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REVIEW ARTICLE

Microwave–Assisted and Green Catalytic Synthesis of Dihydroquinazoline Derivatives: Recent Advances and Pharmacological Significance

Achut R. Shinde*

ABSTRACT: Quinazolines, dihydroquinazolines, and quinazolinones represent a significant class of nitrogen-containing heterocyclic compounds, widely distributed in natural sources such as plants, microorganisms, and animals. Among these, dihydroquinazolines, characterized by the quinazolin-4-(3H)-one core, exhibit a broad spectrum of pharmacological and biological activities, including anticancer, antimicrobial, anti-inflammatory, antiviral, and antitubercular properties. Due to their diverse therapeutic potential, the synthesis of these heterocycles has garnered considerable attention from medicinal and synthetic chemists. Traditional synthetic methods, however, often involve harsh reaction conditions, toxic solvents, and expensive catalysts, prompting the need for more sustainable and efficient approaches. Recent advancements in green chemistry have introduced microwave-assisted synthesis as a powerful tool for the rapid, energy-efficient, and environmentally benign preparation of dihydroquinazoline derivatives. Microwave irradiation facilitates faster reaction rates, higher yields, and reduced energy consumption compared to conventional heating methods. Additionally, the use of green catalysts, such as ionic liquids, nanocatalysts, and biodegradable polymers, further enhances the sustainability of these synthetic protocols. This review comprehensively summarizes the latest developments in microwave-assisted and green catalytic strategies for the synthesis of dihydroquinazoline derivatives over the past decade. Special emphasis is placed on solvent-free conditions, catalyst recyclability, and one-pot multicomponent reactions. By highlighting these eco-friendly methodologies, this review aims to guide researchers in designing more efficient and sustainable synthetic routes for pharmacologically relevant dihydroquinazoline scaffolds.

Keywords: Dihydroquinazoline, Green catalysis, Pharmacological activity, Sustainable chemistry, Heterocyclic compounds

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1. INTRODUCTION

Quinazolines and their derivatives constitute an important class of nitrogen-containing fused heterocyclic compounds, primarily isolated from natural sources such as plants, microorganisms, and animals [1-4]. Among these, quinazolinones and dihydroquinazolines are particularly significant due to their quinazolin-4-(3H)-one core structure, which is responsible for their broad spectrum of biological and pharmacological activities [5-11]. The structural versatility of quinazoline derivatives has led to their widespread application in medicinal chemistry, exhibiting a remarkable range of therapeutic properties, including antimalarial [12], anticancer [13-17], anti-obesity [18], antibacterial [19], antitumor [20], CB2 receptor agonism [21], photochemotherapeutic effects [22], anti-inflammatory [23], antimicrobial, and antioxidant activities [24]. Additionally, they demonstrate efficacy as antiplasmodial agents [25], DNA gyrase inhibitors, tyrosine kinase inhibitors (e.g., JAK2, PDE5) [26], T-type calcium channel blockers [27], antiviral compounds [28], antituberculosis agents [29], antifertility drugs, antifungal agents, monoamine oxidase inhibitors,

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antihypertensive compounds [30], anticonvulsants [31], and analgesics [32-34]. Notably, quinazoline alkaloids such as those derived from *Rutaecarpine*, a plant belonging to the Rutaceae family, further highlight their natural abundance and pharmacological relevance [35, 36].

The synthesis of quinazoline derivatives has traditionally relied on conventional heating methods, which often suffer from drawbacks such as prolonged reaction times, high energy consumption, and the use of hazardous solvents. However, the advent of microwave-assisted organic synthesis (MAOS) has revolutionized the field by offering a more efficient, rapid, and environmentally benign alternative. Microwave irradiation (MWI) serves as a powerful green energy source, enabling cost-effective, uniform, and controlled heating for a wide range of organic transformations [36-40]. The concept of using microwave energy for chemical synthesis was first explored in the 1950s, but it gained significant traction in the 1970s and 1980s with the commercialization of domestic microwave ovens [41]. Early studies demonstrated that reactions conducted under microwave irradiation yielded higher product outputs in significantly shorter durations compared to conventional thermal methods [41]. This breakthrough spurred extensive research into microwave-assisted synthesis, leading to substantial advancements in organic chemistry.

Despite its advantages, early microwave-assisted synthesis faced challenges such as non-uniform energy distribution, difficulty in controlling reaction parameters (temperature and pressure), and safety concerns with flammable solvents [42, 43]. These limitations were addressed through the development of specialized microwave reactors, which provided enhanced reproducibility, precise temperature and pressure regulation, and improved reaction scalability. Modern microwave-assisted synthesis allows for rapid heating at elevated temperatures and pressures, often exceeding the boiling points of conventional solvents, thereby accelerating reaction kinetics and improving yields [44, 45]. The technique offers numerous benefits, including reduced reaction times, energy efficiency, higher selectivity, and minimized byproduct formation, making it an indispensable tool in contemporary synthetic chemistry.

Quinazolines and their derivatives, particularly quinazolinones and dihydroquinazolines, remain highly sought-after scaffolds in pharmaceutical research due to their diverse therapeutic applications. The synthesis of the quinazoline core was first reported by Griess et al. in 1869 via the reaction of anthranilic acid with cyanogen [46], followed by Niementowski's modification in 1895 using amides instead of cyanogen [47]. Since then, numerous synthetic strategies have been developed, employing various precursors such as 2-aminobenzoic acid, anthranilamide, anthranilonitrile, isatoic anhydride, and benzoxazines [48-49]. Over the years, multiple reviews have documented the synthesis of quinazoline derivatives, emphasizing their biological significance [50]. The integration of microwave irradiation as a green and sustainable energy source has further expanded synthetic possibilities, with several studies reporting efficient, high-yielding protocols for quinazoline and quinazolinone synthesis [51-57].

Microwave-assisted synthesis of quinazoline derivatives encompasses a variety of reaction pathways, including intramolecular heterocyclization [58], intramolecular Friedel-Crafts-type cyclization [59], palladium-catalyzed annulation of N-allylamidines [60], and cyclocondensation reactions using ortho esters, benzaldehydes, alcohols, amines, and thiourea derivatives [60-80]. Multicomponent reactions (MCRs) have also been extensively utilized, enabling the rapid assembly of complex quinazoline structures in a single step [81]. Other notable methodologies include Radziszewski's reaction [82], double cyclization strategies [83], intramolecular azido-reductive cyclization [84], Niementowski quinazoline synthesis [85], and metal-catalyzed cyclization of benzoic acids [87-88]. Cyclocondensation has been achieved through various microwave-assisted synthetic methods using ortho esters [89], aldehydes, carboxylic acids [90], triethylamine–formic acid mixture (TEAF) [91], aliphatic and aromatic amines [92], benzyl alcohols [93], thioamides, isothiocyanates, potassium isopropyldithiocarbonate, and three-component reactions (MCR) [94-97]. Despite these advancements, the microwave-assisted synthesis of dihydroquinazoline derivatives remains relatively underexplored compared to their quinazoline and quinazolinone counterparts.

