Newer Synthetic Approaches for Disubstituted Quinoline Derivatives from Aryl Amines

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DOCTOR OF PHILOSOPHY

By

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Dedicated to

My Parents

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Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled **"Newer Synthetic Approaches for Disubstituted Quinoline Derivatives from Aryl Amines"** is the result of investigations carried out by me at the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Professor Abu T. Khan.

In keeping with general practice of reporting scientific observations, due acknowledgment have been made wherever the work described is based on the findings of investigators.

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CERTIFICATE

This is to certify that Saghir Ali (Roll Number: 176122105) has been working under my guidance since 1st February 2018 as a regular registered Ph. D. student at the Department of Chemistry, Indian Institute of Technology Guwahati, India. I am forwarding his thesis entitled "Newer Synthetic Approaches for Disubstituted Quinoline Derivatives from Aryl Amines" being submitted for the award of Ph. D. (Science) of this Institute. I also certify that he has fulfilled all the requirements as per Ph. D. Ordinances & Regulations of this Institute regarding the investigations embodied in his thesis.

(Prof. Abu T. Khan)

Acknowledgement

It is my great pleasure to take this opportunity to express my gratitude and thanks to all the people who have helped and encouraged me during my Ph. D. studies. Nothing would have been possible in this thesis without each and every one of you. Thank you!

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I wish to express my sincere gratitude to IIT Guwahati for providing me research fellowship and all the facilities that were made available to me. I thank DST for providing

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Finally, my deepest gratitude goes to my family for their untiring love, support and blessings throughout my life. My deepest gratitude especially to my mother and father who stood up against all odds just to support me. Their enormous sacrifices and unconditional love in every stage of my life motivated me to overcome all the challenges and I owe my entire life to them.

Last but not the least; I am thankful to Almighty for his continuous blessings during my research to accomplish this remarkable journey.

Saghir Ali

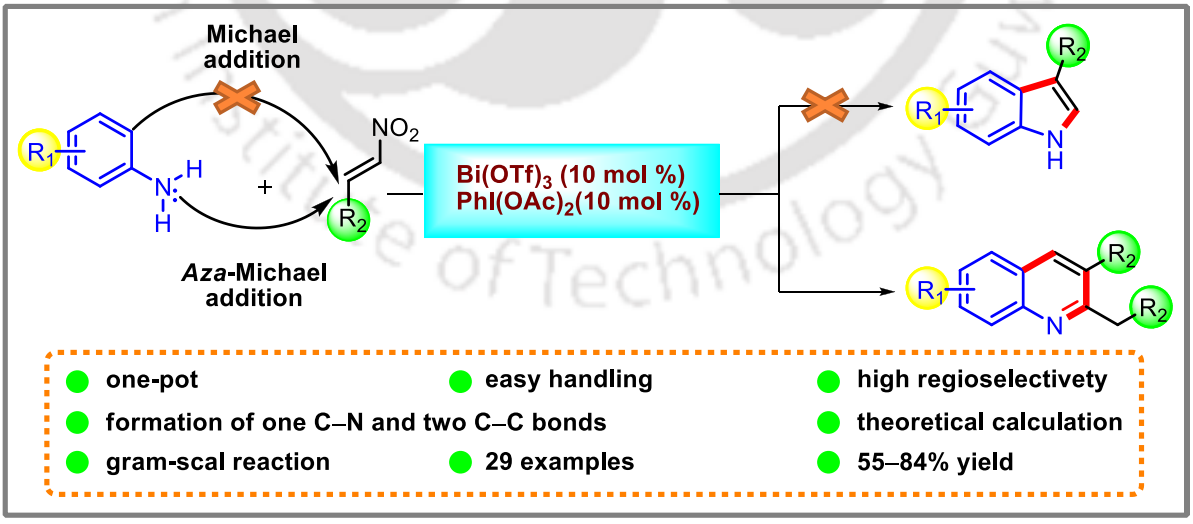
SUMMARY OF THE THESIS

The contents of this thesis entitled "**Newer Synthetic Approaches for Disubstituted Quinoline Derivatives from Aryl Amines**" have been divided into three chapters based on the experimental work carried out at the Department of Chemistry, IIT Guwahati during 1st February 2018 to 1st October 2021.

Chapter I of the thesis presents a brief introduction about the heterocycle compound quinoline. This chapter portraits the importance of quinoline containing biologically active natural and non-natural scaffolds. In addition, it also gives an outline on traditional and recently reported synthetic methods for synthesis of disubstituted quinoline derivatives.

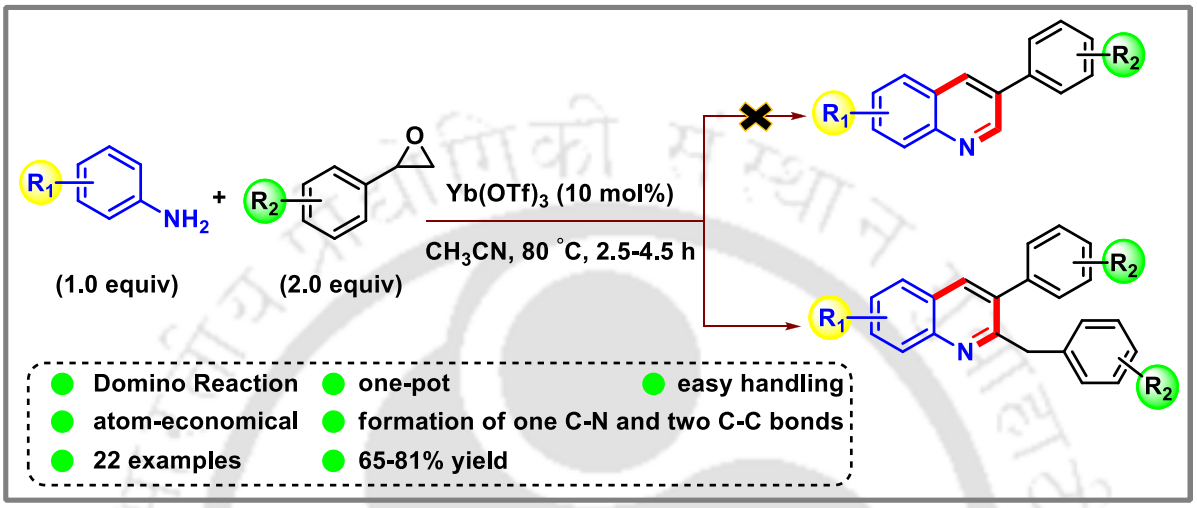
Chapter II of the thesis includes synthesis of 2,3-disubstituted quinolines, which is elaborated into three parts such as **Part A**, **Part B** and **Part C**.

Part A describes the regioselective synthesis of 2,3-dialkylquinoline derivatives from various aryl amines and different aliphatic nitroalkenes using bismuth(III) triflate catalyzed domino reactions. It also presents theoretical studies to establish the mechanistic pathway for formation of products using Gaussian 09 software [B3LYP/6-311+G(d,p)]. Notable advantages of this work are easy operational, high regioselectivity, mild conditions, formation of one C-N and two C-C bonds and a broad substrate scope with high yield.

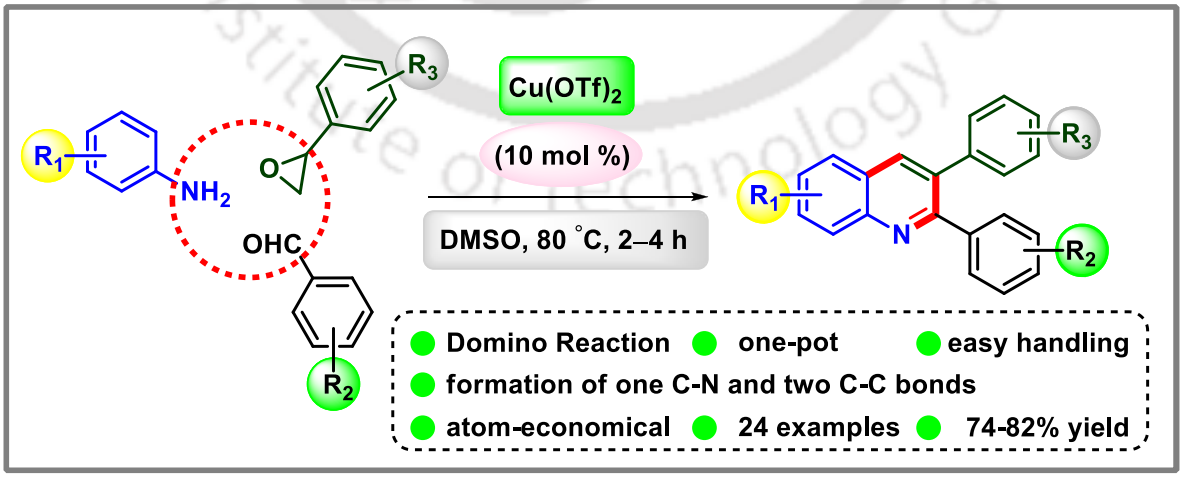


Path B illustrates a straightforward synthetic protocol for synthesis of various substituted 2-benyl-3-phenylquinolines using commercially available aryl amines and styrene oxides or aliphatic

epoxides in presence of 10 mol% ytterbium(III) triflate catalyst in acetonitrile at 80 °C. Ease of handing, high regioselectivity, atom-economical, formation of one C-N and two C-C bonds and access to a wide range of 2-benyl-3-arylquinoline derivatives with high yield are salient features of this methodology.

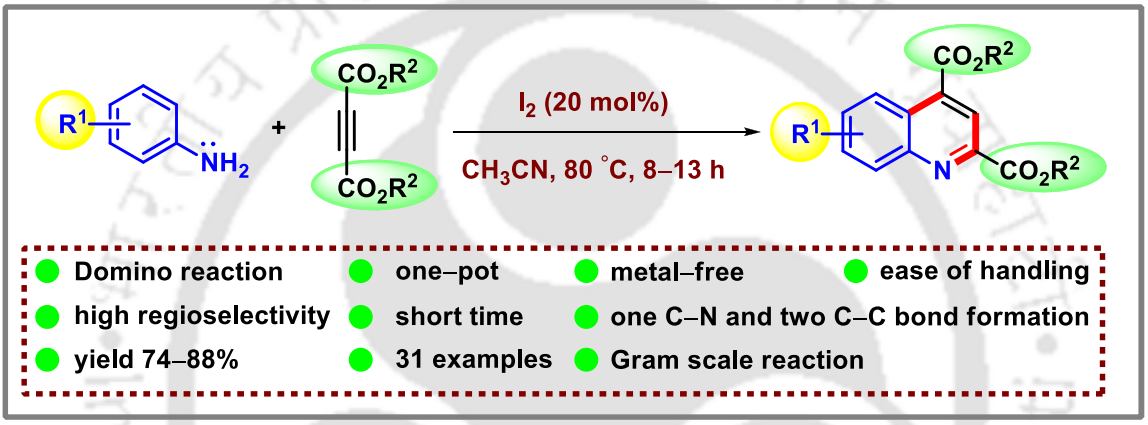


Part C demonstrates a synthetic strategy for 2,3-diarylquinoline derivatives from aryl amines, aryl aldehyde and styrene oxides in the presence of 10 mol% copper(II) triflate in dimethyl sulfoxide at 80 °C through three-component reaction. This particular transformation involves domino reaction using simple building blocks. Advantages of this strategy are one-pot, mild reaction conditions, shorter time, high regioselectivity, easy handling, formation of one C-N and two C-C bonds and an easy access to structurally diverse 2,3-diarylquinoline frameworks with high yield.

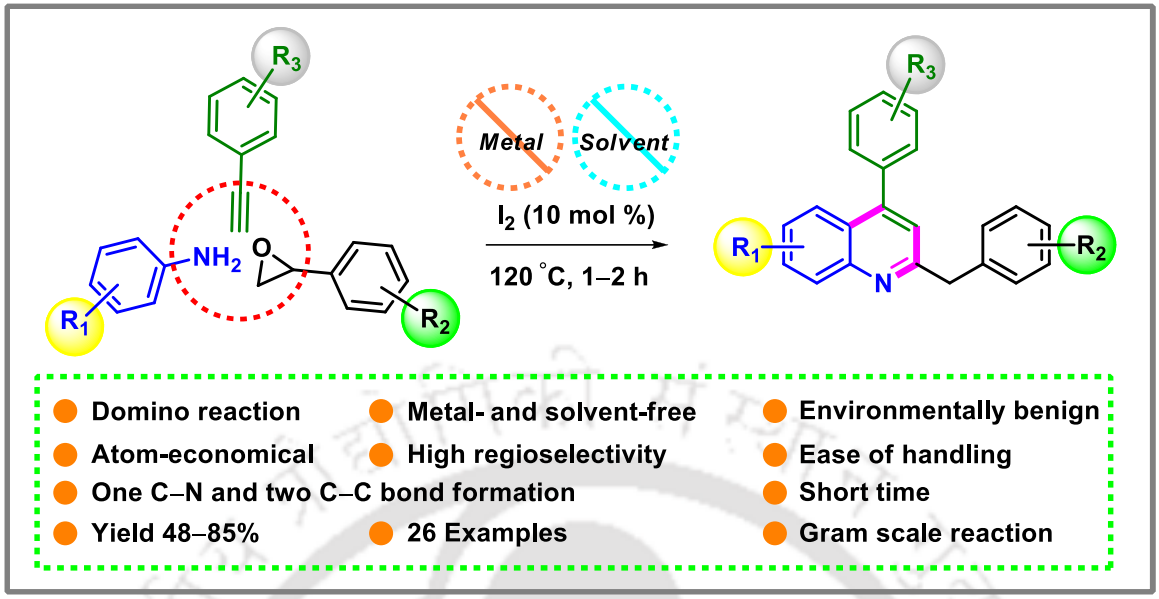


Chapter III of the thesis describes the synthesis of 2,4-disubstituted quinoline derivatives, which is arranged into **Part A** and **Part B**.

Part A explains a simple and an expedient metal-free protocol for synthesis of quinoline-2,4-dicarboxylate scaffolds from pseudo three-component reactions using aryl amines and dimethyl/diethyl acetylenedicarboxylates in the presence of 20 mol% molecular iodine as a catalyst in acetonitrile at 80 °C. This protocol have several advantages, such as the metal-free, the use cost-effective and environmentally benign catalyst, high regioselectivity, the formation of one C-N and two C-C bonds and a broad substrate with high yield.



Part B presents an environmentally benign metal- and solvent-free domino reaction which, leads to synthesis of structurally diverse 2-benzyl-4-arylquinoline scaffolds using simple starting material aryl amines, styrene oxides and aryl acetylenes in the presence of 10 mol% I_2 at 120 °C. Notable features of this methodology are use of simple starting materials, metal- and solvent-free, use of green catalyst, no metal contamination of metal in final product, short reaction time, high regioselectivity, atom-economical, formation of one C-N and two C-C bonds and a broad substrate scope with high yield.



CONTENTS OF THE THESIS

GENERAL REMARKS

The present investigations were carried out at the Department of Chemistry, India Institute of Technology Guwahati, Guwahati – 781039, Assam, India, during the period 1st February 2018 to 1st October 2021 as a Ph. D. student under the supervision of Professor Abu T. Khan.

All the reagents were procured at the highest commercial quality from Sigma Aldrich and Alfa Aeser companies. All solvents were used to carry out reaction without purification. The analytical samples were routinely dried *in vacuo* at 50 °C. In TLC experiment, silica gel G (SRL) or silica gel GF 254 (SRL) were used as adsorbent. Column chromatography was carried out with silica gel (60-120 mesh, Merck or SRL), for purification of reaction mixture. After purification, solvent was usually removed in rotary evaporator using Buchi R-114 V instrument. Melting points were determined on a Buchi melting point apparatus. IR spectra were recorded on Perkin Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz and 100 MHz, 125 MHz and 150 MHz NMR spectrometers (Bruker), respectively. TMS as internal reference; chemical shifts (δ scale) were reported in parts per million (ppm). ^{1}H NMR spectra are reported in order: multiplicity, coupling constant (*J* value) in Hertz (Hz) and no of protons; signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dd (doublet of doublet), dt (doublet of triplet), dq (doublet of quartet) and ddt (doublet of doublet of triplet). HRMS spectra were recorded using ESI (TOF) mode and crystal data was collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromatic MoKα radiation (λ = 0.71073 Å) at 298 K.

ABBREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AuNPS	Gold nanoparticles
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CCDC	Cambridge Crystallographic Data Centre
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
ESI (TOF)	Electrospray Ionisation (Time-of-flight)
Et	Ethyl
EtOH	Ethanol
EWG	Electron-withdrawing Group
EDG	Electron-donating Group
mg	Milligram
h	Hour

HRMS	High Resolution Mass Spectrometer
IBr	Iodine monobromide
ICl	Iodine monochloride
IR	Infrared Spectrosopy
MCR	Multicomponent Reaction
MeOH	Methanol
mp	Melting Point
MS	Molecular Sieves
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Program
PPA	Polyphosphoric Acid
Ph	Phenyl
ppm	Parts Per Million
$TBPA^{+\cdot}$	Tris(4-bromophenyl)ammoniumyl hexachloroantimonate
p-TSA	*p*-Toluenesulfonic Acid
rt	Room Temperature
TEMPO	2,2,6,6-Tetramethyl Pyridine-*N*-Oxide
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
XRD	x-Ray Diffraction

Chapter I

A Review on Disubstituted Quinolines

Introduction to quinolines

Quinoline is an important nitrogen containing heterocyclic compound, which was first extracted in 1834 from coal tar by German Chemist, Friedlieb Ferdinand Runge. Later on in 1842, it was isolated from distillation of decomposed quinine and chinchonine antedates by French Chemist, Charles Gerhardt. It is common subunit in wide range of biologically active nature products, particularly alkaloids as shown in Figure **1.1**.[1] Some of the related natural products have been marketed as potent drugs. Numerous quinoline-based non-natural products along with their biological activities are presented in Figure **1.2**.[1] Very recently, quinoline analogues showed remarkable activity against the SARS-CoV-2 disease caused by novel coronavirus.[2a–c] In addition, quinoline derivatives exhibit a broad spectrum of biological and pharmacological activites,[2d] such as antimalarial,[2e] anti-cancer,[2f,g] antituberculosis,[2h,i] antiasthmatic,[2j] anti-HIV,[2k] and antihypertensive.[2l] Beside biological and pharmacological properties, quinoline derivatives have also shown potential applications in agrochemicals.[3]

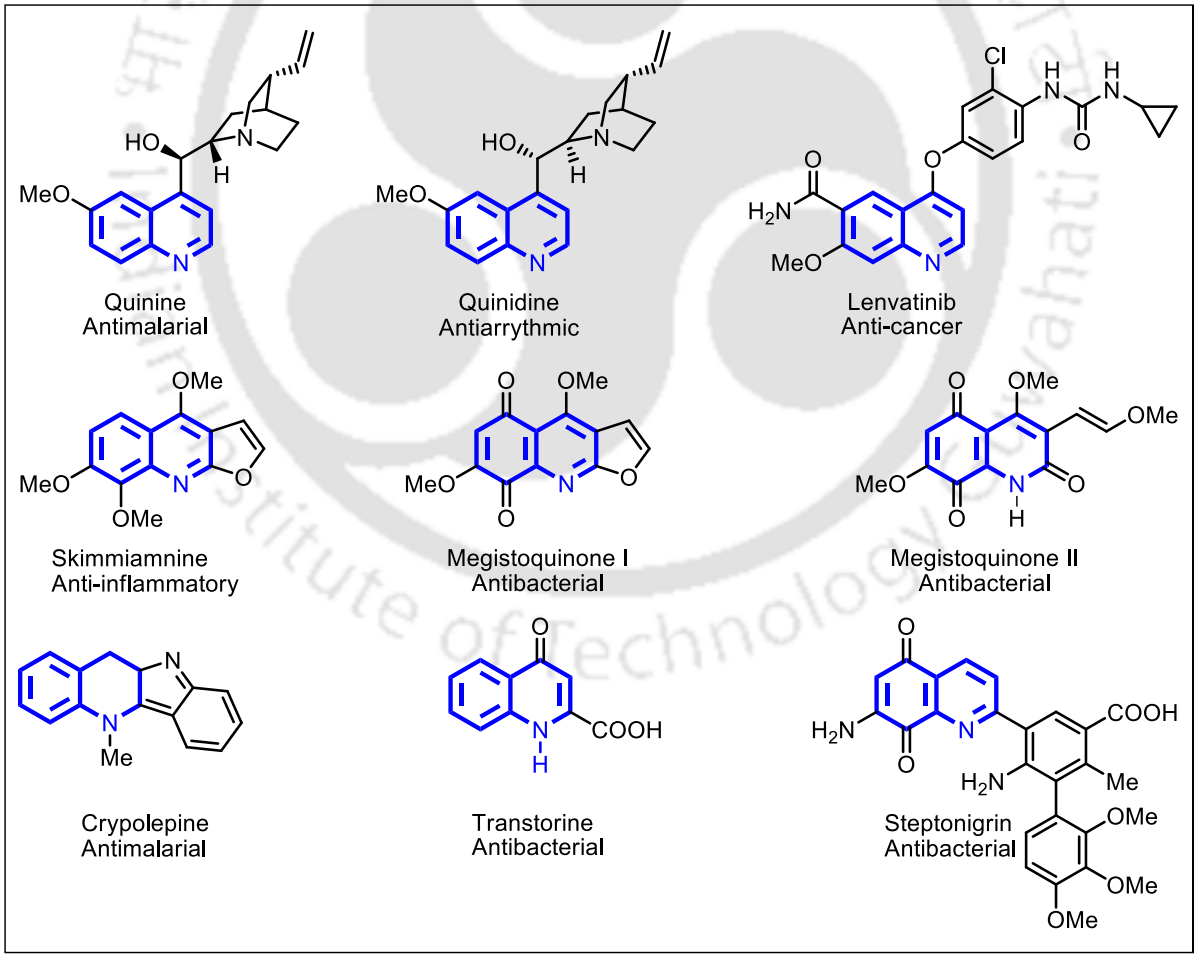


Figure 1.1. Quinoline containing natural products.

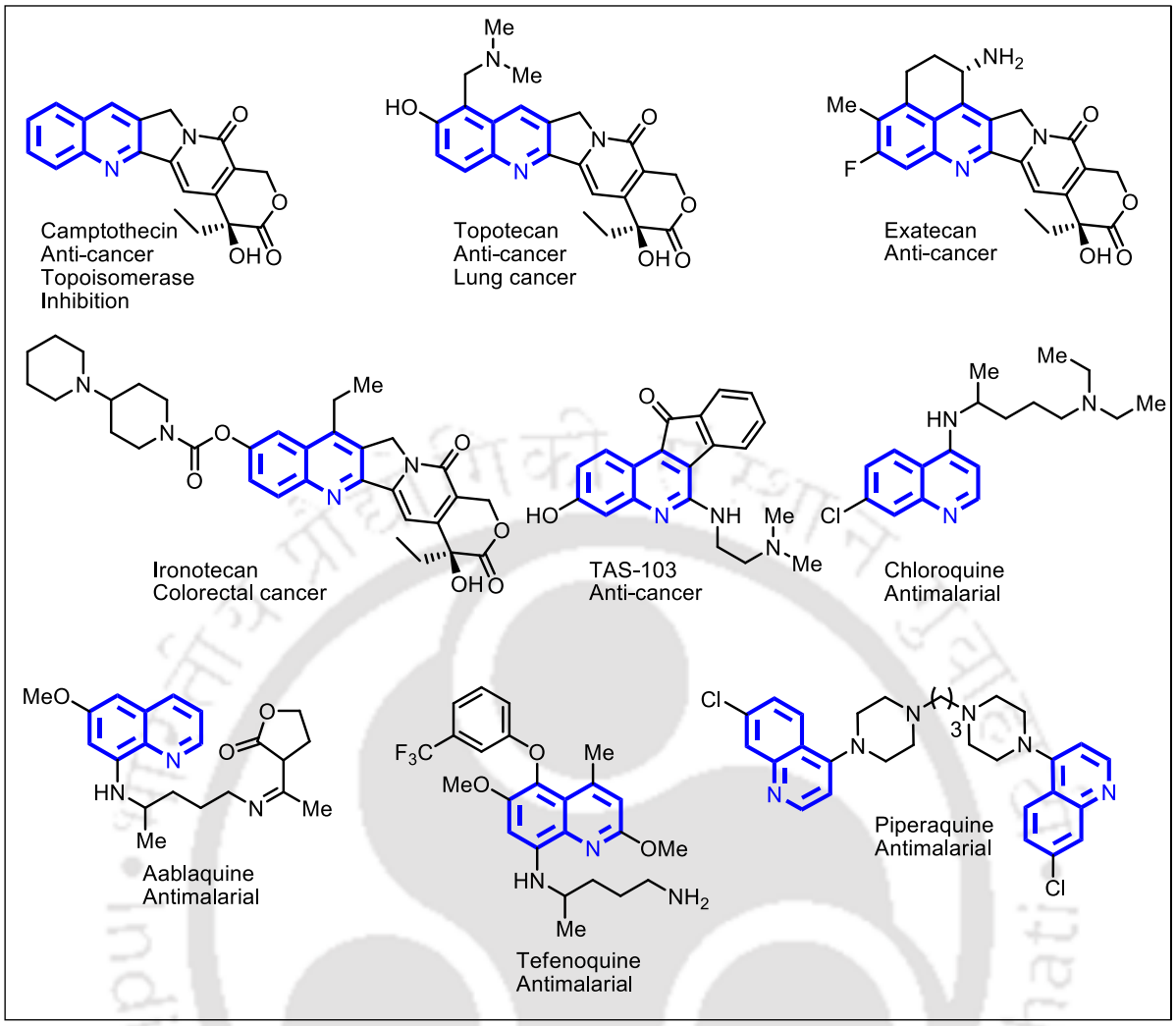


Figure 1.2. Quinoline containing non-natural products.

Moreover, some of the derivatives of quinoline as building blocks have been extensively exploited in material science.[4] Furthermore, naturally occurring cinchonidine and quinine have been utilized as chiral ligands for asymmetric synthesis[5] and in cross coupling.[6] Owing to its widespread applications in diverse fields, such as medicinal chemistry, material science and organic synthesis, synthetic community has put tremendous efforts for synthesis of quinoline derivatives.

Traditional routes for synthesis of quinoline and its analogues from aniline

Over the years, a number of traditional routes towards synthesis of quinoline and its derivatives have been developed. These are well documented in literature as shown in Figure **1.3**. These methods are some popular name reactions, such as Skraup,[7a] Doebner-von-Miller,[7b] Conard-Limpach,[7c] Doebner,[7d] Combes[7e] and Povarov synthesis.[7f] It is noteworthy that aniline is common starting material in all these methods.

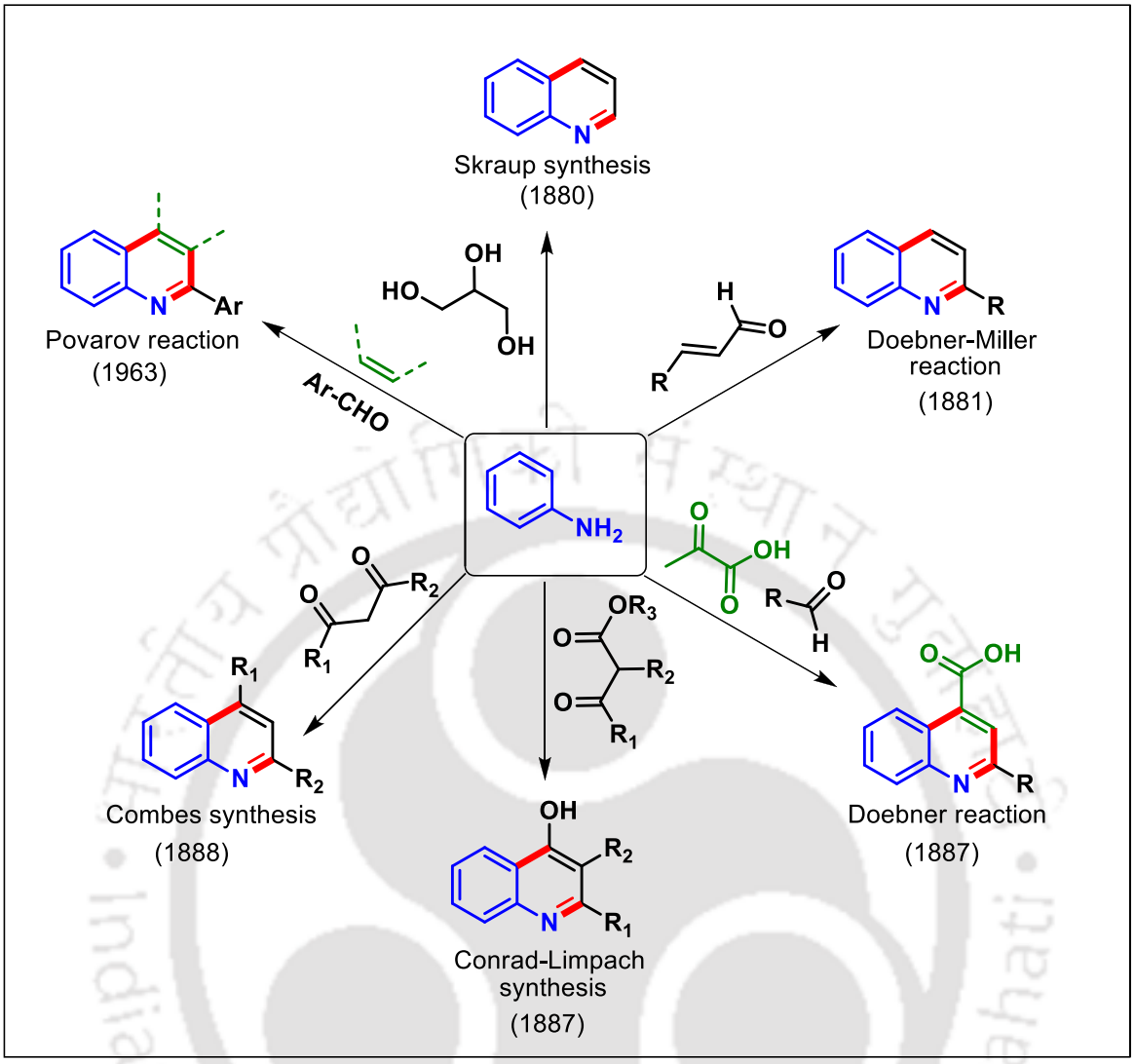
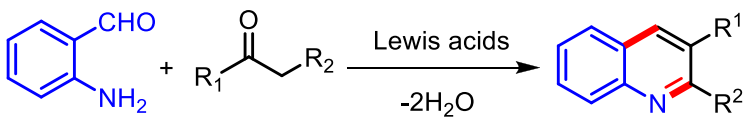


Figure 1.3. Traditional methods for synthesis of quinoline and its analogues from aniline.

Besides these methods in which simple aniline is common starting materials, there are some other classical procedures which involve substituted anilines, namely, Friedländer synthesis, Knorr synthesis and Pfitzinger reaction which have been described below

Friedländer synthesis

In 1882, Friedlander and co-workers[8] reported a simple and expedient method for synthesis of 2,3-disubstituted quinoline derivatives through an acid catalyzed condensation reactions of 2-amino benzaldehyde and ketone as shown in Scheme **1.1**.

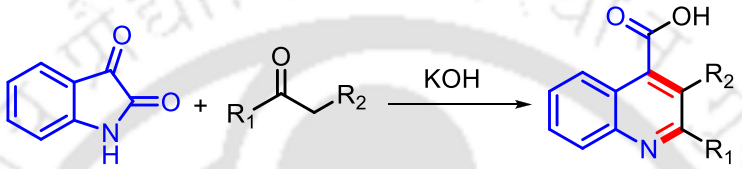


Scheme 1.1

Though this method has been useful to access 2,3-dialkylquinoline scaffolds, it suffers with some drawbacks, such as requirement of harsh reaction conditions, cumbersome work-up procedure, and most importantly, less substrate scope and low yield.

Pfitzinger reaction

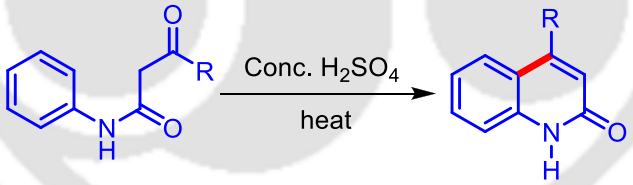
In 1886, Pfitzinger and co-workers[9] achieved synthesis of quinoline-4-carboxylic acids from base catalyzed reactions of isatin and carbonyl compounds. Reaction involves base hydrolysis of isatin to give keto-acid, which subsequently reacts with carbonyl compound to provide final product as presented in Scheme **1.2**.



Scheme 1.2

Knorr quinoline synthesis

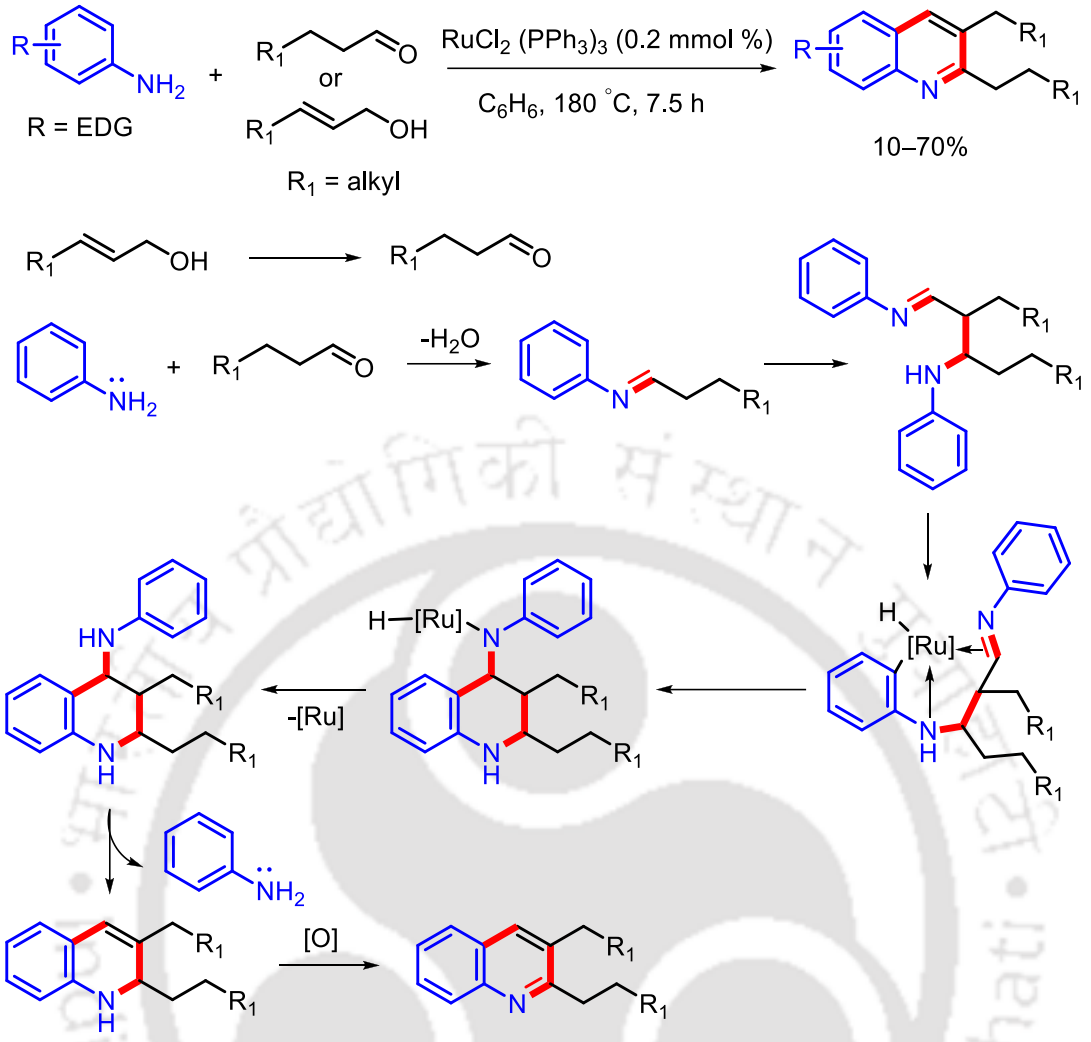
In 1886, Ludwig-Knorr[10] reported an efficient approach for synthesis of 2-hydroxyquinoline *via* intramolecular cyclization reaction of *β*-ketoanilide in presence of conc. sulfuric acid as shown in Scheme **1.3**.



Scheme 1.3

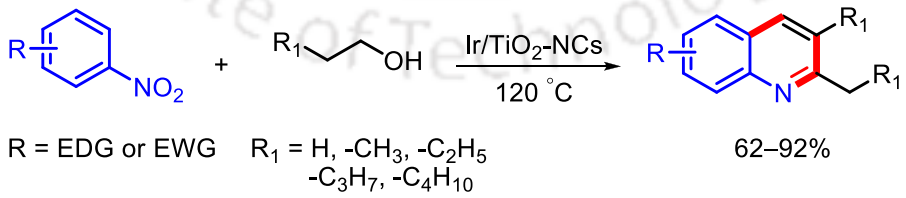
Reported methods for synthesis of 2,3-dialkylquinoline derivatives

Over the past few years, considerable efforts have been devoted to devise different methods for synthesis of 2,3-dialkylquinoline scaffolds. Watanabe and co-workers[11] reported a one-pot dichlorotris(triphenylphosphine)ruthenium complex catalyzed strategy to access 2,3-dialkylquinoline derivatives using substituted anilines and either aliphatic aldehydes or allylic alcohols. This protocol involves isomerization of allylic alcohol to corresponding aldehyde. Subsequently, aliphatic aldehyde reacts with aniline to give Schiff base dimer, which then undergoes cyclization in presence of ruthenium complex to provide 2,3-dialkylquinoline derivatives (Scheme **1.4**).



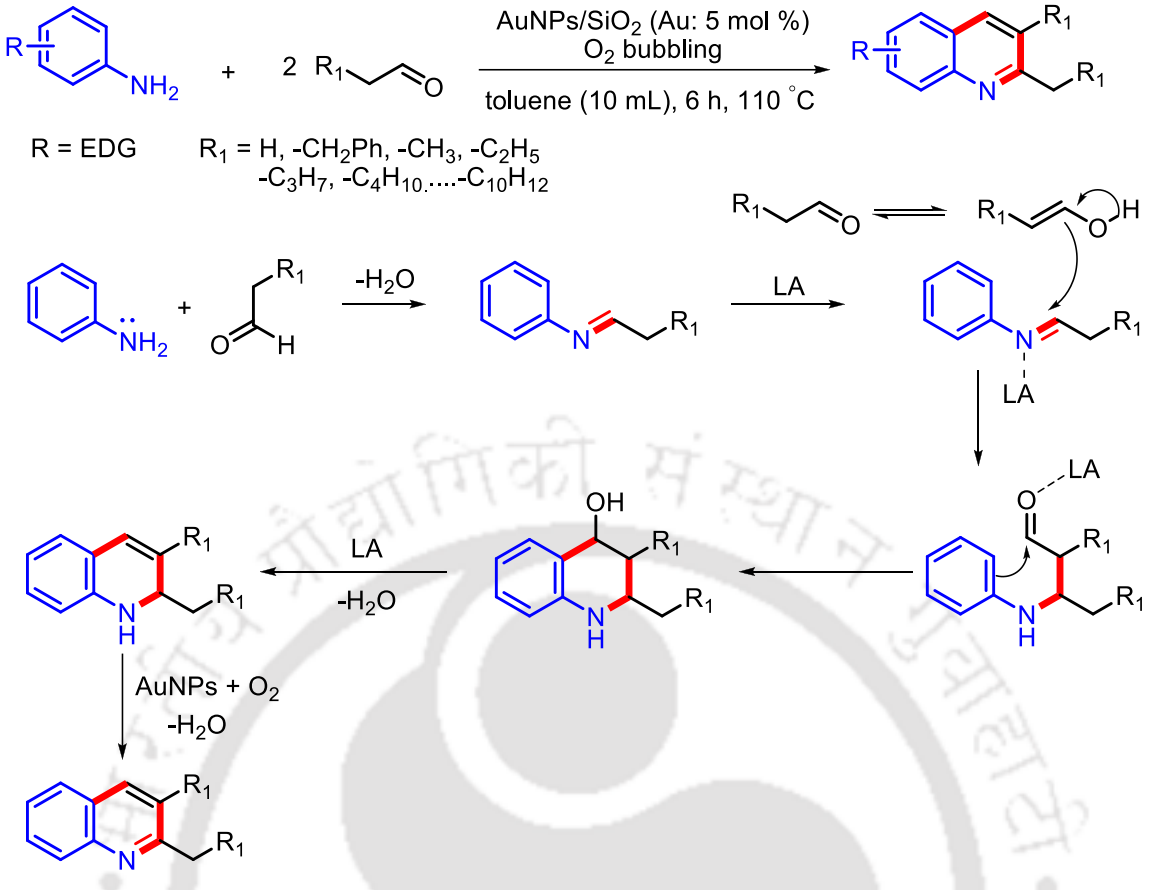
Scheme 1.4

He *et al.*[12] reported synthesis of 2,3-dialkylquinolines using readily available starting material like nitrobenzene and aliphatic alcohol in presence of titanium-supported iridium subnanoclusters as an efficient heterogeneous catalyst (Scheme **1.5**).



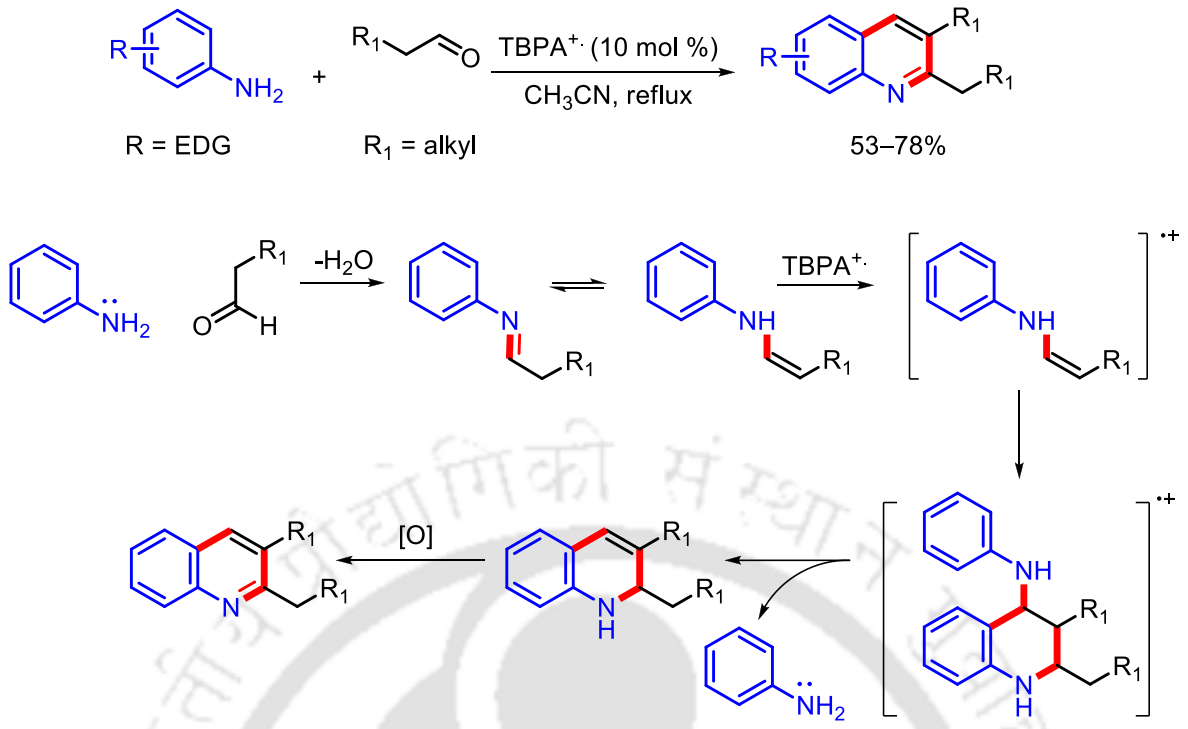
Scheme 1.5

Che and co-workers[13] demonstrated silica gel supported gold nanoparticles catalyzed one-pot tandem aerobic oxidative cyclization reaction of substituted anilines with aliphatic aldehydes to provide 2,3-dialkylquinoline derivatives (Scheme **1.6**).



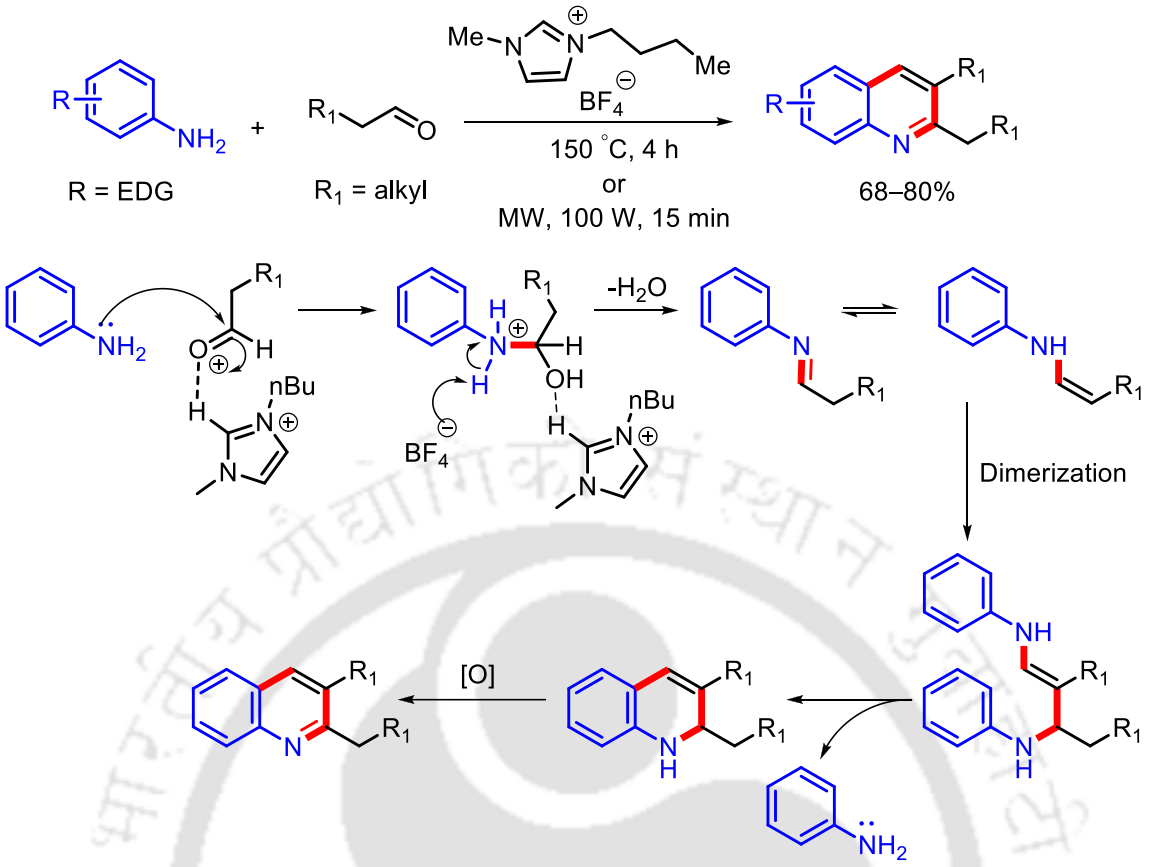
Scheme 1.6

Synthesis of 2,3-dialkylquinoline derivatives was also achieved by Jia *et al.*[14] that involves tandem cyclization of *in-situ* generated imine and enamine from aniline and aliphatic aldehydes under catalytic cation radical salt induced conditions (Scheme **1.7**).



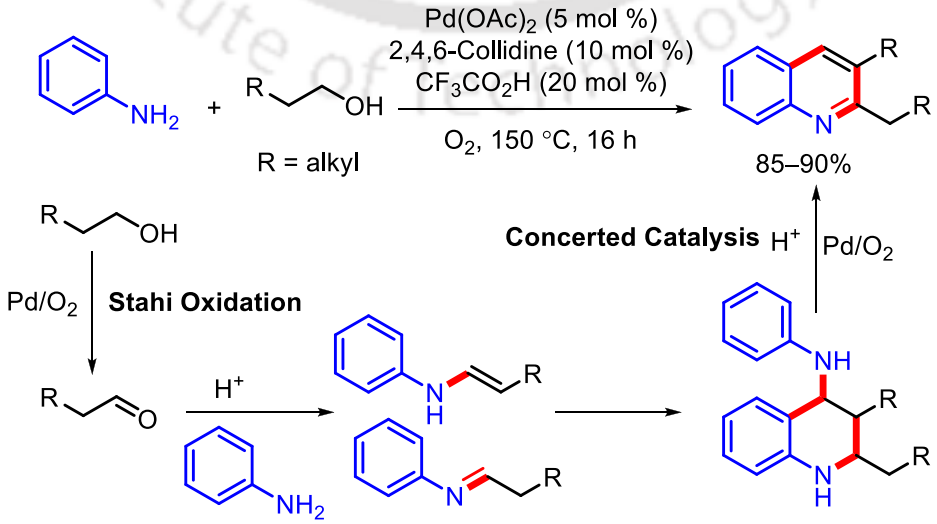
Scheme 1.7

Vishwakarma and co-workers[15] reported a facile protocol for synthesis of 2,3-dialkylquinolines which involves reaction of different aryl amines and aliphatic aldehydes in presence of imidazolium cation-based ionic liquid (Scheme **1.8**). Though this method offers direct access to functionalized quinoline frameworks, its demerits are requirement of high temperature and limited substrate scope with respect to 2,3-dialkylquinoline derivatives.



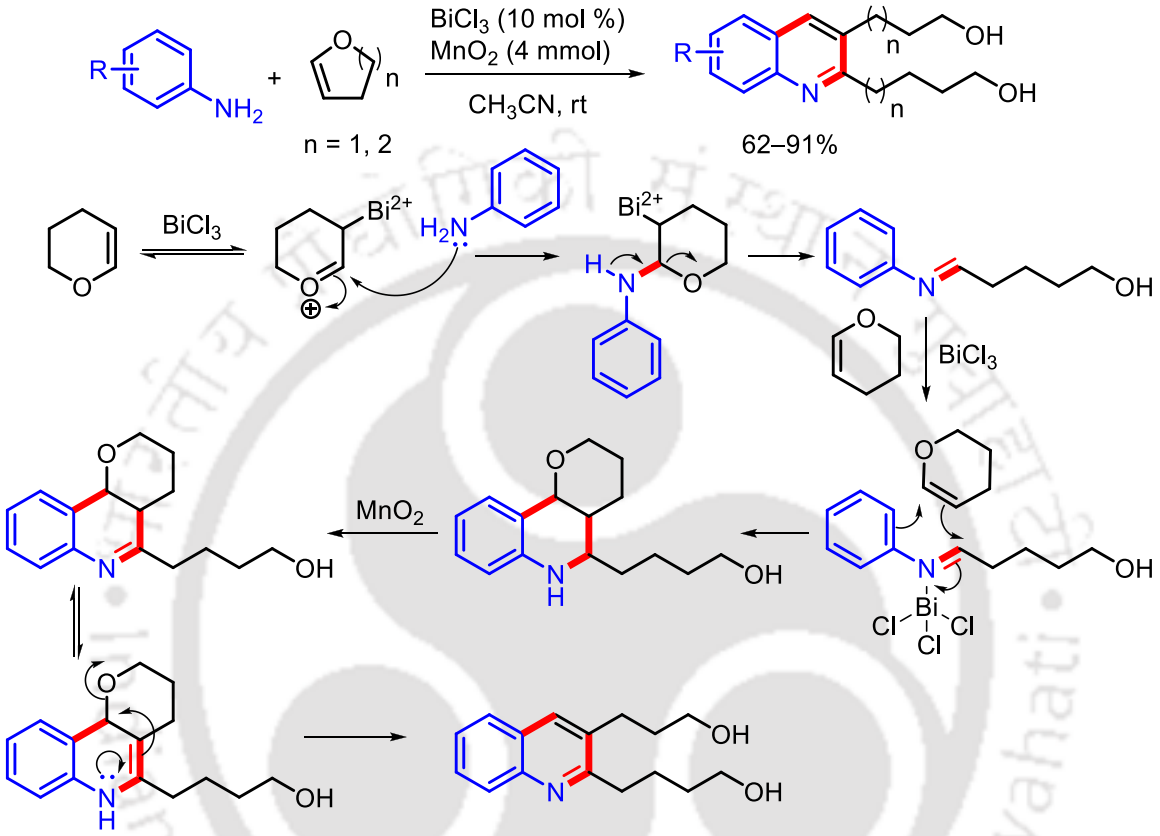
Scheme 1.8

Jiang *et al.*[16] achieved synthesis of 2,3-dialkylquinolines using aryl amines and aliphatic alcohols in presence of $Pd(OAc)_2$/2,4,6-Collidine/Bronsted acid (Scheme **1.9**). This reaction involves *in-situ* oxidation of alcohol to aldehyde which subsequently reacts with aryl amine to give imine. The generated imine tautomerizes to corresponding enamine and then enamine and imine react together to give desired 2,3-dialkylquinoline derivatives.



Scheme 1.9

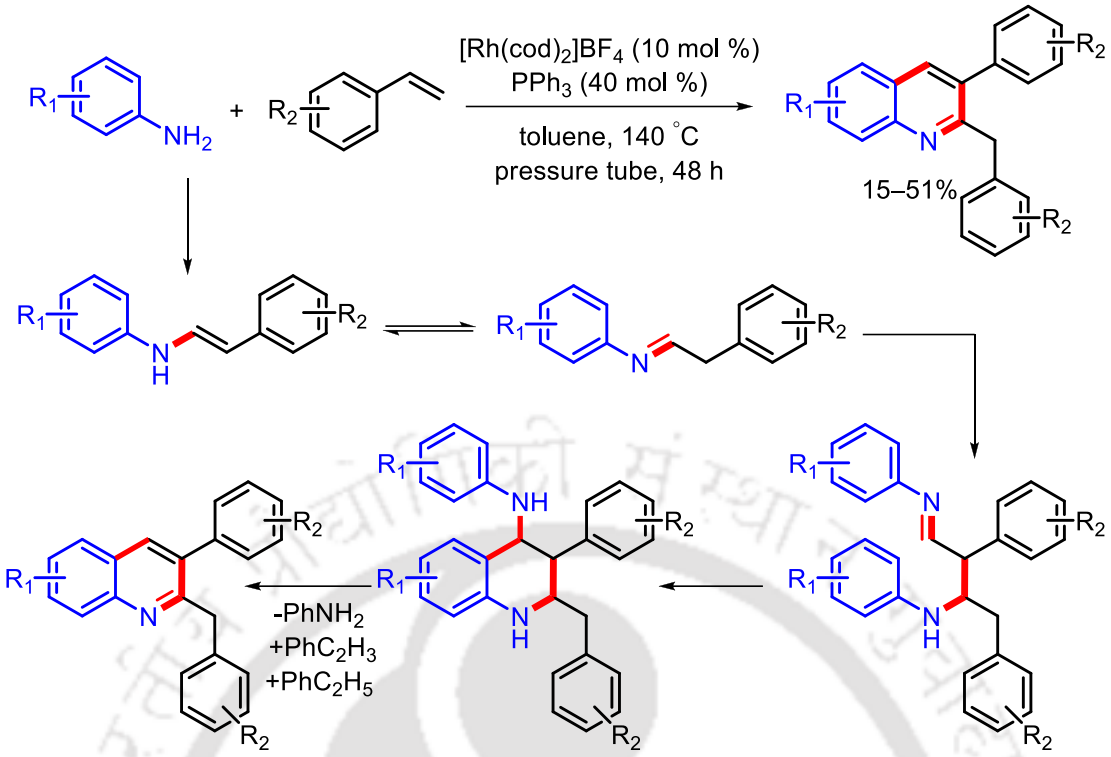
Gómez and co-workers[17] reported a straightforward method for synthesis of 2,3-(hydroxyalkyl)quinoline frameworks *via* $BiCl_3$ catalyzed domino reaction using substituted aryl amines and 2,3-dihydrofuran and 3,4-dihydro-2H-pyran (Scheme **1.10**).



Scheme 1.10

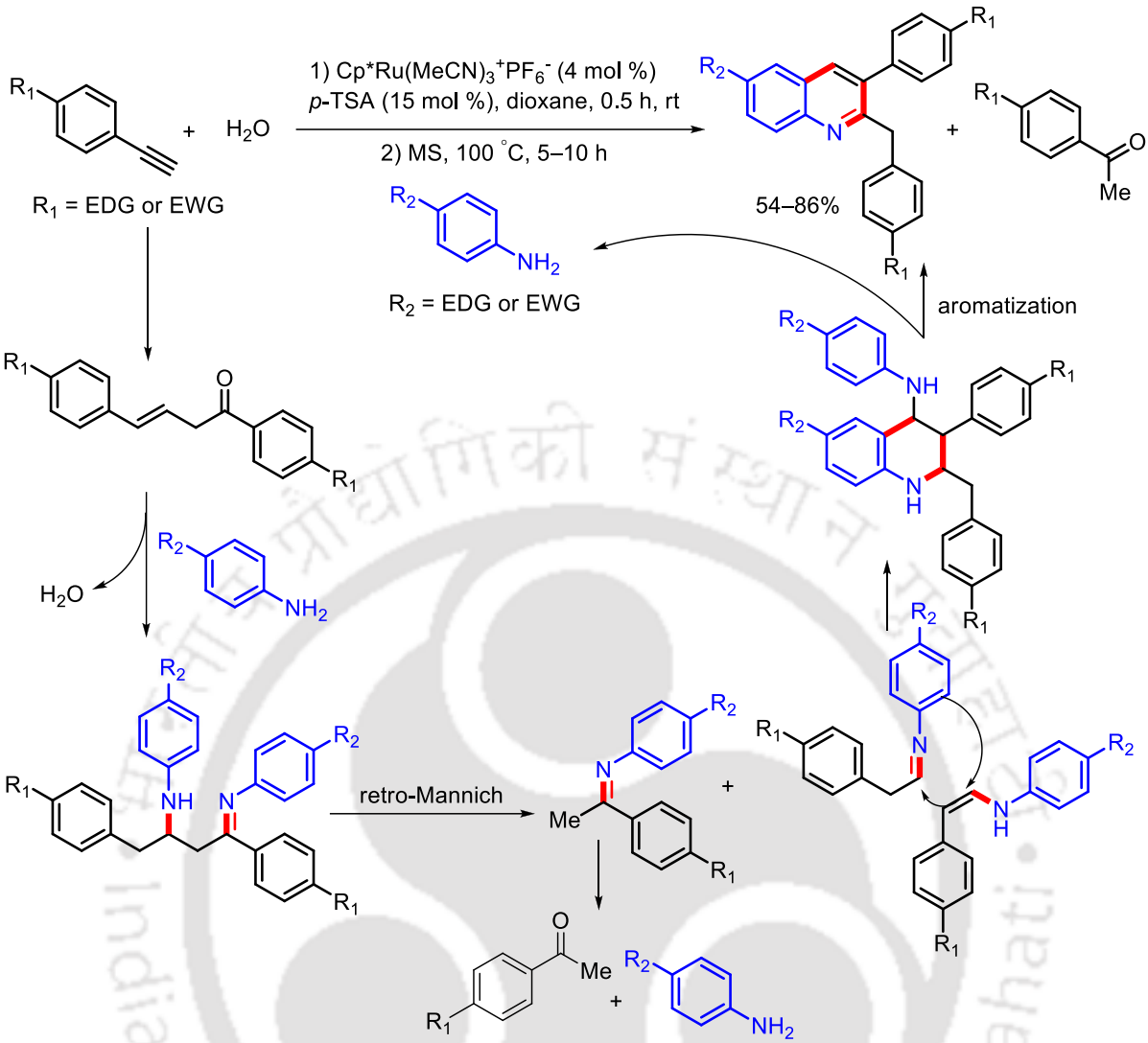
Reported protocols for synthesis of 2-benzyl-3-phenylquinoline derivatives

An extensive literature survey revealed a few methods for synthesis of 2-benzyl-3-phenylquinoline scaffolds. First, Beller and co-workers[18] introduced a method for synthesizing 2-benzyl-3-phenylquinolines from reactions of substituted anilines with aromatic olefins in presence of cationic rhodium catalyst, such as $[Rh(cod)_2]BF_4$, and PPh_3 (Scheme **1.11**). This method involves amination of aromatic olefin followed by formation of enamine intermediate, which tautomerizes to corresponding imine. Finally, enamine reacts with imine followed by cyclization provides expected 2-benzyl-3-phenylquinoline derivatives. Main shortcomings of this method are usage of expensive catalyst, requirement of an inert atmosphere, prolong reaction time, less substrates scope and low yield.

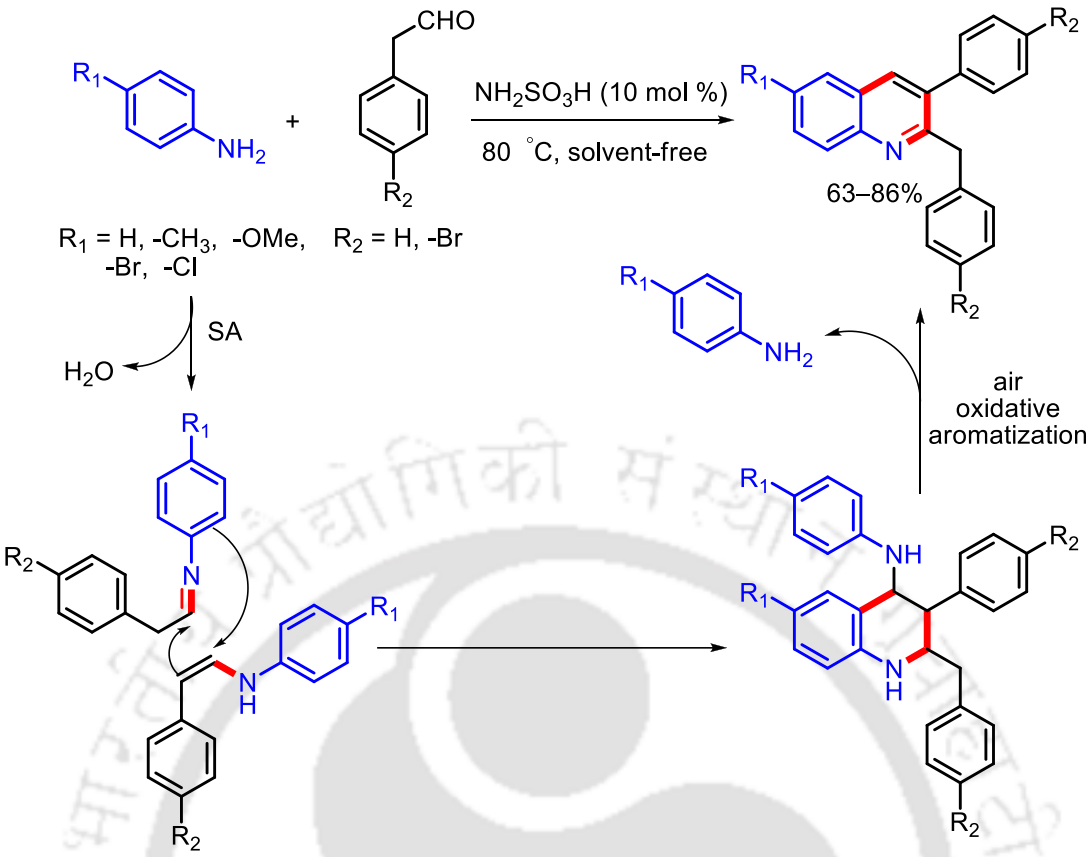


Scheme 1.11

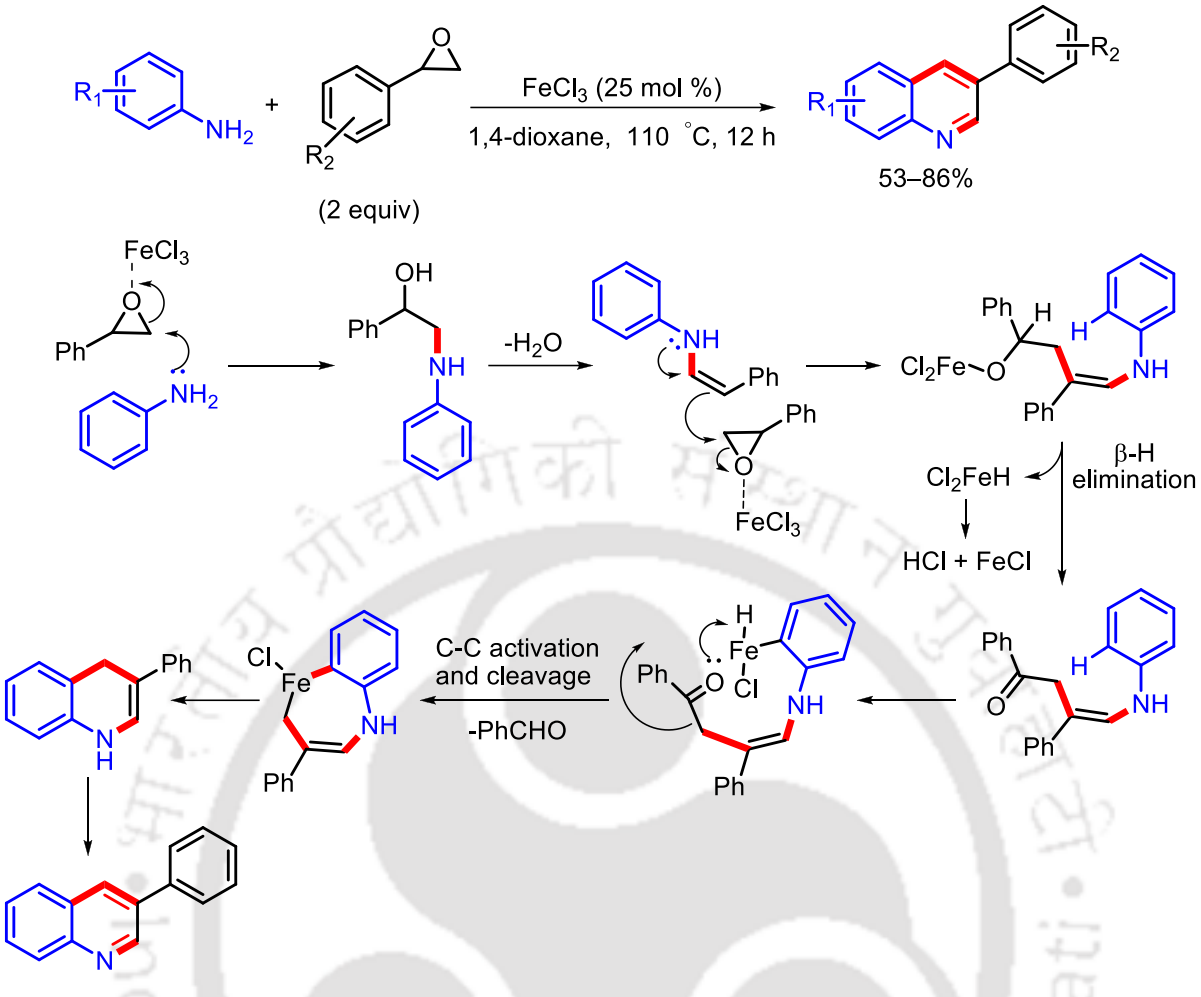
A one-pot strategy for synthesis of 2-benzyl-3-phenylquinolines was reported by Zhang *et al.*[19] from terminal alkynes and anilines *via* sequential ruthenium (II) and *p*-toluenesulfonic acid co-catalyzed reactions. Reaction proceeds through formation of allyl ketone intermediate followed by addition of aniline to give desired quinoline analogues (Scheme **1.12**). Zhang *et al.*[20] devised a solvent-free and sulfamic acid catalyzed reaction of substituted anilines with phenylacetaldehyde derivatives for synthesis of 2-benzyl-3-phenylquinolines (Scheme **1.13**). Although this method provides an easy access to disubstituted quinolines, it suffers particularly from poor substrates scope as they reported a few derivatives of 2-benzyl-3-phenylquinolines. Wang and co-workers[21] demonstrated reactions between aryl amines and styrene oxides in presence of 25 mol% $FeCl_3$ to afford a wide range of 3-arylquinoline scaffolds (Scheme **1.14**). Shortly thereafter, Sharghi *et al.*[22] also reported synthesis of 3-arylquinoline derivatives using similar starting material in presence of mixture of $MeSO_3$ and Al_2O_3 under solvent-free conditions at room temperature (Scheme **1.15**).



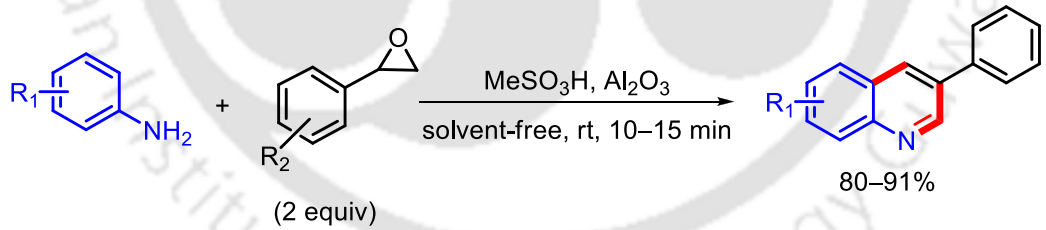
Scheme 1.12



Scheme 1.13



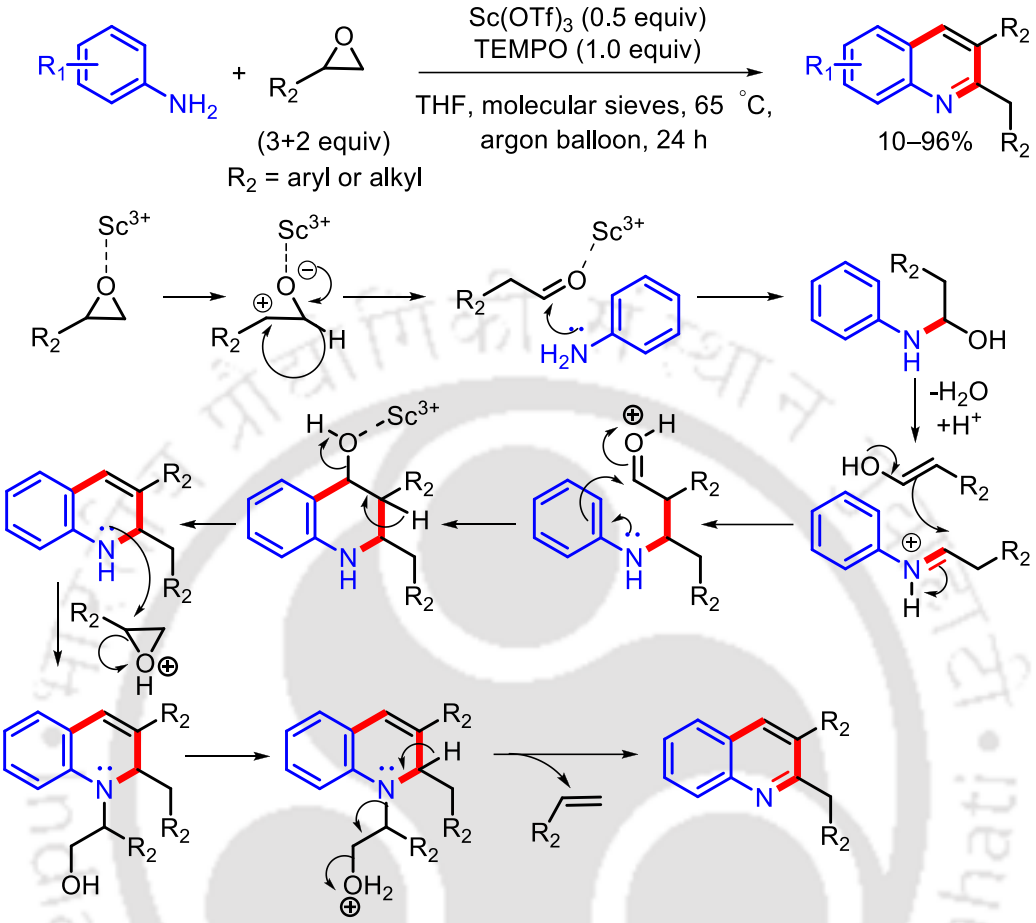
Scheme 1.14



Scheme 1.15

Very recently, Tepe and co-workers[23] also reported synthesis of 2,3-disubstituted quinoline derivatives from reactions of aryl amines and aromatic or aliphatic epoxides in presence of 0.5 equivalents scandium(III) triflate as Lewis acid and TEMPO as an oxygen scavenger under an inert atmosphere (Scheme **1.16**). Though this represents a good method to access 2,3-disubstituted quinolines, it is associated with several shortcomings, such as requirement of a stoichiometric amount of TEMPO (1.0 equiv.), an excess amount styrene oxide (5 equiv), high

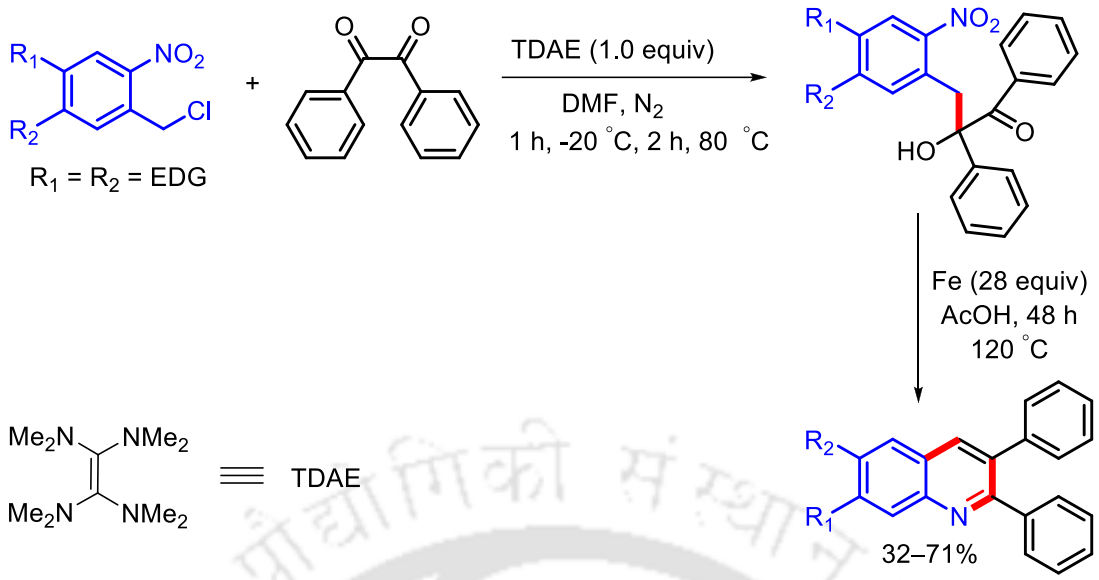
catalyst loading (0.5 equiv), molecular sieves, long reaction time (24 h), and an inert atmosphere of argon.



