Chemical Insights Into the Synthetic Chemistry of Quinazolines: Recent Advances

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In medicinal chemistry, one of the most significant heterocyclic compounds are quinazolines, possessing broad range of biological properties such as anti-bacterial, anti-fungal, anti-HIV, anti-cancer, anti-inflammatory, and analgesic potencies. Owing to its numerous potential applications, in the past two decades, there is an increase in the importance of designing novel quinazolines, exploring promising routes to synthesize quinazolines, investigating different properties of quinazolines, and seeking for potential applications of quinazolines. The present review article describes synthesis of quinazolines via eco-friendly, mild, atom-efficient, multi-component synthetic strategies reported in the literature. The discussion is divided into different parts as per the key methods involved in the formation of quinazoline skeletons, aiming to provide readers an effective methodology to a better understanding. Consideration has been taken to cover the most recent references. Expectedly, the review will be advantageous in future research for synthesizing quinazolines and developing more promising synthetic approaches.

Keywords: pyrimidine, bicyclic compounds, synthesis, green chemistry, quinazolines, quinazolinones

INTRODUCTION

Quinazoline derivatives are among the most significant families of heterocyclic. Quinazoline (1,3-diazanaphthalene; 1) is a moiety made up of two condensed six-membered aromatic rings, a pyrimidine ring, and a benzene ring (Wang and Gao, 2013). It is yellow and amorphous, and its molar mass is 130.15 g mol⁻¹, and the chemical formula is C₈H₆N₂. On the basis of various substitution patterns of nitrogen atoms, it is isomeric with quinoxaline 2, cinnoline 3, and phthalazine 4 (Figure 1). These isomeric forms are also called diazanaphthalenes. Analogs of this family, which contain a pyrazine ring and a benzene ring, are called Quinoxaline 2. These are also known as benzopyrazine. Cinnoline 3 also comprises a pyrazine ring and a benzene ring (Mishra, 2020). Phthalazine 4 is also called benzopyridiazine or benzo-orthodiazine, which contains a benzene ring and a pyridiazine ring. Gabriel (Ranawat et al., 2011) was the first scientist to prepare a quinazoline nucleus in the laboratory in 1903. Widdege (Asif, 2014) was the first scientist to propose the name quinazoline for this nucleus on the basis of its appearance as an isomer with the quinoxaline ring (Mahato et al., 2011). The synthesis of various compounds containing quinazoline as the main nucleus is largely mediated on the patterns of substitution on the 1,3-diazone entity of the system (Kamel et al., 2016).
Quinazolines are noteworthy in medicinal chemistry, on account of a wide range of their anti-viral (Alagarsamy et al., 2018), anti-HIV (Vijaychand et al., 2011), anti-malaria (Patel et al., 2017), anti-inflammatory (Karanam et al., 2008), antifungal (Alagarsamy et al., 2018), anti-bacterial (Bedi et al., 2004), anti-spasm (Wang and Gao, 2013), anti-cytotoxic (Mishra, 2020), anti-virus (Witt and Bergman, 2000), anti-analgesic (Selvam and Kumar, 2011; Kshirsagar, 2015), anti-cancer (Karanam et al., 2008), anti-oxidation (Iino et al., 2009), anti-hypertensive (Honkanen et al., 1983), anti-depressant (El-Sayed et al., 2019), anti-psychothic (Mizuno et al., 2010), anti-diabetes (Uckun et al., 2002), anti-tuberculosis activities (Kunes et al., 2000), and also their inhibitory effects on thymosine kinase, poly-(ADP-ribose) polymerase (PARP), and thymidylate synthase (Eswaran et al., 2010). There are several approved drugs with quinazoline structure in the market such as, prazosin hydrochloride 5, doxazosin mesylate 6, and terazosin hydrochloride 7 (Figure 2) (Jafari et al., 2016; Devi et al., 2017). Also, many quinazoline derivatives act as DNA-binding agents or as effective adrenergic blockers (Kamel et al., 2016). Many quinazoline derivatives also constitute the building blocks for about 150 natural alkaloids isolated from numerous families of the plant kingdom, from animals, and from microorganisms. Earlier studies conducted in the 1950s and 1960s led to the discovery of febrifugine 8, a quinazolinen-based alkaloid, which possesses anti-malarial potential, from the Chinese plant aseru (Wattanapiromsakul et al., 2003). Various quinazolinen-mediated drugs, which include fenquizone 9 and idelalisib 10, have been observed to display a wide range of anti-fungal, anti-tumor, anti-microbial, and cytotoxic potencies (Witt and Bergman, 2000). In combination therapy, lapatinib 11 has been shown to be active for breast cancer (McKee et al., 1947). Dacomitinib 12 is used to treat NSCLC (non-small-cell lung carcinoma) (Kumar et al., 2009). Albonaconazole 13 has potent and broad-spectrum anti-fungal activity. Balaglitazone 14 has been used in trials studying the treatment of diabetes mellitus. Alfuzozin 15, verublin 16, and erlotinib 17 are anti-cancer agents (Figure 2) (Selvam and Kumar, 2011; Kshirsagar, 2015).

