

Synopsis

The work carried out in the research tenure has been accumulated in the form of thesis entitled as “**UTILIZING QUINAZOLINONES FOR THE Ru-, Rh-, Pd-CATALYZED C–C, C–N, C–O BOND FORMATION REACTIONS: SYNTHESIS AND ANTICANCER ACTIVITIES OF N-HETEROCYCLES**”. The main aim of this work was the functionalization of quinazolinones by fine-tuning transition metal-catalysis to obtain heterocycles of biological interest. Further, synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, (*E*)-3-aryl-1-(5-(2-arylimidazo[1,2-*a*]pyridin-3-yl)thiophen-2-yl)prop-2-en-1-ones and evaluation of their anticancer activity. The thesis has been divided into four chapters.

CHAPTER-1: Describes the general introduction of transition metal-catalyzed cross-coupling/annulation, carbenoid insertion, alkenylation and heteroarylation reactions.

CHAPTER-2: Describes the ruthenium as a single catalyst for two steps: one-pot ruthenium(II)-catalyzed aerobic oxidative dehydrogenation of dihydroquinazolinones and cross-coupling/annulation to give N-fused polycyclic heteroarenes.

CHAPTER-3: This chapter consists of two sections.

SECTION-A: This section deals with the rhodium(II)-catalyzed carbenoid insertion of *N*-tosylhydrazones into amide N–H bonds: an efficient approach to *N*³-benzyl/alkyl-2-arylquinazolinones.

SECTION -B: This section describes the palladium(II)-catalyzed direct *O*-alkenylation of 2-arylquinazolinones with *N*-tosylhydrazones: an efficient route to *O*-alkenylquinazolines.

CHAPTER-4: This chapter consists of two sections.

SECTION-A: This section deals with convenient and scalable synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives and their anticancer activities.

SECTION-B: This section illustrates palladium(0)-catalyzed direct C–H heteroarylation of 2-arylimidazo [1,2-*a*]pyridines with (*E*)-1-(5-bromothiophen-2-yl)-3-arylprop-2-en-1-ones and their anticancer activity.

CHAPTER-1

General Introduction of Transition Metal-Catalyzed Cross-Coupling/Annulation, Carbenoid Insertion, Alkenylation and Heteroarylation Reactions.

Introduction: Quinazolinone as a building block occurs widely in natural products that exhibit a broad range of useful biological and pharmacological activities. It is assigned as a privileged skeleton in drug discovery.^[1] The construction of new carbon–carbon and carbon–heteroatom bonds is the most vital tool in organic chemistry, critical for the synthesis of organic compounds that exhibit significant biological, pharmaceutical and material

properties.^[2] In this chapter, we discussed different types of transition metal-catalyzed cross-coupling/annulation, carbenoid insertion, alkenylation and heteroarylation reactions with examples and recent applications of these reactions.

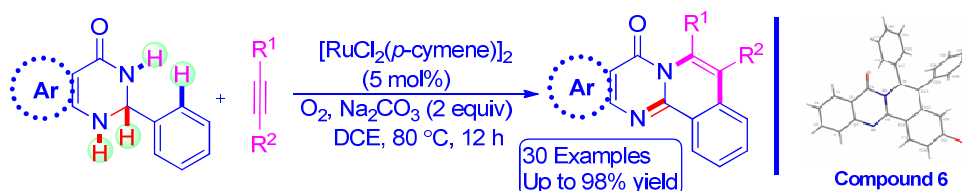
CHAPTER-2

Ruthenium as a Single Catalyst for Two Steps: One-Pot Ruthenium(II)-Catalyzed Aerobic Oxidative Dehydrogenation of Dihydroquinazolinones and Cross-Coupling/Annulation to give N-Fused Polycyclic Heteroarenes. [*Asian J. Org. Chem.* **2015**, *4*, 462–469]

Introduction: Transition metal-mediated C–H bond functionalizations for C–C and C–heteroatom bond formation has evolved as a powerful tool for constructing complex structures.^[3] Due to highly-attractive green and sustainable advantages, molecular oxygen finds increasing use in both the commodities chemical industry and the academic labs.

