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REVIEW

Review on Synthesis Route of Quinazoline Based Hybrid Derivatives

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Quinazolines are amidst the most significant pharmacological compounds in natural and medicinal chemistry, with a wide variety of pharmacological things, including antifungal, antibacterial, anti-inflammatory, anti-HIV, anticancer and analgesic activity. Designing innovative quinazolines, studying possible techniques to synthesize quinazolines, examining diverse features of quinazolines and looking for prospective uses of quinazolines have all become more important in the last two decades due to their multiple possible applications. The current review paper discusses the synthesis of quinazolines using the multi-component synthetic technique that is environmentally friendly, mild and atom-efficient. The discussion is separated into sections based on the key processes used to construct quinazoline scaffolds to provide an efficient approach for a more significant grasp. The most recent references have also been taken into account. The review should prove useful in future research on quinazoline synthesis and developing a more promising synthetic technique.

Keywords: Bicyclic compounds, Pyrimidine, Amidines, Nitriles, Synthesis, Green chemistry, Quinazolines, Quinazolinones.

INTRODUCTION

4(3*H*)-Quinazoline, quinazolinone and even its metabolites represent an effective combination among fused heterocycles which may be found in over 100 biologically active alkaloids [1]. In terms of synthesis, the first 4(3*H*)-quinazolinone molecule (Fig. 1a) was synthesized in 1869 using anthranilic acid and cyanogens [2]. Early in 1950s, febrifugine is an alkaloid which has been clarified (Fig. 1b). A traditional Chinese herbal treatment component for malaria patients [3] sparked a vigorous investigation of physiologically active chemicals that included Series. Meantime in 1951, developed methaqualone (Fig. 1c) as a drug based on 4(3*H*)-quinazolinone [4], which has muscle relaxant and sedative properties. However, as a side effect, it causes photosensitization (methaqualone's commercialization was stopped in 1984). Various commercial medicines with 4-quinazolinone moiety are utilized as hypnotics/sedatives [5].

Cancer has also been treated with 4(3*H*)-quinazolinone derivatives. Raltitrexed (Fig. 1d) (brand name: Tomudex) is an antimetabolite medication used in cancer treatment as an example. Since 1998, it has also been used to treat colorectal cancer and malignant mesothelioma. In Canada and a few European nations, raltitrexed has been approved for usage. An antiviral, anti-inflammatory, anticancer, antimicrobial, antitumor, cholinesterase inhibitor, a protein kinase inhibitor, antifolate and many other functional biological characteristics are found in the 4(3*H*)-quinazolinone systems [6]. These chemicals are biosynthetically generated from anthranilic acid and isolated from a various plant, bacterial and animal taxa. Vasicine (peganine), the first quinazoline alkaloid, was discovered in 1888 by Adhatodavasica. Chrysogine, febrifugine and isofebrifugine are some additional isolated quinazoline alkaloids synthesized [7].

More than 200 naturally occurring alkaloids contain important classes of a fused heterocyclic compound of quinazoline. Indolquinazolinones are primarily found in blue dye-producing plants such as *Polygonum tinctorium* Lour, *Strobilanthes cusia isatis tinctoria* and others. These chemicals have been identified from *Fusarium lateritium* Nees, *Bacillus cereus* 041381, the entomopathogenic fungus *Isaria farinose*, *Streptomyces* species, *Chaetomium* species IFB-EO15, *Aspergillus nidulans* MA-143 and *Penicilium aurantiogriseum* in microorganisms [8]. The heterocyclic category of the quinazoline nucleus is

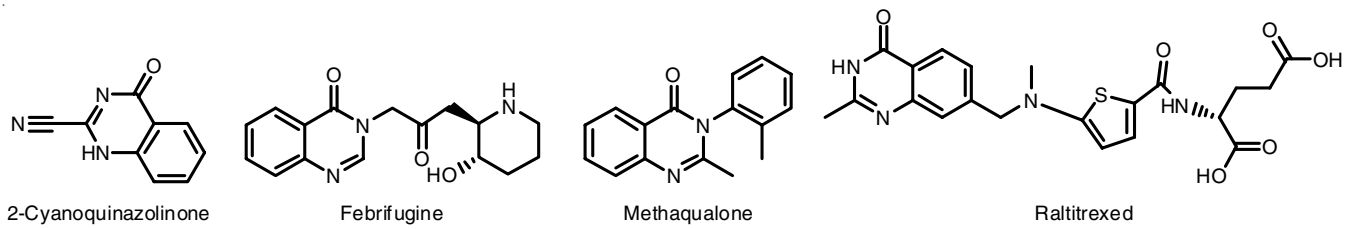
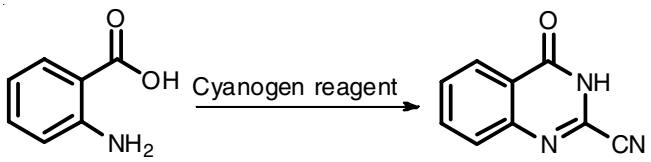


Fig. 1. Chemical structures of 4(3*H*)-quinazolinone molecule and its important derivatives

composed of 2 merged six-membered aromatic rings, *viz*. a pyrimidine ring and a benzene ring. $C_8H_6N_2$ is its chemical formula. Gabriel [9] synthesized the fused bicyclic compound of quinazoline in 1903. Its last name was benzo-1,3-diazine. One of its variants, however, was discovered considerably earlier [10]. It may be classified into three types depending on where the oxo or keto group is located (Fig. 2) [11].

The four quinazolinone compounds as shown above (Fig. 2) are still the most common, either as natural products or as intermediates in diverse biosynthetic pathways [12]. anthranilamide or various esters, Anthranilic acid and anthranilonitrile (isatoicanhydride) anthranilates were used to create this structure. Simultaneously, with nitriles or anthranilonitrile, 2(1*H*)-quinazolinone is primarily a benzamide product [13]. Quinazolines and quinazozolinones are heterocyclic compounds made up of 2 six-membered aromatic rings merged, benzene and pyrimidine [14].

In light of the significance of quinazolinones, several functional synthesized techniques had been established to produce Guiry's complete evaluation of methods for creating 4(3*H*)-quinazolinones up to the year's conclusion in 2004 [15-17]. In 2006, Eguchi published a review of bioactive quinazolinone-based natural alkaloids [18-20]. Following then, a few related studies of quinazolinone synthesis were also published [21]. Carbonylations can introduce carbon into quinazolinones and the carbonylative synthesis of chalcones is the focus of the present research. Consequently, we attempt to provide an overview of the synthetic methods and techniques for highly functionalized 4(3*H*)-quinazolinones that have recently been described. Griess synthesized the whole first quinazoline analog *via* cyanogens reaction with anthranilic acid in 1869 (**Scheme-A1**).

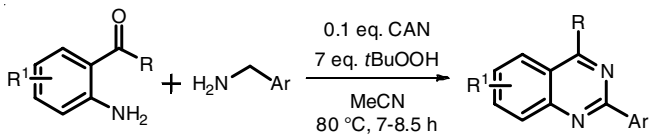


Scheme: A1: Anthranilic acid was used to synthesize 2-cyano-3,4-dihydro-4-oxoquinazoline

Quinazolines were categorized as disubstituted, trisubstituted, 2,3-fused and 3,4-fused derivatives based on the substitution of quinazoline. For 2,3-substituted and 2,3,4-substituted derivatives, the majority of the literature is accessible. Quinazolines were primarily synthesized using anthranilic acid as a starting material to produce various substituted quinazolines in three or four stages, depending on quinazoline substitution. Quinazolinones are biologically active in a variety of ways. As an example, CNS depressants [21], antimicrobials [22], antibacterials [23], analgesics [24], antifungals [25], anticancer [26], antiulcer [27], anticonvulsant [28], dengue virus inhibitors, human Pin1 inhibitors [29], antihypertensive, sedative, anesthetic, tranquilizing, muscle relaxant [30], antipyretic, antitubercular, antiparkinsons [31], *etc*. Antimicrobial compounds have been described using substitution at quinazolin-4(3*H*)-one's C-2 and C-3 locations [32,33]. Quinazolinone derivatives were utilized as an orally accessible Ghrelin receptor antagonist to treat obesity and diabetes. Quinazolines' biological significance: Anticancer drugs EGFR inhibitors (epidermal growth factor receptor) contain 4-aminoquinazolines [34]. Quinazoline and quinazolinone moieties were found in certain commercially available medicines. Antimicrobial agents have been reported when quinazolin-4(3*H*)-one are substituted at C-2 as well as C-3 positions.

Synthetic routes of modified quinazolines: Synthesis of 2-ary1-4-substituted quinazolines using 2-aminobenzophenone and benzyl amines in acetonitrile using ceric ammonium nitrate (CAN) catalyzed-TBHP obtained with 80-85% yields (**Scheme-I**) [35].

The tandem process followed by sp^3, C-H functionalization gave 70-75% yields of 2-phenylquinazolines from benzylic amines and 2-aminobenzophenone (**Scheme-II**) [36].



Scheme-I: Synthesis of 2-phenylquinazolines using 2-aminobenzophenone and benzyl amines catalyzed by ceric ammonium nitrate (CAN)

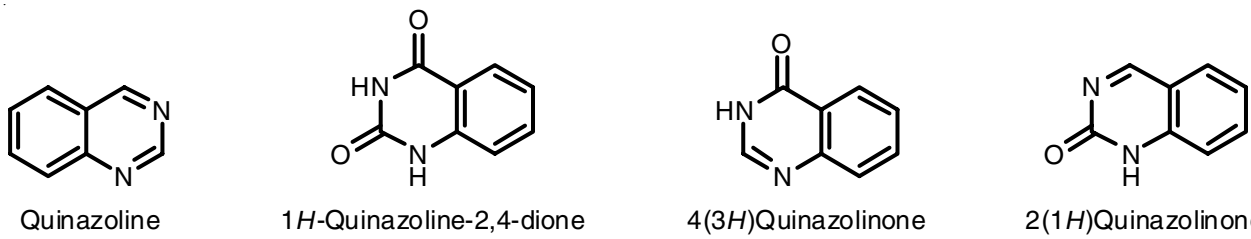
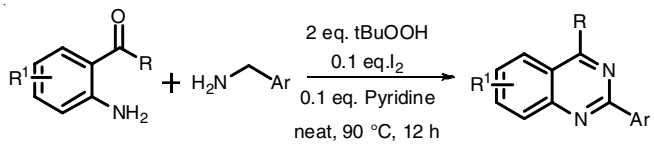
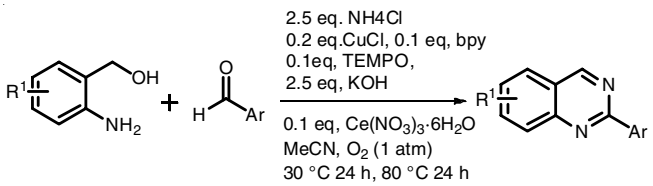


Fig. 2. Chemical structures of four different quinazolinone compounds having different location of oxo or keto group



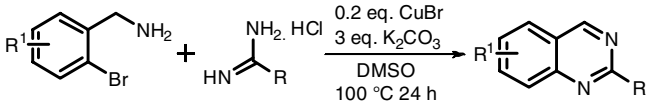
Scheme-II: Synthesis of 2-phenylquinazolines using 2-aminobenzophenone and benzylic amines

The use of $Ce(NO_3)_3$ and ammonium chloride in a copper-catalyzed cascade reaction to synthesize quinazolines from (2-aminophenyl-1)methanol and aryl aldehydes gave 72-76% excellent yields (**Scheme-III**) [37].



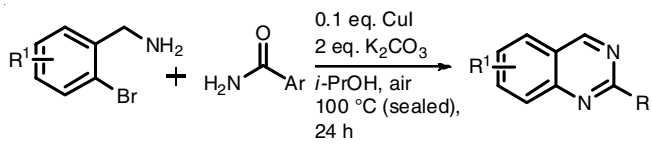
Scheme-III: Synthesis of quinazolines using aldehydes and (2-aminophenyl)-methanol in a copper-catalyzed pathway

The copper-catalyzed cascade technique synthesizes quinazolines from substituted amide hydrochloride and (2-bromophenyl)methylamine. Intramolecular nucleophilic substitution, followed by intermolecular *N*-arylation and aerobic oxidation (72-76% yields) were performed sequentially (**Scheme-IV**) [38].



Scheme-IV: Synthesis of quinazolines from amidine hydrochlorides and substituted (2-bromophenyl)methylamines

Using widely accessible substituted amides and (2-bromophenyl)methylamine as starting material, a copper-catalyzed approach without ligands was used to synthesize quinazoline analogs. The cascade process, which comprises sequential aerobic oxidation and Ullmann-type coupling, allowed for a quick synthesis of quinazoline derivatives (yields 72-76%) (**Scheme-V**) [39].

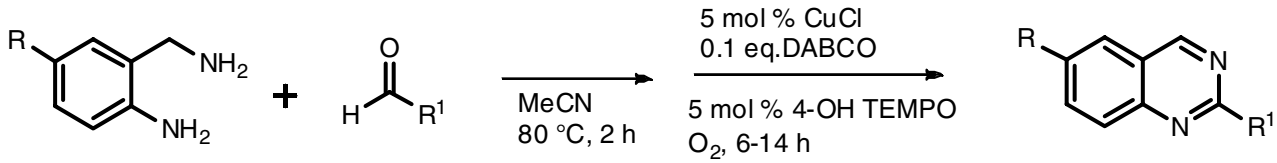


Scheme-V: Synthesis of quinazoline using substituted amide and (2-bromophenyl)methylamine

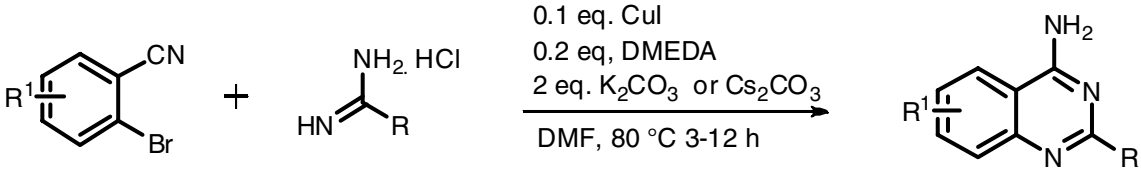
Using CuCl/DABCO and 4-HO-TEMPO as catalysts and O_2 as final oxidants, a one-pot reaction of 2-aminobenzylamine or 2-aminobenzyl alcohol with aldehydes permitted practical workup of aerobic oxidative synthesis to produce 2-substituted quinazoline derivatives having 72-76% yields (**Scheme-VI**) [40].

Copper-catalyzed reactions with DMEDA and K_2CO_3 in DMF solvent shows substituted 2-bromobenzonitriles with amidines and perhaps even guanidine give 72-76% 2,4-diaminoquinazoline and 4-aminoquinazoline derivatives (**Scheme-VII**) [41]. A palladium-catalyzed reaction followed by intramolecular aryl C-H amidation with isocyani de insertion produces 73-78% yields of 4-amino-2-alkyl(aryl)quinazoline derivatives utilizing pure reactant *N*-arylamidines with isonitriles (**Scheme-VIII**) [42].