This review article provides a comprehensive and up-to-date analysis of microwave-assisted synthetic methodologies for dihydroquinazoline derivatives, filling a critical gap in the existing literature. While previous reviews have extensively covered quinazoline and quinazolinone synthesis, there has been limited focus on dihydroquinazolines, particularly those synthesized via green and sustainable approaches. This work systematically consolidates recent advancements in microwave-assisted and catalytic green synthesis, emphasizing solvent-free conditions, recyclable catalysts, and energy-efficient protocols. By highlighting innovative strategies such as nanocatalysis, biocatalysis, and continuous-flow microwave systems, this review serves as a valuable resource for researchers aiming to develop environmentally benign and scalable synthetic routes for pharmacologically relevant dihydroquinazoline scaffolds. The integration of computational and AI-driven approaches for reaction optimization is also discussed, offering forward-looking insights into the future of sustainable heterocyclic chemistry.

Given the pharmacological importance of dihydroquinazoline derivatives and the growing emphasis on sustainable synthesis, this review aims to consolidate and critically evaluate the latest developments in microwave-assisted and green catalytic methodologies. By addressing the existing gaps in the literature, this work seeks to inspire further research into efficient, eco-friendly synthetic routes for dihydroquinazoline-based drug candidates, ultimately contributing to advancements in medicinal chemistry and pharmaceutical sciences.

2. MICROWAVE-ASSISTED SYNTHESIS OF

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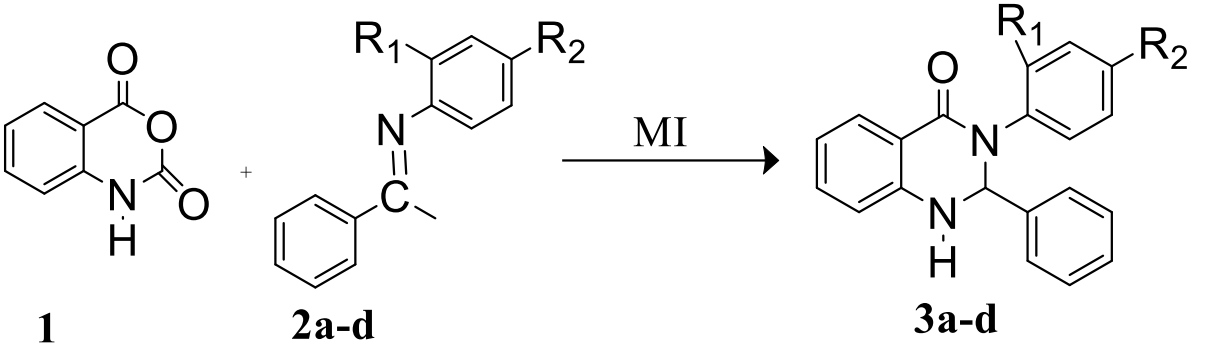
DIHYDROQUINAZOLINE DERIVATIVES

2.1. Solvent-Free Diels-Alder Cycloaddition Approach

Recent developments in microwave-assisted organic synthesis have revolutionized the preparation of dihydroquinazoline derivatives through sustainable and atom-efficient protocols. Jacob et al. [98] pioneered a solvent-free microwave-assisted synthesis of 2,3-diaryl-2,3-dihydroquinazolin-4(1H)-ones via Diels-Alder cycloaddition of azomethines to isatoic anhydride. The methodology employed an equimolar mixture of isatoic anhydride (1) and azomethine derivatives (2a-d) subjected to microwave irradiation, yielding the target dihydroquinazolinones (3a-d) in exceptional yields (71-90%) without requiring organic solvents (Scheme 1). This approach exemplifies the dual advantages of microwave activation in accelerating reaction kinetics while maintaining excellent selectivity, coupled with the environmental benefits of eliminating solvent waste. The reaction mechanism proceeds through a concerted [4+2] cycloaddition, where microwave irradiation enhances molecular dipole rotation, facilitating the formation of the dihydroquinazoline core structure.

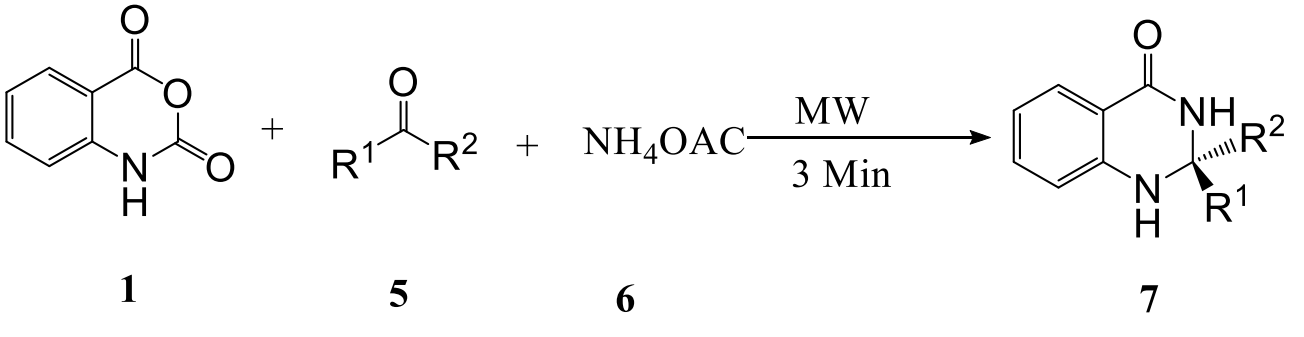
2.2. Multicomponent Reaction Strategies

Significant progress in multicomponent reactions (MCRs) under microwave conditions has been achieved through the work of Gupta et al. [99], who developed a remarkably efficient catalyst- and solvent-free synthesis of 2,3-dihydroquinazolin-4(1H)-ones. Their protocol involves the condensation of isatoic anhydride (1), aldehydes/ketones (5), and ammonium acetate (6) under microwave irradiation (60°C, 300 W) in an open vessel system, producing the desired products (7) within an unprecedented 3-minute reaction time (Scheme 2). The methodology demonstrates excellent functional group tolerance, accommodating both aromatic and aliphatic carbonyl compounds.



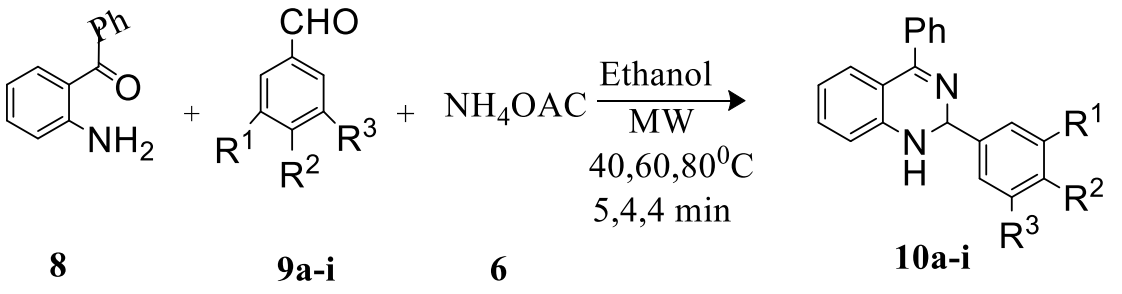
Compound	R	%Yield
2a, 3a	R_1= H, R_2= H	90%
2b, 2b	R_1= H, R_2= Cl	90%
2c, 3c	R_1= H, R_2= CH_3	90%
2c, 3c	R_1= H, R_2= CH_3	71%

Scheme 1. Solvent-free microwave-assisted synthesis of 2,3-diaryl-2,3-dihydroquinazolin-4(1H)-ones via Diels–Alder addition.



