Synthesis of Nitrogen Containing Heterocycles & Anthranilate Esters Utilizing Multicomponent Reaction (MCR) Strategy

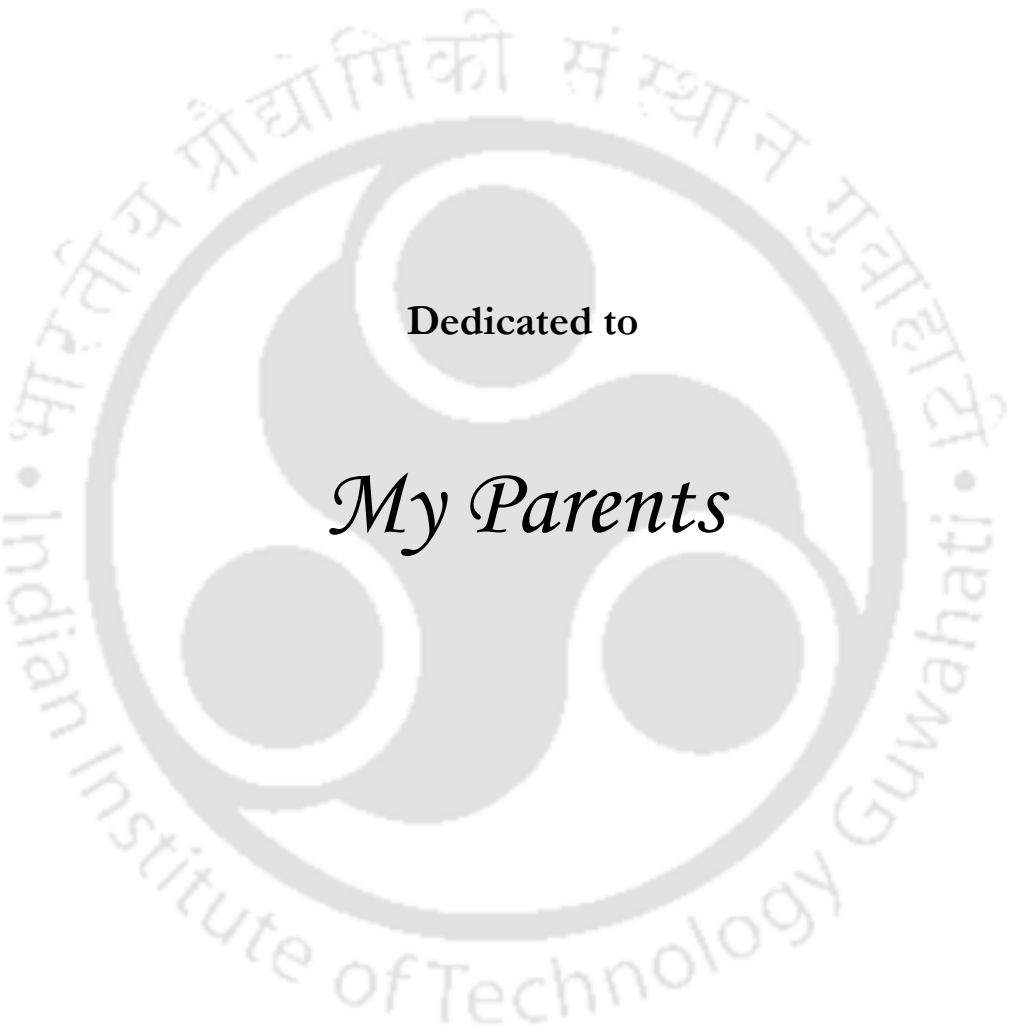
A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of

DOCTOR OF PHILOSOPHY

by

Satavisha Sarkar
Roll No. 10612235

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781 039



Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India, under the guidance of Professor Abu T. Khan. This thesis has been submitted by me to the Department of Chemistry, Indian Institute of Technology Guwahati for the award of the degree of Doctor of Philosophy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. I further declare that this work has not been submitted anywhere else for any degree, diploma, associateship or membership etc. of any Institute or University to the best of my knowledge.

March 24, 2016
IIT Guwahati.

Satavisha Sarkar

Indian Institute of Technology Guwahati
Guwahati – 781039, India
Tel. No.: +91-361-2582305
Fax No.: +91-361-2582349
e-mail: atk@iitg.ernet.in

Dr. Abu T. Khan
Professor of Chemistry

CERTIFICATE

This is to certify that Satavisha Sarkar has been working under my supervision since December, 2010 as a regular registered Ph. D. student in the Department of Chemistry, Indian Institute of Technology Guwahati, India. Her thesis entitled "**Synthesis of Nitrogen Containing Heterocycles & Anthranilate Esters Utilizing Multicomponent Reaction (MCR) Strategy**" contains an authentic record of the results obtained from the research work carried by her. I am forwarding her thesis to submit for the award of Ph. D. (Science) degree from 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.

14th March, 2016.

Prof. A. T. Khan
(Thesis Supervisor)
Department of Chemistry
IIT Guwahati

Indian Institute of Technology Guwahati
Guwahati – 781039, India
Tel. No.: +91 361 258 2319
Fax No.: +91 361 258 2349
E-mail: bmandal@iitg.ernet.in

Dr. Bhubaneswar Mandal
Associate Professor
Department of Chemistry

CERTIFICATE

This is to certify that Satavisha Sarkar has completed her Ph. D. Thesis work from December, 2010 as a regular Institute Research Fellow registered for Ph. D. programme under my colleague Prof. Abu T. Khan. I have been appointed as a Co-supervisor when Prof. Khan joined as Vice-Chancellor of Aliah University in Kolkata, West Bengal on deputation from IIT Guwahati. I am forwarding her thesis as a Co-supervisor entitled "**Synthesis of Nitrogen Containing Heterocycles & Anthranilate Esters Utilizing Multicomponent Reaction (MCR) Strategy**" for submission for the Ph. D. (Science) Degree of this Institute. I also 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.

March 24, 2016

Dr. Bhubaneswar Mandal
(Thesis Co-Supervisor)

Acknowledgement

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

First and foremost, I want to express my deepest respect and most sincere gratitude to my supervisor, Prof. Abu T. Khan, for offering me the great opportunity to be his Ph.D. student. His guidance, scientific ideas, enthusiasm and inspiration helped me a lot to explore the domain of work assembled in this thesis. His believing in me as a chemist gives me the confidence to go forward to further pursue my research career. His support and advise strengthen me in both professional as well as personal aspect which I will treasure my whole life.

I would also like to express my heartiest thanks to my co-supervisor Dr. Bhubaneswar Mandal for his constant guidance, interest and inspiration during my Ph. D. tenure.

I would sincerely like to convey my cordial gratitude to my doctoral committee chairman Prof. Bhisma K. Patel, for his endless support, guidance and inspiration. My heartfelt gratitude for always be there to help me out throughout these years.

I would also like to express my wholehearted thanks to the doctoral committee members, Dr. Mohd. Qureshi and Prof. Mohammad Jawed for their timely evaluation of my work and valuable suggestions. I would like to thank all the staff members of Chemistry department especially Nilyotpal da, Diganta da, Santanu da and Aniruddha da for their friendly and cooperative nature. My sincere thanks to the Central Instrument Facility staffs for their guidance about various analytical instruments during this period. I also wish to thank Dr. Babulal das for his enormous help through these years.

I would obviously like to thank department of Chemistry, IIT Guwahati for providing such excellent instrument facilities and Council of Scientific and Industrial Research (CSIR), India for the financial support.

Next, I wish to express my warm and sincere thanks to my labmates Dr. Md. Musawwer Khan, Dr. Shahzad Ali, Dr. Deb K. Das, Abhik da, Dr. Sidick Basha, Dr Ajaz A. Dar, Dr. Prasanta Ray Bagdi, Arindam, Kobirul, Suchandra, Belal, Karuna and Gattu for their direct and indirect help. I thank my all friends from Patel Sirs' lab like Srimanta Da, Saroj Da, Nilufa, Anupal, Ganesh, Sourav, Wajid, Ahalya, Anju, Prakash and Suresh. I would also like to express my sincere thanks to my friends here in IIT Guwahati as Palash Da, Satya Da, Sukhomoy, Pankaj, Barun, Afsana, Soumi, Arkalekha and Indrani. Thanks to Samir, Najbul and Abhijit for giving their precious time to solve most of the crystals.

I am greatly indebted to my husband, Arghya for his endless support, patience and encouragement throughout these years. His profound apprehension for my career and my life is a treasurable gift. I am thankful to him for not only sharing the blissful moments but also all the sorrows and worries as well as providing me strength all the time.

Finally, my deepest gratitude goes to my parents for their untiring love, support and blessings throughout my life. My deepest gratitude to my parents whose enormous sacrifices in every stages of my life catalyses me to overcome all the hurdles to come upto this stage. I am also grateful to my relatives and family members for their love and affection. Many names are still missing whose contribution is worthy to mention.

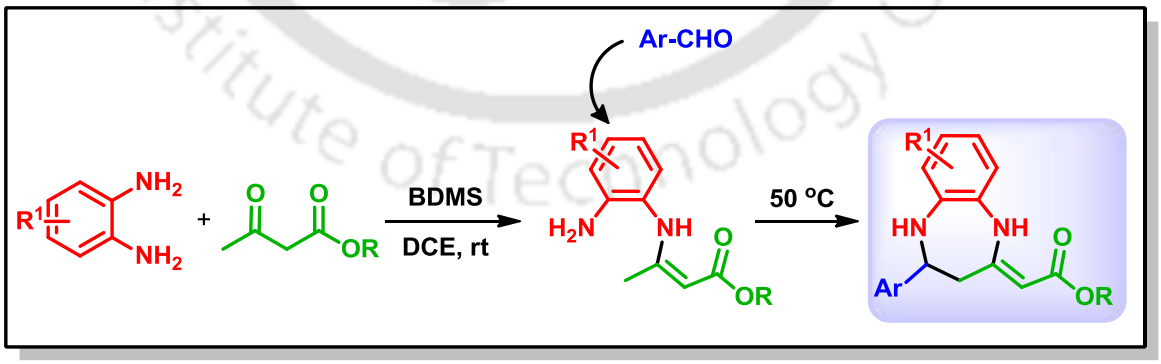
Satavisha Sarkar

SUMMARY OF THE THESIS

The contents of this thesis entitled "**Synthesis of Nitrogen Containing Heterocycles & Anthranilate Esters Utilizing Multicomponent Reaction (MCR) Strategy**" have been divided into five chapters based on the results of experimental works performed during the complete course of the research period.

Chapter I of the thesis represents an outline on different aspects of multicomponent reactions, its application as a useful tool for the synthesis of various organic scaffolds. This chapter mainly emphasizes on the synthesis of different nitrogen containing heterocycles *via* C–C, C–X (X = heteroatom) bond formation. This chapter gives a sketch on the history of multi-component reactions (MCRs), the characteristic features of MCRs, various strategies adopted in modern days, modern MCRs and their applications in organic synthesis.

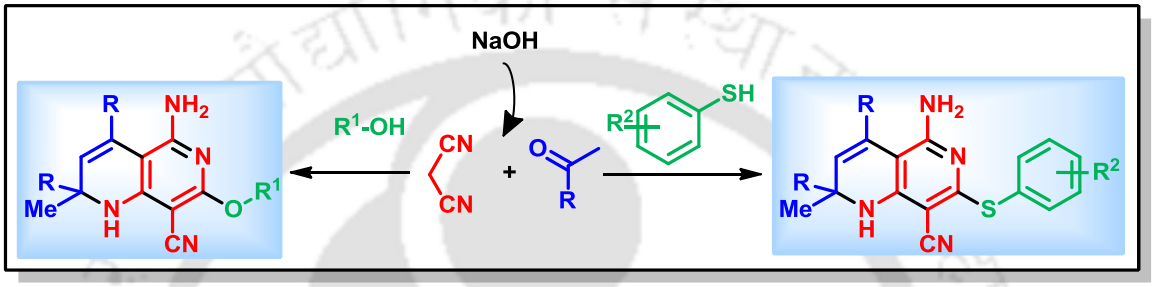
Chapter II illustrates a unique approach for the synthesis of multi-functionalized 1,5-benzodiazepines from *o*-phenylenediamines, β-ketoesters and aromatic aldehydes utilizing one-pot three-component MCR strategy employing BDMS as catalyst. These benzodiazepine scaffolds, which consists of benzene and diazepine moiety have gained a large amount of attention as an important class of nitrogen heterocycles exhibiting a broad spectrum of biological and pharmacological activities. Simple reaction procedure, good yields, mild reaction conditions and applicable to a wide range of substrates are some of the salient features of this protocol.



Scheme 1

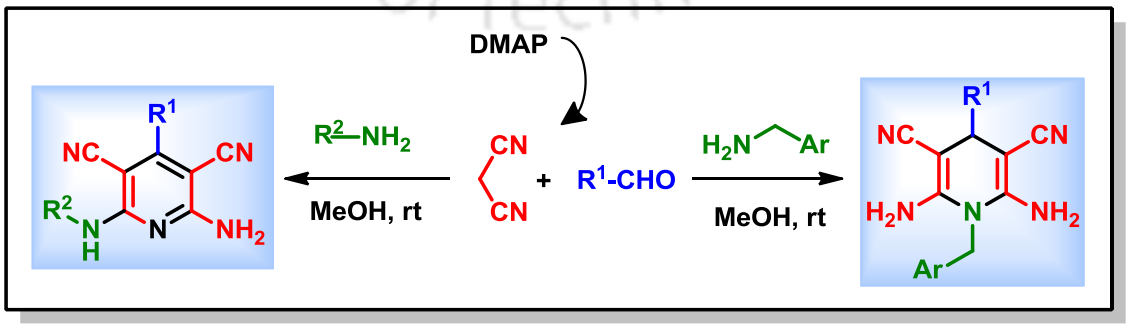
Chapter III describes synthesis of 7-alkoxy-1,6-naphthyridines through one-pot pseudo five-component reaction using aryl methyl ketones/alkyl methyl ketones, malononitrile

and alcohols in the presence of sodium hydroxide under reflux conditions. The reaction was further conducted under identical conditions to produce various 7-(arylthio)-1,6-naphthyridine derivatives from aryl methyl ketones, malononitrile and thiophenols in presence of sodium hydroxide in ethanol. Simultaneous construction of two new pyridine rings as well as two C–N, one C–O or C–S, three C–C bond and one stereocentre, was observed *via* this base-promoted multicomponent reaction in a one-pot operation. High-bond forming efficiency, good yields and use of readily available base are some of the salient features of this multicomponent reaction.



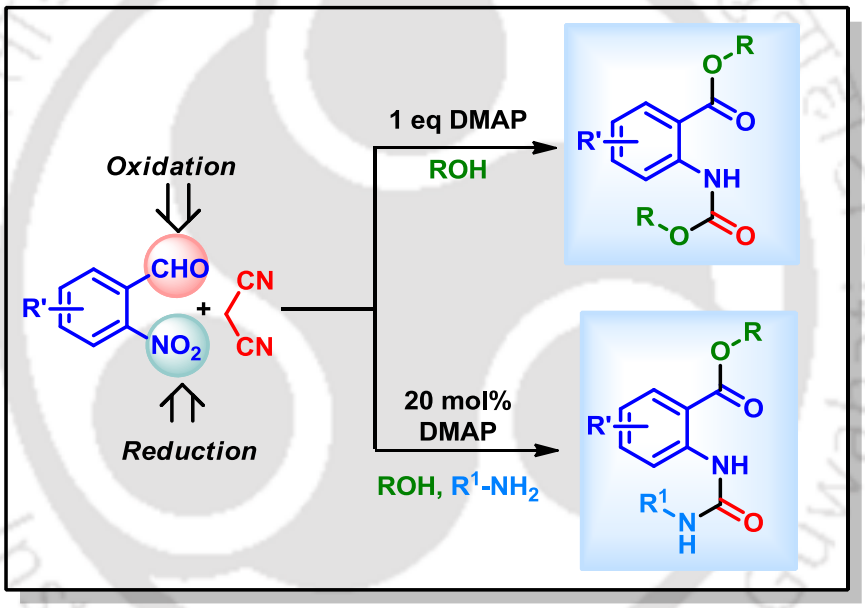
Scheme 2

Chapter IV demonstrates an efficient protocol for the synthesis of pyridines and 1,4-dihydropyridines based on chemoselective multicomponent reactions. Using readily available aldehydes, malononitrile and primary aliphatic amines, this procedure provides a divergent but straightforward access to a wide range of fully substituted pyridines and dihydropyridines *via* primary amine based chemoselective strategy. Simple reaction procedure, good yields, mild reaction conditions, applicablility to a wide range of substrates with the touch of chemoselectivity make this present protocol more original from existing.



Scheme 3

Chapter V illustrates a route for the synthesis of anthranilate esters using 2-nitrobenzaldehyde, malononitrile and an alcohol or amine via a metal and oxidant free multicomponent reaction (MCR) strategy. This process simultaneously installs an ester and urea or urethane functionality *via* C–O and C–N bond formations with concurrent oxidation of the aldehyde group and reduction of the nitro group involving an intramolecular redox process. The synthesis of a variety of symmetrical and unsymmetrical anthranilate esters, of potent synthetic and pharmacological importance, is demonstrated here *via* base-assisted multicomponent reaction utilizing readily available 2-nitrobenzaldehyde, malononitrile and alcohols/aliphatic amines in a highly chemoselective manner.



Scheme 4

Each of these chapters include introduction, previous works, present work, experimental section, references, spectral data and some selected spectra. It is expected that all these methodologies might be applicable in target oriented synthesis and some of the synthesized molecules may exhibit pharmacological activity, which might be useful in future for mankind.

CONTENTS OF THE THESIS

GENERAL REMARKS

The investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, Assam during the period from December, 2010 to March, 2016 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50^{o}C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Büchi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 MHz, Bruker 600 MHz and Bruker 300 MHz spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no. of protons and coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dd (doublet of doublet), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). Mass spectra were collected on Agilent Technologies 6520 Accurate-Mass Q-TOF LC/MS and WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. HPLC grade DMSO and Milli-Q water was used in all the experiments. UV-visible absorption spectra were obtained using a Perkin-Elmer Lambda 25 spectrophotometer. Fluorescence emission spectra were recorded on Horiba Fluoromax-4 spectrofluorometer and Flourimeter (VARIAN Cary Eclipse Fluorescence Spectrophotometer) using 10 mm path length quartz cuvette and a slit width of 3 nm at room temperature.

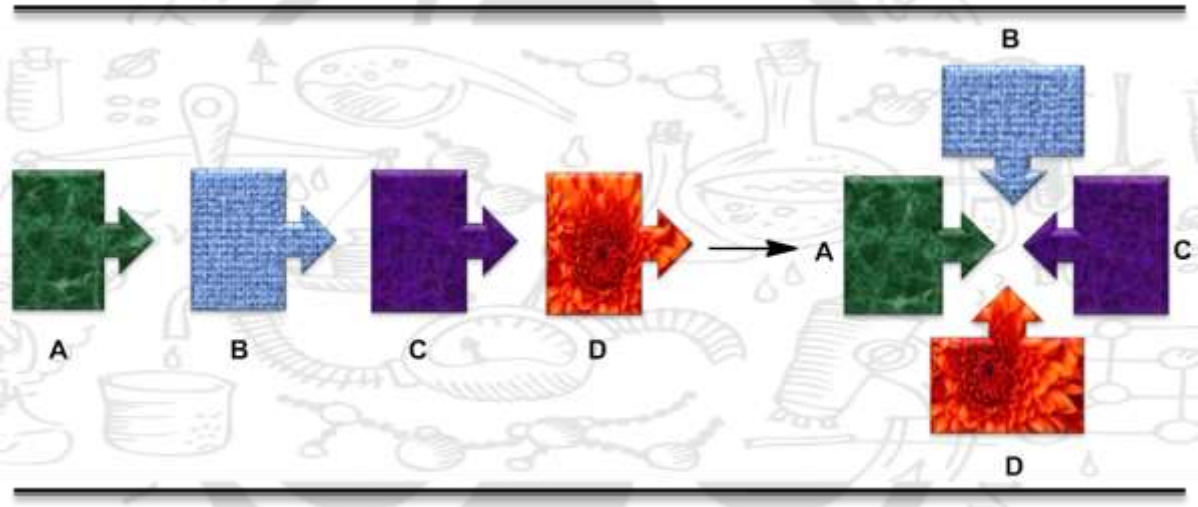
ABBREVIATIONS

Ac	acetyl
AIBN	azobisisobutylnitrile
BA	butyl anthranilate
BDMS	bromodimethylsulfonium bromide
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
Bu	butyl
BuOH	butanol
Bz	benzoyl
CCDC	cambridge crystallographic data centre
DBU	1,8-diazabicycloundac-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEET	*N*,*N*-diethyl-*meta*-toluamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl anthranilate
ee	enantiomeric excess
ESI-MS	electrospray ionisation mass spectrometry
Et	ethyl
EtOH	ethanol
Et_3N	triethylamine
EWG	electron withdrawing group
HRMS	high resolution mass spectrometry
IR	infrared
MCR	multicomponent reaction
m-CPBA	*m*-chloroperoxybenzoic acid
MDA	*N*,*N*-dimethyl anthranilate

MeOH	methanol
mp	melting point
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
ORTEP	oak ridge thermal ellipsoid program
Ph	phenyl
ppm	parts per million
Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
PTSA	*p*-toluenesulfonic acid
rt	room temperature
SAR	Structure activity relationship
TBATB	*n*-tetrabutylammonium tribromide
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl pyridine-*N*-oxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
UDC	Ugi deprotection cyclization
XRD	x-ray diffraction

Chapter I

An Outline on Synthesis of Organic Frameworks Using Multicomponent Reaction (MCR) Strategy



CHAPTER I

An Outline on Synthesis of Organic Frameworks Using Multicomponent Reaction (MCR) Strategy

❒ I.1. Introduction

Multicomponent reactions (MCRs) have evolved as an efficient strategy in the synthetic community to produce targeted complex heterocyclic skeletons in a simple yet selective pathway. The definition of MCRs is generally stated as the category of reactions where three or more starting materials react to form a certain product and basically all or most of the atoms contribute to this newly formed product.[1] Therefore, these reactions encompass a sequence of more than one chemical transformation leading to great molecular diversity and allow creation of libraries of small organic molecules while requiring less time and effort. This strategy is especially effective for the pharmaceutical industry, for which the easy creation of large libraries of compounds with possible biological activity is a priority. Figure 1 shown below describes how various functional groups come together to form certain intermediate which forms different products under different cyclization conditions.

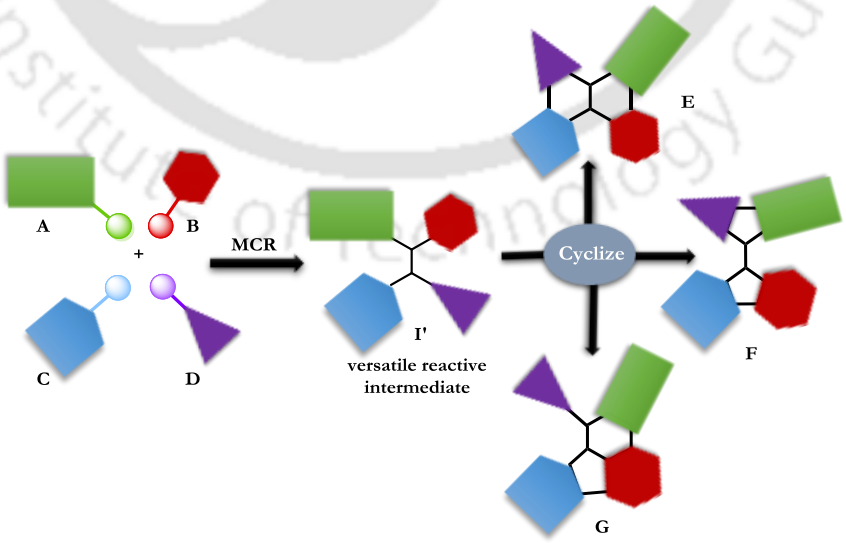


Figure 1. Product diversification using MCR strategy

❒ I.2. Characteristic Features of MCR

Over the last decade, scientists have concentrated to apply productive strategies to synthesize complex scaffolds and highly substituted molecules, combining molecular diversity[2] with ecocompatibility[3]. In effect, the main focus of the scientific fraternity is to design reactions that transform simple and readily available substrates into complex structures in a single reaction. In this context, MCRs have become one of the best established approaches for reaching this goal, since these strategies imply high atom economy[4a] and bond-forming efficiency.[4b]

In MCRs, a molecule is assembled in a convergent chemical step in one pot by simply mixing the corresponding starting materials in contrast to traditional multiple sequential stepwise ways of synthesizing a target molecule over multiple sequential steps. One-pot MCRs approaches are much easier to execute than a complicated multistep synthesis as depicted in Figure 2. The synthesis of the complex molecule with high stereo-, regio- and chemo selectivity can be achieved through multicomponent reactions.[5] MCRs render a facile access to highly convergent and efficient synthesis of diverse molecules and this attribute of MCRs make them superior from other synthetic reactions.

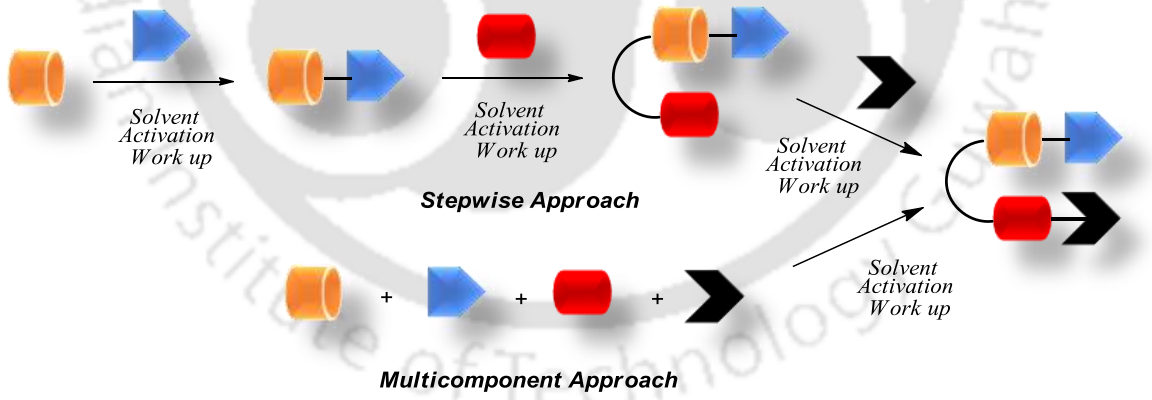


Figure 2. Stepwise *vs* multicomponent approach

This has considerable advantages as it saves time and drastically reduces effort compared to the step wise route. MCRs are experimentally simple to perform, often without the need of dry conditions and inert atmosphere. Therefore, structure–activity relationships (SARs) can be rapidly generated using MCRs, since all property determining moieties are

introduced in one step instead of sequentially.[6] The reason behind the increasing popularity of MCRs have been pointed in Figure 3.

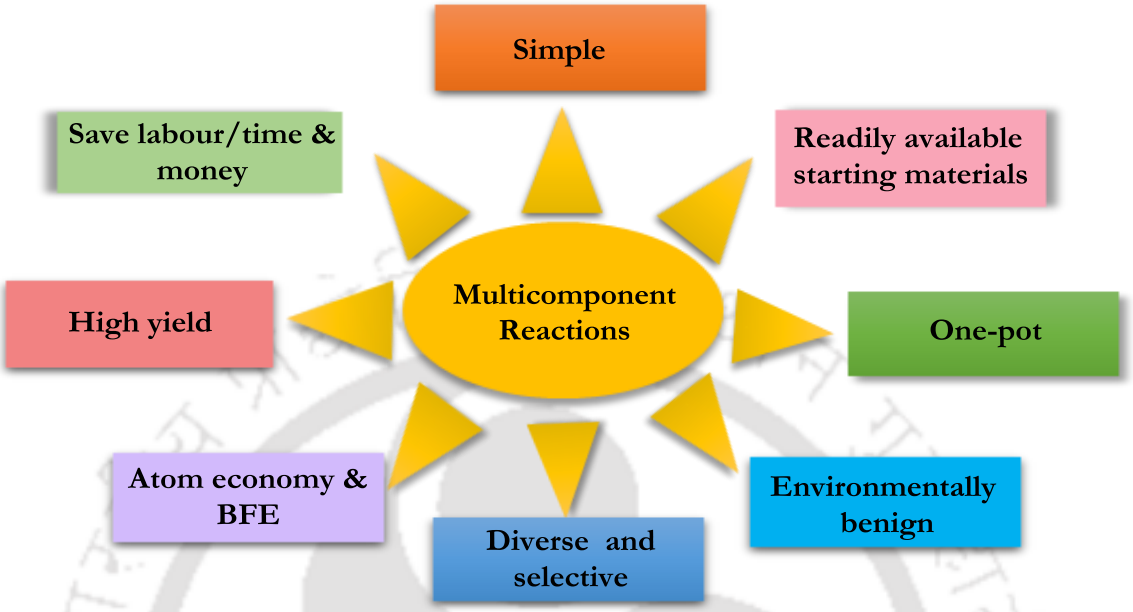


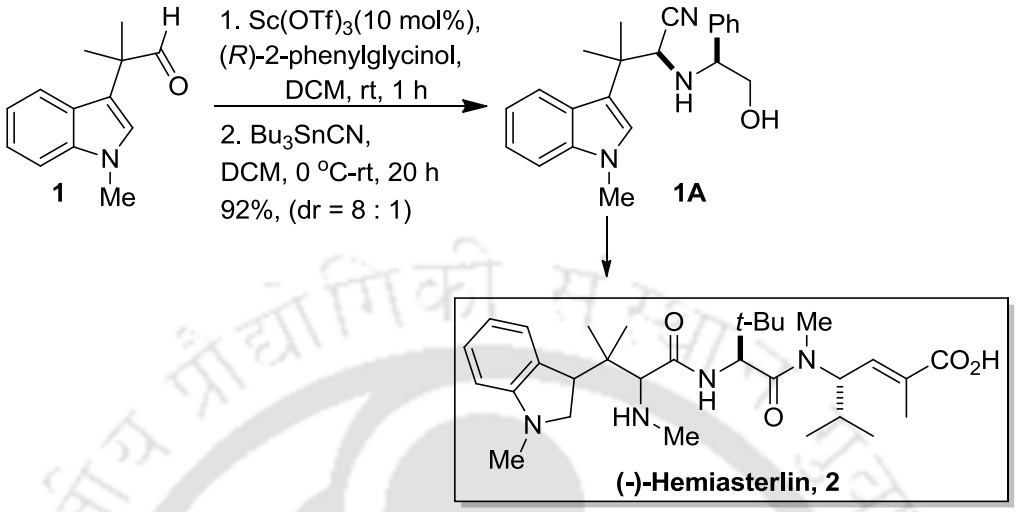
Figure 3. Characteristic features of MCR

❒ I.3. Historical Overview of MCRs

It is very interesting to note that MCRs offer a vast chemical diversity which presently managed to more than 300 different frameworks according to the chemical literature. For example, there are more than 40 diverse routes reported to synthesize substituted piperazine adducts using MCRs.[7] MCR chemistry is relatively quiet old as the history goes decades back in 1851. It should be mentioned that early day chemists did not identify the huge potential of MCRs. However, it required more than 100 years until Ivar Ugi discovered his four component condensation reaction and also noted the profound possibility of MCRs in applied chemistry.[8]

The advent of multicomponent reaction started several decades back in 1850, when Adolph Strecker reported the first multicomponent reaction for the synthesis racemic α-amino nitriles using amines, aldehydes, and cyanide.[9] This traditional synthesis was further improvised utilizing asymmetric auxiliaries or asymmetric catalysts. Vedejs and co-workers[10] exploited the asymmetric Streker reaction for the construction of the key intermediate tetramethyltryptophan **1A** for the enantioselective total synthesis of (-)-

Hemiasterlin (**2**), a marine tripeptide having cytotoxic and antimitotic activity as illustrated in Scheme 1.



Scheme 1. MCR in total synthesis of (-)-Hemiasterlin

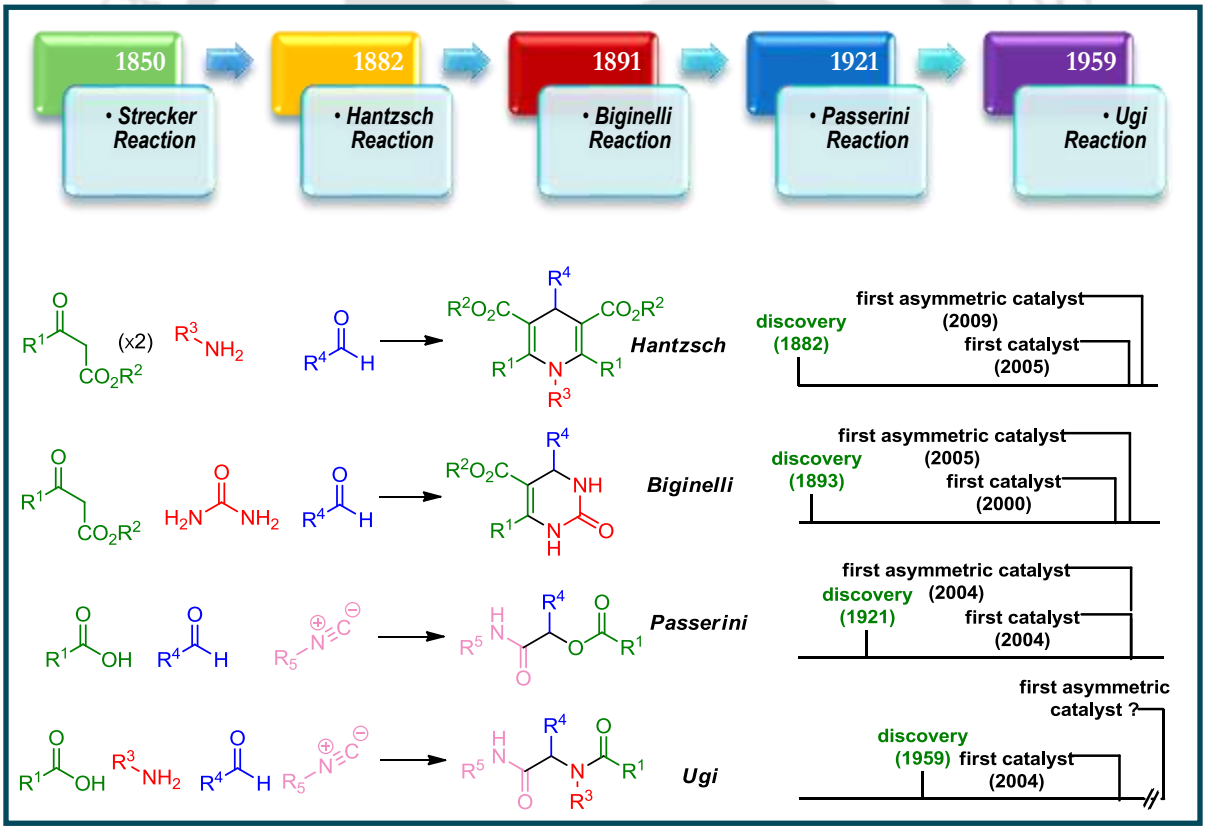
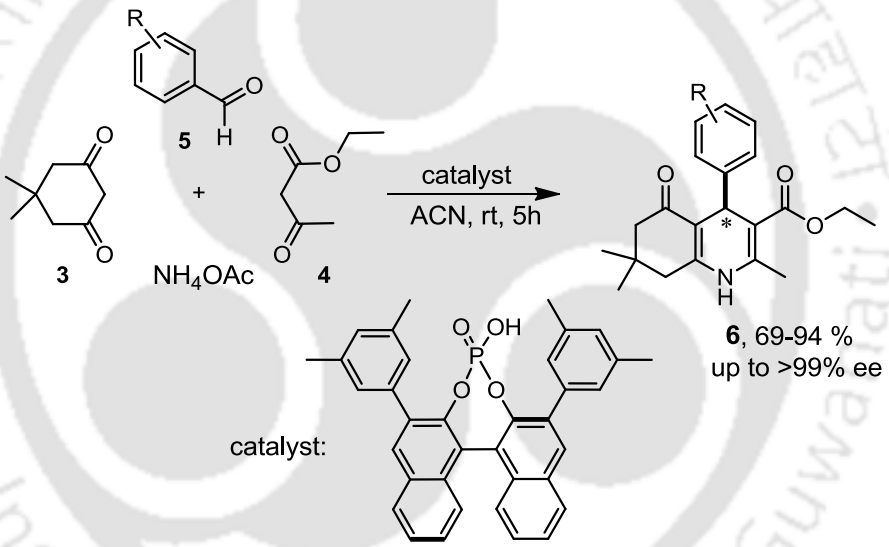


Figure 4. A brief history of MCR

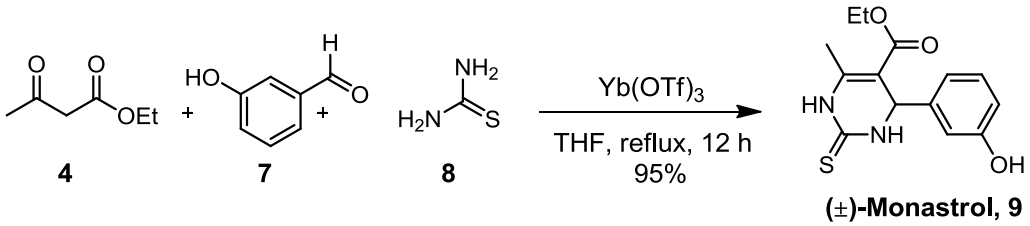
Other MCRs namely Hantzsch,[11] Biginelli,[12] Passerini[13] and Ugi[14] reactions have conveyed a true renaissance during the earlier age of combinatorial chemistry. The figure 4 shows the schematic diagram of these conventional reactions as well as their rough time scale of their discovery, first catalytic as well as asymmetric catalytic approach.[5c]

In 1882, Arthur Rudolf Hantzsch developed a new way for the synthesis of dihydropyridine (DHP) moieties. Though the initial reaction product was a dihydropyridine skeleton which could be further aromatized to a pyridine in a subsequent step. Many significant modifications of Hantzsch reaction have been reported. In this scenario, such a report is mentioned in Scheme 2. Gestwicki *et al.* recently reported[15] an enantioselective route for the synthesis of optically active 1,4-DHP derivatives **6** in good yields using Hantzsch reaction in presence of a chiral organocatalyst, as depicted in Scheme 2.



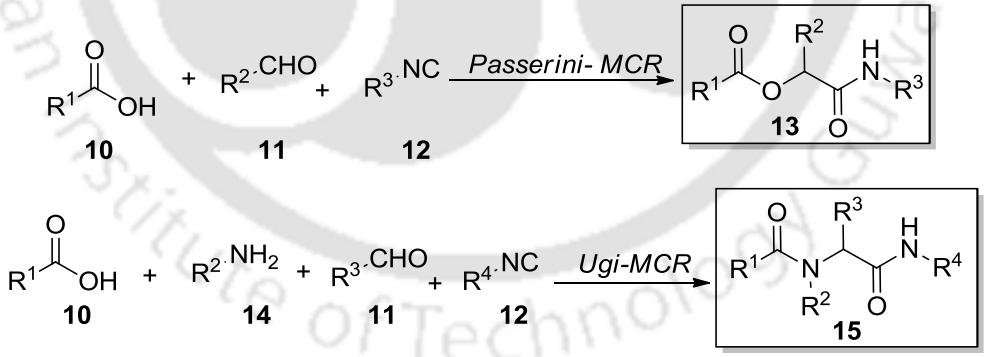
Scheme 2. Hantzsch reaction towards the synthesis of 1,4-DHP derivatives

Next the limelight is focused over the Biginelli 3CR discovered in 1893 by the Italian chemist Pietro Biginelli. He was the first to synthesize functionalized 3,4-dihydropyrimidin-2(1*H*)-ones by one-pot three-component reaction of an aldehyde, urea and ethyl acetoacetate.[12] Dondoni and co-workers reported an improved synthesis of racemic monastrol (**9**) by utilizing the traditional three-component version of the Biginelli reaction. The one-pot three-component reaction between 3-hydroxybenzaldehyde (**7**), ethyl acetoacetate and thiourea (**8**) catalyzed by $Yb(OTf)_3$ resulted in 95% racemic monastrol (**9**) as given in Scheme 3.[16]



Scheme 3. Biginelli reaction utilized to form racemic Monastrol

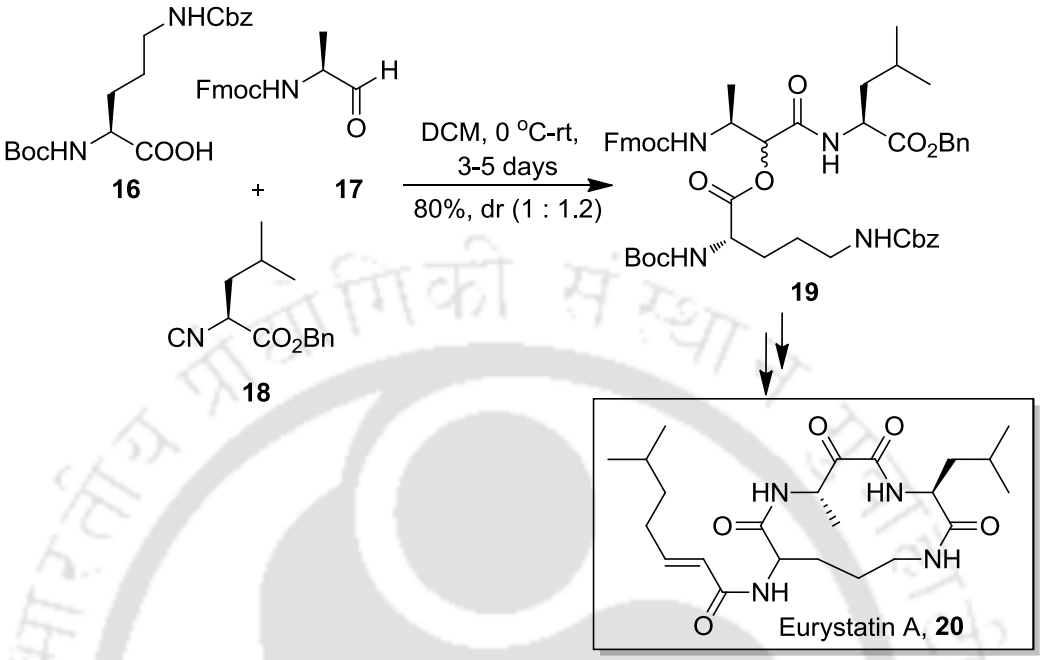
Still today most MCR chemistry performed with isocyanides relates directly or indirectly with the classical Passerini and Ugi reactions (Figure 4).[17,14] Indeed, the large number of different scaffolds now available mostly builds on these two MCRs and their combination with other types of reactions. Passerini reactions involve an oxo component **11**, an isocyanide **12**, and a nucleophile **10**. Ugi reactions are defined as the reaction of a Schiff base or an enamine with a nucleophile **10** and an isocyanide **12**, followed by a rearrangement reaction. Amusingly, Ugi reactions are much more versatile compared to Passerini, not only in terms of library size but also in terms of various scaffold generation. This can be attributed to the many of the different acid components or nucleophiles as well as amine components that have been described till date for the Ugi reaction. In the past decades, several reviews[17c-e] have been appeared on the Ugi and Passerini reaction towards the synthesis *N*-heterocycles.



Scheme 4. Isocyanide based Passerini and Ugi multicomponent reactions

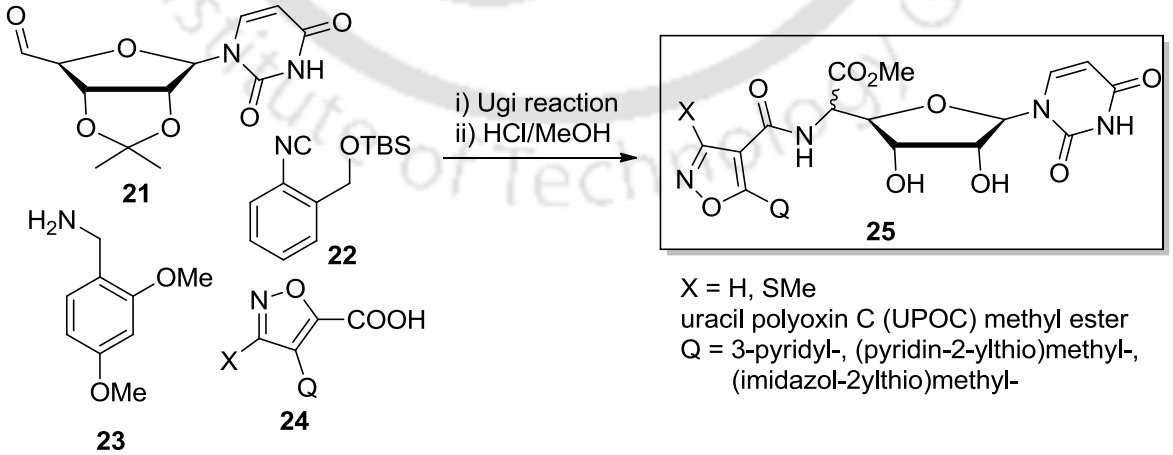
Semple *et al.* utilized such Passerni reaction for the synthesis of eurystatine A (**20**), which is a 13-membered macrocyclic natural product as depicted in Scheme 5.[18] Amine protected acid component **16** reacts with aldehyde **17** and isocyanide **18** functionality to give the

condensed product **19** which further undergoes several steps to form desired macrocyclic unit.



Scheme 5. Passerni reaction for the synthesis of Eurystatine A

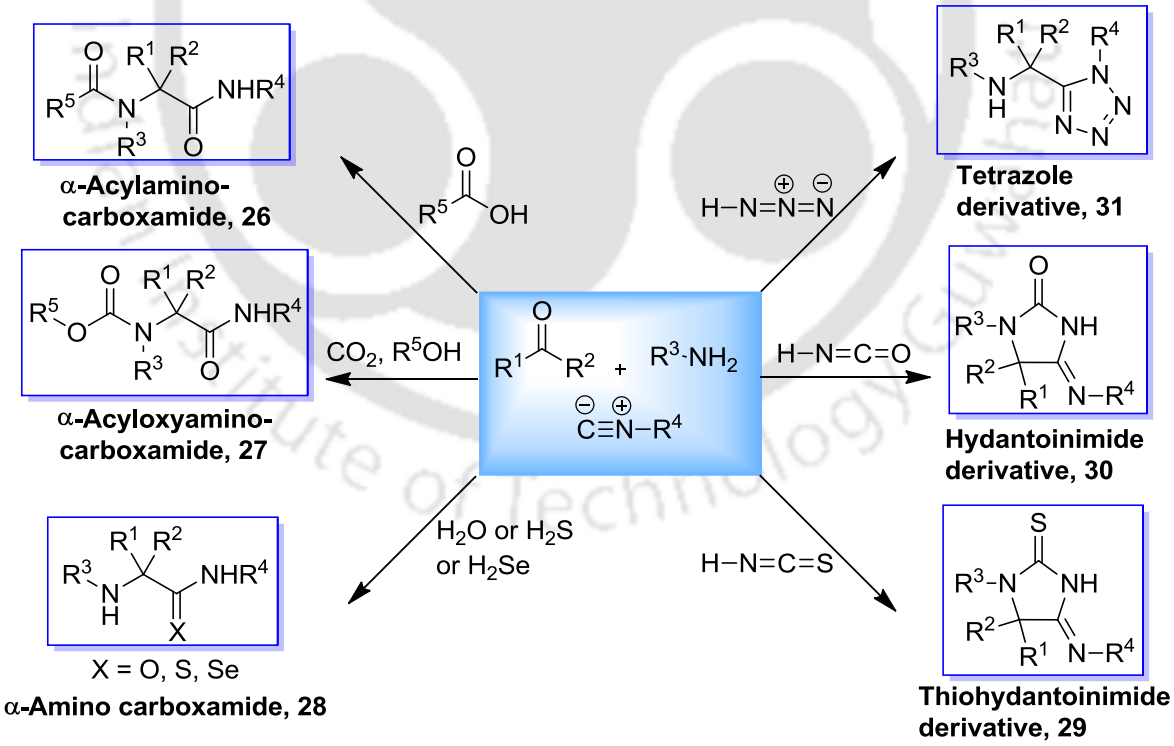
The one pot synthesis of Uracil Polyoxin C analogues **25** using Ugi multicomponent reaction has been described by Williams and co-workers (Scheme 6).[19] The four components employed in the Ugi reaction are 2′,3′-isopropylidine-protected uridine-5′-aldehyde **21**, 2,4 dimethoxybenzylamine **23**, an isoxazolecarboxylic acid **24**, and the convertible isonitrile *N*-(2-{[(*tert*-butyldimethylsilyl)oxy]methyl}phenyl)carbonitrile **22**.



Scheme 6. Synthesis of uracil Polyoxin C analogues using Ugi multicomponent reaction

Following the Ugi reaction, treatment with HCl in MeOH achieves deprotection of the isopropylidene group and the *N*-benzyl group and conversion of the isonitrile-derived amide (the Ugi product) into the corresponding methyl ester. The procedure is amenable to automated multi-parallel synthesis of novel compounds related to the polyoxin and nikkomycin nucleoside-peptide antibiotics.

Moreover, Ugi reaction found widespread applications in combinatorial chemistry as represented in Scheme 7.[8,14,17c-d] The isocyanides undergo a four-component reaction (4-CR) in the presence of an amine and aldehyde or ketone in presence of a nucleophilic source to afford a single condensation product. The most frequently used nucleophiles are carboxylic acids, hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, water, hydrogen sulfide and hydrogen selenide. For all the different cases they received diverse organic frameworks form acyclic carboxamide derivatives to nitrogen containing heterocycles. Still now Ugi reaction is a widely applicable and moreover modified or combined with other reaction to generate complex molecular structure which has been mentioned later.



Scheme 7. Utilization of Ugi reaction for the synthesis of different organic scaffolds

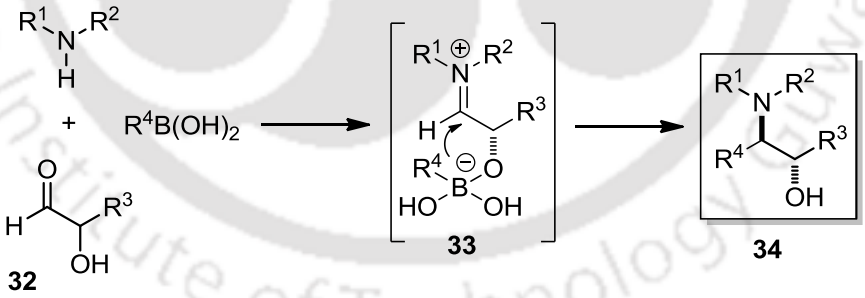
❒ I.4. Modern era of Multicomponent Reaction

Now stepping into the modern era of multicomponent reactions, advanced techniques have been applied over the conventional concepts of MCRs initiating quite a revolution. Some of such strategies have been mentioned below.

I.4.1. Multicomponent Reactions with Organoboron Compounds:

Organoboron reagents, especially boronic acids and boronates, have been widely applied as a suitable and potential reagent for the formation of new C—C bonds in organic synthesis, medicinal chemistry, and material science.[20] Such kind of compounds has received the attention of the modern day scientists not only because of their wide commercial accessibility but more notably, because of their stability toward air and water, the low toxicity and tolerance to several functional groups.

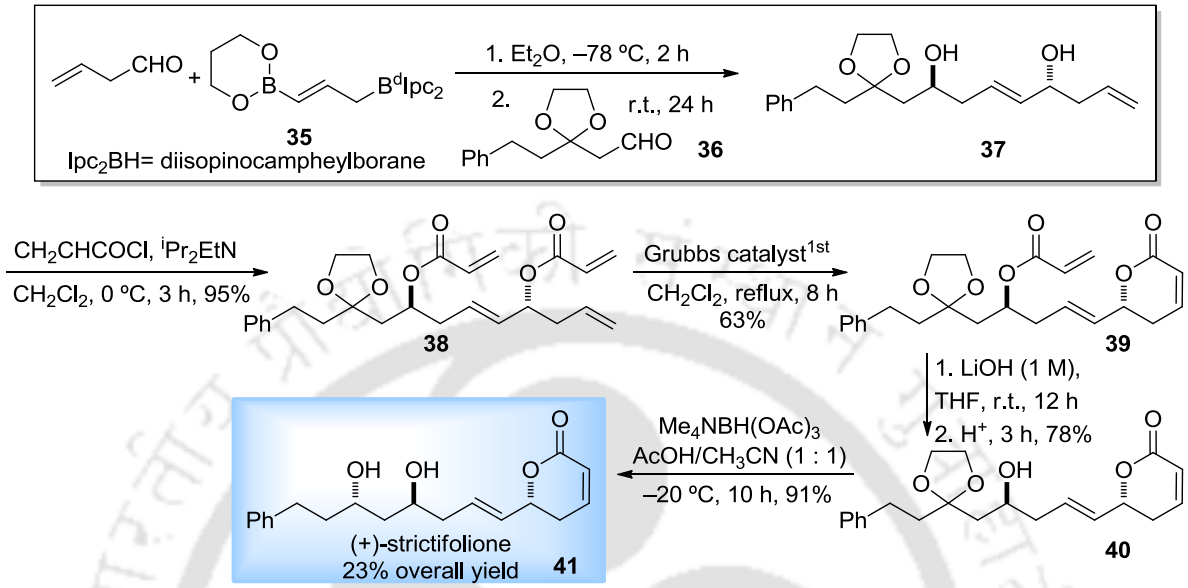
One of the most important and efficient protocols is the multicomponent Petasis-Borono–Mannich (PBM) reaction.[21] In this approach, an amine, an aldehyde, and a boronic acid react to give access to a new amine *via* a C–C bond forming reaction (Scheme 8). The regulating step of this strategy is the migration of the boronic acid substituent to the carbon, which bears an iminium ion intermediate **33**.



Scheme 8. Petasis reaction using α-hydroxy aldehydes

Synthetic applications of boron-based MCRs blanket a wide area from generation of macromolecules to asymmetric allene diboration/α-aminoallylation. In such perspective the efforts of She *et al.* on their successfully attempt for the one-pot double allylboration reaction for the enantio- and diastereoselective preparation of a (*E*)-1,5-*anti*-ene-diol subunit

37 made quite a mark. It is a key fragment in the total synthesis of (+)-strictifolione **41**,[22] a 6-susbtituted α-pyrone with antifungal activity (Scheme 9).[23]



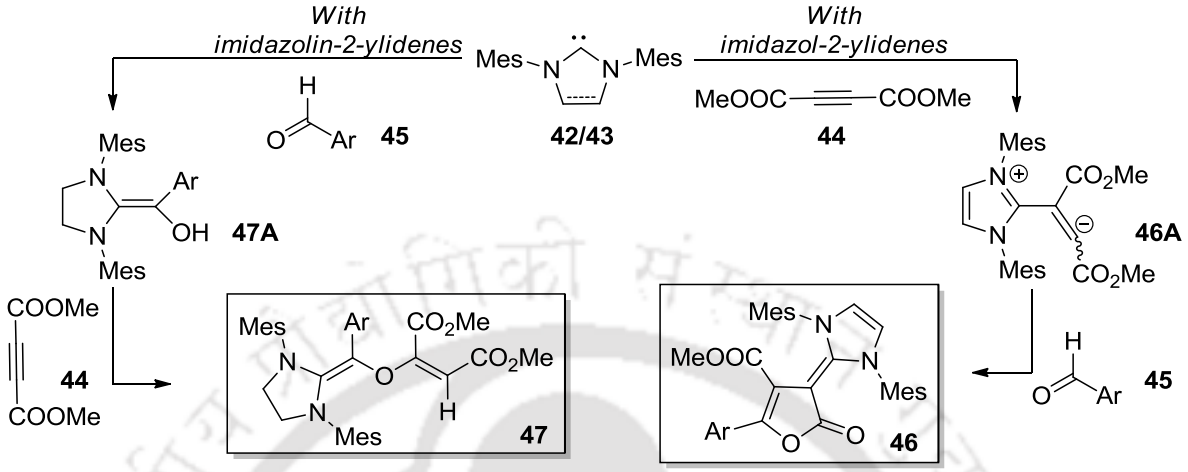
Scheme 9. Use of organoboron compounds in total synthesis

I.4.2. Carbene-Promoted Multicomponent Reactions

Carbenes are neutral species containing a carbon atom with only six valence electrons. They act as reactive intermediates or work as special reagents or activate the functional groups performing as robust catalysts. They are the new area of potential research for developing new technologies. Depending on their role as reagents or catalysts, carbene species are marked within three types 1) Nucleophilic carbenes, 2) Fischer carbene complexes (FCCs) and 3) carbenes as catalysts. The first crystalline and stable *N*-heterocyclic carbenes (NHC) was isolated by Arduengo and coworkers, in the early 1990s. It aroused quite curiosity due to their properties such as relative stability, moderate nucleophilicity or strong basicity.

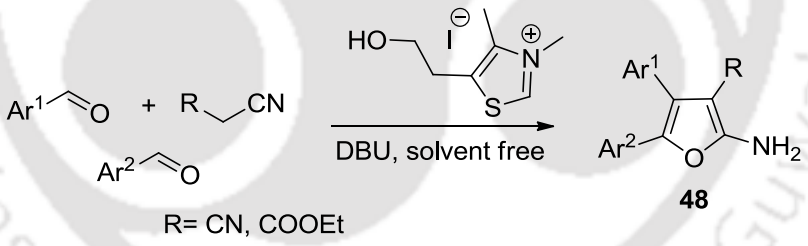
In 2003, Nair and coworkers described the first-ever MCR with Imidazol-2-ylidenes as NHCs, wherein two related carbenes imidazole or imidazolin-2-ylidenes **42/43** reacted differently[24a] *via* two different pathways. In case of imidazol-2-ylidenes **43** (with aromatic stabilization), the reaction first forms a zwitterionic species **46A** which later adds to the aldehyde **45** to generate the corresponding furanone derivatives **46**. On the other hand, the imidazolin-2-ylidenes **42**, the carbene adduct first adds to the aldehyde moiety **45** to give the

electron rich enaminol intermediate **47A**, which undergoes a conjugated addition on the alkyne, to yield 2-oxy-maleate derivatives **47**.



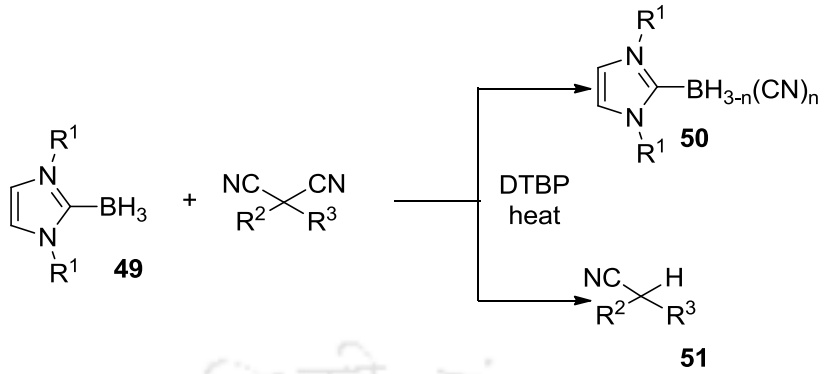
Scheme 10. NHCs supported multicomponent reaction

Yao and coworkers reported an efficient NHC-catalyzed 3CR for the synthesis of 2,3-diarylated fully substituted furans **48** from inexpensive starting materials such as aromatic aldehydes and malononitrile or ethyl cyanoacetate.[24b]



Scheme 11. Synthesis of fully substituted furans catalyzed by NHC

In this context, a two component recent report can be mentioned where NHC-boryl radicals abstract a cyano functionality from various organic nitriles to generate two complementary transformations giving both the products **50** and **51**. The main group chemistry deals with the reactions of various NHC-boranes with simple organic dinitriles **49** to selectively give stable NHC-boryl mono- or dinitriles **50**, depending on the nitrile source. This organic synthesis shows the reaction of malononitriles with organoboron compounds *via* carbene promoted reactions.

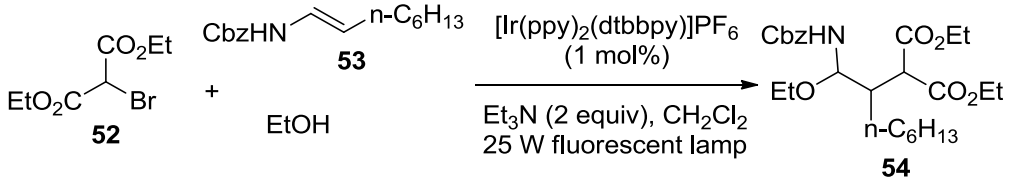


Scheme 12. Reaction of organic nitriles with NHC-boryl radicals *via* carbene mediated pathway

I.4.3. Free-Radical Multicomponent Processes

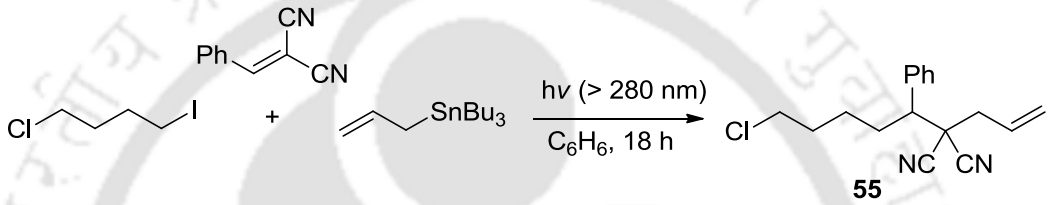
The strategy of new radical MCRs has witnessed a rapid growth in the past 20 years relying on the expansion of suitable mediators capable to endure the radical chain. Thermodynamics stability of new radical species generated during the course of the reaction and kinetics of each step are the key points in the planning of a certain radical mediated MCR. Such free radical reactions generally involve MCRs *via* addition across olefin C=C bonds which can be further categorised as i) addition of aryl radicals to olefins, ii) using sulfonyl derivatives as terminal trap, iii) carboallylation of electron-poor olefins, iv) carbohydroxylation, sulfenylation, phosphorylation of olefins and few more. Other than those, some other type of reaction can be marked as i) free-radical carbonylation ii) free-radical oxygenation and iii) MCRs involving addition across π-C=N bonds. Other than these, many miscellaneous reaction are present which involves free radicals in the reaction medium. Among all the above mentioned strategies visible light induced free readical reactions are mentioned here.

Visible light-mediated photoredox catalysis is currently receiving a growing interest in this certain field. Photocatalysts based on Ru^{2+} and Ir^{3+} complexes allow activation of organic moieties through photo-induced electron transfer (PET).[26] The synergetic effect of light and transition metal catalyst is opening new possibilities towards radical organic synthesis. Masson *et. al* reported a radical addition of bromomalonate **52** onto enecarbamate **53** under photocatalysis conditions (with an Ir^{3+} catalyst), using Et_3N as a reductive quencher (Scheme 13).[27a]



Scheme 13. Photoredox α-alkylation of imines *via* 3 component radical reaction

Allyltin compounds are unique players in radical chemistry. The example below shows tin radical mediated three-component reactions using a mixture of alkyl halides, electron-deficient alkenes and allyltin.[27b]



Scheme 14. Tin radical mediated multicomponent reaction

I.4.4. Transition Metal Catalyzed Multicomponent Reactions

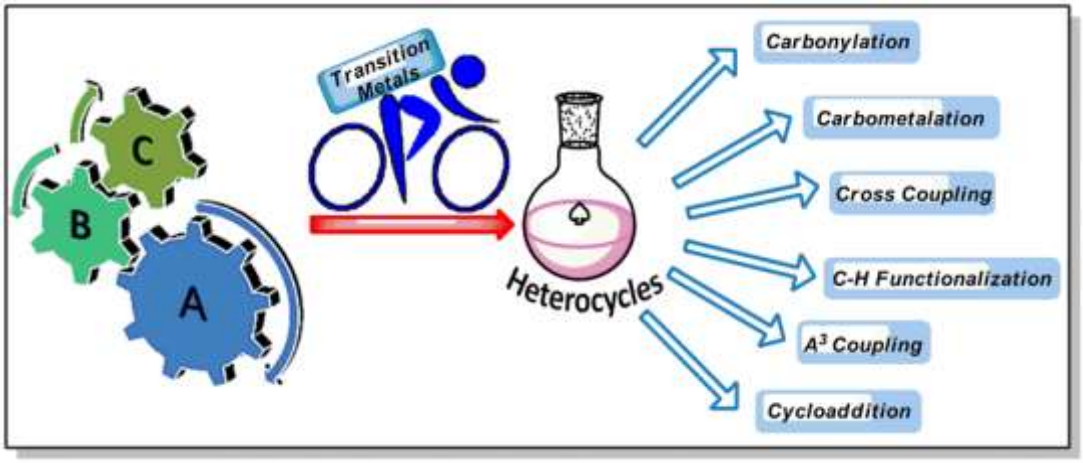
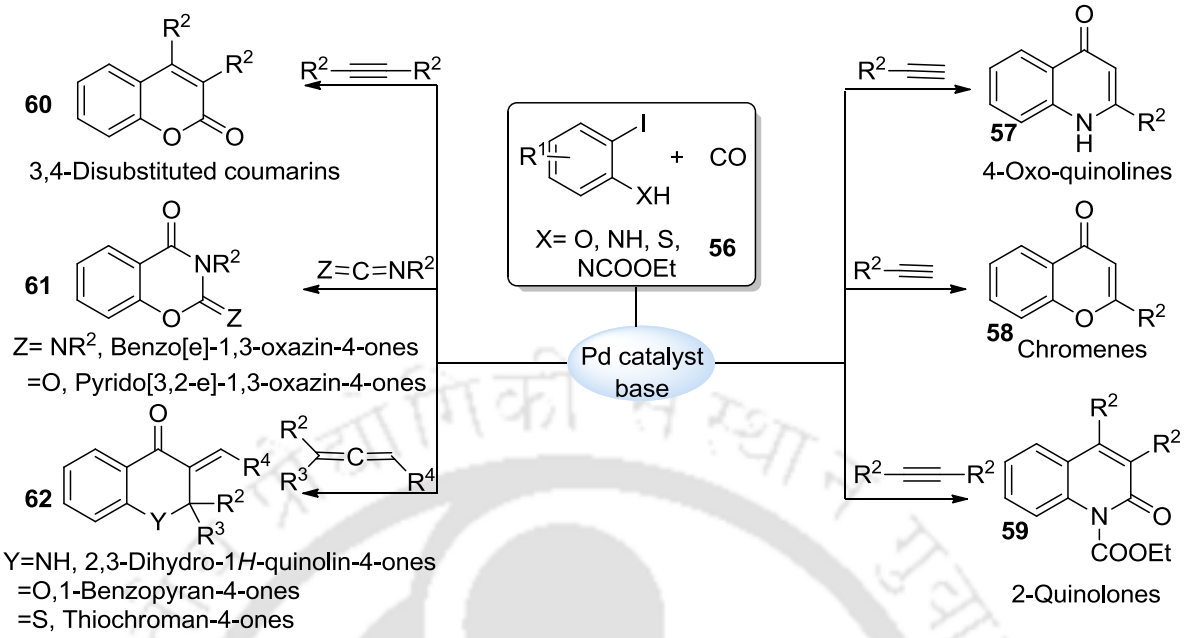


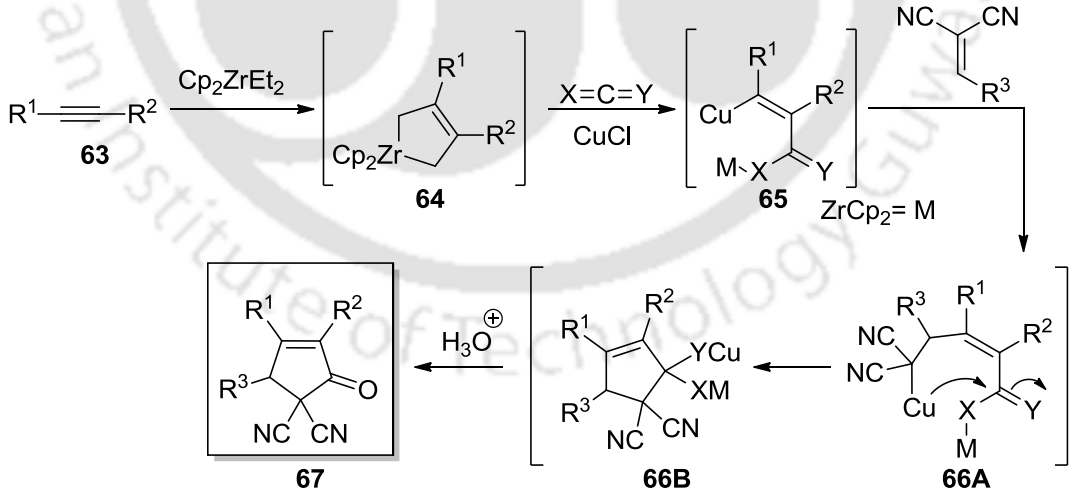
Figure 5. Different strategies adapted for transition metal catalyzed MCRs

Transition metal-catalyzed multicomponent reactions came up as the central theme in this play due to its versatile role for designing new synthetic routes (Figure 5) for the synthesis of various heterocycles. The area encompasses various types of strategies such as carbometallation, carbonylation, cross coupling, C–H functionalization, A^3 coupling and cycloaddition.



Scheme 15. Synthesis of heterocycles *via* carbonylation process

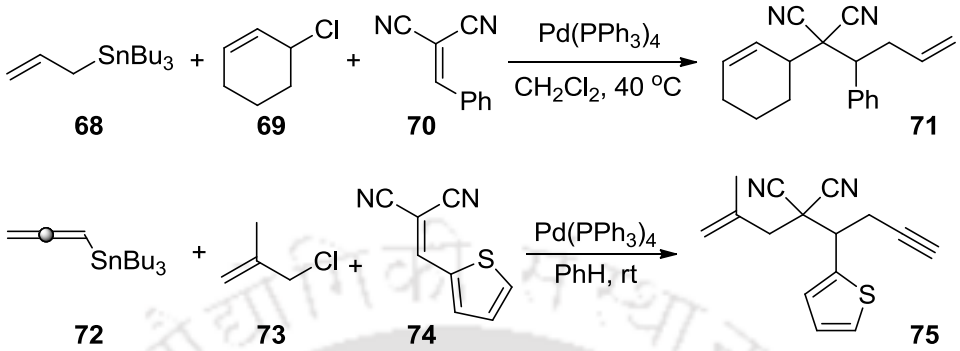
Carbonylative coupling reactions started very early during 1974 by Heck *et al.* however its implications in heterocyclic synthesis started lately. This attractive class of transformation inserts carbon monoxide component in the presence of palladium catalyst during the multicomponent process to produce bioactive heterocycles *viz.* flavones, quinolones, chromenes, coumarins and many more **57**-**62** as shown in Scheme 15.[28]



Scheme 16. Zirconocyclopentadienes utilized in the synthesis of cyclopentenone

Three-component reactions involving zirconocyclopentadienes have been also employed in cyclopentenone (**67**) synthesis. The method combines disubstituted alkynes **63**,

isocyanates, and arylidene or alkylidene malononitriles to assemble polysubstituted cyclopentenones **67** (Scheme 16).[29]



Scheme 17. Use of allylstannanes and allenylstannanes to generate 1,7-dienes or 1,7-enynes

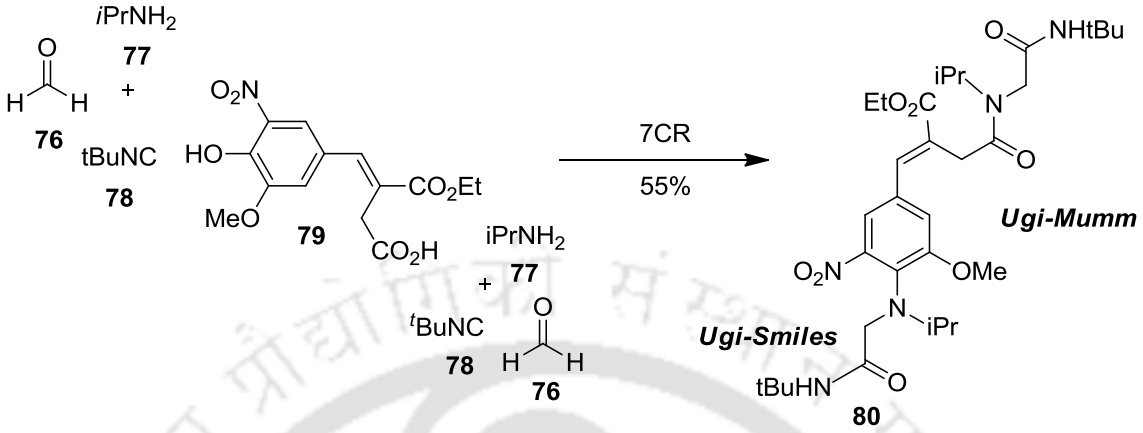
Bis-allylation of unsaturated compounds can be achieved by using amphiphilic bisallylpalladium complexes generated from allylstannanes and allyl chlorides. Yamamoto[30a] and Szabó[30b] have well studied the reactivity of gem-diactivated olefins, essentially acrylonitriles, to synthesize 1,7-dienes **71**. As demonstrated in Scheme 17, high levels of regioselectivity can be achieved when unsymmetrical bis-π-allylpalladium intermediates are involved due to the electronic effects of the substituents on the allyl moieties. Interestingly, besides activated olefins, arenes,[30c] carbon dioxide,[30d] and isocyanates[30e] have also been reported as excellent partners in this reaction. Recently, Cheng[31] has developed a similar process involving allenylstannanes, which opens access to 1,7-enynes **75** (Scheme 17).

I.4.5. Combinatorial Approach in MCR

MCRs are of particular interest for three reasons: efficiency, diversity and their large unexplored chemical space. Among the modern techniques combinatorial approach describes the combination of two or more type of reactions together to perform a higher order reaction which led the organic chemists to a new area of MCRs. An example has been depicted below to explain such method.

Brauch *et al.*[32] reported a seven-component reaction by suitably combining the Ugi–Mumm and the Ugi–Smiles reaction. The sequential multicomponent reaction has led to highly diverse peptide and glycopeptide like structures (**80**) from formaldehyde, isopropyl

amine and *tert*-butyl isonitrile. The Ugi–Mumm/Ugi–Smiles product was formed in 55% yield and the yield for each bond forming step exceeds 90% as depicted in Scheme 18.