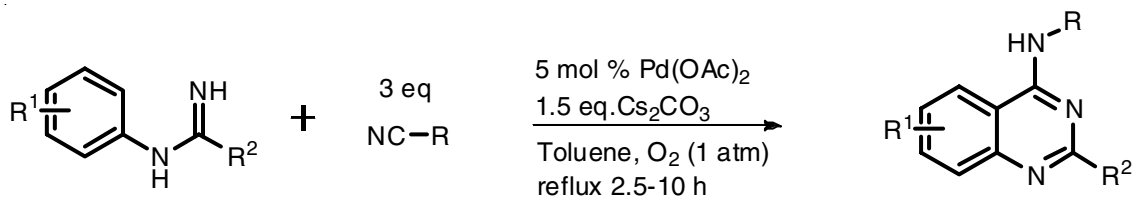
Synthesis of 4(3*H*)-quinazolinone and its derivative: The most popular technique for making 4(3*H*)-quinazolinone was Niementowski quinazolinone synthesis. The Niementowski



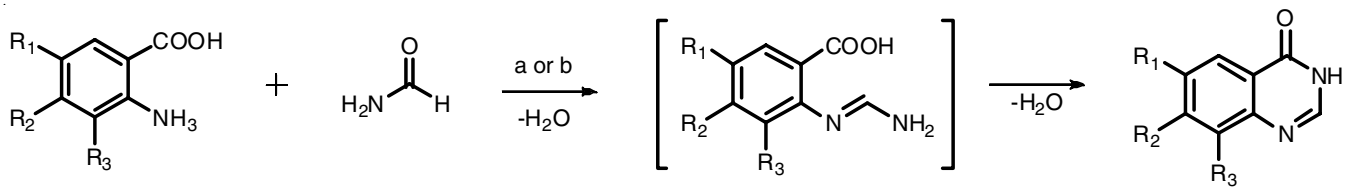
Scheme-VI: Synthesis of 2-substituted quinazolines from 2-aminobenzyl-amines and aldehydes



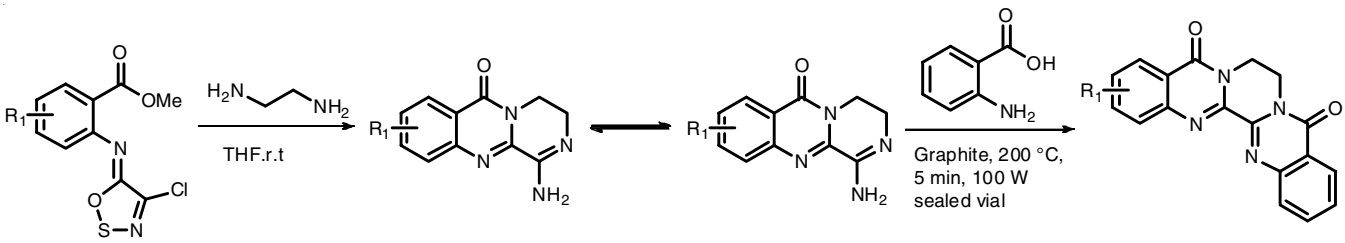
Scheme-VII: Synthesis of 4-aminoquinazoline using amidines from substituted 2-bromo-benzonitriles



Scheme-VIII: Synthesis of 4-amino-2-alkyl(aryl)quinazolines analogs using *N*-arylamidines and isonitriles



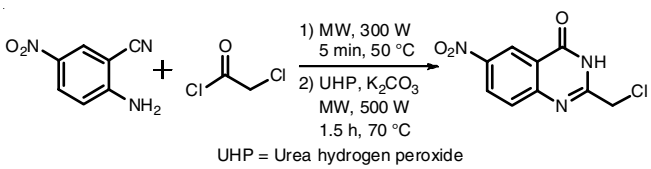
Scheme-IX: Synthesis of quinazoline analogs using anthranilic acid analogs and *o*-amidobenzamide in a microwave-assisted Niementowski method



Scheme-X: Synthesis of new pentacyclic heterocyclic quinazoline analogs using a microwave-assisted Niementowski method

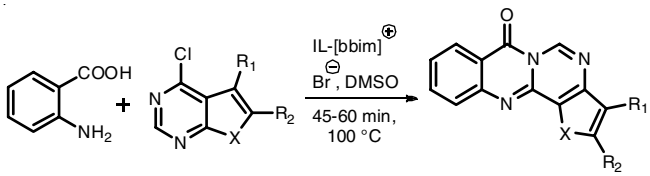
reaction shows anthranilic acid analogs fusing an *o*-amidobenzamide precursor at 130-150 ºC with amides (**Scheme-IX**). In these circumstances, the reaction has a variable yield. Low yields (35-40%) were often difficult to eliminate, even with the recrystallization process or column chromatography, since they were accompanied by a complex combination of carbonaceous compound sand impurities. To address these issues, Besson *et al.* [43] used microwave irradiation to re-investigate the Niementowski synthesis process of the 4(3*H*)-quinazolinone and increased up to 72-76% yields while reducing reaction time. Microwave irradiation techniques were used to develop better, more efficient strategies for making novel merged quinazolinone derivatives shown in **Scheme-X** [44,45].

Instead of 2-substituted derivatives, Desai & Desai [46] used a microwave-assisted Niementowski technique to make 2,3-disubstituted or 3-substituted-4(3*H*)-quinazolinone analogs. This method is non-toxic to the environment and does not require a solvent reaction. In a quinazoline series, Vanelle *et al.* [47] investigated novel anticancer drug precursors. The Niementowski reaction may be carried out efficiently and quickly, yielding the precursor 2-chloromethyl-6-nitroquinazolin-4(3*H*)-one by observing 72-76% as good yields (**Scheme-XI**). This molecule was used as a starting point for creating numerous novel quinazolines with different substituents at position-2.



Scheme-XI: Syntheis of 2-substituted quinazolines using urea hydrogen peroxide

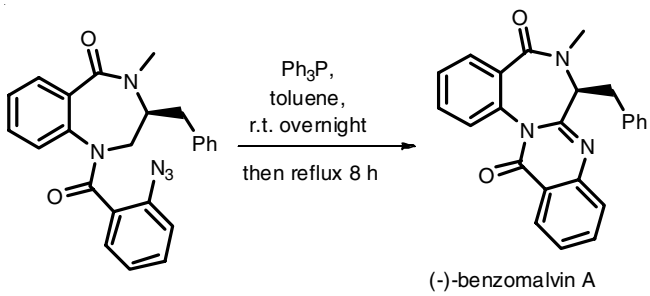
Srinivasan *et al.* [48] described a novel, fast and flexible Niementowski technique of fused 4(3*H*)-quinazolinone analogs (**Scheme-XII**). In this synthetic route, an ionic liquid and DMSO were used. With a simple workup process, isolated yields ranging from 83 to 92% were obtained. The increased reactivity



Scheme-XII: Synthesis of enhanced quinazolinones by Niementowski method

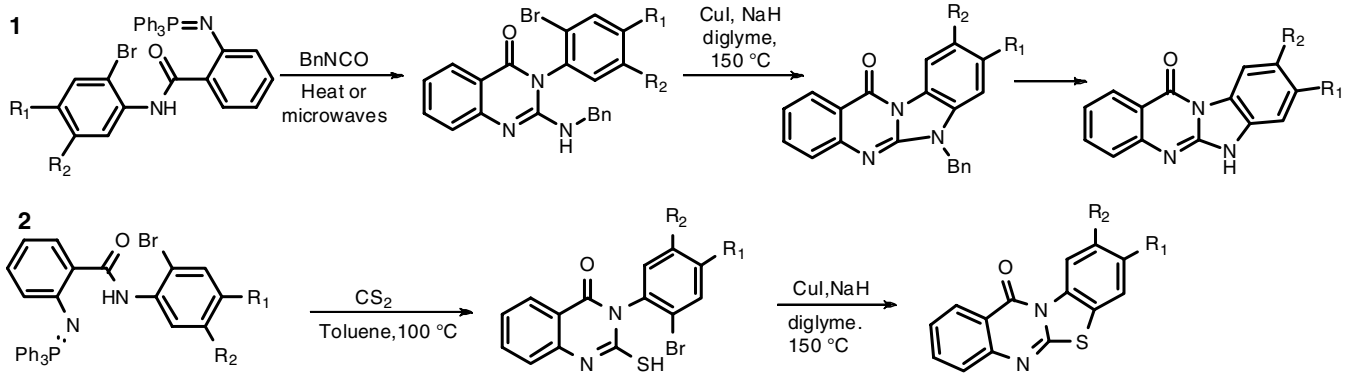
was attributed to the ionic liquid's intrinsic Brønsted acidity and DMSO's high polarity.

The Aza-Wittig procedure to synthesize 4(3*H*)-quinazolinone analogs is based on iminophosphoranes (Eguchi protocol) and has shown to be a reliable method for building heterocyclic nitrogen compounds. The tandem aza-Wittig/cyclization technique was used to incorporate several 2-substituted quinazolinone analogs, initiating functional iminophosphorane relevance and an amide group. The complete convergent synthesis of (-)-benzomalvin-A [49] is a successful, straightforward use of the aza-Wittig technique. The iminophosphorane coupled mostly with imide carbonyl mechanism provides the desired product in an organization resulting from 80-82% as the final play to (-)-benzomalvin-A, used as a microbial spray neurokinin adrenergic receptors. (**Scheme-XIII**).



Scheme-XIII: Synthesis of (-)-benzomalvin

Molina *et al.* [50] developed an effective technique for producing the not generally accessible angular or linear tetracyclic ring structure containing quinazolinone analogs (**Scheme-XIV**)



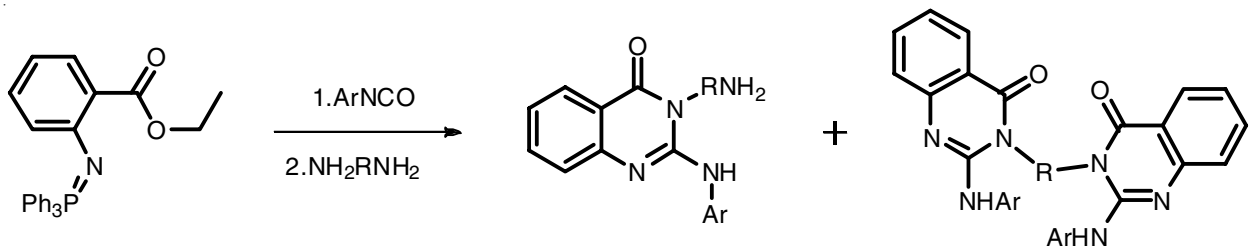
Scheme-XIV: Synthesis of merged tetracyclic quinazolinone analogs

by combining aza-Witting methods CuI-catalyzed hetero-arylation process. *N*-(*o*-substituted-aryl)carboxamide with (aryl-imino) phosphoranes substituents in respective *ortho*-positions was used in the technique. After an aza-Witting reaction/reductive process, the availability of nitrogen functioning in the *N*-aryl anomeric group favours heterocyclization. Iminophosphoranes also interacted with carbon disulfide in an aza-Witting-type reaction to create substituted aryl isothiocyanates.

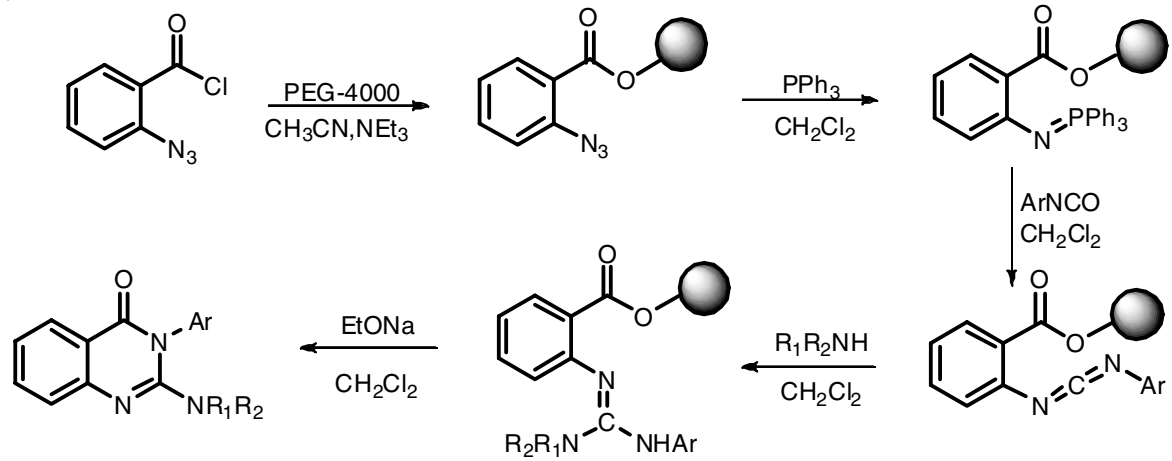
A basic method for synthesizing new 3,3′-disubstituted *bis*-2-arylaminoquinazolin-4(3*H*)-ones and 3-aminoalkyl-2-arylaminoquinazolin-4(3*H*)-ones have been described by the Wu *et al*. [51] using a tandem aza reaction shown in **Scheme-XV**: Witting reaction of 1-aryl-3-(2-ethoxy-carbonyl phenyl) carbodiimides as well as primary diamines in favourable response circumstances, excellent selectivity, produce 81-87% yields, conveniently available starting materials and simple product isolation are all advantages of this technique.

Such polymer-supported catalysts in medicinal chemistry save purification and workup time by allowing for easy filtering. There have been various solid-phase methods to quinazolinones developed so far. In 2006, Vogtle & Marzinzik [52] conducted a review of the relevant literature. Ding *et al*. [53] reported a successful collateral synthesis of 4(3*H*)-quinazolinone analog using polyethylene glycol (PEG) assisted aza-Witting reaction (**Scheme-XVI**). As a soluble polymer basis, commercially available difunctional PEG-4000 was used. This technique of synthesis might be used with a variety of secondary amines and isocyanates. The materials were created in a high-yielding manner as 88-92 % yields.

Since last decade, the synthesis of 4(3*H*)-quinazolinone from 2-aminobenzoic acid *via* a benzoxazinone intermediate has become a standard technique. Chenard *et al.* [54] described a succinct SAR algorithm for detecting piriqualone CP-465,022. An allosteric site allows a powerful opponent to engage with



Scheme-XV: Synthesis of quinazoline analog using tandem aza reaction



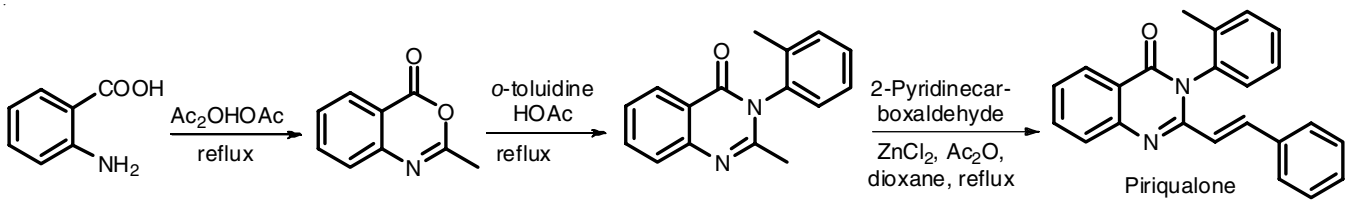
Scheme-XVI: Synthesis of 4(3*H*)-quinazolinone analog using polymer-supported catalyst PEG-4000

the receptor. Three stages are involved in the synthesis of piriqualone (**Scheme-XVII**). In the existence of acetic acid, first 2-aminobenzoic acid permutes to benzoxazin-4-one in warm ethanoic anhydride. Then, *ortho*-toluidine ring was reacted with an appropriate aniline component refluxing in ethanoic acid. Finally, the target compounds were obtained by condensing pyridine-2-carboxaldehyde with 2-methyl-3-aryl-quinazolin-4-one to produced 87-90% yields.

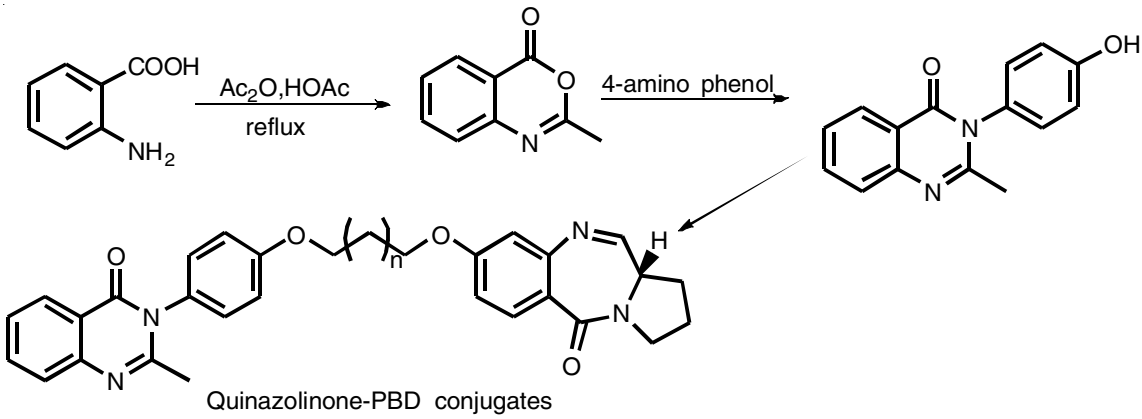
Kamal *et al*. [55] synthesized a series of novel quinazolinone-hybrids pyrrolobenzodiazepine analogs (**Scheme-XVIII**) with high yields (91-93%), showing condensation of 5-hydroxy-2-aminobenzoic acid with ethanoic anhydride produces benzoxazinones in the first synthesis method. They also synthesized various methaqualone analogs and 3-diarylethynequinazolinones using this technique (a new senescence inducers class).