Scheme 2. Three-component, catalyst-free synthesis of 2,3-dihydroquinazolin-4(1H)-ones under microwave irradiation.

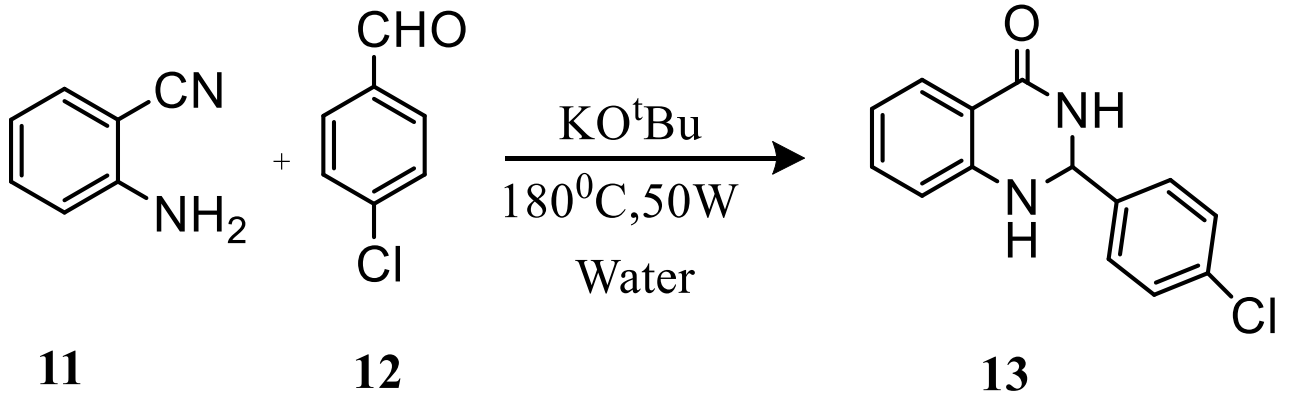
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8 **9a-i** **6** **10a-i**

	a	b	c	d	e	f	g	h	i	Temp in ^{0}C	time in minutes	% yield
R^1	H	H	H	OMe	H	H	H	H	H	40	05	90
R^2	OMe	H	OMe	OMe	Cl	NO_2	H	CN	Br	60	04	96
R^3	H	OMe	OMe	OMe	H	Cl	NO^2	H	H	80	04	96

Scheme 3. One-pot microwave-assisted synthesis of 2-aryl-4-phenyl-1,2-dihydroquinazoline derivatives.



11 **12** **13**

Scheme 4. Base-promoted, metal-free synthesis of 2,3-dihydroquinazolin-4(1H)-ones in aqueous medium under microwave conditions.

Building on this work, Putta et al. [100] established an optimized microwave-assisted one-pot synthesis of 2-aryl-4-phenyl-1,2-dihydroquinazoline derivatives. Their systematic investigation revealed that irradiation at 60-80°C in a CEM Discover microwave reactor equipped with magnetic stirring provided optimal yields (90-96%) of target compounds (10a-i) from 2-aminobenzophenone (8), aryl aldehydes (9a-i), and ammonium acetate (6) in ethanol (Scheme 3). The researchers identified temperature control as a critical parameter, with 80°C proving optimal for most substrates while minimizing side reactions.

2.3. Metal-Free Aqueous Phase Synthesis

Datta and Sarma [101] contributed a significant advancement with their base-promoted, metal-free approach for synthesizing 2,3-dihydroquinazolin-4(1H)-ones in aqueous media under microwave irradiation. Their protocol involves the cyclocondensation of 2-aminonitrile (11) with carbonyl compounds (12) using potassium tert-butoxide (KOtBu) as base in water. Microwave irradiation at 180°C (50 W) for 2 minutes in sealed vessels achieved rapid cyclization, with subsequent ethanol recrystallization yielding products (13) of exceptional purity (Scheme 4). This methodology represents a paradigm shift in sustainable synthesis, combining the advantages of microwave acceleration with the environmental benefits of aqueous media and absence of transition metal catalysts.

2.4 Sequential Multicomponent Functionalization

Firoozi et al. [102] expanded the synthetic toolbox through their innovative one-pot synthesis of 2, 3-dihydroquinazolin-4(1H)-one derivatives (16a-e) followed by subsequent functionalization to oxazolone derivatives (20a-f). Their approach begins with the microwave-assisted condensation

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of isatoic anhydride (1), aromatic aldehydes (14a-e), and 4-aminohippuric acid (15) catalyzed by acetic acid, followed by reaction with additional aromatic aldehydes (17a-c), acetic anhydride (18), and sodium acetate (19) (Scheme 5). This sequential transformation demonstrates the remarkable versatility of microwave irradiation in facilitating complex multi-step syntheses with excellent regiocontrol and high overall yields.

2.5. Iminoester-Based Cyclization Strategy

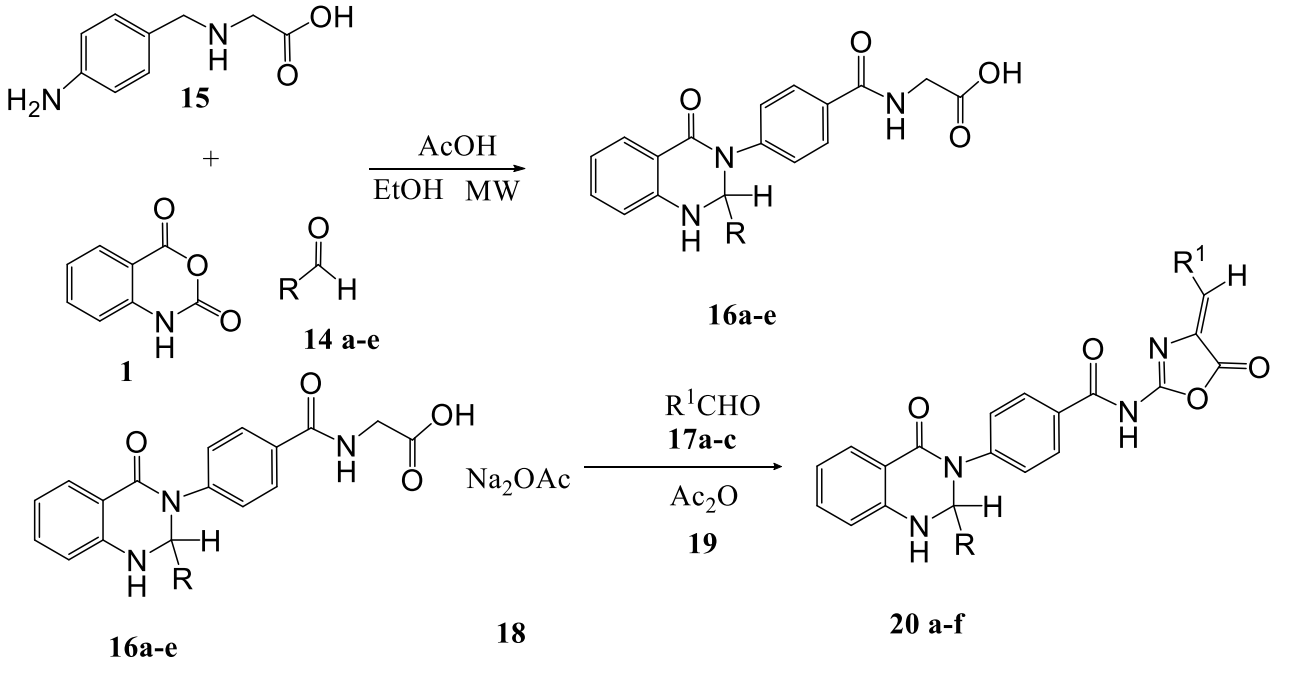
Keraali et al. [103] developed a practical microwave-assisted route to 2,3-dihydroquinazolines via iminoester hydrochlorides (22) derived from nitriles (21). Their protocol involves in situ generation of hydrogen chloride gas from ammonium chloride and sulfuric acid, followed by microwave irradiation of the resulting iminoester hydrochlorides with 2-aminobenzylamine (23) to afford 2-substituted dihydroquinazolines (24) in high yields (Scheme 6). This methodology overcomes the traditional limitations of iminoester chemistry by dramatically reducing reaction times from hours to minutes while maintaining excellent yield and purity.