Scheme 1.16

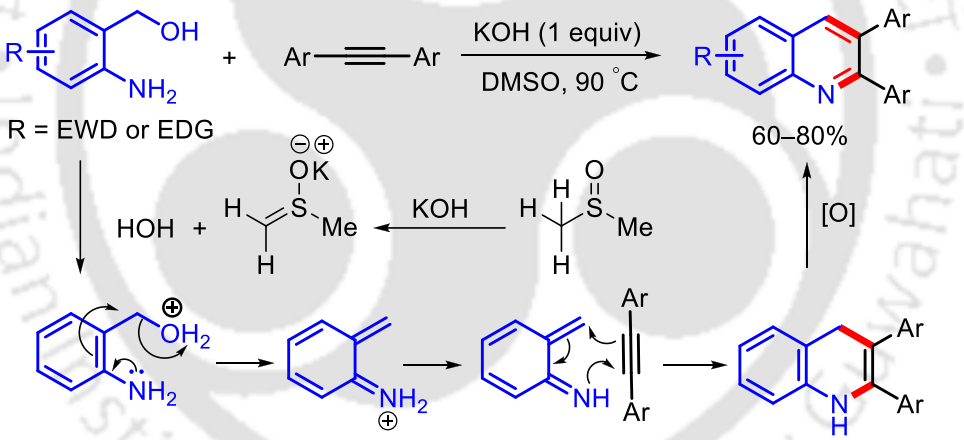
Reported approaches for synthesis of 2,3-diarylquinoline derivatives

Literature survey showed a few methods for synthesis of 2,3-diarylquinoline derivatives. Vanella *et al.*[24] reported two-step strategy for synthesizing 2,3-diarylquinoline analogues (Scheme **1.17**). In first step, *o*-nitrobenzyl chloride reacts with α-diketone in presence of tetrakis(dimethylamino)ethylene (TDAE) to provide α-hydroxyketone. Second step involves reduction of nitro group followed by cyclization to give desired 2,3-diphenylquinoline scaffolds.



Scheme 1.17

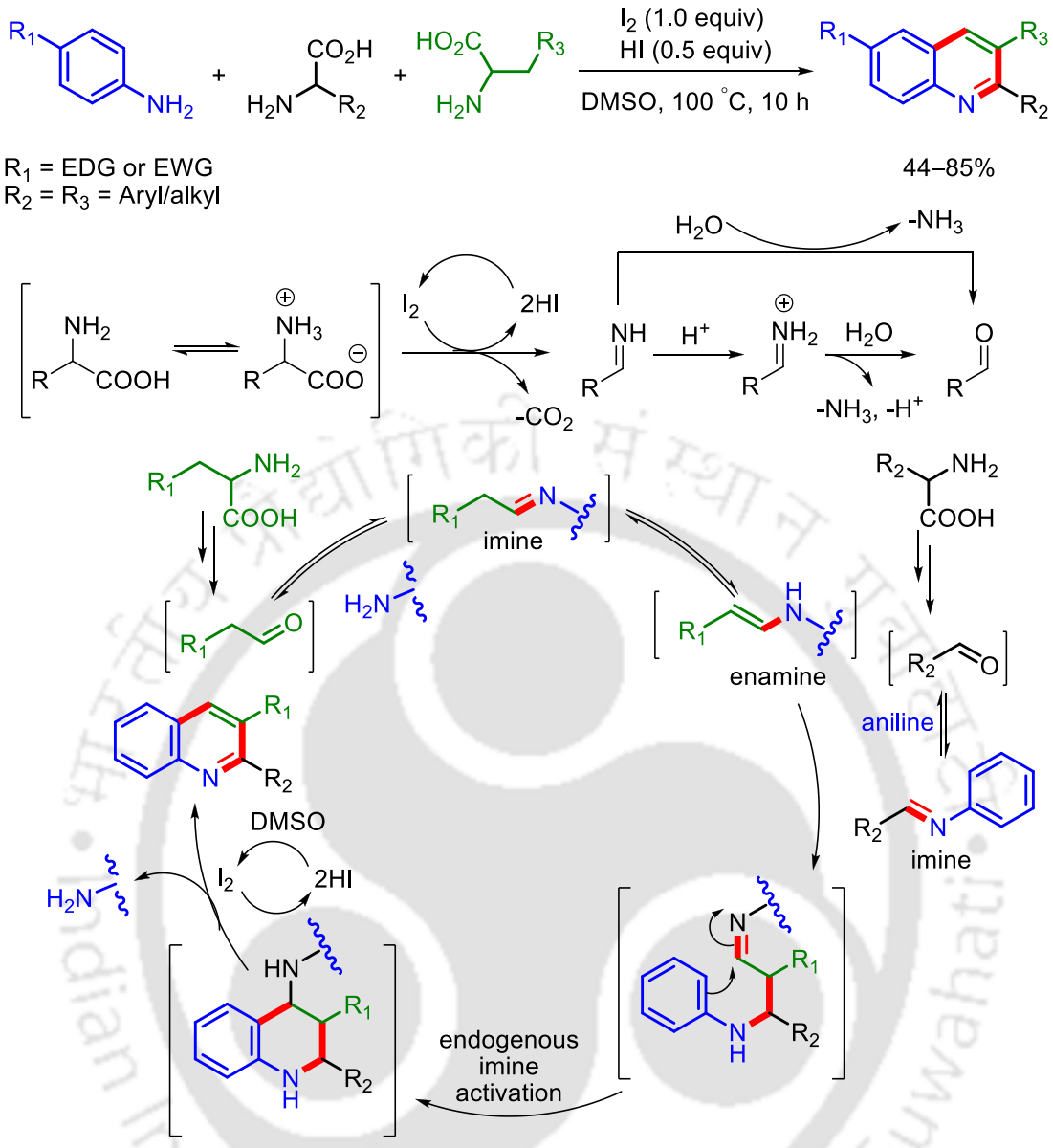
Later on, Verma and co-workers[25] demonstrated a base promoted, protection free and regioselective protocol for synthesis of 2,3-diarylquinoline derivatives (Scheme **1.18**).



Scheme 1.18

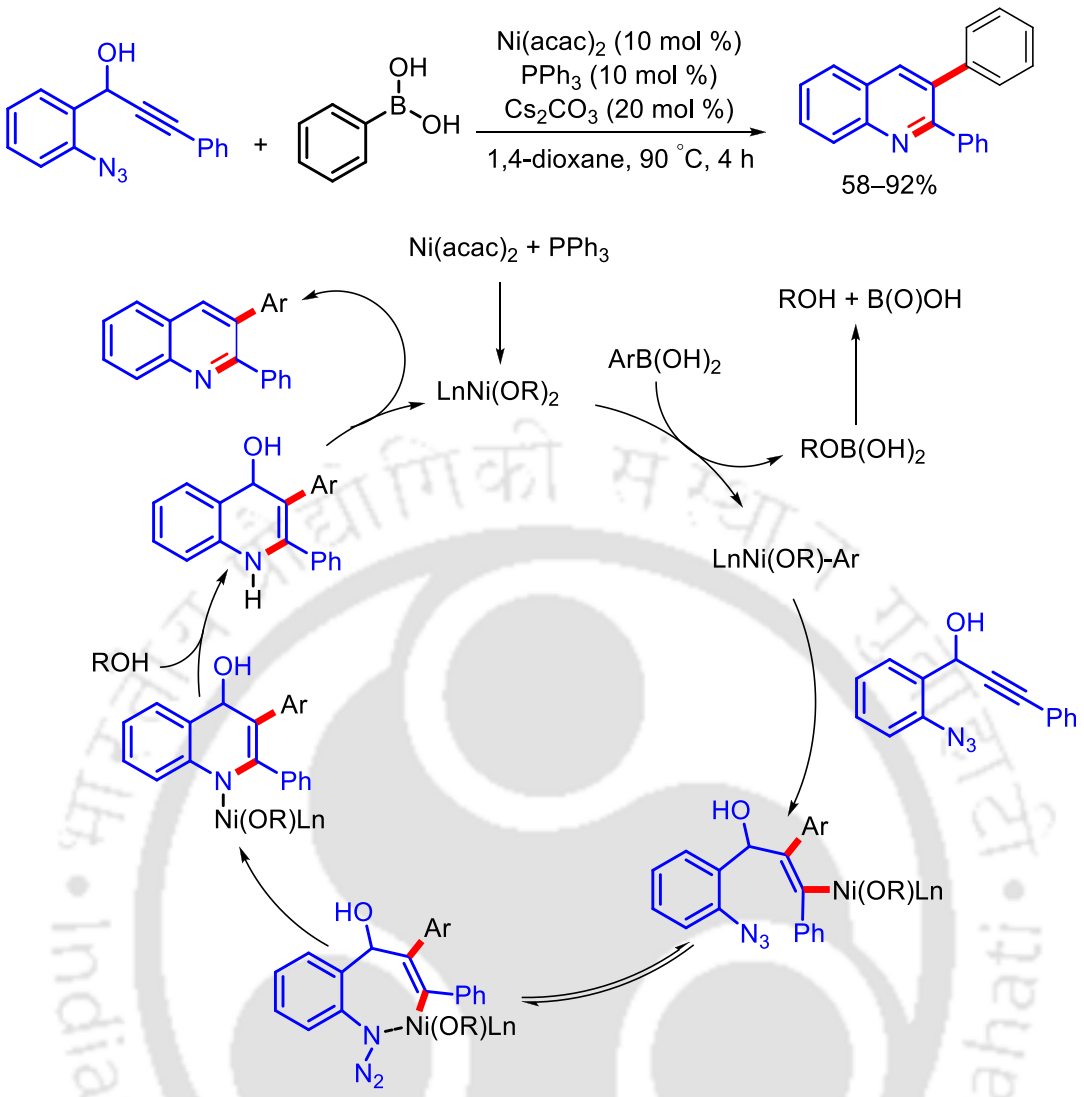
This reaction proceeds *via* [4+2] cycloaddition of *in-situ* generated azadiene from *o*-amino benzyl alcohol with internal alkynes.

Another important and simple method for synthesis of 2,3-diarylquinoline scaffolds was introduced by Wu and co-workers (Scheme **1.19**).[26] In this reaction, substituted anilines react with two different amino acids in presence of catalytic amount of iodine and hydrogen iodide to provide corresponding 2,3-diarylquinoline analogues.



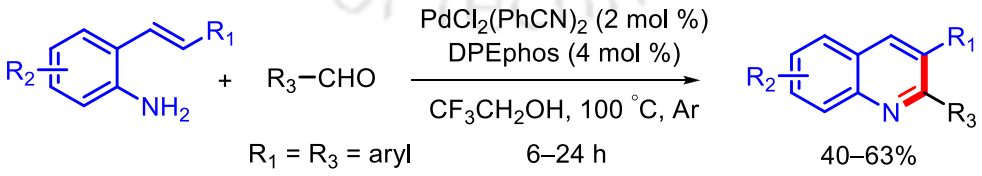
Scheme 1.19

Reddy and co-workers[27] developed a novel and expedient approach to access a variety of 2,3-diarylquinolines with good substrate scope and yield (Scheme **1.20**). This synthetic route involves reaction of 2-azido phenyl propargylic alcohol with wide range of boronic acids in presence of 10 mol% $Ni(acac)_2$ as a catalyst.



Scheme 1.20

Very recently, Youn *et al.*[28] also devised a method for synthesis of 2,3-diarylquinoline derivatives. This strategy involves $PdCl_2(PhCN)_2$ catalyzed annulation reactions using 2-alkenylanilines and aryl aldehydes (Scheme **1.21**).

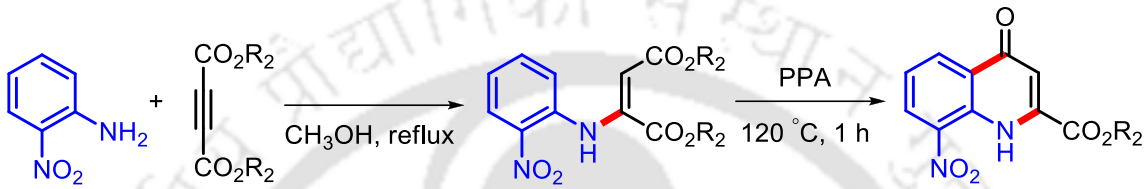


Scheme 1.21

Though this approach is good to provide 2,3-diarylquinoline derivatives, it has some disadvantages, such as use of expensive catalyst and ligand, preparation of 2-alkenylanilines, long reaction time, requirement of an inert atmosphere of argon and low yield.

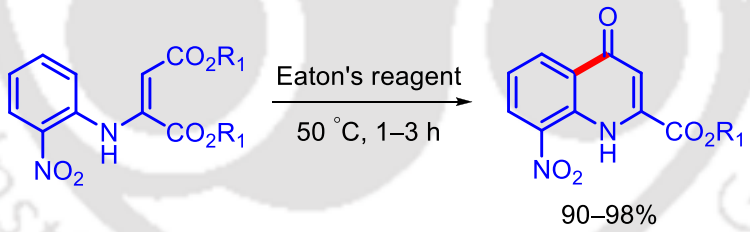
Reported methods for synthesis of quinoline mono-carboxylate and quinoline-2,4-dicarboxylate derivatives

Quinoline-2-carboxylate subunit is an integral part of naturally occurring alkaloids, namely, ascidiathiazone **A** and **B**.[29] Therefore, synthetic community has devoted considerable efforts to develop new synthetic methods for synthesis of quinoline mono-carboxylate derivatives. In 1985, Peet and co-workers[30] first reported antiallergic quinolinone derivatives using *o*-nitroaniline and acetylenedicarboxylate in two steps (Scheme **1.22**). It is to be noted that in this case quinoline-2,4-dicarboxylates was not obtained.



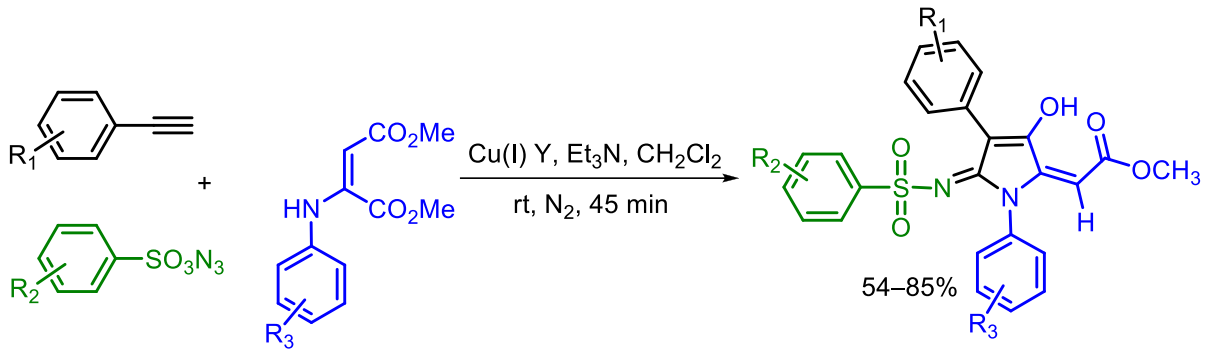
Scheme 1.22

In 2007, Zewge *et al*.[31] demonstrated a mild synthesis of 4-quinolinone derivatives *via* Eaton's reagent promoted intramolecular cyclization of enamine (derived from reaction of aryl amines and acetylenedicarboxylate) (Scheme **1.23**). However, in this case quinoline-2,4-dicarboxylates was also not detected.



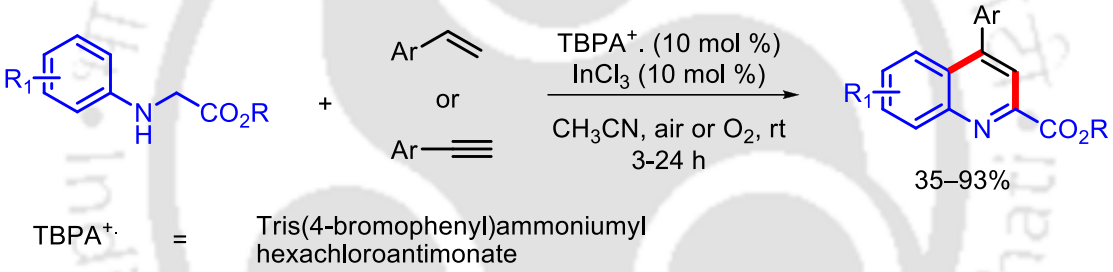
Scheme 1.23

In 2015, Pitchumani and co-workers[32] showed the use of enamines (derived from aryl amines and dimethyl acetylenedicarboxylate) in a multi-component reaction for synthesis of highly functionalized pyrrolidines (Scheme **1.24**). This reaction proceeds in presence of copper(I)-Y zeolite under mild conditions. It is noteworthy that quinoline-2,4-dicarboxylate was not reported in this study.



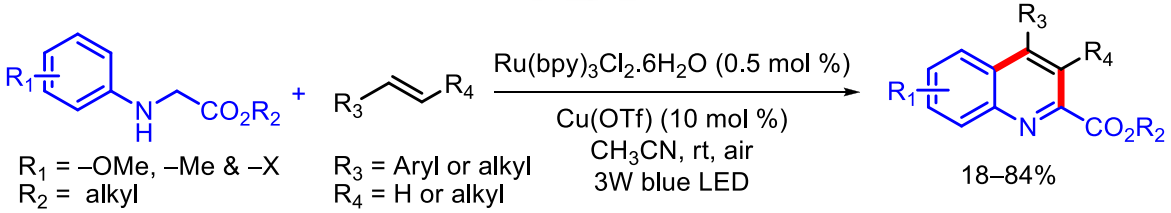
Scheme 1.24

In 2012, Wang *et al.*[33] first reported a simple protocol for synthesis of 4-arylquinoline-2-carboxylate scaffolds from functionalized glycine derivatives and olefins/alkynes under catalytic radical cation salt induced conditions (Scheme **1.25**). This reaction involves oxidation of glycine derivatives to provide corresponding imine, which is subsequently captured by either alkenes or alkynes to furnish desired 4-arylquinoline-2-carboxylate derivatives.



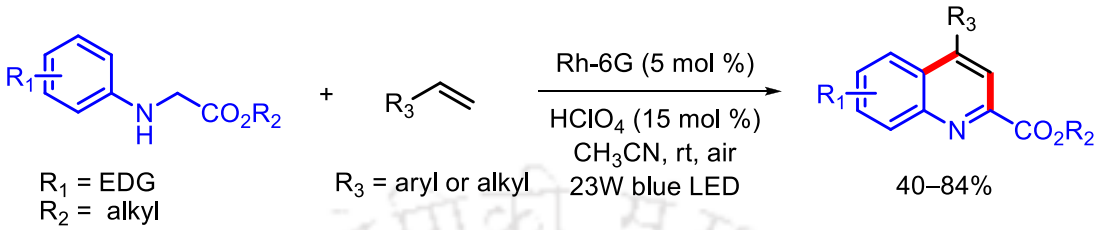
Scheme 1.25

Zhang and co-workers[34] introduced an elegant method for direct access to highly substituted quinoline-2-carboxylate frameworks (Scheme **1.26**). This protocol involves blue LED light induced photocatalytic aerobic oxidative coupling/aromatization tandem reaction of glycine derivatives and various alkenes in presence a photocatalyst and copper(II) triflate.



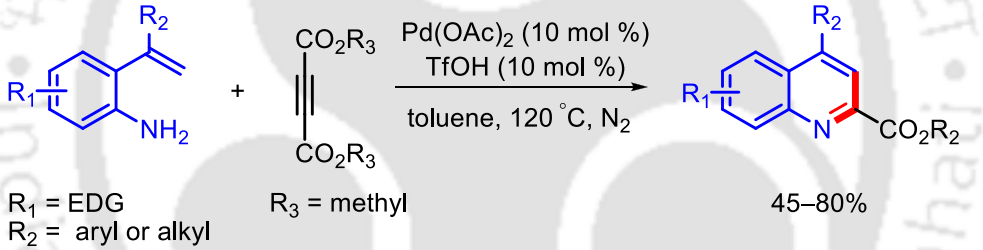
Scheme 1.26

Later on, the same group reported synthesis of substituted quinoline-2-carboxylate analogues through visible-light-induced aerobic oxidative dehydrogenative coupling reaction of similar kind of starting material (Scheme **1.27**).[35] In this transformation $Ru(byp)_3Cl_2.6H_2O$ and copper(II) triflate were replaced by Rh-6G and $HClO_4$ respectively.



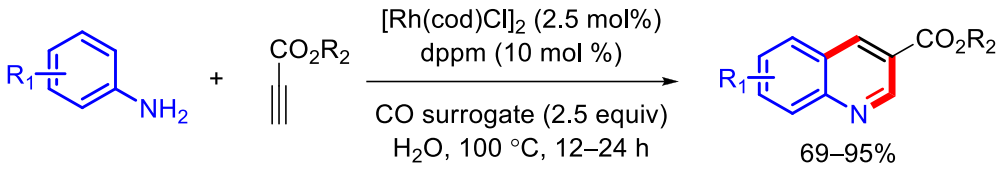
Scheme 1.27

Very recently, Yan *et al.*[36] reported a simple and practical protocol by which substituted quinoline-2-carboxylates can be accessed from tandem *aza*-Michael addition followed by cyclization in presence of 10 mol% palladium acetate and triflic acid (Scheme **1.28**).



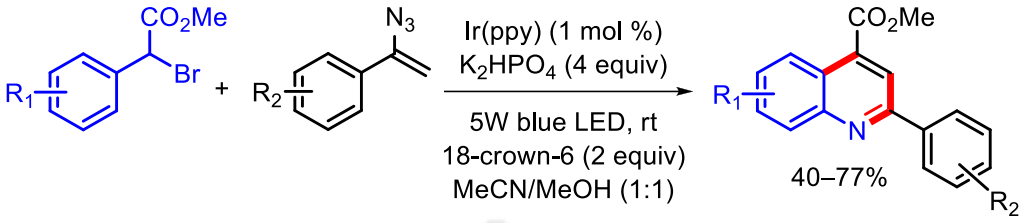
Scheme 1.28

Balaraman and co-workers[37] also reported synthesis of quinoline-3-carboxylate derivatives from aniline and alkyne in presence of a rhodium catalyst (Scheme **1.29**). They devised a rhodium-catalyzed C–H activation protocol which utilizes an unprotected aryl amines and an electron-deficient alkynes to C–C bonded products as a potential intermediate in contrast to C–N bonded products with high levels of regioselectivity.



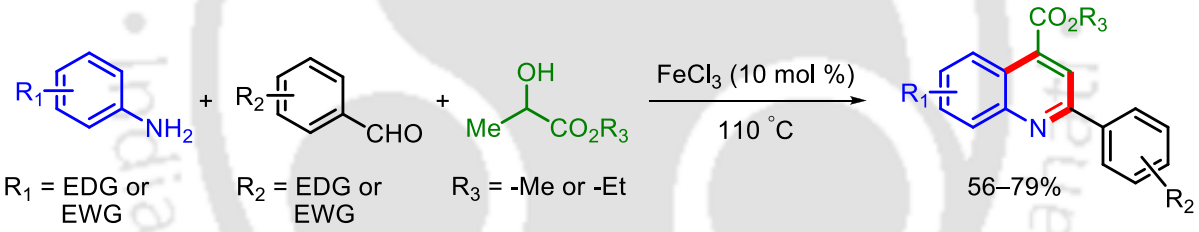
Scheme 1.29

Zhou *et al.*[38] demonstrated a facile route to variety of methyl-2-arylquinoline-4-carboxylate scaffolds through visible-light induced free radical reactions of α-carbonyl benzyl bromides and vinyl azides *via* C-C and C-N bond formation (Scheme **1.30**).



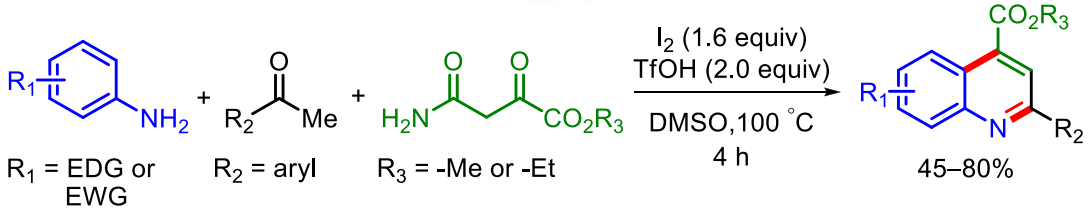
Scheme 1.30

Wan and co-workers[39] developed an unprecedented three-component protocol for synthesis of methyl/ethyl-2-arylquinoline-4-carboxylate derivatives (Scheme **1.31**). Biomass-derived methyl/ethyl lactates were used along with aryl amines and aryl aldehydes in three-component reaction in presence of 10 mol% $FeCl_3$ at 110 °C. In this report, potential application of biomass feedstocks has been demonstrated in synthesis of valuable products.



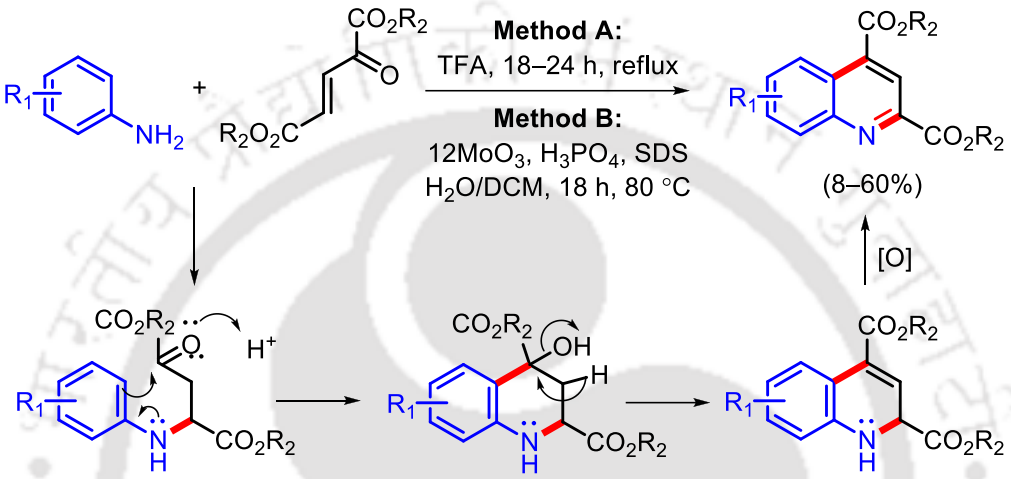
Scheme 1.31

Very recently, Wu *at al.*[40] described synthesis of methyl/ethyl-2-arylquinoline-4-carboxylate frameworks *via* iodine mediated three-component reactions using substituted aryl amines, various acetophenone derivatives and different 1,3-dicarbonyl compounds (Scheme **1.32**).



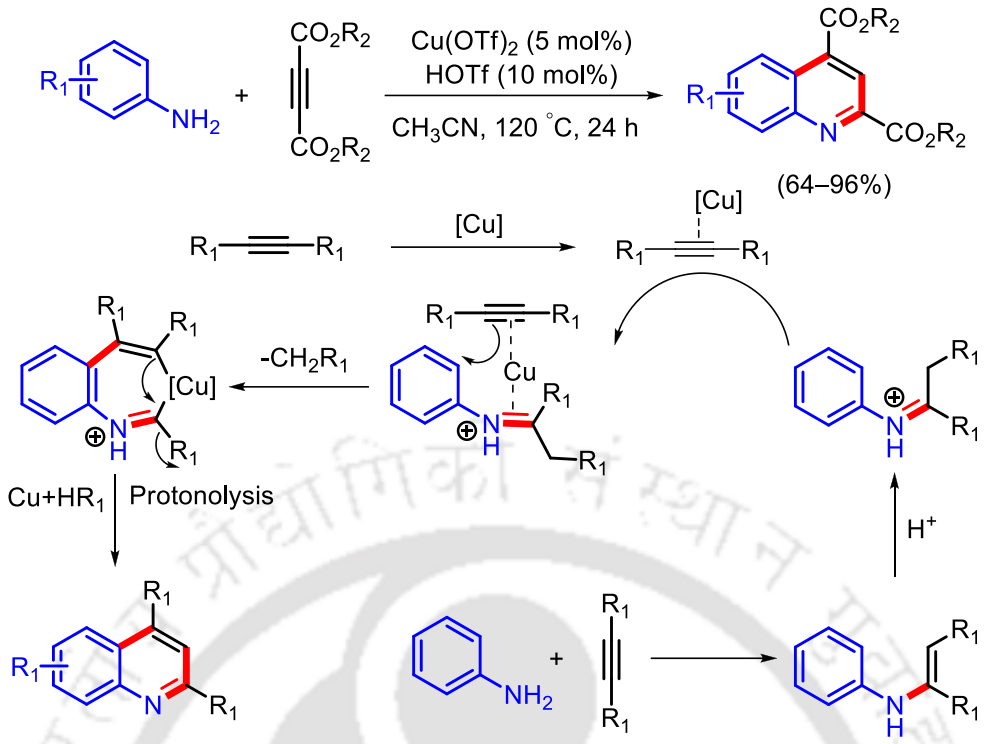
Scheme 1.32

Pietrancosta *et al*.[41] reported a method for synthesis of quinoline-2,4-dicarboxylate derivatives through an improved Doebner Miller reaction using aryl amines and an unsaturated keto-ester (synthesized from ketoglutaric acid in three steps) (Scheme **1.33**). This transformation occurs in presence of either trifluoroacetic acid (TFA) or biphasic phosphomolybdic acid and sodium dodecylsulfate (SDS) as surfactant. Despite the usefulness of this method for synthesizing a variety of quinoline-2,4-dicarboxylates, it suffers from many drawbacks, such as use of hazardous acid, preparation of unsaturated keto-esters in three-steps and longer reaction time.



Scheme 1.33

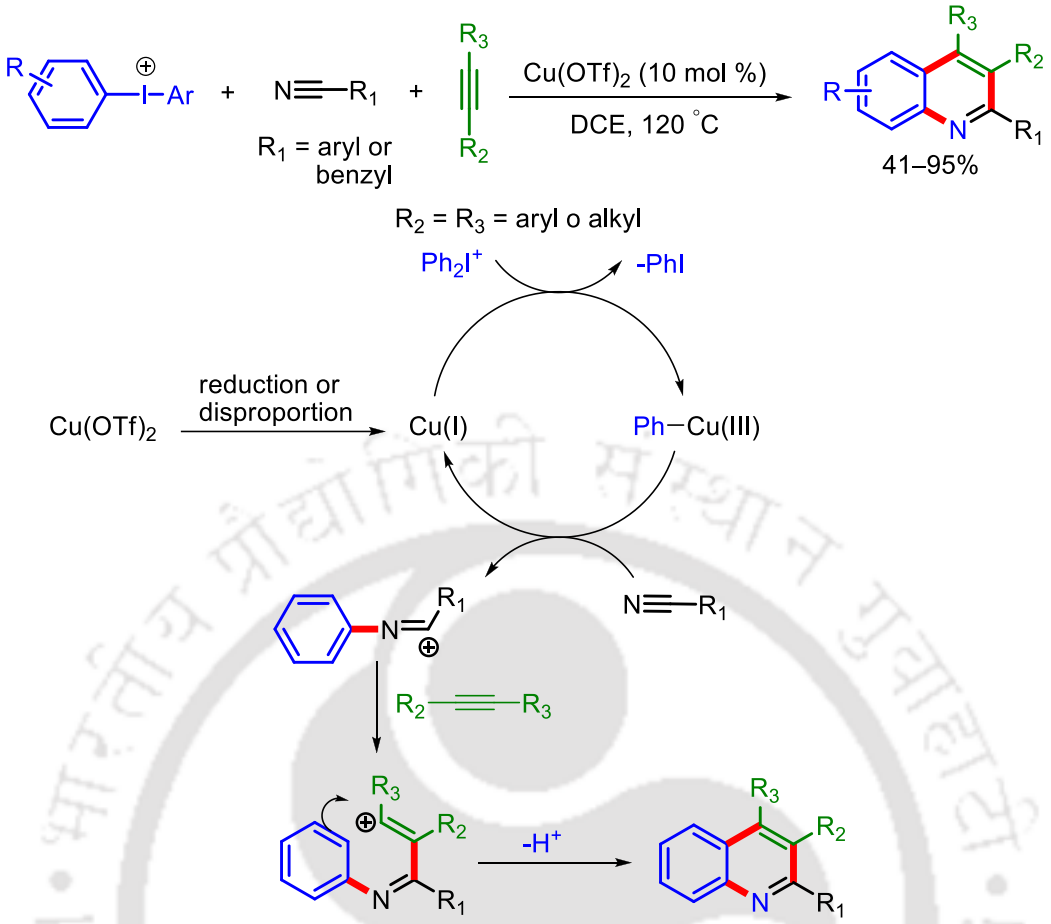
Recently, Yi and co-workers[42] also reported one-pot synthesis of 2,4-disubstituted quinolines through copper(II) triflate catalyzed annulation reaction of aryl amines and acetylenedicarboxylates (Scheme **1.34**). Despite the great utility of this method, they have some demerits, such as use metal catalyst $Cu(OTf)_2$, requirement of hazardous triflic acid, high reaction temperature, longer reaction time and restricted substrate scope.



Scheme 1.34

Previous strategy for synthesis of 2-benzyl-4-phenylquinoline derivatives

Li and co-workers[43] reported a method for synthesis of substituted quinolines, which involves copper(II) triflate catalyzed domino reaction of diphenyliodonium salt, benzonitriles and phenylacetylenes (Scheme **1.35**). In this report, an emphasis was given only on synthesis of 2,3,4-trisubstituted quinoline frameworks. However, only one substrate 2-benzyl-4-phenylquinoline was reported.



Scheme 1.35

From the above literature review it is evident that there are a few reported methods for synthesis of 2,3-disubstituted quinoline derivatives, such as 2,3-dialkylquinolines, 2-benzyl-3-phenylquinolines and 2,3-diarylquinolines. Although each of these methods has its own merits, these have many disadvantages, such as use of hazardous acids and expensive catalysts, requirement of high temperature, long reaction time, tedious work-up procedure and most importantly, limited substrate scope and low yield. Due to the increasing demand for sustainable methods in organic synthesis designing competent and versatile strategies for synthesis of 2,3-disubstituted quinoline scaffolds is necessary to overcome all the hurdles associated with existing methods. Therefore, efforts were made to address all these problems and develop new synthetic approaches for synthesis of 2,3-dialkylquinolines, 2-benzyl-3-phenylquinolines and 2,3-diarylquinolines. Some of aspects of these methods are easy handling, high regioselectivity, use of readily available starting materials and cost-effective and versatile metal triflates as catalyst, mild conditions, short time and broad substrate scope

with high yield. Each of these methods will be discussed in the successive **Part A**, **Part B** and **Part C** of the chapter II in this thesis.

Literature survey showed a few reports for synthesis of quinoline-2,4-dicarboxylates. Despite the great utility of existing methods, these have several shortcomings, such as use of metal catalysts and hazardous acids, preparation of starting material, long reaction time, harsh conditions and restricted substrate scope. There was no report for direct synthesis of 2-benzyl-4-phenylquinoline derivatives. In spite of great importance, synthesis of 2-benzyl-4-phenylquinoline scaffolds was remained unexplored. Therefore, it was highly desirable to focus on synthesis of 2-benzyl-4-phenylquinoline derivatives. From environment and practical standpoint, new green and sustainable synthetic methodologies were devised for rapid access to quinoline-2,4-dicarboxylates and 2-benzyl-4-phenylquinolines. Notable advantages of these methodologies are easy to handle, metal-free, use of simple starting materials and green catalyst molecular iodine, high regioselectivity, mild conditions, short time and an access to wide range of quinoline-2,4-dicarboxylates and 2-benzyl-4-phenylquinolines with high yield. Each of these methodologies will be discussed successively in **Part A** and **Part B** of the chapter III in this thesis.

References:

1. (a) J. B. Harborne and H. Baxter, G. P. Moss (ed.) (1973). *The Phytochemical Dictionary*, a Hand Book of Bioactive Compounds from Plants, 2nd Edition, Taylor and Francis; (c) J. P. Michael, *Nat. Prod. Rep*., 2002, **19**, 742–760.
2. (a) J. Liu, R. Cao, M. Xu, X. Wang, H. Zhang, H. Hu, Y. Li, Z. Hu, W. Zhong and M. Wang, *Cell Discovery*, 2020, **6**, 1–4; (b) J. Gao, Z. Tian and X. Yang, *BioSci. Trends*, 2020, **14**, 72–73; (c) A. Cortegiani, G. Ingoglia, M. Ippolito, A. Giarratano and S. Einav, *J. Crit. Care*, 2020, **57**, 279–283; (d) P. Chung, Z. Bian, H. Pun, D. Chan, A. S. Chan, C. Chui, J. C. Tang and K. Lam, *Future Med. Chem*., 2015, **7**, 947–967; (e) C. Portela, C. M. M. Afonso, M. M. M. Pinto and M. J. Ramos, *Bioorg. Med. Chem*., 2004, **12**, 3313−3321; (f) J. Charris, P. Martinez, J. Dominguez, S. Lopez, J. Angel and G. Espinoza, *Heterocycl. Commun*., 2003, **9**, 251–256; (g) S. Leonce, B. Pfeiffer, P. Renard, G. Guillaumet, C. W. Rees and T. Besson, *Bioorg. Med. Chem. Lett*., 2000, **10**, 2183–2185; (h) A. Nayyar, A. Malde, R. Jain and E. Coutinho, *Bioorg. Med. Chem*., 2006, **14**, 847–856; (i) S. Vangapamdu, M. Jain, R. Jain, S. Kaur and P. P. Singh, *Bioorg. Med. Chem.*, 2004, **12**, 2501–2508; (j) H. Heitsch, *Curr. Med. Chem*., 2002, 9, 913–928; (k) M. A. Fakhfakh, A. Fournet, E. Prina, J. F. Mouscadet, X. R. Franck and B. Hocquemiller, *Bioorg. Med. Chem.*, 2003, **11**, 5013–5023; (l) N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran and J. T. Leonard, *Biol. Pharm. Bull*., 2004, **27**, 1683–1687.
3. M. R. E. Alya, M. M. Ibrahima, A. M. Okaeld and Y. A. M. H. Gherbawy, *Russ. J. Bioorg. Chem*., 2014, **40**, 214–227.
4. (a) J A. K. Agarwal and S. A. Jenekhe, *Macromolecules*, 1991, **24**, 6806–6808; (b) X. Zhang, A. S. Shetty and S. A. Jenekhe, *Macromolecules*,1999, **32**, 7422–7429.
5. (a) W. Adam, R. P. Bheema, H. G. Degen, A. Levai, T. Patonay, and C. R. S. Moller, *J. Org. Chem.*, 2002, **67**, 259–264; (b) M. Wang, L. X. Gao, Ai W. P Mai, X. Xia, F. Wang and S. Bo Zhang, *J. Org. Chem.*, 2004, **69**, 2874–2883; (c) S. Leroux, L. Larquetoux, M. Nicolas and E. Doris, *Org. Lett*., 2011, **13**, 3549–3551; (d) M. K. Thøgersen and K. A. Jørgensen, *Chem. Sci*., 2017, **8**, 8086–8093.
6. C. Cheng and J. F. Hartwig, *J. Am. Chem. Soc*., 2015, **137**, 592−595.
7. (a) S. Kraup, *Ber*., 1880, **13**, 2080−2086; (b) S. E. Denmark and S. Venkatraman, *J. Org. Chem*., 2006, **71**, 1668–1676; (c) E. A. Steck, L. L. Hallock, A. J. Holland and L. T.

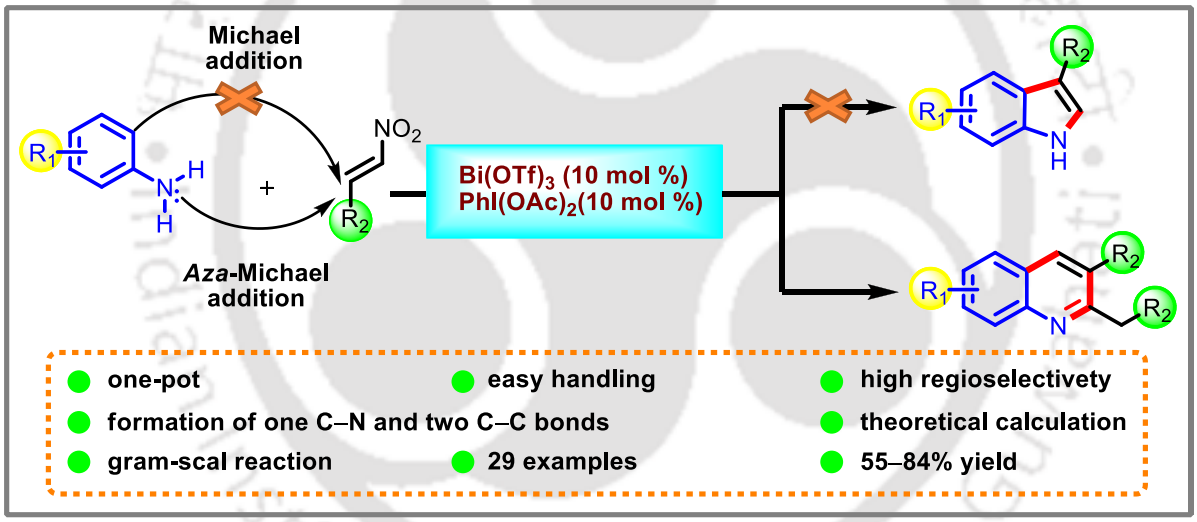
Fletcher, *J. Am. Chem. Soc*., 1948, **70**, 1012–1015; (d) O. Doebner, *Ann.*, 1887, 242–265; (e) A. Combes, *Bull. Chim. Soc. France*., 1888, **49**: 89; (f) L. S. Povarov, B. M. Izv. Mikhailov, *Akad. Nauk SSR, Ser. Khim*., 1963, 953–956.

8. P. Friedlander, *Chemische Berichte*, 1882, **15**, 2572–2575.
9. W. Pfitzinger, *J. Prakt. Chem.*, 1886, **33**, 100.
10. L. Knorr, *Ann*, 1886, **236**, 69.
11. Y. Watanabe, Y. Tsuji, Y. Ohsugi and J. Shida, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 2452–2457.
12. L. He, J. Q. Wang, Y. Gong, Y. M. Liu, Y. Cao, H. Y. He and K. N. Fan, *Angew. Chem. Int. Ed*., 2011, **50**, 10216 –10220.
13. M. H. So, Y. Liu, C. M. Ho, K. Y. Lam and C. M. Che, *ChemCatChem*., 2011, **3**, 386 – 393.
14. X. Jia, F. Peng, C. Qing, C. Huo, Y. Wang and X. Wang, *Tetrahedron Lett*., 2013, **54**, 4950–4952.
15. J. B. Bharate, S. B. Bharate and R. A. Vishwakarma, *ACS Comb. Sci*., 2014, **16**, 624–630.
16. J. Li, J. Zhang, H. Yang and G. Jiang, *J. Org. Chem*., 2017, **82**, 3284–3290.
17. C. M. M. Gómez, M. Marsiglia, R. Escarsena, E. del Olmo and V. V. Kouznetsov, *Tetrahedron Lett*., 2018, **59**, 22–25.
18. M. Beller, O. R. Thiel, H. Trauthwein and C. G. Hartung, *Chem. Eur. J*., 2000, ***6***, 2513–2521.
19. M. Zhang, T. Roisnel, and P. H. Dixneuf, *Adv. Synth. Catal*., 2010, **352**, 1896–1903.
20. M. Zhang, B. Xiong, W. Yang, D. N. T. Kumar and Y. Q. Din, *Monatsh Chem*., 2012, **143**, 471–478.
21. Y. Zhang, M. Wang, P. Li and L. Wang, *Org. Lett*., 2012, **14**, 2206–2209.
22. H. Sharghi, M. Aberi, M. Khataminejad and P. Shiri, *Beilstein J. Org. Chem.* 2017**, 13**, 1977–1981.
23. M. S. Al Mehndi and J. J. Tepe, *J. Org. Chem*., 2020, **85**, 6741−6746.
24. T. Juspin, T. Terme and P. Vanelle, *Synlett*, 2009, **9**, 1485–1489.
25. R. K. Saunthwal, M. Patel and A. K. Verma, *Org. Lett*., 2016, **18**, 2200–2203.
26. J. C. Xiang, Z. X. Wang, Y. Cheng, S. Q. Xia, M. Wang, B. C. Tang, Y. D. Wu and A. X. Wu, *J. Org. Chem*., 2017, **82**, 9210–9216.

27. G. R. Kumar, R. Kumar, M. Rajesha and M. S. Reddy, *Chem. Commun*., 2018, **54**, 759–762.
28. S. S. Jang, Y. H. Kim and S. W. Youn, *Org. Lett*.. 2020, **22**, 9151–9157.
29. A. N. Pearce, E. W. Chia, M. V. Berridge, G. R. Clark, J. L. Harper, L. Larsen, E. W. Maas, M. J. Page, N. B. Perry, V. L. Webb and B. R. Copp, *J. Nat. Prod*., 2007, **70**, 936–940.
30. N. P. Peet, L. E. Baugh, S. Sunder and J. E. Lewis, *J. Med. Chem*., 1985, **28**, 298–302.
31. D. Zewge, C. Y. Chen, C. Deer, P. G. Dormer and D. L. Hughes, *J. Org. Chem.* 2007, **72**, 4276–4279.
32. D. Ramanathan and K. Pitchumani, *Eur. J. Org. Chem*., 2015, 463–467.
33. X. Jia, F. Peng, C. Qing, C. Huo and X. Wang, *Org. Lett*., 2012, **14**, 4030–4033.
34. X. Yang, L. Li, Y. Li and Y. Zhang, *J. Org. Chem*., 2016, **81**, 12433–12442.
35. J. Wang, L. Li, Y. Guo, S. Li, S. Wang, Y. Li and Y. Zhang, *Org. Biomol. Chem*., 2020, **18**, 8179–8185.
36. J. Ni, Y. Jiang, Z. An and R. Yan, *Org. Lett*., 2018, **20**, 1534–1537.
37. S. P. Midya, K. M. Sahoo, V. Landge, P. R. Rajamohanan and E. Balaraman, *Nat. Commun*., 2015, **6**, 8591.
38. Q. Wang, J. Huang and L. Zhou, *Adv. Synth. Catal*., 2015, **357**, 2479–2484.
39. L. Yang and J. P. Wan, *Green Chem*., 2020, **22**, 3074–3078.
40. Y. Zhou, P. Zhao, L. S. Wang, X. X. Yu, C. Huang, Y. D. Wu and A. X. Wu, *Org. Lett.*, 2021, **23**, 6461–6465.
41. Y. Laras, V. Hugues, Y. Chandrasekaran, M. B. Desce, F. C. Acher and N. Pietrancosta, *J. Org. Chem*., 2012, **77**, 8294–8302.
42. W. Wu, Y. Guo, X. Xu, Z. Zhou, X. Zhang, B. Wu and W. Yi, *Org. Chem. Front*., 2018, **5**, 1713–1718.
43. Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem. Int. Ed*., 2013, **52**, 5323–5327.

Chapter II: Part A

Bismuth(III) Triflate Catalyzed Reaction of Aryl Amines with Nitroalkenes: A Regioselective Synthesis of 2,3-Dialkylquinolines

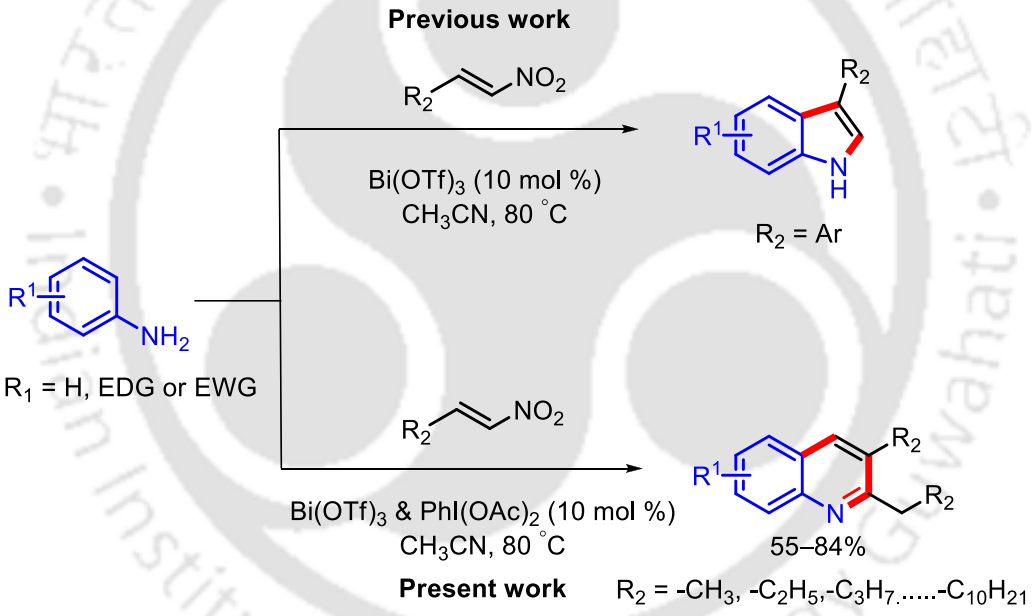


Result & Discussion

Experimental Section

Results and Discussion

The importance of 2,3-dialkylquinolines and methods for their synthesis have already been discussed in chapter I. This part of the chapter II describes regioselective synthesis of 2,3-dialkylquinoline derivatives involving domino reaction using different aryl amines and aliphatic nitroalkenes (Scheme **2.1)**. This particular transformation proceeds in the presence of 10 mol% bismuth(III) triflate as a catalyst and 10 mol% (diacetoxyiodo)benzene as an oxidant under mild conditions. In addition, it also presents theoretical studies using Gaussian 09 software [B3LYP/6-311+G(d,p)] to establish mechanistic pathways, which suggests that aryl amines react with aliphatic nitroalkenes preferably *via* conventional *aza*-Michael fashion over Michael addition. Notable advantages of this work are operational simplicity, high regioselectivity, mild conditions, formation of one C-N and two C-C bonds and a broad substrate scope with high yields.

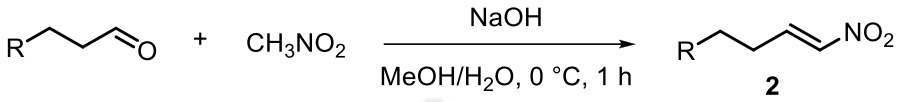


Scheme 2.1. Reactions between anilines and nitroalkenes in previous and present studies.

Recently, Khan and co-workers[1] reported a simple and an efficient route towards synthesis of 3-arylindole derivatives which involves reactions of anilines/N-alkyl anilines with aryl nitroalkenes in the presence of 10 mol% bismuth(III) triflate at 80 °C (Scheme **2.1**). In this reaction, aryl amine reacts with aryl nitroalkene through Michael addition (C–C bond formation) to give 3-arylindole. From this observation, it was assumed that reaction of aryl amine with aliphatic nitroalkene under same reaction conditions might provide 3-alkylindole. Surprisingly, it resulted in formation of 2,3-dialkylquinoline. Encouraged by this result, efforts

were made for synthesis of variety of 2,3-dialkylquinolines and finding reason of reversal of reactivity of aryl amines with aliphatic nitroalkenes.

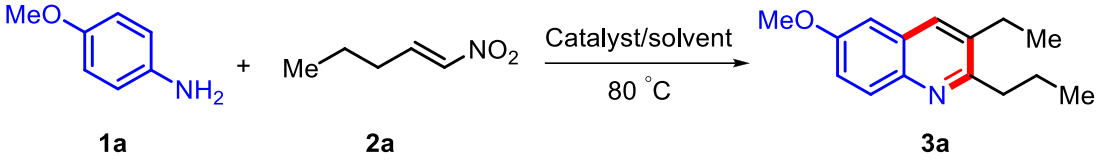
For this study, various aliphatic nitroalkenes **2** were prepared from reaction between suitable aliphatic aldehydes and nitromethane in the presence of sodium hydroxide at 0 °C as shown in Scheme **2.2**.[2]



Scheme 2.2. Preparation of variety of aliphatic nitroalkenes **2**.

This study was started with finding optimization reaction conditions. For this purpose, *p*-anisidine **1a** and (*E*)-1-nitropent-1-ene **2a** were chosen as model substrates and results are summarized in Table 2.1. At first, model reaction was carried out in acetonitrile solvent without any catalyst at room temperature, and subsequently it was heated in a pre-heated oil-bath at 80 °C. No reaction took place in both cases and only starting materials were recovered (Table 2.1, entries 1 and 2). Then, a similar reaction was performed in the presence of 5 mol% $Bi(OTf)_3$ at room temperature, it also did not proceed (Table 2.1, entry 3). However, when same reaction mixture was heated in a pre-heated oil-bath at 80 °C, reaction proceeded slowly, as monitored by TLC. After usual work-up and chromatographic purification, product was isolated in 51% yield as dark brown liquid (Table 2.1, entry 4). Isolated product was expected to be 3-propylindole which must show a characteristic peak at 6.97 ppm as a singlet in the ^{1}H NMR spectra due to presence of H-2.[3] Instead of that, a peak appeared at δ 7.76 as a singlet which is a characteristic of H-4 of quinoline. This downfield shift clearly indicates that peak of H-2 was disappeared. In addition, other peaks were also emerged at 7.01 as a doublet for H-5, 7.26 as a doublet of the doublet for H-7, 7.90 as a doublet for H-8, and 3.90 ppm for one -OMe. Three peaks corresponding to CH_2 were appeared at 2.91 as a triplet, 2.81 as a quartet, and 1.81 as a sextet and two triplets at δ 1.06 and 1.33 ppm for two methyl groups. Two triplets for two methyl groups can be evidence of fact that 2.0 mmol of (*E*)-1-nitropent-1-ene **2a** were being utilized in reaction. From above observation, product was characterized as 3-ethyl-6-methoxy-2-propylquinoline **3a** instead of 3-proylindole. Chemical shift value of protons is also matched with those of earlier reported compound.[4]

Table 2.1. Optimization of reaction conditions for synthesis of 3-ethyl-6-methoxy-2-propylquinoline **3a**.[a,b,c]



1a **2a** **3a**

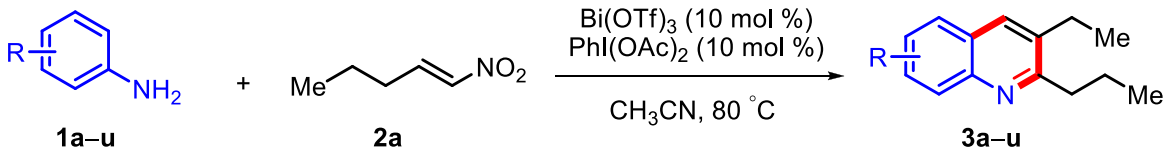
Entry	Catalyst	mol %	$PhI(OAc)_2$ mol %	Solvent	Time	Yield **3a**(%)[b]
1[c]	-	-	-	CH_3CN	24 h	NR
2	-	-	-	CH_3CN	24 h	NR
3[c]	$Bi(OTf)_3$	05	-	CH_3CN	24 h	NR
4	$Bi(OTf)_3$	05	-	CH_3CN	15 h	51
5	$Bi(OTf)_3$	10	-	CH_3CN	10 h	70
6	$Bi(OTf)_3$	20	-	CH_3CN	10 h	68
7	$Sc(OTf)_3$	10	-	CH_3CN	16 h	44
8	$Yb(OTf)_3$	10	-	CH_3CN	18 h	52
9	$Cu(OTf)_2$	10	-	CH_3CN	18 h	Trace
10	AgOTf	10	-	CH_3CN	12 h	55
11	$Cu(OAc)_2$	10	-	CH_3CN	24 h	Trace
12	$FeCl_3$	10	-	CH_3CN	24 h	NR
13	**$Bi(OTf)_3$**	**10**	**10**	**CH_3CN**	**10 h**	**84**
14	$Bi(OTf)_3$	10	10	DMF	24 h	NR
15[d]	$Bi(OTf)_3$	10	10	DCE	24 h	55
16[d]	$Bi(OTf)_3$	10	10	DCM	24 h	NR
17	$Bi(OTf)_3$	10	10	Toluene	24 h	NR
18[d]	$Bi(OTf)_3$	10	10	THF	24 h	NR
19	$Bi(OTf)_3$	10	10	DMSO	24 h	NR
20	$Bi(OTf)_3$	10	10	H_2O	24 h	NR
21	$Bi(OTf)_3$	10	10	MeOH	24 h	NR
22	$Bi(OTf)_3$	10	10	EtOH	24 h	NR

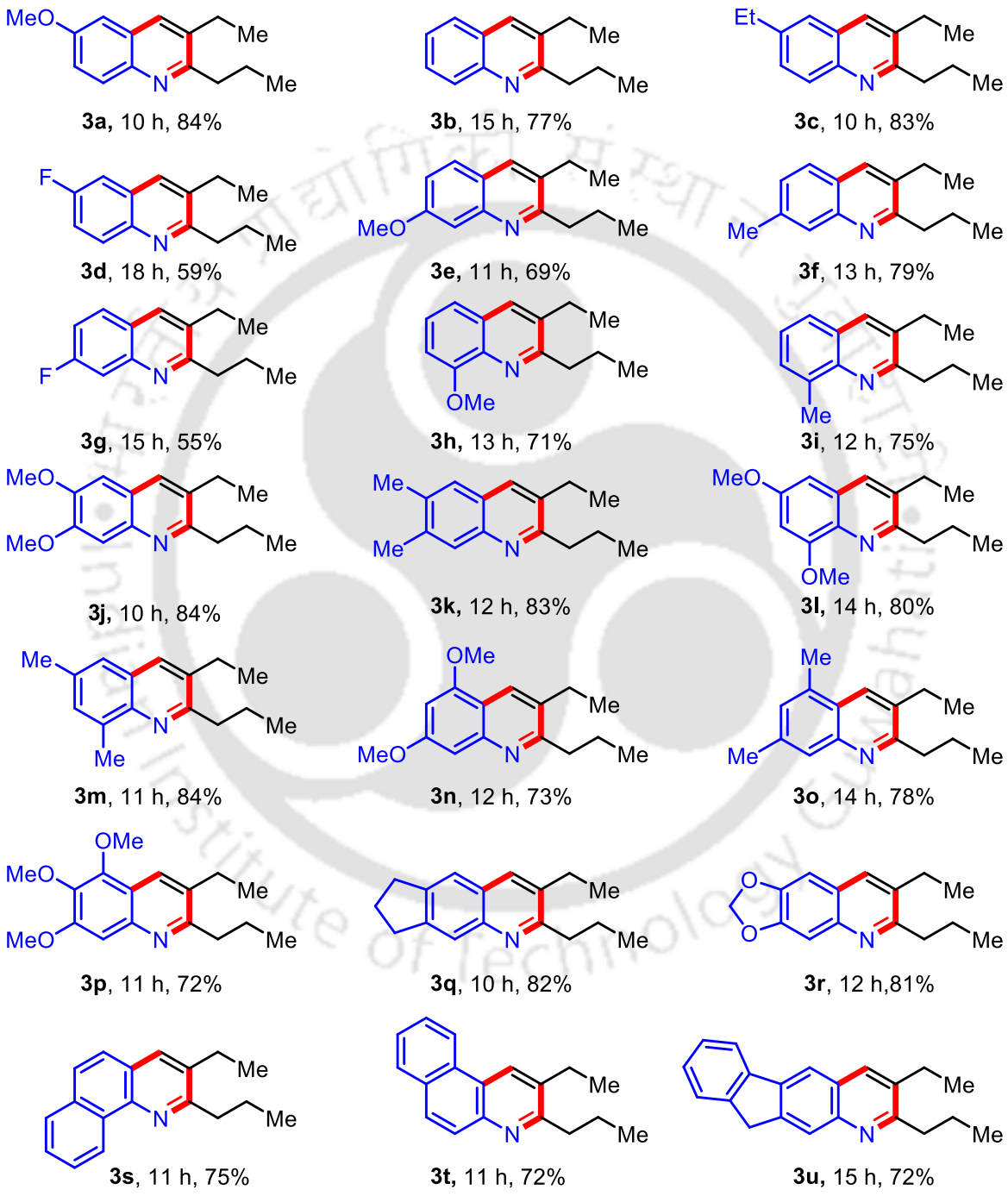
[a]All reactions were carried out using *p*-anisidine **1a** (1.0 mmol) and (*E*)-1-nitropent-1-ene **2a** (2.0 mmol) at 80 °C. [b]Isolated yield. [c]Reactions were carried at out at room temperature. [d]Reactions performed under reflux conditions. NR (no reaction).

To improve the yield of product **3a**, reaction was executed in the presence of 10 mol% $Bi(OTf)_3$; reaction proceeded faster, and yield of product **3a** also increased from 51% to 70% (Table 2.1, entry 5). When reaction was run in the presence of 20 mol% $Bi(OTf)_3$, yield of **3a** did not improve further (Table 2.1, entry 6). To check the efficacy of other catalysts, reactions were examined in presence of various other metal triflates and metal salts. It was observed that $Sc(OTf)_3$, $Yb(OTf)_3$ and $Cu(OTf)_2$, and AgOTf were found to be less effective than $Bi(OTf)_3$ (Table 2.1, entries 7–10). Reaction was also examined in the presence of 10 mol% $Cu(OAc)_2$ and 10 mol% $FeCl_3$, which provided only a trace amount of desired product (Table 2.1, entries 11 and 12). Notably, yield increased from 70% to 84% when a reaction was carried out using a combination of 10 mol% $Bi(OTf)_3$ and 10 mol% $PhI(OAc)_2$ (Table 2.1, entry 13). To verify solvent suitability, same set of reactions was screened using different solvents (Table 2.1, entries 14–22) using 10 mol% $Bi(OTf)_3$ as a catalyst. It was noted that best yield was obtained in acetonitrile (Table 2.1, entry 13). From extensive optimization of reaction conditions, it was concluded that best reaction conditions for formation of product **3a** were use of 10 mol% $Bi(OTf)_3$ and 10 mol% $PhI(OAc)_2$, acetonitrile as a solvent and 80 °C temperature in terms of both time and yield.

Having optimized reaction conditions in hands, scope and generality of this protocol were investigated with different aryl amines **1a–u** containing electron-donating as well as electron-withdrawing groups and (*E*)-1-nitropent-1-ene **2a** as presented in Table 2.2. Reaction of simple aniline **1b** with **2a** provided 3-ethyl-2-propylquinoline **3b** in 77% yield. Similarly, substituted aniline containing an electron-donating group (4-Et) and an electron-withdrawing group (4-F) also gave desired quinolines **3c** and **3d** in 83% and 59% yield, respectively. Likewise, 3-substituted anilines (3-OMe, 3-Me and 3-F) also worked well under standard conditions and furnished expected quinoline scaffolds **3e–g** in 55–79% yield. Substituents (2-OMe and 2-Me) located at 2-position of anilines were well tolerated and gave anticipated quinoline frameworks **3h** and **3i** in 71% and 75% yield, respectively. Reactions of disubstituted anilines containing electron-donating groups (3,4-OMe, 3,4-Me, 2,4-OMe, 2,4-Me, 3,5-OMe and 3,5-Me) also proceeded smoothly to provide corresponding quinolines **3j–o** in 73–84% yield. Fortunately, sterically crowded 3,4,5-OMe aniline also gave expected quinoline **3p** in 72% yield. Delightfully, 5-aminoindane **1q**, 3,4-(methylenedioxy)-aniline **1r**, 1-naphthylamine **1s**, 2-naphthylamine **1t** and 2-aminofluorene **1u** upon reaction with **2a** afforded anticipated quinoline derivatives **3q–u** in 72–82% yield.

Table 2.2. Reactions of different arylamines **1a–u** with (*E*)-1-nitropent1-ene **2a**[a,b]



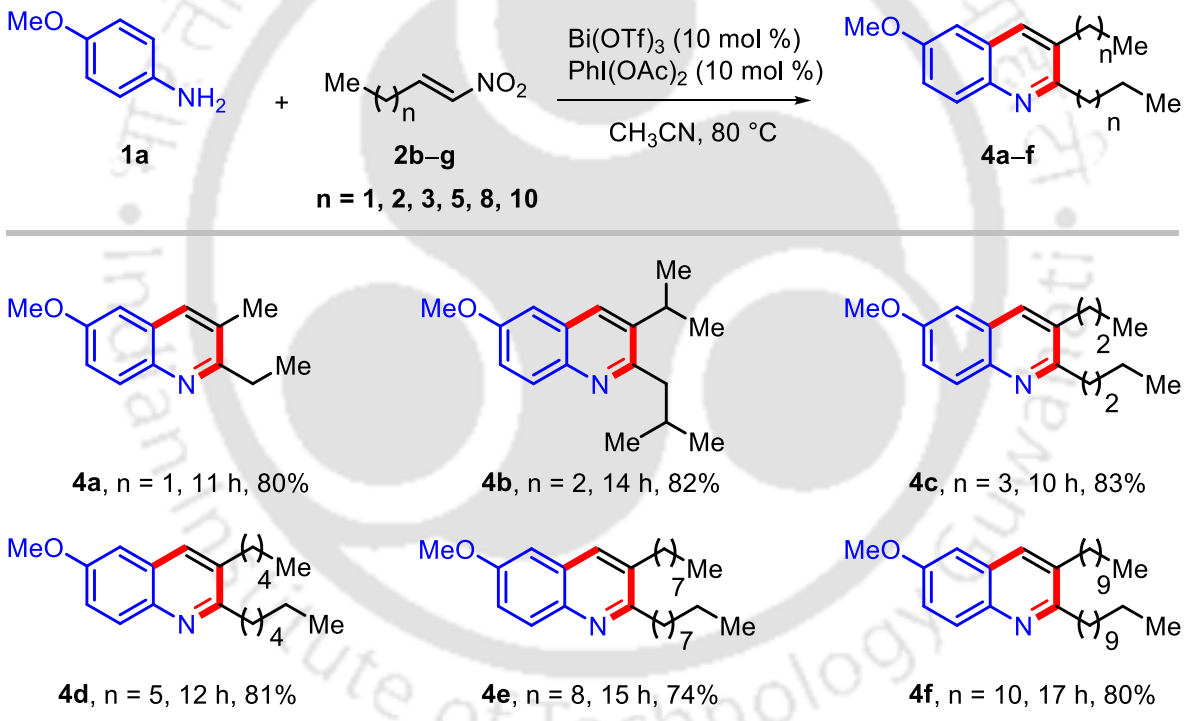


[a]All reactions were carried out using arylamines **1a–u** (1.0 mmol) and (*E*)-1-nitropent-1-ene **2a** (2.0 mmol) in CH_3CN (2.0 mL) at 80 °C. [b]Isolated yield.

Unfortunately, reaction was unsuccessful with 4-substituted anilines containing electron-withdrawing substituents (-Cl, -Br and -NO_2). This can be attributed to participation of lone pair of electrons on nitrogen in conjugation with electron withdrawing groups attached to aniline and $-I$ effect. As a consequence, lone pair on nitrogen may not available for attack.

Inspired by above-discussed successful results, scope and generality of present protocol were further explored using *p*-anisidine **1a** with different aliphatic nitroalkenes **2b–g** and results are presented in Table 2.3. Reaction between *p*-anisidine **1a** and (*E*)-1-nitrobut-1-ene **2b** proceeded well under optimized conditions to give expected product **4a** in 80% yield. Similarly, reactions with branched (*E*)-4-methyl-1-nitropent-1-ene **2c** and (*E*)-1- nitrohex-1-ene **2d** provided desired products **4b** and **4c** in 82% and 83% yield, respectively.

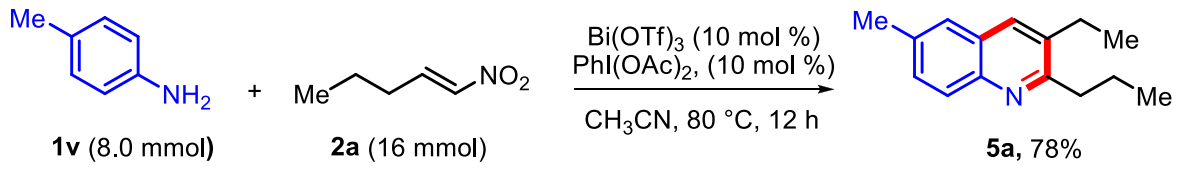
Table 2.3. Reactions of *p*-anisidine **1a** with different (*E*)-nitroalkenes **2b–g**.[a,b]



[a]All reactions were carried out using *p*-ainsidine **1a** (1.0 mmol) and nitroalkenes **2b–g** (2.0 mmol) in CH_3CN (2.0 mL) at 80 °C. [b]Isolated yield.

Efficacy of this method was also examined with elongated alkyl chain nitroalkenes, such as (*E*)-1-nitrooct-1-ene **2e**, (*E*)-1-nitroundec-1-ene **2f** and (*E*)-1-nitrotridec-1-ene **2g**. Reactions occurred smoothly to provide desired quinoline frameworks **4d–f** in 74–81% yield. It is noteworthy that large alkyl groups can be installed at C-2 and C-3 positions of quinoline scaffolds by this method.

To check the efficiency of present approach, a scale-up reaction was performed using *p*-toluidine **1v** and (*E*)-1-nitropent-1-ene **2a** under standard reaction conditions. It was observed that reaction occurred smoothly to provide corresponding quinoline analogue **5a** in 78% yield, as shown in Scheme **2.1c**.



Scheme 2.3. Scale-up reaction.

Structure of all synthesized compounds was elucidated by IR, ^{1}H NMR, ^{13}C NMR and HRMS. In addition, structure of compound **3k** was also confirmed by single X-ray crystallographic data. ORTEP diagram of compound **3k** with 40% probability (CCDC No. 1859531) is shown in Figure **2.1**. The ^{1}H, ^{13}C and HRMS spectra of compounds **3a**, **3b** and **3c** are shown in figure **2.5a**, **2.5b**, **2.5c**, **2.6a**, **2.6b**, **2.6c**, **2.7a**, **2.7b** and **2.7c**, respectively in experimental section.

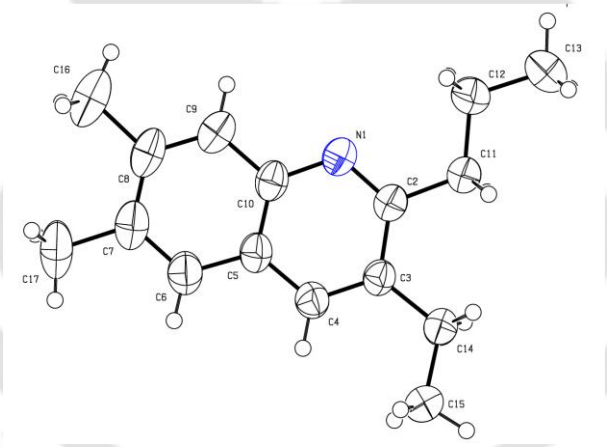
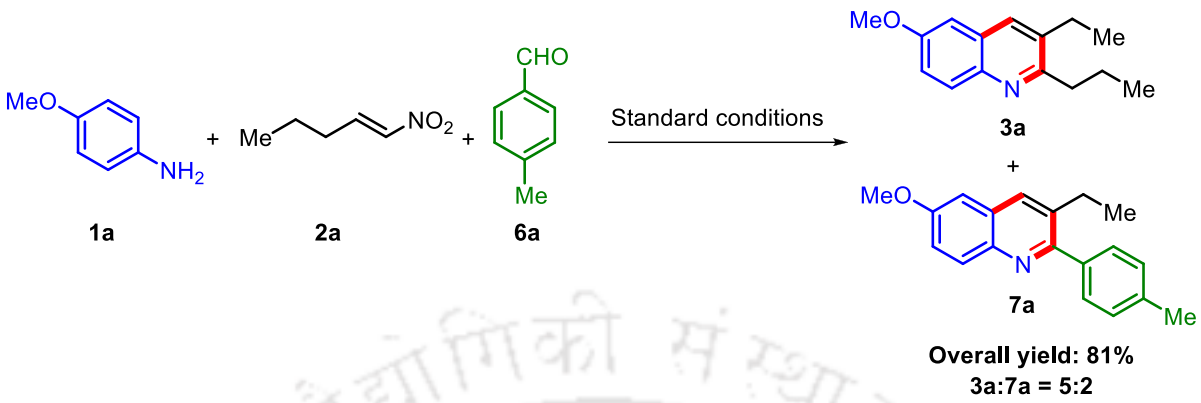


Figure 2.1. ORTEP diagram of compound **3k** with 40% probability.