Liu *et al*. [56] devised a microwave-assisted technique to synthesize 2,3-disubstituted quinazolin-4-(3*H*)-ones. A crucial stage is a one-pot synthesis, a two-step reaction cascade involving carboxylic acid, anthranilic acid and amines. It provides an efficient route to the required heterocycles. Liu *et al*. [57] reported a microwave-assisted three-component one-pot pyrazino-[2,1-*b*]quinazoline-3,6-dione framework (**Scheme-XIX**). A variety of synthesized alkaloids represent the critical biological roles.

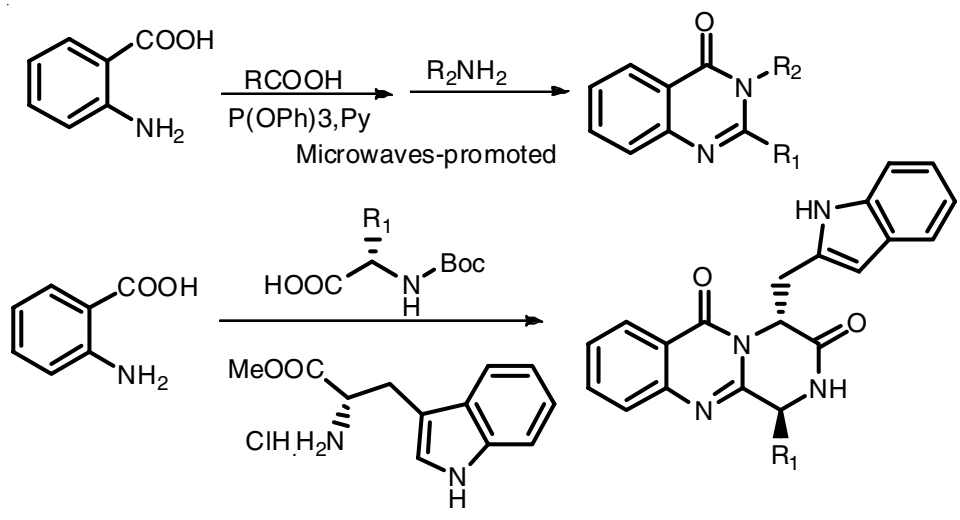
Güngör *et al.* [58] synthesized a novel family of 3-aryl-quinazolines. Even though compounds of general formula were discovered using various techniques depending on the type and locations of the substituents, the majority of them were synthesized using a benzoxazinone precursor. Giridhar *et al.* [59] synthesized and evaluated some 2,3-diaryl-4(3*H*)quina-



Scheme-XVII: Synthesis of piriqualone by reacting pyridine-2-carboxaldehyde and methyl-3-aryl-quinazolin-4-one



Scheme-XVIII: Synthesis of pyrrolobenzodiazepine (PBD) conjugates connected to quinazolinones

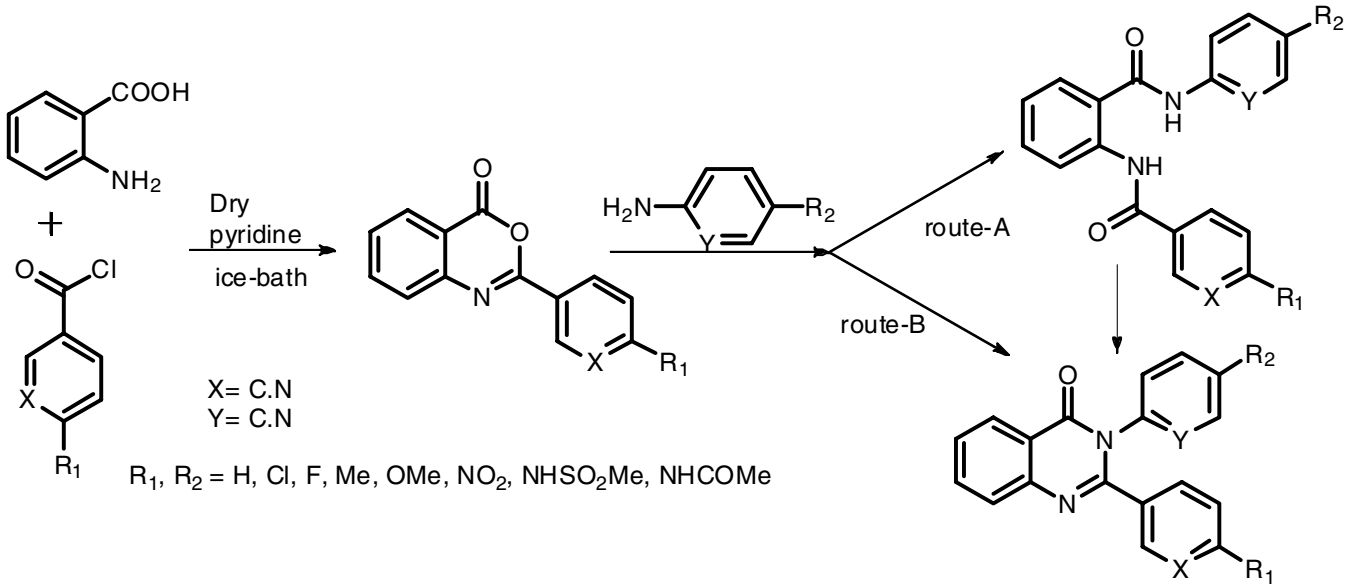


Scheme-XIX: Microwave-assisted quinazolinone analog synthesis using benzoxazinone intermediate

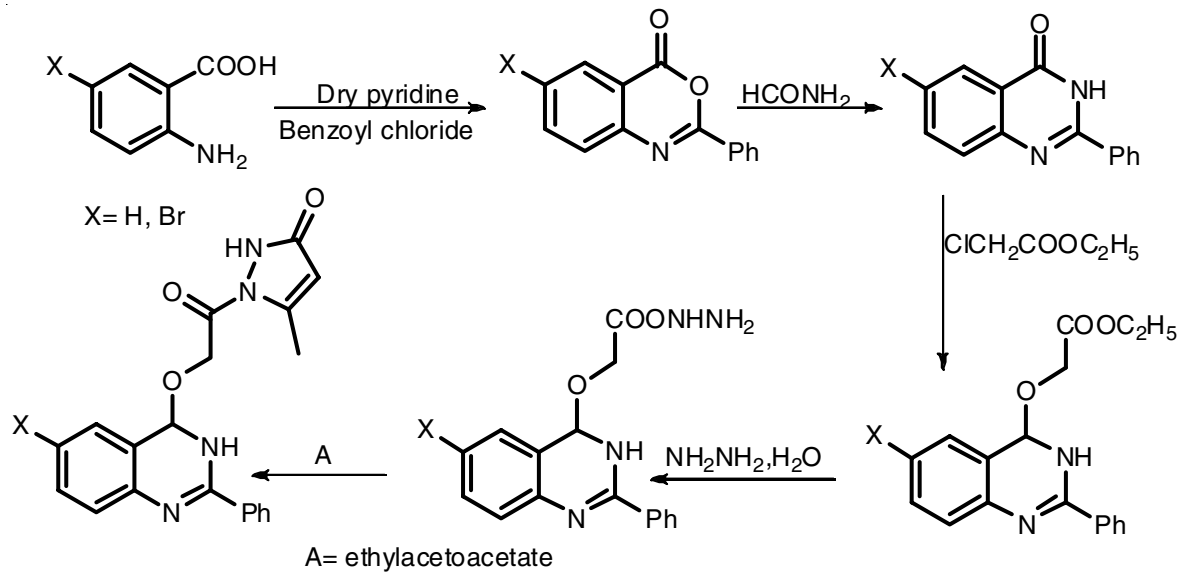
zolinones (**Scheme-XX**) potential anti-inflammatory activity. The reaction of 2-phenyl-3,1-benzoxazin-4(3*H*)-one with 2-aminopyridine produces diamide under favourable conditions (below 100 ºC). But the cyclized product 4(3*H*)-quinazolinone analog was isolated at higher temperatures (≤ 200 ºC) (through route B). This assertion only applied to compounds with pyridyl rings in the amines components or 3,1-benzoxazin-4(3*H*)-one. Anhydrous $ZnCl_2$ was used as a catalyst to cyclize the quinazolinones that resulted (route A). Boyapati *et al.* [60] presented novel quinazolinones' synthesis with replacement of OCH_2CONH_2 (oxy methyl carbamide) group at the 4th position (**Scheme-XXI**) for the development of novel antibacterials which have been shown to exhibit increased biological activity.

Anthranilic acid was cyclized with benzyl chloride at 0-5 ºC in pyridine to provide bentranil, which was used to make the required compounds. The resulting intermediate is then converted to the better foundation quinazolinone-2-phenyl-4(3*H*) [61] *via* a formamide, increasing biological activity. Anthranilic acid was cyclized with benzene carbonyl chloride in pyridine at 0-5 ºC to provide bentranil, which was used to make the required compounds. The resulting intermediate was then converted to more consistent 2-phenyl-4(3*H*) quinazolinone *via* a reaction with formamide. Gupta *et al.* [62] reported the synthesis and biological evaluation of various new quinazolin-4(3*H*)-ones derivatives (**Scheme-XXII**) as anticonvulsants. Condensation of anthranilic acid with benzene carbonyl chloride in the basic medium presence of pyridine is the initial step. 3-Amino-2-phenyl-1*H*-quinazolin-4-one was produced by treating the obtained 2-phenylbenzo[*d*][1,3]oxazin-4-one with hydrazine hydrate. Using a similar method, Alagarsamy & Saravanan [63] synthesized 18 novel quinazolin-4-(3*H*)-one derived pyrazole analogs.

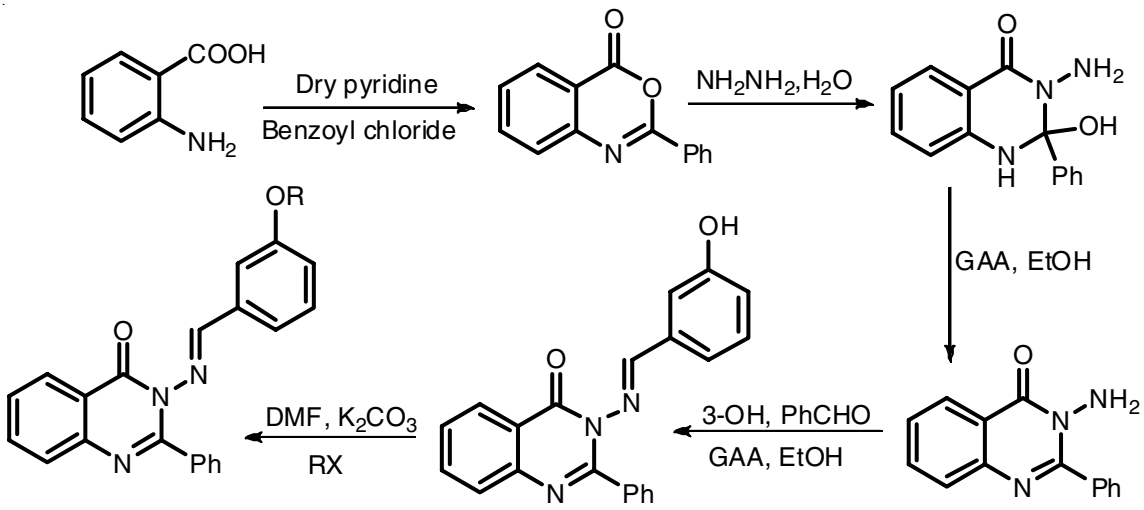
Anthranilic acid, amines and *ortho*-esters or formic acid are all condensed in one pot, a kind of multi-component reaction



Scheme-XX: Synthesis of 2,3-diaryl-4(3*H*)-quinazolinones using 2-aminobenzoic acid and dry pyridine

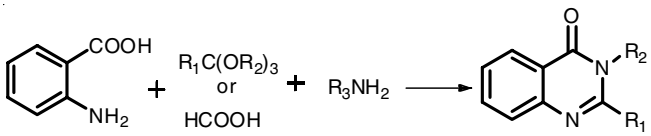


Scheme-XXI: Synthesis of 4-substituted quinazolines using anthranilic acid and benzoyl chloride followed by formamide



Scheme-XXII: Synthesis of quinazolinones derivatives

(MCR), to produce 4(3*H*)-quinazolinones analog (**Scheme-XXIII**). This condensation is known to be affected by several acid catalysts. The condensation was catalyzed by $FeCl_4$ with high to outstanding outputs of 4(3*H*)-quinazolinones. According to Khosropour *et al.* [64], this technique is notable for its moderate reaction conditions (room temperature), visible reaction, better yields with primary amines, anilines improved rates and simplicity of use. This method also has several advantages like stability, reusability and non-toxicity of the catalyst and ionic liquid. Hamdi *et al.* [65] reported that the microwave irradiation combined with Keggin-type heteropolyacids ($H_3PW_{12}O_4Os_{13}H_2O$) allowed for a solvent-free, fast condensation process.

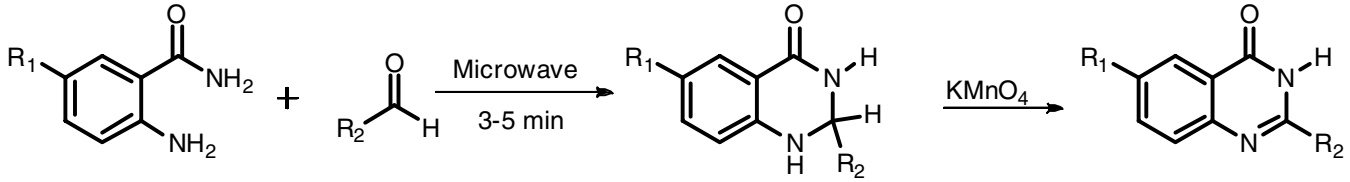


Scheme-XXIII: Synthesis of quinazoline analog using 2-aminobenzoic acid, amines and *o*-esters or formic acid under one pot condensation reaction

The reaction time was 10 times faster than the traditional approach (microwave irradiation takes 13 min, but conventional heating takes 120 min). Heravi *et al.* [66] used Keggin-type heteropolyacids as efficient, reusable and environmentally acceptable heterogeneous inorganic catalysts to develop a simple multi-component synthesis process for 4-arylamino-quinazolines from the reaction of 2-aminobenzamide, *ortho*-ester and substituted anilines. In a similar work, Heravi *et al.* [67] presented another method for producing 4(3*H*)-quinazolinones from the reaction of 2-amino-benzamide, acyl chlorides and ($H_{14}[NaP_5W_{30}O_{11}]$) or SiO_2 in the presence of a catalytic amount under ultrasonic irradiation. Wang *et al.* [68] demonstrated that $SrCl_2S_6H_2O$ is an excellent and recyclable catalyst for the one-pot condensation of anthranilic acid, *ortho*-esters and amines to generate 4(3*H*)-quinazolinone derivatives in good yields at room temperature under solvent-free conditions. The technique has many benefits, including a detailed workup, moderate conditions, a commercially accessible catalyst and a generally clean procedure that shows a new method for making 2-substituted-2-quinazolin-4(3*H*)-one. In 2011, Huang *et al.* [69] used the condensation process of modified 2-amino-benzamide *ortho*-esters to create ones and their derivatives. The reaction happens without an organic solvent and a basic or acidic catalyst, which is unusual. To understand the mechanism of action and study the drug metabolism of 4(3*H*)-quinazolinones, Saemian *et al.* [70] synthesized quinazolin-4(3*H*)-ones [4-14C] from 2-aminobenzoic acid-[carboxy-14C] formic acid and amine. In absence of a solvent or other dehydrating agents, the process was performed in the microwave.