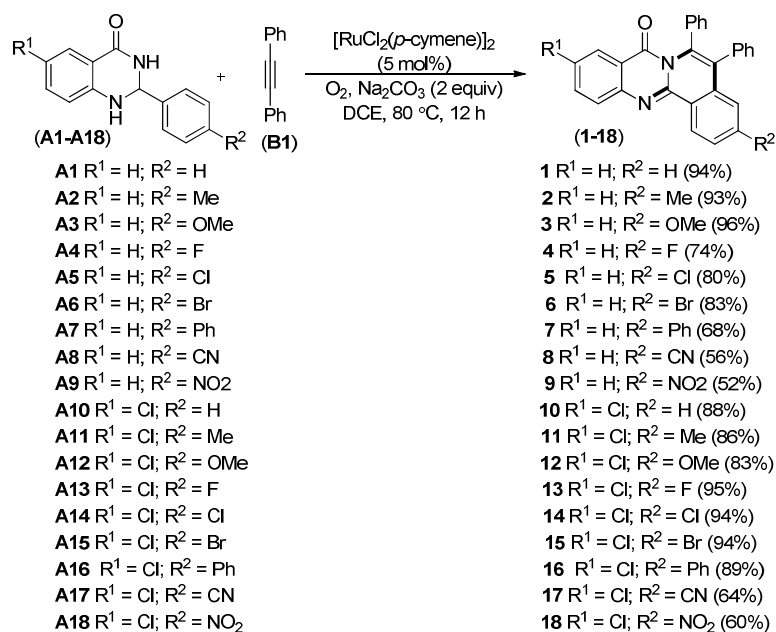
Statement of problem: Ruthenium(II)-catalyzed alkynes annulations with directing group containing arenes reported thus far required the use of additional oxidants, such as copper(II) or silver(I) salts, thereby leading to the formation of undesired stoichiometric metal-containing by-products.

Methodology used:

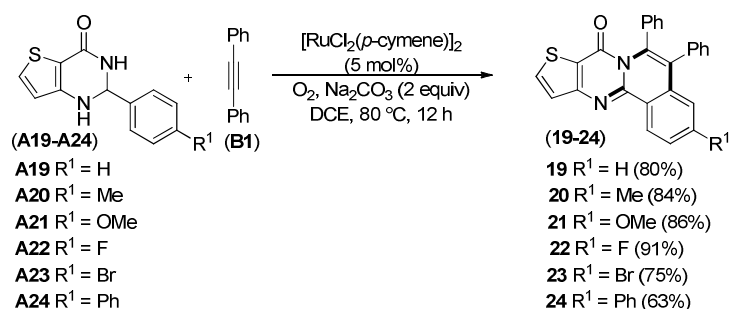


Results and Discussion: One-pot oxidative dehydrogenation of dihydroquinazolinones followed by cross-coupling/annulation with alkynes to access N-fused polycyclic heteroarenes was performed in the presence of [RuCl₂(*p*-cymene)]₂ (5 mol%), O₂ (balloon), Na₂CO₃ (2 equiv) in DCE (2 mL) at 80 °C for 12 h. First, we investigated the dihydroquinazolinones scope (Scheme 1). Products (**1-9**) were obtained in good to excellent yields with excellent functional-group tolerance. Electron-rich substrates gave high yields. The structure of the product **6** was confirmed by single crystal X-ray diffraction. Moreover, 6-chloro-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one derivatives bearing electron-neutral, -donating and -withdrawing groups were tested (**10-18**). We further tested heterocyclic dihydroquinazolinones, corresponding products (**19-24**) were obtained in good to excellent yields (Scheme 2). Scope of alkynes was then investigated using **A1** as the coupling partner (Scheme 3). Aryl alkynes (**B2**) as well as more challenging alkyl alkynes (**B3-B5**) are also tolerated (**25-28**). Regioselectivity of the C–H activation was evaluated (Scheme 4), with