Synthetic chemists prepared a library of quinazolines with different bioactivities by linking several active groups to the quinazoline entity using developing synthetic approaches, and the potential uses of the quinazolines in area of medicine, pesticides, and biology have also been disclosed (Khan et al., 2014, 2015). To be more precise, the position two, six, and eight of quinazoline nucleus is very significant for structural-activity investigations, and 2,3-difunctionalized quinazoline derivatives are observed to possess anti-viral, anti-hypertensive, and anti-bacterial functions (Bouley et al., 2016; Hrast et al., 2017). Incorporation of various heterocycles, such as phenothiazine, triazole, and pyridine, at second position of quinazoline entity results in the development of insecticidal, anti-bacterial, and anti-fungal properties (McKee et al., 1947). The substitution of heteroaryl and aryl moieties at N-3 and C-2, respectively, has shown improved analgesic and anti-inflammatory activities (Iino et al., 2009). Substitution at second and third position, like bridge phenyl ring, phenyl ring, and heterocyclic rings, are shown to contain anti-microbial potency. Development of the lipophilic character at the C-4 position of the quinazoline ring would be desired for novel inhibitory affinity. Deactivating functional groups in the third position provides enhanced hypotensive efficacy. A phenyl ring at the eighth position and a nitro group at the sixth position of quinazoline entity possess improved anti-cancer potency. Quinazoline derivatives when bonded to thiadiazole ring bear anti-HIV, anti-fungal, and antibacterial activities. Incorporation of a styril group at the second position in quinazoline (=O) leads to development of enhanced chemotherapeutic actions. Electron-rich substituents or halogens on the sixth position and substituted amine or simple amine on the fourth position are known to assist the potency against bacteria. The third position should be bonded to diverse heterocyclic rings for enhanced chemotherapeutic action (Kung et al., 1999; Bhattacharjee et al., 2004).

In the recent years, numerous synthetic approaches for the formation of quinazoline scaffolds have been disclosed (Rajput and Mishra, 2012; Srivastava and Srivastava, 2015; Hameed et al., 2018). This review delivers a broad picture of progress for the development of quinazolines over the last decade. To be more precise, the review consists of two parts. The first part provides transition metal-free approaches to afford quinazoline derivatives, including heterogeneous catalytic systems, microwave-assisted reactions, ionic liquid-based reactions, and visible light-mediated synthetic systems. The second part focuses on transition metal-catalyzed approaches to afford quinazoline derivatives, including ruthenium-, zinc-, rhodium-, cobalt-, nickel-, gold-, iron-, palladium-, and copper-catalyzed reactions to synthesize quinazolines. Hopefully, the literature review would be valuable for scientists working in the field of medicinal and synthetic chemistry.
TRANSITION METAL-FREE APPROACH FOR THE SYNTHESIS OF QUINAZOLINES

In heterocyclic chemistry, transition metal-catalyzed coupling reactions have played a significant part for the formation of medicinally vital compounds. However, these reactions have some confronted challenges and limitation to some extent owing to the catalytic system. That is to say, most of the transition metals are toxic in nature, very expensive, and sensitive to moisture, especially oxygen. Also, the huge transition metal consumption does not meet the prerequisite for sustainable development. Alternative methodologies, therefore, for the development of C–N and C–C bonds under transition metal-free conditions are highly required and advantageous. In recent years, transition metal-free coupling reactions have become one of the attractive systems in synthesis to accomplish reactions with high productivity and to study how the reactions operate in the absence of transition metals.

Microwave-Promoted Synthesis
Sarma and Prajapati reported a catalyst- and solvent-free synthesis of quinazoline derivatives 20 from aldehydes 18, 2-aminobenzophenones 19, and ammonium acetate under microwave heating conditions (Scheme 1). The presented protocol was equally operative with a diverse range of electron-deficient and electron-rich benzaldehydes 18, and afforded target quinazolines 20 in good to excellent isolated yields (70–91%) within minutes (Sarma and Prajapati, 2011). The reaction is clean and simple, and provides an eco-friendly alternative toward removing organic solvents from organic synthesis.
4-Dimethylaminopyridine-Catalyzed Three-Component Approach

Boulcina et al. documented a general, efficient, one-pot process for the formation of quinazoline frameworks 20 in good to excellent isolated yields (67–98%) through the DMAP (4-[N,N-dimethylamino] pyridine)-catalyzed reaction of aromatic or hetero-aromatic aldehydes 18 with 2-aminobenzophenone 19 in the presence of NH4OAc under mild conditions (Scheme 2) (Derabli et al., 2014). This technique provides numerous benefits, for example, easy accessibility of starting materials, and high selectivity.

Iodine/Ammonium Acetate-Assisted Three-Component Methodology

Panja et al. described a three-component one-pot methodology for the synthesis of highly substituted quinazoline derivatives 20 (34) via 12-catalyzed reaction of substituted benzaldehydes 18 with substituted α-aminoarylketones 19 in the presence of NH4OAc (Scheme 3). When performed in neat or with EtOH even at moderate temperature, the reaction results in an excellent yield (91–97%) in lesser time. It was observed that iodine is the appropriate catalyst counterpart in this synthetic approach attributed to its oxidizing properties and Lewis acidity. Moreover, this technique is superior in terms of simplicity and non-involvement of chromatographic purification technique (Panja et al., 2012).

Magnetic Ionic Liquid-Catalyzed Synthesis

In another report, Panja et al. documented an ionic liquid (IL) Bmim[FeCl4] (butylimethyldiazolium tetrachloroferrate)-catalyzed one-pot, solvent-free, high yielding, multi-component green methodology for the synthesis of quinazolines 20 by the reaction of substituted aldehydes 18 with 2-aminobenzophenones 19 in the presence of NH4OAc at moderate temperature (Scheme 4). This technique was observed to be more valuable compared to other approaches in terms of its high catalyst stability, easier recyclability, high yield simplicity, and absence of any chromatographic purification technique (Panja and Saha, 2013).

Base-Driven Synthesis in Water

Cho et al. reported sustainable transition-metal-free synthesis of quinazoline derivatives 23 with moderate to good isolated yields (43–78%) from reaction of easily available α,α,α-trihalomtoluenes 21 with o-aminobenzylamines 22 in the presence of molecular oxygen and sodium hydroxide in H2O (Scheme 5) (Chatterjee et al., 2018). The recrystallization process of the crude reaction mixture for the purification of the solid quinazolines eliminates the application of chromatographic purification and huge solvent-consuming workup, which make the overall process more economical and sustainable.