The collective advancements in microwave-assisted synthesis of dihydroquinazoline derivatives demonstrate clear advantages over conventional thermal methods, including order-of-magnitude reductions in reaction times (from hours to minutes), substantial improvements in yields (typically 85-96%), and enhanced sustainability through reduced energy consumption and minimized waste generation. The successful application of various activation modes - including solvent-free conditions, aqueous media, and multicomponent approaches - highlights the versatility of microwave irradiation in heterocyclic synthesis.

Future research directions should focus on several key areas: (1) development of continuous-flow microwave systems to enable scalable production, (2) integration of machine learning algorithms for reaction optimization, (3) exploration of hybrid microwave-photochemical activation methods, and (4) expansion to asymmetric synthesis using chiral microwave effects. The combination of microwave assistance with emerging green chemistry principles promises to further revolutionize the field of heterocyclic synthesis in coming years.

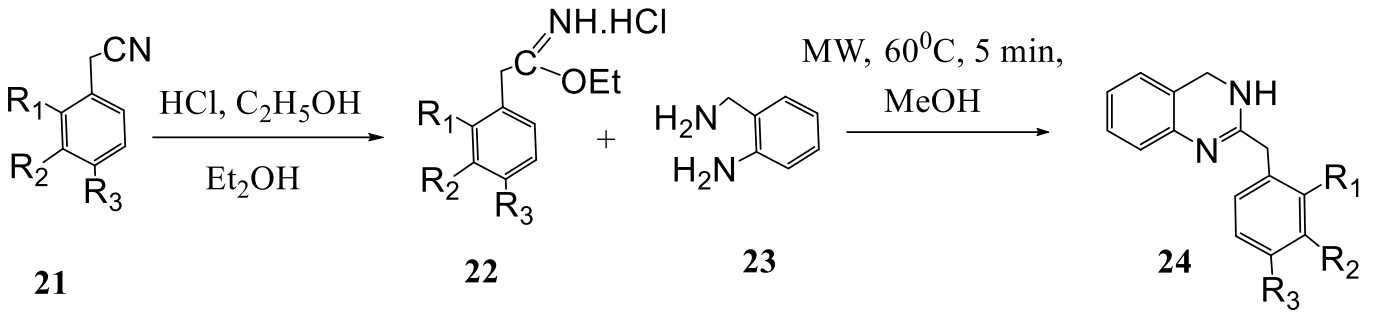
2.6. Base- and Catalyst-Free Microwave Synthesis

Kerdphon and colleagues [104] developed an innovative microwave-assisted protocol for the green synthesis of 2,3-dihydroquinazolinones under base- and catalyst-free conditions. Their methodology involved the cyclocondensation of 2-aminobenzamide (25) with benzaldehyde (26) in a microwave reactor at 80°C for 5 minutes. The researchers conducted extensive solvent optimization studies, evaluating both polar (ethanol, acetonitrile) and nonpolar (toluene) solvents. Ethanol emerged as the optimal solvent, affording the desired 2,3-dihydroquinazolinone (27) in an impressive 91% yield (Scheme 7). This approach exemplifies the advantages of microwave irradiation in promoting rapid molecular transformations while eliminating the need for additional bases or catalysts, thereby enhancing the sustainability of the synthetic process.

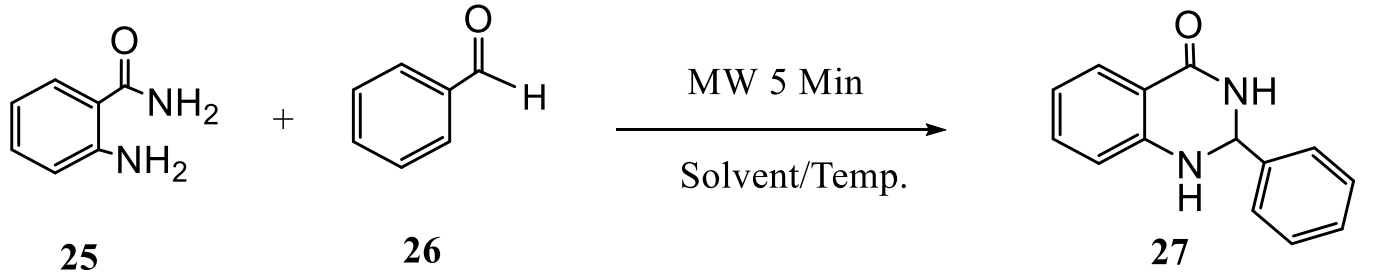


Scheme 5. Multicomponent synthesis of quinazolinones and subsequent transformation to oxazolones.

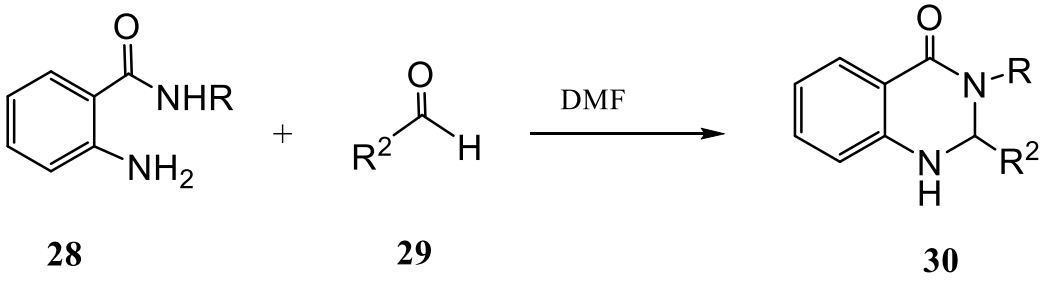
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Scheme 6. Microwave-assisted synthesis of 2,3-dihydroquinazolines from iminoester hydrochlorides.



Scheme 7. Microwave-assisted green synthesis of 2,3-dihydroquinazolinones under base- and catalyst-free conditions.