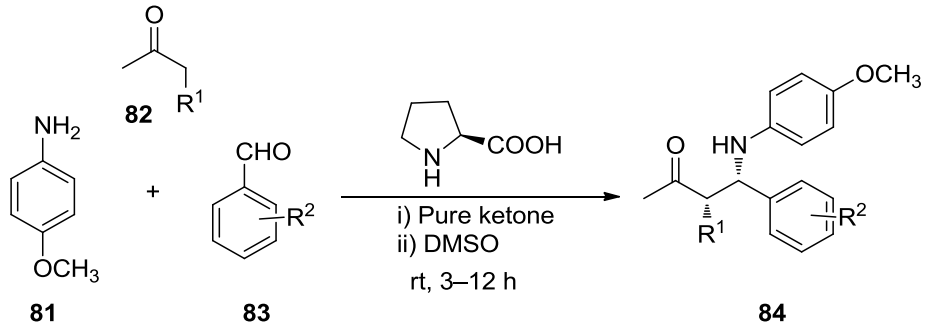


Scheme 18. Combinatorial approach using Ugi–Mumm and the Ugi–Smiles reaction

I.4.6. Organocatalytic Asymmetric Multicomponent Reactions

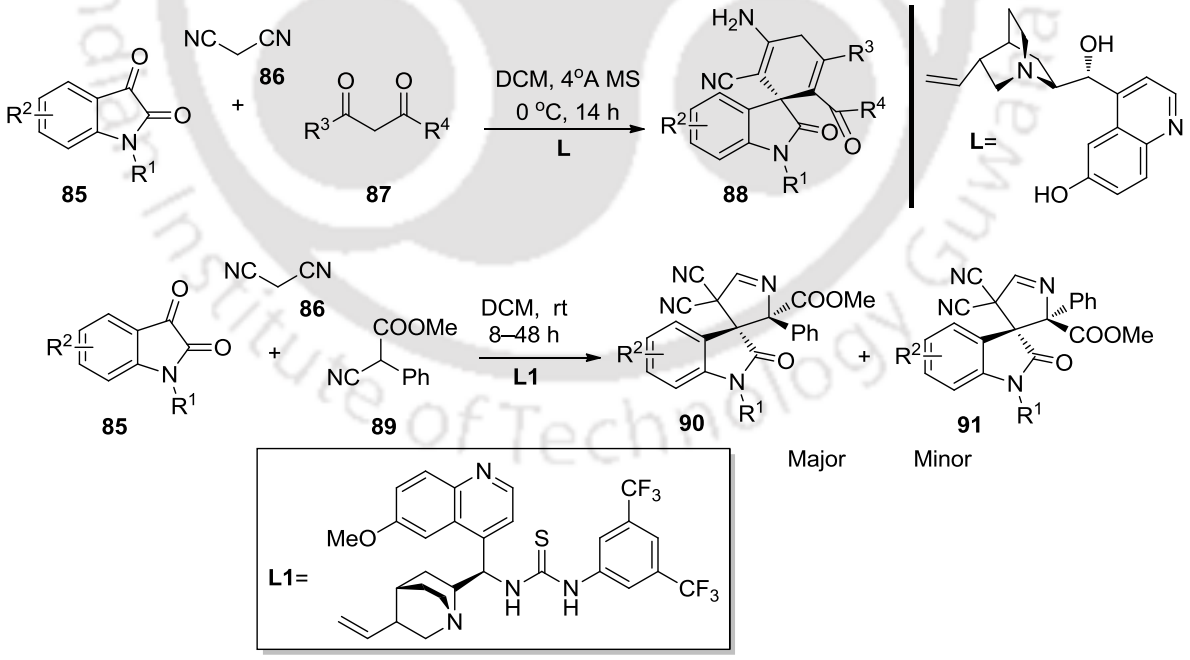
Asymmetric organocatalysis, the practice of small organic molecules as catalysts,[33] is gaining an increasing popularity due to its use as effective alternative to the metal-based and bioorganic methods.[34] Unquestionably, many advantages are related with the use of organocatalytic systems: (i) moderately cheaper, more stable, easier to synthesize, and readily available catalysts; (ii) the reactions can be executed under mild conditions without the consistent requirement of inert atmosphere or dry solvents and (iii) depending upon covalent and noncovalent interactions different modes of activation are possible with respect to substrates, reagents, and reactions. These have carved the pathway for the original reactions providing them access to synthesise unique useful scaffolds.[35] Some of the selected examples are discussed below.

In this context, the exceptional features of organocatalysis have been employed directly upon asymmetric multicomponent Mannich reaction by List *et al*. (*S*)-proline upholds a notable stereogenic control reaction in an enamine-dependent pathway which leads to a direct asymmetric organocatalytic three-component Mannich reaction yielding **84** in good yields (Scheme 19).[36]



Scheme 19. Direct asymmetric organocatalytic three-component Mannich reaction

Organocatalytic approach were further utilized to form chiral spiro compounds in presence of malononitrile *via* asymmetric MCR. Yuan *et al.* reported an elegant example of one-pot three-component reaction *via* domino Michael/cyclization sequence to provide a wide range of optically active spiro[4H-pyran-3,3′-oxindoles] **88** [37] using chiral organocatalyst, cupreine CPN **L** (Scheme 20). In 2012, Yan and coworkers showed that chiral tertiary amine–thiourea **L1** catalyzed three-component reaction between isatins **85**, malononitrile **86** and α-phenyl-isocyanoacetate **89** (Scheme 20) afforded dihydropyryl-spirooxindoles **90**.[38]



Scheme 20. Formation of chiral spiro compounds in presence of malononitrile

I.5. Different Strategies Adapted to Perform a MCR

Generally four strategies have been adopted for the design of novel multicomponent reactions: a) Single reactant replacement (SRR); b) modular reaction sequences (MRS); c) conditions-based divergence (CBD), and d) combination of MCRs (MCR^2). Applications of these strategies mark them as a complex and divergent route to generate an array of organic scaffolds in a simple yet selective way.[39]

I.5.1. Single Reactant Replacement

The expression "single reactant replacement" (SRR, Figure 6) was first claimed by Ganem[40] which involves the development of new range of MCRs through the systematic assessment of the mechanistic or functional role of each component in a known MCR and further replacement of one reactant (C) with a different reactant (D-E) that displays the same essential reactivity mode required for that multicomponent condensation with A and B. By incorporating additional reactivity or functionality into D, the resulting MCR may be directed to a different product scaffold.

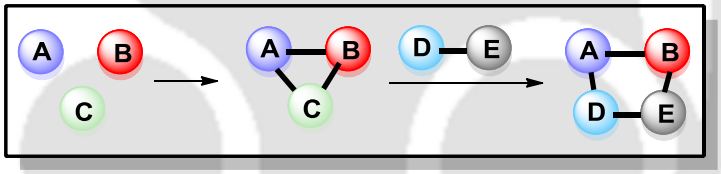
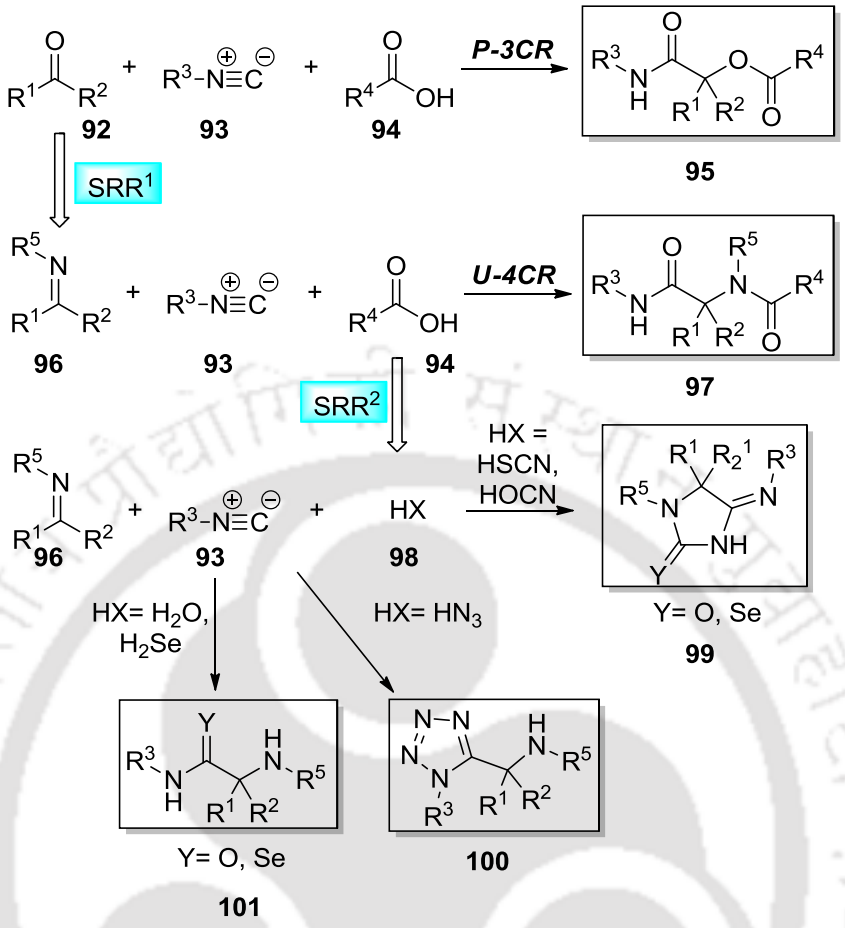


Figure 6. Single reactant replacement (SRR)

Possibly the first leading examples of SRR was reported by Ugi, who swapped the carbonyl **92** moiety in the Passerini 3CR[17] with an imine adduct **96**, which caused the generation of renowned Ugi reaction **97** (Scheme 21).[14] Ugi further replaced the carboxylic acid participation of the Ugi reaction by different acidic components to afford various scaffolds. The carboxylic acid in the classical Ugi reaction may be further replaced by a variety of weak inorganic acids. For example, HOCN and HSCN could be used to afford (thio)hydantoinimides **99** respectively. These are generated from the analogous adducts by cyclization of the intermediate β-amino iso(thio)cyanates. The use of N_3H **98** resulted in the formation of tetrazoles **100** by spontaneous cyclization of α-adduct. The alternative use of water or hydrogen selenide, forces the corresponding adducts to undergo tautomerization forming amides or selenoamides **101**, respectively (Scheme 21).



Scheme 21. Sequential SRR from Passerini to Ugi (SRR^1) to further Ugi variations (SRR^2)

I.5.2. Modular Reaction Sequences

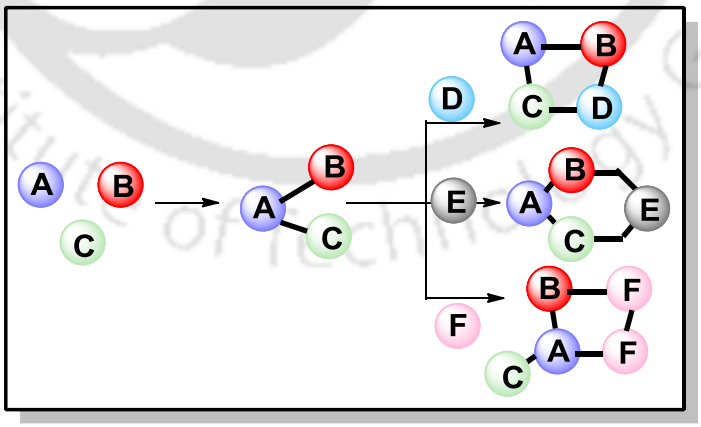
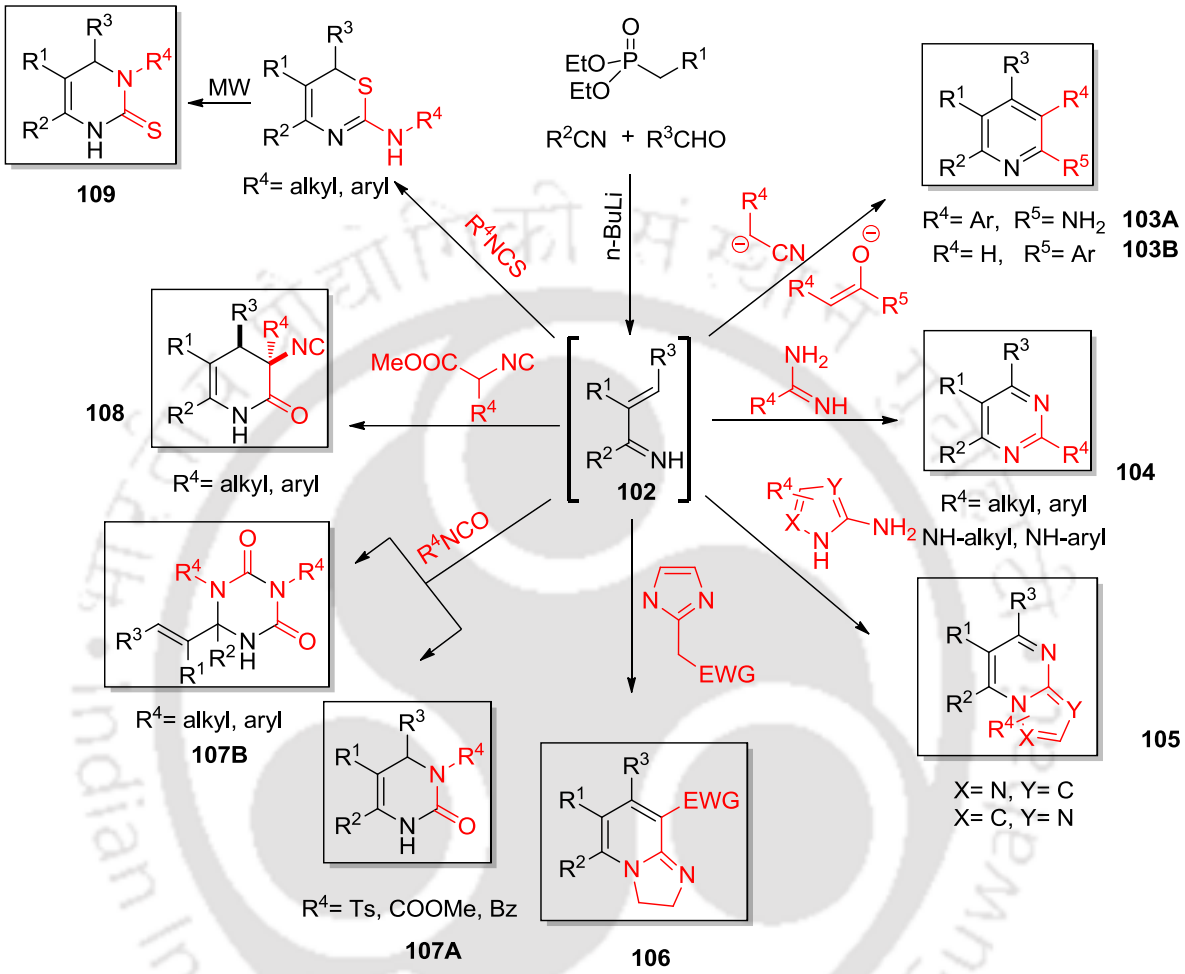


Figure 7. Modular reaction sequences (MRS)

The second strategy for the sighting of novel MCRs encompasses modular reaction sequences (MRSs, Figure 7). This approach is associated to SRR, as it involves a flexible

reactive intermediate which is generated from substrates **A**, **B**, and **C** *via* a preliminary MCR.[41] This reactive intermediate is further treated with a range of final distinguish components (**D**, **E** and **F**) in an *in situ* manner to produce a wide range of scaffolds.



Scheme 22. Modular reaction sequence involving 1-azadiene as the reactive intermediate

One outstanding example, sighted here to explain the concept of MRS, is the use of 1-azadiene **102** as the potential intermediate to yield a diverse set of scaffolds.[42] The 1-azadiene is synthesized *in situ* from a phosphonate, a nitrile, and an aldehyde by a three component Horner–Wadsworth–Emmons (HWE) reaction (Scheme 22).[43] Kiselyov reported the first MCR in 1995 *via* the reaction of 1-azadiene with sodium or potassium salts of arylacetonitriles to form 2-aminopyridines **103A**.[44] The 1-azadiene was also treated with sodium enolates of methyl aryl ketones to generate 2,4,6-substituted pyridines **103B**.[44] After a decade, Kiselyov extended this effort with amidines (R^4=alkyl, aryl) and guanidines (R^4=NHR) to afford polysubstituted pyrimidines **104**.[45] Next, the one-pot reaction of **102**

with 5-aminopyrazoles (X=N, Y=C) or 2-aminoimidazoles (X=C, Y=N) ensued in the construction of bicyclic compounds **105**.[46] In such another one-pot procedure, the dianion of methyl imidazolyl acetate generates imidazo[1,2-a]pyridines **106**.[47] Orru group has also extended the prospective of such 1-azadiene-based MCRs with isocyanates to selectively afford functionalized 3,4-dihydropyrimidine-2-ones **107A** [48] and triazinane diones **107B** [49] depending upon the nature of the isocyanate (Scheme 22). Interestingly, the use of isothiocyanates as the fourth component resulted in the formation of 2-aminothiazines, which could undergo Dimroth rearrangement upon microwave heating to give dihydropyrimidine-2-thiones **109**.[50] Possibly the most exciting reaction in this clan is the reaction of **102** with α-isocyano esters to give isocyano-substituted dihydropyridones **108**.[51] This isocyanide functionality allows combination with isocyanide-based MCRs for further scaffold generation.[52]

I.5.3. Divergence through Changing the Reaction Conditions

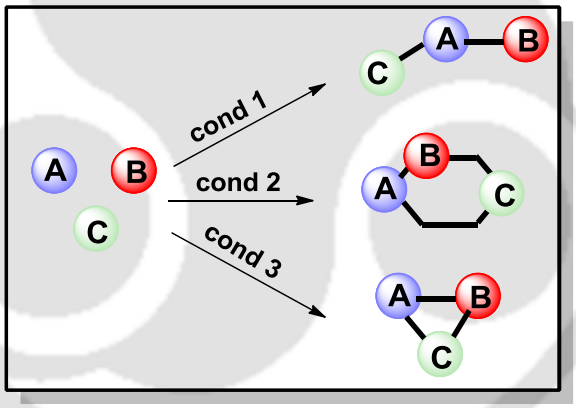
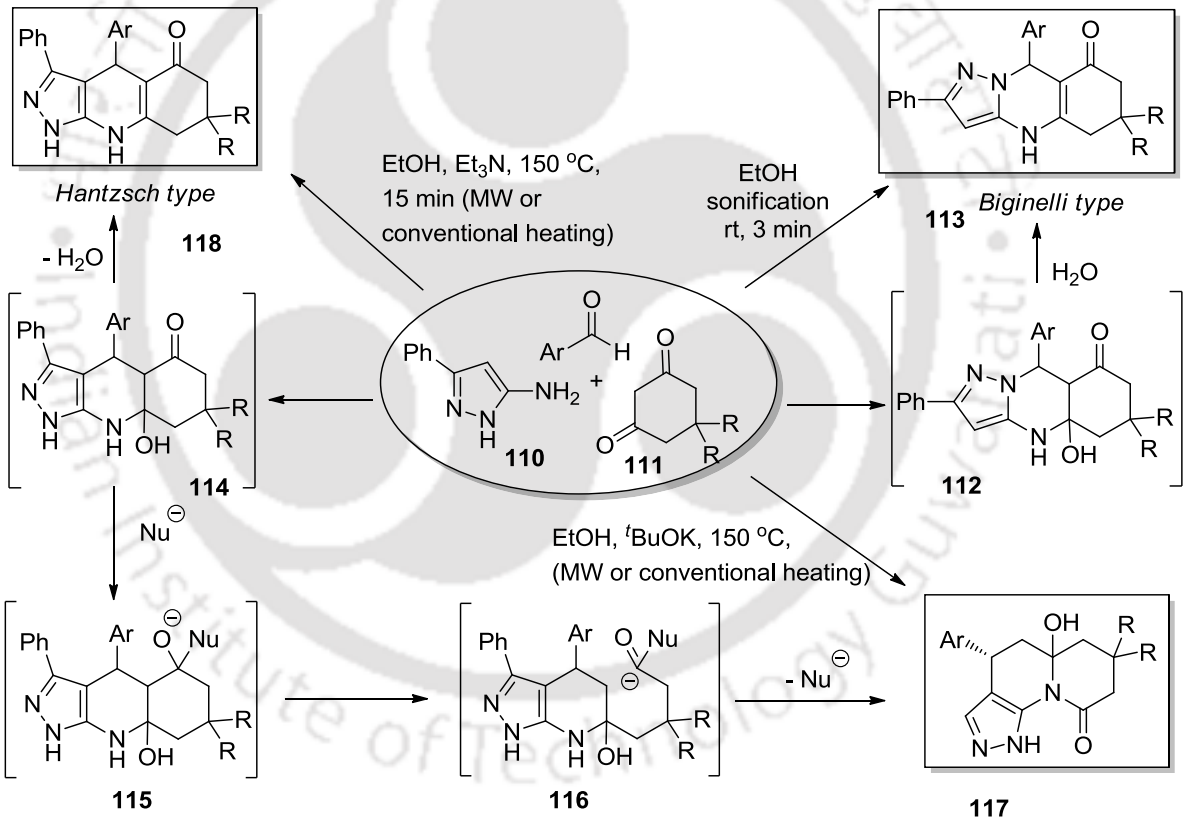


Figure 8. Conditions-based divergence (CBD)

Conditions-based divergence in MCRs (CBD, Figure 8) generates manifold molecular frameworks starting from the same materials by simply applying different reaction conditions. Instinctively, it is very amazing to note that several different potential reaction paths lead to different products due to molecular interactions of three or more components. The tuning of such reactions could be conducted *via* the use of specific catalysts, solvents, or additives changing the course of the reaction along different pathways to produce distinct products. Consequently, optimizing CBD is difficult and is limited only for a number of reported examples.

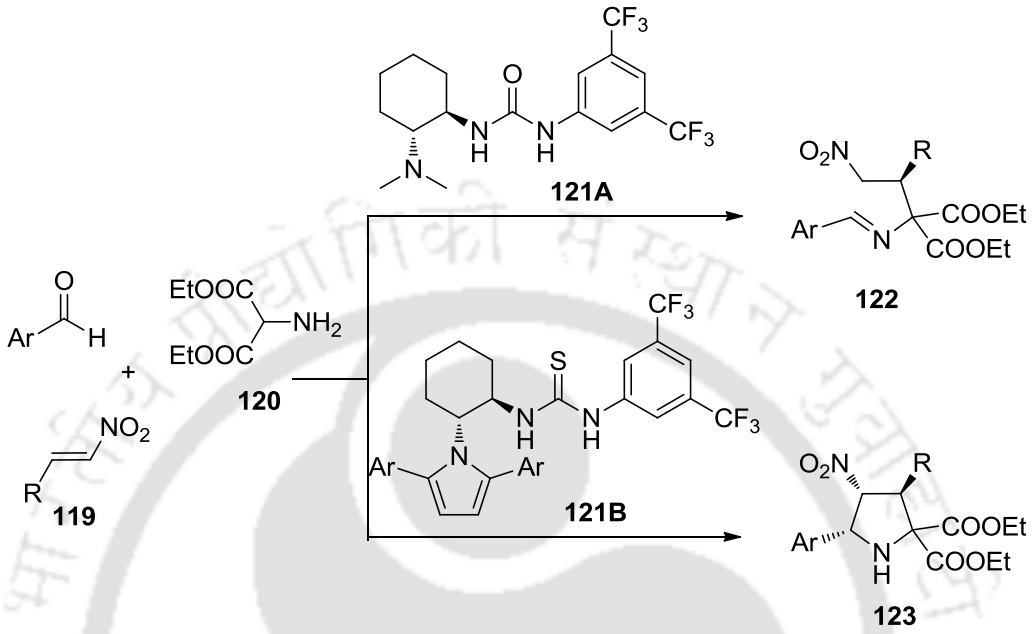
In 2008, Chebanov *et al.* reported an unique example of multicomponent reaction *via* conditions-based divergence approach involving 5-aminopyrazole **110**, cyclic 1,3-diketones **111**, and aromatic aldehydes (Scheme 23).[53] 5-Aminopyrazole consist of at least three non-equivalent nucleophilic centers N1, C4, and NH_2 which led the reaction to three distinct scaffolds (**113**, **117**, and **118**) by changing the reaction conditions. A mixture of **113** and **118** was obtained under conventional heating whereas heating in a sealed vessel led to the exclusive formation of Hantzsch product in the presence of Et_3N **118**.[11] When a strong nucleophilic base such as sodium ethoxide or potassium *tert*-butoxide was used instead under similar conditions, a different reaction product **117** was formed by the nucleophilic attack of the alkoxide on intermediate **114** followed by ring opening/recyclization.



Scheme 23. Tuning a 3CR to three different scaffolds by adapting the reaction conditions

In 2008, Liu and coworkers described this approach involving a organocatalytic assymetric path using aromatic aldehyde, diethyl-α-aminomalonate **120** in presence of nitro styrene **119** to generate two entirely different organic framework, a highly substituted pyrrolidine **123** and another acyclic skeleton with imine functionality **122** by altering the

reaction condition with the help of two different chiral catalyst.[54] By subtle change in the structure of the ligands, introducing a bulky 2,5-diarylpyrrole moiety instead of dimethyl amine afforded different product under similar conditions (Scheme 24).



Scheme 24. Tuning a 3CR to form different products by changing the chiral ligand

I.5.4. Combination of MCRs

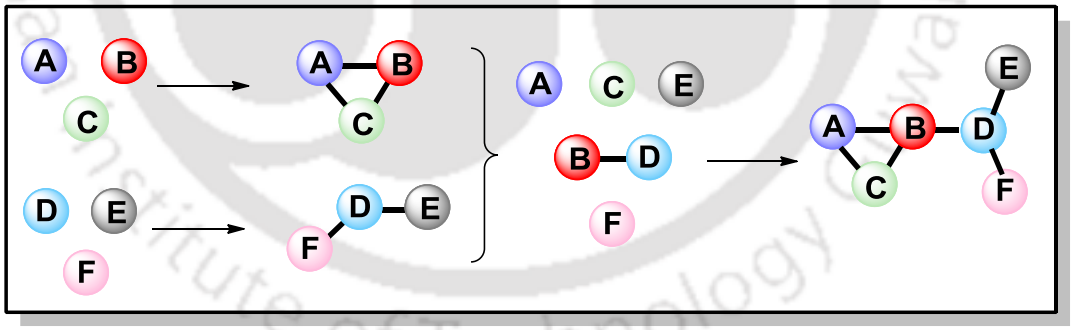
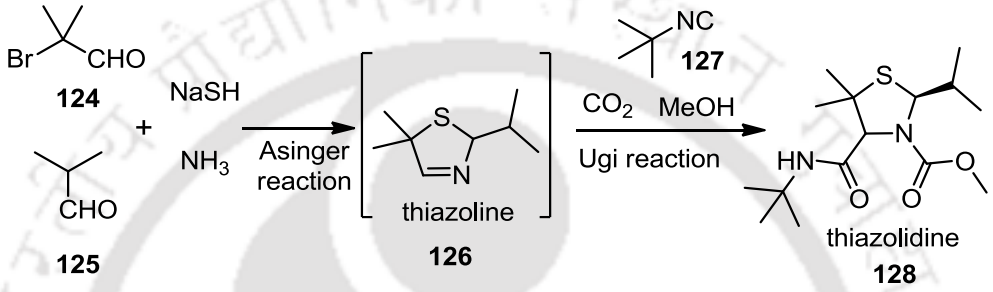


Figure 9. Combination of MCRs (MCR^2)

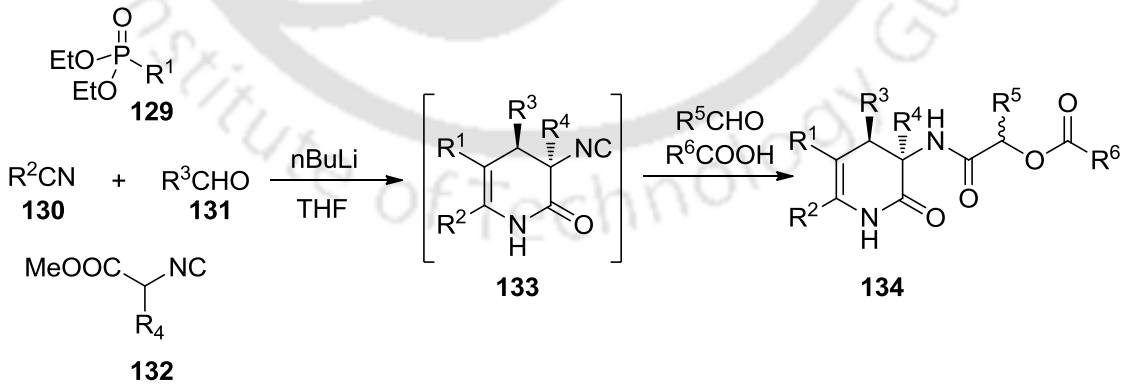
The fourth strategy for the coherent study of novel MCRs is combination of MCRs (MCR^2, Figure 9) that combine two (or more) different types of MCRs in a one-pot process. The presence of orthogonal reactive groups in the product of the primary MCR allows the combination with the secondary MCR. Generally this reactive part is either formed during the primary MCR or present in one of the components.[55] Varying the sequential MCR (for example, by addition of inputs E/F) give rise to diverse and complex scaffolds (Figure 9).

The combination of MCRs was first accustomed by Domling and Ugi who developed a seven-component reaction (7CR) in one pot by blending a modified Asinger 4CR[56] and Ugi 4CR.[57] In this 7CR, an *α*/*β*-haloaldehyde (**124)**, NaSH/NaOH, NH_3, CO_2, an isocyanide **127**, another aldehyde **125** and a primary alcohol as solvent cum reactant are combined to afford complex thiazolidines efficiently **128** (Scheme 25). However, NaSH/NaOH, NH_3 and CO_2 are constant components in this reaction, which considerably limits the diversity as well as the scope of the MCR.



Scheme 25. Combination of Asinger 4CR and Ugi-type MCR to synthesise thiazolidines

Portlock and coworkers reported the combination of the Petasis 3CR and the Ugi 4CR in 2003 to form a pyrimidone moiety.[58] However this approach limited the practicality as an intermediate solvent change was required. In 2007, Orru *et al.* the 4CR preparation of isocyano dihydropyridones was be combined in one pot with the Passerini 3CR to provide constrained depsipeptides **134** (Scheme 26).[59]



Scheme 26. Combination of Asinger 4CR and Ugi-type MCR to synthesise thiazolidines

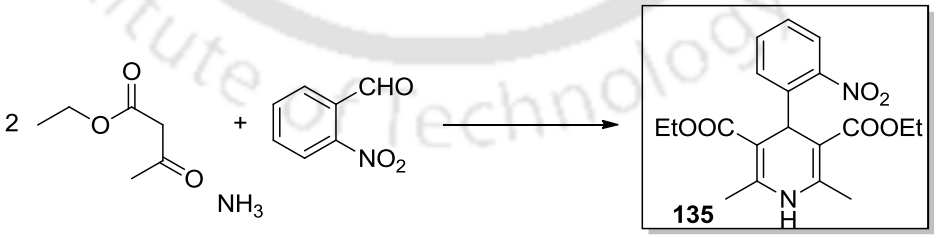
❒ I.6. Application of MCRs.

Wöhler laid the foundation of MCR *via* synthesis of urea in the field of target-oriented organic synthesis.[60] Since then remarkable progress has been achieved by the scientists and many powerful individual bond-forming reactions and asymmetric variants have been developed consequently. These discoveries have carved the path to the stereoselective assembly of complex organic molecules. This part deals with the utility of MCRs in the drug discovery process and natural product synthesis with representative examples presented, demonstrating the successful impact of these reactions.

I.6.1. Applications of Multicomponent Reactions in Drug Discovery

This part deals with the efficacy of MCRs in the drug discovery process. Representative examples demonstrating the successful impact of these reactions at different stages of the lead discovery, lead optimization and pre-clinical process development arenas have been demonstrated herein.

Several decades back in late nineteenth century in Europe, Italian chemist Pietro Biginelli[12] stated the one-pot synthesis of 4-aryl-3, 4-dihydropyrimidin-2(1H)-ones (DHPM) as mentioned earlier in this chapter. Nearly a century later, with the information of DHPMs having similar pharmacological properties as calcium channel modulators to the Nifedipine 2 class was observed. As a result the Biginelli reaction as well as Hantzsch reaction witnessed a dramatic rise in popularity.



The Hantzsch syntheis of Nifedipine

Scheme 27. Biginelli dihydropyrimidine & Hantzsch Nifedipine synthesis

Khanina and co-workers first reported the DHPM calcium channel modulators by demonstrating the moderate hypotensive activity of β-aminoethyl ester **136**.[61] Later Atwal

reported a series of more potent DHPMs as demonstrated by the thiourea derivative **137**. Subtle adaptation resulted in different DHPs which was strikingly more potent *in vitro* than Nifedipine, combined with comparable *in vivo* efficacy and duration of action such as DHP Amlodipine, **138**, a commercially available second generation DHP.[62]

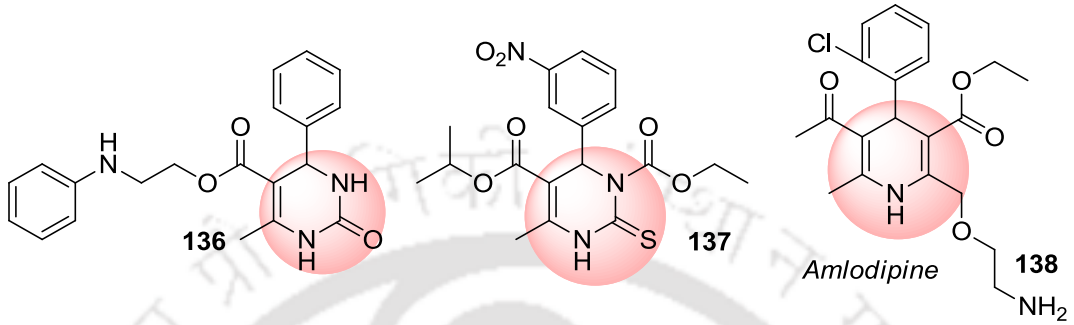
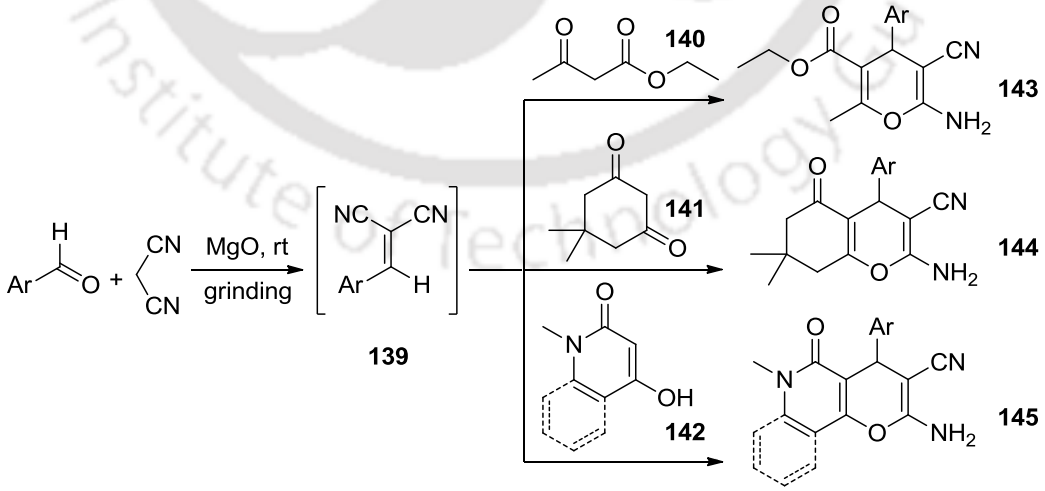


Figure 10. Biologically active dihydropyridine skeletons

Knoevenagel condensation of aldehydes with malononitrile in presence of MgO gave knoevenagel adduct which gave 2-aminopyran skeletons when treated with 1,3-dicarboyl compounds.[63] The resultant adduct, depending on the structure of dicarbonyl compound, exhibited various medicinal activity such as antibacterial activity against *E. coli*, *S. aureus* e.t.c. It is noteworthy to mention that tetrahydrochromenes **144** has found applications as inhibitors of excitatory amino acid transporter. On the other hand pyranoquinolines **145** show antiproliferative and antitubulin activities (Scheme 28). Some of them are shown in Figure 11



Scheme 28. Use of malononitrile for the synthesis of 2-aminopyran skeletons

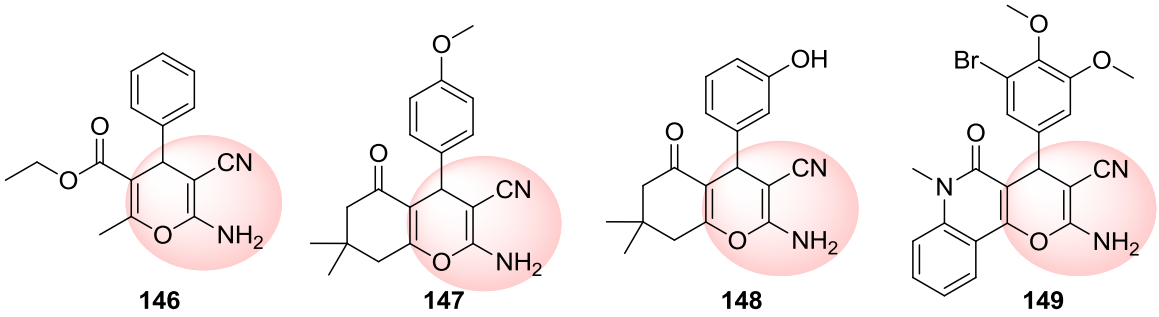
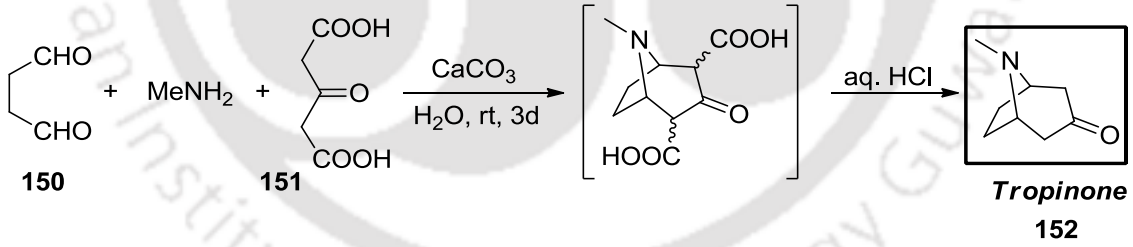


Figure 11. Biologically active 2-aminopyran frameworks

I.6.2. Multicomponent Reactions in the Total Synthesis of Natural Products

This part provides information on the applications of MCRs in the total synthesis of natural products reported since the early 1970s. Many strategies have been developed by chemists in order to facilitate the synthesis of complex natural products.[64] Some of such selected examples are described below.

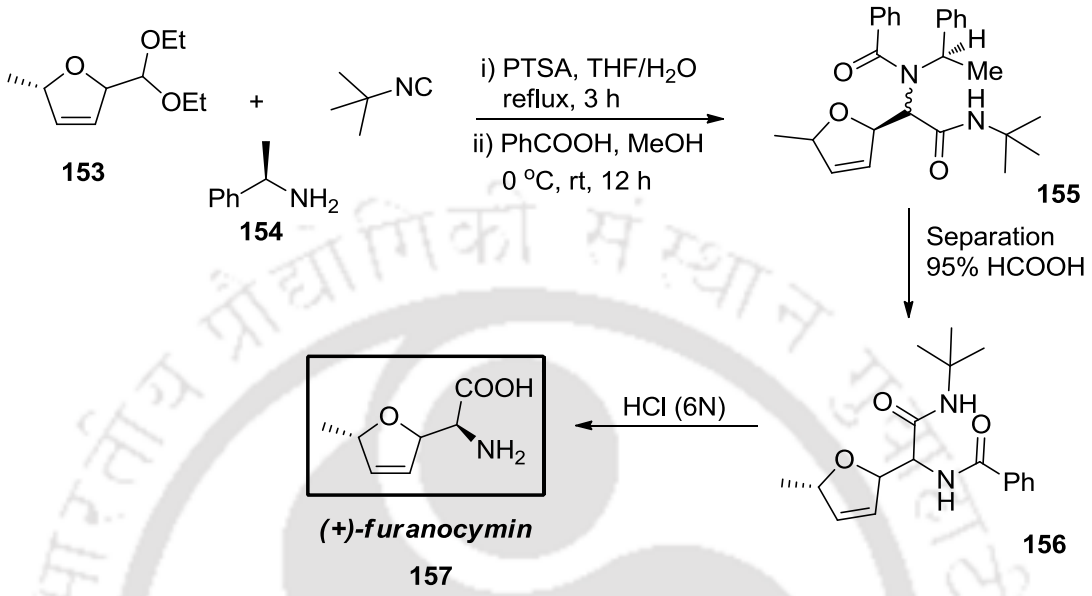
The advantages of MCR were explained by Robinson early in 1917, with the efficient one-step synthesis of the bridged bicyclic alkaloid Tropinone **152** (Scheme 29).[65] After this multicomponent reaction strategies have remained under exploited for many decades.



Scheme 29. Formation of Tropinone *via* MCR

The Ugi four-component reaction (4CR) stands as a potent technique for the synthesis of peptide skeletons. The Ugi reaction has found widespread applications in combinatorial synthesis.[66,14] This powerful four-component reaction can be exploited in target-oriented synthesis. Joullie´ and co-workers used an Ugi four-component reaction[67] as the key step for the synthesis of potent amino acid antibiotic Furanomycin **157** (Scheme 30), isolated from *Streptomyces threomyceticus*.[68] In the presence of *tert*-butyl isocyanide and benzoic acid, enantiopure acetal **153** and α-methyl benzylamine **154** were mixed in methanol to generate

a mixture diastereomeric Ugi 4CR product **155**. Debenzylation using formic acid, followed by acid hydrolysis of the secondary amides gave the desired moiety **157** (Scheme 30).



Scheme 30. Synthesis of furanomycin adducts *via* MCR

I.7 References

1. (a) J. Zhu and H. Bienaymé, *Multicomponent Reactions*; 1st ed; Wiley-VCH, Weinheim, Germany, 2005; (b) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3168; (c) I. Ugi, A. Dömling and W. Horl, *Endeavor*, 1994, **18**, 115.
2. (a) T. E. Nielsen and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2008, **47**, 48 (b) M. D. Burke, E. M. Berger and S. L. Schreiber, Science, 2003, **302**, 613
3. Y. Coquerel, T. Boddaert, M. Presset, D. Mailhol and J. Rodriguez in *Ideas in chemistry and molecular sciences: advances in synthetic chemistry*. B. Pignataro (Ed.) Wiley-VCH Verlag GmbH, Weinheim, Germany, 2010, pp. 187–202.
4. (a) B. M. Trost, *Science*, 1991, **254**, 1471; (b) L. F. Tietze, *Chem. Rev*., 1996, **96**, 115.
5. (a) R. V. A. Orru, and M. de Greef, *Synthesis*, 2003, 1471; (b) A. Dömling, *Chem. Rev*., 2006, **106**, 17; (c) J. E. Biggs-Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol.*, 2010, **14**, 371.
6. (a) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **1**, 51; (b) H. Bienaymé, C. Hulme, G. Oddon and P. Schmitt, *Chem. Eur. J.*, 2000, **6**, 3321; (c) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem. Int. Ed.*, 2011, **50**, 6234.
7. A. Domling and Y. Huang, *Synthesis*, 2010, **17**, 2859.
8. (a) I. Ugi, R. Meyr, U. Fitzer and C. Steinbrücker, *Angew. Chem.*, 1959, **71**, 386; (b) I. Ugi and C. Steinbruckner, *Angew. Chem.*, 1960, **72**, 267; (c) I. Ugi, *Angew. Chem.*, 1962, **74**, 9.
9. A. Strecker, *Justus. Liebigs Ann. Chem.*, 1850, **75**, 27.
10. E. Vedejs and C. A. Kongkittingam, *J. Org. Chem.*, 2001, **66**, 7355.
11. A. Hantzsch, *Justus. Liebigs Ann. Chem.*, 1882, **215**, 1.
12. (a) P. Biginelli, *Gazz. Chim. Ital.* 1891, **21**, 497; (b) P. Biginelli, *Chem. Ber.*, 1891, **24**, 1317; (c) P. Biginelli, *Gazz. Chim. Ital.* 1893, **23**, 360.
13. (a) M. Passerini and L. Simone, *Gazz. Chim. Ital.*, 1921, **51**, 126; (b) M. Passerini and G. Ragni, *Gazz. Chim. Ital.* 1931, **61**, 964.
14. (a) I. Ugi, R. Meyr, U. Fitzer and C. Steinbrücker, *Angew. Chem.*, 1959, **71**, 386; (b) I. Ugi and C. Steinbruckner, *Angew. Chem.*, 1960, **72**, 267; (c) I. Ugi, *Angew. Chem.*, 1962, **74**, 9; (c) Z.-Q. Liu, *Curr Org Chem*., **18**, 719; (d) P. A. Tempest, *Curr. Opin. Drug Discov. Devel*., 2005, **8**, 77.

15. C. G. Evans and J. E. Gestwicki, *Org. Lett.* 2009, **11**, 2957.
16. A. Dondoni, A. Massi and S. Sabbatini, *Tetrahedron Lett.*, 2002, **43**, 5913.
17. (a) M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 181; (b) M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 126; (c) L. Banfi and R. Riva in *Organic reactions*, John Wiley & Sons, Inc., Hoboken, NJ, 2005, Vol. **65**, pp. 1–140; (d) L. Banfi, R. Riva and A. Basso, *Synlett*, 2010, 23; (e) S. Sadjadi and M. M. Heravi, *Tetrahedron*, 2011, **67**, 2707.
18. T. D. Owens, G. L. Araldi, R. F. Nutt and J. E. Semple, *Tetrahedron Lett*., 2001, **42**, 6271.
19. A. Plant, P. Thompson and D. M. Williams, *J. Org. Chem*., 2009, **74**, 4870
20. D. Hall (Ed.), *Boronic acids: preparation and applications in organic synthesis and medicine*, Wiley-VCH Verlag GmbH, Weinheim, Germany, 2005.
21. (a) N. A. Petasis, I. A. Zavialov, 2001, US Patent 6,232,467; (b) N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, **34**, 583; (c) N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1997, **119**, 445; (d) N. A. Petasis, A. Goodman and I. A. Zavialov, *Tetrahedron*, 1997, **53**, 16463; (e) R. A. Batey in *Boronic acids: preparation and applications in organic synthesis and medicine* (D. Hall, Ed.). Wiley-VCH Verlag GmbH, Weinheim, Germany, 2005, pp. 279; (f) M. Sugiura, K. Hirano and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 7182; (g) S. Kobayashi, K. Hirano and M. Sugiura, *Chem. Commun*., 2005, 104; (h) B. Dhudshia, J. Tiburcio and A. N. Thadani, *Chem. Commun*., 2005, 5551.
22. L. D. Juliawaty, M. Kitajima, H. Takayama, S. A. Achmad and N. Aimi, *Phytochemistry*, 2000, **54**, 989.
23. S. Tang, X. Xie, X. Wang, L. He, K. Xu and X. She, *J. Org. Chem.*, 2010, **75**, 8234.
24. (a) V. Nair, S. Bindu, V. Sreekumar and N. Rath, *Org. Lett.*, 2003, **5**, 665; (b) C. Yu, J. Lu, T. Li, D. Wang, B. Qin, H. Zhang and C. Yao, *Synlett*, 2011, 2420.
25. T. Kawamoto, S. J. Geib and D. P. Curran, *J. Am. Chem. Soc.*, 2015, **137**, 8617.
26. (a) Y. Xi, H. Yi and A. Lei, *Org. Biomol. Chem.*, 2013, **11**, 2387; (b) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102.
27. (a) T. Courant and G. Masson, *Chem. Eur. J.*, 2012, **18**, 423; (b) K. Mizuno, M. Ikeda, S. Toda and Y. Otsuji, *J. Am. Chem. Soc.*, 1988, **110**, 1288.

28. (a) S. Torii, H. Okumoto and L. H. Xu, *Tetrahedron Lett.*, 1991, **32**, 237; (b) V. N. Kalinin, M. V. Shostakovsky and A. B. Ponomaryov, *Tetrahedron Lett.*, 1990, **31**, 4073; (c) Q. Yang and H. Alper, *J. Org. Chem.*, 2010, **75**, 948; (d) F. Ye and H. Alper, *J. Org. Chem.*, 2007, **72**, 3218; (e) D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772; (f) D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 9423; (g) R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall and G. Yoganathan, *Tetrahedron Lett.*, 2000, **41**, 7125; (h) W.-J. Xiao and H. Alper, *J. Org. Chem.*, 1999, **64**, 9646; (i) C. Larksarp and H. Alper, *J. Org. Chem.*, 1999, **64**, 9194; (j) K. Okuro and H. Alper, *J. Org. Chem.*, 1997, **62**, 1566.

29. T. Takahashi, Y. Li, F.-Y. Tsai and K. Nakajima, *Organometallics*, 2001, **20**, 595.

30. (a) H. Nakamura; J.-G. Shim and Y. Yamamoto, *J. Am. Chem. Soc*., 1997, **119**, 8113; (b) N. Solin, S. Narayan and K. J. Szabo´, *J. Org. Chem.*, 2001, **66**, 1686; (c) E. Yoshikawa, K. V. Radhakrishnan and Y. Yamamoto, *Tetrahedron Lett.*, 2000, **41**, 729; (d) R. J. Franks and K. M. Nicholas, *Organometallics*, 2000, **19**, 1458; (e) N. Solin, S. Narayan and K. J. Szabo´, *Org. Lett*., 2001, **3**, 909.

31. M. Jeganmohan, M. Shanmugasundaram and C.-H. Cheng, *Org. Lett.* 2003, **5**, 881.

32. S. Brauch and L. Gabriel and B. Westermann, *Chem. Commun.*, 2010, **46**, 3387.

33. D. W. C. MacMillan, *Nature*, 2008, **455**, 304.

34. (a) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2001, **40**, 3726; (b) M. Benaglia, A. Puglisi and F. Cozzi, *Chem. Rev.*, 2003, **103**, 3401; (c) K. N. Houk and B. List, *Acc. Chem. Res.*, 2004, **37**, 487; (d) B. List, *Acc. Chem. Res*., 2004, **37**, 548; (e) B. List, *Adv. Synth. Catal.*, 2004, **346**, 1021; (f) C. M. R. Volla, L. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390; (g) A. Dondoni and A. Massi, *Angew. Chem. Int. Ed.*, 2008, **47**, 4638; (h) L. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 8492; (i) A. Berkessel and H. Gröger, *Asymmetric organocatalysis* Wiley-VCH Verlag GmbH, Weinheim, Germany, 2005.

35. (a) B. List, *Synlett*, 2001, 1675; (b) M. Bella and T. Gasperi, *Synthesis*, 2009, 1583; (c) R. M. de Figueiredo, A. Mazziotta, D. P. de Sant'Ana, C. Palumbo and T. Gasperi, *Curr. Org. Chem.*, 2012, **16**, 2231.

36. B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336.

37. W.-B. Chen, Z.-J. Wu, Q.-L. Pei, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2010, **12**, 3132;
38. W.-T. Wei, C.-X. Chen, R.-J. Lu, J.-J. Wang, X.-J. Zhang and M. Yan, *Org. Biomol. Chem*., 2012, **10**, 5245.
39. E. Ruijter, R. Scheffelaar, and R. V. A. Orru, *Angew. Chem. Int. Ed.*, 2011, **50**, 6234.
40. B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463.
41. J. Zhu, *Eur. J. Org. Chem.*, 2003, **7**, 1133.
42. B. Groenendaal, E. Ruijter and R. V. A. Orru, *Chem. Commun.*, 2008, 5474.
43. (a) K. Lee and D. Y. Oh, *Synthesis*, 1991, 213; (b) W. S. Shin, K. Lee and D. Y. Oh, *Tetrahedron Lett*., 1995, **36**, 281.
44. A. S. Kiselyov, *Tetrahedron Lett.*, 1995, **36**, 9297.
45. A. S. Kiselyov, *Tetrahedron Lett.*, 2005, **46**, 1663.
46. A. S. Kiselyov and L. Smith II, *Tetrahedron Lett.*, 2006, **47**, 2611.
47. A. S. Kiselyov, *Tetrahedron Lett.*, 2006, **47**, 2941.
48. (a) D. J. Vugts, H. Jansen, R. F. Schmitz, F. J. J. De Kanter and R. V. A. Orru, *Chem. Commun*., 2003, 2594; (b) D. J. Vugts, M. M. Koningstein, R. F. Schmitz, F. J. J. De Kanter, M. B. Groen and R. V. A. Orru, *Chem. Eur. J*., 2006, **12**, 7178.
49. (a) B. Groenendaal, E. Ruijter, F. J. J. De Kanter, M. Lutz, A. L. Spek and R. V. A. Orru, *Org. Biomol. Chem.*, 2008, **6**, 3158; (b) B. Groenendaal, D. J. Vugts, R. F. Schmitz, F. J. J. De Kanter, E. Ruijter, M. B. Groen and R. V. A. Orru, *J. Org. Chem.*, 2008, **73**, 719.
50. T. N. Glasnov, D. J. Vugts, M. M. Koningstein, B. Desai, W. M. F. Fabian, R. V. A. Orru and C. O. Kappe, *QSAR Comb. Sci.*, 2006, **25**, 509.
51. (a) M. Paravidino, R. S. Bon, R. Scheffelaar, D. J. Vugts, A. Znabet, F. J. J. de Kanter, M. Lutz, A. L. Spek, M. B. Groen and R. V. A. Orru, *Org. Lett.*, 2006, **8**, 5369; (b) R. Scheffelaar, M. Paravidino, A. Znabet, R. F. Schmitz, F. J. J. de Kanter, M. Lutz, A. L. Spek, C. F. Guerra, F. M. Bickelhaupt, M. B. Groen, E. Ruijter and R. V. A. Orru, *J. Org. Chem.*, 2010, **75**, 1723.
52. (a) M. Paravidino, R. Scheffelaar, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, E. Ruijter and R. V. A. Orru, *J. Org. Chem.*, 2007, **72**, 10239; (b) R. Scheffelaar, R. A. Klein Nijenhuis, M. Paravidino, M. Lutz, A. L. Spek, A. W. Ehlers, F. J. J. de Kanter,

M. B. Groen, R. V. A. Orru and E. Ruijter, *J. Org. Chem.*, 2009, **74**, 660; (c) R. Scheffelaar, M. Paravidino, D. Muilwijk, M. Lutz, A. L. Spek, F. J. J. de Kanter, R. V. A. Orru and E. Ruijter, *Org. Lett.*, 2009, **11**, 125.

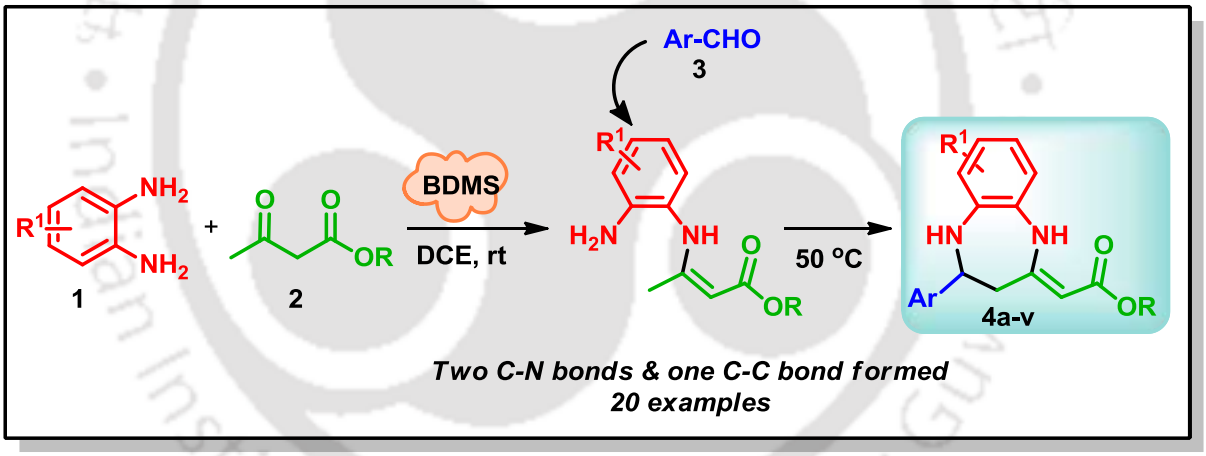
53. V. A. Chebanov, V. E. Saraev, S. M. Desenko, V. N. Chernenko, I. V. Knyazeva, U. Groth, T. N. Glasnov and C. O. Kappe, *J. Org. Chem.*, 2008, **73**, 5110.
54. Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J*., 2008, **14**, 9873
55. (a) A. Dömling, *Curr. Opin. Chem. Biol.*, 2000, **4**, 318; (b) D. J. Ramón and M. Yus, *Angew. Chem. Int. Ed.*, 2005, **44**, 1602.
56. F. Asinger and M. Thiel, *Angew. Chem.*, 1958, **70**, 667.
57. A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 1993, **32**, 563.
58. (a) I. Ugi, A. Demharter, W. Hrl and T. Schmid, *Tetrahedron*, 1996, **52**, 11657; (b) D. Naskar, A. Roy, W. L. Seibel, L. West and D. E. Portlock, *Tetrahedron Lett.*, 2003, **44**, 6297; (c) D. E. Portlock, D. Naskar, L. West, R. Ostaszewski and J. J. Chen, *Tetrahedron Lett.*, 2003, **44**, 5121; (d) D. E. Portlock, R. Ostaszewski, D. Naskar and L. West, *Tetrahedron Lett.*, 2003, **44**, 603.
59. M. Paravidino, R. Scheffelaar, R. F. Schmitz, F. J. J. de Kanter, M. B. Groen, E. Ruijter, R. V. A. Orru, *J. Org. Chem.*, 2007, **72**, 10239.
60. F. Wöhler, *Ann. Phys. Chem.*, 1828, **12**, 253.
61. E. L. Khanina, G. Siliniece, J. Ozols, G. Duburs and A. Kimenis, *Khim.-Farm. Zh.*, 1987, **21**, 948.
62. K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly, *J. Med. Chem.*, 1991, **34**, 806.
63. D. Kumar, V. B. Reddy, S. Sharad, U. Dube and S. Kapur, *Eur. J Med. Chem*., 2009, **44**, 3805
64. (a) P. Deslonchamps, *Aldrichimica Acta*, 1984, **17**, 59; (b) T.-L. Ho, *Tactics of Organic Synthesis*, Wiley- Interscience, New York, 1994. (c) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun*., 2003, 551.
65. R. Robinson, *J. Chem. Soc.*, 1917, 762.
66. (a) A. Dömling and I. Ugi, *Angew. Chem. Int. Ed.*, 2000, **39**, 3169; (b) I. Ugi, *Pure Appl. Chem.*, 2001, **73**, 187.

67. J. E. Semple, P. C. Wang, Z. Lysenko and M. M. Joullié, *J. Am. Chem. Soc.*, 1980, **102**, 7505.

68. K. Katagiri, K. Tori, Y. Kimura, T. Yoshida, T. Nagasaki and H. Minato, *J. Med. Chem.*, 1967, **10**, 1149.

Chapter II

Bromodimethylsulfonium Bromide (BDMS) Catalyzed Synthesis of 1,5-Benzodiazepines using MCR Strategy



Chapter II

Experimental Section

Bromodimethylsulfonium Bromide (BDMS) Catalyzed Synthesis of 1,5-Benzodiazepines using MCR Strategy

CHAPTER II

II. Bromodimethylsulfonium Bromide (BDMS) Catalyzed Synthesis of 1,5-Benzodiazepines using MCR Strategy

II.1. Introduction

Benzodiazepine frameworks are a long-lasting subject of interest to the scientific fraternity due to its great medicinal value.[1] The concept of "privileged medicinal structures or scaffolds" was initially represented[2,3] by the Merck researchers during their work on benzodiazepines. They are well-known for their activities in the central nervous system. These benzodiazepine scaffolds, which consists of fused frameworks of benzene and diazepine moiety have recently achieved a large amount of attention as an important class of nitrogen heterocycles exhibiting a broad spectrum of biological and pharmacological activities, such as anti-inflammatory, anticonvulsant, antianxiety, sedative, anti-depressive, hypnotic,[1,4] antibiotics,[5] anti-cancer[6] and antiviral (HIV) agents[7] and also as an inhibitor of HIV-1 capsid assembly.[8] These benzodiazepine moieties are found to display properties as dyes for acrylic fibers.[9] They are also used as starting materials for the preparation of triaxol[10a] and oxadiazol[10b] derivatives. Some of these scaffolds are even marketed as drug (Figure 1) as for example **I** & **II** are used for the treatment of schizophrenia whereas **III** Colbazam acts as an anxiolytic since 1975, then implemented as an anticonvulsant and of late has been marketed as an inhibitor of HIV-1 capsid assembly. Compounds **IV** & **V** also show sedative and anxiolytic effects.

Multicomponent reactions (MCRs) have emerged as a powerful strategy to construct structurally complex and functionally diverse multi-heterocyclic skeletons with efficient atom-economy. With the help of combinatorial approaches, designing multicomponent strategies for the construction of higher membered cyclic ring junctures to build a wide range of scaffolds having pharmacological interest is a prime target for organic chemists.[11] Utilizing this strategy, the synthesis of 1,5-benzodiazepines have been demonstrated in this chapter.

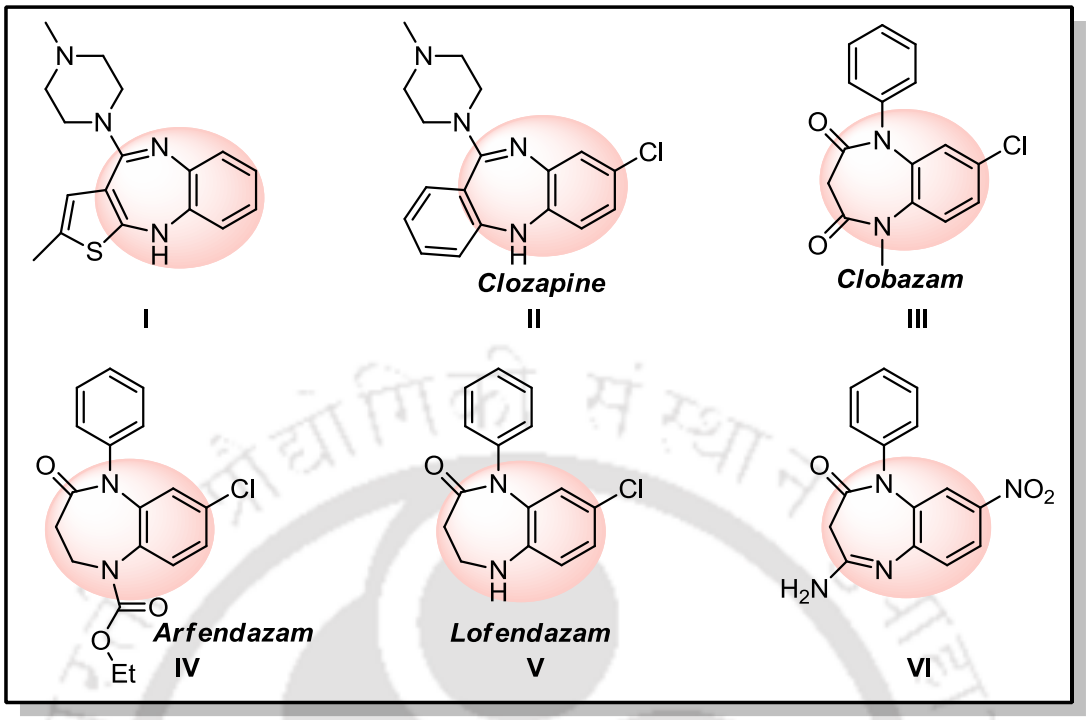
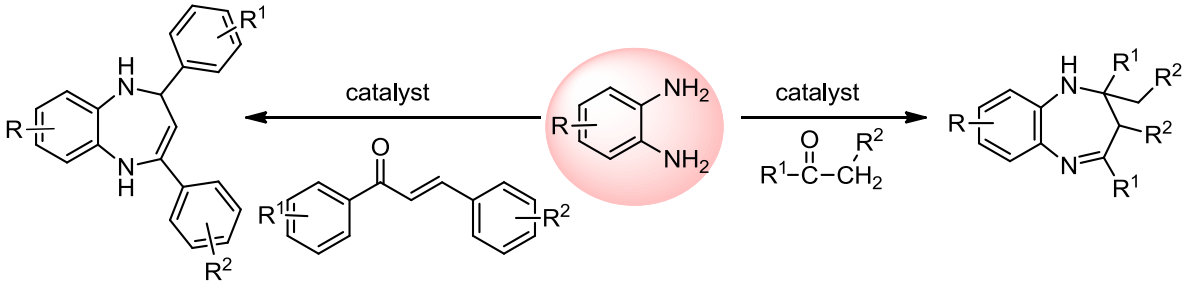


Figure 1. Biologically active benzodiazepines

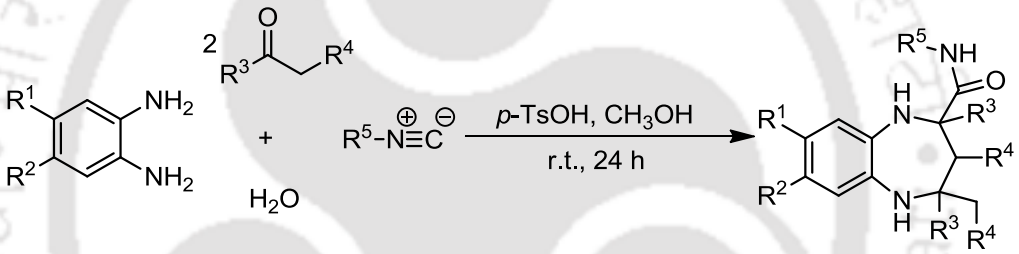
II.2. Strategies for Benzodiazepine Formation

The classical strategies for the construction of these 1,5-benzodiazepine frameworks generally vary on the condensation reactions of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds,[12] β-haloketones,[13] or ketones.[14,12a] Different reagents such as BF_3-etherate, polyphosphoric acid, $NaBH_4$, $MgO/POCl_3$, $Yb(OTf)_3$, $Ga(OTf)_3$, $Pb(NO_3)_2$, L-proline, molecular iodine, acetic acid under microwave conditions and ionic liquids have been used for the synthesis of benzodiazepines. Recently the synthesis of benzodiazepines has also been reported using different solid acid catalysts such as sulfated zirconia, Al_2O_3/P_2O_5, $Ag_3PW_{12}O_{40}$ and zeolite catalysts. Condensation reactions between *o*-phenylenediamine and 2 equiv. of ketonic compound produce biaryl-substituted 1,5-benzodiazepines. The synthetic protocol was further extended for similar reactions with chalcones instead of ketones which lead to the formation of functionalized 1,5-benzodiazepines in good yields (Scheme 1).



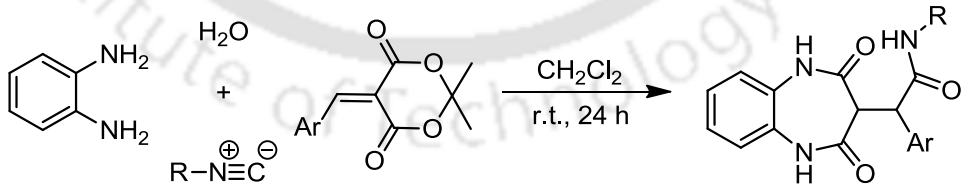
Scheme 1. Synthesis of benzodiazepines utilizing ketones and chalcones

In 2008, Shaabani *et al*. further extended the conventional approach by introducing isocyanide group in the reaction medium (Scheme 2). The synthesis of 1,5-benzodiazepine-2-carboxamide derivative was achieved using an aromatic diamine, linear or cyclic ketone, isocyanide, and water in the presence of catalytic amount of *p*-toluenesulfonic acid at room temperature.[15a]



Scheme 2. Formation of benzodiazepine moieties using isocyanides

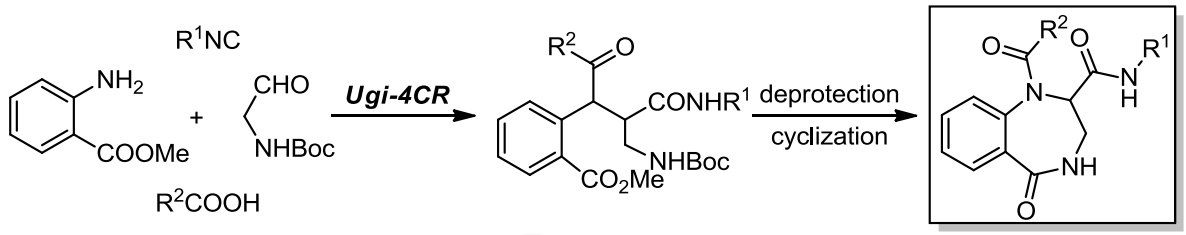
Few years back Bazgir group modified the above mentioned strategy by replacing the carbonyl functionality with benzylidene Meldrum's acid *via* a by a four component reaction to generate 1,5-benzodiazepin-2-phenylacetamides (Scheme 3).[15b]



Scheme 3. Use of benzylidene Meldrum's acid for the synthesis of benzodiazepines

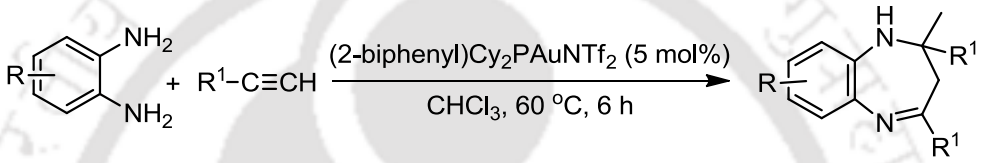
In this context it is worthy to mention the synthesis of diverse benzodiazepine scaffolds *via* Ugi four-component reactions (Ugi-4CR) followed by post condensation modifications. Boc-glycinal compounds have been applied in the Ugi-4CR for the synthesis of

benzodiazepine skeletons *via* the Ugi-deprotection-cyclization (UDC) strategy using methyl anthranilate as the building block in presence of isocyanide and a carboxylic acid.[15c]



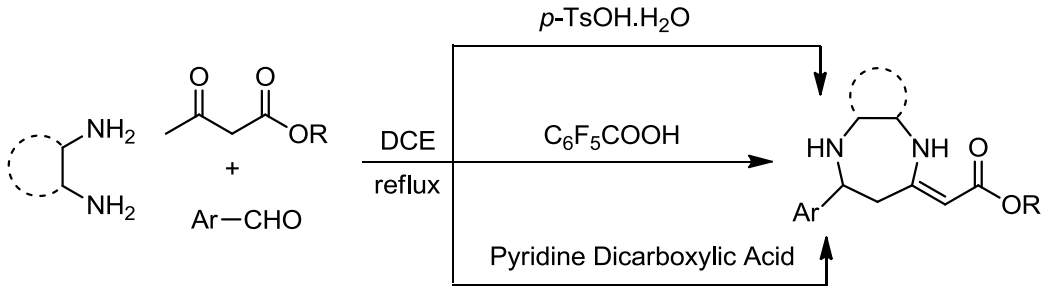
Scheme 4. Synthesis of benzodiazepines using Ugi-4CR strategy followed by DC

Recently cycloaddition reaction has also been explored for the synthesis of 1,5-benzodiazepine derivatives using *o*-phenylenediamines and terminal alkynes.[16]



Scheme 5. Synthesis of benzodiazepines using terminal alkynes

Very few methods have been reported recently describing the one-pot multicomponent synthesis of functionalized benzodiazepine in high regioselectivity using catalysts such as *p*-TSA or pentafluorobenzoic acid (Scheme 6). Kita *et al.* demonstrated construction of 1,4-diazepines with ethylene diamine, aromatic aldehydes, methyl acetoacetate and *p*-TSA as catalyst under inert atmosphere.[17a] However they were further unable to synthesize 1,5-benzodiazepines under identical reaction conditions. In 2008, they extended the idea for the synthesis of 1,5-benzodiazepine using *o*-phenylenediamine, aromatic aldehydes and β-ketoesters with catalytic amount of pentafluorobenzoic acid under nitrogen atmosphere.[17b] Rodriguez *et al.* also established the synthesis of 1,4-diazepine derivatives from 1,2-ethylenediamine, β-ketoesters and aromatic aldehydes in presence of 4 Å molecular sieves in toluene under argon atmosphere under refluxing condition for 24 h. Their strategy for the synthesis of 1,5-benzodiazepines failed under identical conditions using aromatic *o*-phenylenediamine, acyclic β-ketoesters and aromatic aldehydes.[17c-d] Recently the synthesis of 1,5-benzodiazapines has also been reported by our group using organocatalyst 2,6-pyridinedicarboxylic acid.[17e]

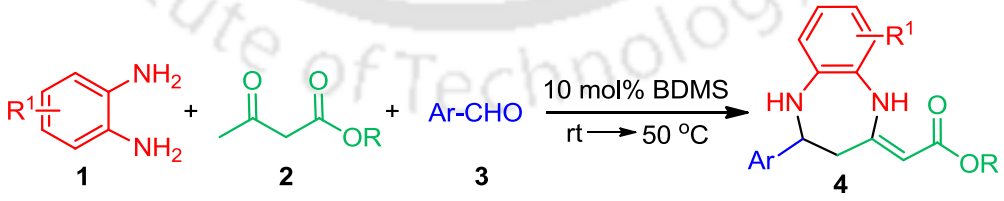


Scheme 6. Synthesis of benzodiazepines using MCR strategy

Unfortunately, all these synthetic methods suffer from limitations such as scope for formation of side products, longer reaction time, lower yields, high reaction temperature[17], inert atmospheric reaction conditions[17a,b,d] or use of expensive catalysts[17b,e]. Earlier reported methods[17] are quite promising nevertheless, there is an immense scope and need for the development of new methodologies aimed to improve and design newer strategy for the synthesis of 1,5-benzodiazepine scaffolds under mild condition with higher efficiency, operational simplicity, economic viability and high regioselectivity.

II.3. Present Work

Recently our group has reviewed the usefulness of bromodimethylsulfonium bromide (BDMS) as a catalyst as well as a brominating reagent in the organic transformations.[18a] BDMS displays efficient catalytic properties as it is capable of generating *in situ* dry HBr and acts as an efficient pre-catalyst for several acid-catalyzed organic reactions.[18b-d] As a part of ongoing efforts to develop new synthetic protocols for the synthesis of biologically active heterocyclic compounds through MCRs, it was perceived that BDMS can be explored further as an efficient catalyst for the synthesis of 1,5-benzodiazapine derivatives.

