Design and Synthesis of Fused Quinazolines *via* Transition Metal-Catalyzed C-N Coupling Reactions

THESIS

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DOCTOR OF PHILOSOPHY

by

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PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled **"Design and Synthesis of Fused Quinazolines *via* Transition Metal-Catalyzed C-N Coupling Reactions"** submitted by **Mr. Nitesh Kumar Nandwana**, ID No. **2013PHXF0425P** for the award of Ph.D. Degree of the Institute embodies the original work done by him under our supervision.

Date: Signature in full of the Supervisor
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Date: Signature in full of the Co-supervisor
Name in capital block letters: **PROF. INDRESH KUMAR**
Designation: Associate Professor

Dedicated to

My Mother, Father and Family

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ABSTRACT

Quinazoline is an important heterocyclic motif in synthetic organic chemistry due to their wide range of application in different fields of science such as medicine, agrochemical and material chemistry. The thesis entitled " **Design and Synthesis of Fused Quinazolines *via* Transition Metal-Catalyzed C-N Coupling Reactions**" deals with the synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines using copper/palladium catalyzed C-N coupling reactions and their antimicrobial activity. The thesis is divided into five chapters.

The first chapter of the thesis gives a brief introduction of quinazolines, different synthetic method of quinazoline under metal-free and metal-catalyzed conditions and their biological applications.

The second chapter of the thesis describes copper-catalyzed tandem multi-component reactions for the synthesis of fused quinazolines. This chapter is divided into three parts: **Part A** presents a simple and efficient one-pot protocol for the synthesis of imidazo[1,2-*c*]quinazoline derivatives through copper-catalyzed tandem reaction between substituted 2-(2-bromophenyl)-1*H*-imidazoles and formamide. The synthetic protocol involves initial Ullmann-type C–N coupling followed by intramolecular dehydrative cyclization. **Part B** describes a tandem multicomponent approach for the synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines. The reaction involves copper-catalyzed reductive amination *via* azidation followed by reduction and oxidative amination of C(sp^3)–H bonds of *N*,*N*-dimethylacetamide in the presence of TBHP as oxidant. The method provides a powerful means of using easily available sodium azide as a nitrogen source and DMA as one carbon source for the synthesis of these *N*-fused heterocycles in good to excellent yields. The reaction is amenable for gram scale synthesis. **Part C** describes practical and concise protocol for the synthesis of fused imidazo/benzimidozo[1,2-*c*]quinazolines through copper-catalyzed tandem multicomponent approach from 2-(2-bromophenyl)-1*H*-imidazoles. The reaction involves copper-catalyzed sequential azidation of 2-(2-bromophenyl)-1*H*-imidazole/benzimidazole through S_NAr reaction and reduction followed by condensation with benzyl alcohol or benzyl amine or benzaldehyde. The salient features of this protocol are use of air as an oxidant, ligand free reaction conditions and broad substrate scope with high efficiency.

The third chapter of the thesis describes copper-catalyzed Ullmann-type C-N coupling and cross-dehydrogenative coupling (CDC) reactions. This chapter is divided into two parts: **Part A** presents an efficient one-pot sequential procedure for the synthesis of novel azole-fused quinazolines through Pd/Cu co-catalyzed, Ullmann-type coupling followed by cross dehydrogenative coupling of various azoles such as 1*H*-imidazole, 1*H*-benzimidazole and 1*H*-1,2,4-triazole with 2-(2-bromophenyl)-1*H*-imidazole/benzimidazoles. The developed strategy has offered good yields (52–81%) of diverse *N*-fused tetra-, penta- and hexa-cyclic frameworks in a single step. **Part B** presents new class of fused quinazolines *via* a copper–catalyzed Ullmann type C–N coupling followed by intramolecular cross-dehydrogenative coupling (CDC) reaction in moderate to good yields. The synthesized compounds were tested for *in vitro* antibacterial activity against three Gram negative (*Escherichia coli, Pseudomonas putida, Salmonella typhi*) and two Gram positive (*Bacillus subtilis, Staphylococcus aureus*) bacteria. Bactericidal assay by propidium-iodide and live-dead bacterial cell screening using mixture of acridine orange/ethidium bromide (AO/Et·Br) showed considerable changes in the bacterial cell membrane, which might be the cause or consequence of cell death. Moreover, the hemolytic activity for most potent compounds showed their safety profile towards the human blood cells.

The fourth chapter of the thesis describes copper–catalyzed tandem reaction of 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles with alkynes and sodium azide for the synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines in moderate to excellent yields (50-85%). The one–pot method involves copper–catalyzed tandem azide–alkyne cycloaddition (CuAAC), intramolecular cross dehydrogenative C–N bonding followed by Ullmann type C–N coupling reaction. The silent features of this protocol are use of air as the oxidant, mild and ligand free reaction conditions and broad substrate scope with high efficiency.

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LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviation	Description
AcOH	Acetic acid
acac	Acetylacetone
Aq	Aqueous
Ar	Aryl
AIDS	Acquired immunodeficiency syndrome
AO	Acridine orange
[Bmim][BF_4]	1-Butyl-3-methylimidazolium tetrafluoroborate
t-BuOK	Potassium *tert*-butoxide
t-BuONO	*tert*-Butyl nitrite
Cat.	Catalytic
^{13}C	Carbon-13
CH_3CN	Acetonitrile
$CDCl_3$	Deuterated chloroform
m-CPBA	*meta*-Chloroperoxybenzoic acid
CDC	Cross-dehydrogenative coupling
COSY	Correlation spectroscopy
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
CMV	Cucumber mosaic virus
CAN	Ceric ammonium nitrate
Cp*	1,2,3,4,5-Pentamethylcyclopenta-1,3-diene
Cu-NP	Copper-nanoparticles
CDIs	1,1'-Carbonyldiimidazole
DMAP	4-Dimethylaminopyridine

d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DNA	Deoxyribonucleic acid
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMA	*N*,*N*-Dimethylacetamide
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO-d_6	Deuterated dimethylsulfoxide
DMSO	Dimethylsulfoxide
DMAc	Dimethylacetamide
DCFH-DA	2',7-Dichlorofluorescein diacetate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EI	Electron Ionization
ESI	Electron Spray Ionization (MS)
EtOAc	Ethyl acetate
equiv.	Equivalent
ESI-MS	Electrospray ionization mass spectrometry
EtOH	Ethanol
EC_{50}	Half maximal effective concentration
Et·Br	Ethidium bromide

g	Gram
GABA	Gamma-aminobutyric acid
h	Hours
HRMS	High Resolution Mass Spectra
Hz	Hertz
HIV	Human immunodeficiency virus
HCMV	Human cytomegalovirus
30% H_2O_2	30% Hydrogen peroxide
IR	Infra-red
IBD	Iodobenzene diacetate
IC_{50}	The half maximal inhibitory concentration
IP	Imidazo[1,2-*a*]pyridines
J	Coupling constant
KOAc	Potassium acetate
Lit.	Literature
mp	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz
min	Minutes
mmol	Millimole
MW	Microwave
MRSA	Methicillin- resistant Staphylococcus aureus
MDR	Multidrug resistant

MES	Maximal electroshock seizure test
MIC	Minimum inhibitory concentration
Mtb	Mycobacterium tuberculosis
N_2	Nitrogen
Nu	Nucleophile
NMR	Nuclear Magnetic Resonance
NBS	*N*-Bromosuccinimide
NIS	*N*-Iodoosuccinimide
NMP	N-Methyl-2-pyrrolidone
NSAIDs	Non-steroidal anti-inflammatory drugs
O_2	Oxygen
OTf	Triflouromethanesulfonate
OD	Optical density
OLEDs	Organic light-emitting diode
PEG400	Polyethylene Glycol400
PIDA	Phenyl iodine (III) diacetate
1,10-Phen	1,10-Phenanthroline
PivoH	Pivalic acid
ppm	Parts per million
PI	Propidium iodide
PBS	Phosphate buffer saline
PDB	Potato dextrose broth

r.t.	Room temperature
ROS	Reactive oxygen species
RBC	Red blood cell
s	Singlet
SET	Single electron transfer
SAR	Structure-activity relationship
TFA	Trifluoroacetic acid
TEA	Triethyl amine
t	Triplet
TMDEA	Tetramethylethylenediamine
TBAB	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide
THF	Tetrahydrofuran
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical,
p-TSA or *p*-TsOH	*p*-Toluenesulfonic acid
qTOF	Quadrupole time-of-flight
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TMSCl	Trimethylsilyl chloride
TMV	Tobacco mosaic virus
TB	Tuberculosis
TNF-α	Tumor necrosis factor-α
TEM	Transmission electron microscopy

ZOI	Zone of inhibition
ZIF-67	Zeolitic Imidazole Framework-67

CHAPTER 1

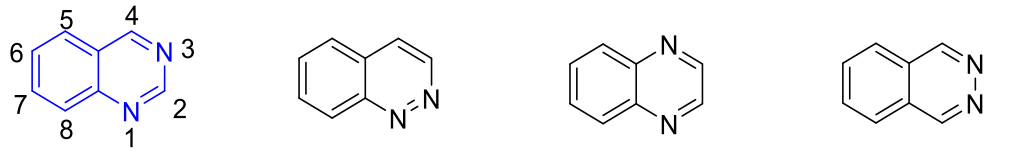
Synthesis and Biological Activities of Quinazolines: An Update

1.1 INTRODUCTION

Heterocyclic compounds are a cyclic structure that contains one or more heteroatom (N, O, S) apart from carbon.[1-3] Heterocyclic compounds constitute the largest and most varied family of organic compounds and play a significant role in the pharmaceutical industry and materials science. Heterocyclic rings system that is derived by fusion with other rings, either carbocyclic or heterocyclic, are essential building blocks and structural units of a variety of bioactive natural products and therapeutic agents.

In literature, there are several heterocyclic compounds which contain a different heteroatom. Among them, *N*-containing heterocyclic compounds have received great attention due to their utility as valuable intermediates for various synthetic transformation and their wide range of application in different areas of science.[4] Aza-fused heterocycles are highly conjugated systems which exhibited interesting pharmacological and photophysical properties. Their DNA intercalating ability makes them suitable candidates as anti-neoplastic and mutagenic agents.[5]

Quinazoline (**1**) is a bicyclic structure containing two fused six-membered rings; one is benzene ring another one is a pyrimidine ring (**Figure 1.1**). It is a yellowish crystalline compound with molecular formula $C_8H_6N_2$. Quinazoline is also known by different names like as 5,6-benzo pyrimidine, benzo[*a*]pyrimidine, 1,3-diazanaphthalene and phennmiazine. It is isomeric with the other diazanaphthalenes of the benzodiazine subgroup, cinnoline (**2**), quinoxaline (**3**) and phthalazine (**4**) (**Figure 1.1**). Quinazoline scaffold has attracted significant attention due to their existence in several drugs and naturally occurring alkaloids.[6]



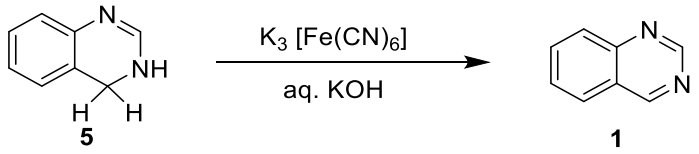
Quinazoline (**1**) Cinnoline (**2**) Quinoxaline (**3**) Phthalazine (**4**)

Figure 1.1 Quinazoline and its isomers

The first reaction for the synthesis of quinazoline was reported in 1895 by August Bischler and Lang through the decarboxylation of the quinazoline-2-carboxylic acid.[7] The discovery of quinazolines commenced with the isolation of quinazoline containing alkaloids febrifugine from Chinese plant Aseru (Dichroa febrifuga Lour) with good antimicrobial activity. The very first time, quinazoline was synthesised by Gabriel in 1903.[8]

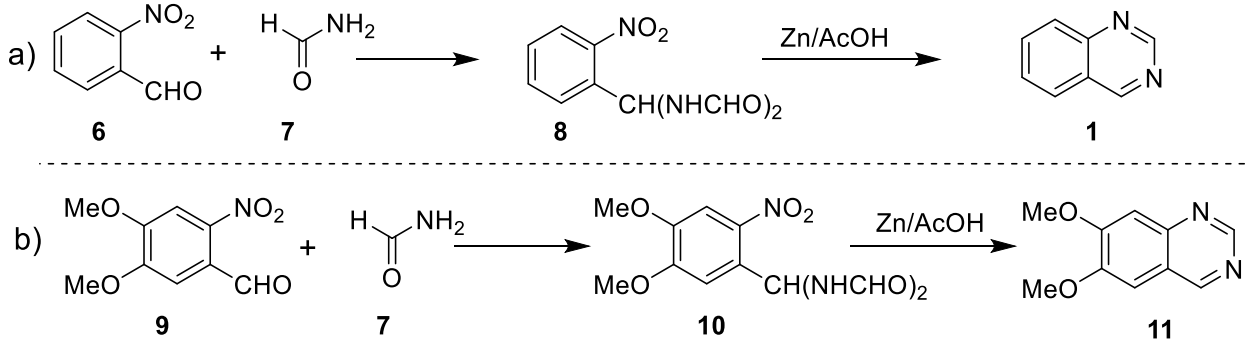
1.2. Synthesis of quinazolines

Due to the great importance of quinazoline derivatives across many fields, several synthetic methods have been developed to access quinazoline scaffolds. In 1903, Gabriel described the synthesis of quinazolines (**1**) by the oxidation of 3,4-dihydroquinazoline (**5**) (**Scheme 1.1**).[8]



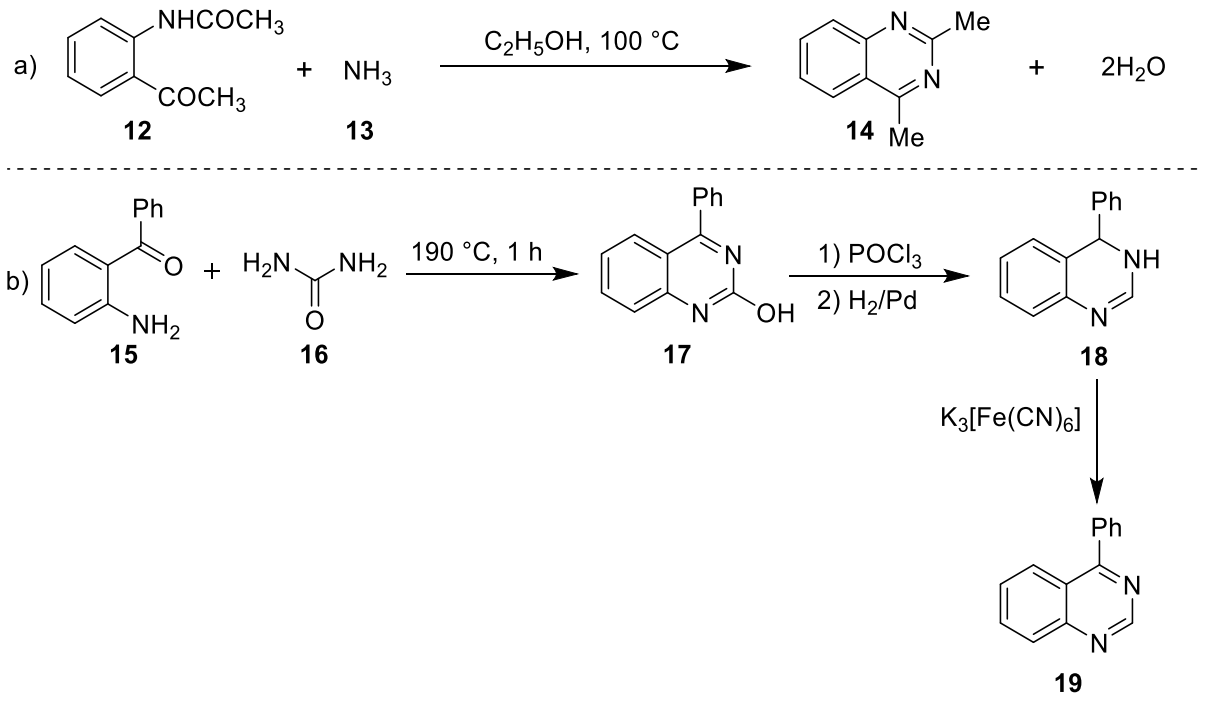
Scheme 1.1 Gabriel method for quinazolines synthesis

In 1905 Riedel described the synthesis of quinazolines (**1**) from *o*-nitrobenzaldehyde (**6**) and amide (**7**) in the presence of zinc and diluted acetic acid, which leads to corresponding quinazolines (**1**) with good yields (**Scheme 1.2a**). Later Riedel modified the reaction condition for the improvement in the reaction yield. This is one of the best methods for quinazolines synthesis which was also applied for the preparation of 6,7-dimethoxyquinazolines (**11**) by using 6-nitro vertraldehyde (**9**) and amide (**7**) under similar reaction conditions (**Scheme 1.2b**).[9,10]



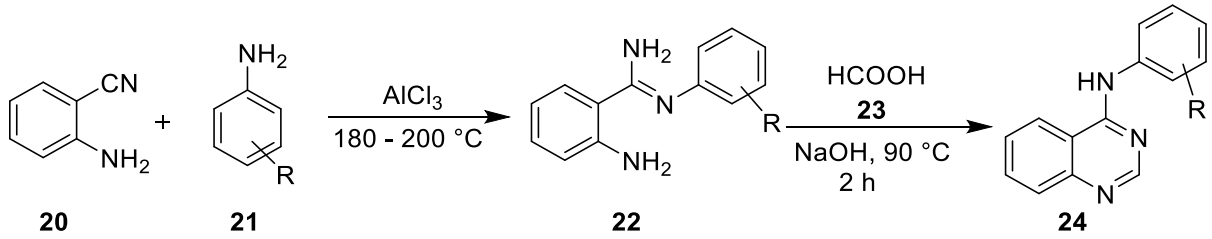
Scheme 1.2 Riedel method for quinazolines synthesis

Schofield *et al*. described the synthesis of 2,4-dimethyl quinazolines (**14**) from substituted *o*-amino acetophenone (**12**) and ammonia (**13**) in ethanol at 100 °C (**Scheme 1.3a**).[11] Subsequently, the same group synthesised 2-hydroxy-4-phenylquinazolines (**17**) by the reaction of *o*-amino benzophenone (**15**) with urea (**16**). The reaction of **17** with $POCl_3$ followed by reductive dehalogenation gave dihydroquinazoline (**18**) which on treatment with $K_3[Fe[CN]_6$ gave 4-phenyl quinazoline (**19**) (**Scheme 1.3b**).



Scheme 1.3 Schofield method for the synthesis of quinazolines from ketones

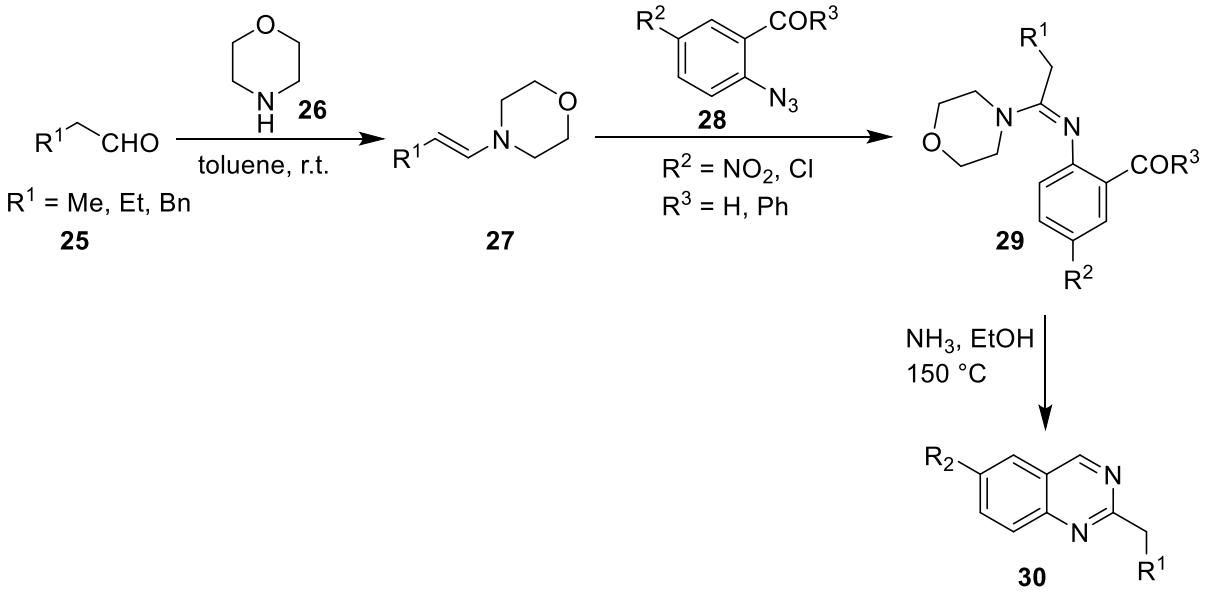
Bujok and his colleagues synthesised quinazolines (**24**) from 2-aminobenzonitrile (**20**) and anilines (**21**) in the presence of anhydrous aluminium chloride.[12] In the first step, amidines (**22**) were formed which on treatment with formic acid (**23**) and sodium hydroxide furnished 4-arylamino quinazolines (**24**) with good to excellent yields (70-92%) (**Scheme 1.4**). Quinazolines were not observed with 3,4-dichloroaniline or nitro anilines under this reaction condition; this may be due to reduced nucleophilicity of the amino group.



Scheme 1.4 Multistep synthesis of quinazolines from 2-aminobenzonitrile and anilines

Erba *et al.* described a multistep approach for the synthesis of quinazolines (**30**) from aldehydes.[13] The reaction of aldehyde (**25**) with morpholine (**26**) under room temperature gave intermediate **27**. The intermediate **27,** when treated with an aryl azide (**28**), afforded **29.** Which on the exposure of

a saturated ethanolic solution of ammonia in a sealed vessel at 150 °C resulted in the formation of quinazolines (**30**) (**Scheme 1.5**).



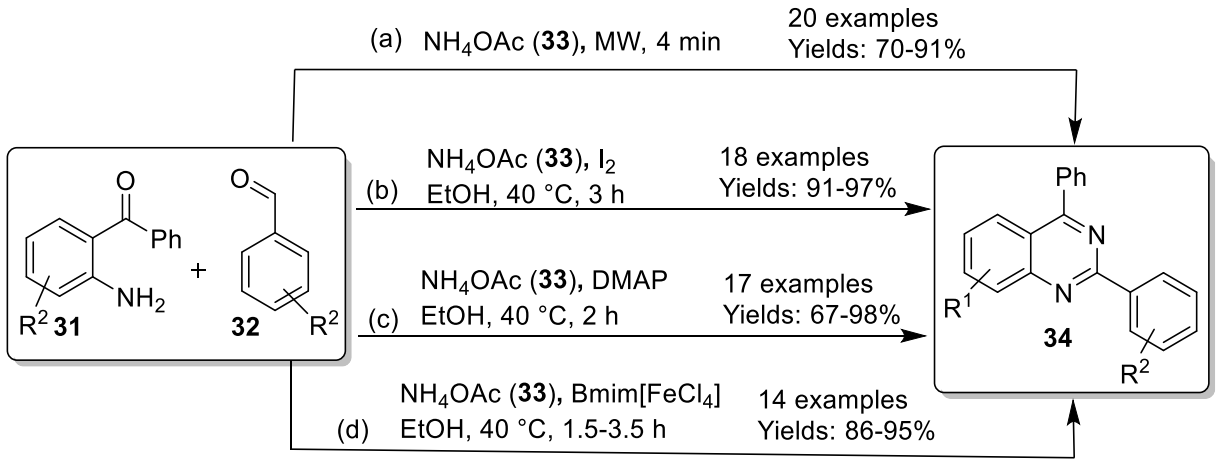
Scheme 1.5 Multistep method for quinazolines from aldehydes and morpholine

The above mentioned synthetic methods developed for quinazolines based on classical transformation suffer from some drawbacks such as harsh reaction conditions and stepwise procedure and limited substrate scope. In the last decade particularly, metal–free and metal-catalyzed reactions have been employed to overcome these issues for the synthesis of quinazolines.

1.2.1. Transition metal–free approach for the synthesis of quinazolines

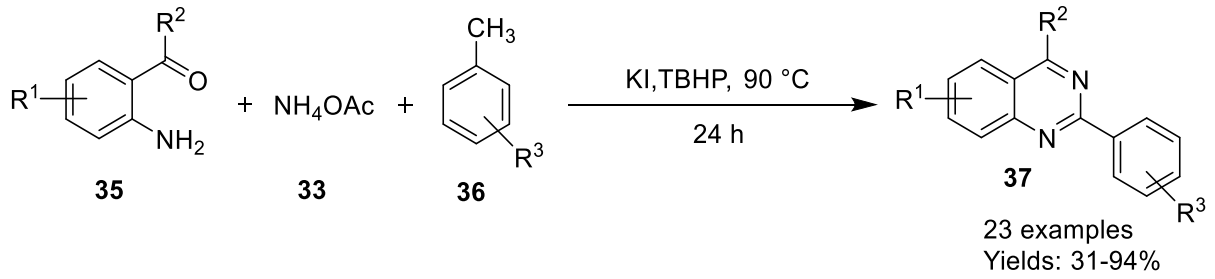
Transition metal–catalysed coupling reactions have played an important role in heterocyclic chemistry for the development of medicinally important motif. Even, these reactions have some limitation and confront challenges to some extent due to the catalytic system. Most of the transition metals are very expensive, toxic in nature, sensitive to oxygen and moisture. Also, the large consumption of transition metals does not fulfil the requirement for sustainable development. Therefore, alternative pathways for the construction of C−C and C–N bonds under transition metal–free conditions are highly desirable. Transition metal–free coupling reactions have become one of the fascinating tools of chemistry in recent years to understand how the reactions work without transition metals.

Prajapati group documented a solvent and catalyst-free synthesis of quinazolines (**34**) and 1,2-dihydroquinazolines from 2-aminobenzophenone (**31**), aldehydes (**32**) and NH_4OAc (**33**) under microwave irradiation. The presented work was equally effective with a variety of electron-rich and electron-deficient benzaldehyde and provided target products in good to excellent yields (70–91%) (**Scheme 1.6a**).[14] Similarly, Saha and co-workers reported iodine–catalysed one–pot three-component approach for highly functionalized quinazoline derivatives (**34**). This method provided desired products with excellent yield (91-97%) without the involvement of chromatographic purifications (**Scheme 1.6b**).[15] Derabli *et al.* described DMAP–catalysed one-pot procedure for the synthesis of 1,2-dihydroquinazoline and quinazolines derivatives in good to excellent yields (67-98%) (**Scheme 1.6c**).[16] Satyen groups achieved ionic liquid (IL) Bmim[$FeCl_4$] catalysed solvent free one-pot multicomponent approach for quinazoline derivatives (**34**). This method was found to be much superior to other methods in terms of its simplicity, easier recyclability and high catalyst stability (**Scheme 1.6d**).[17]



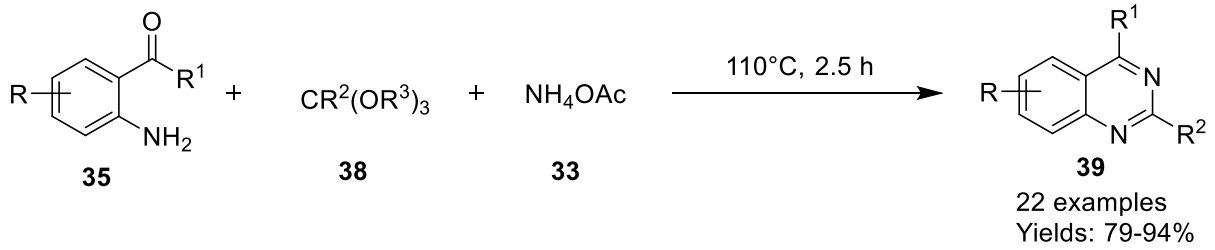
Scheme 1.6 Different metal–free synthetic approaches for the synthesis of quinazolines

Zhao *et al.* achieved 2-arylquinazolines (**37**) *via* one-pot three-component approach under metal-free conditions by the reaction of 2-aminoarylketones (**35**), NH_4OAc (**33**) and methylarene (**36**) as one carbon source (**Scheme 1.7**).[18] The reaction demonstrated a broad range of functional group tolerance including electron–rich and electron–deficient 2-amino-benzophenones and methylarenes. The control experiment results revealed that aryl aldehyde is formed from methylarene *via* radical oxidation in the presence of TBHP which indicate aryl aldehyde is a key intermediate for the reaction pathway.



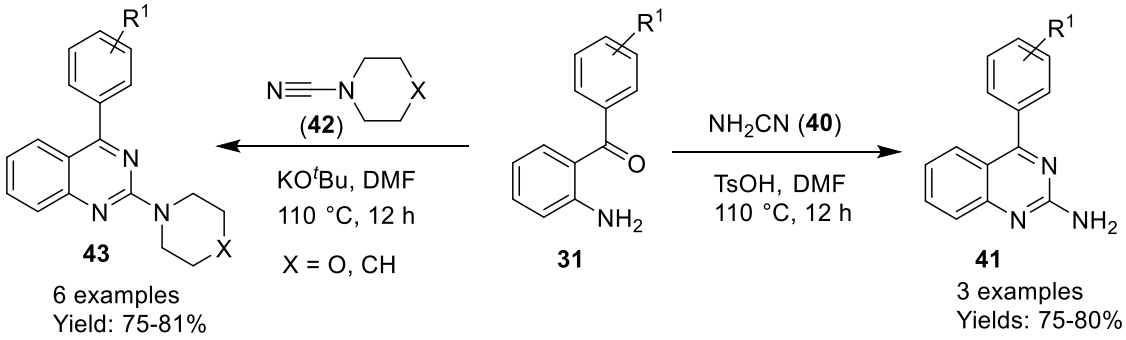
Scheme 1.7 Potassium iodide–catalyzed the synthesis of quinazolines using **35** and **36**

Trivedi and co-workers reported a solvent and catalyst-free green protocol for the synthesis of quinazolines (**39**) from one–pot three-component reactions of 2-aminoaryl ketones (**35**), orthoesters (**38**), and NH_4OAc (**33**) (**Scheme 1.8**).[19] The scope and limitations of reaction were investigated using a variety of substituted 2-aminoarylketones, and trialkyl orthoesters, good to excellent yields (79-94%) were obtained for quinazolines.



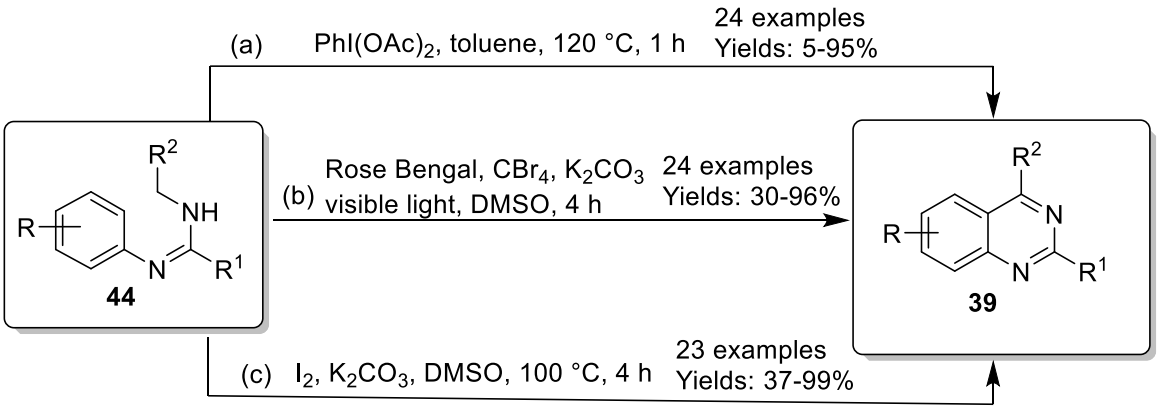
Scheme 1.8 Solvent and catalyst-free synthesis of quinazolines 2-aminoaryl ketones and trialkyl orthoesters

Pandya *et al.* described an effective approach for the synthesis of 2-aminoquinazoline (**41, 43**) from 2-aminobenzophenones (**31**) and cyanamide (**40**) or 4-morpholinecarbonitrile (**42**) (**Scheme 1.9**).[20] The method allowed synthesis of 2-aminoquinazolines which could be further utilized for the generation of potentially biologically important compounds.



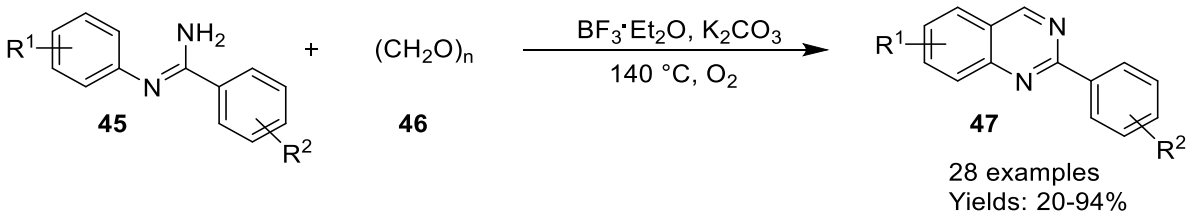
Scheme 1.9 Synthesis of 2-aminoquinazoline from 2-aminobenzophenone

Long and his colleagues reported the synthesis of quinazolines (**39**) from *N*-alkyl-*N′*-arylamidine (**44**) *via* iodine (III)-promoted oxidative C(sp^3)−C(sp^2) and C(sp^2)−N bond formation under metal and base−free reaction conditions (**Scheme 1.10a)**.[21] Substrates containing electron-rich and the electron-deficient substituent on aromatic ring gave the corresponding product in low to excellent yields (5-95%); however, with an aliphatic substituent, the reaction was incompatible. Shen *et al.* described the synthesis of **39** from amidines (**44**) under photo-redox conditions (**Scheme 1.10b**).[22] Later, Chang group developed I_2 promoted oxidative C−C bond formation for the synthesis of quinazolines (**39**). Under the standard condition, all amidine derivatives (**44**) transformed into the expected products in moderate to excellent yields (37-99%) (**Scheme 1.10c**).[23]



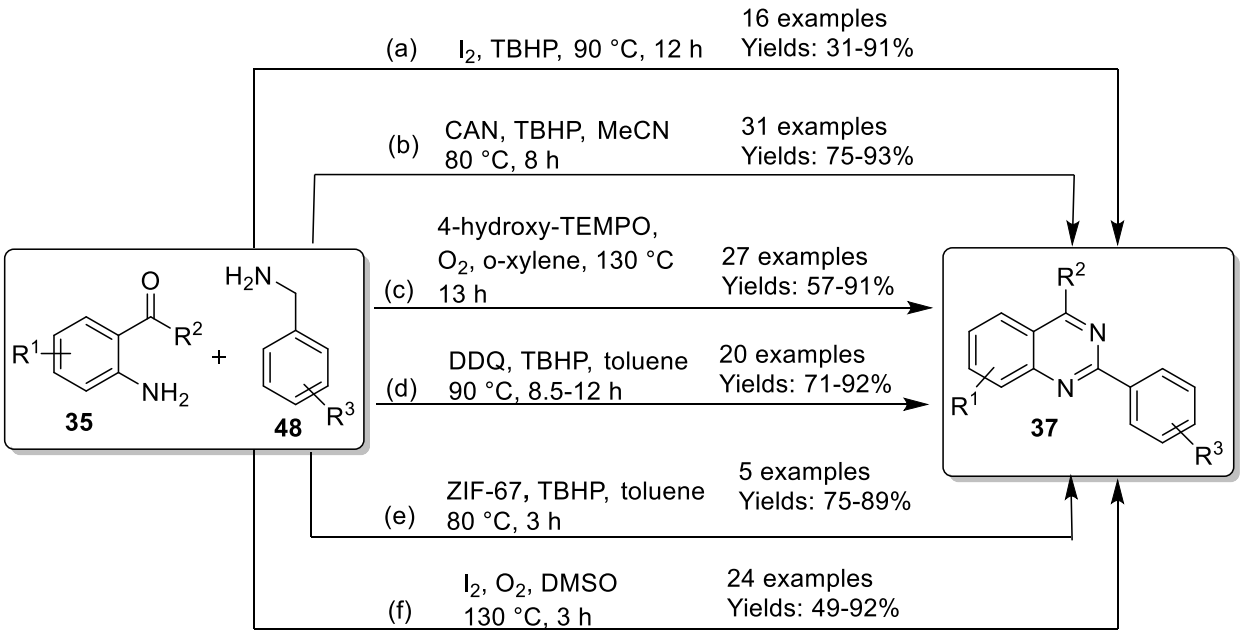
Scheme 1.10 Different synthetic approaches for the synthesis of quinazolines from amidines

Recently, Cheng *et al.* proposed new approach for the development of quinazolines (**47**) scaffold under metal-free conditions from *N*-phenyl-benzimidamide (**45**) and paraformaldehyde (**46**) as one carbon source (**Scheme 1.11**).[24] The optimized reaction condition was well tolerated with electron-rich and the electron-deficient substituent on benzene ring with low to excellent yield of corresponding quinazolines (20-94%). The reaction mechanism started the formation of formaldehyde from paraformaldehyde (**46**) then nucleophilic attack of amine to the aldehyde followed by intramolecular Friedel–Crafts reaction and aerobic oxidation afforded the target product.



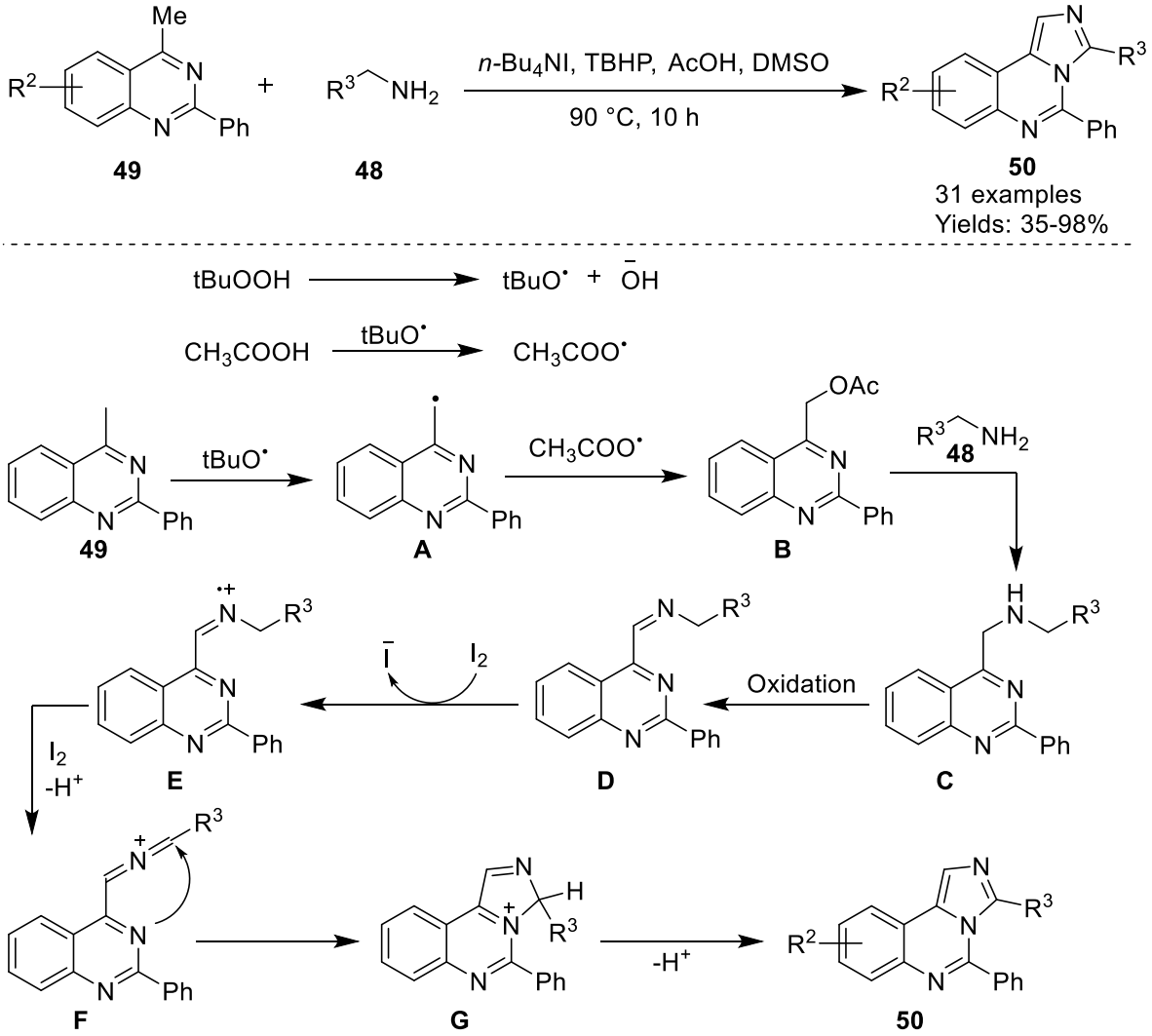
Scheme 1.11 Synthesis of quinazolines from *N*-phenyl-benzimidamide and paraformaldehyde

Wang and co-workers disclosed iodine–catalyzed an efficient approach for the construction of 2-phenylquinazolines (**37**) from 2-aminobenzophenones (**35**) and benzylamines (**48**) through one-pot tandem reaction followed by sp^3 C−H functionalization (**Scheme 1.12a**).[25] Karnakar *et al.* described ceric ammonium nitrate (CAN) catalyzed the synthesis of quinazolines (**37**) with good to excellent yields (75-93%). The reaction yield was decreased when the electron-donating group was present at the para position of the benzylamine. Whereas an electron-withdrawing group slightly increased the product yields (**Scheme 1.12b**).[26] Subsequently, Yang and team explored the synthesis of 2-aryl quinazolines from the same starting material by using 4-hydroxy-TEMPO radical as the catalyst (**Scheme 1.12c)**.[27] Rao and colleagues synthesized quinazolines (**37**) using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as a versatile reagent. The reaction mechanism involved condensation followed by cyclization which afforded the desired product in good to excellent yields (71-92%) (**Scheme 1.12d)**.[28] Phan group used a heterogeneous catalyst (ZIF-67) for the cyclisation reaction of 2-aminobenzoketones (**35**) and benzylamines (**48**) derivatives to form quinazolines product. ZIF-67 catalyst could be reused and recovered without significant degradation in catalytic activity (**Scheme 1.12e**).[29] Very recently, Deshmukh *et al.* described molecular iodine–catalyzed the synthesis of quinazolines (**37**) from 2-aminobenzaldehydes and 2-aminobenzophenones (**35**) with benzyl-amines (**48**). Variously substituted aryl or hetero-aryl amines were treated with an ample range of substituted 2-aminobenzaldehydes and 2-aminobenzophenones to give the substituted quinazolines in moderate to excellent yields (49-92%) (**Scheme 1.12f)**. [30]



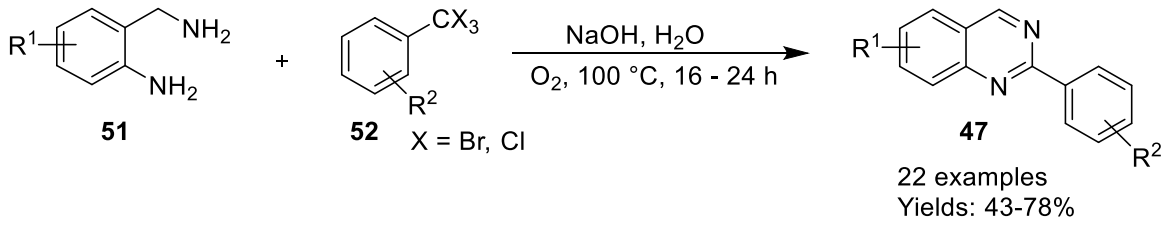
Scheme1.12 Different synthetic approaches for quinazolines from 2-aminobenzophenones and benzylamines

Zhao *et al.* reported *n*-Bu_4NI catalyzed a tandem reaction for the synthesis of imidazo[1,5-*c*]-quinazolines (**50**). This method was examined by reacting different benzylamine (**48**) with 4-methyl-2-phenylquinazoline (**49**) which provided corresponding imidazo[1,5-*c*]quinazolines with good yields (35-98%) (**Scheme 1.13**)[31]. The reaction involved selective dual amination of sp^3 C–H bonds under mild conditions. It is believed that tert-butoxyl radical is generated from TBHP. Then, tert-butoxyl radical abstract proton from acetic acid and **49** to afford acyloxy and benzylic radical (**A**), respectively. These two radicals are coupled to form intermediate **B.** Intermediate **B** converted to **D** by amination followed by oxidation. Intermediate **D** transformed to **G** *via* iodine catalyzed intramolecular cyclization and rearrangement. Finally, **G** led to fused quinazoline (**50**) by deprotonation.



Scheme1.13 Stepwise mechanism for the synthesis of imidazo[1,5-*c*]quinazolines from 4-methyl-2-phenylquinazoline and benzylamine

Chatterjee *et al.* demonstrated metal-free synthesis of quinazolines (**47**) from 2-aminobenzylamines (**51**) and α,α,α-trihalotoluenes (**52**) in the presence of sodium hydroxide and molecular oxygen in the water. The reaction mechanism proceeds through base-promoted intermolecular substitution followed by intramolecular substitution, elimination and subsequent oxidation by molecular oxygen leading to the 2-arylquinazolines with moderate to good yields (43-78%) (**Scheme 1.14**).[32]



Scheme1.14 Synthesis of quinazolines from 2-amibenzylamines

1.2.2. Transition metal–catalyzed approaches

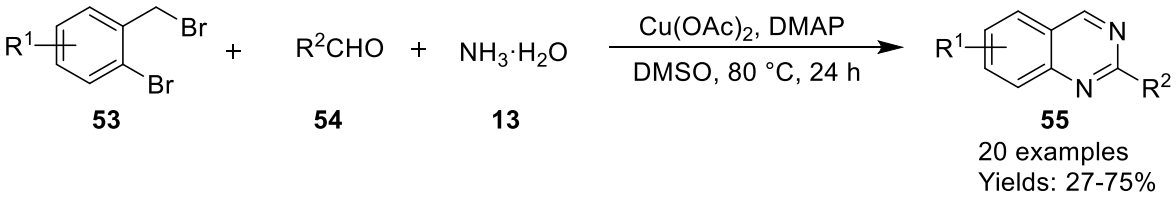
Transition metal catalyzed C−H activation reactions have been studied since the past century and represent a great success and growth of organometallic chemistry. These reactions were started in 1960 as a major topic in organometallic chemistry and become one of the most efficient tools for C−C and C−N bond formation.[33,34] Moreover, transition metal-catalysed C-H activation, and functionalization have some benefits over traditional method such as reduction in the waste generation, no need of pre-functionalization of starting material which provides a more efficient and straightforward approach for the development of fused heterocycles. In the last decade, tremendous efforts have been made for the development of heterocyclic compounds through C−N and C−C bond formation. A brief overview of recent literature of metal–catalyzed the synthesis of quinazolines *via* C–H activation and C–N coupling reactions using transition metal catalyst is described below.

1.2.2.1. Copper-catalyzed reactions for the synthesis of quinazolines

The efficiency of copper catalysts is well demonstrated in literature since last century where these salts have proved to be an efficient catalyst in cross-coupling reactions for the synthesis of natural products and bioactive molecules, because of their economic attractiveness, low toxicity and good functional group tolerance.[35-37] Copper salts have become a potential alternative to their expensive counterparts such as palladium, rhodium, and ruthenium catalysts for the coupling reactions. Copper-catalyzed Ullmann type reaction is the pioneering work in the field of synthetic organic chemistry.[38] Copper-catalyzed coupling reaction has been extensively explored for the newer synthetic method for fused heterocyclic compounds.

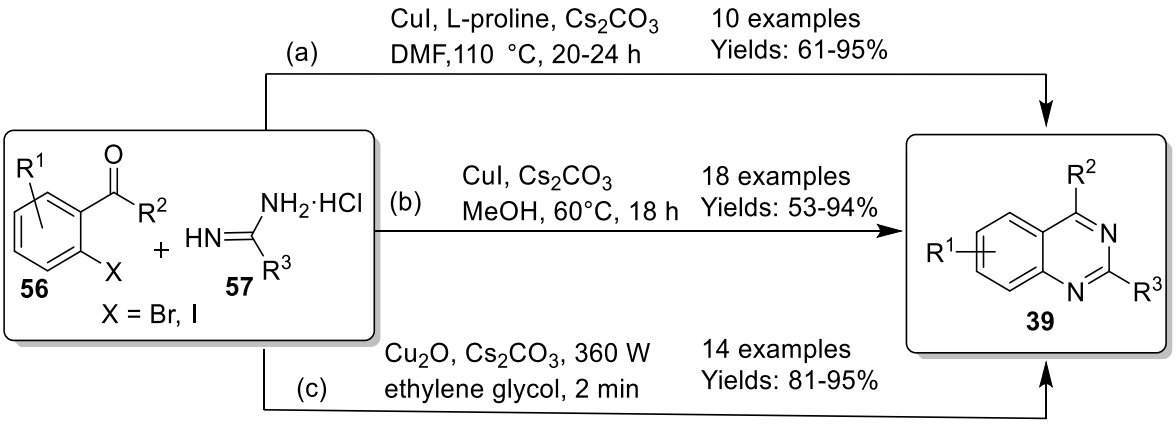
Fan *et al*. disclosed an efficient one-pot method for the synthesis of substituted quinazolines (**55**) from 2-bromobenzyl bromides (**53**), aldehydes (**54**), and aqueous ammonia (**13**) *via* copper–catalyzed tandem reaction (**Scheme 1.15**).[39] The reaction proceeds through Cu(II)–catalyzed

amination of 2-bromobenzyl bromide to 2-aminobenzyl amine then condensation with benzaldehyde followed by intramolecular nucleophilic cyclization and aromatization furnished quinazolines.



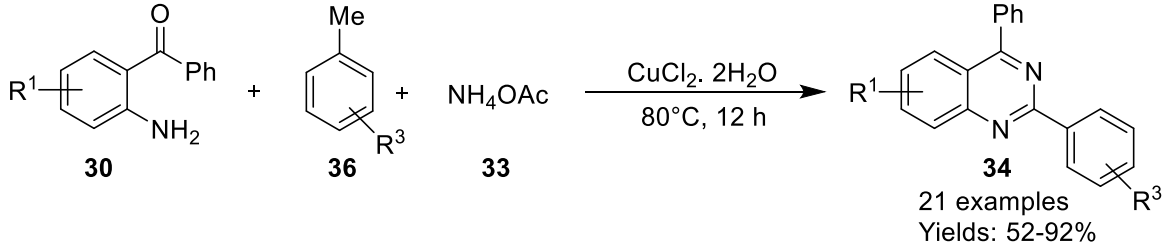
Scheme 1.15 Copper–catalyzed synthesis of quinazolines from 2-bromobenzyl bromides, aldehydes, and aqueous ammonia

Huang *et al*. developed quinazoline analogous (**39**) *via* copper–catalyzed tandem couplings of amidine hydrochlorides (**57**) with substituted 2-halobenzaldehydes, 2-halophenylketones (**56**) (**Scheme 1.16a**).[40] The presented work was equally effective with aliphatic and aromatic amidines and provided target products in good to excellent yields (61–95%). Similarly, Morrow group developed an efficient one-pot approach for highly functionalized quinazoline derivatives (**39**) in the presence of Cs_2CO_3 in methanol at 60 °C *via* copper–catalyzed Ullmann condensation. (**Scheme 1.16b**).[41] Very recently, Bhanage and his colleagues achieved an ultrasound-assisted synthesis of Cu_2O nanocubes at room temperature, and Cu_2O nanocubes were used for the development of quinazolines (**39**) using one–pot tandem cyclization. This method was found to be much superior to others in terms of its simplicity, easier recyclability and high catalyst stability (**Scheme 1.16c**).[42]



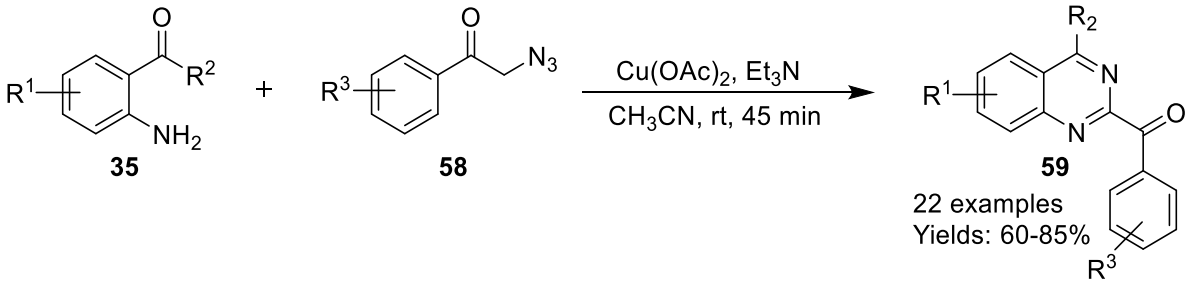
Scheme1.16 Different synthetic approaches for quinazolines from 2-haloaketones and amidines

Wang and team achieved direct access to functionalized quinazolines (**34**) from 2-aminobenzoketones (**30**), toluene (**36**) and NH_4OAc (**33**) in the presence of $CuCl_2$ at 80 °C for 12 h (**Scheme 1.17**).[43] The reaction proceeds through oxidative amination of benzylic C–H bonds of methylarenes with ammonia and 2-aminobenzoketones followed by intramolecular cyclization furnished quinazoline analogues. Moreover, the kinetic isotope effect (KIE) revealed that the C–H bond cleavage was the rate-determining step in this methodology.



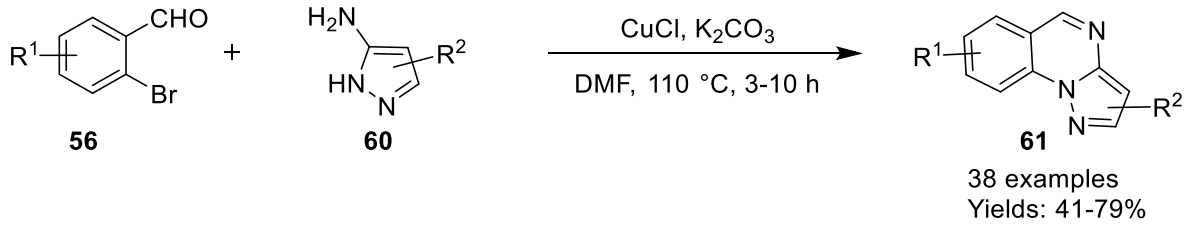
Scheme1.17 Copper–catalyzed the synthesis of substituted quinazolines from 2-aminobenzoketones and toluene

Recently, Sastry *et al.* used phenacyl azides (**58**) and 2-aminobenzophenones (**35**) for the synthesis of quinazolines (**59**) by using $Cu(OAc)_2$, triethylamines in acetonitrile at room temperature (**Scheme 1.18**).[44] The developed protocol proceeded well and constructed two C–N bond in a single operation.



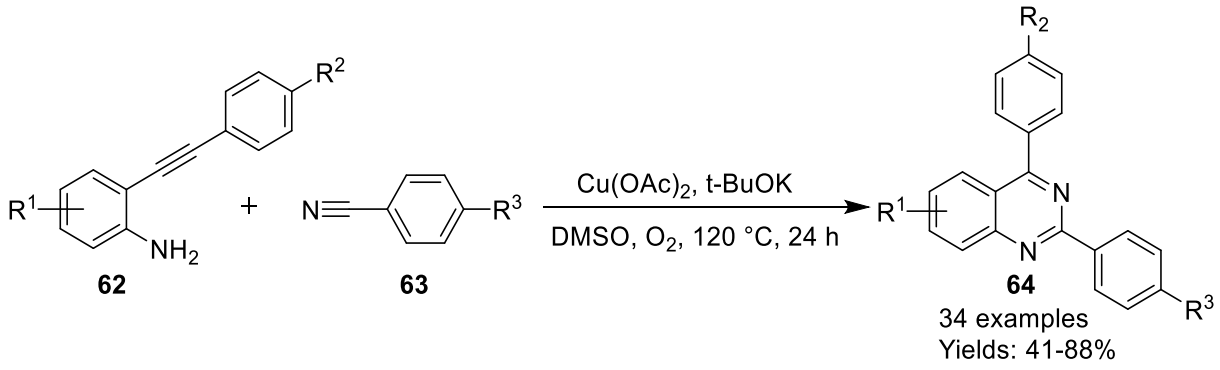
Scheme1.18 Copper–catalyzed the synthesis of quinazolines from 2-aminobenzophenones and phenacyl azides

Fan group developed one-pot tandem approach for the synthesis of pyrazolo[1,5-*a*]quinazolines (**61**) by reacting 2-bromobenzaldehydes (**56**) with 5-aminopyrazoles (**60**) in the presence of K_2CO_3 at 110 °C through copper–catalyzed imine formation followed by Ullmann type coupling led to fused quinazolines. Diverse substituted 2-bromobenzaldehydes and 5-aminopyrazoles tolerated well and furnished corresponding product in moderate to good yields (41-79%)(**Scheme 1.19**).[45]



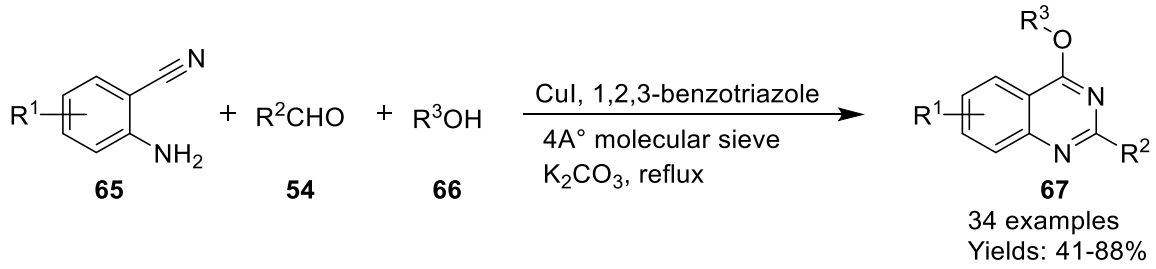
Scheme1.19 Copper–catalyzed one-pot tandem synthesis of fused quinazolines

Very recently, Copper-catalyzed the one-pot process of 2-ethynylanilines (**62**) and benzonitriles (**63**) using molecular oxygen as sole oxidant has been developed for the synthesis of substituted quinazoline (**64**) by Jiang and team (**Scheme 1.20**).[46] The reaction proceeded through effective cleavage of the C−C triple bond and synthesis of new C−N and C−C bonds in a one-pot fashion. Moreover, the reaction showcased a wide range of substituent tolerance with various benzonitriles and 2-ethynylanilines, providing a gallery of quinazolines in moderate to excellent yields (41-88%). These compounds also exhibited aggregation-induced emission phenomenon, good fluorescence quantum yield and lifetime decay which enhanced the value of quinazoline analogues in material science for future aspect.



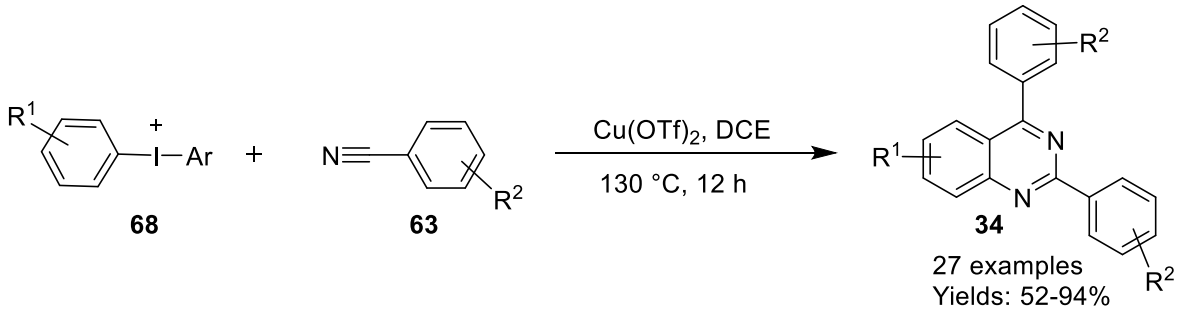
Scheme1.20 Copper–catalyzed the synthesis of quinazolines from 2-ethynylanilines and benzonitriles

Battula *et al.* described copper–catalyzed an efficient strategy for preparing *o*-protected-4-hydroxyquinazolines (**67**) from 2-aminobenzonitriles (**65**), aldehydes (**54**) and alcohol (**66**) through the generation of an *N*–substituted bicyclic intermediate followed by nucleophilic attack of the alkoxy group (**Scheme 1.21**).[47] The reaction was adequately explored with a broad range of substituted 2-aminobenzonitriles, and aldehydes led to corresponding quinazolines in moderate to excellent yields (41-88%).



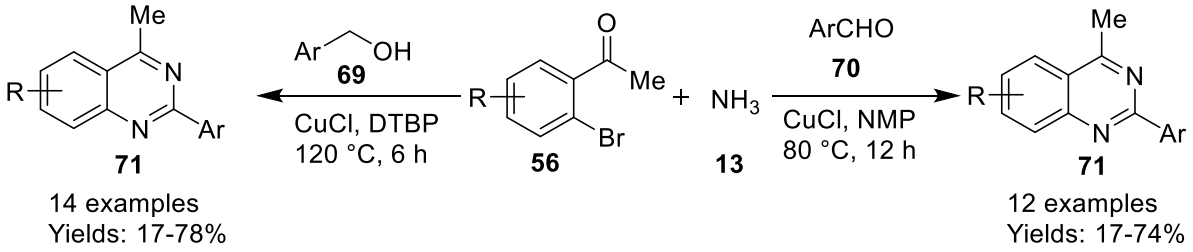
Scheme1.21 Copper–catalyzed the synthesis of *o*-protected-4-hydroxyquinazolines

Li and his colleagues documented an efficient one-pot protocol for the region-selective synthesis of substituted quinazolines (**34**) by using diaryliodonium salts (**68**) and nitriles (**63**) in the presence of $Cu(OAc)_2$, tBuOK in DMSO at 120 °C (**Scheme 1.22**).[10] The developed strategy of electrophilic annulations facilitates great flexibility of the substitution patterns on nitrile and symmetrical or unsymmetrical diaryliodonium salts, afforded respective products in good to excellent yields (52-94%).



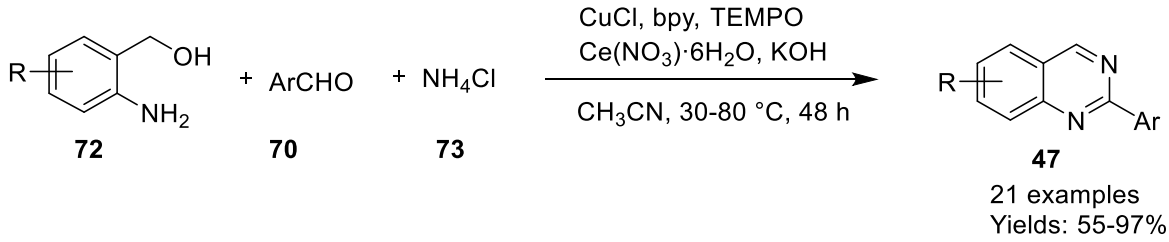
Scheme1.22 Copper–catalysed the region-selective synthesis of substituted quinazolines by using diaryliodonium salts and nitriles

Ju *et al.* reported CuCl–catalyzed the one-pot multicomponent synthesis of quinazolines (**71**) by the reaction of *o*-bromo aromatic ketones (**56**) with aromatic aldehydes (**70**) or aromatic alcohols (**69**) and ammonia in water (**13**) (**Scheme 1.23**).[48] The most significant features of this approach were easily available starting materials, ammonia water used as a nitrogen source, and DTBP used as an oxidant in case of primary alcohol. The reaction provided the target product in good yields with different aromatic aldehydes or aliphatic and aromatic primary alcohols.



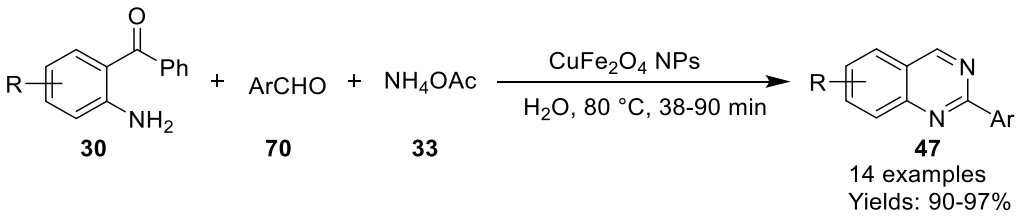
Scheme 1.23 Copper-catalyzed one-pot multi-component synthesis of quinazolines from o-bromo aromatic ketones and aldehydes or alcohols

Chen *et al.* disclosed copper–catalyzed the one-pot tandem reaction of (2-aminophenyl)methanols (**72**) with aldehydes (**70**) and ammonium chloride (**73**) in the presence of cerium nitrate hexahydrate and TEMPO at 80℃ for 24 h. Mechanism of the reaction involved othe xidation of 2-aminobenzylalcohols to 2-aminobenzaldehydes by using CuCl/2,2′-bipyridine(bpy)/TEMPO catalyst system. Subsequently, the reaction of 2-aminobenzaldehyde with aldehyde and NH_4Cl gave cyclized product dihydroquinazolines, which on aromatization lead to quinazolines in moderate to excellent yields (55-97%) (**Scheme 1.24**).[49]



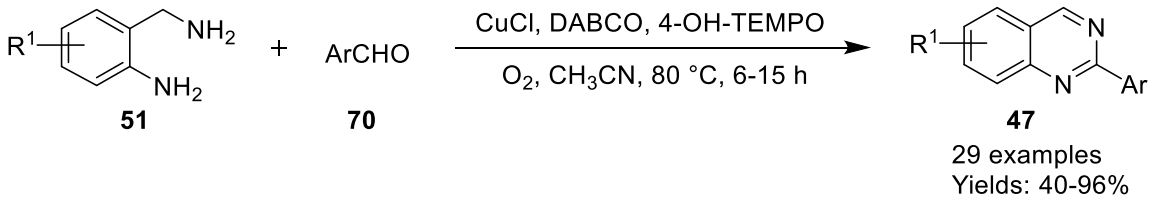
Scheme 1.24 Synthesis of 2-aryl quinazoline from (2-aminophenyl)methanols and aldehydes

Farhang group reported an efficient one-pot synthesis of quinazoline (**47**) derivatives *via* magnetically separable and reusable $CuFe_2O_4$ nanoparticle catalyzed tandem cyclization of 2-amino benzophenones (**30**) with aryl aldehydes (**70**) and NH_4OAc (**33**) (**Scheme 1.25**).[50] The catalytic activity of $CuFe_2O_4$ nanoparticles was evaluated in an aqueous medium which revealed that it is a green and promising catalyst in organic synthesis.



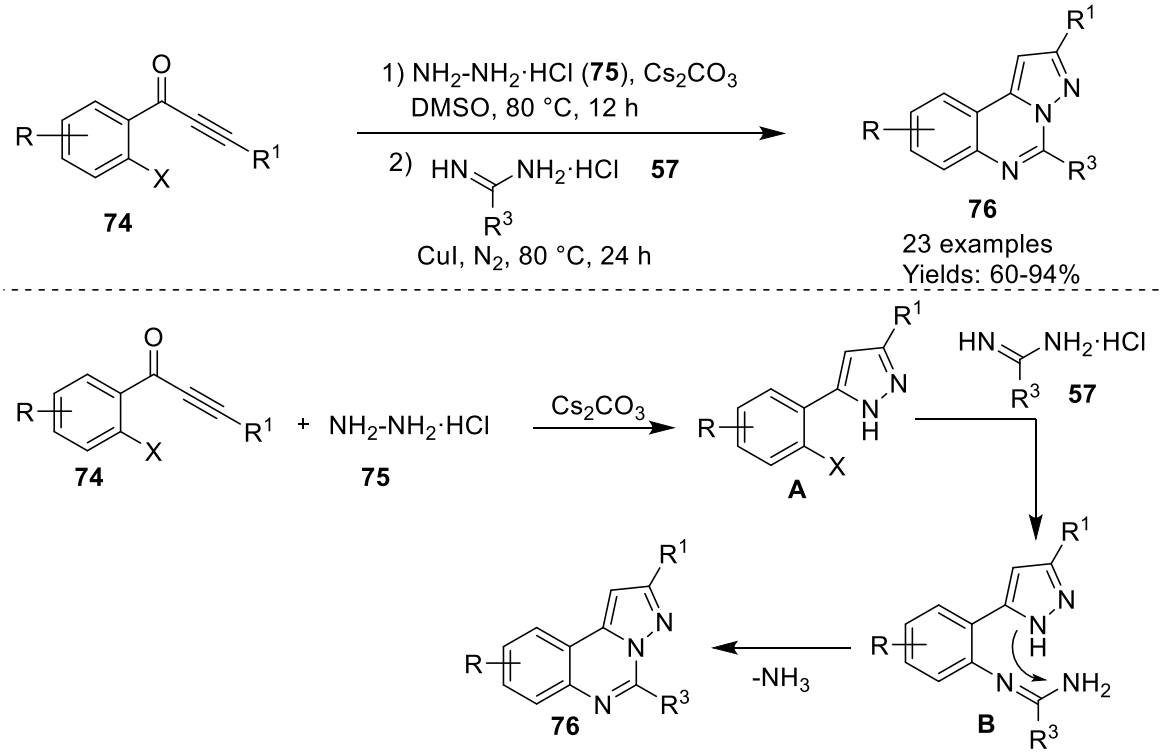
Scheme 1.25 $CuFe_2O_4$ nanoparticles catalyzed the synthesis of 2-aryl quinazolines from **30** and **32**

Yu and colleagues disclosed one–pot reaction of 2-aminobenzylamines (**51**) with arylaldehydes (**32**) for the synthesis of quinazolines (**47**) by employing CuCl/DABCO/4-HO-TEMPO as the catalysts and oxygen as the terminal oxidant (**Scheme 1.26**).[51] Variously substituted aryl or heteroaryl aldehydes were treated with a range of substituted 2-aminobenzylamines and afforded the substituted quinazolines in moderate to excellent yields (40-96%).



Scheme 1.26 Catalytic aerobic oxidative synthesis of quinazolines

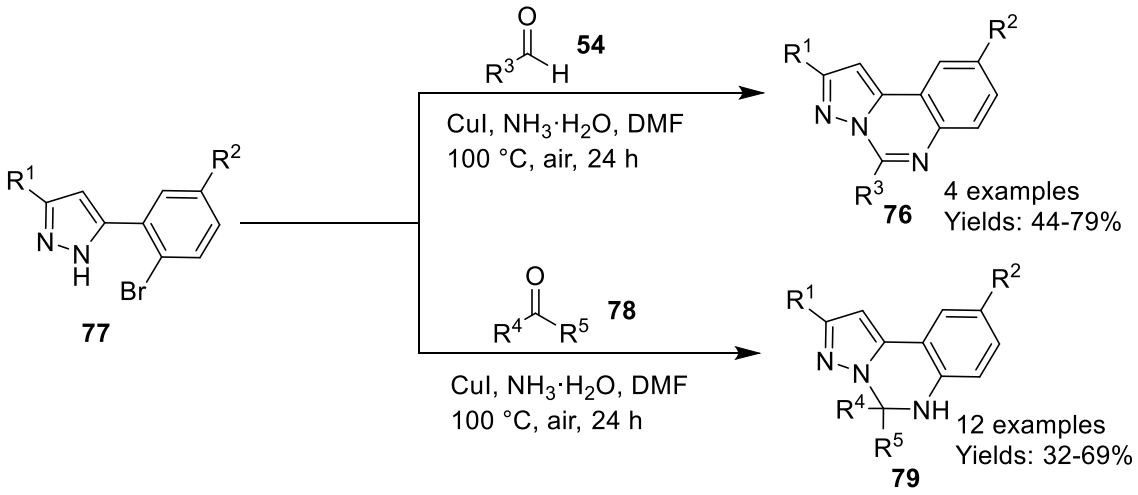
Fu and co-workers described a novel and efficient method for the construction of pyrazolo[1,5-*c*]quinazolines (**76**) through one–pot sequential approach involving easily available substituted 1-(2-halophenyl)-3-alkylprop-2-yn-1-ones (**74**), hydrazine hydrochlorides (**75**), and amidine hydrochlorides (**57**) (**Scheme 1.27**).[52]



Scheme 1.27 Stepwise mechanism for the synthesis of pyrazolo[1,5-*c*]quinazolines

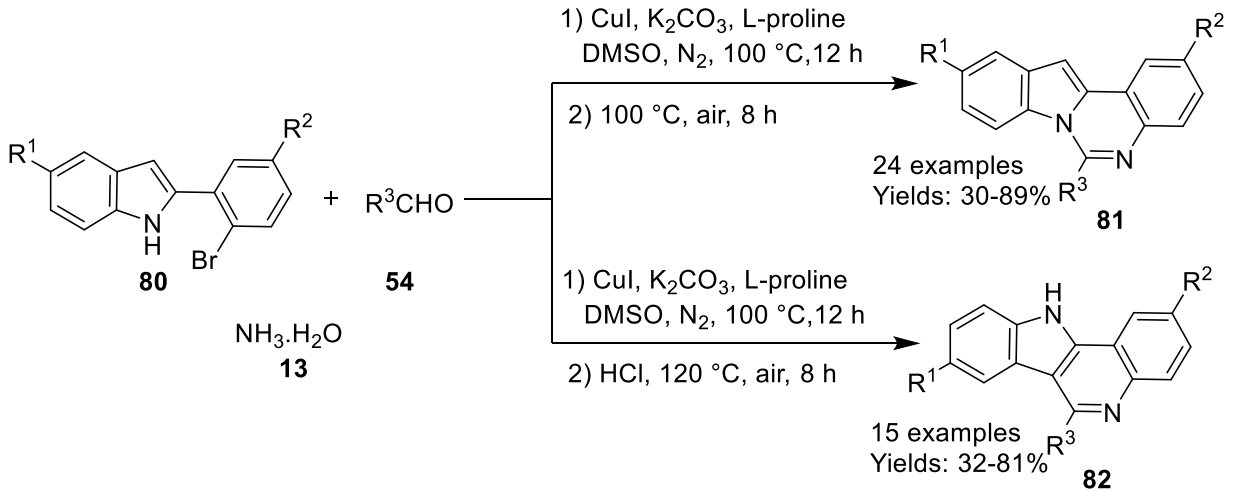
The mechanism of reaction proceeded through coupling of **74** with **75** gave pyrazole (**A**) as an intermediate. Then *N*-arylation of **A** with amidines offered intermediate **B.** Intermediate **B** furnished target product *via* intramolecular nucleophilic addition of pyrazoles with amidines (**Scheme 1.27**).

Gou and his colleagues developed an efficient method for the development of pyrazolo[1,5-*c*]quinazolines (**76**) and 5,6-dihydropyrazolo[1,5-*c*]quinazolines (**79**) *via* copper–catalyzed one-pot tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles (**77**) with aldehydes (**54**) and ketones (**78**) in aqueous ammonia under aerobic condition (**Scheme 1.28**).[53] A diverse range of aldehydes including aryl, alkyl, alkenyl, and hetero-aryl underwent smoothly in this reaction condition and afforded corresponding functionalized quinazoline in moderate to good yields (32-79%). Moreover, the tandem reaction could be done in a four-component manner by starting with 1-(2-bromophenyl)-1,3-diones, hydrazine hydrate, carbonyl compounds, and aqueous ammonia.



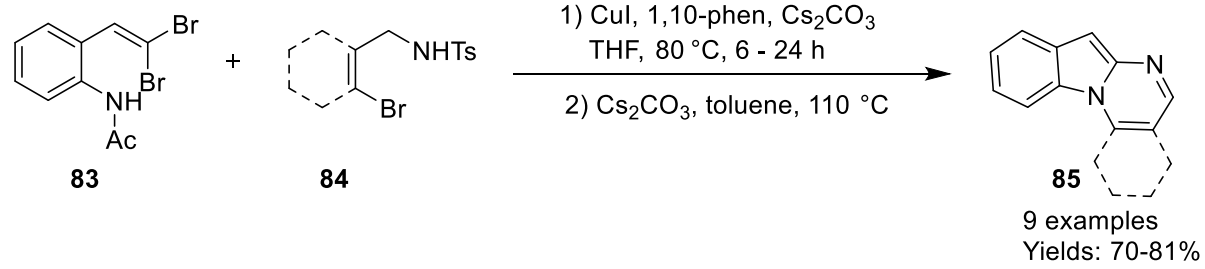
Scheme 1.28 Synthesis of pyrazolo[1,5-*c*]quinazolines from 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes

Similarly, Fan and colleagues described copper–catalyzed one–pot two-step sequential reactions of 2-(2-bromoaryl)-1*H* indoles (**80**), aldehydes (**54**), and aqueous ammonia (**13**) for the selective synthesis of indolo[1,2-*c*]quinazoline (**81**) and 11*H*-indolo[3,2-*c*]quinolone (**82**) (**Scheme 1.29**).[54] The regioselectivity of reaction was controlled by tuning the reaction condition. When the reaction was performed without acid corresponding indolo[1,2-*c*]quinazolines observed in moderate to excellent yields (30-89%). However, under acidic condition, C-C coupling was observed which led to 11*H*-indolo[3,2-*c*]quinoline in good yields (32-81%).



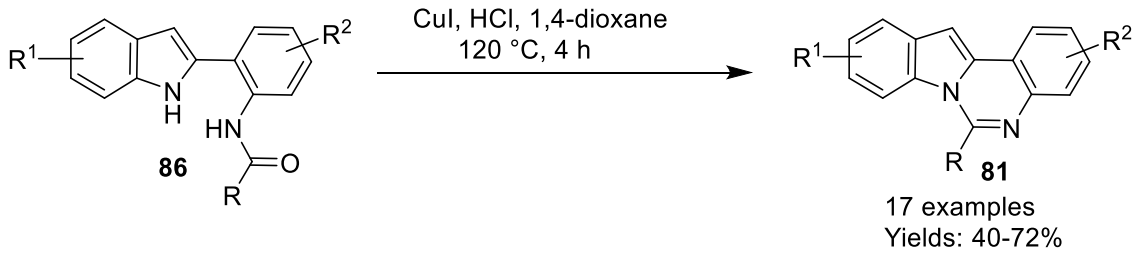
Scheme 1.29 Copper–catalyzed reactions of 2-(2-bromoaryl)-1*H*indoles, aldehydes, and aqueous ammonia

Kiruthika *et al.* described a Cu(I)–catalyzed one–pot, protocol for the rapid synthesis of indolo[1,2-*a*]quinazolines (**85**) from the readily available gem-dibromovinylanilides (**83**) and *N*-tosyl-*o*-bromobenzamides (**84**) by using 1,10-phen and Cs_2CO_3 in THF at 80 °C then refluxed under basic condition (**Scheme 1.30**).[55] The reaction worked well with a variety of *N*-tosyl-*o*-bromobenzamides and transformed into corresponding products with good yields (70-81%). This strategy further extended for the synthesis of 2-amidoindoles.



Scheme 1.30 Copper–catalyzed one-pot synthesis of indolo[1,2-*a*]quinazolines

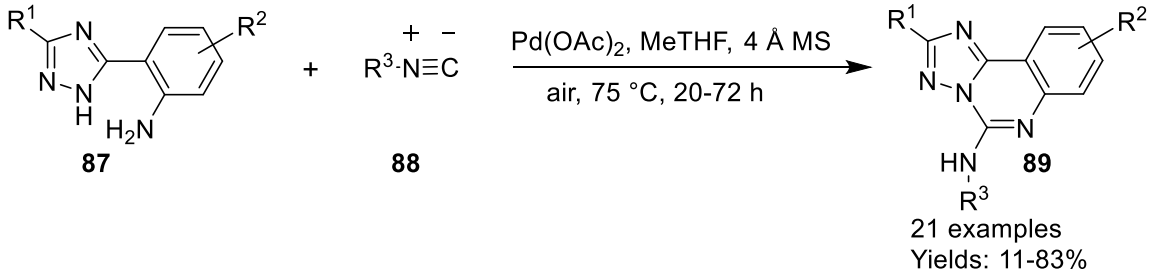
Guo *et al.* disclosed copper-catalyzed intramolecular cyclization reaction of 2-(2-amidoaryl)-1*H*-indoles (**86**) for the preparation of indolo[1,2-*c*]quinazoline (**81**) derivatives in the presence of acid (**Scheme 1.31**).[56] The reaction proceeds through nucleophilic addition followed by dehydration led to corresponding product in moderate to good yields (40-72%).



Scheme 1.31 Synthesis of indolo[1,2-*c*]quinazolines from 2-(2-amidoaryl)-1*H*-indoles

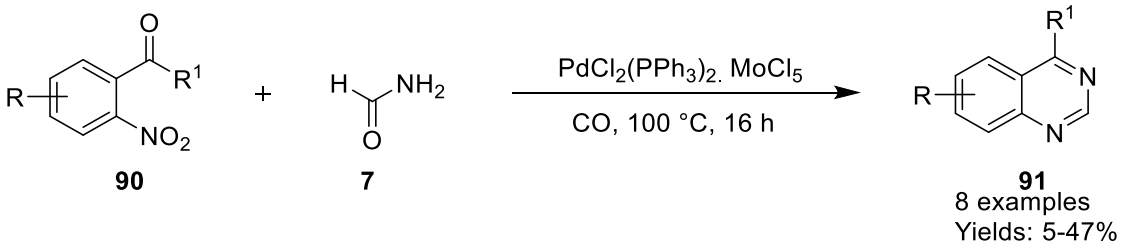
1.2.2.2. Palladium-catalyzed reactions for the synthesis of quinazolines

Ruijter and colleagues described Pd(II)–catalyzed aerobic oxidative coupling of (2 aminophenyl)azoles (**87**) with isocyanides (**88)** for the development of medicinally important azole fused quinazolines (**89**) by using air as oxidant at 75 °C in MeTHF (**Scheme 1.32**).[57] An ample range of triazole substrates was reacted well and afforded annulated product in moderate to excellent yields (11-83%). Also, several hetero-aromatic groups on triazole were applied for annulation after the minor tuning of the catalyst loading and reaction time and delivered corresponding products in lower to excellent yields (11-83%).



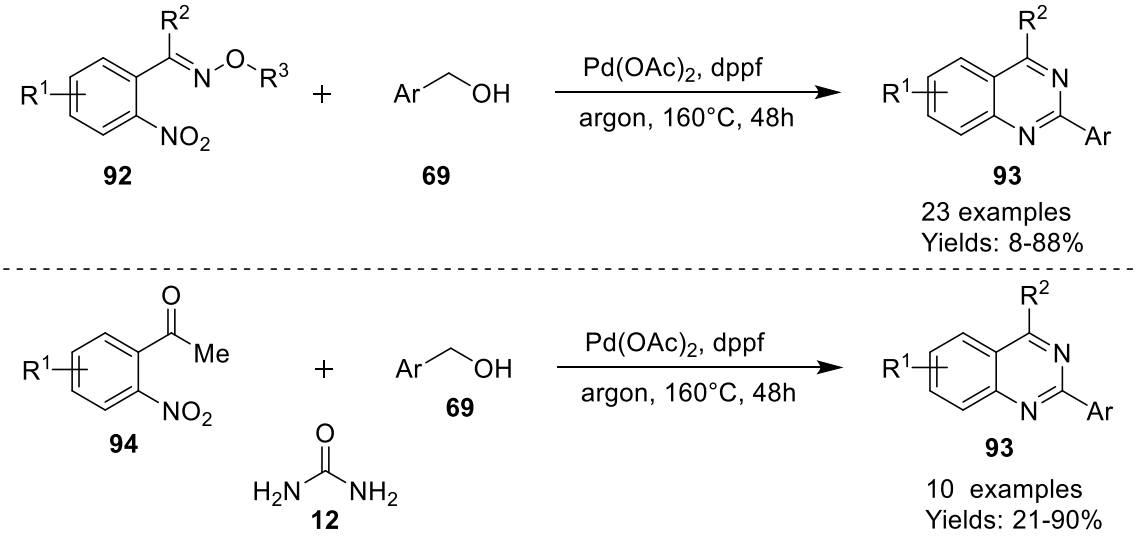
Scheme 1.32 Pd-catalyzed synthesis of quinazolines from oxidative coupling of (2 aminophenyl)azoles with isocyanides

Akazome *et al.* developed $Pd(PPh_3)Cl_2$ and $MoCl_5$ catalyzed intermolecular reductive *N*–heterocyclization reaction of 2-nitrobenzaldehyde or 2-nitrophenyl ketones (**90**) with formamide (**7**) for the synthesis of quinazolines derivatives (**91**) (**Scheme 1.33**).[58] This reaction proceeds through an active nitrene intermediate which could be produced by selective deoxygenation of nitro group by carbon monoxide.



Scheme 1.33 Palladium-catalyzed synthesis of quinazolines from 2-nitrobenzaldehyde and formamide

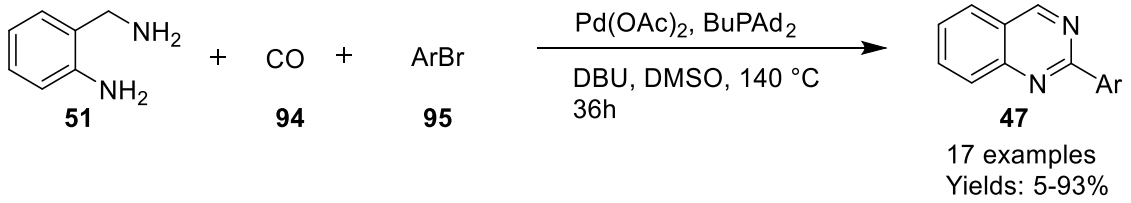
Deng group developed Pd–catalyzed the synthesis of 2,4-disubstituted quinazoline (**93**) by reacting *E*-1-(2′-nitrophenyl)ethanone*o*-methyloximes (**92**) and benzyl alcohols (**69**) in the presence of dppf as ligand under argon at 160 °C through hydrogen transfer methodology (**Scheme 1.34**).[59] It is believed that the reaction proceeds through the dehydrogenation of benzyl alcohol to benzaldehyde then the formation of imine followed by intramolecular cyclization led to the formation of quinazolines. Similarly, the reaction was carried out with 1-(2-nitrophenyl)ethanone (**94**), urea (**12**) and benzyl alcohols (**69**) under optimized condition. The efficient synthesis provides quinazoline analogues in lower to excellent yields (21-90%).



Scheme 1.34 Palladium–catalyzed one-pot synthesis of 2,4-disubstituted quinazolines

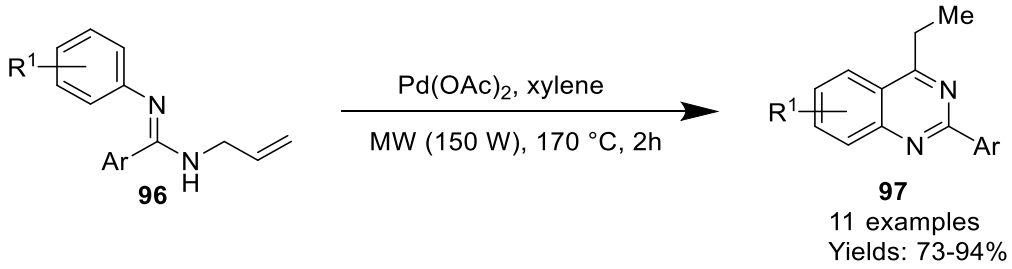
Wu group demonstrated a novel method for the synthesis of quinazoline scaffold (**47**) from 2-aminobenzylamine (**51**) with aryl bromides (**95**) which involves palladium catalyzed aminocarbonylation–condensation–oxidation sequence and facilitates the desired products in poor to excellent yields (5-93%) (**Scheme 1.35**).[60] The generality of the reaction was investigated by

varying different electron releasing (methoxy, dimethylamino, or *tert*-butyl) and withdrawing groups (cyano, trifluoromethyl) containing aryl bromide.



Scheme 1.35 Palladium-catalyzed synthesis of quinazolines from 2-aminobenzylamine and aryl bromides

Wang and his team developed annulation process for the development of quinazolines (**97**) from *N*–allylamidines (**96**) under microwave irradiation by using palladium as an active catalyst in xylene at 170 °C (**Scheme 1.36**).[61] The scope of this methodology was explored by using a range of aryl amidines containing electron rich and electron deficient substituents gave the respective product in good to excellent yields (73-94%).

