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Graphical Abstract

Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue…

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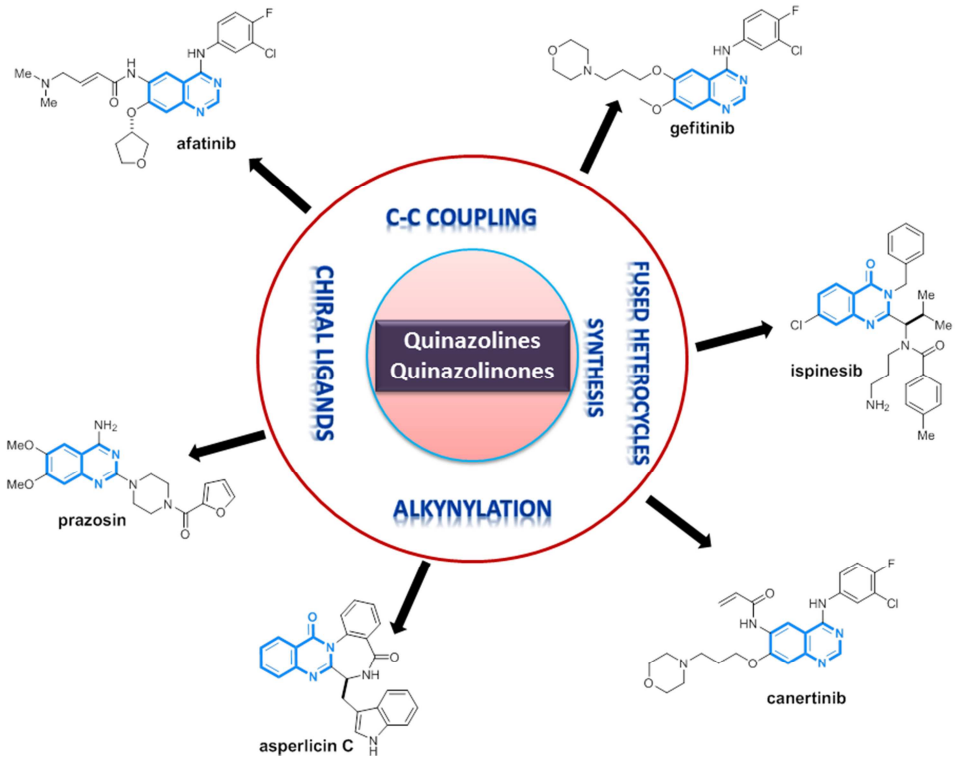
The current review article summarizes the recent developments in synthetic methodologies for the construction of quinazoline and quinazolinone heterocycles. Mechanistic investigations, applications, product manipulations and biological potential have also been discussed.



Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue…

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Abstract

The presence of *N*-heterocycles as an essential structural motif in a variety of biologically active substances has stimulated the development of new strategies and technologies for their synthesis. Among the various *N*-heterocyclic scaffolds, quinazolines and quinazolinones form a privileged class of compounds with their diverse spectrum of therapeutic potential. The easy generation of complex molecular diversity through broadly applicable, cost-effective, practical and sustainable synthetic methods in a straightforward fashion along with the importance of these motifs in medicinal chemistry, received significant attention from researchers engaged in drug design and heterocyclic methodology development. In this perspective, the current review article is an effort to recapitulate recent developments in the eco-friendly and green procedures for the construction of highly challenging and potentially bioactive quinazoline and quinazolinone compounds in order to help medicinal chemists in designing and synthesizing novel and potent compounds for the treatment of different disorders. The key mechanistic insights for the synthesis of these heterocycles along with potential applications and manipulations of the products have also been conferred. This article also aims to highlight the promising future directions for the easy access to these frameworks in addition to the identification of more potent and specific products for numerous biological targets.

Keywords: Bioactive heterocycles, Synthetic methods, Cross-coupling reactions, Inhibitors, Enzymes, Biological potential

1. Introduction

Nitrogen-containing heterocyclic compounds are the most abundant and integral scaffolds that occur ubiquitously in a variety of synthetic drugs, bioactive natural products, pharmaceuticals and agrochemicals. Owing to their widespread applications, these skeletons have long been a subject of immense interest, and substantial efforts have been made to the development of synthetic strategies which could lead to the discovery of new bioactive compounds in medicinal chemistry [1]. Indeed, with particular reference to the pharmaceutical industry, heterocyclic motifs are especially prevalent with over 60% of the top retailing drugs containing at least one heterocyclic nucleus as part of the overall topography of the compound [2].

Quinazoline and quinazolinone derivatives have attracted significant attention due to their diverse pharmacological activities such as antimicrobial [3], antimalarial [4], anti-inflammatory [5], antihypertensive [6], anticonvulsant [7], anti-diabetic [8], anticancer [9], cholinesterase inhibition [10], dihydrofolate reductase inhibition [11], and kinase inhibitory activity [12]. Quinazolines also exhibit a wide variety of biological functions like cellular phosphorylation inhibition [13], ligands for benzodiazepine and GABA receptors in the central nervous system [14], and some of them have acted as DNA binding agents [15]. They also act as effective α-adrenergic blocker, prazosin [16], bunazosin [17], and doxazosin [18], are useful medicines for antihypertensives, proquazone and fluproquazone as non-steroidal anti-inflammatory drugs, afloqualone as muscle relaxant, and diproqualone with sedative analgesic effects. KF31327 was developed as a heart disease remedy and an impotence medicine [19]. In a recent report, 3,4-dihydroquinazoline derivatives have been found to perform excellent T-type calcium channel blocking activity [20]. Some representative examples are displayed in Fig. 1.

<Figure 1>

Quinazolinone and their derivatives [21] are also building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals. Some of the compounds incorporating quinazolinone motif like raltitrexed and thymitaq possess antitumor activities [22].

A vast number of quinazoline derivatives have been synthesized to provide synthetic drugs and to design more effective medicines. There are a number of reviews [23] and monographs [24] on quinazoline and quinazoline alkaloids. Recently, we have documented a formal collection of significant developments (2013) [25] on the synthetic methods through which these heterocycles (quinazolines and quinazolinones) could be accessed, along with diverse biological profile which they possess. Some other groups also published independently the synthesis of quinazolinones [26] and bioactive quinazolines [27], respectively. There has been no discussion on the mechanistic aspects of key transformations. So, in corollary of these fascinating findings as well as part of a programme aimed at discovering heterocyclic structures with various pharmacological properties, in general [28], and in continuation of our previous work [25] on these skeletons, we report here the very recent developments (2014) in the environmentally benign, green, and efficient synthetic protocols (in most cases) to access quinazoline and quinazolinone derivatives from cheap and readily available commercial feedstocks. This review also focuses on the mechanistic insights for the synthesis of these cores for key reactions, while presenting successful synthetic applications and product manipulations along with an array of pharmaceutical and agrochemical applications.

2. Progress in Synthetic Methods

The number of new methodologies regarding the synthesis of quinazoline and quinazolinone cores has dramatically increased from year to year. All these transformations provide rapid

access to new and original quinazoline and quinazolinone compounds, affording the possibility of increasing structural diversity in a straightforward fashion starting from simple and common substrates. The subject matter of current review is aimed at providing a comprehensive overview of recent (2014) developments.

2.1. Synthesis of Quinazolines

In this part, we outline examples dealing with the synthesis of quinazoline skeleton from readily available feedstock.

Long and co-workers [29] developed a simple, fast and efficient divergent synthesis of a broad range of multisubstituted quinazolines **2** by utilizing readily available amidines **1** through iodine(III)-promoted oxidative $C(sp^3)-C(sp^2)$ and $C(sp^2)-N$ bond formation in nonpolar solvents (Scheme 1). Under a fixed set of optimized conditions, the scope of this annulation reaction was explored delivering a range of quinazoline products in excellent yields. Various aromatic groups with electron-withdrawing and electron-donating substituents at various positions were well tolerated, affording the corresponding quinazolines in good to excellent yields. However, the bulky naphthyl group gave quinazoline with lower yield. A significant extension in scope of the reaction was also highlighted by tolerating several other groups like bromo, chloro, or fluoro on the aniline ring.

<Scheme 1>

Vanelle and co-workers [30] unfolded a practical and efficient synthesis of 2,4,6,8-tetrasubstituted quinazolines **9** through one-pot chemoselective sequential bis-S_NAr/bis-Suzuki–Miyaura reactions under microwave irradiation (Scheme 2). This approach allows rapid and efficient access to desired products in high yields.

<Scheme 2>

Prajapati and co-workers [31] succeeded to develop an efficient aza-Diels–Alder protocol for the construction of 2,4-diaryltetrahydroquinazoline derivatives **13** (Scheme 3). The reaction proceeded well under both microwave and thermal conditions and can be tuned by varying the time to obtain dihydroquinazoline derivatives under thermal heating. The cascade nature of the transformation as well as in situ generation of both the diene and dienophile and their subsequent cycloaddition makes this methodology, atom and step economic. The strategy allowed exploring the scope of reaction with a range of substituted aldehydes and the results revealed that the nature of the substituent present in the aromatic ring of the aldehydes does not have any significant impact on the yield of the reaction. Aryl aldehydes with both electron-donating as well as -withdrawing substituents participated in the reaction smoothly with comparable yields. Overall, this one-pot method is simple, rapid and efficient, and provides an alternative for the construction of tetrahydroquinazolines in the absence of harmful organic solvents and additives.

<Scheme 3>

Baghbanian and Farhang [32] described an attractive synthesis of quinazoline derivatives **14** using magnetically separable and reusable $CuFe_2O_4$ nanoparticles in aqueous media (Scheme 4). Nano sized $CuFe_2O_4$ was prepared by the thermal decomposition of $Cu(NO_3)_2$ and $Fe(NO_3)_3$ in water in the presence of sodium hydroxide. Under optimized reaction conditions, various aromatic aldehydes afforded the corresponding products in high yields. The effect of the substituent on 2-aminobenzophenone and aldehyde derivatives with regard to the reaction time and yield has also been examined. In the presence of electron-withdrawing groups at the 5th

position of 2-aminobenzophenone, the reaction time increased compared with electron-donating groups.

<Scheme 4>

The possible mechanism for the synthesis of quinazolines using $CuFe_2O_4$ NPs as the clean catalyst is depicted in Fig. 2. The coordination of $CuFe_2O_4$ NPs with the carbonyl groups of 2-aminoaryl ketones and aldehydes could increase the electrophilicity of carbonyl carbons and enhance the subsequent nucleophilic attack of the amine group and NH_4OAc. Afterwards, the condensation of aldehyde with the amine leads to aldimine **16** and then this intermediate, by the attack of NH_4OAc to the keto group of benzophenone, gives ketimine **17**. Thereafter, intermediate **17**, via the ring closure forms intermediate **18**, which is followed by aromatization through dehydration in conjunction with oxygen from the air to give the quinazoline derivatives in good to excellent yields.

<Figure 2>

Zhang and co-workers [33] demonstrated an elegant synthesis of quinazoline derivatives **20** in good to excellent yields via reaction of *N*-arylamidine **19** and aromatic aldehyde **11** in air using CuO nanoparticles as a recyclable catalyst (Scheme 5). With the best reaction conditions, *N*-arylamidines with a range of substituents were exploited affording desired products with no significant effect on the yield, either with electron-donating or electron-withdrawing groups. However, the position of substituents has an obvious influence on the reaction. Furthermore, CuO nanoparticles can be recycled without significant decrease in catalytic activity.

<Scheme 5>

Kobayashi and Ezaki [34] developed an interesting synthetic procedure for the synthesis of quinazoline derivatives **26** by treating 2-(1-azidoalkyl)-phenyl isocyanides **22** with NaH in DMF at 0 °C via cyclization of 1-(2-isocyanophenyl)alkylideneamine intermediates (Scheme 6).

<Scheme 6>

Beifuss and co-workers [35] developed a facile and efficient CuI-catalyzed domino approach for the synthesis of quinazoline **29** by the reaction of 1-(2-bromophenyl)methanamines **27** and amidines **28** in a single step using K_3PO_4 as the base, pivalic acid as the additive, and aerial oxygen as the oxidant (Scheme 7). This method offers a new access to the desired products in 43-90% yield. Under optimized set of reaction conditions, the potential scope of this annulation was explored using a diverse range of amidinium salts as well as substituted bromophenyl methanamines.

<Scheme 7>

With regard to the mechanism of the CuI-catalyzed domino reaction between 1-(2-halophenyl)methanamines **27** and amidines **28**, it is assumed that either an intermolecular *N*-arylation/intramolecular nucleophilic substitution/aromatization sequence (Fig. 3, path A) or a domino intermolecular nucleophilic substitution/intramolecular *N*-arylation/aromatization is possible (Fig. 3, path B). However, after conducting control experiments, it is assumed that the reaction proceeds via pathway A.

<Figure 3>

Boulcina and co-workers [36] described an elegant, effective and simple one-pot methodology for the synthesis of 1,2-dihydroquinazolines **30** catalyzed by 4-(*N*,*N*-dimethylamino) pyridine

(DMAP) from readily available aromatic or heteroaromatic aldehydes **11**, 2-aminobenzophenone **14**, and ammonium acetate **12** under mild conditions (Scheme 8). Under the optimal reaction conditions, the generality of this one-pot transformation was investigated by employing several aromatic aldehydes. The results revealed that the electronic nature of the substituents on the benzene ring had no significant influence on the reactivity. An unsubstituted phenyl group or aryl groups with electron-donating substituents afforded high yields, as did those with electron-withdrawing groups. However, the presence of 2-chloro-, 4-*N*,*N*-dimethylamino-, or 4-hydroxy-groups on the aromatic ring produced slightly diminished yields of the products. Also, a variety of more challenging heterocyclic aldehydes were reacted in a similar manner with 2-aminobenzophenone and ammonium acetate.

<Scheme 8>

Based on the above observations, two plausible mechanistic pathways were proposed for the present protocol which involve DMAP as a base [37] (Fig. 4). The first reaction mechanism (path a) is proposed to proceed via the condensation of the aldehyde **11** with 2-aminobenzophenone **14** to furnish the corresponding aldimine **31** which on further condensation with ammonium acetate gives diimine **32**. Deprotonation of **32** with the catalyst produces carbanion intermediate **33**, which undergoes intramolecular cyclization to form the target 1,2-dihydroquinazoline **30**. In another possible mechanism (path b), the condensation of aldehyde **11** with NH_4OAc **12** results in the formation of aldimine **34**, which on further reaction with 2-aminobenzophenone **14** leads to the desired product **30**, after dehydration.

<Figure 4>

Trivedi and co-workers [38] developed an efficient green protocol for the synthesis of quinazolines **36** in the absence of solvent and catalyst. 2,4-Disubstituted quinazolines have been synthesized from three-component one-pot reactions of 2-aminoaryl ketones **14**, orthoesters **35**, and ammonium acetate **12** (Scheme 9). The scope and limitations of the present protocol were investigated using a variety of substituted 2-aminoaryl ketones and trialkyl orthoesters. The present method has several advantages including operational simplicity, substrate generality, clean reaction, and high yields (76–94%) of products with moderate reaction time.

<Scheme 9>

2.2. Synthesis of Quinazolinones

This section highlights the different processes used to establish quinazolinone structures from simple and readily available starting precursors in a straightforward fashion.

Liu and co-workers [39] designed a bifunctional IL catalyst, [$HDBU^+$][TFE^-], by neutralization of a superbase (DBU) and a weak proton donor (trifluoroethanol), and found to activate CO_2 and 2-aminobenzonitriles **37** simultaneously to produce quinazoline-2,4(1*H*,3*H*)-diones **38** in excellent yields under atmospheric pressure at room temperature (Scheme 10). Several substituents were tolerated on the aminobenzonitrile substrate which afforded desired products in pleasing yields. In addition, this IL could be easily recovered and reused without loss in its activity and could act as a highly efficient, greener, and stable bifunctional IL catalytic system.

<Scheme 10>

A possible mechanism for the [$HDBU^+$][TFE^-]-catalyzed reaction of CO_2 with 2-aminobenzonitrile **37** to give quinazoline-2,4(1*H*,3*H*)-dione **38** is proposed (Fig. 5). In [$HDBU^+$][TFE^-], 2-aminobenzonitrile is activated by hydrogen bonding with both the cation and

anion of the IL to form the intermediate **39**, while CO_2 is activated by the anion [TFE^-] to form the intermediate **40**. The nucleophilic nitrogen atom of **39** attacks the carbon atom of **40** to form the intermediate **41**, with subsequent nucleophilic cyclization of **41** to produced **42**, which is subsequently converted into **38** after regeneration of [$HDBU^+$][TFE^-] **43**.

<Figure 5>

Work by Zhang *et al*. [40] led to the development of a simple, versatile, efficient one-pot methodology for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **47**, **48** and quinazolin-4(3*H*)-ones **50**, **51** employing CuO nanoparticles as the catalyst (Scheme 11). In the case of amine as the substrates, the reactions afford 2,3-dihydroquinazolin-4(1*H*)-ones in good yields. However, when inorganic ammonium salts as the nitrogen source, the substrates undergo intramolecular electron transfer and rearrangement yielding quinazolin-4(3*H*)-ones (Scheme 12). The easy generation of molecular diversity along with the importance of quinazolinones in medicinal chemistry makes this process an appropriate alternative for the synthesis of potentially bioactive compounds. The important features of this protocol include inexpensive, recyclable, efficient CuO nanoparticles, ultrasonic irradiation and water as a medium to accelerate the reaction rate, and broad functional group tolerance.

<Scheme 11>

<Scheme 12>

Zhang and co-workers [41] investigated and developed an efficient cyclocondesation reaction of *o*-aminobenzonitriles **37** with cycloketones **52** catalyzed by a novel, convenient, more economic, and environmentally benign $SrCl_2$ modified SSA catalyst, in water to afford quinazolin-4-ones

53 (Scheme 13). The results revealed that electron-withdrawing substituents, such as nitro group, seems beneficial to the reaction and gives a higher product yield. It has also indicated that cycloketones with six membered ring are more active to react with enaminocarbonitriles.

<Scheme 13>

Cheon and Kim [42] developed an efficient, user-friendly and highly environmentally benign protocol for the synthesis of 2-substituted and 2,3-disubstituted quinazolinones **55** from anthranilamides **54** and aldehydes **11** via aerobic oxidative cyclization in wet DMSO without any additives (Scheme 14). Under the optimized reaction conditions, various aromatic aldehydes were readily applied to this protocol to investigate the substrate scope which afforded the desired products in high to excellent yields. Stereoelectronic nature of the aldehydes had a little effect on the product formation. Heteroaromatic aldehydes were also applied to this aerobic oxidation protocol without any sacrifice of its efficiency. In addition, this protocol could be extended to *α,β*-unsaturated aldehydes, such as cinnamaldehyde. Aliphatic aldehydes including formaldehyde were also tested in this protocol and the desired products were obtained in good to high yields. In general, this new protocol features operational simplicity, high atom economy, and broad substrate scope.

<Scheme 14>

Hajra and co-workers [43] demonstrated a remarkable and efficient Nano-In_2O_3-catalyzed one-pot three-component condensation of isatoic anhydride **44**, primary amine **45** or ammonium salts **12/49** and aromatic aldehydes **11** for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **56, 57** in aqueous media (Scheme 15). Having established reaction conditions, the scope of this cascade approach was explored by using a range of substituted aromatic aldehydes and amines.

Aldehydes as well as amines containing electron-donating (-OMe) group on the aromatic ring have shown good efficiency. On the other hand, In_2O_3 nanoparticles are easily recyclable without the significant loss of catalytic activities. In general, this one-pot protocol is also applicable on gram-scale synthesis. The significant advantages offered by this method include: (i) use of greener solvent, (ii) good yields, (iii) benign byproducts, (iv) low catalyst loading, and (v) simple operation.

<Scheme 15>

Han and co-workers [44] introduced a simple and novel synthetic route to quinazoline-2,4(1*H*,3*H*)-diones **58** under atmospheric pressure in high yields from the reaction of CO_2 with 2-aminobenzonitriles **37** in the presence of [Bmim]Ac which acts as a dual solvent–catalyst (Scheme 16). To demonstrate the generality of this approach to the synthesis of quinazoline-2,4(1*H*,3*H*)-diones, a range of 2-aminobenzonitrile derivatives were employed. The presence of an electron-donating group had a slight influence on the reaction. This highly-efficient, greener, inexpensive, active and stable catalytic system could potentially find wide applications in the generation of a library of quinazoline-2,4(1*H*,3*H*)-diones from CO_2 and 2-aminobenzonitriles under mild conditions.

<Scheme 16>

A plausible mechanism for the [Bmim]Ac-catalyzed formation of quinazoline-2,4(1*H*,3*H*)-dione **58** from the reaction of 2-aminobenzonitrile **37** and CO_2 is proposed as depicted in Fig. 6. Initially, the acetate anion attacks the amino group, captures a proton, and activates the reactant **37** to produce an intermediate **59** which on reaction with CO_2 rapidly leads to the formation of a carbamate ester **60**. An intramolecular nucleophilic cyclization of **60** affords intermediate **61**

which on subsequent rearrangement forms the isocyanate intermediate **62**, and then **63**. Finally, the title product **58** is obtained from the stabilization of **63**. In addition, the formation of the isocyanate intermediate **62** assisted by the *o*-cyano group appears to be important in the whole catalytic cycle [45].

<Figure 6>

Tajbakhsh and co-workers [46] developed an important and straightforward protocol for the synthesis of dihydroquinazolinones **65** and quinazolinones **66** using $H_3PW_{12}O_{40}$ as a recyclable catalyst in aqueous medium (Scheme 17). This procedure tolerates a range of aldehydes affording title products in ample yields. Sterically encumbered aldehydes are also found as effective coupling partners providing desired products in good yield. On the other hand, this catalyst system possess several advantages including high yields, short reaction times, easy work-up, green procedure avoiding toxic organic solvents, and the use of a readily available, inexpensive and relatively non-toxic catalyst.

<Scheme 17>

Wu and co-workers [47] developed an interesting and straightforward one-pot cascade procedure for the carbonylative synthesis of quinazolinones **68** from commercially available 2-aminobenzonitriles **37** and bromobenzenes **67** (Scheme 18). With the best reaction conditions in hand [$Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), K_2CO_3 (2.5 mmol), DMSO–H_2O (v/v = 1 : 1; 2 mL), CO (10 bar), 120 °C, 16 h], the generality and scope of this convenient methodology was investigated. In the first stage, substituents on 2-aminobenzonitriles were studied. Methyl-, methoxy-, fluoro-, chloro-substituted quinazolinones were produced in good yields from their parent substrates under identical conditions in 55-87% yields. Also, a number of aryl bromides

with various functional groups were tested subsequently. Methyl-, methoxy-, *tert*-butyl-, methylsulfanyl-, and *N*,*N*-dimethylamino- as typical electron-donating functional groups were checked and the corresponding quinazolinones were produced in 74–91% yields. The use of base like Na_2CO_3 or K_3PO_4 instead of K_2CO_3 gave inferior yields [48]. Remarkably, two representative examples of heteroaryl bromides were also successfully applied in this transformation.