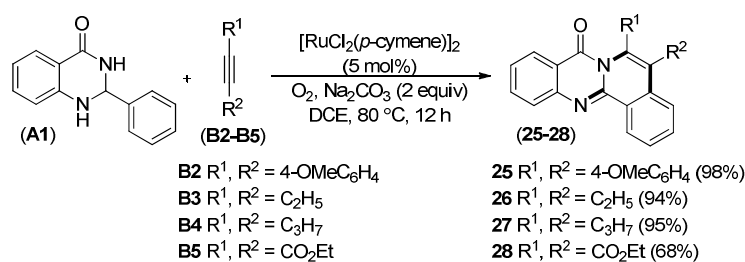
A25 produced exclusively one product **29** in 85% yield. When unsymmetrical alkyne was employed, two regioisomeric products **30a** and **30b** were obtained in 82% and 10% yields



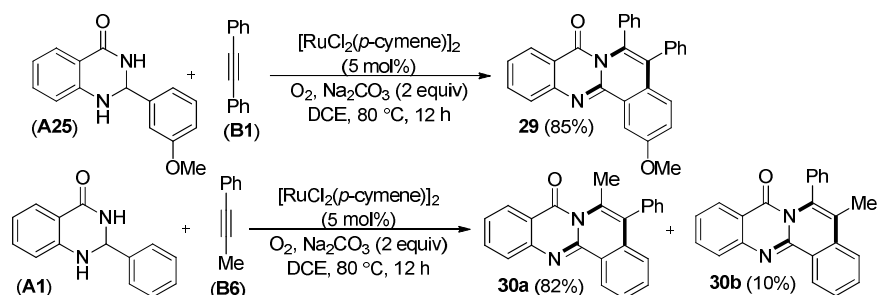
Scheme 1



Scheme 2



Scheme 3



Scheme 4

respectively. For alkynes and dihydroquinazolinones, intermolecular competition experiments were conducted. Results revealed that the aromatic alkyne and dihydroquinazolinone with electron-donating group showed higher reactivity. Mechanistic investigations revealed that CONH group serves as directing group and is essential for the annulation process. Further in two steps one-pot process, oxidative dehydrogenation occurs first, followed by cross-coupling/annulation. Based on the experimental results, a plausible mechanism has been illustrated.

In summary, ruthenium(II)-catalyzed, aerobic oxidative dehydrogenation, cross-coupling/annulation *via* C–H/N–H bond activation of dihydroquinazolinones with alkynes in one-pot to access *N*-fused polycyclic compounds was described.

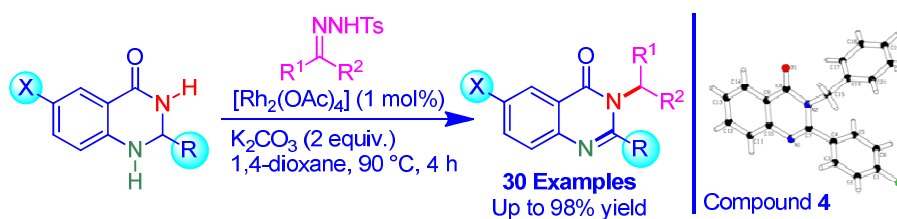
CHAPTER-3 (Section-A)

Rhodium(II)-Catalyzed Carbenoid Insertion of *N*-Tosylhydrazones into Amide N–H Bonds: An Efficient Approach to *N*³-Benzyl/Alkyl-2-arylquinazolinones. [*Adv. Synth. Catal.* **2016**, *358*, 81–89]

Introduction: The transition metal-catalyzed insertion of metal-carbenoids into C–H or X–H (X = heteroatom) bonds represents an excellent and powerful method for the formation of C–C or C–X bonds.^[4]

