Exploration of 1,3-Dicarbonyl Compounds for Multicomponent Reactions (MCRs) Based Syntheses of Heterocycles

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DOCTOR OF PHILOSOPHY

by

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May 2012

Dedicated to

My Parents

&

Grand Mother

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI
Department of Chemistry

DECLARATION

I do hereby declare that the matter embodied in this thesis entitled "***Exploration of 1,3-Dicarbonyl Compounds for Multicomponent Reactions (MCRs) Based Syntheses of Heterocycles***" is the result of investigation carried out by me under the supervision of Prof. Abu T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

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.

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Dr. Abu T. Khan
Professor of Chemistry

CERTIFICATE

This is to certify that Mohan Lal has been working in my research group since 31st July 2007 as a regular registered Ph. D. student. I am forwarding his thesis entitled "*Exploration of 1,3-Dicarbonyl Compounds for Multicomponent Reactions (MCRs) Based Syntheses of Heterocycles*" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
May 14, 2012

Prof. A. T. Khan
(Thesis Supervisor)

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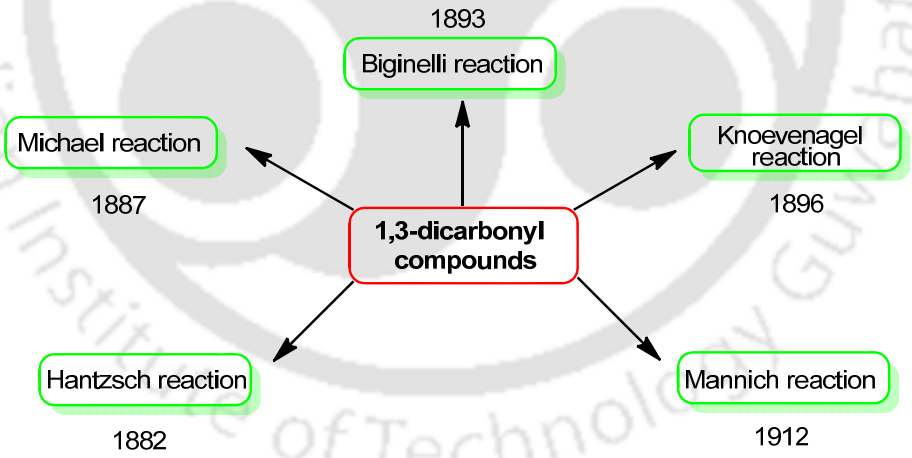
mohan lal

Mohan Lal

SUMMARY OF THE THESIS

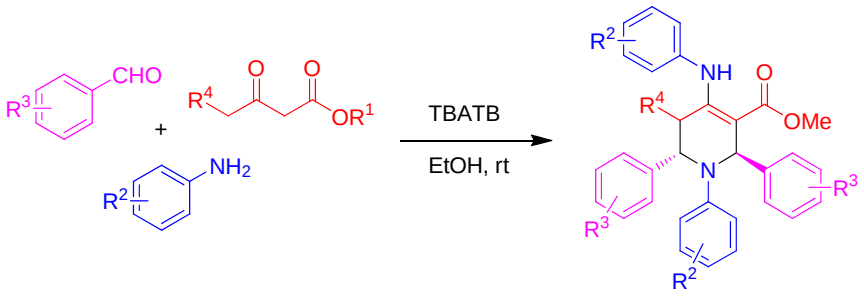
The contents of the thesis entitled "**Exploration of 1,3-Dicarbonyl Compounds for Multicomponent Reactions (MCRs) Based Syntheses of Heterocycles**" has been divided mainly into six chapters based on finding of the experimental results during the complete course of the research work.

Chapter 1 describes a brief review on importance of multicomponent reactions (MCRs) in organic synthesis followed by potentiality of 1,3-dicarbonyl compounds for the syntheses of various heterocycles involving multicomponent reactions (MCRs) and objective of the present research work. In the context of Green Chemistry as well as Sustainable Chemistry, domino multicomponent reactions (MCRs) play an extraordinary role in academic and industry. 1,3-Dicarbonyl derivatives namely β-ketoesters or 1,3-diketones constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations for the construction of new heterocycles. These compounds have enormous potentiality for well-known organic reaction which is displayed below:



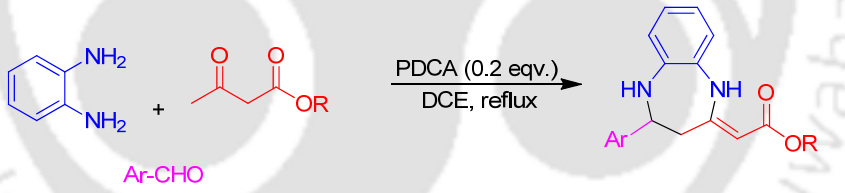
These reactions are utilized for the synthesis of heterocycles through MCR approach which is also given emphasis in the first chapter of the thesis.

Chapter 2 demonstrates the synthesis of the highly functionalized piperidine derivatives from the reaction of β-ketoesters, aromatic aldehydes and amines in ethanol at room temperature in the presence of a catalytic amount of TBATB through one-pot multicomponent reaction in good yields.

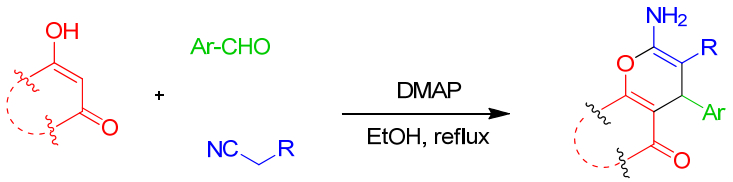


In this chapter, we have also shown that organic ammonium tribromides e.g. *n*-tetrabutylammonium bromide is a very useful and effective catalyst for the above transformation.

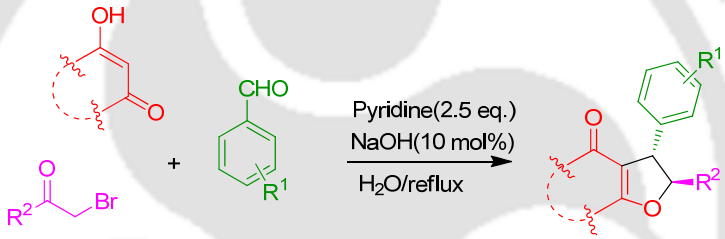
Chapter 3 illustrates on regioselective synthesis of 1,5-benzodiazapine derivatives through one-pot three-component reaction of *o*-phenylenediamine, β-ketoesters and aromatic aldehydes in 1,2-dichloromethane (DCE) in the presence of a catalytic amount of organocatalyst 2,6-pyridinedicarboxylic acid (PDCA) under reflux condition as shown below. The key feature for this protocol is intermolecular hydrogen-bond-driven γ-selective *C-C* bond formation of β-ketoester instead of α-selective *C-C* bond formation for regioselective synthesis of 1,5-benzodiazapine derivatives. To prove the mechanism of the reaction, some experiment has to be done in future.



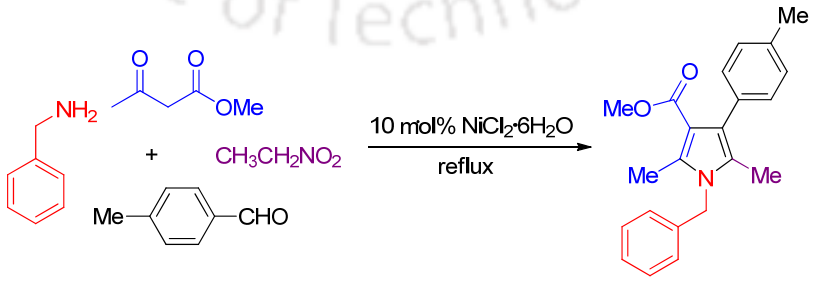
Chapter 4 described the synthesis of pyran annulated heterocyles through one-pot three component condensation reaction of aldehydes, ethyl cyanoacetate or malononitrile and 4-hydroxycoumarin or condensation of aldehydes, malononitrile and cyclic 1,3-diketones in presence of 4-(dimethylamino)pyridine (DMAP). From these successful results, it is evident that DMAP is a valuable catalyst for MCRs and its usefulness may be explored in future.



Chapter 5 elaborates the synthesis of fused *trans*-2,3-dihydrofuran derivatives through one-pot three-component reaction from aromatic aldehydes, cyclic β-diketo compounds involving *in situ* generated pyridinium ylide from either α-phenacyl bromide or 4-nitrobenzyl bromide and pyridine in presence of 10 mol% NaOH solution. In this transformation pyridine has two important roles such as formation of pyridinium salt, which in turn forms nitrogen ylide in presence of a NaOH solution, and it acts as a good leaving group. The characteristic feature of this transformation is without non-involvement of organic solvents.



Chapter 6 demonstrates the synthesis of *tetra*-substituted pyrrole derivatives through one-pot four-component condensation reaction from β-ketoesters, aromatic aldehydes, benzylamines and nitroalkanes in the presence of 10 mol% $NiCl_2{\cdot}6H_2O$ in good yields under reflux conditions. In addition, the present protocol is applicable to a wide range of substrates in moderate to good yields. We have also established that $NiCl_2{\cdot}6H_2O$ is a new catalyst for MCRs. In the present protocol, nitro group acts as a pseudo leaving group.



CONTENTS

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam during the period from 31st July, 2007 to 14th May, 2012 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

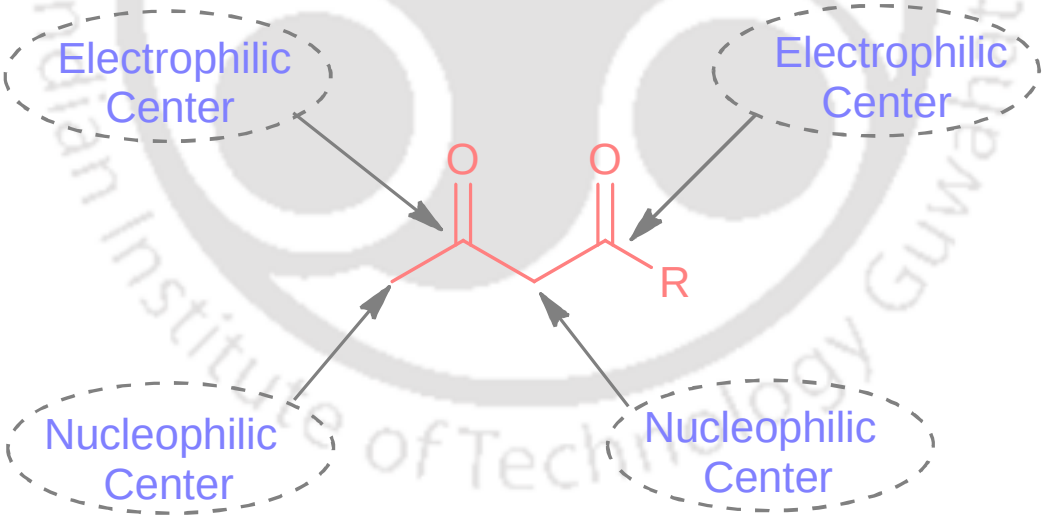
The analytical samples were routinely dried *in vacuo* at 50 ^{o}C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent were used. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buechi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at 25 ºC temperature. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 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), dq (doublet of quartet), dt (doublet of triplet) and ddt (doublet of doublet of triplet). HRMS 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.

ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	cerium(IV)ammonium nitrate
CCDC	cambridge crystallographic data centre
COSY	correlation spectroscopy
DBU	1,8-diazabicycloundac-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
1,4-DHP	1,4-dihydropyridine
DHPMs	Dihydropyrimidines
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enatiomeric axcess
EWG	electron withdrowing groups
IR	infrared
MCR	multicomponent reaction
M.p.	melting point
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
ORTEP	oak ridge thermal ellipsoid program
2,6-PDCA	2,6-pyridinedicarboxylic acid
Ph	phenyl

PMB	*p*-methoxy benzyl
ppm	parts per million
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
rt	room temperature
TBATB	n-tetrabutylammonium tribromide
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
XRD	x-ray diffraction

Brief review on importance of 1,3-dicarbonyl compounds for the syntheses of heterocycles involving multicomponent reactions (MCRs) and its future scope



1.1 Introduction

To device an efficient and chemo-, regio-, diastereo-, and enantioselective synthetic strategy for synthesizing complex organic molecules is one of the most exciting challenges to the synthetic chemists.[1] Due to economic and ecological increasing pressure in society, new concepts and methodologies are in great demand in recent times, which are environmentally benign and acceptable.[2] Among various synthetic strategies, multicomponent reaction[3] (MCR) is one of the most well-designed approaches to achieve complex molecules and they have gained considerable attention nowadays among the synthetic organic chemists by taking into account of the criterion of Green Chemistry and Sustainable Chemistry.[4]

1.2 Multicomponent reactions (MCRs)

The definition of multicomponent reaction is given by Ugi and his co-worker a few years ago as follows:

"Multicomponent reactions (MCRs) are convergent reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product."

A. Dömling, I. Ugi, *Angew. Chem. Intl. Ed.* ***2000****, 39, 3168*

The definition can also be represented schematically as shown in Figure 1.

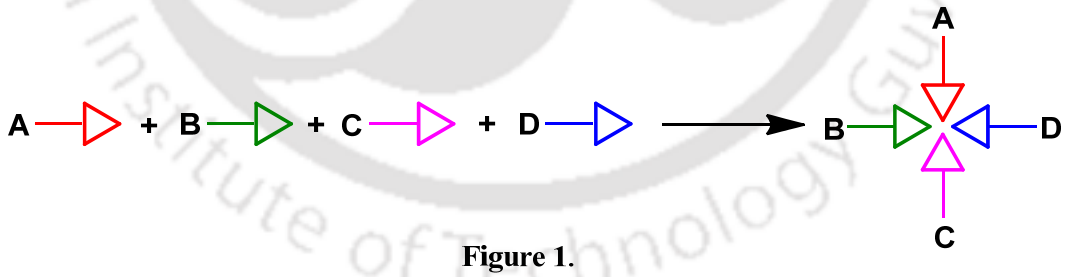


Figure 1.

The formation of *C-C*, *C-N*, *C-O* and *C-S* bonds can be formed in a single step for creating molecular diversity by employing MCRs.[5] Sometimes, the term MCR is also replaced with the word[6] either 'cascade' or 'domino' or 'one-pot' reaction due to its recognition among the synthetic chemists.

MCRs may be classified depending upon the number of molecules and functional groups participating in the reaction[7] as shown in Figure 2.

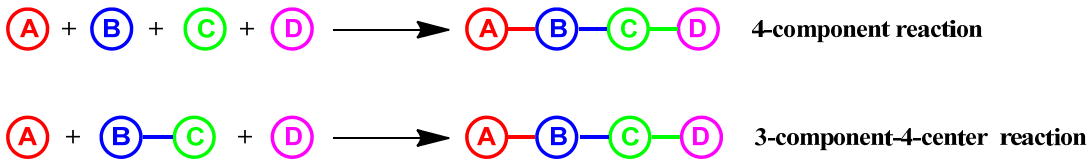


Figure 2.

It can be further subdivided based on their rational design strategies as: a) Single reactant replacement (SRR), b) Modular reaction sequences (MRS), c) Conditions-based divergence (CBD) and d) Combination of MCRs (MCR^2). These classifications were nicely described for better understanding by Orru and his co-workers in their recent review.[8]

The synthetic strategy involving MCRs comprises to provide easy and rapid access to a large library of new organic molecules in a short time, which is also known as starting points for Diversity-Oriented Synthesis (DOS).[9] They are easier to handle as compared to multistep syntheses as it is performed in one-pot, as shown in Figure 3. Coupled with high-throughput library screening, this strategy plays a significant role in the development of drug discovery[10] in the context of rapid identification and optimization of biologically active compounds. Libraries of small organic molecules are perhaps the most important potential drug candidates for future generation.[8] A large libraries can be architecturally constructed within a short period of time from a small number of readily available starting materials, which may then be used in pharmaceuticals. Therefore, MCRs have become a rapidly emerging area of research in the context of drug discovery for the generation of libraries of organic molecules in a time- and cost-effectiveness manner, and they are now expecting as key tools in industry and academic research.

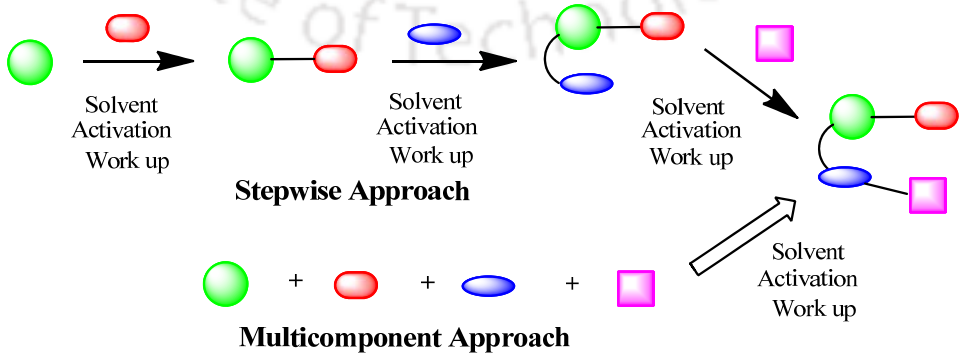
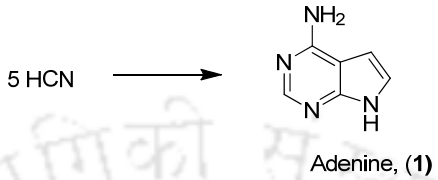


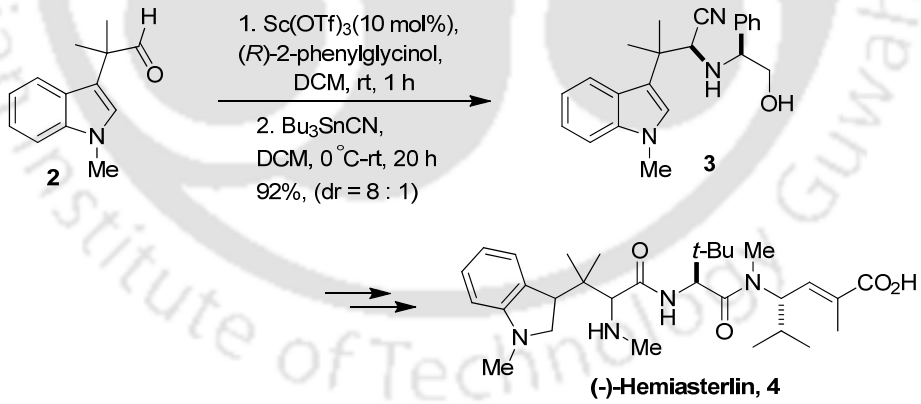
Figure 3. Comparison of Stepwise versus Multicomponent Approach

Nature also plays a key role in evolution of MCR and it has made significant contribution to the synthesis by utilizing similar strategy. For example, adenine (**1**), one of the major constituents of DNA and RNA, was prebiotically synthesized by oligomerization of HCN in presence of NH_4OH at pH 9.2 (Scheme 1).[11]



Scheme 1.

In 1850 Strecker first reported[12] the synthesis of α-amino nitrile derivatives by the condensation of aldehyde/ketone, hydrogen cyanide and amine or its equivalent, which is a major break-through for the modern contribution to the development of multicomponent reaction. His idea was shown by Vedejs and his co-workers[13] for the synthesis of key intermediate amino nitrile **3**, which was ultimately converted into the enantioselective total synthesis of (-)-hemiasterlin (**4**), a marine tripeptide having cytotoxic and antimitotic activity, as illustrated in Scheme 2.



Scheme 2.

In the year 1921, Passerini demonstrated[14] isocyanide-based three-component reaction (3-CR) for the synthesis of depsipeptide-like elements starting from carboxylic acid, carbonyl compound and isocyanide.

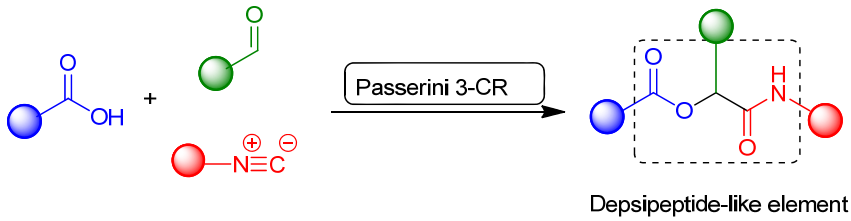


Figure 4. Passerini reaction

Later on, Ugi[15a] and his co-worker have shown remarkable contribution for the construction of dipeptide elements using isocynide based MCRs by adding amine with Passerini's starting material.

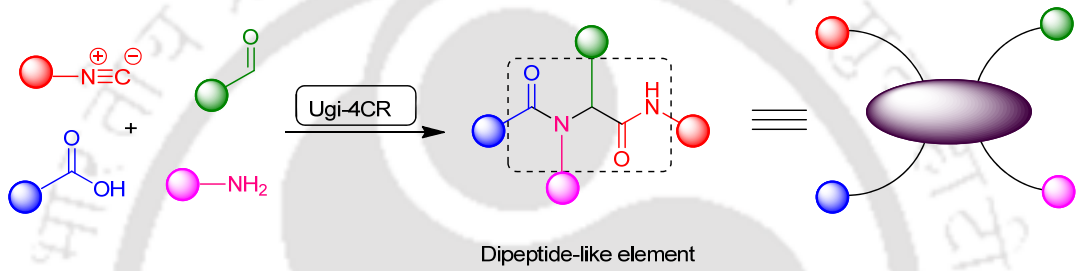


Figure 5. Ugi reaction

By employing isocyanides as one of the key starting materials, Ugi and his co-worker have shown the versatility of multicomponent reaction for synthesizing a large number of new molecules.[15b] Likewise, 1,3-dicarbonyls have been utilized extensively in multicomponent reactions (MCRs) by various research groups for the synthesis of numerous compounds.[16] Therefore, the synthetic application of 1,3-dicarbonyl compounds have been addressed below towards the synthesis of heterocyclic compounds as the aim of my research work to synthesize heterocyclic compounds using similar kind of starting materials.

1.3 Use of 1, 3-Dicarbonyl Compounds in Multicomponent Reactions

1,3-Dicarbonyl compounds are having multi-centres reaction sites in which electrophiles and nucleophiles may react for new bond forming reaction. They have been found to be valuable building blocks in the synthesis of a wide variety of heterocyclic compounds.[16] 1,3-Dicarbonyl compound possess four reacting centres as it contains two electrophilic

and two nucleophilic carbons as depicted in Figure 6, which can react in a selective manner under suitable reaction conditions.

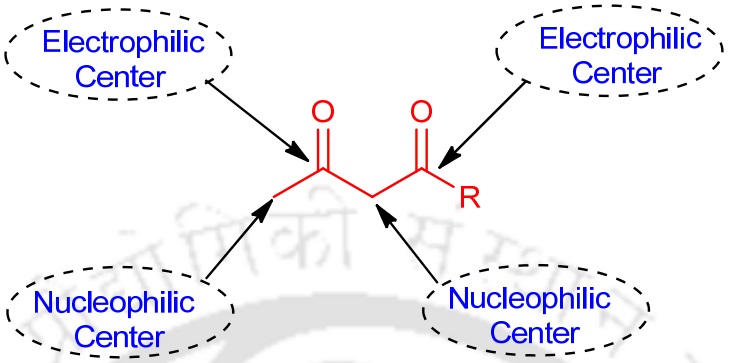


Figure 6.

Generally, these compounds can undergo the following well-known reactions as represented in Figure 7 along with the year it was discovered.

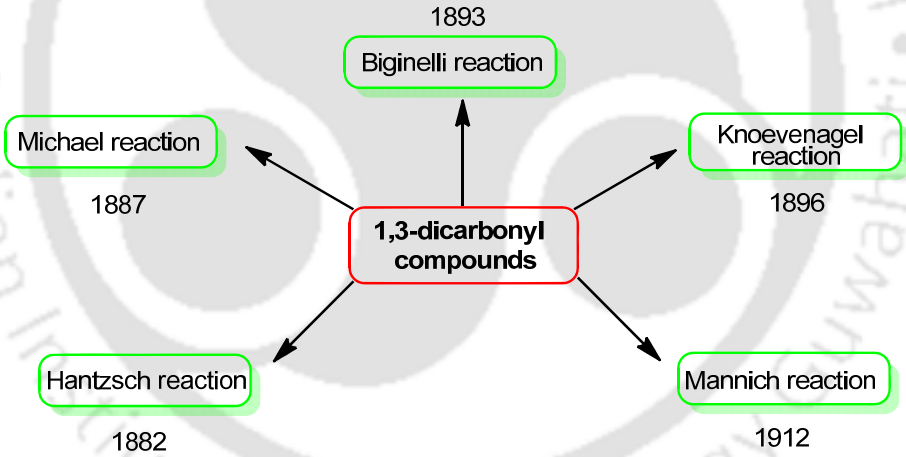
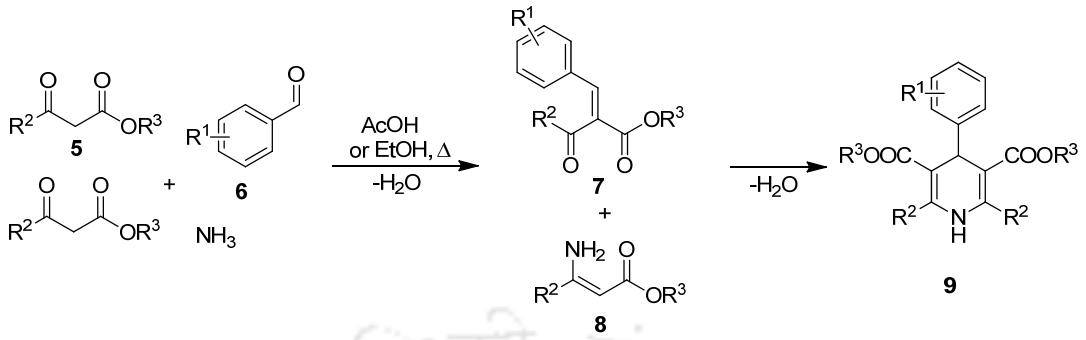


Figure 7.

1.4 Synthesis of heterocycles involving MCRs based on the Hantzsch reaction

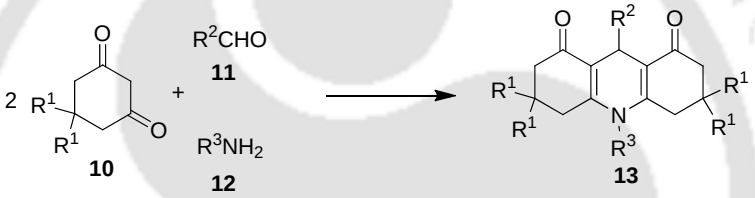
The Hantzsch Reaction

Arthur Rudolf Hantzsch first reported[17] preparation of 1,4-dihydropyridine (1,4-DHP) derivatives **9** starting from acetoacetic ester (**5**), aldehyde **6** and ammonia or ammonium salts, which is shown in Scheme 3. He proposed that the reaction proceeds through the condensation of *in situ* generated alkylidene malonate **7** and enaminoester derivative **8** followed by cyclodehydration for the formation of the final product.



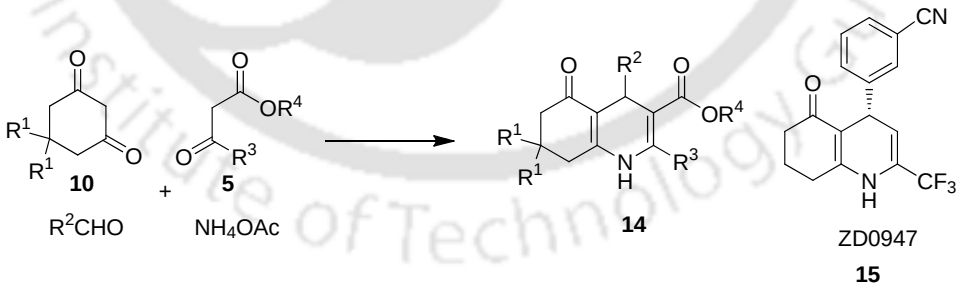
Scheme 3.

Due to their pharmaceutical importance and constitute interesting biomimetic reducing agents, Sambongi *et al.* reported[18] the synthesis of symmetrical 1,4-DHP derivatives **13** from dimedone, aldehyde and amine as shown in Scheme 4.



Scheme 4.

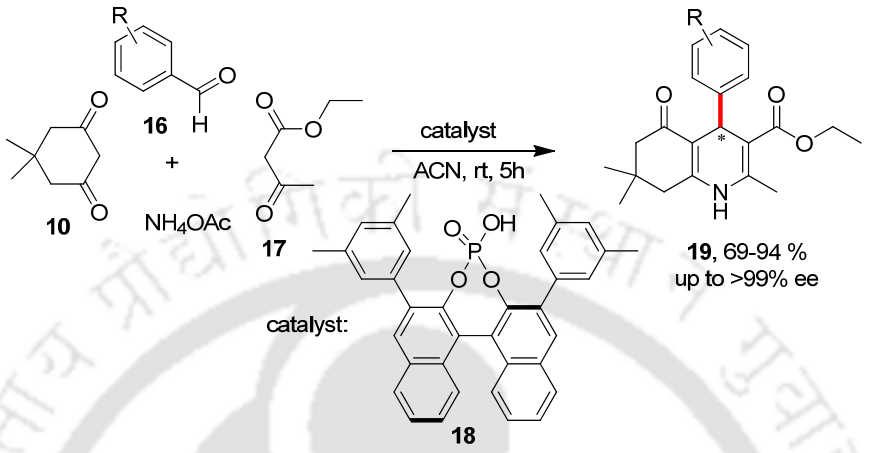
Later on, Moseley demonstrated[19] the synthesis of fused 1,4-dihydropyrdine **14** such as ZD0947 (**15**), a potassium channel opener, involving Hantzsch reaction as shown is Scheme 5.



Scheme 5.

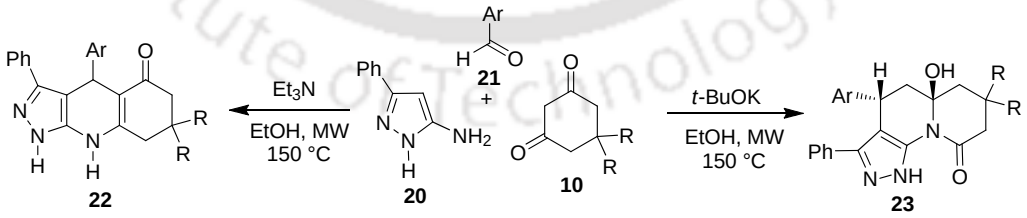
Over the years, several environmentally benign synthetic methods have been developed for the synthesis of this class of compounds by employing Hantzsch reaction using microwave irradiation,[20] ultra-sonication [21] and solar energy.[22]

Gestwicki et al. also recently reported[23] an enantioselective route for the synthesis of optically active 1,4-DHP derivatives **19** in good yields using Hantzsch reaction in presence of a chiral organocatalyst **18**, as depicted in Scheme 6.



Scheme 6.

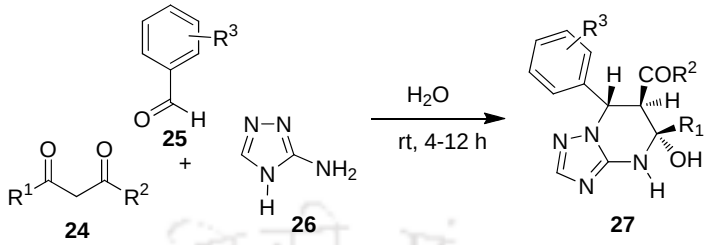
Recently Kappe et al.[24] invented modified-Hantzsch reaction for the synthesis of stereoselective synthesis of pyrazolo[4,3-c]quinolizin-9-ones using microwave irradiation of a mixture of dimedone (**10**), aminopyrazole **20** and aromatic aldehydes in the presence of a base. The linear **22** and angularly fused pyrazolo[4,3-c]quinolizin-9-ones derivatives **23** were obtained in moderate to good yields using two different bases such as *t*-BuOK and Et_3N, as depicted in Scheme 7. They proposed that the intermediate of linear product **22** undergoes further nucleophilic attack with potassium *tert*-butoxide followed by ring-opening and recyclisation of the cyclic 1,3-dikeone fragment leading to the formation of angularly pyrazole derivatives **23.**



Scheme 7.

Interestingly, the synthesis nitrogen-containing polyheterocycles having biological interest[25] can also be achieved by using similar three-component condensation reaction by replacing enamine component with a guanidine moiety. By involving 3-amino-1,2,4-

triazole (**26**), aromatic aldehydes (**25**) and 1,3-dicarbonyl substrates (**24)** in aqueous medium provided bicyclic hemiaminals **27**, as shown in Scheme 8.

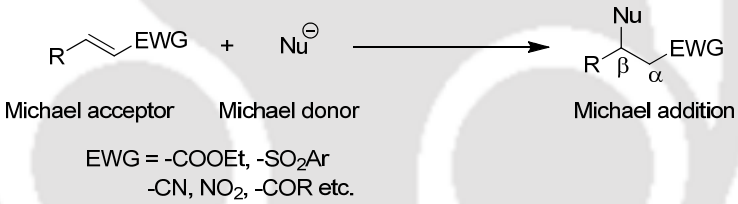


Scheme 8.

1.5 Synthesis of heterocycles involving MCRs based on the Michael reactions

1.5.1 The Michael Addition

The Michael reaction is the reaction of an enolate of a ketone or aldehyde, which acts as a nucleophile, to an α,β-unsaturated carbonyl compounds at the β-carbon,[26a,b] as shown in Scheme 9. According to Kohler, all reaction that involve a 1,4-addition of stabilised carbon nucleophile to an activated π-systems are known as Michael addition reactions.[27]



Scheme 9.

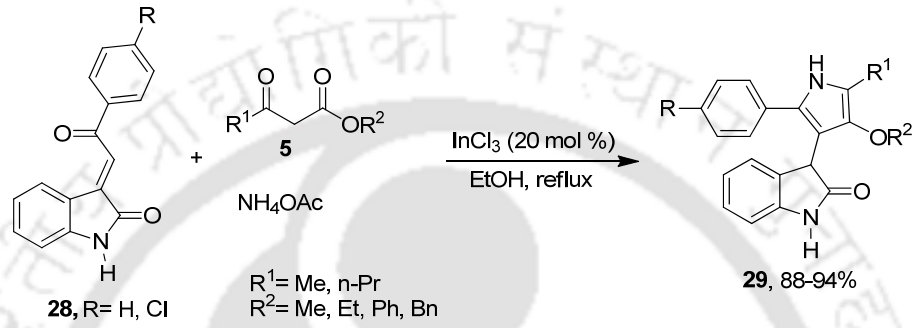
Over the last decades, numerous Michael reactions have been developed such as the aza-Michael,[28] thia-Michael[29] and phospha-Michael reaction.[30] However, oxa-Michael[31a] reactions have been paid less attention by the synthetic organic chemists as compared to the addition of carbon nucleophiles to a conjugate acceptors. By involving Michael reaction in the synthetic plan, numerous heterocyclic compounds can be synthesized very easily involving 1,3-dicarbonyl compounds as the pivotal starting material, which is reviewed recently[31b] and some of their importance is discussed below.

1.5.2 Five-Membered Heterocycles

1.5.2.1 Synthesis of Pyrrole Derivatives

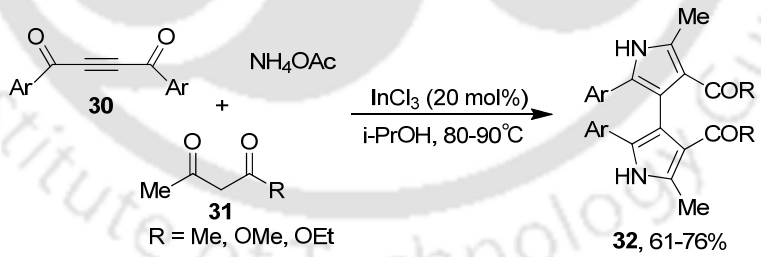
The development of new and simple methods for the synthesis of substituted pyrroles **29** from readily available starting materials still remains an open area of investigations for

organic chemists. In this perspective, Perumal's group demonstrated an $InCl_3$-catalyzed[32] MCR for the efficient synthesis of 2-pyrrolo-3′-yloxindoles (Scheme 10) from 3-phenacylideneoxindole **(28)**, ammonium acetate and β-ketoesters (**5**). The sequence involves the Michael addition of the enol form of the 1,3-dicarbonyl onto the 3-phenacylideneoxindole affording a 1,4-dicarbonyl intermediate, which then undergoes a Paal–Knorr condensation with ammonium acetate to form the pyrrole derivatives **29**.



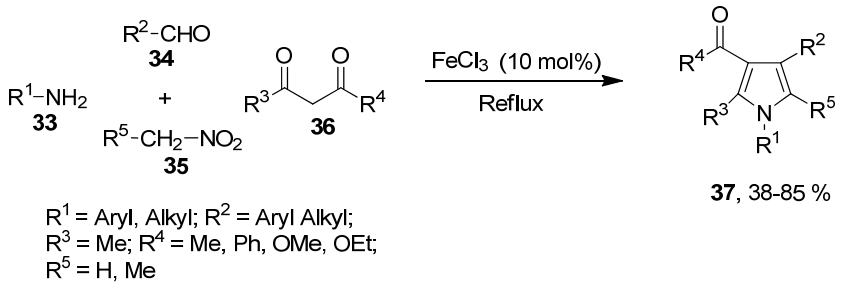
Scheme 10.

Recently Jaisankar et al.[33] devised a very efficient chiral route to 3,3′- bipyrroles **32** via a Lewis acid-catalyzed three-component double Michael additions between diaroyl acetylenes **30**, ammonium acetate and 1,3-dicarbonyls **31** (Scheme 11). Interestingly, these compounds exhibit conducting property as well as a broad range of biological activities.



Scheme 11.

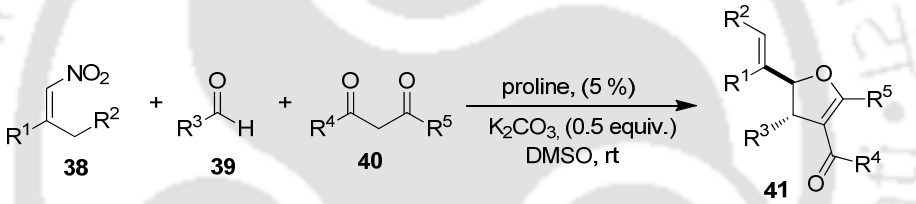
Recently, Jana et al. have reported[34] a novel $FeCl_3$-catalyzed four-component one pot coupling reaction for synthesis of highly functionalized pyrroles **37** from 1,3-dicarbonyl compounds **36**, aldehydes **34**, amines **33**, and nitroalkanes **35** (Scheme 12). In this MCR reaction, nitroalkane plays dual role such as solvent as well as reactant.



Scheme 12.

1.5.2.2 Synthesis of Dihydrofuran Derivatives

Shi et al.[35] described the synthesis of substituted dihydrofuran derivatives **41** through a Lewis base-catalyzed cascade condensation reaction of nitroalkenes **38**, aldehydes **39** and 1,3-dicarbonyl compounds **40** as shown in Scheme 13. The most important feature of this transformation is that the NO_2 group plays crucial role for Michael reaction as well as leaving group for cyclization to obtain final product 41.

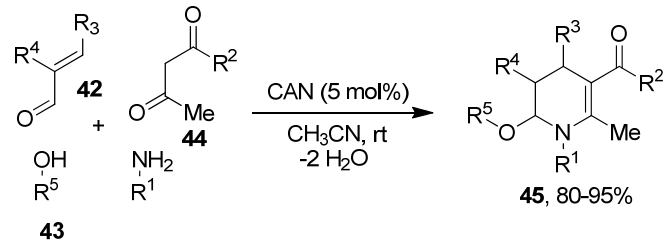


Scheme 13.

1.5.3 Six-Membered Heterocycles

1.5.3.1 Synthesis of Tetrahydropyridines

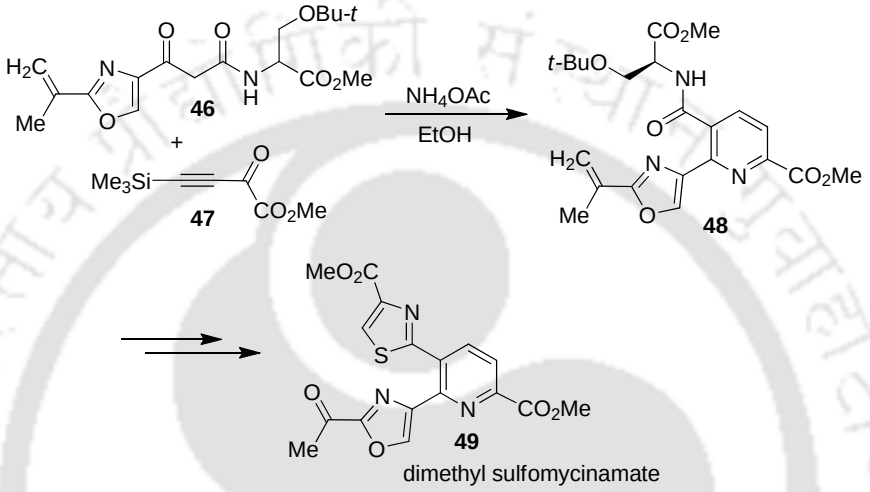
Rodriguez and his co-workers reported first domino reaction using 1,3-dicarbonyl compounds based on Michael reaction for the synthesis of polycyclic *N/O*, *N/S*, *N/N* aminals.[36a] Later on, Menendez et al.[36b] demonstrated a four-component reaction for the synthesis of tetrahydropyridines **45** in high yields by employing primary aliphatic amines, 1,3-dicarbonyls **44**, and α-β-unsaturated aldehydes **42** and alcohols **43** using cerium(IV) ammoniumnitrate (CAN) as catalyst as shown in Scheme 14.



Scheme 14.

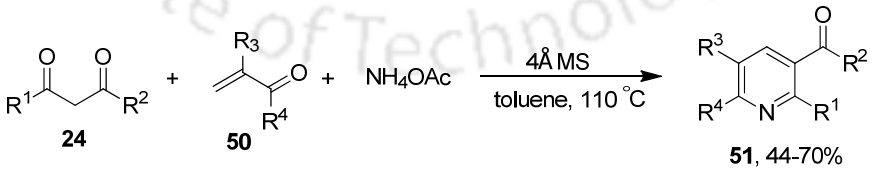
1.5.3.2 Synthesis of Pyridine Derivatives

The functionalized pyridines are one of the most important nitrogen heterocycles found in numerous natural products and pharmaceuticals. Bagley et al. reported useful synthetic strategy[37] for the synthesis of trisubstituted pyridines **48** based on the three-component condensation reaction of 1,3-dicarbonyl compounds **46**, an alkynone **47**, and an ammonium acetate as shown in Scheme 15.



Scheme 15.

Recently Rodriguez et al.[38a] accomplished regioselective and metal-free Michael addition-initiated three-component reactions for the direct pathway of tetrasubstituted pyridines **51** from 1,3-diketones/ β-ketoesters (**24**) or β-ketoamides, α,β-unsaturated aldehydes or ketones **50** and a synthetic equivalent of ammonia in presence of molecular sieves (4Å) as depicted in Scheme 16. The same group further demonstrated[38b] the synthesis of polyfunctionalized pyridines using β,γ-unstaturated α-ketocarbonyls instead of α,β-unsaturated aldehydes or ketones.

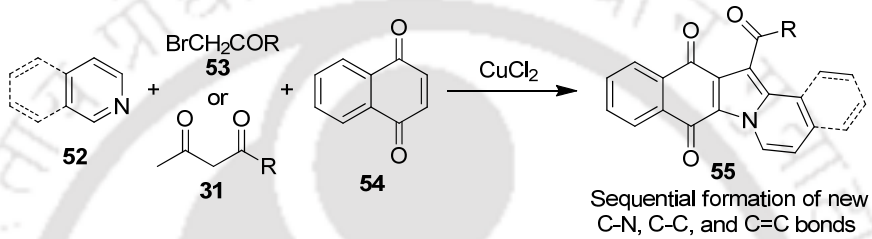


Scheme 16.

1.5.3.3 Indolizines Derivatives

Indolizines and their annulated derivatives have received much attention in recent years. Annulated indolizine framework contains in many naturally occurring alkaloids with important biological activity. Liu et al.[39] achieved the synthesis of benzo[*f*]pyrido[1,2-

a]indole-6,11-diones (**39**) by the using of copper(II) catalyzed four component reactions involving 1,4-naphthoquinone, acyl bromide (**53**), 1,3-dicarbonyl **31** and pyridine or isoquinoline **52**. By this protocol, naphthoquinone (**54**) undergoes C(sp^2)−H difunctionalization by a tertiary amine and an active methylene compound resulting in the successive formation of *C−N* and *C−C* bonds. Subsequent intramolecular nucleophilic cyclization followed by Cu^{2+} mediated oxidative aromatization, it furnishes the benzo[f]pyrido[1,2-a]indole-6,11-dione derivatives **55** from easily accessible starting materials in high yields as shown in Scheme 17.

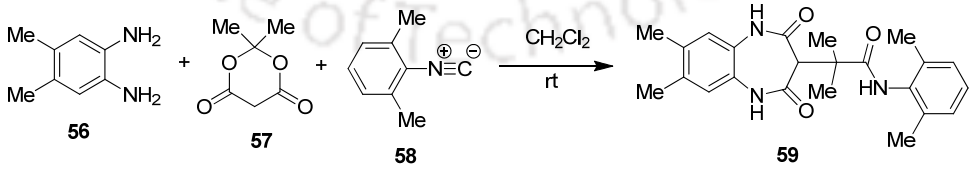


Scheme 17.

1.5.4 Seven membered heterocycles

Diazepines Synthesis

Shaabani et al. have shown an elegant approach[40] for the synthesis of tetrahydro-2,4-dioxo-1*H*-benzo[*b*][1,5]diazepine-3-yl-2-methylpropanamide derivatives **59** using an aromatic diamine **56**, Meldrum's acid (**57)** and an isocyanide **58** in CH_2Cl_2 at ambient temperature in high yields without using any catalysts or activation. The procedure provides an alternative method for the synthesis of benzo[*b*][1,5]diazepine derivatives. These compounds have closely related ring systems such as triflubazam, clobazam, and 1,5-benzodiazepines, which have a broad spectrum of medicinal values.



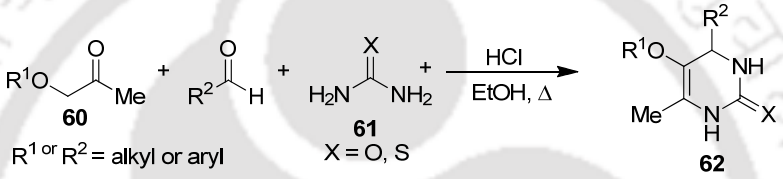
Scheme 18.

From the above discussions, it was noted that numerous heterocyclic compounds can be synthesized through MCRs by employing 1,3-dicarbonyl compounds as main ingradients involving Michael reaction.