Synthesis of 4(3*H*)-quinazolines and their analogs *via* oxidative heterocyclization: Bakavoli *et al.* [71] generated 4(3*H*)-quinazolines in one pot by oxidative heterocyclization of aldehydes with *o*-aminobenzamides in the presence of $KMnO_4$ with microwave irradiation (**Scheme-XXIV**). They also reported the oxidative cyclo-condensation of various aldehydes with *o*-aminobenzamides mediated by I_2/KI [72]. The desired 4(3*H*)-quinazolines were generated in high to excellent yields of 93-96% in boiling water or ethanol-water.

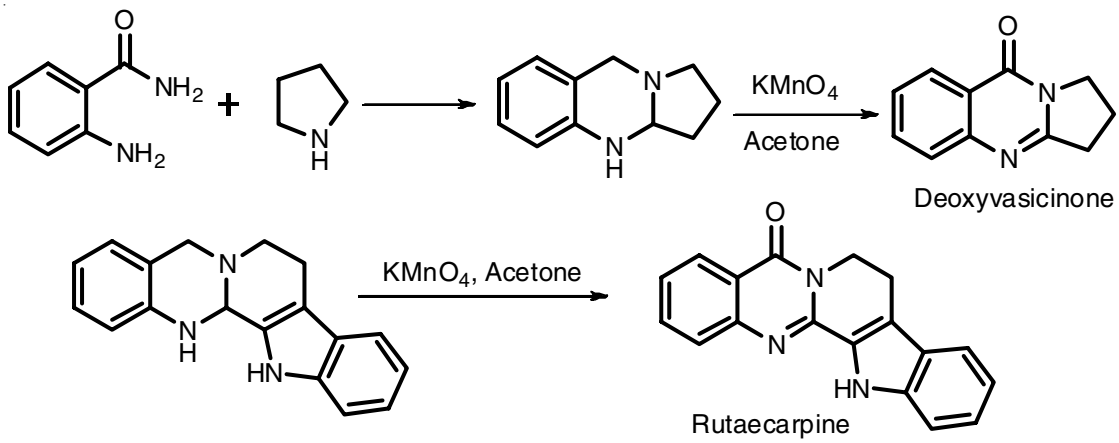
Seidal *et al.* [73] reported that $KMnO_4$ was used to synthesize deoxyvasicinone and rutaecarpine. In turn, *o*-amino benzaldehyde condensation and simple secondary amines (**Scheme-**



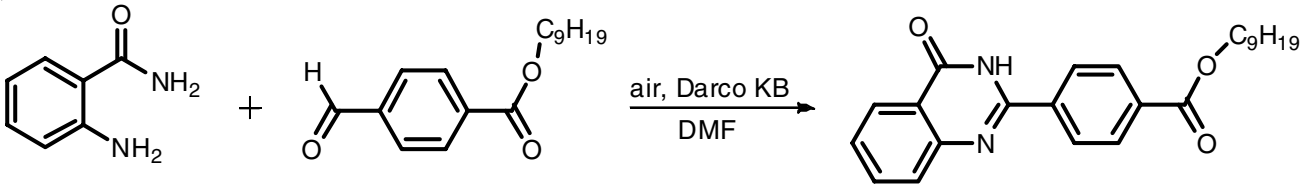
Scheme-XXIV: Microwave activated oxidative heterocyclization for the synthesis of quinazoline analog

XXV) resulted in enhanced oxidation of aminals. Later Seidal *et al.* [74] proved that quinazolinone alkaloids analogs could be generated from their respective aminals who used a copper(II) acetate/O_2 potassium iodide/acetic acid/*tert*-butyl hydroperoxide system. It was discovered that combining CH_3COOH with O_2 and catalytic Cu(II) salts inhibited dihydroquinazoline over oxidation, making it accessible to these structures beneath mild conditions. By oxidative coupling of aromatic/aliphatic aldehydes with 2-aminobenzamide or 2-aminobenzylamines, Hioki *et al*. [75] discovered a solid-phase combinatorial synthesis 2-aryquinazolinones and 2-aryl/alkyl quinazoline. Darco KB, a catalyst based on a kind of activated carbon, was developed (**Scheme-XXVI**). Mulakayala *et al.* [76] described a practical and convenient process using $InCl_3$-catalyzed condensation of 2-aminobenzamides with aromatic aldehydes to produce quinazolinone analog (**Scheme-XXVII**). $InCl_3$ has more excellent operational simplicity, water stability, robust resistance to nitrogen and oxygen-containing compounds, with a functional group than traditional Lewis acids. It is frequently used in catalytic quantities. The researchers recently disclosed an intriguing quinazolinone synthesis method by mixing aldehydes with 2-aminobenzamide using a simple catalyst-free condition [77]. Aromatic aldehydes containing halogen or electron-withdrawing (EWG) functional groups are acceptable and give the required compound having good to exceptional yields. Because heterocycles have fascinating biological properties, As substrates, various heterocyclic aromatic aldehydes were employed. The related 2-heterocyclic substituted quinazolinones were quickly produced and yielded well. Even aliphatic aldehydes provided high yields of complimentary alkyl substituted products when reacting with 2-aminobenzamide, which was difficult in the prior approach. They also used a zinc-catalyzed oxidation method to take advantage of stable alcohol's reactivity in quinazolinone analog synthesis. As predicted, a one-pot with one-step method produced acceptable to outstanding yields for various targeted products.

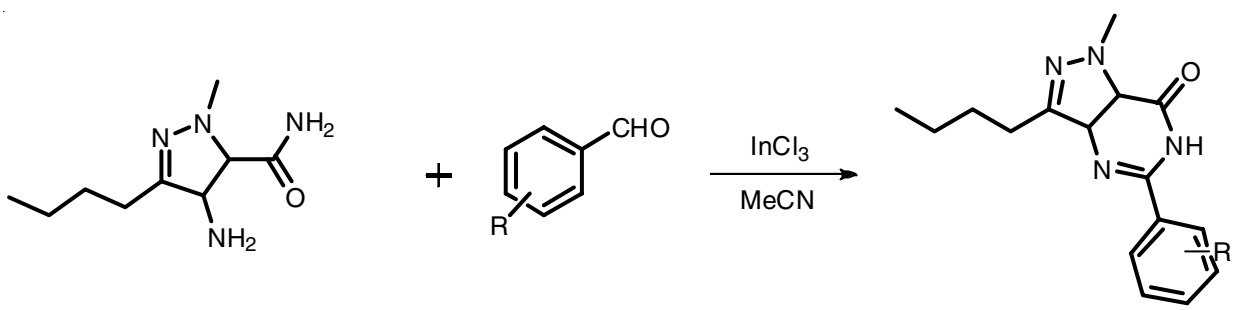
Utilizing a hydrogen transfer method to synthesize quinazolinones and *N*-alkylation of alcohols with amines alcohols has shown to be a helpful technique for forming C-N bonds. This domino reaction chain starts with the dehydrogenation of the alcohol *in situ* to create the corresponding aldehyde or ketone. The *N*-alkylated amine was formed due to further imine production, followed by reduced hydrogen (**Scheme-XXVIII**) [78]. Fang & Zhou [79] used this approach to synthesize natural



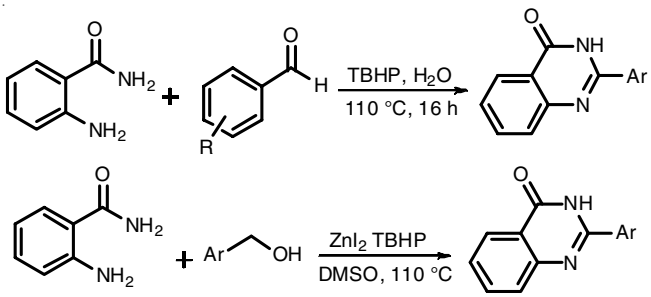
Scheme-XXV: Synthetic route of deoxyvasicinone and rutaecarpine



SchemeXXVI: Darco KB catalyzed oxidative heterocyclization for the synthesis of quinazoline analog

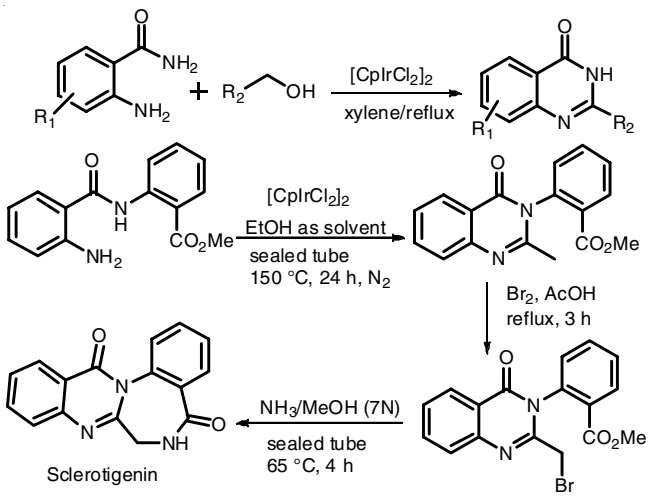


Scheme-XXVII: Synthesis of the design quinazoline analog using $InCl_3$ as catalyst

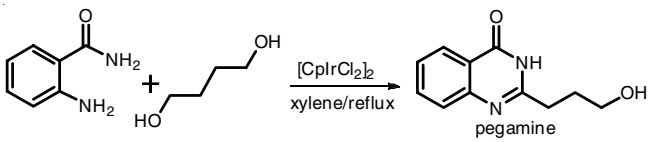


Scheme-XXVIII: Oxidative synthesis of quinazolinone

products like sclerotigenin and pegamine, which was very handy for them. Yokoyama *et al*. [80] described a Pd-catalyzed cascade reactivity of benzyl alcohols with *o*-aminobenzamides (**Scheme-XXIX**) to produce 4-phenylquinazolinones. A mechanism was postulated that was very distinct from the Ir-catalyzed hydrogen transfer process. In aqueous environments, benzyl alcohols are oxidatively added to Pd(0) to form the (h3-benzyl) palladium complex, which is required for both C-H activation *via* benzyl transfer (**Scheme-XXX**).

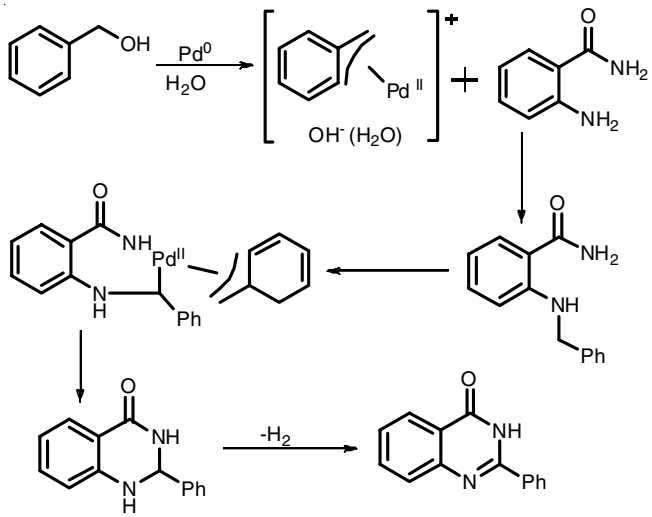


Scheme-XXIX: Synthesis of quinazolinones using an Ir-catalyzed reaction between *o*-aminobenzamides and primary alcohols



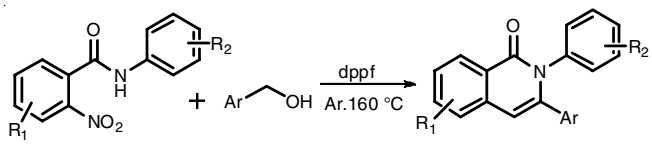
Scheme-XXX: Synthesis of quinazolinones using an Ir-catalyzed reaction between *o*-aminobenzamides.and primary dialcohols

In addition, following C-H activation reactions necessitate the use of an oxidant susceptible to recast palladium to a high oxidation state. In the system, benzyl alcohols help to regenerate Pd(II) species into toluene. Typically, the amino group was created by reducing the matching nitro group with a stoichiometric quantity of hydrogen or acid/metal. It is preferable to employ commercially accessible and affordable nitroarenes and alcohol as starting materials to synthesize quinazolinones. The alcohol may potentially serve two roles in this simple transformation: a hydrogen supply for an alkylating reagent and nitro reduction based on catalytic hydrogen transfer. Deng *et al*. [81] reported that non-toxic iron might be used as a catalyst to synthesize a series of 2,3-dialkyl/arylquinazolinones from alcohols and nitrobenzamides (**Scheme-XXXI**). Halogens and some other activist groups have been well-tolerated together under process conditions.



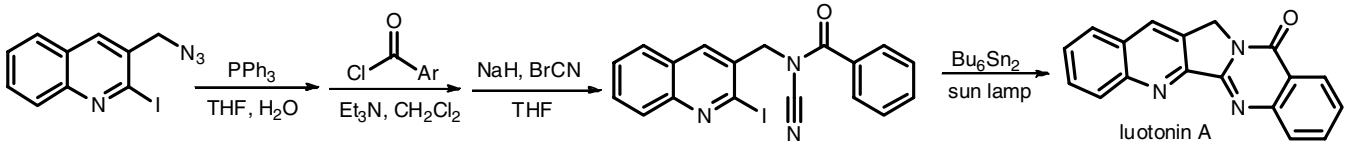
Scheme-XXXI: Synthesis of quinazolinones using Pd-catalyzed processes with benzyl alcohol

Radical chain reaction formed quinazolinones analog: Malacria *et al.* [82,83] described an excellent radical cascade method for the complete synthesis of luotonin-A utilizing *N*-acyl cyanamides (**Scheme-XXXII**). This method may make pyrimidones fused with aryl, alkyl, heteroaryl or heteroaryl moieties. According to a comprehensive mechanistic investigation, the rearomatization-induced radical migration of carbon substituents or a hydrogen atom of the cyclohexadienyl radical was the fundamental characteristic of the reaction, according to a comprehensive mechanistic investigation [84]. Through molecular oxygen-induced oxidative radical structural rearrangement synthesizing 5-aryl-4,5-dihydro-1,2,4-oxadiazoles (**Scheme-XXXIII**), Chiba *et al*. [85,86] established a simple synthesis of physiologically quinazolinone compounds that are active. The product selectivity was achieved by varying the reaction temperature and the solvents and inorganic bases used. This atom and step-economical permitted the straightforward synthesis of quinazolinone centers under tin-free aerobic radical circumstances.

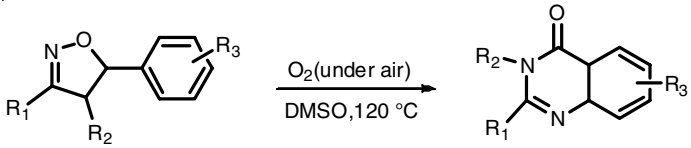


Scheme-XXXII: Synthesis of 2,3-diarylquinazolinones using a Fe-catalyzed reaction

***N*-Arylation catalyzed by transition metals toward quinazolinone synthesis:** Ullmann *N*-arylations catalyzed by transition metals is an integral approach with various applications in synthesizing many different compounds. In this respect, Fu *et al*. [87] reported effective copper-catalyzed *N*-arylations



THF was used as a solvent in the complete synthesis of luotonin-A.