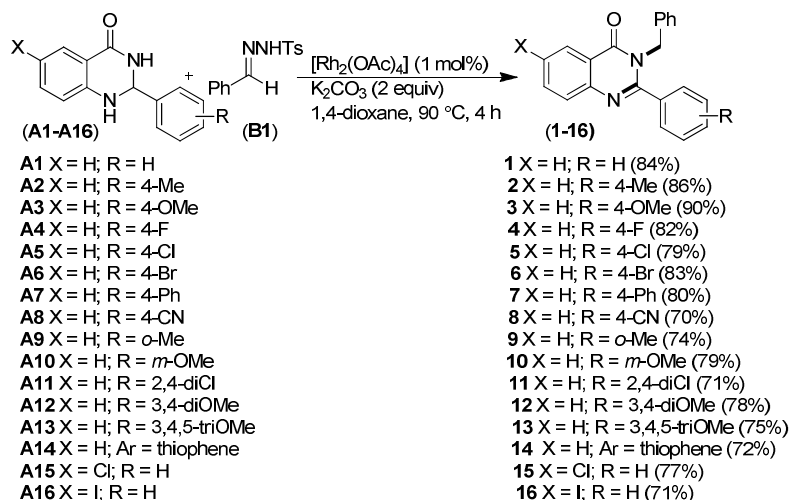
Statement of problem: Carbenoid insertion into N–H bonds is a direct and potentially powerful method of forming C–N bonds, which is an underexploited process with great potential for further development.

Methodology used:

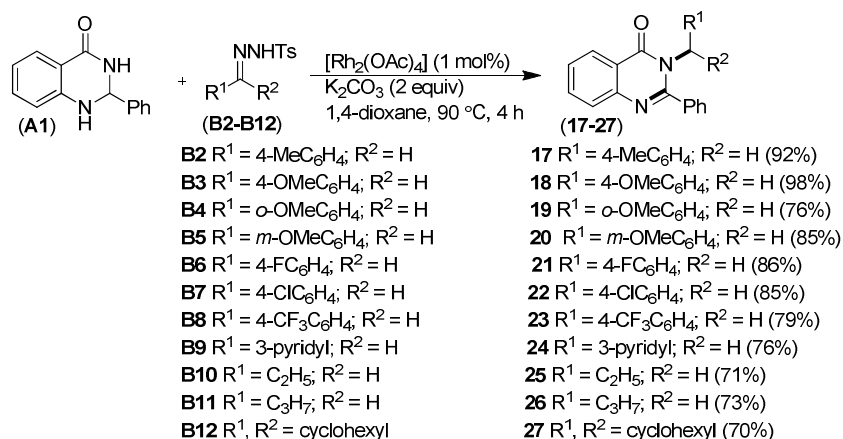


Results and Discussion: Upon screening a variety of reaction conditions, we identified a standard condition as follows: **A1** (0.25 mmol), **B1** (0.3 mmol), K_2CO_3 (0.5 mmol), $[\text{Rh}_2(\text{OAc})_4]$ (1 mol%), in 1,4-dioxane at 90 °C for 4 h. We subsequently investigated the preparative scope of dihydroquinazolinones (**A1–A16**) with benzaldehyde derived *N*-tosylhydrazone (**B1**) to afford the corresponding *N*³-benzyl-2-arylquinazolin-4(3*H*)-ones (**1–16**) with good to excellent yields (Scheme 1). The structure of the product **4** was confirmed by single crystal X-ray diffraction. Next, the scope of *N*-tosylhydrazones (**B2–B12**) was investigated using 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**A1**) as the insertion partner

(Scheme 2). The desired products (**17-27**) were isolated in good yields. We also conduct this reaction in one-pot starting from benzaldehyde; product **1** could be isolated in 80% yield.