1.6 Biginelli Reaction for Heterocyclic Synthesis

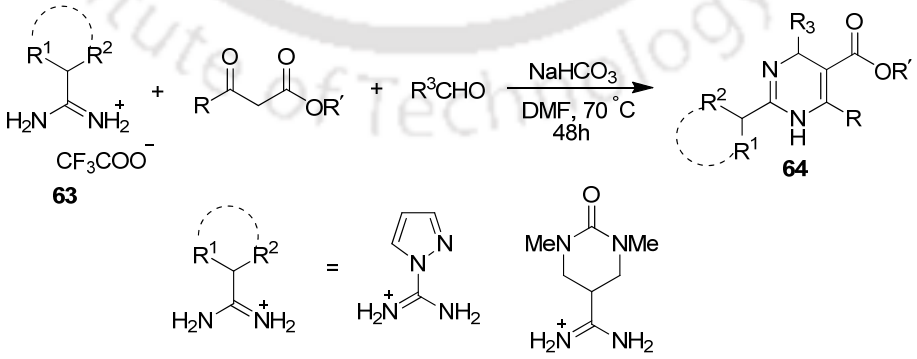
1.6.1 The Biginelli Reaction

The Biginelli reaction is also one of the most popular and useful multicomponent reactions, It was discovered by Pietro Biginelli in 1893 by which the synthesis of dihydropyrimidine derivatives **62** was accomplished from β-ketoester **60**, aldehyde and urea **61** in the presence of acid catalysts[41] (Scheme 19). The same reaction has been explored under a wide variety of reaction conditions and several experimental procedures have been exposed in recent years.[42] This reaction offers an efficient way to access 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs) and related compounds, which display a wide range of pharmacological activities.[43]



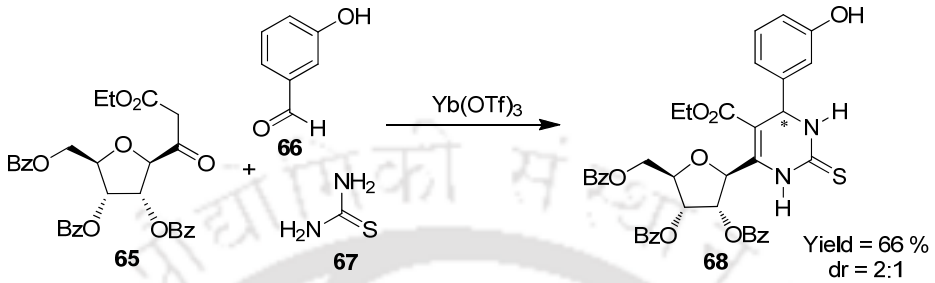
Scheme 19.

Guanidine framework is found in several natural products such as saxitoxin, tetrodotoxin, or batzelladine F and they also show interesting biological activities. Overman et al exposed an interesting approach to the synthesis of cyclic guanidines by employing guanylating agents **63** instead of urea in a Biginelli type multicomponent reaction (Scheme 20).[44] They have shown that pyrazole carboxamidines and triazone-protected guanidines are useful starting material for the synthesis of 2-aminopyrimidines **64** in moderate to good yields.



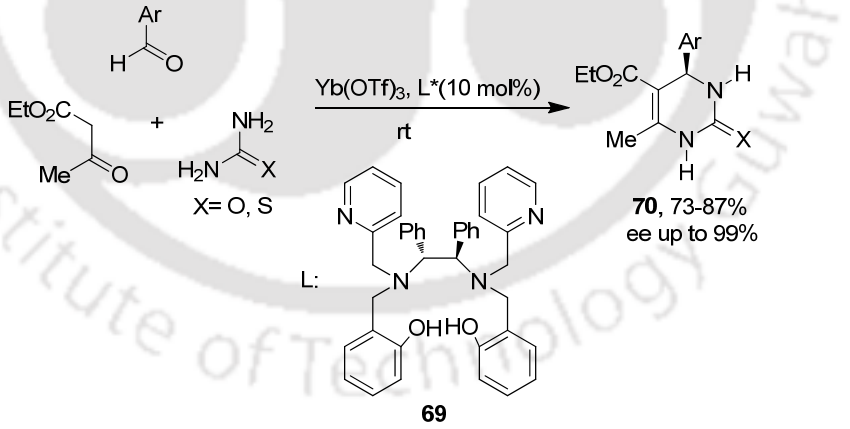
Scheme 20.

Optically active DHPMs **68** were synthesized[45] by Dondoni and his research group through auxiliary-assisted asymmetric synthesis involving chiral starting material such as C-glycosyl substrates **65**, thiourea (**67**) and aromatic aldehydes as shown in Scheme 21.



Scheme 21.

Zhu et al.[46a] described a highly enantioselective multicomponent based Biginelli reaction using a recyclable catalyst $Yb(OTf)_3$ in presence of a novel chiral hexadentate ligand bearing tertiary amine phenol containing pyridine skeleton **69**, The asymmetric products **70** were obtained in high yields with an excellent enantioselectivities (up to 99% ee) as depicted in Scheme 22. Very recently, Gong et al. reviewed[46b] Brønsted-acid catalyzed asymmetric multicomponent reactions for the synthesis of highly enantioenriched nitrogeneous heterocycles.

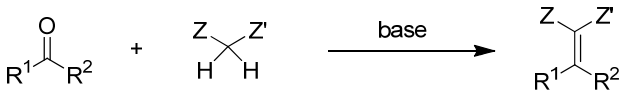


Scheme 22.

1.7 Synthesis of heterocycles through MCRs based Knoevenagel reaction

The Knoevenagel condensation of aldehydes or ketones with active methylene compounds is an important and useful technique for carbon-carbon bond forming reaction (Scheme 23).[47a,b,c] It has been executed in numerous applications namely synthesis of fine chemicals,[48] hetero Diels–Alder reactions[49] synthesis of carbocycles and

heterocycles[50] having potent biological activities. The reactions are usually conducted in the presence of a suitable base.[51]



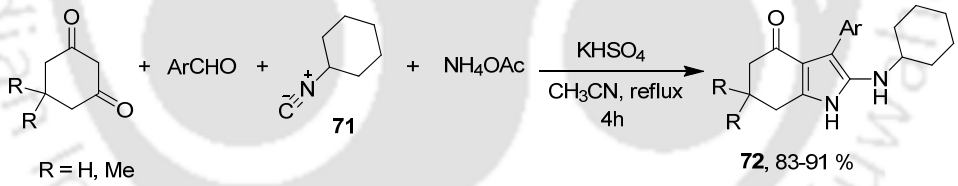
Scheme 23.

It is well established that aldehydes are much more reactive as compared to ketones and active methylene substrates employed are essentially those bearing two electron-withdrawing groups. From the synthetic point of view, β-dicarbonyl compounds are prospective aspirant for Knoevenagel reaction.

1.7.1 Five-Membered Heterocycles

1.7.1.1 Synthesis of Dihydroindolone Derivatives

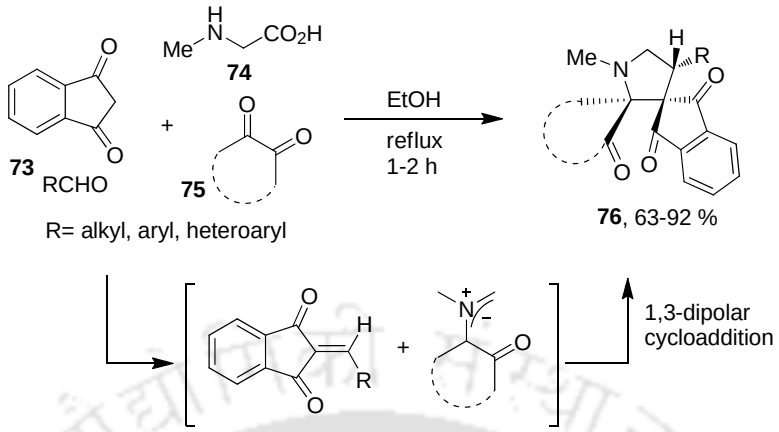
Dihydroindolones **72** have been synthesized by a MCR involving cyclic 1,3-diketones, cyclohexyl isocyanide **71**, aromatic aldehydes, and ammonium acetate in the presence of catalytic amount of $KHSO_4$ in refluxing acetonitrile (Scheme 24).[52] In this reaction, the imine derived from the Knoevenagel adduct reacts with cyclohexyl isocyanide to give the desired product after tautomerization as represented in Scheme 24.



Scheme 24.

1.7.1.2 Synthesis of Bispiropyrrolidine Derivatives

Bispiropyrrolidine derivatives **76**, which are potential antileukemic and anticonvulsant agents possessing antiviral properties, have been achieved by employing Knoevenagel reaction. A mixture of 1,3- indanedione **73**, aldehyde, sarcosine **74** and a cyclic 1,2-dione **75** in ethanol under reflux conditions without any catalyst provided bispiropyrrolidine derivatives[53] as a single diastereomer as shown in Scheme 25. The highly regio- and stereoselective four-component Knoevenagel–Huisgen cyclo-addition sequence is of immense interest for the synthesis of complex molecules.

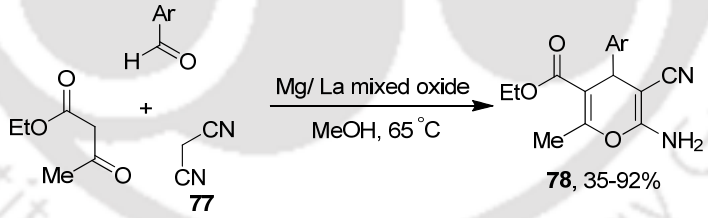


Scheme 25.

1.7.2 Six-Membered Heterocycles

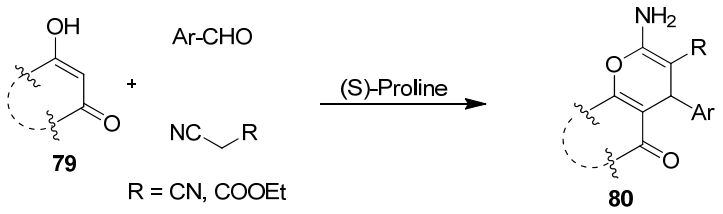
1.7.2.1 Synthesis of Pyran Derivatives:

4H-Pyran and its derivatives are important oxygen heterocycles owing to their biological and pharmaceutical activities. The reaction of arylidenemalononitriles with activated acyclic methylene compounds in the presence of organic bases allows the formation of substituted pyran derivatives *via* three component reaction. Lingaiah et al. reported[54] the synthesis of 5-substituted-2-amino-4-aryl-3-cyano-6-methyl-4H-pyrans **78** using a hetero-geneous mixed oxide of Mg/La as catalyst as depicted in Scheme 26.



Scheme 26.

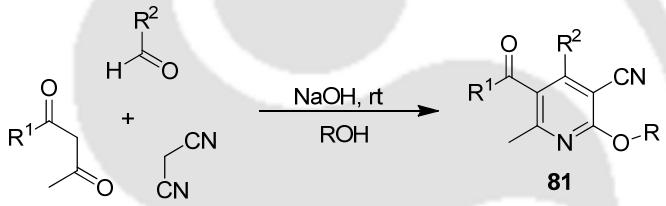
Further this approach has been extended further to cyclic 1,3-dicarbonyls **79** for the synthesis of tetrahydrobenzopyran derivatives, also known as tetrahydrochromenes, due to their wide range of biological activities. The compound **80** was synthesized[55] from aromatic aldehyde, dimedone and malonitrile in aqueous media catalyzed by (S)-proline (Scheme 27). Very recently other catalysts namely DBU[56] and silica nanoparticles[57] have also been utilized to prepare the bicyclic heterocycles in excellent yields.



Scheme 27.

1.7.2.2 Synthesis of Substituted Pyridines

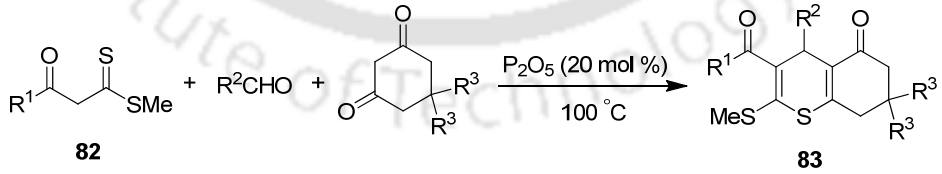
Lin et al.[58] demonstrated a novel synthesis of highly substituted pyridines **81** in a chemo- and regioselective manner *via* a one-pot four component reaction of 1,3-dicarbonyl compounds, aromatic aldehyde and malononitrile in the presence of alcoholic NaOH solution under mild conditions in which alcohol plays dual role such as reactant as well as solvent (Scheme 28)



Scheme 28.

1.7.2.3 Synthesis of Tetrahydrothiochromen-5-ones

Singh et al.[59] reported a novel one-pot three-component regioselective synthesis of 4-aryl-3-aroyl-2-methylsulfanyl-4,6,7,8-tetrahydrothiochromen-5-ones (**83**) by annulation of β-oxodithioesters **82** with aldehydes and cyclic 1,3-diketones under solvent-free conditions promoted by P_2O_5 as shown in Scheme 29.

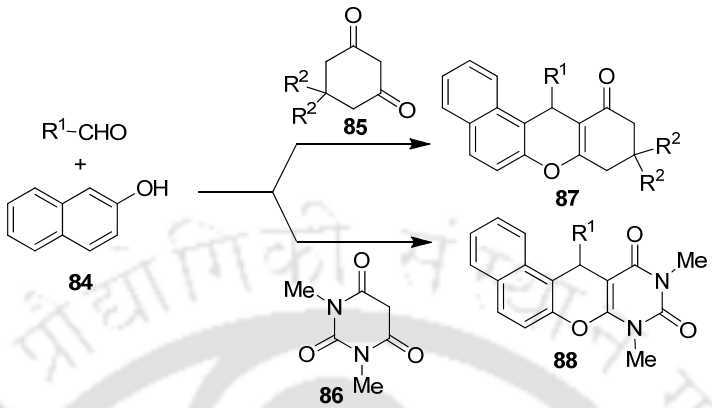


Scheme 29.

1.7.2.4 Synthesis of Tetrahydrobenzoxanthenone Derivatives

Benzoxanthene derivatives **87**, important biologically active heterocycles, have been synthesized by mixing of β-naphthol (**84**), an aromatic or aliphatic aldehyde and 1,3-

dicarbonyl compound involving Knoevenagel-type-initiated multicomponent reaction (Scheme 30).

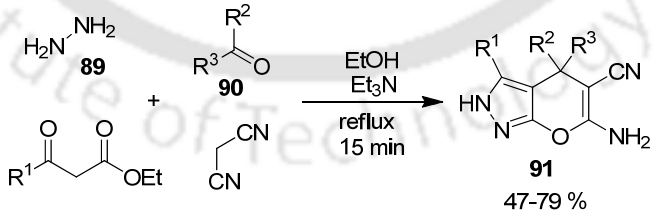


Scheme 30.

To synthesize these compounds, several catalyst have been explored such as indium(III) chloride or phosphorus pentoxide,[60] *n*-tetrabutylammonium fluoride,[61] *p*-toluenesulfonic acid in ionic liquid [bmim]BF_4,[62] molecular iodine[63] and sodium hydrogenosulfate on silica gel.[64]

1.7.2.5 Synthesis of Dihydropyranopyrazole Derivatives

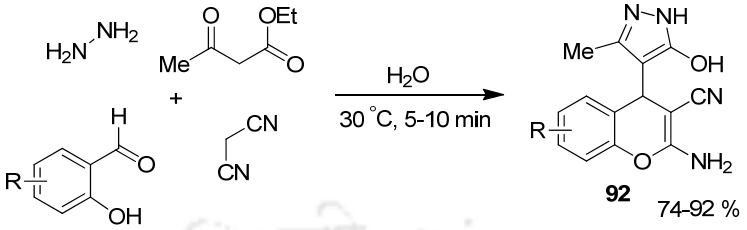
A Knoevenagel-based reaction was recently reported for the synchronized construction of two different fused heterocycles from acyclic precursors. In fact, a four-component Knoevenagel–Michael addition-cyclization sequence has been used for the synthesis of dihydropyranopyrazole derivatives **91** from hydrazine hydrate **89**, malononitrile, β-ketoester, and aldehyde/ketone **90** (Scheme 31).[65]



Scheme 31.

Recently, a variation of this four-component transformation in water was proposed as a green combinatorial synthesis of novel aminochromene derivatives **92** bearing a hydroxymethyl pyrazole functional group in the four-position instead of expected fused skeleton **91**. In this unexpected transformation, 2-hydroxybenzaldhyde plays a crucial

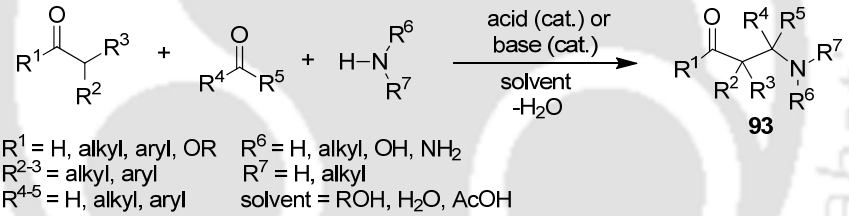
role by reacting selectively with malononitrile to form the chromene intermediate (Scheme 32).[66]



Scheme 32.

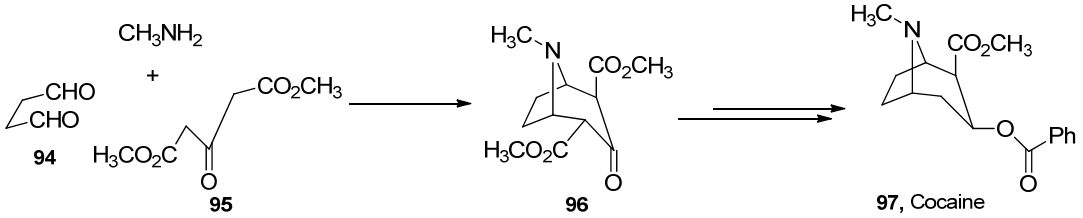
1.8 Synthesis of heterocycles through MCRs based Mannich reaction

The Mannich reaction, which was first recognized by Carl Mannich,[67] involves the condensation of an active methylene compound with a primary or a secondary amine and a non-enolizable aldehyde or ketone to afford β-amino carbonyl derivatives **93** (Scheme 33). Its tremendous synthetic utility has been explored for the synthesis of numerous pharmaceuticals and natural products.[68]



Scheme 33.

It is in great use for the construction of heterocyclic scaffolds, which can be visualized by the synthesis of tropane ring cocaine **97** in (Scheme 34)[69] involving dialdehyde, methylamine and dicarbomethoxyacetone in the presence of acid catalyst. Reaction was enormously utilized for the construction of five- to seven membered ring heterocycles, which is highlighted with few representative examples in below.

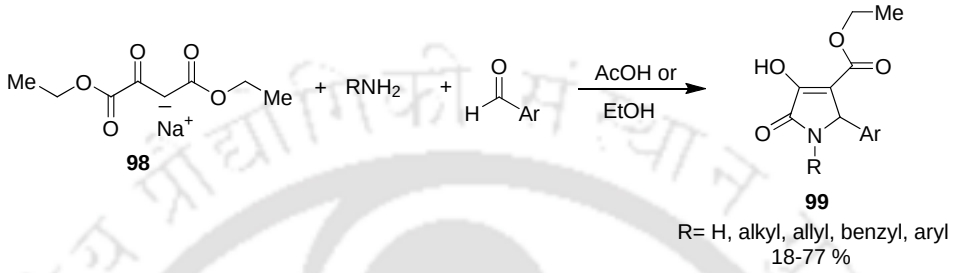


Scheme 34.

1.8.1 Five-Membered Heterocycles

1.8.1.1 Pyrrolidine Derivatives:

The synthesis of 2,3-dioxopyrrolidine derivatives **99** were reported[70] by Dehaen et. al. using sodium ethyl oxalacetate (**98**), ammonia or primary amines and aromatic aldehyde in ethanol or acetic acid through three-component reaction as shown in Scheme 35.

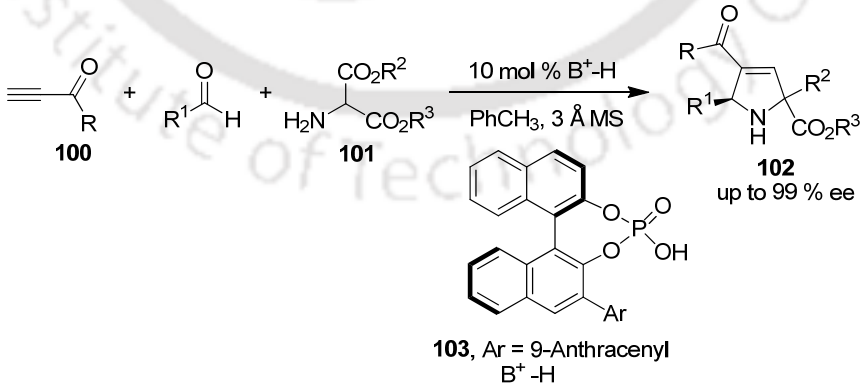


Scheme 35.

This methodology allowed the preparation of a small library of original 2-oxo-5-(hetero)-arylpyrroles, compounds of which the various synthetic and biological potentialities have been largely investigated

1.8.2 2,5-Dihydropyrroles Synthesis

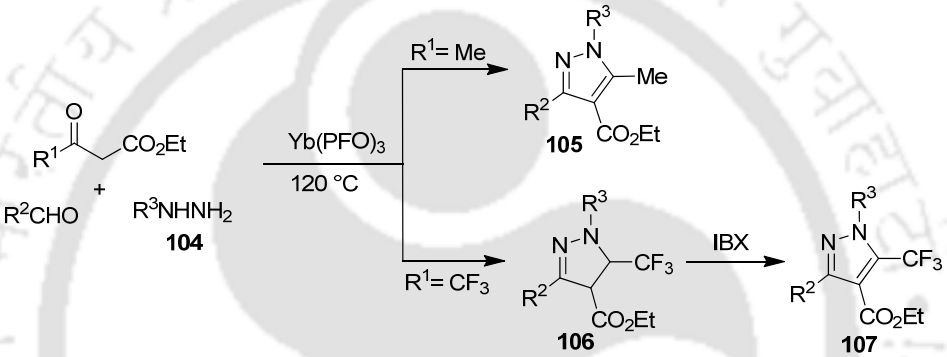
Gong et al.[71] have established the first asymmetric catalytic 1,3-dipolar cycloaddition reaction between electron-deficient carbon-carbon triple bonds **100** with azomethine ylides **101** for the synthesis of biologically active 2,5-dihydropyrrole derivatives **102** (Scheme 36). In this transformation, the chiral phosphoric acid derivative **103** has been used for the synthesis of a wide range of 2,5-dihydropyrrole derivatives.



Scheme 36.

1.8.1.3 Pyrazole Derivatives

Pyrazoles and their derivatives have received special attention due to the wide range of useful biological activities, making these products increasingly important agrochemicals and pharmaceutical agents. Various methods reported for the synthesis of fully substituted pyrazoles, the most general and applicable one consists on the cyclization of 1,3-diketones with substituted hydrazines. Quian et al. and others develop a new approach to synthesis pyrazole derivatives **105, 106** with coupling of aldehydes, phenylhydrazine (**104**), and 1,3-dicarbonyl compounds under solvent-free conditions in presence of ytterbium perfluorooctanoate as a catalyst (Scheme 37).[72]



Scheme 37.

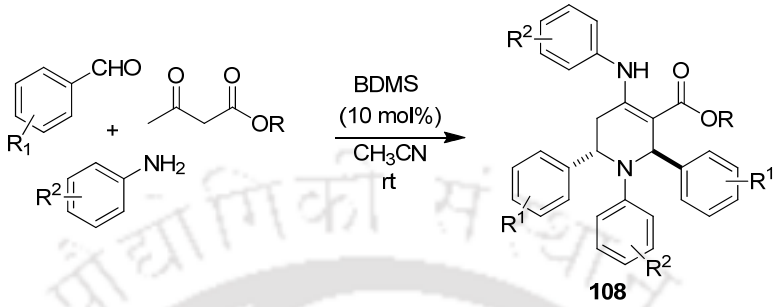
The methodology has been successfully extended to the synthesis of trifluoromethyl-containing pyrazoles[73] starting from ethyl trifluoroacetoacetate, but it is noteworthy to highlight that in this case the three-component reaction stopped at the formation of the corresponding pyrazolines, and a subsequent oxidation with IBX was necessary to obtain the desired pyrazoles **107**.

1.8.2 Six-Membered Heterocycles

Piperidine Derivatives

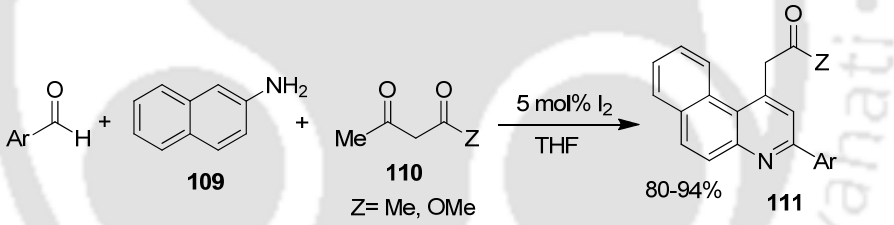
Piperidines and their analogues have been gained attention due to their biological and medicinal interest. In addition, piperidine skeleton is present in naturally occurring alkaloids.[74] A few years ago, Clarke and his co-worker reported[75] the synthesis of tetrahydropiperidine derivatives through five-component reaction using $InCl_3$ as catalyst. Later on, our group also demonstrated similar MCR strategy using less expensive catalyst namely bromodimethylsulfonium bromide (BDMS)[76a] and molecular iodine[76b] for the synthesis to highly functionalized and fully substituted piperidines **108** from 1,3-

dicarbonyls, aromatic aldehydes and aromatic amines (Scheme 38).[76] This strategy is quite interesting illustration of quite rarely exploited potentialities of β-ketoesters to react both at α- and γ-positions with electrophiles for *C–C* bond formations.[77]



Scheme 38.

Later on, we have found in the literature[78] that fused quinoline derivatives **111** were synthesized through three-component reaction from aromatic aldehydes, 2-aminonaphthalene (**109**) and ketones /β-ketoesters **110** using 5 mol% of iodine as shown in Scheme 39, just by changing the reaction conditions.

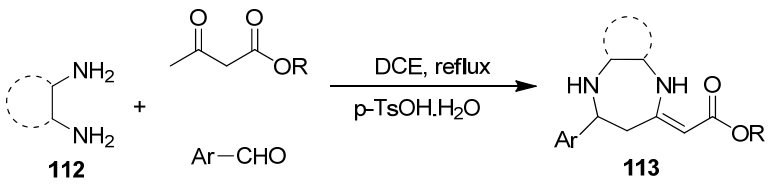


Scheme 39.

1.8.3 Seven-Membered Heterocycles

1,5-Benzodiazepine Derivatives:

The 1,5-benzodiazepin-2-one **113** is a privileged scaffold and its substructures exhibit a wide range of biological activities. Kita et al. first demonstrated[79a] one-pot synthesis of these heterocycles by a cyclodehydrative three-component reaction from 1,3-dicarbonyls, aromatic aldehydes and 1,2-diamines **112**. The similar synthetic strategy is also exploited by others.[79b,c] The reaction goes through the formation of an intermediate imine and enamino ester, which then reacts together to provide final product *via* an intramolecular Mannich-type condensation (Scheme 40). Interestingly, the synthesis of 1,5-benzodiazepine has been less explored using *o*-phenylenediammine instead of 1,2-diamines **112.**



Scheme 40.

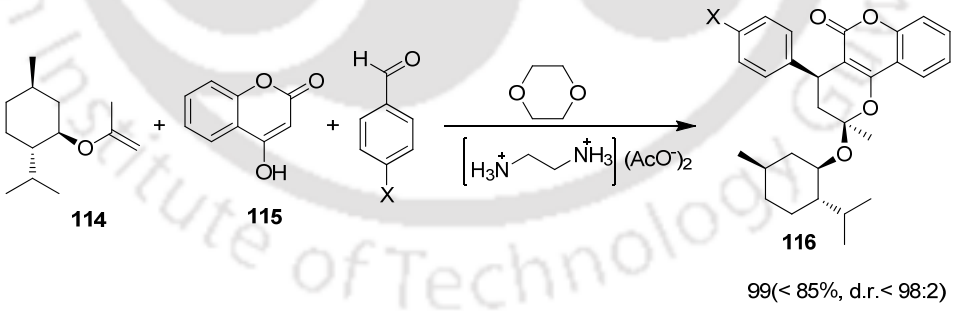
Reactions of 1,3-Dicarbonyl compounds through MCRs

The usefulness of 1,3-dicarbonyl compounds for the synthesis of various heterocyclic compounds through MCRs have been elabotated in the above section. Subsequently, their synthetic potentiality is further highlighted in natural product synthesis below.

1.9 MCRs based Tietze reaction and total synthesis of natural products

1.9.1 Warfarin synthesis

The combined domino Knoevenagel and Diels–Alder reaction is known as the Tietze multicomponent reaction.[80] The first variant of the reaction was developed by a diastereoselective approach and its enantioselective approach has also been achieved. This strategy has been used in the total synthesis of warfarin, which was marketed in the racemic sodium salt. Later on, the synthesis of warfarin was achieved by using chiral alkene (**114**), 4-hydroxycoumarin (**115**) and benzaldehyde in good yield with 88:12 d.r.[81] Finally on the hydrolysis of the compound **116** liberated the corresponding methyl ketone (warfarin) as shown in Scheme 42.

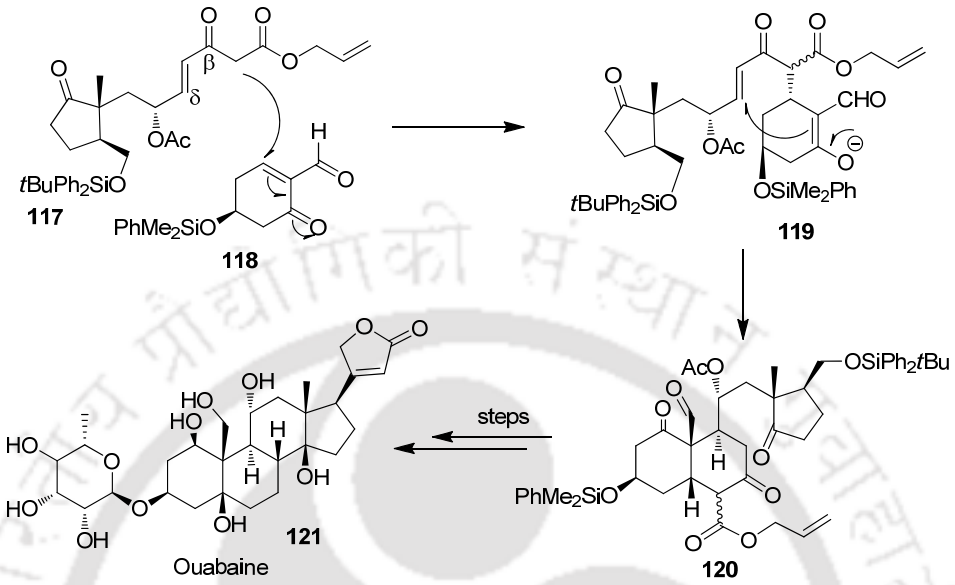


Scheme 41.

1.9.2 Ouabaine synthesis

Suitably designed 1,3-dicarbonyl compound can be utilized for the synthesis of glycosylated steroid ouabaine **121** as shown in Scheme 42.[82] In this case, the electrophilic β position is homologated to the δ position via the incorporation of a

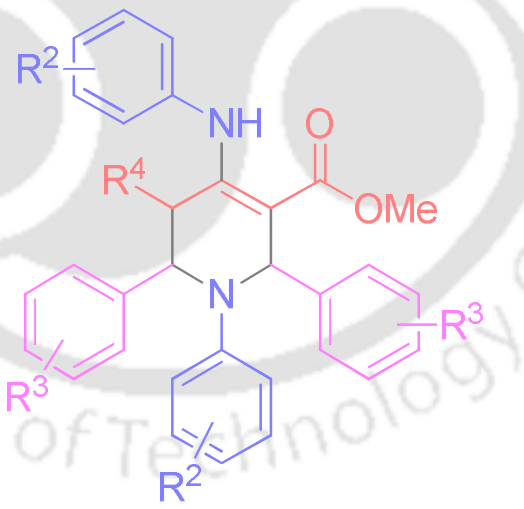
conjugated double bond. This approach was largely developed for the synthesis of steroids.



Scheme 42.

From literature, it is worth-while to mention that 1,3-dicarbonyl compounds are having enormous potentiality for the synthesis of numerous heterocycles as well as natural product synthesis. As a matter of fact, there is a further scope to develop new MCRs using 1,3-dicarbonyl compounds, which may give opportunity to find out new catalysts, different reaction conditions and new products. With this theme in mind, we perceived that 1,3-dicarbonyl compounds can be exploited further for its application in organic synthesis. In this dissertation, we would like to highlight our successful results based on MCRs for the synthesis of heterocycles, which will be discussed in the successive chapters of this thesis.

Synthesis of highly functionalized piperidines using one-pot five-component reaction involving *n*-tetrabutylammonium tribromide (TBATB) as pre-catalyst



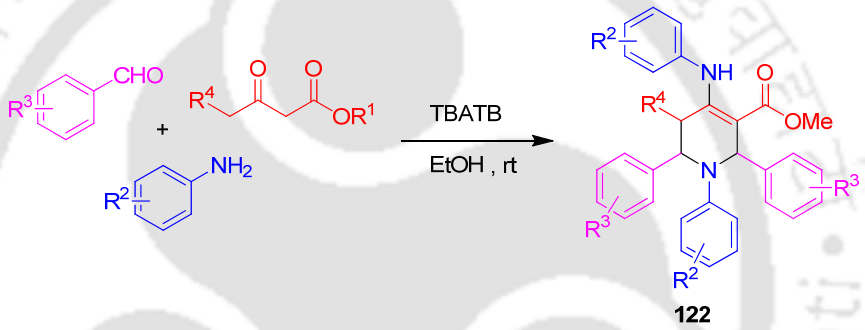
Results and Discussion

The piperidines and its analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active synthetic molecules and organic fine chemicals.[83] Some of them also act as pharmaceutical agents.[84] Compounds containing piperidine structural motif exhibit anti-hypertensive,[85] antibacterial,[86] antimalarial,[87] anticonvulsant and anti-inflammatory activities.[88] Thus, the synthesis of highly substituted piperidines has gained considerable attention[89] and number of procedures have been developed using several approaches such as tandem cyclopropane ring-opening/ Conia-ene cyclization,[90] imino Diels-Alder reactions,[91] aza-Prins-cyclizations,[92] intramolecular Michael reactions[93] and intramolecular Mannich reaction onto iminium ions.[94] The functionalized piperidines have been reported using MCRs strategy by employing bromodimethylsulfonium bromide (BDMS),[76a] InCl[75] and L-Proline/TFA.[87] However, use of expensive and excess amount of catalysts are some of the disadvantages of the above mentioned methods. Therefore, there is a need for highly efficient, versatile and eco-friendly synthetic protocol to obtain these valuable compounds in good yields.

A few years ago, Chaudhuri et al. reported environmentally benign synthesis of tetrabutylammonium tribromide (TBATB) as a useful brominating reagent.[95] The efficacy of these organic ammonium tribromides were demonstrated for several organic transformations such as deprotection of dithioacetals,[96a] conversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[96b] synthesis of α-bromo enones[98c] with various naturally occurring flavone derivatives.[96d] Similarly, a wide variety of organic transformations were developed involving *n*-tetrabutylammonium tribromide (TBATB) by others.[97] Based on the unique properties of the reagent tetrabutylammonium tribromide (TBATB), it was conceived that TBATB could be used as catalyst for the one-pot synthesis of the highly functionalized piperidines by reacting 1,3-dicarbonyl compounds, aromatic aldehydes and amines. In this chapter, one-pot MCR leading to highly functionalized piperidine derivatives along with their mechanistic aspects is discussed (Scheme 43).

For the present study, the catalyst TBATB was prepared by following literature procedure.[95] In the beginning of the study, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol) and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was treated with 10 mol% of TBATB at room temperature. The solid product was filtered and

washed with ethanol to give functionalized piperidine **122a** in 66% yield. The product was fully characterized by recording IR, ^{1}H NMR and ^{13}C NMR spectra, and elemental analysis. Appearance of a strong absorption peak at 1685 cm^{-1} in IR spectrum indicates the presence of carbonyl group. In ^{1}H NMR spectrum the characteristic signals for tetrahydropyridine ring exhibited at δ 2.75 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.86 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 5.11 (d, 1H, J = 3.2 Hz, H-6), 6.39 (s, 1H, H-2) and 10.25 (s, 1H, NH). Similarly, appearance of the peaks at δ 33.8 (C-5), 55.0 (C-2), 58.1 (C-6), 98.2 (C-3), 156.5 (C-4) and 168.8 (C=O) in ^{13}C NMR supports the formation of tetrahydropyridine derivative. From the above, it is quite clear that the functionalized piperidine **122a** was obtained through pseudo five-component reaction.



Scheme 43. Synthesis of functionalized piperidines.

A series of reactions were examined with a combination of 4-methylbenzaldehyde, aniline and methyl acetoacetate to obtain the best result in terms of yield and reaction time for the formation of product **122a** (Table 1). Several solvents were screened and it was found that ethanol is the best solvent. In the neat reaction, the product was obtained in moderate yields (51%), it is probably due to lack of effective interaction of reactants with the catalyst.

Table 1: Optimization of reaction conditions for the synthesis of functionalized piperidine **122a**

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	CH_3CN	no catalyst	12	0
2	CH_3CN	10	12	66
3	EtOH	05	10	56
4	EtOH	10	10	78

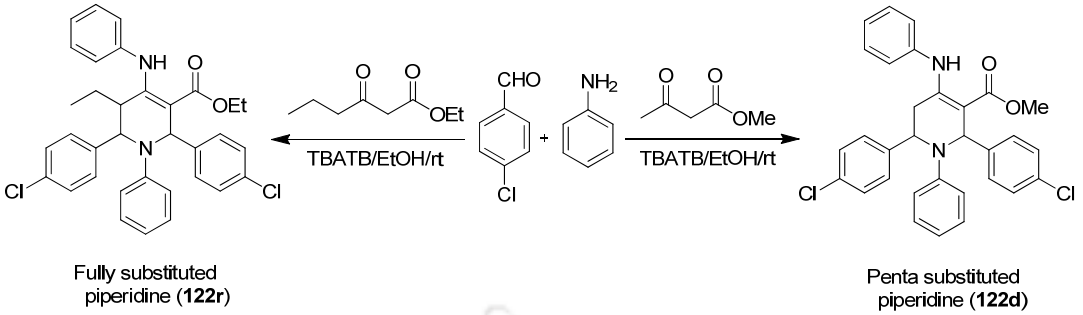
5	EtOH	20	10	69
6	CH_2Cl_2	10	10	54
7	CH_3OH	10	12	68
8	Neat	10	5	51

[a] Isolated yield.

Using the optimal reaction conditions, the reaction of benzaldehyde with aniline and methyl acetoacetate was studied and the product **122b** was obtained in good yield. The reactions of various aromatic aldehydes containing substituents in the aromatic ring such as OMe, Cl, Br, and NO_2 with aniline and methyl acetoacetate were performed under the same reaction conditions. The reaction time and % yield of the products **122c-122h** are shown in Table 2. However, in case of 3- and 4-nitrobenzaldehydes the products were obtained in low yield (Table 2, entries 7 and 8). This may be attributed to the formation of more stable imine having an extra conjugation in the presence of nitro group. This stable imine is less reactive and has less solubility in ethanol. Some of the aldehydes such as β-naphthaldehyde and *n*-butanal, did not give their corresponding functionalized piperidines.

Several aliphatic and aromatic amines were examined to study the generality and scope of the present protocol. Various anilines with substituent such as Me, OMe, Br and NO_2 were treated with 4-methylbenzaldehyde and methyl acetoacetate under identical reaction conditions. All these reactions underwent smoothly to provide the corresponding piperidine derivatives **122i-122l**, in moderate to good yields (Table 2, Entries 9-12). Similarly, aliphatic amines such as *n*-butylamine and benzylamine were also yielded the corresponding piperidines **122m** and **122n**, respectively in moderate yields. The present method failed to furnish the expected piperidine derivative with α-naphthylamine, which may be due to steric hindrance of the bulky naphthyl group.

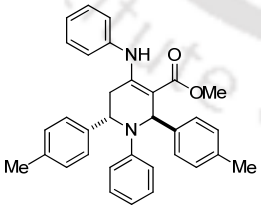
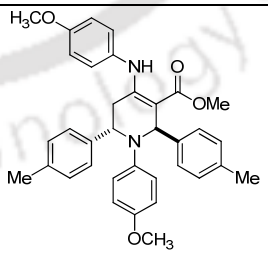
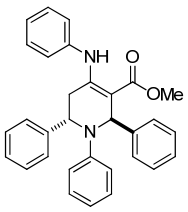
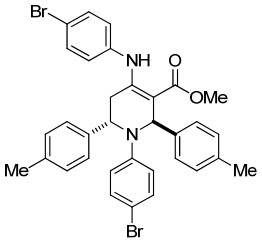
The reactions were further examined with various 1,3-dicarbonyl compounds such as ethyl acetoacetate, allyl acetocetate and *t*-butyl acetoacetate with 4-methyl-benzaldehyde and aniline in ethanol using 10 mol% TBATB as catalyst (Table 2, Entries 15-18). The desired piperidine derivatives (**122o-122q**) were isolated in good yields as shown in Table 2. This confirms that the alkoxy (-OR) moiety present in the ester functionality does not have any major role in determining the course of the reaction.

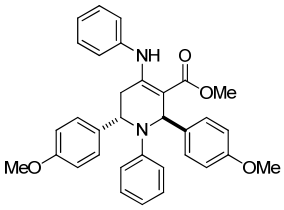
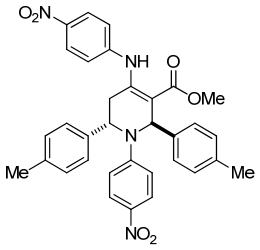
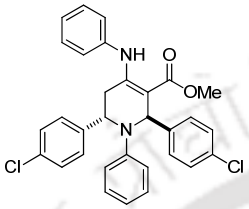
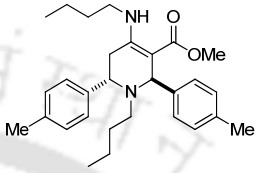
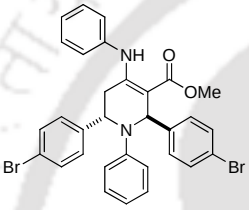
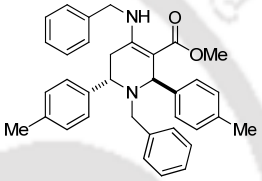
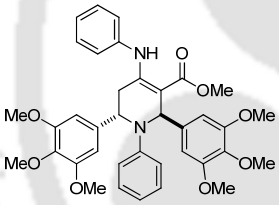
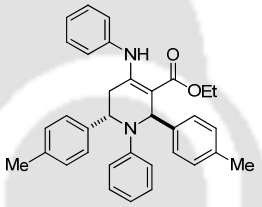
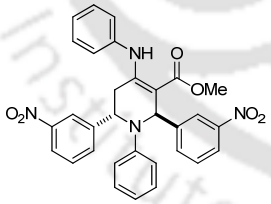
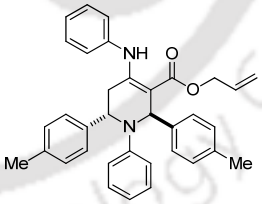
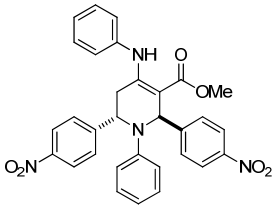
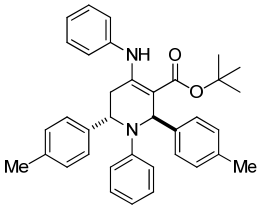


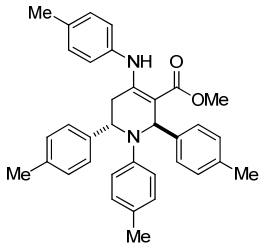
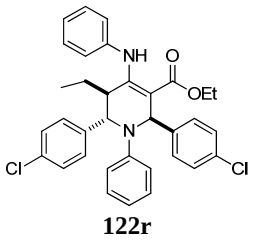
Scheme 44. Criteria for the formation of piperidine derivatives.

In addition, the reaction of ethyl butyrylacetate with 4-chlorobenzaldehyde and aniline was performed under identical reaction conditions to study the effect of an alkyl group at the β position of 1,3-dicarbonyl compound. The product of the reaction was a fully substituted piperidine **122r** in 31% yield. The low yield of product **122r** was due to the steric hindrance of alkyl group. We suggest that not only methyl group but also any enolizable alkyl group in the β position of 1,3-dicarbonyl compounds is sufficient for the formation of highly functionalized piperidines as well as fully functionalized piperidine ring using MCRs (Scheme 44). To prepare a large number of fully functionalized piperidine derivatives are under investigation. All the products were fully characterized from ^{1}H NMR, ^{13}CNMR spactra and elemental analysis. The spectra of the compounds **122a**, **122f**, **122i**, **122l** and **122o** are given in the Figures 9-13 in the Experimental Section.

Table 2 Synthesis of functionalized piperidines using TBATB in ethanol

Entry	Product[a]	Time	Yield[b] (%)	Entry	Product[a]	Time	Yield[b] (%)
1	 **122a**	8	78	10	 **122j**	9	72
2	 **122b**	24	74	11	 **122k**	8	63

3	 **122c**	8	80	12	 **122l**	24	54
4	 **122d**	10	82	13	 **122m**	47	51
5	 **122e**	8	80	14	 **122n**	45	51
6	 **122f**	30	60	15	 **122o**	9	70
7	 **122g**	36	30	16	 **122p**	29	62
8	 **122h**	26	28	17	 **122q**	15	64

9	 **122i**	12	75	18	 **122r**		30	31

[a]All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry and elemental analysis. [b]Isolated yield.

Moreover, the structure of the product was also confirmed from single XRD-data and the ORTEP is shown in Figure 8.

