Lewis Acid Driven Synthetic Approaches for Benzannulated *N*-Heterocycles from 2-Aminobenzonitrile

A dissertation submitted in partial fulfillment for the degree of

Doctor of Philosophy

Submitted by

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November 2024

Dedicated to

My Beloved Parents

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STATEMENT

I hereby declare that the matter embodied in this thesis, titled "**Lewis Acid Driven Synthetic Approaches for Benzannulated *N*-Heterocycles from 2-Aminobenzonitrile**" is the result of my own investigations in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the supervision of Prof. Anil K. Saikia. I have submitted this thesis to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy.

In accordance with the standard scientific reporting practices, I have duly acknowledged the contributions of other researchers wherever their findings are referenced in this work. I also declare that, to the best of my knowledge, this work has not been submitted elsewhere for any degree, diploma, associateship, or membership at any institute or university.

Bikoshita Porashar.

Date: 12th November 2024 **Bikoshita Porashar**

Place: IIT Guwahati

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CERTIFICATE

This is to certify that Bikoshita Porashar has been working under my supervision as a regular registered Ph. D. student since July 2018. Her thesis, entitled "**Lewis Acid Driven Synthetic Approaches for Benzannulated *N*-Heterocycles from 2-Aminobenzonitrile**", is an authentic record of the results obtained from the research work performed in the Department of Chemistry, Indian Institute of Technology Guwahati, Assam, India. I am forwarding her thesis for the award of Doctor of Philosophy in Chemistry at this institute. I certify that she has fulfilled all the requirements according to the rules of this institute regarding the investigations embodied in her thesis, and this work has not been submitted elsewhere for a degree.

Date: 12th November 2024

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ACKNOWLEDGEMENT

With an extreme sense of gratitude, I take this opportunity to thank all the individuals who have supported, guided and encouraged me in this long and crucial journey of my Ph.D. First and foremost, I would like to extend my deepest respect and sincere gratitude to my supervisor, Prof. Anil Kumar Saikia for his excellent guidance and unwavering support throughout my research period. His immense knowledge, passion for research and meticulous attention to detail have significantly shaped this thesis. I will always be grateful for his scientific ideas, insightful critiques, encouragement and words of wisdom.

I also want to thank my doctoral committee members, Prof. Subhas Chandra Pan, Dr. Krishna Pada Bhabak, Prof. V. Venkata Dasu and Dr. Kalyan Raidongia, for timely evaluation of my Ph.D. work and for their insightful comments and valuable suggestions, which added towards the improvement of my thesis. I sincerely acknowledge all the faculty and staff members of the Department of Chemistry, IIT Guwahati, for their cooperative nature and timely help whenever required.

I am very grateful to MHRD, India, for providing financial assistance and IIT Guwahati for all the facilities that were made available to me. I express my gratitude to Central Instrument Facility (CIF) and NECBH, IIT Guwahati for providing the instrument facilities. Together with this, I acknowledge the help rendered by Imdadul Islam and all other NMR, HRMS and SCXRD operators for their efforts in sample analysis and data collection.

Further, I would like to express my gratitude to all the past and present lab members for their friendship and assistance. I am indebted to Dr. Namita Devi for helping me during my initial days in getting acquainted with the laboratory techniques. I am thankful to my seniors Dr. Upasana Borthakur, Dr. Ngangbam Renubala Devi, Malay Das, Dr. Archana Kumari Sahu, Dr. Bipin Kumar Behera, Dr. Sudip Shit and Subhamoy Biswas for their enormous support, stimulating discussions and valuable suggestions that inspired me throughout this journey. I also appreciate my juniors Surjya, Aditya, Rajat, Chinmayee, Ankita and Hunmoina for their help and for maintaining a friendly environment in the lab.

I would like to take this opportunity to acknowledge my colleagues and batchmates (July 2018) at IITG for their help, support and encouragement. I will always remember the trips we took, the camaraderie and the joyful moments we shared in all these years.

Acknowledgement

I would like to express millions of gratitude to my closest friends, seniors and juniors in and out of campus for their unwavering support, care and boundless love that I have received during this challenging academic pursuit. I want to thank Dr. Nikita Chakraborty, Sanjib, Rabu, Kalyani, Nazmin, Vijeta, Adyasa, Sanchari, Prangshu, my friends from Tezpur University, especially Nazia, Aniket, Rajdikshit, Ashim, Biplob, Afjalur, Mubin, Madhurya, Hrishikesh, Anjal. A very special mention to my friends Suravi, Monuranjan and Priyanka for their help and support in every possible way, for staying by my side and for making good times even better and the tough times much easier.

Teachers influence the life of a student in many ways and I have been fortunate to have some amazing personalities as my teacher during the various stages of academic life. I would like to extend my deepest respect and profound gratitude to all the teachers from my school and Tezpur University who have taught me valuable lessons and motivated me to do good in life.

Finally, my sincere regards to my father, Polash Puzari, my mother, Uma Goswami and my sisters Bidisha and Prastuti for their unconditional love, support and encouragement throughout my life. Especially, my mother has been the pillar of strength and my guiding light while navigating through difficult times in life. Their continuous support and belief in my academic pursuits have been instrumental in my success. I also thank my cousins, family members (uncles and aunts) and my late grandmother(Aita) for being there for me in life.

Above all, I owe it all to the Almighty for blessing me with wisdom, health, and strength to accomplish this endeavour.

Bikoshita Porashar

LIST OF ABBREVIATIONS

AcOH	*Acetic acid*	HRMS	*High resolution mass spectrometry*
AgOTf	*Silver trifluoromethanesulfonate*	IR	*Infrared*
^{t}AmOH	*Tertiary amyl alcohol*	KF	*Potassium fluoride*
Ar	*Aryl*	LA	*Lewis acid*
Boc	*tert-butyloxycarbonyl*	LEDs	*Light emitting diodes*
$BF_3{\cdot}OEt_2$	*Boron trifluoride etherate*	Me	*Methyl*
Bn	*Benzyl*	mp	*Melting point*
^{n}Bu	*n-Butyl*	MS	*Molecular sieves*
^{t}Bu	*t-Butyl*	m/z	*Mass to charge ratio*
CCDC	*Cambridge Crystallographic Data Centre*	NBS	*N-Bromosuccinimide*
CH_3CN	*Acetonitrile*	NHC	*N-Heterocyclic carbene*
CO_2	*Carbon dioxide*	NIS	*N-Iodosuccinimide*
CS_2	*Carbon disulfide*	NMR	*Nuclear magnetic resonance*
DDQ	*2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*	NOE	*Nuclear Overhauser Effect*
Et	*Ethyl*	OLED	*Organic light emitting diode*
EWG	*Electron withdrawing group*	ORTEP	*Oak ridge thermal ellipsoid plot*
DCE	*1,2-Dichloroethane*	Ph	*Phenyl*
DCM	*Dichloromethane*	ppm	*Parts per million*
DMAP	*4-Dimethylaminopyridine*	Pr	*Propyl*
DMEDA	*N,N'-Dimethylethylenediamine*	PSSE	*Trimethylsilyl polyphosphate*
DMF	*Dimethylformamide*	rt	*Room temperature*
DMSO	*Dimethylsulfoxide*	TBAI	*Tetrabutylammonium iodide*
dr	*Diastereomeric ratio*	TBHP	*tert-Butyl hydroperoxide*
er	*Enantiomeric ratio*	TfOH	*Triflic acid*
EtOH	*Ethanol*	THF	*Tetrahydrofuran*
EtOAc	*Ethyl acetate*	TLC	*Thin layer chromatography*
HFIP	*Hexafluoroisopropanol*	*p*-TsOH	*p-toluenesulfonic acid*

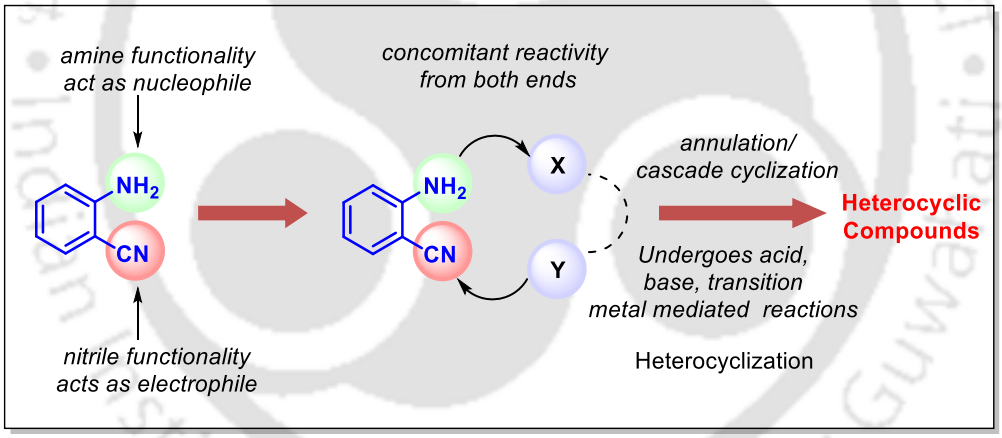
Abbreviations for intensities of ^{1}H-NMR signals:

s	*Singlet*	dt	*Doublet of triplets*
d	*Doublet*	td	*Triplet of doublets*
t	*Triplet*	tt	*Triplet of triplets*
q	*Quartet*	ddd	*Doublet of doublets of doublets*
p	*Pentet(quintet)*	bs	*Broad singlet*
m	*Multiplet*	Hz	*Hertz*
dd	*Doublet of doublets*	Mhz	*Mega hertz*

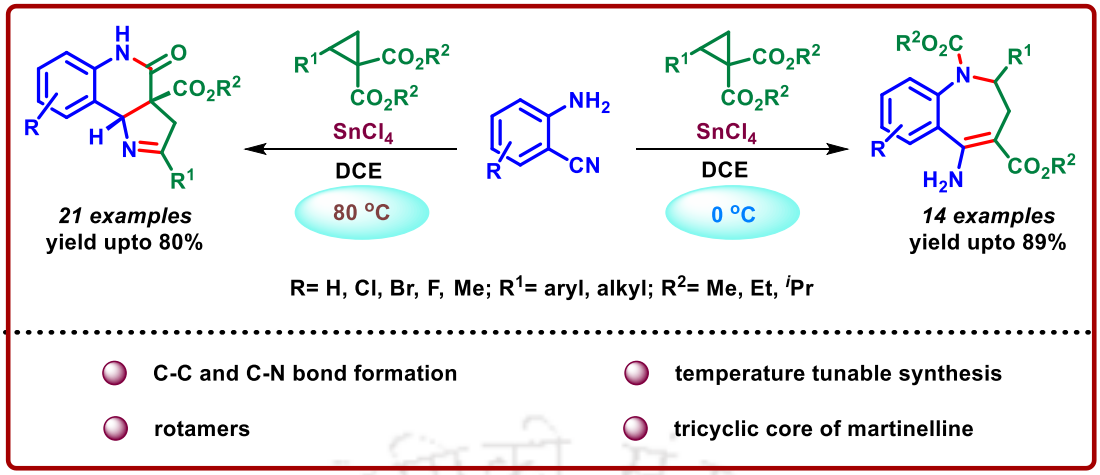
ABSTRACT

The contents of the present thesis entitled as "**Lewis Acid Driven Synthetic Approaches for Benzannulated *N*-Heterocycles from 2-Aminobenzonitrile**" have been divided into five chapters based on the results obtained from the experimental works performed during the entire course of the PhD research programme.

Chapter 1 highlights an overview on nitrogen containing heterocyclic compounds, cascade reactions and the reactivity of 2-aminobenzonitrile. This includes a brief discussion about synthetic reactivity and utility of 2-aminobenzonitrile as a precursor for synthesis of various simple or complex heterocyclic frameworks. It emphasizes on its unique structure bearing both amine and nitrile functionalities, thus undergoing different acid/base/transition-metal promoted cascade reactions with a coupling partner to generate highly functionalized heterocycles.

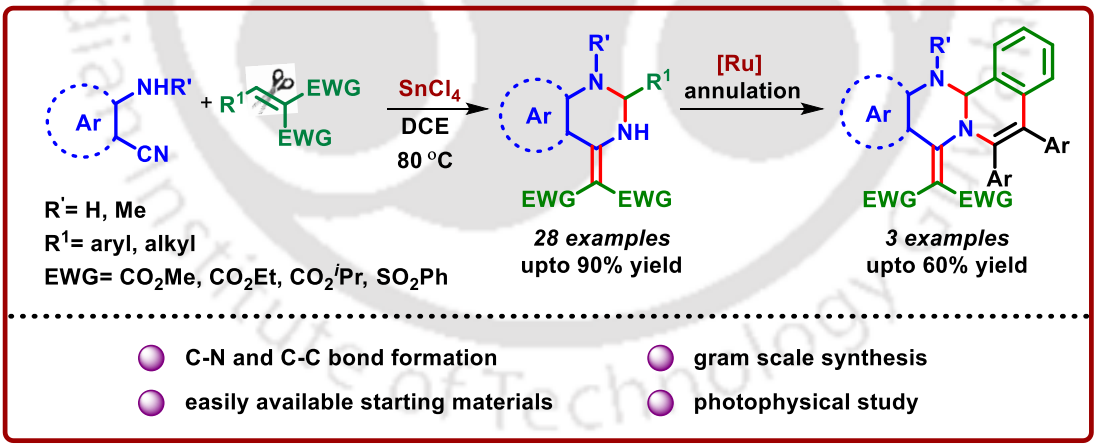


Chapter 2 represents a tunable one pot synthesis of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and dihydro-1*H*-benzo[*b*]azepines from 2-aminobenzonitriles and donor-acceptor cyclopropanes in presence of $SnCl_4$. The reaction proceeds *via* the initial ring opening of cyclopropane ring by 2-aminobenzonitrile followed by nucleophilic attack by amine to give adduct, which after unprecedented rearrangement at two different reaction temperatures provide two sets of structurally diverse nitrogen heterocyclic compounds. This methodology can be used for the synthesis of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones (tricyclic core of martinelline).



Org. Lett. **2022**, *24*, 9038–9042.

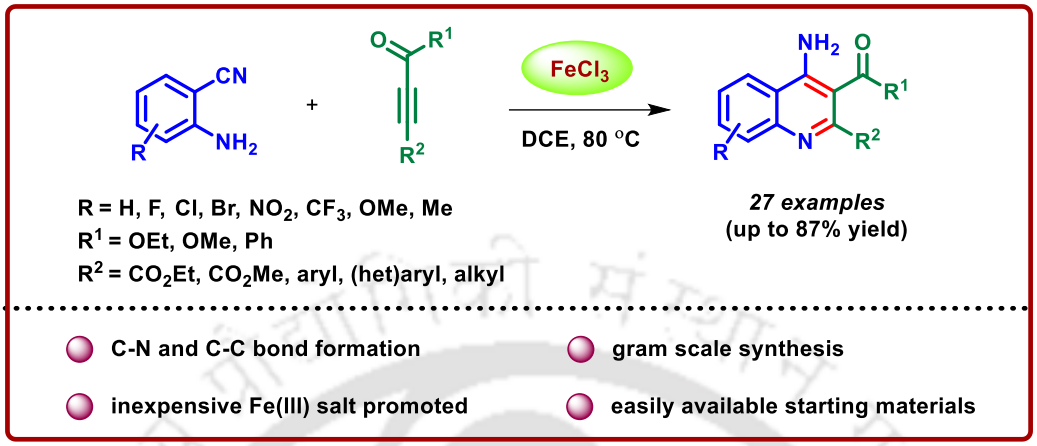
Chapter 3 describes an efficient methodology for the synthesis of highly diverse 4-methylene substituted tetrahydroquinazoline scaffolds from 2-aminobenzonitriles and alkylidene malonates in presence of $SnCl_4$. The reaction proceeds *via* initial 1,4-conjugate addition of 2-aminobenzonitrile to the activated alkene followed by an unprecedented rearrangement. The methodology can be extended towards the synthesis of quinazoline analogues as well as tetracyclic dihydroisoquinolino[1,2-*b*]quinazoline derivatives. Some of the synthesized compounds show excellent photophysical properties.



Chem. Commun. **2024**, *60*, 4358–4361.

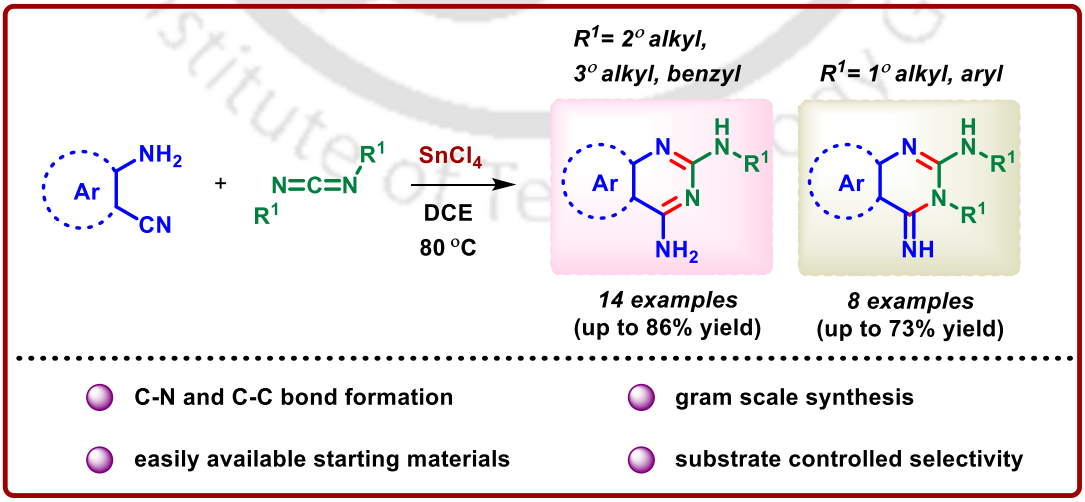
Chapter 4 demonstrates an efficient methodology for the synthesis of highly diverse 2,3-disubstituted 4-aminoquinoline derivatives from 2-aminobenzonitriles and activated alkynes in presence of $FeCl_3$. The reaction proceeds *via* sequential aza-Michael addition and intramolecular annulation to afford highly substituted 4-aminoquinolines in good yields. The salient features of this protocol include the use of a minimally toxic, eco-benign and less

expensive Fe(III)-salt and has high atom-economy with broad substrate scope and operational simplicity. The post synthetic application of the reaction provides 4*H*-benzo[*de*][1,6]naphthyridines.



Synthesis **2024**, *56*, 3131–3141.

Chapter 5 highlights an efficient methodology for the synthesis of 2,4-diaminoquinazolines and 2-amino-4-iminoquinazolines from 2-aminobenzonitriles and carbodiimides. This $SnCl_4$ mediated reaction exhibits substrate driven switchable selectivity in product formation based on the substituents of the carbodiimides used. Aryl and primary alkyl-substituted carbodiimides predominantly give 2-amino-4-iminoquinazolines, while secondary or tertiary alkyl and benzyl-substituted carbodiimides yield 2,4-diaminoquinazolines. The methodology can be extended towards the synthesis of 2-aminoquinazolin-4(3*H*)-one analogues as well as pentacyclic annulated derivatives.



ChemistrySelect **2025**, *10*, e202405899.

CONTENTS

CHAPTER 1

An Overview of Nitrogen Containing Heterocyclic Compounds, Cascade Reactions and Utility of 2-Aminobenzonitrile as a Precursor for *N*-Heterocycles

1.1. Introduction to Nitrogen Containing Heterocyclic Compounds

Organic molecules featuring a ring structure that includes carbon along with at least one heteroatom are called heterocyclic compounds. Generally, nitrogen, oxygen and sulphur are the most common heteroatoms encountered but rings containing other heteroatoms, such as, boron, silicon, phosphorus and selenium are also known. Among these, nitrogen containing heterocycles constitute an important class of naturally occurring and biologically active molecules. Many of the naturally occurring molecules are constituted of a nitrogen containing heterocyclic core unit as key structural component e. g. photosynthesizing pigment chlorophyll, alkaloids. Nitrogen heterocycles are also active members of our biological system, e. g. heme, nucleic acid (purine and pyrimidine bases), vitamins (thiamine, riboflavin, vitamin B_{12}) etc.[1] Pharmaceutically relevant molecular entities are often characterized by nitrogen-richness. A recent comprehensive analysis of US FDA approved small molecules revealed that 59% contain at least one nitrogen heterocycle,[2] which is quite remarkable when compared to the percentage of drugs containing sulphur (26%) or fluorine (13%).[3] Nitrogen heterocycles can be broadly classified as aliphatic and aromatic heterocycles. The aliphatic nitrogen heterocycles are the cyclic analogues of amines. The most common ones with one or two nitrogen atoms in the ring are aziridine (**1**), azetidine (**2**), pyrrolidine (**3**), imidazolidine (**4**), piperidine (**5**), piperazine (**6**) and azepane (**7**) (*Figure 1.1.1.*).

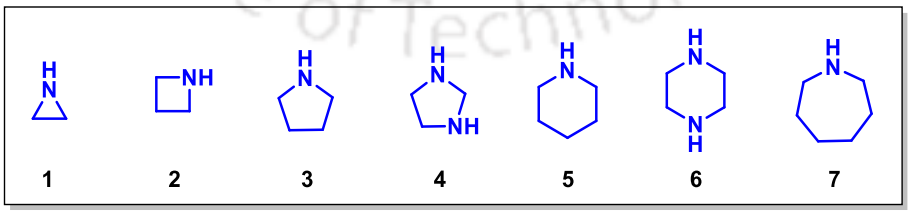


Figure 1.1.1. *Some examples of aliphatic nitrogen heterocycles.*

On the other hand, aromatic nitrogen heterocycles are those which follow Hückel's rule i.e. being conjugated, planar and have (4n+2) π electron system such as pyrrole (**8**), imidazole (**9**), pyridine (**10**), pyrimidine (**11**) and pyrazine (**12**) (*Figure 1.1.2.*).

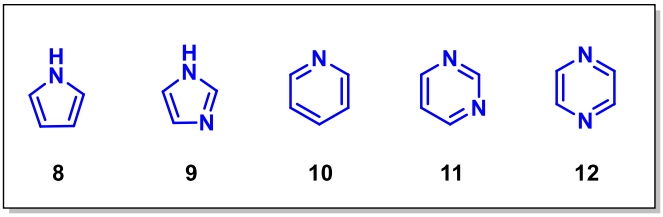


Figure 1.1.2. *Some examples of aromatic nitrogen heterocycles.*

Besides these monocycles, fused heterocyclic ring systems consist a major class of heterocyclic compounds. These are formed by the fusion of heterocycles with other rings, either carbocyclic or heterocyclic. Most common ones feature a benzene ring fused to the heterocyclic ring, called as benzo-fused or benzannulated heterocycles. Some usually encountered benzo-fused nitrogen heterocycles are indole (**13**), benzoimidazole (**14**), indoline (**15**), quinoline (**16**), isoquinoline (**17**), quinazoline (**18**), tetrahydroquinoline (**19**), tetrahydroquinazoline (**20**), benzazepine (**21**), 2,3-dihydro-1*H*-benzo[*b*]azepine (**22**) (*Figure 1.1.3.*).

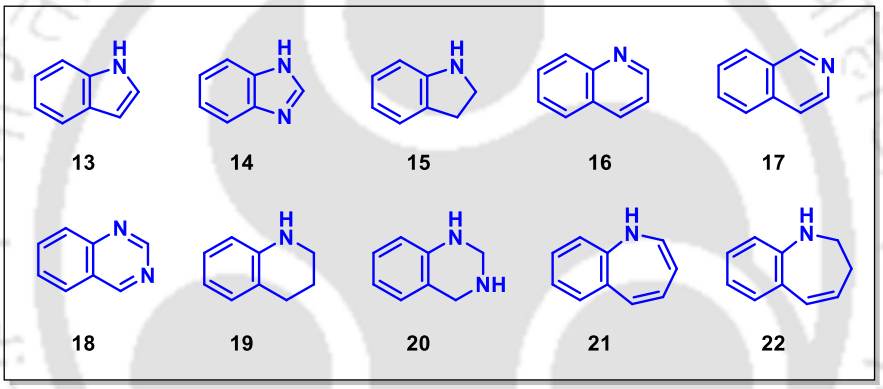


Figure 1.1.3. *Some examples of benzo-fused nitrogen heterocycles.*

Benzo-fused nitrogen heterocycles are frequent motifs in biologically active molecules and synthetic compounds. These materials have a variety of applications including pharmaceuticals, photoactive compounds, and conducting polymers.[4] This introductory chapter is designed to highlight the importance of some benzo-fused nitrogen heterocycles such as quinolines, quinazolines, benzoazepines and their analogues.

1.1.1. Importance of Quinolines, Quinazolines, Benzazepines and their Analogues

Quinolines are a class of benzo-fused nitrogen heterocycles which contain a benzene ring fused to pyridine moiety. Chemically, quinoline is a tertiary amine base that can form a salt with acids and shows both electrophilic and nucleophilic substitution reactions. Quinoline nucleus occurs in several natural compounds (mainly in cinchona alkaloids) and is a versatile pharmacophore possessing anti-malarial, anti-bacterial, antifungal, anthelmintic, cardiotonic, anticonvulsant, anti-inflammatory, and analgesic activities.[5] For instance, quinine (**23**) is an alkaloid with quinoline core, first isolated in 1820, from the bark of cinchona tree which is

native to Peru, has long established anti-malarial properties.[6] Marketed drugs like bosutinib (**24**)[7], used to treat myelogenous leukemia, and antrafenine (**25**)[8], used as an anti-inflammatory and analgesic agent contain 4-aminoquinoline core (*Figure 1.1.1.1.*).

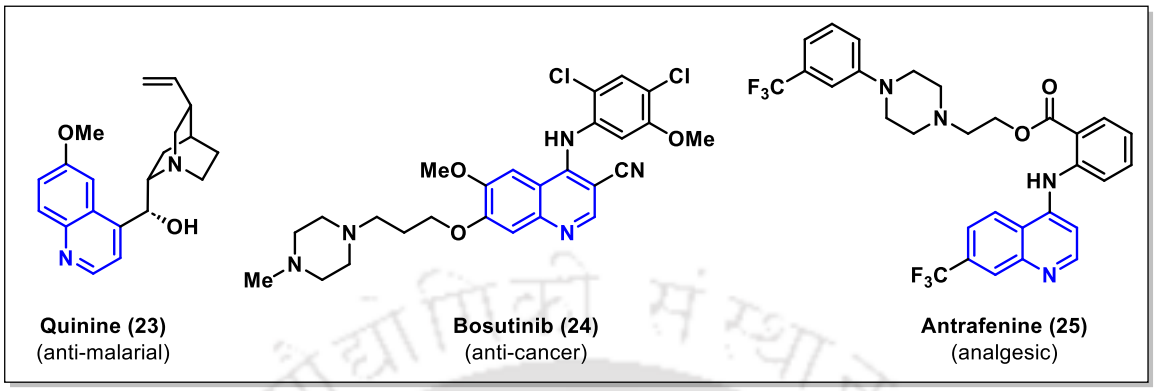


Figure 1.1.1.1. *Examples of bioactive molecules with quinoline skeleton.*

Similarly, quinazolines are another class of bicyclic nitrogen heterocycles consisting of a benzene ring fused to a pyrimidine moiety. Quinazolines make up a significant class of nitrogen heterocycles which exhibit a diverse array of biological activities including anti-microbial, anti-convulsant, anti-cancer, anti-hypertensive, anti-inflammatory, anti-tumor, anti-cholinesterase and kinase inhibitory activities.[9] There are many synthetic and natural product-based drugs, containing quinazoline and its derivatives as core moiety. For example, gefitinib (**26**)[10] is used to treat metastatic non-small cell lung cancer, and trimetrexate (**27**)[11] is a well-known medication for pneumocystis pneumonia. Selurampanel (**28**) is a kainate receptor (KAR) antagonist that has been investigated in clinical trials for the treatment of epilepsy by Novartis (*Figure 1.1.1.2.*).[12]

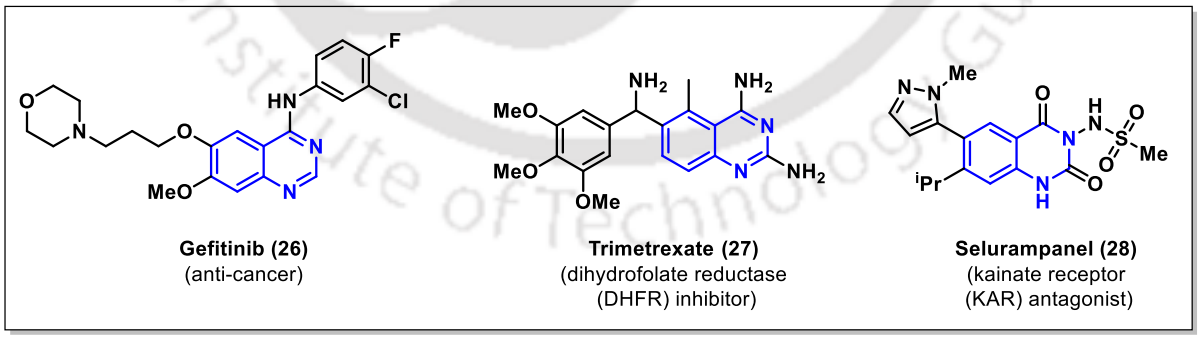


Figure 1.1.1.2. *Examples of bioactive molecules with quinazoline and its derivatives.*

On the other hand, benzazepines represent a particularly important class of seven-membered *N*-heterocycles, characterized by a benzene ring fused to a azepine ring. Benzazepines and its hydrogenated derivatives are embedded in a wide variety of bioactive natural products and pharmaceuticals.[13] Tetrahydro-1-benzazepine scaffold based drug, benazepril (**29**) is commonly used to lower high blood pressure (hypertension) [14] whereas

tolvaptan (**30**) is used clinically to treat autosomal dominant polycystic kidney disease and hyponatremia.[15] Compound **31**, is an orally active CCR5 antagonist for the potential treatment of HIV infection (*Figure 1.1.1.3.*).[16]

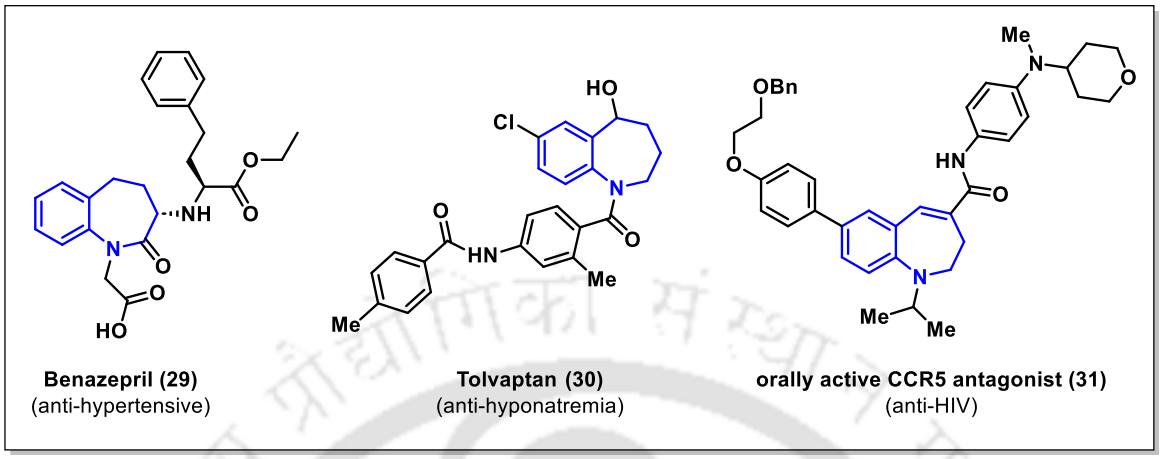


Figure 1.1.1.3. *Examples of bioactive molecules with benzazepine and its derivatives.*

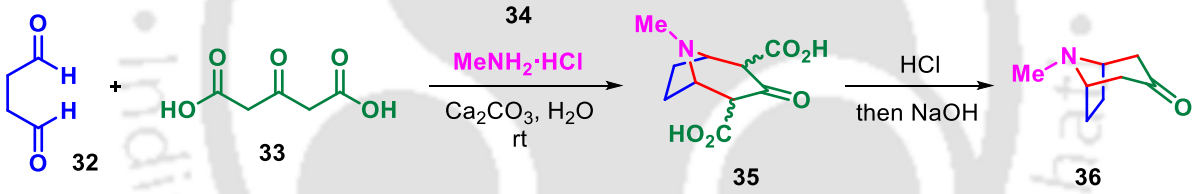
Over the years, several synthetic strategies have been employed to construct these heterocycles. The most prominent methods are the ene reaction, 1,*n*-enyne rearrangement, hetero-Diels-Alder cyclization, cascade reaction, Prins cyclization reaction, ring-closing metathesis and transition-metal catalyzed cyclization. Out of these methods, this thesis particularly focuses on cascade approaches for the synthesis of *N*-heterocycles. In the following section of this chapter, we will explore cascade reactions in detail, highlighting its use as a synthetic tool for *N*-heterocycles.

1.2. Cascade Reaction

Modern synthetic organic chemistry relies on development of methods for the synthesis of heterocycles, that are vital components in various pharmaceuticals, agrochemicals and natural products. Among them, cascade reaction has emerged as a powerful strategy to synthesize structurally diverse heterocycles with molecular complexity offering excellent selectivity. Cascade reactions, also often termed indistinguishably as 'domino', 'tandem', 'sequential', 'concurrent' and 'one-pot' reactions in synthetic chemistry, are chemical processes that streamlines at least two consecutive reactions to result in one synthetic operation.[17] A key point to note here is that subsequent conversion step results from the functionality developed in the previous step in these transformations. Additionally, the subsequent steps (second, third, etc.) after the initial step in a cascade reaction proceed without any external intervention. Also the reaction condition doesn't change among the consecutive steps of a cascade. Cascade reactions, whether planned and somewhat serendipitous, have enhanced our understanding of mechanisms and molecular reactivity. Besides being artistically appealing, it is often associated

with improved atom economy as well as economies of time, labour, resource management, and waste generation and thus also considered to fall under the banner of 'green chemistry'.[17d,17f] They are, therefore, a means to achieve green chemistry and to develop eloquent and economic chemical processes for the manufacture of pharmaceuticals and other fine chemicals.

In 1917, Robert Robinson reported the first cascade reaction with the groundbreaking total synthesis of the alkaloid tropinone **36**.[18] In this remarkable three component single-step transformation, succinaldehyde **32**, acetone dicarboxylic acid **33**, and methylamine hydrochloride **34** reacted in one pot to afford the bridged bicyclic alkaloid tropinone with 42% yield. The key steps involved in this transformation includes various fundamental reactions such as condensation of methylamine with dialdehyde to afford cyclic iminium adduct followed by a double Mannich and subsequent decarboxylation (*Scheme 1.2.1.*). By employing a strategy based on fundamental mechanistic understanding and exploitation of molecular symmetry, four key bonds and two rings are formed all in a single reaction vessel, highlighting the ability of synthesis of complex molecules from simple compounds through the principles of synthetic and retrosynthetic logic.



Scheme 1.2.1. *Robinson's tropinone synthesis.*

Classification of cascade reactions into different categories is somewhat challenging because of the diversity in the steps involved for the transformation. Still, they can be labelled only on the basis of the main theme that is responsible for initiating the cascade sequence and a variety of opinions exist on how such reactions should be distinguished. K. C. Nicolaou classified the cascade reactions based on the mechanism of the key step involved into the following categories:

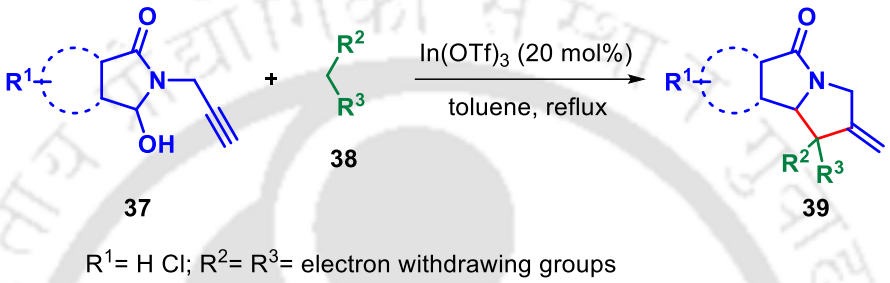
- Nucleophilic cascade
- Electrophilic cascade
- Radical cascade
- Pericyclic cascade
- Transition-metal-catalyzed cascade

However, these reactions are loosely divided into these themes and a variety of opinions exist on how such reactions should be classified. But, the quality and importance of a cascade

reaction can be correlated to the number of bonds generated in such a process and the increase in molecular complexity.

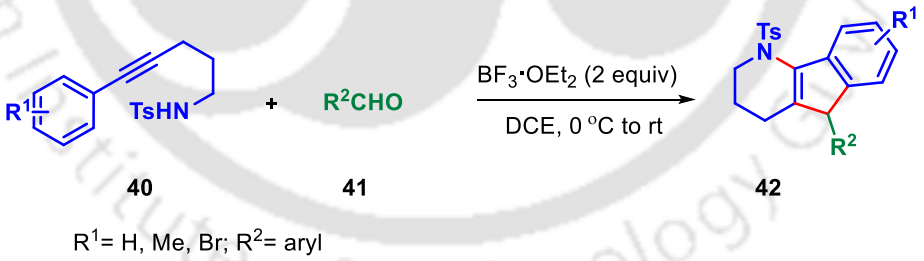
1.2.1. Representative Examples of Cascade Reaction for Synthesis of *N*-Heterocycles

A one-pot cascade protocol has been developed by Saikia and co-workers for the synthesis of substituted tetrahydropyrroloisoindolones **39** from *N*-propargyl amido alcohols **37** and 1,3-dicarbonyl compounds **38** using a catalytic amount of $In(OTf)_3$. This highly regioselective reaction proceeds *via* Mannich reaction followed by a subsequent Conia-ene cyclization to give the products with an exo-cyclic double bond in the pyrrolidine ring (*Scheme 1.2.1.1a*.).[19]



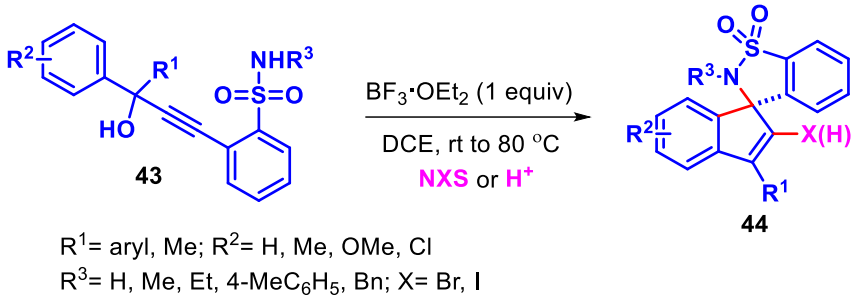
Scheme 1.2.1.1a. *$In(OTf)_3$ catalyzed synthesis of tetrahydropyrroloisoindolones.*

The same group also reported a protocol for the synthesis of 1-tosyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine scaffold **42** from *α*-sulfonamido alkyne **40** with aryl aldehyde **41** under Lewis acidic conditions. The major steps involved in this cascade transformation comprises of the nucleophilic attack of alkyne on the aldehyde, followed by a Friedel-Crafts type reaction (*Scheme 1.2.1.1b*.).[20]



Scheme 1.2.1.1b. *$BF_3{\cdot}OEt_2$ mediated synthesis of tetrahydroindenopyridines.*

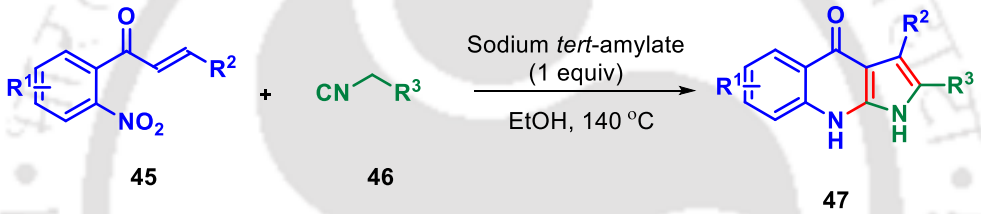
Wang and co-workers also demonstrated another $BF_3{\cdot}OEt_2$-mediated protocol for the synthesis of spiro[indene-benzosultam]s **44** from cascade reaction of propargyl alcohols **43**. The reaction proceeded in a cascade sequence of events, which involves an intramolecular trapping of allene carbocation with sulfonamide, followed by a sequential electrophilic cyclization, and intramolecular Friedel-Crafts alkylation. Moreover, the corresponding *iodo*- or *bromo*-substituted spiro[indene-benzosultam]s can also be obtained with reasonable yields in the presence of NIS or NBS (*Scheme 1.2.1.1c*.).[21]



R^1= aryl, Me; R^2= H, Me, OMe, Cl
R^3= H, Me, Et, 4-MeC_6H_5, Bn; X= Br, I

Scheme 1.2.1.1c. *BF_3·OEt_2 mediated intramolecular synthesis of spiro[indene-benzosultam]s.*

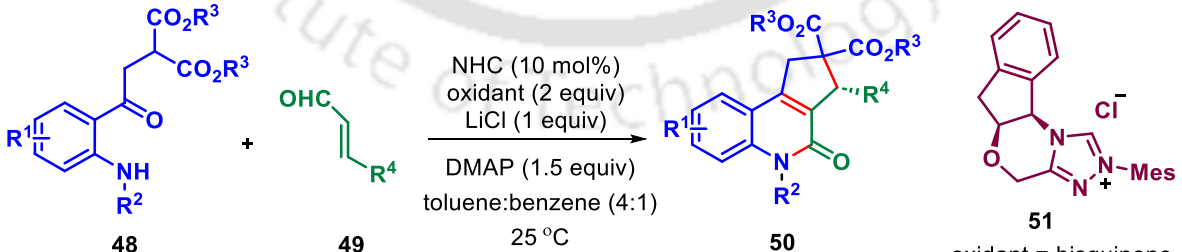
Xu's group described a transition-metal free cascade approach for the efficient synthesis of pyrrolo[2,3-*b*]quinolone derivatives **47** using *ortho*-nitrochalcones **45** with activated methylene isocyanides **46**. This base promoted one-pot protocol proceeds *via* a [3+2] cycloaddition to *in situ* generate the dihydropyrroline moiety and subsequent Cadogan-type reductive cyclization reaction to form the tricyclic framework (*Scheme 1.2.1.1d.*).[22]



R^1= H, Cl, dioxolo; R^2= aryl, alkyl
R^3= CO_2Et, CO_2Me, $CO_2{}^tBu$, 4-$CO_2MeC_6H_4$, 4-CNC_6H_4

Scheme 1.2.1.1d. *Base promoted synthesis of pyrrolo[2,3-b]quinolones.*

Biju's group accomplished a chemo- and enantio-selective synthesis of tricyclic oxoquinolines **50** by reacting enals **49** with malonates bearing a 2-aminophenyl group **48**. The asymmetric synthesis involves an NHC catalyst **51** and follows a domino quadrapole cascade sequence of Michael-aldol-lactamization-dehydration reactions (*Scheme 1.2.1.1e.*).[23]

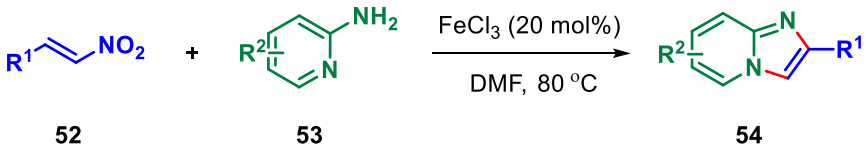


R^1= H, Cl, dioxolo; R^2= Ts, Ms, Ns
R^3=Me, Et, ^iPr, Bn; R^4= aryl, alkyl

Scheme 1.2.1.1e. *NHC-catalyzed enantioselective synthesis of tricyclic oxoquinolines.*

Hajra and co-workers also demonstrated a one-pot cascade reaction involving nitroolefins **52** and 2-aminopyridines **53** for synthesizing imidazo[1,2-*a*]pyridine derivatives **54**. The Fe(III)-

catalyzed reaction proceeds through sequential cascade of Michael addition, intramolecular cyclization and *in situ* denitration (*Scheme 1.2.1.1f.*).[24]

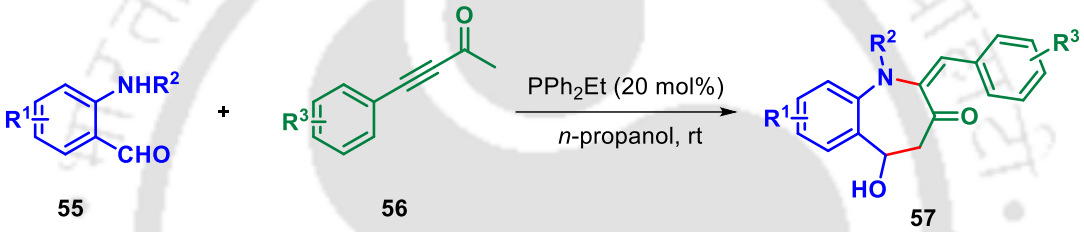


52 **53** **54**

R^1= aryl, alkyl; R^2= H, Cl, Br, Me

Scheme 1.2.1.1f. *$FeCl_3$ catalyzed synthesis of imidazo[1,2-a]pyridines.*

Kwon and co-workers reported phosphine-catalyzed intermolecular cyclization between 2-sulfonamidobenzaldehyes **55** and ynones **56** to access substituted benzo[*b*]azepin-3-ones **57** under mild conditions. The key steps involved in this cascade approach includes phosphine-catalyzed *α*-umpolung addition, followed by an aldol reaction to form the products with exclusive *E*-selectivity (*Scheme 1.2.1.1g.*).[25]

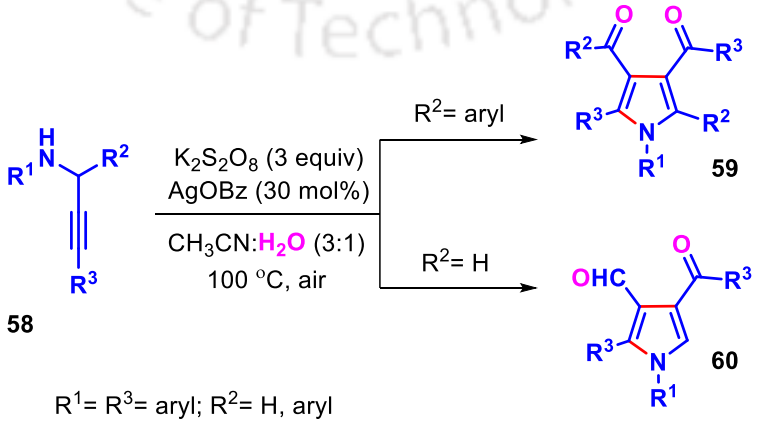


55 **56** **57**

R^1= H, Me,OMe, Cl, I, Br;R^2= Ts, SO_2Ph, $SO_2(4\text{-}MeOC_6H_4)$, $SO_2(4\text{-}BrC_6H_4)$
R^3= H, OMe, Me, Cl

Scheme 1.2.1.1g. *PPh_2Et-catalyzed intermolecular synthesis of benzo[b]azepin-3-ones.*

Saikia's group investigated a radical mediated protocol for oxidative *N*-centered radical initiated self-dimerization of *N*-propargylamines **58** to access tetra- and penta-substituted pyrroles (**60** and **59**). The mechanism depicts *in situ* generation of imine from *N*-propargylamine *via* SET mechanism followed by intermolecular coupling with another molecule of *N*-propargylamine to give the highly functionalized products (*Scheme 1.2.1.1h.*).[26]



58 **59** **60**

R^1= R^3= aryl; R^2= H, aryl

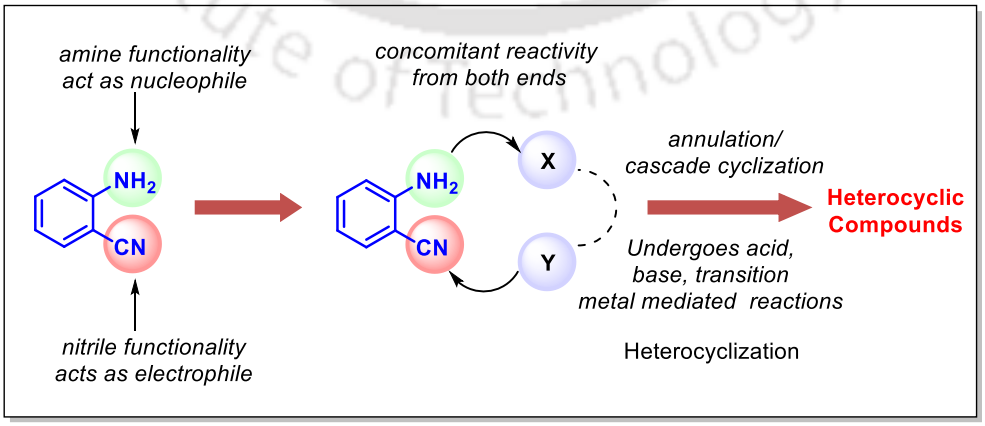
Scheme 1.2.1.1h. *$K_2S_2O_8$ mediated synthesis of multi-substituted pyrroles.*

1.3. An Overview of 2-Aminobenzonitrile as Synthetic Precursor

Naturally occurring or synthetically produced fused nitrogen containing heterocycles are ubiquitous frameworks in many organic materials, pharmaceuticals and important ligands in catalysis. Therefore, there is a strong demand for the development of rapid, efficient, and versatile methods for their synthesis. Thus, new emerging strategies for the synthesis of nitrogen heterocycles using readily available starting precursor with less number of steps, environment-friendly, and accommodating a broad range of substrate scope are still of great interest. In this context, assembling small molecules *via* a tandem reaction to synthesize nitrogen-containing heterocycles has received intensive attention in the past few decades. One such interesting precursor molecule is 2-aminobenzonitrile also synonymously known as 2-cyanoaniline or anthranilonitrile. It features both an amino group and a nitrile group, embedded vicinally to a benzene ring and can participate in a variety of chemical transformations.

1.3.1. Utility of 2-Aminobenzonitrile in Organic Transformations

The utility of 2-aminobenzonitriles is significant in organic synthesis due to their accessibility and versatile reactivity to undergo an organic transformation into a range of diverse functional groups. 2-Aminobenzonitrile is considered as a building block due to the unique positioning of an amine group at the *ortho*-position of a nitrile functionality that enhances the reactivity of the substrate for efficient tandem cyclization and annulations. Conventionally, it behaves as a 1,4-dipolarophile and undergoes intermolecular cyclization with a coupling partner by concomitant attack as a nucleophile from the amine functionality as well as electrophilic attack on the unsaturated nitrile motif. Thus, utilizing 2-aminobenzonitrile as a synthetic precursor for heterocyclization reaction is a well-known concept (*Scheme 1.3.1.1.*). It can be used to synthesize various nitrogen-containing heterocycles such as quinazolines, pyrimidines, or even



Scheme 1.3.1.1. *General reactivity of 2-aminobenzonitrile.*

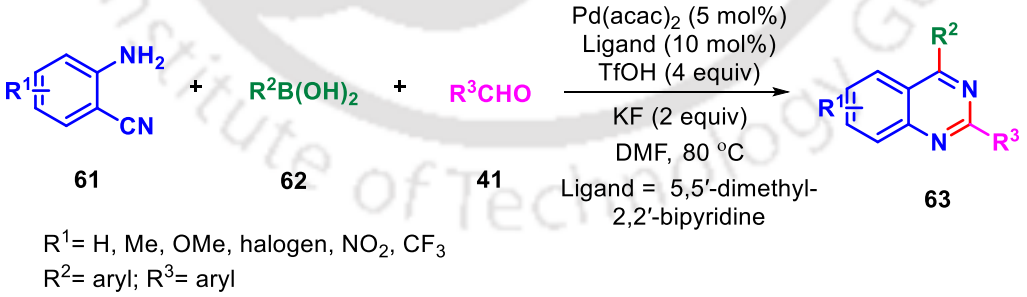
fused bicyclic systems and their derivatives, depending on the reaction conditions and additional reagents used. In this regard, several efficient methodologies have been developed by using tandem multi-component acid, base and transition-metal promoted cascade reactions with a coupling partner to generate highly functionalized benzannulated *N*-heterocycles.

The discussion in the following section of this chapter will be directed to cover various synthetic pathways for benzannulated *N*-heterocycles with 2-aminobenzonitrile as the initial architectonic precursor. Moreover, classification of these reactions is done on the basis of reagents and catalysts used and the examples are enlisted below.

1.3.1.1. Metal Catalyzed Cyclizations

Transition metals are effectively used to initiate various cascade reactions. Besides the nucleophilic amino group, the nitrile functionality of 2-aminobenzonitrile can interact with the metal in two modes i.e. with the π-electron system of the triple bond of the nitrile and with the lone pair of the nitrogen atom.[27] These interactions trigger the catalytic cycle by increasing the possibility of nucleophilic attack on the nitrile carbon atom ultimately leading to product formation.

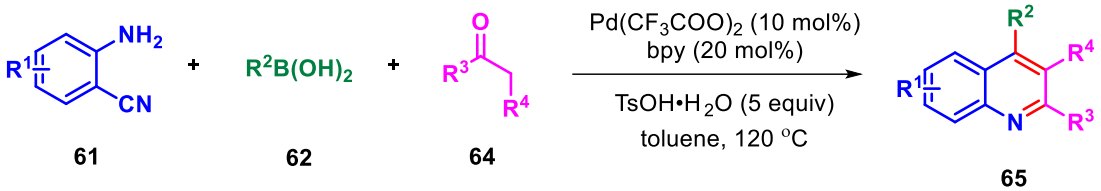
Chen and his group disclosed an efficient strategy for one-pot assembly of diverse quinazolines **63** from 2-aminobenzonitrile **61**, aldehyde **42**, and arylboronic acid **62**. The Pd(II)-catalyzed protocol follows a catalytic cycle with carbopalladation of the cyano group to deliver the products in moderate to good yields (*Scheme 1.3.1.1.1a.*).[28] The method is remarkably chemoselective even with bromo and iodo group substitutions, thus affording versatility for further synthetic manipulations.



Scheme 1.3.1.1.1a. *Pd-catalyzed one-pot synthesis of quinazolines.*

The same group also developed a convenient synthetic route for poly-substituted quinolines **65** by palladium catalysis under acidic conditions from 2-aminobenzonitriles **61**, arylboronic acids **62** and ketones **64**. This operationally simple transformation proceeds through a cascade sequence involving Pd-catalyzed aryl addition to the cyano group, hydrolysis, and Friedländer-

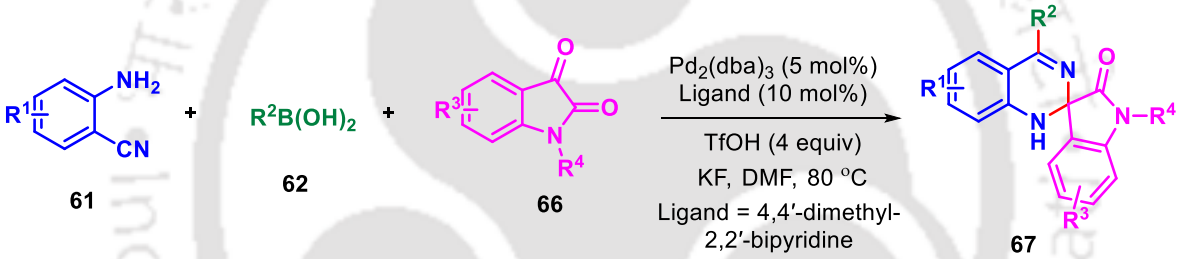
type cyclization to access functionalized quinolines in moderate to good yields with high functional group tolerance (*Scheme 1.3.1.1.1b.*).[29]



R^1= H, Me, OMe, halogen, NO_2, CF_3; R^2= aryl
R^3= aryl, alkyl; R^4= aryl, alkyl, Cl, Br

Scheme 1.3.1.1.1b. *Pd-catalyzed one-pot synthesis of quinolines.*

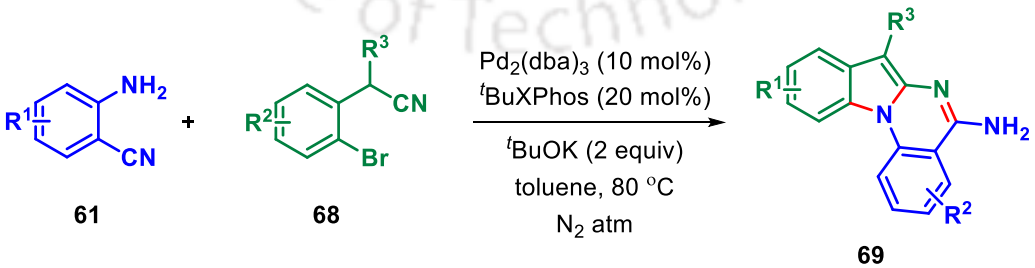
Gogoi and co-workers reported a synthetic approach for the synthesis of functionalized spiro(indoline-3,2′-quinazolin)-2-ones **67** by the reaction of 2-aminobenzonitriles **61**, arylboronic acids **62** and isatins **66**. This multicomponent cascade strategy catalyzed by Pd(II) in presence of a ligand system utilizes readily available starting materials to give the spiro *N*-heterocycles in good yields (*Scheme 1.3.1.1.1c.*).[30]



R^1= H, Me; R^2= aryl; R^3= H, Me, OMe, halogen, NO_2
R^4= H, Me, Ph, Bn

Scheme 1.3.1.1.1c. *Pd-catalyzed one-pot synthesis of spirooxindoles.*

An one-pot domino synthesis of 5-amino-indolo[1,2-*a*]quinazoline derivatives **69** from easily available 2-(2-bromophenyl)acetonitriles **68** and 2-aminobenzonitriles **61** has been described by Yang and his group. This Pd-catalyzed protocol involves a Buchwald–Hartwig type coupling and a base-promoted intramolecular nucleophilic reaction to deliver the indole-

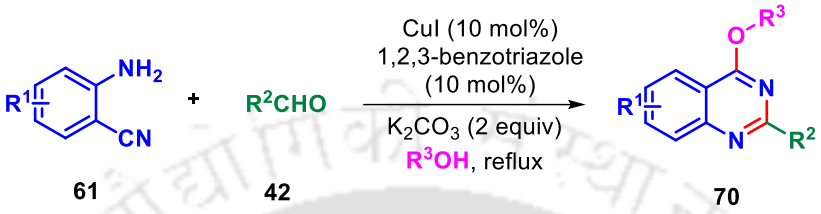


R^1= H, Me, F, CF_3
R^2= H, F, OMe; R^3= CN, CO_2Et

Scheme 1.3.1.1.1d. *Pd-catalyzed cyclization of 2-(2-bromophenyl)acetonitriles and 2-aminobenzonitriles.*

containing heterocycles with excellent yields (*Scheme 1.3.1.1.1d*.).[31]

Ahmed and co-workers developed an approach to *O*-protected-4-hydroxyquinazolines **70** by the reaction of 2-aminobenzonitriles **61** with various aldehydes **42**. The key steps of this copper-benzotriazole (Cu-BtH)-catalyzed transformation are the intramolecular electrophilic cyclization of *in situ* generated *N*-arylimine followed by oxidative coupling with alcohol (*Scheme 1.3.1.1.1e*).[32]

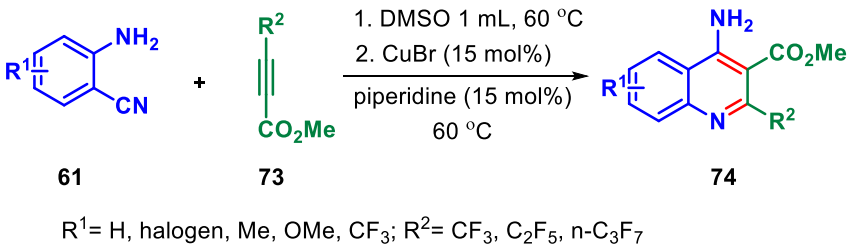


Scheme 1.3.1.1.1e. *(Cu-BtH)-catalyzed synthesis of 4-hydroxyquinazolines.*

A direct oxidative synthesis of quinazolinones **72** has been demonstrated by Li and co-workers from 2-aminobenzonitrile **61** and readily available benzyl alcohols **71**. This copper-catalyzed strategy exhibits a broad substrate scope and a variety of quinazolinones are obtained in moderate to excellent yields with economically and environmentally friendly air as the sole oxidant (*Scheme 1.3.1.1.1f*.).[33]

Scheme 1.3.1.1.1f. *Cu-catalyzed synthesis of quinazolinones.*

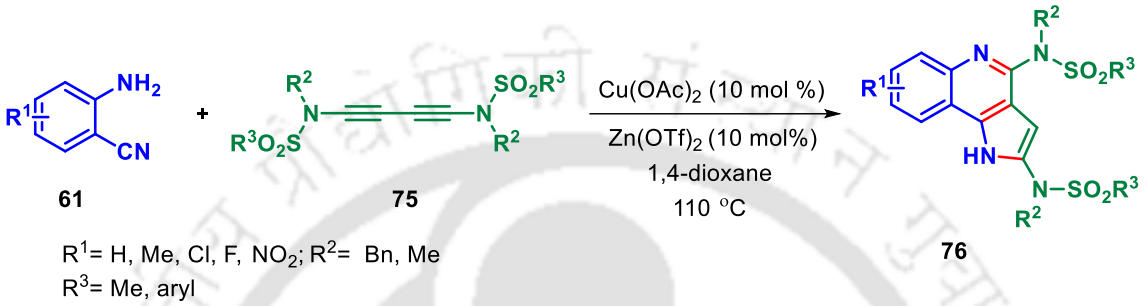
A mild and efficient cyclization of 2-aminobenzonitriles **61** and methyl perfluoroalk-2-ynoates **73** has been reported by Cao and co-workers leading to 2-perfluoroalkylated 4-aminoquinolines **74**. This one-pot coupling protocol utilizes inexpensive copper(I) bromide



Scheme 1.3.1.1.1g. *CuBr-catalyzed synthesis of 2-perfluoroalkylated 4-aminoquinolines.*

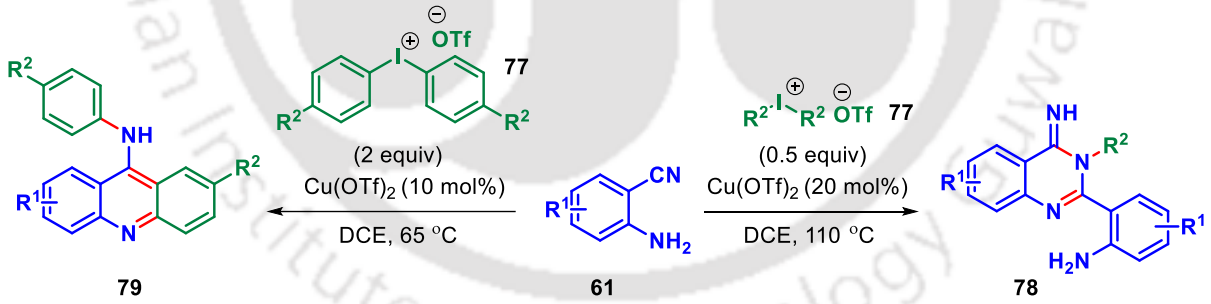
and an organic base in catalytic amount to deliver the perfluoroalkylated quinolones in moderate to excellent yields (*Scheme 1.3.1.1.1g.*).[34]

Ghosh and his group also demonstrated a copper/zinc catalyzed synergetic protocol to synthesize 1*H*-pyrrolo[3,2-*c*]quinoline-2,4-diamine derivatives **76** from 2-aminobenzonitriles **61** and ynamide-derived buta-1,3-diynes **75**. This cascade strategy follows a double cyclization pathway to deliver the multi-fused *N*-heterocycles in moderate to good yields (*Scheme 1.3.1.1.1h.*).[35]



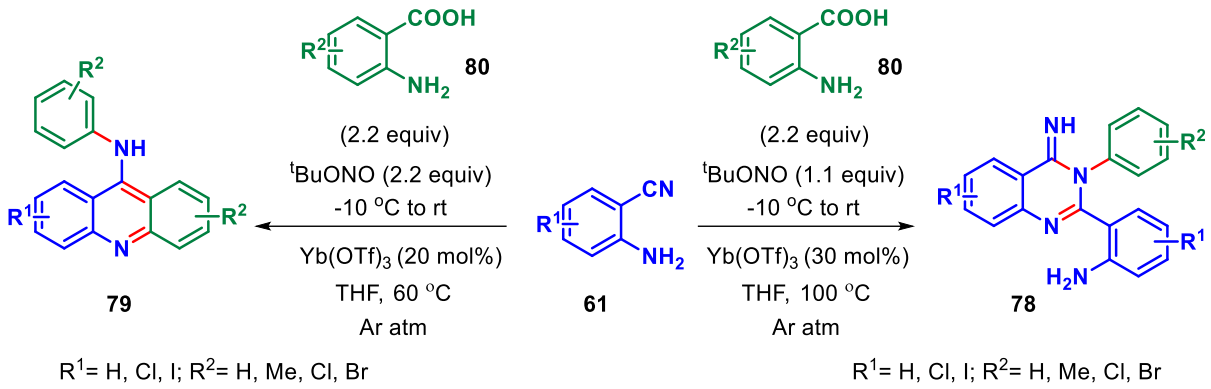
Scheme 1.3.1.1.1h. *Synergetic Cu/Zn catalyzed synthesis of 1H-pyrrolo[3,2-c]quinolines.*

Chen and co-workers reported the synthesis of highly substituted quinazolin-4(3*H*)-imines **78** and acridines **79** by assembling *o*-cyanoanilines **61** and diaryliodonium salts **77**. This copper-catalyzed two component protocol selectively follows two distinct tandem cyclization modes. The method can be tuned to give both the products with good yields under two different conditions (*Scheme 1.3.1.1.1i.*).[36]



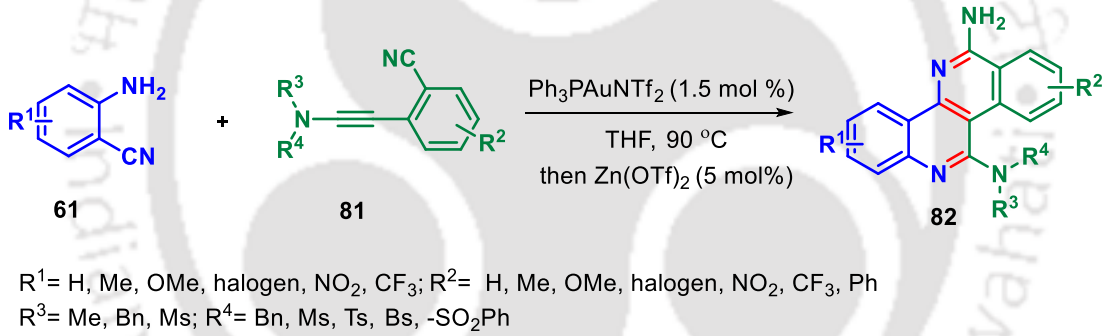
Scheme 1.3.1.1.1i. *Cu-catalyzed synthesis of quinazolin-4(3H)-imines and acridines.*

A similar strategic route to synthesize substituted quinazolin-4(3*H*)-imines **78** and acridines **79** has been reported by Das and co-workers from 2-aminobenzotriles **61** and anthranilic acid derivatives **80**. The reaction is catalyzed by ytterbium(III) triflate, where 2-aminobenzonitrile acts as the 1,4-dipolarophilic species and anthranilic acid as the benzyne precursor leading to selective formation of two different *N*-heterocycles under two set of conditions (*Scheme 1.3.1.1.1j.*).[37]



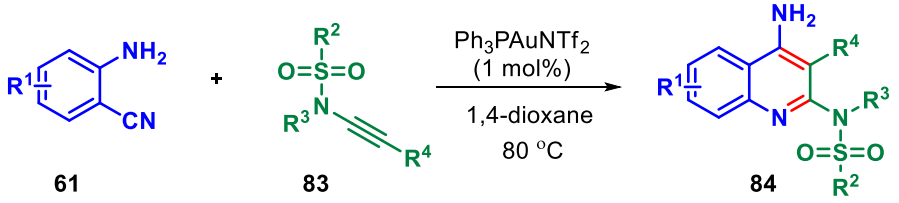
Scheme 1.3.1.1.1j. *Yb-catalyzed synthesis of quinazolin-4(3H)-imines and acridines.*

A dual catalytic cascade strategy for the synthesis of amine-substituted diaryl[*c*,*h*][1,6]naphthyridines **82** from amine-substituted 2-alkynylarylnitriles **81** and 2-aminobenzonitriles **61** has been demonstrated by Ghosh and his group. They employed bimetallic catalytic system comprising of gold(I) and zinc(II) for this two-fold annulation to access tetracyclic heteroaromatic products in good to excellent yields and with high functional group tolerance (*Scheme 1.3.1.1.1k.*).[38]



Scheme 1.3.1.1.1k. *Au and Zn-catalyzed annulation of amine-substituted 2-alkynylarylnitriles and 2-aminobenzonitriles.*

Sahoo's group also devised an efficient Au(I)-catalyzed strategic route featuring direct coupling of ynamides **83** and 2-aminobenzonitriles **61** to access 2,4-diamino-substituted quinolines **84** *via* nitrile activation. This transformation is explicitly regioselective and highlights the *syn*-1,2-difunctionalization of ynamide through the intramolecular 6-*exo*-dig



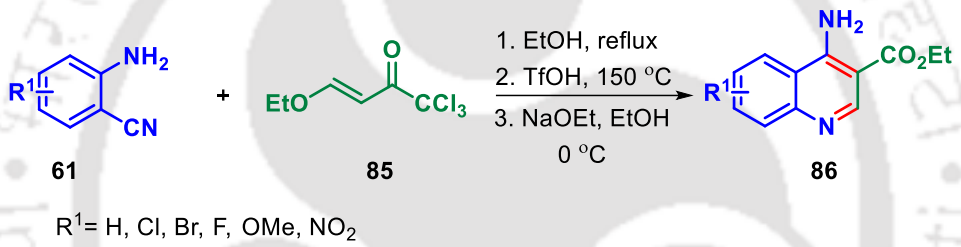
Scheme 1.3.1.1.1l. *Au catalyzed coupling of ynamides and 2-aminobenzonitriles.*

cyclization of ketene aminal to the σ-coordinated nitrile moiety by Au(I) (*Scheme 1.3.1.1.1l.*).[39]

1.3.1.2. Metal-free Cyclizations

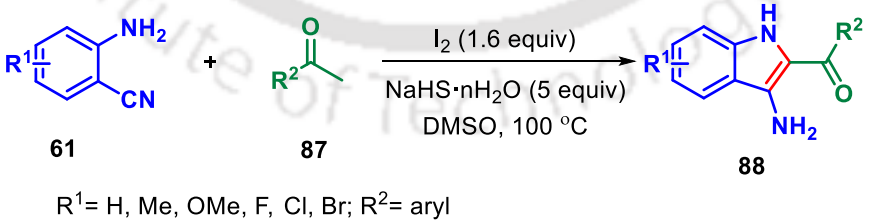
Metal-free reactions have garnered considerable attention in the past two decades. They are recognized as an indispensable tool in organic synthesis, as it is not only cost-effective but also environmentally friendly by eliminating expensive metal complexes and toxic metal contamination. 2-Aminobenzonitrile behaves as a dipolarophile in these reactions with a nucleophilic amine moiety and a weakly coordinating electrophilic nitrile functionality.

Popowycz and co-workers developed a three step synthesis of 2-unsubstituted 4-aminoquinolines **86** starting from substituted 2-aminobenzonitriles **61** and 1,1,1-trichloro-4-ethoxybut-3-enone **85**. The key steps involved in this transformation includes condensation and then cyclization in trifluoromethanesulfonic acid which provided unstable intermediate. This intermediate when treated with NaOEt in ethanol, leads to the formation of the expected esters (*Scheme 1.3.1.2.1a.*).[40]



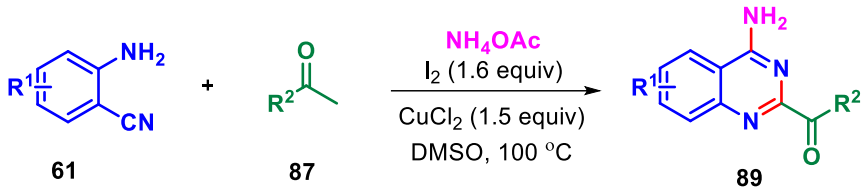
Scheme 1.3.1.2.1a. *TfOH mediated synthesis of 4-aminoquinolines.*

Wu's group reported an efficient method for constructing 2-acyl-3-aminoindoles **88** from methyl ketones **87** and 2-aminobenzonitriles **61** under ambient conditions. The method utilizes sulphur salt $NaHS{\cdot}nH_2O$ as an umpolung reagent and iodine for this transformation where the key step is Eschenmoser sulfide contraction reaction (*Scheme 1.3.1.2.1b.*).[41]



Scheme 1.3.1.2.1b. *Umpolung strategy for synthesis of 2-acyl-3-aminoindoles.*

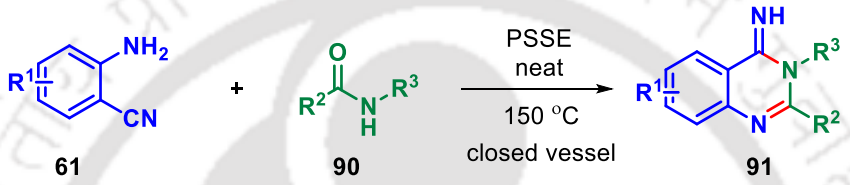
A formal cascade [4+1+1] cyclization for the synthesis of 2-acyl-4-aminoquinazolines **89** has also been reported by Wu's group employing 2-aminobenzonitrile **61**, methyl ketone **87** and ammonium acetate as N source. This operationally simple reaction is co-promoted by iodine and cupric chloride under mild conditions and proceeds *via* $C(sp^3)$–H bond deamination (*Scheme 1.3.1.2.1c.*).[42]



R^1= H, Me, OMe, F, Cl, Br; R^2= aryl

Scheme 1.3.1.2.1c. *I_2/$CuCl_2$-copromoted synthesis of 2-acyl-4-aminoquinazolines.*

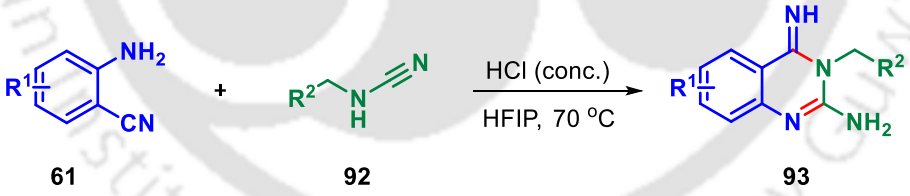
Díaz and co-workers disclosed a novel method for the synthesis of quinazolin-4(3*H*)-imines **91** from 2-aminobenzonitriles **61** and secondary amides **90**. This operationally simple protocol is promoted by trimethylsilyl polyphosphate (PPSE) and allows for the synthesis of N^3-aryl and N^3-alkyl substituted heterocycles affording high yields (*Scheme 1.3.1.2.1d.*).[43]



R^1= H; R^2=R^3= aryl, alkyl

Scheme 1.3.1.2.1d. *PSSE promoted synthesis of quinazolin-4(3H)-imines.*

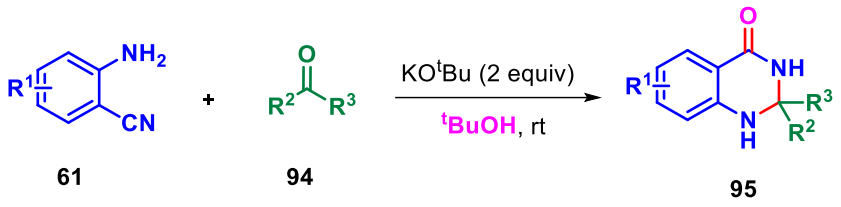
Wu's group reported the synthesis 2-amino-4-iminoquinazoline derivatives **93** by the reaction of 2-aminobenzonitriles **61** with *N*-benzyl cyanamides **92**. A wide range of substrates is tolerated in this acid mediated [4+2] annulation in HFIP giving high yields and good functional group tolerance (*Scheme 1.3.1.2.1e.*).[44]



R^1= H, Me, Cl; R^2= aryl

Scheme 1.3.1.2.1e. *[4+2] annulation of 2-aminobenzonitriles with N-benzyl cyanamides.*

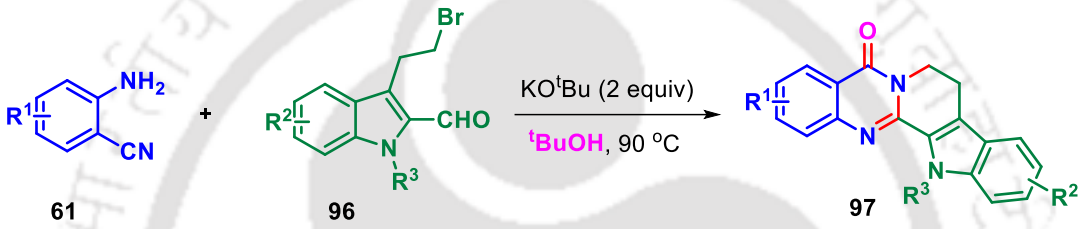
A transition metal-free approach for the synthesis of heterocyclic dihydroquinazolinones **95** has been developed by Dash and co-workers involving the reaction of 2-aminobenzonitriles **61** with aldehydes or ketones **94**. This base mediated method under mild conditions utilizes potassium *tert*-butoxide in *tert*-butanol and follows a radical pathway with a broad substrate scope including a range of aliphatic and aromatic aldehydes and ketones (*Scheme 1.3.1.2.1f.*).[45]



R^1= H, Me; R^2= aryl, alkyl; R^3= aryl, alkyl, H

Scheme 1.3.1.2.1f. *KO^{t}Bu promoted synthesis of dihydroquinazolinones.*

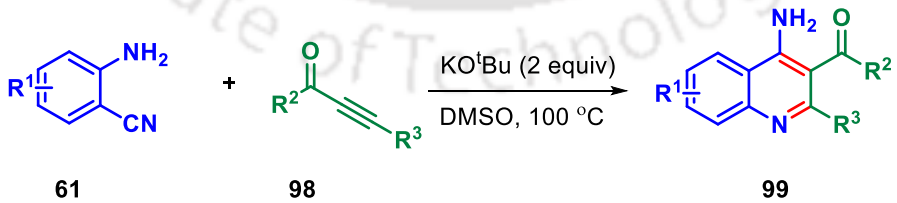
The protocol was later employed for the synthesis of biologically significant analogues of rutaecarpine alkaloid **97** by the same group by replacing aldehyde with indole-2-carbaldehydes **96**. The salient feature of this potassium *tert*-butoxide mediated approach is the promotion of a sequence initiated by radical-driven quinazolinone formation followed by a cyclization process to give the pentacyclic core (*Scheme 1.3.1.2.1g.*).[46]



R^1= H, halogen, Me, OMe, ^{t}Bu; R^2= H, F, Me, OMe
R^3= Me, Et, allyl, Bn

Scheme 1.3.1.2.1g. *KO^{t}Bu promoted synthesis of rutaecarpine alkaloid analogues.*

Verma and his group also developed a base mediated one pot annulation of ynones **98** with 2-aminobenzonitriles **61** to give substituted 2,3–disubstituted 4-aminoquinolines **99**. The reaction was initiated through sequential aza-Michael addition/intramolecular annulation and has high atom economy with broad substrate scope furnishing the products in good to excellent yields (*Scheme 1.3.1.2.1h.*).[47] Additionally, *N*-arylquinolones were obtained when *o*-haloarylynones were used as substrate.

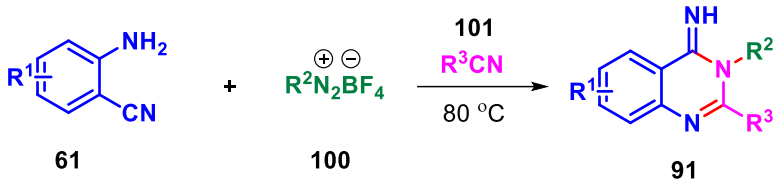


R^1= H, Cl, F, Br, Me, OMe; R^2= aryl ; R^3= aryl, alkyl

Scheme 1.3.1.2.1h. *KO^{t}Bu promoted annulation of ynones and 2-aminobenzonitriles.*

Ramanathan and his group demonstrated a transition metal-free cascade approach for the synthesis of multisubstituted quinazolin-4(3*H*)-imines **91** by assembling aryldiazonium salts **100**, nitriles **101**, and 2-cyanoanilines **61** in a one-pot reaction. This strategy proceeds *via in*

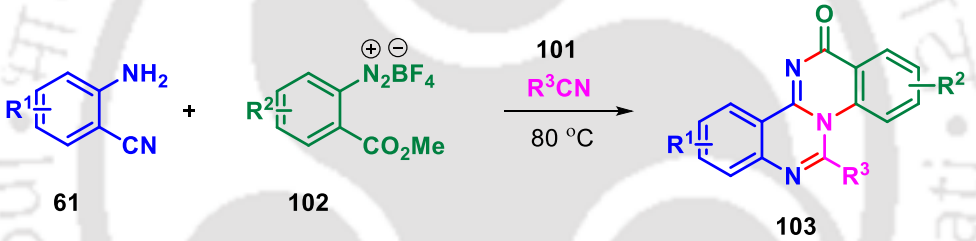
situ formation of reactive N-arylnitrilium intermediate, which undergoes further amination and tandem cyclization with consecutive formation of N−C bonds to afford the heterocycles (*Scheme 1.3.1.2.1i*.).[48]



R^1= H, Cl, Br, 2-MeC_6H_4; R^2= aryl

Scheme 1.3.1.2.1i. *Metal-free synthesis of multisubstituted quinazolin-4(3H)-imines.*

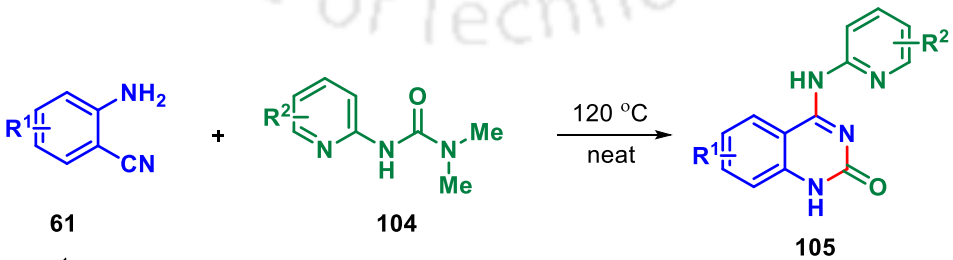
The same group later extended the protocol for the synthesis of tetracyclic quinazolino[3,4-*a*]-quinazolin-13-ones **103** by reacting *o*-(methoxycarbonyl)benzenediazonium salts **102**, nitriles **101**, and 2-aminobenzonitriles **61**. The reaction follows a similar mechanistic pathway of *in situ* generation of reactive N-arylnitrilium ion, followed by further amination, tandem cyclization and amidation to deliver the desired polycyclic scaffolds (*Scheme 1.3.1.2.1j*.).[49]



R^1= H, Cl, Br, I, 2-MeC_6H_4, α-naphthyl;
R^2= Me, Br, I, CO_2CH_2Ph; R^3= alkyl, aryl

Scheme 1.3.1.2.1j. *Metal-free synthesis of multisubstituted quinazolinoquinazolinones.*

Boyarskiy and his co-workers demonstrated a convenient protocol to synthesize *N*-(2-pyridyl)-substituted 4-(amino)quinazolin-2(1*H*)-ones **105** by reacting *N*,*N*-dimethyl-*N*′-pyridylureas **104** with 2-aminobenzonitriles **61**. The method, effective in neat conditions, utilizes *N*,*N*-dimethyl-*N*′-pyridylurea as masked isocyanate under thermal conditions following

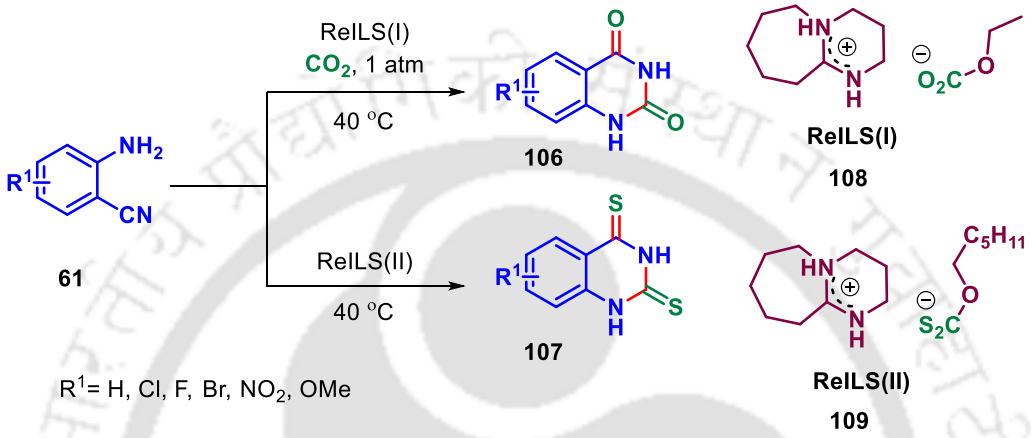


R^1= H, F, Cl, Br, Me, OMe
R^2= H, Cl, CO_2Me, CN, NO_2, Ph, Bn, Me, OMe

Scheme 1.3.1.2.1j. *Annulation of 2-aminobenzonitriles with N′-(pyridin-2-yl)-N,N-dimethyl ureas.*

a Dimroth rearrangement to furnish the products (*Scheme 1.3.1.2.1k.*).[50]

A novel green method of preparing quinazoline derivatives from 2-aminobenzonitriles **60** has been discovered by Zheng and his group in reusable, room-temperature, reversible ionic liquids (ReILs). This green protocol is utilized to capture CO_2 and CS_2 in the ReILs I and II (**108** and **109**) which acted as a catalyst and solvent at the same time to give quinazoline-2,4(1*H*,3*H*)-diones **106** and quinazoline-2,4(1*H*,3*H*)-dithiones **107** respectively under mild conditions and with high yields (*Scheme 1.3.1.2.1l.*).[51]



Scheme 1.3.1.2.1l. *Synthesis of quinazoline derivatives in ReILs by capturing CO_2 and CS_2.*

In summary, the above mentioned literatures give an overview on the strategic use of cascade reactions for the synthesis of *N*-heterocycles. It emphasizes on the synthetic reactivity and utility of 2-aminobenzonitrile as a starting precursor for various benzannulated *N*-heterocycles under different reaction conditions. It also reflects the idea how 2-aminobenzonitrile can be utilized as 1,4-dipolarophilic species that can engage in various cascade approaches.