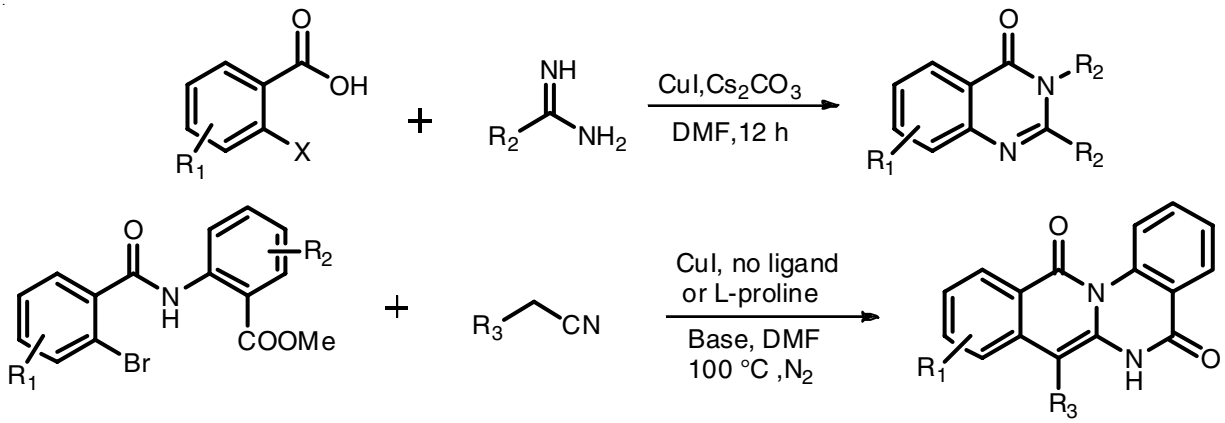


Scheme-XXXIII: Syntheisis of quinazolinones *via* oxidative radical molecular transformation of oxadiazoles analogs

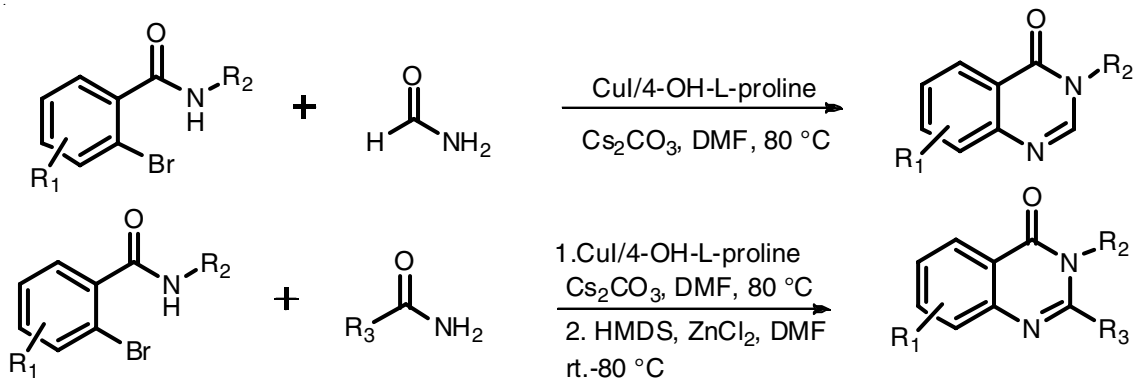
to produce quinazolinone derivatives. They showed that without the need for a ligand or additive, coupling reactions of 2-bromo or 2-iodobenzoic acid derivatives with amidines might be carried out effectively at 25 ºC (**Scheme-XXXIV**). Even non-active substrates like guanidines or 2-chlorobenzoic acid can be readily transformed into the corresponding quinazolinone analogs in the presence of CuI at 80 ºC. This is the first time, *N*-heterocycles have been synthesized at room temperature using ligand-free copper catalysis. Fu *et al*. [88] disclosed an iron-catalyzed cascade synthesis of quinazolinone derivatives and 1,2,4-benzothiadiazine 1,1-dioxide. Using widely accessible amino acids as nitrogen-containing motifs, the same group described a unique and valuable domino approach for building quinazolinones [89]. Using a copper-catalyzed method, Fu *et al*. [90] succeeded in producing isoquinolino[2,3-*a*]quinazolinones. The process includes an Ullman-type *C*-arylation, intramolecular addendum of CN with NH and a nucleophilic attack of amino on the ester group. Under microwave irradiation, Liu *et al*. [91] devised a practical in H_2O and DMF, Fe-catalyzed formulation of different quinazolinone moiety. This is the first time Fe-catalyzed C-N coupling has been reported in aquatic settings, resulting in *N*-heterocycles. Later, Liu *et al*. [92] also reported a microwave irradiated Fe/Cu co-catalyzed production of 2-methylquinazolin-4(3*H*)-one.

To meet the challenges of sustainable organic transformation pathways, Wang *et al.* [93] reported an efficient, reusable and magnetically recoverable Fe_3O_3 nanoparticle supported Cu(I) catalyst and its application cascade reactions of substituted 2-halobenzoic acid and 2-bromocycloalk-1-enecarboxylic acids with amidines to synthesize quinazolinone moiety and bicyclic pyrimidinone. Decanting the sample solution under the influence of an applied magnet is an effective and straightforward way to recover the catalyst and reused it in the process over ten times with no noticeable loss of activity. Ma *et al*. [94] reported a fast and straightforward method for building substituted quinazolinones. Conveniently accessible amides may be used as nucleophiles in coupling reactions with *N*-substituted *o*-bromobenzamides, resulting in 2,3-disubstituted or 3-substituted quinazolinone calmer condensative cyclization by HMDS/$ZnCl_2$ (**Scheme-XXXV**). The formal synthesis of 3-[2-(hydroxymethyl)-4-methoxyphenyl]-6-methoxyquinazolin-4-one and methaqualone has been demonstrated using this protocol. Li *et al.* [95] were motivated to develop a modular synthesis of 3*H*-pyrido[3,4-*d*]pyrimidin-4-one (**Scheme-XXXVI**), an orally active Ca-sensing receptor (CaR) antagonist currently being investigated for the treatment of osteoporosis. The intended product was obtained on the first try utilizing CuI-mediated conditions; however, despite all optimization efforts, the reaction only reaches a 50% conversion rate at best, even without ligands. They soon moved to palladium-catalyzed techniques and reported that the system was produced by the Xantphos/$Pd_2(dba)_3$ complete conversion and a pure HPLC result. In a one-pot synthesis, amidines, *N*-arylation yielded quinazoline-4(3*H*)-one when combined with methyl 2-iodo or 2-bromo benzoate esters.

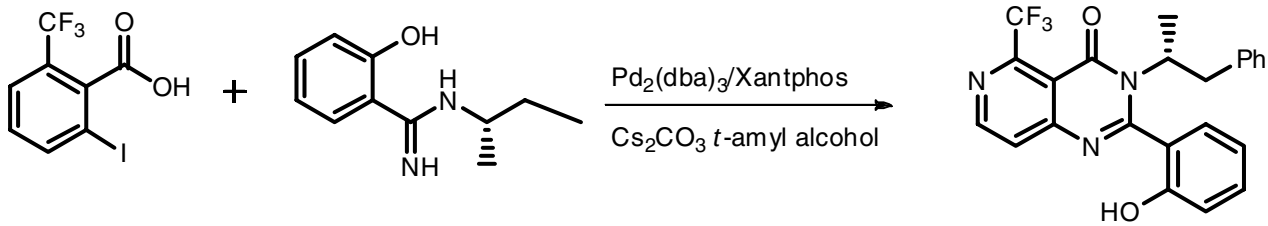
Pd-catalyzed carbonylations have come a long way since 4-(3*H*)-quinazolinones palladium-catalyzed carbonylative synthesis in 1974 [96]. Carbonylative transformation catalyzed by Pd has evolved into a unique, potent and flexible method for generating carbonyl-containing heterocyclic molecules



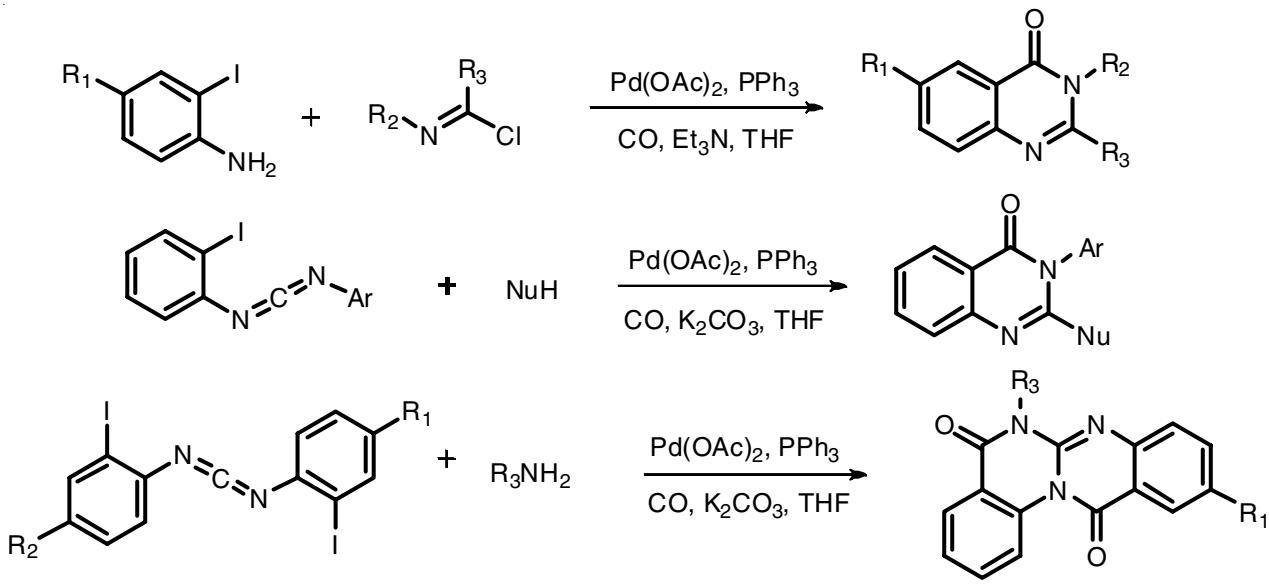
Scheme-XXXIV: Synthesis of quinazolinone moiety using Cu-catalyzed *N*-alkyl 2-halobenzoic acid in DMF



Scheme-XXXV: Synthesis of 2,3-disubstituted quinazolines using Cu-catalyzed aryl amidation

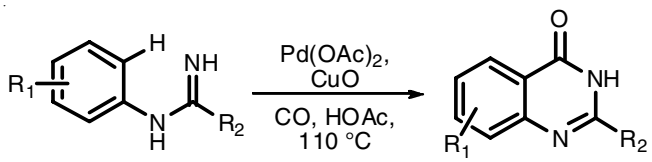


Scheme-XXXVI: Synthesis of 3*H*-pyrido[4,3-*d*]pyrimidin-4-one analogs using xantphos/$Pd_2(dba)_3$ system



Scheme-XXXVII: Synthetic routes of Pd-catalyzed carbonylation of 4(3*H*)-quinazolinone analogs

today. In 2008, Zheng & Alper [97] reported a practical palladium catalyzed three-component synthesis of imidoyl chlorides, *o*-iodoanilines and carbon monoxide (**Scheme-XXXVII**). Using palladium catalyzed intermolecular addition and intramolecular cyclocarbonylation cascade reaction technique, the same group also accomplished a one-step synthesis of a potentially essential 2-heteroquina-zolin-4-(3*H*)-one derivative [98]. The same elegant domino method has been used to synthesize quinazolino[3,2-*a*]quina-zolinones [99]. Zhu *et al.* [100] reported an intriguing Pd-catalyzed intramolecular C(sp^2)-H carboxamidation (**Scheme-XXXVIII**). The reactions were placed in CH_3COOH as a solvent, using one equivalent of cuprous oxide and one bar of carbon monoxide with *N*-arylamidines produced high yields of various quinazolinones. Because no

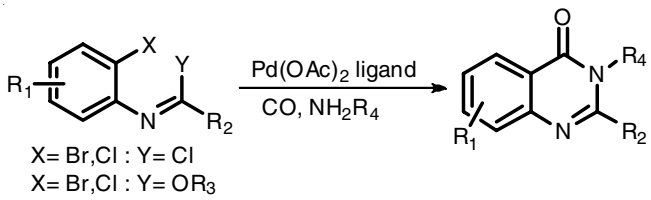


Scheme-XXXVIII: Pd(II)-catalyzed 4(3*H*)-quinazolinone synthesis through C-H carboxamidation of *N*-arylamidine

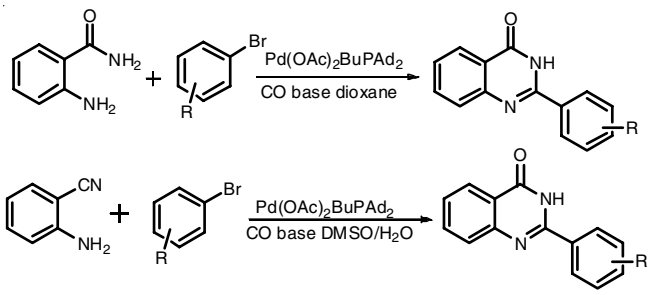
atoms in substrates were lost throughout the process, this technique, unlike other approaches to quinazoline-4(3*H*)-one, has atom economy and step-efficiency.

Willis *et al.* [101] showed that imitates or *N*-(*o*-halophenyl)-imidoyl chlorides may be used as complementary materials for the synthesis of quinazolinones moiety by including Pd-

catalyzed aminocarbonylation reaction workup (**Scheme-XXXIX**). Under CO ambient pressure, good to excellent yields of 2,3-disubstituted quinazolinones was obtained. Quinazolinones were synthesized in high yields with a variety of amine nucleophiles. Wu *et al.* [102] developed a simple carbonylative quinazolinone synthesis using aryl bromides and 2-aminobenzamide (**Scheme-XL**). The synthesis of structurally different quinazolinone products was made possible by a significant difference in the substrates. It is hypothesized that 2-aminobenzonitrile might be used as a substrate to quinazolinones moiety are made by hydration of the nitrile group through an amide group *in situ*. As an attractive alternative to 2-aminobenzamide. Using K_2CO_3 as a cheap base in an aqueous solution, aryl bromides and 2-aminobenzonitriles were used to make quinazolinones [40].



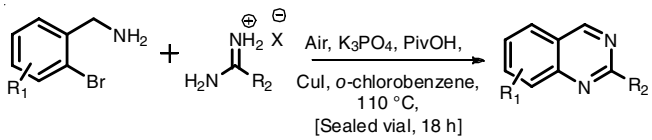
Scheme-XXXIX: Synthesis of 2,3-disubstituted quinazolinones from imidates or *N*-(*o*-halophenyl)imidoyl chlorides



Scheme-XL: Pd catalyst carbonylative synthesis of 4(3*H*)-quinazolinone using the three-component system

Neumann *et al*. [103] reported a simple and convergent Pd-catalyzed four-component carbonylative coupled system for the synthesis of 4(3*H*)-quinazolinone (**Scheme-XLI**), emphasizing the importance of quinazolinones and carbonylative transformations. Starting with economically available 2-bromoaniline, *o*-esters, amines and CO, the required products were separated in high yields in the presence of $BuPAd_2/Pd(OAc)_2$. The method tolerates a wide range of synthetically helpful functional groups, which opens up a new avenue for the efficient and long-term synthesis of highly functionalized amines.

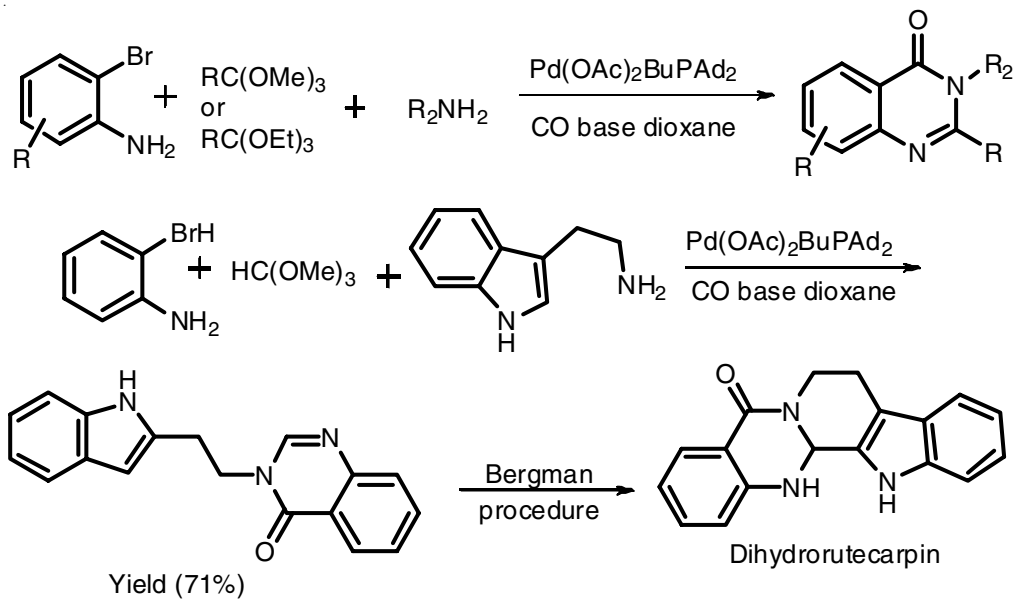
In one step, CuI-catalyzed cascade reactions of amidines and 1-(2-bromophenyl)methenamine with K_3PO_4 as base, pivalic acid as additive and aerial oxygen as the oxidant generate substituted quinazolines having yields ranging from 48 to 90% (**Scheme-XLII**). The stages in the mechanism include Cu(I)-catalyzed intermolecular *N*-arylation, followed by intramolecular nucleo-philic substitution and Cu(II)-catalyzed oxidation. 1-(2-iodo-phenyl)methenamine [104] can be used to replace the amidines and the reaction can be carried out using imitates.