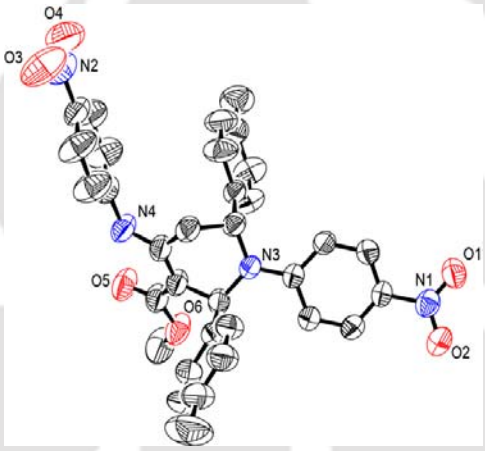
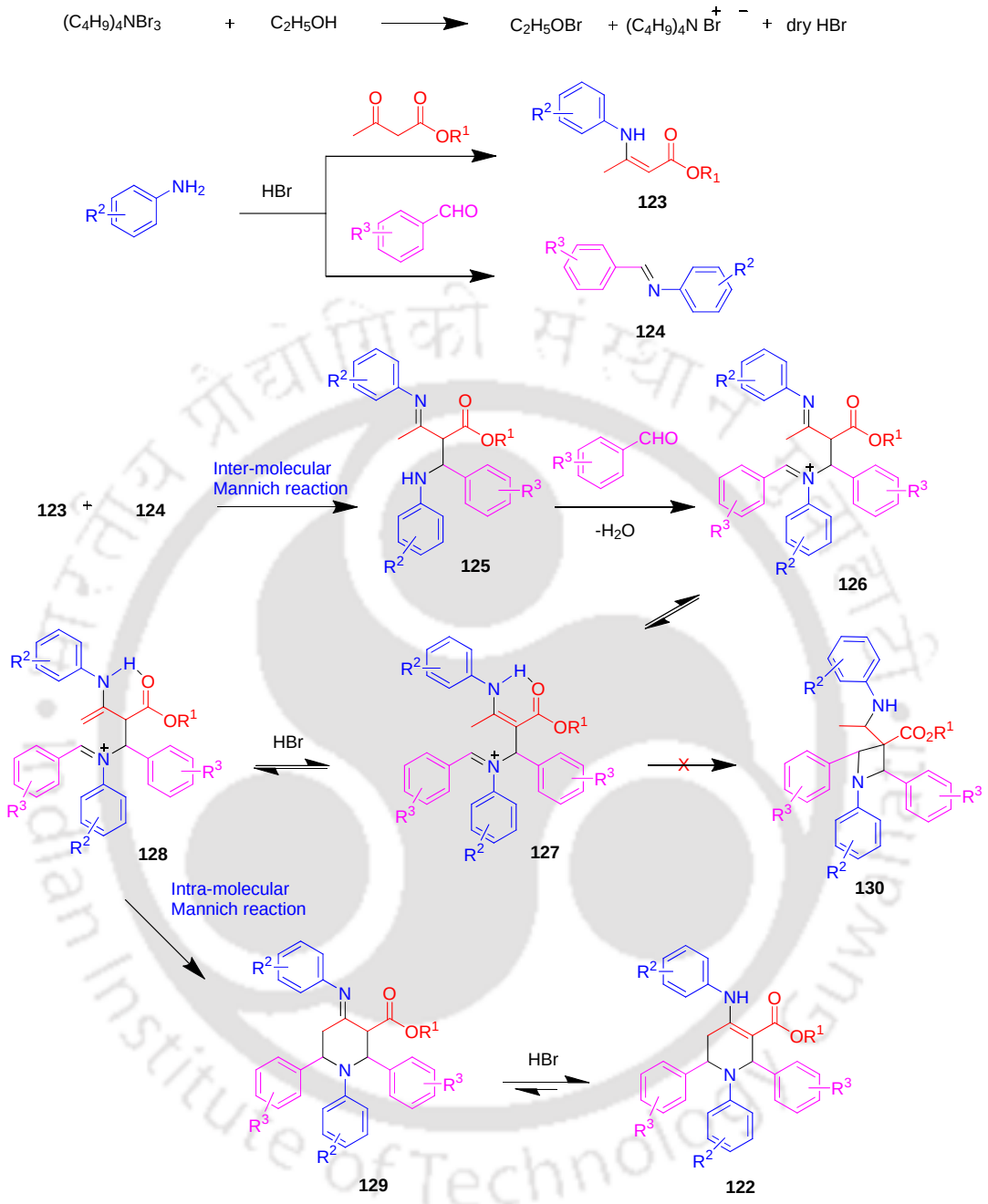


Figure 8. ORTEP diagram of **122l** (CCDC 775694)

The formation of piperidines was proposed by various groups[75,76a,,87] that it undergoes through a Knoevenagel-type intermediate followed by [4 +2] aza-Diels-Alder reaction. It was projected that β-keto ester reacts with amine to give enamine **123**, which reacts further with aldehyde to give a Knoevenagel type product. This acts as a reactive diene and it undergoes aza-Diels-Alder reaction with imine **124** to give substituted piperidines. In support of this mechanism, the intermediate diene isolation was attempted with other reactive dienophiles such as dimethyl acetylenedicarboxylate and maleic anhydride, but in vain. Since no cycloaddition products were obtained, an alternate plausible mechanism by which the product is formed is proposed (see Scheme 45). TBATB reacts with ethanol which yields dry HBr[99e] and subsequently results in the formation of enamine **123** and imine **124**.



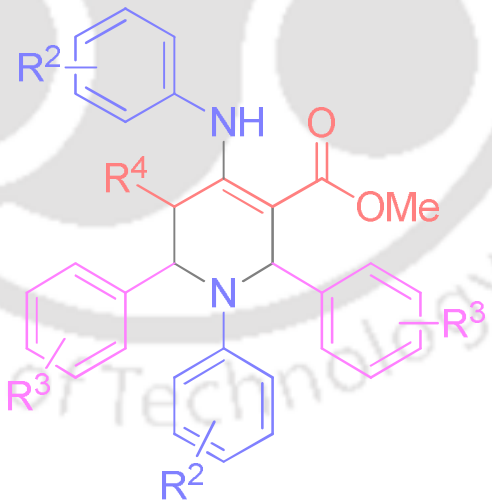
Scheme 45. A plausible mechanism for the formation of highly substituted piperidine.

It is well-known that enamine **123** would be a better nucleophile and the nucleophilic attack will take place preferentially on the activated imine **124** to give intermediate **125** through intermolecular Mannich-type reaction. The intermediate **125** reacts with aldehyde to give intermediate **126** by the elimination of a water molecule. There is a spontaneous tendency in the presence of HBr for tautomerization to give the

intramolecular hydrogen bonded species either **127** or **128**. The tautomer **128** immediately undergoes intramolecular Mannich-type reaction to form intermediate **129**. The tautomer **9** would give a four membered ring product **130**, which is unfavorable. The intermediate **129** tautomerizes to give the final piperidine derivative **122** due to conjugation with the ester group. In conclusion, the product formation is going through inter- and intramolecular Mannich-type reactions.

In conclusion, we have achieved the formation of highly functionalized piperidines in presence of TBATB as catalyst via one-pot five component reaction at room temperature from readily available starting materials. Some advantages of this MCRs protocol are: good yields, mild reaction conditions, environmentally benign catalyst, no tedious separation procedures, superior atom-economy and low cost. In addition, mechanistic studies revealed the possibility for the formation of piperidines through double Mannich-type reactions may not be discarded instead of Knoevenagel-type intermediate.

Synthesis of highly functionalized piperidines using one-pot five-component reaction involving *n*-tetrabutylammonium tribromide (TBATB) as pre-catalyst



CHAPTER II: **Experimental Section**

Experimental:

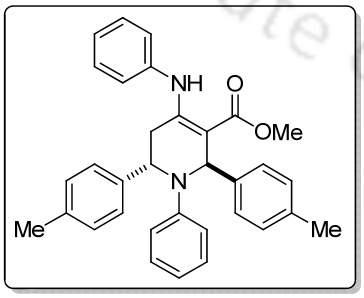
Preparation of n-tetrabutylammonium tribromide (TBATB):

An amount of 0.05 g (0. 27 mmol) of vanadium pentoxide (V_2O_5), was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker (care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic). The reaction mixture was stirred at 0 – 5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. To it was added a solution of 5.67 g (47.65 mmol) potassium bromide (KBr) and 7.7 g (23.81 mmol) of tetrabutylammonium bromide (TBAB), dissolved in 25 mL of 1M H_2SO_4. An orange-yellow precipitate started to appear after 5 minutes of stirring. The mixture was stirred continuously for about 30 minutes subsequent upon which the whole was kept standing in an ice-bath for 1h, to give a bright orange colored compound. The isolated yield was 80%, M.p. 75 °C.

General procedure for the synthesis of highly and fully functionalized piperidines:

To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of ethanol was added TBATB (0.1 mmol) and stirred at room temperature. After 20 min, aromatic aldehyde (2 mmol) was added into the above reaction mixture and stirring was further continued. After completion of the reaction, thick precipitate came out after stipulated reaction time. The solid product was filtered off and washed with ethanol, which was recrystallized from hot ethanol.

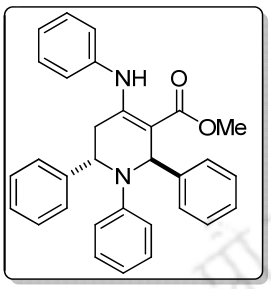
Methyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122a)**



White solid (0.381 g, 78%); M.p. 215-217 °C; **IR** (KBr): 1657, 1591 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H), 2.33 (s, 3H), 2.75 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H), 2.86 (dd, *J* = 5.6, *J* = 15.2 Hz, 1H), 3.92 (s, 3H), 5.11 (d, *J* = 3.2 Hz, 1H), 6.30 (d, *J* = 8.0 Hz, 2H), 6.39 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 2H), 6.59 (t, *J* = 7.2 Hz, 1H), 7.02-7.10 (m, 11H), 7.19 (d, *J* = 8.0 Hz, 2H), 10.25 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.2, 21.3, 33.8, 51.2, 55.0, 58.1, 98.2, 113.0, 116.1, 125.8, 126.0, 126.5, 126.7, 128.9, 129.0, 129.1, 129.4, 136.0, 136.8, 138.1, 139.8, 141.1, 147.2, 156.5,

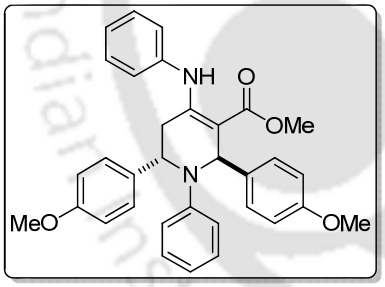
168.8; **Anal. Calcd** for $C_{33}H_{32}N_2O_2$ (488.63): C, 81.12; H, 6.60; N, 5.73; found: C, 80.96, H, 6.55, N, 5.80.

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**122b)**



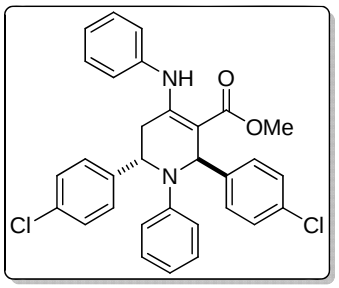
White solid (0.373 g, 81%); M.p. 185-186 °C; **IR** (KBr): 3444, 1661, 1591 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.86 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 3.93 (s, 3H, OCH_3), 5.14 (d, *J* = 4.4 Hz, 1H, 6-H), 6.27 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H, 2-H), 6.51 (d, *J* = 8.8 Hz, 2H), 6.59 (t, *J* = 7.2 Hz, 1H), 7.03-7.10 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.24-7.32 (m, 8H), 10.24 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.2, 55.2 (C-2), 58.3 (C-6), 98.0 (C-3), 113.0 (2C), 116.3, 125.9, 126.0 (2C), 126.5 (3C), 126.8 (2C), 127.3, 128.4 (2C), 128.8 (2C), 128.9 (2C), 129.0 (2C), 137.9, 142.9, 144.0, 147.1, 156.4 (C-4), 168.7 (C=O); **Anal. Calcd** for $C_{31}H_{28}N_2O_2$ (460.57): C, 80.84; H, 6.13; N, 6.08; found: C, 80.72; H, 6.07; N, 6.09.

Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122c)**



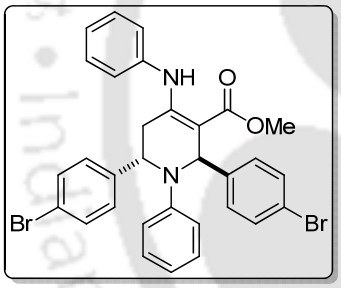
White solid (0.344 g, 66%); M.p. 186-188 °C; **IR** (KBr): 1654, 1593 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.75 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.85 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 3.78 (s, 3H, ArOCH_3), 3.79 (s, 3H, ArOCH_3), 3.92 (s, 3H, OCH_3), 5.07 (d, *J* = 3.2 Hz, 1H, 6-H), 6.34-6.38 (m, 3H), 6.52 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 7.2 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 4H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* =8.8 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 10.27 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.9 (C-5), 51.2, 54.7 (C-2), 55.4 (2C), 57.7 (C-6), 98.2 (C-3), 113.1 (2C), 113.7 (2C), 114.1 (2C), 116.2, 125.8, 125.9 (2C), 127.6 (2C), 127.8 (2C), 129.0 (4C), 134.8, 136.0, 138.1, 147.1, 156.5 (C-4), 158.2, 158.8, 168.8 (C=O); **Anal. Calcd** for $C_{33}H_{32}N_2O_4$ (520.63): C, 76.13; H, 6.20; N, 5.38; found C, 76.01; H, 6.11; N, 5.49.

Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122d)**

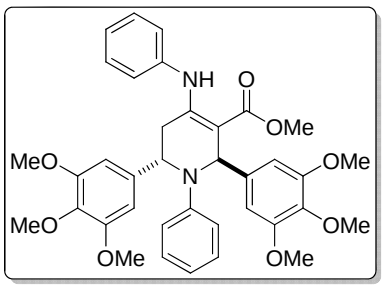


White solid (0.450 g, 85%); M.p. 225-227 °C; **IR** (KBr): 1660, 1591 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.74 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.82 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 3.92 (s, 3H, OCH_3), 5.09 (d, *J* = 2.4 Hz, 1H, 6-H), 6.35 (s, 1H, 2-H), 6.40 (d, *J* = 8.0 Hz, 2H), 6.45 (d, *J* = 8.0 Hz, 2H), 6.64 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.10 (t, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.24 (m, 5H), 10.25 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.3, 54.8 (C-2), 57.5 (C-6), 97.6 (C-3), 113.1 (2C), 116.9, 125.9 (2C), 126.2, 127.9 (2C), 128.2 (2C), 128.6 (2C), 128.9 (2C), 129.2 (4C), 132.3, 133.0, 137.7, 141.0, 142.5, 146.6, 156.2 (C-4), 168.4 (C=O); **Anal. Calcd** for $C_{31}H_{26}N_2O_2Cl_2$ (529.46): C, 70.32; H, 4.95; N, 5.29; found: C, 70.29; H, 4.83; N, 5.34.

Methyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122e)**



Light yellow solid (0.476 g, 77%); M.p. 245-247 °C; **IR** (KBr): 1661, 1590 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.74 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.82 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 3.93 (s, 3H, OCH_3), 5.08 (d, *J* = 3.6 Hz, 1H, 6-H), 6.34 (s, 1H, 2-H), 6.40 (d, *J* = 7.6 Hz, 2H), 6.45 (d, *J* = 8.8 Hz, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 10.24 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.3, 54.9 (C-2), 57.5 (C-6), 97.6 (C-3), 113.0 (2C), 116.9, 120.4, 121.1, 125.9 (2C), 126.2, 128.3 (2C), 128.6 (2C), 129.18 (2C), 129.2 (2C), 131.5 (2C), 131.9 (2C), 137.7, 141.6, 143.0, 146.5, 156.1 (C-4), 168.4 (C=O); **Anal Calcd** for $C_{31}H_{26}N_2O_2Br_2$ (618.37): C, 60.21; H, 4.24; N, 4.53; found: C, 60.45; H, 4.15; N, 4.97.

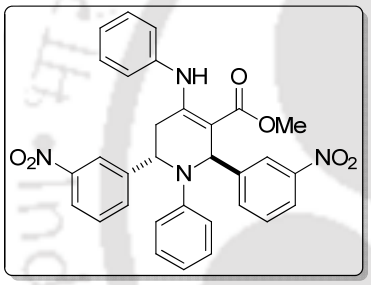


Methyl 2,6-bis(3,4,5-trimethoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropy -ridine-3-carboxylate **(122f)**

Light yellow solid (0.418 g, 65%); M.p. 197-199 °C; **IR** (KBr): 1655, 1594 cm^{-1}; **^{1}H NMR** (400 MHz,

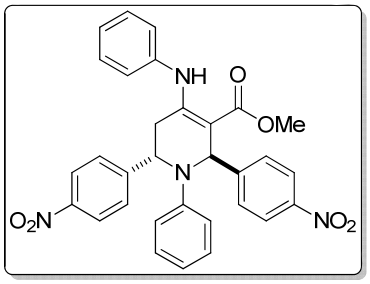
$CDCl_3$): δ 2.77 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.95 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 3.70 (s, 6H, 2 x ArOCH_3), 3.74 (s, 6H, 2 x ArOCH_3), 3.84 (s, 3H, ArOCH_3), 3.85 (s, 3H, ArOCH_3), 3.90 (s, 3H, OCH_3), 5.03 (d, *J* = 3.2 Hz, 1H, 6-H), 6.34(s, 1H, 2-H), 6.35 (s, 2H), 6.39 (d, *J* = 7.7 Hz, 2H), 6.53 (s, 2H), 6.57 (d, *J* = 8.0 Hz, 2H), 6.65 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 10.26 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.1, 55.6 (C-2), 56.0 (4C), 58.3 (C-6), 61.0 (2C), 97.3 (C-3), 103.2 (2C), 103.9 (2C), 113.1 (2C), 116.6, 126.2, 126.3 (2C), 128.9 (4C), 136.5, 137.0, 137.8, 138.5, 139.7, 147.0, 153.1 (2C), 153.4 (2C), 157.0 (C-4), 168.5 (C=O); **Anal. Calcd** for $C_{37}H_{40}N_2O_8$ (640.73): C, 69.36; H, 6.29; N, 4.37.; found C, 69.28; H, 6.24; N, 4.46.

Methyl 2,6-bis(3-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122g)**



Yellow solid (0.198 g, 36%); M.p. 182-183 °C. **IR** (KBr): 3436 (NH), 1655, 1595 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.88 (d, *J* = 4.0 Hz, 2H, 5-CH_2), 3.99 (s, 3H, OCH_3), 5.33 (t, *J* = 4.0 Hz, 1H, 6-H), 6.38-6.41 (m, 2H), 6.44 (d, *J* = 8.8 Hz, 2H), 6.48 (s, 1H, 2-H), 6.70 (t, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 2H), 7.14-7.16 (m, 3H), 7.45-7.50 (m, 3H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 8.10-8.15 (m, 2H), 8.22 (s, 1H), 10.30 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 33.9 (C-5), 51.6, 55.3 (C-2), 57.2 (C-6), 96.9 (C-3), 113.2, 117.9, 121.5, 121.7, 122.0, 122.6, 125.8, 126.7, 129.3, 129.5, 129.8, 132.7, 137.3, 144.6, 145.9, 146.5, 148.7, 148.8, 155.7 (C-4), 168.2; **Anal. Calcd** for $C_{31}H_{26}N_4O_6$ (550.58): C, 67.63; H, 4.76; N, 10.18; found C, 67.51; H, 4.68; N, 10.29.

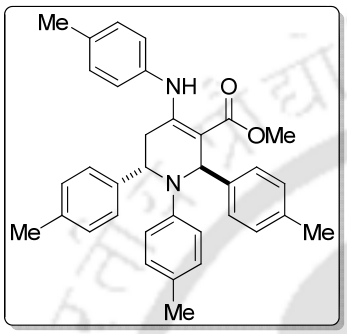
Methyl 2,6-bis(4-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122h)**



Light yellow solid (0.176g, 32%); M.p. 239-241 °C. **IR** (KBr): 3356, 2950, 1660, 1593, 1518, 1499, 1346, 1257, 1072 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 2.85 (2H, d, *J* = 4.0 Hz), 3.95 (3H, s), 5.24-5.25 (1H, m), 6.37-6.42 (4H, m), 6.46 (1H, s), 6.68 (1H, t, *J* = 7.2 Hz), 7.07 (1H, d, *J* = 7.2 Hz), 7.09 (1H, d, *J* = 7.2 Hz), 7.13-7.17 (3H, m), 7.27 (2H, d, *J* = 8.8 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 8.12 (2H, d, *J* = 8.8 Hz), 8.14 (2H,

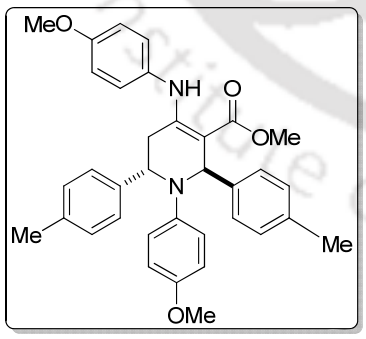
d, *J* = 8.8 Hz), 10.26 (1H, brs). **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 33.7, 51.6, 55.4, 57.5, 96.8, 113.1, 117.8, 123.9, 124.1, 125.7, 126.6, 127.5, 127.6, 129.4, 129.5, 137.3, 145.9, 146.9, 147.5, 149.9, 151.8, 155.7, 168.1. **Anal. Calcd** for $C_{31}H_{26}N_4O_6$ (550.58): C, 67.63; H, 4.76; N, 10.18; found C, 67.51; H, 4.69; N, 10.31.

Methyl 2,6-bis(4-methylphenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2, 5,6-tetrahydropyridine-3-carboxylate **(122i)**



Light yellow solid (0.351 g, 68%); M.p. 206-208 °C; **IR** (KBr): 3249 (NH), 1655, 1594 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.15 (s, 3H, ArC*H*$_3$), 2.27 (s, 3H, ArC*H*$_3$), 2.32 (s, 3H, ArC*H*$_3$), 2.34 (s, 3H, ArC*H*$_3$), 2.72 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H$_a$), 2.82 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H$_b$), 3.91 (s, 3H, OC*H*$_3$), 5.07 (d, *J* = 4.0 Hz, 1H, 6-H), 6.18 (d, *J* = 8.0 Hz, 2H), 6.35 (s, 1H, 2-H), 6.43 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 7.03-7.09 (m, 6H), 7.20 (d, *J* = 8.0 Hz, 2H), 10.17 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.0, 21.2, 21.3, 33.7 (C-5), 51.0, 55.1 (C-2), 58.0 (C-6), 97.7 (C-3), 113.0 (2C), 125.0, 126.1 (2C), 126.5 (2C), 126.7 (2C), 129.0 (2C), 129.4 (2C), 129.5 (4C), 135.4, 135.6, 135.8, 136.6, 140.1, 141.4, 145.1, 156.8 (C-4), 168.8 (C=O); **Anal. Calcd** for $C_{35}H_{36}N_2O_2$ (516.68): C, 81.36; H, 7.02; N, 5.42; found C, 81.24; H, 7.01; N, 5.53.

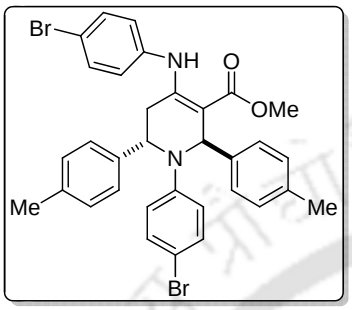
Methyl 2,6-bis(4-methylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5, 6-tetrahydropyridine-3-carboxylate **(122j)**



White solid (0.406 g, 74%); M.p. 230-231 °C; **IR** (KBr): 3442, 1657, 1611 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.31 (s, 3H, ArC*H*$_3$), 2.33 (s, 3H, ArC*H*$_3$), 2.62 (dd, *J* = 2.8 Hz, *J* = 15.2 Hz, 1H, 5-H$_a$), 2.77 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H$_b$), 3.65 (s, 3H, ArOC*H*$_3$), 3.74 (s, 3H, ArOC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 5.00 (d, *J* = 2.8 Hz, 1H, 6-H), 6.21 (d, *J* = 9.2 Hz, 2H), 6.26 (s, 1H, 2-H), 6.43 (d, *J* = 9.2 Hz, 2H), 6.60 (d, *J* = 9.2 Hz, 2H), 6.64 (d, *J* = 9.2 Hz, 2H), 7.02-7.09 (m, 6H), 7.16 (d, *J* = 8.0 Hz, 2H), 10.08 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.8 (C-5), 51.0, 55.6, 55.7, 55.8 (C-2), 58.1 (C-6), 97.3 (C-3), 114.1 (2C), 114.2, 114.3, 114.7 (2C), 126.6 (2C), 126.9 (2C), 128.0 (2C), 129.0 (2C), 129.4 (2C), 131.0, 135.9,

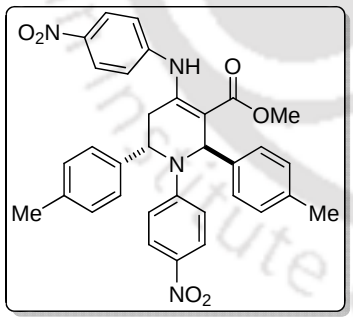
136.7, 140.4, 141.5, 141.9, 151.0 (C-4), 157.2, 157.9, 168.9 (C=O); Anal. Calcd for $C_{35}H_{36}N_2O_4$ (548.69): C, 76.62; H, 6.61; N, 5.11.; found C, 76.56; H, 6.55; N, 5.26.

Methyl 2,6-bis(4-methylphenyl)-1-(4-bromophenyl)-4-(4-bromophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122k)**



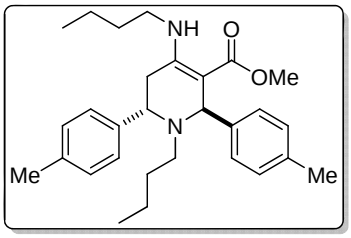
Light yellow solid (0.440g, 68%); M.p. 230-232 °C; **IR** (KBr): 3446, 1650, 1605 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, ArC*H*$_3$), 2.34 (s, 3H, ArC*H*$_3$), 2.70 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H$_a$), 2.84 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H$_b$), 3.93 (s, 3H, OC*H*$_3$), 5.06 (d, *J* = 3.6 Hz, 1H, 6-H), 6.13 (d, *J* = 8.4 Hz, 2H), 6.31 (s, 1H, 2-H), 6.38 (d, *J* = 9.2 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.07-7.15 (m, 8H), 7.20 (d, *J* = 8.4 Hz, 2H), 10.17 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.6 (C-5), 51.3, 55.2 (C-2), 58.1 (C-6), 98.9 (C-3), 108.4, 114.7 (2C), 119.2, 126.4 (2C), 126.6 (2C), 127.4 (2C), 129.2 (2C), 129.6 (2C), 131.7 (2C), 132.1 (2C), 136.3, 137.1, 137.2, 139.2, 140.2, 146.1, 155.6 (C-4), 168.6 (C=O); **Anal. Calcd** for $C_{33}H_{30}N_2O_2Br_2$ (646.42): C, 61.32; H, 4.68; N, 4.33; found C, 61.23; H, 4.57; N, 4.46.

Methyl 2,6-bis(4-methylphenyl)-1-(4-nitrophenyl)-4-(4-nitrophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122l)**



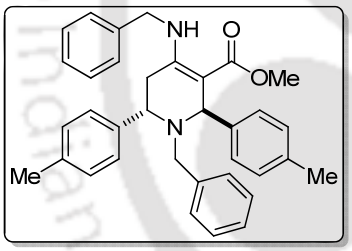
Yellow solid (0.295 g, 51%); M.p. 253-255 °C; **IR** (KBr): 1658, 1587 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.34 (s, 6H, 2 x ArC*H*$_3$), 2.94 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H$_a$), 3.06 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H$_b$), 3.99 (s, 3H, OC*H*$_3$), 5.27 (d, *J* = 3.2 Hz, 1H, 6-H), 6.43 (d, *J* = 9.2 Hz, 2H), 6.48 (s, 1H, 2-H), 6.54 (d, *J* = 9.6 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.13 (s, 6H), 7.97 (d, *J* = 9.6 Hz, 2H), 8.00 (d, *J* = 9.2 Hz, 2H), 10.55 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.8 (C-5), 52.0, 55.8 (C-2), 58.5 (C-6), 102.0 (C-3), 112.3 (2C), 123.1 (2C), 125.1 (2C), 125.9 (2C), 126.1 (2C), 126.2 (2C), 129.7 (2C), 130.0 (2C), 137.2, 137.5, 137.9, 138.1, 138.3, 144.1 (2C), 151.9, 153.3 (C-4), 168.3 (C=O); **Anal. Calcd** for $C_{33}H_{30}N_4O_6$ (578.62): C, 68.50; H, 5.23; N, 9.68; found C, 68.39; H, 5.14; N, 9.88.

Methyl 2,6-bis(4-methylphenyl)-1-butyl-4-(butylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122m)**



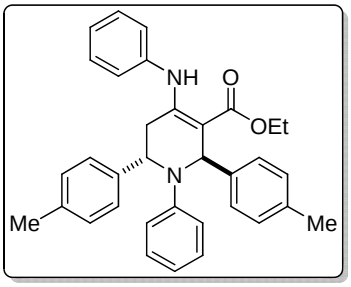
Light yellow solid (0.215 g, 48%); M.p. 158-160 °C; **IR** (KBr): 3428, 1649, 1597 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.79 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 0.98 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.10 -1.23 (m, 2H, C*H*$_2$), 1.26-1.36 (m, 2H, C*H*$_2$), 1.43-1.52 (m, 2H, C*H*$_2$), 1.60-1.68 (m, 2H, C*H*$_2$), 2.08-2.15 (m, 2H, C*H*$_2$), 2.30 (s, 3H, ArC*H*$_3$), 2.32 (s, 3H, ArC*H*$_3$), 2.51 (dd, *J* = 5.2 Hz, *J* = 17.2 Hz, 1H, 5-H$_a$), 2.60 (dd, *J* = 11.2 Hz, *J* = 17.2 Hz, 1H, 5-H$_b$), 3.24-3.38 (m, 2H), 3.55 (s, 3H, OC*H*$_3$), 3.85 (dd, *J* = 5.2 Hz, *J* = 11.6 Hz, 1H, 6-H), 4.92 (s, 1H, 2-H), 7.08 (t, *J* = 7.6 Hz, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 9.22 (t, *J* = 4.8 Hz, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.3, 20.5, 20.6, 21.3 (2C), 25.6, 31.1, 32.5 (C-5), 42.1, 44.7, 50.6, 52.5 (C-2), 58.6 (C-6), 87.9 (C-3), 127.3 (2C), 128.4 (2C), 128.8 (2C), 128.9 (2C), 135.6, 136.4, 139.3, 142.4, 159.7 (C-4), 171.4; **Anal. Calcd** for $C_{29}H_{40}N_2O_2$ (448.64): C, 77.64; H, 8.99; N, 6.24; found C, 77.51; H, 8.91; N, 6.37.

Methyl 2,6-bis(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122n)**



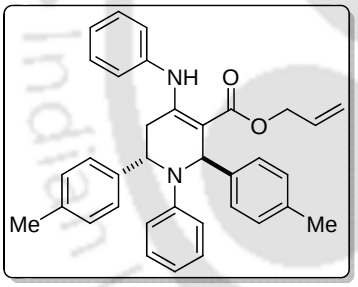
Light yellow solid (0.284 g, 55%); M.p. 172-173 °C; **IR** (KBr): 3272, 1650, 1594 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.28 (s, 3H, ArC*H*$_3$), 2.30 (s, 3H, ArC*H*$_3$), 2.62 (dd, *J* = 5.2 Hz, *J* = 17.2 Hz, 1H, 5-H$_a$), 2.73 (dd, *J* = 11.6 Hz, *J* = 17.2 Hz, 1H, 5-H$_b$), 3.32 (d, *J* = 13.6 Hz, 1H, C*H*$_a$H$_b$), 3.37 (d, *J* = 13.6 Hz, 1H, CH$_a$*H*$_b$), 3.46 (s, 3H, OC*H*$_3$), 4.02 (dd, *J* = 5.2 Hz, *J* = 11.2 Hz, 1H, C*H*$_a$H$_b$), 4.57 (dd, *J* = 6.0 Hz, *J* = 15.6 Hz, 1H, CH$_a$*H*$_b$), 4.63 (dd, *J* = 6.4 Hz, *J* = 15.6 Hz, 1H, 6-H), 4.73 (s, 1H, 2-H), 7.08 (t, *J* = 8.0 Hz, 4H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 4H), 7.37-7.40 (m, 6H), 9.67 (t, *J* = 6.0 Hz, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 25.5, 46.3, 49.7, 50.6, 52.2, 58.1, 89.3, 126.9, 127.0 (2C), 127.4 (2C), 127.6, 128.3 (2C), 128.4 (2C), 128.8 (2C), 129.0 (2C), 129.1 (4C), 135.8, 136.7, 138.7, 139.1, 140.5, 141.9, 159.0 (C-4), 171.3; **Anal. Calcd** for $C_{35}H_{36}N_2O_2$ (516.69): C, 81.36; H, 7.02; N, 5.42.; found C, 81.22; H, 7.07; N, 5.57.

Ethyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122o)**



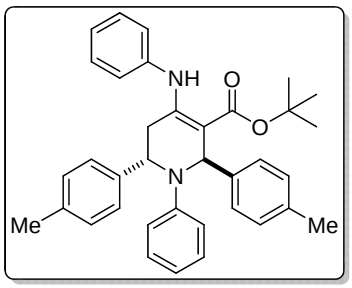
White solid (0.362 g, 72%); M.p. 228-231 °C; **IR** (KBr): 1649, 1592 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.46 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 2.32 (s, 3H, $ArCH_3$), 2.33 (s, 3H, $ArCH_3$), 2.76 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.86 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 4.26-4.36 (m, 1H, OCH_aH_b), 4.40-4.51 (m, 1H, OCH_aH_b), 5.11 (d, *J* = 2.4 Hz, 1H, 6-H), 6.30 (d, *J* = 7.6 Hz, 2H), 6.40 (s, 1H, 2-H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.59 (t, *J* = 7.2 Hz, 1H), 7.02-7.10 (m, 11H), 7.22 (d, *J* = 8.0Hz, 2H), 10.29 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 15.0, 21.2, 21.3, 33.8 (C-5), 55.0 (C-2), 58.1 (C-6), 59.8, 98.5 (C-3), 113.1 (2C), 116.1, 125.7, 125.9 (2C), 126.5 (2C), 126.7 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 129.4 (2C), 135.9, 136.8, 138.2, 139.9, 141.2, 147.2, 156.2 (C-4), 168.4 (C=O); **Anal. Calcd** for $C_{34}H_{34}N_2O_2$ (502.65): C, 81.24; H, 6.82; N, 5.57; found C, 81.13; H, 6.76; N, 5.69.

Allyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine -3-carboxylate **(122p)**



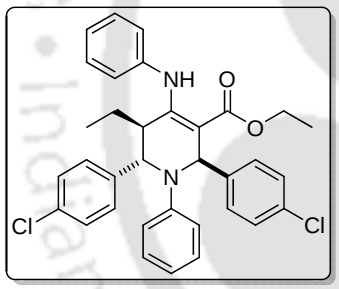
Light yellow solid (0.329 g, 64%); M.p. 186-188 °C; **IR** (KBr) : 3242, 1658, 1591 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.31 (s, 3H, $ArCH_3$), 2.32 (s, 3H, $ArCH_3$), 2.76 (dd, *J* = 2.4 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.86 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 4.80 (ddt, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz, 1H, CH_aH_b), 4.87 (ddt, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz, 1H, CH_aH_b), 5.10 (d, *J* = 3.6 Hz, 1H, 6-H), 5.31 (dq, *J* = 1.2 Hz, *J* = 10.4 Hz, 1H, =CH_aH_b), 5.45 (dq, *J* = 1.2 Hz, *J* = 17.2 Hz, 1H, =CH_aH_b), 6.06-6.15 (m, 1H, =CH), 6.30 (dd, *J* = 2.4 Hz, *J* = 8.0 Hz, 2H), 6.43 (s, 1H, 2-H), 6.52 (d, *J* = 8.4 Hz, 2H), 6.58 (t, *J* = 7.2 Hz, 1H), 7.02-7.15 (m, 11H), 7.21 (d, *J* = 8.0 Hz, 2H), 10.26 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.9 (C-5), 55.1 (C-2), 58.1 (C-6), 64.5, 98.2 (C-3), 113.1 (2C), 116.2, 117.8, 125.8, 126.0 (2C), 126.5 (2C), 126.8 (2C), 128.98 (2C), 129.04 (2C), 129.1 (2C), 129.4 (2C), 133.3, 136.0, 136.8, 138.1, 139.8, 141.2, 147.2, 156.8 (C-4), 168.0 (C=O); Anal. Calcd for $C_{35}H_{34}N_2O_2$ (514.67): C, 81.68; H, 6.66; N, 5.44.; found C, 81.56; H, 6.57; N, 5.51.

Tert-butyl2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate **(122q)**



Light yellow solid (0.308 g, 58%); M.p. 171-173 °C; **IR** (KBr): 3447, 1648, 1592 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.64 (s, 9H, C*Me*$_3$), 2.31(s, 3H, ArC*H*$_3$), 2.33 (s, 3H, ArC*H*$_3$), 2.74 (dd, *J* = 2.8 Hz, *J* = 15.2 Hz, 1H, 5-H_a), 2.82 (dd, *J* = 5.6 Hz, *J* = 15.2 Hz, 1H, 5-H_b), 5.08 (d, *J* = 3.2 Hz, 1H, 6-H), 6.29 (d, *J* = 7.2 Hz, 2H), 6.35 (s, 1H, 2-H), 6.51 (d, *J* = 8.4 Hz, 2H), 6.58 (t, *J* = 7.2 Hz, 2H), 7.03-7.09 (m, 11H), 7.23 (d, *J* = 8.0 Hz, 2H), 10.25 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 29.0 (3C), 33.8 (C-5), 55.4 (C-2), 58.2 (C-6), 80.1 (C*Me*$_3$), 100.2 (C-3), 113.1 (2C), 116.1, 125.4, 125.7 (2C), 126.6 (2C), 126.7 (2C), 128.9 (2C), 129.1 (4C), 129.4 (2C), 135.8, 136.7, 138.5, 140.0, 141.5, 147.4, 155.3 (C-4), 168.4 (C=O); **Anal. Calcd** for $C_{36}H_{38}N_2O_2$ (530.71): C, 81.48; H, 7.22; N, 5.28.; found C, 81.32; H, 7.31; N, 5.37.

Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-5-ethyl-1,2,5,6-tetrahydropyri dine -3-carboxylate **(122r)**



White solid (0.160 g, 28%); M.p. 239-241 °C; **IR** (KBr): 1655, 1594 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.18 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 0.67-0.76 (m, 1H, CH_aH$_b$), 0.77-0.85 (m, 1H, CH$_a$*H*$_b$), 1.22 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 3.04 (m, 1H, 5-H), 4.15-4.07 (m, 1H, CH_aH$_b$), 4.33-4.25 (m, 1H, CH$_a$*H*$_b$), 4.86 (d, *J* = 4.0 Hz, 1H, 6-H), 5.99 (s, 1H, 2-H), 6.78 (d, *J* = 8.0 Hz, 2H), 7.12-7.25 (m, 10H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.38-7.43 (m, 4H), 10.78 (s, 1H, NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.1, 14.6, 22.2, 43.1 (C-5), 60.0, 61.7 (C-2), 63.8 (C-6), 95.6 (C-3), 116.8 (2C), 119.2, 126.3, 126.6 (2C), 128.4 (2C), 128.5 (4C), 128.9 (2C), 129.0 (2C), 129.6 (2C), 132.4, 132.7, 139.1, 139.9, 145.8, 151.2, 161.8 (C-4), 169.2 (C=O); **Anal. Calcd** for $C_{34}H_{32}N_2O_2Cl_2$ (571.54): C, 71.45; H, 5.64; N, 4.90; found: C, 71.34; H, 5.53; N, 5.02.

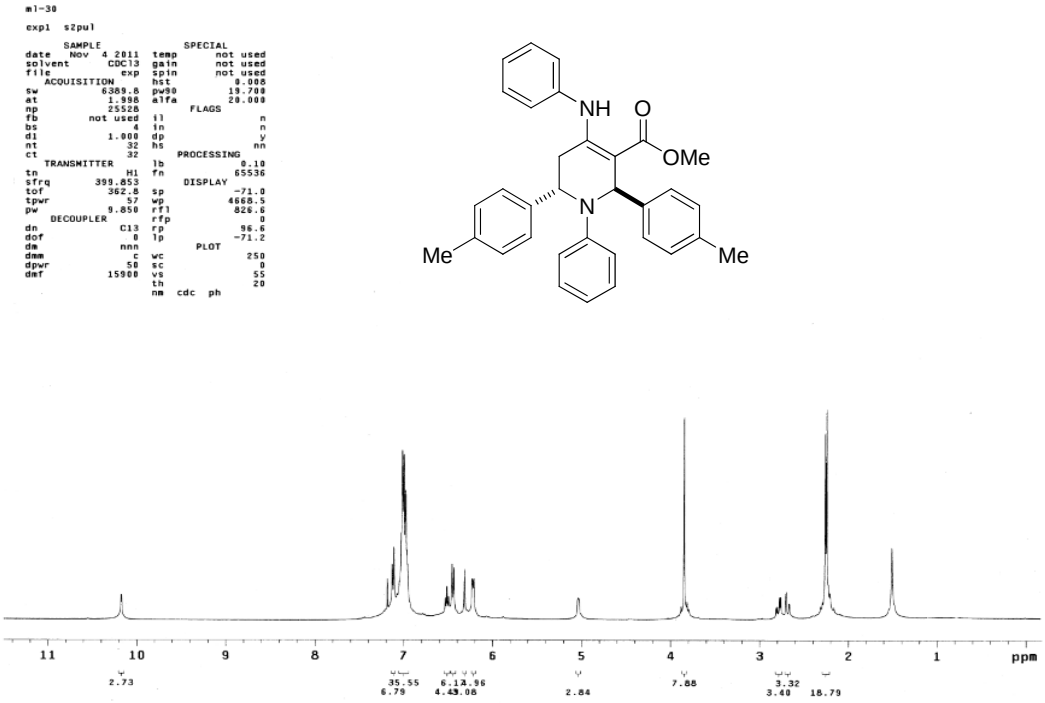
XRD for Compound **122l**

Complete crystallographic data of compound **122l** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 775694. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 3 Crystal data and structures refinement for the compounds **122l**, for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	Compound 122l
Formula	$C_{33}H_{30}N_4O_6$
CCDC number	775694
Formula weight	578.61
T (K)	296 K
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
a (Å)	6.9024(5)Å
b (Å)	11.3349(8)Å
c (Å)	20.6948(14)Å
α (°)	75.901(4)º
β (°)	89.398(4)º
γ (°)	72.491(4)º
V (Å^3)	1494.14(19) Å^3
Z	2
D_{calcd} (g m^{-3})	1.286/cm^3
μ (mm^{-1})	0.090 mm^{-1}
F(0 0 0)	608.0
Reflection collected	7546
Unique reflections	6974
Goodness-of-fit (GOF)[a] on F^2	1.025
R [$I > 2\sigma(I)$]	[b]R_1 = 0.1502, [c]wR_2 = 0.1842
R indices (all data)	[b]R_1 = 0.0602, [c]wR_2 = 0.1418

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**122a**)



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-phenyl-4 (phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate*(**122a**)

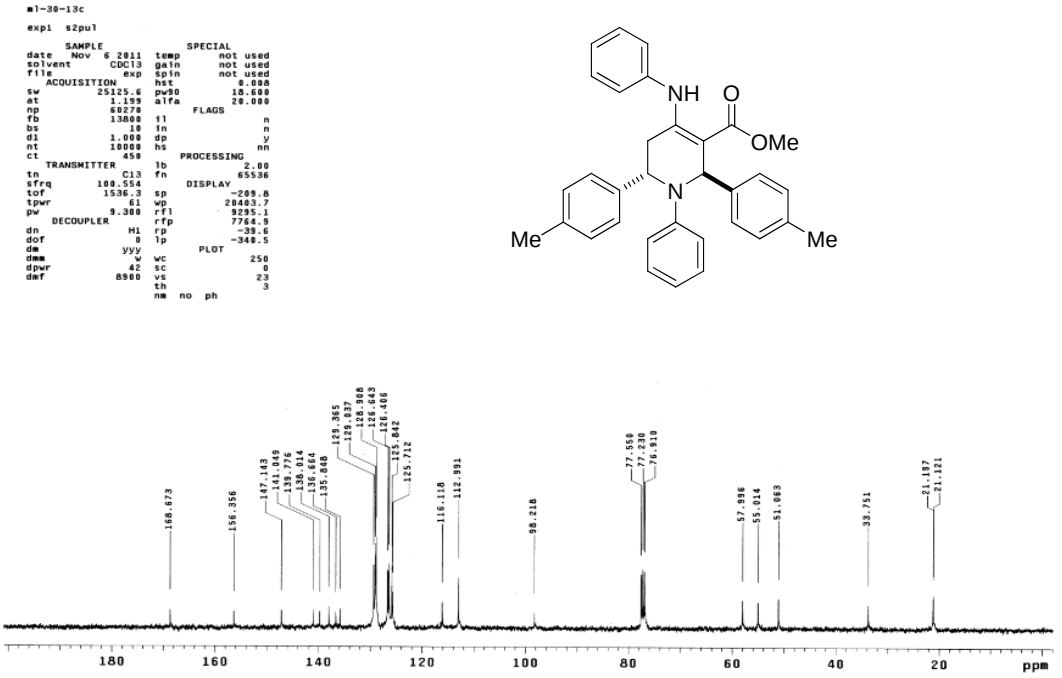
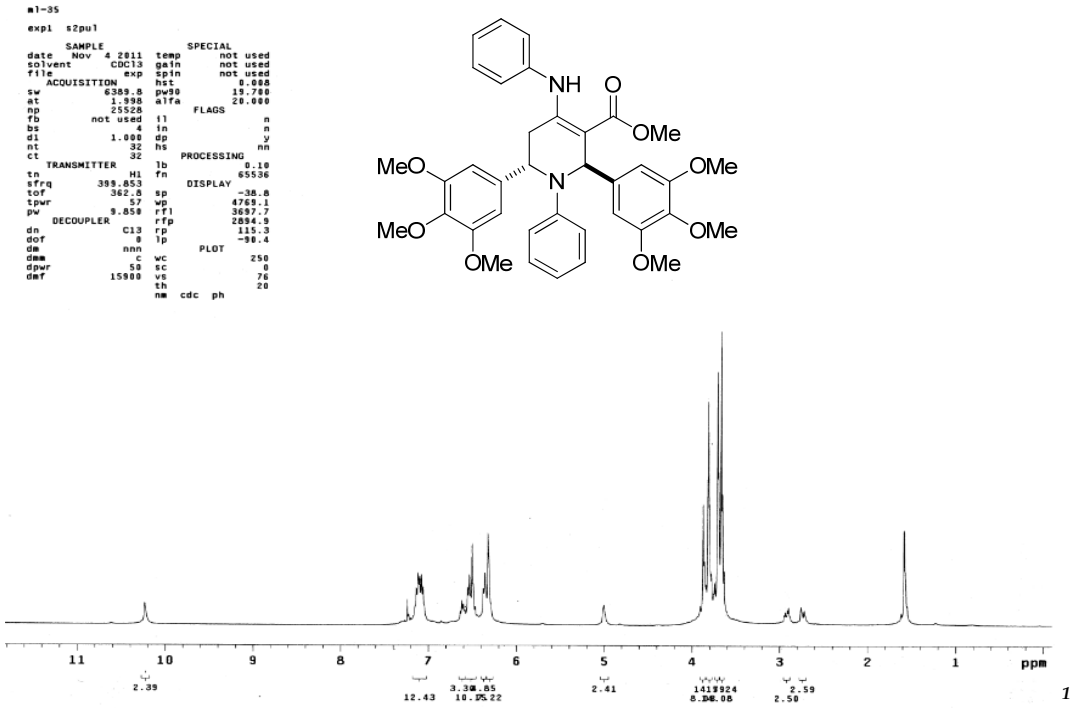


Figure 9.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 2,6-bis(3,4,5-trimethoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**122f**)



^{3}C NMR (100 MHz, $CDCl_3$): *Methyl 2,6-bis(3,4,5-trimethoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate*(**122f**)