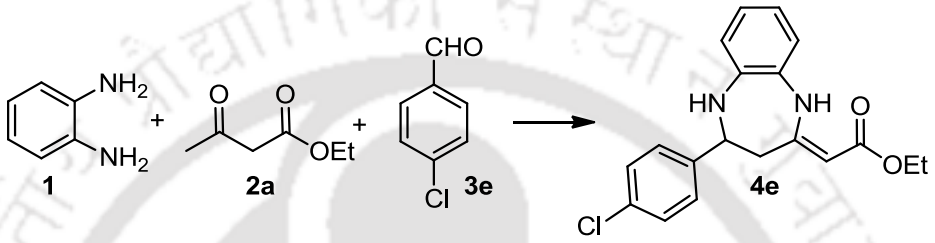


Scheme 7. BDMS catalyzed synthesis of 1,5-benzodiazepine derivatives

To find out a suitable reaction condition, a trial reaction was performed with *o*-phenylenediamine (1 mmol), ethyl acetoacetate (1 mmol) and 4-chlorobenzaldehyde (1 mmol) using 5 mol% of BDMS in acetonitrile as solvent. The gradual progress of the

reaction was monitored by checking the TLC and no further change was observed in the reaction medium after 5 h. After isolating the major product from the crude reaction mixture and analyzing it through ^{1}H NMR, ^{13}C NMR and HRMS data, the product was found to be **4e**, the seven membered benzodiazepine moiety. To obtain best reaction conditions, similar reactions were also executed with 5 mol% of BDMS as well as different solvents like ethanol,

Table 1. Optimization of reaction conditions for the synthesis of 1,5-benzediazepines [a]



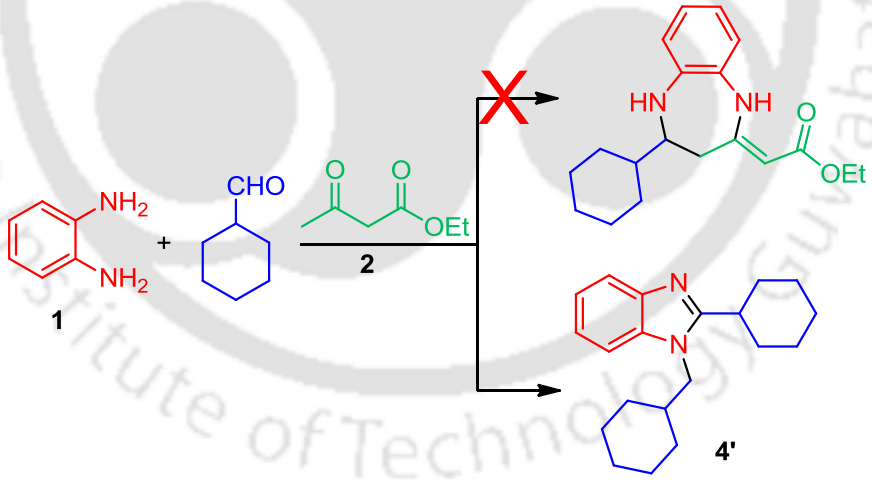
Entry	Catalyst	Solvent	Mol%	Time (h)	Yield[b] (%)
1	BDMS	CH_3CN	5	12	38
2	BDMS	EtOH	5	12	25
3	BDMS	DCM	5	6	35
4	BDMS	DCE	5	5	64
5	**BDMS**	**DCE**	**10**	**4.5**	**72**
6	BDMS	DCE	15	4.5	72
7	Iodine	DCE	10	6	64
8	*p*-TSA	DCE	10	12	25
9	TFA	DCE	10	12	20
10	L-proline	DCE	10	12	27
11	No catalyst	DCE	-----	24	-----

[a]All the reactions were performed with *o*-phenylenediamine (1.0 mmol), ethylacetoacetate (1.0 mmol) and 4-chlorobenzaldehyde (1.0 mmol). [b]Isolated yield.

dichloromethane and dichloroethane, (entries 1-4, Table-1), but DCE was found to be the most suitable solvent. Similar reactions were examined with different catalysts such as molecular iodine, *p*-TSA, TFA and L-proline in DCE solvent (entries 7-10, Table-1). Unfortunately lower yields of the product (**4e**) were obtained with these catalysts (entries 7-10, Table-1). It was noted that the reaction did not proceed at all in absence of the catalyst

(entry 11, Table-1). It was observed that 10 mol% of BDMS catalyst in DCE solvent is the suitable condition (entry 5, Table-1). Further increment of the catalyst did not affect the yield of the product (entry 6, Table-1). From the above observations, it is quite obvious that BDMS plays a crucial role among all other catalysts.

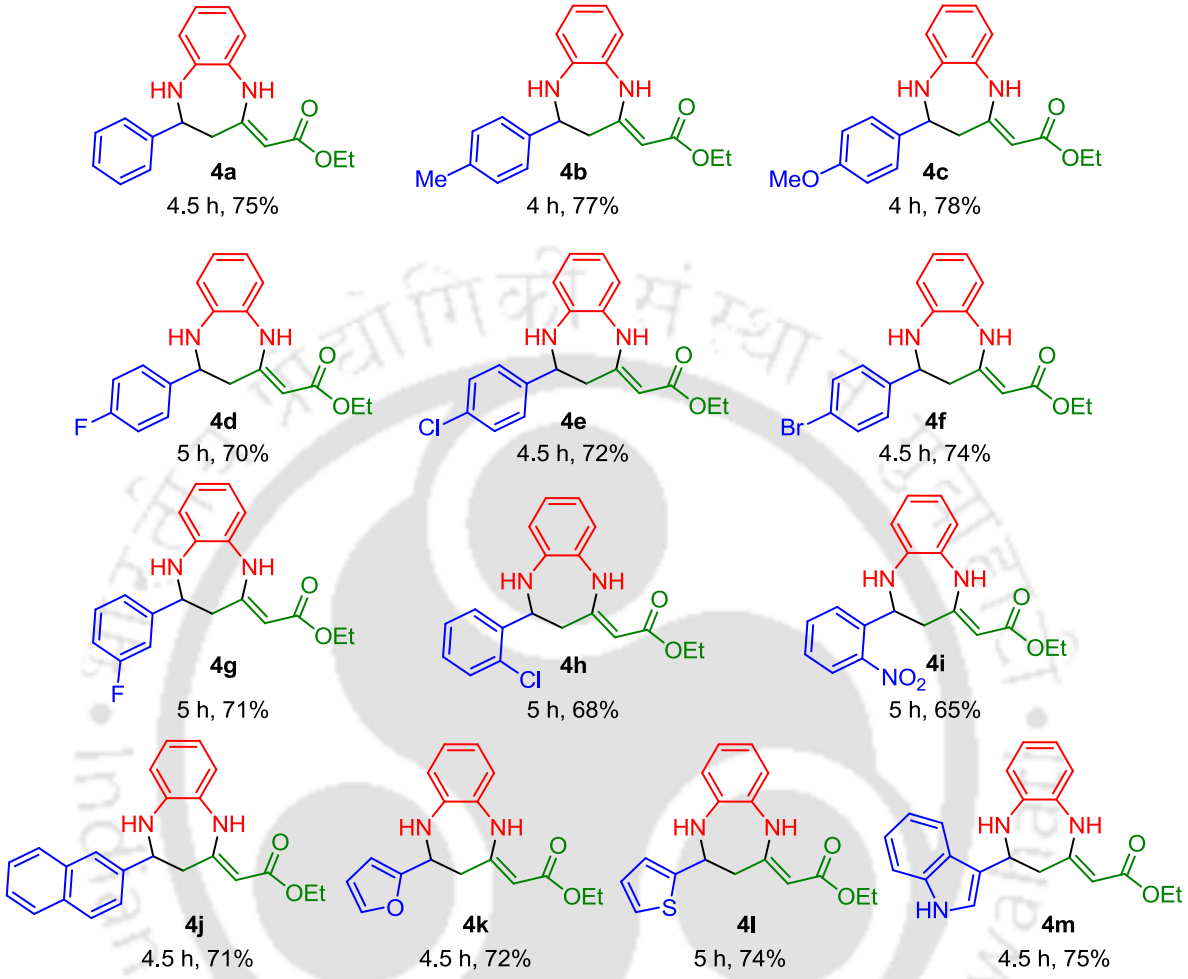
Having the optimized reaction condition in hand, an attempt was made to expand the generality and scope of this reaction using different variety of substituted aromatic aldehydes, β-ketoesters and aromatic diamines. Aromatic aldehydes bearing different substituents were treated with a mixture of *o*-phenylenediamine and ethyl acetoacetate under the optimized reaction conditions and the corresponding products (**4a**-**m**, Table 2) were obtained in good to moderate yields. It was found that aromatic aldehydes with electron-donating functionality such as Me, OMe group (**4b** & **4c**, Table 2) generally gave better yield as compared to the ones having electron-withdrawing groups (**4d-f**, Table 2). The reaction was further performed with *ortho*- and *meta*-substituted aldehydes (**4g-i**, Table 2) as well as fused aldehyde such as naphthaldehyde (**4j**, Table 2). Furthermore, the reaction was also carried out with heteroaromatic aldehydes like furfural aldehyde, thiophene aldehyde and indole aldehyde giving moderate yields (**4k-m**, Table 2).



Scheme 8. BDMS catalyzed reaction in presence of cyclohexanecarboxaldehyde

Unfortunately, the reaction was unsuccessful with aliphatic aldehydes. When the reaction was carried out with cyclohexanecarboxaldehyde, *o*-phenylenediamine and ethylacetoacetate, 2-cyclohexyl-1-(cyclohexylmethyl)-1H-benzo[*d*]imidazole (**4'**) was isolated in 30% yield instead of the desired 1,5-benzodiazepine derivatives (Scheme 8).

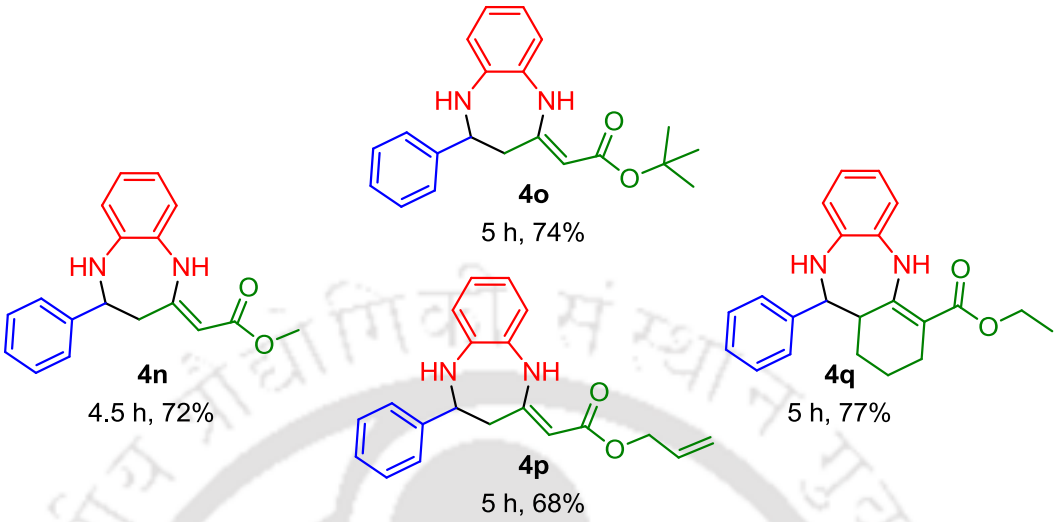
Table 2. Synthesis of 1,5-benzodiazepine derivatives using substituted aromatic aldehyde, ethyl acetoacetate and *o*-phenylenediamine[a]



[a]All the reactions were performed with *o*-phenylenediamine (1.0 mmol), ethylacetoacetate (1.0 mmol) and different aromatic aldehyde (1.0 mmol). [b]Isolated yields.

This reaction was further expanded with various types of β-ketoesters. This reaction was conducted in presence of *o*-phenylenediamine and benzaldehyde with different acyclic β-ketoesters such as methyl acetoacetate or *t*-butyl acetoacetate which gave the desired products in good yields (**4n** & **4o**, Table 3). Even allyl acetoacetate also produced desired 1,5-benzodiazepine scaffold in moderate yields (**4p**, Table 3).

Table 3. Scope of β-ketoesters for the synthesis of 1,5-benzodiazepine derivatives using benzaldehyde and *o*-phenylenediamine[a]



[a]All the reactions were performed with *o*-phenylenediamine (1.0 mmol), benzaldehyde (1.0 mmol) and different β-ketoester (1.0 mmol). [b]Isolated yields.

Successful attempt was made during the synthesis of 1,5-benzodiazepine derivative **4q** using ethyl 2-oxocyclohexanecarboxylate, a cyclic β-ketoester, *o*-phenylenediamine and benzaldehyde under similar condition in 77% yield. The product **4q** was characterized through single XRD data.

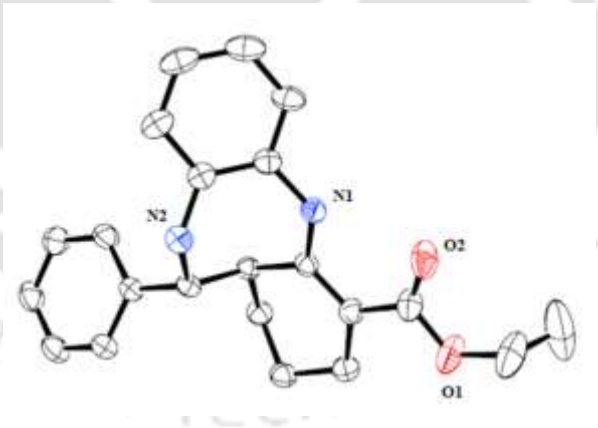
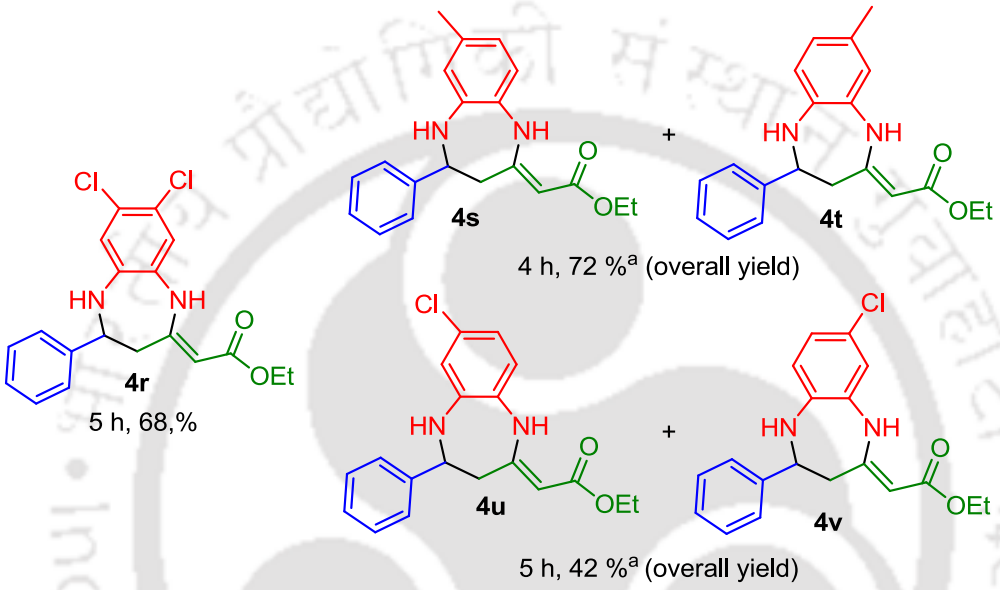


Figure 2. Ortep view of **4q** (CCDC 952358)

Next, the scope this multicomponent reaction was further extended by using substituted mono and symmetrical disubstituted aromatic diamines to produce various substituted 1,5-benzodiazepine derivatives. Although in case of dichloro-substituted aromatic diamine, the single desired product (**4r**) was obtained in good yields, but for mono substituted diamine a

mixture of two inseparable regioisomers was obtained as per anticipation with nearly (6:4) ratio which was determined from ^{1}H NMR. In case of *o*-phenylenediamine having chloro substituent, lower yield have been obtained compared to electron-donating substituent in *o*-phenylenediamine as shown in Table 4.

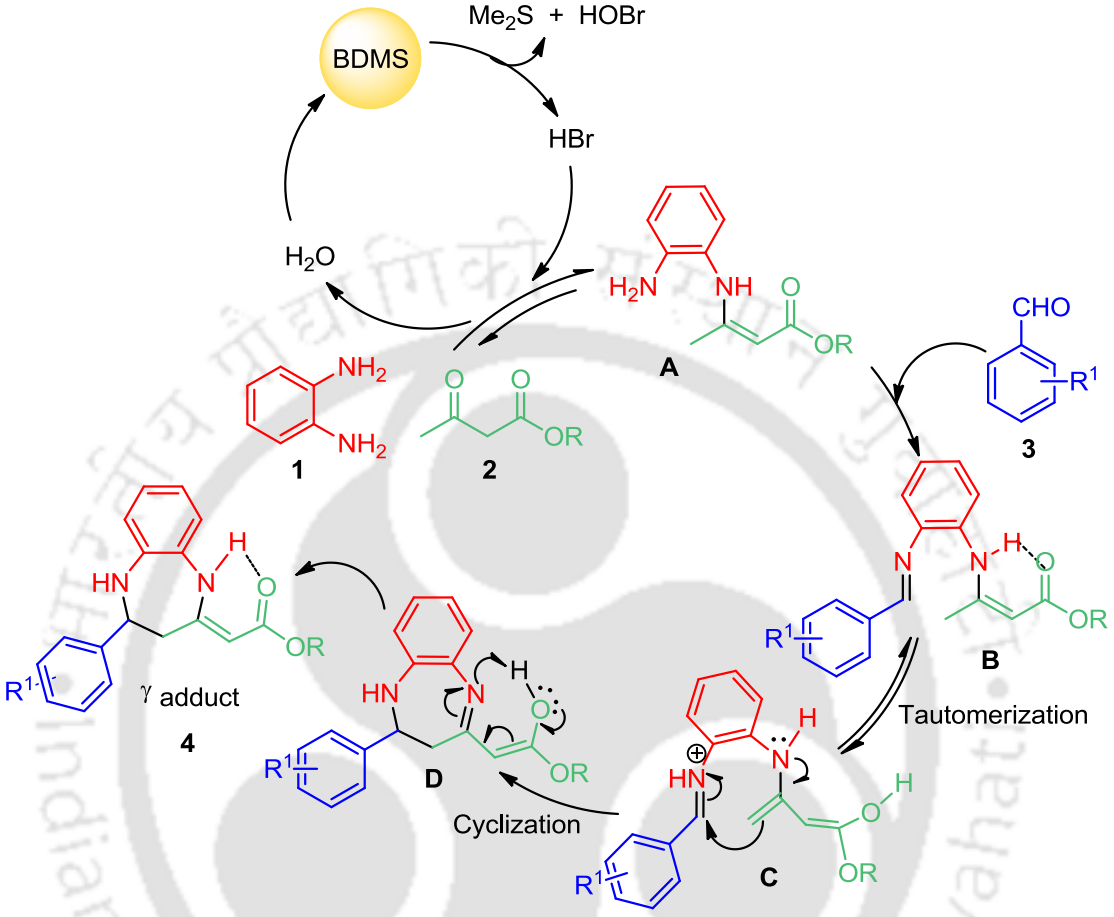
Table 4. Scope of 1,5-benzodiazepine derivatives with substituted diamine, benzaldehyde and ethyl acetoacetate.



[a]Mixture of two inseparable regioisomers with nearly (6:4) ratio of the two isomers determined from 1H-NMR.

Our attention was turned to gain mechanistic insights of this transformation. According, to the literature survey[17b,e] a plausible mechanism has been depicted in Scheme 9. The formation of 1,5-benzodiazepines can be explained as follows: It is proposed that *o*-phenylenediamine (**1**) reacts with β-ketoester (**2**) to form mono enaminoester **A** in the presence of BDMS at room temperature which is a very characteristic reaction of carbonyl compounds in the presence of an acid catalyst. This intermediate compound **A** has also been isolated. It is evident from NMR spectrum that the major product isolated after 15 min, compound **A,** is formed at the first step of transformation. Then, this intermediate reacts with an aromatic aldehyde (**3**) under reflux conditions to form imine-enaminoester intermediate **B**. The intermediate **B**, stabilized by intramolecular hydrogen bonding interaction can provide 1,5-benzodiazepine derivative through γ-selective C–C bond formation. This intermediate **B** tautomerizes to intermediate **C** which further undergoes

cyclization to give intermediate **D**. This intermediate **D** undergoes further rearrangement to form the final product **4**, the γ adduct, which is stabilized due to intramolecular H-bonding.



Scheme 9. Plausible mechanism for the formation of 1,5-benzodiazepine derivatives

II.4. Conclusion

In summary, a simple, environmentally benign synthetic protocol have been devised for the synthesis of 1,5-benzodiazepine derivatives catalyzed by BDMS from *o*-phenylenediamine, β-ketoesters and aromatic aldehydes through one-pot MCRs. Here BDMS acts as pre-catalyst and generates *in situ* HBr which plays a vital role in the synthesis of 1,5-benzodiazepine derivatives. The advantage of this protocol is the use of readily available starting materials as well as presence of cheap, environment friendly BDMS as catalyst without inert atmospheric reaction conditions.

II.5. References

1. O. Randall and B. Kappel, In *Benzodiazepines*, Ed. S. Garattini, E. Mussini and L. O. Randall, Raven Press, New York, 1973, p. 27 (b) H. Schütz, In *Benzodiazepines*, Springer, Heidelberg, 1982.
2. B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson and R. S. Chang, *J. Med. Chem.*, 1988, **31**, 2235.
3. (a) A. A. Patchett and R. P. Nargund Annu., *Rep. Med. Chem.*, 2000, **35**, 289; (b) D. J. Triggle, *Cell. Mol. Neurobiol*., 2003, **23**, 293; (c) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screening*, 2004, **7**, 473; (d) J. Poupaert, P. Carato and E. Colacino, *Curr. Med. Chem.*, 2005, **12**, 877.
4. (a) R. K. Smalley, In *Comprehensive Organic Chemistry*, D. Barton, W. D. Ollis and P. G. Sammes, Eds., Pergamon: Oxford, 1979; Vol. **4**, p 600; (b) J. K. Landquist, In *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, C. W. Rees and O. Meth-Cohn, Eds., Pergamon: Oxford, 1984, Vol. **1**, pp 166.
5. J. Knabe, H. P. Büch and S. Bender, *Arch. Pharm*., 1995, **328**, 59.
6. K. S. Atwal, J. L. Bergey, A. Hedberg and S. Moreland, *J. Med. Chem*., 1987, **30**, 635.
7. M. Di Braccio, G. Grossi, G. Roma, L. Vargiu, M. Mura and M. E. Marongiu, *Eur. J. Med. Chem.*, 2001, **36**, 935.
8. L. D. Fader, R. Bethell, P. Bonneau, M. Bös, Y. Bousquet, M. G. Cordingley, R. Coulombe, P. Deroy, A.-M. Faucher, A. Gagnon, N. Goudreau, C. Grand-Maître, I. Guse, O. Hucke, S. H. Kawai, J.-E. Lacoste, S. Landry, C. T. Lemke, E. Malenfant, S. Mason, S. Morin, J. O'Meara, B. Simoneau, S. Titolo and C. Yoakim, *Bioorg. Med. Chem. Lett*., 2011, **21**, 398.
9. R. C. Harris and J. M. Straley, *US Pat.*, 1,537,757, 1968; R. C. Harris and J. M. Straley, *Chem. Abstr*., 1970, **73**, 100054w.
10. (a) M. C. Aversa, A. Ferlazzo, P. Giannetto and F. H. Kohnke, *Synthesis*, 1986, 230; (b) A. Chimirri, S. Grasso, R. Ottana, G. Romeo and M. J. Zappala, *Heterocyclic Chem*., 1990, **27**, 371.

11. J. Zhu and H. Bienaymé, In *Multicomponent Reactions*, 1st Ed.; Wiley-VCH: Weinheim, Germany, 2005.
12. (a) M. Nardi, A. Cozza, L. Maiuolo, M. Oliverio and A. Procopio, *Tetrahedron Lett*., 2011, **52**, 4827 and references cited therein; (b) S. Goswami, A. Hazra and S. Jana, *J. Heterocycl. Chem*., 2009, **46**, 861; (c) S.-E. Feng, F. Xu and Q. Shen, *Chin. J. Chem.*, 2008, **26**, 1163.
13. W. Ried and E. Torinus, *Chem. Ber.*, 1959, **92**, 2902.
14. (a) C. S. Radatz, R. B. Silva, G. Perin, E. J. Lenardão, R. G. Jacob and D. Alves, *Tetrahedron Lett*., 2011, **52**, 4132 and references cited therein; (b) R. G. Jacob, C. S. Radatz, M. B. Rodrigues, D. Alves, G. Perin, E. J. Lenardão and L. Savegnago, *Heteroat. Chem.*, 2011, **22**, 180; (c) R. Ghorbani-Vaghei and H. Veisi, *Mol. Diversity*., 2010, **14**, 249; (d) A. Shaabani, A. H. Rezayan, S. Keshipour, A. Sarvary and W. Ng S, *Org. Lett.*, 2009, **11**, 3342; (e) M. J. Climent, A. Corma, S. Iborra and L. L. Santos, *Chem. A. Eur. J*., 2009, **15**, 8834; (f) D. V. Jarikote, S. A. Siddiqui, R. Rajagopal, D. Thomas, R. J. Lahoti, and K. V. Srinivasan, *Tetrahedron Lett.*, 2003, **44**, 1835; (g) B. M. Reddy, P. M. Sreekamth and V. R. Reddy, *J. Mol. Catal. A: Chem.*, 2005, **225**, 71; (h) B. Kaboudin and K. Navaee, *Heterocycles*, 2001, **55**, 1443; (i) J. S. Yadav, B. V. S. Reddy, S. Praveenkumar, K. Nagaiah, N. Lingaiah and P. S. Saiprasad, *Synthesis*, 2004, 901.
15. (a) A. Shaabani, A. Maleki and H. Mofakham, *J. Comb. Chem.*, 2008, **10**, 595; (b) A. M. Astaraki and A. Bazgir, *J. Heterocyclic Chem.*, 2013, **50**, 175; (c) Y. Huang, K. Khoury, T. Chanas and A. Dömling, *Org. Lett*., 2012, **14**, 5916.
16. (a) D. Shobha, M. A. Chari, S. T. Selvan, H. Oveisi, A. Mano and K. Mukkanti, *J. Org. Chem*., 2012, **77**, 4484; (b) G. Maiti, U. Kayal, R. Karmakar and R. N. Bhattacharya, *Tetrahedron Lett*., 2012, **53**, 1460.
17. (a) H. Fujioka, K. Murai, O. Kubo, Y. Ohba and Y. Kita, *Org. Lett.*, 2007, **9**, 1687; (b) K. Murai, R. Nakatani, Y. Kita and H. Fujioka, *Tetrahedron*, 2008, **64**, 11034; (c) E. Sotoca, T. Constantieux and J. Rodriguez, *Synlett*, 2008, 1313; (d) E. Sotoca, C. Allais, T. Constantieux and J. Rodriguez, *Org. Biomol. Chem.*, 2009, **7**, 1911; (e) M. Lal, R. S. Basha, S. Sarkar and A. T. Khan, *Tetrahedron Lett.*, 2013, **54**, 4264.
18. (a) L. H. Choudhury, T. Parvin and A. T. Khan, *Tetrahedron*, 2009, **65**, 9513; (b) A. T. Khan, T. Parvin and L. H. Choudhury, *J. Org. Chem*., 2008, **73**, 8398; (c) A. T. Khan, R.

S. Basha and M. Lal, *Tetrahedron Lett.*, 2011, **52**, 5157; (d) A. T. Khan, A. Choudhury, S. Ali and M. M. Khan, *Tetrahedron Lett.*, 2012, **53**, 4852

Experimental Section

General Procedure:

Into an oven dry 25 mL round bottomed flask was taken a mixture of *o*-phenylenediamine (1.0 mmol) and β-ketoesters (1.0 mmol) in 3 mL of dichloroethane. Then, the catalyst BDMS (10 mol%) was added into it and the reaction mixture was kept for stirring at room temperature. After 15 minutes of stirring aromatic aldehyde (1 mmol) was added into it and the reaction mixture was heated in an oil-bath at 55 ^{o}C. TLC was taken after 1 h interval; it indicated the formation of the expected product. The product is UV light active so it was easily visible when TLC plate was placed under UV lamp. The reaction was allowed to run for 4-5 hours until the complete consumption of starting materials. After the reaction was complete, the solvent was removed in rotary evaporator. Then, the crude reaction mixture was extracted with dichloromethane (2 x 10 mL), washed with water and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated *in vacuo* and the crude product was purified after column chromatography. The desired products were eluted with ethylacetate/hexane (5:95) and the products **4**(**a**-**v**) were obtained in 65-78% yields.

Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Compound **4q** empirical formula '$C_{22}H_{24}N_2O_2$', colorless crystal, formula wt 348.4382, Triclinic, P-1, a = 9.0434(7) Å, b = 14.2507(10) Å, c = 15.1105(12) (10) Å, V = 1890.1(3) Å^3, Z = 2, F (0 0 0) = 742.0, GOF(S) = 0.947. Final indices R_{obs} = 0.0803, wR_{obs} = 0.2403 with I > 2r(I); R_{all} = 0.1552, wR_{all} = 0.3256 for all data.

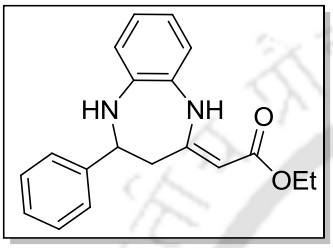
Table 1. Crystal data and structure refinement for **4q**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

	Compound (CCDC)
Identification code	SS-217
Empirical formula	'C_{22} $H_{24}N_2O_2$'
Formula weight	348.4382
Temperature	298(2) K
Wavelength	0.71073Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	
a	9.0434(7) Å
b	14.2507(10) Å
c	15.1105(12) Å
α	100.435(6)º
β	91.179(6)º
γ	98.829(6)º
Volume	1890.1(3) $Å^3$
Z	2
Density (calculated)	1.223 g/cm^3
Absorption coefficient	0.079 mm^{-1}
F(000)	742.0
Theta range for data collection	2.86 to 28.86º
Index ranges	-12<=h<=12, -19<=k<=18, -20<=l<=19
Reflections collected	16386
Independent reflections	9889 R_{int} = 0.0387
Completeness to θº	98.1% (θ = 28.86º)
Refinement method	Full-matrix least-squares on F2
Data / restraints / parameters	9889/ 0 / 471
Goodness-of-fit on F2	0.947

Final R indices [>2sigma(I)]	R_{obs} = 0.0803, wR_{obs} = 0.2403
R indices (all data)	R_{all} = 0.1552, wR_{all} = 0.3256
Largest diff. peak and hole	0.528 and -0.302e.Å^{-3}

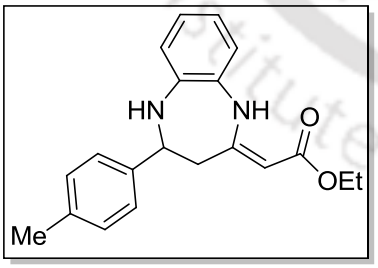
Spectral Data

(Z)-ethyl 2-(4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene)acetate (4a):



Yellow solid (0.213 g, 75%); Mp 73–77 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.54 (dd, *J* = 14.0 & 4.4 Hz, 1H), 2.70 (dd, *J* = 14.0 & 9.2 Hz, 1H), 3.7 (bs, 1H, NH), 4.2-4.1 (m, 2H), 4.61 (s, 1H), 4.85 (dd, *J* = 9.2 & 4.0 Hz, 1H), 6.79-6.76 (m, 1H), 6.85-6.94 (m, 1H), 6.96–7.05 (m, 2H), 7.28–7.32 (m, 1H), 7.32-7.39 (m, 4H), 10.24 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.75, 40.52, 59.05, 65.33, 82.42, 121.01, 121.80, 122.74, 125.19, 126.29, 128.18, 129.03, 130.11, 138.11, 145.07, 158.83, 170.52 ppm; IR (KBr): 1158, 1455, 1618, 1637, 2923, 3415, 3467 cm^{-1}; Anal. Calcd. for $C_{19}H_{20}N_2O_2$ (308.3743): C, 74.00; H, 6.54; N, 9.08; found: C, 74.06; H, 6.59; N, 9.02 ; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$ (M + H^{+}) 309.1598, found 309.1594.

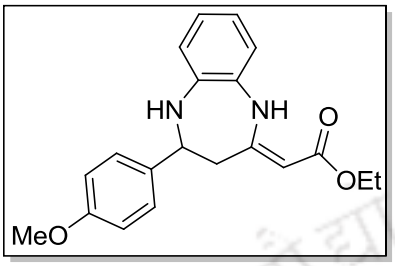
(Z)-ethyl-2-(4-(*p*-tolyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene)acetate (4b):



Yellow solid (0.248 g, 77%); Mp 95–98 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, *J* = 7.2 Hz, 3H), 2.24 (s, 3H), 2.39 (dd, *J* = 13.2 & 3.6 Hz, 1H), 2.57 (dd, *J* = 13.6 & 9.2 Hz, 1H), 3.59 (bs, 1H, NH), 3.98-4.12 (m, 2H), 4.51 (s, 1H), 4.67 (dd, *J* = 9.2 & 4.0 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.70-6.81 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 10.15 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.67, 21.19, 40.51, 58.92, 64.93, 84.23, 120.88, 121.55, 122.61, 125.07, 126.11, 129.55, 129.89, 137.77, 138.07, 142.11, 158.91, 170.43 ppm; IR (KBr): 1179, 1480, 1621, 2922, 3332, 3367 cm^{-1}; Anal. Calcd .for $C_{20}H_{22}N_2O_2$ (322.4009): C, 74.51; H, 6.88; N, 8.69; found:

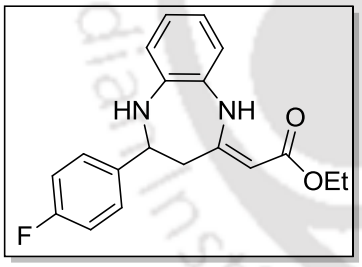
C, 74.55; H, 6.91; N, 8.63. HRMS (ESI) calcd for $C_{20}H_{22}N_2O_2$ (M + H^+) 323.1754, found 323.1759.

(Z)-ethyl-2-(4-(4-methoxyphenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4c):



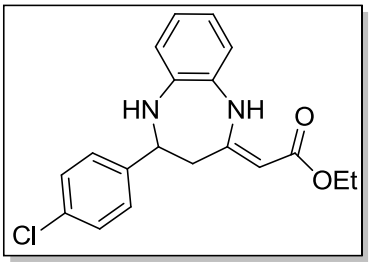
Semi solid (0.264 g, 78%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J* = 7.2 Hz, 3H), 2.52 (dd, *J* = 13.6 & 10.4 Hz, 1H), 2.67 (dd, *J* = 13.6 & 4.8 Hz, 1H), 3.65 (bs, 1H, NH), 3.81 (s, 3H), 4.10-4.20 (m, 2H), 4.60 (s, 1H), 4.80 (dd, *J* = 9.2 & 3.6 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.94-7.00 (m, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 10.24 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.79, 40.70, 55.54, 59.08, 64.79, 84.40, 114.32, 121.03, 121.76, 122.76, 125.18, 127.47, 130.11, 137.35, 138.11, 158.98, 159.51, 170.55 ppm; IR (KBr,): 1484, 1622, 2857, 2917, 3439, cm^{-1}; Anal. Calcd. for $C_{20}H_{22}N_2O_3$ (338.4003): C, 70.99; H, 6.55; N, 8.28; Found: C, 71.00; H, 6.59; N, 8.22; HRMS (ESI) calcd for $C_{20}H_{22}N_2O_3$ (M + H^+) 339.1703, found 339.1714.

(Z)-ethyl-2-(4-(4-fluorophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4d):



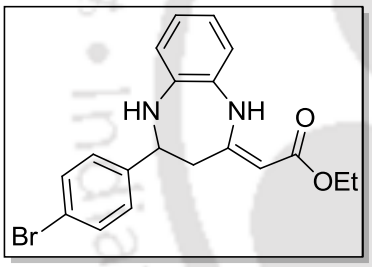
Solid (0.227 g, 70%); ^{1}H NMR ($CDCl_3$, 400 MHz):δ 1.27 (t, *J* =7.2 Hz, 3H), 2.59 (dd, *J* = 13.6 & 4.4 Hz, 1H), 2.74 (dd, *J* = 13.6 & 9.6 Hz, 1H), 3.75 (bs, 1H, NH), 4.03-4.21 (m, 2H), 4.70 (s, 1H), 4.90 (dd, *J* = 9.2 & 4.4 Hz, 1H), 6.18-6.22 (m, 1H), 6.28-6.32 (m, 1H), 6.70-6.76 (m, 1H), 6.90-7.00 (m, 4H), 7.35 (s, 1H), 10.16 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.69, 36.62, 58.92, 59.03, 84.64, 105.52, 110.40, 121.99, 122.41, 122.77, 125.08, 131.40, 137.20, 142.05, 156.40, 158.32, 170.36 ppm; IR (KBr): 1158, 1500, 1616, 2978, 3414 cm^{-1}; Anal. Calcd for $C_{19}H_{19}FN_2O_2$ (326.3648): C, 69.92; H, 5.87; N, 8.58; found: C, 69.98; H, 5.91; N, 8.55; HRMS (ESI) calcd for $C_{19}H_{19}FN_2O_2$ (M + H^+) 327.1503, found 327.1512.

(Z)-ethyl-2-(4-(4-chlorophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4e):



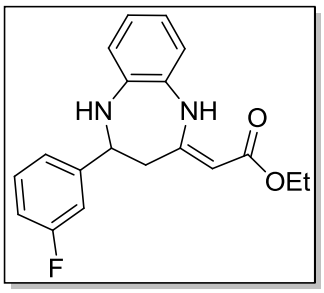
White solid (0.245 g, 72%); Mp 176–180 ^{o}C ;^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.55-2.65 (m, 2H), 3.65 (bs, 1H, -NH), 4.05-4.20 (m, 2H), 4.53 (s, 1H), 4.80-4.90 (m, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.90-7.00 (m, 3H), 7.25-7.35 (m, 4H), 10.20 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.70, 40.12, 59.08, 64.65, 84.81, 121.12, 122.20, 122.68, 125.21, 127.79, 129.03, 130.45, 133.76, 137.96, 143.167, 158.13, 170.37 ppm; IR (KBr): 1159, 1486, 1624, 2923, 3324, 3362, cm^{-1}; Anal. Calcd. For $C_{19}H_{19}ClN_2O_2$ (342.8192): C, 66.57; H, 5.59; N, 8.17; found: C, 66.60; H, 5.63; N, 8.13; HRMS (ESI) calcd for $C_{19}H_{19}ClN_2O_2$ (M + H$^+$) 343.1208, found 343.1215.

(Z)-ethyl-2-(4-(4-bromophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)ylidene) acetate (4f):



Semi solid (0.286 g, 74%);.^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25 (t, *J* = 7.2 Hz, 3H), 2.50-2.60 (m, 2H), 3.62 (bs, 1H, -NH), 4.51 (s, 1H), 4.05-4.2 (m, 2H), 4.80 (dd, *J* = 7.6 & 4.4 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.80-7.05 (m, 3H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 10.18 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.77, 40.13, 59.17, 64.81, 84.91, 121.20, 121.99, 122.33, 122.77, 125.29, 128.21, 130.57, 132.06, 138.0, 143.73, 158.16, 170.45 ppm; IR (KBr): 1159, 1484, 1624, 2924, 3327, 3359 cm^{-1}; Anal. Calcd for $C_{19}H_{19}BrN_2O_2$ (387.2704): C, 58.93; H, 4.95; N, 7.23; found: C, 58.97; H, 4.99; N, 7.18. HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2Br$ (M + H$^+$) 387.0703, found 387.0709.

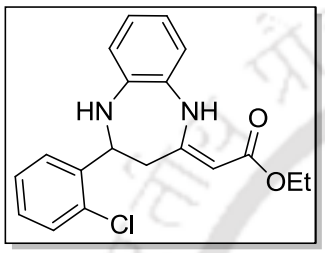
(Z)-ethyl-2-(4-(3-fluorophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4g):



Semi solid (0.228 g, 71%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (t, *J* = 7.6 Hz, 3H), 2.60 (d, *J* = 6.4 Hz, 2H) , 4.05-4.20 (m, 2H) , 4.56 (s, 1H), 4.86 (t, *J* = 6.4 Hz, 1H) , 6.79 (d, *J* = 7.6 Hz, 1H), 6.90-7.02 (m, 4H), 7.10 (d, *J* = 9.6 Hz, 1H) , 7.14 (d, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 13.6 & 7.6 Hz, 1H), 10.21 (s, 1H, -NH) ppm;

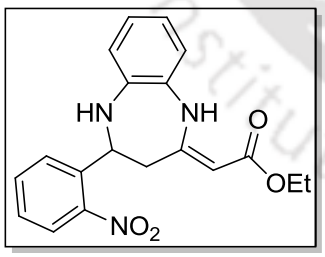
^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.73, 40.16, 59.12, 64.86, 84.75, 113.25, 113.47, 114.93, 115.14, 121.16, 121.97, 122.24, 122.75 125.28, 130.48, 130.56, 137.89, 147.45, 158.18, 173.43 ppm; IR (KBr): 1158 , 1484, 1617, 2978, 3280, 3352 cm^{-1}; Anal. Calcd for $C_{19}H_{19}N_2O_2F$ (326.3648): C, 69.92; H, 5.87; N, 8.58; found: C, 69.97; H, 5.90; N, 8.53; MS (ESI) calcd for $C_{19}H_{19}N_2O_2F$ (M + H^+) 327.1503, found 327.1509.

(Z)-ethyl-2-(4-(2-chlorophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4h):



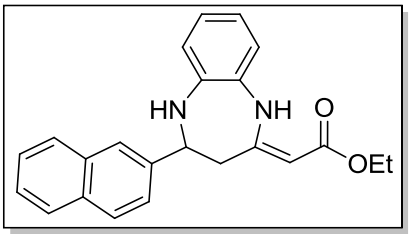
Yellow gummy liquid (0.233 g, 68%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.13 (t, *J* = 7.6 Hz, 3H), 2.45 (dd, *J* = 14.0 & 7.6 Hz, 1H), 2.60 (dd, *J* = 14.0 & 4.4 Hz, 1H), 3.63 (bs, 1H, -NH), 3.90-4.40 (m, 2H), 4.37 (s, 1H), 5.22-5.30 (m, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.75-6.90 (m, 3H), 7.16-7.04 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 1H) , 7.58 (d, *J* = 7.6 Hz, 1H), 10.07 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.58, 37.63, 58.88, 60.77, 84.78, 120.88, 121.82, 122.56, 125.09, 127.24, 128.05, 128.82, 129.59, 130.20, 131.74, 138.29, 141.36, 158.04, 172.22 ppm; IR (KBr): 1157, 1499, 1616, 2977, 3272, 3349 cm^{-1}; Anal. Calcd for $C_{19}H_{19}N_2O_2Cl$ (342.8194): C, 66.57; H, 5.59; N, 8.17; found: C, 66.62; H, 5.64; N, 8.14; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_2Cl$ (M + H^+) 343.1208, found 343.1214.

(Z)-ethyl-2-(4-(2-nitrophenyl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4i):



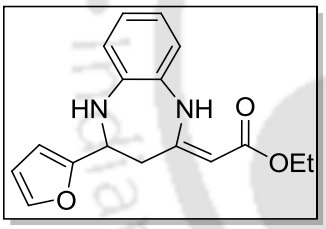
Yellow gummy liquid (0.230 g, 65%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.62 (dd, *J* = 14.0 & 6.0 Hz, 1H), 2.89 (dd, *J* = 13.6 & 4.4 Hz, 1H), 3.80 (bs, 1H, -NH), 4.0-4.22 (m, 2H), 4.45 (s, 1H), 5.40 (t, *J* = 5.2 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.88-7.20 (m, 3H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 10.16 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.57, 38.16, 58.97, 59.53, 85.55, 121.11, 122.39, 122.58, 124.22, 125.21, 128.54, 129.46, 130.66, 133.27, 138.18, 139.04, 148.13, 157.45, 170.19 ppm; IR (KBr): 1159, 1343, 1513, 1484, 1624, 2927, 3326, 3357 cm^{-1}; Anal. Calcd for $C_{19}H_{19}N_3O_4$ (353.3719): C, 64.58; H, 5.42; N, 11.89; found: C, 64.62; H, 5.46; N, 11.84. HRMS (ESI) calcd for $C_{19}H_{19}N_3O_4$ (M + H^+) 354.1448, found 354.1459.

(Z)-ethyl-2-(4-(naphthalen-2-yl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4j):



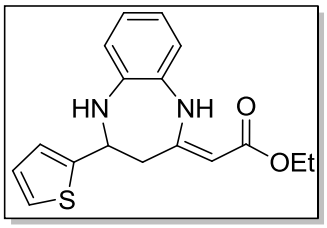
Yellow gummy liquid (0.254 g, 71%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.63 (dd, *J* = 13.6 & 3.6 Hz, 1H), 2.80 (dd, *J* = 14.0 & 9.2 Hz, 1H), 4.10-4.20 (m, 2H), 4.62 (s, 1H), 5.01 (dd, *J* = 9.2 & 4.4 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.92-6.96 (m, 1H), 6.98-7.04 (m, 2H), 7.46-7.54 (m, 3H), 7.78-7.90 (m, 4H), 10.27 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.74, 40.35, 59.07, 65.45, 84.59, 121.11, 121.92, 122.79, 124.34, 125.05, 125.25, 126.31, 126.58, 127.91, 128.19, 128.96, 130.22, 133.30, 133.52, 138.15, 142.26, 158.74, 170.52 ppm; IR (KBr, cm^{-1}): 1152, 1473, 1618, 2923, 3433 cm^{-1}; Anal. Calcd for $C_{23}H_{22}N_2O_2$ (358.4330): C, 77.07; H, 6.19; N, 7.82; found: C, 77.12; H, 6.25; N, 7.78; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_4$ (M + H^+) 359.1754, found 359.1750.

(Z)-ethyl-2-(4-(furan-2-yl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene)acetate (4k):



Yellow solid (0.215 g, 72%); Mp 84–88 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, *J* = 7.2 Hz, 3H), 2.40-2.55 (m, 2H), 3.57 (bs, 1H, -NH), 3.90-4.15 (m, 2H), 4.45 (s, 1H), 4.75 (t, *J* = 6.0 Hz, 1H), 6.67 (d, *J* = 7.6, 1H), 6.75-6.90 (m, 2H), 6.93 (t, *J* = 8.8 Hz, 2H), 7.20-7.30 (m, 2H), 10.13 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.67, 40.35, 59.03, 64.54, 84.69, 115.79, 121.04, 122.03, 122.65, 125.17, 127.93, 128.01, 130.32, 137.99, 140.59, 158.32, 170.37 ppm; IR (KBr): 1157, 1438, 1625, 2824, 3416, cm^{-1}; Anal. Calcd for $C_{17}H_{18}N_2O_3$ (298.3364): C, 68.44; H, 6.08; N, 9.39; found: C, 68.48; H, 6.14; N, 9.33.

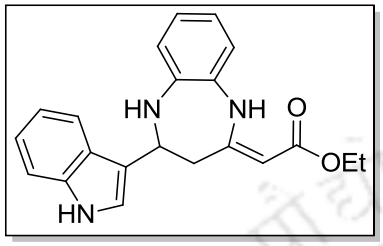
(Z)-ethyl-2-(4-(thiophen-2-yl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4l):



Semi solid (0.232 g, 74%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.20 (t, *J* = 7.2 Hz, 3H), 2.55-2.65 (m, 2H), 3.63 (bs, 1H, -NH), 4.00-4.15 (m, 2H), 4.59 (s, 1H), 5.09 (dd, *J* = 12.0 & 5.6 Hz, 1H), 6.55-6.65 (m, 1H), 6.80-7.00 (m, 5H), 7.10-7.20 (m, 1H), 10.11 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.75, 40.78, 59.11, 61.20, 84.88, 122.04, 122.58, 122.83, 123.67, 124.76, 125.17, 126.89, 131.31, 137.08.

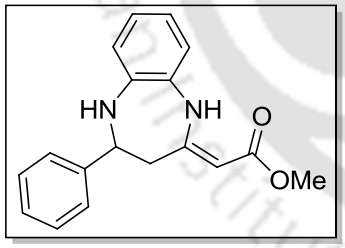
148.43, 158.11, 170.44 ppm; IR (KBr): 1158, 1437, 1616, 2963, 3448 cm^{-1}; Anal. Calcd for $C_{17}H_{18}O_2N_2S$ (314.4020): C, 64.94; H, 5.77; N, 8.91; found: C, 64.99; H, 5.81; N, 8.86.

(Z)-ethyl-2-(4-(1H-indol-3-yl)-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene)acetate (4m):



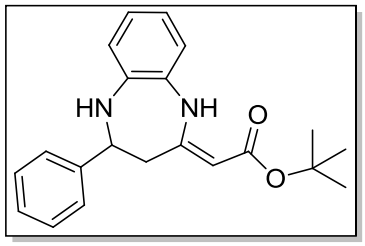
Yellow solid (0.260 g, 75%); Mp 139–143 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.15 (t, *J* = 7.2 Hz, 3H), 2.48 (d, *J* = 13.6 Hz, 1H), 2.79 (dd, *J* = 13.2 & 9.2 Hz, 1H), 3.98-4.18 (m, 2H), 4.52 (s, 1H), 5.00-5.10 (m, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 6.0 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 8.33 (s, 1H, -NH), 10.17 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.65, 39.40, 57.98, 59.06, 84.12, 111.66, 119.10, 119.64, 119.83, 120.96, 121.45, 121.52, 122.47, 122.55, 125.14, 129.68, 136.61, 138.13, 159.82, 170.61 ppm; IR (KBr): 1163, 1442, 1638, 2978, 3418, 3467 cm^{-1}; Anal. Calcd for $C_{21}H_{20}N_3O_2$ (346.4080): C, 72.60; H, 6.09; N, 12.10; found: C, 72.67; H, 6.15; N, 12.05; HRMS (ESI) Calcd for $C_{21}H_{21}N_3O_2$ ($M + H^+$) 348.1707, found 348.1724.

(Z)-methyl-2-(2,3-dihydro-2-phenyl-1H-benzo[*b*][1,4]diazepin-4(5H)-ylidene)acetate (4n):



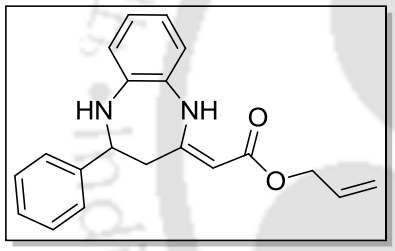
Semi solid (0.212 g, 72%); ^1H NMR ($CDCl_3$, 400 MHz): δ 2.55 (dd, *J* = 13.6 & 3.6 Hz, 1H), 2.66 (dd, *J* = 14.0 & 8.8 Hz, 1H), 3.67 (s, 3H), 4.59 (s, 1H), 4.84 (dd, *J* = 8.8 & 4.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 6.8 Hz, 2H), 7.29-7.35 (m, 5H), 10.20 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 40.38, 50.52, 65.31, 83.97, 121.02, 121.79, 122.71, 125.23, 126.27, 128.14, 128.96, 130.02, 138.13, 144.91, 158.93, 170.78 ppm; IR (KBr): 1161, 1495, 1616, 2946, 3368 cm^{-1}; Anal. Calcd for $C_{18}H_{18}N_2O_2$ (294.3477): C, 73.45; H, 6.16; N, 9.52; found: C, 73.49; H, 6.21; N, 9.48.

(Z)-*tert*-butyl-2-(2,3-dihydro-2-phenyl-1H-benzo[*b*][1,4]diazepin-4(5H)-ylidene)acetate (4o):



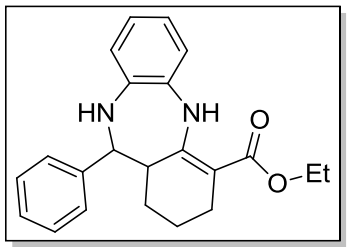
Semi solid (0.248 g, 74%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (s, 9H), 2.43 (dd, *J* = 13.6 & 3.6 Hz, 1H), 2.64 (dd, *J* = 13.6 & 9.6 Hz, 1H), 4.55 (s, 1H), 4.84 (dd, *J* = 9.6 & 4.0 Hz, 1H), 6.72 (d, *J* = 7.2 Hz, 1H), 6.88-6.82 (m, 1H), 6.93 (t, *J* = 6.8 Hz, 2H), 7.22-7.35 (m, 5H), 10.20 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.99, 28.20, 28.64, 40.38, 51.46, 65.19, 78.64, 85.88, 120.86, 121.54, 122.49, 122.71, 124.83, 126.09, 127.95, 128.85, 130.09, 137.85, 145.19, 157.92, 170.32 ppm; IR (KBr): 1140, 1618, 2975, 3417 cm^{-1}; Anal. Calcd. for $C_{21}H_{24}N_2O_2$ (336.4275): C, 74.97; H, 7.19; N, 8.33; found: C, 74.99; H, 7.21; N, 8.29; HRMS (ESI) calcd for $C_{19}H_{19}N_3O_4$ (M + H^+) 337.1911, found 337.1916.

(Z)-allyl 2-(2,3-dihydro-2-phenyl-1H-benzo[*b*][1,4]diazepin-4(5H)-ylidene)acetate (4p):



Semi solid (0.217 g, 68%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.56 (dd, *J* = 14.0 & 4.0 Hz, 1H), 2.69 (dd, *J* = 13.6 & 8.8 Hz, 1H), 3.71 (s, 1H, -NH), 4.59-4.63 (m, 2H), 4.65 (s, 1H), 4.85 (dd, *J* = 8.8 & 4.0 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.59–6.02 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.93–6.88 (m, 1H), 6.94–7.02 (m, 2H), 7.27-7.41 (m, 5H), 10.22 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.47, 63.86, 65.37, 84.04, 117.47, 121.02, 121.79, 122.77, 125.28, 126.28, 127.34, 128.19, 129.00, 129.99, 133.43, 138.15, 144.96, 159.20, 170.01 ppm; IR (KBr): 1159, 1624, 2927, 3326, 3357 cm^{-1}; Anal. Calcd for $C_{20}H_{20}N_2O_2$ (320.3850): C, 74.98; H, 6.29; N, 8.74; found: C, 75.03; H, 6.32; N, 8.68.

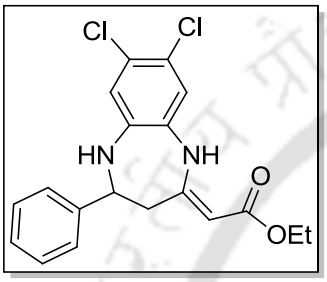
Ethyl-11-phenyl-2,3,5,10,11,11a-hexahydro-1H-dibenzo[*b*,*e*][1,4]diazepine-4-carboxylate (4q):



Yellow Solid (0.268 g, 77%); Mp 110–113 ^{o}C: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15-1.25 (m, 2H), 1.30 (t, *J*= 7.2 Hz, 3H), 1.51-1.55 (m, 2H), 2.25-2.40 (m, 1H), 2.58 (dd, *J* = 16.4 & 4.8 Hz, 1H), 2.89 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.46 (bs, 1H, -NH), 4.05-4.28 (m, 2H), 4.72 (d, *J* = 11.2 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.89-6.98 (m, 3H), 7.18 (dd, *J* = 8.0 & 1.6 Hz, 2H), 7.27-7.35 (m, 3H), 10.83 (s,

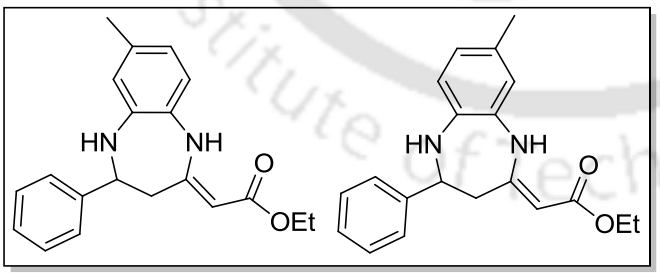
1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.77, 18.04, 24.10, 24.50, 38.45, 59.39, 69.96, 92.02, 122.15, 122.21 (2C), 122.89, 124.31, 126.66, 128.09, 129.02, 132.35, 137.50, 144.17, 156.21, 170.88 ppm; IR (KBr): 1114, 1454, 1638, 2924, 3414, 3464 cm^{-1}; Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.4382): C, 75.83; H, 6.94; N, 8.04; found: C, 75.89; H, 6.99; N, 8.01.

(Z)-ethyl-2-(7,8-dichloro-4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate (4r):



Semi solid (0.256 g, 68%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, *J* = 7.2 Hz, 3H) , 2.54 (dd, *J* = 14.0 & 3.6 Hz, 1H), 2.67 (dd, *J* = 14.0 & 9.2 Hz, 1H), 3.79 (bs, 1H, -NH), 4.03-4.21 (m, 2H), 4.63 (s, 1H), 4.80 (dd, *J* = 9.2 & 3.6 Hz, 1H), 6.82 (s, 1H), 7.02 (s, 1H), 7.35-7.40 (m, 5H), 10.22 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.64, 40.29, 59.30, 64.50, 85.94, 121.35, 123.60, 123.95, 126.14, 127.53, 128.43, 129.15 (2C), 129.44, 137.65, 144.22, 157.75, 170.37 ppm; IR (KBr): 1155, 1455, 1618, 3415, 3467 cm^{-1}; Anal. Calcd for $C_{19}H_{18}N_2O_2Cl_2$ (377.2644): C, 60.49; H, 4.81; N, 7.43; found: C, 60.53; H, 4.86; N, 7.38. HRMS (ESI) calcd for $C_{19}H_{18}N_2O_2Cl_2$ ($M + H^+$) 377.0745, found 377.0751.

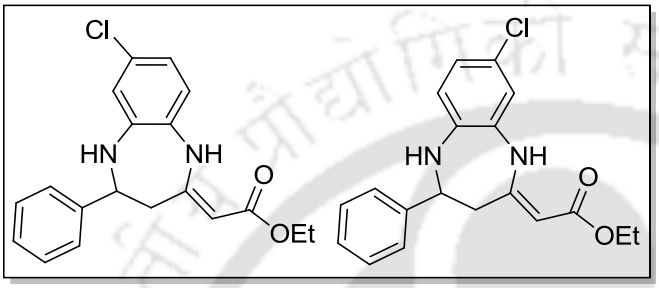
(Z)-ethyl-2-(7-methyl-4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate & (Z)-ethyl-2-(8-methyl-4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4] diazepin-2(3H)-ylidene)acetate (4s + 4t):



Yellow Gummy liquid (0.219 g, 72%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.17 (t, *J* = 7.2 Hz, 3H) , 2.16 & 2.17 (s, 3H), 2.38-2.45 (m, 1H), 2.52-2.61 (m, 1H), 3.98-4.09 (m, 2H), 4.50 & 4.48 (s, 1H), 4.68-4.72 (m, 1H), 6.47 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8 Hz, 1H), 6.65-6.70 (m, 1H), 6.75 (d, J = 8Hz, 1H), 7.10-7.30 (m, 3H), 10.11 (s, 1H, -NH) ppm;^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.26, 14.71, 20.60, 20.93, 40.41, 40.52, 58.91, 65.17, 65.41, 83.80, 84.32, 121.06, 121.29, 122.33, 122.60, 123.10, 125.75, 126.24, 127.34, 128.04, 128.07, 128.90, 128.95, 130.20, 131.54, 134.94,

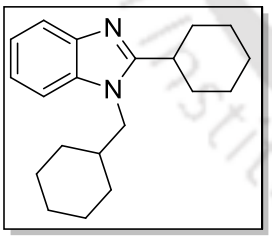
135.55, 137.87, 145.12, 158.87, 159.00, 170.42, 170.48 ppm; IR (KBr): 1155, 1488, 1620, 3445 cm^{-1}; Anal. Calcd for $C_{20}H_{22}N_2O_2$ (322.4009): C, 74.51; H, 6.88; N, 8.69; found: C, 74.54; H, 6.92; N, 8.74.

(Z)-ethyl-2-(7-chloro-4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4]diazepin-2(3H)-ylidene) acetate & (Z)-ethyl-2-(8-chloro-4-phenyl-4,5-dihydro-1H-benzo[*b*][1,4] diazepin-2(3H)-ylidene) acetate (4u + 4v):



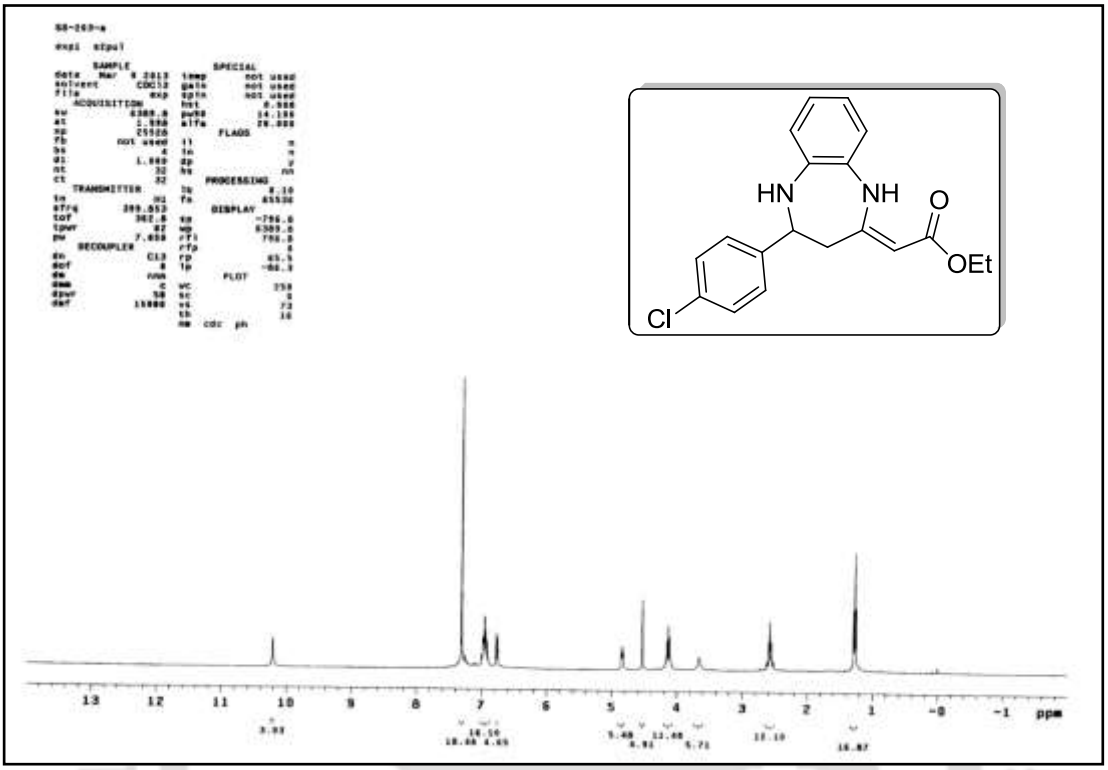
Yellow Gummy liquid (0.144 g, 42%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19-1.38 (m, 3H), 2.38-2.49 (m, 1H), 2.63-2.77 (m, 1H), 4.09-4.21 (m, 2H), 4.63 & 4.61 (s, 1H), 4.79-4.85 (m, 1H), 6.68 (d, *J*=8.4 Hz, 1H), 6.74-6.78 (m, 1H), 6.83-6.91 (m, 1H), 7.27-7.42 (m, 3H), 10.22 (s, 1H, -NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.71, 40.32, 40.44, 59.19, 64.89, 65.08, 84.91, 85.53, 120.24, 121.38, 121.87, 122.40, 123.67, 124.86, 126.22, 128.32, 128.38, 129.09, 129.15, 129.75, 139.08, 144.59, 158.37, 170.53 ppm; IR (KBr): 1159, 1620, 2984, 3418 cm^{-1}; Anal. Calcd for $C_{19}H_{19}ClN_2O_2$ (342.8194): C, 66.57; H, 5.59; N, 8.17; found: C, 66.64; H, 5.62; N, 8.11.

2-Cyclohexyl-1-(cyclohexylmethyl)-1H-benzo[*d*]imidazole (4'):

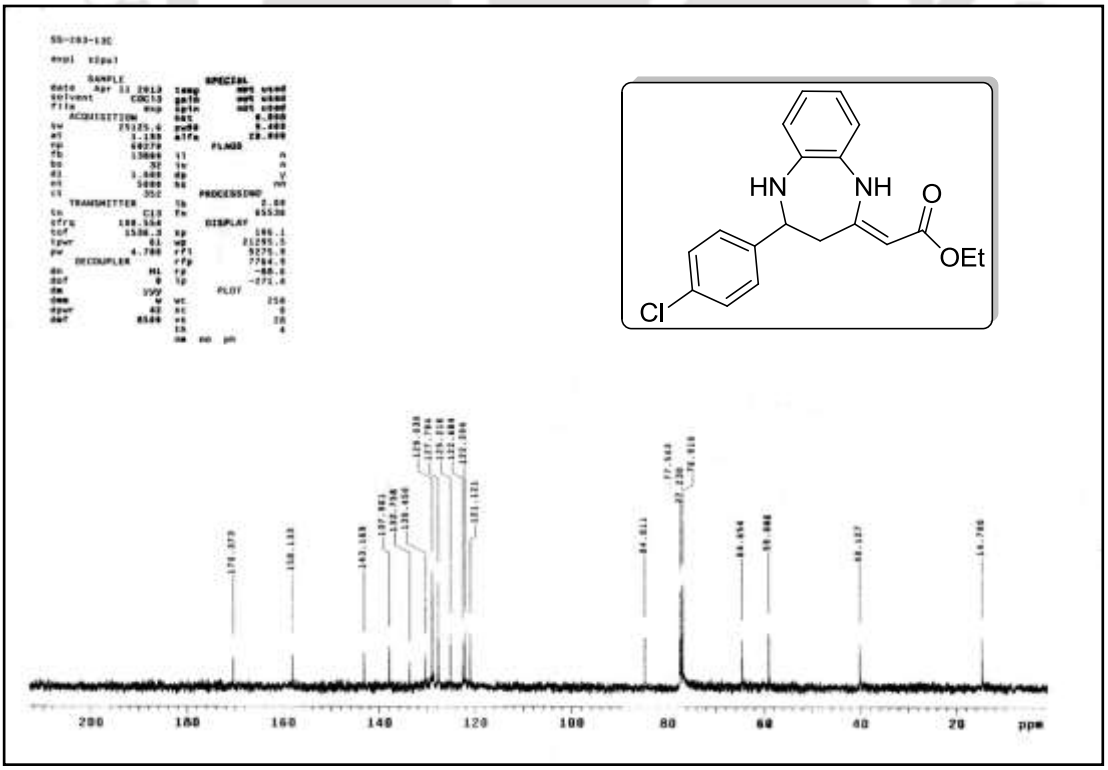


Yellow solid (0.088 g, 30%); Mp 85–88 ^oC :^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.92-1.06 (m, 2H), 1.08-1.19 (m, 3H), 1.22-1.29 (m, 1H), 1.39-1.46 (m, 3H), 1.52-1.66 (m, 3H), 1.67-1.73 (m, 3H), 1.71-1.98 (m, 7H), 3.88 (d, J=7.2 Hz, 2H), 7.13-7.19 (m, 2H), 7.22-7.27 (m, 1H), 7.68-7.75 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.75, 26.18, 26.45, 31.05, 32.15, 36.37, 38.67, 49.71, 109.74, 119.15, 121.52, 121.67, 135.14, 142.67, 159.39 ppm; IR (KBr): 742, 1454, 2848, 2926 cm^{-1}; Anal. Calcd for $C_{20}H_{28}N_2$ (296.4497): C, 81.03; H, 9.52; N, 9.45; found: C, 81.07; H, 9.59; N, 9.41. HRMS (ESI) calcd for $C_{20}H_{28}N_2$ ($M + H^+$) 297.2325, found 297.2328.