1.4. Objective of the Present Work

The primary objective of this research is to explore and develop new synthetic approaches for complex heterocyclic frameworks through the strategic use of cascade reactions. This study aspires to advance the synthesis of privileged heterocyclic frameworks exhibiting a diverse array of bioactivities, such as quinolines, quinazolines, benzazepines, and their various derivatives, by assembling small molecules *via* a cascade approach. The research specifically focuses on designing methodologies for constructing benzannulated *N*-heterocycles from 2-aminobenzonitrile and different coupling partners, such as donor–acceptor cyclopropanes, electron-deficient alkenes, activated alkynes and carbodiimides using Lewis acids. The

motivation of this work is about the potential to innovate and contribute to the field of drug discovery and material sciences.

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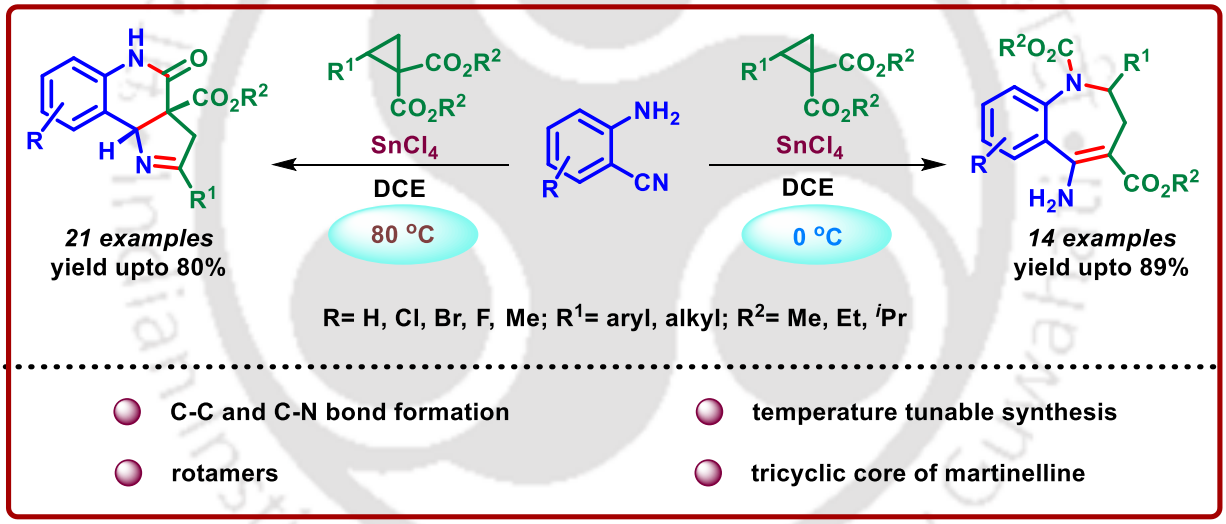
CHAPTER 2

Temperature Tunable Synthesis of Tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and Dihydro-1*H*-benzo[*b*]azepines from 2-Aminobenzonitriles and Donor-Acceptor Cyclopropanes

Abstract: This chapter highlights a tunable one pot synthesis of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and dihydro-1*H*-benzo[*b*]azepines from 2-aminobenzonitriles and donor-acceptor cyclopropanes in presence of $SnCl_4$. The reaction proceeds *via* the initial ring opening of cyclopropane ring by 2-aminobenzonitrile followed by nucleophilic attack by amine to give adduct, which after unprecedented rearrangement at two different reaction temperatures provide two sets of structurally diverse nitrogen heterocyclic compounds. This methodology can be used for the synthesis of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones (tricyclic core of martinelline).



2.1. Introduction

Benzannulated heterocycles are core units of various biologically active molecules which display a wide range of pharmaceutical activities. For instance, benzo[*b*]azepine skeleton represents an important class of benzannulated medium-sized seven membered *N*-heterocycles due to its broad bioactivity and presence as core unit in a variety of natural products and pharmaceutically active molecules. Mozavaptan (**a**) is a nonpeptide vasopressin V2 receptor antagonist and used for the treatment of hyponatremia.[1] Evacetrapib (**b**) is a potent cholesteryl ester transfer protein (CETP) inhibitor, which increases HDL and lowers LDL levels, and therefore, modify the risk of cardiovascular disease.[2] On the other hand, 3,5-bis(trifluoromethyl)benzyl protected 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (**c**) is used for the treatment of dyslipidemia.[3]
Similarly, hexahydropyrrolo[3,2-*c*]-quinolinones are privileged scaffold endowed with diverse and potent pharmacological activities. For example, guanidine alkaloids martinellic acid (**d**) and martinelline (**e**) isolated from *Martinella iquitosensis* roots, found in Amazonian lowland rainforests, possess antibacterial activity and potent antagonist activity toward bradykinin (BK) B1 and B2 receptors (*Figure 2.1.1.*).[4]

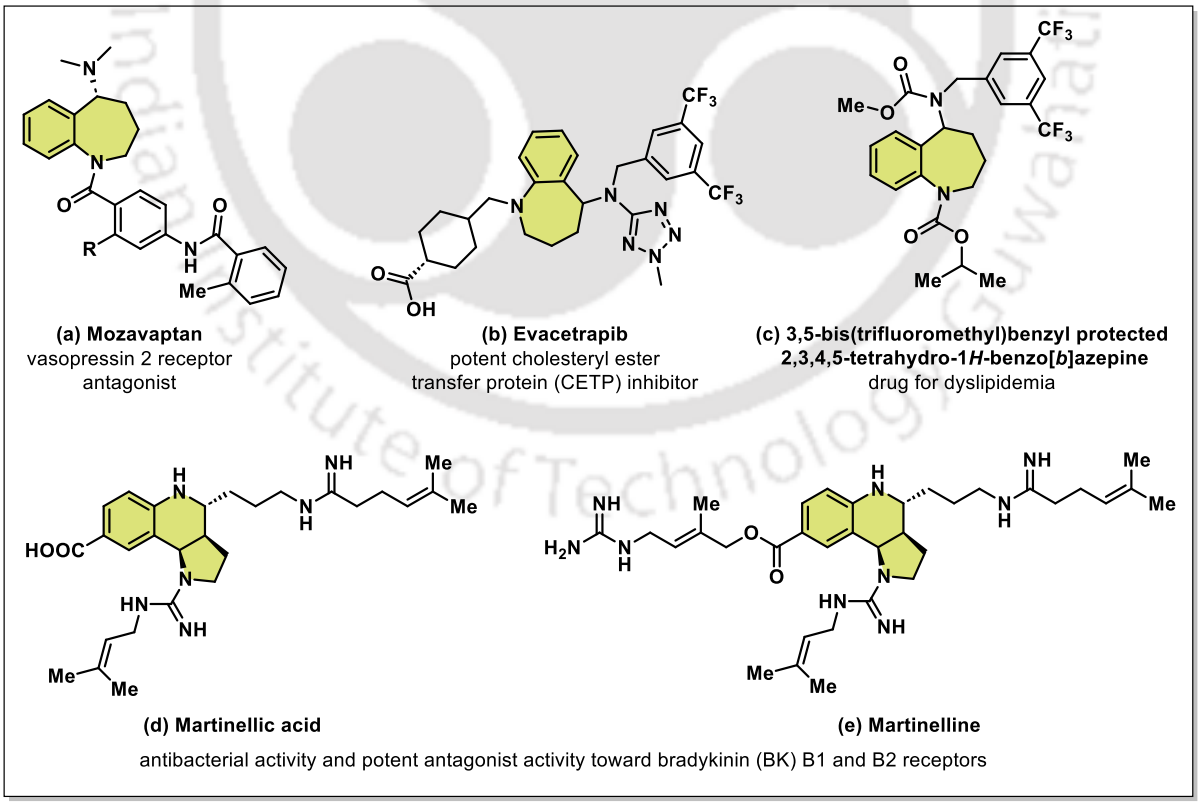


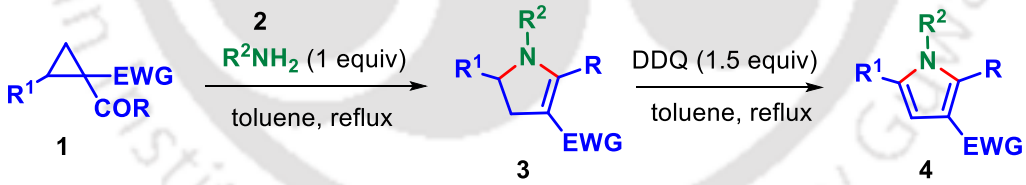
Figure 2.1.1. Some examples of biologically active molecules.

2.2. Literature Survey on Construction of *N*-Heterocycles from Donor–Acceptor Cyclopropanes

Donor–acceptor cyclopropanes (DACs) are known as versatile three-atom carbon-based building blocks in organic synthesis. Over the past two decades, donor–acceptor cyclopropanes are employed as starting precursors in modern organic synthesis due to their ease of synthesis and diverse reactivity under different reaction conditions.[5] The high reactivity of DACs is due to its inherent ring strain along with the additional strain bestowed by push–pull effect of the vicinal donor and acceptor substituents. Thus, the synthetic utility of DACs can be widely exploited by fine tuning the donor and acceptor groups. DACs readily participates in ring opening, rearrangement, annulation and cycloaddition reactions with diverse substrates for the construction of hetero-, and carbocyclic compounds. The ring opening of DACs by Lewis acid and/or nucleophile is one of the important strategies for construction of various complex cyclic and acylic compounds.[5d,6]

2.2.1. *N*-Heterocycles from DACs and Primary Arylamines

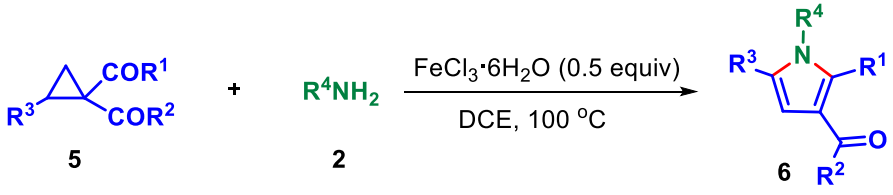
Charette and Wurz developed a protocol for the regiospecific synthesis of highly functionalized dihydropyrroles **3** from doubly activated cyclopropanes **1** and primary amines **2**. This modular synthesis was further extended to yield functionalized pyrroles **4** using DDQ as oxidant (*Scheme 2.2.1.1.*).[7]



R = Me, aryl; R^1 = Ph, aryl;
R^2 = aryl, allyl, Bn; EWG = NO_2, CO_2Me, CN

Scheme 2.2.1.1. *Regiospecific synthesis of functionalized dihydropyrroles.*

Similarly, Zhang and his group also reported an alternative route for the construction of

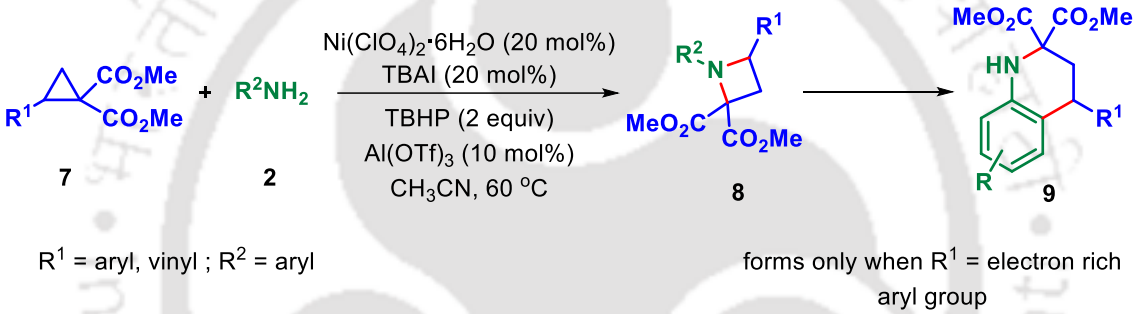


R^1 = Me, Ar; R^2 = NHAr, OMe
R^3 = H, Me; R^4 = Ar, Bn

Scheme 2.2.1.2. *$FeCl_3$ catalyzed synthesis of substituted pyrroles.*

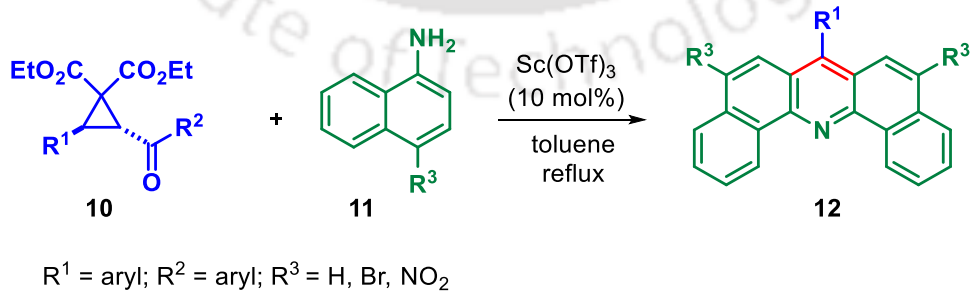
multisubstituted pyrrole derivatives **6** from doubly activated cyclopropanes **5** and anilines **2**. This Fe(III)-catalyzed domino reaction involves sequential ring-opening, cyclization, and dehydrogenation reaction as key steps to give the products in moderate to good yields (*Scheme 2.2.1.2.*).[8]

Luo's group demonstrated a relay catalysis strategy involving [3+1] annulation between cyclopropane 1,1-diester **7** and aromatic amine **2** to synthesize substituted azetidine **8** in presence of Ni(II), tetrabutyl ammonium iodide (TBAI), tertbutylhydroperoxide (TBHP) and $Al(OTf)_3$. The key steps involved includes Lewis acid catalyzed nucleophilic ring opening of cyclopropane 1,1-diester with amine and (hypo)iodite-catalyzed oxidative α-amination of carbonyl compounds. Further, the obtained azetidines rearranged to give tetrahydroquinolines **9** under the catalysis of Lewis acid, when there is an electron-rich aryl group in some cyclopropane 1,1-diesters (*Scheme 2.2.1.3.*).[9]



Scheme 2.2.1.3. *Relay catalysis for synthesis of substituted azetidines.*

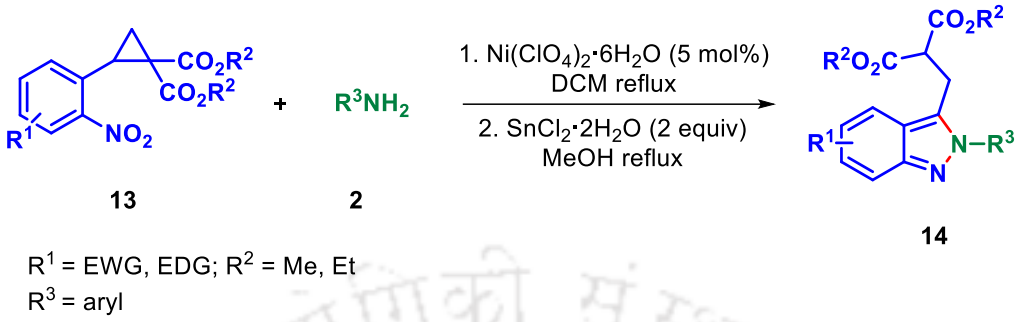
Srinivasan and Thangamani synthesized dibenzo[*c*,*h*]acridines **12** from the reaction of aroyl-substituted donor–acceptor cyclopropanes **10** with two equivalents of 1-naphthylamines **11** in the presence of a catalytic amount of scandium(III)triflate. The key steps of this transformation are the ring opening of cyclopropane, the addition of naphthylamine, fragmentation of resulting intermediate, and subsequent cyclization (*Scheme 2.2.1.4.*).[10]



Scheme 2.2.1.4. *Sc(OTf)₃ catalyzed synthesis of dibenzo[c,h]acridines.*

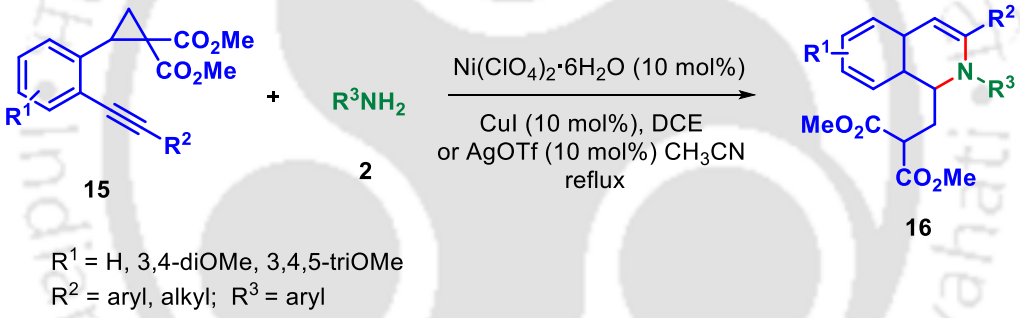
Recently, Saikia and his group also implemented a concise sequential protocol for the synthesis of 3*C*-alkylated active methylene substituted 2*H*-indazole derivatives **14** from *ortho*-nitro aryl substituted donor–acceptor cyclopropanes **13** and primary arylamines **2**. The reaction

is catalyzed by $Ni(ClO_4)_2 \cdot 6H_2O$ for the nucleophilic ring opening reaction (NRO) of cyclopropanes with primary arylamines followed by $SnCl_2 \cdot 2H_2O$ mediated intramolecular reductive cyclization to give the products in moderate to good yields (*Scheme 2.2.1.5.*).[11]



Scheme 2.2.1.5. *Synthesis of 3C-alkylated active methylene substituted 2H-indazoles.*

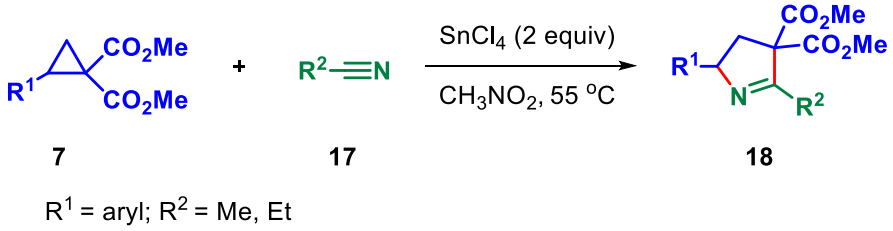
Reddy and his group also disclosed a concise synthetic approach for the synthesis of substituted 1,2-dihydroisoquinolines **16** *via* double nucleophilic addition of primary arylamines **2** to *ortho*-alkynyl aryl substituted donor–acceptor cyclopropanes **15** in the presence of a catalytic $Ni(ClO_4)_2 \cdot 6H_2O$ and CuI/AgOTf system (*Scheme 2.2.1.6.*).[12]



Scheme 2.2.1.6. *Synthesis of 1,2-dihydroisoquinolines via double nucleophilic addition.*

2.2.2. *N*-Heterocycles from DACs and Nitriles

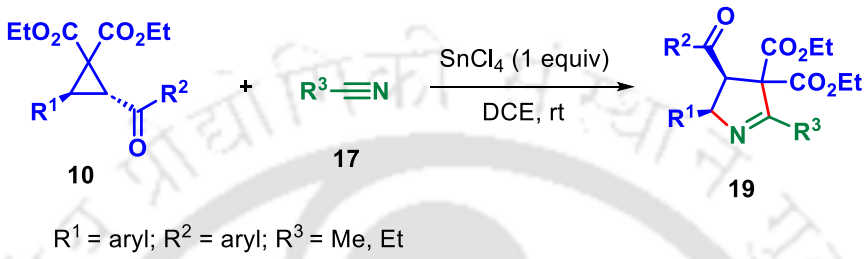
Trushkov and co-workers first reported a formal [3+2] cycloaddition of donor–acceptor cyclopropanes **7** activated by less electron-rich aryl donors but enhanced with germinal ester groups with aceto- and propionitriles **17** under stoichiometric $SnCl_4$ conditions to give highly functionalized 1-pyrrolines **18** in good to excellent yields (*Scheme 2.2.2.1.*).[13] Later, Wang and



Scheme 2.2.2.1. *Synthesis of 1-pyrrolines via formal [3+2] cycloaddition.*

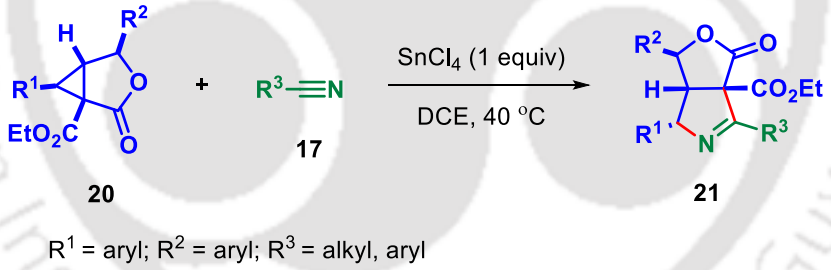
co-workers also reported a catalytic version of this similar [3+2] cycloaddition using triflic acid as the catalyst.[14]

Srinivasan and Sathishkannan also developed a similar but highly diastereoselective synthetic route for functionalized 1-pyrrolines **19** from activated donor–acceptor cyclopropanes **10** and nitriles **17**. The methodology utilizes nitriles as dipolarophiles with *trans*-diastereomers of cyclopropanes in this $SnCl_4$ promoted formal [3+2] cycloaddition to obtain the product as single *cis*-diastereomers in moderate to good yields (*Scheme 2.2.2.2.*).[15]



Scheme 2.2.2.2. *$SnCl_4$ promoted diastereoselective synthesis of functionalized 1-pyrrolines.*

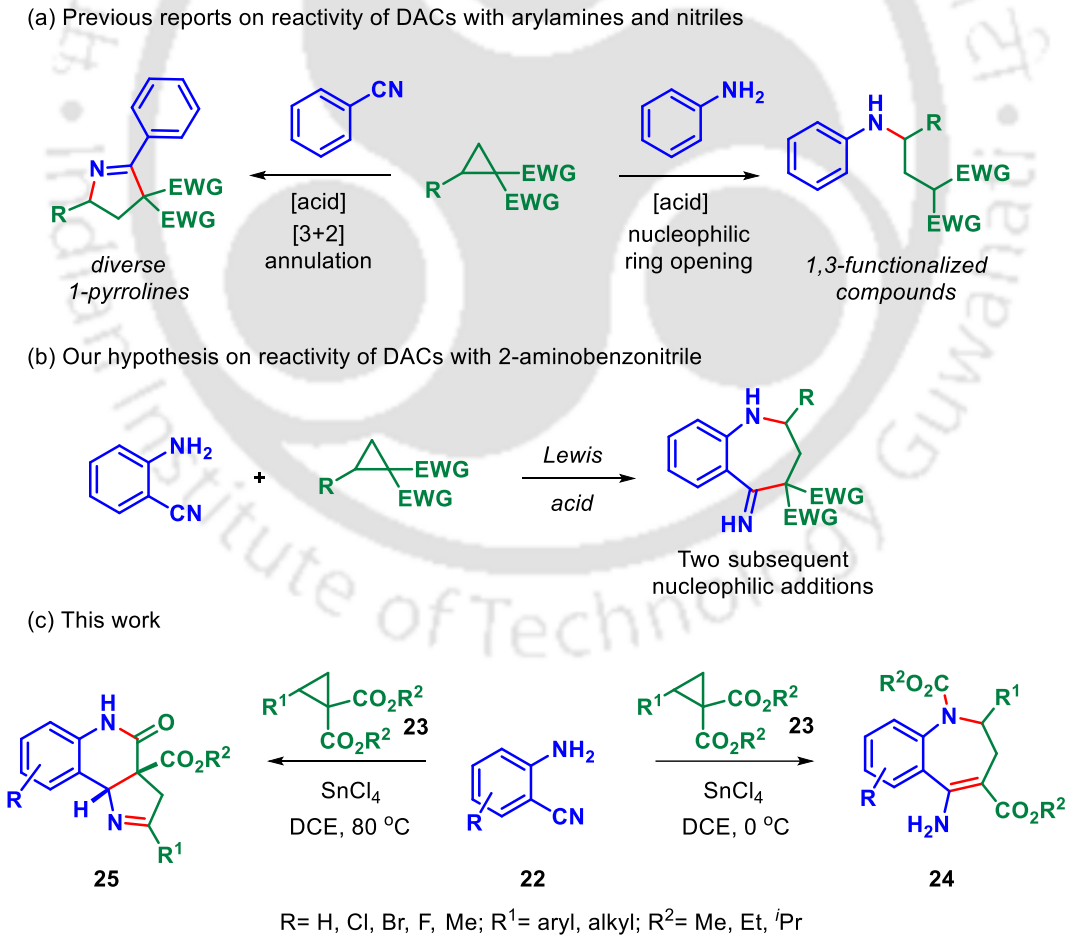
Similarly, Srinivasan and Tamilarasan also explored the [3+2] annulation of γ-butyrolactone-fused donor–acceptor cyclopropanes **20** with nitriles **17** to access γ-butyrolactone-fused 1-pyrrolines **21**. The $SnCl_4$ mediated annulation is highly diastereoselective and the products were obtained as single diastereomers in moderate to good yields (*Scheme 2.2.2.3.*).[16]



Scheme 2.2.2.3. *$SnCl_4$ mediated synthesis of γ-butyrolactone-fused 1-pyrrolines.*

2.3. Present Work

As evident from the literature review, there are several existing reports for the nucleophilic ring opening of donor–acceptor cyclopropanes by primary aryl amines followed by subsequent reactions to form different *N*-heterocycles. Similarly, annulation reaction of donor–acceptor cyclopropanes with nitriles to synthesize *N*-heterocycles is also well established, majorly *via* [3+2] cycloaddition route. However, despite the numerous reports, it may be noted that the reaction of donor–acceptor cyclopropanes with 2-aminobenzonitrile which has vicinal amine and nitrile functionalities to construct heterocycles is not known yet. It was envisioned that 2-aminobenzonitrile will undergo two subsequent nucleophilic additions with donor-acceptor cyclopropanes in the presence of Lewis acid to give the seven membered 5-imino-1,2,3,5-tetrahydro-4*H*-benzo[b]azepine scaffold. But, to our surprise, the proposed reaction provided tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and dihydro-1*H*-benzo[*b*]azepines. Thus, in this chapter, a temperature tunable synthesis of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and



Scheme 2.3.1. *Temperature tunable synthesis of tetrahydro-4H-pyrrolo[3,2-c]quinolin-4-ones and dihydro-1H-benzo[b]azepines.*

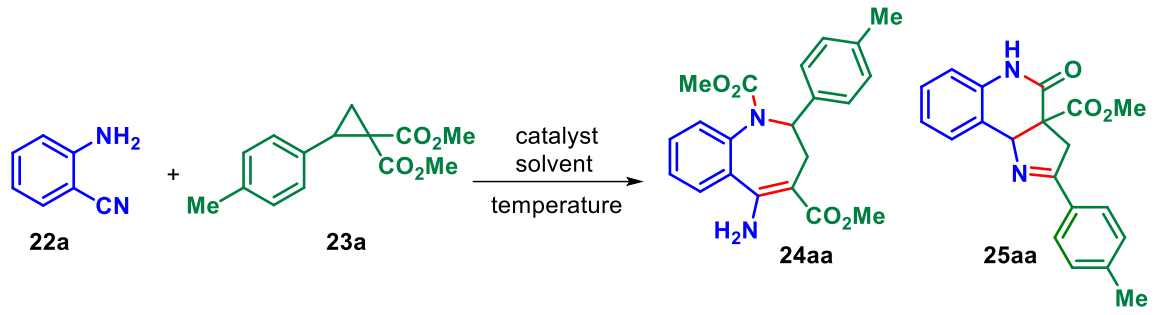
dihydro-1*H*-benzo[*b*]azepines from 2-aminobenzonitriles and donor–acceptor cyclopropane is disclosed. The reaction involves the initial ring opening of cyclopropane ring due to activation by $SnCl_4$ followed by nucleophilic attack by amine to give adduct, which after unprecedented rearrangement at two different reaction temperatures provide two different nitrogen heterocyclic compounds.

2.4. Results and Discussion

2.4.1. Optimization of the Reaction

In the beginning, 2-aminobenzonitrile (**22a**) was treated with dimethyl 2-(*p*-tolyl)cyclopropane-1,1-dicarboxylate (**23a**) in presence of 1.0 equiv of $SnCl_4$ in dichloromethane (DCM) at room temperature under nitrogen atmosphere (*Table 2.4.1.1.*, entry 1). This resulted in the formation of two products dimethyl 5-amino-2-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (**24aa**) and methyl 4-oxo-2-(*p*-tolyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (**25aa**) in 15% and 20% yields, respectively. Encouraged by the result, the reaction was examined with other solvents like DCE and toluene at room temperature, however it failed to produce any satisfactory yield, and selectivity of the products (*Table 2.4.1.1.*, entries 2 and 3). Also, the reaction in acetonitrile failed to give any product (*Table 2.4.1.1.*, entry 4). Further, the reaction was checked with varying load of reagent; use of 1.5, and 2.0 equiv of $SnCl_4$ in DCM at room temperature (*Table 2.4.1.1.*, entries 5 and 6) resulted in no significant increase in yield and selectivity in comparison with the use of 1.0 equiv of $SnCl_4$. However, fortunately when the reaction was performed with 2.0 equiv of $SnCl_4$ in DCM at 40 °C, exclusively product **25aa** was isolated with 45% yield (*Table 2.4.1.1.*, entry 7). When switched the solvent to DCE at 40 °C and 80 °C, yield was increased up to 50% and 55% respectively with exclusive formation of **25aa** (*Table 2.4.1.1.*, entries 9 and 10). Further, optimization condition for the formation of **25aa** exclusively was arrived with 1.2 equiv of $SnCl_4$ in DCE at 80 °C giving 65% yield (*Table 2.4.1.1.*, entry 11). When screened with other Lewis acids such as $In(OTf)_3$, $FeCl_3$, $InCl_3$, $Cu(OTf)_2$ in DCE at 80 °C, the reaction did not proceed at all (*Table 2.4.1.1.*, entries 12-15). Next, to arrive at an optimization condition with the exclusive formation of product **24aa**, the same reaction was performed with 1.2 equiv of $SnCl_4$ in DCE at 0 °C (*Table 2.4.1.1.*, entry 16). To our delight, the product **24aa** was obtained exclusively with 76% yield. Furthermore, the reaction was also performed at –25 °C and –40 °C, but the yield was decreased to 40% and 32% respectively, indicating that the selectivity, as well as the yield of the reaction is highly dependent on temperature (*Table 2.4.1.1.*, entries 17 and 18). The reaction was also

Table 2.4.1.1.: *Optimization of the reaction*[a]



entry	reagent (equiv)	solvent	temp /°C	**24aa** %yield[b]	**25aa** %yield [b]
1.	$SnCl_4$ (1.0)	DCM	25	15	20
2.	$SnCl_4$ (1.0)	DCE	25	13	18
3.	$SnCl_4$ (1.0)	toluene	25	5	7
4.	$SnCl_4$ (1.0)	CH_3CN	25	-	-
5.	$SnCl_4$(1.5)	DCM	25	22	27
6.	$SnCl_4$ (2.0)	DCM	25	28	33
7.	$SnCl_4$ (2.0)	DCM	40	-	45
8.	$SnCl_4$ (3.0)	DCM	40	-	40
9.	$SnCl_4$ (2.0)	DCE	40	-	50
10.	$SnCl_4$ (2.0)	DCE	80	-	55
11.	**$SnCl_4$ (1.2)**	**DCE**	**80**	**-**	**65**
12.	$In(OTf)_3$ (0.5)	DCE	80	-	-
13.	$FeCl_3$ (1.2)	DCE	80	-	-
14.	$InCl_3$ (0.5)	DCE	80	-	-
15.	$Cu(OTf)_2$ (0.5)	DCE	80	-	-
16.	**$SnCl_4$ (1.2)**	**DCE**	**0**	**76**	**-**
17.	$SnCl_4$ (1.2)	DCE	-25	40	-
18.	$SnCl_4$ (1.2)	DCE	-40	32	-
19.	$TiCl_4$ (1.2)	DCE	0	46	-
20.	$AlCl_3$ (2)	DCE	0	-	-
21.	$FeCl_3$ (1.2)	DCE	0	-	-
22.	$InCl_3$ (0.5)	DCE	0	-	-
23.	$In(OTf)_3$ (0.5)	DCE	0	-	-

24.	$Cu(OTf)_2$ (0.5)	DCE	0	-	-
25.	$BF_3{\cdot}OEt_2$ (1.2)	DCE	0	-	-
26.	TfOH (2.0)	DCE	0	-	-

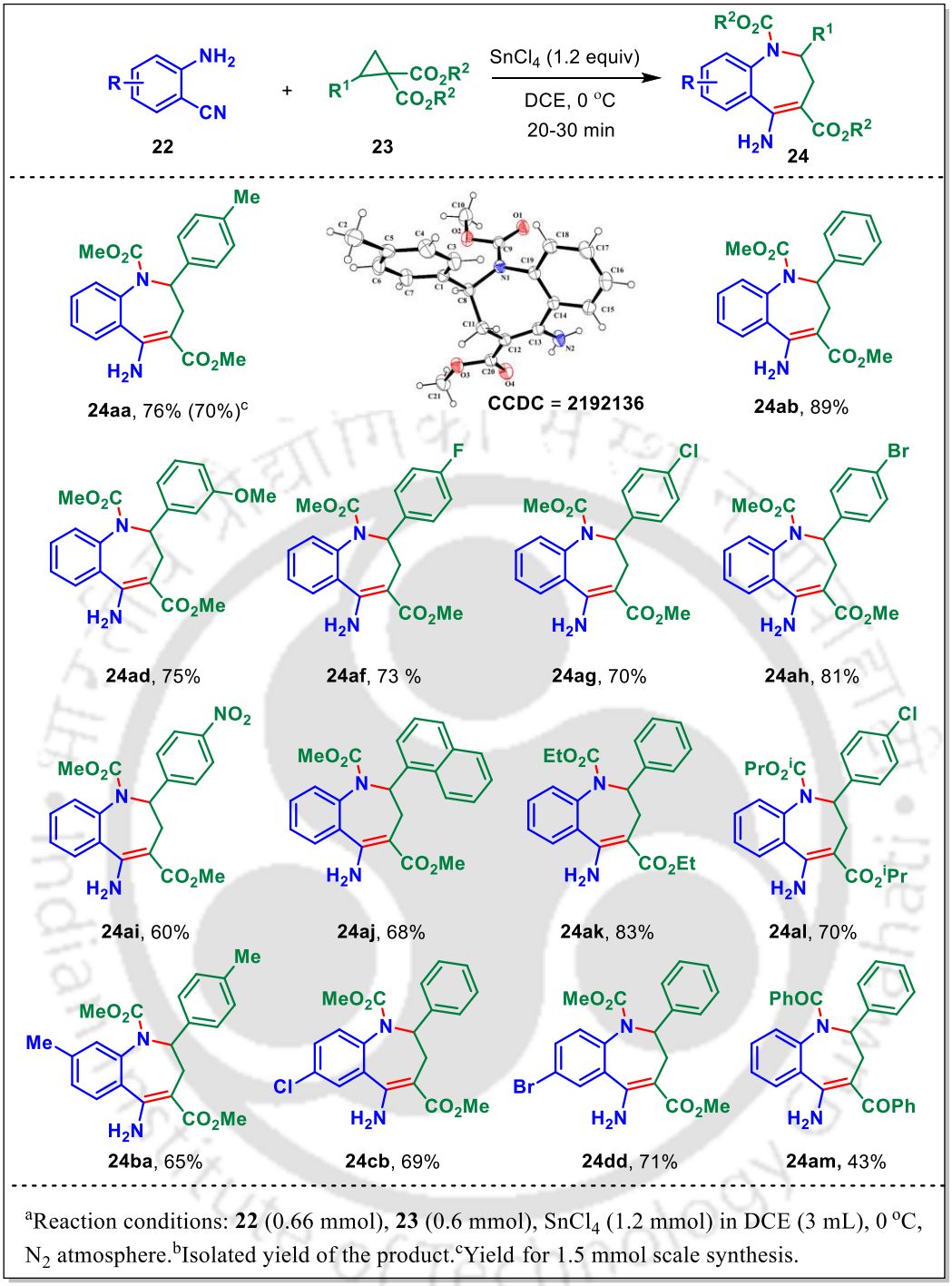
[a]All the reactions were carried out in (0.66 mmol) **22a**, (0.6 mmol) **23a** in 2.0 mL solvent, N_2 atmosphere, [b]Isolated yields.

investigated with other Lewis acids. It was observed that, with $TiCl_4$ (1.2 equiv) in DCE at 0 °C, **24aa** formed with 46% yield (*Table 2.4.1.1.*, entry 19). Other Lewis acids such as $AlCl_3$, $FeCl_3$, $InCl_3$, $In(OTf)_3$, $Cu(OTf)_2$ and $BF_3{\cdot}OEt_2$ failed to give any product (*Table 2.4.1.1.*, entries 20-25). Brønsted acid, TfOH was also totally ineffective in this reaction (*Table 2.4.1.1.*, entry 26). From overall optimization, it was concluded that, 1.2 equiv of $SnCl_4$ in DCE at 0 °C is the best optimum condition for the product **24aa**, whereas 1.2 equiv of $SnCl_4$ in DCE at 80 °C is the optimum condition for the product **25aa**. Among the Lewis acids studied only tetravalent $SnCl_4$ and $TiCl_4$ could produce desired products. However, $SnCl_4$ is superior to $TiCl_4$ in terms of yield and cost.

2.4.2. Substrate Scope

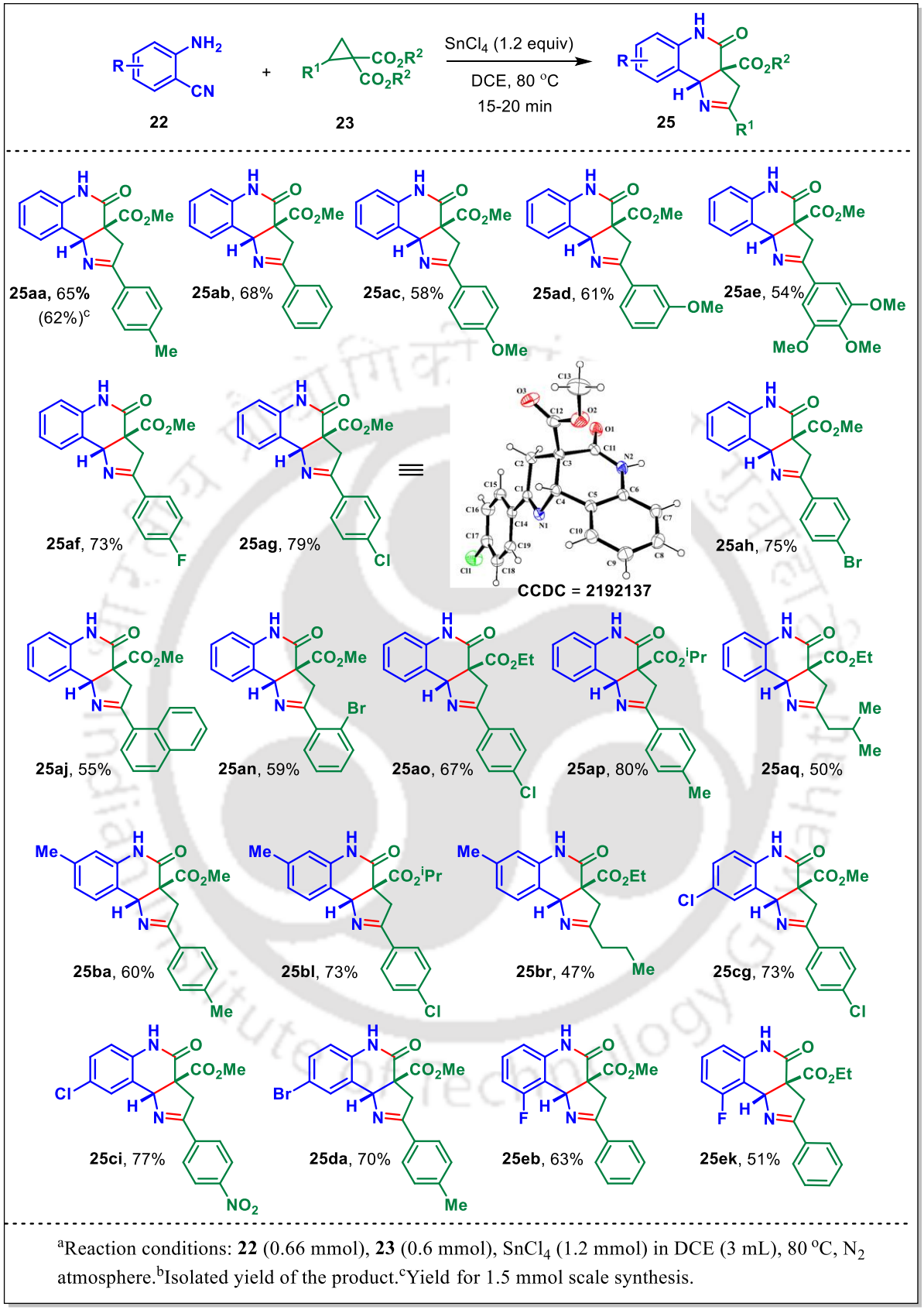
With the optimized reaction conditions in hand, we set out to explore the compatibility and scope for the synthesis of dihydro-1*H*-benzo[*b*]azepines with different donor–acceptor cyclopropanes and substituted 2-aminobenzonitrile derivatives as depicted in *Scheme 2.4.2.1*. It was observed that both electron-donating such as –Me, –OMe and electron-withdrawing groups such as $–NO_2$ and halogens in the aromatic ring of the cyclopropanes were equally well-tolerated providing corresponding products **24aa-24aj** in good yields. The dicarboxylate group of the cyclopropane was also varied to $–CO_2Et$ to form product **24ak** in 83% yield. On the other hand, introducing bulky substituent (isopropyl group) in the dicarboxylate part of the cyclopropane resulted in product **24al** with 70% yield. Also, to increase the substrates scope of the reaction, differently substituted 2-aminobenzonitriles were used, which furnished the corresponding products in good yields (**24ba-24dd**). Reaction of cyclopropane **23m** with benzoyl group gave compound **24am** with 43% yield. The structure of compounds was determined by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy, mass spectrometry and finally, by single crystal X-ray analysis of compound **24aa**.

Similarly, with the second optimal reaction conditions, the scope of this reaction for the synthesis of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones was examined with



Scheme 2.4.2.1. *Scope for the synthesis of dihydro-1H-benzo[b]azepines.*[a,b]

different donor–acceptor cyclopropanes and substituted 2-aminobenzonitrile derivatives as depicted in *Scheme 2.4.2.2*. Interestingly, substrates with both electron-donating such as –Me, –OMe and electron-withdrawing groups such as $–NO_2$ and halogen substitution in the aromatic ring gave corresponding products **25aa-25aj, 25an** in good yields. Even varying the dicarboxylate group in the cyclopropane part also gave product **25ao** and **25ap** in good yields. On the other hand, to increase the substrates



[a]Reaction conditions: **22** (0.66 mmol), **23** (0.6 mmol), $SnCl_4$ (1.2 mmol) in DCE (3 mL), 80 °C, N_2 atmosphere.[b]Isolated yield of the product.[c]Yield for 1.5 mmol scale synthesis.

Scheme 2.4.2.2. *Scope for the synthesis of tetrahydro-4H-pyrrolo[3,2-c]quinolin-4-ones.*[a,b]

scope differently substituted 2-aminobenzonitriles with –Me, –Cl, –Br, –F groups were screened, which furnished the corresponding products in moderate to good yields (**25ba-25ek**). Further the reaction was also successfully carried out with alkyl substituted donor–acceptor cyclopropanes and 2-aminobenzonitrile to give products **25aq** and **25br** in 50% and 47% yields, respectively. The reaction is highly diastereoselective and only one diastereomer was obtained. The structure of compounds was determined by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy, mass spectrometry and finally by single crystal X-ray analysis of compound **25ag**.

2.4.3. Rotamers

Amide C(O)–N bonds possess a rotational barrier because of the double bond character. Rotational isomerism based on such amide bonds plays an important role in the structural and chemical reactivity of substrates having an amide tether. Amide rotamers are generally difficult to isolate because their interconversion occurs easily at room temperature. The compounds **24aa-24ak**, **24ba**, **24cb** and **24dd** are rotamers at room temperature due to the restricted rotation about the amide bond.[17] A variable temperature (VT) ^{1}H NMR experiment was performed to study the dynamic amide bond of **24aa**. At higher temperatures the rotamers convert into single isomer indicating free rotation of the amide bond as evident from the coalescing peaks at 3.4-3.6 ppm and 5.2-5.3 ppm in the plot (*Figure 2.4.3.1.*).

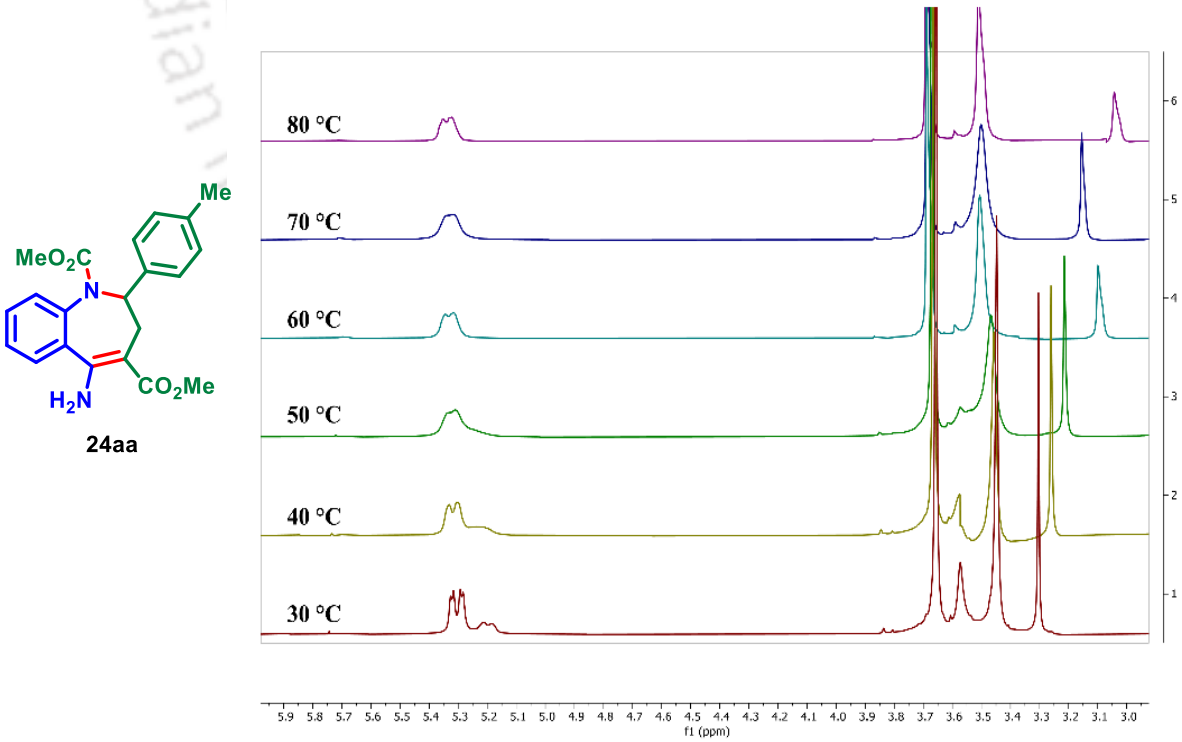
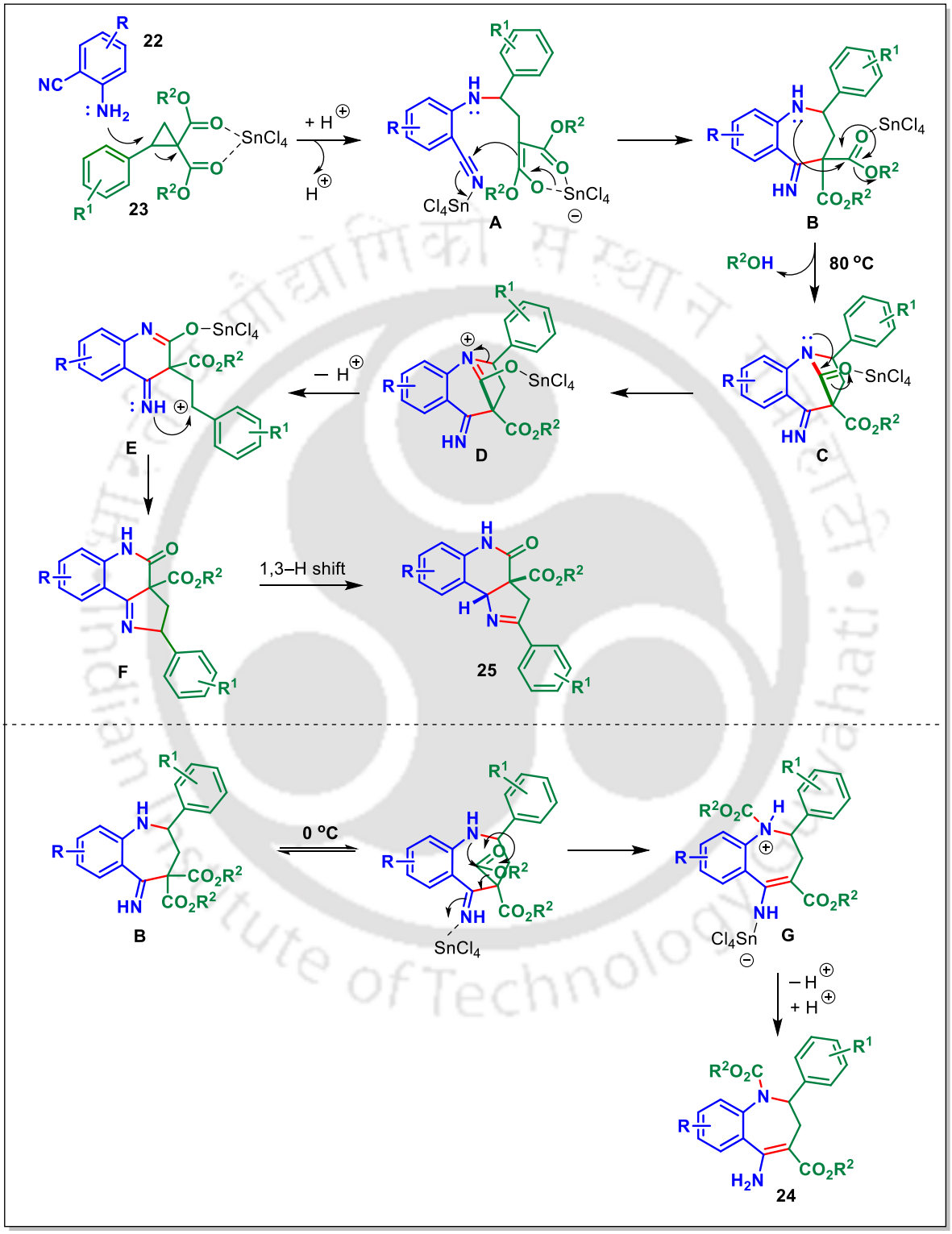


Figure 2.4.3.1. *Variable temperature ^{1}H NMR spectra (400 MHz, DMSO-d_6) of* ***24aa****. Scale is increased to emphasize coalescing peaks at 3.4-3.6 ppm and 5.2-5.3 ppm.*

2.4.4. Plausible Mechanism

A plausible mechanism for the formation of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and dihydro-1*H*-benzo[*b*]azepines is depicted in *Scheme 2.4.4.1.* Initially, $SnCl_4$

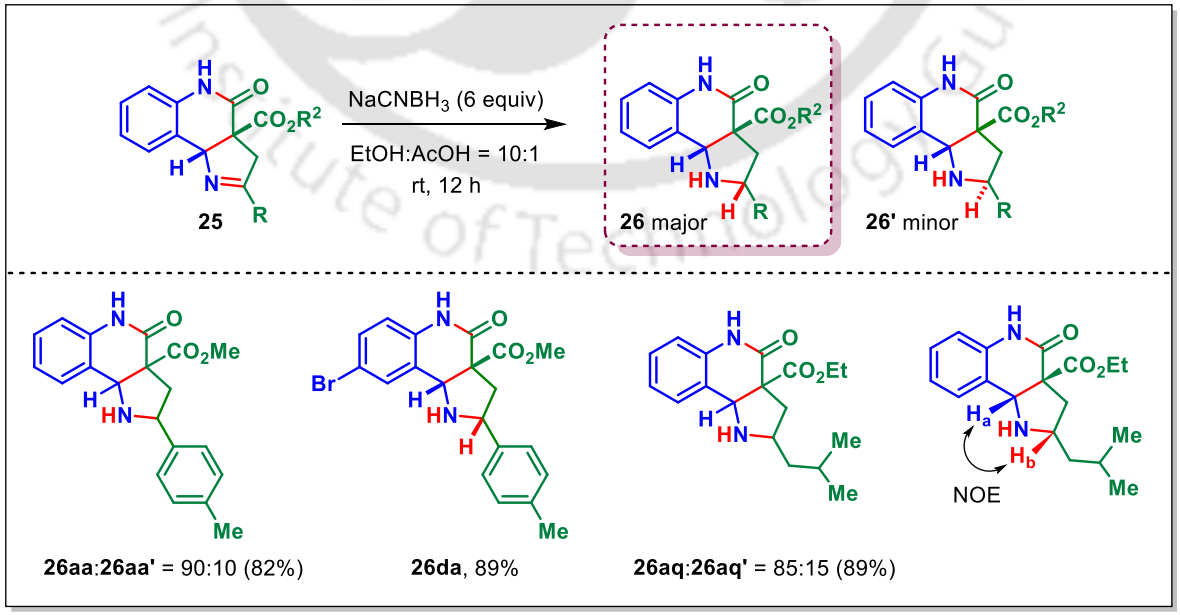


Scheme 2.4.4.1. *Plausible reaction mechanism for synthesis of tetrahydro-4H-pyrrolo[3,2-c]quinolin-4-ones and dihydro-1H-benzo[b]azepines.*

activates the diester moiety of the donor–acceptor cyclopropane **23** for the nucleophilic attack by amine functionality of 2-aminobenzonitrile **22** to generate intermediate **A**. The enolyzed intermediate **A** then undergoes intramolecular attack to the activated nitrile group to form intermediate **B.** The intermediate **B** at 80 °C forms lactam **C** with elimination of an alcohol molecule. The intermediate **C** after enolization and subsequent C–N bond cleavage gives carbocation **E** which is attacked by imine to give intermediate **F**. The intermediate **F** after 1,3-hydrogen shift gives final compound **25**. On the other hand, at 0 °C intermediate **B** forms intermediate **G** *via* nucleophilic attack by amine to one of the ester functionality and subsequent C–C bond cleavage. The intermediate **G** after deprotonation and protonation gives final product **24**. It is worth mentioning that protonated intermediate **A** was isolated after workup and characterized by spectroscopic methods. The intermediate **A** when subjected to standard reaction conditions furnished the corresponding products **24aa** (R = H, R^1 = 4-Me, R^2 = Me) and **25aa** (R = H, R^1 = 4-Me, R^2 = Me), respectively.

2.5. Post-synthetic Applications

The post synthetic application of the methodology was extended towards the synthesis of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones (*Scheme 2.5.1.*). It is noteworthy to mention that tricyclic hexahydropyrrolo[3,2-*c*]quinolinone is core unit of martinelline, an alkaloid isolated from *Martinella iquitosensis* roots, possesses anti-bacterial activity and antagonist activity toward bradykinin (BK) B1 and B2 receptors.[4] Thus, the reaction



Scheme 2.5.1. *Scope for the synthesis of hexahydropyrrolo[3,2-c]quinolinones.*

of tetrahydropyrrolo[3,2-*c*]quinolines **25aa**, **25da** and **25aq** with sodium cyanoborohydride in ethanol and acetic acid (ratio of 10:1) at room temperature resulted in hexahydropyrrolo[3,2-*c*]quinolinones, **26aa** and **26aa′** in 82% yield (diastereomeric ratio 90:10); **26aq** and **26aq′** in 89% yield (diastereomeric ratio 85:15) respectively, whereas hexahydropyrrolo[3,2-*c*]quinolinones, **26da** was obtained as a single diastereomer with 75% yield. The stereochemistry of the compounds was determined by ^{1}H NMR and NOE experiment of **26aq**. The presence of a strong NOE between H_a and H_b of **26aq** clearly indicates that they are *cis* to each other, thus confirming the major diastereomer to have *cis*-configuration.

2.6. Conclusion

In conclusion, a practical and general one-pot procedure for the synthesis of dihydrobenzo[*b*]azepines and tetrahydropyrrolo[3,2-*c*]quinolines from donor-acceptor cyclopropanes and 2-aminobenzonitriles mediated by $SnCl_4$ has been developed. The reaction is tuned at two different temperatures to provide two sets of structurally diverse molecules. The reaction is compatible to a variety of functional groups giving moderate to good yields and can be extended towards the synthesis of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones (tricyclic core of martinelline).

2.7. Experimental Section

2.7.1. General Information and Instrumentation

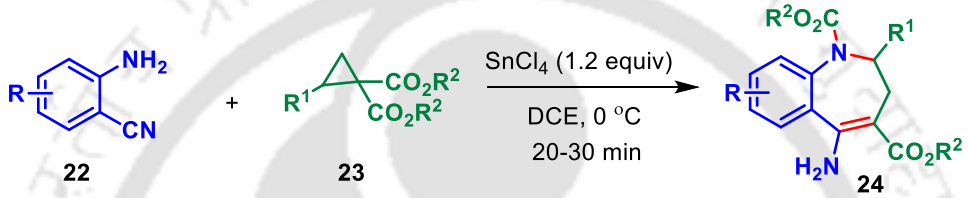
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 500 MHz and 400 MHz) or ^{13}C{^{1}H} (150 MHz, 125 MHz and 100 MHz) NMR. ^{19}F{^{1}H} NMR spectra were recorded at 376MHz and 470 MHz and chemical shifts are relative to hexafluorobenzene in $CDCl_3$ at δ = -164.9 ppm (external reference). Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, t = triplet, q = quartet, m = multiplet, bs = broad singlet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF and microTOF-Q II mass spectrometer.

2.7.2. Reaction Procedure

2.7.2.1. Experimental Procedure for Synthesis of Donor–Acceptor Cyclopropanes

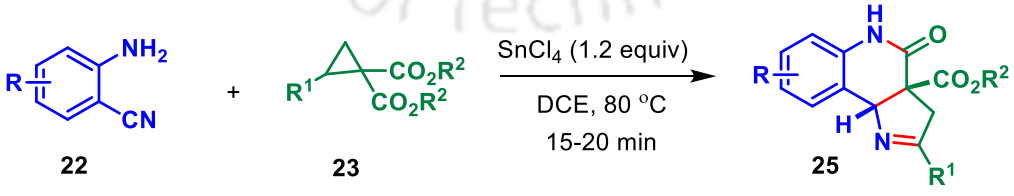
All donor-acceptor cyclopropanes **23a-23q** were synthesized by Knoevenagel/Corey-Chaykovsky reactions sequence from the corresponding aldehydes, previously reported and confirmed by comparison to the reported characterization data.[18-24] The starting material, (2-phenylcyclopropane-1,1-diyl)bis(phenylmethanone) (**23m**) was also synthesized according to a literature report, and the spectroscopic data of the compound is in good agreement with the literature data.[25]

2.7.2.2. General Procedure for the Synthesis of Compounds 24aa-24ab, 24ad, 24af-24am, 24ba, 24cb and 24dd



To a solution of donor–acceptor cyclopropane **23** (0.6 mmol, 1 equiv) and 2-aminobenzonitrile derivatives **22** (0.66 mmol, 1.1 equiv) in 1,2-dichloroethane (2 mL) was added $SnCl_4$ (0.72 mmol, 1.2 equiv) at 0 °C under nitrogen atmosphere. The reaction was continued at 0 °C for 30 min. After completion of the reaction, excess $SnCl_4$ was quenched with $NaHCO_3$ solution at 0 °C. Then the organic layer was extracted with EtOAc (3 x 10 mL) and was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **24**.

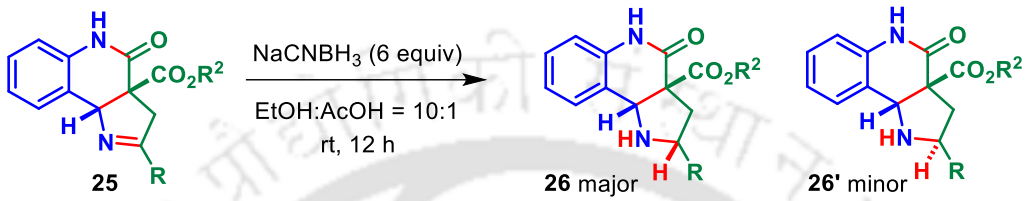
2.7.2.3. General Procedure for the Synthesis of Compounds 25aa-25ah, 25aj, 25an-25aq, 25ba, 25bl, 25br, 25cg, 25ci, 25da, 25eb and 25ek



To a refluxing solution of donor–acceptor cyclopropane **23** (0.6 mmol, 1 equiv) and 2-aminobenzonitrile derivatives **22** (0.66 mmol, 1.1 equiv) in 1,2-dichloroethane (2 mL) was added $SnCl_4$ (0.72 mmol, 1.2 equiv) under nitrogen atmosphere. The reaction was continued for 20 min. After completion of the reaction, the solvent was removed under reduced pressure

and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **25**.

2.7.2.4. General Procedure for the Synthesis of Compounds 26aa, 26aq and 26da



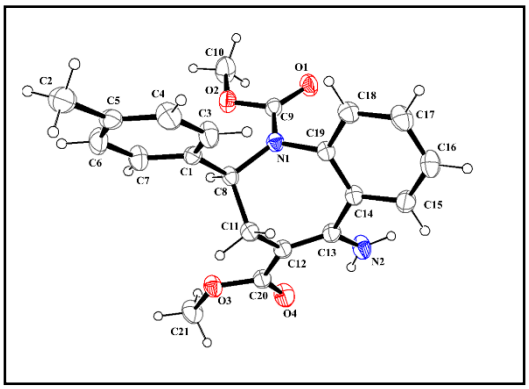
To a solution of tetrahydropyrrolo[3,2-*c*]quinoline derivative **25** (0.45 mmol, 1 equiv) in the mixed solvent of ethanol and acetic acid (10:1, 2 mL) was added sodium cyanoborohydride (6 equiv) at room temperature. The reaction mixture was stirred for 12 h at the same temperature and then quenched with saturated aqueous sodium bicarbonate solution. The mixture was extracted with DCM and the combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **26**.

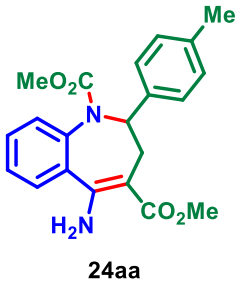
2.7.3. Crystallographic Description

Single crystals of compounds **24aa** and **25ag** were obtained by slow evaporation of ethyl acetate and hexane solution (1:9). Bruker APEX-II CCD diffractometer was used to collect the intensity data. The instrument is equipped with a fine focus 1.75 kW sealed tube Mo Kα radiation (λ = 0.71073 Å) at 297 K. The data acquisition was done with the APEX4 software. APEX4 software was implemented for data integration and reduction. Multi-scan empirical absorption corrections were employed to the data using the program APEX4. Structures were solved by direct methods using SHELXL-2019 and refined with full-matrix least-squares on F2 using SHELXL-2019/1.[a] Structural illustrations have been drawn with ORTEP-3 for Windows.[b] The detailed data collection and structure refinement are summarized in *Tables 2.7.3.1. and 2.7.3.2.*

a. G. M. Sheldrick, SHELXS-2014, Program for the crystal structure solution; University of Göttingen: Göttingen, Germany, 2014.

b. L. J. Farrugia, XRDIFF: simulation of X-ray diffraction patterns, *J. Appl. Crystallogr*. **1997**, *30*, 565.



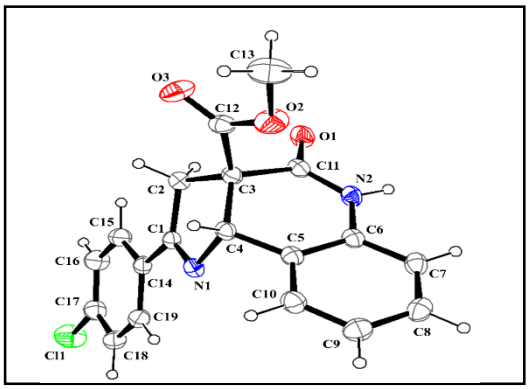


24aa

Figure 2.7.3.1. *ORTEP diagram of compound (**24aa**) with 30% probability.*

Table 2.7.3.1. Crystal parameters of compound **24aa**

	CCDC 2192136
Formula	$C_{21}H_{22}N_2O_4$
Formula weight	366.40
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	9.9656(8)
b/Å	10.1889(9)
c/Å	11.0598(10)
α/°	70.450(3)
β/°	78.962(3)
γ/°	63.006(3)
V/Å^3	941.91(14)
Z	2
Abs. Coeff./mm^{-1}	0.090
Abs. Correction	multi-scan
GOF on F^2	1.070
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0535
R indices [all data]	*wR2* = 0.1128 *R1* = 0.1393 *wR2* = 0.1704



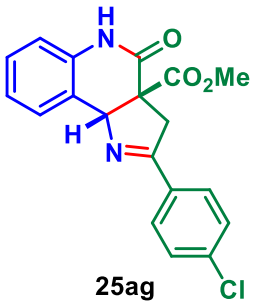


Figure 2.7.3.1. *ORTEP diagram of compound (**25ag**) with 30% probability.*

Table 2.7.3.2. Crystal parameters of compound **25ag**

	CCDC 2192137
Formula	$C_{19}H_{15}ClN_2O_3$
Formula weight	354.78
T/K	296(2)
Crystal system	Triclinic
Space group	P-1
a/Å	7.792(3)
b/Å	10.461(3)
c/Å	11.202(4)
α/°	105.713(8)
β/°	94.629(8)
γ/°	106.548(7)
V/Å^3	830.2(5)
Z	2
Abs. Coeff./mm^{-1}	0.251
Abs. Correction	none
GOF on F^2	1.043
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0421
R indices [all data]	*wR2* = 0.0473
	R1 = 0.1013
	wR2 = 0.1063

2.8. References

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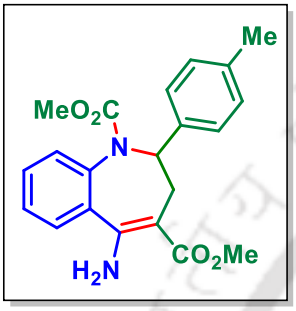
26.

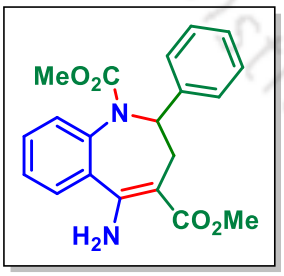
2.9. Characterisation Data

Dimethyl 5-amino-2-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24aa):



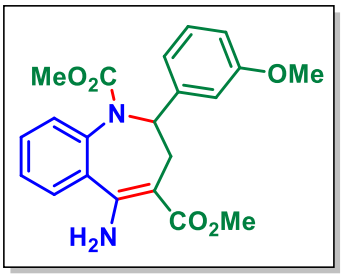
Colourless solid; R_f (hexane/EtOAc, 8:2) 0.40; mp 211-213°C; yield 166 mg, 76%. IR (KBr, neat) ν 3421, 3316, 2953, 1709, 1615, 1536, 1236, 1186, 1057, 770 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1 H), 7.47–7.38 (m, 2 H), 7.19 (d, *J* = 7.7 Hz, 2 H), 7.16–7.09 (m, 3 H), 5.52 (dd, *J* = 13.5 and 4.4 Hz, 1 H, major), 5.33 (dd, *J* = 13.5 and 4.2 Hz, 1 H, minor), 3.76 (s, 3 H, minor), 3.73 (s, 3 H, major), 3.66 (s, 3 H, minor), 3.51 (s, 3 H, major), 2.93 (dd, *J* = 14.7 and 4.5 Hz, 1 H), 2.32 (s, 3 H, minor), 2.31 (s, 3 H, major), 2.15 (dd, *J* = 14.7 and 13.6 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.0, 157.4, 157.0, 156.8, 156.1, 139.9, 139.2, 138.3, 137.8, 137.2, 137.1, 136.6, 136.5, 131.9, 131.7, 130.7, 130.3, 129.2, 128.1, 128.0, 127.2, 127.1, 127.0, 126.6, 93.4, 69.2, 53.1, 53.0, 51.1, 32.7, 31.6, 21.3, 21.2. HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_4$ $(M + H)^+$ 367.1652, found 367.1650.

Dimethyl 5-amino-2-phenyl-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24ab):



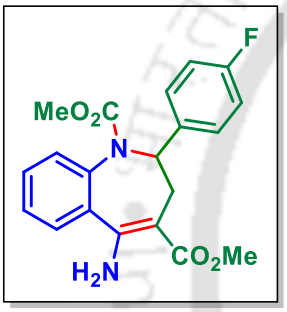
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 187 mg, 89%. IR (KBr, neat) ν 3418, 2953, 1701, 1664, 1536, 1441, 1257,1183, 1037, 765, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58–7.56 (m, 1 H), 7.48–7.41 (m, 2 H), 7.35–7.22 (m, 5 H), 7.14–7.12 (m, 1 H), 5.55 (dd, *J* = 13.6 and 4.4 Hz, 1 H, major), 5.36 (dd, *J* = 13.6 and 4.2 Hz, 1 H, minor), 3.77 (s, 3 H, minor), 3.75 (s, 3 H, major), 3.67 (s, 3 H, minor), 3.54 (s, 3 H, major), 2.96 (dd, *J* = 14.8 and 5.0 Hz, 1 H), 2.16 (dd, *J* = 14.1 and 14.8 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 157.0, 156.2, 142.2, 137.9, 136.6, 131.8, 130.4, 128.6, 128.2, 127.6, 127.1, 127.0, 126.7, 93.5, 93.3, 69.5, 53.1, 52.7, 51.2, 32.8, 31.6. HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_4$ $(M + H)^+$ 353.1496, found 353.1499.

Dimethyl 5-amino-2-(3-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24ad):



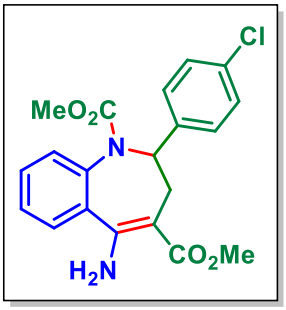
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 171 mg, 75%. IR (KBr, neat) ν 3421, 3316, 2950, 1701, 1607, 1536, 1438, 1249, 1107, 1046, 765, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58-7.56 (m, 1 H), 7.49–7.37 (m, 2 H), 7.23–7.17 (m, 3 H), 6.90–6.78 (m, 3 H), 5.52 (dd, *J* = 13.2 and 4.3 Hz, 1 H, major), 5.33 (dd, *J* = 13.2 and 4.0 Hz, 1 H, minor), 3.77 (s, 3 H, major), 3.75 (s, 3 H, minor), 3.69 (s, 3 H, minor), 3.55 (s, 3 H, major), 2.96 (dd, *J* = 14.8 and 4.7 Hz, 1 H), 2.14 (dd, *J* = 14.8 and 13.2 Hz, 1 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.0, 159.8, 157.0, 156.2, 143.9, 138.0, 136.7, 131.8, 130.8, 130.4, 129.6, 128.3, 127.1, 119.4, 119.0, 113.0, 112.9, 112.5, 93.6, 69.5, 55.4, 53.2, 51.2, 31.8. HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_5$ $(M + H)^+$ 383.1601, found 383.1621.

Dimethyl 5-amino-2-(4-fluorophenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24af):



Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 162 mg, 73%. IR (KBr, neat) ν 3424, 3321, 2953, 1704, 1662, 1509, 1441, 1296, 1186, 1043, 770, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.55 (m, 1 H), 7.45–7.40 (m, 2 H), 7.29–7.22 (m, 2 H), 7.10-7.07 (m, 1 H), 6.97 (t, *J* = 8.6 Hz, 2 H), 5.53 (dd, *J* = 13.4 and 4.4 Hz, 1 H, major), 5.34 (dd, *J* = 13.4 and 4.2 Hz, 1 H, minor), 3.75 (s, 3 H, minor), 3.73 (s, 3 H, major), 3.65 (s, 3 H, minor), 3.51 (s, 3 H, major), 2.93 (dd, *J* = 14.8 and 4.4 Hz, 1 H), 2.13 (dd, *J* = 14.8 and 13.2 Hz, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 162.2 (d, *J* = 243.8 Hz), 157.4, 157.0, 156.5, 156.0, 137.84, 137.8, 137.4, 136.4, 131.5, 130.3, 128.6 (d, *J* = 7.8 Hz), 128.2, 128.1, 127.1, 115.2 (d, *J* = 21.0 Hz), 92.9, 68.5, 53.0, 52.9, 51.0, 32.6, 31.5. ^{19}F NMR (376 MHz, $C_6F_6/CDCl_3$) δ -118.24 (s, -F). HRMS (ESI) calcd. for $C_{20}H_{20}FN_2O_4$ $(M + H)^+$ 371.1402, found 371.1392.

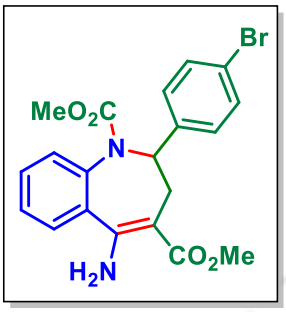
Dimethyl 5-amino-2-(4-chlorophenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24ag):



Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 162 mg, 70%. IR (KBr, neat) ν 3418, 3319, 2950, 1707, 1667, 1615, 1494, 1252, 1091, 1015, 768, 536 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 1 H), 7.40–7.35 (m, 2 H), 7.23–7.10 (m, 4 H), 7.04–7.00 (m, 1 H), 5.43 (dd, *J* = 13.4 and 4.4 Hz, 1 H, major), 5.25 (dd, *J* = 13.4 and 4.2 Hz, 1 H, minor), 3.70 (s, 3 H, minor), 3.67 (s, 3 H, major), 3.61 (s, 3 H, minor), 3.47 (s, 3 H, major), 2.86 (dd, *J* = 14.8 and 4.4 Hz, 1 H), 2.05 (dd, *J* = 14.8 and 13.4

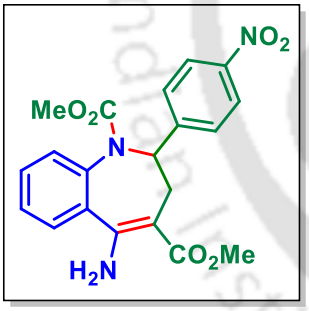
Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.9, 157.0, 156.2, 140.6, 137.5, 136.5, 133.4, 131.6, 130.5, 128.7, 128.5, 128.4, 128.3, 128.1, 127.2, 93.2, 68.7, 53.2, 51.2, 32.6, 31.4. HRMS (ESI) calcd. for $C_{20}H_{20}ClN_2O_4$ $(M + H)^+$ 387.1106, found 387.1110.

Dimethyl 5-amino-2-(4-bromophenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24ah):



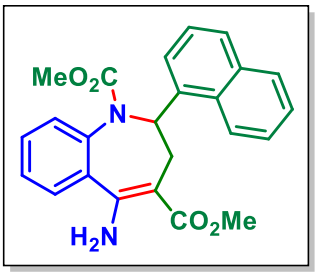
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 209 mg, 81%. IR (KBr, neat) ν 3418, 3324, 2850, 1701, 1662, 1491, 1302, 1252, 1183, 1010, 770, 538 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.56 (m, 1 H), 7.45–7.41 (m, 3 H), 7.32–7.29 (m, 1 H), 7.19–7.07 (m, 3 H), 5.49 (dd, *J* = 13.4 and 4.4 Hz, 1 H, major), 5.31 (dd, *J* = 13.4 and 3.8 Hz, 1 H, minor), 3.77 (s, 3 H, minor), 3.75 (s, 3 H, major), 3.68 (s, 3 H, minor), 3.54 (s, 3 H, major), 2.93 (dd, *J* = 14.8 and 4.6 Hz, 1 H), 2.12 (dd, *J* = 14.8 and 13.2 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 157.0, 156.2, 141.1, 137.5, 136.6, 131.7, 131.6, 130.5, 128.9, 128.4, 128.3, 121.6, 93.2, 68.8, 53.2, 51.2, 32.6, 31.4. HRMS (ESI) calcd. for $C_{20}H_{20}BrN_2O_4$ $(M + H)^+$ 431.0601, found 431.0607.

Dimethyl 5-amino-2-(4-nitrophenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24ai):



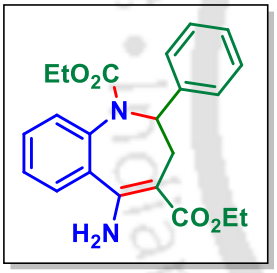
Pale yellow gum; R_f (hexane/EtOAc, 6:4) 0.40; yield 142 mg, 60%. IR (KBr, neat) ν 3411, 3316, 2853, 1701, 1664, 1441, 1344, 1257, 1186, 1096, 770, 556 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 2 H), 7.62–7.60 (m, 1 H), 7.52–7.43 (m, 4 H), 7.14–7.12 (m, 1 H), 5.60 (dd, *J* = 13.3 and 4.3 Hz, 1 H, major), 5.42 (dd, *J* = 13.3 and 4.1 Hz, 1 H, minor), 3.79 (s, 3 H, minor), 3.77 (s, 3 H, major), 3.69 (s, 3 H, minor), 3.57 (s, 3 H, major), 2.98 (dd, *J* = 14.8 and 4.5 Hz, 1 H), 2.17 (dd, *J* = 14.8 and 13.5 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 169.7, 157.0, 156.3, 149.4, 147.4, 137.3, 136.4, 131.5, 130.8, 128.6, 127.9, 127.4, 124.0, 92.8, 68.8, 53.4, 51.3, 31.5. HRMS (ESI) calcd. for $C_{20}H_{20}N_3O_6$ $(M + H)^+$ 398.1347, found 398.1351.

Dimethyl 5-amino-2-(naphthalen-1-yl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 7:3, 24aj):



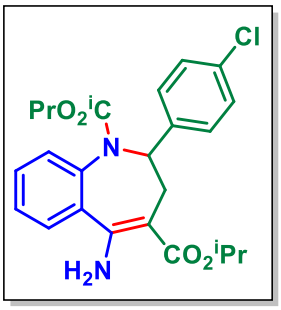
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 215-217 °C; yield 164 mg, 68%. IR (KBr, neat) ν 3418, 3321, 2956, 1686, 1662, 1612, 1441, 1302, 1299, 1191,1047, 770 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6/$CDCl_3$) δ 8.48 (d, *J* = 8.6 Hz, 1 H, major), 8.33 (d, *J* = 8.6 Hz, 1 H, minor), 7.84 (d, *J* = 8.6 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.58–7.51 (m, 2 H), 7.49–7.42 (m, 3 H), 7.40–7.36 (m, 2 H), 6.37 (d, *J* = 13.0 Hz, 1 H, major), 6.22 (d, *J* = 13.0 Hz, 1 H, minor), 3.86 (s, 3 H, minor), 3.84 (s, 3 H, major), 3.53 (s, 3 H, major), 3.52 (s, 3 H, minor), 3.12 (d, *J* = 14.0 Hz, 1 H), 2.12 (dd, *J* = 14.0 and 13.4 Hz, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 169.4, 157.3, 156.9, 156.5, 155.9, 139.8, 139.2, 138.6, 138.0, 136.0, 135.9, 133.6, 133.5, 131.6, 131.5, 130.4, 130.3, 130.1, 130.0, 128.6, 128.5, 127.7, 127.6, 127.5, 127.4, 127.3, 126.0, 125.9, 125.4, 125.2, 125.0, 123.0, 122.6, 121.8, 121.6, 92.8, 66.3, 52.7, 50.8, 33.0, 32.4. HRMS (ESI) calcd. for $C_{24}H_{23}N_2O_4$ $(M + H)^+$ 403.1652, found 403.1656.

Diethyl 5-amino-2-phenyl-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio = 6:4, 24ak):



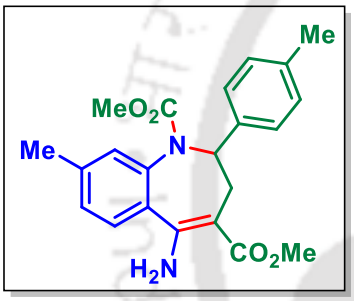
Colourless gum; R_f (hexane/EtOAc, 7:3) 0.40; yield 189 mg, 83%. IR (KBr, neat) ν 3424, 3316, 2937, 1696, 1657, 1615, 1536, 1404, 1299, 1186, 1107, 765, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.2 Hz, 1 H), 7.44–7.20 (m, 7 H), 7.14 (d, *J* = 7.5Hz, 1 H), 5.55 (dd, *J* = 13.4 and 4.4 Hz, 1 H, major), 5.36 (dd, *J* = 13.4 and 5.6 Hz, 1 H, minor), 4.25–4.16 (m, 2 H), 4.06–3.91 (m, 2 H), 2.98 (ddd, *J* = 14.8, 9.2 and 4.5 Hz, 1 H), 2.16 (ddd, *J* = 14.8, 7.4 and 6.7 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.18 (t, *J* = 7.2 Hz, 3 H, minor), 1.01 (t, *J* = 7.2 Hz, 3 H, major). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.4, 169.3, 157.3, 156.9, 156.1, 155.5, 142.9, 142.3, 138.1, 137.7, 136.4, 131.6, 131.5, 130.4, 130.0, 128.4, 128.3, 127.8, 127.7, 127.3, 127.2, 127.1, 126.9, 126.8, 126.5, 93.0, 69.2, 61.8, 61.5, 59.5, 59.4, 32.5, 31.6, 14.6, 14.5, 14.4, 14.3. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $(M + H)^+$ 381.1809, found 381.1793.

Diisopropyl 5-amino-2-(4-chlorophenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (24al):



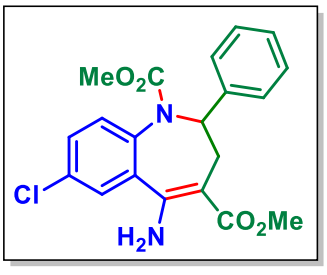
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 185 mg, 70%. IR (KBr, neat) ν 3454, 3375, 2985, 2932, 1720, 1630, 1491, 1380, 1272, 1014, 911, 753, 523 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2 H), 7.41 (d, *J* = 8.5 Hz, 2 H), 7.02 (t, *J* = 7.2 Hz, 1 H), 6.78 (d, *J* = 8.5 Hz, 1 H), 6.63 (t, *J* = 7.2 Hz, 2 H), 6.33 (s, 1 H), 5.17–5.11 (m, 1 H), 4.50–4.44 (m, 1 H), 4.18 (dd, *J* = 17.8 and 2.5 Hz, 1 H), 3.38 (d, *J* = 17.8 and 1.5 Hz, 1 H), 1.30 (d, *J* = 6.2 Hz, 3 H), 1.27 (d, *J* = 6.2 Hz, 3 H), 1.02 (d, *J* = 6.2 Hz, 3 H), 0.62 (t, *J* = 6.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 171.9, 169.0, 168.6, 145.6, 137.3, 132.0, 129.5, 129.0, 128.9, 128.8, 122.8, 118.3, 116.2, 76.1, 70.4, 70.2, 64.9, 45.0, 21.9, 21.6, 21.61, 20.6. HRMS (ESI) calcd. for $C_{24}H_{28}ClN_2O_4$ $(M + H)^+$ 443.1732, found 443.1735.

