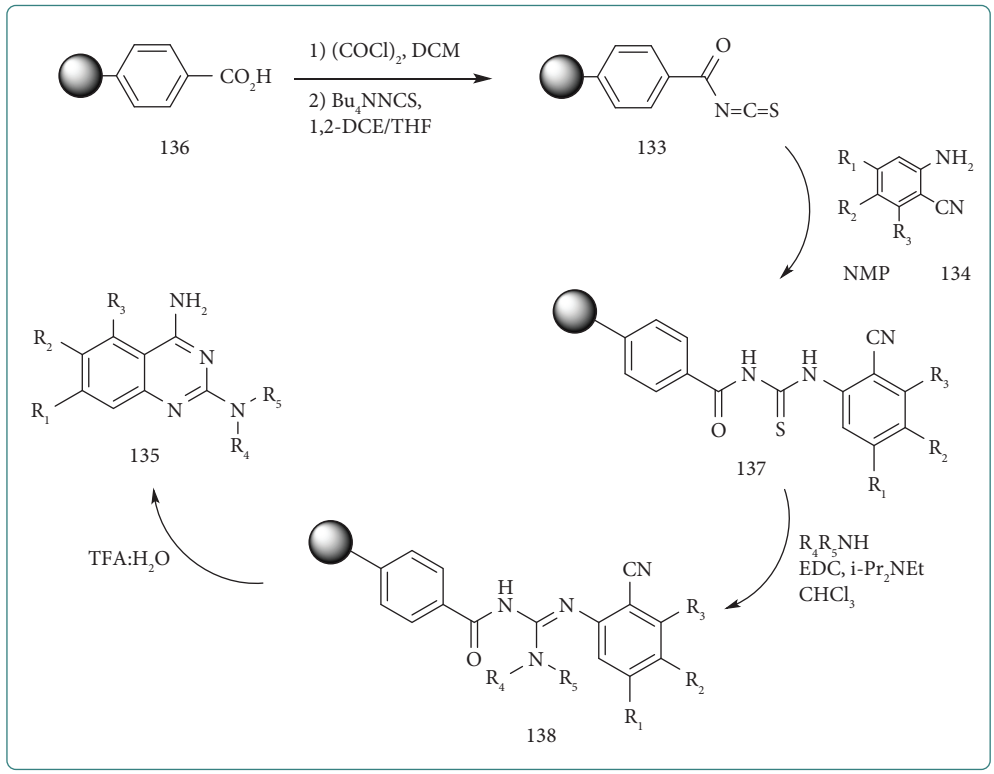
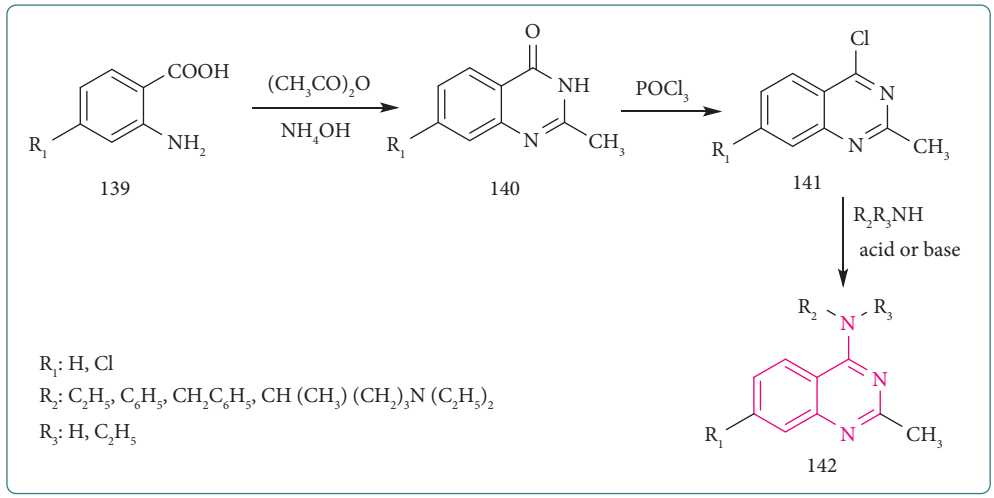


Figure 16: The proposed mechanism for the synthesis of 2,4-diaminoquinazolines using acyl isothiocyanate resin.