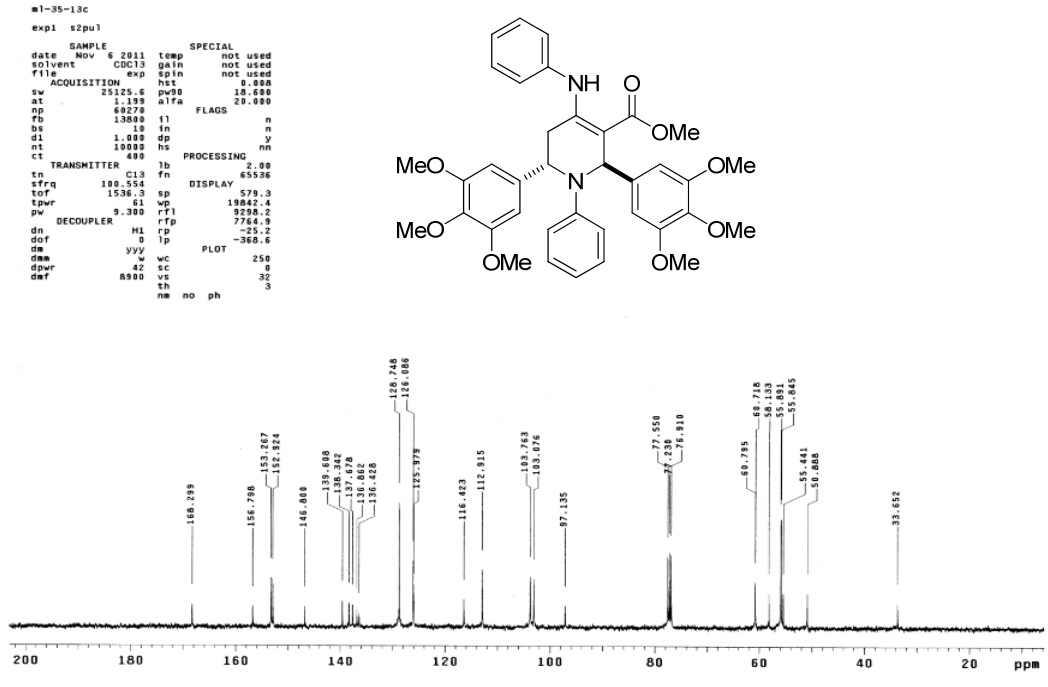
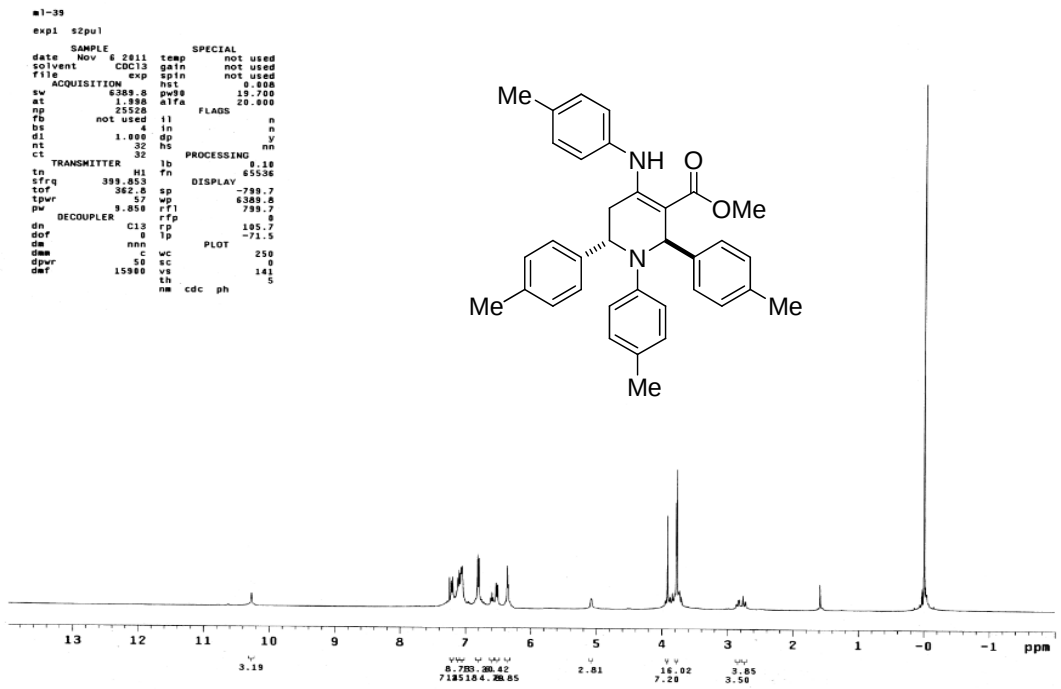


Figure 10.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2, 5,6-tetrahydropyridine-3-carboxylate* (**122i**)



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2, 5,6-tetrahydropyridine-3-carboxylate* (**122i**)

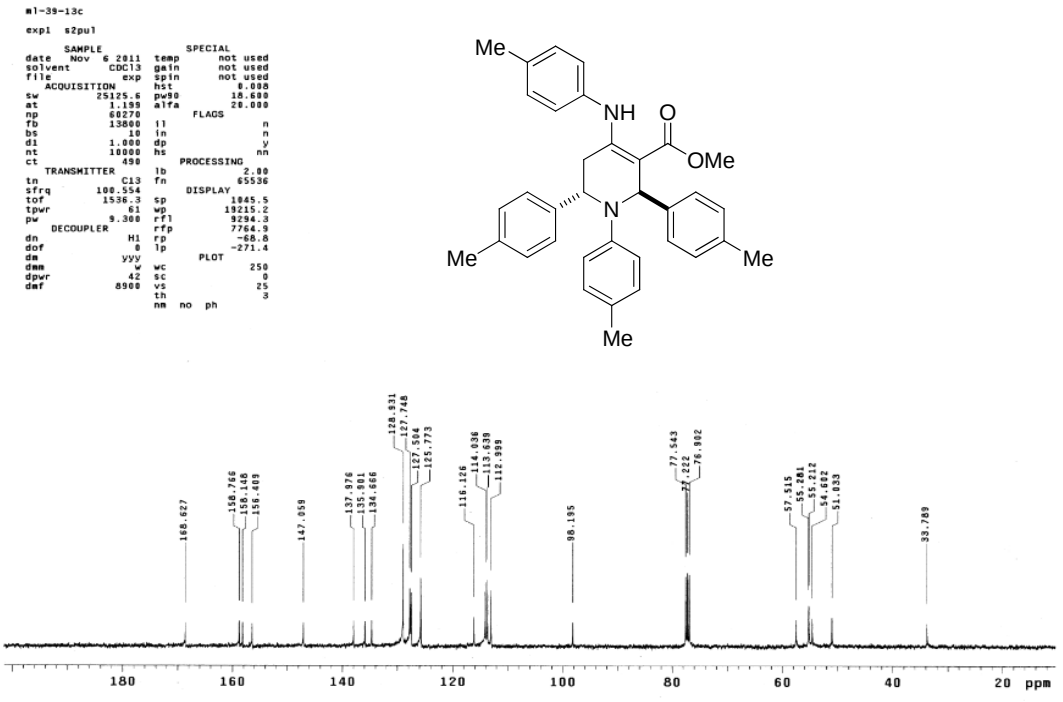
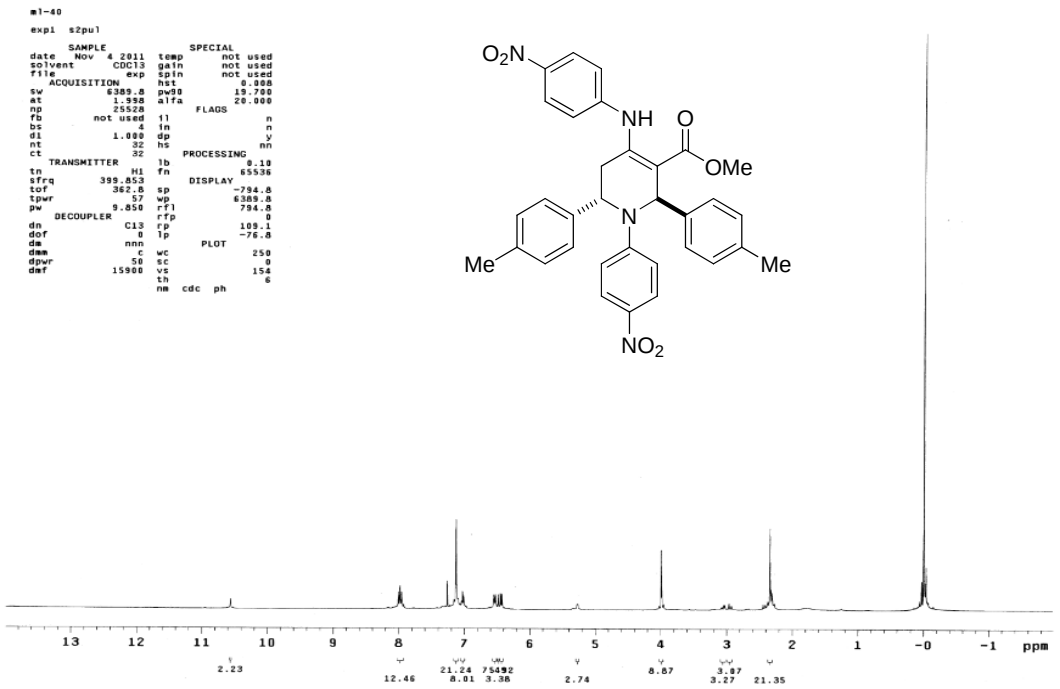


Figure 11.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(4-nitrophenyl)-4-(4-nitrophenylamino)-1,2,5,6-tetrahydropyridine-3arboxylate***(122l)**



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(4-nitrophenyl)-4-(4-nitrophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate***(122l)**

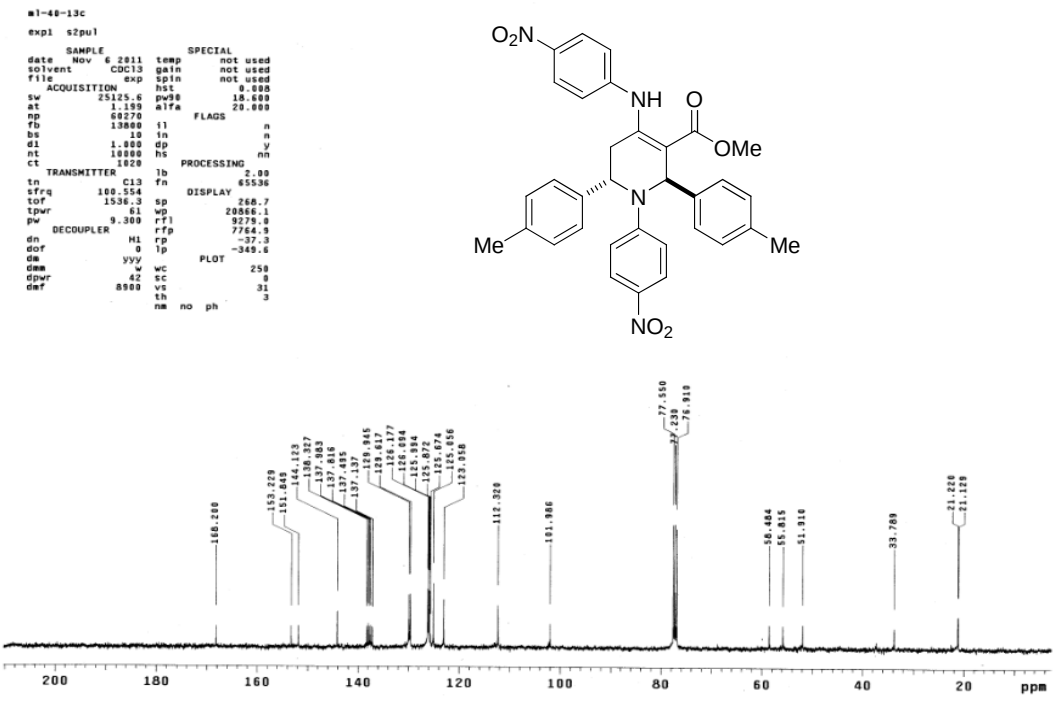
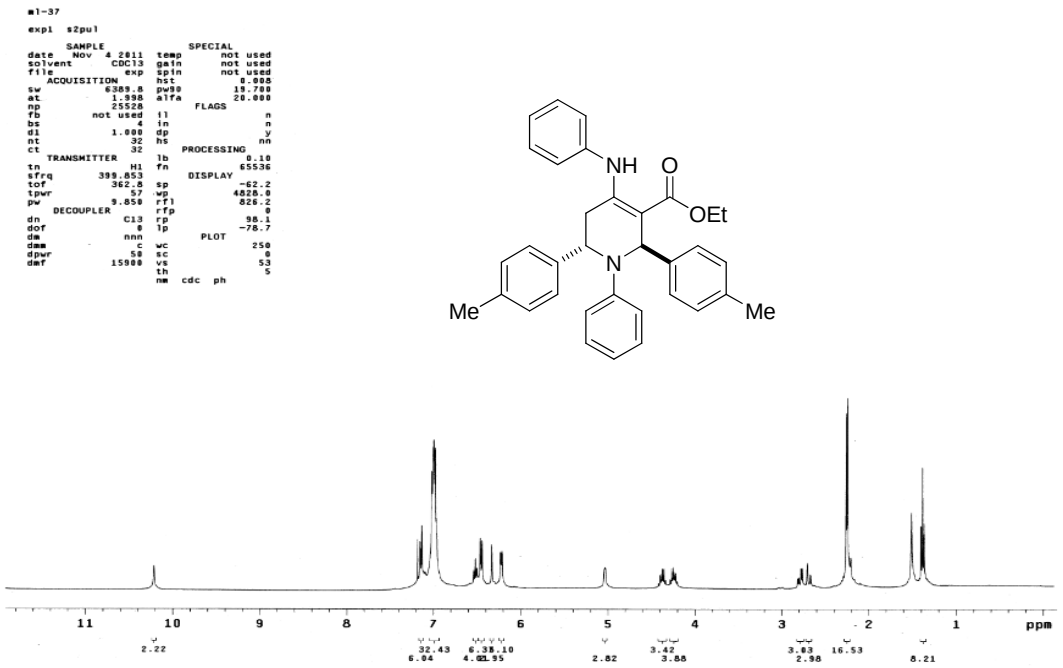


Figure 12.

¹H NMR (400 MHz, $CDCl_3$): *Ethyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**122o**)



¹H NMR (400 MHz, $CDCl_3$): *Ethyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate*(**122o**)

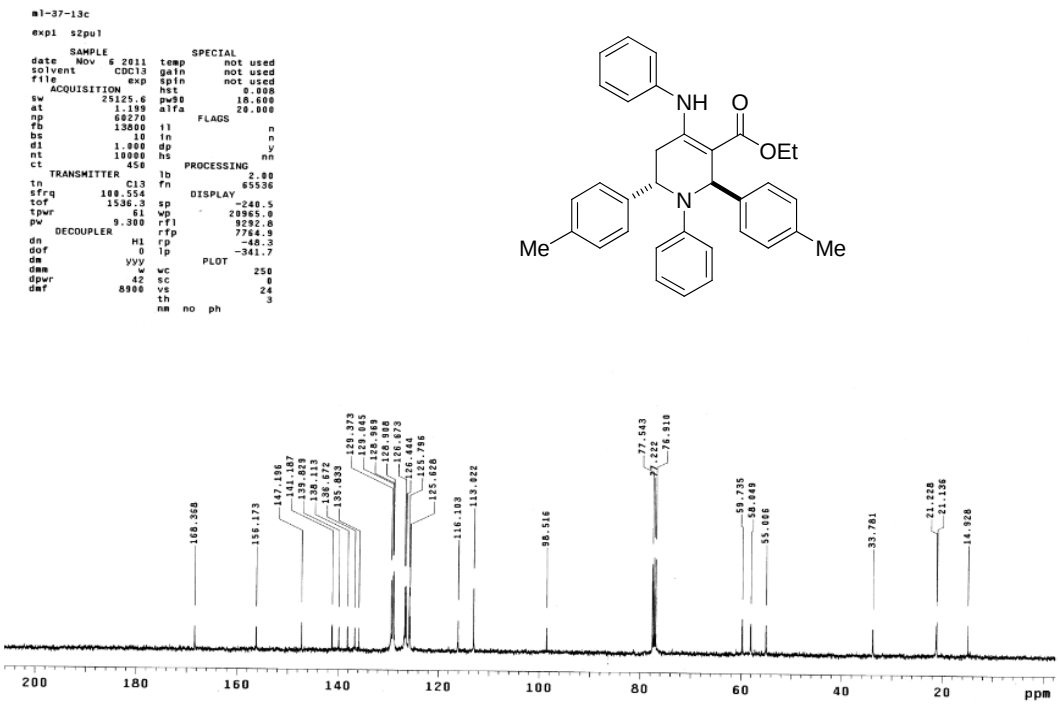
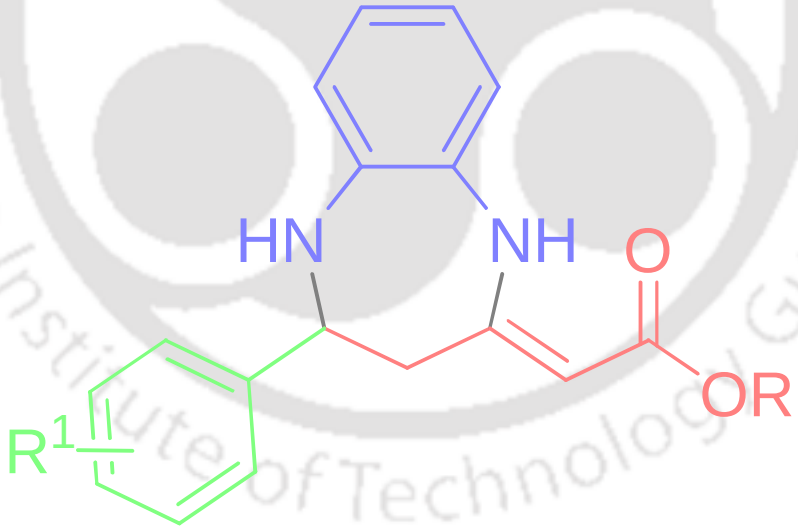


Figure 13.

Hydrogen-bond-mediated regioselective synthesis of 1,5-benzodiazepines by employing organocatalyst 2,6-pyridine dicarboxylic acid

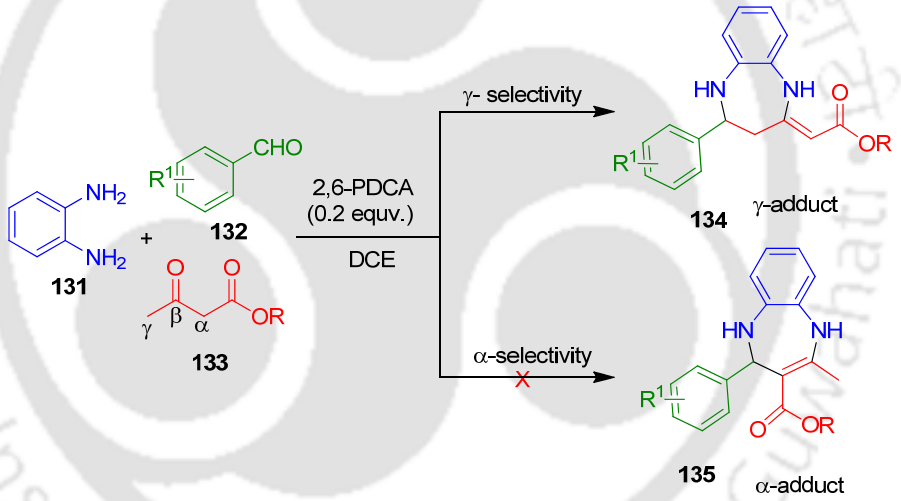


In the second chapter, we have demonstrated the usefulness of β-diketoesters for the synthesis of highly substituted tetrahydropiperidines through MCR using organic ammounim tribromide namely TBATB as catalyst.

Recently, various research groups have demonstrated the usefulness of β-diketo compounds for the synthesis of numerous heterocyclic compounds by employing multicomponent reactions (MCRs), which was mentioned in the introduction part.[3b] We have also proven that β-keto compounds are valuable starting material for the synthesis of β-acetoamido carbonyl compounds,[98] and β-amino carbonyl compounds[99] as well as the synthesis of highly substituted piperidine derivatives[75,76,100] involving carbon-carbon bond formations either at the α position[98,99] or both at the α and γ position[75,76,100] of 1,3-dicarbonyl compounds, respectively. However, the selective *C*-*C* bond formation at the γ position of β-diketo compounds is relatively less explored. In 2007, Kita *et al.* first reported[79a] the synthesis of seven membered 1,4-azepane through multicomponent reaction from aromatic aldehydes, ethylenediamine and β-ketoesters in presence of 10 mol% p-toluene sulfonic acid (p-TSA) by employing C,C-bond formation at the γ position of β-ketoesters. They have also observed that the same reaction did not provide good yield in presence of *p*-TSA for the synthesis of 1,5-benzodiazapines when o-phenylenediamine was used in place of ethylenediamine.[101] Interestingly, the synthesis of 1,5-benzodiazapines was achieved using pentafluorobenzoic acid involving the same combination. Interestingly, they have not mentioned that pentafluorobenzoic acid can form strong hydrogen bond due to which the formation of product took place. Development of new methodology for the synthesis of 1,5-benzodiazepines using new catalyst is of great demand because of their interesting pharmacological activities such as anticonvulsant, anti-inflammatory, analgesic, anti-anxiety, anti-depressive, antibiotics,[102] anti-cancer[103] and anti-viral (HIV) activities.[104] Consequently, there is a further scope to devise a new methodology using less expensive catalyst and simpler reaction procedure.
Recently, organocatalysts have gained tremendous attention amongst organic chemists for various synthetic transformations.[105] It is well known established fact that carboxylic acid usually forms strong intermolecular hydrogen bonding very easily. We perceived that 2,6-pyridinedicarboxylic acid (2,6-PDCA) might be useful organocatalyst for the synthesis of 1,5-benzodiazepines. In the third chapter, we would like to discuss the role of 2,6-pyridinedicarboxylic acid as an organocatalyst for multicomponent reaction

involving β-diketoesters, *o*-phenylenediammine and aromatic aldehydes in which the catalyst can take part in activation through a hydrogen bonding. Hydrogen bond is one of the most essential features for molecular recognition as well as well- defined organization of molecule in chemistry and biology.[106] Hydrogen-bond-assisted approaches have been explored in crystal engineering and self-assembly and this non-covalent interaction has been utilized in organic synthesis[107] because it enhances reactivity or selectivity[108] in certain catalytic transformations such as Diel's Alder reactions,[109] Morita–Baylis–Hillman reaction,[110] aldol reaction,[111] Michael reaction,[112] and epoxidation[113] etc.

In this chapter, we would like to report hydrogen-bond-assisted one-pot three-component reaction for accessing of 1,5-benzodiazepines derivatives using *o*-phenylenediamine, β-ketoesters and aromatic aldehydes as shown in Scheme 46.



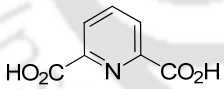
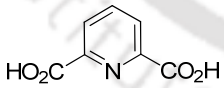
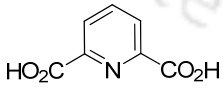
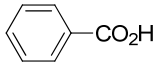
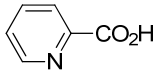
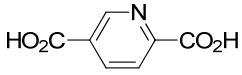
Scheme 46.

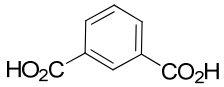
For the present study, the mixture of *o*-phenylenediamine (1 mmol) and methyl acetoacetate (1 mmol) in 3 mL of dichloroethane (DCE) in a 25 mL round bottomed flask was stirred in the presence of 10 mol% 2,6-PDCA for 2 h at room temperature. Then, 4-chlorobenzaldehyde (1 mmol) was added into the above reaction mixture and the reaction flask was transferred in a heated oil-bath for refluxing. After completion of the reaction, it was cooled down to room temperature and the solvent was removed. Finally the crude residue was passed through a silica gel column and the desired product **134a** was obtained in 48 % yield, The product was characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, and elemental analysis. Appearance of a strong absorption peak at 1650

cm^{-1} in IR spectrum indicates the presence of carbonyl group of ester. In ^{1}H NMR spectra the characteristic signals at δ 2.51-2.64 (m, 2H), 3.66 (brs, 3H), 4.52 (s, 1H), 4.84 (dd, *J* = 7.6Hz, 4.8 Hz, 1H), 6.77 (d, *J* = 7.6Hz, 1H), 10.17 (brs, 1H, NH). Similaraly δ 50.57(OMe), 64.69(C-7), 84.44 (C-10), 130.43(C-6), 133.36 (C-17) 138.03(C-5), 143.08(C-14), 158.27(C-9), and 170.68(C=O) in ^{13}C NMR confirmed the formation of 1,5-benzodiazepine **134a** via three component reaction.

For optimizing the reaction conditions, various trial reactions were carried out in a similar manner to increase the yield of the product using a combination of *o*-phenylenediamine, methyl acetoacetate and 4-chlorobenzaldehyde using 20% and 30% catalyst as shown in Table 4. We have observed 20% catalyst is sufficient to obtain maximum yield. Subsequently, the same reaction were investigated with other catalysts such as benzoic acid, pyridine 2-carboxylic acid, and 2,5-pyridinedicarboxylic acid. However, the yield of the product **134a** did not increase significantly. To verify the role of 2,6-PDCA, we have also carried out similar reaction with isophathalic acid. However, the yield did not increase significantly. From these observations, it is quite clear that 2,6-PDCA plays pivotal role among all other organocatalysts.

Table 4 Optimization of reaction condition for the synthesis of 1,5-benzodiazepines (**134a**)

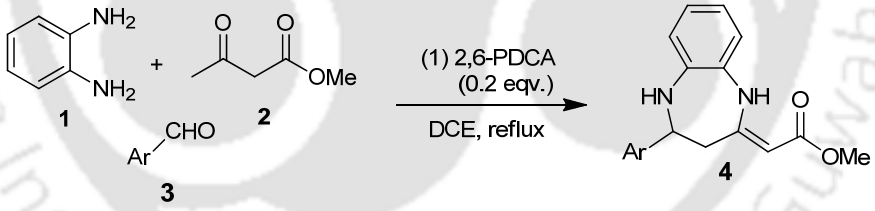
Entry	Organocatalyst	(Mol%)	Time (h)	% Yield[a]
1	No catalyst	—	12	0
2		10	7	48
3		**20**	**5**	**70**
4		30	5	69
5		10	8	21
6		10	8	25
7		10	7	35

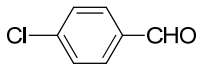
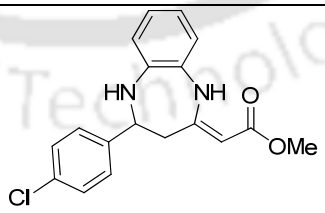
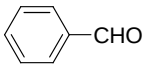
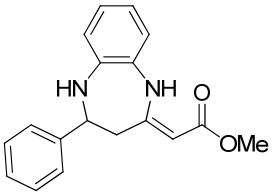
8		10	8	32

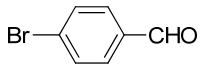
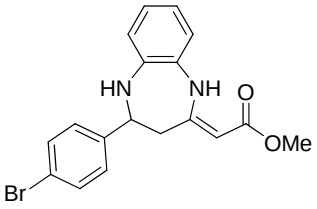
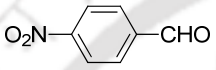
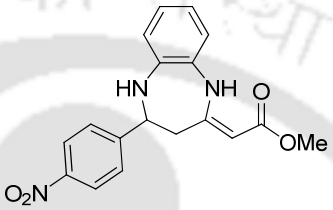
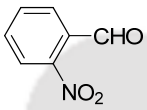
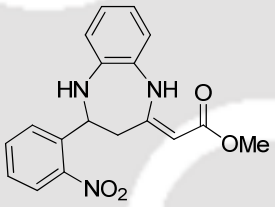
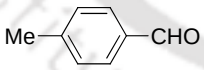
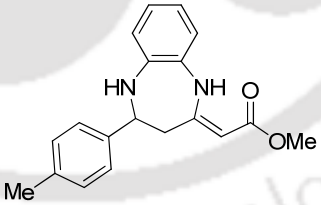
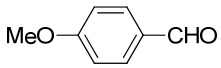
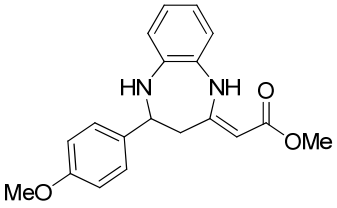
[a]Isolated yield

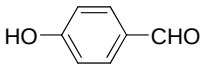
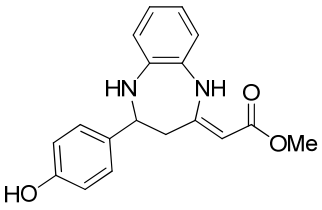
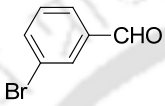
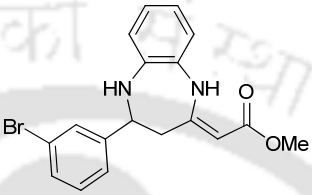
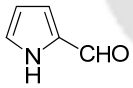
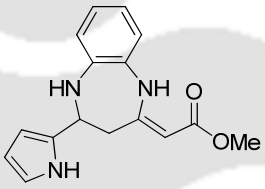
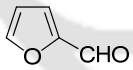
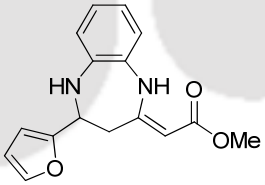
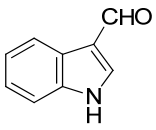
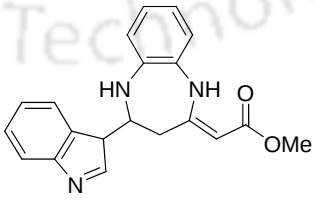
After optimization of the reaction conditions, the reaction of *o*-phenylenediamine, methyl acetoacetate and benzaldehyde was performed under identical manner and it afforded the product **134b** in 62% yield. Encouraged by the above successful results, a wide variety aromatic aldehydes containing different substituents such as -Br, -NO_2, -Me, -OMe, -OH group at various position in the aromatic ring were treated with *o*-phenylenediamine and methyl acetoacetate with 20 mol% 2,6-PDCA under similar reaction conditions and the desired products **134c-i** (Table 5, entries 3-9) were isolated in good yields. To verify the generality and further scope of the present protocol, the similar reactions were carried out with various heterocyclic aldehydes, *ortho*-phenylenediamine and methyl acetoacetate using the same mol% of catalyst under identical reaction conditions. The products (**134j-m**) were obtained in good yields, which are shown in Table 5 (entries 10-13).

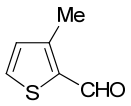
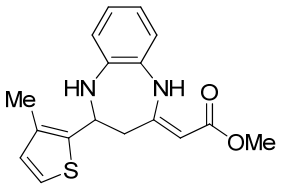
Table 5 Synthesis of 1,5-Benzodiazepines using a combination of o-phenylenediamine, methyl acetoacetate and aromatic aldehydes in presence of 20 mol% 2,6-PDCA



Entry	Aldehydes **132**	Compound **134**[a]	Time (h)	%Yield[b]
1	 **132a**	 **134a**	4	70
2	 **132b**	 **134b**	4.5	62

3	 **132c**	 **134c**	2.5	68
4	 **132d**	 **134d**	4.5	68
5	 **132e**	 **134e**	4	62
6	 **132f**	 **134f**	2.5	71
7	 **132g**	 **134g**	3	70

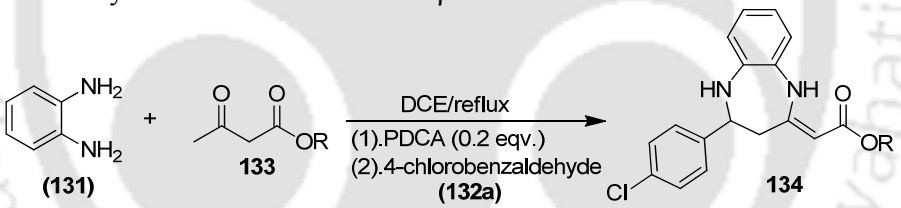
8	 **132h**	 **134h**	4	66
9	 **132i**	 **134i**	3.5	72
10	 **132j**	 **134j**	4	55
11	 **132k**	 **134k**	3	61
12	 **132l**	 **134l**	2.5	55

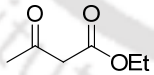
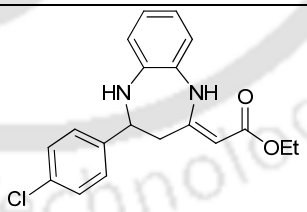
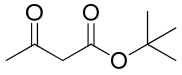
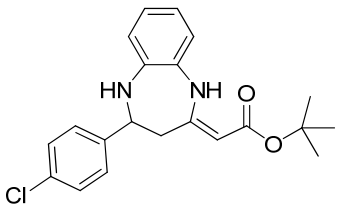
13	 **132m**	 **134m**	2	74

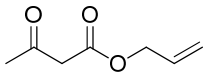
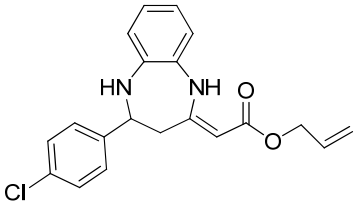
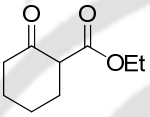
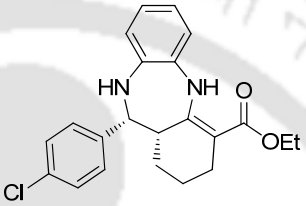
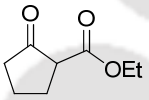
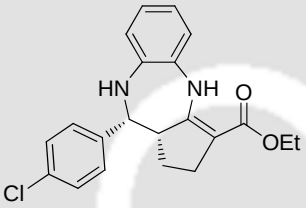
[a]The reaction were performed in 1 mmol scale using β-ketoesters, *o*-phenylenediamine and aromatic aldehyde. [b]Isolated yield.

The scope of the reaction was further examined by performing the reaction with different β-ketoesters, *o*-phenylenediamine and 4-chlorobenzaldehyde by employing 20 mol% PDCA under similar reaction conditions. The desired products (**134n-r**) were isolated in good yields, which are shown in Table 6 (entries-1-5). All the products were characterized from ^{1}H NMR, ^{13}C NMR and HRMS and elemental analysis. The spectral data some of the compounds such as **134a**, **134b**, and **134n** are given in Figure 16-20 in Experimental Section.

Table 6 Formation of 1,5-benzodiazepines by employing o-phenylenediamine, 4-chlorobenzaldehyde reaction with different β-ketoesters



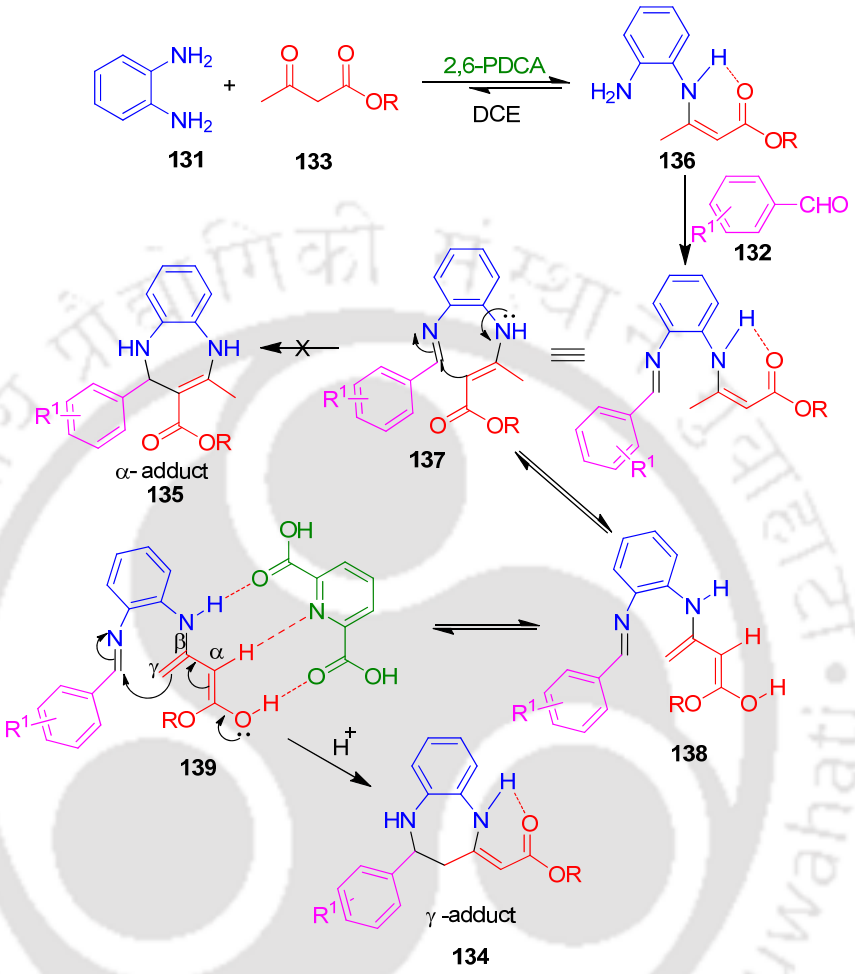
Entry	β-ketoesters **133**	Compound **134**[a]	Time(h)	%Yield[b]
1	 **133n**	 **134n**	2.5	62
2	 **133o**	 **134o**	2	66

3	 **133p**	 **134p**	3	64
4	 **133q**	 **134q**	5	64
5	 **133r**	 **134r**	3	64

[a] The reaction were carried out in 1 mmol scale. [b]Isolated yield.

The formation of 1,5-benzodiazepines can be explained as follows: At first *o*-phenylenediamine (**131**) reacts with β-ketoester (**133**) to give monoenaminoester **136** in presence of 2,6-PDCA at room temperature. Then, the intermediate **136** react with aromatic aldehyde (**132)** under reflux condition to form imine-enamino ester intermediate **137**, which may exist in other alternative form **138** at room temperature. The intermediate **137** can provide 1,5-benzodiazepine derivative **135** through α-selective C-C-bond formation by employing intramolecular Mannich reaction, which is not observed. On the other hand, the intermediate **138**[79b,c] easily forms 1,5-benzodiazepine derivative **134** through γ-selective C-C- bond formation due to the formation of intermolecular hydrogen-bonding with 2,6-pyridinedicarboxylic acid (PDCA) as it forms 14 membered ring formation through non-bonding interaction (Scheme 47). The importance of nitrogen atom in the pyridine ring also plays significant role because the

same reaction does not give the similar result while it was carried out with isophthalic acid.



Scheme 47.

The hydrogen bonded complex was optimized by using the Gaussian 03 software applying the DFT method B3LYP with 6-31G (d) basis set (Figure 14). Hydrogen bonding interactions were found between O1 and H1 (2.143 Å) and O2 and H3 (1.914 Å). The distance pyridine nitrogen N1 and H2 is 2.863 Å which is little longer than the hydrogen bonding range. The N2-H1, C1H2 and O3-H3 bond lengths are 1.014 Å, 1.086 Å and 0.978 Å, respectively while the O1-H1-N2 and O2-H3-O3 bond angles are 142.8° and 157.7°, respectively.

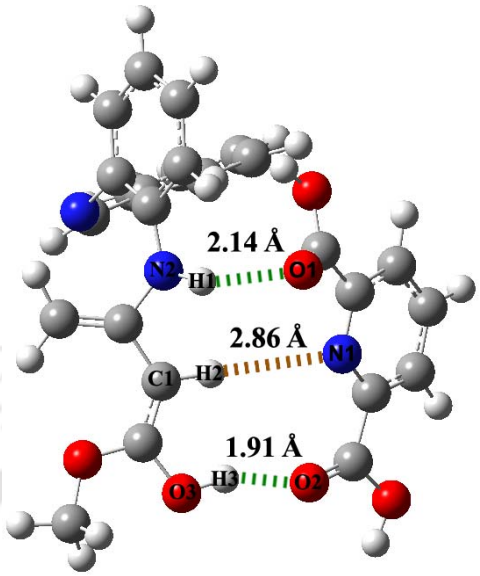


Figure 14. Hydrogen bonded complex

Moreover, the structural assignment and especially the (*Z*)-configuration of the double bond in the cases of acyclic ketoesters is determined based on an X-ray analysis of **134n** (Figure 15).

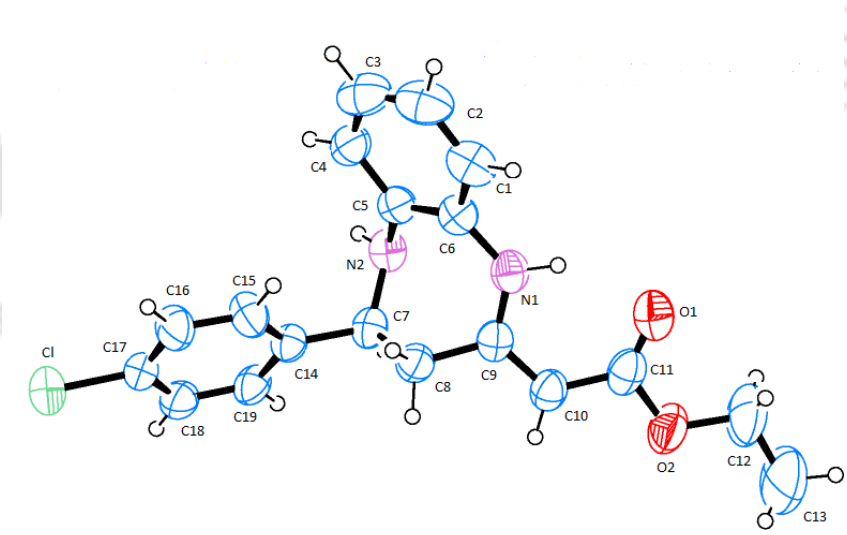
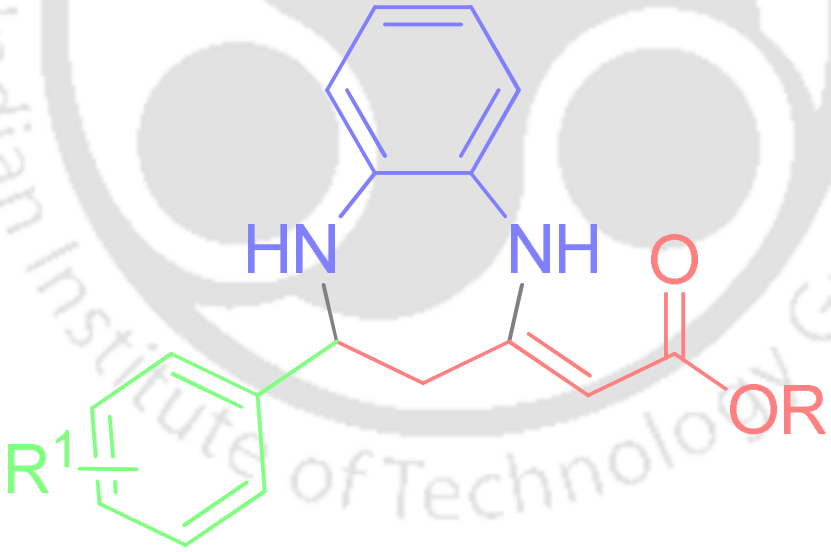


Figure 15. ORTEP Diagram of compound: **134n** (CCDC 827828)

The stereochemistry of compounds **134q** and **134r** were determined by their differential NOE spectra. Thus NOE between the benzylic proton and homobenzylic proton in each compound was observed, which indicates the *cis* configuration in cases of cyclic β-ketoesters.

In summary, we have successfully demonstrated a simple synthetic protocol for the synthesis of 1,5-benzodiazepine derivatives using o-phenylenediamine, β-ketoesters and aromatic aldehydes through one-pot reactions. The organocatalyst 2,6-PDCA plays three role in the above transformation: i) formation of mono enaminoester due to protonation of the other amino group, ii) activation of carbonyl group for the formation of imine during heating conditions, and iii) it also assists selectively C-C bond formation at the *γ*-position of *β*-ketoester, which in turn capable of formation of 1,5-benzodiazepine derivatives **134** in good yields.

Hydrogen-bond-mediated regioselective synthesis of 1,5-benzodiazepines by employing organocatalyst 2,6-pyridine dicarboxylic acid

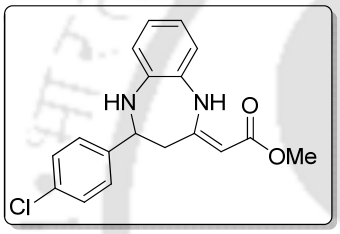


Experimental Section

General procedure for the synthesis of 1,5-benzodiazepines:

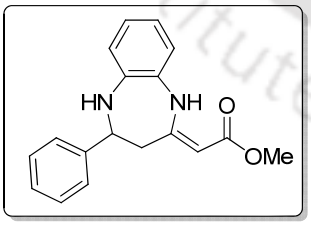
To a stirred mixture of *o*-phenylenediamine (1.0 mmol) and β-ketoesters (1.0 mmol) in 3 mL of dichloroethane in 25 mL round bottomed flask was added 2,6-pyridinedicarboxylic acid (34 mg, 0.2 mmol) and it was kept for stirring for 2 h at room temperature. Then aromatic aldehyde (1 mmol) was added into it and the reaction flask was transferred in a heated oil-bath for refluxing. After usual work up procedure, the crude residue is passed through silica gel column. The product was obtained in good yield after eluting with ethyl acetate and hexane (1:9) mixture.

1,5-benzodiazene derivative (**134a**)



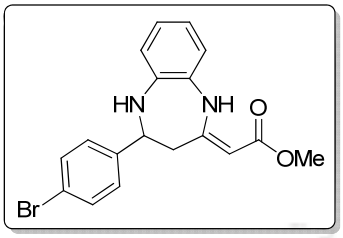
Pale yellow amorphous solid; **IR** (KBr): 1161, 1232, 1266, 1489, 1588, 1615, 1648, 2851, 2925, 3365 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.51-2.64, (m, 2H), 3.66 (brs, 3H), 4.52 (s, 1H), 4.84 (dd, *J* = 7.6, 4.8Hz, 1H), 6.77 (d, *J* = 7.6Hz, 1H), 6.90-7.0 (m, 3H), 7.30 (brs, 4H), 10.17 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.07, 50.57, 64.69, 84.44, 121.15, 122.24, 122.71, 125.29, 127.81, 129.02, 130.43, 133.76, 138.03, 143.08, 158.27, 170.68; Calcd. for $C_{18}H_{17}ClN_2O_2$ $[M + H]^+$: *m/z* = 329.1057; found: 329.1028; **Anal. Calcd** for $C_{18}H_{17}ClN_2O_2$ (328.79): C, 65.75; H, 5.21; N, 8.52; found C, 65.54; H, 5.06; N, 8.38

1,5-benzodiazene derivative (**134b**)



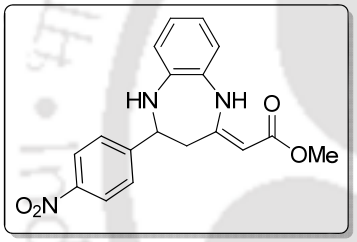
IR (KBr) 3368, 1650,1616,1495,1285, 1231, 1163 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.55 (dd, *J* = 14.4 Hz, 1H), 2.68 (dd, *J* = 14, 8.8 Hz, 1H), 3.67 (s, 3H), 4.59 (s, 1H), 4.84 (dd, *J* = 8.8 Hz, 4.0 Hz, 1H), 6.78 (d, *J* = 8Hz, 1H), 6.89-6.99 (m, 3H), 7.2 9-7.35 (m, 5H), 10.21 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.39, 50.52, 65.32, 83.97, 121.02, 121.79, 122.71, 125.24, 126.28, 128.14, 128.96, 130.02, 138.13, 144.91, 158.93, 170.78; Calcd for $C_{18}H_{18}N_2O_2$ $[M + H]^+$: *m/z* = 295.1447; found: 295.1458; **Anal. Calcd** for $C_{18}H_{18}N_2O_2$ (294.35): C,73.45; H, 6.16; N, 9.52; found C,73.36; H, 6.02; N, 9.35.