<Scheme 18>

A plausible reaction mechanism for this transformation has been proposed in Fig. 7. The reaction started with the reduction of Pd(II) to Pd(0) **69**, followed by the oxidative addition of bromobenzene to Pd(0) affording the organopalladium species **70**. After the coordination and insertion of CO, the key intermediate acylpalladium complex **71** was formed. *N*-(2-Cyanophenyl)benzamide **72** was eliminated after nucleophilic attack of 2-aminobenzonitrile **37** to the acylpalladium complex **71**. Pd(0) can be regenerated under the assistance of base, ready to enter a catalytic cycle. In the presence of water and base, *N*-(2-cyanophenyl)benzamide **72** was hydrolysed into the corresponding *N*-(2-carbamoylphenyl)benzamide **73** which goes to the terminal quinazolinone **68** after intramolecular condensation and thermal 1,3-proton shift. The hydration of the cyano-group is a base induced transformation, and the palladium in this system might behave as a Lewis acid to further assistant K_2CO_3 in achieving the nitrile hydration. In addition, palladium may promote the condensation to give the final product as well.

<Figure 7>

In another study, Wu *et al*. [49] developed an impressive environmentally friendly and mild protocol to obtain 2,3-dihydroquinazolin-4(1*H*)-ones **74** from 2-aminobenzonitriles **37** and

aromatic aldehydes **11** using water as a cheap, green and harmless reaction medium with inorganic base (K_3PO_4) as the only promoter (Scheme 19). Various functional groups were tolerated under these conditions affording the desired products in variable yields. In general, electron-withdrawing groups on the aldehyde or the 2-aminobenzonitrile, respectively, led to the decrease of the yields. Also, methyl-substituents neighboring the cyano-group or the aldehyde function did not give the quinazolinone due to the steric hindrance. The electronic effect may be responsible for the results as well, as the ortho-methyl substituent decreases the activity of the nitrile group. This methodology can also be applied to non-α-protic aldehydes such as cyclohexane carboxaldehyde and isobutanal.

<Scheme 19>

Li and co-workers [50] successfully reported their findings that an iron-catalyzed one-pot single-step oxidative system could be easily applied for the conversion of primary alcohols **75** into quinazolinone derivatives **76** (Scheme 20). With various primary alcohols in hand, the scope of this annulation was investigated under standard reaction conditions. For different substituted benzyl alcohols with electron-donating and electron-withdrawing groups gave moderate to good yields. Notably, heteroaryl substrate like 2-furylmethanol was also examined and the corresponding product was obtained in 76% yield. In order to demonstrate the broad synthetic utility of this system, the investigation was extended to more challenging alkyl primary alcohols such as ethanol and octanol, and fortunately, the desired products were also afforded with moderate yields.

<Scheme 20>

Safari and Gandomi-Ravandi [51] synthesized a series of 2-aryl-2,3-dihydroquinazolin-4(1*H*)-ones **77** from sonication of anthranilamide **64** and an aldehyde **11** as precursors in the presence of Ag–CNTs as a novel catalyst (Scheme 21). This work consistently has the advantages of excellent yields, short reaction times, and simple experimental and work-up procedures. The heterogeneous catalyst could be recovered and recycled several times without any loss of its activity.

<Scheme 21>

In another study, Li and co-workers [52] produced a novel metal-free synthesis of quinazolinones **80** via dual amination of sp^3 C–H bonds (Scheme 22). A wide range of 2-amino benzamides **78** were employed for annulation with methylarenes **79** under the optimized conditions. Most of the toluenes with electron-donating and electron-withdrawing substituents could be converted to the desired products in moderate to good yields. On the other hand, the substituents at the phenyl ring of 2-amino benzamides did not affect the efficiency of this transformation.

<Scheme 22>

A possible mechanism is proposed as shown in Fig. 8. Initially, the homolysis of DTBP gave *tert*-butoxy radicals [53]. The benzyl radical was then generated by abstraction of H from toluene, and subsequent coupling of these two radicals produced the intermediate **82**. Then, **83** was generated from **82** via nucleophilic attack by **78** in the presence of TsOH, followed by oxidation to give **84**. Subsequently, **84** was converted to annulation product **80** via the second amination followed by oxidation.

<Figure 8>

Research group headed by Siddiki [54] reported an effective HBEA zeolite-supported Pt metal nanoclusters (Pt/HBEA) catalyst for direct dehydrogenative synthesis of quinazolinones **86** from *o*-aminobenzamide **64** and alcohols **75** under promoter-free conditions (Scheme 23). The general applicability of the present catalytic system was investigated by isolating a range of the quinazolinones in variable yields. Both electron-rich and electron-poor benzylalcohols were tolerated to give desired products in excellent isolated yields (82–95%). The reaction of a sterically hindered *o*-substituted benzylalcohol also proceeded in good yield. In addition, heteroaromatic alcohols with thienyl, furanyl and pyridinyl groups were also tolerated with good yields (75%, 65% and 78%, respectively). It is important to note that various aliphatic alcohols, including linear and branched aliphatic alcohols also worked well.

<Scheme 23>

Kaeobamrung and co-workers [55] uncovered a domino synthesis of quinazolinone derivatives **89** via a copper-catalyzed Ullmann-type coupling, an intramolecular Michael addition and a retro-Mannich reaction, under mild and simple reaction conditions (Scheme 24). Having established optimized conditions, the scope of the substrates in the copper-catalyzed domino reactions was investigated. A variety of *N*-substituted benzamides **87** and enaminones **88** were applicable for the copper-catalyzed domino reactions. As the size of the substituents on the enaminones increased, the yields of corresponding quinazolinones were dramatically diminished, demonstrating that steric hindrance, especially the substituents on the enaminones, played a crucial role in determining the product yields. On the other hand, *N*-Phenyl substituted benzamides gave low yields due to their low nucleophilicities for Michael additions.

<Scheme 24>

Cai and co-workers [56] developed an efficient and practical two-step protocol for the synthesis of 2-amino-4(3*H*)-quinazolinones **91** via ring-opening of isatoic anhydride **44** and palladium-catalyzed oxidative isocyanide insertion in one-pot (Scheme 25). This regioselective procedure could construct a wide range of 2-amino-4(3*H*)-quinazolinones in moderate to excellent yields. Under the optimized conditions, the reaction occurs smoothly using a variety of amines, isocyanides and isatoic anhydrides. Various amines, including aryl and alkyl amines were also well tolerated. Benzyl amines bearing both electron-rich and electron-deficient aromatic ring furnished the desired products in high yields. With regard to amines bearing heterocycles, the corresponding products were isolated in high yields. Next, scope of this process was extended to isocyanide component which afforded desired products in appreciable yields. When cylcohexyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide were employed instead of *tert*-butyl isocyanide, the reaction worked as expected giving corresponding products in high yields. In addition, the use of different isatoic anhydrides containing electron-donating and halogen groups reacted efficiently, affording expected products in moderate to high yields. Overall, the methodology also had distinct advantages of easily accessible starting materials and operational simplicity.

<Scheme 25>

The proposed mechanism (Fig. 9) starts with the ring-opening reaction of isatoic anhydride **44** with amine **45** generating the bis-nucleophile **90**. Catalyst **92** reacts with the bisnucleophile **90** to form the intermediate **93**. Then, isocaynide insertion reaction occurs, resulting in the species **94** which on subsequent reductive elimination affords the product **91**. Pd(0) species is stabilized by

coordination of multiple isocyanides and then oxidized by silver carbonate to regenerate the catalyst.

<Figure 9>

Chen *et al*. [57] disclosed an efficient and convenient metal-free aerobic oxidative C–N bond cleavage of tertiary amines **95** to construct *N*-heterocycles **96** using molecular oxygen as the sole oxidant with high atom efficiency (Scheme 26). Under the optimized reaction conditions, the substrate scope of this reaction was investigated where *o*-substituted anilines could readily react with aliphatic tertiary amines to produce the corresponding quinazolinone derivatives. It should be noted that the reactivity of the oxidative cyclocondensation was independent of the alkyl chain length, and different aliphatic tertiary amines could efficiently undergo oxidative cyclocondensation with *o*-substituted anilines, giving the quinazolinone derivatives in high yields. On the other hand, several substituted *o*-aminobenzamides with various functionalities also led to the desired products on reaction with tertiary amines.

<Scheme 26>

Based on above results and the reported literature [58], the reaction possibly takes place as shown in Fig. 10. Initially, in the presence of molecular oxygen, the tertiary amine **95** is oxidized to *N*-oxide **97**, followed by protonation to form **98** under suitable pH conditions. Dehydration of **98** affords the immonium ion **99**, which is readily hydrolyzed to produce a secondary amine and an aldehyde [59]. Finally, *N*-heterocyclic compound **96** is produced by condensation/oxidative dehydrogenation of in situ aldehyde with *o*-substituted aniline.

<Figure 10>

Cheng *et al*. [60] successfully synthesized a series of biologically important 4(3*H*)-quinazolinones **101** from readily available 2-amino-*N*-methoxybenzamides **100** and aldehydes **11** via a cascade reaction in good to excellent yields (Scheme 27). By this process, under optimal reaction conditions, the title compounds were readily generated providing insights into the scope and generality of this new one-pot protocol. The results also revealed that several substituted aldehydes bearing electron-withdrawing groups led to the desired products. The method was equally well tolerable of the benzaldehydes bearing electron-rich substituent. In the case of di-substituted benzaldehydes, bearing either electron-withdrawing or electron-donating group, the desired products were obtained in even better yields.

<Scheme 27>

Jiang and co-workers [61] established a novel palladium-catalyzed three-component cascade reaction for the synthesis of quinazolin-4(3*H*)-ones **104** from readily available 2-aminobenzamides **64** and aryl halides **102** via a palladium-catalyzed isocyanide insertion/cyclization sequence (Scheme 28). The scope and generality of this process was investigated using anthranilamides and various aryl halides under optimized reaction conditions. From results it could be concluded that most of the aryl iodides with electron-donating groups give better results than the substrates with electron-withdrawing groups. However, substrates with electron-donating group, *p*-phenyliodobenzene gave a poor yield. The suitability of electron-poor substituents including *p*-fluoro, *p*-chloro, and *p*-trifluoromethyl groups was evaluated which gave the desired products in 41−86% yield. Also, heteroaromatic substrates were converted to the corresponding product in good yield. Overall, this methodology efficiently constructs quinazolin-4(3*H*)-ones in moderate to excellent yields with the advantages of operational simplicity.

<Scheme 28>

A plausible mechanism for this reaction is depicted in Fig. 11. Oxidative addition of aryl halides **102** to the Pd(0) catalyst **105** facilitates the formation of palladium complex **106**, followed by *tert*-butyl isocyanide **103** insertion to get palladium(II) species **107**. Then, under the assistance of *t*-BuONa, the addition of 2-aminobenzamide **64** gives the generation of **108**, which leads to the desired 4(3*H*)-quinazolinones **104** after cyclization with losing *tert*-butylamine.

<Figure 11>

Sarva and co-workers [62] disclosed a simple and highly efficient synthesis of 2-substituted quinazolin-4(3*H*)-ones **110** by the iron(III) chloride catalyzed reaction of isatoic anhydride **44** with various amidoxime derivatives **109** (Scheme 29). The scope of the method was evaluated by using a variety of substituted aryl amidoximes under the optimized conditions, and the results gratifyingly gave the desired products in high yields regardless of the nature of the substituents on the amidoxime. Interestingly, neither electron-donating (methyl, 4-hydroxy, 4-methoxy, 4-amino, or 4-methylsulfanyl) nor electron-withdrawing groups (4-bromo or 4-nitro) on the amidoxime had any effect on the reaction profile and yield. Heteroaromatic aldoximes also gave the corresponding quinazolinones in good yields. Furthermore, several alkyl amidoximes afforded similar results.

<Scheme 29>

Pouramini and Tamaddon [63] discovered an efficient process for the synthesis of quinazolinones **111** via reaction of 2-aminobenzonitrile **37** with carbonyl compounds **11** using macroporous Amberlyst A26 OH in H_2O–EtOH (Scheme 30). To define the scope of the A26

OH-catalyzed synthesis of 2-substituted 2,3-dihydro-4(1*H*)-quinazolinones, various aldehydes were reacted with 2-aminobenzonitrile under optimized reaction conditions. The electronic effects of the substituents of the aldehydes had little effect on the yield, and the products were isolated in high purity by simple filtration of the catalyst and addition of cold water.

<Scheme 30>

The mechanistic cycle (Fig. 12) involve the initial hydration of 2-aminobenzonitrile to **112** occurred efficiently, giving a 93% yield of the corresponding amide. Condensation of the isolated intermediate **112** with benzaldehyde under similar conditions yielded 2-(phenyl)-2,3-dihydro-4(1*H*)-quinazolinone in excellent yield.

<Figure 12>

Alizadeh and co-workers [64] developed an efficient dual-catalyst system of piperidine and molecular iodine for the synthesis of 2-alkyl-2-(2-oxo-2*H*-chromen-3-yl)-2,3-dihydro-4(1*H*)quinazolinone derivatives **116** by a four-component reaction of salicylaldehydes **114**, *β*-keto esters **115**, ammonium acetate **12**, and isatoic anhydride **44** (Scheme 31). The products were obtained in good yields under mild reaction conditions. This protocol tolerates a variety of salicylaldehydes containing both electron-withdrawing and electron-donating substituents.

<Scheme 31>

Li and co-workers [65] disclosed an efficient strategy to access 2-hetarylquinazolin-4(3*H*)-ones **118** via copper-catalyzed direct aerobic oxidative amination of sp^3C-H bonds using cheap and readily available (2-azaaryl)methane **117** (Scheme 32). Having developed a set of standard reaction conditions, a range of substrates were applied in this oxidative amination process to

produce the corresponding 2-hetaryl-quinazolin-4(3*H*)-one products in good yields. The heteroaryl substrates include pyridine, quinoline, pyrazine, quinoxaline, and benzothiazole with different substituent pattern. All these substrates were well tolerated in this transformation affording corresponding products in efficient yields. On the other hand, suitability of the benzamide core was also assessed. Chloro- and methyl-substituted benzamides produced oxidative condensation products in ample yields. Overall, this tandem oxidation−amination−cyclization transformation represents a straightforward protocol to prepare 2-hetaryl-substituted quinazolinones from simple starting materials.

<Scheme 32>

Wu and co-workers [66] developed an efficient, novel and convenient method for the synthesis of quinazolinones **122** from 2-bromoformanilides **119** and organo nitros **120** as substrates, under palladium catalysis (Scheme 33). $Mo(CO)_6$ **121** is used as multiple promoter in this process delivering the desired products in moderate to excellent yields. Under suitable reaction conditions, the scope and limitations of this methodology were examined using a range of substituents like methyl-, isopropyl-, and *tert*-butyl- on nitrobenzene. 1-Nitronaphthalene also gave the corresponding 3-(naphthalen-1-yl)quinazolin-4(3*H*)-one in 81% isolated yield. Moreover, several electron-withdrawing groups substituted aromatic nitro compounds were tested subsequently, which afforded moderate to excellent yields. However, this procedure seems quite sensitive to the steric property of the substrates. On the other hand, 2'-bromoformanilides with a variety of electron-rich and electron-poor functional groups were tolerated which provided different quinazolinones in 63-83% yields.

<Scheme 33>

A plausible reaction pathway is proposed and given in Fig. 13. Initially, oxidative addition of 2'-bromoformanilide **119** to Pd(0) afforded organopalladium intermediate **123** which on coordination and insertion of CO, released from $Mo(CO)_6$, gave acylpalladium complex **124** as the key intermediate. At the same time, nitro compound was reduced by $Mo(CO)_6$ to form an amine which acts as a nucleophile to attack on the acylpalladium complex. Finally, the eliminated 2- formamido-*N*-phenylbenzamide **125** gave the final quinazolinone product **122** after intramolecular condensation which was promoted by palladium or molybdenum salts as Lewis acids.

<Figure 13>

Liu and co-workers [67] demonstrated the synthesis of 2-thioxoquinazolinone derivatives **126** achieved by the condensation of isatoic anhydride **44**, primary amine, and carbon disulfide under microwave irradiation (Scheme 34). The scope was examined with regard to the amine component where aliphatic and aromatic amines bearing electron-rich and electron-poor substituents worked efficiently delivering desired products in good to excellent yields. Also, amines with heterocyclic moiety were also tolerated smoothly. In general, this convenient and efficient method affords the desired products with good to excellent yields under mild conditions with operational simplicity.

<Scheme 34>

Balalaie and co-workers [68] introduced a wide variety of spiroquinazolinone derivatives **129** accessed through a one-pot three-component reaction of isatoic anhydride **44**, hydrazides **127** and cyclic ketones **128** in the presence of catalytic amount (20 mol%) of H_3PO_3 in ethanol (Scheme 35). A range of cyclic ketones were reacted with ISA **44** to examine the scope of this

methodology. The reactions proceeded smoothly in all these cases to afford the corresponding spiro 2,3-dihydroquinazolin-4(1*H*)-ones in good to high yields. It was also notable to observe the influence of ring size on the yield of products. For example, the use of cyclopentane instead of cyclohexane led to lower yields. The type of hydrazide has also efficient role in the yields of products.

<Scheme 35>

2.3. Synthesis of hybrid skeletons

In this section, different methods for the construction of quinazoline- and quinazolinone-hybrid structures from simple starting materials are highlighted.

Guo *et al*. [69] reported an efficient and facile procedure for the preparation of 5,6-dihydropyrazolo[1,5-*c*]quinazolines **131** via CuCl-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles **130** with aldehydes **11** and aqueous ammonia under nitrogen atmosphere (Scheme 36). With the optimized reaction conditions in hand, a variety of aldehydes were reacted with 5-(2-bromoaryl)-1*H*-pyrazoles to investigate the scope of this protocol. The effect of substituents on phenyl ring of aldehydes was examined and the results indicated that electron-donating (Me, MeO, Cl, Br, and F) reacted very well with **130** and aqueous ammonia to afford the desired products **131** in 65-86% yields. 1-Naphthaldehyde and thiophene-2-carbaldehyde also underwent the tandem reactions smoothly, thus generating the corresponding products in 85% and 65% yields, respectively. In addition, alkyl-substituted aldehydes were also found to be compatible with the reaction conditions to provide corresponding conjugated products in 51 and 76% yields. Next, pyrazoles **130** with different substitution patterns were examined, and it was found that the electronic effect and steric hindrance of R^1 and R^2 groups on pyrazoles **130** did not influence the formation of products.

<Scheme 36>

Kumar and Kumar [70] were able to develop a microwave accelerated and expedited cyclocondensation reactions of 2-(3-aryl-1*H*-pyrazol-5-yl)anilines **132** with diverse aryl aldehydes **11** in water to access quinazoline derivatives **133** (Scheme 37). In order to assess the generality and scope of the reaction, **132** was treated with equimolar amount of various aryl aldehydes under the optimized reactions conditions that is microwave in water for 5-15 min.

<Scheme 37>

Chen *et al*. [71] developed a new and facile approach for the synthesis of fused quinazolinone scaffolds **136**, **137** through a palladium-catalyzed carbonylative coupling followed by an intramolecular nucleophilic aromatic substitution (Scheme 38). In this process, base serves as the key modulator. The scope and limitations of this methodology were focused by tolerating a variety of analogues of 1-bromo-2-fluorobenzene which delivered the corresponding products in moderate to good yields. Notably, 4- and 5-substituted substrates gave better yields than 3-substituted substrates. Interestingly, 2-bromo-4-(difluoromethyl)-1-fluorobenzene was successfully converted into the desired product in 60% yield. Chloride substituents and acetyl groups remained intact under reaction conditions to provide valuable products in moderate to good yields. Subsequently, different kinds of 2-aminopyridines were investigated. Methyl- and fluoro-substituted products were isolated without any problem. However, halides attached to the pyridine ring also reacted.

In the case of the angular products, steric and electronic modification of the substrates did not influence the outcome of the reactions. Ortho-methyl- and cyano-substituted 2-aminopyridines delivered the corresponding products in 72 and 64% yield. A methyl group at the para position as

a representative example of an electron-donating group was tolerated well. Substrates with electron-deficient *p*-cyano, *p*-fluoro, and *p*-chloro substituents were also converted into the corresponding angular isomers in moderate yields.

<Scheme 38>

A proposed catalytic cycle for this reaction is given in Fig. 14. The formation of the active catalyst takes place by the reduction of Pd(II) to Pd(0) with CO or amines. The oxidative addition of 1-bromo-2-fluorobenzene **134** to Pd(0) then leads to the corresponding organopalladium species **138**. By the coordination and insertion of CO, the key intermediate acyl palladium complex **139** is formed. In the presence of DBU, 2-imino-2*H*-pyridin-1-ide **140** undergoes nucleophilic attack on the acyl palladium complex **139** with the elimination of **141**. On the other hand, in the presence of NEt_3 as the base, the nucleophilic reaction of 2-aminopyridine with the acyl palladium complex yields compound **142**. Finally, intramolecular nucleophilic aromatic substitution of intermediate **141** or **142** affords the terminal linear **136** or angular product **137**, respectively. The active Pd(0) catalyst is regenerated with the assistance of the base.

<Figure 14>

Vlaar *et al*. [72] have shown that azoles are suitable nucleophiles in the Pd(II)-catalyzed aerobic oxidative coupling of bisnucleophiles and isocyanides. Various medicinally important azolo[*c*]quinazolines **144** or **145** were readily obtained by oxidative coupling of *a*-(2-aminophenyl)azoles **143** with isocyanides **103** using air as the stoichiometric oxidant (Scheme 39). A range of triazole substrates were involved in the Pd-catalyzed coupling with *tert*-butyl isocyanide using the optimized reaction conditions. Pleasingly, a wide range of (hetero)-aromatic

groups the triazole (R^2 position) were subjected to annulation on after minor tuning of the catalyst loading and reaction time. The compatibility of the isocyanides in this reaction was also tested.

<Scheme 39>

Shekarrao *et al*. [74] developed an efficient method for the synthesis of pyrazole fused heterocycles such as pyrazolo[1,5-*a*]quinazolines **148** via the palladium-catalyzed solvent-free reaction of *β*-halovinyl/aryl aldehydes **146** and 3-aminopyrazoles **147** under microwave irradiation in good yields (Scheme 40). Good functional group compatibility was demonstrated with *β*-bromovinyl aldehydes substituted with fluoro- and methyl phenyl rings.

<Scheme 40>

Akbarzadeh and co-workers [74] reported an efficient and novel synthesis of benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives **150** through a 7-*exo*-dig hydroamination of 3-substituted-2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones **149** in the presence of potassium *tert*-butoxide (KO*t*-Bu) in DMF at 130 °C (Scheme 41). Initially, various 2-aminobenzamide derivatives **64** were prepared by the reaction of equimolar amounts of isatoic anhydride **44** and amines **45** in water at room temperature for 2–3 h. Next, these were efficiently reacted with a range of 2-(prop-2-yn-1-yloxy)benzaldehyde derivatives in the presence of potassium carbonate (K_2CO_3) in DMF at 80 °C to give 3-substituted 2-[2-(prop-2-yn-1-yloxy)phenyl]-2,3-dihydroquinazolin-4(1*H*)-ones in good yields (60–75%) which were cyclized to final products using potassium *tert*-butoxide (KO*t*-Bu). Under standard reaction conditions, various benzo[6,7][1,4]oxazepino[4,5-*a*]quinazolinone derivatives were accessed using substrates with both electron-rich as well as electron-poor substituents on aromatic rings.