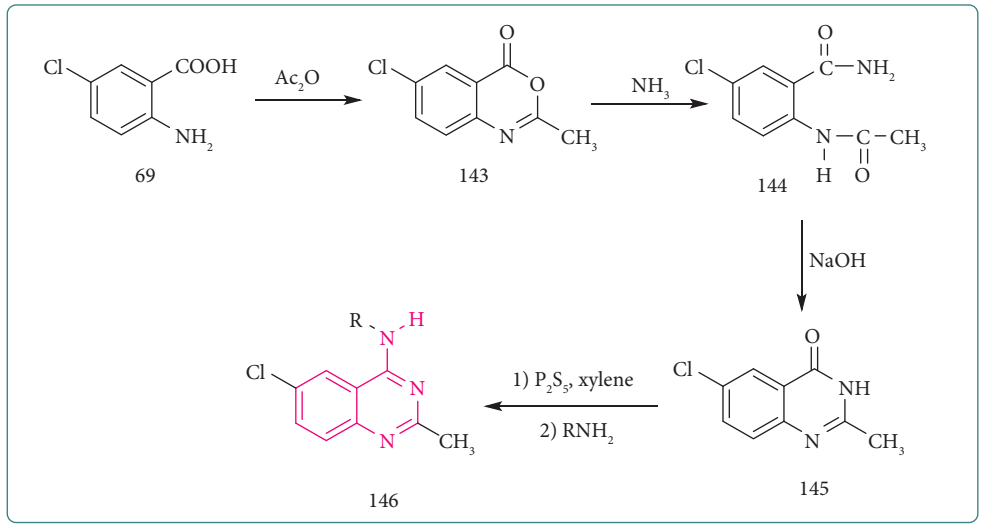
other anilines. The advantages of this procedure are new, inexpensive starting material, simple, efficient, environmental friendly, and safe [45].

Kamal et al. obtained a new set of 4-arylaminoquinazoline-2-carboxylic acid analogues **164** in good yields from the reaction of (*Z*)-2-amino-*N*′-arylbenzimidamides **162** with various anhydrides **163** in dry ethanol under reflux conditions (Scheme 30). The scope of the described procedure explored using substituted (*Z*)-2-amino-*N*′-arylbenzimidamides and various anhydrides. The results revealed that various anhydrides including diphenic anhydride, phthalic anhydride, and succinic anhydride were successfully reacted with (*Z*)-2-amino-*N*′-arylbenzimidamides and afforded the corresponding quinazoline derivatives in high yields. According to the proposed mechanism, the nucleophilic attack of the amine group of **162** to the carbonyl group of **163** results in the formation of intermediate **165** which on subsequent rearrangement forms intermediate **166**. Then, an intramolecular ring closure of **166** leads to the generation of **167,** which is followed by losing a molecule of water and a 1,3-proton transfer to afford **164** (Figure 17) [46].