Tetrabutylammonium Iodide-Catalyzed Amination

Li et al. disclosed tetrabutylammonium iodide (n-Bu4NI)-catalyzed tandem reaction for the formation of imidazo[1,5-c]-quinazolines 26 (Scheme 6). This technique was investigated by reacting various 4-methyl-2-phenylquinazolines 24 with benzyamines 25, which afforded corresponding imidazo[1,5-c]quinazoline derivatives 26 with appropriate yields (35–98%) (Zhao et al., 2014). Selective dual amination of sp3 C–H bond under mild condition is involved in this reaction. Additionally, the reaction exhibited a wide range of substrates, including the common readily available α-amino acids and benzyamines. The novel procedure serves not only as a technique to develop a new series of imidazo-N-heterocycle derivatives 26 but also as a rare example of oxidative amination of benzylic primary C–H bonds with primary amines. This is a very valuable approach to transform simple quinazolines into highly functionalized quinazolines.

Iodine/Tert Butylhydroperoxide-Driven C–H Functionalization

Zhang et al. documented an iodine/TBHP-assisted effective and facile one-pot tandem process for the development of 2-phenylquinazolines 29 with good to excellent isolated yields from benzylamines 27 and 2-aminobenzophenones 28 (Zhang et al., 2010). The method avoids the application of any kind of metal or hazard reagents (Scheme 7).

Ceric Ammonium Nitrate-Catalyzed Synthesis

Nageswar et al. demonstrated the construction of quinazoline scaffolds 29 with good to excellent isolated yields (75–93%) from reaction of benzylamines 27 and 2-aminobenzophenones 28 catalyzed by CAN/TBHP (ceric ammonium nitrate/tert-butyldihydroperoxide) in CH3CN (Scheme 8). The CAN/TBHP system was observed to be efficient, mild, and novel reagent for the facile synthesis of quinazolines 29. The yield of reaction...
was slightly increased when the electron-withdrawing group was present at the para-position of the benzylamine 27, whereas an electron-donating group decreased the yield of product (Karnakar et al., 2011).

4-Hydroxy-TEMPO-Catalyzed C-H Bond Amination
Han et al. described an effective and novel aerobic approach for the oxidative synthesis of 2-aryl quinazoline derivatives.
via amination of benzyl C–H bonds using a one-pot 4-hydroxy-TEMPO radical-catalyzed reaction of 2-aminobenzaldehydes and 2-aminobenzoketones 28 with arylmethanamines 27, without the use of any additives or metals (Scheme 9) (Han et al., 2011).

**Tert Butylhydroperoxide/DDQ-Induced Oxidative Cyclization Approach**

Rachakonda et al. explored the synthesis of 2-arylquinazolines 29 under transition-metal-free and mild conditions from commercially available benzylamines 27 and 2-aminobenzophenones or 2-aminobenzoketones 28 via oxidative and condensation cyclization using DDQ as a versatile reagent (Scheme 10). The mechanism of the reaction involved condensation reaction followed by cyclization, giving the desired 2-arylquinazoline in good to excellent yields (71–92%) (Rachakonda et al., 2012).

**Cobalt Zeolite Imidazolate Framework-Catalyzed Synthesis**

Truong et al. employed a heterogeneous catalytic system (viz. ZIF-67) for the cyclization reaction of benzylamines 27 with 2-aminobenzoketones 28 to afford quinazoline products 29 in excellent isolated yields (Scheme 11). Application of TBHP as an oxidant in toluene solvent at 80°C was observed to be at optimal conditions of reaction. ZIF-67 catalytic system could be regenerated and recycled without important degradation in catalytic potency (Truong et al., 2015).

**Molecular Iodine-Catalyzed C–H Bond Amination Using Oxygen as an Oxidant**

Very recently, Bhanage et al. reported the preparation of I$_2$-catalyzed quinazoline derivatives 29 from reaction of 2-aminobenzaldehydes 28 or 2-aminobenzophenones with benzyl-amines 27 (Scheme 12). Numerous functionalized heteroaryl or aryl amines were investigated with an ample range of functionalized 2-aminobenzaldehydes or 2-aminobenzophenones 28 to give the quinazolines 29 in moderate to excellent yields (49–92%) (Deshmukh and Bhanage, 2018). The application of O$_2$ as an eco-friendly oxidant coupled with the solvent-, additive- and transition-metal-free conditions makes the approach greener and economical. The lack of aqueous workup also improves the productivity of this procedure. Moreover, the procedure uses I$_2$ in catalytic amount and provides benzylic sp$^{3}$ C–H bond functionalization/amination (Eswaran et al., 2010).

**Lewis Acid-Catalyzed Synthesis**

In the recent years, Deng et al. reported an efficient method for the synthesis of quinazoline scaffolds 32 under transition-metal-free conditions from reaction of N-phenyl-benzimidamides 30 and polyoxymethylene 31 as one carbon source (Cheng et al., 2016). The optimized condition of reaction was well-tolerated with electron-deficient and electron-rich substituent on benzene ring with low to excellent yield of respective quinazoline derivatives 32 (20–94%) (Scheme 13). The transition-metal-free reaction and mild conditions are one of most attractive features of this technique. This novel process offers an easily handle-able, eco-friendly, and complementary approach to 2-arylquinazoline scaffolds.

**Iodine (III)-Driven Oxidative C–N and C–C Bond Construction**

Lin et al. documented the preparation of multi-substituted quinazolines 34 from N-alkyl-N′-arylamidines 33 through the formation of iodine (III)-driven oxidative C(sp$^2$)-N and C(sp$^2$)-C(sp$^3$) bonds under base- and metal-free conditions (Lin et al., 2014). Substrates having electron-deficient and electron-rich substituents on the aromatic ring afforded the respective quinazoline in low to excellent yields (5–95%); however, the reaction was incompatible with an aliphatic substituent (Scheme 14).
Visible Light-Assisted Photo-Redox Oxidative Annulation

Tang et al. reported the formation of quinazolines 34 from amidine derivatives 33 via formation of visible light-based oxidative C(sp²)–C(sp³) bond (Scheme 15). This synthesis is a metal-free oxidative coupling assisted by photo-redox catalytic system. The procedure features low loading of catalyst (1 mol %) (Shen et al., 2016). The approach was observed to tolerate a broad spectrum of functional groups.