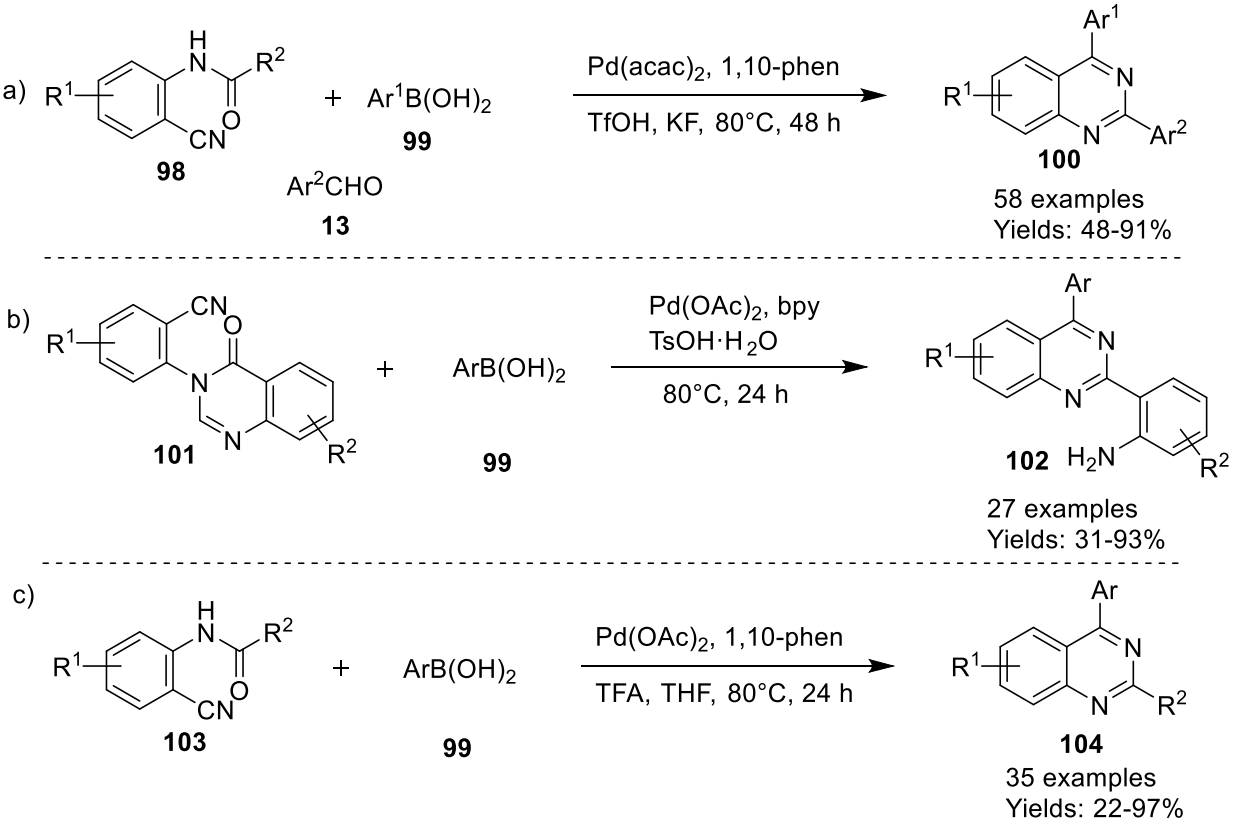


Scheme 1.36 Palladium-catalyzed synthesis of quinazolines from *N*–allylamidines

Chen group proposed palladium–catalyzed one–pot, three component tandem assembly for quinazoline analogous (**100**) by using readily available 2-aminobenzonitriles (**98**), aldehydes (**13**), and aryl boronic acids (**99**) (**Scheme 1.37a**).[62] Subsequently, the same group developed another approach for quinazoline scaffold from 2-(quinazolinone-3(4*H*)-yl)benzonitriles (**101**) and aryl boronic acids (**99**) (**Scheme 1.37b**).[63] The developed protocol proceeds through sequential nucleophilic addition, intramolecular cyclization followed by ring-opening and delivered corresponding product in moderate to excellent yields (31-93%).

Furthermore, Chen group described of 2,4-disubstituted quinazolines by a palladium–catalyzed reaction of aryl boronic acids (**99**) with *N*-(2-cyanoaryl)benzamides (**103**) by using 1,10-phen, TFA in THF at 80°C (**Scheme 1.37c).**[64] It is believed that the reaction mechanism involves nucleophilic addition to the nitrile, forming an imine intermediate followed by an intramolecular

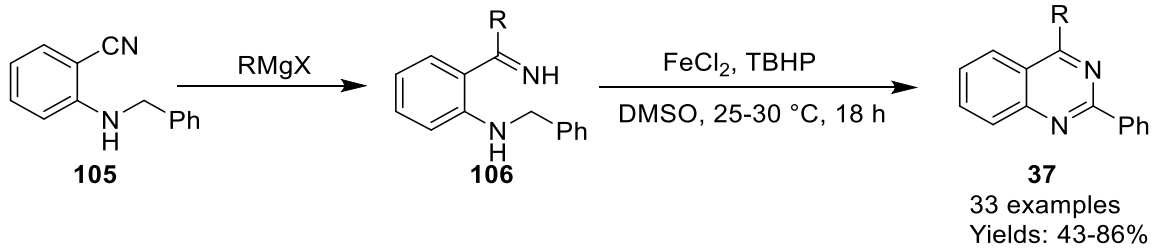
addition to the amide and dehydration led to quinazolines. The reaction demonstrated a broad range of functional group tolerance including electron-rich and electron deficient boronic acids and *N*-(2-cyanoaryl)benzamides.



Scheme 1.37 Palladium–catalyzed different approaches for the synthesis of quinazolines

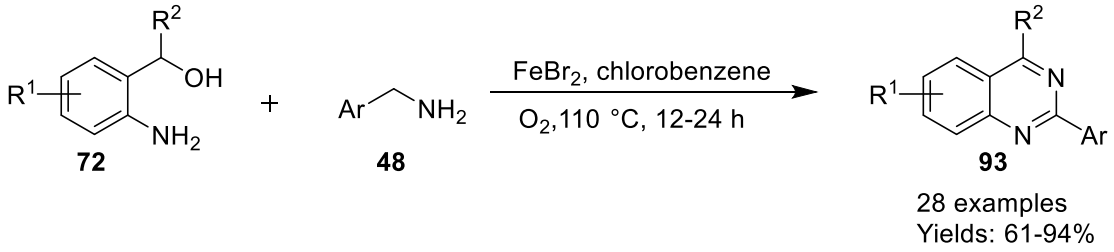
1.2.2.3. Iron-catalyzed reactions for the synthesis of quinazolines

Chen *et al.* demonstrated iron-catalyzed C(sp^3)–H oxidation and intramolecular C−N bond formation for the development of quinaozline (**37**) derivatives using ^{t}BuOOH as terminal oxidant. 2-alkylamino N−H ketamine (**106**) species were synthesized through Grignard reagent from readily available 2-alkylaminobenzonitrile (**105**) (**Scheme 1.38**).[65] Further, $FeCl_2$–catalyzed C(sp^3)–H oxidation of the alkyl group followed by intramolecular C−N bond formation, aromatization led to the formation of quinazolines in moderate to excellent yields (43-86%). It is proposed that the reaction proceeds *via* formation of imine, nucleophilic addition followed by aerial oxidation.



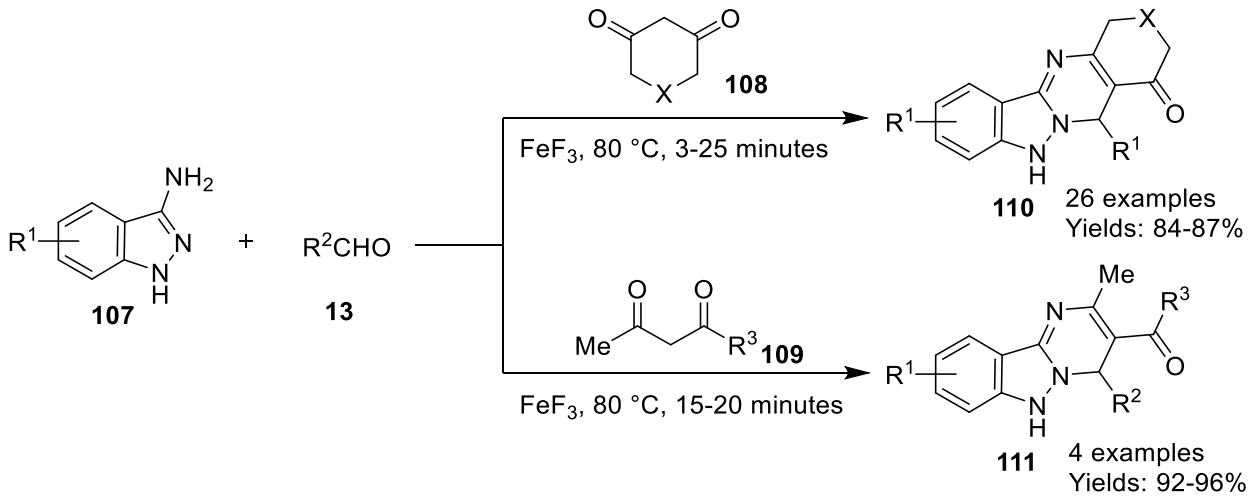
Scheme 1.38 Iron-catalyzed synthesis of quinazolines through C(sp^3)–H oxidation and intramolecular C–N bond formation

Iron-catalyzed one-pot cascade process for the synthesis of quinazoline derivatives (**93**) have been achieved by Devi and coworkers from 2-aminobenzyl alcohols (**72**) with benzylamines (**48**) under an aerobic oxidative condition in chlorobenzene at 110 °C for 12-24 h (**Scheme 1.39**).[66] The reaction proceeds through the formation of *N*–benzylidenebenzylamines oxidative trapping of ammonia followed by intramolecular cyclization. Both aromatic/heteroaromatic benzylamines treated smoothly in this strategy and afforded corresponding quinazolines in good to excellent yields (61-94%).



Scheme 1.39 Iron-catalyzed synthesis of quinazolines from 2-aminobenzyl alcohols and benzylamines

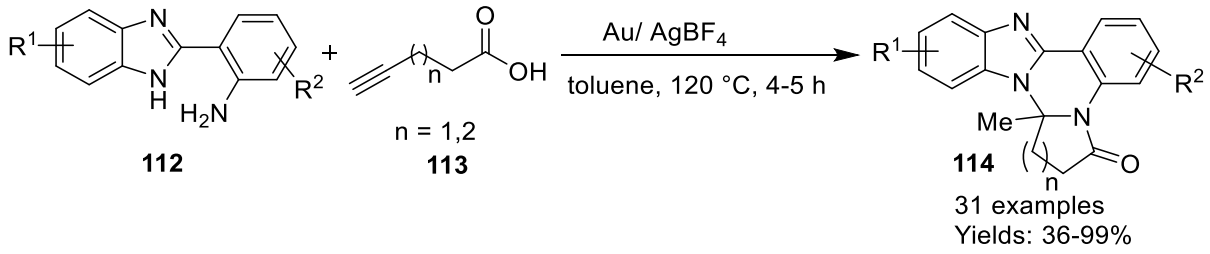
Jeong group developed iron-catalyzed a green and efficient method for the synthesis of functionalized tetrahydroindazolo[3,2-*b*]quinazoline (**110**) from indazol-3-amines (**107**) and aldehydes (**13**) under sonication in solvent-free condition (**Scheme 1.40**).[67] This method has some advantages over conventional methods such as good to excellent yields, shorter reaction time, low cost, easy work-up procedure and without column chromatography.



Scheme 1.40 Iron-catalyzed synthesis of tetrahydroindazolo[3,2-*b*]quinazolines from 1*H*-indazol-3-amines and aldehydes

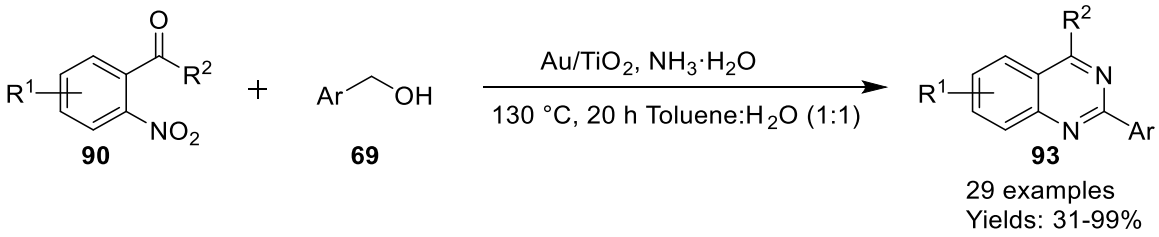
1.2.2.4. Gold-catalyzed reactions for the synthesis of quinazolines

Ji *et al.* described Au(I)/Ag(I)–catalyzed one-pot tandem cyclization reaction for the synthesis of benzo[4,5]imidazo[1,2-*c*]pyrrolo[1,2-*a*]quinazolinones (**114**) through treatment of the substituted 2-(1*H*-benzo[d]imidazol-2-yl)anilines (**112**) with 4-pentynoic acid or 5-hexynoic acid (**113**) (**Scheme 1.41**).[68] Moreover, 2-(1*H*-benzo[d]imidazol-2-yl)anilines also well tolerated in this developed protocol and gave corresponding quinazolinones in moderate to excellent yields (36-99%). The developed strategy was involved three new C–N bonds formation in one–pot fashion.



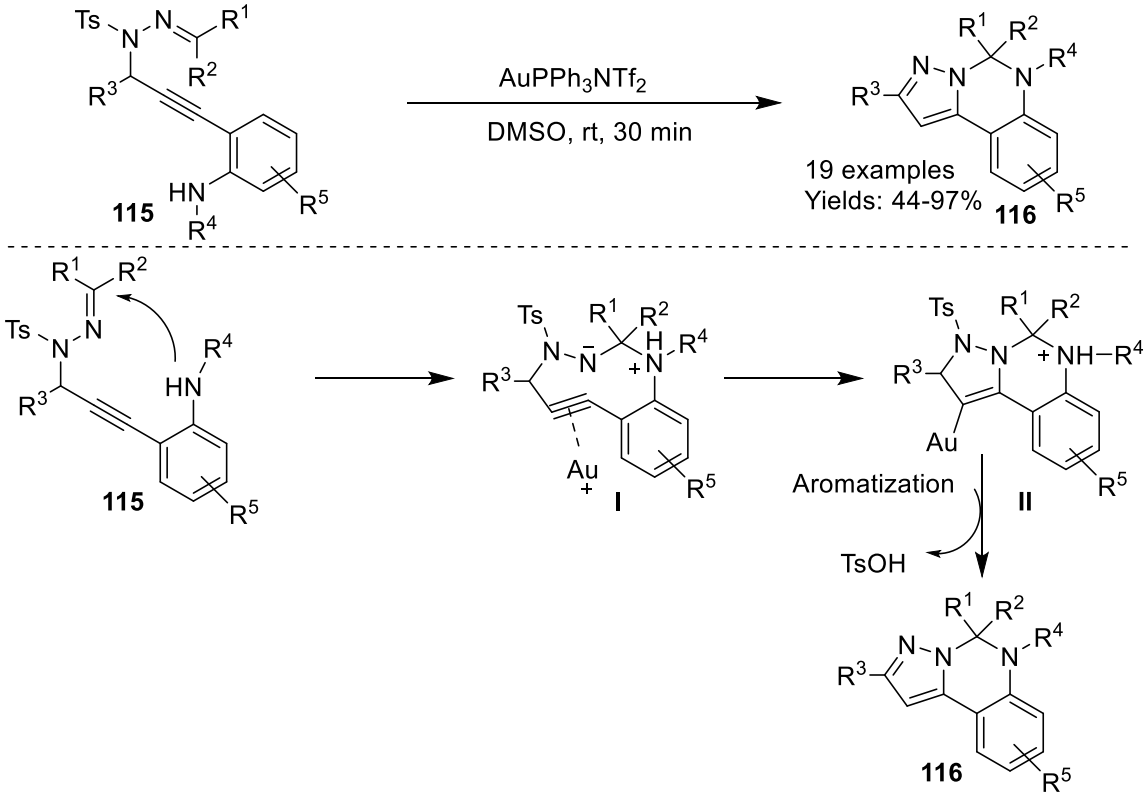
Scheme 1.41 Gold-catalyzed one-pot tandem cyclization reaction for the synthesis of benzo [4,5]imidazo[1,2-*c*]pyrrolo[1,2-*a*]quinazolinones

Alternatively, Tang *et al.* developed Au-nanoparticles catalyzed one-pot reaction of o-nitroacetophenones with alcohols for the development of 2,4-disubstituted quinazolines (**93**) by employing hydrogen-transfer strategy (**Scheme 1.42**).[69] The broad substrate scope, good tolerance to air, water and recyclability of a catalyst made this protocol advantageous.



Scheme 1.42 Gold-catalyzed one-pot tandem cyclization for the synthesis of 2,4-disubstituted quinazolines from o-nitroacetophenones and alcohols

Zhan and coworkers disclosed Au-mediated chemoselective bicyclization of *N*–propargylic sulfonyl hydrazones (**115**) in DMSO at room temperature for the preparation of 5,6 dihydropyrazolo[1,5-*c*]quinazolines (**116**). Various *N*-propargylic sulfonyl hydrazones actively participated under the optimized reaction condition to afford quinazoline in good to excellent yields (44-97%) (**Scheme 1.43**).[70]

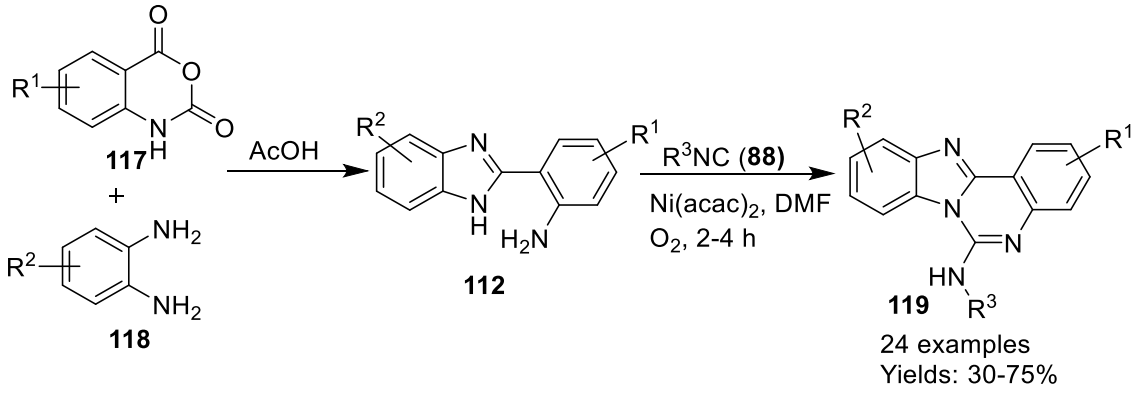


Scheme 1.43 Gold-catalyzed synthesis of 5,6 dihydropyrazolo[1,5-*c*]quinazolines from o-*N*-propargylic sulfonyl hydrazones

The proposed reaction mechanism was depicted in **Scheme 1.43**. Initially, nine-membered cyclic aminal intermediate **I** was formed by the intramolecular nucleophilic addition of the aniline nitrogen to the imino group. Then to activate the alkyne triple bond gold catalyst coordinated with alkyne for nucleophilic attack of the nitrogen anion, leading to the intermediate **II**. Finally, proto-demetallation, aromatization and elimination of p-toluenesulfonic acid resulted in desired quinazoline derivatives (**Scheme 1.43**).

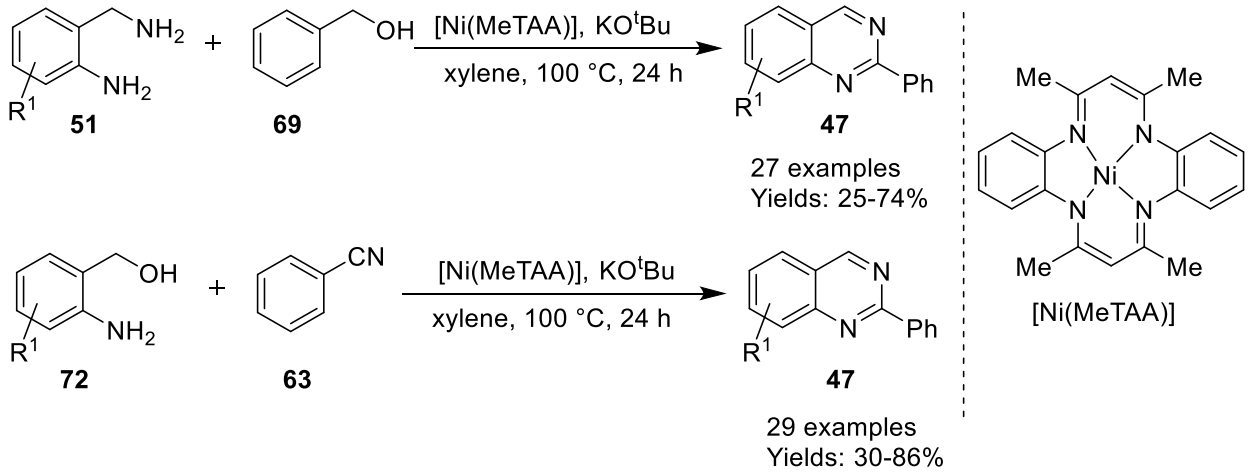
1.2.2.5. Nickel-catalyzed reactions for the synthesis of quinazolines

Shinde *et al.* developed nickel–catalyzed ligand-base-free one-pot sequential tandem strategy for oxidative isocyanide insertion under aerobic conditions with intramolecular bisamine nucleophiles. The tandem strategy involved an opening of isatoic anhydride (**117**), annulation to benzimidazole (**112**) followed by nickel-catalyzed intramolecular isocyanide insertion led to fused quinazolines (**119**) with moderate to excellent yields (30-75%) (**Scheme 1.44**).[71] Fluorescence study revealed that the synthesized compounds exhibit good fluorescence with high quantum yield. These compounds have been proposed to be used as a high fluorescent probe.



Scheme 1.44 Nickel–catalyzed one-pot sequential tandem strategy for the synthesis of quinazolines

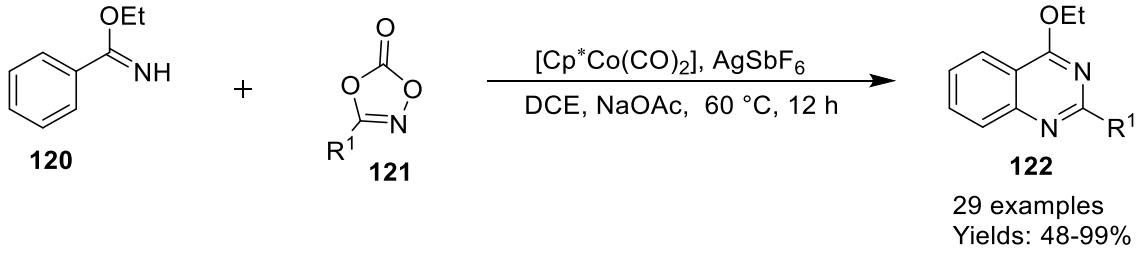
The nickel–catalyzed acceptorless dehydrogenative coupling of 2-aminobenzylamine (**51**) with benzyl alcohol (**69**) and 2-aminobenzylalcohol (**72**) with benzonitrile was developed by Paul and co-workers in the presence of KO^{t}Bu in xylene at 100 °C for 24 h (**Scheme 1.45**)[72]. The broad substrate scope, earth-abundant and easy to prepare nickel catalyst and environmentally benign methodology made this approach advantageous.



Scheme 1.45 Nickel–catalyzed one-pot tandem strategy for the synthesis of quinazolines

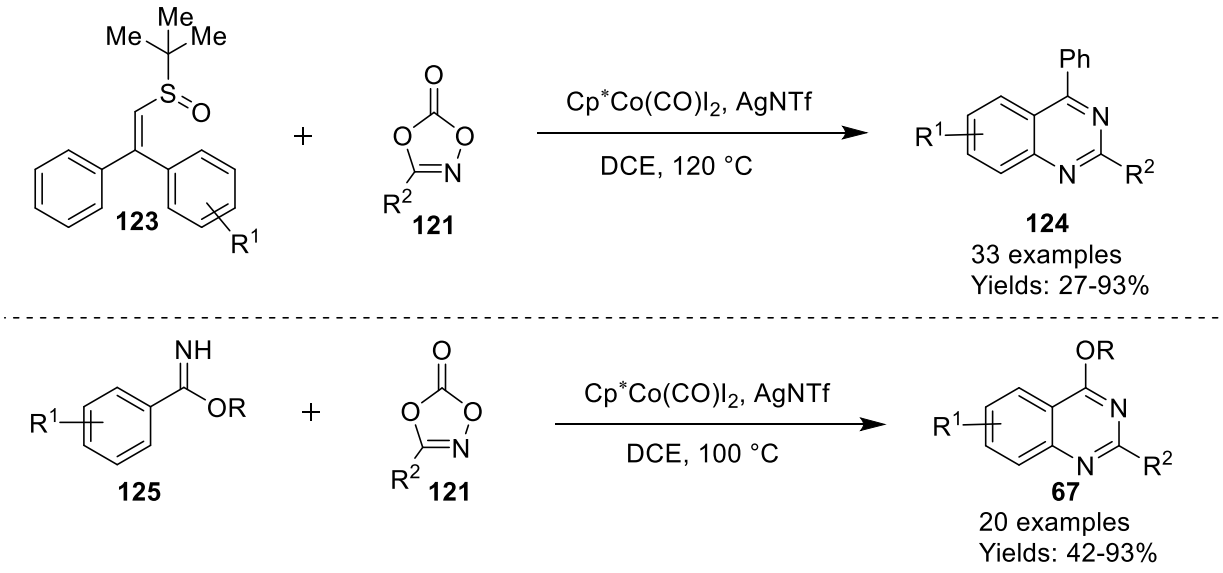
1.2.2.6. Cobalt-catalyzed reactions for the synthesis of quinazolines

Glorius and team demonstrated Cp*Co(III)–catalyzed [4 + 2] cycloaddition of arenes with rarely explored free imines (**120**) and dioxazolones (**121**) for the development of multi-substituted quinazoline derivatives (**122**) (**Scheme 1.46**).[73] The reaction involved cobalt–catalyzed tandem direct C–H amidation followed by intramolecular cyclization to afford quinazoline with moderate to excellent yields (48-99%).



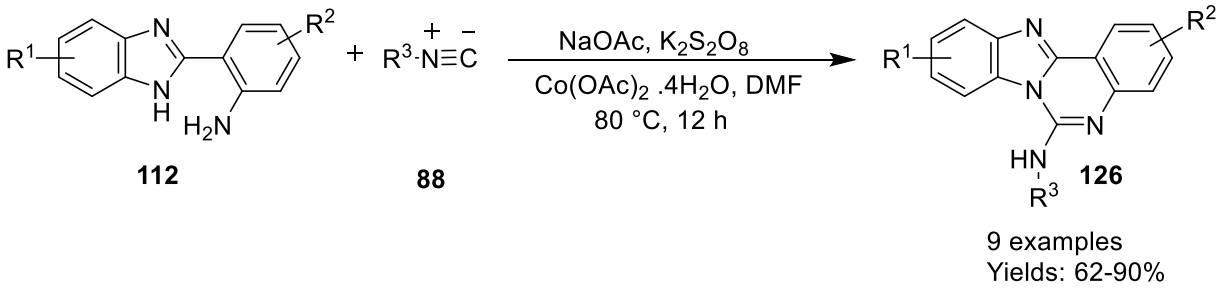
Scheme 1.46 Cobalt–catalyzed [4 + 2] cycloaddition of imines with dioxazolones

Li group reported cobalt–catalyzed direct functionalization of dioxazolones (**121**) with *N*-sulfinylimines (**123**) and benzimidates (**125**) for the rapid synthesis of quinazoline analogous. Various *N*-sulfinylimines, benzimidates and dioxazolones actively participated under the optimized reaction condition and furnished quinazoline in lower to excellent yields (27-97%) (**Scheme 1.47**).[74] The merits of the reaction were high regioselectivity and dioxazolne act as a synthon of nitriles.



Scheme 1.47 Cobalt–catalyzed synthesis of quinazolines from dioxazolones

Alternatively, Ahmadi *et al*. disclosed a simple method for the synthesis of fused quinazoline derivatives (**126**) framework by the reactions of benzo[d]imidazol-anilines (**112**) with isocyanides (**88**) by using cobalt–catalyzed isocyanide insertion cyclization reaction (**Scheme 1.48**).[75]

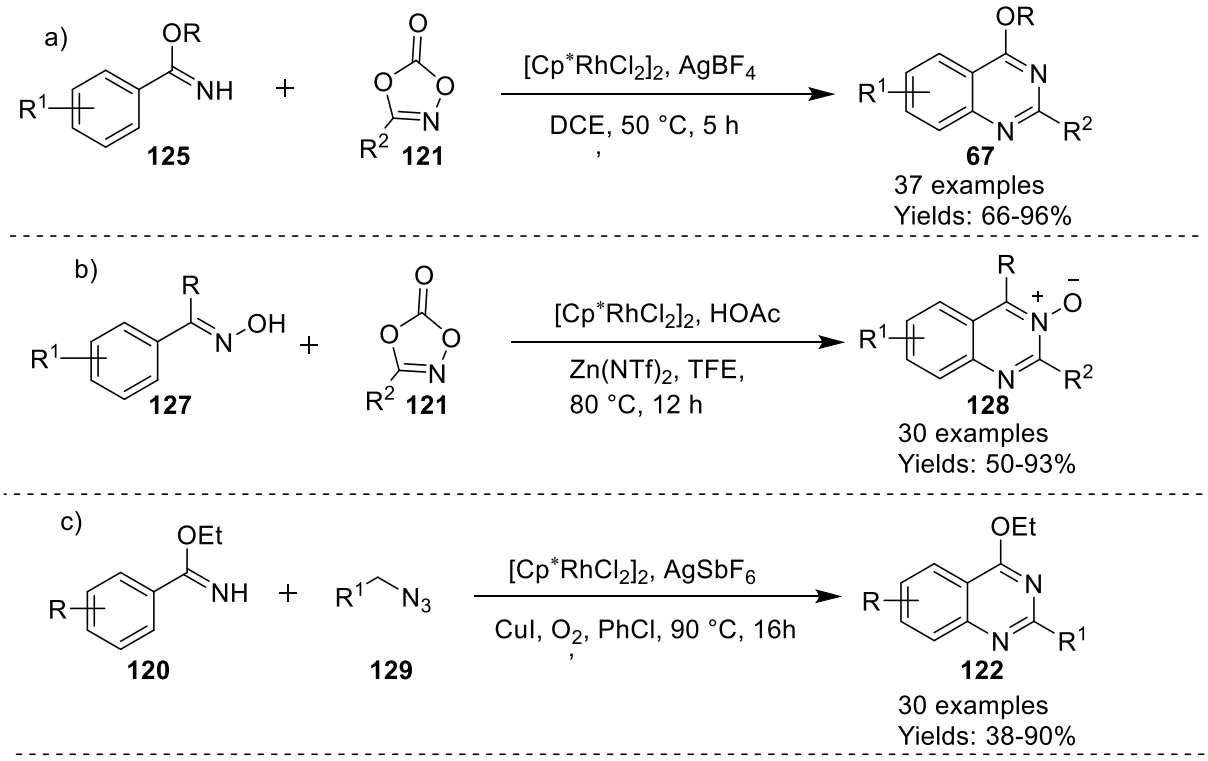


Scheme 1.48 Cobalt–catalyzed synthesis of fused quinazolines from benzo[d]imidazol-anilines and isocyanides

1.2.2.7. Rhodium-catalyzed reactions for the synthesis of quinazolines

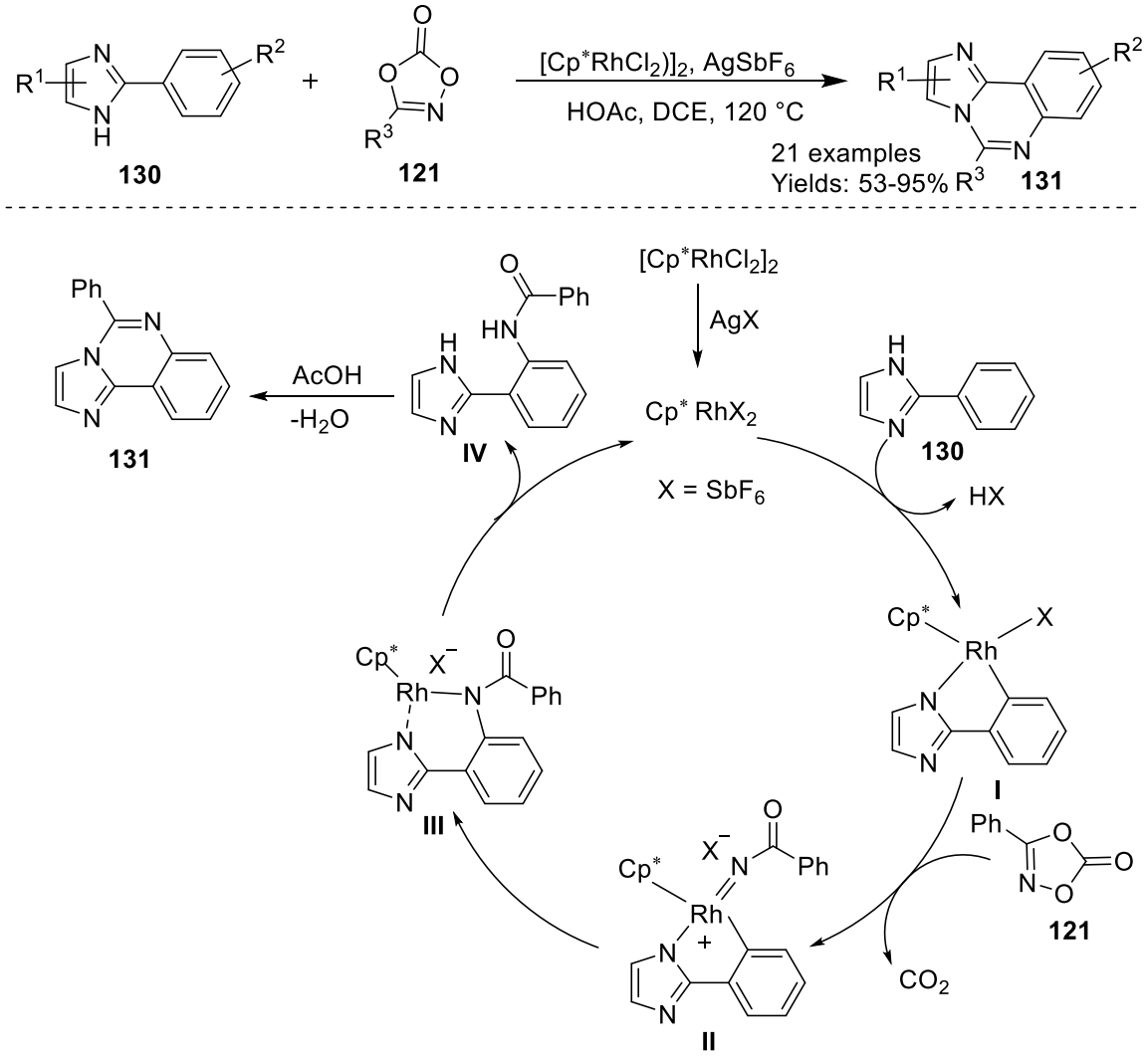
Wang *et al.* prepared rhodium–catalyzed double C–N bond formation sequence for the synthesis of highly substituted quinazolines (**67**) from benzimidates (**125**) and dioxazolones (**121**) (**Scheme 1.49a**).[76] In this reaction dioxazolone also worked as an internal oxidant to maintain the catalytic cycle. A series of benzimidates were converted into respective quinazolines with good to excellent yields (66-96%) in the presence of different types of dioxazolone derivatives. In the same year, Li group developed another approach for the synthesis of quinazoline *N*-oxides (**128**) from ketoximes

(**127**) and dioxazolone (**121**) through Rh(III)\Zn(II)–catalyzed C−H activation–amidation of the ketoximes (**Scheme 1.49b**).[77] This annulation system proceeded well without oxidant and afforded target quinazolines with good to excellent yields (50-93%). Jiao and colleagues demonstrated Rh and Cu co–catalyzed [4+2] C−H annulation of imidates (**120**) and alkyl azides (**129**) for quinazoline (**122**) synthesis (**Scheme 1.49c**).[78]



Scheme 1.49 Rhodium-catalyzed different synthetic approaches for the synthesis of quinazolines

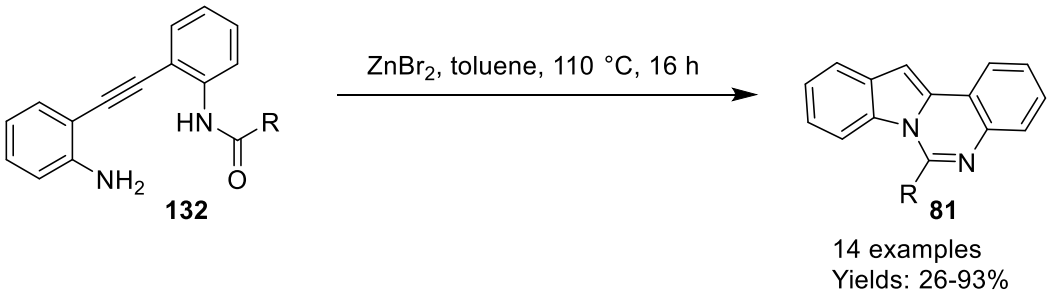
Very recently, Cheng and team described rhodium–catalyzed annulation of 2-arylimidazoles (**130**) with dioxazolones (**121**) for the synthesis of imidazo[1,2-*c*]quinazolines (**131**) (**Scheme 1.50**)[79]. It is proposed that intermediate **I** is formed by chelation assisted cleavage of ortho C–H bond in the presence of Rh(III) and Ag(I). The intermediate **I** on reaction with 1,4,2-dioxazol-5-one gave rhodium carbene species **II**, along with the extrusion of CO_2. The migratory insertion of rhodium carbene species **II** takes place to afford intermediate **III.** Finally, intermediate **III** gets converted to **IV** along with Rh(III) species which fulfil the catalytic cycle. Intermediate **IV** lead to quinazoline by intramolecular cyclization *via* dehydration reaction.



Scheme 1.50 Rhodium-catalyzed synthesis of imidazo[1,2-*c*]quinazolines

1.2.2.8. Zinc–catalyzed reaction for the synthesis of quinazolines

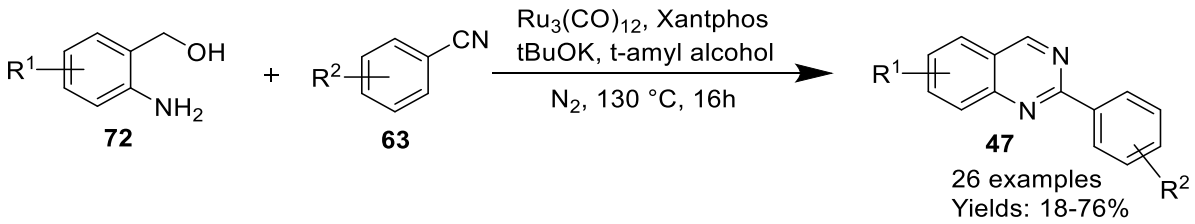
Zu *et al.* reported $ZnBr_2$–promoted domino hydroamination cyclization strategy for the generation of indolo[1,2-*c*]quinazolines (**81**) from acyclic alkyne substrates (**132**) (**Scheme 1.51**).[80] The reaction proceeds through zinc bromide-promoted tandem sequence which involved 5-endo-dig hydroamination and intramolecular cyclization between the indole nitrogen with an amide group and afforded indolo[1,2-*c*]quinazoline derivatives in moderate to excellent yields (26-93%).



Scheme 1.51 Zinc–catalyzed hydro-amination for the synthesis of indolo[1,2-*c*]quinazolines

1.2.2.9. Ruthenium-catalyzed reaction for the synthesis of quinazoline

Jiang and co-workers reported ruthenium–catalyzed dehydrogenative synthesis of 2-arylquinazolines (**47**) from 2-aminoaryl methanols (**72**) and benzonitriles (**63**) by employing $Ru_3(CO)_{12}$, xantphos and t-BuOK catalytic system (**Scheme 1.52**).[81] The developed protocol was examined with different substituted 2-aminoarylalcohol and benzonitriles and afforded cyclized product in lower to good yields (18-76%). The method was found to have several advantages such as operational simplicity, broad substrate scope, high atom efficiency and the use of less environmentally benign halogenated reagents.



Scheme 1.52 Ruthenium–catalyzed synthesis of quinazolines from 2-aminoaryl methanols and benzonitriless

1.3 Biological activities of quinazolines

Quinazoline is an interesting heterocyclic molecule in medicinal chemistry because of its wide - range of application in biological science. A large number of its derivatives are mentioned as "salient synthons" for different pharmaceutical applications, and more than 3,000,000 compounds with quinazoline scaffold are available in literature, and among them, nearly 40,000 compounds are found to be biologically active. [7] A brief overview of the bioactivity of quinazolines is given below.

1.3.1 Naturally occurring quinazoline alkaloids

Approximately 150 naturally occurring quinazoline alkaloids have been isolated from a number of families of the plant kingdom, animals and microorganisms.[82,83] In 1888, the first quinazoline alkaloid, vasicine (**133**) was isolated from *Justicia adhatoda*. Vasicine was studied in combination with vasicinone (**134**). Both the alkaloids (1:1) have shown pronounced bronchodilatory activity *in vivo* as well as *in vitro* (**Figure 1.2**).[84] Since then, many more quinazoline alkaloids have been isolated, synthesized, and found to have diverse pharmacological activities with a broad range of applications in agriculture science and medicinal science.[85] Vasicinol (**135**) and linaric acid (**136**) were obtained from an aerial part of *Linaria vulgaris*. Deoxypeganine[86] (**137**) was isolated from *Peganum harmala* in 1969 together with other alkaloids like peganine (**133**), vasicinone (**134**), peganidine (**138**), peganol (**139**) and deoxypeganidine (**140**) (**Figure 1.2**).[87]

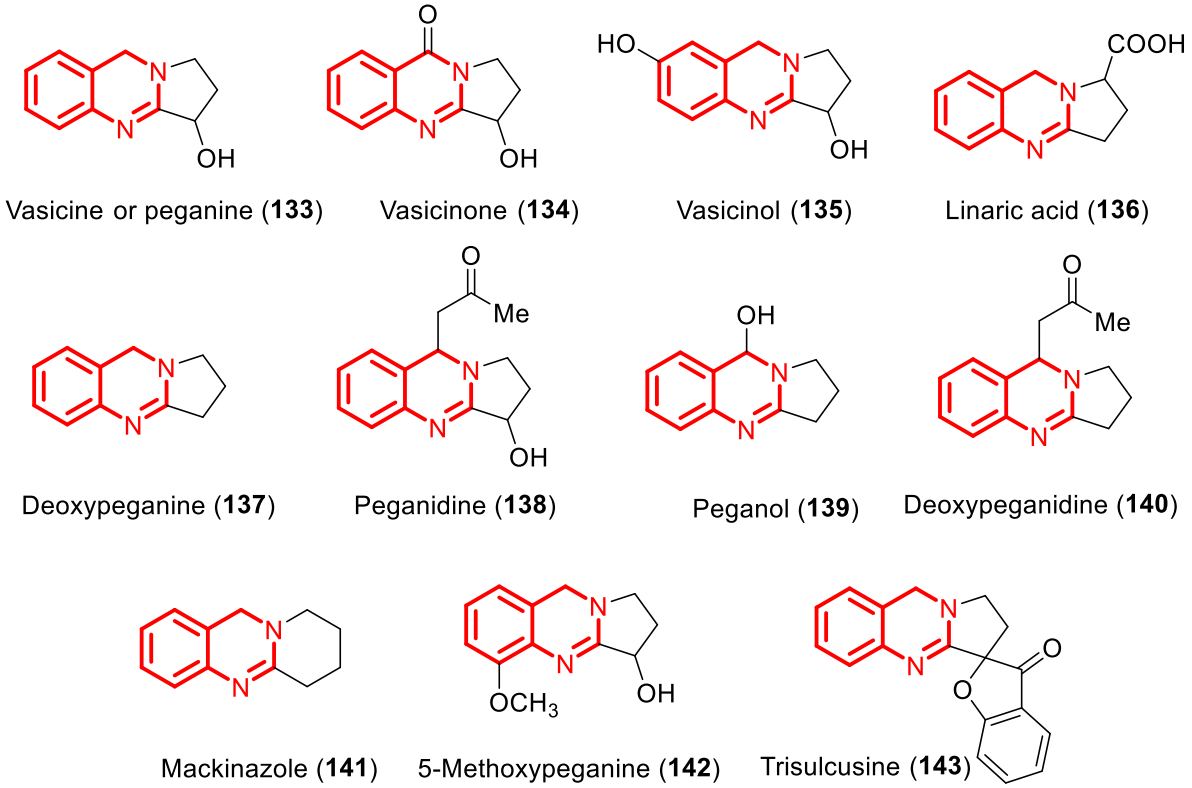


Figure 1.2 Chemical structures of naturally occurring quinazoline alkaloids

The alkaloid deoxypeganine (**140**)[88] is used in medical practice such as peripheral nervous system disease, myasthenia, hemiplegia, and *cornu ventral diseases* (A_4), treatment of Alzheimer' disease, alcoholism, nicotine dependence and narcotics. A tricyclic alkaloid mackinazole (**141**) was isolated from the leaves of *Mackinlaya* species. Trisulcusine (**143**) alkaloids were isolated from

Anisotes trisulcus along with other alkaloids such as vasicine (**133**), vasicinone (**134**) and 5-methoxypeganine (**142**) (**Figure 1.2**).[89]

1.3.2 Pharmacological applications of quinazoline

Quinazoline derivatives exhibited a wide range of pharmacological activities such as antimalarial,[90] antimicrobial,[91] anti-inflammatory,[92,93] anticonvulsant,[94,95] anti-diabetic,[96] antihypertensive[97] and anticancerous,[98,99] antitumorous,[100] anti-cholinesterase, dihydrofolate reductase inhibitory[101,102] and kinase inhibitory activities.[103,104] Quinazoline is the core structure in various pharmacological potent molecules such as gefitinib (**144**), erlotinib (**145**), canertinib (**146**), dacomitinib (**147**) afatinib (**148**) and vandetanib (**149**) and these drugs are used as kinase inhibitors. Some other drugs like prazosin (**150**) and doxazosin (**151**) are useful medicine for the treatment of hypertensive diseases (**Figure 1.3**). KF31327 (**152**) is useful for the treatment of impotency and heart disease remedy (**Figure 1.3**).

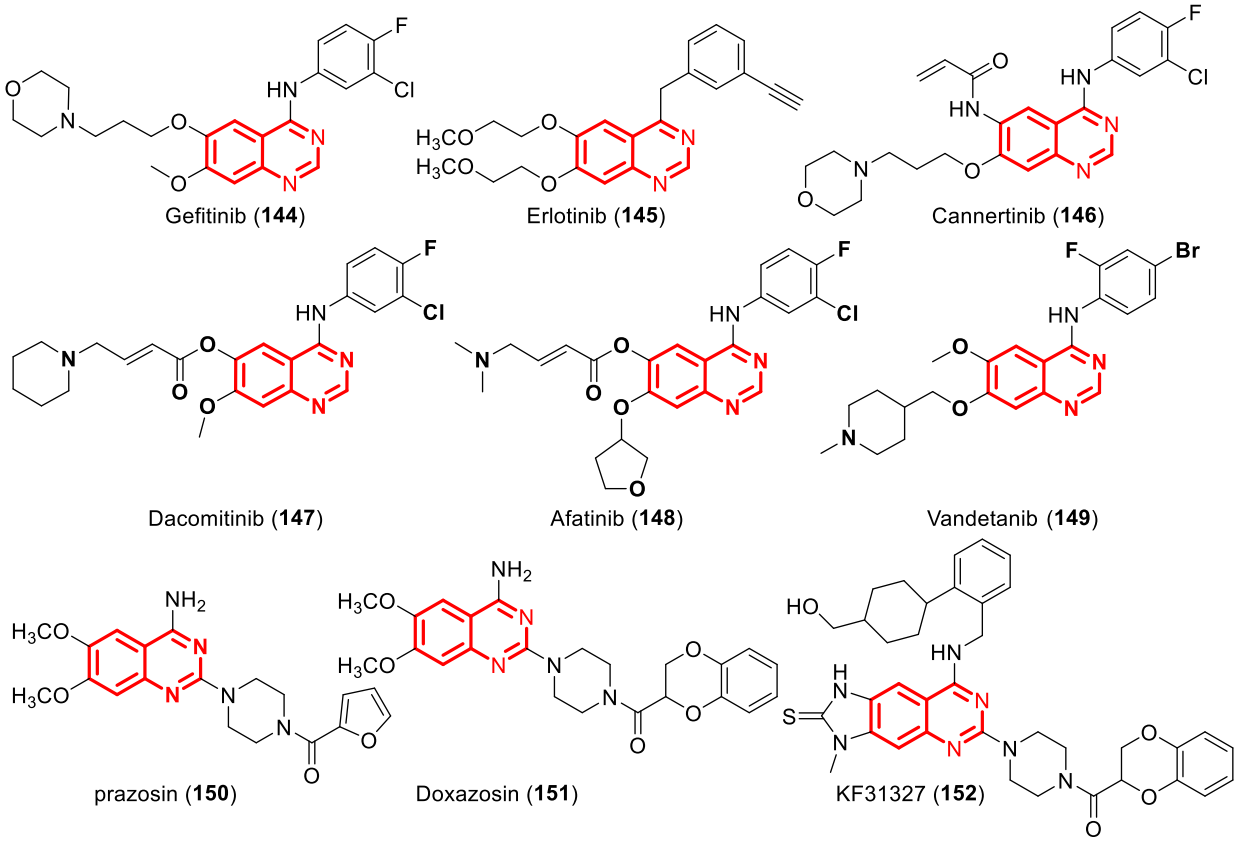


Figure 1.3 Quinazoline containing marketed drugs

Quinazoline also has a variety of biological activities like ligand for benzodiazepine, GABA receptors in the central nervous system, cellular phosphorylation inhibition and DNA binding agents.[105-107] Some activities of quinazolines such as anticancer, antimicrobial, anticonvulsant, anti-inflammatory, antiviral and anti-tuberculosis are described below.

1.3.2.1 Anticancer activity

Cancer is the uncontrolled growth of abnormal cells in a body. These abnormal cells are known as cancer cells or tumour cells. Cancer is the most hazardous and leading cause of death worldwide (8.2 million death) according to the recent report of WHO. Death from cancer is rising, and it will reach an estimated 13.1 million death in 2030 (70% increment). Therefore, it has become the topic of great attention for researchers due to its serious threat to mankind.

Yan *et al.* evaluated fluoro substituted quinazoline derivatives **153** for *in vitro* growth inhibitory activity against human cells. This compound was found to be more potent than cisplatin against SKOV-3, U2-OS, A549 and MCF-7 cells. Yang and co-workers have developed a new series of 5,6,7-trimethoxy-*N*-phenyl (ethyl)-4-aminoquinazoline compounds (**Figure 1.4**).[108] Synthesized compounds were tested for their anticancer activities. Among them, **154** shown strong anticancer and anti-phosphorylation activities. The inhibition rate of **154** against Bcap37, BGC823 and PC3 cells were 90.4 ± 2.8%, 88.2 ± 6.1% and 90.6 ± 9.1%, respectively and the IC_{50} values were 3.1 ± 0.1%, 3.2 ± 0.1% and 6.2 ± 0.9% μM, respectively. Compound **155** showed noteworthy cancer growth inhibition with low host toxicity *in vivo* and exhibited very low IC_{50} against HepG2 cancer cell lines which is lower than Sorafenib drug (**Figure 1.4**).[109] Wiese group synthesized diversely substituted quinazolines scaffold at a different position of quinazoline. Among them, compounds **156** was found to have the highest therapeutic ratio (**Figure 1.4**).[110] Very recently, Zhang group described the new library of quinazoline derivatives and the synthesized compounds were tested for their antiproliferative activities *invitro.*[111] Among the tested derivatives, compound **157** displayed excellent antiproliferative activities against both U-87 MG (IC50 = 0.60 μM) and A549 (IC50 = 1.68 μM) (**Figure 1.4**). Compound **158** shows good anticancer activity against HEPG-2 and MCF-7 cell lines compared to doxorubicin (**Figure 1.4**).[112]

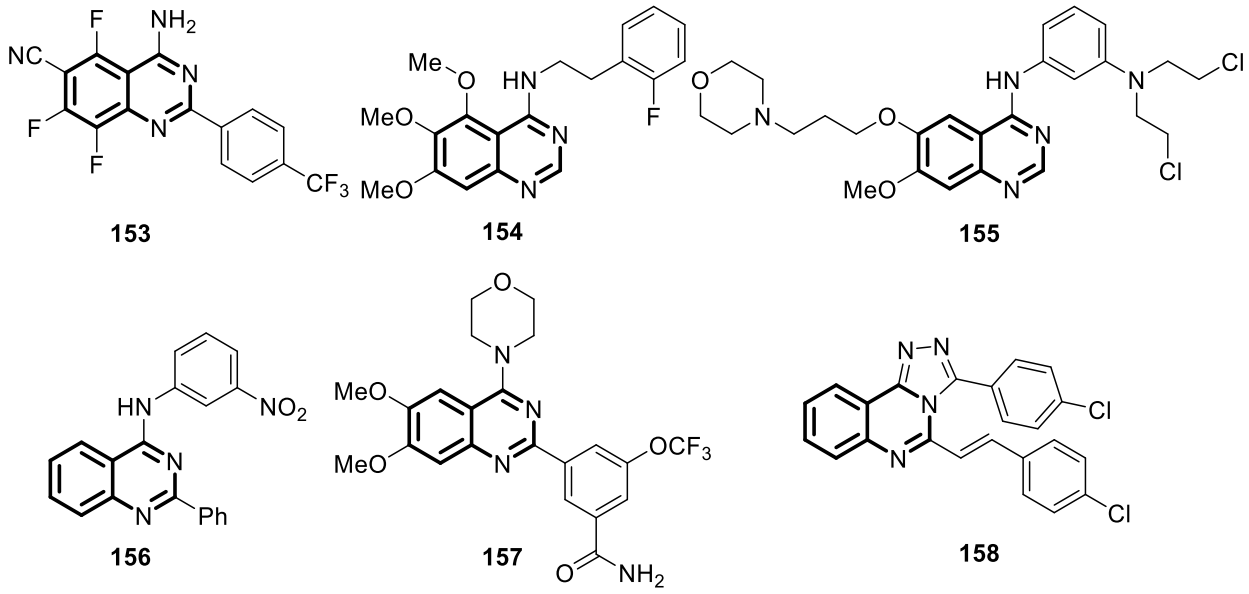


Figure 1.4 Structures of potential anticancer agents based on quinazoline scaffold

1.3.2.2 Antimicrobial activity

Bacterial and fungal infections have become a global challenge for human health due to the lack of sufficient and effective antimicrobial drugs, especially in an immunocompromised patient. The microbial infection can be cause for human death in the near future according to the World Health Organization (WHO).[113] In particular, methicillin-resistant *S. aureus* (MRSA) is a major part of nosocomial infection (hospital acquired infection). Naturally occurring antimicrobial agents (*i.e.* cephalosporin, glycopeptides, *β*-lactam and penicillin) have been proved the potential therapeutics for the treatment of most virulent strains methicillin-resistant *Staphylococcus aureus* (MRSA).[114-117] The treatment of Multidrug-resistant (MDR) like *Acinetobacter baumannii* and other resistant infections are diminishing. Therefore, several methods have been developed by research communities to find new antibiotics to combat microbial resistance.[118-120]

Mabkhob *et al.* reported urea (**159**) and thiourea (**160**) related quinazoline analogues and evaluated their antimicrobial activity against Gram-positive pathogens (*S. aureus,* and *B.cereus*) and Gram-negative pathogens (*E. coli, P. aeruginosa,* and *K. pneumonia*). Compound **159** has shown significant inhibitory efficacy against *S. aureus* at MIC 6.25 mg/mL and *B. cereus* at MIC 12.5 mg/mL, respectively (**Figure 1.5**).[121] Reddy and co-workers designed a new series of quinazolines, and all the synthesized compounds were evaluated for their antibacterial activity using Ampicillin as a standard drug. Compound **161** exhibited maximum zone of inhibition (17 mm) against *E. coli*

and (18 mm) as well as *Staphylococcus aureus* which shown good ZOI than the standard drug ampicillin (**Figure 1.5**).[122] Compounds **162** also showed good antimicrobial activity against both Gram-positive and Gram-negative bacteria at MIC values between 6.25 and 100 mg/mL (**Figure 1.5**).[123]

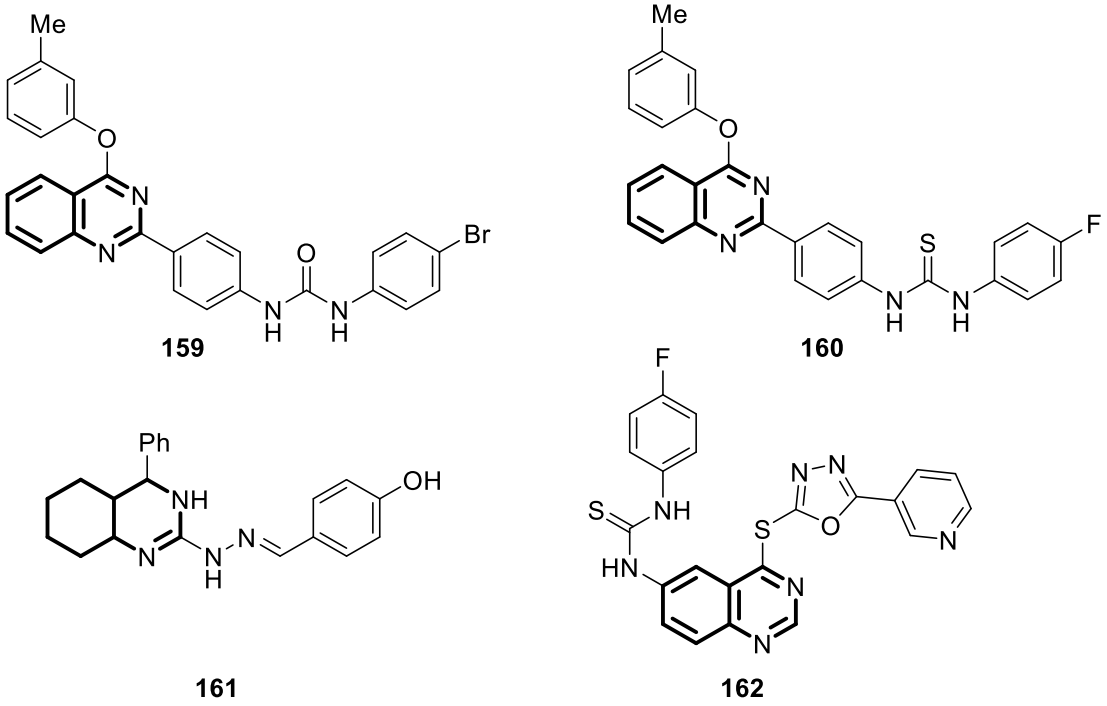


Figure 1.5 Structures of potential antimicrobial agents based on quinazoline scaffold

1.3.2.3 Anticonvulsant activity

Anticonvulsants are used in the treatment of epileptic seizures, bipolar disorder, borderline personality disorder and neuropathic pain. Epilepsy is a neurological disorder disease with high prevalence worldwide, in which brain activity becomes disrupted causing unusual behaviour, seizures and sometimes loss of awareness. According to the world health organization (WHO), maximum cause of epilepsy is reported in developing countries. Therefore, it has become a worldwide topic for researcher due to its serious threat to mankind.

Quan *et al*. described the synthesis of 5-phenyl [1,2,4]triazolo[4,3-*c*] quinazoline-3-amine derivatives (**Figure 1.6**).[95] Synthesized compounds were evaluated for their anticonvulsant activity and neurotoxicity by the maximal electroshock seizure test (MES). Most of the compounds were effective in the MES screens at a dose level of 100 mg/kg. Amongst all, **163** was found to be the

most promising compound. Omar and his colleagues designed and synthesized novel fluorinated quinazolines **164**, **165**, and **166** and evaluated for their anticonvulsant activity (**Figure 1.6**).[124] These compounds exhibit low neurotoxicity and low toxicity in the median lethal dose test compared to the positive control.

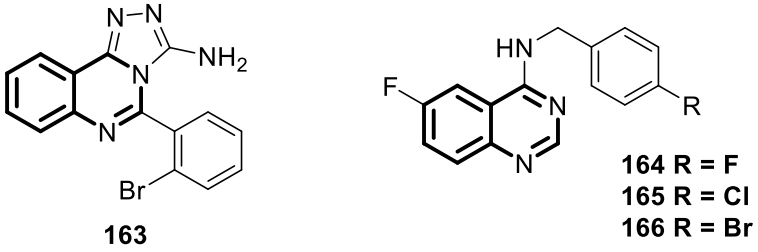


Figure 1.6 Structures of potential anticonvulsant agents based on quinazoline scaffold

1.3.2.4 Anti-inflammatory activity

The anti-inflammatory is the property of a substance which reduces the inflammation or swelling. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the cornerstone of pain, management in patients with osteoarthritis and other painful conditions like mouth sores, chest pain, abdominal pain, fever, and joint pain. Several quinazoline derivatives have been developed which exhibit good anti-inflammatory activity.

Hu *et al.* synthesized a series of 4-amino quinazoline derivatives and evaluated for their anti-inflammatory activity.[125] Amongst all **167**, **168**, and **169** are the most potent compounds which exhibit significant anti-inflammatory activity **(Figure 1.7**).

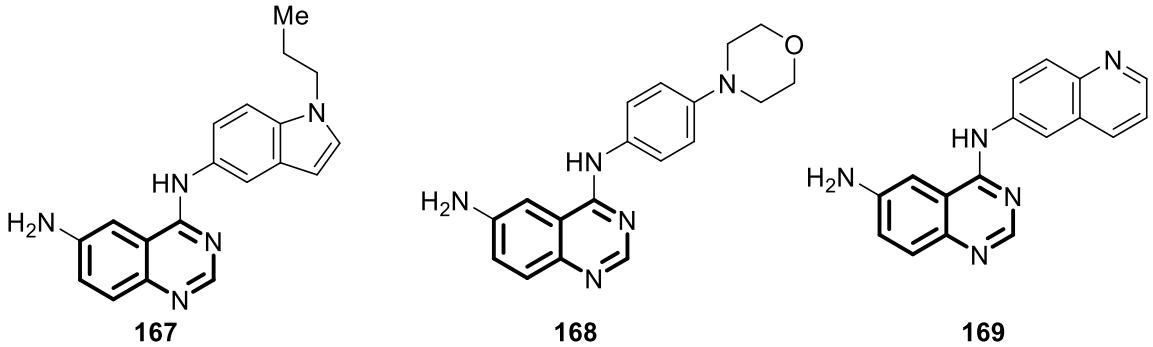


Figure 1.7 Structures of potential anti-inflammatory agents based on quinazoline scaffold

1.3.2.5 Anti-viral activity

The viral disease is widespread serious infectious disease threatening latest therapeutic breakthrough, and high mutation rates are found in viruses. Most of the human viral disease could be fought by our immune system. Even there are several viral diseases which have become a major concern among scientific community such as HIV, Hepatitis B, Hepatitis C, Dengue fever, and Chickenpox.

Held *et al.* reported a one-pot metal-free synthesis of 4,5,7,8-substituted quinazolines which are fluorescent in nature and have potent antiviral activity against human cytomegalovirus (HCMV) with maximum EC_{50} value 0.6±0.1 μM (**170**) (**Figure 1.8**).[126] Song and colleagues described the synthesis of (1E,4E)-1-aryl-5-[2-(quinazolin-4-yloxy)phenyl]-1,4-pentadien-3-one derivatives and evaluated for antiviral activity (**Figure 1.8**).[127] Antiviral study revealed that most of the compounds (**171**, **172**, and **173**) exhibited promising antiviral activity against cucumber mosaic virus (CMV) and tobacco mosaic virus (TMV) at 500 mg/mL.

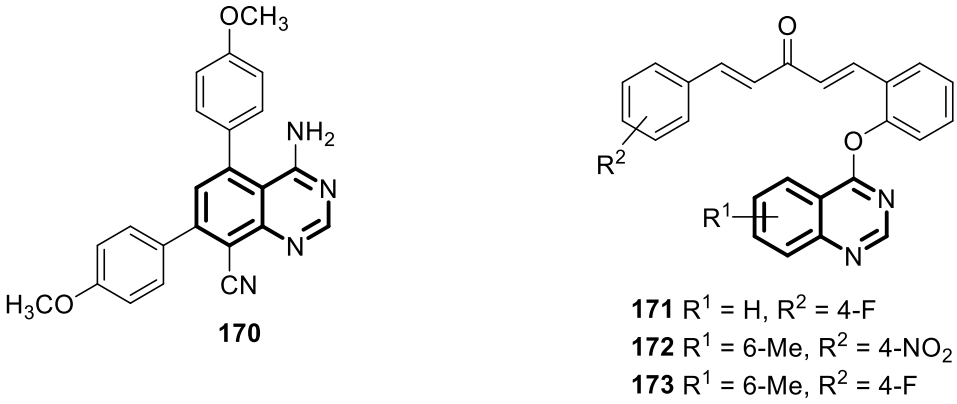


Figure 1.8 Structures of potential anti-viral agents based on quinazoline scaffold

1.3.2.6 Anti-tuberculosis activity

Tuberculosis (TB) is an infectious disease which is caused by the *Mycobacterium tuberculosis* (Mtb) and becomes the second biggest global killer disease. According to the WHO report, 9 million people get sick due to tuberculosis in a year. Notably, in women TB is the most important cause of death in the age of 15 to 44. Continuously, increasing drug resistance of *Mycobacterium tuberculosis* has gained attention around the world to develop new anti-tuberculosis candidates.

Gupta *et al.* designed a library of novel 2-trichloromethyl-4substituted quinazoline derivatives and screened for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv, ATCC using Alamar blue assay. Compound **174**, **175** and **176** were found to exhibit significant anti-tubercular activity against *Mycobacterium tuberculosis* H37R (**Figure 1.9**).[128]

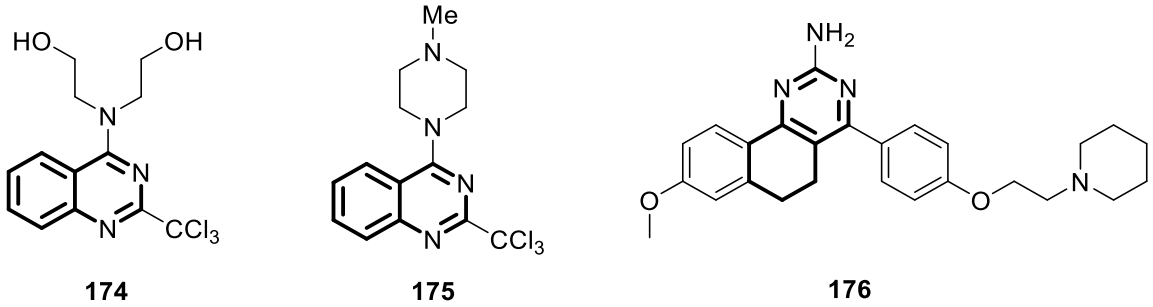


Figure 1.9 Structures of potential anti-tuberculosis agents based on quinazoline scaffold

Quinazoline is the most privileged bioactive heterocyclic compounds in terms of synthetic as well as medicinal chemistry applications. Although several interesting approaches have been reported, still the designing of new selective and potent molecules and their pharmacological activities remains highly desirable.

1.4 CONCLUSIONS

Design and synthesis of the nitrogen-containing heterocyclic framework have played an important role in the development of efficient and environmentally friendly methods. This chapter presents recent advances involving several synthetic methodologies such as metal-free and metal-catalyzed reactions for the development of quinazolines. Apart from notable synthetic advancements, quinazolines were also found to display a diverse set of important biological properties. In general, simple and diverse nature of synthetic methods for the synthesis of quinazoline-based heterocycles with potential biological applications will be useful for further development of medicinal chemistry research. Quinazoline is one of the privileged bioactive heterocyclic compounds in terms of synthetic as well as therapeutic chemistry applications. Although several fascinating approaches have been reported, still the designing of new selective and potent molecules and their pharmacological activities remains highly desirable. After a careful literature survey, we designed new methods for the development of imidazo/benzimidazo[1,2-c]quinazolines by using Cu/Pd–

catalyzed coupling reactions and selected compounds were evaluated for antimicrobial activity. The detail research methodology for quinazoline analogues will be discussed in chapters II-IV.

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CHAPTER 2

Copper-Catalyzed Tandem Multi-Component Reactions for the Synthesis of Fused Quinazolines

2.1 INTRODUCTION

Synthesis of heterocyclic molecules with high efficiency in terms of minimization of synthetic steps and high complexity is a challenging task.[1,2] Therefore, development of new methodology for the synthesis of heterocycles using simple approach is in high demand. In this regards, tandem and multi-component reactions have become the most powerful tool in organic synthesis because of their atom-economical, high yielding and environmentally benign advantages over traditional methods.[3-8] In addition, these reactions also reduce the separation and purification step during the course of reactions.[9-12]

2.1.1 Tandem reaction

The term tandem is defined as a chemical process which consists of at least two consecutive reactions in one–pot and each subsequent reactions occur only in virtue of the chemical functionality formed in the previous step. These types of reactions are also known as cascade or domino reactions. These are classes of reactions where the sequential transformation of the substrate occurs *via* two or more mechanically distinct processes. A simple representation of tandem process is shown in **Figure 2.1.** In the conventional approach, the targeted product is obtained in multi-steps *via an* intermediate stage while the tandem approach provides the same product in a single step.

The major advantages of tandem reactions over traditional reactions are

- avoid isolation of intermediates and reduces the labor work and time
- build a large number of complexity in a single step
- reduce the waste generation

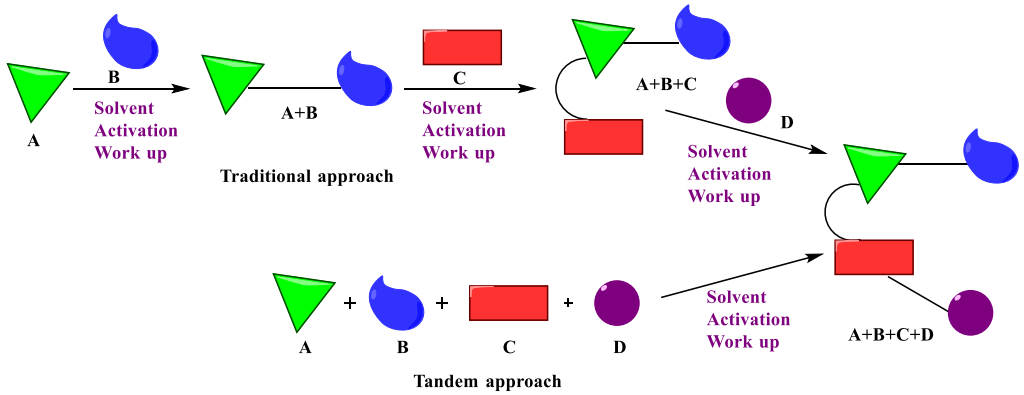


Figure 2.1 Schematic representation of traditional and tandem reactions

2.1.2 Multicomponent reactions

Multicomponent reactions (MCRs) is another strategy in organic chemistry that have become an important tool for the synthesis of organic compounds with a high degree of molecular diversity. This strategy provides a significant advantage over traditional multistep synthesis. In MCRs three or more compounds react together to form a product in a single step without isolation of the intermediate (**Figure 2.2**).[13] These reactions are an efficient and effective method for the synthesis of diversely substituted heterocycles.[14-17] In addition, these reactions are also capable to tolerate diverse functionalities. The most important features of multicomponent reactions are low cost, reducing the number of steps, operational simplicity which allows to these reaction to fulfill the requirements for an environmentally friendly process. In the last decade, transition metal–catalyzed multicomponent reaction have received great interest in the development of new methods for heterocycles.[18] Some of the earliest MCRs are described below**.**

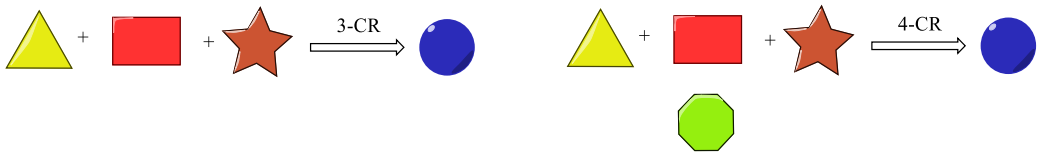
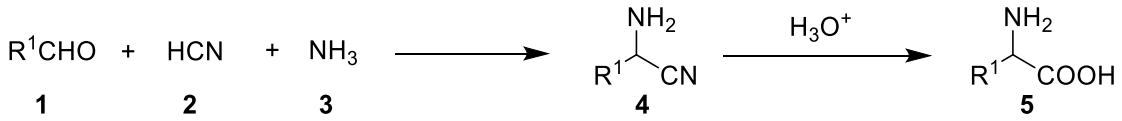


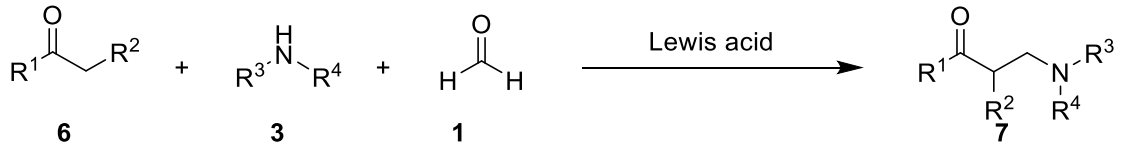
Figure 2.2 General representation of a multi-component reaction

In 1850 Strecker synthesized α-aminonitriles (**4**) from aldehyde (**1**), hydrogen cyanide (**2**) and ammonia (**3**) in one–pot manner (**Scheme 2.1**).[19] The reaction proceeds through the formation of iminium ion by the reaction of aldehyde and ammonia *via* H_2O elimination. In the next step, the nucleophilic attack of cyanide ion on iminium carbon leads to the formation of *α*-aminonitriles (**4**) which on hydrolysis gives corresponding amino acids (**5**).



Scheme 2.1 Strecker synthesis of *α*-amino acids

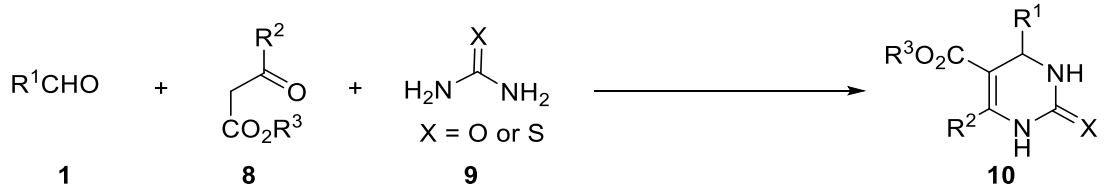
In 1912, Mannich synthesized *β*-amino carbonyl compounds (**7**) *via* three component reaction of carbonyl compounds (**6**), primary or secondary amines (**3**) and formaldehyde (**1**) which are commonly known as Mannich bases (**Scheme 2.2**).[20]



6 **3** **1** **7**

Scheme 2.2 Mannich reaction for the synthesis of *β*-amino carbonyl compounds

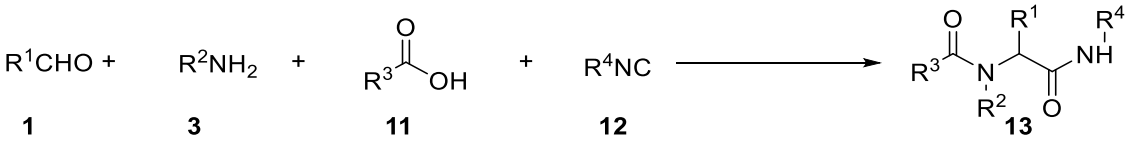
Biginelli described the synthesis of dihydropyrimidine (**10**) *via* acid catalyzed condensation of aryl aldehyde (**1**), *β*-ketoesters (**8**) and urea or thiourea (**9**) (**Scheme 2.3**).[21] The reaction proceeds through the formation of an aldol intermediate by the condensation of aldehyde (**1**) with active methylene compound (**8**) then nucleophilic addition of urea or thiourea (**9**) on aldol adduct with the elimination of H_2O gives the corresponding product (**10**).



1 **8** **9** **10**

Scheme 2.3 Biginelli reaction for the synthesis of dihydropyrimidines

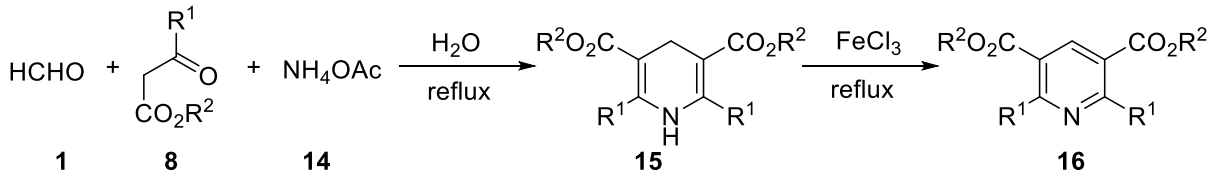
In 1959, Ugi reported four-component reaction for the synthesis of *α*-acylamino amides (**13**). This method is one of the widely employed approach for the synthesis of diamides by the reaction of aldehydes (**1**), primary amines (**3**), carboxylic acid (**11**) and isonitriles (**12**) (**Scheme 2.4**).[22] This reaction created a significant breakthrough in the field of MCRs.



1 **3** **11** **12** **13**

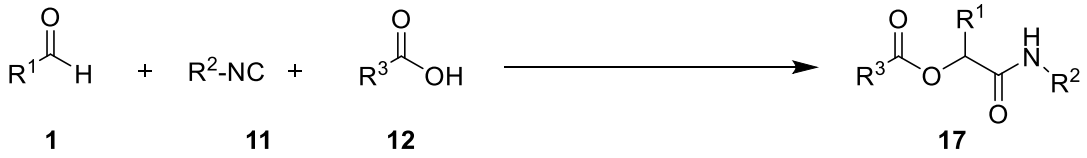
Scheme 2.4 Ugi reaction for the synthesis of *α*-acylamino amides

In 1881, Rudolf Hantzsch developed three-component reaction for the synthesis of pyridine from formaldehyde (**1**), β-keto ester (**8**) and ammonium acetate (**14**) as a nitrogen source. In first step dihydropyridine (**15**) was observed which could be oxidized into a pyridine in the presence of $FeCl_3$ (**16**) (**Scheme 2.5**).[23]



Scheme 2.5 Hantzsch reaction for the synthesis of pyridine

Mario Passerini discovered isocyanide based three-component reaction for the synthesis of α-acyloxy amide in 1921. α-Acyloxy amide (**17**) synthesized from isocyanide (**11**), aldehyde (**1**) and a carboxylic acid (**12**) in a one-pot manner (**Scheme 2.6**).[24] The reaction proceeds through protonation of carbonyl compounds followed by nucleophilic addition of isocyanide to afford nitrilium ion. Further, the addition of a carboxylate on nitrilium ion leads to the desired product (**17**).



Scheme 2.6 Passerini reaction for the synthesis of α-acyloxy amide

In the last decade, a plethora of reports have been disclosed for the synthesis of potential bioactive molecules by improving the reaction conditions with the help of tandem and multi–component reactions (MCRs).[25-27] In addition, several reports have been documented in literature where these tandem reactions are amalgamated with multi–component reactions to access complex structures in a single step.[28-30] Transition metal–catalyzed tandem MCRs have received great attention for the synthesis of diverse molecular assembly in one–pot. With our continued efforts for the synthesis of fused heterocycles using transition metal–catalyzed tandem, multi–component, and C–H functionalization approach we have developed a synthesis of fused imidazo/benzimidazoquinazolines using copper–catalyzed tandem multicomponent reactions involving multiple C–C and C–N bond formation in one–pot.[31]

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CHAPTER 2A

Copper–Catalyzed Tandem Ullmann type C–N Coupling and Dehydrative Cyclization: Synthesis of Imidazo[1,2-*c*]quinazolines

2.2A.1 INTRODUCTION

Nitrogen-containing polyheterocyclic compounds have received much attention from synthetic as well as medicinal chemists, because of the diverse range of their pharmacological properties.[1-5] Among them, quinazoline fused molecules such as indolo-, imidazo- and benzimidazo-quinazolines are found to exhibit a wide range of therapeutic activities such as PI3-kinase inhibition,[6] tumor necrosis factor alpha (TNF-α) production inhibition,[7] antimicrobial activity[8], etc. (**Figure 2.2A.1**). The hybrid structures of benzimidazole and quinazolines derivatives also show interesting properties in organic light-emitting devices (OLEDs). Dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline derivatives have been reported to behave as a selective ratiometric fluorescence chemosensor for iron and aluminum ions (**Figure 2.2A.1**).[9,10] Despite the high importance of these molecules in pharmaceuticals and materials science, synthetic methods for the preparation of quinazoline fused heterocyclic frameworks are limited.[11-14] Moreover, these methods generally require multistep synthesis, strict reaction conditions, and inaccessible starting materials. Therefore, alternative synthetic approaches for quinazoline fused heterocyclic frameworks are desired.

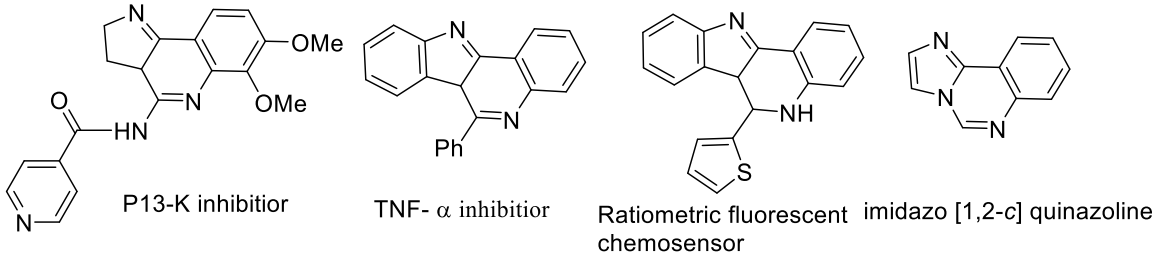
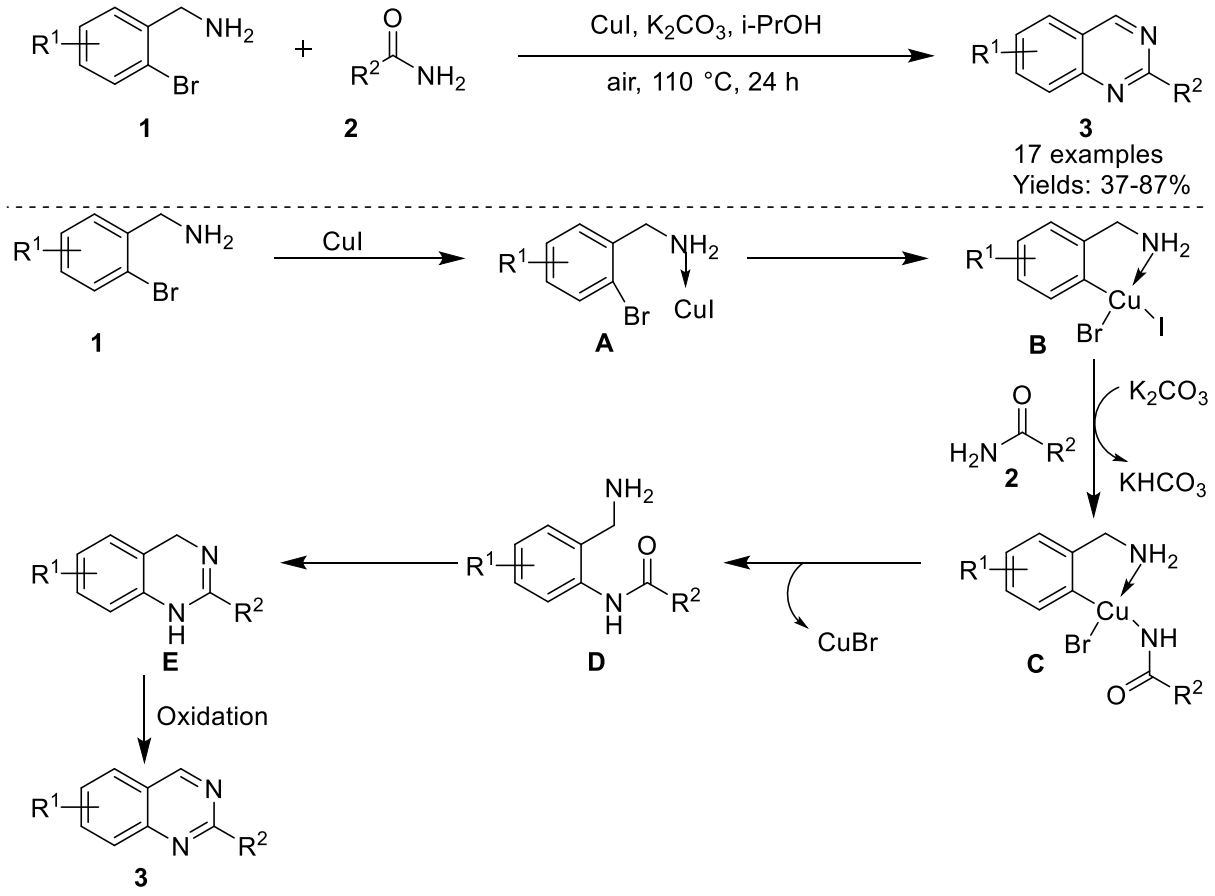


Figure 2.2A.1 Structures of important quinazoline fused heterocyclic compounds

In recent years, copper salts have been proven to be highly efficient catalysts in cross-coupling reactions due to their low toxicity, high functional group tolerance, and economical attractiveness.[15-23] Copper-catalyzed tandem reactions have emerged as powerful tools for the synthesis of polyheterocycles.[24-32] Synthesis of fused heterocyclic compounds *via* copper–catalyzed Ullmann–type coupling has become an everlasting challenge in a recent year. In the last decade, amides, amidines, benzylamines, and amino acid has been utilized for the synthesis of quinazolines through copper–catalyzed coupling and cyclization reaction.

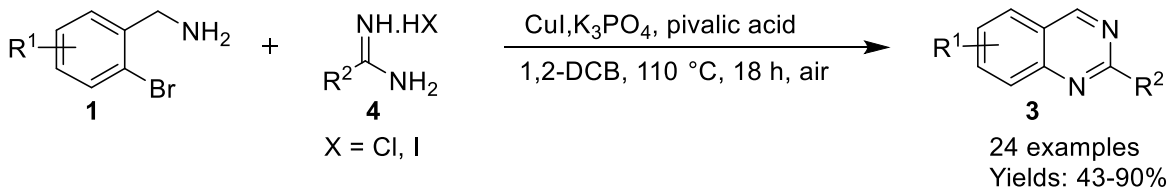
Fu and co-workers reported copper–catalyzed tandem approach for the synthesis of quinazoline derivatives (**3**) from readily available (2-bromophenyl)-methylamines (**1**) and amides derivatives (**2**). This reaction involved copper–catalyzed sequential Ullmann–type coupling (**D**) followed by intramolecular nucleophilic addition (**E**) which furnished the target product (**3**) under aerobic conditions (**Scheme 2.2A.1**).[33] The scope of the methodology was explored by using a range of benzamides with electron–rich (methyl, methoxy) and electron–deficient (F, NO_2) substituents. The moderate to good yields (37-87%) of the products and operational simplicity are the merits of this method.



