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REVIEW ARTICLE

A Review on Advances in the Synthesis and Bioactivity of Quinazolinone Derivative

Patil JP*[1], Amrutkar SV[2], Borole RN[3]

[1]*Dept. of Pharmaceutical Chemistry, AIKTC School of Pharmacy, New Panvel, Navi Mumbai, India.*

[2]*Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nasik, India.*

[3]*Qsafe Consultants (India), Mumbai, Maharastra, India.*

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ABSTRACT

Owing to the significant biological activities, quinazoline derivatives have drawn more and more attention in the synthesis and bioactivities research. Many of the literature synthetic methods for elaboration of this simple ring structure are, however, time consuming, tedious and often low yielding. This review summarizes the recent advances in the synthesis investigations for the construction of the 4(3H)-quinazolinone and quinazoline skeletons. The synthetic methods were divided into five main classifications, including Aza-reaction, Microwave-assisted reaction, Metal-mediated reaction, Ultrasound-promoted reaction and Phase-transfer catalysis reaction. Literature studies on quinazolinones have shown that these derivatives possess a wide variety of biological activities. This review also focused on the few novel biological activities of quinazolinones but emphasis is specified for synthetic methods.

KEYWORDS

Quinazoline, Bioactivity, MAS, PTC, Ultrasound-Promoted Reaction, Aza-Reaction, Metal-Mediated Reaction

INTRODUCTION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases most of the activity in this discipline is direct to new synthetic or natural organic compounds, but organic compounds with increasingly specific pharmacological activities are clearly the dominant force. Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities.

***Address for Correspondence:**
Patil Jayshree P.
AIKTC School of Pharmacy,
Plot 2 & 3, Sector-16,
Near Thane Naka, Khandagaon,
New Panvel, Navi Mumbai-410 206, India.
E-Mail Id: jayshreepatil76@yahoo.com

Heterocycles are among the most frequently encountered scaffolds in drug and pharmaceutically relevant substances. A heterocyclic core is propitious for variations of substitution pattern during Structure Activity Relationship (SAR).

Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer [14], anti-inflammation[5,6], anti-bacterial[7-10], analgesia[5,9], anti-virus[11], anti-cytotoxin[12], anti-spasm[9,13], anti-tuberculosis[14], anti-oxidation[15], anti-malarial[16], anti-hypertension[17], anti-

obesity[18], anti-psychotic[19], anti-diabetes[20], etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored. This review summarized the representative synthetic methods, either traditional or novel, and categorized them into five main classifications, including Aza-reaction, Microwave-assisted reaction, Metal-catalyzed reaction, Ultrasound-promoted reaction and Phase-transfer catalysis. Besides, three other kinds of reactions were also listed out, which were either designed as supplementary methods in most experiments or used as the main methods in some researches, including Oxidative cyclization, Reagent refluxing and One-pot synthesis. In addition, the bioactivity researches of quinazoline derivatives were also discussed in order to provide valuable reference for the future synthesis and biological investigation of these compounds. The present review portrays a concise account of bioactivity and synthesis of quinazolinone alkaloids pertaining strictly to the basic structure and recent developments in the area of the complex quinazolinone products, with an emphasis on new synthetic routes and strategies.

Types of Synthetic Methods

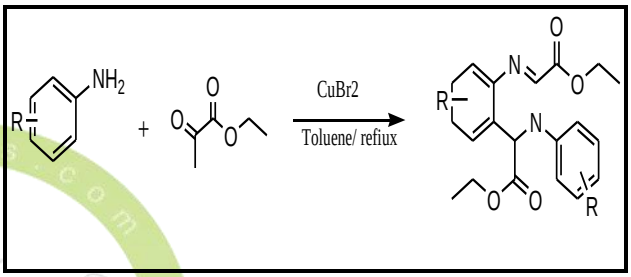
- Aza Reaction
- Microwave-assisted reaction
- Metal-catalyzed reaction
- Ultrasound-promoted reaction
- Phase-transfer catalysis