I₂/KI-Based Oxidative C–C Bond Construction

Lv et al. described the I₂/KI-based oxidative C–C bond construction for the construction of quinazoline derivatives 34.
from \(N,N'\)-difunctionalized amidines 33. Under the standard condition, all \(N,N'\)-disubstituted amidines 33 converted into the corresponding quinazolines 34 in moderate to excellent yields (37–99%) (Scheme 16) (Lv et al., 2016). This environmentally benign and practical technique can also be performed on a gram scale and operates well with crude amidine precursors.

**Potassium Iodide-Promoted Three-Component Synthesis**

Li et al. synthesized 2-arylquinazoline derivatives 41 through a three-component one-pot mild KI-promoted methodology under transition-metal-free conditions by the reaction of 2-aminobenzophenones 28 with methylarenes 40 as one carbon source in the presence of \(\text{NH}_4\text{OAc}\) (Zhao et al., 2015). The reaction demonstrated a wide spectrum of functional group tolerance including electron-deficient and electron-rich 2-aminocarboxylic derivatives 28 and methylarenes 40 (Scheme 19).

**TRANSITION METAL-CATALYZED METHODOLOGIES**

Since the past century, transition metal-catalyzed C–H activation reactions have been investigated, and these reactions represent a promising achievement and development of organometallic chemistry. These reactions were started in 1960 as a key subject in organometallic chemistry and became one of the most effective catalytic systems for the formation of C–N and C–C bonds (Meijere and Diederich, 2004; Diederich and Stang, 2008). Moreover, transition metal-catalyzed C–H activation and functionalization have some advantages over classical technique such as straightforward method for the development of fused heterocyclic compounds, no need of pre-functionalization of starting material, which offers a more efficient reduction in the generation of waste. In the past decade, remarkable efforts have been made for the construction of heterocycles through the formation of C–N and C–C bonds. A brief summary of the recent literature of metal-catalyzed formation of quinazolines via C–H activation and C–N coupling reactions is described below.

**Palladium-Based Catalytic Systems**

Vlaar et al. reported palladium(II) acetate-catalyzed aerobic oxidative coupling of (2-aminophenyl)azole derivatives 42 with isocyanide derivatives 43 for the formation of medicinally
significant azole fused quinazolines 44 by using air as oxidant at 75°C in 2-methyltetrahydrofuran (Vlaar et al., 2014). An ample spectrum of triazole starting materials was reacted well and furnished annulated products in moderate to excellent isolated yields (11–83%) (Scheme 20A). In related development, Wang et al. described the palladium-catalyzed construction of 2-arylquinazoline scaffolds 47 by reacting E-1-(2’-nitrophenyl)ethanone-o-methyloximes 45 and benzyl alcohols 46 in the presence of dppf as ligand under argon at 160°C through hydrogen transfer approach (Wang et al., 2014). It is supposed that the synthesis of quinazolines proceeds through the dehydrogenation of benzyl alcohols to benzaldehydes, followed by the formation of imine and subsequent intramolecular cyclization resulting in the development of quinazolines (Scheme 20B). Likewise, the reaction was performed out with benzyl alcohols 46, urea 48, and 1-(2-nitrophenyl)ethanone 49 under optimized condition. The efficient synthesis delivers quinazolines 50 in lower to excellent isolated yields (21–90%) (Scheme 20C). Similarly, Xu et al. described the annulation process for the formation of multi-substituted quinazolines 52 from N-allylamidines 51 under microwave heating conditions by employing palladium as an active catalyst in xylene at 170°C (Xu et al., 2015). The scope of this methodology was disclosed by using a spectrum of aryl amidines containing electron-deficient and electron-rich substituents, which provided the corresponding product in good to excellent isolated yields (73–94%) (Scheme 20D). In an interesting study, Chen et al. illustrated a novel and practical technique for the preparation
of quinazoline scaffolds 56 from 2-aminobenzylamine 53 with aryl bromides 54 and carbon monoxide 55, involving palladium-catalyzed aminocarbonylation–condensation–oxidation sequence and facilitating the desired quinazolines in poor to excellent isolated yields (5–93%) (Chen et al., 2014). In this procedure, DMSO serves both as oxidant and solvent (Scheme 20E). The generality of the approach was investigated by varying different withdrawing groups (cyano, trifluoromethyl) and electron releasing (methoxy, dimethylamino, or tert-butyl) containing aryl bromide.

Watanabe et al. described MoCl$_5$ and Pd(PPh$_3$)$_2$Cl$_2$ catalyzing intermolecular reductive N-hetero-cyclization reaction of 2-nitrophenyl ketones or 2-nitrobenzaldehyde 57 with methanamide 58 for the formation of quinazoline analogous 59 (Akazome et al., 1995). The reaction proceeds through the formation of an active imene intermediate by selective carbon monoxide-based deoxygenation of nitro species (Scheme 21A). On the other hand, Chen et al. reported Pd-catalyzed three-component, one-pot tandem assembly for quinazolines 63 by using readily available 2-aminobenzonitriles 60, aryl boronic acids 61, and aldehydes 62. The method displays broad substrate scope and amazing chemoselectivity (Scheme 21B). A notable feature of this technique is the tolerance of iodo and bromo moieties, affording flexibility for further synthetic manipulations (Hu et al., 2018). Later, the same research group disclosed another methodology for quinazoline scaffolds 65 from reaction of aryl boronic acids 61 with 2-(quinazolinone-3(4H)-yl)benzonitriles 64. This tandem synthesis involved nucleophilic addition, followed by intramolecular cyclization and subsequent ring-opening, delivering the corresponding product in moderate to excellent isolated yields (31–93%) (Zhang et al., 2018). In another interesting report by Chen et al., the synthesis of 2,4-disubstituted quinazoline derivatives 66 through Pd-catalyzed reaction of aryl boronic acids 61 with N-(2-cyanoaryl)benzamides 60 by employing 1,10-phen, trifluoroacetic acid in THF at 80°C has been described (Scheme 21D). The reaction revealed a wide spectrum of functional group tolerance, including electron-deficient and electron-rich aryl boronic acids 61 with N-(2-cyanoaryl)benzamides 60 (Zhu et al., 2018).
Copper-Mediated Catalytic Systems