Dimethyl 5-amino-8-methyl-2-(*p*-tolyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio= 7:3, 24ba):



Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 148 mg, 65%. IR (KBr, neat) ν 3418, 3319, 2953, 1701, 1609, 1496, 1438, 1307, 1236, 1183, 1120, 762, 534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 1 H), 7.25–6.97 (m, 5 H), 6.93 (s, 1 H), 5.51 (dd, *J* = 13.4 and 4.2 Hz, 1 H, major), 5.33 (dd, *J* = 13.4 and 4.2 Hz, 1 H, minor), 3.74 (s, 3 H, minor), 3.72 (s, 3 H, major), 3.65 (s, 3 H, minor), 3. 52 (s, 3 H, major), 2.92 (dd, *J* = 15.0 and 4.4 Hz, 1 H), 2.37 (s, 3 H), 2.32 (s, 3 H), 2.14 (dd, *J* = 14.2 and 14.0 Hz, 1 H), $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.0, 169.9, 157.7, 157.2, 156.8, 156.1, 141.0, 140.7, 139.9, 139.2, 138.1, 137.5, 137.1, 137.0, 133.6, 133.5, 132.2, 132.1, 130.8, 129.3, 129.1, 128.9, 128.8, 127.6, 126.9, 126.8, 126.5, 93.0, 69.1, 53.0, 52.9, 51.1, 51.0, 32.7, 31.5, 21.6, 21.5, 21.4, 21.2, 21.21, 21.1. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $(M + H)^+$ 381.1809, found 381.1829.

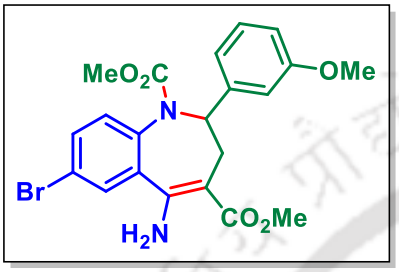
Dimethyl 5-amino-7-chloro-2-phenyl-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio= 7:3, 24cb):



Colourless gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 159 mg, 69%. IR (KBr, neat) ν 3424, 3321, 2956, 1701, 1664, 1615,1444, 1328, 1238, 1186, 1115, 765, 520 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1 H), 7.44–7.38 (m, 1 H), 7.31–7.22 (m, 5 H), 7.06 (d, *J* = 8.6 Hz, 1 H), 5.54 (dd, *J* = 13.5 and 4.3 Hz, 1 H, major), 5.35 (dd, *J* = 13.5 and 4.1 Hz, 1 H, minor), 3.77 (s, 3 H, minor), 3.75 (s, 3 H, major), 3.67 (s, 3 H, minor),

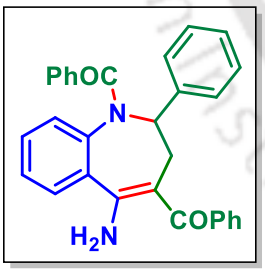
3. 54 (s, 3 H, major), 2.97 (dd, *J* = 15.0 and 4.6 Hz, 1 H), 2.16 (dd, *J* = 14.3 and 14.2 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 156.6, 155.8, 155.5, 142.5, 141.8, 138.0, 136.4, 134.0, 133.2, 133.0, 130.7, 130.4, 128.6, 127.7, 127.6, 127.4, 127.3, 127.0, 126.5, 94.1, 69.5, 69.4, 53.2, 53.1, 51.2, 32.6, 31.6, 31.4. HRMS (ESI) calcd. for $C_{20}H_{19}ClN_2NaO_4$ $(M + Na)^+$ 409.0926, found 409.0925.

Dimethyl 5-amino-7-bromo-2-(3-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-dicarboxylate (rotamer ratio= 7:3, 24dd):



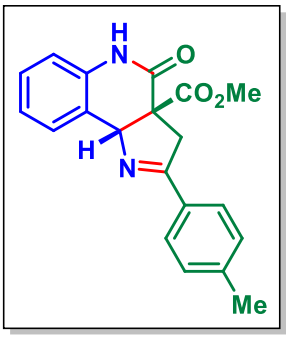
White solid; R_f (hexane/EtOAc, 8:2) 0.40; mp 229-231 °C; yield 195 mg, 71%. IR (KBr, neat) 3426, 3315, 2945, 1701, 1667, 1615, 1438, 1326, 1238, 1186, 1115, 765, 520 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1 H), 7.58–7.54 (m, 1 H), 7.22 (t, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* = 8.4 Hz, 1 H), 6.88–6.78 (m, 3 H), 5.50 (dd, *J* = 13.4 and 4.3 Hz, 1 H, major), 5.31 (dd, *J* = 13.4 and 3.8 Hz, 1 H, minor), 3.78 (s, 3 H, major), 3.75 (s, 3 H, minor), 3.68 (s, 3 H, minor), 3.55 (s, 3 H, major), 2.97 (dd, *J* = 14.8 and 4.6 Hz, 1 H), 2.14 (dd, *J* = 14.8 and 13.4 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 159.8, 155.8, 155.3, 143.5, 138.4, 137.1, 133.7, 133.5, 133.4, 130.3, 129.7, 122.0, 119.3, 118.9, 113.0, 112.9, 112.5, 94.3, 94.0, 69.5, 55.4, 53.2, 51.3, 32.7, 31.5. HRMS (ESI) calcd. for $C_{21}H_{22}BrN_2O_5$ $(M + H)^+$ 461.0707, found 461.0691.

(5-amino-2-phenyl-2,3-dihydro-1*H*-benzo[*b*]azepine-1,4-diyl)bis(phenylmethanone) (24am):



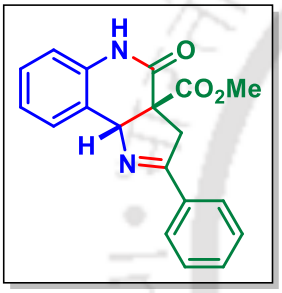
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 114 mg, 43%. IR (KBr, neat) ν 3069, 2924, 2227, 1691, 1596, 1491, 1449, 1391, 1262, 1175, 1023, 760, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2 H), 7.31–7.25 (m, 5 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 6.98-6.93 (m, 5 H), 6.85 (t, *J* = 7.2 Hz, 2 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 5.59 (dd, *J* = 13.8 and 11.5 Hz, 1 H), 3.83 (dd, *J* = 19.5 and 13.9 Hz, 1 H), 3.48 (dd, *J* = 19.5 and 11.7 Hz, 1 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 193.4, 158.7, 144.6, 141.0, 140.5, 133.5, 133.0, 130.6, 130.5, 129.9, 129.6, 129.2, 128.9, 128.5, 127.9, 127.7, 127.4, 126.4, 117.3, 114.9, 112.0, 69.2, 41.5. Anal. Calcd. for $C_{30}H_{24}N_2O_2$: C, 81.06; H, 5.44, found: C, 81.09; H, 5.46.

Methyl 4-*oxo*-2-(*p*-tolyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25aa):



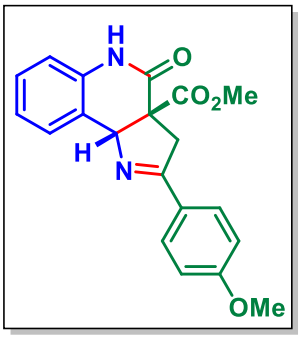
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 170-172 °C; yield 130 mg, 65%. IR (KBr, neat) ν 3212, 3064, 2922, 1738, 1675, 1601, 1430, 1383, 1246, 1185, 1012, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.29–7.25 (m, 1 H), 7.20–7.14 (m, 3 H), 6.83 (d, *J* = 7.8 Hz, 1 H), 5.42 (s, 1 H), 4.06 (dd, *J* = 17.2 and 1.6 Hz, 1 H), 3.95 (dd, *J* = 17.2 and 2.2 Hz, 1 H), 3.70 (s, 3 H), 2.36 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.5, 171.0, 168.3, 142.0, 135.5, 130.5, 130.4, 129.5, 129.4, 128.2, 124.3, 120.6, 116.0, 76.7, 59.4, 53.6, 45.9, 21.7. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_3$ $(M + H)^+$ 335.1391, found 335.1395.

Methyl 4-*oxo*-2-phenyl-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ab):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 232-234 °C; yield 131 mg, 68%. IR (KBr, neat) ν 3209, 3064, 2953, 1736, 1678, 1601, 1496, 1441, 1383, 1340, 1211, 1045, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1 H), 7.86–7.84 (m, 2 H), 7.64 (dd, *J* = 7.2 and 1.4 Hz, 1 H), 7.46–7.38 (m, 3 H), 7.33–7.28 (m, 1 H), 7.18 (dt, *J* = 7.2 and 1.2 Hz, 1 H), 6.86 (dd, *J* = 7.2 and 1.2 Hz, 1 H), 5.46 (t, *J* = 1.8 Hz, 1 H), 4.05 (dd, *J* = 17.2 and 1.6 Hz, 1 H), 4.00 (dd, *J* = 17.2 and 2.2 Hz, 1 H), 3.74 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.6, 170.9, 168.0, 135.5, 133.1, 131.6, 130.6, 129.5, 128.8, 128.2, 124.4, 120.5, 116.0, 76.8, 59.5, 53.7, 45.9. HRMS (ESI) calcd. for $C_{19}H_{17}N_2O_3$ $(M + H)^+$ 321.1234, found 321.1231.

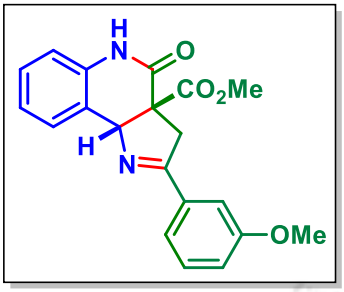
Methyl 2-(4-methoxyphenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ac):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 178-180 °C; yield 121 mg, 58%. IR (KBr, neat) ν 3206, 3069, 2956, 1736, 1678, 1601, 1570, 1343, 1246, 1177, 1032, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 7.5 Hz, 1 H), 7.29–7.25 (m, 1 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 6.88 (d, *J* = 7.5 Hz, 2 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 5.40 (s, 1 H), 4.03 (dd, *J* = 17.0 and 1.2 Hz, 1 H), 3.94 (dd, *J* = 17.0 and 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.70 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.0, 170.9, 168.1, 162.3, 135.5, 130.6,

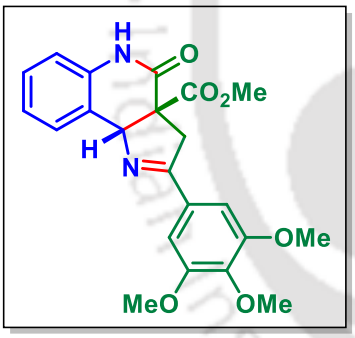
130.0, 129.5, 125.9, 124.3, 120.7, 116.0, 114.1, 76.6, 59.5, 55.6, 53.6, 45.8. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_4$ $(M + H)^+$ 351.1339, found 351.1339.

Methyl 2-(3-methoxyphenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ad):



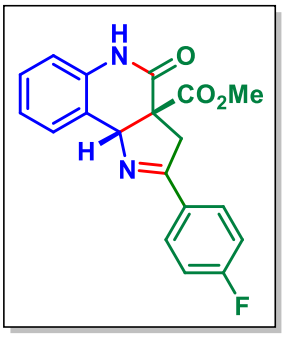
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 163-165 °C; yield 128 mg, 61%. IR (KBr, neat) ν 3206, 3064, 2924, 1736, 1675, 1430, 1377, 1240, 1180, 1030, 830 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1 H), 7.65 (dd, *J* = 7.8 and 1.4 Hz, 1 H), 7.43–7.39 (m, 2 H), 7.34–7.28 (m, 2 H), 7.19 (dt, *J* = 7.8 and 1.2 Hz, 1 H), 7.03–7.00 (m, 1 H), 6.84 (dd, *J* = 8.0 and 1.2 Hz, 1 H), 5.46 (t, *J* = 1.8 Hz, 1 H), 4.07 (dd, *J* = 17.2 and 1.6 Hz, 1 H), 4.00 (dd, *J* = 17.2 and 2.2 Hz, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.6, 170.9, 167.9, 160.0, 135.5, 134.6, 130.7, 129.8, 129.5, 124.3, 121.0, 120.6, 118.2, 115.9, 112.6, 76.8, 59.6, 55.7, 53.7, 46.1. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_4$ $(M + H)^+$ 351.1339, found 351.1340.

Methyl 4-*oxo*-2-(3,4,5-trimethoxyphenyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ae):



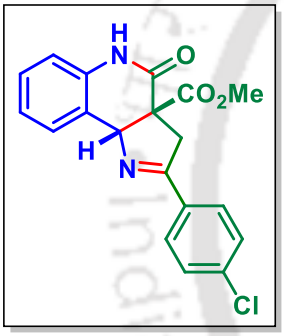
White solid; R_f (hexane/EtOAc, 6:4) 0.40; mp 187-188 °C; yield 132 mg, 54%. IR (KBr, neat) ν 3267, 2851, 1736, 1686, 1501, 1356, 1235, 1124, 1003, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.30 (dt, *J* = 7.8 and 1.5 Hz, 1 H), 7.18 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 7.07 (s, 2 H), 6.81 (dd, *J* = 7.8 and 1.2 Hz, 1 H), 5.42 (s, 1 H), 4.05 (dd, *J* = 17.0 and 1.4 Hz, 1 H), 3.95 (dd, *J* = 17.0 and 2.2 Hz, 1 H), 3.88 (s, 6 H), 3.87 (s, 3 H), 3.72 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.6, 170.8, 167.7, 153.4, 141.2, 135.5, 130.8, 129.6, 128.6, 124.3, 120.6, 115.8, 105.6, 76.7, 61.2, 59.7, 56.5, 53.7, 45.9. HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_6$ $(M + H)^+$ 411.1551, found 411.1551.

Methyl 2-(4-fluorophenyl)-4-*oxo*-3a,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25af):



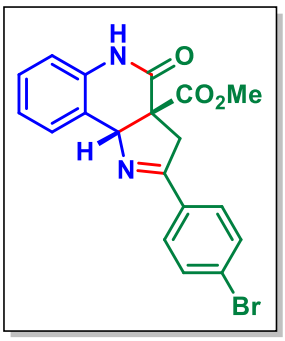
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 164-166 °C; yield 148 mg, 73%. IR (KBr, neat) ν 3206, 3067, 2922, 1738, 1678, 1601, 1430, 1383, 1243, 1106, 1043, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1 H), 7.84–7.81 (m, 2 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.06 (t, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 7.9 Hz, 1 H), 5.42 (s, 1 H), 4.03 (dd, *J* = 17.2 and 1.6 Hz, 1 H), 3.96 (dd, *J* = 17.2 and 2.2 Hz, 1 H), 3.70 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.8, 170.4, 168.2, 164.9 (d, *J* = 250.6 Hz), 135.5, 130.5, 130.4 (d, *J* = 8.6 Hz), 129.5, 129.4, 124.4, 120.3, 116.1, 115.8 (d, *J* = 21.6 Hz), 76.8, 59.5, 53.7, 45.9. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -111.37 (s, -F). HRMS (ESI) calcd. for $C_{19}H_{16}FN_2O_3$ $(M + H)^+$ 339.1140, found 339.1143.

Methyl 2-(4-chlorophenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ag):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 154-156 °C; yield 167 mg, 79%. IR (KBr, neat) ν 3193, 3053, 2919, 1746, 1673, 1593, 1427, 1338, 1238, 1180, 1040, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 9.64 (s, 1 H), 7.79–7.76 (m, 2 H), 7.6–7.58 (m, 1 H), 7.40–7.33 (m, 2 H), 7.30–7.26 (m, 1 H), 7.17– 7.12 (m, 1 H), 6.94 (dd, *J* = 8.0 and 2.8 Hz, 1 H), 5.42 (s, 1 H), 4.02 (dd, *J* = 17.2 and 3.0 Hz, 1 H), 3.93 (dd, *J* = 17.2 and 2.8 Hz, 1 H), 3.72 (dd, *J* = 3.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/DMSO-d_6) δ 170.8, 170.3, 167.3, 137.4, 136.0, 131.6, 130.2, 129.4, 129.3, 128.8, 123.8, 119.8, 116.1, 76.7, 59.3, 53.5, 45.6. HRMS (ESI) calcd. for $C_{19}H_{16}ClN_2O_3$ $(M + H)^+$ 355.0844, found 355.0850.

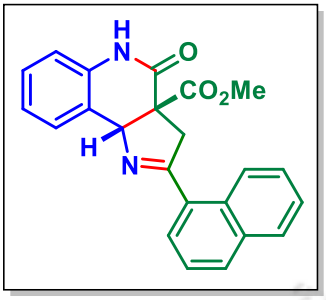
Methyl 2-(4-bromophenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ah):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 183-185 °C; yield 167 mg, 75%. IR (KBr, neat) ν 3193, 3051, 2853, 1746, 1667, 1593, 1430, 1338, 1238, 1180, 1006, 956, 760 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$/DMSO-d_6) δ 9.46 (s, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.25 (t, *J* = 7.6 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 7.6 Hz, 1 H), 5.37 (s, 1 H), 4.00 (d, *J* = 17.2 Hz, 1 H), 3.90 (d, *J* = 17.2 Hz, 1 H), 3.69 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 170.9, 170.5, 167.3, 135.9, 131.90, 131.87, 130.2, 129.6,

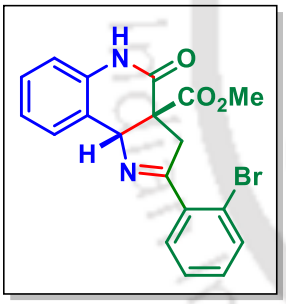
129.4, 126.0, 123.9, 119.8, 116.1, 76.7, 59.3, 53.6, 45.6. HRMS (ESI) calcd. for $C_{19}H_{16}BrN_2O_3$ $(M + H)^+$ 399.0339, found 399.0340.

Methyl 2-(naphthalen-1-yl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25aj):



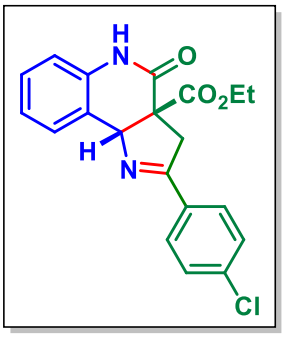
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 206-208 °C; yield 122 mg, 55%. IR (KBr, neat) ν 3212, 3034, 2956, 1736, 1680, 1599, 1441, 1306, 1248, 1009, 803, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/DMSO-d_6) δ 9.83 (s, 1 H), 8.88–8.84 (m, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.86–7.82 (m, 1 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.51–7.46 (m, 3 H), 7.36–7.33 (m, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 8.0 Hz, 1 H), 5.61 (s, 1 H), 4.20–4.10 (m, 2 H), 3.73 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$/DMSO-d_6) δ 172.9, 171.1, 167.7, 135.8, 134.1, 131.6, 131.1, 130.6, 130.5, 129.4, 128.6, 127.6, 126.5, 126.4, 124.9, 124.1, 120.5, 116.0, 77.5, 59.1, 53.6, 49.0. HRMS (ESI) calcd. for $C_{23}H_{19}N_2O_3$ $(M + H)^+$ 371.1391, found 371.1394.

Methyl 2-(2-bromophenyl)-4-*oxo*-3a,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25an):



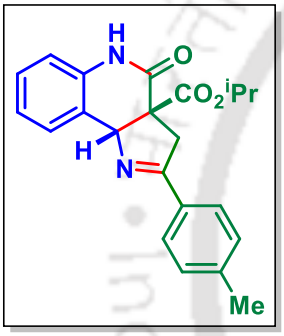
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 190-192 °C; yield 140 mg, 59%. IR (KBr, neat) ν 3209, 3061, 2919, 1738, 1680, 1601, 1430, 1391, 1277, 1019, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 7.51 (dd, *J* = 7.8 and 1.4 Hz, 1 H), 7.47 (dd, *J* = 7.8 and 1.2 Hz, 1 H), 7.37 (dd, *J* = 7.6 and 1.8 Hz, 1 H), 7.22–7.17 (m, 2 H), 7.16–7.12 (m, 1 H), 7.05 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 6.83 (dd, *J* = 7.8 and 1.2 Hz, 1 H), 5.38 (s, 1 H), 4.11–4.00 (m, 2 H), 3.63 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.9, 170.7, 168.1, 135.8, 135.6, 133.5, 131.3, 130.5, 130.4, 129.6, 127.6, 124.3, 121.4, 119.7, 116.2, 76.4, 59.9, 53.7, 48.9. HRMS (ESI) calcd. for $C_{19}H_{16}BrN_2O_3$ $(M + H)^+$ 399.0339, found 399.0343.

Ethyl 2-(4-chlorophenyl)-4-oxo-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3*a*-carboxylate (25ao):



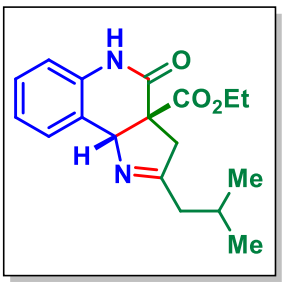
White solid; R_f (hexane/EtOAc, 6:4) 0.50; mp 215-217 °C; yield 147 mg, 67%. IR (KBr, neat) ν 3209, 3064, 2924, 1733, 1678, 1427, 1335, 1275, 1043, 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H), 7.60 (dd, *J* = 7.8 and 1.4 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 7.28 (dt, *J* = 7.8 and 1.8 Hz, 1 H), 7.15 (dt, *J* = 7.6 and 1.2 Hz, 1 H), 6.85 (dd, *J* = 7.8 and 1.2 Hz, 1 H), 5.42 (s, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.03–3.93 (m, 2 H), 1.14 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 137.7, 135.5, 131.6, 130.4, 129.5, 129.4, 129.0, 124.3, 120.2, 116.0, 76.8, 62.7, 59.6, 45.5, 14.1. HRMS (ESI) calcd. for $C_{20}H_{18}ClN_2O_3$ $(M + H)^+$ 369.1000, found 369.0998.

Isopropyl 4-*oxo*-2-(*p*-tolyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ap):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 238-240 °C; yield 173 mg, 80%. IR (KBr, neat) ν 3212, 3061, 2924, 1733, 1678, 1372, 1248, 1185, 1043, 821, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.60 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.29–7.25 (m, 2 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.13 (dt, *J* = 7.6 and 1.0 Hz, 1 H), 6.81 (dd, *J* = 8.0 and 1.2 Hz, 1 H), 5.38 (s, 1 H), 5.03–4.98 (m, 1 H), 4.00 (dd, d, *J* = 17.2 and 1.2 Hz, 1 H), 3.93 (dd, *J* = 17.2 and 1.8 Hz, 1 H), 2.37 (s, 3 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 1.07 (d, *J* = 6.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.8, 169.7, 168.3, 141.9, 135.6, 130.5, 130.4, 129.5, 129.4, 128.2, 124.2, 120.8, 115.8, 70.4, 59.8, 45.1, 21.8, 21.7, 21.6. HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_3$ $(M + H)^+$ 363.1703, found 363.1710.

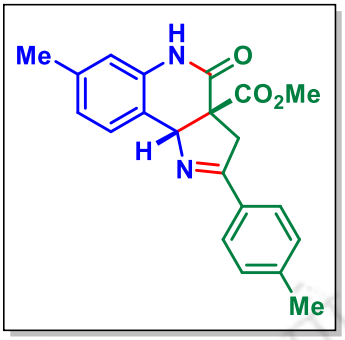
Ethyl 2-isobutyl-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25aq):



Yellow liquid; R_f (hexane/EtOAc, 6:4) 0.40; yield 94 mg, 50%. IR (KBr, neat) ν 3212, 3064, 2866, 1733, 1678, 1601, 1425, 1211, 1101, 1037, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1 H), 7.51 (dd, *J* = 7.8 and 1.4 Hz, 1 H), 7.25 (dt, *J* = 7.4 and 2.2 Hz, 1 H), 7.10 (dt, *J* = 7.4 and 1.2 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 5.23 (s, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.58–3.47 (m, 2 H), 2.25 (dd, *J* = 8.2 and 2.0 Hz, 2 H), 2.03–1.94 (m, 1 H), 1.12 (t, *J* = 7.2 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 177.3, 170.4, 168.6, 135.5, 130.2, 129.3, 124.2,

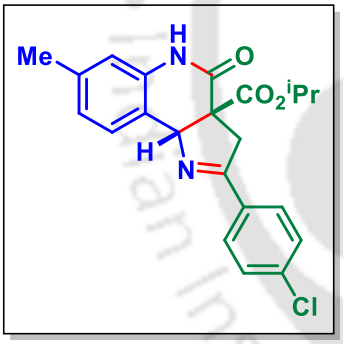
120.5, 115.9, 76.2, 62.5, 59.6, 47.7, 42.7, 26.6, 22.8, 22.7, 14.1. HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3$ $(M + H)^+$ 315.1704, found 315.1705.

Methyl 7-methyl-4-*oxo*-2-(*p*-tolyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ba):



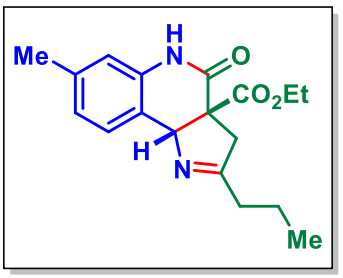
White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 195-197 °C; yield 125 mg, 60%. IR (KBr, neat) ν 3212, 3032, 2956, 1738, 1675, 1607, 1435, 1340, 1277, 1185, 1040, 816 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 6.96 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 6.63 (s, 1 H), 5.38 (s, 1 H), 4.03 (dd, *J* = 17.0 and 1.4 Hz, 1 H), 3.94 (dd, *J* = 17.0 and 2.2 Hz, 1 H), 3.70 (s, 3 H), 2.36 (s, 3 H), 2.33 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.3, 171.1, 168.3, 141.9, 139.7, 135.4, 130.5, 130.4, 129.5, 128.2, 125.2, 117.7, 116.5, 76.6, 59.6, 53.6, 45.9, 21.7, 21.5. HRMS (ESI) calcd. for $C_{21}H_{21}N_2O_3$ $(M + H)^+$ 349.1547, found 349.1544.

Isopropyl 2-(4-chlorophenyl)-7-methyl-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25bl):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 223-225 °C; yield 173 mg, 73%. IR (KBr, neat) ν 3201, 3098, 2856, 1736, 1675, 1372, 1277, 1106, 1014, 829 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.49 (bs, 1 H), 7.77 (dd, *J* = 8.6 and 2.0 Hz, 2 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.36 (dd, *J* = 8.6 and 2.0 Hz, 2 H), 6.96 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 6.62 (s, 1 H), 5.36 (s, 1 H), 5.03–4.98 (m, 1 H), 3.98–3.90 (m, 2 H), 2.33 (s, 3 H), 1.18 (d, *J* = 6.3 Hz, 3 H), 1.09 (d, *J* = 6.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.6, 169.6, 168.3, 139.7, 137.6, 135.5, 131.8, 130.2, 129.5, 129.0, 125.2, 117.5, 116.3, 76.7, 70.5, 60.0, 45.1, 21.7, 21.6, 21.5. HRMS (ESI) calcd. for $C_{22}H_{22}ClN_2O_3$ $(M + H)^+$ 397.1314, found 397.1319.

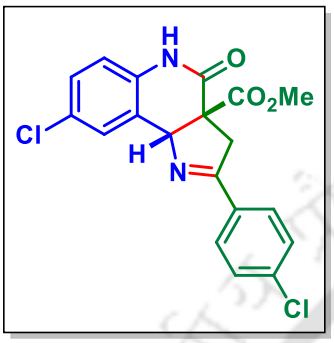
Ethyl 7-methyl-4-oxo-2-propyl-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25br):



Yellow liquid; R_f (hexane/EtOAc, 6:4) 0.40; yield 88 mg, 47%. IR (KBr, neat) ν 3210, 3055, 2870, 1733, 1672, 1601, 1433, 1205, 1108, 1037, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 6.90 (d, *J* = 7.7 Hz, 1 H), 6.63 (s, 1 H), 5.18 (s, 1 H), 4.12 (q, *J* = 7.1 Hz, 1 H), 3.54 (d, *J* = 17.5 Hz,

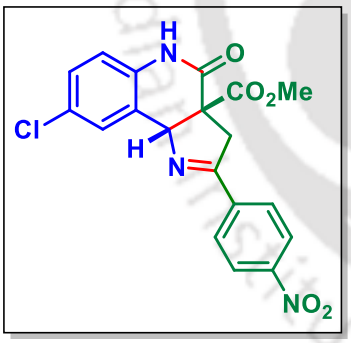
1 H), 3.46 (d, *J* = 17.5 Hz, 1 H), 2.34–2.31 (m, 2 H), 2.30 (s, 3 H), 1.63–1.55 (m, 2 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 0.89 (t, *J* = 7.4 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 177.6, 170.5, 168.7, 139.4, 135.3, 130.0, 125.1, 117.5, 116.4, 76.0, 62.5, 59.5, 47.4, 35.6, 21.4, 19.9, 14.1, 14.0. HRMS (ESI) calcd. for $C_{18}H_{23}N_2O_3$ $(M + H)^+$ 315.1703, found 315.1731.

Methyl 8-chloro-2-(4-chlorophenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25cg):



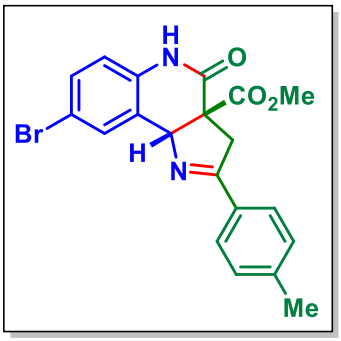
White solid; R_f (hexane/EtOAc, 8:2) 0.40; mp 203-205 °C; yield 169 mg, 73%. IR (KBr, neat) ν 3212, 3067, 2924, 1738, 1683, 1435, 1398, 1243, 1011, 826 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/DMSO-d_6) δ 9.87 (s, 1 H), 7.77 (d, *J* = 8.0 Hz, 2 H), 7.56 (s, 1 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 1 H), 5.35 (s, 1 H), 4.00 (d, *J* = 17.2 Hz, 1 H), 3.92 (d, *J* = 17.2 Hz, 1 H), 3.73 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$/DMSO-d_6) δ 170.8, 170.5, 167.1, 137.6, 134.8, 131.4, 130.0, 129.41, 129.37, 129.0, 128.5, 121.4, 117.5, 76.2, 59.1, 53.6, 45.5. HRMS (ESI) calcd. for $C_{19}H_{15}Cl_2N_2O_3$ $(M + H)^+$ 389.0455, found 389.0461.

Methyl 8-chloro-2-(4-nitrophenyl)-4-*oxo*-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ci):



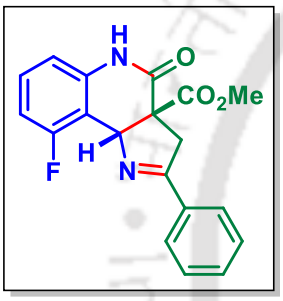
Yellow solid; R_f (hexane/EtOAc, 6:4) 0.40; mp 209-211 °C; yield 184 mg, 77%. IR (KBr, neat) ν 3214, 3075, 2959, 1741, 1678, 1539, 1522, 1430, 1346, 1277, 1111, 1043, 821 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (s, 1 H), 8.26 (d, *J* = 8.4 Hz, 2 H), 8.00 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 2.3 Hz, 1 H), 7.29 (dd, *J* = 8.4 and 2.3 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 5.43 (s, 1 H), 4.07 (dd, *J* = 17.4 and 1.8 Hz, 1 H), 4.02 (dd, *J* = 17.4 and 2.4 Hz, 1 H), 3.75 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 170.3, 170.1, 167.4, 149.7, 138.4, 134.1, 130.6, 129.9, 129.5, 129.2, 124.1, 121.2, 117.3, 76.7, 59.3, 54.0, 45.9. HRMS (ESI) calcd. for $C_{19}H_{15}ClN_3O_5$ $(M + H)^+$ 400.0695, found 400.0698.

Methyl 8-bromo-4-*oxo*-2-(*p*-tolyl)-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25da):



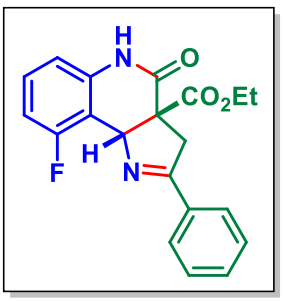
Pale yellow solid; R_f (hexane/EtOAc, 8:2) 0.40; mp 219-221 °C; yield 173 mg, 70%. IR (KBr, neat) ν 3212, 3069, 2953, 1736, 1678, 1567, 1433, 1340, 1275, 1182, 1040, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 7.75–7.70 (m, 3 H), 7.38 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 7.20 (d, *J* = 7.6 Hz, 2 H), 6.75 (d, *J* = 8.4 Hz, 1 H), 5.35 (s, 1 H), 4.03 (dd, *J* = 17.2 and 1.4 Hz, 1 H), 3.95 (dd, *J* = 17.2 and 2.2 Hz, 1 H), 3.71 (s, 3 H), 2.37 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.0, 170.5, 168.2, 142.2, 134.7, 133.3, 132.4, 130.2, 129.6, 128.2, 122.5, 117.7, 116.7, 76.1, 59.2, 53.8, 45.8, 21.8. HRMS (ESI) calcd. for $C_{20}H_{18}BrN_2O_3$ $(M + H)^+$ 413.0495, found 413.0491.

Methyl 9-fluoro-4-*oxo*-2-phenyl-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25eb):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 199-201 °C; yield 127 mg, 63%. IR (KBr, neat) ν 3225, 3064, 2953, 1738, 1680, 1604, 1446, 1343, 1235, 1032, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1 H), 7.86–7.83 (m, 2 H), 7.46–7.36 (m, 3 H), 7.28-7.23 (m, 1 H), 6.88 (dt, *J* = 8.4 and 1.0 Hz, 1 H), 6.70 (dd, *J* = 8.0 and 1.0 Hz, 1 H), 5.64 (s, 1 H), 4.15 (dd, *J* = 17.2 and 1.4 Hz, 1 H), 3.94 (dd, *J* = 17.2 and 2.4 Hz, 1 H), 3.71 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.1, 170.4, 168.4, 161.5 (d, *J* = 247.0 Hz), 137.4 (d, *J* = 6.4 Hz), 133.0, 131.6, 130.8 (d, *J* = 9.8 Hz), 128.8, 128.3, 111.7 (d, *J* = 3.2 Hz), 111.2 (d, *J* = 21.2 Hz), 108.7 (d, *J* = 20.0 Hz), 70.5, 59.2, 53.8, 45.5. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -118.54 (s, -F). HRMS (ESI) calcd. for $C_{19}H_{16}FN_2O_3$ $(M + H)^+$ 339.1140, found 339.1141.

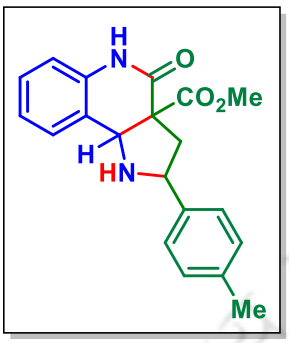
Ethyl 9-fluoro-4-*oxo*-2-phenyl-3,4,5,9b-tetrahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (25ek):



White solid; R_f (hexane/EtOAc, 7:3) 0.40; mp 207-209 °C; yield 107 mg, 51%. IR (KBr, neat) ν 3220, 3064, 2988, 1736, 1675, 1446, 1343, 1275, 1188, 1035, 1022, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.84 (d, *J* = 7.2 Hz, 2 H), 7.46–7.43 (m, 1 H), 7.41–7.38 (m, 2 H), 7.30–7.25 (m, 2 H), 6.90 (t, *J* = 8.0 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 5.63 (s, 1 H), 4.20–4.16 (m, 3 H), 3.91 (dd, *J* = 17.2 and 2.4 Hz, 1 H), 1.16 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 172.3, 169.7, 168.0, 161.6 (d, *J* = 247.2 Hz), 137.5 (d, *J* = 6.4 Hz), 133.1, 131.6, 130.8 (d, *J* = 6.0 Hz), 128.8, 128.3,

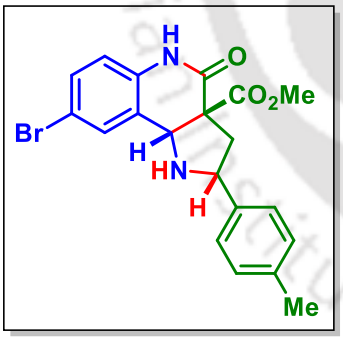
111.4 (d, *J* = 1.0 Hz), 111.2 (d, *J* = 21.4 Hz), 109.0 (d, *J* = 20.2 Hz), 70.5, 62.8, 59.5, 45.2, 14.1. ^{19}F NMR (470 MHz, C_6F_6/$CDCl_3$) δ -118.93 (s, -F). HRMS (ESI) calcd. for $C_{20}H_{18}FN_2O_3$ $(M + H)^+$ 353.1296, found 353.1300.

Methyl (2*R,3a*S**,9b*R**)-4-oxo-2-(*p*-tolyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (diastereomeric mixture; dr = 9:1, 26aa):**



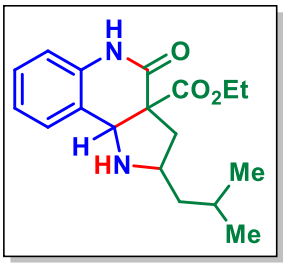
Colourless gum; R_f (hexane/EtOAc, 7:3) 0.40; yield 80 mg, 80%. IR (KBr, neat) ν 3206, 2924, 1733, 1673, 1433, 1214, 1040, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 7.33 (d, *J* = 7.5 Hz, 1 H), 7.30–7.20 (m, 3 H), 7.05–7.01 (m, 3 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 4.80 (s, 1 H, minor), 4.53 (s, 1 H, major), 3.65 (s, 3 H), 3.29 (dd, *J* = 13.1 and 7.3 1 H, minor), 3.11 (dd, *J* = 13.1 and 8.7 Hz, 1 H, major), 2.80 (dd, *J* = 13.8 and 7.8 Hz, 1 H, major), 2.72 (dd, *J* = 13.0 and 8.7 Hz, 1 H, minor), 2.33 (s, 3 H, minor), 2.26 (s, 3 H, major), 2.02 (bs, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.3, 169.6, 139.4, 137.3, 136.2, 129.6, 129.4, 127.1, 123.6, 121.3, 116.2, 65.1, 61.1, 59.6, 53.3, 43.3, 21.2. HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_3$ $(M + H)^+$ 337.1547, found 337.1557.

Methyl (2*R,3a*S**,9b*R**)-8-bromo-4-oxo-2-(*p*-tolyl)-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (26da):**



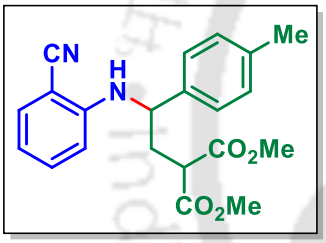
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.40; yield 75 mg, 75%. IR (KBr, neat) ν 3206, 2926, 1733, 1677, 1425, 1256, 1040, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 7.38 (s, 1 H), 7.26 (dd, *J* = 8.4 and 2.2 Hz, 1 H), 7.11 (d, *J* = 7.8 Hz, 2 H), 6.96 (d, *J* = 7.8 Hz, 2 H), 6.72 (d, *J* = 8.4 Hz, 1 H), 4.39 (s, 1 H), 4.35 (t, *J* = 8.2 1 H), 3.59 (s, 3 H), 3.02 (dd, *J* = 13.8 and 8.8 Hz, 1 H), 2.67 (dd, *J* = 13.8 and 7.8 Hz, 1 H), 2.19 (s, 3 H), 2.06 (bs, 1 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.6, 169.1, 139.2, 137.1, 135.1, 132.2, 132.1, 129.2, 126.8, 123.3, 117.4, 115.6, 64.2, 60.6, 59.1, 53.2, 42.8, 21.0. HRMS (ESI) calcd. for $C_{20}H_{20}BrN_2O_3$ $(M + H)^+$ 415.0652, found 415.0649.

Ethyl (2*S,3a*S**,9b*R**)-2-isobutyl-4-oxo-1,2,3,4,5,9b-hexahydro-3a*H*-pyrrolo[3,2-*c*]quinoline-3a-carboxylate (diastereomeric mixture, dr = 85:15, 26aq):**



Pale yellow gum; R_f (hexane/EtOAc, 6:4) 0.40; yield 90 mg, 89%. IR (KBr, neat) ν 3212, 2953, 1733, 1675, 1466, 1246, 1098, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1 H), 7.24 (d, *J* = 7.6 Hz, 1 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 4.47 (s, 1 H, minor), 4.27 (s, 1 H, major), 4.05–3.95 (m, 2 H), 3.39–3.31 (m, 1 H, major), 3.30–3.25 (m, 1 H, minor), 2.87 (dd, *J* = 12.9 and 7.2 Hz, 1 H, minor), 2.81 (dd, *J* = 12.9 and 8.2 Hz, 1 H, major), 2.29 (dd, *J* = 13.6 and 7.6 Hz, 1 H, major), 2.23 (dd, *J* = 13.6 and 8.4 Hz, 1 H, minor), 2.10 (bs, 1 H), 1.62–1.55 (m, 1 H, major), 1.43–1.33 (m, 1 H, minor), 1.31–1.24 (m, 1 H), 1.22–1.18 (m, 1 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 0.84–0.80 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.8, 170.3, 169.5, 136.1, 129.5, 129.4, 129.3, 123.5, 121.3, 116.1, 65.0, 63.4, 62.1, 62.0, 59.1, 56.1, 55.3, 46.5, 45.8, 41.8, 41.1, 26.2, 23.1, 22.8, 14.0. HRMS (ESI) calcd. for $C_{18}H_{25}N_2O_3$ $(M + H)^+$ 317.1860, found 317.1864.

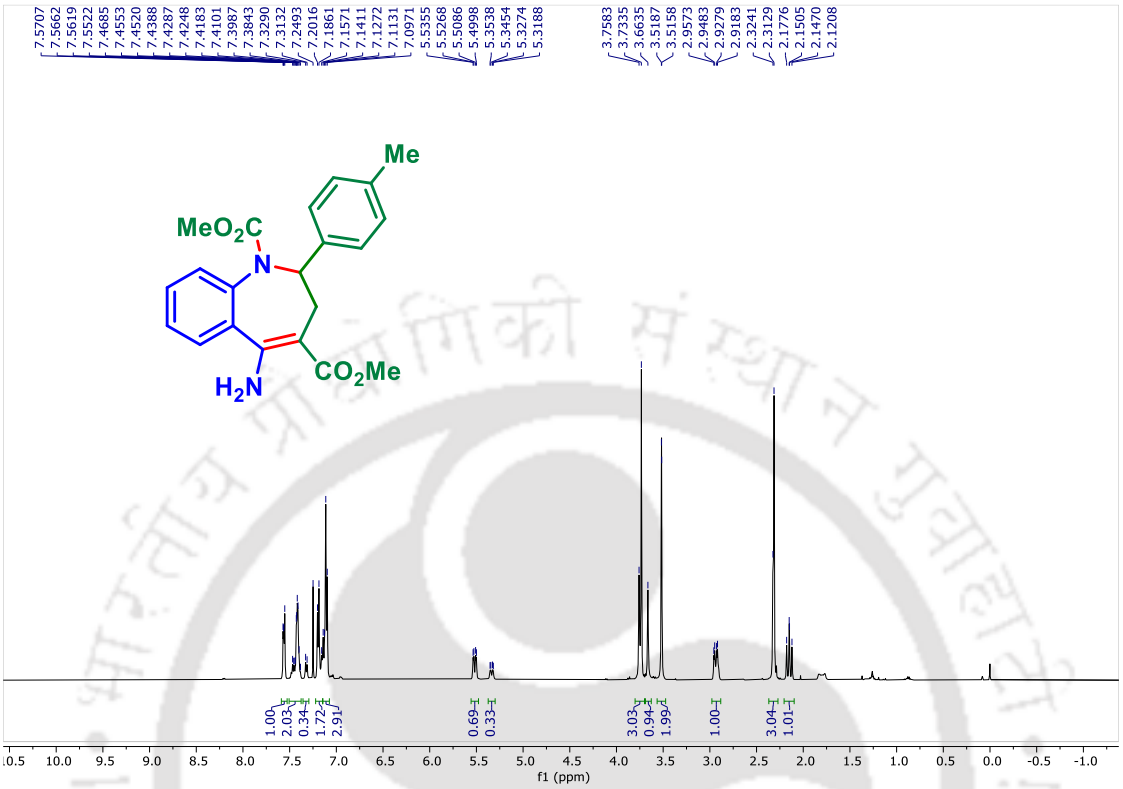
Dimethyl 2-(2-((2-cyanophenyl)amino)-2-(*p*-tolyl)ethyl)malonate (Intermediate A, when R = H, R^1 = R^2 = Me):



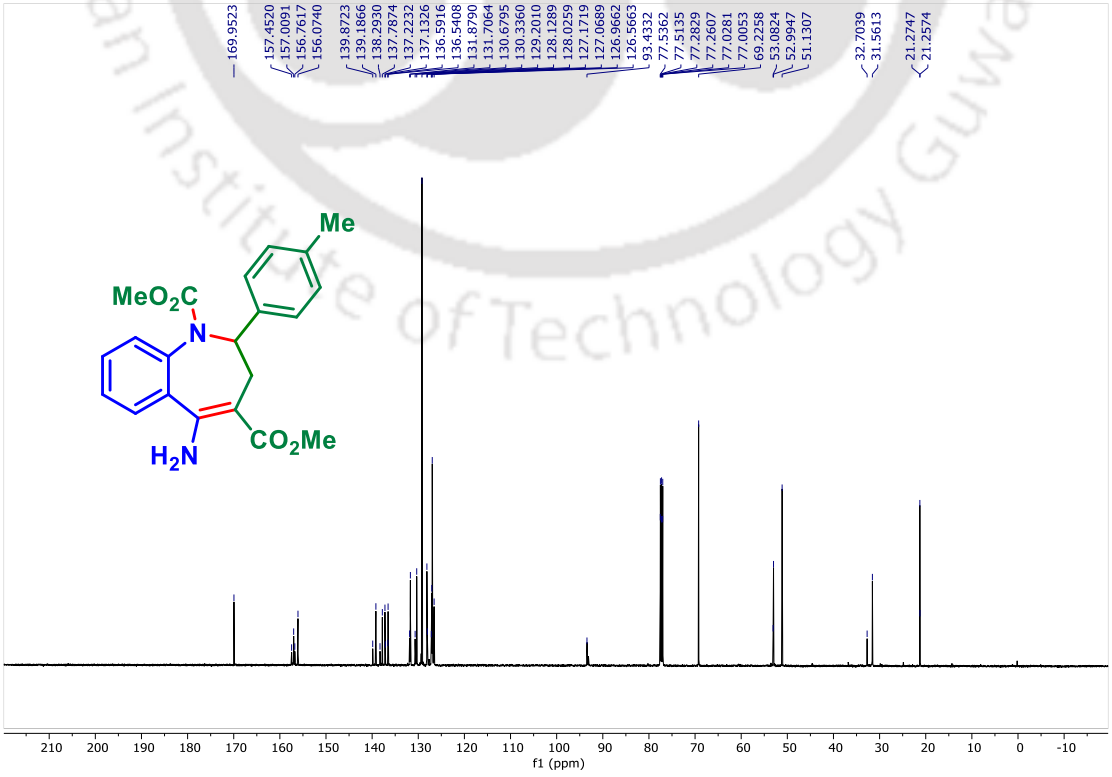
Colourless gum; R_f (hexane/EtOAc, 8:2) 0.50; yield 121 mg, 82%. IR (KBr, neat) ν 3367, 2956, 2213, 1733, 1604, 1580, 1459, 1277, 1078, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 7.8 and 1.6 Hz, 1 H), 7.25–7.19 (m, 3 H), 7.14 (d, *J* = 7.8 Hz, 2 H), 6.62 (t, *J* = 7.6 Hz, 1 H), 6.54 (d, *J* = 8.6 Hz, 1 H), 5.05 (d, *J* = 7.2 Hz, 1 H), 4.53 (q, *J* = 7.2 Hz, 1 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.49 (t, *J* = 7.6 Hz, 1 H), 2.55–2.49 (m, 1 H), 2.44–2.38 (m, 1 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.6, 169.5, 149.2, 138.1, 137.7, 134.2, 132.9, 129.8, 126.3, 117.8, 117.3, 112.2, 96.6, 55.9, 53.0, 52.9, 49.1, 36.7, 21.1. HRMS (ESI) calcd. for $C_{21}H_{22}N_2NaO_4$ $(M + H)^+$ 389.1472, found 389.1493.

2.10. Representative Spectra

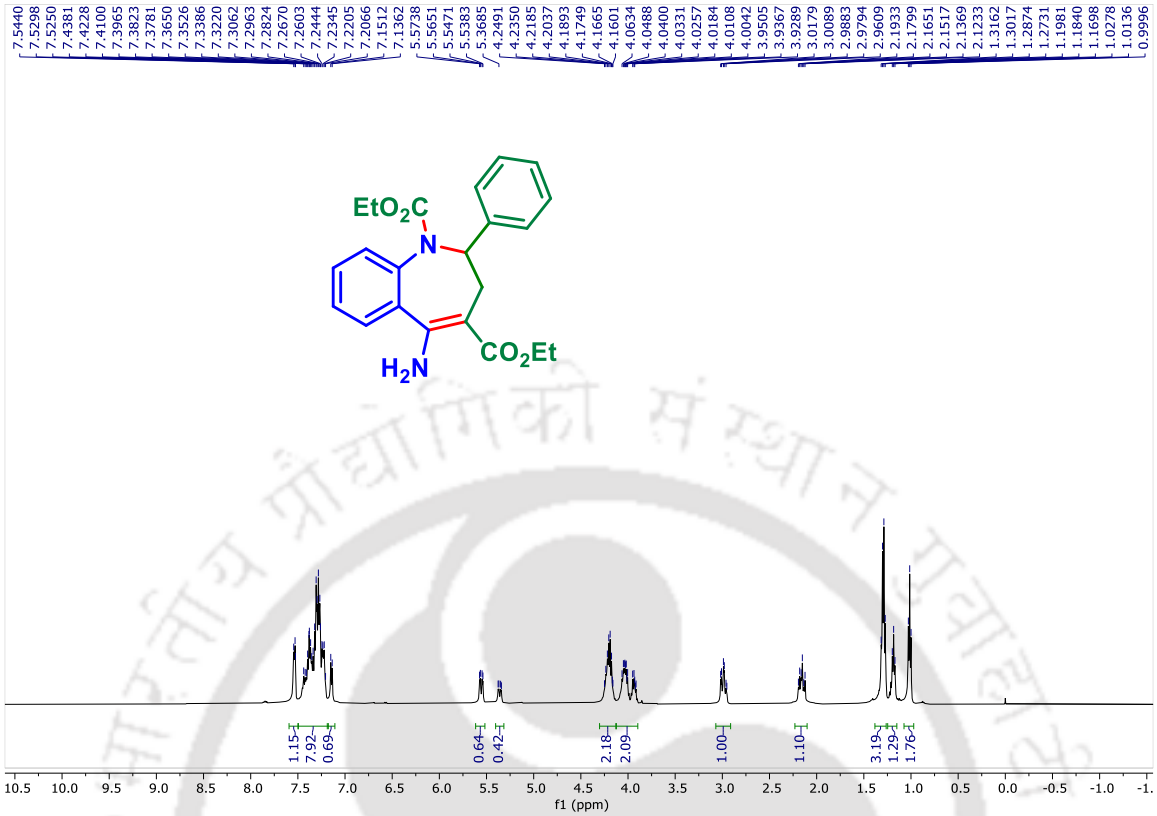
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**24aa**):



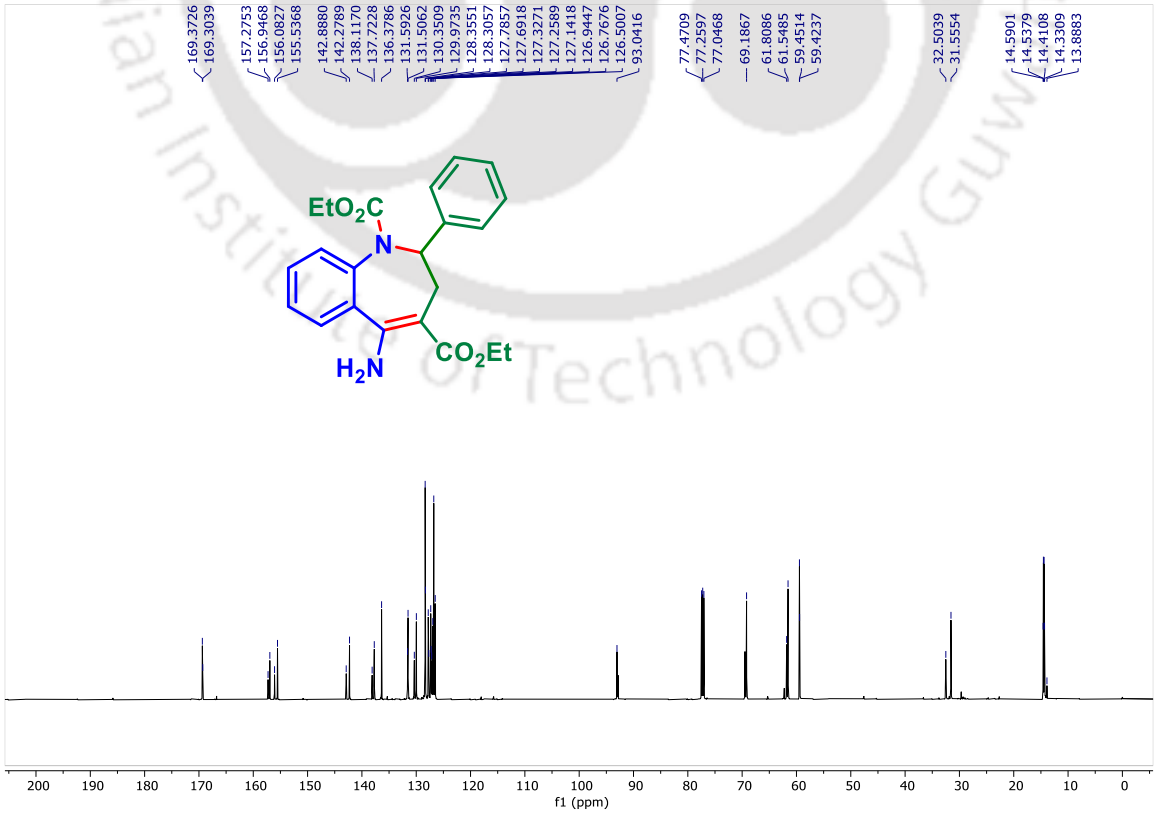
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**24aa**):



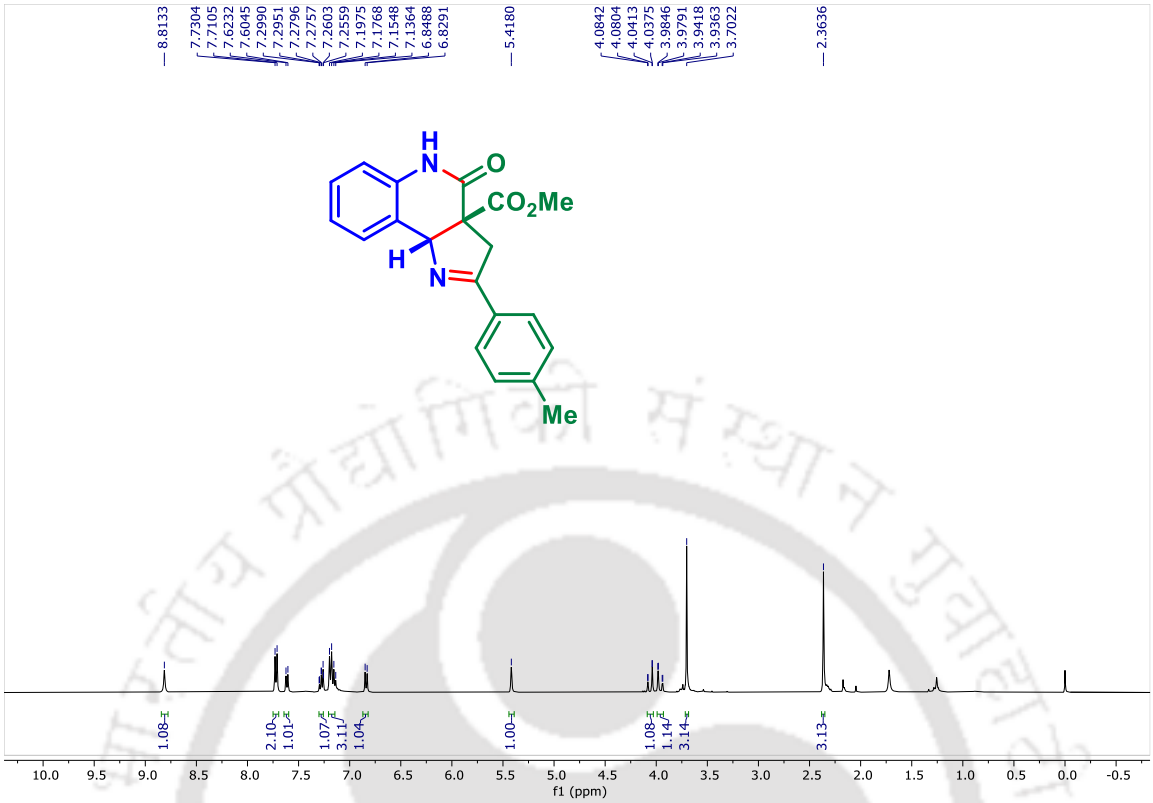
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**24ak**):



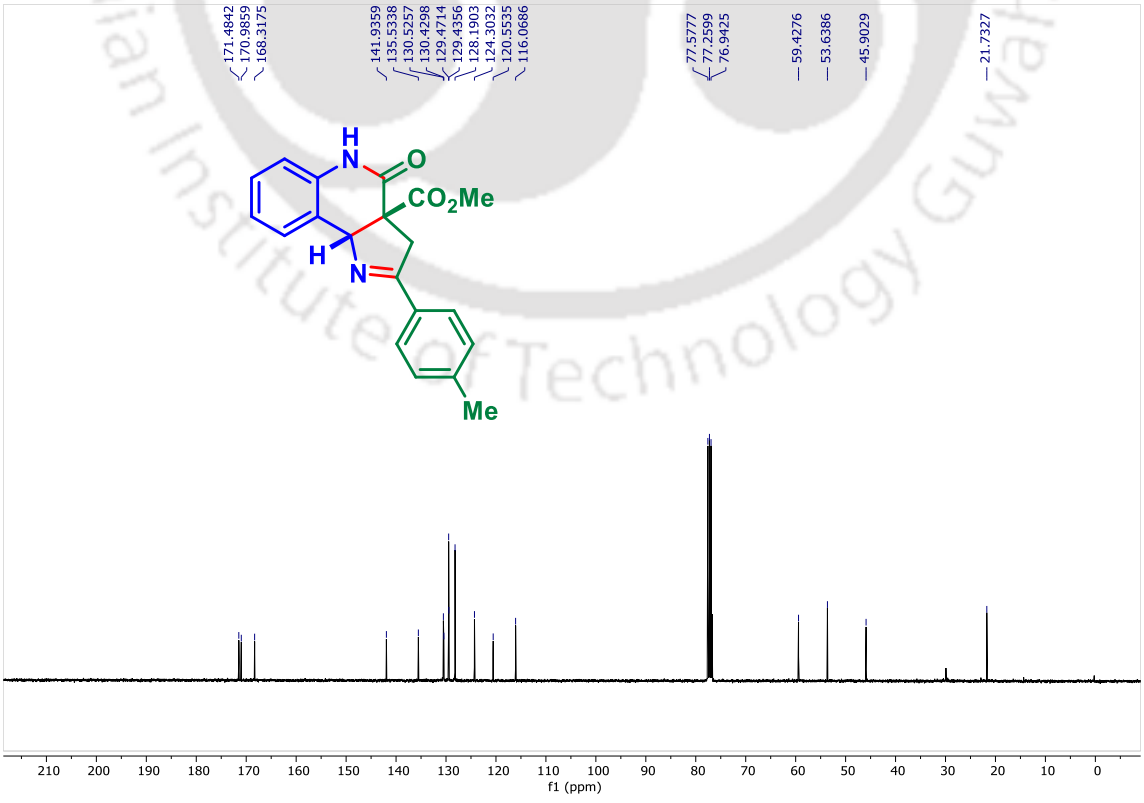
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**24ak**):



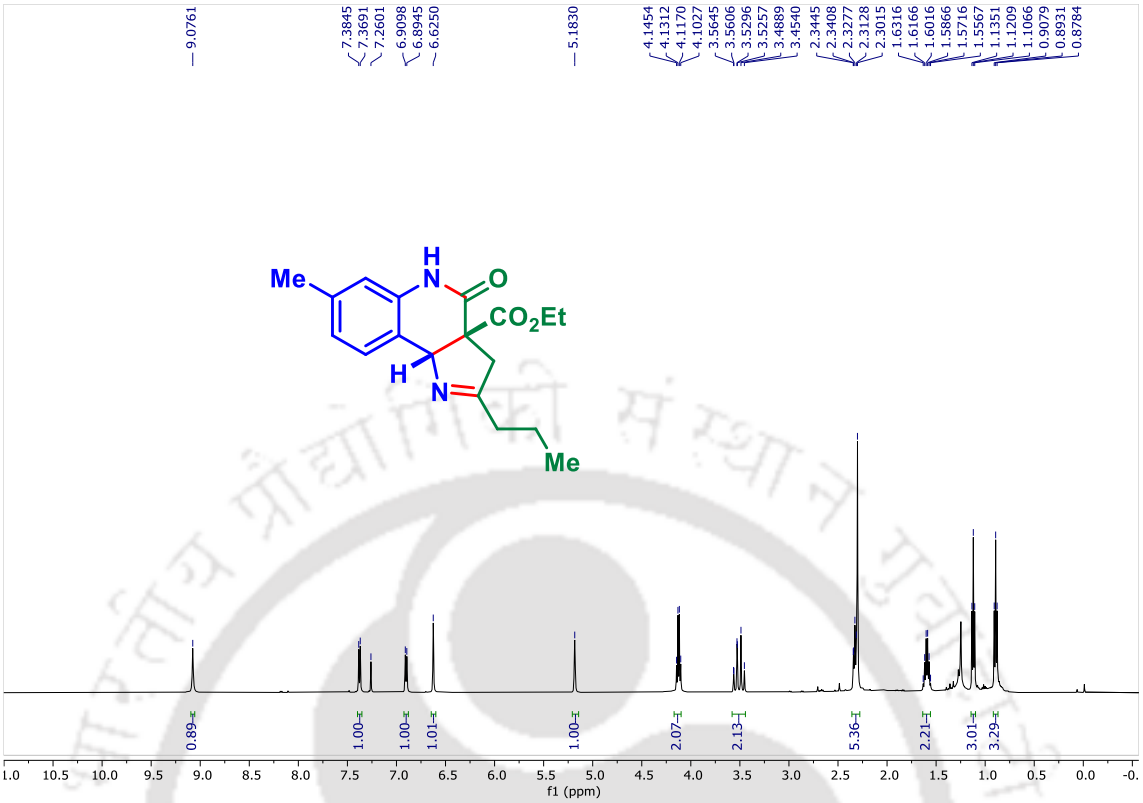
^{1}H ($CDCl_3$, 400 MHz) spectrum of compound (**25aa**):



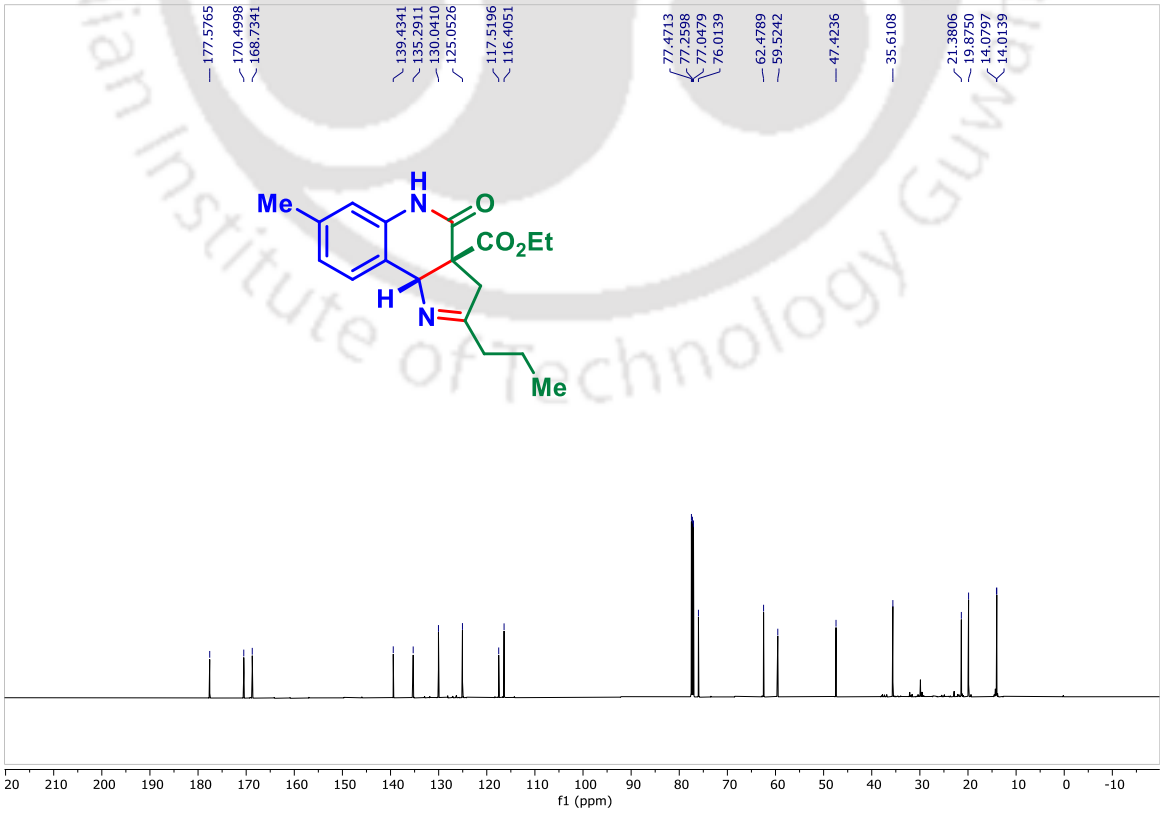
$^{13}C\{^{1}H\}$ ($CDCl_3$, 100 MHz) spectrum of compound (**25aa**):



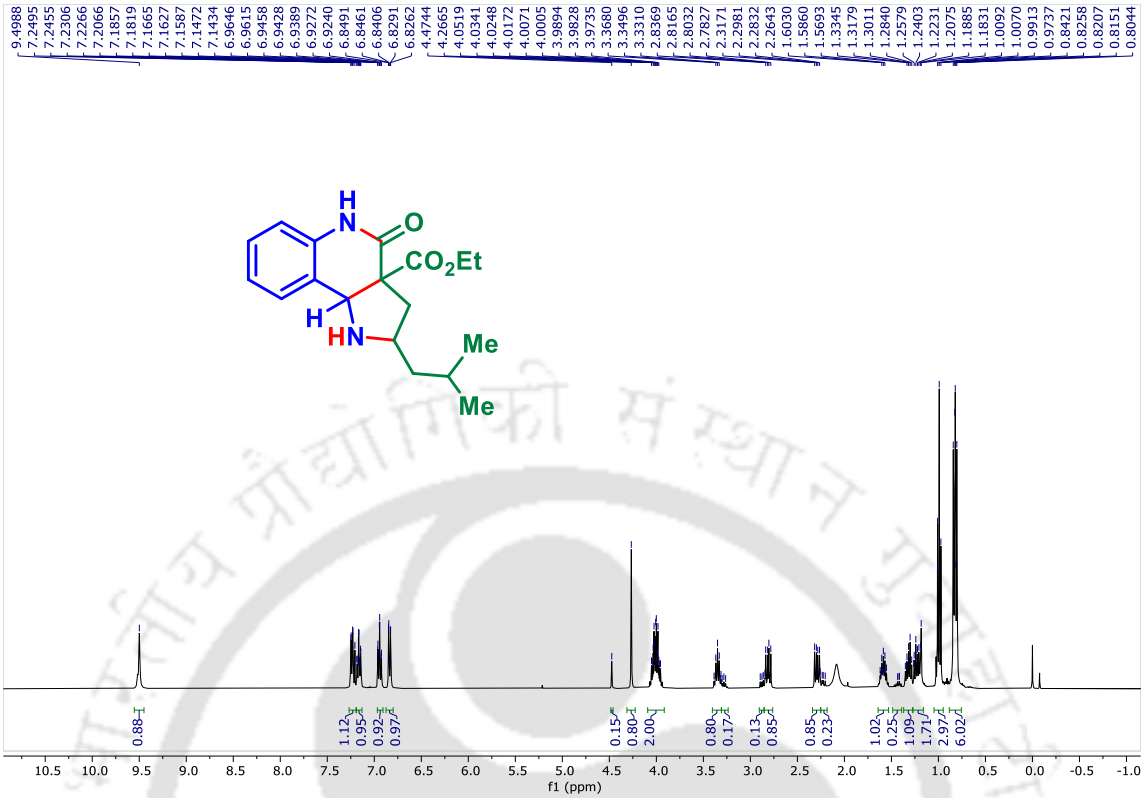
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**25br**):



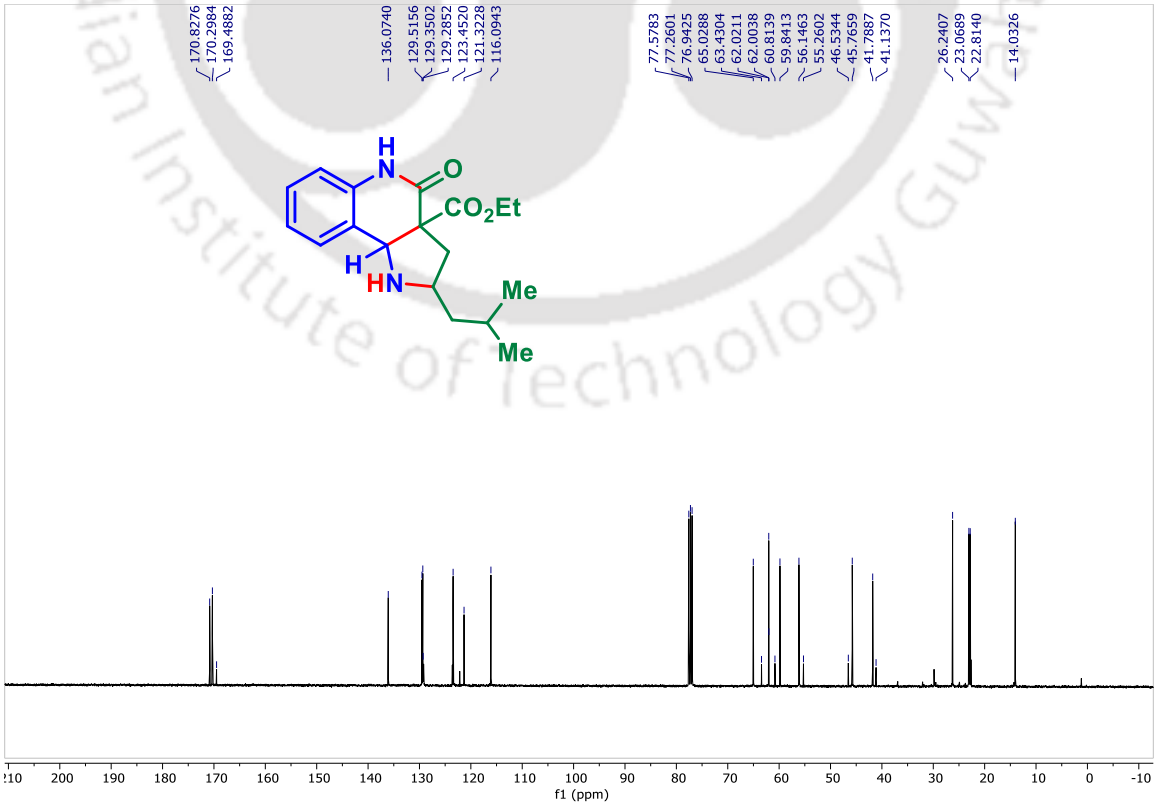
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**25br**):



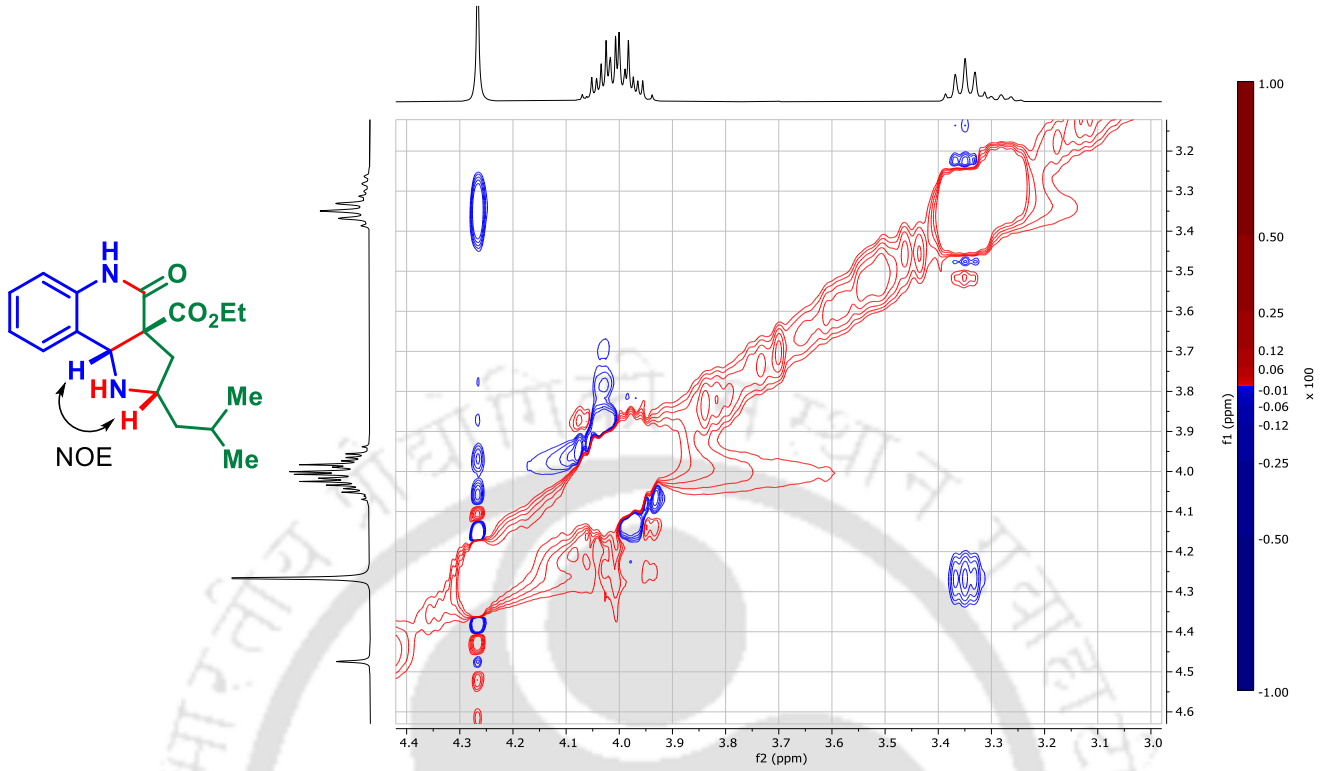
^{1}H ($CDCl_3$, 400 MHz) spectrum of compound (**26aq**):



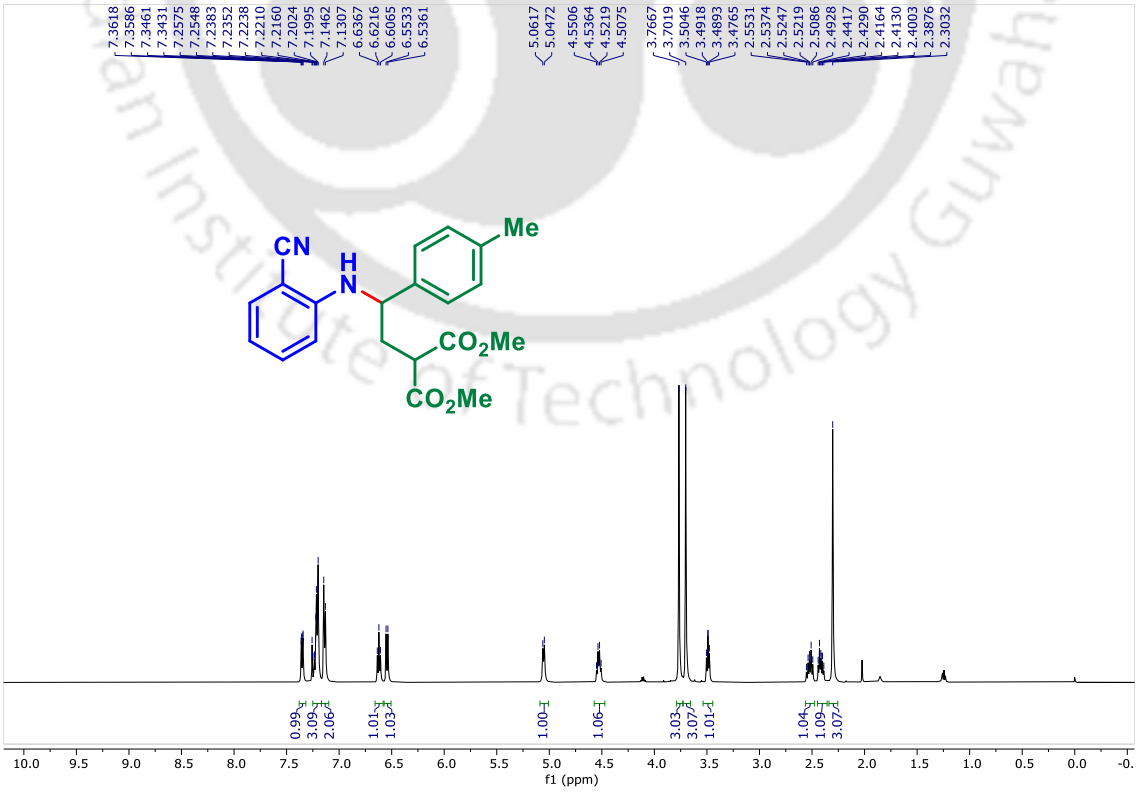
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**26aq**):



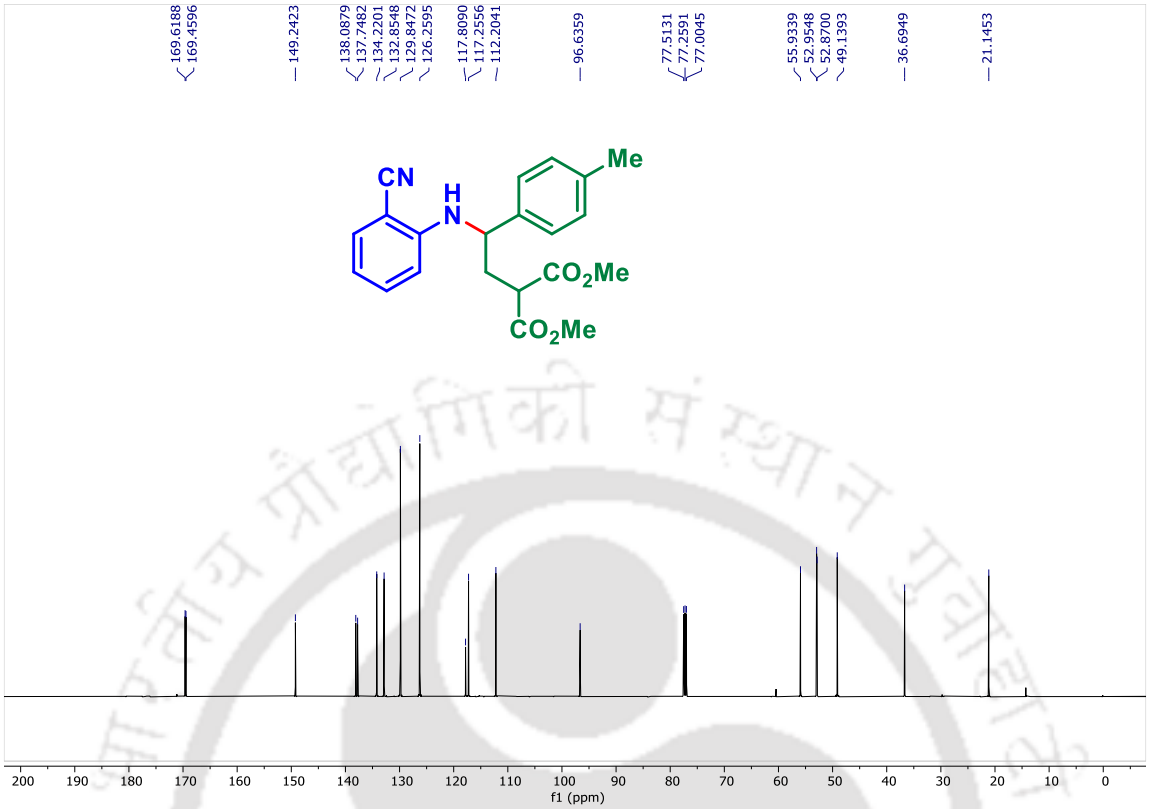
NOE (400MHz, $CDCl_3$) spectrum of compound **26aq**:



^1H ($CDCl_3$, 500 MHz) spectrum of intermediate **A** (R = H, R^1 = R^2 = Me):



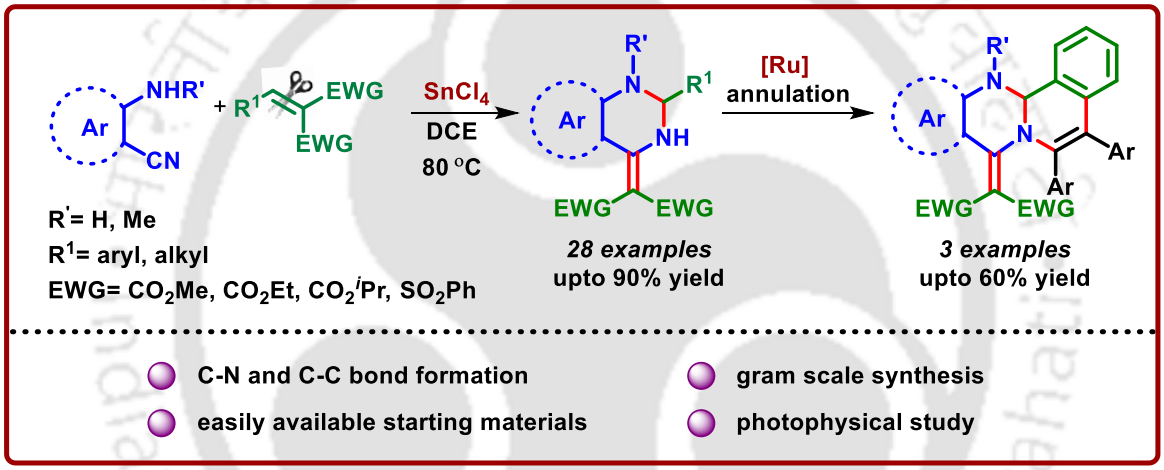
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of intermediate **A** (R = H, R^1 = R^2 = Me):

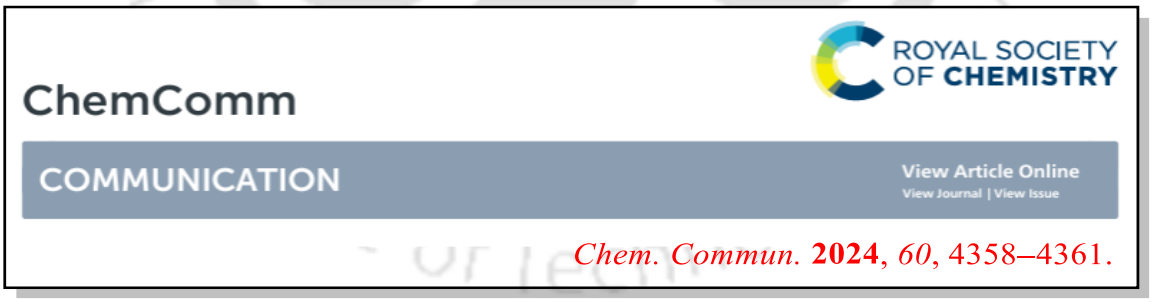


CHAPTER 3

Domino Synthesis of 4-Methylene Substituted Tetrahydroquinazolines from 2-Aminobenzonitriles and Alkylidene Malonates

Abstract: This chapter highlights an efficient methodology for the synthesis of highly diverse 4-methylene substituted tetrahydroquinazoline scaffolds from 2-aminobenzonitriles and alkylidene malonates in presence of $SnCl_4$. The reaction proceeds *via* initial 1,4-conjugate addition of 2-aminobenzonitrile to the activated alkene followed by an unprecedented rearrangement. The methodology can be extended towards the synthesis of quinazoline analogues as well as tetracyclic dihydroisoquinolino[1,2-*b*]quinazoline derivatives. Some of the synthesized compounds show excellent photophysical properties.