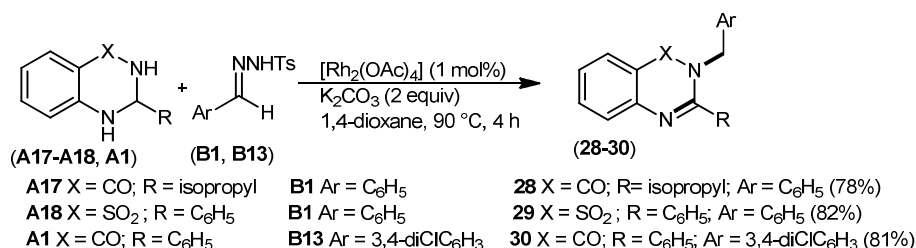


Scheme 1



Scheme 2

Further, 2-isopropyl-2,3-dihydroquinazolin-4(1*H*)-one (**A17**), 3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine 1,1-dioxide (**A18**) and disubstituted *N*-tosylhydrazone (**B13**) were chosen as the substrates (Scheme 3). All reactions proceeded smoothly to form desired products (**28-30**) in 78-81% yield.



Scheme 3

To elucidate the reaction mechanism, we conducted control experiments. Results demonstrate that at first the amine N–H group be would involved in oxidative

dehydrogenation, and then insertion of rhodium-carbenoid into amide N–H bond would take place. A plausible reaction mechanism was illustrated.

In summary, we have demonstrated a general strategy for direct synthesis of *N*³-benzyl/alkyl-2-arylquinazolinones *via* rhodium(II)-carbenoid involved insertion of *N*-tosylhydrazones into the amide N–H bonds of quinazolinones.

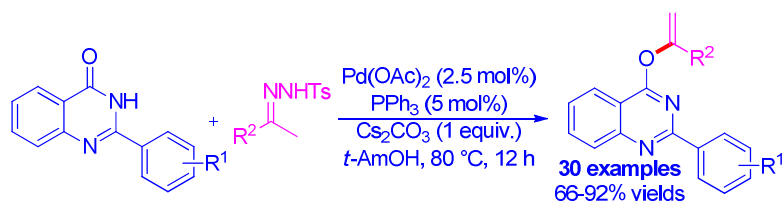
CHAPTER-3 (Section-B)

Palladium(II)-Catalyzed Direct *O*-Alkenylation of 2-Arylquinazolinones with *N*-Tosylhydrazones: An Efficient Route to *O*-Alkenylquinazolines. [*Chem. Commun.* **2017**, 53, 1672–1675]

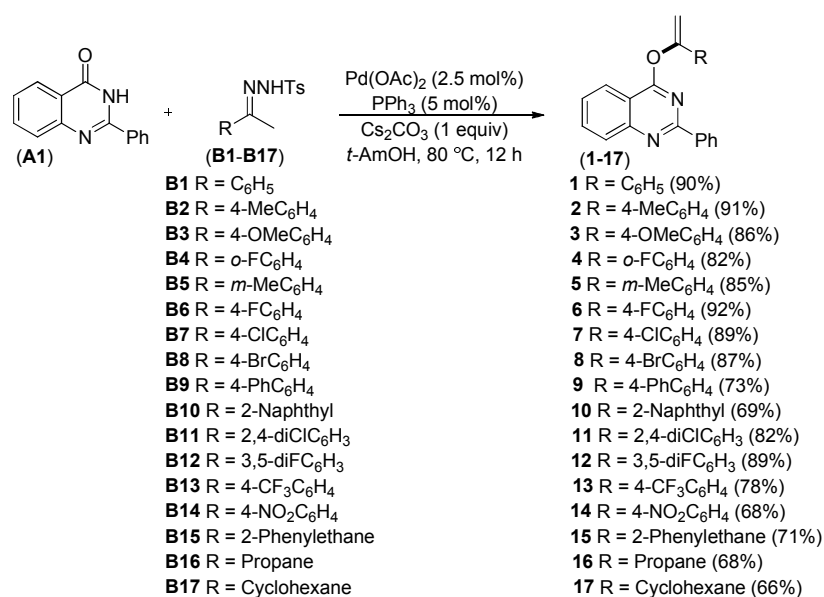
Introduction: The quinazoline moiety, an abundant core of nitrogen-containing heterocycles, is exemplified as a privileged structure that exhibits diverse biological activities. *N*-tosylhydrazones were utilized as versatile coupling partners for cross-coupling reactions.^[5]

Statement of problem: Direct synthesis of *O*-alkenylatedquinazolines starting from 2-arylquinazolinones catalyzed by palladium has until now been unreported with *N*-tosylhydrazones.