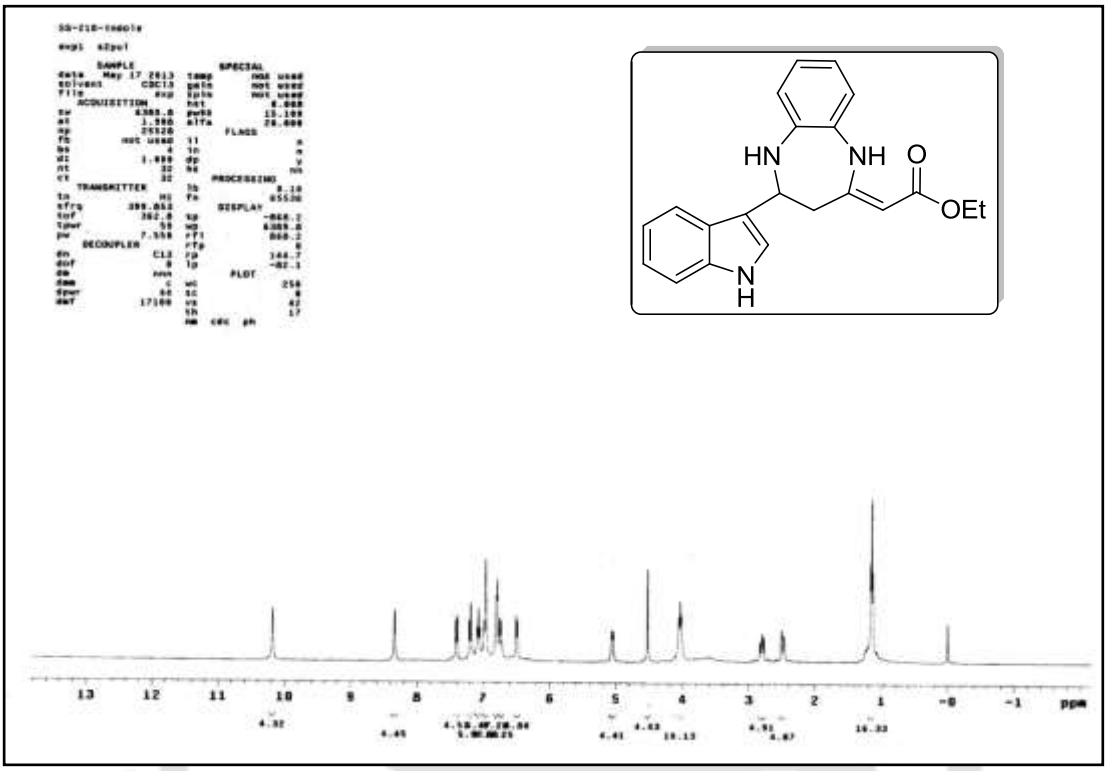
^{1}H NMR Spectra of Compound **4e**



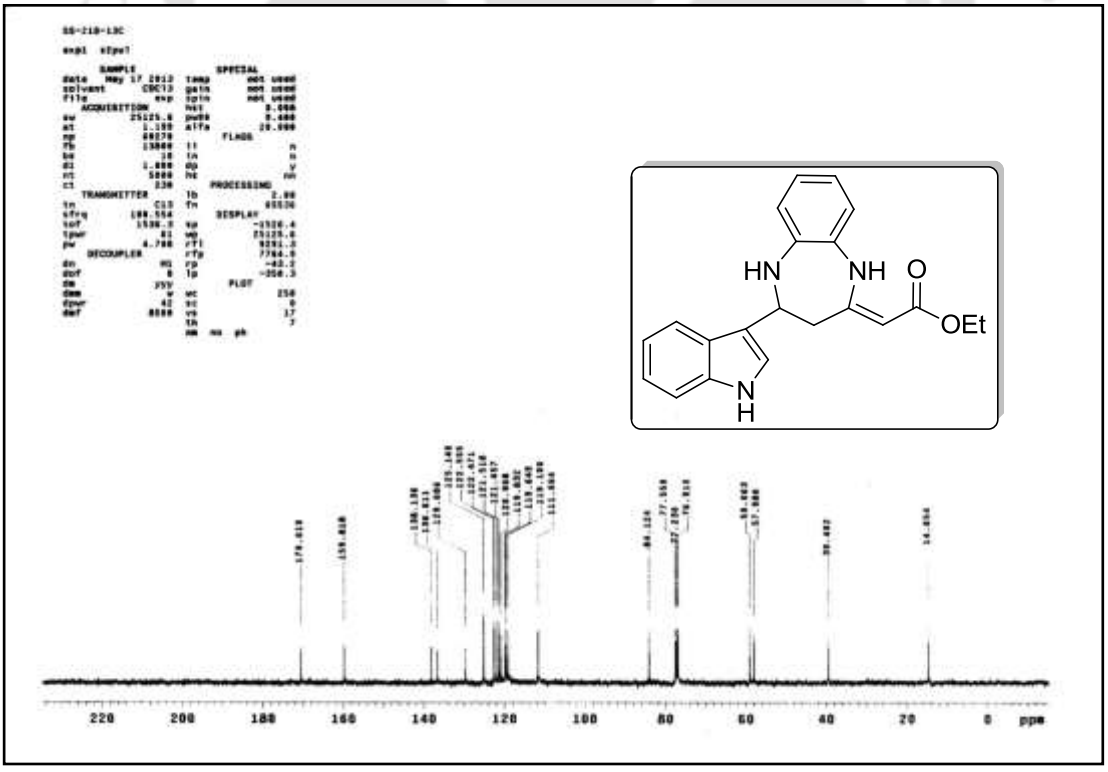
^{13}C NMR Spectra of Compound **4e**



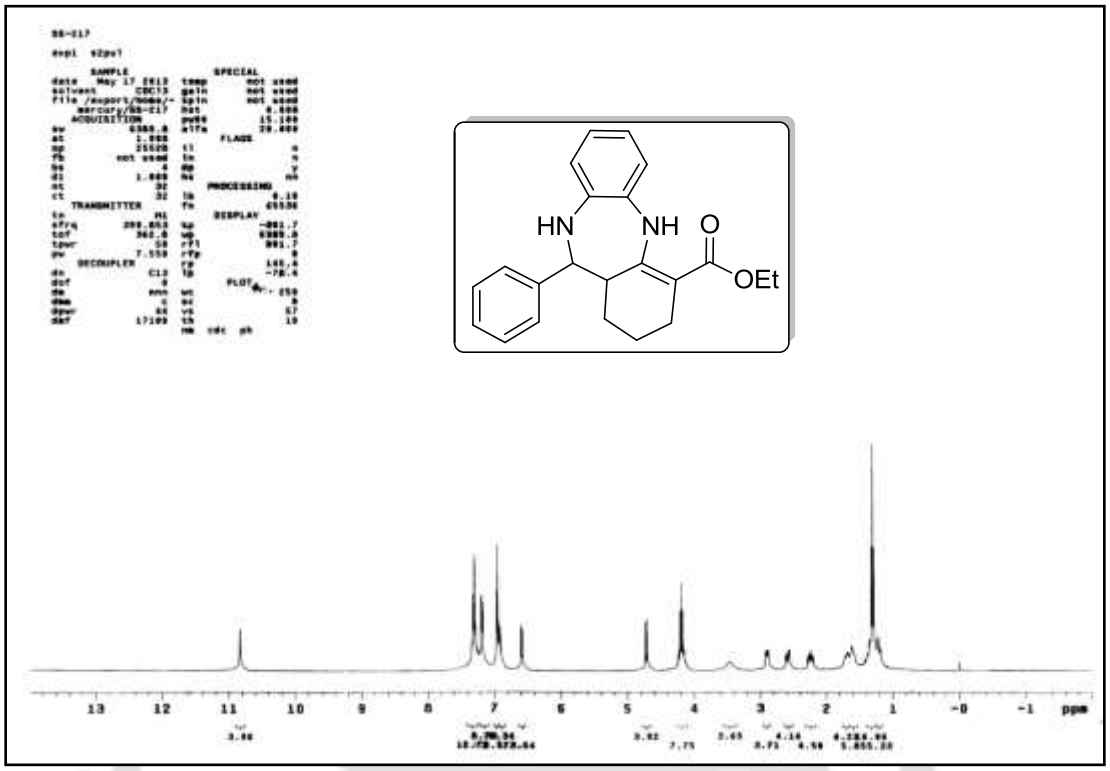
^{1}H NMR Spectra of Compound **4m**



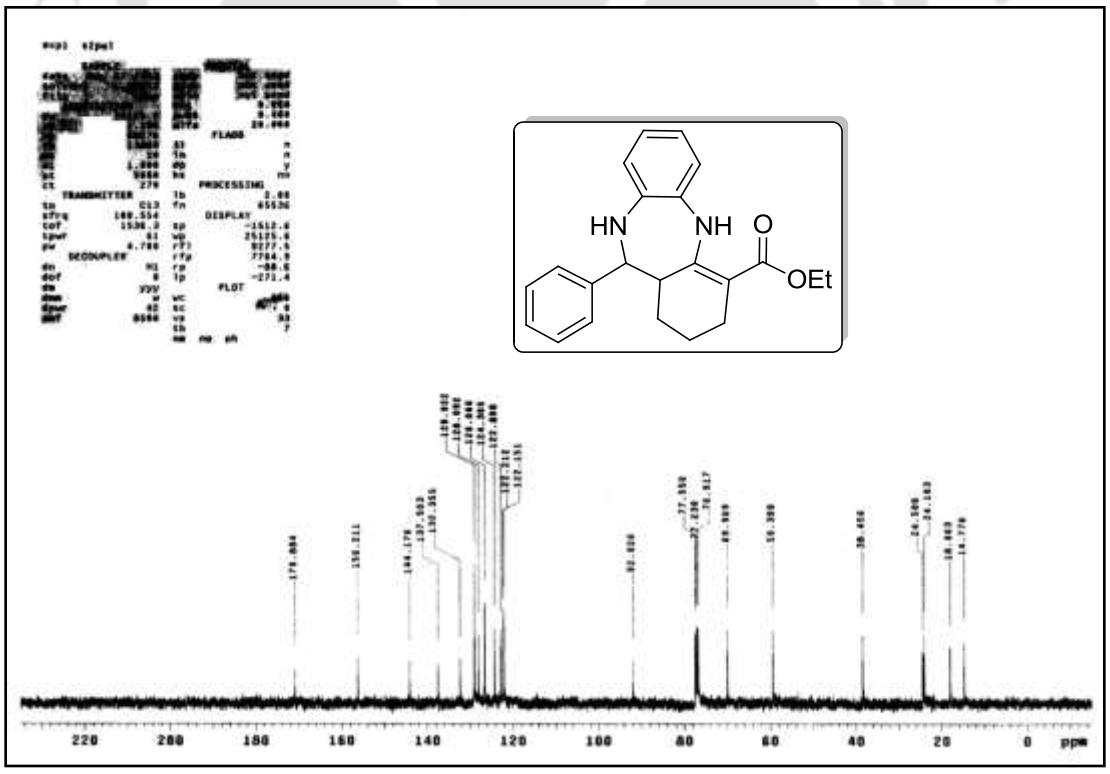
^{13}C NMR Spectra of Compound **4m**



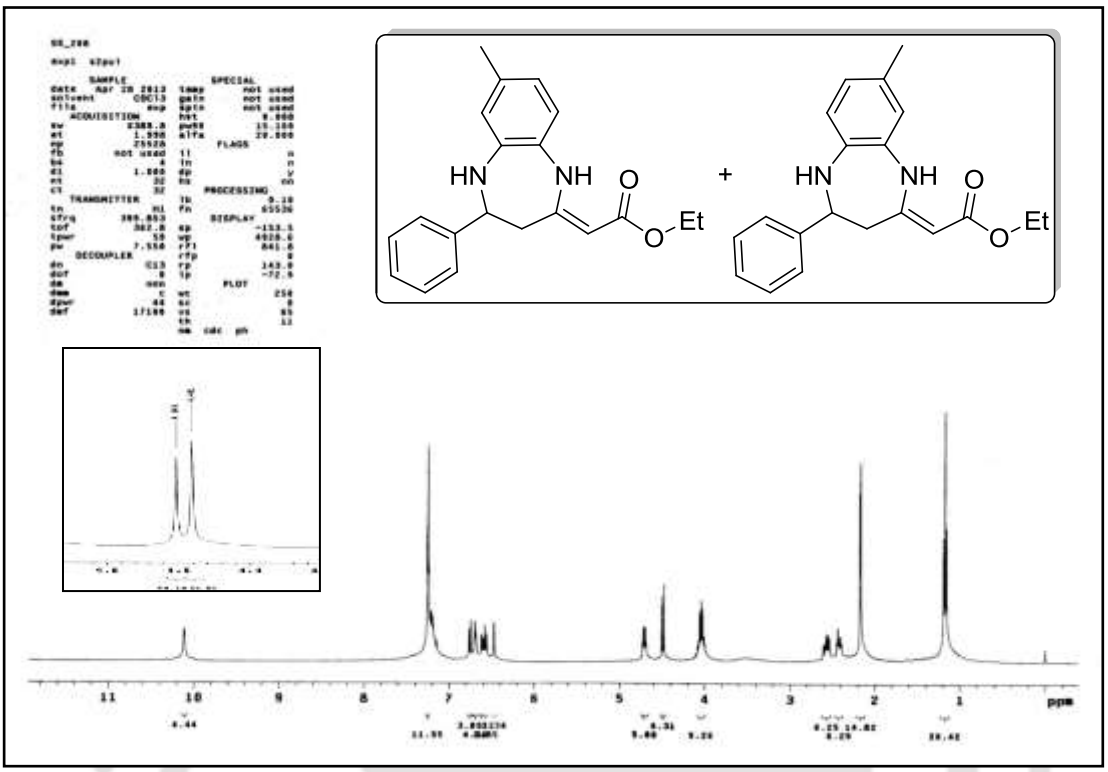
^{1}H NMR Spectra of Compound **4q**



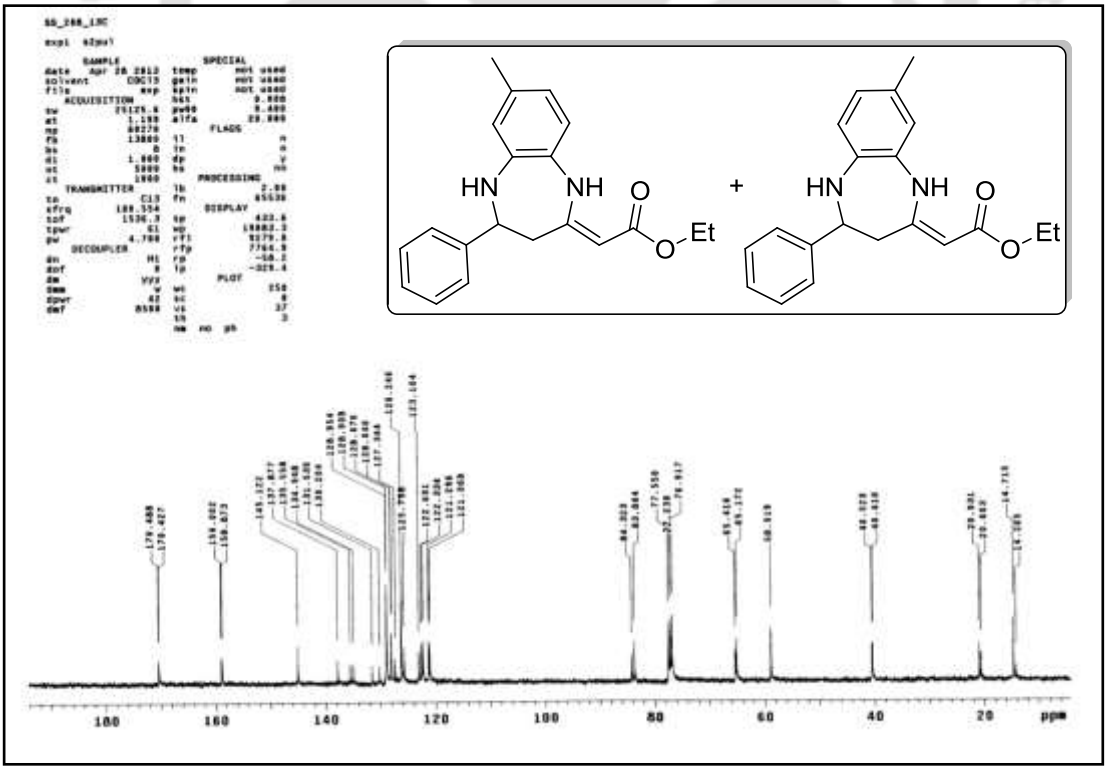
^{13}C NMR Spectra of Compound **4q**



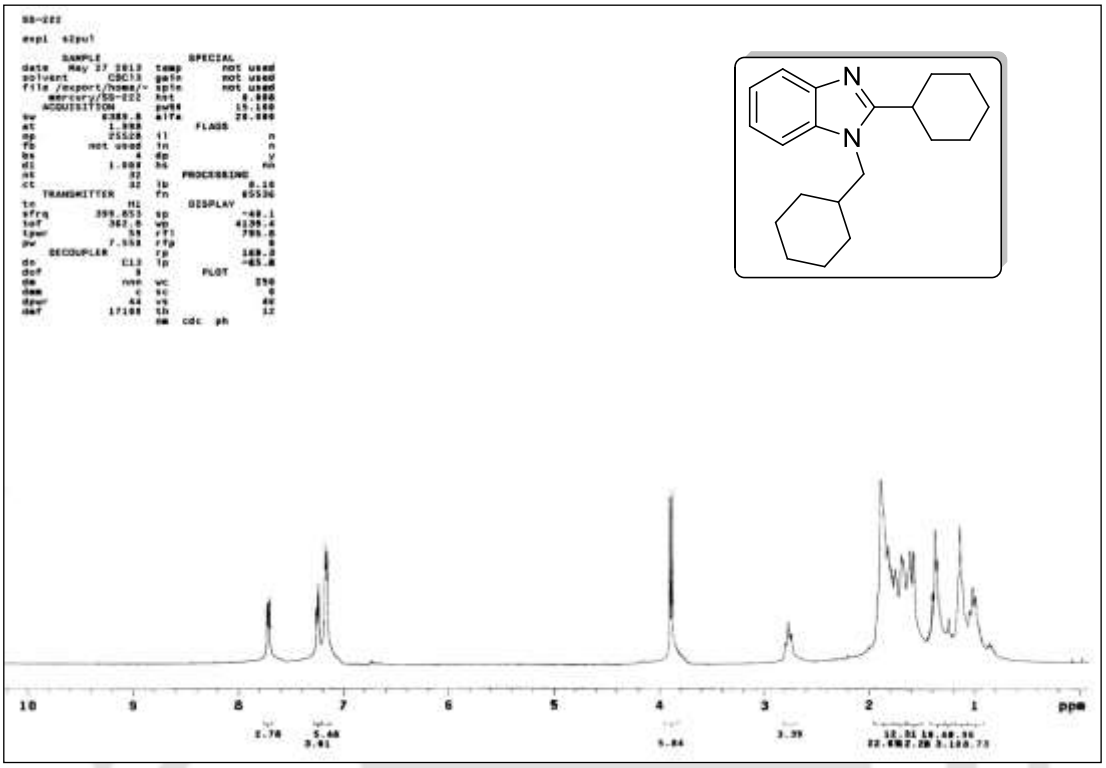
^{1}H NMR Spectra of Compound **4s + 4t**



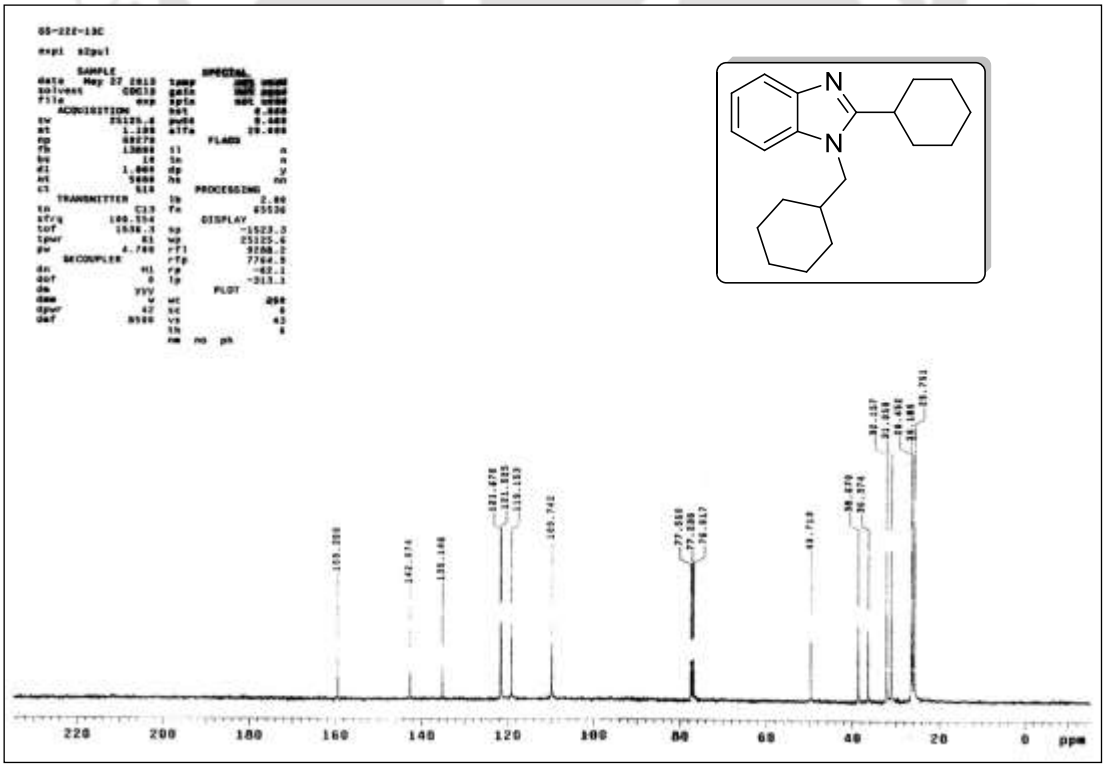
^{13}C NMR Spectra of Compound **4s + 4t**



^{1}H NMR Spectra of Compound **4′**

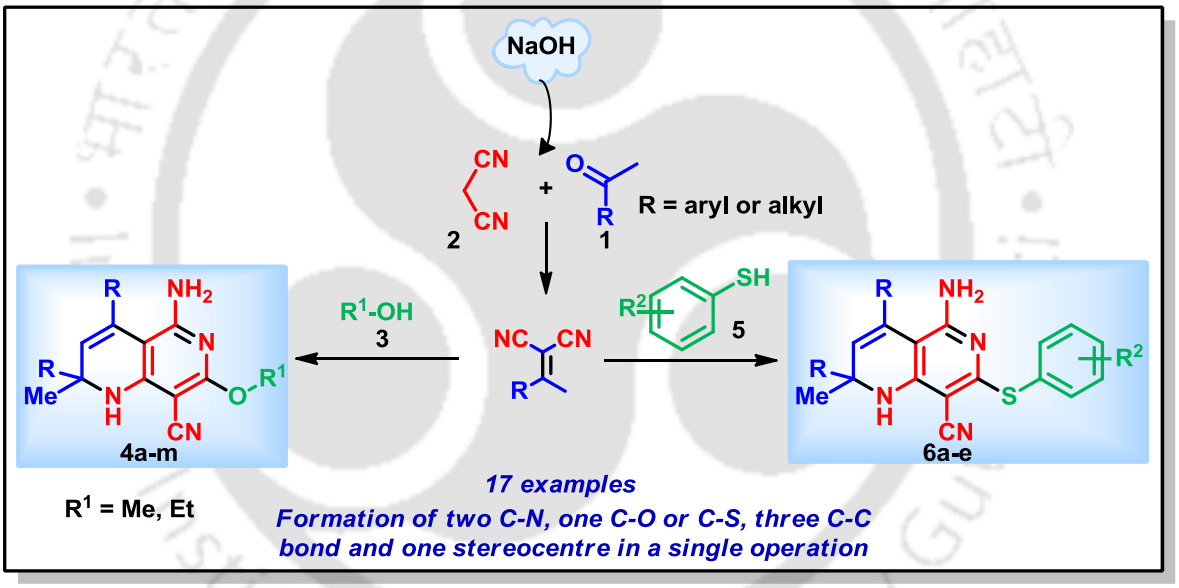


^{13}C NMR Spectra of Compound **4′**



Chapter III

Sodium Hydroxide Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines through One-pot Pseudo Five-component Reaction



Chapter III

Experimental Section

Sodium Hydroxide Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines through One-pot Pseudo Five-component Reaction

CHAPTER III

III. Sodium Hydroxide Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines Through One-pot Pseudo Five-component Reaction

III.1. Introduction

Functionalized [1,6]-naphthyridines and their benzo/hetero fused analogues have attracted much attention from synthetic and medicinal viewpoints.[1] Historically, the word "naphthyridin(e)" was coined by Arnold Reissert in 1893.[2] The 1,6-naphthyridine derivatives are made of two fused pyridine rings through two adjacent carbon atoms with each ring containing only one nitrogen atom. These naphthyridine skeletons are widely distributed in nature and are considered as ''privileged structures'' in drug discovery. The naphthyridines exhibit a wide range of pharmacological activities such as antitumor,[3a] antimicrobial,[3b] allosteric[3c] and antiproliferative activities.[3d] In addition, functionalized 1,6-naphthyridines are well known inhibitors of human cytomegalovirus,[4a] HIV-1 integrase[4b] and selective antagonists of 5-HT4 receptors.[4c] Some of them have been shown below in Figure 1. Moreover compounds incorporating this motif are useful in the treatment of hypertension, myocardial infarction, hyperlipidemia, cardiac arrhythmia, and rheumatoid arthritis.[5] Such a novel class of macrocyclic 1,6-naphthyridine exhibit activities of anti-human cytomegalovirus (HCMV) inhibitors.[6] Due to their immense potentiality, various research groups have put forward considerable efforts to synthesize these compounds in recent times.

The construction of such structurally complex and highly functionalized multi-heterocyclic skeletons is a challenging task in modern organic synthesis. Among various synthetic approaches, multicomponent reactions (MCRs) have emerged as a powerful tool due to the numerous advantages of MCRs. This chapter deals with the synthesis of highly functionalized 1,6-naphthyridines utilizing MCR strategy.

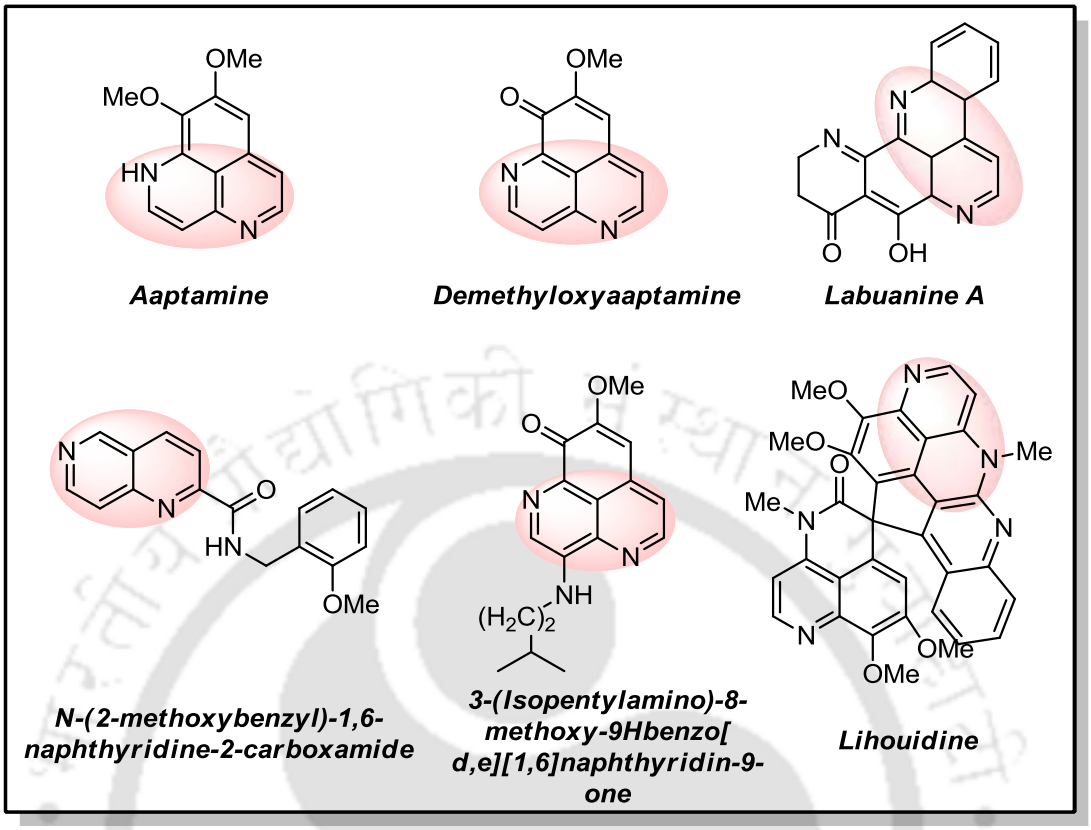
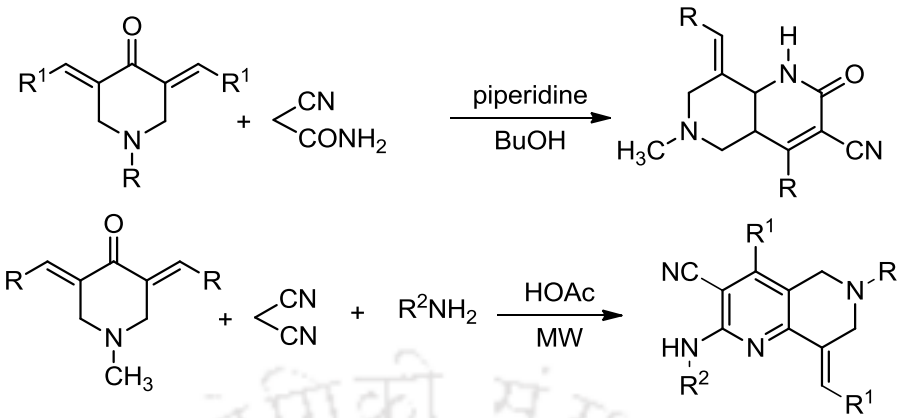


Figure 1. Biologically active naphthyridine moieties

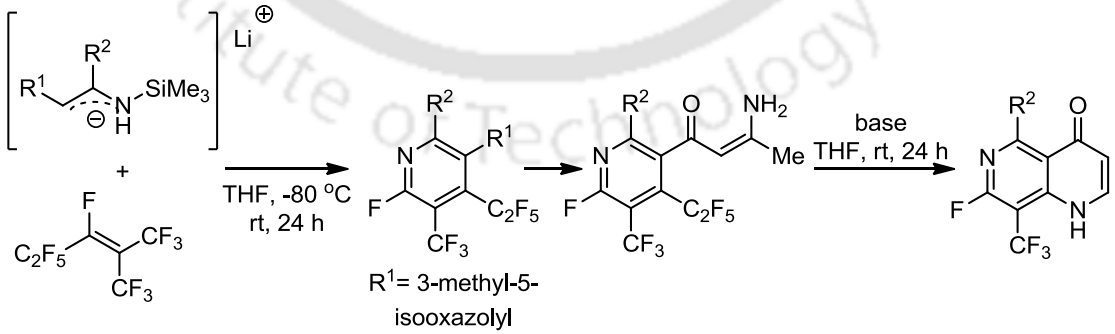
III.2. Strategies for Synthesis of 1,6-Naphthyridines

Over the years, numerous synthetic methods[7] have been developed for the construction of 1,6-naphthyridine derivatives. Heterocyclization of 3,5-diarylidenepiperidin-4-one with cyanoacetamide[8a] or with malononitrile and amines[8b] created a unique approach for the synthesis of naphthyridine skeletons. In 2000, El-Subbagh *et al*. reported the piperidine catalyzed synthesis of 1,6-naphthyridines *via* two component reaction between α,β-unsaturated ketones and cyanoacetamide in BuOH. A decade later this method was further extended by Tu and coworkers by using malononitile instead of cyanoacetamide in presence of amines to give the anticipated naphthyridine skeletons (Scheme 1).



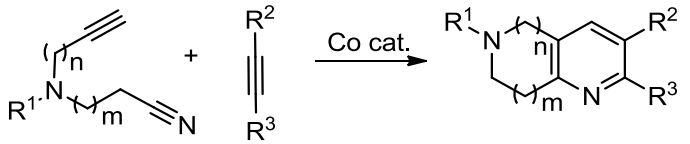
Scheme 1. Synthesis naphthyridine moieties using 3,5-diarylidenepiperidin-4-ones

Base mediated cyclization of a *N*-silyl-1-azaallyl anion with perfluoroalkenes,[9] is an alternative approach for the formation of naphthyridine skeletons. In 2007 Konakahara *et al.* demonstrated a way for the synthesis of naphthyridine adducts *via* a two-step procedure. First the fluorine-containing pentasubstituted pyridine derivatives were synthesized in regioselective manner by the intermolecular cyclization of *N*-silyl-1-azaallylic anion intermediates, generated from functionalized silane and an aromatic/aliphatic nitrile, with perfluoroalkene. It was further extended for the synthesis of naphthyridine skeletons, 7-fluoro-8-(trifluoromethyl)-1H-1,6-napthyridin-4-ones, by the facile reductive ring-opening reaction of the isoxazole ring to form β-aminoenone group which undergoes a consecutive intramolecular cyclization with the perfluoroethyl group on the pyridine ring, providing a practical preparation for the perfluoroalkyl group containing 1,6-naphthyridin-4-one derivatives (Scheme 2).



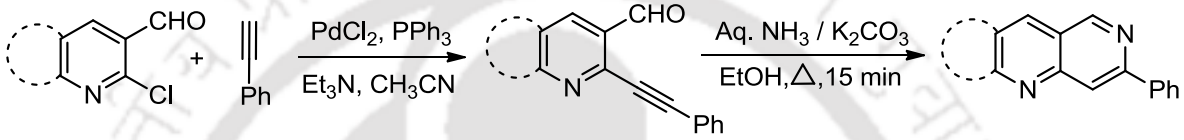
Scheme 2. Base mediated cyclization of *N*-silyl-1-azaallyl anion with perfluoroalkenes

Another approach is the cobalt-catalyzed intramolecular/intermolecular [2+2+2] cyclizations of dialkynylnitriles[10] with microwave promotion (Scheme 3).



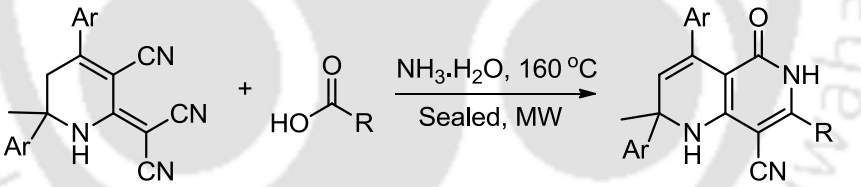
Scheme 3. Intramolecular/intermolecular [2+2+2] cyclization to form naphthyridine

The synthesis of naphthyridine moieties was further reported *via* a copper-free Sonogashira coupling of 2-chloroquinolines with phenyl acetylene followed by one pot facile annulation of resultant 2-alkynylquinoline-3-carboxaldehydes to generate 3-phenylbenzo[*b*][1,6]naphthyridines in aqueous ammonia (Scheme 4).[11]



Scheme 4. Synthesis of naphthyridines *via* Sonogashira coupling followed by annulation

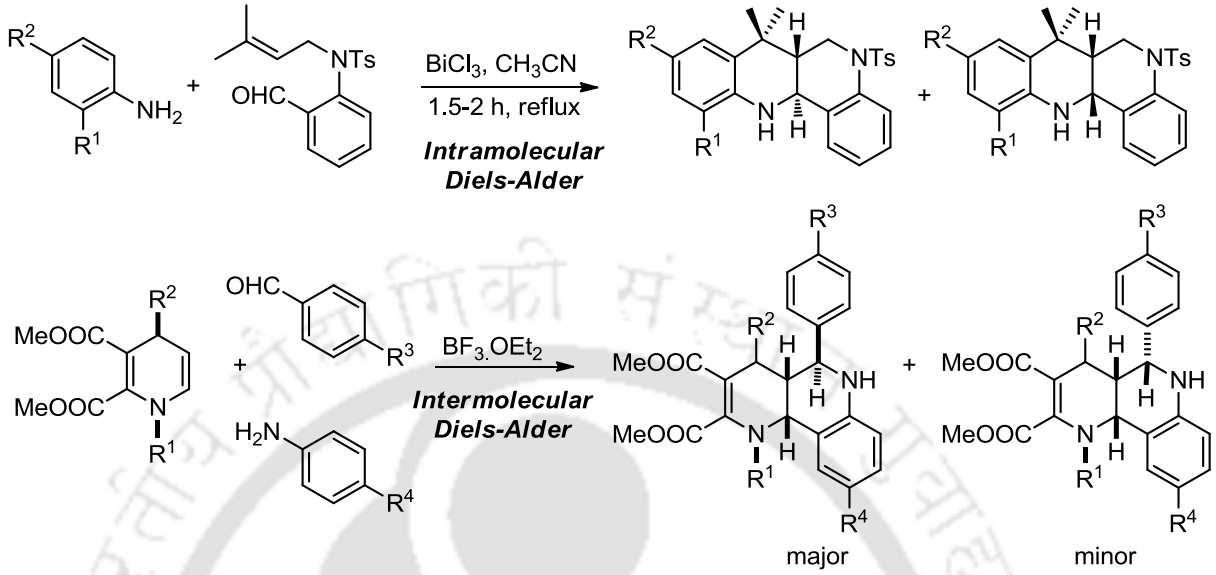
A [5+1] rearrangement-annulation of 2-dicyanomethylenepyridine-3-carbonitrile with aliphatic carboxylic acids[12] also dictates a path for the regioselective formation of polyfunctionalized [1,6]naphthyridines (Scheme 5).



Scheme 5. Highly substituted naphthyridines *via* [5+1] rearrangement-annulation

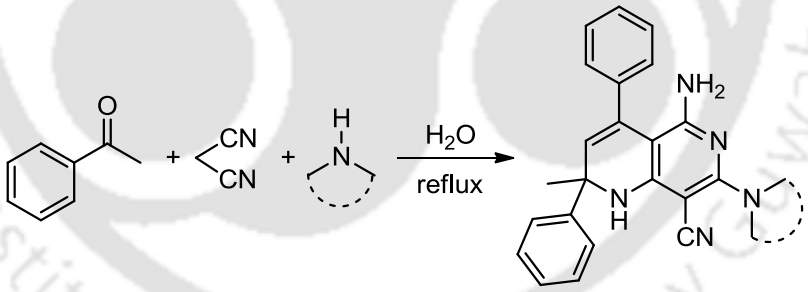
The hydrolysis of dicyanomethylene substituted alkyl-dihydropyridines[13] can also be mentioned as one of the significant method for the synthesis of naphthyridine derivatives. However both intramolecular[14a] as well as intermolecular[14b] [4+2] aza-Diels-Alder reaction have also been explored for the synthesis of fused naphthyridine derivatives. In this context Scheme 6 shows the efficiency of $BiCl_3$ as catalyt for the intramolecular hetero-Diels–Alder reactions of aldimines generated *in situ* from aromatic amines and the *N*-allyl derivative of *o*-aminobenzaldehyde under reflux conditions in acetonitrile to afford a novel class of hexahydro dibenzo[1,6]naphthyridine derivatives. In case of intermolecular reaction, the synthesis of fused-naphthyridine derivatives was accomplished by involving

imino-Diels–Alder reaction using 1,4-dihydropyridines, aromatic aldehydes and aromatic amines.



Scheme 6. Formation of naphthyridines *via* inter or intramolecular Diels-Alder reaction

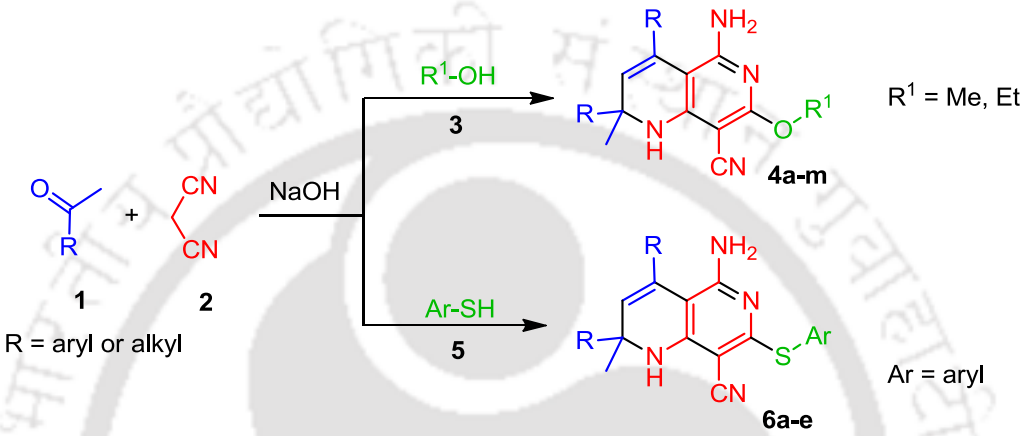
Recently Mukhopadhyay *et al.*[15] reported serendipitous synthesis of highly functionalized 1,2-dihydro-1,6-naphthyridines from methyl ketones, malononitrile and amines through one-pot multicomponent reaction involving ylidene derivative.



Scheme 7. Construction of highly functionalized naphthyridines with secondary amines

Some of these methods are associated with certain drawbacks such as requirement of multistep sequences,[5d,9] use of expensive catalyst[10,11] and sealed tube reaction conditions.[12] Though all these methods are quite useful, still there is a further scope to synthesize highly substituted 1,6-naphthyridine derivatives using inexpensive catalyst. Over the years, a large number of papers have been published for the synthesis of various heterocycles using the Knoevenagel product obtained from aldehydes with malononitrile.[16] However, reports on analogous procedures using ketones are relatively less explored probably due to lower

reactivity of these compounds. Ylidene compounds resulting from the condensation of ketone with malononitrile in presence of a base have been found to be a key intermediate for the construction of important heterocyclic frameworks.[17] Herein, we report a pseudo five-component reaction for the efficient synthesis of highly functionalized 1,6-naphthyridine derivatives using either a combination of aryl methyl ketones/alkyl methyl ketones, malononitrile and alcohols or thiols in presence of sodium hydroxide as shown in Scheme 8.



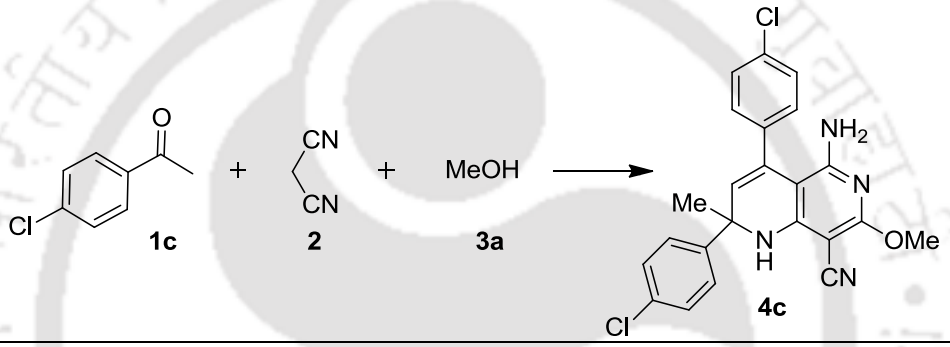
Scheme 8. Base mediated multicomponent reactions for the synthesis of highly functionalized [1,6]-naphthyridine derivatives

III.3. Present Work

In an initial endeavor, a trial reaction was executed with 4'-chloroacetophenone **1c** (1 mmol) and malononitrile **2** (1 mmol) in methanol as solvent in the presence of NaOH (1.0 equiv.) under reflux conditions. The reaction mixture was refluxed for 7 hours and gradual progress of the reaction was monitored by TLC. After usual work up followed by chromatographic purification, a white solid product was isolated in 31% yield, which was characterized as 5-amino-2,4-bis(4-chlorophenyl)-1,2-dihydro-7-methoxy-2-methyl-1,6-naphthyridine-8-carbo nitrile (**4c**) instead of expected Knoevenagel product **A** as shown in mechanism in Scheme 10. The product **4c** was characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and by elemental analysis. In IR spectrum, it showed characteristic absorptions at 3345, 3399 and 3494 cm^{-1} due to the NH and -NH_2 group and a strong absorption at 2204 cm^{-1} for -CN group. Similarly, in the ^{1}H NMR spectrum of **4c** exhibited two broad singlets at δ 5.28 and 4.23 due to NH and NH_2 proton, a singlet at δ 5.44 due to =CH proton at dihydropyridine

ring and two singlets at δ 3.88 and 1.74 for OMe and Me group in the naphthyridine skeleton. However the expected characteristic stretching frequency of -CN group in the Knoevenagel product **A** generally exhibits at 2225 cm^{-1} and in ^1H NMR signals at δ 2.62 and 7.51 as singlets for methyl proton and aromatic protons respectively. From this observation, it was clear that two equivalents of 4'-chloroacetophenone and malononitrile are required for obtaining the product **4c**. The OMe group has incorporated in the final product **4c** from MeOH, which acts as reactant-cum-solvent. The structure of product **4c** was also confirmed by X-ray crystal structure as shown in Figure 2.

Table 1. Optimization of the reaction condition for the synthesis of 1,6-naphthyridine



Entry	Base	Amount (equiv.)	Solvent	Time (h)	Yield[b](%)
1	NaOH	1.0	MeOH	7	62
2	**NaOH**	**1.5**	**MeOH**	**7**	**71**
3	NaOH	2.0	MeOH	7	70
4	KOH	1.5	MeOH	12	60
5	K_2CO_3	1.5	MeOH	12	52
6	$NaHCO_3$	1.5	MeOH	24	22
7	--	--	MeOH	24	N.R.[c]
8	Et_3N	1.5.	MeOH	12	42
9	PPh_3	1.5	MeOH	12	54
10	DMA	1.5	MeOH	12	trace
11	NaOH	1.5	THF[a]	24	N.R.[c]
12	NaOH	1.5	DMF[a]	24	29
13	NaOH	1.5	MeCN[a]	12	21
14	NaOH	1.5	H_2O[a]	12	N.R.[c]

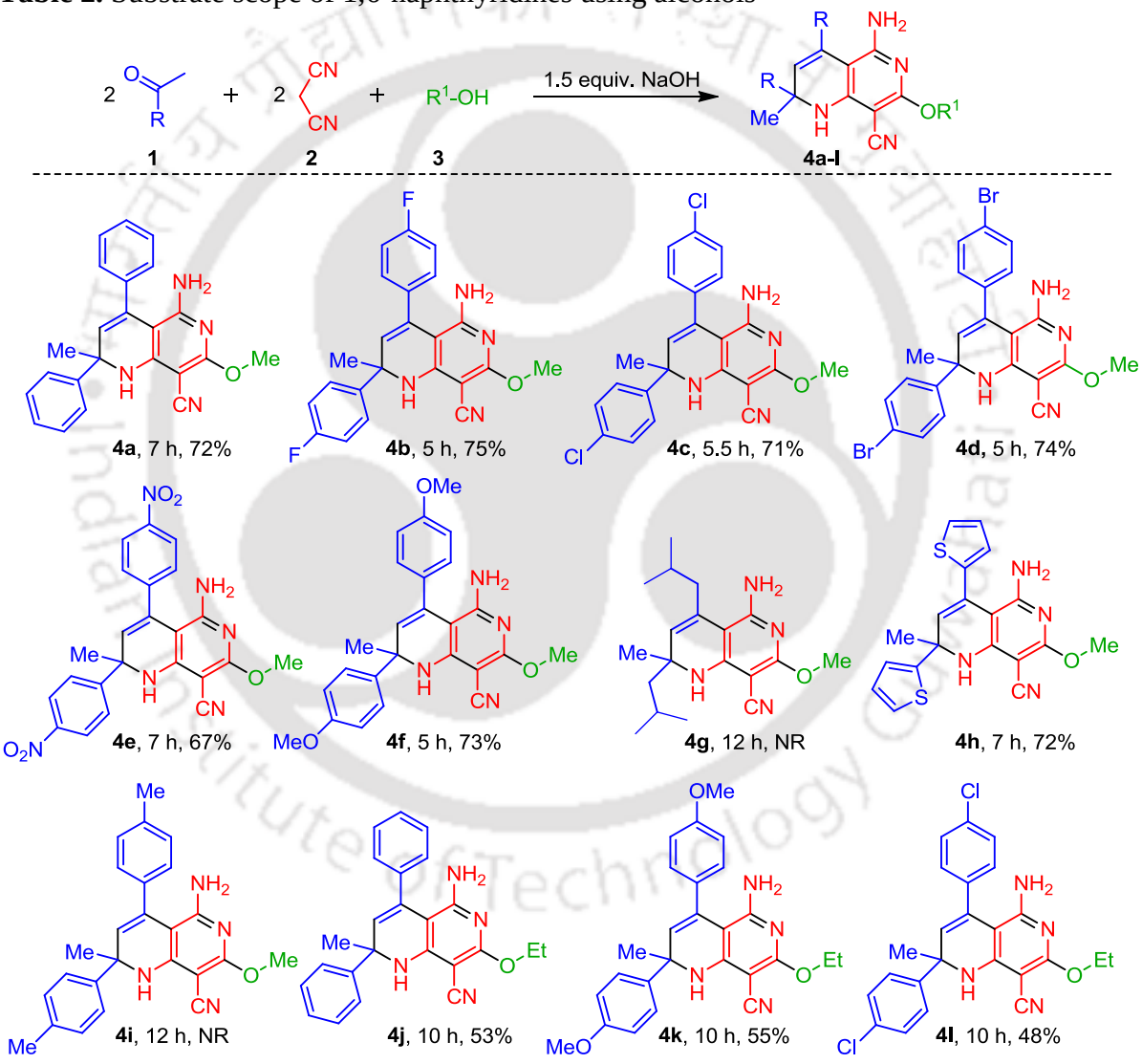
[a]For entries (11-14), MeOH was used 1 equivalent. [b]Isolated yields. [c]NR = no reaction.

Therefore, various reactions using two equivalents of 4'-chloroacetophenone and malononitrile in methanol (3 mL) have been examined with different amount of NaOH. It was noted that increasing the amount of NaOH from 1.0 equiv. to 1.5 equiv. effectively increased the yield from 62 to 71% (Table 1, entries 1-2), yet there was no improvement of yield when the amount of NaOH was further increased to 2.0 equiv. (Table 1, entry 3). To find out efficiency of other bases as well as reaction medium, the same reaction was screened in presence of 1.5 equiv. of KOH, K_2CO_3, and $NaHCO_3$ (Table 1, entries 4–6), respectively. It was also observed that no desired product was obtained in absence of base even after 24 h of refluxing (Table 1, entry 7). Finally, the similar reactions were also verified in presence of other organic bases like Et_3N, PPh_3 or *N*,*N*-dimethylaniline (DMA) (Table 1, entries 8-10). To verify the suitability of other solvent, similar reaction was executed using 4'-chloroacetophenone (2 equiv.) **1c**, malononitrile **2** (2 equiv.) and methanol **3a** (1 equiv.) in THF, DMF, CH_3CN or water, respectively, in presence of 1.5 equiv. of NaOH under reflux conditions. Unfortunately, the yield of the product did not improve significantly (Table 1, entries 11-14).

With the optimized conditions, the scope and general applicability of the present methodology was examined by carrying out the synthesis of substituted 1,6-naphthyridines using different acetophenonone derivatives tethered with either electron-withdrawing or electron-donating groups on the ring (Table 2). It was found that acetophenone derivatives with neutral or electron-withdrawing groups or electron-donating functionality produced 1,6-naphthyridine derivatives **4a-f** in moderate to good yields. The acetophenones with moderately electron withdrawing substituent (F, Cl, Br) procured reasonably better yield (**4b-d)** than naphthyridine moiety (**4e)**, bearing strongly electron withdrawing nitro substituent. Acetophenone frameworks with electron donating substituent such as –OMe gave upto 73% yield (**4f**). Similarly, alkyl methyl ketones such as isobutyl methyl ketone also underwent this reaction smoothly to provide the corresponding 1,6-naphthyridine derivative **4g** in 55% yield. Likewise, heteroaryl methyl ketone such 2-acetyl thiophene, also provided the desired product **4h** in good yield. Unfortunately, no desired product was obtained when the similar reaction was performed with acetophenone derivative containing methyl group on the aromatic ring under identical reaction conditions **4i**. To expand the scope of the above cyclization, a series of reactions were performed with different

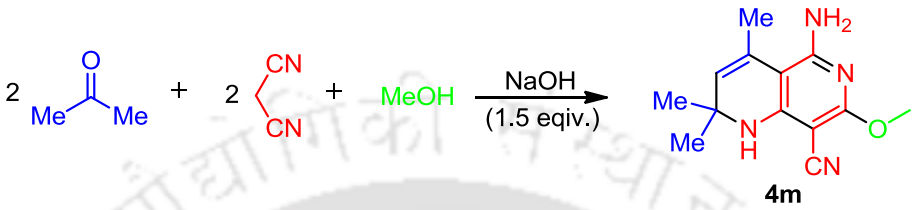
acetophenones, malononitrile in ethanol and the corresponding substituted 1,6-naphthyridine derivatives **4j-l** were obtained in moderate to good yields (Table 2). After obtaining the successful results, we wanted to incorporate other alkoxy group in 1,6-naphthyridine ring using *n*-propanol, *n*-butanol, *t*-butanol and *iso*-propanol. However, we did not obtain the desired products, which may be due to lower nucleophilicity of these alcohols as compared to methanol and ethanol.

Table 2. Substrate scope of 1,6-naphthyridines using alcohols[a,b]



[a]All the reactions were performed with acetophenones (2.0 mmol), malononitrile (2.0 mmol) and alcohols (3 mL).[b]Isolated yields.

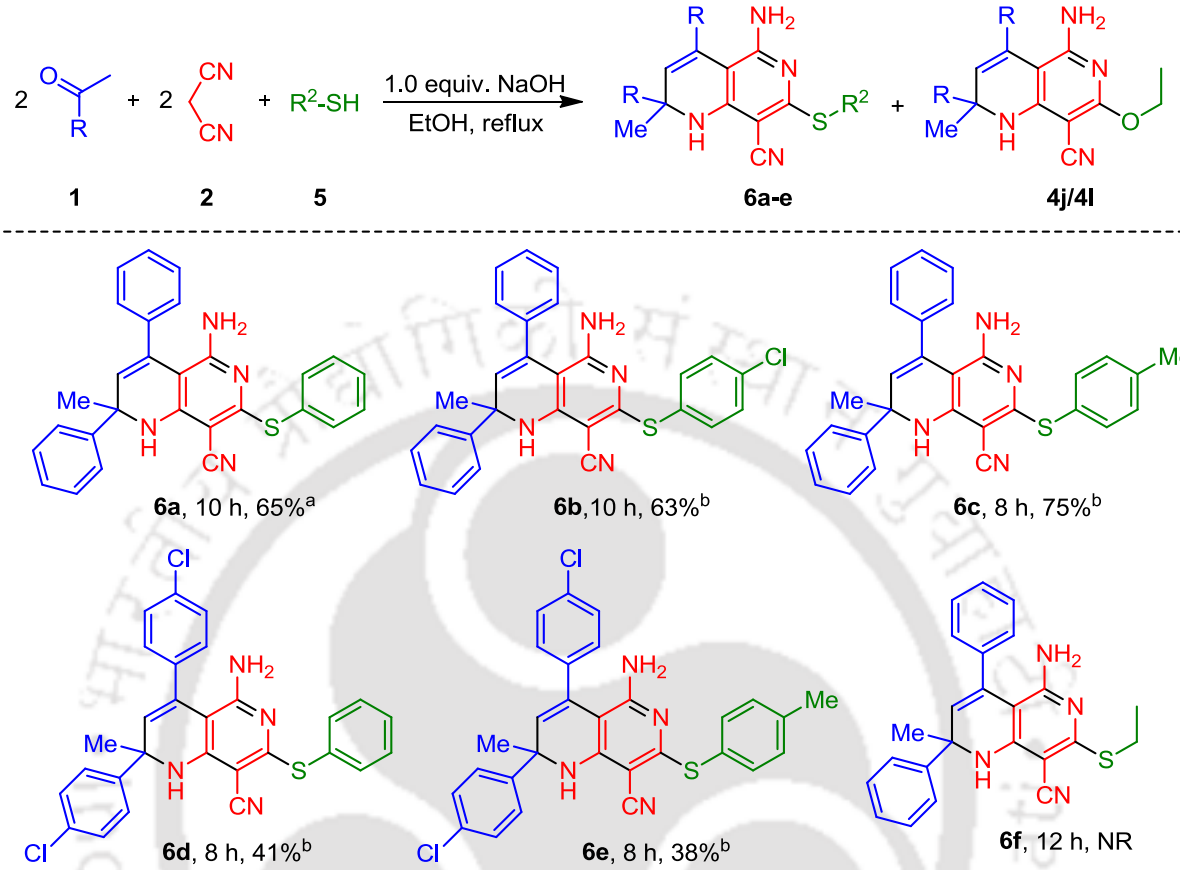
Similar reaction was also carried out with 2-propanone, malononitrile and methanol under optimized reaction conditions, however the expected 1,6-naphthyridine **4m** (5-amino-7-methoxy-2,2,4-trimethyl-1,2-dihydro-1,6-naphthyridine-8-carbonitrile) was isolated in 34% yield, which was confirmed from IR, ^{1}H NMR and Mass spectra of the compound **4m** as shown in scheme 9.



Scheme 9. Synthesis of 1,6-naphthyridine using 2-propanone

Inspired by the above successful results, the generality of this method was further tested by using *S*-alkyl/aryl group in-place of methoxy/ethoxy group during similar synthesis of 1,6-naphthyridines. With this assumption, the reaction of acetophenone (2 mmol), malononitrile (2 mmol) and 4-chlorothiophenol (1 equiv.) in 3 mL of methanol was carried out in presence of 1.5 equivalent of NaOH under reflux conditions. The desired product 5-amino-7-((4-chlorophenyl)thio)-2-methyl-2,4-diphenyl-1,2-dihydro-1,6-naphthyridine-8-carbonitrile **6b** was isolated along with 1,6-naphthyridine **4a** in the ratio (7:3). To get 1,6-naphthyridine **6b** as the exclusive product, several reactions were performed, which showed that 1 eqivalent of NaOH in ethanol gave the product **6b** and **4j** in (9:1) ratio (Table 3). Similarly other aromatic thiols such as thiophenol, 4-methylthiophenol provided the corresponding substituted 1,6-naphthyridine **6a-e** (Table 3) in moderate yields under the similar reaction conditions. In the case of aliphatic thiols such as ethane thiol and 1-propane thiol, reactions were not successful and 1,6-naphthyridine **4j** derived from ethanol (as solvent) was isolated as the major product. It is worth-while to mention that the formation of diaryl disulfide was not observed arising from oxidation of thiophenol using NaOH under experimental conditions. To eliminate the formation of compound **4**, a mixture of acetophenone, malononitrile and 4-chloro-thiophenol was refluxed in presence of 1 equiv. NaOH under solvent-free conditions. Only the Knoevenagel product was isolated instead of the desired naphthyridine product **6b**. Alternatively, the same reaction was carried out using the above combination in presence of *n*-propanol, but we did not get the desired product.

Table 3. Substrate scope for the synthesis of 1,6-naphthyridines using thiols



[a]Solely isolated product. [b]The product was obtained in (9:1) ratio which was determined from ^{1}H NMR spectra of the crude reaction mixture.

The structure of the 1,6-naphthyridine compounds were unambiguously confirmed by the X-ray crystal structure analysis of **4c** and **6b**, which is shown in Figure 2

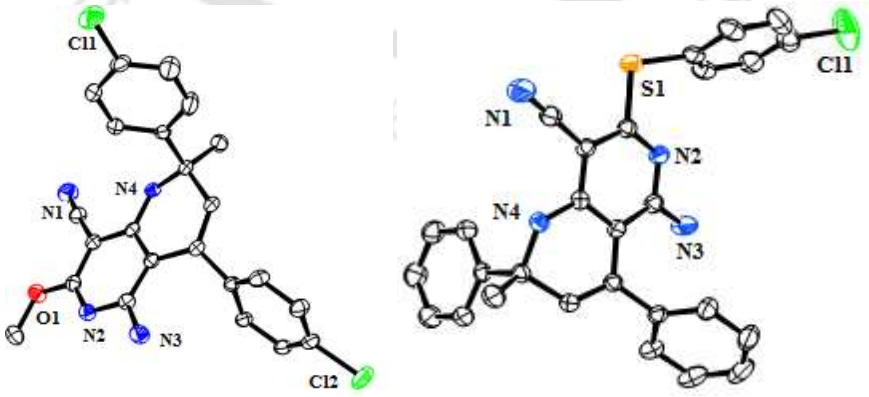
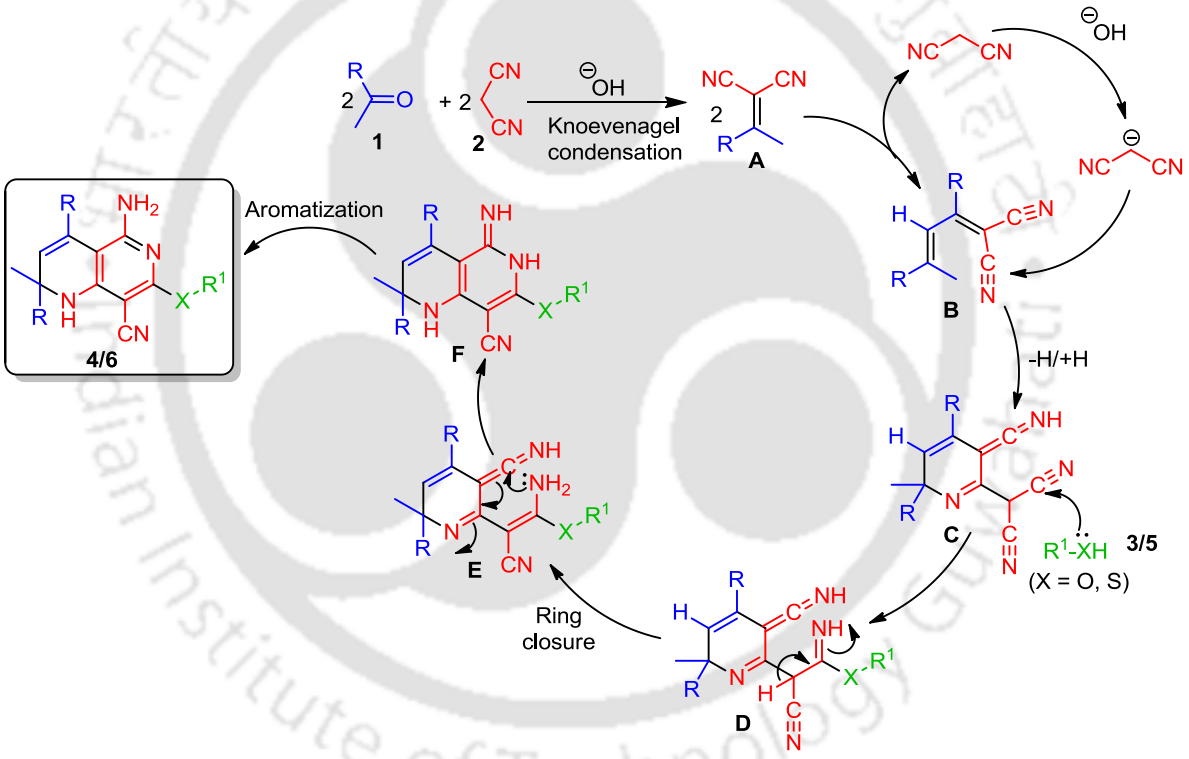


Figure 2. Ortep view of **4c** (CCDC 931090) and **6b** (CCDC 913524)

On the basis of the reported literature,[15] a plausible mechanism for the formation of substituted naphthyridines **4** and **6** is depicted in Scheme 10. In the presence of NaOH, condensation between methyl ketone **1** and malononitrile **2** gives a Knoevenagel product **A**. Subsequent self Michael addition of ylidene **A** followed by elimination of one molecule of malononitrile **2,** leads to the fomation of intermediate **B**, which further reacted with one molecule of malononitrile on cyano group leads to the formation of intermediate **C**. The attack of alcohol or thiols to intermediate **C**, forms intermediate **D**, which undergoes intramolecular cyclization *via* attack of amino group on CN functionality in intermediate **E** forms intermediate **F** which undergoes aromatization *via* an oxidation process gives rise to substituted 1,6-naphthyridine of type **4** and **6**.



Scheme 10. Mechanism for the formation of substituted 1,6-naphthyridine derivatives

It was earlier reported[18a-b] that naphthyridine derivatives can be used as luminescence materials in molecular recognition. Being interested, the photophysical property of the naphthyridine products **4a**, **4e** and **4f** were investigated. The UV–visible spectra of all the 1,6-naphthyridine derivatives contain intense absorption maxima around 315 nm (Table 4).

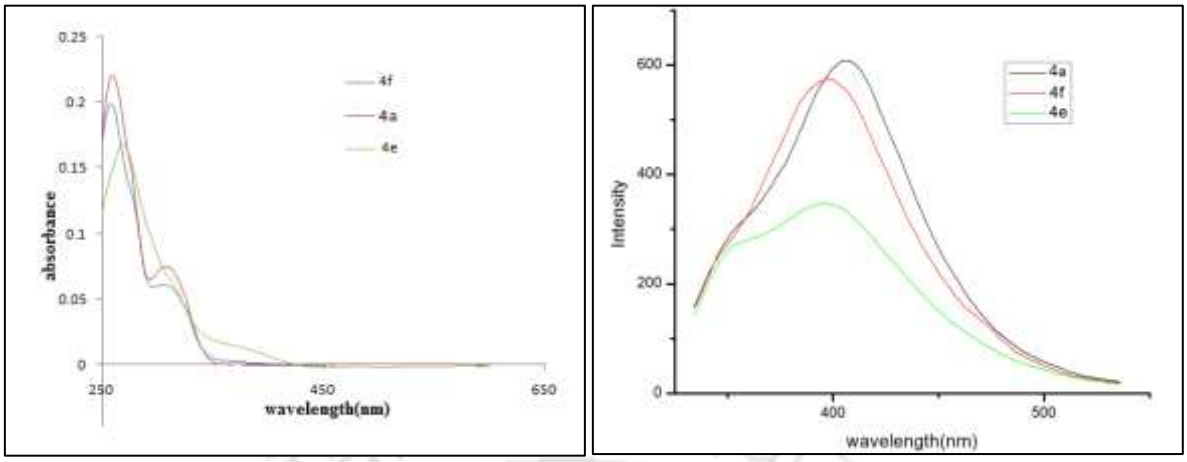


Figure 3. (a) UV-Vis spectra of compound **4a**, **4e** and **4f** in different solvents (0.01 mM, 25ºC). (b) Fluorescence spectra of compound **4a**, **4e** and **4f** in ethanol (0.01 mM, 25 ºC).

Table 4. UV-Vis and fluorescent data of compound **4b**, **4e** and **4f**

Compounds	**λ_{abs} (nm)**	**λ_f (nm)**	**Intensity at λ_f (a.u.)**
4a	315	405	610
4f (-OMe)	315	398	574
4e (-NO_2)	315	395	343

Upon excitation at 315 nm, compound **4a** shows a strong and broad emission at 405 nm, whereas compound **4f** and **4e** emits light at 398 and 395 nm, respectively, as shown in Figure 3 (Table 4). Experimentally, it is observed that introduction of electron-donating as well as electron-withdrawing groups cause decrease in fluorescence intensity along with blue shifts of about 7 nm and 10 nm in case of compound **4f** and **4e**, respectively, in comparison to the fluorescence intensity of **4a** (see Table 4). Thus, it is clear that all of these 1,6-naphthyridine products exhibit strong fluorescence in ethanol. Therefore, the strong fluorescence intensity in protic solvent along with the shift in absorbance indicates these compounds may be used as fluorescent probe for sensing the change in local microenvironment around a biomolecule.[18c-d]

III.4. Conclusion

In conclusion, the great aspect of the present domino reaction is shown by the fact that the simultaneous construction of two new pyridine rings was achieved *via* base-promoted multi-component reaction in a one-pot operation where two cyano groups were converted into two amine groups in an intermolecular manner. A convenient one-pot synthesis of multisubstituted 1,6-naphthyridine of potential synthetic and pharmacological interest have been disclosed *via* base mediated multicomponent reactions. The use of easily available starting materials, mild reaction conditions, high chemoselectivity and moderate to good yields of products are the main advantages of this method. Nevertheless, all the obtained results demonstrated the efficiency and synthetic value of the one-pot multicomponent reaction for the synthesis of substituted 1,6-naphthyridine in which two rings or six new bonds were formed in a highly chemoselective manner. It should be noted that the richness of the functionality in substituted 1,6-naphthyridine, for example amino and cyano groups, may render these compounds as useful synthons in further synthetic organic transformations.

III.5. References

1. (a) S. Aoki, H. Wei, K. Matsui, R. Rachmat and M. Kobayashi, *Bioorg. Med. Chem.* 2003, **11**, 1969; (b) E. L. Larghi, B. V. Obrist and T. S. Kaufman, *Tetrahedron*, 2008, **64**, 5236.
2. C. F. H. Allen, *Chem. Rev.*, 1950, **47**, 275.
3. (a) B. Insuasty, D. Becerra, J. Quiroga, R. Abonia, M. Nogueras and J. Cobo, *Eur. J. Med. Chem*. 2013, **60**, 1; (b) T. Suresh, T. Dhanabal, R. N. Kumar and P. S. Mohan, *Ind. J. Chem*., 2005, **44B**, 2375; (c) Y. Li, J. Liang, T. Siu, E. Hu, M. A. Rossi, S. F. Barnett, D. Defeo-Jones, R. E. Jones, R. G. Robinson, K. Leander, H. E. Huber, S. Mittal, N. Cosford and P. Prasit, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 834; (d) S. Rudys, C. Ríos-Luci, E. Pérez-Roth, I. Cikotiene and J. M. Padrón, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1504.
4. (a) G. Falardeau, L. Chan, T. Stefanac, S. May, H. Jin and J. Lavallèe, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2769; (b) J. P. Guare, J. S. Wai, R. P. Gomez, N. J. Anthony, S. M. Jolly, A. R. Cortes, J. P. Vacca, P. J. Felock, K. A. Stillmock, W. A. Schleif, G. Moyer, L. J. Jin, L. Gabryelski, I. Chen, D. J. Hazuda and S. D. Young, *Bioorg. Med. Chem. Lett*., 2006, **16**, 2900; (c) B. K. Ghotekar, M. G. Ghagare, R. B. Toche and M. N. Jachak, *Monatsh. Chem*., 2010, **141**, 169.
5. (a) H. S. El-Kashef, A. A. Geies, E. D. A. M. Kamal and A. A. Abdel-Hafez, *J. Chem. Technol. Biotechnol.*, 1993, **57**, 15; (b) F. Haglid, *Ark. Kemi*, 1967, **26**, 489; (c) J. S. Skotnicki, *Chem. Abstr.* 1990, **113**, 78372 (U.S. Patent 4902685); (d) J. Blagg, M. J. Fray, M. L. Lewis, J. P. Mathias, M. H. Stefaniak, A. Stobie, *Chem. Abstr*. 2003, **139**, 261314 (Patent WO 2003076427).
6. G. Falardeau, H. Lachance, A. St. Pierre, C. G. Yannopoulos, M. Drouin, J. Bédard and L. Chan, *Bioorg. Med. Chem. Lett.* 2005, **15**, 1693.
7. (a) S. Vanlaer, A. Voet, C. Gielens, M. D. Maeyer and F. Compernolle, *Eur. J. Org. Chem*., 2009, 643; (b) V. J. Colandrea and E. M. Naylor, *Tetrahedron Lett*., 2000, **41**, 8053; (c) Q. Zhang, Q. Shi, H.-R. Zhang and K. K. Wang, *J. Org. Chem*., 2000, **65**, 7977; (d) J. A. Turner, *J. Org. Chem*., 1990, **55**, 4744; (e) P. Victory, N. Busquets, J. I. Borrell, J. Teixidó, B. Serra, J. L. Matallana, H. Junek and H. Sterk, *Heterocycles*, 1995, **41**, 1013.
8. (a) I. Hussein, S. El, M. A. Z. Suhair, A. M. Mona, A. B. Farid and M. A. O. Abdulrahman, *J. Med. Chem.*, 2000, **43**, 2915; (b) Z.-G. Han, C.-B. Miao, F. Shi, N. Ma, G. Zhang and S.-J. Tu, *J. Comb. Chem.*, 2010, **12**, 16; (c) L. D. Fader, R. Bethell, P.

Bonneau, M. Bös, Y. Bousquet, M. G. Cordingley, R. Coulombe, P. Deroy, A.-M. Faucher, A. Gagnon, N. Goudreau, C. Grand-Maître, I. Guse, O. Hucke, S. H. Kawai, J.-E. Lacoste, S. Landry, C. T. Lemke, E. Malenfant, S. Mason, S. Morin, J. O'Meara, B. Simoneau, S. Titolo and C. Yoakim, *Bioorg. Med. Chem. Lett*., 2011, **21**, 398.

9. H. Suzuki, N. Sakai, R. Iwahara, T. Fujiwaka, M. Satoh, A. Kakehi and T. Konakahara, *J. Org. Chem.,* 2007, **72**, 5878.
10. Y. Zhou, J. A. Porco Jr. and J. K. Snyder, *Org. Lett*., 2007, **9**, 393.
11. A. Chandra, B. Singh, S. Upadhyay and R. M. Singh, *Tetrahedron,* 2008, **64**, 11680.
12. M.-S. Tu, Y. Li, X. Wang, B. Jiang, S.-L. Wang and S.-J. Tu, *RSC Adv*., 2013, **3**, 3877.
13. H. Junek, O. S. Wolibeis, H. Sprintschnik and H. Wolny, *Monatsh. Chem*., 1977, **108**, 689.
14. (a) G. Sabitha, E. V. Reddy, C. Maruthi and J. S. Yadav, *Tetrahedron Lett*., 2002, **43**, 1573; (b) A. T. Khan and M. M. Khan, *Tetrahedron Lett*., 2011, **52**, 3455.
15. C. Mukhopadhyay, P. Das and R. J. Butcher, *Org. Lett*., 2011, **13**, 4664;
16. (a) A. T. Khan, M. Lal, S. Ali and M. M. Khan, *Tetrahedron Lett*., 2011, **52**, 5327; (b) X. Xin, Y. Wang, S. Kumar, Y. Liu, X. Linb and D. Dong, *Org. Biomol. Chem.*, 2010, **8**, 3078; (c) H. Wu, W. Lin, Y. Wan, H.-Q. Xin, D.-Q. Shi, Y.-H. Shi, R. Yuan, R.-C. Bo and W. Yin, *J. Comb. Chem.,* 2010**, 12**, 31; (d) B. C. Ranu, R. Jana and S. Sowmiah, *J. Org. Chem.,* 2007, **72**, 3152.
17. (a) D. Villemin, Z. Belhadj, N. Cheikh, N. Choukchou-Braham, N. Bar and J.-F. Lohier, *Tetrahedron Lett*., 2013, **54**, 1664; (b) N. Mahajan, A. Sambyal, A. P. S. Pannu and T. K. Razdan, *Tetrahedron Lett*., 2011, **52**, 1265; (c) P. Li, L.-L. Luo, X.-S. Li and J.-W. Xie, *Tetrahedron*, 2010, **66**, 7590; (d) M. N. Elinson, A. N. Vereshchagin, N. O. Stepanov, A. I. Ilovaisky, A. Y. Vorontsov and G. I. Nikishin, *Tetrahedron*, 2009, **65**, 605; (e) D. Xue, J. Li, Z.-T. Zhang and J.-G. Deng, *J. Org. Chem*., 2007, **72**, 5443; (f) D. M. Barnes, A. R. Haight, T. Hameury, M. A. McLaughlin, J. Mei, J. S. Tedrowy and J. D. R. Toma, *Tetrahedron*, 2006, **62**, 11311; (g) P. Milart, J. Wilamowski and J. J. Sepiol, *Tetrahedron*, 1998, **54**, 15643.
18. (a) R. B. Toche, R. A. Janrao, S. M. Bagul, S. P. Patil, B. P. Pagar and P. S. Nikam, *J. Fluoresc.,* 2011, **21**, 1617; (b) V. K. Indirapriyadharshini, P. Ramamurthy, V. Raghukumar, and V. T. Ramakrishnan, *Spectrochimica Acta Part A,* 2002, **58**, 1535; (c)

Y.-H. Ahn, J.-S. Lee and Y.-T. Chang, *J. Am. Chem. Soc.*, 2007, **129**, 4510; (d) M.-M. Yu , Z.-X. Li, L.-H. Wei, D.-H. Wei and M.-S. Tang, *Org. Lett.*, 2008, **10**, 5115.

Experimental Section

General procedure for the preparation of 1,6-naphthyridines (4a-m)

Into an oven dried 25 mL round bottomed flask was taken aryl methyl ketone or alkyl methyl ketone **1** (2 mmol), malononitrile **2** (2 mmol) and NaOH (0.06 g, 1.5 mmol) in methanol or ethanol (3 mL) and the reaction was refluxed in a pre-heated oil-bath at 120 ºC. The progress of the reaction was monitored by TLC time to time. After completion of the reaction, the solvent was removed in a rotary evaporator. Then, the crude reaction mixture was extracted with ethyl acetate (2 x 10 mL), washed with water and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and the crude product was purified through a silica gel (60-120 mesh) column chromatography. All the products were eluted in ethyl acetate and hexane mixture (1:9) and the products were obtained in 34-75% yields after purification.

General procedure for the preparation of 1,6-naphthyridines (6a-e)

A mixture of methyl ketone **1** (2 mmol), malononitrile **2** (2 mmol) and NaOH (0.040 g, 1 mmol) was taken in ethanol (3 mL) into an oven dried 25 mL two necked round bottomed flask and it was kept for refluxing with stirring in an pre-heated oil-bath at 120 ºC. After 20 minutes, thiophenol **5** (1 mmol) was added into the reaction mixture and the reaction was monitored by checking TLC from time to time. After completion of the reaction, the solvent was removed in a rotary evaporator. Then, the crude reaction mixture was extracted with ethyl acetate (2 x 10 mL), washed with water and the organic layer was dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuo and the pure product was obtained after purification through a silica gel (60-120 mesh) column chromatography. The products were obtained in 38-65% yields, which were eluted in ethyl acetate/hexane mixture (1:9).

Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects.

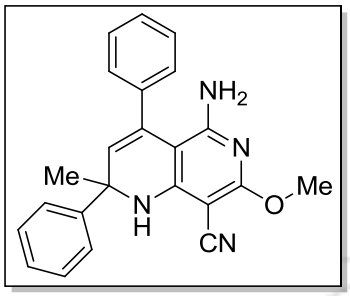
Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

Table 1. Crystal data and structure refinement for **4c** and **6b**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

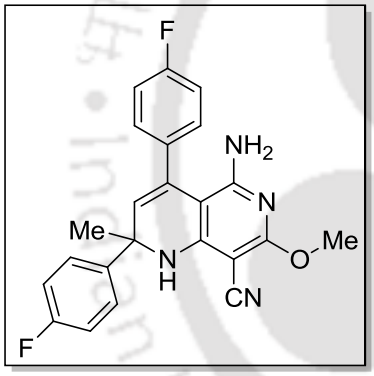
	Compound **4c** (CCDC)	Compound **6b** (CCDC)
Identification code	SS-01	SS-4-A
Empirical formula	'C_{23} $H_{18}Cl_2N_4O$'	'C_{28} H_{20} Cl N_4 S'
Formula weight	437.31	479.99
Temperature	298(2) K	298(2) K
Wavelength	0.71073Å	0.71073 Å
Crystal system	Triclinic	Monoclinic
Space group	P-1	'P 21/c'
Unit cell dimensions		
a	8.2527(7) Å	13.7351(8) Å
b	8.8425(7) Å	16.6866 (10) Å
c	15.7121(10) Å	13.4045(9) Å
α	83.996(6)º	90.00º
β	87.787(6)º	115.706º(3)
γ	67.780(8)º	90.00º
Volume	1055.61(15) $Å^3$	2768.2 (3) $Å^3$
Z	2	5
Density (calculated)	1.376g/cm^3	1.440 g/cm^3
Absorption coefficient	0.330 mm^{-1}	0.293 mm^{-1}
F(000)	452.0	1245
Theta range for data collection	2.89 to 28.82 º	1.65 to 27.48º

Index ranges	-10<=h<=11, -11<=k<=11, -21<=l<=21	-17<=h<=14, -20<=k<=19, -17<=l<=17
Reflections collected	9154	21084
Independent reflections	5443 R_{int} = 0.0264	5927 R_{int} = 0.0615
Completeness to θº	96.3% (θ = 28.82 º)	93.3% (θ = 27.48º)
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data / restraints / parameters	5443 / 0 / 273	5927 / 0 / 340
Goodness-of-fit on F2	0.931	0.996
Final R indices [>2sigma(I)]	R_{obs} = 0.0573, wR_{obs} = 0.2084	R_{obs} = 0.0632, wR_{obs} = 0.1569
R indices (all data)	R_{all} = 0.0878, wR_{all} = 0.2680	R_{all} = 0.1277, wR_{all} = 0.1898
Largest diff. peak and hole	0.268 and -0.349 e.Å^{-3}	0.0.258 and -0.355 e.Å^{-3}

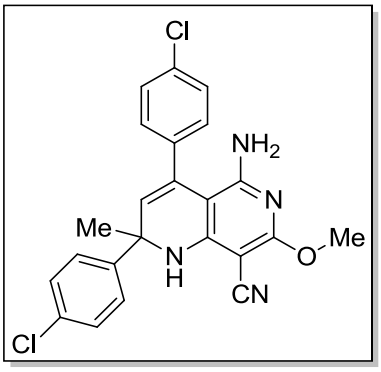
Spectral data

5-Amino-1,2-dihydro-7-methoxy-2-methyl-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile (4a): 

White solid (0.265 g, 72%); Mp 168–170 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 3.87 (s, 3H), 4.22 (bs, 2H), 5.30 (s, 1H), 5.48 (s, 1H), 7.26–7.29 (m, 1H), 7.30–7.37 (m, 7H), 7.40–7.45 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.97, 53.50, 57.01, 69.96, 91.41, 116.01, 124.76, 127.10, 127.37, 128.05, 128.45, 128.54, 131.87, 138.75, 146.92, 154.33, 154.46, 164.28 ppm; IR (KBr,): 1565, 1585, 1630, 2207, 2923, 3323, 3351, 3483 cm^{-1}; Anal. Calcd for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21; found: C, 74.92; H, 5.56; N, 15.28. HRMS calcd for $C_{23}H_{20}N_4O$ (M + H^{+}) 369.1710, found 369.1714.