In literature, the efficiency of copper-based catalytic systems is well-documented since last century where these salts have demonstrated to be an effective catalytic system in cross-coupling reactions for the preparation of bioactive molecules and natural products, on account of their good functional group tolerance, low toxicity, and economic attractiveness (Deutsch et al., 2008; Allen et al., 2013; Guo X.-X. et al., 2015). Copper salts have become a promising alternative to their costly counterparts, for instance ruthenium-, rhodium-, and palladium-based catalytic systems for the cross-coupling reactions. Cu-catalyzed Ullmann reaction is the pioneering work in the area of synthetic organic chemistry (Sambiagio et al., 2014). Cu-catalyzed cross-coupling reaction has been broadly explored for the newer synthetic approach for fused heterocyclic entities.

Fan et al. documented an effective one-pot method for the formation of diversely functionalized quinazolines via copper-catalyzed tandem reaction among 2-bromobenzyl bromide derivatives, aldehyde derivatives, and ammonium hydroxide (Fan et al., 2014). The reaction proceeds through cupric acetate-catalyzed amination of 2-bromobenzyl bromides to 2-aminobenzyl amines, followed by condensation with aldehydes and subsequent intramolecular nucleophilic cyclization and aromatization, furnishing quinazoline derivatives (Scheme 22A). By employing simple aliphatic amines and ammonia as the source of nitrogen, the technique offers a practical and versatile approach. Also, this technique has several benefits, such as structural diversity of products and readily available starting materials. Alternatively, Liu et al. reported the direct approach to substituted quinazolines from reaction among 2-aminobenzoketone derivatives, toluene, and ammonium acetate in the presence of copper(II) chloride at 80°C for 12 h (Liu et al., 2015). The reaction proceeds through oxidative amination of benzylic carbon–hydrogen bonds of methylarenes with 2-aminobenzoketones and ammonia, followed by intramolecular cyclization, affording quinazoline derivatives. Furthermore, the kinetic isotope effect (KIE) suggested that the carbon–hydrogen bond cleavage was the rate-limiting step in this methodology (Scheme 22B). On account of this method, a library of 2-arylquinazoline derivatives can be easily prepared in good isolated yields. Recently, in the same line, Kamal et al. employed 2-aminobenzophenones and phenacyl azides for the construction of quinazolines by using cupric acetate, triethylamines in acetonitrile at ambient temperature (Visweswara Sastry et al., 2017). This procedure proceeded well and constructed two C–N bonds in a single operation (Scheme 22C). Additional, no oxidant or external source of nitrogen is demanded to accomplish the formation of quinazolines. The process is practical for production of numerous functionalized quinazolines.
with high functional group tolerance as well as a broad spectrum of substrates. On the same note, Vishwakarma et al. demonstrated Cu-catalyzed effective approach for forming o-protected-4-hydroxyquinazolines 75 from 2-aminobenzonitriles 73, substituted aldehydes 68, and substituted alcohols 74 through the development of an N-functionalized bicyclic precursor, followed by nucleophilic attack of the alkoxy moiety (Battula et al., 2014). The synthesis was sufficiently explored with a wide spectrum of substituted 2-aminobenzonitriles and aldehydes led to respective quinazolines 75 in moderate to excellent isolated yields (41–88%) (Scheme 22D). Subsequently, Gao et al. disclosed a one-pot tandem method for the efficient and straightforward preparation of pyrazolo[1,5-a]quinazolines 78 by treating 2-bromobenzaldehydes 76 with 5-aminopyrazoles 77 in the presence of potassium carbonate at 110°C through Cu-catalyzed imine creation followed by Ullmann type coupling resulting in fused quinazolines 78 (Scheme 22E). Diverse functionalized 5-aminopyrazoles and 2-bromobenzaldehydes tolerated well and provided respective quinazoline in moderate to good isolated yields (41–79%) (Gao et al., 2014). With benefits such as mild reaction conditions, simple synthetic procedures, and readily available starting materials, the technique developed could be considered as a promising technique. Further, very recently, Wang et al. published Cu-catalyzed one-pot process for the preparation of substituted quinazolines 81 by reaction of 2-ethynylanilines 79 with benzonitriles 80 using O₂ as the sole oxidant (Wang et al., 2018). The reaction proceeded via effective cleavage of the carbon–carbon triple bond and formation of new carbon–nitrogen, and carbon–carbon bonds in a one-pot manner (Scheme 22F). Furthermore, the reaction showcased a broad spectrum of substituent tolerance with several 2-ethynylanilines and benzonitriles, offering an array of quinazoline derivatives in moderate to excellent isolated yields (41–88%). These quinazolines also exhibited good fluorescence...
quantum yield, aggregation-induced emission effect, and lifetime decay, enhancing the importance of quinazolines in material chemistry for future aspect.