1,5-benzodiazene derivative (**134c**)



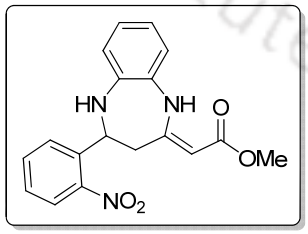
IR KBr: 1160, 1232, 1264, 1434, 1487, 1588, 1614, 1654, 2947, 3258, 3307 Cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.53 (dd, *J* = 14, 8Hz, 1H), 2.61 (dd, *J* = 13.6, 4.8Hz 1H), 3.66 (s, 3H), 4.52 (s, 1H), 4.83 (dd, *J* = 7.6, 4.4 Hz, 1H), 6.76 (d *J* = 7.2 Hz 1H), 6.91-6.98 (m, 3H), 7.25-7.26 (m, 2H), 7.45-7.47 (m, 2H), 10.16 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.05, 50.61, 64.80, 84.52, 121.2, 122.34, 122.76, 125.33, 128.20, 132.03, 143.61, 158.24, 170.72; **Anal. Calcd** for $C_{18}H_{17}BrN_2O_2$ (373.24): C, 57.92; H, 4.59; N, 7.51; found C, 57.78; H, 4.48; N, 7.36.

1,5-benzodiazene derivative (**134d**)



pale yellow amorphous solid; **IR** KBr 1162, 1233, 1266, 1286, 1346, 1436, 1519, 1621, 2934, 3445 Cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.42-2.49 (m, 1H), 2.78 (dd, *J* = 14.4 Hz, 4.4 Hz, 1H), 3.44 (s, 1H), 3.64 (s, 3H), 3.72 (brs, 1H) 4.8 (s, 1H), 5.02 (s, 1H), 6.8 (d, *J* = 7.6Hz 1H), 6.94-7.0 (m, 2H), 7.57 (d *J* = 8.4 Hz 2H) 8.18 (d, *J* = 8 Hz,2H), 10.12 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 39.53, 50.65, 64.61, 85.06, 121.29, 122.81, 124.1, 125.45, 127.54, 130.81, 137.93, 147.74, 151.34, 157.20, 170.51; **Anal. Calcd** for $C_{18}H_{17}N_3O_4$ (339.34): C, 63.71; H, 5.05; N, 12.38; found C, 63.62; H, 4.98; N, 12.32.

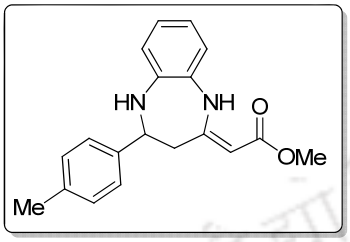
1,5-benzodiazene derivative (**134e**)



IR KBr 1116, 1162, 1231, 1267, 1303, 1350, 1497, 1528, 1615, 2368, 2939, 3436 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.47(dd, *J* = 13.6 Hz, 6.4 Hz, 1H), 2.78 (dd, *J* = 13.6 Hz, 4.4Hz, 1H), 3.62 (s, 3H), 4.38 (s, 1H), 5.01-5.03 (m, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.92-7.01 (m, 2H), 7.5 (t, *J* = 8 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.11-8.13 (m, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 10.12 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 39.66, 50.61, 64.52, 85.02, 121.30, 121.63, 122.78, 123.12, 125.46, 129.83, 130.77, 132.84, 137.94, 146.35, 157.29, 170.5; **Anal.**

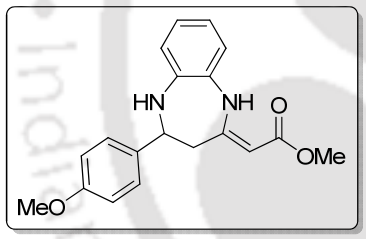
Calcd for $C_{18}H_{17}N_3O_4$(339.35): C, 63.71; H, 5.05; N, 12.38. found C, 63.58; H, 4.96; N, 12.28.

1,5-benzodiazene derivative (**134f**)



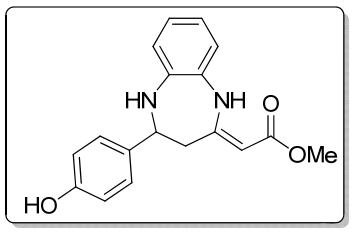
Pale yellow amorphous solid; **IR** KBr 1160, 1231, 1266, 1281, 1299, 1376, 1437, 1497, 1589, 1618, 1654, 2946, 3021, 3364 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): 2.35 (s, 3H), 2.53 (dd, *J* = 13.6 Hz, 3.2 Hz, 1H), 2.67 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 3.68 (brs, 3H), 4.63 (s, 1H), 4.80 (dd, *J* = 8.4 Hz, 3.2 Hz, 1H), 6.75 (d, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 6.4 Hz, 1H), 6.97 (d, *J* = 8 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.2 1H), 10.25 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.20, 40.42, 50.43, 64.95, 83.83, 120.91, 121.58, 122.61, 125.13, 126.11, 129.52, 129.85, 137.75, 138.10, 141.99, 159.02, 170.71; **Anal. Calcd** for $C_{19}H_{20}N_2O_2$ (308.37): C, 74.00; H, 6.54; N, 9.08; found C, 73.85; H, 6.42; N, 8.96.

1,5-benzodiazene derivative (**134g**)



Pale yellow amorphous solid; **IR** KBr 1160, 1249, 1286, 1438, 1509, 1588, 1617, 1654, 2835, 2947, 3274, 3357 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.54 (dd, *J* = 13.6 Hz, 4.0 Hz, 1H), 2.62 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 3.66 (s, 3H) 3.77 (s, 3H), 4.57 (s, 1H), 4.77 (dd, *J* = 8.8 Hz, 4.0 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.84-6.89 (m, 4H), 6.93-6.97 (m, 2H), 7.23-7.26 (m, 2H), 10.19 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.55, 50.47, 55.42, 64.69, 83.93, 114.19, 120.97, 121.68, 122.66, 125.18, 127.40, 129.96, 137.15, 138.12, 159.04, 159.4, 170.76; Anal. Calcd for $C_{19}H_{20}N_2O_3$(324.37): C, 70.35; H, 6.21; N, 8.64; found C, 70.18; H, 6.04; N, 8.48.

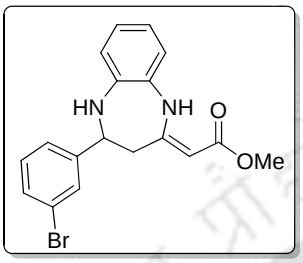
1,5-benzodiazene derivative (**134h**)



IR KBr: 1163, 1229, 1264, 1281, 1497, 1647, 2846, 2923, 3433 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.54 (dd, *J* = 14.4 Hz, 4.0 Hz, 1H), 2.63 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 3.68 (brs, 3H), 4.59 (s, 1H), 4.79 (dd, *J* = 8.8 Hz, 4.4 Hz, 1H), 5.11 (brs, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.78-6.82 (m, 2H), 6.88-6.93 (m, 2H), 6.96-7.0 (m, 2H), 7.21-7.26 (m, 2H), 10.19 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$); δ = 40.55, 50.69, 64.88, 83.98, 115.72, 121.09,

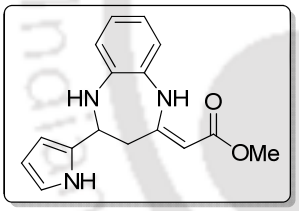
121.87, 122.77, 125.32, 127.7, 130.06, 137.19, 138.14, 155.63, 159.16, 170.95; **Anal. Calcd** for $C_{18}H_{18}N_2O_3$(310.35): C, 69.66; H, 5.85; N, 9.03. found C, 69.52; H, 5.64; N, 8.92.

1,5-benzodiazene derivative (**134i**)



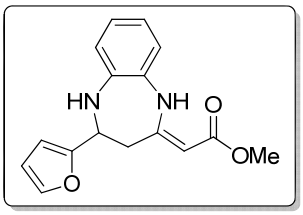
Pale yellow amorphous solid; **IR** KBr 1161, 1267, 1433, 1474, 1621, 1645, 3457 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.59-61 (m, 2H), 3.68 (brs, 3H), 4.56 (s, 1H), 4.84 (t, *J* = 6.4, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.92-7.03 (m, 4H), 7.21-7.26 (m, 1H), 7.33 (d, *J* = 8Hz, 1H), 7.42-7.44 (m, 1H) 7.52 (s, 1H), 10.2 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.08, 50.56, 64.71, 84.44, 121.14, 122.23, 122.75, 122.92, 125.03, 125.32, 129.56, 130.34, 130.55, 131.23, 137.89, 146.95, 158.19, 170.69; **Anal. Calcd** for $C_{18}H_{17}BrN_2O_2$ (373.24): C, 57.92; H, 4.59; Br, 21.41; N, 7.51; O, 8.57; found C, 57.84; H, 4.44; N, 7.51.

1,5-benzodiazene derivative (**134j**)



IR KBr: 1033, 1113, 1157, 1271, 1429, 1413, 1618, 2934, 3431cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.49 (dd J = 14.0 Hz, 6 Hz, 1H), 2.73 (dd, *J* = 13.6 Hz, 5.6 Hz 1H), 3.66 (brs, 3H), 4.6 (s, 1H), 4.92-4.95 (m, 1H), 6.04 (d, *J* = 3.2 Hz, 1H), 6.13 (t, 1H), 6.70-6.71 (m, 1H), 6.77 (d, *J* = 6.8 Hz), 6.94-6.98 (m, 3H), 8.64 (brs, 1H), 10.15 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 39.43, 45.04. 50.61, 59.48, 69.59, 84.59, 105.28, 108.26, 117.90, 121.76, 122.53, 123.13, 125,39, 131.64, 134.22, 138.16, 158.95, 170.74; **Anal. Calcd** for $C_{16}H_{17}N_3O_2$(383.32): C, 67.83; H, 6.05; N, 14.83; found C, 67.68; H, 5.88; N, 14.76.

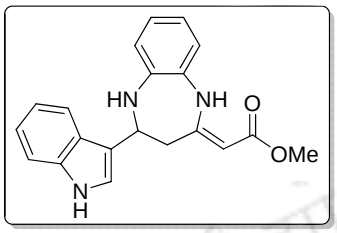
1,5-benzodiazene derivative (**134k**)



IR KBr 1162, 1269, 1297, 1435, 1503, 1636, 2078, 3289 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.59 (dd, *J* = 13.6 Hz, 4.8 Hz, 1H), 2.73 (dd *J* = 13.6 Hz, 9.6 Hz,, 1H), 3.67 (brs, 3H), 4.69 (s, 1H), 4.91 (dd, *J* = 9.6 Hz, 4.8 Hz, 1H), 6.19 (d *J* = 3.2 Hz, 1H), 6.30 (dd, *J* = 3.2 Hz, 2.0 Hz, 1H), 6.72-6.74 (m, 1H), 6.92-6.96 (m, 3H), 7.34-7.35 (m, 1H), 10.12 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 36.57, 50.61, 59.06, 84.25, 105.62, 110.45, 122.09, 122.50, 122.92, 125.23,

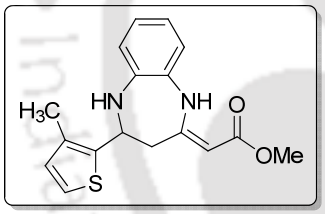
131.43, 137.26, 142.13, 156.35, 158.5, 170.73; **Anal. Calcd** for $C_{16}H_{16}N_2O_3$(284.31): C, 67.59; H, 5.67; N, 9.85; found C, 67.44; H, 5.48; N, 9.72.

1,5-benzodiazene derivative (**134l**)



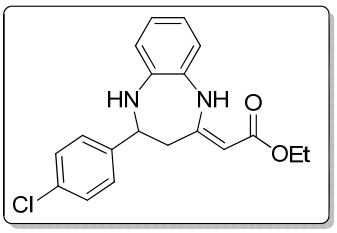
IR KBr: 1044, 1163, 1231, 1267, 1296, 1434, 1451, 1495, 1614, 2947, 2978, 3056, 3404 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.67 (dd *J* = 13.6, 3.6 Hz 1H), 2.95-3.02 (m, 1H), 3.72 (brs, 1H), 4.68 (s, 1H), 5.23 (dd *J* = 9.2 Hz, 3.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.89-6.94 (m, 1H), 6.96-7.0 (m, 2H), 7.12-7.17 (m, 2H), 7.22-7.28 (m, 1H), 7.39 (d, *J* = 8Hz, 1H), 7.58 (d, *J* = 8), 8.83 (s, 1H), 10.32 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 39.58, 45.22, 50.61, 58.14, 83.86, 111.86, 119.23, 119.68, 119.92, 121.12, 121.58, 121.78, 122.56, 122.74, 125.34, 129.79, 136.85, 138.37, 160.11, 171.03; **Anal. Calcd** for $C_{20}H_{19}N_3O_2$ (333.38): C, 72.05; H, 5.74; N, 12.60; found C, 71.92; H, 5.64; N, 12.48.

1,5-benzodiazene derivative (**134m**)



Yellow oily liquid; **IR** KBr: 1160,1232, 1268, 1298, 1496, 1589, 1615, 1651,2946, 2989, 3280, 3349 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.25 (s, 3H), 2.58 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.66 (dd, *J* = 13.6 Hz, 8.8 Hz, 1H), 3.68 (brs, 3H), 4.64 (s, 1H) 5.23 (dd *J* = 8.4 Hz, 4.0 Hz, 1H), 6.76-6.80 (m, 2H), 6.93-6.98 (m, 2H), 6.93-6.98 (m, 3H), 7.11(d *J* = 5.2 1H), 10.18 (br s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 13.93, 40.04, 50.56, 59.09, 84.20, 121.77, 122.43, 122.62, 123.35, 125.20, 130.07, 130.64, 132.49, 137.14, 141.85, 158.48, 170.72; **Anal. Calcd for** $C_{17}H_{18}N_2O_2S$ (314.40): C, 64.94; H, 5.77; N, 8.91; found C, 64.82; H, 5.62; N, 8.76.

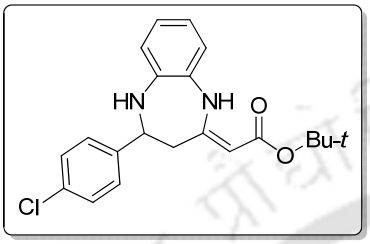
1,5-benzodiazene derivative (**134n**)



Crstaline solid; **IR** KBr 1161, 1234, 1435, 1505, 1618, 1644, 1725, 2949, 3444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, 3H), 2.56 (dd, *J* = 14.0 Hz, 8.0 Hz, 1H), 2.62 (dd, *J* = 14 Hz, 5.2 Hz, 1H), 3.64 (s, 1H), 4.11-4.18 (m, 2H), 4.54 (s, 1H), 4.83-4.87 (m, 1H), 6.73 (d, *J* = 7.6 Hz 1H), 6.91-7.01 (m, 4H), 7.32 (s, 4H), 10.20 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.66, 40.09, 59.04, 64.58, 84.77, 121.07, 122.13, 122.63, 125.17, 127.75, 128.98,

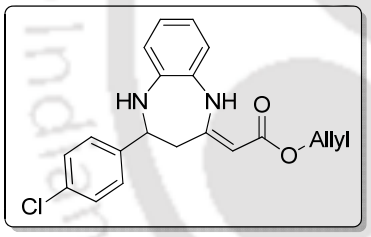
130.38, 133.68, 137.94, 143.14, 158.10, 170.33; Calcd. for $C_{19}H_{19}ClN_2O_2$ $[M + H]^+$: *m/z* = 343.1213; found: 343.1193; **Anal. Calcd** for $C_{19}H_{19}ClN_2O_2$ (342.81): C, 66.57; H, 5.59; N, 8.17; found C, 66.46; H, 5.48; N, 8.08.

1,5-benzodiazene derivative (**134o**)



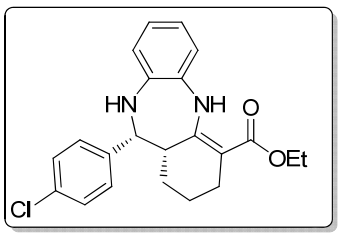
IR KBr: 1146, 1248, 1490, 1614, 1646, 1715, 2362, 2931, 2978, 3059, 3349 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 2.47-2.59 (m, 2H), 3.59 (s, 1H), 4.49 (s, 1H), 4.81 (dd *J* = 8.4, 4.4Hz 1H), 6.74 (d, *J* = 7.6Hz 1H), 6.9-6.98 (m, 3H), 7.24-7.32 (m, 3H), 10.15 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 28.77, 40.20, 64.75, 78.99, 86.45, 121.14, 122.21, 122.69, 125.02, 127.76, 129.09, 130.69, 133.78, 137.75, 143.49, 157.42, 170.39; **Anal. Calcd** for $C_{21}H_{23}ClN_2O_2$ (370.87): C, 68.01; H, 6.25; N, 7.55; found C, 67.88; H, 6.08; N, 7.40..

1,5-benzodiazene derivative (**134p**)



Amorphus solid; **IR** KBr 1091, 1158, 1267, 1490, 1613, 1647, 2938, 3445 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.51-2.63 (m, 2H), 3.64 (s, 1H), 4.54 (s, 1H), 4.55-4.59 (m, 2H), 4.84 (dd, *J* = 3.3 Hz, 5.7 Hz, 1H), 5.18-5.32 (m, 1H), 5.8-5.97 (m, 1H), 6.74 (d, *J* = 6.4 Hz, 2H), 6.89-6.98 (m, 4H), 7.29 (brs, 4H), 10.15 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 40.12, 63.92, 64.79, 84.45, 117.57, 121.18, 122.28, 122.78, 125.37, 127.82, 129.07, 130.4, 133.34, 133.82, 138.02, 143.09, 158.55, 169.92; **Anal. Calcd** for $C_{20}H_{19}ClN_2O_2$(354.83): C, 67.70; H, 5.40; N, 7.89; found C, 67.54; H, 5.18; N, 7.72.

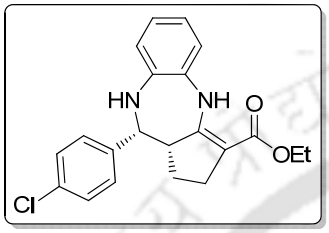
(1,5-benzodiazene derivative (**134q**)



Crystalline solid; **IR** KBr: 1092, 1172, 1186, 1233, 1248, 1264, 1441, 1486, 1608, 1636, 2932, 3456 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.28 (t, 3H), 1.15-1.40 (m, 2H), 1.61 (d, *J* = 4 Hz, 2H), 2.18-2.26 (m, 2H), 2.54-2.58 (m, 2H) 2.84 (dd, *J* = 10.8 Hz, 5.2 Hz, 1H), 4.15-4.21 (m, 2H), 4.69 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 7.6 Hz 1H), 6.89-6.98 (m, 2H), 7.1 (d, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 10.78 (brs, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.78,

18.06, 24.10, 24.45, 38.48, 59.49, 69.25, 92.30, 122.25, 122.35, 123.28, 124.38, 128.05, 129.24, 132.58, 133.87, 137.06, 142.56, 155.78, 170.88; Calcd. for $C_{22}H_{23}ClN_2O_2$ [M + H]$^+$: *m/z* = 383.1526; found: 383.1895; **Anal. Calcd** for $C_{22}H_{23}ClN_2O_2$(382.88): C, 69.01; H, 6.05; N, 7.32; found C, 68.86; H, 5.92; N, 7.32.

1,5-benzodiazene derivative (**134r**)



Amorphus solid; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3H), 2.29-2.31 (m, 1H), 2.40-2.47 (m, 1H), 2.52-2.61 (m, 1H), 3.25 (q, *J* = 6.0 Hz, 1H), 3.71 (s, 1H), 4.21 (dd, *J* = 7.2 Hz, 13.2 Hz, 2H), 4.28 (d, *J* = 10.6 Hz, 1H), 6.60-6.62 (m, 1H), 6.83-6.92 (m, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.35(d, *J* = 7.6 Hz, 2H), 9.57 (s, 1H), **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.88, 26.56, 27.34, 51.55, 59.33, 64.90, 120.77, 121.42, 123.67, 128.85, 129.32, 129.73, 134.14, 136.39, 141.94, 159.91, 165.23, 172.40; **Anal. Calcd** for $C_{21}H_{21}ClN_2O_2$ (368.86): C, 68.38; H, 5.74; Cl, 9.61; N, 7.59; O, 8.68. found C, 68.24; H, 5.58; N, 7.42.

*XRD for compound **134n***

Complete crystallographic data of compound **134n** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 827828. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 7 Crystal data and structures refinement for the compounds **134n**, for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 134n**
Formula	$C_{19}H_{19}ClN_2O_2$
CCDC number	827828
Formula weight	342.81
T (K)	296 K
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
a (Å)	11.2367(5) Å

b (Å)	12.4984(6) Å
c (Å)	14.3746(6) Å
α (°)	82.967(3)º
β (°)	69.273(3)º
γ (°)	68.985(2)º
V (Å^3)	1762.51(14) Å^3
Z	4
D_{calcd} (g m^{-3})	1.292 g/cm^3
μ (mm^{-1})	0.230 mm^{-1}
F(0 0 0)	720.0
Reflection collected	8037
Unique reflections	2745
Goodness-of-fit (GOF)[a] on F^2	0.617
R [$I > 2\sigma(I)$]	[b]$R_1 = 0.0470$, [c]$wR_2 = 0.1213$
R indices (all data)	[b]$R_1 = 0.1385$, [c]$wR_2 = 0.1499$

*^{1}H NMR (400 MHz, $CDCl_3$): 1,5-benzodiazene derivative (**134a**)*

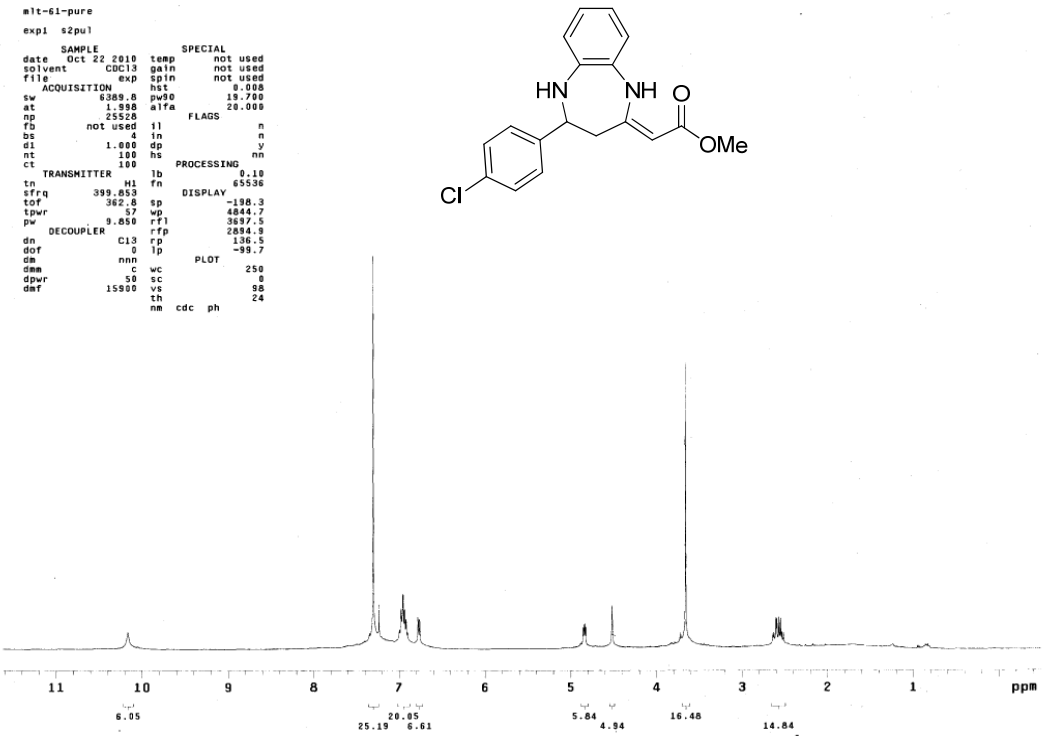
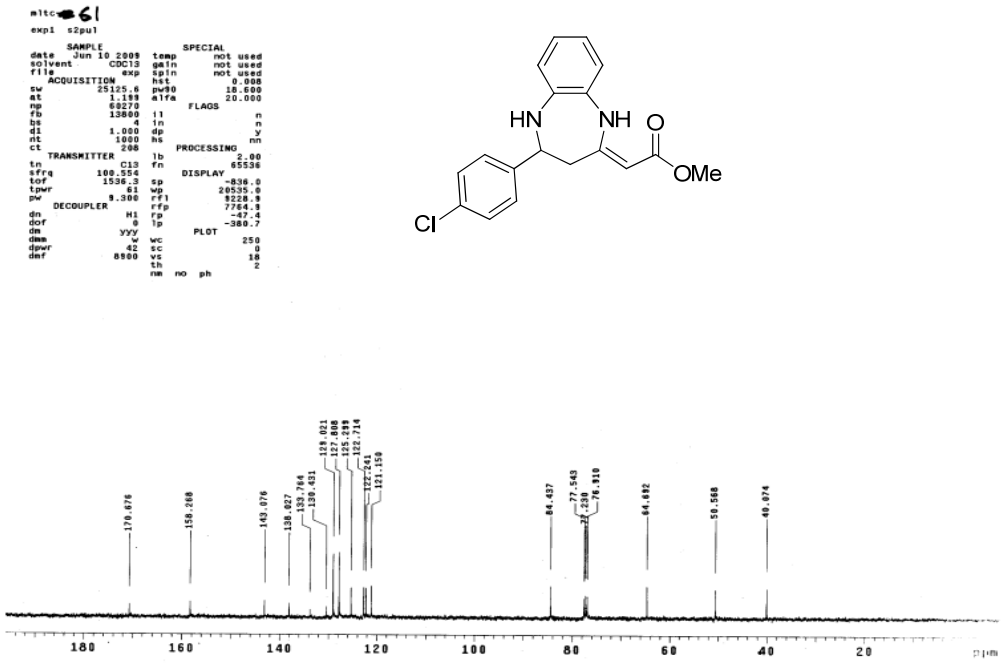


Figure 17.

*^{13}C NMR (100 MHz, $CDCl_3$): 1,5-benzodiazene derivative (**134a**)*



***(HRMS):** 1,5-benzodiazene derivative (**134a**)*

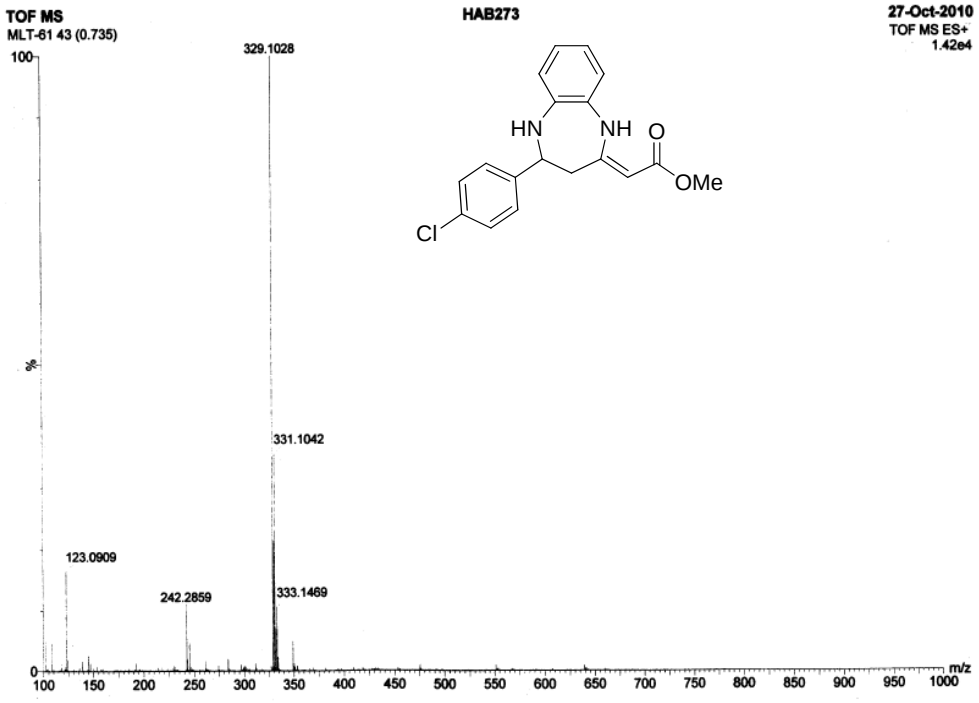
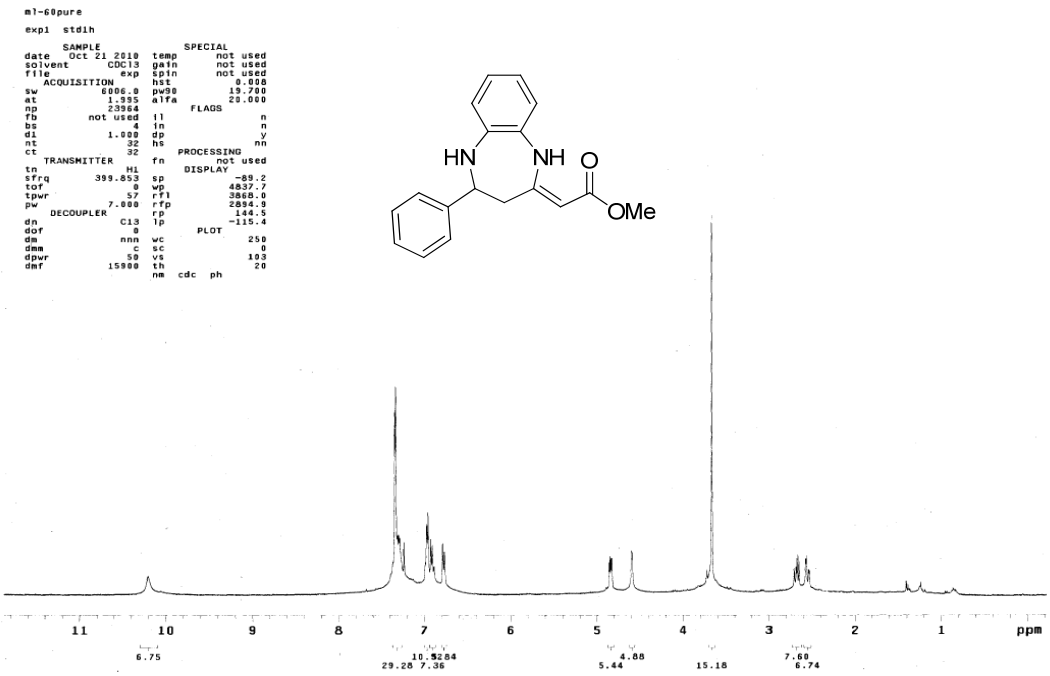


Figure 18. *^{1}H NMR (400 MHz, $CDCl_3$): 1,5-benzodiazene derivative (**134b**)*



***(¹³C NMR (100 MHz, CDCl₃)**: 1,5-benzodiazene derivative (**134b**)*

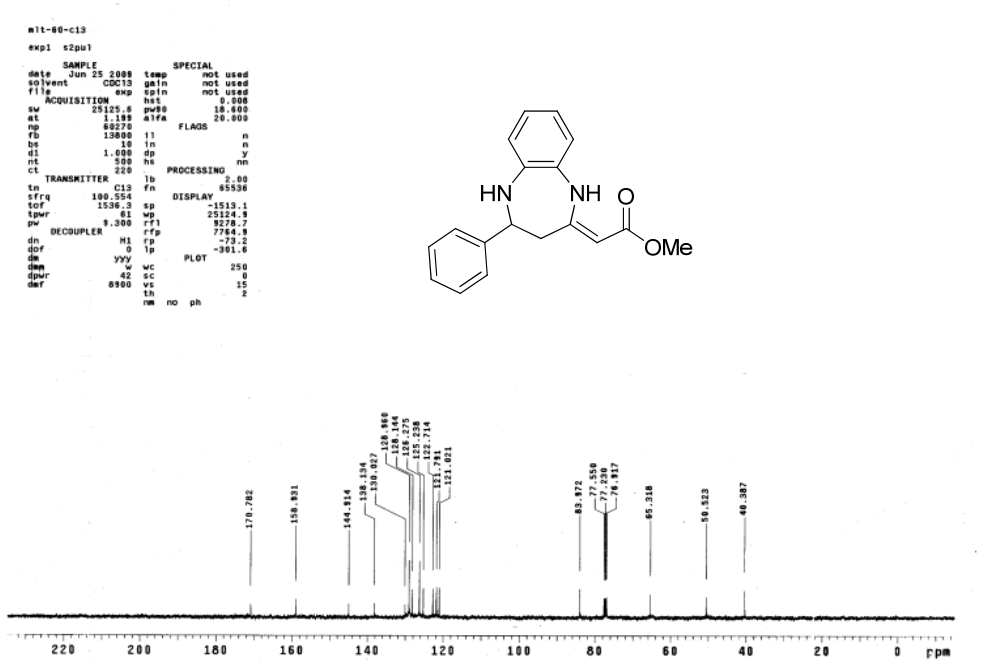
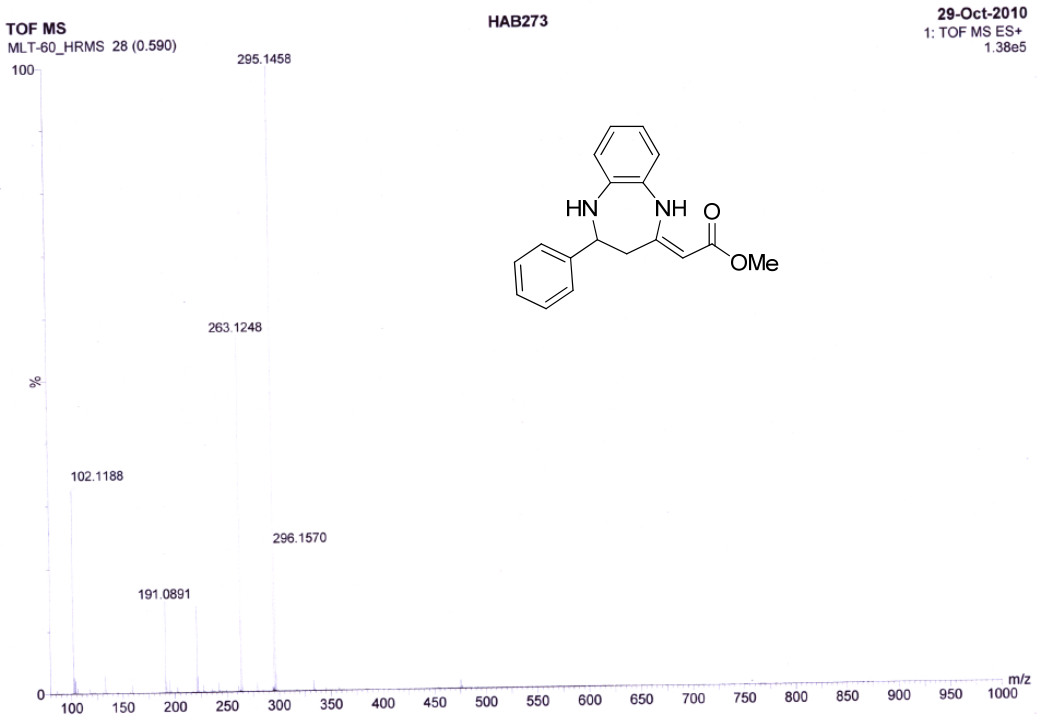
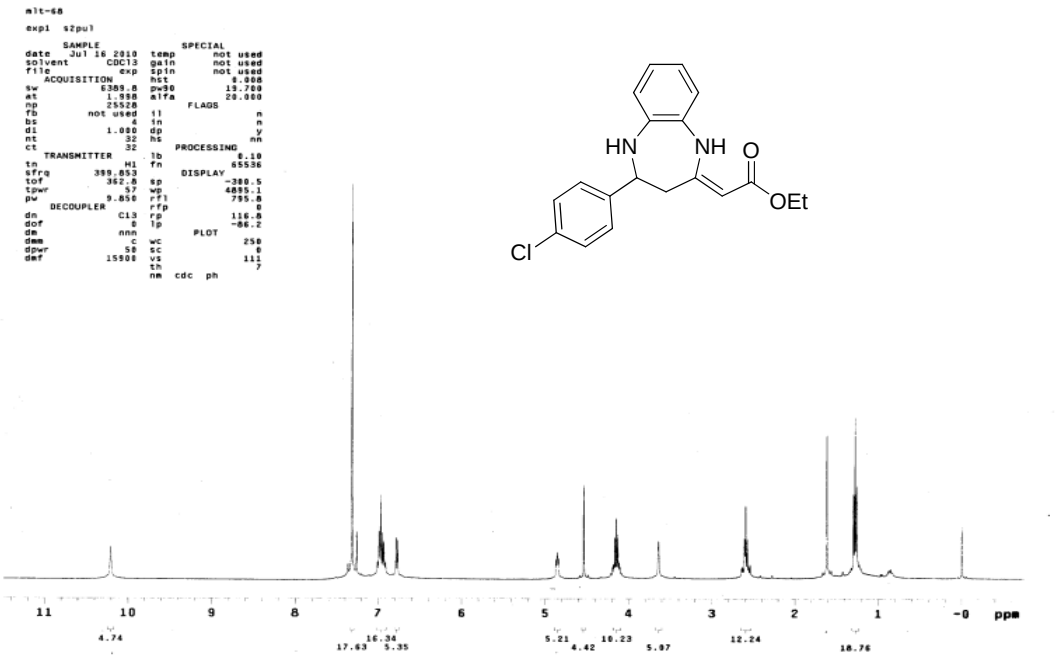


Figure 16.

***(HRMS)**: 1,5-benzodiazene derivative (**134b**)*



*^{1}H NMR (400 MHz, $CDCl_3$): 1,5-benzodiazene derivative (**134n**)*



*^{13}C NMR (100 MHz, $CDCl_3$): 1,5-benzodiazene derivative (**134n**)*

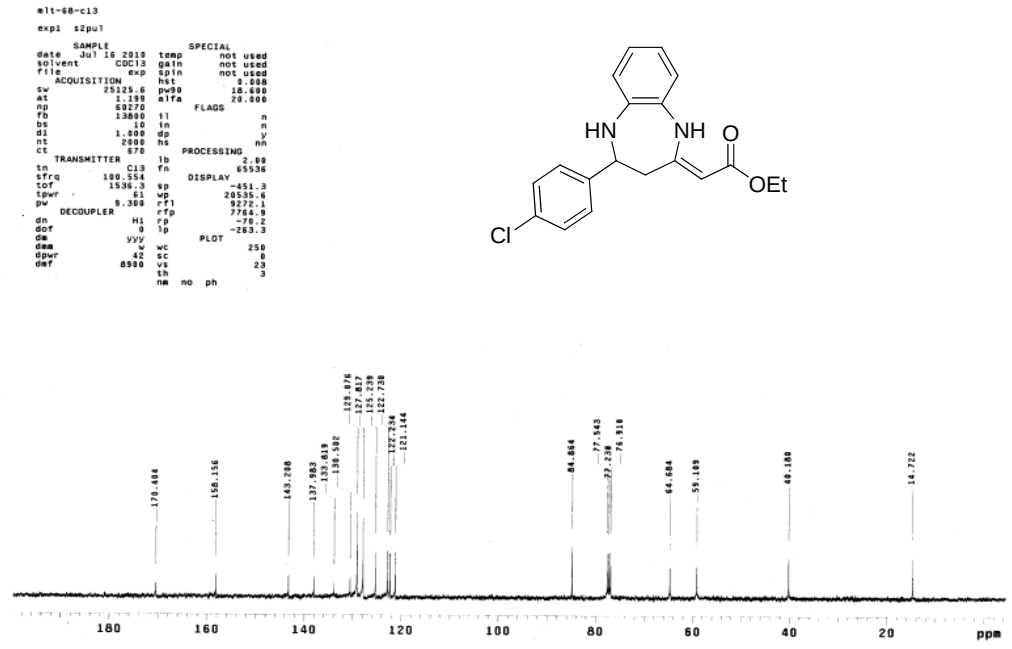


Figure 19.

(HRMS):** 1,5-benzodiazene derivative* (134n***)

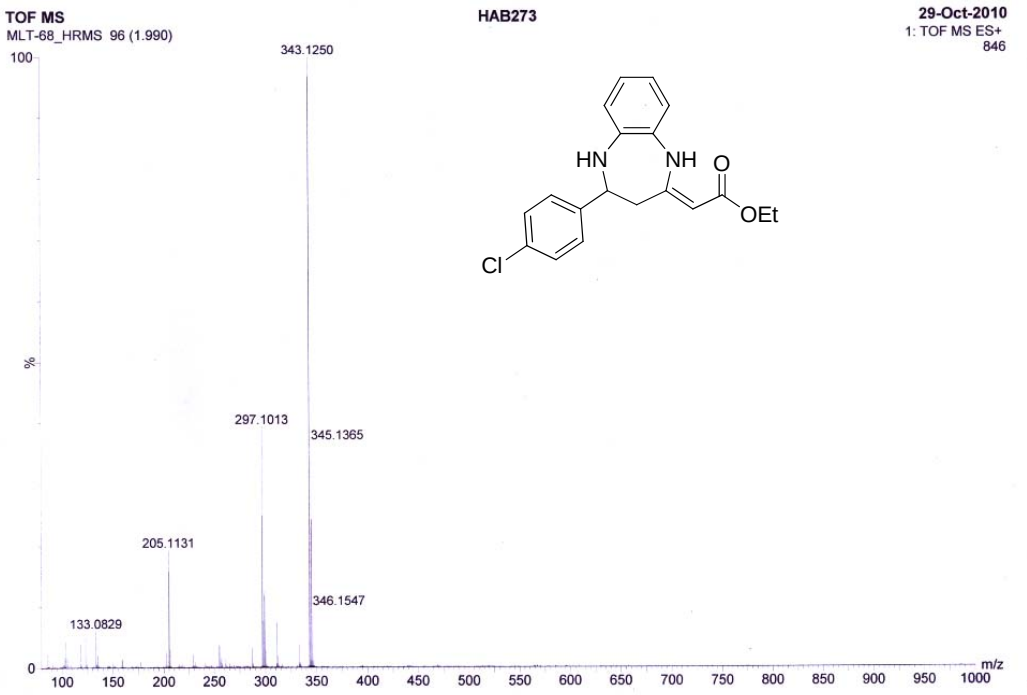
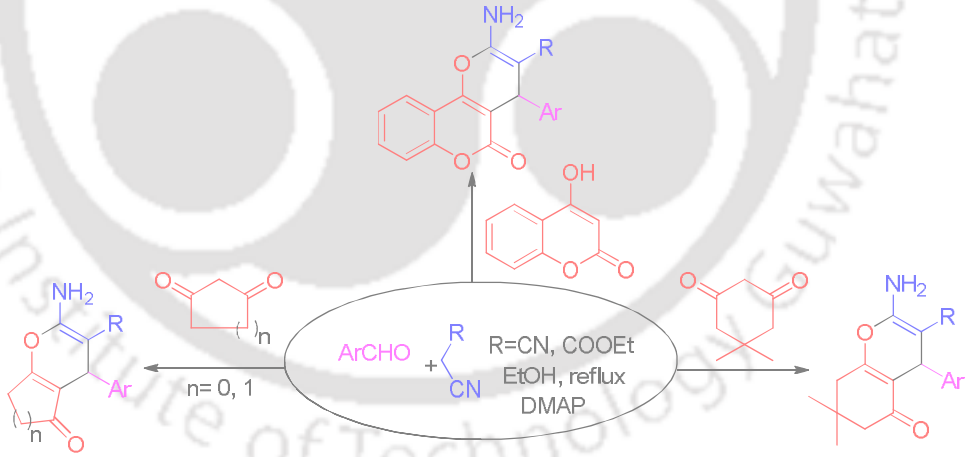


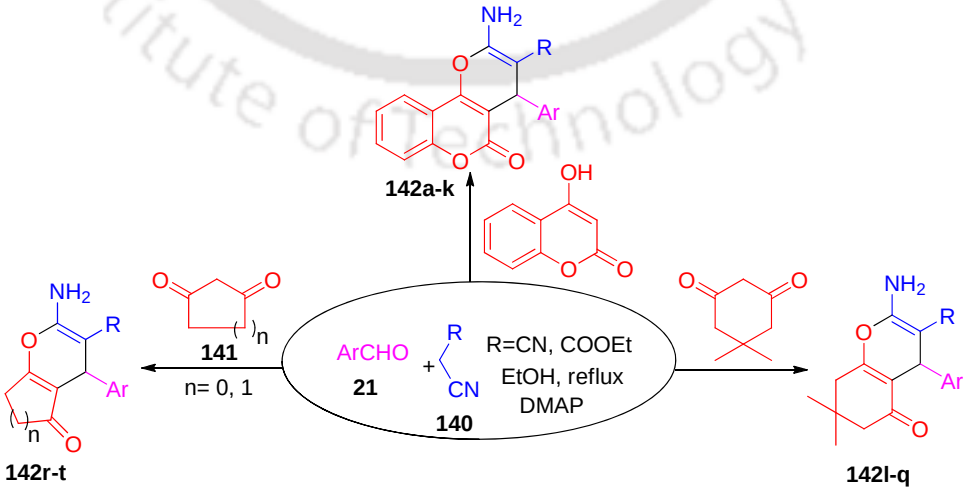
Figure 20.

Synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst through one-pot three-component reaction



In the second and third chapters, we have accomplished the synthesis of highly substituted piperidines[100] and 1,5-benzodiazopines[114] through MCRs involving Mannich reaction by employing β-ketoesters. We conceived that the MCR strategy could be further extended for the synthesis of pyran annulated heterocycles involving 1,3-dicarbonyl compounds using Knoevenagel reaction.

Pyran annulated coumarins are widely distributed in nature[115a] and exhibit diverse physiological activities.[115b] Compounds having dihydropyran structural motif exhibit a wide range of biological activities such as diuretic, analgesic, myorelaxant activity[116] anti-coagulant,[117] anticancer[118] anti-tumoral[119] and anti-HIV.[120] In addition, they are also useful for the treatment of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[121] Moreover, they are also used as cosmetics, pigments[122] and useful as photoactive materials.[123] A considerable efforts have been made for the synthesis of pyran annulated heterocyclic derivatives due to their wide applications. Recently, few methods have been reported by employing three-component reaction using DBU,[56] TBAB,[124a] diammonium hydrogen phosphate,[124b] heteropoly acids.[124c] Though the protocols reported by others are quite useful, still there is a further scope to develop a new methodology using a less expensive catalyst under mild reaction conditions which is applicable to a wide range of substrates. A few years ago, the importance and usefulness of 4-(dimethylamino)pyridine (DMAP) has been reviewed in organic synthesis as an efficient catalyst.[125] We perceived that DMAP might be a useful base for Knoevenagel reaction, which in turn can be executed for pyran annulated hetrocycles.