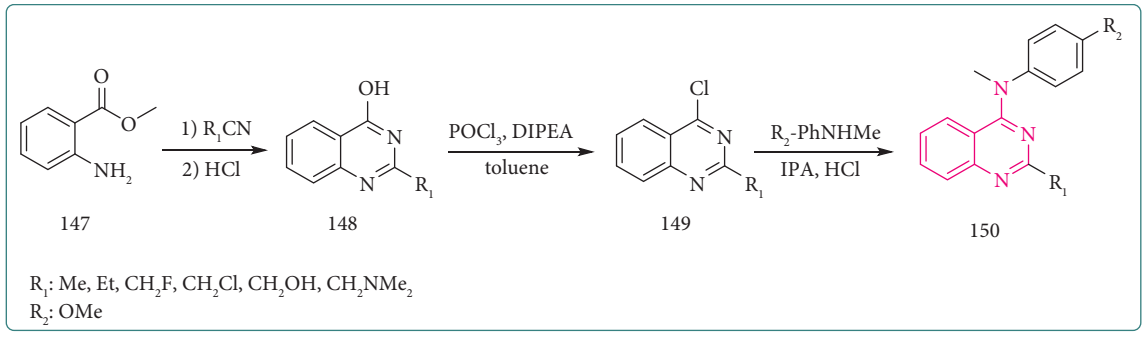
2.7. Direct Amination Methods. Shen et al. developed an efficient direct amination of quinazolin-4(3H)-ones **168** in the presence of hexachlorocyclotriphosphazene (HCCP), diisopropylethylamine (DIPEA), and various amines **169** for the preparation of 4-aminoquinazoline derivatives **170** in good yields (Scheme 31). The scope investigation of this method was performed using various primary and secondary amines, as well as a range of substituted quinazolin-



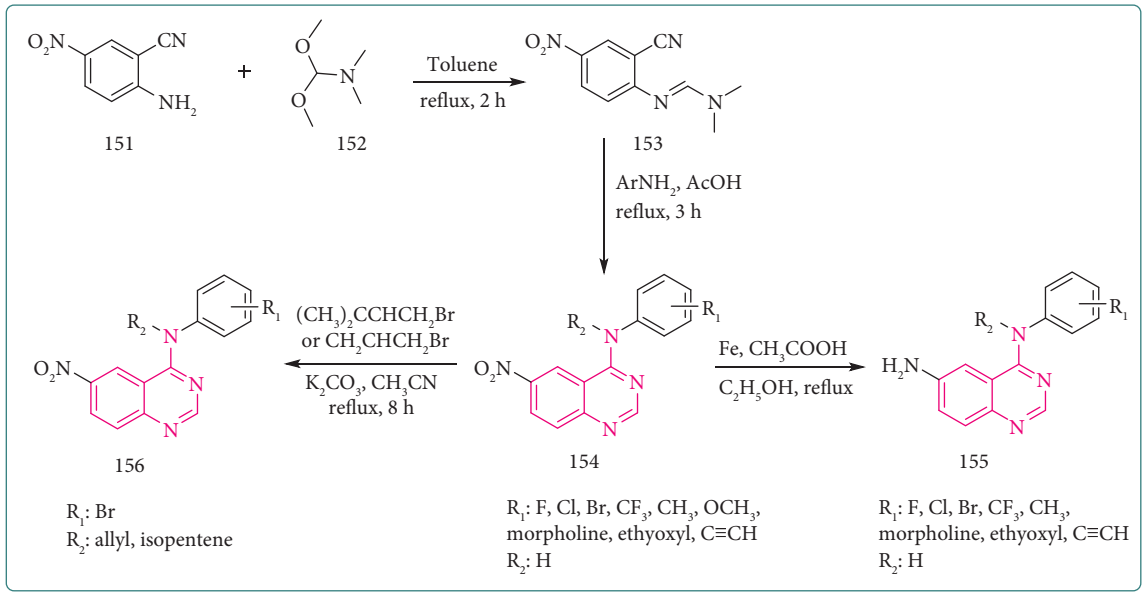
Scheme 25: Synthesis of a series of substituted 4-amino-2-methylquinazolines in the presence of $(CH_3CO)_2O$, NH_4OH, and $POCl_3$.