3.1. Introduction

Quinazolines and its tetrahydro derivatives are well known structural motifs, ubiquitous in natural products, pharmaceutically relevant compounds and value-added clinical drugs.[1] Among them, benzo-fused tetrahydroquinazoline has an interesting structural skeleton with ring fused aminal, where two nitrogen atoms are attached to the same sp^3-carbon atom. They serve as fundamental units in biologically active compounds and are building blocks for a wide range of commercially available pharmaceuticals and potential drug candidates (*Figure 3.1.1.*). For instance, fenquizone (**a**)[2] is a FDA approved diuretic drug that exhibits chronic hypertensive effect, whereas DPC 083 (**c**)[3] is an anti-HIV drug. Quinethazone (**b**),[4] a thiazide diuretic is commonly used for the treatment of hypertensive disorder and compound (**e**)[5] is butyrylcholinesterase inhibitor. Afacifenacin (**d**)[6] is an antimuscarinic drug widely used to treat people with an overactive bladder. Tetrahydroquinazolines possessing strong electron withdrawing group at 4-position also has immense potential with biological activities and enhanced fluorescence properties. It is considered as a privileged scaffold and can be easily tuned to achieve further transformations.

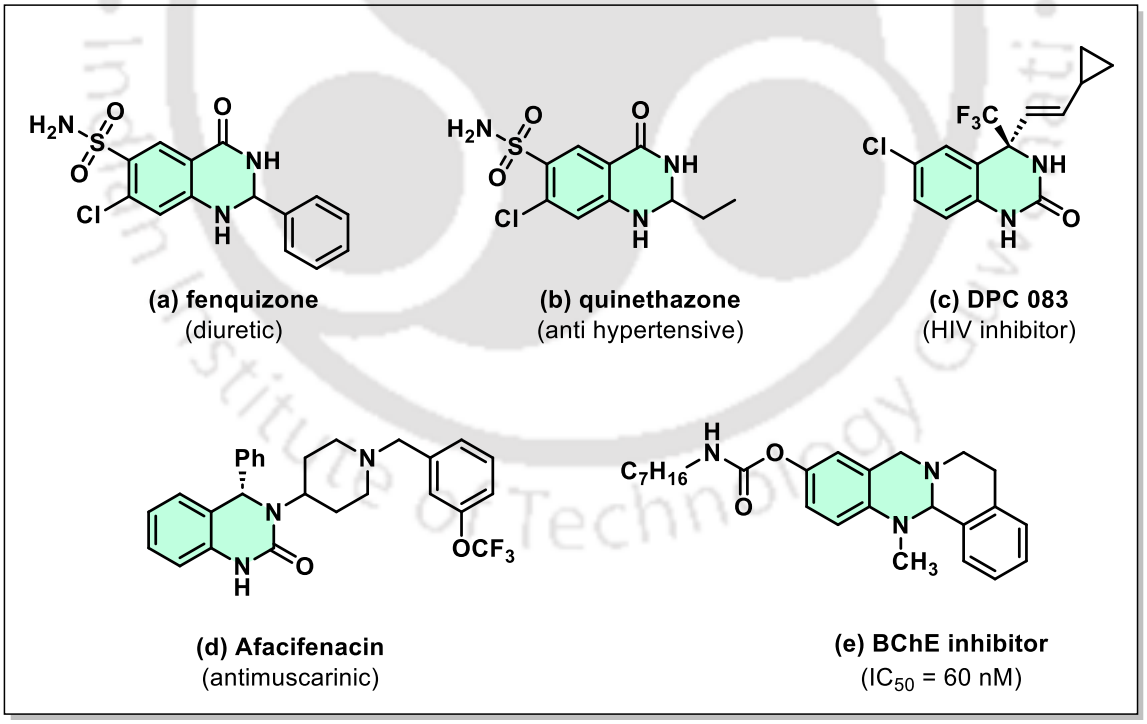
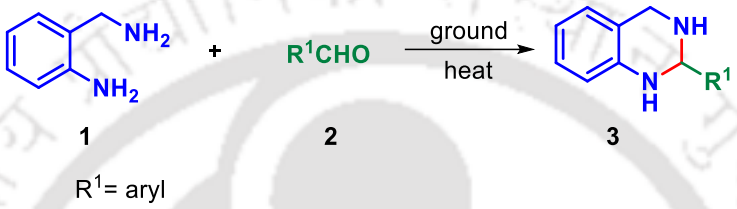


Figure 3.1.1. Some examples of pharmaceutical drugs with tetrahydroquinazoline core.

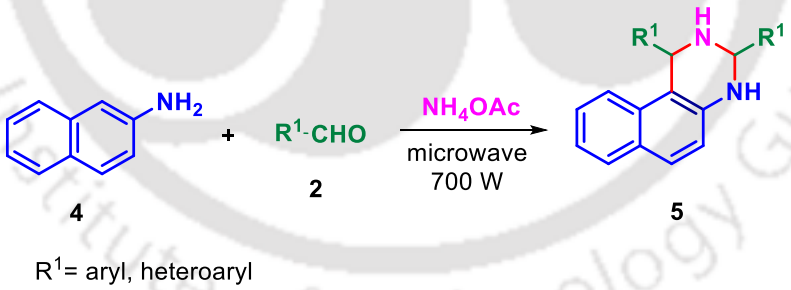
3.2. Literature Survey on Synthesis of Substituted Tetrahydroquinazolines

Traditional approaches for the synthesis of 1,2,3,4-tetrahydroquinazolines are the routine condensation of various 2-(aminomethyl)anilines with aldehydes and ketones in conventional organic media, only providing C2 substituted tetrahydroquinazolines.[7] In 2002, Scott and his co-workers developed a method for synthesis of 2-aryl-1,2,3,4-tetrahydroquinazolines **3** by direct reaction of 2-aminobenzylamine **1** and aryl aldehydes **2**. This solvent– and reagent–free protocol gave excellent yields of the products by simple mixing of the reagents either neat, or as an aqueous slurry (*Scheme 3.2.1.*).[8]



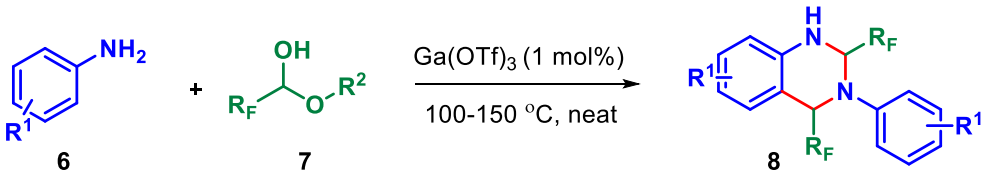
Scheme 3.2.1. *Solvent-free synthesis of 2-aryl substituted tetrahydroquinazolines.*

Prajapati's group also demonstrated a microwave assisted one pot, multicomponent synthesis of 2,4-diaryltetrahydroquinazoline derivatives **5** from 2-naphthyl amine **4**, aryl aldehydes **2** and ammonium acetate as a nitrogen source. This catalyst– and solvent–free cascade strategy proceeds *via in situ* generation of both the diene and the dienophile and their subsequent aza–Diels–Alder cyclization to give the product (*Scheme 3.2.2.*).[9]



Scheme 3.2.2. *Microwave assisted synthesis of 2,4-diaryl substituted tetrahydroquinazolines.*

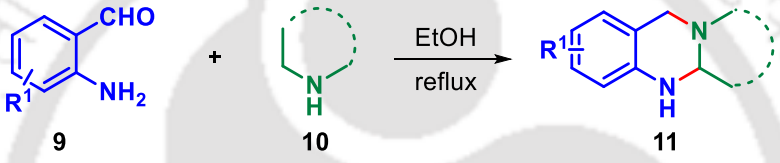
G. K. Surya Prakash and his group reported a Lewis acid catalyzed synthesis of difluoro/trifluoromethylated 1,2,3,4-tetrahydroquinazolines **8** from anilines **6** and difluoro/trifluoroacetaldehyde methyl/ethyl hemiacetal **7**. This one pot protocol follows a sequential condensation–cyclization reaction to form fluorinated products in good yields (*Scheme 3.2.3.*).[10]



R^1= Me, Et, ^{i}Pr, Bu, OMe, F, Cl; R^2= Me, Et
R_F= CF_3, CF_2H

Scheme 3.2.3. *Synthesis of difluoro/trifluoromethylated 1,2,3,4-tetrahydroquinazolines.*

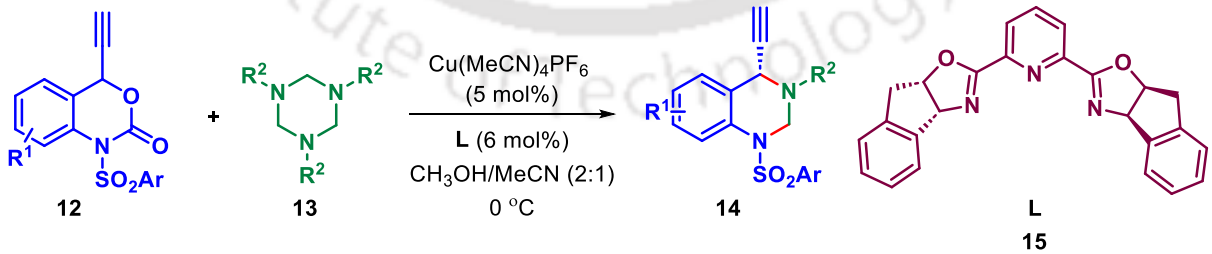
In 2008, Siedel and his co-workers explored a *α*–amination reaction of secondary amines **10** with *ortho*–aminobenzaldehydes **9** to access fused 1,2,3,4-tetrahydroquinazolines **11**. This thermally promoted transition metal free protocol follows a redox neutral cascade condensation and 1,6–hydrogen transfer/cyclization to give the product in good to excellent yields (*Scheme 3.2.4.*).[11]



R^1= H, Cl, Br, Me, CO_2Me, OMe, Ph, CN

Scheme 3.2.4. *Redox neutral α–amination reaction of secondary amines.*

Sun and co-workers disclosed an asymmetric formal [4+2]-cycloaddition of ethynyl benzoxazinanones **12** and hexahydro-1,3,5-triazines **13** providing chiral tetrahydroquinazolines **14**. This copper catalyzed cycloaddition features the formation of *in situ* generated copper–allenylidene complex and formaldimine during the reaction process to give chiral tetrahydroquinazoline in moderate to good yields and up to 98% enantiomeric excess (*Scheme 3.2.5.*).[12]

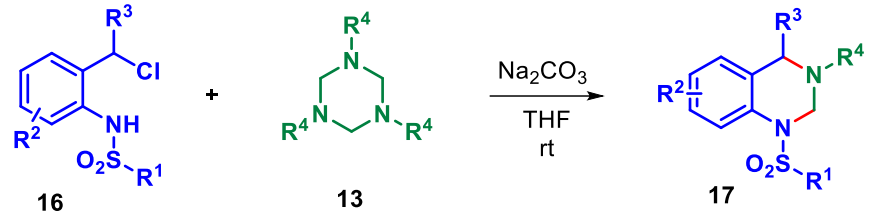


R^1= H, Me, Cl, Br, CF_3; R^2= aryl, alkyl

Scheme 3.2.5. *Copper catalyzed asymmetric synthesis of chiral tetrahydroquinazolines.*

Similarly, Liu and co-workers developed a base promoted synthetic route featuring inverse–electron–demand [4+2]–cycloaddition for the synthesis of functionalized tetrahydroquinazolines **17**. This mild protocol involves cycloaddition reaction of *in situ*

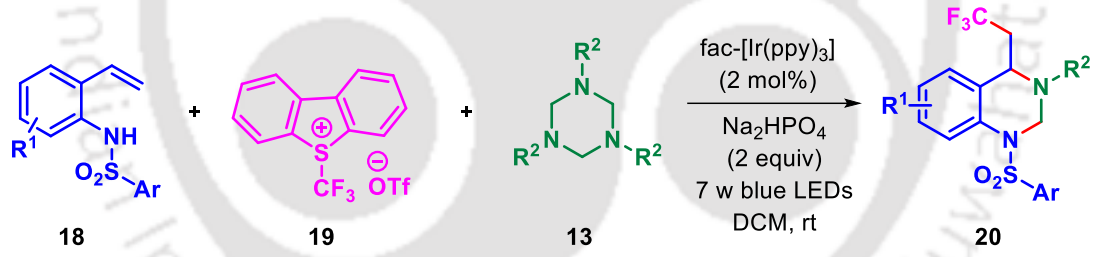
generated aza–*ortho*–quinone methides from *N*–(*o*–chloromethyl) aryl amides **16** with 1,3,5-triazinanes **13** to form products with good to excellent yields (*Scheme 3.2.6.*).[13]



R^1= aryl; R^2=H, Cl, Br, F, Me, OMe
R^3= H, Me; R^4= aryl, benzyl

Scheme 3.2.6. *Base mediated inverse–electron–demand [4+2]–cycloaddition for synthesis of tetrahydroquinazolines.*

Later, Chen and his group also reported an inverse–electron–demand [4+2]–cycloaddition reaction to access perfluoroalkylated tetrahydroquinazolines **20** utilizing an iridium complex as photocatalyst. This key steps in this redox neutral method include photocatalytic radical mediated generation of aza–*ortho*–quinone methides from 2-vinylanilines **18** and perfluoroalkyl radical precursors **19** and subsequent reaction with the formaldimines from 1,3,5-triazinanes **13** to deliver the products with moderate to good yields (*Scheme 3.2.7.*).[14]

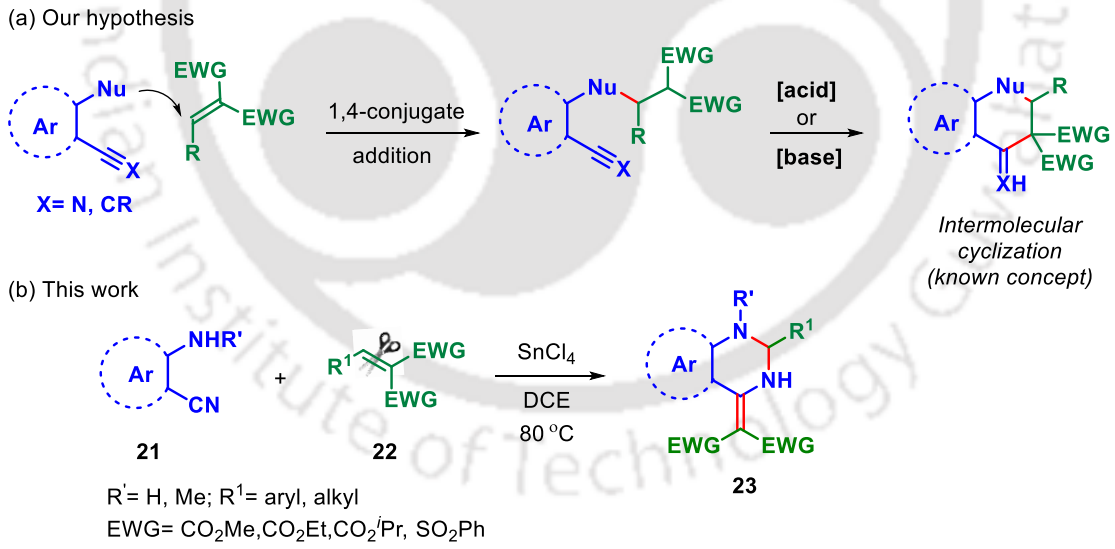


R^1= H, Cl, Br, F, Me, OMe, CN, CF_3
R^2= benzyl, alkyl, aryl

Scheme 3.2.7. *Photocatalyzed cycloaddition for synthesis of perfluoroalkylated tetrahydroquinazolines.*

3.3. Present Work

As already revealed, highly substituted tetrahydroquinazolines are frequently found in various natural products and pharmaceuticals, making their synthesis a significant challenge for synthetic chemists. Despite the numerous existing literature reports for synthesis of various substituted tetrahydroquinazolines, it may be noted substituted tetrahydroquinazolines bearing active methylene group at 4-position has not been reported yet. As per the existing literature reports, conventionally an inter-molecular method with concomitant attack of a nucleophile on an electron deficient alkene, followed by electrophilic attack on an unsaturated heteroatom motif can lead to the generation of different functionalized heterocycles. In this context, we hypothesized that the reaction of 2-aminobenzonitrile with electron deficient alkylidene malonate would yield 4-imino-1,4-dihydroquinoline moiety, however, tetrahydroquinazoline was isolated. Thus, this chapter describes $SnCl_4$ mediated efficient protocol for the synthesis of 4-methylene substituted tetrahydroquinazolines from 2-aminobenzonitriles and alkylidene malonates. The reaction proceeds *via* initial 1,4-conjugate addition of 2-aminobenzonitrile to the activated alkene followed by an unprecedented rearrangement with the migration of electron withdrawing groups.



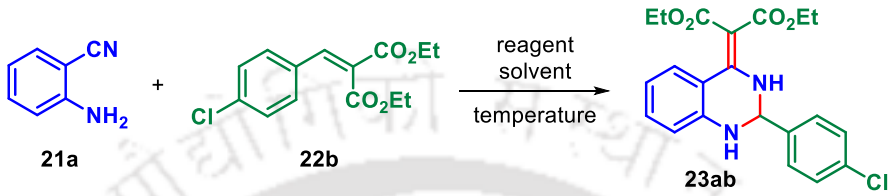
Scheme 3.3.1. *Domino synthesis of 4-methylene substituted tetrahydroquinazolines.*

3.4. Results and Discussion

3.4.1. Optimization of the Reaction

In the beginning, we initiated the optimization studies by treating diethyl 2-(4-chlorobenzylidene)malonate (**22b**) with 2-aminobenzonitrile (**21a**) in the presence of 2.0 equiv of $SnCl_4$ in DCM at room temperature under an inert atmosphere (*Table 3.4.1.1.*, entry 1). To

Table 3.4.1.1.: *Optimization of the reaction*[a]



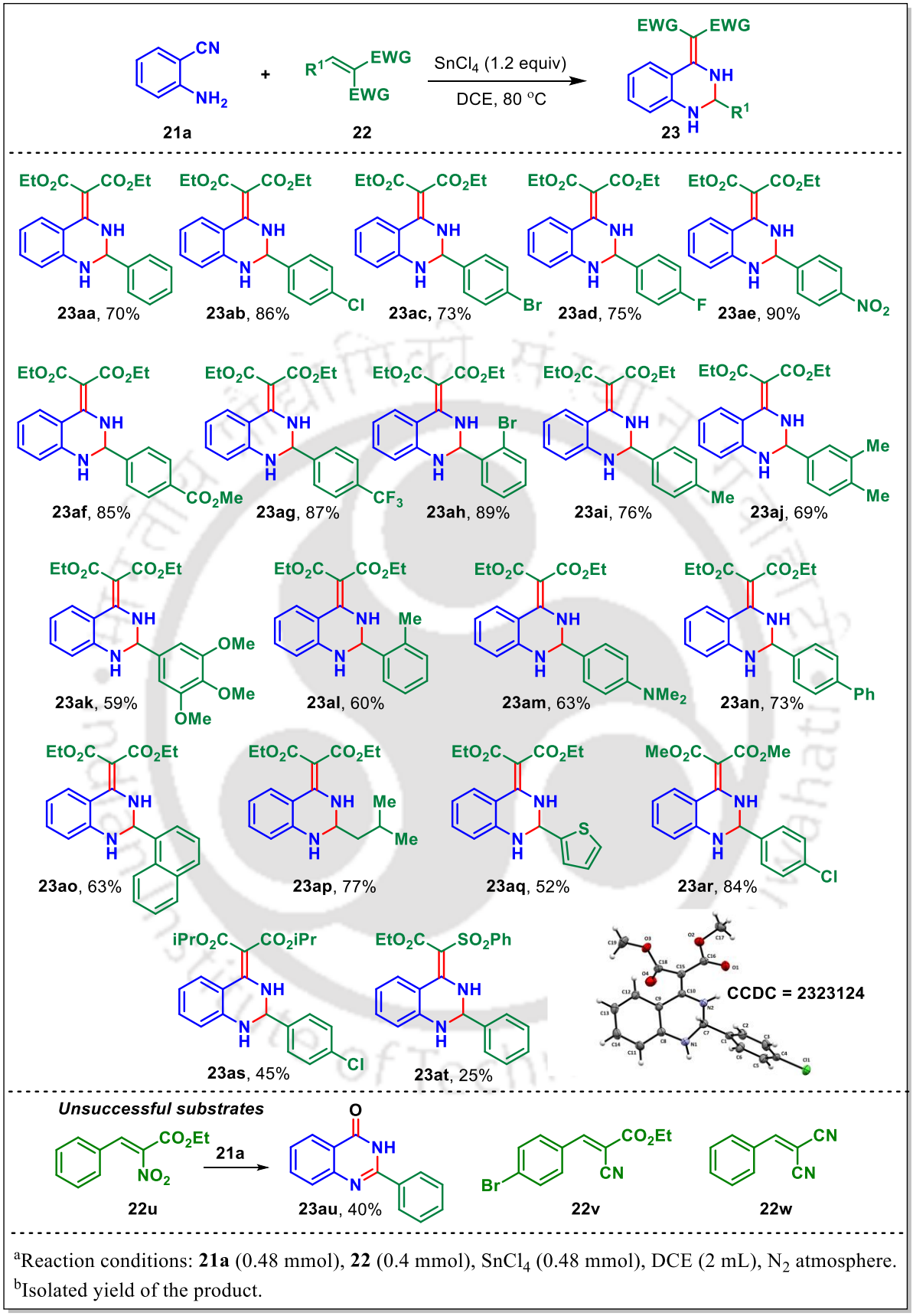
entry	reagent (equiv)	solvent	temp/°C	%yield[b]
1.	$SnCl_4$ (2.0)	DCM	25	52
2.	$SnCl_4$ (2.0)	DCE	25	55
3.	$SnCl_4$ (2.0)	toluene	25	20
4.	$SnCl_4$ (2.0)	THF	25	-
5.	$SnCl_4$ (2.0)	CH_3CN	25	-
6.	$SnCl_4$ (2.0)	DCE	40	65
7.	$SnCl_4$ (2.0)	DCE	80	83
8.	**$SnCl_4$ (1.2)**	**DCE**	**80**	**86**
9.	$SnCl_4$ (0.5)	DCE	80	52
10.[c]	$SnCl_4$ (1.2)	DCE	100	77
11.[d]	$SnCl_4$ (1.2)	DCE	80	46
12.	$TiCl_4$ (1.2)	DCE	25	35
13.	$AlCl_3$ (2.0)	DCE	25	-
14.	$FeCl_3$ (1.5)	DCE	80	-
15.	$InCl_3$ (0.5)	DCE	80	-
16.	$In(OTf)_3$ (0.5)	DCE	80	-
17.	$Cu(OTf)_2$ (0.5)	DCE	80	-
18.	$BF_3{\cdot}OEt_2$ (1.2)	DCE	25	-
19.	TfOH (1.2)	DCE	25	-
20.	*p*-TsOH (2.0)	DCE	25	-

[a]All the reactions were carried out in (0.48 mmol) **21a**, (0.4 mmol) **22b** in 2.0 mL solvent, N_2 atmosphere, [b]Isolated yields, [c]In a sealed tube, [d]O_2 atmosphere.

our delight, the reaction occurred to deliver the product diethyl 2-(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (**23ab**) in 52% yield. Encouraged by the result, we attempted the reaction in a set of non-polar and polar solvents like DCE, toluene, THF and acetonitrile at room temperature. Similar yield was obtained with DCE (*Table 3.4.1.1.*, entry 2) whereas toluene produced inferior yield (*Table 3.4.1.1.*, entry 3). The reaction did not proceed at all with moderately and highly polar solvents such as THF and acetonitrile, respectively (*Table 3.4.1.1.*, entries 4 and 5). However, increasing the reaction temperature to 50 °C in DCE resulted in 65% yield of **23ab** (*Table 3.4.1.1.*, entry 6). Further elevating the temperature to 80 °C in DCE led to 83% yield (*Table 3.4.1.1.*, entry 7). Decreasing the loading of $SnCl_4$ to 1.2 equiv and 0.5 equiv in DCE at 80 °C resulted in a synchronous yield of 86% (*Table 3.4.1.1.*, entry 8) and an inferior yield of 52% (*Table 3.4.1.1.*, entry 9) respectively. The reaction was performed at 100 °C in DCE in a sealed tube resulting in a decreased yield of 77% (*Table 3.4.1.1.*, entry 10). When the reaction was performed with 1.2 equiv of $SnCl_4$ in DCE at 80 °C under O_2 atmosphere, it produced an inferior yield of 46% (*Table 3.4.1.1.*, entry 11). The reaction was also investigated under different Lewis and Brønsted acidic conditions. It was observed that, with $TiCl_4$ (1.2 equiv) in DCE at room temperature **23ab** was formed with 35% yield (*Table 3.4.1.1.*, entry 12). Other Lewis acids such as $AlCl_3$, $FeCl_3$, $InCl_3$ in DCE at 80 °C failed to give any product (*Table 3.4.1.1.*, entries 13-15). Metal triflates such as indium and copper triflates and $BF_3{\cdot}OEt_2$ were also screened for the reaction but did not give any products (*Table 3.4.1.1.*, entries 16-18). Brønsted acids TfOH and *p*-TsOH in DCE at room temperature were also found to be ineffective (*Table 3.4.1.1.*, entries 19 and 20). Therefore, 1.2 equiv of $SnCl_4$ in DCE at 80°C are the optimum conditions for the reaction.

3.4.2. Substrate Scope

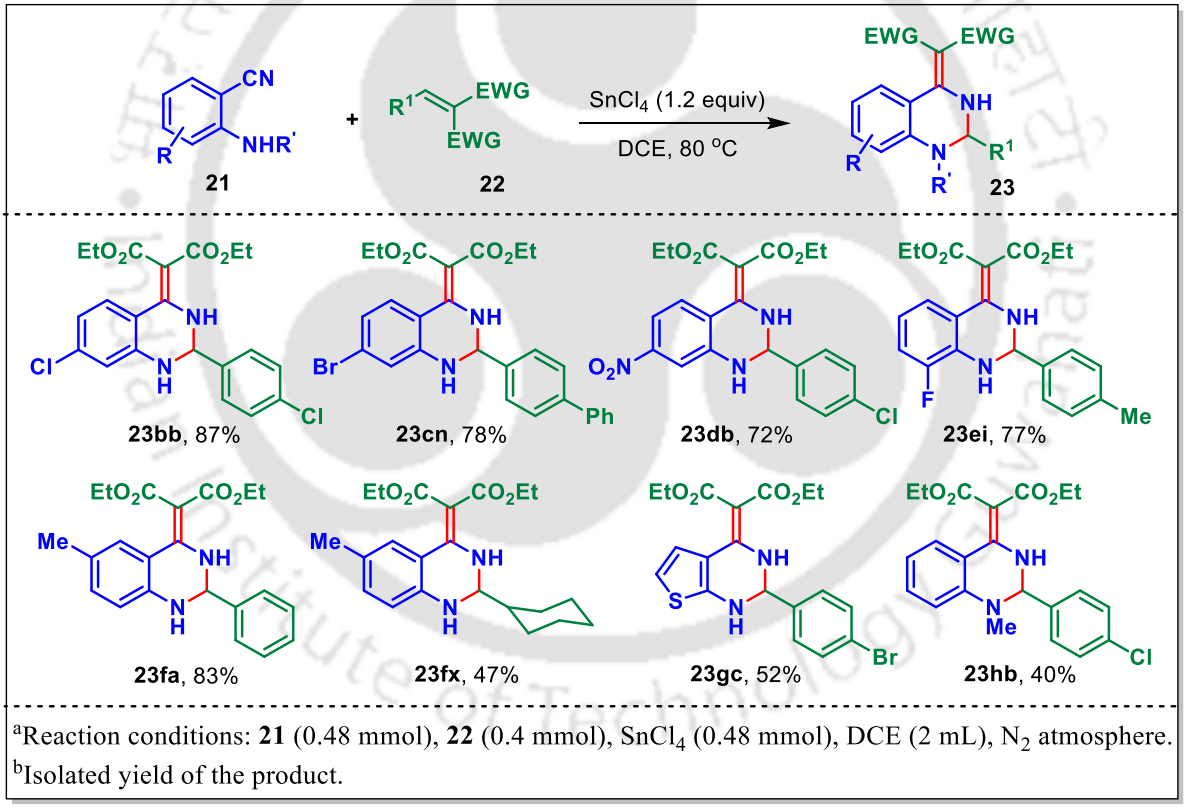
With the established optimal conditions in hand, the generality of the reaction was explored with different substrates as depicted in *Scheme 3.4.2.1.* It was observed that the reaction proceeds well with a series of arylidene malonates having both electron-donating and electron-withdrawing groups at different positions of the aromatic ring. The reaction of 2-aminobenzonitrile **21a** with moderately electron-withdrawing halo groups in the *ortho*- and *para*-position of the aromatic ring of arylidene malonates provided the corresponding products **23ab**-**23ad** and **23ah** in good yields. Whereas, arylidene malonates with strong electron-withdrawing groups such as $-NO_2$, $-CO_2Me$ and $-CF_3$ furnished excellent yields up to 90%, of the corresponding products **23ae**, **23af** and **23ag**, respectively. Likewise, the reaction when



[a]Reaction conditions: **21a** (0.48 mmol), **22** (0.4 mmol), $SnCl_4$ (0.48 mmol), DCE (2 mL), N_2 atmosphere.
[b]Isolated yield of the product.

Scheme 3.4.2.1. *Scope for the formation of substituted tetrahydroquinazolines with different alkyl/arylidene malonates.*[a,b]

screened with arylidene malonates bearing weak electron-donating methyl group at the *para*- and *ortho*- positions provided the products **23ai** and **23al** in 76% and 60% yields, respectively. On the other hand, both di- and tri-substituted arylidene malonates with moderate and strong electron donating groups furnished the expected products **23aj** and **23ak** in moderate yields. The reaction was also tested with bulky aromatic polysubstituted arylidene malonate **22o**, which produced the corresponding product **23ao**, in 63% yield. Intriguingly, biphenyl as well as electron rich 4-*N*,*N*-dimethylamino substituted arylidene malonates gave the desired products **23an** and **23am** in 63% and 73% yields, respectively. Heteroaromatic i.e. 2-thiophene substituted arylidene malonate was also compatible with the reaction conditions affording the respective product **23aq** in 52% yield. Primary alkylidene malonate also proceeded well in this reaction conditions giving the product **23ap** with 77% yield. Even varying the dicarboxylate part of the arylidene malonates gave products **23as** and **23ar** in moderate and good yields.



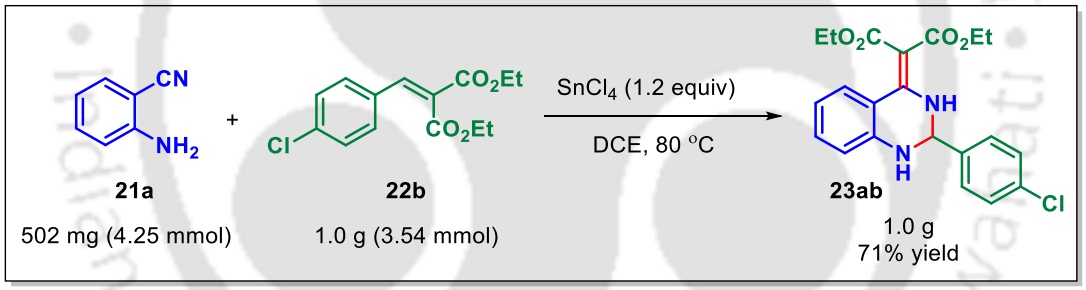
Scheme 3.4.2.2. *Scope for the formation of substituted tetrahydroquinazolines with different alkyl/arylidene malonates and substituted 2-aminobenzonitriles.* [a,b]

Electron-deficient alkenes having two different electron-withdrawing groups such as ester and sulfone also produced the corresponding product **23at** but with a low yield. Interestingly, alkylidene substrate **22u** having nitro and ester groups provided 2-phenylquinazolin-4(3*H*)-one **23au** in 40% yield. The spectroscopic data of compound **23au** was in agreement with literature

reports.[15] On the other hand, substrates having nitrile group **22v** and **22w** failed to give any product. This might be due to the low reactivity of nitrile group compared to ester group.

To further ascertain the scope, additionally different electron-donating and electron-withdrawing substituted 2-aminobenzonitriles were screened, which furnished the corresponding products in good yields **23bb-23fx** as shown in *Scheme 3.4.2.2*. Moreover, when 2-aminobenzonitrile was substituted with 2-aminothiophene-3-carbonitrile under the standard set of reaction conditions afforded the desired product **23gc** with 52% yield. *N*-methyl substituted 2-aminobenzonitrile also react with the arylidene malonate to give the expected product **23hb**. The structure of the compounds was determined by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy, mass spectrometry and finally by X-ray crystallographic analysis of the compound **23ar**.

A gram scale synthesis was carried out to check the scalability of the methodology (*Scheme 3.4.2.3.*). 2-Aminobenzonitrile (**21a**) (502 mg, 4.25 mmol) reacted with diethyl 2-(4-chlorobenzylidene)malonate (**22b**) (1.0 g, 3.54 mmol) under the standard conditions to provide the corresponding product **23ab** with 71% (1.0 g) yield.

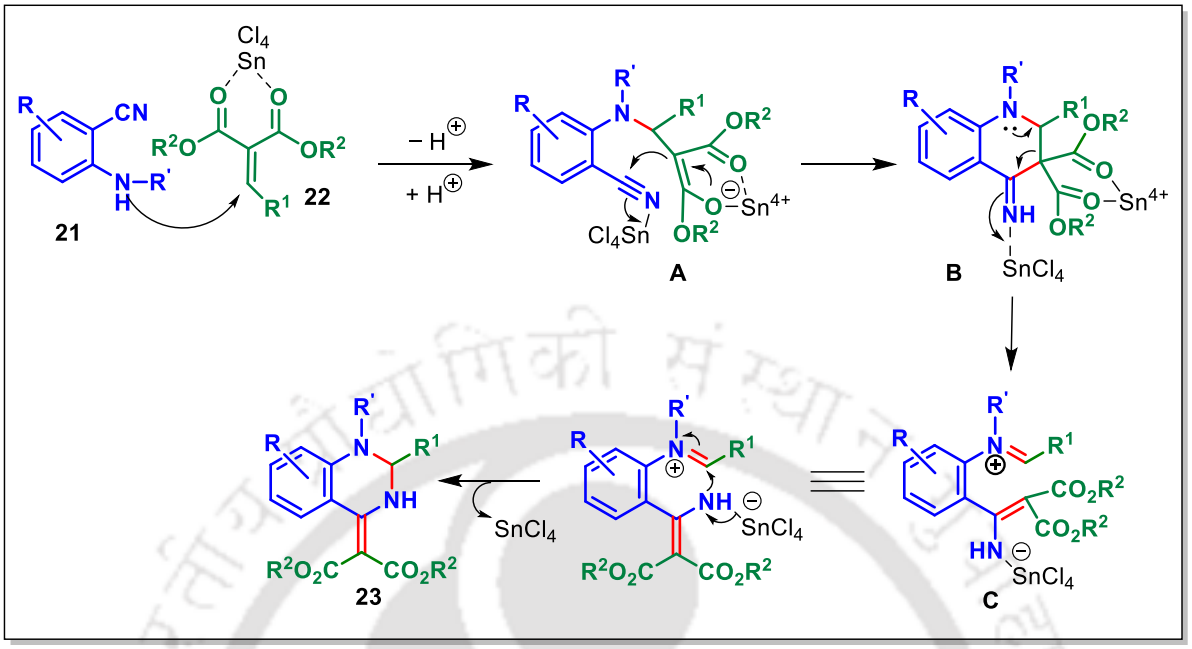


Scheme 3.4.2.3. *Gram-scale synthesis.*

3.4.3. Plausible Mechanism

A plausible mechanism for the formation of tetrahydroquinazoline is depicted in *Scheme 3.4.3.1*. Initially, $SnCl_4$ activates the alkylidene malonate **22** *via* coordination with ester functionality for the conjugate addition of 2-aminobenzonitrile **21** leading to 1,4 adduct **A**. Under Lewis acidic conditions, the enolyzed intermediate **A** undergoes intramolecular addition to the activated nitrile group to form adduct **B**. Further, the unstable intermediate **C** is generated *via* delocalisation of nitrogen lone pair followed by C–C bond cleavage of adduct **B** under the action of $SnCl_4$. The intermediate **C** subsequently proceeds through intramolecular Mannich type reaction to give our final product **23**. It is evident from the mechanism that $SnCl_4$ activates alkylidene malonate, diester moiety, nitrile as well as imine functionality during the reaction. Also, a

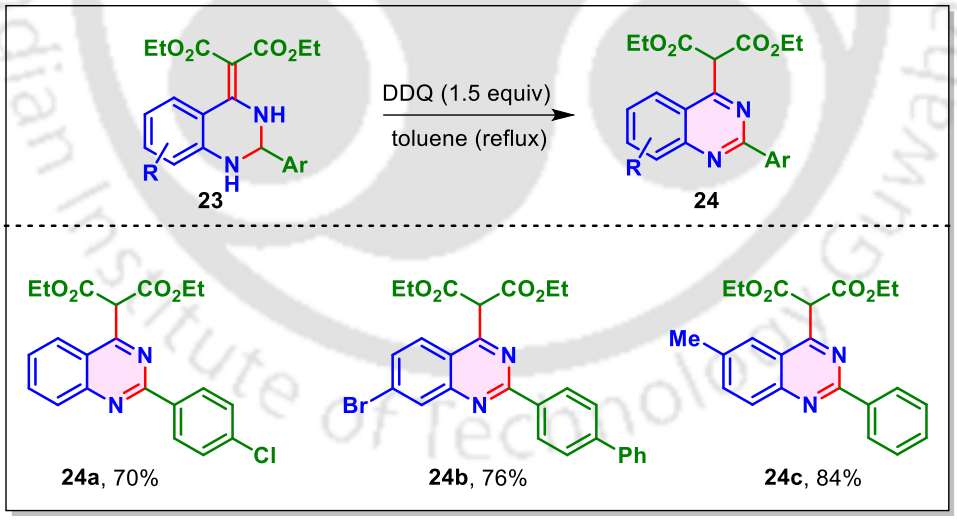
stoichiometric amount of $SnCl_4$ is required because it is neutralized by the basic nitrogen atoms formed in the product (Lewis complex).



Scheme 3.4.3.1. *Plausible reaction mechanism.*

3.5. Post-synthetic Applications

3.5.1. Synthesis of Quinazolines

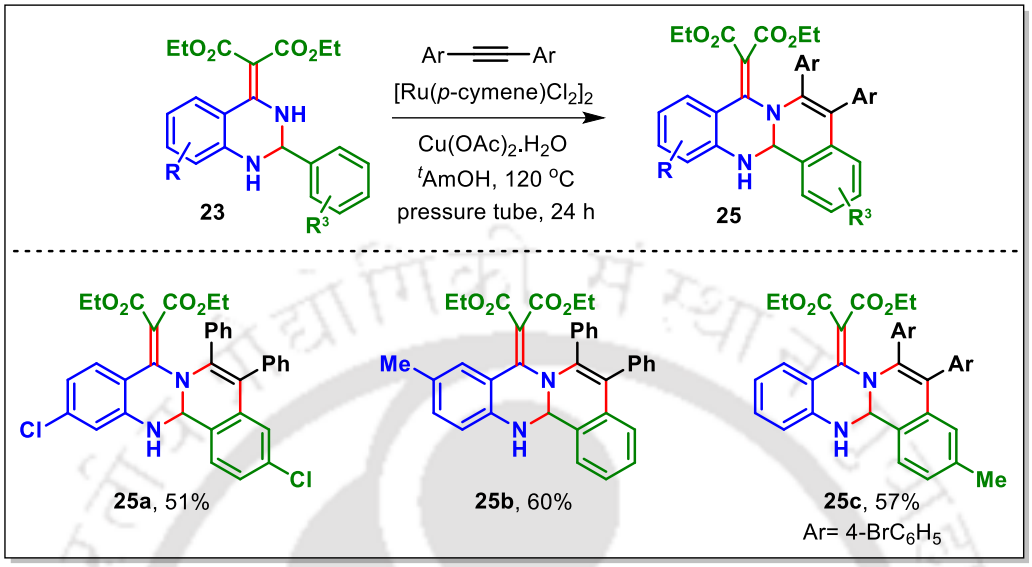


Scheme 3.5.1.1. *Scope for the synthesis of quinazolines.*

The utility of the methodology can be further extended towards the synthesis of quinazolines. Aromatization of the products **23ab**, **23cn** and **23fa** with DDQ in toluene under reflux conditions lead to the formation of 2,4-disubstituted quinazoline derivatives **24a**, **24b** and **24c** respectively with 70%, 76% and 84% yields (*Scheme 3.5.1.1.*). It may be noted that some quinazolines and its derivatives exhibit diverse spectrum of pharmacological activities such as

anti-inflammatory and anti-cancer activities.[16] They are also used as synthetic precursors in organic synthesis.[17]

3.5.2. Synthesis of Tetracyclic Annulated Compounds



Scheme 3.5.2.1. *Scope for the synthesis of tetracyclic annulated compounds.*

The methodology can also be further expanded towards the synthesis of highly fluorescent annulated tetracyclic products giving moderate to good yields. The products **23bb**, **23fa** and **23ai** undergo selective C–H, N annulation at one of the phenyl rings with diphenylacetylene derivatives in the presence of a Ru(II) catalyst giving annulated products **25a**, **25b** and **25c** respectively with 51%, 60% and 57% yields. (*Scheme 3.5.2.1.*).

3.5.3. Photophysical Studies

The π-conjugated nitrogen containing heterocyclic compounds are excellent fluorescent compounds, suitable for various applications such as the fluorescent probe for bio-imaging,[18] solar cells,[19] and OLED.[20] Thus, the photophysical properties of some selected synthesized compounds were studied considering their potential in photoelectronic field. The ultraviolet absorbance (λ_{abs}) and fluorescence emission (λ_{em}) for compounds **23ab**, **23ac**, **23ah**, **23am**, **23db**, **25a**, **25b** and **25c** were studied in dichloromethane, which are shown in *Figures 3.5.3.1.(a)* and *3.5.3.1.(b)*, respectively. The absorbance at λ_{max} and calculated molar extinction coefficient (ϵ) are summarized in (*Table 3.5.3.1.*). It was observed that the compounds **23ab**, **23ac**, **23ah**, **23am** and **23db** with 340 nm photoexcitation showed fluorescent emission band at 430 nm, which might be due to the formation of excited species because of the presence of adjacent nitrogen atom in conjugation with the active methylene group. However, there is a

drastic enhancement of fluorescence and red shift in the compounds **25a**, **25b** and **25c** in the range of 450-490 nm, due to the extra conjugation offered by the diphenyl-1,2-dihydroisoquinoline moiety. As the compounds exhibit fluorescence, they may find potential application in various fields of material science.

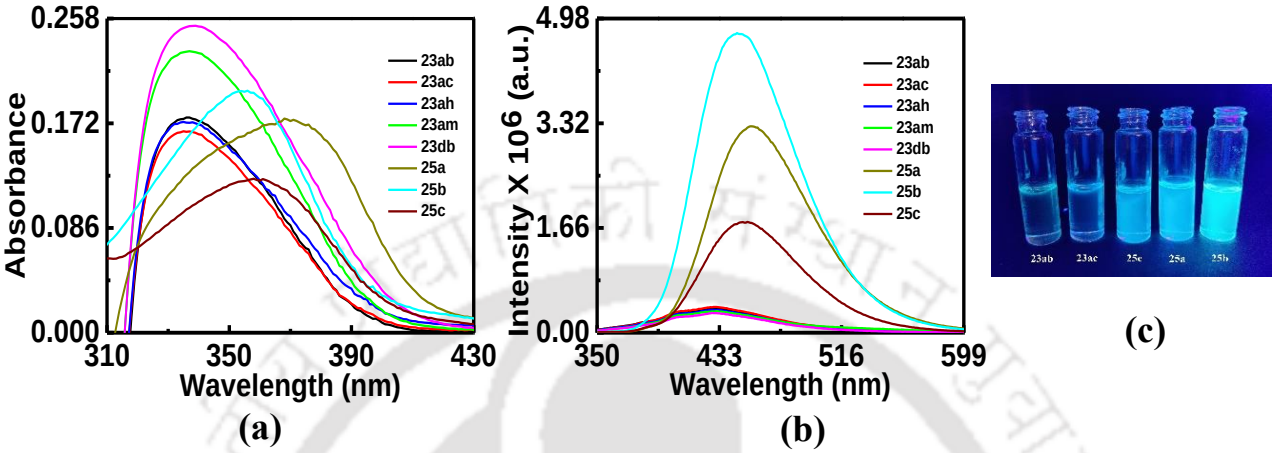


Figure 3.5.3.1. *(a) UV-vis and (b) Fluorescence Spectra (c) Compounds* ***23ab***, ***23ac***, ***25c***, ***25a*** *and* ***25b*** *under UV irradiation at 365 nm.*

Table 3.5.3.1. *UV-vis and photoluminescence parameters.*

entry	compound	λ_{max} (nm)[a]	absorbance at λ_{max}	ε (1 x 10^4 $M^{-1}cm^{-1}$)	λ_{em} (nm)[b]
1.	23ab	335	0.176	1.76	430
2.	23ac	336	0.165	1.65	430
3.	23ah	336	0.172	1.72	431
4.	23am	338	0.231	2.31	431
5.	23db	339	0.252	2.52	430
6.	25a	369	0.174	1.74	476
7.	25b	356	0.199	1.99	466
8.	25c	360	0.126	1.26	471

[a] Absorption wavelengths. [b] Emission wavelengths in DCM at a concentration of 1×10^{-5} M.

3.6. Conclusion

In summary, we have described a general procedure for the synthesis of methylene substituted tetrahydroquinazoline derivatives from 2-aminobenzonitriles and activated alkenes. The reaction is compatible to a variety of functional groups giving moderate to

good yields. The methodology can be extended towards the synthesis of quinazoline analogues as well as tetracyclic dihydroisoquinolino[1,2-*b*]quinazoline derivatives. Some of the synthesized compounds show excellent photophysical properties.

3.7. Experimental Section

3.7.1. General Information and Instrumentation

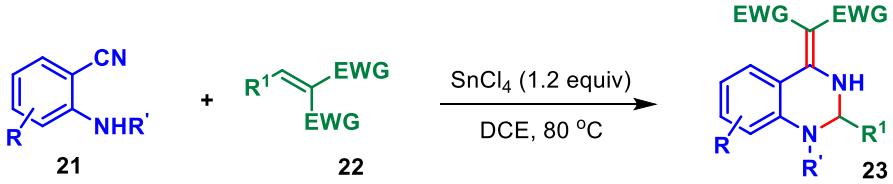
All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz and 125 MHz) NMR. $^{19}F\{^1H\}$ NMR spectra were recorded at 470 MHz and chemical shifts are relative to hexafluorobenzene in $CDCl_3$ at δ = -164.9 ppm (external reference). Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, bs = broad singlet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF and microTOF-Q II mass spectrometer. All UV experiments were performed in 1mL quartz cuvettes of path length 1cm at 25 °C in UV/Vis spectrometer in HPLC grade solvent.

3.7.2. Reaction Procedure

3.7.2.1. Experimental Procedure for Synthesis of Alkylidene Malonates

All starting materials **22a-22x** were synthesized by Knoevenagel reaction from the corresponding aldehydes[21], as per literature reports and confirmed by comparison to the reported characterization data.[22]

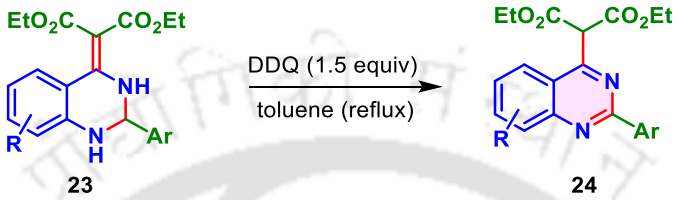
3.7.2.2. General Procedure for the Synthesis of Compounds 23aa-23at, 23bb, 23cn, 23db, 23ei, 23fa, 23fx, 23gc and 23hb



To a solution of electron deficient alkene **22** (0.4 mmol, 1 equiv) and 2-aminobenzonitrile derivative **21** (0.48 mmol, 1.1 equiv) in 1,2-dichloroethane (2 mL) was added $SnCl_4$ (0.72 mmol, 1.2 equiv) at 0 °C under nitrogen atmosphere. The reaction was then heated in an oil

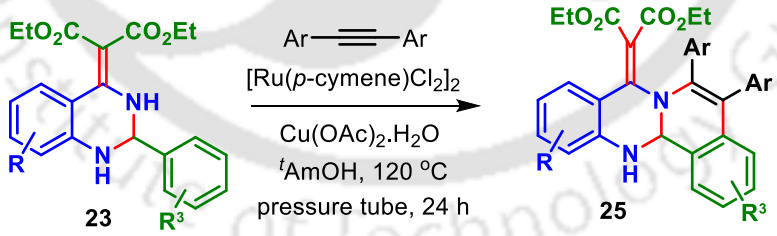
bath at 80 °C for 30 min. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **23**.

3.7.2.3. General Procedure for the Synthesis of Compounds 24a, 24b and 24c



To a solution of 4-methylene substituted tetrahydroquinazoline derivative **23** (0.3 mmol, 1 equiv) in toluene (2 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.45 mmol, 1.5 equiv) portionwise at room temperature. The reaction mixture was stirred in an oil bath under reflux for 12 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated aqueous sodium bicarbonate solution. The mixture was extracted with DCM and the combined organic layers were washed with brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **24**.

3.7.2.4. General Procedure for the Synthesis of Compounds 25a, 25b and 25c



To an oven-dried pressure tube containing a magnetic bar was added 4-methylene substituted tetrahydroquinazoline derivative **23** (0.2 mmol, 1 equiv), diphenylacetylene derivative (0.4 mmol, 2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol, 0.05 equiv), $Cu(OAc)_2.H_2O$ (0.02 mmol, 0.1 equiv), and ^{t}AmOH. The reaction mixture was stirred in an oil bath preheated at 120 °C for 24 h. After completion of the reaction (monitored by TLC analysis), the reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with ethyl acetate (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude

material was purified using column chromatography on silica gel (n-hexane/EtOAc eluent) to give the desired product **25**.

3.7.2.5. Experimental Procedure for the Gram-Scale Synthesis of 23ab

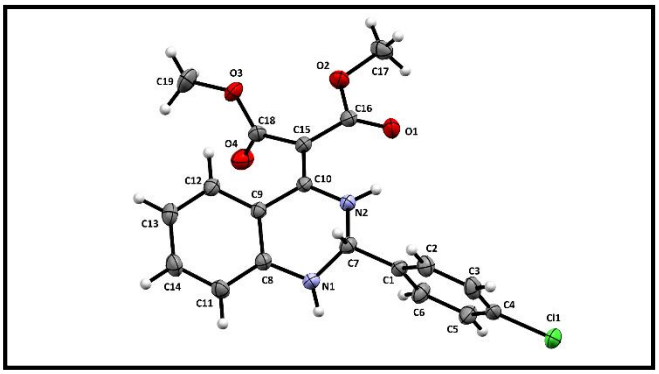
To a solution of diethyl diethyl 2-(4-chlorobenzylidene)malonate (**22b**) (1.0 g., 3.54 mmol) and 2-aminobenzonitrile (**21a**) (502 mg, 4.25 mmol) in 1,2-dichloroethane (12 mL) was added $SnCl_4$ (0.5 mL,4.25 mmol) at 0 ^oC under nitrogen atmosphere. The reaction was then heated in an oil bath at 80 ^oC for 30 min. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel with n-hexane/EtOAc as eluents to give the corresponding product **23ab** with 71% yield (1.0 g, yellow solid).

3.7.3. Crystallographic Description

Single crystals of compound **23ar** was obtained by slow evaporation of ethyl acetate and hexane solution (1:9). Bruker APEX-II CCD diffractometer was used to collect the intensity data. The instrument is equipped with a fine focus 1.75 kW sealed tube Mo Kα radiation (λ = 0.71073 Å) at 297 K. The data acquisition was done with the APEX4 software. APEX4 software was implemented for data integration and reduction. Multi-scan empirical absorption corrections were employed to the data using the program APEX4. Structures were solved by direct methods using SHELXL-2019 and refined with full-matrix least-squares on F2 using SHELXL-2019/1.[a] Structural illustrations have been drawn with ORTEP-3 for Windows.[b] The detailed data collection and structure refinement are summarized in *Table 3.7.3.1*.

a. G. M. Sheldrick, SHELXS-2014, Program for the crystal structure solution; University of Göttingen: Göttingen, Germany, 2014.

b. L. J. Farrugia, XRDIFF: simulation of X-ray diffraction patterns, *J. Appl. Crystallogr*. **1997**, *30*, 565.



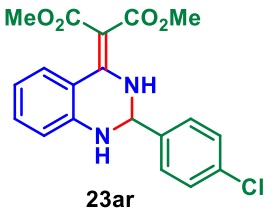


Figure 3.7.3.1. *ORTEP diagram of compound (**23ar**) with 30% probability.*

Table 3.7.3.1. Crystal parameters of compound **23ar**

	CCDC 2323124
Formula	$C_{19}H_{17}ClN_2O_4$
Formula weight	366.40
T/K	297
Crystal system	Triclinic
Space group	P -1
a/Å	9.6699 (15)
b/Å	9.6753 (15)
c/Å	10.4512 (16)
α/º	76.908 (4)
β/º	71.347 (4)
γ/º	71.318 (4)
V/Å^3	869.2 (2)
Z	2
Abs. Coeff./mm^{-1}	0.248
Abs. Correction	multi-scan
GOF on F^2	1.037
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0369
R indices [all data]	*wR2* = 0.0927 *R1* = 0.0403 *wR2* = 0.0966

3.8. References:

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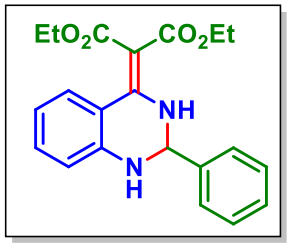
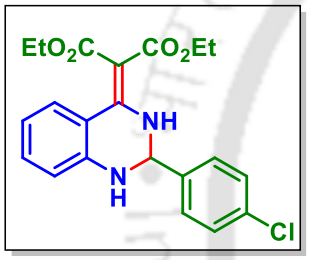
3.9. Characterisation Data

Diethyl 2-(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23aa):



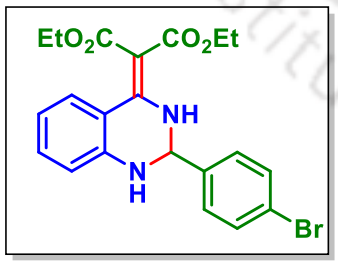
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 133-135 °C; yield 102 mg, 70%; IR (KBr, neat) ν 3326, 2981, 1643, 1556, 1478, 1267, 1234, 1153, 1115, 1073, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 7.40 (dd, *J* = 5.9 and 3.8 Hz, 2 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.27-7.25 (m, 3 H), 7.11 (t, *J* = 7.7 Hz, 1 H), 6.66 (t, *J* = 7.8 Hz, 1 H), 6.60 (d, *J* = 8.1 Hz, 1 H), 5.20 (d, *J* = 1.9 Hz, 1 H), 4.75 (s, 1 H), 4.06-3.95 (m, 4 H), 1.13-1.04 (m, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.7, 169.1, 155.2, 147.3, 138.1, 132.6, 130.1, 129.3, 128.5, 127.9, 119.7, 117.2, 116.4, 89.7, 66.7, 61.1, 59.9, 14.6, 14.0. HRMS (ESI) calcd. for $C_{21}H_{23}N_2O_4$ $(M + H)^+$ 367.1652, found 367.1656.

Diethyl 2-(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ab):



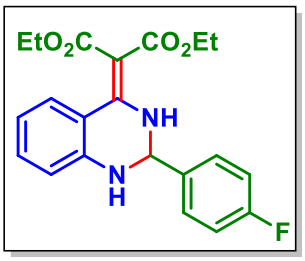
Yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 150-152 °C; yield 138 mg, 86%; IR (KBr, neat) ν 3321, 2980, 1644, 1590, 1556, 1480, 1266, 1234, 1153, 1075, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1 H), 7.53-7.45 (m, 3 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.27-7.23 (m, 1 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 5.37 (d, *J* = 1.8 Hz, 1 H), 4.60 (s, 1 H), 4.22-4.10 (m, 4 H), 1.27-1.15 (m, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.7, 169.1, 154.9, 147.0, 136.8, 136.0, 132.7, 129.5, 129.3, 128.4, 119.8, 117.1, 116.5, 89.9, 65.9, 61.2, 60.0, 14.6, 14.0. HRMS (ESI) calcd. for $C_{21}H_{22}ClN_2O_4$ $(M + H)^+$ 401.1263, found 401.1285 and 403.1253.

Diethyl 2-(2-(4-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ac):



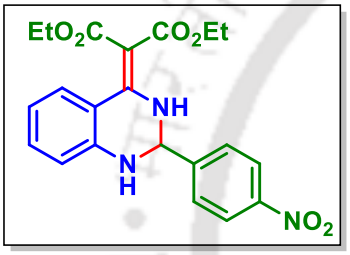
Bright yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 174-176 °C; yield 129 mg, 73%; IR (KBr, neat) ν 3322, 2980, 1644, 1557, 1480, 1266, 1235, 1153, 1074, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.54 (d, *J* = 7.9 Hz, 2 H), 7.44 (dd, *J* = 13.5 and 7.9 Hz, 3 H), 7.25 (t, *J* = 7.7 Hz 1 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 5.36 (d, *J* = 2.0 Hz, 1 H), 4.60 (s, 1H), 4.22-4.08 (m, 4 H), 1.26-1.15 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 169.1, 154.9, 147.0, 137.4, 132.7, 132.4, 129.6, 128.4, 124.2, 119.9, 117.1, 116.5, 89.9, 66.0, 61.2, 60.0, 14.6, 14.0. HRMS (ESI) calcd. for $C_{21}H_{22}BrN_2O_4$ $(M + H)^+$ 445.0758, found 445.0768 and 447.0750.

Diethyl 2-(2-(4-fluorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ad):



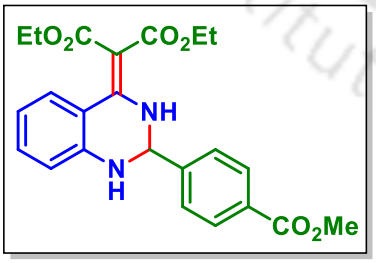
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 144-146 °C; yield 115 mg, 75%; IR (KBr, neat) ν 3328, 2983, 1690, 1567, 1453, 1266, 1212, 1155, 1073, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1 H), 7.56-7.53 (m, 2 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.27-7.23 (m, 1 H), 7.09 (t, *J* = 8.5 Hz, 2 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 5.37 (d, *J* = 1.8 Hz, 1 H), 4.60 (s, 1 H), 4.24-4.10 (m, 4 H), 1.26-1.15 (m, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.7, 169.1, 163.7 (d, *J* = 247.6 Hz), 155.0, 147.2, 134.2 (d, *J* = 3.1 Hz), 132.7, 129.9 (d, *J* = 8.3 Hz), 128.4, 119.7, 117.0, 116.4, 116.3, 116.1, 89.8, 66.0, 61.2, 60.0, 14.5, 14.0. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -114.21 (s, -F). HRMS (ESI) calcd. for $C_{21}H_{22}FN_2O_4$ $(M + H)^+$ 385.1558, found 385.1562.

Diethyl 2-(2-(4-nitrophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ae):



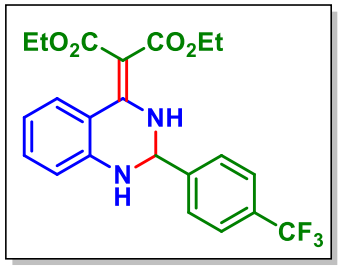
Primrose yellow solid; R_f (hexane/EtOAc,7:3) 0.40; mp 179-181 °C; yield 148 mg, 90%; IR (KBr, neat) ν 3329, 2982, 1723, 1644, 1523, 1345, 1239, 1153, 1075, 762 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6) δ 10.22 (d, *J* = 4.0 Hz, 1 H), 8.25 (d, *J* = 8.8 Hz, 2 H), 7.72 (d, *J* = 8.2 Hz, 2 H), 7.61 (s, 1 H), 7.27 (t, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 1 H), 6.89 (d, *J* = 8.1 Hz, 1 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 5.89 (s, 1 H), 4.09-4.04 (m, 4 H), 1.13 (t, *J* = 7.1 Hz, 6 H). 13C{1H} NMR (150 MHz, DMSO-d6) δ 168.2, 153.8, 148.1, 147.5, 146.6, 132.9, 128.2, 127.4, 123.7, 118.1, 116.5, 115.3, 88.6, 62.3, 59.7, 14.0. HRMS (ESI) calcd. for $C_{21}H_{22}N_3O_6$ $(M + H)^+$ 412.1503, found 412.1526.

Diethyl 2-(2-(4-(methoxycarbonyl)phenyl)-2,3-dihydroquinazolin-4(1H)-ylidene)malonate (23af):



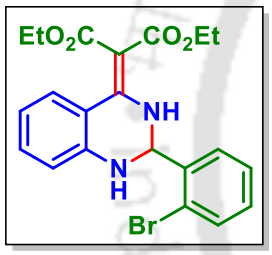
Yellow solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 188-190 °C; yield 144 mg, 85%; IR (KBr, neat) ν 3323, 2986, 1705, 1609, 1553, 1335, 1234, 1123, 1036, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 8.07 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 8.0 Hz, 2 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.29-7.26 (m, 1 H), 6.82 (t, *J* = 7.7 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 5.47 (d, *J* = 1.9 Hz, 1 H), 4.56 (s, 1 H), 4.23-4.17 (m, 1 H), 4.15-4.08 (m, 3 H), 3.92 (s, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.16 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.6, 169.1, 166.7, 154.9, 146.8, 143.0, 132.8, 131.8, 130.5, 128.5, 128.0, 120.0, 117.2, 116.5, 90.1, 66.1, 61.3, 60.1, 52.6, 14.6, 14.0. HRMS (ESI) calcd. for $C_{23}H_{25}N_2O_6$ $(M + H)^+$ 425.1707, found 425.1725.

Diethyl 2-(2-(4-(trifluoromethyl)phenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ag):



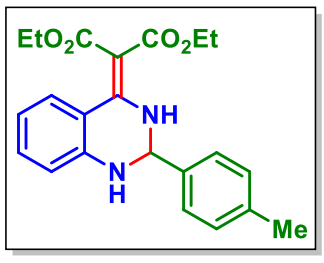
Pale yellow solid; R_f (hexane/EtOAc,7:3) 0.50; mp 145-147 °C; yield 151 mg, 87%; IR (KBr, neat) ν 3320, 2983, 1700, 1643, 1555, 1321, 1234, 1115, 1034, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.16 (s, 1 H), 7.71 (dd, *J* = 14.0 and 8.4 Hz, 4 H), 7.51 (dd, *J* = 8.1 and 1.4 Hz, 1 H), 7.31-7.28 (m, 1 H), 6.87-6.84 (m, 1 H), 6.76 (dd, *J* = 8.0 and 1.2 Hz, 1 H), 5.51 (d, *J* = 1.9 Hz, 1 H), 4.44 (s, 1 H), 4.26-4.10 (m, 4 H), 1.26 (t, *J* = 6.9 Hz, 3 H), 1.18 (t, *J* = 7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.6, 169.2, 154.7, 146.7, 142.2, 132.8, 132.4 (q, *J* = 32.2 Hz), 128.5 (d, *J* = 7.7 Hz), 126.4 (q, *J* = 3.6 Hz), 124.9, 123.1, 120.3, 117.3, 116.6, 90.5, 66.1, 61.3, 60.2, 14.6, 14.1. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -66.27 (s, -CF_3). HRMS (ESI) calcd. for $C_{22}H_{22}F_3N_2O_4$ $(M + H)^+$ 435.1526, found 435.1521.

Diethyl 2-(2-(2-bromophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ah):



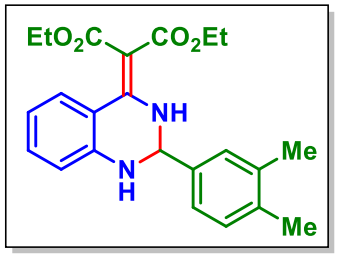
Bright yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 171-173 °C; yield 158 mg, 89%; IR (KBr, neat) ν 3323, 2980, 1699, 1645, 1592, 1558, 1475, 1237, 1154, 1076, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.28 (s, 1 H), 7.68 (dd, *J* = 7.7 and 1.8 Hz, 1 H), 7.58 (dd, *J* = 8.1 and 1.3 Hz, 1 H), 7.50 (dd, *J* = 8.1 and 1.3 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.25-7.22 (m, 2 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 5.90 (d, *J* = 2.8 Hz, 1 H), 4.69 (s, 1 H), 4.18 (p, *J* = 7.0 Hz, 4 H), 1.29-1.17 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 169.2, 155.1, 146.3, 137.6, 133.5, 132.8, 131.1, 129.2, 128.5, 128.4, 123.0, 119.9, 117.1, 116.6, 90.3, 64.8, 61.3, 60.1, 14.6, 14.1. HRMS (ESI) calcd. for $C_{21}H_{22}BrN_2O_4$ $(M + H)^+$ 445.0757, found 445.0775 and 447.0757.

Diethyl 2-(2-(*p*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ai):



Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 159-161 °C; yield 116 mg, 76%; IR (KBr, neat) ν 3326, 2982, 1643, 1585, 1550, 1479, 1268, 1238, 1153, 1074, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.43 (d, *J* = 7.8 Hz, 2 H), 7.27-7.23 (m, 1 H), 7.21 (d, *J* = 7.8 Hz, 2 H), 6.80 (t, *J* = 7.7 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 5.33 (d, *J* = 1.8 Hz, 1 H), 4.51 (s, 1 H), 4.21-4.11 (m, 4 H), 2.36 (s, 3 H), 1.30-1.15 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 169.1, 155.3, 147.4, 140.1, 135.2, 132.6, 129.9, 128.5, 127.8, 119.6, 117.2, 116.3, 89.5, 66.5, 61.1, 59.9, 21.4, 14.6, 14.0. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $(M + H)^+$ 381.1819, found 381.1809.

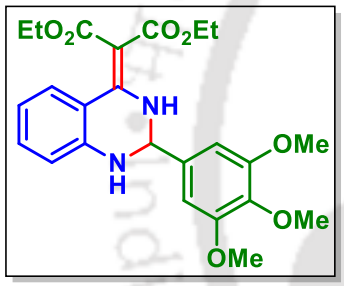
Diethyl 2-(2-(3,4-dimethylphenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23aj):



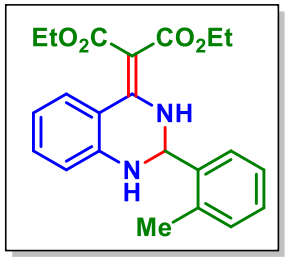
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 138-140 °C; yield 108 mg, 69%; IR (KBr, neat) ν 3318, 2978, 1643, 1588, 1555, 1477, 1232, 1151, 1114, 1074, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.33 (d, *J* = 2.0 Hz, 1 H), 7.26-7.23 (m, 2 H), 7.15 (d, *J* = 7.8 Hz, 1 H), 6.79 (t, *J* = 7.7 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 5.29 (d, *J* = 1.7 Hz, 1 H), 4.52 (s, 1 H), 4.20-4.05 (m, 4 H), 2.27 (s, 6 H), 1.26-1.13 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 169.1, 155.4, 147.5, 138.7, 137.6, 135.5, 132.6, 130.3, 129.0, 128.5, 125.3, 119.5, 117.2, 116.3, 89.4, 66.5, 61.0, 59.9, 20.0, 19.8, 14.6, 14.0. HRMS (ESI) calcd. for $C_{23}H_{27}N_2O_4$ $(M + H)^+$ 395.1965, found 395.1982.

Diethyl 2-(2-(3,4,5-trimethoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ak):

Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 184-186 °C; yield 108 mg, 59%; IR (KBr, neat) ν 3327, 2978, 1643, 1590, 1555, 1463, 1234, 1121, 1075, 761 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.99 (s, 1 H), 7.47 (d, *J* = 8.1 Hz, 1 H), 7.28 (t, *J* = 7.3 Hz, 1 H), 6.82 (t, *J* = 7.7 Hz, 1 H), 6.78-6.75 (m, 3 H), 5.30 (d, *J* = 1.7 Hz, 1 H), 4.61 (s, 1 H), 4.23-4.19 (m, 1 H), 4.16-4.07 (m, 3 H), 3.85 (d, *J* = 6.2 Hz, 9 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.8, 169.1, 155.2, 153.7, 147.5, 139.0, 133.6, 132.7, 128.5, 119.7, 116.9, 116.3, 104.9, 89.5, 67.1, 61.2, 61.0, 60.0, 56.4, 14.6, 14.0. HRMS (ESI) calcd. for $C_{23}H_{27}N_2O_4$ $(M + H)^+$ 457.1969, found 457.1970.

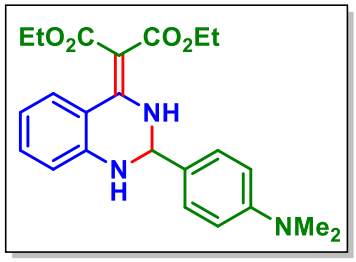


Dimethyl 2-(2-(*o*-tolyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23al):



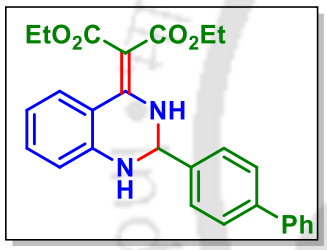
Yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 118-120 °C; yield 91 mg, 60%; IR (KBr, neat) ν 3326, 2980, 1643, 1589, 1556, 1478, 1267, 1237, 1153, 1074, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.68 (dd, *J* = 7.3 and 1.9 Hz, 1 H), 7.51 (d, *J* = 8.1 Hz, 1 H), 7.32-7.25 (m, 3 H), 7.21 (dd, *J* = 7.0 and 1.9 Hz, 1 H), 6.82 (t, *J* = 7.7 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 5.61 (d, *J* = 1.9 Hz, 1 H), 4.44 (s, 1 H), 4.20-4.09 (m, 4 H), 2.43 (s, 3 H), 1.26-1.16 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.7, 169.1, 155.3, 147.9, 136.8, 135.6, 132.6, 131.4, 129.7, 128.6, 127.7, 127.0, 119.7, 117.3, 116.5, 89.8, 63.5, 61.1, 59.9, 19.3, 14.6, 14.1. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $(M + H)^+$ 381.1809, found 381.1818.

Diethyl 2-(2-(4-(dimethylamino)phenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23am):



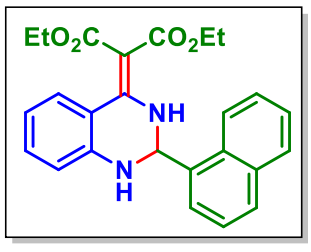
Light green solid; R_f (hexane/EtOAc,7:3) 0.50; mp 174-176 °C; yield 103 mg, 63%; IR (KBr, neat) ν 3331, 2980, 1612, 1704, 1648, 1587, 1554, 1361, 1237, 1152, 1073, 755 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 7.29-7.27 (m, 1 H), 6.82 (t, *J* = 7.6 Hz, 1 H), 6.75-6.72 (m, 3 H), 5.31 (d, *J* = 1.8 Hz, 1 H), 4.43 (s, 1 H), 4.22-4.08 (m, 4 H), 3.00 (s, 6 H), 1.28 (d, *J* = 8.2 Hz, 3 H), 1.17 (d, *J* = 8.0 Hz, 3 H). $^{13}C\{^1H\}$ (150 MHz, $CDCl_3$) δ 169.9, 169.1, 155.7, 151.8, 147.8, 132.5, 128.9, 128.6, 125.1, 119.4, 117.2, 116.2, 112.6, 89.1, 66.6, 61.1, 59.8, 40.7, 14.7, 14.1. HRMS (ESI) calcd. for $C_{23}H_{28}N_3O_4$ $(M + H)^+$ 410.2074, found 410.2069.

Diethyl 2-(2-([1,1'-biphenyl]-4-yl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23an):



Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 149-151 °C; yield 129 mg, 73%; IR (KBr, neat) ν 3326, 2981, 1628, 1560, 1480, 1270, 1234, 1153, 1115, 1073, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.65 (s, 4 H), 7.59 (d, *J* = 7.7 Hz, 2 H), 7.51 (d, *J* = 8.1 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.29 (t, *J* = 7.7 Hz, 1 H), 6.84 (t, *J* = 7.7 Hz, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 5.45 (d, *J* = 1.9 Hz, 1 H), 4.48 (s, 1 H), 4.24-4.09 (m, 4 H), 1.28-1.16 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 169.2, 155.2, 147.3, 143.3, 140.6, 137.0, 132.7, 129.1, 128.6, 128.5, 128.1, 128.0, 127.5, 119.9, 117.3, 116.4, 89.8, 66.6, 61.2, 60.0, 14.7, 14.1. HRMS (ESI) calcd. for $C_{27}H_{27}N_2O_4$ $(M + H)^+$ 443.1965, found 443.1981.

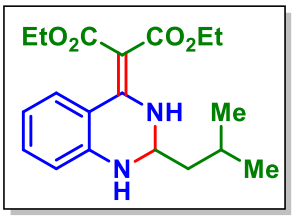
Diethyl 2-(2-(naphthalen-1-yl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ao):



Yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 143-145 °C; yield 104 mg, 63%; IR (KBr, neat) ν 3324, 2980, 1644, 1589, 1554, 1478, 1368, 1233, 1150, 1073, 762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.23 (s, 1 H), 8.35 (d, *J* = 8.0 Hz, 1 H), 7.92 -7.90 (m, 2 H), 7.80 (d, *J* = 7.2 Hz, 1 H), 7.57-7.48 (m, 4 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 6.85 (t, *J* = 7.7 Hz, 1 H), 6.75 (d, *J* = 8.0 Hz, 1 H), 6.07 (d, *J* = 1.9 Hz, 1 H), 4.61 (s, 1 H), 4.25-4.06 (m, 4 H), 1.23-1.19 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 169.1, 155.3, 147.8, 134.4, 132.7, 132.6, 131.0, 130.7, 129.3, 128.7, 127.1, 126.5, 126.4, 125.5, 123.7, 119.8,

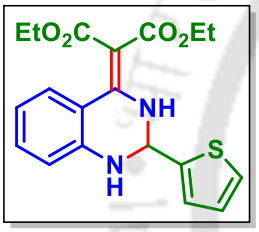
117.4, 116.5, 90.1, 64.6, 61.2, 59.9, 14.6, 14.1. HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_4$ $(M + H)^+$ 417.1809, found 417.1827.

Diethyl 2-(2-isobutyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ap):



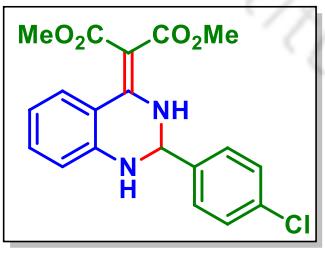
White solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 142-144 °C; yield 107 mg, 77%; IR (KBr, neat) ν 3338, 2927, 1690, 1640, 1576, 1428, 1288, 1117, 1077, 787 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1 H), 7.44-7.42 (m, 1 H), 7.25-7.22 (m, 1 H), 6.78 (t, *J* = 7.7 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 4.85-4.46 (m, 1 H), 4.27 (s, 1 H), 4.21-4.15 (m, 3 H), 4.09 (s, 1 H), 1.93-1.82 (m, 1 H), 1.76-1.69 (m, 1 H), 1.64-1.59 (m, 1 H), 1.34 - 1.11 (m, 6 H), 0.99 (t, *J* = 7.2 Hz, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 169.3, 155.8, 147.5, 132.5, 128.5, 119.6, 117.8, 116.6, 89.2, 61.6, 61.0, 59.9, 43.5, 24.4, 23.1, 22.6, 14.6, 14.1. HRMS (ESI) calcd. for $C_{19}H_{27}N_2O_4$ $(M + H)^+$ 347.1965, found 347.1965.

Diethyl 2-(2-(thiophen-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23aq):



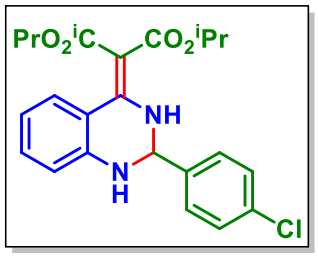
Light yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 150-152 °C; yield 77 mg, 52%; IR (KBr, neat) ν 3320, 2980, 1643, 1589, 1555, 1476 1422, 1236, 1150, 1071, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.19 (s, 1 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.36 (d, *J* = 5.1 Hz, 1 H), 7.29-7.26 (m, 1 H), 7.21 (d, *J* = 3.5 Hz, 1 H), 7.00 (t, *J* = 4.3 Hz, 1 H), 6.83 (t, *J* = 7.7 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 5.73 (s, 1 H), 4.64 (s, 1 H), 4.25-4.08 (m, 4 H), 1.32-1.14 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.6, 169.1, 154.6, 146.6, 141.4, 132.7, 128.5, 127.6, 127.5, 127.1, 120.1, 117.4, 116.6, 90.1, 62.2, 61.2, 60.1, 14.6, 14.0. HRMS (ESI) calcd. for $C_{19}H_{21}N_2O_4S$ $(M + H)^+$ 373.1217, found 373.1205.

Dimethyl 2-(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23ar):



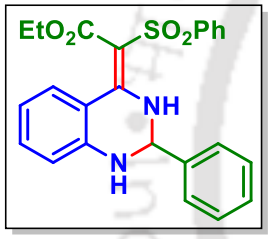
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 138-140 °C; yield 124 mg, 84%; IR (KBr, neat) ν 3320, 2976, 1649, 1589, 1480, 1277, 1234, 1150, 1120, 1073, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.12 (s, 1 H), 7.52 (d, *J* = 8.4 Hz, 2 H), 7.41 (dd, *J* = 8.7 and 2.4 Hz, 3 H), 7.31-7.28 (m, 1 H), 6.87-6.84 (m, 1H), 6.76 (d, *J* = 8.1 Hz, 1 H), 5.41 (d, *J* = 1.8 Hz, 1 H), 4.58 (s, 1 H), 3.67 (d, *J* = 23.0 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.1, 169.4, 155.6, 147.0, 136.6, 136.2, 132.9, 129.5, 129.3, 128.3, 120.0, 117.0, 116.6, 89.1, 66.0, 52.3, 51.5. HRMS (ESI) calcd. for $C_{19}H_{18}ClN_2O_4$ $(M + H)^+$ 373.0950, found 373.0969 and 375.0937.

Diisopropyl 2-(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23as):



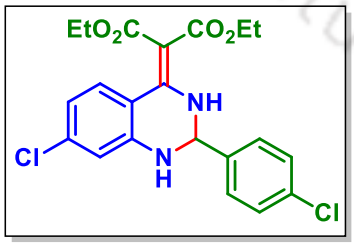
Pale yellow solid; R_f (hexane/EtOAc, 17:3) 0.50; mp 142-144 °C; yield 77 mg, 45%; IR (KBr, neat) ν 3324, 2978, 1697, 1641, 1590, 1558, 1480, 1237, 1195, 1072, 757 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.95 (s, 1 H), 7.56 (d, *J* = 8.1 Hz, 1 H), 7.49 (d, *J* = 8.3 Hz, 2 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.23 (t, *J* = 7.4 Hz, 1 H), 6.79 (t, *J* = 7.7 Hz, 1 H), 6.69 (d, *J* = 8.0 Hz, 1 H), 5.36 (d, *J* = 2.0 Hz, 1 H), 5.08 (p, *J* = 6.3 Hz, 1 H), 4.96 (p, *J* = 6.2 Hz, 1H), 4.52 (s, 1 H), 1.32 (d, *J* = 6.3 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 1.19 (dd, *J* = 12.2 and 6.3 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.2, 168.7, 153.7, 147.0, 137.0, 136.0, 132.6, 129.5, 129.4, 128.4, 119.8, 117.0, 116.4, 91.2, 68.5, 67.2, 66.0, 22.3, 21.9, 21.6. HRMS (ESI) calcd. for $C_{23}H_{26}ClN_2O_4$ $(M + H)^+$ 429.1576, found 429.1575 and 431.1570.

Ethyl (Z)-2-(2-phenyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)-2-(phenylsulfonyl)acetate (23at):



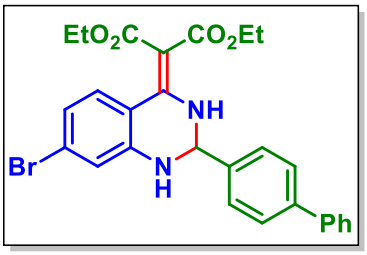
Orange gum; R_f (hexane/EtOAc, 7:3) 0.50; yield 43 mg, 25%; IR (KBr, neat) ν 3325, 2985, 1742, 1615, 1548, 1447, 1252, 1189, 1080, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.81 (d, *J* = 4.5 Hz, 1 H), 7.88-7.85(m, 3 H), 7.60-7.53 (m, 3 H), 7.49-7.46 (m, 2 H), 7.36-7.29 (m, 4 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 6.61 (t, *J* = 7.6 Hz, 1 H), 5.86 (s, 1 H), 3.84-3.73 (m, 2 H), 0.85 (t, *J* = 7.0 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 165.7, 156.9, 147.5, 145.4, 139.5, 134.4, 131.9, 130.3, 128.7, 128.5, 128.4, 126.7, 126.2, 117.4, 116.2, 114.9, 90.8, 62.6, 59.5, 13.6. HRMS (ESI) calcd. for $C_{24}H_{23}N_2O_4S$ $(M + H)^+$ 435.1373, found 435.1386.

Diethyl 2-(2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23bb):



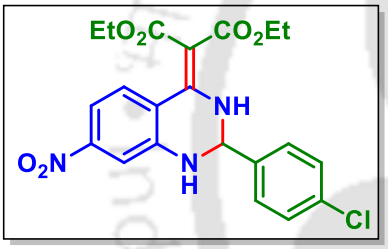
Yellow solid; R_f (hexane/EtOAc,17:3) 0.50; mp 156-158 °C; yield 151 mg, 87%; IR (KBr, neat) ν 3323, 2928, 1647, 1586, 1555, 1478, 1231, 1153, 1112, 1079, 825, 648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.49 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 2.2 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.20 (dd, *J* = 8.5 and 2.3 Hz, 1 H), 6.66 (d, *J* = 8.6 Hz, 1 H), 5.36 (d, *J* = 1.9 Hz, 1 H), 4.64 (s, 1 H), 4.25-4.10 (m, 4 H), 1.24 (td, *J* = 7.2 and 2.6 Hz, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.3, 145.5, 136.5, 136.2, 132.5, 129.6, 129.3, 128.0, 124.8, 118.2, 117.7, 90.7, 66.0, 61.6, 60.2, 14.6, 14.1. HRMS (ESI) calcd. for $C_{21}H_{21}Cl_2N_2O_4$ $(M + H)^+$ 435.0873, found 435.0886 and 437.0857.

Diethyl 2-(2-([1,1'-biphenyl]-4-yl)-7-bromo-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23cn):



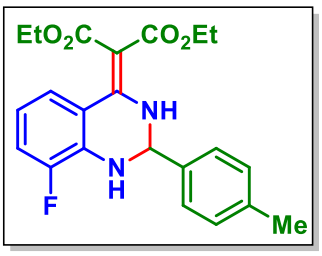
Yellow solid; R_f (hexane/EtOAc, 17:3) 0.50; mp 181-183 °C; yield 162 mg, 78%; IR (KBr, neat) ν 3344, 2926, 1738, 1646, 1552, 1475, 1369, 1246, 1153, 1071, 765, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.65-7.56 (m, 7 H), 7.48-7.44 (m, 2 H), 7.40-7.37 (m, 1H), 7.35 (dd, *J* = 8.5 and 2.2 Hz, 1 H), 6.64 (d, *J* = 8.6 Hz, 1 H), 5.40 (d, *J* = 1.8 Hz, 1 H), 4.63 (s, 1 H), 4.29-4.10 (m, 4 H), 1.27-1.22 (m, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.3, 169.0, 153.5, 146.2, 143.4, 140.5, 136.7, 135.2, 131.1, 129.1, 128.4, 128.1, 128.0, 127.4, 118.8, 118.0, 111.6, 90.5, 66.4, 61.5, 60.2, 14.6, 14.2. HRMS (ESI) calcd. for $C_{27}H_{26}BrN_2O_4$ $(M + H)^+$ 521.1071, found 521.1076 and 523.1059.