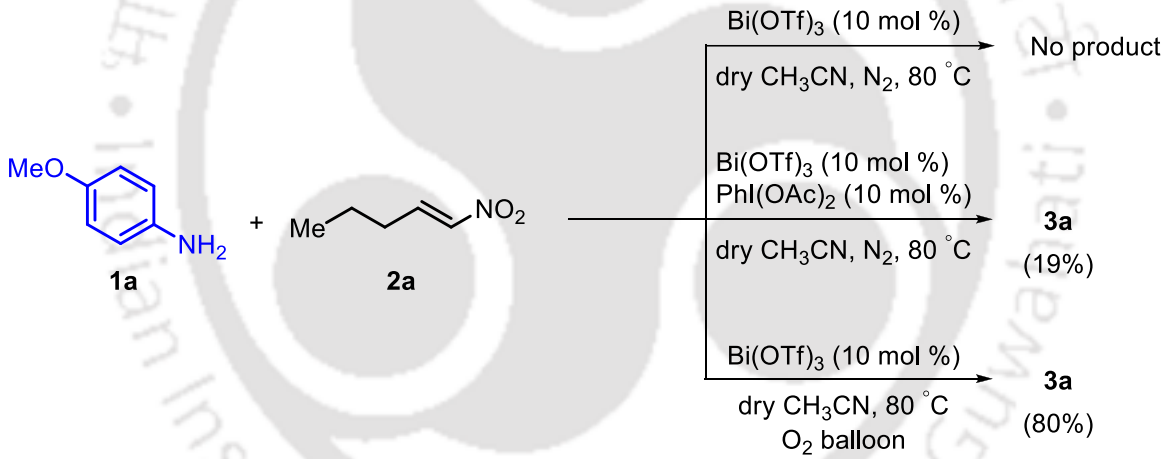
To extend the scope and generality of this method further, an attempt was made to install an aryl group at C-2 position of quinoline moiety. It was assumed that 3-ethyl-6-methoxy-2-*p*-tolylquinoline **7a** could be obtained through trapping activated imine (derived from *in-situ* reaction of *p*-anisidine **1a** and *p*-tolualdehyde **6a**) by *in-situ* generated enamine (generated from reaction of *p*-anisidine **1a** and (*E*)-1-nitropent-1-ene **2a**). When reaction was performed with *p*-anisidine **1a**, (*E*)-1-nitropent-1-ene **2a** and *p*-tolualdehyde **6a** under identical reaction conditions, a mixture of products **3a** and **7a** (5:2) was obtained (Scheme **2.4**). From this observation, it is clear that when nitroalkenes and arylamines are used, formation of 2,3-

dialkylquinoline is preferred over 3-alkyl-2-arylquinoline, which may be due to the slow rate of formation of Schiff base using *p*-anisidine **1a** and *p*-tolualdehyde **6a**.[5]



Scheme 2.4. Reaction of *p*-anisidine **1a**, (*E*)-1-nitropent-1-ene **2a** and *p*-tolualdehyde **6a**.

To examine the role of $PhI(OAc)_2$ as an oxidant in reaction, following control experiments were carried out as shown in Scheme **2.5**.

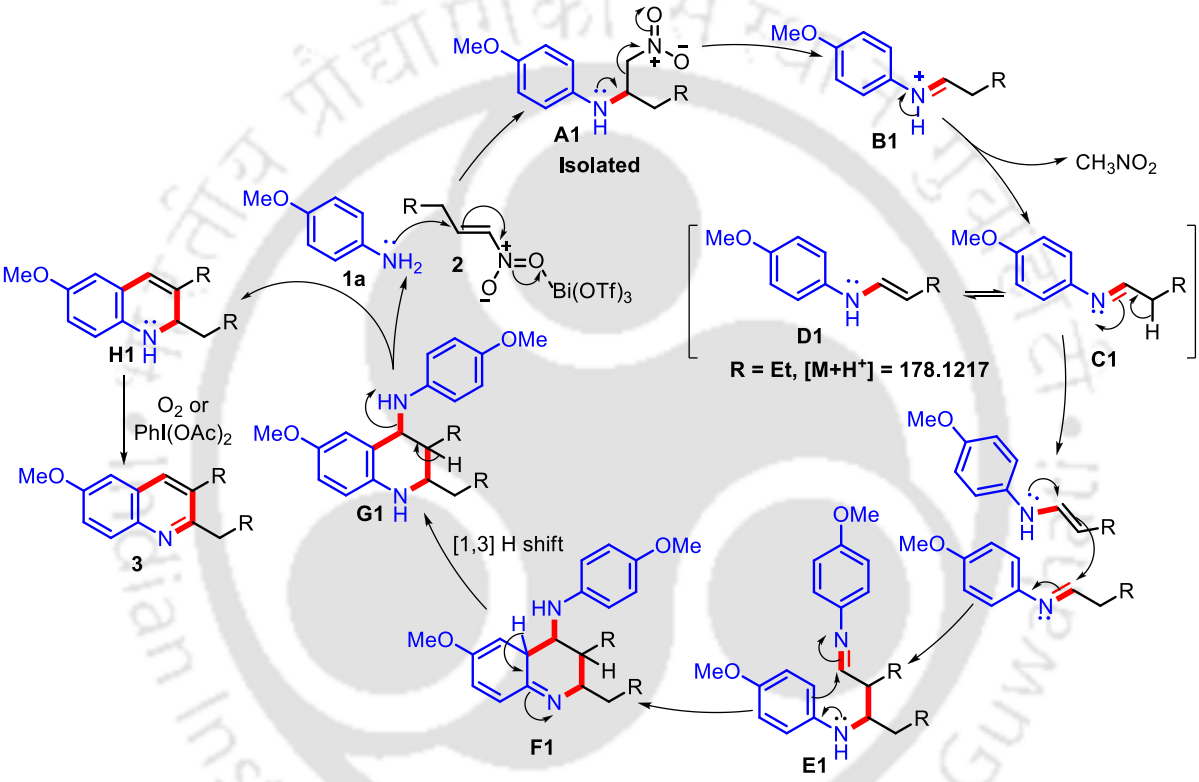


Scheme 2.5. Control experiment.

Reaction did not occur in the presence of 10 mol% $Bi(OTf)_3$ under an inert atmosphere. Desired product **3a** was obtained in 19% yield when reaction was carried out in the presence of 10 mol% $Bi(OTf)_3$ and 10 mol% $PhI(OAc)_2$ under an inert atmosphere. Same reaction underwent well in the presence of 10 mol% $Bi(OTf)_3$ under an oxygen atmosphere, it proceeded well and provided product **3a** in 80% yield. Based on control experiments, it can been seen that intermediate **H1** might be oxidized by either $PhI(OAc)_2$ or oxygen.

Based on control experiments, a plausible mechanism for formation of product **3** is depicted in Scheme **2.6**. Initially, *p*-anisidine **1a** reacts with nitroalkene **2** *via aza*-Michael fashion to form an *aza*-Michael adduct **A1** which upon elimination of nitromethane generates an imine

intermediate **C1**, which can tautomerize to corresponding enamine **D1**. Then, generated imine **C1** and enamine **D1** react together to give intermediate **E1** which subsequently undergoes intramolecular cyclization followed [1,3] H shift to give the intermediate **G1**. Elimination of *p*-anisidine **1a** to provide **H1**. Finally, oxidation of intermediate **H1** by either $PhI(OAc)_2$[6a] or atmospheric oxygen gave desired product **3**. It is worth mentioning that *aza*-Michael adduct **A1** was isolated and characterized by IR, ^1H, ^{13}C NMR and HRMS which suggested formation of imine **C1** and enamine **D1**. In addition, imine **C1** and enamine **D1** were also detected by HRMS.



Scheme 2.6. A plausible mechanism for formation of product **3**.

To rationalize selective C–N bond formation in comparison to possible C–C bond formation in initial step of reaction pathway, density functional theory (DFT) calculations were performed using model systems of aniline **1A** and (*E*)-nitrobut-1-ene **2**. Very first step of pathway is formation of complex **2A** between substrate **2** and Lewis acid by releasing 1.3 kcal mol^{-1} of energy. Positive charge at β carbon of **2** increases after complexation with $Bi(OTf)_3$, resulting in an increase in electrophilic character of *β* carbon (Figure **2.2**).

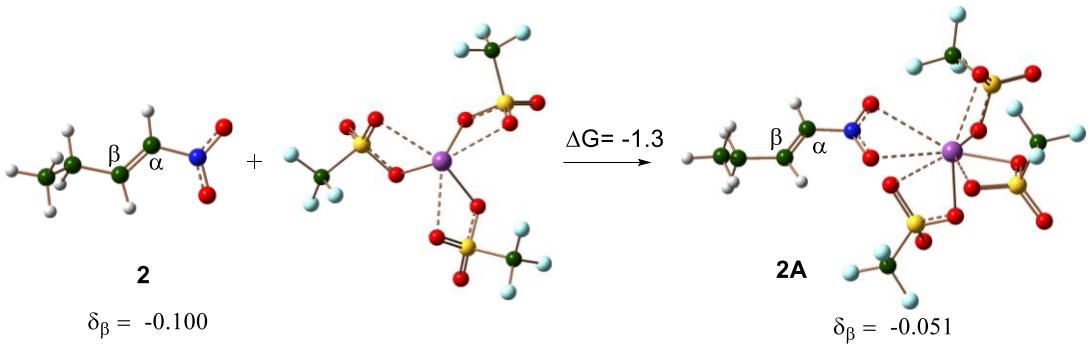


Figure 2.2. Energetics of formation of substrate–Lewis acid complex **2A**. Energy is given in kcal mol^{-1}; δ_β represents partial negative charge on C-2 carbon.

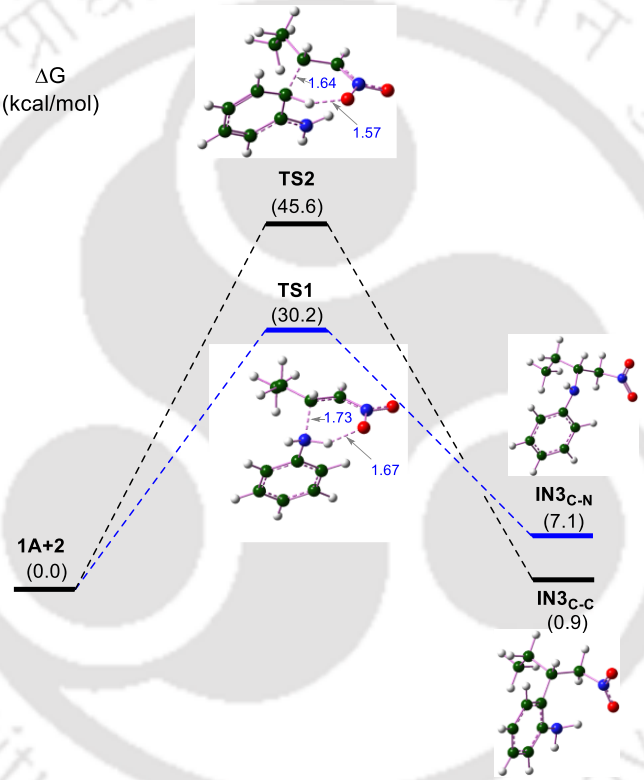


Figure 2.3. Potential energy diagram for formation of intermediate **IN3$_{C–N}$** *via* C–N bond formation and **IN3$_{C–C}$** *via* C–C bond formation without Bi(OTf)$_3$.

In absence of Bi(OTf)$_3$, formation of C–C bond and C–N bond requires activation energies of 45.6 kcal mol^{-1} and 30.2 kcal mol^{-1} , respectively (Figure **2.3**).

Next, potential energy diagram shown in Figure **2.4** begins with reaction of complex **2A** with aniline **1A**. This step will lead to formation of Michael addition intermediate **IN1$_{C–C}$** *via* C–C bond formation or *aza*-Michael addition intermediate **IN1$_{C–N}$** *via* C–N bond formation.

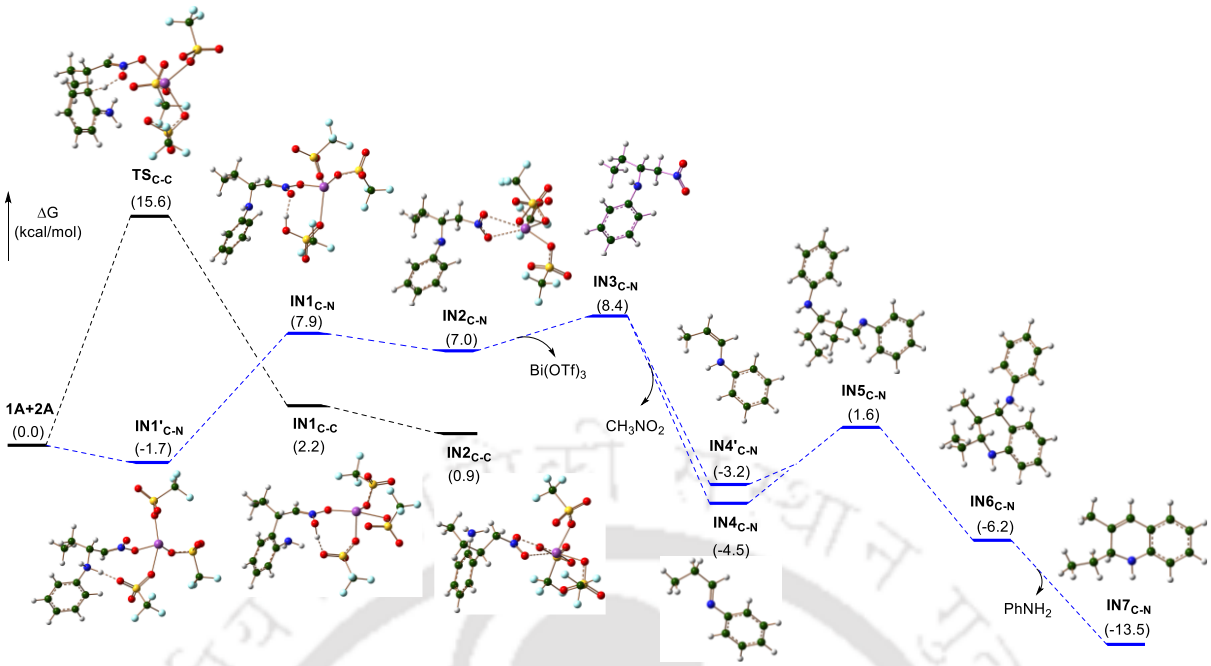


Figure 2.4. Potential energy diagram for formation of intermediate **IN4** in *aza*-Michael addition reaction pathway. Step one is comparison of energy profiles for Michael addition reaction *via* C–C bond formation (black curve) and *aza*-Michael addition *via* C–N bond formation (blue curve). (The energies are Gibbs free energy in kcal mol^{-1}; bond distances are given in Å.

After inclusion of Bi(OTf)$_3$ in reaction, activation energy was reduced by approximately 30 kcal mol^{-1} and formation of **IN1**$_{C-C}$ required an activation energy of 15.6 kcal mol^{-1}. **IN1**$_{C-N}$ is formed through another stable intermediate **IN1′**$_{C-N}$, with an exothermicity of 1.7 kcal mol^{-1}. Transition state for formation of **IN1**$_{C-N}$ could not be traced and optimization ended with formation of stable intermediate **IN1′**$_{C-N}$ thus, indicating that C–N bond formation is a spontaneous process. Therefore, *aza*-Michael addition more preferred than Michael addition under these reaction conditions. Proton shift from nitrogen to oxygen of OTf to form **IN1**$_{C-N}$ requires 9.6 kcal mol^{-1} of energy. However, this intermediate is thermodynamically less stable than **IN1**$_{C-C}$ by 5.7 kcal mol^{-1}. Subsequent formation of **IN2**$_{C-N}$ takes place by proton transfer from triflic acid to α carbon, which is exothermic by only 0.9 kcal mol^{-1}. This suggests that formation of *aza*-Michael product is assisted by triflic acid, which plays a crucial role in proton transfer from amine nitrogen to α carbon. Release of Bi(OTf)$_3$ requires 1.4 kcal mol^{-1} of energy to form **IN3**$_{C-N}$, which is transformed into **IN4**$_{C-N}$ by release of nitromethane (CH_3NO_2) as a side product and 12.9 kcal mol^{-1} of energy. **IN4**$_{C-N}$ may exists as its tautomer **IN4′**$_{C-N}$, which is less stable by only 1.3 kcal mol^{-1} and is formed *via* a bimolecular C–N 1,3-prototropic shift.

Next, **IN4$_{C–N}$** and **IN4′$_{C–N}$** form an unstable intermediate **IN5$_{C–N}$**, which produces the 4 + 2 cycloaddition product **IN6$_{C–N}$** after aromatization, releasing 7.8 kcal mol−1 of energy. Finally, aniline is eliminated to form a more stable intermediate **IN7$_{C–N}$** (7.3 kcal mol−1 exothermic). **IN7$_{C–N}$** is then oxidized to form final product. It is noteworthy that imine to enamine tautomerism can only take place in the case of aliphatic nitroalkenes where CH_2 protons are available at γ position. In case of aromatic nitroalkenes, imine to enamine tautomerism is not possible due to absence of γ protons.

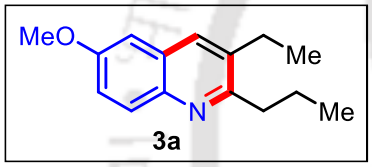
In conclusion, aryl amines prefer *aza*-Michael addition reaction pathway with aliphatic nitroalkenes rather than expected Michael addition has been proved by theoretical studies. An alternate method has been devised for synthesis of 2,3-dialkylquinoline derivatives. In this particular transformation, 10 mol% $Bi(OTf)_3$ as a catalyst and 10 mol% PhI $(OAc)_2$ as an oxidant have been used under mild reaction conditions. A similar conversion is also feasible using molecular oxygen in a balloon without using 10 mol% $PhI(OAc)_2$. Notable features of this protocol are use of readily accessible aryl amines and aliphatic nitroalkenes, a change in reaction pathway and usage of inexpensive metal catalyst, high regioselectivity, one C–N and two C–C bonds formation and a broad substrate scope with good yield.

Experimental Section

General Procedure for Synthesis 2, 3-Disubstituted Quinolines 3 and 4

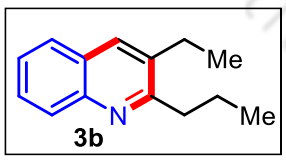
A mixture of *p*-anisidine **1** (1.0 mmol) and nitroalkene **2** (2.0 mmol) was taken in acetonitrile (2 mL) into a 10 mL round-bottomed flask. Then, $Bi(OTf)_3$ (0.1 mmol %, 65 mg) and $PhI(OAc)_2$ (0.1 mmol, 32 mg) were added into the above reaction mixture and it was kept for stirring at 80 °C in a pre-heated oil-bath under air atmosphere. After completion of reaction as monitored by TLC, the reaction flask was brought to room temperature and then it was extracted with EtOAc (2 x 10 mL). The organic layer was washed with water (2 x 10 mL) followed by with 5 mL of brine solution and dried over anhydrous sodium sulphate. Finally, the solvent was removed in a rotatory evaporator and the crude residue was purified using silica gel (60–120 mesh) column chromatography to obtain desired product **3** and **4**.

3-Ethyl-6-methoxy-2-propylquinoline (3a):[6b] (193 mg, 84%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 7.91 (1H, d, *J* = 9.2 Hz, H-8), 7.76 (1H, s, H-4), 7.26 (1H, dd, J_1= 8 Hz, J_2 = 4 Hz, H-7), 7.01 (1H, d, *J* = 2.8 Hz, H-5), 3.90 (3H, s, OCH_3), 2.92 (2H, t, *J* = 8 Hz, CH_2), 2.81 (2H, q, *J* = 7.5 Hz, CH_2), 1.81 (2H, sext, *J* = 7.4 Hz, CH_2), 1.33 (3H, t, *J* = 7.5 Hz, CH_3), 1.06 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 157.4, 142.6, 135.8, 133.2, 130.0, 128.4, 121.0, 104.9, 55.7, 37.7, 25.4, 23.2, 14.7, 14.5; **IR (KBr)ν_{max}** 2961(C–H), 1623 (C=C),1224 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}NO$ 230.1545 ($M + H^+$); Found 230.1560.



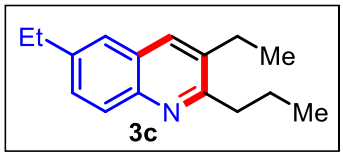
3a

3-Ethyl-2-propylquinoline (3b):[6b] (153 mg, 77%, brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (1H, d, *J* = 8.4 Hz, H-8), 7.83 (1H s, H-4), 7.70 (1H, d, *J* = 8.0 Hz, H-5), 7.58 (1H, t, *J* = 7.4 Hz, H-7), 7.41 (1H, t, *J* = 7.4 Hz, H-6), 2.93 (2H, t, *J* = 7.3 Hz, CH_2), 2.81 (2H, q, *J* = 7.5 Hz, CH_2), 1.80 (2H, sext, *J* = 7.5 Hz, CH_2), 1.31 (3H, t, *J* = 7.5 Hz, CH_3), 1.04 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.2, 146.5, 135.5, 134.1, 128.6, 128.5, 127.5, 127.1, 125.7, 38.0, 25.3, 23.1, 14.6, 14.6; **IR (KBr)ν_{max}** 2978 (C–H), 1630 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{18}N$ 200.1439 ($M + H^+$); Found 200.1472.



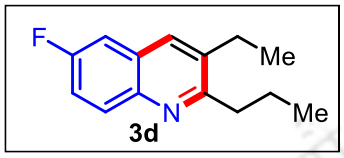
3b

3,6-Diethyl-2-propylquinoline (3c): (188 mg, 83%, brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.6 Hz, H-8), 7.78 (1H, s, H-4), 7.47 (1H, d, *J* = 1.9 Hz H-5), 7.45 (1H, dd, *J* = 8.6, 1.9 Hz, H-7), 2.91 (2H, t, *J* = 7.4 Hz, CH_2), 2.78 (4H,dq, *J*



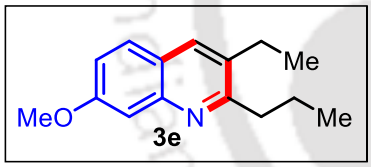
= 12.0, 7.5 Hz, $2CH_2$), 1.78 (2H, dq, *J* = 15.1, 7.4 Hz, CH_2), 1.29 (6H, m, $2CH_3$), 1.03 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.3, 145.2, 141.8, 135.5, 133.8, 129.8, 128.3, 127.6, 124.7, 37.9, 29.0, 25.4, 23.2, 15.7, 14.6, 14.5; **IR (KBr)ν_{max}** 2963 (C–H), ,1634 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}N$ 228.1752 ($M + H^+$); Found 228.1765.

3-Ethyl-6-fluoro-2-propylquinoline (3d): (128 mg, 59%, brown liquid); **^{1}H NMR**



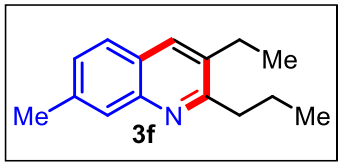
(600 MHz, $CDCl_3$) δ 7.99 (1H, dd, *J* = 9.1, 5.3 Hz, H-8), 7.80 (1H, s, H-4), 7.37 (1H, dd, *J* = 8.8, 2.8 Hz, H-5), 7.34 (1H, dd, *J* = 9.0, 2.8 Hz, H-7), 2.94 (2H, t, *J* = 7.5 Hz, CH_2), 2.83 (2H, q, *J* = 7.5 Hz, CH_2), 1.82 (2H, sext, 7.4 Hz, CH_2), 1.34 (3H, t, *J* = 7.5 Hz, CH_3), 1.07 (3H, t, *J* = 7.4 Hz, CH_3); **^{19}F NMR** (377 MHz $CDCl_3$) δ -115.34 (1F, s, F-6); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.5, 161.5, 161.0, 159.3, 143.6, 136.4, 133.4, 133.4, 131.0, 130.9, 128.0, 127.9, 118.6, 118.4, 110.1, 109.9, 37.8, 25.3, 23.0, 14.6, 14.5; **IR (KBr)ν_{max}** 2963 (C–H), 1628 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{17}FN$ 218.1345 ($M + H^+$); Found 218.1370.

3-Ethyl-7-methoxy-2-propylquinoline (3e): (158 mg, 69%, dark brown liquid); **^{1}H NMR**



(600 MHz, $CDCl_3$) δ 7.76 (1H, s, H-4), 7.58 (1H, d, *J* = 8.9 Hz, H-5), 7.33 (1H, d, *J* = 2.4 Hz, H-8), 7.07 (1H, dd, *J* = 8.9, 2.5 Hz, H-6), 3.90 (3H, s, OCH_3), 2.91 (2H, t, *J* = 7.5 Hz, CH_2), 2.77 (2H, q, *J* = 7.5 Hz, CH_2), 1.78 (2H, sext, *J* = 7.5 Hz, CH_2), 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 1.03 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.4, 160.1, 148.0, 134.1, 133.2, 128.1, 122.7, 118.8, 106.6, 55.7, 38.0, 25.2, 23.4, 14.8, 14.6; **IR (KBr)ν_{max}** 2957 (C–H), 1621 (C=C), 1215 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}NO$ 230.1545 ($M + H^+$); Found 230.1565.

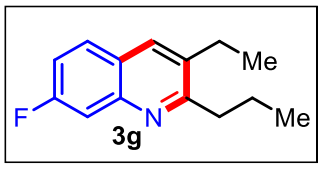
3-Ethyl-7-methyl-2-propylquinoline (3f): (168 mg, 79%, brown liquid); **^{1}H NMR**



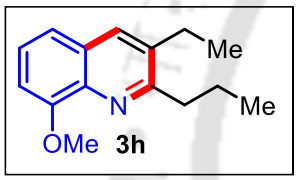
(600 MHz, $CDCl_3$) δ 7.78 (1H, s, H-4), 7.77 (1H, s, H-8), 7.59 (1H, d, *J* = 8.2 Hz, H-5), 7.25 (1H, dd, *J* = 8.2, 1.4 Hz, H-6), 2.91 (2H, t, *J* = 7.5 Hz, CH_2), 2.79 (2H, q, *J* = 7.5 Hz, CH_2), 2.50 (3H, s, 7-CH_3), 1.78 (2H, sext, *J* = 7.5 Hz, CH_2), 1.30 (3H, t, *J* = 7.5 Hz, CH_3), 1.03 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.1, 146.7, 138.6, 134.6, 133.9, 127.9, 127.6, 126.7, 125.5, 37.9, 25.3, 23.1,

22.0, 14.7, 14.6; IR (KBr) ν_{max}/cm^{-1} 2958 (C-H), 1623 (C=C), 1226 (C-O); HRMS (ESI) Calcd For $C_{15}H_{20}N$ 214.1596 ($M + H^+$); Found 214.1613.

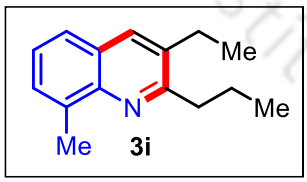
3-Ethyl-7-fluoro-2-propylquinoline (3g): (119 mg, 55%, brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 (1H, s, H-4), 7.68 (1H, dd, *J* = 8.9, 6.1 Hz, H-5), 7.61 (1H, dd, *J* = 10.4, 2.4 Hz, H-8), 7.20 (1H, td, *J* = 8.6, 2.5 Hz, H-6), 2.91 (2H, t, *J* = 7.5 Hz, CH_2), 2.79 (2H, q, *J* = 7.5 Hz, CH_2), 1.78 (2H, sext, *J* = 7.5 Hz, CH_2), 1.30 (3H, t, *J* = 7.5 Hz, CH_3), 1.03 (3H, t, *J* = 7.3 Hz, CH_3); **^{19}F NMR** (377 MHz; $CDCl_3$) δ -116.83 (1F, s, F-7); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 163.5, 163.4, 161.8, 147.4, 147.3, 134.9, 134.9, 134.0, 129.0, 128.9, 124.5, 116.2, 116.0, 112.4, 112.2, 77.4, 77.2, 77.2, 37.9, 25.3, 23.0, 14.6, 14.6.; **IR (KBr)ν_{max}** 2963 (C–H), 1627 (C=C) cm^{-1}; HRMS (ESI) Calcd For $C_{14}H_{17}FN$ 218.1345 ($M + H^+$); Found 218.1364.



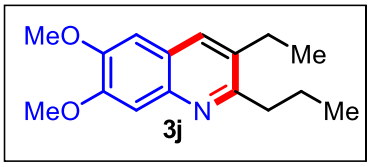
3-Ethyl-8-methoxy-2-propylquinoline (3h):[6b] (162 mg, 71%, dark brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (1H, s, H-4), 7.37 (1H, t, *J* = 7.9 Hz, H-6), 7.32 (1H, d, *J* = 7.9 Hz, H-5), 6.98 (1H, d, *J* = 7.6 Hz, H-7), 4.08 (3H, s, 8-OCH_3), 3.02 (2H, t, *J* = 7.5 Hz, CH_2), 2.86 (2H, q, *J* = 7.5 Hz, CH_2), 1.84 (2H, sext, *J* = 7.5 Hz, CH_2), 1.35 (3H, t, *J* = 7.5 Hz, CH_3), 1.07 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.3, 155.1, 138.4, 136.0, 134.1, 128.7, 125.7, 119.1, 106.9, 56.2, 38.2, 25.3, 23.4, 14.6, 14.6; **IR (KBr)ν_{max}** 2960 (C–H), 1623 (C=C), 1262 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}NO$ 230.1545 ($M + H^+$); Found 230.1557.



3-Ethyl-8-methyl-2-propylquinoline (3i):[6b] (160 mg, 75%, yellow liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (1H, s, H-4), 7.54 (1H, d, *J* = 8.1 Hz, H-5), 7.42 (1H, d, *J* = 6.9 Hz, H-7), 7.30 (1H, t, *J* = 8.1 Hz, H-6), 2.92 (2H, t, *J* = 7.5 Hz, CH_2), 2.81 – 2.77 (2H, m, CH_2), 2.76 (3H, s, 8-CH_3), 1.91 (2H, sext, *J* = 7.5 Hz, CH_2), 1.30 (3H, t, *J* = 7.5 Hz, CH_3), 1.05 (3H, t, *J* = 7.4 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.5, 145.5, 136.8, 135.2, 133.9, 128.4, 127.3, 125.4, 125.0, 37.6, 25.3, 22.0, 18.0, 14.6, 14.5; **IR (KBr)ν_{max}** 2963 (C–H), 1635 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}N$ 214.1596 ($M + H^+$); Found 214.1619.

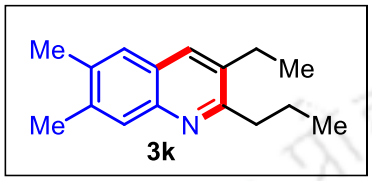


3-Ethyl-6,7-dimethoxy-2-propylquinoline (3j): (218 mg, 84%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 7.72 (1H, s, H-4), 7.37 (1H, s, H-8), 6.98 (1H, s, H-5), 4.00 (3H, s, 7-OCH_3), 3.98 (3H, s, 6-OCH_3), 2.90 (2H, t, *J* = 7.5 Hz, CH_2), 2.79 (2H, q, *J* =

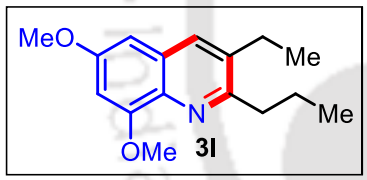


7.5 Hz, CH_2), 1.79 (2H, sext, *J* = 7.5 Hz, CH_2), 1.31 (3H, t, *J* = 7.5 Hz, CH_3), 1.05 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 151.5, 149.0, 143.0, 133.4, 132.7, 122.5, 107.2, 104.6, 56.0, 55.9, 37.5, 25.0, 23.1, 14.7, 14.3; **IR (KBr)ν_{max}** 2961 (C–H), 1623 (C=C), 1267 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}NO_2$ 260.1651 ($M + H^+$); Found 260.1611.

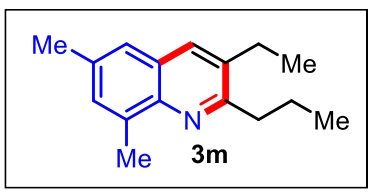
3-Ethyl-6,7-dimethyl-2-propylquinoline (3k): (188 mg, 83%, yellow solid); mp 72–73˚C; **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 7.71 (1H, s, H-4), 7.67 (1H, s, H-8), 7.38 (1H, s, H-5), 2.85 (2H, t, *J* = 7.5 Hz, CH_2), 2.73 (2H, q, *J* = 7.5 Hz, CH_2), 2.36 (3H, s, 7-CH_3), 2.33 (3H, s, 6-CH_3), 1.74 (2H, sext, *J* = 7.5 Hz, CH_2), 1.24 (3H, t, *J* = 7.5 Hz, CH_3), 0.98 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.1, 145.7, 138.5, 135.4, 134.6, 133.2, 128.0, 126.3, 126.1, 37.9, 25.4, 23.2, 20.5, 20.1, 14.7, 14.5; **IR (KBr)ν_{max}** 2942 (C–H), 1646 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}N$ 228.1752 ($M + H^+$); Found 228.1775.



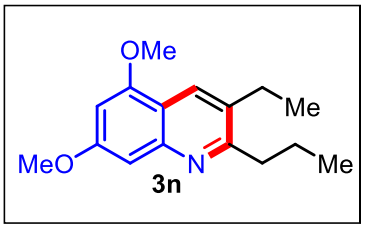
3-Ethyl-6,8-dimethoxy-2-propylquinoline (3l): (207 mg, 80%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$,) δ 7.66 (1H, s, H-4), 6.56 (1H, s, H-5), 6.53 (1H, s, H-7), 3.95 (3H, s, 8-OCH_3), 3.83 (3H, s, 6-OCH_3), 2.89 (2H, t, *J* = 7.5 Hz, CH_2), 2.74 (2H, q, *J* = 7.5 Hz, CH_2), 1.74 (2H, sext, *J* = 7.5 Hz, CH_2), 1.25 (3H, t, *J* = 7.5 Hz, CH_3), 0.97 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 157.4, 155.9, 136.3, 134.9, 133.1, 128.9, 100.1, 96.4, 56.1, 55.4, 37.7, 25.1, 23.1, 14.5, 14.4; **IR (KBr)ν_{max}** 2959 (C–H), 1621 (C=C), 1260 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}NO_2$ 260.1651 ($M + H^+$); Found 260.1661.



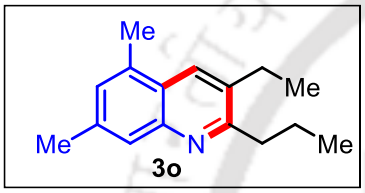
3-Ethyl-6,8-dimethyl-2-propylquinoline (3m):[6b] (191 mg, 84%, yellow liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (1H, s, H-4), 7.31 (1H, s, H-5), 7.27 (1H, s, H-7), 2.91 (2H, t, *J* = 7.5 Hz, CH_2), 2.78 (2H, q, *J* = 7.5 Hz, CH_2), 2.74 (3H, s, 8-CH_3), 2.44 (3H, s, 6-CH_3), 1.90 (2H, sext, *J* = 7.5 Hz, CH_2), 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 1.05 (3H, t, *J* = 7.4 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.5, 144.1, 136.3, 135.2, 134.9, 133.3, 130.7, 127.3, 123.9, 37.5, 25.3, 22.1, 21.7, 17.9, 14.6, 14.5; **IR (KBr)ν_{max}** 2961 (C–H), 1605 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}N$ 228.1752 ($M + H^+$); Found 228.1769.



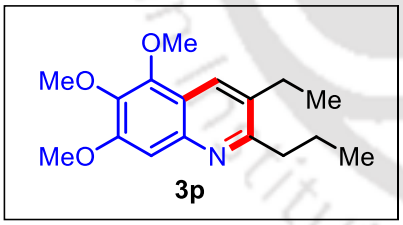
3-Ethyl-5,7-dimethoxy-2-propylquinoline (3n): (189 mg, 73%, light solid); mp 70-71˚C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (1H, s, H-4), 6.93 (1H, d, *J* = 1.9 Hz, H-8), 6.41 (1H, d, *J* = 2.1 Hz, H-6), 3.92 (3H, s, 5-OCH_3), 3.88 (3H, s, 7-OCH_3), 2.87 (2H, t, *J* = 7.5 Hz, CH_2), 2.76 (2H, q, *J* = 7.5 Hz, CH_2), 1.76 (2H, sext, *J* = 7.5 Hz, CH_2), 1.28 (3H, t, *J* = 7.5 Hz, CH_3), 1.02 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 162.6, 160.5, 155.7, 148.5, 132.3, 129.1, 115.6, 99.1, 97.40, 55.9, 55.7, 38.0, 25.4, 23.4, 15.0, 14.6; **IR (KBr)ν_{max}** 2958 (C–H), 1622 (C=C), 1258 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}NO_2$ 260.1651 ($M + H^+$); Found 260.1657.



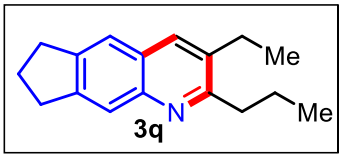
3-Ethyl-5,7-dimethyl-2-propylquinoline (3o): (177 mg, 78%, dark orange liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.95 (1H, s, H-4), 7.66 (1H, s, H-8), 7.12 (1H, s, H-6), 2.94 (2H, t, *J* = 7.5 Hz, CH_2), 2.84 (2H, q, *J* = 7.5 Hz, CH_2), 2.62 (3H, s, 7-CH_3), 2.48 (3H, s, 6-CH_3), 1.81 (2H, sext, *J* = 7.5 Hz, CH_2), 1.34 (3H, t, *J* = 7.5 Hz, CH_3), 1.06 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.5, 147.0, 138.2, 134.2, 133.5, 130.7, 128.6, 125.9, 124.8, 37.8, 25.7, 23.2, 21.9, 18.7, 15.1, 14.6; **IR (KBr)ν_{max}** 2963 (C–H), 1620 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{22}N$ 228.1752 ($M + H^+$); Found 228.1762.



3-Ethyl-5,6,7-trimethoxy-2-propylquinoline (3p): (208 mg, 72%, yellow liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.99 (1H s, H-4), 7.19 (1H, s, H-8), 3.98 (3H, s, 5-OCH_3), 3.91 (3H, s, 6-OCH_3), 3.89 (3H, s, 7-OCH_3), 2.85 (2H, t, *J* = 7.5 Hz, CH_2), 2.75 (2H, q, *J* = 7.5 Hz, CH_2), 1.73 (2H, sext, *J* = 7.5 Hz, CH_2), 1.26 (3H, t, *J* = 7.5 Hz, CH_3), 0.99 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.5, 155.2, 146.7, 144.2, 140.3, 133.3, 128.8, 118.2, 103.5, 61.7, 61.4, 56.3, 37.8, 25.5, 23.5, 15.1, 14.6; **IR (KBr)ν_{max}** 2961 (C–H), 1618 (C=C), 1256 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{24}NO_3$ 290.1756 ($M + H^+$); Found 290.1767.

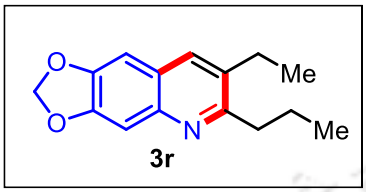


3-Ethyl-2-propyl-7,8-dihydro-6H-cyclopenta[g]quinoline (3q): (196 mg, 82%, dark brown solid); mp 68–69 ˚C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 (1H, s, H-4), 7.74 (1H, s, H-8), 7.48 (1H, s, H-5), 3.04 (2H, t, *J* = 7.4 Hz, CH_2), 3.00 (2H, t, *J* = 7.3 Hz, CH_2), 2.90 (2H, t, *J* = 7.5 Hz, CH_2), 2.78 (2H, q, *J* = 12.0, 6.0 Hz, CH_2), 2.11 (2H quint, *J* = 7.4 Hz,



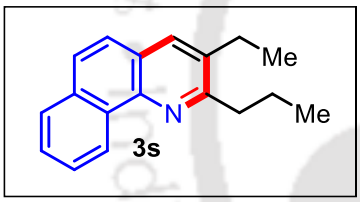
CH_2), 1.77 (2H, sext, *J* = 7.5 Hz, CH_2), 1.29 (3H, t, *J* = 7.5 Hz, CH_3), 1.02 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.6, 146.4, 146.1, 143.0, 134.1, 133.7, 126.4, 122.6, 120.8, 37.7, 32.9, 32.5, 26.2, 25.1, 23.1, 14.6, 14.4; **IR (KBr)ν_{max}** 2931 (C–H), 1644 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{22}N$ 240.1752 ($M + H^+$); Found 240.1778.

7-Ethyl-6-propyl-[1,3]dioxolo[4,5-g]quinoline (3r): (192 mg, 81% dark brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.62 (1H, s, H-4), 7.27 (1H, s, H-8), 6.91 (1H, s, H-5), 5.99 (2H, s, CH_2), 2.83 (2H, t, *J* = 7.4 Hz, CH_2), 2.72 (2H, q, *J* = 7.5 Hz, CH_2), 1.74 (2H, sext, *J* = 7.5 Hz, CH_2), 1.25 (3H, t, *J* = 7.5 Hz, CH_3), 1.00 (3H, t, *J* = 7.4 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.5, 149.9, 147.1, 144.4, 133.5, 133.5, 124.0, 105.3, 102.3, 101.5, 37.64, 25.1, 23.2, 14.8, 14.5; **IR (KBr)ν_{max}** 2962 (C–H), 1620 (C=C), 1217 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{18}NO_2$244.1338 ($M + H^+$); Found 244.1347.



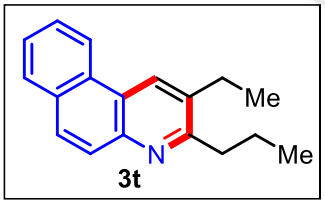
3r

3-Ethyl-2-propylbenzo[h]quinoline (3s): (187 mg, 75%, yellow liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.30 (1H, d, *J* = 8.1 Hz), 7.84 (2H, d, *J* = 9.7 Hz), 7.70 (1H, d, *J* = 8.8 Hz), 7.64 – 7.68 (1H, m), 7.62 – 7.59 (2H, m), 3.00 (2H, t, *J* = 7.5 Hz, CH_2), 2.84 (2H, q, *J* = 7.5 Hz, CH_2), 1.99 (2H, sext, *J* = 7.3 Hz, CH_2), 1.33 (3H, t, *J* = 7.5 Hz, CH_3), 1.09 (3H, t, *J* = 7.4 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.1, 144.1, 136.0, 134.2, 133.5, 131.8, 127.8, 127.6, 126.8, 126.7, 125.3, 124.9, 124.5, 37.5, 25.4, 22.3, 14.7, 14.6; **IR (KBr)ν_{max}** 2961 (C–H), 1623 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{18}H_{20}N$ 250.1596 ($M + H^+$); Found 250.1615.



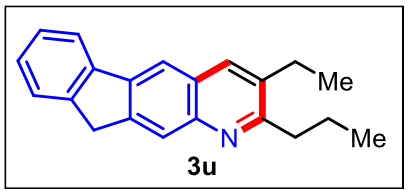
3s

2-Ethyl-3-propylbenzo[f]quinoline (3t): (179 mg, 72%, red solid); mp 63–64 ˚C, **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.65 (1H, s, H-4), 8.59 (1H, d, *J* = 8.2 Hz), 7.91 (1H, d, *J* = 9.1 Hz,), 7.88 (1H, d, *J* = 2.8 Hz), 7.87 (1H, d, *J* = 4.5 Hz), 7.60 – 7.65 (1H, m), 7.54 – 7.59 (1H, m), 2.95 (2H, t, *J* = 7.5 Hz, CH_2), 2.91 (2H, q, *J* = 7.5 Hz, 2H CH_2), 1.83 (2H, sext, *J* = 7.5 Hz, CH_2), 1.38 (3H, t, *J* = 7.6 Hz, CH_3), 1.06 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.3, 146.1, 135.6, 131.6, 129.9, 129.8, 129.7, 128.8, 127.9, 126.8, 126.8, 124.0, 122.6, 37.7, 25.9, 23.4, 15.2, 14.6; **IR (KBr)ν_{max}** 2955 (C–H), 1611 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{18}H_{20}N$ 250.1596 ($M + H^+$); Found 250.1615.

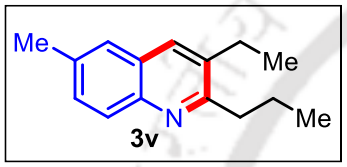


3t

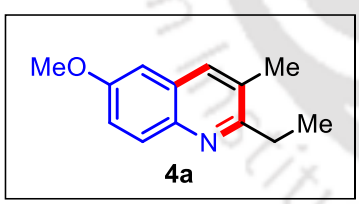
3-Ethyl-2-propyl-10H-indeno[1,2-g]quinoline (3u): (207 mg, 72%, dark brown solid); mp 73–74 ˚C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.11 (1H, s, H-4), 8.05 (1H, s), 7.94 (1H, s), 7.88 (1H, d, *J* = 7.5 Hz), 7.55 (1H, d, *J* = 7.4 Hz), 7.39 (1H, t, *J* = 7.4 Hz), 7.33 (1H, t, *J* = 7.4 Hz), 4.09 (2H, s, CH_2), 2.95 (2H, t, *J* = 7.5 Hz, CH_2), 2.83 (2H q, *J* = 7.5 Hz, CH_2), 1.82 (2H, sext, *J* = 7.4 Hz, CH_2), 1.34 (3H, t, *J* = 7.5 Hz, CH_3), 1.05 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.3, 143.9, 140.7, 140.1, 136.5, 134.8, 127.6, 127.0, 126.8, 125.3, 123.9, 123.8, 120.6, 116.5, 37.7, 36.7, 25.2, 23.0, 14.5, 14.4; **IR (KBr)ν_{max}** 2961 (C–H), 1635 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{21}H_{22}N$ 288.1752 ($M + H^+$); Found 288.1772.



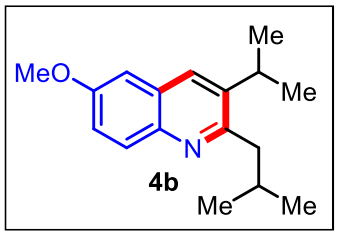
3-Ethyl-6-methyl-2-propylquinoline (3v):[6b] (1.48 gm,78%, yellow liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.5 Hz, H-8), 7.77 (1H, s, H-4), 7.49 (1H, s, H-5), 7.44 (1H, dd, *J* = 8.6, 1.8 Hz, H-7), 2.95 (2H, t, *J* = 7.5 Hz, CH_2), 2.82 (2H, q, *J* = 7.5 Hz, CH_2), 2.50 (3H, s, 6-CH_3), 1.82 (2H, sext, *J* = 7.5 Hz, CH_2), 1.33 (3H, t, *J* = 7.5 Hz, CH_3), 1.06 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 161.2, 145.2, 135.5, 135.4, 133.6, 130.8, 128.8, 127.6, 126.0, 37.9, 25.4, 23.2, 21.7, 14.7, 14.6; **IR (KBr)ν_{max}** 2963 (C–H), 1607 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}N$ 214.1596 ($M + H^+$); Found 214.1590.



2-Ethyl-6-methoxy-3-methylquinoline (4a):[6b] (161 mg, 80%, dark brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 9.1 Hz, H-8), 7.74 (1H, s, H-4), 7.26 (1H, dd, *J* = 9.1, 2.8 Hz, H-7), 6.98 (1H, d, *J* = 2.7 Hz, H-5), 3.90 (3H, s, 6-OCH_3), 2.96 (2H, q, *J* = 7.6 Hz, CH_2), 2.46 (3H, s, 3-CH_3), 1.35 (3H, t, *J* = 7.6 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 160.9, 157.3, 142.8, 135.0, 130.0, 129.9, 128.3, 120.9, 104.6, 55.6, 29.4, 19.3, 13.2; **IR (KBr)ν_{max}** 2966 (C–H), 1611 (C=C), 1226 (C-O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{16}NO$ 202.1232 ($M + H^+$); Found 202.1244.

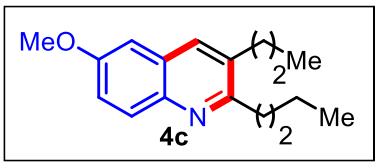


2-Isobutyl-3-isopropyl-6-methoxyquinoline (4b):[6b] (211 mg, 82%, brown liquid); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 9.1 Hz, H-8), 7.86 (1H, s, H-4), 7.27 (1H, dd, *J* = 9.1, 2.8 Hz, H-7), 7.03 (1H, d, *J* = 2.8 Hz, H-5), 3.92 (3H, s, 6-OCH_3), 3.27 – 3.34 (1H, m, CH), 2.88 (2H, d, *J* = 7.3 Hz, CH_2), 2.18 – 2.25 (1H,



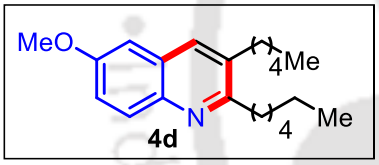
m, CH), 1.32 (6H, d, *J* = 6.8 Hz, 2CH_3), 0.98 (6H, d, *J* = 6.6 Hz, 2CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.3, 157.3, 142.4, 141.2, 130.8, 130.1, 128.3, 121.2, 104.8, 55.7, 44.1, 29.7, 28.9, 24.1, 22.8; **IR (KBr)ν_{max}** 2944 (C–H), 1615 (C=C), 1230 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{24}NO$ 258.1858 ($M + H^+$); Found 258.1883.

2-Butyl-6-methoxy-3-propylquinoline (4c):[6b] (213 mg, 83%, brown liquid); **^{1}H NMR**



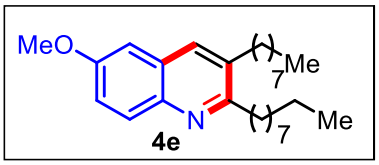
(600 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 9.2 Hz, H-8), 7.77 (1H, s, H-4), 7.28 (1H, dd, *J* = 9.1, 2.8 Hz, H-7), 7.00 (1H, d, *J* = 2.8 Hz, H-5), 3.91 (3H, s, 6-OCH_3), 2.95 (2H, t, *J* = 7.4 Hz, CH_2), 2.75 (2H, t, *J* = 7.4 Hz, CH_2), 1.69 – 1.78 (4H, m, 2CH_2), 1.48 (2H, dt, *J* = 14.8, 7.4 Hz, CH_2), 1.05 (3H, t, *J* = 7.3 Hz, CH_3), 0.98 (3H, t, *J* = 7.4 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.8, 157.4, 142.4, 134.5, 134.3, 129.9, 128.2, 121.2, 104.8, 55.7, 35.45, 34.5, 32.2, 23.8, 23.3, 14.3, 14.2; **IR (KBr)ν_{max}** 2957 (C–H), 1624 (C=C), 1230 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{24}NO$ 258.1858 ($M + H^+$); Found 258.1875.

2-Hexyl-6-methoxy-3-pentylquinoline (4d):[6b] (254 mg, 81%, brown liquid); **^{1}H NMR**



(600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 9.1 Hz, H-8), 7.75 (1H, s, H-4), 7.27 (1H, dd, *J* = 9.1, 2.8 Hz, H-7), 7.00 (1H, d, *J* = 2.7 Hz, H-5), 3.90 (3H, s, 6-OCH_3), 2.90 – 2.95 (2H, m, CH_2), 2.73 – 2.78 (2H, m, CH_2), 1.76 (2H, dt, *J* = 15.7, 7.9 Hz, CH_2), 1.68 (2H, dt, *J* = 15.3, 7.5 Hz, CH_2), 1.46 (2H, t, *J* = 7.5 Hz, CH_2), 1.40 (4H, dd, *J* = 9.1, 6.3 Hz, 2CH_2), 1.31 – 1.35 (4H, m, 2CH_2), 0.93 (3H, t, *J* = 7.0 Hz, CH_3), 0.89 (3H, t, *J* = 7.0 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.9, 157.2, 142.6, 134.6, 134.1, 129.9, 128.2, 121.0, 104.7, 55.6, 35.9, 32.6, 31.9, 30.5, 30.1, 29.8, 22.8, 22.7, 14.3, 14.2; **IR (KBr)ν_{max}** 2927 (C–H), 1625 (C=C),1227 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{21}H_{32}NO$ 314.2484 ($M + H^+$); Found 314.2482.

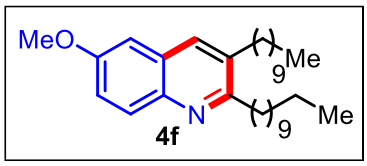
6-Methoxy-2-nonyl-3-octylquinoline (4e): (294 mg, 74%, yellow liquid); **^{1}H NMR**



(600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.1 Hz, 1H), 7.75 (s, 1H), 7.26 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 3.91 (s, 3H), 2.94 – 2.90 (m, 2H), 2.77 – 2.73 (m, 2H), 1.75 (tt, *J* = 10.9, 7.9 Hz, 2H), 1.67 (dd, *J* = 15.4, 7.8 Hz, 2H), 1.44 (tt, *J* = 14.1, 7.0 Hz, 4H), 1.32 – 1.21 (m, 18H), 0.88 (q, *J* = 7.0 Hz, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.9, 157.3, 142.6, 134.6, 134.1, 130.0, 128.2, 121.0, 104.7, 55.7, 32.1, 32.1, 30.8, 30.2, 30.2, 29.8, 29.7, 29.7, 29.5, 29.5, 22.9, 22.9, 14.3;

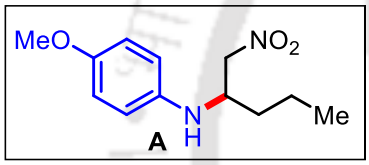
IR (KBr)ν_{max} 2925 (C–H), 1625 (C=C), 1227 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{27}H_{44}NO$ 398.3423 ($M + H^+$); Found 398.3444.

3-Decyl-6-methoxy-2-undecylquinoline (4f): (362 mg, 80%, yellow liquid); **^{1}H NMR**



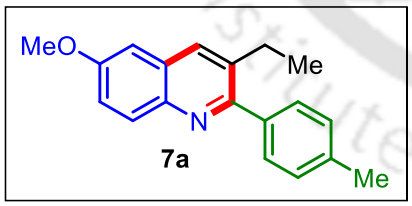
(600 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 9.2 Hz, H-8), 7.75 (1H, s, H-4), 7.27 (1H, dd, *J* = 9.1, 2.8 Hz, H-7), 7.00 (1H, d, *J* = 2.7 Hz, H-5), 3.90 (3H, s, 6-OCH_3), 2.92 (2H, t, *J* = 7.4 Hz, CH_2), 2.75 (2H, t, *J* = 7.5 Hz, CH_2), 1.73 – 1.78 (2H, m, CH_2), 1.66 – 1.70 (2H, m, CH_2), 1.40 – 1.47 (4H, m, $2CH_2$), 1.36 (4H, d, *J* = 3.8 Hz, $2CH_2$), 1.24 – 1.32 (22H, m, $11CH_2$), 0.88 (6H, td, *J* = 7.0, 2.9 Hz, $2CH_3$); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.9, 157.3, 142.5, 134.6, 134.2, 129.9, 128.2, 121.0, 104.7, 55.6, 32.1, 32.1, 30.8, 30.1, 30.1, 29.8, 29.8, 29.8, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.5, 22.9, 14.3; **IR (KBr)ν_{max}** 2924 (C–H), 1624 (C=C), 1227 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{31}H_{52}NO$ 454.4049 ($M + H^+$); Found 454.4056.

4-Methoxy-N-(1-nitropentan-2-yl) aniline (A): (100 mg, 42%, Brown liquid); **^{1}H**



NMR (600 MHz, $CDCl_3$) δ 6.81 (2H, d, *J* = 8.9 Hz, Ph), 6.65 (2H, d, *J* = 8.9 Hz, Ph), 4.46 (2H, ddd, *J* = 51.5, 11.7, 5.6 Hz, CH_2), 3.95 – 4.00 (1H, m, CH), 3.76 (3H, s, OCH_3), 1.56 – 1.66 (2H, m, CH_2), 1.39 – 1.56 (2H, m, CH_2), 0.95 (3H, t, *J* = 7.3 Hz, CH_3); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 153.0, 140.1, 116.5, 115.5, 115.2, 114.9, 78.2, 55.8, 53.4, 35.1, 19.3, 13.9; **IR (KBr)ν_{max}** 2959 (C–H), 1617 (C=C), 1435 and 1318 (NO_2) cm^{-1}; **HRMS** (ESI) Calcd For $C_{12}H_{19}N_2O_3$ 239.1396 ($M + H^+$); Found 239.1410.

3-Ethyl-6-methoxy-2-(p-tolyl)quinoline (7a): (59 mg, 21%, brown liquid); **^{1}H NMR**



(400 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 9.2 Hz, H-8), 7.93 (1H, s, H-4), 7.43 (2H, d, *J* = 8.0 Hz, H-2'), 7.31 (1H, dd, J = 8.0, 2.8 Hz, H-7), 7.26 (2H, d, *J* = 2.3 Hz, H-3'), 7.07 (1H, d, *J* = 2.8 Hz, H-5), 3.94 (3H, s, 6-OCH_3), 2.78 (2H, q, *J* = 7.4 Hz, CH_2), 2.42 (3H, s, 4'-CH_3), 1.19 (3H, t, *J* = 7.5 Hz, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 157.9, 142.7, 138.3, 137.8, 135.8, 133.9, 130.9, 129.1, 128.9, 128.8, 121.6, 104.6, 55.7, 26.2, 21.5, 14.9.; **IR (KBr)ν_{max}** 2918 (C–H), 1644 (C=C), 1228 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{19}H_{20}NO$ 278.1545 ($M + H^+$); Found 278.1559.

XRD for compound (3k): All the data for the structural analysis of compound **3k** has been deposited to the Cambridge Crystallographic Data Centre, **CCDC No. 1859531**. The file of this information can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk).

Table 2.4. Crystal data and structure refinement for compound 3k

Entry	Identification code	Compound 3k
01	Empirical formula	$C_{16}H_{21}N$
02	Formula weight	227.34
03	Temperature	293(2)K
04	Wavelength	0.71073
05	Radiation type	MoK\a
06	Radiation source	'fine-focus sealed tube'
07	Crystal system	Triclinic
08	Space group	P-1
09	Cell length	a=7.4928(7)b=8.7755(11)c=11.1633(11)
10	Cell Angle	α 84.247(9)β 78.666(8)δ 76.675(10)
11	Cell Volume	699.17(13)
12	Density	1.080
13	Completeness to theta	0.999-25.046
14	Absorption correction	multi-scan
15	Refinement method	Full-matrix least-squares on F2
16	Index ranges	$-11 \leq h \leq 11, -11 \leq k \leq 11, -14 \leq l \leq 16$
17	Reflection number	4702
18	Theta range	2.840-25.046
19	Cell formula units Z	4
20	CCDC no	1859531

^{1}H NMR (400 MHz, $CDCl_3$): 3-ethyl-6-methoxy-2-propylquinoline **(3a)**

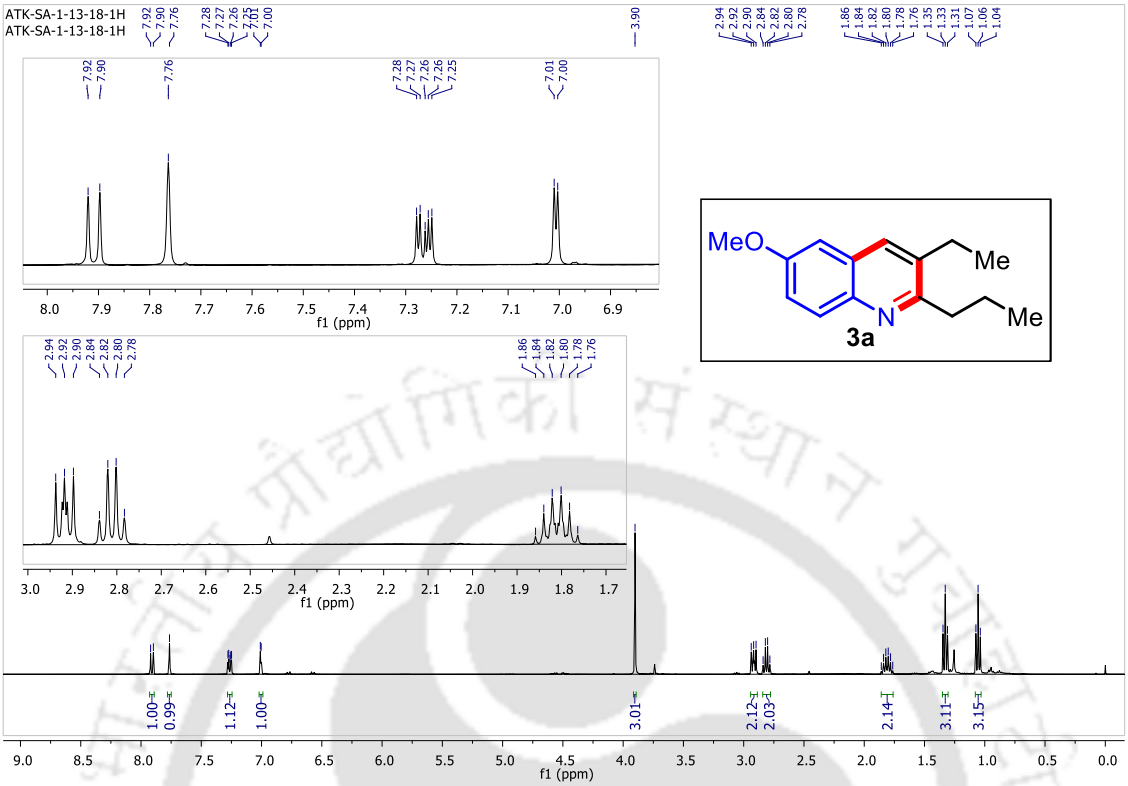


Figure 2.5a

^{13}C NMR (100 MHz, $CDCl_3$): 3-ethyl-6-methoxy-2-propylquinoline **(3a)**

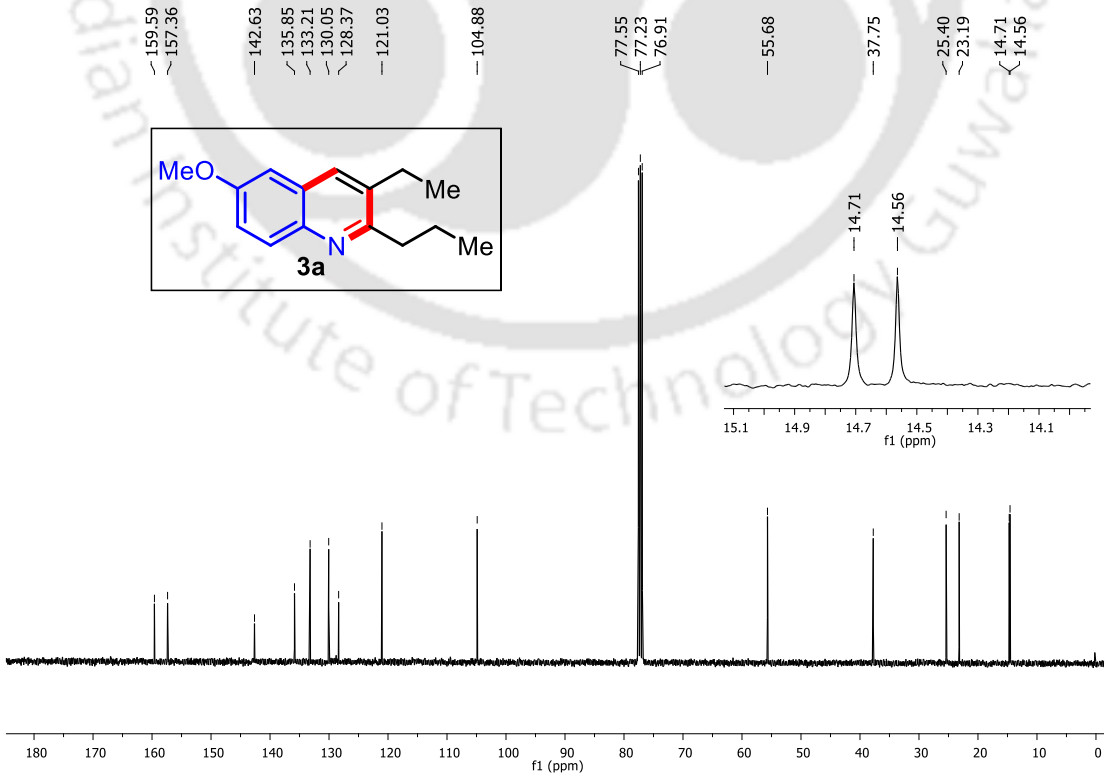


Figure 2.5b

HRMS spectrum: 3-ethyl-6-methoxy-2-propylquinoline **(3a)**

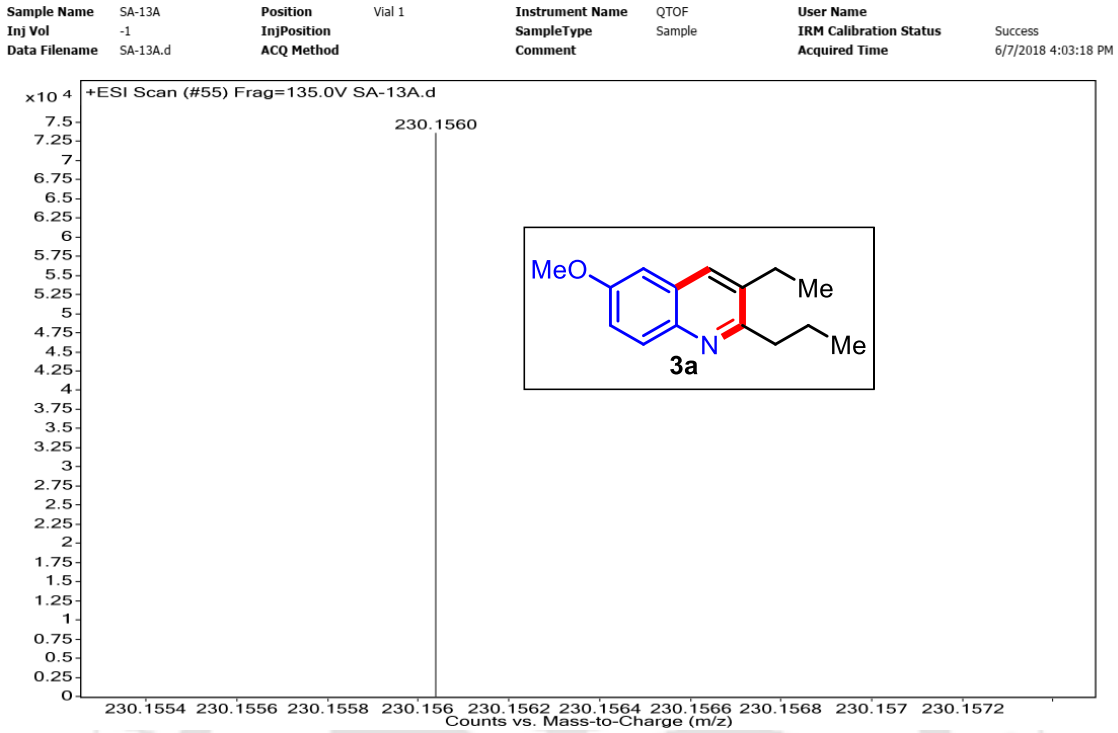


Figure 2.5c

^{1}H NMR (600 MHz, $CDCl_3$): 3-ethyl-2-propylquinoline **(3b)**

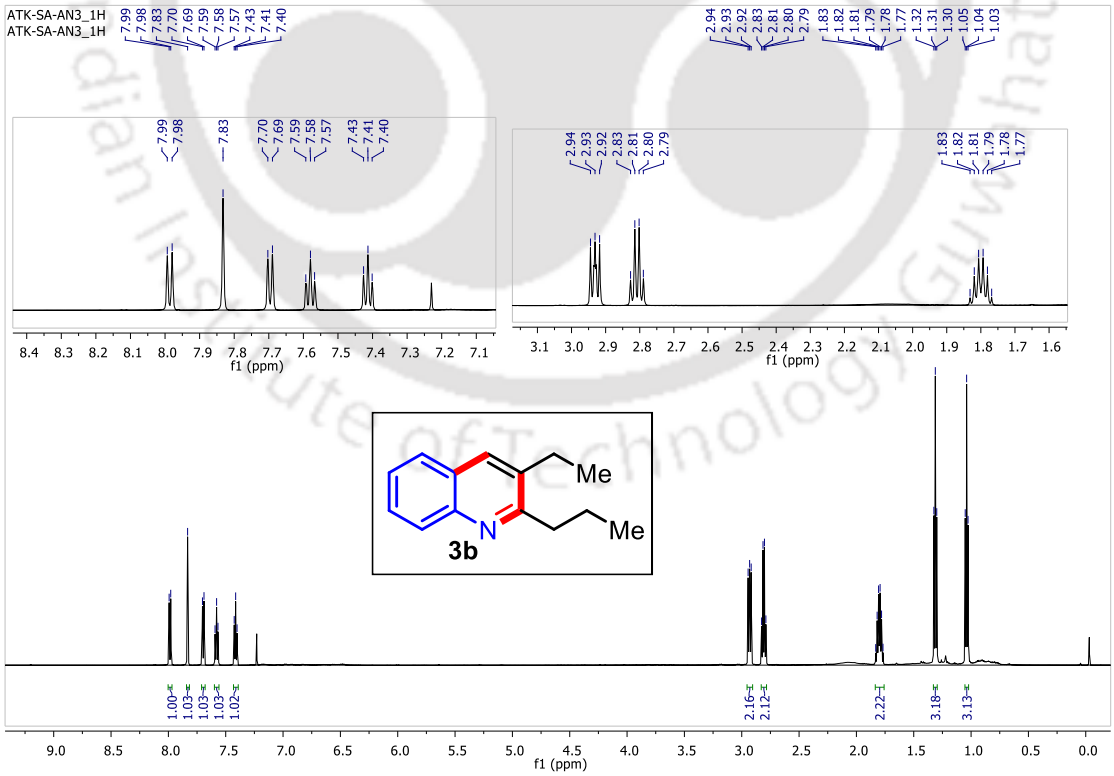


Figure 2.6a

^{13}C NMR (600 MHz, $CDCl_3$): 3-ethyl-2-propylquinoline **(3b)**

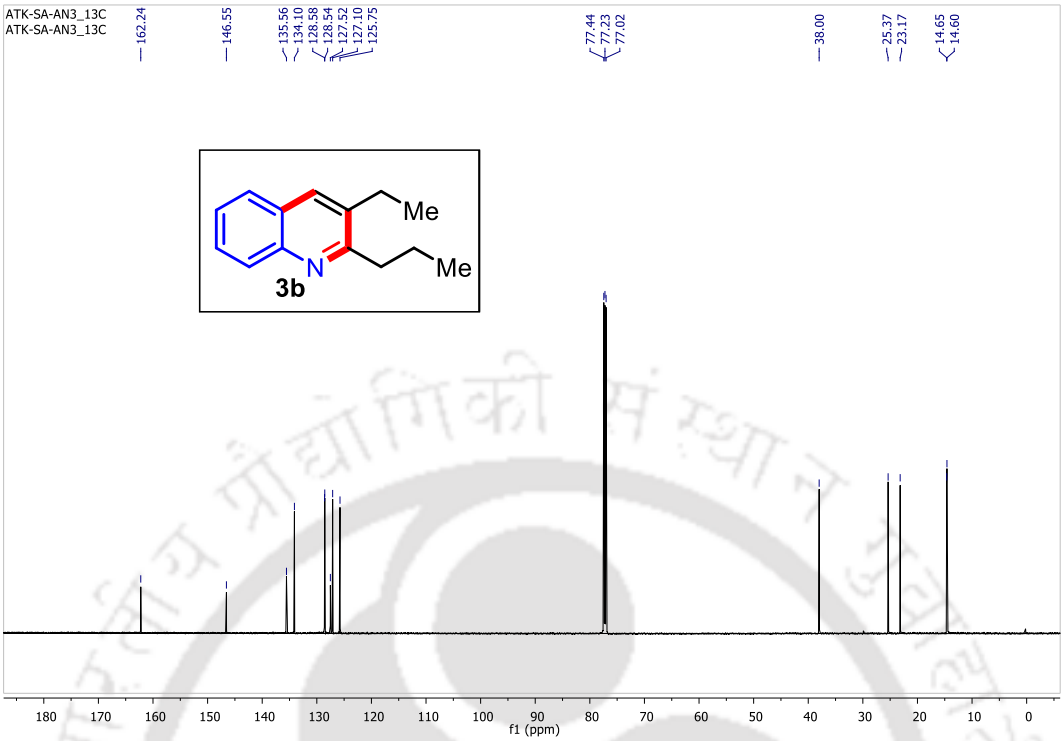


Figure 2.6b

HRMS spectrum: 3-ethyl-2-propylquinoline **(3b)**

Sample Name	SA-AN3	**Position**	Vial 1	**Instrument Name**	QTOF	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-AN3.d	**ACQ Method**		**Comment**		**Acquired Time**	7/26/2018 10:21:21 AM