5-Amino-2,4-bis(4-fluorophenyl)-1,2-dihydro-7-methoxy-2-methyl-1,6-naphthyridine-8-carbonitrile (4b): 

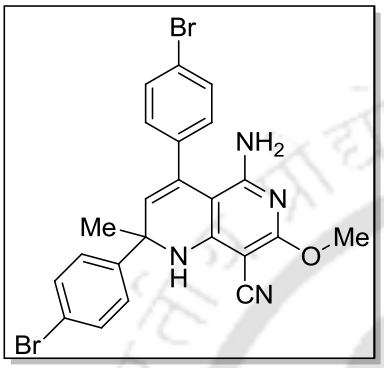
White solid (0.303 g, 75%); Mp 199–200 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (s, 3H), 3.87 (s, 3H), 4.22 (bs, 2H), 5.25 (s, 1H), 5.41 (s, 1H), 7.01–7.10 (m, 4H), 7.25–7.30 (m, 2H), 7.36–7.41 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.03, 53.78, 56.85, 70.36, 91.48, 115.36, 115.57, 115.65, 115.86, 116.00, 126.76, 126.84, 127.53, 129.95, 130.03, 131.36, 134.71, 142.80, 154.50, 160.70, 161.42, 163.15, 163.89, 164.60 ppm; IR (KBr): 1506, 1563, 1602, 2214, 2925, 3296, 3403, 3510 cm^{-1}; Anal. Calcd for $C_{23}H_{18}F_2N_4O$: C, 68.31; H, 4.49; N, 13.85; found: C, 68.37; H, 4.53; N, 13.76; HRMS calcd for $C_{23}H_{18}F_2N_4O$ (M + H^{+}) 405.1521, found 405.1526.

5-Amino-2,4-bis(4-chlorophenyl)-1,2-dihydro-7-methoxy-2-methyl-1,6-naphthyridine-8-carbonitrile (4c): 

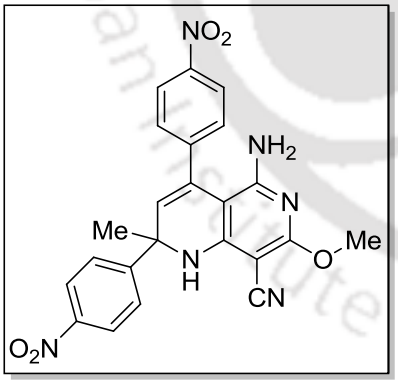
White solid (0.310 g, 71%); Mp 176–180 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (s, 3H), 3.88 (s, 3H), 4.23 (bs, 2H), 5.28 (s, 1H), 5.44 (s, 1H), 7.23–7.26 (m, 2H), 7.32–7.38 (m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.82, 53.60, 56.66, 70.14, 91.23, 115.80, 126.24, 127.30,

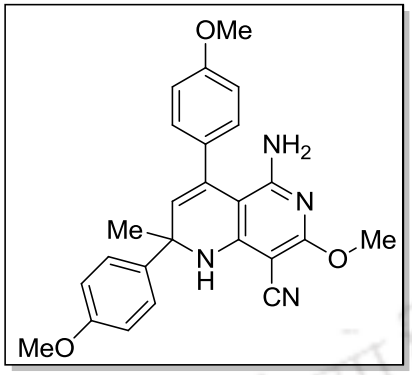
128.53, 128.73, 129.38, 131.40, 132.91, 134.09, 136.87, 145.38, 154.27, 154.50, 164.43 ppm; IR (KBr): 1564, 1585, 1604, 2204, 2945, 3345, 3399, 3494 cm^{-1}. Anal. Calcd for $C_{23}H_{18}Cl_2N_4O$: C, 63.17; H, 4.15; N, 12.81; found: C, 63.24; H, 4.22; N, 12.78; HRMS calcd for $C_{23}H_{18}Cl_2N_4O$ ($M + H^+$) 437.093, found 437.0947.

5-Amino-2,4-bis(4-bromophenyl)-1,2-dihydro-7-methoxy-2-methyl-1,6-naphthyridine-8-carbonitrile (4d): White solid (0.389 g, 74%); Mp 207–213 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.73 (s, 3H), 3.87 (s, 3H), 4.23 (bs, 2H), 5.30 (s, 1H), 5.44 (s, 1H), 7.17 (d, *J* = 8 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.04, 53.85, 56.93, 70.45, 91.36, 115.92, 121.40, 122.50, 126.73, 127.35, 129.88, 131.68, 131.77, 131.92, 137.54, 146.02, 154.45, 154.63, 164.65 ppm; IR (KBr): 1563, 1591, 1606, 2204, 2925, 3329, 3413, 3520 cm^{-1}; Anal. Calcd for $C_{23}H_{18}Br_2N_4O$: C, 52.50; H, 3.45; N, 10.65; found: C, 52.58; H, 3.49; N, 10.58; HRMS calcd for $C_{23}H_{18}Br_2N_4O$ ($M + H^+$) 526.9901, found 526.9906.

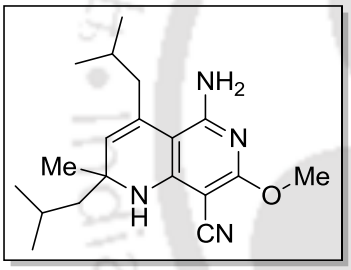


5-Amino-1,2-dihydro-7-methoxy-2-methyl-2,4-bis(4-nitrophenyl)-1,6-naphthyridine-8-carbonitrile (4e): Yellow solid (0.307 g, 67%); Mp 250–252 ^oC; ^1H NMR (DMSO-D_6, 400 MHz): δ 1.77 (s, 3H), 3.82 (s, 3H), 5.63 (bs, 2H), 5.91 (s, 1H), 6.01 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.8 Hz , 2H), 8.14–8.21 (m, 4H) ppm; ^{13}C NMR (DMSO-D_6, 75 MHz): δ 23.78, 47.48, 50.83, 62.33, 84.90, 109.87, 117.18, 117.49, 120.38, 122.98, 123.39, 124.62, 126.43, 138.74, 140.38, 140.81, 148.85, 149.13, 158.81 ppm; IR (KBr): 1341, 1563, 1592, 2201, 2926, 3361, 3395, 3461 cm^{-1}; Anal. Calcd for $C_{23}H_{18}N_6O_5$: C, 60.26; H, 3.96; N, 18.33; found: C, 60.31; H, 4.03; N, 18.21. HRMS (ESI) calcd for $C_{23}H_{18}N_6O_5$ ($M + H^+$) 459.1411, found 459.1419.

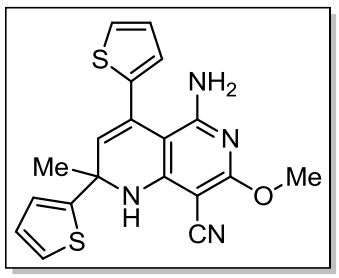


5-Amino-1,2-dihydro-7-methoxy-2,4-bis(4-methoxyphenyl)-2-methyl-1,6-naphthyridine-8-carbonitrile (4f): 

White solid (0.312 g, 73%); Mp 180–183 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72 (s, 3H), 3.79 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.30 (bs, 2H), 5.27 (s, 1H), 5.39 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.11, 53.74, 55.41, 55.44, 56.91, 70.27, 91.83, 114.03, 114.20, 116.29, 126.40, 127.48, 129.58, 131.34, 131.44, 139.50, 154.63, 154.66, 158.85, 159.68, 164.55 ppm; IR (KBr): 1508, 1567, 1596, 2209, 2935, 3311, 3384, 3502 cm^{-1}; Anal. Calcd for $C_{25}H_{24}N_4O_3$: C, 70.08; H, 5.65; N, 13.08; found: C, 70.13; H, 5.69; N, 12.98. MS (ESI) calcd for $C_{25}H_{24}N_4O_3$ (M + H$^+$) 429.48, found 429.09.

5-Amino-1,2-dihydro-2,4-diisobutyl-7-methoxy-2-methyl-1,6-naphthyridine-8-carbonitrile (4g): 

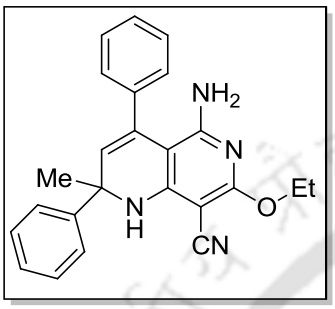
Gummy liquid (0.180 g, 55%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (d, *J* = 3.2 Hz, 3H), 0.90 (d, *J* = 1.6 Hz, 3H), 0.94 (d, *J* = 2.0 Hz, 3H), 0.95 (d, *J* = 2.0 Hz, 3H), 1.04 (dd, *J* = 6.8 & 12.8 Hz, 2H), 1.32–1.48 (m, 2H), 1.56 (s, 3H), 1.74–1.83 (m, 2H), 3.84 (s, 3H), 4.69 (bs, 2H), 4.72 (s, 1H), 5.03 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.51, 24.62, 24.72, 24.80, 27.04, 27.61, 30.44, 50.24, 53.52, 54.05, 55.12, 69.01, 92.61, 116.71, 125.67, 134.12, 152.54, 155.57, 163.64 ppm; IR (KBr): 1574, 2202, 2956, 3219, 3351, 3497 cm^{-1}; Anal. Calcd for $C_{19}H_{28}N_4O$: C, 63.48; H, 8.59; N, 17.06; found: C, 63.59; H, 8.67; N, 16.95.

5-Amino-1,2-dihydro-7-methoxy-2-methyl-2,4-di(thiophen-2-yl)-1,6-naphthyridine-8-carbonitrile (4h): 

Pale yellow solid (0.273 g, 72%); Mp 209–212 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.83 (s, 3H), 3.87 (s, 3H), 4.55 (bs, 2H), 5.31 (s, 1H), 5.62 (s, 1H), 6.93–6.98 (m, 2H), 7.01–7.06 (m, 2H), 7.24 (dd, *J* = 4.8 & 1.6 Hz, 1H), 7.30 (dd, *J* = 5.2 & 1.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.05, 53.63, 55.22, 70.23, 91.42, 115.74, 123.05, 125.23, 126.12, 126.81, 126.89, 127.17, 128.40, 139.78, 151.23, 153.69, 154.58, 164.41 ppm; IR

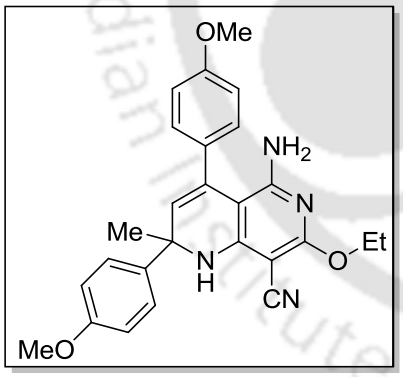
(KBr): 1211, 1440, 1564, 1588, 1602, 2215, 2928, 3291, 3375, 3489 cm^{-1}; Anal. Calcd for $C_{19}H_{16}N_4OS_2$: C, 59.98; H, 4.24; N, 14.73; found: C, 60.06; H, 4.28; N, 14.67. HRMS (ESI) calcd for $C_{19}H_{16}N_4OS_2$ (M + H^+) 381.0838, found 381.0845.

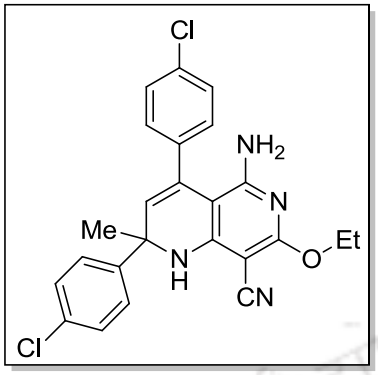
5-Amino-7-ethoxy-1,2-dihydro-2-methyl-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile



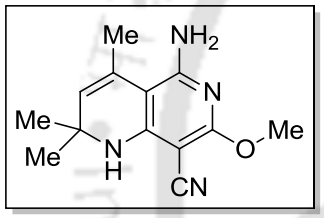
(4j): Yellow gummy liquid (0.202 g, 53%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.74 (s, 3H), 4.19 (bs, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 5.30 (s, 1H), 5.46 (s, 1H), 7.23–7.74 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.48, 30.10, 57.09, 62.15, 70.26, 91.43, 116.23, 124.87, 127.20, 127.34, 128.17, 128.38, 128.55, 128.63, 132.00, 138.97, 147.07, 154.45, 154.55, 164.15 ppm; IR (KBr): 1565, 1583, 1602, 2219, 2977, 3288, 3396, 3510 cm^{-1}; Anal. Calcd for $C_{24}H_{22}N_4O$: C, 70.37; H, 5.80; N, 14.65; found: C, 70.43; H, 5.88; N, 14.57. MS (ESI) calcd for $C_{24}H_{22}Cl_2N_4O$ (M + H^+) 383.18, found 383.13.

5-Amino-7-ethoxy-1,2-dihydro-2,4-bis(4-methoxyphenyl)-2-methyl-1,6-naphthyridine-8-carbonitrile (4k): Yellow gummy liquid (0.243 g, 55%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (t, *J* = 6.8 Hz, 3H), 1.72 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.27 (bs, 2H), 4.28 (q, J = 7.2 Hz, 2H), 5.23 (s, 1H), 5.38 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.04, 29.84, 53.55, 55.16, 55.19, 56.63, 69.90, 91.55, 113.72, 113.91, 116.16, 126.16, 127.24, 129.32, 130.96, 131.18, 139.21, 154.40, 158.53, 159.37, 164.30 ppm; IR (KBr): 1250, 1510, 1600, 2205, 2964, 3313, 3362, 3494 cm^{-1}; Anal. Calcd for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66; found: C, 70.63; H, 6.08; N, 12.57. MS (ESI) calcd for $C_{26}H_{26}N_4O_3$ (M + H^+) 443.2078, found 443.2085.

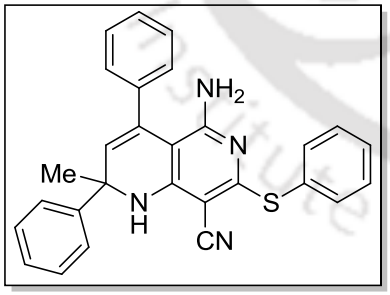


5-Amino-2,4-bis(4-chlorophenyl)-7-ethoxy-1,2-dihydro-2-methyl-1,6-naphthyridine-8 carbonitrile (4l): 

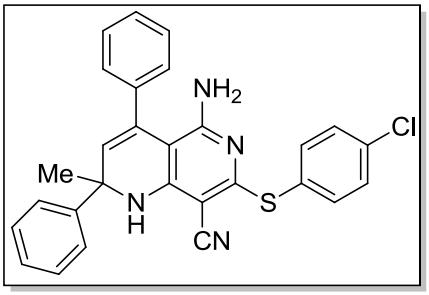
Yellow gummy liquid (0.216 g, 48%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (t, *J* = 6.8 Hz, 3H), 1.73 (s, 3H), 4.22 (bs, 2H), 4.30 (q, *J* = 6.8 Hz, 2H), 5.34 (s, 1H), 5.43 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.32–7.42 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.47, 29.98, 56.74, 62.32, 70.46, 91.21, 115.97, 126.30, 126.71, 127.21, 128.47, 128.70, 128.85, 129.49, 131.54, 133.13, 134.23, 137.06, 145.45, 154.40, 154.53, 164.28 ppm; IR (KBr): 1586, 1604, 2212, 2923, 3296, 3386, 3494 cm^{-1}; Anal. Calcd for $C_{24}H_{20}Cl_2N_4O$: C, 63.87; H, 4.47; N, 12.41; found: C, 63.93; H, 5.54; N, 12.32.

5-amino-7-methoxy-2,2,4-trimethyl-1,2-dihydro-1,6-naphthyridine-8-carbonitrile (4m): 

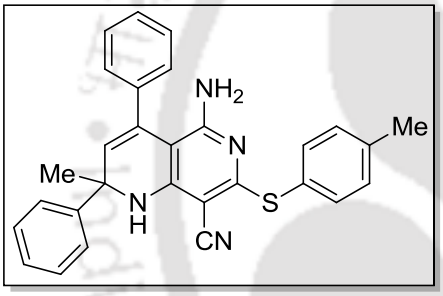
Yellow gummy liquid (0.083 g, 34%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 6H), 1.77 (s, 3H), 3.83 (s, 3H), 4.84 (bs, 2H, NH_2), 5.60 (bs, 1H, NH), 5.86 (s, 1H) ppm; IR (KBr): 1211, 1567, 1606, 2205, 2958, 3354, 3399, 3527 cm^{-1}; Anal. Calcd for $C_{13}H_{16}N_4O$: C, 63.91; H, 6.60; N, 22.93; found: C, 63.98; H, 6.64; N, 22.88. MS (ESI) calcd for $C_{13}H_{16}N_4O$ (M + H$^+$) 245. 1397, found 245.1397.

5-Amino-1,2-dihydro-2-methyl-2,4-diphenyl-7-(phenylthio)-1,6-naphthyridine-8-carbonitrile (6a): 

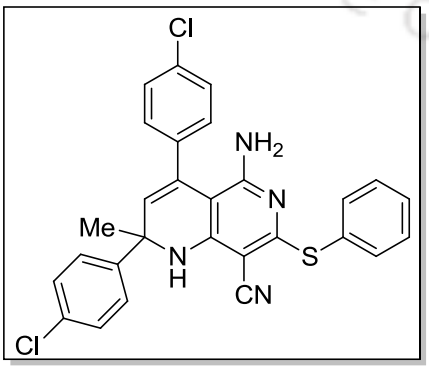
White solid (0.312 g, 65%); Mp 200–205 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 4.15 (bs, 2H), 5.29 (s, 1H), 5.54 (s, 1H), 7.25–7.29 (m, 4H), 7.33–7.39 (m, 7H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.52–7.54 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.38, 56.69, 81.59, 94.09, 115.98, 124.85, 126.77, 127.92, 128.04, 128.31, 128.52, 129.12, 129.57, 129.92, 131.75, 133.87, 138.07, 148.08, 152.82, 153.81, 154.79, 159.76 ppm; IR (KBr): 1436, 1567, 1602, 1626, 2199, 3297, 3327, 3394 cm^{-1}; Anal. Calcd for $C_{28}H_{22}N_4S$: C, 75.31; H, 4.97; N, 12.55; found: C, 75.37; H, 5.08; N, 12.47. HRMS (ESI) calcd for $C_{28}H_{22}N_4S$ (M + H$^+$) 447.1638, found 447.1639.

5-Amino-7-((4-chlorophenyl)thio)-2-methyl-2,4-diphenyl-1,2-dihydro-1,6-naphthyridine-8-carbonitrile (6b): 

White solid (0.289 g, 63%); Mp 119–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.77 (s, 3H), 4.15 (bs, 2H), 5.29 (s, 1H), 5.54 (s, 1H), 7.24–7.32 (m, 5H), 7.35–7.40 (m, 5H), 7.41–7.47 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.10, 57.35, 82.93, 94.20, 115.84, 124.98, 127.48, 128.04, 128.19, 128.38, 128.72, 129.00, 129.20, 131.75, 134.98, 136.09, 138.44, 146.77, 152.53, 154.44, 160.35 ppm; IR (KBr): 1434, 1541, 1571, 1598, 2199, 2924, 3312, 3392, 3505 cm^{1}; Anal. Calcd for $C_{28}H_{21}N_4SCl$: C, 69.92; H, 4.40; N, 11.65; found: C, 69.98; H, 4.49; N, 11.58. MS (ESI) calcd for $C_{28}H_{21}N_4SCl$ (M + H$^+$) 481.1248, found 481.1252.

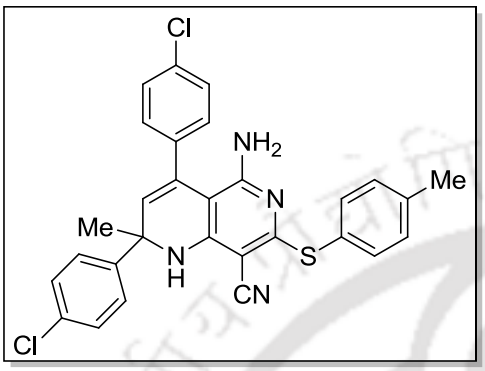
7-(p-tolylthio)-5-amino-1,2-dihydro-2-methyl-2,4-diphenyl-1,6-naphthyridine-8-carbonitrile (6c): 

White solid (0.335 g, 75%); Mp 163–165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.76 (s, 3H), 2.34 (s, 3H), 4.14 (bs, 2H), 5.27 (s, 1H), 5.52 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.24–7.28 (m, 3H), 7.33–7.37 (m, 5H), 7.38–7.44 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.23, 30.04, 57.21, 82.57, 93.98, 116.02, 124.91, 125.75, 127.36, 128.13, 128.25, 128.63, 128.97, 129.60, 131.80, 134.89, 138.41, 138.86, 146.80, 152.52, 154.40, 161.44 ppm; IR (KBr): 1434, 1539, 1599, 2198, 2924, 3307, 3390, 3506 cm^{-1}; Anal. Calcd for $C_{29}H_{24}N_4S$: C, 75.62; H, 5.25; N, 12.16; found: C, 75.71; H, 5.28; N, 12.03. MS (ESI) calcd for $C_{29}H_{24}N_4S$ (M + H$^+$) 461.17, found 461.04.

5-Amino-2,4-bis(4-chlorophenyl)-2-methyl-7-(phenylthio)-1,2-dihydro-1,6-naphthyridine-8-carbonitrile (6d): 

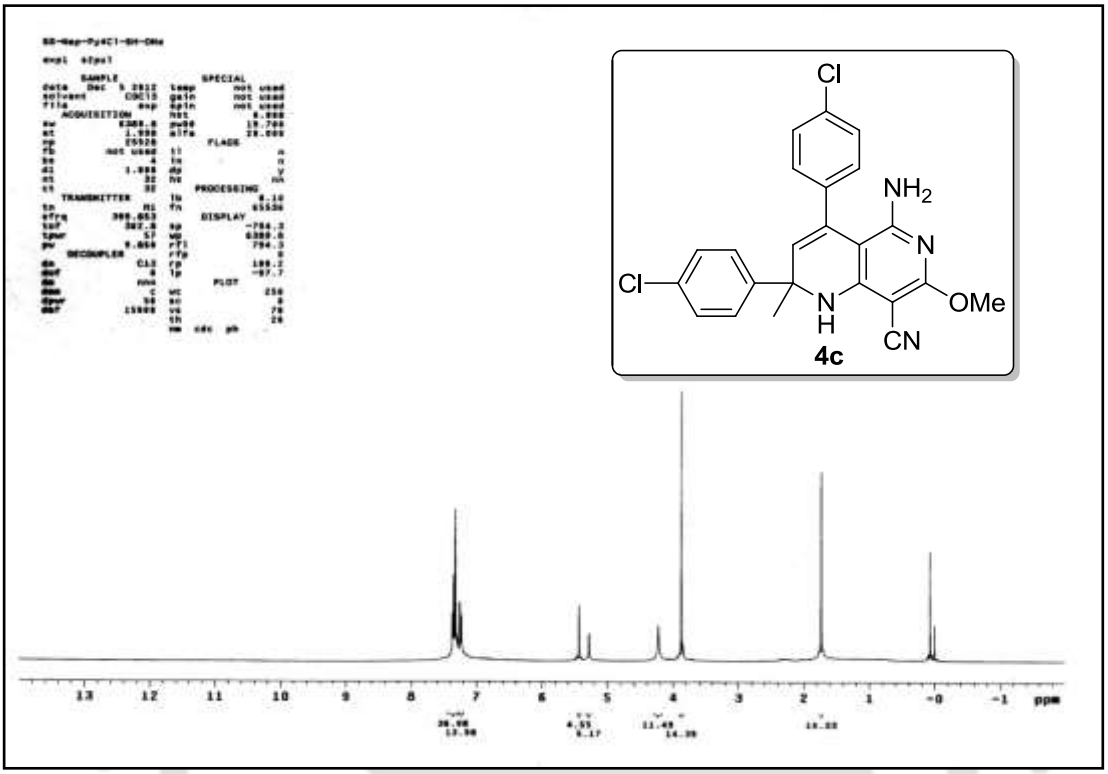
White solid (0.211 g, 41%); Mp 280–282°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.67 (s, 3H), 4.09 (bs, 2H), 5.27 (s, 1H), 5.41 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.21–7.29 (m, 9H), 7.42–7.46 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.95, 56.91, 82.91, 93.86, 115.71, 126.36, 128.77, 128.84, 128.89, 129.28, 129.47, 131.32, 133.36, 134.43, 134.81, 136.52, 145.19, 152.52, 154.30, 161.50 ppm; IR (KBr): 1432, 1567, 1596, 2199, 2923, 3394,

3472 cm^{-1}; Anal. Calcd for $C_{29}H_{20}N_4SCl_2$: C, 65.24; H, 3.91; N, 10.87; found: C, 65.32; H, 3.96; N, 10.91. MS (ESI) calcd for $C_{29}H_{20}N_4SCl_2$ ($M + H^+$) 515.46, found 514.94.

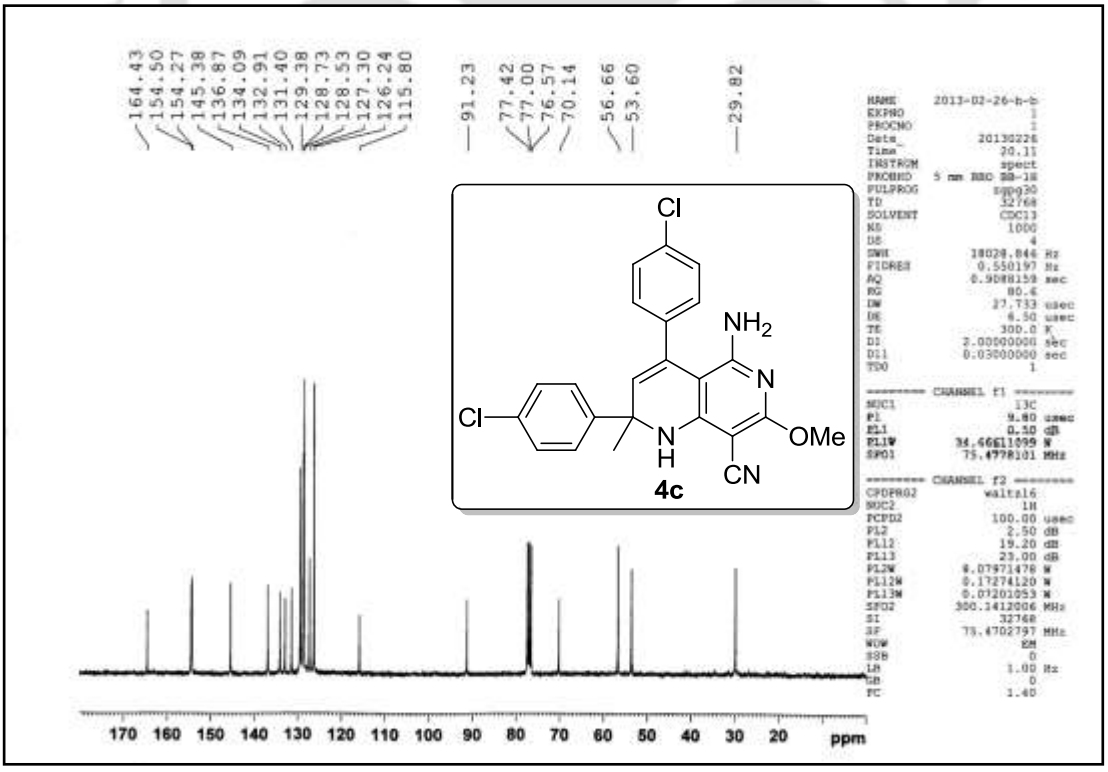
5-Amino-2,4-bis(4-chlorophenyl)-2-methyl-7-(p-tolylthio)-1,2-dihydro-1,6-naphthyridine-8-carbonitrile (6e): 

Semi solid (0.200 g, 38%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.74 (s, 3H), 2.36 (s, 3H), 4.17 (bs, 2H), 5.27 (s, 1H), 5.49 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.29–7.37 (m, 6H), 7.42 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.40, 30.27, 57.48, 82.93, 94.23, 116.14, 125.13, 126.11, 127.57, 128.38, 128.45, 128.85, 129.15, 129.78, 132.05, 135.11, 138.77, 139.03, 147.05, 152.74, 154.63, 161.66 ppm; IR (KBr): 1434, 1539, 1599, 2199, 2923, 3307, 3388, 3500 cm^{-1}; Anal. Calcd for $C_{29}H_{22}N_4SCl_2$: C, 65.78; H, 4.19; N, 10.58; found: C, 65.84; H, 4.25; N, 10.51. MS (ESI) calcd for $C_{29}H_{22}N_4SCl_2$ ($M + H^+$) 529.1015, found 529.1023.

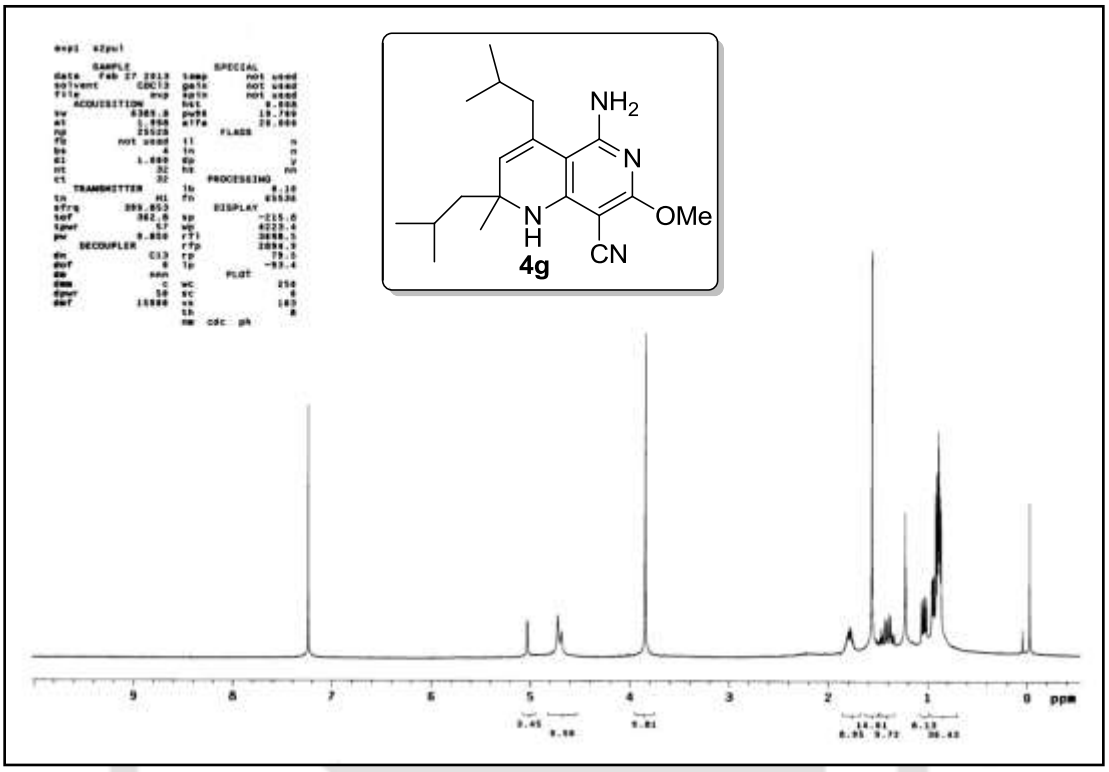
^{1}H NMR Spectra of Compound **4c**



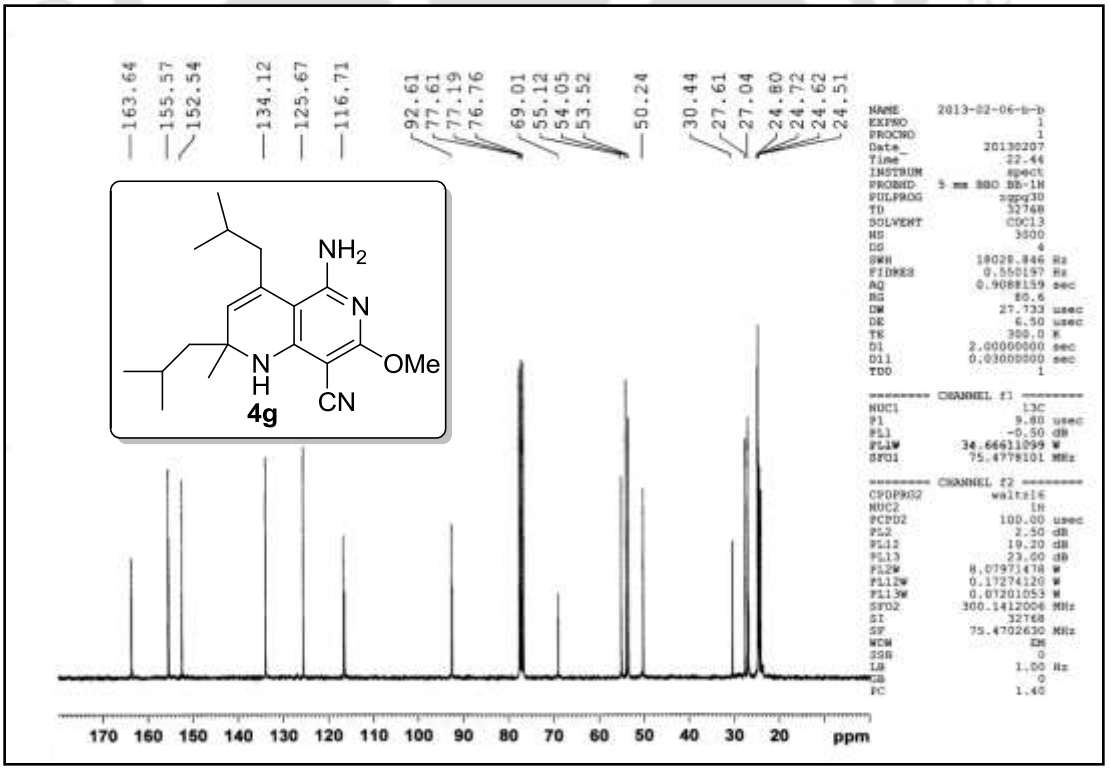
^{13}C NMR Spectra of Compound **4c**



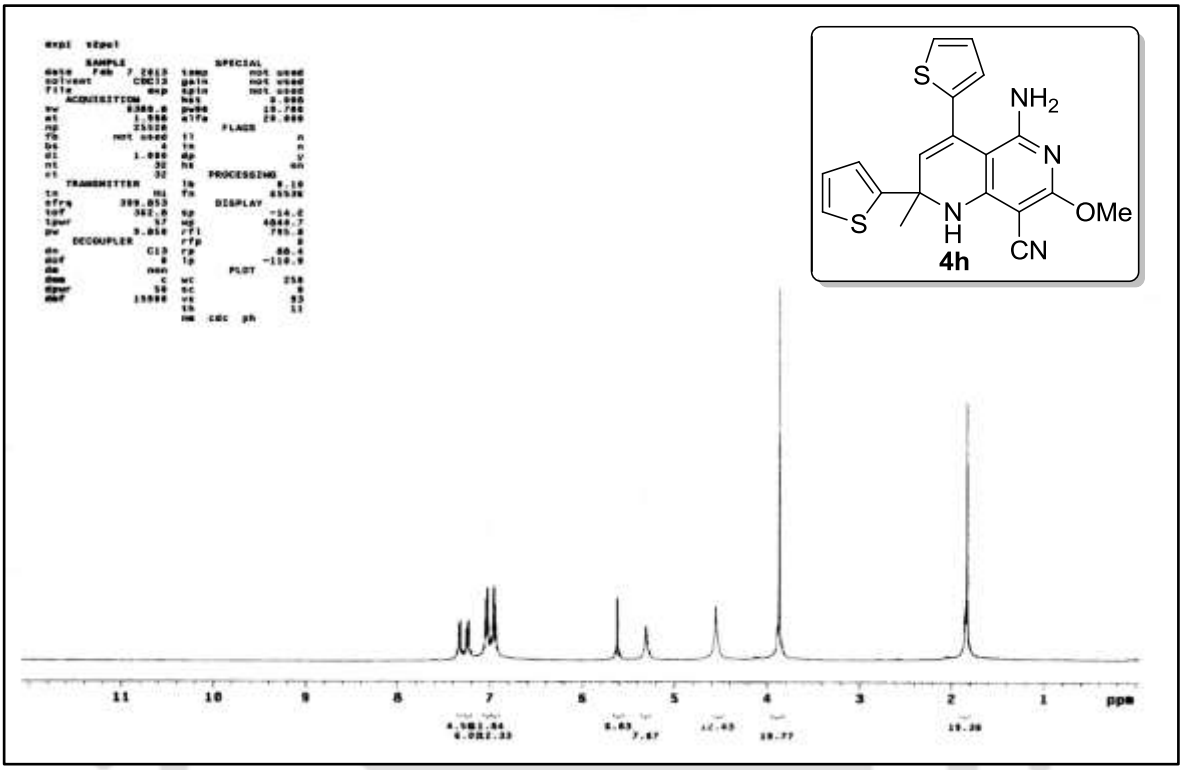
^{1}H NMR Spectra of Compound **4g**



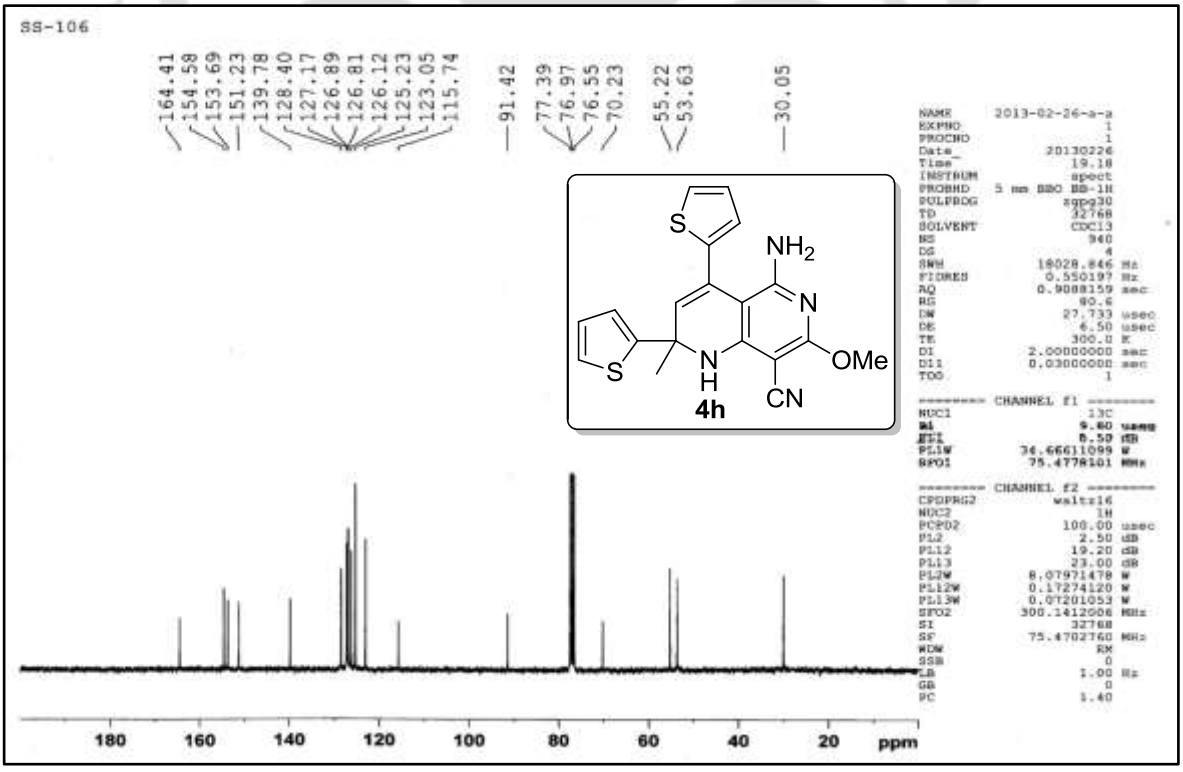
^{13}C NMR Spectra of Compound **4g**



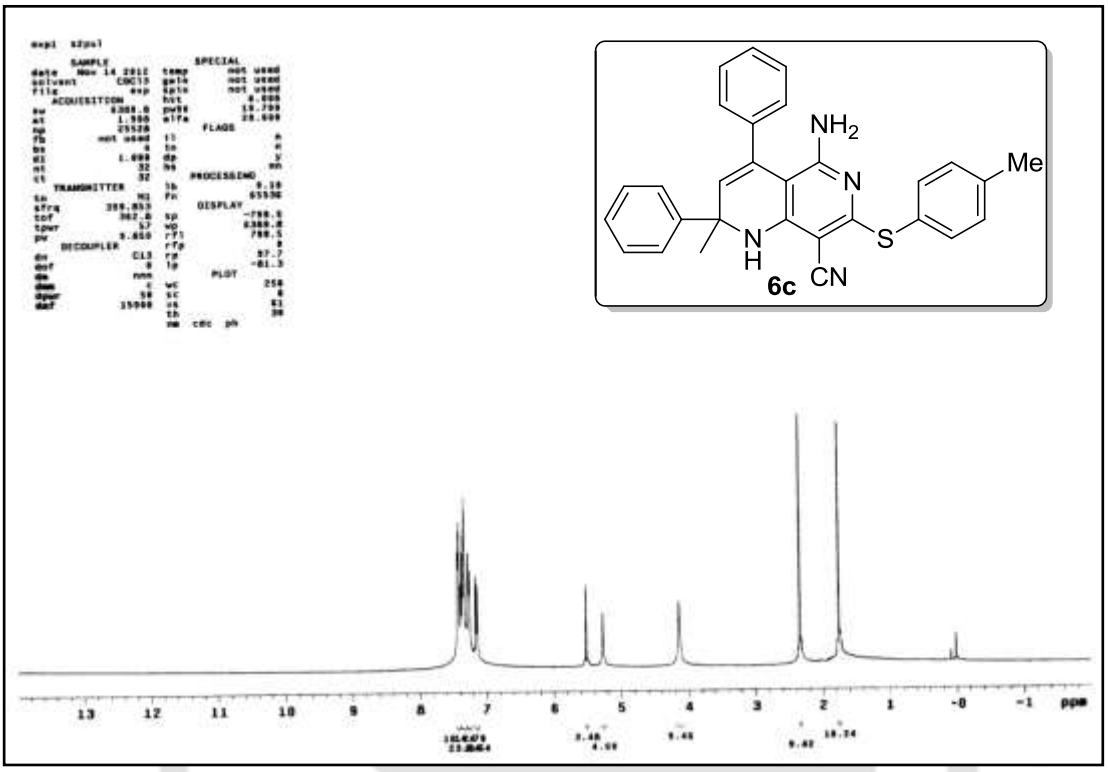
^{1}H NMR Spectra of Compound **4h**



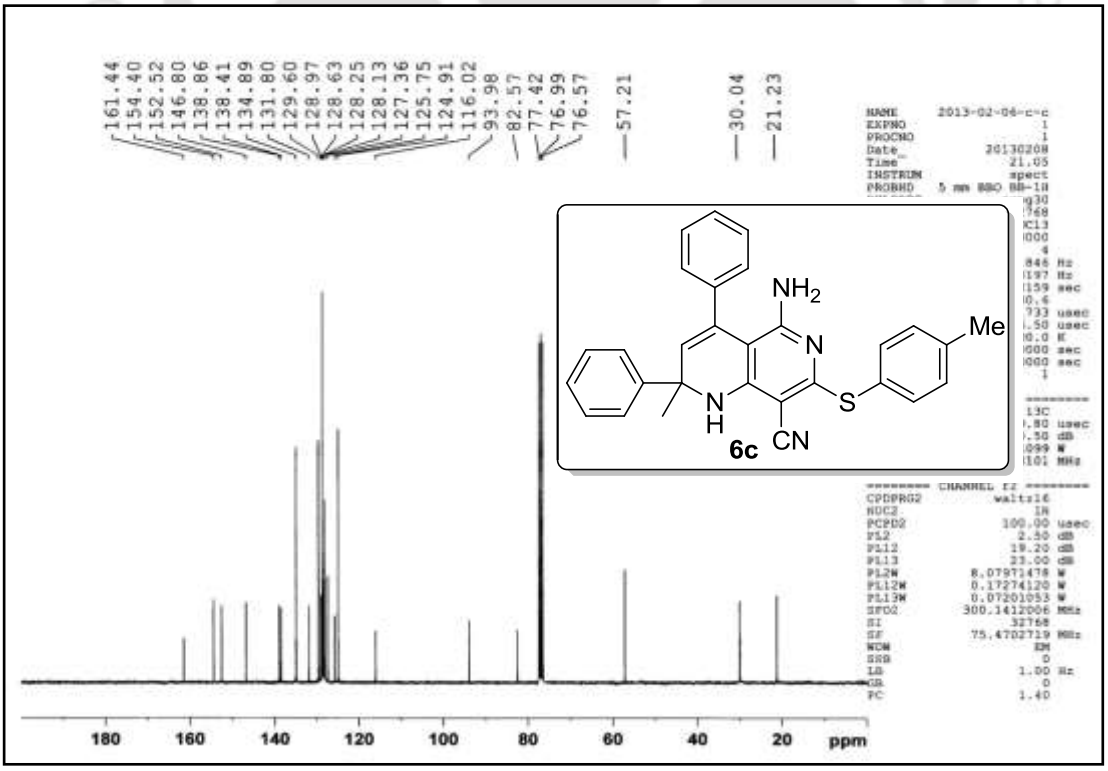
^{13}C NMR of Compound **4h**



^{1}H NMR Spectra of Compound **6c**

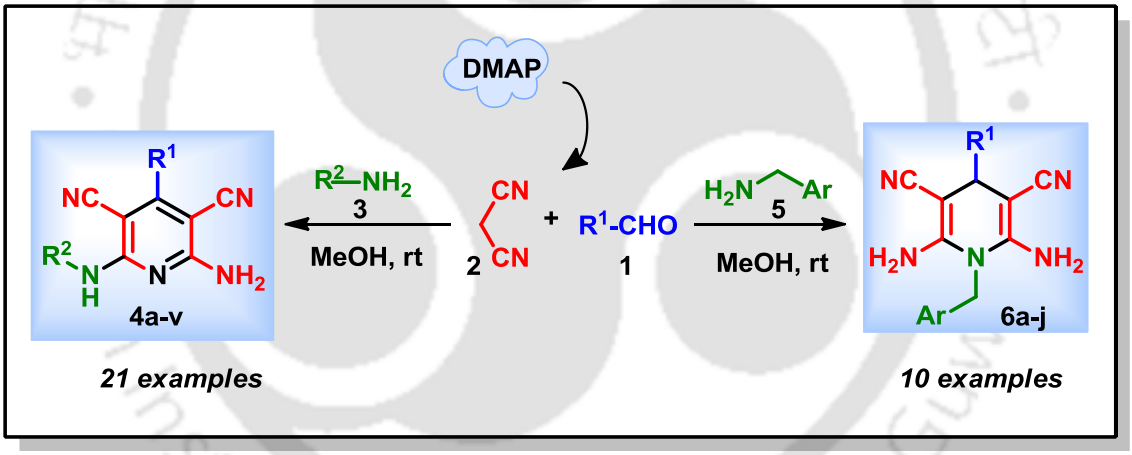


^{13}C NMR Spectra of Compound **6c**



Chapter IV

Synthesis of Fully-substituted Pyridines and Dihydropyridines in a Highly Chemoselective Manner



Chapter IV

Experimental Section

Synthesis of Fully-substituted Pyridines and Dihydropyridines in a Highly Chemoselective Manner

CHAPTER IV

Synthesis of Fully Substituted Pyridines and Dihydropyridines in a Highly Chemoselective Manner

IV.1. Introduction

The discovery of the pyridine nucleus (Pyr, meaning fire in Greek, and idine, suffix used for aromatic bases) is related to a peculiar experiment carried out by Anderson in 1846, who was studying the pyrolysis of bones and isolated picoline, the first known pyridine.[1] After the correct structure was proposed by Körner (1869) and Dewar (1871), this ring really became one of the most studied aromatics due to its wide applications in diverse chemical domains. Among all heteroaromatic compounds, highly substituted pyridines are unrivaled and also considered as "privileged medicinal scaffolds" because they are partial structures of many natural products, pharmaceuticals and synthetic organic moieties.[2,3] These pyridine skeletons are the most predominant due to their broad spectrum of potential biological activities as antimitotic agents,[4a] anti-inflammatory agents[4b] and anticonvulsants.[5] They display significant pharmacological properties for regulation of arterial pressure[6] and cholesterol levels in blood.[7] Some polysubstituted pyridines are used as non-linear optical materials,[8] electrical materials,[9] chelating agents in metal ligand chemistry[10] and as fluorescent liquid crystals.[11] Moreover, 2-amino-3-cyanopyridine derivatives have raised significant response as potent inhibitors of HIV-1.[12]

Dihydropyridines and their derivatives are key intermediates for the synthesis of several biological active compounds used in the treatment of cardiovascular disease and hypertension,[13] potent calcium channel antagonist and agonist.[14] They also have prospective application in other pharmacological activities.[15] Some of these biologically active scaffolds are shown in Figure 1.

As a consequence, chemists have developed a plethora of methods to synthesize these structures. In such scenario, chemoselective MCRs represent a unique process to construct different molecular frameworks via fine tuning of the reaction conditions. In the past

decades, many investigators have reported the chemoselectively controlled MCRs with various metal catalysts,[16a-d] solvents[16e-g] and substrate pattern.[16h] This chapter demonstrates the synthesis of fully substituted pyridines and dihydropyridine moieties in a highly chemoselective manner.

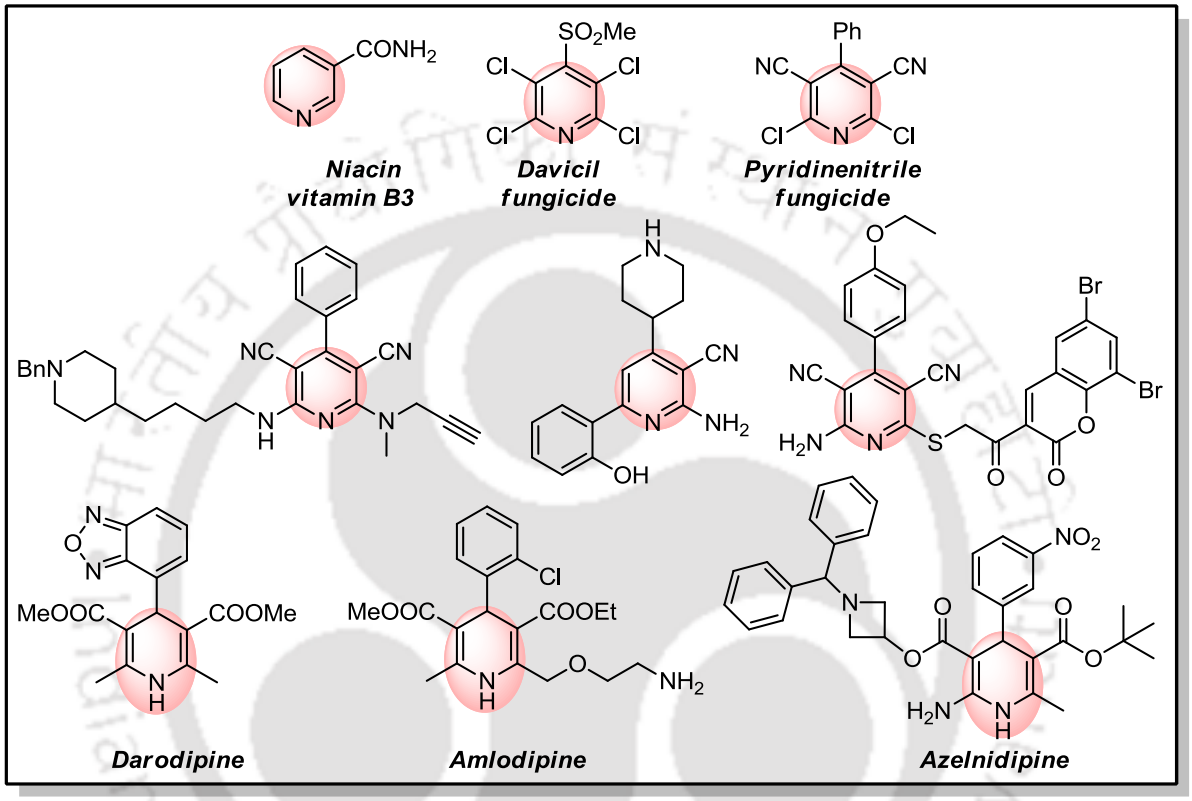


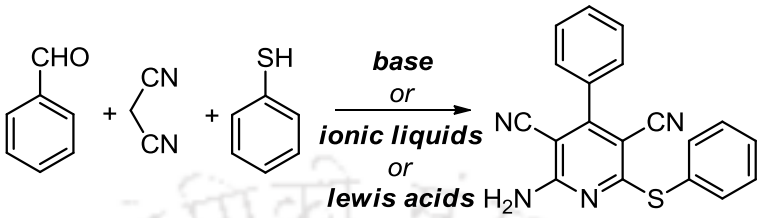
Figure 1. Some biologically active pyridine and dihydropyridine moieties

IV.2. Strategies for Pyridine and Dihydropyridine Formation

The traditional recipes for the construction of pyridine derivatives such as the Hantzsch,[17] Knoevenagel[18] and Chichibabin[19] reactions generally involve condensation of amines and carbonyl compounds.

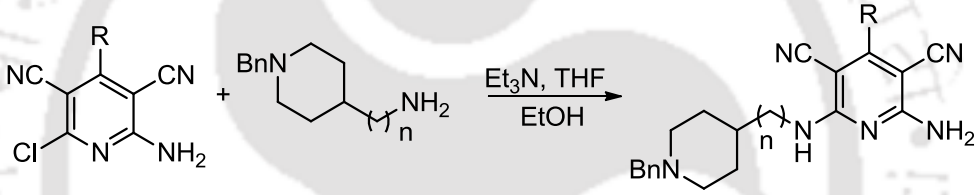
From the 19th century several efficient synthetic procedures have been developed for the synthesis of pyridine derivatives, mostly based on cycloaddition reactions or cross-coupling chemistry, which initiates the search for new approaches that offer concise and regiospecific strategies, making it topic of considerable interest.[20] Several scientists have used the MCR strategy to synthesize highly dense 6-thio-pyridine skeletons from aldehydes, malononitrile

and aromatic thiols under basic enviroments[21] or in presence of ionic liquids (Scheme 1).[22] Now-a-days Lewis acid catalysts are also used to produce aryl thiol substituted pyridine moieties.[23]



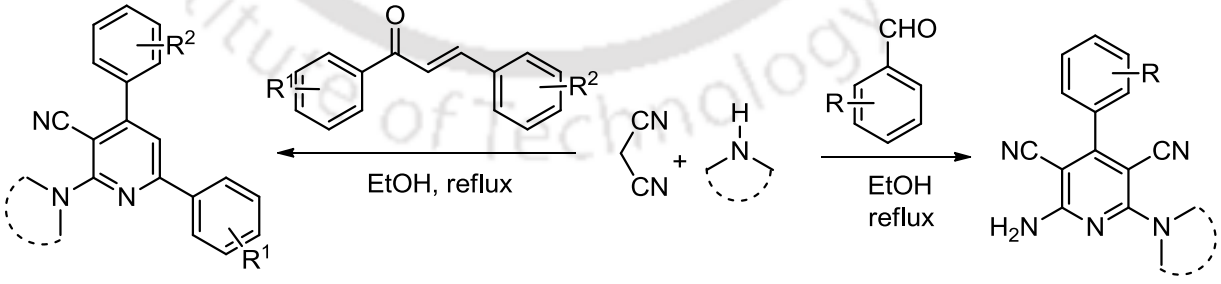
Scheme 1. Synthesis of thiol substituted pyridine moieties

It was found during literature survey that the 2-amino-6-alkylamino-3,5-dicyano pyridine derivatives can be synthesized directly from 2-chloro-pyridine moieties[24] or from thio-pyran derivatives (Scheme 2).[25]



Scheme 2. Use of 2-chloro-pyridines under basic enviroment

The use of secondary amines as nucleophiles has been explored only by some groups for the synthesis of pyridine moieties. Ramakrishnan *et al.* synthesized[26a] pyridine skeletons utilizing secondary amines and chalcones as well as aromatic aldehydes under reflux conditions for several hours (Scheme 3).

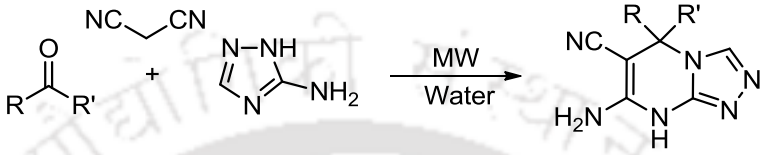


Scheme 3. Synthesis of pyridine moieties under reflux conditions

Similar use of such secondary amines with aldehydes and malononitrile was also mentioned by Choudhury *et al.* during their synthesis and photo-physical studies of

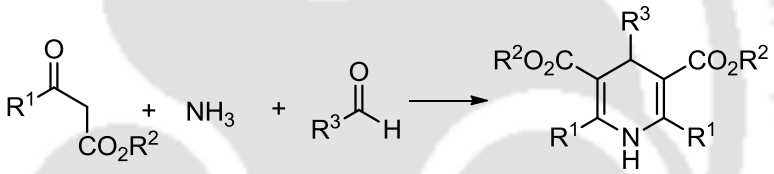
substituted pyridine derivatives.[26b] They modified the approach by using KOH as base. Fully substituted pyridine skeletons can also be synthesized using aqueous solution of methyl amine or dimethyl amine in excess amounts.[26c]

In 2006 Dandia *et al.* stated a microwave/ultrasound promoted route for the synthesis of triazolopyrimidines from amino triazole, malononitrile and carbonyl compounds in an aqueous medium (Scheme 4).[26d]



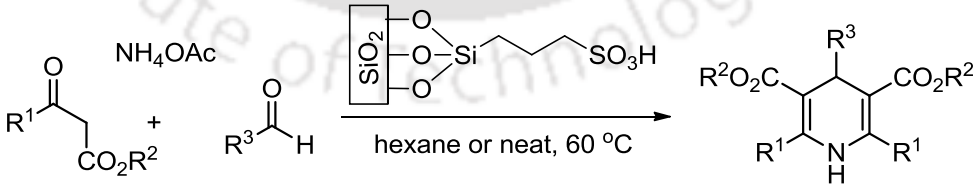
Scheme 4. Microwave promoted synthesis of triazolopyrimidines from amino triazoles

In this scenario some routes for the synthesis of dihydropyridine moieties should also be mentioned. The conventional route for the synthesis of dihydropyridine moiety is the Hantzsch dihydropyridine synthesis (Scheme 5).[27]



Scheme 5. Hantzsch dihydropyridine synthesis

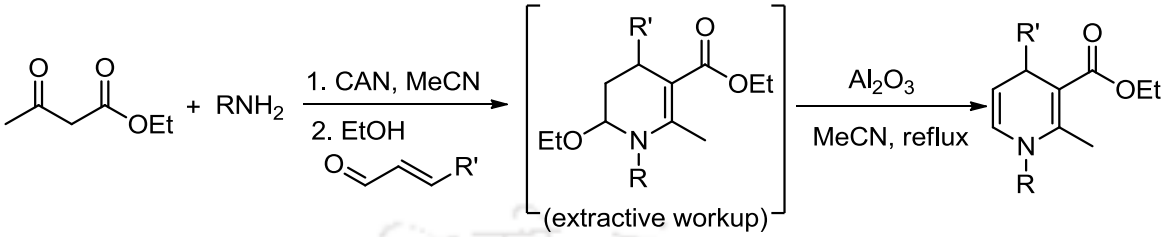
Other groups have improvised this methodology by introducing ammonium acetate as the nitrogen source. An efficient one-pot synthesis of Hantzsch 1,4-dihydropyridines catalyzed by sulfonic acid covalently anchored onto the surface of silica gel is shown below (Scheme 6).[28]



Scheme 6. Syntheis of dihydropyridine skeletons catalyzed by silica supported sulfonic acid

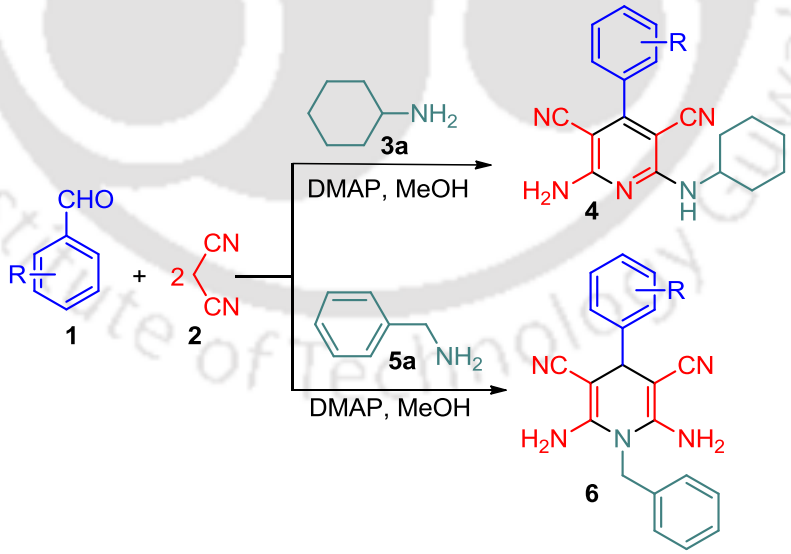
Some other groups have also made their mark in this pathway. Menéndez *et al.* treated 6-alkoxy-1,4,5,6-tetrahydropyridines with neutral alumina (activity grade I) suspended in

refluxing acetonitrile, to afford 1,4-dihydropyridines. This method allowed an efficient synthesis of 5,6-unsubstituted dihydropyridines (Scheme 7).[29]



Scheme 7. Syntheis of dihydropyridine moieties with neutral alumina

The demerits of the above mentioned procedures are longer reaction time, reflux conditions and/or use of excess reagents.[24-26] Over the past several years, various nucleophiles mainly the thiophenols have been used in these reactions.[21-23] However, the use of aliphatic amines as nucleophiles in these reactions were rarely explored. In this paper, we report a novel one-pot primary aliphatic amine based multicomponent domino reaction for the synthesis of polysubstituted pyridine and dihydropyridine derivatives in a highly chemoselective manner from simple and readily available aliphatic amines, aromatic as well as aliphatic aldehydes and malononitrile with good yields under mild reaction conditions (Scheme 8).

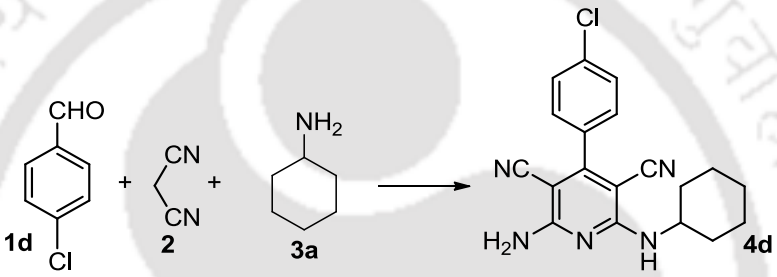


Scheme 8. Differential selectivity during synthesis of fully substituted pyridines and dihydropyridines

IV.3. Present Work

As an initial endeavor, a trial reaction was performed with 1 mmol of 4-chlorobenzaldehyde (**1d)**, 2 mmol of malononitrile (**2**) and 1 mmol of cyclohexylamine (**3a**) in methanol solvent in the presence of 15 mol% 4-dimethylaminopyridine (DMAP) as the catalyst. After 5 h, a solid precipitate (**4d**) was separated out which was characterized from spectroscopic techniques and was found to be the desired fully substituted pyridine derivative (Table 1, entry 1).

Table 1. Optimization of reaction conditions for the synthesis of functionalized pyridine (**4d**)[a]



Sl. No.	Catalyst	(Mol%)	Solvent	Time (h)	Yield (%)[b]
1	DMAP	(15)	MeOH	5	74
2	**DMAP**	**(20)**	**MeOH**	**4.5**	**81**
3	DMAP	(30)	MeOH	4.5	82
4	DMAP	(20)	EtOH	9	35
5	DMAP	(20)	CH_3CN	10	26
6	DMAP	(20)	CH_2Cl_2	8	57
7	DMAP	(20)	H_2O	12	<10
8	DBU	(20)	MeOH	7	65
9	Et_3N	(20)	MeOH	6	68
10	PPh_3	(20)	MeOH	6.5	62
11	DMA	(20)	MeOH	8	57
12	-		MeOH	17	14

[a]All the reactions were performed with 4-chlorobenzaldehyde (1.0 mmol), malononitrile (2.0 mmol) and cyclohexylamine (1.0 mmol) at rt. [b]Isolated yields.

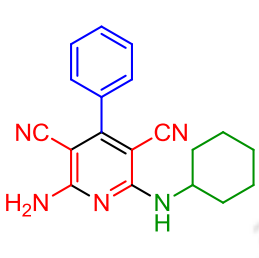
It was observed that the yield increased upto 81% in presence of 20 mol% of DMAP, however increasing the amount of catalyst up to 30 mol% did not affect the product yield any longer (Table 1, entries 2-3). To verify the effect of solvents the similar reaction was executed with different solvents such as EtOH, CH_3CN, CH_2Cl_2 and H_2O (Table 1, entries 4-7). Catalysts with basic nature such as DBU, Et_3N, PPh_3, *N*,*N*-dimethyl aniline (DMA) provided either lower yields or required longer reaction time (Table 1, entries 8-11). The reaction prolonged with very poor yield in absence of the catalyst (Table 1, entry 12). It has been observed the 20 mol% DMAP in presence of MeOH is the best reaction conditions for this particular reaction.

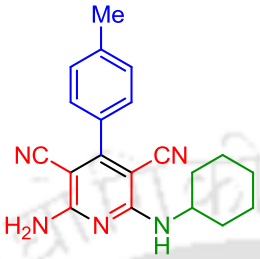
With the condition optimized, the scope and generality of this reaction was verified with various aromatic aldehydes using malononitrile and cyclohexylamine to generate our desired pyridine moiety. Aromatic aldehydes with electron donating functionalities such as –Me, –OMe (**4b** & **4c**) procured better yields as compared to electron withdrawing groups as –Cl, –Br (**4d** & **4e**). Unfortunately, no desired product (**4f**) was obtained when the similar reaction was performed with highly electron deficient 4-nitrobenzaldehyde. Still satisfactory results were gained for 4-formylbenzonitrile, 3-fluorobenzaldehyde and 3-nitrobenzaldehyde (**4g-4i)** under identical reaction conditions. Even cyclohexanecarboxaldehyde gave the desired pyridine moiety (**4j**). Apart from cyclohexanecarboxaldehyde, other aliphatic aldehydes such as long chain butyraldehyde or 3-methylbutyraldehyde produced the expected pyridine skeletons (**4k** & **4l**) in moderate yields.

The scope of the reaction was further extended with a series of different primary aliphatic amines utilizing benzaldehyde and malononitrile under similar reaction conditions. From strained cyclopropylamine to acyclic butyl-1-amine and long chain hexadecan-1-amine led to our desired 6-alkyl amino pyridine derivatives (**4m-4o**) in good to moderate yields. Even cyclohexylmethylamine gave corresponding pyridine derivatives **4p** in good yields. The chiral primary amines such as (R/S)-1-phenylethanamine gave the corresponding pyridine moieties (**4q** & **4r**) bearing chiral centre in the product. Next, the reactions of malononitrile and benzaldehyde or 4-methylbenzaldehyde were carried out with secondary amines such as piperidine or pyrrolidine under similar reaction conditions to generate the anticipated pyridine moieties (**4s-4v**) in good to moderate yields.

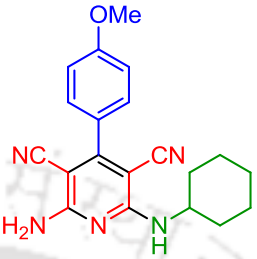
Table 2. Scope of various substituted pyridine derivatives[a]

1 2 3 4a-v

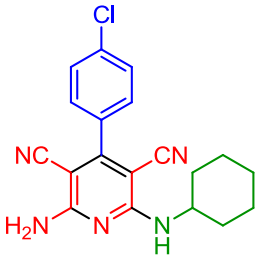

78%, 4.5 h, **4a**



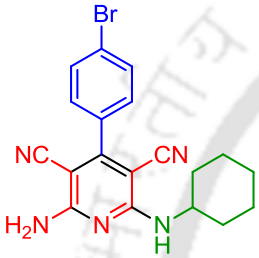
84%, 4 h, **4b**



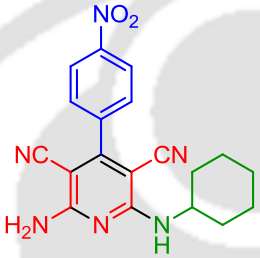
86%, 4 h, **4c**



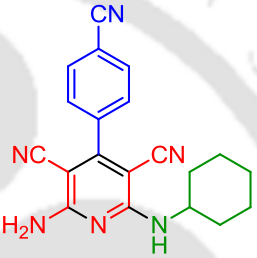
81%, 4 h, **4d**



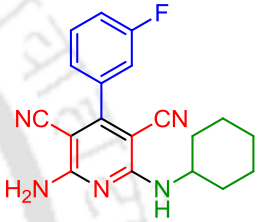
76%, 5.5 h, **4e**



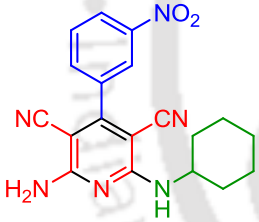
N.R, 12 h, **4f**



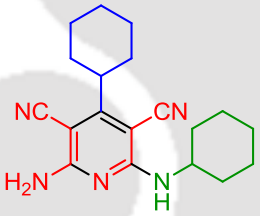
67%, 7 h, **4g**

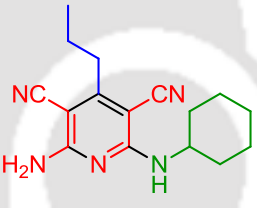


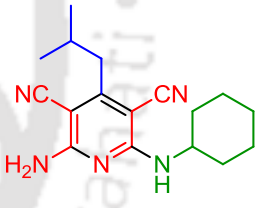
72%, 6 h, **4h**

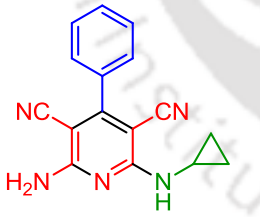


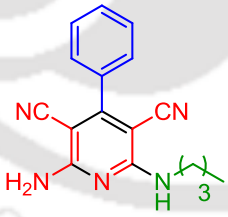
65%, 6 h, **4i**


69%, 6 h, **4j**

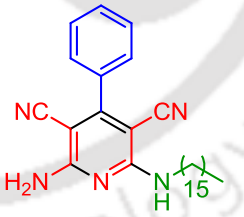

62%, 7 h, **4k**


67%, 6 h, **4l**

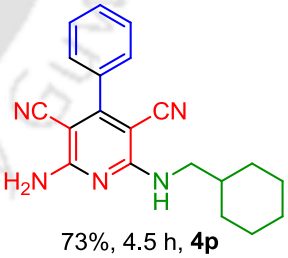

67%, 5.5 h, **4m**

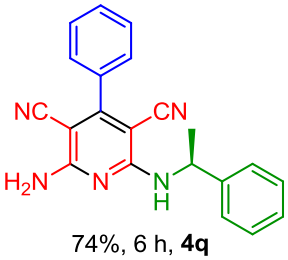


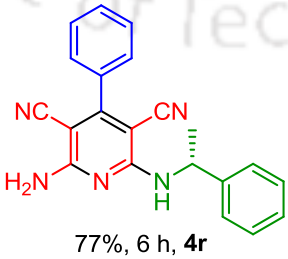
74%, 6 h, **4n**

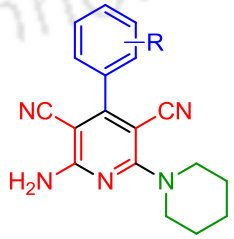


62%, 7 h, **4o**

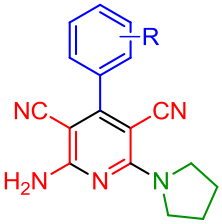

73%, 4.5 h, **4p**


74%, 6 h, **4q**


77%, 6 h, **4r**



R= H, **4s,** 83%, 7 h
R= Me, **4t,** 85%, 7 h

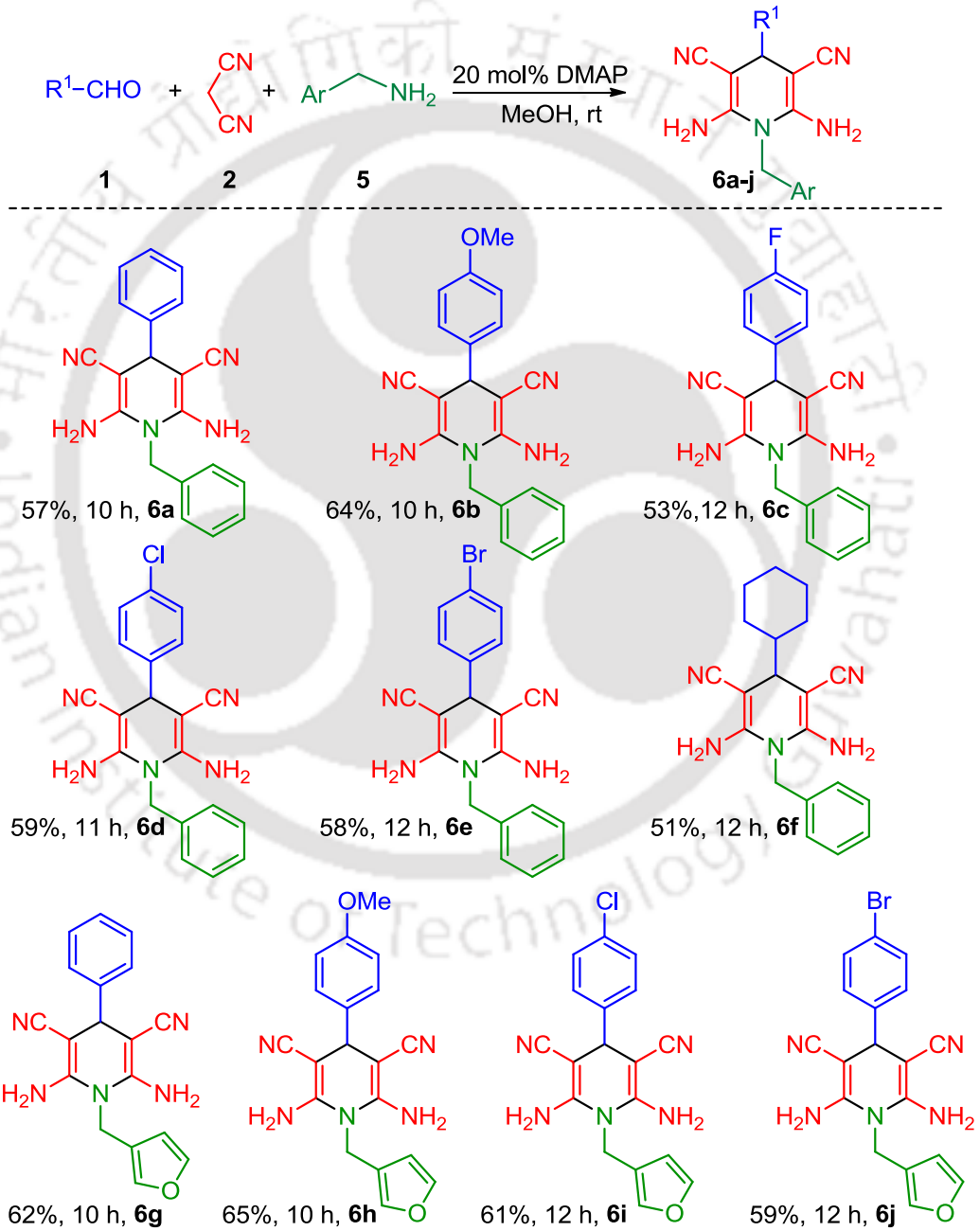


R= H, **4u,** 79%, 7 h
R= Me, **4v,** 82%, 7 h

[a]Isolated yields.