Diethyl 2-(2-(4-chlorophenyl)-7-nitro-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23db):



Yellow solid; R_f (hexane/EtOAc,7:3) 0.50; mp 157-159 °C; yield 128 mg, 72%; IR (KBr, neat) ν 3336, 2980, 1612, 1594, 1488, 1329, 1235, 1152, 1089, 829, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 8.45 (d, *J* = 2.4 Hz, 1 H), 8.05 (dd, *J* = 9.0 and 2.4 Hz, 1 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 6.69 (d, *J* = 9.0 Hz, 1 H), 5.50-5.48 (m, 2 H), 4.35-4.24 (m, 2 H), 4.21-4.09 (m, 2 H), 1.32 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.4, 168.8, 151.7, 151.6, 140.1, 136.6, 135.9, 129.8, 129.2, 127.8, 125.1, 116.2, 115.2, 100.0, 65.5, 62.1, 60.5, 14.5, 14.1. HRMS (ESI) calcd. for $C_{21}H_{21}ClN_3O_6$ $(M + H)^+$ 446.1113, found 446.1131 and 448.1100.

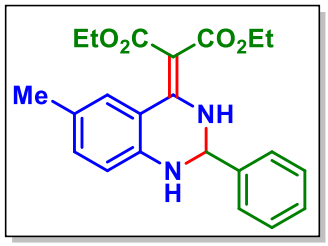
Diethyl 2-(8-fluoro-2-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-ylidene)malonate (23ei):



Bright yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 137-139 °C; yield 122 mg, 77%; IR (KBr, neat) ν 3333, 2978, 1707, 1645, 1565, 1311, 1234, 1125, 1033, 762 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 10.53 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.24-7.22 (m, 3 H), 6.57-6.53 (m, 2 H), 5.26 (d, *J* = 2.4 Hz, 1 H), 4.59 (s, 1 H), 4.25-4.07 (m, 4 H), 2.38 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.9, 168.3, 161.5 (d, *J* = 251.8 Hz), 153.1, 149.8 (d, *J* = 5.5 Hz), 149.77, 140.4, 134.4, 133.2 (d, *J* = 11.1 Hz), 130.1, 127.9, 112.0 (d, *J* = 3.2 Hz), 107.8 (d, *J* = 15.5 Hz), 107.3 (d, *J* = 23.6 Hz), 91.2, 66.5, 60.5, 60.1, 21.5, 14.6, 14.2. ^{19}F NMR (470 MHz,

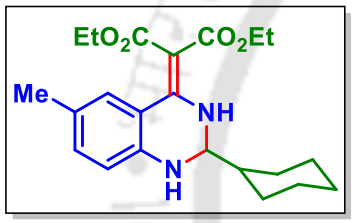
C_6F_6/$CDCl_3$) δ -109.93 (s, -F). HRMS (ESI) calcd. for $C_{22}H_{24}FN_2O_4$ $(M + H)^+$ 399.1715, found 399.1706.

Diethyl 2-(6-methyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23fa):



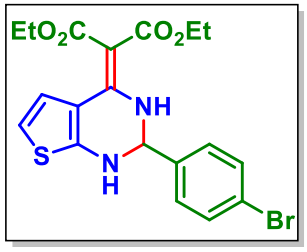
Pale yellow solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 128-130 °C; yield 126 mg, 83%; IR (KBr, neat) ν 3333, 2980, 1645, 1557, 1479, 1268, 1234, 1150, 1111, 1074, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1 H), 7.55-7.53 (m, 2 H), 7.42-7.40 (m, 3 H), 7.36 (d, *J* = 8.3 Hz, 1 H), 6.63 (dd, *J* = 8.2 and 1.7 Hz, 1 H), 6.52 (s, 1 H), 5.36 (d, *J* = 1.8 Hz, 1 H), 4.46 (s, 1 H), 4.22-4.11 (m, 4 H), 2.28 (s, 3 H), 1.26-1.20 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.9, 169.2, 155.4, 147.3, 143.6, 138.3, 130.1, 129.2, 128.4, 127.9, 121.0, 116.7, 114.5, 89.1, 66.7, 61.0, 59.8, 21.8, 14.5, 14.1. HRMS (ESI) calcd. for $C_{22}H_{25}N_2O_4$ $(M + H)^+$ 381.1809, found 381.1808.

Diethyl 2-(2-cyclohexyl-6-methyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23fx):



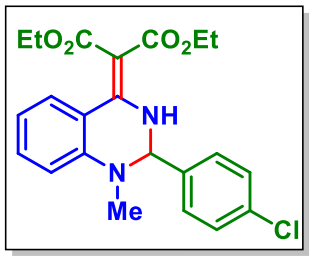
White solid; R_f (hexane/EtOAc,7:3) 0.50; mp 143-145 °C; yield 73 mg, 47%; IR (KBr, neat) ν 3340, 2928, 1694, 1640, 1588, 1445, 1268, 1117, 1077, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.20 (s, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 6.58 (d, *J* = 8.2 Hz, 1 H), 6.52 (s, 1 H), 4.21-4.15 (m, 4 H), 2.28 (s, 3 H), 1.93 (d, *J* = 12.9 Hz, 1 H), 1.85-1.79 (m, 3H), 1.72-1.66 (m, 2H), 1.61 (d, *J* = 5.0 Hz, 2 H), 1.29-1.17 (m, 9 H), 1.16-1.06 (m, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 170.0, 156.0, 147.3, 143.4, 128.4, 120.7, 116.8, 114.7, 88.4, 67.6, 61.0, 60.0, 41.3, 28.3, 28.2, 26.3, 25.99, 25.96, 21.8, 14.4. HRMS (ESI) calcd. for $C_{22}H_{31}N_2O_4$ $(M + H)^+$ 387.2278, found 387.2276.

Diethyl 2-(2-(4-bromophenyl)-2,3-dihydrothieno[2,3-*d*]pyrimidin-4(1*H*)-ylidene)malonate (23db):



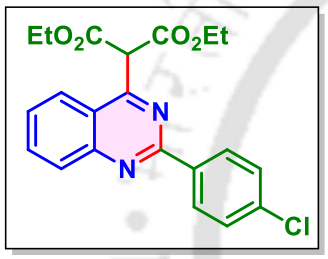
Yellow solid; R_f (hexane/EtOAc,4:1) 0.35; mp 167-169 °C; yield 94 mg, 52%; IR (KBr, neat) ν 3285, 2981, 1734, 1645, 1572, 1368, 1257, 1098, 1071, 737 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.51 (d, *J* = 2.2 Hz, 1 H), 8.38 (s, 1 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.44 (d, *J* = 8.4 Hz, 2 H), 6.61 (d, *J* = 5.8 Hz, 1 H), 6.53 (d, *J* = 5.9 Hz, 1 H), 5.84 (s, 1 H), 4.08 (q, *J* = 7.1 Hz, 4 H), 1.17 (t, *J* = 7.1 Hz, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 168.0, 156.7, 150.1, 139.4, 131.5, 128.9, 122.7, 122.0, 111.6, 110.0, 87.1, 64.8, 59.6, 14.0. HRMS (ESI) calcd. for $C_{19}H_{20}BrN_2O_4S$ $(M + H)^+$ 451.0322, found 451.0328 and 453.0327.

Diethyl 2-(2-(4-chlorophenyl)-1-methyl-2,3-dihydroquinazolin-4(1*H*)-ylidene)malonate (23hb):



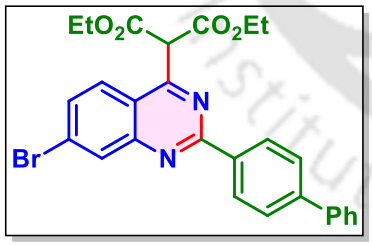
Yellow solid; R_f (hexane/EtOAc, 4:1) 0.60; mp 150-152 °C; yield 66 mg, 40%; IR (KBr, neat) ν 2927, 1712, 1644, 1587, 1488, 1266, 1243, 1115, 1087, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.38 (s, 1 H), 7.49 (d, *J* = 8.3 Hz, 1 H), 7.36 (t, *J* = 7.8 Hz, 1 H), 7.30 (q, *J* = 8.6 Hz, 4 H), 6.83 (t, *J* = 7.6 Hz, 1 H), 6.78 (d, *J* = 8.3 Hz, 1 H), 5.22 (d, *J* = 3.4 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 4 H), 2.68 (s, 3 H), 1.29-1.13 (m, 6H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.7, 169.3, 155.0, 147.8, 136.6, 135.5, 133.3, 129.4, 129.2, 128.4, 119.3, 118.3, 114.4, 89.4, 71.1, 61.2, 60.1, 35.5, 14.6, 14.1. HRMS (ESI) calcd. for $C_{22}H_{24}ClN_2O_4$ $(M + H)^+$ 415.1420, found 415.1393 and 417.1429.

Diethyl 2-(2-(4-chlorophenyl)quinazolin-4-yl)malonate (24a):



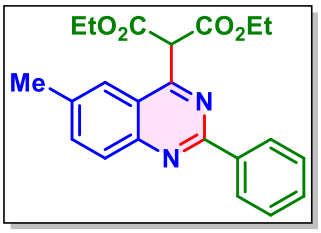
White solid; R_f (hexane/EtOAc, 4:1) 0.50; mp 140-142 °C; yield 84 mg, 70%; IR (KBr, neat) ν 2985, 1730, 1591, 1511, 1496, 1333, 1241, 1165, 1032, 708 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, *J* = 8.6 Hz, 2 H), 8.14-8.12 (m, 2 H), 8.09-8.04(m, 1 H), 7.79-7.75 (m, 1 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 6.26 (s, 1 H), 4.30-4.23 (m, 4 H), 1.20 (t, *J* = 7.1 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 166.5, 163.6, 157.6, 150.3, 136.1, 135.7, 135.2, 129.7, 129.0, 128.8, 128.5, 125.0, 121.9, 61.8, 57.0, 14.0. HRMS (ESI) calcd. for $C_{21}H_{20}ClN_2O_4$ $(M + H)^+$ 399.1107, found 399.1116 and 401.1084.

Diethyl 2-(2-([1,1'-biphenyl]-4-yl)-7-bromoquinazolin-4-yl)malonate (24b):



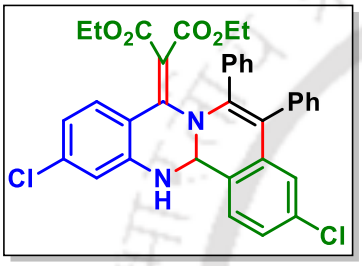
White solid; R_f (hexane/EtOAc, 4:1) 0.4; mp 150-152 °C; yield 118 mg, 76%; IR (KBr, neat) ν 2980, 1735, 1599, 1499, 1445, 1331, 1249, 1168, 1032, 710 cm^{-1}; ^1H NMR (600 MHz, DMSO-d6) δ 8.57 (d, *J* = 8.2 Hz, 2 H), 8.46 (d, *J* = 2.1 Hz, 1 H), 8.20 (dd, *J* = 9.0 and 2.2 Hz, 1 H), 8.08 (d, *J* = 8.9 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 7.2 Hz, 2 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 6.40 (s, 1 H), 4.30 (q, *J* = 7.1 Hz, 4 H), 1.23 (t, *J* = 7.1 Hz, 6 H). $^{13}C\{^1H\}$ (150 MHz, DMSO-d6) δ 166.9, 163.3, 159.1, 149.7, 143.3, 139.7, 138.6, 135.9, 131.5, 129.6, 129.1, 128.6, 127.9, 127.6, 127.3, 123.5, 121.5, 62.3, 57.3, 14.4. HRMS (ESI) calcd. for $C_{27}H_{24}BrN_2O_4$ $(M + H)^+$ 519.0914, found 519.0929 and 521.0912.

Diethyl 2-(6-methyl-2-phenylquinazolin-4-yl)malonate (24c):



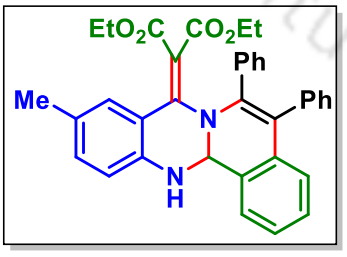
White solid; R_f (hexane/EtOAc, 4:1) 0.42; mp 143-145 °C; yield 95 mg, 84%; IR (KBr, neat) ν 2982, 1737, 1598, 1549, 1496, 1348, 1245, 1173, 1031, 708 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ 8.50-8.48 (m, 2 H), 8.03 (d, *J* = 8.5 Hz, 1 H), 7.92 (s, 1 H), 7.60-7.56 (m, 4 H), 6.24 (s, 1 H), 4.29-4.25 (m, 4 H), 2.58 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150 MHz, DMSO-d_6) δ 167.1, 163.3, 159.1, 151.1, 146.2, 137.4, 131.5, 130.8, 129.3, 128.4, 128.0, 125.1, 120.6, 62.2, 57.4, 22.1, 14.4. HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_4$ $(M + H)^+$ 379.1652, found 379.1642.

Diethyl 2-(3,11-dichloro-5,6-diphenyl-13,13a-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-ylidene)malonate (25a):



Off white solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 228-230 °C; yield 62 mg, 51%; IR (KBr, neat) ν 3340, 1744, 1710, 1604, 1571, 1445, 1248, 1091, 1014, 817, 695 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 -7.54 (m, 2 H), 7.49 (d, *J* = 8.2 Hz, 1 H), 7.39-7.37 (m, 2 H), 7.30-7.24 (m, 4 H), 7.23-7.20 (m, 3 H), 7.12-7.11 (m, 3 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 5.49 (s, 1 H), 4.70 (s, 1 H), 4.32-4.22 (m, 2 H), 4.20-4.14 (m, 1 H), 4.06-4.01 (m, 1 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 1.07 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.2, 167.1, 153.7, 152.5, 143.8, 141.0, 138.7, 136.6, 134.77, 134.75, 133.0, 132.2, 132.0, 130.8, 130.6, 129.2, 128.4, 127.5, 127.4, 127.1, 126.9, 120.2, 116.6, 109.9, 68.6, 62.3, 61.8, 61.8, 14.2, 14.0. HRMS (ESI) calcd. for $C_{35}H_{29}Cl_2N_2O_4$ $(M + H)^+$ 611.1499, found 611.1509 and 613.1488.

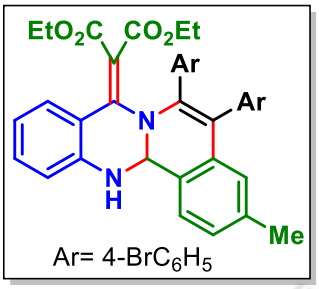
Diethyl 2-(10-methyl-5,6-diphenyl-13,13a-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-ylidene)malonate (25b):



Off white solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 178-180 °C; yield 66 mg, 63%; IR (KBr, neat) ν 3346, 1739, 1707, 1621, 1577, 1446, 1256, 1095, 1024, 839, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.64-7.63 (m, 2 H), 7.42-7.37 (m, 8 H), 7.35 (dd, *J* = 7.3 and 2.1 Hz, 1 H), 7.28-7.26 (m, 1 H), 7.16-7.13 (m, 3 H), 6.84 (s, 1 H), 6.65 (d, *J* = 1.3 Hz, 1 H), 5.57 (s, 1 H), 4.65 (s, 1 H), 4.38-4.32 (m, 2 H), 4.20-4.15 (m, 1 H), 4.05-4.00 (m, 1 H), 2.36 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.06 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.5, 167.5, 153.2, 149.5, 144.3, 141.9, 140.9, 138.7, 138.2, 137.6, 131.6, 131.4, 130.9, 129.6, 129.1, 128.7, 128.5, 128.5, 128.1, 127.4, 127.3, 127.0,

115.3, 113.9, 110.6, 68.7, 62.9, 62.0, 61.5, 22.8, 14.3, 14.0. HRMS (ESI) calcd. for $C_{36}H_{33}N_2O_4$ $(M + H)^+$ 557.2435, found 557.2427.

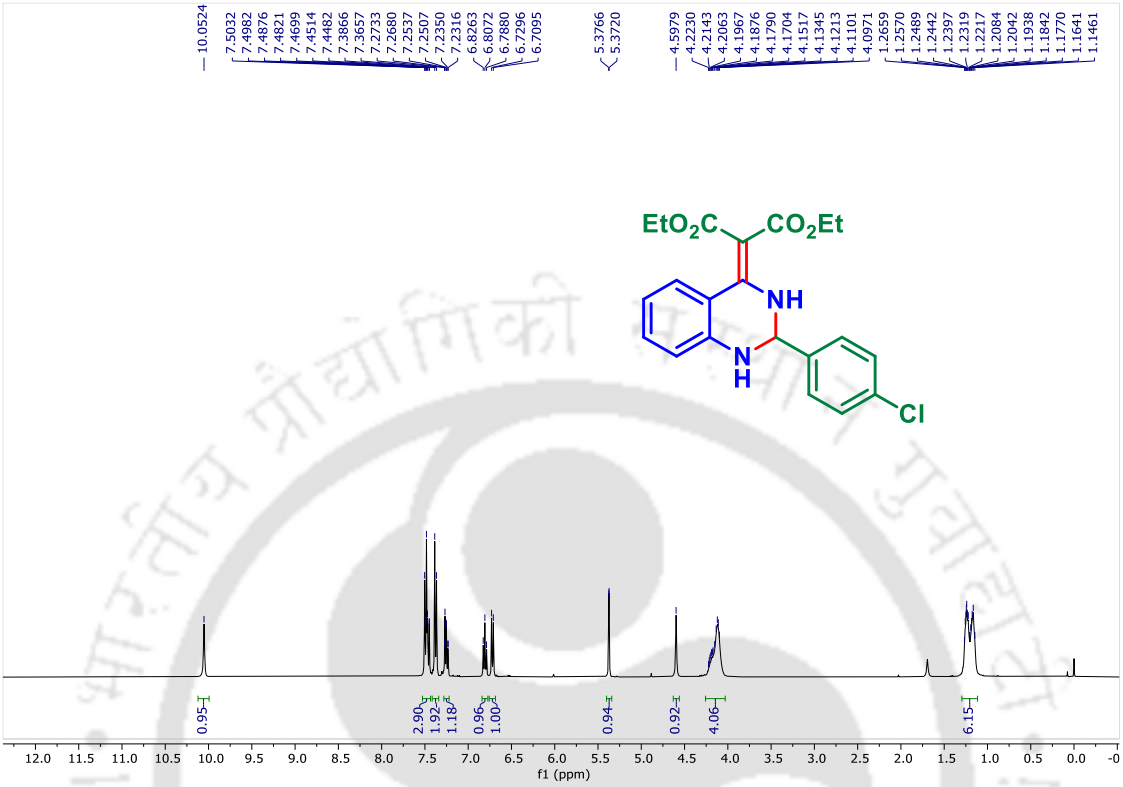
Diethyl 2-(5,6-bis(4-bromophenyl)-3-methyl-13,13a-dihydro-8*H*-isoquinolino[1,2-*b*]quinazolin-8-ylidene)malonate (25c):



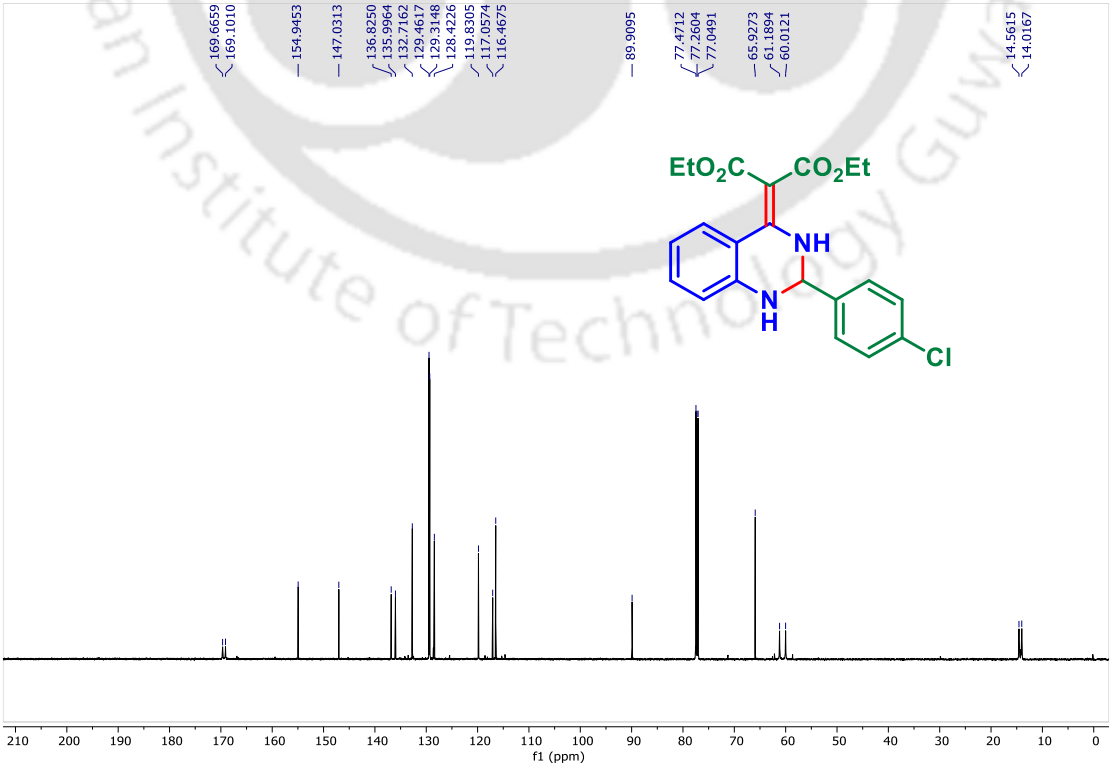
Off white solid; R_f (hexane/EtOAc, 9:1) 0.50; mp 232-234 °C; yield 81 mg, 57%; IR (KBr, neat) ν 3343, 1732, 1710, 1618, 1579, 1458, 1247, 1096, 1020, 830, 696 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 2 H), 7.47 (d, *J* = 7.6 Hz, 2 H), 7.41 (t, *J* = 7.8 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.23-7.17 (m, 5 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 5.50 (s, 1 H), 4.70 (s, 1 H), 4.33-4.27 (m, 2 H), 4.18-4.13 (m, 1 H), 4.03-3.97 (m, 1 H), 2.39 (s, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.04 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.3, 167.3, 154.2, 148.0, 144.8, 139.4, 138.7, 137.2, 136.7, 135.2, 133.08, 133.05, 132.5, 132.03, 132.00, 131.8, 130.8, 129.0, 128.94, 128.91, 122.0, 121.8, 115.4, 115.3, 109.2, 68.7, 62.8, 62.1, 61.6, 21.5, 14.4, 14.0. HRMS (ESI) calcd. for $C_{36}H_{31}Br_2N_2O_4$ $(M + H)^+$ 713.0645, found 713.0648 and 715.0640.

3.10. Representative Spectra

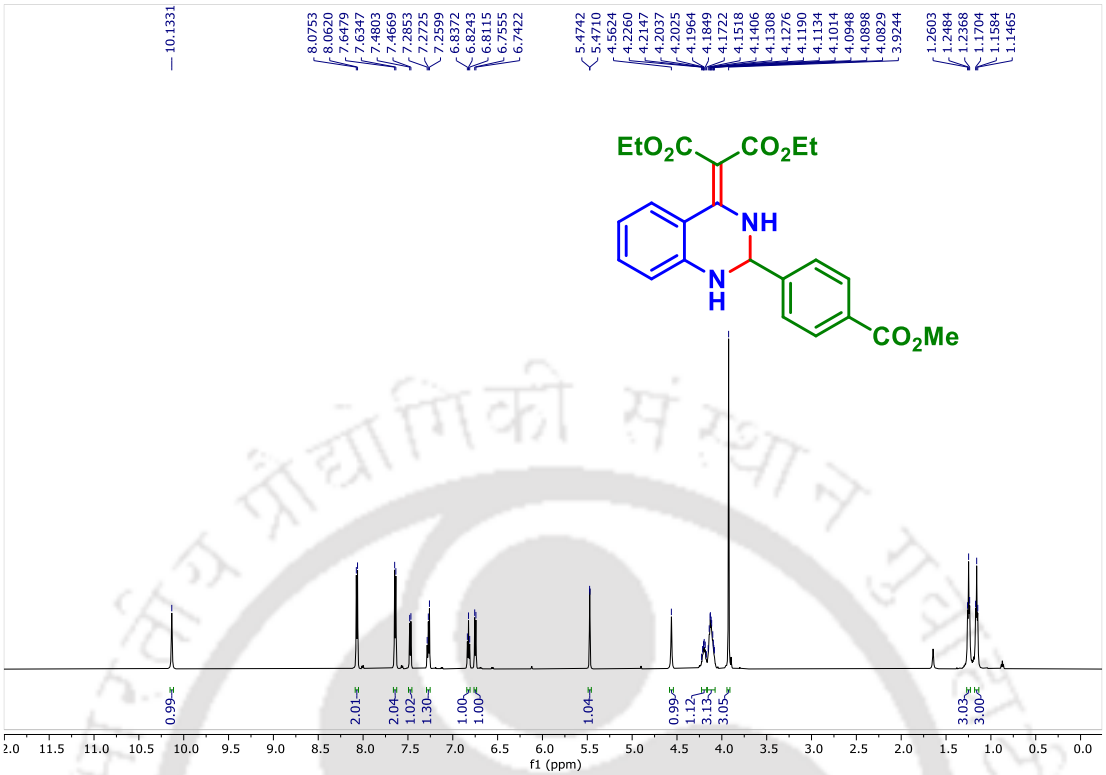
^{1}H ($CDCl_3$, 400 MHz) spectrum of compound (**23ab**):



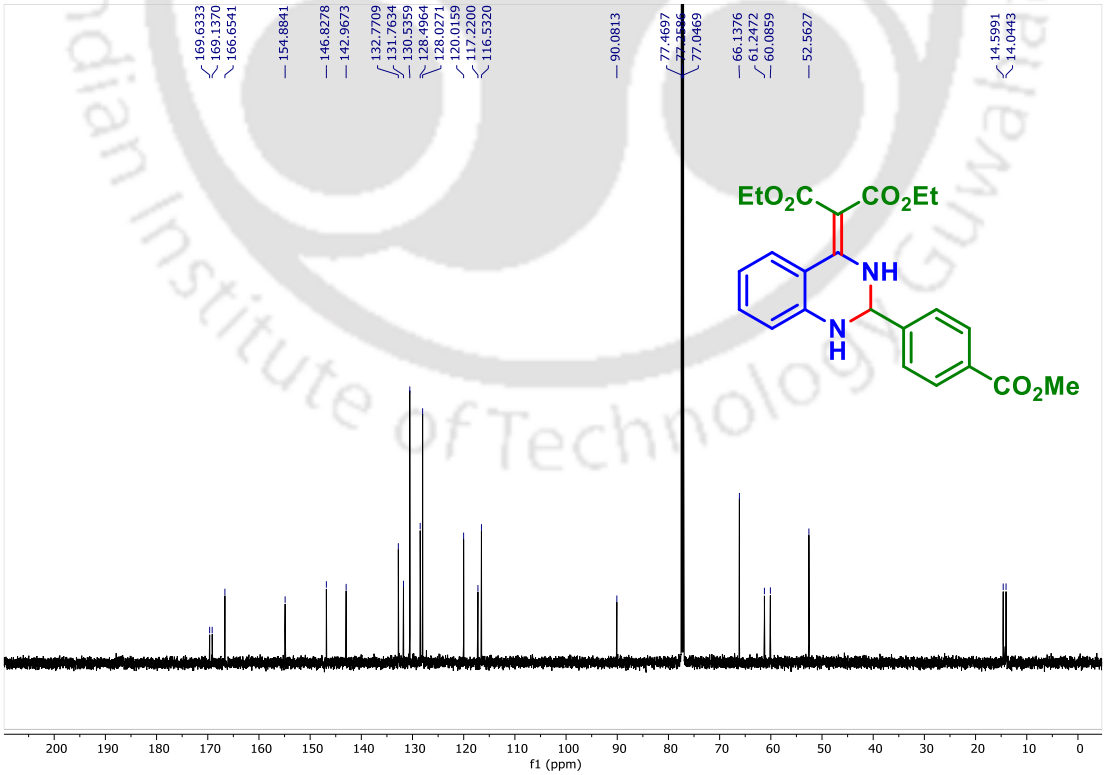
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**23ab**):



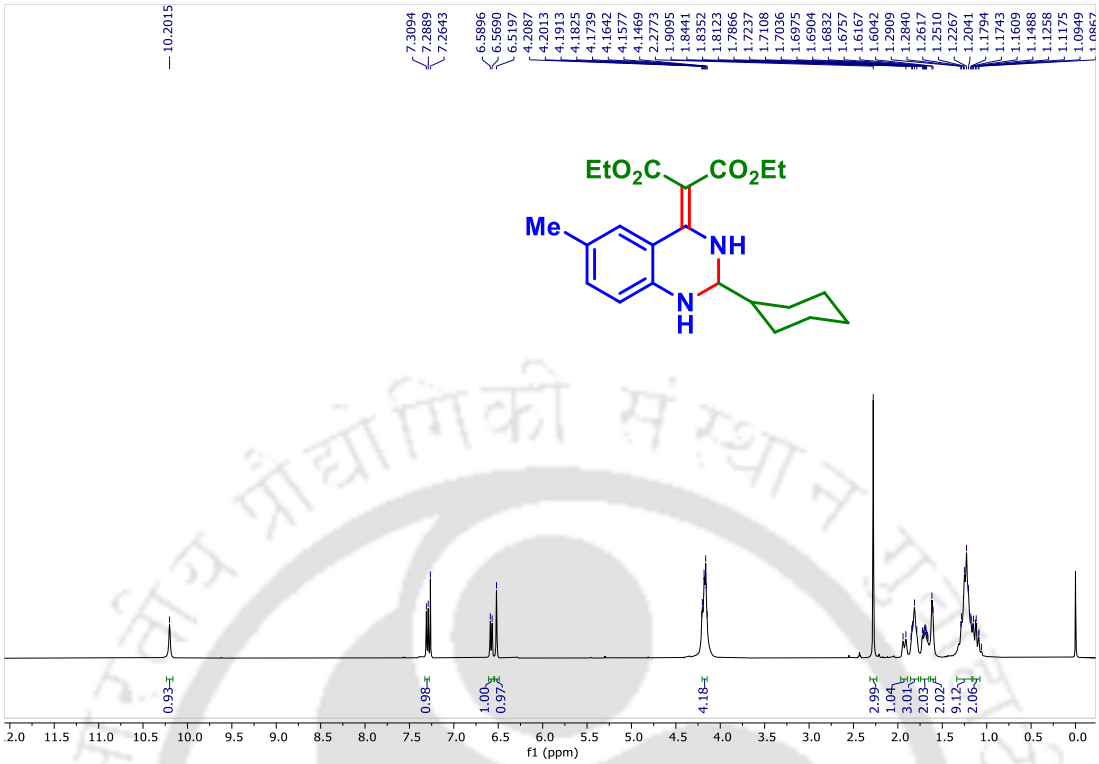
^{1}H ($CDCl_3$, 600 MHz) spectrum of compound (**23af**):



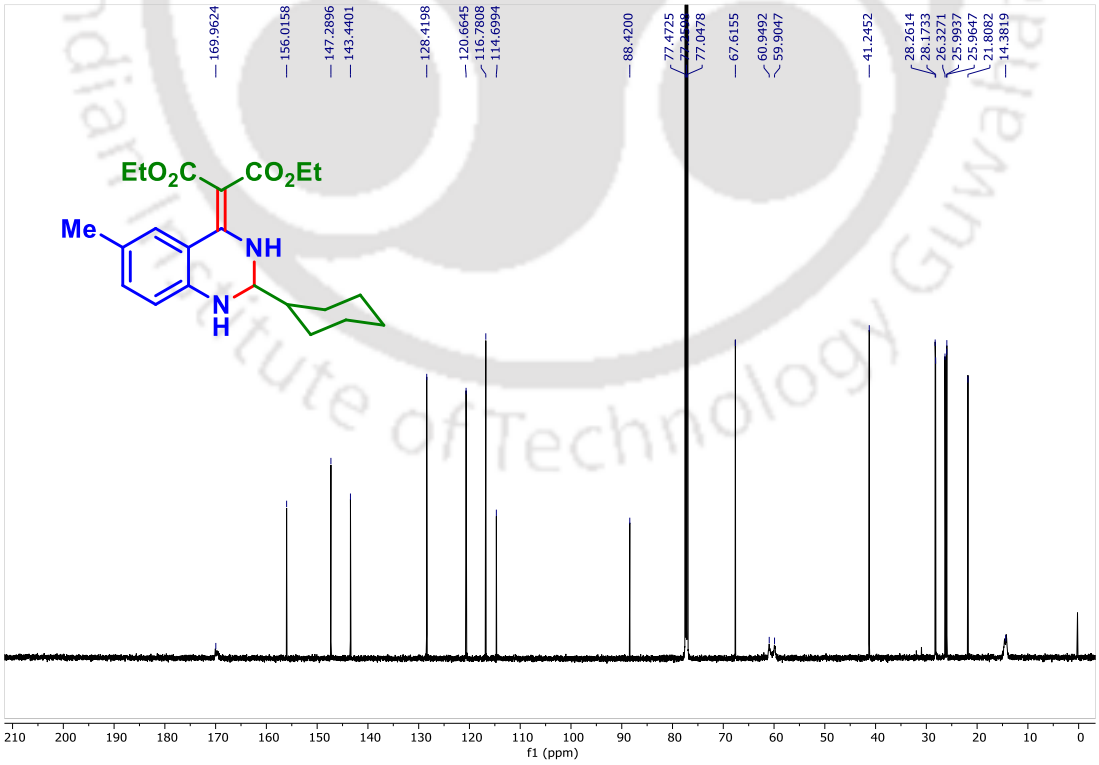
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**23af**):



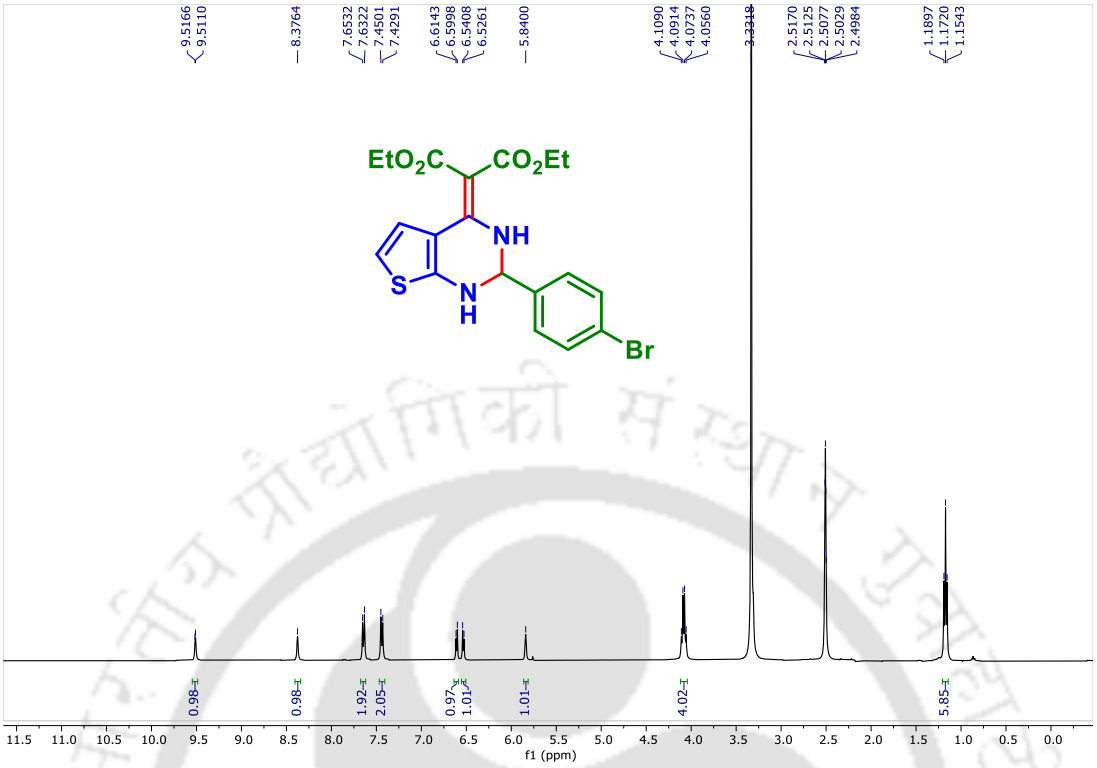
^{1}H ($CDCl_3$, 400 MHz) spectrum of compound (**23fx**):



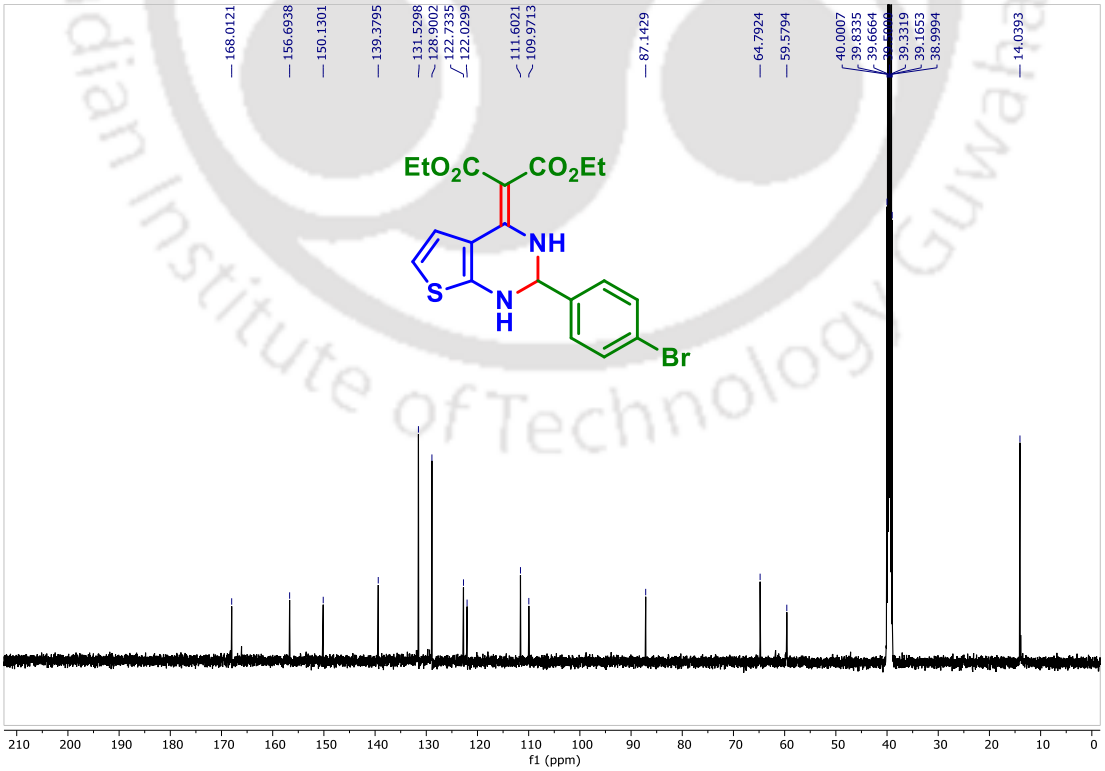
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**23fx**):



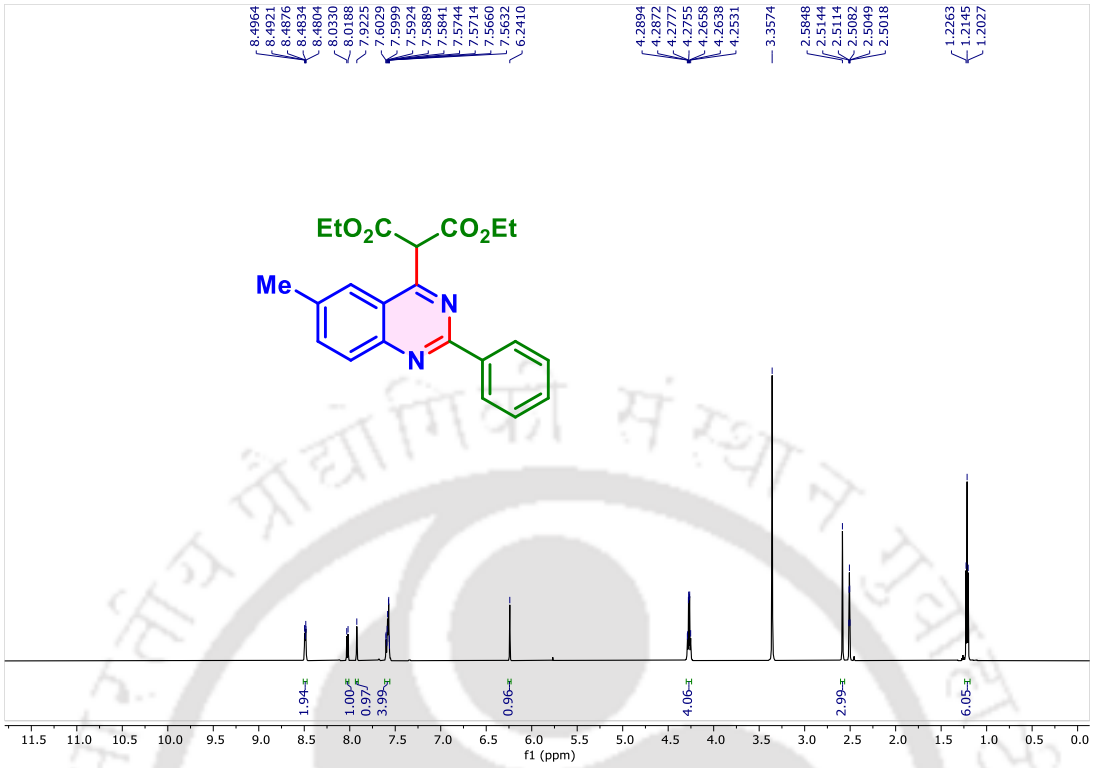
^{1}H (DMSO-d$_6$, 400 MHz) spectrum of compound (**23gc**):



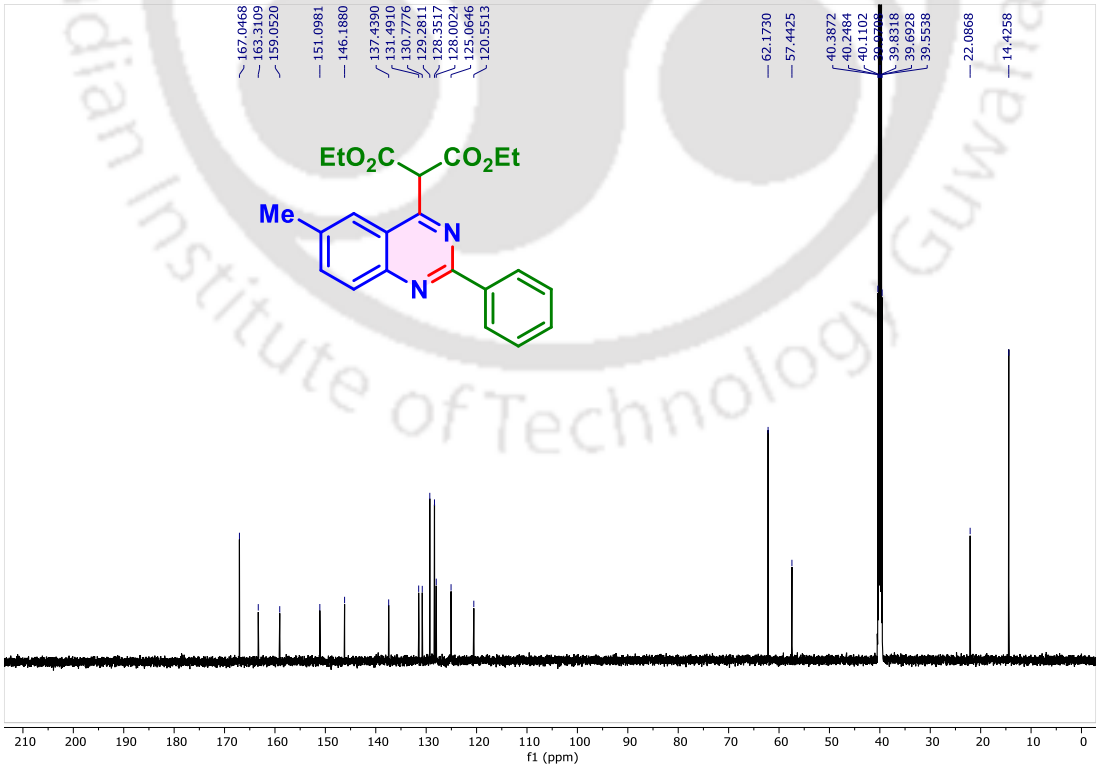
^{13}C{^{1}H} (DMSO-d$_6$, 125 MHz) spectrum of compound (**23gc**):



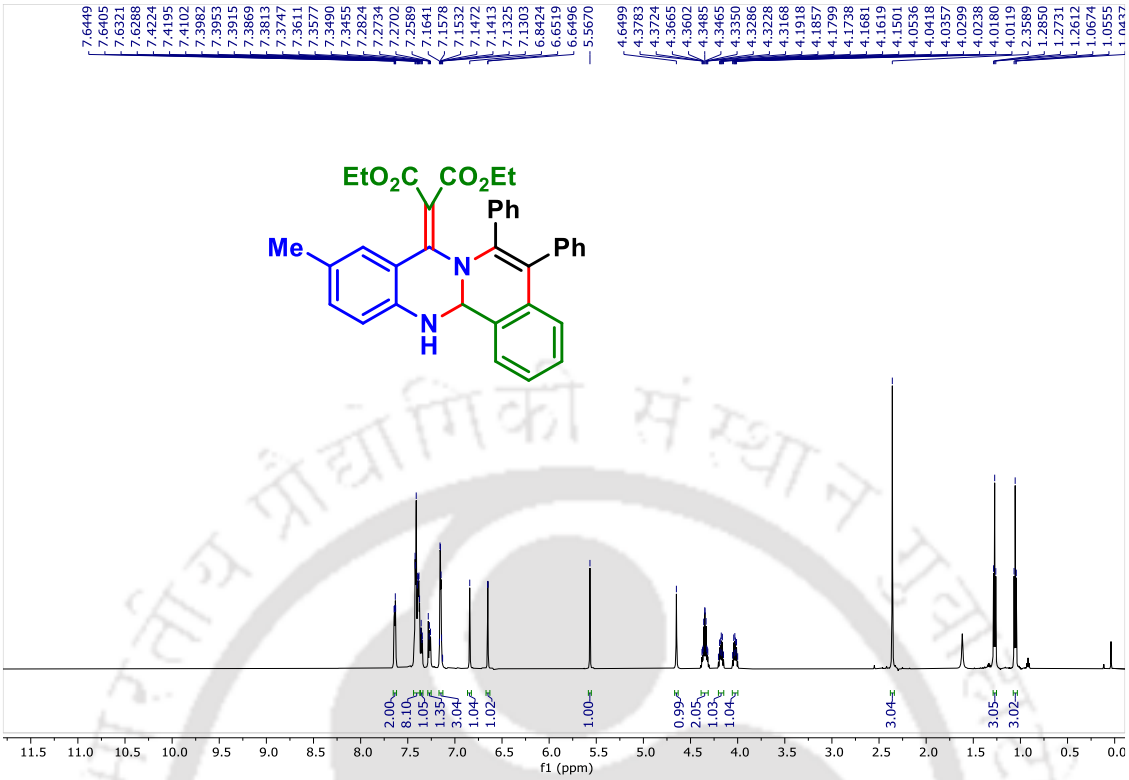
^{1}H (DMSO-d$_6$, 400 MHz) spectrum of compound (**24c**):



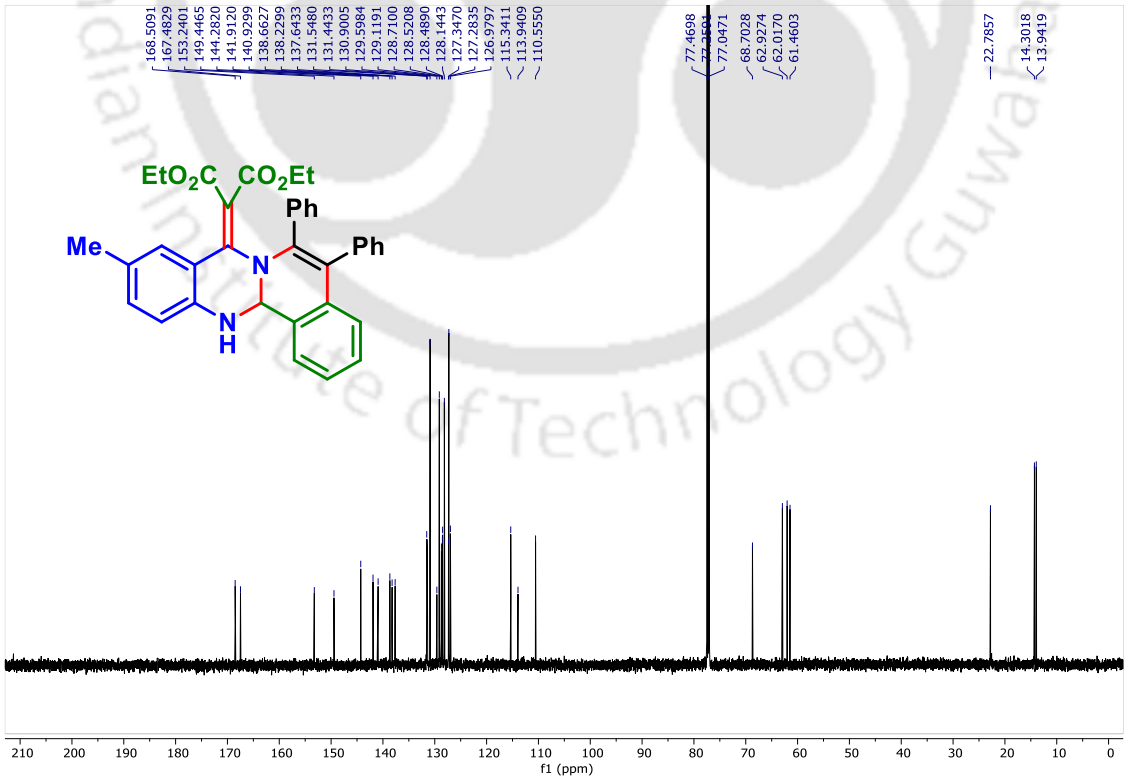
^{13}C{^{1}H} (DMSO-d$_6$, 150 MHz) spectrum of compound (**24c**)**:**



^{1}H ($CDCl_3$, 600 MHz) spectrum of compound (**25b**):



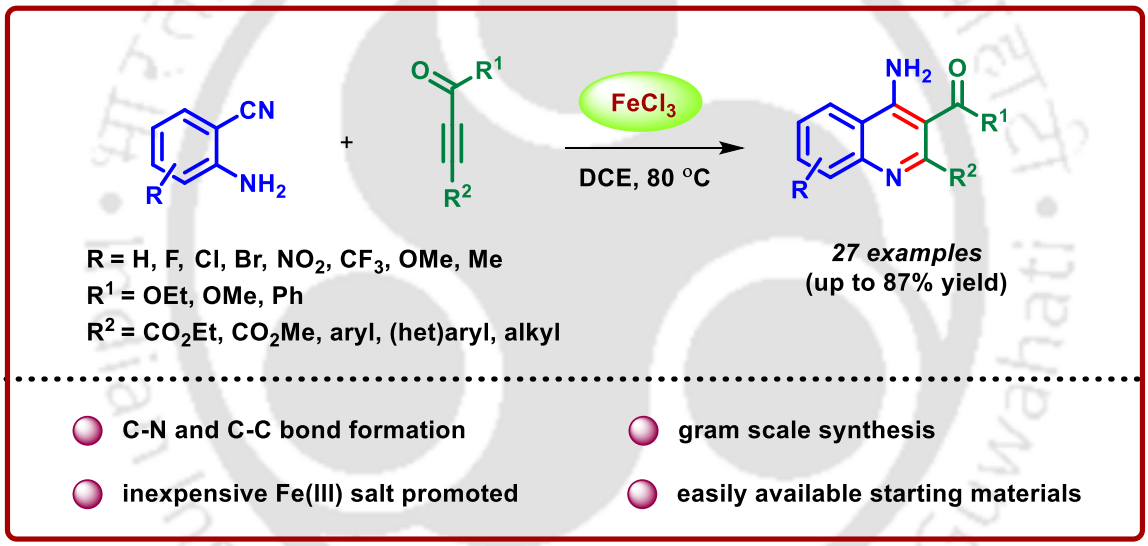
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**25b**):

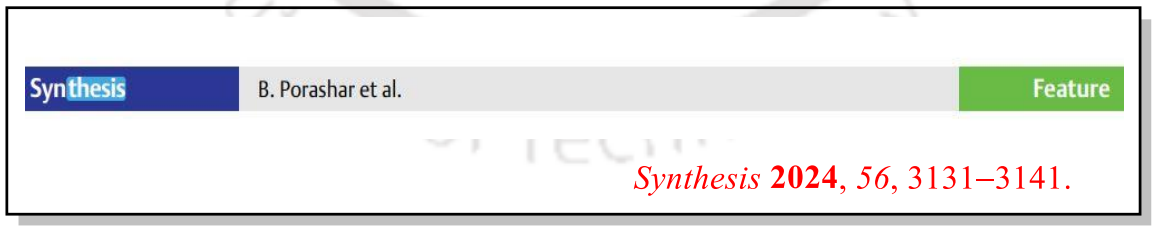


CHAPTER 4

Lewis Acid Mediated Synthesis of 4-Aminoquinoline Derivatives from 2-Aminobenzonitriles and Activated Alkynes

Abstract: This chapter highlights an efficient methodology for the synthesis of highly diverse 2,3-disubstituted 4-aminoquionoline derivatives from 2-aminobenzonitriles and activated alkynes in presence of $FeCl_3$. The reaction proceeds *via* sequential aza-Michael addition and intramolecular annulation to afford highly substituted 4-aminoquinolines in good yields. The salient features of this protocol include the use of a minimally toxic, eco-benign and less expensive Fe-(III) salt and has high atom-economy with broad substrate scope and operational simplicity. The post synthetic application of the reaction provides 4*H*-benzo[*de*][1,6]naphthyridines.





4.1. Introduction

Quinolines are important class of *N*-heterocycles which exhibit significant biological activities and are widely employed in the manufacture of pharmaceutical drugs, synthetic intermediates and building blocks.[1] Among them, 4-aminoquinolines have gained extensive research interest as they serve as potent chemotherapeutic agents majorly treating erythrocytic plasmodial infections and is still of high interest for developing novel anti-malarials.[2] However, this privileged scaffold is also present in tremendous number of other approved anti-cancer, anti-bacterial, anti-inflammatory drugs (*Figure 4.1.1.*). For example, marketed drugs like chloroquine (**a**),[3] discovered in 1934, and amodiaquine (**b**)[4] has been extensively utilized for the treatment of malaria for more than half century. However, complications associated with these drugs such as resistance and toxicity have led to the development of other promising structural analogues such as isoquine (**c**).[5] Similarly, commercially available floctafenine (**d**)[6] is a non-steroidal anti-inflammatory analgesic drug, whereas, tacrin (**e**)[7] is a centrally acting acetylcholinesterase inhibitor drug for treatment of Alzheimer's disease. Nerlynx (**f**)[8] is a targeted breast cancer drug possessing 4-aminoquinoline as the core unit. Thus, 4-Aminoquinolines also appear as a significant assembly motif for developing new drug entities.

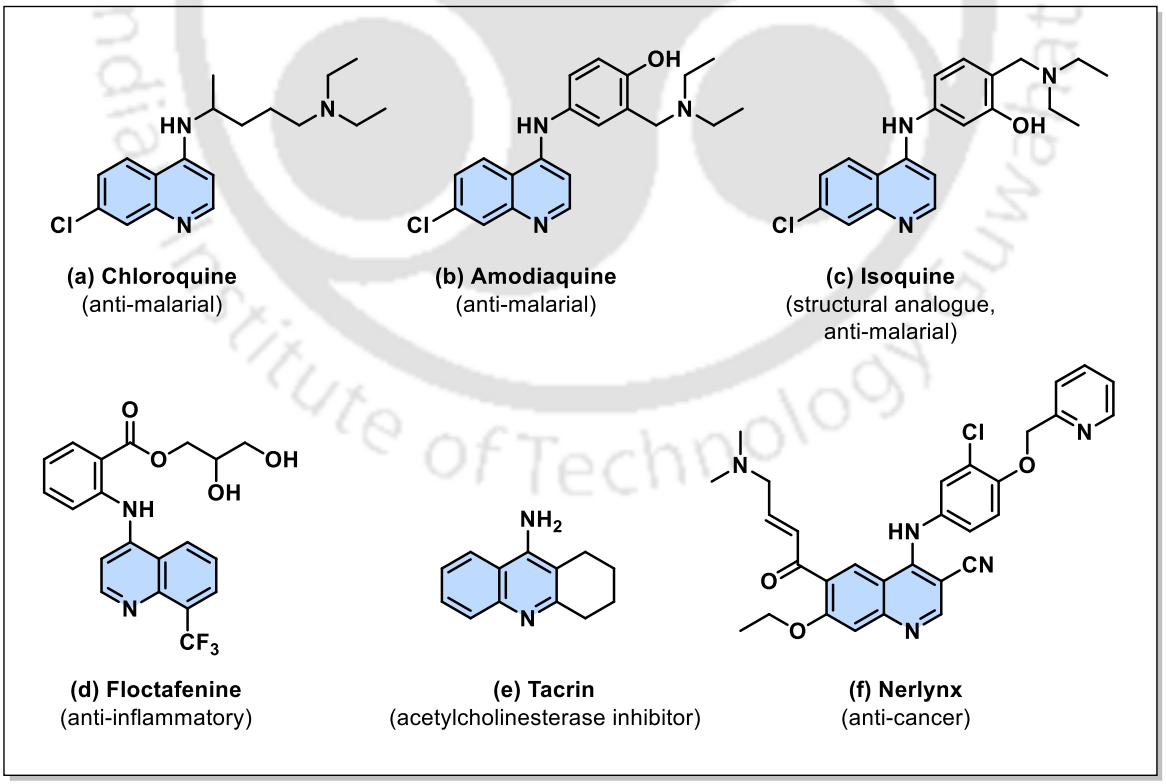
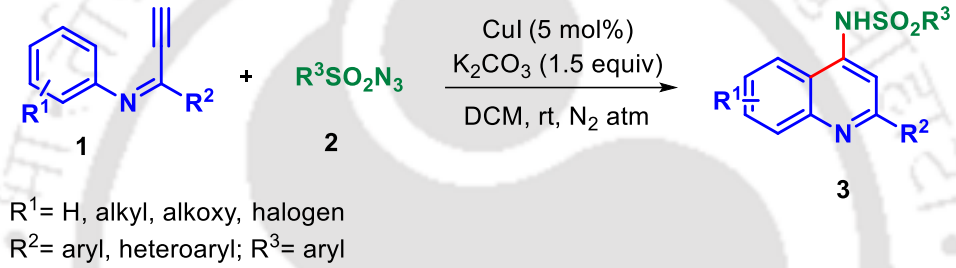


Figure 4.1.1. Some examples of pharmaceutical drugs with 4-aminoquinoline core.

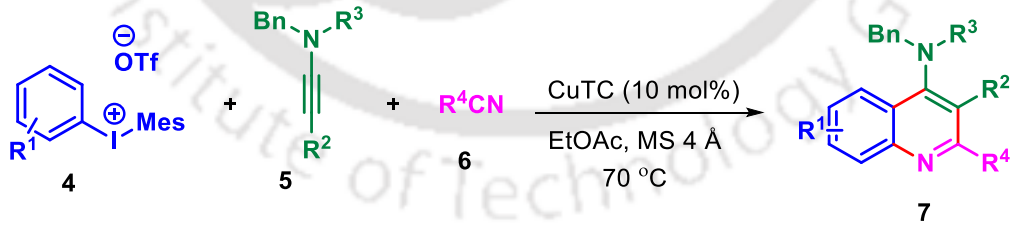
4.2. Literature Survey on Synthesis of Substituted 4-Aminoquinolines

4-Aminoquinolines can be directly accessed by selective displacement of the corresponding 4-halogen atom in the original heteroaryl halide backbone of 4-halo substituted quinolines. Traditional methods mainly involve S_NAr reactions by amines with conventional heating at elevated temperatures, microwave irradiation or catalysis by costly reagents.[9] Other approaches are transition metal catalyzed annulation of multicomponent systems, intramolecular cascade reactions as well as cycloadditions. In 2013, Cui and Cheng reported the synthesis of 4-sulfonamidoquinolines **3** using sulfonyl azides **2** with alkynyl imines **1**. This copper catalyzed cascade protocol involves 1,3-dipole cycloaddition, ketenimine formation, 6π-electrocyclization and [1,3]-H shift reaction to give products in moderate to good yields under mild reaction conditions (*Scheme 4.2.1.*).[10]



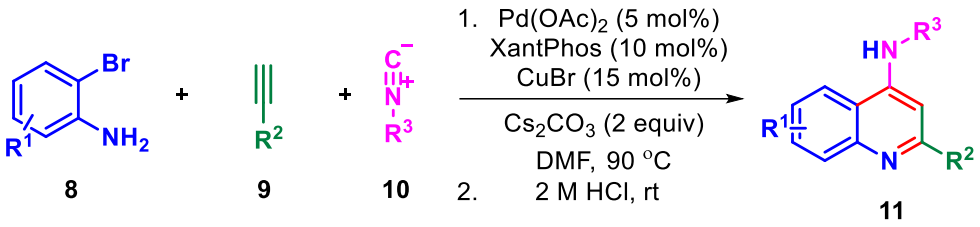
Scheme 4.2.1. *Copper catalyzed synthesis of 4-sulfonamidoquinolines.*

Park's group disclosed a modular synthesis of highly functionalized 4-aminoquinolines **7** using nitriles **6**, diaryliodonium salts **4** and ynamides **5**. This regiocontrolled [2+2+2] three-component tandem reaction is catalyzed by Cu catalyst giving the products in good to excellent yields (*Scheme 4.2.2.*).[11]



Scheme 4.2.2. *Regiocontrolled tandem synthesis of functionalized 4-aminoquinolines.*

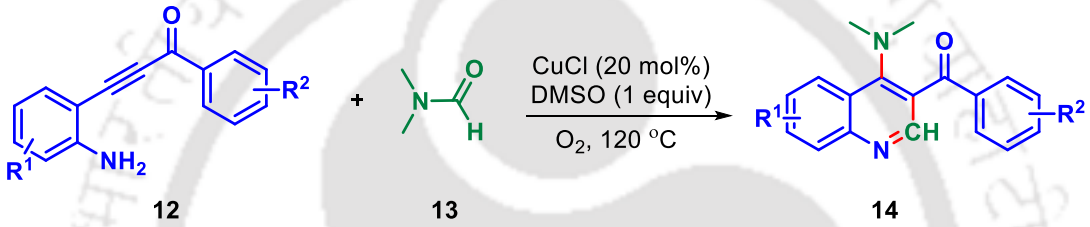
Ruijter and his group also developed a three component modular synthetic route for 2-substituted 4-aminoquinolines **11** from *o*-bromoanilines **8**, terminal alkynes **9** and isocyanides **10**. This Pd catalyzed one-pot protocol involves an imidoylative Sonogashira coupling, followed by acid mediated cyclization facilitating the products in good yields (*Scheme 4.2.3.*).[12]



R^1= H, Me, OMe, F, Cl, CO_2Et
R^2= R^3= aryl, alkyl

Scheme 4.2.3. *Pd catalyzed modular synthesis of 2-substituted 4-aminoquinolines.*

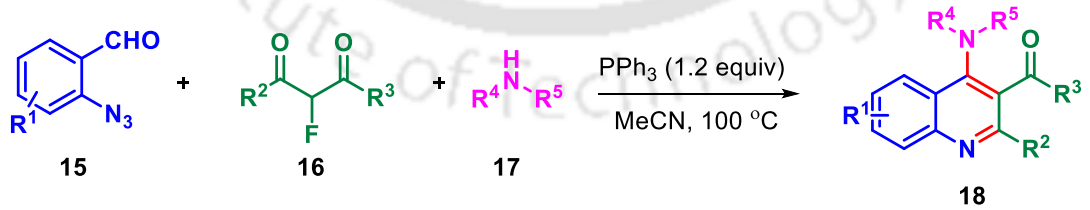
Lin and co-workers also demonstrated an efficient synthesis of 3-acyl-4-aminoquinolines **14** from β-(2-aminophenyl)-α,β-ynones **12**. This Cu(I)-catalyzed aerobic cyclization utilizes dimethylformamide **13** as a dual synthon to afford both methine source as C2 carbon and a nitrogen source to incorporate amino functionality in the 4th position (*Scheme 4.2.4.*).[13]



R^1= H, alkyl, halogen, CF_3, CO_2Et, NO_2, SMe, SPh
R^2= H, alkyl, halogen, CF_3

Scheme 4.2.4. *Cu catalyzed synthesis of 3-acyl-4-aminoquinolines.*

Zhang and his group also explored a one-pot synthetic route for synthesis of 2,3-disubstituted 4-aminoquinolines **18** using 2-azidobenzaldehydes **15**, *α*-fluoro-*β*-ketoesters **16** and amines **17**. This three component atom and step economic protocol involves cascade Mannich, aza-Wittig and dehydrofluorinative aromatization to give the products in moderate to good yields (*Scheme 4.2.5.*).[14]

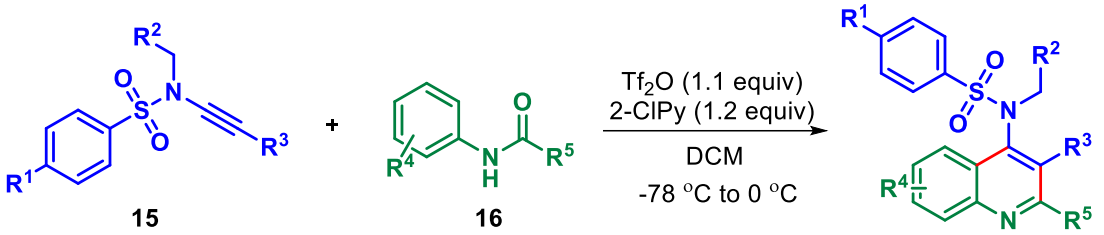


R^1= H, OMe, Cl, Br; R^2= aryl, alkyl; R^3= OEt, OPh
R^4=R^5= H, alkyl

Scheme 4.2.5. *PPh_3 mediated synthesis of 2,3-disubstituted 4-aminoquinolines.*

Bräse and co-workers synthesized a diverse set of highly substituted 4-aminoquinolines **17** from ynamides **15** and amides **16** using triflic anhydride and 2-chloropyridine as reagents.

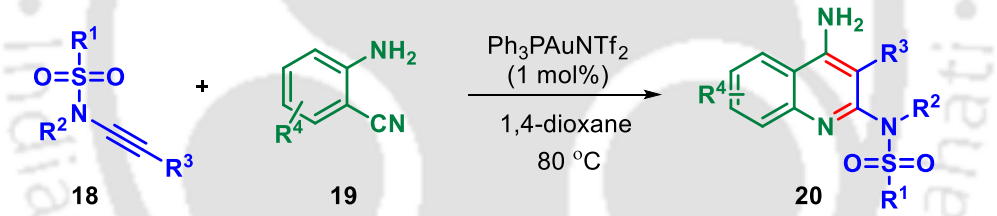
Electrophilically activated amides react readily with sulfonyl amides in this one-pot procedure to give highly functionalized 4-aminoquinolines in good yields (*Scheme 4.2.6.*).[15]



R^1= Me, CO_2H, CO_2Me; R^2=aryl; R^3= H, aryl, alkyl
R^4= H, Cl, alkyl, CF_3; R^5= alkyl

Scheme 4.2.6. *Tf_2O mediated synthesis of highly functionalized 4-aminoquinolines.*

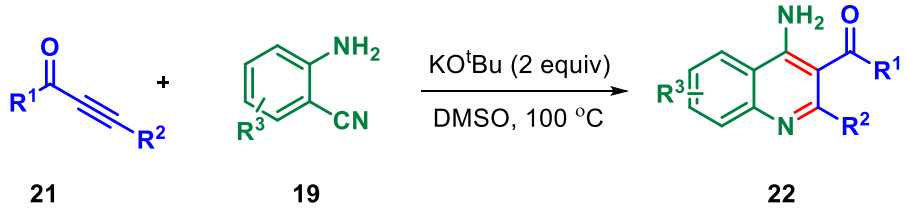
Similarly, several synthetic approaches for synthesis of 4-aminoquinolines from 2-aminobenzonitriles have also been reported.[16] In 2018, Sahoo's group demonstrated Au(I) catalyzed strategic route featuring direct coupling of ynamides **18** and 2-aminobenzonitriles **19** to access 2,4-diamino-substituted quinolones **20** *via* nitrile activation. This transformation is explicitly regioselective, showcasing broad scope and tolerates various functional groups (*Scheme 4.2.7.*).[17]



R^1= aryl, Bn, ^nBu; R^2= Me, Bn, cyclopropyl
R^3= aryl, alkyl; R^4= H, Cl, F, NO_2, Me

Scheme 4.2.7. *Au(I) catalyzed synthesis of 2,4-diamino-substituted quinolines.*

Other promising approaches include base promoted synthesis of 2-perfluoroalkylated 4-aminoquinolines from 2-aminobenzonitriles by reacting with perfluoroalk-2-ynoates or fluorinated alkynyl phosphonates.[18] Recently, Verma and his group also developed a base mediated one pot annulation of ynones **21** with 2-aminobenzonitriles **19** to give substituted 2,3-



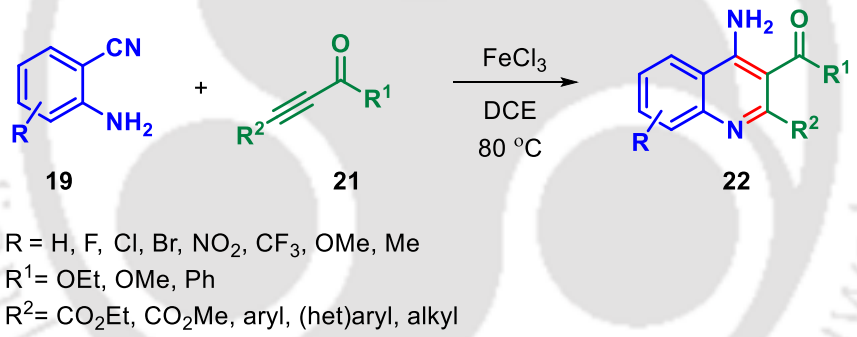
R^1= aryl ; R^2= aryl, alkyl; R^3= H, Cl, F, Br, Me, OMe

Scheme 4.2.8. *Base promoted synthesis of multisubstituted 4-aminoquinolines.*

disubstituted 4-aminoquinolines **22**. The reaction has high atom economy with broad substrate scope furnishing the products in good to excellent yields (*Scheme 4.2.8.*).[19]

4.3. Present Work

Since 4-aminoquinolines occur as core unit in various natural products and pharmaceuticals, development of strategies for their synthesis is a significant challenge for synthetic chemists. As evident from the literature reports, it was observed that although the existing methods are unique and elegant, the limitations include requirement of an expensive catalyst, additives, inert atmospheric reaction conditions and harsh reaction conditions. Thus, in this chapter we introduce a Lewis acid mediated convenient and simple protocol to access of 2,3-disubstituted 4-aminoquinolines from 2-aminobenzonitriles and activated alkynes as an alternative approach. Notably, the reaction follows an aza-Michael reaction followed by annulation to give the *N*-heterocycles. The salient features of this protocol include the use of a minimally toxic, eco-benign and less expensive iron(III) salt along with broad substrate scope and operational simplicity.



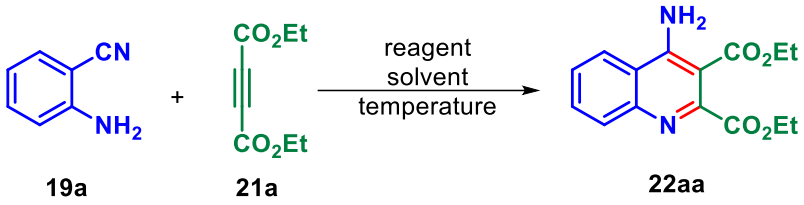
Scheme 4.3.1. *$FeCl_3$ promoted synthesis of substituted 4-aminoquinolines.*

4.4. Results and Discussion

4.4.1. Optimization of the Reaction

Initially, we commenced our optimization studies by treating diethyl but-2-ynedioate (**21a**) with 2-aminobenzonitrile (**19a**) in the presence of 0.2 equiv of $In(OTf)_3$ in DCE at room temperature (*Table 4.4.1.1.*, entry 1). However, no product was obtained even after continuing it up to 24 h. To our delight, the reaction occurred to deliver the product diethyl 4-aminoquinoline-2,3-dicarboxylate (**22aa**) in 24% yield when the temperature was raised to 60 °C (*Table 4.4.1.1.*, entry 2). Further elevation of temperature to 80 °C led to comparative increase of yield to 38% (*Table 4.4.1.1.*, entry 3). Encouraged by the results, the reaction was

Table 4.4.1.1.: *Optimization of the reaction*[a]



19a **21a** **22aa**

entry	reagent (equiv)	solvent	temp/°C	%yield[b]
1.	$In(OTf)_3$ (0.2)	DCE	25	-
2.	$In(OTf)_3$ (0.2)	DCE	60	24
3.	$In(OTf)_3$ (0.2)	DCE	80	38
4.	$In(OTf)_3$ (0.2)	toluene	110	40
5.	$In(OTf)_3$ (0.2)	THF	65	-
6.	$In(OTf)_3$ (0.2)	CH_3CN	80	-
7.	$In(OTf)_3$ (0.2)	DMF	100	-
8.	$Bi(OTf)_3$ (0.2)	DCE	80	17
9.	$Cu(OTf)_2$ (0.2)	DCE	80	20
10.	$Zn(OTf)_2$ (0.2)	DCE	80	15
11.	AgOTf (0.2)	DCE	80	35
12.	$AlCl_3$ (0.5)	DCE	80	-
13.	$FeCl_3$ (0.5)	DCE	80	58
14.	**$FeCl_3$ (1.2)**	**DCE**	**80**	**82**
15.	$FeCl_3$ (2.0)	DCE	80	80
16.	$BF_3{\cdot}OEt_2$ (1.2)	DCE	25	-
17.	TfOH (2.0)	DCE	25	-
18.	p-TsOH (2.0)	DCE	25	-

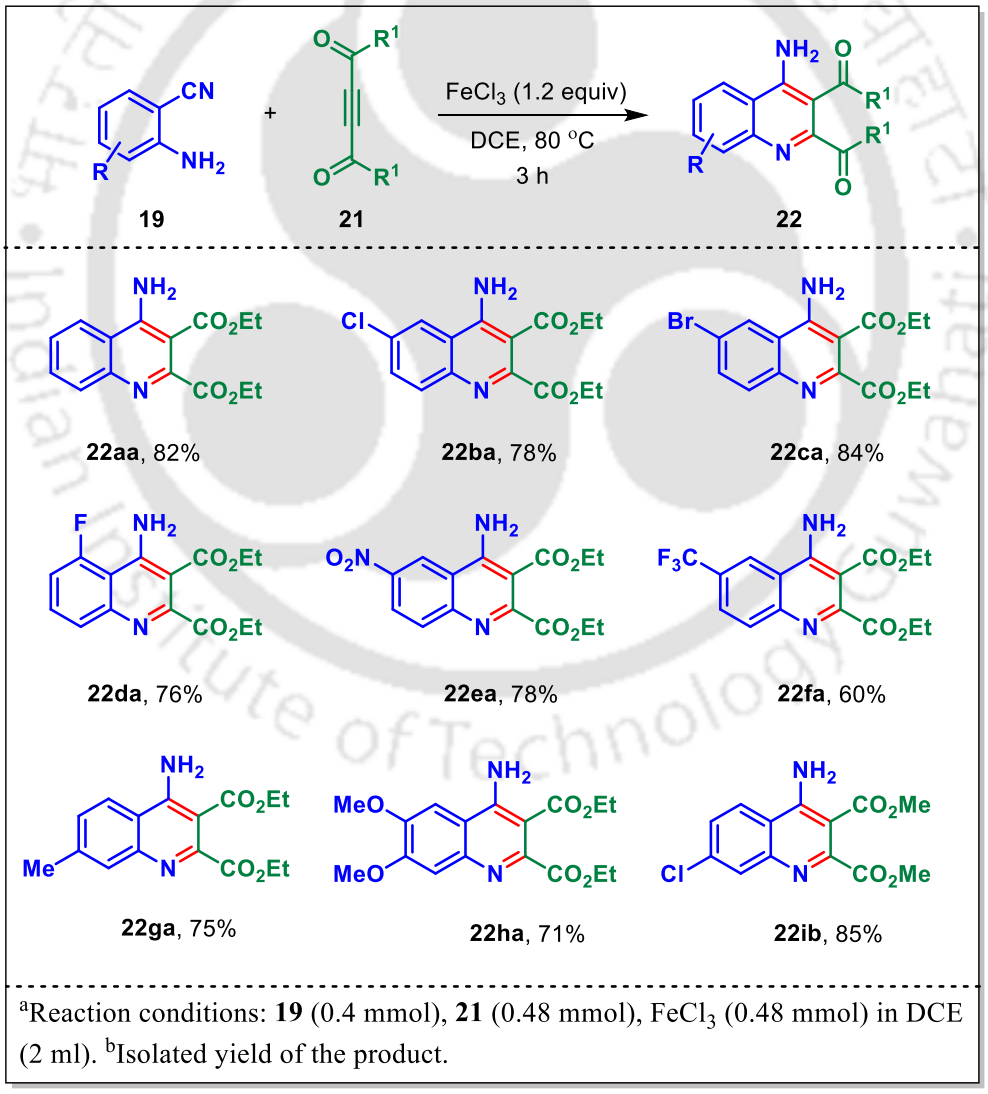
[a]All the reactions were carried out in (0.4 mmol) **19a**, (0.48 mmol) **21a** in 2.0 ml solvent, [b]Isolated yields.

performed in a series of non-polar as well as polar solvents like toluene, THF, acetonitrile and DMF. While toluene produced similar yield of 40% (*Table 4.4.1.1.*, entry 4), the reaction didn't proceed at all with moderately and highly polar solvents (*Table 4.4.1.1.*, entries 5-7). The reaction was then screened in a set of different Lewis and Brønsted acids. Metal triflates like AgOTf (*Table 4.4.1.1.*, entry 11) gave the desired product with 35% yield, whereas other metal triflates i.e. $Bi(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$ produced inferior yield (*Table 4.4.1.1.*, entries 8-10). Lewis acid, $AlCl_3$ also failed to give any product (*Table 4.4.1.1.*, entry 12). Gratifyingly,

when the reaction was performed with 0.5 equiv of $FeCl_3$ in DCE at 80 °C, the desired product was obtained with a better yield of 58% (*Table 4.4.1.1.*, entry 13). Increasing the reagent to a stoichiometric amount of 1.2 equiv furnished **22aa** with an optimum yield of 82% (*Table 4.4.1.1.*, entry 14). However, further increasing the reagent loading to 2.0 equiv did not lead to any significant improvement in the yield (*Table 4.4.1.1.*, entry 15). On the other hand, other non–metal Lewis acids like BF_3·OEt2 and Brønsted acids such as TfOH and *p*-TsOH in DCE at room temperature was also found to be ineffective (*Table 4.4.1.1.*, entries 16-18). Therefore, 1.2 equiv $FeCl_3$ in DCE at 80 °C are the optimum conditions for the reaction.

4.4.2. Substrate Scope

With the optimized reaction conditions in hand, we set out to explore the compatibility and scope of the reaction with different activated alkynes and 2-aminobenzonitrile substrates as



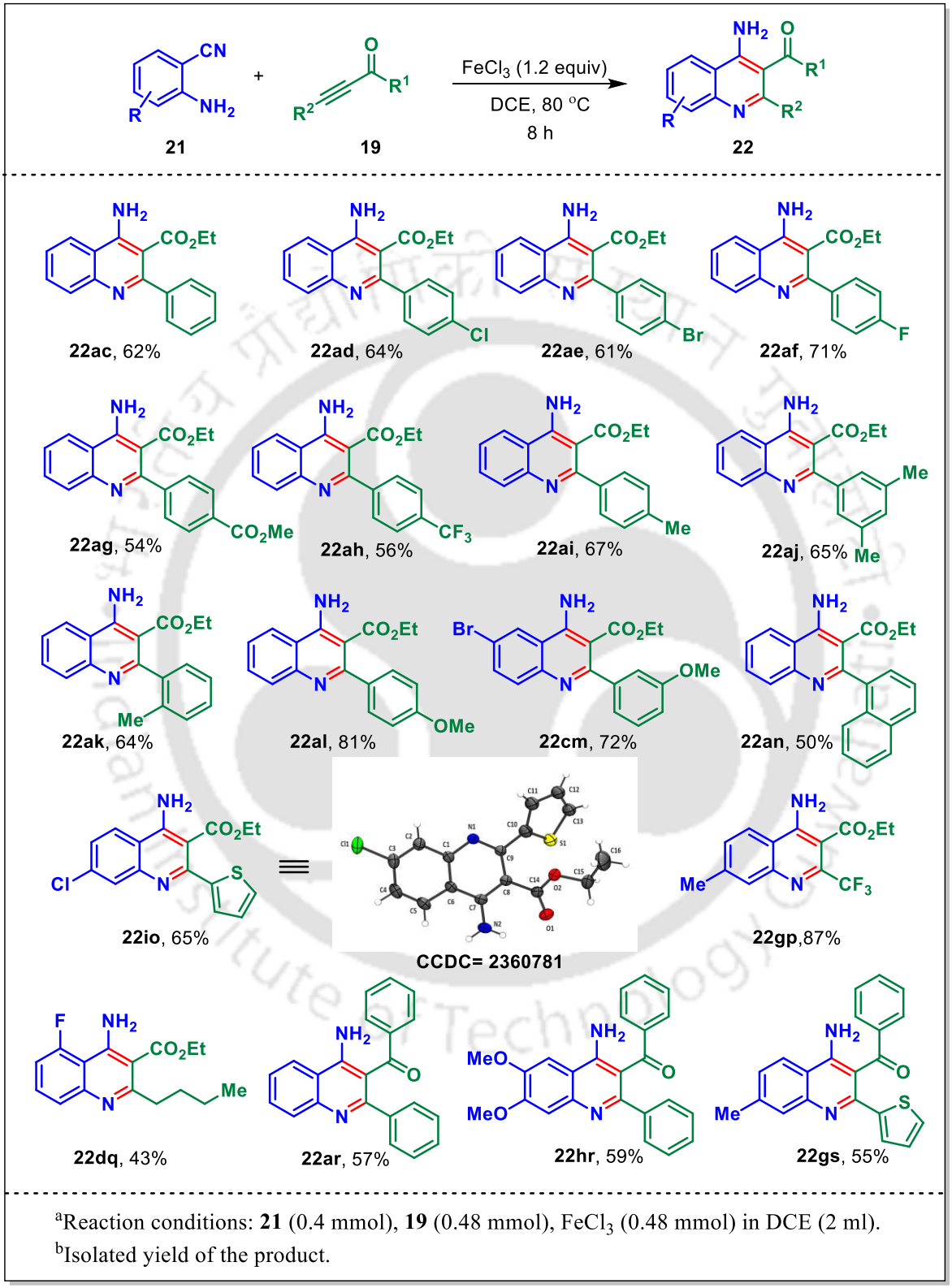
[a]Reaction conditions: **19** (0.4 mmol), **21** (0.48 mmol), $FeCl_3$ (0.48 mmol) in DCE (2 ml). [b]Isolated yield of the product.

Scheme 4.4.2.1. *Scope for the formation of substituted 4-aminoquinolines with different substituted 2-aminobenzonitriles.*[a,b]

depicted in *Scheme 4.4.2.1*. Initially, the influence of R substituents on the 2-aminobenzonitriles were investigated with the introduction of various electron donating as well as electron withdrawing groups. The reaction was not significantly affected by electronic effects, steric effects and position of the substituent groups on the benzene ring of 2-aminobenzonitriles. The reaction of substituted 2-aminobenzonitriles (**19b**-**19d**) having moderately electron-withdrawing halo substituents such as 5-Cl, 5-Br and 6-F with diethyl but-2-ynedioate furnished the corresponding products **22ba**, **22ca** and **22da** in good yields up to 84%. On the other hand, 2-aminobenzonitriles with strongly electron-withdrawing groups -CF_3 and -NO_2 at 5– position was well tolerated providing the desired products **22fa** and **22ea** with 60% and 78% yields, respectively. Different substituted 2-aminobenzonitriles (**19g** and **19h**) with electron-donating substituents such as 4-methyl and 4,5-dimethoxy group gave the corresponding products **22ga** and **22ha** with good yields. The reaction of 2-amino-4-chlorobenzonitrile with dimethyl but-2-ynedioate furnished the expected product **22ib** with an excellent yield of 85%.