<Scheme 41>

Li *et al*. [75] were able to combining commercially available bromoanilines **152** and bromobenzonitriles **151** in a novel double carbonylation process providing access to a straightforward synthesis of isoindolo[1,2-*b*]quinazoline-10,12-diones **153** (Scheme 42). Under optimized reaction conditions, generality and limitations of this methodology was explored using 2-bromobenzonitrile with nine different bromoanilines and the corresponding products were obtained in pleasing yields. Aniline with chloro substituent was found to stay intact under these conditions, and a good yield (70%) of corresponding product was obtained. Anilines with electron-withdrawing substituents were submitted to this reaction which afforded the desired products in 57–63% yield. Gratifyingly, when acetyl substitued aniline was reaction partner, reaction worked-well, delivering fused product in 87% isolated yield. Similarly, 82% of the desired product was produced by using the corresponding cyano-substituted 2-bromoaniline as a substrate. To further demonstrate the applicability of this procedure, a range of 2-bromoaniline with ten different 2-bromobenzonitriles were reacted in this coupling reactions. In general, good yields of products were obtained with methyl, methoxy, fluoro or iodo substituents on benzonitrile part.

<Scheme 42>

The mechanistic cycle (Fig. 15) starts with the first aminocarbobylation of bromoaniline **152** and bromobenzonitrile **151** to afford amide **154** (**cycle A**). It is also noteworthy that the oxidative insertion of the active palladium species occurs preferentially at **152** due to the higher reactivity. Next, base-catalyzed isomerization–cyclization forms the iminoisoindolinone **155** [76].

Interestingly, unexpected isomerization of **155** to **156** occurs, probably due to steric effects. Subsequent intramolecular carbonylative coupling forms **153** as the final product (**cycle B**).

<Figure 15>

In a following study, the same group [77] developed a convenient procedure for the carbonylative synthesis of isoindoloquinazolinones **159** by using 1,2-dibromobenzenes **158** and 2-aminobenzyl amine **157** as substrates under palladium catalysis (Scheme 43). The desired products were isolated in moderate to good yields with the installation of two molecules of carbon monoxide. With the best reaction conditions, several derivatives of isoindoloquinazolinones were produced and isolated in moderate to good yields. 1,2-Dibromo-4,5-dimethoxybenzene was also used as a substrate affording corresponding product in 84% yield. Moderate yields of the desired products were isolated when similar electron property substrates were applied.

<Scheme 43>

Sorra and co-workers [78] achieved the first total synthesis of (–)-auranomide C **173** which incorporate quinazolinone moiety. The short synthetic strategy involves a reductive dehydrocyclization and the nucleophilic ring opening of a fused *γ*-lactam. The synthetic approach started with the reductive amination of dimethyl glutamate **160** with benzaldehyde using sodium borohydride to afford the *N*-benzyl glutamate **161** (Scheme 44) which was coupled with 2-nitrobenzoyl chloride to afford **162** in 61% yield over two steps. The reduction followed by concomitant cyclization of **162** furnished 1,4-benzodiazepine-2,5-dione **163** in 82% yield with >99% ee. At this point, compound **163** was converted to **168** through two different pathways.

<Scheme 44>

On the other hand, the dilactam compound **169** was synthesized by the dehydrocyclocondensation of isatoic anhydride **44** with glutamate **160** in good yield (Scheme 45). The intramolecular cyclization of **169** to the tricyclic intermediate **170** was accomplished by heating in dimethylacetamide (DMA) at 180 °C [79]. It was gratifying to note that the amidation of compound **170** with 2-nitrobenzoyl chloride followed by reductive dehydrocyclization proceeded smoothly to furnish compound **172** in good yields and high enantiomeric excess (>98%). The final stage, nucleophilic ring opening of fused *γ*-lactam **172** with ammonia, afforded auranomide C **173** in high yield with 97.7% ee [80].

<Scheme 45>

Cui and co-workers [81] reported a new strategy for the synthesis of indole-fused quinazolinone derivatives **176** through Rh(III)-catalyzed selective coupling of *N*-methoxy-1*H*-indole-1-carboxamide **174** and aryl boronic acids **175** (Scheme 46). The coupling is mild and efficient toward diverse product formation, with selective C−C and C−C/C−N bond formation. A broad range of indoles and aryl boronic acids were amenable to the reaction. Functionalized boronic acids with methyl, phenyl, methoxy, chloro, bromo substitution and polysubstituted boronic acids were compatible with the oxidative coupling system to deliver the cyclized 5-methoxyindolo[1,2-*c*]-quinazolin-6(5*H*)-ones in moderate to good yields. The slightly lower yields of products were observed due to the electron-withdrawing nature and steric hindrance of the starting boronic acids. Structurally and electronically varied indoles were also explored and found applicable in this coupling furnishing the corresponding cyclized heterocycles in moderate to good yield.

<Scheme 46>

Mechanistic cycle (Fig. 16) for this transformation starts with the *N*-metalation of **174** in the presence of Cp*Rh(III) to form intermediate **177**, which on an intramolecular electrophilic addition of lead to the seven-membered rhodacycle **178**. Subsequent reductive elimination would afford the [4 + 2] cyclization product **176** and the Rh(I) species. Reoxidation of Rh(I) to Cp*Rh(III) by Ag_2O to start a new catalytic cycle.

<Figure 16>

Decker and co-workers [82] reported a novel, short and versatile method for expeditious syntheses of rutaecarpine and its analogues **179**, **180** giving high yields from a simple heterocyclic fusion reaction of isatoic anhydride **44** involving a spontaneous dehydrogenation upon heating (Scheme 47). This process avoids tedious purification procedures, multi-step syntheses, and any special reagents or starting materials. Applying this fusion reaction, 20 different analogues were generated.

<Scheme 47>

2.4. Functionalization of quinazoline and quinazolinone skeletons

This section will focus on the utilization of quinazoline and quinazolinone cores as synthetic intermediate or chiral ligands for further key transformations.

2.4.1. Dual amination of sp^3 C–H bonds

Li and co-workers [83] developed a facile and efficient approach for the synthesis of imidazo[1,5-*c*]-quinazolines **183** by an *n*-Bu_4NI catalyzed domino reaction that involves

selective dual amination of sp^3 C–H bonds under mild conditions (Scheme 48). The scope of this protocol was examined by treating various benzylamines **182** with 4-methyl-2-phenylquinazoline **181** to afford the corresponding imidazo[1,5-*c*]quinazolines showing high functional group compatibility. It has been observed that the steric hindrance had little influence on the reaction. In all cases, both electron-donating and electron-withdrawing substituents in the phenyl ring were well tolerated, and gave pleasant yields. Notably, functional groups such as F, Cl and Br were also compatible with the reaction conditions, which provided an additional handle for further functionalization of the products. Moreover, naphthalen-1-ylmethanamine and several heterocyclic benzylamines were also proved applicable, giving the desired products in good yields. On the other hand, a variety of quinazolines were also reacted smoothly. With regard to quinazolines part, substitution at 2-position with alkyl, methoxy, fluoro and chloro groups were well tolerated to deliver expected products with excellent yields, and those with strong electron-withdrawing groups, such as trifluoromethyl and nitro group still gave target products in good yield.

<Scheme 48>

2.4.2. Buchwald-Hartwig amination

Nowak *et al*. [84] reported the synthesis of 6-(morpholin-4-yl)benzo[*h*]quinazolin-4(3*H*)-one derivatives **191** prepared by Buchwald-Hartwig conditions by reacting 6-bromobenzo[*h*]quinazolin-4(3*H*)-ones **190** with morpholine in the presence of a $Pd(OAc)_2$/XantPhos system in 1,4-dioxane as solvent (Scheme 49). The starting 6-bromobenzo[*h*]quinazolin-4(3*H*)-ones **189** were synthesized via condensation of the ethyl 1-

amino-4-bromonaphthalene-2-carboxylate **188** with formamide, and then reaction of the obtained benzoquinazolinone **189** with appropriates benzyl bromides.

<Scheme 49>

2.4.3. Free radical cyclization

Al-Said and co-workers [85] described an efficient synthetic protocol based on a free radical cascade reaction for the synthesis of a new heterocyclic compound with appropriate substituents to access benzoazepinoquinazolinones which should allow the formation of cyclopropanequinone system found in duocarmycins. This methodology starts with the condensation of anthranilamide **64** with 5-hydroxy-2-bromobenzaldehyde **192** (Scheme 50). Initially an iodine-catalyzed aerobic oxidative cascade coupling of **64** with **192** in refluxing ethanol for 48 h, afforded 2-aryl-substituted quinazolinone derivative **194**. The radical acceptor was introduced by *N*-allylation of **194** with (*E*/*Z*)-1,3-dichloropropene under standard reaction conditions (acetone, K_2CO_3). This reaction afforded the expected product **195** in 80% yield. The reaction of **195** in benzene at reflux temperature under N_2, afforded the cyclized product seco-cyclopropaneazepinoquinazolinone derivative **198** in reasonable yield (45%). Similar free radical rearrangements have been observed in cyclopropylfurano[*e*]indoline systems [86].

<Scheme 50>

2.4.4. As chiral ligands in catalytic enantioselective processess

Karabuga and co-workers [87] synthesized a series of readily known enantiomerically pure 3-aminoquinazolinones from easily accessible chiral pool α-hydroxy acids and α-amino acids. These quinazolinones were examined as chiral ligands for catalytic enantioselective diethylzinc and phenylacetylene additions to aldehydes **11** (Scheme 51). Under standard conditions, the

desired chiral alcohols **199** were obtained in up to 86% ee. 3-Aminoquinazolinones were also shown to be very useful ligands in enantioselective alkynylations of aldehydes. Based upon the optimized conditions, the corresponding propargylic alcohols **200** were obtained in up to 94% ee.

<Scheme 51>

2.4.5. NIS-mediated regioselective amidation

Nagarajan and Ghosh [88] developed an efficient, metal-free methodology for direct amidation regioselectively at C2 in indoles and pyrroles with quinazolinones (Scheme 52). A series of novel indolyl- and pyrrolylquinazolinones (**202** and **203)** were prepared with free or protected indoles and pyrroles. Under optimized conditions, the generality and scope of the reaction was explored for a range of 3-substituted indole, as well as 1,3-disubstituted indole, with quinazolinone derivatives. From results it could be revealed that a variety of functional groups such as moderate electron-withdrawing and electron-releasing groups in substituted indoles were well tolerated to give moderate to good yield of indolylquinazolinone products. When electron-donating substituents at indole C3 were coupled with quinazolinones, a good yield of the corresponding products was obtained. However, 6-bromoquinazolinone and benzoquinazolinone, which are electron-deficient, gave a lower yield of the product, whereas when methyl was substituted with a moderate electron-withdrawing group, the yields of the corresponding products remained almost unaffected. The reaction scope was also extended to the pyrrole substrates which also proved to be the competent partners. Furthermore, a highly functionalized 1,3-diazepine compound **205**, which might be a useful bioactive macrocycle, was accessed by the manipulation of product (Scheme 53).

<Scheme 52>

<Scheme 53>

The potential mechanistic cycle (Fig. 17) involves the iodination on C3 of indole with NIS producing the intermediate **206**, which undergoes an immediate nucleophilic substitution with the iminol form **207** to generate the intermediate **208**. Then, subsequent elimination of HI led to the expected product **202**.

<Figure 17>

2.4.6. Addition of *α*-Lithiated Nitriles to quinazolines

Anderson and co-workers [89] reported a procedure for the addition of *α*-deprotonated nitriles to azaheterocycles such as quinazolines **209** followed by rearomatization (Scheme 54). Using the optimized one-pot procedure, the scope of secondary nitriles was evaluated in the reaction sequence. Simple nitriles performed best in this reaction. Common amine protecting groups such as Boc, Bn, and Cbz were unaffected in the synthetic sequence. In addition, both the 2-chloroquinazoline and ethyl quinazoline-2-carboxylate gave products with reduced yields. The compound with methyl ketone derivative gave product in 37% yield [90].

<Scheme 54>

2.4.7. Cross-coupling reactions of quinazolines

Mphahlele and co-workers [91] reported the Sonogashira cross-coupling of 2-aryl-6,8-dibromo-4-chloroquinazolines **211** with terminal acetylenes at room temperature to afford novel 2-aryl-6,8-dibromo-4-(alkynyl)quinazoline derivatives **212** (Scheme 55). Further transformation of the 2-aryl-6,8-dibromo-4-(phenylethynyl)quinazolines via Suzuki-Miyaura cross-coupling with arylboronic acids occurred without selectivity to afford the corresponding 2,6,8-triaryl-4-

(phenylethynyl)quinazolines **213**. The absorption and emission properties of these polysubstituted quinazolines were also determined.

<Scheme 55>

2.4.8. Selective debenzylation of dihydroquinazolinones and tetrahydroquinazolines

Decker and co-workers [92] developed conditions for the selective cleavage of different benzyl bonds within tetrahydroquinazoline and dihydroquinazolinones derived structures by employing different reduction and debenzylation conditions, thereby providing selective removal of *O*-benzyl protection groups as well as the cleavage of the ring structure within the quinazoline and quinazolinone systems (Scheme 56).

<Scheme 56>

2.4.9. In the synthesis of bioactive fused-heterocycles

Sarg and co-workers [93] synthesized numerous bioactive heterocycles based on quinazoline and quinazolinone motifs (Scheme 57). Starting with the synthesis of 2-methyl-quinazolin-4-one **223** from the fusion of anthranilic acid **221** with thioacetamide **220**, which was utilized as a building unit for novel quinazoline and fused quinazolinone compounds under different set of conditions. The extent of the pharmacological effect of a quinazolinone derivative depends on the active group which is attached to it. Recently, several reports elucidated that in quinazolinone system sites like position 2 and 3, can be suitably modified by the introduction of various heterocyclic moieties to show excellent pharmacological results [94].

<Scheme 57>

2.10. Alkynylation of quinazolines

Peng and co-workers [95] described a coupling reaction of quinazoline-4-tosylates **230** with terminal alkynes **231** using *N*-heterocyclic carbenes (NHC) as ligands providing 4-alkynylquinazolines **232** in good to excellent yields under Pd-Cu cocatalysis (Scheme 58). This transformation proceeds under mild conditions with high efficiency, which is attractive for focused compound library construction. With this promising initial results, the scope of this transformation was explored with a range of alkynes. Both aryl and alkyl substituted acetylenes were demonstrated as very compatible in the transformation. Moreover, it was found that substrates with electron-withdrawing groups on R^3 were less reactive to some extent than those with electron-donating groups when the R^3 group is phenyl. For example, the reactions of electron-withdrawing substituted substrates such as *p*-chloro or *m*-fluoro phenylacetylene gave the corresponding product in 74% or 65% yield, while the reactions of electron-donating substituted substrates such as *p*-methoxyl, *p*-ethoxyl or *p*-ethylphenylacetylene afforded the corresponding product in 92%, 92% or 75% yields. On the other hand, the reactivity of tosylates with different substituents was also evaluated.

<Scheme 58>

3. Therapeutic potential of quinazolines and quinazolinones

Quinazolines and quinazolinones are among the most useful heterocyclic compounds from both synthetic and medicinal chemistry aspects. The structural design of these scaffolds has attracted a great deal of attention because of their ready accessibility, diverse chemical reactivity, and broad spectra of biological activities. Although, a large number of literature is reported with numerous examples of these motifs exhibiting potential biological activities, we have highlighted here the most recent (2014) developments in the activity profile of these compounds.

3.1. Antitumor activity

Sun and co-workers [96] designed and synthesized two series of novel tricyclic oxazine and oxazepine fused quinazolines. The synthesized derivatives were assessed for their *in vitro* antitumor effect on N87, A431, H1975, BT474 and Calu-3 cell lines. Erlotinib and gefitinib were used as standard compounds. From the careful observation of results, it was revealed that several compounds were found to demonstrate more potent antitumor activities as compared to the standard drugs. So, keeping in view the activity results, these compounds were further screened for their *in vitro* inhibition of EGF-induced receptor autophosphorylation in the KB nasopharyngeal carcinoma cell line. Finally, these compounds were chosen for further evaluation of EGFR and HER2 *in vitro* kinase inhibitory activity. Several derivatives could counteract EGF-induced phosphorylation of EGFR in cells, and their potency was comparable to the reference compounds. Among them, various compounds effectively inhibited the *in vitro* kinase activity of EGFR and HER2 with similar efficacy as erlotinib and gefitinib. The activity of compound **233** was found to be 33-fold and 18-fold more potent than gefitinib and erlotinib, respectively.

Barraja and co-workers [97] were able to conveniently prepare a new series of fused heterocycles like pyrrolo[3,4-*h*]quinazolines. A large number of derivatives were accessed with a broad range of substitution pattern. The synthesized compounds were screened for their cellular cytotoxicity *in vitro* against 5 different human tumor cell lines with GI_{50} values reaching the low micromolar level (1.3-19.8 μM). These compounds were able to induce cell death mainly by apoptosis through a mitochondrial dependent pathway. Selected compounds showed antimitotic activity and a reduction of tubulin polymerization in a concentration-dependent manner. Most of the compounds reduced cell survival in at least one or more cell lines. The most cytotoxic compounds were found to be **234-238**. From the activity results, structure-activity relationship can be made. For the derivatives with no substitution on position 2, the most active ones present

lipophilic substituents with high steric hindrance in positions 7 and 8: an ethyl ester (**234** and **235**) or a phenyl (**236** and **237**) in 7 and a *p*-methylbenzyl group (**234** and **236**) or a *p*-methoxybenzyl group (**235** and **237**) in 8. The substituent at any of the two positions is detrimental to activity and lead to the reduced cytotoxic effects.

El-Azab and co-workers [98] designed and synthesized a novel series of 6-chloro-2-*p*-tolylquinazolinone derivatives and evaluated for their *in-vitro* antitumor activity. The results of this study demonstrated that compound **239** revealed selective activities toward non-small cell lung cancer, in addition to other compounds which possess weak antitumor activity. On the other hand, **240** and **241** possessed remarkable broad-spectrum antitumor activity. Compound **241** was carried over and tested against a panel of 60 different tumor cell lines at a 5-log dose rang. Three response parameters, GI_{50}, TGI and LC_{50} were calculated for each cell line, using the known drug 5-Fluorouracil (5-FU) as a positive control. Compound **241** was also found to be a particularly active growth inhibitor of the renal cancer (GI_{50} = 4.07 μM), CNS cancer (GI_{50} = 7.41 μM), ovarian cancer (GI_{50} = 7.41 μM) and non-small cell lung cancer (GI_{50} = 7.94 μM). Compound **241** ranks as nearly 1.5-fold more potent (GI_{50} = 15.8 μM) compared with 5-FU (GI_{50} = 22.6 μM). This structure possess a chloro substituent at quinazoline phenyl ring and *p*-tolyl group at 2-position along with an azomethine functionality tethered to quinazoline nitrogen which may play crucial role for enhanced activity.

Palop *et al*. [99] reported the synthesis of quinazolines and their hydroselenite salts and the *in vitro* growth inhibitory activity against tumoral PC-3 cell line. It was observed from the results of biological assays that several compounds exhibited potent growth inhibitory activity (IC_{50} < 8.0 μM) and were more potent than standard drug methylseleninic acid (IC_{50} = 8.4 μM). In addition, some of them were more active than topotecan with IC_{50} below 4.0 μM. On the ground of the

biological results, some structural features were inferred to be beneficial to the antitumor activity of such compounds. Cytotoxic data confirmed that molecular symmetry is a valid approach to obtain potent antitumor agents. In general, the hydroselenite salt formulation had a beneficial effect on the cytotoxic activity for 2 and 2 and 4-phenylalkylamino derivatives when the aryl ring was not functionalizated. Meanwhile, the modification of the length in the alkyl chain substituent was not accompanied by alteration of antitumor activity. Two compounds **242** and **243** exhibited strong cytotoxic activities in comparison to the positive controls and they were selected for further studies related to caspase-3 activity and cell cycle regulation. Compound **242** provoked caspase-3 activation and cell cycle arrest in a time-dependent manner being these effects less marked for **243**. In addition, the described compounds seem to present desirable ADME properties that could be an important information about the promising potential of these derivatives. These compounds may become a promising class of cytotoxic agents and the results provide an insight for future direction in the development of new molecules.

<Figure 18>

3.2. Bronchodilatory activity

Špulák *et al*. [100] reported a series of quinazoline and quinazolinone derivatives and screened for their *in vitro* bronchodilatory activity on isolated rat trachea using theophylline and (-)vasicinone as standard drugs. It is noteworthy that the biological effect of almost all derivatives was higher than that of theophylline. The 4-alkylsulfanyl derivatives displayed the most pronounced effect and were more potent than their alkoxy and alkylamino analogues. Among them, compound **244** with the 1-piperidylpropyl fragment was the most active one, with ED_{50} in the micromolar range. All these findings taken together render the compounds interesting targets for further systematic investigation and development.

<Figure 19>

3.3. Anticonvulsant activity

Zayed [101] demonstrated the synthesis of a novel series of fluorinated quinazolinone derivatives. The synthesized compounds were tested for their anticonvulsant activity and neurotoxicity. The anticonvulsant activity of the newly synthesized compounds was compared to that of phenytoin as the reference drug at the same dose, 100 mg/kg. The inspection of the structure–activity relationship of these compounds suggests that the presence of a halogen substituent at the sixth position from the distal aromatic ring of the quinazolinone moiety greatly enhanced the anticonvulsant activity of the newly synthesized compounds when compared with other compounds. Several compounds exhibited promising anticonvulsant activity, revealing the effect of substitution pattern on the aromatic ring leading to the variable anticonvulsant activity. Some compounds incorporating mono halogen substituents at the para position from the distal aromatic ring of the quinazolinone moiety gave maximum protection against seizures induced by MES. Compound **245**, which contains a mono bromo substitution, was the most active, while compounds **246** and **247**, which contain an electron-donating group (methoxy) and 3,5 dichloro substitution, had the least anticonvulsant activity. Substitution of the aromatic ring of the quinazolinone system by electron-donating or electron-withdrawing groups may thus play a key role in their anticonvulsant activity.