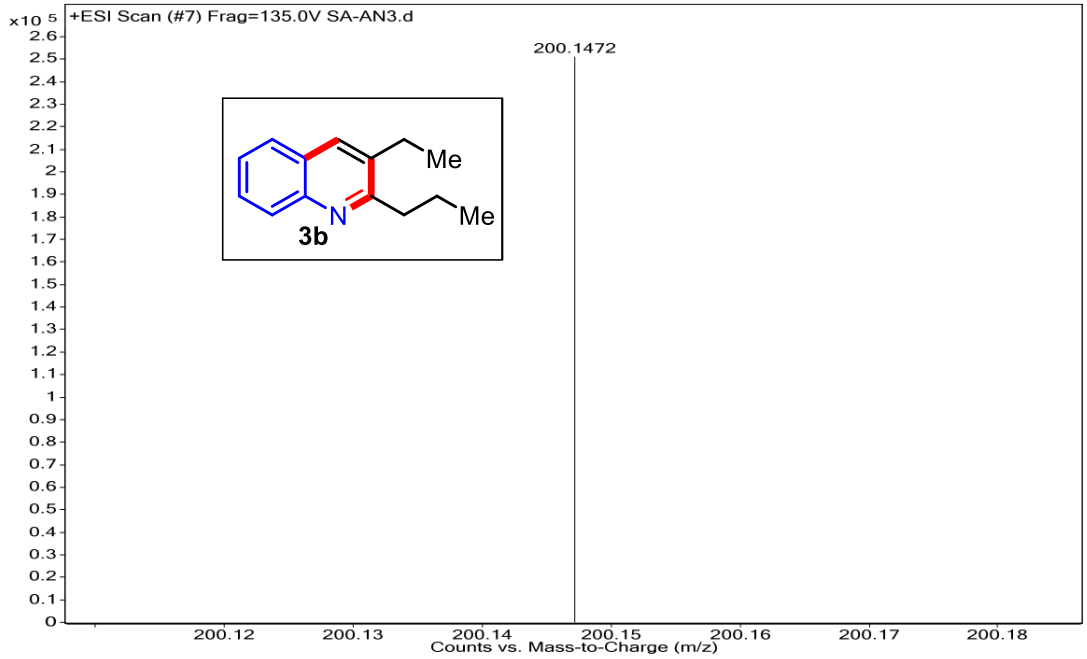


Figure 2.6c

^{1}H NMR (600 MHz, $CDCl_3$): 3-ethyl-6-ethyl-2-propylquinoline **(3c)**

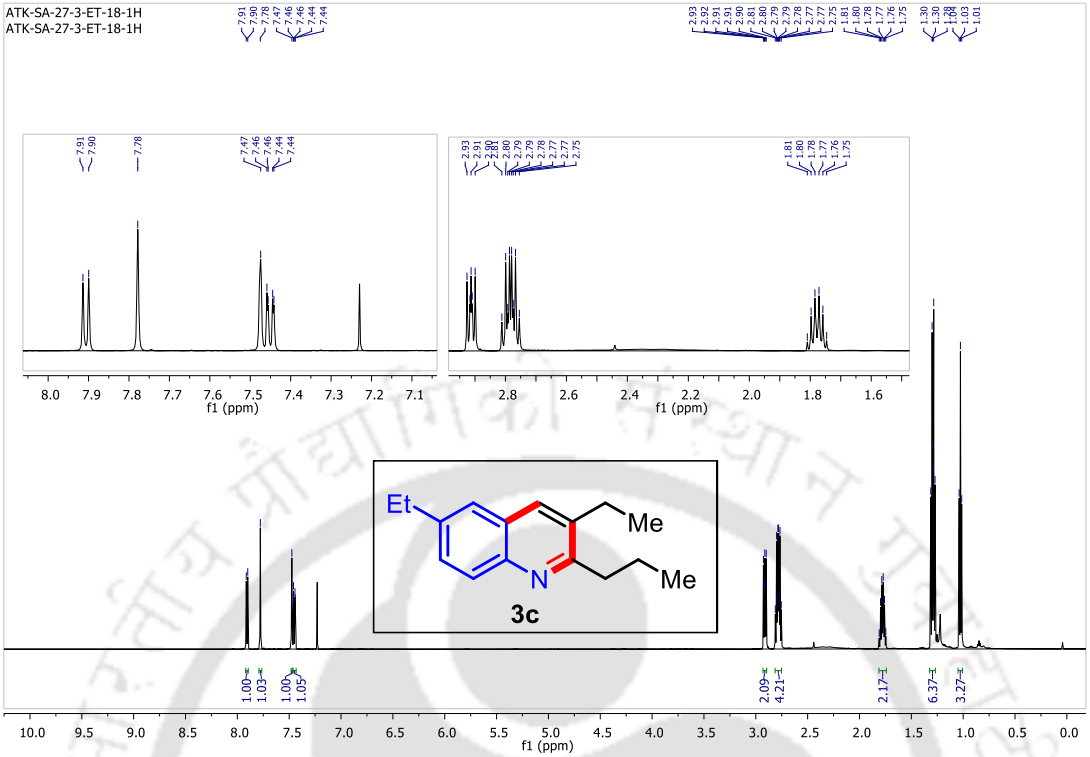


Figure 2.7a

^{13}C NMR (150 MHz, $CDCl_3$): 3-ethyl-6-ethyl-2-propylquinoline **(3c)**

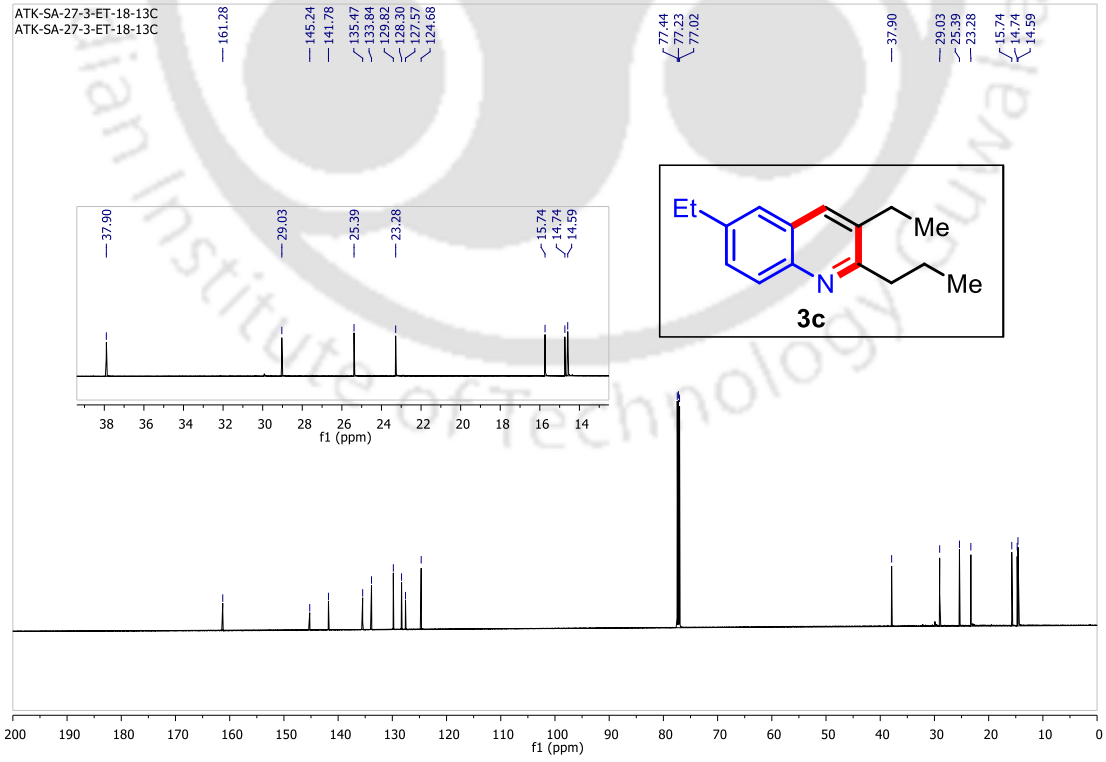


Figure 2.7b

HRMS spectrum: 3-ethyl-6-ethyl-2-propylquinoline **(3c)**

Sample Name	SA-4-ET-2	**Position**	Vial 1	**Instrument Name**	QTOF	**User Name**	
Inj Vol	-1	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4-ET-2.d	**ACQ Method**		**Comment**		**Acquired Time**	6/7/2018 4:01:39 PM

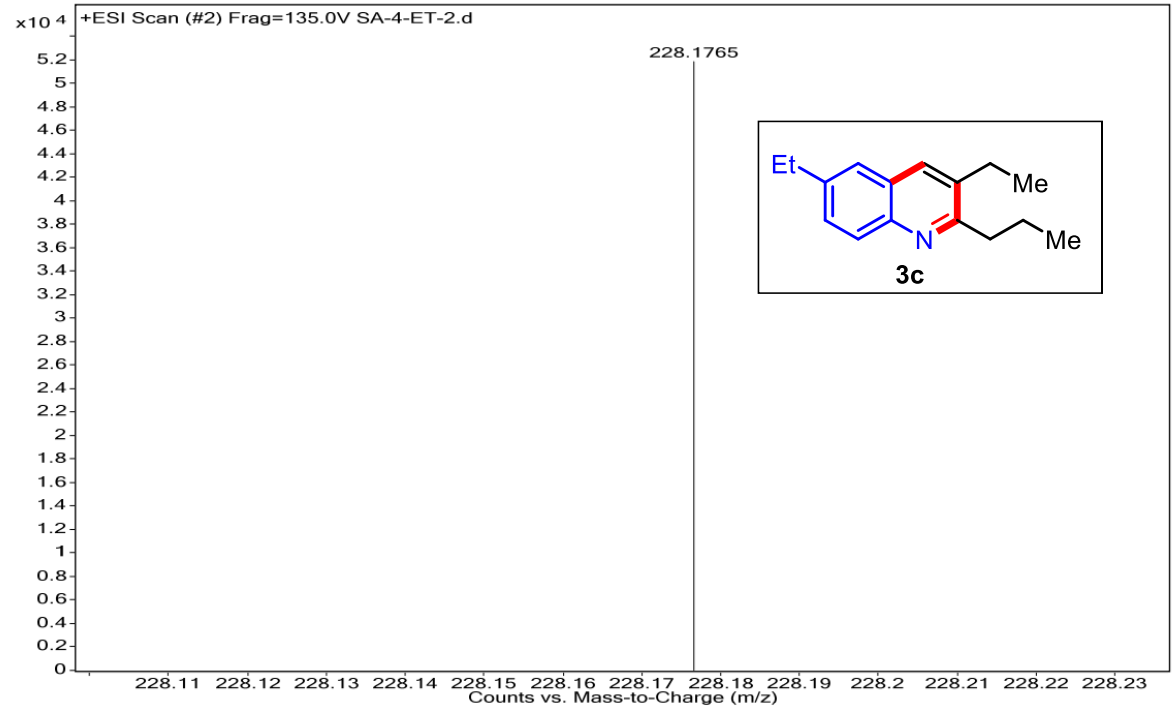


Figure 2.7c

^{1}H NMR (600 MHz, $CDCl_3$): 3-ethyl-6-fluoro-2-propylquinoline **(3d)**

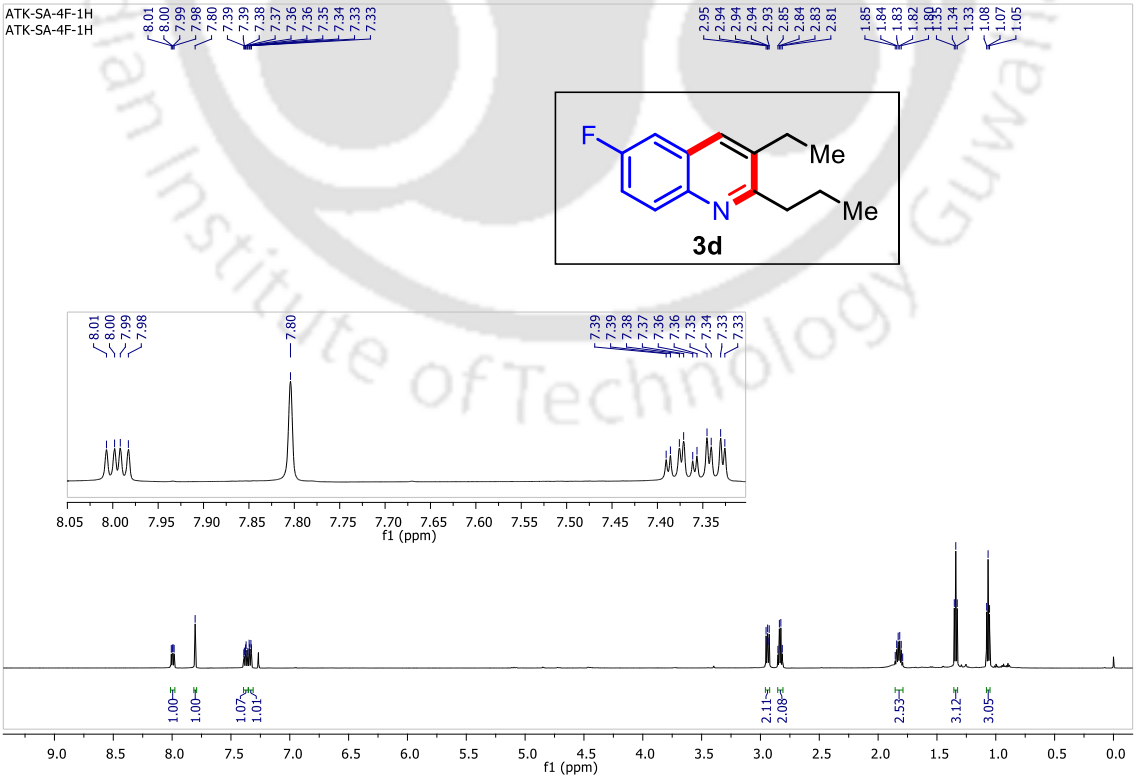


Figure 2.7d

^{13}C NMR (600 MHz, $CDCl_3$): 3-ethyl-6-fluoro-2-propylquinoline **(3d)**

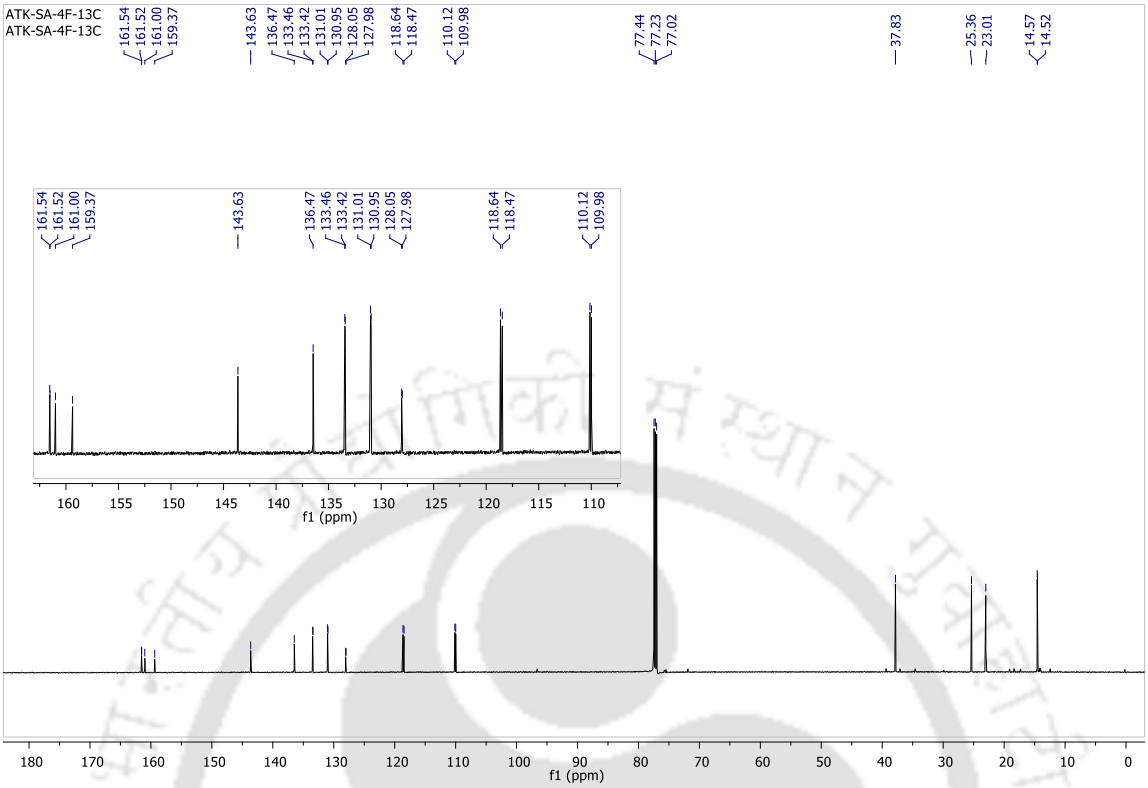


Figure 2.7e

^{1}H NMR (600 MHz, $CDCl_3$): 3-ethyl-7-fluoro-2-propylquinoline **(3d)**

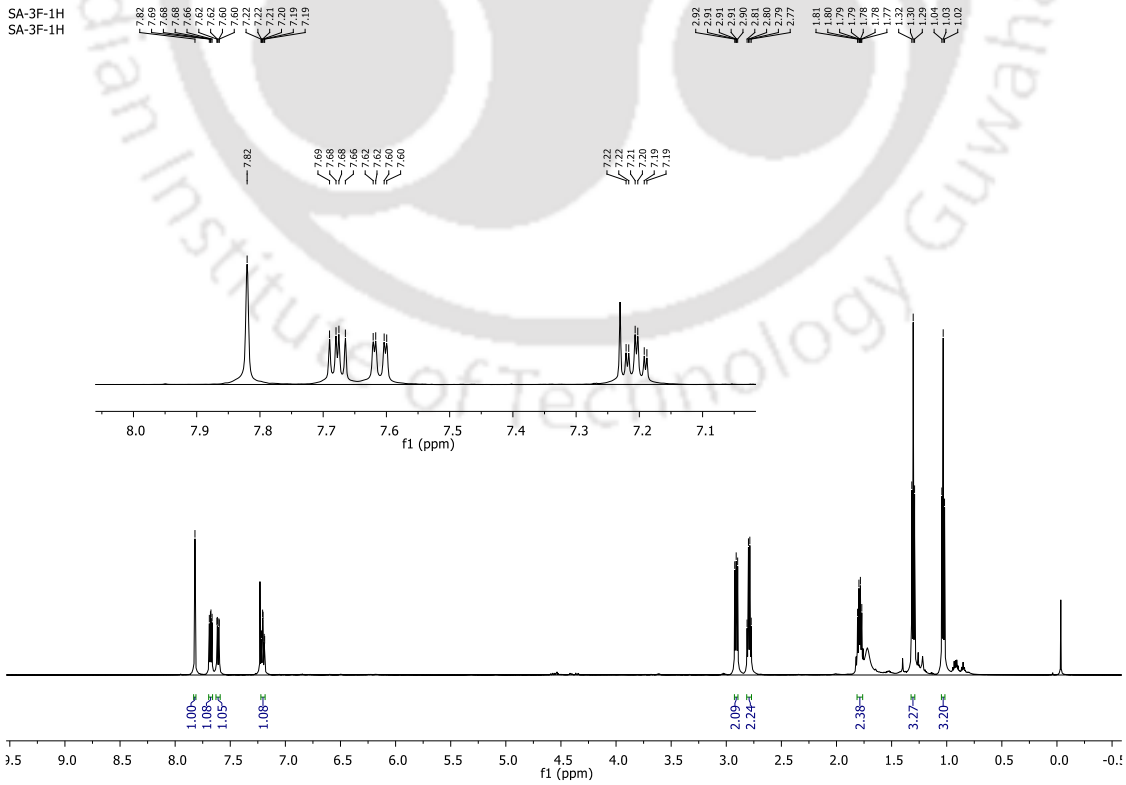


Figure 2.7f

^{13}C NMR (600 MHz, $CDCl_3$): 3-ethyl-7-fluoro-2-propylquinoline **(3d)**

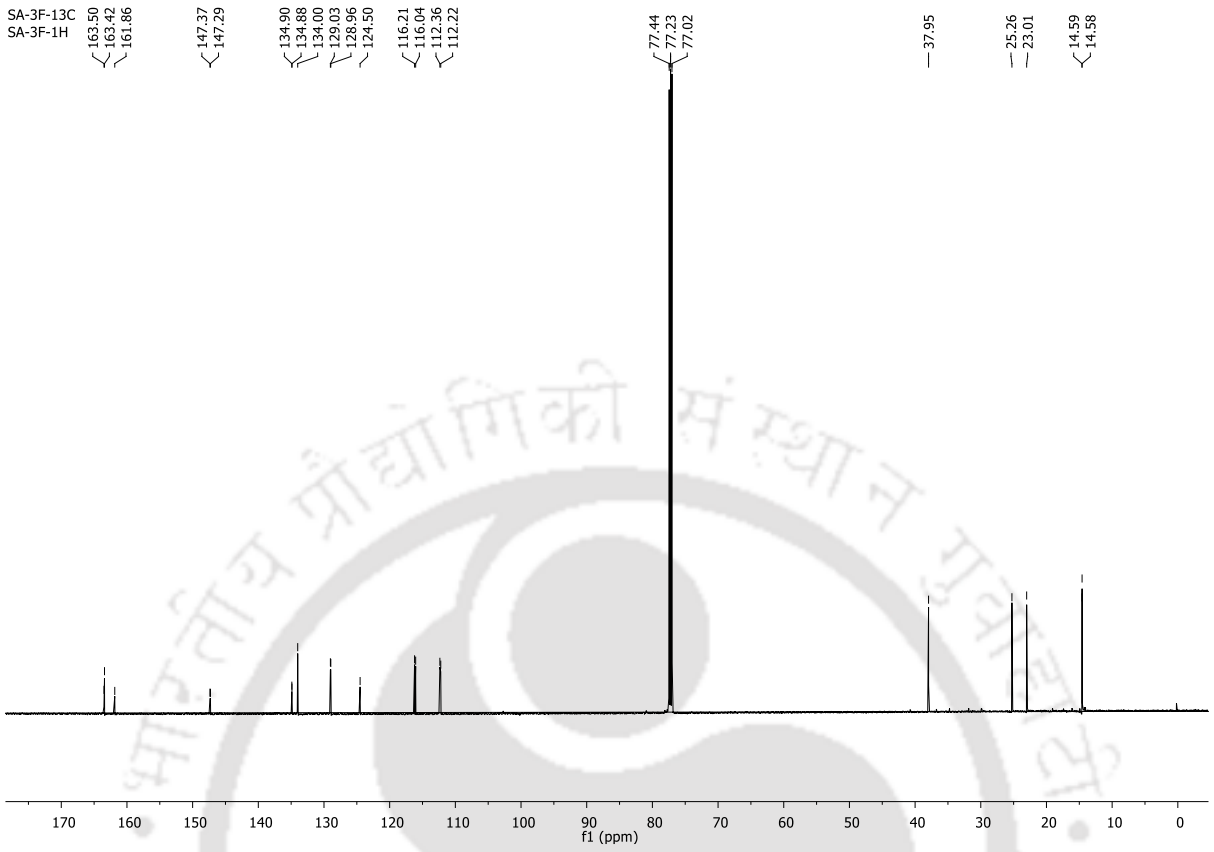
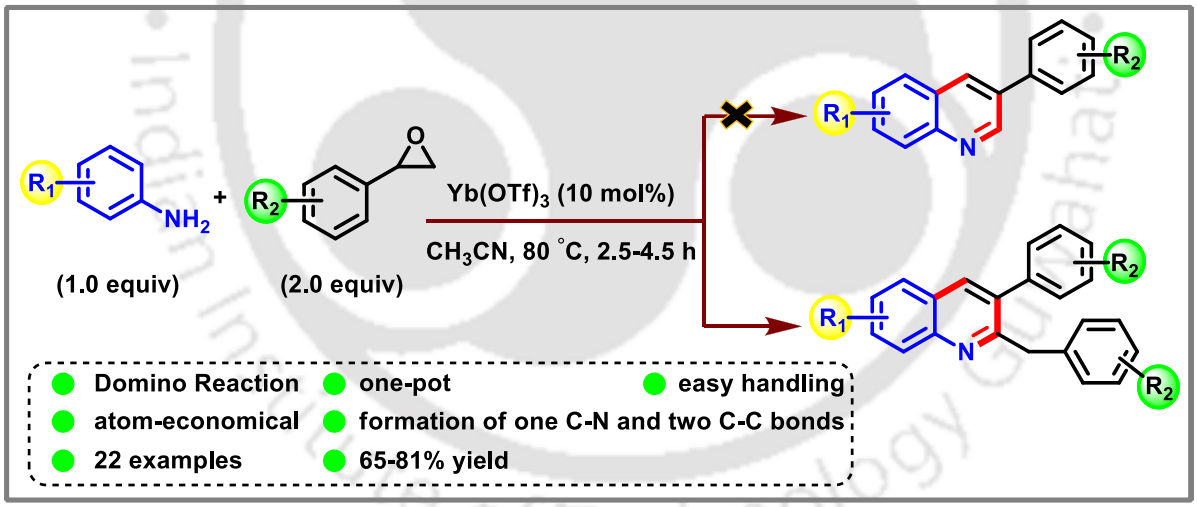


Figure 2.7g

Chapter II: Part B

Synthesis of 2-Benzyl-3-arylquinoline Derivatives through the Ytterbium(III) Triflate Catalyzed Domino Reaction of Aryl Amines and Styrene Oxides

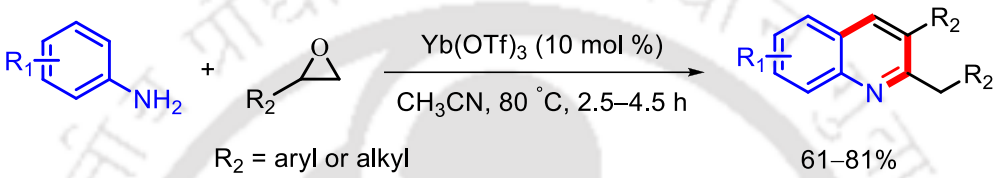


Result & Discussion

Experimental Section

Results and Discussion

The importance and synthetic strategies for synthesis of 2-benyl-3-phenylquinoline scaffolds have already been discussed in chapter I. This part of the chapter II presents a facile and an efficient method for synthesis of 2-benyl-3-phenylquinoline frameworks involving ytterbium(III) triflate catalyzed domino reaction of commercially available building blocks aryl amines and styrene oxides or aliphatic epoxides in acetonitrile at 80 °C (Scheme **2.7**). Ease of handing, high regioselectivity, atom-economical, formation of one C-N and two C-C bonds and access to a wide range of 2-benyl-3-phenylquinoline and 2,3-dialkylquinoline derivatives with high yield are salient features of this methodology.

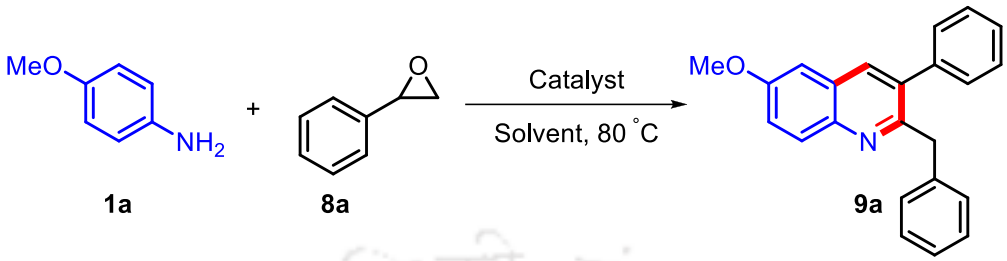


Scheme 2.7. Synthetic strategy for synthesis of 2-benzyl-3-phenylquinolines and 2,3-dialkylquinoline derivatives.

This study was started with ascertaining suitable reaction conditions. For this purpose, *p*-anisidine **1a** and styrene oxide **8a** were chosen as model substrates and results have been summarized in Table 2.5. Initially, model reaction was carried out with *p*-anisidine **1a** and styrene oxide **8a** in acetonitrile solvent without a catalyst. It was noted that reaction did not proceed at room temperature or at 80 °C (Table 2.5, entries 1 and 2). Reaction also did not occur in the presence of 5 mol% $Yb(OTf)_3$ at room temperature (Table 2.5, entry 3), however, upon heating at 80 °C for 6 h, **9a** was formed in 46% yield (Table 2. 5, entry 4). When catalyst loading was increased from 5% to 10% reaction completed within 3 h and yield of product **9a** also increased from 46% to 81% (Table 2. 5, entry 5,). However, further increasing catalyst loading to 15 mol%, did not improve yield (Table 2. 5, entry 6). To examine the efficiency of other metal triflates, reactions were performed in the presence of 10 mol% $Sc(OTf)_3$, $Bi(OTf)_3$, and $Cu(OTf)_2$ (Table 2. 5, entries 7–9), and it was found that $Sc(OTf)_3$ and $Bi(OTf)_3$ provided lower yields compared to $Yb(OTf)_3$. Additionally, reaction did not undergo with $Cu(OTf)_2$. Next, different solvents, such as water, methanol, tetrahydrofuran, 1,2-dichloroethane, dimethyl sulfoxide, *N*,*N*-dimethylformamide and toluene were examined (Table 2. 5, entries 10–16,), using10 mol% $Yb(OTf)_3$ as catalyst. In all these solvents, either reaction did not take place or yield was low. The best yield was obtained in acetonitrile. After screening all these

solvents and catalysts, 10 mol% $Yb(OTf)_3$ in acetonitrile at 80°C were found to be the optimized conditions in terms of both yield and reaction time (Table 2. 5, entry 5).

Table 2.5. Optimization of reaction conditions.[a,b,c,d]

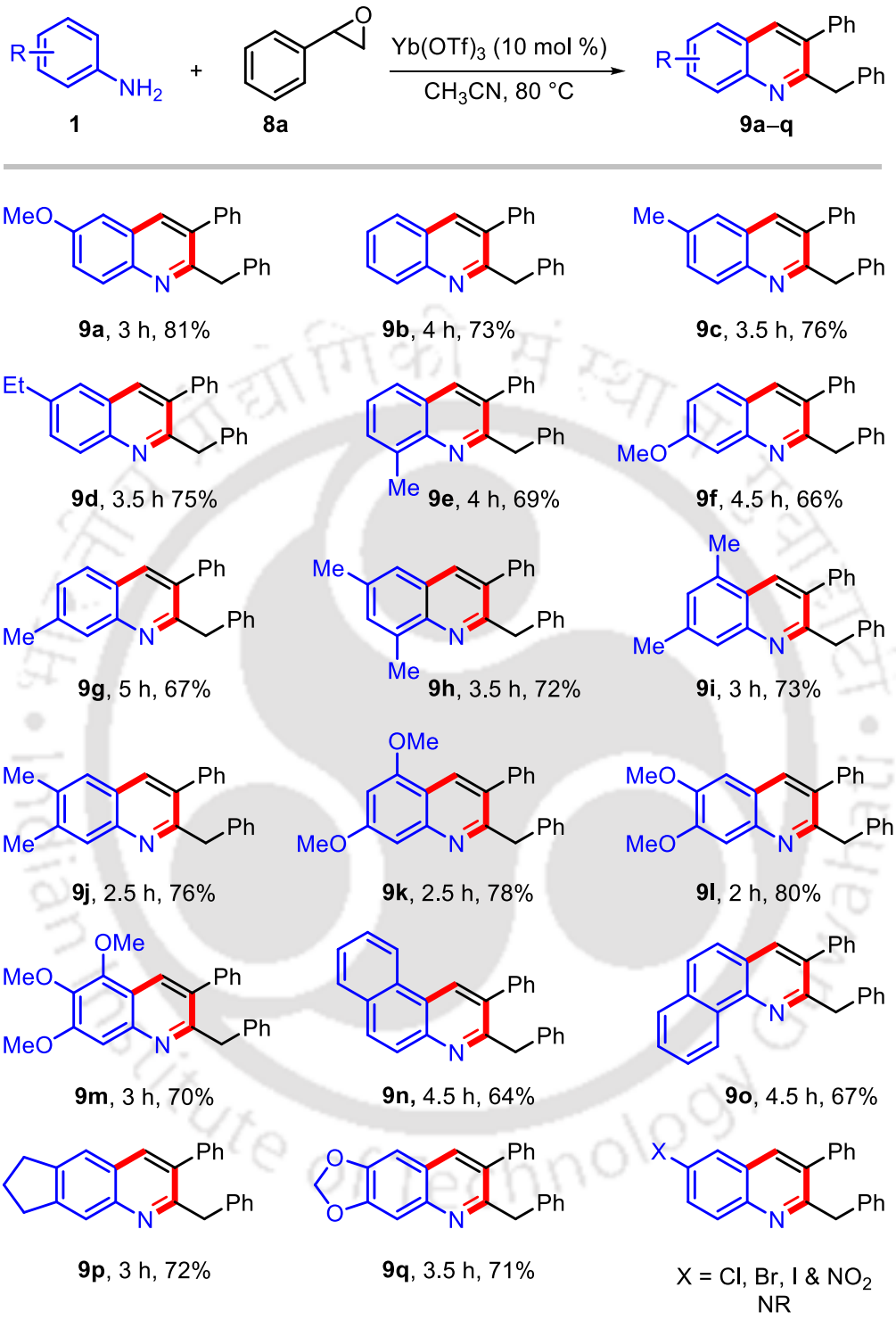


Entry	Catalyst	Mol%	Solvent	Time	Yield 9a (%)[b]
1[c]	–	–	CH_3CN	10 h	NR
2	–	–	CH_3CN	10 h	NR
3[c]	$Yb(OTf)_3$	5	CH_3CN	10 h	NR
4	$Yb(OTf)_3$	5	CH_3CN	6 h	46
5	**$Yb(OTf)_3$**	**10**	**CH_3CN**	**3 h**	**81**
6	$Yb(OTf)_3$	15	CH_3CN	3 h	76
7	$Sc(OTf)_3$	10	CH_3CN	6 h	46
8	$Bi(OTf)_3$	10	CH_3CN	6 h	62
9	$Cu(OTf)_2$	10	CH_3CN	6 h	NR
10	$Yb(OTf)_3$	10	H_2O	6 h	NR
11[d]	$Yb(OTf)_3$	10	CH_3OH	6 h	NR
12[d]	$Yb(OTf)_3$	10	THF	6 h	43
13	$Yb(OTf)_3$	10	$(CH_2Cl)_2$	6 h	NR
14	$Yb(OTf)_3$	10	DMSO	6 h	35
15	$Yb(OTf)_3$	10	DMF	6 h	NR
16	$Yb(OTf)_3$	10	Toluene	6 h	NR

[a]Reaction conditions: All the reactions were carried out using *p*-anisidine **1a** (1.0 mmol), styrene oxide **8a** (2.0 mmol) and solvent (1.0 mL) at 80 °C. [b]Isolated yield. [c]Reaction performed at room temperature. [d]Reaction performed under reflux condition. NR (No Reaction).

With optimal reaction conditions in hand, scope and generality of developed protocol were investigated using different aryl amines **1** with styrene oxide **8a** as presented in Table 2.6. Reaction of simple aniline with styrene oxide **8a** afforded 2-benzyl-3-phenylquinoline **9b** in 73% yield.

Table 2.6. Reactions of different aryl amines **1** and styrene oxide **8a**[a,b]

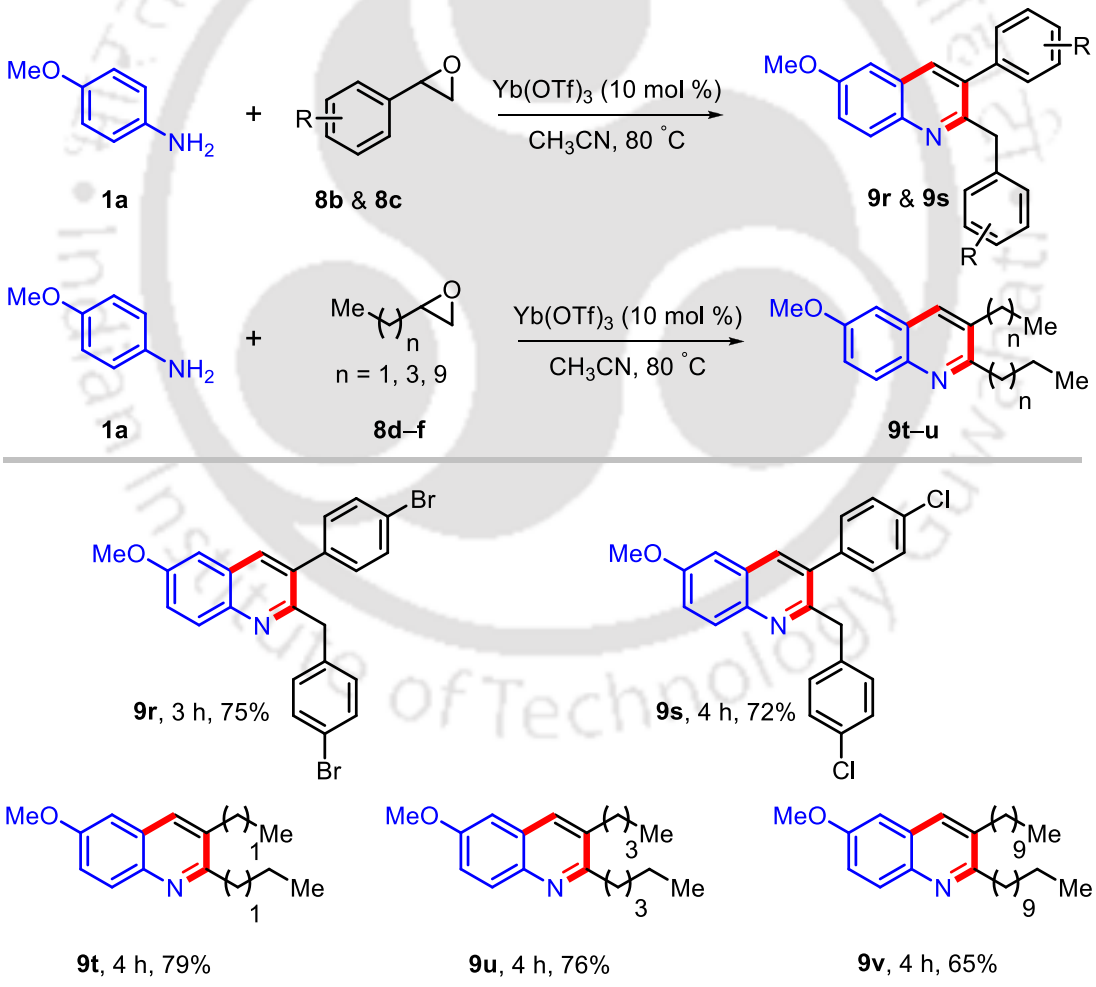


[a]All the reaction were carried out using arylamines **1** (1.0 mmol), styrene oxide **8a** (2.0 mmol) and $Yb(OTf)_3$ (10 mol%) in CH_3CN (1.0 mL) at 80°C. [b]Isolated yield. NR (no reaction).

Similarly, arylamines containing electron-donating groups (4-Me and 4-Et) located at 4-position, gave corresponding quinoline scaffolds **9c** and **9d** in 76% and 75% yield, respectively.

Reaction with aryl amine containing a methyl group at 2-position gave desired product **9e** in 69% yield. Aryl amines having substituents (3-OMe and 3-Me) at the 3-position, provided expected products **9f** and **9g** in 66% and 67% yield, respectively. Similarly, disubstituted aryl amines containing groups (2,4-Me, 3,5-Me, 3,4-Me, 3,5-OMe, and 3,4-OMe) also worked well and furnished anticipated quinoline scaffolds **9h–l** in 72–80% yield. Notably, sterically crowded 3,4,5-OMe-aniline also gave corresponding quinoline framework **9m** in 70% yield. Gratifyingly, bicyclic aryl amines, such as 2-naphthylamine, 1-naphthylamine, 5-aminoindan, and 3,4-(methylenedioxy)aniline afforded corresponding fused quinoline derivatives **9n–q** in 64–72% yield. However, reaction was unsuccessful with 4-substituted anilines containing electron-withdrawing groups, such as -Cl, -Br, -I and -NO_2.

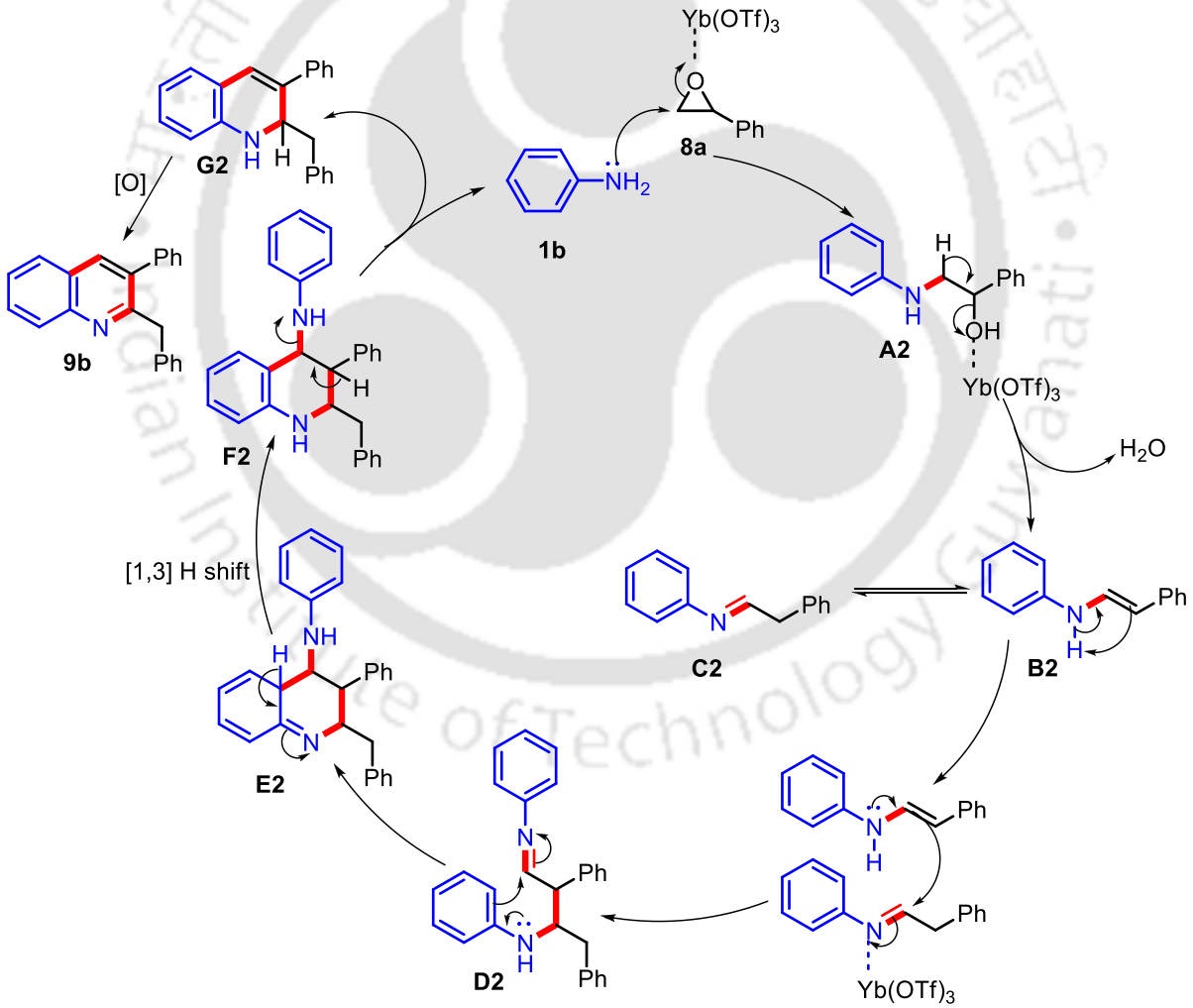
Table 2.7. Reactions of *p*-anisidine **1a** with styrene oxides **8b** and **8c** and different aliphatic epoxides **8d–f**[a,b]



[a]All reaction of *p*-anisidine **1a** (1.0 mmol) with styrene oxides **8b** and **8c** (2.0 mmol) and different aliphatic epoxides **8d–f** (2.0 mmol) and $Yb(OTf)_3$ (10 mol%) in CH_3CN (1.0 mL) at 80°C. [b]Isolated yield.

Inspired by above-mentioned results, scope and generality of this method were further explored with substituted styrene oxides **8b** and **8c** as well as aliphatic epoxides **8d–f** and successful results are shown in Table 2.7. Reactions of *p*-anisidine **1a** with styrene oxides **8b** and **8c** containing (-Br and -Cl) substituents at 4-position gave desired quinolines **9r** and **9s** in 75% and 72% yield, respectively. In order to incorporate aliphatic chains at C–2 and C–3 positions of quinoline derivatives, reaction using *p*-anisidine **1a** and 1,2-epoxybutane **8d** was carried out which gave desired product 3-ethyl-6-methoxy-2-propylquinoline **9t** in 79% yield. Furthermore, reactions with epoxides containing extended alkyl chains (e.g., 1,2-epoxyhexane **8e** and 1,2-epoxydodecane **8f**) proceeded well to provide anticipated products **9u** and **9v** in 76% and 65% yield, respectively.

A plausible mechanism for product formation is outlined in Scheme **2.8**.



Scheme 2.8. A plausible mechanism for formation of product **9b**.

Initially, aniline **1b** reacts with styrene oxide **8a** in presence of $Yb(OTf)_3$ which acts as a Lewis acid to provide *β*-aminoalcohol **A2** by attacking less hindered side.[7] Subsequently, removal of water from intermediate **A2** affords enamine **B2** that can be tautomerized to corresponding imine **C2**. Based on proposed mechanism by Beller and co-workers,[8a] intermediates **B2** and **C2** react *via* an intermolecular Mannich reaction to generate intermediate **D2**, which undergoes intramolecular electrophilic aromatic substitution followed by [1,3] H shift to give cyclized intermediate **F2**. Finally, elimination of aniline **1b** from intermediate **F2** forms dihydroquinoline **G2**, which upon aerial oxidation gives desired product **9b**.

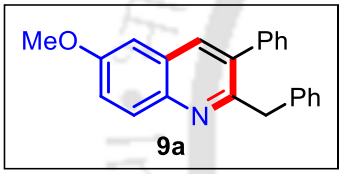
In summary, a new, one-pot methodology for straightforward access to a variety of 2-benzyl-3-phenylquinoline scaffolds has been developed. In this protocol, domino reaction of readily available substituted aryl amines and epoxide derivatives has been used as an efficient synthetic tool in the presence of 10 mol% $Yb(OTf)_3$ in acetonitrile at 80 °C under an air atmosphere. Notable advantages of this strategy are its ease of handling, consecutive formation of two C–N and two C–C bonds, and broad substrate scope with good yield. It is noteworthy that aliphatic epoxides also worked well to afford 2,3-dialkylquinoline derivatives under standard reaction conditions.

Experimental Section

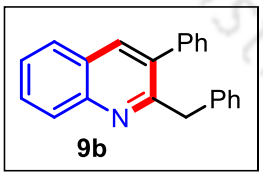
General Procedure for the Synthesis of 2-Benzyl-3-phenylquinoline Derivatives 9

Aryl amine (**1**, 1.0 mmol) and epoxide (**8**, 2.0 mmol) were dissolved in acetonitrile (1.0 mL) into 10 mL round-bottomed flask. After adding $Yb(OTf)_3$ (0.1 mmol, 62 mg) to the reaction mixture, it was kept in a pre-heated oil-bath with constant stirring under air atmosphere at 80 °C. The progress of reaction was monitored by checking TLC time to time. After the completion of reaction, it was brought to room temperature. The acetonitrile was removed in the rotary evaporator and EtOAc (2 x 5 mL) was added to the reaction mixture to extract the product. The combined organic layer was washed with water (2 x 5 mL) followed by brine solution (5 mL) and finally dried over anhydrous sodium sulphate. Finally, the solvent was removed in the rotary evaporator and crude residue was purified on silica gel (60–120 mesh) column chromatography to obtain the expected product **9**.

2-Benzyl-6-methoxy-3-phenylquinoline (9a):[8a] (364 mg, 81%, light yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.86 (s, 1H), 7.40 – 7.37 (m, 4H), 7.22 – 7.18 (m, 2H), 7.12 – 7.09 (m, 3H), 7.06 (d, *J* = 2.8 Hz, 1H), 6.94 (d, *J* = 6.1 Hz, 2H), 4.30 (s, 2H), 3.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 156.6, 143.4, 139.9, 139.8, 136.5, 136.0, 130.5, 129.6, 129.0, 128.4, 128.2, 128.0, 127.7, 126.0, 122.3, 105.1, 55.8, 42.6; **IR (KBr)ν_{max}** 3027 (C–H), 2926 (C–H), 1622 (C=C), 1372 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}NO$ 326.1545 ($M + H^+$); Found 326.1534.



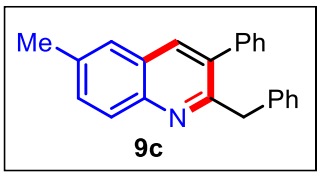
9a



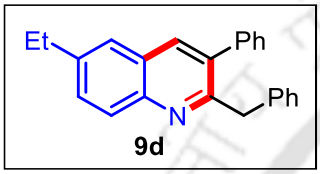
9b

2-Benzyl-3-phenylquinoline (9b):[8a] (216 mg, 73%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.96 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.23 – 7.19 (m, 2H), 7.16 – 7.07 (m, 3H), 6.95 (d, *J* = 7.7 Hz, 2H), 4.35 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.3, 147.3, 139.8, 139.5, 137.1, 136.3, 129.6, 129.0, 128.6, 128.4, 128.2, 127.8, 127.7, 127.6, 127.1, 126.6, 126.1, 42.9; **IR (KBr)ν_{max}** 3058 (C–H), 2923 (C=H), 1599 (C–C), 1228 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{18}N$ 296.1439 ($M + H^+$); Found 296.1449.

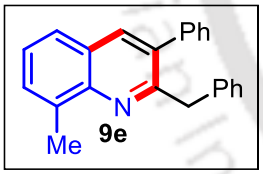
2-Benzyl-6-methyl-3-phenylquinoline (9c):[8a] (235 mg, 76%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.1 Hz, 1H), 7.86 (s, 1H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.36 (m, *J* = 4.9, 1.8 Hz, 3H), 7.19 (m, *J* = 6.4, 3.1 Hz, 2H), 7.09 (m, *J* = 5.6, 3.9 Hz, 3H), 6.95 – 6.91 (m, 2H), 4.31 (s, 2H), 2.53 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.3, 145.9, 140.0, 139.7, 136.5, 136.4, 136.3, 131.9, 129.6, 129.0, 128.8, 128.4, 128.2, 127.7, 127.2, 126.5, 126.0, 42.9, 21.8; **IR (KBr)ν_{max}** 3028 (C–H), 2922 (C–H), 1600 (C=C), 1450, 1369(C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 (M + H^+); Found 310.1595.



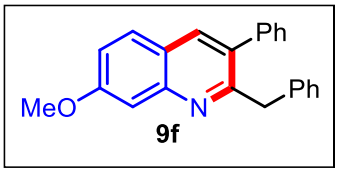
2-Benzyl-6-ethyl-3-phenylquinoline (9d): (243 mg, 75%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.90 (s, 1H), 7.61 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.58 (s, 1H), 7.38 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.22 – 7.18 (m, 2H), 7.13 – 7.08 (m, 3H), 6.94 (d, *J* = 7.8 Hz, 2H), 4.33 (s, 2H), 2.85 (q, *J* = 7.6 Hz, 2H), 1.35 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.3, 146.1, 142.6, 139.9, 139.6, 136.7, 136.2, 130.8, 129.6, 129.0, 128.9, 128.3, 128.2, 127.6, 127.1, 126.0, 125.1, 42.9, 29.0, 15.7; **IR (KBr)ν_{max}** 3058 (C–H), 2963 (C–H), 1614 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 (M + H^+); Found 324.1762.



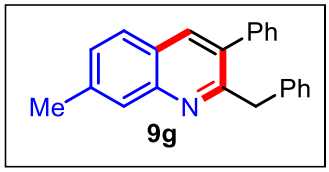
2-Benzyl-8-methyl-3-phenylquinoline (9e): (214 mg, 69%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.32 – 7.27 (m, 4H), 7.15 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.07 – 7.02 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 2H), 4.23 (s, 2H), 2.77 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 146.4, 140.1, 139.9, 137.2, 136.9, 135.7, 129.7, 129.4, 129.3, 128.4, 128.1, 127.6, 126.8, 126.2, 126.0, 125.5, 42.9, 18.1; **IR (KBr)ν_{max}** 3058 (C–H), 2922 (C–H), 1598 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 (M + H^+); Found 310.1617.



2-Benzyl-7-methoxy-3-phenylquinoline (9f):[8a] (215 mg, 66%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.42 (s, 1H), 7.32 – 7.27 (m, 3H), 7.15 – 7.10 (m, 3H), 7.08 – 7.01 (m, 3H), 6.88 (d, *J* = 6.4 Hz, 2H), 4.24 (s, 2H), 3.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.8, 159.1, 139.5, 136.7, 133.9, 129.9, 129.8, 129.5, 128.8, 128.2, 128.0, 127.9, 127.4, 125.8, 122.1, 119.6, 106.9, 55.6, 42.7; **IR (KBr)ν_{max}** 2924 (C–H), 1621 (C=C), 1228 (C–O); **HRMS** (ESI) Calcd For $C_{23}H_{20}NO$ 326.1545 (M + H^+); Found 326.1559.

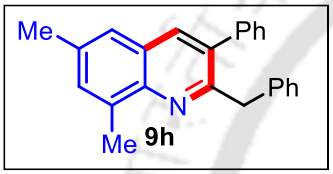


2-Benzyl-7-methyl-3-phenylquinoline (9g): (208 mg, 67%, dark yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 7.96 (s, 1H), 7.92 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 4.9, 1.8 Hz, 4H), 7.21 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.12 (dt, *J* = 6.9, 2.0 Hz, 3H), 6.98 – 6.95 (m, 2H), 4.33 (s, 2H), 2.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.1, 147.5, 139.9, 139.8, 139.6, 136.8, 135.4, 129.7, 129.0, 128.8, 128.3, 128.2, 128.1, 127.6, 127.3, 126.0, 125.1, 42.9, 22.1; **IR (KBr)ν_{max}** 3057 (C–H), 2921 (C–H), 1600 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 ($M + H^+$); Found 310.1612.



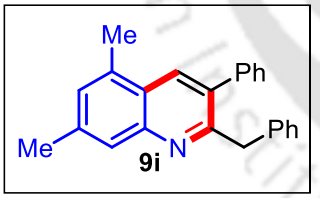
9g

2-Benzyl-6,8-dimethyl-3-phenylquinoline (9h): (233 mg, 72%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.45 – 7.34 (m, 5H), 7.25 – 7.20 (m, 2H), 7.16 – 7.08 (m, 3H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.29 (s, 2H), 2.81 (s, 3H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.9, 145.1, 140.3, 140.0, 136.8, 136.4, 135.9, 135.7, 131.8, 129.7, 129.3, 128.4, 128.1, 127.6, 126.9, 125.9, 124.3, 42.9, 21.8, 18.1; **IR (KBr)ν_{max}** 3058 (C–H), 2920 (C–H), 1625 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1735.



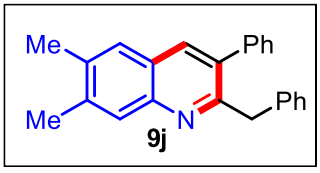
9h

2-Benzyl-5,7-dimethyl-3-phenylquinoline (9i): (236 mg, 73%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.80 (s, 1H), 7.52 – 7.47 (m, 1H), 7.40 – 7.37 (m, 3H), 7.24 – 7.18 (m, 3H), 7.13 – 7.09 (m, 2H), 6.94 (d, *J* = 7.9 Hz, 2H), 4.32 (s, 2H), 2.61 (s, 3H), 2.54 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6, 147.9, 140.4, 139.8, 139.5, 138.6, 134.9, 134.3, 133.6, 129.8, 129.4, 129.0, 128.6, 128.4, 128.2, 128.1, 127.7, 127.7, 126.4, 126.0, 124.5, 42.9, 22.1, 18.7; **IR (KBr)ν_{max}** 3057 (C–H), 2921 (C–H), 1621 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1756.



9i

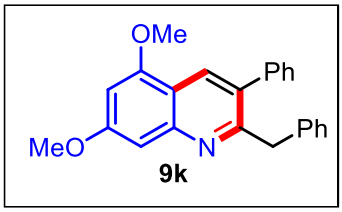
2-Benzyl-6,7-dimethyl-3-phenylquinoline (9j): (246 mg, 76%, brown solid); mp 76–78 °C, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.75 (s, 1H), 7.43 (s, 1H), 7.27 (dd, *J* = 4.9, 1.9 Hz, 3H), 7.10 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.01 (td, *J* = 6.5, 6.1, 2.9 Hz, 3H), 6.85 (d, *J* = 7.6 Hz, 2H), 4.22 (s, 2H), 2.40 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 146.5, 140.1, 139.8, 136.4, 136.1, 135.4, 129.7, 129.0, 128.4, 128.3, 128.3, 128.2, 127.5, 126.8, 125.9, 125.7, 42.8,



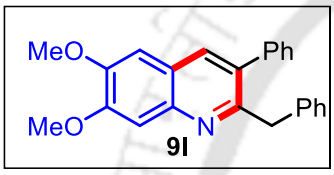
9j

20.7, 20.2; **IR (KBr)ν_{max}** 3024 (C–H), 2922 (C–H), 1600 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1771**.**

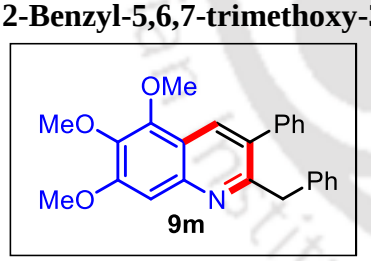
2-Benzyl-5,7-dimethoxy-3-phenylquinoline (9k): (278 mg, 78%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.38 – 7.32 (m, 3H), 7.23 – 7.18 (m, 2H), 7.15 – 7.08 (m, 4H), 6.96 (d, *J* = 6.5 Hz, 2H), 6.51 (d, *J* = 2.1 Hz, 1H), 4.30 (s, 2H), 3.97 (s, 3H), 3.94 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 159.6, 156.2, 149.5, 140.3, 139.8, 133.2, 132.0, 129.8, 128.9, 128.3, 128.2, 127.4, 126.0, 115.4, 99.5, 98.1, 55.9, 55.9, 42.8; **IR (KBr)ν_{max}** 3026 (C–H), 2935 (C–H), 1623 (C=C), 1244 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}NO_2$ 356.1651 ($M + H^+$); Found 356.1666.



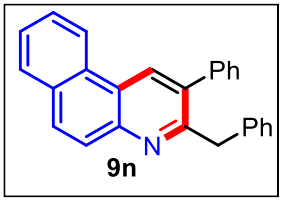
2-Benzyl-6,7-dimethoxy-3-phenylquinoline (9l):[8b] (284 mg, 80%, light brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.50 (s, 1H), 7.36 (t, *J* = 4.0 Hz, 3H), 7.23 – 7.19 (m, 2H), 7.15 – 7.08 (m, 3H), 7.03 (s, 1H), 6.95 (d, *J* = 6.5 Hz, 2H), 4.29 (s, 2H), 4.06 (s, 3H), 4.00 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.6, 152.6, 149.9, 144.2, 140.1, 139.9, 135.6, 134.5, 129.7, 128.9, 128.3, 128.2, 127.5, 125.9, 122.5, 107.7, 104.9, 56.4, 56.2, 42.5; **IR (KBr)ν_{max}** 3026 (C–H), 2929 (C–H), 1621 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}NO_2$ 356.1651 ($M + H^+$); Found 356.1646.



2-Benzyl-5,6,7-trimethoxy-3-phenylquinoline (9m): (272 mg, 70%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.30 – 7.26 (m, 3H), 7.25 (s, 1H), 7.15 – 7.11 (m, 2H), 7.02 (t, *J* = 8.0 Hz, 3H), 6.85 (d, *J* = 6.4 Hz, 2H), 4.21 (s, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 156.1, 147.1, 145.0, 140.9, 140.1, 139.7, 133.9, 131.6, 129.7, 128.9, 128.3, 128.2, 127.5, 126.0, 118.0, 103.8, 61.7, 61.4, 56.3, 42.5; **IR (KBr)ν_{max}** 3058 (C–H), 2937 (C–H), 1616 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{25}H_{24}NO_3$ 386.1756 ($M + H^+$); Found 386.1758.

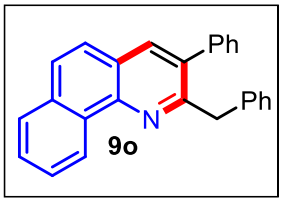


3-Benzyl-2-phenylbenzo[f]quinoline (9n): (223 mg, 64%, light yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.59 – 8.54 (m, 1H), 8.09 (d, *J* = 9.1 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.97 – 7.92 (m, 1H), 7.68 – 7.61 (m, 2H), 7.44 (ddt, *J* = 5.8, 4.0, 2.1 Hz, 3H), 7.34 – 7.28 (m, 2H), 7.14 (dq, *J* = 6.8, 5.8, 5.0 Hz, 3H), 7.02 (d, *J* = 6.6 Hz, 2H), 4.40 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 147.1, 140.1, 139.8, 136.1, 132.4, 131.9, 130.9, 129.8, 129.7, 129.0, 128.9, 128.5, 128.3, 127.9, 127.8, 127.3, 127.2, 126.1, 123.9, 122.8, 42.5; **IR**

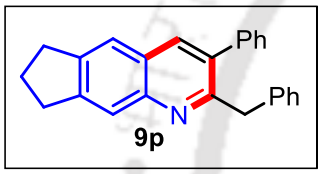


(KBr)ν_{max} 3058 (C–H), 2924 (C–H), 1608 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{26}H_{20}N$ 346.1596 ($M + H^+$); Found 346.1626.

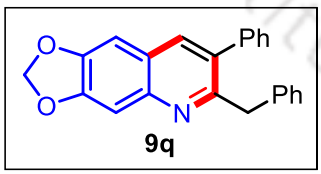
2-Benzyl-3-phenylbenzo[h]quinoline (9o): (232 mg, 67%, light yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.44 (dd, *J* = 5.2, 1.9 Hz, 3H), 7.32 (dt, *J* = 6.6, 2.3 Hz, 3H), 7.22 – 7.13 (m, 5H), 4.42 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 145.3, 140.1, 140.0, 136.9, 136.3, 133.8, 131.7, 129.7, 129.3, 128.5, 128.3, 128.2, 127.9, 127.7, 127.6, 127.1, 126.1, 125.2, 124.8, 124.7, 42.7; **IR (KBr)ν_{max}** 3059 (C–H), 2922 (C–H), 1600 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{26}H_{20}N$ 346.1596 ($M + H^+$); Found 346.1582.



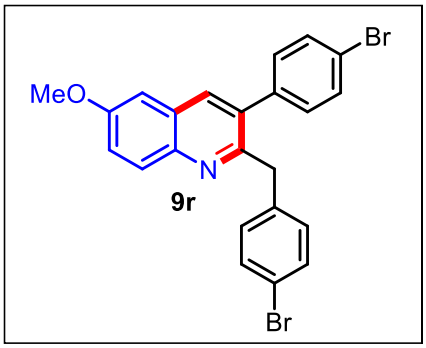
2-Benzyl-3-phenyl-7,8-dihydro-6H-cyclopenta[g]quinoline (9p): (238 mg, 71%, grey solid); mp 81–83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.87 (s, 1H), 7.58 (s, 1H), 7.36 (dd, *J* = 4.9, 1.8 Hz, 3H), 7.22 – 7.17 (m, 2H), 7.15 – 7.04 (m, 3H), 6.94 (d, *J* = 7.9 Hz, 2H), 4.31 (s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 3.07 (t, *J* = 7.3 Hz, 2H), 2.18 (p, *J* = 7.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 147.8, 144.1, 140.1, 139.9, 136.7, 135.2, 129.7, 129.0, 128.6, 128.3, 128.2, 127.5, 126.2, 125.9, 123.3, 121.6, 76.9, 42.8, 33.2, 32.7, 26.4; **IR (KBr)ν_{max}** 3022 (C–H), 2922 (C–H), 1599 (C=C) cm^{-1}; **HRMS** (ESI) Calcd For $C_{25}H_{22}N$ 336.1752 ($M + H^+$); Found 336.1725.



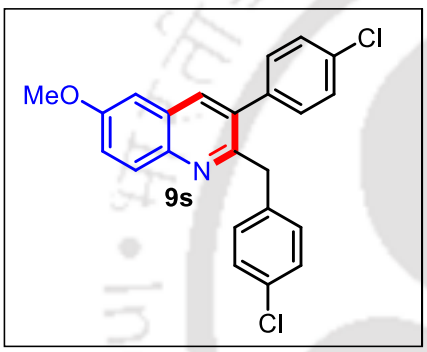
6-Benzyl-7-phenyl-[1,3]dioxolo[4,5-g]quinoline (9q):[8b] (245 mg, 72%, brown solid); mp 73–75 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.44 (s, 1H), 7.39 – 7.34 (m, 3H), 7.22 – 7.18 (m, 2H), 7.16 – 7.08 (m, 3H), 7.02 (s, 1H), 6.99 – 6.91 (m, 2H), 6.10 (s, 2H), 4.26 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.7, 150.9, 147.9, 145.6, 140.0, 139.9, 136.2, 134.5, 129.7, 129.0, 128.4, 128.2, 127.6, 126.0, 123.9, 105.7, 102.6, 101.8, 42.5; **IR (KBr)ν_{max}** 3021 (C–H), 2927 (C–H), 1610 (C=C), 1228 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{18}NO_2$ 340.1338 ($M + H^+$); Found 340.1334.



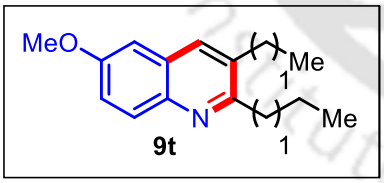
2-(4-Bromobenzyl)-3-(4-bromophenyl)-6-methoxyquinoline (9r): (362 mg, 75%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.2 Hz, 1H), 7.82 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.25 (d, *J* = 6.0 Hz, 2H), 7.06 – 7.02 (m, 3H), 6.81 (d, *J* = 8.4 Hz, 2H), 4.19 (s, 2H), 3.92 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 155.6, 143.6, 138.8, 138.6, 136.1, 135.1, 131.6, 131.4, 131.2, 130.7, 129.3, 128.0, 122.7, 122.2, 120.2, 105.1, 55.8, 42.1; **IR (KBr)ν_{max}** 3022 (C–H), 2924 (C–H), 1623 (C=C), 1225 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{18}Br_2NO$ 481.9755 ($M+H^+$); found 481.9962**.**



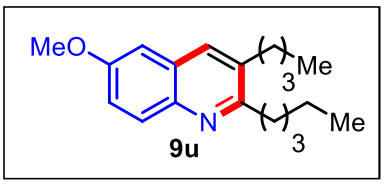
2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-6-methoxyquinoline (9s): (284 mg, 72%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.83 (s, 1H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 4H), 7.05 (d, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.22 (s, 2H), 3.93 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 155.8, 143.6, 138.3, 138.1, 136.2, 135.2, 134.1, 130.9, 130.6, 130.3, 128.9, 128.7, 128.5, 128.0, 122.7, 105.1, 55.8, 42.1; **IR (KBr)ν_{max}** 3028 (C–H), 2922 (C–H), 1623 (C=C), 1228 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{18}Cl_2NO$ 394.0765 ($M+H^+$); found 394.0683.



3-Ethyl-6-methoxy-2-propylquinoline (9t):[6b] (181 mg, 79%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.2 Hz, 1H), 7.76 (s, 1H), 7.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 3.90 (s, 3H), 2.91 (t , *J* = 7.5 Hz, 2H), 2.81 (q, *J* = 7.5 Hz, 2H), 1.81 (sext, *J* = 7.4 Hz, 2H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.5, 157.3, 142.6, 135.8, 133.1, 130.0, 128.3, 121.0, 104.9, 55.6, 37.7, 25.4, 23.1, 14.7, 14.5; **IR (KBr)ν_{max}** 3034 (C–H), 2960 (C–H), 1619 (C=C), 1224 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{20}NO$ 230.1545 ($M+H^+$); found 230.1542.

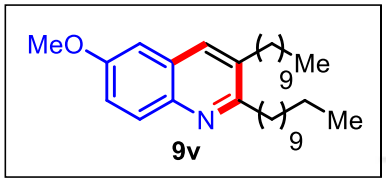


3-Butyl-6-methoxy-2-pentylquinoline (9u): (217 mg, 70% dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.2 Hz, 1H), 7.74 (s, 1H), 7.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 3.90 (s, 3H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.76 (t, *J* = 8.0 Hz, 2H), 1.77 (quint, *J* = 8.0 Hz, 2H), 1.66 (quint, *J* = 8.0 Hz, 2H), 1.48 –



1.38 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 3H), 0.93 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 157.3, 142.7, 134.5, 134.1, 130.0, 128.2, 121.0, 104.8, 55.6, 35.8, 32.9, 32.3, 32.3, 29.7, 22.9, 22.8, 14.3, 14.2; **IR (KBr)ν_{max}** 3025 (C–H), 2952 (C=H), 1623 (C=C), 1233 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{19}H_{28}NO$ 286.2171 ($M+H^+$); found 286.2173.

3-Decyl-6-methoxy-2-undecylquinoline (9v): (297 mg, 65%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.2 Hz, 1H), 7.74 (s, 1H), 7.26 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 3.89 (s, 3H), 2.92 (t, *J* = 7.3 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 1.77 (quint, *J* = 7.7 Hz, 2H), 1.67 (quint, *J* = 7.5 Hz, 2H), 1.48 – 1.41 (m, 4H), 1.35 (d, *J* = 6.6 Hz, 26H), 0.90 – 0.87 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 157.3, 142.7, 134.6, 134.0, 130.1, 128.2, 120.9, 104.8, 55.6, 35.9, 32.6, 32.1, 32.1, 30.8, 30.1, 30.0, 29.9, 29.8, 29.8, 29.8, 29.8, 29.7, 29.5, 29.5, 22.9, 14.3; **IR (KBr)ν_{max}** 3028 (C–H), 2921 (C–H), 1622 (C=C), 1274 (C–O) cm^{-1}; **HRMS** (ESI) Calcd For $C_{31}H_{52}NO$ 454.4049 ($M+H^+$); found 454.4058.