Further, to demonstrate the substrate scope of this method, activated alkynes with aryl/alkyl and keto/ester groups were also employed in the reaction as depicted in *Scheme 4.4.2.2*. The reaction of ethyl 3-phenylpropiolate (**19c**) with **21a** under the optimized condition yielded the expected product ethyl 4-amino-2-phenylquinoline-3-carboxylate (**22ac)** with 62% yield. Decoration of the aryl group with various substituents led to the desired 2,3-disubstituted 4-aminoquinolines in moderate to good yields. A variety of ethyl 3-phenylpropiolates (**19b**-**19g**) with moderately electron-withdrawing halo groups as well as strongly electron-withdrawing CO_2Me and -CF_3 substituents at the *para*-position on phenyl ring underwent reaction with 2-aminobenzonitrile (**21a**), providing the corresponding products **22ad**-**22ah** in 54-71% yields. Likewise, installing electron-donating substituents, such as -Me and -OMe, at the *para*-, *meta*- and *ortho*-positions resulted in the expected products **22ai**-**22al** and **22cm** in 64-81% yields. The reaction was also tested with bulky polyaromatic substituted propiolate **19n**, which produced the corresponding product **22an**, in a low yield of 50%. Intriguingly, heteroaromatic, i.e. thiophen-2-yl-substituted propiolate, when treated with 2-amino-4-chlorobenzonitrile furnished the respective product **22io** in 65% isolated yield. Subsequently, the protocol also exhibited compatibility with 3-alkylpropiolates like ethyl 4,4,4-trifluorobut-2-ynoate (**19p**) and ethyl hep-2-ynoate (**19q**) resulting in the alkyl-substituted 4-aminoquinolines **22gp** and **22dq** with 87% and 43% yields, respectively. The low yield in the case of ethyl hept2-ynoate (**19q**) was attributed to deactivation of alkyne group. The reaction was also screened with ynones and

gave corresponding 4-aminoquinolines **22ar**, **22hr**, and **22gs** with moderate yields. It was evident that electron-withdrawing groups in the side chain of alkynes provided better yield

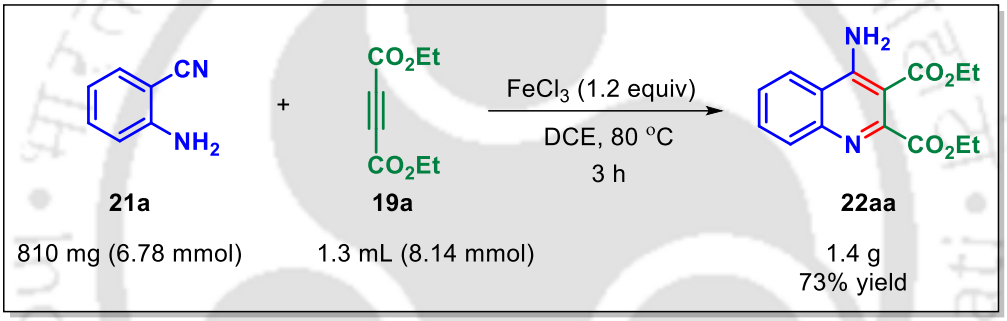


[a]Reaction conditions: **21** (0.4 mmol), **19** (0.48 mmol), $FeCl_3$ (0.48 mmol) in DCE (2 ml).
[b]Isolated yield of the product.

Scheme 4.4.2.2. *Scope for the formation of substituted 4-aminoquinolines with different activated alkynes.*[a,b]

(**22ab-22ib**, *Scheme 4.4.2.1.*), (**22gp**, *Scheme 4.4.2.2.*) compared to electron-donating groups (**22ac-22io**, **22dq**, *Scheme 4.4.2.2.*). This is attributed to the increase in electrophilicity of activated alkyne in case of electron-withdrawing groups in the side chain of the alkyne. The present Lewis acid protocol has advantages over the conventional basic conditions as base-mediated protocol is strictly limited to ynones,[19] whereas in Lewis acidic conditions both ynones **19r** and **19s** and propiolates can be carried out. The structure of the compounds was determined by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy, mass spectrometry and finally by X-ray crystallographic analysis of the compound **22io**.

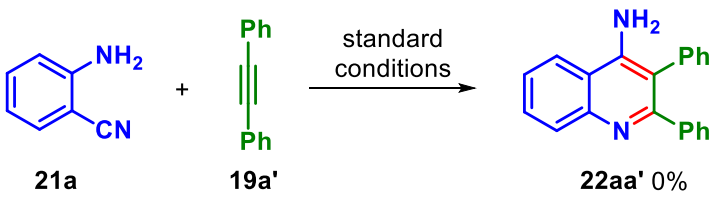
A scale up experiment was also performed using 2-aminobenzonitrile (**21a**) (800 mg, 6.78 mmol) and diethyl but-2-ynedioate (**19a**) (1.3 mL, 8.14 mmol) under the standard conditions to provide 73% (1.4 g) yield of the corresponding product **22aa** (*Scheme 4.4.2.3.*).



Scheme 4.4.2.3. *Gram-scale synthesis.*

4.4.3. Control Experiments

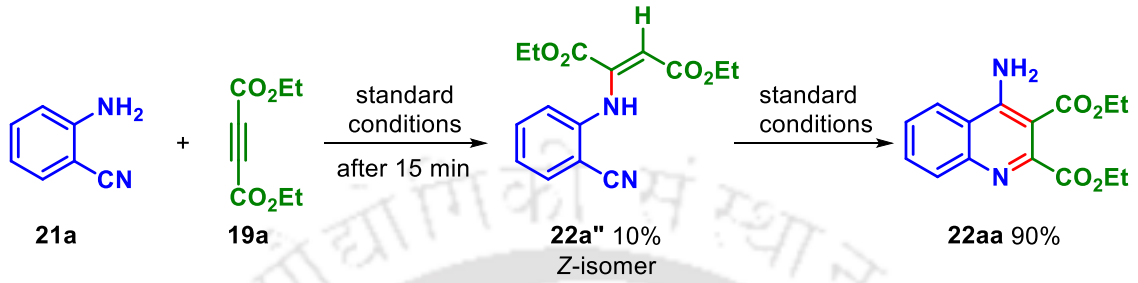
To gain insight of the reaction pathway, two control experiments were performed. The substrate **21a** when reacted with diphenylacetylene (**19a′**) under the standard conditions failed to give the desired product **22aa′** which indicates that the alkyne group is not activated by $FeCl_3$ to facilitate the hydroamination reaction followed by cyclization reaction (*Scheme 4.4.3.1.*).



Scheme 4.4.3.1. *Control experiment for reaction route.*

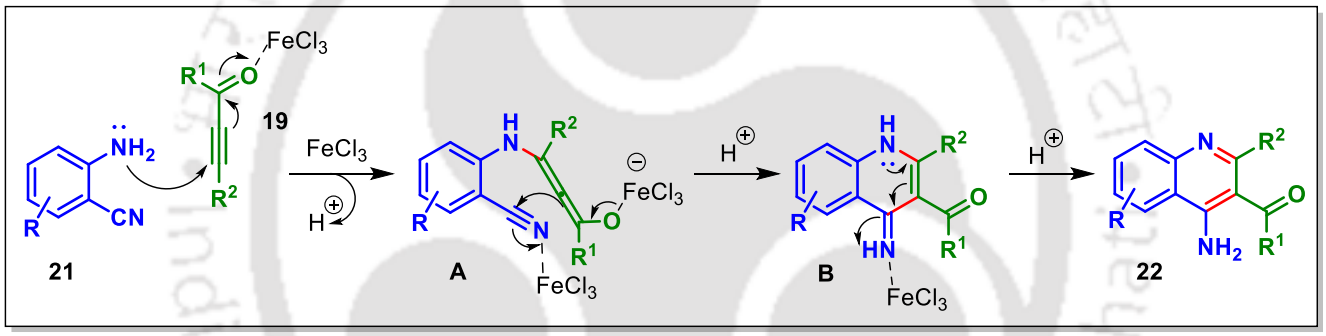
When the reaction of **21a** with **19a** under the standard reaction conditions was quenched after 15 minutes, the aza-Michael product **22a″** was isolated with 10% yield

as *Z*-isomer. The *Z*-configuration of **22a″** was determined from NOE experiment as there was no interaction between –NH and olefinic –CH protons. The intermediate **22a″** was subjected to standard reaction conditions and it was observed that it provided desired product **22aa** with 90% yield. This indicates that the reaction proceeds *via* aza-Michael reaction followed by annulation (*Scheme 4.4.3.2*.).



Scheme 4.4.3.2. *Control experiment for intermediate **22a″**.*

4.4.4. Plausible Mechanism



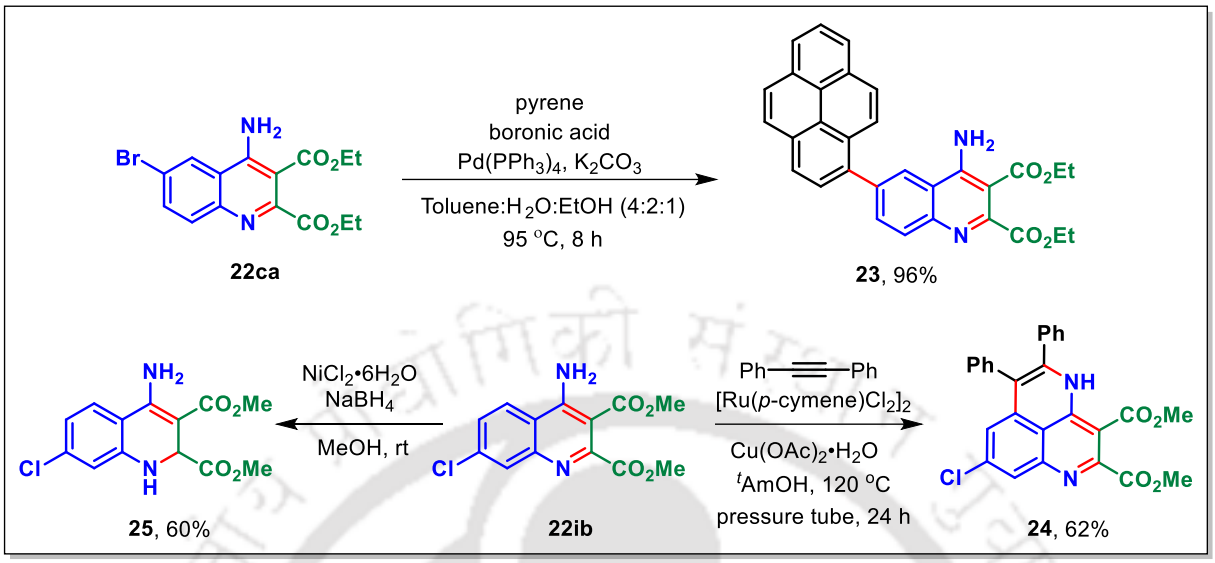
Scheme 4.4.4.1. *Plausible reaction mechanism.*

Based on the previous reports[19] and control experiments, a plausible mechanism is postulated as shown in *Scheme 4.4.4.1.* Lewis acid activates the carbonyl group of the alkyne **19** for aza-Michael reaction with 2-aminobenzonitrile to form enolic allene intermediate **A**. The intermediate **A** after nucleophilic attack to activated nitrile forms unstable quinoline-4(1*H*)-imines **B** which after aromatization forms stable product **22**.

4.5. Post-synthetic Applications

The synthetic utility of the products is demonstrated by performing a few synthetic transformations as depicted in *Scheme 4.5.1.* For instance, functionalization in the backbone of product **22ca** with pyrene moiety was accomplished by using palladium catalysis (Suzuki Cross coupling reaction), delivering **23** in 96% yield. The product **22ib** was transformed into annulated product **24** in the presence of a Ru(II) catalyst *via* selective C–H, N annulation at the phenyl ring with diphenylacetylene derivatives. Additionally, selective reduction of the C–N

bond of the pyridine ring of **22ib** was also achieved using the $NiCl_2$–$NaBH_4$ combination to give **25** with 60% yield.



Scheme 4.5.1. *Post synthetic modifications.*

4.6. Conclusion

In conclusion, we have developed an efficient Lewis acid promoted annulation of alkynyl esters or ynones with 2-aminobenzonitrile for the synthesis of multi-substituted 4-aminoquinolines in good to excellent yields. The reaction proceeds *via* aza-Michael addition and intramolecular annulation reaction. The present strategy is inexpensive, and highly atom-economical with broad substrate scope. Additionally, 4*H*-benzo[*de*][1,6]naphthyridine was obtained as a post synthetic modification of 4-aminoquinoline. Similarly, 1,2-dihydroquinolin-4-amine was also synthesized from 4-aminoquinoline by selective reduction with $NiCl_2$–$NaBH_4$.

4.7. Experimental Section

4.7.1. General Information and Instrumentation

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^1H\}$ (150 MHz and 125 MHz) NMR. $^{19}F\{^1H\}$ NMR spectra were recorded at 470 MHz

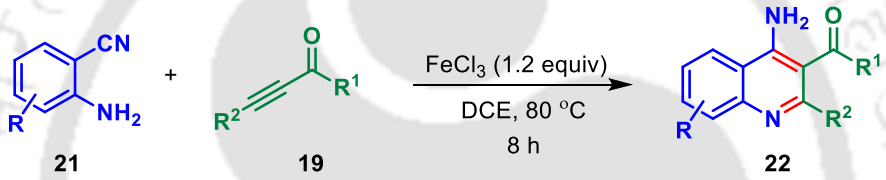
and chemical shifts are relative to hexafluorobenzene in $CDCl_3$ at δ = -164.9 ppm (external reference). Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, dd = doublet of doublets, m = multiplet, bs = broad singlet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF and microTOF-Q II mass spectrometer.

4.7.2. Reaction Procedure

4.7.2.1. Experimental Procedure for Synthesis of Activated Alkynes

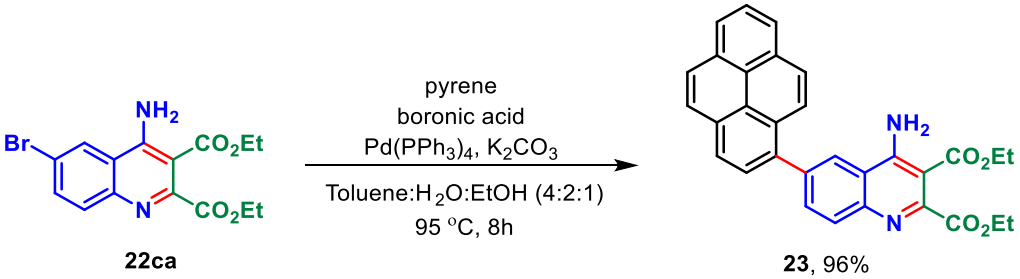
Propiolate derivatives **19c-19o, 19q** were synthesized according to literature reports[20] and confirmed by comparison to the reported characterization data. Ynones **19r** and **19s** were also prepared using the standard reported procedure.[19]

4.7.2.2. General Procedure for the Synthesis of Compounds 22aa-22ha, 22ib, 22ac-22al, 22an, 22ar, 22cm, 22io, 22gp, 22dq, 22hr and 22gs



To a solution of 2-aminobenzonitrile derivatives **21** (0.4 mmol, 1 equiv) and activated alkyne **19** (0.48 mmol, 1.2 equiv) in 1,2-dichloroethane (2 mL) was added $FeCl_3$ (0.48 mmol, 1.2 equiv). The reaction was then heated in an oil bath at 80 °C. The progress of the reaction was monitored by TLC analysis technique. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel (n-hexane/EtOAc eluent) to give the corresponding product **22**.

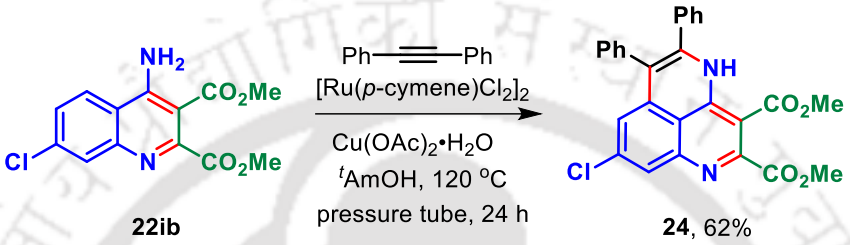
4.7.2.3. Experimental Procedure for the Synthesis of Compound 23



To an oven-dried Schlenk Tube containing a magnetic bar, **22ca** (50 mg, 0.14 mmol, 1 equiv), pyrene-1-boronic acid (52 mg, 0.21 mmol, 1.5 equiv), anhydrous K_2CO_3 (93 mg, 2.7 mmol,

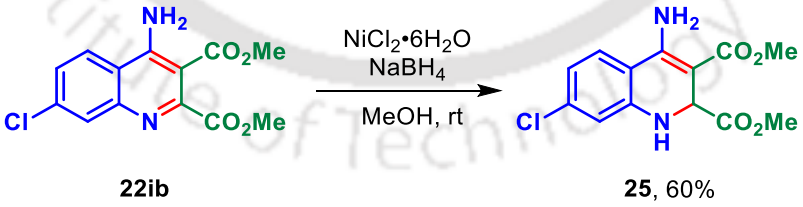
5.0 equiv), $Pd(PPh_3)_4$ (8 mg, 0.007 mmol, 5 mol%), H_2O (1.0 mL), EtOH (0.5 mL) and toluene (2.0 mL) were added. The reaction vessel was charged with nitrogen and sealed. The mixture was heated to 95 °C using an oil bath and stirred for 8 h. The mixture was filtered over a small pad of Celite and diluted with CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic layer was washed with brine solution, dried over anhydrous Mg_2SO_4, concentrated, and then residue was purified by column chromatography on silica gel using ethyl acetate/ hexane as the eluent to afford the desired product **23**.

4.7.2.4. Experimental Procedure for the Synthesis of Compound 24



To an oven-dried pressure tube containing a magnetic bar was added **22ib** (50 mg, 0.17 mmol, 1 equiv), diphenylacetylene (68 mg, 0.38 mmol, 2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mg, 0.009 mmol, 5 mol%), $Cu(OAc)_2.H_2O$ (3 mg, 0.017 mmol, 10 mol%), and ^{t}AmOH (2 mL). The reactions mixture was stirred in an oil bath preheated at 120 °C for 24 h. After completion of the reaction (monitored by TLC analysis), the reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with ethyl acetate (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (n-hexane/EtOAc eluent) to give the desired product **24**.

4.7.2.5. Experimental Procedure for the Synthesis of Compound 25



In an oven dried round bottomed flask, **22ib** (50 mg, 0.17 mmol, 1 eqiuv) was taken with $NiCl_2{\cdot}6H_2O$ (81 mg, 0.34 mmol, 2 equiv) in methanol and stirred at room temperature for 5 minutes. To this reaction mixture $NaBH_4$ (25 mg, 0.68 mmol, 4 equiv) was added in portions at 0 °C and allowed to stir at room temperature for 8 h. After completion of the reaction as confirmed by TLC, the solvent was removed under vacuum. The organic phase was extracted with ethyl acetate and washed with brine solution. The organic layer was dried over anhydrous

Na_2SO_4, concentrated, and then residues were purified by column chromatography with ethyl acetate/hexane eluents to afford the desired product **25**.

4.7.2.6. Experimental Procedure for the Gram-Scale Synthesis of 22aa

To a solution of 2-aminobenzonitrile (**21a**) (810 mg, 6.78 mmol, 1 equiv) and diethyl but-2-ynedioate (**19a**) (1.3 mL, 8.14 mmol, 1.2 equiv) in 1,2-dichloroethane (10 mL) was added $FeCl_3$ (1.3 g, 8.14 mmol, 1.2 equiv). The reaction was then heated in an oil bath at 80 ^oC. The progress of the reaction was monitored by TLC analysis technique. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 30 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel using hexane and ethyl acetate (3:2) as eluents to obtain the desired product **22aa** in 73% yield (1.4 g, green gum).

4.7.3. Crystallographic Description

Single crystals of compound **26io** was obtained by slow evaporation of ethyl acetate and hexane solution (1:9). Bruker APEX-II CCD diffractometer was used to collect the intensity data. The instrument is equipped with a fine focus 1.75 kW sealed tube Mo Kα radiation (λ = 0.71073 Å) at 297 K. The data acquisition was done with the APEX4 software. APEX4 software was implemented for data integration and reduction. Multi-scan empirical absorption corrections were employed to the data using the program APEX4. Structures were solved by direct methods using SHELXL-2019 and refined with full-matrix least-squares on F2 using SHELXL-2019/1.[a] Structural illustrations have been drawn with ORTEP-3 for Windows.[b] The detailed data collection and structure refinement are summarized in *Table 4.7.3.1*.

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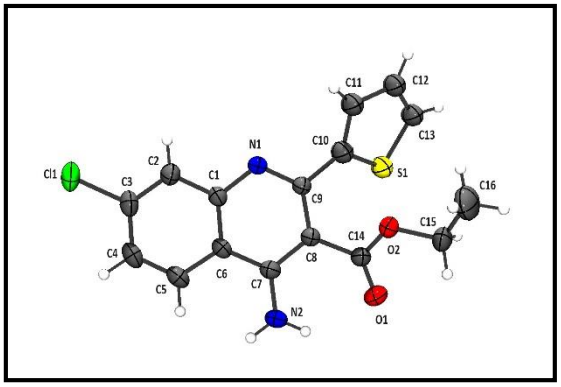
b. L. J. Farrugia, XRDIFF: simulation of X-ray diffraction patterns, *J. Appl. Crystallogr*. **1997**, *30*, 565.



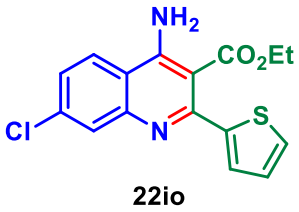


Figure 4.7.3.1. *ORTEP diagram of compound (**22io**) with 50% probability.*

Table 4.7.3.1. Crystal parameters of compound **22io**

	CCDC 2360781
Formula	$C_{16}H_{15}ClN_2O_3S$
Formula weight	350.81
T/K	302
Crystal system	Triclinic
Space group	P -1
a/Å	8.4115 (4)
b/Å	9.1740 (4)
c/Å	12.4619 (6)
α/°	111.1010 (10)
β/°	94.2160 (10)
γ/°	111.6360 (10)
V/Å^3	810.03 (7)
Z	2
Abs. Coeff./mm^{-1}	0.380
Abs. Correction	multi-scan
GOF on F^2	1.099
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0829
	wR2 = 0.1931
R indices [all data]	*R1* = 0.0898
	wR2 = 0.1985

4.8. References:

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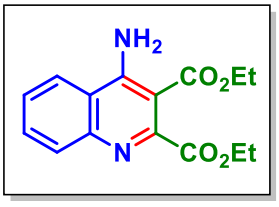
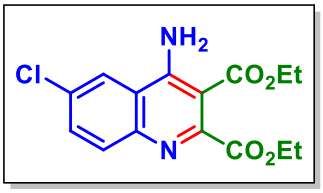
4.9. Characterisation Data

Diethyl 4-aminoquinoline-2,3-dicarboxylate (22aa):



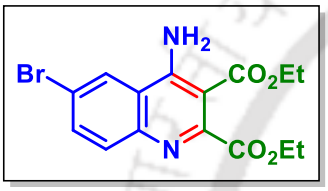
Light green oil; R_f (hexane/EtOAc, 4:1) 0.40; yield 94 mg, 82%. IR (KBr, neat) ν 3450, 3332, 2982, 1734, 1613, 1557, 1247, 1095, 1029, 766, 556 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.64 (t, *J* = 7.7 Hz, 1 H), 7.46 (bs, 2 H), 7.42–7.40 (m, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 1.39–1.33 (m, 6 H).$^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 168.3, 167.2, 154.5, 153.7, 147.4, 132.0, 130.1, 126.6, 121.1, 118.0, 98.4, 62.1, 61.4, 14.2, 14.2. HRMS (ESI) calcd. for $C_{15}H_{17}N_2O_4$ $(M + H)^+$ 289.1183, found 289.1187.

Diethyl 4-amino-6-chloroquinoline-2,3-dicarboxylate (22ba):



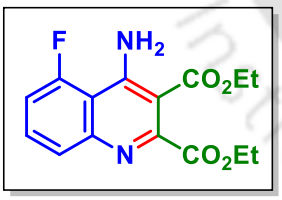
White solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 96-98 °C; yield 100 mg, 78%. IR (KBr, neat) ν 3450, 3319, 2984, 1716, 1621, 1549, 1249, 1107, 1027, 831, 593 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2 H), 7.54 (dd, *J* = 8.9 and 2.2 Hz, 1 H), 7.44 (bs, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 1.38 (t, *J* = 7.2 Hz, 3 H), 1.33 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.1, 166.9, 153.8, 153.7, 145.8, 132.6, 132.4, 131.6, 120.8, 118.9, 99.0, 62.2, 61.6, 14.2, 14.2. HRMS (ESI) calcd. for $C_{15}H_{16}ClN_2O_4$ $(M + H)^+$ 323.0793, found 323.0786.

Diethyl 4-amino-6-bromoquinoline-2,3-dicarboxylate (22ca):



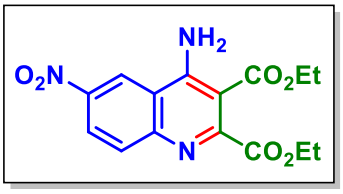
White solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 100-102 °C; yield 123 mg, 84%. IR (KBr, neat) ν 3450, 3326, 2980, 1719, 1621, 1545, 1257, 1101, 1029, 833, 591 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.74 (d, *J* = 8.9 Hz, 1 H), 7.66 (d, *J* = 8.8 Hz, 1 H), 7.46 (bs, 2 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 1.37 (t, *J* = 7.2 Hz, 3 H), 1.32 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.1, 166.9, 153.9, 153.6, 146.1, 135.2, 131.7, 124.1, 120.4, 119.4, 99.0, 62.2, 61.6, 14.2, 14.2. HRMS (ESI) calcd. for $C_{15}H_{16}BrN_2O_4$ $(M + H)^+$ 367.0288, found 367.0292.

Diethyl 4-amino-5-fluoroquinoline-2,3-dicarboxylate (22da):



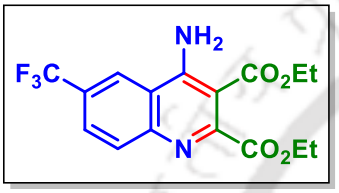
Colorless gum; R_f (hexane/EtOAc, 4:1) 0.30; yield 93 mg, 76%. IR (KBr, neat) ν 3520, 3305, 2991, 1742, 1687, 1603, 1557, 1250, 1045, 827, 537 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.65 (m, 1 H), 7.52–7.48 (m, 1 H), 7.02–6.98 (m, 1 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H), 1.30 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.6, 166.8, 160.3 (d, *J* = 251.0 Hz), 154.6, 154.5 (d, *J* = 2.9 Hz), 149.4, 131.6 (d, *J* = 11.5 Hz), 126.2 (d, *J* = 3.6 Hz), 111.6 (d, *J* = 23.9 Hz), 108.5 (d, *J* = 6.6 Hz), 98.4 (d, *J* = 1.8 Hz), 61.9, 61.4, 14.1, 14.0. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -116.96 (s, -F). HRMS (ESI) calcd. for $C_{15}H_{16}FN_2O_4$ $(M + H)^+$ 307.1089, found 307.1110.

Diethyl 4-amino-6-nitroquinoline-2,3-dicarboxylate (22ea):



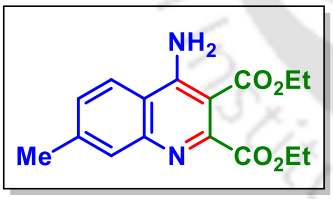
Yellow solid; R_f (hexane/EtOAc, 4:1) 0.40; mp 175-177 °C; yield 104 mg, 78%. IR (KBr, neat) ν 3445, 3336, 2985, 1732, 1622, 1521, 1335, 1251, 1091, 1030, 847, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.4 Hz, 1 H), 8.39 (dd, *J* = 9.2 and 2.3 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1 H), 7.85 (bs, 2H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 1.42–1.35 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.5, 166.6, 156.6, 155.6, 150.4, 145.1, 131.6, 125.5, 119.0, 117.4, 99.6, 62.5, 62.1, 14.2, 14.2. HRMS (ESI) calcd. for $C_{15}H_{16}N_3O_6$ $(M + H)^+$ 334.1034, found 334.1039.

Diethyl 4-amino-6-(trifluoromethyl)quinoline-2,3-dicarboxylate (22fa):



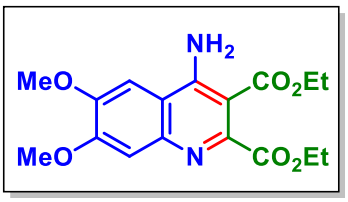
White gum; R_f (hexane/EtOAc, 5:1) 0.40; yield 85 mg, 60%. IR (KBr, neat) ν 3463, 3334, 2988, 1724, 1613, 1521, 1319, 1246, 1161, 1091, 838, 515 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 8.22 (s, 1 H), 8.00 (d, *J* = 8.7 Hz, 1 H), 7.81 (dd, *J* = 8.8 and 1.9 Hz, 1 H), 7.70 (bs, 2 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 1.39 (t, *J* = 7.2 Hz, 3 H), 1.35 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 167.9, 166.9, 155.5, 155.0, 148.9, 131.1, 128.2 (q, *J* = 32.7 Hz), 127.8 (q, *J* = 3.2 Hz), 123.9 (q, *J* = 270.8 Hz), 119.6 (d, *J* = 4.4 Hz), 117.4, 99.3, 62.4, 61.8, 14.2, 14.1. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -65.37 (s, -F). HRMS (ESI) calcd. for $C_{16}H_{16}F_3N_2O_4$ $(M + H)^+$ 357.1057, found 357.1061.

Diethyl 4-amino-7-methylquinoline-2,3-dicarboxylate (22ga):



Light brown gum; R_f (hexane/EtOAc, 5:1) 0.40; yield 91 mg, 75%. IR (KBr, neat) ν 3458, 3333, 2983, 1735, 1619, 1564, 1251, 1099, 1034, 795, 551 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 2 H), 7.41 (bs, 2 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 4.39 (q, *J* = 7.2 Hz, 2 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 2.41 (s, 3 H), 1.39–1.31 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.3, 167.1, 154.5, 153.6, 147.3, 142.5, 128.9, 128.3, 121.2, 115.7, 97.7, 61.9, 61.2, 21.6, 14.1. HRMS (ESI) calcd. for $C_{16}H_{19}N_2O_4$ $(M + H)^+$ 303.1339, found 303.1337.

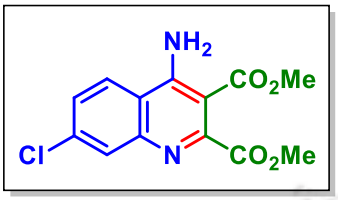
Diethyl 4-amino-6,7-dimethoxyquinoline-2,3-dicarboxylate (22ha):



Red solid; R_f (hexane/EtOAc, 1:1) 0.40; mp 118-120 °C; yield 99 mg, 71%. IR (KBr, neat) ν 3450, 3340, 2981, 1731, 1621, 1505, 1234, 1112, 1030, 857, 519 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 1 H), 7.13 (bs, 2 H), 6.98 (s, 1 H), 4.43 (q, *J* =

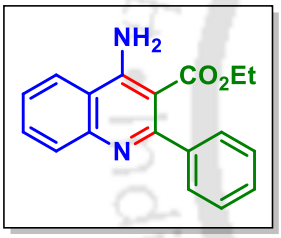
7.2 Hz, 2 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.96 (s, 3 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.5, 167.2, 153.8, 153.2, 151.9, 149.5, 144.0, 112.0, 108.8, 100.3, 98.0, 62.0, 61.3, 56.3, 56.2, 14.18, 14.15. HRMS (ESI) calcd. for $C_{17}H_{21}N_2O_6$ $(M + H)^+$ 349.1394, found 349.1390.

Dimethyl 4-amino-7-chloroquinoline-2,3-dicarboxylate (22ib):



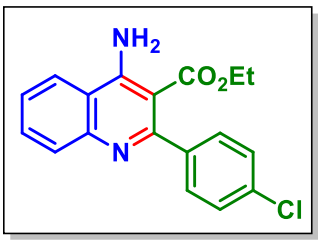
Off white solid; R_f (hexane/EtOAc, 3:1) 0.40; mp 193-195 °C; yield 100 mg, 85%. IR (KBr, neat) ν 3373, 3152, 2941, 1749, 1685, 1603, 1432, 1232, 1105, 911, 794, 557 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.77-7.75 (m, 1 H), 7.49-7.47 (m, 1 H), 7.29 (bs, 2 H), 4.01 (s, 3 H), 3.91 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 168.3, 167.4, 154.6, 154.1, 148.3, 138.4, 129.6, 127.6, 122.4, 116.4, 99.0, 53.1, 52.6. HRMS (ESI) calcd. for $C_{13}H_{12}ClN_2O_4$ $(M + H)^+$ 295.0480, found 295.0479.

Ethyl 4-amino-2-phenylquinoline-3-carboxylate (22ac):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 167-169 °C; yield 72 mg, 62%. IR (KBr, neat) ν 3407, 3166, 2970, 1679, 1618, 1544, 1240, 1167, 1078, 767, 573 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 1 H), 7.82 (d, *J* = 8.3 Hz, 1 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 6.4 Hz, 2 H), 7.47 (t, *J* = 7.7 Hz, 1 H), 7.42–7.37 (m, 3 H), 6.75 (bs, 2 H), 3.95 (q, *J* = 7.1 Hz, 2 H), 0.74 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 169.8, 160.7, 153.0, 147.8, 143.5, 131.5, 130.3, 128.3, 128.2, 128.1, 125.7, 120.8, 117.2, 103.2, 60.8, 13.3. HRMS (ESI) calcd. for $C_{18}H_{17}N_2O_2$ $(M + H)^+$ 293.1285, found 293.1282.

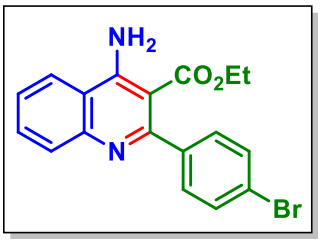
Ethyl 4-amino-2-(4-chlorophenyl)quinoline-3-carboxylate (22ad):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 184-186 °C; yield 83 mg, 64%. IR (KBr, neat) ν 3407, 3164, 2980, 1680, 1614, 1544, 1237, 1089, 1016, 769, 598 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.47 (d, *J* = 8.2 Hz, 2 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 2 H), 6.85 (bs, 2 H), 3.98 (q, *J* = 7.1 Hz, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) δ 169.5, 159.6, 153.2, 147.7, 142.2, 134.0, 131.6, 130.2,

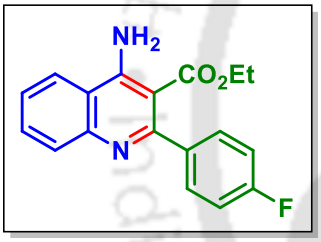
129.6, 128.2, 125.8, 120.8, 117.2, 102.6, 60.9, 13.4. HRMS (ESI) calcd. for $C_{18}H_{16}ClN_2O_2$ (M + H)$^+$ 327.0895, found 327.0898.

Ethyl 4-amino-2-(4-bromophenyl)quinoline-3-carboxylate (22ae):



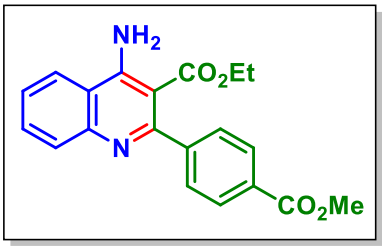
Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 153-155 °C; yield 91 mg, 61%. IR (KBr, neat) ν 3406, 3164, 2980, 1678, 1616, 1542, 1236, 1068, 1011, 768, 585 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 8.1 Hz, 2 H), 6.85 (bs, 2 H), 3.98 (q, *J* = 7.2 Hz, 2 H), 0.82 (t, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.4, 159.6, 153.3, 147.7, 142.6, 131.7, 131.2, 130.2, 130.0, 125.8, 122.2, 120.8, 117.2, 102.6, 60.9, 13.4. HRMS (ESI) calcd. for $C_{18}H_{16}BrN_2O_2$ (M + H)$^+$ 371.0390, found 371.0338.

Ethyl 4-amino-2-(4-fluorophenyl)quinoline-3-carboxylate (22af):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 215-217 °C; yield 88 mg, 71%. IR (KBr, neat) ν 3405, 3166, 2982, 1679, 1618, 1546, 1219, 1155, 1080, 768, 557 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 7.72–7.69 (m, 1 H), 7.53–7.50 (m, 2 H), 7.48–7.44 (m, 1 H), 7.10 (t, *J* = 8.7 Hz, 2 H), 6.79 (bs, 2 H), 3.98 (q, *J* = 7.1 Hz, 2 H), 0.82 (t, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.6, 163.0 (d, *J* = 245.3 Hz), 159.6, 153.1, 147.7, 139.7 (d, *J* = 3.2 Hz), 131.6, 130.2, 130.1 (d, *J* = 8.11 Hz), 125.7, 120.8, 117.2, 115.1 (d, *J* = 21.4 Hz), 102.9, 60.9, 13.5. ^{19}F NMR (470 MHz, C_6F_6/$CDCl_3$) δ -117.65 (s, -F). HRMS (ESI) calcd. for $C_{18}H_{16}FN_2O_2$ (M + H)$^+$ 311.1190, found 311.1189.

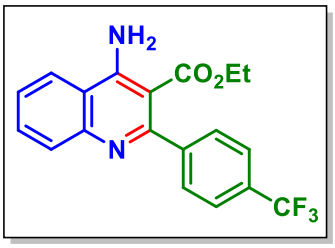
Ethyl 4-amino-2-(4-(methoxycarbonyl)phenyl)quinoline-3-carboxylate (22ag):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 206-208 °C; yield 76 mg, 54%. IR (KBr, neat) ν 3405, 3169, 2953, 1719, 1681, 1615, 1544, 1271, 1174, 1099, 771, 566 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.9 Hz, 2 H), 8.01 (d, *J* = 8.5 Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.72 (t, *J* = 7.7 Hz, 1 H), 7.60 (d, *J* = 7.9 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 6.89 (bs, 2 H), 3.97–3.92 (m, 5 H), 0.72 (t, *J* = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.3, 167.3, 159.9, 153.4, 148.4, 147.8,

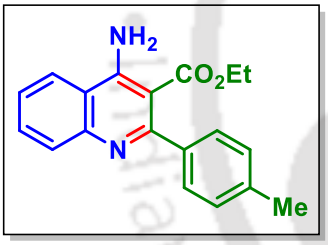
131.7, 130.4, 129.5, 129.4, 128.4, 126.0, 120.8, 117.3, 102.6, 60.9, 52.4, 13.4. HRMS (ESI) calcd. for $C_{20}H_{19}N_2O_4$ $(M + H)^+$ 351.1339, found 351.1348.

Ethyl 4-amino-2-(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (22ah):



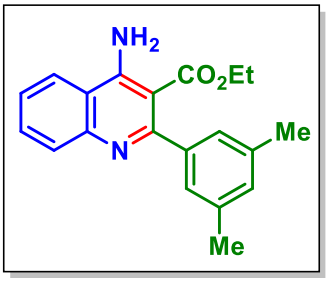
Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 193-195 °C; yield 80 mg, 56%. IR (KBr, neat) ν 3403, 3162, 2993, 1682, 1620, 1548, 1321, 1244, 1118, 1064, 772, 579 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.5 Hz, 1 H), 7.74 (t, *J* = 7.7 Hz, 1 H), 7.66 (dd, *J* = 23.4 and 8.1 Hz, 4 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 6.92 (bs, 2 H), 3.96 (q, *J* = 7.2 Hz, 2 H), 0.73 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.2, 159.6, 153.5, 147.8, 147.6, 131.8, 130.0 (q, *J* = 32.1 Hz), 128.6, 126.1, 125.1 (q, *J* = 3.8 Hz), 124.8 (q, *J* = 270.4 Hz), 120.8, 117.3, 102.43 60.9, 13.2. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -65.58 (s, -F). HRMS (ESI) calcd. for $C_{19}H_{16}F_3N_2O_2$ $(M + H)^+$ 361.1158, found 361.1110.

Ethyl 4-amino-2-(*p*-tolyl)quinoline-3-carboxylate (22ai):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 144-146 °C; yield 82 mg, 67%. IR (KBr, neat) ν 3409, 3167, 2978, 1678, 1617, 1542, 1236, 1166, 1076, 770, 559 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.3 Hz, 1 H), 7.70–7.66 (m, 1 H), 7.44–7.41 (m, 3 H), 7.20 (d, *J* = 7.7 Hz, 2 H), 6.70 (bs, 2 H), 3.97 (q, *J* = 7.1 Hz, 2 H), 2.38 (s, 3 H), 0.77 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.9, 160.7, 152.8, 147.8, 140.6, 137.9, 131.4, 130.2, 128.8, 128.2, 125.4, 120.8, 117.1, 103.3, 60.8, 21.5, 13.4. HRMS (ESI) calcd. for $C_{19}H_{18}N_2O_2$ $(M + H)^+$ 307.1441, found 307.1451.

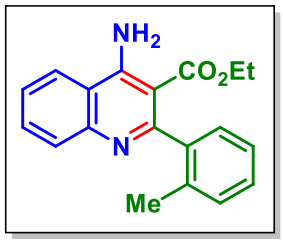
Ethyl 4-amino-2-(3,5-dimethylphenyl)quinoline-3-carboxylate (22aj):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 135-137 °C; yield 83 mg, 65%. IR (KBr, neat) 3400, 3158, 2981, 1681, 1615, 1550, 1249, 1170, 1094, 765, 576 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.70–7.66 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 1 H), 7.14 (s, 2 H), 6.99 (s, 1 H), 6.67 (bs, 2 H), 4.00–3.95 (m, 2 H), 2.33 (s, 6 H), 0.78 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.9, 161.0, 152.7, 147.9, 143.3, 137.5, 131.3,

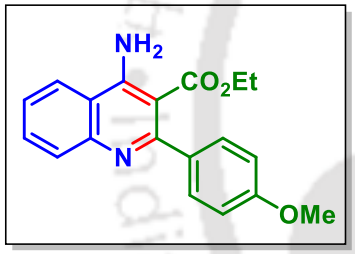
130.3, 129.6, 126.1, 125.4, 120.8, 117.1, 103.4, 60.7, 21.5, 13.3. HRMS (ESI) calcd. for $C_{20}H_{21}N_2O_2$ $(M + H)^+$ 321.1598, found 321.1589.

Ethyl 4-amino-2-(o-tolyl)quinoline-3-carboxylate (22ak):



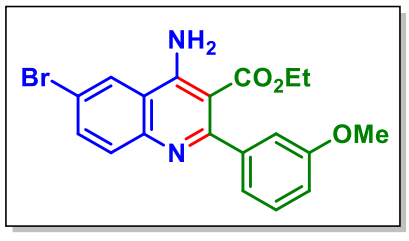
Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 97-99 °C; yield 78 mg, 64%. IR (KBr, neat) 3408, 3168, 2978, 1679, 1616, 1542, 1234, 1168, 1076, 775, 559 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.3 Hz, 1 H), 7.70 (t, *J* = 7.6 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.22–7.16 (m, 4 H), 7.02 (bs, 2 H), 3.90 (q, *J* = 7.2 Hz, 2 H), 2.21 (s, 3 H), 0.70 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.4, 161.3, 153.5, 147.8, 143.7, 135.2, 131.5, 130.2, 129.9, 127.8, 127.5, 125.6, 125.5, 120.8, 117.2, 103.3, 60.6, 19.8, 13.2. HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_2$ $(M + H)^+$ 307.1441, found 307.1447.

Ethyl 4-amino-2-(4-methoxyphenyl)quinoline-3-carboxylate (22al):



Off white solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 128-130 °C; yield 104 mg, 81%. IR (KBr, neat) ν 3404, 3161, 2927, 1676, 1608, 1541, 1244, 1166, 1074, 771, 560 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.5 and 1.3 Hz, 1 H), 7.79 (dd, *J* = 8.4 and 1.3 Hz, 1 H), 7.70–7.67 (m, 1 H), 7.50 (d, *J* = 8.8 Hz, 2 H), 7.45–7.42 (m, 1 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 6.66 (bs, 2 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 3.84 (s, 3 H), 0.83 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.0, 160.1, 160.0, 152.7, 147.8, 136.0, 131.4, 130.2, 129.7, 125.4, 120.8, 117.0, 113.7, 103.3, 60.9, 55.7, 13.6. HRMS (ESI) calcd. for $C_{19}H_{19}N_2O_3$ $(M + H)^+$ 323.1390, found 323.1395.

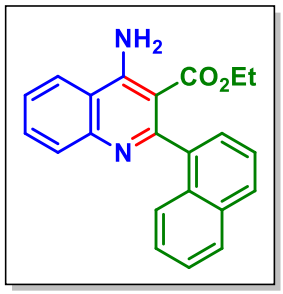
Ethyl 4-amino-7-bromo-2-(3-methoxyphenyl)quinoline-3-carboxylate (22cm):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 103-105 °C; yield 115 mg, 72%. IR (KBr, neat) ν 3458, 3350, 2980, 1685, 1613, 1552, 1251, 1102, 1043, 755, 565 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.1 Hz, 1 H), 7.86 (d, *J* = 8.9 Hz, 1 H), 7.72 (dd, *J* = 8.9 and 2.1 Hz, 1H), 7.28 (t, *J* = 7.86 Hz, 1 H), 7.11 (s, 1 H), 7.06–7.04 (m, 1H), 6.92–6.90 (m, 1 H), 6.72 (bs, 2 H), 3.97 (q, *J* = 7.2 Hz, 2 H), 3.82 (s, 3 H), 0.78 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 169.4, 160.8, 159.6, 151.9, 146.4, 144.4, 134.6, 131.9, 129.2, 123.7, 120.9, 119.2, 118.6,

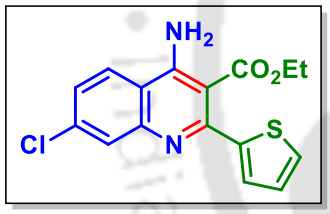
114.4, 113.3, 103.8, 61.0, 55.6, 13.4. HRMS (ESI) calcd. for $C_{19}H_{18}BrN_2O_3$ $(M + H)^+$ 401.0495, found 401.0483.

Ethyl 4-amino-2-(naphthalen-1-yl)quinoline-3-carboxylate (22an):



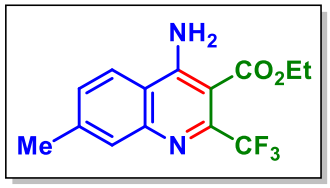
Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 140-142 °C; yield 68 mg, 50%. IR (KBr, neat) ν 3410, 3169, 2977, 1675, 1608, 1542, 1244, 1167, 1075, 769, 565 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1 H), 7.89–7.85 (m, 3 H), 7.74 (t, *J* = 7.6 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.51 (q, *J* = 7.1 Hz, 2 H), 7.46–7.42 (m, 2 H), 7.38–7.35 (m, 1 H), 7.06 (bs, 2 H), 3.68–3.61 (m, 1 H), 3.57–3.50 (m, 1 H), 0.19 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.2, 160.2, 153.5, 148.0, 141.9, 133.7, 132.1, 131.6, 130.5, 128.2, 127.8, 126.2, 125.9, 125.73, 125.71, 125.49, 125.46, 120.8, 117.5, 104.2, 60.4, 12.6. HRMS (ESI) calcd. for $C_{22}H_{19}N_2O_2$ $(M + H)^+$ 343.1441, found 343.1458.

Ethyl 4-amino-7-chloro-2-(thiophen-2-yl)quinoline-3-carboxylate (22io):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 121-123 °C; yield 86 mg, 65%. IR (KBr, neat) ν 3471, 3367, 2978, 1686, 1606, 1554, 1437, 1241, 1096, 788, 707cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.40 (d, *J* = 5.0 Hz, 1 H), 7.30 (dd, *J* = 8.8 and 2.1 Hz, 1 H), 7.18 (d, *J* = 3.6 Hz, 1 H), 7.05 (t, *J* = 4.4 Hz, 1 H), 6.47 (bs, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 0.99 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.4, 154.1, 152.0, 148.5, 144.8, 137.4, 129.0, 127.7, 127.3, 127.2, 126.2, 122.3, 115.6, 103.9, 61.3, 13.6. HRMS (ESI) calcd. for $C_{16}H_{14}ClN_2O_2S$ $(M + H)^+$ 333.0459, found 333.0450.

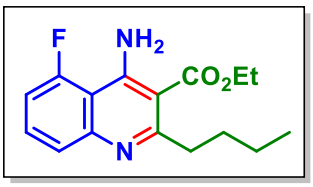
Ethyl 4-amino-7-methyl-2-(trifluoromethyl)quinoline-3-carboxylate (22gp):



Off white solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 142-144 °C; yield 103 mg, 87%. IR (KBr, neat) ν 3478, 3367, 2987, 1696, 1619, 1454, 1259, 1182, 1018, 978, 796 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.66 (d, *J* = 8.6 Hz, 1 H), 7.35 (dd, *J* = 8.5 and 2.2 Hz, 1 H), 6.60 (bs, 2 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 2.50 (d, *J* = 2.1 Hz, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.8, 152.8, 147.0 (q, *J* = 33.3 Hz), 146.6, 142.7, 130.1 (d, *J* = 2.7 Hz), 129.7, 121.8 (q, *J* = 274.4 Hz), 120.5, 116.1, 101.4, 62.1, 21.8,

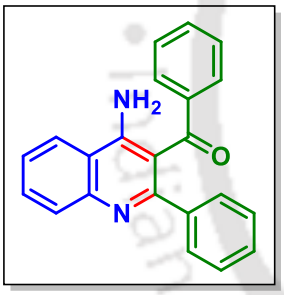
13.9. ^{19}F NMR (470 MHz, C_6F_6/$CDCl_3$) δ –66.38 (s, -F). HRMS (ESI) calcd. for $C_{14}H_{14}F_3N_2O_2$ $(M + H)^+$ 299.1002, found 299.1005.

Ethyl 4-amino-2-butyl-5-fluoroquinoline-3-carboxylate (22dq):



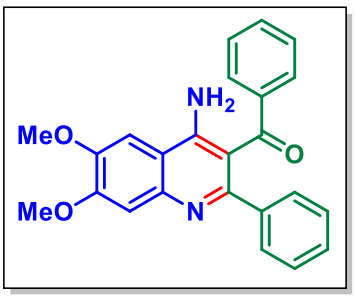
Yellow oil; R_f (hexane/EtOAc, 9:1) 0.30; yield 50 mg, 43%. IR (KBr, neat) ν 3468, 3338, 2985, 1691, 1619, 1459, 1259, 1152, 1040, 796 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 1 H), 7.52 (q, *J* = 8.0 Hz, 1 H), 7.43 (bs, 2 H), 6.99 (dd, *J* = 14.2 and 7.8 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 3.09–3.06 (m, 2 H), 1.72–1.66 (m, 2 H), 1.45–1.39 (m, 5 H), 0.94 (t, *J* = 7.3 Hz, 3 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.4, 164.3, 160.5 (d, *J* = 251.0 Hz), 153.6 (d, *J* = 3.1 Hz), 149.9, 130.8 (d, *J* = 11.8 Hz), 125.4 (d, *J* = 3.4 Hz), 110.0 (d, *J* = 24.1 Hz), 107.9 (d, *J* = 6.4 Hz), 103.1 (d, *J* = 1.9 Hz), 61.3, 39.8, 32.6, 23.4, 14.4, 14.3. ^{19}F NMR (470 MHz, C_6F_6/$CDCl_3$) δ -118.03 (s, -F). HRMS (ESI) calcd. for $C_{16}H_{20}FN_2O_2$ $(M + H)^+$ 291.1503, found 291.1502.

(4-Amino-2-phenylquinolin-3-yl)(phenyl)methanone (22ar):



Light yellow solid; R_f (hexane/EtOAc, 4:1) 0.30; mp 222-224 °C; yield 74 mg, 57%. IR (KBr, neat) ν 3464, 3364, 3055, 1612, 1547, 1256, 762, 695 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 8.2 Hz, 1 H), 7.75 (t, *J* = 7.7 Hz, 1 H), 7.52–7.48 (m, 3 H), 7.39 (d, *J* = 7.6 Hz, 2 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 7.13–7.07 (m, 5 H), 6.43 (s, 2 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 199.7, 160.2, 151.6, 148.3, 141.9, 140.2, 132.2, 131.4, 130.4, 129.9, 129.4, 128.7, 128.3, 128.0, 125.7, 121.0, 117.3, 111.0. HRMS (ESI) calcd. for $C_{22}H_{17}N_2O$ $(M + H)^+$ 325.1336, found 325.1331.

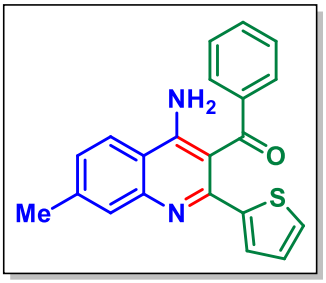
(4-amino-6,7-dimethoxy-2-phenylquinolin-3-yl)(phenyl)methanone (22hr):



Light yellow solid; R_f (hexane/EtOAc, 2:1) 0.30; mp 220-222 °C; yield 91 mg, 59%. IR (KBr, neat) ν 3459, 3370, 2933, 1619, 1503, 1232, 1001, 919, 728 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (s, 1 H), 7.44 (d, *J* = 7.3 Hz, 2 H), 7.38 (d, *J* = 7.7 Hz, 2 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.11–7.05 (m, 6 H), 6.32 (s, 2 H), 4.03 (s, 3 H), 4.00 (s, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 199.8, 158.5, 153.8, 150.6, 149.2, 145.0, 141.5, 140.4, 132.1, 129.9, 129.4, 128.5, 128.2, 127.9,

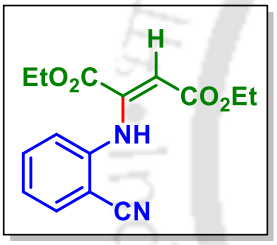
111.3, 110.8, 109.2, 99.9, 56.5, 56.4. HRMS (ESI) calcd. for $C_{24}H_{21}N_2O_3$ $(M + H)^+$ 385.1547, found 385.1536.

(4-amino-7-methyl-2-(thiophen-2-yl)quinolin-3-yl)(phenyl)methanone (22gs):



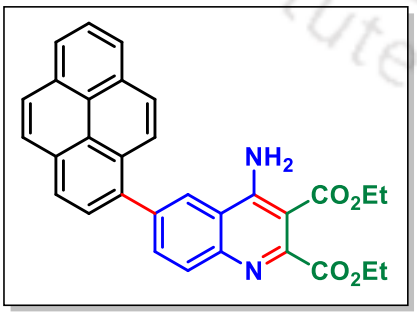
Yellow solid; R_f (hexane/EtOAc, 5:1) 0.30; mp 240-242 °C; yield 76 mg, 55%. IR (KBr, neat) ν 3373, 3075, 3055, 1618, 1550, 1437, 1253, 886, 699 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 (s, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.7 Hz, 2 H), 7.30 (q, *J* = 7.5 Hz, 2 H), 7.20–7.15 (m, 3 H), 6.98 (d, *J* = 3.7 Hz, 1 H), 6.70 (s, 1 H), 6.23 (s, 2 H), 2.54 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 198.9, 152.9, 151.1, 148.5, 144.8, 142.0, 139.6, 132.5, 130.3, 129.4, 129.3, 128.4, 128.2, 127.7, 127.4, 120.8, 115.0, 110.1, 21.9. HRMS (ESI) calcd. for $C_{21}H_{17}N_2OS$ $(M + H)^+$ 345.1057, found 345.1059.

***Z*-Diethyl 2-((2-cyanophenyl)amino)fumarate (22a″):**



Yellow oil; R_f (hexane/EtOAc, 9:1) 0.30; yield 12 mg, 10%. IR (KBr, neat) ν 3473, 3379, 2984, 2217, 1730, 1620, 1265, 1209, 1030, 756 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.90 (s, 1 H), 7.58 (d, *J* = 7.7 Hz, 1 H), 7.44 (t, *J* = 7.9 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1 H), 5.71 (s, 1 H), 4.26–4.17 (m, 4 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.15 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.1, 163.6, 145.8, 143.9, 133.4, 133.3, 123.9, 121.3, 116.7, 105.1, 99.5, 62.6, 60.8, 14.5, 13.9. HRMS (ESI) calcd. for $C_{15}H_{17}N_2O_4$ $(M + H)^+$ 289.1183, found 289.1192.

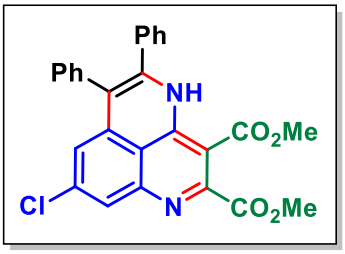
Diethyl 4-amino-6-(pyren-2-yl)quinoline-2,3-dicarboxylate (23):



Off white solid; R_f (hexane/EtOAc, 5:1) 0.40; mp 170-172 °C; yield 66 mg, 96%. IR (KBr, neat) ν 3374, 3278, 2981, 1741, 1686, 1616, 1557, 1246, 1100, 1028, 844, 763, 553 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.6 Hz, 2 H), 8.09 (d, *J* = 8.1 Hz, 2 H), 8.05 (s, 2 H), 8.00–7.95 (m, 2 H), 7.94–7.92 (m, 2 H), 7.90–7.86 (m, 2 H), 7.35 (bs, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 1.36 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.2, 167.3, 154.5, 153.9, 146.6, 139.5, 136.3, 134.6, 131.6, 131.1, 131.0, 130.0, 128.6, 128.2, 127.9, 127.8, 127.5, 126.4, 125.6, 125.3, 125.0,

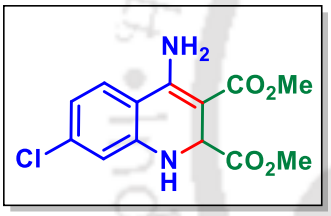
124.9, 124.8, 124.7, 122.8, 118.0, 98.9, 62.1, 61.5, 14.3, 14.2. HRMS (ESI) calcd. for $C_{31}H_{25}N_2O_4$ $(M + H)^+$ 489.1809, found 489.1812.

Dimethyl 8-chloro-5,6-diphenyl-4*H*-benzo[*de*][1,6]naphthyridine-2,3-dicarboxylate (24):



Light green solid; R_f (hexane/EtOAc, 5:1) 0.40; mp 208-210 °C; yield 50 mg, 62%. IR (KBr, neat) ν 3172, 2946, 1754, 1671, 1593, 1441, 1255, 1213, 1081, 998, 701, 561 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 11.94 (s, 1 H), 7.58 (d, *J* = 1.9 Hz, 1 H), 7.41–7.35 (q, *J* = 6.0, 5.4 Hz, 3 H), 7.32–7.28 (m, 5 H), 7.20 (d, *J* = 7.0 Hz, 2 H), 6.85 (d, *J* = 1.8 Hz, 1 H), 4.00 (s, 3 H), 3.89 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 168.0, 167.4, 155.9, 149.8, 148.7, 140.6, 138.4, 137.6, 134.8, 134.7, 131.0, 129.5, 129.4, 129.0, 128.9, 128.3, 122.2, 121.6, 118.4, 117.0, 94.2, 53.0, 52.5. HRMS (ESI) calcd. for $C_{27}H_{20}ClN_2O_4$ $(M + H)^+$ 471.1106, found 471.1106.

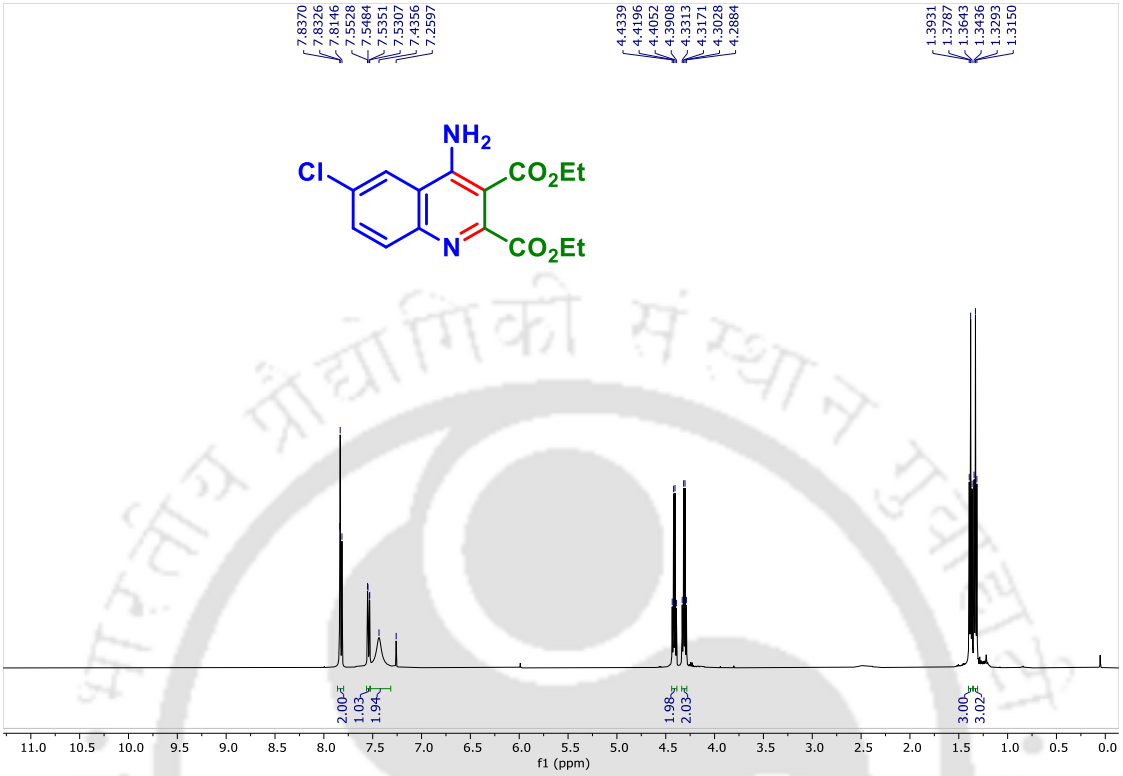
Dimethyl 4-amino-7-chloro-1,2-dihydroquinoline-2,3-dicarboxylate (25):



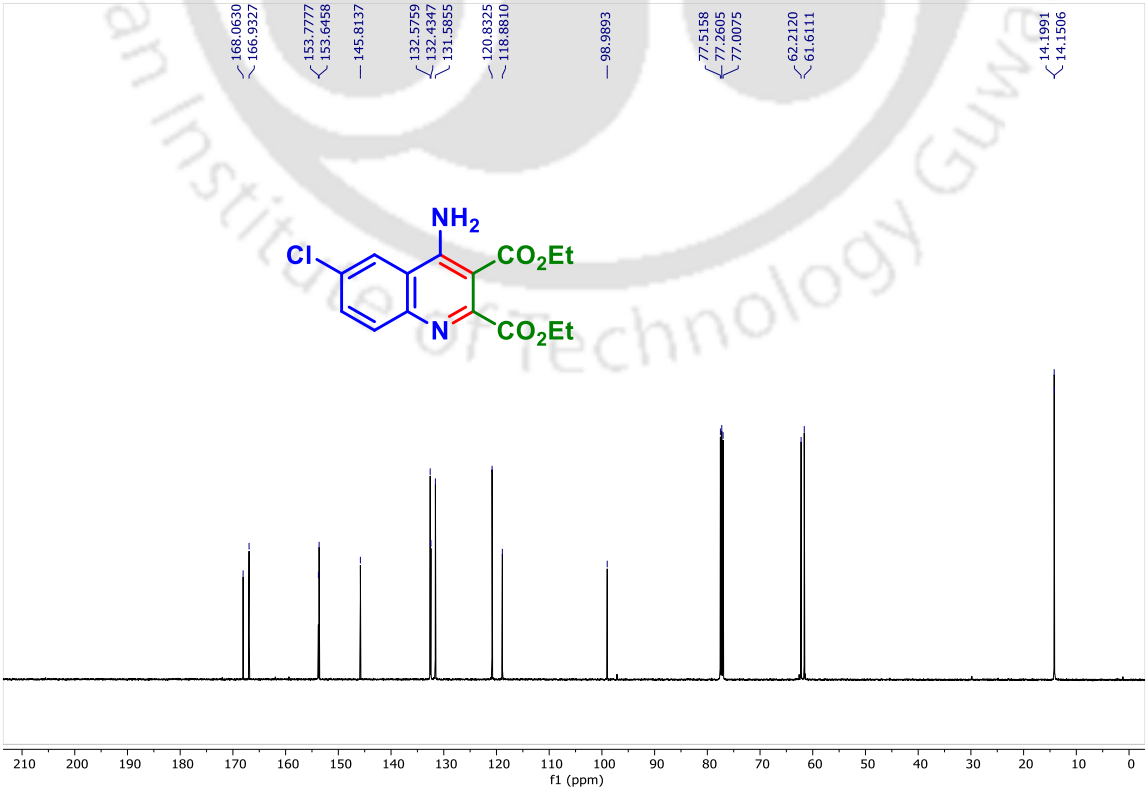
Light green gum; R_f (hexane/EtOAc, 4:1) 0.40; yield 30 mg, 60%. IR (KBr, neat) ν 3454, 3332, 2953, 1734, 1607, 1439, 1242, 1082, 792 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.3 Hz, 1 H), 6.76–6.72 (m, 2 H), 5.00 (d, *J* = 2.3 Hz, 1 H), 4.90 (s, 1 H), 3.77 (s, 3 H), 3.63 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 174.0, 168.8, 150.2, 147.3, 137.9, 124.4, 119.3, 115.3, 115.0, 88.3, 52.73, 52.71, 51.4. HRMS (ESI) calcd. for $C_{13}H_{14}ClN_2O_4$ $(M + H)^+$ 297.0637, found 297.0636.

4.10. Representative Spectra

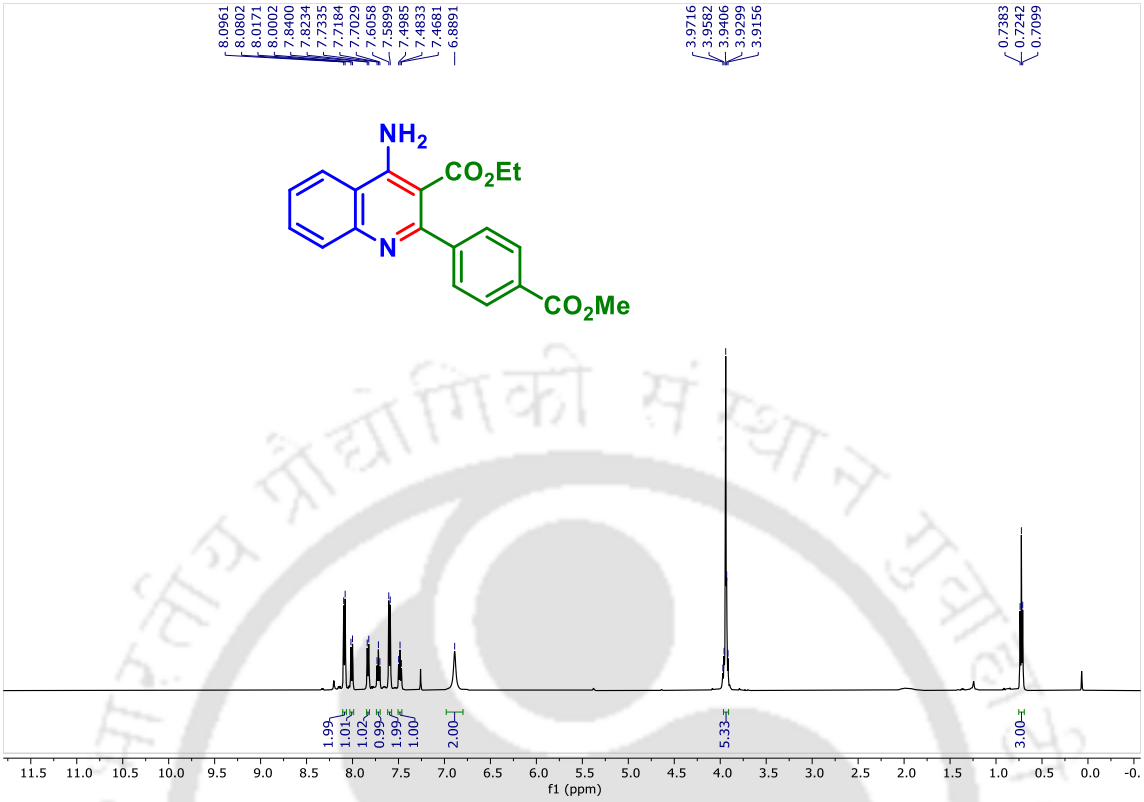
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**22ab**):



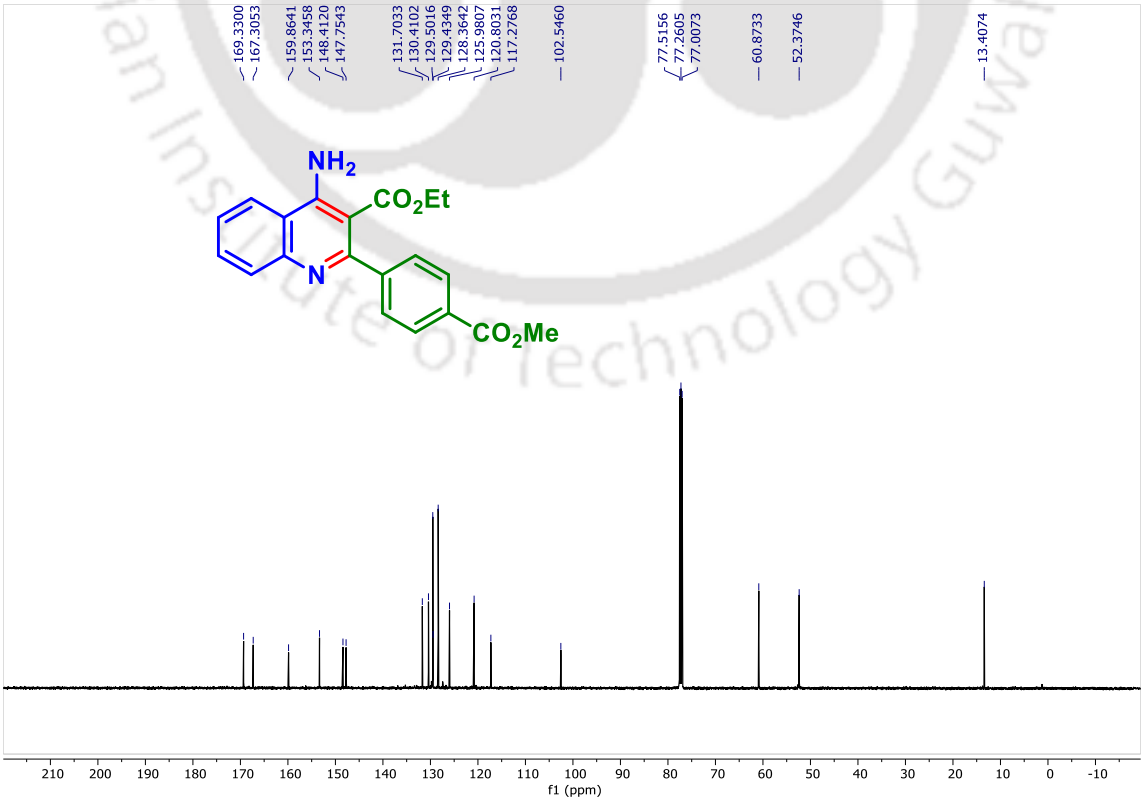
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**22ab**):



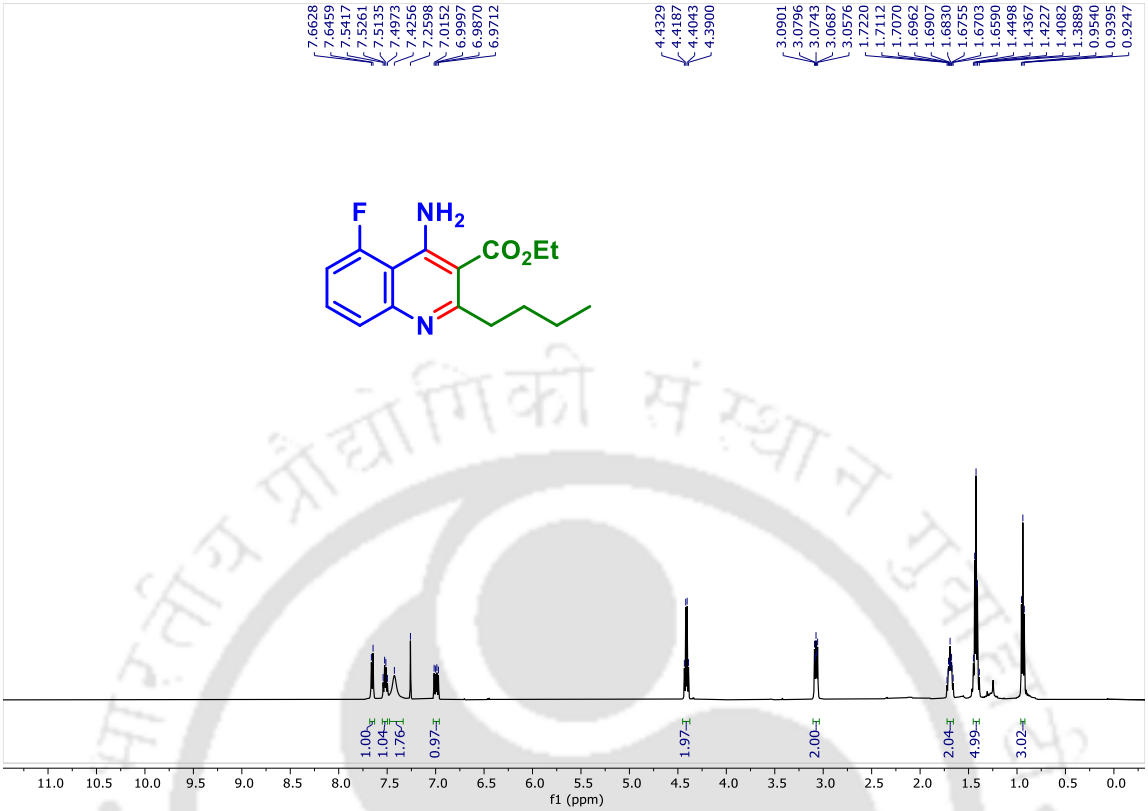
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**22ag**):



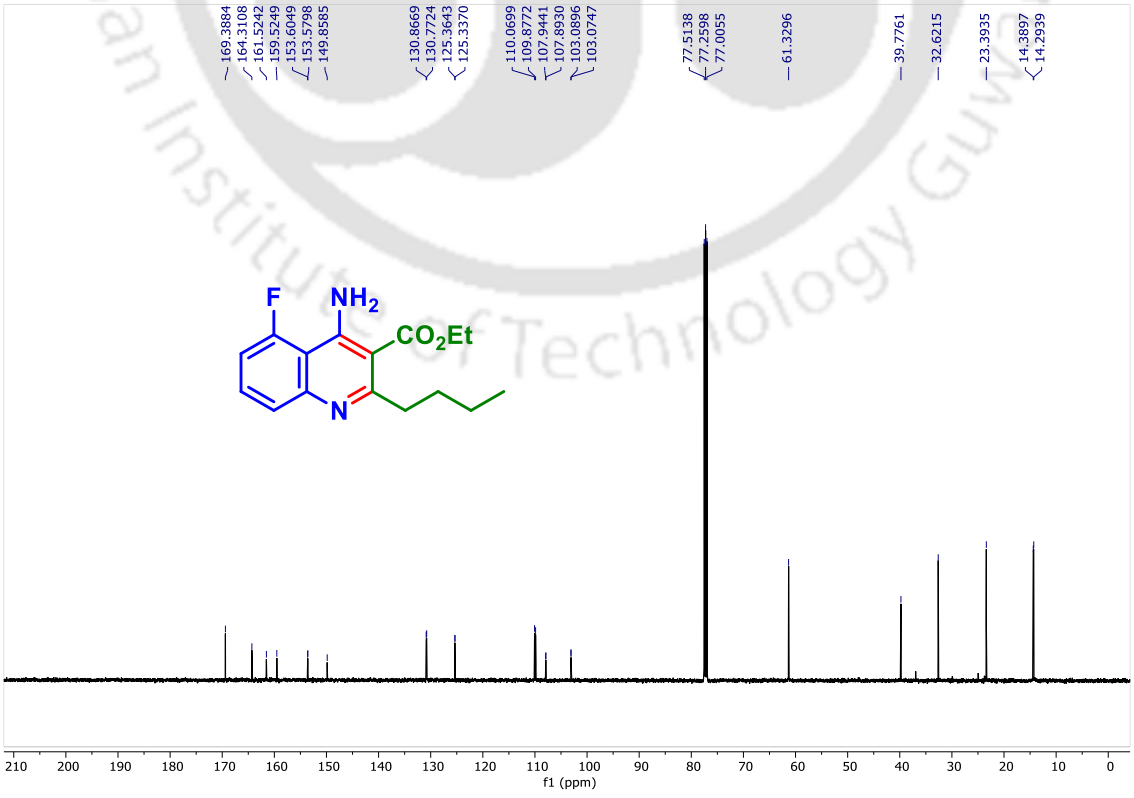
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**22ag**):



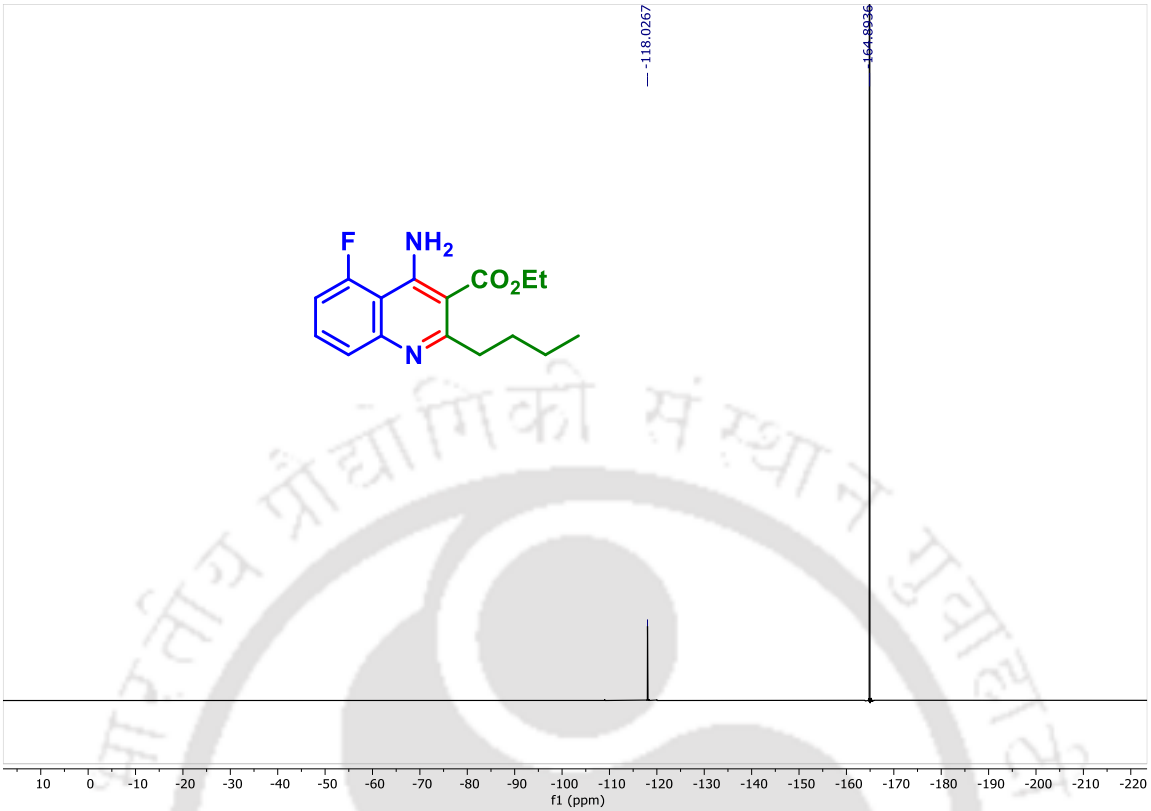
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**22dq**):



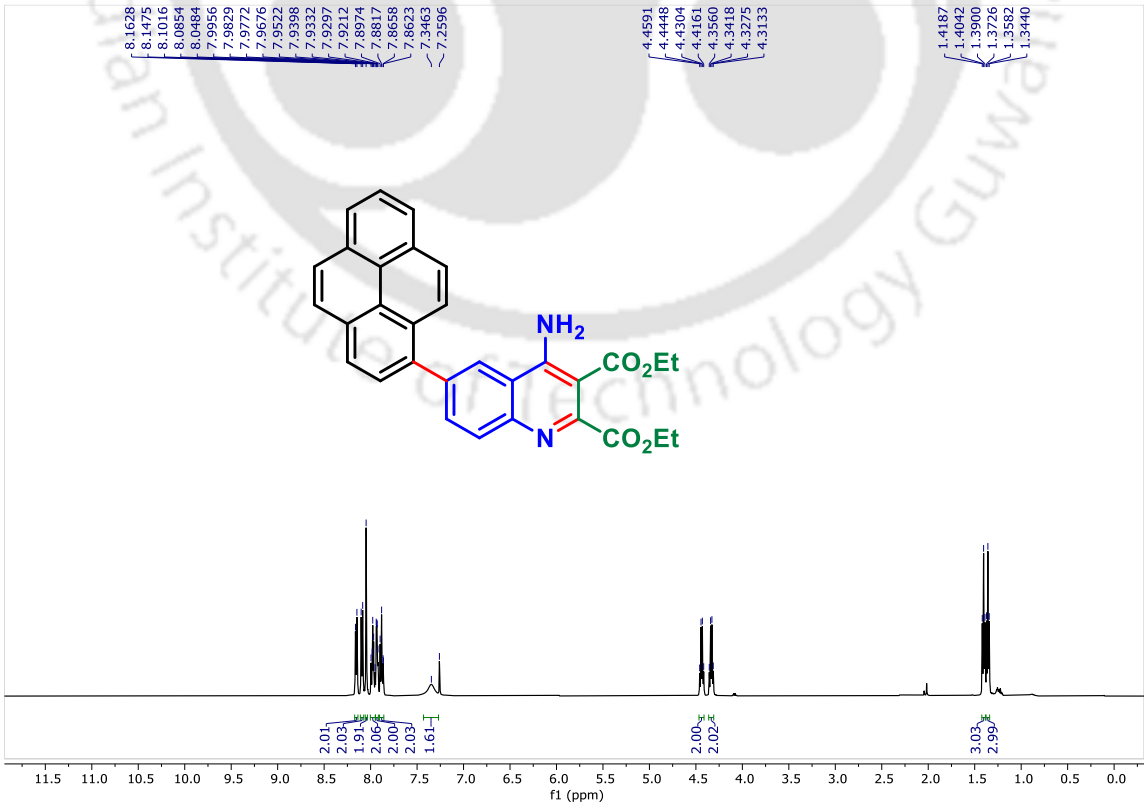
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**22dq**):



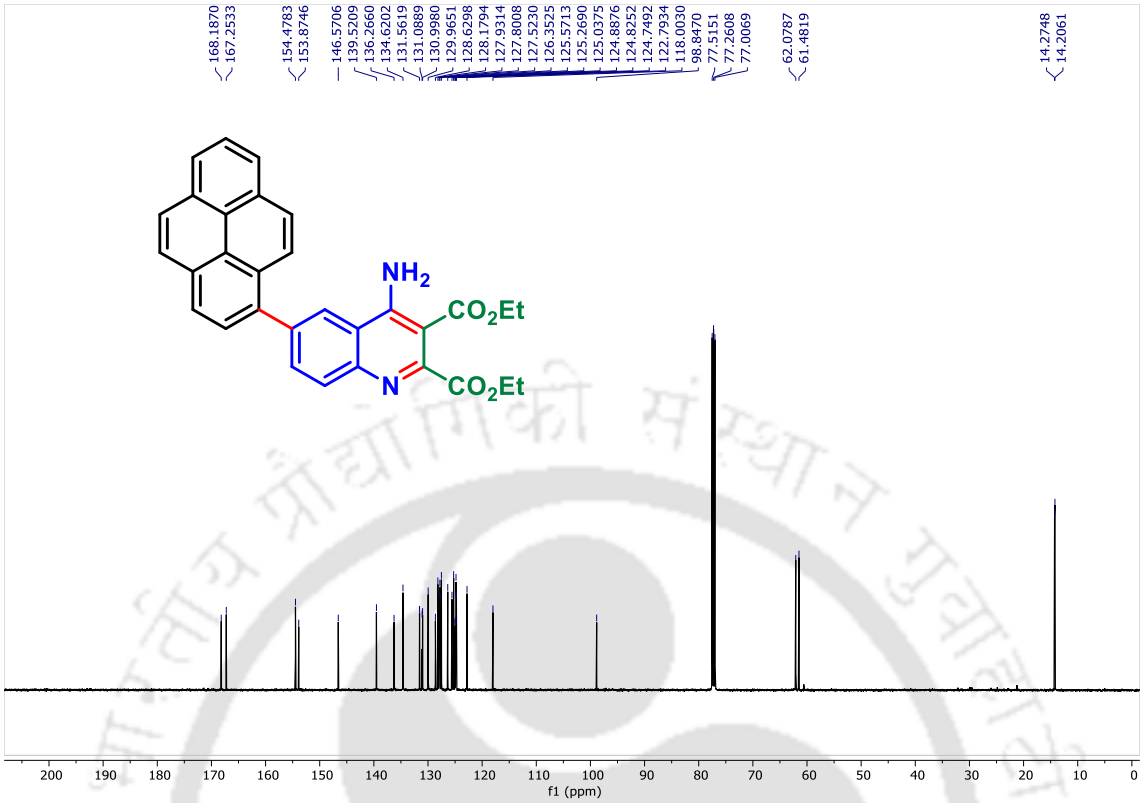
^{19}F (C_6F_6/$CDCl_3$, 470 MHz) spectrum of compound (**22dq**):