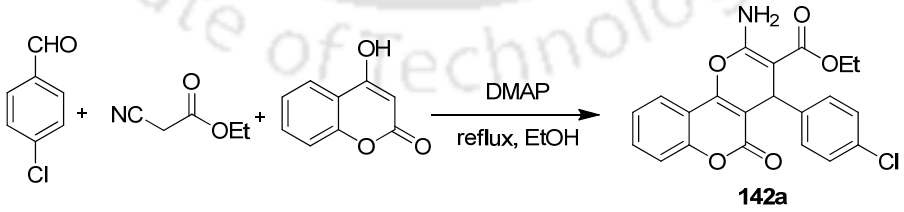
Scheme 48. Synthesis of pyran annulated heterocycles

In this chapter, we would like to discuss one-pot three component condensation reaction of aldehydes, ethyl cyanoacetate or malononitrile and 4-hydroxycoumarin as well as condensation of aldehydes, malononitrile and cyclic 1,3-diketones for the synthesis of pyran annulated heterocyles using DMAP as catalyst, as depicted in Scheme 48.

For this study, a mixture of 4-chlorobenzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) in ethanol was treated with DMAP (0.1 mmol) at room temperature. After consumption of starting aldehyde as checked by TLC, 4-hydroxycoumarin was added to the reaction mixture and kept for stirring under reflux conditions. After the completion of the reaction monitored by TLC, the reaction mixture was brought to room temperature and the solid precipitate was filtered off. The desired product **142a** was obtained in 61% yield, The product was fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. In the IR spectrum, it gives two characteristics peaks at 3468, 3315 cm^{-1} due to primary amino group and two peaks at 1715, 1668 cm^{-1} for the presence of two carbonyl groups. In ^{1}H NMR spectrum the signals appear at δ 4.87 (s, 1H, C8-H), 6.42 (brs, 2H, NH_2) for pyran ring. In the ^{13}C NMR spectrum the peaks are appeared at δ 35.2 (C-8), 79.7 (C-9), 107.5 (C-10), 153.4 (C-11), 158.1 (C-7) 160.9 (C-21) and 168.7 of ester C=O. The spectral data indicate the formation of pranannulated heterocycle (**142a**).

The reaction was optimized using different catalysts for obtaining the best yield of **142a** are summarized in Table 8. It was noted that 20 mol% of the DMAP in ethanol provides the best result in the terms of yield and time. Under solvent-free conditions, the product was obtained in a moderate yield (56%).

Table 8. Optimization of reaction conditions



142a

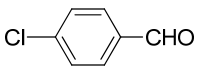
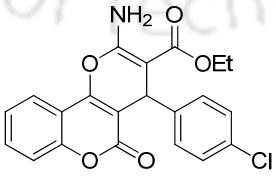
Entry	Catalyst	Solvent	Catalytic Amount (mol %)	Time (h)	% Yield[a]
1	DMAP	Neat	20	3	56

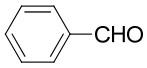
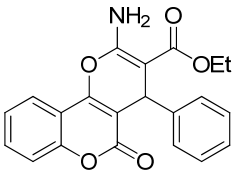
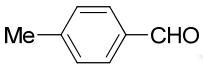
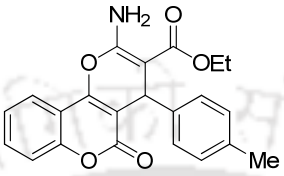
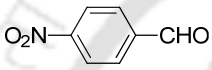
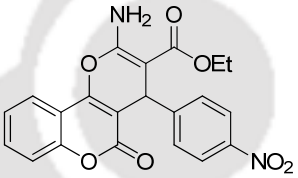
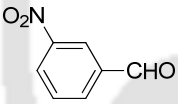
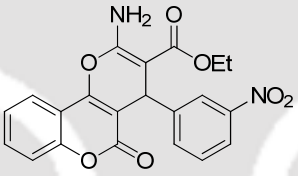
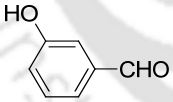
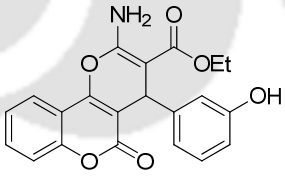
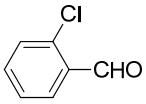
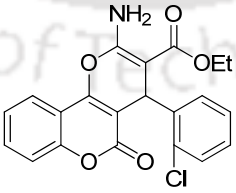
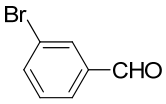
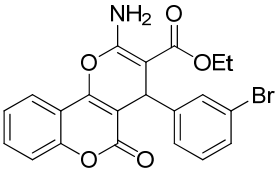
2	Piperdine	EtOH	20	4	40
3	DMAP	EtOH	10	5	61
4	DMAP	EtOH	20	3	78
5	DMAP	EtOH	30	3	76
6	DMAP	MeOH	20	3	69
7	DMAP	Water	20	4	62

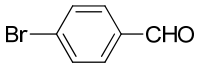
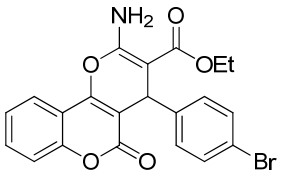
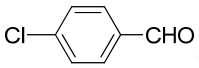
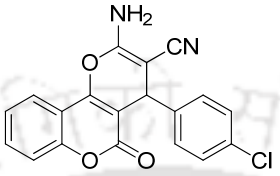
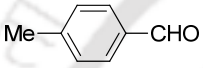
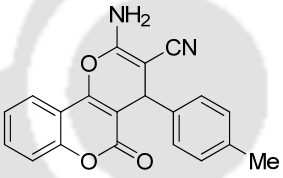
[a]Isolated yield

After the optimization of the reaction conditions, the reaction of benzaldehyde with ethyl cyanoacetate and 4-hydroxycoumarin was carried out under the same reaction conditions and it afforded the product **142b** in 76% yield. The reactions were examined with various aromatic aldehydes having substituents such as Me, NO_2, OH, Cl and Br in the ring with ethyl cyanoacetate and 4-hydroxycoumarin using under identical reaction conditions and the desired products (**142c-i**) were obtained in good yields (Table 9, entries 3-9). Similarly, the reactions were also carried with aromatic aldehydes, malononitrile and 4-hydroxycoumarin out using same mol% of DMAP under identical reaction conditions and the products **142j-k** were isolated in excellent yields.

Table 9. Synthesis of dihydropyrano[3,2-c]chromene derivatives using aromatic aldehydes, ethyl cyanoacetate or malononitrile and 4-hydroxycoumarin catalyzed by DMAP

Entry	Aromatic aldehydes	Product	Time h/[min]	Yield[a] %	M.p. °C [lit.]
1		 **142a**	2.5	78	194-195 [192-194][14a]

2		 **142b**	3.5	76	187-189
3		 **142c**	4.0	76	114-117
4		 **142d**	1.5	82	241-244 [241-243][14a]
5		 **142e**	3.5	80	242-245 [247-250][14c]
6		 **142f**	3.0	67	208-210
7		 **142g**	5.0	64	209-212
8		 **142h**	4.5	81	196-198

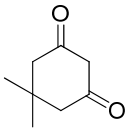
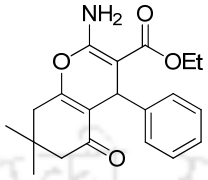
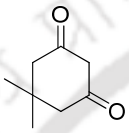
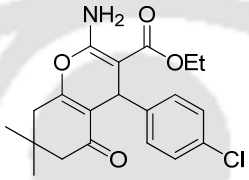
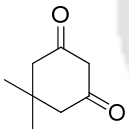
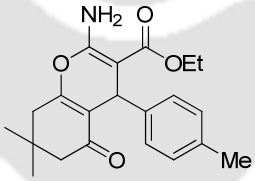
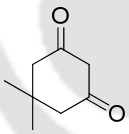
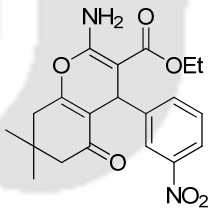
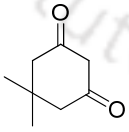
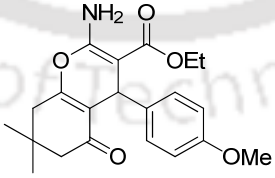
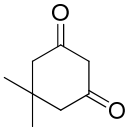
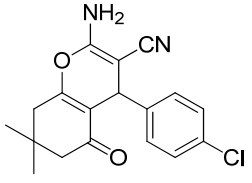
9		 **142i**	4.0	80	142-144
10		 **142j**	[5]	94	264-266 [263-265][14d]
11		 **142k**	[10]	92	258-260 [253-255][14a]

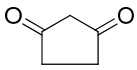
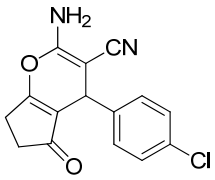
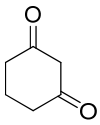
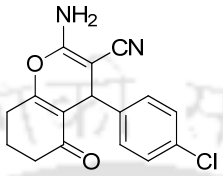
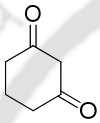
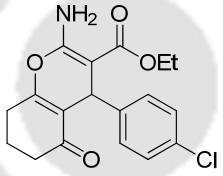
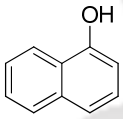
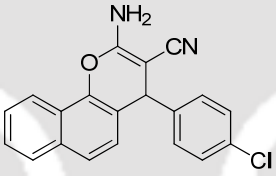
[a]Isolated yield

The present protocol was extended using dimedone and the reaction of benzaldehyde, ethyl cyanoacetate and dimedone was carried out under similar reaction conditions. The desired product **142l** was obtained in 94% yield. The reaction of other aromatic aldehydes substituted with Cl, Me, NO_2 and MeO were also performed with dimedone and ethyl cyanoacetate, the desired products **142m-p** were isolated in good yields (Table 10, entries 2-5). The reaction of 4-chloroaldehyde with malononitrile and dimedone was performed and product **142q** was obtained in good yield.

The scope of presented protocol further investigated with other C-H activated acidic compounds such as 1,3-cyclopentadione and 1,3-cyclohexadione using 4-chlorobenzaldehyde and malononitrile under similar reaction condition and the results were summarized in Table 10 (entries 7-9). The reaction of 4-chloroaldehyde with malononitrile and α-naphthol was performed and product **142u** was obtained in good yield. From the above observation, it is important to mention that the reaction was fast and also provided better yields using either aldehyde having electron withdrawing group *viz* NO_2 or with malononitrile. All the products were characterized from ^{1}H NMR, ^{13}CNMR and elemental analysis. The spectral data of the compounds **142a**, **142b**, **142f, 142j, 142p** and **142t** are given in Figure 23-28 in Experimental Section.

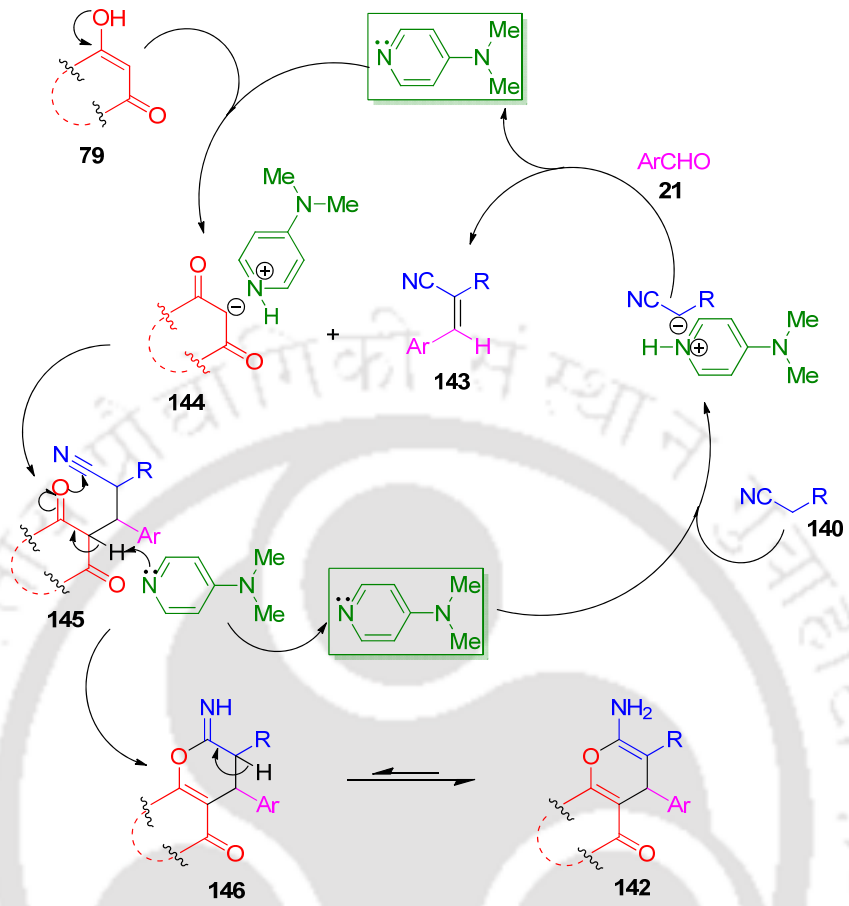
Table 10. Synthesis of chromene derivatives using diketones, ethyl cyanoacetate or malononitrile and aromatic aldehydes catalyzed by DMAP

Entry	1,3-Diketones	Product	Time h/[min]	Yield[a] %	M.p. °C [lit.]
1		 **142l**	3.5	94	144-146
2		 **142m**	5.0	92	139-142
3		 **142n**	4.5	91	151-152
4		 **142o**	1.5	91	154-156
5		 **142p**	3.5	91	131-134
6		 **142q**	[15]	94	213-215 [212-214][14e]

7		 **142r**	[10]	98	216-218
8		 **142s**	[10]	95	241-243
9		 **142t**	2.5	95	163-165
10		 **142u**	[20]	92	244-243

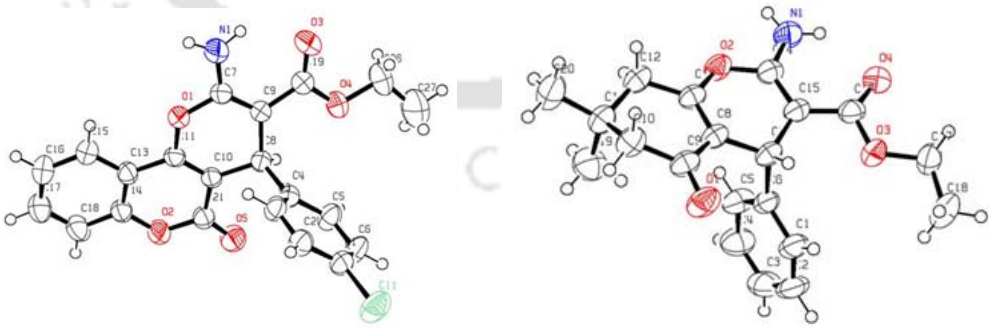
[a] Isolated Yields

The formation of various pyran annulated heterocyclic compounds can be rationalized as follows. Initially, the Knovengel product **143** was formed by the reaction of aldehyde and alkyl nitrile in the presence of DMAP, which reacts with *in situ* generated carbanion from activated C-H acidic compounds to give intermediate **145**. The intermediate **145** was cyclized to **146** in the presence of DMAP. Finally, **146** tautomerized to give desired product **142** as shown in Scheme 49.



Scheme 49. Plausible mechanism for the formation of pyran-annulated heterocyclic compounds

Moreover, the structure of compound **142a** and **142l** were further confirmed by X-ray crystallographic analysis (Figure 21).



142a **142l**

Figure 21. ORTEP diagram of **142a** (CCDC 819069) and **142l** (CCDC 828132)

Further the role of catalyst was ascertained by carrying out two successive reactions involving 4-chlorobenzaldehyde, malononitrile and 4-hydroxycoumarin in the presence of catalyst DMAP as well as without catalyst, respectively. The desired product **142j** was obtained within 5 min in 94% yield in presence of catalyst, whereas the same reaction gave only 63% yield after 1h without catalyst.

The reusability test was performed as follows: A mixture of 4-chlorobenzaldehyde (2 mmol), malononitrile (2 mmol), 4-hydroxycoumarin and DMAP (0.4 mmol) was stirred in ethanol (8 mL) under reflux condition. After completion of the reaction, the solid precipitate was filtered using a Buchner funnel. The precipitate was washed with ethanol (0.5 mL). The filtrate containing catalyst was reused for similar scale of reaction for the same substrates. The procedure was repeated five times which is depicted in Figure 22.

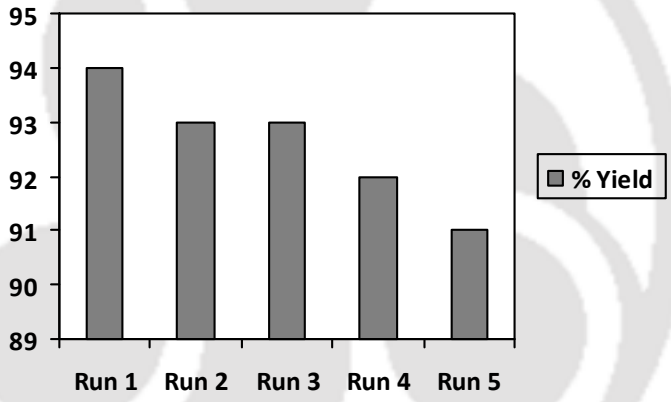
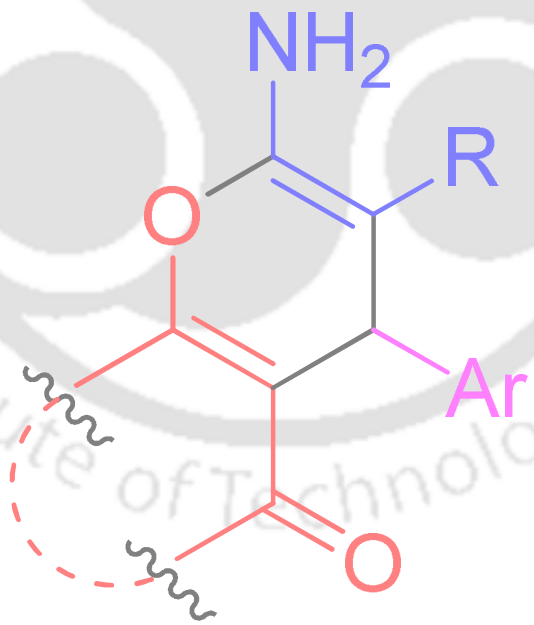


Figure 22. Reusability of the catalyst

In conclusion, we have devised a simple and efficient protocol for the synthesis of pyran-annulated heterocycles using DMAP as catalyst *via* one-pot three component condensation reaction of an aldehyde, ethyl cyanoacetate or malononitrile and either 4-hydroxycoumarin or 1,3-cyclic ketones or 1-naphthol in excellent yields. The advantages of the present protocol are cost-effective, no need of chromatographic separation and reusability of the catalyst. The significant features of this protocol are good yields and applicable to the broad range of substrates to provide the desired pyran annulated heterocycles.

Synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst through one-pot three-component reaction



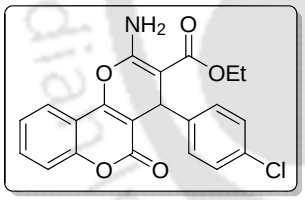
Experimental Section

Genaral procedure for the synthesis of pyran annulated heterocyclic compounds:

Into a mixture of an aromatic aldehyde (1 mmol) and ethyl cyanoacetate or malononitrile (1 mmol) in 4 mL of ethanol was added the catalyst DMAP (0.025g, 0.2 mmol) and kept for stirring at room temperature. The solid precipitate was formed immediately in case of malononitrile or it took 20-30 min for ethyl cyanoacetate. Then C-H activated acidic compound (1 mmol) was added into the reaction mixture and it was kept for stirring under reflux conditions. After sometime, the reaction mixture was converted into clear solution. After the completion of the reaction, the solid precipitate came out under hot conditions at the stipulated time mentioned in the Table 9 and Table 10. The reaction mixture was brought to room temperature and the solid precipitate was filtered off to obtain the desired product.

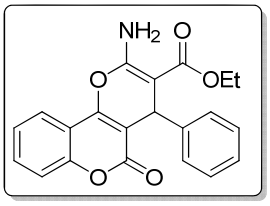
Spectral data of Compounds

Ethyl 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxy late (**142a**)



Solid, Yield (0.310 g, 78%); M.p. 194–195 °C; **IR** (KBr): 3468, 3315, 3049, 2978, 1715, 1668, 1660, 1530, 1491, 1374, 1289, 1197 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.15 (t, J = 7.2 Hz, 3H), 4.01-4.09 (m, 2H), 4.87 (s, 1H), 6.42 (brs, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.3, 35.2, 60.2, 79.7, 107.5, 113.5, 117.0, 116.9, 122.4, 124.5, 128.3, 130.0, 132.5, 143.0, 152.7, 153.4, 158.1, 160.9, 168.7; **Anal. Calcd** for $C_{21}H_{16}ClNO_5$ (397.81): C, 63.40; H, 4.05; N, 3.52; found C, 63.31; H, 3.98; N, 3.61.

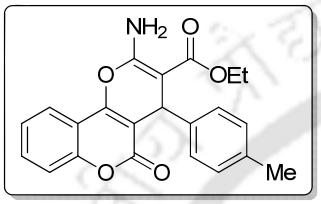
*Ethyl 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142b**)*



Solid, Yield (0.275 g, 76%); M.p. 187-189 °C. **IR** (KBr): 3403, 3290, 2983, 1714, 1651, 1693, 1610, 1526, 1492, 1376, 1284, 1107 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.2 Hz, 3H), 4.04-4.11 (m, 2H), 4.93 (s, 1H), 6.43 (brs, 2H), 7.14 -7.18

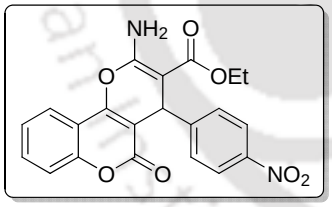
(m, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.31-7.38 (m, 4H), 7.56 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.84 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.3, 35.7, 60.1, 80.3, 108.1, 113.6, 116.9, 122.4, 124.4, 126.9, 128.2, 128.6, 132.3, 144.4, 152.7, 153.3, 158.1, 160.9, 168.9; **Anal. Calcd** for $C_{21}H_{17}NO_5$ (363.36): C, 69.41, H,4.72; N,3.85; found C, 69.34; H, 4.64; N, 3.72.

Ethyl 2-amino-5-oxo-4-(4-methylphenyl)-4,5-dihydropyrano[3,2-c]chromene-3-carboxy late (**142c**)



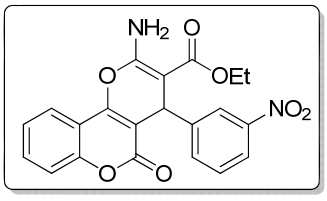
Solid, Yield (0.286 g, 76%); M.p. 114-117°C; **IR** (KBr): 3395, 3284, 1682, 1651, 1612, 1532, 1376, 1288, 1081 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 4.08 (q, *J* = 7.2 Hz, 2H), 4.90 (s, 1H), 6.40 (brs, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.30-7.36 (m, 2H), 7.55 (td, *J* = 1.6 Hz, 7.2 Hz , 1H), 7.83 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$/ DMSO-d_6): δ = 13.5, 20.2, 34.3, 58.8, 77.8, 106.9, 112.8, 115.7, 121.8, 123.5, 127.4, 127.8, 131.4, 135.1, 141.2, 151.7, 152.6, 157.9, 159.8, 167.7; **Anal. Calcd** for $C_{22}H_{19}NO_5$ (377.39): C, 70.02; H, 5.07, N, 3.71; found C, 69.93; H, 4.98; N, 3.59.

Ethyl 2-amino-4-(4-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxy -late (**142d**)



Solid, Yield (0.334 g, 82%). M.p. 241-244°C. **IR** (KBr): 3441, 3326, 1719, 1688, 1611, 1533, 1512, 1377, 1346 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3H), 4.02-4.12 (m, 2H), 5.03 (s, 1H), 6.55 (brs, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.60 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.86 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 35.9, 60.41, 78.9, 106.5, 113.3, 117.2, 122.5, 123.5, 124.7, 129.7, 132.9, 146.8, 151.9, 152.9, 153.8 158.2, 160.7, 168.4; **Anal. Calcd** for $C_{21}H_{16}N_2O_7$ (408.36): C, 61.77; H, 3.95; N, 6.86; found C, 61.69; H, 3.87; N, 6.71.

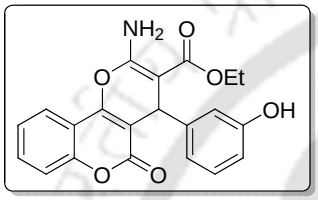
Ethyl 2-amino-4-(3-nitrophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxyl ate (**142e**)



Solid, Yield (0.326 g, 80%); M.p. 242-245°C. **IR** (KBr): 3435, 3316, 1711, 1688, 1659, 1651, 1622, 1609, 1537, 1520, 1376, 1344 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =

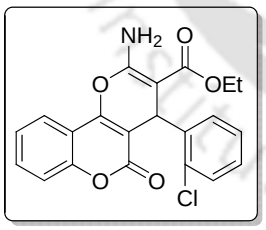
1.16 (t, *J* = 7.2 Hz, 3H), 4.04-4.09 (m, 2H), 5.00 (s, 1H), 7.21 (brs, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.6 (t, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.02 (dt, *J* = 1.2 Hz, 6.8 Hz, 1H), 8.17 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.1, 35.6, 59.8, 77.8, 106.1, 113.1, 116.7, 121.6, 122.6, 123.3, 124.4, 128.7, 132.5, 135.0, 146.8, 147.9, 152.6, 153.8, 158.4, 160.5, 168.1; **Anal. Calcd** for $C_{21}H_{16}N_2O_7$ (408.36): C, 61.77; H, 3.95; N, 6.86; found C, 61.66; H, 3.86; N, 6.72.

Ethyl 2-amino-4-(3-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142f**)



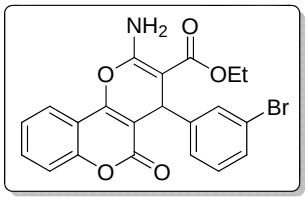
Solid, Yield (0.254 g, 67%); M.p. 208-210°C; **IR** (KBr): 3430, 3296, 1713, 1686, 1645, 1610, 1588, 1527, 1378 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 7.2 Hz, 3H), 4.02(q, *J* = 7.2 Hz, 2H), 4.63 (s, 1H), 6.54 (d, *J* = 6.8 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 7.48-7.42 (m, 2H), 7.67 (t, *J* = 8.4 Hz, 1H), 7.81 (brs, 2H-NH_2), 7.96 (d, *J* = 8 Hz, 1H), 9.24 (s, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 14.2, 34.9, 59.1, 77.2, 107.0, 113.2, 113.5, 114.8, 116.5, 118.6, 122.4, 124.6, 128.9, 132.7, 146.3, 152.1, 153.1, 157.0, 158.6, 159.9, 167.6 ppm. **Anal. Calcd** for $C_{21}H_{17}NO_6$ (379.36): C, 66.49; H, 4.52; N, 3.69; found C, 66.41; H, 4.46; N, 3.61.

Ethyl 2-amino-4-(2-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142g**)



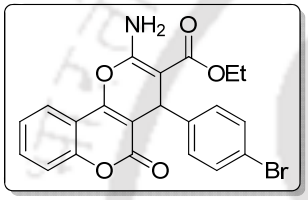
Solid, Yield (0.254 g, 64%); M.p. 209-212°C; **IR** (KBr): 3401, 3258, 3131, 1715, 1688, 1641, 1608, 1552, 1375 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 1.04 (t, *J* = 7.2 Hz, 3H), 3.94 (q, *J* = 7.2 Hz, 2H), 5.06 (s, 1H), 7.15 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.21 (td, *J* = 1.6 Hz, 7.6 Hz, 1H), 7.29 (td, *J* = 1.6 Hz, 8.0 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.47 (t, *J* = 8.4 Hz, 1H), 7.68 (td, *J* = 1.6, Hz, 8.8 Hz, 1H), 7.91 (brs, 2H-NH_2), 7.97 (dd, *J* = 1.6 Hz, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.1, 33.7, 58.9, 75.7, 105.1, 112.9, 116.5, 122.6, 124.6, 126.7, 127.9, 129.4, 132.2, 132.8, 133.0, 141.5, 152.1, 153.4, 158.6, 159.5, 167.7; **Anal. Calcd** for $C_{21}H_{16}ClNO_5$ (397.81): C, 63.40, H, 4.05; N, 3.52; found C, 63.30; H, 3.97; N, 3.39.

Ethyl 2-amino-4-(3-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142h**)



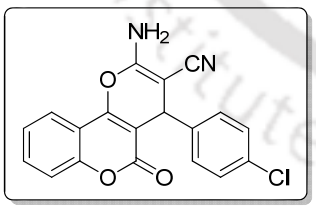
Solid, Yield (0.356 g, 81%); M.p. 196-198 °C; **IR** (KBr): 3407, 3307, 1728, 1688, 1655, 1611, 1526, 1375 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 1.09 (t, J = 6.8 Hz, 3H), 3.98 (q, J = 6.8 Hz, 2H), 4.64 (s, 1H), 7.23-7.16 (m, 2H), 7.32 (d, J = 7.6 Hz, 1H), 7.43-7.36 (m, 3H), 7.62 (t, J = 7.6 Hz, 1H), 7.89 (brs, 2H-NH_2), 7.95 (d, J = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 14.1, 35.3, 59.1, 76.4, 105.9, 113.4, 116.5, 121.3, 122.5, 124.5, 127.1, 129.3, 130.2, 131.1, 132.7, 147.7, 152.1, 153.3, 158.5, 159.8, 167.4; **Anal. Calcd** for $C_{21}H_{16}BrNO_5$ (442.26): C, 57.03; H, 3.65; N, 3.17; found C, 56.96; H, 3.59; N, 3.03.

Ethyl 2-amino-4-(4-bromophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbox ylate (**142i**)



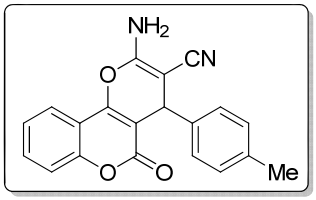
Solid, Yield (0.350 g, 81%); M.p. 142-144 °C; **IR** (KBr): 3421, 3295, 1715, 1692, 1652, 1610, 1519, 1491, 1375 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.18 (t, J = 7.2 Hz, 3H), 4.01-4.09 (m, 2H), 4.90 (s, 1H), 6.47 (brs, 2H), 7.24 (d, J = 8.4 Hz, 2H), 7.32-7.37 (m, 4H), 7.57 (td, J = 1.6, Hz, 8.0 Hz, 1H), 7.68 (dd, J = 1.6 Hz, 8.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.3, 35.3, 60.2, 79.6, 107.4, 113.4, 117.0, 120.7, 122.4, 124.5, 130.4, 131.2, 132.5, 143.6, 152.7, 153.4, 158.1, 160.9, 168.6; **Anal. Calcd** for $C_{21}H_{16}BrNO_5$ (442.26): C, 57.03; H, 3.65; N, 3.17; found C, 47.01; H, 3.59; N, 3.30.

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**142j**)



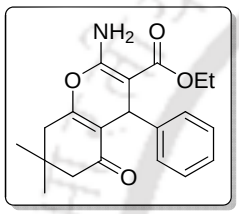
Solid, Yield (0.329 g, 94%); M.p. 264-266°C; **IR** (KBr): 3483, 3311, 3292, 3190, 2193, 1714, 1678, 1610, 1377 cm^{-1}. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 4.48 (s, 1H), 7.29 (d, J = 6.8 Hz, 2H), 7.36 (d, J = 6.8 Hz, 2H), 7.44 (br s, 3H), 7.48 (t, J = 7.6 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 36.2, 57.5, 103.5, 112.9, 116.5, 112.9, 116.5, 119.1, 122.5, 124.6, 128.4, 129.6, 131.7, 132.9, 142.3, 152.2, 153.5, 157.9, 159.5; **Anal. Calcd** for $C_{19}H_{11}ClN_2O_3$ (350.76): C, 65.06; H, 3.16; N, 7.99; found C, 65.01; H, 3.08; N, 7.86.

2-Amino-5-oxo-4-(4-methylphenyl)-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**142k**)



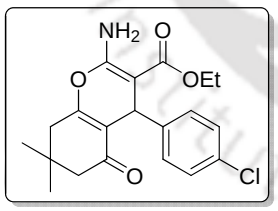
Solid, Yield (0.303 g, 92%); M.p. 258-260°C; **IR** (KBr): 3390, 3313, 3294, 3194, 2195, 1715, 1678, 1610, 1377 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 2.25 (s, 3H), 4.39 (s, 1H), 7.12 (s, 2H), 7.36 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.70 (t, J = 7.6 Hz, 2H), 7.90 (d, J = 7.6 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 20.6, 36.6, 58.3, 104.2, 112.9, 116.5, 119.3, 122.5, 124.7, 127.6, 129.1, 132.9, 136.4, 140.4, 152.1, 153.3, 158.0, 159.6; **Anal. Calcd** for $C_{20}H_{14}N_2O_3$ (330.34): C, 72.72; H, 4.27; N, 8.48; found C, 72.64; H, 4.21; N, 8.33.

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxy late (**142l**)



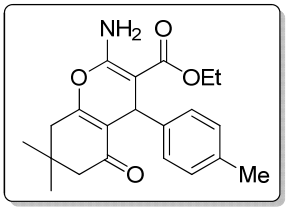
Solid, Yield (0.320 g, 94%); M.p. 144-146°C; **IR** (KBr): 3403, 3290, 2956, 1667, 1614, 1524, 1371 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.10 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.19 (q, J = 16.4 Hz, 2H), 2.42 (s, 2H), 3.98-4.07 (m, 2H), 4.70 (s, 1H), 6.17 (brs, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 27.5, 29.2, 32.4, 33.9, 40.8, 50.9, 59.8, 80.9, 116.9, 126.2, 127.9, 128.4, 145.9, 158.5, 161.5, 169.3, 196.5; **Anal. Calcd** for $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10; found C, 70.29; H, 6.71; N, 4.01.

Ethyl 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142m**)



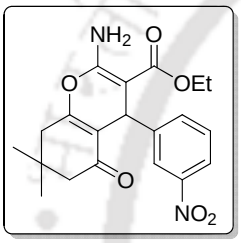
Solid; Yield (0.345 g, 92%); M.p. 139-142°C; **IR** (KBr): 3479, 3331, 2975, 2956, 1687, 1659, 1622, 1525, 1489, 1369 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 0.86 (s, 3H), 1.04 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H), 2.13 (d, J = 16.0 Hz, 1H), 2.23 (d, J = 16.0 Hz, 1H), 2.40-2.54 (m, 2H), 3.88-3.94 (m, 2H), 4.45 (s, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.54 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.3, 27.4, 29.2, 32.3, 33.6, 40.7, 50.8, 59.8, 80.3, 116.5, 128.0, 129.8, 131.7, 144.6, 158.5, 161.7, 169.1, 196.5; **Anal. Calcd** for $C_{20}H_{22}ClNO_4$ (375.85): C, 63.91; H, 5.90; N, 3.73; found C, 63.82; H, 5.81; N, 3.60.

Ethyl 2-amino-7,7-dimethyl-5-oxo-4-(4-methylphenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142n**)



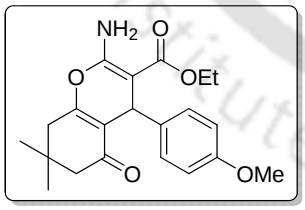
Solid, Yield (0.323 g, 91%); M.p. 151-152°C; **IR** (KBr): 3408, 3294, 2980, 2966, 1687, 1668, 1654, 1623, 1523, 1366 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.09 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H), 2.19 (q, J = 16.4 Hz, 2H), 2.26 (s, 3H), 2.42 (s, 2H), 3.98-4.09 (m, 2H), 4.66 (s, 1H), 6.14 (brs, 2H), 7.01 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 21.2, 27.6, 29.3, 32.4, 33.5, 40.8, 50.9, 59.8, 81.1, 117.1, 128.2, 128.7, 135.6, 143.0, 158.5, 161.5, 169.3, 196.6; **Anal. Calcd** for $C_{21}H_{25}NO_4$ (355.43): C, 70.96; H, 7.09; N, 3.94; found C, 70.88; H, 6.98; N, 3.79.

Ethyl 2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142o**)



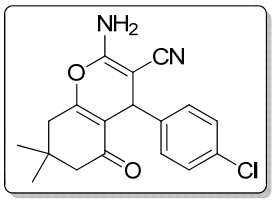
Solid, Yield (0.385 g, 91 %); M.p. 154-156°C. **IR** (KBr): 3441, 3301, 2954, 1691, 1673, 1522, 1369, 1345 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.11 (s, 3H), 1.15 (t, J = 7.2 Hz, 3H), 2.21 (q, J = 16 Hz, 2H), 2.47 (s, 2H), 4.01-4.05 (m, 2H), 4.79 (s, 1H), 6.28 (brs, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.98 (d, J = 8.0 Hz, 1H), 8.09 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.3, 27.5, 29.2, 32.4, 34.3, 40.8, 50.7, 60.0, 79.6, 115.7, 121.5, 123.3, 128.7, 135.1, 148.3, 158.6, 162.3, 168.8, 196.5; **Anal. Calcd** for $C_{20}H_{22}N_2O_6$ (386.39): C, 62.17; H, 5.74; N, 7.25; found C, 62.09; H, 5.66; N, 7.18.

Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene -3-carboxylate (**142p**)



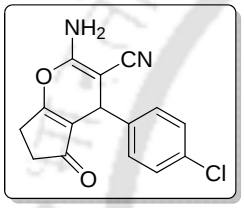
Solid, Yield (0.337 g, 91%) M.p. 131-134°C; **IR** (KBr): 3413, 3304, 2958, 1915, 1686, 1669, 1622, 1584, 1526, 1509, 1367 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.10 (s, 3H), 1.17 (t, J = 7.2 Hz, 3H), 2.19 (q, J = 16.4 Hz, 2H), 2.42 (s, 2H), 3.75 (s, 3H), 4.00-4.07 (m, 2H), 4.65 (s, 1H), 6.13 (brs, 2H), 6.75 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 27.5, 29.2, 32.3, 33.1, 40.7, 50.8, 55.2, 59.7, 81.0, 113.3, 117.1, 129.3, 138.3, 157.9, 158.5, 161.3, 169.7, 196.6; **Anal. Calcd** for $C_{21}H_{25}NO_5$ (371.43): C, 67.91; H, 6.78; N, 3.77; found C, 67.85; H, 6.71; N, 3.65.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrie (**142q**)



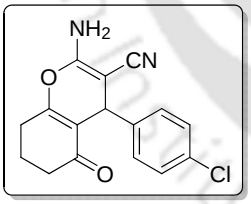
Solid, Yield (0.320 g, 94%); M.p. 213-215°C; **IR** (KBr): 3381, 3184, 2959, 2188, 1674, 1635, 1604, 1491, 1365 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 0.94 (s, 3H), 1.03 (s, 3H), 1.06 (d, *J* = 7.2 Hz, 1H), 2.09 (d, *J* = 16.4 Hz, 1H), 2.24 (d, *J* = 16 Hz, 1H), 4.18 (s, 1H), *4.2.18.* 4.39 (t, *J* = 4.8 Hz, 1H), 7.04 (brs, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 18.6, 26.9, 28.4, 31.8, 35.2, 50.0, 57.9, 112.4, 119.6, 128.3, 129.2, 131.2, 143.8, 158.6, 162.7, 195.8; **Anal. Calcd** for $C_{18}H_{17}ClN_2O_2$ (328.79): C, 65.75; H, 5.21; N, 8.52; found C, 65.67; H, 5.19; N, 8.41.

2-Amino-4-(4-chlorophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonytrile (**142r**)



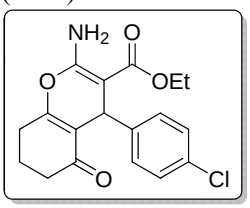
Crystalline Solid; Yield (0.280 g, 98%); M.p. 216-218°C; **IR** (KBr): 3405, 3323, 3210, 2195, 1670, 1640, 1600, 1372 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 2.08 (s, 1H), 2.37 (s, 1H), 2.67-2.78 (m, 2H), 4.23 (s, 1H), 7.21-7.23 (m, 4H), 7.36 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 24.7, 33.5, 35.0, 40.1, 57.3, 116.5, 119.6, 128.4, 129.7, 131.6, 141.6, 159.6, 176.5, 201.2; **Anal. Calcd** for $C_{15}H_{11}ClN_2O_2$ (286.71): C, 62.84; H, 3.87; N, 9.77; found C, 62.77; H, 3.78; N, 9.86.

2-Amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonytrile (**142s**)



Crystalline Solid; Yield (0.285 g, 95%); M.p. 241-243°C; **IR** (KBr): 3415, 3334, 3216, 2194, 1681, 1654, 1364 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 1.88-1.96 (m, 2H), 2.24-2.30 (m, 2H), 2.60 (s, 1H), 4.19 (s, 1H), 5.72 (s, 1H), 7.02 (s, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 19.8, 26.5, 35.1, 36.3, 57.8, 113.5, 119.6, 128.3, 129.1, 131.2, 143.8, 158.5, 164.7, 195.9; **Anal. Calcd** for $C_{16}H_{13}ClN_2O_2$ (300.07): C, 63.90; H, 4.36; N, 9.31; found C, 63.81; H, 4.29; N, 9.23.

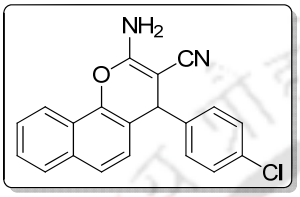
Ethyl 2-amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142t**)



Solid, Yield (0.330 g, 95%); M.p. 163-165°C; IR (KBr): 3477, 3324, 2977, 2946, 1683, 1660, 1621, 1525, 1366 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3H), 1.90-2.06 (m,

2H), 2.27-2.38 (m, 2H), 2.49-2.61 (m, 2H), 3.98-4.07 (m, 2H), 4.69 (s, 1H), 6.19 (brs, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 14.4, 20.3, 27.1, 33.6, 37.0, 59.9, 80.3, 117.8, 128.1, 129.8, 131.8, 144.8, 158.4, 163.3, 169.1, 196.7; **Anal. Calcd** for $C_{18}H_{18}ClNO_4$ (347.79): C, 62.16; H, 5.22; N, 4.03; found C, 62.11; H, 5.16; N, 4.16.

2-Amino-4-(4-chlorophenyl)-4H-benzo[h]chromene-3-carbonitrile (**142u**)



Solid, Yield (0.304 g, 92%); M.p. 242-243°C; **IR** (KBr): 3455, 3333, 2194, 1670, 1603, 1407, 1378, 1104 cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 4.92 (s, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 7.2 (s, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.55-7.64 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 1H), 8.23 (d, *J* = 8.4 Hz, 1H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 40.5, 56.2, 117.6, 120.8, 121.1, 123.0, 124.4, 126.3, 127.1, 127.3, 128.0, 129.0,129.8, 131.9, 133.1, 143.0, 144.9, 160.5; Anal. Calcd for $C_{20}H_{13}ClN_2O$ (332.78): C, 72.18; H, 3.94; N, 8.42; found C, 72.11; H, 3.86; N, 8.30.

*XRD for compounds **142a** and **142l***

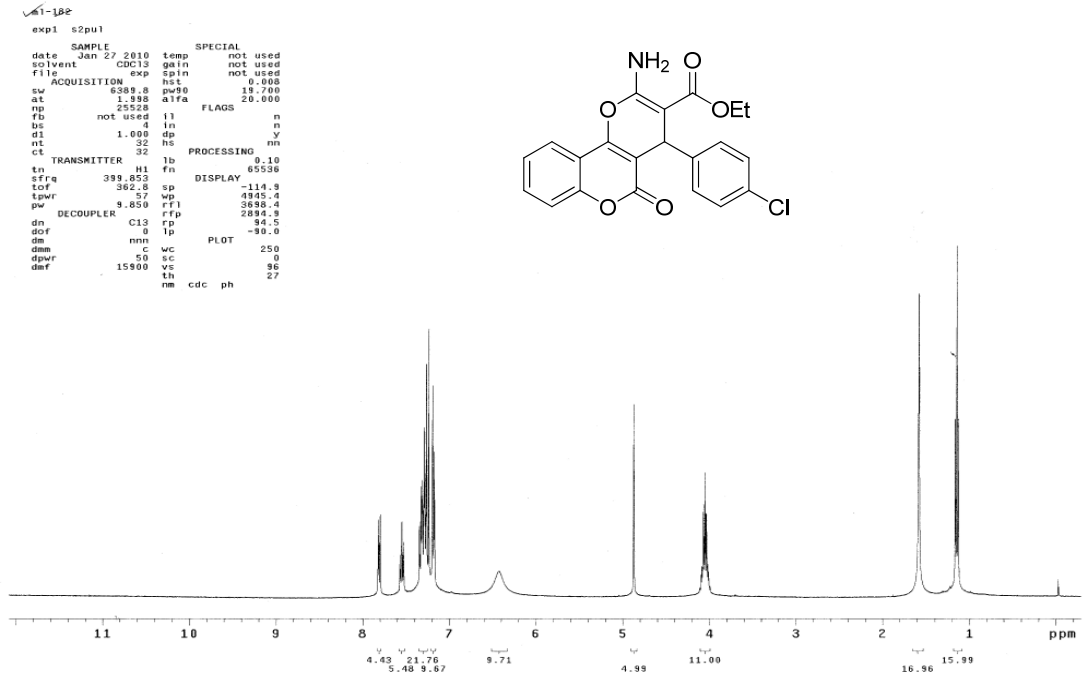
Complete crystallographic data of compounds **142a** and **142l** for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos.: 819069 and 828132. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 11 Crystal data and structures refinement for the compounds **142a and 142l** for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF

Parameters	**Compound 142a**	**Compound 142l**
Formula	$C_{21}H_{16}ClNO_5$	$C_{20}H_{23}NO_4$
CCDC number	819069	828132
Formula weight	397.80	341.39
T (K)	296 K	296 K
Wavelength (Å)	0.71073	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	P -1	P -1

a (Å)	5.7600(4) Å	8.2825(2)Å
b (Å)	10.0964(8) Å	9.6138(3)Å
c (Å)	17.1024(14) Å	12.1594(4)Å
α (°)	80.486(6)º	82.605(2)º
β (°)	83.149(6)º	74.289(2)º
γ (°)	80.114(6)º	83.014(2)º
V (Å^3)	962.11(13) Å^3	920.46(5)Å^3
Z	2	2
D_{calcd} (g m^{-3})	1.373g/cm^3	1.232/cm^3
μ (mm^{-1})	0.231mm^{-1}	0.086 mm^{-1}
F(0 0 0)	412.0	364.0
Reflection collected	3780	3243
Unique reflections	1258	2526
Goodness-of-fit (GOF)[a] on F^2	0.533	0.533
R [$I > 2\sigma(I)$]	[b]R_1 = 0.1431, [c]wR_2 = 0.1517	[b]R_1 = 0.0481, [c]wR_2 = 0.1089
R indices (all data)	[b]R_1 = 0.0494, [c]wR_2 = 0.1161	[b]R_1 = 0.0371, [c]wR_2 = 0.1001

Ethyl2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate ***(142a)***



Ethyl 2-amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (***142a***)

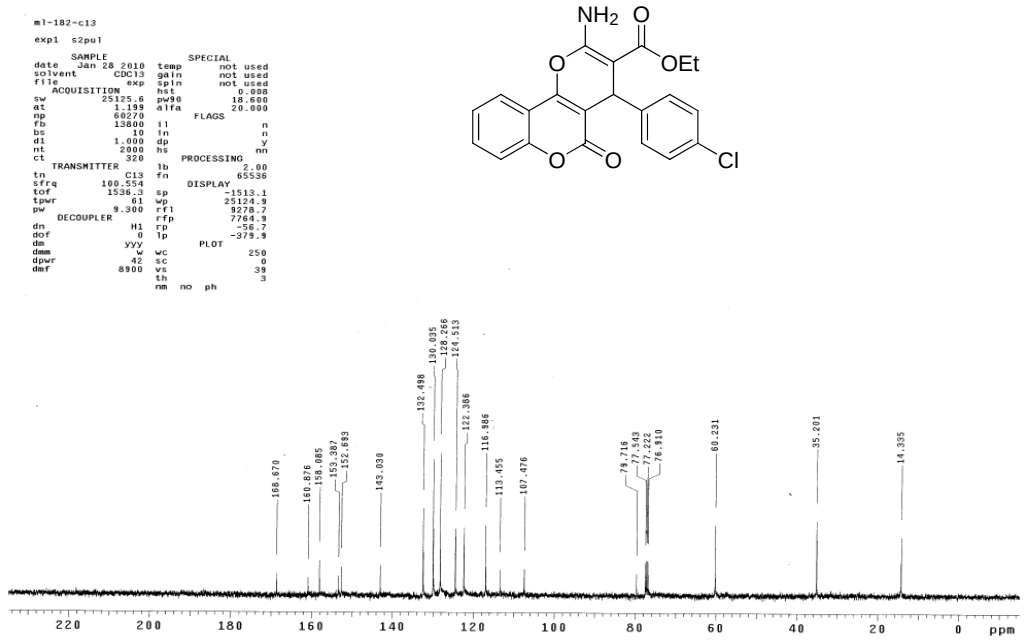
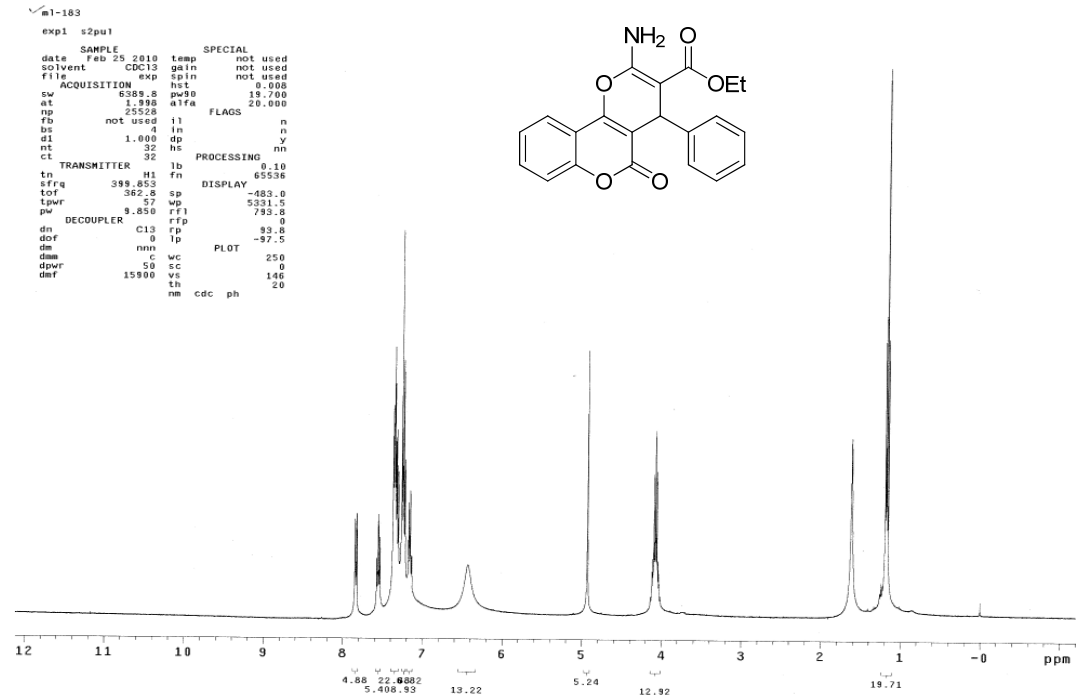


Figure 23.