9v

^{1}H NMR (400 MHz, $CDCl_3$): 2-benzyl-6-methoxy-3-phenylquinoline **(9a)**

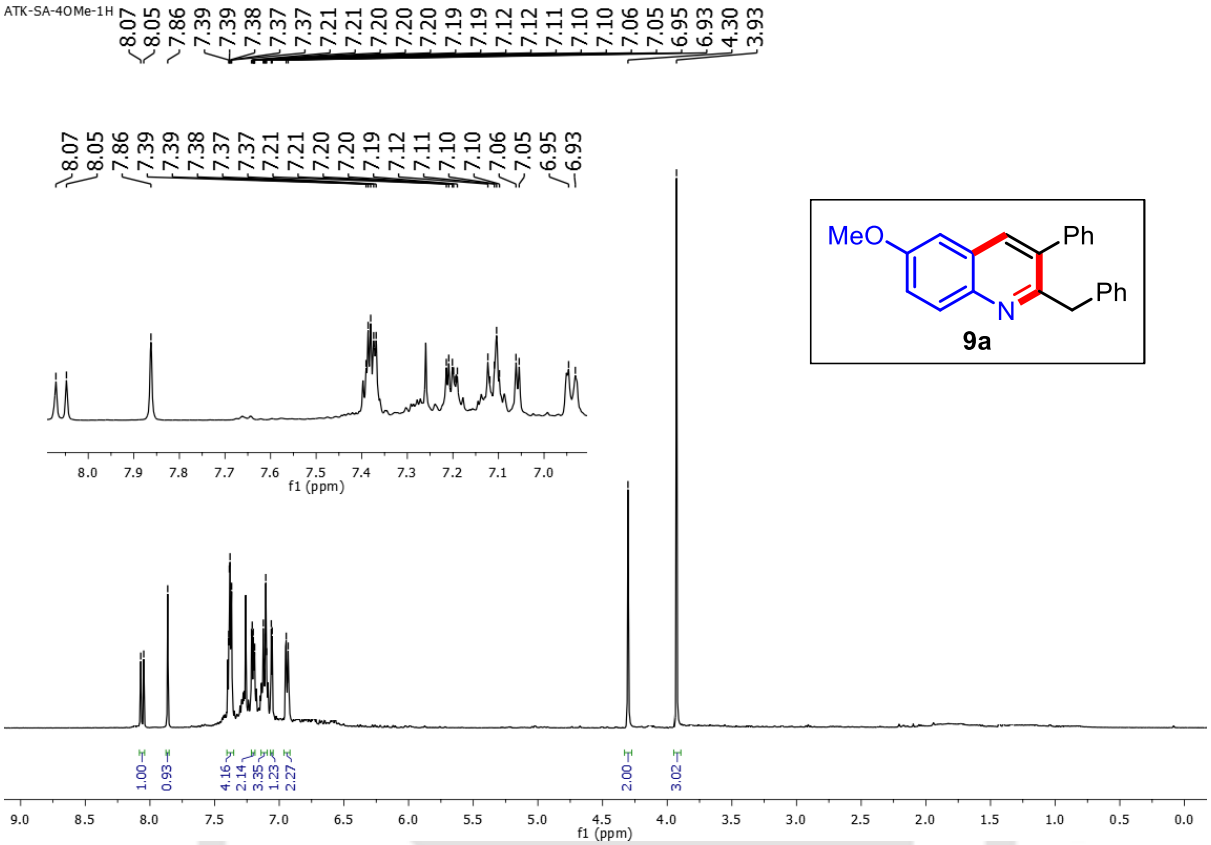


Figure 2.8a

^{13}C NMR (100 MHz, $CDCl_3$): 2-benzyl-6-methoxy-3-phenylquinoline **(9a)**

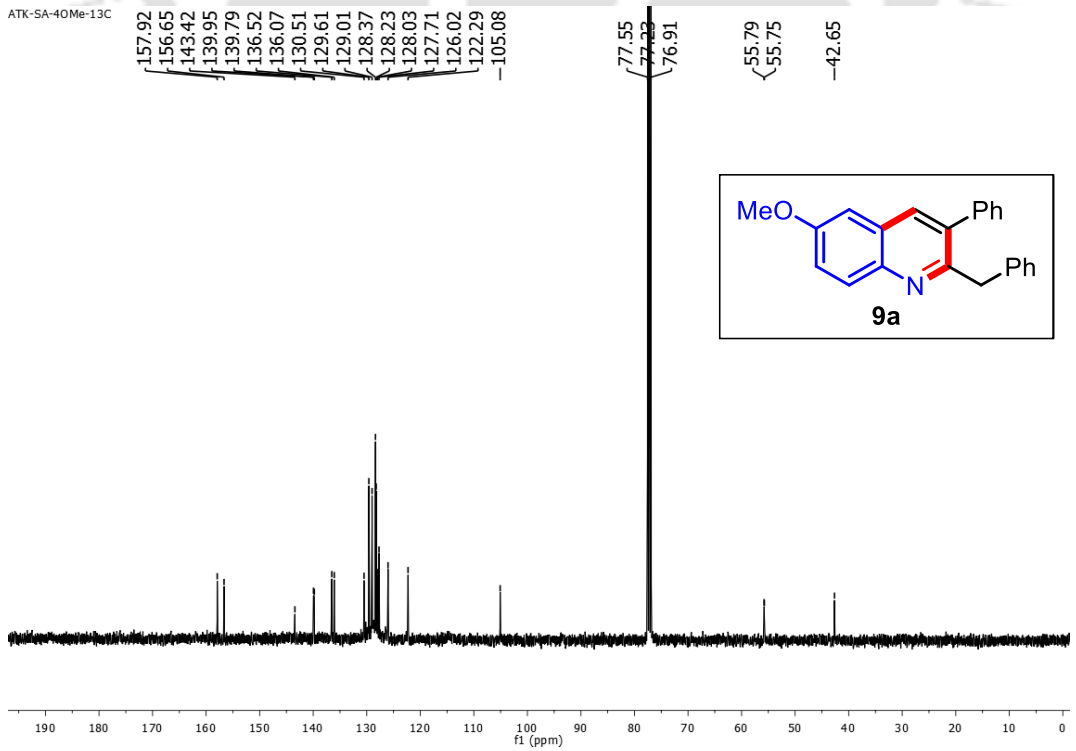


Figure 2.8b

HRMS spectrum: 2-benzyl-6-methoxy-3-phenylquinoline **(9a)**

Sample Name	SA-4-OME	**Position**	P1-B4	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4-OME.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	1/8/2019 11:07:34 AM

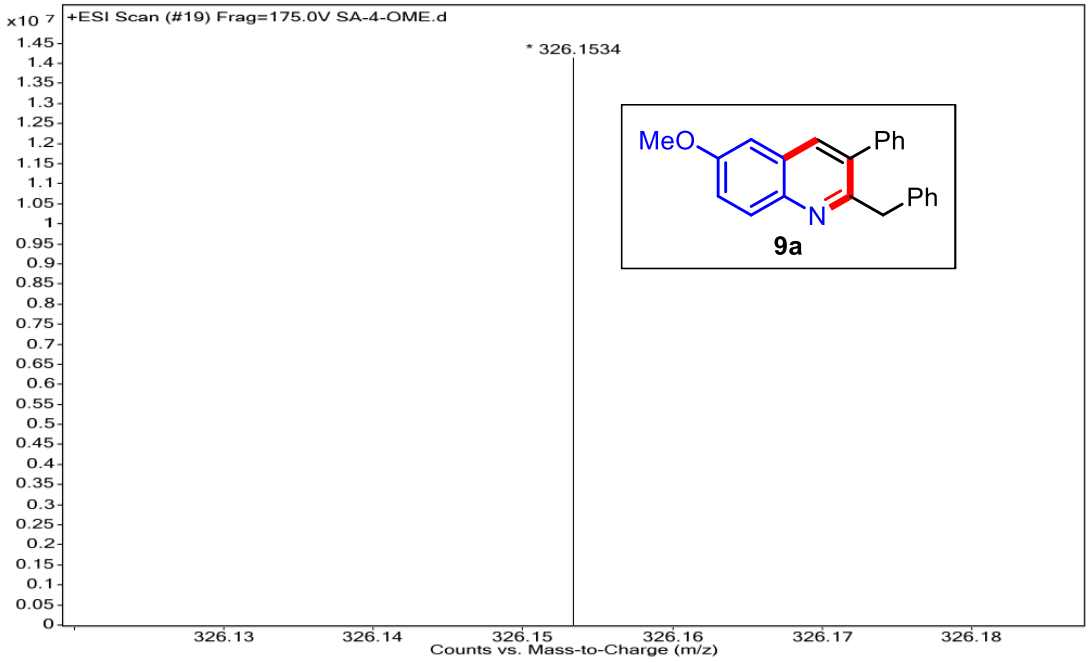
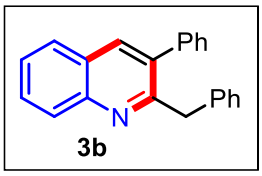


Figure 2.8c

^{1}H NMR (400 MHz, $CDCl_3$): 2-benzyl-3-phenylquinoline **(9b)**



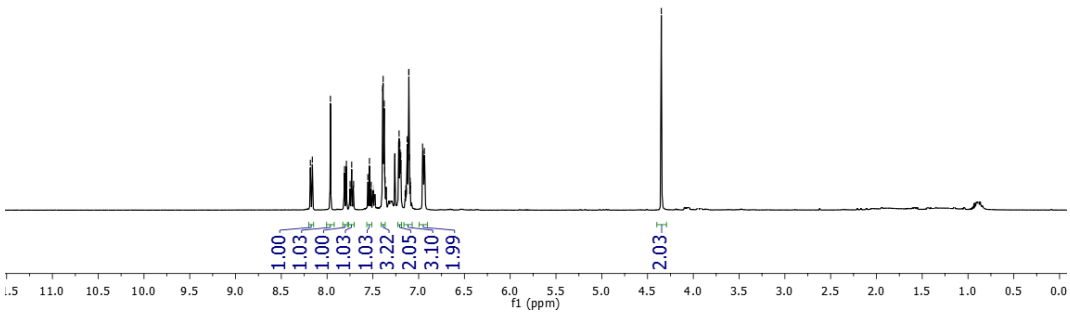


Figure 2.9a

^{13}C NMR (100 MHz, $CDCl_3$): 2-benzyl-3-phenylquinoline **(3b)**

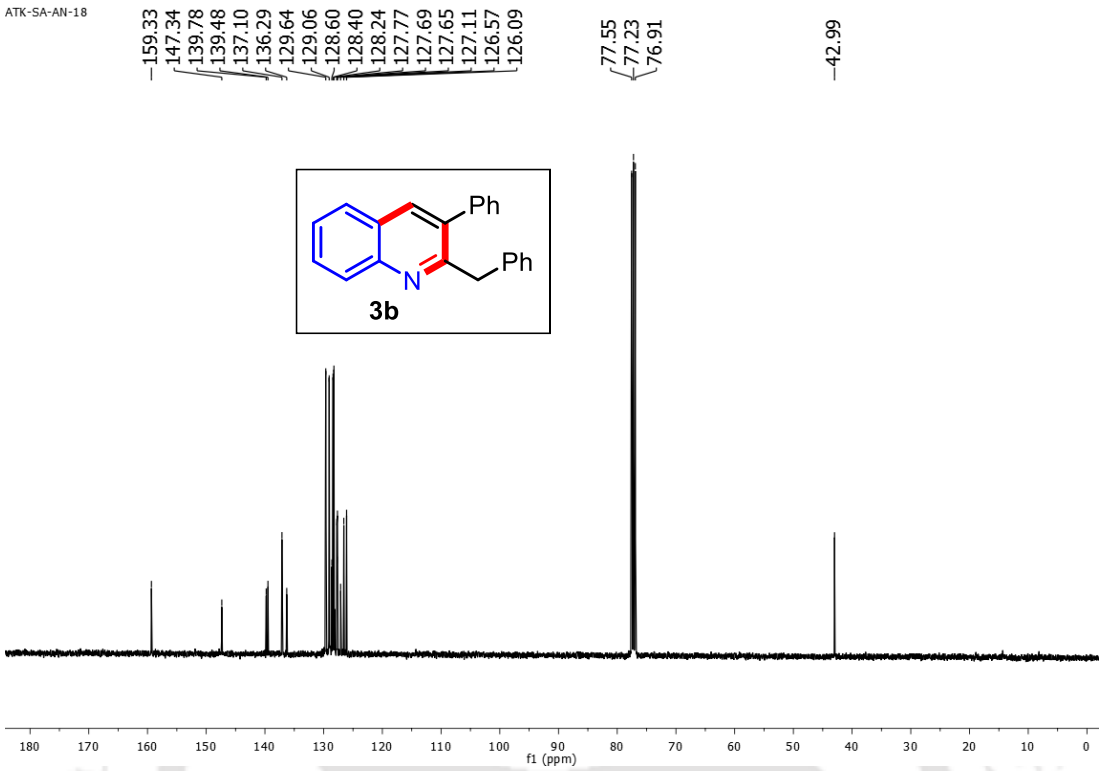


Figure 2.9b

HRMS spectrum: 2-benzyl-3-phenylquinoline **(3b)**

Sample Name	SA-AN-18	**Position**	P1-E7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-AN-18.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	1/22/2019 11:11:54 AM

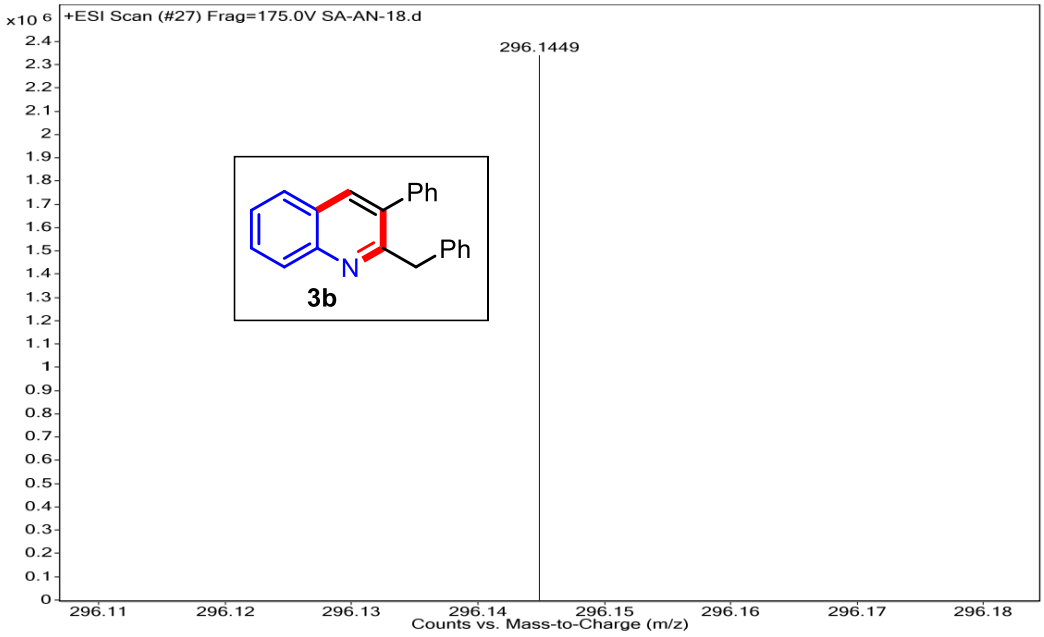


Figure 2.9c

^{1}H NMR (400 MHz, $CDCl_3$): 2-benzyl-3-phenylquinoline **(9d)**

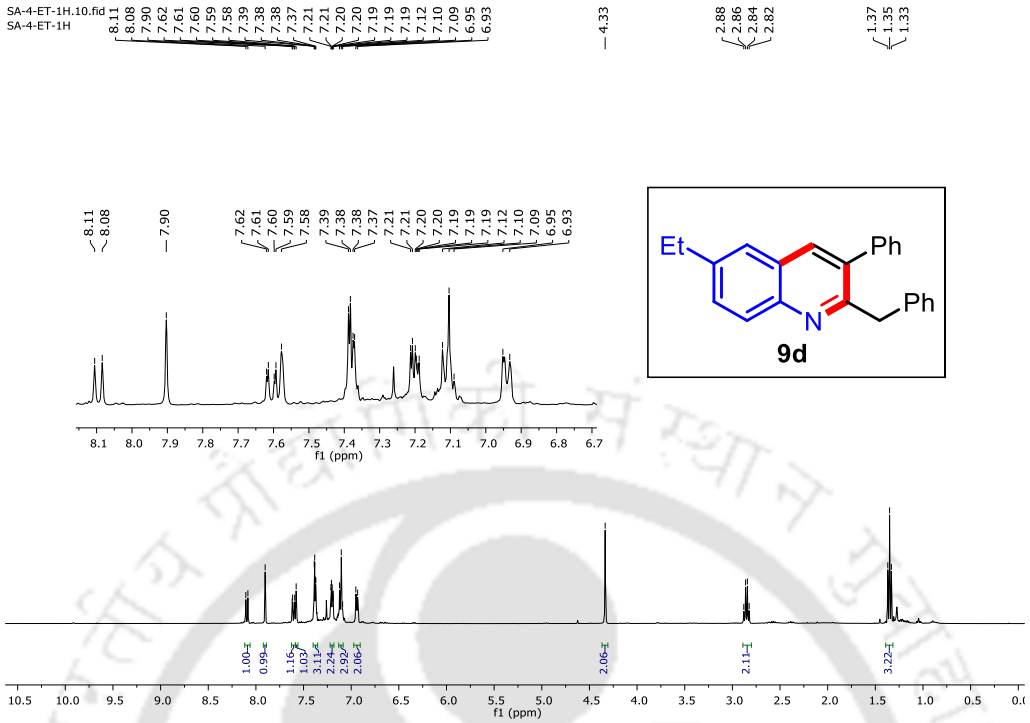


Figure 2.10a

^{13}C NMR (100 MHz, $CDCl_3$): 2-benzyl-3-phenylquinoline **(9d)**

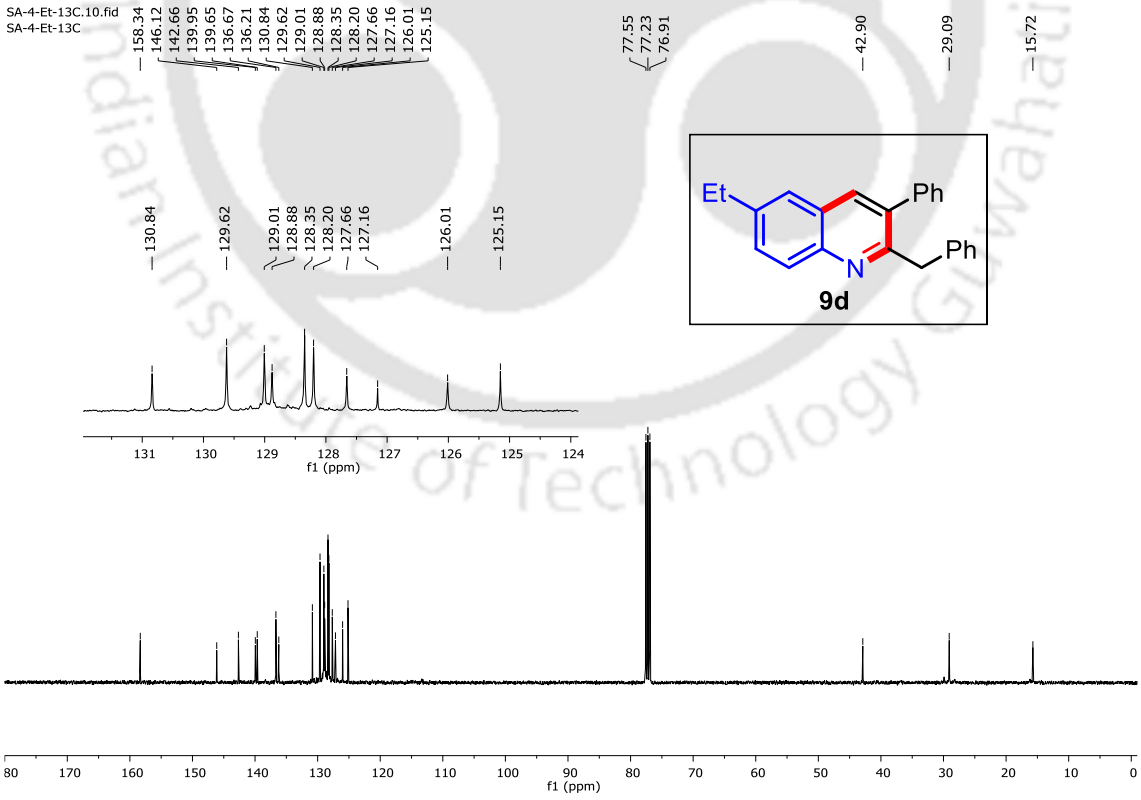


Figure 2.10b

HRMS spectrum: 2-benzyl-3-phenylquinoline **(9d)**

Sample Name	SAMPLE 73	**Position**	P1-E6	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4-ET.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	1/23/2019 6:19:44 PM

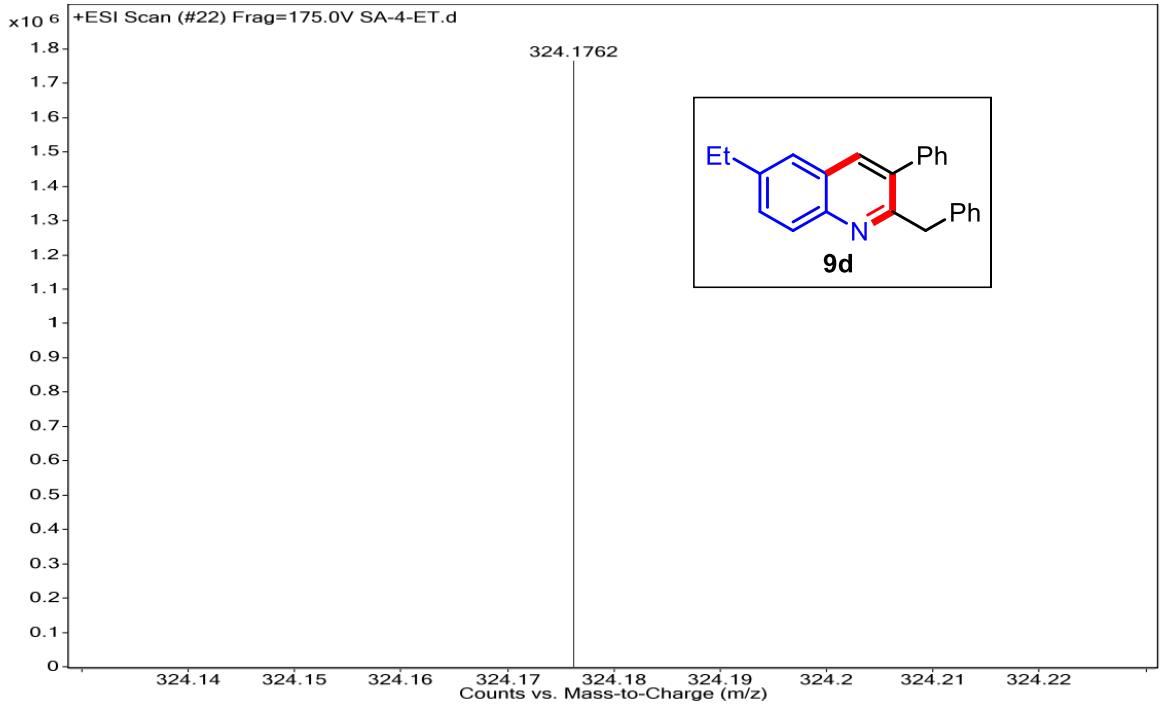
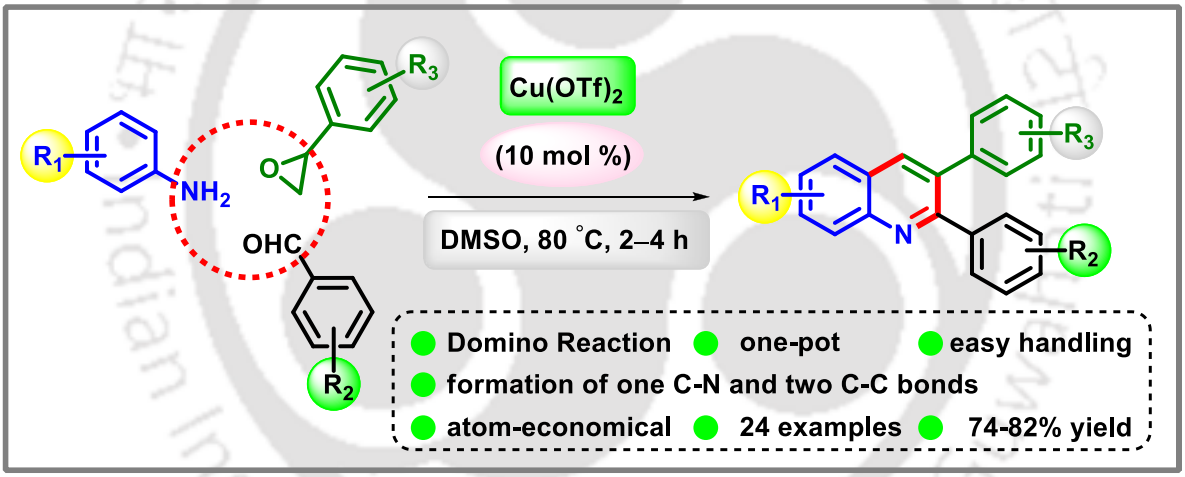


Figure 2.10c

Chapter II: Part C

Synthesis of 2,3-Diarylquinoline Derivatives through Three-component Reaction of Aryl Amines, Aryl Aldehydes and Styrene Oxides in Presence of Copper(II) Triflate Catalyst

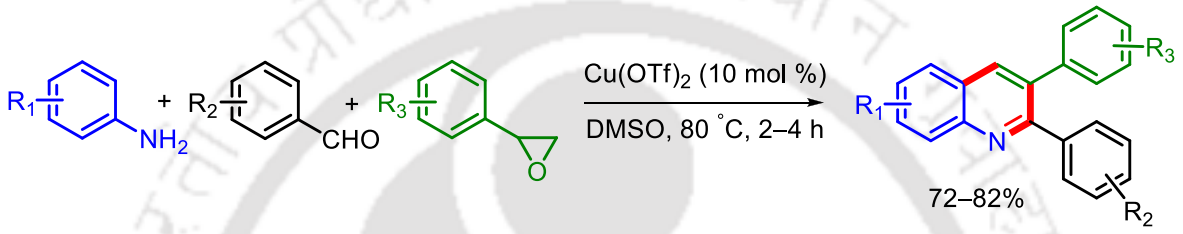


Result & Discussion

Experimental Section

Results and Discussion

The importance and synthetic strategies for synthesizing 2-benzyl-3-arylquinolines have already been described in chapter I. This part of the chapter II illustrates an efficient and expedient synthetic protocol to access a wide range of 2,3-diarylquinoline derivatives from three-component reactions of readily available aryl amines, aryl aldehydes and styrene oxides in the presence of 10 mol% copper(II) triflate under mild conditions (Scheme **2.9**). Advantages of this strategy are one-pot, mild reaction conditions, shorter time, high regioselectivity, easy handling, formation of one C-N and two C-C bonds and an easy access to structurally diverse 2,3-diarylquinoline frameworks with high yield.

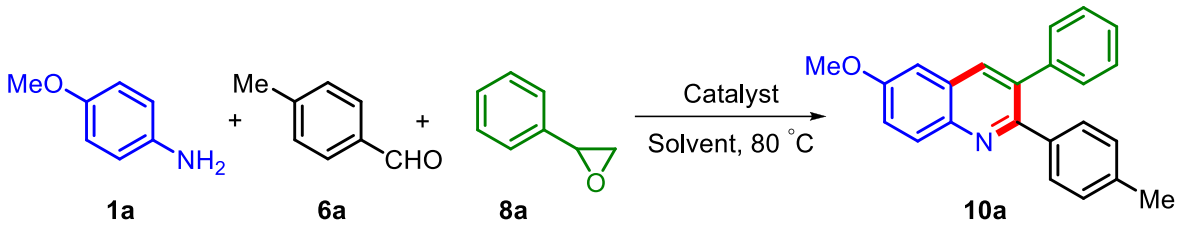


Scheme 2.9. Synthetic approach for synthesis of various 2,3-diarylquinolines.

Multicomponent reactions (MCRs) are well-known and well established synthetic approaches, which are extensively explored in synthesis of bioactive heterocycles, combinatorial and medicinal chemistry.[9] These reactions are usually one-pot, in which three or more reactants react sequentially to form a product, where all or most of atoms are incorporated into the newly formed product.[10*a–e*] Notable features of this class of reactions are high atom economy, efficiency, diversity, speed and environmentally benign nature.[11*a,b*] Over the years, synthetic community has put much effort in designing new MCRs for synthesizing structurally complex molecules due to numerous advantages.[11–12] In the view of above-mentioned advantages of MCRs, this tool has been explored for synthesis of 2,3-diarylquinoline scaffolds.

This study was started with finding optimized reaction conditions. For this purpose, *p*-anisidine **1a**, *p*-tolualdehyde **6a** and styrene oxide **8a** were chosen as model substrates and results have been presented in Table 2.8. At first, a reaction was carried out without a catalyst in DMSO at room temperature as well as heating at 80 °C (Table 2. 8, entries 1 & 2). No desired product was obtained in both cases other than imine formation. Reaction also did not proceed when it was performed in the presence of 5 mol% $Cu(OTf)_2$ at room temperature (Table 2. 8, entry 3). Interestingly, an identical reaction provided **10a** in 31% yield upon heating at 80 °C (Table 2. 8, entry 4).

Table 2.8. Optimization of reaction conditions[a,b]



Entry	Catalyst	Mol %	Solvent	Time	Yield 10a (%)[b]
1[c]	–	–	DMSO	4 h	NR
2	–	–	DMSO	4 h	NR
3[c]	$Cu(OTf)_2$	5	DMSO	4 h	NR
4	$Cu(OTf)_2$	5	DMSO	4 h	31
5	**$Cu(OTf)_2$**	**10**	**DMSO**	**2 h**	**81**
6	$Cu(OTf)_2$	15	DMSO	2 h	72
7	$Bi(OTf)_3$	10	DMSO	2 h	36
8	$Sc(OTf)_3$	10	DMSO	2 h	28
9	$Yb(OTf)_3$	10	DMSO	2 h	25
10	AgOTf	10	DMSO	2 h	30
11	$Cu(OTf)_2$	10	dioxane	2 h	30
12	$Cu(OTf)_2$	10	$(CH_2Cl)_2$	2 h	35
13	$Cu(OTf)_2$	10	THF	2 h	26
14	$Cu(OTf)_2$	10	DMF	2 h	NR
15	$Cu(OTf)_2$	10	EtOH	2 h	NR
16	$Cu(OTf)_2$	10	H_2O	2 h	NR

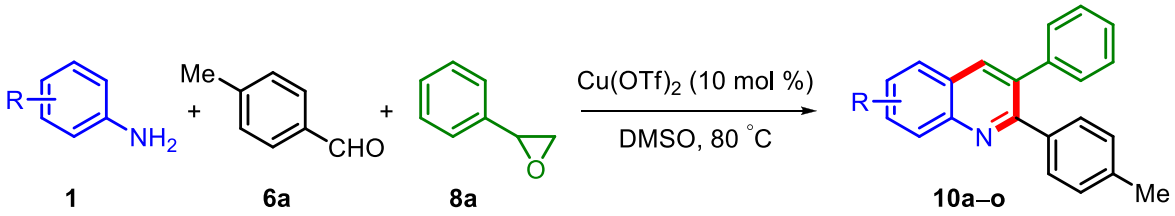
[a]Reaction conditions: All reactions were performed using *p*-anisidine **1a** (1.0 mmol), *p*-tolualdehyde **6a** (1.0 mmol), and styrene oxide **8a** (1.0 mmol) in solvent (1.0 mL) at 80 °C. [b]Isolated yield. [c]Reaction performed at room temperature. NR (no desired product).

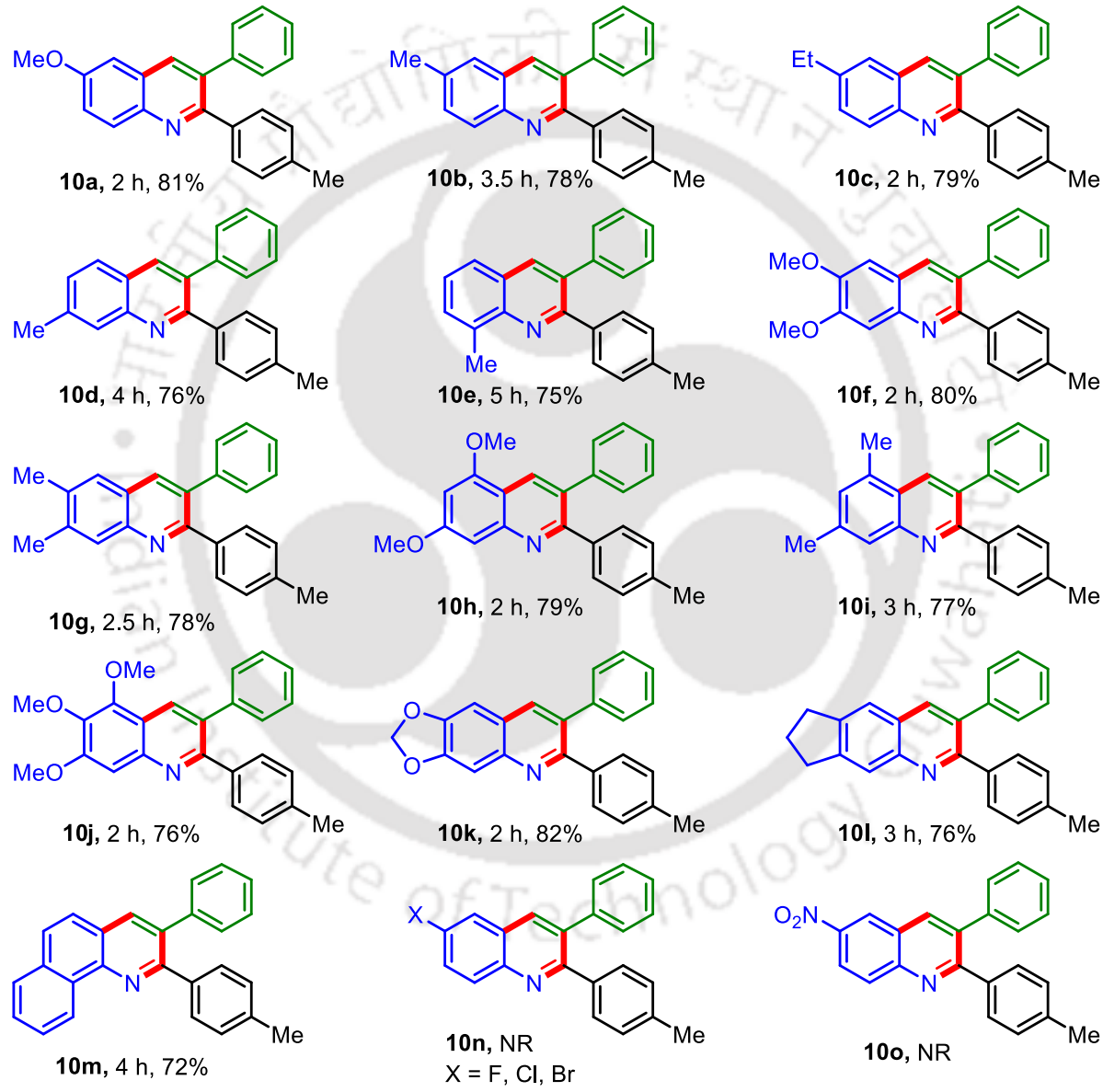
Next, attempts were made to improve yield of desired product **10a** by screening different parameters, such as catalyst loadings, changing catalysts and solvents. Firstly, effect of loading of catalyst was tested and model reactions were carried out in the presence of 10 mol% $Cu(OTf)_2$ (Table 2. 8, entry 5). It was noted that reaction proceeded faster and completed in 2 h. The yield of product **10a** also improved significantly. When catalyst loading increased from 10 to 15 mol% $Cu(OTf)_2$, yield of product **10a** (Table 2. 8, entry 6) did not increase. In order

to check the efficacy of other catalysts, similar reaction was screened with different catalysts, such as $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$ and AgOTf (Table 2. 8, entries 7–10). It was observed that none of them found to be better than $Cu(OTf)_2$ amongst various Lewis acids. To verify the effect of solvent, same set of reactions was performed in the presence of 10 mol% $Cu(OTf)_2$ in different solvents, such as 1,4-dioxane, 1,2-dichloroethane $(CH_2Cl)_2$, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), ethanol (EtOH) and water (H_2O). It was found that these solvents gave either low yield or no reaction at all (Table 2. 8, entries 11–16). In view of the above extensive optimization, best reaction conditions to obtain desired products were: 10 mol% $Cu(OTf)_2$ as a catalyst in DMSO solvent and heating at 80 °C in terms of both time and yield.

After achieving optimized reaction conditions, the scope and applicability of developed method were investigated using different substituted anilines **1** with *p*-tolualdehyde **6a** and styrene oxide **8a**; successful results have been shown in Table 2.9. Reactions occurred smoothly with anilines containing electron-donating groups at various positions of aromatic ring. Reaction with anilines containing electron-donating groups (4-Me and 4-Et) at 4-position underwent very well and produced corresponding products **10b** and **10c** in 78% and 79% yield, respectively. Substituent (3-Me and 2-Et) at 3- and 2-positions of aniline also showed very good results and reactions underwent quickly to afford anticipated products **10d** and **10e** in 76% and 75% yield, respectively. Similarly, disubstituted anilines containing (3,4-OMe, 3,4-Me, 3,5-OMe and 3,5-Me) under optimized conditions provided expected products **10e–h** in 80–77% yield. Gratifyingly, aniline containing (3,4,5-OMe) being sterically crowded also gave corresponding quinoline derivative **10j** in 76% yield. Fused aniline derivatives, such as 3,4-(methylenedioxy)aniline, 5-aminoindane and 1-naphthylamine, showed good reactivity and delivered desired structurally complex quinoline derivatives **10k–m** in 82–72% yield. Other regioisomers of compounds **10d**, **10f**, **10g**, **10k** and **10l** were not obtained due to steric hindrance of methyl group at the 3-position of the aniline moiety as well as more electron density at 4-position with respect to methyl or -OMe group due to the *-I* effect. Unfortunately, aniline having electron-withdrawing substituents (-F and $-NO_2$) did not provide corresponding products **10n** and **10o** as expected under identical reaction conditions because of less electron density at the 2-position with respect to amine group. In case of substituents (-Cl and -Br) also, reaction failed because it enhanced electron density at 4-position due to delocalization of electrons on halogen atoms rather than increasing at 2-position with respect to amino group.

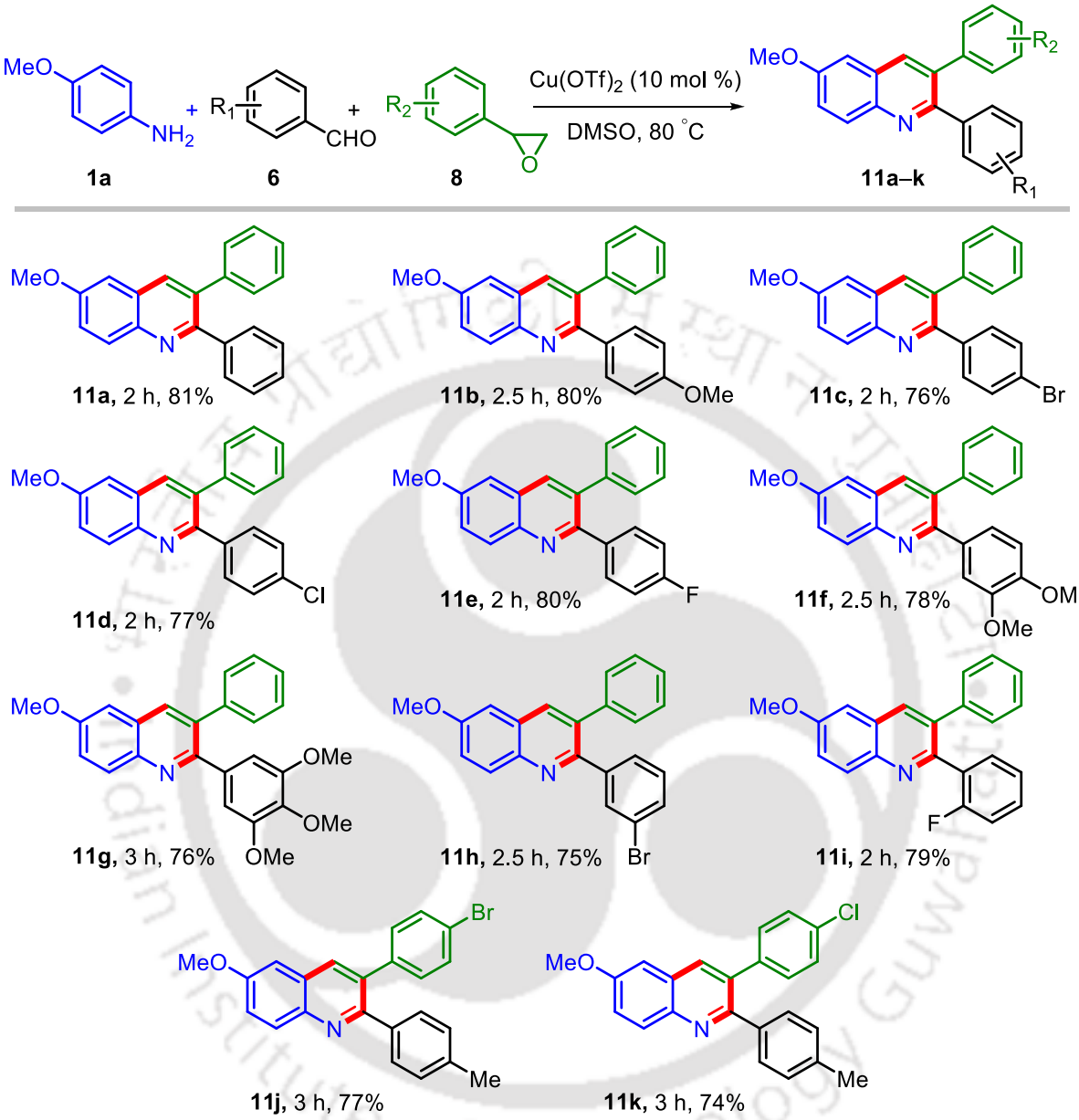
Table 2.9. Reactions of different substituted anilines **1** with *p*-tolualdehyde **6a** and styrene oxide **8a**[a,b]





[a]Reaction conditions: All reactions were carried out using substituted anilines **1** (1.0 mmol), *p*-tolualdehyde **6a** (1.0 mmol), styrene oxide **8a** (1.0 mmol), $Cu(OTf)_2$ (10 mol%) and DMSO (1.0 mL) at 80 °C. [b]Isolated yield. NR (no desired product).

Table 2.10. Reactions of *p*-anisidine **1a** with different benzaldehyde **6** and styrene oxide derivatives **8**[a,b]



[a]Reaction conditions: All reactions were carried out using *p*-anisidine **1** (1.0 mmol), benzaldehyde **6** (1.0 mmol), styrene oxides **8** (1.0 mmol), $Cu(OTf)_2$ (10 mol%), and DMSO (1.0 mL) at 80 °C. [b]Isolated yield.

Inspired by successful results described above, scope and generality of this strategy were explored further with *p*-anisidine **1a** and different benzaldehyde **6** and styrene oxides **8** under optimized conditions; successful results have been presented in Table 2.10. It is noteworthy that electron-donating and electron-withdrawing substituents present on benzaldehyde **6** were well tolerated. Reaction of *p*-anisidine**1a** with simple benzaldehyde and styrene oxide **8a** proceeded well to furnish desired product **11a** in 81% yield. Similarly, benzaldehyde

containing substituents (4-OMe, 4-Br, 4-Cl and 4-F) at 4-position showed good reactivity under optimized conditions, and provided expected products **11b–e** in very good yield. Likewise, benzaldehydes containing strong electron-donating groups (2,4-OMe and 3,4,5-OMe) upon reaction with *p*-anisidine **1a** and styrene oxide **8a** also gave corresponding products **11f** and **11g** in 78% and 76% yield, respectively. Benzaldehydes having groups (3-Br and 2-F) found to be reactive enough and provided desired products **11h** and **11i** in 75% and 79% yield, respectively. Reactions of styrene oxides having groups (4-Br and 4-Cl) with *p*-anisidine **1a** and *p*-tolualdehyde **6a** successfully afforded expected products **11j** and **11k** in 77% and 74% yield, respectively.

Structure of all synthesized compounds was elucidated by IR, ^{1}H NMR, ^{13}C NMR and HRMS. In addition, structure of compound **11e** was also confirmed by single X-ray crystallographic data. The ^{1}H, ^{13}C and HRMS spectra of compounds **10a**, **10b**, **11b** are shown in figures **2.12a**, **2.12b**, **2.12c**, **2.13a**, **2.13b**, **2.13c, 2.14a**, **2.14b** and **2.14c**, respectively in experimental section.

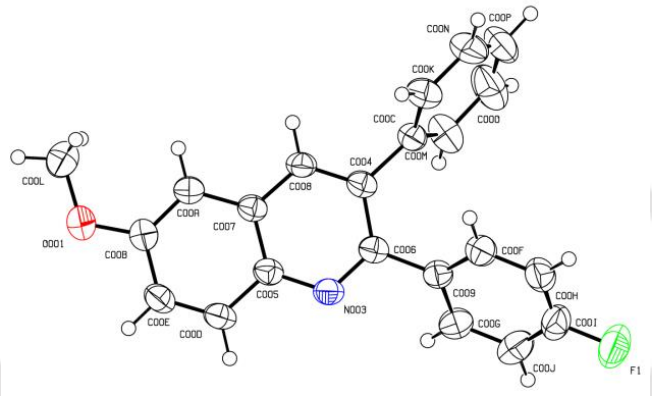
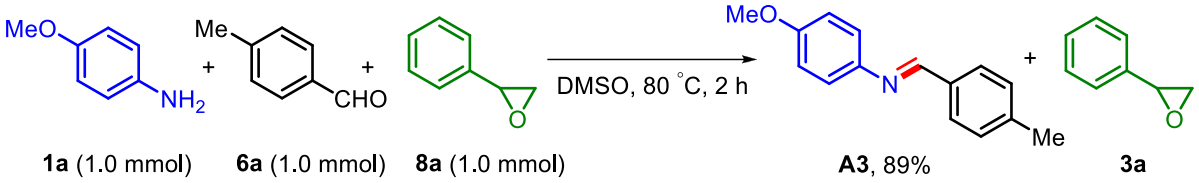


Figure 2.11. ORTEP diagram of compound **11e** with 40% probability.

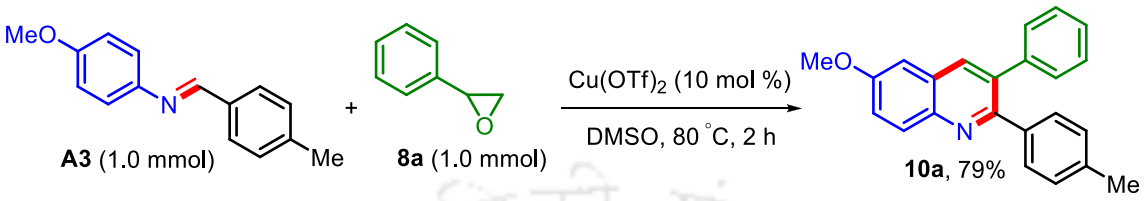
ORTEP diagram of compound **11e** with 40% probability (CCDC No. 2040858) is shown in Figure **2.11**.

In order to gain insights into reaction mechanism, control experiments were performed (Scheme **2.10**). First an experiment was carried out using *p*-anisidine **1a**, *p*-tolualdehyde **6a** and styrene oxide **8a**. After stirring reaction mixture for 2 h, intermediate **A3** (Schiff's base) was isolated in 89% yield and characterized by ^{1}H NMR, ^{13}C NMR and HRMS (Scheme **2.10a**). Thereafter, another experiment was performed using intermediate **A3** and styrene oxide **8a** under standard conditions (Scheme **2.10b**). It was observed that reaction completed in 2 h under standard conditions to give product **10a** in 79% yield. These observation suggests formation of Schiff's base and its involvement in reaction mechanism.

Scheme 2.10a

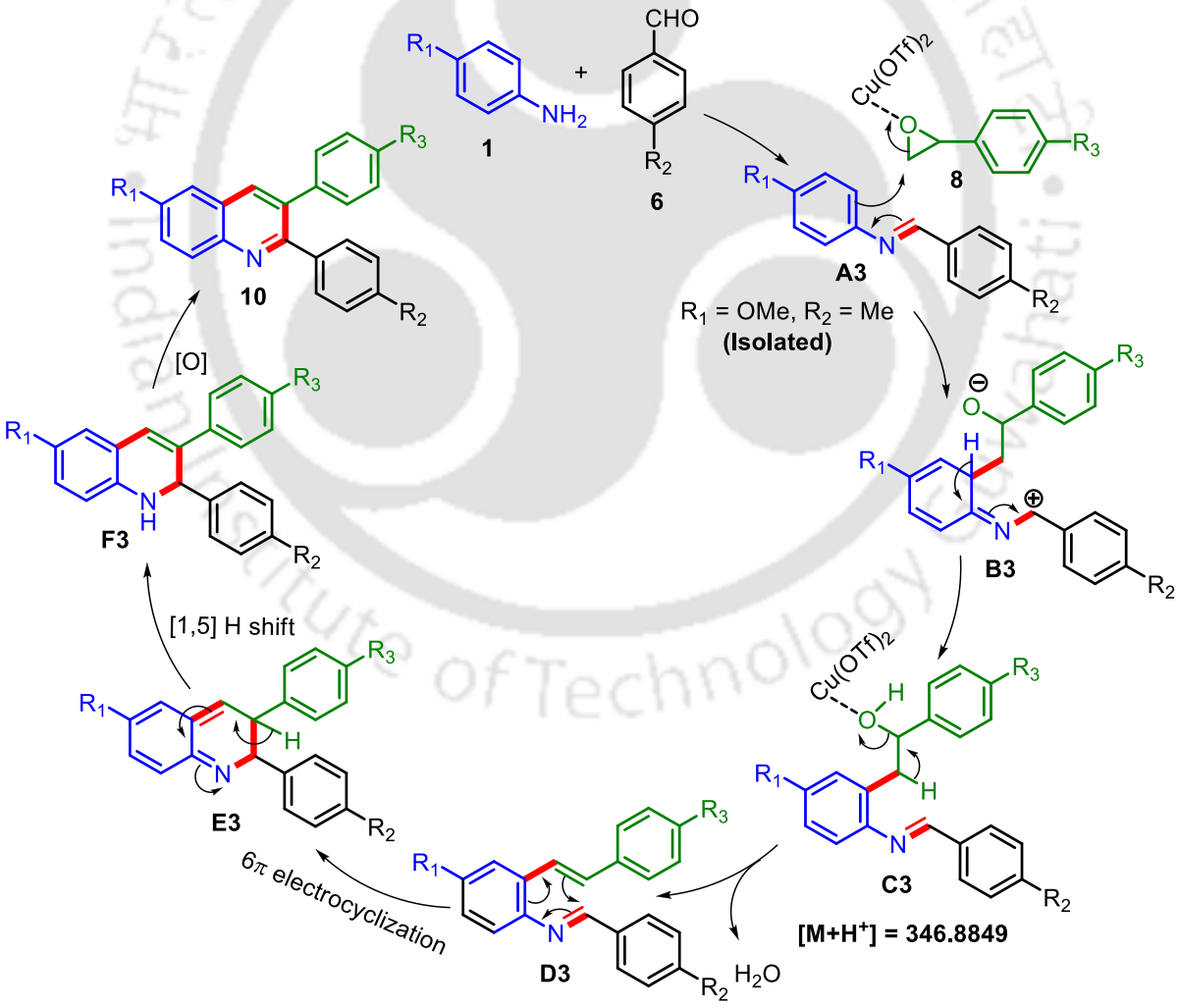


Scheme 2.10b



Scheme 2.10. Control experiments.

Base on control experiments, a plausible mechanism for formation of 2,3-diarylquinoline derivatives has been shown in Scheme **2.11**.



Scheme 2.11. A plausible mechanism for formation of product **10**.

At first, aryl amine **1** reacts with benzaldehyde **6** to give an intermediate **A3** (Schiff's base),[13] which subsequently reacts with styrene oxide **8** to give intermediate **B3**. Then, intermediate **B3** gets aromatized to provide intermediate **C3**. It is noteworthy that intermediate **C3** was detected by HRMS. Elimination of water from intermediate **C3** generates **D3**, which undergoes 6π-electrocyclic ring closure[14] to produce intermediate **E3**. Intermediate **E3** involves a [1,5] H shift[14b] to give dihydroquinoline **F3** followed by aerial oxidation[14b] provides desired quinoline **10**.

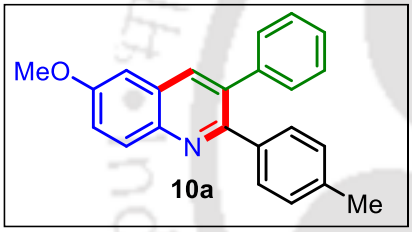
In summary, an efficient and straightforward novel route towards synthesis of a wide range of 2,3-diarylquinoline derivatives of biological importance has been developed. This protocol involves copper(II) triflate catalyzed three-component reaction using readily available building blocks aryl amines, aryl aldehydes and styrene oxides in DMSO solvent at 80 °C. Salient features of this methodology are use of cost-effective catalyst, high atom-economy, high regioselectivity, easy to handle, shorter reaction time, consecutive one C–N and two C–C bond formation and an access to broad range of 2,3-diarylquinoline derivatives with good yield.

Experimental Section

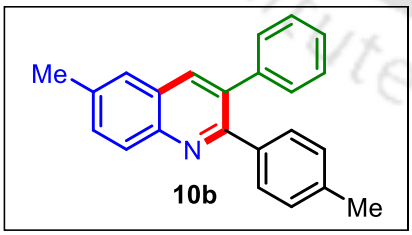
General procedure for the synthesis of 2,3-diarylquinoline derivatives 10 and 11

Aryl amine **1** (1.0 mmol), aryl aldehyde **6** (1.0 mmol) and styrene oxide **8** (1.0 mmol) were taken in dimethyl sulfoxide solvent (1.0 mL) in a round-bottomed flask (10 mL). To the reaction mixture, copper(II) triflate (10 mol%, 36 mg) was added. The resulting reaction mixture was kept under stirring in an oil-bath at 80 °C. The reaction progress was checked by TLC. After the completion of the reaction, the mixture was cooled to room temperature. To extract the product, EtOAc (3 × 5 mL) was added to the reaction mixture. The combined organic layer was washed with water (2 × 5 mL) followed by brine solution (5 mL) and dried over anhydrous sodium sulphate. The solvent was removed in a rotary evaporator and the crude residue was purified using silica gel (60–120 mesh) column chromatography to obtain the desired products **10** and **11**.

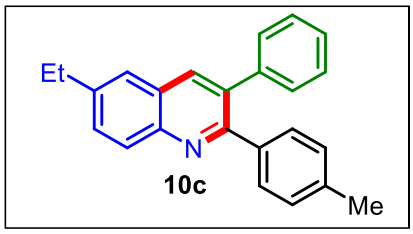
6-Methoxy-3-phenyl-2-p-tolylquinoline (10a): (263 mg, 81%, yellowish semi-liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 8.04 (s, 1H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.26 (m, 5H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 2H), 3.95 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 156.1, 143.7, 140.5, 137.8, 137.7, 136.6, 134.9, 131.0, 130.1, 129.9, 128.8, 128.4, 128.3, 127.2, 122.5, 105.0, 55.8, 21.4; **IR (KBr)ν_{max}** 2923, 1622, 1482, 1376, 1232 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}NO$ 326.1545 ($M + H^+$); Found 326.1571.



6-Methyl-3-phenyl-2-p-tolylquinoline (10b): (242 mg, 78%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.6 Hz, 1H), 7.98 (s, 1H), 7.53 (s, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.23 – 7.17 (m, 5H), 6.99 (d, *J* = 7.9 Hz, 2H), 2.48 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.7, 146.1, 140.5, 137.9, 137.7, 137.2, 136.7, 134.7, 132.1, 130.1, 129.9, 129.2, 128.8, 128.4, 127.4, 127.2, 126.4, 21.9, 21.5; **IR (KBr)ν_{max}** 3027, 2924, 1600, 1490, 1370 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 ($M + H^+$); Found 310.1589.

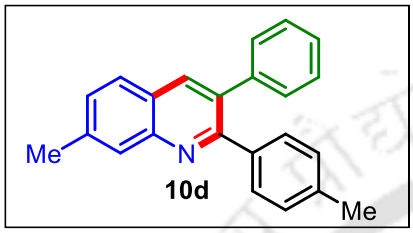


6-Ethyl-3-phenyl-2-p-tolylquinoline (10c): Yield 79% (255 mg), dark brown liquid, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.6 Hz, 1H), 7.98 (s, 1H), 7.52 (s, 1H), 7.49 (d, *J* = 8.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.18 (ddd, *J* = 13.9, 6.5, 3.3 Hz, 5H), 6.97 (d, *J* = 7.9 Hz,



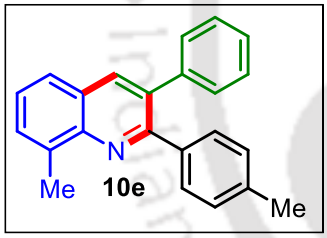
2H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.22 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.7, 146.3, 142.9, 140.6, 137.8, 137.8, 137.3, 134.6, 131.0, 130.1, 129.9, 129.9, 129.3, 128.8, 128.3, 127.2, 125.1, 76.9, 29.1, 21.4, 15.6; **IR (KBr)ν_{max}** 3032, 2964, 1680, 1600, 1375 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1775.

7-Methyl-3-phenyl-2-p-tolylquinoline (10d): (234 mg, 76%, yellow liquid); **^{1}H NMR** (400



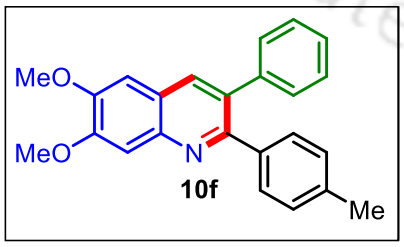
MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.97 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.38 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.25 (m, 4H), 7.07 (d, *J* = 7.9 Hz, 2H), 2.58 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.5, 147.7, 140.6, 140.0, 137.9, 137.9, 137.5, 133.9, 130.1, 129.9, 129.9, 129.1, 128.8, 128.6, 128.6, 128.4, 127.3, 127.2, 125.4, 22.1, 21.4; **IR (KBr)ν_{max}** 3034, 2922, 1601, 1493, 1373 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 ($M + H^+$); Found 310.1620.

8-Methyl-3-phenyl-2-p-tolylquinoline (10e): (232 mg, 75%, greenish liquid); **^{1}H NMR** (400



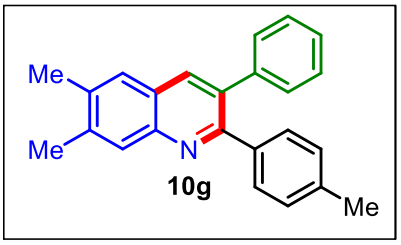
MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 6.9 Hz, 1H), 7.46 – 7.40 (m, 3H), 7.36 – 7.28 (m, 5H), 7.08 (d, *J* = 7.9 Hz, 2H), 2.88 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.74, 146.5, 140.8, 138.0, 138.0, 137.6, 134.2, 130.5, 130.1, 129.9, 129.71, 128.7, 128.5, 127.2, 127.2, 126.5, 125.5, 21.5, 18.1; **IR (KBr)ν_{max}** 3034, 2919, 1600, 1475, 1270 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}N$ 310.1596 ($M + H^+$); Found 310.1620.

6,7-Dimethoxy-3-phenyl-2-p-tolylquinoline (10f): (285 mg, 80%, white solid); mp 120–122

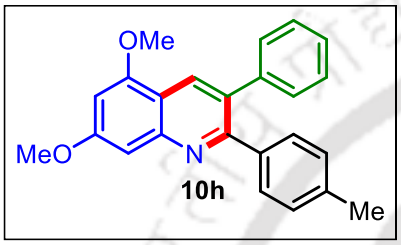


°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.45 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.17 (m, 5H), 6.98 (d, *J* = 9.8 Hz, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2, 152.8, 150.1, 144.2, 140.6, 137.8, 137.6, 136.1, 132.9, 130.0, 129.9, 128.7, 128.3, 127.0, 122.8, 108.1, 104.9, 56.3, 56.2, 21.4; **IR (KBr)ν_{max}** 2924, 1619, 1495, 1385, 1231 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}NO_2$ 356.1651 ($M + H^+$); Found 356.1650.

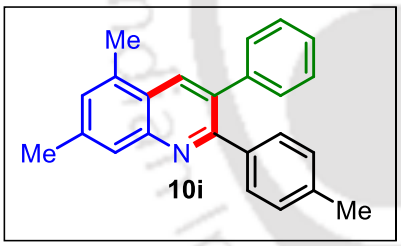
6,7-Dimethyl-3-phenyl-2-p-tolylquinoline (10g): (252 mg, 78%, yellowish semi-solid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.90 (s, 1H), 7.51 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.16 (m, 5H), 6.99 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H), 2.39 (s, 3H), 2.25 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 146.6, 140.7, 140.1, 137.8, 136.9, 136.8, 133.9, 130.2, 129.9, 128.8, 128.4, 127.1, 126.8, 126.0, 21.5, 20.7, 20.3; **IR (KBr)ν_{max}** 3029, 2921, 1599, 1450, 1367 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1750.



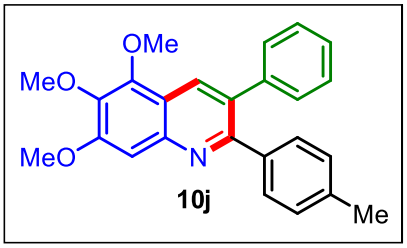
5,7-Dimethoxy-3-phenyl-2-p-tolylquinoline (10h): (281 mg, 79%, brown semi-solid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.13 (m, 5H), 7.05 (s, 1H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.44 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 158.9, 156.2, 149.5, 140.8, 137.9, 137.8, 132.8, 131.6, 130.1, 130.0, 128.8, 128.3, 126.9, 115.8, 99.8, 98.3, 55.9, 55.9, 21.4; **IR (KBr)ν_{max}** 2928, 1620, 1452, 1382, 1211 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}NO_2$ 356.1651 ($M + H^+$); Found 356.1637.



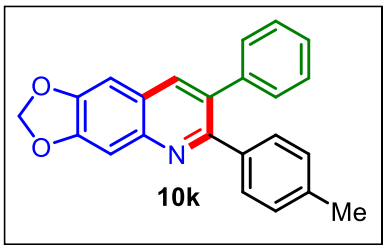
5,7-Dimethyl-3-phenyl-2-p-tolylquinoline (10i): (250 mg 77%, yellow solid); mp 111–113 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.76 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.24 – 7.18 (m, 5H), 7.14 (s, 1H), 6.99 (d, *J* = 7.9 Hz, 2H), 2.59 (s, 3H), 2.45 (s, 3H), 2.24 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 148.1, 140.9, 139.7, 137.9, 137.8, 134.3, 134.2, 133.4, 130.2, 130.0, 129.6, 128.8, 128.4, 127.2, 126.7, 124.7, 22.1, 21.4, 18.7; **IR (KBr)ν_{max}** 3032, 2922, 1601, 1447, 1374 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1752.



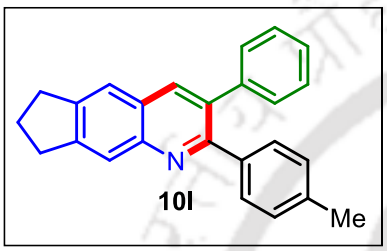
5,6,7-Trimethoxy-3-phenyl-2-p-tolylquinoline (10j): (281 mg, 76%, brown semi-solid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.27 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.13 (m, 5H), 6.95 (d, *J* = 7.9 Hz, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 2.20 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 157.7, 156.1, 146.9, 145.1, 140.9, 140.6, 137.7, 137.7, 132.3, 132.1, 129.9, 129.9, 128.7, 128.2, 126.9, 118.2, 104.2, 61.7, 61.3, 56.2, 21.3; **IR (KBr)ν_{max}** 2935, 1610, 1474, 1369, 1225 cm^{-1}; **HRMS** (ESI) Calcd For $C_{25}H_{24}NO_3$ 386.1756 ($M + H^+$); Found 386.1750.



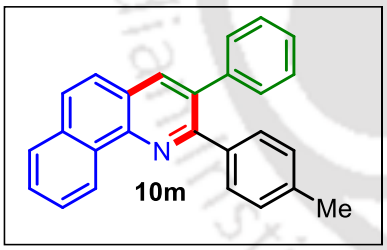
7-Phenyl-6-p-tolyl-[1,3]dioxolo[4,5-g]quinoline (10k): (278 mg, 82%, dark brown semi-solid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.40 (s, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.21 – 7.12 (m, 5H), 6.98 (d, *J* = 9.8 Hz, 3H), 6.02 (s, 2H), 2.23 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.1, 150.9, 148.1, 145.6, 140.4, 137.7, 137.6, 136.8, 132.9, 130.0, 129.9, 128.8, 128.4, 127.1, 124.2, 105.9, 102.5, 101.8, 21.4; **IR (KBr)ν_{max}** 2913, 1611, 1459, 1389, 1220 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{18}NO_2$ 340.1338 ($M + H^+$); Found 386.1365.



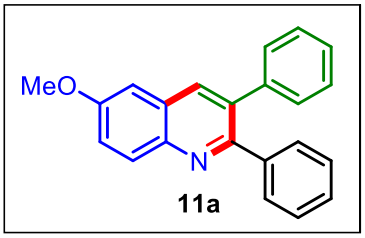
3-Phenyl-2-p-tolyl-7,8-dihydro-6H-cyclopenta[g]quinoline (10l): (255 mg, 76%, yellow solid); mp 110–112°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.92 (s, 1H), 7.55 (s, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.22 – 7.17 (m, 5H), 6.99 (d, *J* = 7.9 Hz, 2H), 3.07 – 2.98 (m, 4H), 2.24 (s, 3H), 2.10 (quint, *J* = 7.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.3, 148.0, 147.3, 144.5, 140.7, 137.7, 137.4, 133.6, 130.1, 129.9, 128.8, 128.4, 128.3, 127.1, 126.5, 123.7, 121.5, 33.2, 32.7, 26.4, 21.4; **IR (KBr)ν_{max}** 3029, 2948, 1599, 1464, 1377 cm^{-1}; **HRMS** (ESI) Calcd For $C_{25}H_{22}N$ 336.1752 ($M + H^+$); Found 336.1752.



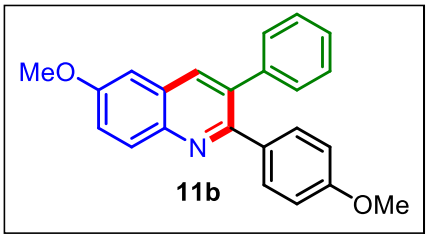
3-Phenyl-2-p-tolylbenzo[h]quinoline (10m): (249 mg, 72%, white solid); mp = 140–143 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.92 (d, *J* = 7.1 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.74 – 7.69 (m, 3H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.34 (s, 4H), 7.12 (d, *J* = 7.9 Hz, 2H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 145.5, 140.7, 138.0, 137.9, 134.9, 133.9, 131.8, 130.6, 129.9, 128.8, 128.5, 128.3, 127.9, 127.6, 127.3, 127.1, 125.2, 125.2, 125.1, 21.5; **IR (KBr)ν_{max}** 2923, 1590, 1438, 1402 cm^{-1}; **HRMS** (ESI) Calcd For $C_{26}H_{20}N$ 346.1596 ($M + H^+$); Found 346.1609.



6-Methoxy-2,3-diphenylquinoline (11a): (311 mg, 81%, dark solid); mp 123–125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.2 Hz, 1H), 8.06 (s, 1H), 7.43 – 7.37 (m, 3H), 7.28 – 7.25 (m, 8H), 7.12 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 156.1, 143.6, 140.7, 140.3, 136.6, 134.9, 131.1, 130.2, 129.9, 128.4, 128.4, 128.1, 127.9, 127.3, 122.6, 105.1, 55.8; **IR (KBr)ν_{max}** 3059, 2834, 1623, 1488, 1375 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{18}NO$ 312.1388 ($M + H^+$); Found 312.1411.

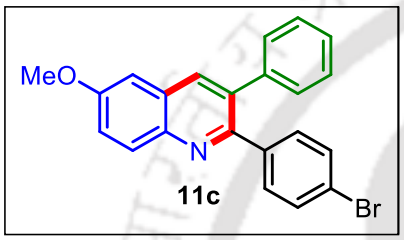


6-Methoxy-2-(4-methoxyphenyl)-3-phenylquinoline (11b): (274 mg, 80%, brown liquid);



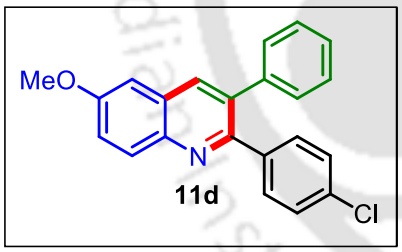
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.97 (s, 1H), 7.31 (dd, *J* = 8.9, 4.0 Hz, 3H), 7.23 (t, *J* = 5.0 Hz, 3H), 7.18 (t, *J* = 3.8 Hz, 2H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H), 3.72 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.8, 158.2, 155.5, 143.2, 140.4, 137.1, 134.9, 131.7, 130.6, 129.9, 129.5, 128.5, 128.3, 127.4, 122.7, 113.6, 105.1, 55.8, 55.4; **IR (KBr)ν_{max}** 2929, 1619, 1488, 1376 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{20}NO_2$ 342.1494 ($M + H^+$); Found 342.1542.

2-(4-Bromophenyl)-6-methoxy-3-phenylquinoline (11c): (296 mg, 76%, brown solid); mp



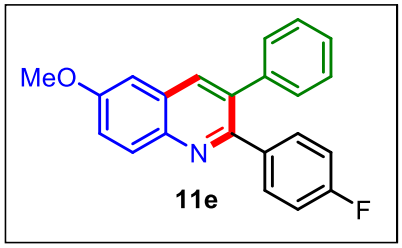
142–144 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.8, 2.3 Hz, 3H), 7.33 – 7.30 (m, 5H), 7.23 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.12 (d, *J* = 2.8 Hz, 1H), 3.96 (s, 3H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 158.4, 154.7, 143.7, 140.0, 139.6, 136.8, 134.8, 131.9, 131.3, 131.1, 129.9, 128.6, 128.5, 127.6, 122.8, 122.5, 105.0, 55.8; **IR (KBr)ν_{max}** 2925, 1622, 1488, 1377, 1233 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{17}BrNO$ 390.0494 ($M + H^+$); Found 390.0483.

2-(4-Chlorophenyl)-6-methoxy-3-phenylquinoline (11d): (266 mg, 77%, brown solid); mp



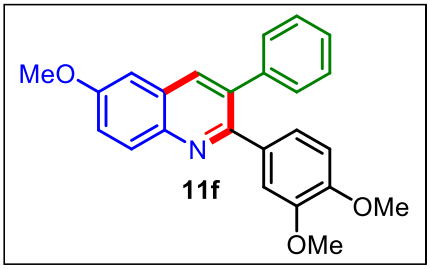
148–150 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.38 (m, 1H), 7.38 – 7.36 (m, 2H), 7.32 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.26 – 7.22 (m, 4H), 7.12 (d, *J* = 2.7 Hz, 1H), 3.96 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 154.7, 143.7, 140.0, 139.2, 136.8, 134.8, 134.1, 131.6, 131.0, 129.9, 128.6, 128.5, 128.3, 127.5, 122.8, 104.9, 55.8; **IR (KBr)ν_{max}** 2926, 1623, 1488, 1377, 1232 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{17}ClNO$ 346.0999 ($M + H^+$); Found 346.1026.

2-(4-Fluorophenyl)-6-methoxy-3-phenylquinoline (11e): (266 mg, 80%, brown solid); mp

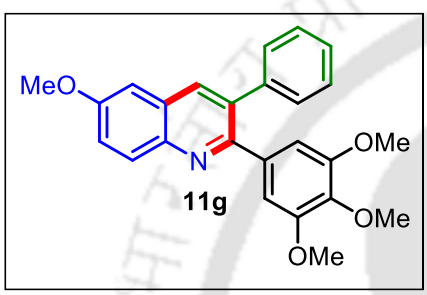


95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.9 Hz, 2H), 7.43 – 7.37 (m, 3H), 7.31 (dd, *J* = 5.0, 1.8 Hz, 3H), 7.23 (dd, *J* = 6.6, 3.1 Hz, 2H), 7.12 (d, *J* = 2.8 Hz, 1H), 6.95 (t, *J* = 8.8 Hz, 2H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 155.0, 143.7, 140.2, 136.7, 134.8, 132.1, 131.9, 131.0, 129.9, 128.5, 128.4, 127.5, 122.7, 115.2, 114.9, 105.0, 55.8; **IR (KBr)ν_{max}** 2926, 1623, 1510, 1377, 1230 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{17}FNO$ 330.1294 ($M + H^+$); Found 330.1321.

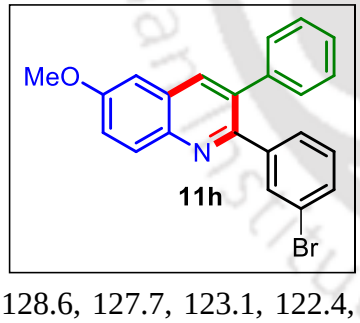
2-(3,4-Dimethoxyphenyl)-6-methoxy-3-phenylquinoline (11f): (292 mg, 78%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 8.04 (s, 1H), 7.38 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.29 (dt, *J* = 7.2, 4.8 Hz, 5H), 7.11 (dd, *J* = 8.1, 2.2 Hz, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.1, 155.6, 149.1, 148.3, 143.7, 140.8, 136.7, 134.9, 133.2, 131.0, 129.9, 128.5, 128.2, 127.3, 123.0, 122.5, 113.8, 110.9, 105.1, 56.1, 55.8, 55.8; **IR (KBr)ν_{max}** 2929, 1623, 1515, 1458 cm^{-1}; **HRMS** (ESI) Calcd For $C_{24}H_{22}NO_3$ 372.1600 ($M + H^+$); Found 372.1627.



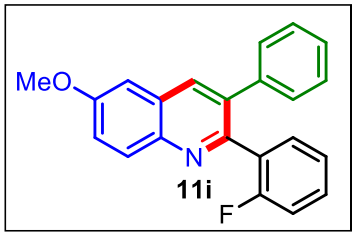
6-Methoxy-3-phenyl-2-(3,4,5-trimethoxyphenyl)quinoline (11g): (308 mg, 76%, dark brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.0 Hz, 1H), 8.09 (s, 1H), 7.41 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.13 (d, *J* = 2.7 Hz, 1H), 6.68 (s, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 3.64 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 155.44, 152.9, 140.649, 138.7, 137.0, 135.0, 130.7, 129.8, 128.6, 128.4, 127.4, 122.93, 115.1, 115.0, 108.0, 105.1, 65.4, 61.1, 56.1, 55.83; **IR (KBr)ν_{max}** 2934, 1590, 1503, 1380 cm^{-1}; **HRMS** (ESI) Calcd For $C_{25}H_{24}NO_4$ 402.1705 ($M + H^+$); Found 402.1749.



2-(3-Bromophenyl)-6-methoxy-3-phenylquinoline (11h): (293 mg, 75%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.64 (s, 1H), 7.35 (dd, *J* = 9.1, 2.9 Hz, 2H), 7.27 – 7.23 (m, 3H), 7.19 – 7.15 (m, 4H), 7.06 (d, *J* = 2.7 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.6, 154.2, 143.4, 139.7, 137.0, 134.9, 133.2, 131.1, 130.9, 129.9, 129.4, 129.0, 128.7, 128.6, 127.7, 123.1, 122.4, 105.0, 55.8; **IR (KBr)ν_{max}** 3066, 2929, 1622, 1487, 1376 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{17}BrNO$ 390.0494 ($M + H^+$); Found 390.0510.

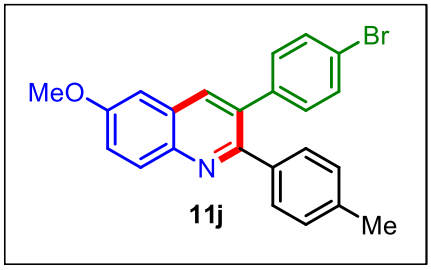


2-(2-Fluorophenyl)-6-methoxy-3-phenylquinoline (11i): (260 mg, 79%, black solid); mp 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.3 Hz, 1H), 8.02 (s, 1H), 7.46 (td, *J* = 7.4, 1.8 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.23 – 7.14 (m, 6H), 7.11 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.08 (t, *J* = 2.7 Hz, 1H), 6.80 (t, *J* = 8.7 Hz, 1H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.1, 158.5, 151.8, 143.3, 139.6, 136.2, 135.9, 132.0, 131.9, 130.9, 130.3, 130.2, 129.4, 128.9, 128.2, 127.5, 124.3, 124.3,

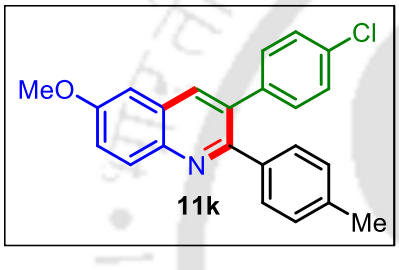


122.8, 115.8, 115.62, 105.1, 55.8; **IR (KBr)ν_{max}** 2920, 1622, 1586, 1448, 1377 cm^{-1}; **HRMS** (ESI) Calcd For $C_{22}H_{17}FNO$ 330.1294 ($M + H^+$); Found 330.1322.

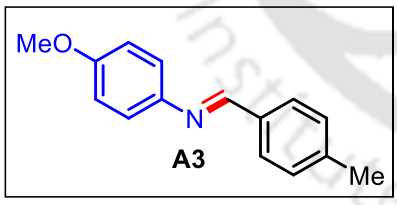
3-(4-Bromophenyl)-6-methoxy-2-p-tolylquinoline (11j): (312 mg, 77%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.39 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.06 (m, 5H), 3.95 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 155.8, 143.8, 139.5, 137.9, 137.5, 136.5, 133.7, 131.8, 131.6, 131.5, 131.1, 130.0, 129.0, 122.8, 121.6, 104.9, 55.8, 21.5; **IR (KBr)ν_{max}** 2924, 1620, 1486, 1376 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{19}BrNO$ 404.0650 ($M + H^+$); Found 404.0670.



3-(4-Chlorophenyl)-6-methoxy-2-p-tolylquinoline (11k): (281 mg, 78%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 8.01 (s, 1H), 7.39 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.28 (dd, *J* = 9.9, 8.6 Hz, 4H), 7.21 – 7.15 (m, 2H), 7.10 (dd, *J* = 8.0, 5.4 Hz, 3H), 3.95 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.23, 155.92, 143.78, 139.03, 137.99, 137.48, 136.56, 133.67, 133.45, 131.20, 131.07, 130.05, 129.00, 128.66, 128.23, 122.78, 104.97, 55.81, 21.47; **IR (KBr)ν_{max}** 2929, 1623, 1488, 1375 cm^{-1}; **HRMS** (ESI) Calcd For $C_{23}H_{19}ClNO$ 360.1155 ($M + H^+$); Found 360.1167.



(*E*)-4-methoxy-N-(4-methylbenzylidene)aniline (A3):[16a] (200 mg, 89%, gray solid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.19 (m, 4H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$, Me_4Si) δ 158.59, 158.31, 145.29, 141.60, 134.08, 129.63, 128.76, 122.32, 114.54, 77.55, 77.23, 76.91, 55.63, 21.74; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO$ 226.1236 ($M + H^+$); Found 226.1237.