Shrivastava and co-workers [102] reported a novel series of 3-aryl/heteroaryl-substituted 2-(2-chlorostyryl)-6,7-dimethoxy-quinazolin-4(3*H*)-one derivatives. The synthesized compounds were evaluated for their anticonvulsant activity in various physicochemically induced seizure models. Few of the compounds displayed their ability to prevent seizure spread in the various seizure models used for the *in vivo* screening. The N3 phenyl and 3-methoxyphenyl derivative of

quinazolin-4(3*H*)-one (**248** and **249**) were found to be least active against all seizure models compared to the other derivatives. In MES test, it was revealed that a methylene spacer **250** in between the phenyl ring and quinazolin-4(3*H*)-one nucleus tends to moderately increase the potency. Mono substitution of methyl group at the meta position of N3 aryl moiety **251** showed potent activity, while disubstitution of methyl group **252** results in marked decrease in activity. Considering the compounds with N3 heteroaryl substitution, the pyridin-4-yl derivative **253** showed good activity (ED_{50} 66.4 μmol/kg) against MES-induced seizure. Among all the compounds, **254** and **255** exhibited promising activity. In particular, **254** with N3 para nitrophenyl substitution with an median effective dose (ED_{50}) of 41.3 μmol/kg demonstrated comparable potency as that of GYKI 52466. Unlike **254**, striking difference in activity was observed with the N3 ortho nitrophenyl **256** derivative (ED_{50} 98.2 μmol/kg).

<Figure 20>

3.4. *β*-Glucuronidase inhibitors

Khan and co-workers [103] synthesized a new series of 2-arylquinazolin-4(3*H*)-one analogues from anthranilamide and various benzaldehydes using $CuCl_2.2H_2O$ as a catalyst. The synthesized 2-arylquinazolin-4(3*H*)-ones evaluated for their *β*-glucuronidase inhibitory potential using D-saccharic acid 1,4-lactone (IC_{50} = 45.75 ± 2.16 μM). Based on the obtained activity results, structure–activity relationship was investigated for these compounds which suggested that the *β*-glucuronidase inhibitory activities of this class of compounds are mainly dependent upon the substitutions on the phenyl ring, present at C-2 of the quinazolin-4(3*H*)-one skeleton. Among all the evaluated structures, compound **257** (IC_{50} = 0.6 ± 0.45 μM) showed the highest *β*-glucuronidase inhibition which is 76-folds higher than the standard D-saccharic acid 1,4-lactone. The two methoxy groups at C-3' and C-4' demonstrated most appropriate arrangement to interact

with the enzyme. When one methoxy group at C-3' was replaced with a hydrogen as in compound **258** (IC_{50} = 1.1 ± 0.05 μM), the activity decreased to almost half. Replacement of hydroxyl group at C-3' with a methoxy group, as in compound **259** (IC_{50} = 2.8 ± 0.05 μM), the activity declined five times. Replacement of both the methoxy groups of compound **257** by hydroxyl groups, as in compound **260** (IC_{50} = 2.1 ± 0.06 μM), a decline trend in activity was observed. Compound **261** (IC_{50} = 0.7 ± 0.01 μM) exhibited 65-folds more potent activity than the standard. Replacement of ethoxy group with nitro or chloro resulted in two-fold decline in activity. Similarly, the exchange of ethoxy with hydroxyl group lowered the activity by 14-folds. Overall, a trend of inhibition IC_{50} against the enzyme in the range of 0.6–198.2 μM, was observed and compared with the standard.

<Figure 21>

3.5. Dihydrofolate reductase inhibitors

El-Subbagh and co-workers [104] synthesized a new series of tetrahydro-quinazoline derivatives and tested for their DHFR inhibition. The synthesized compounds were subjected to the National Cancer Institute (NCI) *in vitro* disease-oriented human cells screening panel assay for *in vitro* antitumor activity. A single dose (10 μM) of the test compounds were used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; Leukemia, Non-small cell lung, Colon, CNS, Melanoma, Ovarian, Renal, Prostate, and Breast cancer cells [105]. Among the tested compounds, several compounds were identified to possess potent antitumor potency of various magnitudes. Several alterations were performed to define the structure requirements and features that enhance selectivity and specificity for the tight binding to DHFR active site. It seems that the type of substituent attached to those two ring systems manipulate the biological activity. The 2-methyl-tetrahydroquinazoline analogues **262** and **263** with 8-(dimethoxy- or

trimethoxy-benzylidene)- and 4-(dimethoxy- or trimethoxy-phenyl)-substituents showed DHFR inhibition potency with IC_{50} values of 0.1 and 0.5 μM, respectively. Replacement of the 2-methyl function of **262** and **263** by 2-amino group produced compounds with diminished DHFR inhibition activity with IC_{50} range of 14-21 μM.

Nerkar and Sahu [106] designed, synthesized and characterized a new series of quinazoline and quinazolinone derivatives as potent inhibitors of human DHFR for anticancer activity. The present work leads to the development of quinazolinone derivatives as anticancer leads by in silico design. Compounds **264-266** were found to be active in cytotoxicity assay *in vitro* as compared with methotrexate used as standard drug and can be considered as useful template for further anticancer lead development.

<Figure 22>

3.6. Antiproliferative activity

Arya and co-workers [107] reported an efficient and facile synthesis of fluorinated benzothiazolo[2,3-*b*]quinazoline-2*H*-ones analogues via one-pot reaction of 2-amino-6-chlorobenzothiazole, fluorinated aldehydes and dimedone using microwave irradiation in the presence of ionic liquid. The one-pot three component reaction went smoothly in an ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate) and gave the corresponding fluorinated benzothiazolo[2,3-*b*]quinazoline derivatives in excellent yields. The antiproliferative activity of fluorinated benzothiazolo[2,3-*b*]quinazoline derivatives was primarily assessed on HL-60 cell line. The potency of the antiproliferative effect of the tested compounds was compared with 5-fluorouracil which was used as standard drug. In the dark, only **267-269** displayed a strong photocytotoxicity with GI_{50} averaging GI_{50} = 2.8 ± 0.5–0.9 ±0.7 μM. On the basis of the reported results, it seems that the substituent effect on the phenyl ring plays a vital role in antiproliferative

activities. It is noteworthy that the activity seems to be affected by the nature (electron-donating or electron-withdrawing) of the substituents in the phenyl group position. Compounds **267-270** all carry electron-withdrawing groups on ortho- and para position of phenyl ring, but in compounds **267**, fluorine atom on phenyl ring would show weak electron-withdrawing power compared to CF_3 group on phenyl ring in compounds **269**. Same as compounds **270** less active toward antiproliferative activity due to presence of fluorine atom at ortho position on phenyl ring. After UV irradiation, only four derivatives exerted moderate activities against HL-60 cell lines. However, **269** displayed strong photocytotoxicity with GI_{50} averaging 0.9 ± 0.7 μM.

<Figure 23>

3.7. Kinase inhibitors

Hou *et al*. [108] designed and synthesized a novel type of quinazoline derivatives by the combination of quinazoline and oxazole scaffolds in one heteroaromatic unit. The synthesized structures were tested for their anti-proliferative activities and EGFR inhibitory potency. From results, it is obvious that compounds **271** and **272** possessing substituent of oxazole scaffold at the 7-positions, demonstrated more potent inhibitory activities for EGFR (IC_{50}＝1.21 and 0.95 μmol/L) than those of compounds **273** and **274** only incorporating nitro or amino group at the 7-positions. Their activities positively correlated with antiproliferative activities and had the same trends. Although the results were less comparable to the positive control Erlotinib (IC_{50} = 0.03 μmol/L for EGFR), it is possible and necessary to proceed with the investigation of modification and bioactivity of quinazoline analogues substitued by oxazole scaffold for discovery of new EGFR inhibitors.

Barreiro and co-workers [109] designed and synthesized a novel series of 2-chloro-4-anilino-quinazolines as EGFR and VEGFR-2 dual inhibitors and evaluated for inhibitory effects. The biological data obtained proved the potential of 2-chloro-4-anilino-quinazoline derivatives as EGFR and VEGFR-2 dual inhibitors. Those derivatives containing a hydrogen bond donor at the para position of the aniline moiety presented lower IC_{50} values. Most active compound was found to be **275** with IC_{50} = 0.90 μM for EGFR and 1.17 μM for VEGFR-2. This compound was approximately 7-fold more potent on VEGFR-2 and approximately 11-fold more potent on EGFR compared to the prototype **276**. SAR and docking studies allowed the identification of pharmacophoric groups for both kinases and demonstrated the importance of a hydrogen bond donor at the para position of the aniline moiety for interaction with conserved Glu and Asp amino acids in EGFR and VEGFR-2 binding sites.

Trivedi and co-workers [110] designed and synthesized a new series of novel 4-anilinoquinazoline derivatives and evaluated as potential inhibitors for protein kinases implicated in Alzheimer's disease. The synthesized 6,7-dimethoxy-*N*-phenylquinazolin-4-amines were tested for their potential inhibitory effect on five different kinases namely CDK5/p25 (CDK5/p25), CK1δ/ε (casein kinase 1), GSK-3*α*/*β* (Glycogen Synthase Kinase 3*α*/*β*), DYRK1A (dual-specificity, tyrosine phosphorylation regulated kinase) and CLK1 (cdc2-like kinase 1). The results of kinase inhibitory assays demonstrated that none of the synthesized anilino quinazolines showed any inhibitory activity against CDK5/p25, DYRK1A and CK1δ/ε at the maximum concentration tested (10 μM). The 4-anilinoquinazolines appeared to be most effective towards CLK1 as four compounds **277-280** showed inhibitory activity on the enzyme. Two among the 10 anilinoquinazolines synthesized (**279** and **280**) showed significant inhibitory potency against CLK1 at less than 10 μM concentrations. It is noteworthy that compound **279** bearing 3,4

dimethoxy substitution on the aryl ring of the aniline moiety shows less than 5 μM inhibition towards both CLK1 (IC_{50} = 1.5 μM) and GSK-3*α/β* (IC_{50} = 3 μM) enzymes. Surprisingly, compound **280** with 3-fluoro and 4-chloro substitution in the aryl ring exhibited a 5-fold reduced inhibition on CLK1 (IC_{50} = 7.6 μM) and no inhibition on GSK-3*α/β*. Docking studies were also performed to elucidate the binding mode of the compounds to the active site of CLK1 and GSK-**278**. The results of this study suggested that compound **279** may serve as a valuable template for the design and development of dual inhibitors of CLK1 and GSK-3*α/β* enzymes with potential therapeutic application in Alzheimer's disease.

<Figure 24>

3.8. Anti-angiogenesis activity

Xiong and co-workers [111] designed and synthesized a series of new 2,4-disubstituted quinazoline derivatives. The prepared compounds were assayed for their cytotoxic activities against human tumor cell lines CNE-2 (human nasopharyngeal cancer), PC-3 (human prostatic carcinoma), SMMC-7721 (human liver cancer) and Human Umbilical Vein Endothelial Cells (HUVECs) using the MTT cytotoxicity assay. The biological results showed that most of the 2,4-disubstituted quinazoline derivatives possessed high cytotoxicity against human tumor cell lines and moderate cytotoxicity against HUVECs. Among all the derivatives, **281** was the most potent in inhibiting the tumor cell proliferation with the lowest IC_{50} values of 9.3 ± 0.2 μM (CNE-2), 9.8 ± 0.3 μM (PC-3) and 10.9 ± 0.2 μM (SMMC-7721), respectively. Compound **281** also showed the most potent inhibition of HUVEC adhesion, with an inhibitory rate of as much as 65.8 ± 0.2% at a dose of 15 μM and 71.2 ± 0.1% at a dose of 30 μM after 3 h incubation at 37 °C. This remarkable inhibitive effect against the migration, adhesion of HUVECs and significant anti-angiogenesis activities in the chick embryo chorioallantoic membrane (CAM) assay could

be attributed to the three carbon chain length and *N*-methylpiperazino group present in compound **281**.

<Figure 25>

3.9. Allosteric modulators of glutamate receptors

Lindsley and co-workers [112] designed and synthesized a new series of substituted pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones as negative allosteric modulators of metabotropic glutamate receptors 2 and 3 ($mGlu_2$ and $mGlu_3$, respectively). SAR profile of these compounds was fairly steep, with small structural changes leading to significant losses in efficacy. When the R^1 position was held constant as a phenyl ring, and R^3 was held as a methyl, installation of a 3-sulfonylphenyl or 3-pyridyl group at R^2 yielded inhibitors with low-micromolar to high nanomolar IC_{50}s at both mGlu2 and mGlu3. In contrast, installation of a phenyl or 4-methoxyphenyl at this position yielded compounds with very little effect. Truncation of this position to a methyl group also resulted in much attenuated activity at both receptors. Overall, several compounds were found to be potent inhibitors, including 4-methyl-2-phenyl-8-(pyrimidin-5-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **282**, were discovered with potent *in vitro* activity as dual $mGlu_2$/$mGlu_3$ NAMs, with excellent selectivity versus the other mGluRs.

<Figure 26>

3.10. Cathepsin inhibitors

Raghav and Singh [113] designed and synthesized new analogues of bischalcones based quinazoline-2(1*H*)-ones and quinazoline-2(1*H*)-thiones. The synthesized compounds were screened for their potency as novel inhibitors of cathepsin B and cathepsin H. Among the various, it was found that 3,4,5,6,7,8-hexahydro-3-phenylallylidene)-4-styrylquinazoline-2(1*H*)-

one **283** showed maximum inhibition, i.e., 100% inhibition at 1.0 × 10^{-4} M concentration and 50% inhibition at ~0.1 × 10^{-4} M concentration. Effect of substituted benzylidene-3,4,5,6,7,8-hexahydro-quinazoline-2(1*H*)-thione derivatives on cathepsin B activity was also assessed. Maximum inhibitory effect was exerted by that 3,4,5,6,7,8-hexahydro-3-phenylallylidene)-4-styrylquinazoline-2(1*H*)-one **284**, i.e., 100% inhibition at 0.50 × 10^{-4} M concentration and half maximum inhibition at ~0.01 × 10^{-4} M concentration. Similarly, the activities of cathepsin H were estimated at varying concentrations of synthesized benzylidene-3,4,5,6,7,8-hexahydro-quinazoline-2(1*H*)-one and benzylidene-3,4,5,6,7,8-hexahydro-quinazoline-2(1*H*)-one derivatives. Among quinazoline derivatives, 2,6-bis(4□-(dimethyl amino) benzylidene)cyclo hexanone **285** was found to exhibit maximum inhibition which showed 100% inhibition at 1.0 × 10^{-4} M concentration and half maximum inhibition at ~0.15 × 10^{-4} M concentration. In benzylidene-3,4,5,6,7,8-hexahydro-quinazoline-2(1*H*)-one derivatives also, 2,6-bis(4□-(dimethyl amino) benzylidene) cyclo hexanone **286** was found to demonstrate maximum inhibition which showed 100% inhibition at ~0.25 × 10^{-4} M concentration.

<Figure 27>

3.11. Phosphodiesterase inhibitors

Humphrey *et al*. [114] disclosed a new class of selective, CNS penetrable quinazoline PDE1 inhibitors discovered through SAR development of two file screen hits. In a combination of parallel and traditional organic synthesis, and with the aid of X-ray crystallography and molecular modeling, structural refinement of the lead compounds led to the aminoquinazoline **287** (PF-04471141) and the indanylquinazoline **288** (PF-04822163). These compounds are among the most potent and selective inhibitors of PDE1 reported to date. Pharmacokinetic investigations in rodents indicate that each compound achieves systemic concentrations in excess

of their IC_{50} values. Thus, compounds **287** and **288** offer considerable potential as chemical probes to further investigate biological processes of the CNS impacted by PDE1 function, and to assess the potential of pan-PDE1 inhibition as a therapy for the treatment of neuropsychiatric illness.

Abdel-Aziz and co-workers [115] designed and synthesized a novel series of quinazolin-4(3*H*)-one/Schiff base hybrids. The prepared compounds were evaluated for *in vitro* activity to inhibit phosphodiesterase 4 (PDE4), where Rolipram was used as a positive reference for PDE4 inhibition. Several of them showed good-to-moderate activity compared to rolipram. Among them, compound **289** showed potent PDE4 inhibition in this series, with an IC_{50} of 1.60 μM. The activity results revealed that the presence of the hydroxyl-substituted phenyl of Schiff base part is crucial for inhibitory activity. Thus, the trihydroxyphenyl Schiff base **289** showed the highest PDE4B inhibitory activity in this series, while Schiff base **290** showed moderate inhibitory activity with IC_{50} of 29.3 μM. The methoxyphenyl containing Schiff bases were the least active in this series, suggesting the importance of the free OH groups on the Schiff base aryl ring. Furthermore, the 5-methyl substitution did not improve the inhibitory activity of the synthesized compounds. The active compounds that showed PDE4 inhibition were further assessed for antiproliferative activity using different human tumor cell lines. Among them, compound **290** exhibited significant antiproliferative activity with IC_{50} values of 140, 79, and 320 nM in breast, lung, and colon tumor cells, respectively. Furthermore, docking of compound **289** in the active site of PDE4B was carried out to identify the possible binding mode and provides insight for further optimizations of this novel scaffold for inhibiting PDE4.

<Figure 28>

3.12. Antimycobacterial activity

Kumari and co-workers [116] reported two series of novel urea/thiourea-based quinazoline analogues by C–C Suzuki coupling reaction of quinazoline and phenyl ring followed by condensation of various *N*-phenyl isocyanates/isothiocyanates. The synthesized analogues were investigated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv. Rifampicin, isoniazid, ethambutol, and pyrazinamide were used as standard antimycobacterial drugs. The activity results demonstrated that the bromo-substituted thiourea analogue **291** has displayed highest antimycobacterial efficacy at MIC 12.5 μg/mL with 99% inhibition. This analogue was considered to display half-fold efficacy to the standard drug pyrazinamide. However, some other derivatives were moderately active.

<Figure 29>

3.13. Antihistamine agents

Alagarsamy and co-workers [117] designed and synthesized a series of novel 3-(4-chlorophenyl)-2-(2-(4-substituted)-2-oxoethylthio)quinazolin-4(3*H*)-one by the reaction of 2-(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-ylthio)acetyl chloride with various amines. All the synthesized compounds were tested for their *in vivo* H_1-antihistaminic activity on conscious guinea pigs at the dose level of 10 mg/kg using chlorpheniramine maleate as the reference standard. All the tested compounds were found to exhibit good antihistaminic activity. Percentage protection data showed that all test compounds of the series showed significant protection in the range of 65–71 %. Biological studies indicated that different substituents over the third position of quinazoline ring exerted varied biological activity. The presence of piperazinyl group (**292**, Log *P* = 3.43) showed significant activity. When the hetero atom nitrogen of piperazinyl was replaced by oxygen compound morpholinyl substitution (**293**, Log *P* = 3.27) and elimination of the nitrogen of piperazinyl yielded pyrrolidinyl substitution (**294**, Log

P = 3.99) results in retaining of potency. Placement of ethyl and diethyl substituents showed decrease in activity. In general, compound 3-(4-chlorophenyl)-2-(2-(4-methylpiperazin-1-yl)-2-oxoethylthio)quinazolin-4(3*H*)-one **292** emerged as the most potent compound of the series. It clearly indicates that lipophilicity (Log *P*) plays an important role for their antihistaminic activity.

<Figure 30>

3.14. Antihypertensive agents

Marzouk and co-workers [118] synthesized and characterized a novel series of 1,2,4-triazolo[1,5-*a*]quinazoline derivatives. The synthesized compounds were evaluated for their *in vivo* antihypertensive activity by tail cuff method using Muromachi Blood Pressure Monitor for rats and mice (Model MK 2000). From the obtained results, it was revealed that the nature of substituents and substitution pattern on the tricyclic systems may have had a considerable impact on the heart rate and blood pressure. Among the screened compounds, **295-300** have abolished completely the tachycardia of the parent compounds, they may be studied as potential adrenoblockers. Compounds **297** and **301** may be modified to enhance their hypotensive activity. Furthermore, compound **298** seem to be a cardiac stimulant and it will be studied further for this concern. Finally, the structure–activity relationship (SAR) study of the compounds provided some useful insights about the characteristic requirements, which may be taken into consideration in the design of new antihypertensive agents.

Shahar Yar and co-workers [119] synthesized a new series of 7-substituted-3-(4-(3-(4-substitutedphenyl)-4,5-dihydroisoxazol-5-yl)phenyl)-2-substituted quinazolin-4(3*H*)-one by the cyclization of (*E*)-3-(4-(3-substitutedphenyl)acrylolyl)phenyl)-2-(substitutedphenyl)-7-substituted quinazolin-4-(3*H*)-one with hydroxylamine hydrochloride. The synthesized

compounds were examined for their *in vivo* antihypertensive activity using albino rats. All the synthesized compounds exhibited good to moderate antihypertensive activity. Compounds 7-chloro-3-(4-(3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)phenyl)-2-*p*-tolylquinazolin-4(3*H*)-one **302** and 7-chloro-3-(4-(3-(4-chlorophenyl)-4,5-dihydroisoxazol-5-yl)phenyl)-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one **303** exhibited potent antihypertensive activity through their anticipated α_1-adrenergic receptor blocking property similar to its clinically used analogue, prazosin, without affecting heart rate with prolonged duration of action when tested in adrenaline induced hypertension in anaesthetized rats.

<Figure 31>

3.15. Anticancer activity

Sarg and co-workers [93] synthesized various quinazoline compounds fused with a range of heterocycles through different chemical reactions. The synthesized compounds were evaluated for their *in vitro* antitumor activity against HEPG2 and MCF-7 cell lines compared to the reference drug (doxorubicin). Among the evaluated compounds, **304-308** were found to be the most active against both cell lines exhibiting IC_{50} values ranging from 10.82-29.46 μM/L and 7.09-31.85 μM/L against Hep-G2 and MCF-7 cell lines, respectively. These compounds were further docked into the active sites of thymidylate synthase and dihydrofolate reductase enzymes. Sangshetti and co-workers [120] developed a simple, multicomponent, water-mediated synthesis of benzothiazolo [2,3-*b*] quinazolin-1-ones from aminobenzthiazoles, cyclic β diketone, and aromatic aldehydes. This methodology offers several advantages like simplicity, easy work up, short reaction time, and use of environmentally benign water as a solvent. The newly synthesized compounds were evaluated for cytotoxicity against a panel of human cancer cell lines (U-937, Hep-2, vero, and MCF-7). Among the synthesized compounds, the compounds **309** and **310**

showed higher anticancer activity. The IC_{50} values of the compounds revealed that the substitution of methoxy and chloro at benzothiazolo [2,3-*b*] quinazolinones moiety increases the anticancer activity. It was also revealed that substitution of methyl group decreases the anticancer activity of compounds. The result of DNA fragmentation analysis showed that the compound **310** induced dose dependent apoptosis.

<Figure 32>

3.16. Cholinesterase inhibitors

A straightforward synthesis for 6-substituted quinazolinones was developed using 6-(benzyloxy)-1*H*-benzo[*d*][1,3]oxazine-2,4-dione as starting material by Decker and co-workers [121]. All target compounds were tested for their ability to inhibit acetylcholinesterase and butyrylcholinesterase. It was found that tacrine shows a 3-fold lower potency (IC_{50} = 71.5 nM) on the human enzyme compared to the IC_{50} value of 24.1 nM measured on eeAChE. The piperidinyl inhibitors **311-316** showed 7 to 39-fold higher inhibitory activities toward the electric eel derived AChE. Docking studies were also carried out to investigate the possible binding mode with respect to AchE.