Encouraged by the above results, the scope of this method was extended utilizing benzylamine with benzaldehyde and malononitrile under similar reaction conditions. After the usual spectroscopic analysis, it was found that the product was 2,6-diamino-1-benzyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile instead of our expected substituted pyridine derivatives i.e. 2-amino-6-(benzylamino)-4-phenylpyridine-3,5-dicarbonitrile. The ^{1}H NMR

Table 3. Scope of various substituted 1,4-dihydropyridine derivatives[a]



[a]Isolated yields.

spectrum of **6a** showed one broad singlet at δ = 6.26 due to the four NH_2 protons, a singlet at δ = 3.96 ppm due to the -CH proton of the dihydropyridine ring and in ^{13}C NMR two peaks at the region of δ = 75-80 ppm, for the carbon atoms attached with the –CN groups in the pyridine rings, were found to be missing. From these observations, it was quite obvious that instead of fully substituted pyridine ring totally substituted dihydropyridine skeleton was formed.

To examine the generality of this protocol, the reactions of malononitrile and benzyl amine was performed with different aromatic aldehydes under the optimized condition. The aromatic aldehydes with electron donating substituents as –OMe (**6b**) provided better yield than the electron deficient substituents as –F, –Cl, –Br (**6c-6e**). When the reaction was extended for aliphatic aldehydes, the desired dihydropyridine moiety (**6f**) was obtained as product. Replacing the aromatic moiety of the benzyl amine skeleton with heteroaromatic one such as furan-3-ylmethanamine gave the expected highly substituted dihydropyridine ring (**6g**). These reactions were also repeated successfully even with aromatic aldehydes having different substituents such as –OMe, –Cl, –Br (**6h-6j**) in the ring. However, the reaction did not proceed in presence of aromatic amines. When the reaction was carried with 4-chlorobenzaldehyde, malononitrile and aniline under similar reaction conditions, we isolated only the Knoevenagel product. As these pyridine scaffolds are utilized in multistep reactions or in natural product synthesis, we wanted to examine its efficiency in large scale. During the synthesis of **4d** in multigram quantities we carried out the reaction in 10 mmol scale to give 2.25 g of the final product.

The formation of these fully substituted pyridines and dihydropridines were further established by X-ray crystallographic structure analysis of the compound **4a** and **6d.**

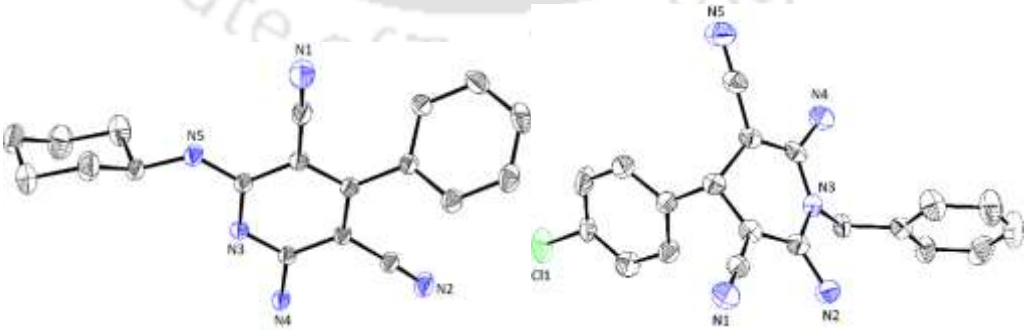
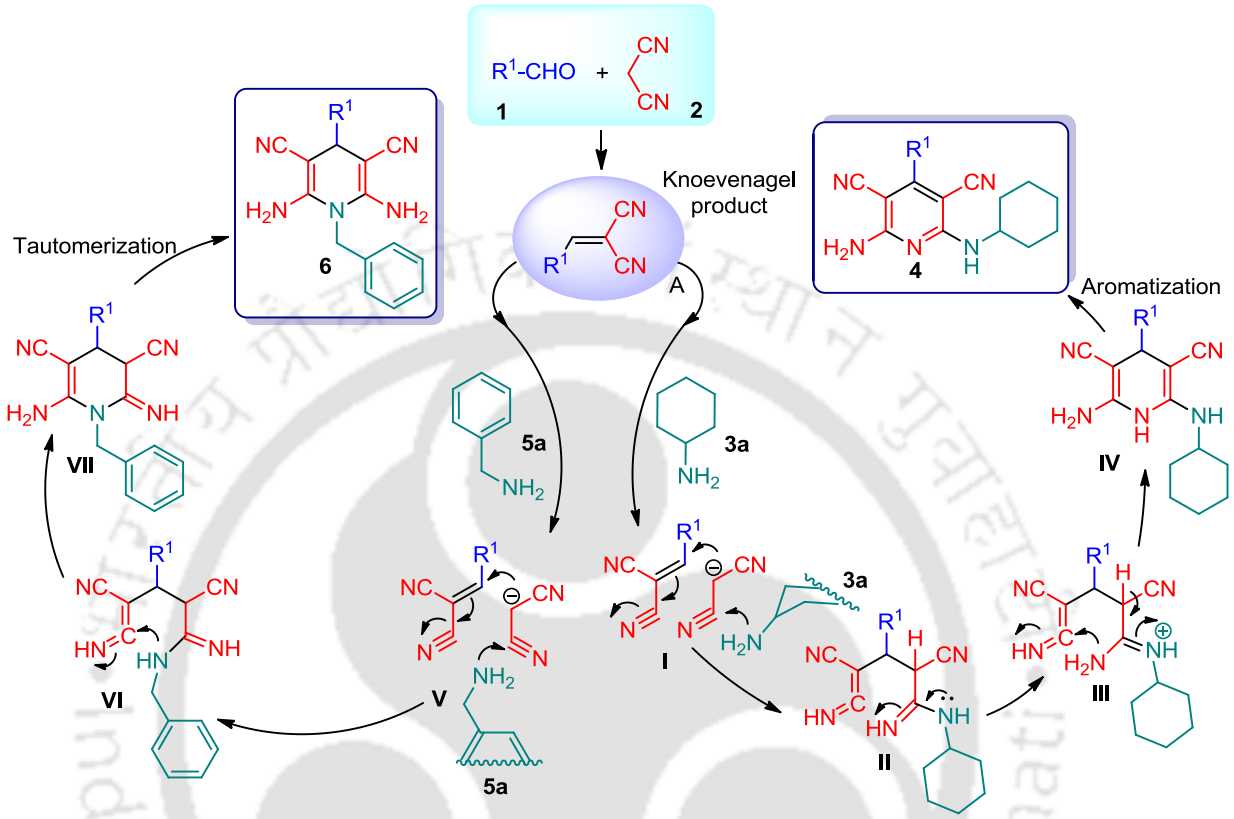


Figure 2. Ortep view of **4a** (CCDC 1006358) and **6d** (CCDC 913525)

Based on literature reports,[21,26] a plausible mechanism for the formation of these fully substituted pyridine **4** and dihydropyridine **6** rings is shown in Scheme 9. The mechanistic approach involves the Knoevenagel condensation of aromatic aldehyde and malononitrile forming adduct **A** in the first step, followed by Michael addition with malononitrile to form a tetracyano intermediate **II** & **VI** by amine. In the next step, the intermediates **III** & **VI** forms dihydropyridine moieties through cyclization as shown in intermediates **IV** & **VII** which is further followed by aromatization for cyclohexylamines and tautomerization for benzyl amines and to form 2-amino-6-alkylamino-3,5-dicyanopyridines **4** and 2,6-diamino-3,5-dicyano dihydropyridines **6** respectively.

The synthesis of pyridine and dihydropyridine moiety depends mainly on two major characters of the amine groups, the strength of the amine and its steric effect. In a polar protic solvent like MeOH, nucleophilicity as well as basicity of amines together regulate the chemoselectivity issue. According to the literature survey[30] benzylamine is less basic (having lower pKa values <10) compared to other amines *viz.* cyclohexylamine, cyclohexylmethylamine, heptylamine, piperidine, pyrrolidine, etc (pKa values >10). On the other hand for the amines the effect of delocalization (free bases and its conjugate acids) increases with increasing the basic strength. Thus delocalization is preferred for amines having higher pKa values (>10) i.e. having higher basicity which is followed by further attack of other $-NH_2$ functionality of the amidine group to generate cyclic intermediate **IV** from **III**. However amines containing lower pKa values (<10) *viz.* benzylamine and furfuryamine, both prefer to behave as nucleophile rather than base. Thus for both these two amines (benzylamine and furfuryamine) the nitrogen atom directly attacks to form the cyclized moiety **VII** from **VI**. The other regulating factor could be attributed to the steric effect caused by the cyclic ring or aliphatic group present next to the amine group, forcing the amine to take the 6th position in the ring instead of initiating the amine group to involve in the ring formation directly. As for the benzylic amines, the carbon atom adjacent to the amine group is substituted by planar aromatic ring. Interestingly in case of C-methyl-substituent in benzylamines the presence of both methyl and phenyl group in carbon atom adjacent to the amine creates strong steric hinderence to form pyridine ring over dihydropyridine moiety. In case of pyridine rings, the nitrogen atom from the malononitrile

is solely responsible for forming the ring where as in dihydropyridines the nitrogen atom of the ring comes from benzyl amines or methyl-furfural amines.



Scheme 9. Plausible mechanism for the formation of pyridine and dihydropyridine

IV.4. Conclusions

In summary, a convenient one-pot synthesis of fully substituted pyridine and dihydropyridine molecule of potent synthetic and pharmacological importance have been disclosed *via* base catalyzed multicomponent reaction utilizing readily available primary aliphatic amines in a highly chemoselective manner. Besides simple and mild reaction conditions, chemoselective switch in reaction procedure are the remarkable features of this present protocol. It should be noted that the richness of the functionality in the fully substituted pyridine and dihydropyridine moieties, for example amino and cyano groups, may render these compounds as useful synthons for further synthetic organic transformations.

IV.5. References

1. T. Anderson, *Ann. Phys.*, 1846, **60**, 86.
2. (a) G. Jones, In *Comprehensive Heterocyclic Chemistry II*, Vol. **5**; A. R. Katrisky, C. W. Rees, E. F. V. Scriven and A. McKillop, Eds.; Pergamon: Oxford, 1996; pp 167-243; (b) K. Joule and K. Mills, *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Cambridge, 2000; pp 63-120; (c) P. E. Alford, In *Progress in Heterocyclic Chemistry*, Vol. **22**; G. W. Gribble and J. A. Joule, Eds.; Elsevier: Amsterdam, 2011; pp 349-392.
3. (a) A. V. R. Rao, G. R. Reddy and B. V. Rao, *J. Org. Chem.*, 1991, **56**, 4545; (b) M. Beley, S. Chodorowski-Kimmes, J.-P. Collin, P. Lainė, J.-P. Launay and J.-P. Sauvage, *Angew. Chem. Int. Ed. Engl.*, 1994, **33**, 1775; (c) L. Jayasinghe, C. P. Jayasooriya, N. Hara and Y. Fujimoto, *Tetrahedron Lett.*, 2003, **44**, 8769; (d) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043; (e) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627; (f) T. Kubota, T. Nishi, E. Fukushi, J. Kawabata, J. Fromont and J. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 4983.
4. (a) Jr. C. Temple, G. A. Rener, W. R. Waud and P. E. Noker, *J. Med. Chem.*, 1992, **35**, 3686; (b) X.-F. Wang, E. Ohkoshi, S.-B. Wang, E. Hamel, K. F. Bastow, S. L. Morris-Natschke, K.-H. Lee and L. Xie, *Bioorg. Med. Chem.*, 2013, **21**, 632; (c) F. Manna, F. Chimenti, A. Bolasco, B. Bizzarri, W. Filippelli, A. Filippelli and L. Gagliardi, *Eur. J. Med. Chem*., 1999, **34**, 245.
5. N. Siddiqui, W. Ahsan, M. S. Alam, R. Ali and K. Srivastava, *Arch. Pharm. Chem. Life Sci.*, 2012, **345**, 185.
6. J. Mercier, M. Gavend, V. V. Luv and S. Dessaigne, *Congr. Union-Ther. Int.*, [C.R], 8th 1963, 361.
7. G. Dorner and F. W. Fischer, *Arzneimittel. Forsch.*, 1961, **11**, 110.
8. H. Wang, R. Helgeson, B. Ma and F. Wudl, *J. Org. Chem.*, 2000, **65**, 5862.
9. T. Kanbara, K. Kushida, N. Saito, I. Kuwajima, K. Kubota and T. Yamamoto, *Chem. Lett.*, 1992, **21**,583.
10. T. J. Meyer, *Acc. Chem. Res.*, 1989, **22**, 163.
11. A. I. Pavluchenko, V. F. Petrov and N. I. Smirnova, *Liq. Cryst.*, 1995, **19**, 811.
12. (a) T. Murata, M. Shimada, S. Sakakibara, T. Yoshino, H. Kadono, T. Masuda, M. Shimazaki, T. Shintani, K. Fuchikami, K. Sakai, H. Inbe, K. Takeshita, T. Niki, M.

Umeda, K. B. Bacon, K. B. Ziegelbauer and T. B. Lowinger, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 913; (b) J. Deng, T. Sanchez, L. Q. Al-Mawsawi, R. Dayam, R. A. Yunes, A. Garofalo, M. B. Bolger and N. Neamati, *Bioorg. Med. Chem.*, 2007, **15**, 4985.

13. (a) M. F. Gordeev, D. V. Patel and E. M. Gordon, *J. Org. Chem.*, 1996, **61**, 924.
14. (a) R. Shan, C. Velaskez and E. E. Knaus, *J. Med. Chem*., 2004, **47**, 254; (b) D. J. Triggle and D. Rampe, *Trends Pharmacol. Sci.*, 1989, **10**, 507.
15. (a) V. Klusa, *Drugs Future*, 1995, **20**, 135; (b) I. O. Donkor, X. Zhou, J. Schmidt, K. C. Agrawal and V. Kishore, *Bioorg. Med. Chem.*, 1998, **6**, 563; (c) T. Straub, C. Boesenberg, V. Gekeler and F. Boege, *Biochemistry*, 1997, **36**, 10777; (d) H.-A. S. Abbas, W. A. El Sayed and N. M. Fathy, *Eur. J. Med. Chem.*, 2010, **45**, 973; (e) J. Robert and C. Jarry, *J. Med. Chem.*, 2003, **46**, 4805; (f) A. Hilgeroth, *Mini-Rev. Med. Chem*., 2002, **2**, 235; (g) A. Hilgeroth and H. Lilie, *Eur. J. Med. Chem.*, 2003, **38**, 495.
16. (a) A. Padwa and D. J. Austin, *Angew. Chem*., 1994, **106**, 1881; (b) J. Seo, H. M. P. Chui, M. J. Heeg and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 476; (c) M. G. Organ, E. A. Arvanitis, C. E. Dixon and J. T. Cooper, *J. Am. Chem. Soc*., 2002, **124**, 1288; (d) H. Lebel and V. Paquet, *Org. Lett*., 2002, **4**, 1671; (e) S. Tu, B. Jiang, Y. Zhang, R. Jia, J. Zhang, C. Yao and F. Shi, *Org. Biomol. Chem*., 2007, **5**, 355; (f) J. Wang, R. Mason, D. V. Derveer, K. Feng and X. R. Bu, *J. Org. Chem.*, 2003, **68**, 5415; (g) M.-L. Lin, S. J. Maddirala and R.-S. Liu, *Org. Lett.*, 2005, **7**, 1745; (h) X. Wang, X.-P. Xu, S.-Y. Wang, W. Zhou and S.-J. Ji, *Org. Lett.*, 2013, **15**, 4246.
17. A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1.
18. J. Colonge, J. Dreux and M. Thiers, *Bull. Soc. Chim. Fr.*, 1959, 1461.
19. A. E. Chichibabin and O. A. Zeide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1212.
20. For recent synthesis of multisubstituted pyridines, see: (a) Y.-F. Wang, K. K. Toh, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **133**, 6411; (b) Y. S. Chun, J. H. Lee, J. H. Kim, Y. O. Ko and S.-G. Lee, *Org. Lett.*, 2011, **13**, 6390; (c) T. J. Donohoe, J. A. Basutto, J. F. Bower and A. Rathi, *Org. Lett.*, 2011, **13**, 1036; (d) D. Coffinier, L. E. Kaim, L. Grimaud and S. Hadrot, *Tetrahedron Lett.*, 2010, **51**, 6186; (e) M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc.*, 2006, **128**, 4592; (f) M. Movassaghi, M. D. Hill and O. K. Ahmad, *J. Am. Chem. Soc.*, 2007, **129**, 10096; (g) M. Z. Chen and G. C. Micalizio, *J. Am. Chem. Soc.*, 2012, **134**, 1352.

21. (a) T. R. K. Reddy, R. Mutter, W. Heal, K. Guo, V. J. Gillet, S. Pratt and B. Chen, *J. Med. Chem.*, 2006, **49**, 607; (b) N. M. Evdokimov, A. S. Kireev, A. A. Yakovenko, M. Y. Antipin, I. V. Magedov and A. Kormienko, *J. Org. Chem.*, 2007, **72**, 3443; (c) R. Mamgian, R. Singh and D. S. Rawat, *J. Heterocycl. Chem.*, 2009, **46**, 69; (d) K. Guo, M. J. Thompson and B. Chen, *J. Org. Chem.*, 2009, **74**, 6999.
22. B. C. Ranu, R. Jana and S. Sowmiah, *J. Org. Chem.*, 2007, **72**, 3152.
23. (a) M. Sridhar, B. C. Ramanaiah, C. Narsaiah, B. Mahesh, M. Kumaraswamy, K. R. R. Mallu, V. M. Ankathi and P. S. Rao, *Tetrahedron Lett.*, 2009, **50**, 3897; (b) P. V. Shinde, S. S. Sonar, B. P. Shingate and M. S. Shingare, *Tetrahedron Lett.*, 2010, **51**, 1309.
24. A. Samadi, M. Estrada, C. Pérez, M. I. Rodríguez-Franco, I. Iriepa, I. Moraleda, M. Chioua and J. Marco-Contelles, *Eur. J. Med. Chem.*, 2012, **57**, 296.
25. H. Z. Shams, Y. M. Elkholy, N. S. Ibrahim and M. H. Elnagdi, *J. Prakt. Chem.*, 1988, **330**, 817.
26. (a) V. Raghukumar, D. Thirumalai, V. Ramakrishnan, V. Karunakara and P. Ramamurthy, *Tetrahedron*, 2003, **59**, 3761; (b) M. N. Khan, S. Pal, T. Parvin and L. H. Choudhury, *RSC Adv.*, 2012, **2**, 12305; (c) C. Jiao, M. Zhen and Y. Chao-Guo, *Chem. Res. Chinese Univ.*, 2010, **26**, 937; (d) A. Dandia, P. Sarawgia, K. Aryab and S. Khaturia, *Arkivoc*, 2006, **xvi**, 83.
27. A. Hantzsch, *Chem. Ber.*, 1881, **14**, 1637.
28. R. Gupta, R. Gupta, S. Paul and A. Loupy, *Synthesis*, 2007, 2835.
29. S. Maiti and J. C. Menéndez, *Synlett*, 2009, 2249.
30. H. K. Hall, *J. Am. Chem. Soc.* 1957, **79**, 5441.

Experimental Section

General procedure: In a dried 25 mL round-bottomed flask was taken a mixture of aldehyde (1.0 mmol), malononitrile (2.0 mmol) and 20 mol% 4-dimethylaminopyridine (DMAP). It was kept for stirring for 1 h at room temperature. After adding the requisite amine (1.0 mmol) into it, the reaction mixture was left for stirring. A thick precipitate separated out after some time, which was then filtered off through a Büchner funnel and the precipitate was washed with 30 mL of hexane-ethyl acetate (7:3) to remove unreacted starting material, if any. In case of aliphatic aldehydes, after completion of the reaction the solvent was removed in rotary evaporator. It was extracted with dichloromethane (2 x 10 mL), washed with water and dried over anhydrous Na_2SO_4. It was concentrated *in vacuo* and purified through column chromatography.

Crystallographic Description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions.

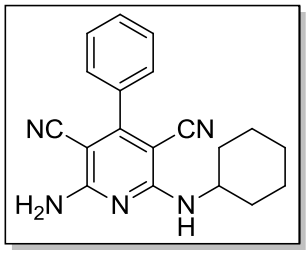
Table 1.Crystal data and structure refinement for **4a** and **6d**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

	Compound (CCDC)	Compound (CCDC)
Identification code	SS-**4a**	SS-**6d**
Empirical formula	‘$C_{19}H_{19}N_5$’	'$C_{20}H_{16}ClN_5$
Formula weight	318.1719	362.1172
Temperature	298(2) K	296(2) K
Wavelength	0.71073Å	0.71073Å

Crystal system	Triclinic	Monoclinic
Space group	P-1	P 21/n
Unit cell dimensions		
a	8.5845(3) Å	12.968(2)Å
b	10.8223(3) Å	10.2902(18)Å
c	12.5073(4) Å	13.385(2)Å
α	84.207(2) º	90.00º
β	72.287(2) º	98.889(12)º
γ	75.180(2) º	90.00º
Volume	1069.73(6) $Å^3$	1764.7(5)$Å^3$
Z	2	4
Density (calculated)	1.228 g/cm^3	1.362g/cm^3
Absorption coefficient	0.172 mm^{-1}	0.230 mm^{-1}
F(000)	420.0	752
Theta range for data collection	1.71 to 28.42 º	2.04 to 24.99 º
Index ranges	-11<=h<=11, -13<=k<=13, -16<=l<=14	-15<=h<=15, -11<=k<=12, -15<=l<=15
Reflections collected	13065	12046
Independent reflections	5294 R_{int} = 0. 0606	2962 R_{int} = 0.1004
Completeness to θº	98.3 % (θ = 28.42º)	95.4% (θ = 24.99º)
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data / restraints / parameters	5294 / 0 / 268	2962 / 0 / 237
Goodness-of-fit on F2	1.086	1.010
Final R indices [>2sigma(I)]	R_{obs} = 0. 0772, wR_{obs} = 0. 2353	R_{obs} = 0.1537, wR_{obs} = 0.3668
R indices (all data)	R_{all} = 0. 0952, wR_{all} = 0. 2513	R_{all} = 0.1914, wR_{all} = 0.3821
Largest diff. peak and hole	1.109 and -1.204e.$Å^{-3}$	0.964 and -0.525e.$Å^{-3}$

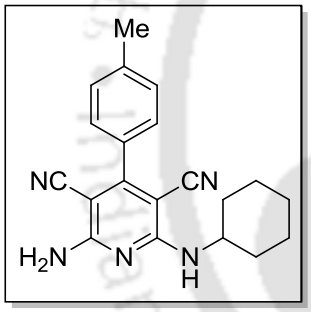
Spectral data

2-Amino-6-(cyclohexylamino)-4-phenylpyridine-3,5-dicarbonitrile (4a):



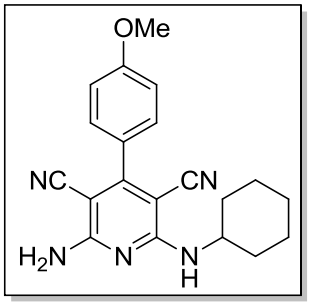
White solid (0.247 g, 78%); Mp 250–254 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.08–1.15 (m, 1H), 1.22–1.31 (m, 2H), 1.38–1.46 (m, 2H), 1.58–1.61 (m, 1H), 1.71–1.80 (m, 4H), 3.96–4.18 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.95 (bs, 2H), 7.40–7.51 (m, 5H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.10, 25.14, 31.79, 49.50, 78.97, 80.43, 116.43, 116.57, 128.26, 128.59, 129.85, 135.22, 158.14, 159.72, 161.00 ppm; IR (KBr): 1559, 1630, 2205, 2925, 3333, 3363, 3484 cm^{-1}; Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07; found: C, 71.98; H, 6.12; N, 21.96. HRMS (ESI) calcd for $C_{19}H_{19}N_5$ (M + H$^+$) 318.1719, found 318.1725

2-Amino-6-(cyclohexylamino)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile (4b):



White solid (0.278 g, 84%); Mp 213–216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.15–1.31 (m, 3H), 1.32–1.48 (m, 2H), 1.59–1.70 (m, 1H), 1.71–1.88 (m, 2H), 1.95–2.09 (m, 2H), 2.40 (s, 3H), 3.95–4.05 (m, 1H), 5.44 (s, 1H), 5.47 (s, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.58, 24.99, 25.57, 32.92, 50.21, 80.04, 82.53, 116.91, 117.07, 128.33, 129.21, 129.53, 129.63, 131.59, 140.85, 158.86, 159.47, 161.22 ppm; IR (KBr): 1508, 1567, 1596, 2209, 2935, 3311, 3383, 3502 cm^{-1}; Anal. Calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found: C, 72.57; H, 6.46; N, 21.04. HRMS (ESI) calcd for $C_{20}H_{21}N_5$ (M + H$^+$) 332.1875, found 332.1867.

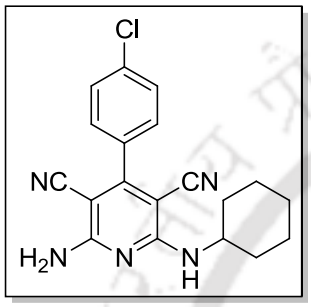
2-Amino-6-(cyclohexylamino)-4-(4-methoxyphenyl)pyridine-3,5-dicarbonitrile (4c):



White solid (0.297 g, 86%); Mp 208–211 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.05–1.19 (m, 1H), 1.20–1.34 (m, 2H), 1.35–1.50 (m, 2H), 1.55–1.65 (m, 1H), 1.67–1.85 (m, 4H), 3.83 (s, 3H), 3.95–4.19 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.28 (bs, 2H), 7.41 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C NMR

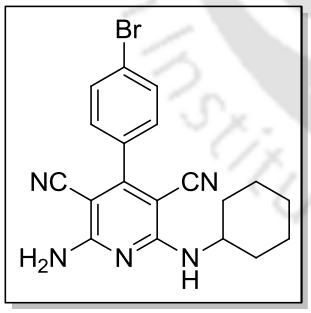
(DMSO-D_6, 150 MHz): δ 25.40, 25.46, 32.14, 49.78, 55.63, 79.28, 80.72, 114.27, 117.00, 117.12, 127.50, 130.28, 158.60, 159.68, 160.77, 161.43 ppm; IR (KBr):1482, 1559, 1626, 2208, 2927, 3307, 3341, 3447 cm^{-1}; Anal. Calcd for $C_{20}H_{21}N_5O$: C, 69.14; H, 6.09; N, 20.16; found: C, 69.26; H, 6.18; N, 20.03. HRMS (ESI) calcd for $C_{20}H_{21}N_5O$ (M + H^+) 348.1824, found 348.1826.

2-Amino-4-(4-chlorophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile (4d):



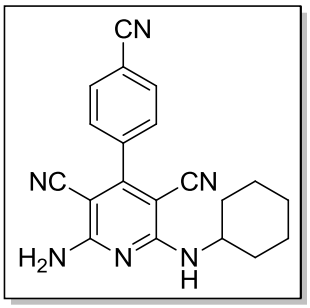
White solid (0.285 g, 81%); Mp 227–230 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.02–1.20 (m, 1H), 1.21–1.32 (m, 2H), 1.38–1.49 (m, 2H), 1.56–1.65 (m, 1H), 1.68–1.72 (m, 4H), 4.00–4.09 (m, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.36 (bs, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.06, 25.09, 31.73, 49.47, 78.87, 80.33, 116.24, 116.37, 128.69, 128.82, 130.24, 130.34, 134.04, 134.70, 158.00, 158.52, 160.86 ppm; IR (KBr): 1480, 1539, 1629, 2208, 2936, 3311, 3328, 3471 cm^{-1}; Anal. Calcd for $C_{19}H_{18}ClN_5$: C, 64.86; H, 5.16; N, 19.91; found: C, 64.97; H, 5.27; N, 19.78. HRMS (ESI) calcd for $C_{19}H_{18}ClN_5$ (M + H^+) 352.1329, found 352.1336.

2-Amino-4-(4-bromophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile (4e):



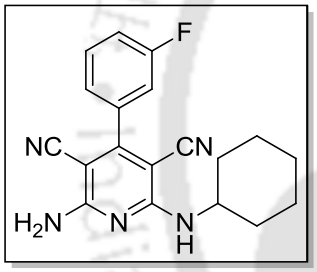
White solid (0.301 g, 76%); Mp 239–242 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.06–1.15 (m, 1H), 1.21–1.31 (m, 2H), 1.38–1.47 (m, 2H), 1.57–1.63 (m, 1H), 1.69–1.82 (m, 4H), 3.85–4.10 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.36 (bs, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.08, 25.11, 31.75, 49.51, 78.80, 80.28, 116.27, 116.40, 123.46, 130.47, 130.55, 131.66, 131.79, 134.44, 158.01, 158.60, 160.88 ppm; IR (KBr): 1479, 1551, 1628, 2208, 2937, 3225, 3309, 3472 cm^{-1}; Anal. calcd for $C_{19}H_{18}BrN_5$: C, 57.59; H, 4.58; N, 17.67; found: C, 57.68; H, 4.67; N, 17.56. HRMS (ESI) calcd for $C_{19}H_{18}BrN_5$ (M +H^+) 396.0824, found 396.0828.

2-Amino-4-(4-cyanophenyl)-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile (4g):



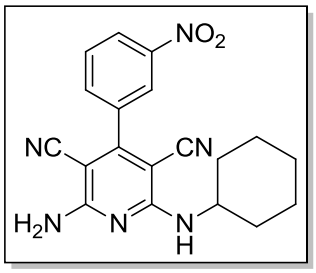
Yellow solid (0.229g, 67%); Mp 221–223 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.79–0.91 (m, 2H), 1.35–1.46 (m, 2H), 1.58–1.61 (m, 2H), 1.77–1.82 (m, 2H), 1.96–2.08 (m, 2H), 3.85–4.10 (m, 1H), 5.48 (d, *J* = 7.8 Hz, 1H), 5.53 (s, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.01, 25.61, 32.95, 50.52, 79.85, 80.53, 114.62, 116.05, 116.24, 118.12, 129.43, 132.90, 138.92, 157.20, 158.70, 161.08 ppm; IR (KBr): 1498, 1577, 1625, 2208, 2932, 3222, 3327 cm^{-1}; Anal. calcd for $C_{20}H_{18}N_6$: C, 70.16; H, 5.30; N, 24.54; found: C, 70.24; H, 3.43; N, 24.41. MS (ESI) calcd for $C_{20}H_{18}N_6$ (M +H^+) 343.1671, found 343.2391.

2-Amino-6-(cyclohexylamino)-4-(3-fluorophenyl)pyridine-3,5-dicarbonitrile (4h):



White solid (0.241 g, 72%); Mp 264–268 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.06–1.15 (m, 1H), 1.20–1.31 (m, 2H), 1.38–1.49 (m, 2H), 1.57–1.62 (m, 1H), 1.69–1.85 (m, 4H), 3.98–4.09 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.34–7.40 (m, 2H), 7.55–7.61 (m, 1H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.06, 25.09, 31.71, 49.47, 78.89, 80.36, 115.35, 115.51, 116.14, 116.28, 116.59, 116.72, 124.56, 130.80, 130.86, 137.31, 137.37, 157.96, 158.28, 160.83, 160.89, 165.52 ppm; IR (KBr):1479, 1559, 1630, 2203, 2926, 3375, 3416, 3490 cm^{-1}; Anal. Calcd for $C_{19}H_{18}FN_5$: C, 68.04; H, 5.41; N, 20.88; found: C, 68.13; H, 5.48; N, 20.79. HRMS (ESI) calcd for $C_{19}H_{18}FN_5$ (M +H^+) 336.1624, found 336.1631.

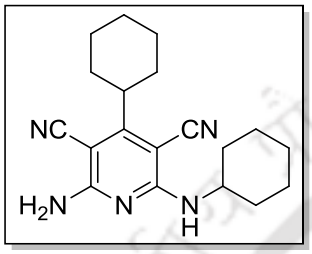
2-Amino-6-(cyclohexylamino)-4-(3-nitrophenyl)pyridine-3,5-dicarbonitrile (4i):



White solid (0.235 g, 65%); Mp 210–213 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 1.04–1.18 (m, 1H), 1.19–1.36 (m, 2H), 1.38–1.50 (m, 2H), 1.55–1.68 (m, 1H), 1.69–1.84 (m, 4H), 3.98–4.11 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.43 (s, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.34–7.42 (m, 1H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.09, 31.75, 49.59, 78.97,

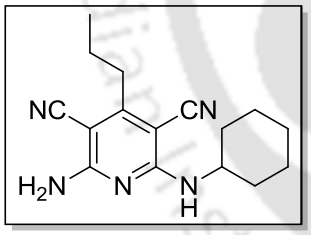
80.48, 116.16, 116.28, 123.37, 124.70, 130.56, 135.18, 136.72, 147.67, 157.42, 157.97, 160.85 ppm; IR (KBr): 1347, 1559, 1653, 2207, 2925, 3331, 3465, 3496 cm^{-1}; Anal. Calcd for $C_{19}H_{18}N_6O_2$: C, 62.97; H, 5.01; N, 23.19; found: C, 63.11; H, 5.18; N, 23.28. HRMS (ESI) calcd for $C_{19}H_{18}N_6O_2$ (M +H^+) 363.1569, found 363.8621.

2-Amino-4-cyclohexyl-6-(cyclohexylamino)pyridine-3,5-dicarbonitrile (4j):



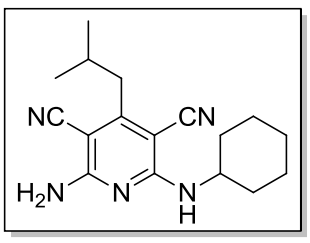
Semi solid (0.223 g, 69%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.07–1.24 (m, 3H), 1.25–1.42 (m, 4H), 1.59–1.64 (m, 2H), 1.65–1.80 (m, 5H), 1.82–1.86 (m, 2H), 1.87–2.10 (m, 4H), 2.83–2.96 (m, 1H), 3.85–3.98 (m, 1H), 5.29 (s, 1H), 5.35 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.98, 25.43, 25.63, 26.52, 30.09, 32.97, 44.94, 50.11, 79.08, 81.64, 116.96, 117.27, 159.27, 161.68, 165.45 ppm; IR (KBr): 1483, 1572, 1631, 2215, 2199, 2926, 3218, 3317, 3403 cm^{-1}; Anal. Calcd for $C_{19}H_{25}N_5$: C, 70.56; H, 7.79; N, 21.65; found: C, 70.65; H, 7.86; N, 21.52. HRMS (ESI) calcd for $C_{19}H_{25}N_5$ (M + H^+) 324.2188, found 324.2194.

2-Amino-6-(cyclohexylamino)-4-propylpyridine-3,5-dicarbonitrile (4k):



Solid (0.175 g, 62%); Mp 180–183 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.89–0.97 (m, 1H), 1.02 (t, *J* = 7.8 Hz, 3H), 1.06–1.25 (m, 3H), 1.32–1.42 (m, 2H), 1.61–1.67 (m, 1H), 1.68–1.79 (m, 3H), 1.93–2.00 (m, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 3.88–3.98 (m, 1H), 5.28 (d, *J* = 7.8 Hz, 1H), 5.34 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.04, 23.28, 25.03, 25.66, 33.06, 36.01, 50.18, 80.41, 82.87, 116.37, 116.55, 158.84, 161.07, 162.05 ppm; IR (KBr): 1465, 1582, 1628, 2206, 2220, 2854, 3307, 3353, 3495 cm^{-1}; Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71; found: C, 67.94; H, 7.61; N, 24.58. MS (ESI) calcd for $C_{16}H_{21}N_5$ (M + H^+) 284.1875, found 284.2983.

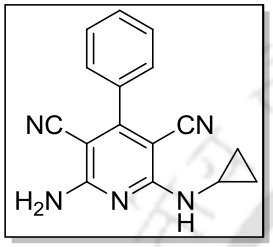
2-Amino-6-(cyclohexylamino)-4-isobutylpyridine-3,5-dicarbonitrile (4l):



Solid (0.198 g, 67%); Mp 174–177 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.01 (d, *J* = 6.6 Hz, 6H), 1.16–1.27 (m, 2H), 1.32–1.41 (m, 2H), 1.61–1.69 (m, 2H), 1.78–1.80 (m, 2H), 1.94–2.00 (m,

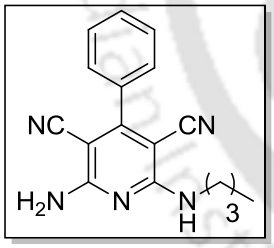
2H), 2.08–2.16 (m, 1H), 2.63 (d, *J* = 7.8 Hz, 2H), 3.89–3.98 (m, 1H), 5.28 (d, *J* = 7.8 Hz, 1H) 5.33 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 22.56, 25.04, 25.67, 29.88, 33.07, 42.83, 50.20, 80.93, 83.43, 116.57, 116.76, 158.81, 161.02, 161.17 ppm; IR (KBr): 1484, 1581, 1629, 2202, 2218, 2927, 3216, 3372, 3499 cm^{-1}; Anal. Calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55; found: C, 68.78; H, 7.92; N, 23.67.

2-Amino-6-(cyclopropylamino)-4-phenylpyridine-3,5-dicarbonitrile (4m):



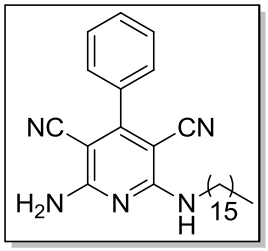
White solid (0.185 g, 67%); Mp 245–248 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 0.64–0.79 (m, 4H), 2.88–3.00 (m, 1H), 7.30–7.46 (m, 2H), 7.46–7.50 (m, 1H), 7.51–7.60 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 100 MHz): δ 6.41, 24.67, 79.50, 80.53, 116.22, 116.47, 128.27, 128.53, 129.79, 135.12, 159.55, 160.22, 160.87 ppm; IR (KBr): 1481, 1510, 1628, 2203, 3327, 3371, 3488 cm^{-1}; Anal. Calcd for $C_{16}H_{13}N_5$: C, 69.80; H, 4.76; N, 25.44; found: C, 69.91; H, 4.83. N, 25.36. HRMS (ESI) calcd for $C_{16}H_{13}N_5$ (M +H$^+$) 276.1249, found 276.1247.

2-Amino-6-(butylamino)-4-phenylpyridine-3,5-dicarbonitrile (4n):



White solid (0.217 g, 74%); Mp 175–177 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 0.81–0.95 (m, 3H), 1.25–1.41 (m, 2H), 1.45–1.62 (m, 2H), 3.38–3.45 (m, 2H), 5.40 (s, 2H), 5.53 (s, 1H), 7.40–7.52 (m, 5H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 13.93, 20.18, 31.09, 41.43, 80.26, 82.69, 116.72, 116.88, 128.46, 129.00, 130.20, 130.65, 134.52, 159.35, 159.77, 161.24 ppm; IR (KBr): 1484, 1559, 1653, 2202, 2925, 3337, 3350, 3460 cm^{-1}; Anal. Calcd for $C_{17}H_{17}N_5$: C, C, 70.08; H, 5.88; N, 24.04; found: C, 70.17; H, 5.97; N, 24.16.

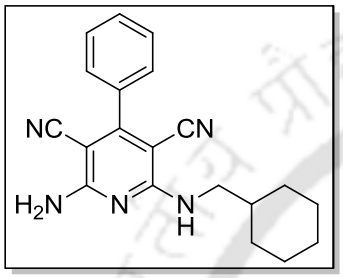
2-Amino-6-(hexadecylamino)-4-phenylpyridine-3,5-dicarbonitrile (4o):



White solid (0.285 g, 62%); Mp 90–94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.75–0.88 (m, 3H), 1.09–1.38 (m, 26H), 1.42–1.59 (m, 2H), 3.30–3.42 (m, 2H), 5.46 (s, 2H), 5.62 (s, 1H), 7.38–7.46 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.25, 22.81, 25.10, 27.00,

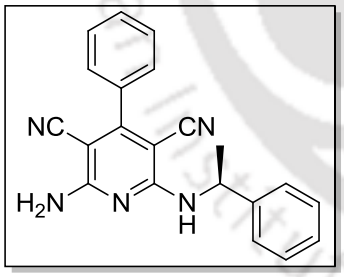
29.37, 29.44, 29.49, 29.67, 29.74, 29.82, 32.05, 36.74, 41.71, 80.19, 82.62, 116.68, 116.84, 128.43, 128.84, 128.94, 129.28, 129.34, 134.52, 159.29, 159.72, 161.22 ppm; IR (KBr): 1485, 1558, 1628, 2208, 2918, 3228, 3332, 3500 cm^{-1}; Anal. Calcd for $C_{29}H_{41}N_5$: C, 75.77; H, 8.99; N, 15.24; found: C, 75.86; H, 9.12; N, 15.15. HRMS (ESI) calcd for $C_{29}H_{41}N_5$ (M + H^+) 460.3440, found 460.3442.

2-Amino-6-((cyclohexylmethyl)amino)-4-phenylpyridine-3,5-dicarbonitrile (4p):



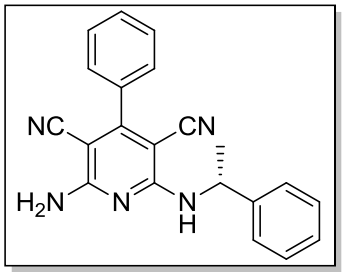
Yellow solid (0.242 g, 73%); Mp 187–191 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.94–1.03 (m, 2H), 1.12–1.31 (m, 2H), 1.55–1.66 (m, 2H), 1.66–1.72 (m, 1H), 1.72–1.84 (m, 4H), 3.33 (t, *J* = 6.6 Hz, 2H), 5.47 (s, 1H), 5.68 (s, 2H), 7.48–7.57 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 25.92, 26.50, 31.00, 37.79, 47.80, 80.27, 82.70, 116.71, 116.86, 128.44, 128.99, 130.64, 134.51, 159.32, 159.91, 161.17 ppm; IR (KBr): 1482, 1558, 1627, 2203, 2925, 3353, 3369, 3488 cm^{-1}; Anal. Calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13; found: C, 72.53; H, 6.48; N, 21.27. HRMS (ESI) calcd for $C_{20}H_{21}N_5$ (M + H^+) 332.1875, found 332.1871.

(S)-2-Amino-4-phenyl-6-((1-phenylethyl)amino)pyridine-3,5-dicarbonitrile (4q):



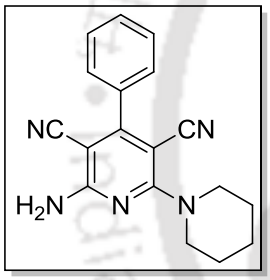
Yellow solid (0.251 g, 74%); Mp 220–223 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.53 (d, *J* = 6.6 Hz, 3H), 5.39–5.45 (m, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.42–7.47 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.50–7.54 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 1H) ppm; ^{13}C NMR (DMSO-D_6, 100 MHz): δ 21.29, 49.45, 79.32, 80.40, 116.32, 116.48, 126.75, 126.78, 128.18, 128.19, 128.28, 128.59, 129.87, 135.16, 144.20, 158.07, 159.92, 160.76 ppm; IR (KBr): 1553, 1622, 2209, 3217, 3339, 3475 cm^{-1}; Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63; found: C, 74.44; H, 5.12; N, 20.57. HRMS (ESI) calcd for $C_{21}H_{17}N_5$ (M + H^+) 340.1562, found 340.1573.

(R)-2-Amino-4-phenyl-6-((1-phenylethyl)amino)pyridine-3,5-dicarbonitrile (4r):



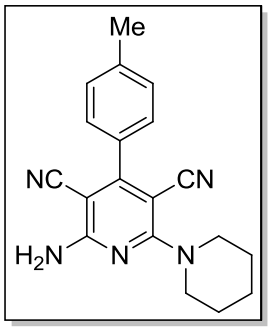
Yellow solid (0.262 g, 77%); Mp 217–219 °C; ^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 1.53 (d, *J* = 6.8 Hz, 3H), 5.37–5.50 (m, 1H), 7.20–7.26 (m, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.42–7.48 (m, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.50–7.63 (m, 3H), 7.72 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C NMR (DMSO-D$_6$, 150 MHz): δ 21.22, 49.41, 79.31, 80.40, 116.24, 116.39, 126.69, 128.12, 128.22, 128.51, 129.78, 135.13, 144.13, 158.03, 159.83, 160.71 ppm; IR (KBr): 1487, 1553, 1622, 2209, 3217, 3339, 3475 cm^{-1}; Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.32; H, 5.05; N, 20.63; found: C, 74.41; H, 5.15; N, 20.51. HRMS (ESI) calcd for $C_{26}H_{26}N_4O_3$ (M + H$^+$) 340.1562, found 340.1565.

2-Amino-4-phenyl-6-(piperidin-1-yl)pyridine-3,5-dicarbonitrile (4s):



Yellow solid (0.252 g, 83%); Mp 199–203 °C; ^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 1.45–1.76 (m, 6H), 3.61–3.78 (m, 4H), 7.36–7.60 (m, 5H) ppm; ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 23.87, 25.54, 48.41, 80.85, 81.50, 116.16, 117.72, 128.50, 128.61, 129.91, 135.35, 159.70, 160.66, 161.76 ppm; IR (KBr): 1025, 1489, 1568, 1625, 2202, 3414 cm^{-1}; Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09; found: C, 71.34; H, 5.57; N, 23.16. HRMS (ESI) calcd for $C_{18}H_{17}N_5$ (M + H$^+$) 304.1562, found 304.1571.

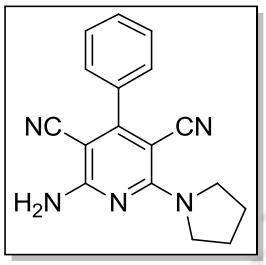
2-Amino-6-(piperidin-1-yl)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile (4t):



White solid (0.273 g, 85%); Mp 208–210 °C; ^{1}H NMR (DMSO-D$_6$, 600 MHz): δ 1.67–1.78 (m, 6H), 2.49 (s, 3H), 3.78–3.83 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 2H) ppm; ^{13}C NMR (DMSO-D$_6$, 150 MHz): δ 20.95, 23.93, 25.60, 48.49, 80.80, 81.52, 116.36, 117.90, 128.68, 129.12, 132.44, 139.76, 159.83, 160.85, 161.78 ppm; IR (KBr): 1497, 1579, 1623, 2201, 2936, 3221, 3327, 3478 cm^{-1}; Anal. Calcd for $C_{19}H_{19}N_5$: C, 71.90; H, 6.03; N, 22.07;

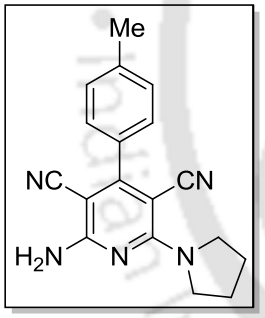
found: C, 72.04; H, 6.14; N, 22.21. HRMS (ESI) calcd for $C_{19}H_{19}N_5$ (M + H^+) 318.1719, found 318.1718.

2-Amino-4-phenyl-6-(pyrrolidin-1-yl)pyridine-3,5-dicarbonitrile (4u):



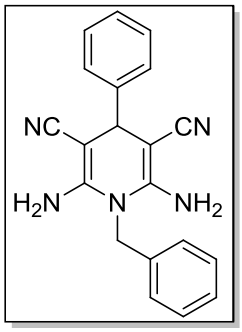
White solid (0.228 g, 79%); Mp 213–215 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.85–1.94 (m, 4H), 3.65–3.76 (m, 4H), 7.26 (bs, 2H), 7.42–7.47 (m, 2H), 7.50–7.56 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 24.92, 49.15, 80.01, 80.17, 116.47, 118.18, 128.45, 128.50, 129.74, 135.57, 157.19, 159.59, 161.59 ppm; IR (KBr): 1487, 1531, 1624, 2209, 3217, 3319, 3475 cm^{-1}; Anal. Calcd for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.21; found: C, 70.68; H, 5.31; N, 24.13. HRMS (ESI) calcd for $C_{17}H_{15}N_5$ (M + H^+) 290.1406, found 290.1414

2-Amino-6-(pyrrolidin-1-yl)-4-(*p*-tolyl)pyridine-3,5-dicarbonitrile (4v):



White solid (0.248 g, 82%); Mp 280–283 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 1.85–1.93 (m, 4H), 2.38 (s, 3H), 3.65–3.72 (m, 4H), 7.24 (bs, 2H), 7.30–7.36 (m, 4H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 20.92, 24.89, 49.12, 79.16, 80.13, 116.54, 118.23, 128.41, 129.02, 132.62, 139.41, 157.27, 159.62, 161.56 ppm; IR (KBr): 1487, 1565, 1624, 2195, 2209, 3217, 3319, 3475 cm^{-1}; Anal. Calcd for $C_{18}H_{17}N_5$: C, 71.27; H, 5.65; N, 23.09; found: C, 71.36; H, 5.79; N, 22.94. HRMS (ESI) calcd for $C_{18}H_{17}N_5$ (M + H^+) 304.1562, found 304.1565.

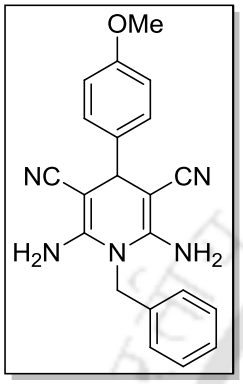
2,6-Diamino-1-benzyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (6a):



White solid (0.310 g, 57%); Mp 221–223 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 3.96 (s, 1H), 4.94 (s, 2H), 6.26 (s, 4H), 6.82–6.88 (m, 2H), 7.11–7.16 (m, 3H), 7.17–7.22 (m, 2H), 7.27–7.33 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.75, 61.30, 121.44, 126.50, 126.63, 127.63, 127.70, 128.16, 128.40, 136.61, 145.17, 152.36 ppm; IR (KBr): 1435, 1651, 2170, 3358, 3379, 3450 cm^{-1}; Anal. Calcd for

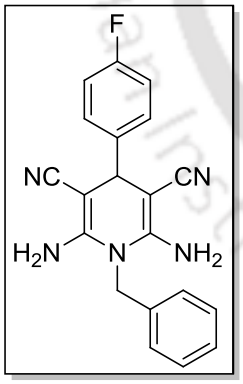
$C_{20}H_{17}N_5$: C, 73.37; H, 5.23; N, 21.39; found: C, 73.42; H, 5.31; N, 21.27. HRMS (ESI) calcd for $C_{20}H_{17}N_5$ (M + H^+) 328.1562, found 328.1573.

2,6-Diamino-1-benzyl-4-(4-methoxyphenyl)-1,4-dihydropyridine -3,5-dicarbonitrile (6b):



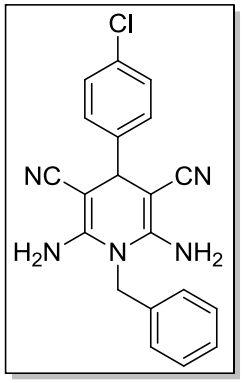
White solid (0.310 g, 64%); Mp 204–206 ^oC; ^1H NMR (DMSO-D_6, 400 MHz): δ 3.70 (s, 3H), 3.93 (s, 1H), 4.95 (s, 2H), 6.24 (s, 4H), 6.71 (d, J = 8.4 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.17–7.22 (m, 2H), 7.30–7.38 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.80, 55.06, 61.78, 113.58, 113.92, 121.53, 126.30, 127.67, 127.75, 128.42, 128.47, 129.80, 136.69, 137.35, 152.22, 158.00 ppm; IR (KBr): 1430, 1667, 2186, 3214, 3311, 3430 cm^{-1}; Anal. Calcd for $C_{21}H_{19}N_5O$: C, 70.57; H, 5.36; N, 19.59; found: C, 70.64; H, 5.45; N, 19.68. HRMS (ESI) calcd for $C_{21}H_{19}N_5O$ (M + H^+) 358.1668, found 358.1659.

2,6-Diamino-1-benzyl-4-(4-fluorophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6c):



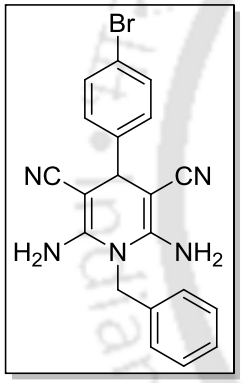
White solid (0.310 g, 53%); Mp 198–201 ^oC; ^1H NMR (DMSO-D_6, 600 MHz): δ 4.01 (s, 1H), 4.95 (s, 2H), 6.29 (s, 4H), 6.84–6.91 (m, 2H), 6.97 (t, *J* = 8.4 Hz, 2H), 7.16–7.24 (m, 2H), 7.30–7.38 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 100 MHz): δ 47.07, 61.47, 114.88, 115.10, 121.48, 127.82, 127.91, 128.63, 136.63, 141.50, 152.57 ppm; IR (KBr): 1429, 1568, 1656, 2161, 2192, 3236, 3340, 3420 cm^{-1}; Anal. Calcd for $C_{20}H_{16}FN_5$: C, 69.55; H, 4.67; N, 20.28; found: C, 69.67; H, 4.76; N, 20.16. HRMS (ESI) calcd for $C_{20}H_{16}FN_5$ (M + H^+) 346.1468, found 346.1470.

2,6-Diamino-1-benzyl-4-(4-chlorophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6d):



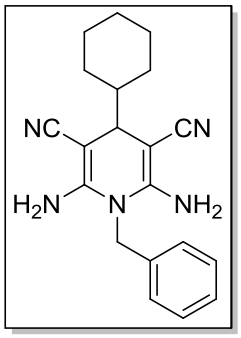
White solid (0.310 g, 59%); Mp 254–256 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 4.03 (s, 1H), 4.97 (s, 2H), 6.31 (s, 4H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.15–7.26 (m, 4H), 7.29–7.38 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 100 MHz): δ 47.05, 61.09, 121.38, 127.82, 127.88, 128.24, 128.60, 131.23, 136.61, 144.28, 152.63 ppm; IR (KBr): 1431, 1560, 1665, 2188, 3224, 3270, 3324, 3440 cm^{-1}; Anal. Calcd for $C_{20}H_{16}ClN_5$: C, 66.39; H, 4.46; N, 19.36; found: C, 66.47; H, 4.55; N, 19.21. HRMS (ESI) calcd for $C_{20}H_{16}ClN_5$ (M + H$^+$) 362.1172, found 362.1175.

2,6-Diamino-1-benzyl-4-(4-bromophenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6e):



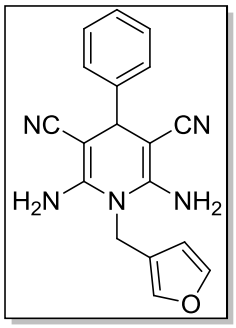
White solid (0.310 g, 58%); Mp 254–256 °C; ^{1}H NMR (DMSO-D_6, 400 MHz): δ 4.00 (s, 1H), 4.95 (s, 2H), 6.33 (s, 4H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.23–7.27 (m, 2H), 7.30–7.38 (m, 5H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 46.99, 60.95, 119.68, 121.36, 127.79, 127.86, 128.59, 128.97, 131.13, 136.58, 144.70, 152.61 ppm; IR (KBr): 1435, 1575, 1652, 2178, 3213, 3257, 3322, 3449 cm^{-1}; Anal. Calcd for $C_{20}H_{16}BrN_5$: C, 59.13; H, 3.97; N, 17.24; found: C, 59.21; H, 4.08; N, 17.11. HRMS (ESI) calcd for $C_{20}H_{16}BrN_5$ (M + H$^+$) 406.0667, found 406.0672.

2,6-Diamino-1-benzyl-4-cyclohexyl-1,4-dihydropyridine-3,5-dicarbonitrile (6f):



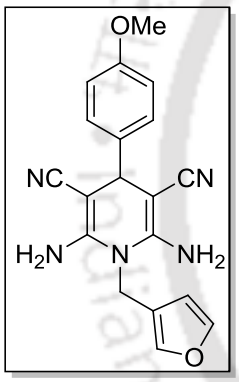
Pale yellow solid (0.170 g, 51%); Mp 213–215 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 0.51–0.60 (m, 1H), 0.62–0.73 (m, 2H), 0.70–0.99 (m, 3H), 1.39–1.44 (m, 2H), 1.45–1.57 (m, 3H), 2.29 (d, *J* = 6.6 Hz, 1H), 4.86 (s, 2H), 6.12 (s, 4H), 7.21–7.24 (m, 2H), 7.25–7.34 (m, 3H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 25.73, 26.11, 29.27, 46.55, 47.47, 60.04, 122.55, 127.84, 128.38, 128.40, 136.71, 153.14 ppm; IR (KBr): 1437, 1568, 1654, 2186, 2930, 3329, 3434, 3463 cm^{-1}; Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00; found: C, 72.17; H, 7.08; N, 21.11.

2,6-Diamino-1-(furan-3-ylmethyl)-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (6g):



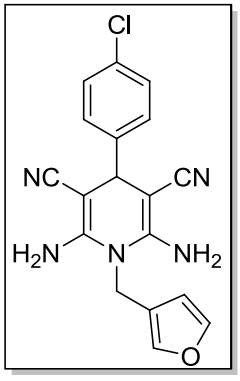
White solid (0.310 g, 62%); Mp 207–210 ^{o}C; ^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 3.87 (s, 1H), 4.98 (s, 2H), 6.29 (s, 4H), 6.25–6.27 (m, 1H), 6.42–6.47 (m, 1H), 7.46–7.6 (m, 5H), 7.64 (s, 1H) ppm; ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 40.83, 62.02, 109.33, 110.45, 121.26, 126.44, 128.25, 142.88, 145.20, 149.61, 152.37 ppm; IR (KBr): 1433, 1649, 2178, 3216, 3322, 3449 cm^{-1}; Anal. calcd for $C_{18}H_{15}N_5O$: C, 68.13; H, 4.76; N, 22.07; found: C, 68.26; H, 4.84; N, 22.16;. HRMS (ESI) calcd for $C_{18}H_{15}N_5O$ (M + H$^+$) 318.1355, found 318.1358.

2,6-Diamino-1-(furan-3-ylmethyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6h):



White solid (0.310 g, 65%); Mp 209–214 ^{o}C; ^{1}H NMR (DMSO-D$_6$, 600 MHz): δ 3.70 (s, 3H), 3.82 (s, 1H), 4.97 (s, 2H), 6.22 (s, 4H), 6.29–6.35 (m, 1H), 6.41–6.49 (m, 1H), 6.67–6.81 (m, 4H), 7.67 (s, 1H) ppm; ^{13}C NMR (DMSO-D$_6$, 150 MHz): δ 40.87, 55.03, 62.45, 109.31, 110.50, 113.66, 121.35, 127.52, 137.43, 149.33, 152.20, 157.93 ppm; IR (KBr): 1435, 1508, 1649, 2170, 2187, 3219, 3321, 3448 cm^{-1}; Anal. Calcd for $C_{19}H_{17}N_5O_2$: C, 65.69; H, 4.93; N, 20.16; found: C, 65.77; H, 5.14; N, 20.02. HRMS (ESI) calcd for $C_{19}H_{17}N_5O_2$ (M + H$^+$) 348.1460, found 348.1470.

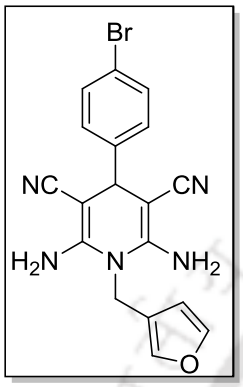
2,6-Diamino-4-(4-chlorophenyl)-1-(furan-3-ylmethyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6i):



White solid (0.310 g, 61%); Mp >300 ^{o}C; ^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 3.86 (s, 1H), 4.98 (s, 2H), 6.23–6.26 (m, 1H), 6.35 (s, 4H), 6.41–6.45 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.70 (s, 1H) ppm; ^{13}C NMR (DMSO-D$_6$, 100 MHz): δ 40.98, 61.65, 109.43, 110.57, 121.08, 128.26, 131.05, 143.03, 144.25, 149.54, 152.54 ppm; IR (KBr): 1432, 1562, 1663, 2187, 3225, 3272, 3324, 3445 cm^{-1}; Anal. Calcd for $C_{18}H_{14}ClN_5O$: C, 61.46; H, 4.01; N, 19.91; found: C,

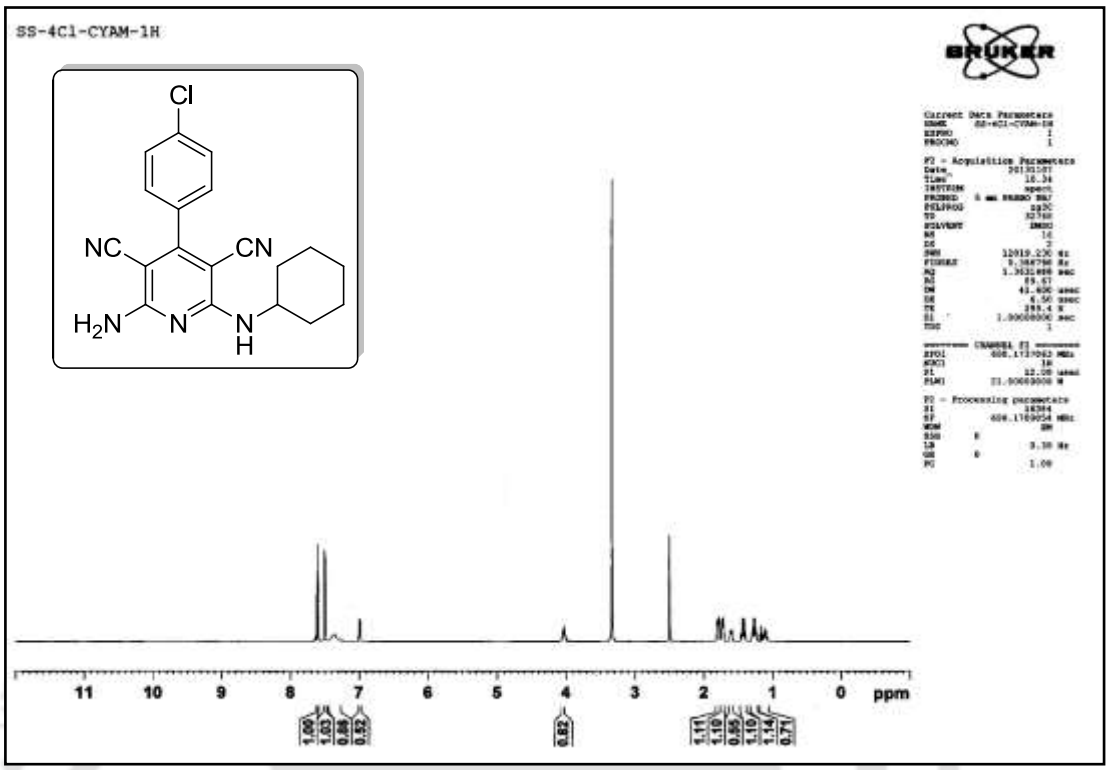
61.54; H, 4.12; N, 20.02. HRMS (ESI) calcd for $C_{18}H_{14}ClN_5O$ (M + H^+) 352.0965, found 352.0973.

2,6-Diamino-4-(4-bromophenyl)-1-(furan-3-ylmethyl)-1,4-dihydropyridine-3,5-dicarbonitrile (6j):

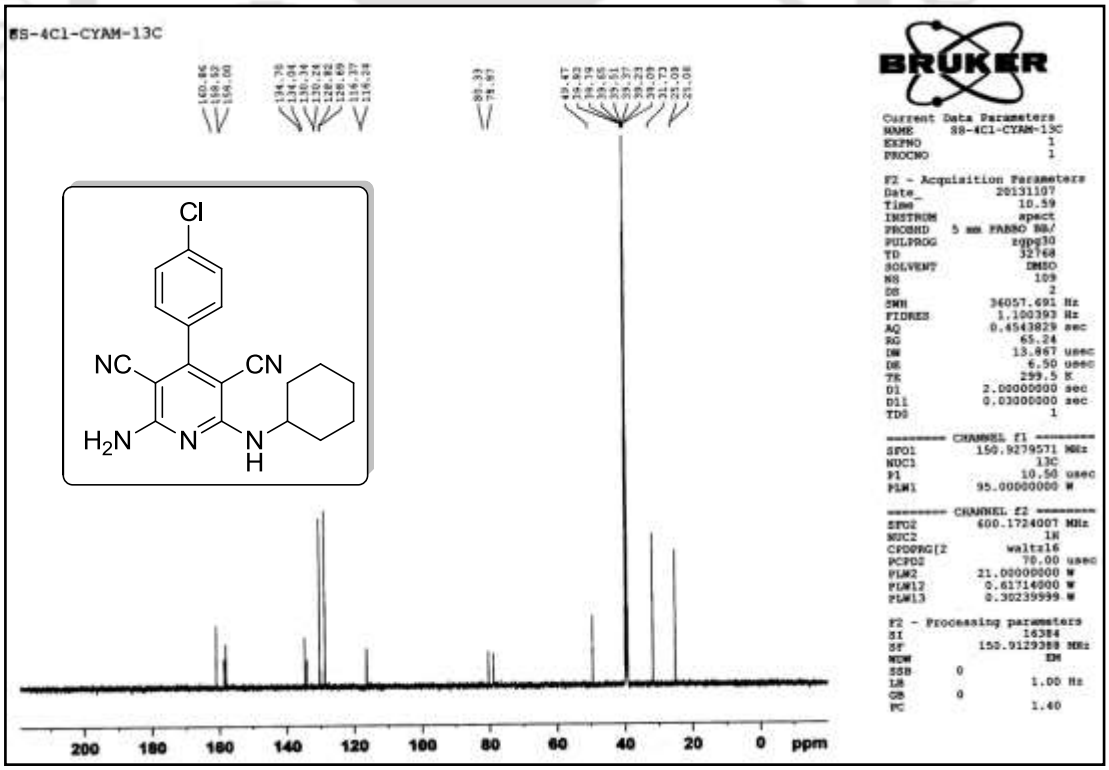


White solid (0.310 g, 59%); Mp > 300 °C; ^{1}H NMR (DMSO-D_6, 600 MHz): δ 3.90 (s, 1H), 4.97 (s, 2H), 6.28–6.32 (m, 1H), 6.33 (s, 4H), 6.43–6.49 (m, 1H), 6.76 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 1H) ppm; ^{13}C NMR (DMSO-D_6, 150 MHz): δ 40.96, 61.54, 109.45, 110.59, 119.55, 121.09, 128.68, 131.16, 143.07, 144.69, 149.53, 152.55 ppm; IR (KBr): 1431, 1559, 1665, 2186, 3224, 3271, 3324, 3440 cm^{-1}; Anal. Calcd for $C_{18}H_{14}BrN_5O$: C, 54.56; H, 3.56; N, 17.67; found: C, 54.64; H, 3.67; N, 17.55; HRMS (ESI) calcd for $C_{18}H_{14}BrN_5O$ (M + H^+) 396.0460 found 396.0469.