XRD for compound (11e): All the data for the structural analysis of compound **11e** has been deposited to the Cambridge Crystallographic Data Centre, **CCDC No. 2040858**. The file of this information can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk).

Table 2.11. Crystal data and structure refinement for compound 11e

Entry	Identification code	Compound 11e
01	Empirical formula	$C_{22}H_{16}FNO$
02	Formula weight	329.12
03	Temperature	296 K
04	Wavelength	0.71073
05	Radiation type	MoK\a
06	Radiation source	'fine-focus sealed tube'
07	Crystal system	Monoclinic
08	Space group	P 21/c
09	Cell length	A = 13.9206 (6), b = 9.0995(4), c = 14.8399(6)
10	Cell Angle	$\alpha = 90$, $\beta = 116.476(1)$, $\gamma = 90$
11	Cell Volume	1682.63(12)
12	Density	1.3
13	Completeness to theta	0.999-28.489
14	Absorption correction	multi-scan
15	Refinement method	Full
16	Index ranges	$-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-14 \leq l \leq 16$
17	Reflection number	83679
18	R factor	0.0593
18	Theta range	1.634-28.489
19	Cell formula units Z	1
20	CCDC no (Deposition no.)	2040858

^{1}H NMR (400 MHz, $CDCl_3$): 6-methoxy-3-phenyl-2-p-tolylquinoline **(10a)**

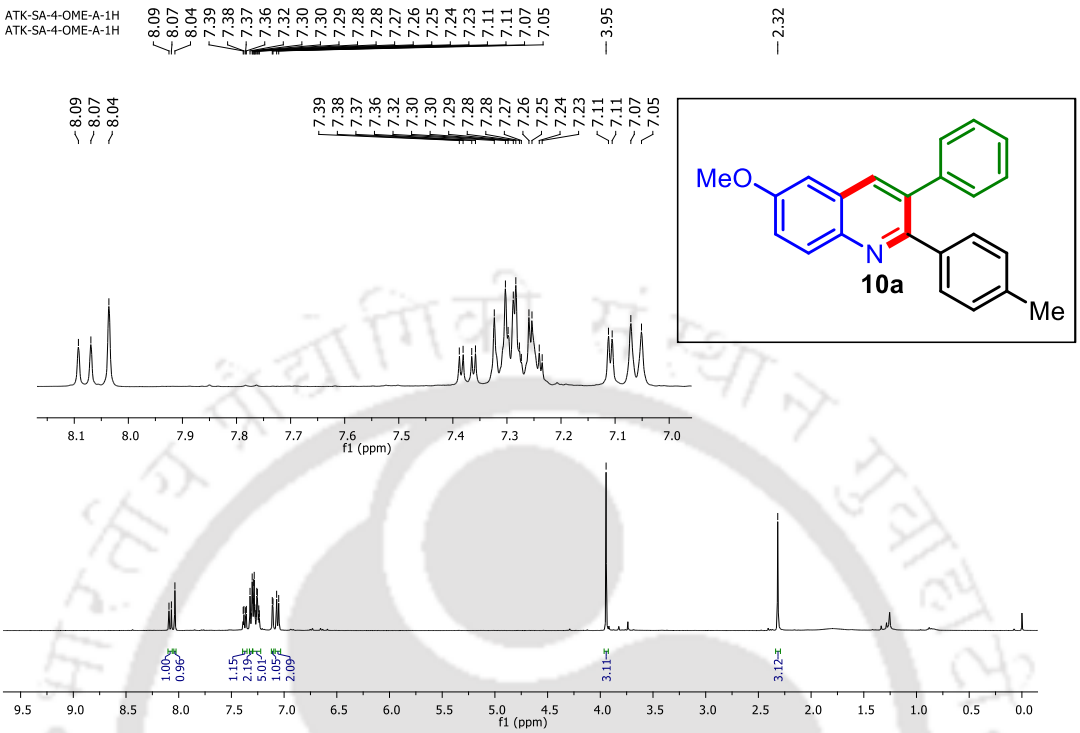


Figure 2.12a

^{13}C NMR (100 MHz, $CDCl_3$): 6-methoxy-3-phenyl-2-p-tolylquinoline **(10a)**

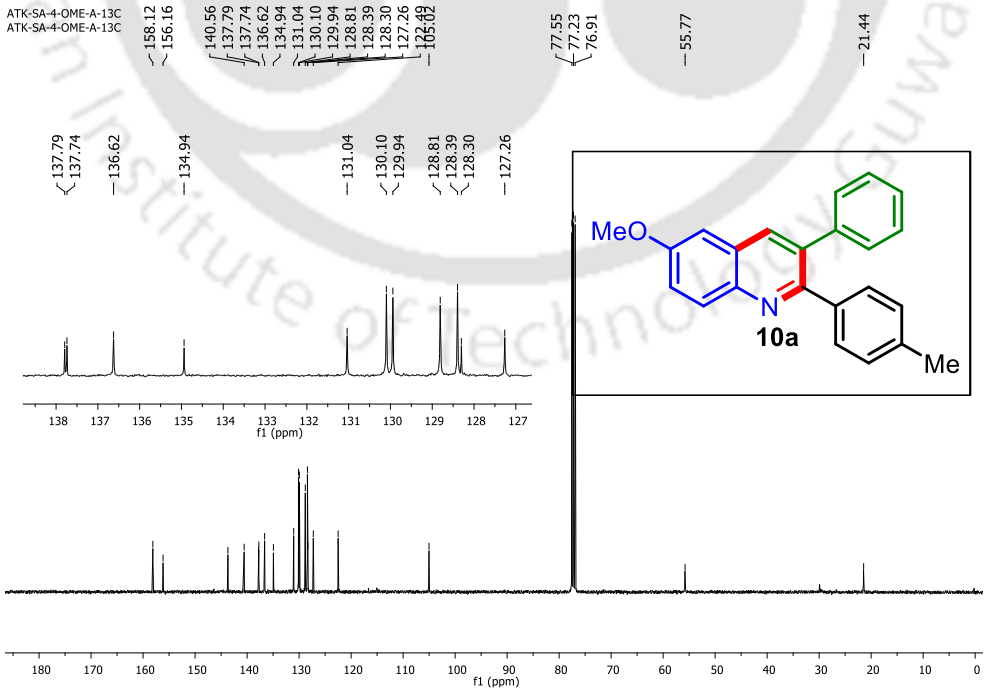


Figure 2.12b

HRMS spectrum: 6-methoxy-3-phenyl-2-p-tolylquinoline **(10a)**

Sample Name	SAMPLE 36	**Position**	P2-D4	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	ATK-SA-4-OME.d	**ACQ Method**	ESI ALS 100-1000.m	**Comment**		**Acquired Time**	8/9/2019 6:10:27 PM

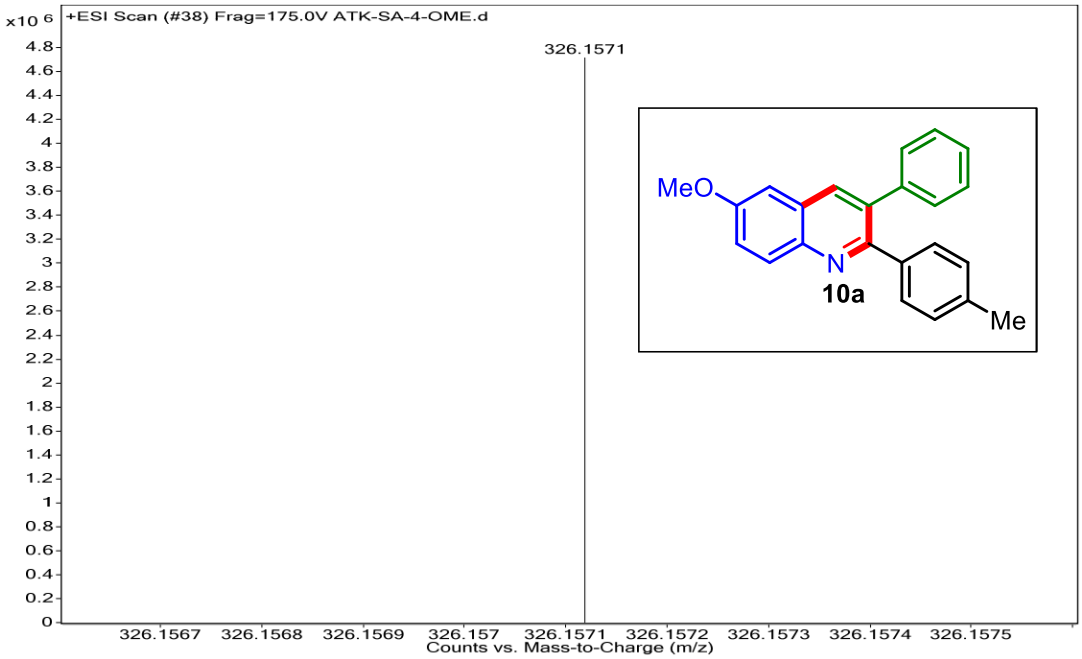


Figure 2.12c

^{1}H NMR (400 MHz, $CDCl_3$): 6-methyl-3-phenyl-2-p-tolylquinoline **(10b)**

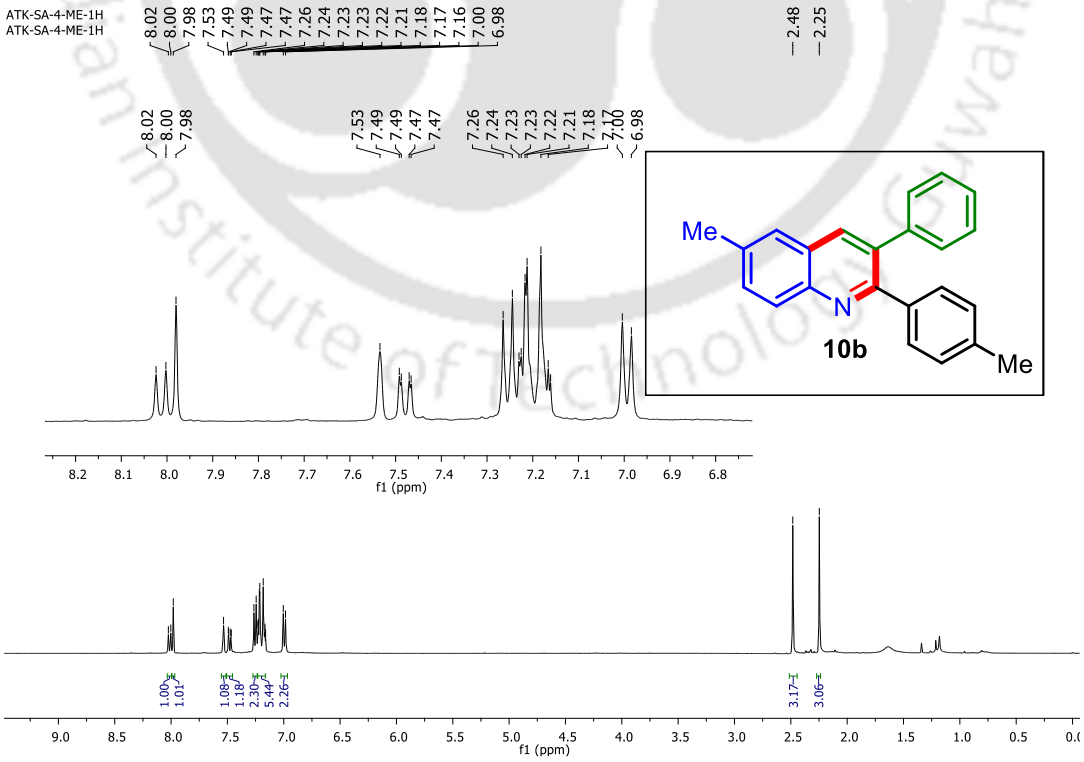


Figure 2.13a

^{13}C NMR (100 MHz, $CDCl_3$): 6-methyl-3-phenyl-2-p-tolylquinoline **(10b)**

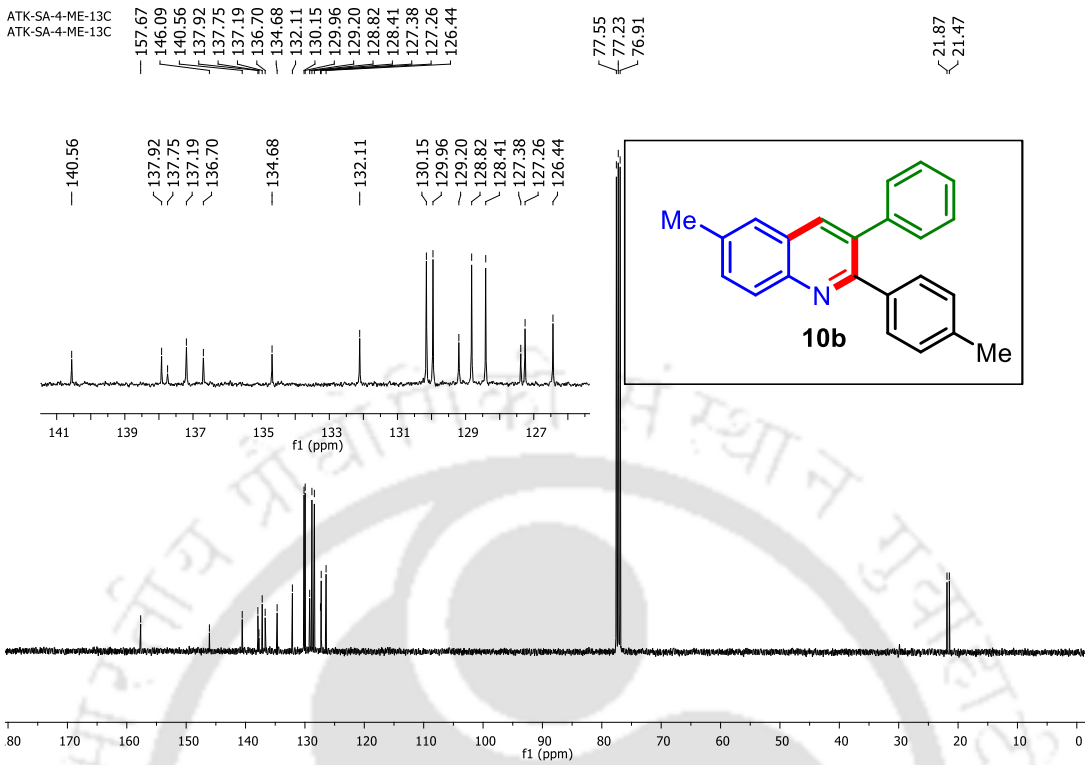


Figure 2.13b

HRMS spectrum: 6-methyl-3-phenyl-2-p-tolylquinoline **(10b)**

Sample Name	SAMPLE	**Position**	P2-C11	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	ATK-SA-4-ME.d	**ACQ Method**	ESI ALS 100-800.m	**Comment**		**Acquired Time**	8/1/2019 5:56:15 PM

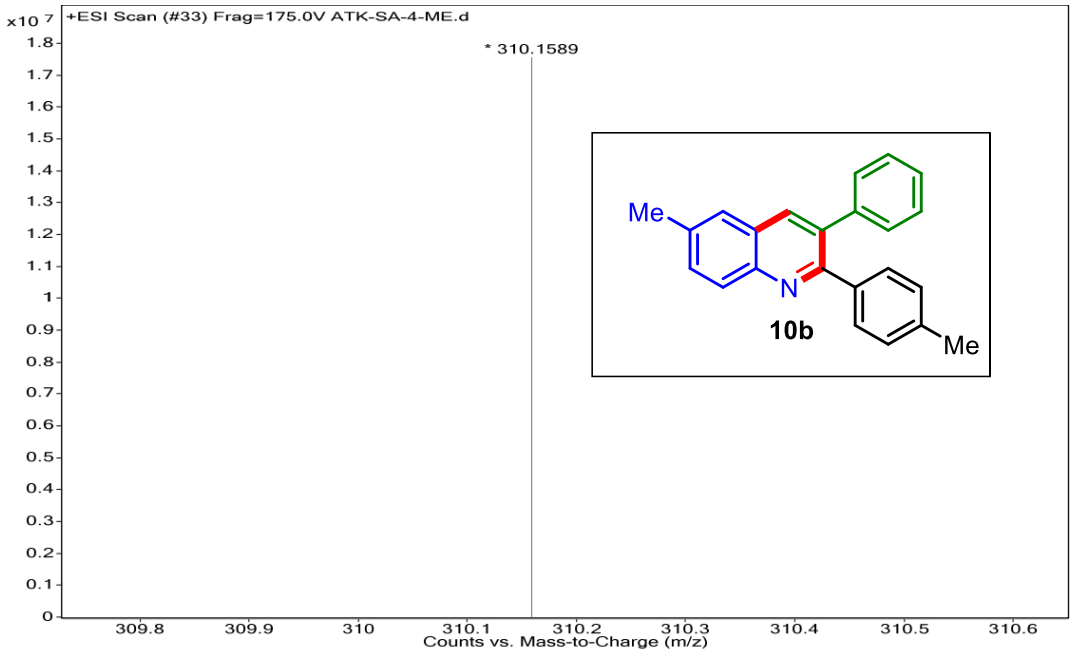


Figure 2.13c

^{1}H NMR (400 MHz, $CDCl_3$): 6-methoxy-2-(4-methoxyphenyl)-3-phenylquinoline **(11b)**

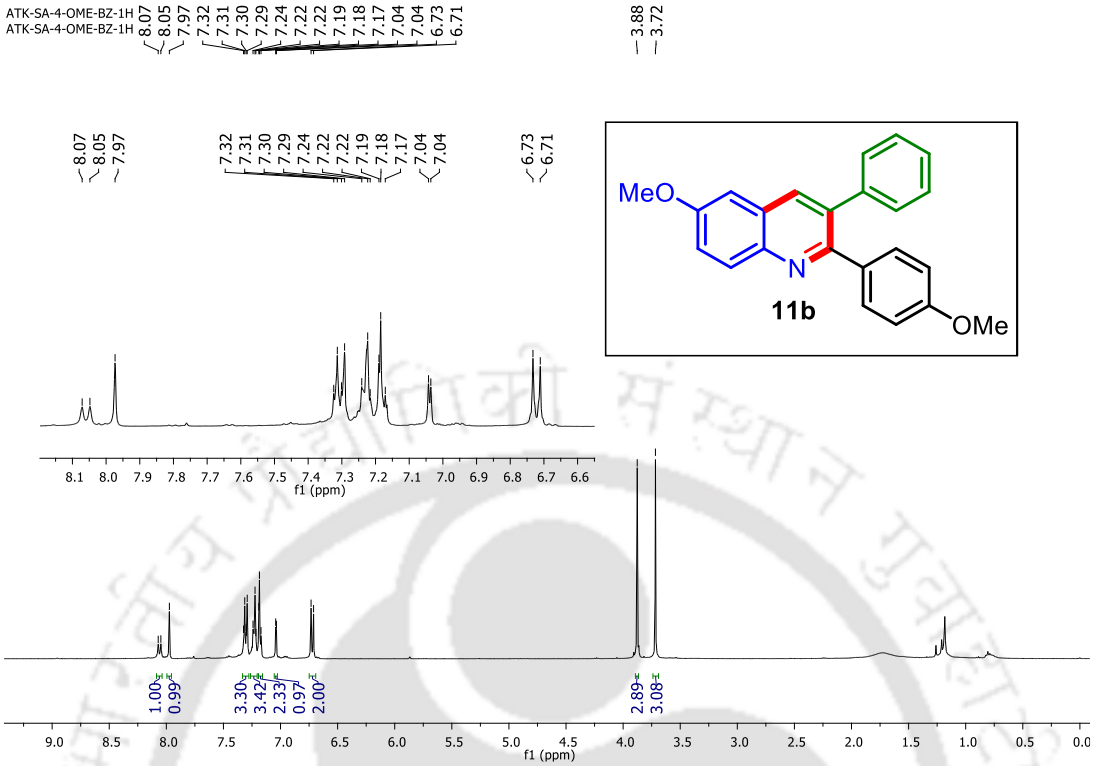


Figure 2.14a

^{13}C NMR (400 MHz, $CDCl_3$): 6-methoxy-2-(4-methoxyphenyl)-3-phenylquinoline **(11b)**

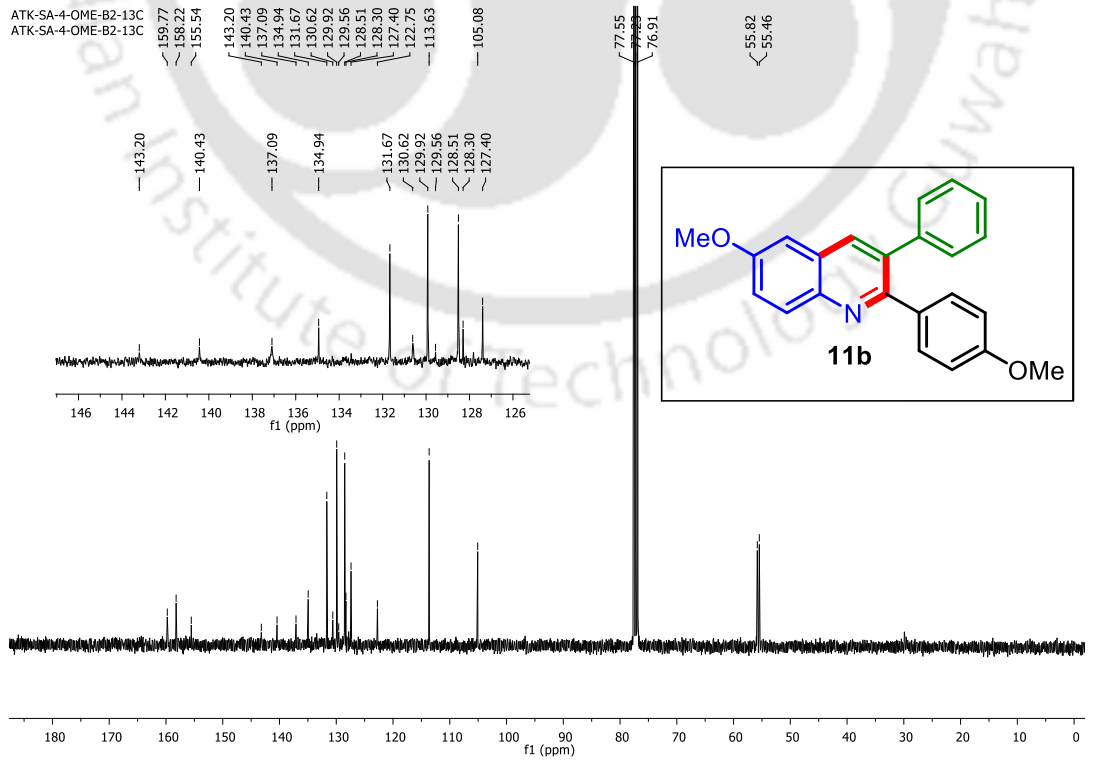


Figure 2.14b

HRMS spectrum: 6-methoxy-2-(4-methoxyphenyl)-3-phenylquinoline **(11b)**

Sample Name	SAMPLE	**Position**	P1-F6	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4OME-BZ.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	2/6/2020 6:17:47 PM

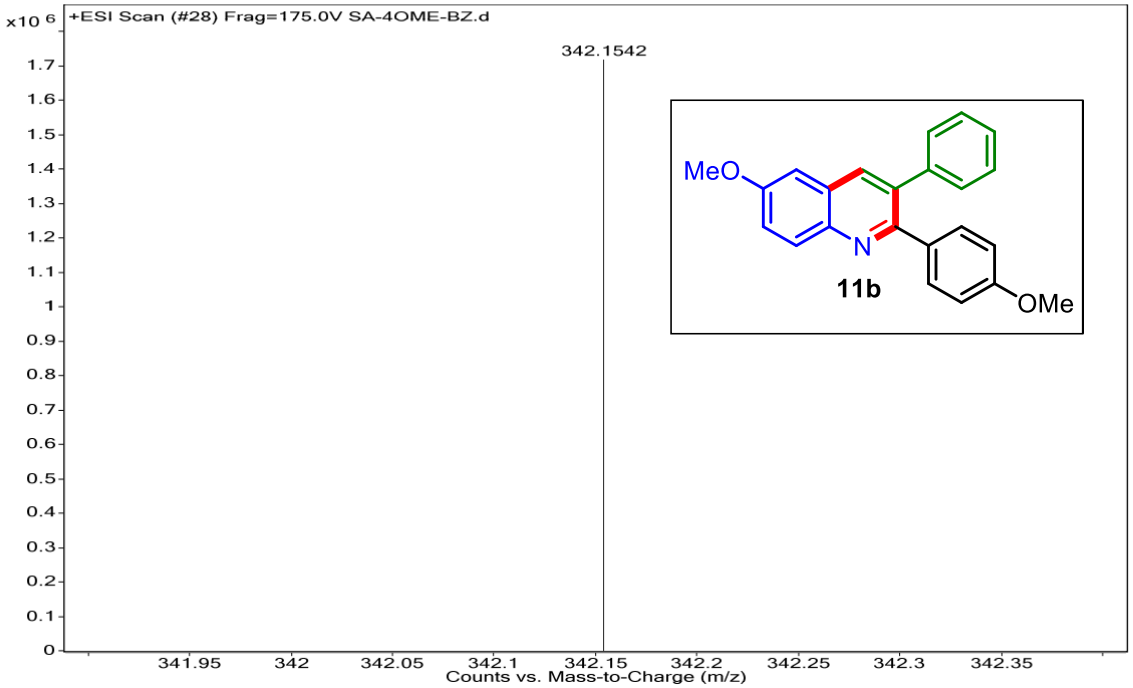


Figure 2.14c

References:

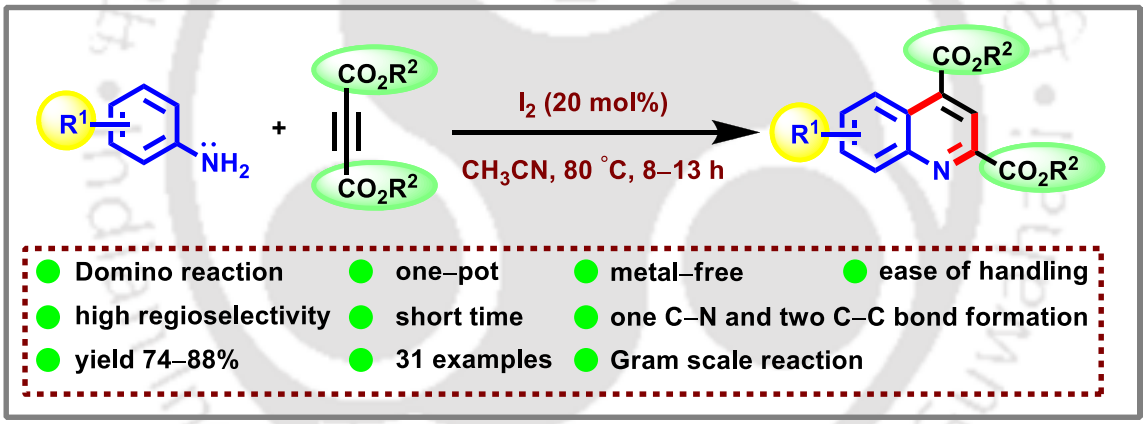
1. R. Gattu, S. Bhattacharjee, K. Mahato and A. T. Khan, *Org. Biomol. Chem*., 2018, **16**, 3760–3770.
2. G. Zhang, *Org. Biomol. Chem*., 2012, **10**, 2534–2536.
3. I. Choi, H. Chung, J. W. Park and Y. K. Chung, *Org. Lett*., 2016, **18**, 5508–5511.
4. X. Jia, F. Peng, C. Qing, C. Huo, Y. Wang and X. Wang, *Tetrahedron Lett*., 2013, **54**, 4950.
5. J. A. Leitch, A. L. F. de Arriba, J. Tan, O. Hoff, C. M. Martınez and D. J. Dixon, *Chem. Sci*., 2018, **9**, 6653–6658.
6. (a) R. Cheng, T. Guo, D. Z. Negrerie, Y. Du and K. Zhao, *Synthesis*, 2013, **45**, 2998–3006; (b) X. Jia, F. Peng, C. Qing, C. Huo, Y. Wang and X. Wang, *Tetrahedron Lett*., 2013, 54, 4950–4952.
7. M. Zhang, B. Xiong, T. Wang, Y. Q. Ding, L. Wang, *Heterocycles*, 2011, **83**, 2289–2298.
8. (a) M. Beller, O. R. Thiel, H. Trauthwein, C. G. Hartung, *Chem. Eur. J*., 2000, **6**, 2513; (b) J. B. Bharate, S. B. Bharate and R. A. Vishwakarma, *ACS Comb. Sci*. 2014, **16**, 624–630.
9. P. Slobbe, E. Ruijter and R. V. A. Orru, *Med. Chem. Commun*., 2012, **3**, 1189–1218.
10. (a) A. Domling and I. Ugi, *Angew. Chem., Int. Ed*., 2000, **39**, 3168–3210; (b) A. Domling, *Chem. Rev*., 2006, **106**, 17–89; (c) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed*., 2011, **50**, 6234– 6246; (d) C. de. Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev*., 2012, **41**, 3969–4009; (e) A. Domling, W. Wang and K. Wang, *Chem. Rev*., 2012, **112**, 3083–3135.
11. (a) B. M. Trost, *Science*, 1991, **254**, 1471–1477; (b) B. M. Trost, *Angew. Chem*., 1995, **107**, 285–307, (*Angew. Chem., Int. Ed. Engl*., 1995, **34**, 259–281).
12. (a) B. U. W. Maes, R. V. A. Orru and E. Ruiter, *Synthesis of Heterocycles via Multicomponent Reactions I & II*, Springer, Heidelberg, Germany, 2010; (b) R. V. A. Orru and M. de Greef, *Synthesis*, 2003, 1471–1499; (c) J. Zhu and H. Bienayme, *Multicomponent Reactions*, Wiley-VCH, Weilhein, Germany, 1st edn, 2005.
13. (a) L. Keinicke, P. Fristrup, P. Norrby and R. Madsen, *J. Am. Chem. Soc*., 2005, **127**, 15756–15761; (b) B. Asadi, A. L. Isfahani, I. M. Baltork, S. Tangestaninejad, M. Moghadam, V. Mirkhani and H. A. Rudbari, *ACS Comb. Sci*., 2017, **19**, 356–364; (c)

J. A. Leitch, T. Rogova, F. Duarte and D. J. Dixon, *Angew. Chem*., 2020, **59**, 4121–4130.

14. (a) S. S. Jang, Y. H. Kim and S. W. Youn, *Org. Lett*., 2020, **22**, 9151–9157; (b) L. G. Qiang and N. H. Baine, *J. Org. Chem*., 1988, **53**, 4218–4222; (c) X. Zhang, X. Xu, L. Yu and Q. Zhao, *Tetrahedron Lett*., 2014, **55**, 2280–2282.

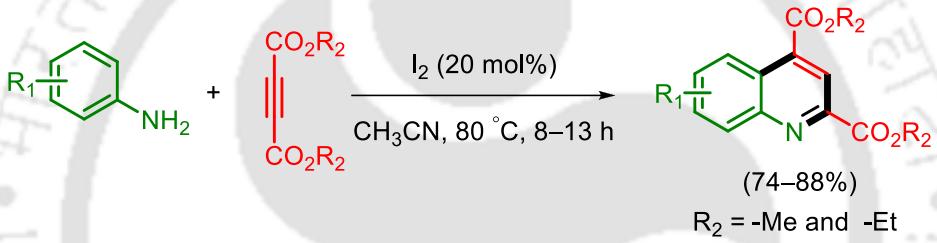
Chapter III: Part A

Metal-Free Pseudo Three-component Reaction of Aryl Amines and Acetylenedicarboxylates: An Easy Access to Quinoline-2,4-dicarboxylates



Results and Discussion

The importance quinoline-2,4-dicarboxylates and synthetic strategies for their synthesis have already been discussed in chapter I. In addition, Bayer Pharma Group utilized quinoline-2,4-carboxylate as key precursor for synthesis of glucose transport inhibitors, namely N^4-(2-(4-cyanobenzyl)-4-methylthiazol-5-yl)quinoline-2,4-dicarboxylates.[1] It reflects the importance of this key precursor in medicinal chemistry. This part of the chapter III presents a simple and an expedient protocol for synthesis of quinoline-2,4-dicarboxylate scaffolds from pseudo three-component reaction involving aryl amines and dimethyl/diethyl acetylenedicarboxylates in the presence of 20 mol% molecular iodine as a catalyst in acetonitrile at 80 °C (Scheme **3.1**). This protocol has several advantages, such as metal-free, use of cost-effective and environmentally benign catalyst, high regioselectivity, formation of one C-N and two C-C bonds and a broad substrate with high yield.

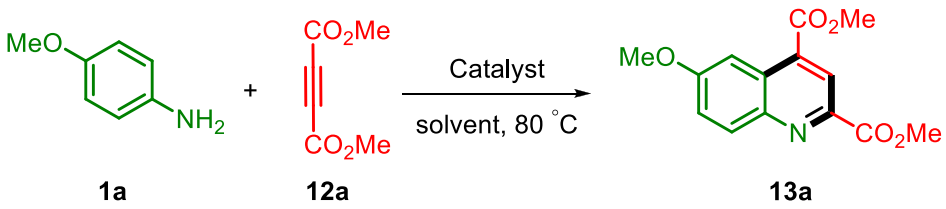


Scheme 3.1. Synthetic protocol for synthesis of dimethyl/diethyl quinoline-2,4-dicarboxylate derivatives.

Molecular iodine has emerged as a Lewis acid catalyst that has been utilized in various organic transformations.[2] Recently, our research group has shown the efficacy of molecular iodine for synthesis of various nitrogen heterocycles.[3a–e] Inspired by this, a new methodology has been developed for synthesis of quinoline-2,4-dicarboxylate derivatives using molecular iodine as a catalyst due its low cost, easy availability, nontoxicity, versatility and environmental friendliness.[3f] Iodine has structural features and reactivity patterns that are similar to those of transition metals [3f–h] and it can be used in place of transition metals to make a process greener and eco-friendly for various organic transformation. Keeping in mind the growing concerns about environment protection and waste generation, molecular iodine has been used to develop a sustainable method for synthesis of dimethyl/diethyl quinoline-2,4-dicarboxylate derivatives.

This study was commenced with finding optimization reaction conditions. For this purpose, *p*-anisidine **1a** and dimethyl acetylenedicarboxylate **12a** were chosen as model substrates; results are presented in Table 3.1.

Table 3.1. Optimization of reaction conditions[a,b,c,d]



1a **12a** **13a**

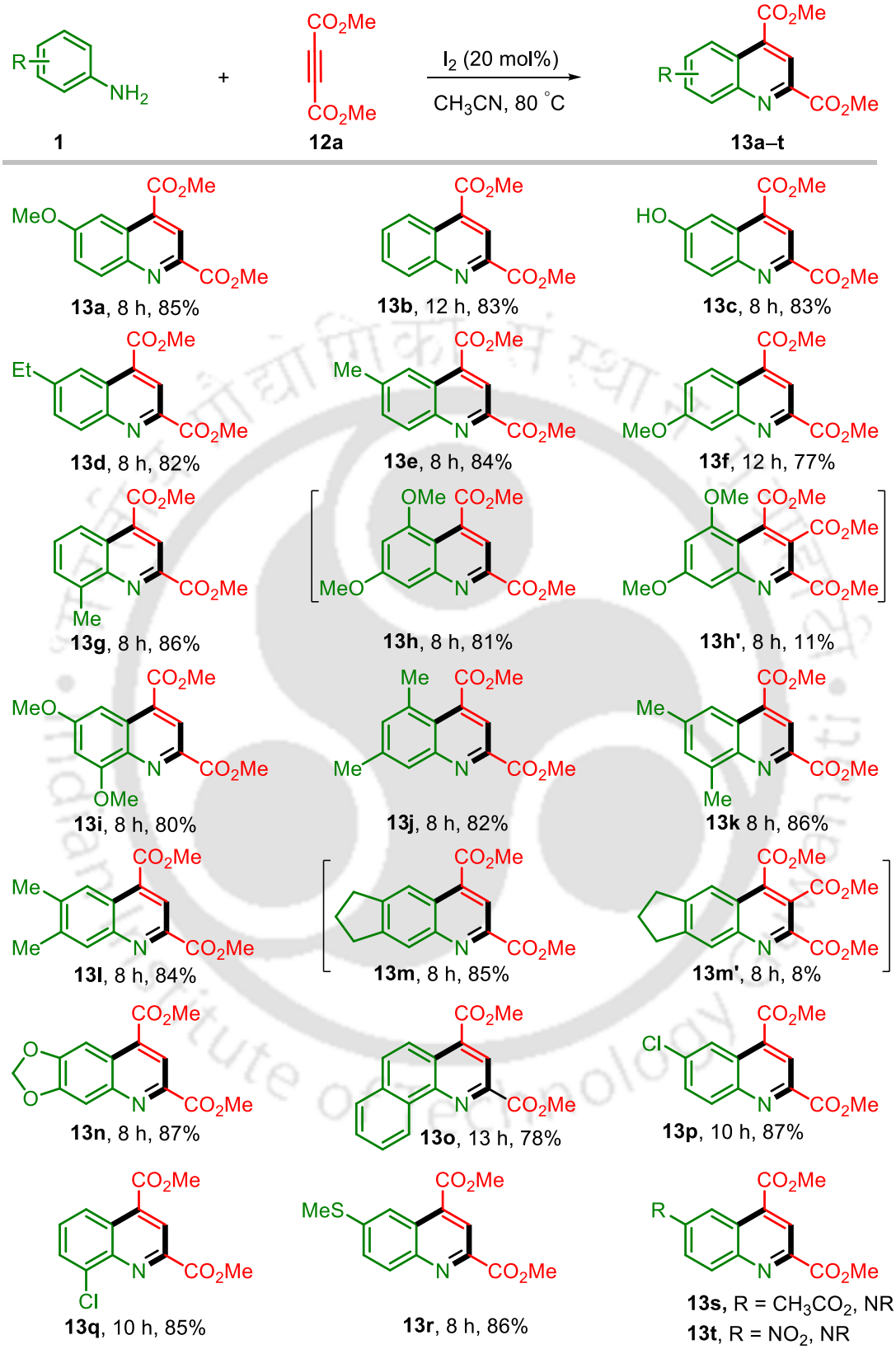
Entry	Catalyst	Mol %	Solvent	Time	Yield 13a (%)[b]
1[c]	–	–	–	24 h	NR
2	–	–	–	24 h	NR
3[c]	–	–	CH_3CN	24 h	NR
4	–	–	CH_3CN	24 h	NR
5[c]	I_2	5	CH_3CN	24 h	NR
6	I_2	5	CH_3CN	18 h	28
7	I_2	10	CH_3CN	18 h	50
8	I_2	15	CH_3CN	12 h	68
9	**I_2**	**20**	**CH_3CN**	**8 h**	**85**
10	I_2	25	CH_3CN	8 h	83
11	$PhI(OAc)_2$	20	CH_3CN	8 h	NR
12	IBr	20	CH_3CN	8 h	25
13	ICl	20	CH_3CN	8 h	20
14	I_2	20	dioxane	8 h	NR
15[d]	I_2	20	CH_2Cl_2	8 h	NR
16	I_2	20	$(CH_2Cl)_2$	8 h	NR
17[d]	I_2	20	THF	8 h	NR
18	I_2	20	DMF	8 h	NR
19	I_2	20	DMSO	8 h	NR
20[d]	I_2	20	MeOH	8 h	62
21	I_2	20	H_2O	8 h	48

[a]Reaction conditions: all reactions were performed using *p*-anisidine **1a** (1.0 mmol) and dimethyl acetylenedicarboxylate **12a** (2.0 mmol) in solvent (3.0 mL) at 80 °C. [b]Isolated yield. [c]Reaction performed at room temperature. [d]Reaction performed under reflux conditions. NR (no desired product).

Initially, model reaction was carried out using *p*-anisidine **1a** and dimethyl acetylenedicarboxylate **12a** without any solvent and catalyst (Table 3.1, entries 1 and 2). Reaction did not occur at room temperature as well as upon heating at 80 °C. Reaction also did not proceed even when it was examined in acetonitrile in absence of a catalyst at room temperature as well as at 80 °C (Table 3.1, entries 3 and 4). Reaction did not occur in the presence of 5 mol% I_2 at room temperature (Table 3.1, entry 5); however, upon heating at 80 °C for 18 h, product **13a** was isolated in 28% yield (Table 3.1, entry 6). Encouraged by this successful result, attempts were made to increase the yield of desired product **13a** by examining different reaction parameters, such as catalyst loading, using different catalysts and screening various solvents. When catalyst loading was increased from 5 mol% to 10 mol%, **13a** was obtained in 50% yield (Table 3.1, entry 7). Upon increasing catalyst loading from 10 mol% to 15 mol%, reaction time was reduced to 12 h and yield of **13a** was also improved further (Table 3.1, entry 8). When catalyst loading was increased to 20 mol%, reaction completed in 8 h and yield of **13a** increased significantly (Table 3.1, entry 9). However, a further increase in catalyst loading to 25 mol% did not improve yield of **13a** (Table 3.1, entry 10). Next, model reaction was executed in presence of different iodine containing non-metallic catalysts, such as $PhI(OAc)_2$, IBr and ICl (Table 3.1, entries 11–13). It was observed that none of them was more efficient than I_2. Next, to check the efficiency of solvent, different solvents, such as 1,4-dioxane, dichloromethane, tetrahydrofuran, dimethyl sulfoxide, methanol and water were tested (Table 3.1, entries 14–21) using 20 mol% I_2 as catalyst. It was noted that in all solvents, either reaction did not occur or yield of **13a** found to be low. Therefore, best yield of **13a** was obtained in acetonitrile. From all above observations, optimum reaction conditions were 20 mol% I_2 in acetonitrile at 80 °C (Table 3.1, entry 9) in terms of both reaction time and yield.

With optimized reaction conditions in hand, scope and generality of developed method were explored using different aryl amines **1** and dimethyl acetylenedicarboxylate **12a** (Table 3.2). Reaction of *p*-anisidine **1a** with dimethyl acetylenedicarboxylate **12a** provided desired product **13a** in 85% yield. Reaction of simple aniline with **12a** proceeded well and gave expected product **13b** in 83% yield. Similarly, aryl amine containing a hydroxyl group at 4-position afforded corresponding product **13c** in 83% yield. Similarly, aryl amines containing electron-donating groups (4-Et and 4-Me) also worked well and gave expected quinoline derivatives **13d** and **13e** in 82% and 84% yield, respectively.

Table 3.2. Reactions of different aryl amines **1** with dimethyl acetylenedicarboxylate **12a**[a,b]

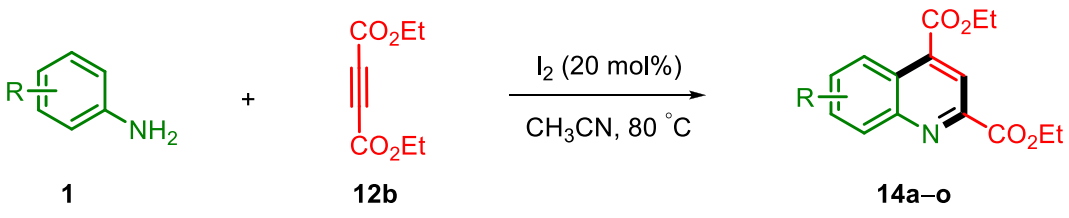


[a]Reaction conditions: all reactions were performed using aryl amines **1** (1.0 mmol) and dimethyl acetylenedicarboxylate **12a** (2.0 mmol) in CH_3CN (3.0 mL) at 80 °C. [b]Isolated yield. NR (no desired product).

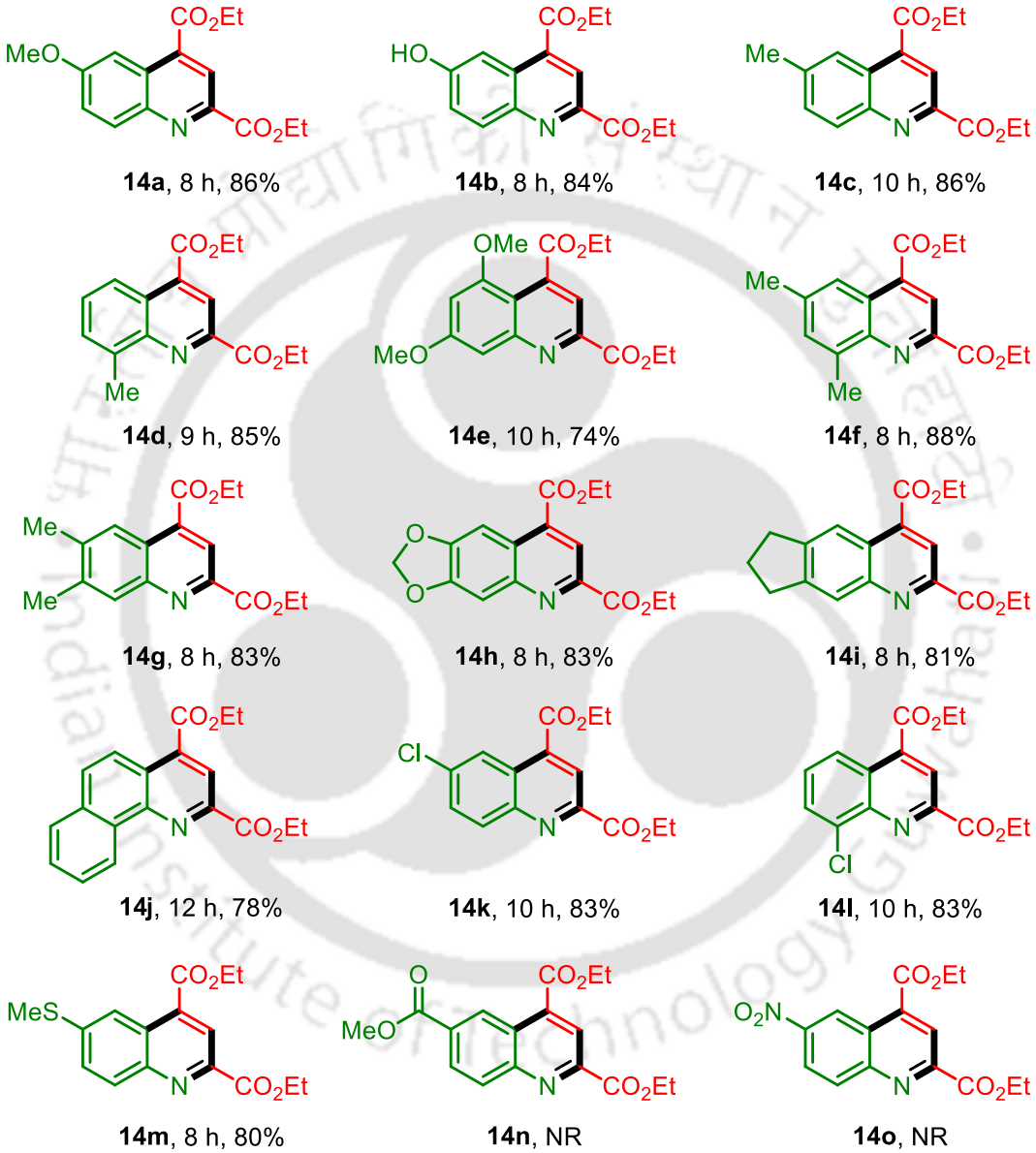
Likewise, reactions of aryl amines containing (3-OMe and 2-Me) groups with **12a** provided quinoline scaffolds **13f** and **13g** in 77% and 86% yield, respectively. Reactions of aryl amines containing (3,5-OMe, 2,4-OMe, 3,5-Me, 2,4-Me and 3,4-Me) groups with **12a** proceeded smoothly and gave corresponding quinoline derivatives **13h–l** in 80–86% yield. It is noteworthy that triester quinoline **13h′** obtained in 11% yield along with quinoline **13h**. Notably, bicyclic aryl amines, such as 5-aminoindan, 3,4-(methylenedioxy)aniline, and 1-naphthylamine, upon reaction with **12a** provided fused quinoline derivatives **13m–o** in 78–87% yield. Interestingly, in reaction with 5-aminoindan, triester quinoline **13m′** was also isolated in 8% yield along with desired product **13m**. Gratifyingly, aryl amines containing electron-withdrawing (4-Cl and 2-Cl) groups also gave corresponding quinolines **13p** and **13q** in 87% and 85% yield respectively. In addition, 4-(methylthio)aniline also provided desired quinoline **13r** in 86% yield. Unfortunately, aryl amines containing strong electron-withdrawing (-CO_2Me and -NO_2) groups at 4-position did not give anticipated products under standard conditions due to less electron density at 2-position with respect to -NH_2 group.

Inspired by above-discussed successful results, scope and generality of present protocol were further extended using different aryl amines **1** with diethyl acetylenedicarboxylate **12b** (Table 3.3). Reaction of *p*-anisidine **1a** with diethyl acetylenedicarboxylate **12b** under standard conditions proceeded smoothly and gave desired quinoline **14a** in 86% yield. Similarly, hydroxyl group at 4-position of aryl amine was well tolerated and afforded corresponding quinoline **14b** in 84% yield. Aryl amines containing (4-Me and 2-Me) groups also worked well and provided desired quinoline derivatives **14c** and **14d** in 86% and 85% yield, respectively. Disubstituted aryl amines containing (3,5-OMe, 2,4-Me and 3,4-Me) groups upon reaction with **12b** gave expected quinoline scaffolds **14e–g** in 74–88% yield. Notably, reaction of bicyclic amines, such as 3,4-(methylenedioxy)aniline, 5-aminoindan, and 1-naphthylamine with **12b** also gave anticipated quinoline derivatives **14h–j** in 78–83% yield. Interestingly, aryl amines having electron-withdrawing (4-Cl and 2-Cl) groups provided desired quinolines **14k** and **14l** in 83% and 83% yield, respectively. Additionally, 4-(methylthio)aniline afforded corresponding quinoline **14m** in 80% yield under standard conditions. Unfortunately, aryl amines containing strong electron-withdrawing (-CO_2Me and -NO_2) groups at 4-position did not produce expected products under standard conditions due to less electron density at *ortho* position with respect to -NH_2 group.

Table 3.3. Reactions of different aryl amines **1** with diethyl acetylenedicarboxylate **12b**[a,b]



1 **12b** **14a–o**



14a, 8 h, 86% **14b**, 8 h, 84% **14c**, 10 h, 86%

14d, 9 h, 85% **14e**, 10 h, 74% **14f**, 8 h, 88%

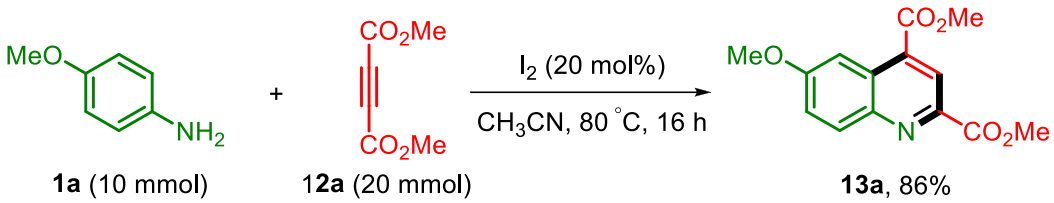
14g, 8 h, 83% **14h**, 8 h, 83% **14i**, 8 h, 81%

14j, 12 h, 78% **14k**, 10 h, 83% **14l**, 10 h, 83%

14m, 8 h, 80% **14n**, NR **14o**, NR

[a]Reaction conditions: all the reactions were performed using aryl amines **1** (1.0 mmol) and diethyl acetylenedicarboxylate **12b** (2.0 mmol) in CH_3CN (3.0 mL) at 80 °C. [b]Isolated yield. NR (no desired product).

To check the efficiency of this methodology, a scale up reaction was performed using *p*-anisidine **1a** and dimethyl acetylenedicarboxylate **12a**. Reaction proceeded smoothly to provide desired product **13a** in 86% yield (Scheme **3.2**).



Scheme 3.2. Gram-scale reaction.

Structures of all synthesized compounds were elucidated by IR, ^{1}H NMR, ^{13}C NMR and HRMS. In addition, structure of compound **13k** was also confirmed by single X-ray crystallographic data. ORTEP diagram of compound **13k** with 40% probability (CCDC No. 2053801) is shown in Figure 3.1. ^{1}H NMR, ^{13}C NMR spectra of compounds **13e**, **13p** and **14f** are shown in Figures **3.2a**, **3.2b**, **3.3c**, **3.3a**, **3.3b**, **3.3c**, **3.4a**, **3.4b and 3.4c**, respectively in experimental section.

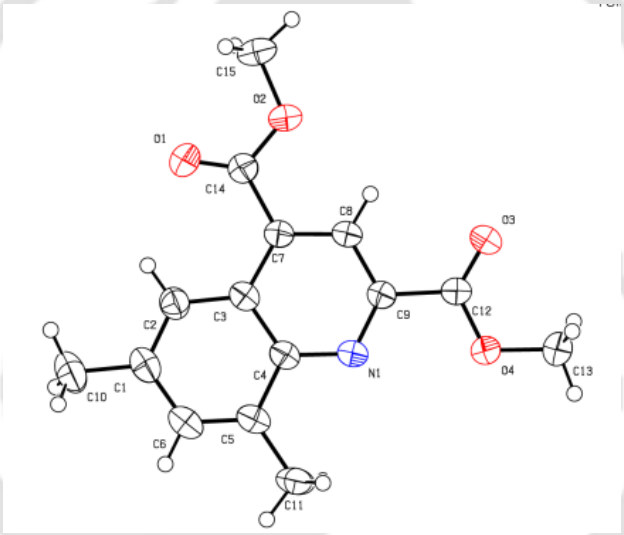
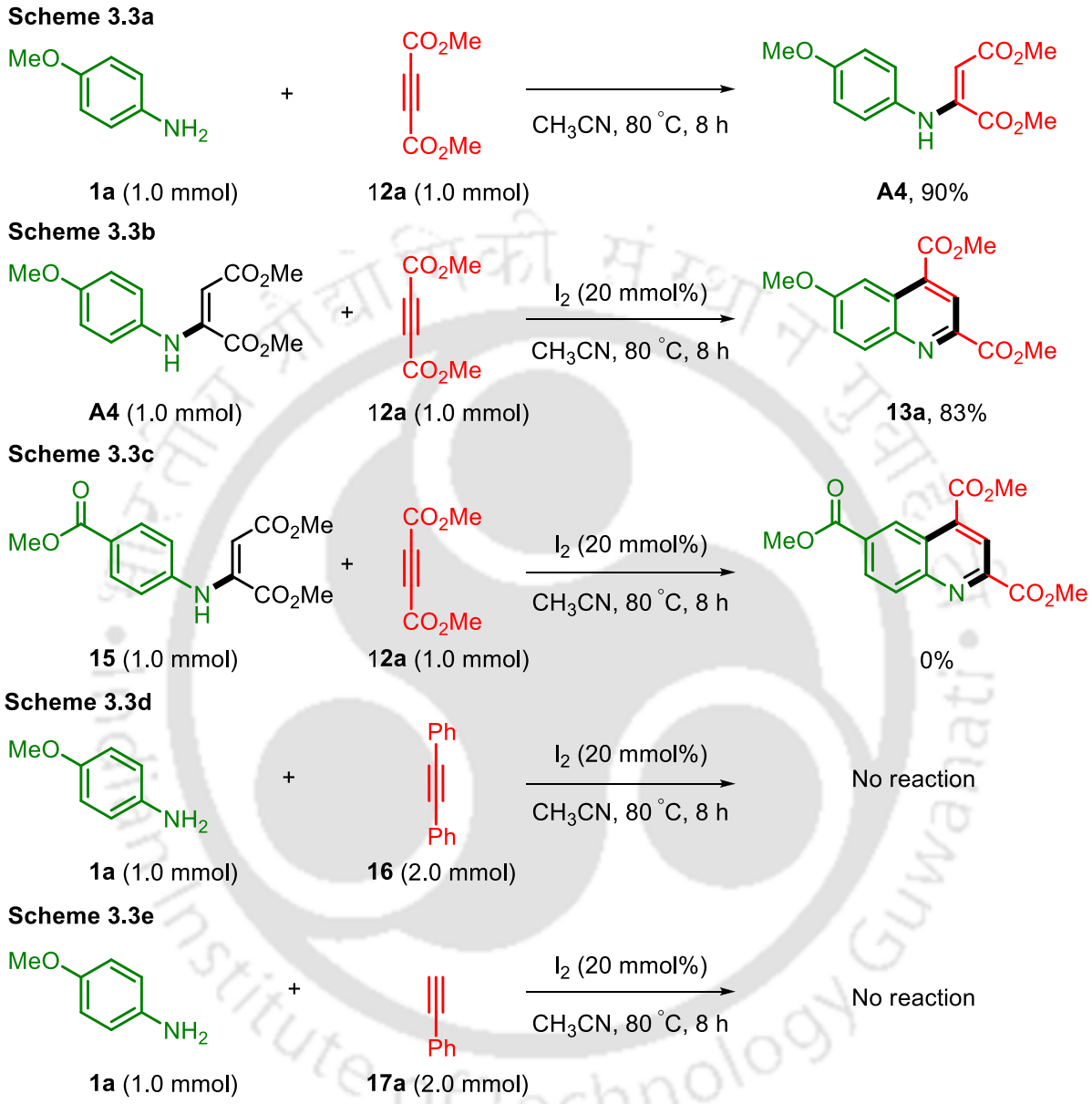


Figure 3.1. ORTEP diagram of compound **13k** with 40% probability.

To gain insights into reaction mechanism, a series of control experiments were carried out (Scheme **3.3**). At first, a reaction was performed using *p*-anisidine **1a** with dimethyl acetylenedicarboxylate **12a** in the absence of molecular iodine (Scheme **3.3a**). After heating reaction mixture for a period of 8 h, hydroamination intermediate **A4** (*aza*-Michael product) was isolated and characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. A similar observation has also been reported by Peet and co-workers.[4] Next, a reaction was executed using intermediate **A4** and dimethyl acetylenedicarboxylate **12a** under standard conditions (Scheme **3.3b**). Reaction completed in another 8 h and produced quinoline **13a** in 83% yield. This suggests formation of intermediate **A4** and its involvement in reaction mechanism. Reaction using intermediate **15** with dimethyl acetylenedicarboxylate **12a** under identical conditions did

not provide expected product (Scheme **3.3c**). Reason for reaction failure might be less electron density at *o*-position of ring with respect to -NH group due to presence of strong electron-withdrawing ester group.

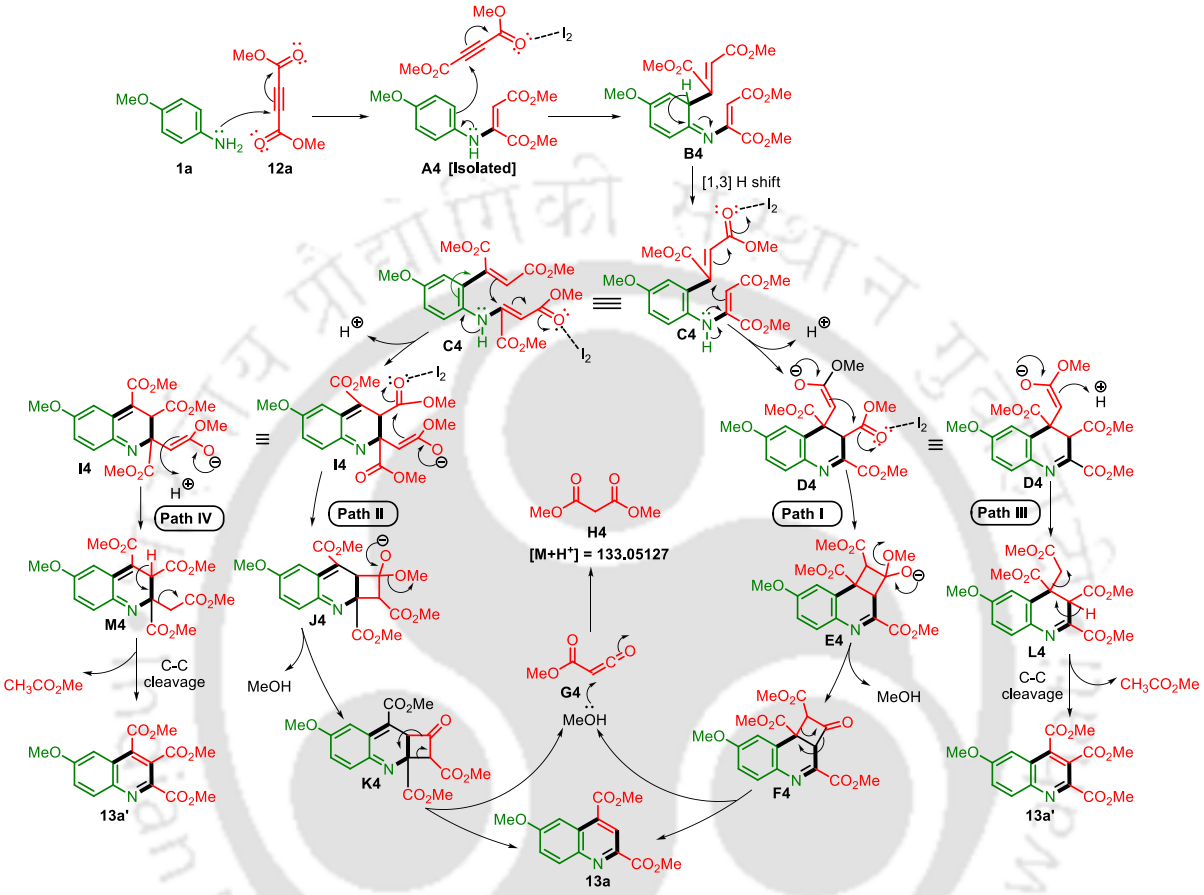


Scheme 3.3. Control experiments.

Next, reactions were performed using *p*-anisidine **1a** with diphenylacetylene **16** and phenylacetylene **17a** under identical conditions; reactions did not proceed at all in both cases (Scheme **3.3d** and **3.3e**). In both cases, formation of four membered ring fused tetrahydroquinoline intermediate is not possible. Therefore, corresponding products were not obtained using diphenylacetylene and acetylene. These two experiments suggest that presence

of two ester groups in acetylene is necessary for formation of product, which also supports our proposed reaction mechanism.

Based on observation of control experiments, a plausible mechanism for formation of quinoline-2,4-dicarboxylate and triester quinoline derivatives is shown in Scheme **3.4**.



Scheme 3.4. A plausible mechanism for formation of quinoline derivative **13a** and triester quinolines **13h**' and **13m**'.

It was presumed that reaction may occur *via* two pathways, path **I** or path **II**, to form desired diester products. According to path **I**, at first, *p*-anisidine **1a** reacts with dimethyl acetylenedicarboxylate **12a** to give *aza*-Michael product **A4**.[5] Intermediate product **A4** reacts with second molecule of **12a** assisted by molecular iodine *via* Michael reaction, leading to formation of intermediate **B4**. Then, intermediate **B4** undergoes a [1,3] H shift to provide intermediate **C4**, which on intramolecular cyclization *via* Michael reaction promoted by molecular iodine affords reactive anion species **D4**. Next, intermediate **D4** undergoes intramolecular cyclization which is also assisted by molecular iodine to generate a four membered ring fused with tetrahydroquinoline **F4** through intermediate **E4**. Due to ring strain, intermediate **F4** undergoes cleavage to give desired quinoline **13a** and reactive ketene

intermediate **G4**, which is attacked by generated methanol in reaction medium to give malonic ester **H4**. Alternatively, formation of diesters can also be explained through path **II**. It is noteworthy that malonic ester **H4** was detected in crude ^{1}H NMR spectrum of compound **13a**. In addition, malonic ester **H4** was also detected by HRMS.

Formation of minor product, triester quinoline derivatives, occurs *via* two possible pathways, path **III** or path **IV**. According to path **III**, intermediate **L4** can also be formed from intermediate **D4** after protonation, which undergoes C–C bond cleavage with elimination of CH_3CO_2Me to give expected triester quinoline derivatives. In path **IV**, intermediate **M4** can also be generated after protonation from intermediate **I4**, which undergoes an almost similar type of reaction like C–C bond cleavage to provide triester quinoline derivatives. Similar C–C bond cleavage has also been reported by others.[6] Formation of products **13h** and **13h′** and **13m** and **13m′** occurs *via* all four possible pathways among which path **I** and path **II** are more predominant; otherwise, in all other cases, path **I** and path **II** are solely favoured for formation of diesters.

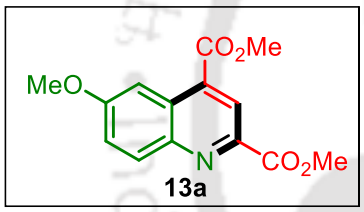
In summary, a simple and efficient method has been devised for synthesis of dimethyl/diethyl quinoline-2,4-dicarboxylate derivatives by employing pseudo three-component reactions using readily available aryl amines and acetylenedicarboxylates in the presence of 20 mol% I_2 under mild conditions. This transformation occurs under metal-free conditions, avoiding use of metal catalysts with no formation of metal waste. Important features of this protocol are its ease of handling, use of low cost and environmentally benign catalysts, high regioselectivity, use of commercially available starting materials, no requirement of an inert atmosphere or dry solvent, shorter reaction time, consecutive formation of one C–N and two C–C bonds and a broad substrate scope with good to excellent yield.

Experimental Section

General procedure for the synthesis of quinoline-2,4-dicarboxylate derivatives 13 and 14

Into a 10 mL round-bottomed flask, a mixture of aryl amine **1** (1.0 mmol) and acetylenedicarboxylate 1**2** (2.0 mmol) were taken in 3 mL of acetonitrile. After five minutes of stirring, molecular iodine (20 mol%, 50 mg) was added into it. The resultant mixture was stirred at room temperature for 10 min and subsequently it was kept for heating at 80 °C in a pre-heated oil-bath. After completion of the reaction, it was brought to room temperature and acetonitrile was evaporated on a rotary evaporator. After this, saturated solution of sodium thiosulphate was added drop-wise to the reaction mixture. Then, it was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water (2 x 5 mL) followed by brine solution (5 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated on a rotary evaporator. Finally, the crude mixture purified using a silica gel (60–120 mesh) column chromatography to obtain the desired products **13** and **14**.

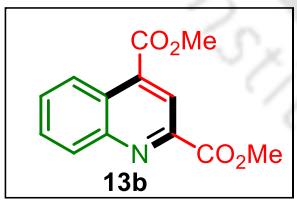
Dimethyl 6-methoxyquinoline-2,4-dicarboxylate (13a):[6a] (234 mg, 85%, light yellow solid);



13a

mp 152–153 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.30 (d, *J* = 2.8 Hz, 1H), 8.23 (d, *J* = 9.3 Hz, 1H), 7.48 (dd, *J* = 9.3, 2.8 Hz, 1H), 4.09 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.5, 165.7, 161.3, 145.3, 144.7, 133.4, 132.9, 128.7, 124.2, 123.4, 103.2, 55.9, 53.5, 52.9; **IR (KBr)ν_{max}** 2926, 1745, 1640, 1478, 1336 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{14}NO_5$ 276.0872 ($M + H^+$); Found 276.0872.

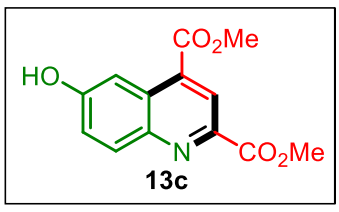
Dimethyl 6-methoxyquinoline-2,4-dicarboxylate (13b):[6a] (204 mg, 83%, yellow solid); mp



13b

128–129 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.5 Hz, 1H), 8.70 (s, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 165.6, 148.8, 147.7, 136.3, 131.5, 130.8, 130.6, 126.5, 125.77, 122.5, 53.6, 53.1; **IR (KBr)ν_{max}** 2956, 1721, 1507, 1434, 1355 cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{12}NO_4$ 246.0766 ($M + H^+$); Found 246.0766.

Dimethyl 6-hydroxyquinoline-2,4-dicarboxylate (13c): (217 mg, 83%, yellow solid); mp

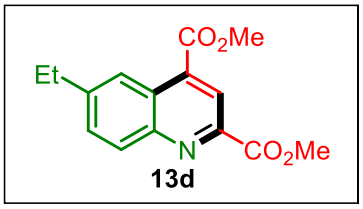


13c

215–216 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.44 (s, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 8.07 (d, *J* = 2.5 Hz, 1H), 7.50 (dd, *J* = 9.2, 2.6 Hz, 1H), 3.99 (s, 3H), 3.95 (s, 3H); **^{13}C NMR** (100 MHz, DMSO-d_6,) δ 165.7, 164.8, 159.5, 143.6,

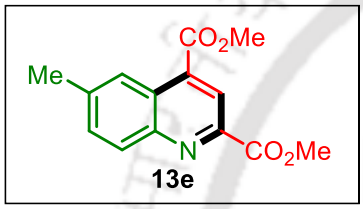
143.4, 132.7, 132.7, 127.6, 123.8, 122.1, 106.2, 52.9, 52.6; **IR (KBr)ν_{max}** 3394, 1722, 1655, 1600, 1354 cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{12}NO_5$ 262.0715 ($M + H^+$); Found 262.0715.

Dimethyl 6-ethylquinoline-2,4-dicarboxylate (13d): (224 mg, 86%, light yellow solid); mp



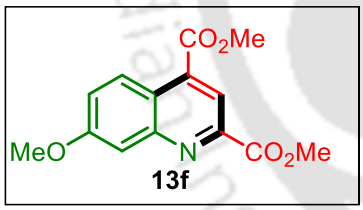
136–137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.63 (d, *J* = 0.8 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.71 (dd, *J* = 8.7, 1.9 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.36 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 165.7, 147.7, 147.4, 146.7, 135.4, 132.1, 131.3, 126.7, 123.3, 122.6, 53.5, 53.0, 29.7, 15.4; **IR (KBr)ν_{max}** 2964, 1725, 1649, 1498, 1333 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_4$ 274.1079 ($M + H^+$); Found 274.1093.

Dimethyl 6-methylquinoline-2,4-dicarboxylate (13e):[6a] (218 mg, 84%, gray solid); mp



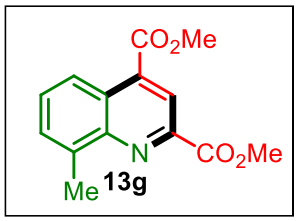
131–132 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.58 (s, 1H), 8.22 (d, *J* = 8.7 Hz, 1H), 7.65 (dd, *J* = 8.6, 1.1 Hz, 1H), 4.08 (s, 3H), 4.04 (s, 3H), 2.59 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 165.6, 147.5, 146.6, 141.3, 135.2, 133.1, 131.1, 126.5, 124.4, 122.5, 53.5, 53.0, 22.5; **IR (KBr)ν_{max}** 2962, 1721, 1633, 1500, 1352 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{14}NO_4$ 260.0923 ($M + H^+$); Found 260.0923.

Dimethyl 7-methoxyquinoline-2,4-dicarboxylate (13f): (214 mg, 77%, light yellow solid);



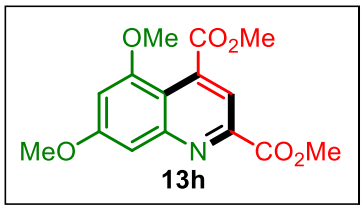
mp 148–149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 9.4 Hz, 1H), 8.56 (s, 1H), 7.66 (d, *J* = 2.5 Hz, 1H), 7.41 (dd, *J* = 9.4, 2.5 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 3.97 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 165.7, 161.4, 150.9, 147.8, 135.9, 126.7, 124.2, 122.0, 120.4, 108.7, 55.9, 53.6, 53.1; **IR (KBr)ν_{max}** 2968, 1738, 1615, 1600, 1366 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{14}NO_5$ 276.0872 ($M + H^+$); Found 276.0895.

Dimethyl 8-methylquinoline-2,4-dicarboxylate (13g):[6a] (224 mg, 86%, light yellow solid);



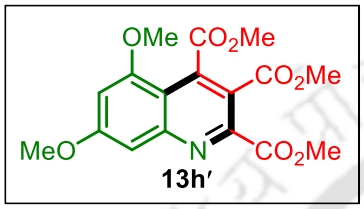
mp 125–126 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (t, *J* = 3.9 Hz, 2H), 7.71 – 7.61 (m, 2H), 4.08 (s, 3H), 4.06 (s, 3H), 2.91 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 165.8, 148.0, 146.4, 139.53, 136.4, 130.8, 130.3, 126.5, 123.5, 122.1, 53.3, 53.1, 18.6; **IR (KBr)ν_{max}** 2920, 1725, 1654, 1492, 1344 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{14}NO_4$ 260.0923 ($M + H^+$); Found 260.0924.

Dimethyl 5,7-dimethoxyquinoline-2,4-dicarboxylate (13h): (248 mg, 81%, light yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.2 Hz, 1H), 6.63 (s, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 4.04 (s, 3H), 3.95 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 162.7, 162.1, 155.9, 149.9, 140.5, 108.2, 107.7, 100.0, 97.4, 56.5, 55.8, 53.7, 52.7; **IR (KBr)ν_{max}** 2948, 1739, 1621, 1596, 1348 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_6$ 306.0978 ($M + H^+$); Found 306.0979.



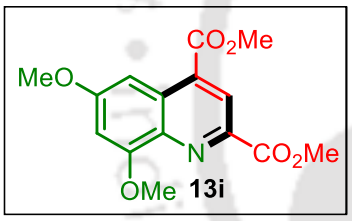
13h

Trimethyl 5,7-dimethoxyquinoline-2,3,4-tricarboxylate (13h′): (41 mg, 11%, yellow liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, J = 2.2 Hz, 1H), 6.63 (d, J = 2.2 Hz, 1H), 4.01 (s, 3H), 3.99 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 166.4, 165.6, 163.8, 156.1, 150.8, 150.1, 139.9, 118.8, 112.1, 101.9, 101.4, 57.0, 56.2, 53.5, 53.3, 52.9; **IR (KBr)ν_{max}** 2935, 1728, 1666, 1550 cm^{-1}; **HRMS** (ESI) Calcd For C17H18NO8 364.1032 ($M + H^+$); Found 364.1059.