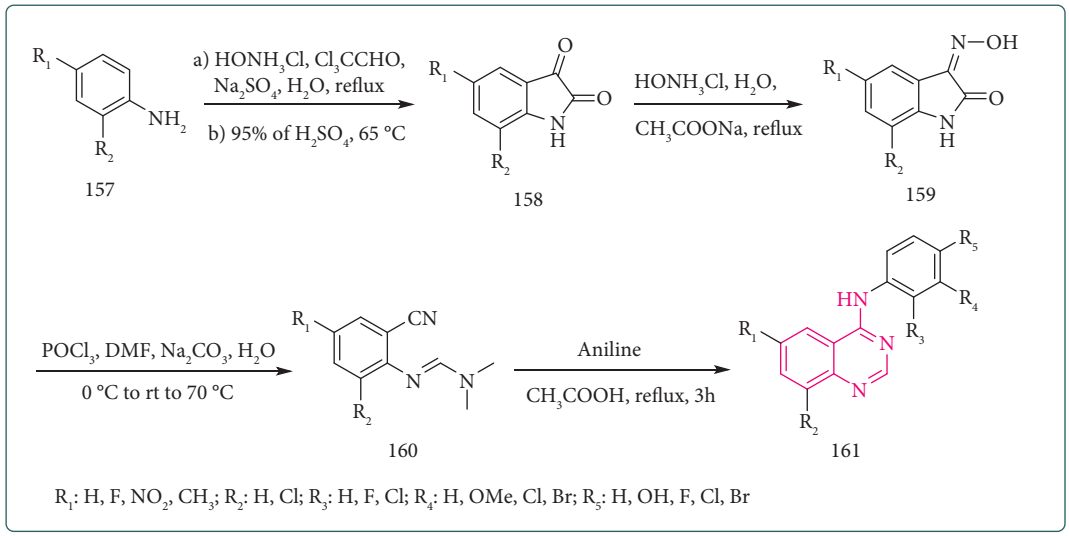
Scheme 26: Synthesis of 4-aminoquinazoline derivatives in the presence of acetic anhydride, NH_3, and P_2S_5.



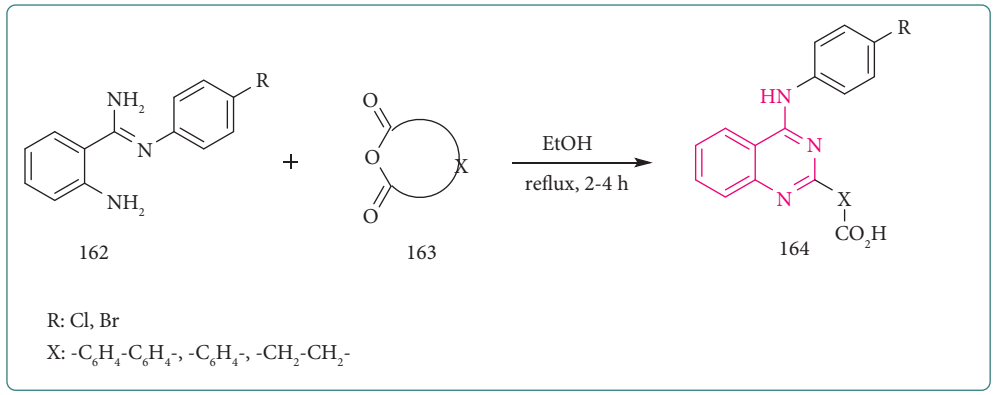
Scheme 27: Synthesis of 4-aminoquinazoline derivatives using 2-aminobenzoic acid methyl ester in the presence of $POCl_3$ and DIPEA.



Scheme 28: Synthesis of a new series of 4-aminoquinazolinone derivatives using 2-cyano-4-nitro-aniline.



Scheme 29: Synthesis of 4-aminoquinazoline derivatives using Cl_3CCHO, $HONH_3Cl$, and $POCl_3$.



Scheme 30: Synthesis of 4-arylaminoquinazoline-2-carboxylic acid analogues.