Fu et al. described quinazoline derivatives via Cu-catalyzed tandem couplings of functionalized 2-halophenylketones or 2-halobenzaldehydes with amidine hydrochlorides under mild conditions (Huang et al., 2008). The approach was equally operable with aromatic as well as with aliphatic and delivered target quinazolines in good to excellent isolated yields (61–95%) (Scheme 23A). Moreover, the method showed simple, practical, and economical advantages. Similarly, Truong et al. reported an effective one-pot approach for highly functionalized quinazolines in good to excellent isolated yields via ligand-free Cu-catalyzed Ullmann condensation of o-iodobenzaldehyde derivatives with substituted amidine hydrochlorides in the presence of CS₂CO₃ in methanol at 60°C (Truong and Morrow, 2010). Mild reaction conditions as well as one-pot conditions make this procedure a striking alternative for the preparation of this family of compounds (Scheme 23B). In the recent years, Raut et al. achieved a facile and green ultrasonic-assisted formation of cuprous oxide nano-cubes as a heterogeneous nanocatalytic system at ambient temperature, and cuprous oxide nano-cubes were utilized for the construction of quinazoline frameworks using one-pot tandem cyclization of 2-bromobenzaldehyde derivatives with amidine hydrochlorides without using any ligands (Scheme 23C). Numerous quinazoline derivatives could be synthesized in excellent isolated yields within a few minutes. Additionally, the cuprous oxide nanocatalytic system could be regenerated and recycled up to four times without any important loss of catalytic potency (Raut et al., 2017). Along the same line, Wang et al. developed an effective one-pot procedure for the region-selective formation of functionalized quinazoline analogous by using diaryl-1,3,5-iodanes and nitriles in the presence of cupric acetate and potassium tert-butoxide in dimethyl sulfoxide at 120°C (Wang et al., 2013). This approach of electrophilic annulations permits the use of commercially available materials and facilitates great flexibility of the substitution patterns on unsymmetrical or symmetrical diaryl-1,3-iodanes and nitriles, respectively (Scheme 23D). In another approach, Hua et al. disclosed cuprous chloride-catalyzed multicomponent one-pot formation of quinazoline analogous by the reaction of o-bromo aromatic ketones with aromatic aldehydes or aromatic alcohols and ammonia in H₂O (Ju et al., 2012). The most important features of this synthetic tool include good isolated yields and air or DTBP (when primary alcohols are used) as oxidants (Scheme 23E). In a related development, Farhang and Baghbanian documented an effective and eco-friendly one-pot formation of quinazolines via magnetically isolable and recyclable CuFe₂O₄ nanoparticles catalyzed tandem cyclization reaction among aryl aldehydes, 2-amino benzophenones, and ammonium acetate (Baghbanian and Farhang, 2014). Nanoparticles of CuFe₂O₄ were easily synthesized by the thermal decomposition of Fe(NO₃)₃ and Cu(NO₃)₂ in H₂O in the presence of NaOH (Scheme 23F). The catalytic potency of CuFe₂O₄ nanoparticles was investigated in aqueous media, revealing that this system is applicable as a promising, reusable, and green catalyst in organic synthesis. Moreover, the main benefits of the technique are (i) chemoselectivity, (ii) an insignificant loss of activity by using recycled catalyst, and (iii) simplicity in the extraction of the substrate/product from the catalysts. In the same connection, Han et al. explored a facile and effective one-pot reaction of 2-aminobenzylamine derivatives with arylaldehyde derivatives for the synthesis of quinazoline skeletons by using DABCO/CuCl/4-HO-TEMPO as the catalytic system and oxygen as the terminal oxidizing agent (Han et al., 2012). Various substituted heteroaryl or aryl aldehydes were treated with a variety of functionalized 2-aminobenzylamines and furnished the functionalized quinazolines in moderate to excellent isolated yields (40–96%) (Scheme 23G).

Wu et al. reported the Cu-catalyzed one-pot tandem reaction among aldehydes, (2-aminophenyl)methanols and NH₄Cl in the presence of TEMPO and cerium trinitrate at 80°C for 24 h. The technique represents a practical and convenient strategy for the formation of 2-functionalized quinazolines (Scheme 24A). The reaction mechanism involved functionalization of 2-aminobenzylalcohols to 2-aminobenzaldehydes by using CuCl/TEMPO/2,2′-bipyridine(bpy) catalytic system. Following, the reaction of 2-aminobenzaldehydes with alcohols and ammonium chloride afforded cyclized entity dihydroquinazolines, which on aromatization result in the formation of quinazoline frameworks in moderate to excellent isolated yields (55–97%) (Chen et al., 2013). Likewise, Yang et al. documented an efficient and novel process for the production of pyrazolo[1,5-c]quinazoline derivatives via two-step one-pot reactions of commercially available oxidized reagents 1-(2-halophenyl)-3-alkylprop-2-yn-1-one derivatives, amidine hydrochlorides, and hydrazine hydrochloride under mild conditions, and the respective pyrazolo[1,5-c]quinazoline derivatives were achieved in good to excellent isolated yields (Scheme 24B). The unique process can offer useful and diverse N-fused heterocycles for medicinal chemistry and combinatorial chemistry (Yang et al., 2012). In an interesting study, Kiruthika and Perumal disclosed a copper-catalyzed one-pot, intermolecular procedure for the rapid construction of indolo[1,2-a]quinazoline derivatives from the commercially available gen-dibromovinylanilide derivatives and N-tosyl-o-bromobenzamide derivatives by employing Cs₂CO₃ and 1,10-phen in refluxing THF, followed by refluxing under basic conditions (Kiruthika and Perumal, 2014). The protocol operated well with a diverse range of N-tosyl-obromobenzamide derivatives and converted into respective quinazolines with good isolated yields (70–81%) (Scheme 24C). Moreover, this technique is practical, economical, and more reliable in terms of scalability, yield, and time. Keeping this in view, Gou et al. illustrated an effective technique for the development of pyrazolo[1,5-c]quinazolines and 5,6-dihydropyrazolo[1,5-c]quinazoline derivatives via one-pot Cu-catalyzed tandem reaction of 5-(2-bromoaryl)-1H-pyrazole derivatives with ketones or aldehydes in ammonium hydroxide under aerobic conditions (Gou et al., 2021).
A diverse spectrum of ketones and aldehydes, including hetero-aryl, alkenyl, alkyl, and aryl underwent efficiently in this reaction conditions and furnished corresponding functionalized quinazolines in moderate to good isolated yields (32–79%) (Scheme 24D). This synthetic process has the benefits of inexpensive starting materials and reagents, simple operation
process, and broad scope of substrates. In another report by Fan et al., copper-catalyzed two-step one-pot sequential reactions of 2-(2-bromoaryl)-1H indole derivatives with substituted aldehydes, and ammonium hydroxide for the selective preparation of indolo[1,2-c]quinazolines and H-indolo[3,2-c]quinolones has been described (Guo S. et al., 2015). The regioselectivity of synthesis was maintained by regulating the reaction conditions. When the reaction was performed under acidic conditions, carbon–carbon coupling was observed, leading to the formation of 11H-indolo[3,2-c]quinolones in good isolated yields (32–81%). Having said that, in the absence of acid, formation of indolo[1,2-c]quinazolines was observed in moderate to excellent isolated yields (30–89%) (Scheme 24E). The current procedure features simple operation procedures and easily controlled selectivity. Very recently, Fan et al. described Cu-catalyzed aerobic oxygenation of 2-(2-amidoaryl)-1H indoles, followed by intramolecular cyclization reaction under acidic conditions, resulting in the
construction of quinazolines 102 in moderate to good isolated yields (40–72%) (Scheme 24F) (Guo et al., 2018).