Scheme 2.2A.1 Stepwise mechanism for the synthesis of quinazolines from (2-bromophenyl)-methylamines and amides

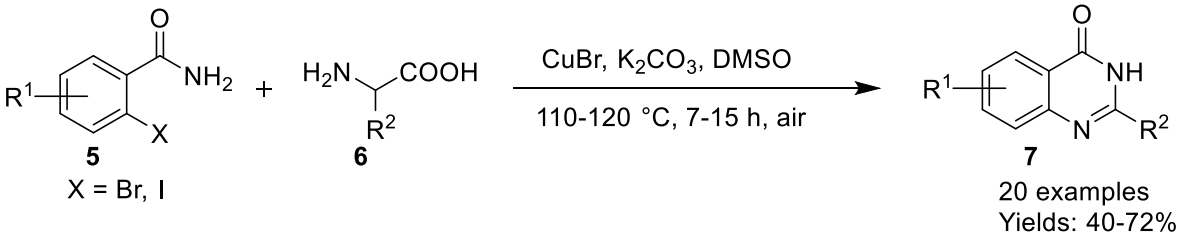
Omar *et al*. disclosed an efficient one-pot method for the synthesis of substituted quinazolines (**3**) between 1-(2-bromophenyl)methanamines (**1**) and amidines (**4**) *via* copper–catalyzed tandem

reaction. The reaction proceeded as a Cu(I)–catalyzed intermolecular *N*–arylation followed by an intramolecular nucleophilic substitution and Cu(II)–catalyzed aerial oxidation (**Scheme 2.2A.2**).[34]



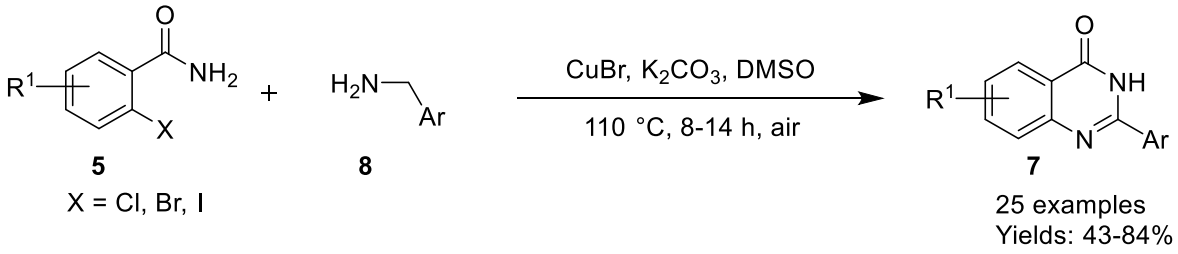
Scheme 2.2A.2 Synthesis of quinazolines from (2-bromophenyl)-methylamines and amidines

Fu group disclosed copper–catalyzed one-pot tandem strategy for the construction of quinazolinones (**7**) from readily available starting material 2-halobenzamides (**5**) and amino acids (**6**) (**Scheme 2.2A.3**).[35] The tandem reaction underwent copper-catalyzed Ullmann–type *N*–arylation, C–H amidation and aerial oxidation followed by decarboxylation reaction.



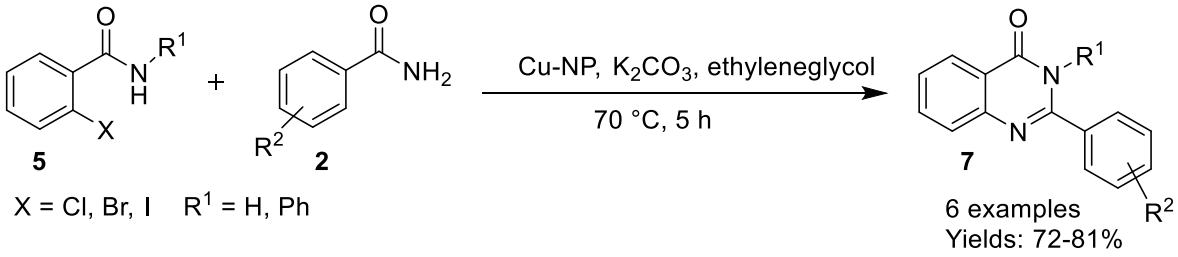
Scheme 2.2A.3 Copper-catalyzed synthesis of quinazolinones from 2-halobenzamides and amino acids

Fu and his team developed copper–catalyzed method for the development of substituted quinazolinones (**7**) in one–pot fashion from 2-halobenzamides (**5**) and arylamines (**8**) (**Scheme 2.2A.4**).[36] The designed tandem approach proceeds ligand and additive free Ullmann–type coupling, aerobic oxidation, and an intramolecular nucleophilic addition process. Various functional group containing arylamines and 2-halobenzamides were well tolerated with the standard reaction conditions which provide diversely substituted quinazolinones in good to excellent yields (43-84%).



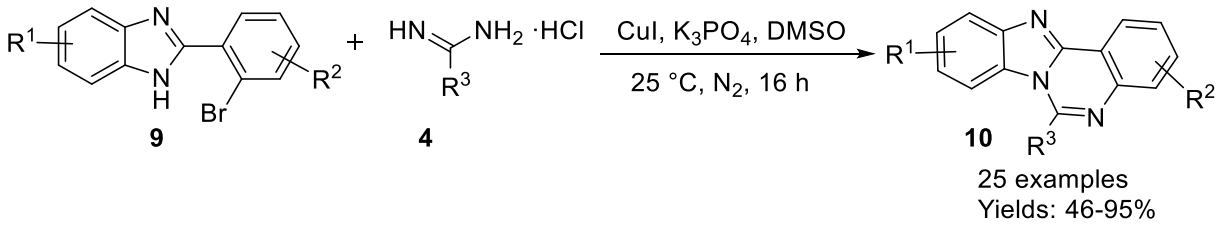
Scheme 2.2A.4 Copper–catalyzed the synthesis of quinazolinones from 2-halobenzamides and aryl amines

Bishnoi group described CuI–nanoparticle catalyzed ligand-free synthesis of quinazolinones (**7**) from 2-halobenzamides (**5**) and amides (**2**) *via* intermolecular amidation reaction followed by cyclization (**Scheme 2.2A.5**).[37] TEM images of the CuI–NP catalyst revealed well dispersed, and spherical particles which show more surface area for the reactivity, therefore, this Cu–NP have good recyclability.



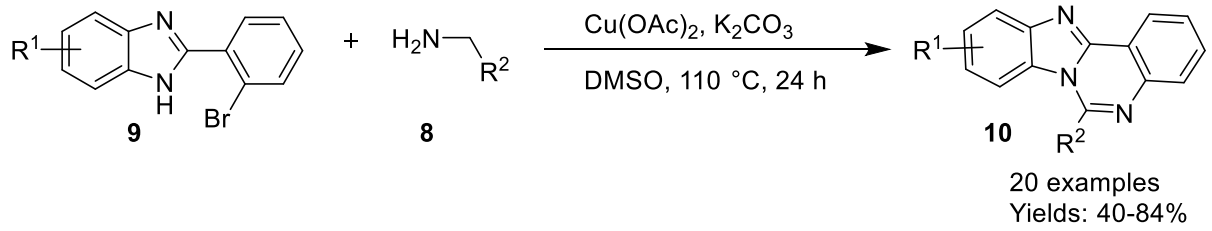
Scheme 2.2A.5 Synthesis of quinazolinones from 2-halobenzamides and amides

Xu *et al*. developed a convenient and efficient copper-catalyzed cascade method for the synthesis of quinazolines **(10)** from easily available 2-(2-bromophenyl)-*1H*-benzo[*d*]imidazole **(9)** by reacting with amidines **(4)** using CuI as catalyst under mild reaction condition (**Scheme 2.2A.6**).[38] This reaction involved copper–catalyzed C–N coupling followed by oxidative elimination provided fused quinazolines in good to excellent yields (46-95%).



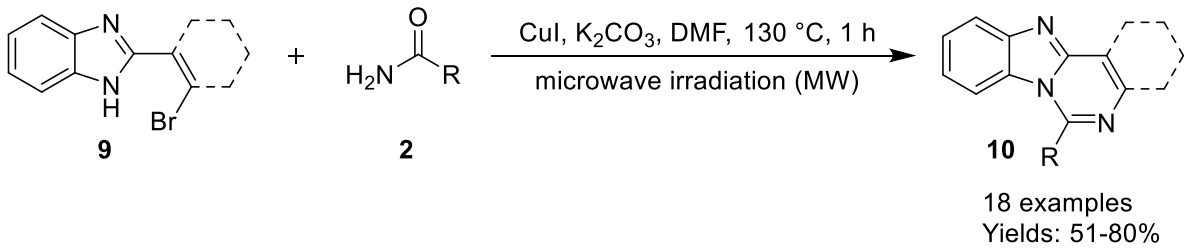
Scheme 2.2A.6 Synthesis of quinazolines from 2-(2-bromophenyl)-*1H*-benzo[*d*]imidazole and amidines

Sang *et al*. reported copper–catalyzed sequential Ullmann–type *N*-arylation and aerobic oxidative C–H amination of 2-(2-bromophenyl)-*1H*-benzo[d]imidazole **(9)** and benzylamine **(8)** for the development of 6-phenylbenzo[4,5]imidazo[1,2-*c*]quinazoline derivatives **(10)** by using K_2CO_3 in DMSO at 110°C(**Scheme 2.2A.7**).[39]



Scheme 2.2A.7 Synthesis of quinazolines from 2-(2-bromophenyl)-*1H*-benzo[*d*]imidazole and benzylamine

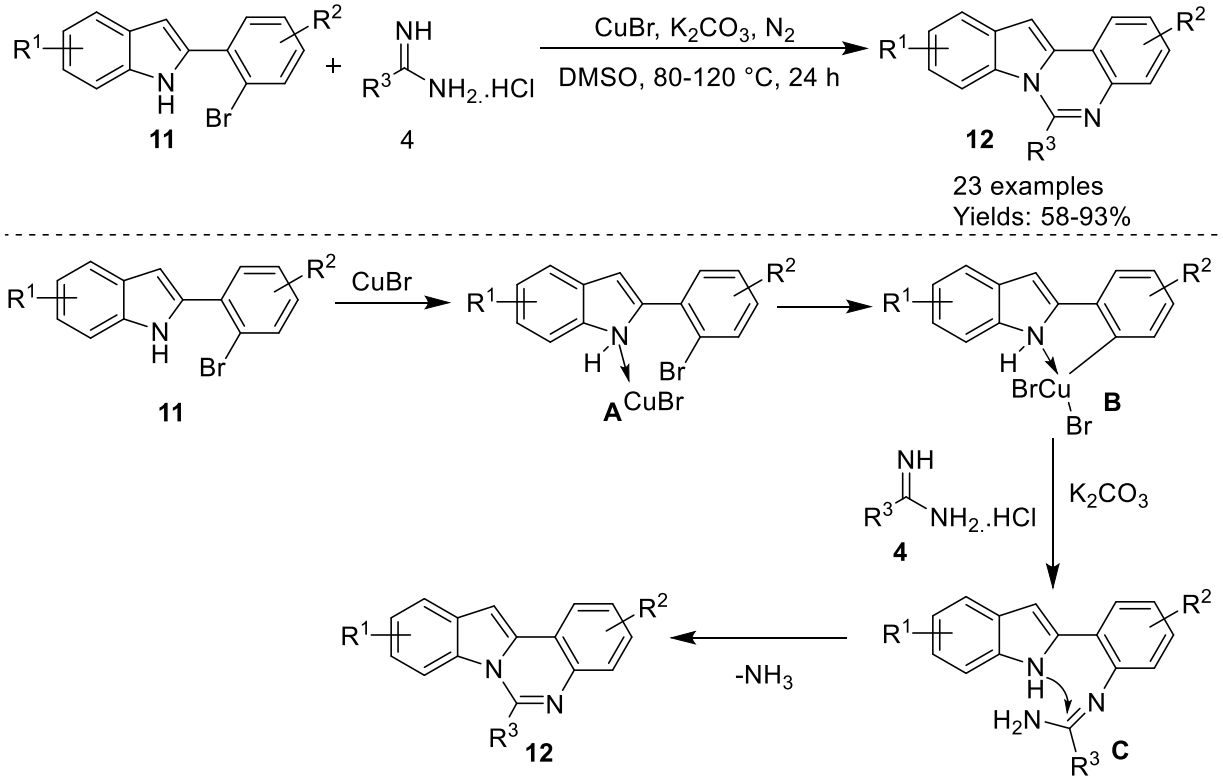
Very recently, Dao *et al*. demonstrated copper–catalyzed synthesis of benzo[4,5]imidazo[1,2-*c*]quinazolines (**10**) under microwave irradiation from (2-Bromovinyl) or 2-(2-bromoaryl)-benzimidazoles (**9**) and primary amides (**2**) (**Scheme 2.2A.8**).[40] Further, treatment of benzo[4,5]imidazo[1,2-*c*]quinazolines containing methoxy group on benzimidazole with ceric ammonium nitrate provides benzo[4,5]imidazo[1,2-*c*]-quinazoline-8,11-diones with good yields.



Scheme 2.2A.8 Synthesis of quinazolines from 2-(2-bromoaryl)-benzimidazoles and amides

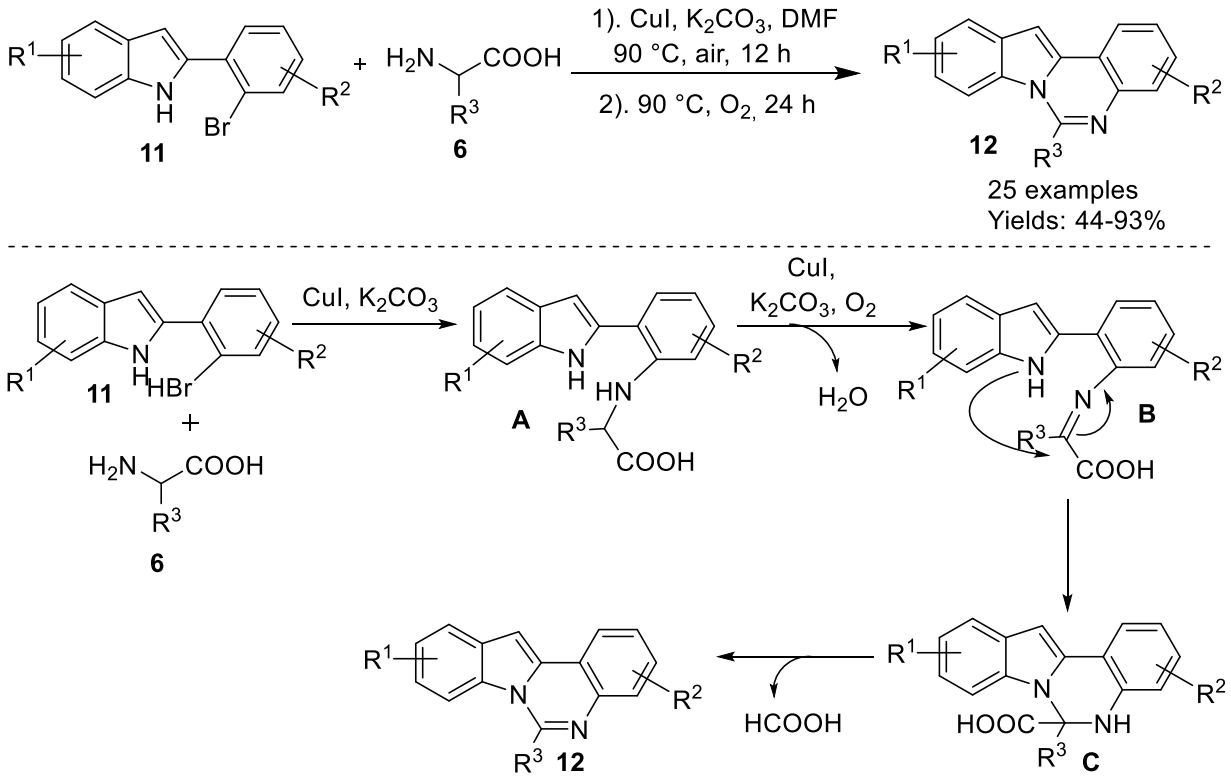
A simple and efficient synthesis of 1*H*-indolo[1,2-*c*]quinazolines (**12**) was developed by Fu and team from 2-(2-halophenyl)indoles (**11**) and amidines (**4**) by using copper-catalyzed tandem approach (**Scheme 2.2A.9**).[41] Different amidines such as aliphatic as well as aromatic were well compatible with the standard reaction conditions which access diversely substituted indolo[1,2-*c*]quinazolines with good to excellent yields (58-93%). Based on the control experiments result the reaction mechanism was proposed. Initially, coordination of 2-(2-bromophenyl)-1*H*-indole with CuBr gives **A** then oxidative addition of **A** gives **B**. Intermediate **B** coupled with amidine and

provides intermediate **C,** and the intramolecular nucleophilic addition of indole NH to the carbon of amidine, afford target product **12** (**Scheme 2.2A.9**).



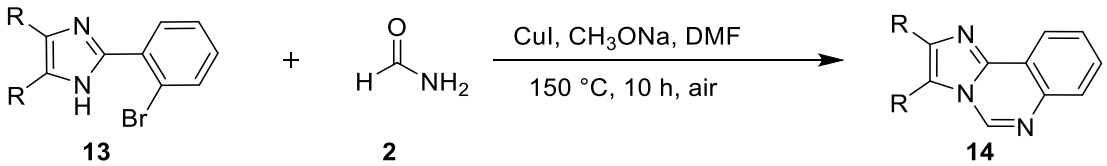
Scheme 2.2A.9 Synthesis of 1*H*-indolo[1,2-*c*]quinazolines from 2-(2-halophenyl)indoles and amidines

Fu *et al.* reported copper–catalyzed aerobic oxidative method for the synthesis of indolo[1,2-*c*]quinazolines (**12**) by using readily available starting material such as 2-(2-bromophenyl)-1*H*-indole (**11**) and α-amino acid (**6**) (**Scheme 2.2A.10**).[42] The reactions proceeded through *N*-arylation, aerobic oxidative dehydrogenation followed by intramolecular cyclization *via* dissociation of formic acid which leads to quinazolines in moderate to excellent yields (44-93%) (**Scheme 2.2A.10**).



Scheme 2.2A.10 Synthesis of indolo[1,2-*c*]quinazolines from 2-(2-bromophenyl)-1*H*-indole and α-amino acid

According to the literature report, *N*-fused heterocycles can be constructed in one–pot by using Ullmann type C-N coupling. These methods have added some advantage over the conventional method for the synthesis of *N*-containing heterocycles. In continuation of our work for the synthesis of fused heterocycles, this chapter described a convenient and efficient ligand-free copper–catalyzed synthesis of imidazo[1,2-*c*]quinazolines derivatives (**14**) *via* sequential Ullmann–type C–N coupling followed by dehydrative cyclization of 2-(2-bromophenyl)-1*H*-imidazoles (**13**) and formamide (**2**) (**Scheme 2.2A.11**).



Scheme 2.2A.11 Copper-catalyzed the synthesis of imidazo[1,2-*c*]quinazolines from 2-(2-bromophenyl)-1*H*-imidazoles and formamide

2.2A.2 RESULTS AND DISCUSSION

Our initial study commenced with the model reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**13a**) with formamide (**2a**) in the presence of $CuCl_2$ (10 mol %), and K_2CO_3 (2.0 equiv.) in dimethylformamide (DMF) at 150 °C under air for 10 h. To our delight 2,3-diphenylimidazo[1,2-*c*]quinazolines (**14aa**) was isolated in 30% yield (**Table 2.2A.1**, entry 1).

The structure of **14aa** was confirmed by NMR (^{1}H and ^{13}C) and mass spectrometry data. In the ^{1}H NMR spectrum, a characteristic singlet at 8.72 ppm was observed for C-5 proton along with expected peaks for other protons. The peaks in the ^{13}C NMR spectrum were also in accordance with the structure of **14aa**. Finally, the presence of a peak at *m/z* 322.1344 in the HRMS corresponding to molecular ion $C_{22}H_{16}N_3^+$ $[M+H]^+$ confirmed the structure of **14aa**. The ^{1}H and ^{13}C spectrum of **14aa** is depicted in **Figure 2.2A.2.**

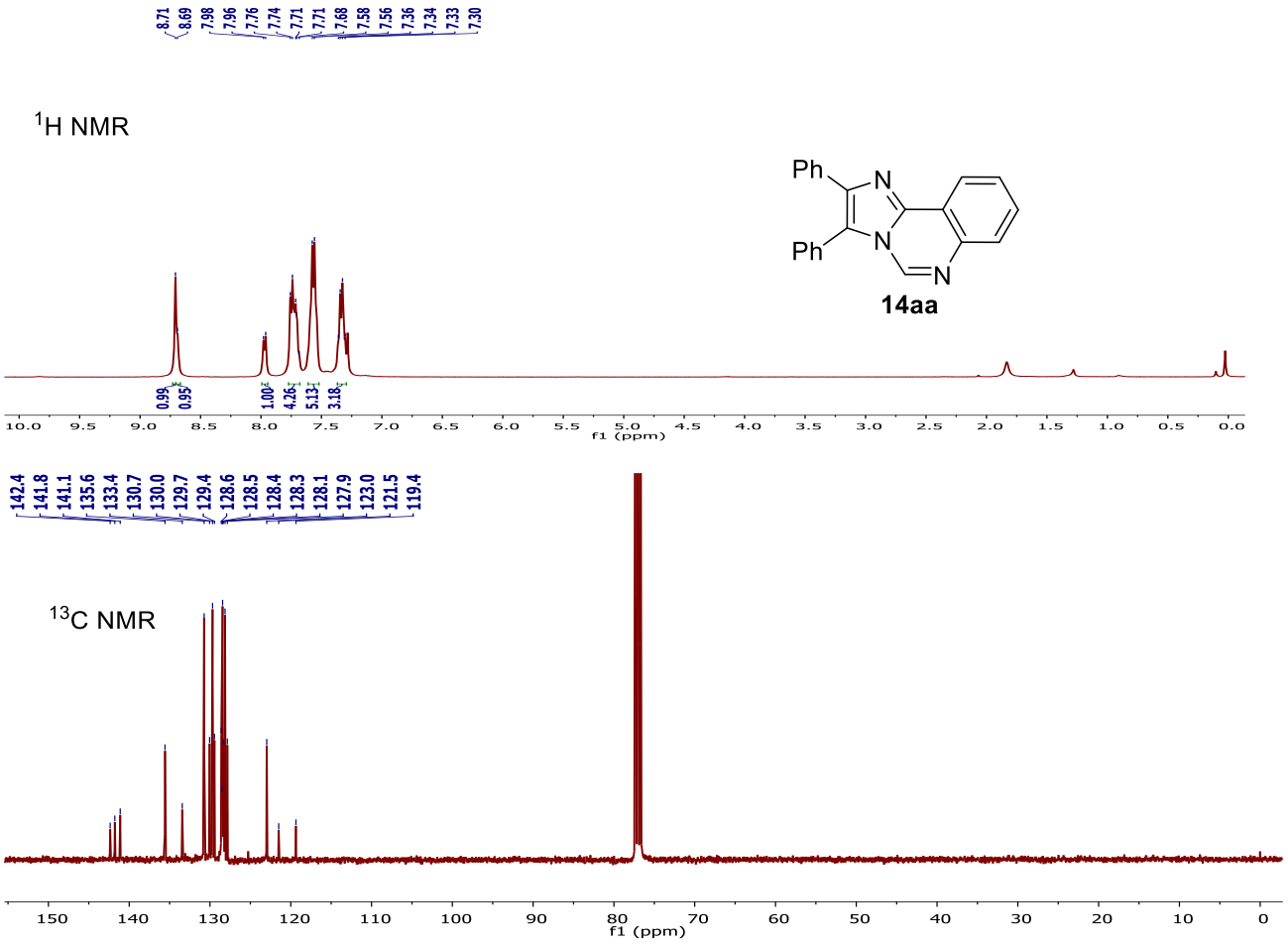


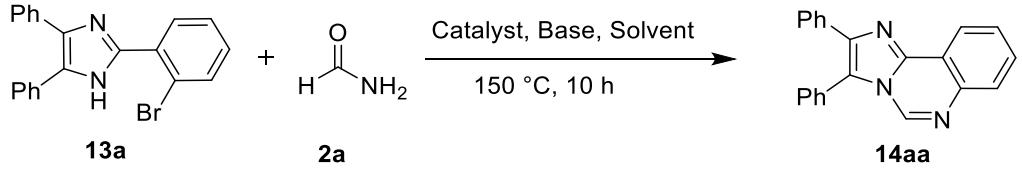
Figure 2.2A.2 ^{1}H and ^{13}C NMR spectra of 2,3-diphenyl imidazo[1,2-*c*]quinazoline (**14aa**) in $CDCl_3$

Encouraged by the results of the model reaction, the task of reaction optimization for improved yield of **14aa** was undertaken by varying the bases, catalysts, and solvents. The results for various optimization experiments are summarized in **Table 2.2A.1**. Screening of various copper–catalysts such as $CuCl_2$, CuBr, $Cu(OAc)_2 \cdot H_2O$, $Cu(OTf)_2$ and CuI revealed that among all the screened copper salts, CuI was found to give the highest yield (45%) of **14aa** using 10 mol % catalyst loading (**Table 2.2A.1**, entries 1–5). Subsequently, the effect of catalyst loading was investigated. Initially, a significant increment in the yield of **14aa** was observed by increasing the loading of CuI from 10 mol % to 30 mol %. However, a further increase in the loading of CuI did not improve the yield of **14aa** (**Table 2.2A.1**, entries 5–8). Formation of **14aa** was not observed in the absence of the catalysts even after allowing the reaction to proceed for a longer time (**Table 2.2A.1**, entry 9).

Next, we evaluated the effect of different bases such as K_3PO_4, KOH, KO^tBu, and CH_3ONa on the yield of **14aa** in the presence of CuI as the catalyst (**Table 2.2A.1**, entries 10–13). Among these bases, the use of CH_3ONa gave the highest yield of **14aa** (**Table 2.2A.1**, entry 13). Variation of the solvent for the model reaction revealed that polar aprotic solvents such as DMF, DMA, and DMSO are suitable for this transformation (**Table 2.2A.1**, entries 13–15). Formation of **14aa** was not observed when nonpolar aprotic solvents such as toluene and 1,4-dioxane were used (**Table 2.2A.1**, entries 16 and 17). It is also important to mention that the use of different additives such as zinc iodide, potassium persulphate, and pivolic acid and ligands such as 1,10-phenanthroline, and L-proline did not improve the yield of **14aa**.

After having the optimized reaction conditions in hand (**Table 2.2A.2**, entry 13), the generality of the tandem process was investigated by employing variously substituted 2-(2-bromophenyl)- 1*H*-imidazoles (**Table 2.2A.2**). Reactions of 2-(2-bromophenyl)-4,5-diaryl-1*H*-imidazoles having substituted aryl rings at C4- and C5- positions of imidazole with formamide gave the corresponding imidazo[1,2-*c*]quinazolines (**14aa**–**fa**) in 35–70% yields. Similarly, reaction of 2-(2-bromophenyl)-1*H*-imidazoles with different substituents such as fluoro, methyl, and methoxy on both aryl rings at C4- and C5- positions as well as at the C2- position of imidazole with formamide gave the corresponding imidazo[1,2-*c*]quinazolines (**14ga**–**qa**) in 31–58% yields. The structure of all the synthesized imidazo[1,2-*c*]quinazolines was elucidated by NMR and HRMS data.

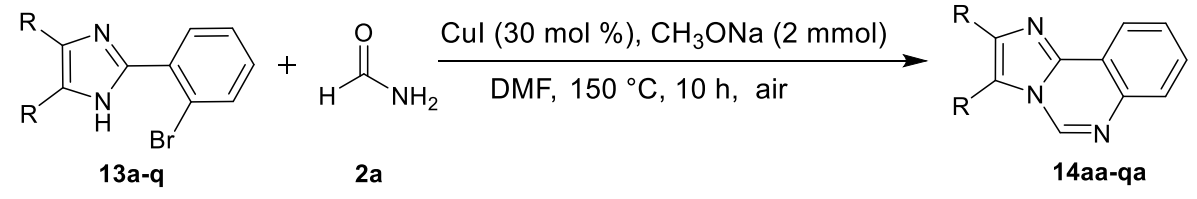
Table 2.2A.1 Optimization of reaction conditions for the synthesis of **14**[a]

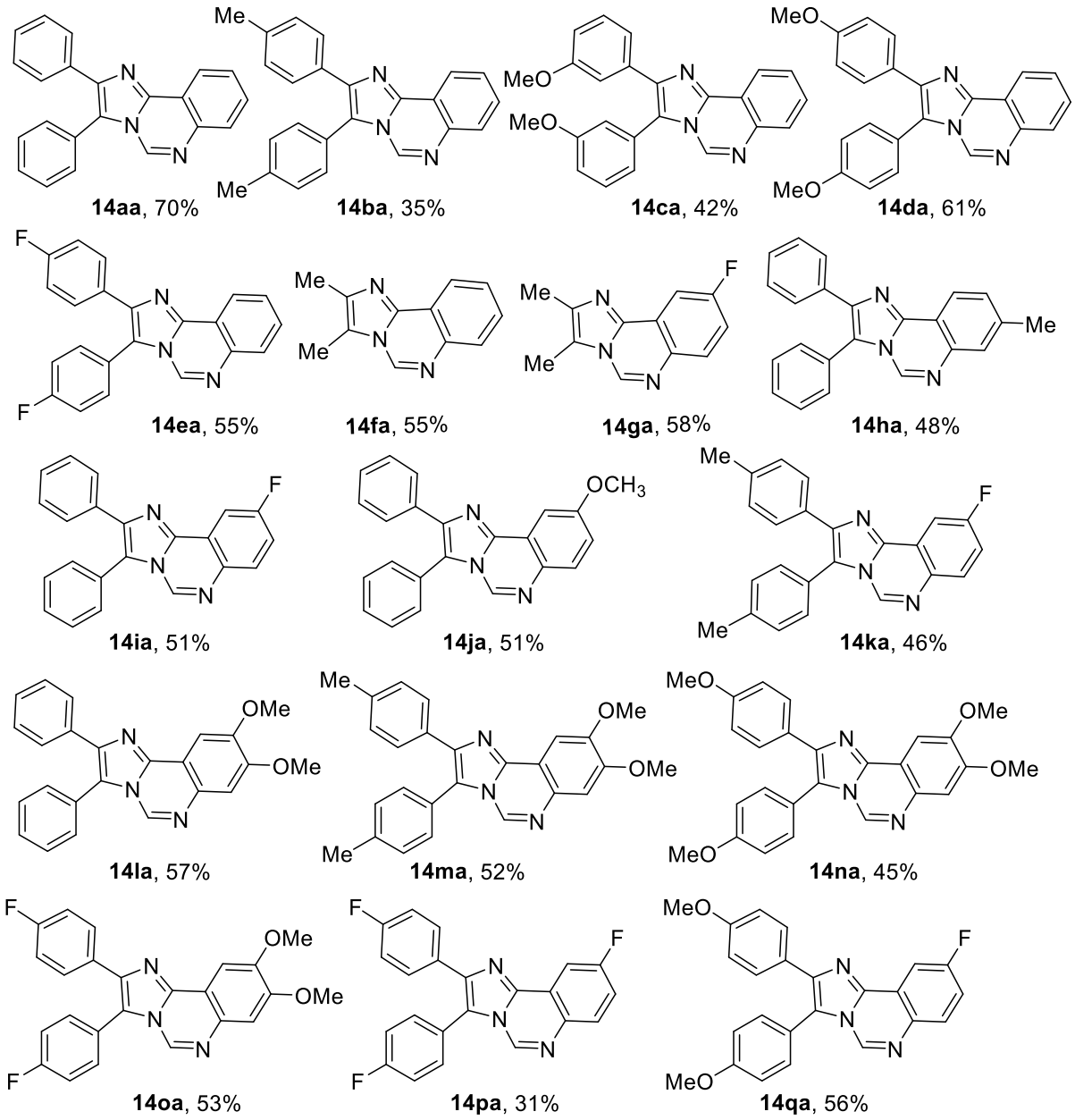


Entry	Catalyst (mol %)	Base	Solvent	% Yield[b]
1	$CuCl_2$ (10)	K_2CO_3	DMF	30
2	CuBr (10)	K_2CO_3	DMF	34
3	$Cu(OAc)_2 \cdot H_2O$ (10)	K_2CO_3	DMF	39
4	$Cu(OTf)_2$ (10)	K_2CO_3	DMF	33
5	CuI (10)	K_2CO_3	DMF	45
6	CuI (20)	K_2CO_3	DMF	52
7	CuI (30)	K_2CO_3	DMF	60
8	CuI (40)	K_2CO_3	DMF	61
9	–	K_2CO_3	DMF	NR[c]
10	CuI (30)	K_3PO_4	DMF	45
11	CuI (30)	KOH	DMF	56
12	CuI (30)	*t*-BuOK	DMF	48
13	CuI (30)	CH_3ONa	DMF	70
14	CuI (30)	CH_3ONa	DMA	62
15	CuI (30)	CH_3ONa	DMSO	60
16	CuI (30)	CH_3ONa	Toluene	NR
17	CuI (30)	CH_3ONa	Dioxane	NR
18	CuI (30)	CH_3ONa	DMF	trace[d]
19	CuI (30)	CH_3ONa	DMF	62[e]
20	CuI (30)	CH_3ONa	DMF	58[f]
21	CuI (30)	CH_3ONa	DMF	63[g]
22	CuI (30)	CH_3ONa	DMF	65[h]
23	CuI (30)	CH_3ONa	DMF	63[i]

[a]Reaction conditions: **13a** (1.0 mmol), **2a** (10 mmol), catalyst (0.3 mmol), base (2.0 mmol), solvent (2.0 mL), 150 °C, 10 h. [b]Isolated yields. [c]NR = no reaction. [d]Under N_2 atm. [e]Zinc iodide (30 mol %) used as an additive. [f]Potassium per sulphate (50 mol %) used as an additive. [g]Pivolic acid (30 mol %) used as an additive. [h]1,10-Phenanthroline (40 mol %) used as a ligand. [i]L-Proline (40 mol %) used as a ligand.

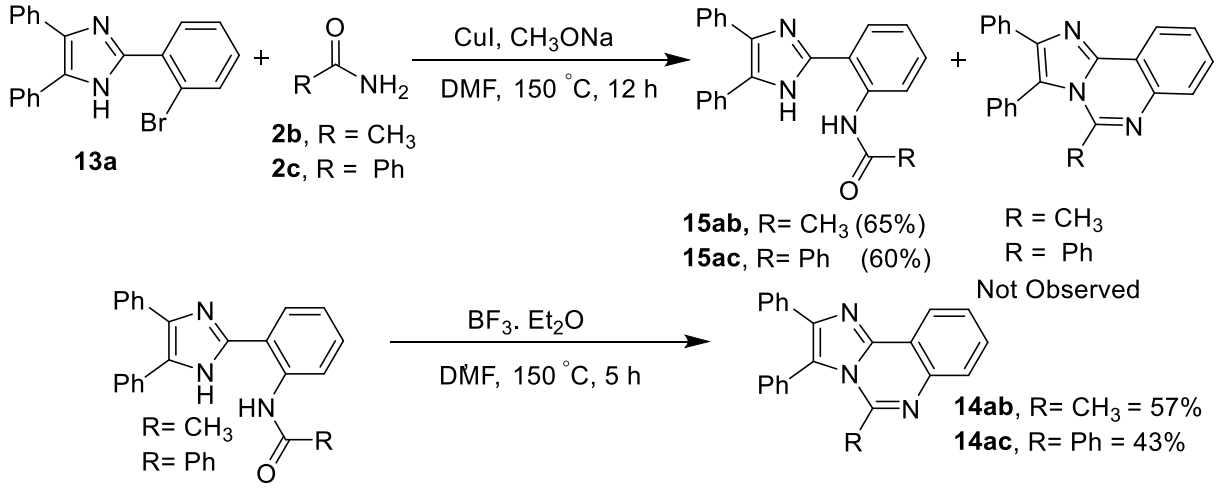
Table 2.2A.2 Substrate scope for synthesis of imidazo[1,2-*c*]quinazoline (**14**)[a]





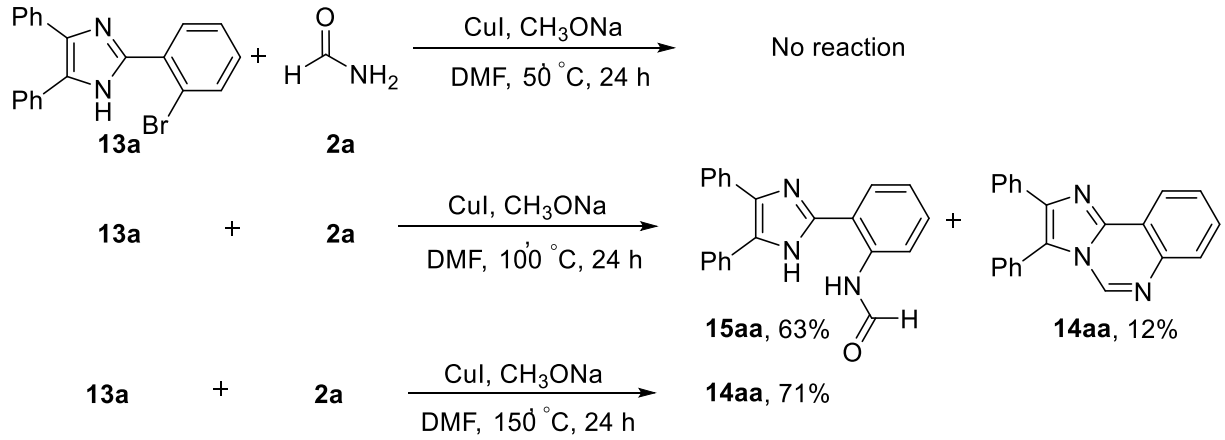
[a]Reaction conditions: **13** (1.0 mmol), **2** (10.0 mmol), CuI (0.3 mmol), CH_3ONa (2.0 mmol), DMF (2.0 mL), 150 °C, 10 h. [b]Isolated yields.

Further reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**13a**) with acetamide (**2b**) and benzamide (**2c**) under the optimized reaction conditions gave the C–N coupled products *N*-(2-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)acetamide (**15ab**) and *N*-(2-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)benzamide (**15ac**) in 65% and 60% yields, respectively (**Scheme 2.2A.12**). The expected imidazo[1,2-*c*]quinazolines were not observed from these reactions even after longer reaction time. This might be due to relatively low electrophilicity of the amide carbonyl group in these amides compared to formamide. However, on treating **15ab** and **15ac** with $BF_3{\cdot}OEt_2$ (2 equiv.) in DMF at 150 °C for 5 h corresponding imidazo[1,2-*c*]quinazolines **14ab** and **14ac** were obtained in 57% and 43%, respectively



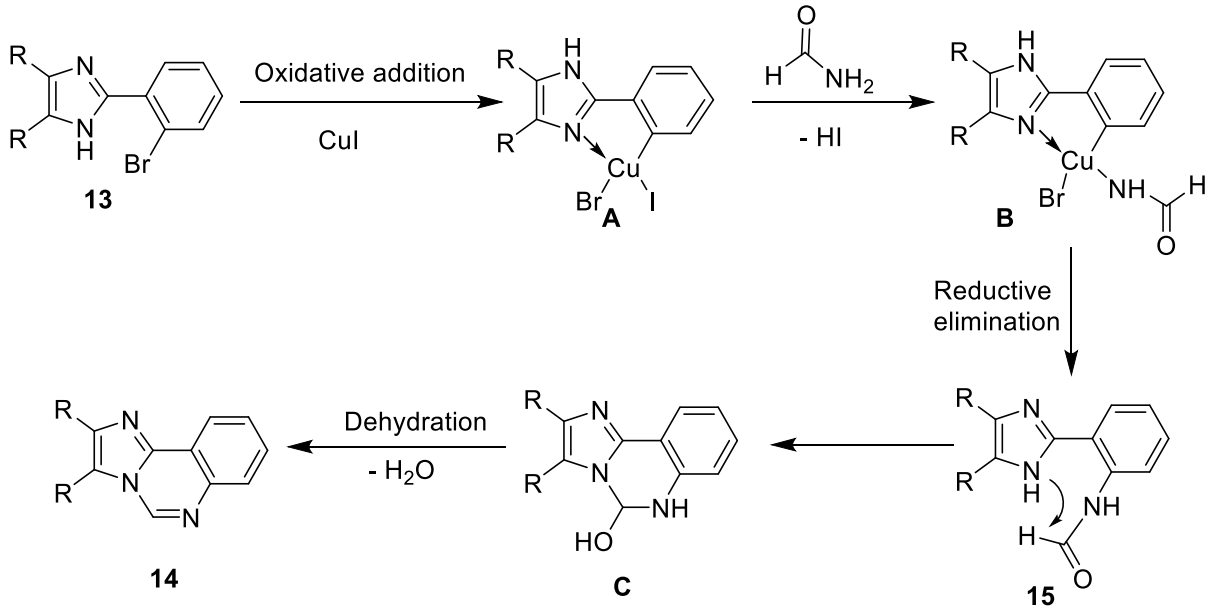
Scheme 2.2A.12 Reaction of **13a** with acetamide (**2b**) and benzamide (**2c**).

To investigate the possible reaction pathway for this tandem approach, we performed some control experiments (**Scheme 2.2A.13**). A temperature dependent study was performed for the reaction of **13a** with **2a** in the presence of CuI and CH_3ONa in DMF. No product formation was observed up to 50 °C, but when the reaction mixture was heated at 100 °C for 24 h along with the expected imidazo[1,2-*c*]quinazoline (**14aa**), the C–N coupled product, N-(2-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl) formamide (**15aa**), was also observed in 63% yield. Further, imidazo[1,2-*c*]quinazoline (**14aa**) was obtained in 71% yield under the optimized reaction conditions.



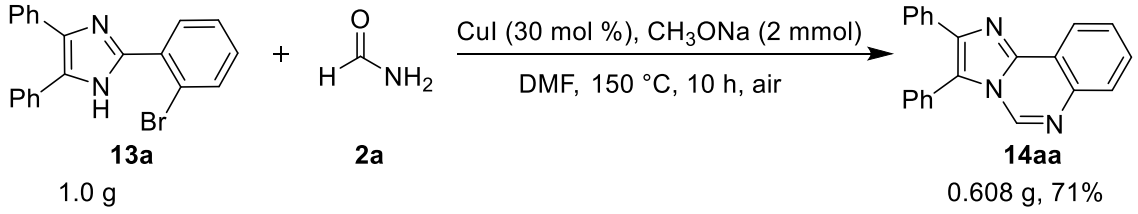
Scheme 2.2A.13 The reaction of **13a** with **2a** at different temperature

On the basis of literature reports[38–40] and experimental results, a plausible mechanism for the synthesis of imidazo[1,2-*c*]quinazolines is outlined in **Scheme 2.2A.14**. It is believed that oxidative addition of CuI with 2-(2-bromophenyl)-4,5-diphenyl-1*H* imidazole leads to the formation of the copper (III) intermediate **A**. This step is assisted by the presence of the internal directing group from imidazole which also acts as a ligand for this reaction. Further, substitution of iodide from **A** with formamide in the presence of CH_3ONa affords intermediate **B** which then undergoes reductive elimination to give *N*–arylated amide **15**. Finally, copper catalyst assisted intramolecular dehydrative cyclization of **C** *via* intermediate **15** results in the formation of fused quinazoline derivative **14**. Formation of imidazo[1,2-*c*]quinazolines **14ab** and **14ac** by adding Lewis acid $BF_3{\cdot}OEt_2$ to **15ab** and **15ac** is also in agreement with the involvement of intermediate **15** *via* nucleophilic addition to the amidic carbonyl group.



Scheme 2.2A.14 Probable reaction mechanism of imidazo[1,2-*c*]quinazolines

Finally, to evaluate the scalability of the protocol, a model reaction was performed at a gram scale, and **14aa** was isolated in 608 mg (71%) from the reaction of **13a** with **2a** under the optimized reaction conditions (**Scheme 2.2A.15**).



Scheme 2.2A.15 Gram scale synthesis of 2,3-diphenylimidazo[1,2-*c*]quinazolines

2.2A.3 CONCLUSIONS

We have successfully developed a novel and efficient copper-catalyzed one-pot tandem approach for the synthesis of imidazo[1,2-*c*]quinazolines from 2-(2-bromoaryl)-1*H*-imidazoles and formamide. The protocol involved sequential copper–catalyzed Ullmann–type coupling of formamide followed by dehydrative cyclization to give the target compounds in moderate to good yields. This method is also applicable with acetamide and benzamide under slightly modified in optimized reaction condition.

2.2A.4 EXPERIMENTAL SECTION

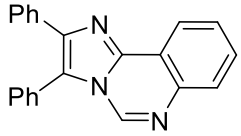
2.2A.4.1 General Materials and Methods

Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel $F^{2}54$ plates (Merck). The chemical structures of the final products were determined by their NMR spectra (^{1}H and ^{13}C NMR) using a Bruker AV 400 MHz spectrometer. ^{13}C NMR spectra are fully decoupled. High resolution mass spectra (HRMS) were recorded using a quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). 2-(2-Bromoaryl)-1H-imidazoles were synthesized through one–pot, three component condensation of benzils, 2-bromoarylaldehydes and ammonium acetate using L-proline as the catalyst. All other chemicals were obtained from the commercial suppliers and used without further purification.

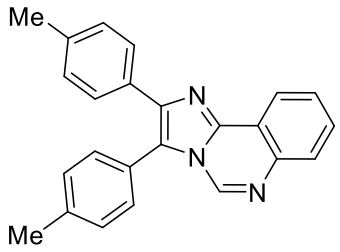
2.2A.4.2 Representative procedure for imidazo[1,2-*c*]quinazoline derivatives:

A clean oven dried 10 mL round bottom flask charged with **13** (1.0 mmol), **2a** (10 mmol), CH_3ONa (2 mmol), and CuI (0.3 mmol) in DMF (2.0 mL) was stirred at 150 °C for 10 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool to ambient temperature, diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by column chromatography to obtain the desired imidazo[1,2-*c*]quinazoline.

2,3-Diphenylimidazo[1,2-*c*]quinazoline (14aa). Yield 70%, Brown solid, mp 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.69 – 8.66 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.77 – 7.69 (m, 4H), 7.61 – 7.52 (m, 5H), 7.36 – 7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 141.8, 141.1, 135.6, 133.4, 130.7, 130.0, 129.7, 129.4, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 123.0, 121.5, 119.4; HRMS (ESI) calcd for $C_{22}H_{16}N_3$ $[M + H]^+$ 322.1339 found 322.1344.

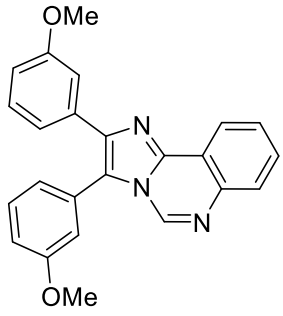


2,3-Di-*p*-tolylimidazo[1,2-*c*]quinazoline (14ba). Yield 35%, Off-white solid, mp 188 – 190 °C;



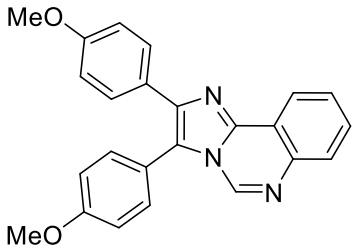
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.69 – 8.68 (m, 1H), 7.97 – 7.95 (m, 1H), 7.72 – 7.69 (m, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 2.50 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.7, 141.1, 139.4, 137.6, 135.7, 130.6, 130.6, 130.4, 129.9, 129.1, 128.5, 128.3, 127.9, 125.5, 122.9, 121.2, 119.4, 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3$ $[M + H]^+$ 350.1652 found 350.1655.

2,3-Bis(3-methoxyphenyl)imidazo[1,2-*c*]quinazoline (14ca). Yield 42%, Off-white solid, mp



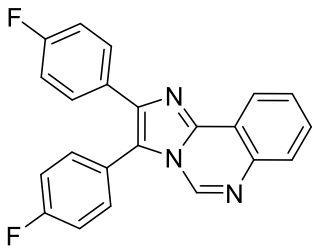
160 – 162 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 8.54 (m, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.79 – 7.76 (m, 2H), 7.56 – 7.52 (m, 1H), 7.27 – 7.17 (m, 4H), 7.19 – 7.15 (m, 2H), 6.88 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 160.4, 159.6, 141.6, 141.1, 140.4, 137.0, 135.1, 131.2, 130.8, 130.0, 129.8, 129.2, 128.6, 123.5, 122.8, 122.2, 120.3, 119.1, 116.5, 115.8, 113.9, 113.3, 55.8, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ $[M + H]^+$ 382.1550 found 382.1543.

2,3-Bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline (14da). Yield 61%, Off-white solid, mp



195 – 196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.67 – 8.66 (m, 1H), 7.96 – 7.94 (m, 1H), 7.72 – 7.66 (m, 4H), 7.45 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.93 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.3, 142.0, 141.4, 141.1, 135.7, 132.1, 129.9, 129.2, 128.5, 128.3, 126.1, 122.9, 120.5, 120.4, 119.3, 115.2, 113.9, 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ $[M + H]^+$ 382.1550 found 382.1556.

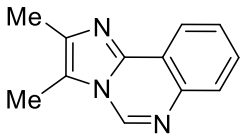
2,3-Bis(4-fluorophenyl)imidazo[1,2-*c*]quinazoline (14ea). Yield 55%, Off-white solid, mp 230



°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.66 – 8.64 (m, 1H), 7.98 – 7.96 (m, 1H), 7.76 –7.67 (m, 4H), 7.54 –7 .50 (m, 2H), 7.33 – 7.28 (m, 2H), 7.04 (t, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 250.8 Hz), 162.6 (d, J = 247.8 Hz), 142.4, 141.1, 135.2, 132.7 (d, J = 8.4 Hz), 130.3, 129.8 (d, J = 8.1 Hz), 129.4 (d, J = 3.2

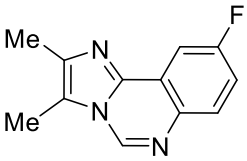
Hz), 128.7, 128.4, 124.3 (d, *J* = 3.5 Hz), 122.9, 120.1, 119.2, 117.1 (d, *J* = 21.8 Hz), 115.5 (d, *J* = 21.5 Hz); HRMS (ESI) calcd for $C_{22}H_{14}F_2N_3$ $[M + H]^+$ 358.1150 found 358.1153.

2,3-Dimethylimidazo[1,2-*c*]quinazoline (14fa). Yield 55%, Off-white solid, mp 180 – 182 °C;



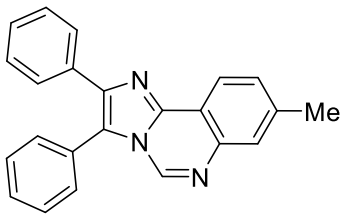
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.52 (m, 1H), 7.96 – 7.93 (m, 1H), 7.69 – 7.62 (m, 2H), 2.53 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.5, 138.7, 135.1, 129.5, 128.4, 128.2, 122.3, 119.0, 116.1, 13, 8.1; HRMS (ESI) calcd for $C_{12}H_{12}N_3$ $[M + H]^+$ 198.1026 found 198.1032.

9-Fluoro-2,3-dimethylimidazo[1,2-*c*]quinazoline (14ga). Yield 58%, Brown solid, mp 190 °C;



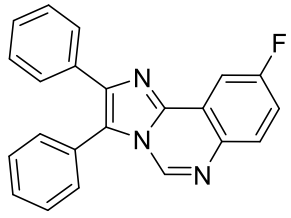
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.10 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.92 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.36 (td, *J* = 8.6, 2.9 Hz, 1H), 2.52 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, *J* = 249.2 Hz), 140.8 (d, *J* = 4.4 Hz), 139.1, 137.1, 134.4 (d, *J* = 2.5 Hz), 130.7 (d, *J* = 9.2 Hz), 120.3 (d, *J* = 10.5 Hz), 118.0 (d, *J* = 24.4 Hz), 116.6, 107.3 (d, *J* = 24.6 Hz), 13.0, 8.1; HRMS (ESI) calcd for $C_{12}H_{11}FN_3$ $[M + H]^+$ 216.0932 found 216.0926.

8-Methyl-2,3-diphenylimidazo[1,2-*c*]quinazoline (14ha). Yield 48%, Brown solid, mp 210 °C;



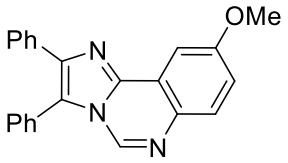
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.58 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.58 –7.53 (m, 5H), 7.36 – 7.28 (m, 4H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.6, 141.3, 140.6, 135.61, 133.5, 130.7, 130.2, 129.6, 129.4, 128.6, 128.4, 128.1, 128.1, 127.8, 122.7, 121.2, 116.9, 21.6; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ $[M + H]^+$ 336.1495 found 336.1499.

9-Fluoro-2,3-diphenylimidazo[1,2-*c*]quinazoline (14ia). Yield 51%, Brown solid, mp 230 °C;

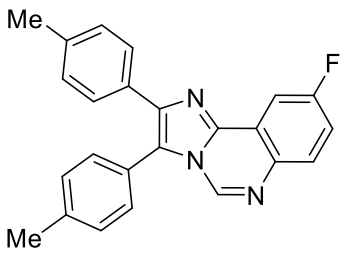


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.97 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.60 – 7.53 (m, 5H), 7.46 – 7.41 (m, 1H), 7.36 – 7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, *J* = 249.7 Hz), 141.7 (d, *J* = 4.4 Hz), 137.74 (d, *J* = 1.9 Hz), 134.87 (d, *J* = 2.5 Hz), 133.2, 130.8 (d, *J* = 9.2 Hz), 130.7, 129.7, 129.6, 128.6, 128.5, 128.3, 128.11, 127.99, 127.9, 121.8, 120.8, 120.7, 118.6 (d, *J* = 24.3 Hz), 108.1 (d, *J* = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{15}FN_3$ $[M + H]^+$ 340.1245 found 340.1248.

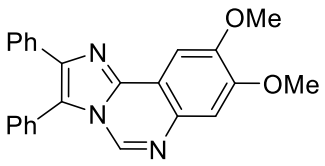
9-Methoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline (14ja). Yield 51%, Off-white solid, mp 220 – 222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.03 (d, J = 2.7 Hz, 1H), 7.87 (d, J = 9.0 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.61 – 7.53 (m, 5H), 7.37 – 7.29 (m, 4H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 142.3, 141.7, 135.8, 133.5, 133.4, 130.7, 130.0, 129.7, 129.4, 128.58, 128.5, 128.2, 127.8, 121.5, 120.6, 120.4, 102.7, 56.0; HRMS (ESI) calcd for $C_{23}H_{18}N_3O$ $[M + H]^+$ 352.1444 found 352.1420.



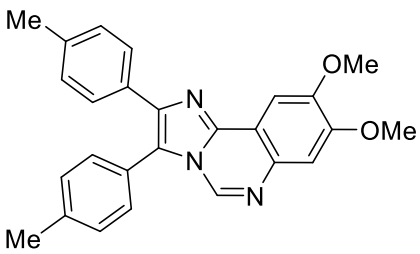
9-Fluoro-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (14ka). Yield 46%, Brown solid, mp 235 – 240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.31 (dd, J = 8.6, 2.6 Hz, 1H), 7.96 (dd, J = 8.9, 5.1 Hz, 1H), 7.63 (d, 2H), 7.46 – 7.36 (m, J = 8.1 Hz, 5H), 7.16 (d, J = 7.9 Hz, 2H), 2.51 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J = 249.4 Hz), 141.5 (d, J = 4.2 Hz), 139.6, 137.8, 137.7, 135, 135.0, 130.7 (d, J = 9.1 Hz), 130.5, 130.4, 129.2, 127.9, 125.3, 121.5, 120.7 (d, J = 10.5 Hz), 118.5 (d, J = 24.3 Hz), 108.1 (d, J = 24.6 Hz), 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3$ $[M + H]^+$ 368.1558 found 368.1561.



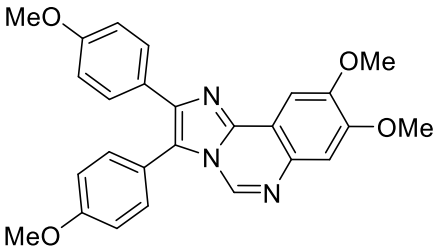
8,9-Dimethoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline (14la). Yield 57%, Off-white solid, mp 207 – 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.00 (s, 1H), 7.73 – 7.71 (m, 2H), 7.60 – 7.52 (m, 5H), 7.38 – 7.29 (m, 4H), 4.13 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 150.5, 142.5, 141.7, 136.8, 134.1, 133.6, 130.7, 129.6, 129.3, 128.7, 128.5, 128.2, 127.8, 120.9, 113.3, 108.9, 102.5, 56.6, 56.2; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ $[M + H]^+$ 382.1550 found 381.1553.



8,9-Dimethoxy-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (14ma). Yield 52%, Greyish solid, mp 190 – 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.99 (s, 1H), 7.66 – 7.62 (m, 2H), 7.40 – 7.37 (m, 5H), 7.15 – 7.11 (m, 2H), 4.14 (s, 3H), 4.04 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.4, 142.3, 141.5, 139.2, 137.5, 136.7, 134.2, 130.8, 130.6, 130.3, 129.1, 127.0, 125.8, 120.5, 113.3, 108.9, 102.5, 56.6, 56.2, 21.5, 21.3; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ $[M + H]^+$ 410.1863 found 410.1867.

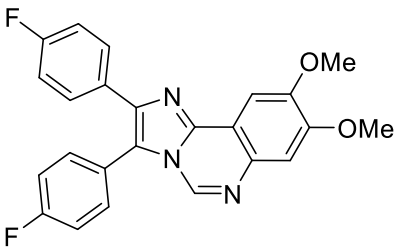


8,9-Dimethoxy-2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazolines (14na). Yield 45%,



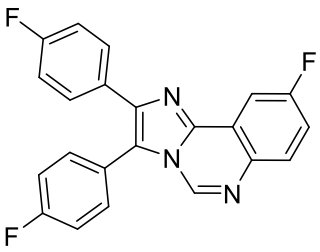
Brown solid, mp 170 – 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.99 (s, 1H), 7.67 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 7.9 Hz, 3H), 7.37 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 4.12 (s, 3H), 4.04 (s, 3H), 3.93 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.2, 158.9, 151.6, 150.4, 136.7, 134.2, 132.1, 129.3, 129.1, 126.3, 120.8, 119.8, 115.1, 114.0, 113.2, 109.0, 102.4, 56.5, 56.2, 55.4, 55.3; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_4$ $[M + H]^+$ 442.1761 found 442.1765.

2,3-Bis(4-fluorophenyl)-8,9-dimethoxyimidazo[1,2-c]quinazolines (14oa). Yield 53%, Light



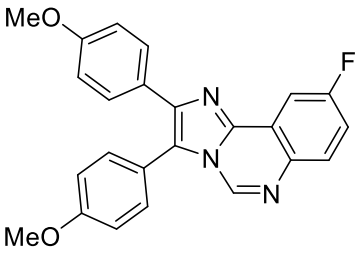
brown solid, mp 255 – 257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.96 (s, 1H), 7.67 (s, 2H), 7.50 (s, 2H), 7.37 (s, 1H), 7.28 (s, 2H), 7.03 (s, 2H), 4.13 (s, 3H), 4.05 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 250.6 Hz), 162.6 (d, J = 248.0 Hz), 151.9, 150.6, 142.5, 141.01, 136.83, 133.78, 132.7 (d, J = 8.3 Hz), 129.8 (d, J = 8.1 Hz), 129.6, 124.5, 119.4, 117.1 (d, J = 21.8 Hz), 115.5 (d, J = 21.5 Hz), 113.1, 108.9, 102.4, 56.5, 56.2; HRMS (ESI) calcd for $C_{24}H_{18}F_2N_3O_2$ $[M + H]^+$ 418.1362 found 418.1365.

8-Fluoro-2,3-bis(4-fluorophenyl)imidazo[1,2-*c*]quinazolines (14pa). Yield 31%, Off white

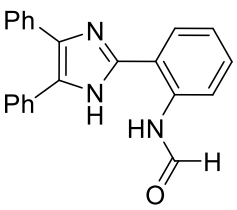


solid, mp 261– 263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.29 (dd, J = 8.6, 2.8 Hz, 1H), 7.97 (dd, J = 9.0, 5.1 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.51 – 7.49 (m, 2H), 7.47 – 7.42 (m, 1H), 7.33 – 7.28 (m, 2H), 7.07 – 7.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J = 251.0 Hz), 162.6 (d, J = 248.1 Hz), 162.0 (d, J = 250.1 Hz), 141.8 (d, J = 4.4 Hz), 141.3, 137.7, 134.5 (d, J = 2.5 Hz), 132.7 (d, J = 8.4 Hz), 130.8 (d, J = 9.2 Hz), 129.8 (d, J = 8.2 Hz), 129.1 (d, J = 3.3 Hz), 124.0 (d, J = 3.6 Hz), 120.5 (d, J = 10.5 Hz), 120.3, 118.8 (d, J = 24.4 Hz), 117.2 (d, J = 21.9 Hz), 115.6 (d, J = 21.6 Hz), 108.1 (d, J = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ $[M + H]^+$ 376.1056 found 376.1062.

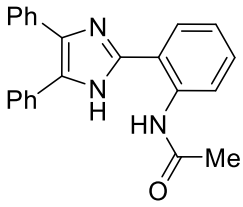
9-Fluoro-2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazolines (14qa). Yield 56%, Off -white solid, mp 218 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.30 (dd, J = 8.7, 2.8 Hz, 1H), 7.95 (dd, J = 9.0, 5.1 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.46 – 7.30 (m, 3H), 7.13 – 7.09 (m, 2H), 6.91 – 6.87 (m, 2H), 3.94 (s, 3H), 3.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J = 249.3 Hz), 160.4, 159.4, 141.7, 141.4 (d, J = 3.9 Hz), 137.7 (d, J = 1.8 Hz), 135.0 (d, J = 2.5 Hz), 132.1, 130.7 (d, J = 9.2 Hz), 129.2, 125.9, 120.7, 120.7 (d, J = 10.3 Hz), 118.4 (d, J = 24.3 Hz), 120.3, 115.2, 113.9, 108.0 (d, J = 24.5 Hz), 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3O_2$ $[M + H]^+$ 400.1456 found 400.1461.



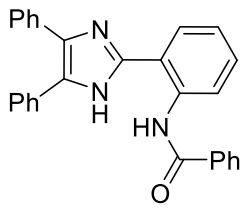
***N*-(2-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenyl)formamide (15aa).** Yield 63%, White solid, mp 218 – 220 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.99 (s, 1H), 12.66 (s, 1H), 8.65 (d, J = 5.8 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.60 – 7.52 (m, 4H), 7.51 – 7.31 (m, 7H), 7.27 – 7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO) δ 162.9, 160.8, 145.9, 136.5, 136.2, 134.5, 130.9, 129.9, 129.6, 129.3, 129.2, 128.9, 128.8, 127.6, 126.9, 123.7, 121.0, 116.4; HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ 340.1444 found 340.1447 $[M + H]^+$.



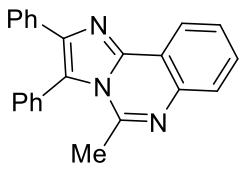
***N*-(2-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenyl)acetamide (15ab).** Yield 65%, Off-white solid, mp 248 – 250 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.00 – 12.99 (m, 2H), 8.63 (d, J = 8.2 Hz, 1H), 8.11 (d, J = 7.0 Hz, 1H), 7.58 – 7.54 (m, 4H), 7.51 – 7.43 (m, 3H), 7.39 – 7.32 (m, 3H), 7.30 – 7.25 (m, 1H), 7.19 – 7.15 (m, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 168.7, 145.5, 137.5, 135.7, 134.6, 130.8, 129.6, 129.4, 129.2, 128.9, 128.8, 128.4, 127.4, 127.1, 126.5, 123.0, 119.9, 115.8, 25.7; HRMS (ESI) calcd for $C_{23}H_{20}N_3O$ $[M+ H]^+$ 354.1601 found 354.1604.



***N*-(2-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenyl)benzamide (15ac).** Yield 65%, Off-white solid, mp 242 – 245 °C; ^{1}H NMR (400 MHz, DMSO) δ 13.68 (s, 1H), 13.05 (s, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 7.7 Hz, 1H), 8.09 (d, J = 7.5 Hz, 2H), 7.64 – 7.58 (m, 1H), 7.57 – 7.34 (m, 13H), 7.25 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 165.5, 145.6, 137.5, 136.4, 135.4, 134.5, 132.3, 130.6, 129.6, 129.2, 128.9, 128.7, 128.5, 128.01, 127.9, 127.6, 126.7, 123.5, 120.4, 116.6; HRMS (ESI) calcd for $C_{28}H_{22}N_3O$ $[M + H]^+$ 416.1757 found 416.1761.

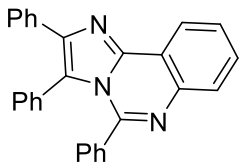


5-Methyl-2,3-diphenylimidazo[1,2-*c*]quinazoline (14ab). Yield 57%, White solid, mp 138 – 142



°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 7.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.77 – 7.65 (m, 2H), 7.63 (d, J = 6.7 Hz, 2H), 7.60 – 7.47 (m, 5H), 7.35 – 7.24 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 143.5, 142.1, 140.5, 133.7, 132.5, 131.9, 130.0, 129.63, 128.7, 128.3, 127.9, 127.7, 127.5, 127.2, 122.9, 122.7, 118.8, 24.4; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ 336.1495 found 336.1492 $[M + H]^+$.

2,3,5-Triphenylimidazo[1,2-*c*]quinazoline (14ac). Yield 43%, White solid, mp 230 – 232 °C; ^{1}H



NMR (400 MHz, $CDCl_3$) δ 8.80 (dd, J = 7.7, 1.5 Hz, 1H), 8.0 (dd, J = 7.7, 1.5 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.57 – 7.52 (m, 2H), 7.29 – 7.24 (m, 5H), 7.18 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.97 – 6.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 144.4, 142.7, 140.6, 133.9, 133.8, 131.3, 130.5, 130.1, 129.3, 128.7, 128.7, 128.2, 128.2, 128.0, 127.8, 127.6, 127.6, 123.4, 123.0, 118.7; HRMS (ESI) calcd for $C_{28}H_{20}N_3$ 398.1652 found 398.1657 $[M + H]^+$.

2.2A.5 REFERENCES

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CHAPTER 2B

Direct Access to Imidazo[1,2-*c*]quinazolines through Tandem Reductive Amination of Aryl Halides and Oxidative Amination of C(sp^3)–H Bond

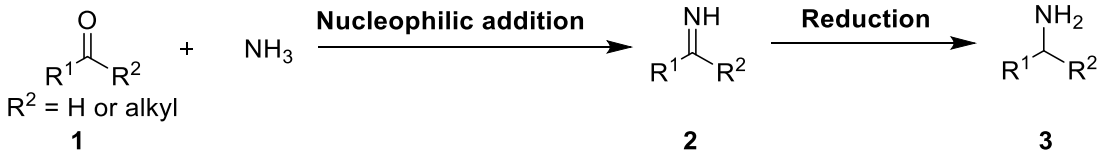
2.2B.1 INTRODUCTION

The development of a sustainable and greener approach by using inexpensive and readily available feedstock and reagents for an efficient organic synthesis is a major challenge of chemical research.[1,2] The replacement of hazardous and waste-generating reagents is one of the noteworthy tasks for academic and industrial research. In the last few years, different carbon synthons have been used for the integral and prevalent functionalities in chemicals, biomolecules and pharmaceuticals. Therefore, the development of a simple and convenient method for the synthesis of *C*–methylated, *N*–methylated and *O*–methylated products are highly desirable which attracts the interest of researchers. In laboratory and drug discovery, these compounds are synthesized by using toxic methyl compounds such as diazomethane, methyl iodide and dimethyl sulphate.[3] Especially, *N*-methyl amines are synthesized *via* reductive amination using formaldehyde, which is carcinogen for human.[4] However, in recent years *N*,*N*-dimethylformamide (DMF),[5-9] DMF-dimethyl acetal,[10] *N*,*N*-dimethylacetamide (DMA)[11-14] and dimethylsulfoxide (DMSO)[15,16] have been increasingly utilized as one carbon source in various organic transformations and these solvents are considered to be the suitable alternative of traditional reagents. On the other hand, reductive amination and oxidative amination of C(sp^3)–H bonds of inert hydrocarbons have become an attractive and vital tool for construction of C–N bond.[17,18]

2.2B.1.1 Reductive amination

Aldehydes and ketones are converted into an amine by reductive amination. The reductive amination is carried out in two-step (**Scheme 2.2B.1**).

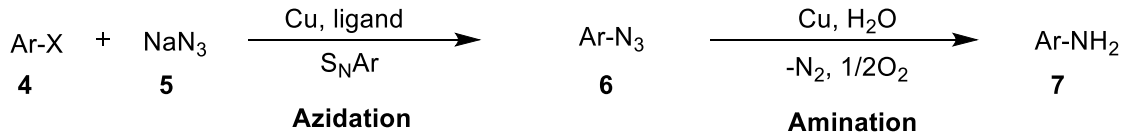
1) The first step is the nucleophilic addition of the carbonyl group to form an imine
2) The second step is the reduction of imine to an amine.



Scheme 2.2B.1 General representation of reductive amination of carbonyl compounds

The conversion of aryl halide to aryl amine is another kind of reductive amination. In the last decade, several groups used sodium azide as a nitrogen source for the development of fused heterocycles *via* copper catalyzed azidation followed by amination (**Scheme 2.2B.2**). Therefore,

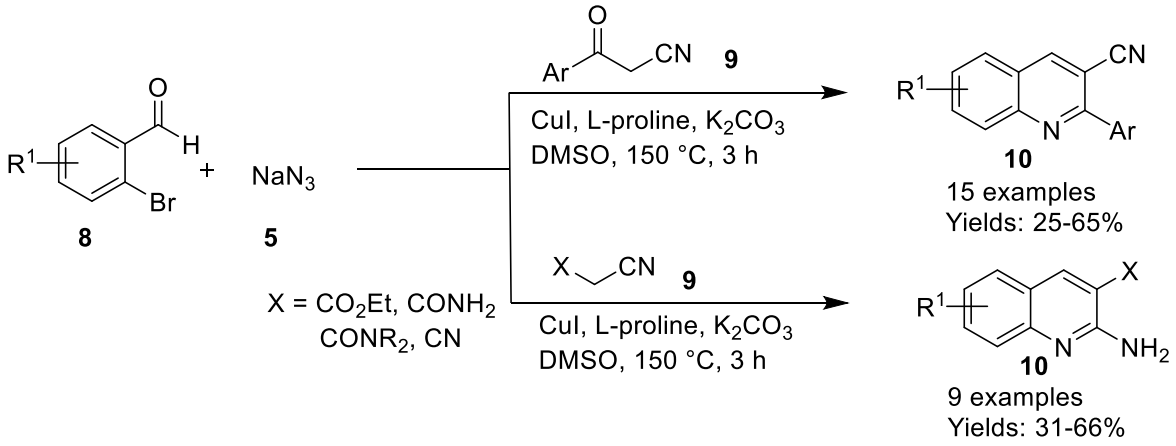
synthesis of aryl amine from aryl halide by using sodium azide (NaN_3), has emerged as a powerful nitrogen source for the assembly of nitrogen-containing frameworks.[19-26]



Scheme 2.2B.2 General representation of reductive amination of aryl halides

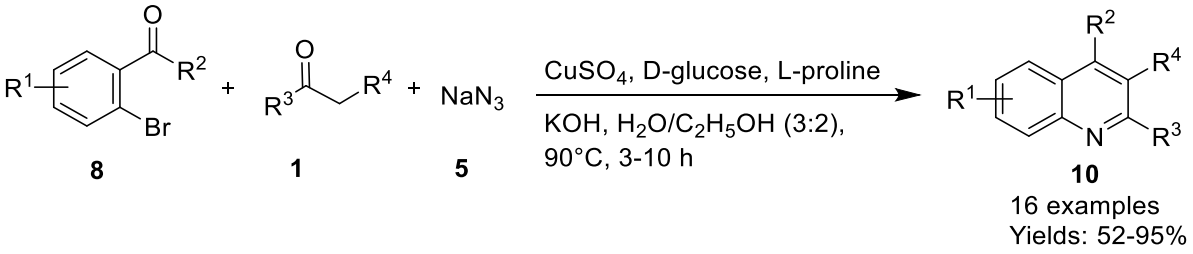
In literature several reports has been documented by using sodium azide, herein some of the reports is described below

Kumar group developed copper–catalyzed the regioselective synthesis of 2-arylquinoline-3-carbonitriles and 2-aminoquinolines (**10**) from easily available 2-bromobenzaldehydes (**8**), active methylene nitriles (**9**) and sodium azide (**5**) (**Scheme 2.2B.3**).[23] The reaction proceeded through Knoevenagel condensation of ortho-bromobenzaldehyde with active methylene nitriles followed by copper-catalyzed reductive amination and intramolecular cyclization and afforded substituted quinoline derivatives with moderate to good yields (25-66%).



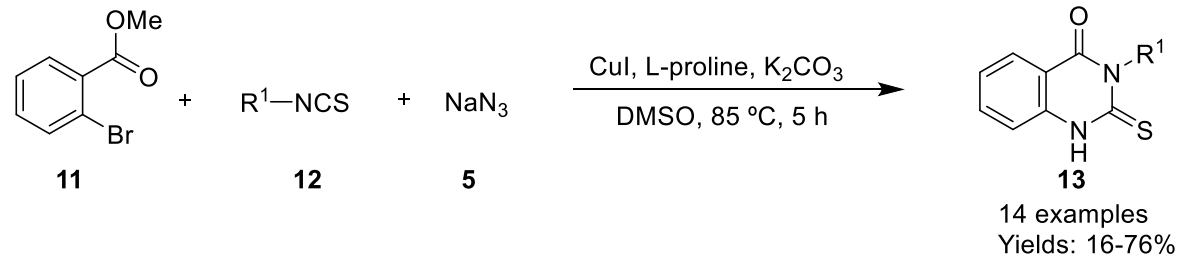
Scheme 2.2B.3 Copper-catalyzed synthesis of 2-arylquinoline-3-carbonitriles and 2-aminoquinolines from 2-bromobenzaldehydes

Anand *et al.* reported one-pot tandem multi–component reaction for the development of functionalized/ annulated quinolones (**10**) from 2-bromobenzaldehydes/ketones (**8**), α-methylene ketones (**1**) and sodium azide (**5**) (**Scheme 2.2B.4**).[27] The reaction involved sequential S_NAr, reduction and Friedlander annulation steps and formation of three new bonds in one-pot, broad substrate scope and good to excellent yields (52-95%) were the main features of the reaction.



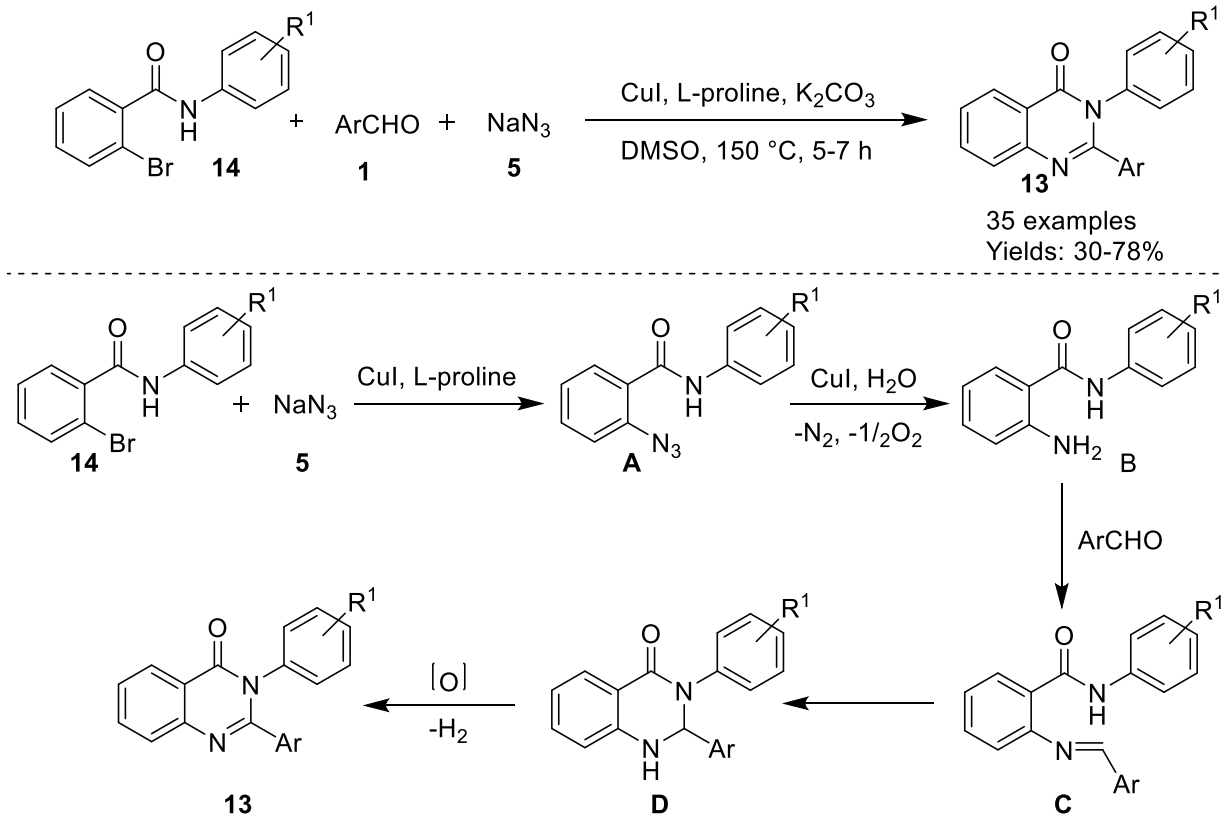
Scheme 2.2B.4 Copper–catalyzed synthesis of quinolines from 2-bromobenzaldehydes/ketones

Very recently, Sayahi *et al.* developed tandem multi–component reaction of methyl 2-bromobenzoate (**11**), phenylisothiocyanate (**12**), and sodium azide (**5**) for the synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one (**13**) (**Scheme 2.2B.5**).[28] The developed method well tolerated with electron releasing and electron poor substituents on isothiocyanates and afforded respective products in moderate to good yields (16-76%).



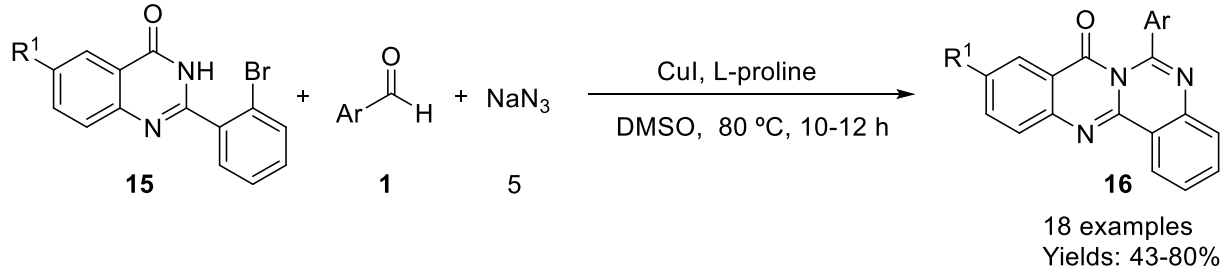
Scheme 2.2B.5 Copper–catalyzed synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones from *o*-bromobenzoates

Very recently, Kumar and his team described one–pot three–component tandem approach for the synthesis of quinazolin-4(3*H*)-ones (**13**) from 2-bromobenazamides (**14**), aldehyde (**1**), and sodium azide (**5**) as a one nitrogen source (**Scheme 2.2B.6**).[25] Merits of this method like, good functional group tolerance, mild reaction condition and readily available starting materials made attractive and environmentally friendly method. The mechanism of reaction involved reductive amination, imine formation, C–N bond formation *via* intramolecular oxidative amidation followed by aerobic oxidation (**Scheme 2.2B.6**).



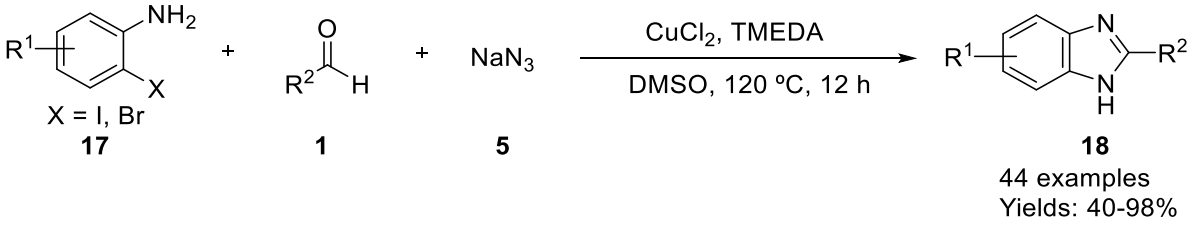
Scheme 2.2B.6 Stepwise mechanism for copper-catalyzed synthesis of quinazolin-4(3*H*)-ones

Alla group accomplished copper–catalyzed one-pot reaction of 2-bromophenylquinazolin-4(*3H*)-ones (**15**), aldehyde (**1**) and sodium azide (**5**) for the synthesis of quinazolino[4,3-*b*]quinazoline derivatives (**16**) (**Scheme 2.2B.7**).[29] The reaction mechanism includes reductive amination followed by condensation with the aldehyde and an oxidative cyclization to afford the target compounds in moderate to good yields (43-80%).



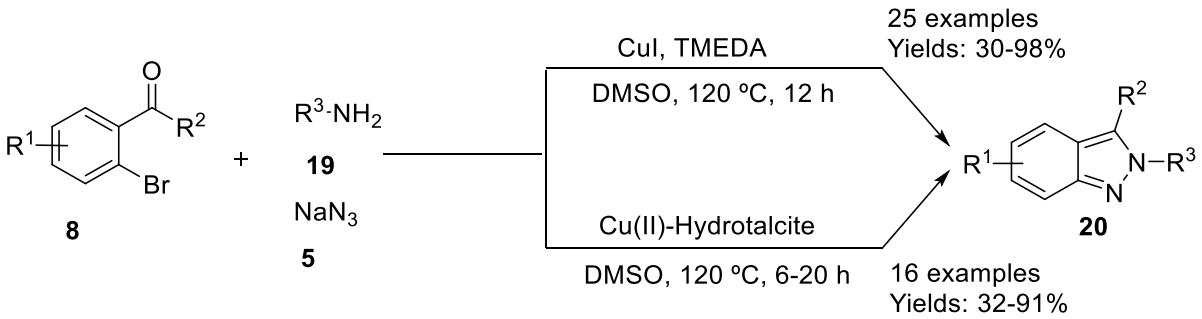
Scheme 2.2B.7 Copper–catalyzed formation of quinazolino[4,3-*b*]quinazoline derivatives from 2-bromophenylquinazolin-4(*3H*)-ones

Lee and coworkers achieved one–pot multi-component process for the synthesis of benzimidazole derivatives (**18**) from *o*-haloanilines (**17**), aldehydes (**1**) and sodium azide (**5**) in the presence of TEMDA at 120 °C for 12 h (**Scheme 2.2B.8**).[30] Aromatic, heteroaromatic and aliphatic aldehydes were participated well and gave respective benzimidazoles in moderate to excellent yields (40-98%).



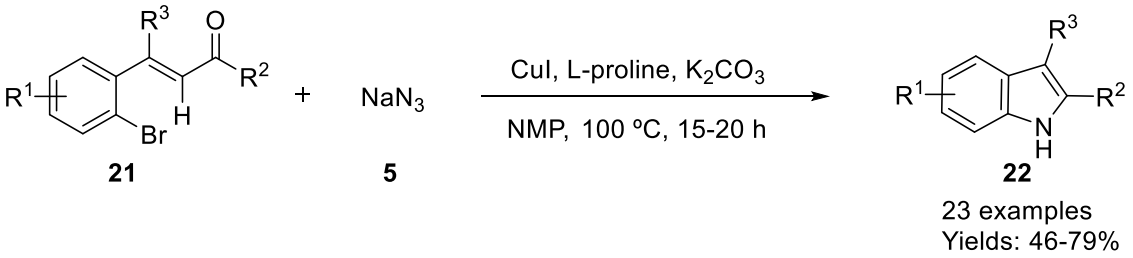
Scheme 2.2B.8 Copper-catalyzed synthesis of benzimidazole derivatives from *o*-haloanilines

Lee and Reddy group developed indazole (**20**) derivatives through copper–catalyzed multi component reaction of 2-bromobenzaldehydes (**8**), amines (**19**), and sodium azide (**5**) (**Scheme 2.2B.9**). [31,32]



Scheme 2.2B.9 Synthesis of indazoles through Cu–catalyzed multi–component reaction

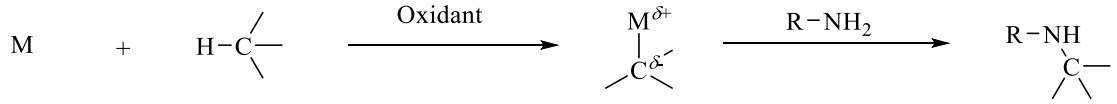
Goriya *et al.* achieved copper–catalyzed one-pot tandem approach for the synthesis of substituted indoles derivatives (**22**) from 2-bromochalcones (**21**) and sodium azide (**5**) (**Scheme 2.2B.10**).[33] The mechanism of this reaction was completed in three steps *i.e.* (a) nucleophilic aromatic substitution reaction with azide (b) conversion of azide to reactive nitrene intermediate (c) intramolecular C–N bond formation.



Scheme 2.2B.10 Copper–catalyzed synthesis of functionalized indoles from 2-bromochalcones

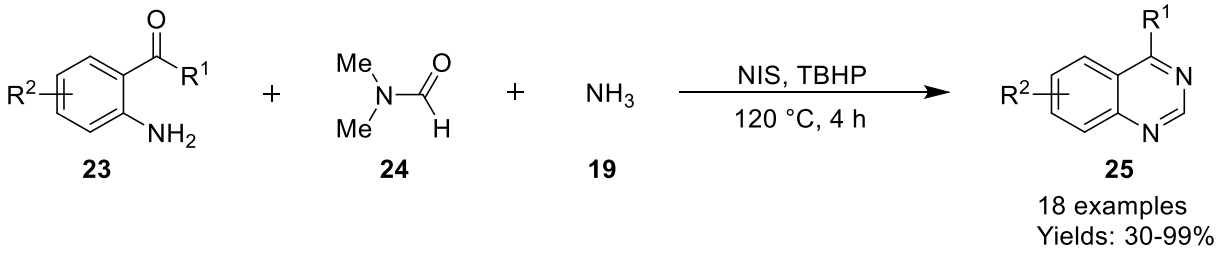
2.2B.2 Oxidative amination

Oxidative amination has been reported by Fritz Ullmann which opened a new window for organic chemist for the development of heterocycles. Further, Buchwald and Hartwig independently developed a modern approach for the synthesis of C(sp^2)–N bond, which is known as Buchwald–Hartwig reaction (**Scheme 2.2B.11**).[17]



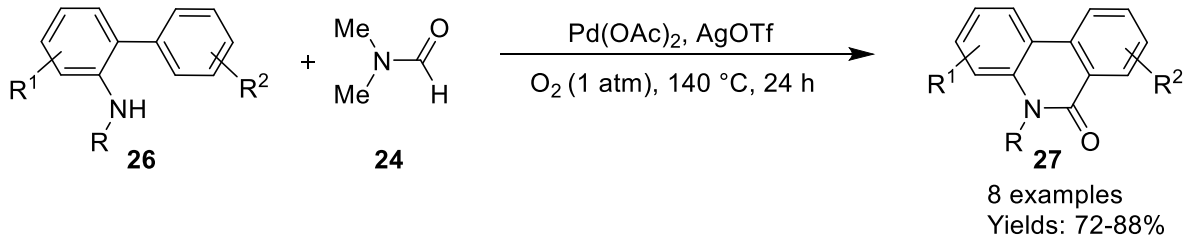
Scheme 2.2B.11 Oxidative amination through cross–dehydrogenative couplings

Wang and co-workers developed facile and efficient iodine–catalyzed tandem method for the synthesis of quinazolines (**25**) by the reaction of orthocarbonyl-substituted anilines (**23**), ammonia (**19**) as a nitrogen source and DMF (*N*,*N*-dimethyl formamide) (**24**) as a one carbon synthon (**Scheme 2.2B.12)**.[34] The reaction mechanism involved oxidative amination of C(sp^3)–H bond followed by intramolecular C-N bond formation lead to quinazoline products. The scope of this annulation reaction was explored using a diverse range of carbon source as well as substituted orthocarbonyl anilines.