Synthetic Methods

Aza-Reaction

Aza-Diels-Alder reaction

Imino-Diels-Alder reaction[21] containing the coupling of imine and electron-rich alkene gradually became a powerful tool for the synthesis of quinazoline derivatives[22]. In Povarov imino-Diels-Alder reaction, aniline and ethyl glyoxalate were chosen as substrates. And two molecules of α-iminoesters, which were got from the condensation of aniline and ethyl glyoxalate, were hypothesized to form the direct additive product. Cascade Imino-Diels-Alder reaction conducted by Chen et al.[23] was extended from the Povarov Imino-Diels-Alder reaction. In this research, researchers chosed the same substrates as in the Povarov Imino-Diels-Alder reaction, and adopted various kinds of Lewis acid as catalysts, then the reagents were refluxed in toluene for one day, and finally produced quinazoline derivatives. $CuBr_2$ was determined as the optimized catalyst with highest yields (Scheme 1).



Scheme 1: Synthesis of derivatives 3 by cascade imino-Diels-Alder reaction

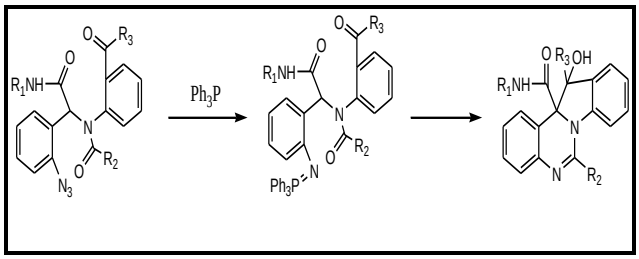
Aza-Wittig reaction

Aza-Wittig reaction, which generally precedes in cascade with easy operation under mild reaction conditions, is widely used in the synthesis of N-heterocycles[24]. He et al. reported a kind of tandem Staudinger–Aza-Wittig–Nucleophilic addition reaction to synthesize indolo[1,2-c]quinazolines recently[25]. The main synthetic procedure of this research was using azides and triphenylphosphine to react in toluene for 2 h at room temperature, and then heating at reflux for 6–24 h. Results showed that the nitrogen evolution through the Staudinger reaction halted during the initial 2 h, and surprisingly produced the final product indolo[1,2- c] quinazolines directly from the reaction mixture (Scheme 2).

Microwave-Assisted Synthesis (MAS)

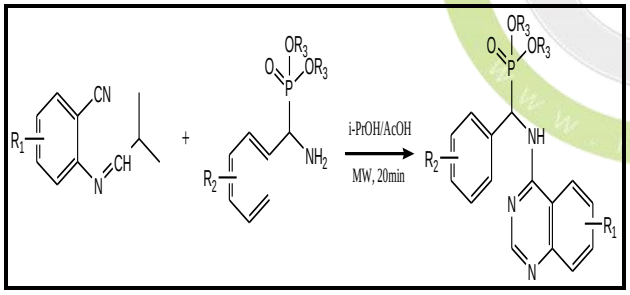
Compared to traditional heating methods, microwave heating could expand reaction range as well as shorten the reaction time from a few days or hours to a few minutes. Thus, when

applied in fields of organic synthesis, pharmaceutical chemistry and high-throughput chemistry, microwave heating shows greater advantage than traditional heating methods[28-31].



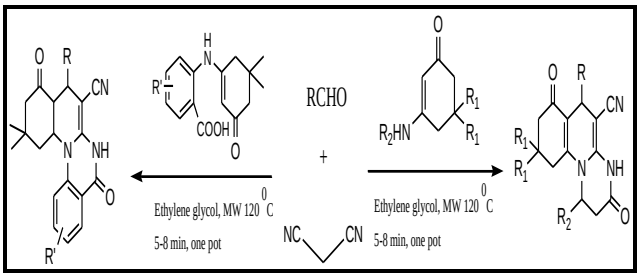
Scheme 2: Synthesis of indolo[1,2-c]quinazolines from azides

Luo et al. reported the first microwave-assisted synthesis of new quinazoline derivates containing α-aminophosphonate[32]. In their method, N'-(substituted-2-cyanophenyl)-N,N-dimethyl-formamidine derivatives and dialkyl amino (phenyl) were adopted as the raw materials to react in 4:1 volume ratio of isopropanol to acetic acid solvent for 20 min under microwave irradiation (100°C, 100 psi), and obtained twenty-four quinazoline compounds, two of which had similar activity as commercial reagent Ningnanmycin (Scheme 3).