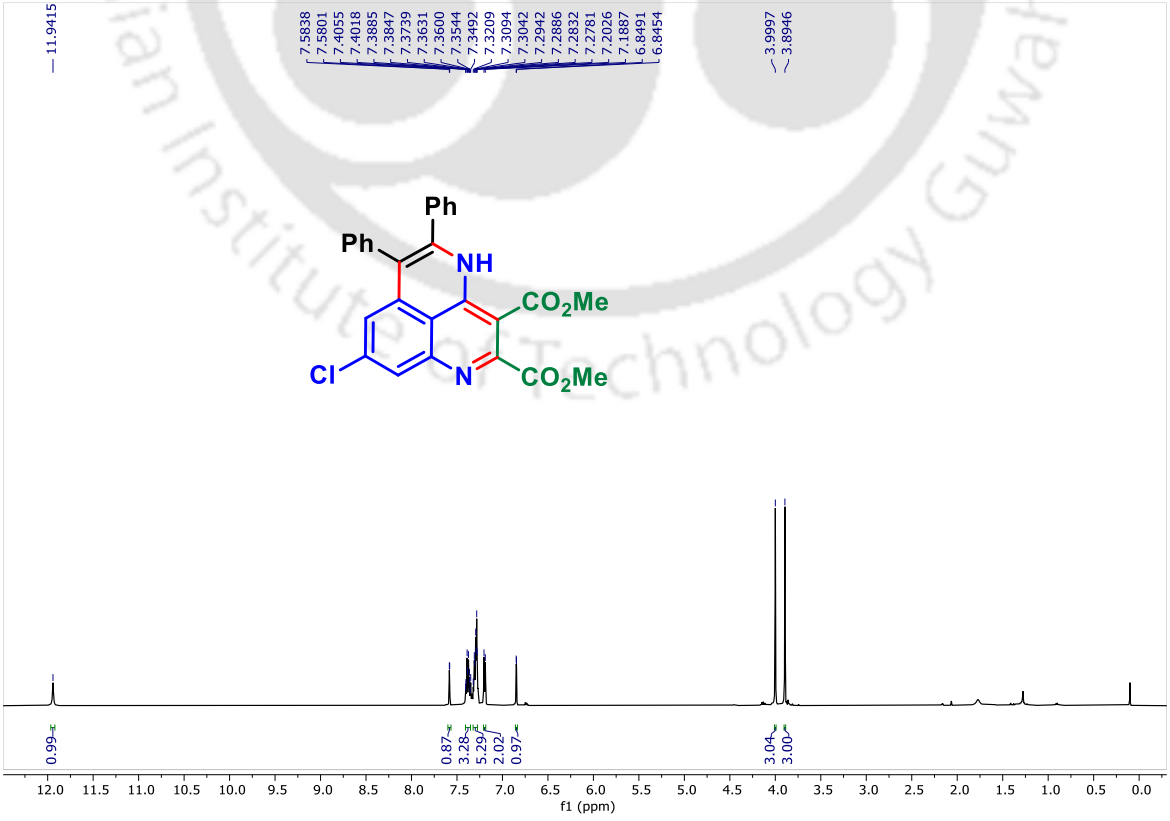
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**23**):



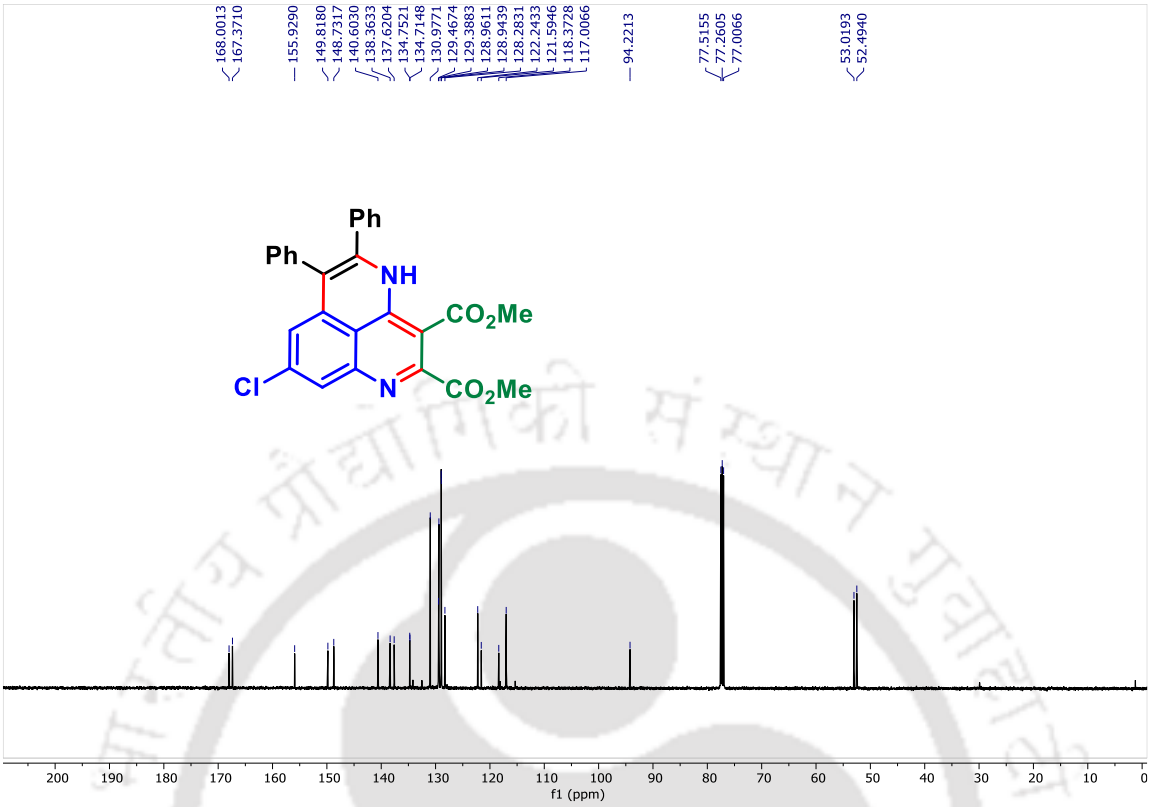
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**23**):



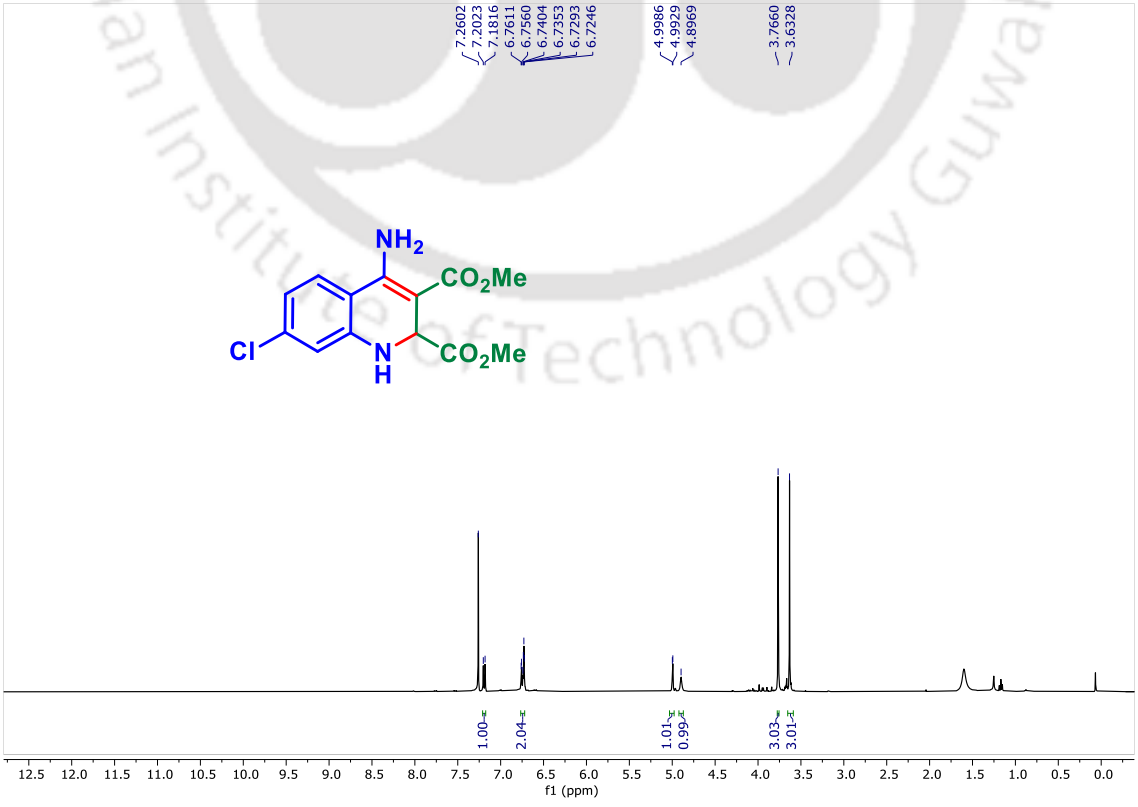
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**24**):



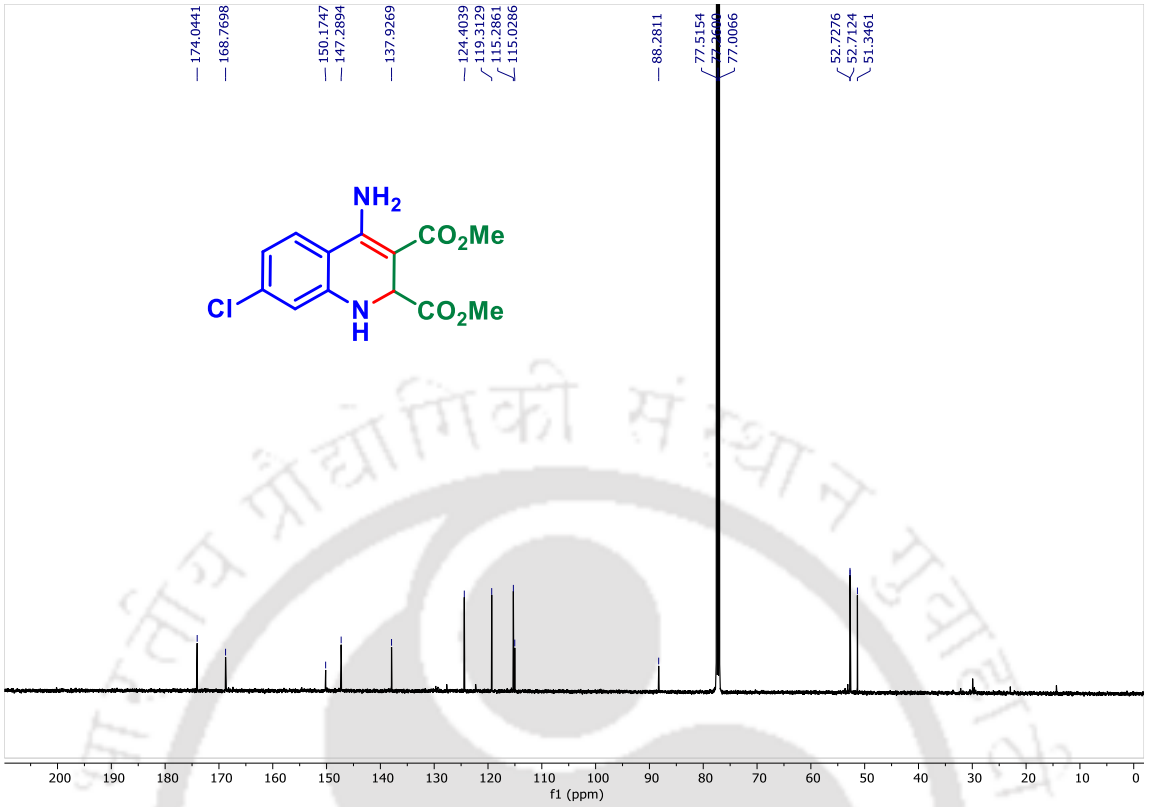
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**24**):



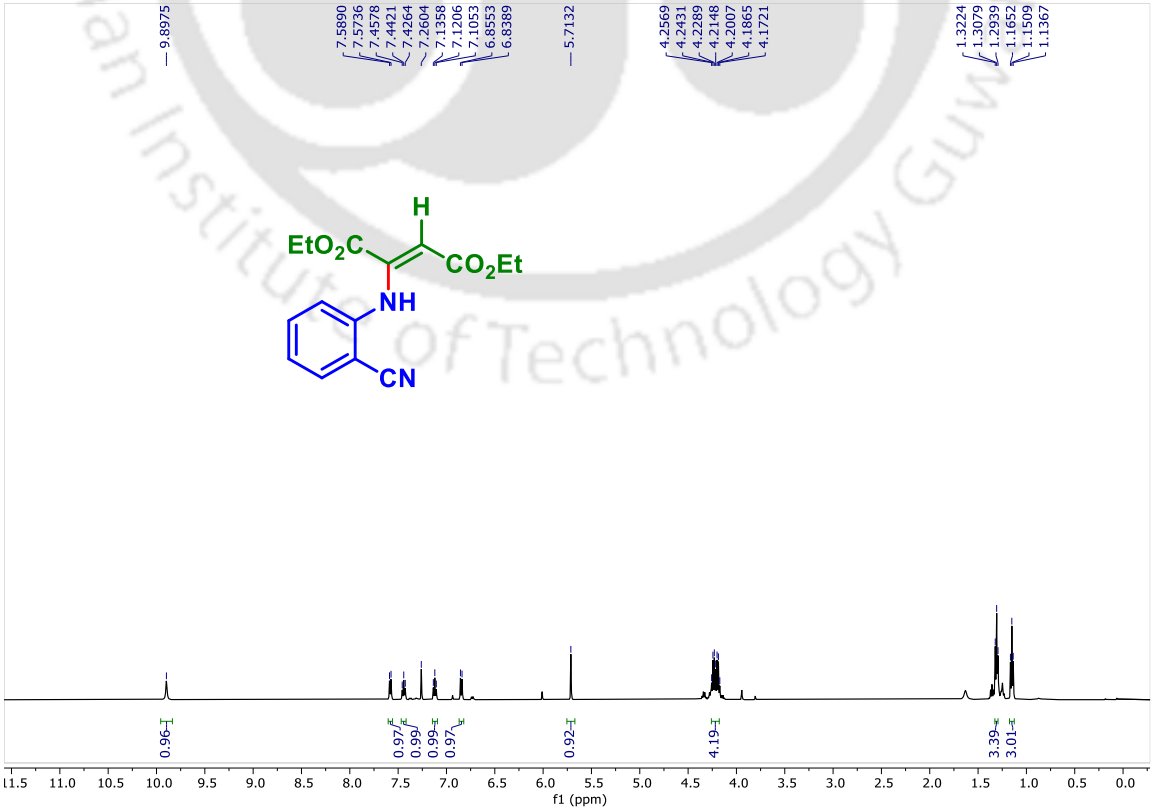
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**25**):



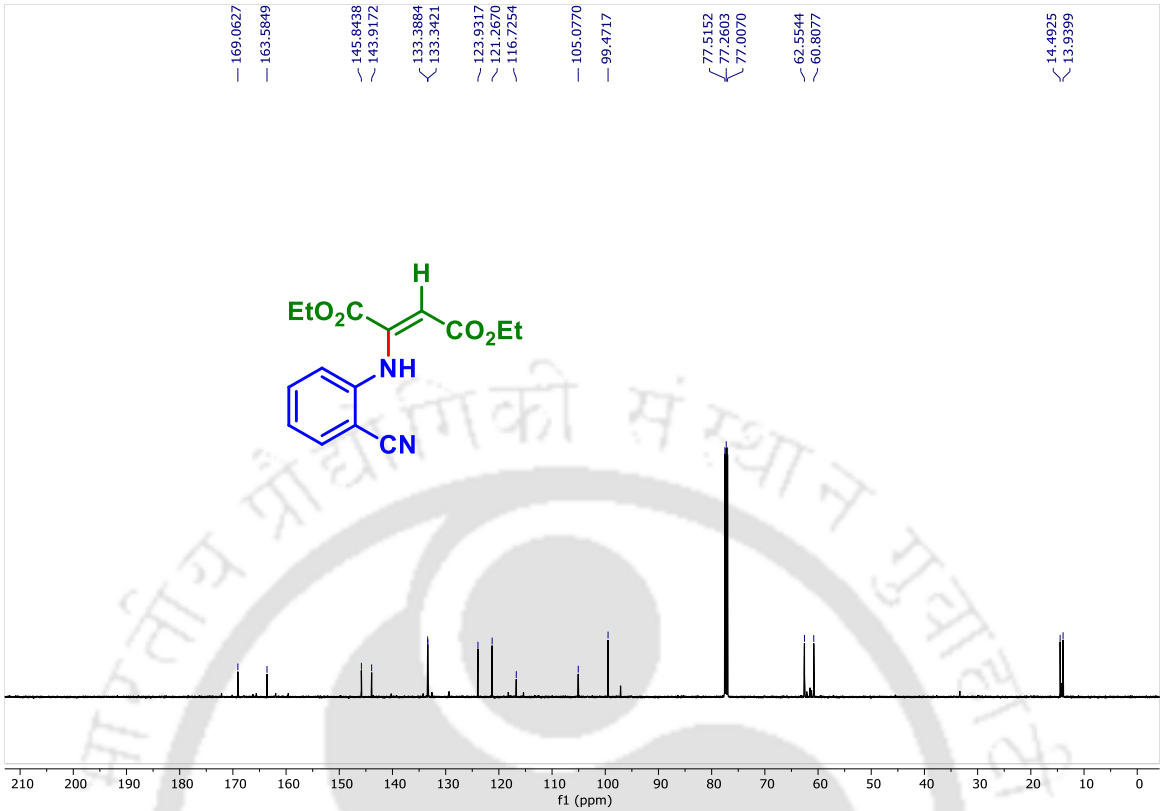
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**25**):



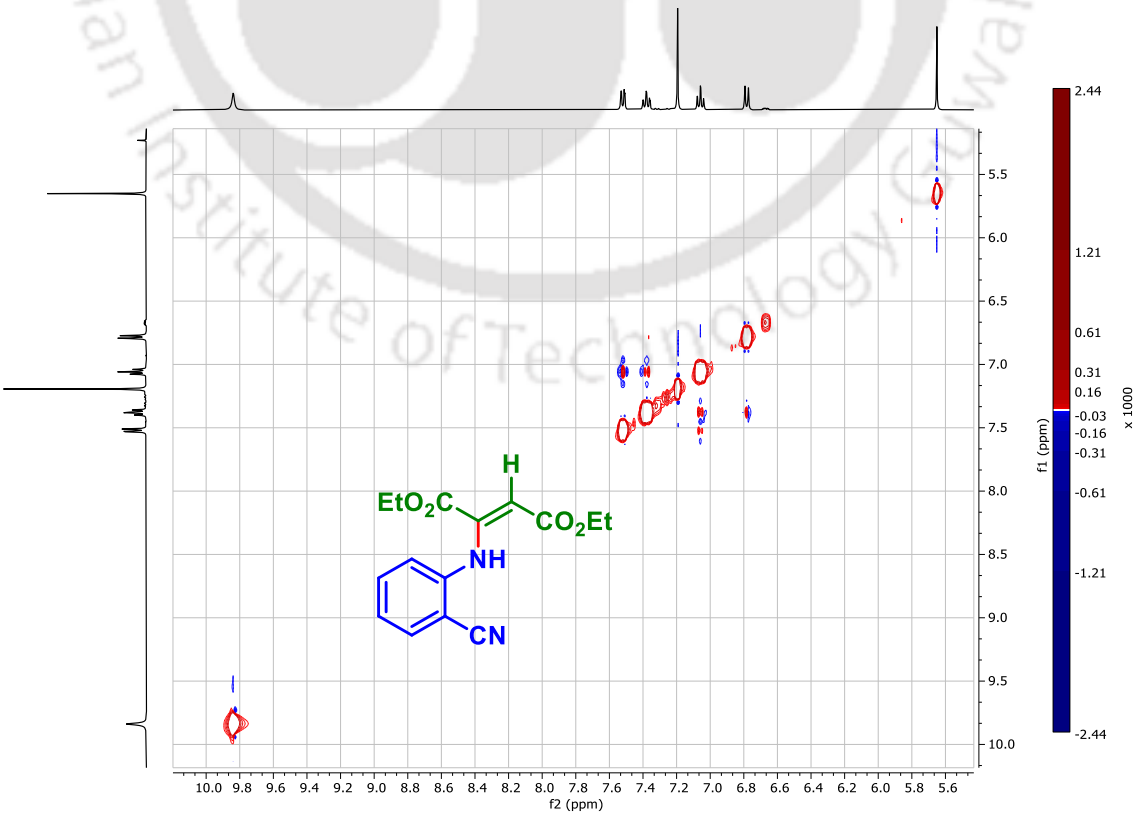
^{1}H ($CDCl_3$, 500 MHz)) spectrum of compound (**22a″**):



$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**22a″**):



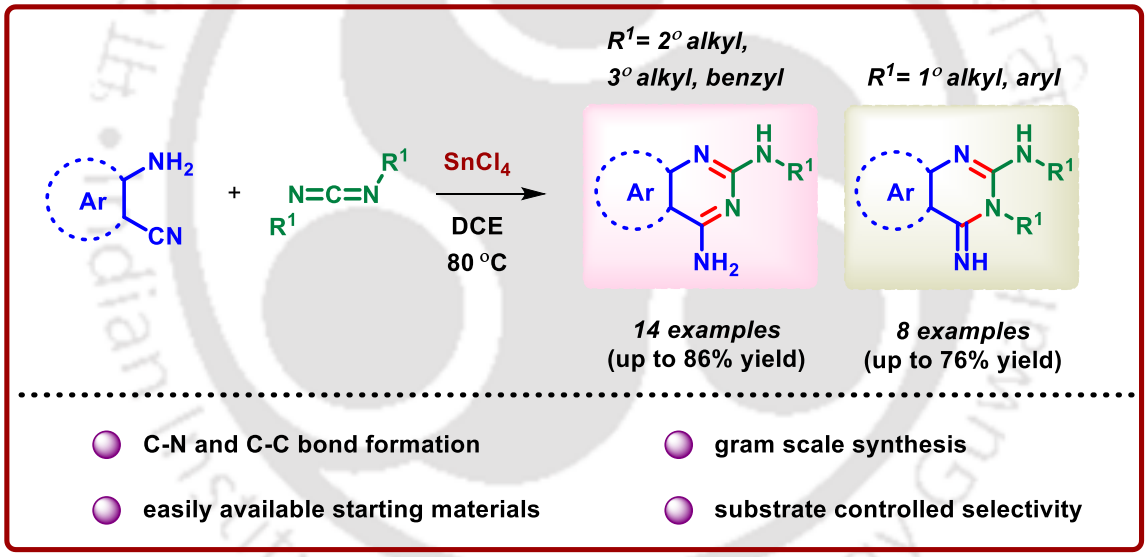
NOE (400MHz, $CDCl_3$) spectrum of compound **22a″**:



CHAPTER 5

Synthesis of 2,4-Diaminoquinazolines and 2-Amino-4-iminoquinazolines *via* Substrate-Controlled Annulation of 2-Aminobenzonitriles and Carbodiimides

Abstract: This chapter highlights an efficient methodology for the synthesis of 2,4-diaminoquinazolines and 2-amino-4-iminoquinazolines from 2-aminobenzonitriles and carbodiimides. This $SnCl_4$ mediated reaction exhibits substrate driven switchable selectivity in product formation based on the substituents of the carbodiimides used. Aryl and primary alkyl-substituted carbodiimides predominantly give 2-amino-4-iminoquinazolines, while secondary or tertiary alkyl and benzyl-substituted carbodiimides yield 2,4-diaminoquinazolines. The methodology can be extended towards the synthesis of 2-aminoquinazolin-4(3*H*)-one analogues as well as pentacyclic annulated derivatives.



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ChemistrySelect **2025**, *10*, e202405899.

5.1. Introduction

Quinazolines represent a pre-eminent class of annulated six-membered *N*-heterocycles with diverse bioactivities, like anti-inflammatory,[1] antifungal,[2] antibacterial,[3] antitumor[4] and analgesic activities.[5] Numerous approved quinazoline based drugs known for their therapeutic applications are in clinical use to manage various medical conditions. Marketed drugs like prazosin (**a**), an α-adrenergic blocker anti-hypertensive drug[6a] and alfuzosin (**b**), used to treat benign prostatic hyperplasia[6b,c] have 2,4-diaminoquinazoline scaffold as core unit. Also, erlotinib is a well-known drug with *N*-phenylquinazolin-4-amine skeleton, is used for the treatment of pancreatic cancer.[7] Similarly, quinazolin-4(3*H*)-imines such as (**d**) and (**e**), are another important subclass which exhibit biological activities like antimicrobial, antiproliferative, cholinesterase, and cMET kinase inhibitory properties.[8] Further interest stems in for its role as a key precursor to its oxo-analogues quinazolin-4(3*H*)-ones, which are regarded as "privileged" skeletons, ubiquitous in natural products, synthetic compounds and pharmaceutically active molecules.[9] For example, Nolatrexed (**c**) an aromatic sulphur containing drug with quinazolin-4(3*H*)-one scaffold acts as thymidylate synthase inhibitor (*Figure 5.1.1.*).[10] Thus, quinazoline derivatives also appear as a significant assembly motif for developing new drug entities.

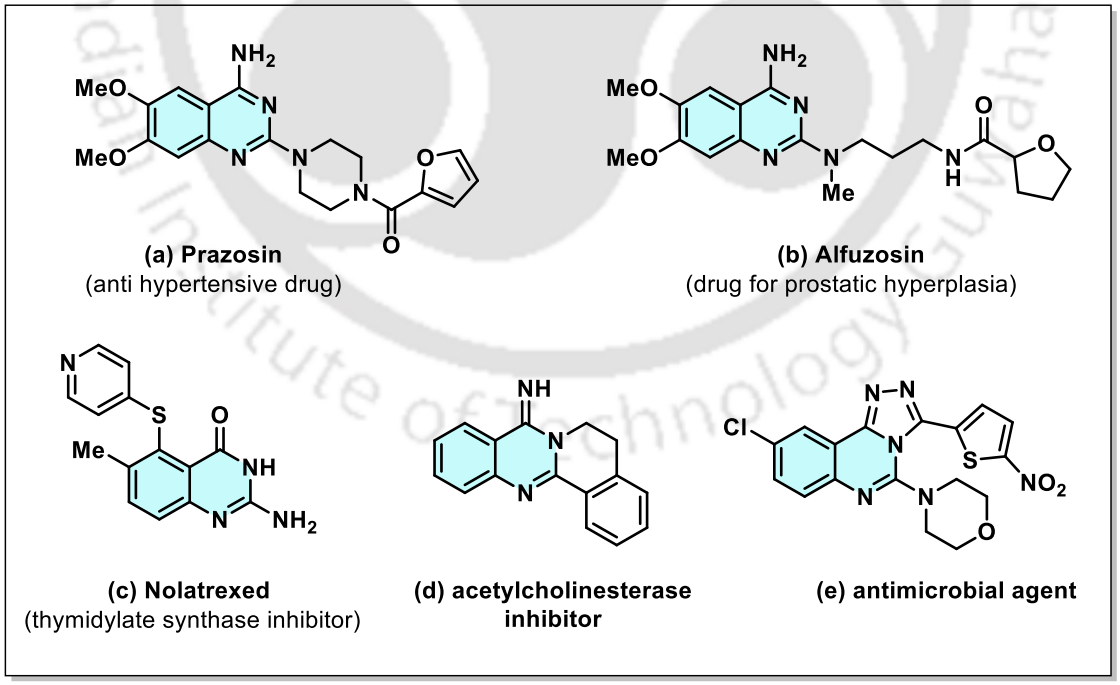
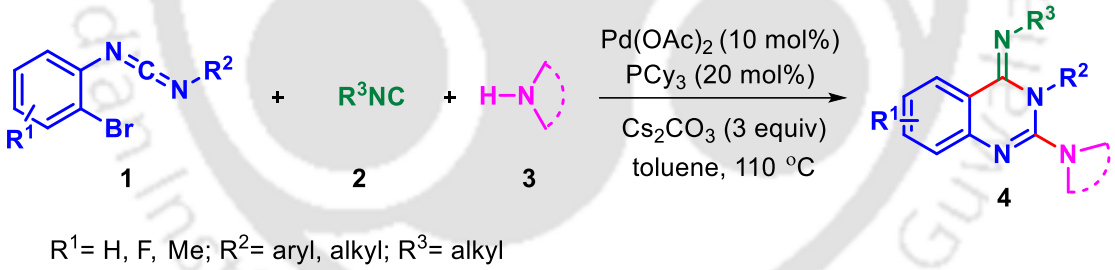


Figure 5.1.1. Some examples of bioactive molecules with quinazoline skeleton.

5.2. Literature Survey on Synthesis of Substituted 2-Amino-4-iminoquinazolines and 2,4-Diaminoquinazolines

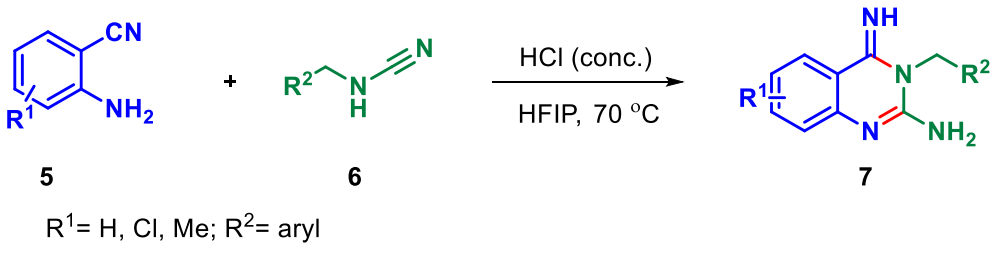
Over the years, several synthetic efforts have been prompted in the literature for quinazoline synthesis.[11] Because of the impressive biological activity of amino- and imino-quinazolines development of methodologies for constructing these moieties are gaining importance in organic synthesis. Recent methods for the synthesis of quinazolin-4(3*H*)-imines include reaction of 2-aminobenzonitriles with aryldiazonium salts and nitriles,[12] copper catalyzed reaction of diaryliodonium salts[13] and polyphosphoric acid ester promoted reaction with secondary amides.[14] Other notable approaches for these heterocycles are base mediated reaction of 2-cyanoimidoyl chlorides and primary amines[15] and synthesis of phenanthridine-fused quinazoliniminiums by cyclization of heteroenyne-allenes.[16] On the contrary, there are just a handful of literature reports for the synthesis of 2-amino-4-imino-quinazolines.

Pu and his co-workers reported an efficient route for the synthesis of substituted 2-amino-quinazolin-4(3*H*)-imines **4** by assembling *ortho*-bromo substituted carbodiimide **1**, isocyanide **2**, and cyclic amine **3**. The palladium-catalyzed three component protocol follows a tandem reaction pathway to give the products with good yields, where the insertion of isocyanide was illustrated to be the key step (*Scheme 5.2.1.*).[17]



Scheme 5.2.1. *Pd-catalyzed synthesis of substituted 2-amino-quinazolin-4(3H)-imines.*

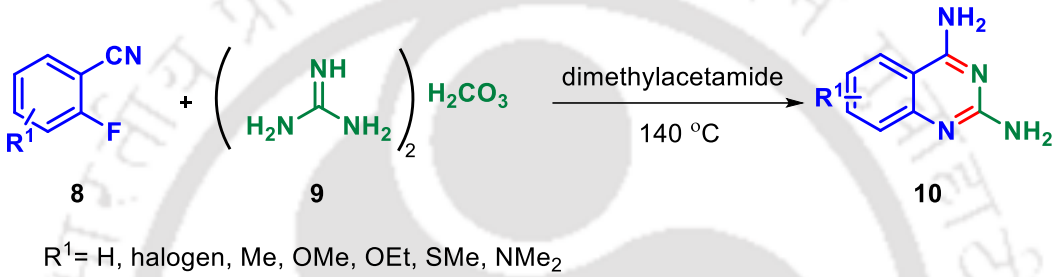
Wu and his group also demonstrated the synthesis of 2-amino-4-iminoquinazoline derivatives **7** from *N*-benzyl cyanamides **6** and 2-aminobenzonitriles **5**. The methodology utilizes hydrochloric acid as a mediator in the [4+2] annulation reaction and tolerates a wide range of substrates and exhibit good functional group tolerance (*Scheme 5.2.2.*).[18]



Scheme 5.2.2. *Acid mediated synthesis of 2-amino-quinazolin-4(3H)-imines.*

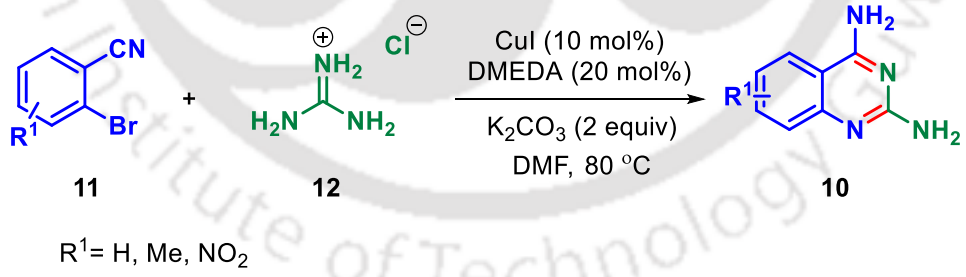
Conversely, various distinct methods have also been implemented to synthesize 2,4-diaminoquinazolines. Conventionally, *N*-substituted 2,4-diaminoquinazolines can be obtained directly from 2,4-dichloroquinazolines that can be efficiently prepared from quinazoline-2,4-diones by refluxing in phosphorus oxychloride.[19] Routine techniques also involve cyclization of substituted 2-fluorobenzonitriles or 2-aminobenzonitriles with guanidine carbonate, dicyandiamide, or chloroformamidine hydrochloride to give 2,4-diaminoquinazolines.[20]

Hynes and his group developed a direct method for synthesis of 2,4-diaminoquinazolines **10** from substituted 2-fluorobenzonitriles **8** and guanidine carbonate **9**. The reaction is operated at elevated temperature with dimethylacetamide as solvent to give the products in good to excellent yields (*Scheme 5.2.3.*).[21]



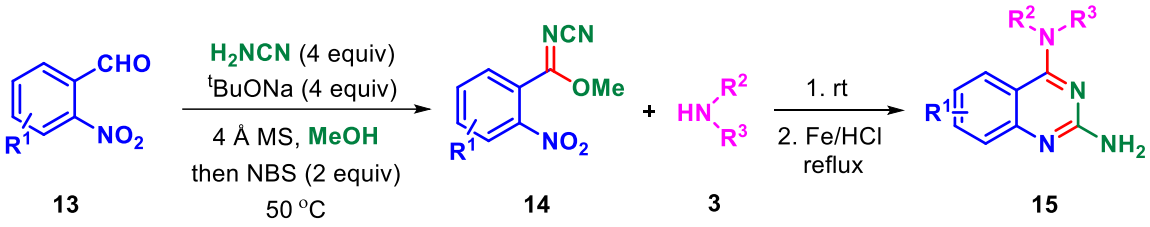
Scheme 5.2.3. *Direct synthesis of 2,4-diaminoquinazolines from 2-fluorobenzonitriles.*

Qiao and his group later reported another efficient synthetic route for 2,4-diaminoquinazolines **10** from substituted 2-bromobenzonitriles **11** and guanidine hydrochloride **12**. This economical and operationally simple copper-catalyzed reaction undergoes Ullmann-type cross coupling to give the products in good yields (*Scheme 5.2.4.*).[22]



Scheme 5.2.4. *Direct synthesis of 2,4-diaminoquinazolines from 2-bromobenzonitriles.*

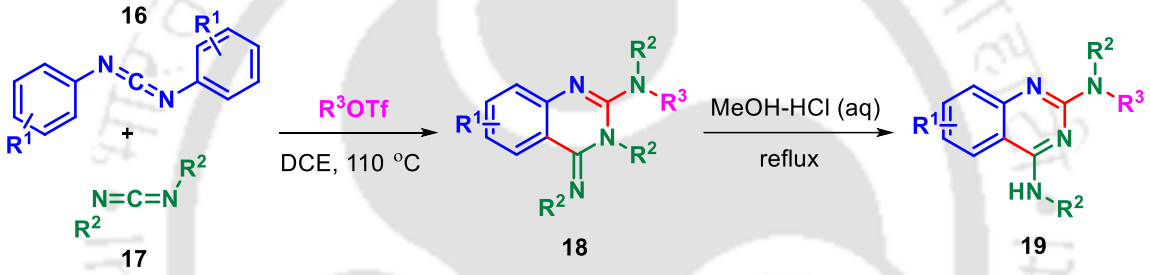
He and his co-workers disclosed a two-step protocol for the synthesis of N^4-substituted 2,4-diaminoquinazolines **15** with *ortho*-nitroaldehyde **13** as the starting precursor. The method involves cyanoimidation of *ortho*-nitroaldehyde to give *N*-cyano-2-nitrobenzimidate **14**, followed by condensation of cyanoimidate-amine and reductive cyclization in iron-HCl system furnishing the aminated quinazolines in good yields (*Scheme 5.2.5.*).[23]



R^1= H, Cl, Br, OMe; R^2= alkyl
R^3= H, alkyl

Scheme 5.2.5. *Two-step synthesis of N^4-substituted 2,4-diaminoquinazolines.*

Xi and co-workers also reported a triflate triggered coupling of carbodiimides to access 2,4-diaminoquinazolines **19**. This metal-free, one pot and two-step protocol proceeds *via* alkyl triflate induced intermolecular cyclization of two carbodiimides (**16** and **17**) to provide 2-amino-4-imino-quinazoline **18**, which after hydrolysis can be easily transformed to 2,4-diaminoquinazolines in high yields (*Scheme 5.2.6.*).[24]



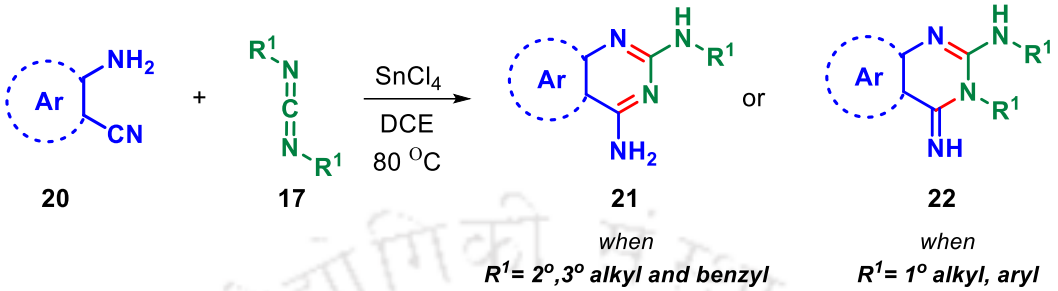
R^1= H, F, Cl, CF_3, Me, OMe; R^2= alkyl
R^3= Me, Et

Scheme 5.2.6. *Alkyl triflate induced synthesis of 2,4-diaminoquinazolines from carbodiimides.*

5.3. Present Work

Since 2,4-diaminoquinazolines as well as 2-amino-4-iminoquinazolines occur as core unit in various natural products and pharmaceuticals, development of strategies for their synthesis is of prime interest for synthetic chemists. While there are many methods available for synthesis of 2-aminoquinazolines and 4-aminoquinazolines in the literature, it is very limited for 2,4-diaminoquinazolines. Also as evident from the previous reports, it was observed that although the few existing methods provide access to 2,4-diaminoquinazolines, their applications are limited by a lack of suitable substrates, poor substitution diversity, and the requirement for harsh reaction conditions. Accordingly, there is a considerable need in developing newer paths for synthesis of 2,4-diaminoquinazolines. Thus, we envisioned to develop a more practical and economic route utilizing carbodiimides and 2-aminobenzonitriles as the initial architectonic

precursors for the synthesis of 2,4-diaminoquinazolines. This chapter demonstrates a Lewis acid mediated substrate controlled synthesis of substituted 2,4-diaminoquinazolines from 2-aminobenzonitriles and carbodiimides. Furthermore, 2-amino-4-iminoquinazoline derivatives are selectively formed with aryl and primary alkyl substituted carbodiimides.



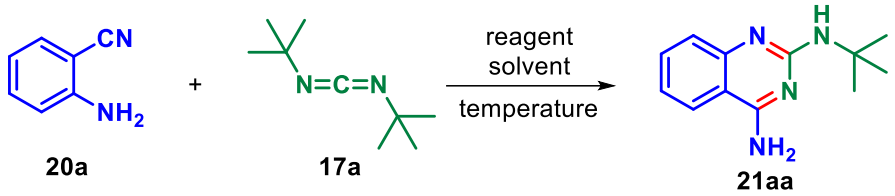
Scheme 5.3.1. *Substrate-controlled synthesis of 2-amino-4-iminoquinazolines and 2,4-diaminoquinazolines.*

5.4. Results and Discussion

5.4.1. Optimization of the Reaction

Initially, we commenced our preliminary investigation by treating di-*tert*-butylmethanediimine (**17a**) with 2-aminobenzonitrile (2**0a**) in the presence of 1.2 equiv of $FeCl_3$ in DCM at room temperature (*Table 5.4.1.1.*, entry 1). However, no product was obtained even after continuing it up to 24 h. Next, we switched the solvent to DCE, but the reaction failed to take place (*Table 5.4.1.1.*, entry 2). To our delight, the reaction occurred to deliver the product N^2-(*tert*-butyl)quinazoline-2,4-diamine **21aa** in 48% yield when the temperature was raised to 80 °C (*Table 5.4.1.1.*, entry 3). Encouraged by the results, the reaction was performed in a series of non-polar as well as polar solvents like toluene, acetonitrile and DMF. While toluene produced similar yield of 50% (*Table 5.4.1.1.*, entry 4), the reaction didn't proceed at all with moderately and highly polar solvents (*Table 5.4.1.1.*, entries 5 and 6). The reaction was then screened in a set of different Lewis acids. Metal triflates like $In(OTf)_3$, $Bi(OTf)_3$, $Cu(OTf)_2$ and $Zn(OTf)_2$ (*Table 5.4.1.1.*, entries 8-11) gave the desired product with inferior yield, whereas metal chloride $InCl_3$ also gave the product with a low yield of 23% (*Table 5.4.1.1.*, entry 7). Fortunately, when the reaction was performed with 1.2 equiv of $SnCl_4$ in DCE at 80 °C, the desired product was obtained with an excellent yield of 86% (*Table 5.4.1.1.*, entry 12). The reaction was also optimized by varying the reagent load, where increasing it to 2 equiv furnished similar yield of 85% (*Table 5.4.1.1.*, entry 14), decreasing it to 0.5 equiv dropped the yield to 50% (*Table 5.4.1.1.*, entry 13). On the other hand, non–metal Lewis acids

Table 5.4.1.1.: *Optimization of the reaction*[a]



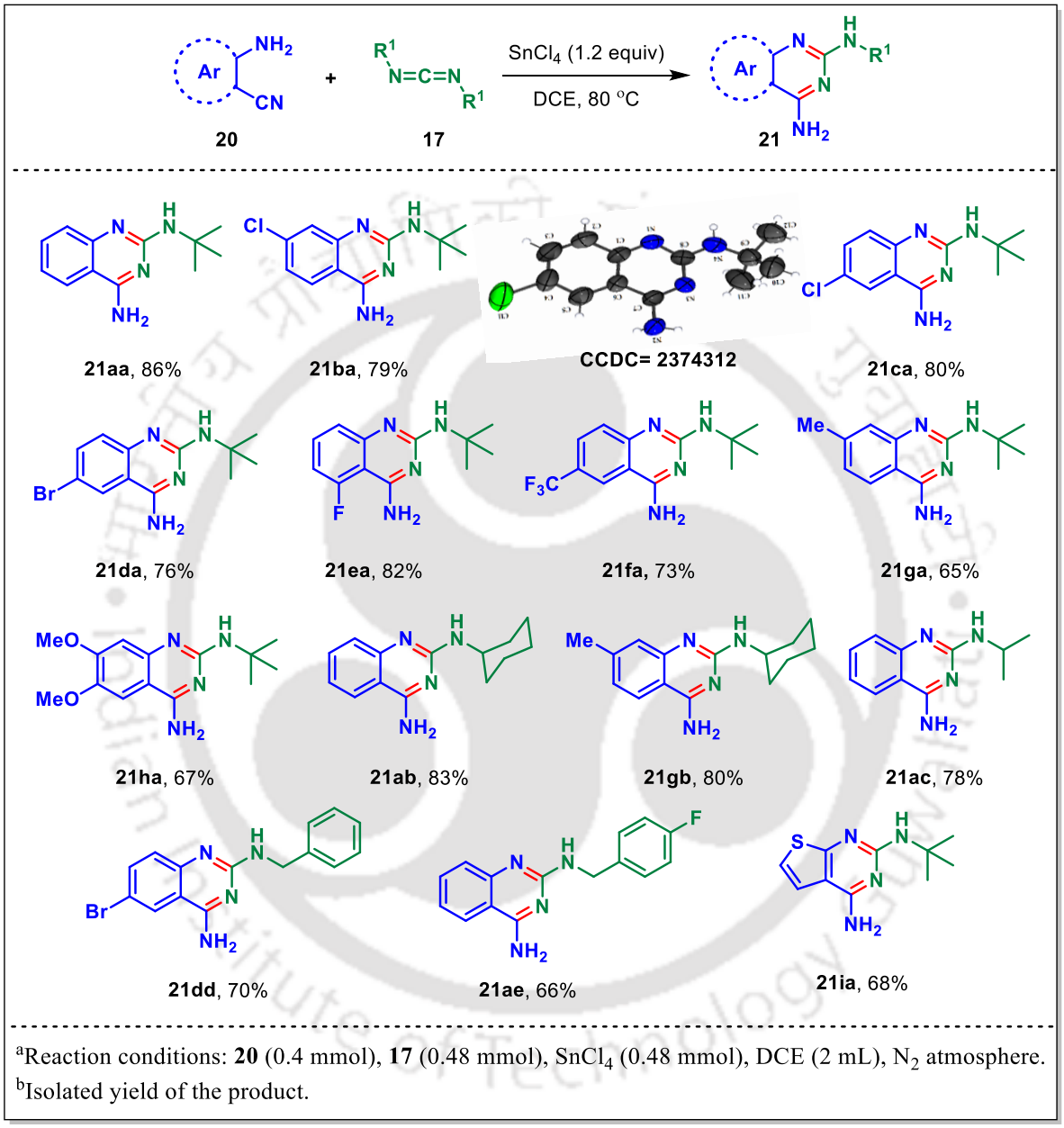
entry	reagent (equiv)	solvent	temp/°C	%yield[b]
1.	$FeCl_3$ (1.2)	DCM	25	-
2.	$FeCl_3$ (1.2)	DCE	25	-
3.	$FeCl_3$ (1.2)	DCE	80	48
4.	$FeCl_3$ (1.2)	toluene	110	50
5.	$FeCl_3$ (1.2)	CH_3CN	80	-
6.	$FeCl_3$ (1.2)	DMF	100	-
7.	$InCl_3$ (0.5)	DCE	80	23
8.	$In(OTf)_3$ (0.5)	DCE	80	13
9.	$Bi(OTf)_3$ (0.5)	DCE	80	trace
10.	$Cu(OTf)_2$ (0.2)	DCE	80	12
11.	$Zn(OTf)_2$ (0.2)	DCE	80	20
12.	**$SnCl_4$ (1.2)**	**DCE**	**80**	**86**
13.	$SnCl_4$ (0.5)	DCE	80	50
14.	$SnCl_4$ (2)	DCE	80	85
15.	$BF_3{\cdot}OEt_2$ (1.2)	DCE	25	-
16.	TfOH (2)	DCE	25	-
17.	*p*-TsOH (2)	DCE	25	-

[a]All the reactions were carried out in (0.4 mmol) **20a**, (0.48 mmol) **17a** in 2.0 mL solvent, N_2 atmosphere, [b]Isolated yields.

like $BF_3{\cdot}OEt_2$ and Brønsted acids such as TfOH and *p*-TsOH in DCE at room temperature was also found to be ineffective (*Table 5.4.1.1.*, entries 15-17). Based on our observation it was concluded that 1.2 equiv of $SnCl_4$ in DCE at 80 °C are the optimum conditions for the annulation.

5.4.2. Substrate Scope

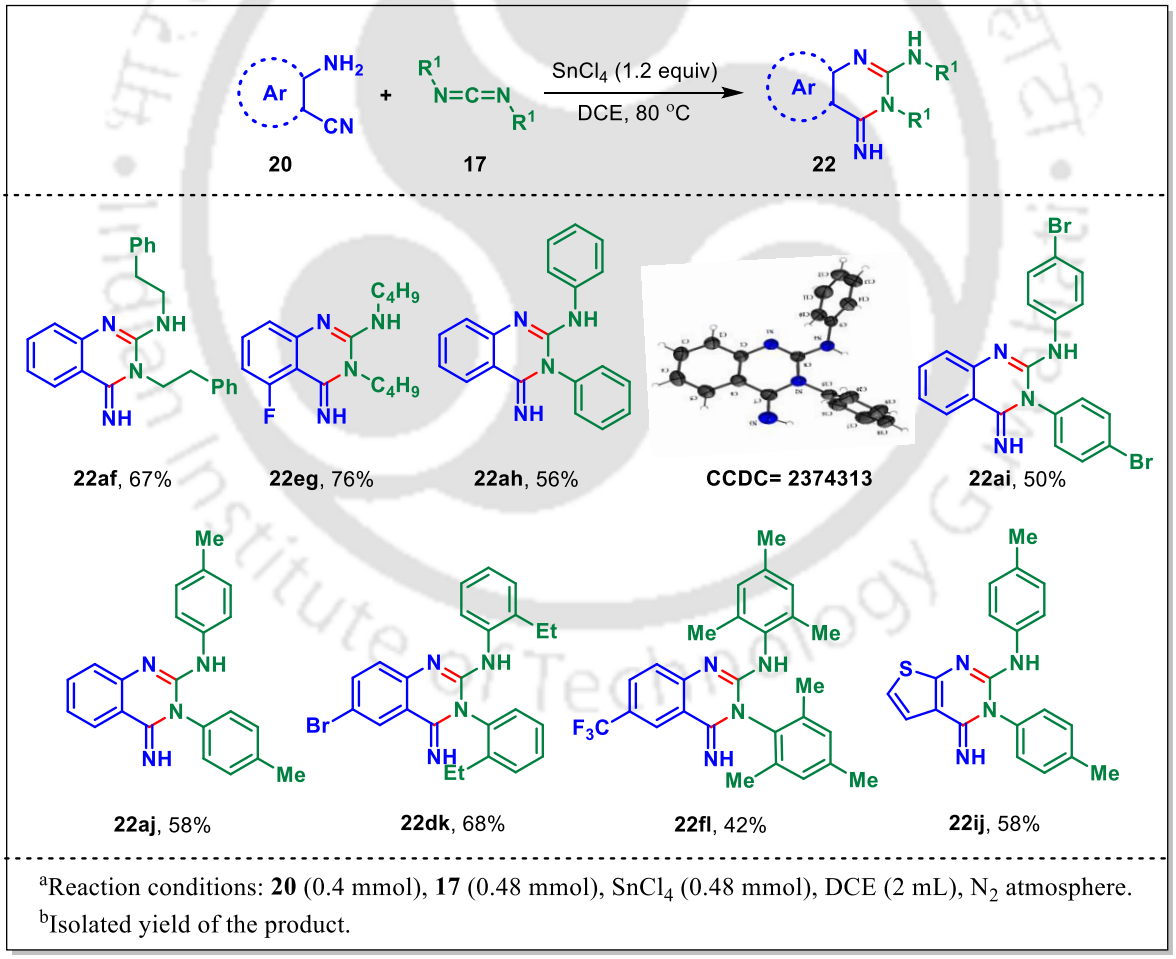
With the optimized reaction conditions in hand, we set out to explore the compatibility and scope of the reaction with carbodiimides and 2-aminobenzonitrile derivatives as depicted in *Scheme 5.4.2.1.* Initially, a series of differently substituted 2-aminobenzonitriles with various



Scheme 5.4.2.1. *Scope for the synthesis of substituted 2,4-diaminoquinazolines.*[a,b]

electron donating as well as electron withdrawing groups was successfully used in this tandem reaction. It was observed that the transformation was very general and also a pronounced dependence of the product yield on the electronic or steric effect of the substituent or its position in the benzene ring of 2-aminobenzonitriles was not observed. The reaction of 2-aminobenzonitriles (**20b**-**20e**) having moderately electron-withdrawing halo substituents such as 4-Cl, 5-Cl, 5-Br and 6-F with di-*tert*-butylmethanediimine furnished the corresponding

products **21ba-21ea** in good yields up to 82%. On the other hand, 2-aminobenzonitrile with strongly electron-withdrawing group -CF_3 at 5–position was well tolerated providing the desired product **21fa** with 73% yield. 2-Aminobenzonitriles (**20g** and **20h**) with electron-donating substituents such as 4-methyl and 4,5-dimethoxy group gave the corresponding products **21ga** and **21ha** with moderate yields. Furthermore, the protocol was checked with other alkyl carbodiimides such as di-cyclohexyl and di-*iso*-butyl carbodiimide derivatives (**17b** and **17c**) with substituted 2-aminobenzonitriles, which also afforded the corresponding diaminated products **21ab**, **21gb** and **21ac** in good yields. The reaction of di-benzylcarbodiimides also furnished the substituted 2,4-diaminoquinazolines **21ae** and **21dd** with 66% and 70% yields, respectively. We attempted to expand the reaction scope to include 2-aminothiophene-3-carbonitrile (**20i**) (a product of the Gewald reaction) as an aminonitrile component. Excitingly, the reaction underwent smoothly with di-*tert*-butylcarbodiimide to give the thiophene unit installed substrate **21ia** with a moderate yield of 68%.



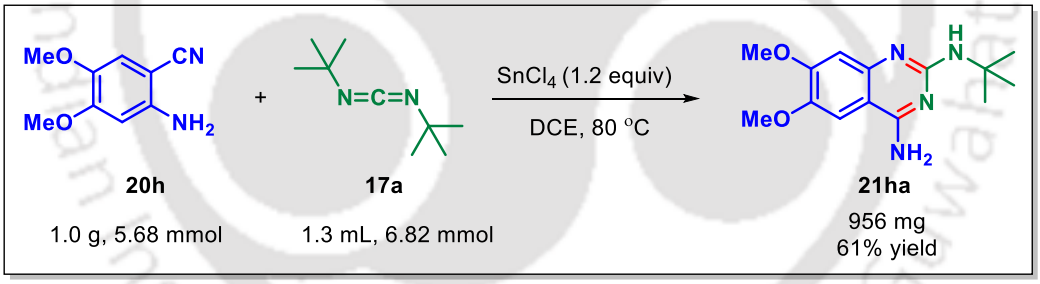
[a]Reaction conditions: **20** (0.4 mmol), **17** (0.48 mmol), $SnCl_4$ (0.48 mmol), DCE (2 mL), N_2 atmosphere.
[b]Isolated yield of the product.

Scheme 5.4.2.2. *Scope for the synthesis of substituted 2-amino-4-iminoquinazolines.*[a,b]

To further extend the substrate scope, different substituted carbodiimides were also employed in the reaction as depicted in *Scheme 5.4.2.2*. When the reaction was tested with primary alkyl

substituted carbodiimides (**17f** and **17g**), interestingly the unexpected product 2-amino-4-iminoquinazoline (**22af** and **22eg**) was obtained instead of the aromatized products in 67% and 76% isolated yields, respectively. Besides, we examined various aryl carbodiimides to assess the diversity of our protocol. However, when switched to *N*,*N*′- phenylcarbodiimide (**17h**) selective formation of 2-amino-4-iminoquinazoline (**22ah**) was observed. The substrates containing both electron-donating (e.g., −CH_3, −C_2H_5) and moderately electron-withdrawing (e.g., −Br) groups on the aryl ring of the carbodiimide were efficiently reacted with different substituted 2-aminobenzonitrile derivatives to give the corresponding products **22ai**, **22aj**, **22dk** and **22fl** in 42-68% yields. Moreover, *N*,*N*′-*p*-tolylcarbodiimide also reacted with 2-aminothiophene-3-carbonitrile under the standard set of reaction conditions to afford the desired product **22ij** with 58% yield. The reaction exhibits switchable selectivity in product formation depending on the nature of the substituents of the carbodiimides used. The structure of the compounds was determined by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, mass spectrometry and finally by X-ray crystallographic analysis of the compounds **21ca** and **22ah**.

A scale up experiment was also performed using 2-amino-4,5-dimethoxybenzonitrile **20h** (1 g, 5.68 mmol) and di-*tert*-butylmethanediimine **17a** (1.3 mL, 6.82 mmol) under the standard conditions to provide 61% (956 mg) yield of the corresponding product **21ha** (*Scheme 5.4.2.3.*).

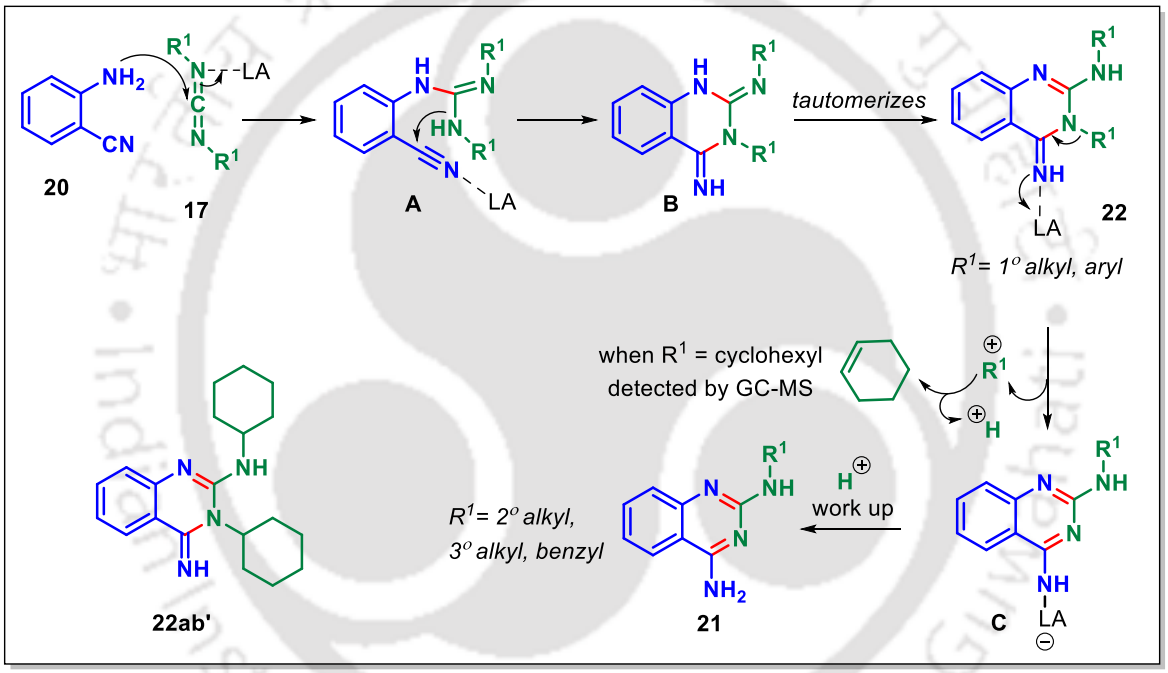


Scheme 5.4.2.3. *Gram-scale synthesis.*

5.4.3. Plausible Mechanism

A plausible mechanism for the reaction is depicted in *Scheme 5.4.3.1.* Initially, Lewis acid activates the carbodiimide **17** *via* coordination for the nucleophilic attack of 2-aminobenzonitrile **20** leading to adduct **A**. The adduct **A** subsequently undergoes an intramolecular nucleophilic attack by amine to the activated cyano group and cyclizes into intermediate **B**. The intermediate **B** tautomerizes to form 2-amino-4-iminoquinazoline **22**, which is the final product obtained for aryl/primary alkyl substituted carbodiimides. However, for secondary, tertiary and benzyl substituted carbodiimides, the reaction continues under the influence of Lewis acidic conditions. Elimination of R^1 substituent takes place that leads to the formation of aromatized intermediate **C**, which after work up gives the final product **21**. Also,

it may be noted that the intermediate carbocation R^1 may be further converted into corresponding alkenes or alcohols. GC-MS analyses of the crude reaction mixture of the substrate **21ab** where cyclohexyl group was present in carbodiimide indicated the formation of cyclohexene. It is worth mentioning that the intermediate **22ab′** where R^1 is cyclohexyl group was isolated, when the reaction was quenched after 1 h and characterized by spectroscopic methods. The intermediate, *N*,3-dicyclohexyl-4-imino-3,4-dihydroquinazolin-2-amine (**22ab′**) on further being subjected to standard reaction conditions furnished the corresponding product **21ab** with 88% yield. From the mechanism, it is evident that Lewis acid is coordinated to the nitrogen-containing species until the work-up process. Therefore, a stoichiometric amount of Lewis acid is used in the reaction process.

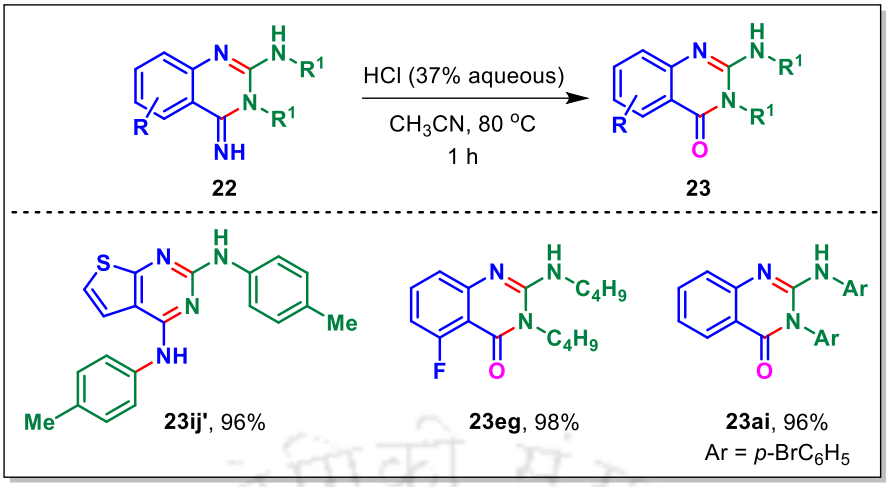


Scheme 5.4.3.1. *Plausible reaction mechanism.*

5.5. Post-synthetic Applications

5.5.1. Synthesis of 2-Aminoquinazolin-4(3*H*)-ones

The utility of the methodology can be further extended towards the synthesis of 2-aminoquinazolin-4(3*H*)-ones. Hydrolysis of compounds **22eg** and **22ai** with conc. HCl in acetonitrile at 80 °C resulted in the formation of its oxo-analogue 2-aminoquinazolin-4(3*H*)-ones **23eg** and **23aj** with 98% and 96% yields, respectively (*Scheme 5.5.1.1.*). Interestingly, treatment of compound **22ij** with conc. HCl in acetonitrile at 80 °C gave the rearranged product

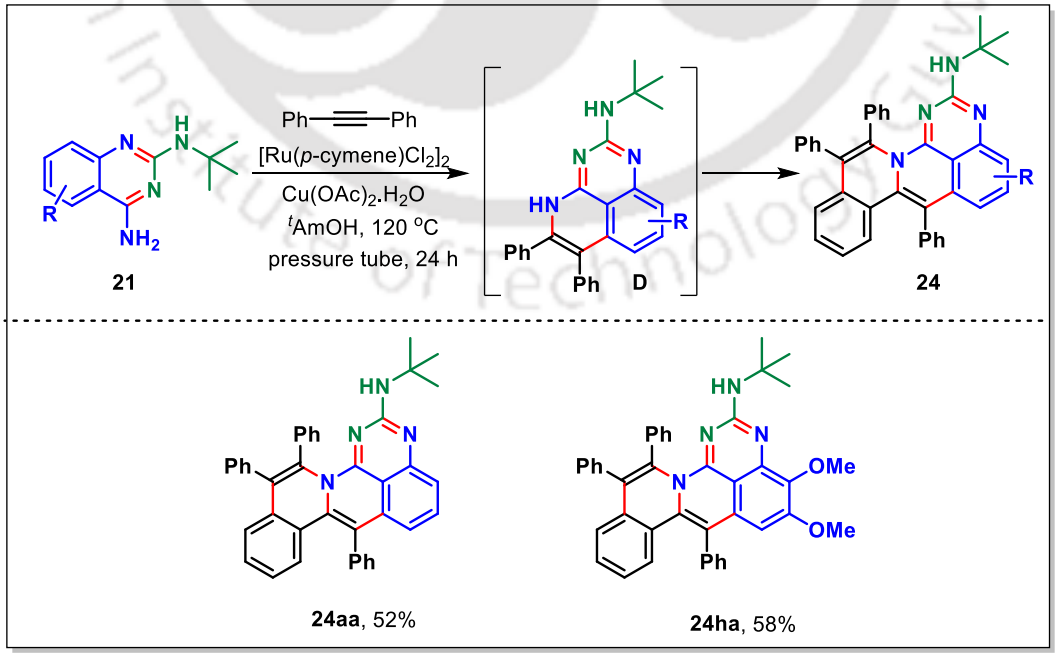


Scheme 5.5.1.1. *Scope for the synthesis of 2-aminoquinazolin-4(3H)-ones.*

23ij′ instead of its oxo-analogue. The reaction follows Dimroth type rearrangement pathway under acidic conditions.[25]

5.5.2. Synthesis of Pentacyclic Annulated Compounds

The methodology can be further extended towards the synthesis of π-conjugated nitrogen containing heterocyclic compounds with good yields. The products **21** undergo unprecedented two-fold C–H, N annulation in the presence of a Ru(II) catalyst giving annulated products **24** (*Scheme 5.5.2.1.*). This tandem reaction proceeds with initial selective C–H, N annulation at the phenyl ring of **21** with diphenylacetylene, followed by a subsequent annulation of the *in situ* generated intermediate **D** with another molecule of diphenylacetylene to give the highly conjugated pentacyclic product.



Scheme 5.5.2.1. *Scope for the synthesis of pentacyclic annulated compounds.*

5.6. Conclusion

In summary, we have developed an efficient Lewis acid promoted annulation of carbodiimides with 2-aminobenzonitrile for the synthesis of substituted 2,4-diaminoquinazolines and 2-amino-4-iminoquinazolines in good to excellent yields. This cyclization accomplishes the selective synthesis of two nitrogen heterocycles depending on the substituents of the carbodiimide moiety. The protocol demonstrates characteristics involving readily available starting materials, relatively wide substrate scope, high reaction efficiency, and readily scaled up. The methodology can be extended towards the synthesis of 2-aminoquinazolin-4(3*H*)-one analogues as well as pentacyclic annulated derivatives.

5.7. Experimental Section

5.7.1. General Information and Instrumentation

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF254 (0.25 mm). Melting points were recorded in an open capillary tube and are uncorrected. Fourier transform-infra red (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 500 MHz and 400 MHz) or $^{13}C\{^{1}H\}$ (100 MHz, 150 MHz and 125 MHz) NMR. $^{19}F\{^{1}H\}$ NMR spectra were recorded at 470 MHz and chemical shifts are relative to hexafluorobenzene in $CDCl_3$ at δ = -164.9 ppm (external reference). Chemical shifts (δ) are reported in ppm with abbreviations, s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, dd = doublet of doublets, m = multiplet, bs = broad singlet and spin-spin coupling constants (*J*) are given in Hz. HRMS spectra were recorded using Q-TOF and microTOF-Q II mass spectrometer.

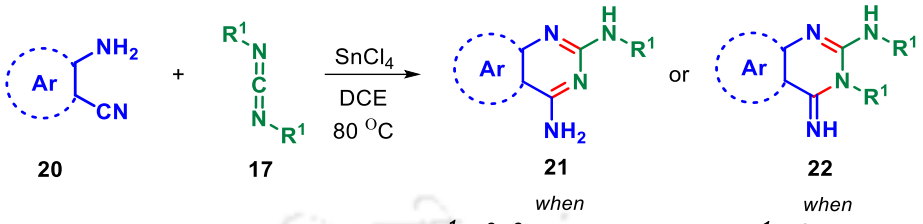
5.7.2. Reaction Procedure

5.7.2.1. Experimental Procedure for Synthesis of Carbodiimides

The starting materials dibenzylcarbodiimide (**17d**), di(n-butyl)carbodiimide (**17g**), diphenylcarbodiimide (**17h**), di(*p*-bromophenyl)carbodiimide (**17i**), di(*p*-tolyl)carbodiimide (**17j**), di(*o*-ethylphenyl)carbodiimide (**17k**) and dimesitylcarbodiimide (**17l**) were prepared according to the literature reported procedures and confirmed by comparison to the reported characterization data.[26-29] The

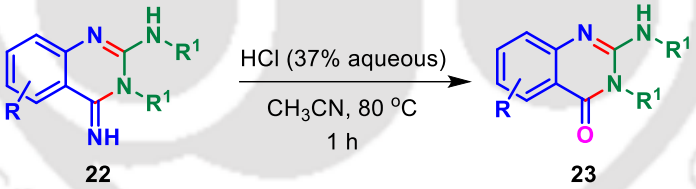
remaining starting materials (**17e)** and (**17f**) were also prepared following the literature reports[26].

5.7.2.2. General Procedure for the Synthesis of Compounds 21aa-21ia, 21ab, 21ac, 21ae, 21dd, 21gb, 22af, 22ah-22aj, 22dk, 22eg, 22fl and 22ij



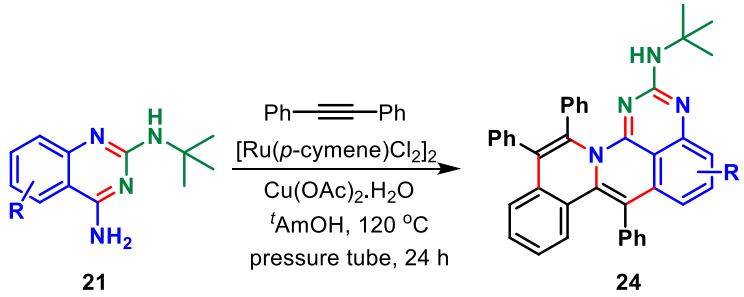
To a solution of carbodiimide **17** (0.48 mmol, 1.2 equiv) and 2-aminobenzonitrile derivative **20** (0.4 mmol, 1 equiv) in 1,2-dichloroethane (2 mL) was added $SnCl_4$ (0.72 mmol, 1.2 equiv) at 0 °C under nitrogen atmosphere. The reaction was then heated in an oil bath at 80 °C. The progress of the reaction was monitored through TLC. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel to give the corresponding product **21** or **22**.

5.7.2.3. General Procedure for the Synthesis of Compounds 23eg, 23ai and 23ij′



To a stirring solution of 2-amino-4-iminoquinazoline **22** (0.1 mmol, 1 equiv) in acetonitrile (1 mL) conc. HCl (37% aqueous, 25 µL) was added dropwise at room temperature. The reaction was then heated in an oil bath at 80 °C for 1 h. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 10 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel to give the corresponding product **23**.

5.7.2.4. General Procedure for the Synthesis of Compounds 24aa and 24ha



To an oven-dried pressure tube containing a magnetic bar was added 2,4-diaminoquinazoline derivative **21** (0.2 mmol, 1 equiv), diphenylacetylene derivative (0.4 mmol, 2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (0.01 mmol, 0.05 equiv), $Cu(OAc)_2.H_2O$ (0.02 mmol, 0.1 equiv), and ^tAmOH. The reaction mixture was stirred in an oil bath preheated at 120 °C for 24 h. After completion of the reaction (monitored by TLC analysis), the reaction mixture was cooled to ambient temperature, filtered through a small plug of Celite and then washed with ethyl acetate (3 × 10 mL). The solvents were evaporated under reduced pressure and the crude material was purified using column chromatography on silica gel (n-hexane/EtOAc eluent) to give the desired product **24**.

5.7.2.5. Experimental Procedure for the Gram-Scale Synthesis of 21ha

To a solution of di-*tert*-butylmethanediimine (**17a**) (1.3 mL, 6.82 mmol) and 2-amino-4,5-dimethoxybenzonitrile (**20h**) (1 g, 5.68 mmol) in 1,2-dichloroethane (12 mL) was added $SnCl_4$ (0.8 mL, 6.82 mmol) at 0 ^oC under nitrogen atmosphere. The reaction was then refluxed at 80 ^oC. The progress of the reaction was monitored through TLC. After completion of the reaction, the solvent was removed under reduced pressure and diluted with saturated $NaHCO_3$ solution. Then the organic layer was extracted with EtOAc (3 x 30 mL). The organic layer was further washed with brine solution for 2-3 times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in rotary evaporator. The crude mixture was subjected to column chromatography over silica gel with EtOAc and hexane as eluents to give the corresponding product **21ha** with 61% yield (956 mg, brown gum).

5.7.3. Crystallographic Description

Single crystals of compounds **21ca** and **22ah** was obtained by slow evaporation of ethyl acetate and hexane solution (1:9). Bruker APEX-II CCD diffractometer was used to collect the intensity data. The instrument is equipped with a fine focus 1.75 kW sealed tube Mo Kα radiation (λ = 0.71073 Å) at 297 K. The data acquisition was done with the APEX4 software. APEX4 software was implemented for data integration and reduction. Multi-scan empirical absorption corrections were employed to the data using the program APEX4. Structures were

solved by direct methods using SHELXL-2019 and refined with full-matrix least-squares on F2 using SHELXL-2019/1.[a] Structural illustrations have been drawn with ORTEP-3 for Windows.[b] The detailed data collection and structure refinement are summarized in *Tables 5.7.3.1.* and *5.7.3.2.*

a. G. M. Sheldrick, SHELXS-2014, Program for the crystal structure solution; University of Göttingen: Göttingen, Germany, 2014.

b. L. J. Farrugia, XRDIFF: simulation of X-ray diffraction patterns, *J. Appl. Crystallogr*. **1997**, *30*, 565.

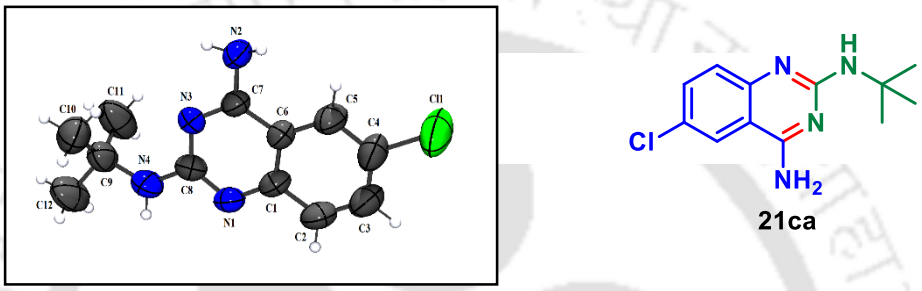
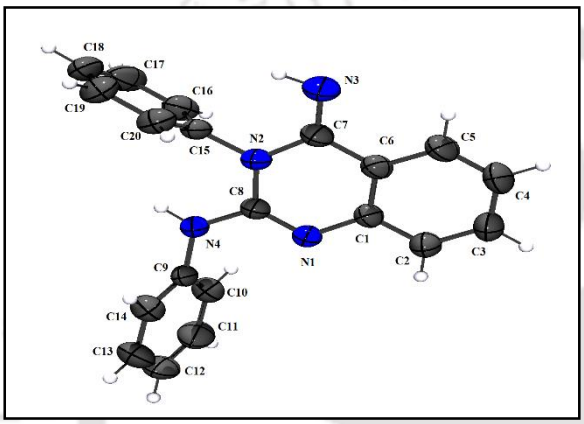


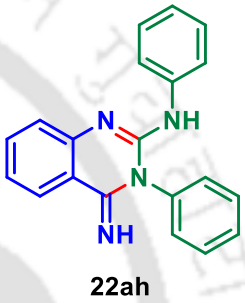
Figure 5.7.3.1. *ORTEP diagram of compound (**21ca**) with 50% probability.*

Table 5.7.3.1. Crystal parameters of compound **21ca**

	CCDC 2374312
Formula	$C_{12}H_{15}ClN_4$
Formula weight	250.73
T/K	295
Crystal system	Trigonal
Space group	R-3
a/Å	24.5851 (18)
b/Å	24.5851 (18)
c/Å	13.1673 (15)
α/°	90
β/°	90
γ/°	120
V/Å^3	6892.4 (13)
Z	18
Abs. Coeff./mm^{-1}	0.236

Abs. Correction	multi-scan
GOF on F^2	1.016
Final *R* indices [$I > 2\sigma(I)$]	*R1* = 0.0904
	wR2 = 0.1992
R indices [all data]	*R1* = 0.1852
	wR2 = 0.2642





22ah

Figure 5.7.3.2. *ORTEP diagram of compound (**22ah**) with 50% probability.*

Table 5.7.3.2. Crystal parameters of compound **22ah**

	CCDC 2374313
Formula	$C_{20}H_{16}N_4$
Formula weight	312.37
T/K	297
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.3381 (12)
b/Å	9.1140 (10)
c/Å	15.7488 (17)
α/°	90
β/°	94.520 (3)
γ/°	90

V/Å^3	1622.3 (3)
Z	4
Abs. Coeff./mm^{-1}	0.078
Abs. Correction	multi-scan
GOF on F^2	1.058
Final R indices [I> 2σ(I)]	$R1$ = 0.0437 $wR2$ = 0.1058
R indices [all data]	$R1$ = 0.0583 $wR2$ = 0.1215

5.8. References

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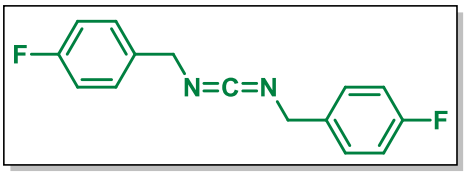
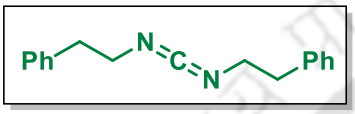
5.9. Characterisation Data

Bis(4-fluorobenzyl)methanediimine (17e):



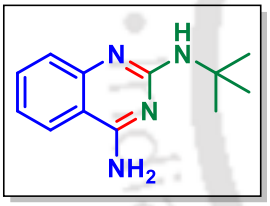
Yellow liquid; R_f (hexane/EtOAc, 100:1) 0.50; yield 760 mg, 68%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 8.4 and 5.4 Hz, 4 H), 6.99 (t, *J* = 8.4 Hz, 4 H), 4.25 (s, 4 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4 (d, *J* = 244.4 Hz), 141.4, 134.3 (d, *J* = 3.2 Hz), 129.4 (d, *J* = 8.0 Hz), 115.6 (d, *J* = 21.4 Hz), 49.81. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -117.82 (s, -F).

Diphenethylmethanediimine (17f):



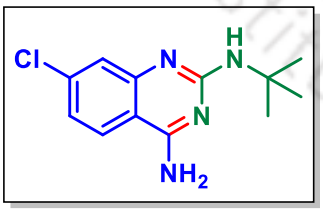
Yellow liquid; R_f (hexane/EtOAc, 100:1) 0.50; yield 560 mg, 65%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.5 Hz, 4 H), 7.13–7.10 (m, 2 H), 7.09–7.07 (m, 4 H), 3.21 (t, *J* = 7.0 Hz, 4 H), 2.65 (t, *J* = 7.0 Hz, 4 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 140.4, 139.0, 129.0, 128.6, 126.7, 47.8, 37.6.

***N*^{2}-(*tert*-butyl)quinazoline-2,4-diamine (21aa):**



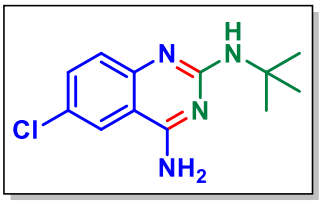
Pale yellow gum; R_f (hexane/EtOAc, 1:1) 0.50; yield 74 mg, 86%; IR (KBr, neat) ν 3327, 2981, 1643, 1567, 1491, 1422, 1210, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2 H), 7.43 (d, *J* = 8.6 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 5.61 (s, 2 H), 5.03 (s, 1 H), 1.46 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.8, 159.2, 152.5, 133.2, 125.8, 122.1, 121.1, 110.2, 51.0, 29.5. HRMS (ESI) calcd. for $C_{12}H_{17}N_4$ $(M + H)^+$ 217.1448, found 217.1451.

***N*^{2}-(*tert*-butyl)-7-chloroquinazoline-2,4-diamine (21ba):**



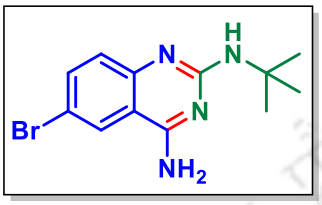
Off white solid; R_f (hexane/EtOAc, 3:1) 0.50; mp 132-134 °C; yield 79 mg, 79%; IR (KBr, neat) ν 3333, 2963, 1616, 1566, 1276, 1210, 829, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.37 (m, 2 H), 6.92 (dd, *J* = 8.7 and 2.1 Hz, 1 H), 5.68 (s, 2 H), 5.08 (s, 1 H), 1.43 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.5, 159.7, 153.6, 139.0, 124.9, 123.4, 121.6, 108.7, 51.1, 29.4. HRMS (ESI) calcd. for $C_{12}H_{16}ClN_4$ $(M + H)^+$ 251.1058, found 251.1059.

***N*^{2}-(*tert*-butyl)-6-chloroquinazoline-2,4-diamine (21ca):**



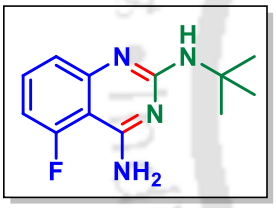
Off white solid; R_f (hexane/EtOAc, 2:1) 0.50; mp 136-138 °C; yield 80 mg, 80%; IR (KBr, neat) ν 3333, 2965, 1616, 1566, 1271, 1220, 829, 756 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2 H), 7.37 (d, *J* = 8.9 Hz, 1 H), 5.28 (s, 2 H), 4.98 (s, 1 H), 1.47 (s, 9 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 160.8, 159.3, 151.4, 133.8, 127.7, 125.9, 121.3, 110.7, 51.2, 29.5. HRMS (ESI) calcd. for $C_{12}H_{16}ClN_4$ $(M + H)^+$ 251.1058, found 251.1060.

6-Bromo-N^2-(*tert*-butyl)quinazoline-2,4-diamine (23da):



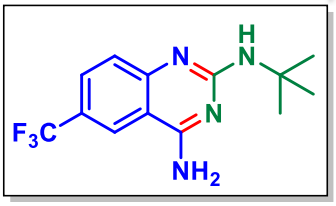
Off white solid; R_f (hexane/EtOAc, 7:3) 0.50; mp 144-146 °C; yield 89 mg, 76%; IR (KBr, neat) ν 3336, 2964, 1613, 1564, 1475, 1276, 1210, 828, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.58 (d, *J* = 8.6 Hz, 1 H), 7.31 (d, *J* = 8.6 Hz, 1 H), 5.27 (s, 2 H), 5.01 (s, 1 H), 1.47 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.7, 159.3, 151.6, 136.4, 127.9, 124.5, 113.2, 111.4, 51.2, 29.5. HRMS (ESI) calcd. for $C_{12}H_{16}BrN_4$ $(M + H)^+$ 295.0553, found 295.0548

N^2-(*tert*-butyl)-5-fluoroquinazoline-2,4-diamine (21ea):



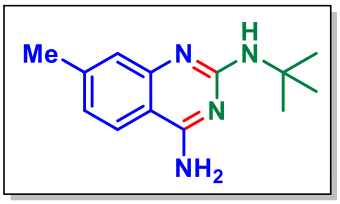
Brown liquid; R_f (hexane/EtOAc, 4:1) 0.50; yield 77 mg, 82%; IR (KBr, neat) ν 3309, 2961, 1606, 1564, 1391, 1208, 1058, 812, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (q, *J* = 7.7 Hz, 1 H), 7.18 (d, *J* = 7.7 Hz, 1 H), 6.66 (dd, *J* = 12.2 and 7.7 Hz, 1 H), 5.87 (s, 2 H), 4.98 (s, 1 H), 1.47 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.8 (d, *J* = 248.1 Hz), 159.6 (d, *J* = 4.1 Hz), 159.5, 155.0, 132.5 (d, *J* = 11.8 Hz), 121.5 (d, *J* = 1.2 Hz), 105.6 (d, *J* = 23.2 Hz), 100.4 (d, *J* = 10.5 Hz), 50.8, 29.2. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -116.59 (s, -F). HRMS (ESI) calcd. for $C_{12}H_{16}FN_4$ $(M + H)^+$ 235.1354, found 235.1359.