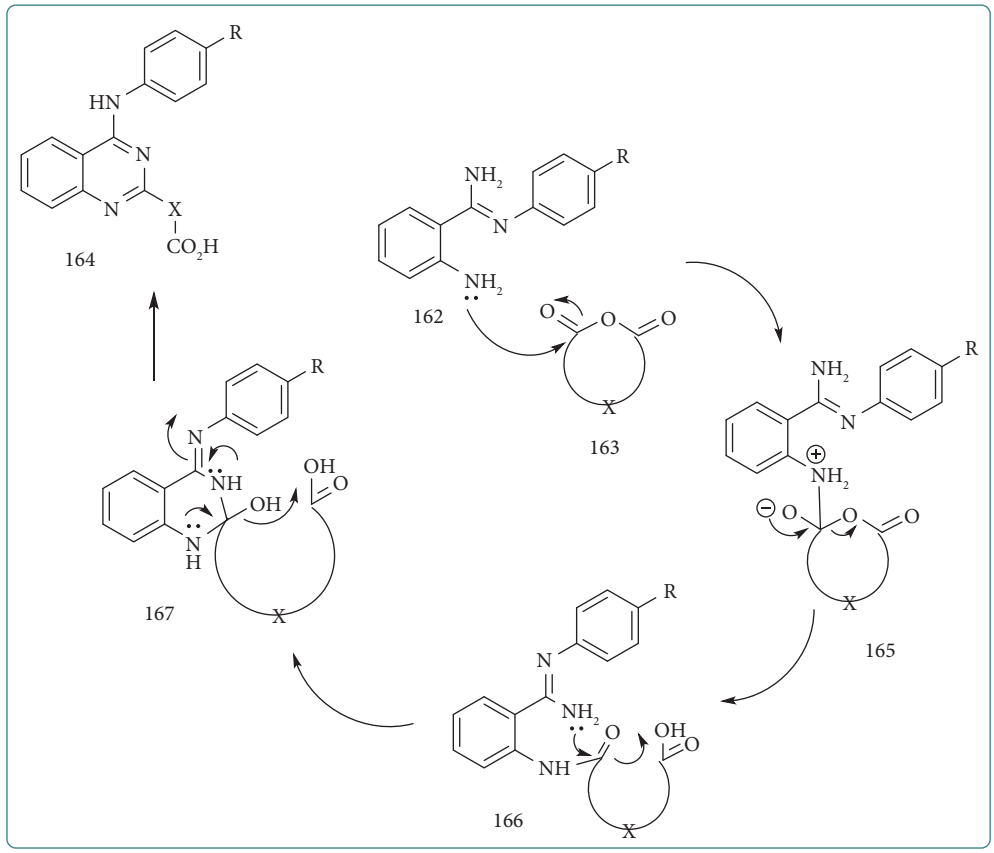
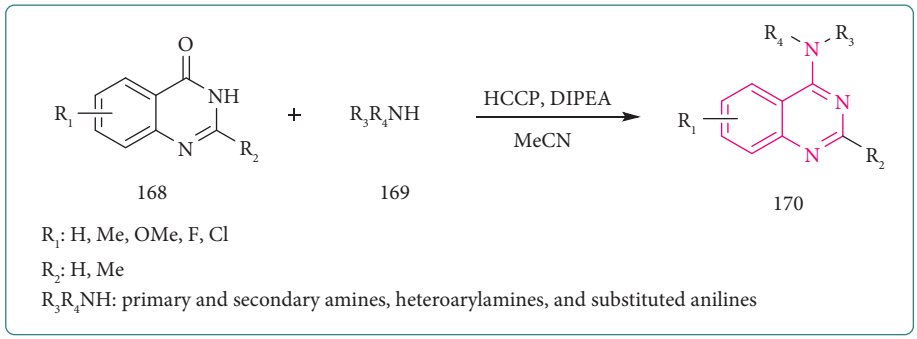


Figure 17: The proposed mechanism for the synthesis of 4-arylaminoquinazoline-2-carboxylic acid derivatives.