R = H, Ar, Phenylamine, Benzimdazole

R^2 = Ar, Alkyl, Furan, 7- Methoxycumarine, 7, 8, dimethoxycumarine

Scheme 8. Catalyst-free microwave-assisted synthesis of 2-aryl/alkyl-3-(1H-benzo[d]imidazol-2-yl)-2,3-dihydroquinazolin-4(1H)-ones.

2.7. Catalyst-Free Synthesis of Benzimidazole-Fused Derivatives

Kumar et al. [105] reported a significant advancement in the microwave-assisted synthesis of structurally complex 2-aryl/alkyl-3-(1H-benzo[d]imidazol-2-yl)-2,3-dihydroquinazolin -4 (1H)-ones (30). Their catalyst-free methodology employed the condensation of 2-aminobenzamide (28) with diverse aromatic, aliphatic, and heterocyclic aldehydes (29) in dimethylformamide (DMF) under microwave irradiation at 180°C for 10-20 minutes. Through systematic solvent optimization studies, the authors demonstrated that nonpolar solvents consistently provided superior yields compared to their polar counterparts (Scheme 8). This work represents an important contribution to the field by showcasing the versatility of microwave irradiation in facilitating the construction of complex heterocyclic systems without requiring metal catalysts or harsh reaction conditions.

2.8. Bisulfite Adduct-Mediated Synthesis

Bera and coworkers [106] developed a novel microwave-assisted synthetic route to 2,3-dihydroquinazolin-4(1H)-ones (32) utilizing bisulfite adducts derived from various ketones (31). Their methodology involved the efficient reaction of

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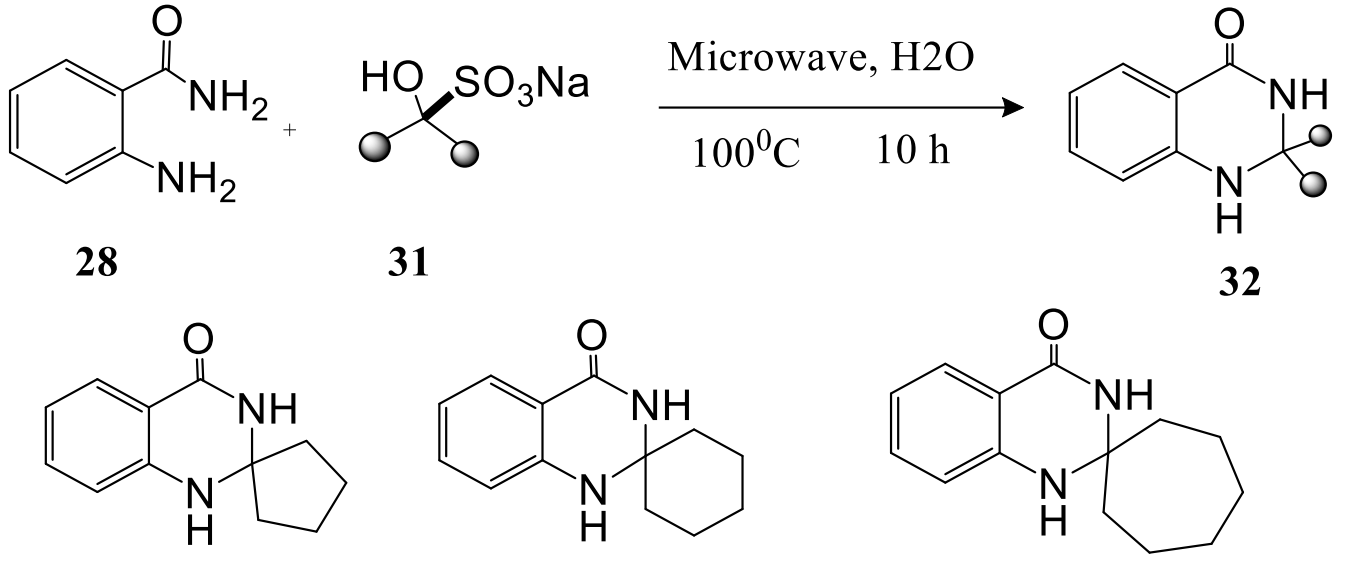
anthranilamide (28) with bisulfite adducts of five-, six-, and seven-membered cyclic ketones under microwave conditions (Scheme 9). This approach offers several advantages, including the ability to incorporate diverse cyclic systems into the dihydroquinazoline scaffold and the utilization of readily available starting materials. The bisulfite adducts serve as effective precursors for the cyclization reaction, demonstrating the potential of this methodology for the synthesis of structurally diverse dihydroquinazoline derivatives.

2.9. Nanocatalyst-Mediated Aqueous Phase Synthesis

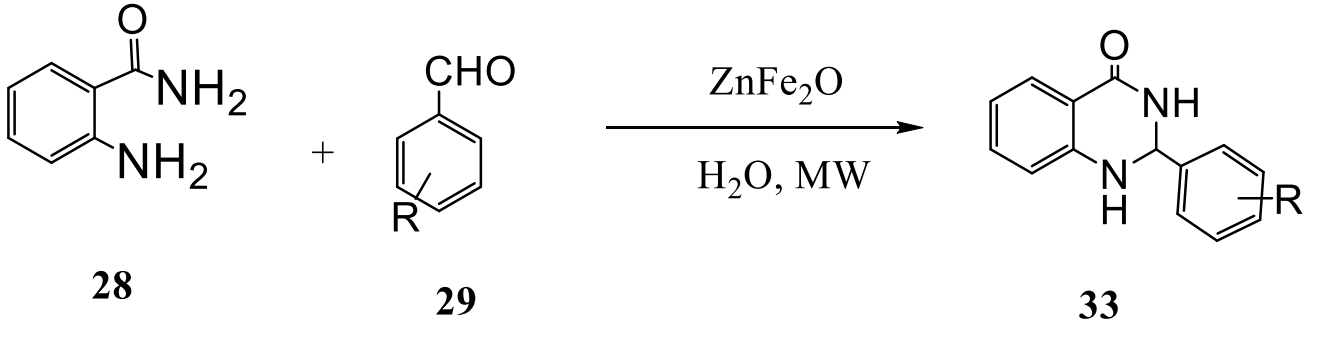
Rupnar et al. [107] reported an environmentally benign protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones (33) using zinc ferrite (ZnFe2O4) as a magnetic nanocatalyst in aqueous medium. The reaction between 2-aminobenzamide (28) and various aldehydes (29) was efficiently promoted by microwave irradiation (210 W) for 5-15 minutes in the presence of the ZnFe2O4 catalyst (Scheme 10). The aqueous reaction medium, combined with the magnetic properties of the nanocatalyst, facilitated easy separation and recovery of the catalyst, significantly enhancing the sustainability of the process. This work highlights the growing importance of nanocatalysts in modern synthetic chemistry and their compatibility with microwave-assisted methodologies.