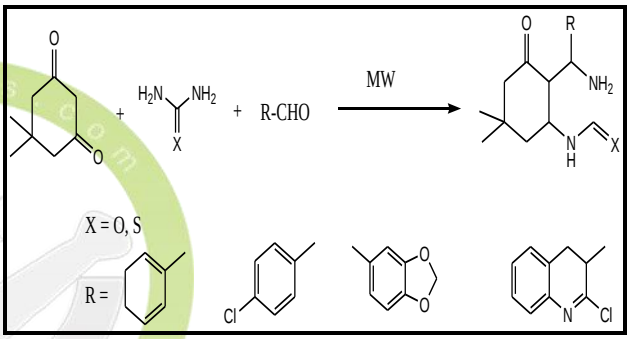
Scheme 3: Synthesis of quinazoline compounds containing α-aminophosphonate

Tu et al. reported a fast, one-pot, microwave-assisted synthesis of polysubstituent imidazo[1,2-a]quinoline, pyrimido[1,2-a]quinoline and quinolino[1,2-a]quinazoline derivatives[33]. They explored the optimal reagent, volume and heating temperature by testing different reagents under different reaction time and temperature. Then under the optimal conditions (2.0 mL glycol and 120°C), several aldehydes were separately reacted with various enaminones and malononitrile to obtain different products (Scheme 4).



Scheme 4: Microwave-assisted one-pot synthesis of quinazoline compounds

In the synthetic research conducted by Kidwai et al.[34], the target compounds quinazoline derivatives were obtained by heating an equimolar amount of aldehyde, 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and urea/thiourea under microwave irradiation in the absence of solvent and catalyst (Scheme 5).

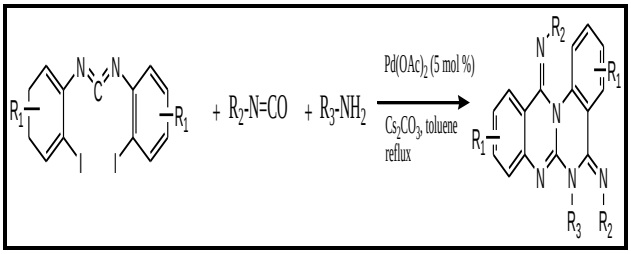


Scheme 5: Solvent-catalyst-free microwave-assisted synthesis of quinazolines

Metal-Mediated Reaction

Palladium-Catalyzed Reaction

Palladium-catalyzed coupling reaction, which plays a vital role in the pharmaceutical industry, is widely applied in chemical synthesis industry and laboratories as an efficient method for the formation of C-C and C-heteroatom bond.

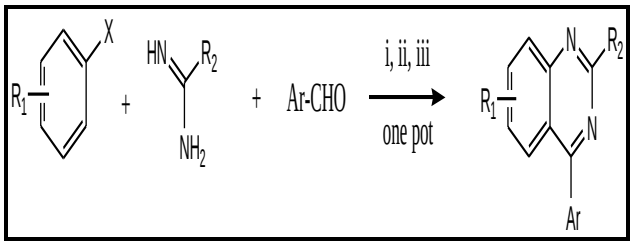


Scheme 6: Synthesis of quinazolino [3, 2-a] quinazolines

Qiu et al. determined the optimum conditions for the palladium-catalyzed three-component

synthesis of quinazolino[3,2-a]quinazolines as follows: amine (3.0 equiv), isocyanide (3.0 equiv), carbodiimide (0.2 mmol), $Pd(OAc)_2$ (5 mol%) and Cs_2CO_3 (3.0 equiv) in 3.0 ml toluene (Scheme 6)[36].