*Ethyl 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142b**)*



*Ethyl 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (**142b**)*

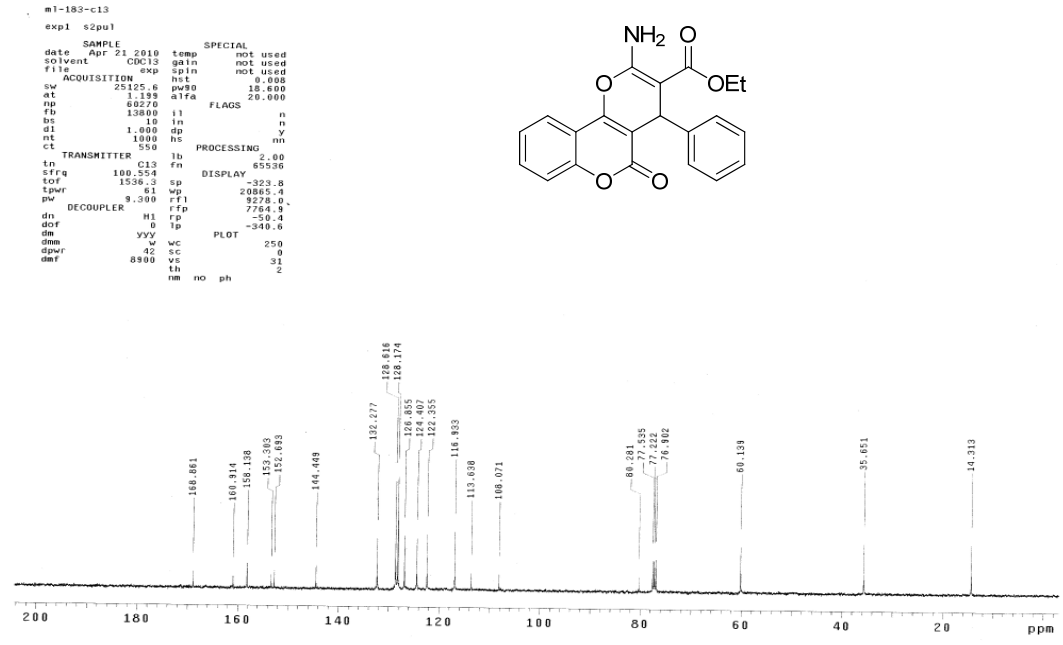
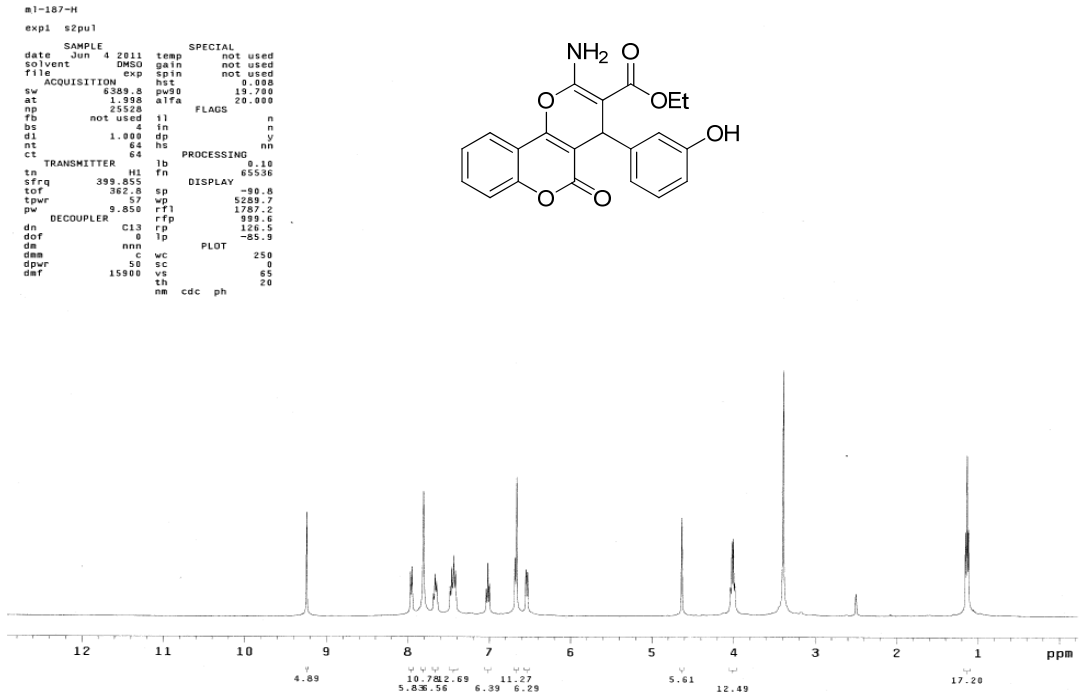


Figure 24.

Ethyl 2-amino-4-(3-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (***142f***)



Ethyl 2-amino-4-(3-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate (***142f***)

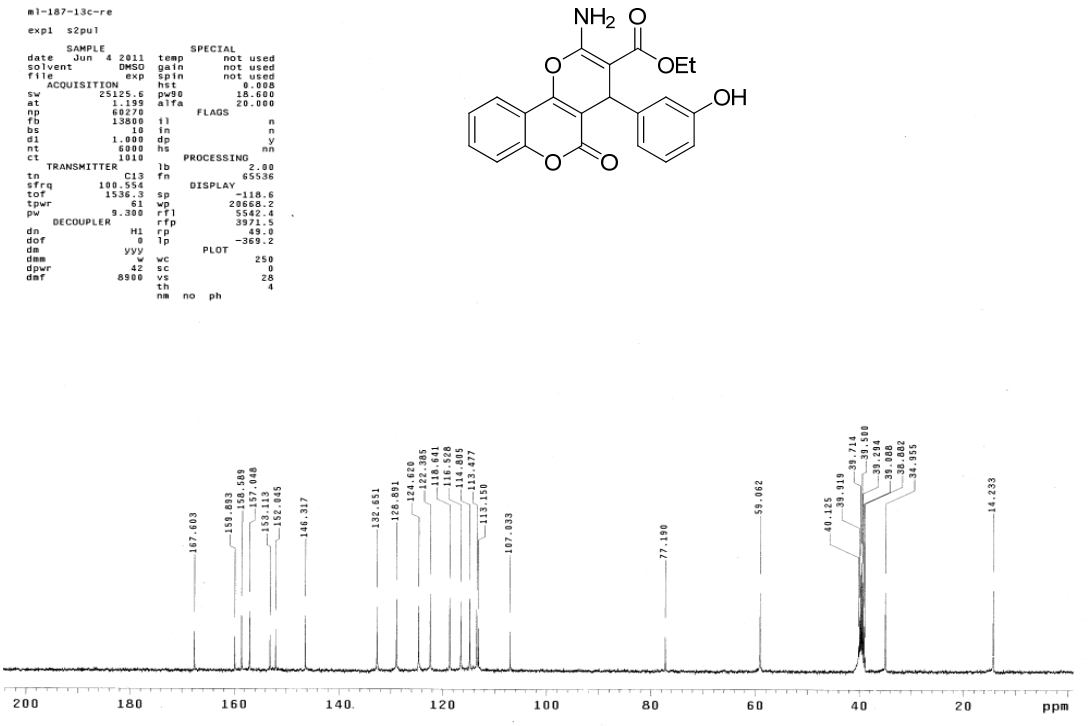
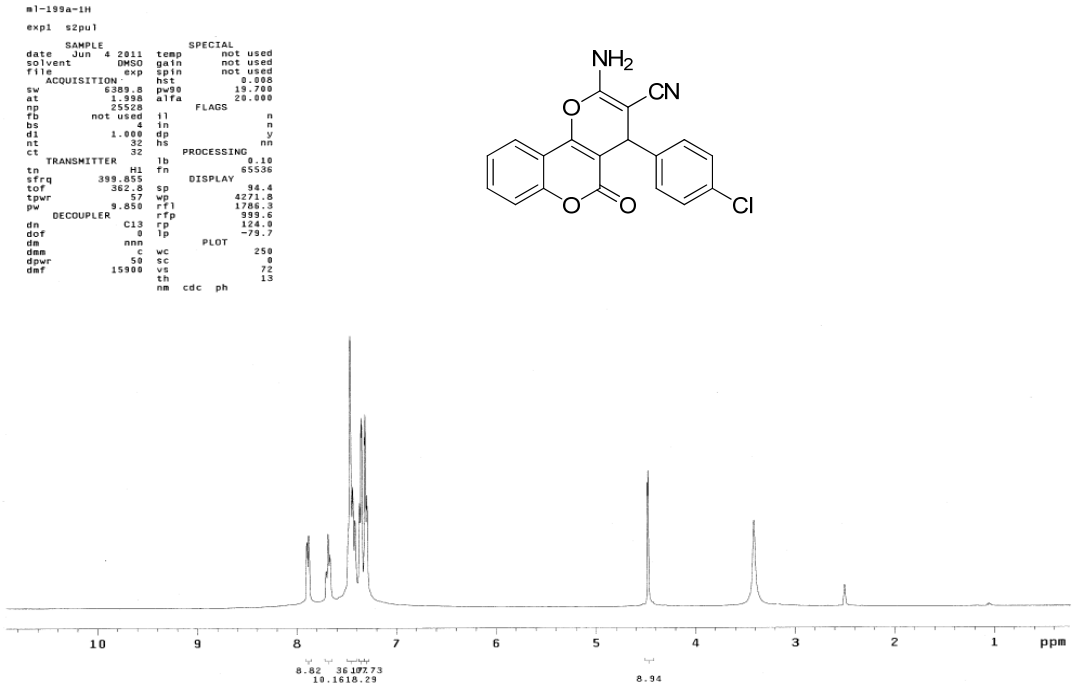


Figure 25.

*2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**142j**)*



*2-Amino-4-(4-chlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**142j**)*

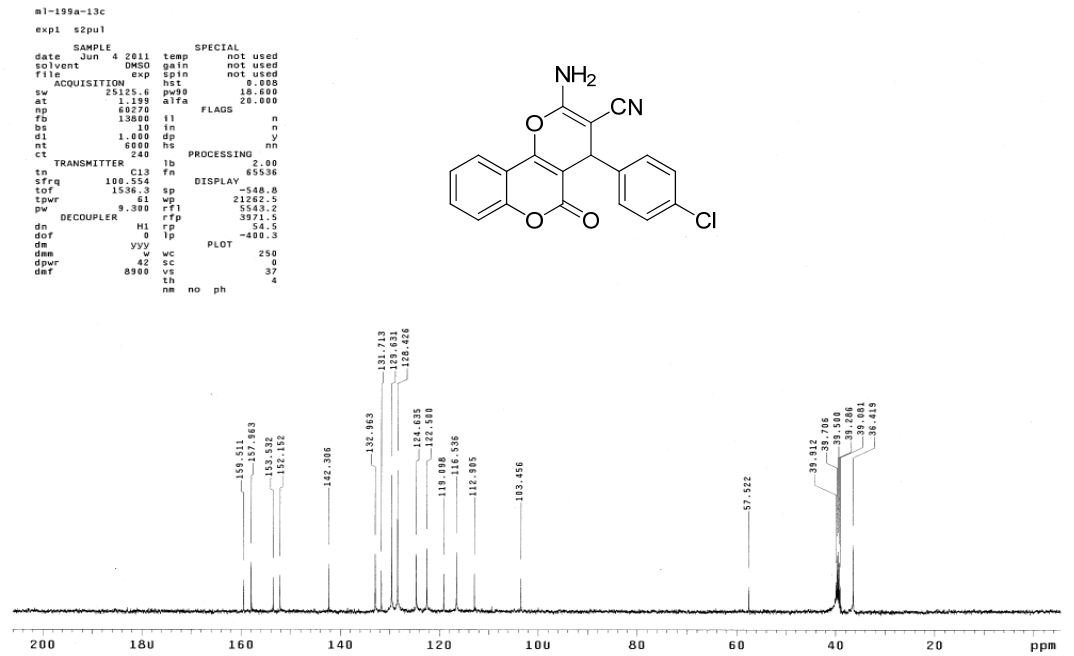
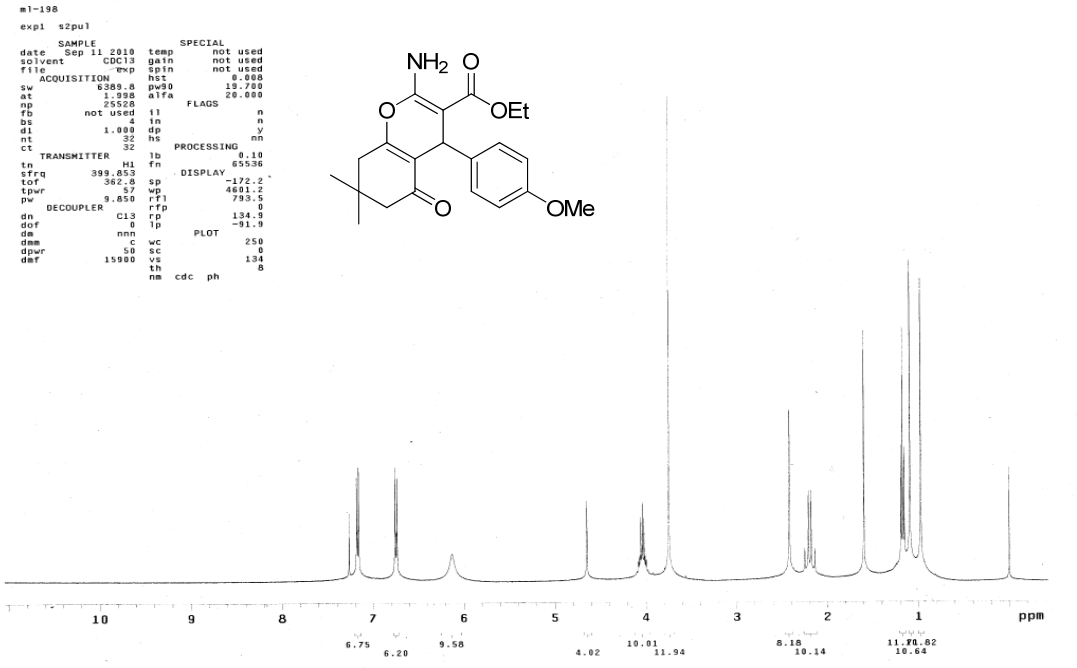


Figure 26.

*Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carb oxylate (**142p**)*



*Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carb oxylate**(142p)***

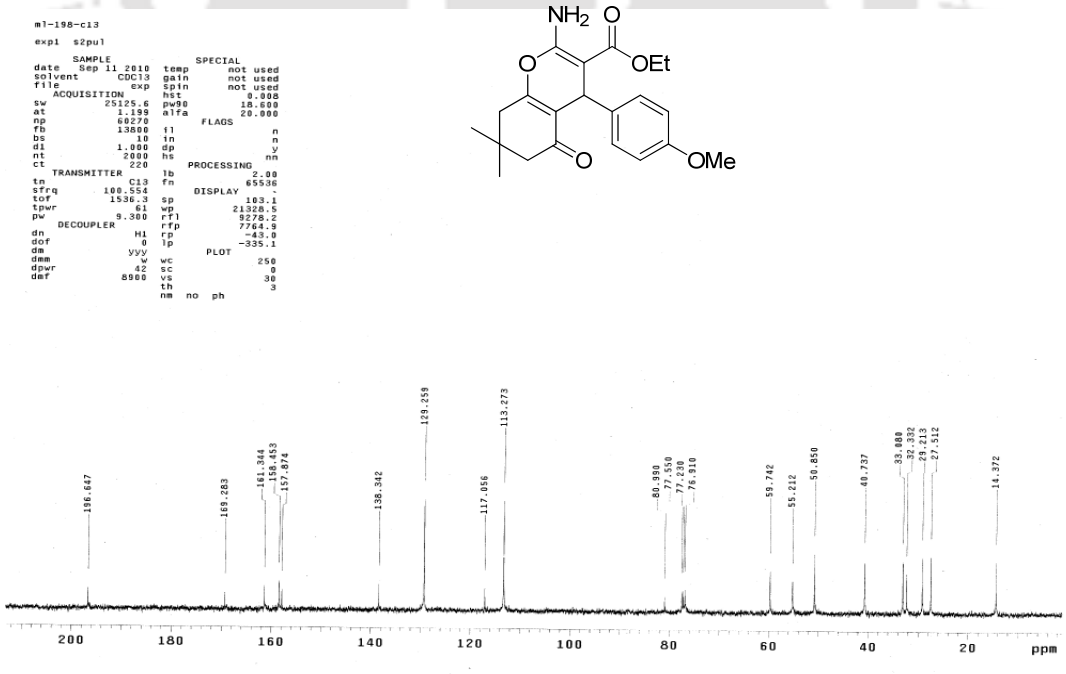
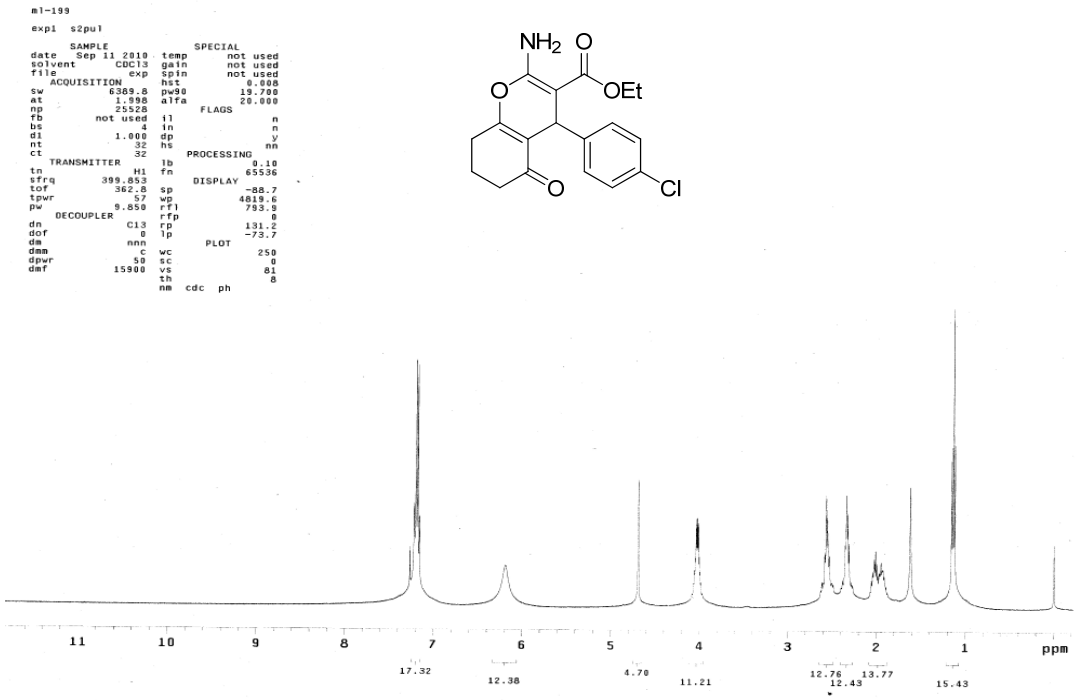


Figure 27.

*Ethyl 2-amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142t**)*



*Ethyl 2-amino-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (**142t**)*

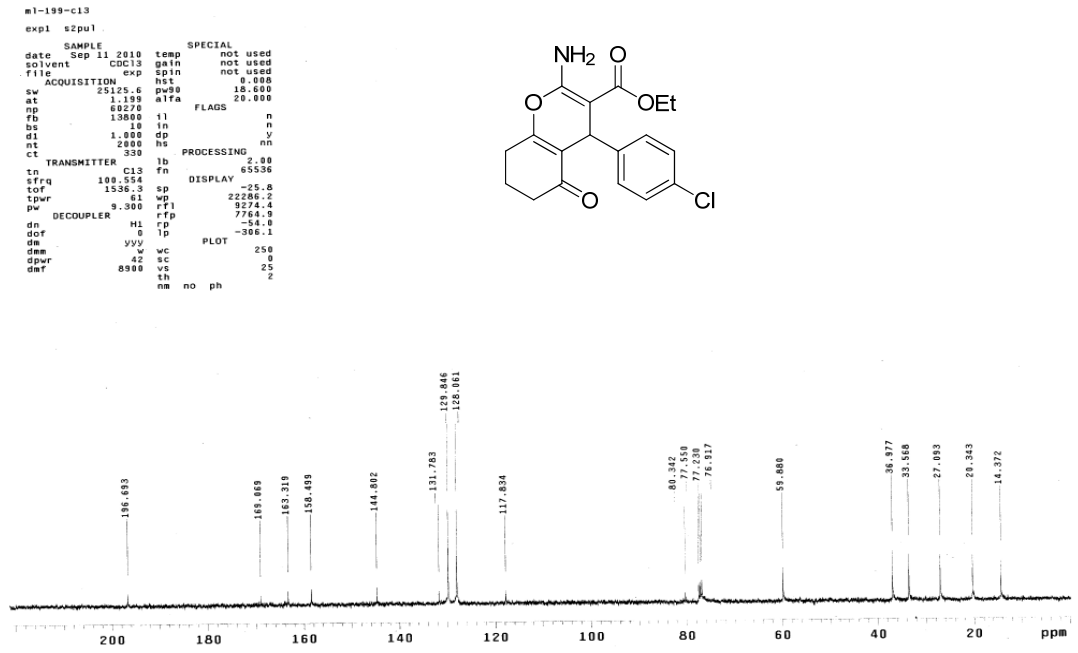
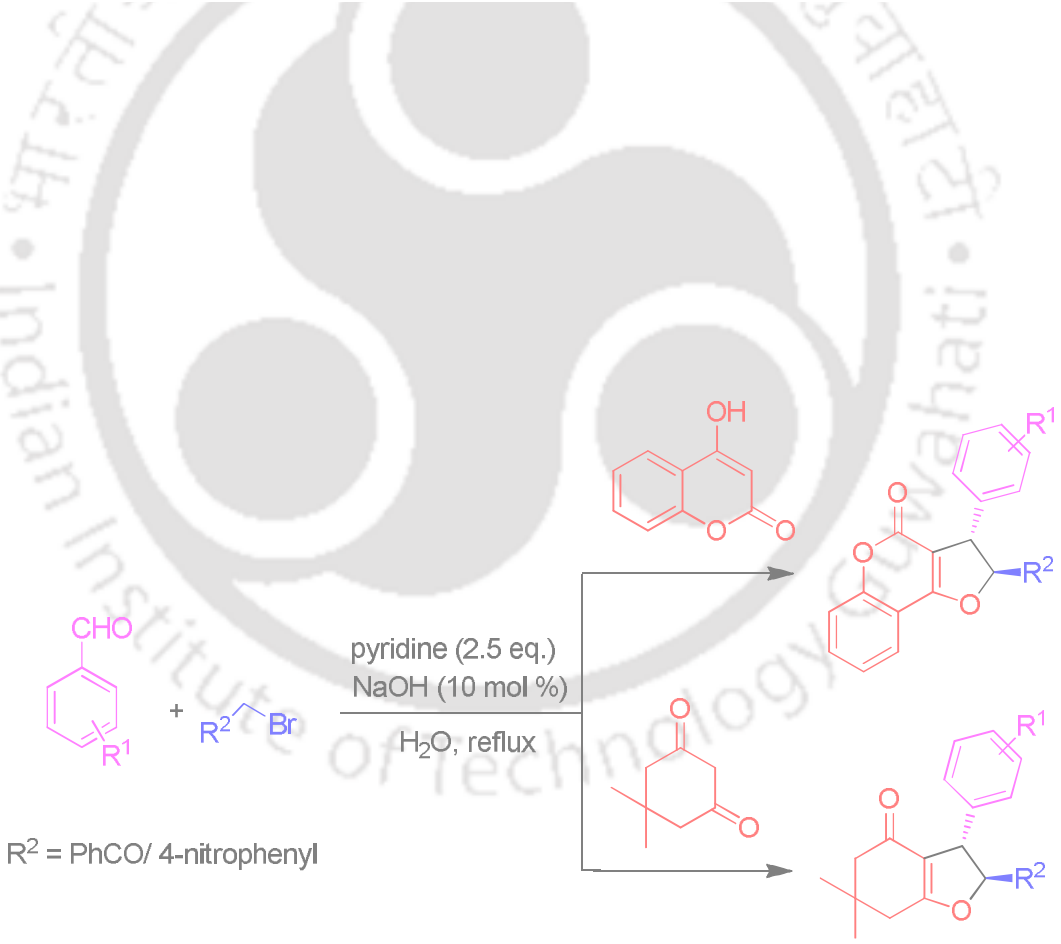


Figure 28.

Pyridinium ylide mediated one-pot three-component regio- and diastereoselective synthesis of *trans*-2,3-dihydrofuran derivatives



In the previous chapter, the synthetic application of 1,3-dicarbonyl compounds have been exploited for the synthesis of pyran-annualed heterocycles through MCRs using Knoevenagel reaction.[126] It is well-known fact that MCR strategy fulfills many tenets of Green Chemistry, we thought that heterocyclic compounds can be synthesized involving β-dicarbonyl compounds if the reaction is carried out in aquesous medium. In recent times, organic reactions in aqueous medium have gained[127] considerable attention in chemistry in conformity with the concept of Sustainable and Green Chemistry.[2] To carry out reaction in water medium is preferred due to its ease of natural abundance, highly polar in nature and environmentally acceptable. Sometimes it provides higher reactivity and selectivity as compared to many organic solvents due to its strong hydrogen bonding ability.[128] Numerous reactions have been carried out in aqueous medium for *C,C*-bond formations, which was reviewed[129] by Li in 2005. MCRs are also gaining popularity for carrying out the reactions in an environmentally benign solvent such as water[130]

Oxygen containing heterocycles are widely distributed in nature exhibiting interesting pharmacological activities.[121a,131] Dihydrofuran structural motif is present in many naturally occurring compounds, which display a wide range of biological activities.[132] For example, the natural product rocaglamide, which was isolated from *Aglaia elliptifolia* in 1982, exhibits antileukemic activity.[133] Similarly, naturally occurring angelmarin is used as cytoxic,[134] While 6-C-β-mannopyranosyl apigenin mostly used as anti-inflammatory and chemo preventive for colon cancer[135] The structure of these compounds are shown in Figure 29.

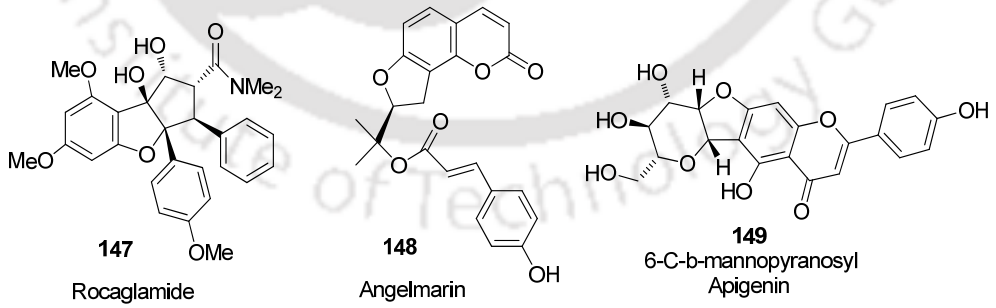
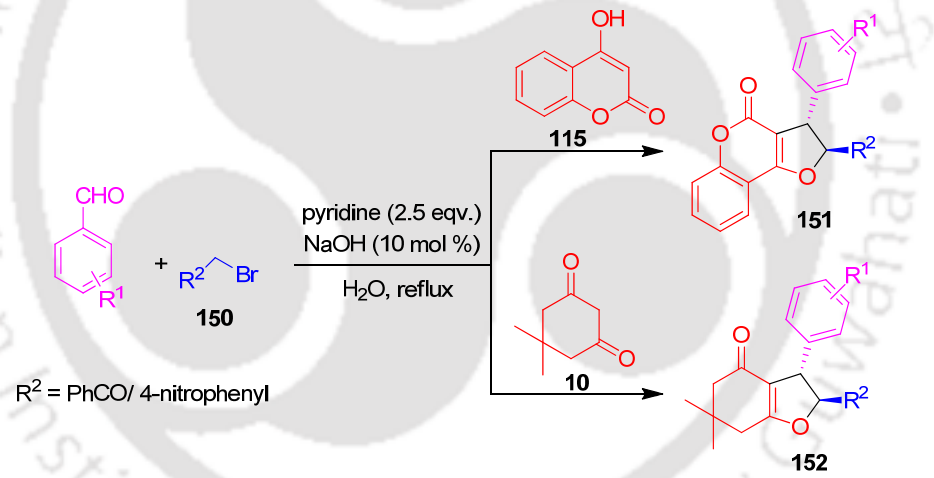


Figure 29. Some representative example natural product containing furan ring

Pyridinium ylides can be considered as a stabilized carbanion with a leaving group, which have been used as good reagents for the construction of cyclopropane ring[136] through Michael Initiated Ring Closure (MIRC) reaction as well as synthesis of various five membered oxygen[137a] and nitrogen heterocycles.[137b] Recently *in situ* generated

pyridinium ylide from α-phenacyl bromide and pyridine,[138a] or α-phenacyl chloride and DABCO[138b] or *N*-phenacylpyridinium bromide[138c] has been utilized for the construction of *trans*-2,3-dihydrofuran derivatives. Previously, sulfonium[139] and arsonium[140] ylides have also been utilized for the synthesis of *trans*-2,3-dihydrofuran derivatives. Very recently the synthesis of fused *trans*-2,3-dihydrofuran derivatives have been demonstrated by employing oxidative cyclisation.[141] Though these are quite useful methods, some of them have demerit such as requirement of large excess catalyst like triethylamine.[138a]

In this chapter, we have achieved the synthesis of fused *trans* 2,3-dihydrofuran derivatives (**151** & **152**) by one-pot three-component reaction involving aromatic aldehydes, dimedone/4-hydroxycoumarin, α-phenacyl bromide or 4-nitrobenzyl, and pyridine in the presence of a catalytic amount of sodium hydroxide in water under reflux condition as shown in Scheme 50.



Scheme 50. Three-component reaction for the synthesis of fused *trans*-2,3-dihydrofuran derivatives

To optimize the reaction conditions, various trial reactions were carried out with a combination of α-phenacyl bromide, pyridine, 4-chlorobenzaldehyde and 4-hydroxycoumarin, in presence of catalytic amount of sodium hydroxide in water under reflux conditions. The yields of the desired product **151a** in different reaction conditions are shown in Table 12. It has been observed that 10 mol % of NaOH gave the best result in terms of yield and reaction time. It was also noted that similar transformation is also viable using $NaHCO_3$ and K_2CO_3. Indeed the present study was carried out with NaOH

as it is cheaper as compared to other two bases. The product **151a** was characterized from IR, ^{1}H NMR, ^{13}C NMR spectra and HRMS as well as elemental analysis. It gives two strong absorption peaks at 1713 cm^{-1} and 1650 cm^{-1} in the IR spectrum indicate the presence of two carbonyl groups. In the ^{1}H NMR spectrum, the characteristic signals appear at δ 2.36 (s, 3H, Ph-*CH*$_3$), 4.74 (d, J = 4.8 Hz, 1H, C2-H) and 6.17 (d, J = 4.8 Hz, 1H, C3-H) indicate the formation of product. Similarly, in the ^{13}C NMR spectrum signals appear at δ 21.3 (Ph-Me), 49.3 (C3-H), 92.9 (C2-H), 105.6 (C4-H), 166.5 (C5-H), and 192.4, respectively. The observed HRMS value for the compound **151a** is 383.1273 with the expected value 383.1278. All these data support the formation of the desired product.

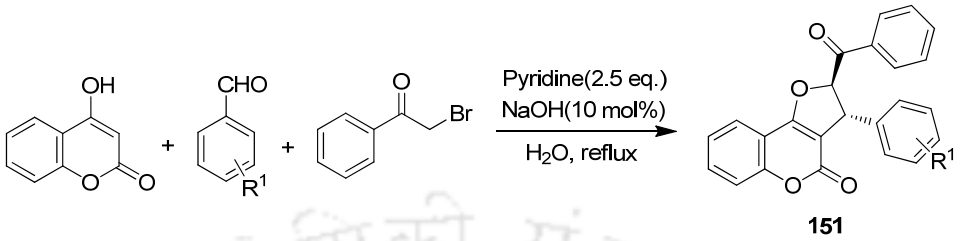
Table 12 Optimization of the reaction conditions

Entry	Base	Equiv.	Time/h	% Yield of **151a**[a]
1	No catalyst	-	14	-
2	NaOH	0.05	8	70
3	NaOH	0.1	6	88
4	NaOH	1.0	8	60
5	K_2CO_3	0.1	8	84
6	$NaHCO_3$	0.1	8	86

[a] Isolated yield

After optimization, the reaction of 4-hydroxycoumarin, benzaldehyde and α-phenacyl bromide afforded the desired product **151b** in 82 % yield in presence of 10 mol % of NaOH under identical reaction conditions. The scope and generality of the present protocol was further verified by carrying out the reactions with various aromatic aldehydes containing substituent such as Cl, Br and OMe (Table 13, entries 3-6) with 4-hydroxycoumarin and α-phenacyl bromide using 10 mol% NaOH as a catalyst under similar reaction conditions. The products (**151c-f)** were obtained in good yields as mentioned in Table 13. It was also noted that similar transformation can be carried out in 10-20 mmol scale in presence of 2.1 equivalent pyridine instead of using 2.5 equivalent of pyridine. Interestingly, lactone ring of 4-hydroxycoumarin did not open in the presence of 10 mol% NaOH solution under the experimental conditions.

Table 13 Synthesis of fused *trans*-2,3-dihydrofuran derivatives through three component reaction

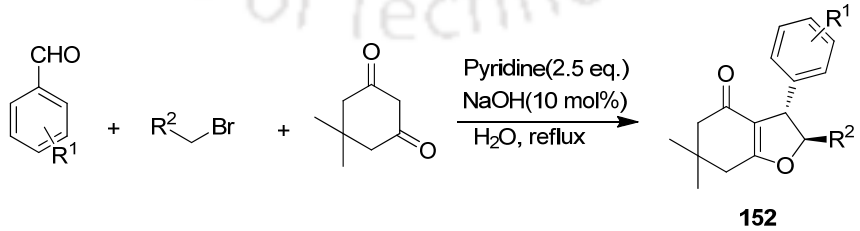


Entry	R^1	Time(h)	Product[a]	Yield %[b]	M.p.(°C)
1	4-Me	6	**151a**	88	203-204
2	H	8	**151b**	82	196-198
3	4-Cl	6	**151c**	85	171-172
4	4-OMe	8	**151d**	81	182-183
5	4-Br	6	**151e**	87	180-181
6	3-Br	8	**151f**	78	157-159

[a]The reactions were carried out in each case with 1 mmol scale, [b]Isolated yield,

To evaluate the scope of this three component reaction, the reactions were studied with dimedone with aromatic aldehydes and α-phenacyl bromide in presence of 10 mol% NaOH under identical reaction conditions. The desired products (**152a-f)** were obtained in 70-87 % yields as shown in Table 14 (entries 1-6). Next, the reaction was carried out with 4-nitrobenzyl bromide for the construction of fused *trans*-2,3-dihydrofuran derivatives under identical reaction conditions. The yields of the products **152g-i** are mentioned in Table 14 (entries 7-9).

Table 14 Synthesis of *trans*-2,3-dihydrofuran derivatives by using three-component reaction



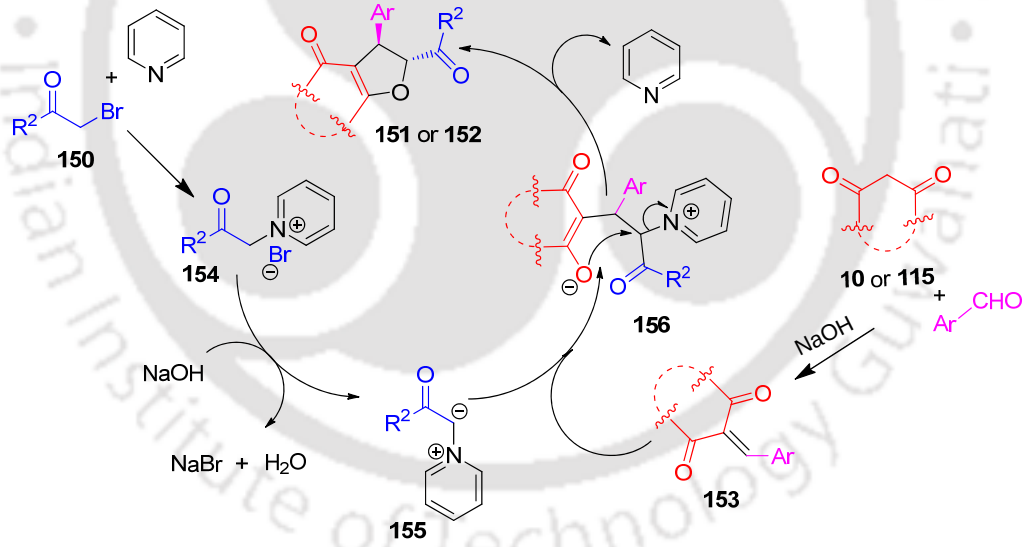
Entry	R^1	R^2	Time (h)	Product[a]	Yield %[b]	M.p.(°C)
1	4-Cl	-COC_6H_5(**150a**)	10	**152a**	81	124-126
2	4-Me	**150a**	10	**152b**	80	162-165

3	4-F	**150a**	11	**152c**	78	141-143
4	4-OMe	**150a**	12	**152d**	75	143-146
5	4-Br	**150a**	10	**152e**	87	132-134
6	4-NO_2	**150a**	13	**152f**	70	179-181
7	C_6H_5	4-$NO_2C_6H_4$- (**150b**)	11	**152g**	80	162-163
8	4-Cl	**150b**	10	**152h**	85	163-164
9	4-Me	**150b**	10	**152i**	80	166-167

[a]The reactions were carried out in each case with 1 mmol scale, [b]isolated yield,

All these products were characterized from ^{1}H NMR, ^{13}CNMR spectra as well as from elemental analysis. The spectral data of compounds **151b**, **152a**, **152e and 152h** are given in Figure 32-37, respectively in Experimental Section.

The proposed mechanism of this one pot three component reaction is illustrated in Scheme 51.



Scheme 51. Plausible Mechanism for the formation of *trans*-2,3-dihydrofuran derivatives

The formation of the product can be explained as follows: aromatic aldehyde reacts with dimedone (**10**) or 4-hydroxycoumarin (**115**) in the presence of NaOH at room temperature to give the Knoevenagel product, α-ylidene-β-diketones **153**. Similarly, α-phenacyl bromide (**150a)** or 4-nitrobenzyl bromide (**150b**) react with pyridine to form α-phenacylpyridinium bromide/1-(4-nitrobenzyl)pyridinium bromide salt **154** on

deprotonation in presence of NaOH provides the reactive pyridinium ylide **155**, which reacts instantly with the Knoevenagel product **153** to form the zwitterionic intermediate **156.** The intermediate **156** undergoes concomitant cyclisation with the elimination of pyridine to give the desired product *trans*-2,3-dihydrofuran derivatives **151** or **152** in a regio- and diastereoselective manner through similar to Michael Initiated Ring Closure (MIRC) reaction.

The *trans* stereochemistry of both the products **151** and **152** were established from the coupling constant values of the two methine protons at the position C2 and C3. Coupling constant was observed at $J_{2,3}$ is 2.8-6.0 Hz for the *trans* isomer. It was earlier reported that *cis*-2,3-dihydrofuran derivative the coupling constant value[142] would have been 10 Hz, which is higher than *trans* isomer as shown in Figure 30.

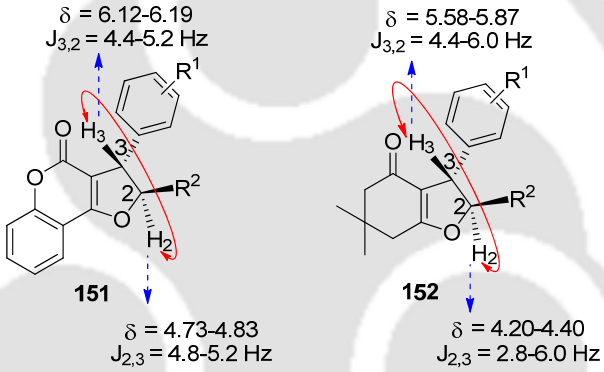


Figure 30. Diagnostic ^{1}H NMR of compounds **151** and **152**

Moreover, the structures as well as the relative stereochemistry of fused *trans*-2,3-dihydrofuran derivatives **152e** was further confirmed by single XRD crystallographic data where the dihedral angle between C2 and C3 are 109.66°, 109.37°, respectively, which resembles with the *trans* isomer.[141c] The ORTEP diagram is shown in Figure 31.

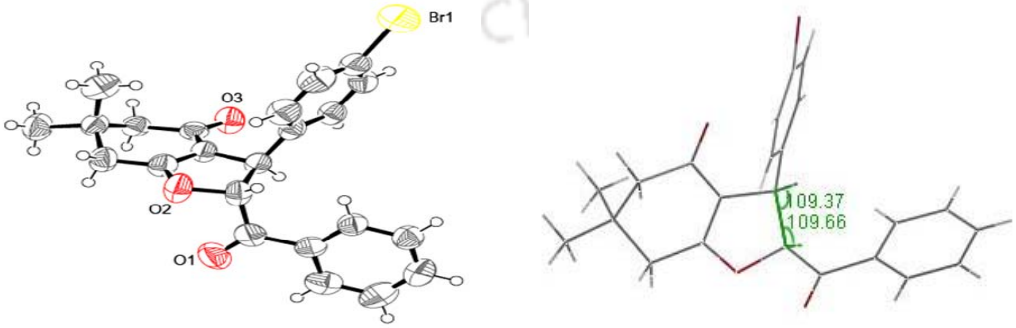
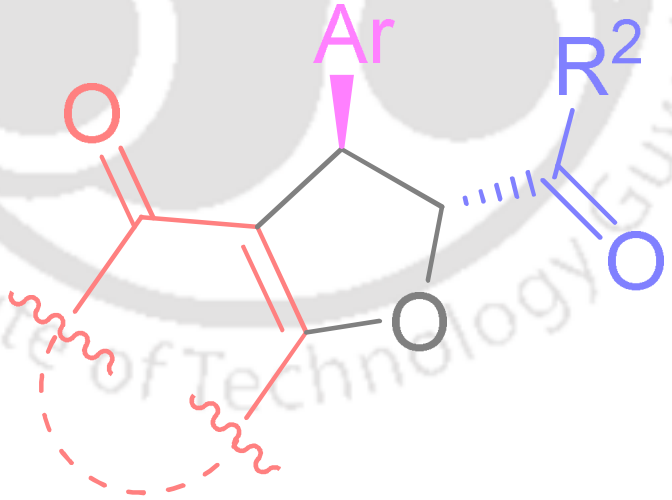


Figure 31. (ORTEP structure and CCDC 838374 of compound **152e**)

In summary, we have devised a simple and efficient protocol for the synthesis of *trans* 2,3-dihydrofuran derivatives in good yields *via* one-pot three-component condensation reaction from aromatic aldehydes, dimedone or 4-hydroxycoumarin, α-phenacyl bromide/4-nitrobenzyl bromide and pyridine in presence of 10% aqueous NaOH solution. In the present method, pyridine plays a dual role such as formation of stabilized nitrogen ylide in presence of a base as well as good leaving groups for Michael Initiated Ring Closure reaction. It is also noted that cyclic 1,3-diketones and pseudo cyclic 1,3-diketones only give this kind of transformation. The other merits of the present protocol include no need of chromatographic separation, easy to handle, without involvement of organic solvent at any stage and applicable to a wide range of substrates.