2.10. Ionic Liquid-Catalyzed Multicomponent Synthesis

Yang and coworkers [108] developed an efficient one-pot three-component synthesis of 2,3-dihydroquinazolin-4(1H)-ones (37) catalyzed by heteropolyanion-based ionic liquids under solvent-free microwave conditions. Their methodology involved the reaction of isatoic anhydrides (34) with amines and aldehydes or ketones (35) in the presence of ionic liquid catalysts (36) under microwave irradiation (Scheme 11). The authors reported excellent catalyst recovery and recyclability, with the ionic liquid catalyst maintaining its activity over multiple reaction cycles. This approach combines the advantages of microwave irradiation with the unique properties of ionic liquids, offering a sustainable and efficient route to dihydroquinazoline derivatives.

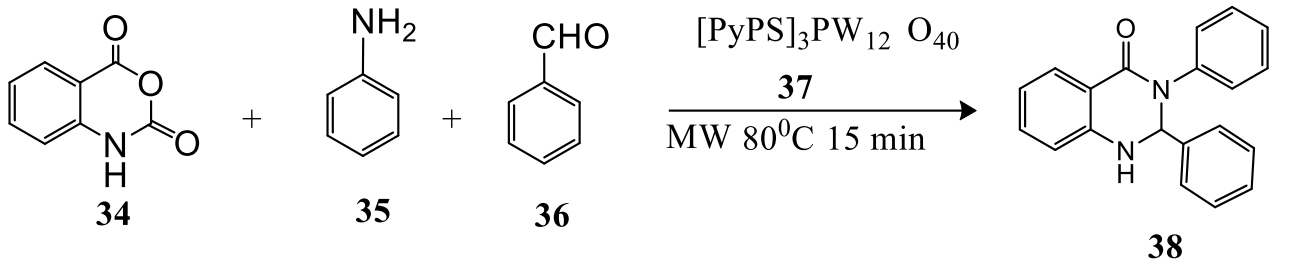


Scheme 9. Bisulfite adduct-mediated synthesis of 2,3-dihydroquinazolin-4(1H)-ones under microwave irradiation.

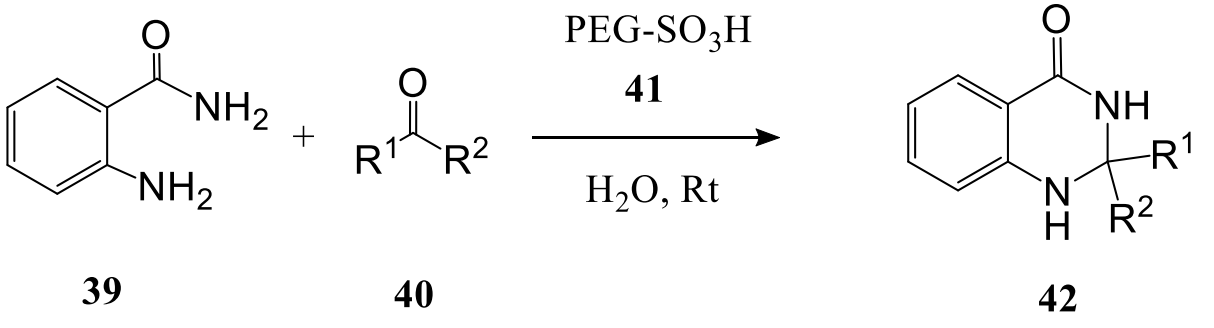


Scheme 10. $ZnFe_2O_4$-catalyzed aqueous phase synthesis of 2,3-dihydroquinazolin-4(1H)-ones under microwave conditions.

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Scheme 11. Ionic liquid-catalyzed one-pot three-component synthesis of 2,3-dihydroquinazolin-4(1H)-ones under solvent-free microwave conditions.



Scheme 12. PEG-SO₃H-catalyzed green synthesis of 2,3-dihydroquinazolin-4(1H)-ones in aqueous medium.

3. GREEN CATALYTIC APPROACHES FOR DIHYDROQUINAZOLINE SYNTHESIS

3.1 Polymer-Supported Acid Catalysis

Huang and colleagues [109] reported a highly efficient and environmentally benign method for synthesizing 2,3-dihydroquinazolin-4(1H)-ones (42) using polyethylene glycol-supported sulfonic acid (PEG-SO3H) as a recyclable polymeric catalyst. The reaction between 2-aminobenzamide (39) and various aldehydes or ketones (40) proceeded smoothly in water at room temperature in the presence of the PEG-SO3H catalyst (41) (Scheme 12). The aqueous reaction medium, combined with the mild reaction conditions and excellent recyclability of the polymeric catalyst, makes this methodology particularly attractive from a green chemistry perspective. The authors demonstrated the broad substrate scope of this transformation, including both aromatic and aliphatic carbonyl compounds.

3.2 Catalyst-Free Aqueous Synthesis

Olyaei and coworkers [110] developed a remarkably simple and efficient protocol for the catalyst-free synthesis of 2,3-dihydroquinazolin-4(1H)-ones (47, 48) in water. Their three-component coupling reaction involved isatoic anhydride (43), aromatic aldehydes (44), and either aniline (45) or ammonium acetate (46) under reflux conditions (Scheme 13). The complete absence of catalysts, combined with the use of water as the sole solvent, makes this approach exceptionally green and sustainable. The authors reported excellent yields for a wide range of substrates, demonstrating the general applicability of this methodology.

3.3 Biocatalytic Approaches

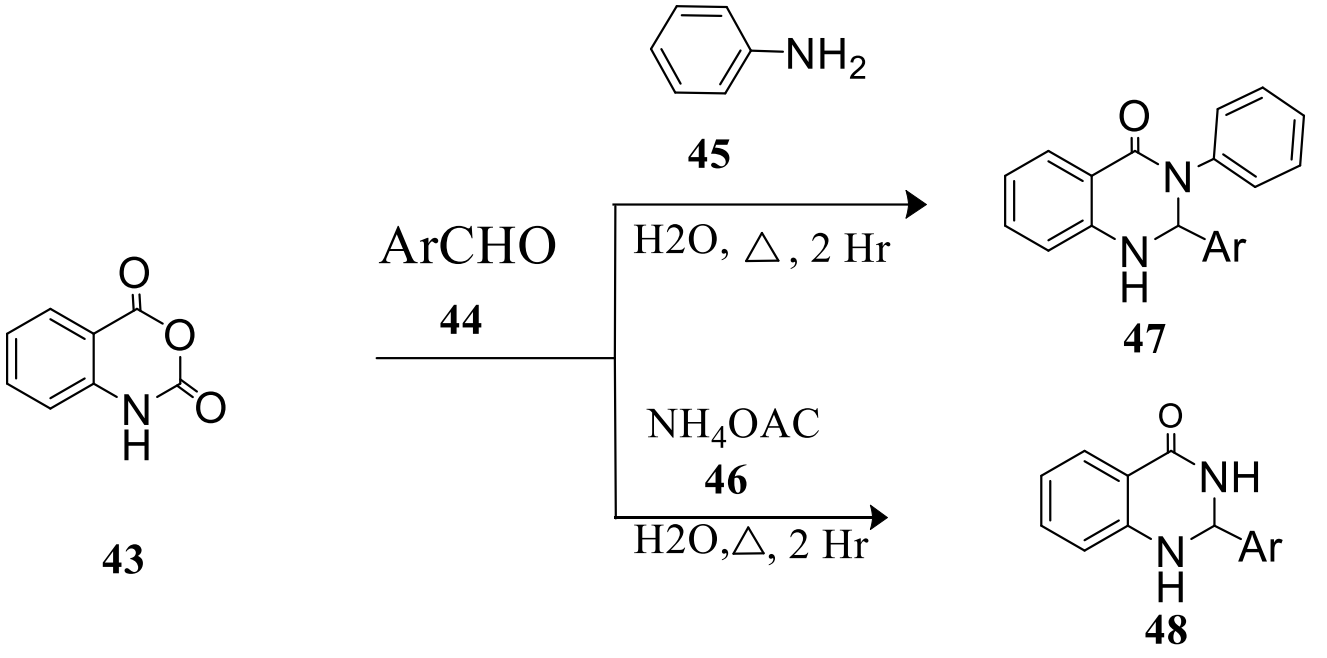
Mirjalili and colleagues [111] introduced an innovative biocatalytic approach for the synthesis of 2,3-dihydroquinazolinones (52) using nano-ovalbumin as a non-toxic biocatalyst. The reaction between 2-aminobenzamide (49) and various aldehydes (50) was efficiently catalyzed by nano-ovalbumin (51) in an ethanol-water mixture under reflux conditions (Scheme 14). This methodology represents a significant advancement in green chemistry, as it employs a biocompatible and biodegradable catalyst derived from natural sources. The easy separation of the catalyst and products, combined with the mild reaction conditions, makes this approach particularly attractive for pharmaceutical applications.