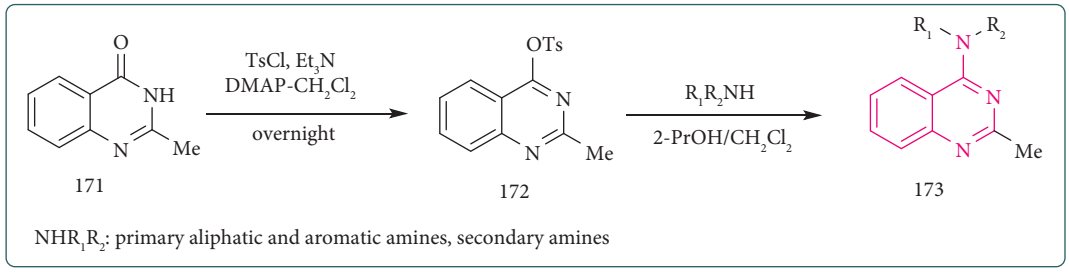
4(3H)-ones under optimized reaction conditions. The results indicated that primary and secondary amines with low steric hindrance smoothly reacted with quinazolin-4(3H)-ones and produced the target products in good yields, while the reaction of sterically hindered amines such as tert-butylamine, gave low yields despite increasing the reaction temperature. Furthermore, nitrogen heterocycles, like pyrrolidine, piperidine, morpholine, and imidazole were also tested and afforded the desired products in high yields. Since anilines were much weaker nucleophiles compared to the alkylamines, no products were generated at room temperature, although moderate yields were obtained under reflux conditions. Anilines with electron-neutral and electron-donating substituents gave better yields compared to the anilines with electron-withdrawing substituents such as Cl. In the case of substituted quinazolin-4(3H)-ones, it was found that all the substituted quinazolin-4(3H)-ones with H, Me, Cl, and F substituents were suitable substrates for this process and afforded the corresponding products in good yields. Furthermore, 6,7-dimethoxyquinazolin-4(3H)-one with two methoxy groups, benzo[g]quinazolin-4(3H)-one and pyrido [2, 3-d] pyrimidin-4(3H)-one substrates were well tolerated and produced the corresponding products in 65–85% yield. This method has several advantages including mild, economical, and suitable for a broad range of amines. [47].

Lockman et al. reported a synthetic route to provide the 4-aminoquinazoline derivatives **173** from the reaction of 2-methyl-3H-quinazolin-4-one **171** with various amines (Scheme 32). Initially, the reaction of **171** with p-toluenesulfonyl chloride (TsCl) in the presence of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP) in CH_2Cl_2 led to the quinazoline sulfonate ester intermediate **172** in excellent yield. In the following step, the reaction of the sulfonate ester intermediate with various amines in 2-propanol and CH_2Cl_2 led to the desired products in high yields. The scope of this method was investigated using a range of primary aliphatic and aromatic amines as well as secondary amines with different sizes and electronic properties. The results indicated that all the tested amines except the extremely hindered derivatives such as diisopropylamine and diphenylamine, afforded the expected derivatives in excellent yields [48].

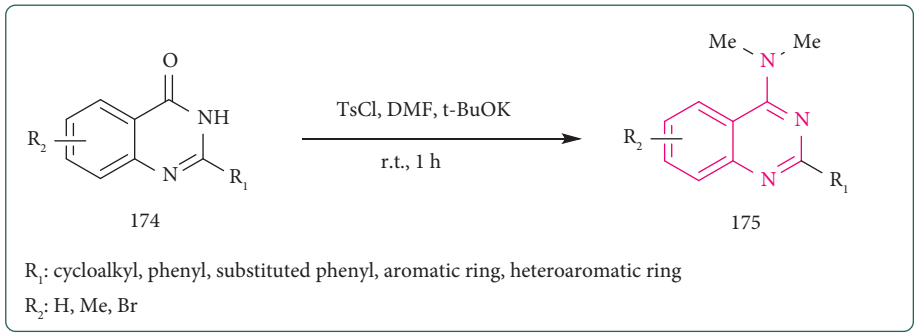
Chen et al. described an efficient one-pot procedure for the preparation of 4-(dimethylamino)quinazoline derivatives **175** in high yields, via direct amination of quinazolin-



Scheme 31: Synthesis of 4-aminoquinazoline derivatives in the presence of HCCP and DIPEA.