N^2-(*tert*-butyl)-6-(trifluoromethyl)quinazoline-2,4-diamine (21fa):



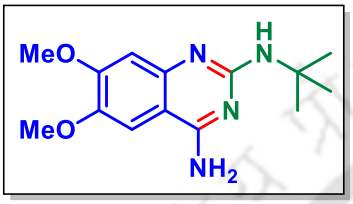
White gum; R_f (hexane/EtOAc, 4:1) 0.50; yield 83 mg, 73%; IR (KBr, neat) ν 3327, 2925, 1634, 1574, 1440, 1317, 1283, 1118, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.68 (d, *J* = 8.1 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 5.44 (s, 2 H), 5.09 (s, 1 H), 1.48 (s, 9 H).$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.8, 160.3, 154.8, 129.1 (q, *J* = 3.1 Hz), 126.8, 124.5 (q, *J* = 269.7 Hz), 122.5 (q, *J* = 32.1 Hz), 120.1 (q, *J* = 4.2 Hz), 109.3, 51.4, 29.5. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -64.83 (s, -F). HRMS (ESI) calcd. for $C_{13}H_{16}F_3N_4$ $(M + H)^+$ 285.1322, found 285.1325.

N^2-(*tert*-butyl)-7-methylquinazoline-2,4-diamine (21ga):



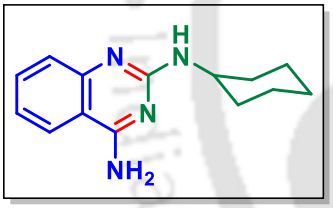
Red gum; R_f (hexane/EtOAc, 7:3) 0.50; yield 60 mg, 65%; IR (KBr, neat) ν 3328, 2961, 1621, 1566, 1497, 1427, 1209, 877, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 1 H), 7.24 (s, 1 H), 6.87 (d, *J* = 8.2 Hz, 1 H), 5.41 (s, 2 H), 5.07 (s, 1 H), 2.39 (s, 3 H), 1.47 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.6, 159.2, 152.5, 143.9, 125.1, 123.2, 121.8, 108.1, 51.1, 29.6, 22.1. HRMS (ESI) calcd. for $C_{13}H_{19}N_4$ $(M + H)^+$ 231.1604, found 231.1604.

N^2-(*tert*-butyl)-6,7-dimethoxyquinazoline-2,4-diamine (21ha):



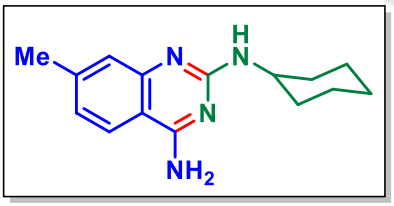
Brown gum; R_f (hexane/EtOAc, 1:1) 0.50; yield 74 mg, 67%; IR (KBr, neat) ν 3378, 2961, 1625, 1573, 1496, 1206, 1001, 789, 735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.87 (s, 1 H), 6.82 (s, 1 H), 5.47 (s, 2 H), 5.27 (s, 1 H), 3.93 (s, 3 H), 3.88 (s, 3 H), 1.46 (s, 9 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 160.7, 158.1, 155.4, 148.0, 145.9, 104.6, 102.8, 101.9, 56.4, 56.3, 51.3, 29.6. HRMS (ESI) calcd. for $C_{14}H_{21}N_4O_2$ $(M + H)^+$ 277.1659, found 277.1669.

N^2-cyclohexylquinazoline-2,4-diamine (21ab):



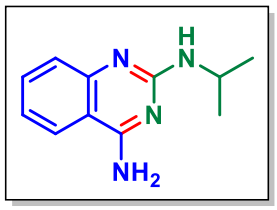
Colourless gum; R_f (hexane/EtOAc, 3:1) 0.30; yield 80 mg, 83%; IR (KBr, neat) ν 2928, 2853, 1655, 1598, 1566, 1491, 1407, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.50 (m, 2 H), 7.44 (d, *J* = 7.9 Hz, 1 H), 7.06–7.02 (m, 1 H), 5.60 (s, 2 H), 4.92 (s, 1 H), 3.98–3.89 (m, 1 H), 2.06–2.02 (m, 2 H), 1.74–1.69 (m, 2 H), 1.63–1.58 (m, 1 H), 1.45–1.34 (m, 2 H), 1.25–1.14 (m, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3, 159.0, 152.9, 133.4, 125.6, 122.2, 121.2, 110.5, 49.5, 33.8, 26.0, 25.2. HRMS (ESI) calcd. for $C_{14}H_{19}N_4$ $(M + H)^+$ 243.1604, found 243.1617.

N^2-cyclohexyl-7-methylquinazoline-2,4-diamine (21gb):



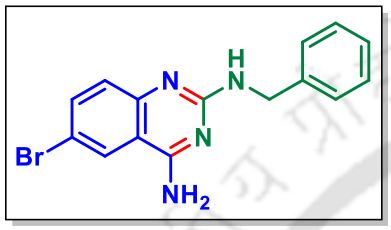
Colourless gum; R_f (hexane/EtOAc, 7:3) 0.30; yield 82 mg, 80%; IR (KBr, neat) ν 2932, 2853, 1659, 1586, 1543, 1491, 1402, 759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 1 H), 7.26 (s, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 5.36 (s, 2 H), 3.95–3.88 (m, 1 H), 2.41 (s, 3 H), 2.11–2.03 (m, 2 H), 1.76–1.72 (m, 2 H), 1.64–1.60 (m, 1 H), 1.46–1.37 (m, 2 H), 1.26–1.21 (m, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 162.1, 158.7, 144.4, 124.5, 123.4, 121.9, 108.2, 49.7, 33.7, 26.1, 25.2, 22.1. HRMS (ESI) calcd. for $C_{15}H_{21}N_4$ $(M + H)^+$ 257.1761, found 257.1754.

N^2-isopropylquinazoline-2,4-diamine (21ac):



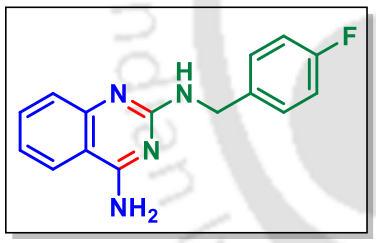
Colourless gum; R_f (hexane/EtOAc, 3:1) 0.30; yield 63 mg, 78%; IR (KBr, neat) ν 3319, 2969, 1617, 1562, 1501, 1421, 1281, 1173, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1 H), 7.53–7.49 (m, 1 H), 7.43 (d, *J* = 8.3 Hz, 1 H), 7.07–7.03 (m, 1 H), 4.23 (q, *J* = 6.5 Hz, 1 H), 1.21 (d, *J* = 6.5 Hz, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.4, 158.3, 151.0, 133.7, 124.5, 122.6, 121.6, 110.3, 42.9, 23.3. HRMS (ESI) calcd. for $C_{11}H_{15}N_4$ $(M + H)^+$ 203.1291, found 203.1299.

N^2-benzyl-6-bromoquinazoline-2,4-diamine (21dd):



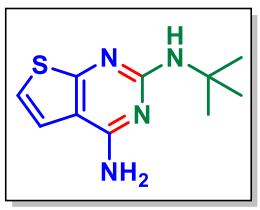
Colourless gum; R_f (hexane/EtOAc, 7:3) 0.30; yield 92 mg, 70%; IR (KBr, neat) ν 3339, 2968, 1613, 1578, 1455, 1270, 1198, 845, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.2 Hz, 1 H), 7.53 (dd, *J* = 8.9 and 2.2 Hz, 1 H), 7.31–7.25 (m, 4 H), 7.24–7.19 (m, 2 H), 5.71 (s, 2 H), 4.64 (d, *J* = 5.3 Hz, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.4, 159.7, 151.4, 139.7, 136.5, 128.7, 127.6, 127.5, 127.3, 124.8, 113.6, 112.0, 45.4. HRMS (ESI) calcd. for $C_{15}H_{14}BrN_4$ $(M + H)^+$ 329.0397, found 329.0395.

N^2-(4-fluorobenzyl)quinazoline-2,4-diamine (21ae):



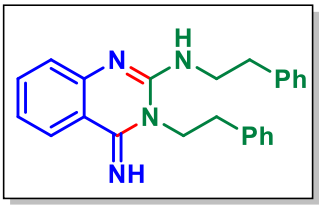
Colourless gum; R_f (hexane/EtOAc, 1:1) 0.40; yield 64 mg, 66%; IR (KBr, neat) ν 3323, 2967, 1618, 1556, 1450, 1273, 1201, 848, 751 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59–7.53 (m, 2 H), 7.48 (d, *J* = 8.4 Hz, 1 H), 7.32 (dd, *J* = 8.4 and 5.5 Hz, 2 H), 7.13–7.09 (m, 1 H), 6.97 (t, *J* = 8.7 Hz, 2 H), 5.56 (s, 2 H), 4.66 (d, *J* = 4.8 Hz, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.3, 162.2 (d, *J* = 243.1 Hz), 159.4, 152.4, 135.7 (d, *J* = 3.2 Hz), 133.7, 129.4 (d, *J* = 7.9 Hz), 125.8, 122.1, 121.8, 115.5 (d, *J* = 21.2 Hz), 110.7, 44.9. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -119.08 (s, -F). HRMS (ESI) calcd. for $C_{15}H_{14}FN_4$ $(M + H)^+$ 269.1197, found 269.1195.

N^2-(*tert*-butyl)thieno[2,3-*d*]pyrimidine-2,4-diamine (21ia):



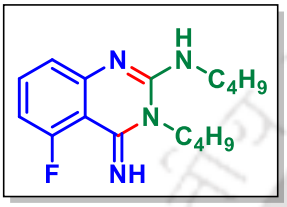
Green oil; R_f (hexane/EtOAc, 7:3) 0.50; yield 60 mg, 68%; IR (KBr, neat) ν 3328, 2963, 1613, 1542, 1443, 1212, 787, 734, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 5.8 Hz, 1 H), 6.75 (d, *J* = 5.8 Hz, 1 H), 5.22 (s, 2 H), 4.94 (s, 1 H), 1.42 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.4, 159.6, 158.0, 117.7, 116.8, 109.0, 51.1, 29.4. HRMS (ESI) calcd. for $C_{10}H_{15}N_4S$ $(M + H)^+$ 223.1012, found 223.1016.

4-Imino-*N*,3-diphenethyl-3,4-dihydroquinazolin-2-amine (22af):



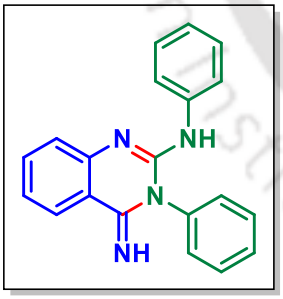
White gum; R_f (hexane/EtOAc, 7:3) 0.50; yield 99 mg, 67%; IR (KBr, neat) ν 3333, 2924, 1598, 1567, 1474, 1298, 1144, 992, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0 and 1.4 Hz, 1 H), 7.49–7.45 (m, 1 H), 7.35–7.28 (m, 6 H), 7.25–7.21 (m, 3 H), 7.14–7.08 (m, 3 H), 4.18 (s, 3 H), 4.01 (s, 1 H), 3.54 (t, *J* = 6.9 Hz, 2 H), 2.96 (t, *J* = 7.2 Hz, 2 H), 2.75 (t, *J* = 7.2 Hz, 2 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.5, 149.7, 146.4, 139.3, 139.0, 132.9, 129.2, 129.03, 129.01, 127.1, 126.9, 125.8, 124.0, 122.7, 116.1, 45.3, 43.2, 35.4, 33.2. HRMS (ESI) calcd. for $C_{24}H_{25}N_4$ $(M + H)^+$ 369.2074, found 369.2079.

_N_,3-dibutyl-5-fluoro-4-imino-3,4-dihydroquinazolin-2-amine (22eg):



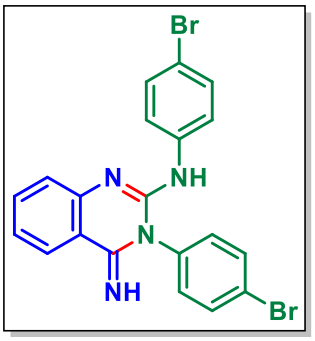
Yellow liquid; R_f (hexane/EtOAc, 7:3) 0.50; yield 88 mg, 76%; IR (KBr, neat) ν 3397, 2957, 1607, 1557, 1467, 1291, 1146, 1055, 812, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (q, *J* = 8.4 Hz, 1 H), 7.00 (d, *J* = 8.2 Hz, 1 H), 6.65 (dd, *J* = 12.9 and 8.2 Hz, 1 H), 4.48 (s, 1 H), 4.03 (t, *J* = 8.0 Hz, 2 H), 3.48–3.44 (m, 2 H), 1.69 (p, *J* = 8.0 Hz, 2 H), 1.61 (p, *J* = 7.3 Hz, 2 H), 1.47–1.37 (m, 4 H), 0.98–0.94 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.9 (d, *J* = 250.8 Hz), 154.9 (d, *J* = 3.7 Hz), 150.4, 148.8, 132.3 (d, *J* = 12.2 Hz), 121.1 (d, *J* = 3.4 Hz), 108.3 (d, *J* = 23.6 Hz), 106.0 (d, *J* = 3.4 Hz), 41.9, 41.5, 31.8, 29.0, 20.5, 20.3, 14.0. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -122.04 (s, -F). HRMS (ESI) calcd. for $C_{16}H_{24}FN_4$ $(M + H)^+$ 291.1980, found 291.1976.

4-Imino-_N_,3-diphenyl-3,4-dihydroquinazolin-2-amine (22ah):



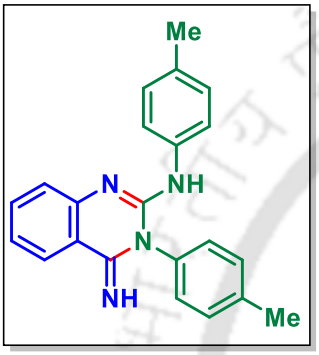
White solid; R_f (hexane/EtOAc, 1:2) 0.50; mp 158-160 °C; yield 70 mg, 56%; IR (KBr, neat) ν 3345, 2963, 1616, 1554, 1472, 1279, 1146, 1033, 840, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.9 Hz, 1 H), 7.70 (t, *J* = 7.9 Hz, 2 H), 7.64 (t, *J* = 7.5 Hz, 1 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.48–7.41 (m, 5 H), 7.30 (t, *J* = 7.8 Hz, 2 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 5.75 (s, 2 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 157.0, 145.7, 145.5, 138.3, 135.0, 133.1, 131.6, 130.7, 129.9, 128.9, 125.7, 125.2, 123.8, 123.6, 120.9, 118.4. HRMS (ESI) calcd. for $C_{20}H_{17}N_4$ $(M + H)^+$ 313.1448, found 313.1454.

_N_,3-bis(4-bromophenyl)-4-imino-3,4-dihydroquinazolin-2-amine (22ai):



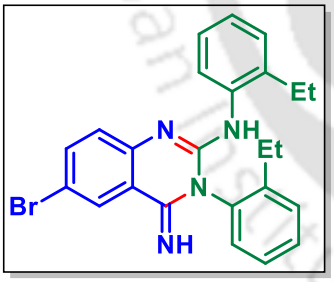
White gum; R_f (hexane/EtOAc, 7:3) 0.30; yield 94 mg, 50%; IR (KBr, neat) ν 3326, 2964, 1619, 1545, 1472, 1283, 1167, 1048, 840, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 7.40 (s, 5 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 7.19 (s, 1 H), 5.66 (s, 1 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 157.6, 145.2, 137.3, 135.0, 134.4, 133.4, 132.0, 131.6, 126.1, 125.1, 124.2, 122.8, 118.0, 116.7. HRMS (ESI) calcd. for $C_{20}H_{15}Br_2N_4$ $(M + H)^+$ 470.9638, found 470.9630.

4-Imino-*N*,3-di-*p*-tolyl-3,4-dihydroquinazolin-2-amine (22aj):



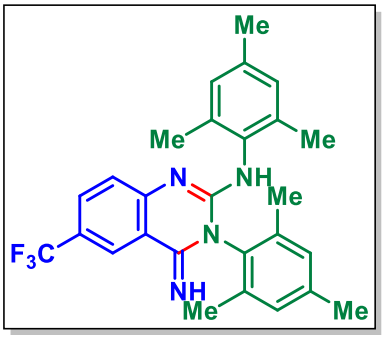
White gum; R_f (hexane/EtOAc, 1:1) 0.30; yield 79 mg, 58%; IR (KBr, neat) ν 3333, 2959, 1616, 1557, 1471, 1279, 1111, 1033, 845, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 1 H), 7.53–7.47 m, 3 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 8.1 Hz, 2 H), 2.50 (s, 3 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.2, 146.2, 145.8, 141.2, 135.8, 133.6, 133.1, 132.4, 132.2, 129.7, 129.5, 125.7, 125.4, 123.5, 121.4, 118.4, 21.6, 21.0. HRMS (ESI) calcd. for $C_{22}H_{21}N_4$ $(M + H)^+$ 341.1761, found 341.1751.

6-Bromo-*N*,3-bis(2-ethylphenyl)-4-imino-3,4-dihydroquinazolin-2-amine (22dk):



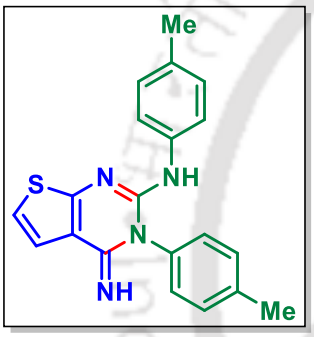
White gum; R_f (hexane/EtOAc, 3:2) 0.50; yield 122 mg, 68%; IR (KBr, neat) ν 3345, 2961, 1603, 1567, 1445, 1211, 1138, 1045, 848, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.4 Hz, 1 H), 8.16 (d, *J* = 8.1 Hz, 1 H), 7.62 (d, *J* = 4.2 Hz, 2 H), 7.58 (dd, *J* = 8.7 and 2.3 Hz, 1 H), 7.56–7.53 (m, 1 H), 7.37 (d, *J* = 7.7 Hz, 1 H), 7.26–7.23 (m, 3 H), 7.11–7.04 (m, 2 H), 5.76 (s, 1 H), 2.59 (q, *J* = 7.6 Hz, 2 H), 2.15 (q, *J* = 7.6 Hz, 2 H), 1.22 (t, *J* = 7.6 Hz, 3 H), 0.84 (t, *J* = 7.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.7, 146.4, 145.1, 143.8, 136.1, 135.7, 134.6, 132.5, 131.6, 131.3, 130.0, 129.3, 129.0, 128.2, 127.5, 126.9, 124.9, 123.1, 120.1, 116.3, 24.7, 23.8, 14.07, 14.05. HRMS (ESI) calcd. for $C_{24}H_{24}BrN_4$ $(M + H)^+$ 447.1179, found 447.1165.

4-Imino-*N*,3-dimesityl-6-(trifluoromethyl)-3,4-dihydroquinazolin-2-amine (22fl):



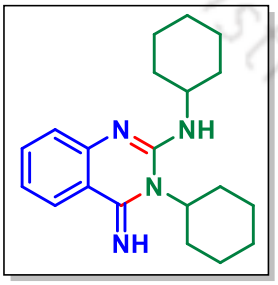
Colourless gum; R_f (hexane/EtOAc, 4:1) 0.30; yield 78 mg, 42%; IR (KBr, neat) ν 3368, 2989, 1617, 1578, 1490, 1245, 1146, 1056, 849, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.63 (d, *J* = 8.6 Hz, 1 H), 7.28 (d, *J* = 8.6 Hz, 1 H), 7.19 (s, 2 H), 6.90 (s, 2 H), 5.38 (s, 1 H), 2.40 (s, 3 H), 2.29 (s, 3 H), 2.28 (s, 6 H), 2.16 (s, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 154.0, 149.8, 148.0, 141.3, 137.5, 137.4, 135.8, 131.34, 131.32, 129.4, 129.3 (q, *J* = 3.6 Hz), 128.8, 126.0, 124.63 (q, *J* = 269.9 Hz), 124.59 (q, *J* = 32.7 Hz), 123.7 (q, *J* = 4.1 Hz), 117.7, 21.4, 21.2, 18.9, 17.6. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -64.84 (s, -F). HRMS (ESI) calcd. for $C_{27}H_{28}F_3N_4$ $(M + H)^+$ 465.2261, found 465.2257.

4-Imino-*N*,3-di-*p*-tolyl-3,4-dihydrothieno[2,3-*d*]pyrimidin-2-amine (22ij):



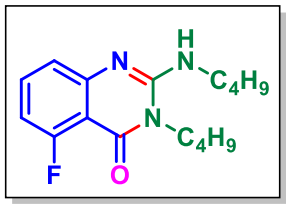
Colourless gum; R_f (hexane/EtOAc, 2:1) 0.40; yield 80 mg, 58%; IR (KBr, neat) ν 3348, 2960, 1611, 1578, 1490, 1222, 1100, 1039, 853, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.9 Hz, 2 H), 7.31–7.29 (m, 2 H), 7.28–7.26 (m, 2 H), 7.24 (s, 1 H), 7.10 (d, *J* = 8.1 Hz, 2 H), 6.88 (d, *J* = 5.8 Hz, 1 H), 5.79 (s, 1 H), 2.79 (bs, 1 H), 2.50 (s, 3 H), 2.31 (s, 3 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.2, 155.2, 147.6, 141.2, 135.2, 134.2, 132.4, 132.1, 129.6, 129.5, 121.9, 121.8, 118.2, 117.1, 21.7, 21.1. HRMS (ESI) calcd. for $C_{20}H_{19}N_4S$ $(M + H)^+$ 347.1325, found 347.1322.

***N*,3-dicyclohexyl-4-imino-3,4-dihydroquinazolin-2-amine (22ab′):**



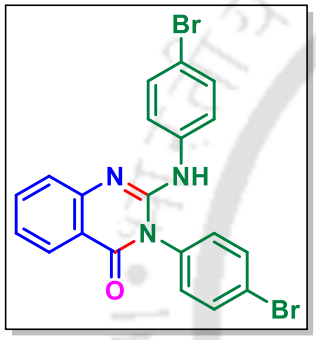
White solid; R_f (hexane/EtOAc, 3:1) 0.30; mp 145-147 °C; yield 67 mg, 52%; IR (KBr, neat) ν 3389, 2970, 1610, 1556, 1477, 1280, 1234, 1145, 1067, 758 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.1 and 1.4 Hz, 1 H), 7.38–7.36 (m, 1 H), 7.20 (d, *J* = 8.1 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 5.46–5.42 (m, 1 H), 4.54 (d, *J* = 7.5 Hz, 1 H), 4.09–4.05 (m, 1 H), 2.11–2.06 (m, 4 H), 1.96–1.89 (m, 4 H), 1.79–1.78 (m, 1 H), 1.73–1.69 (m, 2 H), 1.65–1.61 (m, 1 H), 1.55–1.44 (m, 4 H), 1.33–1.24 (m, 3 H), 1.20–1.11 (m, 1H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 160.1, 149.3, 146.5, 132.3, 125.1, 124.0, 121.8, 116.8, 54.5, 49.8, 33.3, 30.6, 26.8, 26.02, 25.97, 24.8. HRMS (ESI) calcd. for $C_{42}H_{37}N_4O_2$ $(M + H)^+$ 325.2387, found 325.2380.

3-Butyl-2-(butylamino)-5-fluoroquinazolin-4(3*H*)-one (23eg):



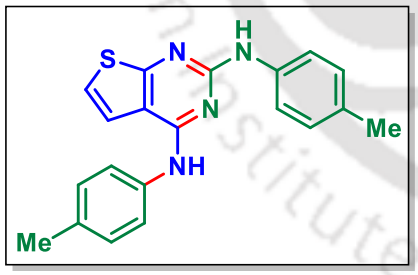
Colourless liquid; R_f (hexane/EtOAc, 7:3) 0.50; yield 29 mg, 98%; IR (KBr, neat) ν 3383, 2957, 1661, 1554, 1469, 1352, 1148, 1070, 812, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 1 H), 7.12 (d, *J* = 8.3 Hz, 1 H), 6.74 (dd, *J* = 11.0 and 8.0 Hz, 1 H), 4.69 (s, 1 H), 3.98 (t, *J* = 7.8 Hz, 2 H), 3.53–3.49 (m, 2 H), 1.61–1.61 (m, 4 H), 1.45–1.39 (m, 4 H), 0.98–0.94 (m, 6 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.0 (d, *J* = 261.9 Hz), 159.9 (d, *J* = 4.3 Hz), 151.5, 150.3, 134.4 (d, *J* = 11.0 Hz), 120.9 (d, *J* = 3.8 Hz), 108.8 (d, *J* = 21.0 Hz), 106.9 (d, *J* = 5.7 Hz), 42.0, 40.6, 31.6, 29.8, 20.44, 20.36, 14.00, 13.9. ^{19}F NMR (470 MHz, $C_6F_6/CDCl_3$) δ -115.71 (s, -F). HRMS (ESI) calcd. for $C_{16}H_{23}FN_3O$ $(M + H)^+$ 292.1820, found 292.1814.

3-(4-Bromophenyl)-2-((4-bromophenyl)amino)quinazolin-4(3*H*)-one (23ai):



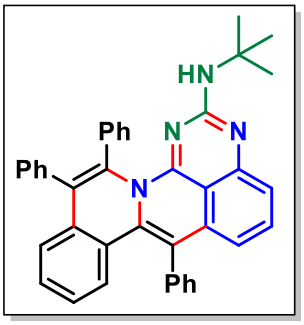
White gum; R_f (hexane/EtOAc, 4:1) 0.50; yield 45 mg, 96%; IR (KBr, neat) ν 3380, 2963, 1659, 1559, 1460, 1380, 1129, 1079, 815, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 7.8 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.39 (s, 4 H), 7.25 (d, *J* = 8.4 Hz, 4 H), 5.82 (s, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 148.3, 145.8, 137.0, 135.3, 134.5, 133.6, 132.1, 131.0, 127.5, 125.9, 125.0, 124.4, 122.8, 118.5, 117.1. HRMS (ESI) calcd. for $C_{20}H_{14}Br_2N_3O$ $(M + H)^+$ 471.9478, found 471.9479.

***N*²,*N*⁴-di-*p*-tolylthieno[2,3-*d*]pyrimidine-2,4-diamine (23ij′):**



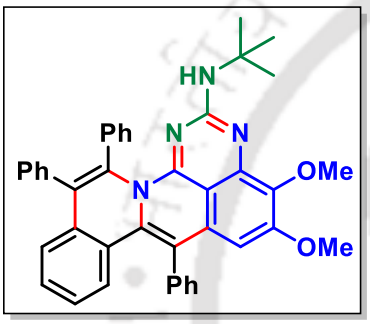
White solid; R_f (hexane/EtOAc, 2:1) 0.40; mp 286-288 °C; yield 40 mg, 98%; IR (KBr, neat) ν 3404, 2923, 1653, 1600, 1535, 1316, 964, 819, 749 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, *J* = 6.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 6.0 Hz, 1 H), 6.17 (s, 1 H), 2.55 (s, 3 H), 2.32 (s, 3 H). $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 167.9, 152.7, 146.1, 144.5, 136.3, 133.9, 133.4, 129.9, 128.2, 127.7, 123.5, 122.8, 122.4, 111.2, 21.8, 21.2. HRMS (ESI) calcd. for $C_{20}H_{18}N_3OS$ $(M + H)^+$ 347.1325, found 347.1328.

***N*-(*tert*-butyl)-7,12,13-triphenylbenzo[8,9]quinolizino[4,3,2-*de*]quinazolin-2-amine (24aa):**



Yellow gum; R_f (hexane/EtOAc, 4:1) 0.40; yield 52 mg, 59%; IR (KBr, neat) ν 3056, 2961, 1623, 1572, 1490, 1322, 826, 753, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.37 (m, 6 H), 7.21–7.15 (m, 4 H), 7.12 (t, *J* = 7.3 Hz, 3 H), 7.04–7.00 (m, 2 H), 6.95–6.90 (m, 6 H), 6.78–6.74 (m, 1 H), 6.59 (d, *J* = 7.7 Hz, 1 H), 1.16 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.1, 156.4, 138.6, 137.0, 136.95, 136.7, 134.5, 134.2, 134.0, 131.9, 131.8, 129.94, 129.91, 129.1, 128.6, 128.4, 128.2, 128.1, 127.2, 126.9, 126.5, 125.6, 120.8, 119.1, 114.2, 114.0, 50.9, 29.4. HRMS (ESI) calcd. for $C_{40}H_{33}N_4$ $(M + H)^+$ 569.2700, found 569.2696.

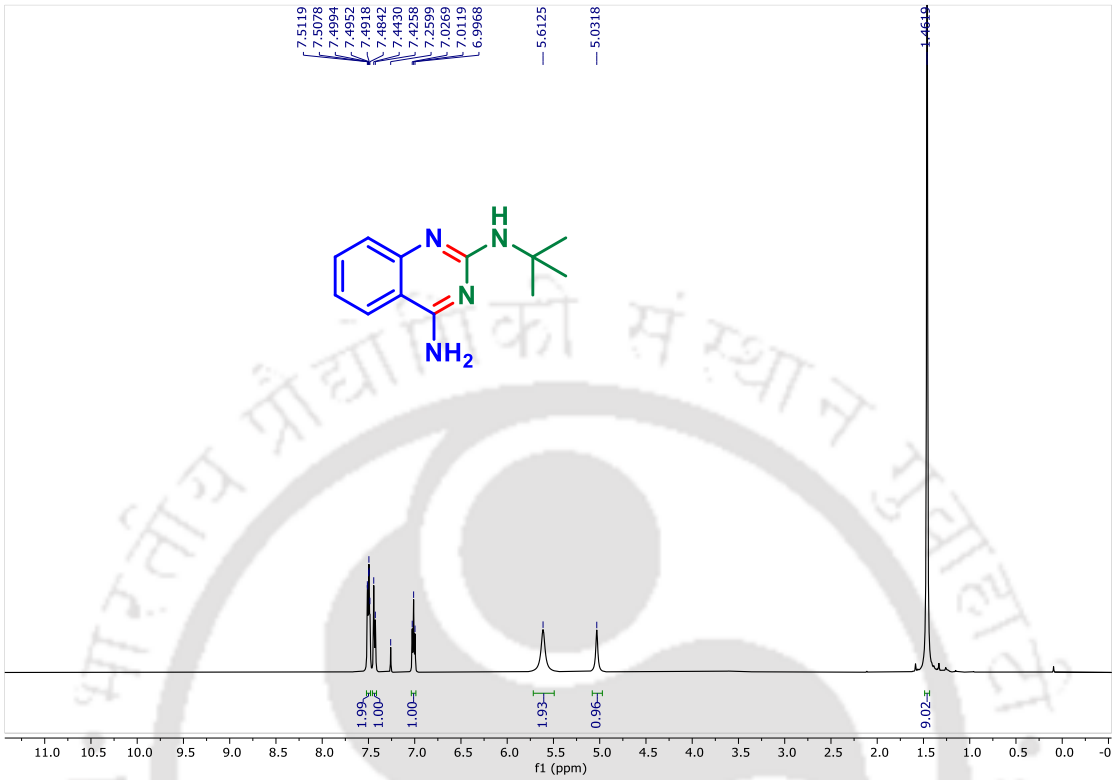
***N*-(*tert*-butyl)-4,5-dimethoxy-7,12,13-triphenylbenzo[8,9]quinolizino[4,3,2-*de*]quinazolin-2-amine (24ha):**



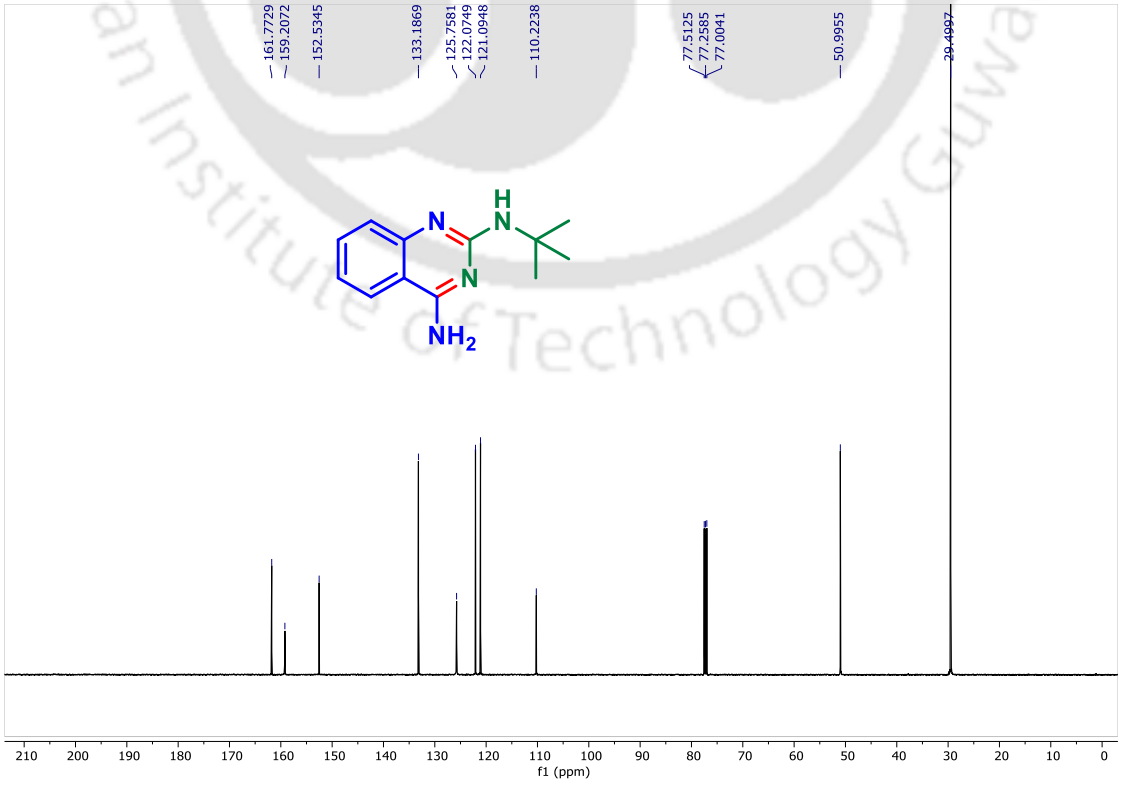
Yellow gum; R_f (hexane/EtOAc, 3:1) 0.40; yield 73 mg, 58%; IR (KBr, neat) ν 3055, 2962, 1618, 1562, 1460, 1397, 1211, 832, 752, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.36 (m, 2 H), 7.32–7.28 (m, 3 H), 7.21–7.18 (m, 3 H), 7.17–7.12 (m, 3 H), 7.01–6.99 (m, 2 H), 6.93–6.88 (m, 5 H), 6.75–6.69 (m, 3 H), 3.84 (s, 3 H), 3.08 (s, 3 H), 1.13 (s, 9 H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.7, 155.7, 139.3, 138.1, 136.81, 136.75, 136.65, 134.7, 134.4, 131.9, 131.3, 129.9, 129.7, 128.7, 128.3, 128.1, 128.0, 127.5, 127.2, 127.1, 126.9, 126.2, 125.3, 125.2, 119.2, 109.5, 102.1, 61.8, 56.1, 50.9, 29.5. HRMS (ESI) calcd. for $C_{42}H_{37}N_4O_2$ $(M + H)^+$ 629.2911, found 629.2912.

5.10. Representative Spectra

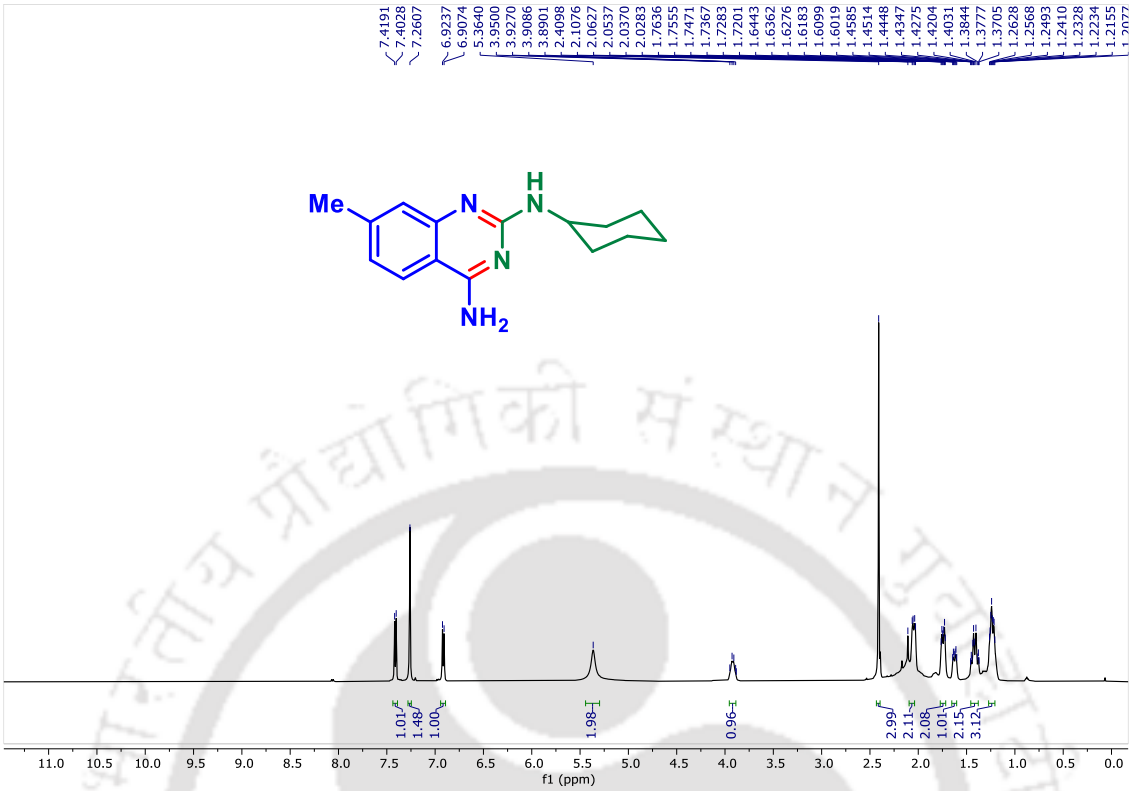
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**21aa**):



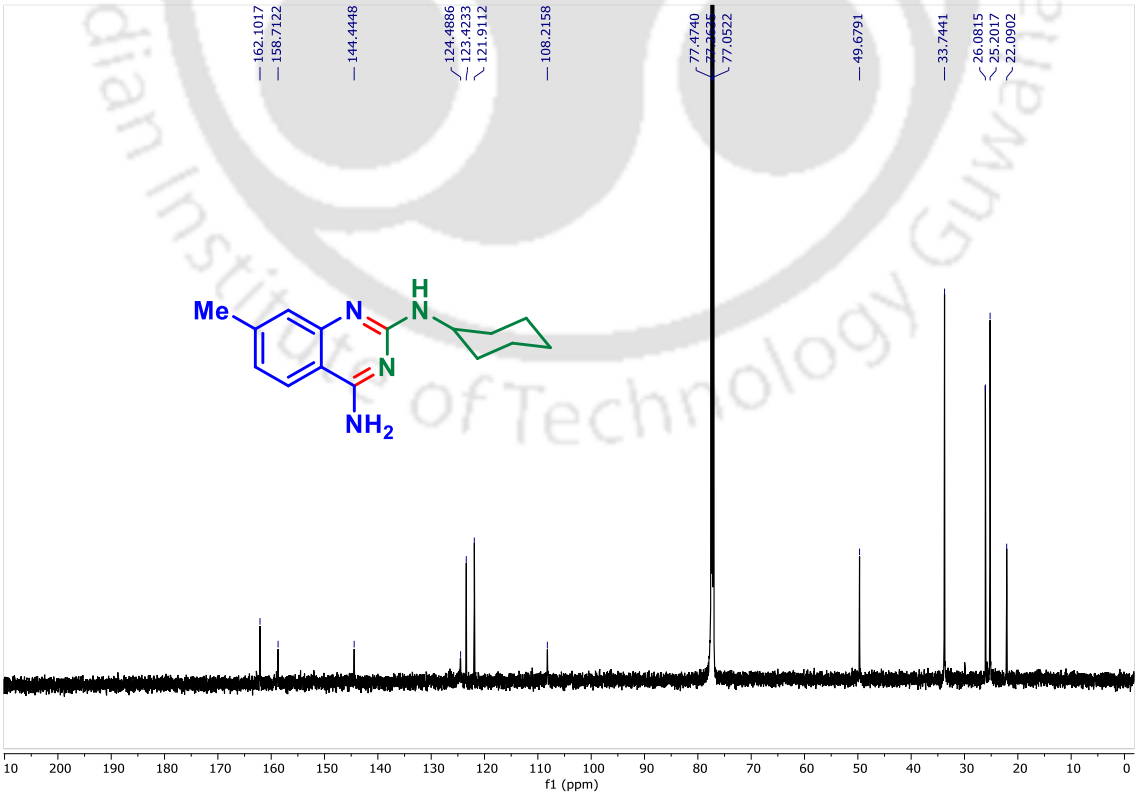
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**21aa**):



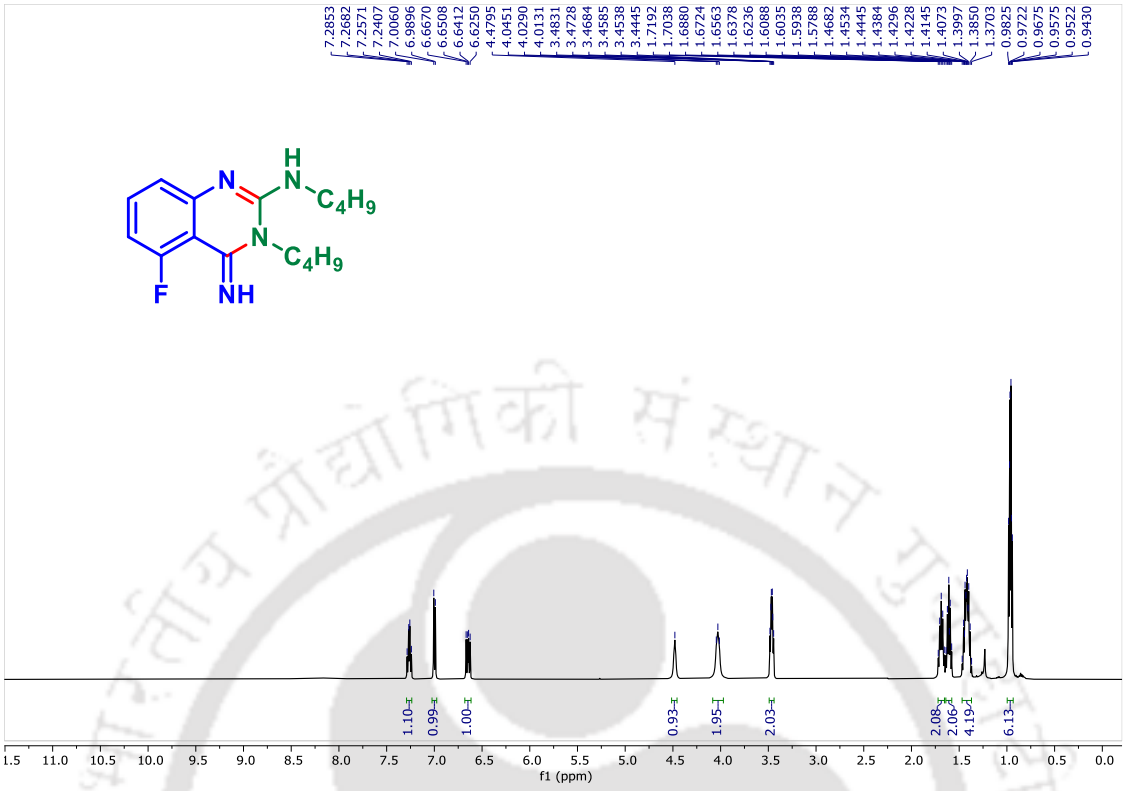
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**21gb**):



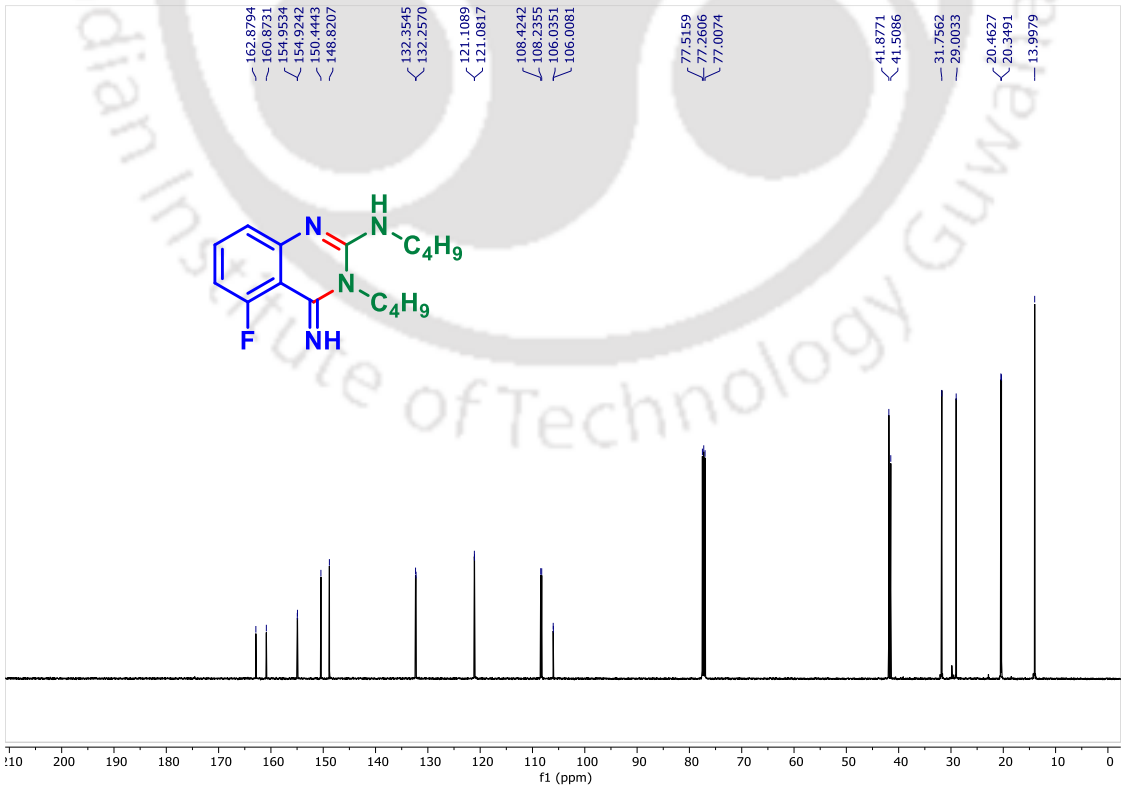
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**21gb**):



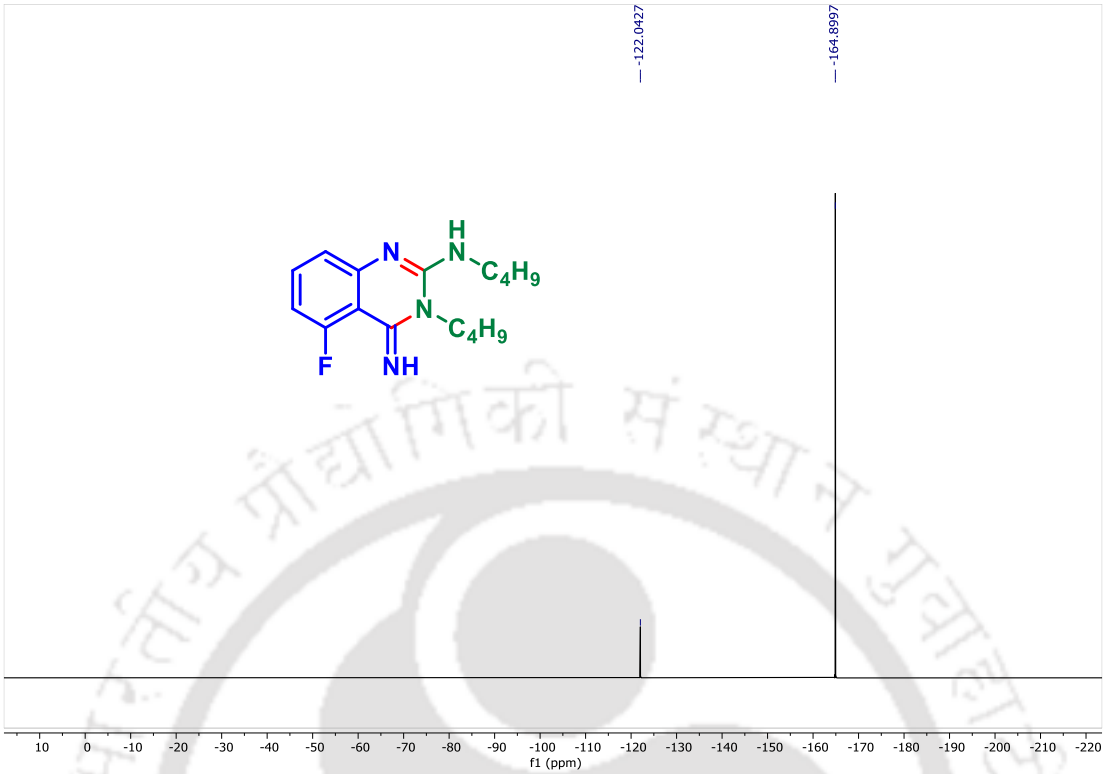
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**22eg**):



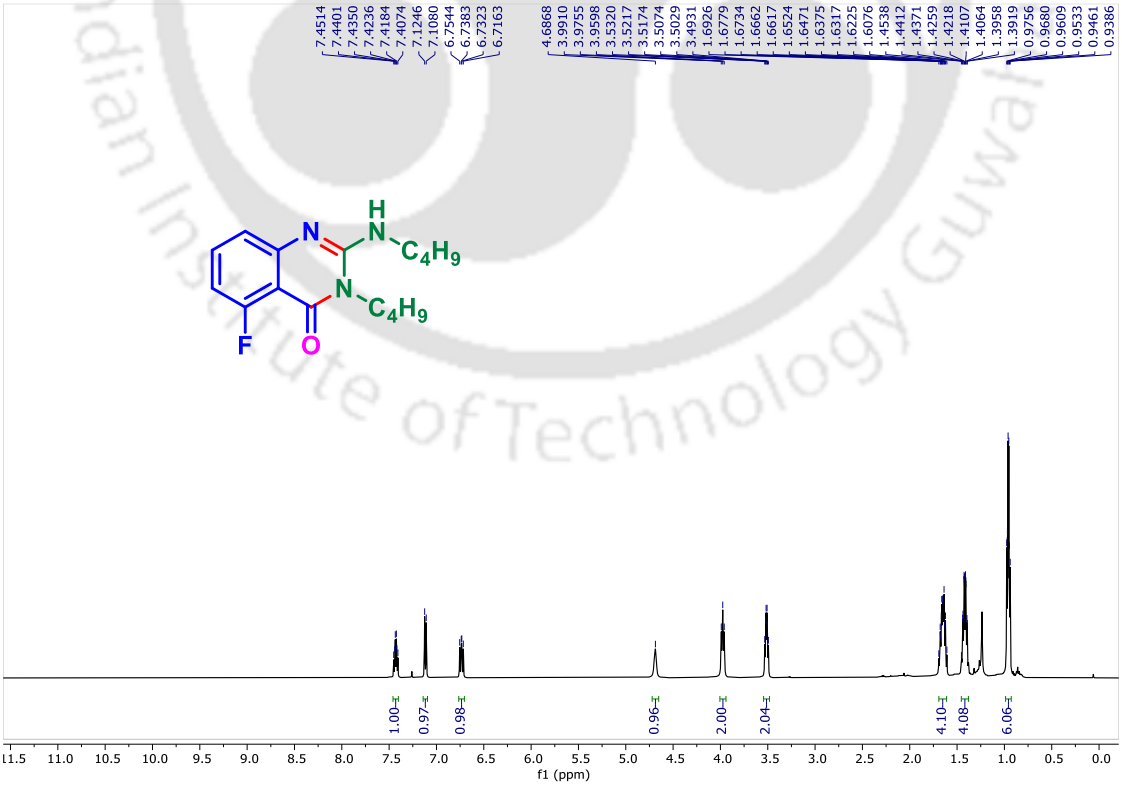
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**22eg**):



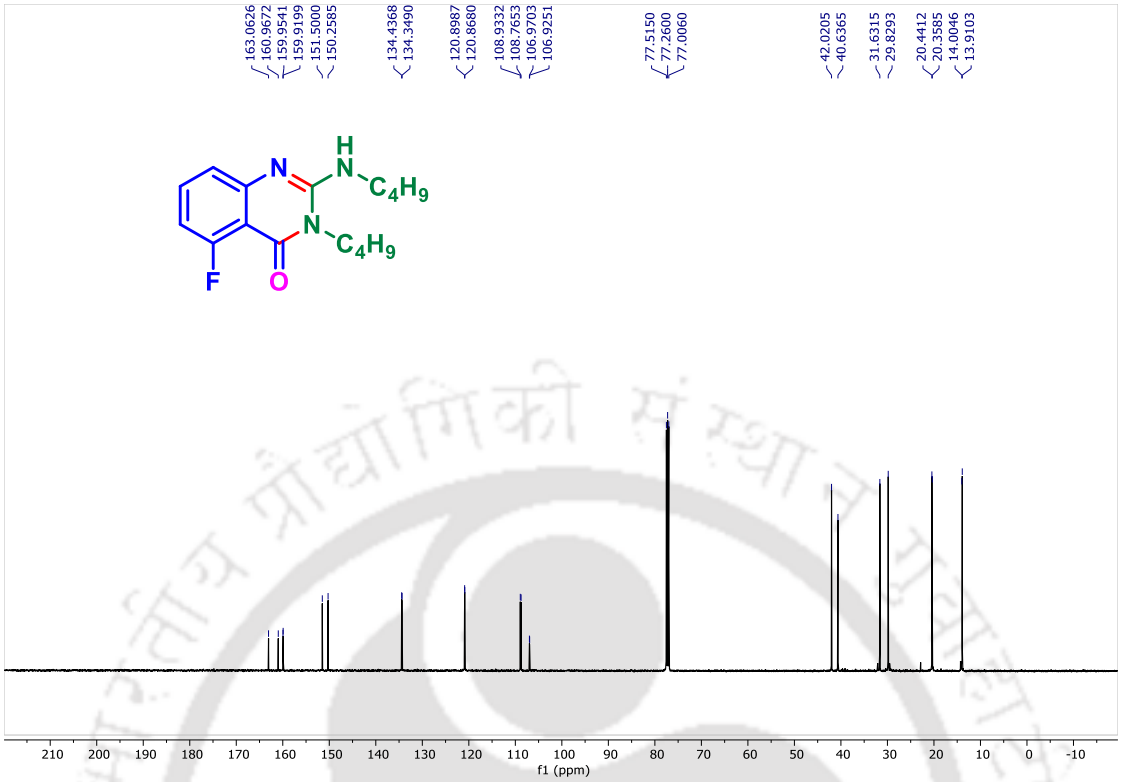
^{19}F ($CDCl_3$, 470 MHz) spectrum of compound (**22eg**):



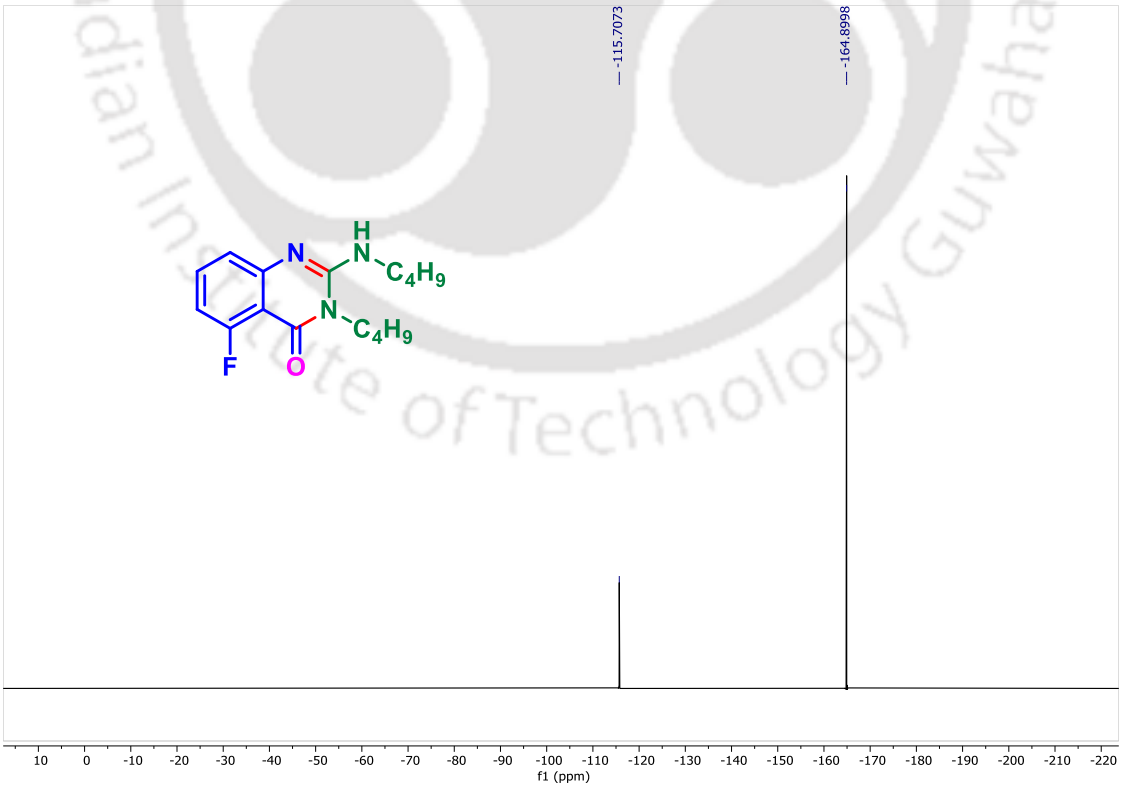
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**23eg**):



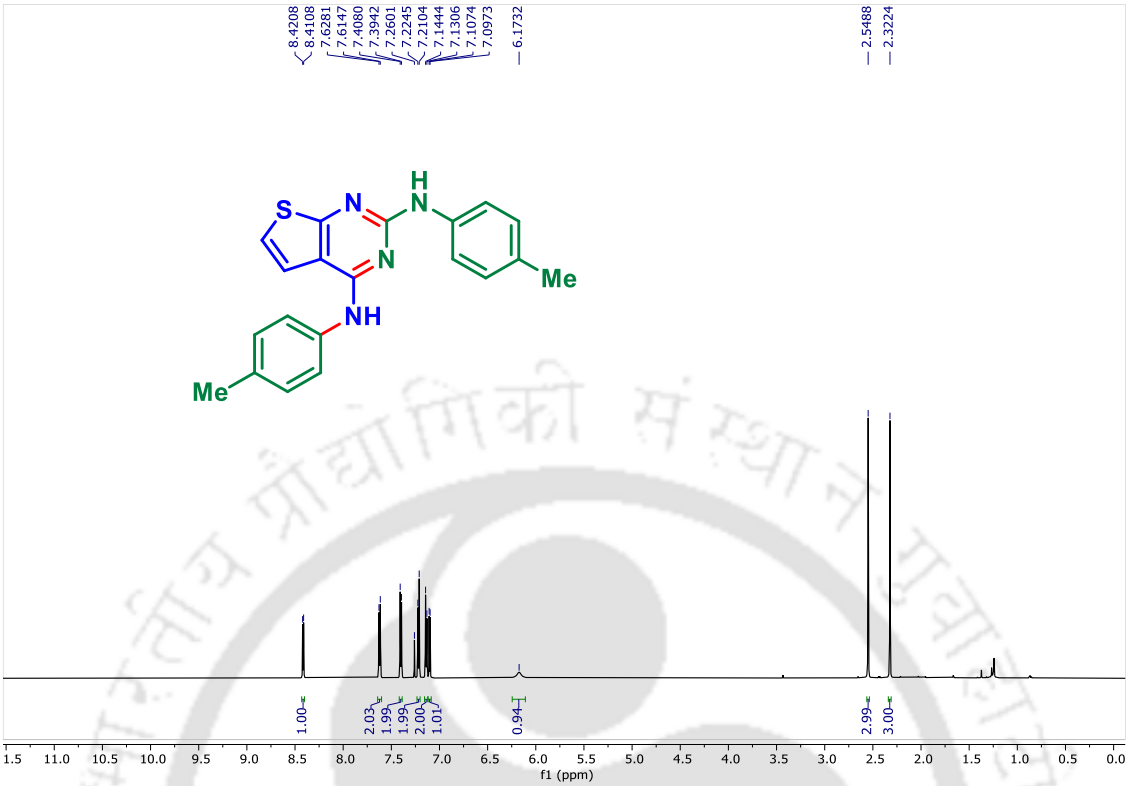
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**23eg**):



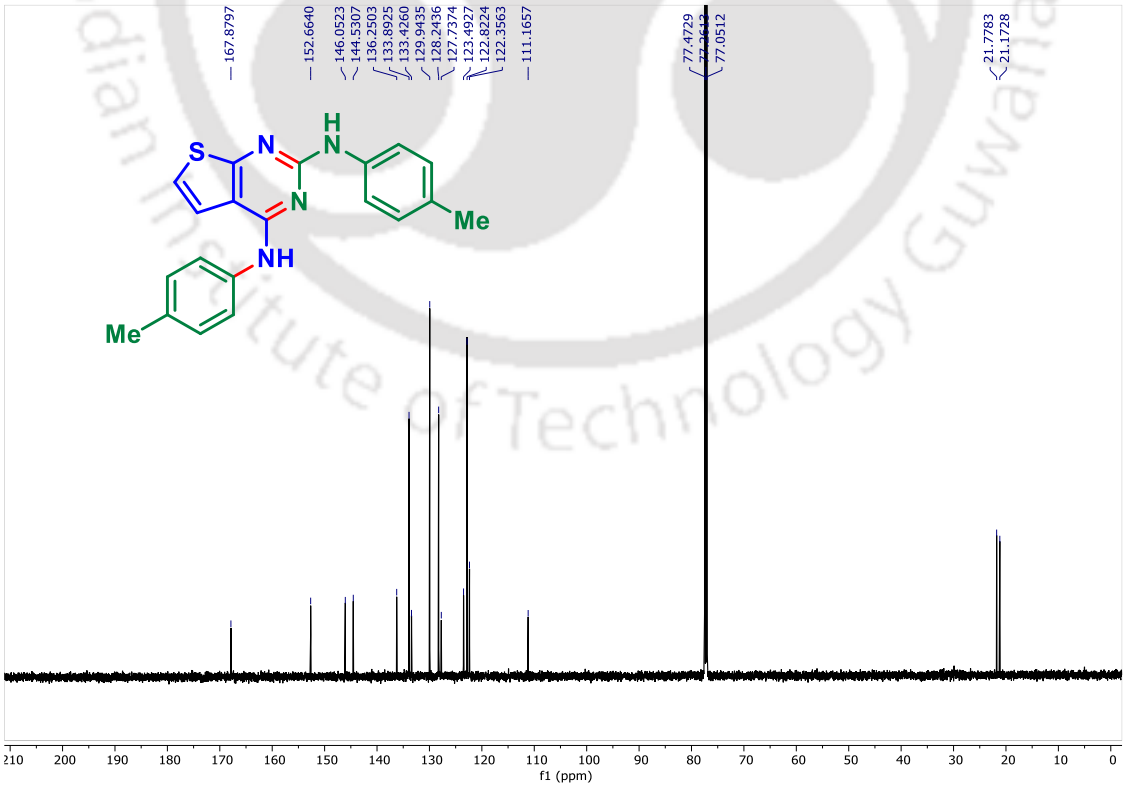
^{19}F ($CDCl_3$, 470 MHz) spectrum of compound (**23eg**):



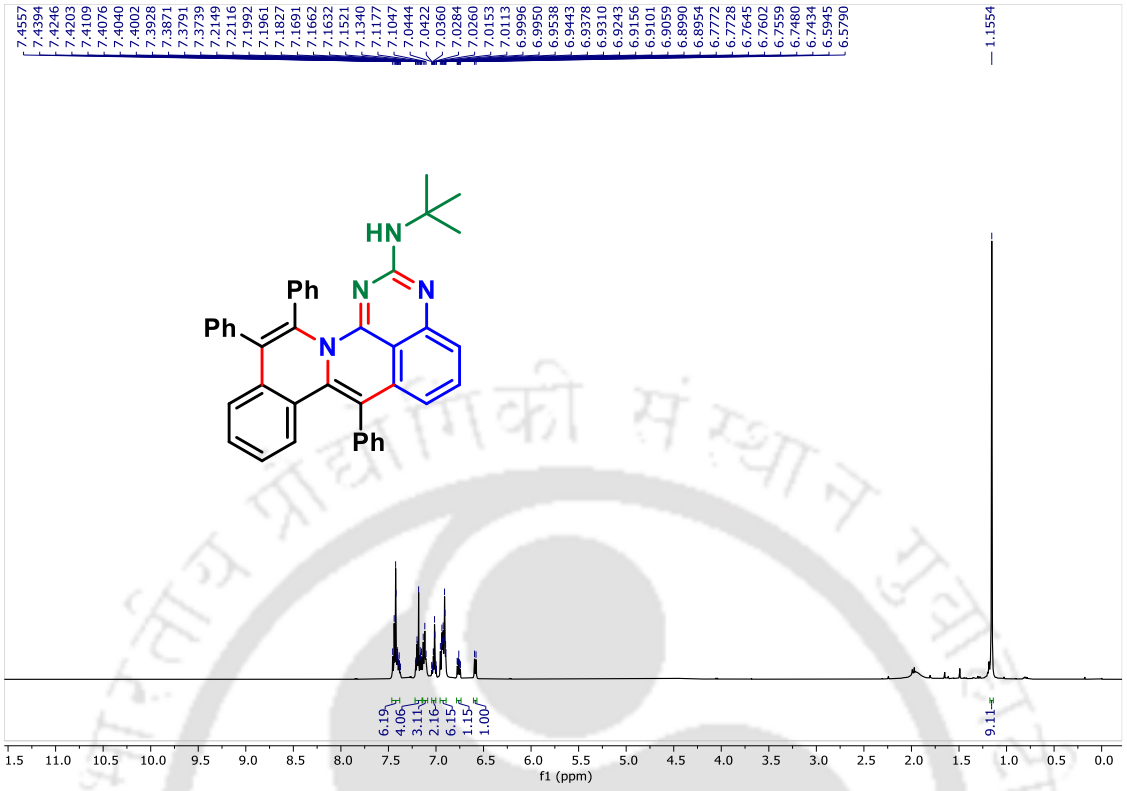
^{1}H ($CDCl_3$, 600 MHz) spectrum of compound (**23ij′**):



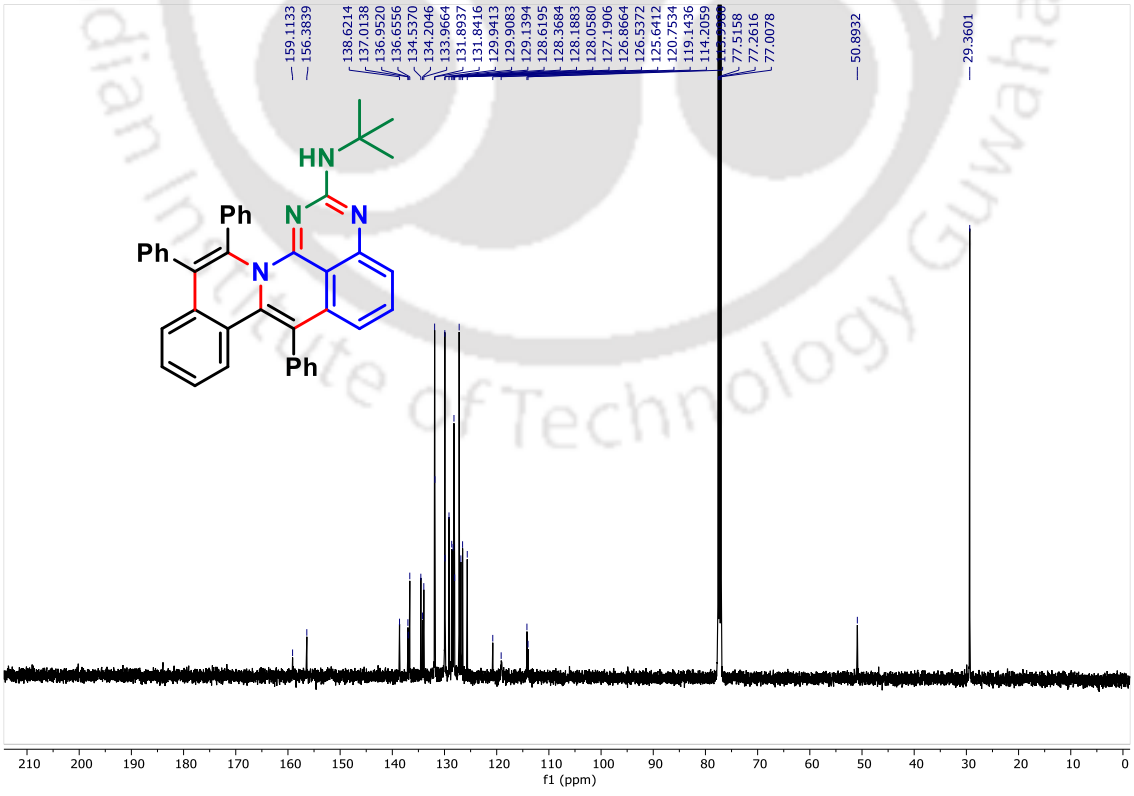
$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of compound (**23ij′**):



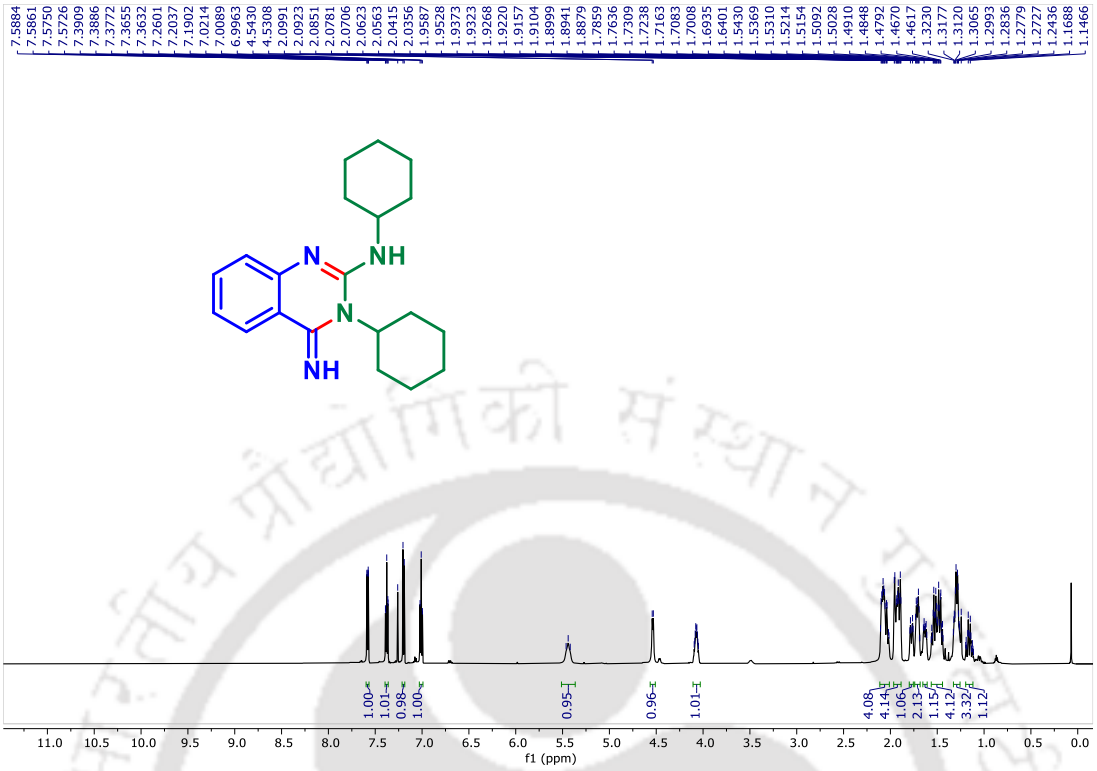
^{1}H ($CDCl_3$, 500 MHz) spectrum of compound (**24aa**):



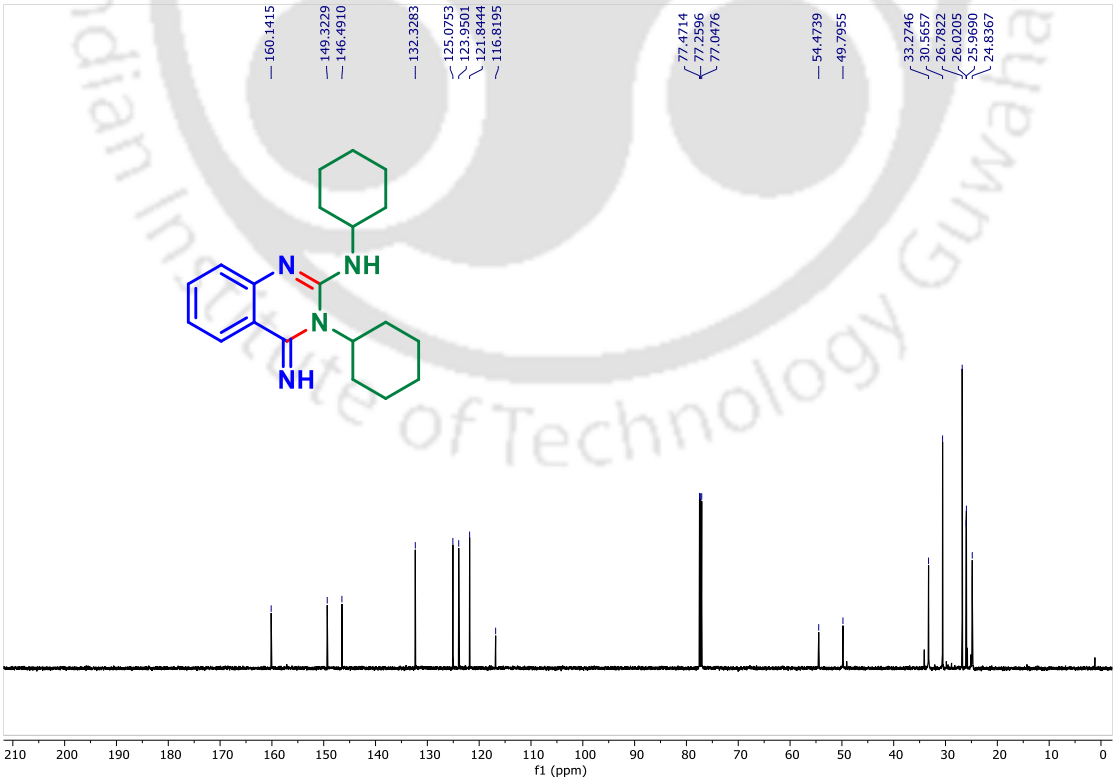
$^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz) spectrum of compound (**24aa**):



^{1}H ($CDCl_3$, 600 MHz) spectrum of intermediate (**22ab′**):

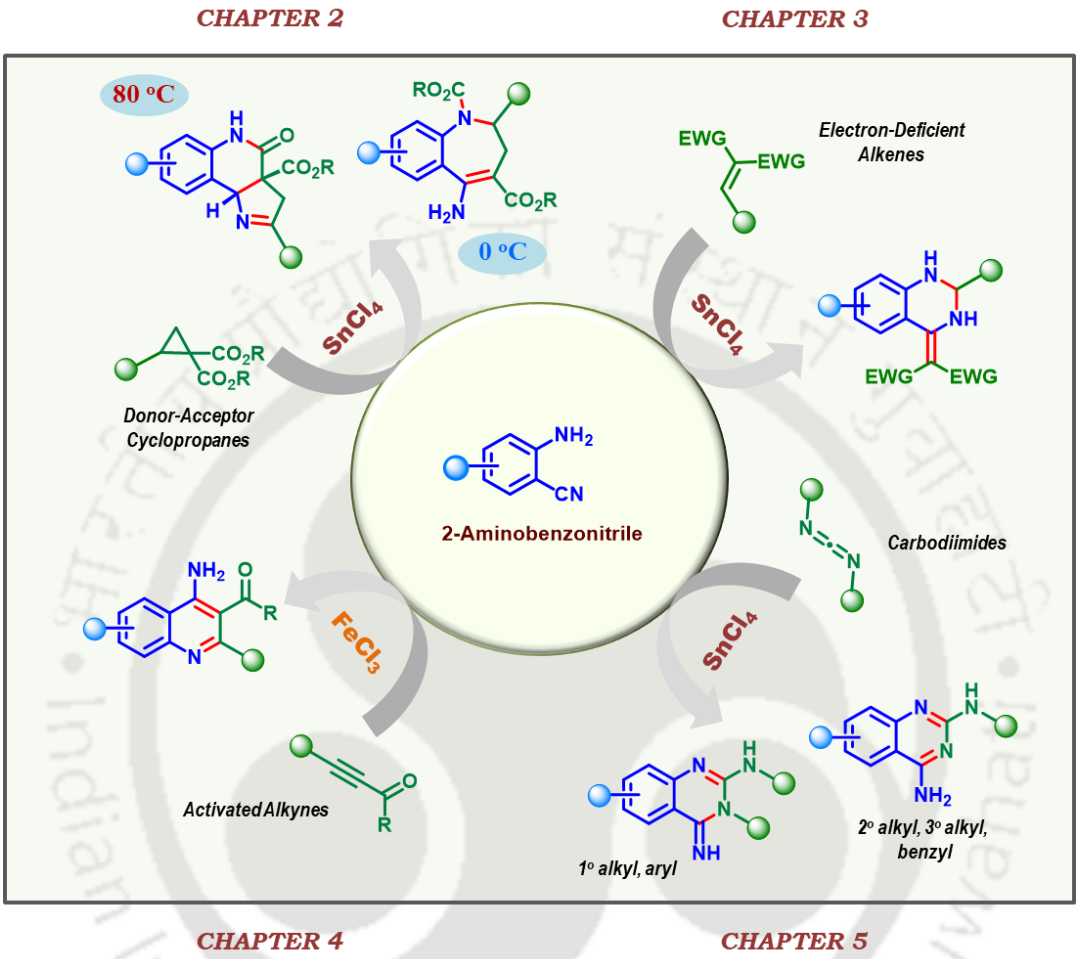


$^{13}C\{^{1}H\}$ ($CDCl_3$, 150 MHz) spectrum of intermediate (**22ab′**):



SUMMARY AND OUTLOOK

Thesis Overview



This thesis focuses on development of synthetic pathways for benzannulated *N*-heterocycles with 2-aminobenzonitrile as the initial architectonic precursor.

Chapter 1 highlights an overview on nitrogen containing heterocyclic compounds, cascade reactions and the reactivity of 2-aminobenzonitrile. This includes a brief discussion about synthetic reactivity and utility of 2-aminobenzonitrile as a precursor for synthesis of various simple or complex heterocyclic frameworks.

Chapter 2 represents a tunable one pot synthesis of tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and dihydro-1*H*-benzo[*b*]azepines from 2-aminobenzonitriles and donor-acceptor cyclopropanes in presence of $SnCl_4$. The reaction proceeds *via* the initial ring opening of cyclopropane ring by 2-aminobenzonitrile followed by nucleophilic attack by amine to give adduct, which after unprecedented rearrangement at two different reaction temperatures

provide two sets of structurally diverse nitrogen heterocyclic compounds. This methodology can be used for the synthesis of tricyclic hexahydropyrrolo[3,2-*c*]quinolinones (tricyclic core of martinelline).

Chapter 3 describes an efficient methodology for the synthesis of highly diverse 4-methylene substituted tetrahydroquinazoline scaffolds from 2-aminobenzonitriles and alkylidene malonates in presence of $SnCl_4$. The reaction proceeds *via* initial 1,4-conjugate addition of 2-aminobenzonitrile to the activated alkene followed by an unprecedented rearrangement. The methodology can be extended towards the synthesis of quinazoline analogues as well as tetracyclic dihydroisoquinolino[1,2-*b*]quinazoline derivatives. Some of the synthesized compounds show excellent photophysical properties.

Chapter 4 demonstrates an efficient methodology for the synthesis of highly diverse 2,3-disubstituted 4-aminoquinoline derivatives from 2-aminobenzonitriles and activated alkynes in presence of $FeCl_3$. The reaction proceeds *via* sequential aza-Michael addition and intramolecular annulation to afford highly substituted 4-aminoquinolines in good yields. The salient features of this protocol include the use of a minimally toxic, eco-benign and less expensive Fe(III)-salt and has high atom-economy with broad substrate scope and operational simplicity. The post synthetic application of the reaction provides 4*H*-benzo[*de*][1,6]naphthyridines.

Chapter 5 highlights an efficient methodology for the synthesis of 2,4-diaminoquinazolines and 2-amino-4-iminoquinazolines from 2-aminobenzonitriles and carbodiimides. This $SnCl_4$ mediated reaction exhibits substrate driven switchable selectivity in product formation based on the substituents of the carbodiimides used. Aryl and primary alkyl-substituted carbodiimides predominantly give 2-amino-4-iminoquinazolines, while secondary or tertiary alkyl and benzyl-substituted carbodiimides yield 2,4-diaminoquinazolines. The methodology can be extended towards the synthesis of 2-aminoquinazolin-4(3*H*)-one analogues as well as pentacyclic annulated derivatives.

List of Publications

1. **Porashar, B.**; Biswas, S.; Sahu, A. K.; Chutia; A.; Saikia, A. K. Temperature Tunable Synthesis of Tetrahydro-4*H*-pyrrolo[3,2-*c*]quinolin-4-ones and Dihydro-1*H*-benzo[*b*]azepines from 2-Aminobenzonitriles and Donor–Acceptor Cyclopropanes. *Org. Lett*. **2022**, *24*, 9038–9042.
2. **Porashar, B.**; Behera, B. K.; Phukon, H.; Saikia, A. K. Synthesis of tetrahydroquinazolines from 2-aminobenzonitriles and alkylidene malonates *via* 1,4-conjugate addition and an unprecedented rearrangement reaction. *Chem. Commun*. **2024**, *60*, 4358–4361.
3. **Porashar, B.**; Saikia, A. K. Lewis Acid Mediated Synthesis of 4-Aminoquinoline Derivatives from 2-Aminobenzonitriles and Activated Alkynes *via* Aza-Michael and Annulation Reaction. *Synthesis* **2024**, *56*, 3131–3141.
4. **Porashar, B.**; Choudhury, C.; Saikia, A. K. Synthesis of 2,4-Diaminoquinazolines and 2-Amino-4-iminoquinazolines via Substrate-Controlled Annulation of 2-Aminobenzonitriles and Carbodiimides. *ChemistrySelect* **2025**, *10*, e202405899.
5. Biswas, S.; **Porashar, B.**; Arandhara, P. J.; Saikia, A. K. Synthesis of pyrimido[2,1-*a*]isoindolone and isoindolo[2,1-*a*]quinazolinone *via* intramolecular aza-Prins type reaction. *Chem. Commun*. **2021**, *57*, 11701–11704.
6. Biswas, S.; **Porashar, B.**; Deka, M. J.; Saikia, A. K. Recent Developments in Prins Cyclization Towards the Synthesis of Spirocyclic Scaffolds. *Asian J. Org. Chem.* **2025**, e202500116.
7. Behera, B. K.; Arandhara, P. J.; **Porashar, B.**; Bora, S. K.; Saikia, A. K. Base-Promoted [4+2] Annulation Reaction of *In Situ*-Generated Azadienes from *N*-Propargylamines with Active Methylene Compounds: Access to Highly Functionalized 2-Pyridones. *J. Org. Chem.* **2023**, *88*, 15041–15059.
8. Sarkar, S.; Devi, N.; **Porashar, B.**; Ruidas, S.; Saikia, A. K. Stereoselective Synthesis of 4-*O*-Tosyltetrahydropyrans via Prins Cyclization Reaction of Enol Ethers. *SynOpen.* **2019**, *03*, 36–45.