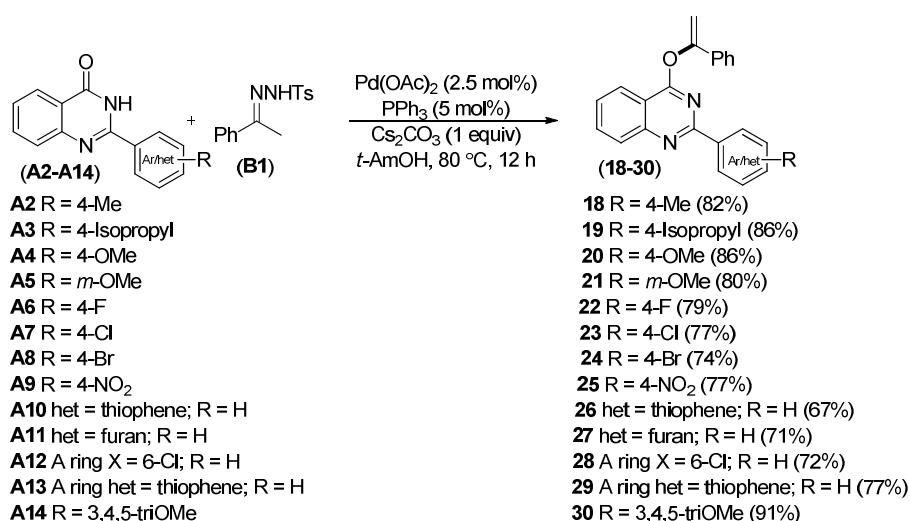
Methodology used:



Results and Discussion: After extensive optimization studies, we identified a standard condition as follows: **A1** (0.5 mmol), **B1** (0.5 mmol), Pd(OAc)₂ (2.5 mol%), PPh₃ (5 mol%),



Scheme 1



Scheme 2

Cs₂CO₃ (1 equiv.), in *t*-AmOH (3 mL), at 80 °C, open to air for 12 h. We then investigated the scope of *N*-tosylhydrazones (**B1-B17**). Aryl as well as aliphatic *N*-tosylhydrazones reacted smoothly, to give desired products (**1-17**) in 66-92% yields (Scheme 1). Next, the scope of 2-aryl-quinazolinones was examined using **B1** as the olefin source (Scheme 2). The reaction is significantly affected by the position of substituent on the aromatic ring. It is noteworthy that chloro and bromo substituents are tolerated, which is advantageous for further transformations. Moreover, hetero aryl bearing quinazolinones also worked well in the reaction (**26-27**). 2-Phenylthieno[3,2-*d*]pyrimidin-4(3*H*)-one also successfully employed as substrate (**29**). Gram-scale synthesis of **1** was performed in excellent yield. Preliminary mechanistic experiments were conducted, a plausible mechanism was illustrated.

In conclusion, we have developed an efficient Pd(II)-catalyzed direct *O*-alkenylation reaction of 2-aryl-quinazolinones with simple ketone-derived *N*-tosylhydrazones as the alkene source to give *O*-alkenylated quinazolines.

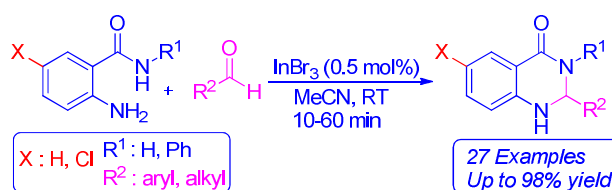
CHAPTER-4 (Section-A)

Convenient and Scalable Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one Derivatives and Their Anticancer Activities [*Synth. Commun.* **2015**, *45*, 1893–1901]