Scheme 32: Synthesis of 4-aminoquinazoline derivatives in the presence of TsCl, Et_3N, and DMAP as catalyst.



Scheme 33: Synthesis of 4-(dimethylamino) quinazolines via direct amination in the presence of TsCl, DMF, and t-BuOK.

4(3*H*)-ones **174** in the presence of readily available *N*, *N*-dimethylformamide (DMF) as the nitrogen source (Scheme 33). 4-Toluenesulfonyl chloride (TsCl) promotes the one-pot direct amination through effective activation of the C-OH bond at room temperature. Further investigation indicated that without TsCl no reaction occurred and for this process potassium *tert*-butoxide and DMF was the best base and solvent, respectively. Under the optimized reaction conditions, the scope examination of this method was performed using different substituted 2-arylquinazolin-4(3H)-ones. The results indicated that 2-arylquinazolin-4(3*H*)-ones with electron-neutral (H); electron-donating (Me, OMe, and NMe_2); or electron-withdrawing (Cl, Br, CN, and CF_3) substituents on the aryl group (R_1) provided the target products are in good to excellent yields. Furthermore, quinazolinones containing H, Me, and Br groups on the phenyl ring (R_2) were tested, which afforded the expected derivatives in good yields. 2-(1-Naphthyl)- and 2-heteroarylquinazolin-4(3H)-ones also gave the target compounds in moderate to high yields. Further investigation showed

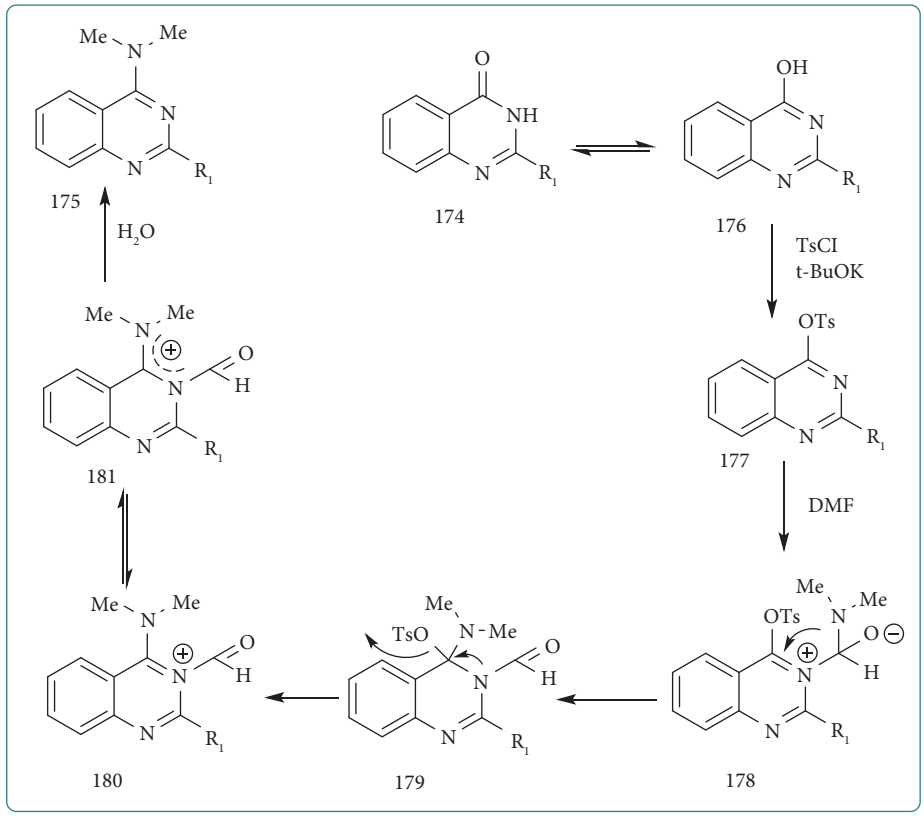
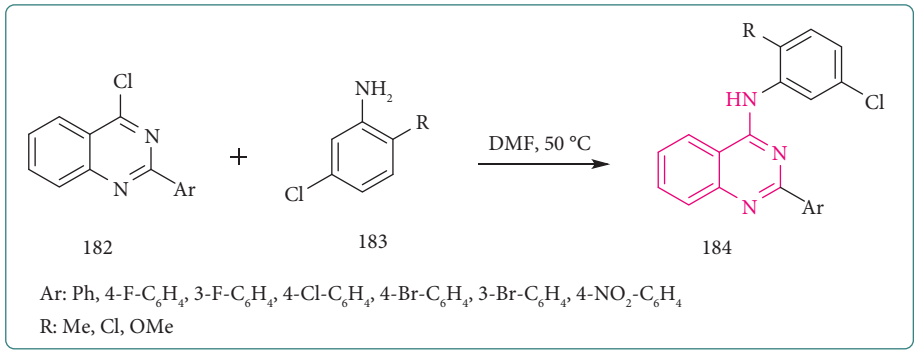