<Figure 33>

3.17. Cytotoxic activity

Shekarrao *et al*. [74] developed an efficient microwave-assisted procedure for the synthesis of pyrazolo[1,5-*a*]quinazolines in good yields. The newly synthesized compounds were screened *in vitro* for their cytotoxic activities against cervical HeLa cancer cell line and prostate DU 205 cancer cell line using MTT-micro cultured tetrazolium assay [122]. Doxorubicin was used as a positive control in this assay. Among the screened quinazoline analogues, none of the

compounds showed good cytotoxic effects which clearly demonstrate that this type of compounds need more attention to be further developed as cytotoxic agents.

Prajapati and Panchal [123] synthesized a new series of quinazoline derivatives. All the obtained compounds were evaluated for their cytotoxicity by MTT assay. Among all the synthesized derivatives, compound **317** exhibited promising anticancer activity as compared to other synthesized derivatives. This was indicated by the IC_{50} value of (7.1 and 5.5 μM) respectively, for the synthesized derivatives **317** and **318** as compared to gefitinib (IC_{50} = 4.9 μM).

<Figure 34>

3.18. Anti-inflammatory activity

Zayed and Hassan [124] synthesized a new series of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3*H*)-ones bearing sulfonamide derivatives in good yields. The synthesized compounds were evaluated for their anti-inflammatory activity using the carrageen an induced rat paw edema method using ibuprofen as a reference drug. From the observation of results, compounds with aliphatic side chain **319** and **320** were more active than that with aromatic one. Compound **320**, the most active compound among all the test compounds, contains aliphatic side chain. The relative potency of this compound was 74% of the reference's potency. Pyridine containing compound **321** was more active than those with pyrimidine or oxazole instead. Hence, necessary structural modifications could be made to increase the anti-inflammatory activity. In general, the present study showed that compound **320** was the most active compound with combined ability to inhibit the inflammation.

<Figure 35>

3.19. Chitin synthase inhibitors

Ji *et al*. [125] designed, synthesized and characterized a series of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives. The prepared compounds were assayed for their inhibitory activity against CHS by means of one-step ELISA analysis of chitin formed from UDP-Glc-NAc with horse-radish peroxidase (HRP)-labeled wheat germ agglutinin (WGA) as the probe. Polyoxin B was the positive control in this assay. The half-inhibition concentration of each compound (IC_{50}) was determined. Among the evaluated compounds, several analogues exhibited good inhibition activities against CHS and their IC_{50} values were lower than that of Polyoxin B whose IC_{50} was 0.18 mmol. Compound **322** with IC_{50} value of 0.08 mmol/L is the strongest inhibitor among these compounds. The inhibitory activities of **323-325** were comparable to that of polyoxin B. Some other compounds showed moderate to low inhibition. In these active compounds, the use of aryl R^2 as substituent produced higher inhibitory activities against CHS than the use of alkyl R^2. In aryl R^2, electron-donating substituent is more favorable than electron-withdrawing substituent on aromatic ring to enhance inhibitory activities.

<Figure 36>

3.20. Antimalarial activity

Kikuchi and co-workers [126] synthesized new analogues of febrifugine, a quinazoline alkaloid isolated from *Dichroa febrifuga* roots, shows powerful antimalarial activity against *Plasmodium falciparum*. The synthesized new derivatives of febrifugine were evaluated for their *in vitro* and *in vivo* antimalarial activities to develop antimalarials that are more effective and safer. From the results it is revealed that tetrahydroquinazoline derivative **326** exhibit potent antimalarial activity with a very high therapeutic selectivity both *in vitro* and *in vivo*.

<Figure 37>

3.21. Antimicrobial activity

Song and co-workers [127] designed and synthesized novel imine derivatives of quinazolin-4(3*H*)-one by using aminoethyl moieties to increase the amine bridge of quinazolin-4(3*H*)-one amine and then introducing various aromatic aldehydes. The antibacterial activity of all the tested compounds were determined against tobacco and tomato bacterial wilts by performing a turbidimeter test [128]. The primary *in vitro* bioassay results revealed that all the tested compounds at 100 mg/mL or 200 mg/mL exhibited moderate to excellent antibacterial activities against tobacco and tomato bacterial wilts. Among them, compound **327** exhibited stronger antibacterial activities against tobacco and tomato bacterial wilts compared with the commercial plant bactericide thiodiazole copper. SAR analysis indicated that stronger activities against tobacco bacterial wilt compared with thiadiazole copper were demonstrated by the compounds with H and 2-OH-5-CH_3-Ph, 2- H-5-OCH_3-Ph, or 4-*N*,*N*-di-CH_3-Ph group. A close analysis of the screening results and structures of the active compounds revealed that the electron-donating substituents of the phenyl ring can increase antimicrobial activity. These results indicated that novel Schiff base derivatives containing the 4(3*H*)-quinazolinone moiety can effectively control tobacco and tomato bacterial wilts.

Garrepalli *et al*. [129] synthesized a series of 2-(2-arylidene hydrazinyl)-4-phenyl-3,4,5,6,7,8-hexahydroquinazolines by treating 2-hydrazinyl- 4-phenyl-3,4,5,6,7,8-hexahydroquinazoline with the different substituted aromatic aldehydes in the presence of glacial acetic acid. All the newly synthesized quinazoline derivatives were evaluated for their antibacterial activity by cup plate method by measuring zone of inhibition using Ampicillin as a standard drug. Among the evaluated samples, compound **328** showed maximum zone of inhibition (18mm) against *S. aureus* as well as *E. coli* (17mm) which is higher than the standard drug Ampicillin.

Arora and co-workers [130] synthesized several quinazolinone compounds with a schiff base nucleus. The synthesized compounds were screened for their antibacterial and antifungal activities against three pathogenic bacteria and two pathogenic fungi. Antimicrobial result indicated that compounds showed significant activity against tested fungi and bacteria. Among them, compounds **329** and **330** emerged as broad spectrum antibacterial agents whereas **331-334** showed broad spectrum antifungal properties.

Zayed and Hassan [124] synthesized a new series of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(3*H*)-ones bearing sulfonamide derivatives in good yields. The synthesized compounds were evaluated for their antibacterial activity against Gram-positive and Gram-negative bacteria. Antibacterial assay of all the test compounds showed good activities against both of Gram-positive and Gram-negative bacteria. These activities were ranged from 61.91 to 95.23% from the activity of the standard. Compounds **319** and **320** were found to possess highest levels of activity among the tested compounds.

Ji *et al*. [125] designed, synthesized and characterized a series of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives. The prepared compounds were assayed for their antifungal potential. The minimum inhibition concentration (MIC) of each compound was estimated. Fluconazole and polyoxin B acted as the positive controls. Interestingly, comparing with the two controls, most designed compounds displayed comparable or better inhibitory activities against tested pathogenic fungi. To *Candida albicans*, compounds **335** and **336** whose MIC values were both 4.0 mg/L exhibited much higher inhibitory activities than those of fluconazole and polyoxin B whose values were 32 and 16 mg/L, respectively. From SAR analysis, it could be concluded that these designed compounds had more favorable activities against *Candida albicans* and

Aspergillus flavus. Therefore, these novel compounds may be promising leads of antifungal agents.

Ji and co-workers [131] designed and synthesized a series of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives and evaluated for their antimicrobial activities against six strains of bacteria and five fungi *in vitro*. Streptomycin and fluconazole were used as positive control for antibacterial and antifungal activity, respectively. Most of the synthesized compounds showed moderate to good antibacterial activities against the tested bacteria, some compounds showed higher antibacterial activities than streptomycin. All compounds exhibited high activities against MRSA and *B. subtilis* while showed weak activities against *S. aureus*. Compounds **337-339** showed good activity against *B. subtilis* with the MIC values of 4 μg/mL while the MIC value of streptomycin was 32 μg/mL. Compounds **339-341** showed good activity against MRSA with the MIC values of 4 μg/mL.

Kumari and co-workers [132] reported two series of novel urea/thiourea-based quinazoline analogues by C–C Suzuki coupling reaction of quinazoline and phenyl ring followed by condensation of various *N*-phenyl isocyanates/isothiocyanates. The synthesized analogues were investigated for their antimicrobial activity against two Gram-positive bacteria (*S. aureus*, MTCC 96 and *B. cereus*, MTCC 430), three Gram-negative bacteria (*E. coli*, MTCC 739; *P. aeruginosa*, MTCC 741; and *K. pneumoniae*, MTCC 109), and two fungal species (*A. niger*, MTCC 282 and *C. albicans*, MTCC 183) using ampicillin, gentamicina, and fluconazole as standard drugs. The results revealed that majority of synthesized analogues showed varying degrees of inhibition against the test panel of mentioned microorganisms. Bromo-group-substituted thiourea derivative **342** has shown extremely significant inhibitory efficacy against Gram-positive bacteria *S. aureus* at MIC 6.25 μg/mL and *B. cereus* at MIC 12.5 μg/mL with

zone of inhibition 29 and 26 mm, respectively. It was also found to be active against some Gram-negative bacteria such as *K. pneumoniae* at MIC 12.5 μg/mL and *P. aeruginosa* at MIC 25 μg/mL with zone of inhibition of 27 and 25 mm, respectively. However, urea linked analogue **343** with similar bromo-functional group showed good activity but was lesser than that of analogue **342**. Moreover, the *in vitro* antifungal activity of synthesized analogues indicated that the halogenated thiourea-substituted quinazoline analogues have shown high efficacy against *C. albicans*. Fluoro-substituted thiourea analogue was found 50% more potent than the standard fluconazole (MIC 12.5 μg/mL) against *C. albicans.*

Mabkhot *et al*. [132] synthesized a new series of quinazolinone derivatives from 2-aminobenzamide derivatives in high yields, assisted by microwave and classical methods. Some of these substituted quinazolinones were tested for their antimicrobial activity against Gram-negative bacteria (*Pseudomonas aeruginosa* and *Esherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus*, and *Bacillus subtilis*), and anti-fungal activity against (*Aspergillus fumigatus*, *Saccharomyces cervevisiae*, and *Candida albicans*) using agar well diffusion method. Among the prepared products, 3-benzyl-2-(4-chlorophenyl)quinazolin-4(3*H*)-one **344** was found to exhibit the most potent *in vitro* anti-microbial activity with MICs of 25.6 ± 0.5, 24.3 ± 0.4, 30.1 ± 0.6, and 25.1 ± 0.5 μg/mL against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Esherichia coli*, respectively. Compound **344** was also found to exhibit the most potent *in vitro* anti-fungal activity with MICs of 18.3 ± 0.6, 23.1 ± 0.4, and 26.1 ± 0. 5 μg/mL against *Aspergillus fumigatus*, *Saccharomyces cervevisiae* and *Candidaal bicans*, respectively. Docking studies were also carried out to explore the binding pattern of synthesized compounds against against methicillin resistant *Staphylcoccus aureus*.

<Figure 38>

3.22. Anti-asthmatic activity

Rayees *et al*. [133] synthesized a series of azepino [2,1-*b*] quinazoline derivatives and evaluated for their anti-asthmatic activity using a murine model of asthma. The compounds **345-349** caused a notable decrease Th2 cytokine secretion and eosinophilia in asthma-induced animals. However, the decrease was highly significant in case of **349**-treated animals. Molecular modelling studies were done for the compound **349** with transcription factors STAT6 and GATA3 which are the main transcription factors responsible for Th2 cell differentiation. Also the pharmacokinetics of **349** was carried out in mice after oral and intravenous administrations.

<Figure 39>

4. Agrochemical Applications

4.1. Insecticidal activity

Wu and co-workers [134] synthesized a series of 6,8-dichloro-quinazoline derivatives bearing a sulfide group. All the synthesized compounds were tested for their insecticidal activity against *Plutella xylostella in vitro* using Chlorpyrifos, one of the most effective insecticides as the positive control. The results indicated that the synthesized compounds possess good insecticidal activity. From these data it can be concluded that the introduction of 2-chloro-substituted pyridine and thiazole enhances the insecticidal activity, e.g. compounds **350** and **351** displayed better insecticidal activity than other compounds. These may prove useful as insecticidal agents.

<Figure 40>

5. Summary and Outlook

This review article seeks to provide an up-to-date overview of the latest advances involving the development of straightforward and diversity-oriented reactions to construct quinazoline and

quinazolinone skeletons which have always been of a paramount chemical significance for pharmaceutical and synthetic chemists. In this review, we have presented a broad range of novel, efficient, extremely mild, and operationally simple synthetic methods to access a library of highly functionalized quinazoline and quinazolinone scaffolds through several strategies including Lewis acid- and metal-catalyzed reactions, MCR, and microwave-irradiation and conventional heating methods. Several inexpensive metals like copper, iron and indium have been shown to perform the required transformations. In addition, a range of highly efficient, greener and stable catalyst systems have been developed to catalyze these reactions. This article is also focused on the discussion of reaction conditions, substrate generality and development of new reaction types. We have also tried to emphasize the scope and the possible mechanistic approaches for key transformations while presenting successful applications in the synthesis of relevant natural compounds.

Apart from notable synthetic advancements, we have clearly shown that these ring systems play an important role in medicinal chemistry being evaluated against numerous biological targets. A large amount of work has been made toward quinazoline- and quinazolinone-based medicinal chemistry. Numerous outstanding achievements revealed that these structures possess extensive potential applications as medicinal drugs. In particular, a large number of quinazoline- and quinazolinone-based compounds as antitumor agents and kinase inhibitors, have been successfully developed, marketed, and extensively used in the clinic in preventing and treating various types of diseases with low toxicity, high bioavailability, and good biocompatibility and curative effects. The structure-activity relationship (SAR) of the reported compounds revealed that the choice of a suitable substitution pattern including electron-donating, electron-withdrawing groups as well as some heterocyclic moieties, on the basic skeleton plays a key role

in regulating the biological potential of the synthesized compounds. This would also help medicinal chemists to choose appropriate functional groups in order to design more effective and safer molecules for treatment of various disorders.

However, some limitations still subsist for several methods due to the use of harsh reaction conditions and restricted substrate generality. The scope of some described reactions needs to be expanded with the use of sterically encumbered substrates with optimal yields of the products. It is also highly desirable to focus on developing more eco-friendly processes which are in accordance with the green chemistry protocols. The extensive medicinal potentiality will ineluctably draw more and more researchers to engage in the medicinal research of quinazoline and quinazolinone derivatives. Much effort will contribute to structural modification of clinical drugs to retain the advantages of these drugs and overcome their shortcomings. One important strategy is to employ some functional groups or structural fragments that are helpful for improving physicochemical properties and affinity with target sites to modify clinical drugs. This intention is to increase their biological activities, broaden active spectrum, and overcome drug resistances. Furthermore, exploitation of structurally novel types of quinazoline and quinazolinone derivatives for all possibly medicinal application will become an actively important direction. Structurally novel derivatives might exert a new mechanism of action that might exhibit different bioactivity. This strategy includes the combination of these rings with other pharmacophores and the development of new structural skeletons different from traditional clinical drugs. Furthermore, due to the simple and diverse nature of synthetic methods enabling to construct core motifs of numerous commercial drugs with potential biological applications, we sincerely hope that this article will serve as a handy reference for chemists working in this field.

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Abbreviations

AChE: Acetylcholinesterase

AIBN: Azobisisobutyronitrile

Bmim: 1-Butyl-3-methylimidazolium

CDK: Cyclin-dependent kinase

CNTs: Carbon nanotubes

CTAB: Cetyltrimethylammonium bromide

DABCO: 1,4-Diazabicyclo[2.2.2]octane

DHFR: Dihydrofolate reductase

DIPEA: *N*,*N*-Diisopropylethylamine

DMAP: 4-Dimethylaminopyridine

DMA: Dimethylacetamide

DNA: Deoxyribonucleic acid

DPPP: 1,3-Bis(diphenylphosphino)propane

DTBP: Di-*tert*-butyl peroxide

EGFR: Epidermal growth factor receptor

GABA: gamma-aminobutyric acid

HMPA: Hexamethylphosphoramide

MCR: Multi-component reaction

MES: Maximal electroshock seizure

MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium

MW: Microwave

NBS: *N*-Bromosuccinimide

NIS: *N*-Iodosuccinimide

PDE: Phosphodiesterase

RT: Room temperature

SAR: Structure-activity relationship

TBHP: *tert*-Butyl hydroperoxide

TEMPO: 2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl

VEGFR: Vascular endothelial growth factor receptor

Research Highlights

- Quinazolines and quinazolinones are promising bioactive scaffolds in medicinal chemistry
- Mild, efficient and environmentally benign procedures employed for synthesis are focused
- Proposed mechanistic investigations have also been concentrated
- Useful synthetic applications and product manipulations have been displayed
- A diverse spectrum of biological activities has been presented

Legends

Figure 1: Selected structures of some commercial drugs and alkaloids incorporating quinazoline and quinazolinone motifs

Figure 18: Compounds with antitumor activity

Figure 19: Bronchodilatory agent

Figure 20: Structures of compounds with anticonvulsant potential

Figure 21: Glucuronidase inhibitors

Figure 22: Structures of dihydrofolate reductase inhibitors

Figure 23: Compounds with antiproliferative activity

Figure 24: Kinase inhibitors

Figure 25: Compound with anti-angiogenesis activity

Figure 26: Allosteric modulator

Figure 27: Cathepsin inhibitors

Figure 28: Phosphodiesterase inhibitors

Figure 29: Compound with antimycobacterial activity

Figure 30: Antihistamine agents

Figure 31: Structures of compounds with antihypertensive activity

Figure 32: Compounds with anticancer potential

Figure 33: Cholinesterase inhibitors

Figure 34: Compounds with cytotoxic activity

Figure 35: Compounds with anti-inflammatory potential

Figure 36: Chitin synthase inhibitors

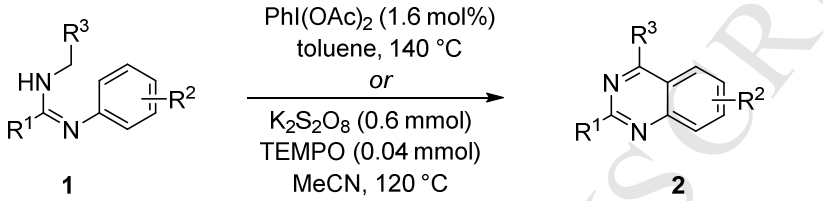
Figure 37: Structure of antimalarial compound

Figure 38: Compounds with antimicrobial potential

Figure 39: Compounds with anti-asthmatic activity

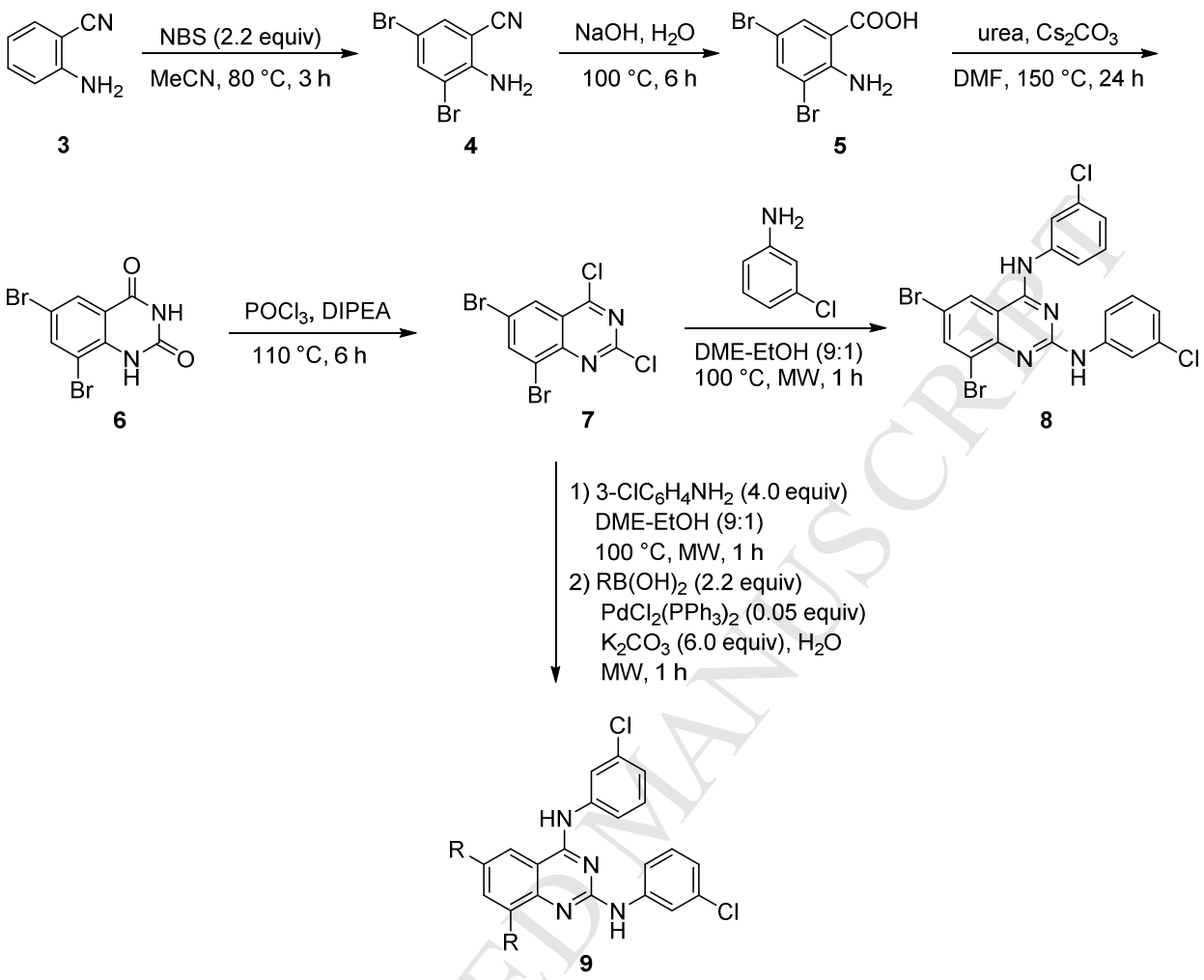
Figure 40: Compounds with insecticidal activity

Schemes



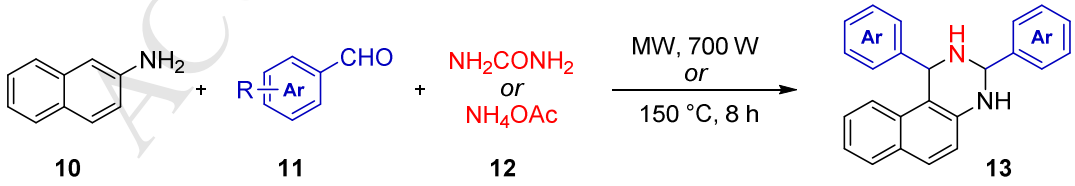
R^1 = Ph, 2-F-Ph, 3-CF_3-Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-OMe-Ph, *t*-Bu, naphthyl
R^2 = Br, CF_3, Cl, OMe, Me, *t*-Bu
R^3 = Me, Ph, 4-OMe-Ph, 4-F-Ph, 3-CF_3-Ph, 3,4-diMe-Ph, cyclopropyl, pyridyl