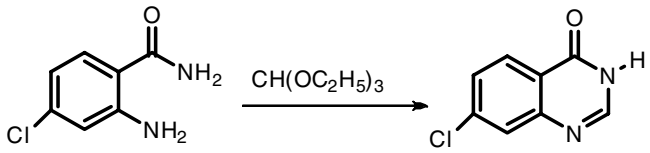
SchemeXLII: Synthesis of substituted quinazolines using CuI-catalyzed reactions of 1-(2-bromophenyl)methenamine and amidines

The synthetic route of 7-chloro-substituted quinazolinone analog *via* condensation reaction of 2-amino-4-chlorobenzamide using (diethoxymethoxy)ethane as a condensing reagent [105] (**Scheme-XLIII**). Quinazolin-4(3*H*)-one analog was then made by reacting 2-aminobenzoic acid with an excess amount of methanamide at 120 ºC (**Scheme-XLIV**). The Niementowski reaction [106] is another name for this reaction.

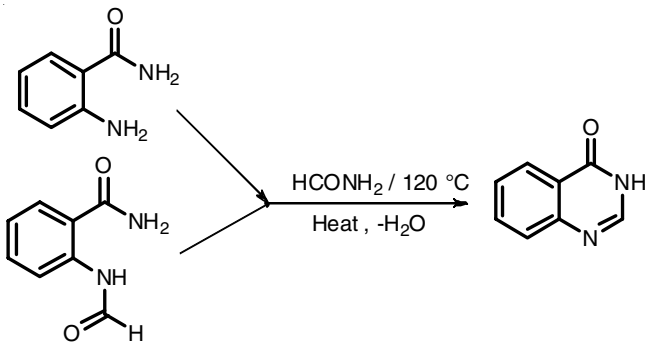
3-Phenyl cinnamoyl chloride with halo substituted 2-aminobenzonitrile, 2-styryl-4(3*H*)-quinazolinone moiety was synthe-



Scheme-XLI: Pd catalyst carbonylative synthesis of quinazolin-4(3*H*)-one analog using a four-component system



Scheme-XLIII: Synthesis of substituted quinazolines using condensation reaction of 2-amino-4-chlorobenzamide with triethyl ortho-formate

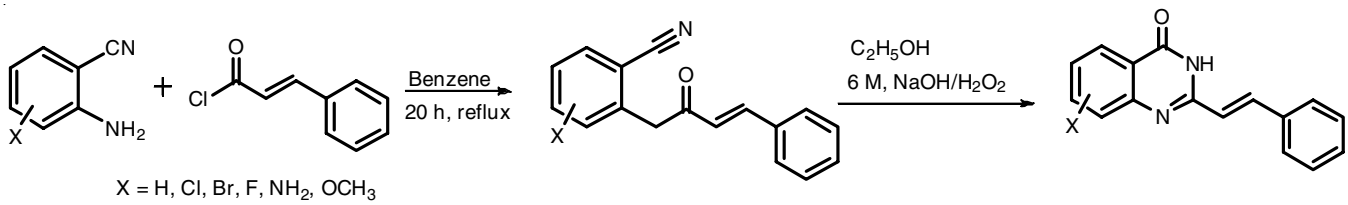


SchemeXLIV: Synthesis of quinazolin-4(3*H*)-one from anthranilic acid and formamides

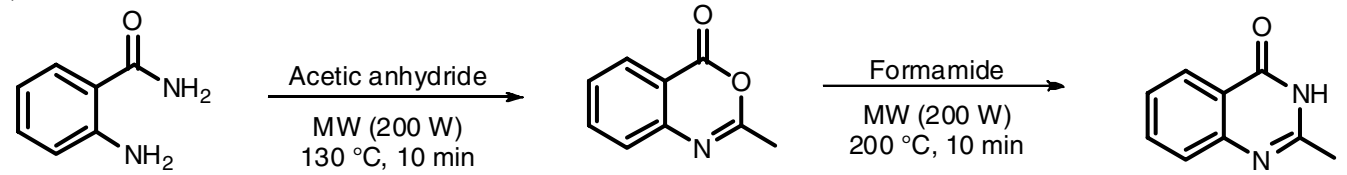
sized using the starting material. Under alkaline circumstances, 2-styryl-4(3*H*)-quinazolinone was obtained *via* intramolecular cyclization of cinnamate derivatives (**Scheme-XLV**). This method has been demonstrated to work with a wide range of substituted aromatic rings [107]. The response of 2-aminobenzoic acid with ammonium acetate was observed utilizing methanamide beneath microwave condition at 200 W to synthesize the preferred 2-substituted-4(3*H*)-quinazolinones products [108] (**Scheme-XLVI**). Under reflux circumstances, anthranilamide was reacted with substituted aldehydes or ketone in the presence of TEE to produced 2,2-disubstituted-2,3-dihydro-4(1*H*)-quinazolinone analogs in moderate yields [109] (**Scheme-XLVII**).

In the synthesis of 2-amino-quinazolin-4(3*H*)-one analog used the response of methyl anthranilate and an extra quantity of guanidine in the presence of ethyl alcohol with NaOH to produce sodium ethoxide at 130 ºC and 5 h to received an average yield [110] (**Scheme-XLVIII**). 4-Arylaminoquinazolines offer a lot of potential as anticancer medicines. By treating 2-aminobenzonitrile and other substituted amino benzene with anhydrous $AlCl_3$, substituted amidines were quickly synthesized (**Scheme-XLIX**) [111].

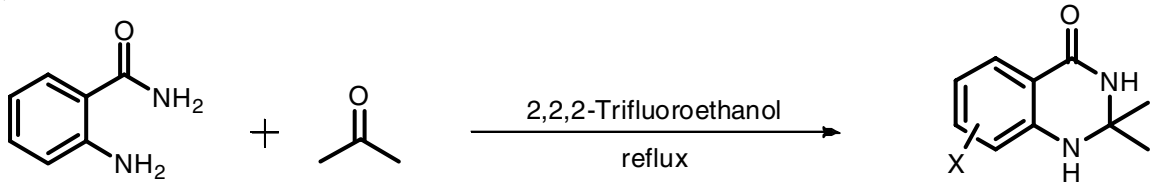
2,3-Alkyl/aryl-disubstituted-4(3*H*)-quinazolinone moiety were synthesized by reacting 2-acetamidobenzoic acid with a suitable arylamine presence phosphoryl chloride to give the desired product having excellent yields [112] (**Scheme-L**). The most often used synthesis intermediates of 2,3-alkyl/aryl-



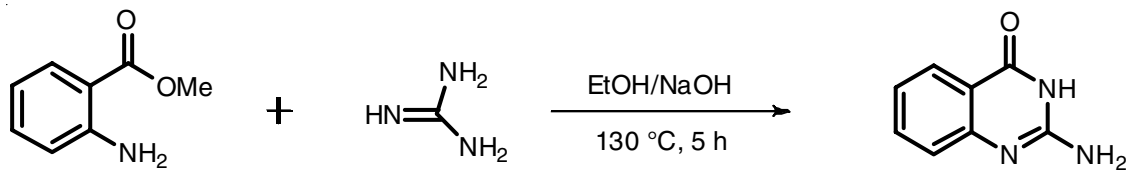
SchemeXLV: Synthesis of 2-[(*E*)-2-phenylethenyl]-3*H*-quinazolin-4-one derivatives using 2-aminobenzonitrile as starting material



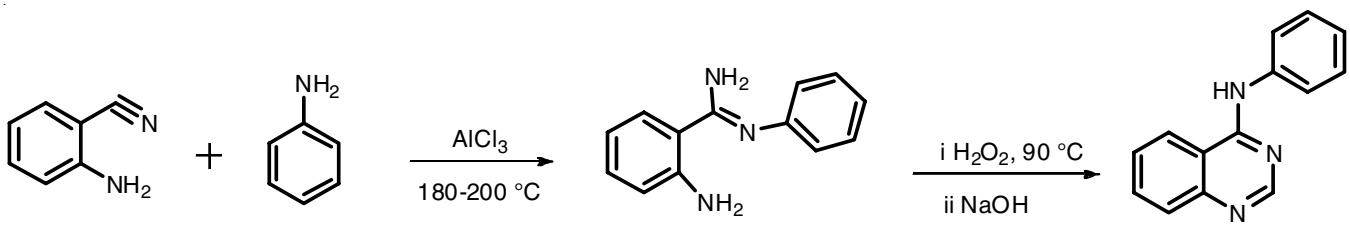
Scheme-XLVI: Synthesis of 2-substituted-4(3*H*)-quinazolinones from 2-aminobenzoic acid with ammonium acetate followed by Methanamidation



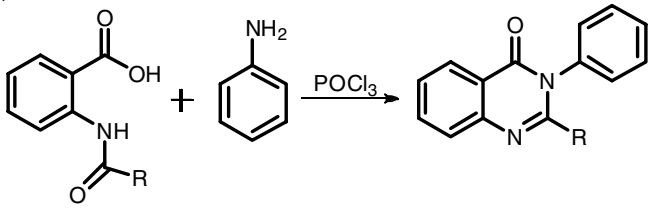
Scheme-XLVII: Synthesis of 2,2-disubstituted-2,3-dihydro-4(1*H*)-quinazo-linone analog from anthranilamide and aldehydes/ketone in the presence of TEE under reflux conditions



SchemeXLVIII: Synthesis of 2-aminoquinazolin-4(3*H*)-one using methyl anthranilate and guanidine



Scheme-XLIX: Synthesis of 4-arylaminoquinazolines as anticancer drugs

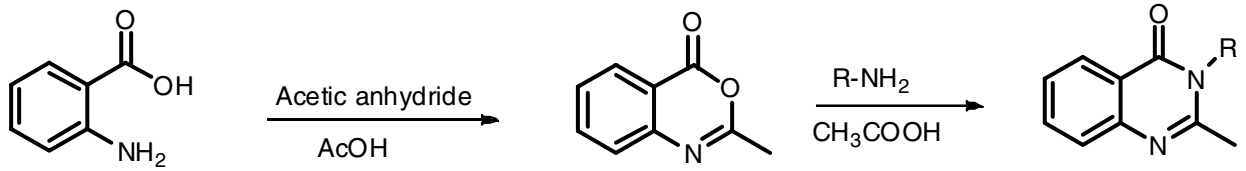


Scheme-L: Synthesis of 2,3-disubstituted-4(3*H*)-quinazolinone moiety using phosphorous oxychloride as catalyst

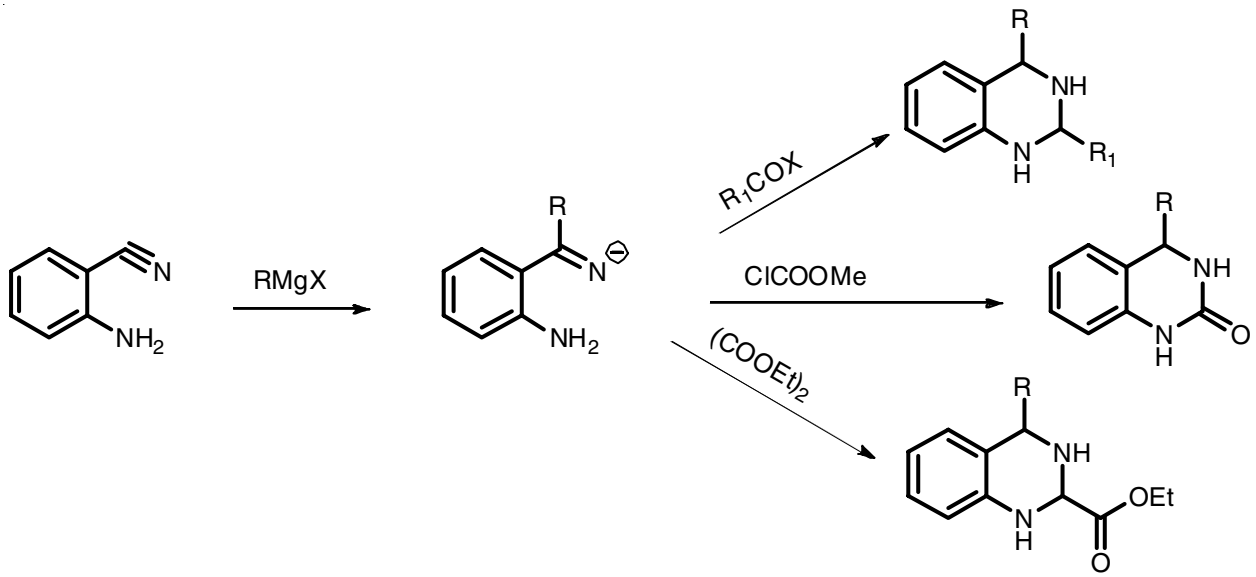
disubstituted quinazolinone moiety are benzoxazinone derivatives. A refluxing combination of 2-aminobenzoic acid and ethanoic anhydride in ethanoic acid yielded 2-methyl-3,1-benzoxaza-4-one with moderate to high yields (**Scheme-LI**) [113]. The intermediates were synthesized by reacting 2-aminobenzonitrile with alkyl magnesium halide (Grignard reagents) (**Scheme-LII**). The resulting intermediate derivatives were crucial in the production of various quinazolinone moieties. Furthermore, the corresponding quinazoline derivatives were obtained in yields that range from good to exceptional when cyclized with acid chlorides, anhydrides and forms. As a result, this generic technique for making different 2,4-alkyl/aryl-disubstituted quinazoline moieties is extraordinarily versatile and valuable [114].

2-(Chloromethyl)-4-methylquinazoline moiety were synthesized by reacting 1-(2-aminophenyl)ethanone with HCl gas in the anhydrous state in the presence of chloroacetonitriles, as illustrated in **Scheme-LIII**. The molecule was treated with various amines derivatives in a basic condition using potassium carbonate in DMF solvent, yielding 2-chloromethyl-4-methyl-quinazoline moiety with good yields [107]. A three-component reaction using isotonic anhydride, aliphatic/aromatic amine and oxaldehydic acid; hydrate as reactants in PEG-400 using freshly prepared lemon juice at room temperature (25-30 ºC) under ultrasound irradiation condition moderate yields obtained [115] (**Scheme-LIV**).