Figure 18: The proposed mechanism for the synthesis of 4-(dimethylamino) quinazolines via direct amination of quinazolin-4(3H)-one.



Scheme 34: Synthesis of 4-aminoquinazoline derivatives in DMF solvent at 50°C.

that 2-unsubstituted quinazolin-4(3H)-one and 2-cyclohexylquinazolin-4(3H)-one substrates did not react even with longer reaction time, which could be due to the difficulty of forming corresponding intermediates without the delocalization effect of the 2-aryl group. The suggested mechanism for this method is shown in Figure 18. Initially, the isomerization of quinazolinone **174** to quinazolin-4-ol **176** occurs. Afterwards, the reaction of quinazolinone with TsCl leads to the tosylate **177**. The nitrogen atom of **177** attacks the carbonyl group of DMF to form intermediates **178**, **179**, **180**, and **181**. Finally, hydrolysis of **181** affords the target product **175**. The significant advantages of this procedure are efficient, facile, one-pot cascade, mild conditions, cheap, and high yield of products [2].

Rahmannejadi et al. reported a simple and efficient approach for the preparation of 4-aminoquinazoline derivatives **184** using 4-chloro-2-arylquinazolines **182** and various 2-substituted 5-chloroanilines **183** in DMF at 50°C with moderate to good yields (Scheme 34). The obtained results showed that various anilines with Me,

OMe, and Cl substituents at *R* position were good substrates for this reaction. In addition, it was observed that the aryl groups with electron-withdrawing (F Cl, Br, and NO_2) and electron-neutral (H) substituents on the quinazoline ring (Ar) gave the target products in good yields. The significant advantages of this reaction are selectivity, mild reaction conditions, good yields, and straightforward product isolation [49].

3. Conclusion

Quinazoline is a heterocycle structure of great importance in the field of medicinal chemistry that is present in the structure of various FDA-approved drugs like prazosin, alfuzosin, trimetrexate, erlotinib, gefitinib, and vandetanib, as well as clinical candidates and biologically active molecules. Among the various substituted quinazolines, 4-aminoquinazoline scaffolds have great importance due to their diverse spectrum of therapeutic potential. In this review, we have presented a wide range of new, efficient, extremely mild condition, and operational simplicity synthetic strategies to provide various 4-aminoquinazoline derivatives using readily available and inexpensive starting reagents. According to the reports, several strategies have been used successfully to prepare this scaffold, including the nucleophilic substitution reaction, metal-catalyzed approaches, microwave irradiation methods, cyclocondensation approaches, and direct amination. This review is also focused on the description of reaction conditions, substrate scope, and mechanism of the reactions. We hope that this review provide insight to medicinal chemist for the design and development of novel methods for the synthesis of 4-aminoquinazoline derivatives.

Data Availability

No data were used in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Financial assistance from the Shiraz University of Medical Sciences by way of grant no. 26645 is gratefully acknowledged.

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