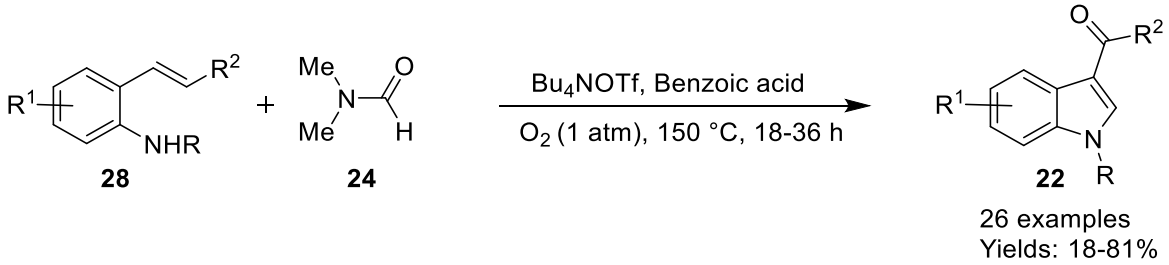
Scheme 2.2B.12 Iodine–catalyzed tandem method for the synthesis of quinazolines from orthocarbonyl-substituted anilines

Das group synthesized Pd/Ag catalyzed pyrido–fused phenanthridinone (**27**) scaffolds *via* direct carbonylation of C(sp^2)−H bonds utilizing DMF (**24**) as the carbon source under oxygen from *N*-alkyl-[1,1'-biphenyl]-2-amine (**26**) derivatives (**Scheme 2.2B.13**).[9]



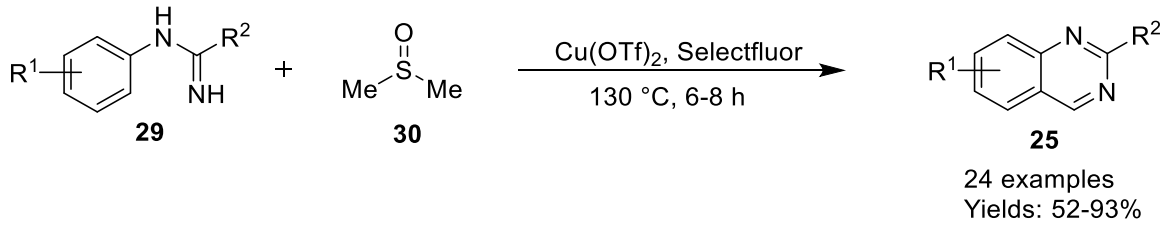
Scheme 2.2B.13 Pd/Ag–catalyzed pyrido–fused quinazolinone and phenanthridinone

Very recently, Deng group described metal free one-pot cascade reaction for the synthesis of 3-acylindoles (**22**) from 2-alkenylanilines (**28**) with DMF (*N*,*N*-dimethylformamide) (**24**) as a one–carbon synthon and dioxygen used as terminal oxidant as well as oxygen donor (**Scheme 2.2B.14**).[35] This reaction involved cascade C–N, C–C and C–O multiple bond formation leading 3-acyl indole in lower to excellent yields (18-81%) under optimized condition.



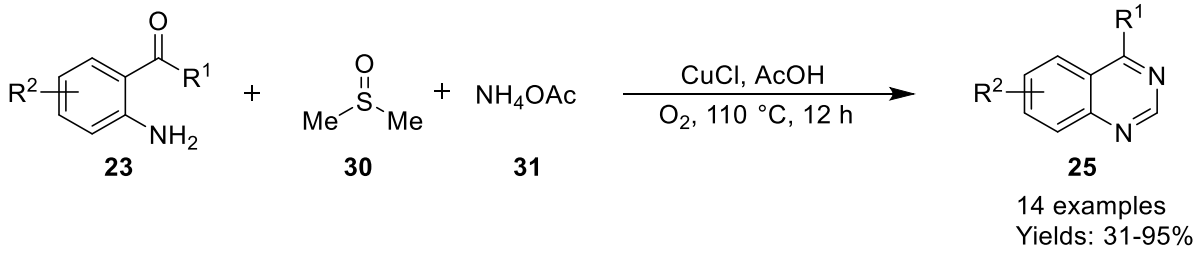
Scheme 2.2B.14 Synthesis of 3-acylindoles from 2- alkenylanilines with DMF

Lv *et al.* successfully, developed an efficient copper-catalyzed one-pot reaction for the synthesis of quinazolines (**25**) from amidines (**26**) and DMSO (**27**) through oxidative amination of C(sp^3)–H bond with N–H bond by intramolecular C–C bond formation reactions (**Scheme 2.2B.15**)[36]. The scope of this reaction was explored by delivering a range of quinazolines product with good to excellent yields (52-93%) from readily available amidine and different carbon sources like DMF, DMA, NMP, and TMEDA.



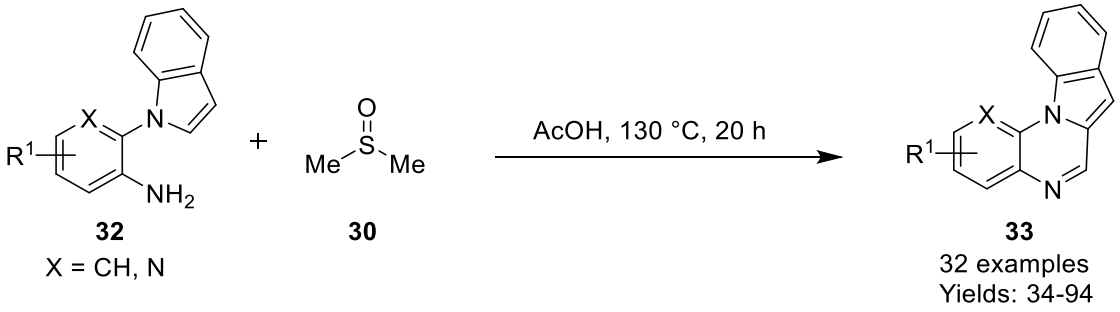
Scheme 2.2B.15 Copper-catalyzed synthesis of quinazolines from amidines and DMSO

Ma group reported a one–pot three-component synthesis of quinazolines (**25**) from ortho– carbonyl anilines (**23**) *via* CuCl–catalyzed oxidative amination reaction using NH_4OAc (**31**) as a nitrogen source and DMSO (**30**) as a carbon source (**Scheme 2.2B.16**).[37] The developed protocol tolerated well with a different substituent on ortho–carbonyl anilines (**23**) and afforded respective products in moderate to excellent yields (31-95%).



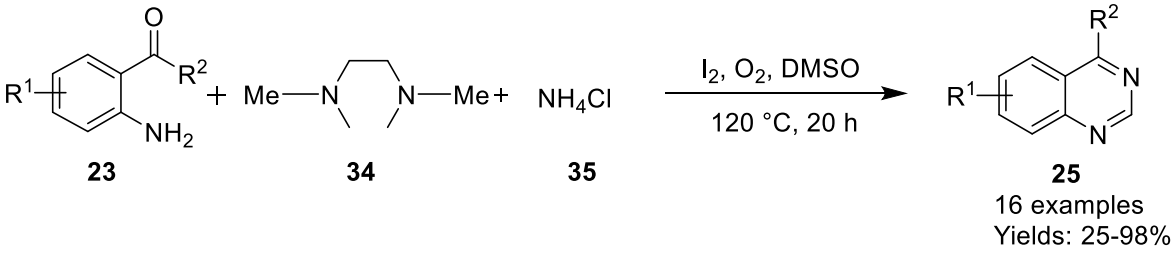
Scheme 2.2B.16 Copper-catalyzed synthesis of quinazolines from ortho– carbonyl anilines

Ma group has developed an efficient, green and novel method for the development of fused quinoxalines (**33**) from substituted 2-(1*H*-pyrrol-1-yl)aniline (**32**) and DMSO (**30**) under acidic condition (**Scheme 2.2B.17**).[38] A variety of products, including pyrrolo[1,2-*a*]quinoxalines, indolo[1,2-*a*]quinoxalines, 1*H*-pyrrolo[3,2-*c*]quinolines, and benzo[4,5]imidazo[1,2-*c*]quinazolines were observed with good to excellent yields (34-94%) under optimized condition.



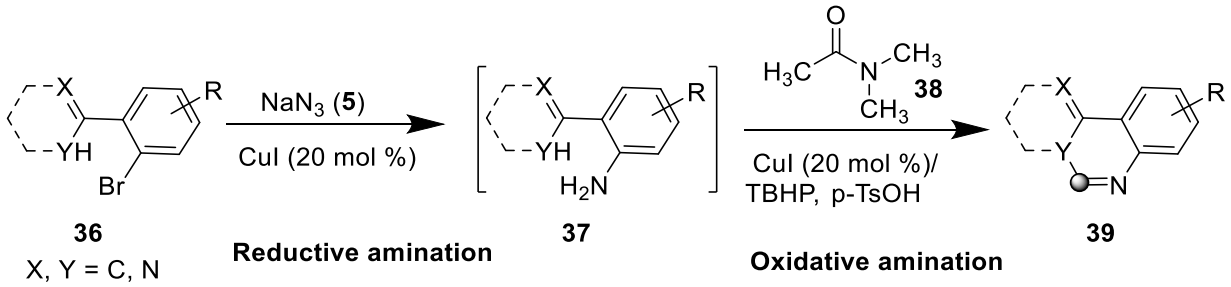
Scheme 2.2B.17 Synthesis of quinoxalines from 2-(1*H*-pyrrol-1-yl)aniline and DMSO

Liu and his colleagues described an efficient, atom–economy, eco–friendly, and metal–free domino strategy for the construction of highly functionalized quinazolines (**25**) derivatives through one-pot reaction of 2-aminobenzophenone (**23**) derivatives and TMEDA (**34**) by using iodine as a catalyst (**Scheme 2. 2B.18**).[39] The reaction involved two C–N bond formation in one–pot fashion and afforded corresponding quinazoline derivatives.



Scheme 2.2B.18 Synthesis of quinazolines from 2-aminobenzophenone and TMEDA

In last decade, several reports have been developed for the synthesis of fused heterocyclic compounds by using different carbon source and sodium azide as one nitrogen source, but still there is a gap to design a new approach for the synthesis of fused quinazolines by using NaN_3 as a nitrogen source and DMA as one carbon synthon. In continuation of our work for the development of fused quinazoline. This chapter described a copper-catalyzed reductive amination of aryl halides with sodium azide[18] followed by oxidative amination of C(sp^3)–H bond of DMA for the synthesis of imidazo[1,2-*c*]quinazolines, quinazolinones and quinolines through one-pot tandem multicomponent reaction (**Scheme 2. 2B.19**).



Scheme 2.2B.19 Synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines

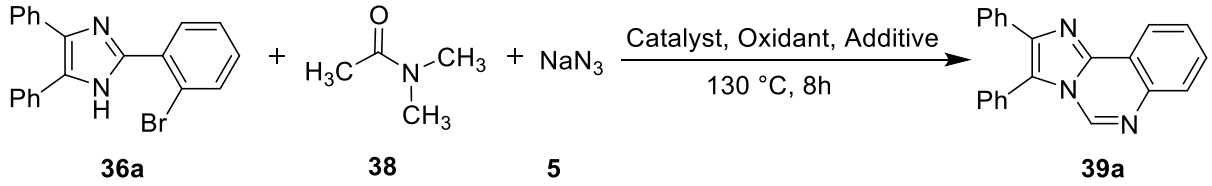
2.2B.2 RESULTS AND DISUSSION

To realize the feasibility of our envisioned methodology, reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**36a**) was performed with DMA (**38**) and sodium azide (**5**) in the presence of 20 mol % CuI and *p*-toluenesulfonic acid (p-TsOH) at 130 ºC in the air. To our satisfaction the desired 2,3-diphenylimidazo[1,2-*c*]quinazoline (**39a**) was obtained in 41% yield (**Table 2.2B.1**, entry 1). The structure of **39a** was confirmed by NMR (^{1}H and ^{13}C) and mass spectrometry data. In the ^{1}H NMR spectrum, a characteristic singlet at 8.72 ppm was observed for C-5 proton along with expected peaks for other protons. The peaks in the ^{13}C NMR spectrum were also in accordance with the structure of **39a**. The NMR and HRMS spectra of **39a** has already been discussed in the previous chapter.

Encouraged by the result of the model reaction, we performed a series of experiments by varying different catalysts, oxidants, and additives to optimize the reaction conditions. The results of various optimization experiments are summarized in **Table 2.2B.1**. Firstly, screening of copper catalysts such as CuI, $CuCl_2$, and $Cu(OAc)_2.H_2O$ revealed that CuI was best suited for this transformation giving 41% yield of **39a** (**Table 2.2B.1**, entries 1-3). Significant improvement in the yield of **39a** was observed by adding oxidants such as $K_2S_2O_8$, IBD, and TBHP along with CuI and *p*-TsOH (**Table 2.2B.1**, entries 4-6). However, the use of DDQ proved to be insignificant (**Table 2.2B.1**, entries 7). Best yield (82%) of **39a** was obtained by using TBHP as oxidant along with CuI (20 mol %) and *p*-TsOH (1 equiv.) (**Table 2.2B.1**, entry 6).

Subsequently, the effect of catalyst amount was investigated by increasing the loading of CuI from 10 mol % to 30 mol % and found that 20 mol % was optimum amount for the catalysts for this transformation (**Table 2.2B.2**, entries 6, 8 and 9). Changing acidic additive with $BF_3.OEt_2$, CH_3COOH (AcOH), and CF_3SO_3H (TfOH) did not improve the yield of **39a** albeit gave slightly lower yield than that of *p*-TsOH (**Table 2.2B.2**, entries 6, 10-12). It is worth mentioning that the targeted product **39a** was observed in a trace amount in the absence of an acidic additive (**Table 2.2B.2**, entry 13) and no product formation was observed in the absence of copper salt (**Table 2.2B.2**, entries 14-15).

Table 2.2B.1 Optimization of the reaction conditions.[a]



36a **38** **5** **39a**

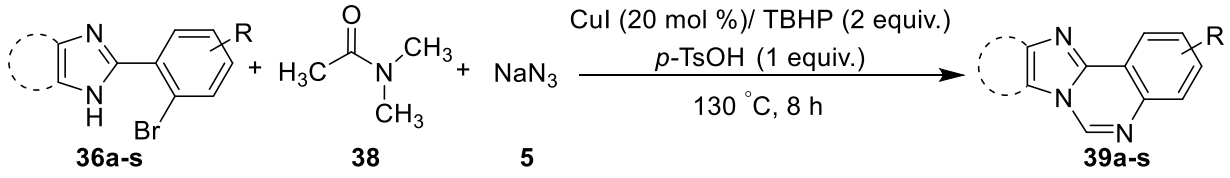
Entry	Catalyst (mol %)	Oxidant	Additive	Yield (%)[b]
1	CuI (20)	-	TsOH	41
2	$CuCl_2$ (20)	-	TsOH	30
3	$Cu(OAc)_2$ (20)	-	TsOH	35
4	CuI (20)	$K_2S_2O_8$	TsOH	65
5	CuI (20)	IBD	TsOH	60
6	CuI (20)	TBHP	TsOH	82
7	CuI (20)	DDQ	TsOH	10
8	CuI (10)	TBHP	TsOH	55
9	CuI (30)	TBHP	TsOH	80
10	CuI (20)	TBHP	$BF_3.Et_2O$	63
11	CuI (20)	TBHP	AcOH	65
12	CuI (20)	TBHP	TfOH	77
13	CuI (20)	TBHP	-	trace
14	KI (20)	TBHP	TsOH	NR[c]
15	-	TBHP	TsOH	NR[c]

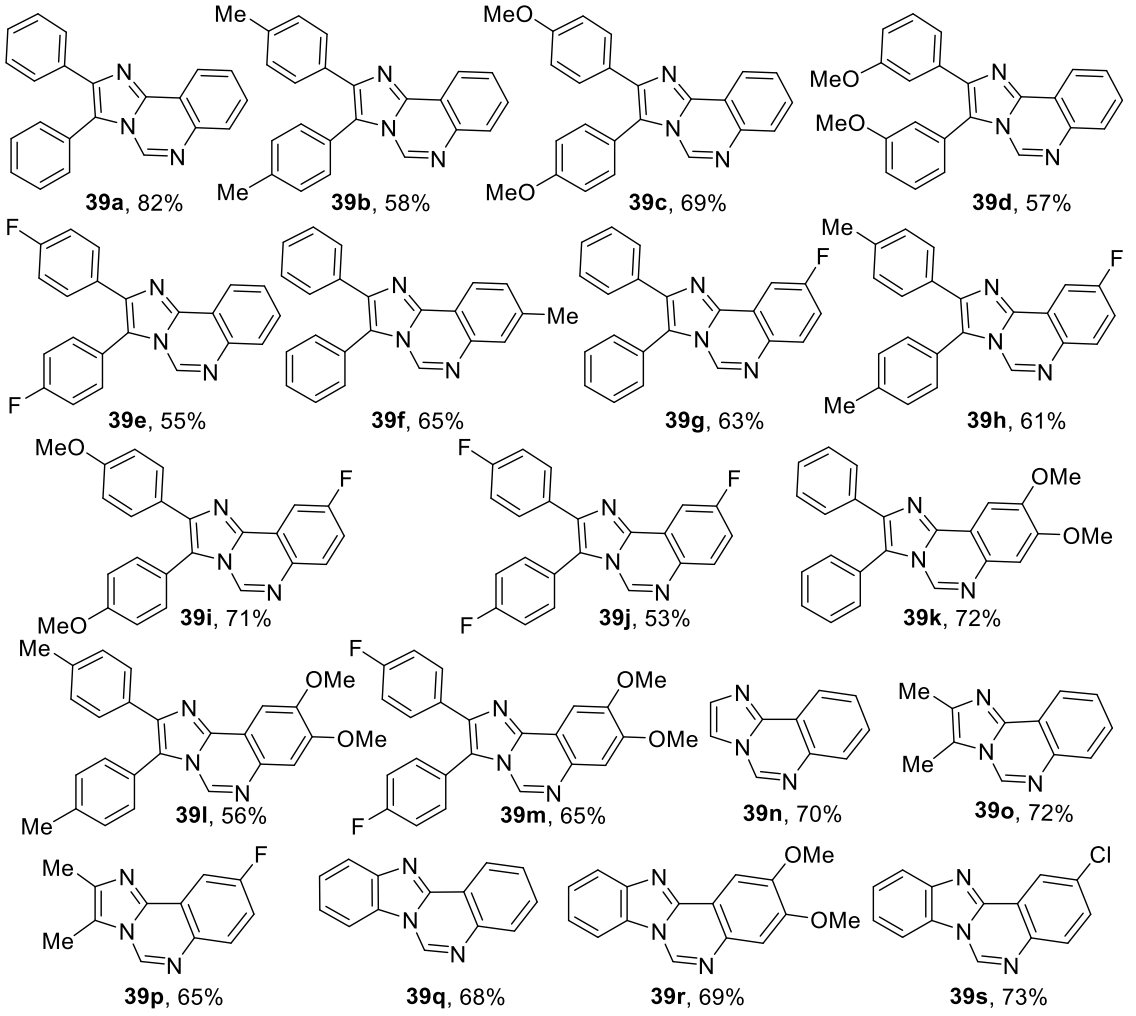
[a]Reaction conditions: **36a** (0.27 mmol), **38** (2.0 ml), NaN_3 (0.54 mmol), catalyst (0.054 mmol), oxidant (0.54 mmol), additive (0.27 mmol), 130 °C, 8 h. [b]Isolated yields. [c]NR = no reaction.

Having optimal condition in hand, we next investigated the scope of this process by reacting a series of 2-(2-bromophenyl)-1*H* imidazoles. As shown in **table 2.2B.2**, the developed method worked very well with 4,5-diaryl-2-(2-bromoaryl)-1*H*-imidazoles with different substituents such as fluoro, methyl, methoxy on aryl rings at C2-, C4- and C5-positions of imidazole to give corresponding imidazo[1,2-*c*]quinazolines **(39a-m)** in moderate to good yields (53-82%). Different substituents on aryl rings at C2-, C4- and C5-position of imidazole did not have a significant effect on the yield of the reaction. The reaction also worked well with 2-(2-

bromophenyl)-1*H*-imidazole (**36n**) and 2-(2-bromophenyl)-4,5-dimethyl-1*H*-imidazoles (**36o** and **36p**) to give corresponding imidazo[1,2-*c*]quinazolines **39n, 39o** and **39p** in 70, 72 and 65% yields, respectively. Similarly, reaction of different substituted 2-(2-bromophenyl)-*1H*-benzo[*d*]imidazoles (**36q-s**) gave corresponding benzo[4,5]imidazo[1,2-*c*]quinazolines (**39q-s**) in good yields (68-73%).

Table 2.2B.2 Substrate scope for the synthesis of imidazo[1,2-*c*]quinazolines[a,b]

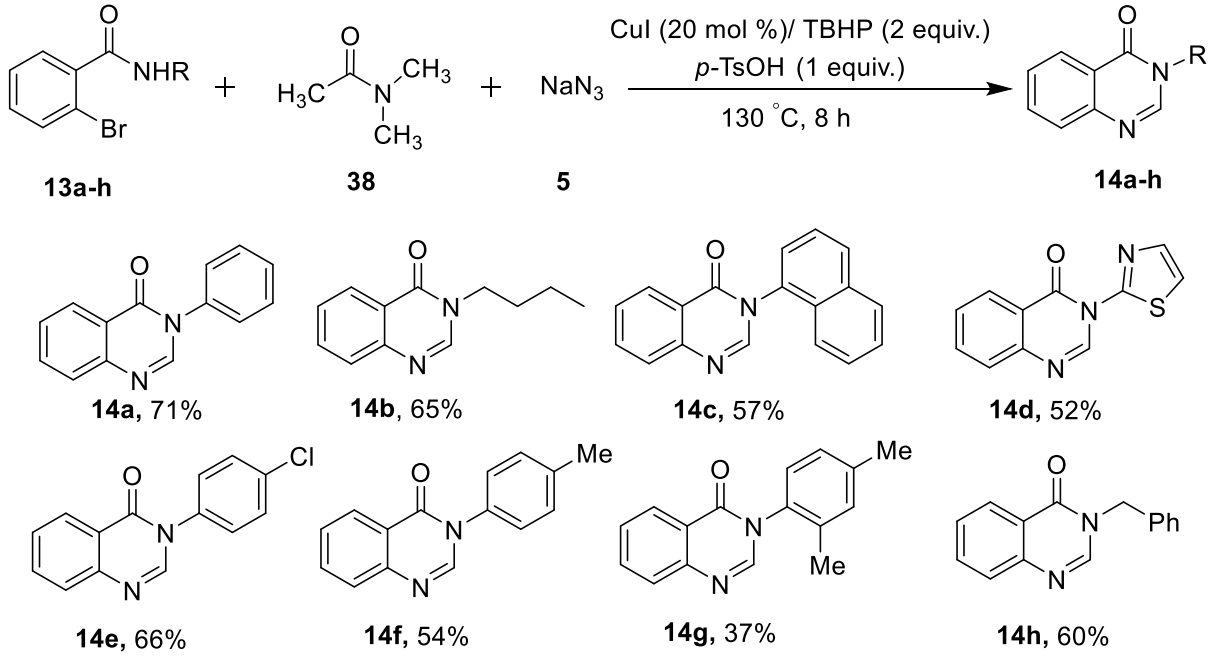




[a]Reaction conditions: **36** (0.27 mmol), **38** (2.0 mL), NaN_3 (0.54 mmol), CuI (0.054 mmol), TBHP (0.54 mmol), *p*-TsOH (0.27 mmol), 130 °C, 8 h. [b]Isolated yields.

Next, we were interested in applying this methodology for the synthesis of 3-unsubstituted quinazolin-4(3*H*)-ones (**14**). To our immense gratification, the reaction of 2-bromobenzamide (**13a**) with DMA (**14**) and NaN_3 (**5**) under the optimized conditions gave quinazolin-4(3*H*)-one (**14a**) in 71% yield. The substrate scope of this reaction was demonstrated by using *N*-substituted 2-bromobenzamides (**13a-h**) to give corresponding quinazolin-4(3*H*)-one (**14a-h**) in moderate to good (37-71%) yields (**Table 2.2B.3**).

Table 2.2B.3 Substrate scope for the synthesis of quinazolin-4(3*H*)-one [a,b]



[a]Reaction conditions: **13** (0.27 mmol), **38** (2.0 mL), NaN_3 (0.54 mmol), CuI (0.054 mmol), TBHP (0.54 mmol), *p*-TsOH (0.27 mmol), 130 °C, 10 h. [b]Isolated yields.

The structure of **14a** was confirmed by NMR (^1H and ^{13}C) and mass spectrometry data. In the ^1H NMR spectrum, a characteristic singlet at 8.15 ppm was observed for C-2 proton along with expected peaks for other protons. The peaks in the ^{13}C NMR spectrum were also in accordance with the structure of **14a (Figure 2.2B.1)**. Finally, the presence of a peak at *m/z* 223.0870 in the HRMS corresponding to molecular ion $C_{14}H_{11}N_2O^+$ $[M+H]^+$ confirmed the structure of **14a.**

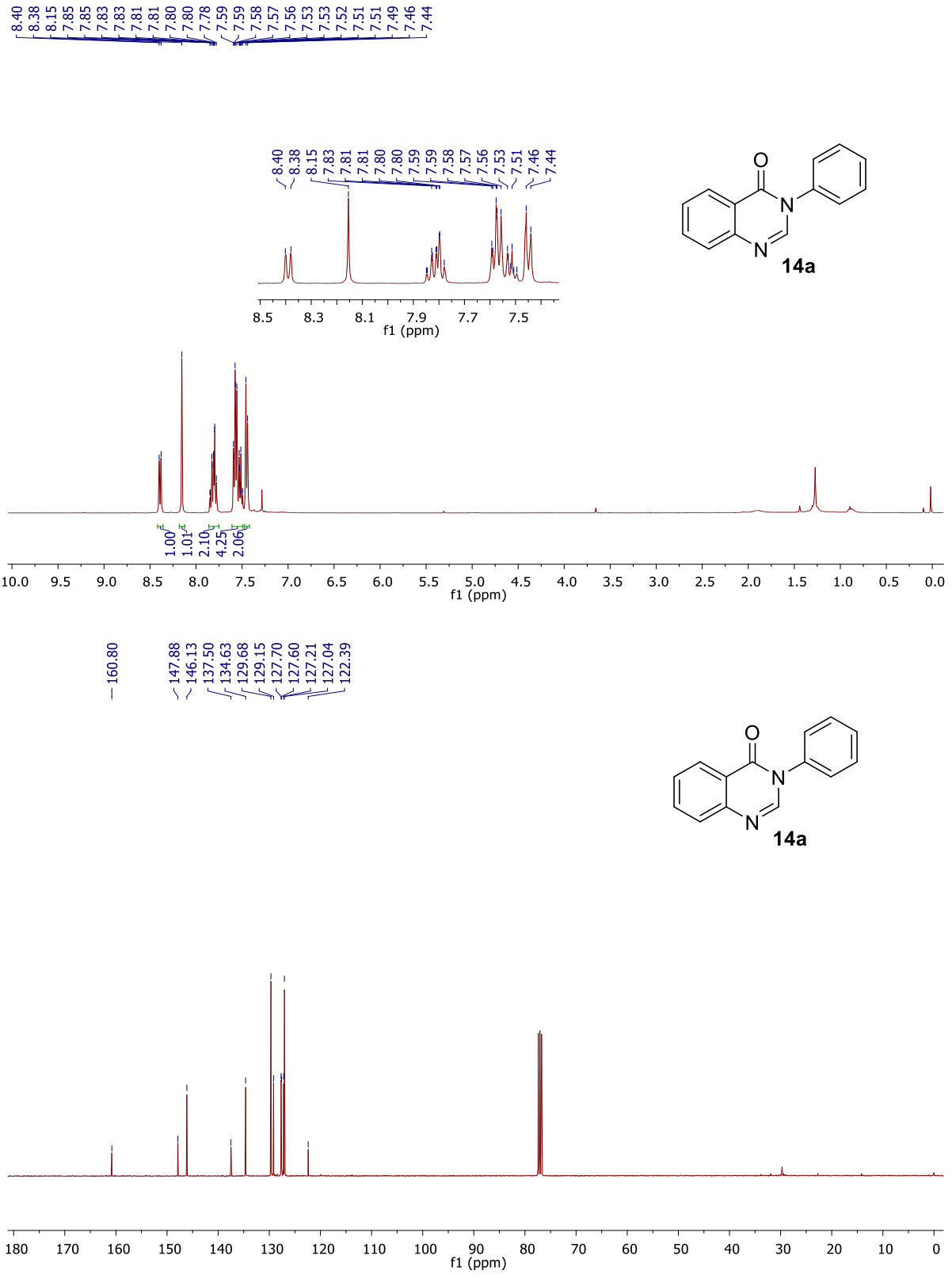
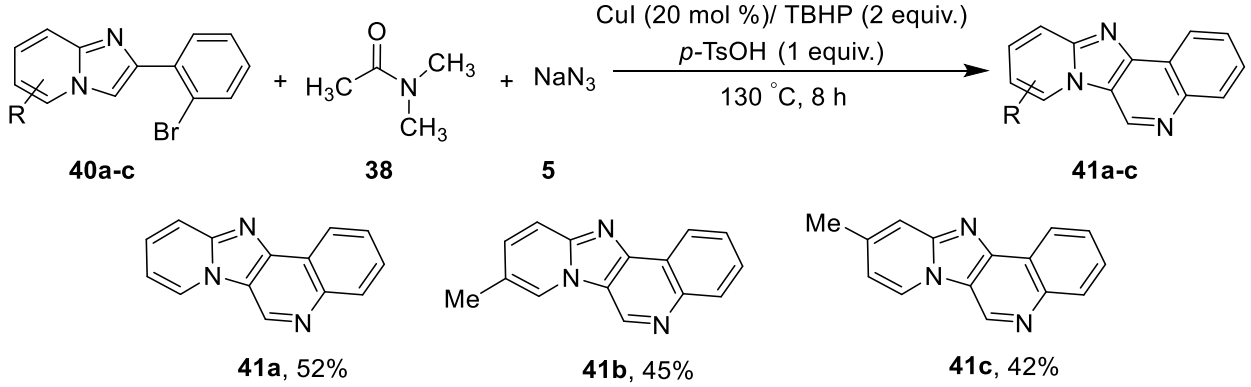


Figure 2.2B.1 ^{1}H and ^{13}C NMR spectra of 3-phenylquinazolin-4(3*H*)-one (**14a**) in $CDCl_3$

To further extend the scope of the process, synthesis of imidazo[4,5-*c*]quinoline derivative (**41**) was attempted by reacting 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**40a**) with DMA (**38**) and NaN_3 (**5**) under the optimized conditions. As expected, pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (**41a**) was obtained in 52% yield. Importantly, this reaction involves the formation of C–N and C–C bond formation in the cyclization step. Different functional group on imidazopridyl ring were tolerated to give corresponding imidazo[4,5-*c*]quinolones (**41b-c**) in good (42-45%) yields (**Table 2.2B.4**).

Table 2.2B.4 Substrate scope for the synthesis of imidazo[4,5-*c*]quinolines[a,b]



[a]Reaction conditions: **40** (0.27 mmol), **38** (2.0 mL), NaN_3 (0.54 mmol), CuI (0.054 mmol), TBHP (0.54 mmol), *p*-TsOH (0.27 mmol), 130 °C, 8 h. [b]Isolated yields.

The structure of **41a** was confirmed by NMR (^1H and ^{13}C) and mass spectrometry data. In the ^1H NMR spectrum, a characteristic singlet at 9.77 ppm was observed along with expected peaks for other protons. The peaks in the ^{13}C NMR spectrum were also in accordance with the structure of **41a (Figure 2.2B.2)**. Finally, the presence of a peak at *m/z* 220.0876 in the HRMS corresponding to molecular ion $C_{14}H_{10}N_3^+$ $[M+H]^+$ confirmed the structure of **41a.**

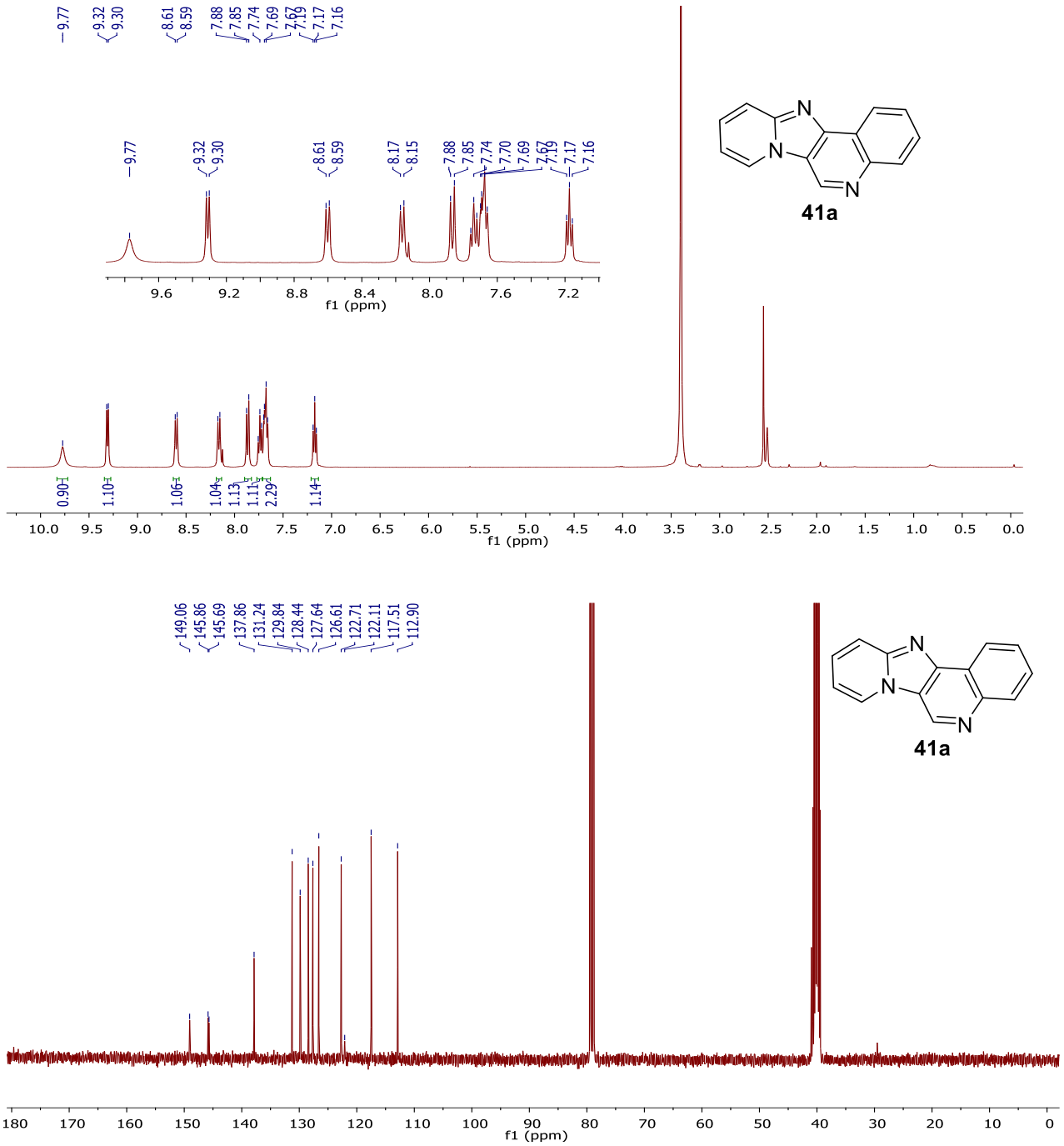
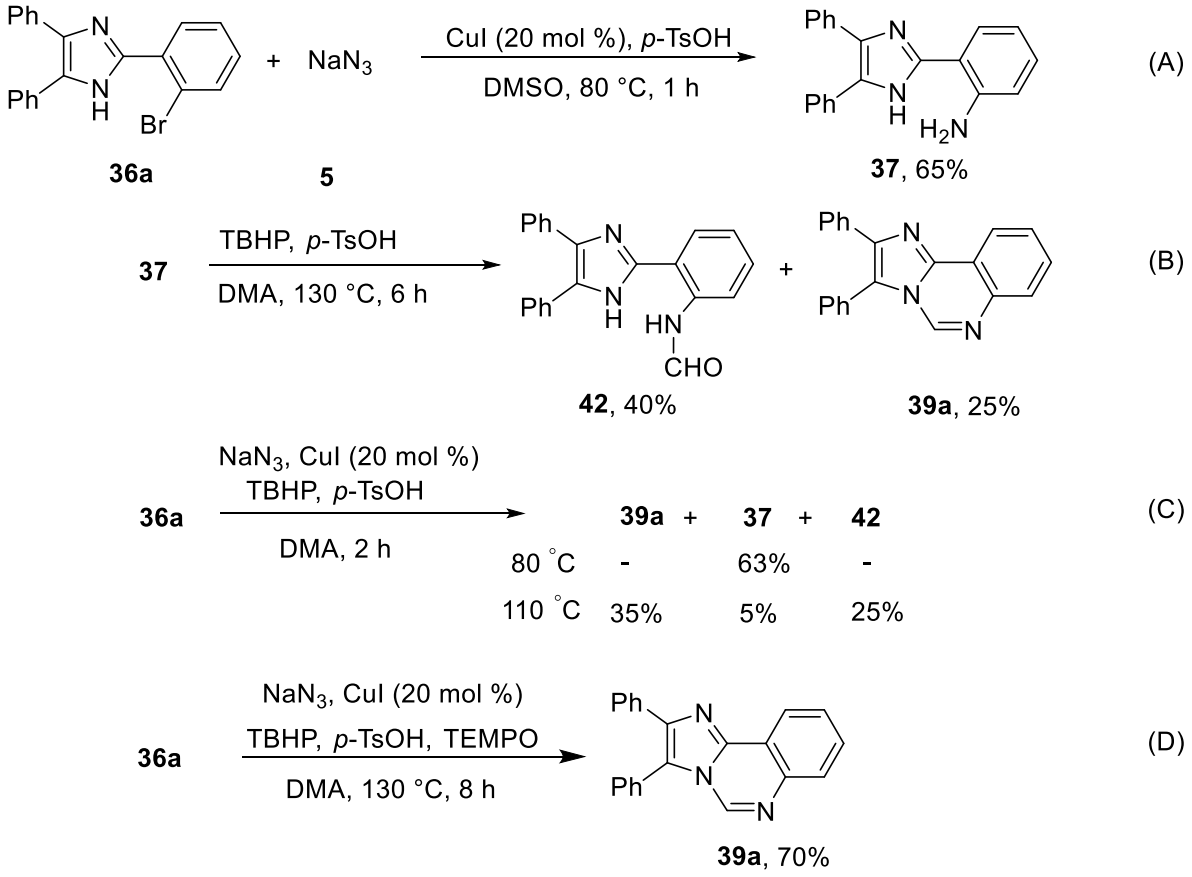


Figure 2.2B.2 ^{1}H and ^{13}C NMR spectra pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (**41a**) in DMSO

To gain insight into the mechanism of the reaction, a series of control experiments were performed (**Scheme 2.2B.20**). Reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**36a**) with sodium azide (**5**) in the presence of CuI, *p*-TsOH in DMA at 80 °C for 1 h provided 2-(2-aminophenyl)-4,5-diphenyl-*1H*-imidazole (**37**) in 65% yield (**Scheme 2.2B.20A**). Further treating **5** with DMA

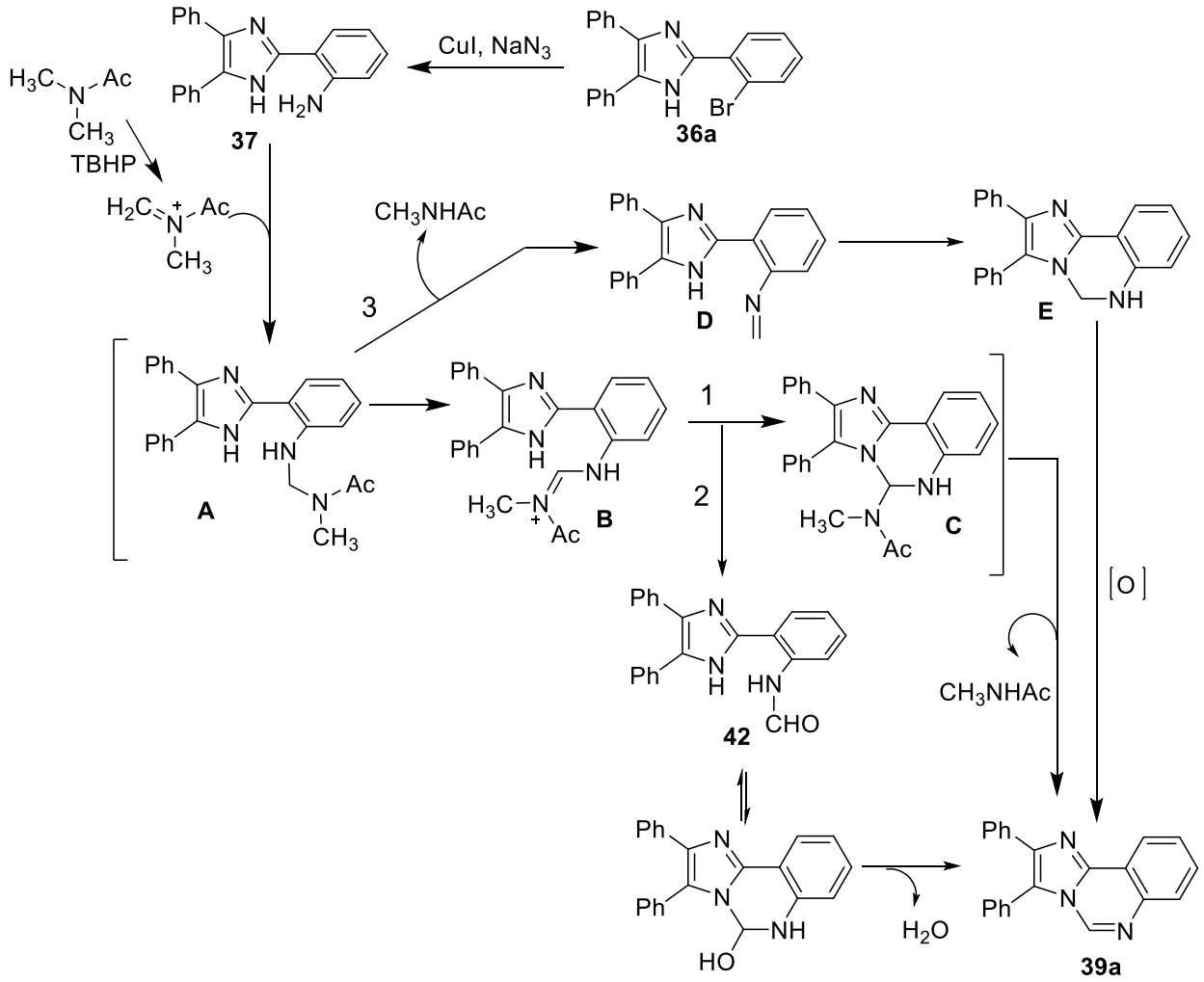
in the presence of TBHP for 5 h at 130 °C, **39a** was obtained in 25% along with 40% of *N*-formylated intermediate **42** (**Scheme 2.2B.20B**). This result showed that **42** might be an intermediate in this transformation. When the model reaction was performed at 80 °C only **37** was formed in 63% yield but on increasing reaction temperature to 110 °C **39a** was obtained in 35% yield along with **37** and **42** in 5% and 25% yields, respectively (**Scheme 2.2B.20C**). The model reaction in the presence of a radical scavenger TEMPO (2 equiv.) also resulted in the formation of **39a** in 70% yield suggesting that reaction mechanism does not involve free radical pathway (**Scheme 2.2B.20D**). Use of DMF and DMSO instead of DMA as carbon source gave **39a** in 63% and 35% yields, respectively whereas no product was formed when toluene was used instead of DMA.



Scheme 2.2B.20 Control experiments to propose a mechanism

Based on the control experiment results and literature reports, a proposed mechanism for the tandem reaction is shown in **Scheme 2.2B.21**. Initially, copper-catalyzed reductive amination of **36a** using sodium azide produces 2-(2-aminophenyl)-4,5-diphenyl-1*H*-imidazole (**37).** This is in

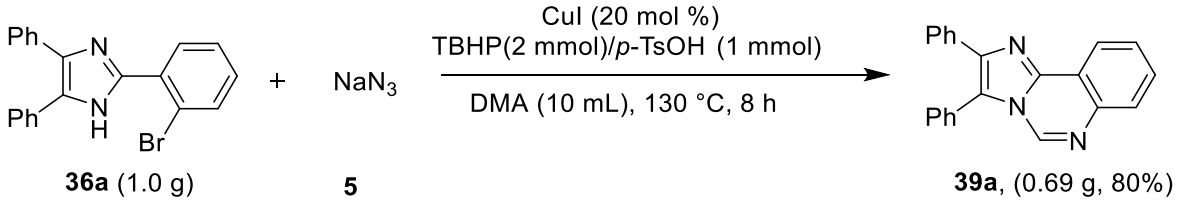
accordance with earlier reports wherein sodium azide/$TMSN_3$ has been used as ammonia surrogate to prepare primary amines and nitrogen-containing heterocycles in a copper-catalyzed reductive amination of aryl halides.[18] Subsequently, C-N bond formation *via* cross-dehydrogenative coupling (CDC) reaction[19] of C(sp^3)-H of DMA and N-H of amino group generates intermediate **A** which then oxidizes to cationic intermediate **B** under oxidative conditions. Intermediate **B** can follow two pathways 1) *via* intermediate **C** or 2) *via* intermediate **42** to generate **39a.** Additionally, intermediate **A** can directly form an imine **D** by the loss of CH_3NHAc which then on cyclization can produce intermediate **E** (pathway 3). Oxidation of intermediate **E** can lead to **39a**.



Scheme 2.2B.21 Proposed mechanism of 2,3-diphenylimidazo[1,2-*c*]quinazoline (**39a**)

Finally, to evaluate the efficiency and scope of this tandem reaction at gram scale, the reaction of 1g of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole **(36a)** was performed. Interestingly, 2,3-

diphenylimidazo[1,2-*c*]quinazoline (**39a**) was isolated in 80% yield (0.69 g) in 10 h without compromising the optimized reaction conditions (**Scheme 2.2B.22**).



36a (1.0 g) **5** **39a**, (0.69 g, 80%)

Scheme 2.2B.22 Gram scale synthesis 2,3-diphenylimidazo[1,2-*c*]quinazoline (**39a**)

2.2B.3 CONCLUSIONS

An efficient and straightforward method for the synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines has been disclosed through a tandem multicomponent reaction. The reaction involved sequential azidation through S_NAr, reduction, oxidative amination of C(sp^3)–H bonds of DMA. The method provided a powerful means of using easily available sodium azide as a nitrogen source and DMA as a carbon source for the synthesis of these *N*-fused heterocycles in good to excellent yields and the reaction was amenable for gram scale synthesis.

2.2B.4 EXPERIMENTAL SECTION

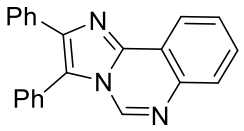
2.2B.4.1 General materials and methods

Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 400 spectrometer. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (TMS) as internal standard. High resolution mass spectra (HRMS-ESI) were carried out using a quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). All chemicals were obtained from the commercial suppliers and were used without further purification.

2.2B.4.2 General procedure for 2,3-diaryldiimidazo[1,2-*a*:1',2'-*c*]quinazoline derivatives: A clean oven dried 10 mL round bottom flask was charged with **36a** (1.0 mmol), DMA (**38**) (2.0 mL), NaN_3 (**5**) (2 mmol), TBHP (2.0 mmol), *p*-TsOH (1.0 mmol) and CuI (0.20 mmol). The

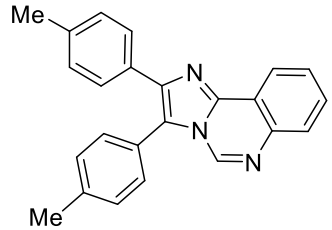
reaction mixture was heated with stirring at 130 °C under air atmosphere for 8 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool to ambient temperature, diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Desired product **39a** (70 mg, 82%) was isolated by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (10-20%) as eluent.

2,3-Diphenylimidazo[1,2-*c*]quinazoline (39a). Yield 82%, Brown solid, mp 175 – 177 °C; ^{1}H



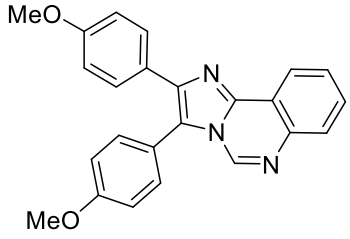
NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.69 – 8.66 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.77 – 7.69 (m, 4H), 7.61 – 7.52 (m, 5H), 7.36 – 7.30 (m, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 142.4, 141.8, 141.1, 135.6, 133.4, 130.7, 130.0, 129.7, 129.4, 128.6, 128.5, 128.4, 128.3, 128.1,127.9, 123.0, 121.5, 119.4; HRMS (ESI) calcd for $C_{22}H_{16}N_3$ [M+H$^+$] 322.1339 found 322.1344.

2,3-Di-*p*-tolylimidazo[1,2-*c*]quinzoline (39b). Yield 58%, Off-white solid, mp 188 – 190 °C; ^{1}H



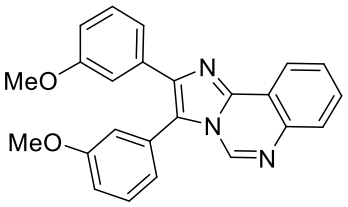
NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.69 –8.68 (m, 1H), 7.97 – 7.95 (m, 1H), 7.72 – 7.69 (m, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.43 – 7.37 (m, 4H), 7.16 (d, J = 8.0 Hz, 2H), 2.50 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.7, 141.1, 139.4, 137.6, 135.7, 130.6, 130.6, 130.4, 129.9, 129.1, 128.5, 128.3, 127.9, 125.5, 122.9, 121.2, 119.4, 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3$ [M+H$^+$] 350.1652 found 350.1655.

2,3-Bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline (39c). Yield 69%, Off-white solid, mp 195



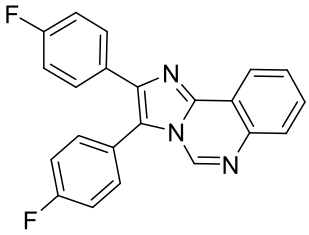
– 196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.67 – 8.66 (m, 1H), 7.96 – 7.94 (m, 1H), 7.72 – 7.66 (m, 4H), 7.45 (d, J = 8.7 Hz, 2H), 7.10 (d, J =8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.93 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.3, 142.0, 141.4, 141.1, 135.7, 132.1, 129.9, 129.2, 128.5, 128.3, 126.1, 122.9, 120.5, 120.4, 119.3, 115.2, 113.9, 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ [M+H$^+$] 382.1550 found 382.1556.

2,3-Bis(3-methoxyphenyl)imidazo[1,2-*c*]quinazoline (39d). Yield 57%, Off-white solid, mp



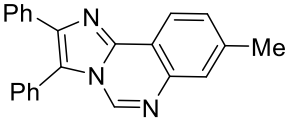
160 – 162 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.75 (s, 1H), 8.54 (m, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.79 – 7.76 (m, 2H), 7.56 – 7.52 (m, 1H), 7.27 – 7.17 (m, 4H), 7.19 – 7.15 (m, 2H), 6.88 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 160.4, 159.6, 141.6, 141.1, 140.4, 137.0, 135.1, 131.2, 130.8, 130.0, 129.8, 129.2, 128.6, 123.5, 122.8, 122.2, 120.3, 119.1, 116.5, 115.8, 113.9, 113.3, 55.8, 55.3; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ [M+H$^+$] 382.1550 found 382.1543.

2,3-Bis(4-fluorophenyl)imidazo[1,2-*c*]quinazoline (39e). Yield 55%, Off-white solid , mp 230



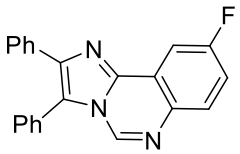
°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.66 – 8.64 (m, 1H), 7.98 – 7.96 (m, 1H), 7.76 – 7.67 (m, 4H), 7.54 – 7.50 (m, 2H), 7.33 – 7.28 (m, 2H), 7.04 (t, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 250.8 Hz), 162.6 (d, J = 247.8 Hz), 142.4, 141.1, 135.2, 132.7 (d, J = 8.4 Hz), 130.3, 129.8 (d, J = 8.1 Hz), 129.4 (d, J = 3.2 Hz), 128.7, 128.4, 124.3 (d, J = 3.5 Hz), 122.9, 120.1, 119.2, 117.1 (d, J = 21.8 Hz), 115.5 (d, J = 21.5 Hz); HRMS (ESI) calcd for $C_{22}H_{14}F_2N_3$ [M+H$^+$] 358.1150 found 358.1153.

8-Methyl-2,3-diphenylimidazo[1,2-*c*]quinazoline (39f). Yield 65%, Brown solid, mp 210 °C; ^{1}H



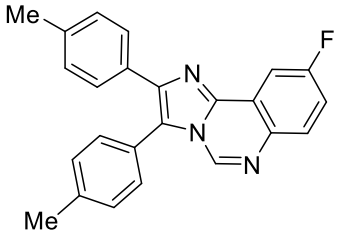
NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.58 (d, J = 8.1 Hz, 1H), 7.77 – 7.73 (m, 3H), 7.58 – 7.53 (m, 5H), 7.36 – 7.28 (m, 4H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.6, 141.3, 140.6, 135.6, 133.5, 130.7, 130.2, 129.6, 129.4, 128.6, 128.4, 128.1, 128.1, 127.8, 122.7, 121.2, 116.9, 21.6; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ [M+H$^+$] 336.1495 found 336.1499.

9-Fluoro-2,3-diphenylimidazo[1,2-*c*]quinazoline (39g). Yield 63%, Brown solid , mp 230 °C;

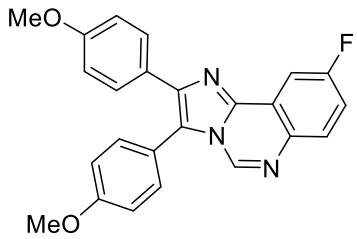


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.32 (dd, J = 8.7, 2.8 Hz, 1H), 7.97 (dd, J = 9.0, 5.1 Hz, 1H), 7.74 – 7.72 (m, 2H), 7.60 – 7.53 (m, 5H), 7.46 – 7.41(m, 1H), 7.36 – 7.31 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 249.7 Hz), 141.7 (d, J = 4.4 Hz), 137.7 (d, J = 1.9 Hz), 134.9 (d, J = 2.5 Hz), 133.2, 130.8 (d, J = 9.2 Hz), 130.7, 129.7, 129.6, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 121.8, 120.8, 120.7, 118.6 (d, J = 24.3 Hz), 108.1 (d, J = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{15}FN_3$ [M+H$^+$] 340.1245 found 340.1248.

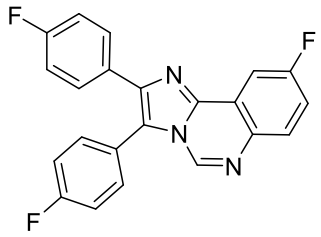
9-Fluoro-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (39h). Yield 46%, Brown solid, mp 235 – 240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.31 (dd, J = 8.6, 2.6 Hz, 1H), 7.96 (dd, J = 8.9, 5.1 Hz, 1H), 7.63 (d, 2H), 7.46 – 7.36 (m, J = 8.1 Hz, 5H), 7.16 (d, J = 7.9 Hz, 2H), 2.51 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J = 249.4 Hz), 141.5 (d, J = 4.2 Hz), 139.6, 137.8, 137.7, 135.0, 135.0, 130.7 (d, J = 9.1 Hz), 130.5, 130.4, 129.2, 127.9, 125.3, 121.5, 120.7 (d, J = 10.5 Hz), 118.5 (d, J = 24.3 Hz), 108.1 (d, J = 24.6 Hz), 21.5, 21.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3$ [M+H$^+$] 368.1558 found 368.1561.



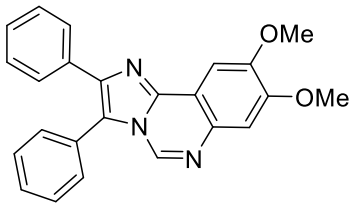
9-Fluoro-2,3-bis(4-methoxyphenyl)imidazo[1,2-*c*]quinazoline (39i). Yield 71%, Off-white solid, mp 218 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.30 (dd, J = 8.7, 2.8 Hz, 1H), 7.95 (dd, J = 9.0, 5.1 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.46 – 7.30 (m, 3H), 7.13 – 7.09 (m, 2H), 6.91 – 6.87 (m, 2H), 3.94 (s, 3H), 3.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, J = 249.3 Hz), 160.4, 159.4, 141.7, 141.4 (d, J = 3.9 Hz), 137.7 (d, J = 1.8 Hz), 135.0 (d, J = 2.5 Hz), 132.1, 130.7 (d, J = 9.2 Hz), 129.2, 125.9, 120.7, 120.7 (d, J = 10.3 Hz), 118.4 (d, J = 24.3 Hz), 120.3, 115.2, 113.9, 108.0 (d, J = 24.5 Hz), 55.4, 55.3; HRMS (ESI) calcd for $C_{24}H_{19}FN_3O_2$ [M+H$^+$] 400.1456 found 400.1461.



8-Fluoro-2,3-bis(4-fluorophenyl)imidazo[1,2-*c*]quinazoline (39j). Yield 53%, Off-white solid, mp 261 – 263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.29 (dd, J = 8.6, 2.8 Hz, 1H), 7.97 (dd, J = 9.0, 5.1 Hz, 1H), 7.70 – 7.65 (m, 2H), 7.51 – 7.49 (m, 2H), 7.47 – 7.42 (m, 1H), 7.33 – 7.28 (m, 2H), 7.07 –7.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J = 251.0 Hz), 162.6 (d, J = 248.1 Hz), 162.0 (d, J = 250.1 Hz), 141.8 (d, J = 4.4 Hz), 141.3, 137.7, 134.5 (d, J = 2.5 Hz), 132.7 (d, J = 8.4 Hz), 130.8 (d, J = 9.2 Hz), 129.8 (d, J = 8.2 Hz), 129.1 (d, J = 3.3 Hz), 124.0 (d, J = 3.6 Hz), 120.5 (d, J = 10.5 Hz), 120.3, 118.8 (d, J = 24.4 Hz), 117.2 (d, J = 21.9 Hz), 115.6 (d, J = 21.6 Hz), 108.1 (d, J = 24.6 Hz); HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ [M+H$^+$] 376.1056 found 376.1062.

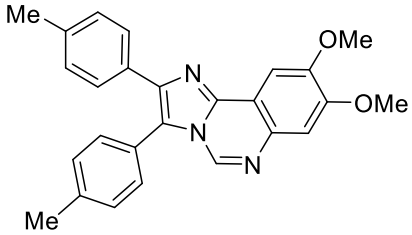


8,9-Dimethoxy-2,3-diphenylimidazo[1,2-*c*]quinazoline (39k). Yield 72%, Off-white solid, mp



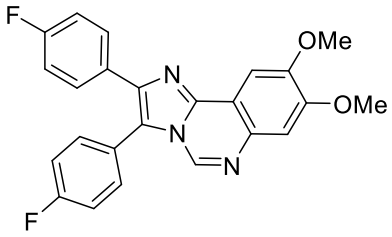
207 – 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.00 (s, 1H), 7.73 – 7.71 (m, 2H), 7.60 – 7.52 (m, 5H), 7.38 – 7.29 (m, 4H), 4.13 (s, 3H), 4.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 150.5, 142.5, 141.7, 136.8, 134.1, 133.6, 130.7, 129.6, 129.3, 128.7, 128.5, 128.2, 127.8, 120.9, 113.3, 108.9, 102.5, 56.6, 56.2; HRMS (ESI) calcd for $C_{24}H_{20}N_3O_2$ [M+H$^+$] 382.1550 found 382.1553.

8,9-Dimethoxy-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (39l). Yield 56%, Greyish solid, mp



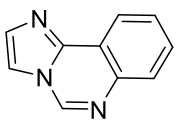
190 – 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.99 (s, 1H), 7.66 – 7.62 (m, 2H), 7.40 – 7.37 (m, 5H), 7.15 – 7.11 (m, 2H), 4.14 (s, 3H), 4.04 (s, 3H), 2.49 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.4, 142.3, 141.5, 139.2, 137.5, 136.7, 134.2, 130.8, 130.6, 130.3, 129.1, 127.0, 125.8, 120.5, 113.3, 108.9, 102.5, 56.6, 56.2, 21.5, 21.3; HRMS (ESI) calcd for $C_{26}H_{24}N_3O_2$ [M+H$^+$] 410.1863 found 410.1867.

2,3-Bis(4-fluorophenyl)-8,9-dimethoxyimidazo[1,2-*c*]quinazoline (39m). Yield 55%, Light



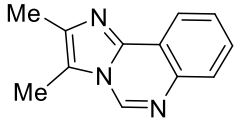
brown solid, mp 255 – 257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.96 (s, 1H), 7.67 (s, 2H), 7.50 (s, 2H), 7.37 (s, 1H), 7.28 (s, 2H), 7.03 (s, 2H), 4.13 (s, 3H), 4.05 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 250.6 Hz), 162.6 (d, J = 248.0 Hz), 151.9, 150.6, 142.5, 141.0, 136.8, 133.8, 132.7 (d, J = 8.3 Hz), 129.8 (d, J = 8.1 Hz), 129.6, 124.5, 119.4, 117.1 (d, J = 21.8 Hz), 115.5 (d, J = 21.5 Hz), 113.1, 108.9, 102.4, 56.5, 56.2; HRMS (ESI) calcd for $C_{24}H_{18}F_2N_3O_2$ [M+H$^+$] 418.1362 found 418.1365.

Imidazo[1,2-*c*]quinazolines (39n). Yield 70%, White solid, mp 132 – 134 ºC; ^{1}H NMR (400



MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.55 (dd, J = 7.7, 1.5 Hz, 1H), 7.99 – 7.95 (m, 1H), 7.75 – 7.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.8, 136.9, 133.0, 130.1, 128.8, 128.4, 122.6, 119.7, 112.0; HRMS calcd for $C_{10}H_8N_3$ [M+H$^+$] 170.1950, found 170.1947.

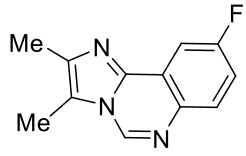
2,3-Dimethylimidazo[1,2-*c*]quinazoline (39o). Yield 70%, Off-white solid, mp 180 – 182 °C; ^{1}H



NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.52 (m, 1H), 7.96 – 7.93 (m, 1H), 7.69 – 7.62 (m, 2H), 2.53 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)

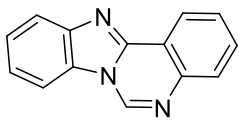
δ 141.4, 140.5, 138.7, 135.1, 129.5, 128.4, 128.2, 122.3, 119.0, 116.1, 13, 8.1; HRMS (ESI) calcd for $C_{12}H_{12}N_3$ [M+H$^+$] 198.1026 found 198.1032.

9-Fluoro-2,3-dimethylimidazo[1,2-*c*]quinazoline (39p). Yield 65%, Brown solid, mp 190 °C;



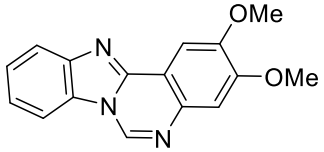
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.10 (dd, J = 8.8, 2.8 Hz, 1H), 7.92 (dd, J = 9.0, 5.1 Hz, 1H), 7.36 (td, J = 8.6, 2.9 Hz, 1H), 2.52 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 249.2 Hz), 140.8 (d, J = 4.4 Hz), 139.1, 137.1, 134.4 (d, J = 2.5 Hz), 130.7 (d, J = 9.2 Hz), 120.3 (d, J = 10.5 Hz), 118.0 (d, J = 24.4 Hz), 116.6, 107.3 (d, J = 24.6 Hz), 13.0, 8.1; HRMS (ESI) calcd for $C_{12}H_{11}FN_3$ [M+H$^+$] 216.0932 found 216.0926.

Benzo[4,5]imidazo[1,2-*c*]quinazolines (39q). Yield 58%, Orange solid, mp 219 – 222 ºC; ^{1}H



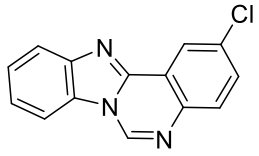
NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.69 (d, J = 7.6 Hz, 1H), 8.06 – 7.96 (m, 3H), 7.81 (t, J = 7.2 Hz, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 143.9, 142.6, 136.1, 131.8, 128.7, 128.5, 128.1, 126.2, 124.2, 123.3, 120.3, 119.3, 110.1; HRMS calcd for $C_{14}H_{10}N_3$ [M+H$^+$] 220.2545, found 220.2549.

2,3-Dimethoxybenzo[4,5]imidazo[1,2-*c*]quinazolines (39r). Yield 57%, Yellow solid; mp 192



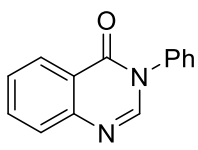
– 195 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.0 7.95 (m, 3H), 7.58 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.41 (s, 1H), 4.12 (s, 3H), 4.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 150.3, 146.4, 144.1, 138.4, 134.8, 128.1, 126.1, 122.6, 119.8, 112.8, 110.1, 109.2, 103.60, 56.6, 56.3; HRMS calcd for $C_{16}H_{14}N_3O_2$ [M+H$^+$] 280.3065, found 280.3063.

2-Chlorobenzo[4,5]imidazo[1,2-*c*]quinazolines (39s). Yield 63%, Off -white solid, mp 258 –



260 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.68 (d, J = 2.1 Hz, 1H), 8.02 (dd, J = 15.4, 8.1 Hz, 2H), 7.94 (d, J = 8.7 Hz, 1H), 7.74 (dd, J = 8.7, 2.2 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 143.9, 140.9, 136.3, 134.6, 132.2, 130.0, 128.1, 126.5, 123.7, 123.7, 120.5, 120.4, 110.2; HRMS calcd for $C_{14}H_9ClN_3$ [M+H$^+$] 254.6995, found 254.6993.

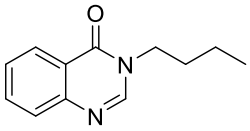
3-Phenylquinazolin-4(3*H*)-one (14a). Yield 71%, Pale yellow solid, mp145 – 148ºC; ^{1}H NMR



(400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.7 Hz, 1H), 8.15 (s, 1H), 7.85 – 7.78 (m, 2H), 7.59 – 7.49 (m, 4H), 7.45 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz,

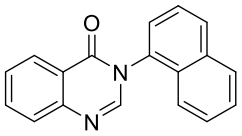
$CDCl_3$) δ 160.8, 147.9, 146.1, 137.5, 134.6, 129.7, 129.1, 127.7, 127.6, 127.2, 127.0, 122.4; HRMS calcd for $C_{14}H_{11}N_2O$ [M+H$^+$] 223.0866, found 223.0870.

3-Butylquinazolin-4(3*H*)-one (14b). Yield 65%, Off-white solid, mp 95 – 98 ºC; ^{1}H NMR (400



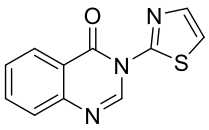
MHz, $CDCl_3$) δ 8.32 (dd, J = 8.0, 0.9 Hz, 1H), 8.04 (s, 1H), 7.78 – 7.70 (m, 2H), 7.55 – 7.48 (m, 1H), 4.01 (t, J = 7.4 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.47 – 1.37 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 148.1, 146.6, 134.1, 127.4, 127.2, 126.7, 122.2, 46.8, 31.4, 19.9, 13.7; HRMS calcd for $C_{12}H_{15}N_2O$ [M+H$^+$] 203.1179, found 203.1182.

3-(Naphthalen-1-yl)quinazolin-4(3*H*)-one (14c). Yield 57%, White solid, mp 142 – 145 ºC; ^{1}H



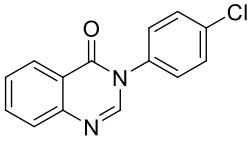
NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 7.7 Hz, 1H), 8.14 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.68 – 7.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 148.2, 146.9, 134.8, 134.4, 134.1, 130.3, 129.8, 128.7, 127.8, 127.8, 127.7, 127.3, 126.9, 126.0, 125.5, 122.4, 122.0; HRMS calcd for $C_{18}H_{13}N_2O$ [M+H$^+$] 273.1022, found 203.1026.

3-(Thiazol-2-yl)quinazolin-4(3*H*)-one (14d). Yield 52%, White solid, mp 200 – 202 ºC; ^{1}H NMR



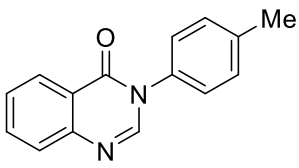
(400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.43 (d, J = 7.5 Hz, 1H), 7.89 – 7.81 (m, 2H), 7.77 – 7.71 (bs, 1H), 7.65 – 7.56 (m, 1H), 7.36 (d, J = 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 154.9, 146.5, 141.1, 138.2, 135.3, 128.3, 128.0, 127.3, 120.9, 118.5; HRMS calcd for $C_{18}H_8N_3OS$ [M+H$^+$] 230.0383, found 230.0380.

3-(4-Chlorophenyl)quinazolin-4(3*H*)-one (14e). Yield 66%, White solid, mp 182 – 185 ºC; ^{1}H



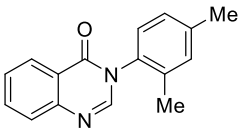
NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 7.8 Hz, 1H), 8.11 (s, 1H), 7.86 – 7.76 (m, 2H), 7.61 – 7.52 (m, 3H), 7.43 – 7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 147.8, 145.6, 135.9, 135.2, 134.8, 129.9, 128.3, 127.9, 127.7, 127.2, 122.2; HRMS calcd for $C_{14}H_{10}ClN_2O$ [M+H$^+$] 257.0476, found 257.0472.

3-(*p*-Tolyl)quinazolin-4(3*H*)-one (14f). Yield 54%, White solid, mp 141 – 143 ºC; ^{1}H NMR

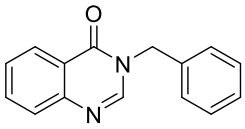


(400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.87 – 7.75 (m, 2H), 7.57 (t, J = 7.1 Hz, 1H), 7.38 –7.32 (m, 4H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 147.9, 146.3, 139.3, 134.9, 134.5, 130.3, 127.6, 127.6, 127.2, 126.7, 122.4, 21.2; HRMS calcd for $C_{15}H_{13}N_2O$ [M+H$^+$] 237.2815, found 237.2819.

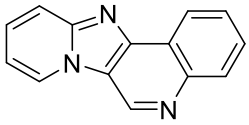
3-(2,4-Dimethylphenyl)quinazolin-4(3*H*)-one (14g): Yield 45%, Viscous liquid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 7.8 Hz, 1H), 8.02 (s, 1H), 7.87 – 7.79 (m, 2H), 7.60 – 7.55 (m, 1H), 7.23 (s, 1H), 7.20 – 7.14 (m, 2H), 2.43 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.1, 146.7, 139.8, 135.4, 134.55, 134.1, 132.1, 131.3, 128.0, 127.6, 127.6, 127.2, 122.5, 21.2, 17.7; HRMS calcd for $C_{16}H_{15}N_2O$ [M+H$^+$] 251.3085, found 251.3079.



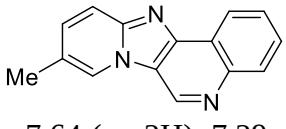
3-Benzylquinazolin-4(3*H*)-one (14h). Yield 60%, White solid, mp 94 – 97 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 7.9 Hz, 1H), 8.14 (s, 1H), 7.81 – 7.71 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.42 – 7.32 (m, 5H), 5.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 148.0, 146.3, 135.7, 134.3, 129.0, 128.3, 128.0, 127.5, 127.4, 126.9, 122.2, 49.6; HRMS calcd for $C_{15}H_{13}N_2O$ [M+H$^+$] 237.2815, found 237.2819.



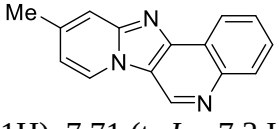
Pyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (41a). Yield 52%, Off-white solid, mp 253 – 255 °C; ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 9.77 (s, 1H), 9.31 (d, J = 6.7 Hz, 1H), 8.60 (d, J = 7.7 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 9.1 Hz, 1H), 7.74 (t, J = 7.1 Hz, 1H), 7.71 – 7.62 (m, 2H), 7.17 (t, J = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) δ 149.1, 145.9, 145.7, 137.9, 131.2, 129.8, 128.4, 127.6, 126.6, 122.7, 122.1, 117.5, 112.9; HRMS for $C_{14}H_{10}N_3$ [M+H$^+$] calcd 220.0869 found 220.0876.



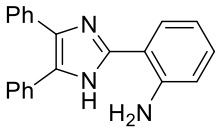
9-Methylpyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (41b). Yield 45%, Off-white solid, mp 228 – 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 8.62 (d, J = 7.7 Hz, 1H), 8.26 (s, 1H), 8.19 (d, J = 8.2 Hz, 1H), 7.72 (t, J = 7.0 Hz, 1H), 7.67 – 7.64 (m, 2H), 7.29 – 7.25 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 146.1, 145.5, 135.6, 133.4, 129.6, 128.3, 126.6, 122.7, 122.6, 122.5, 122.0, 121.7, 117.1, 18.1; HRMS for $C_{15}H_{12}N_3$ [M+H$^+$] calcd 234.1026 found 234.1032.



10-Methylpyrido[2',1':2,3]imidazo[4,5-*c*]quinoline (41c). Yield 42%, Off-white solid, mp 243 – 245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 8.53 (d, J = 6.9 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.71 (t, J = 7.3 Hz, 1H), 7.61 (s, 1H), 6.85 (dd, J = 6.8, 0.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 146.7, 145.7, 142.1, 135.4, 129.7, 128.4, 126.6, 124.3, 122.7, 116.4, 115.3, 22.0; HRMS for $C_{15}H_{12}N_3$ [M+H$^+$] calcd 234.1026 found 234.1032.

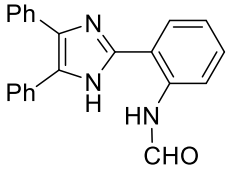


2-(4,5-Diphenyl-1H-imidazol-2-yl)aniline (37). Yield 65%, Off-white solid, mp 216 – 218 °C;



^{1}H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 7.83 (dd, J = 7.9, 1.2 Hz, 1H), 7.57 – 7.49 (m, 4H), 7.46 (t, J = 7.4 Hz, 2H), 7.42 – 7.36 (m, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.10 – 7.04 (m, 1H), 7.00 (s, 2H), 6.79 (dd, J = 8.1, 0.8 Hz, 1H), 6.63 – 6.56 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.2, 147.1, 135.7, 135.4, 131.4, 129.4, 129.1, 129.1, 128.8, 128.3, 127.2, 127.1, 126.9, 126.8, 116.2, 115.4, 111.4; HRMS for $C_{21}H_{18}N_3$ [M+H$^+$] calcd 312.3955 found 312.3951.

N-(2-(4,5-Diphenyl-1H-imidazol-2-yl)phenyl)formamide (42). Yield 40%, White solid, mp 218



– 220 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.99 (s, 1H), 12.66 (s, 1H), 8.65 (d, J = 5.8 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.60 – 7.52 (m, 4H), 7.51 – 7.31 (m, 7H), 7.27 – 7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 160.8, 145.9, 136.5, 136.2, 134.5, 130.9, 129.9, 129.6, 129.3, 129.2, 128.9, 128.8, 127.6, 126.9, 123.7, 121.0, 116.4; HRMS (ESI) calcd for $C_{22}H_{13}F_3N_3$ [M+H$^+$] 340.1444 found 340.1447.

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CHAPTER 2C

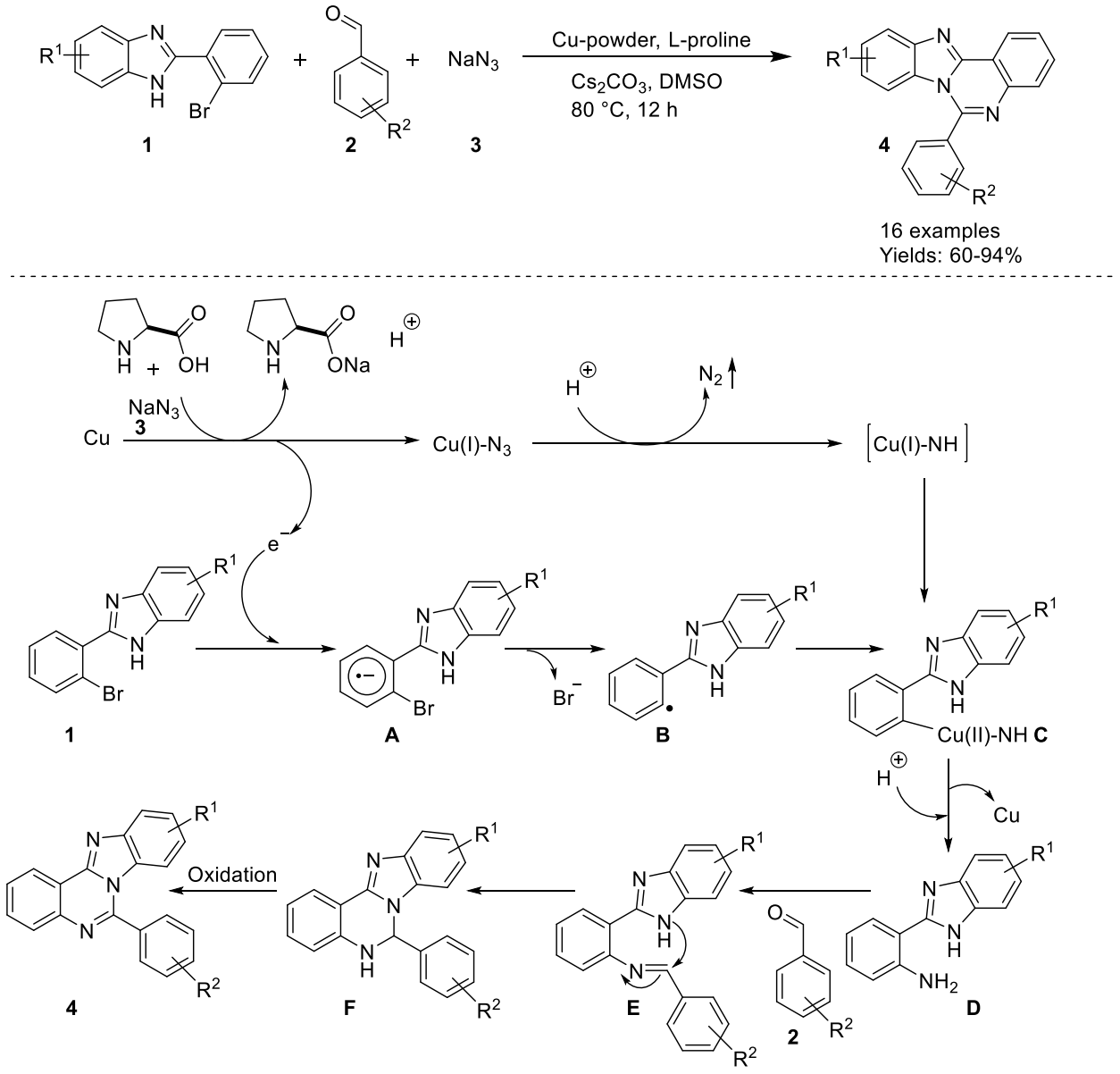
Copper–Catalyzed Three–Component Tandem Strategy: Expeditious Synthesis of Imidazo/benzimidazo[1,2-*c*]quinazolines

2.2C.1 INTRODUCTION

As described in chapter 1, quinazoline is a highly privileged and potentially bioactive heterocycle and possessing noteworthy attention due to their diverse pharmacological activities. [1-5] In last decade, a vast number of a synthetic method have been developed for the preparation of functionalized quinazoline motif and the level of attention in the current domain is cleared by the number of publications with a high output of results.[6-16] In recent year, sodium azide has been utilized as one nitrogen synthon for the development of functionalized quinazolines. Therefore, the synthesis of aryl amine from aryl halide by reductive amination has emerged as an important approach for the assembly of nitrogen-containing frameworks.[17-24] The detail investigation of reductive amination has been discussed in the previous chapter.

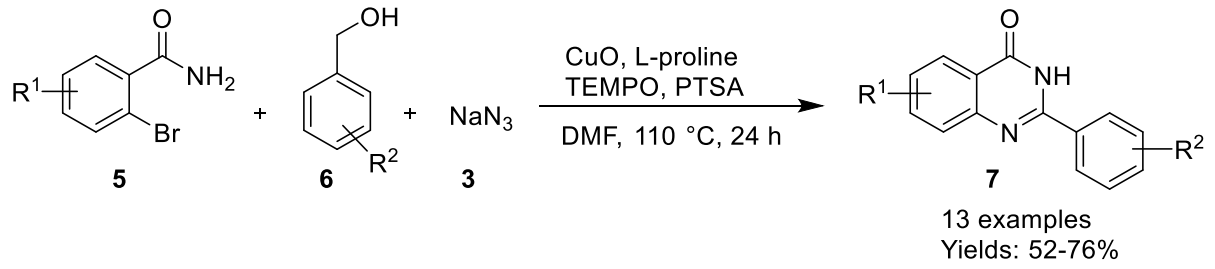
The profound importance of these bioactive molecules has opened up new gateways for a chemist to develop biological potent quinazoline conjugates with other heterocycles. Although, several approaches have been reported for the synthesis of fused heterocycles from complex preparative substrates.[25,26]

A copper-catalyzed one–pot multi–component reaction demonstrated by Kumar and group by using 2-(2-halophenyl)benzoimidazoles (**1**), aldehydes (**2**) and sodium azide (**3**) as a nitrogen source. This reaction involved three C-N bond formation (**Scheme 2.2C.1**).[27] Initially, azidation of arylhalide with sodium azide then *in situ* conversion of aryl azide to aryl amine through reduction which on condensation with benzaldehyde underwent oxidative cyclization to afford benzimidazo[1,2-*c*]quinazoline in good to excellent yields (60-94%).



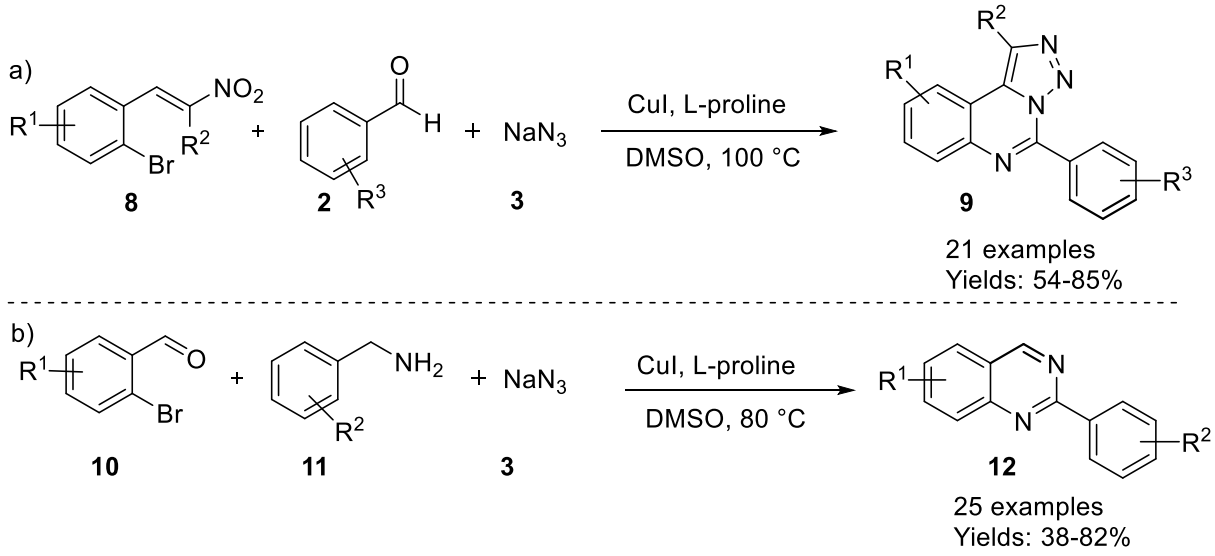
Scheme 2.2C.1 Copper-catalyzed one–pot multi–component reaction of fused quinazolines

Shinde *et al.* demonstrated copper–catalyzed tandem multi–component redox reaction for the development of quinazolinones (**7**) starting from easily available 2-bromobenzamide (**5**), benzylic alcohol (**6**) and sodium azide (**3**) as nitrogen source (**Scheme 2.2C.2**).[24] The developed approach involved copper–catalyzed azidation of 2-brmobenzamide *via* S_NAr reaction and oxidation of benzyl alcohol followed by sequential reduction–condensation and oxidation. The scope of this methodology was explored by using a range of benzamide and benzyl alcohol containing electron rich and electron deficient substituents which gave the corresponding product in good yields (52-75%).



Scheme 2.2C.2 Copper–catalyzed tandem multi-component redox reaction for the synthesis of quinazolinones

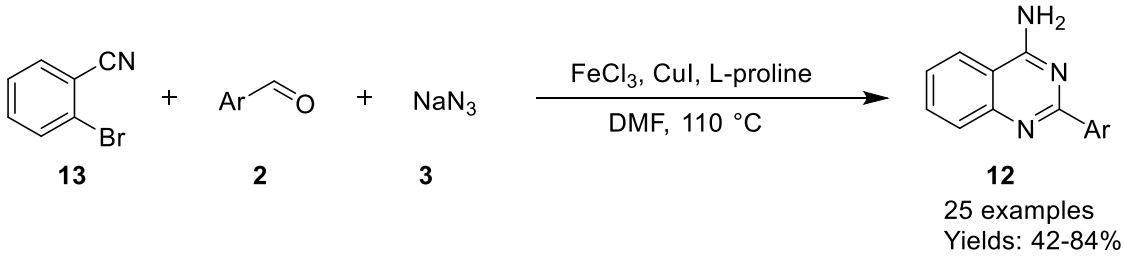
Jia *et al.* described tandem multi-component approach for the development of triazolo[1,5-*c*]quinazolines (**9**) by using [3+2] cycloaddition, copper-catalyzed S_NAr, reduction, cyclization, and oxidation sequences (**Scheme 2.2C.3a**).[28] Later on, the same group synthesized quinazoline derivatives (**12**) from 2-bromoaldehydes (**10**), benzylamines (**11**), and sodium azide (**3**) which involved sequential copper–catalyzed S_NAr, oxidation/cyclization, and denitrogenation (**Scheme 2.2C.3b**).[29]



Scheme 2.2C.3 Copper-catalyzed tandem multi–component reactions for the synthesis of quinazolines

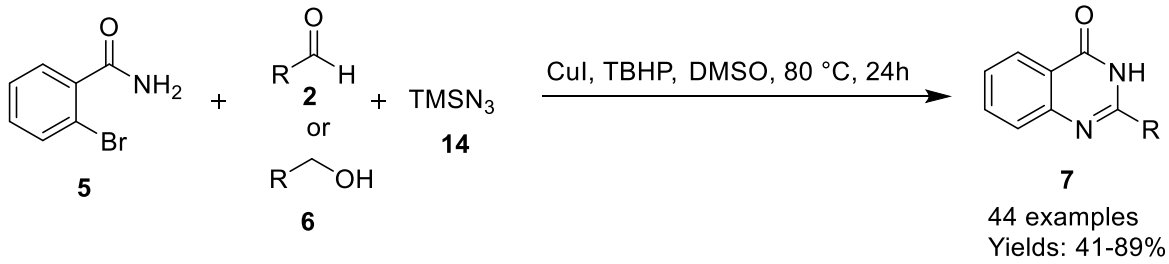
Wu and co-workers described a highly efficient Fe/Cu relay–catalyzed domino protocol for the synthesis of 2-phenylquinazolin-4-amines (**12**) from commercially available ortho-halogenated benzonitriles (**13**), aldehydes (**2**), and sodium azide (**3**) (**Scheme 2.2C.4**).[30] This one-pot tandem reaction involved consecutive iron-mediated [3+2] cycloaddition, copper-catalyzed S_NAr,

reduction, cyclization, oxidation, and copper-catalyzed denitrogenation sequences. In this reaction, sodium azide acted as a dual nitrogen source.