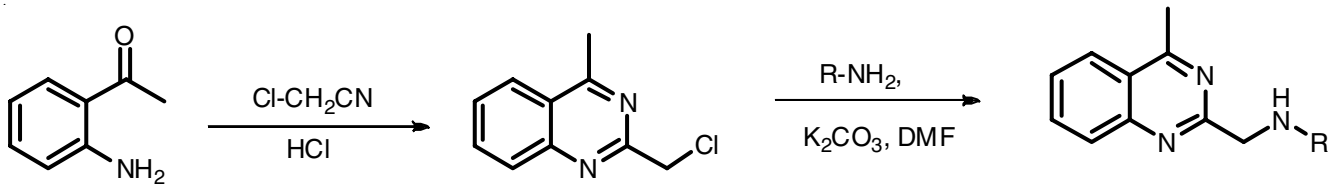
A four-component method based on aniline, aromatic aldehydes and ammonium iodide was developed for synthesizing substituted quinazolines derivatives. In anilines, the C-H bond was immediately functionalized in a metal-free environment in the direction of the amino group. Two moles of aromatic aldehydes were used in this synthesis and ammonium iodide



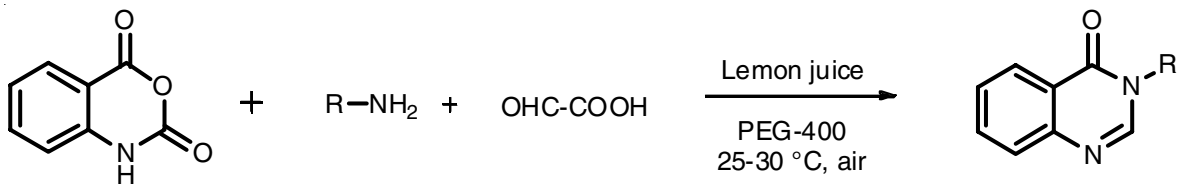
Scheme-LI: Synthesis of 2,3-alkyl/aryl-disubstituted quinazolinone derivatives using anthranilic acid, acidic anhydride and primary amine



Scheme-LII: Synthesis of several 2,4-disubstituted quinazoline derivatives using 2-aminobenzonitrile



Scheme-LIII: Synthesis of 2-chloromethyl-4-methyl-quinazoline moiety using 1-(2-aminophenyl)-ethanone and HCl gas



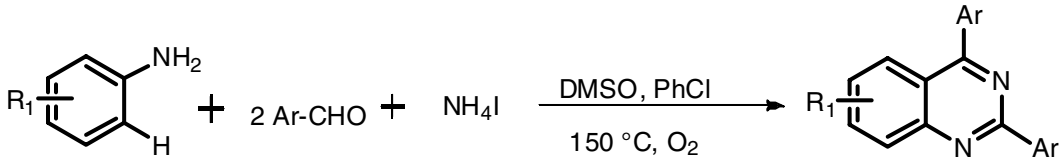
Scheme-LIV: Synthesis of substituted quinazolines using isotonic anhydride, amine and oxaldehydic acid; hydrate in three-component reaction

as a nitrogen source. The reaction allows substituted quinazolines to be made from simple anilines and other widely accessible compounds. The most often described procedure for the preparation of substituted quinazolines moiety from *ortho* functionalized anilines derivatives such as 2-carbonyl anilines, 2-aminobenzylamine and 2-aminobenzonitriles, have been described as starting materials for the formation of benzo-heterocyclic compounds by condensation with aldehydes, benzylamine, benzylic acid or benzonitrile (**Scheme-LV**). Others discovered that the most stable *o*-nitroacetophenone might be utilized as a raw material to make substituted quinazolines using a hydrogen transfer method in addition to *ortho*-functionalized anilines. *N*-Arylamides were being used as starting materials for the intramolecular cyclization observed in quinazoline synthesis. The aniline ring does not need to be preactivated in the ortho configuration. In recent years, other activated nitrogen containing rea gents, such as aryl diazonium salts, 2-ethynylanilines, 2-alkylaminobenzonitriles, *N*-sulfinyl imines, imines and amidines are various alternative substrates for the synthesis of substituted quinazolinone analogs [116].

The efficient metal-free synthesis of 2,4-dialkyl/diaryl/alkyl, aryl-substituted quinazolines have been established using a hydrogen peroxide-mediated one-pot containing three component reaction involving 2-aminoaryl ketone, aromatic or aliphatic aldehydes and ammonium ethanoate (**Scheme-LVI**). The transition occurred fast under favourable conditions in the corporation of commercially available hydrogen peroxide. The lack of a transition metal catalyst, the moderate reaction conditions and the broad substrate scope are all key advantages of this technique. Additionally, this method is compatible with the last 2,4-substituted quinazoline manufacturing techniques [117].

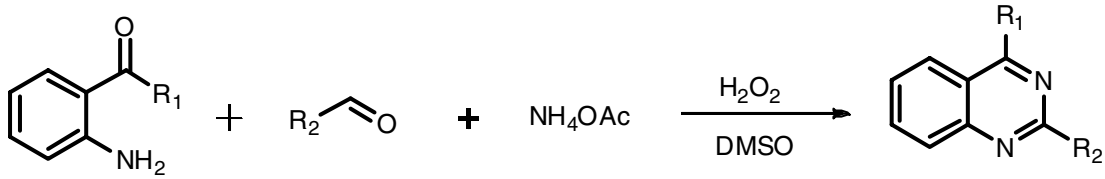
Synthesis assisted by microwaves: Sarma & Prajapati [118] used microwave heating to synthesize quinazoline moiety from aromatic aldehydes, 2-aminobenzophenone and ammonium ethanoate without the need of a catalyst or solvent (**Scheme-LVII**). The technique was tested on a variety of electron-rich and electron-deficient groups and it produced the required quinazoline analog in satisfied isolated yields (70-91%) in under a minute. Furthermore, the reaction is clean and straightforward and it provides an environmentally acceptable method for removing organic solvents in medicinal chemistry through organic synthesis [118].

Synthesis in water driven by bases: Cho *et al.* [119] reported a transition/catalytic metal-free synthesis of quinazoline moiety from readily available trihalotoluene and *o*-amino-



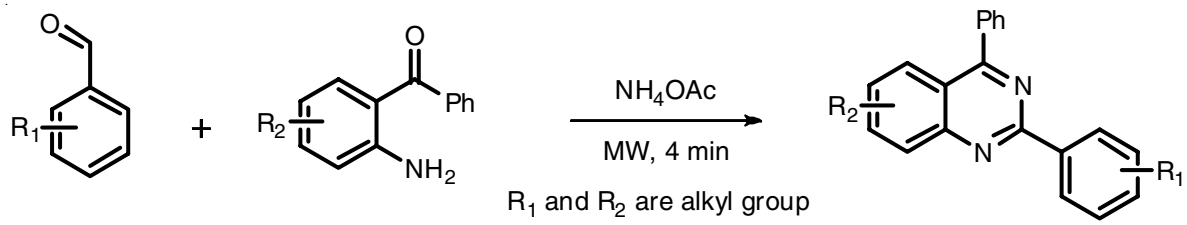
Four-component, Aniline C-H Functionalization, NH_4I as a nitrogen source, metal- Free.

Scheme-LV: Synthesis of substituted quinazolines from aniline using NH_4I as a nitrogen source



R_1 = Aryl, Me. R_2 = Aryl, Heteroaryl, Alkyl

Scheme-LVI: Synthesis of quinazoline under three-component one-pot process using green oxidant without metals



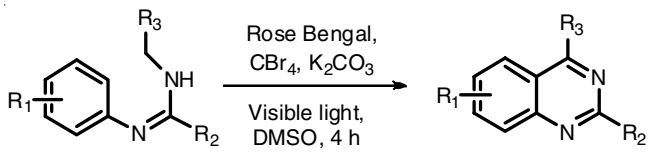
Scheme-LVII: Synthesis of aldehydes and 2-amino benzophenone under microwave heating conditions

benzylamines in H_2O, with isolated yields ranging from 43 to 78% (**Scheme-LVIII**). This method is the more cost-effective and sustainable due to the recrystallization of the crude reaction mixture for purification and the considerable solvent-consuming workup.

Imidazolate framework synthesis catalyzed by cobalt zeolite: Truong *et al.* [120] achieved excellent yields of quinazoline compounds by cyclizing benzylamines with 2-aminobenzoketones using a heterogeneous catalytic system (*via* ZIF-67) (**Scheme-LIX**). At 80 ºC, TBHP was demonstrated to have good reaction conditions as an oxidant in methylbenzene solvent. Furthermore, ZIF-67 functions as a catalyst in a system while regenerating or recycling much of its catalytic activity.

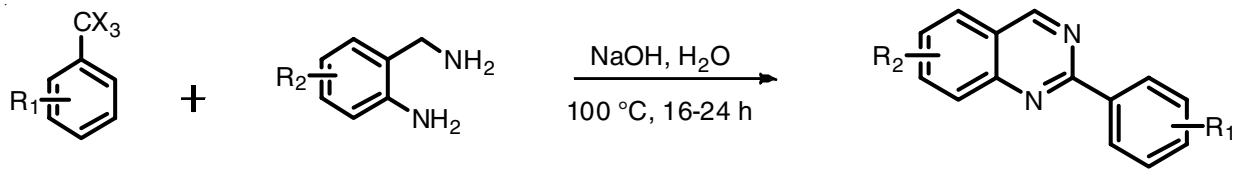
Synthesis using Lewis acid as catalyst: Deng *et al.* [121] proposed a method to synthesize quinazoline scaffolds under transition/catalytic-metal-free conditions using polyoxymethylene and *N*-phenyl-benzimidamides as carbon sources. The enhanced reaction state was well sustained with electron-rich and electron-deficient substituents on the aromatic ring, giving moderate to suitable yield of 45-92% (**Scheme-LX**). Transition/catalytic-metal-free reaction and medium settings are two of this approach's most appealing features. This novel method also provides a straightforward, ecologically benign and complementary method for producing 2-arylquinazoline scaffolds.

Photo-redox oxidative annulation assisted by visible light: The oxidative C(sp^2)-C(sp^3) bond formation in the synthesis of substituted quinazoline moiety from amidine derivatives using visible light (**Scheme-LXI**). This is a metal-free oxidative coupling with the help of a photo-redox catalytic device. Having a broad range of functional groups was found to be tolerated by the technique [122].

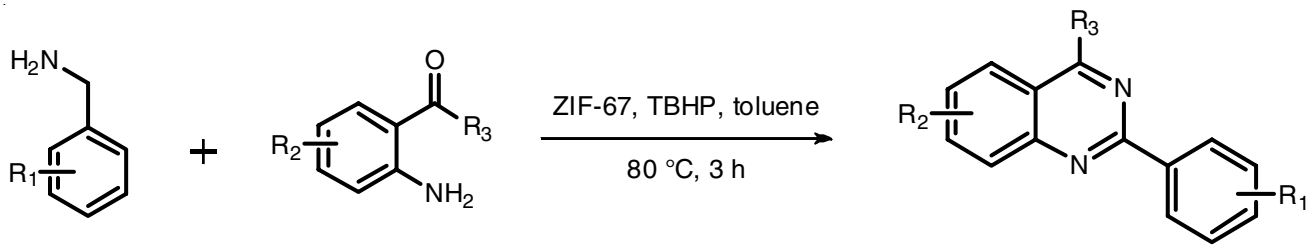


Scheme-LXI: Arylamide cyclization catalyzed by a photo-redox organocatalyst

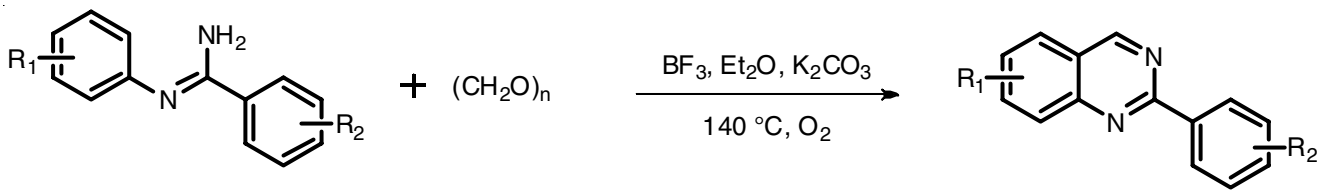
Carbonitrile or cyanamide-based metal-free oxidative annulation: North *et al.* [123] established a viable technique for synthesizing substituted 2-aminoquinazoline analogs in moderate to excellent yields from 2-amino benzophenone and 4-morpholine carbonitrile or cyanamide. This method is



Scheme-LVIII: Reaction of *o*-aminobenzylamines with α,α,α-trihalotoluenes in water to produce quinazoline derivatives



Scheme-LIX: ZIF-67 catalyzes the reaction of substituted benzylamines with 2-aminoacetophenones



Scheme-LX: Lewis acid-catalyzed reaction of polyoxymethylene with *N*-phenyl benzimidamide moiety

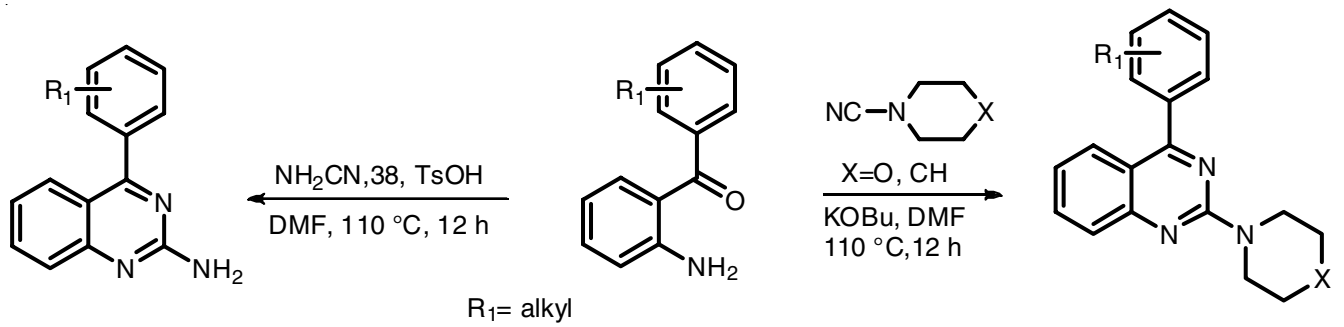
transition/catalytic metal-free and mild (**Scheme-LXII**), which enables the synthesis of bioactive substituted 2-aminoquinazoline analogs using a cyclic substituted amine or a free amine in DMF, ensuring atomic economics and biological properties.

Catalytic systems based on iron: Chen *et al.* [124] used 2-hydroperoxy-2-methylpropane (TBHP) as a terminal oxidant to demonstrate iron dichloride-catalyzed carbon-hydrogen oxidation and intramolecular carbon-nitrogen bond formation synthesize substituted quinazolines. Grignard reagent treatment of 2-alkylaminobenzonitrile produced 2-alkylamino N-H ketamines. The method had a wide range of 2,4-dialkyl/diaryl/alkyl-aryl disubstituted quinazoline analogs, ranging from 43 to 86% (**Scheme-LXIII**).

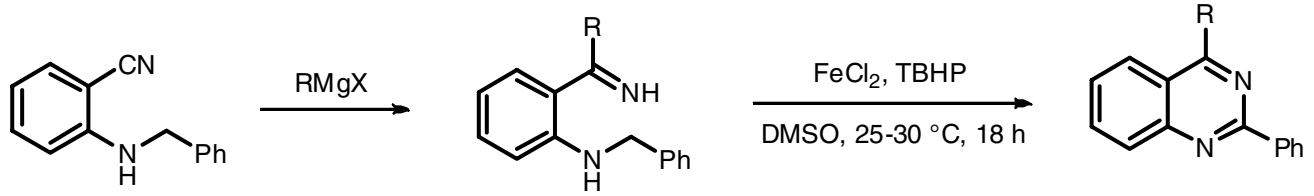
Gopalaiah *et al.* [125] used an iron(III)bromide-catalyzed one-pot cascade to make quinazoline analogs from 2-hydroxymethylanilines and aromatic amines in benzene chloride at 110 ºC for 12-14 h under aerobic oxidative conditions. The process starts with *N*-benzylidene benzylamine intermediate contraction, followed by ammonia intramolecular cyclization through oxidative trapping (**Scheme-LXIV**). In this method, both heteroaromatic and aromatic amines worked well, giving matching substituted quinazoline moiety in good to outstanding isolated yields of 61-94%. Since, the O_2 molecule was employed as an oxidant and inexpensive and plentiful iron salts were used as a catalyst, this conversion is exceptionally sustainable and practicable.

Using ultrasonication and ferric fluoride as a catalyst, Jeong & Shinde [126] reported a green and efficient method for synthesizing substituted quinazoline moiety from indazol-3-amine analog and aliphatic aldehydes (**Scheme-LXV**). Furthermore, without compromising the quinazoline, the catalytic system can regenerate and recycle for at least four cycles. Through a one-pot three-component reaction combining *o*-amino aryl ketone, ammonium acetate and aldehydes, a unique and effective method for manufacturing 2,4-disubstituted quinolines has been developed (**Scheme-LXVI**). Compatibility with a broad spectrum of functional groups, neutral conditions, atom economy and simple workup processes is advantageous [127].