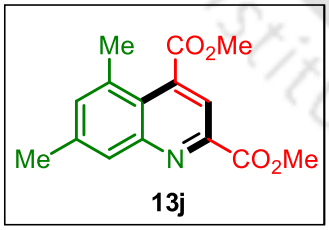
13h′

Dimethyl 6,8-dimethoxyquinoline-2,4-dicarboxylate (13i): (245 mg, 80%, yellow solid); mp 161–162 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.89 (s, 1H), 6.78 (s, 1H), 4.06 (s, 3H), 4.05 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.5, 165.8, 162.4, 157.3, 143.2, 138.1, 133.3, 129.6, 124.1, 102.4, 95.2, 56.5, 56.0, 53.3, 52.9; **IR (KBr)ν_{max}** 2954, 1720, 1615, 1436, 1285 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_6$ 306.0978 ($M + H^+$); Found 306.0978.



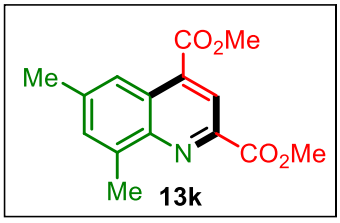
13i

Dimethyl 5,7-dimethylquinoline-2,4-dicarboxylate (13j): (225 mg, 82%, yellow solid); mp 133–134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.99 (s, 1H), 7.36 (s, 1H), 4.07 (s, 3H), 4.03 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 165.5, 149.4, 146.7, 140.9, 139.9, 134.7, 133.5, 128.9, 122.5, 119.2, 53.5, 53.3, 21.7, 21.0; **IR (KBr)ν_{max}** 2953, 1732, 1631, 1561, 1338 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_4$ 274.1079 ($M + H^+$); Found 274.1079.



13j

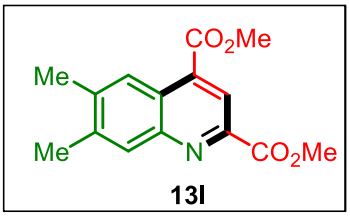
Dimethyl 6,8-dimethylquinoline-2,4-dicarboxylate (13k):[6a] (236 mg, 86%, light yellow solid); mp 138–139 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.40 (s, 1H), 7.53 (s, 1H), 4.07 (s, 3H), 4.05 (s, 3H), 2.87 (s, 3H), 2.55 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.7, 165.9, 146.7, 145.3, 140.9, 138.9, 135.4, 133.3, 126.7, 122.3, 122.2,



13k

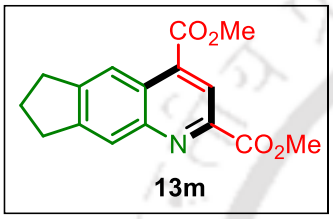
53.3, 52.9, 22.6, 18.4; **IR (KBr)ν_{max}** 2956, 1728, 1627, 1568, 1339 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_4$ 274.1079 ($M + H^+$); Found 274.1079.

Dimethyl 6,7-dimethylquinoline-2,4-dicarboxylate (13l): (231 mg, 84%, white solid); mp 139–140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.59 (s, 1H), 8.12 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 2.52 (s, 3H), 2.50 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 165.8, 148.1, 146.6, 141.6, 141.4, 134.9, 132.2, 130.6, 124.8, 121.8, 53.5, 53.0, 21.0, 20.5; **IR (KBr)ν_{max}** 2923, 1723, 1614, 1585, 1356 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_4$ 274.1079 ($M + H^+$); Found 274.1096.



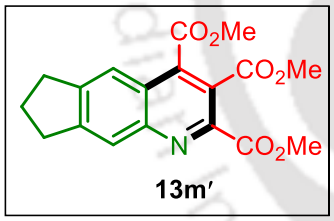
13l

Dimethyl 7,8-dihydro-6H-cyclopenta[g]quinoline-2,4-dicarboxylate (13m): (244 mg, 85%, yellow solid); mp 142–143 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.59 (s, 1H), 8.15 (s, 1H), 4.09 (s, 3H), 4.06 (s, 3H), 3.14 (t, *J* = 7.3 Hz, 4H), 2.20 (quint, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 165.8, 149.4, 149.2, 148.8, 146.3, 135.5, 125.8, 125.6, 121.6, 119.6, 53.4, 53.0, 33.4, 32.9, 26.2; **IR (KBr)ν_{max}** 2953, 1725, 1614, 1436, 1351 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{16}NO_4$ 286.1079($M + H^+$); Found 286.1079.



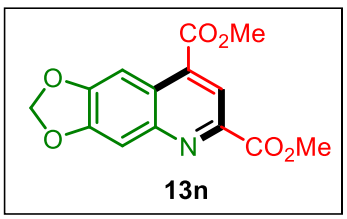
13m

Trimethyl7,8-dihydro-6H-cyclopenta[g]quinoline-2,3,4- tricarboxylate (13m′): (28 mg, 8%, brown liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.81 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.95 (s, 3H), 3.15 – 3.10 (m, 4H), 2.20 (quint, J = 7.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 166.5, 166.2, 151.4, 149.0, 147.8, 146.7, 139.6, 125.0, 123.2, 122.2, 119.7, 53.6, 53.4, 53.4, 33.2, 33.1, 26.1; **IR (KBr)ν_{max}** 2922, 1731, 1650, 1554 cm^{-1}; **HRMS** (ESI) Calcd For $C_{18}H_{18}NO_6$ 344.1134 ($M + H^+$); Found 344.1137.



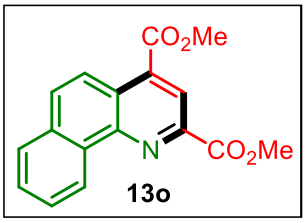
13m′

Dimethyl [1,3]dioxolo[4,5-g]quinoline-6,8-dicarboxylate (13n): (252 mg, 87%, gray solid); mp 164–165 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.25 (s, 1H), 7.61 (s, 1H), 6.19 (s, 2H), 4.08 (s, 3H), 4.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.5, 165.7, 151.7, 151.7, 147.9, 145.2, 134.2, 125.2, 121.4, 107.1, 102.7, 101.3, 53.4, 53.0; **IR (KBr)ν_{max}** 2948, 1738, 1640, 1578, 1367 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{12}NO_6$ 290.0665 ($M + H^+$); Found 290.668.



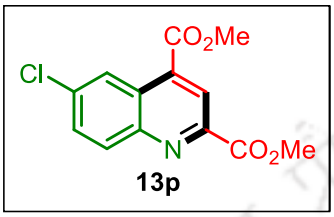
13n

Dimethyl benzo[h]quinoline-2,4-dicarboxylate (13o): (233 mg, 78%, gray solid); mp 172–173 °C; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.44 (d, *J* = 8.1 Hz, 1H), 8.78 (s, 1H), 8.70 (d, *J*



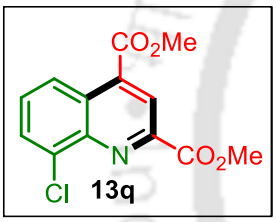
= 9.3 Hz, 1H), 8.03 (d, *J* = 9.3 Hz, 1H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.82 – 7.77 (m, 2H), 4.13 (s, 3H), 4.09 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 166.6, 165.8, 147.7, 146.0, 135.9, 133.5, 132.2, 131.6, 129.6, 128.2, 128.0, 126.0, 125.6, 123.1, 122.2, 53.4, 53.2; **IR (KBr)ν_{max}** 2965, 1739, 1642, 1600, 1368 cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{14}NO_4$ 296.0923(M + H^+); Found 296.0927.

Dimethyl 6-chloroquinoline-2,4-dicarboxylate (13p): (243 mg, 87%, light yellow solid); mp



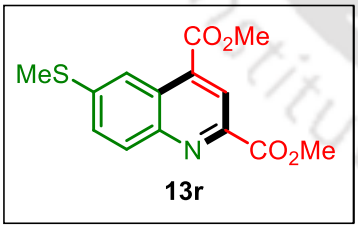
152–153 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.3 Hz, 1H), 8.71 (s, 1H), 8.28 (d, *J* = 9.1 Hz, 1H), 7.78 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.11 (s, 3H), 4.08 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.7, 165.2, 147.9, 147.2, 137.2, 135.1, 132.8, 131.9, 127.0, 124.9, 123.4, 53.57, 53.19; **IR (KBr)ν_{max}** 2959, 1722, 1606, 1494, 1236 cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{11}ClNO_4$ 280.0381 (M + H^+); Found 280.0391.

Dimethyl 8-chloroquinoline-2,4-dicarboxylate (13q): (239 mg, 85%, light yellow solid); mp



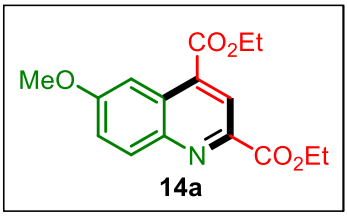
143–144 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 8.7 Hz, 1H), 8.71 (s, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 8.7 Hz, 1H), 4.09 (s, 3H), 4.06 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.8, 165.3, 148.2, 145.2, 136.9, 135.7, 130.9, 130.2, 127.9, 124.8, 123.2, 53.5, 53.2; **IR (KBr)ν_{max}** 2962, 1728, 1450, 1242 cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{11}ClNO_4$ 280.0381 (M + H^+); Found 280.0390.

Dimethyl 6-(methylthio)quinoline-2,4-dicarboxylate (13r): (253 mg, 86%, light yellow



solid); mp 138–139 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.63 (s, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 4.08 (s, 3H), 4.05 (s, 3H), 2.63 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2, 165.5, 147.1, 146.1, 143.9, 133.4, 131.1, 129.7, 127.2, 123.5, 118.7, 53.5, 52.9, 15.2; **IR (KBr)ν_{max}** 2988, 1718, 1632, 1645, 1228 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{14}SNO_4$ 292.0644 (M + H^+); Found 292.0655.

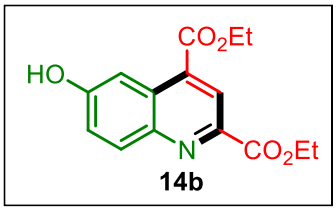
Diethyl 6-methoxyquinoline-2,4-dicarboxylate (14a): (261 mg, 86%, yellow solid); mp



158–159 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.28 (s, 1H), 8.24 (d, *J* = 9.3 Hz, 1H), 7.47 (d, *J* = 9.2 Hz, 1H), 4.55 (dq, *J* = 22.1, 7.0 Hz, 4H), 4.00 (s, 3H), 1.50 (t, *J* = 6.9 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.2, 165.3, 161.2, 145.4,

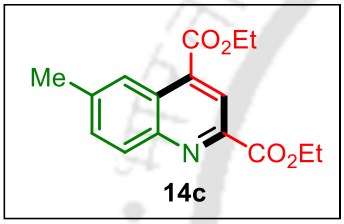
145.2, 133.9, 133.0, 128.6, 124.0, 123.2, 103.2, 62.5, 62.1, 55.9, 14.6, 14.5; **IR (KBr)ν_{max}** 2981, 1719, 1622, 1600, 1229 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{18}NO_5$ 304.1185 ($M + H^+$); Found 304.1188.

Diethyl 6-hydroxyquinoline-2,4-dicarboxylate (14b): (243 mg, 84%, light yellow solid); mp



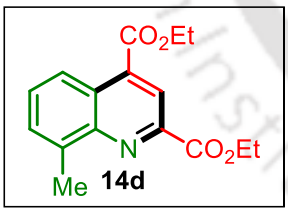
220–221 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.12 (d, J = 9.2 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.49 (dd, J = 9.2, 2.6 Hz, 1H), 4.44 (dq, J = 14.3, 7.1 Hz, 4H), 1.39 (dt, J = 12.1, 7.2 Hz, 6H); **^{13}C NMR** (100 MHz, DMSO- d_6) δ 165.3, 164.4, 159.4, 143.7, 143.6, 133.2, 132.6, 127.5, 123.8, 121.9, 106.1, 61.8, 61.5, 14.2, 14.0; **IR (KBr)ν_{max}** 3397, 2946, 1719,1655, 1310 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{16}NO_5$ 290.1028 ($M + H^+$); Found 290.1028.

Diethyl 6-methylquinoline-2,4-dicarboxylate (14c): (247 mg, 86%, yellow solid); mp



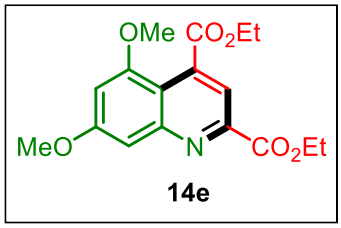
135–136 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.59 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.7 Hz, 1H), 4.58 (q, J = 7.2 Hz, 2H), 4.54 (q, J = 7.2 Hz, 2H), 2.61 (s, 3H), 1.50 (td, J = 7.2, 3.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.1, 165.3, 147.6, 147.1, 141.1, 135.8, 132.9, 131.2, 126.6, 124.5, 122.4, 62.6, 62.2, 22.6, 14.6, 14.5; **IR (KBr)ν_{max}** 2982, 1722, 1623, 1369, 1234 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{18}NO_4$ 288.1236 ($M + H^+$); Found 288.1238.

Diethyl 8-methylquinoline-2,4-dicarboxylate (14d): (244 mg, 85%, light yellow solid); mp



126-127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (d, J = 12.7 Hz, 2H), 7.68 (d, J = 7.0 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 4.54 (p, J = 7.8 Hz, 4H), 2.92 (s, 3H), 1.50 (q, J = 7.3 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.3, 165.4, 148.0, 146.8, 139.6, 136.9, 130.7, 130.1, 126.5, 123.5, 121.8, 62.36, 62.27, 18.50, 14.53; **IR (KBr)ν_{max}** 2983, 1717, 1619, 1468, 1342 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{18}NO_4$ 288.1236 ($M + H^+$); Found 288.1237.

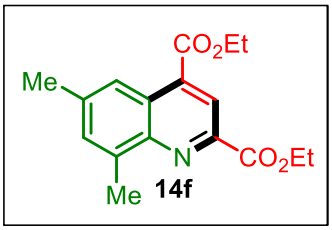
Diethyl 5,7-dimethoxyquinoline-2,4-dicarboxylate (14e): (248 mg, 74%, light yellow



liquid); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (d, J = 2.3 Hz, 1H), 6.61 (s, 1H), 6.41 (d, J = 2.3 Hz, 1H), 4.48 (q, J = 7.1 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 1.41 (dt, J = 9.1, 7.1 Hz, 6H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 169.4, 162.5, 162.0, 155.9, 150.1, 140.8, 108.1, 107.9, 99.9, 97.2, 62.1, 61.8,

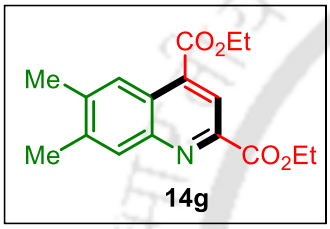
56.2, 55.8, 14.8, 14.5; **IR (KBr)ν_{max}** 2938, 1737, 1623, 1596, 1332 cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{20}NO_6$ 334.1291 ($M + H^+$); Found 334.1294.

Diethyl 6,8-dimethylquinoline-2,4-dicarboxylate (14f): (265mg, 88%, light yellow solid);



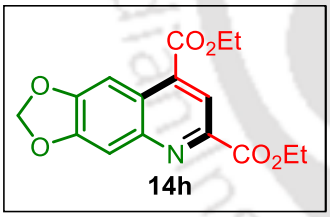
mp 144–145 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.38 (s, 1H), 7.52 (s, 1H), 4.53 (quint, *J* = 7.1 Hz, 4H), 2.87 (s, 3H), 2.55 (s, 3H), 1.49 (td, *J* = 7.2, 5.6 Hz, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.5, 165.5, 146.8, 145.7, 140.7, 139.0, 135.9, 133.1, 126.6, 122.3, 121.9, 62.3, 62.1, 22.5, 18.4, 14.5, 14.5; **IR (KBr)ν_{max}** 2983, 1717,1619, 1468, 1342 cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{20}NO_4$ 302.1392 ($M + H^+$); Found 302.1394.

Diethyl 6,7-dimethylquinoline-2,4-dicarboxylate (14g): (258 mg, 85%, light yellow solid);



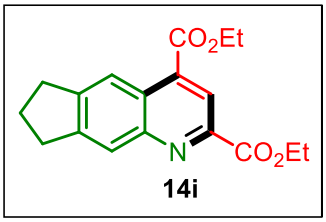
mp 147–148 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.0 Hz, 2H), 8.13 (s, 1H), 4.60 – 4.55 (m, 2H), 4.52 (t, *J* = 7.2 Hz, 2H), 2.52 (s, 3H), 2.50 (s, 3H), 1.49 (td, *J* = 7.1, 3.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.2, 165.4, 148.2, 147.1, 141.2, 141.2, 135.4, 130.7, 125.2, 124.8, 121.6, 62.5, 62.1, 20.9, 20.4, 14.6, 14.5; **IR (KBr)ν_{max}** 2981, 1721, 1464, 1230 cm^{-1}; **HRMS** (ESI) Calcd For $C_{17}H_{20}NO_4$ 302.1392 ($M + H^+$); Found 302.1397.

Diethyl [1,3]dioxolo[4,5-g]quinoline-6,8-dicarboxylate (14h): (264 mg, 83%, yellow solid);



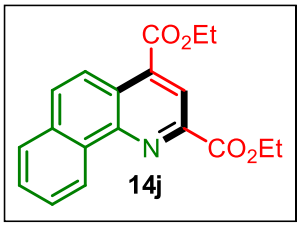
mp 175–176 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.22 (s, 1H), 7.61 (s, 1H), 6.19 (s, 2H), 4.54 (q, *J* = 7.1 Hz, 2H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.48 (td, *J* = 7.1, 4.5 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 159.9, 156.8, 151.5, 147.9, 145.7, 134.7, 125.1, 121.2, 107.3, 102.6, 101.3, 62.5, 62.2, 14.6, 14.5; **IR (KBr)ν_{max}** 2993, 1721, 1621, 1477, 1233 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{16}NO_6$ 318.0978 ($M + H^+$); Found 318.0985.

Diethyl 7,8-dihydro-6H-cyclopenta[g]quinoline-2,4-dicarboxylate (14i): (256 mg, 81%,



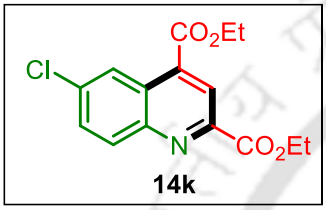
light yellow solid); mp 150–152 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.60 (s, 1H), 8.55 (s, 1H), 8.15 (s, 1H), 4.60 – 4.55 (m, 2H), 4.54 – 4.49 (m, 2H), 3.14 (t, *J* = 7.4 Hz, 4H), 2.20 (p, *J* = 7.4 Hz, 2H), 1.49 (td, *J* = 7.2, 5.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.4, 165.4, 149.1, 148.9, 148.9, 146.7, 135.9, 125.7, 125.7, 121.4, 119.6, 62.5, 62.2, 33.4, 32.9, 26.2, 14.6, 14.5; **IR (KBr)ν_{max}** 2979, 1719, 1454, 1369, 1232 cm^{-1}; **HRMS** (ESI) Calcd For $C_{18}H_{20}NO_4$ 314.1492 ($M + H^+$); Found 314.1495.

Diethyl benzo[h]quinoline-2,4-dicarboxylate (14j): (253 mg, 78%, yellow solid); mp



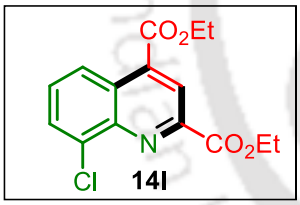
184–185 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.45 (d, *J* = 7.7 Hz, 1H), 8.74 (s, 1H), 8.67 (d, *J* = 9.3 Hz, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.84 – 7.75 (m, 2H), 4.62 – 4.53 (m, 4H), 1.52 (dd, *J* = 14.0, 7.1 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.3, 165.4, 147.6, 146.4, 136.4, 133.5, 131.9, 131.7, 129.4, 128.1, 127.9, 125.9, 125.7, 122.8, 122.2, 62.4, 62.4, 14.6, 14.5; **IR (KBr)ν_{max}** 2982, 1720, 1605, 1368, 1237 cm^{-1}; **HRMS** (ESI) Calcd For $C_{19}H_{18}NO_4$ 324.1236 ($M + H^+$); Found 324.1236.

Diethyl 6-chloroquinoline-2,4-dicarboxylate (14k): (257 mg, 83%, yellow solid); mp



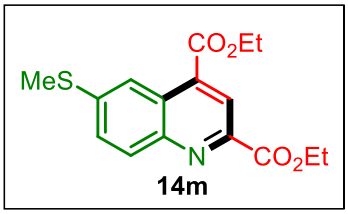
163–164 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.3 Hz, 1H), 8.69 (s, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 7.77 (dd, *J* = 9.1, 2.3 Hz, 1H), 4.56 (dd, *J* = 16.0, 7.2 Hz, 4H), 1.50 (q, *J* = 4.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.4, 164.8, 148.3, 147.3, 137.0, 135.6, 132.9, 131.8, 127.1, 124.9, 123.3, 62.8, 62.6, 14.6, 14.5; **IR (KBr)ν_{max}** 2987, 1723, 1605, 1448, 1240 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{15}ClNO_4$ 308.0690 ($M + H^+$); Found 308.0697.

Diethyl 8-chloroquinoline-2,4-dicarboxylate (14l): (254 mg, 82%, light yellow solid); mp



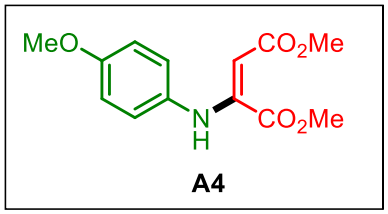
157–158 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.83 (d, *J* = 2.3 Hz, 1H), 6.61 (s, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 1.41 (dt, *J* = 9.1, 7.1 Hz, 6H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 169.4, 162.5, 162.0, 155.9, 150.1, 140.8, 108.1, 107.9, 99.9, 97.2, 62.1, 61.8, 56.2, 55.8, 14.8, 14.5; **IR (KBr)ν_{max}** 2983, 1722, 1446, 1370, 1239 cm^{-1}; **HRMS** (ESI) Calcd For $C_{15}H_{15}ClNO_4$ 308.0690 ($M + H^+$); Found 309.0709.

Diethyl 6-(methylthio)quinoline-2,4-dicarboxylate (14m): (258 mg, 80%, light yellow



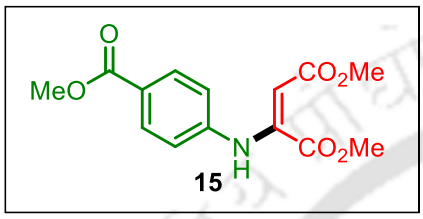
solid); mp 152–153 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.63 (s, 1H), 8.21 (d, *J* = 9.1 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 4.55 (dq, *J* = 22.6, 7.1 Hz, 4H), 2.64 (s, 3H), 1.50 (td, *J* = 7.1, 2.7 Hz, 6H); **^{13}C NMR** (125MHz, $CDCl_3$) δ 165.9, 165.2, 147.2, 146.6, 143.6, 134.0, 131.3, 129.7, 127.2, 123.4, 118.8, 62.6, 62.2, 15.2, 14.6, 14.5; **IR (KBr)ν_{max}** 2924, 1719,1602,1448, 1234 cm^{-1}; **HRMS** (ESI) Calcd For $C_{16}H_{18}NO_4S$ 320.0957 ($M + H^+$); Found 320.0962.

Dimethyl 2-(4-methoxyphenylamino)maleate (A4): (240 mg, 90%, yellow liquid); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 5.27 (s, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.1, 164.9, 157.0, 149.1, 133.5, 123.1, 114.5, 91.7, 55.5, 52.7, 51.1; **IR (KBr)ν_{max}** 3287, 2952, 1739, 1669, 1277 cm^{-1}; **HRMS** (ESI) Calcd For $C_{13}H_{16}NO_5$ 266.1028 ($M + H^+$); Found 266.1041.



A4

Dimethyl 2-(4-(methoxycarbonyl)phenylamino)maleate (15): (232 mg, 79%, yellow liquid); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.93 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.6, 166.6, 164.6, 146.5, 144.6, 131.0, 125.3, 119.2, 96.9, 53.1, 52.1, 51.5; **IR (KBr)ν_{max}** 3286, 2949, 1716, 1597, 1268 cm^{-1}; **HRMS** (ESI) Calcd For $C_{14}H_{16}NO_6$ 294.0978 ($M + H^+$); Found 294.0992.



15

XRD for compound (13k): All the data for the structural analysis of compound **13k** has been deposited to the Cambridge Crystallographic Data Centre, **CCDC No. 2053801**. The file of this information can be obtained from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk).

Table 3.4. Crystal data and structure refinement for compound **13k**

Entry	Identification code	Compound 13k
01	Empirical formula	$C_{15}H_{15}NO_4$
02	Formula weight	273.1001
03	Temperature	296 (2)K
04	Wavelength	0.71073
05	Radiation type	MoK\a
06	Radiation source	'fine-focus sealed tube'
07	Crystal system	Monoclinic
08	Space group	P 21/n
09	Cell length	a=3.9964(3)b=38.647(3)c=8.7063(5)
10	Cell Angle	α 90(9)β 97.942(3)γ90
11	Cell Volume	1331.77(3)
12	Density	1.363
13	Completeness to theta	0.998-28.293
14	Absorption correction	multi-scan
15	Refinement method	Full
16	Index ranges	$-5 \leq h \leq 5, -55 \leq k \leq 55, -11 \leq l \leq 11$
17	Reflection number	3314
18	R-Factor	0.0587
18	Theta range	2.108-28.293
19	Cell formula units Z	4
20	CCDC no	2053801

^{1}H NMR (400 MHz, $CDCl_3$): dimethyl 6-methylquinoline-2,4-dicarboxylate **(13e)**

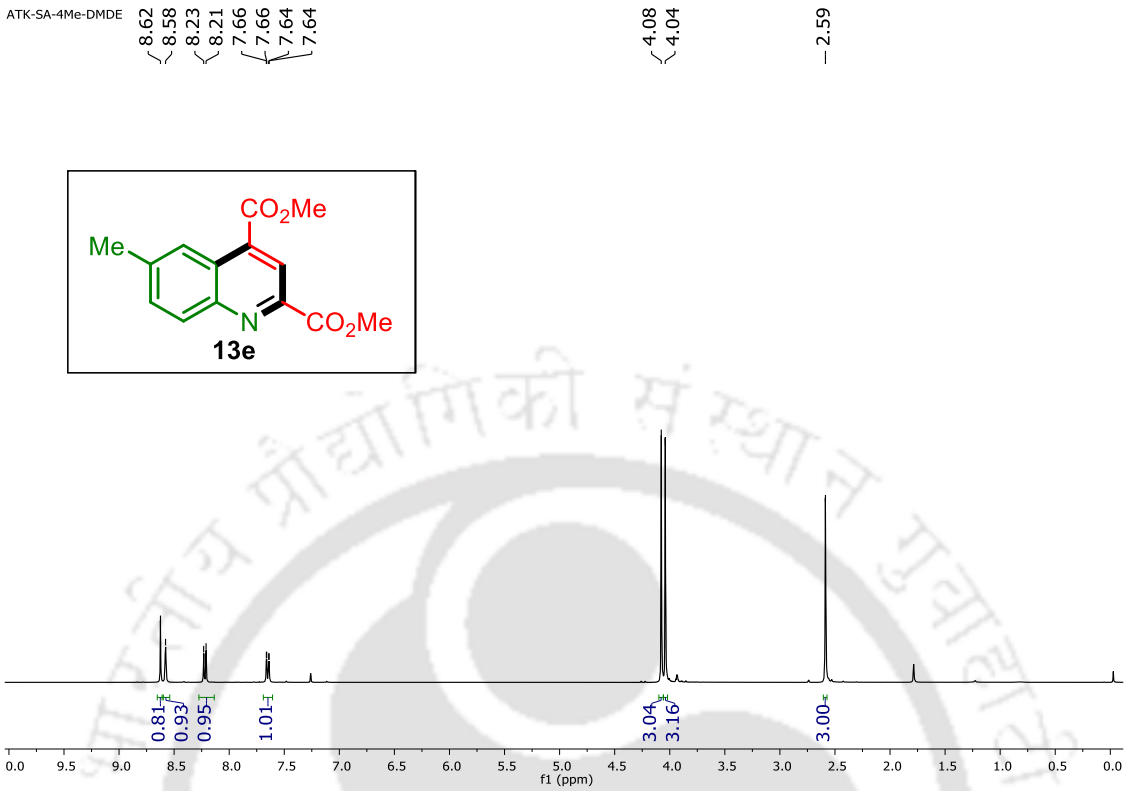


Figure 3.2a

^{13}C NMR (100 MHz, $CDCl_3$): dimethyl 6-methylquinoline-2,4-dicarboxylate **(13e)**

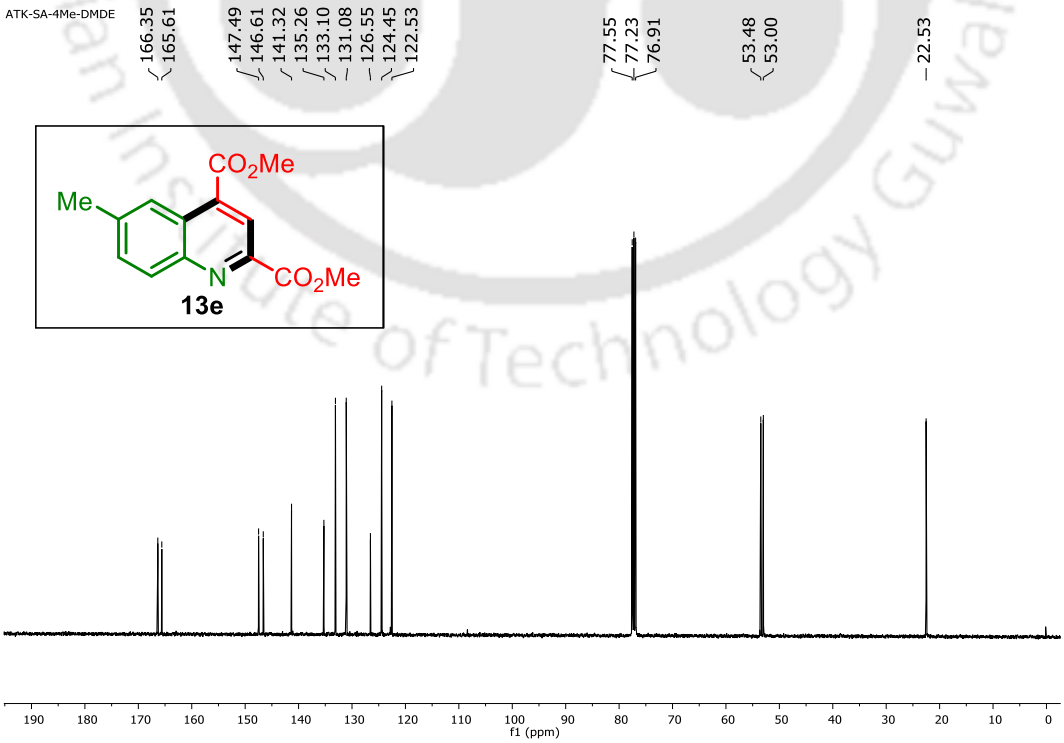


Figure 3.2b

HRMS spectrum: dimethyl 6-methylquinoline-2,4-dicarboxylate **(13e)**

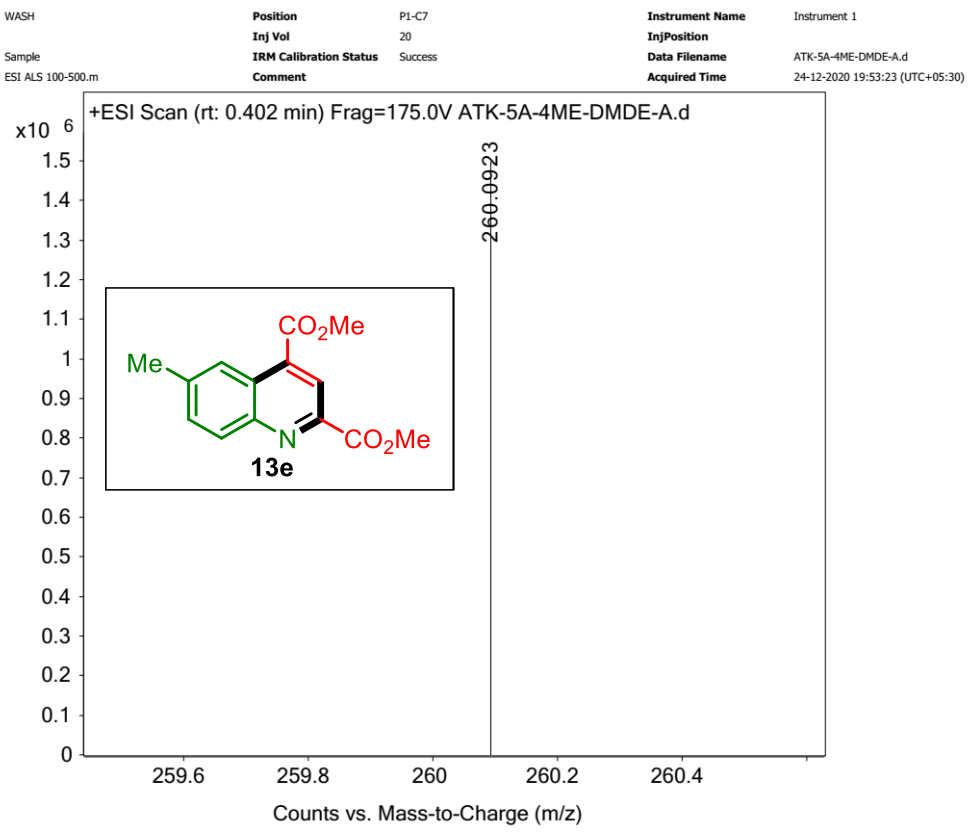


Figure 3.2c

^{1}H NMR (400 MHz, $CDCl_3$): dimethyl 6-chloroquinoline-2,4-dicarboxylate **(13p)**

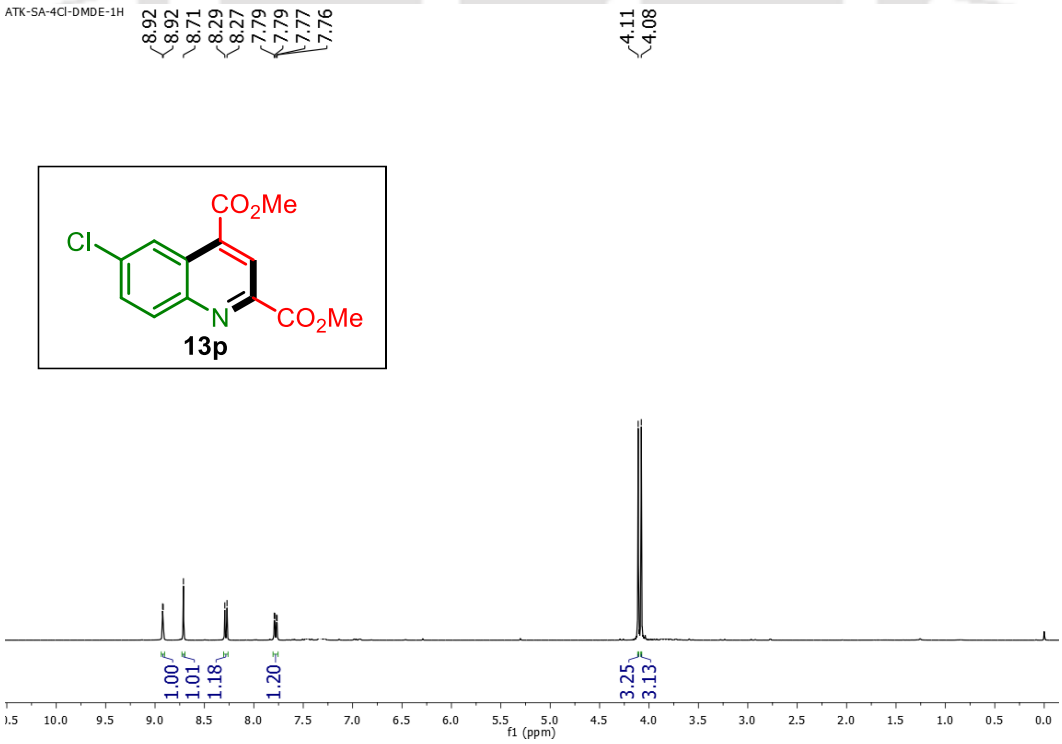


Figure 3.3a

^{13}C NMR (100 MHz, $CDCl_3$): dimethyl 6-chloroquinoline-2,4-dicarboxylate **(13p)**

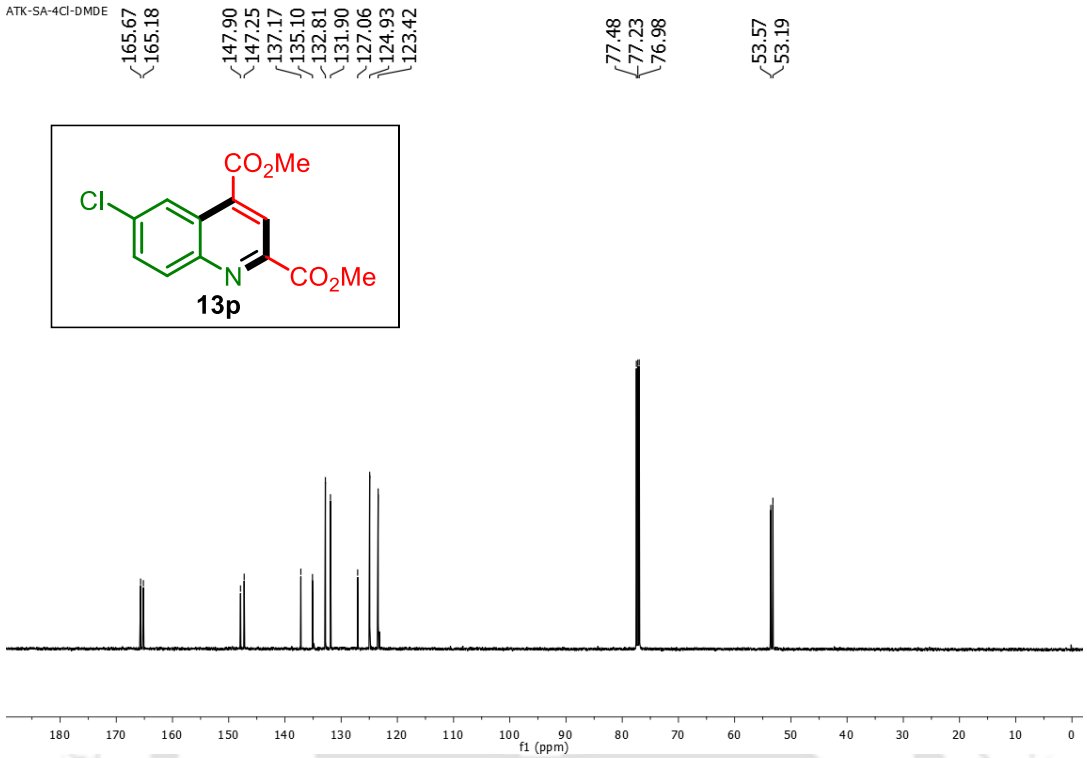


Figure 3.3b

HRMS spectrum: dimethyl 6-chloroquinoline-2,4-dicarboxylate **(13p)**

Sample Name	SAMPLE 32	**Position**	P1-C9	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4-CL-DMDE-4.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	3/19/2021 4:37:15 PM

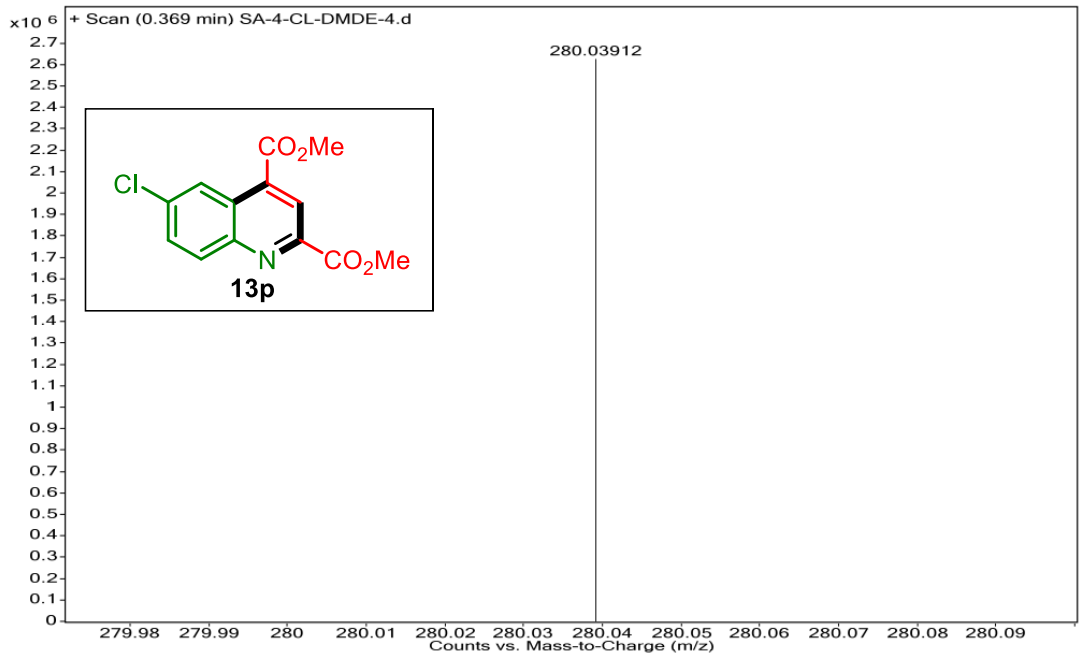


Figure 3.3c

^{1}H NMR (400 MHz, $CDCl_3$): diethyl 6,8-dimethylquinoline-2,4-dicarboxylate **(14f)**

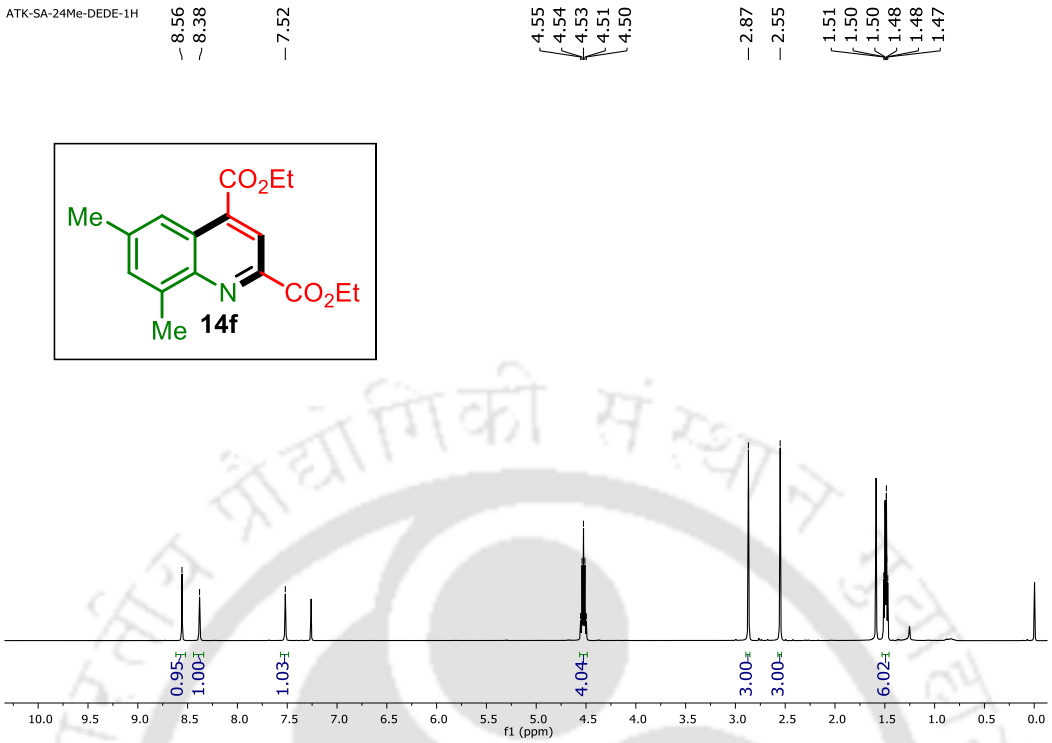


Figure 3.4a

^{13}C NMR (400 MHz, $CDCl_3$): diethyl 6,8-dimethylquinoline-2,4-dicarboxylate **(14f)**

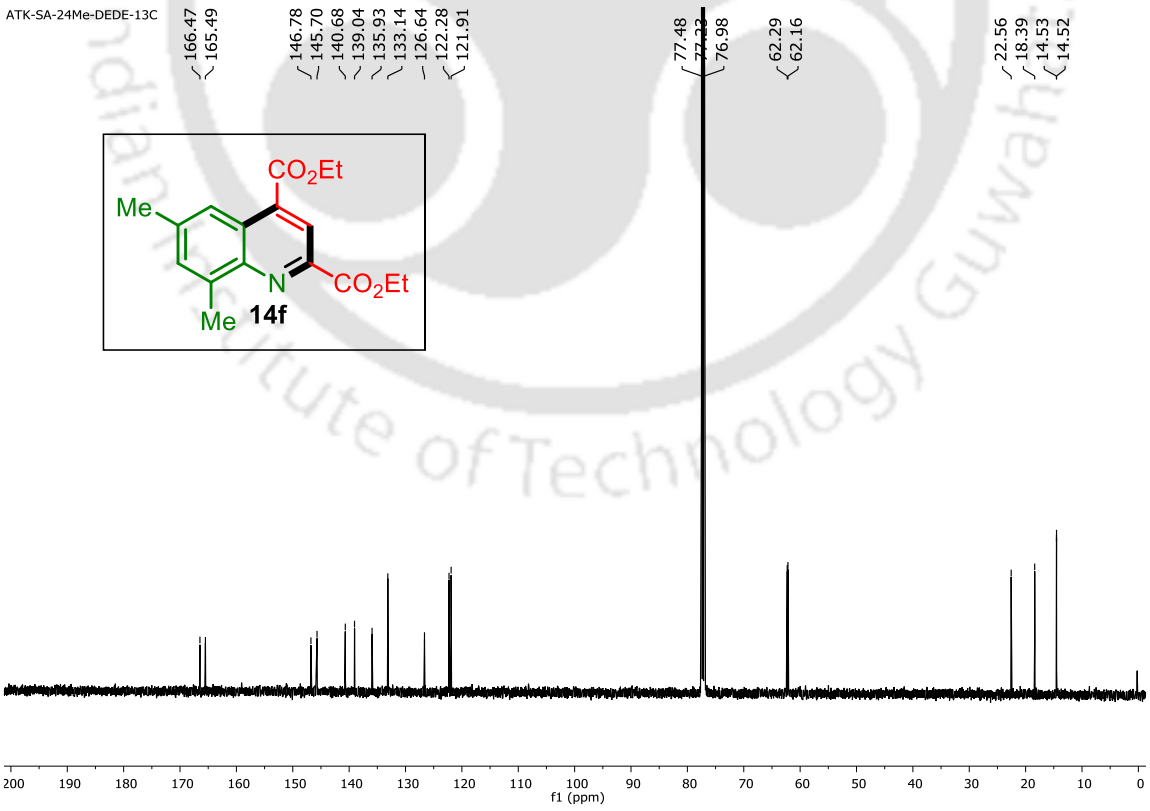


Figure 3.4b

HRMS spectrum: diethyl 6,8-dimethylquinoline-2,4-dicarboxylate **(14f)**

Sample Name	SAMPLE	**Position**	P1-A7	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-24ME-DEDE-1.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	2/11/2021 12:29:51 PM

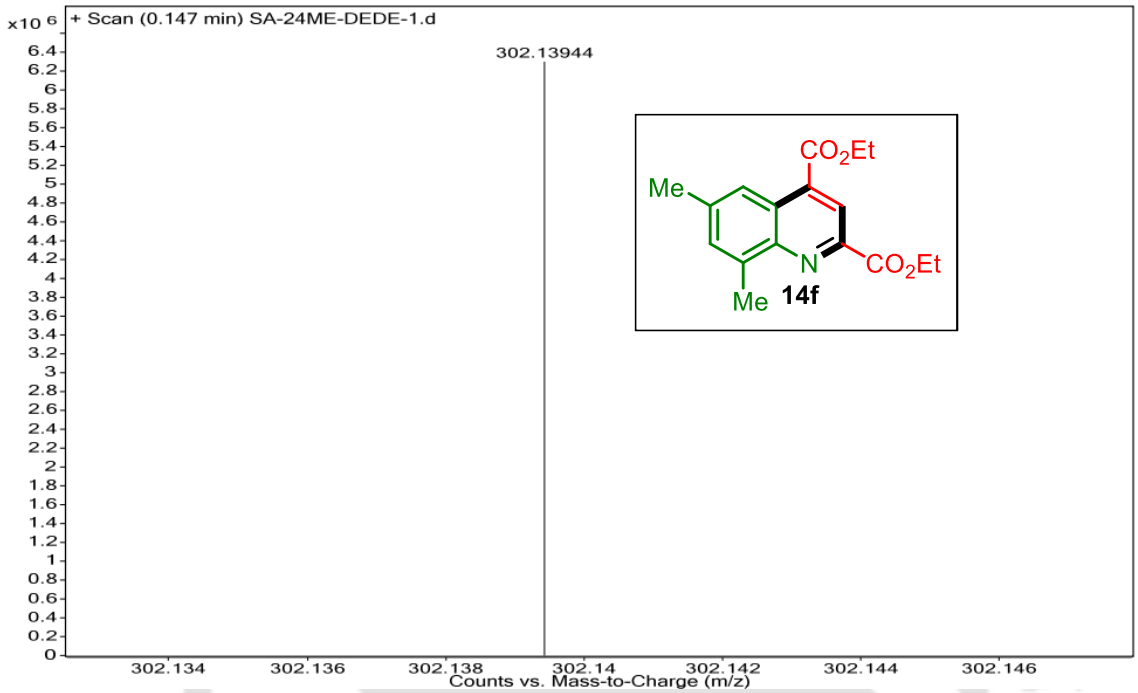
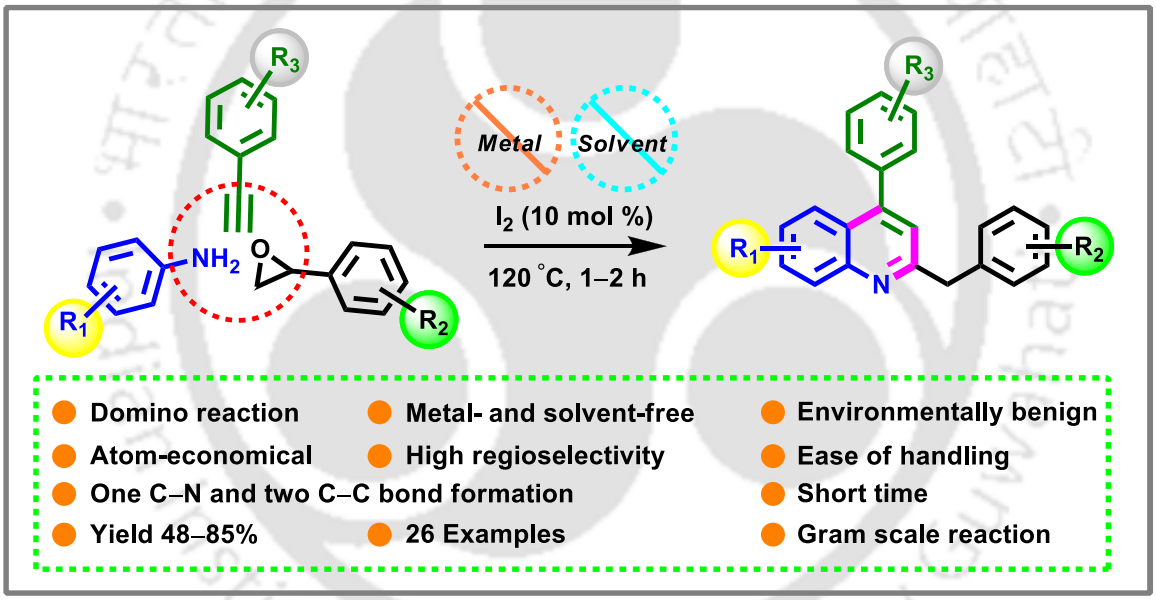


Figure 3.4c

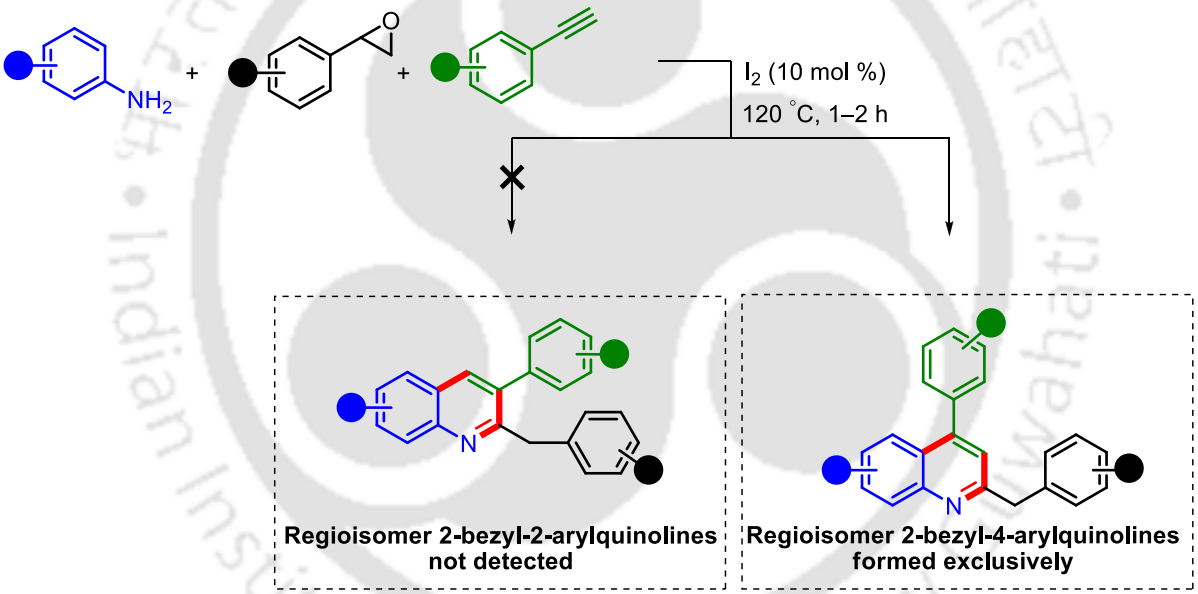
Chapter III: Part B

Metal- and Solvent-Free Regioselective Synthesis of 2-Benzyl-4-arylquinoline Derivatives Using Aryl Amines, Styrene Oxides and Aryl Acetylenes



Results and Discussion

The importance and synthetic method for synthesis of 2-benzyl-4-arylquinolines have already been discussed in chapter I. This part of the chapter III demonstrates an unprecedented novel metal- and solvent-free domino reaction which leads to formation of structurally diverse 2-benzyl-4-phenylquinoline scaffolds using simple building blocks aryl amines, styrene oxides and aryl acetylenes in the presence of 10 mol% molecular iodine at 120 °C (Scheme **3.5**). There is a possibility of forming two regioisomers in this reaction. It is noteworthy to mention that regioisomer 2-benzyl-4-phenylquinoline was obtained exclusively, however, other regioisomer 2-benzyl-3-phenylquinoline was not detected. Notable features of this methodology are use of simple starting materials, metal- and solvent-free, use of green catalyst, short reaction time, high regioselectivity, atom-economical, formation of one C-N and two C-C bonds and a broad substrate scope with high yield.

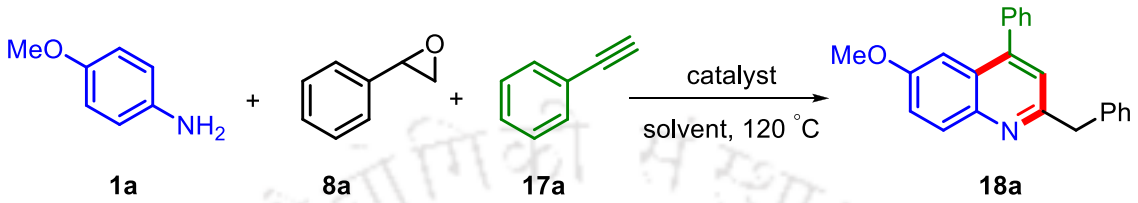


Scheme 3.5. Synthetic method for synthesis of 2-benzyl-4-phenylquinoline derivatives.

This study was initiated with ascertaining optimum reaction conditions. For this purpose, *p*-anisidine **1a**, styrene oxide **8a** and phenylacetylene **17a** were chosen as model substrates; results are summarized in Table 3.5. At first, a model reaction using *p*-anisidine **1a**, styrene oxide **8a** and phenylacetylene **17a** was executed without solvent and in absence of any catalyst (Table 3.5, entries 1 and 2). It was observed that reaction did not proceed at all at room temperature and even upon heating at 120 °C. Model reaction also did not undergo in the presence of 5 mol% I_2 at room temperature (Table 3.5, Entry 3). However, upon heating at 120 °C for 2 h, it proceeded slowly and major product **18a** was isolated in 44% yield (Table 3.5,

Entry 4). After the analysis of IR, ^{1}H NMR, ^{13}C NMR spectra and HRMS, compound **18a** was found to be 2-benzyl-6-methoxy-4-phenylquinoline. Motivated by this successful result, an attempt was made to increase the yield of product **18a**. At first, effect of catalyst loading was tested.

Table 3.5. Optimization of reaction conditions[a,b,c]



1a **8a** **17a** **18a**

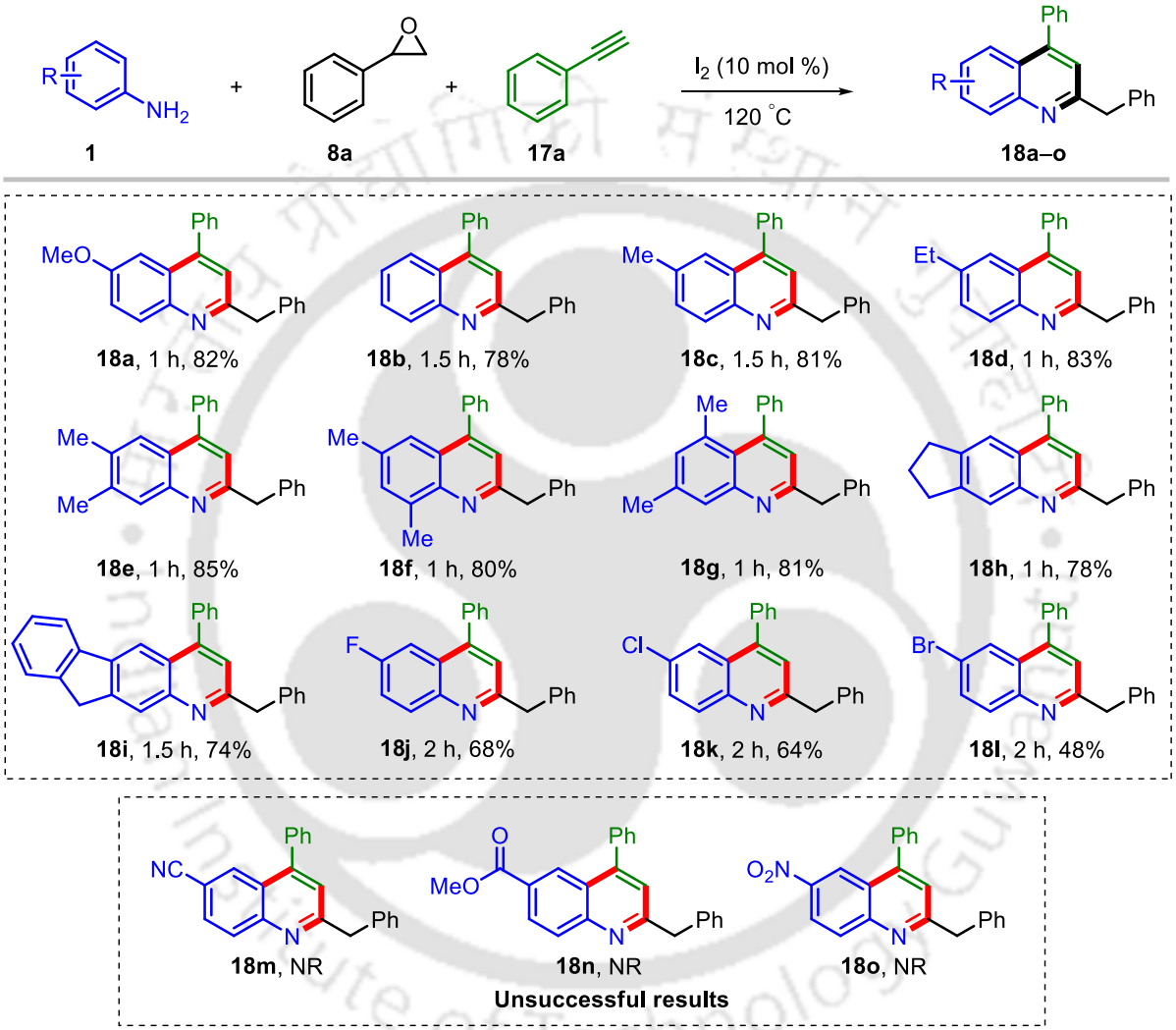
Entry	Catalyst	Mol %	Solvent	Time	Yield 18a (%)[b]
1[c]	–	–	–	5 h	NR
2	–	–	–	5 h	NR
3[c]	I_2	5	–	2 h	NR
4	I_2	5	–	2 h	44
5	**I_2**	**10**	–	**1 h**	**82**
6	I_2	15	–	1 h	79
7	$PhI(OAc)_2$	10	–	1 h	NR
8	IBr	10	–	1 h	28
9	ICl	10	–	1 h	22
10	I_2	10	DMF	1 h	NR
11	I_2	10	DMSO	1 h	NR
12	I_2	10	1,4-Dioxane	1 h	NR
13	I_2	10	CH_3CN	1 h	NR
14	I_2	10	Toluene	1 h	NR

[a]Reaction conditions: All reactions were performed using *p*-anisidine **1a** (1.0 mmol) and styrene oxide **8a** (1.0 mmol) and phenylacetylene **17a** (1.0 mmol) at 120 °C. [b]Isolated yield. [c]Reaction performed at room temperature. NR (No desired product).

When amount of catalyst was increased from 5 to 10 mol%, reaction completed within 1h and yield of **18a** also increased significantly from 44% to 82% (Table 3.5, Entry 5). Further increase in amount of catalyst to 15 mol% did not improve yield of product **18a** (Table 3.5, Entry 6). Next, efficacy of different iodine containing other catalysts, such as $PhI(OAc)_2$, IBr and ICl was tested (Table 3.5, Entries 7–9). It was noted that molecular iodine found to be more effective compared to all these catalysts. Finally, effect of different solvents, such as

dimethylformamide, tetrahydrofuran, 1,4-dioxane, acetonitrile and toluene using 10 mol% I_2 was examined (Table 3.5, Entries 10–14). It was observed that reaction was futile in all solvents. From all these above observations, it was concluded that best reaction conditions were 10 mol% I_2 and 120 °C in terms of both yield and reaction time.

Table 3.6. Reactions of different aryl amines **1** with styrene oxide **8a** and phenylacetylene **17a**[a,b]



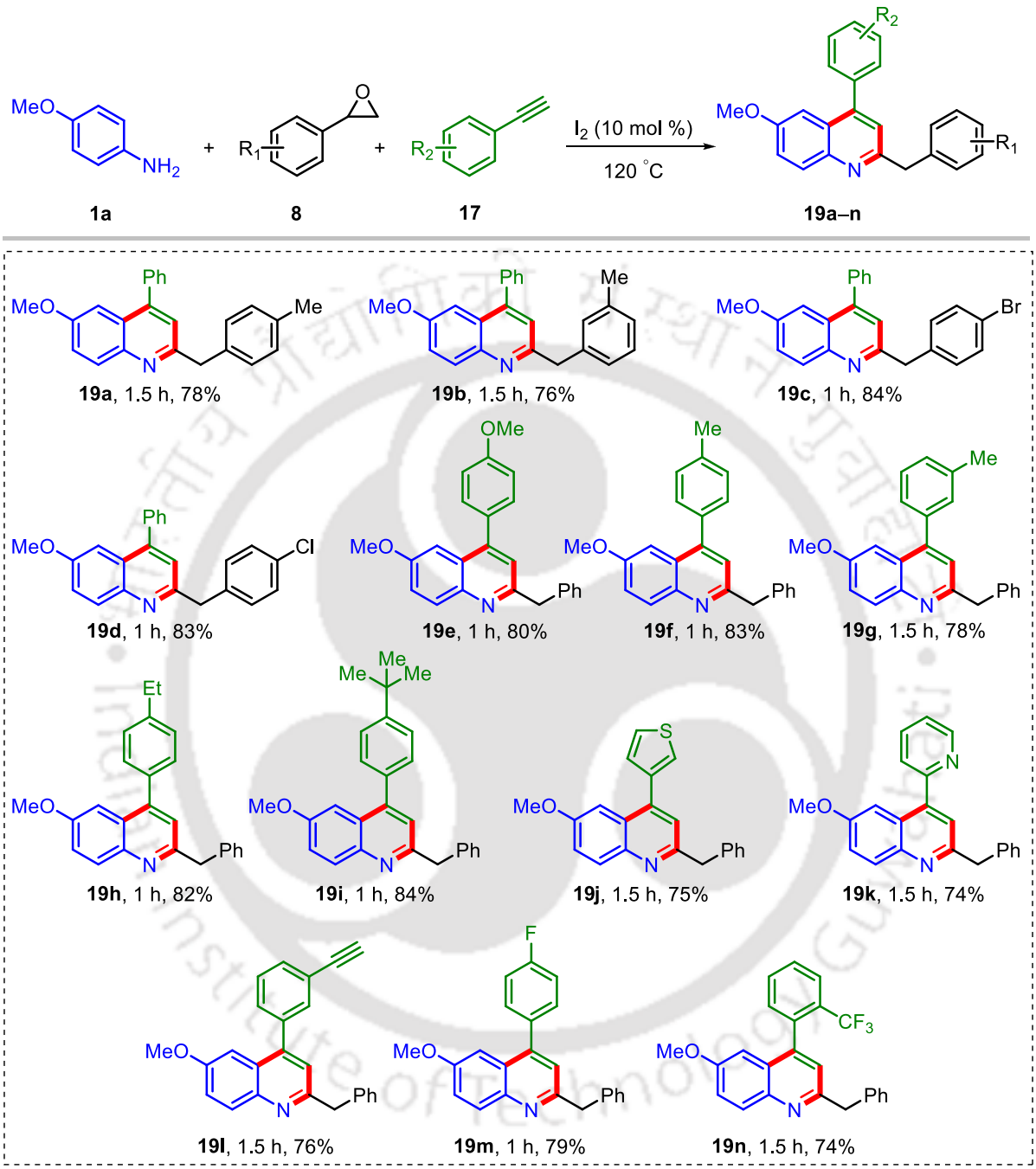
[a]Reaction conditions: All reactions were performed using different substituted anilines **1** (1.0 mmol), styrene oxide **8a** (1.0 mmol), phenylacetylene **17a** (1.0 mmol), I_2 (10 mol%) and 120 °C. [b]Isolated yield. NR (no desired product).

Having established optimal reaction conditions, scope and generality of present method were investigated using different aryl amines **1**, styrene oxide **8a** and phenylacetylene **17a** (Table 3.6). Reaction of simple aniline with styrene oxide **8a** and phenylacetylene **17a** proceeded well under identical reaction conditions and provided corresponding quinoline **18b** in 78% yield. Similarly, electron-donating groups (4-Me and 4-Et) located at 4-position of aryl amines

were well tolerated and afforded desired quinolines **18c** and **18d** in 81% and 83% yield, respectively. Disubstituted arylamines containing electron-donating groups (3,4-Me, 2,4-Me and 3,5-Me) also worked well under standard conditions and provided expected quinolines **18e–g** in 81–85% yield. Delightfully, bicyclic amine, such as 5-aminoindan gave anticipated quinoline **18h** in 78% yield. Likewise, tricyclic amine, such as 2-aminofluorene produced structurally complex quinoline **18i** in 74% yield. Gratifyingly, electron-withdrawing groups (4-F, 4-Cl and 4-Br) present at 4-position of aryl amines were tolerated and provided corresponding quinoline derivatives **18j–l** in 48–68% yield. Unfortunately, reactions with aryl amines containing strong electron-withdrawing groups (-CN, $-CO_2Me$ and $-NO_2$) failed to afford expected products **18m–o**. The cause of reaction failure might be less electron density present at *ortho* position with respect to $–NH_2$ due to presence of these strongly electron-withdrawing groups.

Motivated by above-mentioned successful results, the scope and generality of developed protocol was further investigated using *p*-anisidine **1a** and different styrene oxides **8** and various phenylacetylene derivatives **17** (Table 3.7). Firstly, reactions of *p*-anisidine **1a** and different **8** and phenylacetylene **17a** were carried out under standard conditions. Electron-donating groups (4-Me and 3-Me) present at ring of styrene oxides were tolerated and provided corresponding quinoline derivatives **19a** and **19b** in 78% and 76% yield, respectively. Likewise, electron-withdrawing groups (4-Br and 4-Cl) located at rings of styrene oxides were also well tolerated and furnished expected quinoline scaffolds **19c** and **19d** in 84% and 83% yield, respectively. Next, the efficiency of this approach was investigated using *p*-anisidine **1a** and styrene oxide **8a** and different phenylacetylene derivatives **17**. Reactions with phenyl acetylenes containing electron-donating groups (4-OMe, 4-Me, 3-Me, 4-Et and 4-t-Butyl) proceeded very well under standard conditions and provided desired quinoline analogues **19e–i** in 80–84% yield. To our delight, 3-ethynylthiophene and 2-ethynylpyridine gave anticipated quinolines **19j** and **19k** in 75% and 74% yield, respectively. Reaction of 1,3-diethynylbenzene also afforded expected quinoline **19l** in 76% yield. Gratifyingly, phenyl acetylenes containing electron-withdrawing groups (4-F and $2\text{-}CF_3$) also gave desired quinolines **19m** and **19n** in 79% and 74% yields, respectively.

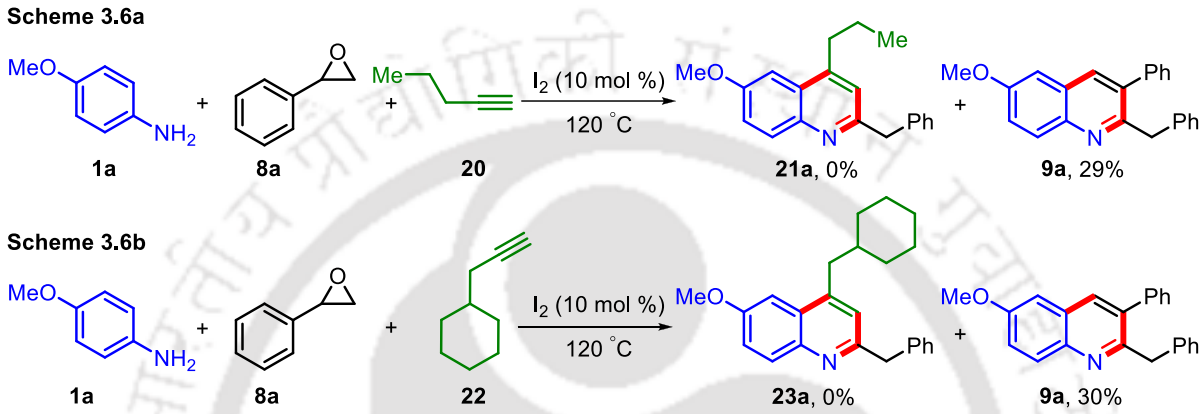
Table 3.7. Reactions of *p*-anisidine **1a** with various styrene oxides **8** and phenylacetylene derivatives **17**[a,b]



[a]Reaction conditions: All reactions were performed using various substituted anilines **1a** (1.0 mmol), styrene oxide **8** (1.0 mmol), phenylacetylene **17** (1.0 mmol), I_2 (10 mol%) and 120 °C. [b]Isolated yield. NR (no desired product).

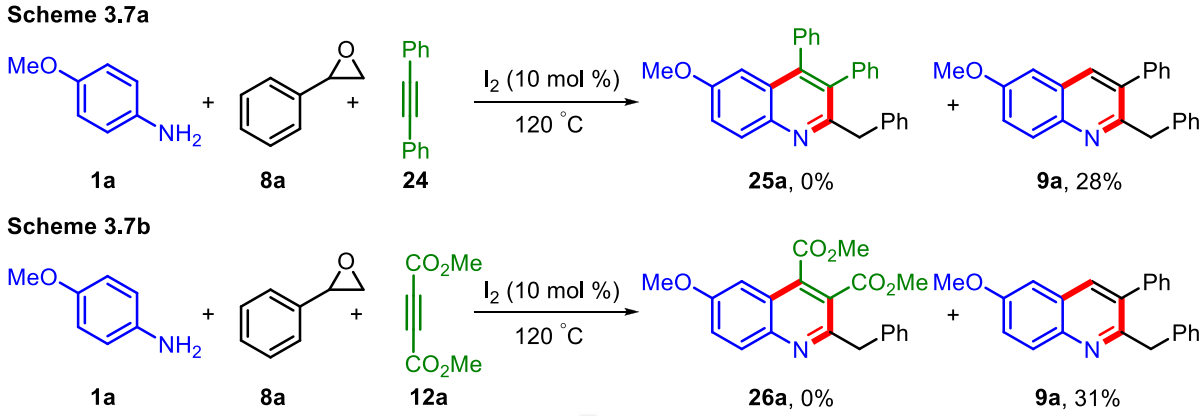
To verify the scope of this present protocol with aliphatic terminal alkynes, two reactions using *p*-anisidine **1a**, styrene oxide **8a** and 1-pentyne **20** as well as 3-cyclohexyl-1-propyne **22** were performed under identical reaction conditions as shown in Schemes (**3.6a** & **3.6b**). Unfortunately, reactions did not provide desired products **21a** and **23a**, respectively. In lieu of

that corresponding 2-benzyl-6-methoxy-3-phenylquinoline **9a** was isolated in 29% and 30% yield, respectively, (from reaction of *p*-anisidine **1a** and styrene oxide **8a**) along with unreacted 1-pentyne **20** and 3-cyclohexyl-1-propyne **23**. Failure of these two reactions suggests that reaction may not proceed through [4+2] imino-Diel-Alder pathway. Instead of that, reaction is going through step-wise manner: (1) trapping of activated imine by terminal alkyne to give a vinylic cation is more stable than alkyl vinylic cation (derived from the attack of aliphatic terminal alkynes). Consequently, in case of aliphatic alkynes, the reaction did not occur.