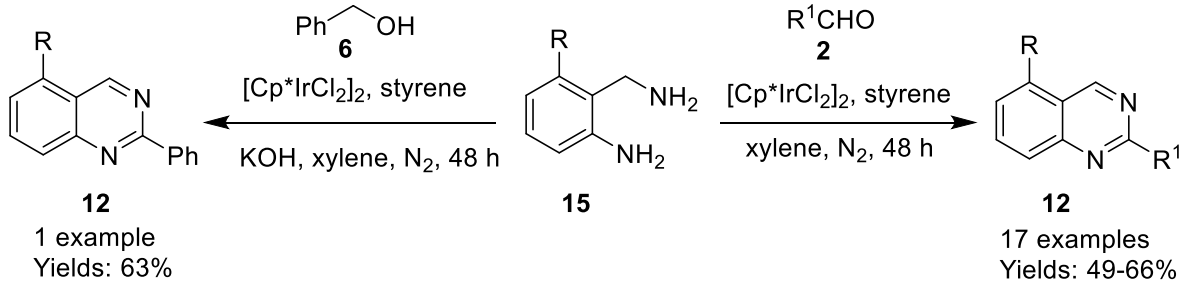
Scheme 2.2C.4 Synthesis of 2-Phenylquinazolin-4-amines *via* a Fe/Cu relay–catalyzed domino strategy

Upadhyaya *et al*. designed ligand and base free one-pot protocol for the synthesis of 2-substituted quinazolinones (**7**) from 2-bromobenzamide (**5**), aldehyde (**2**) or alcohol (**6**) and $TMSN_3$ (**14**) as nitrogen source (**Scheme 2.2C.5)**.[31] This reaction involved oxidative addition, reductive amination, an intermolecular oxidative nitrogenation of a benzylic C(sp^3)−H bond, intramolecular cyclization, and oxidative dehydrogenation, afforded the desired product in moderate to excellent yields (41-89%).



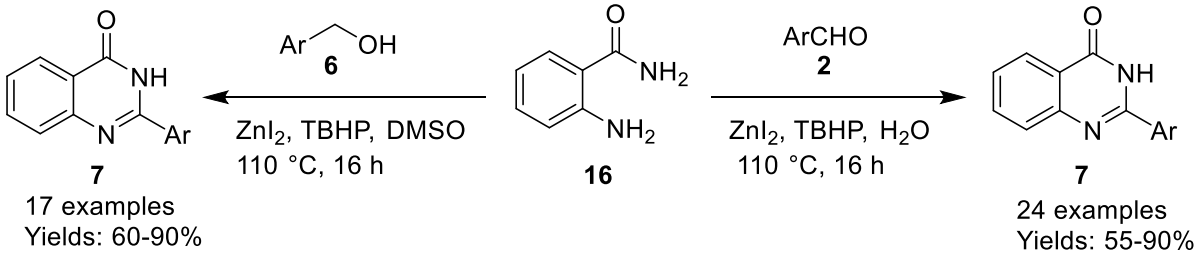
Scheme 2.2C.5 One-pot copper–catalyzed the tandem cyclooxidative synthesis of quinazolinones

Fang *et al*. described one-pot synthesis of 2-substituted quinazolines (**12**) from easily available 2-aminobenzylamines (**15**) and aldehydes (**2**) *via* iridium–catalyzed hydrogen transfers using styrene as a hydrogen acceptor (**Scheme 2.2C.6**).[32] Both aliphatic and aromatic aldehydes were reacted smoothly with 2-aminobenzylamines and afforded the corresponding quinazolines in good yields (49-66%). Furthermore, the reaction was also applied with benzyl alcohol under optimized condition lead to the target product in satisfactory yield (61%) in the presence of the base additive.



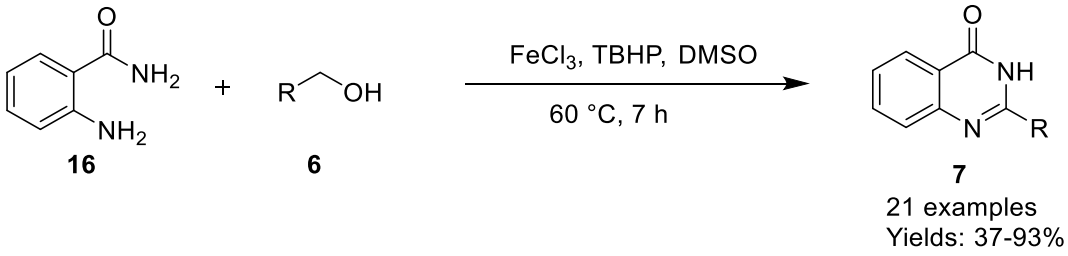
Scheme 2.2C.6 Synthesis of 2-substituted quinazolines *via* iridium catalysis

Wu and co-workers designed interesting zinc–catalyzed oxidative methodology for the synthesis of quinazolinones (**7**) between 2-aminobenzamide (**16**) and benzyl alcohols (**6**) using TBHP in H_2O at 110 °C (**Scheme 2.2C.7**).[33] In addition, the reaction was also performed with aldehydes (**2**) under the optimized condition, and targeted quinazolinones were isolated in good yields (55-90%).



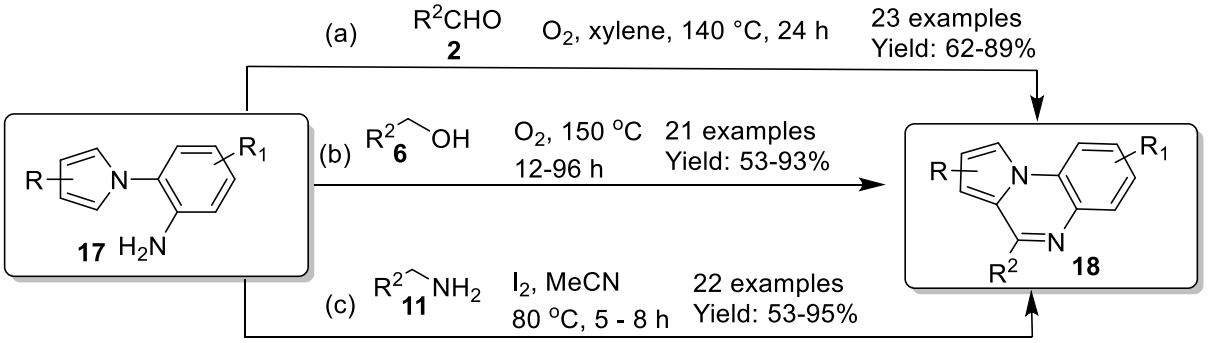
Scheme 2.2C.7 Synthesis of 2-substituted quinazolinones *via* zinc catalysis

Similarly, Li and co-workers reported an iron-catalyzed one–pot single-step oxidative system for the synthesis of quinazolinones (**7**) from 2-aminobenzamide (**16**) and benzyl alcohols (**6**) (**Scheme 2.2C.8**). [34] The scope of this annulation reaction was investigated by varying different substituted benzyl alcohols with electron-donating and electron-withdrawing groups. Notably, a heteroaryl substrate like 2-furylmethanol and primary alcohols such as ethanol and octanol was examined under the optimized condition, and desired products were isolated in moderate to excellent yields (37-93%).



Scheme 2.2C.8 Synthesis of 2-substituted quinazolinones *via* iron catalysis

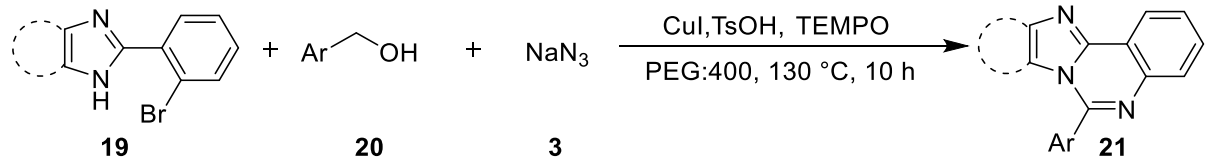
Wang *et al*. documented an environmentally benign protocol for the synthesis of pyrrolo[1,2-*a*]quinoxalines (**18**) with the reaction of 1-(2-aminophenyl)pyrrole (**17**) and aldehyde (**2**) (**Scheme 2.2C.9a**).[35] The work was equally effective with aromatic and aliphatic aldehyde, and the corresponding product was observed in good yields (62-89%). Jiang and co-workers reported the synthesis of pyrrolo[1,2-*a*]quinoxalines (**18**) from **17** and alcohol (**6**) through a cascade reaction which involved the oxidation, imine formation, intramolecular cyclization and oxidative dehydrogenation (**Scheme 2.2C.9b**).[36] The developed protocol was well tolerated with different alcohol and served as a green methodology for quinoxalines in a step and economical fashion. Jayaprakash group described iodine–catalyzed one-pot strategy for the development of pyrrolo[1,2-*a*]quinoxalines (**18**) from the benzylamine (**11**) and 1-(2-aminophenyl) pyrrole (**17**) (**Scheme 2.2C.9c**).[37]



Scheme 2.2C.9 Metal–free synthesis of pyrrolo[1,2-*a*] quinoxalines

To complement of these reports, It becomes highly desirable to develop an environmentally benign protocol for the development of fused quinazoline by using sodium azide as one nitrogen source and alcohol or amine or aldehyde as one carbon source as a potential pharmacological lead. As part of our ongoing interest towards the development of a new assembly of *N*-fused heterocycles. In this chapter, we wish to disclose synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines *via* ligand-free copper–catalyzed reductive amination of aryl halides with sodium azide followed by

condensation of benzaldehyde and *in situ* generated aryl partner from benzylamine and benzyl alcohol using one–pot multi–component reaction (**Scheme 2.2C.10**).



Scheme 2.2C.10 Copper–catalyzed synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines from 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole/benzimidazole

2.2C.2 RESULTS AND DISCUSSION

Our initial investigations commenced by recognizing a suitable reaction condition for the envisioned tandem approach, and the results are summarized in **Table 2.2C.1** Initially 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**19a**) was treated with (4-methoxyphenyl)methanol (**20b**) and NaN_3 (**3**) in the presence of CuI (20 mol %), K_2CO_3 (1 mmol) and TEMPO (0.5 mmol) at 130 °C under air for 10 h. To our satisfaction 5-(4-methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline (**21ab**) was obtained with 65% yield (**Table 2.2C.1**, entry 1). The structure of **21ab** was characterized by detail spectroscopic analysis. The ^{1}H NMR spectrum and ^{13}C NMR spectrum is well agreed with structure. The ^{1}H and ^{13}C spectrum of **21ab** is depicted in **Figure 2.2C.1**

With the encouraging result, we focused our attention towards optimized the reaction condition by varying different catalysts, additives, oxidants, and solvents. Screening of various catalyst revealed that CuI was the most appropriate catalyst for this transformation, whereas no product was observed with $NiCl_2$ and $FeCl_3$ (**Table 2.2C.1**, entries 1-5). Among all additive (K_2CO_3, Cs_2CO_3, $NaHCO_3$, Et_3N, and TsOH), TsOH was found to be more relevant which afforded desired product with 70% yield (**Table 2.2C.1**, entries 1, 6-11). Screening of various oxidants such as TEMPO, TBHP, DTBP, $Cu(OAc)_2 \cdot H_2O$ and IBD suggest that TEMPO is good oxidant for the oxidation of (4-methoxyphenyl)methanol to 4-methoxy benzaldehyde (**Table 2.2C.1**, entries 9-13). While the use of O_2 afforded only 40% of the desired product (**21ab**) (**Table 2.2C.1**, entry 14). It is worth to mention that the desired product (**21ab**) was not observed without oxidant (**Table 2.2C.1**, entry 15). Finally, a brief survey of solvents revealed that solvents such as DMF, DMA, DMSO, and PEG: 400 were more effective for this transformation whereas desired product was not observed in water, toluene and 1,4-dioxane (**Table 2.2C.1**, entries 9, 16-21). From a solvent survey, we

concluded that green solvent PEG: 400 is the most suitable solvent for this transformation in the point of green aspect. The target product **21ab** was not observed without copper catalyst (**Table 2.2C.1**, entry 22).

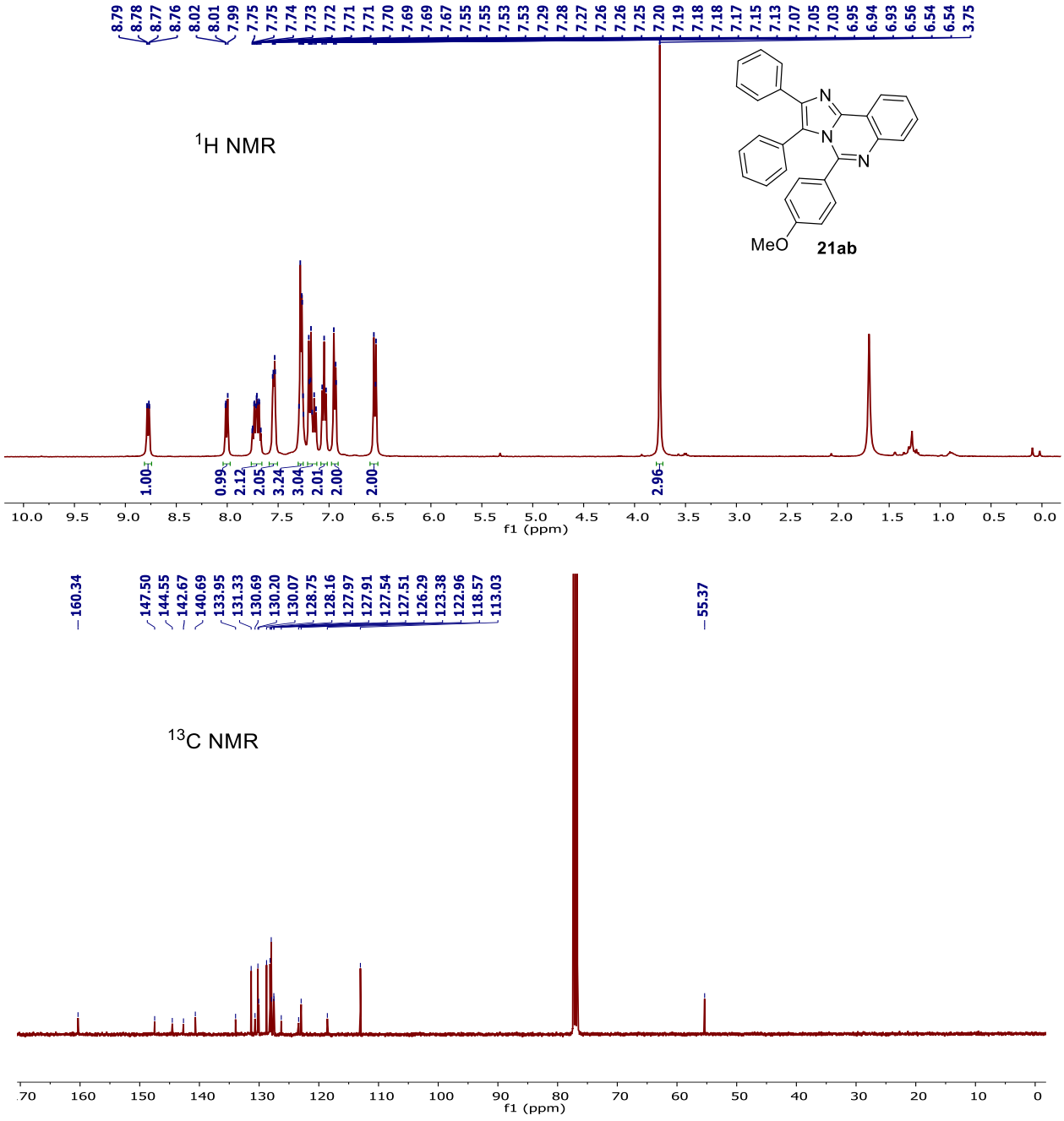
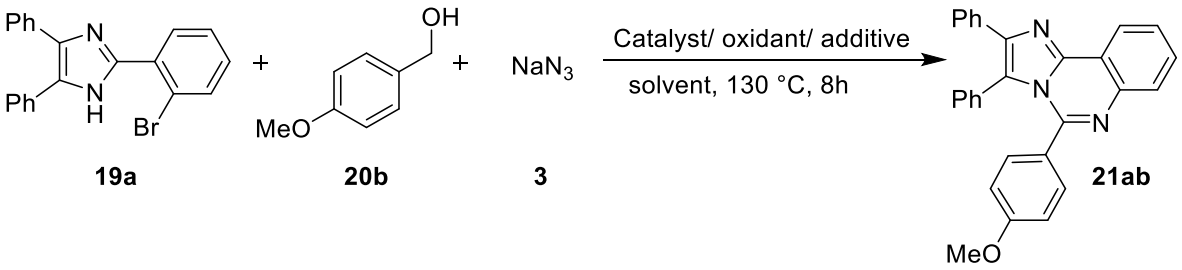


Figure 2.2C.1 ^{1}H and ^{13}C NMR spectra of 5-(4-methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline (**21ab**) in $CDCl_3$

Table 2.2C.1 Optimization of reaction conditions[a]



Entry	Catalyst	Additive	Oxidant	Solvent	Yield (%)[b]
1	CuI	K_2CO_3	TEMPO	DMF	65
2	CuBr	K_2CO_3	TEMPO	DMF	59
3	$CuCl_2$	K_2CO_3	TEMPO	DMF	56
4	$NiCl_2$	K_2CO_3	TEMPO	DMF	NR
5	$FeCl_3$	K_2CO_3	TEMPO	DMF	NR
6	CuI	Cs_2CO_3	TEMPO	DMF	64
7	CuI	$NaHCO_3$	TEMPO	DMF	58
8	CuI	Et_3N	TEMPO	DMF	50
9	CuI	TsOH	TEMPO	DMF	70
10	CuI	K_2CO_3	TBHP	DMF	trace
11	CuI	K_2CO_3	DTBP	DMF	trace
12	CuI	K_2CO_3	$Cu(OAc)_2 \cdot H_2O$	DMF	NR
13	CuI	K_2CO_3	IBD	DMF	NR
14	CuI	K_2CO_3	O_2	DMF	40
15	CuI	K_2CO_3		DMF	NR
16	CuI	TsOH	TEMPO	DMA	67
17	CuI	TsOH	TEMPO	DMSO	64
18	CuI	TsOH	TEMPO	PEG:400	73
19	CuI	TsOH	TEMPO	Water	NR
20	CuI	TsOH	TEMPO	Toluene	NR
21	CuI	TsOH	TEMPO	Dioxane	NR
22	-	TsOH	TEMPO	PEG:400	NR

[a]Reactions conditions: **19a** (1.0 mmol), **20b** (1.5 mmol), NaN_3 (1.5 mmol), TsOH (0.5 mmol), TEMPO (0.5 mmol) catalyst (20 mol %), solvent (2 mL) under air at 130 °C, 10 h. [b]Isolated yield.

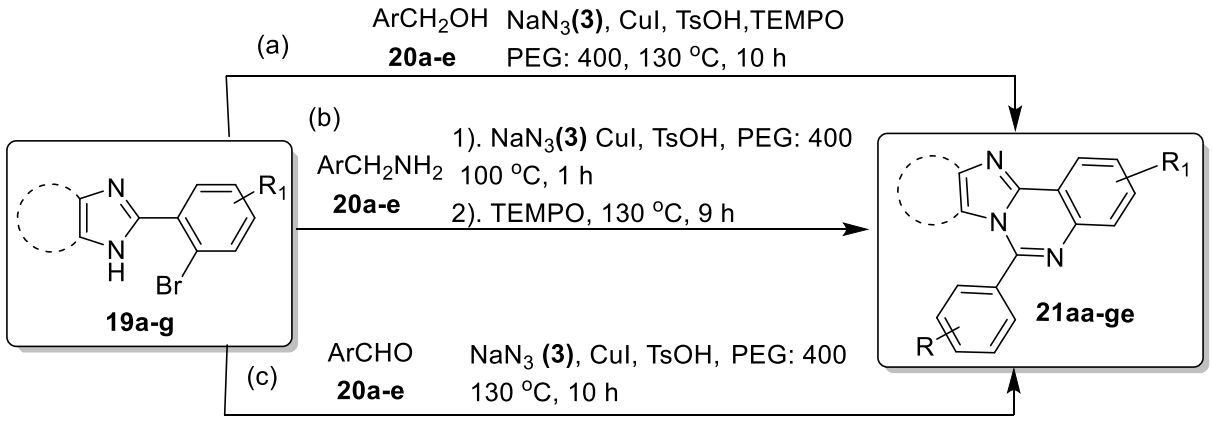
After optimized these reaction conditions, various 2-(2-bromophenyl)-1*H*-imidazoles/benzimidazoles (**19a-g)** were subjected to investigate the reaction scope, and several representative results are summarized in **Table 2.2C.2**. To our delight, the developed protocol well tolerated with different substituents such as fluoro, methyl, methoxy on aryl rings at C2-, C4- and

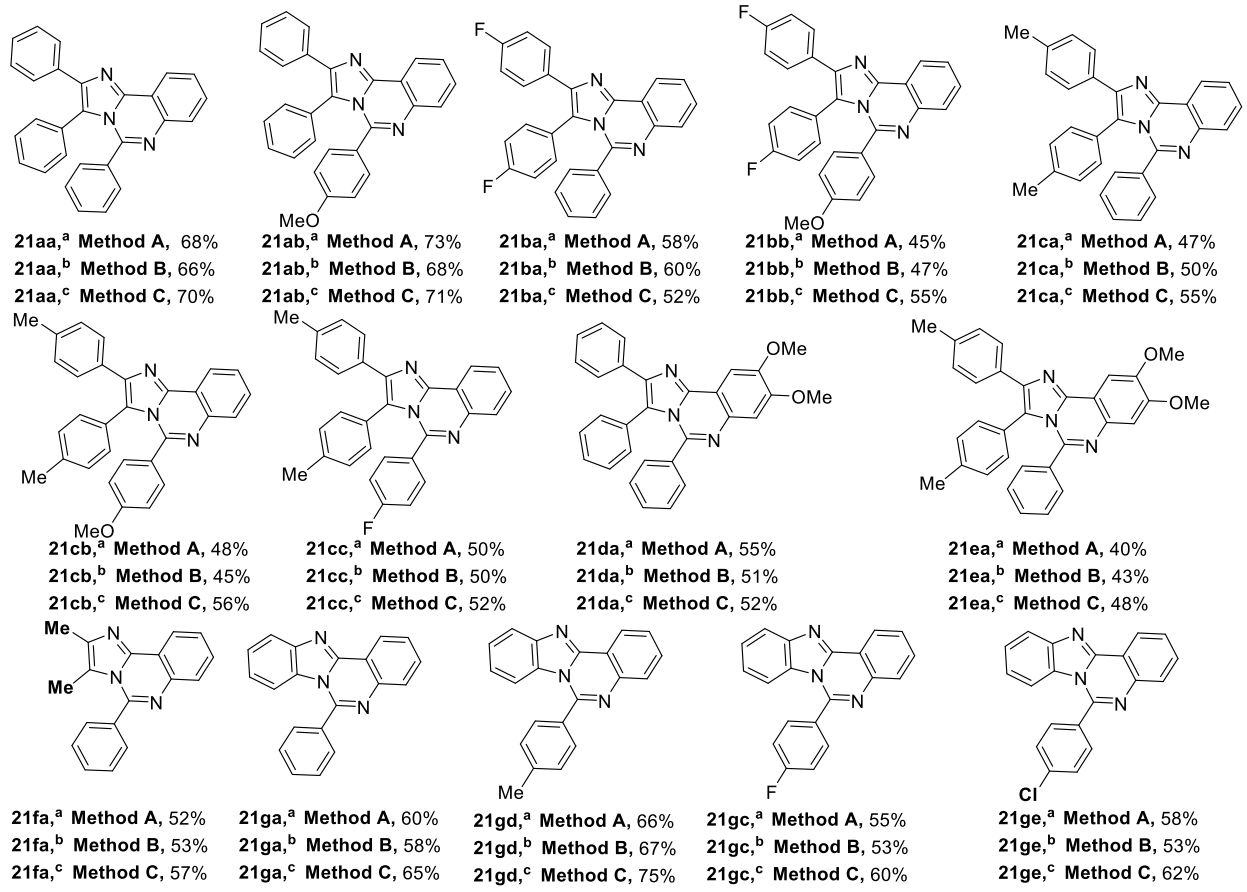
C5-positions of imidazole and delivered the corresponding benzimidazo\imidazo[1,2-*c*]quinazolines (**21aa-ge**) with good yields (40-73%). After achieved the successful application with a wide range of 2-(2-bromophenyl)-1*H*-imidazole/benzimidazole (**19a-g)**, we investigated the scope of different benzyl alcohol (**20a-e**) under the optimized condition. We found that both electron-rich (Me, OMe) and electron poor substituents (F, Cl) underwent smoothly and afforded the desired quinazolines with moderate to good yields (**68aa-ge**).

Next, we were interested in applying benzylamine derivatives for the synthesis of benzimidazo\imidazo[1,2-*c*]quinazolines (**21aa-ge**). Initially 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**19a**) was treated with NaN_3 (**3**) in the presence of CuI (20 mol %), TsOH (0.5 mmol) at 100 °C under air for 1 h then one–pot sequential addition of (4-methoxyphenyl)methanol (**20b**) and TEMPO (0.5 mmol) at 130 °C for 9 h. To our immense gratification, 5-(4-methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline (**21ab**) was obtained with 68% yield. Afterward, we optimized the reaction condition by varying different catalysts, additives, oxidants, and solvents and observed the reaction condition was used for benzyl alcohol also an optimum condition for benzylamine derivatives. After optimized the reaction condition, we investigated the scope of different benzylamine (**20a-e**) and observed electron releasing group (ERG) and electron withdrawing group (EWG) were tolerated well and afforded the corresponding product with good yields (40-68%).

To further extend the scope of the process, synthesis of 5-(4-methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline (**21ab**) was attempted by reacting 2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**19a**) with 4-methoxybenzaldehyde (**20b)** and NaN_3 (**3**) in the presence of CuI (20 mol %), TsOH (0.5 mmol) at 130 °C under air for 10 h in one-pot tandem fashion. As expected, **21ab** was obtained in 71% yield. The developed protocol worked well with different substituents such as fluoro, methyl, methoxy on aryl rings of imidazole at C2-, C4- and C5-positions and substituted benzaldehydes under standard reaction condition which led to corresponding benzimidazo\imidazo[1,2-*c*]quinazolines (**21aa-ge**) with good yields (52-75%).

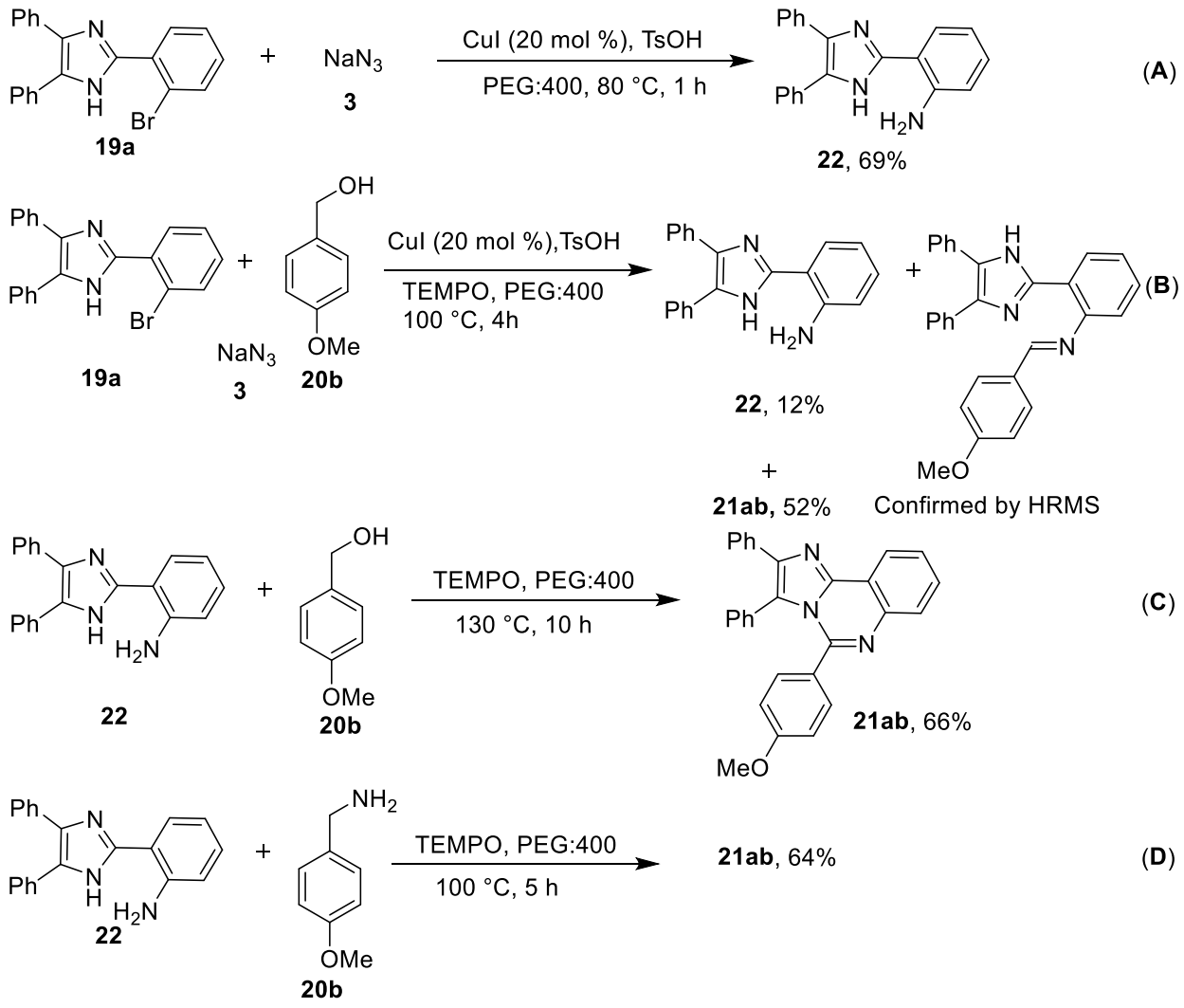
Table 2.2C.2 Substrate scope for the synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines.





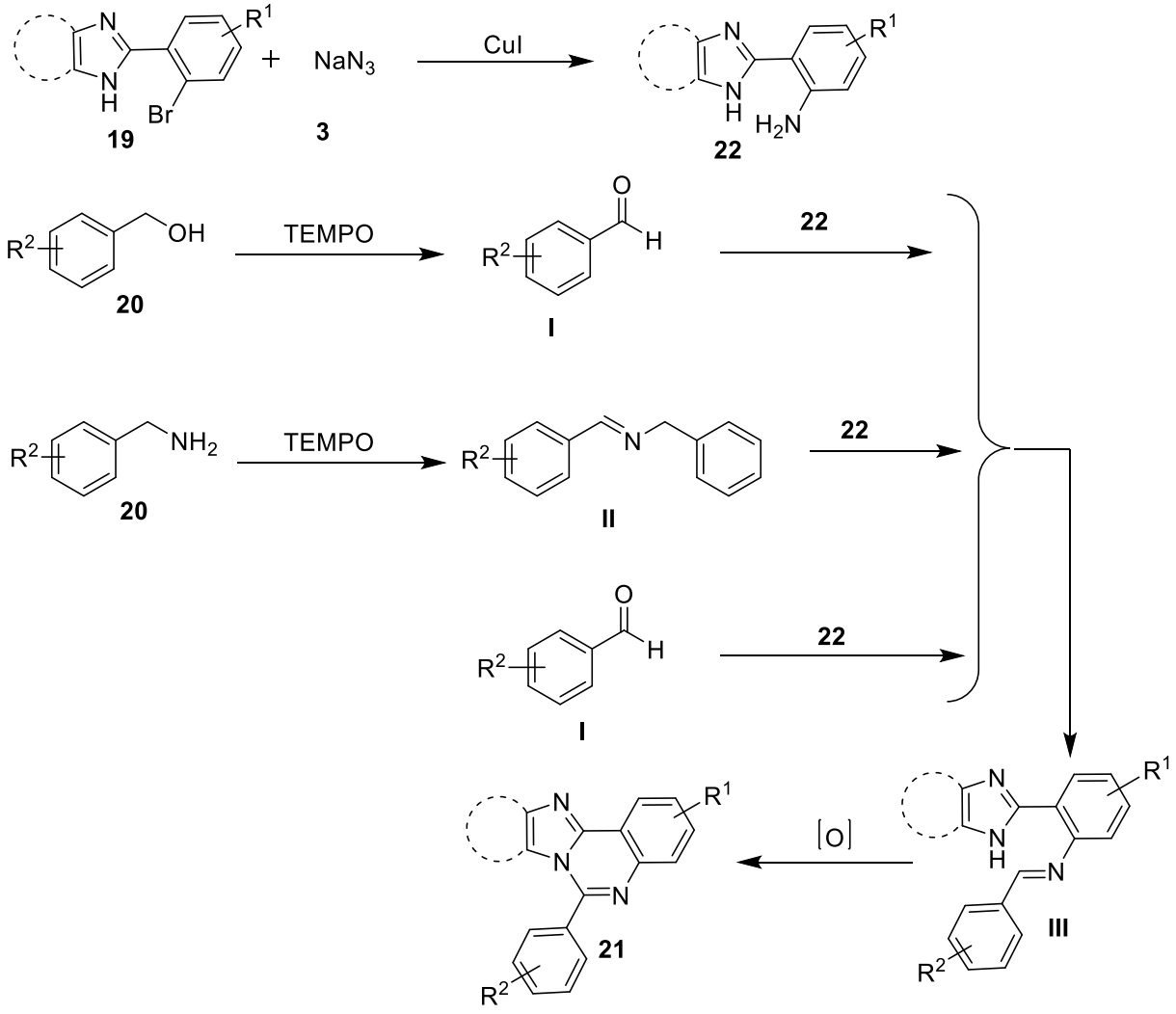
[a]Reactions conditions (**Method a**): **19** (1.0 mmol), **20** (benzyl alcohols) (1.5 mmol), NaN_3 (1.5 mmol), TsOH (0.5 mmol), TEMPO (0.5 mmol) CuI (20 mol %), solvent (2 mL) at 130 °C, 10 h. [b]Isolated yield. (**Method b**): Reaction of **19** (1.0 mmol), NaN_3 (1.5 mmol), TsOH (0.5 mmol) at 100 °C, 1 h then addition of benzylamines in one-pot sequential manner. (**Method c**): **19** (1.0 mmol), **20** (benaldehydes) (1.5 mmol), NaN_3 (1.5 mmol), TsOH (0.5 mmol) at 130 °C, 10 h.

To gain insight into the mechanism of the reaction, a set of control experiments were performed. The reaction of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**19a**) with sodium azide (**3**) in the presence of CuI, *p*-TsOH in PEG:400 at 80 °C for 1 h provided 2-(2-aminophenyl)-4,5-diphenyl-*1H*-imidazole (**22**) in 68% yield (**Scheme 2.2C.11A**). When the reaction was carried out at 100 °C for 4h, the desired product **21ab** was observed in 52% yields along with **22** and (E)-*N*-(2-(4,5-diphenyl-1*H*-imidazol-2-yl)phenyl)-1-(4-methoxyphenyl)methanimine (**Scheme 2.2C.11B**). The reaction of **22** with **20b** under metal-free condition provided **21ab** in 66% yield (**Scheme 2.2C.11C**). Further **22** treated with 4-methyl benzylamine (**20b)** under metal-free condition afford desired product **61ab** in 64% yield (**Scheme 2.2C.11D**).



Scheme 2.2C.11 Control experiments to propose a mechanism

On the basis of the literature report and controlled experiments result, a plausible reaction pathway was depicted in **Scheme 2.2C.12**. Initially, copper-catalyzed S_NAr reaction of **19** with NaN_3 (**3**) through reduction provides 2-(2-aminophenyl)-4,5-diphenyl-1*H*-imidazole (**22**), according to previous report wherein sodium azide/$TMSN_3$ has been used as ammonia surrogate to prepare primary amines. In the presence of TEMPO, benzyl alcohol (**20**) oxidized into benzaldehyde (**I**). However, in the case of benzylamine reaction underwent through an intermediate (**II**). The intermediate **I** and **II** were treated with **22** under optimized conditions to furnish the transamination product (**III**). Which undergo oxidative aromatization and lead to the formation of quinazoline derivatives **21** *via* aerobic oxidation.



Scheme 2.2C.12 Plausible mechanism of benzimidazo\imidazo[1,2-*c*]quinazolines

2.2C.3 CONCLUSIONS

Copper–catalyzed one–pot tandem multicomponent approach for the synthesis of fused imidazo/benzimidazo[1,2-*c*]quinazolines has been developed *via* sequential azidation through S_NAr, reduction followed by condensation with benzyl alcohol or benzaldehyde or benzyl amine derivatives. The present reaction provided a new approach for synthesis of *N*-fused hybrid heterocycles from readily available starting materials.

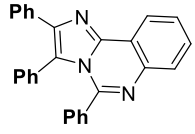
2.2C.4 EXPERIMENTAL SECTION

2.2C.4.1 General Materials and Methods

Melting points were determined in open capillary tubes on an EZ-Melt Automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV 400 spectrometer. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (TMS) as internal standard. High resolution mass spectra (HRMS-ESI) were carried out using a quadrupole time of-flight (Q-TOF) mass spectrometer (Applied Biosystem). All chemicals were obtained from the commercial suppliers and were used without further purification.

2.2C.4.2 General procedure for 5-(4-methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline: A clean oven dried 10 mL round bottom flask was charged with **19a** (1.0 mmol), **20b** (1.5 mmol), NaN_3 (1.5 mmol), TEMPO (0.5 mmol), *p*-TsOH (0.5 mmol) and CuI (0.20 mmol). The reaction mixture was heated with stirring at 130 °C under air atmosphere for 10 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature, diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Desired product **21ab** (73%) was isolated by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (20-30%) as eluent. The yield of all synthesized compounds (**21aa-ge**) has been mentioned in **Table 2.2C.2.**

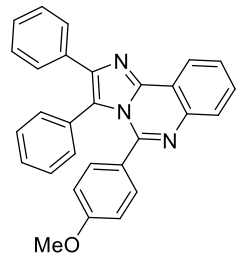
2,3,5-Triphenylimidazo[1,2-*c*]quinazoline (21aa). Pale yellow solid, mp 227 – 229 °C; ^{1}H NMR



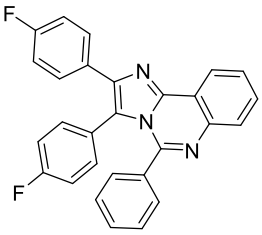
(400 MHz, Chloroform-d) δ 8.81 – 8.78 (m, 1H), 8.04 – 8.01 (m, 1H), 7.77 – 7.69 (m, 2H), 7.56 – 7.53 (m, 2H), 7.28 – 7.25 (m, 5H), 7.20 – 7.16 (m, 1H),

7.14 – 7.08 (m, 1H), 7.07 – 7.01 (m, 4H), 6.96 – 6.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 144.4, 142.7, 140.59, 133.8, 133.8, 131.2, 130.5, 130.1, 129.3, 128.7, 128.7, 128.2, 128.2, 128.0, 127.8, 127.6, 127.6, 123.3, 123.0, 118.6. HRMS (ESI) calcd for $C_{28}H_{20}N_3$ $[M+H]^+$ 398.1652 found 398.1648.

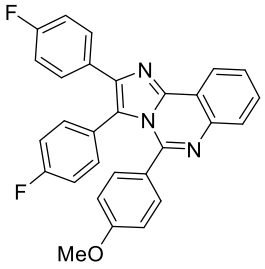
5-(4-Methoxyphenyl)-2,3-diphenylimidazo[1,2-*c*]quinazoline (21ab). Light gray solid, mp 185 – 187 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.78 (dd, J = 7.6, 1.6 Hz, 1H), 8.01 – 7.99 (m, 1H), 7.75 – 7.67 (m, 2H), 7.55 – 7.52 (m, 2H), 7.28 – 7.25 (m, 3H), 7.19 – 7.12 (m, 3H), 7.05 (t, J = 7.6 Hz, 2H), 6.94 (d, J = 7.2 Hz, 2H), 6.55 (d, J = 8.4 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.5, 144.5, 142.7, 140.7, 133.9, 131.3, 130.7, 130.2, 130.0, 128.7, 128.2, 128.0, 127.9, 127.5, 127.5, 126.3, 123.4, 123.0, 118.6, 113.0, 55.4. HRMS (ESI) calcd for $C_{29}H_{22}N_3O$ $[M+H]^+$ 428.1757 found 428.1757.



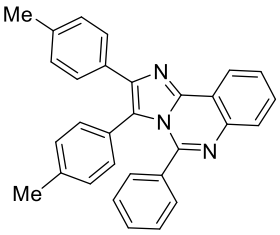
2,3-Bis(4-fluorophenyl)-5-phenylimidazo[1,2-*c*]quinazoline (21ba). Off white solid, mp 200 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.75 (m, 1H), 8.03 – 8.01 (m, 1H), 7.78 – 7.70 (m, 2H), 7.52 – 7.48 (m, 2H), 7.26 – 7.23 (m, 3H), 7.13 – 7.09 (m, 2H), 7.01 – 6.96 (m, 2H), 6.92 – 6.88 (m, s, 2H), 6.73 (t, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4(d, J = 247.6 Hz), 162.2 (d, J = 249.3 Hz), 147.3, 144.5, 142.0, 140.6, 133.7, 133.0 (d, J = 8.4 Hz), 130.4, 130.3, 130.3, 129.8 (d, J = 3.2 Hz), 129.5, 128.8, 128.4, 128.0, 127.7, 126.4 (d, J = 3.6 Hz) 122.9, 121.9, 118.5, 115.4, 115.2. HRMS (ESI) calcd for $C_{28}H_{18}F_2N_3$ $[M+H]^+$ 434.1463 found 434.1455.



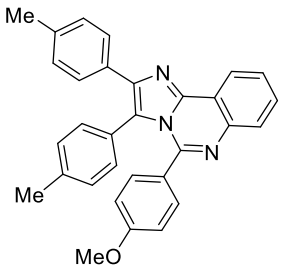
2,3-Bis(4-fluorophenyl)-5-(4-methoxyphenyl)imidazo[1,2-*c*]quinazolines (21bb). Medium gray solid, mp 226–228 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 8.0, 1.6 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.52 – 7.48 (m, 2H), 7.17 (d, J = 8.7 Hz, 2H), 6.99 (t, J = 8.4 Hz, 2H), 6.91 – 6.88 (m, 2H), 6.77 (t, J = 8.4 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 247.5 Hz), 162.2 (d, J = 249.1 Hz), 160.6, 147.2, 144.6, 142.0, 140.7, 133.0 (d, J = 8.3 Hz), 130.4, 130.3, 130.3, 129.9, 128.0 (d, J = 16.0 Hz), 126.7, 126.0, 122.9, 122.0, 118.5, 115.3 (d, J = 7.3 Hz), 115.1 (d, J = 7.6 Hz).113.1, 55.4. HRMS (ESSI) calcd for $C_{29}H_{20}F_2N_3O$ $[M+H]^+$ 464.1569 found 464.1569.



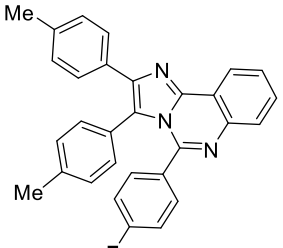
5-Phenyl-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (21ca). Off white solid, mp 235 – 237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.77 (m, 1H), 8.02 – 7.99 (m, 1H), 7.75 – 7.67 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.23 – 7.16 (m, 3H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (t, J = 7.6 Hz, 2H), 6.80 (bs, 4H), 2.33 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 144.2, 142.3, 140.5, 137.6, 137.3, 134.0, 131.1, 131.0, 130.0, 128.9, 128.8, 128.8, 128.7, 128.5, 128.1, 128.0, 127.5, 127.4, 123.1, 123.0, 118.6, 21.3. HRMS (ESI) calcd for $C_{23}H_{24}N_3$ $[M+H]^+$ 426.1965 found 426.1946.



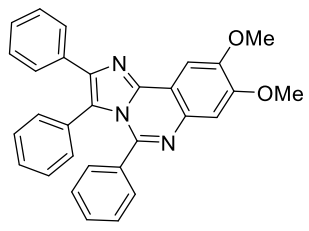
5-(4-Methoxyphenyl)-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (21cb). White solid, mp 216 – 218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J = 8.0, 1.6 Hz, 1H), 7.99 (dd, J = 8.4, 1.3 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.47 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.85 – 6.79 (m, 4H), 6.55 – 6.53 (m, 2H), 3.76 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 147.6, 144.3, 142.3, 140.6, 137.3, 137.2, 131.2, 131.0, 130.2, 130.0, 128.9, 128.6, 128.5, 127.9, 127.9, 127.7, 126.3, 123.1, 123.0, 118.5, 112.9, 55.3, 21.3, 21.2. HRMS (ESI) calcd for $C_{31}H_{26}N_3O$ $[M+H]^+$ 456.2070 found 456.2044



5-(4-Fluorophenyl)-2,3-di-*p*-tolylimidazo[1,2-*c*]quinazoline (21cc). Yellow solid, mp 228 – 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.76 (m, 1H), 7.99 (dd, J = 8.4, 2.0 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.23 – 7.19 (m, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 7.6 Hz, 2H), 6.81– 6.79 (m, 2H), 6.73 (t, J = 8.4 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, J = 249.8 Hz), 146.7, 144.2, 142.5, 140.4, 138.0, 137.3, 131.2, 130.9, 130.8 (d, J = 8.7 Hz), 130.0, 128.9, 128.8, 128.4, 128.2, 127.9, 127.5, 123.0, 122.9, 118.7, 114.5 (d, J = 22.1 Hz), 21.3, 21.2. HRMS (ESI) calcd for $C_{30}H_{23}FN_3$ $[M+H]^+$ 444.1871 found 444.1850.

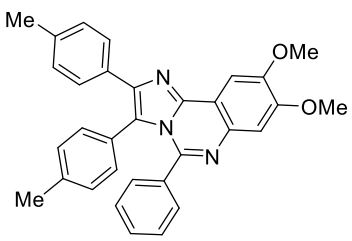


8,9-Dimethoxy-2,3,5-triphenylimidazo[1,2-*c*]quinazoline (21da). Off white solid, mp 224 – 226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.53 (dd, J = 8.0, 2.4 Hz, 2H), 7.46 (s, 1H), 7.28 – 7.22 (m, 5H), 7.18 – 7.14 (m, 1H), 7.09 – 6.97 (m, 5H), 6.94 – 6.92 (m, 2H), 4.17 (s, 3H), 4.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 150.3, 146.3, 144.4, 142.6, 136.3, 133.9,



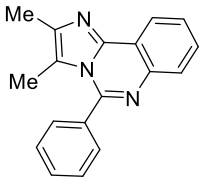
133.9, 131.2, 130.5, 129.1, 128.8, 128.7, 128.2, 128.0, 127.6, 127.6, 127.5, 122.7, 112.5, 108.6, 102.5, 56.6, 56.2. HRMS (ESI) calcd for $C_{30}H_{24}N_3O_2$ $[M+H]^+$ 458.1863 found 444.1850.

8,9-dimethoxy-5-phenyl-2,3-di-*p*-tolylimidazo[1,2-c]quinazoline (21ea). Off white solid, mp



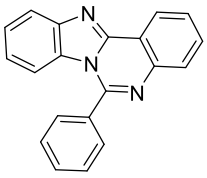
240 – 242 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.57 – 7.36 (m, 4H), 7.25 – 6.97 (m, 7H), 6.78 (bs, 3H), 4.16 (s, 3H), 4.03 (s, 3H), 2.32 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.2, 146.3, 144.2, 142.3, 137.4, 137.1, 136.2, 134.1, 131.2, 131.1, 128.9, 128.7, 128.6, 128.5, 127.6, 127.4, 122.5, 112.6, 108.6, 102.5, 56.6, 56.2, 21.2. HRMS (ESI) calcd for $C_{32}H_{28}N_3O_2$ $[M+H]^+$ 486.2176 found 486.2181.

2,3-Dimethyl-5-phenylimidazo[1,2-*c*]quinazoline (21fa). Pale yellow solid, mp 196 – 198 °C;



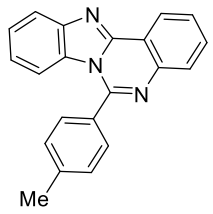
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.2 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.68 – 7.56 (m, 7H), 2.42 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 143.0, 140.1, 139.7, 134.9, 130.19, 129.6, 128.8, 128.4, 128.0, 128.0, 122.2, 118.4, 118.3, 13.4, 12.0. HRMS (ESI) calcd for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339 found 274.1345.

6-Phenylbenzo[4,5]imidazo[1,2-*c*]quinazoline (21ga). White solid, mp 238 – 240 °C; ^{1}H NMR



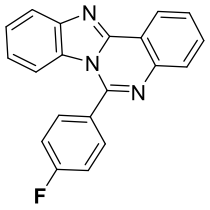
(400 MHz, $CDCl_3$) δ 8.78 (dd, J = 8.0, 1.6 Hz, 1H), 8.03 (t, J = 8.8 Hz, 2H), 7.85 – 7.81 (m, 1H), 7.78 – 7.66 (m, 6H), 7.50 – 7.47 (m, 1H), 7.16 – 7.12 (m, 1H), 6.63 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 148.0, 144.4, 142.4, 134.3, 131.9, 131.0, 129.3, 128.4, 128.3, 128.2, 125.6, 124.2, 122.6, 120.0, 118.4, 114.4. HRMS (ESI) calcd for $C_{21}H_{16}N_3$ $[M+H]^+$ 310.1339 found 310.1332.

6-(*p*-Tolyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (21gd). Off white solid, mp 210 – 212 °C; ^{1}H

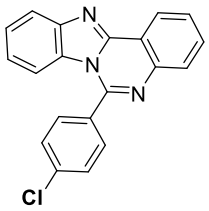


NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 7.9 Hz, 1H), 8.01 (dd, J = 8.0, 4.8 Hz, 2H), 7.80 (t, J = 7.2 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.50 – 7.46 (m, 3H), 7.14 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.1, 144.4, 142.5, 141.2, 131.8, 131.4, 129.9, 129.3, 128.3, 128.2, 128.2, 125.6, 124.2, 122.5, 119.9, 118.4, 114.5. 21.7 HRMS (ESI) calcd for $C_{21}H_{16}N_3$ $[M+H]^+$ 310.1339 found 310.1329.

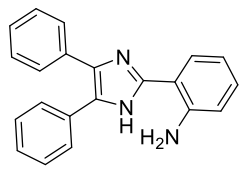
6-(4-fluorophenyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (21gc). Off white solid, mp 201 – 203 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 7.6 Hz, 1H), 8.01 (d, J = 8.0 Hz, 2H), 7.83 – 7.77 (m, 3H), 7.72 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 8.4 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (d, J = 251.9 Hz), 148.0, 147.5, 144.4, 142.3, 130.7 (d, J = 8.7 Hz), 130.44, 130.41, 129.1 (d, J = 9.7 Hz), 128.5, 128.2, 125.8, 124.2, 122.7, 120.1, 118.4, 116.6 (d, J = 22.0 Hz), 114.1. HRMS (ESI) calcd for $C_{20}H_{13}FN_3$ $[M+H]^+$ 314.1088 found 314.1056.



6-(4-Chlorophenyl)benzo[4,5]imidazo[1,2-*c*]quinazoline (21ge). Cream solid, mp 240 – 242 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.0 Hz, 1H), 7.99 (bs, 2H), 7.80 – 7.65 (m, 6H), 7.49 (t, J = 7.6 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.3, 144.4, 142.2, 137.3, 132.7, 131.9, 130.0, 129.6, 129.0, 128.5, 128.2, 125.8, 124.2, 122.7, 120.1, 118.4, 114.1. HRMS (ESI) calcd for $C_{20}H_{13}ClN_3$ $[M+H]^+$ 330.0793 found 330.0776.



2-(4,5-Diphenyl-1*H*-imidazol-2-yl)aniline (22): Off white solid, mp 216 – 218 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.48 (s, 1H), 7.83 (dd, J = 7.9, 1.2 Hz, 1H), 7.57 – 7.49 (m, 4H), 7.46 (t, J = 7.4 Hz, 2H), 7.42 – 7.36 (m, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.2 Hz, 1H), 7.10 – 7.04 (m, 1H), 7.00 (s, 2H), 6.79 (dd, J = 8.1, 0.8 Hz, 1H), 6.63 – 6.56 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 147.2, 147.1, 135.7, 135.4, 131.4, 129.4, 129.1, 129.1, 128.8, 128.3, 127.2, 127.1, 126.9, 126.8, 116.2, 115.4, 111.4; HRMS for $C_{21}H_{18}N_3$ $[M+H^+]$ calcd 312.3955 found 312.3951.



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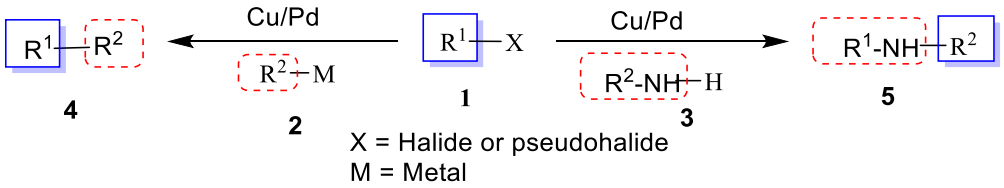
CHAPTER 3

Copper-Catalyzed Ullmann-Type C-N Coupling and Cross-Dehydrogenative Coupling (CDC) Reactions

3.1 INTRODUCTION

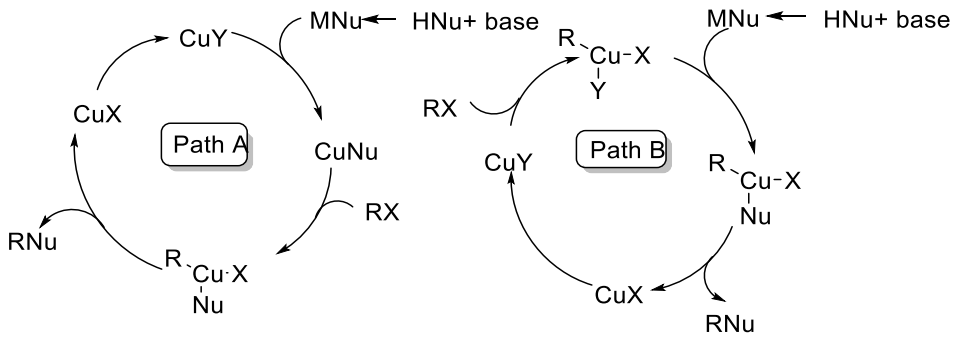
Synthesis of nitrogen-containing fused heterocyclic compounds *via* transition metal–catalyzed C–C and C–N bond formation have become an everlasting demand in organic chemistry because these heterocycles are used as a core structure in many natural products and pharmacologically potent molecules. Especially, construction of the C–N bond by copper and palladium–catalyzed Ullmann–type reaction or Buchwald reactions are a common procedure to access functionalized heterocycles. Many efficient methods have been developed by using simple starting material from the perspective of green and sustainable chemistry (**Scheme 3.1**).



Scheme 3.1: Copper and palladium-catalyzed C−C and C−N coupling reactions

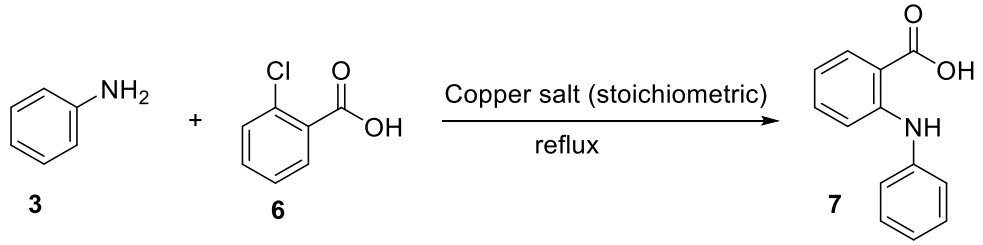
3.1.1 Ullmann C-N coupling

The synthesis of heterocycles *via* C−N, C−S, and C−O bond formation has been known for a century and serve good method in synthetic chemistry.[1] The Ullmann reaction is the reaction of aryl halides with nucleophiles in the presence of copper. However, the mechanism of the reaction follows two possible pathways (**Scheme 3.2**).[2] In path A, copper catalyst reacts with a nucleophile to afford more reactive complex which further reacts with the aryl halide to produce the coupled product. In path B, copper first reacts with aryl halide and create more electrophilic intermediate which reacts with a nucleophile and results in the formation of the coupled product. (**Scheme 3.2**, Path A or B).[3]



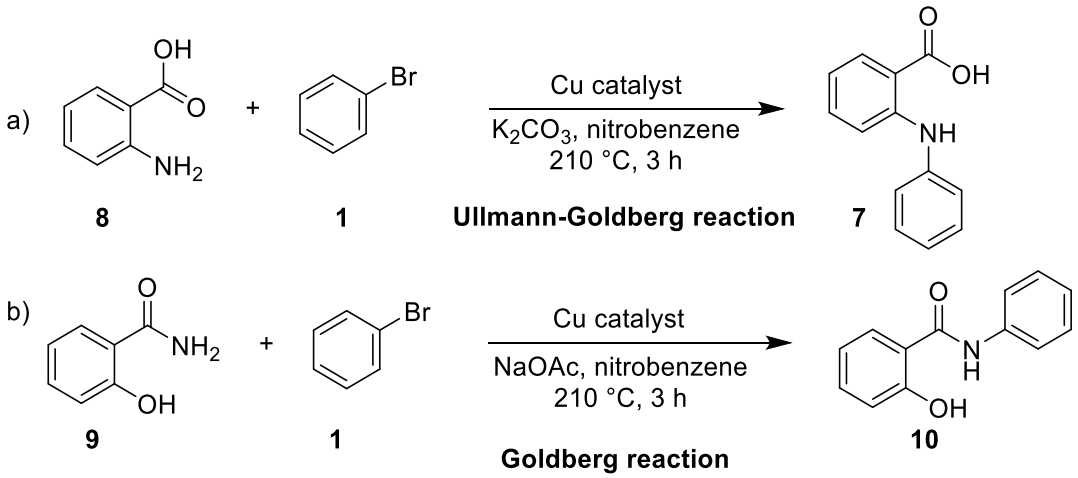
Scheme 3.2 Possible catalytic paths for Ullmann C−N coupling

In 1903, Ullmann developed a new method for the synthesis of 2-phenylaminobenzoic acid (**7**) from aniline (**3**) and 2-chlorobenzoic acid (**6**) in the presence of a stoichiometric amount of copper salt. (**Scheme 3.3**).[4-6]



Scheme 3.3 Ullmann C–N coupling reaction

A couple of years later, the copper-catalyzed reaction of 2-aminobenzoic (**8**) with an aryl (**1**) for direct amination (**7**) was described by Goldberg which is known as Ullmann–Goldberg amination reaction (**Scheme 3.4a**). Subsequently, Goldberg developed amidation reaction from 2-hydrobenzamide and aryl halide (**Scheme 3.4b**).[7,8]

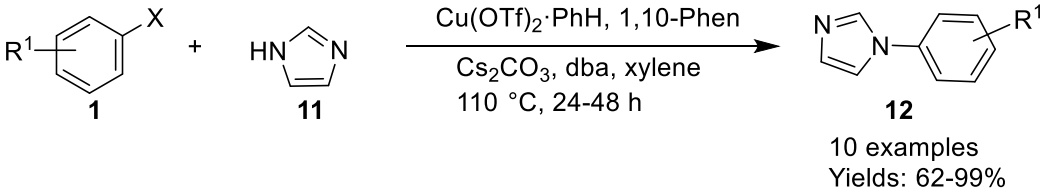


Scheme 3.4 Copper–catalyzed amination and amidation of aryl halides

Ullmann condensation was not explored completely till 2000 because of some problem associated with this reaction such as stoichiometric amounts of copper reagents, high temperatures, low yields, and limited substrate scopes.[2,9] These reactions required activated aryl halide and strong bases such as ^{t}BuOK, ^{t}BuONa, which make it incompatible with the broader range of functionality. To overcome these limitations in 1998, Buchwald and Hartwig independently described palladium–catalyzed *N*–arylation reaction which is applicable for all kind of amines and delivered mild and ligand tunable reaction condition. Despite their great importance, Buchwald reaction

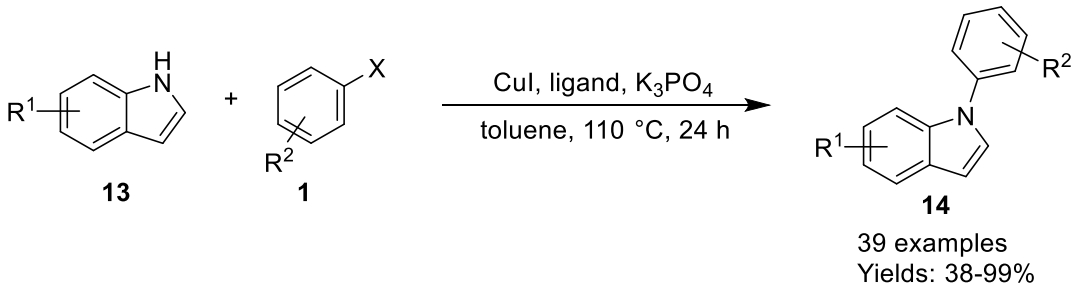
failed to overcome all issues such as high cost of palladium, functional group tolerance, air, and moisture sensitive reaction. Therefore, copper-catalyzed *N*–arylation reaction has emerged as a potential tool over palladium-catalyzed reactions due to cheaper and more environment friendly nature of copper salts.[10]

Buchwald group developed copper–catalyzed *N*–arylation (**12**) of imidazoles (**11**) by using 1,10-phenanthroline as a ligand, trans-dibenzylideneacetone (dba) as an additive, Cs_2CO_3 as a base in xylene at 110-125 °C (**Scheme 3.5**).[11] Electron–rich and electron–poor aryl halides and imidazole were tolerated well and afforded a corresponding product with good to excellent yields. However, the reaction yield was decreased in case of *ortho* substitution of aryl halide.



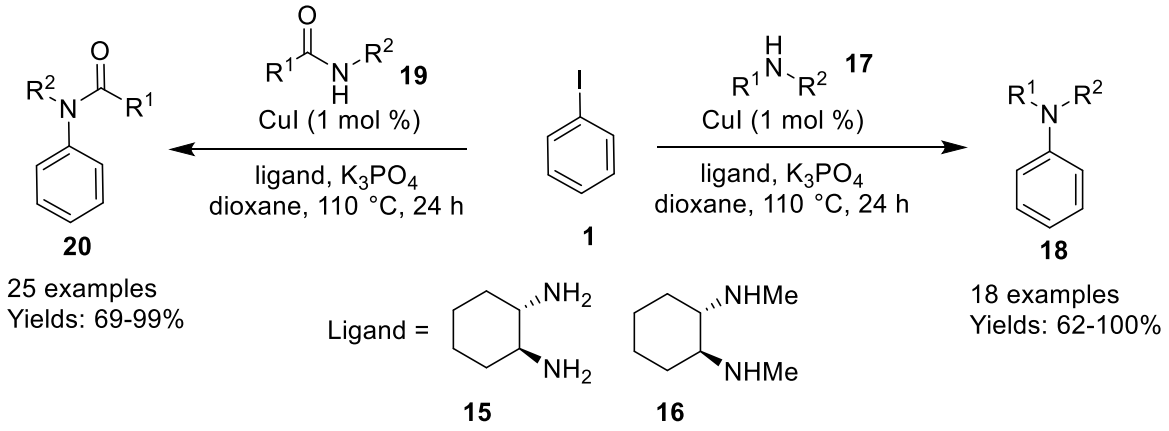
Scheme 3.5 Copper–catalyzed *N*–arylation of imidazole and aryl halide

Further same group extended their approach and developed copper–catalyzed an efficient method for *N*–arylation (**14**) by the reaction of aryl bromides and iodides (**1**) with indoles (**13**) in the presence *N*, *N*-dimethyl-1,2-diamine as a ligand, K_3PO_4 as a base in toluene at 110 °C (**Scheme 3.6**).[12]



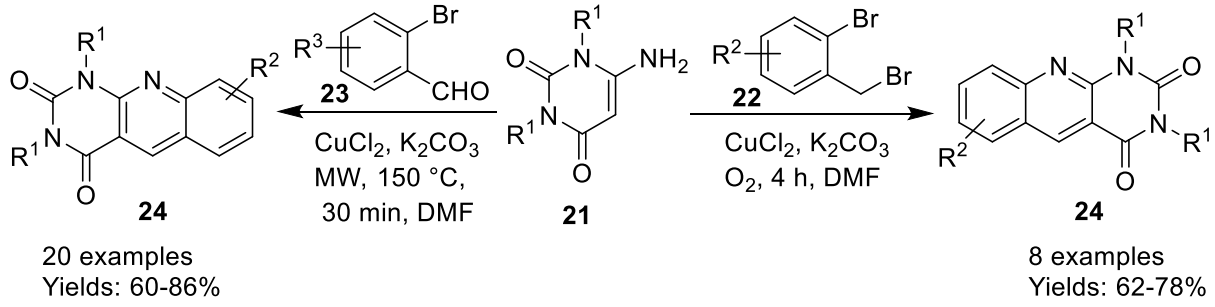
Scheme 3.6 Copper–catalyzed *N*–arylation of indoles

Buchwald and his team achieved an efficient, inexpensive catalytic system for amination and amidation of aryl halides (**1**) using CuI, ligands (**15** and **16**), K_3PO_4 in dioxane at 110 °C. (**Scheme 3.7**).[13] An ample range of amide derivatives (**19**) and different *N*-heterocycles such as indazoles, pyrazoles, phthalazinonepyrroles, 7-azaindoles, and carbazoles tolerated well and transformed into corresponding products with good to excellent yields (62-100%).



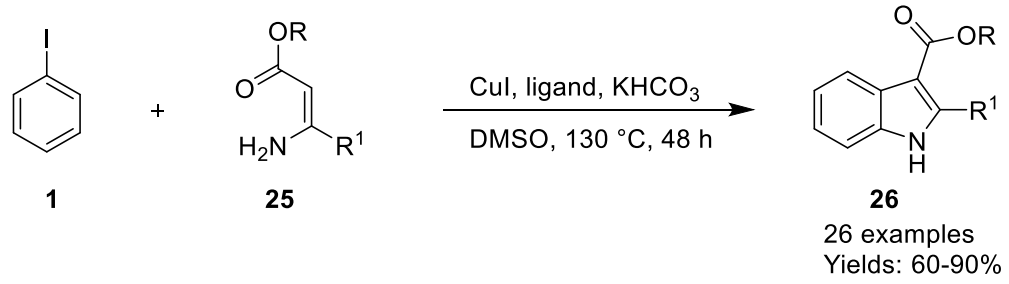
Scheme 3.7 Copper–catalyzed amidation of aryl halides and *N*–arylation of *NH*-heterocycles

Very recently, Choudhury group demonstrated copper–catalyzed one-pot synthesis of pyrimidine fused quinolines (**24**) using the reaction of 6-aminouracils (**21**) with 2-bromobenzyl bromide (**22**) or 2-bromobenzaldehydes (**23**) derivatives through C−C and C−N bond-forming strategy (**Scheme 3.8**).[14]



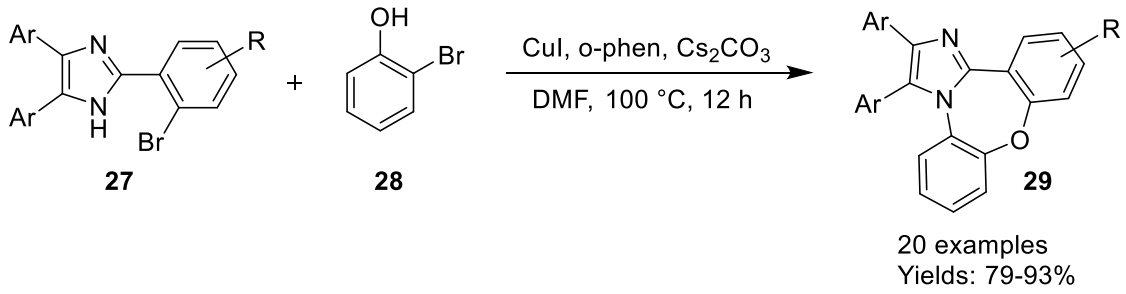
Scheme 3.8 Copper–catalyzed one-pot synthesis of pyrimidine fused quinolines

Li *et al.* described copper–catalyzed one-pot tandem arylation process for the synthesis of multisubstituted indoles (**26**) from enamines (**25**) and aryl iodides (**1**) through Ullmann–type C−N and cross–dehydrogenative coupling reaction (**Scheme 3.9**).[15] The reaction was adequately explored with a broad range of substituted enamine substrates and afforded corresponding indoles in good to excellent yields (60-90%).



Scheme 3.9 Copper–catalyzed one-pot synthesis of indole derivatives

Recently, Wang and his team reported a copper-catalyzed reaction between 4,5-diaryl-2-(2-bromophenyl)-1*H*-imidazoles (**27**) and 2-bromophenols (**28**) for the synthesis of dibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]oxazepines (**29**) (**Scheme 3.10**).[16] The reaction proceeded through two times Ullmann couplings for the construction of a C(sp^2)–O and a C(sp^2)–N bond and provided respective products in good yields.



Scheme 3.10 Copper–catalyzed synthesis of dibenzo[*b*,*f*]imidazo[1,2-*d*][1,4]oxazepines

3.1.2 Cross dehydrogenative coupling (CDC).

The direct functionalization of C−H bonds has two fundamental challenges to an organic chemist:

a) Reactivity: Activation of single C−H bond to make it prone for chemical attack.

b) Selectivity: There is no much difference in reactivity of various C−H bonds. Therefore, to activate a specific C−H bond is very difficult.

To overcome these challenges, In last decades transition metal–catalyzed, cross–dehydrogenative couplings (CDC) and oxidative cyclization have emerged as a challenging goal in catalysis for the synthesis of C–C and C–X (X = S, N, O) bond from simple and commercially available starting materials. The oxidative coupling reactions between two hetero arenes give an excellent opportunity for the rapid assembly of heterocycles and exploitation of their application in pharmaceutical and material science.[17] These protocols have received great attention due to their

advantageous features such as atom economy, reduced multistep synthesis, low cost, and no by-product generation. Therefore, the development of new synthetic methodology could be considered as a way of pursuing a novel method for prolonging the carbon chain *via* transition metal–catalyzed coupling reactions. Among transition metal, Pd and Cu–catalyzed reactions are the most useful methods for the oxidative C–C, C–N, and C–O bond formations.[17-20] Therefore noticeable efforts have been devoted by various research groups towards metal catalyzed cross-dehydrogenative (CDC) coupling reactions in different organic scaffolds. Some of the recent approaches are described below.

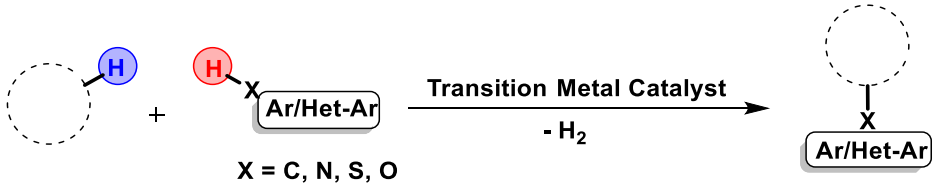
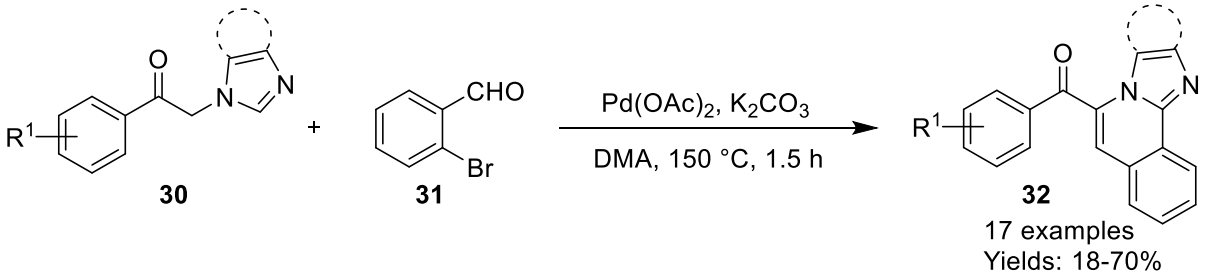


Figure 3.1 A generalized representation of the cross–dehydrogenative coupling

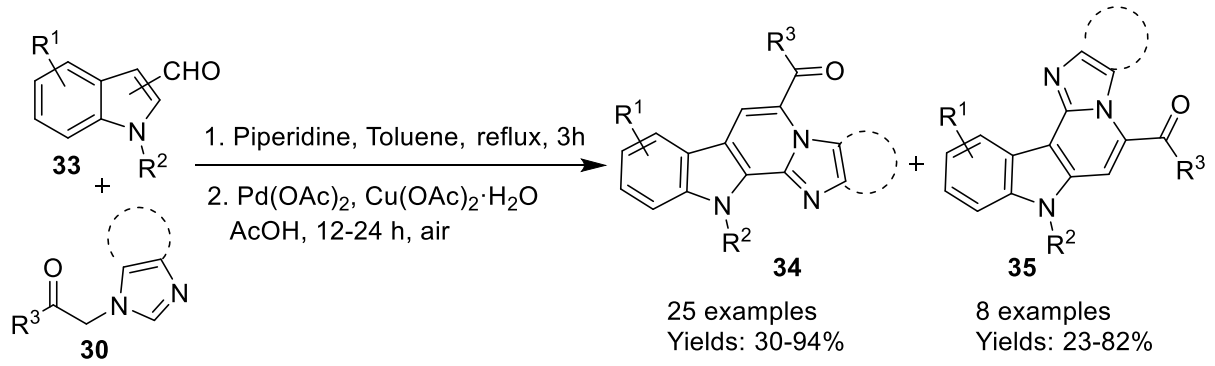
Kumar and his colleagues reported Pd–catalyzed tandem approach for C−H functionalization of imidazoles using diversely substituted imidazoles (**30**) and 2-bromobenzaldehyde (**31**). The tandem reaction involved cross aldol condensation followed by intramolecular direct arylation and provided respective imidazo/benzimidazo fused isoquinolines (**32**) in moderate to good yields (**Scheme 3.11**).[21]



Scheme 3.11 Pd–catalyzed synthesis of imidazo fused isoquinolines

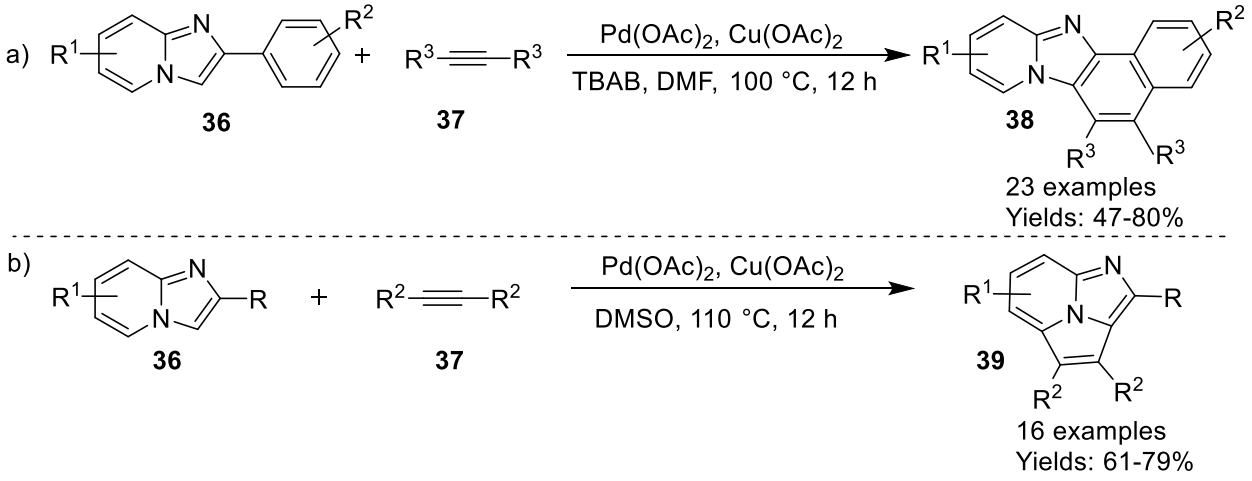
Subsequently, the same group developed Pd–catalyzed one-pot sequential approach for the synthesis of imidazopyridine-fused indoles (**34** and **35**) using diversly substituted methylene azole (**30**) and *N*-substituted-1*H*-indole-3-carboxaldehydes or *N*-substituted-1*H*-indole-2-carboxaldehydes (**33**) (**Scheme 3.12**).[22] The reaction proceeds through Knovenagel condensation followed by an intramolecular cross dehydrogenative coupling reaction. Moreover, the reaction

showcased a wide range of substituent tolerance with various methylene azole and providing a gallery of imidazopyridine-fused indoles in lower to excellent yields (23-94%).



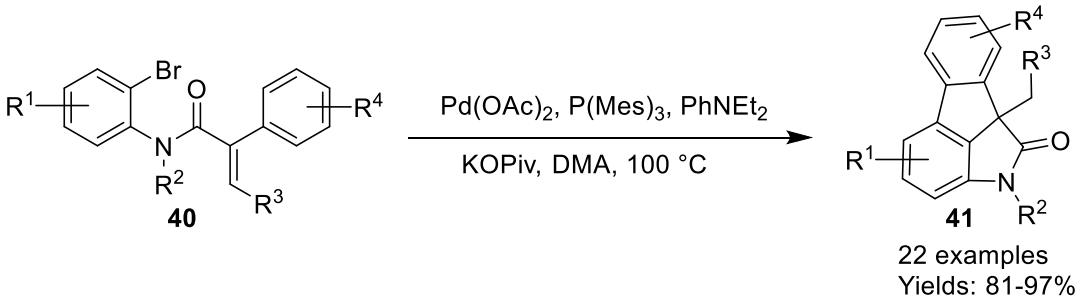
Scheme 3.12 Pd–catalyzed synthesis of imidazopyridine-fused indoles

Li *et al.* documented Pd–catalyzed oxidative cycloaromatization of substituted 2-phenylimidazo[1,2-*a*]pyridine (**36**) with internal alkyne (**37**) (**Scheme 3.13a**).[23] In the same year, Hajra group described direct dehydrogenative annulation of imidazo[1,2-*a*]pyridines with alkynes affording imidazo[5,1,2-*cd*]indolizine (**39**) in good yields (61-79%) (**Scheme 3.13b**).[24]



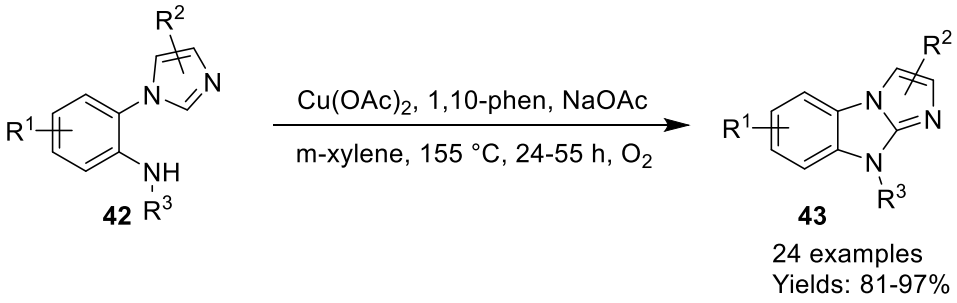
Scheme 3.13 Pd–catalyzed synthesis of fused imidazo[1,2-*a*]pyridines

Bunescu *et al.* reported a simple and efficient method through Pd–catalyzed a tandem reaction for the synthesis of tetracyclic[3,4]-fused oxindoles (**41**) from simple *o*-bromoanilides (**40**) (**Scheme 3.14**).[25] Moreover, the reaction showcased a wide range of substituent tolerance and providing a series of fused oxindoles in excellent yields (81-97%).



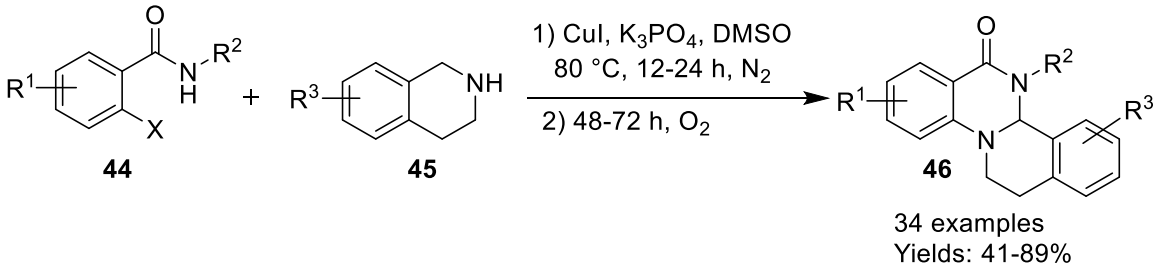
Scheme 3.14 Pd–catalyzed synthesis of fused oxindoles

Wang *et al.* developed Cu–catalyzed an intramolecular reaction of 2-(1*H*-imidazol-1-yl)-*N*-alkylbenzenamines (**42**) for the synthesis of imidazobenzimidazoles (**43**) (**Scheme 3.15**).[26] The reaction underwent through copper-catalyzed intramolecular cross-dehydrogenative coupling reaction, provided a respective product with excellent yields (81-97%).



Scheme 3.15 Copper–catalyzed synthesis of imidazobenzimidazoles

The same group developed another copper–catalyzed approach for the development of tetrahydroisoquinolino[2,1-*a*]quinazolinone (**46**) (**Scheme 3.16**).[27] The one–pot sequential method proceeded *via* copper–catalyzed *N*-arylation followed by intramolecular aerobic oxidative cyclization led to fused quinazolinone in moderate to excellent yields (41-89%)



Scheme 3.16 Copper–catalyzed synthesis of tetrahydroisoquinolino[2,1-*a*]quinazolinone

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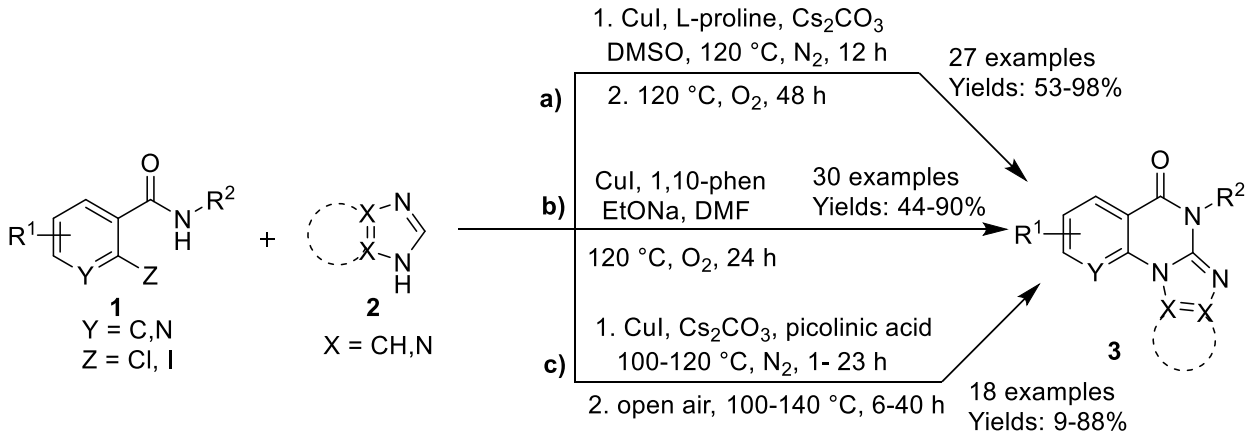
CHAPTER 3A

Synthesis of Azole-Fused Quinazolines *via* One-Pot Sequential Ullmann-Type Coupling Followed by Intramolecular Dehydrogenative C–N Bonding

3.3A.1 INTRODUCTION

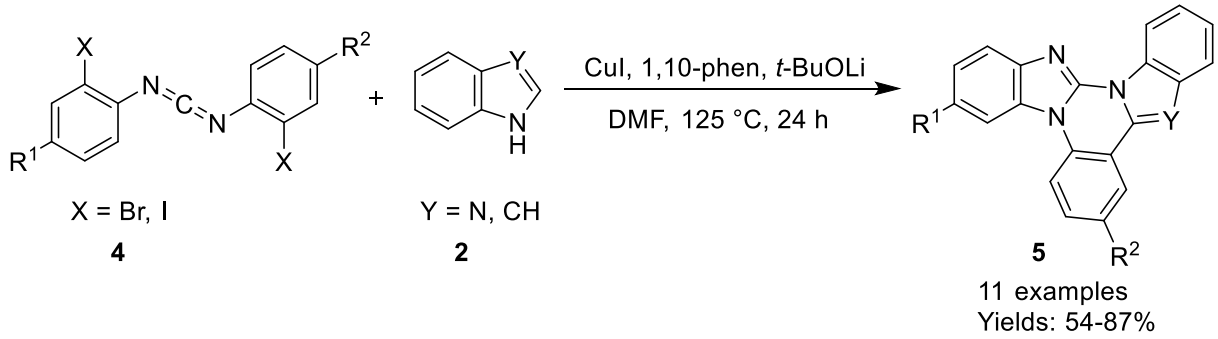
Synthesis of nitrogen-containing fused heterocycles is a constant demand in organic chemistry as these heterocycles are used in many natural products and pharmacologically potent molecules.[1-8] Construction of the C–N bond by Ullmann-type reaction or Buchwald coupling is a common procedure to access functionalized azaheterocycles.[9-20] In recent years, transition metal–catalyzed, cross–dehydrogenative coupling and oxidative cyclization emerged as an efficient and straightforward method for the synthesis of functionalized azaheterocycles from simple and commercially available non-prefunctionalized starting materials.[21,22] These approaches have received great attention in recent years due to their advantageous features such as atom economy, reduced byproduct generation, and multistep synthesis.[23-26] It is believed that the fusion of two or more bioactive heterocycles may lead to new hybrid motifs with interesting properties. In addition, fused polycyclic structures derived from a fusion of quinazolines with azoles have been studied as organic light-emitting devices (OLEDs).[27] Despite their importance in medicinal chemistry and material science, very few synthetic methods are available to access these fused frameworks, which might be due to the unavailability of starting materials and complex multistep procedures. A brief review of azole fused heterocycles is discussed below.