**Ruthenium-Mediated Catalytic System**

Chen et al. explored straightforward Ru-catalyzed dehydrogenative synthetic protocol to afford 2-arylquinazoline derivatives 23 from the reaction of 2-aminomethanol derivatives 88 with benzonitrile derivatives 103 in the presence of triruthenium dodecacarbonyl, potassium tert-butoxide, and Xantphos (Chen et al., 2015). A library of 2-aminomethanol derivatives 88 was successfully transformed in combination with various kinds of benzonitrile derivatives 103 into numerous desired quinazolines 23 in moderate to good isolated yields (18–76%) (Scheme 25). In this process, there is no need for the utilization of less eco-friendly halogenated substrates, providing a significant basis for constructing 2-arylquinazolines.

**Zinc-Based Catalytic System**

Wang et al. reported the zinc bromide (ZnBr₂)-catalyzed domino hydro-amination cyclization approach for the development of indolo[1,2-c]quinazoline frameworks 105 from acyclic alkyn reactants 104 (Xu et al., 2013). The synthesis proceeds through ZnBr₂-aided tandem sequence, involving 5-endo-dig hydro-amination and intramolecular cyclization between an amide group with the indole nitrogen and gave indolo[1,2-c]quinazolines 105 in moderate to excellent isolated yields (26–93%) (Scheme 26). The method features mild condition as well as non-iodine substrates, which are suitable for the formation of a panel of indolo[1,2-c]quinazolines.

**Rhodium-Mediated Catalytic Systems**

Zhu et al. described the [Cp*RhCl₂]₂/AgBF₄-catalyzed double carbon–nitrogen bond formation sequence for the construction of highly functionalized quinazolines 108 from reaction of benzimidate derivatives 106 with dioxazolone derivatives 107 (Wang J. et al., 2016). In this reaction, dioxazolone derivatives 107 also functioned as an internal oxidizing agent to regulate the catalytic cycle. A library of benzimidate derivatives 106 were transformed into corresponding quinazolines 108 with good to excellent isolated yields (66–96%) (Scheme 27A). The synthetic process proceeded with the benefits of operational simplicity, and high atom efficiency, and offered a significant basis for access to quinazoline derivatives. In the same year, Li et al. reported an effective synthetic procedure to access quinazoline N-oxides oxides 109 from ketoamide derivatives 106 and dioxazolone derivatives 107 through Zn(II)/Rh(III)-catalyzed carbon–hydrogen activation–amidation of the ketoamide derivatives (Wang Q. et al., 2016). This annulation tool proceeded effectively in the absence of any oxidant and delivered target quinazoline N-oxides oxides with good to excellent isolated yields (50–93%) (Scheme 27B). Furthermore, the reaction proceeded in high efficiency under mild conditions with water and carbon dioxide as the byproducts. Interestingly, Wang and Jiao documented an efficient and novel copper- and rhodium-co-catalyzed [4 + 2] carbon–hydrogen bond activation and annulation for the formation of biologically active quinazolines 112 from reaction of imidate derivatives 110 with alkyl azide derivatives 111 (Wang and Jiao, 2016). This aerobic oxidative procedure offers a valuable utilization of simple alkyl azide derivatives 111 in N-heterocycle synthesis with nitrogen and water as co-products (Scheme 27C). High atom efficiency and good functional group tolerance make this procedure suitable in accessing numerous functionalized quinazolines (Patel and Patel, 2019).

In the recent years, Wu et al. described a rhodium-catalyzed direct and unique methodology for forming a library of 5-arylimidazo[1,2-c]quinazoline derivatives 114 in moderate to excellent isolated yields from annihilation of ketones 107 and 2-arylimidazoles 113 (Scheme 28). This process is characterized by (i) free of halo functionalization handles; and (ii) commercially available starting material (Wu et al., 2018).

**Cobalt-Based Catalytic Systems**

Wang et al. developed cyclopentadienylcobalt dicarbonyl-catalyzed [4 + 2] cycloaddition of rarely explored dioxazolones 107 with imines 110 for the formation of multi-functionlized quinazolines 115 (Wang X. et al., 2016). The reaction involved cobalt-mediated tandem direct carbon–hydrogen amidation followed by intramolecular cyclization to deliver quinazolines with moderate to excellent isolated yields (48–99%) (Scheme 29). Cobalt-based catalytic system is exclusively suited to this conversion owing to its high sensitivity to steric hindrance and strong Lewis acidity.

Wang et al. documented cobalt-catalyzed direct functionalization of N-sulfinylimines 116 and benzimides 118 with dioxazolones 107 for the rapid formation of quinazolines (117 and 75) (Scheme 30). Numerous dioxazolones 107, benzimides 118, and N-sulfinylimines 116 actively contributed under the optimized reaction condition and afforded quinazolines in lower to excellent isolated yields (27–97%) (Wang F. et al., 2016). The synthesis of quinazolines proceeded with high mono-/di- and regioselectivity. In these synthetic tool, the dioxazolone coupling partners serve as a synthon of (the oxidized form of) nitriles.
SCHEME 26 | Zinc-catalyzed domino hydro-amination-cyclization for accessing quinazolines.