Scheme 1



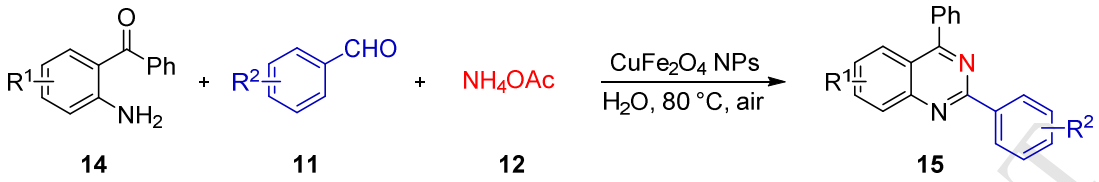
R = Ph, 4-F-Ph, 4-Me-Ph, 4-Cl-Ph, 3-NO_2-Ph, 3-CF_3-Ph, 3,4,5-tri-OMe-Ph, 3-pyridyl, 2-naphthyl

Scheme 2



R = H, 4-F-Ph, 4-NO_2-Ph, 2-Cl-Ph, 3-Cl-Ph, 4-Cl-Ph, 3-Br-Ph, 2-Br-Ph, 2-Me-Ph, 4-OMe-Ph, 2-thienyl

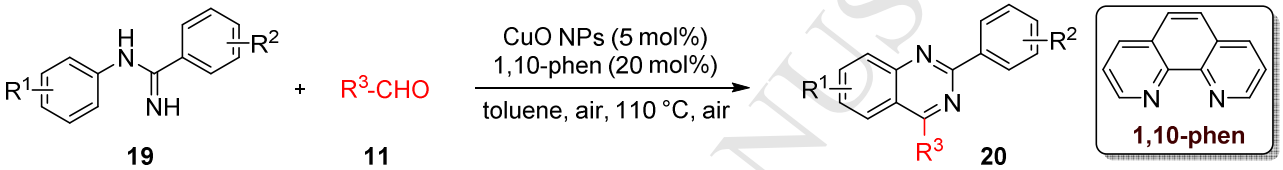
Scheme 3



14 11 12 15

R^1 = H, Cl, NO_2
R^2 = H, 4-Cl, 4-NO_2, 4-F, 4-Me, 2,4-Cl_2, 2-pyridyl

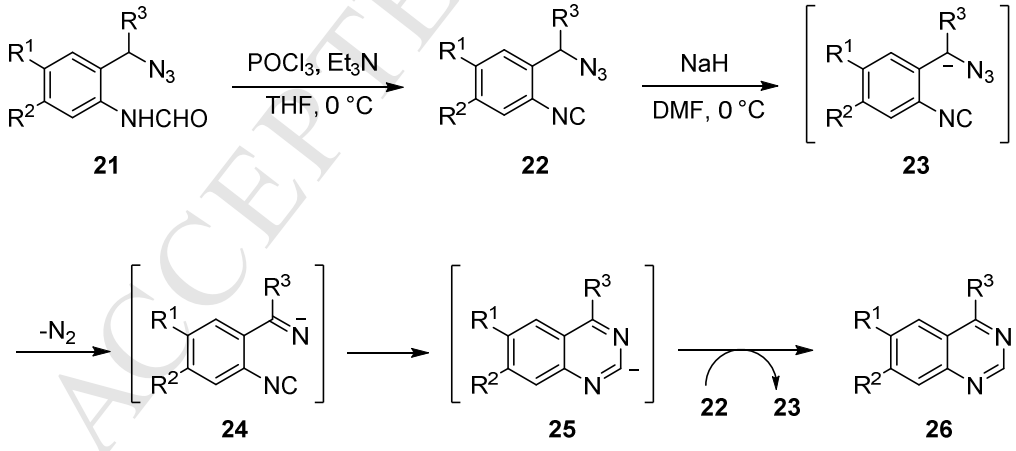
Scheme 4



19 11 20

R^1 = H, 4-Cl, 4-Me, 4-F, 2-Me, 3-Me
R^2 = H, 2-Me, 3-Me, 4-Me, 2-Cl, 4-Cl
R^3 = Ph, 4-Cl-Ph, 4-CN-Ph, 4-NO_2-Ph, 4-Me-Ph, 4-OMe-Ph, 2-OEt-Ph

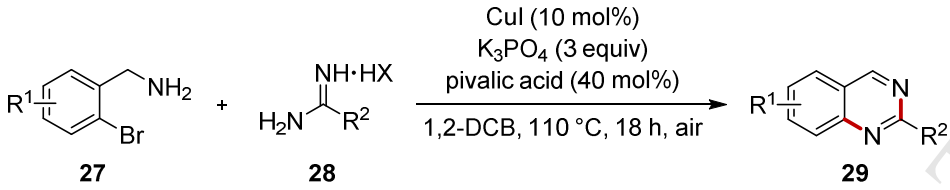
Scheme 5



21 22 23 24 25 26

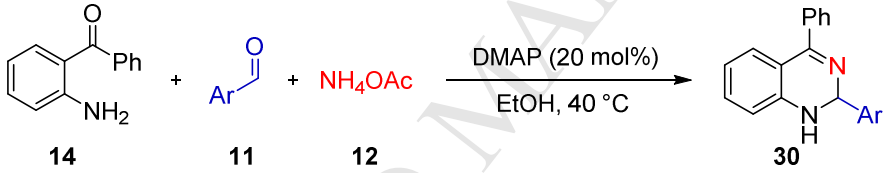
R^1 = H, Cl, Me, OMe
R^2 = H, OMe
R^3 = H, Me, Ph, 4-Cl-Ph, 4-Me-Ph

Scheme 6



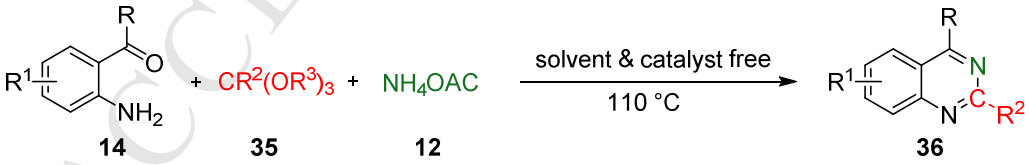
X = Cl, I
R^1 = H, Me, F
R^2 = Ph, 4-Me-Ph, 4-Cl-Ph, 3-NO_2-Ph, pyridyl, cyclopropyl

Scheme 7



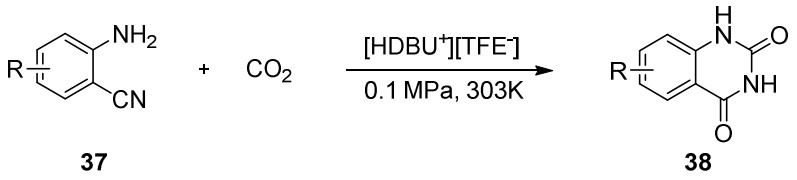
Ar = Ph, 4-Me-Ph, 2-Cl-Ph, 4-Cl-Ph, 3-NO_2-Ph, 4-Br-Ph, 3-I-Ph, biphenyl

Scheme 8



R = Me, Ph, 2-F-Ph
R^1 = H, 5-Cl, 5-NO_2, 4,5-diOMe
R^2 = H, Me, Et, Bu
R^3 = Me, Et

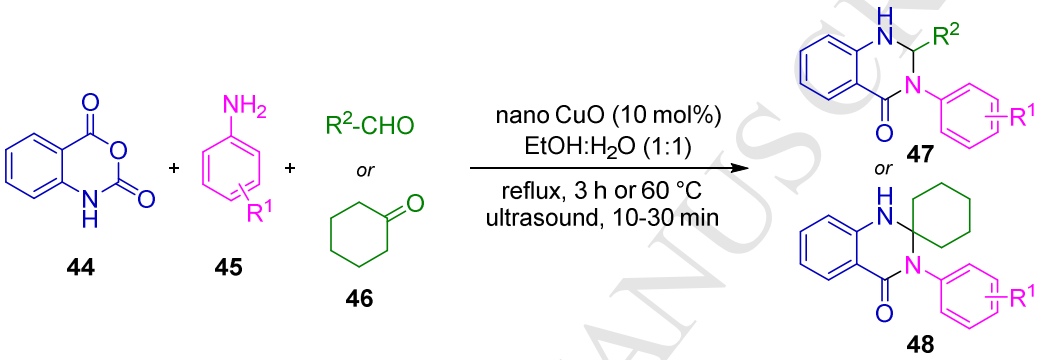
Scheme 9



37 38

R = H, Me, OMe, Cl, F, Br

Scheme 10

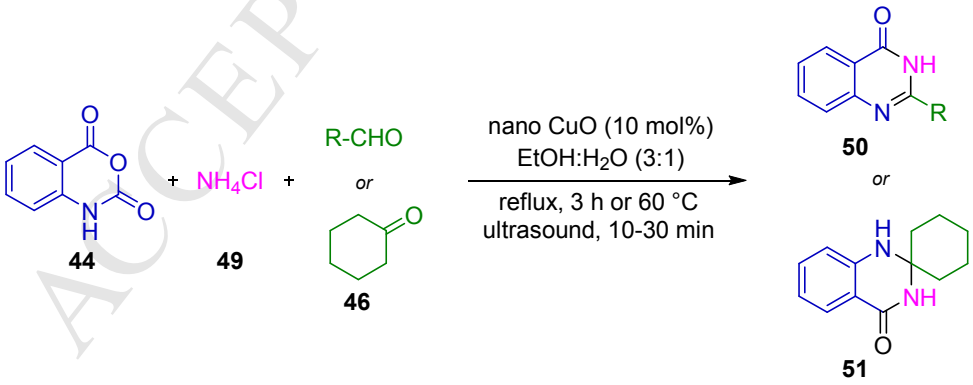


44 45 46 47 48

R^1 = H, OMe, NO_2

R^2 = Ph, 4-OMe-Ph, 4-OH-Ph, 4-NO_2-Ph, 4-*i*Pr-Ph, *i*-Pr, styryl, pyridyl, furyl

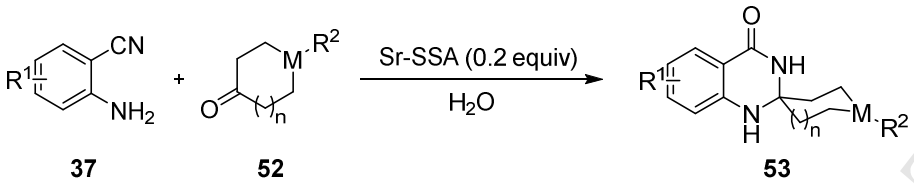
Scheme 11



44 49 46 50 51

R = Ph, 4-OMe-Ph, 2-OH-Ph, 4-NO_2-Ph, 4-*i*Pr-Ph, *i*-Pr, styryl, pyridyl, furyl

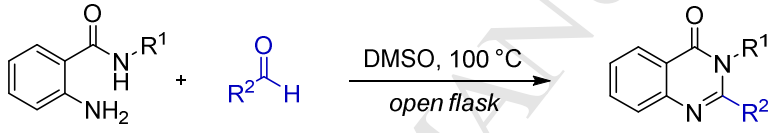
Scheme 12



37 **52** **53**

n = 0, 1
R^1 = H, 5-NO_2, 4-Cl, 4,5-diOMe
R^2 = H, Me, Bn

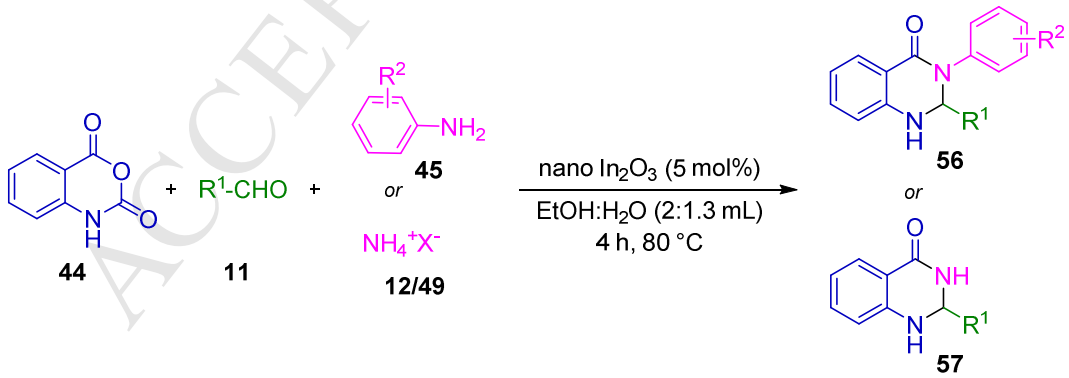
Scheme 13



54 **11** **55**

R^1 = Me, Ph, Bn
R^2 = H, Ph, C_6F_5, 4-OMe-Ph, 4-Me-Ph, 4-Cl-Ph, 4-NC-Ph, 2-Cl-Ph, naphthyl, furyl, pyridyl, thienyl, styryl, *n*-hexyl

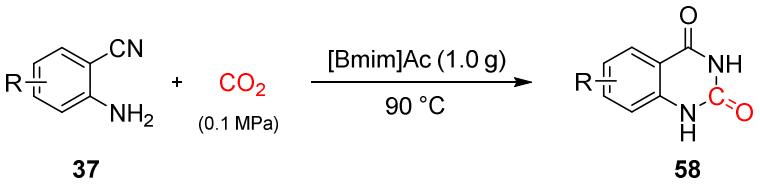
Scheme 14



44 **11** **12/49**

X^- = OAc, Cl, CO_3
R^1 = Ph, 4-Me-Ph, 4-Cl-Ph, 4-OMe-Ph, 4-NO_2-Ph, 2-Br-Ph, piperonyl
R^2 = Ph, 4-OMe-Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-Me-Ph, 4-Br-Ph, 2-Cl-Ph

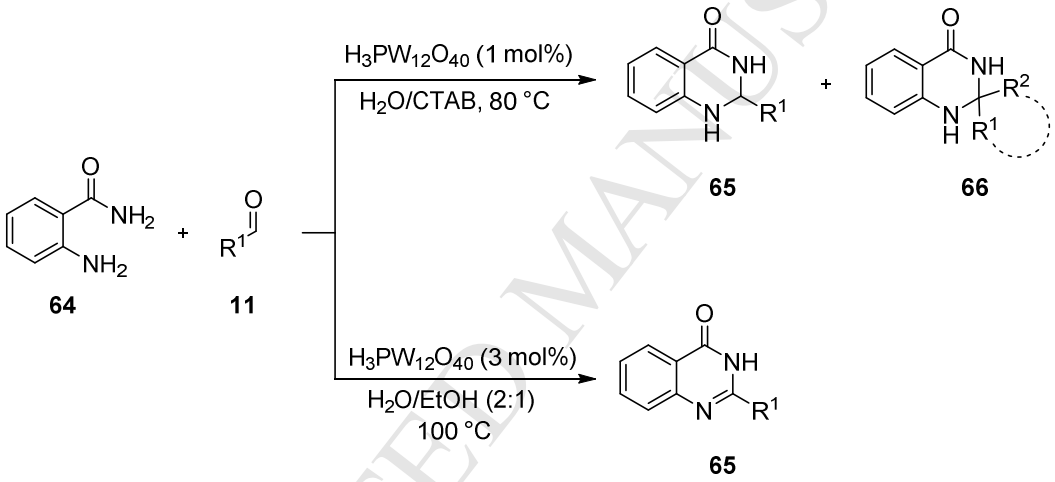
Scheme 15



37 58

R = H, 4-Cl, 5-Cl, 5-Br, 4,5-diOMe

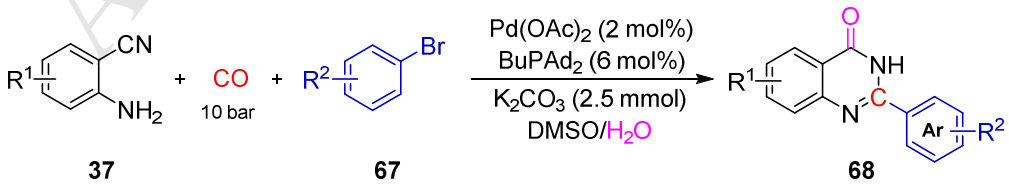
Scheme 16



64 11 65 66 65

R^1 = Ph, 4-Me-Ph, 4-Cl-Ph, 4-F-Ph, 3-NO_2-Ph, 3-Br-Ph, 4-NC-Ph, pyridyl, naphthyl
R^1 = R^2 = acetone, 2-butanone, acetophenone, isatin, 5-chloroisatin

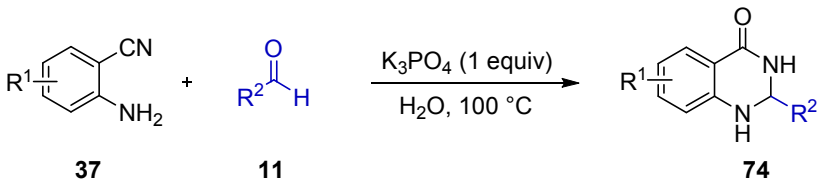
Scheme 17



37 67 68

R^1 = H, 5-Me, 6-Me, 5-Cl, 3,4-diOMe, 4,5-diOMe
R^2 = H, 2-Me, 4-Me, 4-NMe_2, 4-*t*Bu, 4-F, 4-CF_3, biphenyl, naphthyl, pyridyl, indolyl

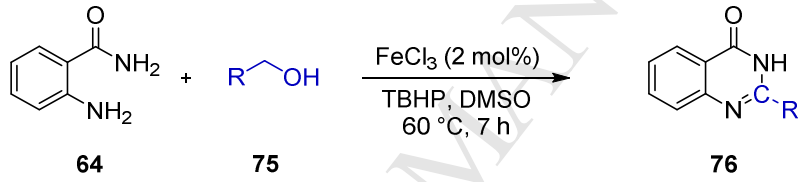
Scheme 18



37 **11** **74**

R^1 = H, 3-Cl, 5-Cl, 6-F, 5-Me, 6-Me, 3,4-diOMe
R^2 = *i*-Pr, Ph, 3,4-Cl_2-Ph, 2-Me-Ph, 4-F-Ph, cyclohexyl, pyridyl, benzothiazolyl, indolyl

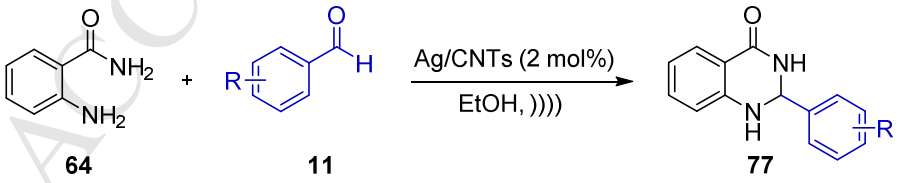
Scheme 19



64 **75** **76**

R = Me, Ph, 4-Me-Ph, 4-OMe-Ph, 4-F-Ph, 4-Cl-Ph, 2-Br-Ph, furyl, heptyl, naphthyl

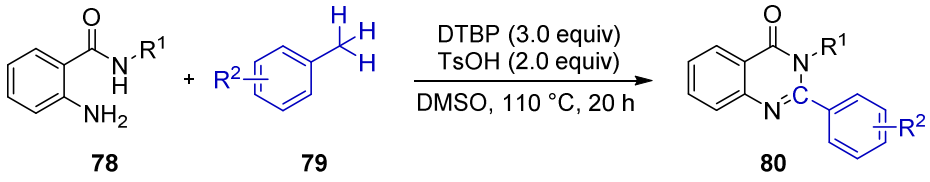
Scheme 20



64 **11** **77**

R = H, 2-OH, 4-F, 4-Br, 3-Cl, 2-F, 2-NO_2, 2,4-Cl_2, 2,3-Cl_2, 4-NMe_2, 2-OMe, 2,3-diOMe

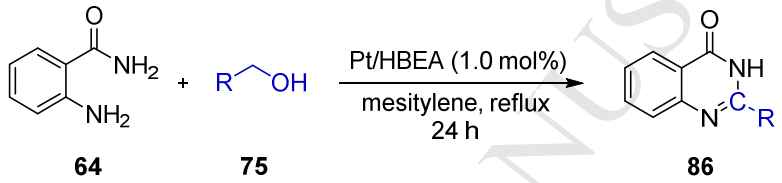
Scheme 21



78 79 80

R^1 = H, Me, Ph, *n*-Pr, *i*-Bu
R^2 = 2-Me,3-Me, 4-Me, 4-F, 4-OMe, 2-Cl, 4-F, 4-CF_3

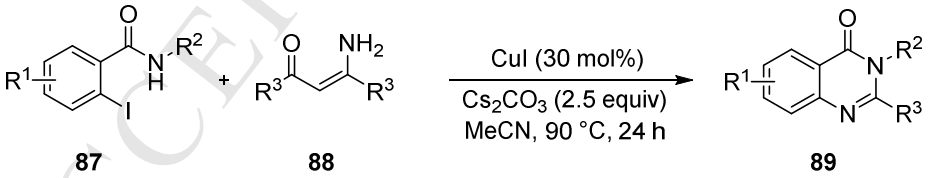
Scheme 22



64 75 86

R = Ph, 4-Me-Ph, 4-*t*-Bu-Ph, 4-Cl-Ph, 4-F-Ph, pyridyl, thienyl, furyl, cyclohexyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-nonyl, isopropyl

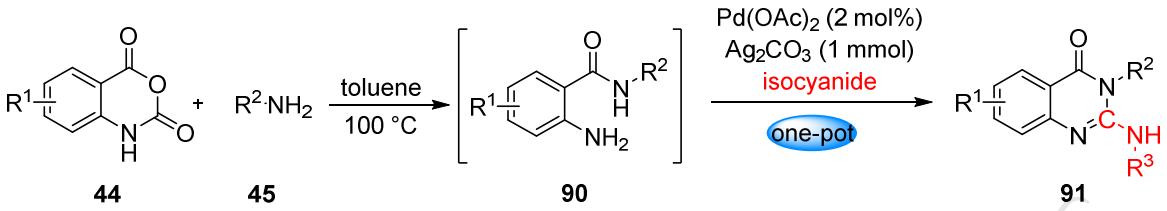
Scheme 23



87 88 89

R^1 = H, Br, Cl, OMe
R^2 = Me, Ph, Bn
R^3 = Me, *i*-Pr, *i*-Bu, Ph, 4-OMe-Ph

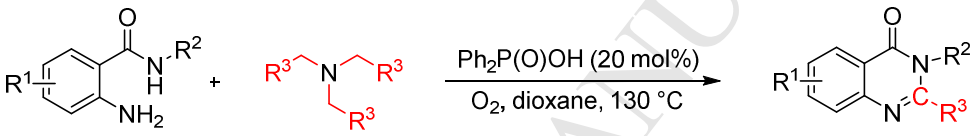
Scheme 24



44 45 90 91

R^1 = H, F, Cl, Me
R^2 = Ph, *i*-Pr, Bn, 4-Me-Ph, 4-Cl-Ph
R^3 = *i*-Bu, cyclohexyl