Synthesis of imidazo/benzimidazo quinazolinones *via* copper–catalyzed Ullmann type N–arylation and intramolecular C–H amidation was described by Fu group under oxygen atmosphere in DMSO at 120 °C, affording the corresponding quinazolinones (**3)** from different amides (**1)** and azole like imidazole and benzimidazole (**2)** in good to excellent yields (53-98%) (**Scheme 3.3A.1a)**.[28] Subsequently, Bao and co-workers employed one-pot method for the development of quinazolinones by improving the reaction time (**Scheme 3.3A.1b)**.[29] Recently, Hognasbacka *et al.* have developed tricyclic heterocycles under aerobic oxidation. However, this approach was also useful for direct arylation reaction (**Scheme 3.3A.1c)**.[30]



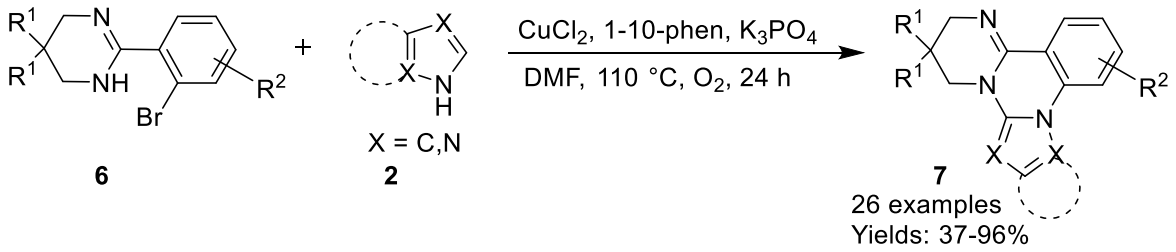
Scheme 3.3A.1 Copper-catalyzed one-pot synthesis of azole fused quinazolinones

Lv and colleagues reported an efficient copper-catalyzed domino approach for the synthesis of azole fused quinazolines (**5)** *via* double cyclization. The developed tandem approach involved nucleophilic addition, intramolecular C–N coupling and intramolecular sp^2 C–H arylation of azole (**2**) with bis-(*o*-haloaryl)-carbodiimide (**4**) (**Scheme 3.3A.2)**.[27] Variously substituted azoles and substituted bis-(*o*-haloaryl)-carbodiimides were participated well under the optimized condition, provided azole fused quinazolines with good to excellent yields (54-87%).



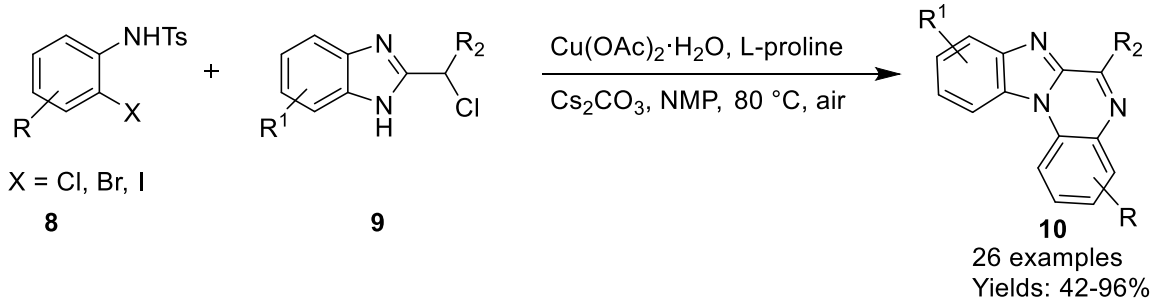
Scheme 3.3A.2 Copper–catalyzed tandem method for the synthesis of azole–fused quinazolines

Chen *et al.* disclosed the copper-catalyzed double C–N coupling for the synthesis of azole-fused pyrimido[1,2-*c*]quinazolines and imidazo[1,2-*c*]quinazolines (**7**). The developed protocol proceed through C–N cross-coupling followed by C–H functionalization reaction of 2-(2-bromophenyl)-1,4,5,6 tetrahydropyrimidines (**6**) with azoles (**2**) (**Scheme 3.3A.3**).[31] The scope of the reaction was examined by varying different azoles such as benzimidazoles, pyrazoles, and 1,2,4-triazoles which were compatible under the optimized condition and gave the target compounds in moderate to excellent yields (37-96%).



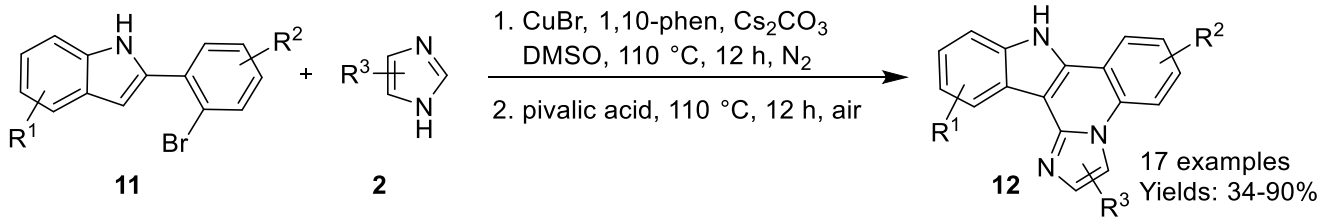
Scheme 3.3A.3 Copper-catalyzed one-pot synthesis of fused quinazolines

Ma group accessed one-pot process for the construction of benzo[4,5]imidazo[1,2-*a*]quinoxalines (**10**) by employing intermolecular nucleophilic substitution followed by copper-catalyzed C–N arylation of *N*-(2-halophenyl)-4-methylbenzenesulfonamide (**8)** with 2-(chloromethyl)-1*H*-benzo[*d*]imidazole (**9)** (**Scheme 3.3A.4)**.[32] All the substituent participated well under the standard condition and afforded quinoxalines in moderate to excellent yields (42-96%).



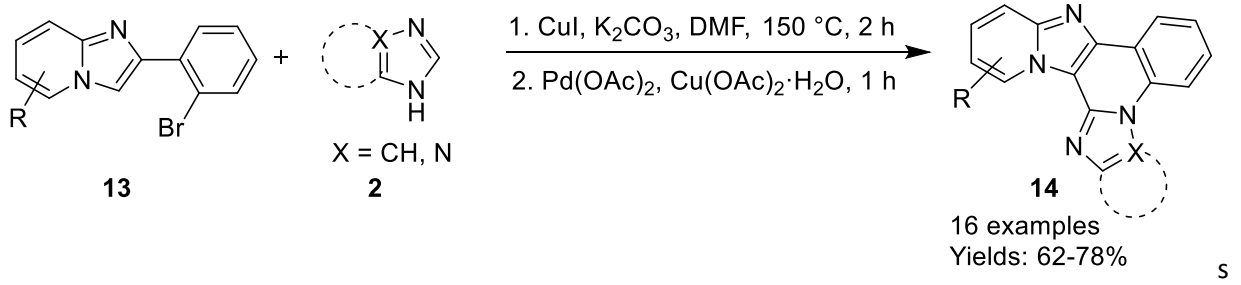
Scheme 3.3A.4 Synthesis of benzo[4,5]imidazo[1,2-*a*]quinoxaline through copper–catalyzed domino approach

Wang *et al.* disclosed copper–catalyzed one-pot synthesis of indoloimidazoquinolines (**12**) from 2-(2-bromophenyl)-1*H*-indoles (**11**) and imidazoles/benzimidazoles (**2**) under aerobic condition. This reaction involved sequential copper–catalyzed intermolecular *N*-arylation followed by an intramolecular cross–dehydrogenative coupling (CDC) reaction (**Scheme 3.3A.5**).[33]



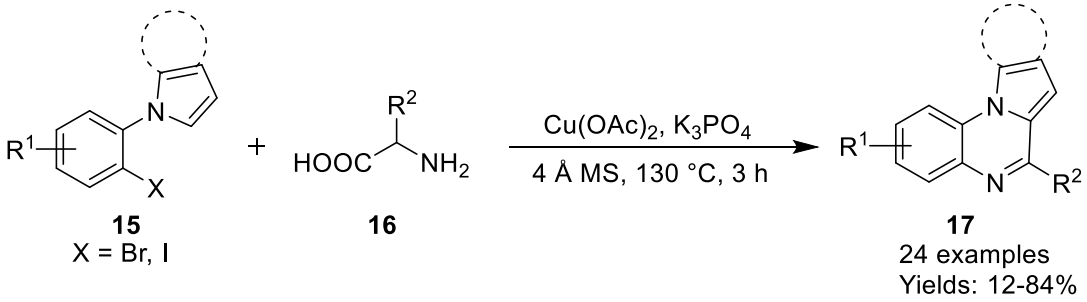
Scheme 3.3A.5 Copper–catalyzed one-pot synthesis of indolo[3,2-*c*]quinoline derivatives

Kumar and his team developed a simple one-pot protocol for the synthesis of novel azole fused imidazo[1,2-*a*]pyridine (**14**) by sequential copper–catalyzed Ullmann type C–N coupling and palladium-catalyzed intramolecular cross–dehydrogenative coupling involving substituted 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**13**) and different azoles (**2)** (**Scheme 3.3A.6)**.[34] The substrate scope was examined under an optimized condition which afforded the corresponding azole fused imidazo[1,2-*a*]pyridine **(14)** in good yields (62-78%). This method provided a new strategy for the construction of useful polyheterocyclic compounds for medicinal purpose.



Scheme 3.3A.6 Synthesis of azole-fused imidazo[1,2-*a*]pyridines *via* C–N coupling

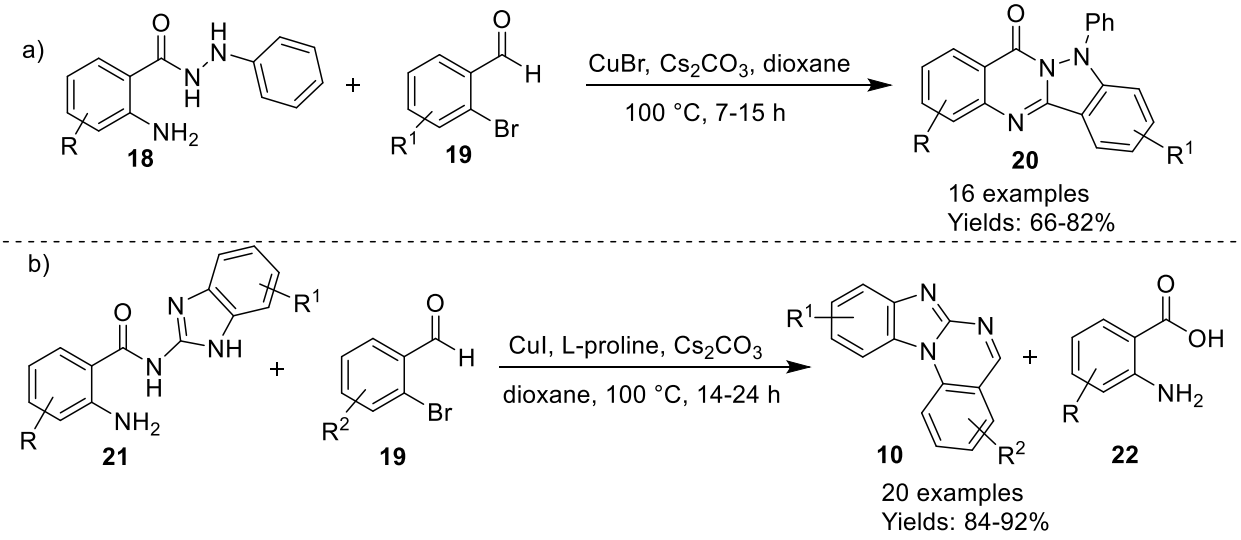
Ma group developed copper–catalyzed one-pot tandem reaction from 1-(2-halophenyl)-1*H*-pyrroles (**15**) and α-amino acids (**16**) for the synthesis of pyrrolo[1,2-*a*]quinoxalines (**17**). The reaction proceeded through sequential copper–catalyzed Ullmann-type *N*-arylation, aerobic oxidation, intramolecular addition followed by decarboxylation (**Scheme 3.3A.7).**[35]



Scheme 3.3A.7 Synthesis of pyrrolo[1,2-*a*]quinoxalines from 1-(2-halophenyl)-1*H*-pyrroles

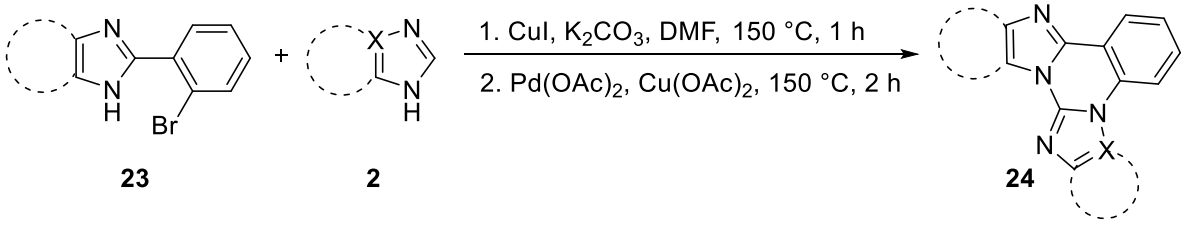
Wang group demonstrated a copper-catalyzed reaction of 2-amino-*N*-arylbenzohydrazide (**18**) with 2-bromo benzaldehyde (**19)**, affording 5-aryl indazolo[3,2-*b*]quinazolin-7(5*H*) (**20**) in good to excellent yields (66-82%). The mechanism of this reaction completed in three steps through one-pot tandem reaction *i.e.* (a) formation of dihydroquinazolinon, (b) oxidation of dihydroquinazolinone to quinazolinone under aerobic condition, (c) C−N coupling reaction. The key step of the reaction is C–N coupling of hydrazine with a halide (**Scheme 3.3A.8a)**.[36]

Subsequently, the same group synthesized benzimidazo[1,2-*a*]quinazolines (**10**) through copper–catalyzed tandem reaction of *N*-(2-benzimidazolyl)-2-aminobenzamide (**21**) with 2-bromo benzaldehyde (**19)**. The reaction proceeded through sequential copper–catalyzed Ullmann *N*-arylation followed by two C–N bond cleavage reaction (**Scheme 3.3A.8b)**.[37]



Scheme 3.3A.8 Synthesis of fused heterocycles *via* copper–catalyzed C–N coupling

As evident from the literature report azole fused, heterocycles can be developed by employing Ullmann type C–N coupling and cross–dehydrogenative coupling reaction in one–pot fashion. These methods are also good from the viewpoint of green and sustainable chemistry. As a part of our continued interest in the assembly of nitrogen-containing polyheterocyclic compounds by employing C–H functionalization, this chapter disclosed the synthesis of azole–fused quinazolines through a sequential Ullmann–type C–N coupling followed by palladium–catalyzed cross–dehydrogenative coupling reaction.



Scheme 3.3A.9 Synthesis of azole–fused quinazolines from 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole and azoles

3.3A.2 RESULTS AND DISCUSSION

To evaluate the feasibility of our proposed synthetic pathway, initially, we reacted 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**23a**) and 1*H*-imidazole (**2a**) in the presence of CuI (20 mol %) and K_2CO_3 (2 equiv.) at 150 °C under air for 24 h. To our satisfaction 2,3-diphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (**24aa**) was obtained in 8% yield. On the basis of Mori *et al*. and Schreiber *et al*. reports,[11] we investigated that a catalytic amount of copper could enable for dual C–N bonding, Ullmann–type coupling and oxidative C–N bonding, between **23a** and **2a** to furnish the targeted fused quinazolines, (**Scheme 3.3A.9**).

The structure of **24aa** was confirmed by NMR spectroscopic analysis (^{1}H and ^{13}C) and mass spectrometry data. In the ^{1}H NMR spectrum, all peaks are well agreed with structure. The peaks in the ^{13}C NMR spectrum were also consistent with the structure of **24aa**. Finally, the presence of a peak at *m/z* = 361.1443 in the HRMS spectrum corresponding to molecular ion $C_{24}H_{17}N_4^+$ $[M+H]^+$ confirmed the structure of **24aa**. The ^{1}H and ^{13}C spectrum of **24aa** is depicted in **Figure 3.3A.1.**

From the initial reaction, we then screened various palladium catalysts, oxidants, bases, and solvents to obtain the optimum conditions for a sequential one–pot, two-step reaction (**Table 3.3A.1**). Among different palladium catalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ screened for the oxidative C–N coupling, $Pd(OAc)_2$ offered the highest yield of **24aa** (entries 2–4, **Table 3.3A.1**). The yield of **24aa** was diminished when K_2CO_3 was replaced with other bases such as Cs_2CO_3, K_3PO_4, Na_2CO_3, and *t*-BuOK (entries 7–10, **Table 3.3A.1**). Simultaneously, various solvents were screened, and we determined that DMF and *N*, *N*-dimethylacetamide (DMA) are suitable solvents for the sequential process while other solvents, including 1,4-dioxane, toluene and acetonitrile, offered low yields of **24aa** (entries11–14, **Table 3.3A.1**). Attempts to replace $Cu(OAc)_2 \cdot H_2O$ with other oxidants such as $PhI(OAc)_2$, Ag_2CO_3, $CuCl_2$, Cu_2O, and $CuSO_4$ were unsuccessful (entries 15–19, **Table 3.3A.1**). Only traces of **24aa** were detected when the sequential process was carried out in the absence of palladium catalyst (entry 20, **Table 3.3A.1**).

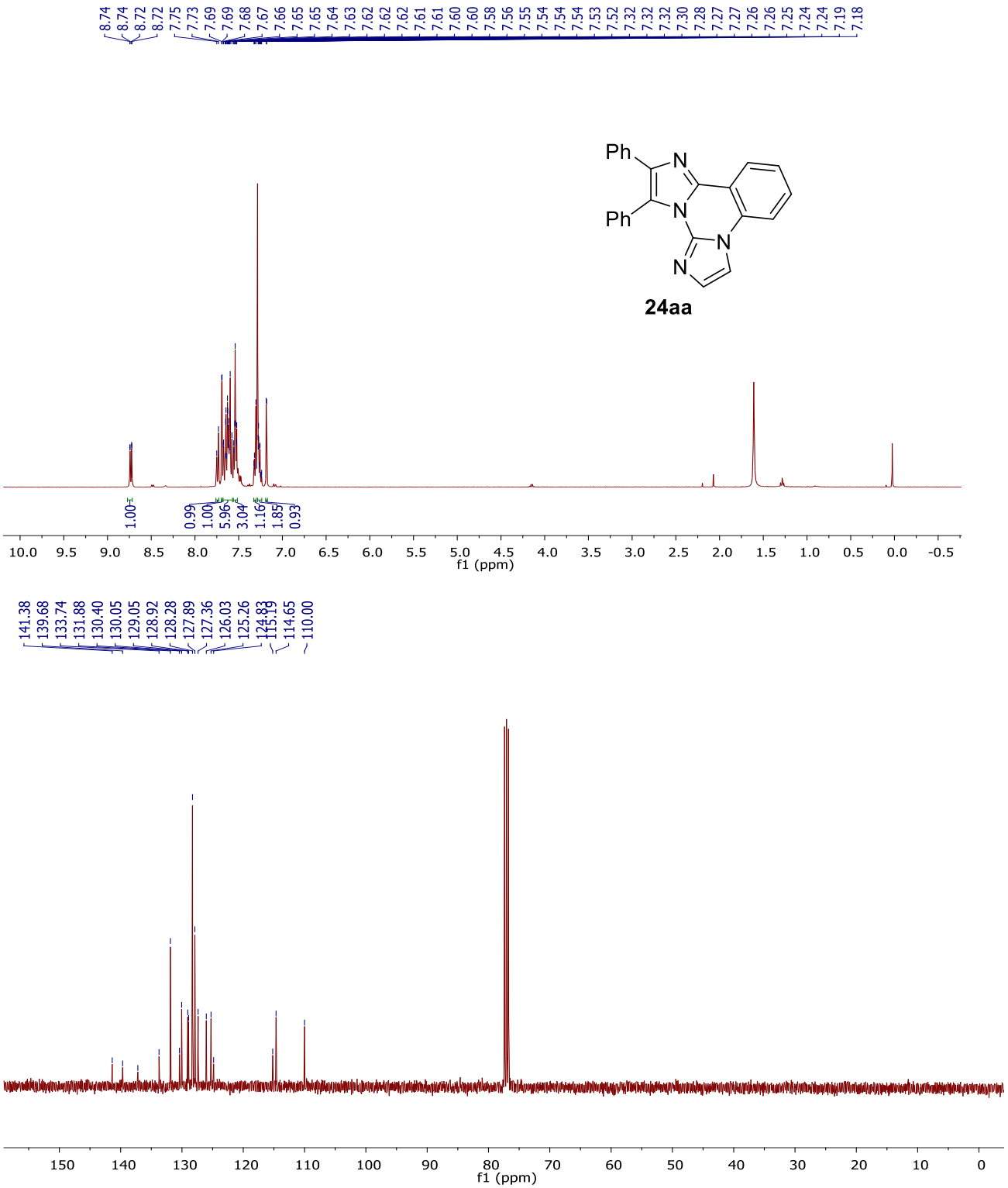
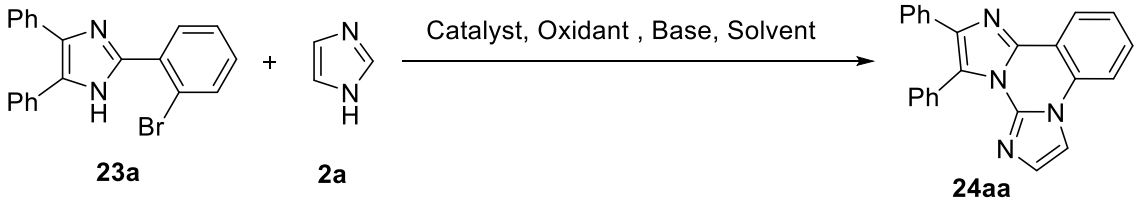


Figure 3.3A.1 ^{1}H and ^{13}C NMR spectra of 2,3-diphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (**24aa**) in $CDCl_3$

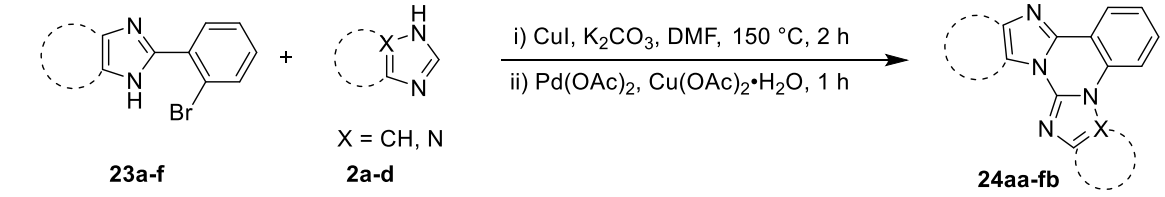
Table 3.3A.1 Optimization of the reaction condition



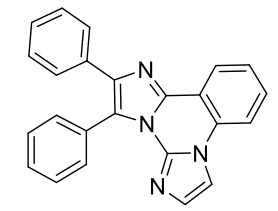
Entry	Catalyst	Oxidant	Base	Solvent	Yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	65
2	$Pd(PPh_3)_4$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	38
3	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2.H_2O$	K_2CO_3	DMF	45
4	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	71
5	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	67[c]
6	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	63[d]
7	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	Cs_2CO_3	DMF	52
8	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_3PO_4	DMF	48
9	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	Na_2CO_3	DMF	28
10	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	t-BuOK	DMF	21
11	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMA	65
12	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	1,4-dioxane	-[e]
13	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	Toluene	20
14	$Pd(OAc)_2$	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	CH_3CN	52
15	$Pd(OAc)_2$	$PhI(OAc)_2$	K_2CO_3	DMF	42
16	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DMF	38
17	$Pd(OAc)_2$	$CuCl_2$	K_2CO_3	DMF	64
18	$Pd(OAc)_2$	Cu_2O	K_2CO_3	DMF	-[e]
19	$Pd(OAc)_2$	$CuSO_4$	K_2CO_3	DMF	61
20	-[f]	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	Trace

[a]Reaction conditions: **23a** (1.0 mmol), **2a** (1.2 mmol), CuI (20 mol %), base (2.0 mmol), solvent (2 ml), 150 °C, 1 h followed by palladium catalyst (5 mol %), oxidant (2.0 mmol), 150 °C, 2 h. [b] Isolated yield. [c]1.2 mmol of $Cu(OAc)_2{\cdot}H_2O$ were used. [d]1.2 mmol of K_2CO_3 were used. [e]Only **25** was formed. [f]Reaction was performed in the absence of palladium catalyst.

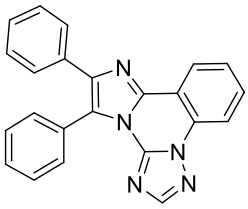
Table 3.3A.2 Substrate scope for sequential dual C–N bonding[a,b]



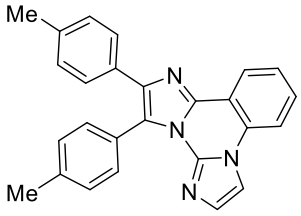
23a-f **2a-d** **24aa-fb**



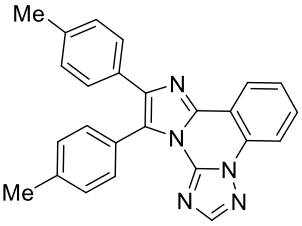
24aa, 71%



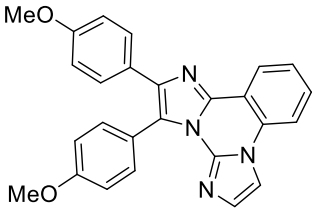
24ab, 62%



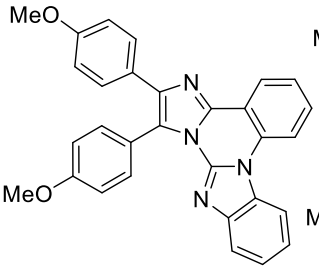
24ba, 56%



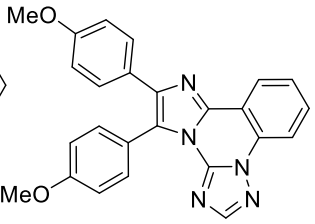
24bb, 61%



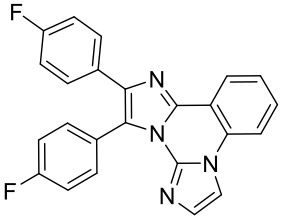
24ca, 56%



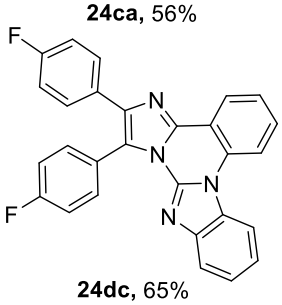
24cc, 52%



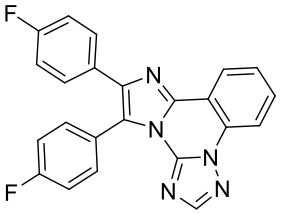
24cb, 58%



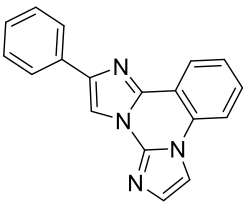
24da, 81%



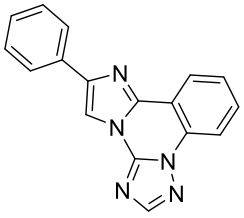
24dc, 65%



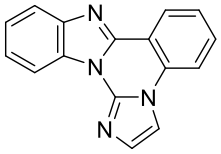
24db, 79%



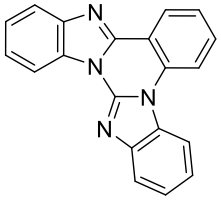
24ea, 58%



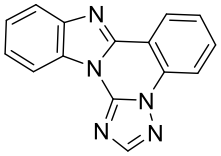
24eb, 52%



24fa, 62%



24fc, 68%



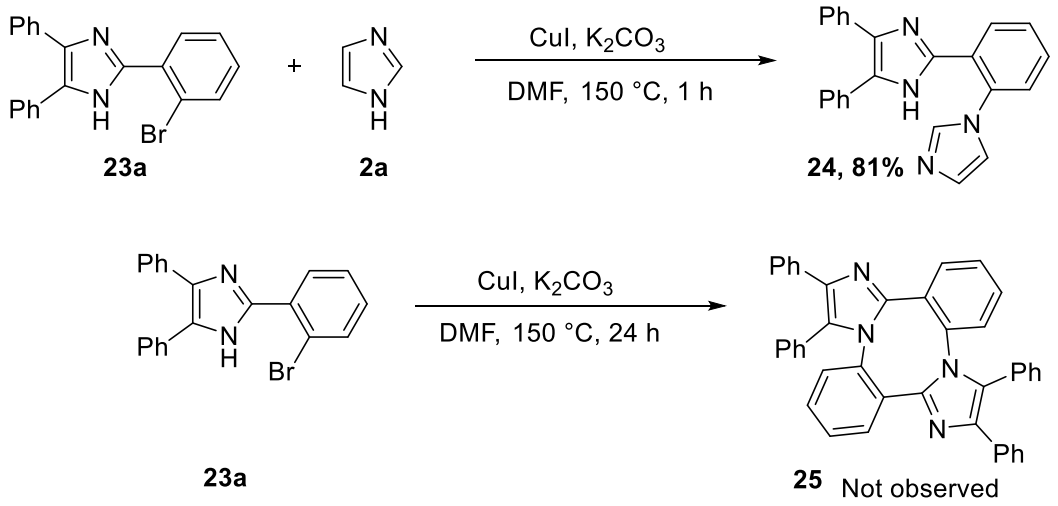
24fb, 61%

[a]Reaction conditions: **23** (1.0 mmol), **2** (1.2 mmol), CuI (20 mol%), K_2CO_3 (2.0 mmol), DMF (3 ml), 150 °C, 1 h then $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol), 150 °C, 2 h. [b]Isolated yield.

With the established condition in hand (entry 4, **Table 3.3A.1),** we then focused our attention on evaluating substrate scope for the sequential process and results are summarized in **Table 3.3A.2** Different azole like 1*H*-imidazoles, 1*H*-benzimidazoles, 1*H*-1,2,4-triazoles, tolerated well and

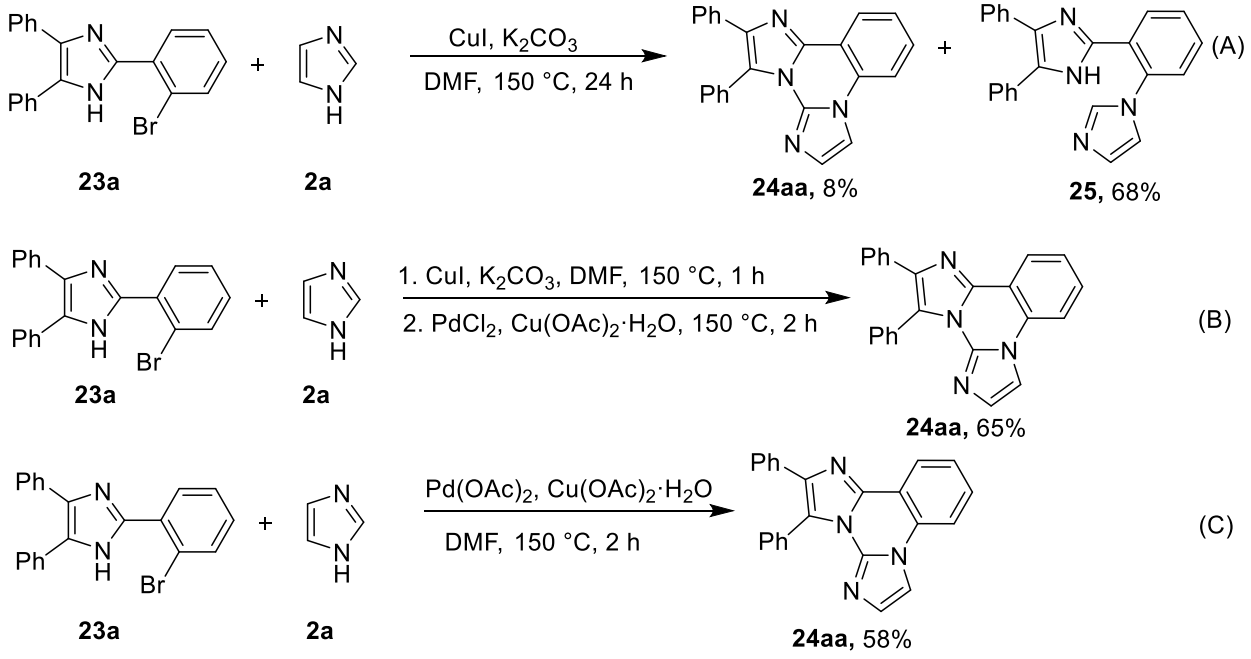
gave moderate to good yields of *N*-fused structures under standard conditions. Diversely substituted 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazoles smoothly participated in one–pot reactions and delivered corresponding fused structures with good yields (**24aa–db, Table 3.3A.2**). Imidazole's with electron–withdrawing groups such as fluoro on aryl rings at C–4 and C–5 positions furnished higher yields of fused quinazolines when compared to electron-rich groups such as methyl and methoxy on aryl rings at these positions. Unsymmetrical imidazole also tolerated well under optimized condition (**24ea–eb**, **Table 3.3A.2**). Similarly, 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole also underwent smoothly. Initially, Ullmann–type coupling followed by oxidative cyclization and offered polycyclic *N*–fused structures in good yields (**24fa–fb**, **Table 3.3A.2**).

To gain insight into the mechanism of the reaction some designed control experiments were conducted. Copper-catalyzed, Ullmann–type coupling of **23a** with imidazole (**2a)** in the presence of CuI (20 mol%) and K_2CO_3 (2 equiv.) in *N*,*N*-dimethylformamide for 1 h at 150 °C resulted in formation of 2-(2-(1*H*-imidazol-1-yl)phenyl)-4,5-diphenyl-1*H*-imidazole (**25**) in 81% yield (**Scheme 3.3A.10**). The reaction was found to be clean, and no side product was observed in this reaction. The reaction of **23a** was performed in the absence of **2a** under these conditions to examine selectivity of the reaction. The formation of 2,3,10,11-tetraphenyldibenzo[*c*,*g*]diimidazo[1,2-*a*:1′,2′-*e*][1,5]diazocine (**26**) was not observed even after longer reaction time, and **23a** was recovered in almost quantitative yield (**Scheme 3.3A.10**).



Scheme 3.3A.10 Control experiments for the synthesis of azole fused quinazolines

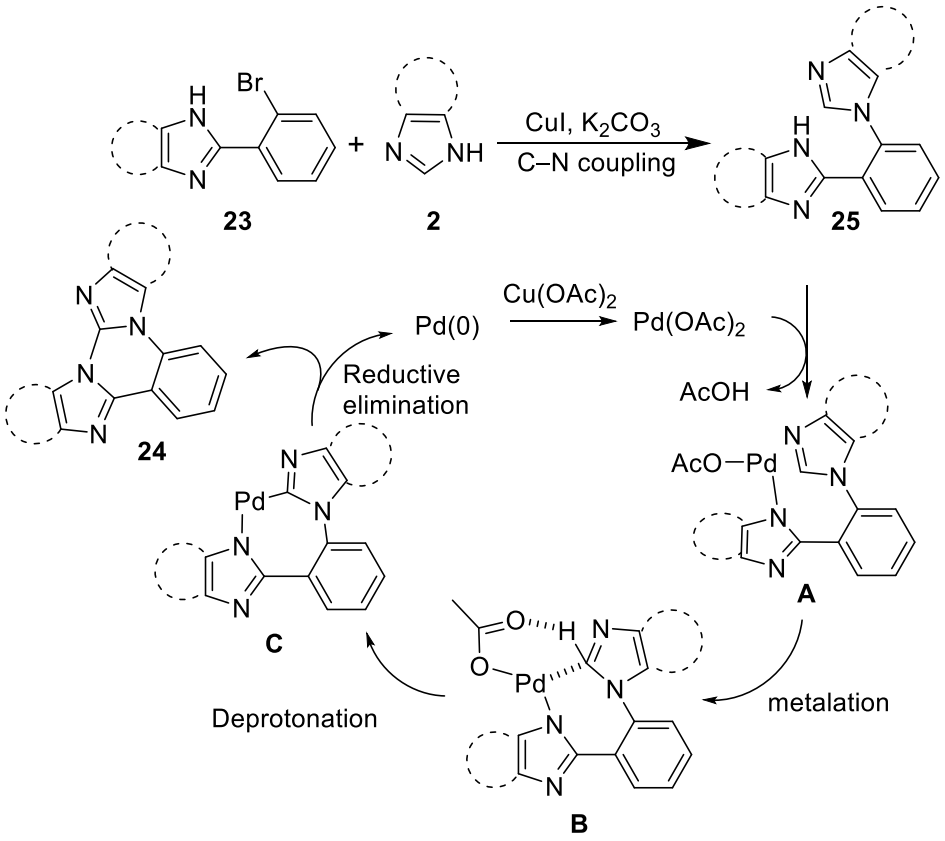
Further, azole–fused quinazoline (**24aa)** was synthesized under a copper-catalyzed oxidative C–N coupling reaction; the reaction was continued for 24 h at 150 °C. As expected, the targeted molecule **24aa** was detected in the reaction mass albeit in 8% yield (**Scheme 3.3A.11A**). The major product isolated from this experiment was Ullmann–coupled product, 2-(2-(1*H*-imidazol- 1-yl)phenyl)-4,5-diphenyl-1*H*-imid-azole (**25**, 68%). This might be due to less reactivity of azole N–H toward the oxidative cyclizations. To improve the efficiency of dehydrogenative C–N coupling, a catalytic amount of $PdCl_2$ (5 mol %) together with the $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv.) was added. The Pd/Cu system effectively promoted the oxidative C–N bonding through C–H activation/functionalization to deliver fused quinazoline **24aa** in 65% yield in shorter reaction time (**Scheme 3.3A.11B**). It is also worth mentioning that the one-step reaction of **23a** and **2a** in the presence of $Pd(OAc)_2$ (5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ gave fused quinazolines **24aa** in 58% yield (**Scheme 3.3A.11C**).



Scheme 3.3A.11 Control experiments to propose mechanism

On the basis of literature precedence, the following mechanism has been proposed for the formation of **24** starting from **23** and **2** (**Scheme 3.3A.12**). In the presence of copper (I), **23** and **2** undergo Ullman–type C–N coupling to give the intermediate **25**. With the assistance of base, $Pd(OAc)_2$ binds with N–H of **25** and offers **A**, which then undergoes intramolecular deprotonation

and metallation to give intermediate **C**. Finally, reductive elimination of **C** furnishes the desired product **24**, and the oxidation of resultant Pd(0) to Pd(II) in the presence of $Cu(OAc)_2 \cdot H_2O$ completes the catalytic cycle.



Scheme 3.3A.12 Plausible mechanism for the synthesis of azole–fused quinazoline.

3.3A.3 CONCLUSIONS

An expedient and straightforward method has been developed for the synthesis of diversely substituted *N*–fused polycyclic structures by employing copper–catalyzed Ullmann–type C–N coupling followed by Pd/Cu co–catalyzed intramolecular cross–dehydrogenative coupling reaction. The designed strategy necessitates simple and easily accessible precursors and builds fused structures with high complexity in a single step.

3.3A.4 EXPERIMENTAL SECTION

3.3A.4.1 Experimental section

Melting points were determined in open capillary tubes on an automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates. The chemical structures of the final products were determined by their NMR and mass analysis. NMR spectra were recorded on Bruker Ascend 400. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard or deuterated solvent peak ($CDCl_3$) and DMSO-d_6). The HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. All other chemicals were obtained from the commercial suppliers and used without further purification.

3.3A.4.2 General procedure for the synthesis of 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole.

A clean oven dried 50 mL round bottom flask was charged with benzil (1 mmol), 2-bromobenzaldehyde (1 mmol), NH_4OAc (4 mmol), L-proline (20 mol %) and MeOH (3 mL). The reaction mixture was heated with stirring at 80 °C under reflux for 12 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature, and MeOH was evaporated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (2 × 20 mL). Organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude solid was washed with hexane twice to remove impurity to afford 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole(79% yield); mp 203-205 °C.

3.3A.4.3 General procedure for the synthesis of 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole.

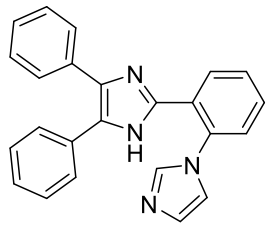
A clean oven dried 50 ml round bottom flask was charged with 1,2-phenylenediamine (1mmol), 2-bromobenzaldehyde (1mmol), TsOH (2mmol) and DMF (3 ml). The reaction mixture was heated with stirring at 100 °C under air for 5 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature. The residue was diluted with water (20 mL) and extracted with EtOAc (2 × 20 mL). Organic layers were combined, dried over Na_2SO_4 and concentrated under reduced

pressure. The crude solid was washed with hexane twice to remove impurity to afford 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazolein 70% yield; mp 210-213 ˚C.

3.3A.4.4 General procedure for synthesis of 2,3-diphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (24aa).

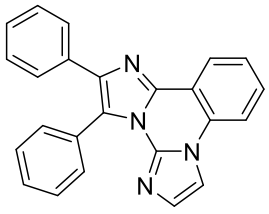
A clean oven dried 10 mL round bottom flask was charged with **23a** (1 mmol), **2a** (1.2 mmol), K_2CO_3 (2 mmol), CuI (0.20 mmol) and DMF (2 mL). The resulting solution was stirred at 150 ˚C for 1 h. On completion of first step, $Pd(OAc)_2$ and $Cu(OAc)_2 \cdot H_2O$ (2 mmol) was added in same flask without isolating intermediate and again the reaction mass was stirred at 150 ˚C for 2 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature, diluted with water and extracted with EtOAc (2 ×10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (100-200 mesh) using ethyl acetate/hexane (15%, v/v) as eluent.

2-(2-(1*H*-imidazol-1-yl)phenyl)-4,5-diphenyl-1*H*-imidazole (25). Yield 81%, Off-white solid,



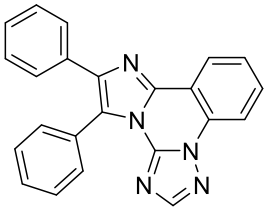
mp 144 –147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 7.1 Hz, 1H), 7.71 – 7.54 (m, 8H), 7.53 – 7.45 (m, 4H), 7.8 – 7.19 (m, 4H), 7.14 (d, J = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 139.7, 137.2, 133.7, 131.9, 130.4, 130.0, 130.0, 129.0, 128.8, 128.29, 128.3, 127.9, 127.4, 126.0, 125.2, 124.8, 115.2, 114.6, 110.0. HRMS (ESI) calcd for $C_{24}H_{19}N_4$ 363.1604 found 363.1607 $[M+H]^+$.

2,3-Diphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (24aa). Yield 71%, Off-white solid, mp 231–

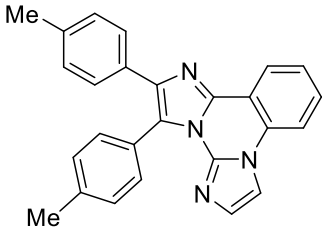


234 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 7.9, 1.1 Hz, 1H), 7.74 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.68 – 7.57 (m, 6H), 7.56 – 7.51 (m, 3H), 7.33 – 7.29 (m, 1H), 7.28 – 7.23 (m, 2H), 7.18 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 139.7, 137.2, 133.7, 131.9, 130.4, 130.0, 129.0, 128.92, 128.3, 127.9, 127.4, 126.0, 125.3, 124.8, 115.2, 114.6, 110.0; HRMS (ESI) calcd for $C_{24}H_{17}N_4$ 361.1448 found 361.1443 $[M+H]^+$.

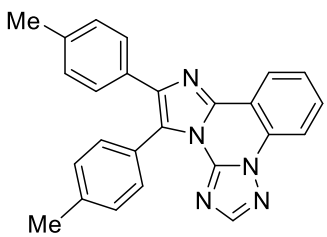
5,6-Diphenylimidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (24ab). Yield 62%, Off-white solid, mp 260 – 261 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.01 (s, 1H), 7.72 (t, J = 7.4 Hz, 1H), 7.68 – 7.60 (m, 3H), 7.60 – 7.47 (m, 5H), 7.31 – 7.22 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.2, 143.8, 142.0, 140.4, 133.2, 131.8, 130.8, 130.7, 129.5, 129.0, 128.5, 128.4, 127.9, 127.7, 127.0, 124.7, 115.5, 114.6; HRMS (ESI) calcd for $C_{23}H_{16}N_5$ 362.1400 found 362.1403 $[M+H]^+$.



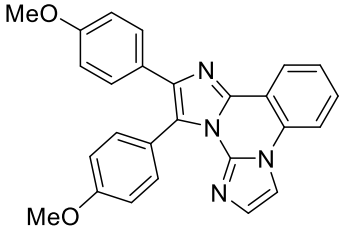
2,3-Di(*p*-tolyl)diimidazo[1,2-*a*:1',2'-*c*]quinazoline (24ba). Yield 56%, Brown solid, mp 224 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 7.8 Hz, 1H), 7.72 – 7.58 (m, 3H), 7.58 – 7.44 (m, 5H), 7.31 (d, J = 7.8 Hz, 2H), 7.18 (s, 1H), 7.11 (d, J = 7.9 Hz, 2H), 2.49 (s, 3H), 2.34 (s, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 139.4, 138.7, 137.2, 137.0, 131.6, 130.8, 130.3, 129.9, 129.1, 129.0, 128.9, 127.8, 126.9, 126.0, 125.2, 124.5, 115.1, 114.6, 109.9, 21.7, 21.3; HRMS (ESI) calcd for $C_{26}H_{21}N_4$ 389.1761 found 389.1764 $[M+H]^+$.



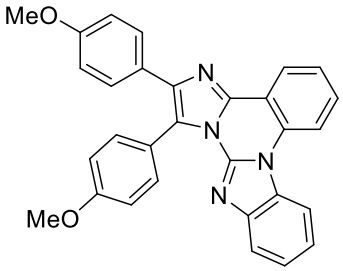
5,6-Di(*p*-tolyl)imidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (24bb). Yield 61%, Off - white solid, mp 266 – 268 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 2.51 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 143.8, 142.0, 140.2, 139.3, 137.5, 131.6, 130.7, 130.6, 130.3, 129.3, 129.0, 127.8, 127.0, 126.0, 124.7, 124.4, 115.5, 114.5, 21.8, 21.3; HRMS (ESI) calcd for $C_{25}H_{20}N_5$ 390.1713 found 390.1719 $[M+H]^+$.



2,3-Bis(4-methoxyphenyl)diimidazo[1,2-*a*:1',2'-*c*]quinazoline (24ca). Yield 56%, Brown solid, mp 223 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 7.8 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.63 – 7.48 (m, 6H), 7.18 (s, 1H), 7.03 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 158.9, 141.0, 139.3, 137.2, 133.1, 130.3, 129.9, 129.0, 128.8, 126.3, 126.0, 125.2, 123.8, 122.0, 115.0, 114.6, 113.8, 113.7, 109.9, 55.2, 55.2; HRMS (ESI) calcd for $C_{26}H_{21}N_4O_2$ 421.1659 found 421.1658 $[M+H]^+$.

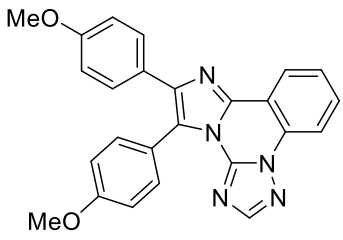


1,2-Bis(4-methoxyphenyl)benzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazoline (24cc). Yield



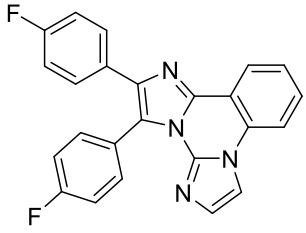
52%, Brown solid, mp 253 – 255 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, J = 7.6 Hz, 1H), 8.37 (d, J = 8.2 Hz, 1H), 8.16 (d, J = 7.1 Hz, 1H), 7.71 (dd, J = 16.1, 7.8 Hz, 2H), 7.57 (dd, J = 19.1, 8.3 Hz, 5H), 7.43 – 7.33 (m, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.3 Hz, 2H), 3.96 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 159.0, 142.0, 141.3, 140.3, 133.4, 18.7, 18.3, 130.4, 130.1, 129.2, 125.9, 125.5, 125.3, 124.7, 124.0, 123.1, 122.0, 120.8, 115.0, 114.7, 113.7, 113.7, 112.8, 55.3, 55.2; HRMS (ESI) calcd for $C_{30}H_{23}N_4O_2$ 471.1816 found 471.1816 $[M+H]^+$.

5,6-Bis(4-methoxyphenyl)imidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (24cb). Yield 58%,



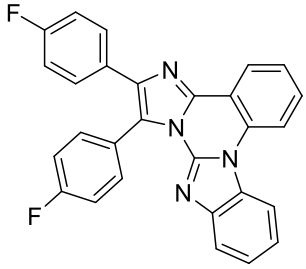
Brown solid, mp 226 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 7.8 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.05 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.66 – 7.56 (m, 3H), 7.50 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.3 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 159.2, 151.2, 143.8, 141.8, 140.0, 133.0, 130.7, 130.6, 129.1, 127.0, 125.9, 124.6, 123.7, 121.0, 115.5, 114.5, 114.0, 113.8, 55.2; HRMS (ESI) calcd for $C_{25}H_{20}N_5O_2$ 422.1612 found 422.1619 $[M+H]^+$.

2,3-Bis(4-fluorophenyl)diimidazo[1,2-*a*:1',2'-*c*]quinazoline (24da). Yield 81%, Off-white



solid, mp 250 – 253 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 7.9 Hz, 1H), 7.78 – 7.66 (m, 3H), 7.62 – 7.52 (m, 5H), 7.26 – 7.15 (m, 3H), 7.05 – 6.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.8, 133.8, 133.7, 131.9, 130.4, 130.2, 129.6, 129.5, 128.8, 128.3, 126.1, 125.8, 125.2, 115.7, 115.5, 115.4, 115.2, 115.0, 114.7, 110.1; HRMS (ESI) calcd for $C_{24}H_{15}F_2N_4$ 397.1259 found 397.1256 $[M+H]^+$.

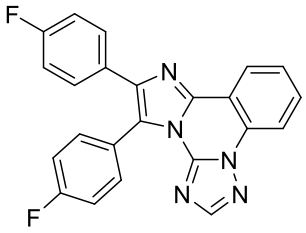
5,6-Bis(4-fluorophenyl)imidazo[1,2-c]benzimidazolo[1,5-*a*]quinazoline (24dc). Yield 65%;



Off-white solid, mp 307 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J = 7.9, 1.4 Hz, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.22 (dd, J = 7.2, 1.7 Hz, 1H), 7.83 – 7.60 (m, 1H), 7.72 – 7.67 (m, 1H), 7.65 – 7.55 (m, 5H), 7.48 – 7.39 (m, 2H), 7.28 – 7.19 (m, 2H), 7.07 – 6.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 134.0, 133.9, 18.8, 130.6, 129.7, 129.7, 129.5,

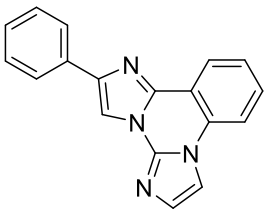
125.5, 125.4, 124.1, 123.3, 120.8, 115.5, 115.46, 115.3, 115.2, 114.9, 114.8, 112.9, 112.8, 112.8; HRMS (ESI) calcd for $C_{28}H_{17}F_2N_4$ 447.1416 found 447.1421 $[M+H]^+$.

5,6-Bis(4-fluorophenyl)imidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (24db). Yield 79%,



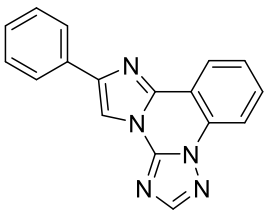
Off-white solid, mp 264 – 266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 8.0, 0.9 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.83 – 7.75 (m, 1H), 7.70 – 7.60 (m, 3H), 7.59 – 7.53 (m, 2H), 7.27 – 7.21 (m, 2H), 7.06 – 7.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (d, J = 95.3 Hz), 161.7 (d, J = 93.1 Hz), 151.2, 143.7, 141.5, 140.5, 133.7 (d, J = 8.4 Hz), 131.0, 130.8, 129.6 (d, J = 8.1 Hz), 129.1 (d, J = 2.9 Hz), 127.2, 124.8, 124.76 (d, J = 3.6 Hz), 123.4, 115.9 (d, J = 21.8 Hz), 115.6, 115.4 (d, J = 21.5 Hz), 114.4; HRMS (ESI) calcd for $C_{23}H_{14}F_2N_5$ 398.1212 found 398.1206 $[M+H]^+$.

2-Phenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (24ea). Yield 58%, Off-white solid, mp 188 – 190



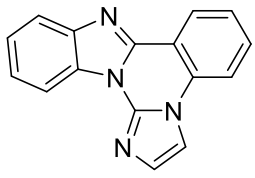
°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 1.3 Hz, 1H), 7.62 (d, J = 7.9 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.51 – 7.44 (m, 3H), 7.38 – 7.33 (m, 1H), 7.31 (d, J = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 140.2, 136.6, 133.1, 130.3, 130.0, 128.8, 128.7, 127.9, 126.0, 125.8, 125.1, 114.8, 114.7, 110.8, 108.0; HRMS (ESI) calcd for $C_{18}H_{13}N_4$ 285.1135 found 285.1131 $[M+H]^+$.

6-Phenylimidazo[1,2-c][1,2,4]triazolo[1,5-*a*]quinazoline (24eb). Yield 52%, Brown solid, mp



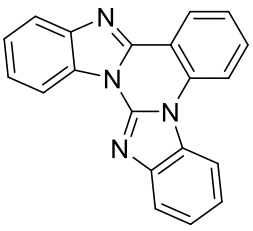
203 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 8.0 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.14 (s, 1H), 8.11 (s, 1H), 7.93 – 7.88 (m, 1H), 7.68 – 7.62 (m, 1H), 7.56 – 7.51 (m, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 145.7, 143.2, 141.2, 18.6, 130.8, 130.8, 128.9, 128.4, 127.2, 126.0, 124.8, 115.6, 114.4, 108.2; HRMS (ESI) calcd for $C_{17}H_{12}N_5$ 286.1087 found 286.1094 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*]quinazoline (24fa). Yield 62%, Brown solid, mp 192 –

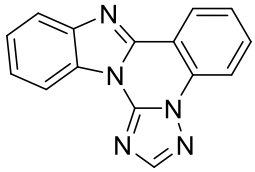


195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, J = 14.9, 5.6 Hz, 2H), 7.95 (d, J = 5.5 Hz, 1H), 7.67 – 7.59 (m, 3H), 7.55 – 7.43 (m, 3H), 7.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.2, 137.5, 131.9, 131.8, 129.7, 128.9, 126.4, 126.1, 125.0, 124.2, 119.5, 114.8, 114.4, 114.2, 110.0; HRMS (ESI) calcd for $C_{16}H_{11}N_4$ 259.0978 found 259.0984 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*a*]benzo[4,5]imidazo[1,2-*c*]quinazoline (24fc). Yield 68%. Off-white solid, mp 221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.70 (m, 1H), 8.67 (dd, J = 7.9, 1.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.84 (dd, J = 7.8, 0.9 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.56 – 7.51 (m, 2H), 7.50 – 7.45 (m, 1H), 7.42 – 7.8 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 143.8, 142.5, 141.6, 134.0, 18.0, 130.3, 130.0, 126.6, 125.3, 125.3, 124.4, 124.2, 123.0, 120.0, 119.6, 115.0, 114.9, 114.5, 112.6; HRMS (ESI) calcd for $C_{20}H13N_4$ 309.1135 found 309.118 $[M+H]^+$.



Benzo[4,5]imidazo[1,2-*c*][1,2,4]trizolo[1,5-*a*]quinazoline (24fb). Yield 61%, Off-white solid, mp 170 – 172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 7.9 Hz, 1H), 8.42 – 8.34 (m, 1H), 8.19 (d, J = 7.3 Hz, 2H), 7.94 – 7.87 (m, 1H), 7.75 (t, J = 7.8 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.52 – 7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 151.5, 144.1, 143.9, 143.5, 18.3, 18.1, 129.2, 127.1, 125.8, 125.6, 124.6, 120.0, 115.6, 114.0, 113.6; HRMS (ESI) calcd for $C_{15}H_{10}N_5$ 260.0931 found 260.0936 $[M+H]^+$.



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CHAPTER 3B

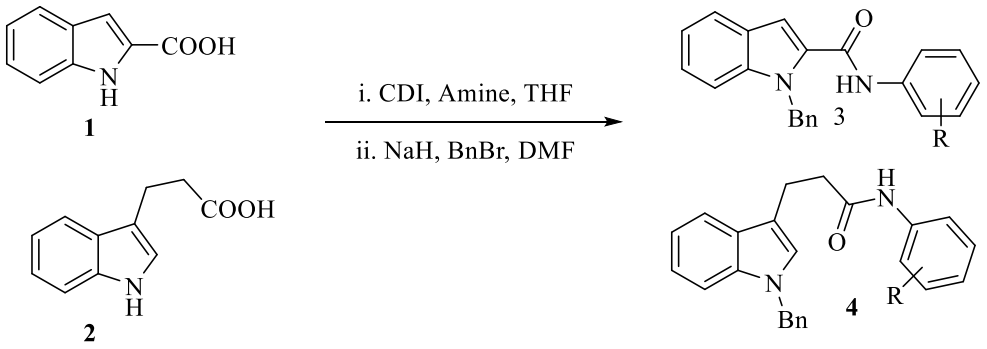
Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and their Antimicrobial Activity

3.3B.1 INTRODUCTION

Bacterial and fungal infections have become a global challenge for human health because of the lack of sufficient and effective antimicrobial drugs, especially in immune-compromised patients. The increase in prevalence and emergence of multidrug-resistance among bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) has endangered the *efficacy of antibiotics* in the advent of modern medicine.[1] Antimicrobial resistant bacteria result in increased mortality rate as well as increased healthcare cost. According to a study by world health organization (WHO) microbial infection can become one of the most serious cause for human death in the near future.[2] Considering these facts, there is an urgent need to develop new effective antibacterial agents that circumvent the emergence of resistance, and thus there have been tremendous efforts by researchers to find new antibiotics to combat microbial resistance.[3-5]

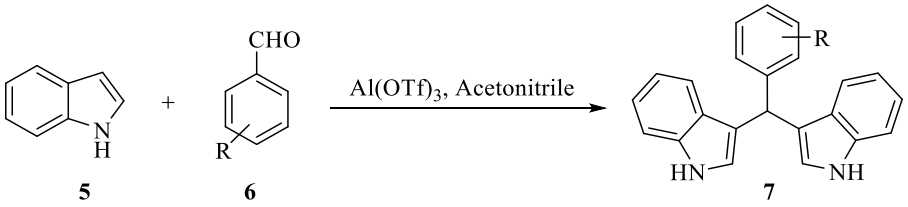
Nitrogen-containing heterocyclic compounds are the most abundant and integral scaffolds due to their distinct biological and industrial activities.[6-10] In the past, a number of azole and quinazoline based compounds have been shown to be promising antimicrobial agents (**Figure 3.4**).[11-13]Azole containing drugs are extensively utilized for the treatment of fungal infection.[14,15] Imidazole, 1,2,4-triazoles, benzimidazole are common azole scaffold having a broad spectrum of antifungal agents like Econazole, Ketoconazole, Fluconazole, Itraconazole, Miconazole, Econazole and Isoconazole.[16] The azole drugs have low toxicity then Amphotericin B and azole drugs are far better than echinocandin antifungal agents due to their oral administration.[17] A brief overview of some recent reports on the antimicrobial activity of azole-based heterocycles is described below

Olgen *et al.* described the synthesis of indole carboxamide (**3**) and propanimide (**4**) derivatives from indole-2-carboxylic acid (**1**) and 3-(1*H*-indol-3-yl)propanoic acid (**2**) and evaluated their antimicrobial activity against *S. aureus, B. subtilis, E. coli* and *A. niger*, which exhibited zone of inhibition in the range of 10-22 mm (**Scheme 3.3B.1**).[18-20]



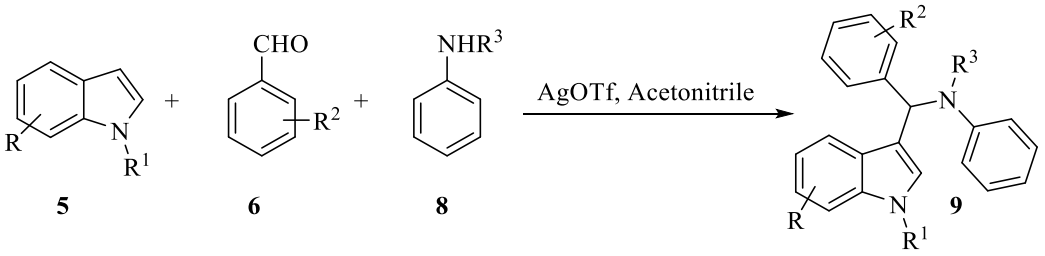
Scheme 3.3B.1 Synthesis of indolyl-carboxamides propanimide (**4**) derivatives

Kamal group developed the reaction of indoles (**5**) with aldehydes (**6**) in the presence of aluminum catalyst for the synthesis of bis-indolylmethanes (**7)** (**Scheme 3.3B.2**).[21] All the synthesized compounds were screened for their antimicrobial activity against a series of bacterial and fungal stain. In addition, their zone of inhibition was measured at the concentration of 100 and 150 µg/mL. Most of the compounds were observed inactive against *K. pneumoniae* only nitrofuryl or thienyl group containing scaffolds showed promising antibacterial activity with zone of inhibition 16-19 mm.



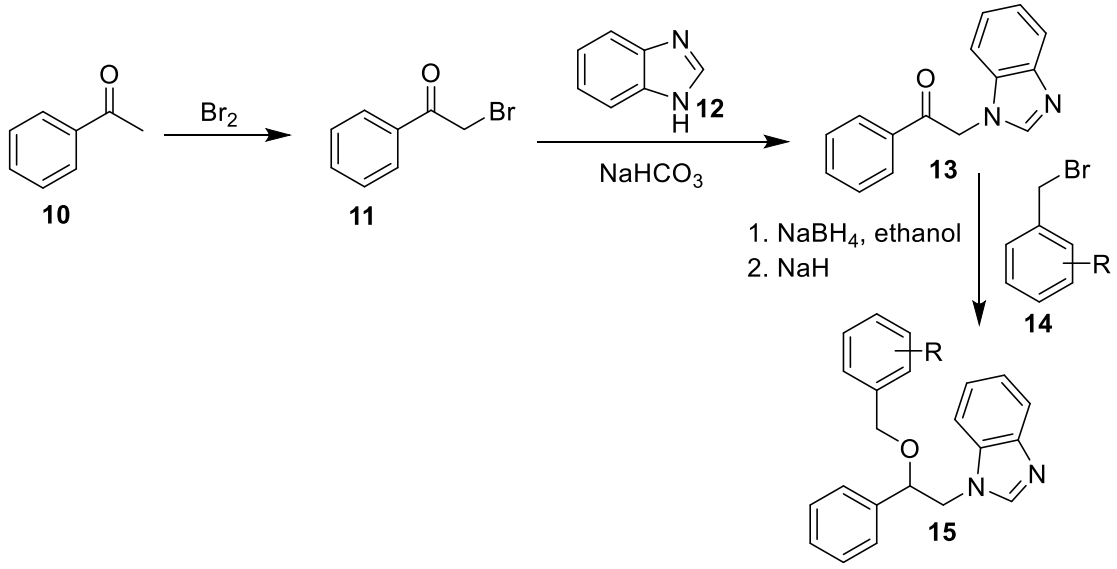
Scheme 3.3B.2 Synthesis of bis-indolyl methanes from indoles and aldehydes

Rao *et al.* achieved silver–catalyzed one-pot multicomponent reaction for the synthesis of 3-aminoalkylated indoles (**9)** by the reaction of substituted indoles (**5)** with aldehydes (**6**) and amines (**8**) (**Scheme 3.3B.3**).[22] The synthesized compounds were studied for their antibacterial activity against Gram positive and Gram-negative bacteria *B. subtilis, S. aureus* and *E. coli*. All compounds showed good zone of inhibition (10-18 mm) and MIC (64-128 µg/mL) value against the bacterial stain.



Scheme 3.3B.3 One-pot synthesis of 3-aminoalkylated indoles from indoles, aldehydes and amine derivatives

Guven and his team synthesized multistep synthesis of benzimidazole containing antimicrobial agents (**15**) from acetophenones (**10**), benzimidazoles (**12**) and benzylbromide (**14**) (**Scheme 3.3B.4**).[23] All compounds were evaluated for their *in-vitro* antibacterial as well as antifungal action against *S. aureus*, Methicillin-resistant *S. aureus, E. coli*, *C. albicans, C. krusei*. The most potent compounds showed good antibacterial action against *S. aureus* and fungi *C. albicans, C. krusei* with MIC value 3.12 µg/mL, 12.5 µg/mL and 12.5 µg/mL, respectively.



Scheme 3.3B.4 Synthesis of benzimidazole containing antimicrobial agents

Kung *et al.* found that quinazolines derived compounds (**16**) have exhibited good antibacterial activity against *E. coli*, *S. aureus* and *K. pneumonia* with MIC values ranging from 0.2-12 µM.[24] A few quinazolines fused molecules such as indolo-, imidazo- and benzimidazo-quinazolines have also been found to exhibit potential antifungal and antibacterial activities (**Figure 3.3B.1**).[25-30] For

example, indolo[1,2-*c*]quinazoline (**17**) have also been found to possess good antimicrobial activity with MIC values ranging from 2.5-20 μg/mL.[25] Based on the high degree of bio-activity shown by molecules based on indole, quinazoline and benzimidazole moieties and also in continuation of our research interest for the synthesis of fused heterocycles,[31-34]we become interested towards designing a novel imidazo/benzimidazo[1,2-*c*]quinazoline structural framework (**18**) that incorporate all these three moieties into a single molecular framework and evaluate their potential additive effects on the antimicrobial activities.

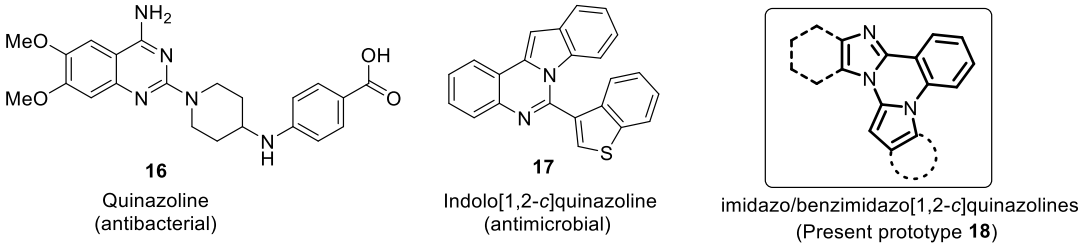
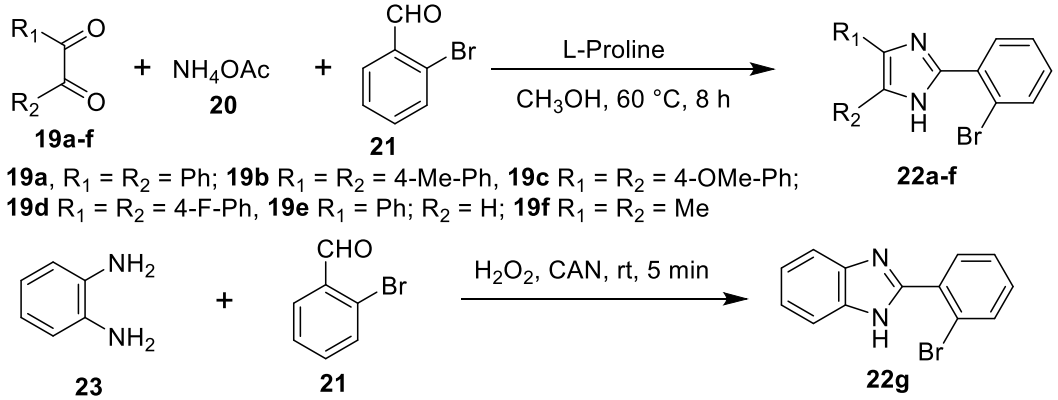


Figure 3.3B.1 Anti-microbial agents with indole and quinazoline motifs and designed imidazo/benzimidazo[1,2-*c*]quinazolines.

3.3B.2 RESULTS AND DISCUSSION

3.3B.2.1 Chemistry

Initially, benzil and related dicarbonyl compounds (**19a-f**), 2-bromoaryl aldehyde (**21**) and ammonium acetate (**20**) were reacted in the presence of L-proline/MeOH to provide a series of 2-(2-bromoaryl)-1*H*-imidazole (**22a-f)** *via* a multicomponent strategy.[35] Similarly, the reaction of 2-bromoaryl aldehyde (**21**) with 1,2-diaminobenzene (**23**) in the presence of H_2O_2/CAN gave 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**22g**) (**Scheme 3.3B.5**).[36]



Scheme 3.3B.5 Synthesis of 2-(2-bromoaryl)-1*H*-imidazole (**22a-f**) and 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**22g**).

The designed prototype *i.e.* fused imidazo/benzimidazo quinazolines (**18**) were synthesized by using our previous approach with a slight modification in the reaction conditions.[36] Interestingly, in the present approach, we have successfully established a copper-catalyzed cross-dehydrogenative coupling instead of palladium-catalyzed CDC strategy reported earlier. Copper-catalyzed Ullmann type C-N coupling between 2-(2-bromophenyl)-1*H*-imidazole/ benzimidazole (**22**) with azoles (**12**) in the presence of CuI (20 mol %), K_2CO_3 in DMF at 150 ^oC, followed by cross-dehydrogenative coupling in the presence of $Cu(OAc)_2 \cdot H_2O$ resulted the desired fused imidazo/benzimidazo quinazolines (**18aa**).

The structure of **18aa** was confirmed by NMR spectroscopic analysis (^1H and ^{13}C) and mass spectrometry data. In the ^1H NMR spectrum, a characteristic singlet at $\delta = 8.05$ ppm was observed along with the expected peaks for the other protons. The peaks in the ^{13}C NMR spectrum were also consistent with the structure of **18aa (Figure 3.3B.2)**. Finally, the presence of a peak at *m/z* = 362.1400 in the HRMS spectrum corresponding to molecular ion $C_{23}H_{16}N_5^+$ $[M+H]^+$ confirmed the structure of **18aa (Figure 3.3B.3)**.

After achieving suitable reaction condition, we explored substrate scope to synthesize azole fused quinazolines. The aryl substitution at C4 and C5- position on 2-(2-bromophenyl)-1*H*-imidazole was treated with different azoles such as 1,2,4-triazole, imidazole, and indoles to afford corresponding imidazo[1,2-c]quinazolines (**18aa**-**ae**) in 40-65% yields (**Table 3.3B.1**). The 2-(2-bromophenyl)-1*H*-imidazole having different substituents such as -Me, -OMe and -F at the *p*-position of aryl ring at C4 and C5- position of imidazole smoothly reacted with imidazoles and pyrazole to give corresponding imidazo[1,2-*c*]quinazolines (**18bf**-**df**) in 45-60% yields. Similarly, the reaction of C4-arylated 2-(2-bromophenyl)-1*H*-imidazole with imidazole and benzimidazole produced corresponding imidazo[1,2-*c*]quinazolines (**18ef**-**eg**) in 62-70% yields. Furthermore, methyl substituted imidazole at C4 and C5- position well tolerated under standard reaction conditions and afforded the target product **18fb** in 45% yield (**Table 3.3B.1**). Similarly, 2-(2-bromophenyl)benzimidazole (**22g**) also reacted with different azoles (**12**) to afforded corresponding benzimidazo[1,2-*c*]quinazolines (**18gf, 18ga, 18gh, 18gc, 18gi,** and **18gd**) in 35-70% yields. The molecular structure of the synthesized imidazo/benzimidazo[1,2-*c*]quinazoline derivatives (**18**) was confirmed by ^1H and ^{13}C NMR, and ESI-HRMS analysis.

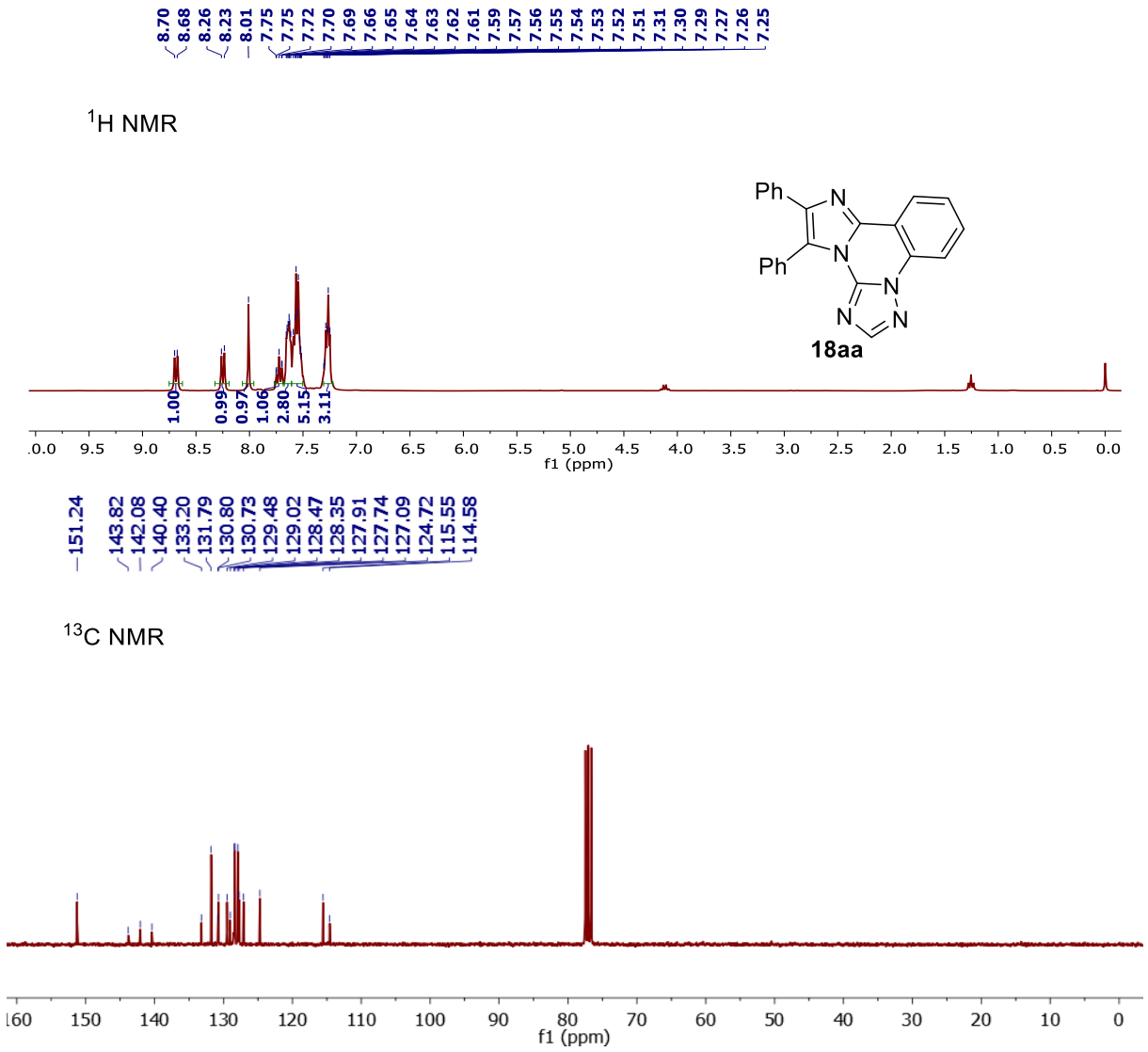


Figure 3.3B.2 ^{1}H and ^{13}C NMR spectra of 5,6-diphenylimidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline **(18aa)** in $CDCl_3$

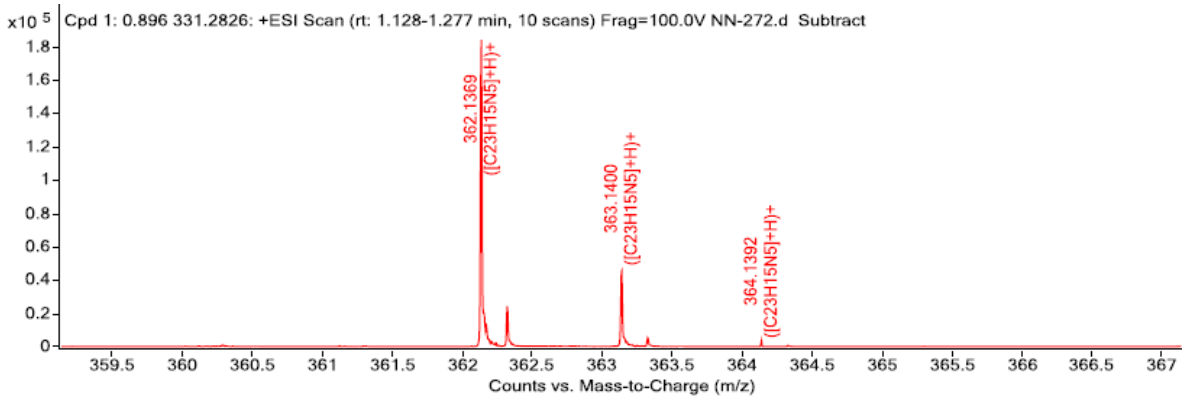
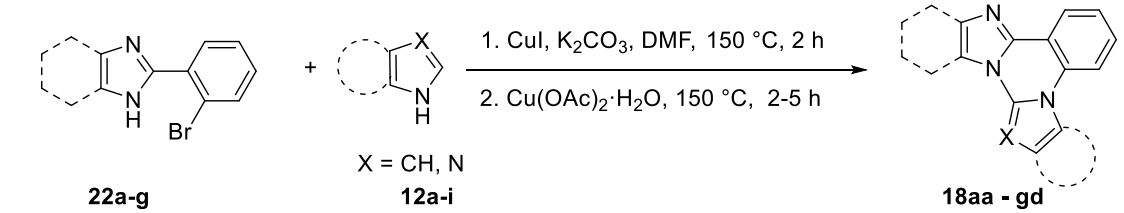
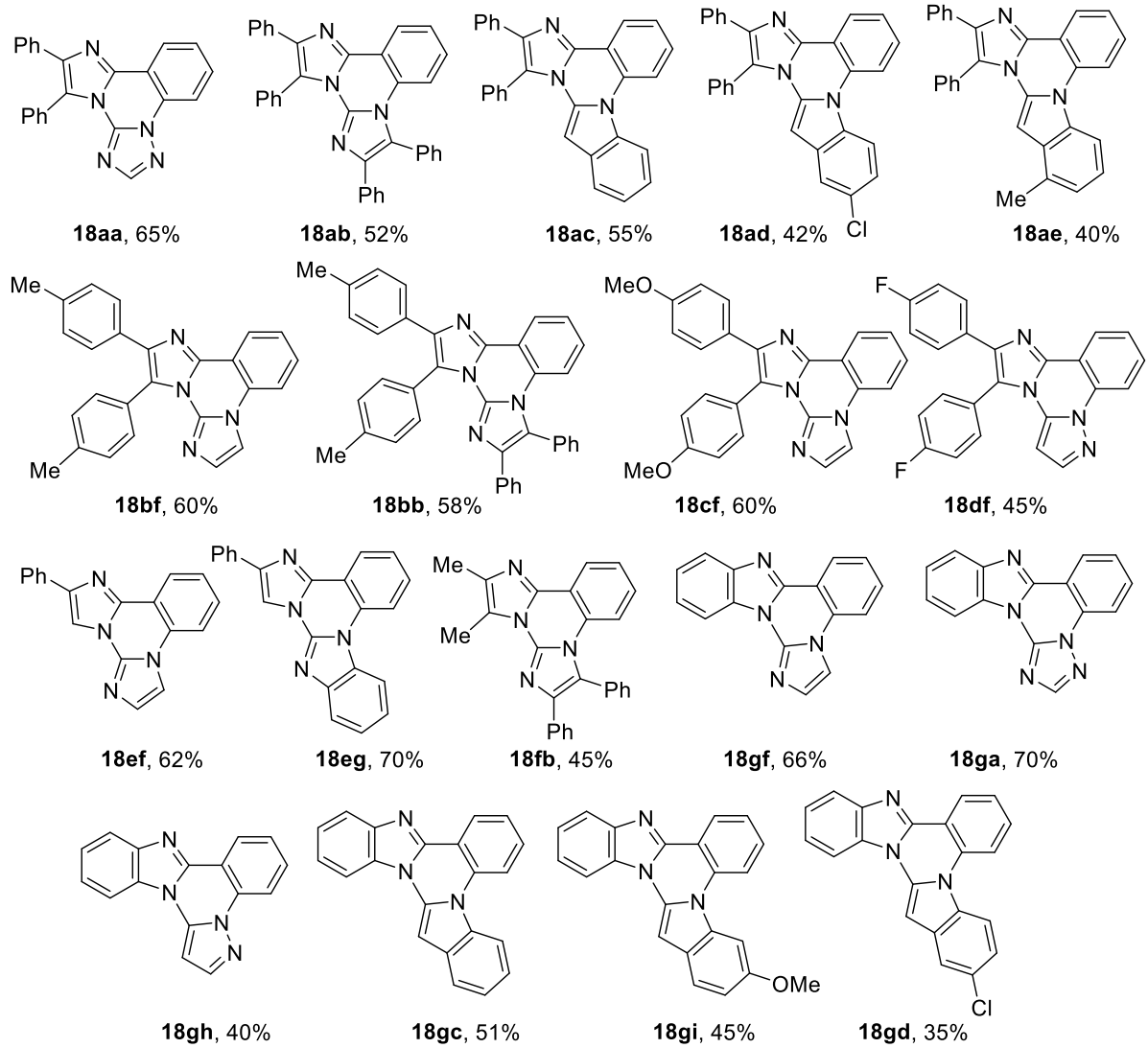


Figure 3.3B.3 LC-HRMS of 5,6-diphenylimidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (**18aa**)

Table 3.3B.1 Synthesis of fused imidazo/benzimidazo [1,2-*c*]quinazolines (**18**).[a,b]





[a]Reaction conditions: **22** (1.0 mmol), **12** (1.2 mmol), CuI (20 mol %), K_2CO_3 (2.0 mmol), DMF (2mL) under air at 150 ^oC for 2 h followed by addition of $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol), 150 ^oC, 2-5 h. [b]Isolated yield.

3.3B.2.2 Biology

3.3B.2.2.1 Antimicrobial activity

Antibacterial evaluation of imidazo/benzimidazo[1,2-*c*]quinazoline derivatives (**18**) was carried out against a panel of three Gram-negative strains *viz*. *Escherichia coli* (*E. coli*), *Pseudomonas putida* (*P. putida*), *Salmonella typhi* (*S. typhi*) and two Gram-positive *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus* (*S. aureus*) using ciprofloxacin as a standard drug. Antifungal efficacy was evaluated against pathogenic strains *viz*. *Candida albicans (C. albicans)* and *Aspergillus niger* (*A.niger*) using amphotericin B as a positive control.

Table 3.3B.2 Antimicrobial activity of fused imidazo/benzimidazo [1,2-*c*]quinazolines (**18**).

Compounds	MIC (µg/mL)						
	Bacteria					Fungi	
	Gram-negative			Gram-positive			
	E. coli	***P. putida***	***S. typhi***	***B. subtilis***	***S. aureus***	***C. albicans***	***A. niger***
18aa	>32	>32	32	64	64	>32	>32
18ab	64	>32	64	32	32	-[a]	-[a]
18ac	64	>64	64	>64	64	128	>64
18ad	32	32	>32	32	32	-[a]	-[a]
18ae	>64	64	64	>32	>32	64	64
18bf	>32	32	>32	32	32	32	32
18bb	>16	32	32	>16	>16	>32	>32
18cf	32	>32	32	32	>32	>128	>128
18df	>16	16	16	>16	>16	64	>64
18ef	32	>32	>32	>32	>32	32	32
18eg	32	32	32	32	>32	64	64
18fb	64	64	>64	>32	>32	128	128
18gf	>32	**32**	>32	**32**	>32	**16**	**16**
18ga	**4**	**4**	**>4**	32	32	**32**	**>32**
18gh	16	16	16	16	16	32	32
18gc	**4**	**4**	32	**4**	**>4**	**32**	**32**
18gi	16	>16	>16	16	>16	>16	>16
18gd	**4**	**>4**	**4**	**>4**	**>4**	**16**	**16**
Ciprofloxacin	6.25	6.25	6.25	6.25	6.25	-	-
Amphotericin B	-	-	-	-	-	30	30

MIC: minimum inhibitory concentration in µg/mL, [a]No activity, **18ga**, **18gc**, **18gd** was observed as the most potent compounds.

The results of antimicrobial activity are shown in **Table 3.3B.2**. Initially, to understand the antibacterial effect of the synthesized compounds, the zone of inhibition (ZOI) was measured through a disc diffusion method. Presence of these compounds in the culture medium increased the ZOI diameter by 1 to 7 mm. Compounds **18ga, 18gc,** and **18gd**, with an increase of 6-7 mm in inhibition zone diameter were found to be the most promising candidate for antibacterial activity. Next, for quantitative measurement of the antibacterial activity of **18aa-gd**, minimum inhibitory concentration (MIC) was evaluated. It was found that the compounds (**18aa-gd**) effectively inhibited the growth of pathogenic strains with MIC in the range of 4–64 μg/mL. Among all the tested compounds, **18ga, 18gc,** and **18gd** were found to be the most effective compounds with MIC in the range of 4–32 μg/mL.

With respect to antifungal activity, compounds **18bf**, **18ef, 18gf, 18ga, 18gh, 18gc, 18gi** and **18gd** exhibited good to excellent activity against *A. niger* and *C. albicans*. Compounds **18bf**, **18ef** and **18gh** were found equally potent (MIC in the range of 32μg/mL) in comparison to the reference drug amphotericin B, while compounds **18gf**, **18ga, 18gc, 18gi** and **18gd** even showed better activity than the positive control with MIC in the range of 32–16 μg/mL.

3.3B.2.2.2 Bactericidal assay by propidium iodide (PI)

Propidium iodide (PI) dye penetrates only the damaged or compromised membrane and hence can be used to detect the dead cells.[37] The dye PI intercalates with double-stranded DNA and subsequent fluorescence detection allows assessment of the number of non-viable/dead cells.[38] The most potent compounds **18ga, 18gc** and **18gd** were further tested for their effect against the total cell population of *P. putida* using PI dye. The microscopic images of the bacterial culture treated with the compounds showed significant cell death at 2X MIC, which is similar to the number of cells for positive control treated with TBHP (*tert*-butyl hydroperoxide) bacterial culture (**Figure 3.3B.4**). This result reveals that the compounds **18ga, 18gc** and **18gd** have potent bactericidal activity.

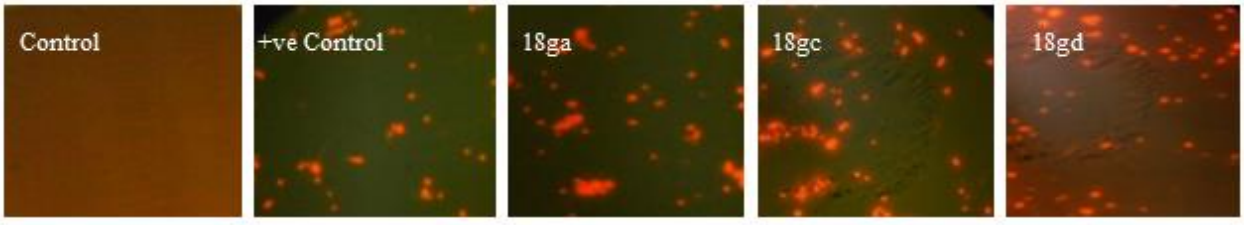


Figure 3.3B.4 Bactericidal assay against *P. putida* for compound **18ga, 18gc** and **18gd**.

3.3B.2.2.3 Live-dead bacteria cell screening

Acridine orange (AO) is a vital dye and will stain both the live and dead cells whereas ethidium bromide (Et·Br) will stain only cells that have lost membrane integrity.[39,40] The cell death assay caused by most efficient compounds **18ga, 18gc,** and **18gd** was evaluated by AO/Et·Br dual staining assay (**Figure 3.3B.5**).In this assay, the *P. putida* cells were stained with a mixture of AO and Et·Br. The dye AO can enter inside the living cells and binds with the living cells DNA to emit green fluorescence, whereas Et·Br enters only through modified cell membrane of dead cells and emits red fluorescence. The untreated bacterial cells displayed green fluorescence, while the cells treated with the compounds **18ga, 18gc** and **18gd** exhibited red fluorescence along with minor green fluorescence (**Figure 3.3B.5**). This bacterial cell viability assay demonstrated that the compounds **18ga, 18gc,** and **18gd** cause cell damage by making the loss of cell membrane integrity and thus illustrates the bactericidal potential of these compounds.