3.4 Lactic Acid-Catalyzed Solvent-Free Synthesis

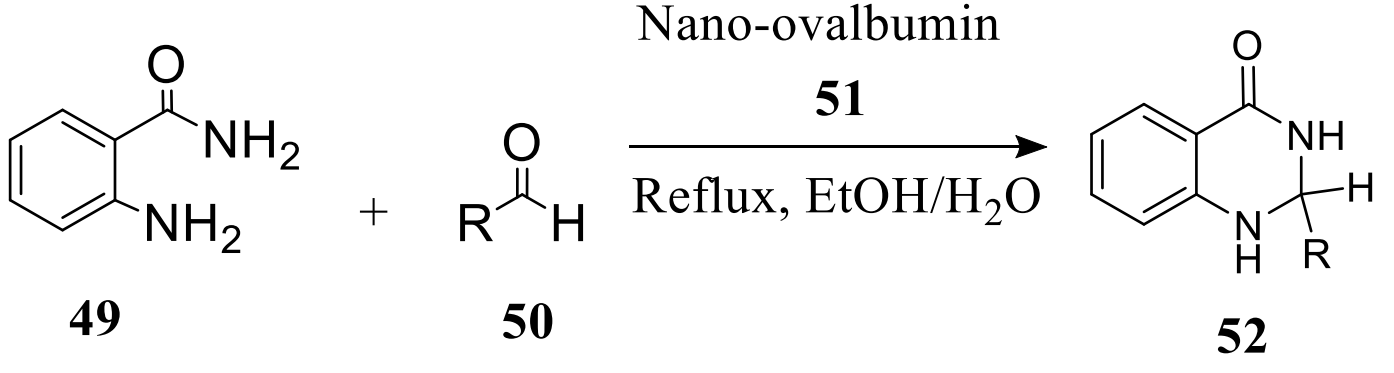
Zhaleh et al. [112] developed two distinct green protocols for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones (56) using lactic acid as a biodegradable catalyst under solvent-free conditions. The first method involved the reaction of 2-aminobenzamide (53) with aldehydes (54) catalyzed by lactic acid (55) at 70°C (Scheme 15). The second approach

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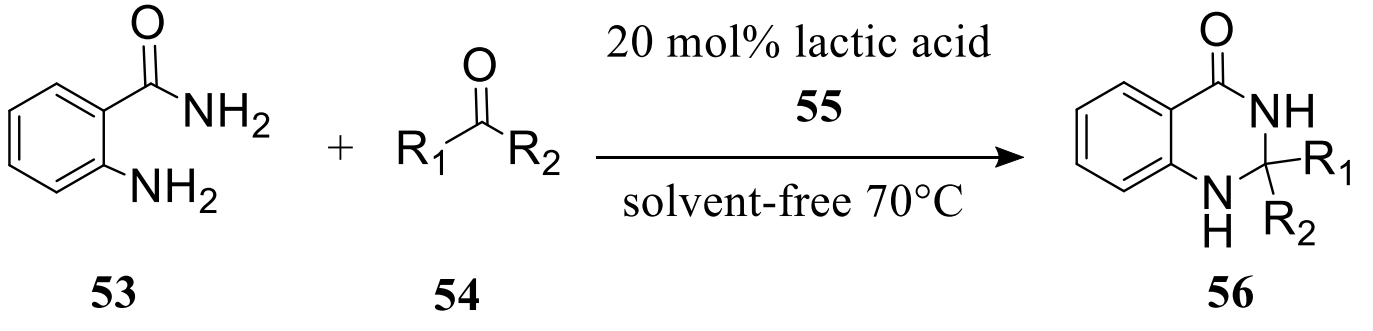
employed a three-component reaction of isatoic anhydride (57), aldehydes (58), and ammonium acetate (59) in the presence of lactic acid (60) under similar conditions (Scheme 16). Both methods provided excellent yields while avoiding the use of organic solvents, demonstrating the versatility of lactic acid as a green catalyst for heterocyclic synthesis.



Scheme 13. Catalyst-free aqueous synthesis of 2,3-dihydroquinazolin-4(1H)-ones via three-component coupling.

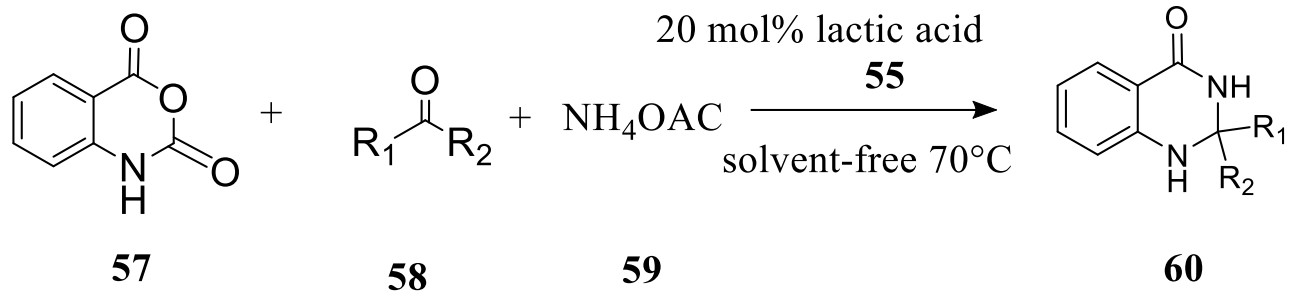


Scheme 14. Nano-ovalbumin catalyzed biocatalytic synthesis of 2,3-dihydroquinazolin-4(1H)-ones.