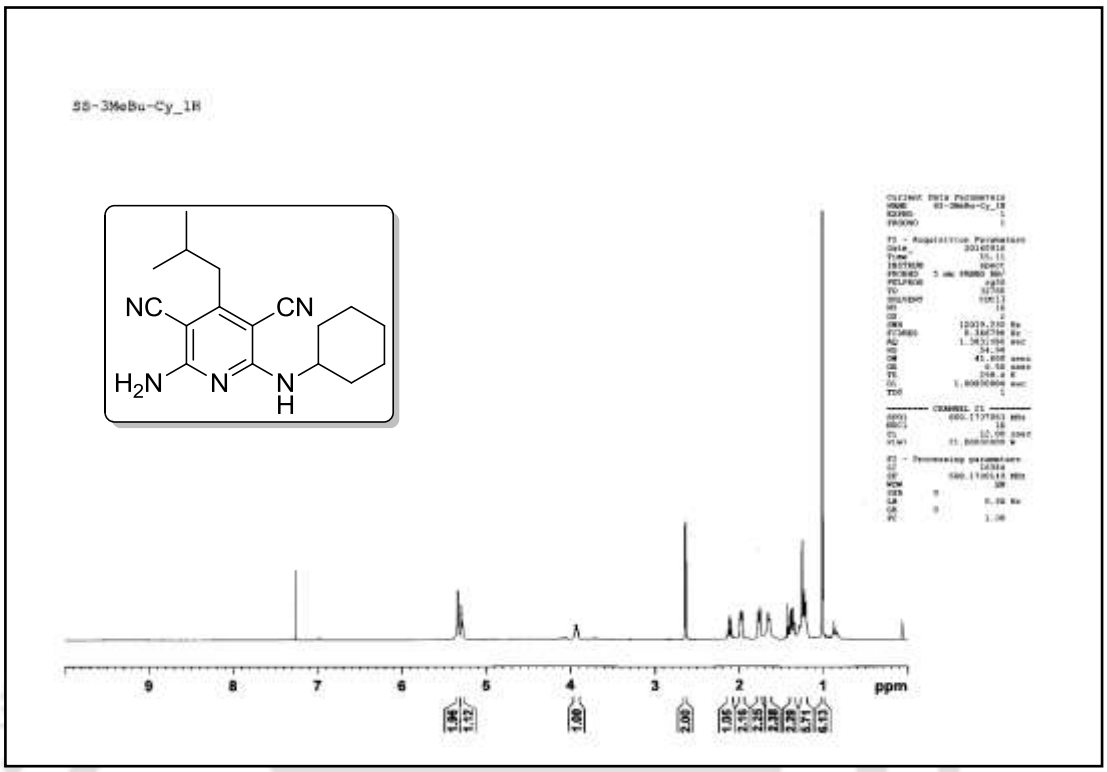
^{1}H-NMR spectra of compound **4d**



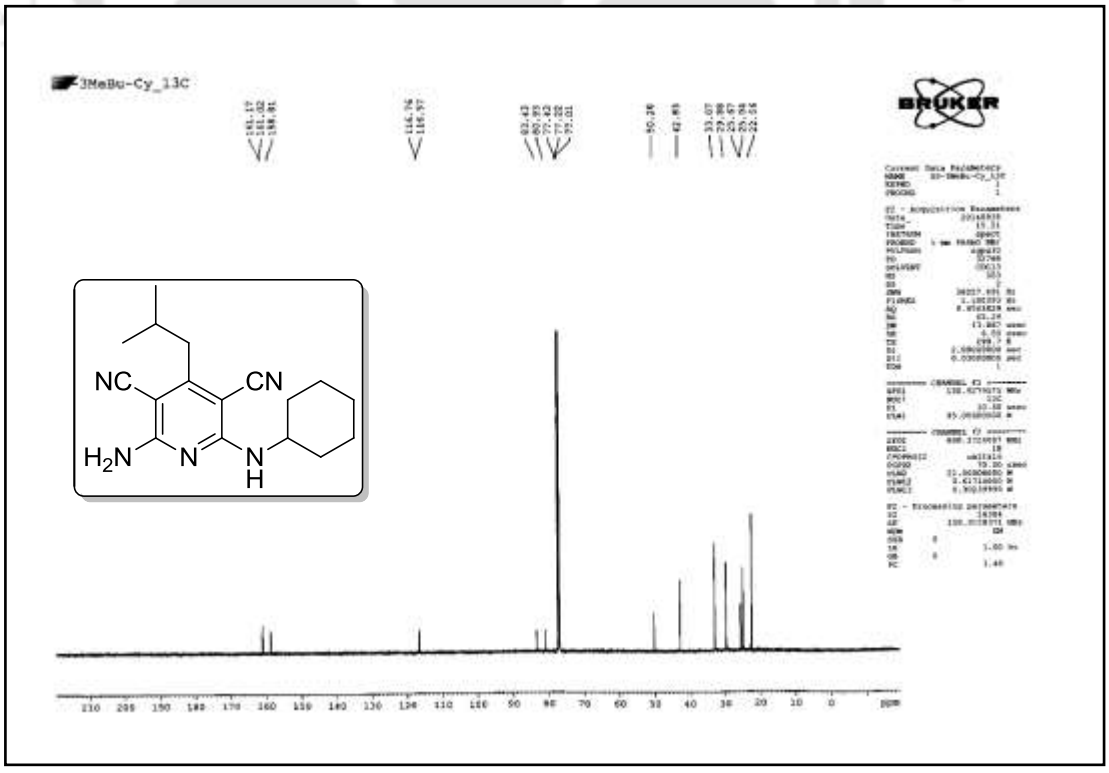
^{13}C-NMR spectra of compound **4d**



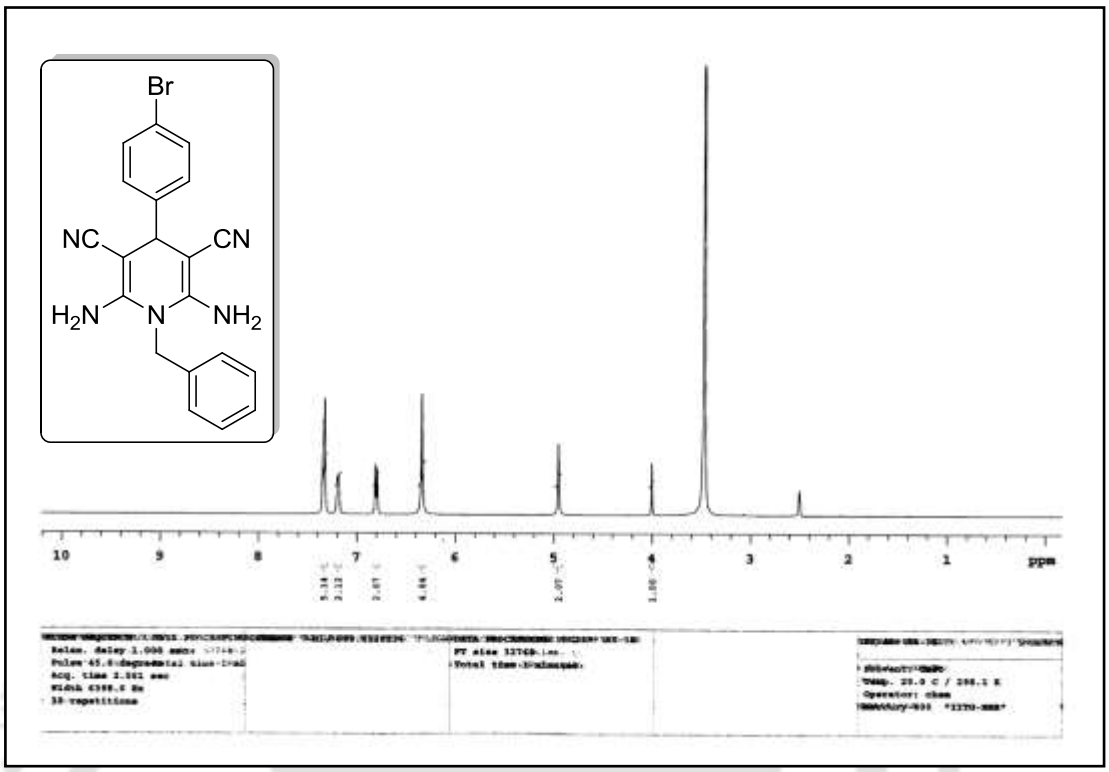
^{1}H-NMR spectra of compound **4l**



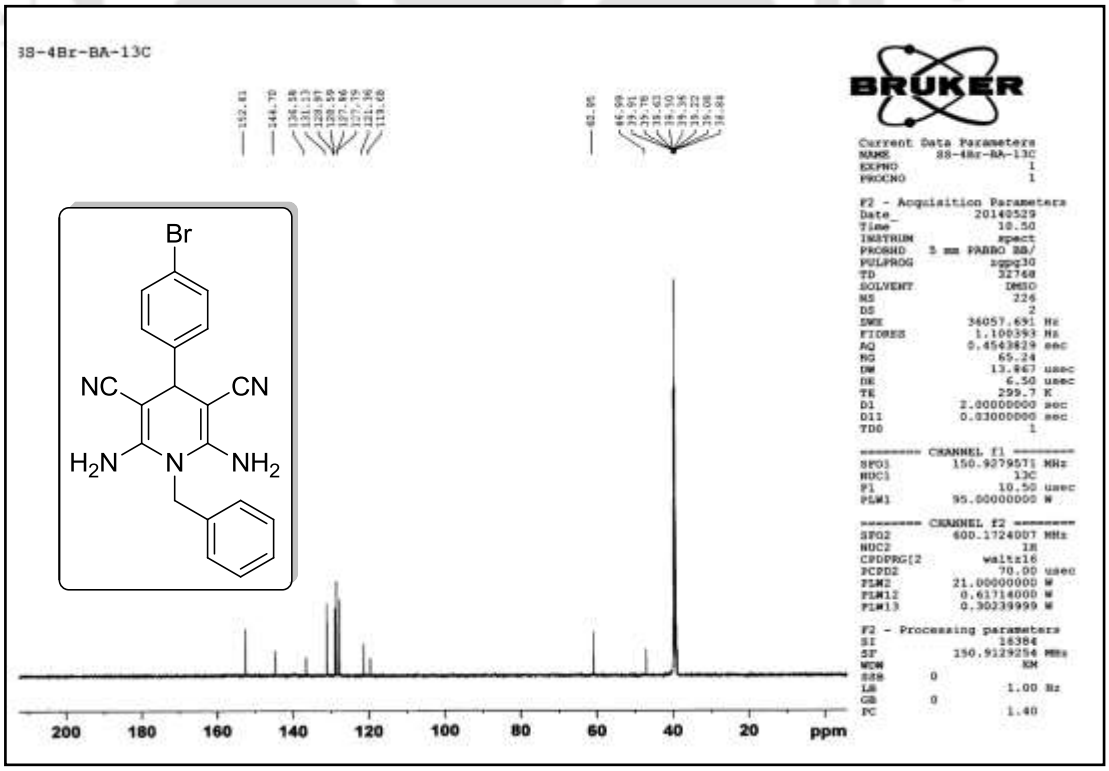
^{13}C-NMR spectra of compound **4l**



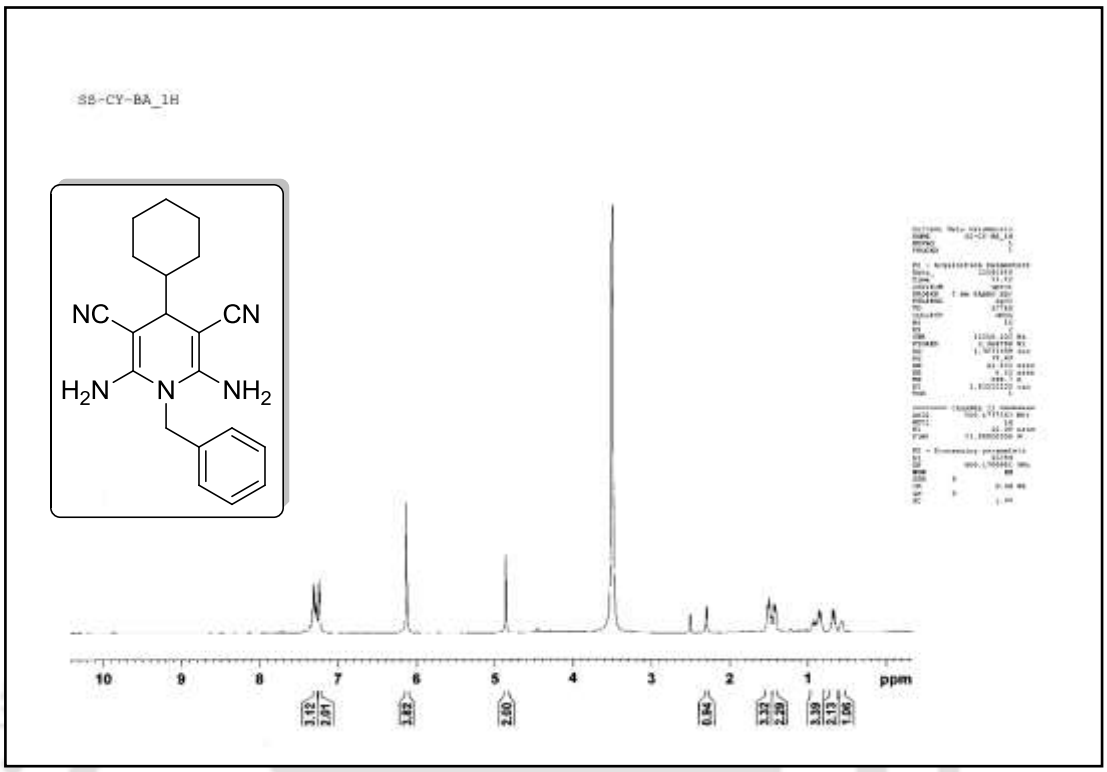
^{1}H-spectra of compound **6e**



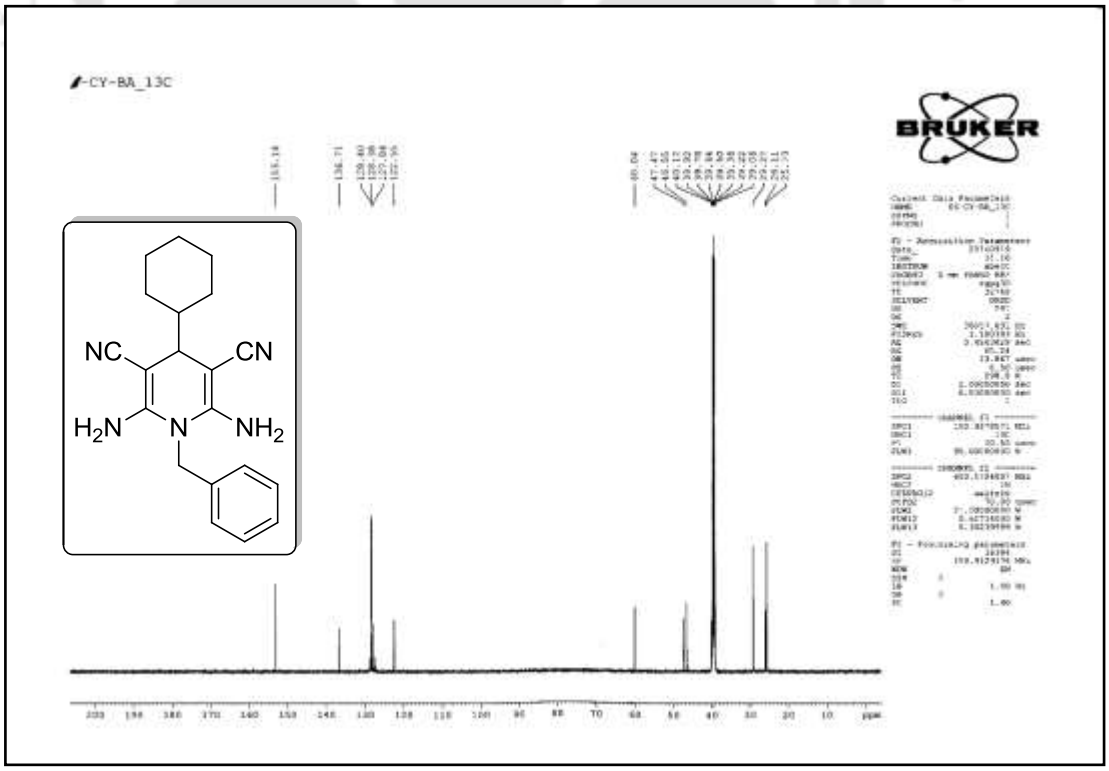
^{13}C-spectra of compound **6e**



^{1}H-spectra of compound **6f**

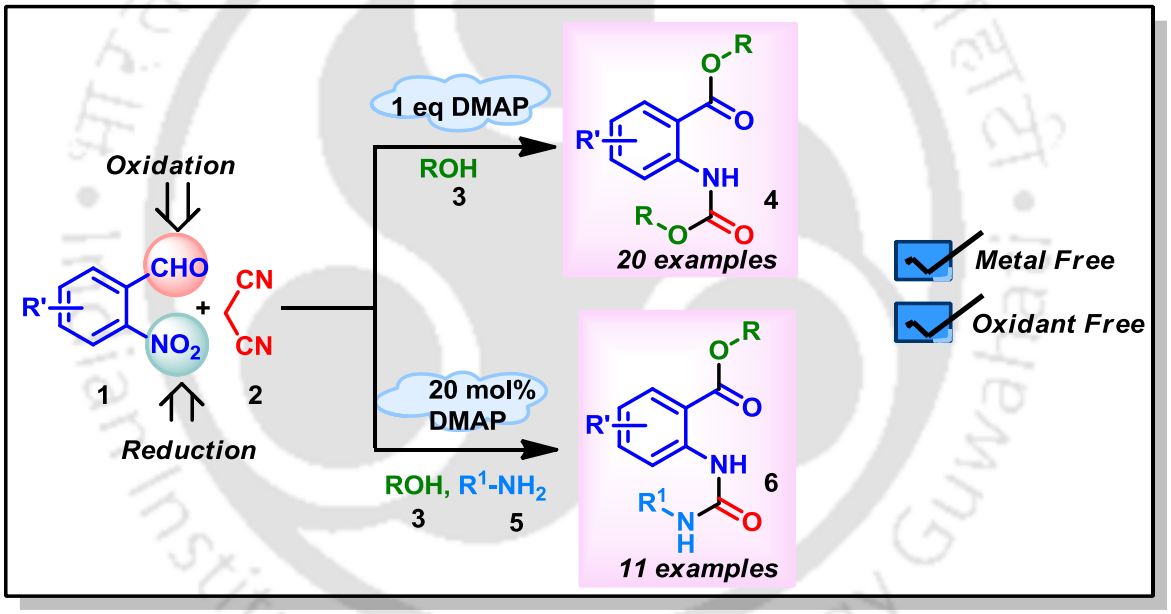


^{13}C-spectra of compound **6f**



Chapter V

Beyond Conventional Routes, an Unprecedented Metal-free Chemoselective Synthesis of Anthranilate Esters



Chapter V

Experimental Section

Beyond Conventional Routes, an Unprecedented Metal-free Chemoselective Synthesis of Anthranilate Esters

CHAPTER V

V. Beyond Conventional Routes, an Unprecedented Metal-Free Chemoselective Synthesis of Anthranilate Esters

V.1. Introduction

Anthranilic acids have been extensively employed as useful key building blocks in a multitude of natural products *viz.* quinazolinones, benzoxazinones, indoles, acridinones, saccharin and they exhibit a broad spectrum of biological activities in medicinal chemistry (Figure 1).[1]

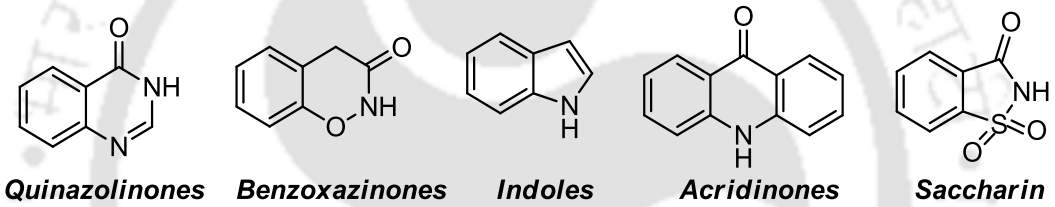


Figure 1. Important molecular skeletons synthesised from anthranilic acids

Ester derivatives of such anthranilic acids *viz. N*,*N*-dimethyl anthranilate (MDA), ethyl anthranilate (EA) and butyl anthranilate (BA) are used commercially in perfume industry as well as flavoring agent (Figure 2). The importance of anthranilic acid esters was recognized by Walbum in 1899 when he reported the occurrence of methyl anthranilate in the oil of neroli.[2] They are also employed as insect repellents as these compounds target the same neurons that respond to DEET (*N*,*N*-Diethyl-*meta*-toluamide). Recently Kain *et al.* reported these anthranilate esters as suitable substitution of DEET as they are less toxic as well as affordable.[3] In this perspective tremendous efforts have been made from the very past for the synthesis of anthranilic acid derivatives through cheap and easy synthetic routes.

Multicomponent reactions (MCRs) have achieved a significant benchmark as they can give a direct access to unexplored territories of chemical entities or discover unique routes for the synthesis of structurally complex scaffolds. Attaining the desired chemoselectivity in such strategies certainly provides additional flavors.[4] Moreover, when these distinct processes are blended with intramolecular redox chemistry, the essence of such reactions

amplifies in many fold.[5] This chapter deals with the metal-free chemoselective synthesis of anthranilate esters *via* an intramolecular redox process.

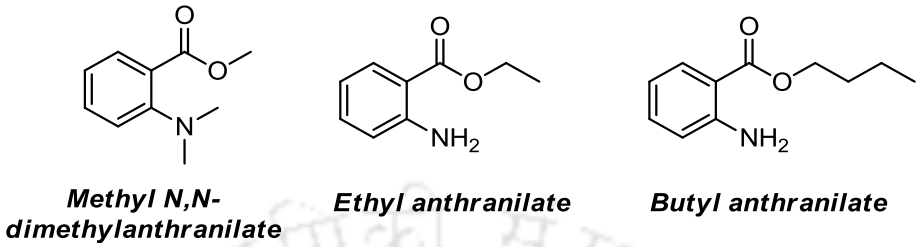
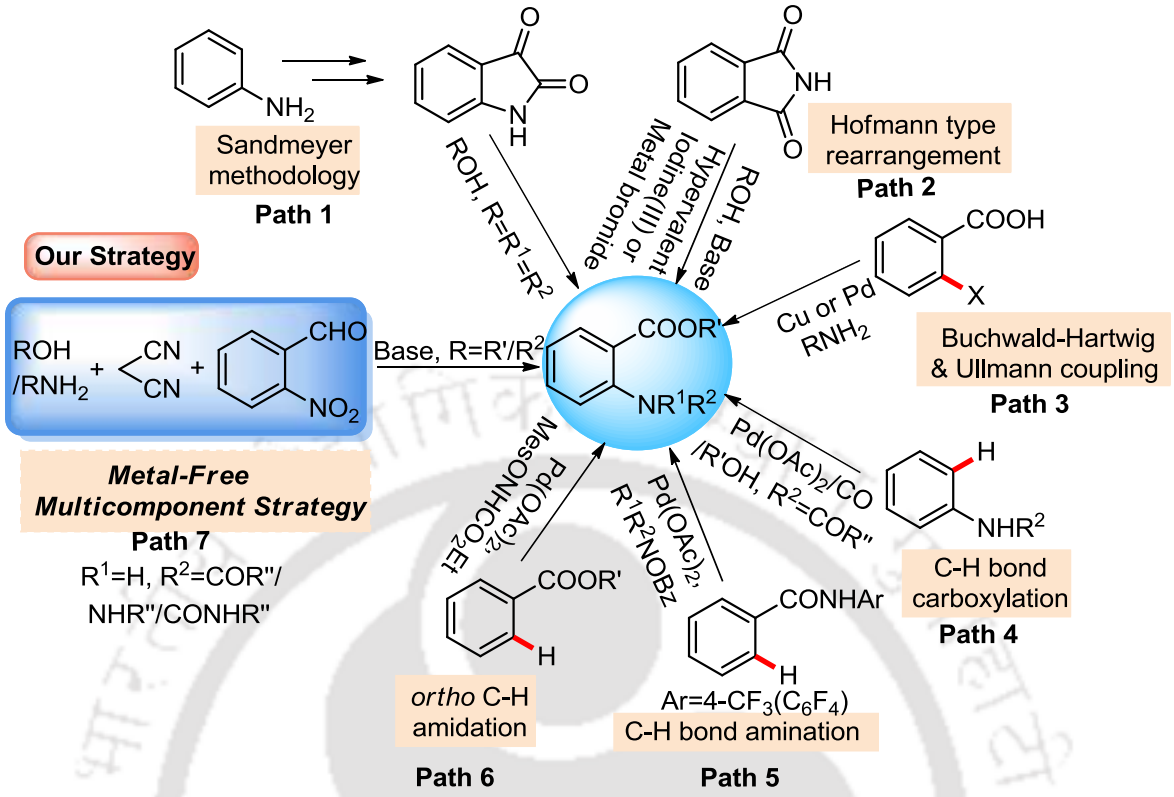


Figure 2. Anthranilate esters used as insect repellents

V.2. Strategies for Synthesis of Anthranilate Esters

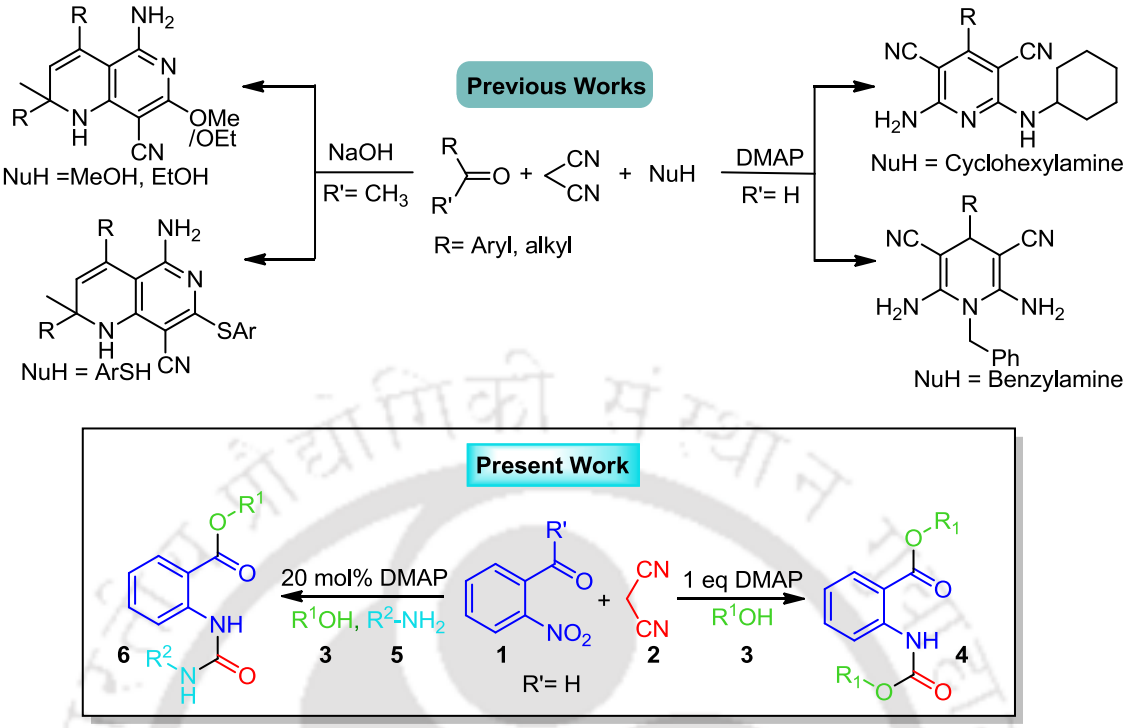
The classical recipe for the synthesis of substituted anthranilic acids is *via* reaction of isatins starting from anilines using the multistep Sandmeyer methodology (Scheme 1, Path 1).[6] Over the years, numerous synthetic strategies have been developed for the construction of anthranilic acid derivatives as follows: Hofmann type rearrangement of aromatic/aliphatic imides using hypervalent iodine (III) and metal bromide (Scheme 1, Path 2)[7] or Buchwald-Hartwig cross-coupling and Ullmann type[8] coupling reactions using *ortho*-halo benzoic acid with arylamines (Scheme 1, Path 3) or C–H functionalization reactions through Pd-catalyzed *N*-directed C–H carboxylation of anilides, *N*-arylureas and *N*-substituted anilines (Scheme 1, Path 4).[9] Very recently anthranilate esters are even synthesized using Pd-catalyzed *ortho* C–H amidation of *N*-aryl benzamides and benzoic acids using their nitrogen (*N*) and oxygen (*O*) donor atoms respectively (Path 5 and 6).[10,11] Unfortunately, all these methods discussed above mostly rely on the use of precious transition metals like Pd and require harsh conditions such as high reaction temperature, CO atmospheric condition or scope for the formation of side products and prolonged reaction time.

Hence, a mild, cheap and metal-free synthetic route is necessary to overcome all these limitations. Herein an unprecedented route for the synthesis of anthranilic acid derivatives has been reported using 2-nitrobenzaldehyde, malononitrile and alcohol or amine *via* a metal and oxidant free multicomponent strategy at room temperature.



Scheme 1. Various routes for the formation of anthranilic acid derivatives

Taking accounts of our earlier studies, the substrate-selective reactions of different carbonyl moieties with malononitriles and nucleophiles under basic environments have shown unique selectivity in every means. We have demonstrated the chemoselective synthesis of pyridine and dihydropyridine skeletons using aldehydes as carbonyl source and varying the nucleophiles from cyclohexylamines to benzylamines in presence of malononitrile (Chapter IV).[12] Switching from aldehydes to ketones in the presence of malononitrile, highly substituted 1,6-naphthyridine moiety was also synthesized by our group using alcohol or thiol as the nucleophilic source (Chapter III).[13] In this context the use of 2-nitrobenzaldehyde instead of simple benzaldehyde as the carbonyl moiety in the presence of malononitrile and amine or alcohol as nucleophilic source provided anthranilate esters in an unprecedented way instead of anticipated pyridine or dihydropyridine skeletons (Scheme 2). In this scenario, simultaneous installation of ester and urethane or urea functionality *via* a C–O and C–N bond formation through a chemoselective intramolecular redox process makes this metal and oxidant free strategy highly attractive and novel over the existing methods.



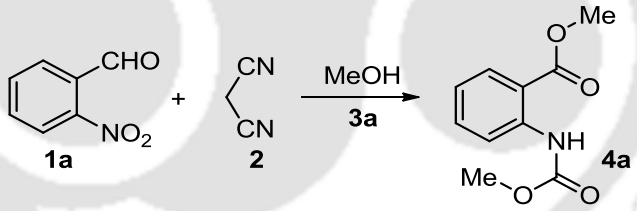
Scheme 2. Substrate dependent selectivity in multicomponent reaction

V.3. Present Work

Buyout by this unusual result, an initial foray was intended using 2-nitrobenzaldehyde as the carbonyl source, malononitrile as nucleophile in MeOH using DMAP as the catalyst. After chromatographic purification, a white semi-solid product (**4a**) was isolated in 31% yield, which was characterized through spectroscopic analysis. In IR spectrum, it showed two characteristic strong absorptions at 1739 and 1692 cm^{-1} due to the carbonyl groups but the strong absorption around 2200 cm^{-1} for –CN group was found to be missing. Similarly, in the ^{1}H NMR spectrum **4a** exhibited two singlets at δ 3.91 and 3.78 due to –OMe groups and in the ^{13}C spectrum peaks at δ 168, 154 stated the presence of the carbonyl type skeleton. It would have expected to exhibit characteristic stretching frequency at 2240 cm^{-1} for the –CN group for the Knoevenagel product (**A**) and in ^{1}H NMR signals at δ 8.97 as a singlet for the Knovenegel proton. These observations indicate that the final product so obtained was methyl 2-(methoxycarbonylamino) benzoate (**4a**), an entirely different compound containing ester and urethane functionality along with two –OMe groups from reactant-cum-solvent MeOH.

To ascertain the optimized conditions, the same set of reactions was carried out using 0.5 equiv., 1 equiv. and 1.5 equiv. of DMAP (Table 1, entries 1-3) successively. It can be stated here that increasing the amount of DMAP from 0.5 equiv. to 1 equiv. effectively increased the yield from 54% to 72% (Table 1, entries 1-2). However, there was no effective improvement of yield when the amount of base was further increased upto 1.5 equiv. (Table 1, entry 3). To examine the effectiveness of other bases, the reaction was screened not only with various other organic bases such as DBU, PPh_3, Et_3N, DMA but also with an inorganic base as NaOH (Table 1, entries 4-8). Unfortunately, DBU and PPh_3 exhibited poor reactivity compared to Et_3N and NaOH. To scrutinize the effect of solvent, the same reaction was carried out with various solvents using MeOH as reactant. It was observed that except for acetonitrile (Table 1, entry 9) other solvents led to lower yield or took prolonged reaction time (Table 1, entries 10-12). As CH_3CN showed competent efficacy as solvent it was concluded that this reaction can also be carried out commendably using alcohol as reactant. It is noteworthy to mention here that in the absence of any base only the Knoevenagel product was obtained along with no traces of our desired anthranilate ester moiety (Table 1, entry 13).

Table 1. Optimization of reaction conditions for the synthesis of anthranilate esters **4a**[a]



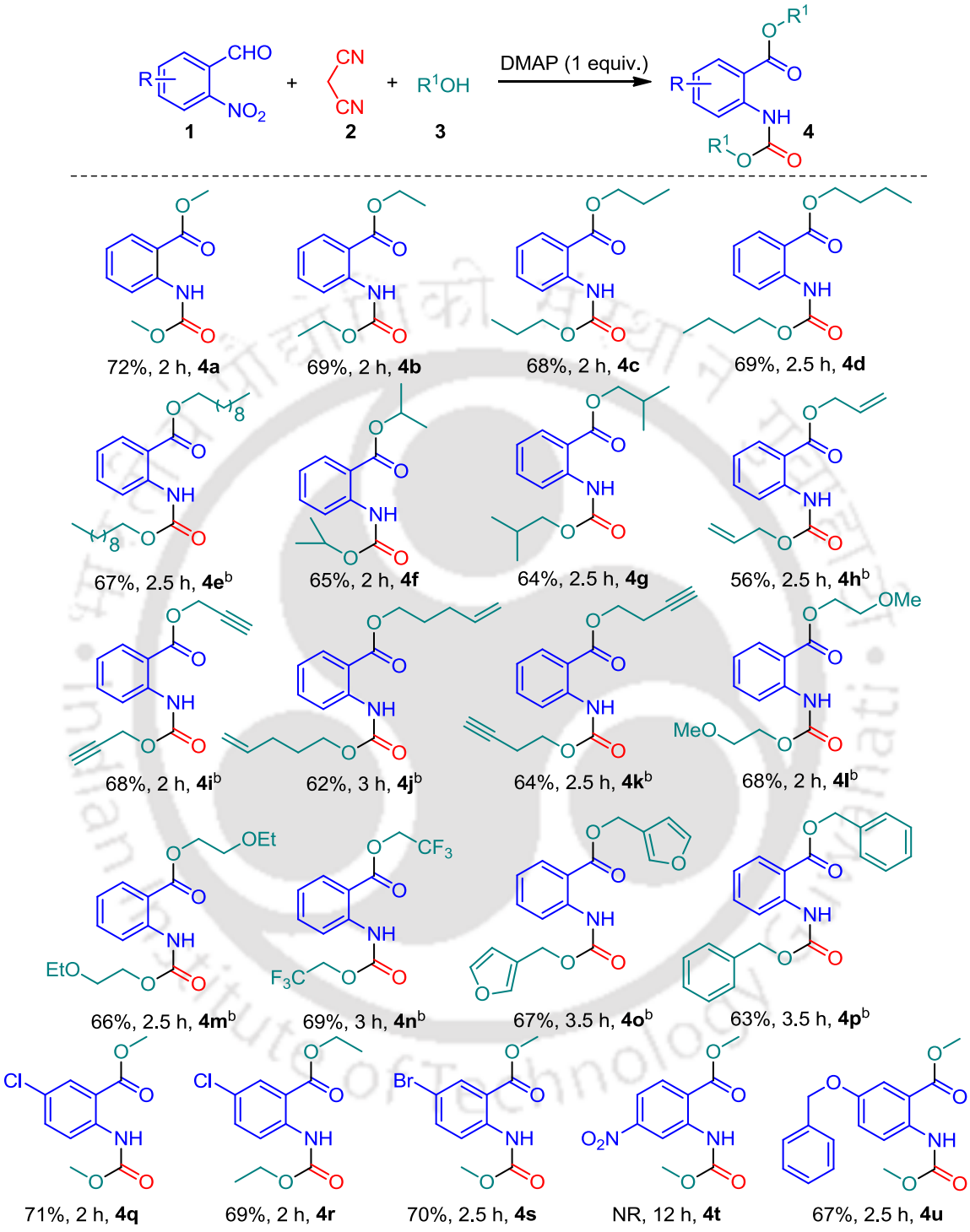
Sl. No.	Catalyst	Amount of catalyst (equiv.)	Solvent	Time (h)	Yield (%)[b]
1	DMAP	0.5	MeOH	3	54
2	**DMAP**	**1.0**	**MeOH**	**2**	**72**
3	DMAP	1.5	MeOH	2	73
4	DBU	1.5	MeOH	5	15
5	PPh_3	1.5	MeOH	4	52
6	Et_3N	1.5	MeOH	3	64
7	DMA	1.5	MeOH	12	---
8	NaOH	1.5	MeOH	3	61
9	DMAP	1.5	CH_3CN[c]	2	71

10	DMAP	1.5	DMF[c]	10	7
11	DMAP	1.5	DCE[c]	5	17
12	DMAP	1.5	H_2O[c]	12	---
13	---	---	MeOH	12	---

[a]Reaction conditions: 2-nitrobenzaldehyde and malononitrile taken in 1:1.5 ratio at rt. [b]Isolated yields. [c]MeOH (2 equiv.) was used as reactant.

With the optimized condition in our hand, the scope of this reaction was explored with various types of alcohol moieties. The reaction was performed with easily available homologous alcohols *viz.* methanol, ethanol, *n*-propanol and *n*-butanol (**3a-d**). Although the yield decreased from methanol to ethanol slightly, but further increase of the length of the straight-chain didn't affect the product yield. Even reactions with long chain such as *n*-decanol provided **4e** with moderate yields under optimized reaction conditions. Next the reaction was performed with alcohols such as isopropyl alcohol, a secondary alcohol and isobutyl alcohol to give desired esters **4f** & **4g** in good yields (Table 2). Unfortunately, when the reaction was further performed with *t*-butanol, no product was formed due to the steric effect of the bulky tertiary butyl group. To observe the effect of sensitive functional groups present in the alcohol skeleton, this reaction was performed in the presence of allyl alcohol, propargyl alcohol, 4-pentene-1-ol and 3-butyene-1-ol (**3h-k**). All these reactions provided our desired product in 56-68% yields. To see the influence of donating property in the alcohols, when the reaction was conducted with 2-methoxyethanol or 2-ethoxyethanol, good to moderate yields (**4l** & **4m**) were observed with the –OMe or –OEt group as substituents in ethanol. But the reaction did not proceed at all with 2-cyanoethanol may be due to the presence of the strongly electron withdrawing cyano (-CN) moiety. Contrary to this observation this reaction provided the desired anthranilate ester **4n** when trifluoroethanol (CF_3CH_2OH) was used under the optimized reaction condition. The use of heteroaromatic and aromatic alcohols such as furfurylalcohol (**3o**) and benzylalcohol (**3p**) also provided the desired anthranilate esters (**4o** & **4p**) with moderate yields. Next reactions of substituted 2-nitrobenzaldehydes were carried out using MeOH and EtOH as nucleophiles under otherwise identical reaction conditions. 5-Chloro- and 5-bromo 2-nitrobenzaldehyde provided the anthranilate esters **4q-s** in good yields. Likewise, the substrate O-benzyl moiety

Table 2. Synthesis of anthranilate esters from various alcohol derivatives[a]

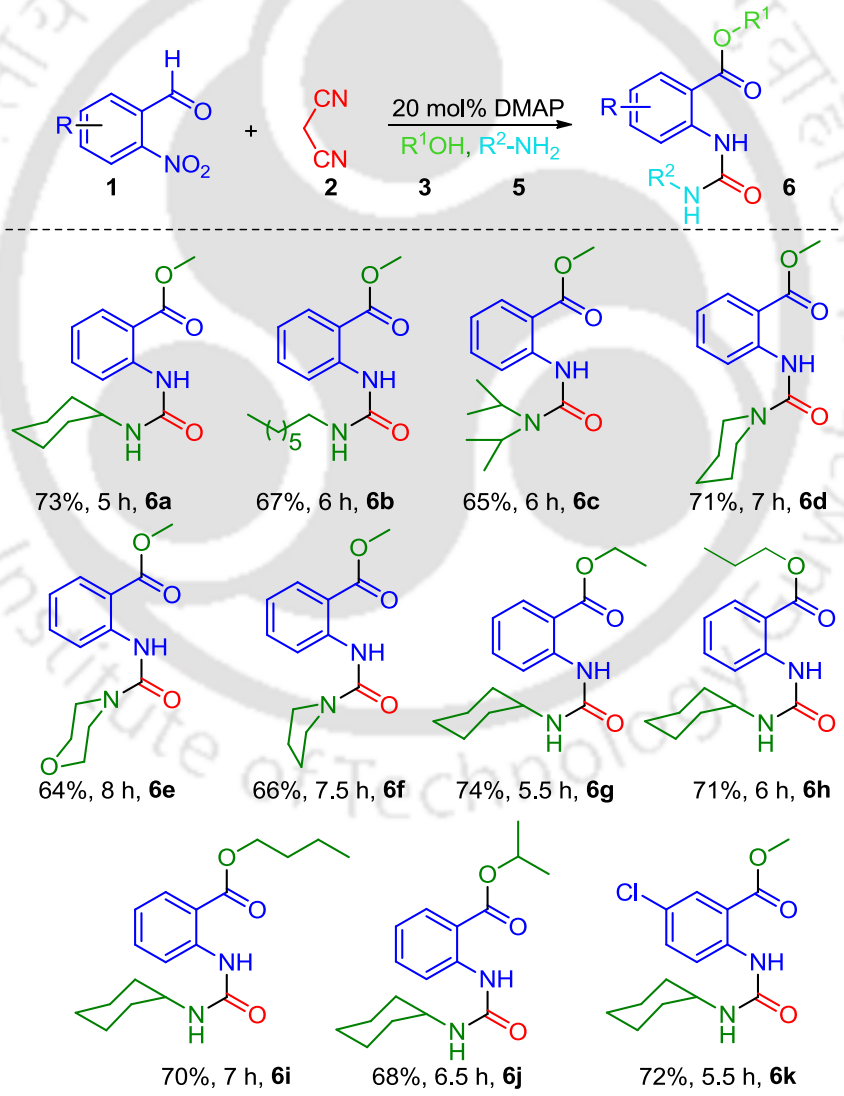


[a]All the reactions were performed with 2-nitrobenzaldehyde (1.0 mmol), malononitrile (1.5 mmol) in presence of DMAP (1 equiv.) in alcohol as solvent at rt. [b]Alcohol (2.0 mmol) used as reactant in CH_3CN solvent.

in 2-nitrobenzaldehyde afforded the desired product **4u** with moderate yield (Table 2). However, the reaction did not occur with the substrate 2,4-dinitrobenzaldehyde under identical conditions may be due to strong electron withdrawing nature of nitro group.

Encouraged by the above results, the generality of this protocol was further extended in the presence of various aliphatic amines. Due to the more basic nature of such amines compared to alcohol, catalytic amounts of DMAP was used during the reaction. Thus reaction conducted with primary amines such as cyclohexylamine and heptyl amine in methanol gave our desired products **6a-b** in good to moderate yields (Table 3). The formation of

Table 3. Synthesis of anthranilate esters from various amine derivatives[a]



[a]All reactions performed with 2-nitrobenzaldehyde (1.0 mmol), amine (1.0 mmol) and malononitrile (1.5 mmol) in presence of DMAP (20 mol%) in alcohol at rt.

unsymmetrical anthranilate esters by the addition of amine as well as alcoholic moiety in the skeleton rather than the symmetrical esters derived from both side alcoholic components was quite remarkable.

To extend the scope of this reaction, similar reactions were also performed with different secondary amines as diisopropyl amine, piperidine, morpholine and pyrrolidine (**5c-f**) under optimized reaction conditions which provided the desired products (**6c-f**) in fair yields. Further, this reaction was conducted with other easily available solvents such as EtOH, PrOH, BuOH in the presence of cyclohexylamine as the urea source to give anticipated products **6g** to **6i**, respectively. The yield didn't effect significantly with the growth in the length of the chain from MeOH to BuOH. The yield of the reaction further slightly decreased upto 68% (**6j**) while conducting this reaction in presence of isopropanol. Moreover, the reaction with the substrate 5-chloro-2-nitrobenzaldehyde provided the desired unsymmetrical anthranilate ester (**6k**) in good yield.

The structure of such anthranilate esters and alkyl 2-ureido-benzoate derivatives were unambiguously confirmed by the X-ray crystal structure analysis of **4n** and **6a**, which is shown in Figure 3.

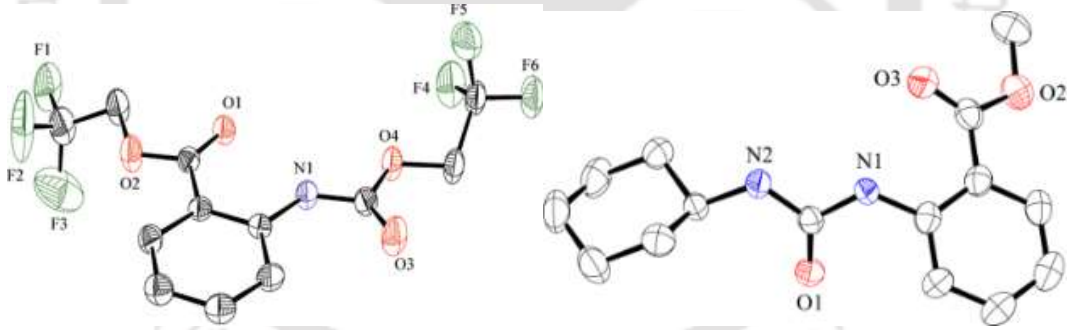
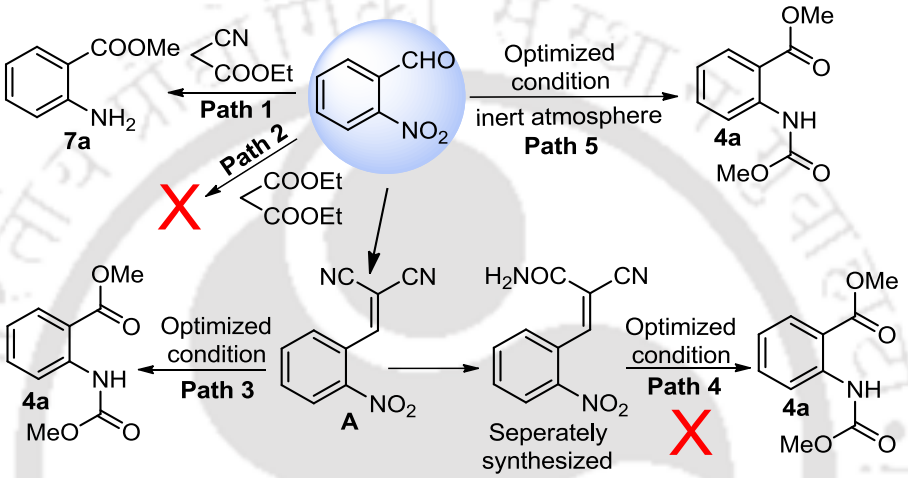


Figure 3. Ortep view of **4n** (CCDC 1054296) & **6a** (CCDC 1060211)

In order to elucidate the possible mechanism for the reaction, a series of control experiments were carried out. The reaction was found to take place solely in the presence of malononitrile. When this reaction was conducted with ethyl cyanoacetate in lieu of malononitrile, methyl-2-aminobenzoate (**7a**) was formed (Scheme 3, Path 1). However, the reaction didn't proceed at all in the presence of diethyl malonate (Scheme 3, Path 2). Both these results demonstrate the inevitable role of the –CN groups in this reaction.

Actual question arises whether it goes through an intramolecular or an intermolecular pathway. This specific redox reaction does not occur for benzaldehydes having the nitro group at *meta* or *para* position. A control reaction was carried out with benzaldehyde, nitrobenzene under optimized conditions to see whether the reaction proceeds utilizing nitro group and aldehyde moieties from two different components *via* intermolecular fashion or not. Unfortunately, the reaction didn't proceed at all confirming that the reaction goes through an intramolecular pathway.

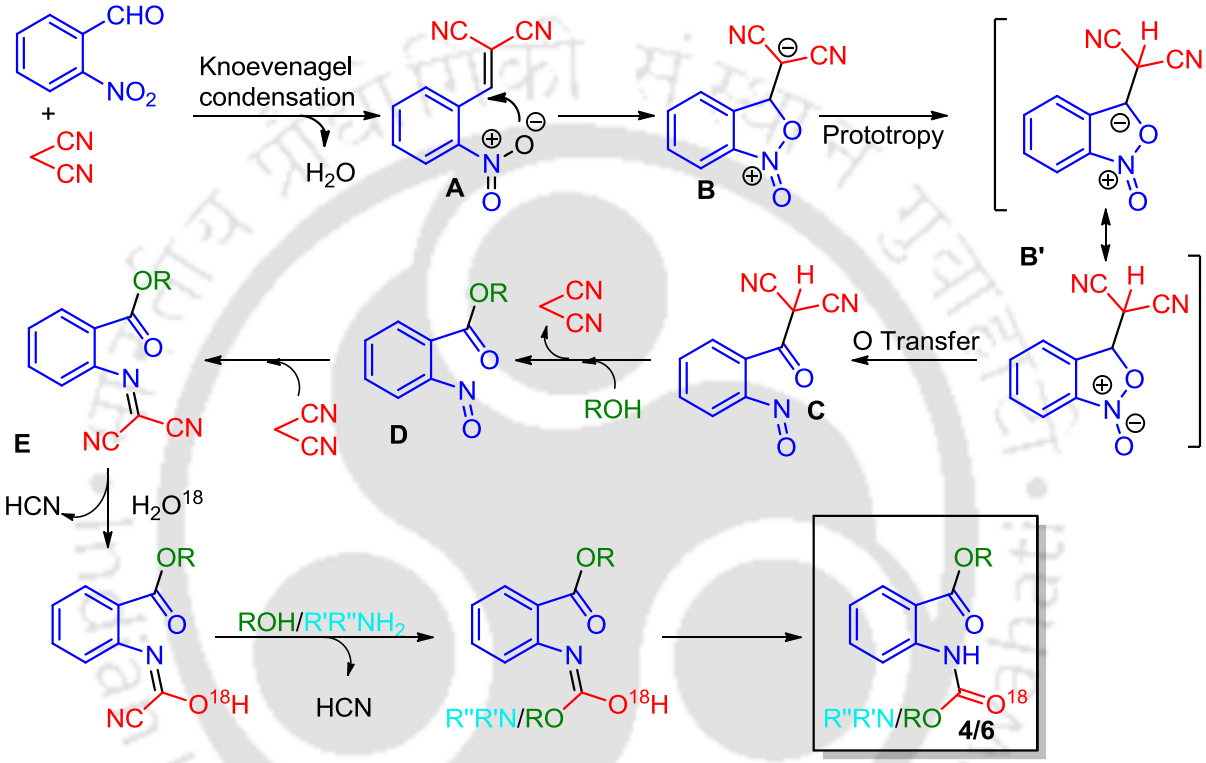


Scheme 3. Various control experiments during mechanistic study

Separately synthesized Knoevenagel product (**A**) of corresponding 2-nitrobenzaldehyde and malononitrile provided our desired product (**4a**) under optimized reaction conditions (Scheme 3, Path 3). This signifies that the reaction is going *via* a Knoevenagel product (**A**). According to a literature survey a nitro group can directly react with an amine functionality to give –N=N– frameworks under basic environment.[14] However, in our case the reaction of pre-synthesized starting material 2-cyano-3-phenylacrylamide[15] was unsuccessful to provide the desired product under optimized reaction condition (Scheme 3, Path 4). This concludes that the –CN group is not reduced to the corresponding amide during the reaction.

Literature survey conveys the involvement of aerial oxygen during metal-free cyanation of α,β–unsaturated carbonyl compounds.[16] Keeping this observation in mind when our reaction was conducted under inert atmosphere, reaction proceeds with equal ease (Scheme 3, Path 5). This control experiment excludes the presence of aerial oxygen as the ester oxygen source.

To ascertain whether this reaction is going through a radical pathway or not, both 2,2,6,6-tetramethylpyridine-*N*-oxide (TEMPO) and azobisisobutylnitrile (AIBN) were employed as radical quencher and radical initiator respectively to note any influence over the reaction. However there was no substantial change in the product yield indicating the reaction may not be going through a radical pathway.

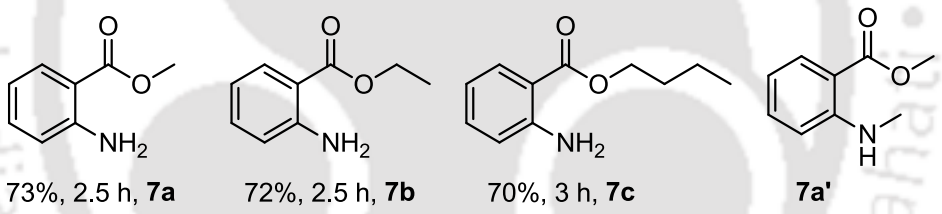


Scheme 4. Plausible mechanism for the formation of anthranilate esters

Although the exact mechanism is still unclear, taking into account of all the above observations a plausible mechanism for the formation of anthranilate esters (**4** & **6**) is depicted below. The first step is the condensation of malononitrile with the aldehyde group leading to the ß,ß-dicyanovinyl derivative **A**. Then Michael-type addition[17] of the nitro group to the dicyanovinyl moiety takes place leading to the formation of five membered isoxazolium moiety **B** (Scheme 4). In the next step prototropic tautomerism **B'** occurs and subsequent O-transfer to give the intermediate **C**. Alcoholysis of this compound **C** provides the 2-nitroso-benzoic acid ester **D** and malononitrile. The nitroso group further reacts with *in situ* generated malononitrile leading to a dicyanomethylidene imine **E** and one molecule of

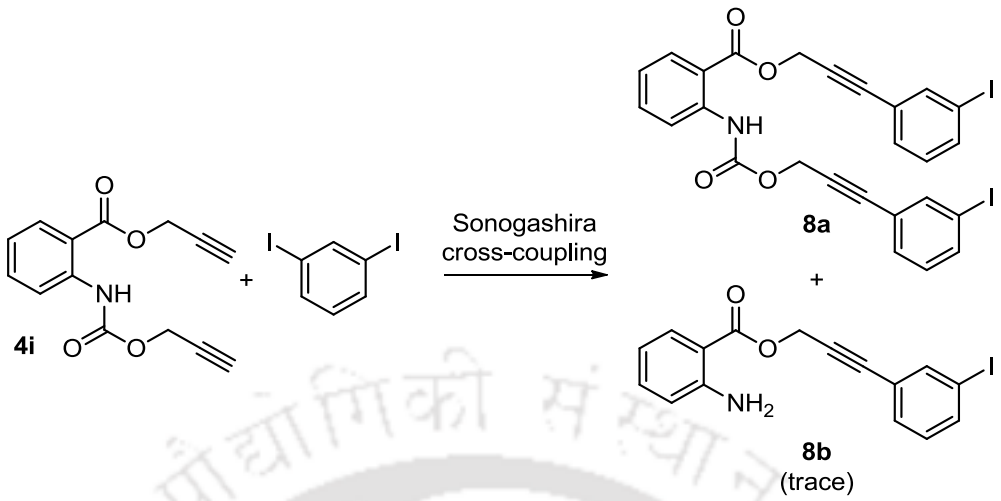
water. Hydrolysis with the water molecule followed by alcoholysis gives the product and two molecules of HCN. The explanation of the mechanism presumably dictates the delicate role of malononitrile throughout this intramolecular redox chemical process for the generation of this unexpected anthranilate esters. To confirm the possible oxygen source of urethane moiety the reaction of 2-nitrobenzaldehyde was conducted in the presence of 20 equiv. of H_2O^{18} under otherwise identical condition. The anthranilate ester **4a** obtained herein contains slight amount of O^{18} incorporation indicating H_2O as the possible oxygen source.

As mentioned earlier, ester derivatives of such anthranilic acid *viz* methyl anthranilate (MA), ethyl anthranilate (EA) and butyl anthranilate (BA) and dimethylanthranilate (MDA) are used widely as insect repellents.[2,3] They are even engaged commercially as flavoring agent or in perfume industry. In the above mentioned procedure synthesize of MA, EA, BA (**7a**, **7b** & **7c**) can be conducted direct from ethyl cyanoacetate (Scheme 3, Path-1). MDA (**7a'**) can synthesized through mono-*N*-methylation of MA **7a** (Scheme 5).



Scheme 5. Synthesis of insect repellent MA, EA, BA and MDA utilizing this method

It should be marked that the richness of the functionality in these anthranilate esters may render these compounds as beneficial synthons in further synthetic organic conversions. The compound **4i** containing alkyne functionality can be further used in Sonogashira Cross-coupling reactions with 1,3-di-iodobenzene (Scheme 6).



Scheme 6: Application of **4i** in Sonogashira cross-coupling

V.4. Conclusion

In summary, a convenient and novel route have been developed for the synthesis of anthranilate esters of potent synthetic and pharmacological importance *via* base assisted multicomponent reaction utilizing readily available 2-nitrobenzaldehyde, malononitrile and alcohols / aliphatic amines in a highly chemoselective manner. This strategy demonstrates a mild, cheap, metal-free chemoselective intramolecular redox process where simultaneously oxidation of the aldehyde functionality as well as reduction of nitro group takes place in the presence of malononitrile as the carbonyl source. By subtle change of the basic strength, a variety of symmetrical and unsymmetrical anthranilate esters can be efficiently synthesized in a highly chemoselective manner.

V.5. References

1. (a) B. D. Palmer, K. Henare, S.-T. Woon, R. Sutherland, C. Reddy, L.-C. S. Wang, C. Kieda and L.-M. Ching, *J. Med. Chem.*, 2007, **50**, 3757; (b) P. Wiklund and J. Bergman, *Curr. Org. Synth.*, 2006, **3**, 379; (c) X. Deng, Q. Yang, N. Kwiatkowski, T. Sim, U. McDermott, J. E. Settleman, J.-D. Lee and N. S. Gray, *ACS Med. Chem. Lett.*, 2011, **2**, 195; (d) Y.-D. Cheng, T.-L. Hwang, H.-H. Wang, T.-L. Pan, C.-C. Wu, W.-Y. Chang, Y.-T. Liu, T.-C. Chu and P.-W. Hsieh, *Org. Biomol. Chem.*, 2011, **9**, 7113.
2. G. D. Yadav and M. S. Krishnan, *Org. Process Res. Dev.*, 1998, **2**, 86.
3. P. Kain, S. M. Boyle, S. K. Tharadra, T. Guda, C. Pham, A. Dahanukar and A. Ray, *Nature*, 2013, **502**, 507.
4. (a) A. Padwa and D. J. Austin, *Angew. Chem.*, 1994, **106**, 1881; (b) J. Seo, H. M. P. Chui, M. J. Heeg and J. Montgomery, *J. Am. Chem. Soc.*, 1999, **121**, 476; (c) M. G. Organ, E. A. Arvanitis, C. E. Dixon and J. T. Cooper, *J. Am. Chem. Soc.*, 2002, **124**, 1288; (d) H. Lebel and V. Paquet, *Org. Lett.*, 2002, **4**, 1671; (e) S. Tu, B. Jiang, Y. Zhang, R. Jia, J. Zhang, C. Yao and F. Shi, *Org. Biomol. Chem.*, 2007, **5**, 355; (f) J. Wang, R. Mason, D. V. Derveer, K. Feng and X. R. Bu, *J. Org. Chem.*, 2003, **68**, 5415; (g) M.-Y. Lin, S. J. Maddirala and R.-S. Liu, *Org. Lett.*, 2005, **7**, 1745; (h) X. Wang, X.-P. Xu, S.-Y. Wang, W. Zhou and S.-J. Ji, *Org. Lett.*, 2013, **15**, 4246.
5. (a) J. Barluenga, A. Fernández, F. Rodríguez, and F. J. Fañanás, *Chem. Eur. J.*, 2009, **15**, 8121; (b) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (c) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1; (d) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (e) D. E. Fogg and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365.
6. J. F. M. da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.*, 2001, **12**, 273.
7. (a) K. Moriyama, K. Ishida and H. Togo, *Chem. Commun.*, 2012, **48**, 8574; (b) K. Moriyama, K. Ishida and H. Togo, *Org. Lett.*, 2012, **14**, 946.
8. (a) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (b) D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27; (c) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534.

9. (a) R. Giri, J. K. Lam and J.-Q. Yu, *J. Am. Chem. Soc*., 2010, **132**, 686; (b) C. E. Houlden, M. Hutchby; C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem. Int. Ed*., 2009, **48**, 1830; (c) W. Li, Z. Duan, R. Jiang and A. Lei, *Org. Lett.*, 2015, **17**, 1397.
10. E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc*., 2011, **133**, 7652
11. K.-H. Ng, F.-N. Ng and W.-Y. Yu, *Chem. Commun.*, **2012**, 48, 11680.
12. S. Sarkar, D. K. Das and A. T. Khan, *RSC Adv.*, 2014, **4**, 53752.
13. S. Sarkar, D. K. Das and A. T. Khan, *Eur. J. Org. Chem.*, 2013, 6823.
14. G. Guerrini, A. Costanzo, G. Ciciani, F. Bruni, S. Selleri, C. Costagli, F. Besnard, B. Costa, C. Martini, G. De Sienad and P. Malmberg-Aiellod, *Bioorg. Med. Chem.*, 2006, **14**, 758.
15. X. Xin, D. Xiang, J. Yang, Q. Zhang, F. Zhou and D. Dong, *J. Org. Chem.*, 2013, **78**, 11956.
16. E. Wei, B. Liu, S. Lin and F. Liang, *Org. Biomol. Chem.*, 2014, **12**, 6389.
17. A. Taher, S. Ladwa, S. T. Rajan and G. W. Weaver, *Tetrahedron Lett.*, 2000, **41**, 9893.

Experimental Section

General procedure for the preparation of symmetric anthranilate esters (4a-u) from alcohols: In a dried 25 mL round-bottomed flask a mixture of 2-nitrobenzaldehyde (1.0 mmol) and malononitrile (1.5 mmol) was taken in 3 mL of desired alcohol (**3a-d**, **f-g** & **q-u**) as reactant-cum-solvent. In rest of the cases required alcohol was used as reactant (2.0 mmol) with acetonitrile as solvent. Then, 4-dimethylaminopyridine (DMAP) (1 equiv.) was added into it and the reaction mixture was kept for stirring at room temperature. The progress of the reaction was supervised through TLC time to time. After the reaction was complete, the solvent was removed in rotary evaporator. It was extracted with dichloromethane (2 x 10 mL), washed with water and dried over anhydrous Na_2SO_4. It was concentrated in vacuo. The desired products **(4a-u)** were obtained in 56-72 % yield after purification through column chromatography using ethylacetate/hexane (5:95) eluent.

General procedure for the preparation of unsymmetrical anthranilate esters (6a-k) from amine & alcohols: In a dried 25 mL round-bottomed flask a mixture of 2-nitrobenzaldehyde (1.0 mmol), malononitrile (1.5 mmol) and requisite amine (1.0 mmol) was taken in 3 mL of desired alcohol as solvent. Then, 4-dimethylaminopyridine (DMAP) (20 mol%) was added into it and the reaction mixture was kept for stirring at room temperature. The progress of the reaction was monitored time to time through TLC. After completion of the reaction, the solvent was removed in rotary evaporator. It was then extracted with dichloromethane (2 x 10 mL), washed with water and dried over anhydrous Na_2SO_4. It was concentrated in vacuo, purified through column chromatography with ethylacetate/hexane (15:85) and the desired products **(6a-k)** were obtained in 64-74 % yields.

Procedure for the preparation of cross-coupling products (8a-b): This reaction was conducted maintaining the procedure mentioned in the following paper, C. J. Taylor, M. Motevalli, and C. J. Richards, *Organometallics*, 2006, **25**, 2899.

Procedure for the O^{18} labelling reaction with H_2O^{18}: In an oven dried 25 mL double necked round-bottomed flask a mixture of 2-nitrobenzaldehyde (1.0 mmol) and 4-

dimethylaminopyridine (DMAP) (1 equiv.) was taken under argon atmosphere. 20 Equivalent of H_2O^{18} was added into it with 3 mL of anhydrous MeOH (**3a)**. At last 1.5 equiv. of malononitrile was added and the reaction mixture was let to sitrr at room temperature for 2h. After the reaction was complete, the solvent was removed in rotary evaporator. It was extracted with dichloromethane (2 x 10 mL), washed with water and dried over anhydrous Na_2SO_4. It was concentrated *in vacuo*. The desired product **4a** was obtained after purification through column chromatography using ethylacetate/hexane (5:95) eluent.

Crystallographic Description:

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K. Cell parameters were retrieved using SMART software and refined with SAINT on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS. The structure was solved by direct methods implemented in SHELX-97 program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically.

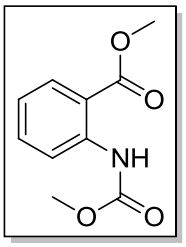
Table 1. Crystal datas and structure refinements for **4n** and **6a**. For atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

	Compound **4n**	Compound **6a**
Formula	$C_{12}H_9F_6NO_4$	$C_{15}H_{20}N_2O_3$
Mol. wt.	345.20	276.33
Crystal system	Monoclinic	Monoclinic
Space group	P1 21/c 1	P 21/c
Temperature /K	293 (2)	296
Wavelength /Å	0.71073	0.71073
a /Å	13.0242 (6)	4.8164 (4)
b /Å	13.3563 (6)	12.3382 (7)
c /Å	8.2205 (3)	24.06776(19)

α/°	90.00	90.00
β/°	100.660 (4)	94.39(7)
Ɣ/°	90.00	90.00
V/ Å^3	1405.31 (10)	1426.02(17)
Z	4	4
Density/Mgm^{-3}	1.632	1.287
Abs. co-eff. /mm^{-1}	0.171	0.090
Abs. correction	multi-scan	multi-scan
F(000)	696	592
Total no. of reflections	2472	2652
Reflections, $I > 2\sigma(I)$	1634	1434
Max. 2θ/°	25.00	25.25
Ranges (h, k, l)	-15≤h ≤15 -15≤ k ≤15 -9≤ l ≤ 6	-5≤h ≤5 -14≤ k ≤14 -29≤ l ≤ 29
Complete to 2θ (%)	99.9	99.9
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goof (F^2)	1.078	1.016
R_1 all	0.0986	0.1241
R_1 (σ > 2I)	0.0725	0.0669
wR_2 all	0.2215	0.1366
wR_2 (σ > 2I)	0.1985	0.1125

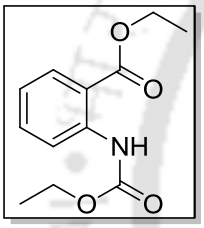
Spectral data

Methyl 2-((methoxycarbonyl)amino)benzoate (4a):



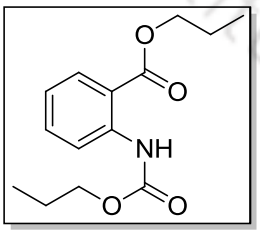
Gummy liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.78 (s, 3H), 3.91 (s, 3H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 10.49 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 52.46, 114.78, 119.02, 121.75, 131.07, 134.79, 141.98, 154.31, 168.71 ppm; IR (KBr): 1145, 1213, 1529, 1692, 1739, 2926, 3301 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{11}NO_4$ (M + H^+) 210.0766, found 210.0763.

Ethyl 2-((ethoxycarbonyl)amino)benzoate (4b):



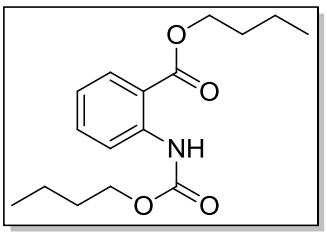
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.35 (q, *J* = 7.6 Hz, 2H), 6.99 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 10.49 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.39, 14.70, 61.33, 61.47, 114.95, 118.97, 121.56, 131.04, 134.65, 142.13, 153.92, 168.30 ppm; IR (KBr): 1242, 1529, 1591, 1690, 1737, 2982, 3300 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}NO_4$ (M + H^+) 238.1079, found 238.1079.

Propyl 2-((propoxycarbonyl)amino)benzoate (4c):



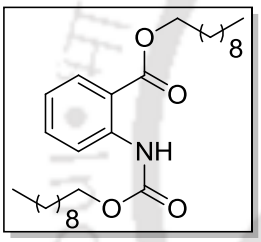
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, *J* = 7.6 Hz, 3H), 1.04 (t, *J* = 7.6 Hz, 3H), 1.65-1.86 (m, 4H), 4.13 (t, *J* = 6.8 Hz, 2H), 4.28 (t, *J* = 6.4 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 10.51 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 10.55, 10.70, 22.18, 22.43, 66.99, 67.02, 115.00, 119.00, 121.56, 131.03, 134.64, 142.14, 154.04, 168.33 ppm; IR (KBr): 1240, 1528, 1591, 1690, 1738, 2969, 3300 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}NO_4$ (M + H^+) 266.1392, found 266.1394.

Butyl 2-((butoxycarbonyl)amino)benzoate (4d):



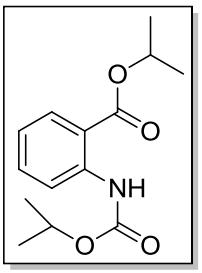
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91-1.02 (m, 6H), 1.38-1.54 (m, 4H), 1.61-1.70 (m, 2H), 1.71-1.82 (m, 2H), 4.16 (t, *J* = 6.4 Hz, 2H), 4.31 (t, *J* = 6.8 Hz, 2H), 7.01 (t, *J* = 7.2 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 10.50 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.92, 19.29, 19.47, 30.81, 31.14, 65.26, 65.32, 114.99, 118.99, 121.56, 131.03, 134.63, 142.13, 154.04, 168.33 ppm; IR (KBr): 1242, 1528, 1561, 1690, 1737, 2960, 3299 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}NO_4$ (M + H^+) 294.1705, found 294.1707.

Decyl 2-(((decyloxy)carbonyl)amino)benzoate (4e):



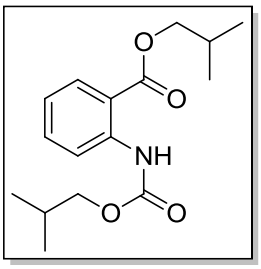
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.81-0.93 (m, 6H), 1.20-1.49 (m, 28H), 1.52-1.62 (m, 2H), 1.63-1.72 (m, 2H), 4.15 (t, *J* = 6.6 Hz, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 7.01 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 10.49 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.31, 22.89, 26.10, 26.25, 28.80, 29.13, 29.47, 29.52, 29.74, 32.11, 65.62, 65.66, 115.05, 119.04, 121.58, 131.05, 134.66, 142.16, 154.08, 168.37 ppm; IR (KBr): 1241, 1528, 1591, 1691, 1739, 2925, 3310 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{47}NO_4$ (M + H^+) 462.3583, found 462.3573.

Isopropyl 2-((isopropoxycarbonyl)amino)benzoate (4f):



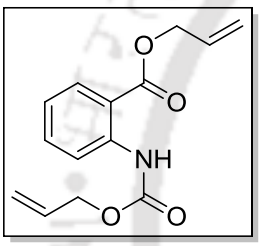
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.30 (d, *J* = 6.0 Hz, 6H), 1.38 (d, *J* = 6.0 Hz, 6H), 4.94-5.07 (m, 1H), 5.28-5.31 (m, 1H), 7.00 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 10.49 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 22.08, 22.27, 68.80, 69.11, 115.26, 118.92, 121.40, 131.06, 134.53, 142.27, 153.57, 167.83 ppm; IR (KBr): 1259, 1384, 1596, 1682, 1726, 2926, 3443 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}NO_4$ (M + H^+) 266.1392, found 266.1401.

Isobutyl 2-((isobutoxycarbonyl)amino)benzoate (4g):



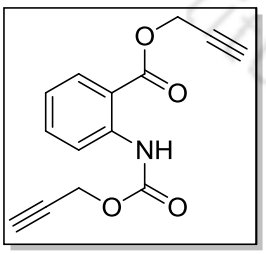
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): 0.95 (d, *J* = 6.0 Hz, 6H), 1.01 (d, *J* = 6.8 Hz, 6H), 1.91-2.02 (m, 1H), 2.04-2.15 (m, 1H), 3.93 (d, *J* = 6.4 Hz, 2H), 4.07 (d, *J* = 6.0 Hz, 2H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 8.0 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 8 Hz, 1H), 10.49 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.28, 19.37, 27.99, 28.12, 71.47, 71.51, 115.00, 119.03, 121.59, 130.99, 134.66, 142.14, 154.04, 168.27 ppm; HRMS (ESI) calcd for $C_{16}H_{23}NO_4$ (M + H^+) 294.1705, found 294.1713.

Allyl 2-(((allyloxy)carbonyl)amino)benzoate (4h):



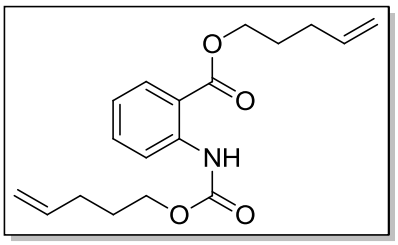
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): 4.65 (d, *J* = 6.0 Hz, 2H), 4.80 (d, *J* = 6.0 Hz, 2H), 5.24 (d, *J* = 10.8 Hz, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 5.37 (t, *J* = 17.2 Hz, 2H), 5.89-6.04 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 10.51 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 65.99, 66.03, 114.81, 118.34, 118.94, 119.10, 121.81, 131.13, 131.98, 132.69, 134.88, 142.07, 153.55, 167.91 ppm; IR (KBr): 1239, 1529, 1591, 1692, 1739, 2931, 3406 cm^{-1}.

Prop-2-yn-1-yl 2-(((prop-2-yn-1-yloxy)carbonyl)amino)benzoate (4i):



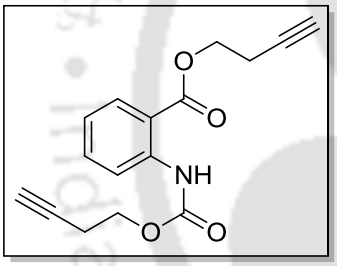
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.51 (s, 1H), 2.55 (s, 1H), 4.78 (s, 2H), 4.92 (s, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 10.50 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 52.92, 75.16, 75.64, 78.05, 114.28, 119.18, 122.22, 131.33, 135.31, 141.79, 152.77, 167.41 ppm; IR (KBr): 1256, 1384, 1596, 1689, 1721, 2128, 2951, 3245, 3283 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}NO_4$ (M + H^+) 258.0766, found 258.0758.

Pent-4-en-1-yl 2-(((pent-4-en-1-yloxy)carbonyl)amino)benzoate (4j):



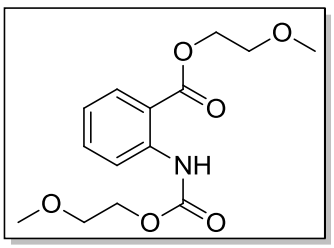
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): 1.74-1.82 (m, 2H), 1.86-1.94 (m, 2H), 2.01-2.20 (m, 2H), 2.21-2.28 (m, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 4.98-5.12 (m, 4H), 5.12-5.89 (m, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 10.50 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 27.95, 28.27, 30.19, 30.32, 64.85, 67.51, 115.46, 115.78, 119.03, 121.64, 131.03, 134.74, 137.45, 137.48, 137.76, 142.12, 153.93, 168.29 ppm; IR (KBr): 1241, 1384, 1528, 1591, 1690, 1737, 2943, 3451, 3486 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}NO_4$ (M + H^+) 318.1705, found 318.1719.

But-3-yn-1-yl 2-(((but-3-yn-1-yloxy)carbonyl)amino)benzoate (4k):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.02 (t, *J* = 2.4 Hz, 1H), 2.04 (t, *J* = 2.4 Hz, 1H), 2.60 (td, *J* = 2.4 & 7.2 Hz, 2H), 2.68 (td, *J* = 2.4 & 6.6 Hz, 2H), 4.28 (t, *J* = 7.2 Hz, 2H), 4.42 (t, *J* = 7.2 Hz, 2H), 7.04 (t, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 10.45 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 19.21, 19.47, 63.08, 70.22, 70.48, 79.89, 80.18, 114.68, 119.10, 121.96, 131.21, 134.98, 141.89, 153.36, 167.92 ppm; IR (KBr): 1146, 1266, 1384, 1596, 1688, 1718, 2126, 2923, 3280, 3447 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}NO_4$ (M + H^+) 286.1079, found 286.1086.

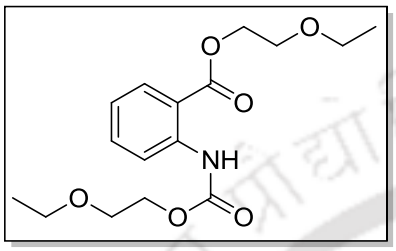
2-Methoxyethyl 2-(((2-methoxyethoxy)carbonyl)amino)benzoate (4l):



Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.39 (s, 3H), 3.41 (s, 3H), 3.62-3.65 (m, 2H), 3.69-3.73 (m, 2H), 4.30-4.34 (m, 2H), 4.43-4.47 (m, 2H), 7.01 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 10.44 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz):

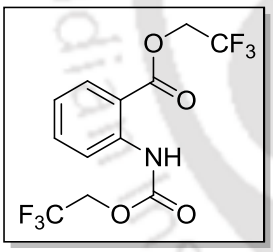
δ 59.15, 59.25, 64.38, 70.51, 70.81, 114.85, 119.05, 121.79, 131.25, 134.79, 141.86, 153.68, 168.04 ppm; IR (KBr): 1262, 1592, 1686, 1737, 2889, 3299 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}NO_6$ ($M + H^+$) 298.1291, found 298.1294.