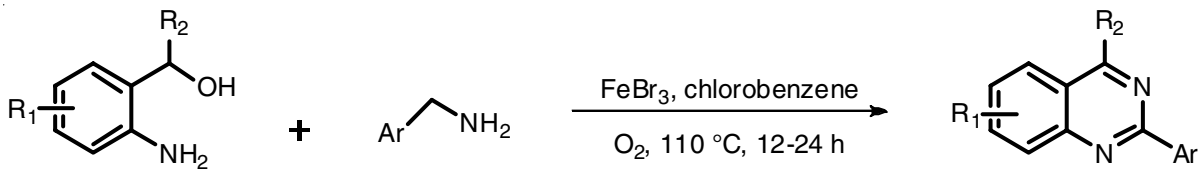
The benzylic Csp^3-H bond amination of 2-amino benzaldehyde, 2-aminobenzophenone or 2-aminobenzyl alcohol with phenylmethanamine was catalyzed by molecular iodine, resulting in moderate to high yields of the quinazoline moiety



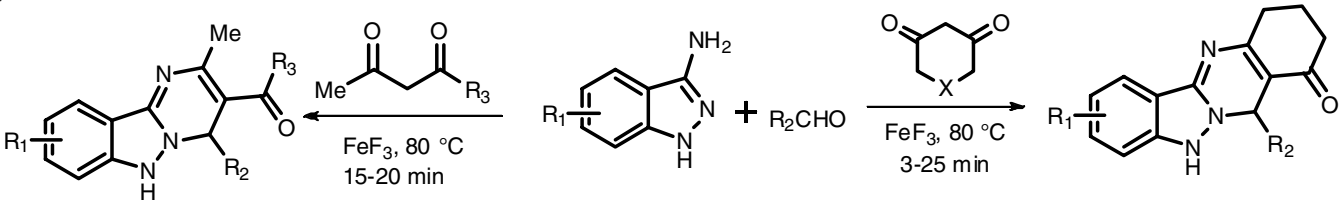
Scheme-LXII: Reaction of 2-Amino benzophenone with 4-morpholinecarbonitrile or cyanamide to form 4-morpholinecarbonitrile or cyanamide



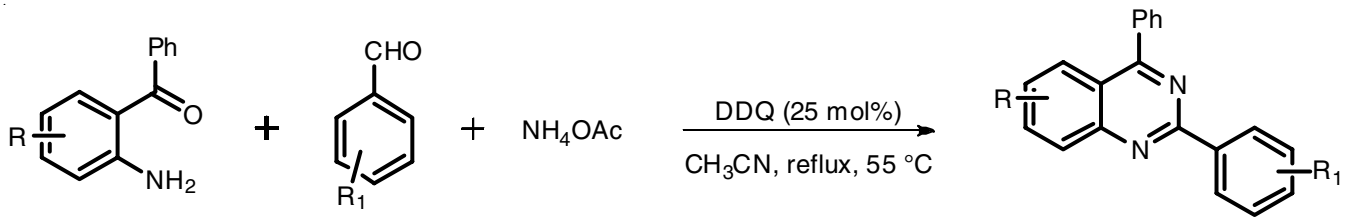
Scheme-LXIII: $FeCl_2$/TBHP mediates oxidative amination of 2-alkylamino N-H ketamines in DMSO



Scheme-LXIV: Reaction of 2-hydroxymethylanilines with benzylamines catalyzed by ferric bromide

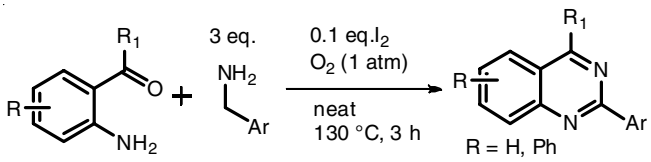


Scheme-LXV: Synthesis of high functionalized quinazolines using sonochemical ferric fluoride in a solvent-free environment

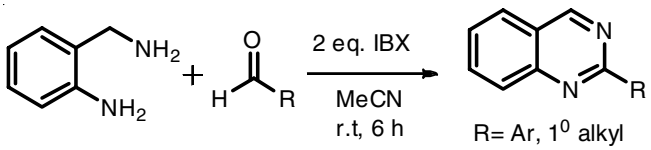


Scheme-LXVI: Synthesis of 2,4-disubstituted quinolones using one-pot three-component process

(**Scheme-LXVII**). Because of the oxidant O_2 molecules and the transition/catalytic metal, reagent and solvent-free conditions [128]. A mild *o*-iodoxybenzoic acid (IBX) mediated tandem reaction of widely accessible *o*-aminobenzylamine and aromatic/aliphatic aldehydes allows the synthesis of variously modified quinazolines, 2-alkyl quinazolines analog in good yields in the presence of acetonitrile at room temperature [129] (**Scheme-LXVIII**).



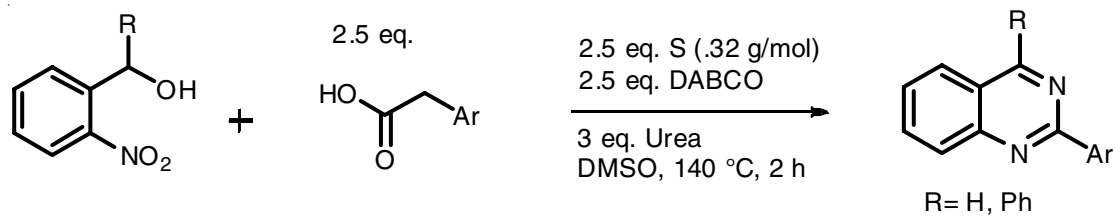
Scheme-LXVII: Amination of 2-amino benzaldehyde and 2-amino benzophenone with benzylamines catalyzed by molecular iodine



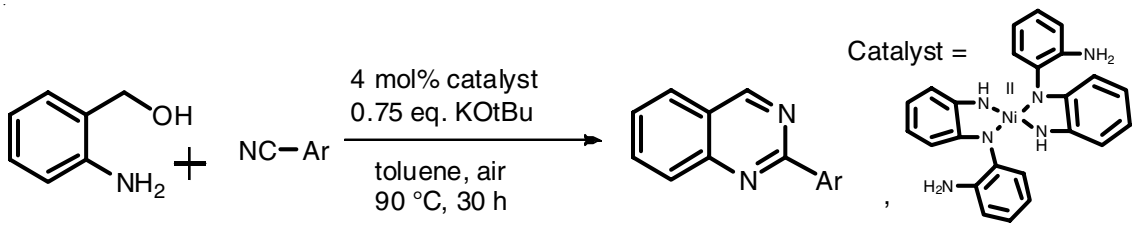
Scheme-LXVIII: Synthesis of quinazoline using *o*-aminobenzylamine and aldehydes

Substituted quinazolines are produced by condensation of substituted 2-nitrophenyl methanol with aryl acetic acid in urea as a nitrogen source, elemental sulphur as an activator, DABCO as base and DMSO as solvent (**Scheme-LXIX**). Fluoro, chloro thienyl, trifluoromethyl and indolyl groups are tolerated by the reaction [130]. Singlet diradical Ni(II) with two antiferromagnetically paired singlet diradical diamine type ligands catalyzes the direct atom-efficient synthesis of alkyl/aryl substituted quinolines 2-aminoquinolines and substituted quinazolines in moderate to good yields using toluene as solvent at 90 ºC *via* biomimetic dehydrogenative coupling/condensation reactions (**Scheme-LXX**) [131].

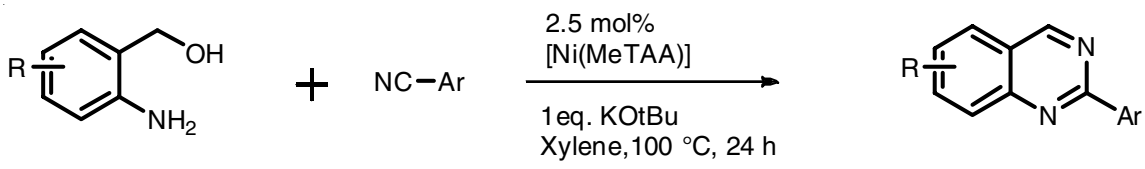
The modified synthesis of quinazolines was accomplished by combining benzyl alcohol with 2-aminobenzylamine and 2-aminobenzyl alcohol with benzonitrile in an accepting or less dehydrogenative manner. Nickel catalysts use low-cost, easy-to-make tetraaza macrocyclic ligands to catalyze the reactions (**Scheme-LXXI**). As a result, a broad range of modified quinazolines analogs with good yields was synthesized [132]. A highly selective reaction of dehydrogenation coupling in amines with a 2-aminophenyl ketone employing an *in situ* generated ruthenium catalyst allows the synthesis of quinazoline compounds. Quinazolinones were synthesized by combining 2-amino-



Scheme-LXIX: Synthesis of substituted quinazolines via condensation of 2-nitrophenyl methanol with aryl acetic acid



Scheme-LXX: Synthesis of quinazoline derivatives using Ni(II) complex as catalyst



MeTAA = Tetramethyltetraaza[14]annulene

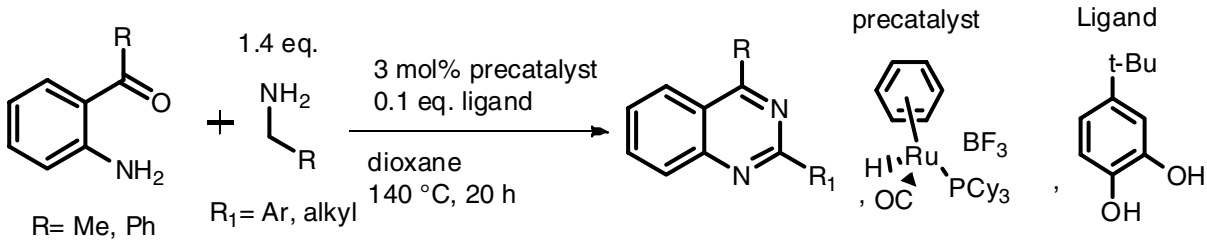
Scheme-LXXI: Synthesis of quinazoline compounds using [Ni(MeTAA)] as catalyst

benzamide with amines in a deaminative reaction (**Scheme-LXXII**) [133].

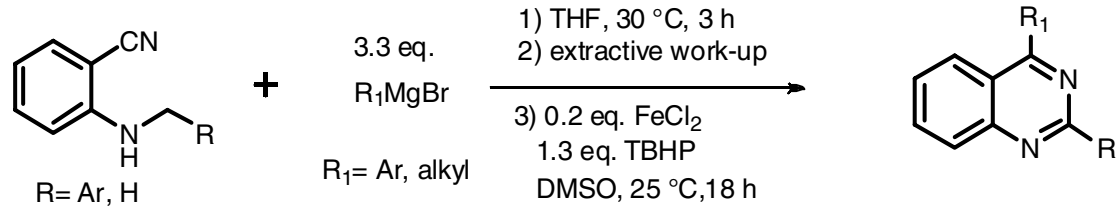
The efficient synthesis of quinazolines moiety using 2-alkylamino N-H ketamine analogs was produced by various organometallic reagents and DMSO as a solvent used in 2-alkylaminobenzonitriles is enabled Fe-catalyzed sp^3 hybridized carbon-hydrogen corrosion, intramolecular C-N bond formation, followed by aromatization (**Scheme-LXXIII**) [124]. A copper catalyzed formulation of benzonitriles with 2-ethynylanilines produced substituted quinazolines by cleaving the C-C triple bond link in two aromatic rings and generating new C=N and C-C bonds throughout the availability of oxygen molecules (O_2) act as the oxidant in reaction (**Scheme-LXXIV**) [134]. Anthranils catalyzed by Cu/Ag annulate 3-aryl-2*H*-azirines, yielding (quinazolin-2-yl)methanone moiety (**Scheme-LXXV**). The copper-catalyzed breakdown of both the N-C azirins link and the N-O bond in anthranil results in a 1,3-hydroxyl group migration followed by *N*-elimination [135]. A highly effective one-pot in DMF as a solvent synthesis of 4-aminoquinazoline derivatives from conveniently accessible 2-bromo or 2-iodobenzimidamides, sodium azide and aldehydes was accomplished using Cu-catalyzed ArSN substitution, followed by reduction with cyclization and oxidation followed by tautomerization (**Scheme-LXXVI**) [136].

Conclusion

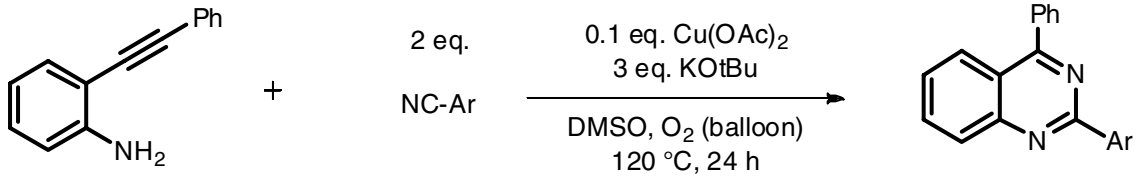
In recent decades, more emphasis has been placed on producing better medicines with fewer adverse effects. This



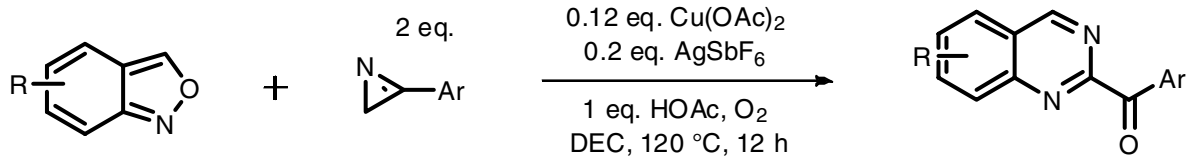
Scheme-LXXII: Synthesis of quinazoline derivatives using precatalyst and ligand



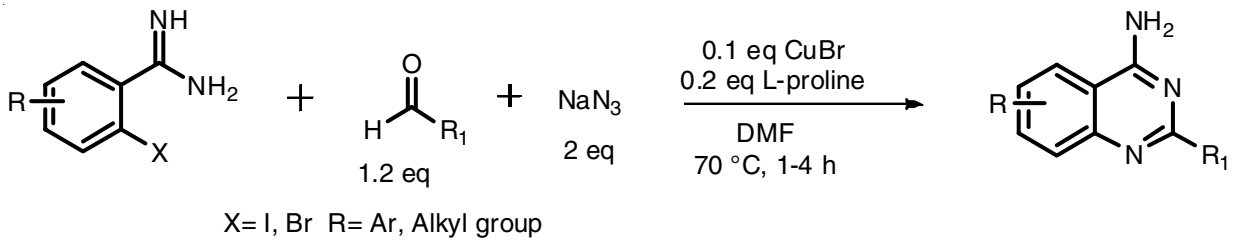
Scheme-LXXIII: Synthesis of quinazolines from 2-alkylamino N-H ketamine derivatives



Scheme-LXXIV: Synthesis of quinazoline derivatives using copper-catalyzed reaction of benzonitriles and 2-ethynylanilines



Scheme-LXXV: Annulation reaction of 3-aryl-2*H*-azirines



Scheme-LXXVI: Copper-catalyzed SNAr substitution for the synthesis of 4-aminoquinazoline

review article covers a wide range of synthetic techniques for 4(3*H*)-quinazolinone and quinazolinones analogs. The quinazoline moiety results in the formation of wide variety of products. The activity of quinazoline was determined by the substituent present at the favourable location. To emphasize the current advancement as in 4(3*H*)-quinazolinone analogs synthesis, a favoured analog mainly in the pharmaceutical chemistry for its medicinal potential managing various diseases. The complementarity of simple techniques aids the ability to build libraries of synthesized 4(3*H*)-quinazolinone variants. There is the possibility for future advancement when novel research in a related sector of medicinal chemistry is performed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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