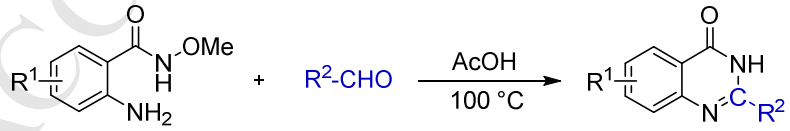
Scheme 25



90 95 96

R^1 = H, Me, Cl
R^2 = H, Me
R^3 = Me, Et, *n*-Pr, Ph

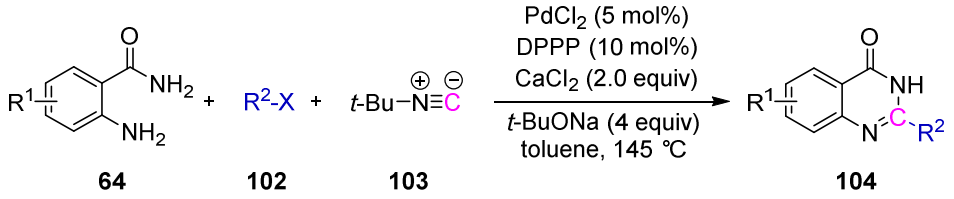
Scheme 26



100 11 101

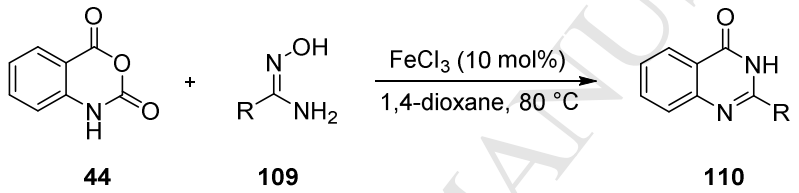
R^1 = H, 5-Br, 3-Me, 4-OMe, 6-Cl, 4-F
R^2 = Ph, 4-Me-Ph, 3-Cl-Ph, 4-F-Ph, 4-Br-Ph, 4-OH-Ph, *n*-Pr, Me, *i*-Pr

Scheme 27



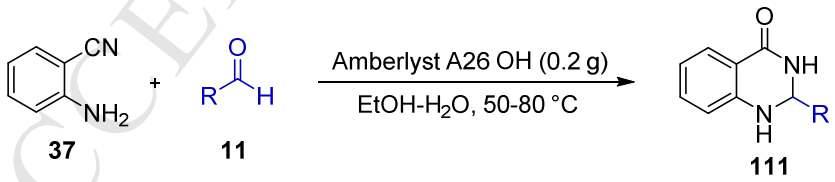
X = I, Br
R^1 = F, Cl, Me
R^2 = Ph, 4-Me-Ph, 4-Cl-Ph, 4-F-Ph, 3-OMe-Ph, 4-CF_3-Ph, thienyl, biphenyl, naphthyl

Scheme 28



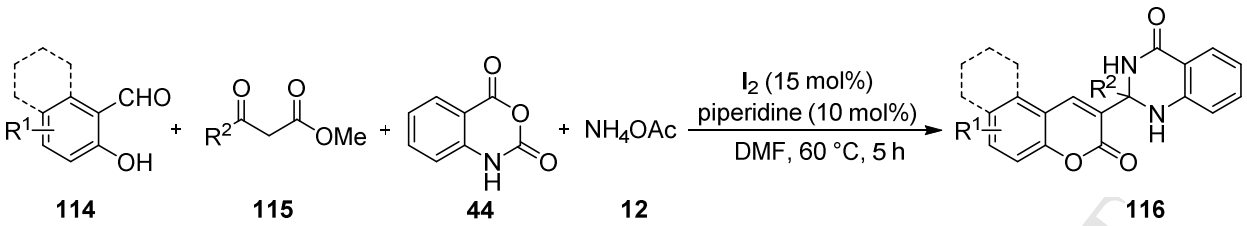
R = Ph, 4-Me-Ph, 4-Br-Ph, 4-OH-Ph, 4-NH_2-Ph, 4-F-Ph, 4-OMe-Ph, *t*-Bu, pyridyl

Scheme 29



R = Ph, 4-Me-Ph, 4-F-Ph, 4-Cl-Ph, 4-NO_2-Ph, 4-OMe-Ph, *n*-Pr, pyridyl

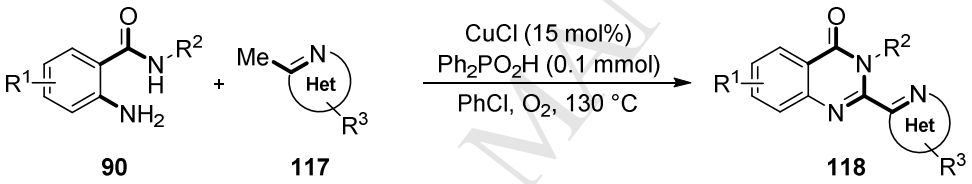
Scheme 30



114 **115** **44** **12** **116**

R^1 = H, 3-OMe, 5-Me, 3,5-Cl_2, 3,5-Br_2, 2-OH
R^2 = Me, *n*-Pr, *i*-Pr, *t*-Bu

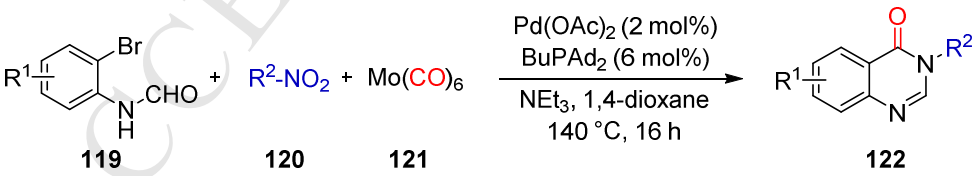
Scheme 31



90 **117** **118**

R^1 = H, Cl, Me
R^2 = H, Me
R^3 = Pyridyl, 3-Et-pyridyl, 2-Me-pyridyl, quinolyl, benzothiazolyl, thiazolyl

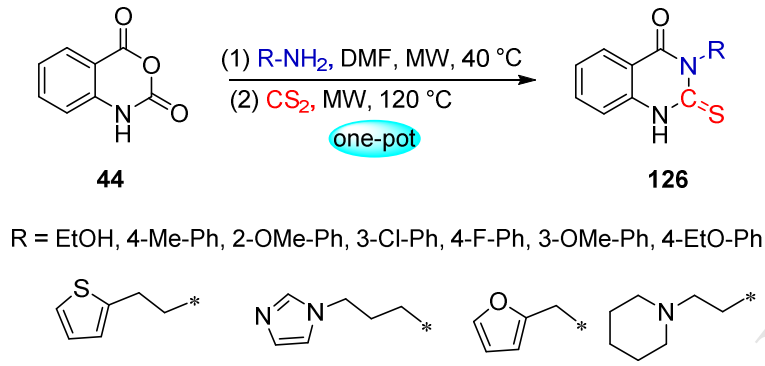
Scheme 32



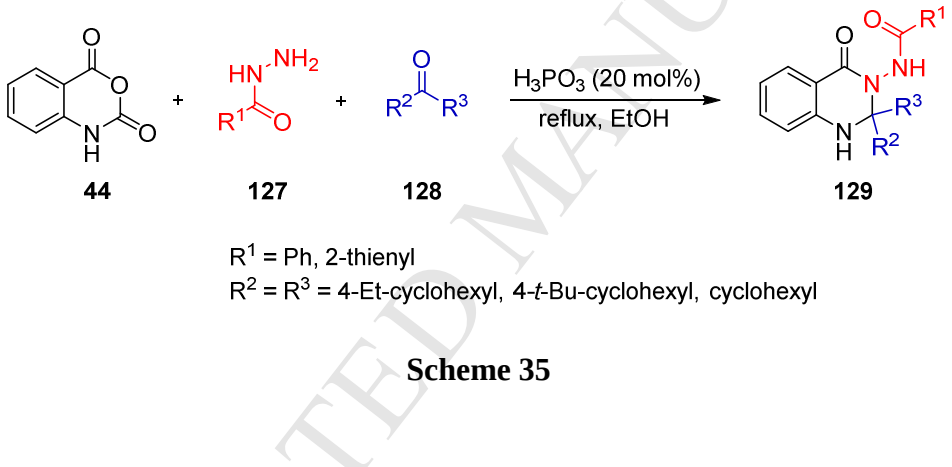
119 **120** **121** **122**

R^1 = 5-Me, 4-Me, 4-Cl, 6-F, 5-CF_3, 5-OCF_3
R^2 = Ph, 4-Me-Ph, 4-*i*Pr-Ph, biphenyl, naphthyl

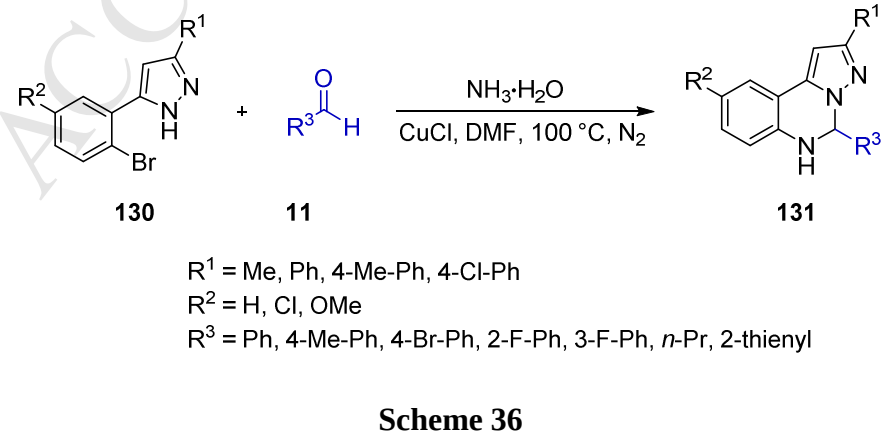
Scheme 33



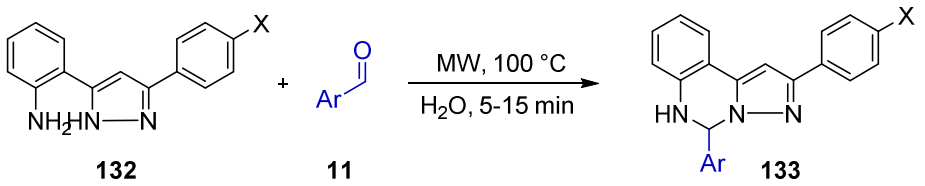
Scheme 34



Scheme 35



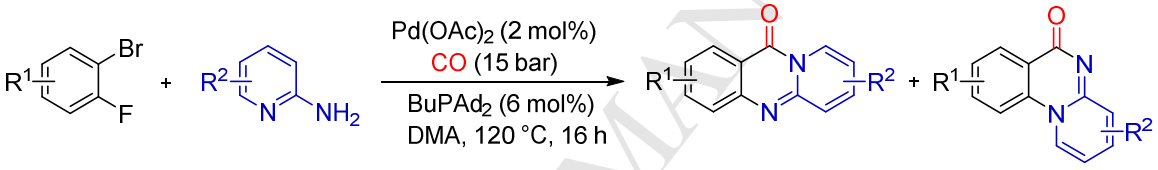
Scheme 36



132 11 133

X = H, Cl
Ar = 4-OH-3-OMe-Ph, 4-OMe-3-OH-Ph, 2,5-diOMe-Ph, 4-OH-Ph, 4-NC-Ph, 2-NO_2-Ph, 3-NO_2-Ph, indolyl

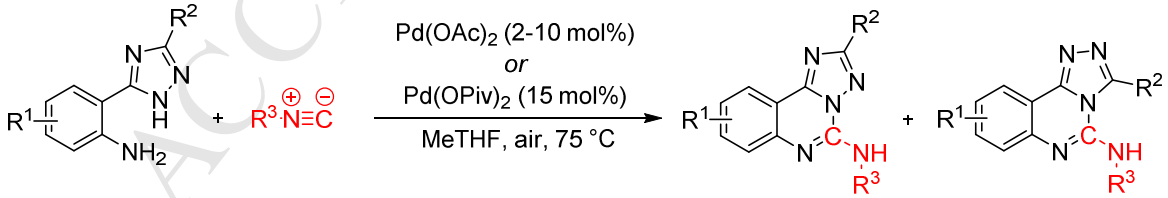
Scheme 37



134 135 136 137

R^1 = H, F, Cl, COMe
R^2 = H, F, Cl, Me, CN

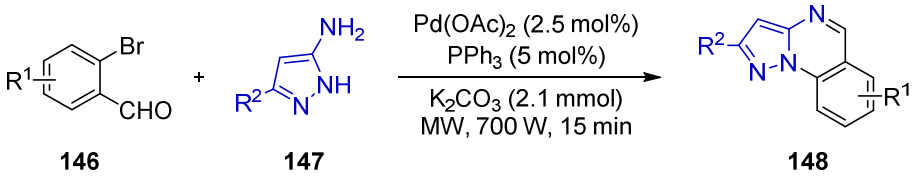
Scheme 38



143 103 144 145

R^1 = H, 9-Cl, 9-F, 7-Me, 8,9-diOMe
R^2 = Ph, 4-CF_3-Ph, 2-furyl, 3-pyridyl
R^3 = *i*-Pr, *t*-Bu, *n*-Pent, Bn, *c*-Hex

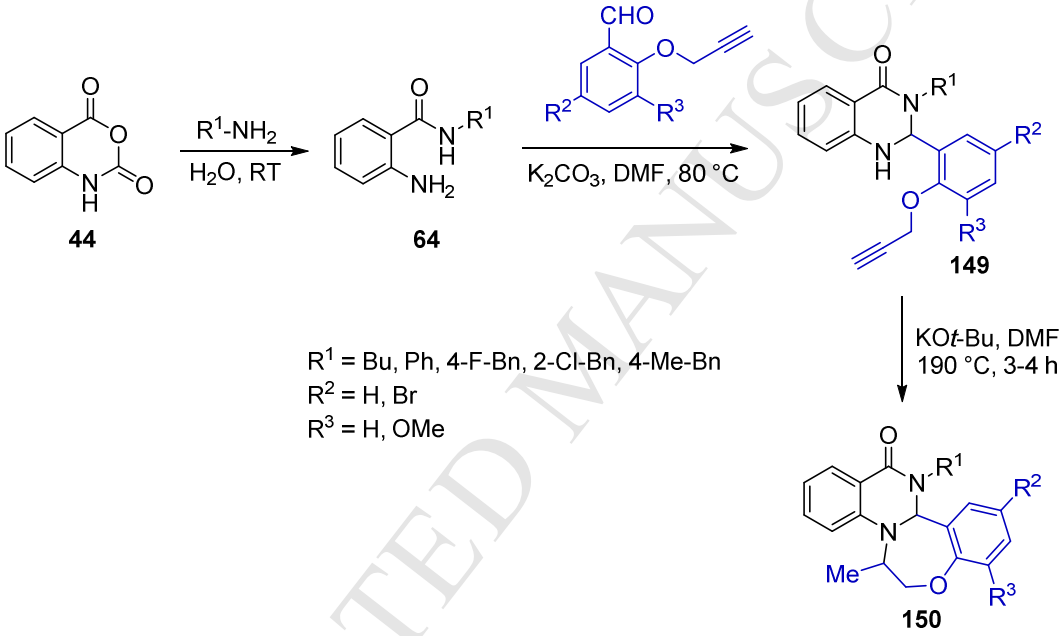
Scheme 39



146 147 148

R^1 = H, Me, F
R^2 = H, Me

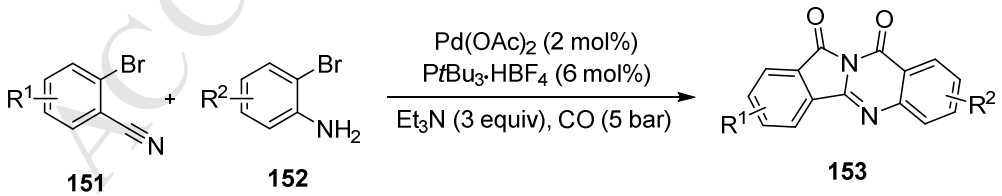
Scheme 40



44 64 149 150

R^1 = Bu, Ph, 4-F-Bn, 2-Cl-Bn, 4-Me-Bn
R^2 = H, Br
R^3 = H, OMe

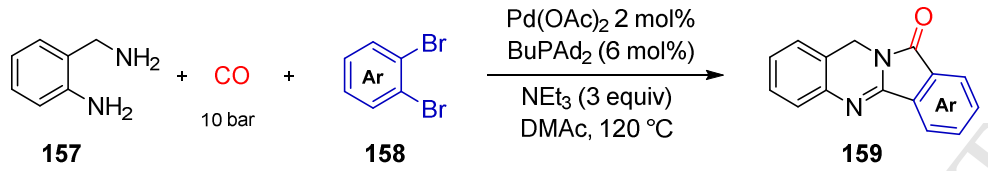
Scheme 41



151 152 153

R^1 = 2-Me, 4-Me, 5-Me, 5-OMe, 4-F, 6-F
R^2 = H, 4-Cl, 4,6-diF, 4-F,6-Cl, 4-Ac

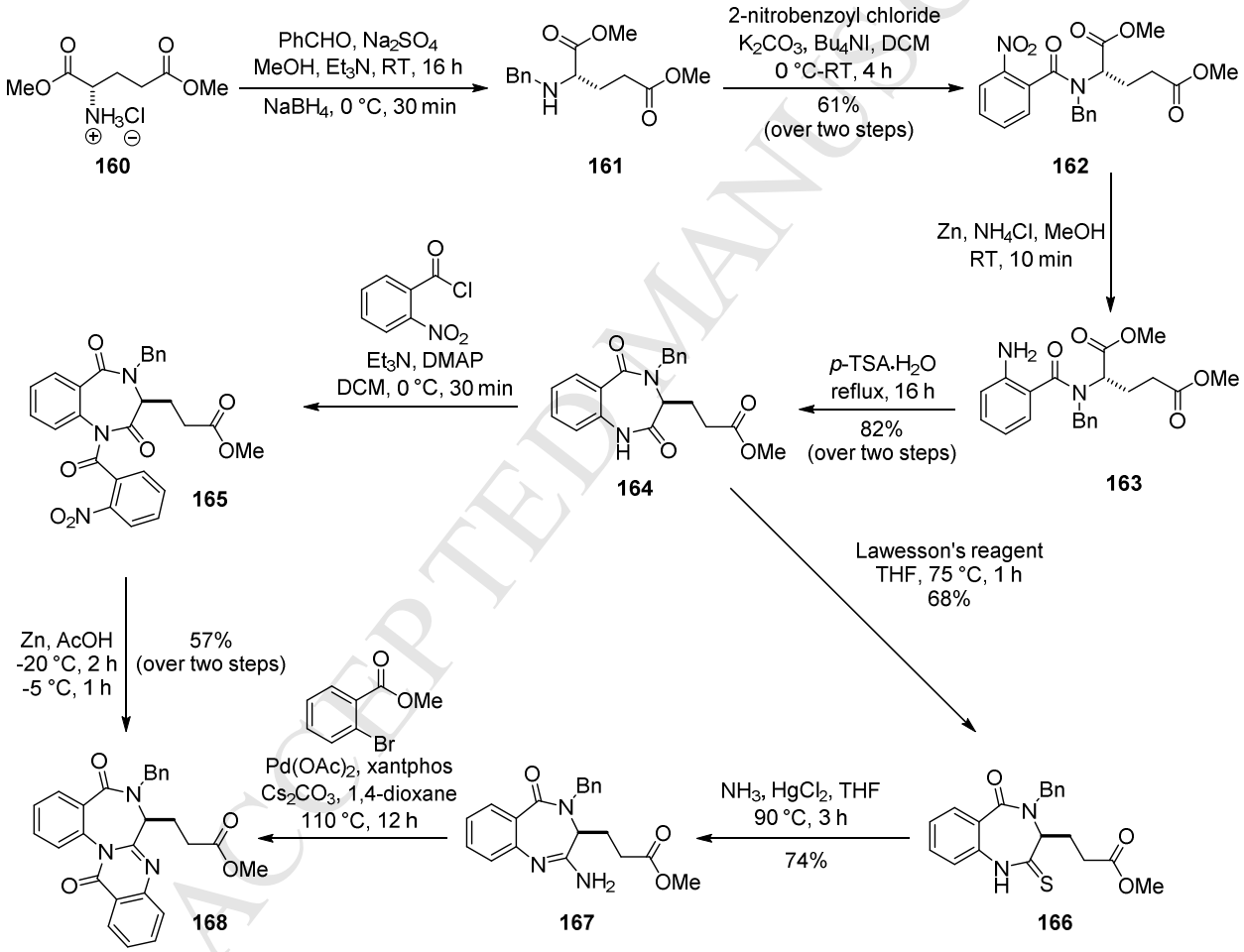
Scheme 42



157 158 159

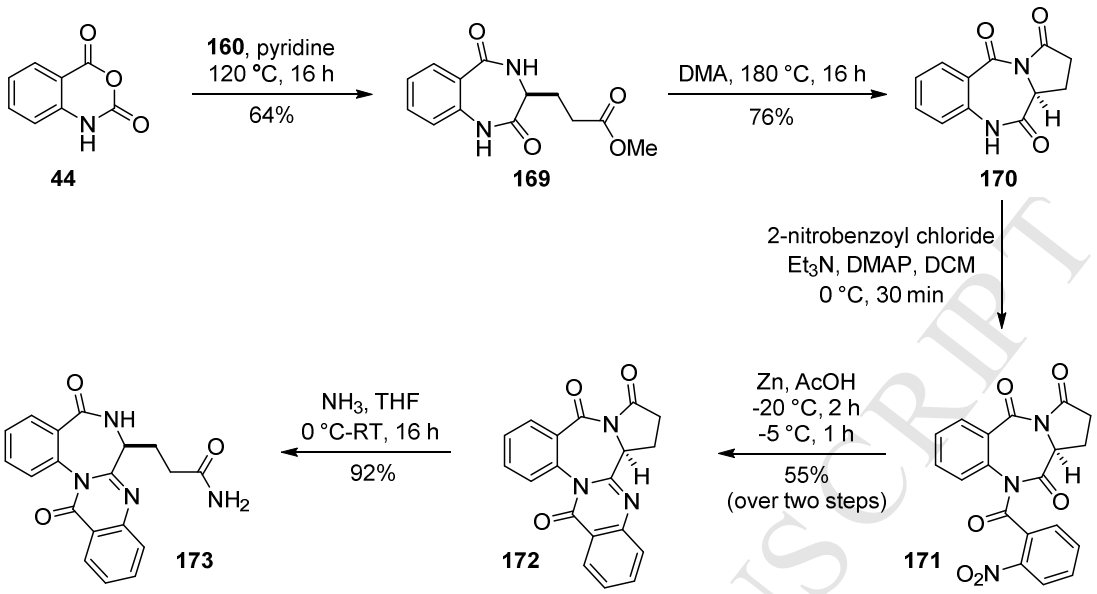
R = H, 5-Me, 4,5-diMe, 4,5-diOMe, 5-Me-pyridyl, benzothiazolyl