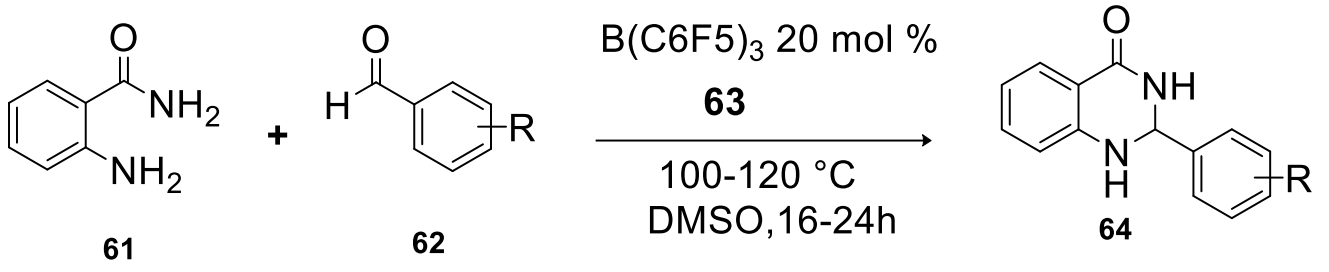


Scheme 15. Lactic acid-catalyzed solvent-free synthesis of 2,3-dihydroquinazolin-4(1H)-ones from 2-aminobenzamide and aldehydes.

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Scheme 16. Three-component synthesis of 2,3-dihydroquinazolin-4(1H)-ones catalyzed by lactic acid under solvent-free conditions.



Scheme 17. $B(C_6F_5)_3$-catalyzed cascade synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones.

3.5 Boron-Catalyzed Cascade Synthesis

Shinde and coworkers [113] reported an efficient one-pot synthesis of 2-substituted 2,3-dihydroquinazolin-4(1H)-ones (64) catalyzed by tris(pentafluorophenyl)borane [B(C6F5)3]. The reaction between 2-aminobenzamide (61), benzaldehyde (62), and the boron catalyst (63) in DMSO at 100-120°C provided the desired products in good to excellent yields (Scheme 17). The authors proposed a cascade reaction mechanism involving initial imine formation followed by cyclization. This methodology represents an important addition to the toolbox of catalytic approaches for dihydroquinazoline synthesis, particularly for the preparation of more complex derivatives.

The methodologies discussed in this section demonstrate the remarkable progress achieved in the green synthesis of dihydroquinazoline derivatives. From polymer-supported catalysts to biocatalytic approaches, these methods exemplify the principles of sustainable chemistry while maintaining high efficiency and selectivity. The continued development of such environmentally benign synthetic protocols will be crucial for meeting the growing demand for sustainable pharmaceutical production.

4. FUTURE DIRECTIONS

The field of microwave-assisted and green catalytic synthesis of dihydroquinazoline derivatives holds immense potential for future advancements, driven by the increasing demand for sustainable and efficient synthetic methodologies in pharmaceutical chemistry. One promising direction involves the integration of advanced nanocatalysts with microwave irradiation to further enhance reaction efficiency and selectivity. Recent developments in magnetic nanoparticles, metal-organic frameworks (MOFs), and graphene-based catalysts offer high surface area, recyclability, and improved catalytic activity, which could be leveraged for the synthesis of structurally diverse dihydroquinazoline scaffolds. Exploring bimetallic and hybrid nanocatalysts may also provide synergistic effects, enabling milder reaction conditions and higher yields.

Another critical area for future research is the development of continuous-flow microwave systems, which combine the benefits of microwave heating with flow chemistry. This approach can facilitate large-scale production of dihydroquinazoline derivatives while maintaining precise control over reaction parameters such as temperature, pressure, and residence time. Continuous-flow systems minimize energy consumption, reduce waste, and improve reproducibility, making them ideal for industrial applications. Additionally, the incorporation of in-line analytical techniques, such as real-time NMR or mass spectrometry, could enable automated optimization of reaction conditions, accelerating drug discovery processes.

The exploration of biocatalytic routes for dihydroquinazoline synthesis represents an underexplored yet highly sustainable avenue. Enzymes and whole-cell biocatalysts can operate under mild, aqueous conditions with high enantioselectivity, reducing the need for toxic reagents and harsh conditions. Future studies could focus on engineering robust enzymes or microbial strains capable of

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catalyzing key cyclization and condensation reactions involved in dihydroquinazoline formation. Combining biocatalysis with microwave activation may further enhance reaction rates and yields, offering a greener alternative to traditional chemical methods.

Computational chemistry and artificial intelligence (AI) are poised to play a transformative role in optimizing microwave-assisted synthetic routes. Machine learning algorithms can analyze vast datasets of reaction conditions, catalyst performances, and substrate reactivities to predict optimal synthetic pathways. Density functional theory (DFT) calculations could aid in understanding reaction mechanisms, facilitating the design of more efficient catalysts and reducing trial-and-error experimentation. Virtual screening of dihydroquinazoline derivatives for pharmacological activity could also streamline the identification of lead compounds, bridging the gap between synthesis and drug development.

Finally, expanding the scope of sustainable solvents beyond water—such as deep eutectic solvents (DES), supercritical CO_2, and bio-based solvents—could further improve the environmental footprint of dihydroquinazoline synthesis. Investigating solvent-free mechanochemical approaches, where reactants are ground together in the presence of a catalyst under microwave irradiation, may also offer energy-efficient alternatives. Collaborative efforts between synthetic chemists, material scientists, and computational experts will be essential to drive these innovations, ultimately paving the way for greener, faster, and more cost-effective routes to biologically active dihydroquinazolines.

5. CONCLUSION

The synthesis of dihydroquinazoline derivatives has evolved significantly with the advent of microwave-assisted and green catalytic methodologies, offering substantial advantages over conventional synthetic routes. Traditional methods often suffer from drawbacks such as prolonged reaction times, high energy consumption, toxic solvents, and the need for expensive metal catalysts. In contrast, microwave irradiation enables rapid, uniform heating, leading to accelerated reaction kinetics, improved yields, and enhanced selectivity under milder conditions. Furthermore, the integration of green catalysts, including recyclable ionic liquids, nanocatalysts, and biodegradable polymers, minimizes environmental impact while maintaining high catalytic efficiency. This review highlights various innovative approaches, such as solvent-free microwave synthesis, one-pot multicomponent reactions, and the use of water as a green solvent, which collectively contribute to sustainable and atom-economical synthetic pathways. Notably, methodologies employing heteropolyanion-based ionic liquids and polymer-supported catalysts demonstrate excellent recyclability, reducing waste generation and cost. Additionally, biocatalytic approaches using non-toxic nanomaterials further align with the principles of green chemistry by eliminating hazardous reagents. The pharmacological significance of dihydroquinazoline derivatives underscores the importance of developing efficient synthetic strategies. Microwave-assisted techniques not only expedite the discovery of novel bioactive compounds but also facilitate scalability for industrial applications. Future research should focus on optimizing reaction conditions, exploring new green catalysts, and expanding substrate scope to access structurally diverse derivatives. The integration of computational modeling and machine learning could further refine reaction parameters, enhancing efficiency and sustainability. In conclusion, the shift toward microwave-assisted and green catalytic synthesis represents a paradigm change in heterocyclic chemistry, offering a balance between efficiency, cost-effectiveness, and environmental responsibility. This review serves as a valuable resource for researchers aiming to develop sustainable synthetic routes for dihydroquinazoline-based drug candidates, ultimately contributing to advancements in medicinal chemistry and pharmaceutical sciences.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

Achut R. Shinde prepared this manuscript.

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