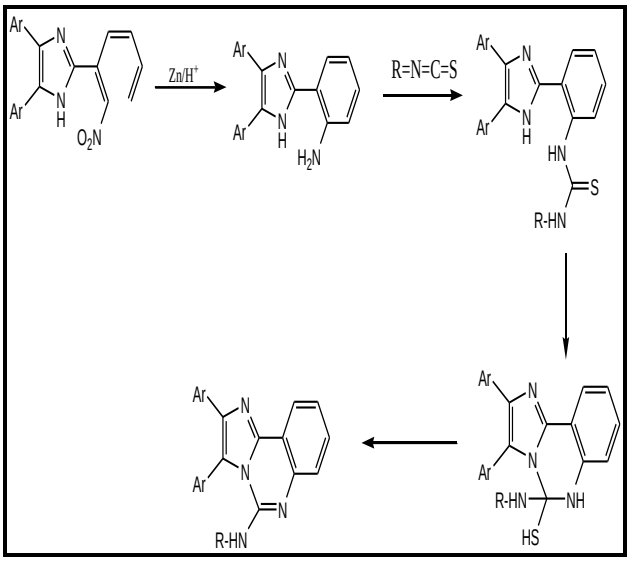
McGowan et al. developed a palladium-catalyzed one-pot synthesis of quinazoline derivatives[37]. The reaction process was shown in Scheme 7.



Scheme 7: Palladium-catalyzed one-pot synthesis of quinazolines

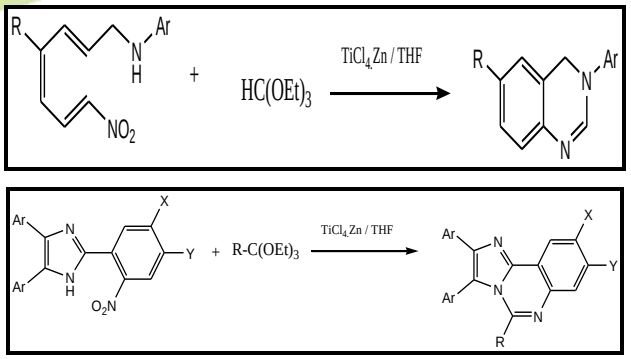
Zinc-Reduced Synthesis

Zinc is the first capable metal found to participate in water-phase Barbier reaction. It could catalyze the allylation of carbonyl and carbonyl compounds as well as participate in the benzylation of carbonyl and some special alkylation. Apart from participating in the carbon-oxygen double bond Barbier reaction, Zinc could also be applied to carbon-nitrogen double bond Barbier reaction, such as the allylation of imine and α-amino aldehyde. In short, Zinc could stably exist in water phase with relatively strong activity. Active zinc obtained from ultrasonic-electrical method could even improve the reaction efficiency by more than three times. Although it often causes a few side effects, the cost-effectiveness and low-toxicity of zinc made it a good catalyst for organic reduction and synthetic reaction. In the synthetic research of imidazo[1,2-c]quinazoline derivatives designed by Shi et al.[38], 2-(2-nitro-phenyl)-1H-imidazoles was reduced by Zn/H^+ to 2-(2-aminophenyl)-1H-imidazoles, which then reacted with isothiocyanates to get intermediate. Cylization of compound by nucleophilic attack of the nitrogen atoms on C = S group was afford the intermediates. Finally, the desired products were obtained from by losing of H_2S (Scheme 8).



Scheme 8: Synthesis of imidazo[1,2-c]quinazoline derivative

Low-valent titanium reagents, which aroused an increasing concern in the field of organic synthesis, could effectively improve the coupling of carbonyl compounds[39]. A synthetic method assisted by low-valent titanium reagent was reported by the same group mentioned above[40]. In this synthesis, a series of quinazoline derivatives were afforded by adopting anhydrous THF as solvent and the $TiCl_4$-Zn system as reducing agent. Several representative synthetic routes were selected, which were shown in Scheme 9.