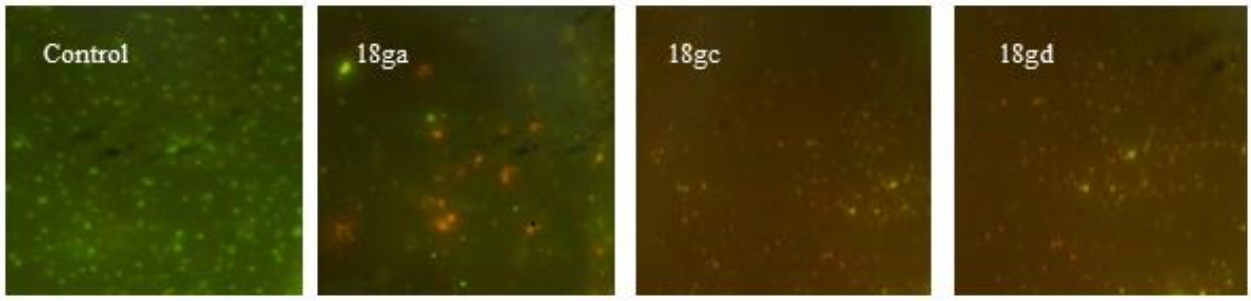


Figure 3.3B.5 Live-dead bacterial cell screening by the compounds **18ga, 18gc** and **18gd** using AO/Et·Br dual staining.

3.3B.2.2.4 Evaluation of ROS production

A moderate ROS generation plays a crucial role in cell proliferation and differentiation, whereas the excess production of ROS induces oxidative damage to cellular lipids, proteins, and DNA in bacteria which leads to cell death. Therefore, the effect of compounds **18ga, 18gc,** and **18gd** on cellular ROS level of *P. putida* bacterial cells were measured using 2',7'-dichlorofluorescein diacetate dye (DCFH-DA). A significant increase in ROS level was observed by the chemically synthesized compounds **18ga, 18gc** and **18gd** against *P. putida* cells (**Figure 3.3B.6**). Compared to the untreated control cells, compound treated bacterial cell showed an enhanced generation of intracellular ROS. This intracellular accumulated ROS may also be responsible for the bactericidal activity.

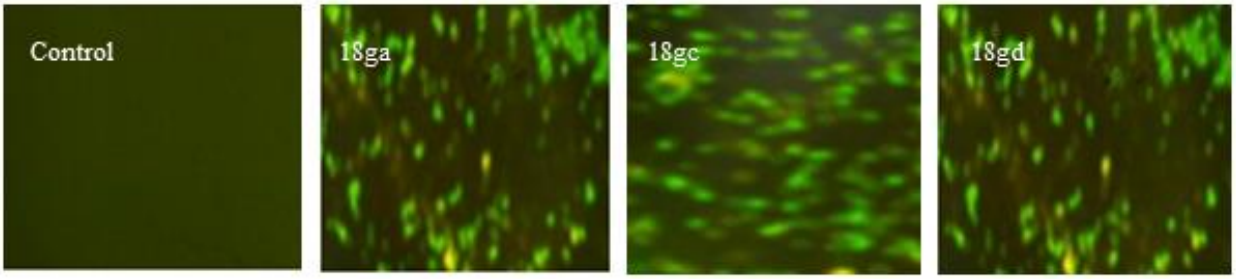


Figure 3.3B.6 Evaluation of ROS production against *P. putida* using fluorescent dye DCFH-DA as a probe.

3.3B.2.2.5 Hemolytic activity

To ascertain the toxicity profile of synthesized compounds, the hemolytic activity was evaluated. The hemolytic activity can occur by several mechanisms, from increased permeability of cell membranes to complete cell lysis. The evaluation of the hemolytic activity is to check the damage caused by synthesized compounds to the membranes of RBCs (erythrocytes), which leads to the release of hemoglobin. It is an additional tool to verify the importance of synthesized compounds against red blood cells and may also give an idea to promote such compounds as a drug level (**Figure 3.3B.7**). The toxicity profile of chemically synthesized compounds on human red blood cells was determined at a fixed concentration of 100 µM. The observed results showed that most of the compounds caused by 3-28% hemolysis. Interestingly, the efficient antibacterial compounds **18ga, 18gc,** and **18gd** showed less than 10% hemolysis at high concentration of 100 µM, suggesting that these compounds are negligible toxic to human blood cells (**Figure 3.3B.7**). The results of hemolytic activity further support the significance of the present study.

After the preliminary hemolytic activity of tested compounds at 100 µM concentrations, the concentration-dependent activity of one of the most potent compound **18ga** was performed at different concentration (20-100 µM). The study demonstrated that on increasing the concentration of **18ga** from 20-60 µM, there is no significant change in the hemolytic activity was observed (**Figure 3.3B.8)** However, we observed a slight enhancement in hemolysis activity at 80 µM concentration which is less than 10% hemolysis. The observed results of compound **18ga** at different concentrations showed its negligible toxicity to human blood cells.

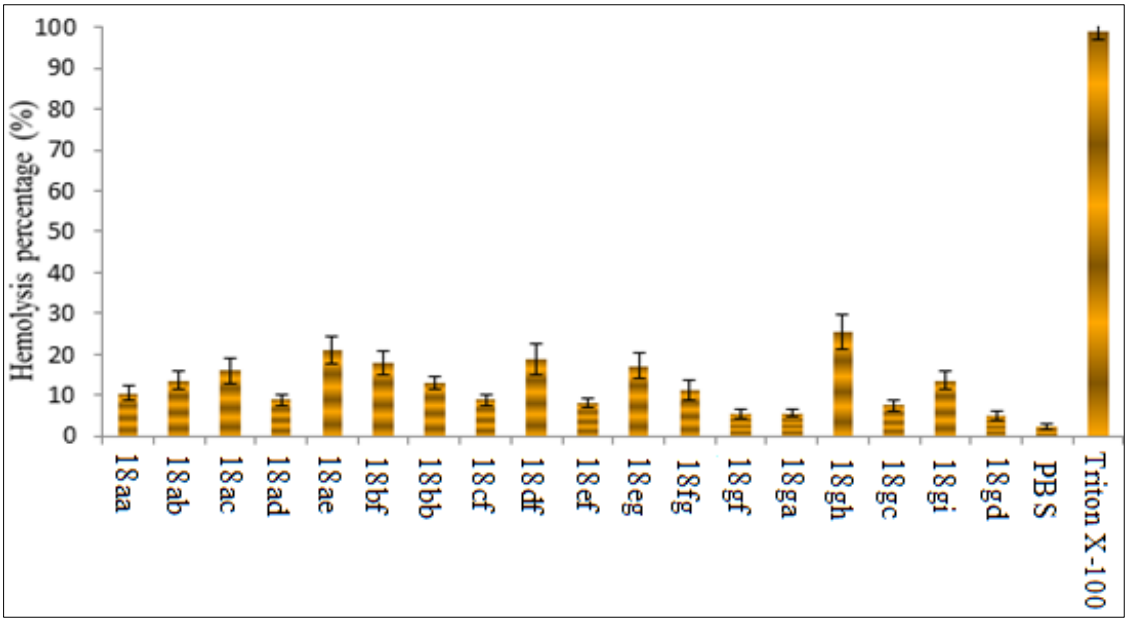


Figure 3.3B.7 Hemolytic activity on human red blood cells using **18aa-gd** at 100 µM. Data was analyzed by mean ±SD (standard deviation) of triplicate (n = 3) samples.

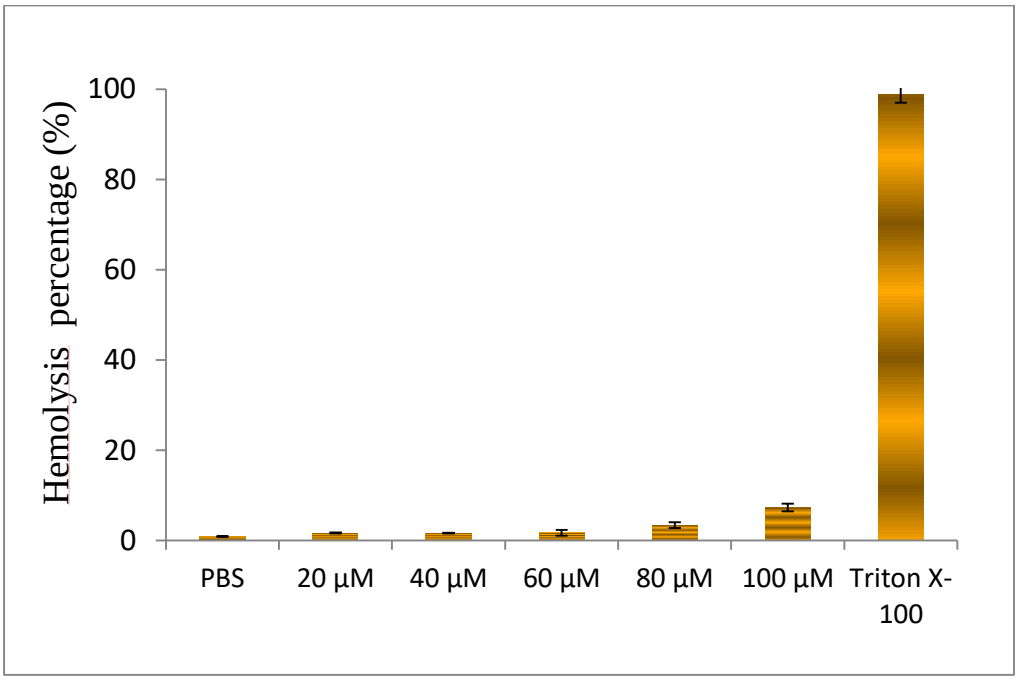


Figure 3.3B.8 Hemolytic activity of compound **18ga** on human red blood cells at different concentration 20-100 µM. Data was analyzed by mean ±SD (standard deviation) of triplicate (*n*=3) samples.

3.3B.2.2.6 Biofilm inhibition

Bacterial biofilm is an extracellular polymeric substance and composed of extracellular polysaccharides and proteins, causing chronic infections in humans *via* hospital and community environments. Biofilm formation provides the resistance to microbes against phagocytosis and other components of the body's defense system. Thus, compounds having anti-biofilm activity could prevent the contamination of biomedical implants.

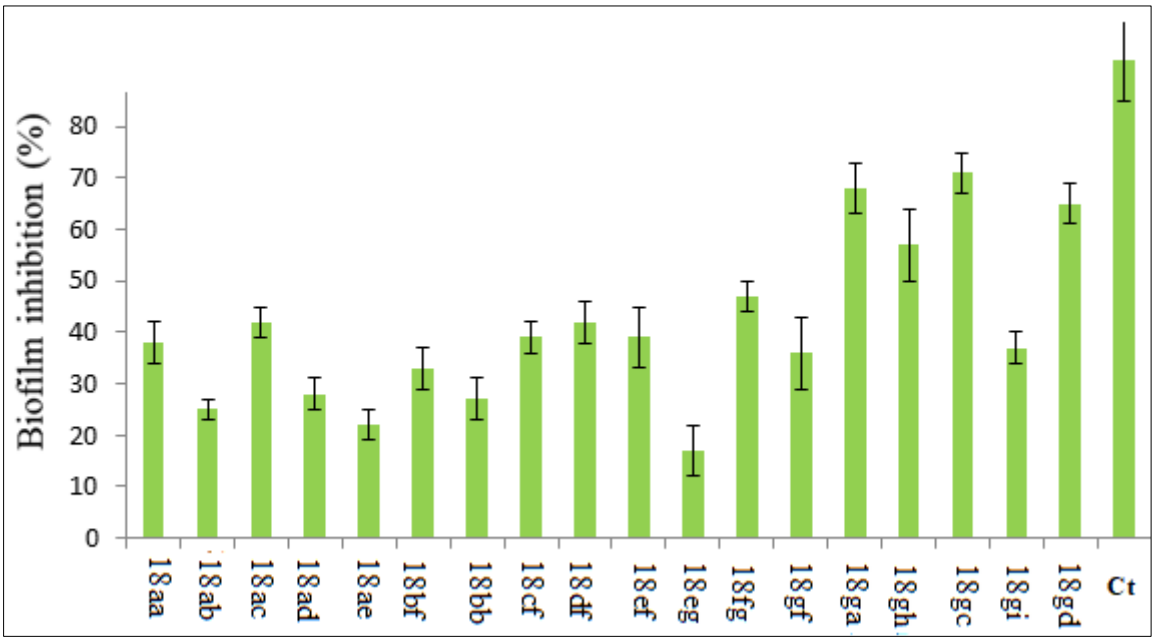


Figure 3.3B.9 Biofilm inhibition assay against strain *Staphylococcus aureus* by **18aa-gd** at 50 µg/mL. All the experiments were carried out in triplicates, and the values are indicated as mean ± SD.

In our study, we observed that most of the compounds showed anti-biofilm activity in the range of 20-70%, as compared to positive control ciprofloxacin (**Figure 3.3B.9**). The highest inhibitory activity was shown by compounds **18gc** (70%) followed by **18ga** (67%), and **18gd** (63%) (**Figure 3.3B.9**). Compounds can modulate the biofilm formation through non-microbicidal or biocidal mechanism. Moreover, these molecules weaken the biofilm either by degradation of extracellular matrix or targeting of extracellular and intracellular signaling molecules.

3.3B.2.2.7 Structure-activity relationship and plausible mode of mechanism

The antibacterial activity follows a trend for the corresponding designed prototype *i.e.* fused imidazo/benzimidazo quinazolines (**18**). It was observed that benzimidazole derivatives

substituted with indole (**18gc-gd**) and azoles (1,2,4-triazole (**18ga**), imidazole (**18gf**) and pyrazole (**18gh**)) exhibited better antibacterial activity in comparison to the imidazole substrate containing similar motifs (**18aa-fb**). The analysis of antibacterial activity confirmed their efficacy against tested bacteria due to damage to membranes and the effects of oxidative stress as evident by live-dead bacterial assay and ROS production, respectively. Generation of ROS lead to a lethal effect on bacterial cells and can increase the bactericidal process. The acute change in response to compounds treatment may cause the release and degradation of membrane proteins; this leads to the loss of membrane integrity and bacterial cell morphology, the formation of fissures and perforations in the cell membrane. The formation of fissures and perforation leads to the leakage of cytoplasmic contents from the cell; this increases the death consequences. More specifically, benzimidazole bearing electron withdrawing group containing indole exhibited comparatively better activity than electron neutral group on indole followed by electron donating group containing indoles.

Similarly, benzimidazole substrate fused with indole and azoles (1,2,4-triazole, imidazole and pyrazole) exhibited better antifungal activity in comparison to the imidazole substrate containing similar scaffold. The overall study concludes that the benzimidazole derivatives bearing the indole, 1,2,4-triazole, imidazole and pyrazole group induced greater oxidative stress and morphological changes like membrane damage. Moreover, pathological outcome such as DNA damage, alterations to specific proteins and enzymes responsible for different physiological processes at the molecular level need further investigation. With the help of the study reported herein, future work can be directed towards studying the *in vitro* and *in vivo* biological consequences in response to compounds treatment.

3.3B.3 CONCLUSIONS

A new series of imidazo/benzimidazo[1,2-*c*]quinazolines has been synthesized *via* copper catalyzed Ullmann type C–N coupling followed by intramolecular cross–dehydrogenative (CDC) coupling reaction. All the synthesized compounds were evaluated for their antimicrobial activity. Among all, compounds **18gf**, **18ga**, **18gc** and **18gd** exhibited most promising antibacterial (MIC 4–32 µg/mL) and antifungal (MIC 4–16 µg/mL) activity. The structure-activity relationship of synthesized compounds revealed that benzimidazo[1,2-*c*]quinazolines showed better antimicrobial activity than the imidazo[1,2-*c*]quinazoline derivatives. More specifically, benzimidazole derivatives substituted with 1,2,4- triazole (**18ga**) and indole motifs (**18gc** and **18gd**) exhibited

better antimicrobial activity as compared to other azoles. The live dead bacteria cell screening and increased ROS production upon treatment with most active compounds **18ga, 18gc** and **18gd**, illustrates their efficient membrane penetration ability which might be the main cause of bacterial cell death. Furthermore, synthesized compounds were also evaluated for hemolytic activity which showed negligible toxicity profile towards the human blood cells. The overall study concludes that compounds **18ga, 18gc** and **18gd** may serve as potential antimicrobial candidates for lead optimization.

3.3B.4 EXPERIMENTAL SECTION

All the reagents and solvents were obtained from the commercial suppliers and used without further purification unless otherwise mentioned. The progress of the reactions was monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F_{254} plates. The chemical structures of the final products were determined by NMR (^{1}H and ^{13}C) and HRMS analysis. The ^{1}H NMR and ^{13}C NMR spectra were a record on a 400 MHz and 100 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard or deuterated solvent peak ($CDCl_3$ and DMSO-d_6). The HRMS data were recorded on a mass spectrometer with electrospray ionization and TOF mass analyzer. Melting points were determined in open capillary tubes on an automated melting point apparatus and are uncorrected. All tested compounds were ≥95% pure by HPLC with detection at 270 nm. Starting substrates 2-(2-bromophenyl)-4,5-diaryl-1*H*-imidazole and 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole were prepared by following reported procedure.[35,36]

3.3B.4.1 General procedure for the synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines

A clean oven dried 10 mL round bottom flask was charged with **22** (1.0 mmol), **12** (1.2 mmol), K_2CO_3 (2.0 mmol), CuI (0.20 mmol) and DMF (2 mL). The resulting solution was stirred at 150 °C for 2 h. On completion of the first step, $Cu(OAc)_2 \cdot H_2O$ (0.5 mmol) was added in same flask without isolating the intermediate and the reaction mass was further stirred at 150 °C for 2-5 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature, diluted with water (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatographyon silica gel (100-200 mesh) using ethyl acetate/hexane (15%, *v/v*) as an eluent.

3.3B.4.2 Antimicrobial Activity

3.3B.4.2.1 Antibacterial activity

The compounds **18** were tested for antibacterial activity against three Gram-negative bacteria including the *Escherichia coli* (MTCC 1652), *Pseudomonas putida* (MTCC 102) *Salmonella typhi* (932) and two Gram-positive *Bacillus subtilis* (MTCC 121) *Staphylococcus aureus* (MTCC 96) as per standard method.[41] The tested strains were collected from the Microbial type culture collection and gene bank (MTCC, India). The autoclaved Luria-bertani agar medium was poured into sterile glass petri-dishes (90 mm) under aseptic conditions. After solidification of the medium, 100 µL culture of each pathogenic culture (10^7 cfu/mL) was spread using a sterile glass spreader and left for 15 min for complete adsorption. After adsorption, well size of 6 mm diameter was made by the sterile metallic borer and the solution of working compound of different concentration was poured into the wells. After incubation at 37 °C for 24 h, the diameter of the zone of inhibition (ZOI) was measured in comparison with standard antibiotic 'Ciprofloxacin'. Solvent, DMSO was used as negative control, while antibiotic 'Ciprofloxacin' as a positive control. For the MIC assay, test compounds were prepared in the concentrations of 2, 4, 8, 16, 32, 64, 128 and 256 µg/mL in DMSO and serial diluted test samples of each compound (200 µL) were added in 96 well micro-trays. The test microorganism was added to micro-trays well to obtain a final volume of 400 µL and incubated at 37 °C for 24 h. MIC value is defined as the lowest concentration of compound that inhibit the visible growth of bacteria (OD_{600} less than 0.06). Each assay was performed in duplicate sets.

3.3B.4.2.2 Antifungal activity

The compounds **18** were tested for antifungal activity by agar well diffusion method against the fungal strains *Candida albicans* (MTCC 39532) and *Aspergillus niger* (MTCC 9933). For the experimental work, a loopful of each strain was grown in potato dextrose broth (PDB, HiMedia, India) medium at 28 °C for 4-5 days. Following optimal growth of each fungal strain, 100 µL of culture was uniformly spread on the potato dextrose agar medium plate. Following adsorption, wells of 6 mm was prepared by the sterile metallic borer and solution of working compound of

different concentration was poured into the wells. Plates were incubated at 28 °C for 4-5 days under dark conditions. Mean diameter of inhibition zone was measured to determine the antifungal activity. For the MIC assay, sterile test tubes containing 5 mL of sterilized czapeks dox broth medium was inoculated with 100 µL of a freshly grown culture of each test strain, and an appropriate amount of compound was added to achieve the desired concentrations. The tubes were incubated at 28 °C for 5 days under dark conditions and carefully observed for the presence of turbidity. Amphotericin B was used as positive control. The experiment was performed in duplicate sets.

3.3B.4.3 Bactericidal assay by propidium iodide

The single colony of bacterium *P. putida* was inoculated into the sterile nutrient-broth medium and kept in an incubator shaker (150 rpm) till the optical density (OD) of culture reached up to 0.8. The culture was treated with selected compounds at 2×MIC for 4h. After the treatment, the culture was centrifuged at 5,000g for 10 min and the cell pellet was stained with 1.0 mg/mL of propidium iodide (PI) (Sigma-Aldrich, USA). The stained colony was streaked on the clean glass-slide and covered with a glass-slip. The population of PI-positive bacterial cells was compared with untreated cells by epi-fluorescence microscopy. During the experiment, bacterial culture treated with *tert*-butyl hydroperoxide was taken as positive control.

3.3B.4.4 Live-dead Bacteria Screening through Fluorescence Microscopy

To discriminate the live and dead bacterial cells, freshly grown culture of *P. putida* (10^7 cfu mL^{-1}) was treated with the compounds **18ga, 18gc** and **18gd** for 4 h. Following treatment, 5 µL each of acridine orange (AO) (15 µg mL^{-1}) and ethidium bromide (Et·Br) (50 µg mL^{-1}) was added in a 500 µL of *P. putida* culture. The working solution of acridine orange and ethidium bromide were prepared in the PBS buffer. The suspension was centrifuged at 5,000 g for 10 min and supernatant was discarded. The cell pellet was washed with 1X PBS buffer (pH 7.2) three times to remove any traces of unbound dyes. Washed cell pellet was streaked on the glass slide with a cover slip on top of it and viewed under epi-fluorescence microscope (Olympus-CKX41, Olympus, Japan) at intensity between 450 and 490 nm using 100X objective lens and 10X eyepiece lens.

3.3B.4.5 Evaluation of ROS production

To evaluate the intracellular reactive oxygen species formation after the compounds treatment, fluorescent dye 2′,7′-dichlorofluorescein diacetate (DCFH-DA) was used as probes. The DCFH is non-fluorescent dye, but is oxidized to the highly fluorescent 2',7'-dichlorofluorescein (DCF) by intracellular H_2O_2 or nitric oxide. At the mid log phase of bacterial growth, compounds were added to the bacterial suspension (*P. putida*) for 2 h and then treated with 2 µM of DCFH-DA at 37 °C for 30 min. The emitted fluorescence of DCF was measured at 530 nm after excitation at 485 nm by fluorescence microscopy and qualitatively screened for ROS production.

3.3B.4.6 Hemolytic Activity

The compounds **18** were tested for hemolytic activity on human red blood cells (RBC) following the standard protocol with minor modifications.[42] The healthy human blood samples of males between 25-28 age group were collected from hospital of BITS Pilani campus following Institutional Ethics Committee guidelines and washed with sterile phosphate buffer saline (PBS) solution at least three times. After washing, blood was centrifuged at 2,500 rpm for 6 min at room temperature and RBC pellet was suspended in PBS buffer. The RBC suspension of 0.1 ml was mixed with 0.5 ml buffer solution containing 100 µg/mL of each compound in DMSO (1%, *v/v*) in PBS buffer. DMSO (1%, *v/v*) in PBS buffer and Triton X-100 (1 %) were used as negative and positive control, respectively. The samples were incubated at room temperature for 3 h. Following incubation, samples were centrifuged at 8,000 rpm and absorbance of supernatant was recorded at 540 nm. The percentage hemolysis was calculated by using following equation:

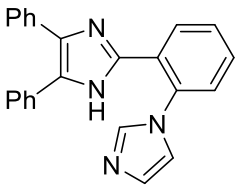
[% Hemolysis= (A540 test sample - A540 negative control/A540 positive control - Absorbance 540 negative control)×100]. Each sample was analyzed in triplicate sets.

3.3B.4.7 Biofilm inhibition assay

The pathogenic bacterial strain *Staphylococcus aureus* was cultured in tryptic-soy broth medium and optical density of bacterial suspension was adjusted to 1×10^6cfu mL^{-1}. The synthesized compounds having concentrations of 50 µg/mL were mixed to the grown bacterial culture and properly mixed. The aliquots of 100 µl were distributed in to the 96-well polystyrene micro-titer plates (Tarson, India) and kept under static condition at 37 ºC for 24 h. The medium was discarded with the micro pipettes and the plate was washed with PBS buffer (1X, pH 7.2) to wash away the

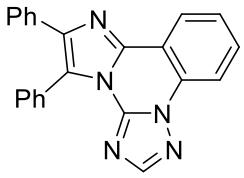
non-adherent bacterial culture. The well of micro-titer plates were stained with 100 µL of 0.1% crystal violet solution for 30 min at room temperature. After incubation, the staining solution was discarded and wells were washed with autoclaved Milli-Q water and kept for air drying at room temperature. The stained biofilm were solubilized with 100 µl of 95% ethanol and absorbance was taken at 540 nm. Blank wells were taken as background control. All the experiments were carried out in triplicates and the values are indicated as mean ± SD.

2-(2-(1*H*-imidazol-1-yl)phenyl)-4,5-diphenyl-1*H*-imidazole (23). Yield 81%, Off-white solid,



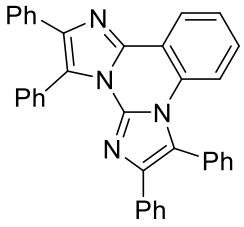
mp 144 –147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 7.1 Hz, 1H), 7.71 – 7.54 (m, 8H), 7.53 – 7.45 (m, 4H), 7.32 – 7.19 (m, 4H), 7.14 (d, J = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 139.7, 137.2, 133.7, 131.9, 130.4, 130.0, 130.0, 129.0, 128.8, 128.29, 128.3, 127.9, 127.4, 126.0, 125.2, 124.32, 115.2, 114.6, 110.0. HRMS (ESI) calcd for $C_{24}H_{19}N_4$ 363.1604 found 363.1607 $[M+H]^+$.

5,6-Diphenylimidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazoline (18aa): Yield 65%, Off-white



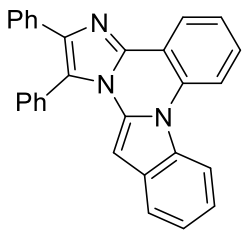
solid; mp 260-261 °C (lit. = 260 – 261 °C)[36]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.05 (s, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.69 – 7.56 (m, 8H), 7.33 – 7.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 143.8, 142.0, 140.4, 133.2, 131.8, 130.8, 130.7, 129.5, 129.0, 128.5, 128.3, 127.9, 127.7, 127.0, 124.7, 115.5, 114.6; HRMS (ESI) calcd for $C_{23}H_{16}N_5$ 362.1400 found 362.1400 $[M+H]^+$.

2,3,6,7-Tetraphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (18ab): Yield 52%, Off white solid; mp



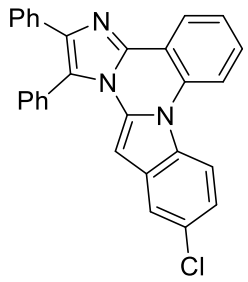
255–257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 7.9 Hz, 1H), 7.77 – 7.71 (m, 4H), 7.65 – 7.57 (m, 8H), 7.43 (t, J = 7.6 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.23 – 7.12 (m, 6H), 6.93 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.8, 136.7, 136.7, 133.8, 133.6, 132.2, 132.1, 132.0, 131.8, 130.5, 130.0, 129.3, 128.8, 128.3, 128.0, 128.0, 127.8, 127.3, 126.9, 126.6, 125.4, 125.2, 125.0, 122.6, 116.0, 115.9; HRMS (ESI) calcd for $C_{36}H_{25}N_4$ 513.2074, found 513.2073 $[M+H]^+$.

1,2-Diphenylimidazo[1,2-*c*]indolo[1,2-*a*]quinazoline (18ac): Yield 55%, Off white solid; mp



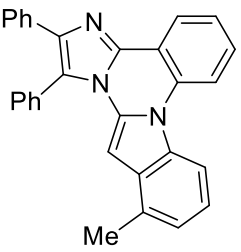
240–243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 7.9, 1.6 Hz, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.70 – 7.66 (m, 4H), 7.63 – 7.61 (m, 4H), 7.51 – 7.45 (m, 2H), 7.39 – 7.34 (m, 1H), 7.32 – 7.30 (m, 2H), 7.26 – 7.23 (m, 2H), 5.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 139.1, 134.2, 133.8, 131.9, 131.7, 130.9, 130.7, 130.1, 129.8, 129.1, 128.8, 128.3, 127.3, 127.2, 125.3, 125.0, 124.0, 122.4, 122.3, 121.0, 115.2, 113.4, 87.9; HRMS (ESI) calcd for $C_{29}H_{20}N_3$ 410.1652 found 410.1672 $[M+H]^+$.

11-Chloro-1,2-diphenylimidazo[1,2-*c*]indolo[1,2-*a*]quinazoline (18ad): Yield 42%, Brown



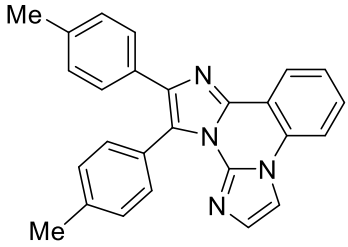
solid; mp ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 7.8 Hz, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.70 – 7.60 (m, 8H), 7.51 – 7.47 (m, 2H), 7.32 – 7.28 (m, 4H), 5.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.0, 133.8, 133.6, 132.7, 131.8, 130.5, 130.2, 130.1, 129.9, 129.2, 128.3, 128.0, 127.3, 125.4, 125.0, 124.4, 122.3, 120.3, 115.3, 115.0, 114.3, 87.3; HRMS (ESI) calcd for $C_{29}H_{19}ClN_3$ 444.1262 found 444.1237 $[M+H]^+$.

12-Methyl-1,2-diphenylimidazo[1,2-*c*]indolo[1,2-*a*]quinazolines (18ae): Yield 40%, White



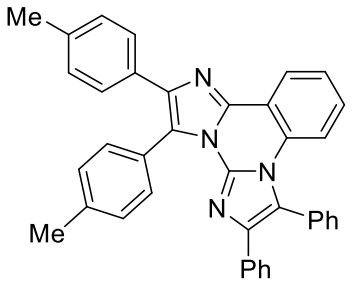
solid, mp 272 –274 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.8 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.54 – 7.30 (m, 15H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 132.4, 131.0, 130.9, 130.7, 130.2, 128.9, 128.4, 128.2, 127.2, 126.3, 125.2, 123.6, 123.0, 122.2, 119.0, 115.3, 114.6, 113.8, 99.9, 19.3; HRMS (ESI) calcd for $C_{30}H_{22}N_3$ 424.1808 found 424.1808 $[M+H]^+$.

2,3-Di-*p*-tolyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (18bf): Yield 60%, Brown solid; mp 224 –

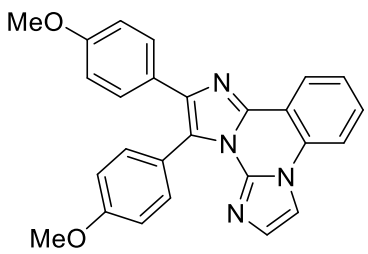


226 °C (lit. = 224 °C)[36]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 7.8 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.55 – 7.47 (m, 5H), 7.3 (d, J = 7.8 Hz, 2H), 7.18 (s, 1H), 7.10 (d, J = 7.9 Hz, 2H), 2.49 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 139.5, 138.7, 137.3, 137.0, 131.6, 130.9, 130.3, 129.9, 129.1, 129.0, 128.9, 127.7, 127.0, 126.0, 125.2, 124.6, 115.2, 114.6, 109.9, 21.7, 21.3. HRMS (ESI) calcd for $C_{26}H_{21}N_4$ 389.1761 found 389.1771 $[M+H]^+$.

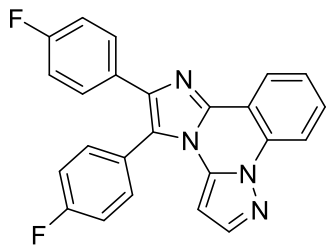
6,7-Diphenyl-2,3-di-*p*-tolyldiimidazo[1,2-*a*:1',2'-*c*]quinazolines (18bb): Yield 58%, White solid, mp 251–253 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 7.9 Hz, 1H), 7.70 – 7.57 (m, 9H), 7.42 – 7.37(m, 4H), 7.25 – 7.15 (m, 7H), 6.94 (d, J = 8.7 Hz, 1H), 2.57 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.6, 138.5, 137.0, 136.7, 136.7, 133.7, 132.2, 132.1, 131.9, 131.8, 131.1, 129.9, 129.9, 129.1, 129.0, 128.7, 128.0, 127.7, 126.8, 126.7, 125.4, 125.2, 124.8, 122.52, 116.0, 115.9, 21.6, 21.3; HRMS (ESI) calcd for $C_{38}H_{29}N_4$ 541.2387 found 541.2382 $[M+H]^+$.



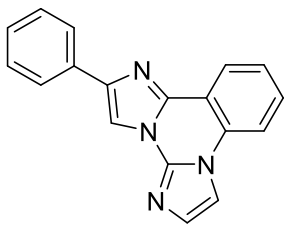
2,3-Bis(4-methoxyphenyl)diimidazo[1,2-*a*:1',2'-*c*]quinazolines (18cf): Yield 60%, Brown solid; mp 223 °C (lit. = 223 °C)[36]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 7.8 Hz, 1H), 7.70 – 7.49 (m, 8H), 7.18 – 7.16 (m, 1H), 7.03 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 158.9, 141.0, 139.3, 137.2, 133.1, 130.3, 129.9, 129.0, 128.8, 126.3, 126.0, 125.2, 123.8, 122.0, 115.0, 114.6, 113.8, 113.7, 109.9, 55.2, 55.2; HRMS (ESI) calcd for $C_{26}H_{21}N_4O_2$ 421.1659 found 421.1676 $[M+H]^+$.



2,3-Bis(4-fluorophenyl)imidazo[1,2-*c*]pyrazolo[1,5-*a*]quinazoline (18df): Yield 45%, Off white solid, mp 257 – 260 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + Formic acid) δ 8.60 (d, J = 8.0 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.78 – 7.74 (m, 2H), 7.62 – 7.51 (m, 5H), 7.30 (t, J = 8.5 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 5.41 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J = 252.0 Hz), 162.8 (d, J = 249.0 Hz), 141.5, 139.2, 138.7, 133.7 (d, J = 8.4 Hz), 133.4, 132.6, 132.1, 130.0 (d, J = 8.3 Hz), 127.0, 126.9, 124.7, 123.9 (d, J = 3.6 Hz), 123.4, 116.8 (d, J = 21.8 Hz), 115.7 (d, J = 21.7 Hz), 115.6, 112.3, 92.5; HRMS (ESI) calcd for $C_{24}H_{15}F_2N_4$ 397.1259 found 397.1262 $[M+H]^+$.

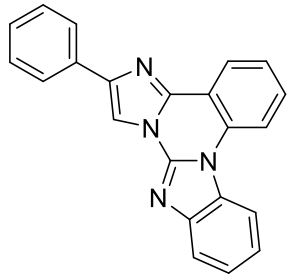


2-Phenyldiimidazo[1,2-*a*:1',2'-*c*]quinazoline (18ef): Yield 62%, Off-white solid; mp 190 °C (lit. = 188 – 190 °C)[36]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.3 Hz, 2H), 7.66 (d, J = 1.32 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.50 – 7.45 (m, 3H), 7.36 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 140.2, 136.6,



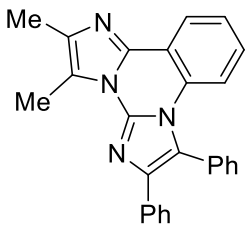
133.1, 130.3, 130.0, 128.8, 128.7, 127.9, 126.0, 125.8, 125.1, 114.8, 114.7, 110.7, 108.0; HRMS (ESI) calcd for $C_{18}H_{13}N_4$ 285.1135 found 285.1112 $[M+H]^+$.

2-Phenylbenzo[4,5]imidazo[1,2-*a*]imidazo[1,2-*c*]quinazolines (18eg): Yield 70%, Brown solid;



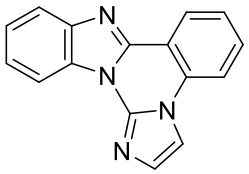
mp 208 – 210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J = 7.9, 1.6 Hz, 1H), 8.40 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.19 (dd, J = 7.6, 1.7 Hz, 1H), 8.04 (dd, J = 8.4, 1.5 Hz, 2H), 7.92 – 7.90 (m, 1H), 7.77 – 7.73 (m, 1H), 7.59 – 7.55 (m, 1H), 7.52 – 7.47 (m, 4H), 7.41 – 7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 142.0, 141.2, 140.8, 132.8, 132.7, 130.9, 130.6, 128.9, 128.2, 125.9, 125.5, 125.4, 124.6, 123.3, 120.0, 115.0, 114.9, 113.1, 108.8; HRMS (ESI) calcd for $C_{22}H_{15}N_4$ 335.1291 found 335.1287 $[M+H]^+$.

2,3-Dimethyl-6,7-diphenyldiimidazo[1,2-*a*:1',2'-*c*]quinazolines (18fb): Yield 45%, White



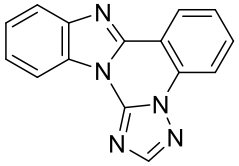
solid, mp 271–273 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 – 7.56 (m, 7H), 7.35 (t, J = 7.5 Hz, 1H), 7.26 – 7.22 (m, 3H), 7.15 – 7.10 (m, 1H), 6.93 (d, J = 8.6 Hz, 1H), 3.00 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 137.5, 137.2, 133.8, 132.0, 131.8, 131.6, 129.8, 128.4, 128.2, 127.1, 127.0, 125.4, 124.3, 122.5, 121.4, 116.0, 116.0, 12.9, 11.2; HRMS (ESI) calcd for $C_{26}H_{21}N_4$ 389.1761 found 389.1777 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*c*]imidazo[1,2-*a*]quinazoline (18gf): Yield 66%, Brown solid; mp 192 –



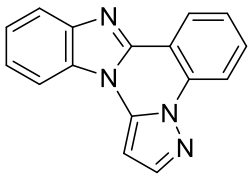
195 °C (lit. = 192 – 195 °C)[36]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.69 (m, 1H), 8.64 – 8.61 (m, 1H), 8.00 – 7.98 (m, 1H), 7.72 – 7.71 (m, 3H), 7.58 – 7.52 (m, 3H), 7.42 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.4, 137.7, 132.0, 131.8, 129.8, 129.0, 126.5, 126.2, 125.0, 124.2, 119.6, 114.9, 114.6, 114.3, 110.1; HRMS (ESI) calcd for $C_{16}H_{11}N_4$ 259.0978 found 259.0972 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*c*][1,2,4]triazolo[1,5-*a*]quinazolines (18ga): Yield 70%, Off-white



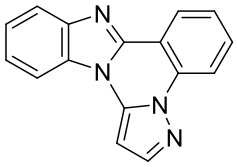
solid; mp 170 –172 °C (lit. = 170 – 172 °C)[36]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 7.9 Hz, 1H), 8.39 – 8.36 (m, 1H), 8.20 – 8.17 (m, 2H), 7.92 – 7.89 (m, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.7 Hz, 1H), 7.50 – 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 144.1, 143.9, 143.5, 132.3, 132.1, 129.2, 127.1, 125.8, 125.6, 124.6, 120.0, 115.6, 114.0, 113.6; HRMS (ESI) calcd for $C_{15}H_{10}N_5$ 260.0931 found 260.0941 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*c*]pyrazolo[1,5-*a*]quinazolines (18gh): Yield 40%, Off white solid, mp



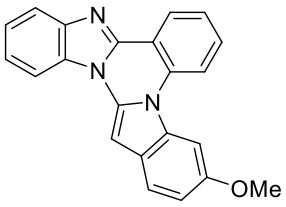
146 – 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (dd, J = 7.8, 1.4 Hz, 1H), 8.38 (dd, J = 8.4, 1.1 Hz, 1H), 8.01 – 7.99 (m, 2H), 7.87 – 7.85 (m, 1H), 7.80 – 7.75 (m, 1H), 7.58 – 7.50 (m, 3H), 6.77 (d, J = 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 143.8, 141.9, 134.4, 133.9, 132.3, 129.9, 126.2, 125.8, 124.8, 123.9, 120.3, 115.5, 113.6, 111.3, 90.4; HRMS (ESI) calcd for $C_{16}H_{11}N_4$ 259.0978 found 259.1002 $[M+H]^+$.

Benzo[4,5]imidazo[1,2-*c*]indolo[1,2-*a*]quinazolines (18gc): Yield 51%, Off white solid, mp



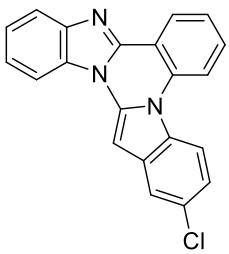
178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.8 Hz, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.98 – 7.93 (m, 2H), 7.72 – 7.66 (m, 2H), 7.50 – 7.48 (m, 2H), 7.41 (t, J = 7.6 Hz, 1H), 7.34 – 7.31 (m, 2H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 144.0, 135.6, 131.9, 131.8, 130.9, 130.7, 129.4, 126.6, 124.4, 124.0, 123.7, 122.6, 122.4, 120.8, 120.0, 115.3, 114.3, 113.3, 112.1, 86.4; HRMS (ESI) calcd for $C_{21}H_{14}N_3$ 308.1182 found 308.1165 $[M+H]^+$.

3-Methoxybenzo[4,5]imidazo[1,2-*c*]indolo[1,2-*a*]quinazoline (18gi): Yield 45%, White solid,



mp 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 7.9, 1.6 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 9.1 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.76 – 7.72 (m, 1H), 7.54 – 7.52 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.24 (d, J = 2.6 Hz, 1H), 7.01 (dd, J = 9.1, 2.6 Hz, 1H), 6.92 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 144.2, 144.2, 135.5, 132.4, 132.0, 130.7, 130.6, 126.7, 125.9, 124.5, 123.9, 123.6, 120.0, 114.9, 114.2, 112.1, 111.3, 103.0, 86.4, 55.7; HRMS (ESI) calcd for $C_{22}H_{16}N_3O$ 338.1288 found 338.1285 $[M+H]^+$.

2-Chlorobenzo[4,5]imidazo[1,2-*c*]indolo[1,2-*a*]quinazolines (18gd): Yield 35%, Off white



solid, mp 245–247 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.8 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 7.4s Hz, 1H), 7.68 (t, J = 7.2 Hz, 1H), 7.63 (d, J = 2.2 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.26 – 7.25 (m, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 143.8, 135.0, 132.7, 132.0, 130.6, 130.6, 129.2, 128.2, 126.7, 124.6, 124.5, 123.9, 122.4, 120.1, 115.0, 114.3, 114.2, 112.04, 85.7; HRMS (ESI) calcd for $C_{21}H_{13}ClN_3$ 342.0793 found 342.0799 $[M+H]^+$.

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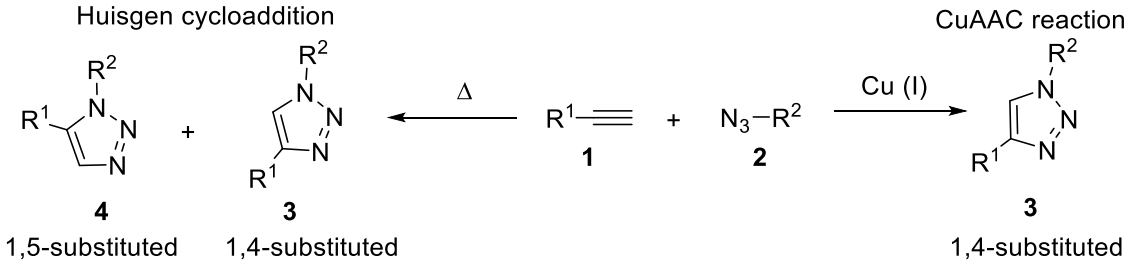
CHAPTER 4

Copper-Catalyzed Synthesis of Imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines

4.1. INTRODUCTION

1,2,3-triazoles are found to have a broad range of applications in the field of synthetic, medicinal as well as material chemistry. Synthesis of 1,2,3-triazoles can be efficiently achieved by the cycloaddition reaction of alkynes (**1**) with azides (**1**).[1-5] The first time the reaction of an alkyne with azide was explained by Huisgen; therefore, this reaction is known as Huisgen cycloaddition reaction (**Scheme 4.1**). [6,7] However, this reaction has some limitation like higher temperature, and mixture of 1,4- (**3**) and 1,5-regioisomeric (**4**) triazoles was obtained during the reaction.



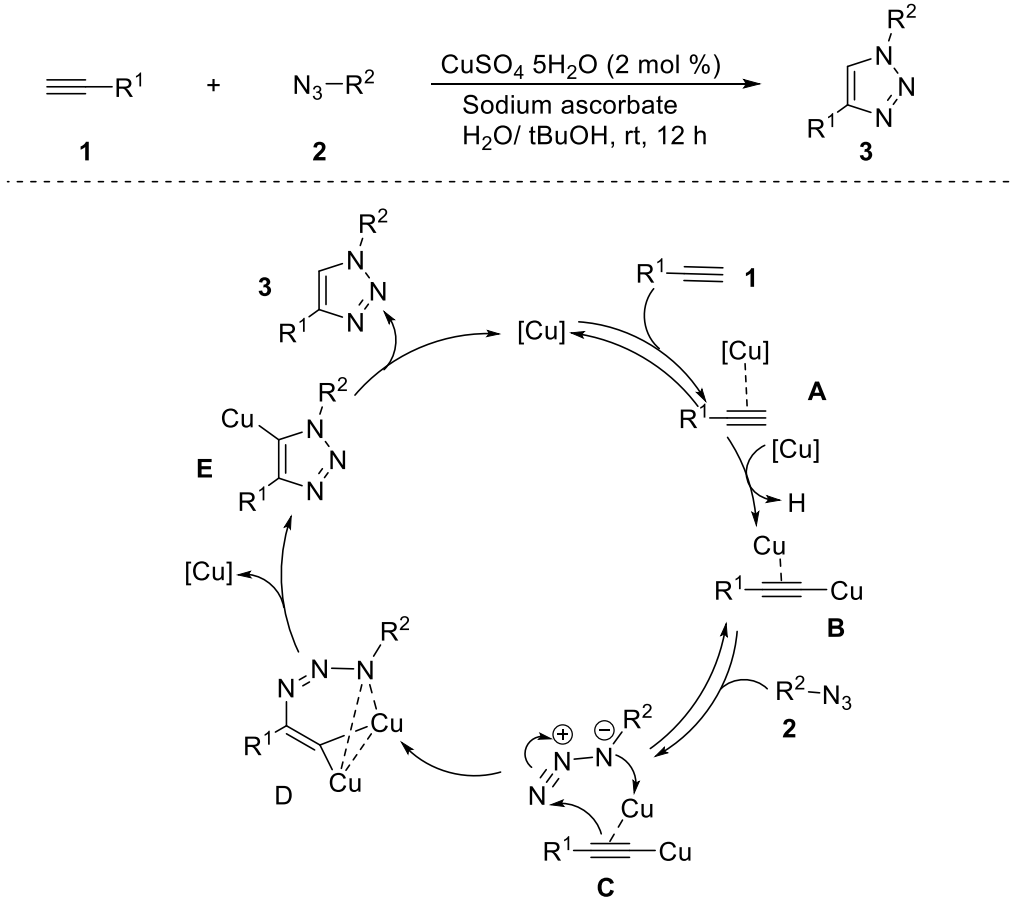
Scheme 4.1: Synthesis of triazoles through the Huisgen cycloaddition and CuAAC

To overcome these limitations, in 2002, Sharpless and Meldal presented a milestone for the regioselective synthesis of 1,4-disubstituted triazole (**3**) by the reaction of azides with alkynes in the presence of copper salt. This kind of reaction is known as copper-catalyzed azide-alkyne cycloaddition (CuAAC) or click reaction (**Scheme 4.1**).[8,9]

Since the pioneering work done by Sharpless and Meldel groups, copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become the finest way to generate 1,4-substituted-1,2,3-triazoles. The copper (I)–catalyzed azide-alkyne cycloaddition (CuAAC) has emerged as the premier example of click chemistry.[10-13] This reaction has crossed traditional disciplinary boundaries and has found applications in pharmaceutical, biology and materials for generating large libraries of compounds for screening in discovery research due to excellent regioselectivity and unprecedentedly high efficiency.[14,15] Therefore, synthesis of fused heterocyclic compounds *via* copper catalyzed azide-alkyne cycloaddition (CuAAc) have become a great demand in synthetic chemistry due to their broad range of application in a different area of science.

The copper-catalyzed reaction of an alkyne with azide gives 1,2,3-triazole through 1,3-cycloaddition reaction. The mechanistic part of this reaction was explained by Fokin through DFT study (**Scheme 4.2**). Initially, the interaction of alkyne (**1**) with copper to form π-complex (**A)** with triple bond and base abstracts proton to form Cu-acetylide intermediate (**B**) which react with azide

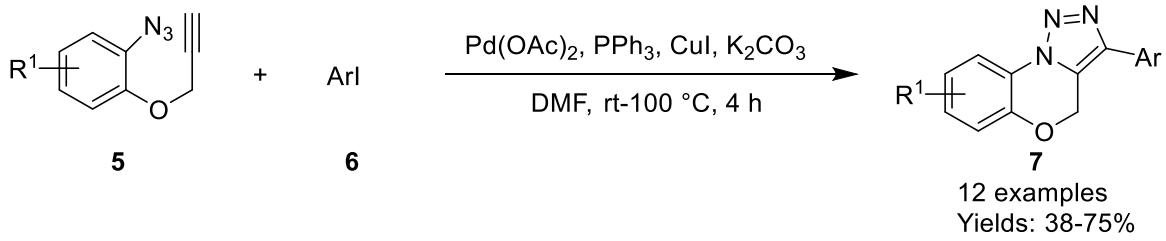
via 1,3-dipolar cycloaddition to give copper-azide-acetylide complex (**D**). Complex **D** dissociate which lead to C-Cu intermediate **E.** Intermediate **E** on hydrolysis provide 1,2,3-triazole (**3**) along with copper catalyst.[16]



Scheme 4.2: Reaction mechanism for CuAAC reaction

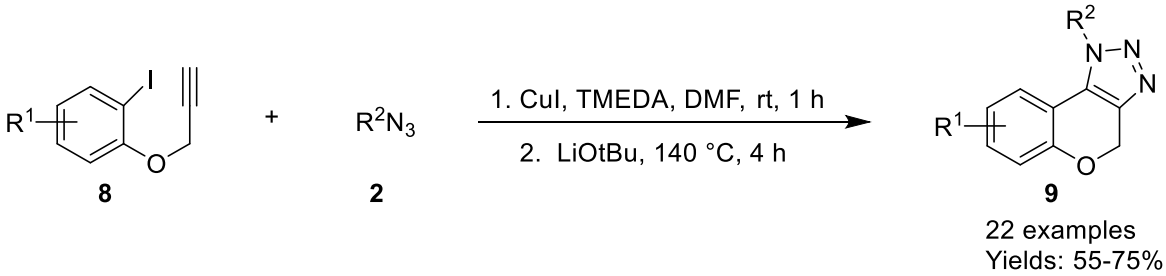
In recent year, click chemistry has been utilized for the synthesis of 1,2,3-triazoles in one–pot fashion.[17-31] A brief overview of triazole chemistry is presented below.

Choudhary group described Pd/Cu–catalyzed tandem reactions for the synthesis of [1,2,3]triazolo[5,1-c][1,4]benzoxazines (**7**) from 1-azido-2-(prop-2-ynyloxy)benzenes (**5**) and aryl iodides (**6**) (**Scheme 4.3**).[32] The reaction proceeded through C−C bond formation of aryl iodides with a terminal alkyne in Sonogashira fashion then intramolecular 1,3-dipolar cycloaddition which lead to the targeted fused azoles in good yields.



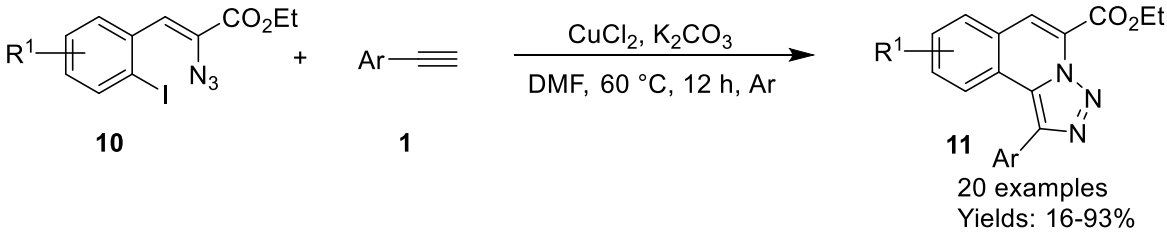
Scheme 4.3 Pd/Cu−catalyzed synthesis of [1,2,3]triazolo[5,1-*c*][1,4]benzoxazines

Kumara Swamy *et al*. achieved copper–catalyzed one-pot tandem reaction for synthesized 1,4-dihydrochromeno[3,4-d][1,2,3]triazole (**9**) from *ortho*-halo substituted *O*-propargylated phenols (**8**) and azides (**2**) (**Scheme 4.4**).[33] This protocol proceeded through CuAAC followed by intramolecular direct arylation.



Scheme 4.4 Copper– catalyzed one-pot synthesis of 1,4-dihydrochromeno[3,4-d][1,2,3]triazole

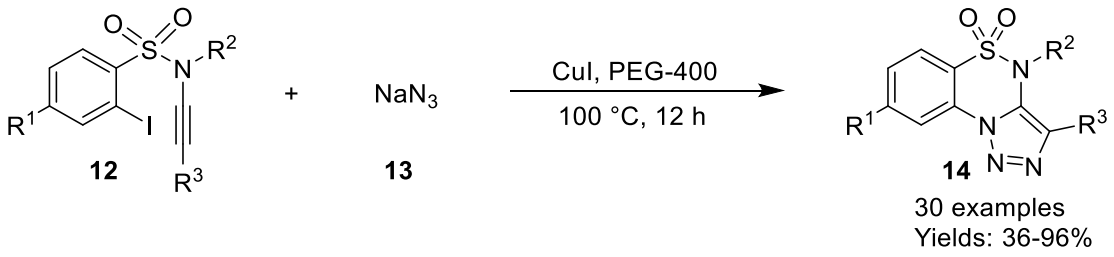
Liang and his colleagues developed one-pot synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines (**11)** by using ethyl 2-azido-3-(2-iodoaryl)acrylates (**10**) and arylalkynes (**1**) (**Scheme 4.5**).[34] The reaction involved copper–catalyzed Sonogashira coupling followed by 1,3-dipolar [3+2] cycloaddition reaction.



Scheme 4.5 Copper–catalyzed synthesis of [1,2,3]triazolo[5,1-*a*]isoquinolines

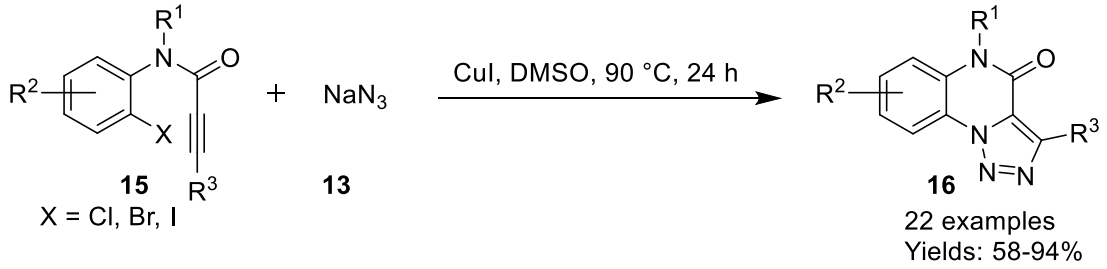
Swamy *et al.* demonstrated a copper-catalyzed one-pot tandem approach for the development of triazolo-1,2,4-benzothiadiazine-1,1-dioxides (**14**) by the reaction of functionalized ynamides (**12**) and sodium azide (**13**) (**Scheme 4.6**).[35] The reaction proceeds *via* intermolecular azidation using NaN_3 followed by cycloaddition reaction between ynamide and azide. The three consecutive C-N

bond formation was observed in a single step in this reaction. A range of *N*-alkynyl-2-iodo-benzenesulfonamides with electron donating groups (ERG) and electron withdrawing groups (EWG) were well tolerated and furnished the desired product in moderate to excellent yields (36-96%).



Scheme 4.6 Copper–catalyzed synthesis of triazolo1,2,4-benzothiadiazine1,1-dioxides from *N*-alkynyl-2-iodo-benzene sulfonamides and sodium azide

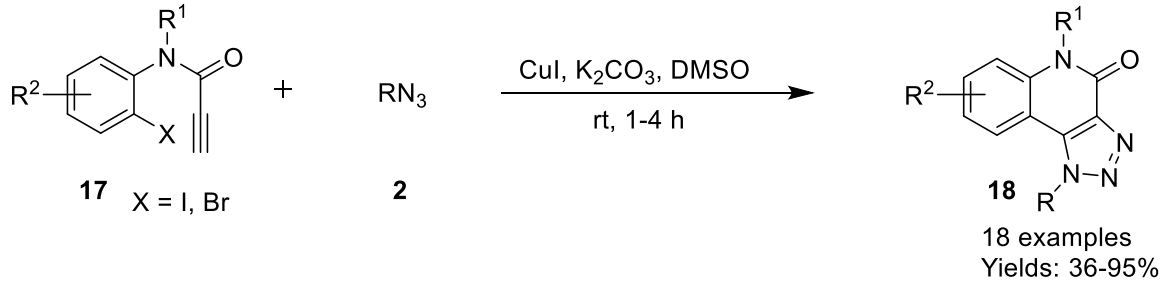
Cai *et al.* described the synthesis of [1,2,3]-triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones (**16**) from 1-(2-haloaryl)-propamides (**15**) and sodium azide (**13**) through copper–catalyzed tandem azide-alkyne cycloaddition followed by intramolecular C–N coupling (**Scheme 4.7**).[36] The scope of the methodology was explored by using a range of 1-(2-haloaryl)propionamides incorporating several electron donating groups (ERG) and electron withdrawing groups (EWG), and the corresponding reaction products were obtained in good to excellent yields (58-94%).



Scheme 4.7 Copper–catalyzed synthesis of [1,2,3]-triazolo[1,5-*a*]quinoxalin-4(5*H*)-ones from of *N*-(2-haloaryl)-propamides and sodium azide

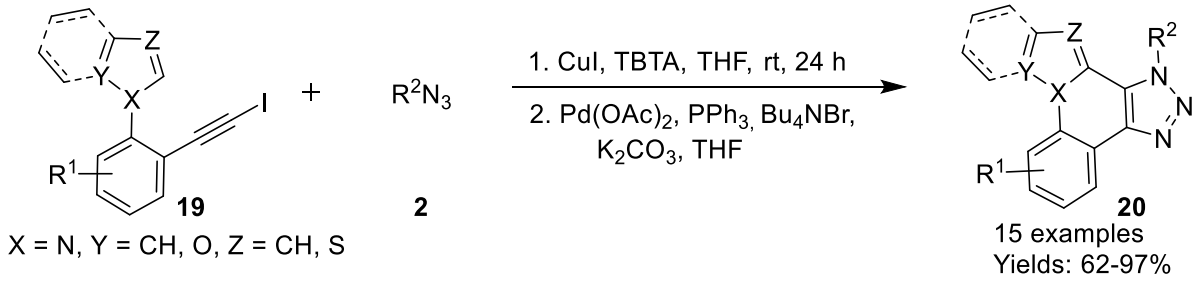
Ding and co-workers developed an efficient method for the synthesis of 1,2,3-triazolo[4,5-*c*]quinolin-4-one derivatives (**18)** from 1-(2-haloaryl)-propamides (**17**) and alkyl azide (**2**) (**Scheme 4.8**).[37] The reaction involved copper-catalyzed azide alkyl cycloaddition (CuAAC) followed by intermolecular C–C bond formation. The key step of this reaction is the trapping of

the C-Cu intermediate which led to the formation of C–C bond through Ullmann type coupling reaction.



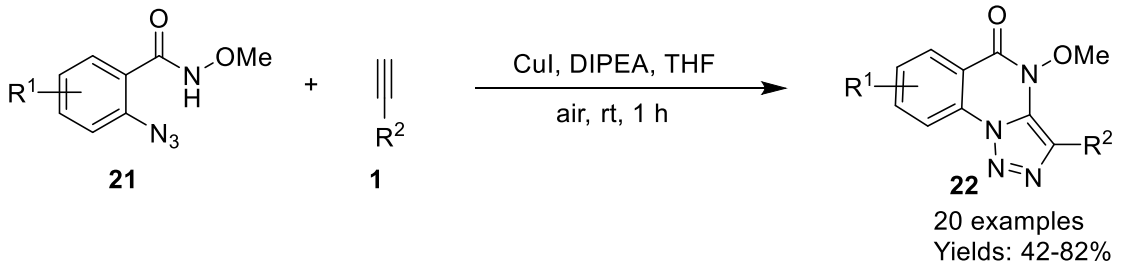
Scheme 4.8 Copper–catalyzed synthesis of 1,2,3-triazolo[4,5-*c*]quinolin-4-one

Lautens *et al.* described Cu/Pd–catalyzed one-pot tandem reaction for the synthesis of fused 1,2,3-triazoles (**20**) *via* [3+2] cycloaddition of alkynyl halides (**19**) and alkyl azides (**2**) followed by intramolecular direct arylations (**Scheme 4.9**).[38] This reaction gives moderate to good yield with heterocyclic nucleophiles like pyrrole, indole, furan, and thiophene.



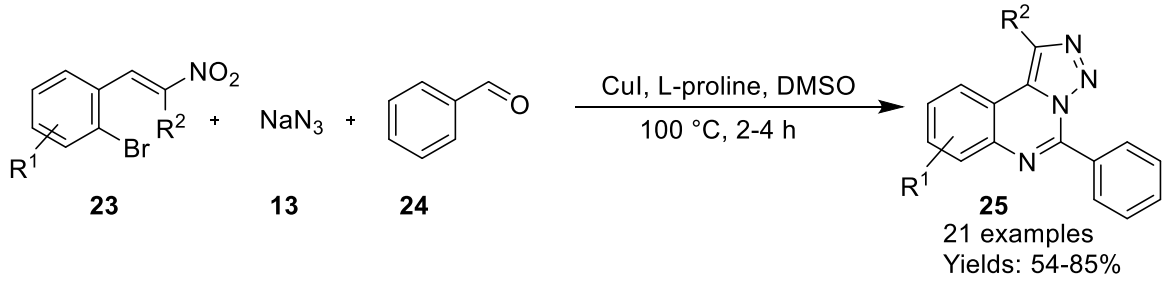
Scheme 4.9 Cu/Pd–catalyzed reactions of *N*-(2-iodoaryl)-propionamides with alkyl azide

Sun *et al.* synthesized triazoloquinazolinones (**22**) *via* copper–catalyzed azide-alkyne cycloaddition (CuAAC) reaction from 2-azido-*N*-methoxybenzamide derivatives (**21)** and alkynes (**1)** (**Scheme 4.10**).[39] The synthetic methodology involved sequential one-pot click reaction and aerobic intramolecular C–H amidation in the presence of copper catalyst without any external ligand.



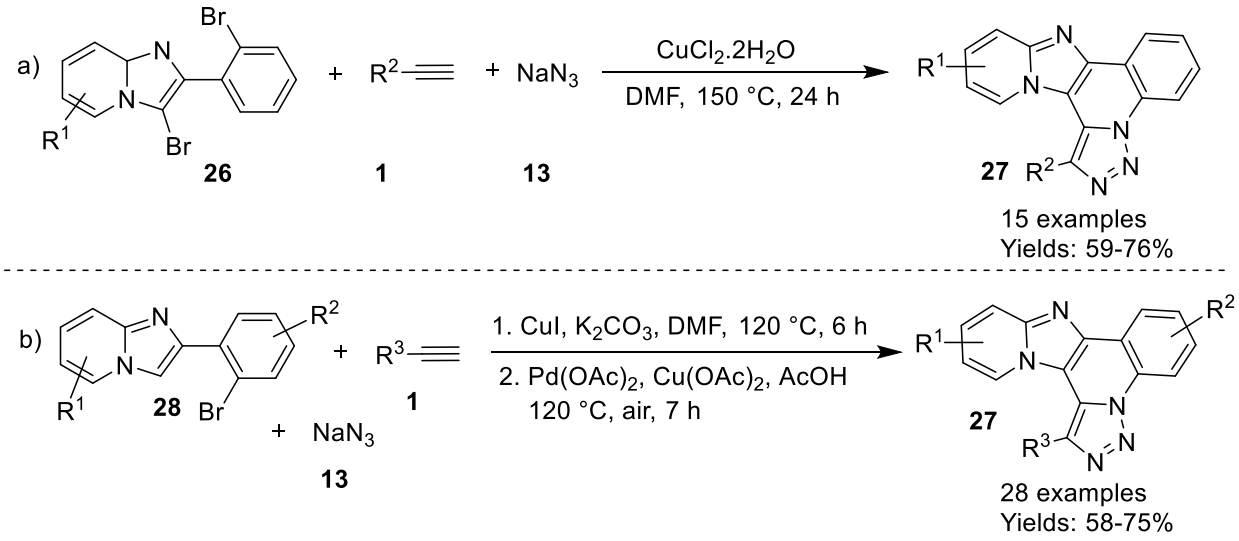
Scheme 4.10 Synthesis of triazoloquinazolinones *via* one-pot CuAAC and C–H amidation

Wu and co-workers reported an efficient one-pot multi–component synthesis of 5-phenyl-[1,2,3]triazolo[1,5-*c*]quinazolines (**25**) from readily available (*E*)-1-bromo-2-(2-nitrovinyl)benzenes (**23**), aldehydes (**24**), and sodium azide (**13**) (**Scheme 4.11**).[40] This tandem process involved consecutive [3+2] cycloaddition, copper-catalyzed S_NAr, reduction, cyclization, and oxidation sequences. The key point of this reaction is that NaN_3 act as a dual nitrogen source for the construction of these novels fused *N*–heterocycles.



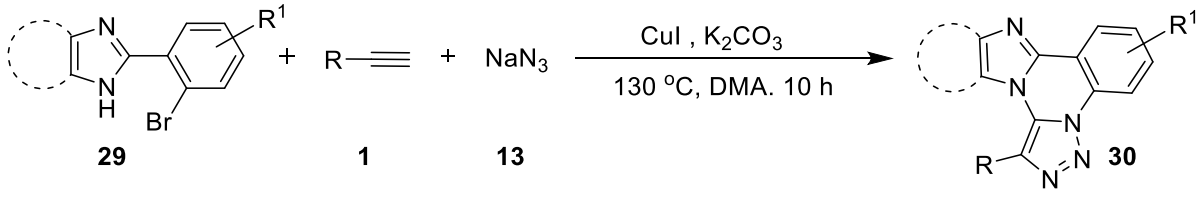
Scheme 4.11 A copper-catalyzed multi–component synthesis of fused [1,2,3]-triazolo[1,5-*c*]quinazolines

Kumar *et al.* have developed a simple one-pot protocol for the synthesis of 1,2,3-triazole-fused imidazo[1,2-*a*]pyridine **(27)** using tandem azide-alkyne cycloaddition Ullmann-type C–N coupling followed by intramolecular direct arylation (**Scheme 4.11a**).[41] Recently, Fan group modified this method and synthesized 1,2,3-triazole-fused imidazo[1,2-*a*]pyridine (**27**) using one–pot sequential method involving CuAAC and cross–dehydrogenative coupling reaction (**Scheme 4.11b**).[42] The scope of the methodology was explored by using a range of imidazo[1,2-*a*]pyridine and alkyne incorporating several electron donating groups (ERG) and electron withdrawing groups (EWG), and the corresponding reaction products were obtained in moderate to good yields (58-75%).



Scheme 4.12 Synthesis of novel azole–fused imidazo[1,2-*a*]pyridines *via* C–N coupling

As the evidence from literature *N*-fused heterocyclic frameworks with high molecular complexity can be easily constructed in one–pot by employing MCR, CuAAC and Ullmann type C–N coupling reactions in tandem fashion. These methods have added advantages of high atom economy and reduced waste generation which is very much expected from the viewpoint of sustainable and green chemistry. In continuation of our work for the synthesis of fused quinazolines. Herein, we wish to report the synthesis of novel imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines *via* ligand-free copper–catalyzed one-pot tandem reaction involving CuAAC reaction, intramolecular dehydrogenative C–N bond formation and Ullmann type C–N coupling (**Scheme 4.13**).



Scheme 4.13 Copper–catalyzed one-pot synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines

4.3 RESULTS AND DISCUSSION

To evaluate the feasibility of our proposed synthetic pathway, initially we reacted 2-(2-bromophenyl)-4,5-diphenyl-1*H*-imidazole (**29**), phenylacetylene (**1**) and NaN_3 (1**3**) in the presence of $CuCl_2$ (20 mol %) and K_2CO_3 (1 equiv.) at 130 °C under air for 10 h. To our satisfaction 3,5,6-triphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30aa**) was obtained in 52% yield (**Scheme 4.13**).

The structure of **30aa** was confirmed by NMR spectroscopic analysis (^1H and ^{13}C) and mass spectrometry data. In the ^1H NMR spectrum, a characteristic doublet at δ = 8.70 ppm was observed along with the expected peaks for the other protons. The peaks in the ^{13}C NMR spectrum were also consistent with the structure of **30aa (Figure 4.1)**. Finally, the presence of a peak at *m/z* = 438.1739 and *m/z* = 460.1568 in the HRMS spectrum corresponding to molecular ion $C_{29}H_{20}N_5^+$ $[M+H]^+$ and $C_{29}H_{19}N_5Na^+$ $[M+Na]^+$ respectively confirmed the structure of **30aa (Figure 4.2)**.

From the initial reaction, we then focused our attention towards optimizing the reaction condition by varying various parameters like catalysts, bases, and solvents. Screening of various copper salts revealed that CuI was the most suitable catalyst for this transformation giving 65% yield of **30aa** (**Table 4.1**, entries 1-4). Decreasing loading of CuI to 10 mol % decreased the yield of **30aa** to 45% whereas increasing loading of CuI to 30 mol % did not affect the yield of **30aa** (**Table 4.1**, entries 4-6). It is also worth to mention that **30aa** was not formed in the absence of copper catalyst even after keeping reaction for a longer time (**Table 4.1**, entry 7). Among different bases screened (K_2CO_3, Cs_2CO_3, Na_2CO_3, Et_3N, and DIPEA), use of K_2CO_3 gave the highest yield 65% of **30aa** (**Table 4.1**, entry 4, 8-11). Finally, a brief survey of solvents revealed that polar aprotic solvents such as DMA, DMF, and DMSO were found to be more effective for this transformation whereas formation of desired product was not observed in toluene, 1,4-dioxane, CH_3OH, and CH_3CN (**Table 4.1**, entries 4, 12-17). Use of additional oxidants such as $Cu(OAc)_2 \cdot H_2O$, IBD and TBHP were found to be ineffective in enhancing the yield of **30aa** (**Table 4.1**, entries 18-20).

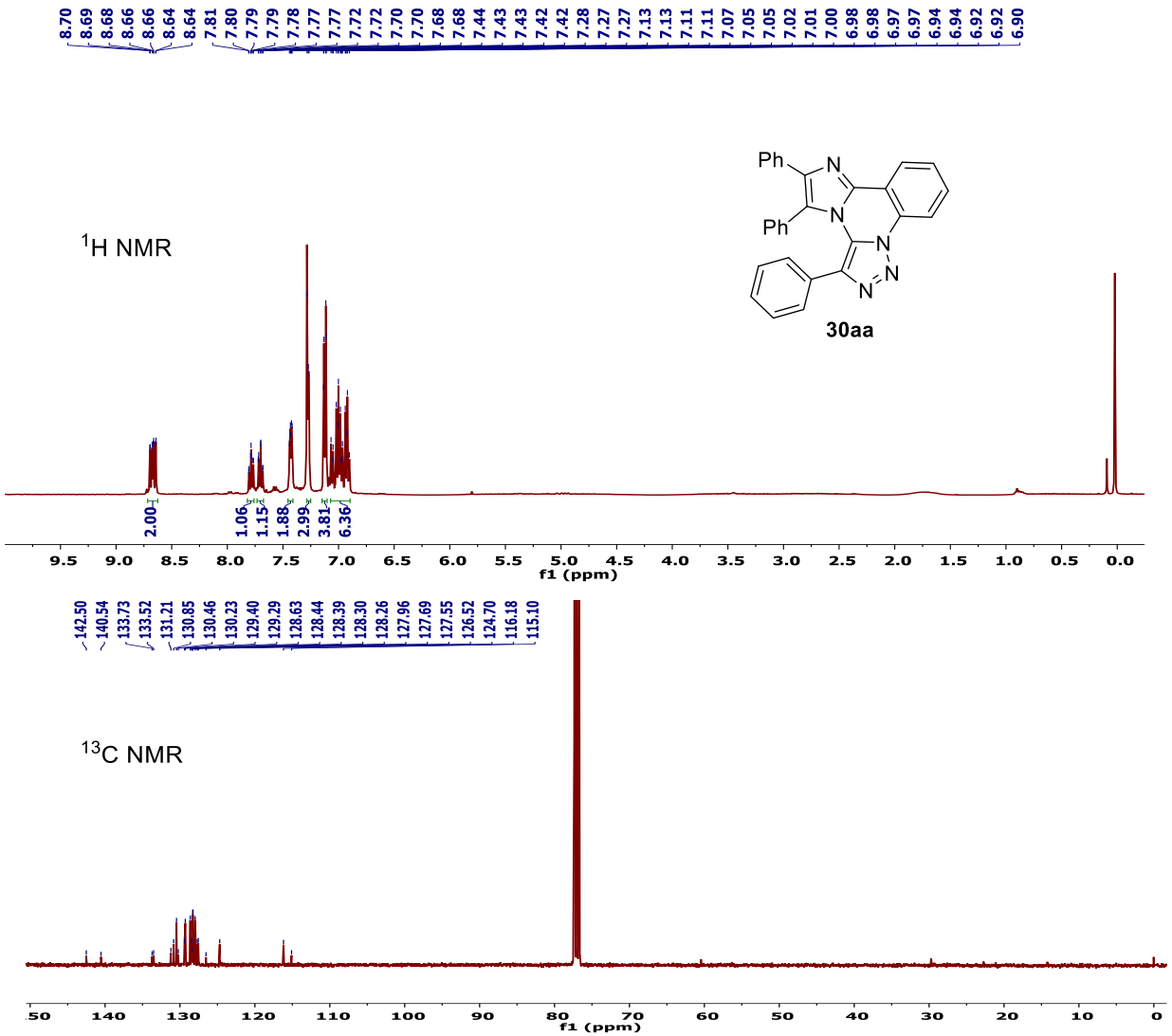


Figure 4.1 ^{1}H and ^{13}C NMR spectra of 3,5,6-triphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30aa**) in $CDCl_3$

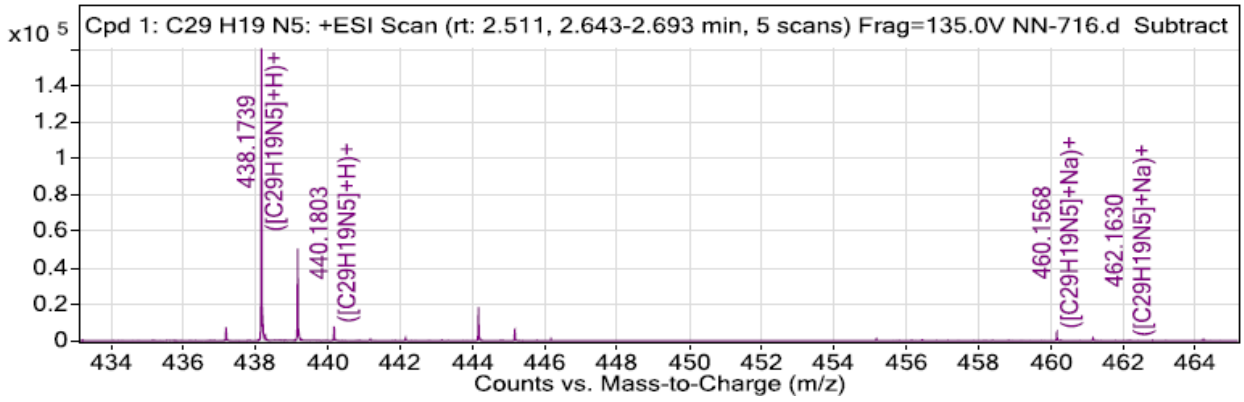
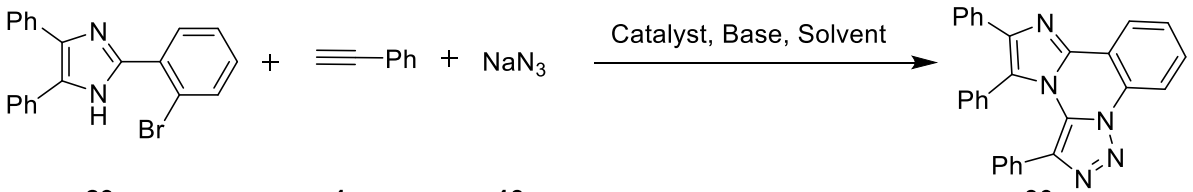


Figure 4.2 LC-HRMS of 3,5,6-triphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30aa**)

Table 4.1: Optimization of the reaction conditions[a]

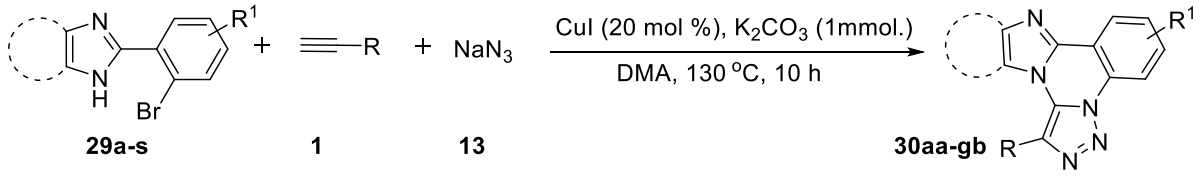


29a **1a** **13** **30aa**

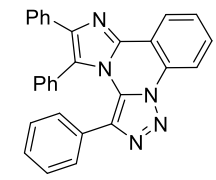
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	$CuCl_2$	K_2CO_3	DMA	52
2	$Cu(OAc)_2·H_2O$	K_2CO_3	DMA	50
3	CuBr	K_2CO_3	DMA	55
4	CuI	K_2CO_3	DMA	65
5	CuI	K_2CO_3	DMA	45[c]
6	CuI	K_2CO_3	DMA	65[d]
7	-	K_2CO_3	DMA	NR[e]
8	CuI	Cs_2CO_3	DMA	60
9	CuI	Na_2CO_3	DMA	62
10	CuI	Et_3N	DMA	55
11	CuI	DIPEA	DMA	60
12	CuI	K_2CO_3	DMF	61
13	CuI	K_2CO_3	DMSO	60
14	CuI	K_2CO_3	Toluene	NR[e]
15	CuI	K_2CO_3	Dioxane	NR[e]
16	CuI	K_2CO_3	CH_3OH	NR[e]
17	CuI	K_2CO_3	CH_3CN	NR[e]
18	CuI	K_2CO_3	DMA	62[f]
19	CuI	K_2CO_3	DMA	60[g]
20	CuI	K_2CO_3	DMA	60[h]

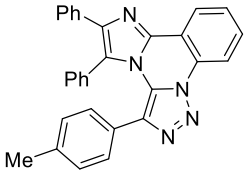
[a]Reaction conditions: **29a** (0.27 mmol), **1a** (0.32 mmol), **13** (0.40 mmol), catalyst (20 mol %), base (0.27 mmol), solvent (2.0 mL) under air at 130 °C, 10 h. [b]Isolated yield. [c]10 mol % of CuI was used. [d]30 mol % of CuI was used. [e]NR = no reaction. [f]In the presence of $Cu(OAc)_2·H_2O$ (2 equiv.). [g]In the presence of iodobenzene diacetate (2 equiv.). [h]In the presence of TBHP (2 equiv.).

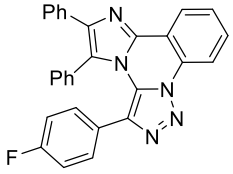
Table 4.2. Substrate scope for the synthesis of imidazo[1,2-*c*]quinazolines[a,b]

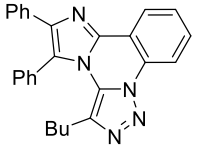


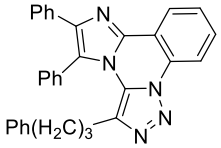
29a-s **1** **13** **30aa-gb**

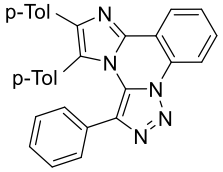

30aa, 65%

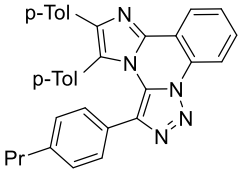

30ab, 60%

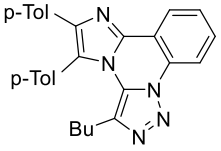

30ac, 50%


30af, 58%


30ag, 50%


30ba, 61%


30bd, 70%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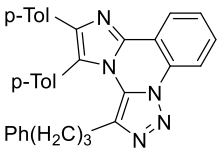
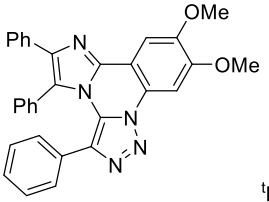
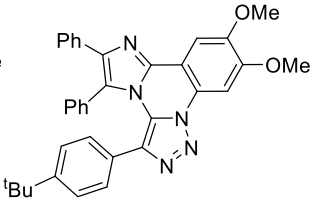
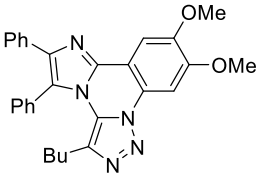
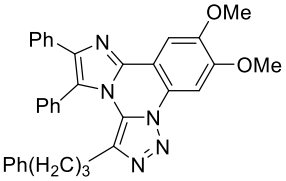
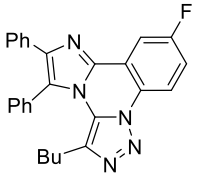

30bg, 75%

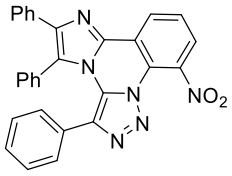

30ca, 58%

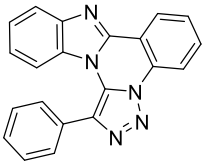

30ce, 56%

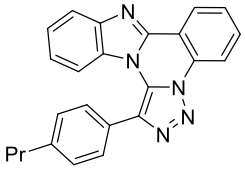

30cf, 50%

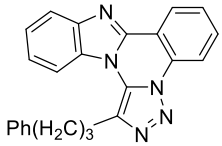

30cg, 61%

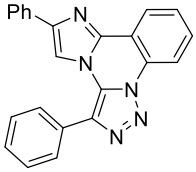

30df, 51%

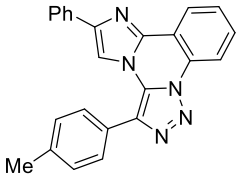

30ea, 0%

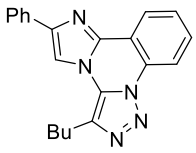

30fa, 60%

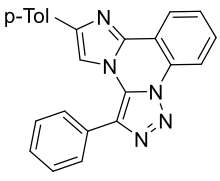

30fd, 67%

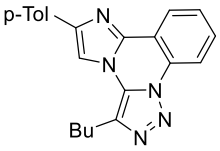

30fg, 62%

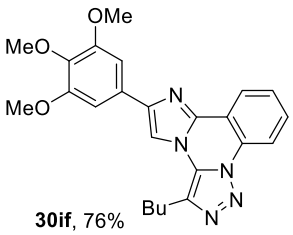

30ga, 51%


30gb, 64%


30gf, 85%


30ha, 59%


30hf, 70%

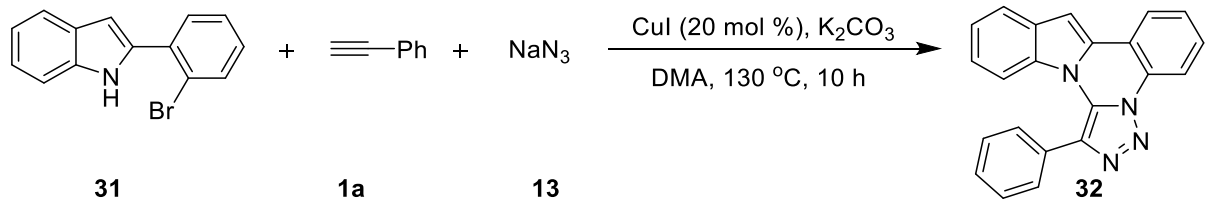

30if, 76%

[a]Reaction conditions: **29** (0.27 mmol), **1** (0.32 mmol), **13** (0.4 mmol), CuI (20 mol %), K_2CO_3 (0.27 mmol), DMA (2.0 mL) under air at 130 °C,10 h. [b]Isolated yield.

After achieving optimum reaction conditions, we explored substrate scope to synthesize imidazo-fuzed[1,2,3]triazolo[1,5-*a*]quinazolines (**30**) by reacting substituted imidazoles, benzmidazoles, and alkynes. Results for substrate scope are shown in **Table 4.2**. As can be seen from **Table 4.2**, both aliphatic and aromatic alkynes reacted smoothly with 4,5-diaryl-2-(2-bromoaryl)-1*H*-imidazole containing different substituent such as fluoro, methyl and methoxy on aryl ring at C-2, and C-4 & C-5 position of imidazole to give corresponding imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (**30aa-db**) in moderate to good yield (45-75%). Imidazole with 3-nitrophenyl as a substituent at C-2 position did not react under the optimized reaction condition. Further, 2-(2-bromophenyl)-1*H*-benzo[*d*]imidazole (**29f**) also reacted smoothly with alkynes to give corresponding benzo[4,5]imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30fa-ff**) in good yields (60-67%). Structure of all the compounds was ascertained by NMR (^{1}H and ^{13}C) and mass spectrometry data.

Further, we were interested to apply this methodology for the synthesis of 1-phenylindolo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**32**). To our immense gratification, Reaction of 2-(2-bromophenyl)-1*H*-indole (**31**) with **1a** and NaN_3 (**13**) under standard reaction conditions provided **32** in 35% yield.

The structure of **32** was confirmed by NMR spectroscopic analysis (^{1}H and ^{13}C) and mass spectrometry data. In the ^{1}H NMR spectrum, a characteristic singlet at δ = 7.35 ppm was observed along with the expected peaks for the other protons. The peaks in the ^{13}C NMR spectrum were also consistent with the structure of **32**. Finally, the presence of a peak at *m/z* = 335.1296 in the HRMS spectrum corresponding to molecular ion $C_{22}H_{15}N_4^+$ $[M+H]^+$.



Scheme 4.12. Synthesis of 1-phenylindolo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline.

Unsymmetrically substituted, 2-(2-bromophenyl)-4-phenyl-1*H*-imidazole (**29g**) also reacted smoothly with 4-tolylacetylene (**1b**) and sodium azide (**13**) to give corresponding 6(5)-phenyl-3-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30gb**). The correct structure to **30gb** from two possible isomers (**A** and **B**) was assigned by COSY and ID-NOE studies. Irradiation at a frequency corresponding to singlet at δ 7.94 resulted in enhanced of the two doublets at δ 7.72

and δ 7.88. Further irradiating at a frequency corresponding to signal at δ 7.88 resulted in the enhancement of the doublet at δ 7.42 and singlet at δ 7.94. Irradiation at a frequency corresponding to signal at δ 7.72 ppm resulted in the enhancement of singlet at δ 7.94 and doublet at δ 7.44 ppm (**Figure 4.4**). Based on these experiments, the structure of **30gb** is assigned that of isomer **A**.