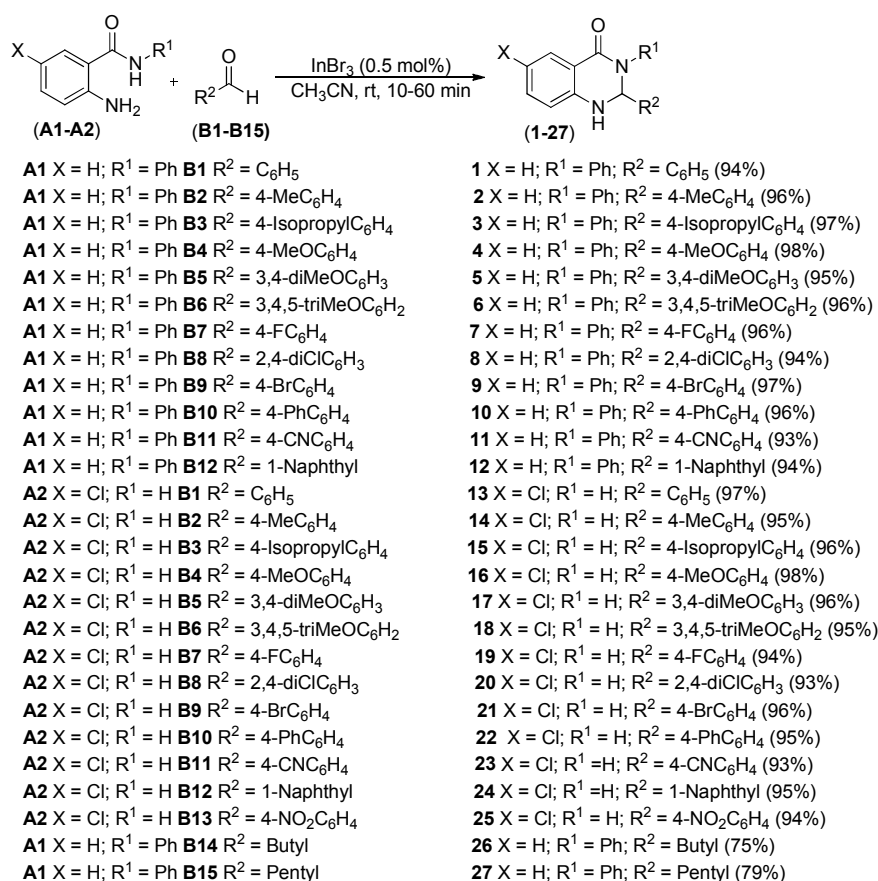
Introduction: Cancer is a systemic disease characterized by uncontrolled growth of abnormal cells and is a leading cause of fatality worldwide.^[6] 2,3-Dihydroquinazolin-4(1*H*)-one derivatives are an important class of fused N-containing heterocycles with various biological, medicinal, and pharmacological activities.

Statement of problem: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives requires harsh reaction conditions, excess catalyst loading, and prolonged time.

Methodology used:



Results and Discussion: We carried out the cyclocondensation reaction between 2-aminobenzanilide (**A1**) and benzaldehyde (**B1**) under various conditions. It was found that 0.5 mol% of InBr_3 efficiently catalyzed the reaction. We extended the scope of this method by synthesizing an array of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**1-25**) bearing either electron-donating or -withdrawing groups on the aromatic ring (Scheme 1). Further, aliphatic aldehydes were also tested in the reaction (**26** and **27**). Finally, the reaction is accessible on a high scale (10 mmol of 2-aminobenzanilide and benzaldehyde), requiring only 60 min to achieve excellent yield of 92%. A plausible mechanism was illustrated to account for the InBr_3 -catalyzed reaction. Synthesized compounds were evaluated for their



Scheme 1

in vitro cytotoxicity against four different human cancer cell lines, i.e., lung cancer (A549), breast cancer (MCF7), cervical cancer (HeLa), and prostate cancer (DU145). Doxorubicin is used as a reference drug in this study. Compounds **24**, **15**, **21**, and **14** exhibited promising