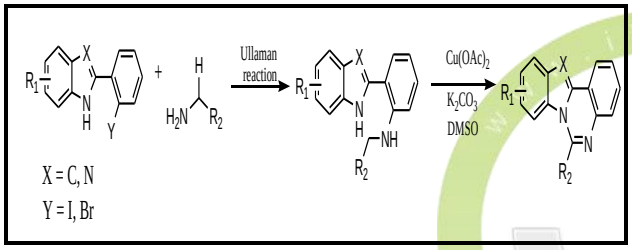


Scheme 9: $TiCl_4$-Zn-mediated reduced synthesis of quinazoline derivatives

Copper-Catalyzed Reaction

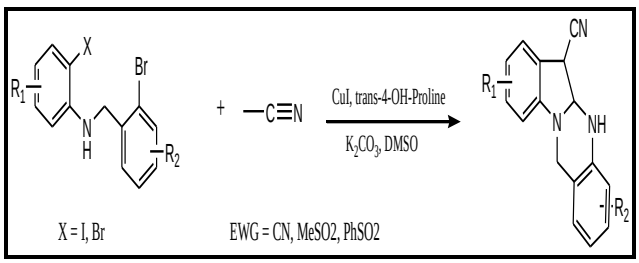
Aryl ether, alkyl ether, aryl amine, alkyl amine, aryl sulfide, alkyl sulfide, etc., which are all very important structural fragments in many chemical molecules, have an urgent need for better synthetic methods. Classical copper-

catalyzed Ullmann reaction has been widely studied due to its significant role in this regard. It raised attention from many chemists and became one of the focal point in organic chemistry research in recent years. Sang et al. reported a copper-catalyzed sequential Ullmann N-arylation and aerobic oxidative C-H amination for the convenient synthesis of indolo[1,2-c]quinazoline derivatives[41]. In their research, 2-(2-halophenyl)-1H-indoles and (aryl)methanamines were adopted as raw materials to generate corresponding Schiff base via Ullmann reaction. Then gas as oxidant, 3 equiv K_2CO_3 as base, DMSO as solvent and 10 mol% $Cu(OAc)_2$ as catalyst were revealed as the optimum conditions, to conduct aerobic oxidative C-H amination under 110°C (Scheme 10).



Scheme 10: Copper-catalyzed synthesis of indolo [1, 2-c]quinazoline derivatives

Jiang et al. also reported a copper-catalyzed one-pot synthesis of 5,12-dihydroindolo[2,1-b]quinazolines[42]. The best conditions of catalyst, ligand, base and solvent were determined as 10 mol% of CuI, 20 mol% of trans-4-hydroxyl-L-proline, 3.0 equiv of K_2CO_3, DMSO and 90°C, respectively. N-(2-bromobenzyl)-2-iodoani-line and malononitrile were adopted as the raw materials to afford desired compound through copper-catalyzed intramolecular C-N coupling reaction (Scheme 11).



Scheme 11: Copper-catalyzed one-pot synthesis of quinazolines derivatives

Ultrasound-Promoted Synthesis

An environmentally friendly and mild Bischler cyclization was developed to access quinazolines with diverse substitution. In critical synthesis, ultrasonic assistance is needed to meet the high requirements for temperature and pressure. For instance, in Bischler cyclization[44-46], the most traditional synthetic methods for quinazoline derivatives, high temperature (above 120°C) and high pressure are needed for at least 5 h in saturated ammonia alcohol solution. Various syntheses applying this method contains the passage of ammonia through a mixed melt of the amino compound and sodium acetate at a temperature higher than 160°C[47], in which ultrasonic promotion is demanded.