Scheme 43

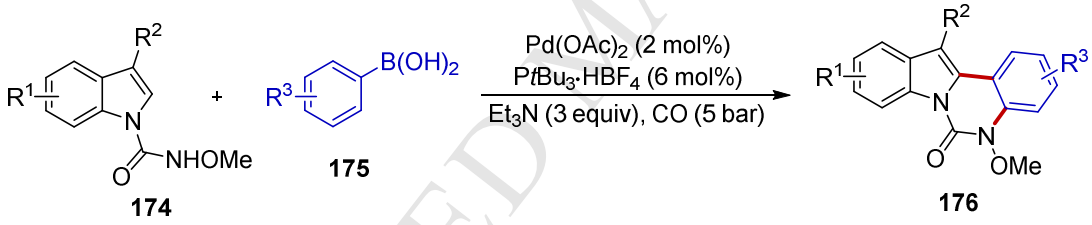


160 161 162 163 164 165 166 167 168

Scheme 44

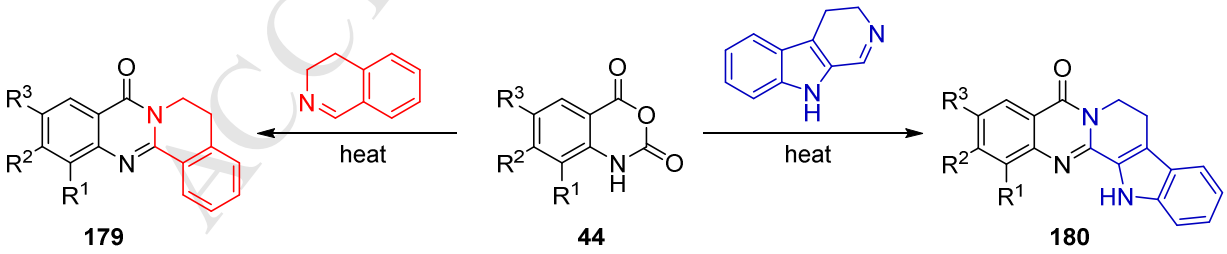


Scheme 45



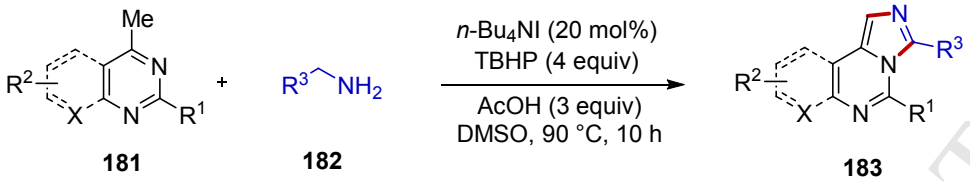
R^1 = Me, OMe, Br, OBn
R^2 = H, Me, OMe, OBn
R^3 = H, 2-Me, 4-Me, 2-OMe, 4-OMe, 4-Ph, 4-Cl, 4-Br, 3,5-diMe

Scheme 46



R^1 = H, OMe, Br
R^2 = H, OMe
R^3 = H, OH, OMe, OBn, Me, Cl, NO_2

Scheme 47

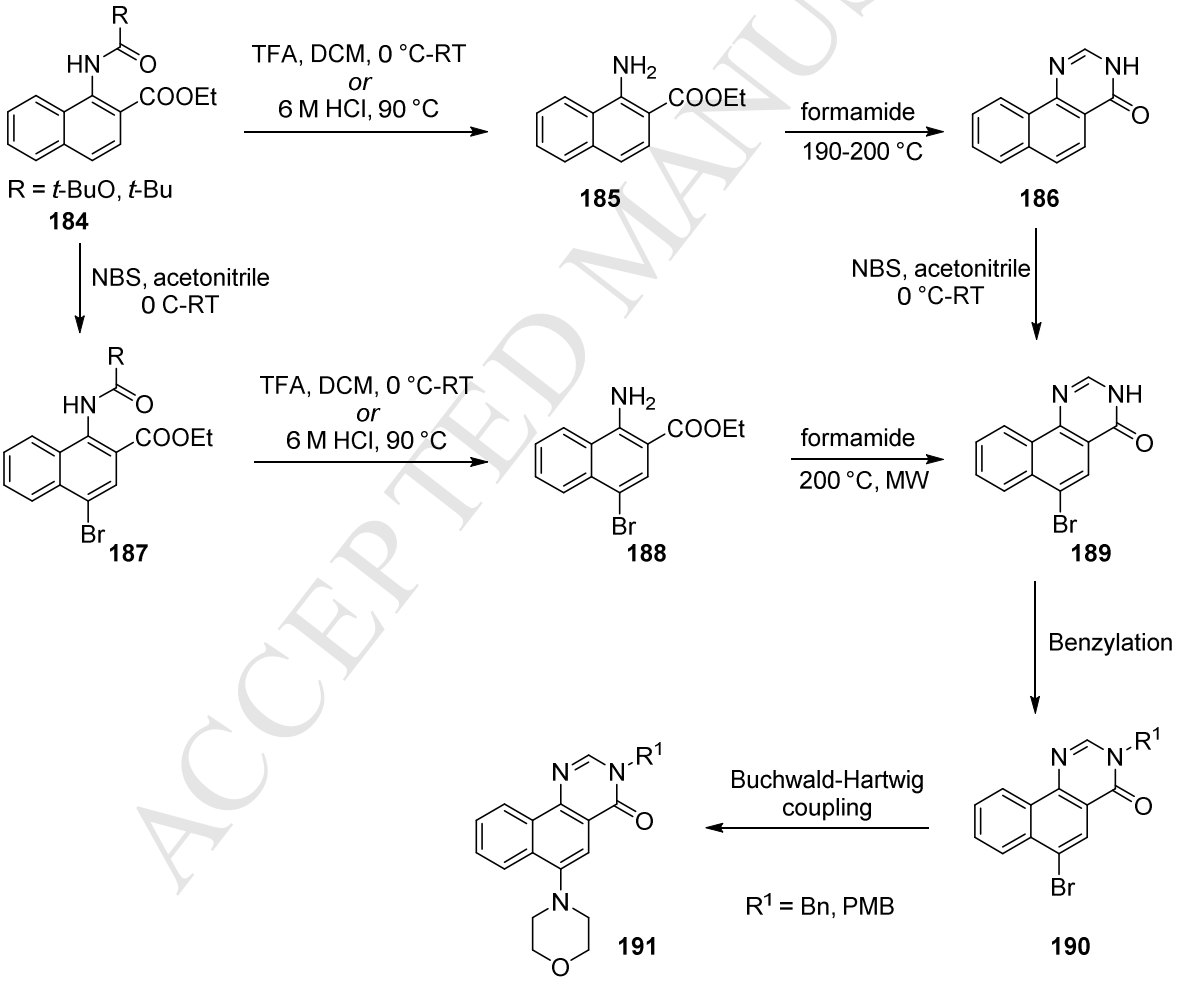


X = C, N

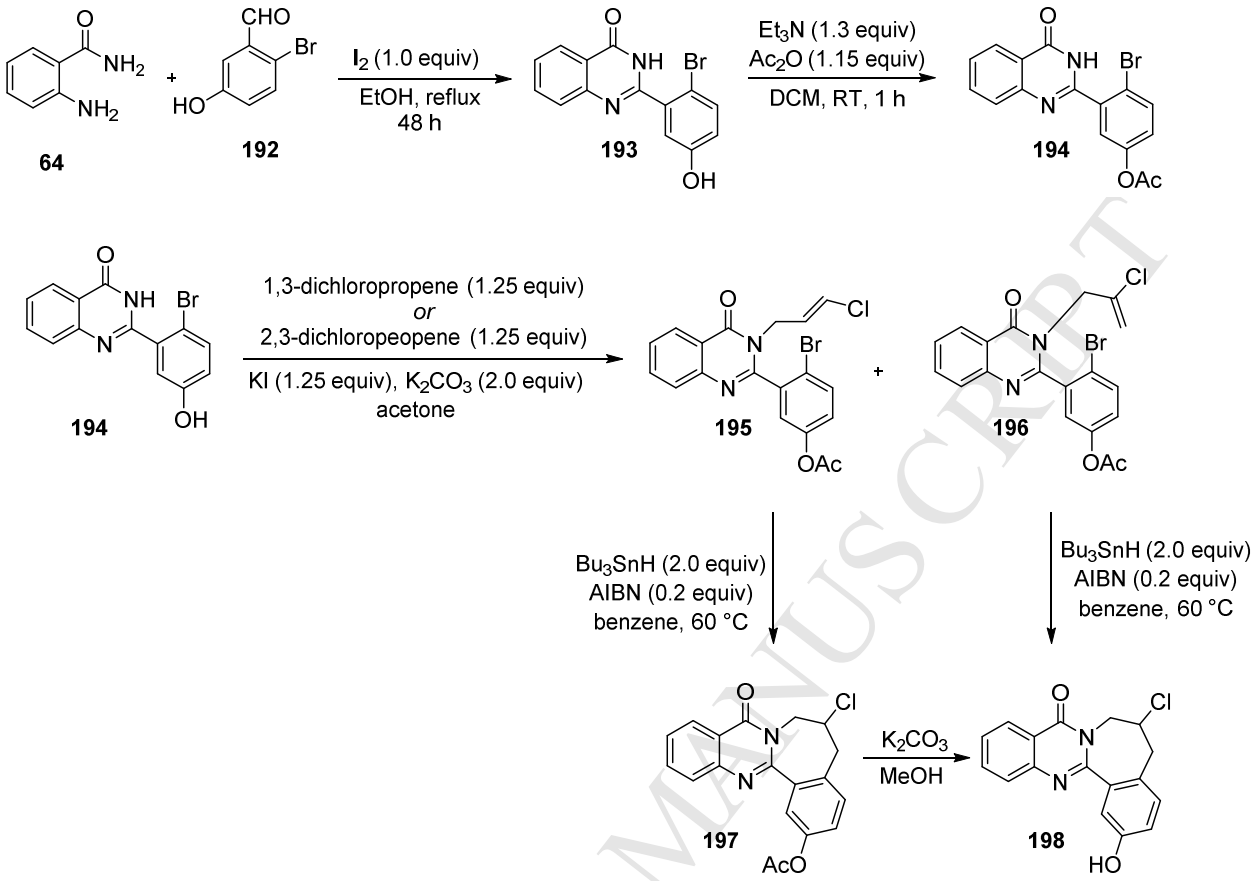
R^1 = Ph, 4-*t*-Bu-Ph, 4-OMe-Ph, 4-CF_3-Ph, 4-NO_2-Ph, 3-Cl-Ph, 2-F-Ph, cyclopropyl, cyclohexyl, thienyl, furyl, pyridyl, morpholinyl, piperidyl

R^3 = Ph, 2-Me-Ph, 3-Me-Ph, 4-Me-Ph, 4-OMe-Ph, 4-F-Ph, 4-Cl-Ph, 4-Br-Ph, 4-CF_3-Ph, naphthyl, thienyl, furyl, pyridyl

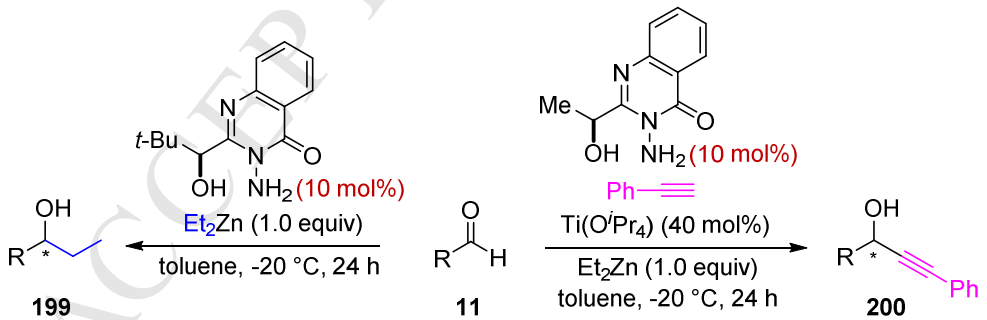
Scheme 48



Scheme 49

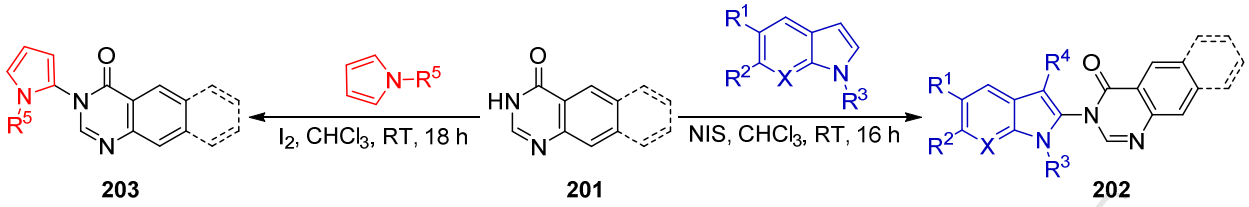


Scheme 50



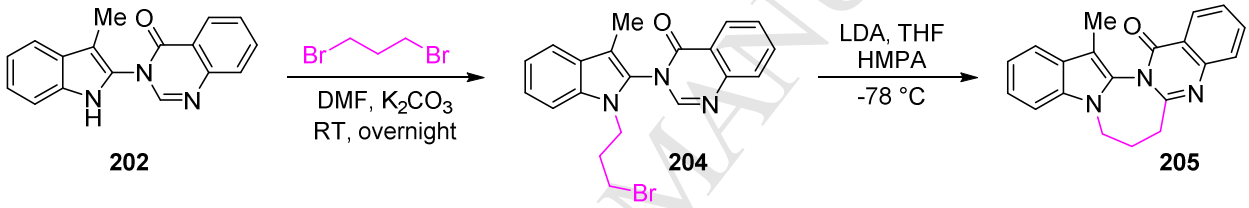
R = Ph, 2-Cl-Ph, 2-OMe-Ph, 4-Me-Ph, naphthyl, pyridyl, cyclohexyl

Scheme 51

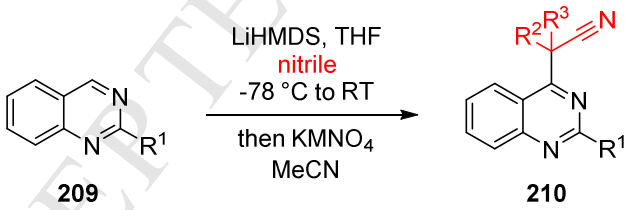


X = H, N
R^1 = H, Br, OMe
R^2 = H, Br
R^3 = H, Me, SO_2Ph, *n*-Bu
R^4 = H, I
R^5 = H, Me, Bn

Scheme 52

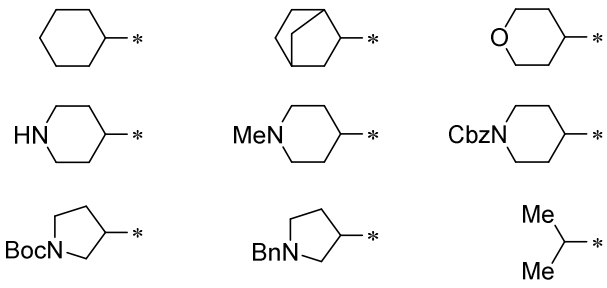


Scheme 53

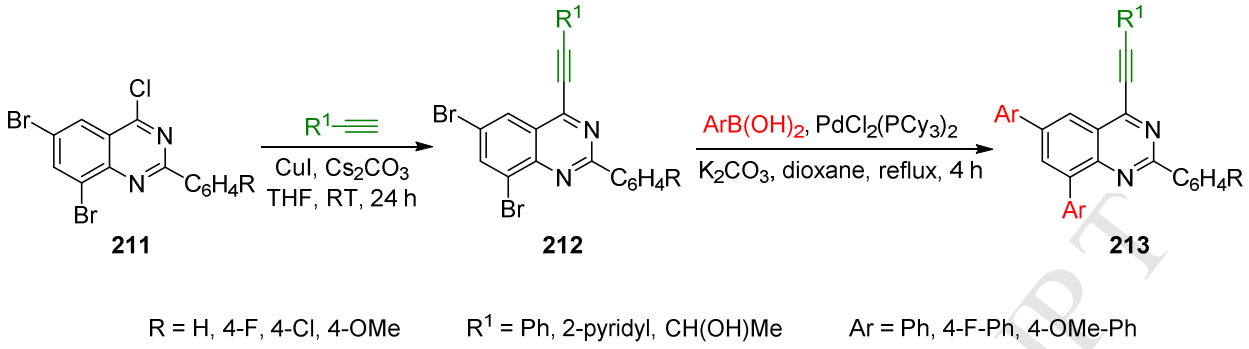


R^1 = H, Cl, COOEt

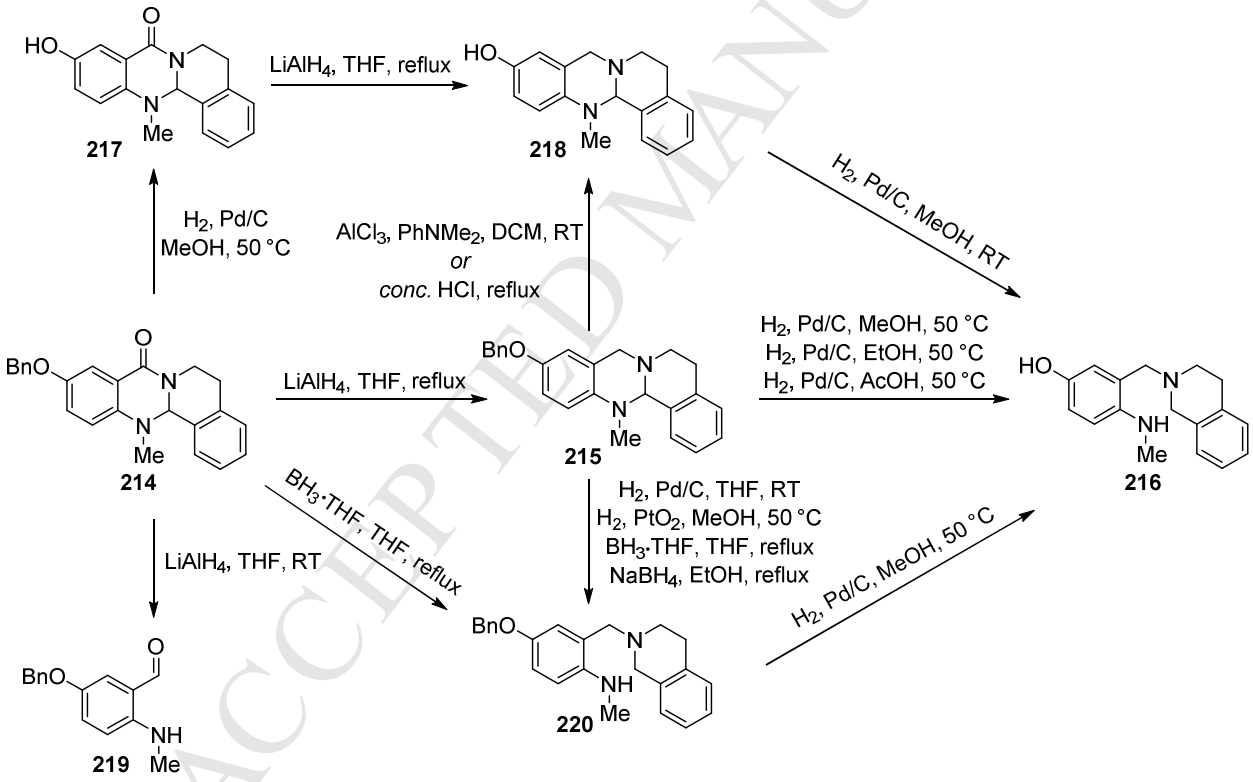
R^2 = R^3 =



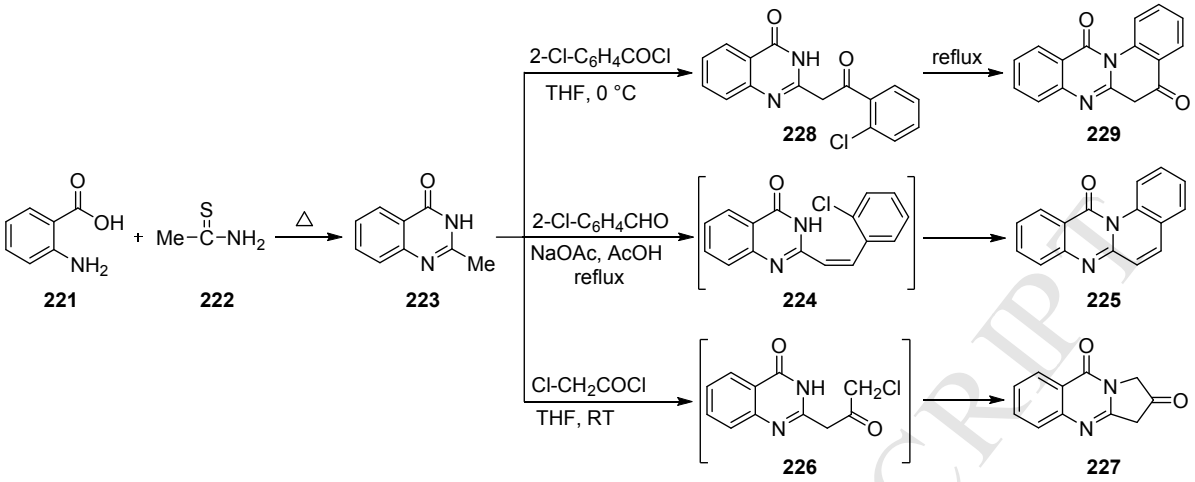
Scheme 54



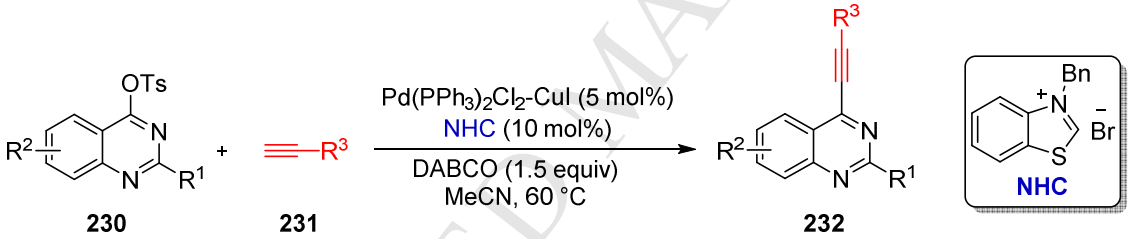
Scheme 55



Scheme 56



Scheme 57



R^1 = Ph, 4-OMe-Ph, 4-Me-Ph, 4-*i*Pr-Ph
R^2 = H, Cl
R^3 = Ph, 4-OMe-Ph, 4-Cl-Ph, 3-F-Ph, 4-OEt-Ph, 4-Et-Ph, *n*-Bu, cyclopropyl

Scheme 58