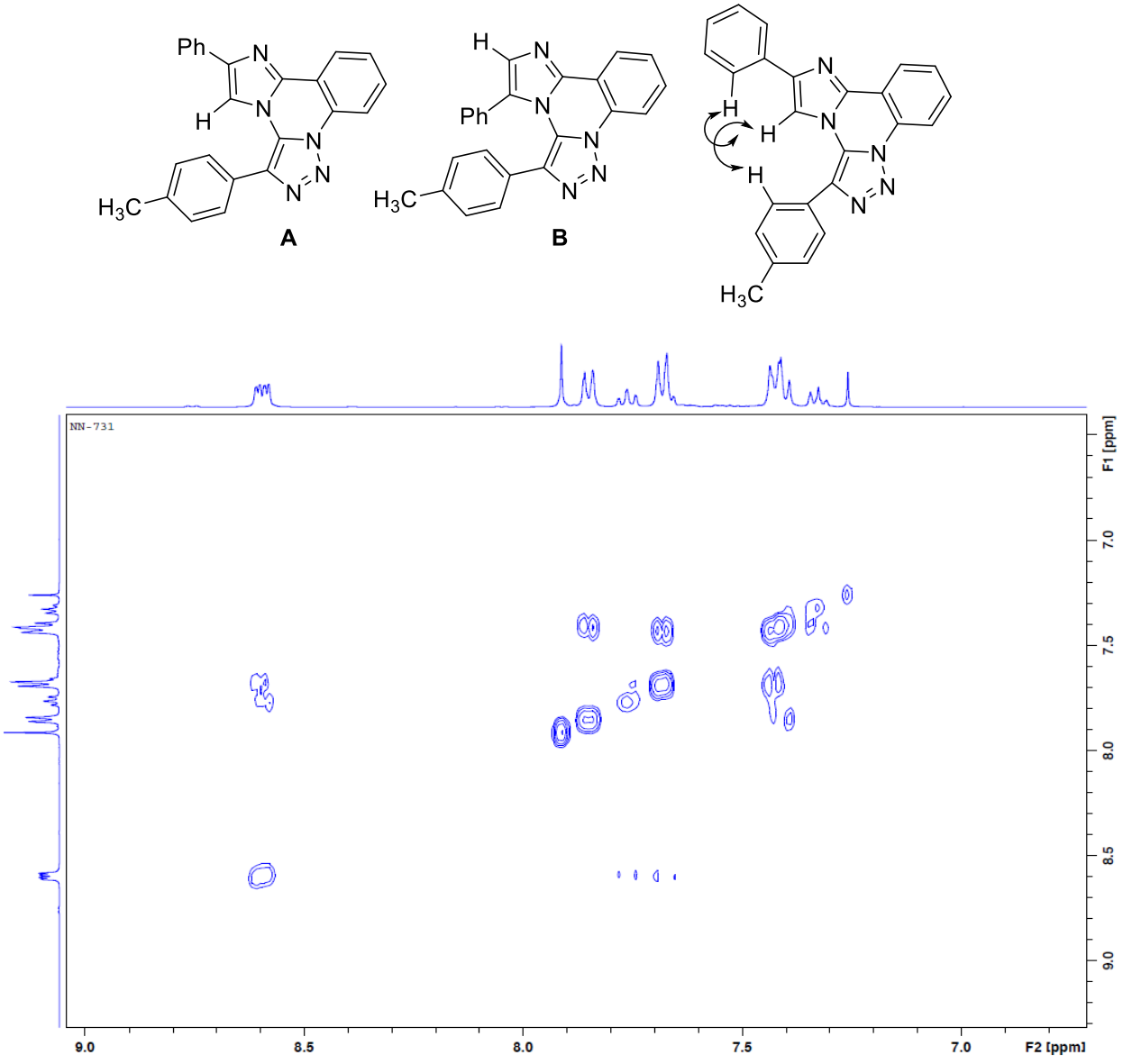


Figure 4.3 Possible regioisomers and 2D-COSY of compound **30gb**

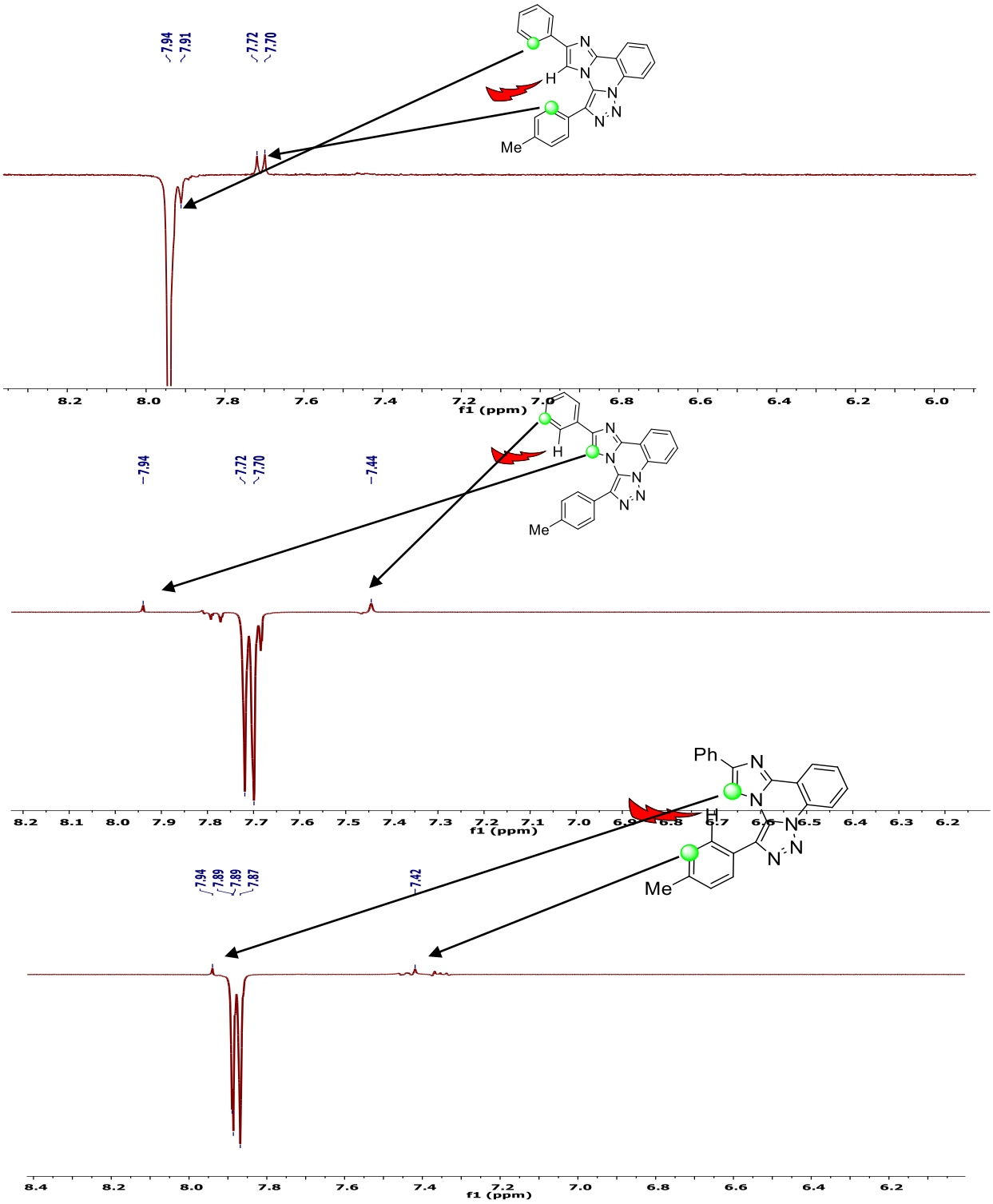
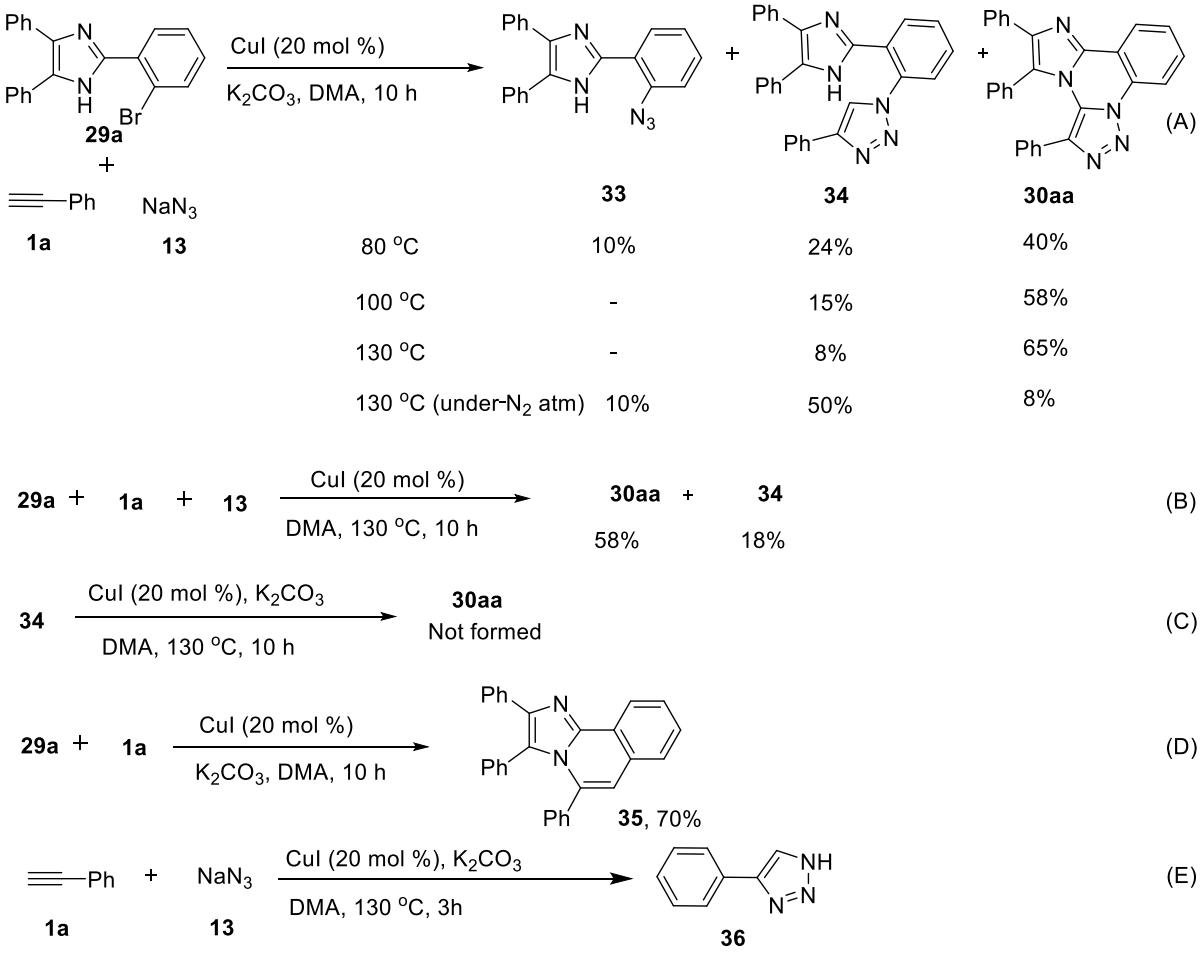


Figure 4.4 1D-NOE of 6-phenyl-3-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**30gb**)

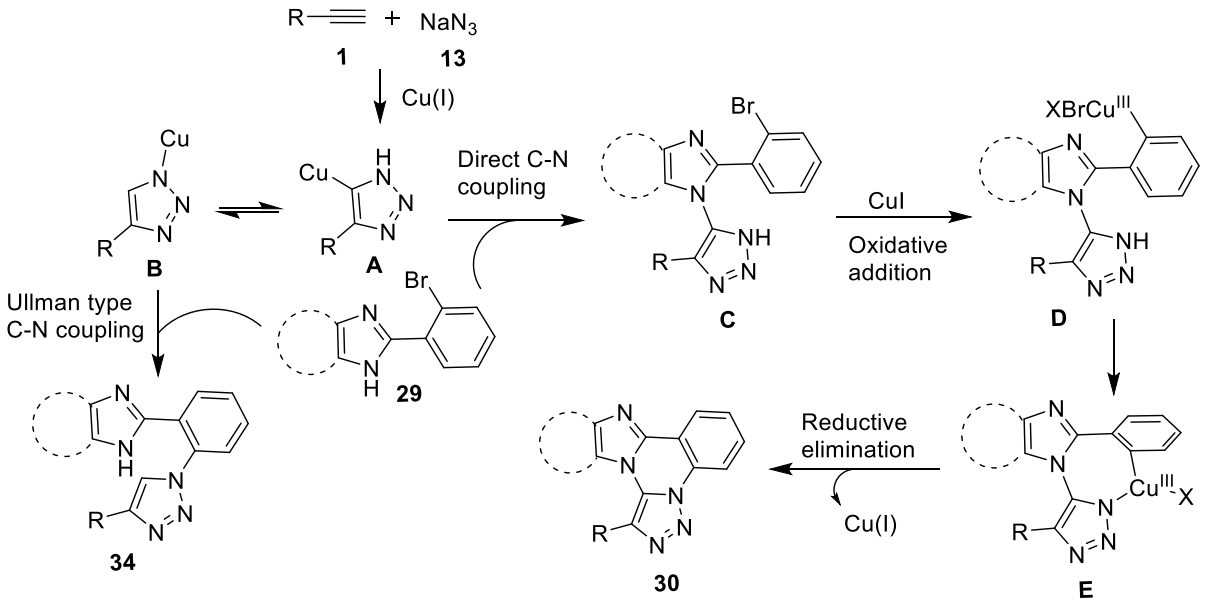
To gain insight into the mechanism of the reaction, some designed control experiments were conducted (**Scheme 4.13**). Intermediate **33** and **34** were obtained along with **30aa** when **29a**, **1a** and **13** were allowed to react in the presence of CuI (20 mol %), K_2CO_3 in DMA at 80 °C (**Scheme 4.13A**). When the reaction mass was heated at 100 ºC, **30aa** was obtained in 58% yield along with 15% triazole intermediate, 1-(2-(4,5-diphenyl-*1H*-imidazol-2-yl)phenyl)-4-phenyl-*1H*-1,2,3-triazole (**34**) Increasing temperature of the reaction to 130 °C led to an increase in the yield of **30aa** (65%), however, further increase in the reaction temperature to 150 °C did not improve the yield of **30aa**. When the reaction of **29a**, **1a** and **13** was performed under a nitrogen atmosphere, **30aa** was obtained only in 8% yield along with **33** and **34** in 10% and 50% yield, respectively. This indicated that oxygen is required as the oxidant to get cyclized product **30aa**. In the absence of the base, **30aa** was obtained in 58% yield along with 18% of triazole intermediate **34** (**Scheme 4.13B**). The reaction of **34** in the presence of CuI (20 mol %), K_2CO_3 in DMA at 130 °C for 10 h did not result in the formation of **30aa** (**Scheme 4.13C**). This suggested that **34** is not the intermediate of the reaction and it involves a two-step sequential approach *via* a concerted mechanism. The reaction of **29a** with **1a** under standard conditions resulted in the formation of 2,3,5-triphenylimidazo[2,1-*a*]isoquinoline (**32**) in 70% yield (**Scheme 4.13D**). On the other hand, the reaction of **1a** with **13** under standard reaction conditions resulted in the formation of cycloaddition product **36** (**Scheme 4.13E**).



Scheme 4.13. Control experiments.

Based on the control experiment results and literature reports,[42-45] a tentative mechanism for the tandem reaction is proposed in **scheme 4.14**. It is believed that initially, CuAAC reaction between alkyne (**1**) and sodium azide (**13**) results in the formation of C-Cu intermediate **A**, which can undergo a copper-hydrogen exchange to give intermediate **B**. Intermediate **A** on direct C–N bond formation *via* cross–dehydrogenative C–N coupling gives intermediate **C**. Intermediate **C** then undergoes Ullmann type C–N coupling through intermediate **D** and **E** to give product **27**. The proposed sequence is based on the fact that the isolated **34**, which could be formed by the reaction of intermediate **B** with **29** *via* Ullmann type C–N coupling does not lead to the formation of product **30**. However, another mechanistic scenario where Ullmann type C–N coupling takes place before the cross–dehydrogenative C–N coupling, also cannot be ruled out at this time. Since the reaction happens in a tandem fashion, we were unable to isolate the intermediates **C**, **D,** and **E** to

authenticate the proposed mechanism. Further, achieving higher yields of **30** was the challenging task because of the two inevitable competing reactions of intermediate **A** and **B**.



Scheme 4.14: A plausible mechanism for the synthesis of [1,2,3]triazolo[1,5-*a*]quinazolines

4.4 CONCLUSIONS

A simple and attractive process for the synthesis of imidazo[1,2-c][1,2,3]triazolo[1,5-*a*]quinazolines has been developed by copper–catalyzed tandem multi–component reaction in one-pot manner with moderate to excellent (50-85%) yields. The reaction involved sequential CuAAC reaction, dehydrogenative C–N bonding followed by Ullmann type C–N coupling. The developed method have shown good functional group tolerance and demonstrated broad substrate scope.

4.5 EXPERIMENTAL SECTION

4.5.1 General Materials and Methods

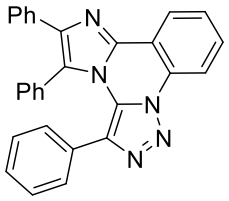
Melting points were determined in open capillary tubes on an automated melting point apparatus and are uncorrected. Reactions were monitored by using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates. Nuclear magnetic resonance (NMR) spectra were recorded on a 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) using deuterated solvent peak or tetramethylsilane (TMS) as internal standard. High resolution mass spectra (HRMS-ESI) were carried out using a quadrupole time-of-flight (Q-TOF) mass spectrometer. All

chemicals were obtained from the commercial suppliers and were used without further purification.

4.5.2 General procedure for synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1,5- *a*]quinazolines:

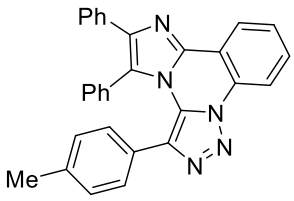
A clean oven dried 10 mL round bottom flask was charged with **29** (0.27 mmol), **1** (0.32 mmol), NaN_3 (0.40 mmol), DMA (2.0 mL), K_2CO_3 (0.27 mmol) and CuI (0.054 mmol). The reaction mixture was heated with stirring at 130 °C under air atmosphere for 10 h. Reaction progress was monitored by TLC. After completion, the reaction mass was allowed to cool at ambient temperature, diluted with water (20 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. Desired product **30** was isolated by column chromatography on silica gel (100-200 mesh) using hexane/ethyl acetate (15-25%) as eluent.

3,5,6-Triphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30aa). Yield 65%, Brown



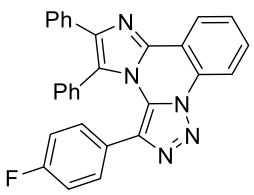
solid, mp 226 – 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.63 (m, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.44 – 7.43 (m, 2H), 7.28 – 7.27 (m, 3H), 7.13 – 7.12 (m, 4H), 7.07 – 6.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.5, 133.7, 133.5, 131.2, 130.8, 130.5, 130.2, 129.4, 129.3, 128.6, 128.4, 128.4, 128.3, 128.3, 128.0, 127.7, 127.5, 126.5, 124.7, 116.2, 115.1; HRMS (ESI) calcd for $C_{29}H_{20}N_5$ $[M+H]^+$ 438.1713 found 438.1739.

5,6-Diphenyl-3-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ab). Yield 60%,



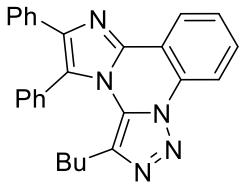
Yellow solid, mp 202 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 – 8.64 (m, 2H), 7.78 (t, J = 7.7 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.42 (dd, J = 6.3, 2.8 Hz, 2H), 7.28 – 7.26 (m, 3H), 7.10 (d, J = 7.3 Hz, 2H), 7.02 – 6.96 (m, 3H), 6.91 (t, J = 7.6 Hz, 2H), 6.78 (d, J = 7.7 Hz, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.5, 137.1, 133.7, 133.6, 130.8, 130.6, 130.2, 130.2, 129.2, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 127.9, 127.6, 126.5, 125.2, 124.7, 116.1, 115.0, 21.2; HRMS (ESI) calcd for $C_{30}H_{22}N_5$ $[M+H]^+$ 452.1870 found 452.1896.

3-(4-Fluorophenyl)-5,6-diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ac). Yield



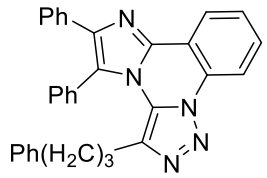
50%, Off-white solid, mp 227 – 229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.64 (m, 2H), 7.79 (t, J = 7.6 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.42 – 7.41 (m, 2H), 7.29 – 7.25 (m, 3H), 7.14 – 7.08 (m, 5H), 6.99 (t, J = 7.3 Hz, 2H), 6.69 (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 248.0 Hz), 142.7, 140.5, 133.4, 132.6, 131.2, 131.0 (d, J = 21.0 Hz), 130.6, 130.2, 129.3, 128.7, 128.5, 128.5, 128.3, 127.7, 127.3 (d, J = 3.4 Hz),126.3, 124.7, 116.2, 115.1, 115.0, 114.9; HRMS (ESI) calcd for $C_{29}H_{19}FN_5$ $[M+H]^+$ 456.1619 found 456.1618.

3-Butyl-5,6-diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30af). Yield 58%, White



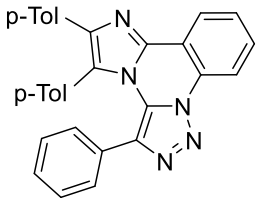
solid, mp 205 – 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.7 Hz, 1H), 8.56 (d, J = 8.2 Hz, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.58 – 7.52 (m, 6H), 7.29 – 7.28 (m, 3H), 1.67 – 1.59 (m, 2H), 1.44 – 1.36 (m, 2H), 1.05 – 0.96 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.0, 133.4, 133.0, 131.6, 130.7, 130.3, 130.2, 130.1, 129.5, 128.3, 128.3, 128.0, 127.7, 127.5, 125.4, 124.6, 116.0, 114.7, 31.7, 25.4, 22.2, 13.8; HRMS (ESI) calcd for $C_{27}H_{24}N_5$ $[M+H]^+$ 418.2046 found 418.2047.

5,6-Diphenyl-3-(3-phenylpropyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ag).



Yield 50%, Off-white solid, mp 193 – 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 7.8 Hz, 1H), 8.55 (d, J = 8.2 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.70 – 7.47 (m, 9H), 7.29 (d, J = 6.5 Hz, 2H), 7.22 (t, J = 7.4 Hz, 2H), 7.13 (t, J = 7.1 Hz, 1H), 7.05 (d, J = 7.4 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 1.80 – 1.74 (m, 2H), 1.72 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.7, 140.1, 133.3, 132.5, 131.5, 130.7, 130.2, 130.1, 129.6, 128.5, 128.3, 128.3, 128.2, 128.1, 127.8, 127.6, 125.7, 125.3, 124.6, 116.0, 114.7, 35.0, 31.0, 25.2; HRMS (ESI) calcd for $C_{32}H_{26}N_5$ $[M+H]^+$ 480.2183 found 480.2213.

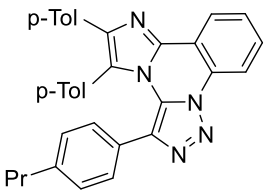
3-Phenyl-5,6-di-*p*-tolylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ba). Yield 61%,



Yellow solid, mp 220 – 222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 –8.63 (m, 2H), 7.76 (t, J = 7.7 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.14 – 7.06 (m, 5H), 7.03 – 6.95 (m, 4H), 6.67 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 140.2, 139.0, 137.4, 133.6, 131.3, 130.7, 130.6, 130.5, 130.0, 129.5, 129.4, 129.0, 128.4, 128.0, 127.9,

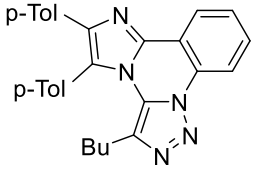
127.7, 126.7, 126.3, 125.3, 124.6, 116.1, 115.1, 21.3, 21.2; HRMS (ESI) calcd for $C_{31}H_{24}N_5$ $[M+H]^+$ 466.2026 found 466.2033.

3-(4-Propylphenyl)-5,6-di-*p*-tolylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (30bd).



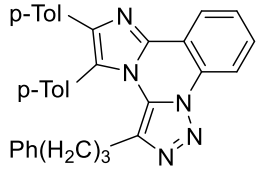
Yield 70%, White solid, mp 218 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.61 (m, 2H), 7.79 – 7.71 (m, 1H), 7.71 – 7.63 (m, 1H), 7.36 (d, J = 7.4 Hz, 2H), 7.09 (d, J = 7.2 Hz, 2H), 7.03 – 6.94 (m, 4H), 6.83 (d, J = 7.2 Hz, 2H), 6.70 (d, J = 7.1 Hz, 2H), 2.57 – 2.49 (m, 2H), 2.34 (s, 3H), 2.18 (s, 3H), 1.65 – 1.61 (m, 2H), 1.01 – 0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.7, 140.2, 138.8, 137.3, 133.7, 130.7, 130.6, 130.4, 130.2, 129.3, 129.2, 128.9, 128.5, 128.3, 128.0, 127.7, 126.3, 125.5, 124.6, 116.1, 115.1, 37.9, 29.7, 24.5, 21.2, 14.0; HRMS (ESI) calcd for $C_{34}H_{30}N_5$ $[M+H]^+$ 508.2496 found 508.2500.

3-Butyl-5,6-di-*p*-tolylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30bf). Yield 60%,



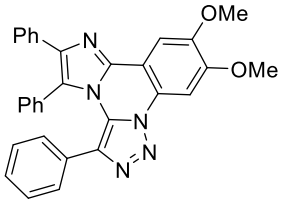
White solid, mp 205 – 206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 7.1 Hz, 1H), 8.55 (d, J = 8.1 Hz, 1H), 7.71 (t, J = 8.36 Hz, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.46 – 7.35 (m, 4H), 7.36 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.52 (s, 3H), 2.34 (s, 3H), 1.68 – 1.63 (m, 2H), 1.46 – 1.38 (m, 2H), 1.04 – 0.96 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 140.3, 139.8, 137.2, 132.9, 131.5, 130.6, 130.5, 130.2, 130.1, 129.0, 128.4, 128.0, 127.6, 127.4, 125.1, 124.6, 116.0, 114.8, 31.7, 25.5, 22.2, 21.5, 21.2, 13.7; HRMS (ESI) calcd for $C_{29}H_{28}N_5$ $[M+H]^+$ 446.2339 found 446.2342.

3-(3-Phenylpropyl)-5,6-di-*p*-tolylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30bg).



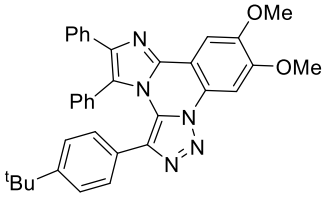
Yield 75%, White solid, mp 182 – 184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 7.8 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.63 (t, J = 7.92 Hz, 1H), 7.45 – 7.35 (m, 6H), 7.24 (t, J = 7.4 Hz, 2H), 7.17 – 7.06 (m, 5H), 2.55 (s, 3H), 2.39 – 2.29 (m, 5H), 1.82 – 1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 141.7, 140.2, 139.8, 137.3, 132.4, 131.5, 130.6, 130.5, 130.3, 130.0, 129.0, 128.5, 128.2, 128.2, 128.0, 127.6, 127.4, 125.7, 125.0, 124.5, 116.0, 114.8, 35.1, 31.1, 25.3, 21.7, 21.2; HRMS (ESI) calcd for $C_{34}H_{30}N_5$ $[M+H]^+$ 508.2496 found 508.2502.

9,10-Dimethoxy-3,5,6-triphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ca). Yield



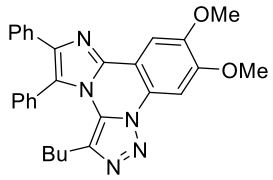
58%, Yellow solid, mp 200 – 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.02 (s, 1H), 7.43 – 7.41 (m, 2H), 7.28 – 7.26 (m, 3H), 7.13 – 7.11 (m, 4H), 7.13 – 6.89 (m, 6H), 4.15 (s, 3H), 4.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 150.0, 142.2, 141.0, 133.6, 133.6, 131.4, 130.7, 130.4, 129.6, 129.3, 128.6, 128.4, 128.2, 127.9, 127.7, 127.6, 127.4, 126.0, 124.9, 108.2, 104.9, 98.5, 56.8, 56.7; HRMS (ESI) calcd for $C_{31}H_{24}N_5O_2$ $[M+H]^+$ 498.1925 found 498.1932.

3-(4-(*tert*-Butyl)phenyl)-9,10-dimethoxy-5,6-diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-



***a*]quinazoline (30ce).** Yield 56%, Off-white solid, mp 220 – 222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.01 (s, 1H), 7.42 – 7.40 (m, 2H), 7.29 – 7.25 (m, 3H), 7.12 (d, J = 6.8 Hz, 2H), 7.06 – 6.99 (m, 4H), 6.94 – 6.87 (m, 3H), 4.14 (s, 3H), 4.13 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 149.9, 149.7, 142.2, 140.7, 133.7, 133.6, 130.5, 129.13, 129.0, 128.6, 128.4, 128.4, 128.2, 127.6, 126.0, 125.0, 125.9, 108.2, 104.9, 98.5, 56.7, 56.6, 34.4, 31.2; HRMS (ESI) calcd for $C_{35}H_{32}N_5O_2$ $[M+H]^+$ 554.2551 found 554.2557.

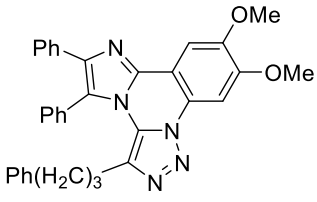
3-Butyl-9,10-dimethoxy-5,6-diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30cf).



Yield 50%, Off-white solid, mp 197 – 199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.96 (s, 1H), 7.60 – 7.52 (m, 7H), 7.30 – 7.26 (m, 3H), 4.11 (s, 3H), 4.11 (s, 3H), 1.64 (t, J = 8 Hz, 2H), 1.44 – 1.35 (m, 2H), 1.02 – 0.95 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 149.7, 141.4, 140.2, 133.5, 132.9, 131.7, 130.5, 130.0, 129.5, 128.3, 128.2, 127.8, 127.5, 124.9, 124.8, 107.8, 104.8, 98.3, 56.6, 56.6, 31.7, 25.5, 22.2, 13.8; HRMS (ESI) calcd for $C_{29}H_{28}N_5O_2$ $[M+H]^+$ 478.2238 found 478.2236.

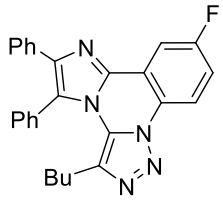
9,10-Dimethoxy-5,6-diphenyl-3-(3-phenylpropyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-

***a*]quinazoline (30cg).** Yield 61%, Off-white solid, mp 193 – 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$)



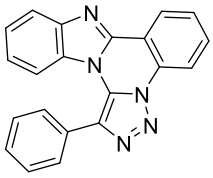
δ 7.96 (brs, 2H), 7.56 – 7.53 (m, 6H), 7.34 – 7.17 (m, 6H), 7.16 – 7.02 (m, 3H), 4.11 (brs, 6H), 2.31 (t, J = 6.9 Hz, 2H), 1.76 – 1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 149.7, 141.8, 141.5, 140.3, 133.5, 132.4, 132.3, 131.6, 130.4, 130.0, 129.5, 128.3, 128.2, 127.8, 127.5, 125.7, 124.9, 124.8, 107.8, 104.8, 98.3, 56.6, 56.6, 35.0, 31.0, 25.3; HRMS (ESI) calcd for $C_{34}H_{30}N_5O_2$ $[M+H]^+$ 540.2394 found 540.2396.

3-Butyl-9-fluoro-5,6-diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (30df). Yield



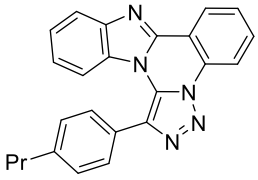
51%, White solid, mp 203 – 205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, J = 8.0, 3.8 Hz, 1H), 8.29 (d, J = 7.1 Hz, 1H), 7.66 – 7.50 (m, 7H), 7.43 (t, J = 8.0 Hz, 1H), 7.32 – 7.25 (m, 3H), 1.67 – 1.58 (m, 2H), 1.45 – 1.35 (m, 2H), 1.05 – 0.96 (m, 2H), 0.78 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 248.7 Hz), 142.0, 139.2 (d, J = 3.5 Hz), 133.0, 133.0, 131.6, 130.3, 130.1, 129.6, 128.3, 128.0, 127.7, 126.6, 126.6, 125.8, 118.7, 118.5, 118.4, 116.5 (d, J = 9.8 Hz), 110.4 (d, J = 25.6 Hz), 31.6, 25.4, 22.2, 13.8; HRMS (ESI) calcd for $C_{27}H_{23}FN_5$ $[M+H]^+$ 436.1932 found 436.1935.

1-Phenylbenzo[4,5]imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30fa). Yield 60%, Brown



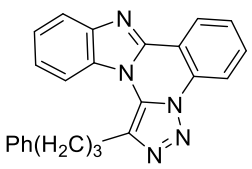
solid, mp 175 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.70 (m, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 7.2 Hz, 1H), 7.75 (t, J = 7.3 Hz, 1H), 7.68 – 7.60 (m, 5H), 7.43 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 6.58 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 144.0, 132.6, 132.2, 131.4, 130.5, 130.2, 129.7, 128.5, 128.4, 126.0, 124.9, 123.7, 120.2, 116.3, 114.5, 114.4; HRMS (ESI) calcd for $C_{21}H_{14}N_5$ $[M+H]^+$ 336.1244 found 336.1248.

1-(4-Propylphenyl)benzo[4,5]imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (30fd). Yield



67%, Yellow solid, mp 206 – 208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, J = 8.0, 0.8 Hz, 1H), 8.67 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.87 (t, J = 8.5 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.41 – 7.38 (m, 3H), 7.01 (t, J = 8.0 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 2.79 (t, J = 7.4 Hz, 2H), 1.83 – 1.77 (m, 2H), 1.06 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 144.3, 143.8, 132.5, 132.3, 131.4, 131.3, 130.2, 128.9, 128.6, 128.5, 127.7, 126.0, 124.8, 123.5, 120.1, 116.2, 114.6, 114.3, 37.9, 24.6, 13.6; HRMS (ESI) calcd for $C_{24}H_{20}N_5$ $[M+H]^+$ 378.1713 found 378.1720.

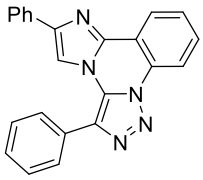
1-(3-Phenylpropyl)benzo[4,5]imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (30fg). Yield



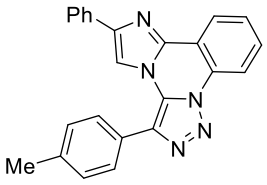
62%, Yellow solid, mp 145 – 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 7.5 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.87 – 7.73 (m, 2H), 7.63 (t, J = 7.3Hz, 1H), 7.45 (t, J = 7.1Hz, 1H), 7.31 – 7.21 (m, 6H), 3.43 (t, J = 8.0 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H), 2.38 – 2.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 143.7, 141.3, 132.4, 131.3, 131.0, 130.5, 129.1, 128.7, 128.5, 128.2, 126.0,

125.9, 124.9, 124.2, 120.7, 116.0, 114.0, 112.0, 35.5, 32.3, 27.3; HRMS (ESI) calcd for $C_{24}H_{20}N_5$ $[M+H]^+$ 378.1713 found 378.1744.

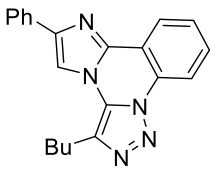
3,6-Diphenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ga). Yield 51%, Pale yellow solid, mp 210 – 212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.65 (m, 2H), 7.95 (s, 1H), 7.90 (d, J = 7.4 Hz, 2H), 7.84 – 7.80 (m, 3H), 7.77 – 7.69 (t, J = 7.6 Hz, 1H), 7.67 – 7.58 (m, 3H), 7.45 (t, J = 7.4 Hz, 2H), 7.41 – 7.33 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 140.5, 132.5, 130.9, 130.0, 129.4, 129.1, 128.8, 128.5, 128.3, 125.8, 124.8, 116.1, 114.5, 109.0; HRMS (ESI) calcd for $C_{23}H_{16}N_5$ $[M+H^+]$ 362.1400 found 362.1397.



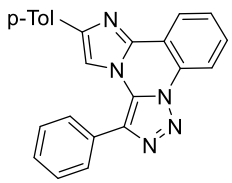
6-Phenyl-3-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30gb). Yield 64%, Off-white solid, mp 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.56 (m, 2H), 7.91 (s, 1H), 7.88 – 7.83 (m, 2H), 7.79 – 7.74 (m, 1H), 7.69 – 7.66 (m, 3H), 7.44 – 7.39 (m, 4H), 7.33 (t, J = 7.3 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 140.4, 139.4, 132.6, 132.3, 130.9, 130.0, 129.8, 129.2, 128.8, 128.4, 128.2, 127.2, 126.3, 125.8, 124.7, 116.1, 114.4, 109.0, 21.5; HRMS (ESI) calcd for $C_{24}H_{18}N_5$ $[M+H]^+$ 376.1557 found 376.1568.



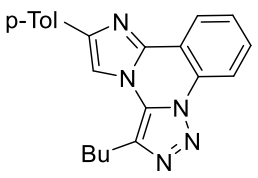
3-Butyl-6-phenylimidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30gf). Yield 85%, Pale brown solid, mp 172 – 174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 8.49 (m, 2H), 7.96 (d, J = 7.4 Hz, 2H), 7.91 (s, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.38 (t, J = 7.2 Hz, 1H), 3.14 (t, J = 7.4 Hz, 2H), 1.95 – 1.88 (m, 2H), 1.61 – 1.52 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 140.1, 132.6, 130.7, 130.0, 128.8, 128.3, 128.1, 125.7, 124.7, 115.9, 114.3, 108.2, 31.4, 25.2, 22.4, 13.9; HRMS (ESI) calcd for $C_{21}H_{20}N_5$ $[M+H]^+$ 342.1713 found 342.1727.



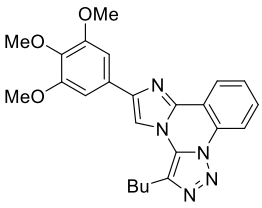
3-Phenyl-6-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30ha). Yield 59%, Off-white solid, mp 192 – 195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.62 (m, 2H), 7.90 (s, 1H), 7.85 – 7.71 (m, 6H), 7.68 – 7.59 (m, 3H), 7.24 (d, J = 7.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 140.3, 138.2, 132.2, 130.8, 129.9, 129.7, 129.5, 129.4, 129.3, 129.1, 128.4, 125.7, 124.8, 116.1, 114.5, 108.6, 21.3; HRMS (ESI) calcd for $C_{24}H_{18}N_5$ $[M+H]^+$ 376.1557 found 376.1558.



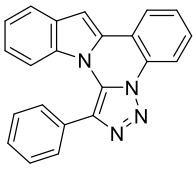
3-Butyl-6-(*p*-tolyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (30hf). Yield 70%, Pale green solid, mp 133 – 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.47 (m, 2H), 7.89 – 7.76 (m, 3H), 7.70-7.62 (m, 2H), 7.28 – 7.23 (m, 2H), 3.15 – 3.08 (m, 2H), 2.41 (s, 3H), 1.89 – 1.92 (m, 2H), 1.58 – 1.54 (m, 2H), 1.02 – 1.07 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 140.0, 138.1, 131.5, 130.6, 129.9, 129.8, 129.5, 128.0, 125.5, 124.6, 115.8, 114.3, 107.8, 31.34, 25.2, 22.4, 21.3, 13.9; HRMS (ESI) calcd for $C_{22}H_{22}N_5$ $[M+H]^+$ 356.1870 found 356.1905.



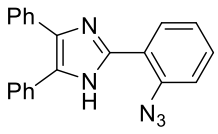
3-Butyl-6-(3,4,5-trimethoxyphenyl)imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (30if). Yield 76%, white solid, mp 174 – 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.51 (m, 2H), 7.88 (s, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.1 Hz, 1H), 7.19 – 7.18 (m, 2H), 4.02 (s, 6H), 3.93 (s, 3H), 3.16 (t, *J* = 6.5 Hz, 2H), 1.97 – 1.88 (m, 2H), 1.58 – 1.54 (m, 2H), 1.05 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 145.6, 140.1, 138.5, 131.6, 130.8, 130.0, 128.3, 128.1, 127.6, 124.7, 115.9, 114.2, 108.0, 103.2, 61.0, 56.4, 31.3, 25.1, 22.3, 13.8; HRMS (ESI) calcd for $C_{24}H_{26}N_5O_3$ $[M+H]^+$ 432.2030 found 432.2039.



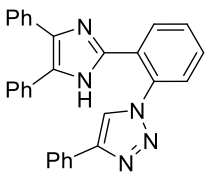
1-Phenylindolo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines (32). Yield 35%, Yellow solid, mp 218 – 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, J = 8.0, 1.4 Hz, 1H), 8.13 (dd, J = 7.8, 1.5 Hz, 1H), 7.76 (dt, J = 8.0, 1.0 Hz, 1H), 7.67 – 7.50 (m, 7H), 7.35 (s, 1H), 7.28 – 7.23 (m, 1H), 6.95 (ddd, J = 8.5, 7.1, 1.3 Hz, 1H), 6.66 (dd, J = 8.6, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 131.7, 131.6, 131.5, 131.0, 129.7, 129.5, 129.4, 129.0, 128.9, 128.2, 128.0, 123.9, 122.7, 122.6, 120.8, 117.1, 116.4, 115.0, 99.8. HRMS (ESI) calcd for $C_{22}H_{15}N_4$ $[M+H^+]$ 335.1291 found 335.1296.



2-(2-Azidophenyl)-4,5-diphenyl-1*H*-imidazole (33). Yield 10%, Red solid, mp 286 – 288 °C; ^{1}H NMR (400 MHz, DMSO) δ 11.75 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.47 – 7.43 (m, 7H), 7.38 – 7.32 (m, 2H), 7.29 – 7.23 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 145.8, 143.7, 140.5, 135.8, 133.9, 131.7, 131.4, 131.0, 128.7, 128.6, 128.2, 127.8, 125.7, 123.7, 123.4, 115.9, 112.7; HRMS (ESI) calcd for $C_{21}H_{16}N_5$ $[M+H]^+$ 338.1400 found 338.1301.

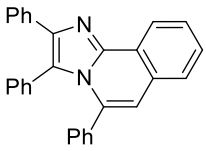


1-(2-(4,5-Diphenyl-1*H*-imidazol-2-yl)phenyl)-4-phenyl-1*H*-1,2,3-triazole (34). Yield 50%,



White solid, mp 230 – 232 °C; ^{1}H NMR (400 MHz, DMSO) δ 12.72 (s, 1H), 8.94 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 7.3 Hz, 2H), 7.79 – 7.65 (m, 2H), 7.67 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.43 – 7.38 (m, 6H), 7.24 (d, J = 7.1 Hz, 2H), 7.06 – 6.98 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ 146.3, 146.3, 142.5, 137.3, 135.1, 135.0, 131.4, 131.3, 130.7, 129.7, 129.5, 129.3, 129.1, 128.8, 128.6, 128.4, 128.3, 128.2, 127.3, 127.1, 126.8, 125.8, 125.5; HRMS (ESI) calcd for $C_{29}H_{22}N_5$ $[M+H]^+$ 440.1870 found 440.1889.

2,3,5-Triphenylimidazo[2,1-*a*]isoquinolines (35). Yield 70%, White solid, mp 205 – 207 °C; ^{1}H



NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 8.2 Hz, 1H), 7.75 – 7.48 (m, 5H), 7.32 – 7.20 (m, 4H), 7.14 – 6.92 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 141.7, 137.0, 134.8, 134.4, 131.9, 131.4, 131.2, 130.8, 129.3, 129.2, 128.5, 128.3, 127.8, 127.4, 127.3, 126.9, 126.5, 124.5, 123.7, 123.4, 115.75; HRMS (ESI) calcd for $C_{29}H_{21}N_2$ $[M+H^+]$ 397.1699 found 397.1706.

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CHAPTER 5

Conclusions

5.1 General conclusions

Heterocycles have occupied a central position in organic chemistry, and have a vital role in the agrochemical and pharmaceutical industries. The fascinating and challenging molecular architectures of nitrogen-containing heterocycles with potential bioactive properties have received significant attention from researchers engaged in drug design and the development of synthetic methodology.

Among various *N*-heterocycles, quinazoline has been recognized as one of the unique scaffolds due to its diverse spectrum of therapeutic potential. Over the past several years, intensive efforts have been directed to generate numerous structurally functionalized quinazoline derivatives. Synthesis of quinazolines under environmentally benign reaction conditions is a highly desirable and challenging task.

The present thesis entitled **"Design and synthesis of fused Imidazo/benzimidazo[1,2-*c*] quinazolines and their antimicrobial study"** deals with the synthesis of fused quinazolines through copper and palladium-catalyzed C–C and C–N bond formation and study of antimicrobial activity of selected derivatives.

5.2 Specific conclusions

The thesis entitled **"Design and Synthesis of fused Imidazo/benzimidazo[1,2-*c*]quinazolines and their antimicrobial study"** is divided into five chapters. A brief overview of these chapters is discussed below.

The first chapter of the thesis highlights the different synthetic approach of quinazolines under metal–free and metal-catalyzed conditions and their application as bioactive molecules in medicinal chemistry (**Figure 5.2.1**).

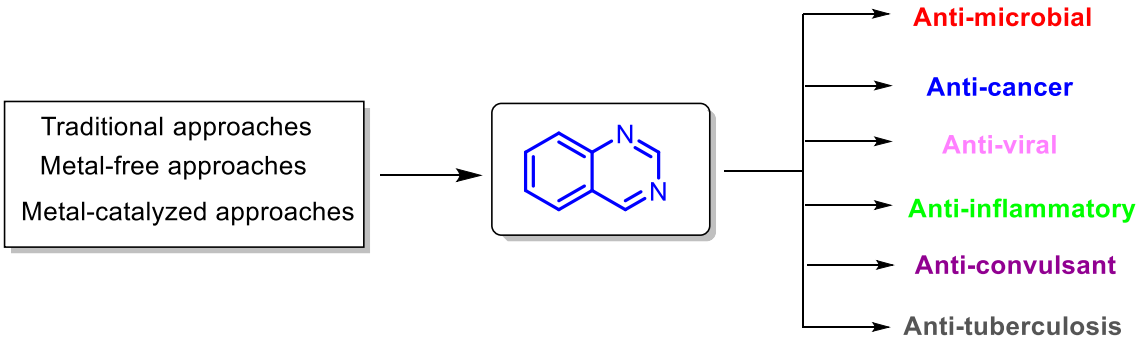

Figure 5.2.1 A graphical representation of quinazolines and their application

The second chapter of the thesis is divided into three parts where different approaches have been developed for the synthesis of fused imidazo/benzimidazo[1,2-*c*]quinazolines.

In **part-A** copper–catalyzed one-pot tandem protocol has been described for the synthesis of imidazo[1,2-*c*]quinazolines by using easily available starting material such as substituted 2-(2-bromophenyl)-1*H*-imidazoles and formamide. The developed protocol involved initially, copper-catalyzed Ullmann–type C–N coupling, intramolecular nucleophilic addition followed by intramolecular dehydrative cyclization to access fused quinazolines. This reaction was also carried out with acetamide and benzamide with slight modification in optimized reaction condition. Finally, to evaluate the scalability of the protocol, a model reaction was performed at a gram scale, and quinazoline was isolated with 71% yield (**Figure 5.2.2**).

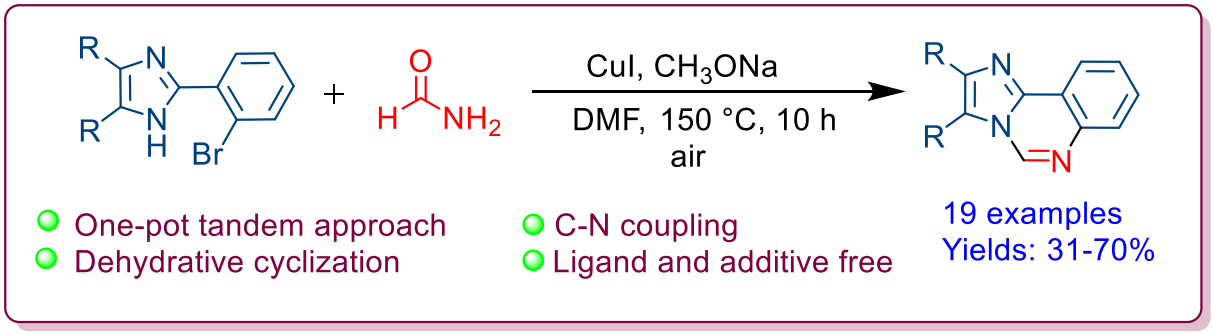

Figure 5.2.2 Copper–catalyzed tandem Ullmann type C–N coupling and dehydrative cyclization

In **part-B** an efficient one-pot tandem multicomponent approach has been developed for the synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines. The reaction involved sequential azidation through S_NAr, reduction, followed by oxidative amination of C(sp^3)–H bonds of *N*, *N*-dimethylacetamide (DMA) in the presence of TBHP as the oxidant. The method provides a powerful means of using easily available sodium azide as a nitrogen source and DMA as one carbon source for the synthesis of these *N*-fused heterocycles in good to excellent yields, and the reaction is amenable for gram scale synthesis. Also, different carbon sources such as DMF and DMSO also worked well under optimized condition (**Figure 5.2.3**).

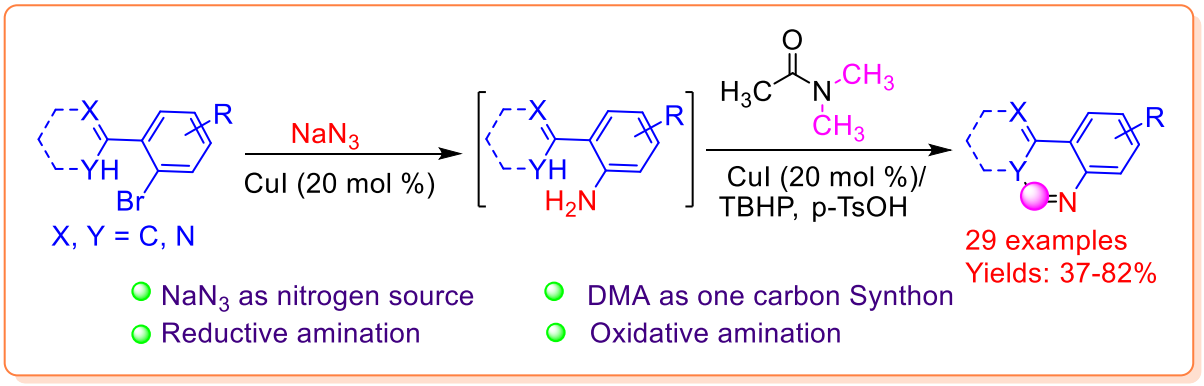

Figure 5.2.3 Synthesis of quinazolines through sequential reductive amination and oxidative amination of C(sp^3)–H bond

In **part-C,** a copper-catalyzed one-pot tandem method for the synthesis of fused imidazo/benzimidozo[1,2-*c*]quinazolines is described. The reaction involves copper–catalyzed sequential azidation of 2-(2-bromophenyl)-1*H*-imidazole/benzimidazole through S_NAr reaction and reduction followed by condensation with benzaldehyde or derived aldehyde from benzyl alcohol or benzylamine in the presence of TEMPO. This approach provides a one-pot assembly of quinazoline derivatives with moderate to good yield by using readily available starting material. The salient features of this method are the use of air as an oxidant, ligand-free reaction condition and green solvent (**Figure 5.2.4**).

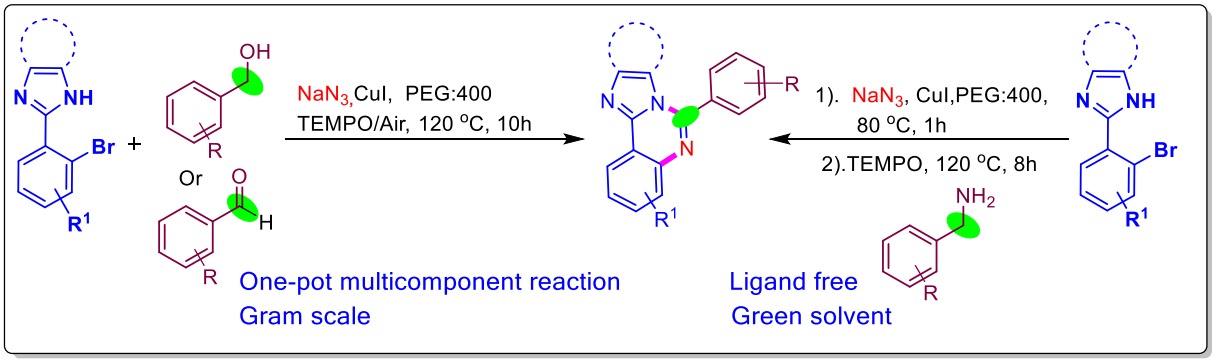

Figure 5.2.4 Copper–catalyzed one-pot tandem assembly for fused quinazolines.

The third chapter of the thesis describes copper–catalyzed Ullmann-type C–N coupling and cross–dehydrogenative coupling (CDC) reactions for the synthesis of azole fused imidazo/benzimidazo[1,2-*c*]quinazolines. This chapter is divided into two parts.

In **part-A**, an efficient one-pot sequential procedure has been described for the synthesis of novel azole–fused quinazolines through Pd/Cu co–catalyzed, Ullmann–type coupling followed by a cross–dehydrogenative coupling of various azoles such as 1*H*-imidazole, 1*H*-benzimidazole and 1*H*-1,2,4-triazole with 2-(2-bromophenyl)-1*H*-imidazole/benzimidazoles. The developed strategy has offered good yields (52–81%) of diverse *N*-fused tetra-, penta- and hexacyclic frameworks in a single step (**Figure 5.2.5**).

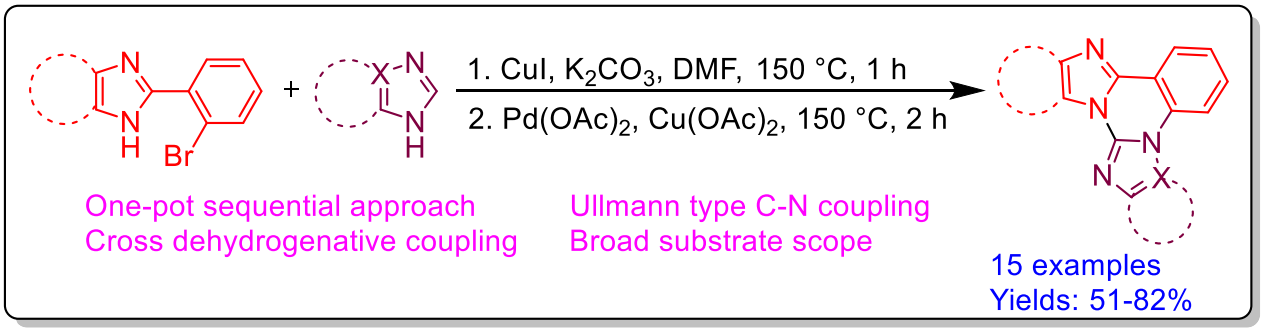

Figure 5.2.5 Cu\Pd–catalyzed Ullmann-type C–N coupling and CDC for the synthesis of imidazo/benzimidazo [1,2-*c*]quinazolines.

In **part-B**, a new class of fused quinazolines has been designed and synthesized *via* a copper-catalyzed Ullmann type C–N coupling followed by an intramolecular cross–dehydrogenative coupling (CDC) reaction in moderate to good yields. The synthesized compounds were tested for *in vitro* antibacterial activity against three Gram-negative (*Escherichia coli, Pseudomonas putida, Salmonella typhi*) and two Gram-positive (*Bacillus subtilis, Staphylococcus aureus*) bacteria. Among all tested compounds, three compounds exhibited promising MIC values (4–8 µg/mL. The synthesized compounds were also evaluated for their *in vitro* antifungal activity and showed pronounced antifungal activity (MIC values 8–16 µg/mL) against both strains. Moreover, the haemolytic activity of the synthesized compounds showed their safety profile towards the human blood cells (**Figure 5.2.6**).

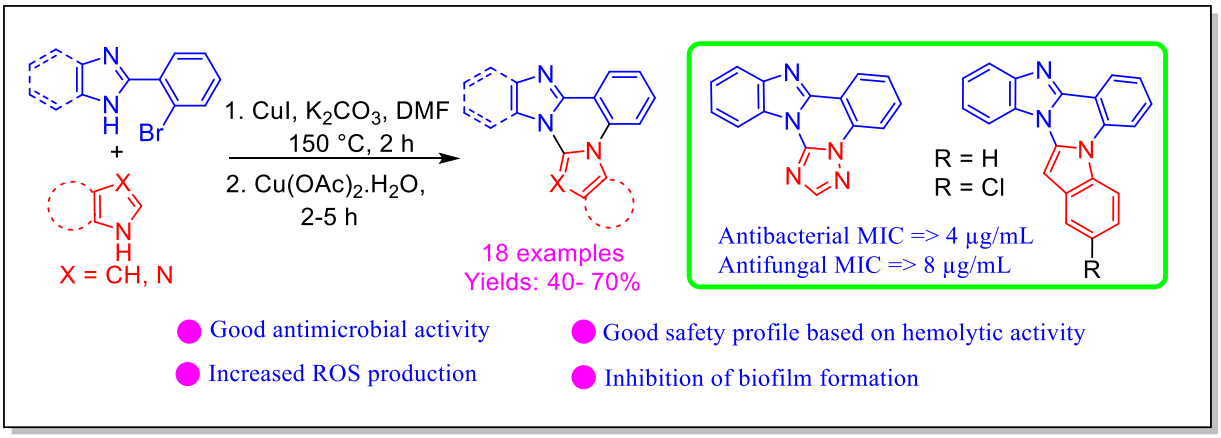

Figure 5.2.6 Cu–catalyzed Ullmann-type C–N coupling and CDC for the synthesis of imidazo/benzimidazo [1,2-*c*]quinazolines.

The fourth chapter of the thesis described copper–catalyzed tandem reaction of 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles with alkynes and sodium azide for the synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines in moderate to excellent yields (50-85%). The one–pot method involved copper–catalyzed tandem azide-alkyne cycloaddition (CuAAC), intramolecular cross dehydrogenative C–N bonding followed by Ullmann type C–N coupling reaction. The silent features of this protocol are the use of air as the oxidant, mild and ligand-free reaction conditions and broad substrate scope with high efficiency. The detail mechanistic pathway for the synthesis imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines has been studied by a series of control experiments (**Figure 5.2.7**).

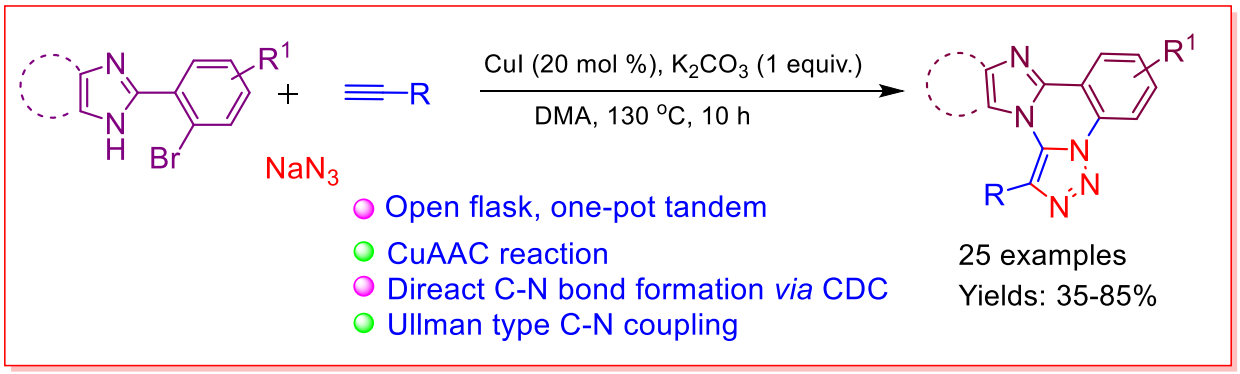

Figure 5.2.7 Synthesis of imidazo[1,2- *c*][1,2,3]triazolo[1,5-*a*]quinazolines.

5.3 Future scope of the research work

N–Containing fused heterocycles have received great attention in organic chemistry due to their wide range of application in the different field of science. More specifically, in medicinal chemistry and materials science. In materials science, organic fluorescent molecules undergoing excited state intramolecular proton transfer (ESIPT) have become important molecules in organic light-emitting diodes (OLEDs) because of their desirable unique photo-physical properties with multiple applications like in spanning laser dyes, chemosensors, photonics, bioimaging, and molecular switches. Therefore, design and synthesis of a π-conjugated system with good optical properties have become one of the challenging areas for a chemist.

Although the thesis mainly focused on the synthesis of fused imidazo/benzimidozo[1,2-*c*]quinazolines from 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles, still, there is plenty of scopes to develop fused *N*-heterocycles from 2-phenyl benzimidazole by ortho activation of aryl ring of imidazole. Some target molecules are given in figure 5.3.1 which can be synthesized to evaluate their photophysical activities (**Figure 5.3.1**).

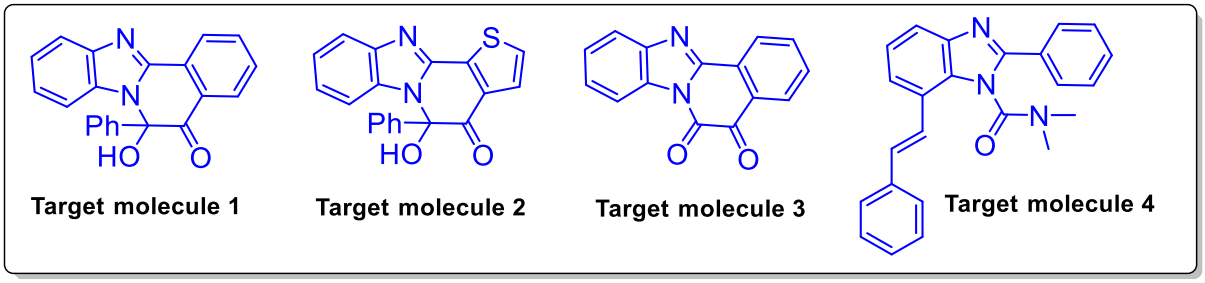

Figure 5.3.1 Metal-catalyzed synthesis of fused heterocycles.

Appendices

Appendices

List of Publications *[A-1]*

1. **Nitesh Kumar Nandwana**, Kasiviswanadharaju Pericherla, Pinku Kaswan and Anil Kumar, Synthesis of novel azole-fused quinazolines *via* one–pot, sequential Ullmann–type coupling and intramolecular dehydrogenative C–N bonding, *Org. Biomol. Chem*. **2015,** *13*, 2947.
2. **Nitesh Kumar Nandwana**, Shiv Dhiman, Ganesh M. Shelke and Anil Kumar, Copper–catalyzed tandem Ullmann type C–N coupling and dehydrative cyclization: synthesis of imidazo[1,2-*c*]quinazolines, *Org. Biomol. Chem*. **2016**, *14*, 1736.
3. **Nitesh Kumar Nandwana**, Shiv Dhiman, Hitesh Kumar Saini and Anil Kumar, Synthesis of quinazolinones, imidazo[1,2-*c*] quinazolines and imidazo[4,5-*c*] quinazolines through tandem reductive amination of aryl halides and oxidative amination of C(sp^3)-H bonds, *Eur. J. Org. Chem.* **2017**, 514.
4. **Nitesh Kumar Nandwana**, Vikki N. Shinde, Hitesh Kumar Saini and Anil Kumar, Copper–catalyzed one–pot tandem reaction for the synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1.5-*a*]quinazolines, *Eur. J. Org. Chem*. **2017**, 6445.
5. **Nitesh Kumar Nandwana**, Rajnish Prakash Singh, Om P. S. Patel, Shiv Dhiman, Hitesh Kumar Saini, Prabhat N. Jha and Anil Kumar, Design and synthesis of imidazo/benzimidazo[1,2-*c*]quinazoline derivatives and evaluation of their antimicrobial activity, *ACS Omega*, **2018**, 3, 16338.
6. Pinku Kaswan, **Nitesh Kumar Nandwana**, Brenton De-Boef and Anil Kumar Vanadium–catalyzed methylation of imidazo[1,2-*a*]pyridines using dimethylacetamide as a carbon source: direct access to bis(imidazo[1,2-*a*]pyridine-3-yl)methanes, *Adv. Synth. Catal.* **2016**, *358*, 2108.
7. Shiv Dhiman, **Nitesh Kumar Nandwana**, Hitesh Kumar Saini, Dalip Kumar and Anil Kumar, A facile synthesis of quinazolin-4(*3H*)-ones *via* copper–catalyzed one–pot, three–component tandem reactions, *Chem Select*. **2017**, *2*, 8016.
8. Hitesh Kumar Saini, **Nitesh Kumar Nandwana**, Shiv Dhiman and Anil Kumar, Sequential copper–catalyzed sonogashira coupling, hydroamination and palladium–catalyzed intramolecular direct arylation: synthesis of azepino-fused isoindolinones, *Eur. J. Org. Chem*. **2017**, *18*, 7277**.**

9. Shiv Dhiman, **Nitesh Kumar Nandwana**, Hitesh Kumar Saini, Dalip Kumar and Anil Kumar, Nickel–catalyzed tandem cross–aldol/intramolecular direct arylation: synthesis of pyrazolo[5,1-*a*]isoquinoline derivatives, *Adv. Synth. Catal*. **2018**, *360,* 1973.
10. Om P. S. Patel, **Nitesh Kumar Nandwana** and Anil Kumar, "tert-Butyl hydroperoxide as carbon source and hydrogen acceptor: regioselective aminomethylenation of imidazoheterocycles *via* intermolecular cross–dehydrogenative strategy, *Org. Biomol. Chem.* **2018**, 16, 8620.
11. Shiv Dhiman, Kasiviswanadharaju Pericherla**, Nitesh Kumar Nandwana**, Dalip Kumar and Anil Kumar, Synthesis of aza-fused isoquinolines through domino cross-aldol condensation and palladium–catalyzed intramolecular direct arylation, *J. Org. Chem.* **2014**, *79,* 7399.
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13. Hitesh Kumar Saini, Shiv Dhiman, **Nitesh Kumar Nandwana** and Anil Kumar, Copper–catalyzed sonogashira coupling, intramolecular hydroamination and palladium–catalyzed intramolecular heck reaction toward one–pot synthesis of fused isoindolinones *Org. Biomol. Chem.* **2019**.
14. **Nitesh Kumar Nandwana**, Shiv Dhiman, Hitesh Kumar Saini and Anil Kumar, Synthesis of novel azole-fused imidazo[1,2-*a*]pyridine derivatives and their photophysical properties (Manuscript under preparation).
15. **Nitesh Kumar Nandwana**, Shiv Dhiman and Anil Kumar, Expeditious synthesis of imidazo/benzimidazo[1,2-*c*]quinazolines *via* copper–catalyzed one–pot tandem multi–component strategy (Manuscript under preparation).
16. **Nitesh Kumar Nandwana** and Anil Kumar, Ruthenium–catalyzed ortho-activation of 2-phenylbenzimidazole: highly selective detection of H^+ and OH^- ions and their solvatochromism study (Manuscript under preparation).
17. **Nitesh Kumar Nandwana**, Om P. S. Patel, Manu R Srivatsa and Anil Kumar, Dual role of glyoxal in metal-free dicarbonylation reaction: synthesis of symmetrical and unsymmetrical dicarbonyl imidazoheterocyles (ACS Omega Submitted).

List of Presentations in Conferences

Poster:

1. **Nitesh Kumar Nandwana**, Kasiviswanadharaju Pericherla, Pinku Kaswan and Anil Kumar, Synthesis of Novel Azole Fused-Quinazolines *via* One–Pot Sequential Ullmann−type Coupling and Intramolecular Dehydrogenative C−N Bonding, 20th Indian Society of Chemist and Biologists, Department of Chemistry, University of Delhi, Delhi, India, March 1-4, 2014.
2. **Nitesh Kumar Nandwana** and Anil Kumar, Synthesis of Azole Fused-Quinazolines *via* One–pot Sequential Ullmann−type Coupling and Dehydrogenative C−N Bonding, 21th Indian Society of Chemist and Biologists, Department of Chemistry, Central Drug Research Institute (CDRI), Lucknow, India, February 25–28, 2015.
3. **Nitesh Kumar Nandwana,** Shiv Dhiman, Ganesh M. Shelke and Anil Kumar, Copper–Catalyzed Tandem Ullmann type C–N Coupling and Dehydrative Cyclization: Synthesis of Imidazo[1,2-*c*]quinazolines, International Conference on Nascent Development in Chemical Science, Department of Chemistry, BITS Pilani, Pilani Campus, India, October 16–18, 2015.
4. **Nitesh Kumar Nandwana,** Shiv Dhiman, Ganesh M. Shelke and Anil Kumar, Copper–Catalyzed Tandem Ullmann type C–N Coupling and Dehydrative Cyclization: Synthesis of Imidazo[1,2-*c*]quinazolines, New Frontiers in Chemistry from Fundamental to Applications, Department of Chemistry, BITS Pilani KK Birla Goa Campus, India, December 18–19, 2015.
5. **Nitesh Kumar Nandwana,** Shiv Dhiman, Hitesh Kumar Saini and Anil Kumar, Copper–Catalyzed Tandem Ullmann type C–N Coupling and Dehydrative Cyclization for the Synthesis of Imidazo[1,2-*c*]quinazolines, National Conference on Organic Chemistry in Sustainable Development, Department of Chemistry, BITS Pilani, Pilani Campus, India, August 29–30, 2016.
6. **Nitesh Kumar Nandwana** and Anil Kumar, Design and Synthesis of π–Conjugated Fused Heterocyclic Compound *via* Transition Metal Catalyzed C–N Coupling Reactions, Symposium on Emerging Trends in Agro science Chemistry and Technology, Syngenta Bioscience Private Limited, Goa, India, November 22–23, 2016

7. **Nitesh Kumar Nandwana** and Anil Kumar, Synthesis of π-Conjugated Fused Quinazolines and Quinolines *via* copper–catalyzed C–C and C–N bond formation and their application, 18th Tetrahedron Symposium, New Development in Organic Chemistry, Budapest, Hungary, June 27–30, 2017.
8. **Nitesh Kumar Nandwana,** Shiv Dhiman, Hitesh Kumar Saini and Anil Kumar, Synthesis of π-conjugated Fused Imidazo[1,2-*a*]pyridine and their Photophysical Applications, Nano and Functional Material, Department of Chemistry, BITS Pilani, Pilani Campus, India, November 16–18, 2017
9. **Nitesh Kumar Nandwana** and Anil Kumar, Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and their Antimicrobial Activity, Frontiers in Chemical Science, Department of Chemistry, IIT Guwahati, Guwahati, India, December 6–8, 2018.
10. **Nitesh Kumar Nandwana** and Anil Kumar, Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and their Antimicrobial Activity, 25th Indian Society of Chemist and Biologists, Hotel golden Tulip, Lucknow, India, January 12–14, 2019.

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Metal-free synthesis of aminomethylated imidazoheterocycles: dual role of *tert*-butyl hydroperoxide as both an oxidant and a methylene source†

Om P. S. Patel, Nitesh Kumar Nandwana, Ajay Kumar Sah and Anil Kumar *

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A novel and efficient aminomethylation approach has been developed for the regioselective functionalization of imidazoheterocycles under metal-free conditions. A wide range of imidazoheterocycles and 2/4-aminoazaheterocycles successfully provided corresponding aminomethylated imidazoheterocycles in moderate to excellent (33–80%) yields. The isotopic labelling study suggested that TBHP played a dual role as both an oxidant and a methylene source in this transformation. The developed protocol follows a radical pathway which is supported by radical trapping experiments.

FULL PAPER DOI: 10.1002/adsc.201701519

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Nickel-Catalyzed Tandem Knoevenagel Condensation and Intramolecular Direct Arylation: Synthesis of Pyrazolo[5,1-*a*]-isoquinoline Derivatives

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Design and Synthesis of Imidazo/Benzimidazo[1,2-*c*]quinazoline Derivatives and Evaluation of Their Antimicrobial Activity

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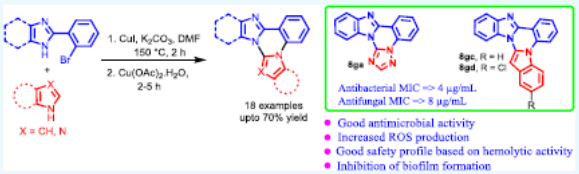
Supporting Information

ABSTRACT: A new class of fused quinazolines has been designed and synthesized via copper-catalyzed Ullmann type C−N coupling followed by intramolecular cross-dehydrogenative coupling reaction in moderate to good yields. The synthesized compounds were tested for in vitro antibacterial activity against three Gram negative (*Escherichia coli*, *Pseudomonas putida*, and *Salmonella typhi*) and two Gram positive (*Bacillus subtilis*, and *Staphylococcus aureus*) bacteria. Among all tested compounds, **8ga**, **8gc**, and **8gd** exhibited promising minimum inhibitory concentration (MIC) values (4−8 μg/mL) for all bacterial strains tested as compared to the positive control ciprofloxacin. The synthesized compounds were also evaluated for their in vitro antifungal activity against *Aspergillus niger* and *Candida albicans* and compounds **8ga**, **8gc**, and **8gd** having potential antibacterial activity also showed pronounced antifungal activity (MIC values 8−16 μg/mL) against both strains. The bactericidal assay by propidium iodide and live−dead bacterial cell screening using a mixture of acridine orange/ethidium bromide (AO/Et·Br) showed considerable changes in the bacterial cell membrane, which might be the cause or consequence of cell death. Moreover, the hemolytic activity for most potent compounds (**8ga**, **8gc**, and **8gd**) showed their safety profile toward human blood cells.



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EurJOC European Journal of Organic Chemistry

Full Paper

Nitrogen Heterocycles

Synthesis of Quinazolinones, Imidazo[1,2-*c*]quinazolines and Imidazo[4,5-*c*]quinolines through Tandem Reductive Amination of Aryl Halides and Oxidative Amination of C(sp^3)–H Bonds

Nitesh Kumar Nandwana,[a] Shiv Dhiman,[a] Hitesh Kumar Saini,[a] Indresh Kumar,[a] and Anil Kumar*[a]

Abstract: A tandem multicomponent approach has been described for the synthesis of quinazolinones, imidazo[1,2-*c*]quinazolines and imidazo[4,5-*c*]quinolines. The reaction involves a copper-catalyzed reductive amination through azidation followed by reduction and oxidative amination of C(sp^3)–H bonds of *N*,*N*-dimethylacetamide in the presence of TBHP (*tert*-butylhydroperoxide) as oxidant. The method uses the easily available sodium azide as a nitrogen source and DMA (*N*,*N*-dimethylacetamide) as a one-carbon source for the synthesis of these *N*-fused heterocycles in good to excellent yields. The reaction can also be used for gram-scale synthesis.

FULL PAPERS DOI: 10.1002/adsc.201600225 Advanced Synthesis & Catalysis

Vanadyl Acetylacetonate Catalyzed Methylenation of Imidazo[1,2-*a*]pyridines by Using Dimethylacetamide as a Methylene Source: Direct Access to Bis(imidazo[1,2-*a*]pyridin-3-yl)methanes

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Abstract: An efficient protocol has been developed for the methylenation of imidazo[1,2-*a*]pyridines using dimethylacetamide (DMA) as methylene source in the presence of vanadyl acetylacetonate [$VO(acac)_2$] as the catalyst and iodobenzene diacetate as the oxidant. The reaction involves coupling of sp^3- and sp^2-hybridized carbons and proceeds through the formation of an iminium ion. A wide variety of imidazo[1,2-*a*]pyridines were converted to bis(imidazo[1,2-*a*]pyridin-3-yl)methanes in good to excellent yields. A gram-scale reaction demonstrated the potential for the scale-up processes.

Keywords: bis(imidazo[1,2-*a*]pyridin-3-yl)methanes; C–H functionalization; imidazo[1,2-*a*]pyridines; methylenation; vanadium catalyst

ChemPubSoc Europe DOI: 10.1002/ejoc.201701221 EurJOC European Journal of Organic Chemistry Communication

Domino Reactions

Copper-Catalyzed One-Pot Tandem Reaction for the Synthesis of Imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines

Nitesh K. Nandwana,[a] Vikki N. Shinde,[a] Hitesh K. Saini,[a] and Anil Kumar*[a]

Abstract: A copper-catalyzed tandem reaction of 2-(2-bromoaryl)imidazoles/2-(2-bromoaryl)benzimidazoles, alkynes, and sodium azide was developed for the synthesis of imidazo[1,2-*c*][1,2,3]triazolo[1,5-*a*]quinazolines in moderate to excellent yields (50–85 %). The one-pot method involves copper-catalyzed azide–alkyne cycloaddition (CuAAC), intramolecular cross-dehydrogenative C–N bond formation, and Ullmann-type C–N coupling. This protocol involves the use of air as the oxidant under mild and ligand-free reaction conditions, and the reaction can be performed with a broad range of substrates with high efficiency.

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Communication

Sequential Reaction

Sequential Copper-Catalyzed Sonogashira Coupling, Hydroamination and Palladium-Catalyzed Intramolecular Direct Arylation: Synthesis of Azepino-Fused Isoindolinones

Hitesh Kumar Saini,[a] Nitesh Kumar Nandwana,[a] Shiv Dhiman,[a] Krishnan Rangan,[b] and Anil Kumar*[a]

Abstract: A sequential copper-catalyzed Sonogashira coupling followed by an intramolecular hydroamination and palladium-catalyzed intramolecular direct arylation reaction was developed to provide a convenient and modular approach for the synthesis of useful azepino-fused isoindolinones. Nineteen azepino-fused isoindolinones were prepared in moderate to high (22–90 %) yields. The developed protocol tolerated various functional groups and involved the formation of one carbon–nitrogen and two carbon–carbon bonds in a one-pot fashion. The palladium-catalyzed intramolecular direct arylation step involved formation of an unusual eight-membered palladacycle.

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Organic & Supramolecular Chemistry

A Facile Synthesis of Quinazolin-4(3*H*)-ones via Copper-Catalyzed One-Pot, Three-Component Tandem Reaction

Shiv Dhiman, Nitesh K. Nandwana, Shreemala Dhayal, Hitesh K. Saini, Dalip Kumar, and Anil Kumar*[a]

A simple and convenient one-pot, three-component tandem reaction has been developed for the synthesis of substituted quinazolin-4(3H)-ones using CuI/L-proline as catalytic system. A series of 35 quinazolin-4(3H)-ones was synthesized in good to high yield. The method involves copper-catalyzed double C–N coupling, reductive amination, condensation, cyclization and aerobic oxidation. Good functional group tolerance, mild reaction condition, readily available starting materials and user friendly procedure makes this protocol practically good and attractive method for the synthesis of quinazolin-4(3H)-ones.

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Cite this: *RSC Adv.*, 2016, **6**, 23987

Copper-catalyzed synthesis of quinoline derivatives *via* tandem Knoevenagel condensation, amination and cyclization†‡

Shiv Dhiman, Hitesh Kumar Saini, Nitesh Kumar Nandwana, Dalip Kumar and Anil Kumar*

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A novel regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles is described *via* copper-mediated tandem reaction. Formation of substituted quinolines involves Knoevenagel condensation of *ortho*-bromobenzaldehyde with active methylene nitriles followed by copper-catalyzed reductive amination and intramolecular cyclization.

Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2015, **13**, 2947

Synthesis of novel azole-fused quinazolines *via* one-pot, sequential Ullmann-type coupling and intramolecular dehydrogenative C–N bonding†

Nitesh Kumar Nandwana, Kasiviswanadharaju Pericherla, Pinku Kaswan and Anil Kumar*

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Accepted 23rd December 2014

DOI: 10.1039/c4ob02375g

www.rsc.org/obc

An efficient one-pot sequential procedure is described for the synthesis of novel azole-fused quinazolines through Pd/Cu co-catalyzed, Ullmann-type coupling followed by cross dehydrogenative coupling of various azoles such as 1*H*-imidazole, 1*H*-benzimidazole and 1*H*-1,2,4-triazole with 2-(2-bromophenyl)-1*H*-imidazole/benzimidazoles. The developed strategy has offered good yields (52–81%) of diverse *N*-fused tetra-, penta- and hexa-cyclic frameworks in a single step.

Organic & Biomolecular Chemistry

PAPER

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Cite this: *Org. Biomol. Chem.*, 2016, **14**, 1736

Copper-catalyzed tandem Ullmann type C–N coupling and dehydrative cyclization: synthesis of imidazo[1,2-*c*]quinazolines†

Nitesh K. Nandwana, Shiv Dhiman, Ganesh M. Shelke and Anil Kumar*

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www.rsc.org/obc

A simple and efficient one-pot protocol has been demonstrated for the synthesis of imidazo[1,2-*c*]quinazoline derivatives through a copper catalyzed tandem reaction between substituted 2-(2-bromophenyl)-1*H*-imidazoles and formamide. The synthetic protocol involves initial Ullmann-type C–N coupling followed by intramolecular dehydrative cyclization. The method uses readily available 2-(2-bromophenyl)-1*H*-imidazoles as the starting materials to afford imidazo[1,2-*c*]quinazolines in moderate to good yields and provided 610 mg (71%) yield of **3a** from a gram scale reaction.

JOC The Journal of Organic Chemistry

Article

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Synthesis of Aza-Fused Isoquinolines through Domino Cross-Aldol Condensation and Palladium-Catalyzed Intramolecular Direct Arylation

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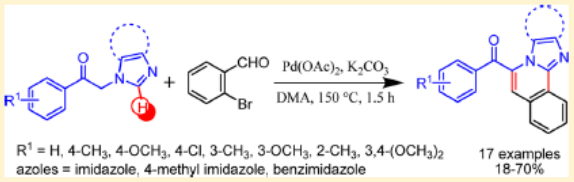
Supporting Information

ABSTRACT: A straightforward method has been developed for the synthesis of aroyl-substituted imidazo-/benzimidazo-fused isoquinolines. The cascade reaction proceeds via a cross-aldol condensation of 2-(1*H*-imidazol-1-yl/benzimidazolyl-1-yl)-1-arylethanones and 2-bromobenzaldehyde followed by palladium-catalyzed intramolecular C–H functionalization. This approach offers a simple and efficient alternative one-pot protocol for the assembly of imidazo/benzimidazo[2,1-*a*]isoquinolines in moderate to good yields.



Brief Biography of the candidate *[A-3]*

Nitesh Kumar Nandwana was born in June 1989 in small village Padasliya of Kota district in Rajasthan, India. He obtained his graduate degree in Chemistry from University of Kota, Kota, India during 2007-10 and post graduate degree in Organic Chemistry from University of Delhi, India during 2010-12. In June 2013, he cleared the Joint CSIR-UGC NET for Lectureship (LS) by CSIR, New Delhi. He joined as project fellow in the CSIR sponsored project under Prof. Anil Kumar in December 2013. He also registered for PhD program in January 2014 at Department of Chemistry, BITS Pilani, Pilani campus, India. In April 2018 he was awarded CSIR-SRF fellowship. During the tenure of PhD he was actively involved in the synthesis of fused imidazo/benzimidazo quinazolines and quinolines and their application in medicinal chemistry and materials science. In addition, he has also synthesized conjugated fused heterocyclic which can be efficiently used in ESIPT, AIE and acid-base sensing. He has published fourteen research articles in peer reviewed international journals and four research articles are under preparation. He presented papers in three national and seven international conferences. He also attended Tetrahedron symposium in Budapest Hungary which was supported by DST SERB.

His main research area lies in the development of new methods for the synthesis of quinazolines and poly heterocyclic molecules using C−C, C−N bond formation *via* metal free and metal-catalyzed reactions.

Brief Biography of the Supervisor *[A-4]*

Dr. Anil Kumar is Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. He obtained his PhD degree from Department of Chemistry, University of Delhi, Delhi, India under the guidance of Professor SMS Chauhan in 2004. During his doctoral studies Dr. Kumar worked on development of heterogeneous catalyst for organic synthesis with emphasis on green chemistry. He was postdoctoral fellow at Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, USA in Prof. KeykavousParang group during May 2004 to April 2006. In his postdoctoral studies he has worked on synthesis of novel Src kinase inhibitory agents and solid phase synthesis. He joined Department of Chemistry, Birla Institute of Technology and Science, Pilani, India as Assistant Professor in 2006 and was promoted to Associate Professor on February 2013 and Professor on August 2018. Dr. Kumar has also served as Associate Dean, Work Integrated Learning Programmes (WILP) during May 2014 – August 2018 and Head of Department of Chemistry, BITS Pilani, Pilani Campus during September 2014 – August 2016. He has visited University of Rhode Island, Kingston, USA and Chapman University, Irvine, USA as visiting scientist, and Acadia University, Wolfville, Canada as Harrison McCain visiting Professor.

Dr. Kumar is recipient of Prof. S. Vankateswaran Faculty Excellence Award from BITSAA for 2017, Dr. Arvind Kumar Memorial Award from Indian Council of Chemists for 2014, ISCB Young Scientist award in Chemical Sciences for 2013, and Harrison McCain Foundation award from Acadia University, Canada for 2012. He has 19 year of research experience and over 12 year of teaching experience. His research interest lies in development of reaction methodologies using transition metal catalyzed C-C coupling reactions, green chemistry, ionic liquids and medicinal chemistry. He has published 150 research papers in international journals of repute in the area of synthetic organic chemistry, green chemistry and medicinal chemistry and contributed two book chapters. He has participated in several national and international symposiums/ conferences and delivered more than 40 invited lectures. He has guided ten PhD students as supervisor and two as co-supervisor. Currently he is supervising six PhD students as supervisor. He has completed four research project as PI sponsored by DST, CSIR and UGC, and one as Co-PI sponsored by DST. Currently, he has one major projects from SERB. He is member of editorial advisory board for The Open Catalysis Journal and also served as a reviewer for several journals. He is life member of Chemical Research Society of India, Bangalore; Indian Society of Chemists and Biologists, Lucknow; and Indian Council of Chemists, Agra.

Brief Biography of the Co-Supervisor *[A-5]*

Dr. Indresh Kumar is Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. Dr. Kumar did his B.Sc. (Chemistry) and M.Sc. (Organic Chemistry) from Ch. Charan Singh University, Meerut (U.P) India. He completed his PhD degree in Organic Chemistry from National Chemical Laboratory (CSIR), Pune with Dr. C. V. Rode (Scientist-F) during 2007-08. He did his Post-doctoral research work with Prof. Yujiro Hayashi at Tokyo University of Sciences, Tokyo. He joined at Shri Mata Vaishno Devi University, Katra, (J&K), India as Assistant Professor in Chemistry in 2009 and continued till January 2012.

Dr. Indresh Kumar is recipient of "IASc-INSA-NASI Summer Research Fellowship in 2011, "INSA-Visiting Scientist Fellowship-**2013**" by INSA-New Delhi, Outstanding Potential for Excellence in Research and Academics (OPERA) during **2014-15** from BITS Pilani and ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2016. He has 12 years of research experience and 8 years of teaching experience. Dr. Kumar has authored 34 research paper in the peer-reviewed international journals in the area of synthetic organic chemistry. His research work has been widely recognized and highly cited in the scientific community. He has participated in several national and international symposia/conferences and delivered more than 30 invited lectures. He is currently supervising five Ph.D students and two students has been awarded PhD degree. He has completed three research projects as Principal Investigator sponsored by UGC, DST New Delhi and BITS Pilani. Currently, he has one major project from BITS Pilani He has also served as a reviewer for several journals. He is life the member of Indian Society of Chemists and Biologists, Lucknow and Chemical Research Society of India, Bangalore.

His main research interests are asymmetric organocatalysis, development of new synthetic methodology, and total synthesis of biologically active compounds.