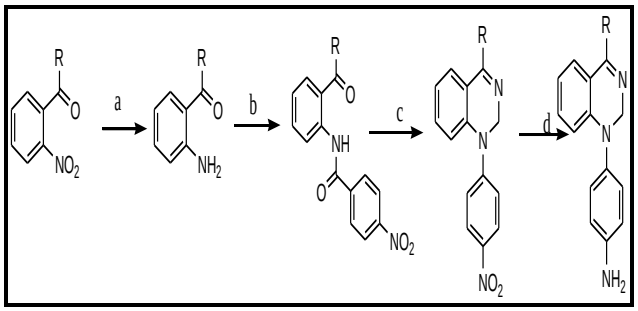
Zhang et al. reported an ultrasound-assisted synthesis of novel quinazoline derivatives, including a four-step synthesis of quinazoline core and the optimization of the Bischler cyclization[48]. The optimum reagents and conditions of the four steps were as follows:

a) Iron powder(reductant), concentrated HCl(catalyst), ethanol/water(co-solvents with V:V of 5:1), 50°C;

b) 4-nitrobenzoic acid chloride(1 equiv), TEA(1.2 equiv), DCM, 0°C;

c) 25% ammonia water, water, ultrasound 250 W, 80°C, 3 h;

d) Iron powder, concentrated HCl, ethanol/water, 50°C (Scheme 12).



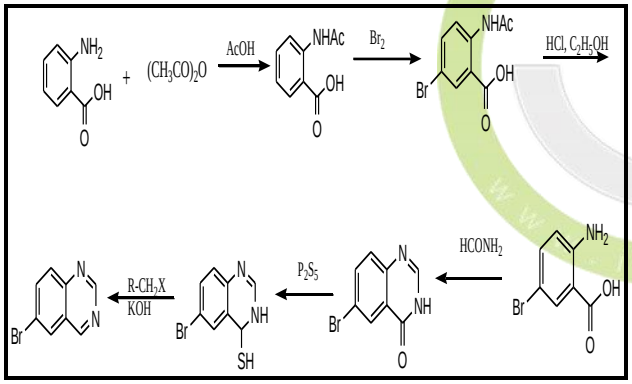
Scheme 12: Ultrasound-assisted four-step synthesis of novel quinazoline derivatives

Phase-Transfer Catalysis

Phase-transfer catalysis (PTC) is considered to be one of the promising methods in organic

synthesis of specialty chemicals. The previous 20 years sees a steady increment in articles and patents dealing with PTC topics and their applications. Currently, rather than be simply used in replacement reactions, PTC is widely applied in polymer chemistry, heterocyclic chemistry, organometallic synthesis, agrochemicals, dyes, flavours, spices, and pharmaceutical technology[49-51]. A phase-transfer catalyst or PTC is a catalyst that facilitates the migration of a reactant from one phase into another phase where reaction occurs. It is general green methodology in organic synthesis.

Yao et al. designed an investigation to bring bromine into the active structure of quinazoline sulfide[53]. Anthranilic acid was adopted as the starting material to generate a series of 6-bromo-4-alkylthioquinazoline compounds via phase-transfer catalysis through a sequence of reaction, including acylation, bromination, hydrolysis, ring formation, vulcanization and thioether substitution (Scheme 13).



Scheme 13: PTC synthesis of 4-alkylthio-quinazoline derivatives

Apart from the five synthetic methods listed above, several other methods could also be used as main researching methods in some situation, while most of the time, they were set as auxiliary methods or necessary methods in experimental design. Here, several examples of such methods were listed.

Oxidative Cyclization

A three-step synthesis of mono- and bis-indolo[1,2-c]quinazolines was reported by Rohini et al. in 2010 [7]. In this research, the key indole precursor A was got from Fischer indole cyclization. And the corresponding intermediate mono and bis-2-(o arylidineaminophenyl)indole, obtained from indole precursor A, then was put on oxidative cyclization with powdered $KMnO_4$ in acetone to afford the desired products mono and bis-indolo[1,2-c]quinazoline.

In 2009, they also reported another synthesis of mono- and bis-6-arylbenzimidazo[1,2-c]quinazolines from corresponding 2-O-arylideneaminophenylbenzimidazoles by oxidative cyclization[54].