SCHEME 27 | Various Rh-catalyzed synthetic methodologies for the formation of quinazoline skeletons.

SCHEME 28 | Rhodium-catalyzed annulation of carbon-hydrogen bonds.

SCHEME 29 | Co-catalyzed [4 + 2] cycloaddition of imine with dioxazolone.
In an interesting report, Ahmadi and Bazgir described a cobalt-assisted isonitrile insertion cyclization reaction for the formation of fused quinazoline frameworks 120. To be more precise, treatment of isocyanides 43 with benzo[d]imidazol-anilines 119 in the presence of cobalt catalyst, sodium acetate, and potassium persulfate afforded quinazolines 120 (Ahmadi and Bazgir, 2016). The simple technique is highly useful, and it offers a straightforward methodology to a library of benzoimidazo-quinazoline amines (Scheme 31).

Gold-Based Catalytic Systems
Liu et al. described facile and efficient Ag(I)/Au(I)-catalyzed cascade technique for one-pot formation of benzo[4,5]imidazo[1,2]pyrrolo[1,2]quinazolinones 128 through the reaction of the functionalized 2-(1H-benzo[d]imidazol-2-yl)aniline derivatives 119 with 5-hexynoic acid or 4-pentynoic acid 127 (Ji et al., 2013). Furthermore, in the described procedure, substituent functionality in aniline derivatives 119 was generally well tolerated and gave respective quinazolinone derivatives 128 in moderate to excellent isolated yields (36–99%) (Scheme 34). The approach involved three new carbon–nitrogen bond formation in one-pot fashion.

Alternatively, Wang et al. demonstrated hydrogen-transfer strategy for the preparation of 2,4-difunctionalized quinazolines 47 through a highly effective and selective nitrogen source-assisted reaction of aromatic alcohols 46 with o-nitroacetophenones 57 in the presence of Au/TiO2 as a catalytic system (Tang L. et al., 2015). The synthetic protocol is a wide substrate scope, has good tolerance to water and air, and signifies a novel avenue for economical and practical multiple carbon–nitrogen bond formation (Scheme 35). More significantly, no additional reductant, oxidant, and additive are demanded in the synthesis, and the catalytic system can be regenerated and recycled readily.

Tang et al. described gold-catalyzed chemo-selective cyclization of N-propargylic sulfonyl hydrazones 129 in dimethyl sulfoxide at ambient temperature for the development of 5,6-dihydropyrazolo[1,5-c]quinazoline derivatives 130 (Scheme 36). Numerous N-propargylic sulfonyl hydrazones actively converted under the optimized reaction condition to furnish quinazolines in good to excellent isolated yields (44–97%) (Tang H.-T. et al., 2015).
SCHEME 31 | Co-catalyzed isocyanide insertion-cyclization for constructing benzoimidazoquinazoline frameworks.

SCHEME 32 | Ni-catalyzed sequential double annulation cascade (SDAC) approach to access fused quinazolines.

SCHEME 33 | Ni-catalyzed acceptorless dehydrogenative coupling for accessing poly-substituted quinazolines.

SCHEME 34 | Au-catalyzed cascade method for the formation of quinazolones.

SCHEME 35 | Ammonia-promoted and Au-catalyzed formation of quinazolines in water.
Iron-Based Catalytic Systems

Chen et al. reported ferrous chloride-catalyzed carbon–hydrogen oxidation and intramolecular carbon–nitrogen bond formation for the construction of quinazolines 133 using tert-butyl hydroperoxide as terminal oxidant. 2-Alkylamino N-H ketamines 132 were prepared via reaction of commercially available 2-alkylaminobenzonitrile 131 with Grignard reagent (Chen et al., 2018). The process delivered a broad variety of 2,4-difunctionalized quinazoline derivatives in good to excellent isolated yields (43–86%) (Scheme 37). The oxidation of the N-alkyl moiety in this procedure employs cheap and non-toxic iron salts (FeCl₂) in the absence of any privileged ligands.

Ferrous bromide-catalyzed one-pot cascade approach for the preparation of quinazoline analogs 47 have been disclosed by Gopalaiah et al. from 2-hydroxymethylanilines 134 with aromatic amines 135 under an aerobic oxidative condition in benzene chloride at 110°C for 12–24 h (Gopalaiah et al., 2017). In a one-pot manner, the reaction proceeds through the construction of N-benzylidenebenzylamine intermediate and...
CONCLUSION AND PERSPECTIVES

In the review article, a broad spectrum of simple, mild, effective, novel synthetic routes to afford various functionalized quinazolines through cheap and commercially available starting materials have been reviewed. Clearly, a lot of work has been done for the construction of quinazoline frameworks in the recent past. Magnetic ionic liquid synthesis, nickel- and palladium-catalyzed synthesis, base-driven synthesis in water and microwave-promoted synthesis are highly advanced, novel approaches, with numerous positive aspects like mild reaction conditions, time efficient, recyclable catalysts, and use harmless solvents. Most importantly, several strategies including Lewis acid-catalyzed synthesis, cobalt zeolite imidazolate framework-catalyzed synthesis, CAN-catalyzed synthesis, base-driven synthesis in water, iron-catalyzed synthesis, and zinc-catalyzed synthesis have been successfully utilized to attain diversely decorated frameworks of quinazoline, which are important in agrochemical and pharmaceutical industries. The regularly improved synthetic approaches better the synthetic research on quinazolines with a tendency of faster, more convenient, and more diverse. Furthermore, because of the simplicity of synthetic methods enabling the construction of core scaffolds of many marketed drugs, we hope to see further research in the design of novel functionalized quinazoline derivatives, with exploitation of their biological activities in diverse ways.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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