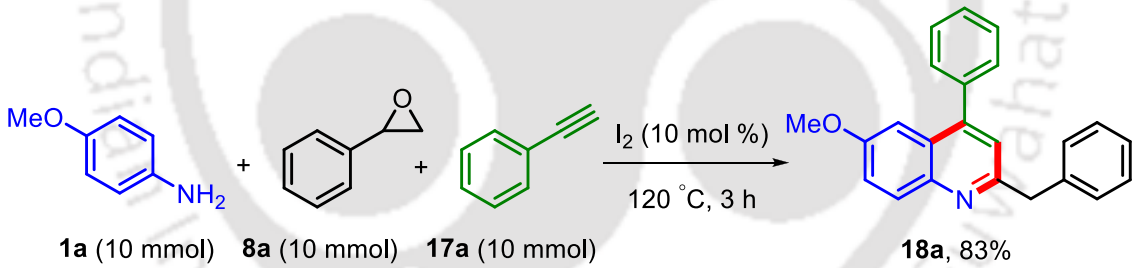
Scheme 3.6. Reactions between *p*-anisidine **1a** (1.0 mmol), styrene oxide **8a** (1.0 mmol) and 1-pentyne **20** and 3-cyclohexyl-1-propyne **23** (1.0 mmol) under standard conditions.

Next, efforts were put to examine with internal alkynes, such as diphenylacetylene **24** and dimethyl acetylenedicarboxylate **12a**. For this purpose, two reactions were carried out using *p*-anisidine **1a** and styrene oxide **8a** with diphenylacetylene **24** as well dimethyl acetylenedicarboxylate **12a** under same reaction conditions as presented in Schemes (**3.7a** & **3.7b**). Both reactions were failed to furnish anticipated products **25a** and **26a**. Instead of that, 2-benzyl-6-methoxy-3-phenylquinoline **9a** was obtained in 28% and 31% yield, respectively, (from reaction of *p*-anisidine **1a** and styrene oxide **8a**) along with unreacted diphenylacetylene **24** and dimethyl acetylenedicarboxylate **12a.** Reaction failure in case of diphenylacetylene **24** can be understood in such a way that developed negative charge on either carbons of diphenylacetylene is in the conjugation with 6π electrons of phenyl ring. As a result, electron density gets decreased and it may not react with imine to generate benzylic vinylic cation. Dimethyl acetylenedicarboxylate **12a** being electron deficient due to presence of two strong electron-withdrawing groups can not attack the imine. From above-mentioned observations, it may be concluded that reactions do not occur through [4+2] imino-Diels-Alder fashion. If reactions had proceeded through [4+2] imino-Diels-Alder way, expected products **25a** and **26a** would have obtained.



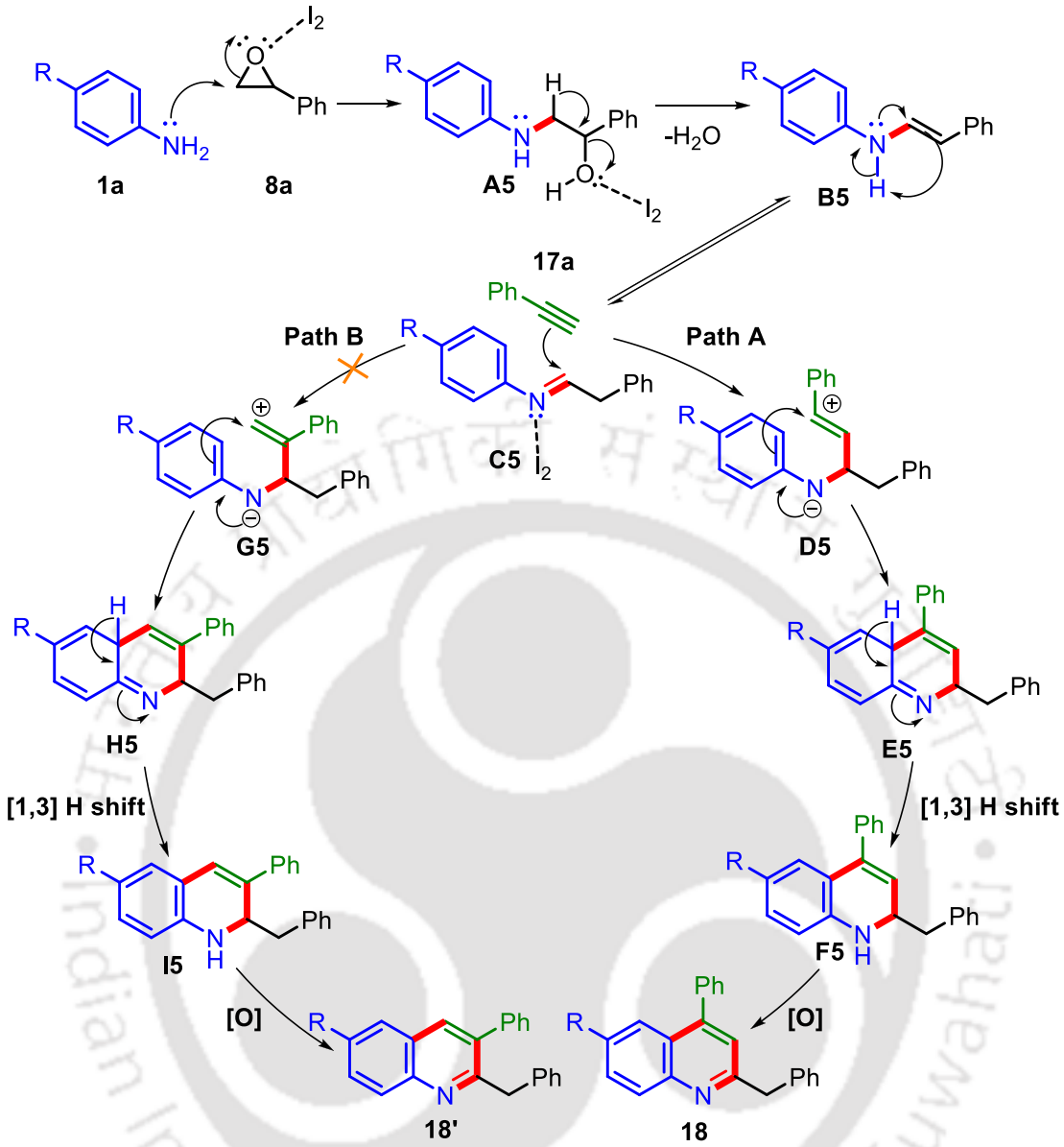
Scheme 3.7. Reactions between *p*-anisidine **1a** (1.0 mmol), styrene oxide **8a** (1.0 mmol) and diphenylacetylene **24** and dimethyl acetylenedicarboxylate **12a** (1.0 mmol) under standard conditions.

In order to show the efficacy of present protocol, we carried out a scale up reaction using *p*-anisidine **1a**, styrene oxide **8a** and phenyl acetylene **17a** under similar reaction conditions as presented in Scheme **3.8**. The reaction proceeded smoothly and provided the expected product **18a** in 83% yield. The structures of all these compounds were elucidated from IR, ^{1}H NMR, ^{13}C NMR spectra and HRMS.



Scheme 3.8. Gram-scale reaction.

Based on above-discussed results in Schemes (**3.6** and **3.7**), a plausible mechanism for formation of product **18** is depicted in Scheme **3.9**. Initially, *p*-anisidine **1a** reacts with styrene oxide **8a** in presence of molecular iodine, which acts as a Lewis acid, to give the β-amino alcohol[7] **A5** by attacking from less hindered side of styrene oxide. Elimination of water molecule provides enamine **B5** which tautomerizes to corresponding imine **C5**.[8] Phenylacetylene **17a** can trap activated imine **C5** *via* either path **A** or path **B**. If reaction goes through path **A**, it generates benzylic vinylic cation **D5**, which is more stable than the intermediate **G5** forming through path **B**.



Scheme 3.9. A plausible mechanism for formation of product **18a**.

Therefore, exclusive formation of regioisomer **18** is preferred over other regioisomer 1**8**'. Intermediate **D5** undergoes intramolecular cyclization to provide species **E5**, which subsequently involves the [1,3] H shift to afford the dihydroquinoline **F5**. Finally, aerial oxidation of **F5** gives desired product **18**.

In conclusion, a novel and an expedient method has been devised which offers a direct access to diverse 2-benzyl-4-arylquinoline frameworks. It is noteworthy to mention that all compounds are new except compound **18b**. This strategy involves metal- and solvent-free domino reaction using a commercially available variety of aryl amines, styrene oxides and phenyl acetylenes at 120 °C under air atmosphere. Tolerance of a wide range of functional

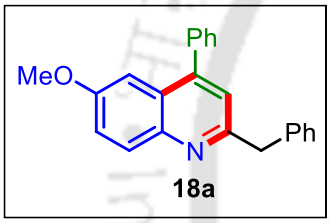
groups present on aryl amines, styrene oxides and phenyl acetylenes is reflecting the generality of this straightforward and efficient protocol. From economic and environmental perspectives, use of 10 mol% molecular iodine (cheap, nontoxic and environmentally benign) and solvent-free conditions make this approach greener and sustainable.

Experimental Section

General procedure for the synthesis of 2-benzyl-4-arylquinolines 18 and 19.

Aryl amine **1** (1.0 mmol), styrene oxide **8** (1.0 mmol), phenylacetylene **17** (1.0 mmol) and molecular iodine (10 mol%, 25 mg) were taken into a 10 mL of round-bottomed flask. The resulted reaction mixture was kept on stirring at 120 °C in a pre-heated oil-bath. The reaction progress was monitored by checking TLC. After the completion of reaction, it was brought to room temperature and diluted with ethyl acetate (5 mL). Then, 0.1% aqueous solution of sodium thiosulphate (5 mL) was added to the reaction mixture. The product was extracted by ethyl acetate (2 x 5 mL). After this, combined organic layer was washed with water (2 x 5 mL) followed by brine (5 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced vacuum on rotary evaporator. Eventually, the crude mixture was purified by column chromatography on silica gel (60–120 mesh).

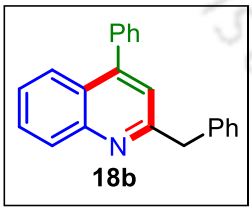
2-Benzyl-6-methoxy-4-phenylquinoline (18a): (267 mg, 82%, yellow solid); mp 61–62 °C;



18a

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.3 Hz, 1H), 7.49 – 7.44 (m, 4H), 7.40 – 7.25 (m, 6H), 7.22 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 2.7 Hz, 1H), 7.13 (s, 1H), 4.34 (s, 2H), 3.77 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 157.7, 147.8, 144.4, 139.6, 138.6, 130.9, 129.5, 129.4, 128.8, 128.9, 128.5, 126.6, 126.4, 122.3, 121.7, 104.0, 55.6, 45.4; **IR (KBr)ν_{max}** 3024, 2924, 1620, 1361, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{23}H_{20}NO$ 326.1545 ($M + H^+$); Found 326.1561.

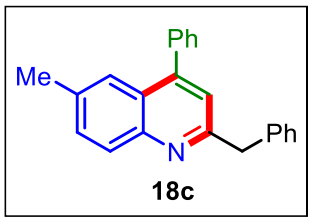
2-Benzyl-4-phenylquinoline (18b):[9] (231 mg, 78%, yellow solid); mp 57–58 °C (reported mp



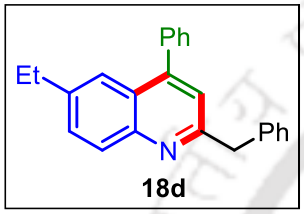
18b

57–61°C); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.71 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.50 – 7.42 (m, 6H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.18 (s, 1H), 4.38 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.9, 149.1, 148.5, 139.4, 138.4, 129.7, 129.6, 129.4, 128.8, 128.7, 128.54126.7, 126.3, 125.9, 125.6, 121.9, 45.8 **IR (KBr)ν_{max}** 3059, 2923, 1591, 1491, 1358 cm^{-1}; **HRMS** (ESI) Calcd for $C_{22}H_{18}N$ 296.1439 ($M + H^+$); Found 296.1432.

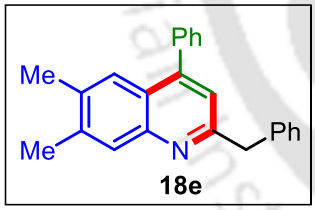
2-Benzyl-6-methyl-4-phenylquinoline (18c): (251 mg, 81%, yellow solid); mp 63–64 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 1H), 7.60 (s, 1H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 10.4, 6.9 Hz, 3H), 7.43 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.34 (d, *J* = 7.1 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.14 (s, 1H), 4.36 (s, 2H), 2.45 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.9, 148.4, 147.0, 139.5, 138.5, 136.1, 131.8, 129.7, 129.4, 129.2, 128.8, 128.7, 128.4, 126.6, 125.5, 124.6, 121.9, 45.6, 21.9; **IR (KBr)ν_{max}** 3059, 2920, 1589, 1448, 1230 cm^{-1}; **HRMS** (ESI) Calcd for $C_{23}H_{20}N$ 310.1596 ($M + H^+$); Found 310.1601.



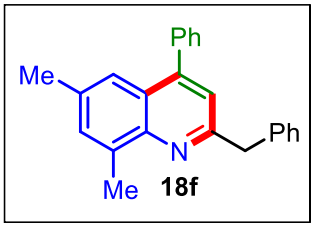
2-Benzyl-6-ethyl-4-phenylquinoline (18d): (269 mg, 83%, yellow solid); mp 68–69 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 1H), 7.63 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.52 – 7.42 (m, 5H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.15 (s, 1H), 4.37 (s, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.7 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.0, 148.6, 147.3, 142.4, 139.6, 138.6, 130.6, 129.7, 129.4, 129.4, 128.8, 128.7, 128.4, 126.6, 125.5, 123.5, 121.9, 45.7, 29.3, 15.8; **IR (KBr)ν_{max}** 3027, 2964, 1588, 1357, 1222 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1773.



2-Benzyl-6,7-dimethyl-4-phenylquinoline (18e): (276 mg, 85%, yellow solid); mp 72–73 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.57 (s, 1H), 7.52 – 7.39 (m, 5H), 7.31 (dd, *J* = 15.2, 7.4 Hz, 4H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.07 (s, 1H), 4.34 (s, 2H), 2.47 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.9, 148.2, 139.8, 139.6, 138.7, 136.1, 131.8, 129.7, 129.4, 129.0, 128.8, 128.6, 128.3, 126.6, 125.0, 124.0, 121.2, 45.7, 20.5, 20.4; **IR (KBr)ν_{max}** 3033, 2921, 1588, 1446, 1233 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}N$ 324.1752 ($M + H^+$); Found 324.1767.

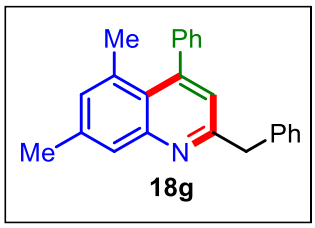


2-Benzyl-6,8-dimethyl-4-phenylquinoline (18f): (259 mg, 80%, yellow solid); mp 68–69 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 – 7.43 (m, 2H), 7.42 – 7.35 (m, 6H), 7.28 (td, *J* = 7.7, 1.7 Hz, 3H), 7.19 (td, *J* = 7.3, 1.4 Hz, 1H), 7.11 (s, 1H), 4.34 (s, 2H), 2.84 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 148.3, 146.2, 140.0, 139.2, 137.1, 135.3, 131.8, 129.8, 129.5, 128.7, 128.5, 128.1, 126.5, 125.4, 122.5, 121.6, 45.9, 21.9, 18.5; **IR**



(KBr)ν_{max} 3025, 2917, 1590, 1358, 1224 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}N$ 324.1752 (M + H^+); Found 324.1769.

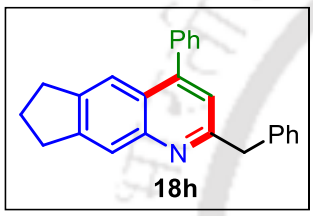
2-Benzyl-5,7-dimethyl-4-phenylquinoline (18g): (263 mg, 81%, yellow solid); mp 56–56 °C;



18g

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.38 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 2.6 Hz, 3H), 7.08 (s, 1H), 6.98 (s, 1H), 4.30 (s, 2H), 2.49 (s, 3H), 1.94 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.4, 149.9, 149.4, 142.8, 139.5, 139.2, 135.3, 131.8, 129.4, 128.9, 128.8, 128.0, 127.8, 127.5, 126.6, 123.2, 123.1, 45.3, 24.5, 21.6; **IR (KBr)ν_{max}** 3027, 2923, 1582, 1341, 1230; **HRMS** (ESI) Calcd for $C_{24}H_{22}N$ 324.1752 (M + H^+); Found 324.1754.

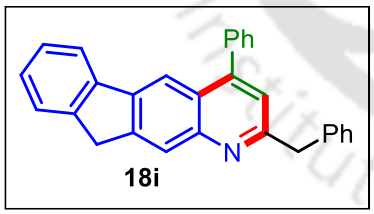
2-Benzyl-4-phenyl-7,8-dihydro-6H-cyclopenta[g]quinoline (18h): (262 mg, 78%, brown



18h

liquid); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.31 (d, *J* = 6.9 Hz, 2H), 7.29 – 7.25 (m, 4H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.04 (s, 1H), 4.32 (s, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.87 (p, *J* = 7.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.8, 148.7, 148.4, 143.1, 141.6, 139.7, 139.6, 129.7, 129.4, 129.3, 128.8, 128.5, 127.9, 127.8, 126.9, 126.6, 123.1, 45.4, 35.3, 33.4, 25.8; **IR (KBr)ν_{max}** 3027, 2915, 1584, 1490, 1358 cm^{-1}; **HRMS** (ESI) Calcd for $C_{25}H_{22}N$ 336.1752 (M + H^+); Found 336.1774.

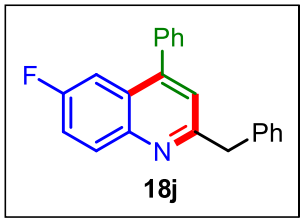
2-Benzyl-4-phenyl-10H-indeno[1,2-g]quinoline (18i): (284 mg, 74%, brown liquid); **^{1}H**



18i

NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.17 (s, 1H), 7.79 – 7.73 (m, 1H), 7.58 – 7.50 (m, 6H), 7.38 – 7.31 (m, 6H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.17 (s, 1H), 4.39 (s, 2H), 4.15 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 149.2, 148.3, 145.3, 144.0, 140.9, 139.6, 138.8, 129.8, 129.5, 128.8, 128.8, 128.5, 128.0, 127.8, 127.2, 126.7, 125.5, 125.1, 125.1, 121.6, 120.8, 115.4, 45.7, 36.8; **IR (KBr)ν_{max}** 3027, 2922, 1590, 1488, 1359, 1251 cm^{-1}; **HRMS** (ESI) Calcd for $C_{29}H_{22}N$ 384.1752 (M + H^+); Found 384.1756.

2-Benzyl-6-fluoro-4-phenylquinoline (18j): (213 mg, 68%, brown solid); mp 63–64 °C; **^{1}H**

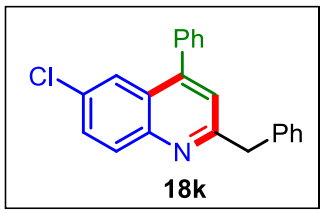


18j

NMR (500 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 10.1, 5.5 Hz, 1H), 7.51 – 7.44 (m, 5H), 7.40 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.35 – 7.27 (m, 4H), 7.22 (d, *J* = 7.2 Hz, 1H), 7.20 (s, 1H), 4.35 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.6, 160.3, 160.3, 159.7, 148.7, 148.6, 145.6,

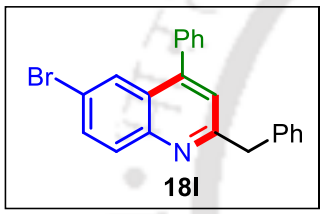
139.3, 137.9, 132.0, 131.9, 129.5, 129.4, 128.9, 128.8, 126.8, 126.4, 126.3, 122.5, 119.7, 119.5, 109.4, 109.2, 45.6; **IR (KBr)ν_{max}** 3028, 2919, 1622, 1594, 1204; **HRMS** (ESI) Calcd for $C_{22}H_{17}FN$ 314.1345 ($M + H^+$); Found 314.1764.

2-Benzyl-6-chloro-4-phenylquinoline (18k): (211 mg, 64%, yellow solid); mp 72–73 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.43 – 7.39 (m, 2H), 7.32 (ddd, *J* = 12.6, 7.9, 6.2 Hz, 4H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.20 (s, 1H), 4.36 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.3, 148.4, 147.0, 139.1, 137.7, 132.2, 131.3, 130.4, 129.6, 129.4, 128.9, 128.8, 126.8, 126.4, 124.7, 122.6, 45.7; **IR (KBr)ν_{max}** 3027, 2921, 1590, 1485, 1452 cm^{-1}; **HRMS** (ESI) Calcd for $C_{22}H_{17}ClN$ 330.1050 ($M + H^+$); Found 330.1063.



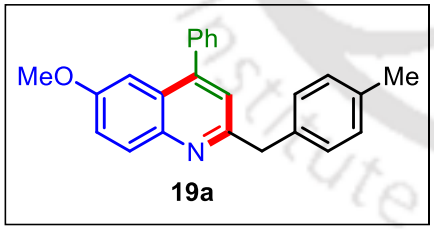
18k

2-Benzyl-6-bromo-4-phenylquinoline (18l): (180 mg, 48%, brown liquid); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 8.3 Hz, 1H), 7.50 – 7.42 (m, 6H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 (s, 1H), 4.38 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.9, 149.1, 148.5, 139.4, 138.4, 129.7, 129.6, 129.4, 128.8, 128.7, 128.5, 126.7, 126.3, 125.9, 125.6, 121.9, 45.8; **IR (KBr)ν_{max}** 3027, 2922, 1590, 1448, 1356 cm^{-1}; **HRMS** (ESI) Calcd for $C_{22}H_{17}BrN$ 374.0544 ($M + H^+$); Found 374.0549.



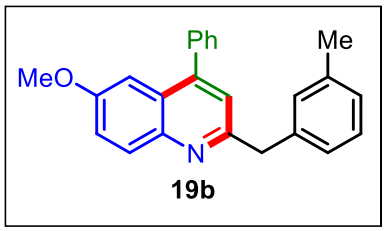
18l

6-Methoxy-2-(4-methylbenzyl)-4-phenylquinoline (19a): (265 mg, 78%, brown solid), mp 74–75 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 1H), 7.51 – 7.41 (m, 5H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 2.8 Hz, 1H), 7.14 (s, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 4.30 (s, 2H), 3.77 (s, 3H), 2.31 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.7, 157.6, 147.8, 144.4, 138.6, 136.5, 136.1, 130.9, 129.5, 129.2, 128.7, 128.4, 126.3, 122.2, 121.6, 103.9, 55.6, 45.0, 21.2; **IR (KBr)ν_{max}** 3016, 2926, 1618, 1357, 1262 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}NO$ 340.1701 ($M + H^+$); Found 340.1721.



19a

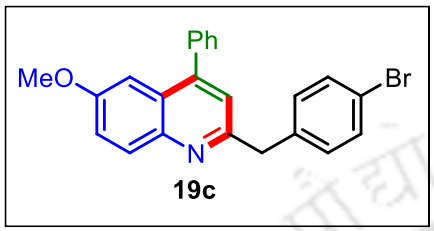
6-Methoxy-2-(3-methylbenzyl)-4-phenylquinoline (5b): (259 mg, 76%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 7.51 – 7.43 (m, 5H), 7.38 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.21 – 7.12 (m, 5H), 7.02 (d, *J* = 7.4 Hz, 1H), 4.30 (s, 2H), 3.78 (s, 3H), 2.31 (s, 3H);



19b

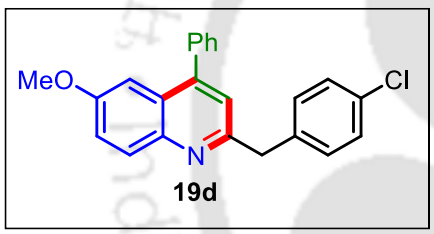
^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 157.6, 147.8, 144.4, 139.5, 138.6, 138.4, 130.9, 130.1, 129.5, 128.8, 128.7, 128.4, 127.4, 126.4, 122.3, 121.7, 103.9, 55.6, 45.4, 21.6; **IR (KBr)ν_{max}** 3018, 2925, 1617, 1357, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}NO$ 340.1701 ($M + H^+$); Found 340.1717.

2-(4-Bromobenzyl)-6-methoxy-4-phenylquinoline (19c): (339 mg, 84%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.2 Hz, 1H), 7.47 (dt, *J* = 19.7, 6.9 Hz, 5H), 7.38 (dd, *J* = 13.9, 8.3 Hz, 3H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.15 (s, 1H), 7.09 (s, 1H), 4.26 (s, 2H), 3.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.9, 157.7, 148.0, 144.6, 138.7, 138.5, 131.8, 131.1, 130.9, 129.5, 128.8, 128.5, 126.5, 122.0, 121.8, 120.6, 104.1, 55.6, 44.8; **IR (KBr)ν_{max}** 3059, 2929, 1619, 1359, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{23}H_{19}BrNO$ 404.0650 ($M + H^+$); Found 404.0660.



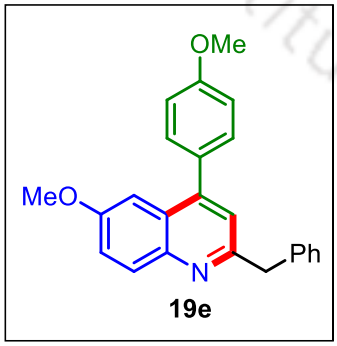
19c

2-(4-Chlorobenzyl)-6-methoxy-4-phenylquinoline (19d): (298 mg, 83%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.2 Hz, 1H), 7.47 (dt, *J* = 20.6, 7.1 Hz, 5H), 7.37 (d, *J* = 9.1 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 4H), 7.15 (s, 1H), 7.09 (s, 1H), 4.28 (s, 2H), 3.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.9, 157.8, 148.0, 144.6, 138.6, 138.2, 132.5, 131.0, 130.7, 129.5, 128.9, 128.8, 128.5, 126.5, 122.1, 121.8, 104.1, 55.6, 44.7; **IR (KBr)ν_{max}** 3059, 2929, 1619, 1360, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{23}H_{19}ClNO$ 360.1155 ($M + H^+$); Found 360.1174.



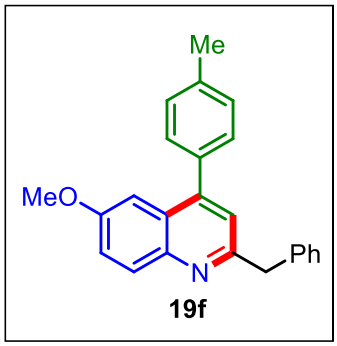
19d

2-Benzyl-6-methoxy-4-(4-methoxyphenyl)quinoline (19e): (284 mg, 80%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.40 – 7.32 (m, 5H), 7.30 (d, *J* = 6.8 Hz, 2H), 7.20 (q, *J* = 5.0, 2.7 Hz, 2H), 7.11 (s, 1H), 7.02 (d, *J* = 7.5 Hz, 2H), 4.33 (s, 2H), 3.88 (s, 3H), 3.79 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.4, 157.7, 147.6, 144.4, 139.7, 132.3, 130.9, 130.9, 130.7, 129.4, 128.8, 127.6, 126.6, 122.2, 121.7, 114.3, 104.2, 55.7, 55.6, 45.4; **IR (KBr)ν_{max}** 3001, 2918, 1609, 1248 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}NO_2$ 356.1651 ($M + H^+$); Found 356.1640.



19e

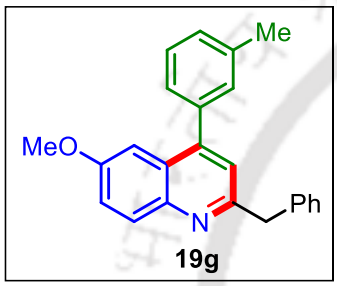
2-Benzyl-6-methoxy-4-p-tolylquinoline (19f): (282 mg, 83%, brown solid), mp 66–67 °C;



19f

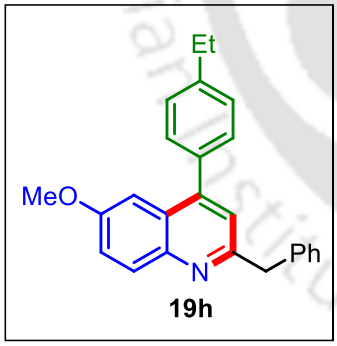
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H), 7.37 – 7.32 (m, 5H), 7.29 (d, *J* = 6.9 Hz, 4H), 7.25 (s, 1H), 7.18 (s, 1H), 7.11 (d, *J* = 1.6 Hz, 1H), 4.32 (s, 2H), 3.78 (s, 3H), 2.43 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 157.7, 147.9, 144.6, 139.7, 138.3, 135.7, 130.9, 129.5, 129.4, 129.4, 128.8, 127.0, 126.6, 122.2, 121.6, 104.2, 55.7, 45.5, 21.5; **IR (KBr)ν_{max}** 3024, 2926, 1617, 1360, 1225 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}NO$ 340.1701 ($M + H^+$); Found 340.1694.

2-Benzyl-6-methoxy-4-m-tolylquinoline (19g): (267 mg, 78%, yellow liquid), **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.24 (m, 10H), 7.16 (d, *J* = 2.8 Hz, 1H), 7.12 (s, 1H), 4.33 (s, 2H), 3.78 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.4, 157.7, 148.0, 144.5, 139.7, 138.6, 138.5, 130.9, 130.2, 129.4, 129.2, 128.8, 128.6, 126.6, 122.2, 121.6, 114.9, 104.3, 55.67, 45.51, 21.67; **IR (KBr)ν_{max}** 3030, 2923, 1619, 1490, 1229 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{22}NO$ 340.1701 ($M + H^+$); Found 340.1709.



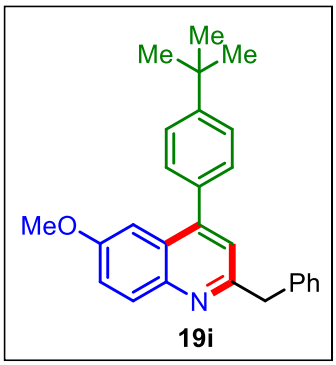
19g

2-Benzyl-4-(4-ethylphenyl)-6-methoxyquinoline (19h): (290 mg, 82%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.34 (m, 3H), 7.30 (dt, *J* = 18.5, 7.8 Hz, 6H), 7.21 – 7.18 (m, 2H), 7.11 (s, 1H), 4.32 (s, 2H), 3.78 (s, 3H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 157.7, 147.9, 144.6, 144.6, 139.7, 135.9, 131.0, 129.5, 129.4, 128.8, 128.3, 126.6, 126.5, 122.2, 121.5, 104.3, 55.7, 45.5, 28.8, 15.6; **IR (KBr)ν_{max}** 3027, 2928, 1618, 1591, 1263 cm^{-1}; **HRMS** (ESI) Calcd for $C_{25}H_{24}NO$ 354.1858 ($M + H^+$); Found 354.1867.



19h

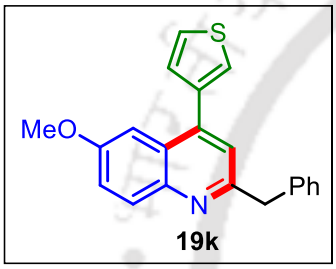
2-Benzyl-4-(4-tert-butylphenyl)-6-methoxyquinoline (19i): (321 mg, 84%, gray solid), mp



19i

67–68 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.5 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.38 (dd, *J* = 10.7, 4.9 Hz, 3H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 6.9 Hz, 2H), 7.23 (s, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.12 (s, 1H), 4.32 (s, 2H), 3.79 (s, 3H), 1.38 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 157.7, 151.6, 147.8, 144.6, 139.7, 135.7, 131.0, 129.4, 129.2, 128.8, 126.6, 126.5, 125.7, 122.3, 121.4, 104.5, 55.7, 45.5, 34.9, 31.6; **IR (KBr)ν_{max}** 3033, 2960, 1618, 1362, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{27}H_{28}NO$ 382.2171 ($M + H^+$); Found 382.2167.

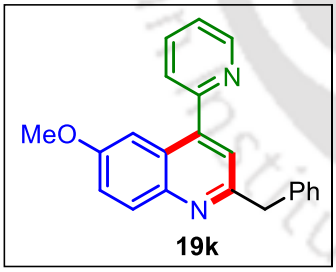
2-Benzyl-6-methoxy-4-(thiophen-3-yl)quinoline (5j): (245 mg, 75%, brown liquid), **^{1}H**



19k

NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.1 Hz, 1H), 7.48 – 7.44 (m, 3H), 7.38 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.35 – 7.32 (m, 2H), 7.30 (ddd, *J* = 8.2, 4.4, 2.4 Hz, 4H), 7.18 (s, 1H), 4.33 (s, 2H), 3.83 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 157.9, 144.6, 142.6, 139.7, 139.2, 131.1, 129.5, 129.4, 128.8, 128.8, 126.6, 126.4, 124.7, 122.0, 121.7, 104.0, 55.7, 45.5; **IR (KBr)ν_{max}** 3033, 2929, 1619, 1368, 1263 cm^{-1}; **HRMS** (ESI) Calcd for $C_{21}H_{18}NOS$ 332.1109 ($M + H^+$); Found 332.1122.

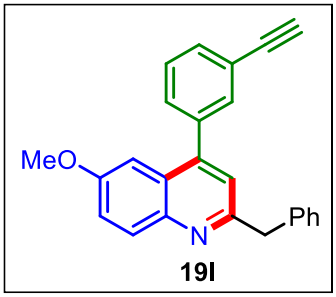
2-Benzyl-6-methoxy-4-(pyridin-2-yl)quinoline (19k): (242 mg, 74%, brown liquid), **^{1}H**



19k

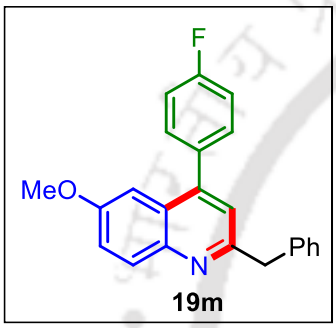
NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.47 – 7.44 (m, 3H), 7.39 – 7.37 (m, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.13 (s, 1H), 4.34 (s, 2H), 3.77 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.5, 157.8, 147.9, 144.6, 141.4, 139.7, 138.7, 131.0, 129.5, 129.4, 128.8, 128.8, 128.5, 126.6, 125.9, 122.2, 121.7, 104.2, 55.7, 45.5; **IR (KBr)ν_{max}** 3064, 2924, 1620, 1362, 1223 cm^{-1}; **HRMS** (ESI) Calcd for $C_{22}H_{19}N_2O$ 327.1497 ($M + H^+$); Found 327.1496.

2-Benzyl-4-(3-ethynylphenyl)-6-methoxyquinoline (19l): (266 mg, 76%, gray liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.38 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.24 – 7.19 (m, 1H), 7.11 (s, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 4.34 (s, 2H), 3.78 (s, 3H), 3.11 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.4, 157.8, 146.7, 144.4, 139.5, 138.8, 132.9, 132.1, 131.0, 129.9, 129.3, 128.8, 128.8, 126.7, 122.2, 121.8, 103.7, 83.2, 78.2, 55.7, 45.4; **IR (KBr)ν_{max}** 3286, 3030, 2932, 2108, 1618, 1358, 1264 cm^{-1}; **HRMS** (ESI) Calcd for $C_{25}H_{20}NO$ 350.1545 ($M + H^+$); Found 350.1566.



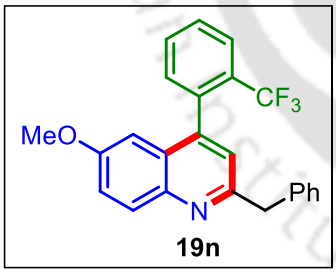
19l

2-Benzyl-4-(4-fluorophenyl)-6-methoxyquinoline (19m): (271 mg, 79%, brown solid), mp 77–78 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.39 (dt, *J* = 16.9, 7.5 Hz, 3H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.17 (dq, *J* = 20.4, 11.7, 9.5 Hz, 3H), 7.08 (d, *J* = 8.9 Hz, 2H), 4.32 (s, 2H), 3.77 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 163.9, 162.0, 158.4, 157.9, 146.7, 144.5, 139.6, 131.2, 131.2, 131.1, 129.5, 129.4, 128.8, 126.6, 126.4, 122.2, 121.7, 115.9, 115.7, 103.9, 55.6, 45.5; **IR (KBr)ν_{max}** 3062, 2938, 1605, 1359, 1263 cm^{-1}; **HRMS** (ESI) Calcd for $C_{23}H_{19}FNO$ 344.1451 ($M + H^+$); Found 344.1447.



19m

2-Benzyl-6-methoxy-4-(2-(trifluoromethyl)phenyl)quinoline (19n): (291 mg, 74%, brown liquid), **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.47 (dt, *J* = 13.8, 5.3 Hz, 5H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 2H), 7.21 (t, *J* = 7.1 Hz, 1H), 7.14 (d, *J* = 10.2 Hz, 2H), 4.34 (s, 2H), 3.77 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.4, 157.7, 147.8, 144.4, 139.6, 138.5, 130.9, 129.5, 129.4, 128.8, 128.8, 128.5, 126.6, 126.4, 122.3, 121.7, 103.9, 55.6, 45.4; **IR (KBr)ν_{max}** 3024, 2901, 1619, 1492, 1222 cm^{-1}; **HRMS** (ESI) Calcd for $C_{24}H_{19}F_3NO$ 394.1419 ($M + H^+$); Found 394.1418.



19n

^{1}H NMR (400 MHz, $CDCl_3$): 2-benzyl-6-methoxy-4-phenylquinoline **(18a)**

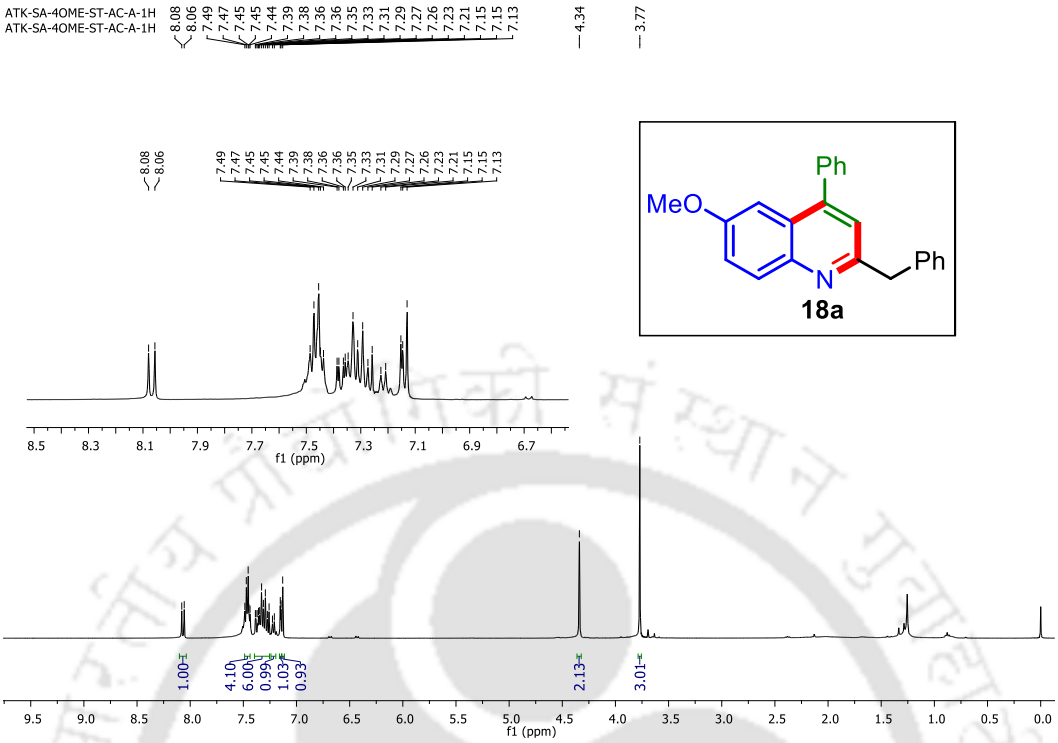


Figure 3.5a

^{13}C NMR (100 MHz, $CDCl_3$): 2-benzyl-6-methoxy-4-phenylquinoline **(18a)**

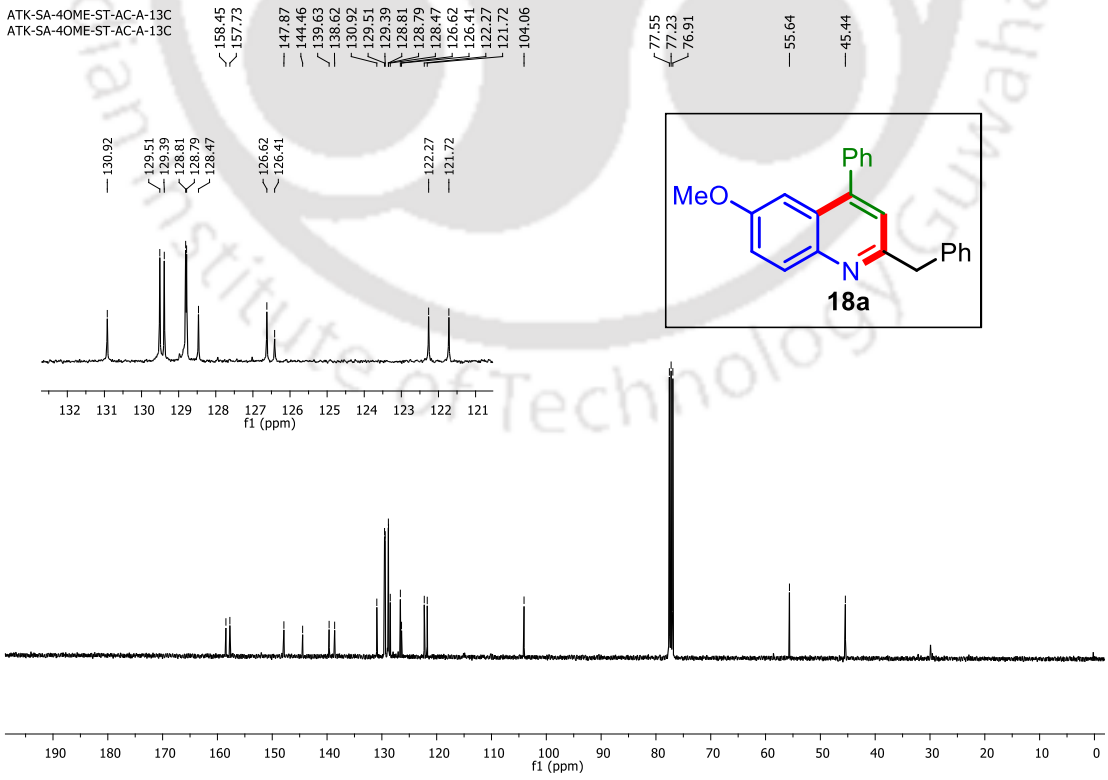


Figure 3.5b

HRMS spectrum: 2-benzyl-6-methoxy-4-phenylquinoline **(18a)**

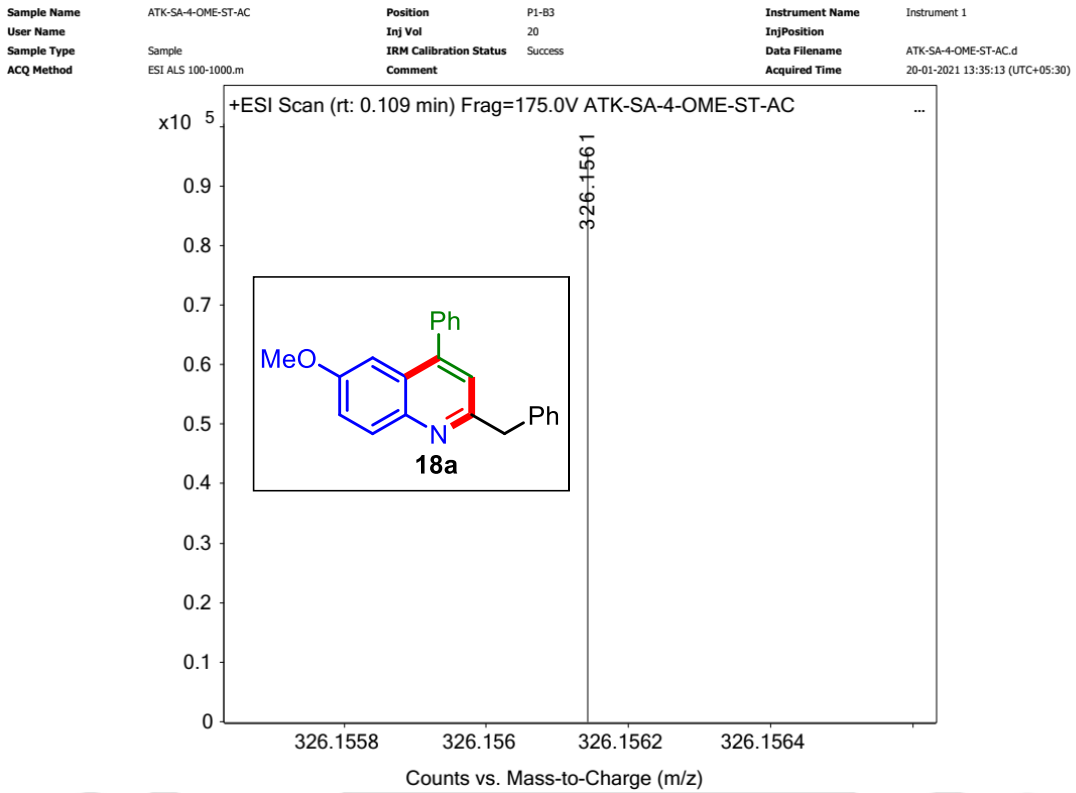


Figure 3.5c

^{1}H NMR (400 MHz, $CDCl_3$): 2-benzyl-6-methyl-4-phenylquinoline **(18c)**

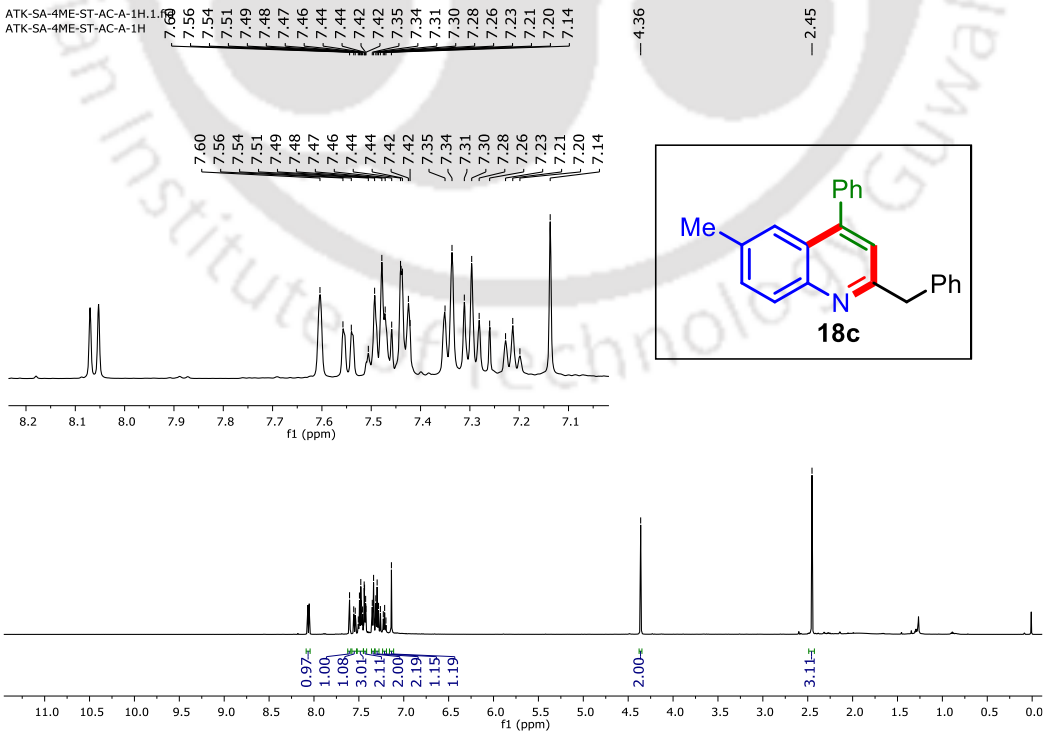


Figure 3.6a

^{13}C NMR (100 MHz, $CDCl_3$): 2-benzyl-6-methyl-4-phenylquinoline **(18c)**

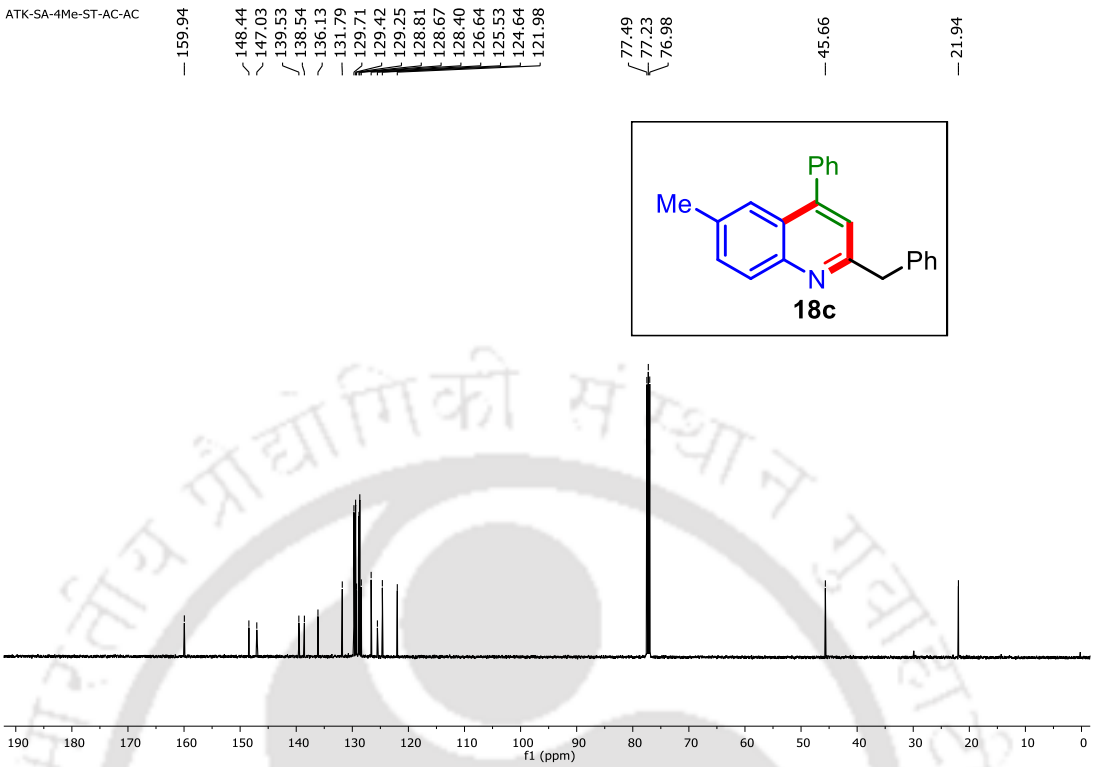


Figure 3.6b

HRMS spectrum: 2-benzyl-6-methyl-4-phenylquinoline **(18c)**

Sample Name	SAMPLE 11	**Position**	P1-A8	**Instrument Name**	Instrument 1	**User Name**	
Inj Vol	20	**InjPosition**		**SampleType**	Sample	**IRM Calibration Status**	Success
Data Filename	SA-4ME-ST-AC-1R.d	**ACQ Method**	ESI ALS 100-500.m	**Comment**		**Acquired Time**	2/11/2021 12:39:30 PM

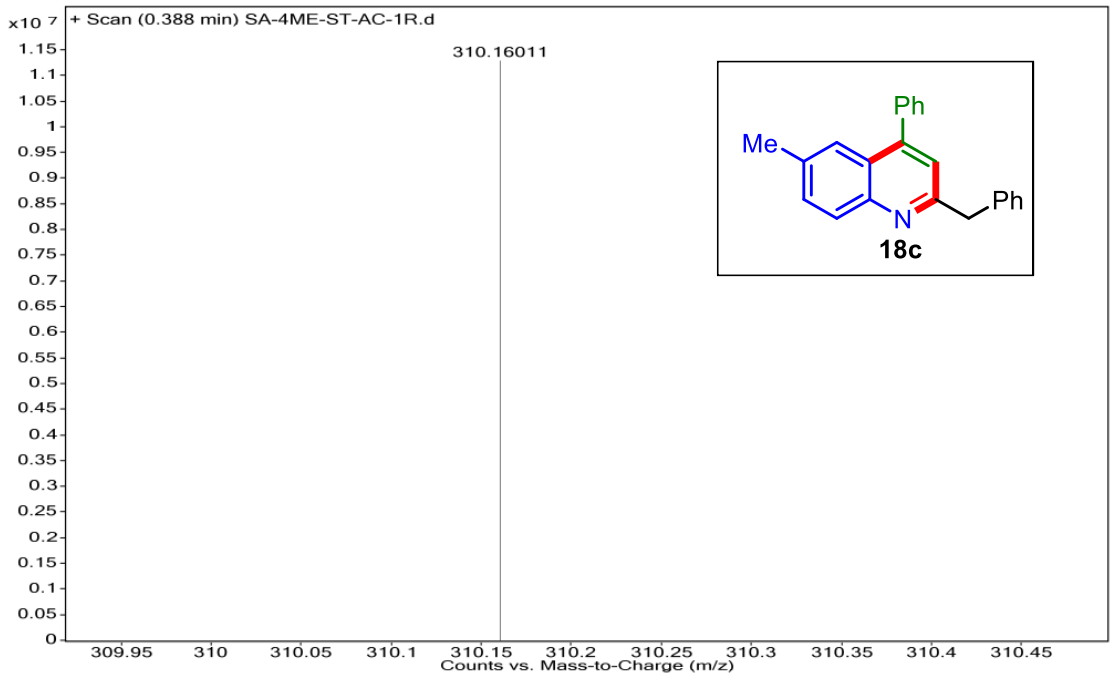


Figure 3.6c

^{1}H NMR (400 MHz, $CDCl_3$): 6-methoxy-2-(4-methylbenzyl)-4-phenylquinoline **(19a)**

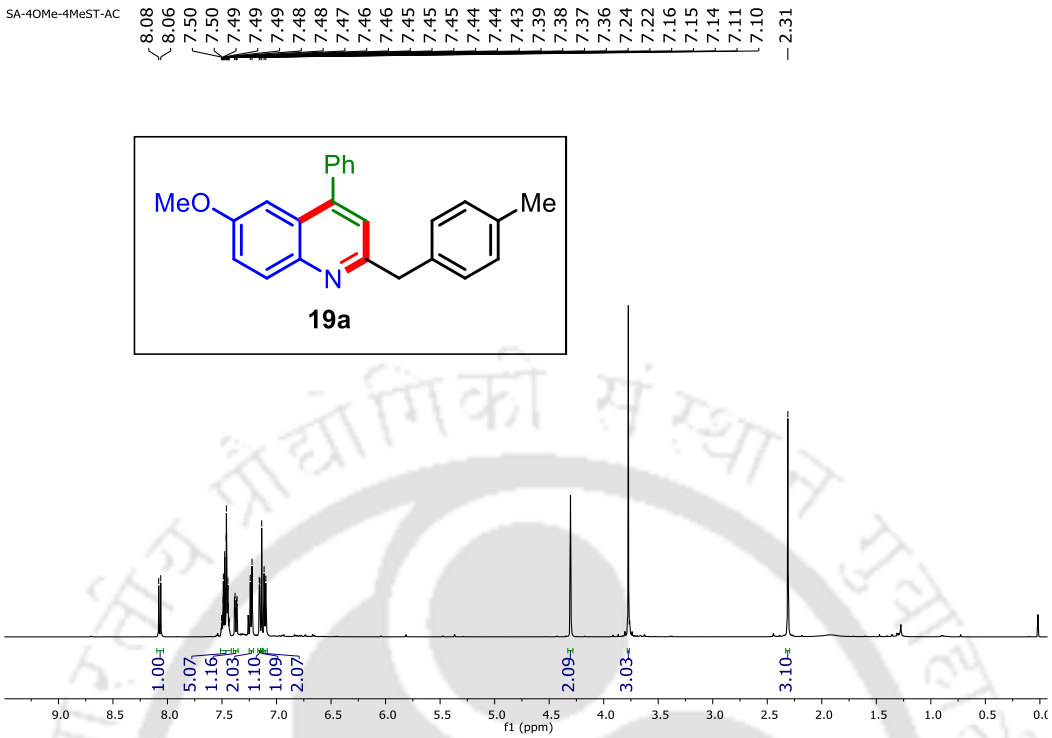


Figure 3.7a

^{13}C NMR (100 MHz, $CDCl_3$): 6-methoxy-2-(4-methylbenzyl)-4-phenylquinoline **(19a)**

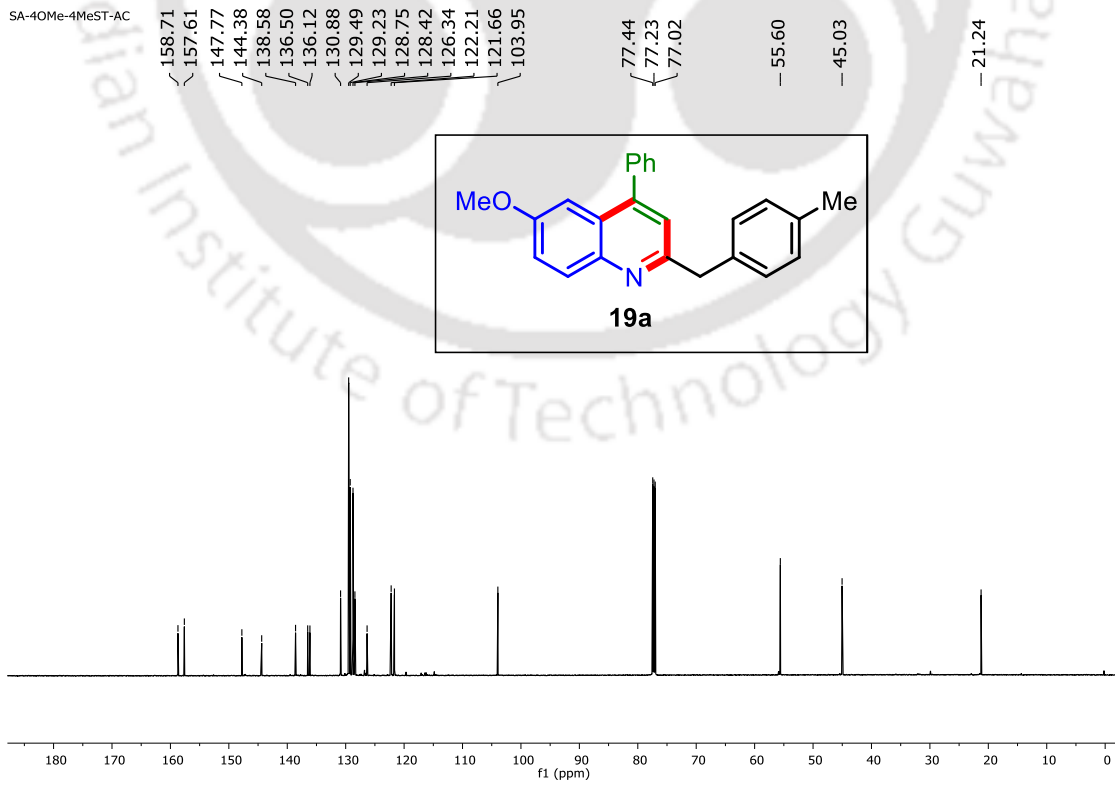


Figure 3.7b

HRMS spectrum: 6-methoxy-2-(4-methylbenzyl)-4-phenylquinoline **(19a)**

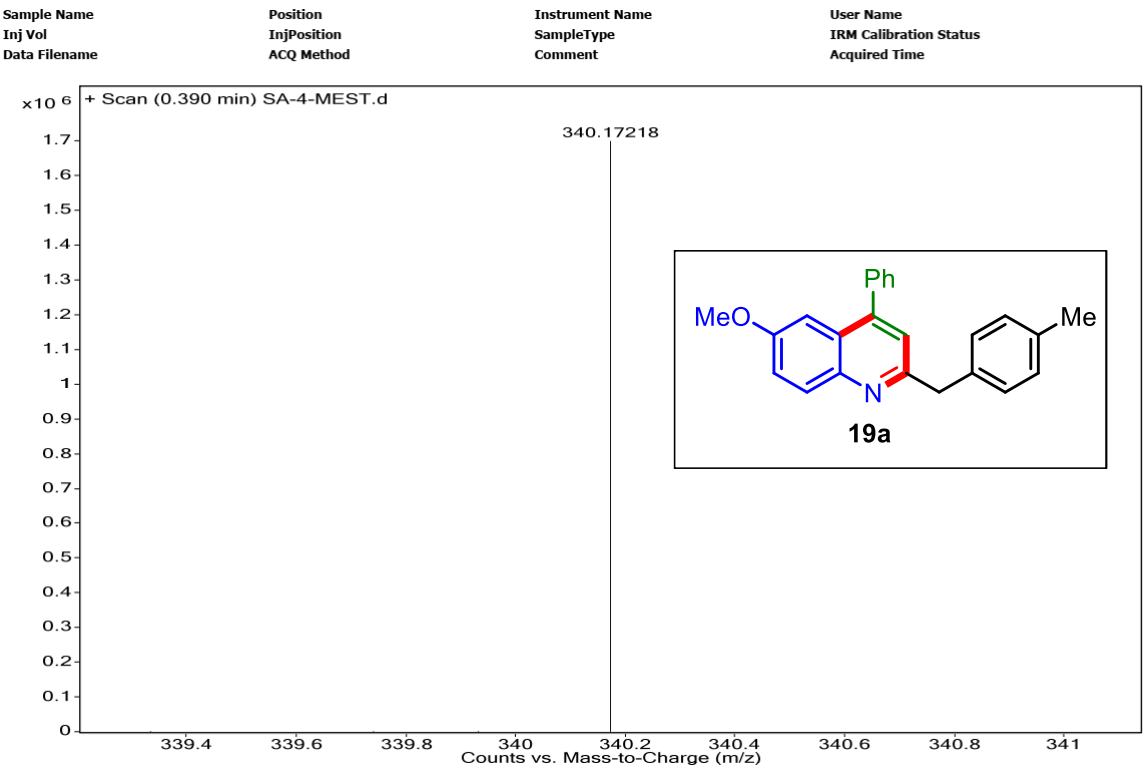


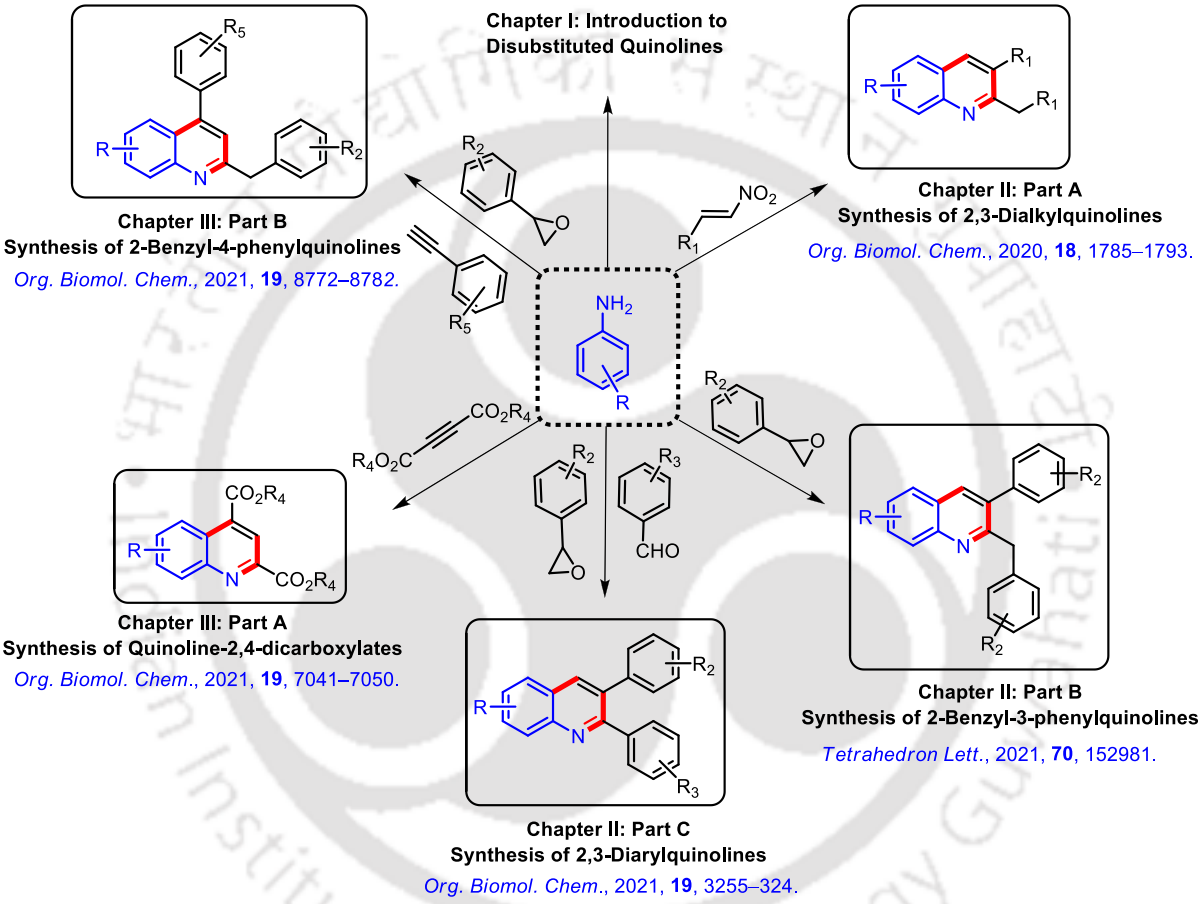
Figure 3.7c

References:

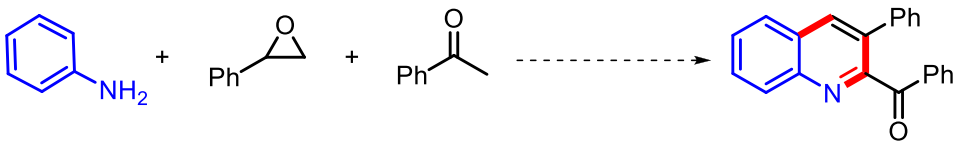
1. H. Iring, B. Bernd, C. Arwed, H. Melanie, N. Roland, P. Heike, Q. S. Maria and K. C. Christine, *DE Pat* WO2016/ 202935A1, 2016.
2. (a) J. Wu, H. G. Xia and K. Gao, *Org. Biomol. Chem*., 2006, **4**, 126–129; (b) A. Hazra, P. Paira, K. B. Sahu, S. Banerjee and N. B. Mondal, *Catal. Commun*., 2008, **9**, 1681–1684; (c) B. P. Bandgar and K. A. Shaikh, *Tetrahedron Lett*., 2003, **44**, 1959–1961; (d) J. S. Yadav, B. V. S. Reddy, K. Sadasiv and G. Satheesh, *Tetrahedron Lett*., 2002, **43**, 9695.
3. (a) A. T. Khan, M. M. Khan and K. K. R. Bannuru, *Tetrahedron Lett*., 2010, **66**, 7762–7772; (b) A. T. Khan, D. K. Das, K. Islam and P. Das, *Tetrahedron Lett*., 2012, **53**, 6418–6422; (c) A. T. Khan, A. Ghosh and M. M. Khan, *Tetrahedron Lett*., 2012, **53**, 2622–2626; (d) M. Belal and A. T. Khan, *ChemistrySelect*, 2018, **3**, 2431–2434; (e) M. Belal and A. T. Khan, *RSC Adv*., 2015, **5**, 104155–104163; (f) M. S. Yusubov and V. V. Zhdankin, *Resour.-Effic. Technol*., 2015, **1**, 49–67; (g) M. Breugst and D. von der Heiden, *Chem. Eur. J*., 2018, **24**, 9187–9199; (h) T. Duhamel, C. J. Stein, C. Martínez, M. Reiher and K. Muñiz, ACS Catal., 2018, **8**, 3918–3925.
4. N. P. Peet, L. E. Baugh, S. Sunder and J. E. Lewis, *J. Med. Chem*., 1985, **28**, 298–302.
5. H. Xu, H. W. Liu, K. Chen and G. W. Wang, *J. Org. Chem*., 2018, **83**, 6035–6049.
6. (a) W. Wu, Y. Guo, X. Xu, Z. Zhou, X. Zhang, B. Wu and W. Yi, *Org. Chem. Front*., 2018, **5**, 1713–1718; (b) Z. Li, J. Dong, X. Chen, Q. Li, Y. Zhou and S.-F. Yin, *J. Org. Chem*., 2015, **80**, 9392–9400; (c) M. S. Mayo, X. Yu, X. Zhou, X. Feng, Y. Yamamoto and M. Bao, *Org. Lett*., 2014, **16**, 764–767.
7. M. Zhang, B. Xiong, T. Wang, Y. Q. Ding, L. Wang, *Heterocycles*, 2011, **83**, 2289–2298.
8. M. Beller, O. R. Thiel, H. Trauthwein, C. G. Hartung, *Chem. Eur. J*., 2000, **6**, 2513.
9. Y. Wang, C. Chen, J. Peng and Ming Li, *Angew. Chem. Int. Ed*. 2013, **52**, 5323 –5327.

CONCLUSION AND FUTURE PERSPECTIVES

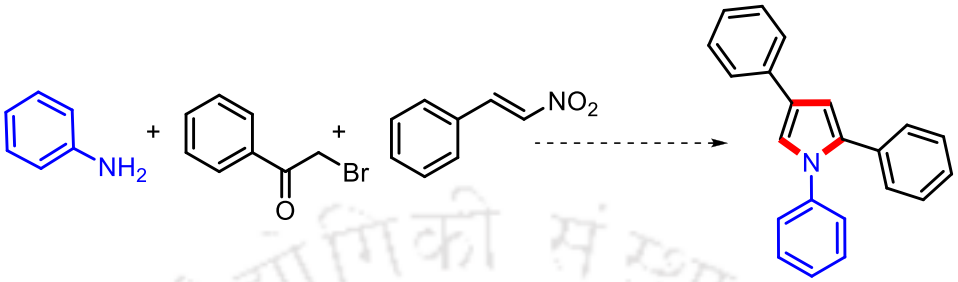
During the tenure of Ph. D., my research work mainly focused on synthesis of disubstituted quinoline derivatives, such as 2,3-dialkylquinolines, 2-benzyl-3-phenylquinolines, 2,3-diarylquinolines, quinoline-2,4-dicarboxylates and 2-benzyl-3-phenylquinolines using aryl amines. The summarized results are shown below schematically.



In future, my research interest will be in exploring aryl amines further for synthesis of structurally diverse quinoline and pyrrole derivatives of biological importance as shown in Schemes (**A** & **B**). Moreover, synthesized compounds are useful which could be studied for their biological activities in collaboration of other research groups.



Scheme A



Scheme B

LIST OF PUBLISHED PAPERS

1. **Saghir Ali** and Abu T. Khan. An environmentally benign regioselective synthesis of 2-benzyl-4-arylquinoline derivatives using aryl amines, styrene oxides and aryl acetylenes. *Org. Biomol. Chem.*, 2021, **19**, 8772–8782.
2. **Saghir Ali** and Abu T. Khan. Metal-free synthesis of quinoline-2,4-dicarboxylate derivatives using aryl amines and acetylenedicarboxylates through pseudo three-component reaction. *Org. Biomol. Chem*., 2021, **19**, 7041–7050.
3. **Saghir Ali** and Abu T. Khan. Copper(II) triflate catalyzed three-component reaction for the synthesis of 2,3-diarylquinoline derivatives using aryl amines, aryl aldehydes and styrene oxides. *Org. Biomol. Chem*., 2021, **19**, 3255–324.
4. **Saghir Ali** and Abu T. Khan. Ytterbium(III) triflate catalyzed domino reaction of arylamines and styrene oxides: Synthesis of 2-benzyl-3-arylquinoline derivatives. *Tetrahedron Lett*., 2021, **70**, 15298162.
5. **Saghir Ali**, Radhakrishna Gattu, Varun Singh, Santa Mondal, Abu T. Khan, Gurudutt Dubey and P. V. Bharatam, Reaction behaviour of arylamines with nitroalkenes in the presence of bismuth(III) triflate: An easy access to 2,3-diarylquinolines. *Org. Biomol. Chem*., 2020, **18**, 1785–1793.
6. Santa Mondal, Karuna Mahato, Neha Arora, Dheerendra Kankane, Umed Pratap Singh, **SaghirAli**, Aftab Hossain Khan, Siddhartha S. Ghosh and Abu T. Khan, Newly synthesized 3-sulfenylindole derivatives from 4-hydroxydithiocoumarin using an oxidative cross dehydrogenative coupling reaction (OCDCR): potential lead molecules for antiproliferative activity. *Org. Biomol. Chem.*, 2020, **18**, 4104–4113.
7. Radhakrishna Gattu, Santa Mondal, **Saghir Ali** and Abu T. Khan. Iodine monobromide catalysed regioselective synthesis of 3-arylquinolines from α-aminoacetophenones and trans-β-nitrostyrenes. *Org. Biomol. Chem.*, 2019, **17**, 347–353.