Reagent Refluxing

Chandrika et al. synthesized desired products from the intermediate obtained from reagent refluxing[12]. In the synthesis of tri-substituted products triazolo[4,3-a]-quinazolin-7-ones by Pandey et al.[55], the corresponding Schiff base was obtained from refluxing of key intermediate with isatin in methanol, which then cyclodehydrated to the products in concentrated sulfuric acid. Aside from these two researches, in some other synthetic researches[5,34,56], the intermediates or products were also obtained from refluxing of raw materials or intermediates in solvent.

One-pot Synthesis

In order to make the synthetic methods more convenient, many researchers gradually tend to integrate one-pot synthesis into their synthesis investigations. Such as microwave-assisted synthesis reported by Tu et al.[33], Copper-catalyzed domino synthesis reported by Jiang et al.[42], Palladium-catalyzed reaction reported by McGowan et al.[37] and Zinc-reduced synthesis reported by Shi et al.[38]. All of these reported methods were combined with one-pot synthesis.

Bioactivity Research

The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, CNS depressant, anticonvulsant, anticoccidial, anti-parkinsonism, and cancer activities. Compounds of both synthetic and natural origin comprising a

diverse group of chemical structure have been reported following novel activities.

Melanin-Concentrating Hormone Receptor 1 Antagonists

MCHR1 antagonising quinazoline derivatives are proved to possess distinct anti-obesity activity. Sasmal et al. investigated the potential anti-obesity activity of quinazoline derivatives, which were determined as MCHR1 antagonists [18]. A series of compounds were obtained by the change of substituent groups, including 4-propyl-quinazolinone, 4-pyrrolidin-quinazolinone, 4-hydroxypiperidine-quinazoline, 4-pyrrolidin-quinazoline, 4-morpholinyl-quinazoline, etc.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Researchers suggest that EGFR tyrosine kinase inhibiting quinazoline derivatives possess significant anti-cancer activity. 4-Anilinoquinazoline showed a potent and highly selective inhibition for EGFR tyrosine kinase through ATP-competitive binding mechanism [60-66]. And quinazoline derivatives with aliphatic branch at 4-position of quinazoline core have moderate inhibitory activity for cyclin-dependent kinase[67].

Chandregowda et al. synthesized novel 4-anilinoquinazolines and evaluated their anti-cancer activity [1]. The new results indicated that quinazoline derivatives with alkyl-thiobenzothiazole side chain in 6-position and electron withdrawing group substituted in 4-aniline contain better biological activities

Platelet-Derived Growth Factor Receptor Phosphorylation Inhibitors

Cell proliferation induced by unusual platelet-derived growth factor receptor (PDGFR) will lead to a variety of proliferative diseases such as atherosclerosis, restenosis following PTCA, glomerulonephritis, glomerulosclerosis, liver cirrhosis, pulmonary fibrosis, and cancer[76-86]. PDGFR phosphorylation inhibitors are potential treatments for these proliferative disease Li *et al.* synthesized and biologically evaluated a series of 4-quinazoline oxime ether compounds in purpose of discovering novel acaricides [11]. Bioassays showed that drugs also exhibited favorable inhibitory activities against CMV, PVX and PVY after virus vaccinations[87].

CONCLUSION

Traditional synthetic methods for quinazoline derivatives, still in general use, including Aza-synthetic method, refluxing, oxidative cyclization, are fundamental methods for the synthesis of this important heterocyclic compounds. It could be seen from the examples compiled above that some novel synthetic methods are in constant development, and different methods are adopted in the synthesis of different quinazoline analogues, such as phase-transfer synthesis, ultrasound-promoted synthesis, etc. The gradually improved synthetic methods better the synthetic research on quinazoline derivatives with a tendency of faster, more diverse and more convenient. Then, for another, it is known that substituents at different positions affect the activity differently. It is worth mentioning that N-heterocyclic quinazolines with more rigid and complicated structure were synthesized successively.

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