2-Ethoxyethyl 2-(((2-ethoxyethoxy)carbonyl)amino)benzoate (4m):



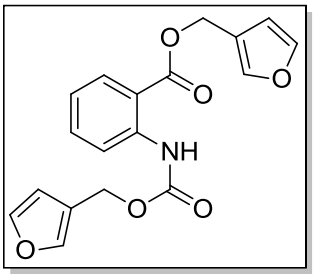
Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.12-1.21 (m, 6H), 3.41-3.55 (m, 4H), 3.62 (t, *J* = 4.8 Hz, 2H), 3.69 (t, *J* = 4.8 Hz, 2H), 4.25 (t, *J* = 4.8 Hz, 2H), 4.39 (t, *J* = 4.8 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.98 (dd, *J* = 0.8 & 7.6 Hz, 1H), 8.36 (d, *J* = 8.8 Hz, 1H), 10.39 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 15.34, 64.65, 64.68, 66.88, 66.96, 68.39, 68.74, 114.96, 119.10, 121.78, 131.29, 134.79, 141.92, 153.76, 168.11 ppm; IR (KBr): 1125, 1260, 1529, 1591, 1691, 1739, 2975, 3286, 3448 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}NO_6$ ($M + H^+$) 326.1604, found 326.1613.

2,2,2-Trifluoroethyl 2-(((2,2,2-trifluoroethoxy)carbonyl)amino)benzoate (4n):



White solid; Mp 89–91 ºC; ^1H NMR ($CDCl_3$, 600 MHz): δ 4.58 (q, *J* = 8.4 Hz, 2H), 4.70 (q, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.62 (td, *J* = 8.0 & 1.2 Hz, 1H), 8.08 (dd, *J* = 1.2 & 6.6 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 1H), 10.41 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 60.78, 60.85, 61.03, 61.10, 61.27, 61.35, 61.52, 61.59, 113.66, 119.36, 122.16, 122.22, 122.89, 124.00, 124.06, 131.47, 136.00, 141.51, 151.65, 166.45 ppm; IR (KBr): 1259, 1597, 1702, 1750, 2924, 3280, 3473 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_9F_6NO_4$ ($M + H^+$) 346.0514, found 346.0516.

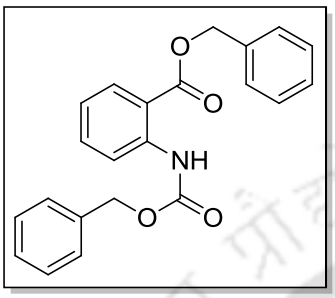
Furan-3-ylmethyl 2-(((furan-3-ylmethoxy)carbonyl)amino)benzoate (4o):



Gummy; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.14 (s, 2H), 5.25 (s, 2H), 6.28-6.31 (m, 2H), 6.50-6.42 (m, 2H), 7.98 (t, *J* = 7.6 Hz, 1H), 7.45-7.36 (m, 2H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 10.46 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 58.88, 110.80, 110.87, 110.97, 111.35, 114.68, 119.08, 121.91, 131.32, 134.97,

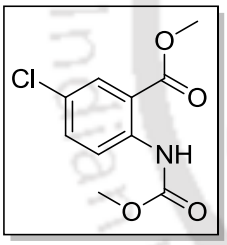
141.94, 143.48, 143.70, 149.21, 149.88, 153.37, 167.76 ppm; IR (KBr): 1242, 1591, 1691, 1738, 2925, 3302 cm^{-1}.

Benzyl 2-(((benzyloxy)carbonyl)amino)benzoate (4p):



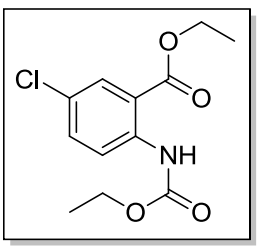
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.22 (s, 2H), 5.34 (s, 2H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.32-7.41 (m, 6H), 7.42-7.47 (m, 4H), 7.53 (t, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 10.56 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): 67.10, 67.13, 114.79, 119.09, 121.83, 128.40, 128.42, 128.47, 128.53, 128.66, 128.74, 128.79, 128.88, 131.20, 134.90, 142.05, 153.64, 167.99 ppm; IR (KBr): 1145, 1260, 1498, 1591, 1688, 1739, 2927, 3294, 3451 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}NO_4$ (M + H^+) 362.1392, found 362.1394.

Methyl 5-chloro-2-((methoxycarbonyl)amino)benzoate (4q):



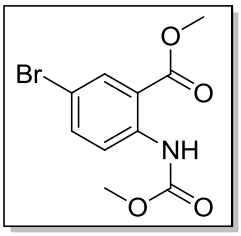
White solid; Mp 120–123 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.78 (s, 3H), 3.91 (s, 3H), 7.47 (dd, *J* = 2.4 & 9.0 Hz, 1H), 7.96 (d, *J* = 3.0 Hz, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 10.40 (s, 1H, NH), ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 52.61, 52.73, 115.89, 120.46, 126.82, 130.58, 134.61, 140.56, 154.14, 167.61 ppm; IR (KBr): 1059, 1263, 1464, 1743, 2854, 2925, 3439 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{10}ClNO_4$ (M + H^+) 244.0377, found 244.0378.

Ethyl 5-chloro-2-((ethoxycarbonyl)amino)benzoate (4r):



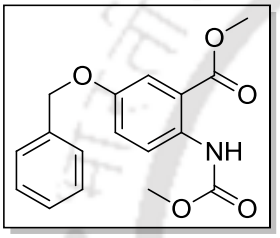
White solid; Mp 90–92 ºC; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.2 Hz, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.46 (dd, *J* = 2.4 & 9.0 Hz, 1H), 7.97 (d, *J* = 2.4 Hz, 1H), 8.41 (d, *J* = 9.0 Hz, 1H), 10.42 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.35, 14.67, 61.56, 61.94, 116.12, 120.46, 126.63, 130.54, 134.48, 140.74, 153.77, 167.24 ppm; IR (KBr): 1058, 1240, 1595, 1697, 1731, 2854, 2925, 3248 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}ClNO_4$ (M + H^+) 272.0690, found 272.0692.

Methyl 5-bromo-2-((methoxycarbonyl)amino)benzoate (4s):



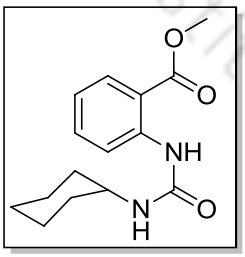
White solid; Mp 128–130 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.78 (s, 3H), 3.91 (s, 3H), 7.61 (dd, *J* = 2.4 & 9.0 Hz, 1H), 8.11 (d, *J* = 2.4 Hz, 1H), 8.35 (d, *J* = 9.0 Hz, 1H), 10.41 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 52.62, 52.75, 114.03, 116.24, 120.74, 133.54, 137.47, 141.02, 154.09, 167.52 ppm; IR (KBr): 1067, 1252, 1430, 1588, 1690, 1743, 2953, 3259 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{10}BrNO_4$ (M + H^+) 287.9871, found 287.9870.

Methyl 5-(benzyloxy)-2-((methoxycarbonyl)amino)benzoate (4u):



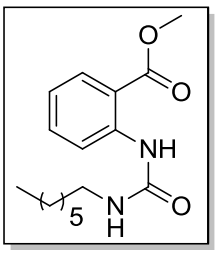
White solid; Mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.76 (s, 3H), 3.91 (s, 3H), 5.05 (s, 2H), 7.19 (dd, *J* = 3.0 & 9.0 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 3.0 Hz, 1H), 8.33 (d, *J* = 9.6 Hz, 1H), 10.20 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 52.43, 52.56, 70.74, 115.73, 116.05, 120.67, 122.32, 127.77, 128.32, 128.83, 135.83, 136.85, 153.24, 154.47, 168.32 ppm; IR (KBr): 1019, 1263, 1527, 1690, 1729, 2854, 2924, 3309 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}NO_5$ (M + H^+) 316.1185, found 316.1185.

Methyl 2-(3-cyclohexylureido)benzoate (6a):



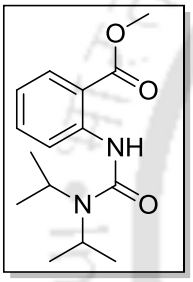
White solid; Mp 153–155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.00-1.18 (m, 3H), 1.21-1.40 (m, 2H), 1.52-1.61 (m, 1H), 1.62-1.73 (m, 2H), 1.86-2.02 (m, 2H), 3.53-3.57 (m, 1H), 3.81 (s, 3H), 4.63 (s, 1H), 6.86 (t, *J* = 6.4 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 10.20 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.11, 25.75, 33.87, 49.56, 52.28, 113.72, 119.59, 120.61, 130.85, 134.76, 143.70, 154.42, 169.41 ppm; IR (KBr): 1249, 1550, 1653, 1699, 2924, 3293 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}N_2O_3$ (M + H^+) 277.1552, found 277.1541.

Methyl 2-(3-heptylureido)benzoate (6b):



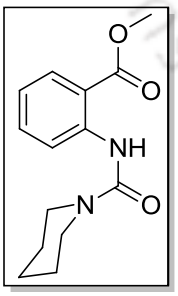
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 (t, *J* = 6.8 Hz, 3H), 1.29-1.30 (m, 4H), 1.31-1.38 (m, 4H), 1.49-1.60 (m, 2H), 3.24 (q, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 4.71 (s, 1H), 6.92 (t, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 8.4 Hz, 1H), 10.30 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.26, 22.81, 27.05, 29.20, 30.22, 31.97, 40.86, 52.34, 113.78, 119.65, 120.74, 130.88, 134.84, 143.63, 155.24, 169.45 ppm; IR (KBr) : 1261, 1547, 1607, 1654, 2929, 3319, 3454, cm^{-1}; MS (ESI) calcd for $C_{16}H_{24}N_2O_3$ ($M + H^+$) 293.1865, found 293.1900.

Methyl 2-(3,3-diisopropylureido)benzoate (6c):



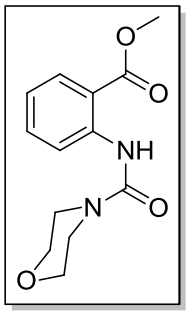
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (s, 6H), 1.36 (s, 6H), 3.87 (s, 3H), 3.88-3.95 (m, 2H), 6.89 (td, *J* = 1.2 & 7.6 Hz, 1H), 7.43 (td, *J* = 1.2 & 7.6 Hz, 1H), 7.94 (dd, *J* = 2.0 & 8.4 Hz, 1H), 8.39 (dd, *J* = 0.8 & 8.4 Hz, 1H), 10.29 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.36, 46.59, 52.31, 114.23, 120.37, 130.87, 134.51, 144.06, 154.55, 169.36 ppm; IR (KBr): 1254, 1448, 1588, 1670, 1723, 2969, 3317 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_3$ ($M + H^+$) 279.1709, found 279.1717.

Methyl 2-(piperidine-1-carboxamido)benzoate (6d):



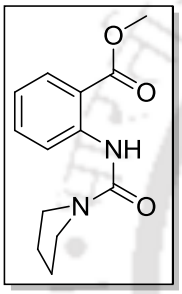
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.71-1.55 (m, 6H), 3.56-3.48 (m, 4H), 3.88 (s, 3H), 6.92 (t, *J* = 8.4 Hz, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 10.64 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 24.75, 25.98, 45.20, 52.39, 113.95, 119.81, 120.60, 130.87, 134.78, 144.02, 154.77, 169.60 ppm; IR (KBr): 2930, 1589, 1252, 1671, 1687, 3316 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}N_2O_3$ ($M + H^+$) 263.1396, found 263.1409.

Methyl 2-(morpholine-4-carboxamido)benzoate (6e):



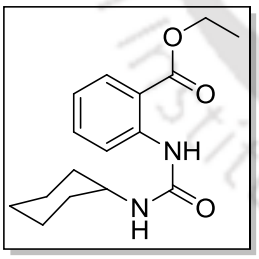
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 3.58 (t, *J* = 4.8 Hz, 4H), 3.76 (t, *J* = 4.8 Hz, 4H), 3.91 (s, 3H), 6.98 (t, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 9.0, 1.2 Hz, 1H), 8.0 (dd, *J* = 7.8 & 1.2 Hz, 1H), 8.55 (d, *J* = 9.0 Hz, 1H), 10.76 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 44.23, 52.51, 66.83, 114.11, 119.73, 121.11, 130.97, 134.95, 143.53, 154.95, 169.71 ppm; IR (KBr): 1261, 1384, 1604, 1754, 2924, 3446 cm^{-1}; MS (ESI) calcd for $C_{13}H_{16}N_2O_4$ ($M + H^+$) 265.1188, found 265.1224.

Methyl 2-(pyrrolidine-1-carboxamido)benzoate (6f):



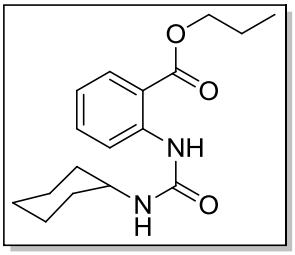
Gummy; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01-1.34 (m, 4H), 3.51-3.39 (m, 4H), 3.83 (s, 3H), 6.87 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 8.57 (d, *J* = 8.8 Hz, 1H), 10.40 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.76, 45.98, 52.35, 113.75, 119.52, 120.60, 130.87, 134.85, 143.89, 154.16, 169.54 ppm; IR (KBr): 1252, 1532, 1606, 1671, 2925, 3315 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}N_2O_3$ ($M + H^+$) 249.1239, found 249.1237.

Ethyl 2-(3-cyclohexylureido)benzoate (6g):



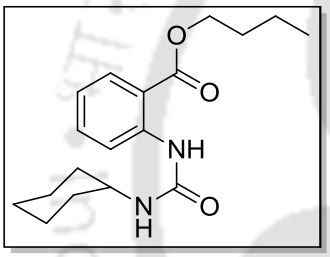
White solid; Mp 164–167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.09-1.21 (m, 3H), 1.29-1.36 (m, 2H), 1.37 (t, *J* = 6.4 Hz, 3H), 1.54-1.62 (m, 1H), 1.66-1.80 (m, 2H), 1.92-2.00 (m, 2H), 3.54-3.68 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.60 (s, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 10.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.39, 25.11, 25.76, 33.88, 49.53, 61.33, 113.94, 119.52, 120.56, 130.85, 134.69, 143.73, 154.44, 169.05 ppm; IR (KBr): 1261, 1553, 1655, 1697, 2930, 3281 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}N_2O_3$ ($M + H^+$) 291.1709, found 291.1700.

Propyl 2-(3-cyclohexylureido)benzoate (6h):



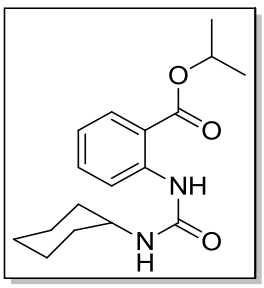
White solid; Mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.08-1.21 (m, 3H), 1.30-1.44 (m, 2H), 1.56-1.64 (m, 1H), 1.65-1.82 (m, 4H), 1.93-2.04 (m, 2H), 3.54-3.67 (m, 1H), 4.22 (t, *J* = 6.8 Hz, 2H), 4.60 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 10.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.70, 22.18, 25.10, 25.75, 33.86, 49.51, 66.88, 113.96, 119.52, 120.55, 130.80, 134.67, 143.71, 154.43, 169.07 ppm; IR (KBr): 1245, 1549, 1657, 1697, 2936, 3292 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}N_2O_3$ ($M + H^+$) 305.1865, found 305.1863.

Butyl 2-(3-cyclohexylureido)benzoate (6i):



White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, *J* = 7.2 Hz, 3H), 1.05-1.24 (m, 3H), 1.32-1.41 (m, 2H), 1.42-1.53 (m, 2H), 1.56-1.65 (m, 1H), 1.66-1.80 (m, 4H), 1.92-2.06 (m, 2H), 3.58-3.69 (m, 1H), 4.28 (t, *J* = 6.4 Hz, 2H), 4.66 (s, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 10.34 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): 13.90, 19.46, 25.10, 25.75, 30.82, 33.85, 49.53, 65.18, 113.98, 119.54, 120.57, 130.80, 134.67, 143.69, 154.47, 169.08 ppm; IR (KBr): 1250, 1551, 1652, 1699, 2923, 3292 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{26}N_2O_3$ ($M + H^+$) 319.2022, found 319.2024.

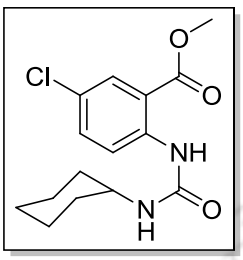
Isopropyl 2-(3-cyclohexylureido)benzoate (6j):



White solid; Mp 138–141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.78-0.92 (m, 3H), 1.08-1.22 (m, 2H), 1.34 (d, *J* = 6.4 Hz, 6H), 1.56-1.64 (m, 1H), 1.65-1.77 (m, 2H), 1.93-2.14 (m, 2H), 3.54-3.68 (m, 1H), 4.60 (s, 1H), 5.12-5.24 (m, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 10.36 (s, 1H, NH), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.30, 22.05, 22.84, 25.12, 25.77, 31.78, 33.88, 49.54, 68.97, 114.31, 119.48, 120.51, 130.84, 134.57, 143.72, 154.48, 168.57 ppm; IR

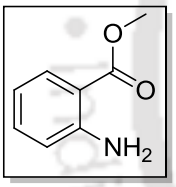
(KBr): 1245, 1549, 1657, 1697, 2969, 3292 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}N_2O_3$ (M + H^+) 305.1865, found 305.1864.

Methyl 5-chloro-2-(3-cyclohexylureido)benzoate (6k):



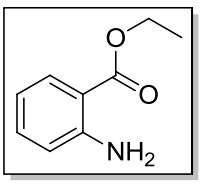
White solid; Mp 188–190 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.10-1.22 (m, 3H), 1.32-1.45 (m, 2H), 1.58-1.65 (m, 1H), 1.68-1.81 (m, 2H), 1.93-2.05 (m, 2H), 3.58-3.65 (m, 1H), 3.90 (s, 3H), 4.66 (s, 1H), 7.41 (dd, *J* = 9.6 & 3.0 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 8.52 (d, *J* = 9 Hz, 1H), 10.19 (s, 1H, NH), ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.08, 25.71, 33.83, 49.63, 52.61, 114.75, 121.06, 125.57, 130.28, 134.62, 142.29, 154.14, 168.40 ppm; IR (KBr): 1108, 1240, 1554, 1648, 1712, 2855, 2923, 3298, 3330 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}ClN_2O_3$ (M + H^+) 311.1162, found 311.1162.

Methyl 2-aminobenzoate (7a):



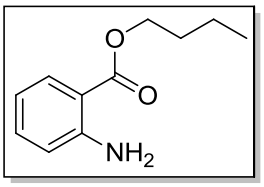
Gummy liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.76 (s, 3H), 5.35 (s, 2H, NH_2), 6.49-6.61 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.60, 110.82, 116.36, 116.80, 131.31, 134.19, 150.54, 168.68 ppm; IR (KBr): 1694, 1106, 1162, 1248, 1617, 2951, 3373, 3482 cm^{-1}; HRMS (ESI) calcd for $C_8H_9NO_2$ (M + H^+) 152.0712, found 152.0711.

Ethyl 2-aminobenzoate (7b):



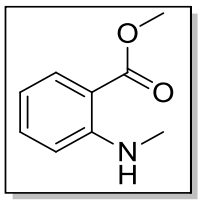
Gummy; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.37 (t, *J* = 6.6 Hz, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 5.72 (s, 2H, NH_2), 6.61-6.67 (m, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 9.0 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.49, 60.41, 111.18, 116.33, 116.80, 131.35, 134.10, 150.61, 168.31 ppm; IR (KBr): 1103, 1161, 1246, 1589, 1616, 1689, 2981, 3373, 3483 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}NO_2$ (M + H^+) 166.0868, found 166.0867.

Butyl 2-aminobenzoate (7c):



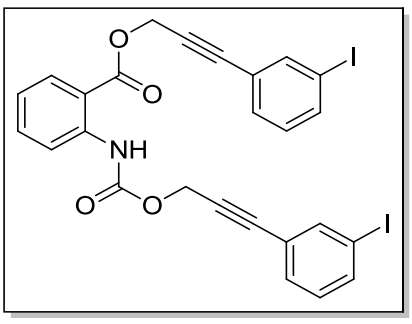
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 0.88 (t, *J* = 7.8 Hz, 3H), 1.31-1.42 (m, 2H), 1.58-1.71 (m, 2H), 4.18 (t, *J* = 6.6 Hz, 2H), 5.65 (s, 2H, NH_2), 6.53-6.61 (m, 2H), 7.15 (td, *J* = 1.8 & 9.0 Hz, 1H), 7.78 (dd, *J* = 1.2 & 7.8 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.89, 19.44, 30.92, 64.30, 111.34, 116.49, 116.93, 131.30, 134.08, 150.34, 168.32 ppm; IR (KBr): 1104, 1161, 1246, 1589, 1616, 1692, 2960, 3373, 3485 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NO_2$ (M + H^+) 194.1181, found 194.1184.

Methyl 2-(methylamino)benzoate (7a'):



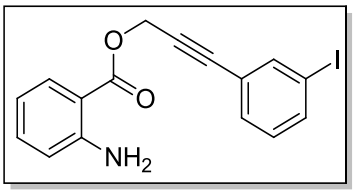
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.94 (s, 3H), 3.87 (s, 3H), 6.76 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.93 (dd, *J* = 1.2 & 7.8 Hz, 1H),ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 31.12, 51.95, 111.70, 112.98, 116.72, 131.80, 134.98, 150.36, 168.97 ppm; IR (KBr): 1161, 1173, 1244, 1261, 1580, 1607, 1686, 2949, 3381 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}NO_2$ (M + H^+) 166.0868, found 166.0859.

3-(3-iodophenyl)prop-2-yn-1-yl 2-((((3-(3-iodophenyl)prop-2-yn-1-yl)oxy)carbonyl) amino)benzoate (8a):



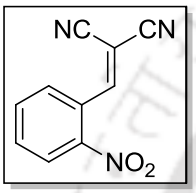
White solid; Mp 114–116 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 4.99 (s, 2H), 5.13 (s, 2H), 7.02-7.07 (m, 3H), 7.39-7.45 (m, 2H), 7.56-7.61 (m, 1H), 7.64-7.71 (m, 2H), 7.80-7.87 (m, 2H), 8.10 (dd, *J* = 1.2 & 7.8 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 10.54 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 53.57, 53.60, 84.06, 84.76, 85.00, 85.42, 93.73, 114.37, 119.18, 122.20, 124.21, 124.46, 130.00, 130.05, 131.20, 131.22, 131.40, 135.31, 137.96, 138.15, 140.68, 141.84, 152.85, 167.49 ppm; IR (KBr): 1051, 1208, 1384, 1419, 1604, 1685, 1739, 2923, 3281, 3444 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{17}I_2NO_4$ (M + K^+) 699.8884, found 699.8880.

3-(3-iodophenyl)prop-2-yn-1-yl 2-aminobenzoate (8b):



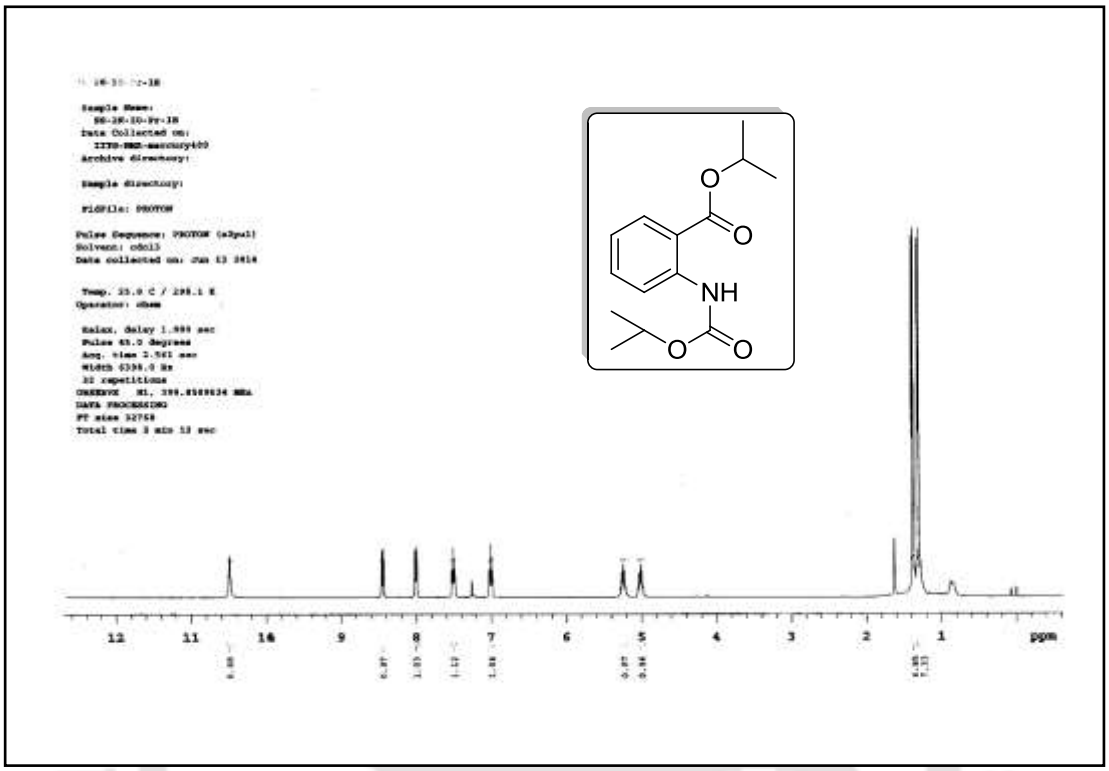
Gummy; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 5.08 (s, 2H), 5.72 (s, 2H), 6.62-6.71 (m, 2H), 7.00-7.08 (m, 1H), 7.25-7.31 (m, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.64-7.71 (m, 1H), 7.83 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H) ppm; IR (KBr): 1114, 1384, 1419, 1604, 1679, 2922, 3241, 3440 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}INO_2$ ($M + H^+$) 377.9991, found 378.0006.

2-(2-nitrobenzylidene)malononitrile (A):

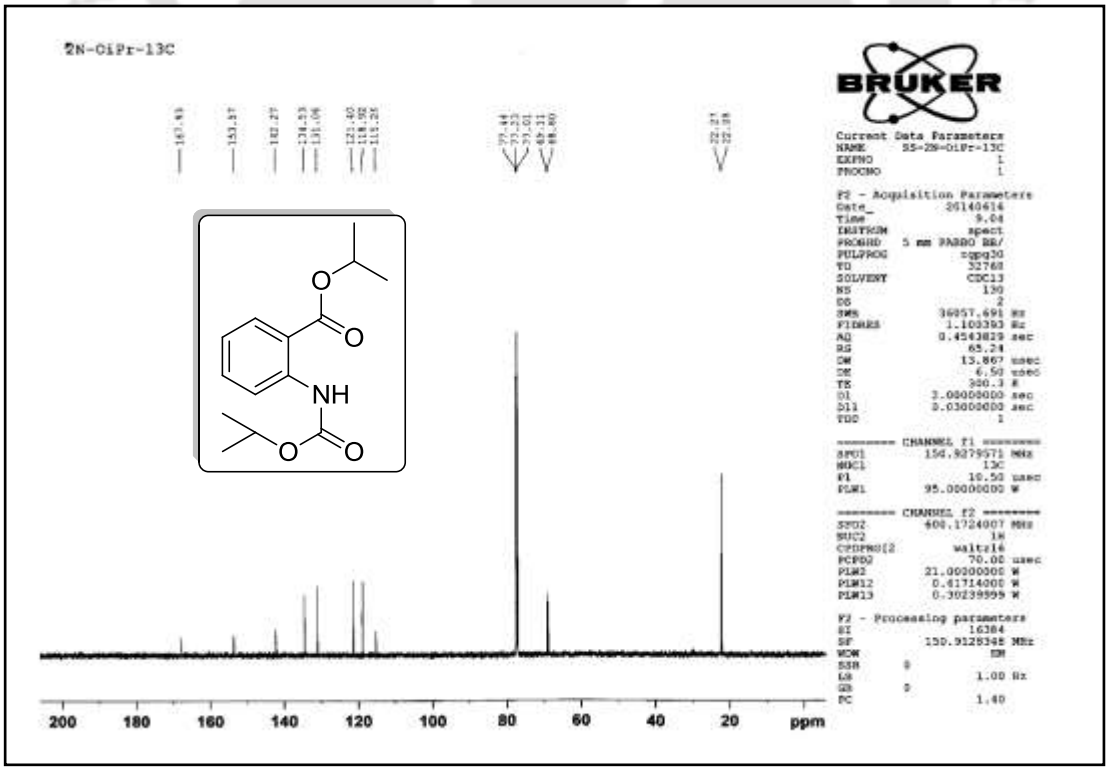


Yellow Solid; ^{1}H NMR ($DMSOD_6$, 400 MHz): δ 7.89 (t, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 6.8 Hz, 1H), 8.01 (t, *J* = 8.4 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.97 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 87.04, 111.77, 113.08, 125.40, 127.54, 130.43, 133.32, 135.03, 146.79, 161.32 ppm; IR (KBr): 870, 1347, 1521, 1568, 2240, 3047 cm^{-1}.

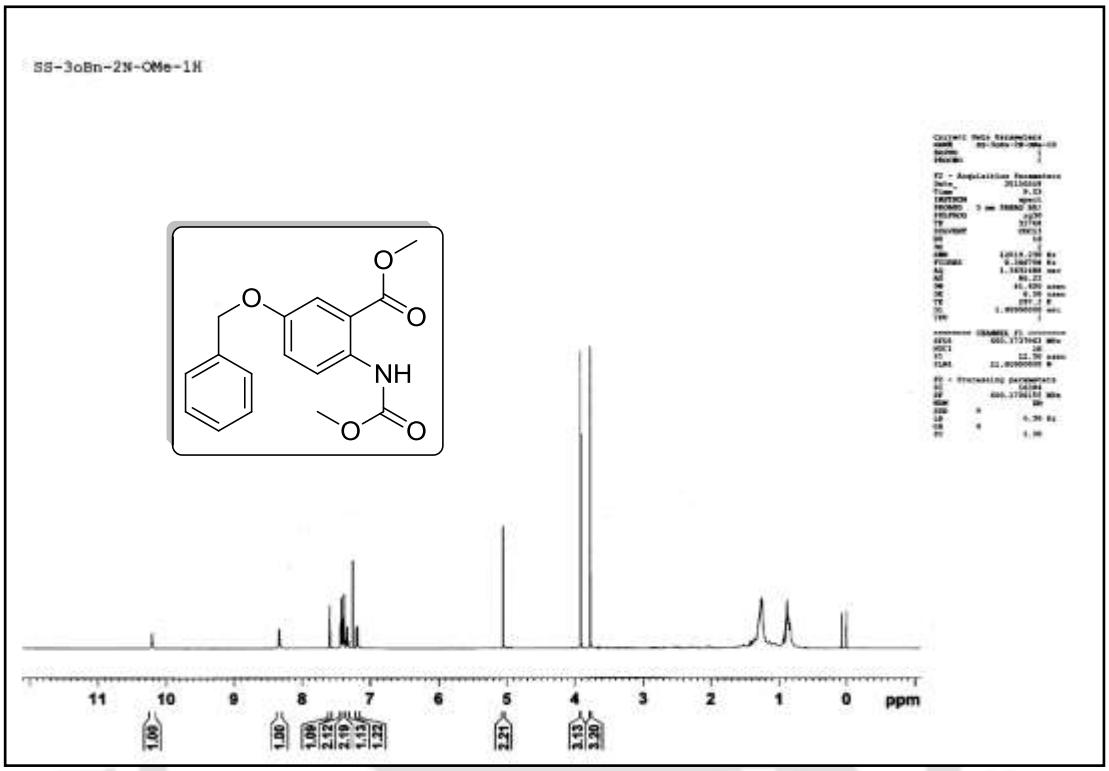
^{1}H NMR Spectra of Compound **4f**



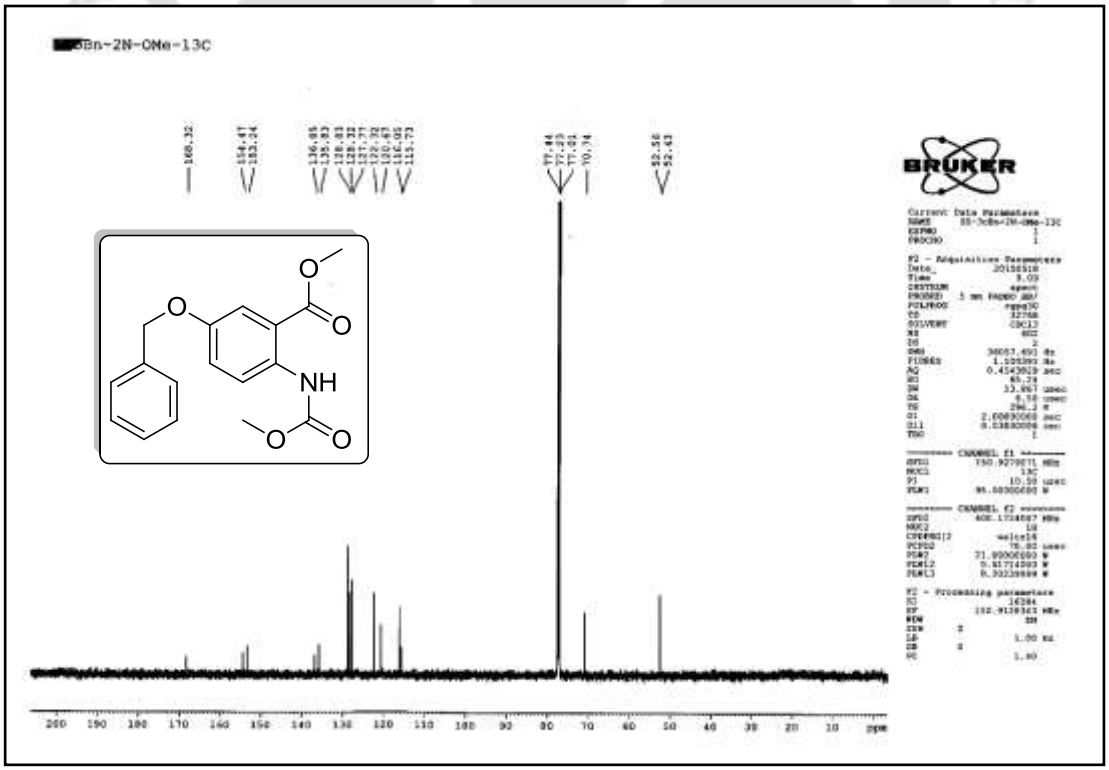
^{13}C NMR Spectra of Compound **4f**



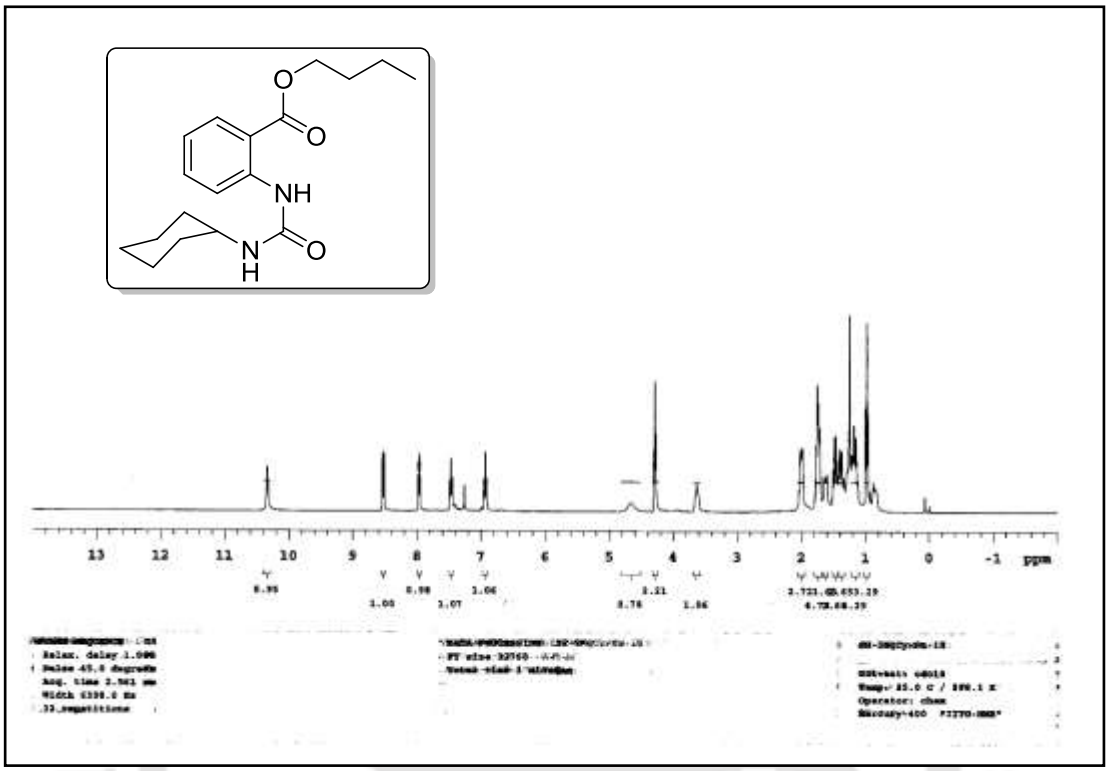
^{1}H NMR Spectra of Compound **4u**



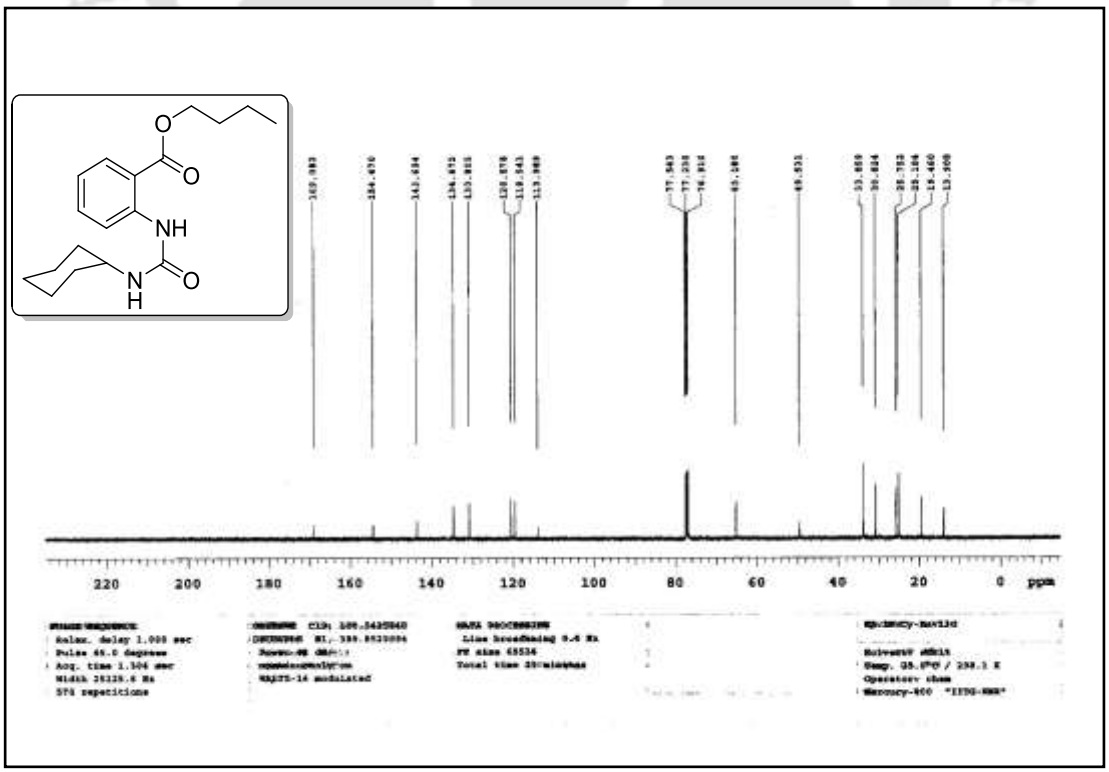
^{13}C NMR Spectra of Compound **4u**



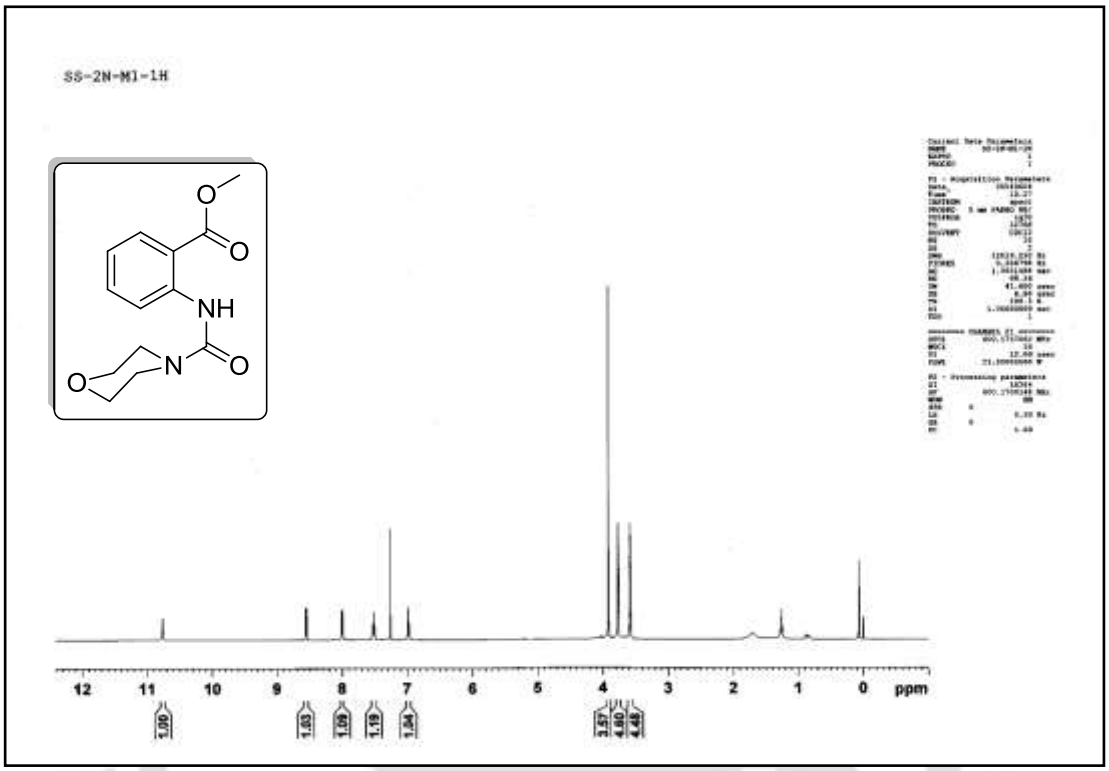
^{1}H NMR Spectra of Compound **6i**



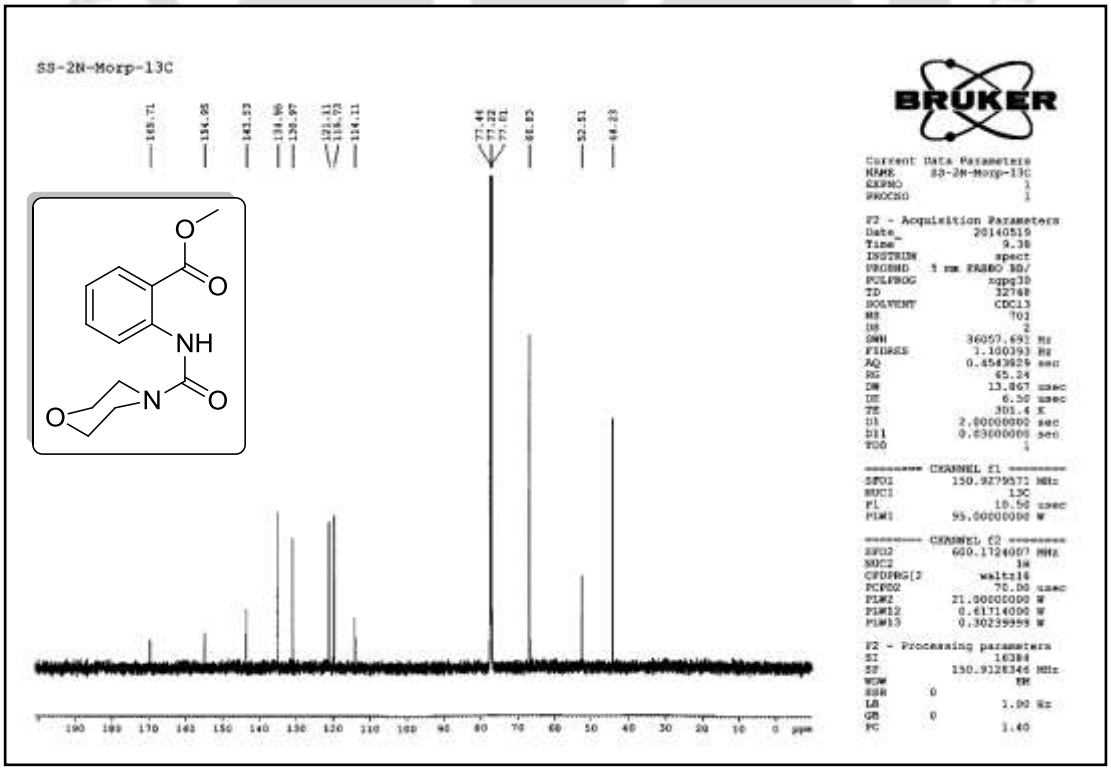
^{13}C NMR Spectra of Compound **6i**



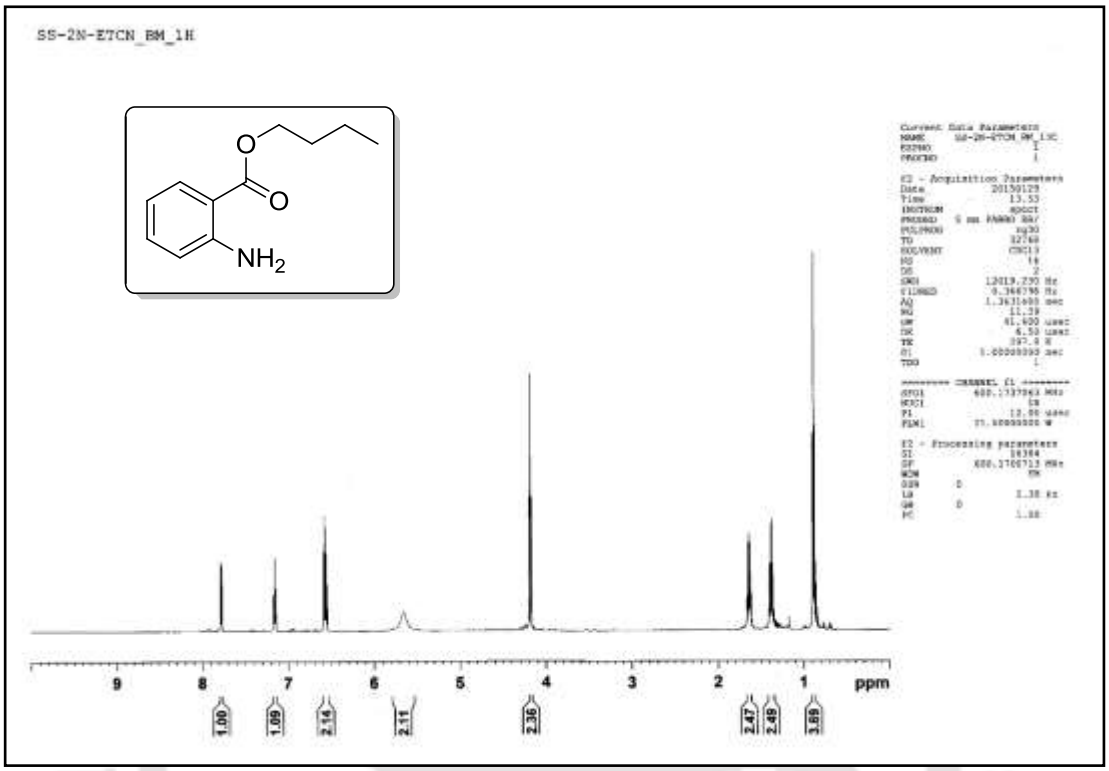
^{1}H NMR Spectra of Compound **6e**



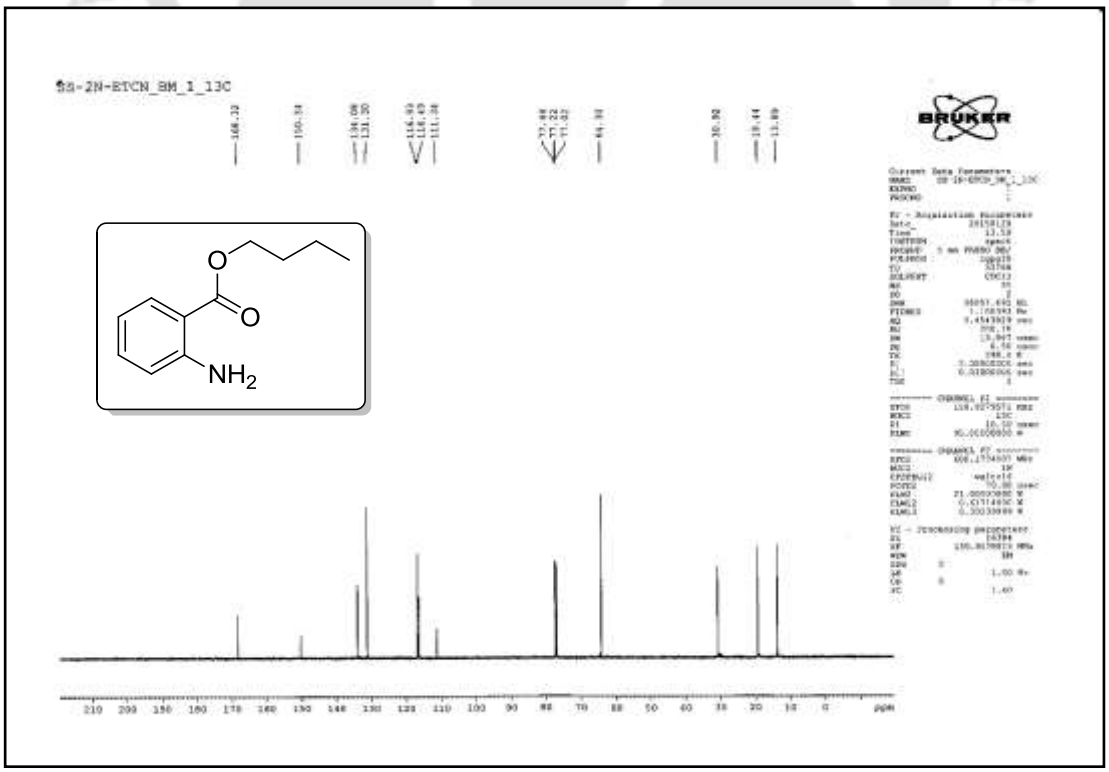
^{13}C NMR Spectra of Compound **6e**



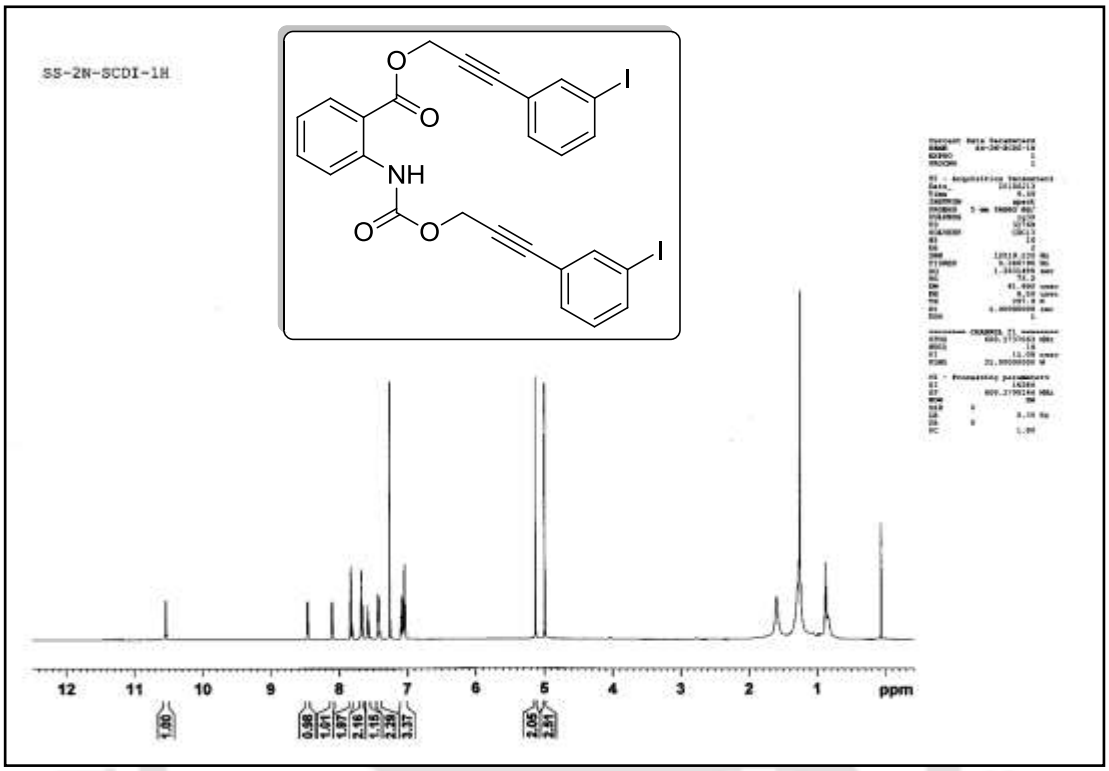
^{1}H NMR Spectra of Compound **7c**



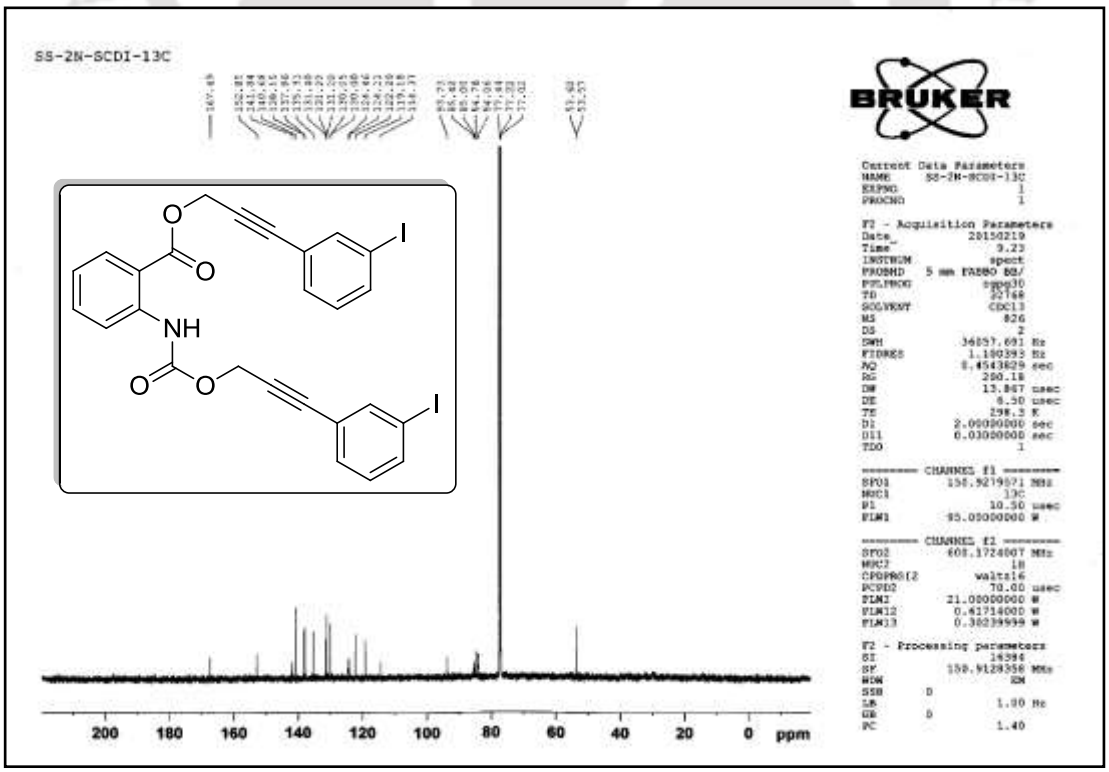
^{13}C NMR Spectra of Compound **7c**



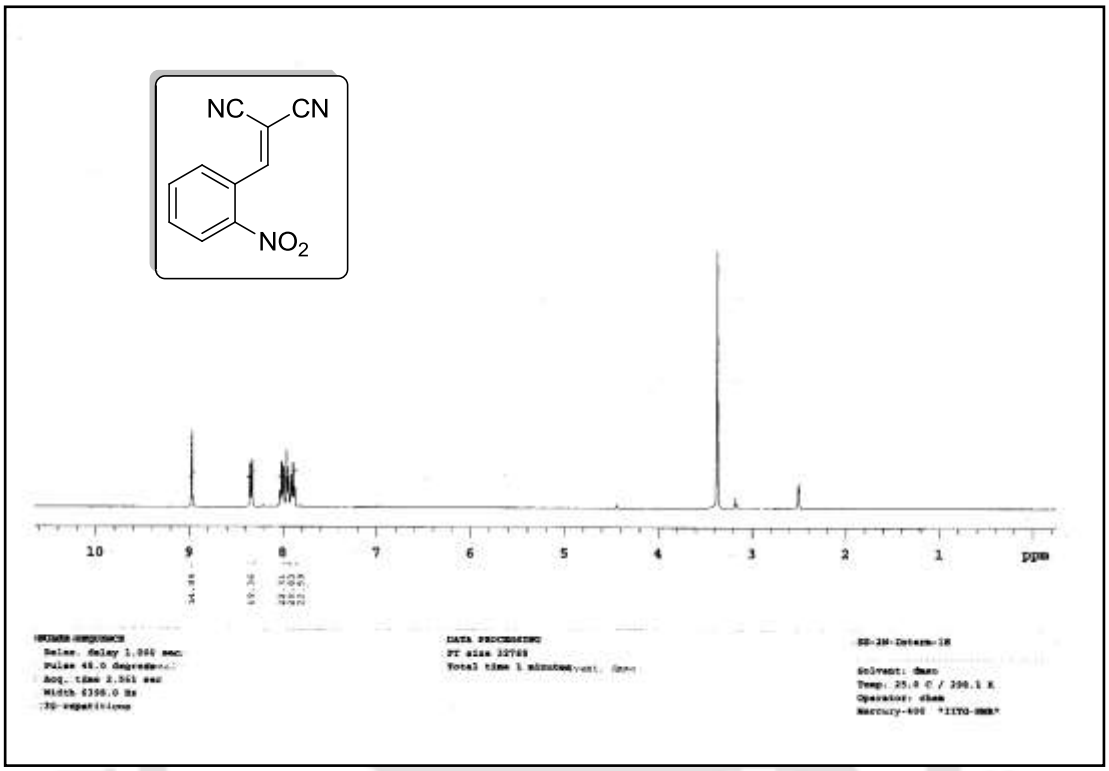
^{1}H NMR Spectra of Compound **8a**



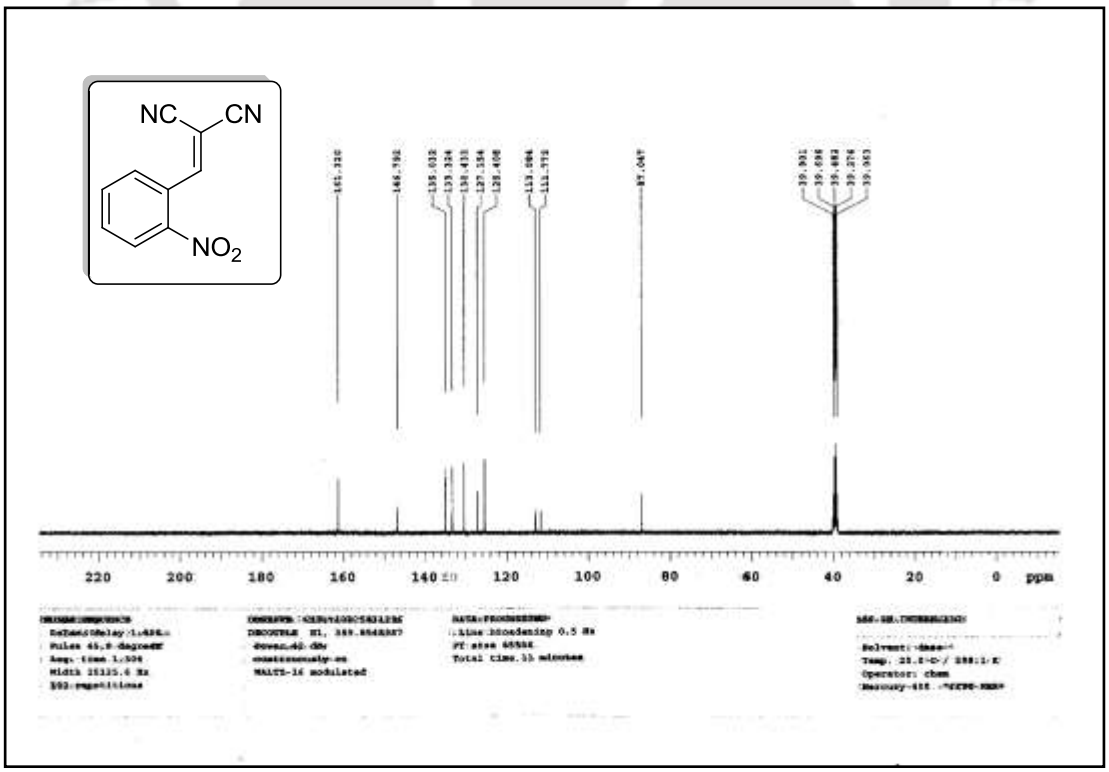
^{13}C NMR Spectra of Compound **8a**



^{1}H NMR Spectra of Compound **A**

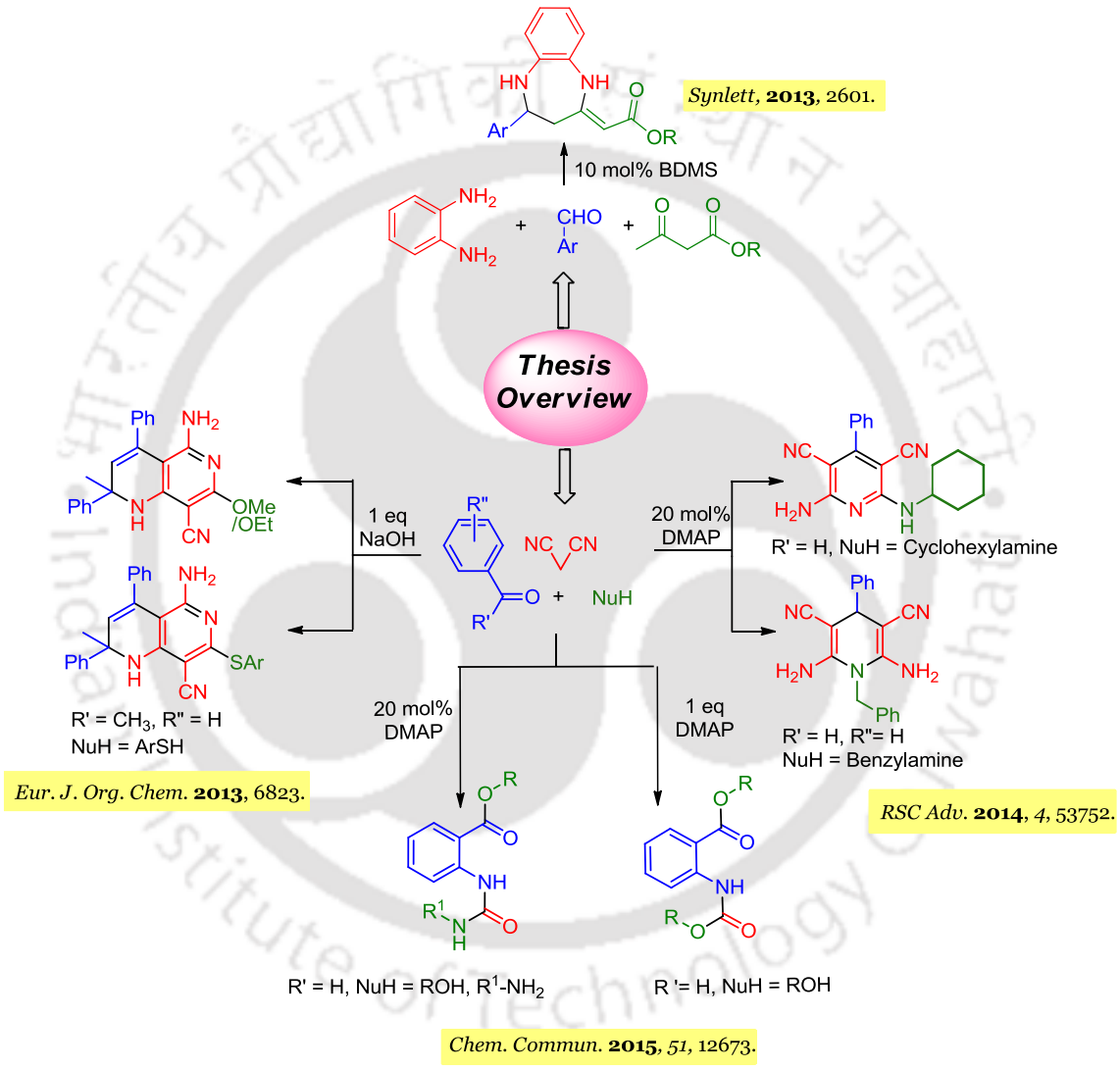


^{13}C NMR Spectra of Compound **A**



Conclusion and Schematic Overview of the Thesis

In conclusion, the thesis demonstrated the synthesis of nitrogen containing heterocycles such as seven membered benzodiazepines, highly substituted naphthyridines and fully substituted pyridines or dihydropyridines. It also described the synthesis of anthranilate esters in a highly chemoselective manner. A brief outline of the thesis has been shown below in Scheme 1

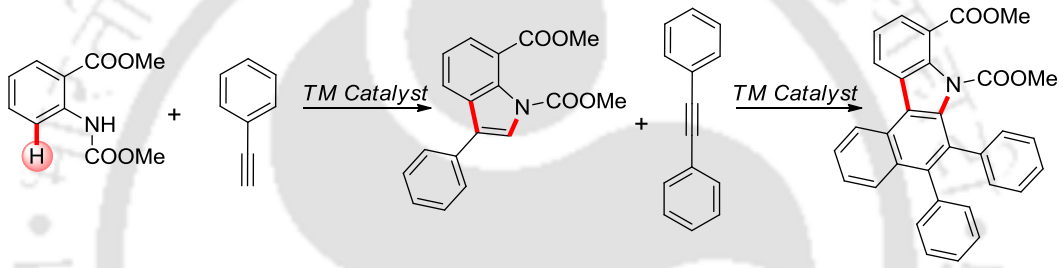


Scheme 1. Brief outline of the thesis

Future Perspectives

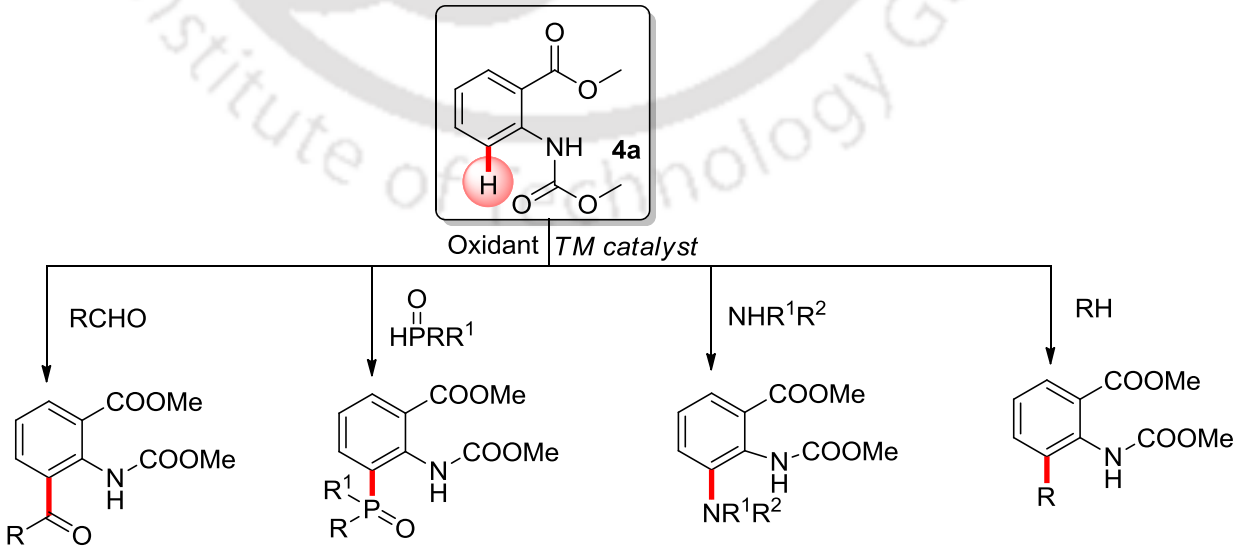
Functionalization of inert carbon-hydrogen bond through C-H activation is an increasingly dynamic area of research due to its broad potential in synthetic organic field. The C-H activation strategy can be executed in anthranilate ester and benzodiazepine to accomplish new molecules which may exhibit biological activities.

Anthranilic acid esters have been extensively employed as useful key building blocks in a multitude of natural products. Presence of *ortho* directing group, the *N*-donor of urethane, can enable them for synthesis of indole moiety *via* strong *N*-donor directing site in presence of suitable transition metals (TM). This indole moiety can be further transformed to carbazole moiety *via* oxidative annulation (Scheme 1).



Scheme 1. *C–H annulation of anthranilate esters using terminal alkynes*

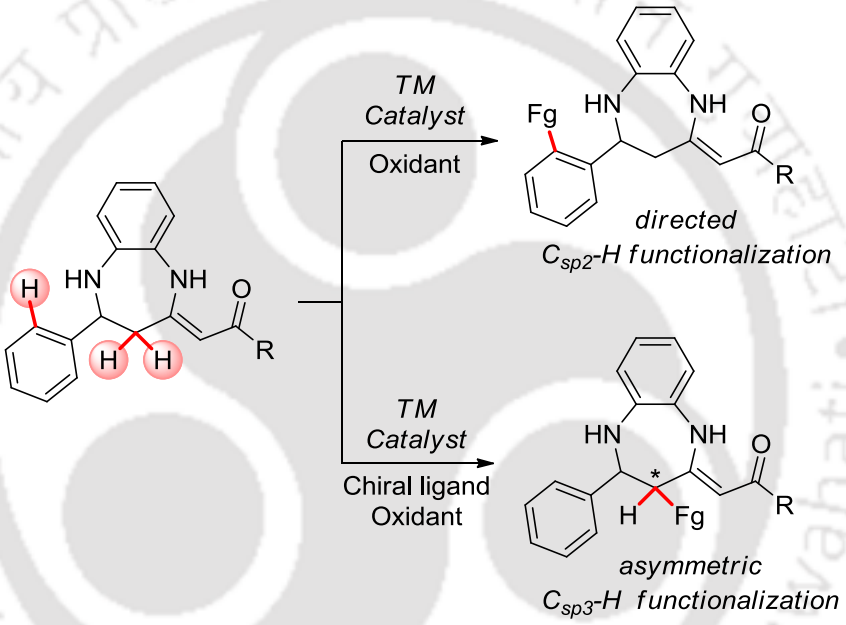
The directing group i.e the urethane in the anthranilate ester moiety can also be further utilized for other diverse *ortho* C–H functionalization strategies other than formation of heterocycles as shown above. Some of the *ortho*-directed processes such as *o*-aroylation,



Scheme 2. *C–C / C–N/ C–P bond formation through ortho C–H activation*

o-phosphoroylation, *o*-amination and *o*-arylation can be achieved *via* the *N*-directed *ortho* site of this anthranilate ester in presence of suitable transition metal/oxidant combination (Scheme 2).

Benzodiazepine moieties are considered as one of the most popular organic frameworks due to its wide range of biological activity. These benzodiazepine skeletons can be further utilized to explore its potential in both C_{sp3}–H and C_{sp2}–H functionalization. Due to presence of two different types of C–H bonds, the directed C_{sp2}–H functionalization and non-directed C_{sp3}–H functionalization can be selectively achieved using suitable catalytic conditions (Scheme 3).



***Scheme 3**. Chemoselective C_{sp3}–H and C_{sp2}–H functionalization in benzodiazepines*

List of Publications:

1. Beyond conventional routes, an unprecedented metal-free chemoselective synthesis of anthranilate esters *via* a multicomponent reaction (MCR) strategy
   Satavisha Sarkar and Abu T. Khan, *Chem. Comm.,* 2015, **51**, 12673.
2. Synthesis of fully-substituted pyridines and dihydropyridines in a highly chemoselective manner utilizing a multicomponent reaction (MCR) strategy
   Satavisha Sarkar, Deb K. Das and Abu T. Khan, *RSC Adv.*, 2014, **4**, 53752.
3. Sodium-Hydroxide-Mediated Synthesis of Highly Functionalized [1,6]-Naphthyridines in a One-Pot Pseudo Five-Component Reaction
   Satavisha Sarkar, Deb K. Das and Abu T. Khan, *Eur. J. Org. Chem.*, 2013, 6823.
4. Bromodimethylsulfonium Bromide (BDMS) Catalyzed Synthesis of 1,5-Benzodiazepines using a multicomponent reaction strategy
   Satavisha Sarkar, Jugal Kishore Rai Deka, Jagadish P. Hazra and Abu T. Khan, *Synlett* **2013**, 2601.
5. Synthesis of fused tetrahydropyrido[2,3-c]-coumarin derivatives as potential inhibitors for dopamine d3 receptors, catalyzed by hydrated ferric sulfate
   Deb K. Das, Satavisha Sarkar and Abu T. Khan, *RSC Adv.*, 2013, **4**, 3581.
6. A mild and efficient method for large scale synthesis of 3-aminocoumarins and its further application for the preparation of 4-bromo-3-aminocoumarins
   Deb K. Das, Satavisha Sarkar, Musawwer Khan, Md. Belal and Abu T. Khan
   Tetrahedron Lett., 2014, **55**, 4869.
7. 2,6-Pyridinedicarboxylic acid as organocatalyst for the synthesis of 1,5-benzodiazepines through one-pot reaction
   Mohan Lal, R. Siddick Basha, Satavisha Sarkar and Abu T. Khan, *Tetrahedron Lett*., 2013, **54**, 4264.