Pyridinium ylide mediated one-pot three-component regio- and diastereoselective synthesis of *trans*-2,3-dihydrofuran derivatives

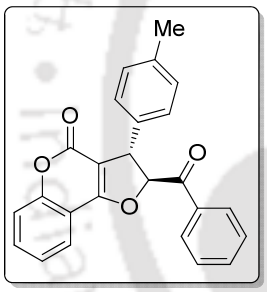


Experimental Section

General procedure for the synthesis of 2,3-Dihydrofurans:

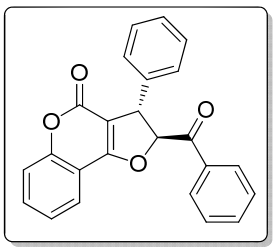
Into a 25 mL round bottomed flask was taken a mixture of either α-phenacyl bromide (1 mmol) or *p*-nitrobenzyl bromide (1 mmol) and pyridine (0.2 mL, 2.5 mmol) and kept for stirring at rt. The solid precipitate appeared after 5 min. and then aromatic aldehyde (1 mmol) and dimedone or 4-hydroxycoumarin (1 mmol) was added into the above reaction mixture. Subsequently, 4 mL 10% aqueous solution of NaOH and the reaction mixture was transferred into a heated oil bath under reflux conditions. After 0.5 h, the solid reaction mixture was completed dissolved. Finally the solid precipitate reappeared after 5 h during hot conditions, which was filtered and dried. Finely the product was recrystallized by ethanol to obtain pure product.

*2-benzoyl-3-p-tolyl-2,3-dihydrofuro[3,2-c]chromen-4-one (**151a**)*



Off-white amorphus, (0.336 g, 88%); M.p. 203-204 °C; **IR**(KBr): 3043, 2912, 1713, 1703, 1650, 1410, 1240, 1197, 1087, 1041, 936 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 4.74 (d, J = 4.8 Hz, 1H), 6.17 (d, J = 4.8 Hz, 1H), 7.19 (s, 4H), 7.35 (t, J = 7.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H), 7.66 (t, J = 6.8 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 49.3, 92.9, 105.6, 112.4, 117.2, 123.4, 124.3, 127.6, 129.1, 129.2, 130.1, 133.0, 133.3, 134.6, 136.7, 138.1, 155.5, 159.5, 166.5, 192.4; Anal. calcd for $C_{25}H_{18}O_4$ (382.41): C, 78.52;H, 4.74%; found C, 78.44; H, 4.67%; **HRMS** (ESI): MH^+, calcd for $C_{25}H_{18}O_4$ 383.1278; found 383.1273.

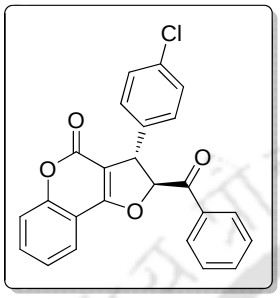
*2-benzoyl-3-phenyl-2,3-dihydrofuro[3,2-c]chromen-4-one (**151b**)*



White crystal, (0.302 g, 82%);. M.p. 196-198 °C; **IR**(KBr): 3065, 1717, 1703, 1651, 1497, 1411, 1239, 1200, 1089, 1041, 932 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.8 (d, J = 4.8 Hz, 1H), 6.19 (d, J = 4.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.51 (t, J = 7.6 Hz, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H);. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.5, 92.8, 105.5, 112.4, 117.2, 123.4,

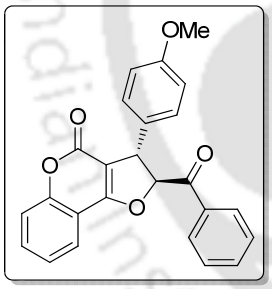
124.4, 127.7, 128.4, 129.2, 129.3, 129.5, 133.1, 133.3, 134.6, 139.7, 155.6, 159.5, 166.6, 192.3. **Anal. calcd** for $C_{24}H_{16}O_4$ (368.38): C, 78.25; H, 4.38%; found C, 78.18; H, 4.32%.

*2-benzoyl-3-(4-chlorophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one (**151c**)*

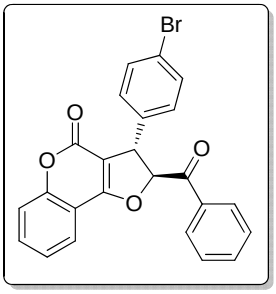


Pale yellow solid, (0.342 g, 85%); M.p. 171-172 °C; **IR**(KBr): 3061, 2967, 2923, 1712, 1648, 1498, 1449, 1416, 1237, 1223, 1200, 1089, 1042, 937 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.82 (d, J = 5.2 Hz 1H), 6.12 (d, J = 5.2 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.34-7.37 (m, 2 H), 7.40 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.60-7.70 (m, 3H), 7.83 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 48.8, 92.5, 105.1, 109.9, 112.2, 117.2, 123.4, 124.4, 129.1, 129.2, 129.6, 133.2, 133.3, 134.2, 134.7, 138.2, 155.6, 159.3, 166.6, 192.0. **Anal. calcd** for $C_{24}H_{15}ClO_4$ (402.83): C, 71.56; H, 3.75%; found C, 71.48; H, 3.68%; **HRMS** (ESI): MH^+, calcd for $C_{24}H_{15}ClO_4$, 403.0737; found 403.0742.

*2-benzoyl-3-(4-methoxyphenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one (**151d**)*



Off-white amorphous, (0.322 g, 81%), M.p. 182-183°C; **IR**(KBr): 1723, 1694, 1648, 1607, 1512, 1410, 1254, 1201, 1239, 1175, 1088, 1027, 933 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 4.73 (d, J = 5.2 Hz, 1H), 6.15 (d, J = 4.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 77.59-.68 (m, 2H), 7.85 (dd, J = 7.6 , 1.6 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.0, 55.5, 92.9, 105.6, 112.4, 114.8, 117.2, 123.4, 124.3, 128.8, 129.2, 129.3, 131.8, 133.0, 133.3, 134.6, 155.5, 159.5, 159.6, 166.4, 192.4. **Anal. calcd** for $C_{25}H_{18}O_5$(398.41): C, 75.37; H, 4.55%; found C, 75.29; H, 4.48%; **HRMS** (ESI): MH^+, calcd for $C_{25}H_{18}O_5$ 399.1227; found 399.1233.

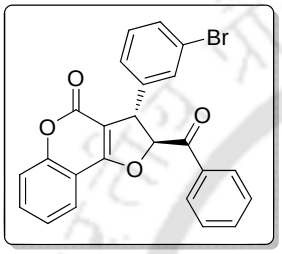


*2-benzoyl-3-(4-bromophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one (**151e**)*

Yellow crystal, (0.390 g, 87%), M.p.180-181°C; IR(KBr): 3054, 2961, 2928, 1712, 1650, 1449, 1415, 1087, 1041, 937

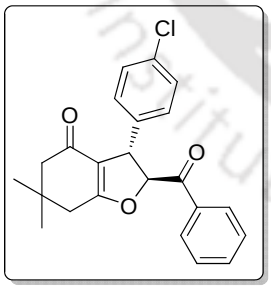
cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.80 (d, J = 4.8 Hz. 1H), 6.12 (d, J = 5.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.46-7.53 (m, 4H), 7.62 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.90 (J = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 48.8, 92.4, 105.0, 112.2, 117.2, 122.3, 123.4, 124.4, 129.2, 129.5, 132.5, 133.2, 133.3, 134.3, 138.7, 155.5, 159.3, 166.6, 191.9. Anal. calcd for $C_{24}H_{15}BrO_4$(447.28): C, 64.45; H, 3.38%; found C, 64.39; H, 3.28%.

*2-benzoyl-3-(3-bromophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one (**151f**)*



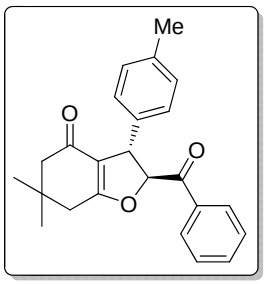
Yellow crystal, (0.348 g, 78%); M.p. 157-159 °C; **IR**(KBr): 1718, 1690, 1650, 1604, 1497, 1414, 1203, 1089, 1031, 932 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.83 (d, J = 4.4 Hz, 1H), 6.12 (d, 5.2 Hz, 1H), 7.25 (d, J = 6.4 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.43 (d, J = 3.2 Hz, 1H), 7.45-7.48 (m, 1H), 7.54 (t, J = 8.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 1H), 7.65-7.69 (m, 1H), 7.83 (d, J =8.0 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 48.8, 92.5, 104.9, 112.2, 117.3, 123.4, 123.6, 124.4, 126.7, 129.2, 129.3, 130.6, 130.9, 131.5, 133.3, 133.4, 134.8, 142.0, 155.6, 159.3, 166.7, 191.9**. Anal. calcd** for $C_{24}H_{15}BrO_4$ (447.28): C, 64.45; H, 3.38%; found C, 64.37; H, 3.31%. **HRMS** (ESI): MH^+, calcd for $C_{24}H_{16}O_4$, 369.1136; found 369.1121.

*2-benzoyl-3-p-chlorophenyl-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**152a**)*



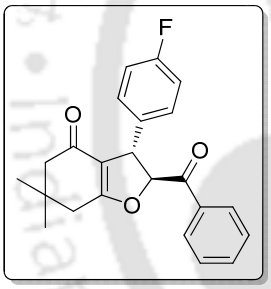
White solid, (0.308 g, 81%). M.p. 124-126 °C; **IR**(KBr): 2950, 1698, 1645, 1390, 1215, 1089, 962. cm^{-1}; **^{1}H NMR** (400 MHz, CDCl3): δ 1.16 (s, 6H). 2.18 (d, J = 16.4 Hz, 1H), 2.25 (d, J = 16.0 Hz, 1H), 2.50-2.64 (m, 2H), 4.40 (d, J = 4.0 Hz, 1H), 5.84 (d, J = 4.8 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 8 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.81 (d, J = 8.0 Hz 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 29.1, 34.5, 37.8, 48.4, 51.2, 91.6, 114.9, 128.8, 129.0, 129.1, 129.4, 133.3, 133.5, 134.4, 139.8, 176.5, 192.7, 193.6. **Anal. calcd** for $C_{23}H_{21}ClO_3$ (380.86): C, 70.53; H, 5.56; %; found C, 70.49; H, 5.50%. **HRMS** (ESI): MH^+, calcd for $C_{23}H_{21}ClO_3$, 381.1252; found, 381.1257.

2-benzoyl-6,6-dimethyl-3-(4-methylphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152b)***



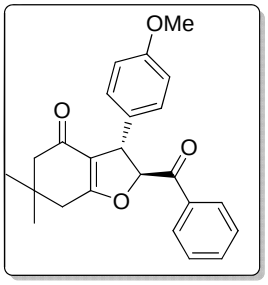
White amorphous, (0.288 g, 80%); M.p. 162-165 °C; **IR**(KBr): 1225, 2958, 2940, 1694, 1632, 1395, 962 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 2.17 (d, J = 16.4 Hz, 1H), 2.24 (d, J = 16 Hz, 1H), 2.34 (s, 3H), 2.51-2.66 (m, 2H), 4.34 (d, J = 2.8 Hz, 1H), 5.87 (d, J = 4.4 Hz, 1H), 7.11-7.17 (m, 4H), 7.45 (t, J = 7.6 Hz, 2H), 7.59-7.63 (m, 1H), 7.82 (dd, J = 8.4, 1.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.3, 28.5, 29.2, 34.4, 37.8, 48.8, 51.3, 92.1, 115.4, 127.3, 129.0, 129.1, 129.8, 133.3, 134.2, 137.4, 138.4, 176.3, 193.0, 193.7. **Anal. calcd** for $C_{24}H_{24}O_3$ (360.45): C, 79.97; H, 6.71 %; found C, 79.91; H, 6.66 %. **HRMS** (ESI): MH^+, calcd for $C_{24}H_{24}O_3$, 361.1798; found, 361.1791.

2-benzoyl-3-(4-flourophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152c)***



Brown solid, (0.284g, 78%); M.p. 141-143°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.13 (s, 6H), 2.15 (d, J = 16.4 Hz, 1H), 2.22 (d, J = 16.4 Hz, 1H), 2.48-2.62 (m, 2H), 4.38 (d, J = 3.6 Hz, 1H), 5.82 (d, J = 4.8 Hz 1H), 7.01 (t, J = 8.4 Hz, 2H), 7.18 (dd, J = 8.4, 5.2 Hz, 2H), 7.44 (t, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.6, 29.2, 34.5, 37.8, 48.4, 51.3, 91.9, 115.2, 116.0, 116.2, 129.0, 129.1, 133.4, 134.4, 137.2, 176.5, 192.9, 193.8. **Anal. calcd** for $C_{23}H_{21}FO_3$ (364.41) C, 75.81; F, 5.21; O, 13.17; found C, 75.71; F, 5.08; O, 13.10.

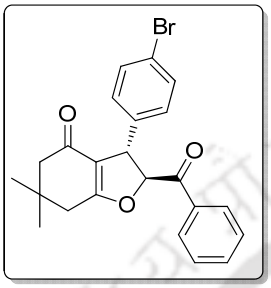
2-benzoyl-3-(4-methoxyphenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152d)***



White crystal, (0.282 g, 75%); M.p. 143-146 °C; **IR**(KBr): 3022, 2956, 1693, 1630, 1509, 1395, 1247, 1225, 1028, 962 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 2.17 (d, J = 16.4 Hz, 1H), 2.24 (d, J = 16.4 Hz, 1H), 2.53 (d, J = 17.6 Hz, 1H), 2.63 (d, J = 18.0 Hz, 1H), 3.80 (s, 3H), 4.32 (d, J = 3.6 Hz, 1H), 5.86 (d, J = 4.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.62 (t, J = 6.4 Hz, 1H), 7.82 (d, J = 8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 29.2, 34.5, 37.8, 48.6, 51.3, 55.4, 92.1, 114.6, 115.4, 128.5,

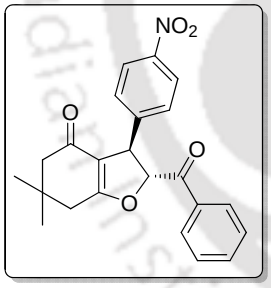
129.1, 133.3, 133.5, 134.3, 159.1, 176.3, 193.1, 193.8. **Anal. calcd** for $C_{24}H_{24}O_4$ (376.44): C, 76.57; H, 6.43%; found C, 76.49; H, 6.35%. **HRMS** (ESI): MH^+, calcd for $C_{24}H_{24}O_4$, 377.1747; found, 377.1739.

2-benzoyl-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152e)***

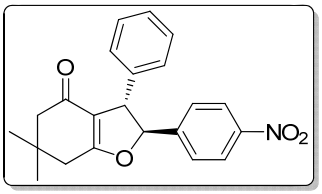


Off-white crystal, (0.370 g, 87%); M.p. 132-134 °C; **IR**(KBr): 1699 (C=O), 1646 (C=C) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (s, 6H), 2.18 (d, J = 16.4 Hz, 1H), 2.25 (d, J = 16.4 Hz, 1H), 2.53 (d, J = 18.0 Hz, 1H), 2.62 (d, J = 17.6 Hz, 1H), 4.38 (d, J = 4.0 Hz, 1H), 5.85 (d, J = 4.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.45-7.49 (m, 4H), 7.61-7.65 (m, 1H), 7.81 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 29.2, 34.5, 37.7, 48.5, 51.2, 91.6, 114.9, 121.7, 129.0, 129.1, 129.2, 132.3, 133.2, 134.4, 140.4, 176.6, 192.6, 193.6. **Anal. calcd** for $C_{23}H_{21}BrO_3$ (425.32): C, 64.95; H, 4.98%; found C, 64.88; H, 4.91%. **HRMS** (ESI): MH^+, calcd for $C_{23}H_{21}BrO_3$, 425.0747; found, 425.0743.

2-benzoyl-6,6-dimethyl-3-(4-nitrophenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152f)***



Pale yellow crystal, (l0.273 g, 70%); M.p. 179-181°C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17 (s, 6H). 2.19 (d, J = 16 Hz, 1H), 2.27 (d, J = 16.8 Hz, 1H), 2.65-2.52 (m, 2H), 4.62 (d, J = 4.0 Hz, 1H), 5.86 (d, J = 5.2 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.48 (t, J = 8.4 Hz, 2H), 7.67-7.63 (m , 1H), 7.83 (d, J = 8.4 2H), 8.22 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.5, 29.1, 34.6, 37.8, 48.4, 51.2, 91.2, 114.6, 124.5, 128.6, 129.1, 129.2, 133.4, 134.6, 147.6, 148.7, 176.9, 192.2, 193.6. **Anal. calcd** for $C_{23}H_{21}NO_5$ (391.42): C, 70.58; H, 5.41; N, 3.58%; found C, 70.49; H, 5.40; N, 3.51%. **HRMS** (ESI): MH^+, calcd for $C_{23}H_{21}NO_5$ 392.1492; found 392.1488.

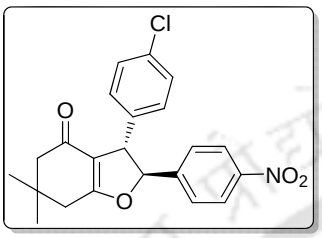


6,6-dimethyl-2-(4-nitrobenzoyl)-3-phenyl-2,3,6,7-tetrahy drobenzofuran-4(5H)-one ***(152g)***

Solid, (0.313 g, 80%); M.p. 162-163 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.23 (s, 3H), 2.28 (s, 2H), 2.63-2.53 (m, 2H), 4.24 (d, J = 6.0 Hz, 1H), 5.63 (d, J = 6.0 Hz, 1H), 7.21 (d, J = 6.8 Hz, 2H), 7.24 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.2 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.8, 29.1, 34.5,

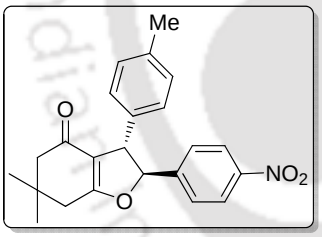
38.1, 51.5, 54.8, 93.2, 114.8, 124.4, 126.1, 127.3, 127.7, 129.3, 141.7, 147.6, 175.8, 193.9. **Anal. calcd** for $C_{23}H_{21}NO_5$ (391.42): C, 70.58; H, 5.41, N, 3.58%; found C, 70.51; H, 5.34; N, 3.50%.

*3-(4-chlorophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-2,3,6,7-tetrahydrobenzofuran-4(5H) -one (**152h**)*



Pale yellow amorphous, (0.361 g, 85%); M.p. 163-164 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.22 (s, 3H), 2.28 (s, 2H), 2.56-2.58 (m, 2H), 4.22 (d, J = 6.0 Hz, 1H), 5.58 (d, J = 6.0 Hz, 1H), 7.15 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 8.26 (d, J = 9.2 Hz, 2H); **IR**(KBr): 3081, 2964, 2928, 2871, 1651, 1637, 1605, 1515, 1396, 1346, 1220, 1090, 1041, 1013, 961 cm^{-1}; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 28.8, 29.0, 34.5, 37.9, 51.4, 54.2, 92.9, 114.4, 124.4, 126.1, 128.7, 129.4, 133.4, 140.0, 147.2, 148.1, 176.0 193.8. **Anal. calcd** for $C_{23}H_{20}ClNO_5$ (425.86): C, 64.87; H, 4.73; N, 3.29 %; found C, 64.81; H, 4.65; N, 3.21%.

*6,6-dimethyl-2-(4-nitrobenzoyl)-3-p-tolyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**152i**)*



Pale yellow crystal, (0.324 g, 80%); M.p. 166-167 °C; **IR**(KBr): 3081, 2963, 2870, 1654, 1639, 1605, 1514, 1397, 1346, 1217, 1043, 960 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.22 (s, 3H), 2.27 (s, 2H), 2.34 (s, 3H), 2.57 (d, J = 6.4 Hz, 2H), 4.20 (d, J = 5.6 Hz, 1H), 5.61 (d, J = 5.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 28.7, 29.0, 34.4, 37.9, 51.4, 54.4, 93.1, 114.8, 124.3, 126.0, 127.2, 129.9, 137.2, 138.6, 147.7, 147.9, 175.6, 193.8. **Anal. calcd** for $C_{24}H_{23}NO_5$ (405.44): C, 71.10; H, 5.72; N, 3.45%; found C, 71.03; H, 5.65; N, 3.37%.

*XRD for compound **152e***

Complete crystallographic data of compound **152e** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 838374. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-

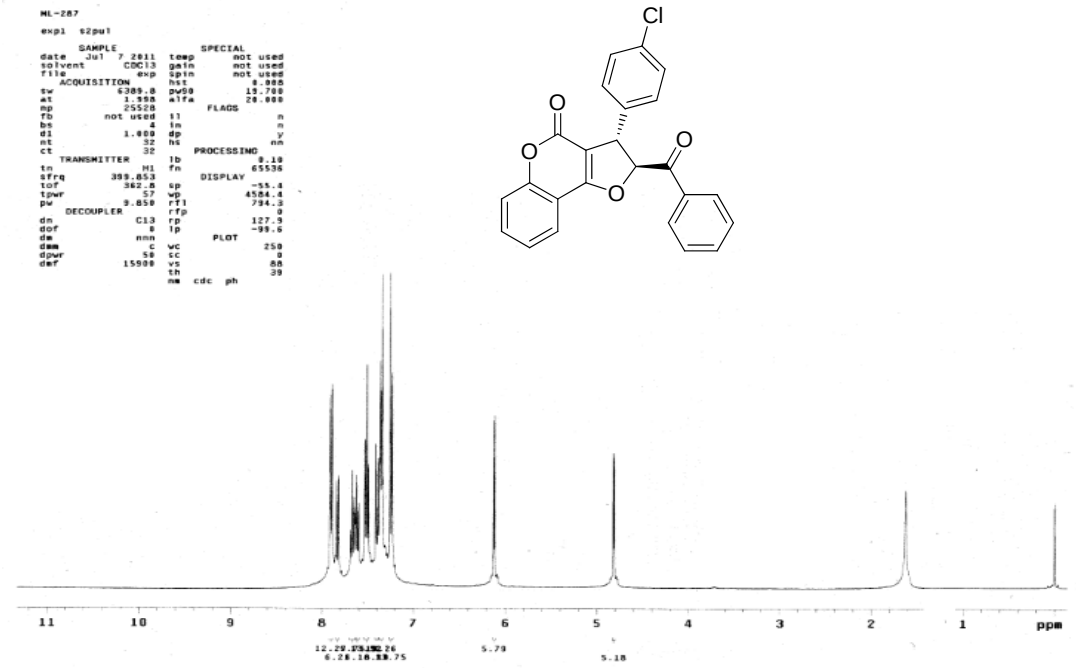
1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 15 Crystal data and structures refinement for the compounds **152e**, for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 152e**
Formula	$C_{23}H_{21}BrO_3$
CCDC number	838374
Formula weight	425.30
T (K)	296 K
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C 2/c
a (Å)	27.3190(8)Å
b (Å)	12.3068(4)Å
c (Å)	13.5814(4)Å
α (°)	90º
β (°)	119.623(1)º
γ (°)	90º
V (Å^3)	3969.4(2) Å^3
Z	8
D_{calcd} (g m^{-3})	2.091mm^{-1}
μ (mm^{-1})	0.090 mm^{-1}
F(0 0 0)	1744.0
Reflection collected	4914
Unique reflections	1684
Goodness-of-fit (GOF)[a] on F^2	0.815
R [$I > 2\sigma(I)$]	[b]R_1 = 0.1502, [c]wR_2 = 0.0976
R indices (all data)	[b]R_1 = 0.0356. [c]wR_2 = 0.0855

^{1}H NMR (400 MHz, $CDCl_3$): *2-benzoyl-3-(4-chlorophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one*

(151b)



^{13}C NMR (100 MHz, $CDCl_3$)*: 2-benzoyl-3-(4-chlorophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one* ***(151b)***

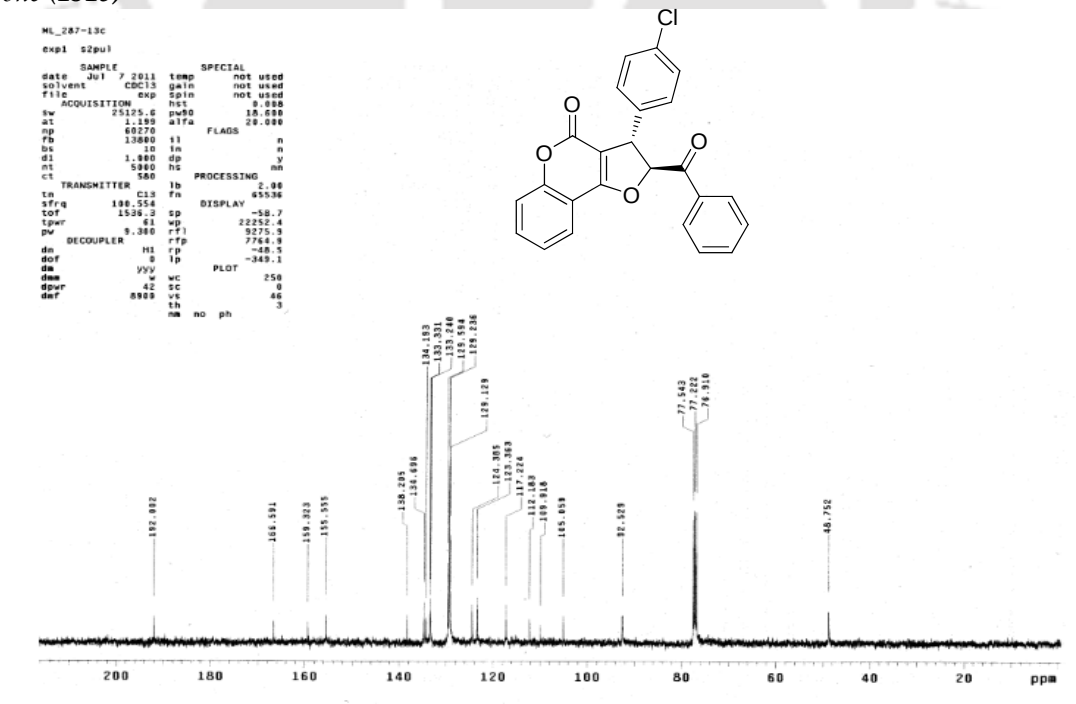
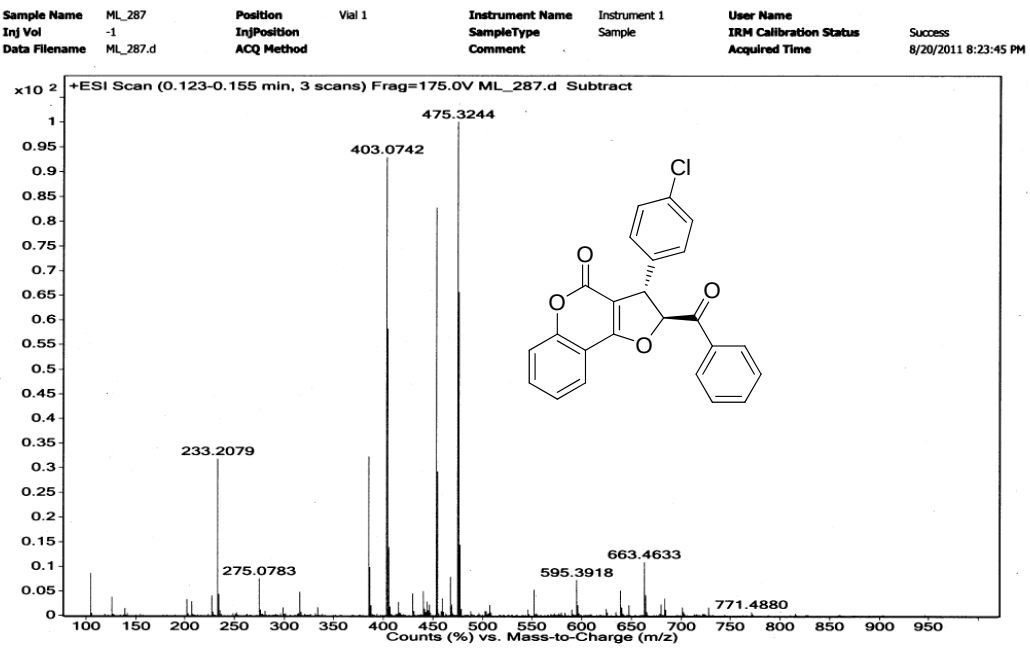


Figure 32.

(HRMS) *2-benzoyl-3-(4-chlorophenyl)-2,3-dihydrofuro[3,2-c]chromen-4-one* ***(151b)***



^{1}H NMR (400 MHz, $CDCl_3$): *2-benzoyl-3-(4-chlorophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152a)***

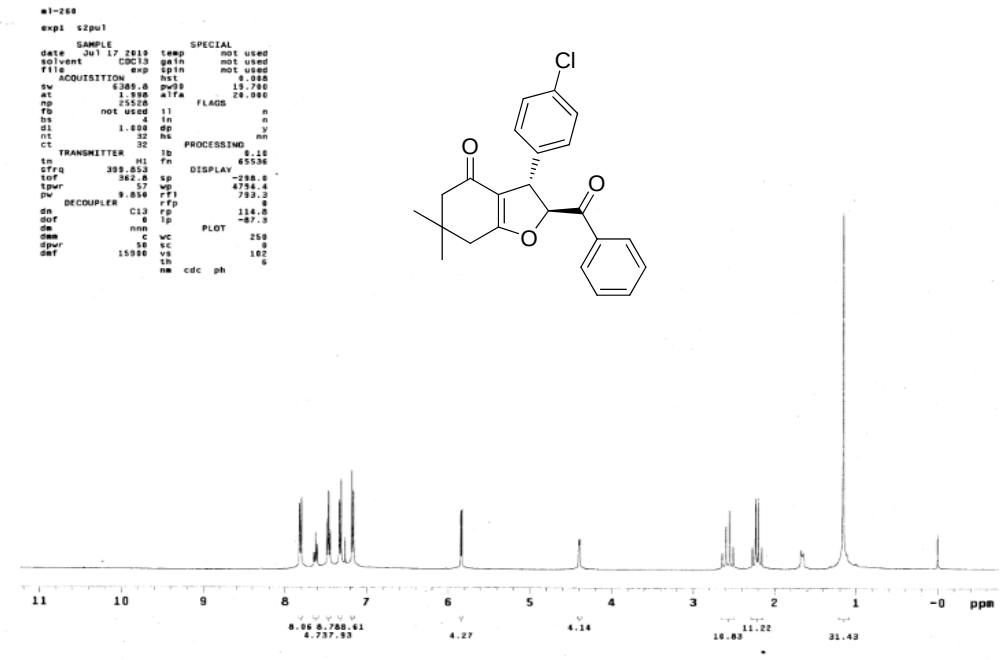
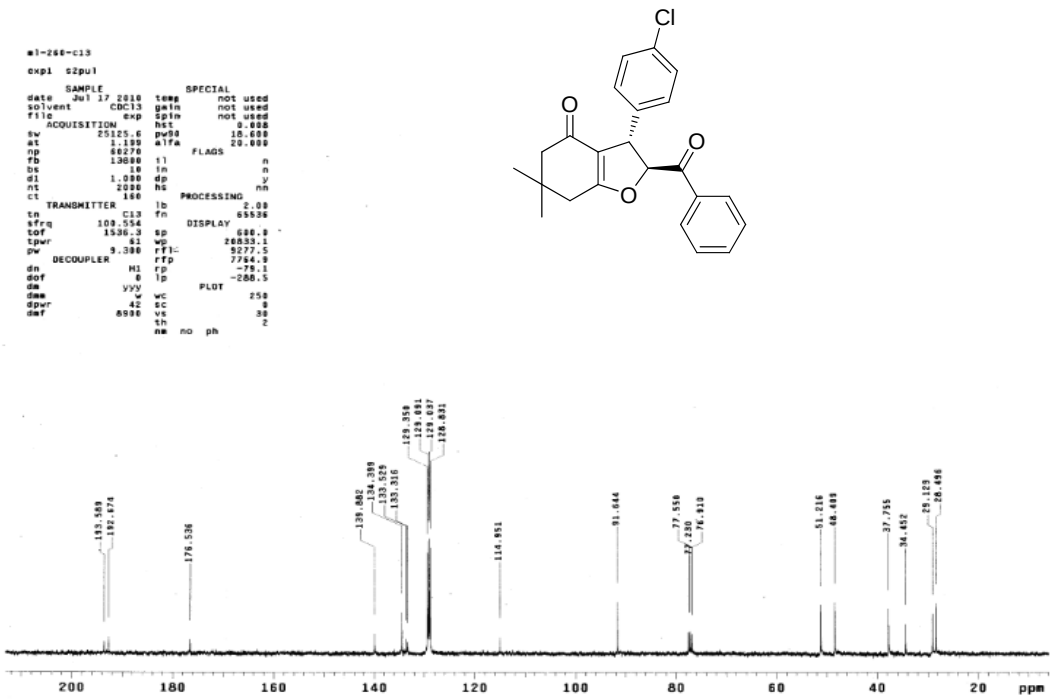


Figure 33.

(¹³C NMR (100 MHz, $CDCl_3$): 2-benzoyl-3-(4-chlorophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one ***(152a):***



(HRMS) *2-benzoyl-3-(4-chlorophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152a)***

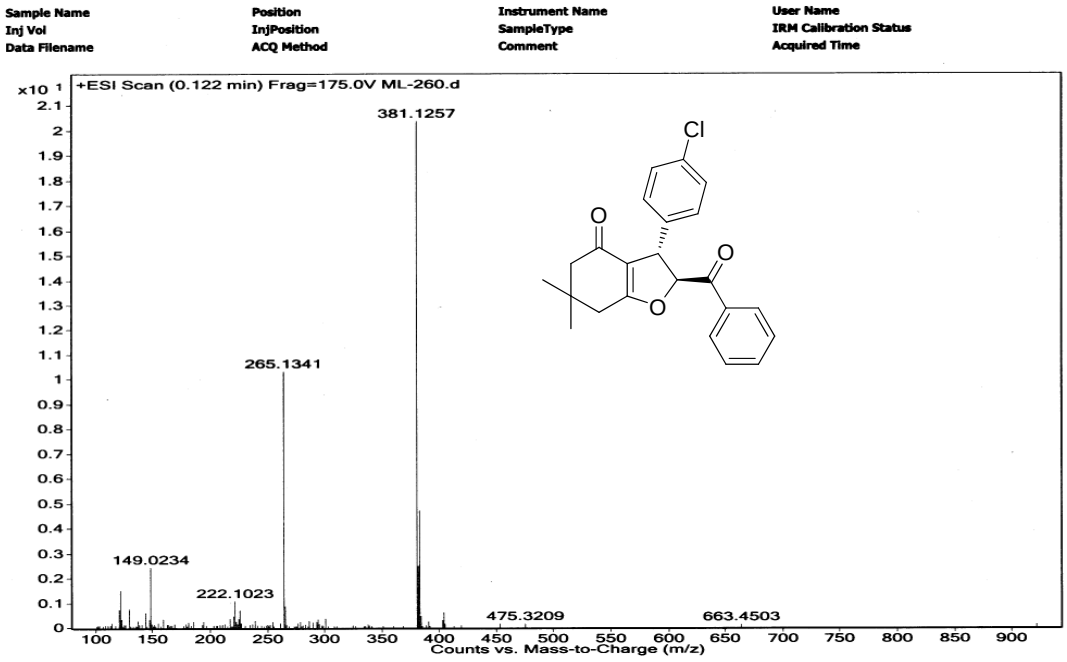
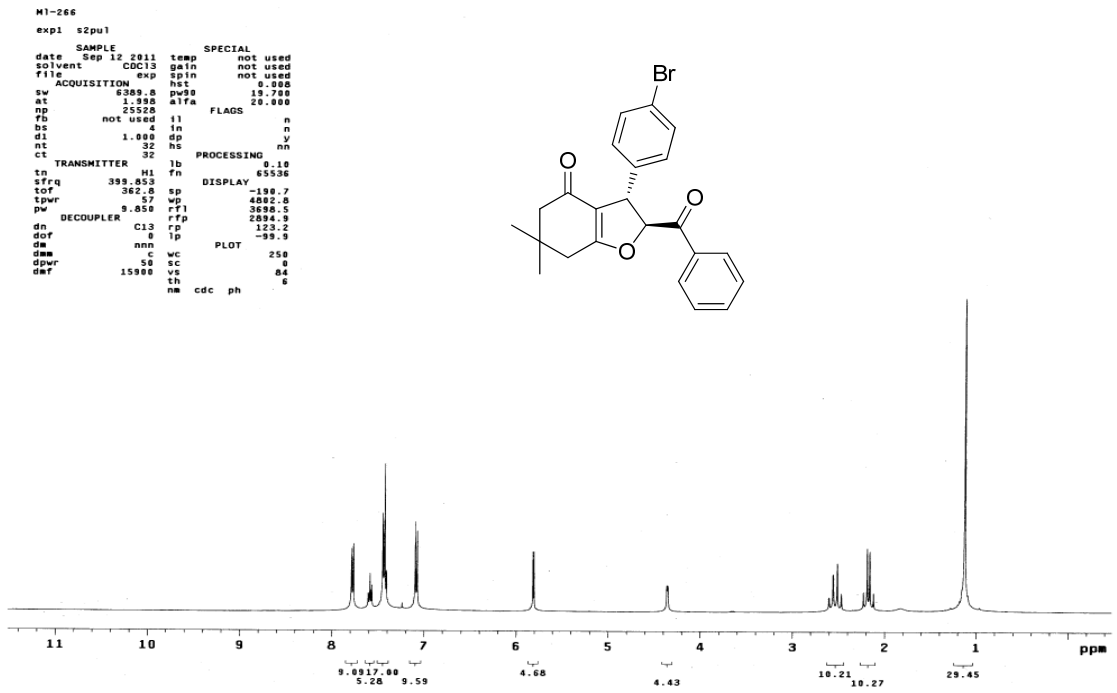


Figure 34.

^{1}H NMR (400 MHz, $CDCl_3$): *2-benzoyl-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152e)*:**



^{1}H NMR(cosy) (400 MHz, $CDCl_3$): *2-benzoyl-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152e)*:**

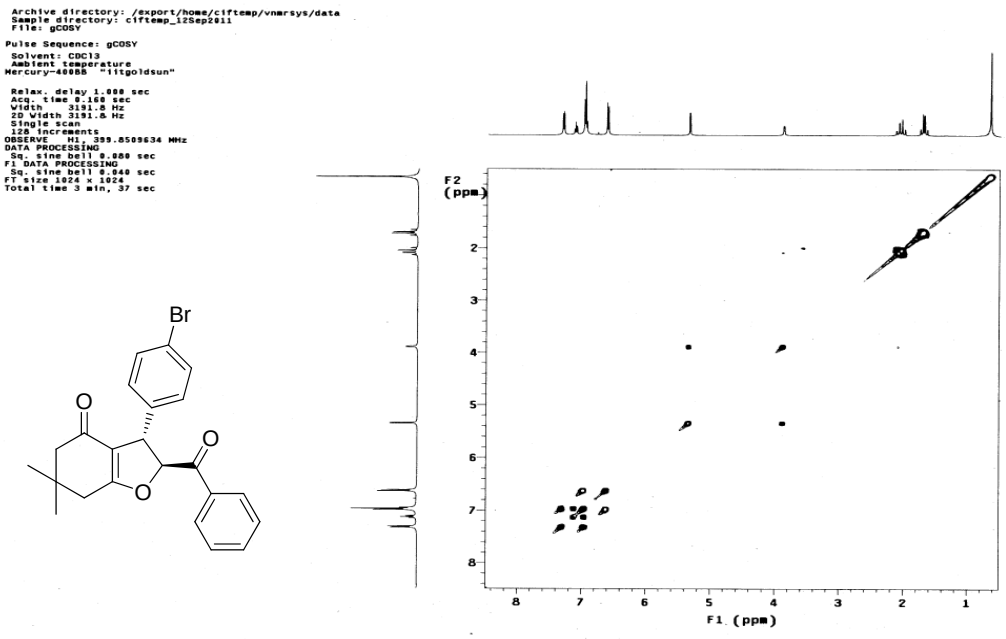
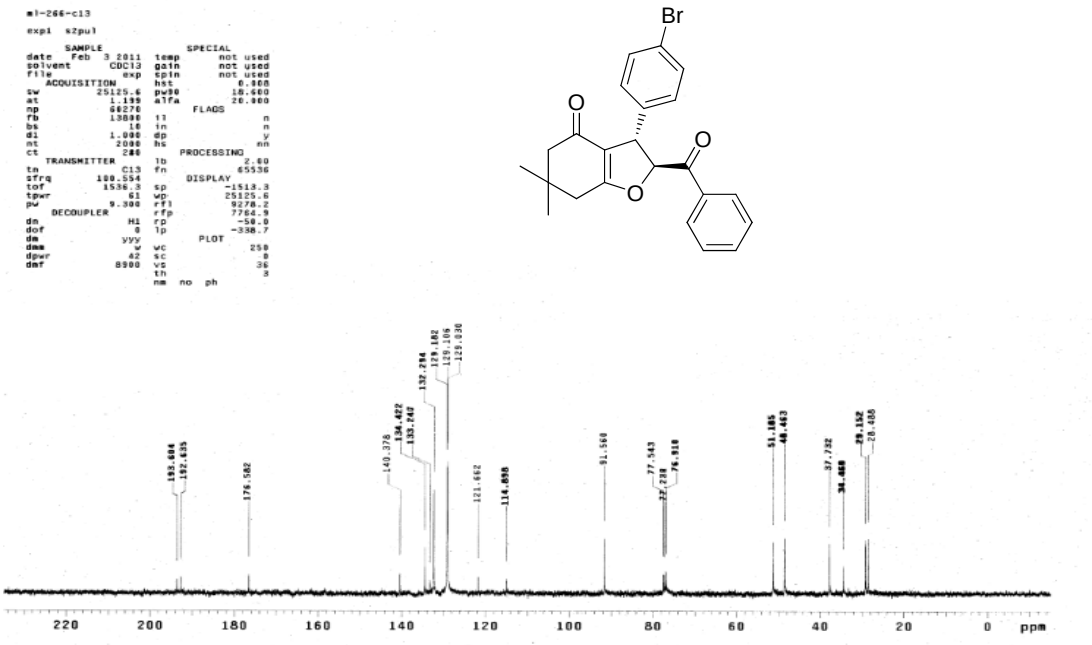


Figure 35.

^{13}C NMR (100 MHz, $CDCl_3$)**: 2-benzoyl-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(152e)



(HRMS)** 2-benzoyl-3-(4-bromophenyl)-6,6-dimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one **(152e)

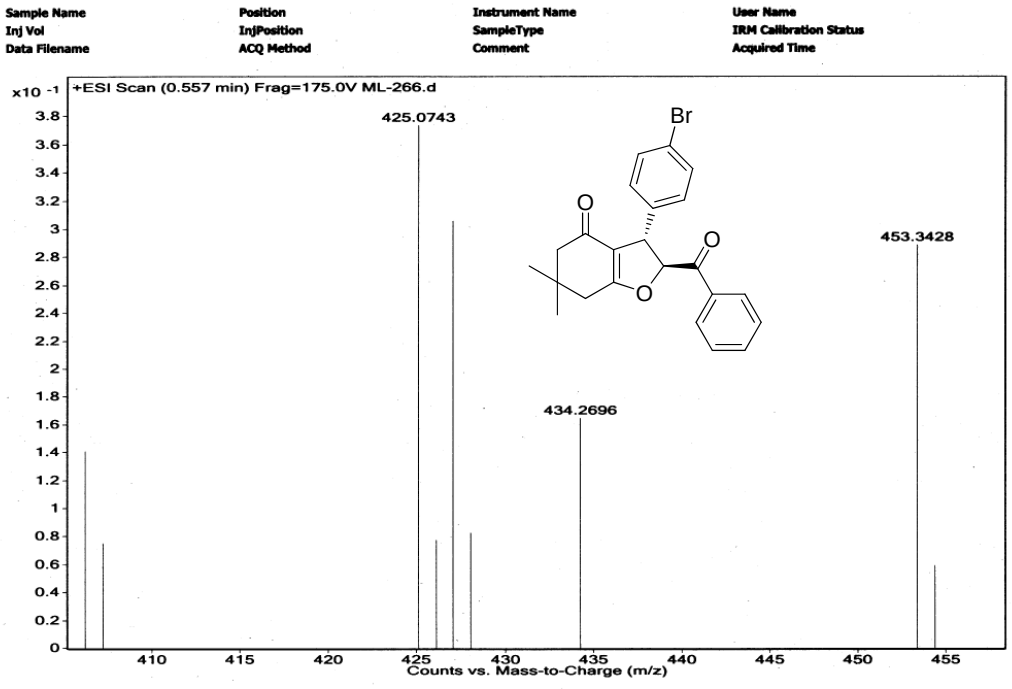
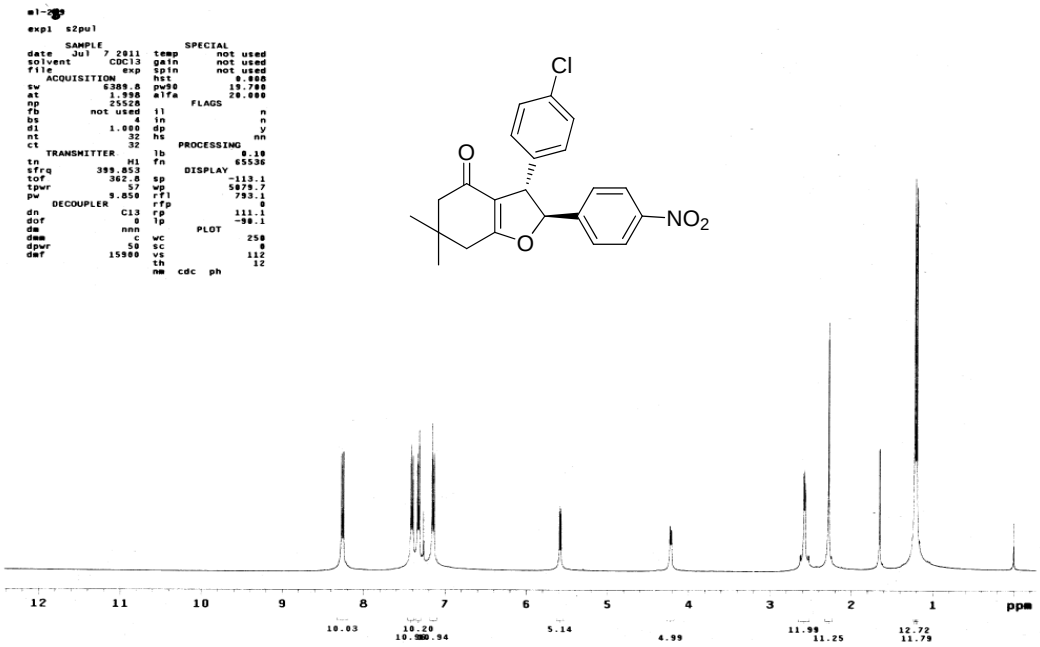


Figure 36.

^{1}H NMR (400 MHz, $CDCl_3$): *3-(4-chlorophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152h)***



^{13}C NMR (100 MHz, $CDCl_3$): *3-(4-chlorophenyl)-6,6-dimethyl-2-(4-nitrobenzoyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one* ***(152h)***

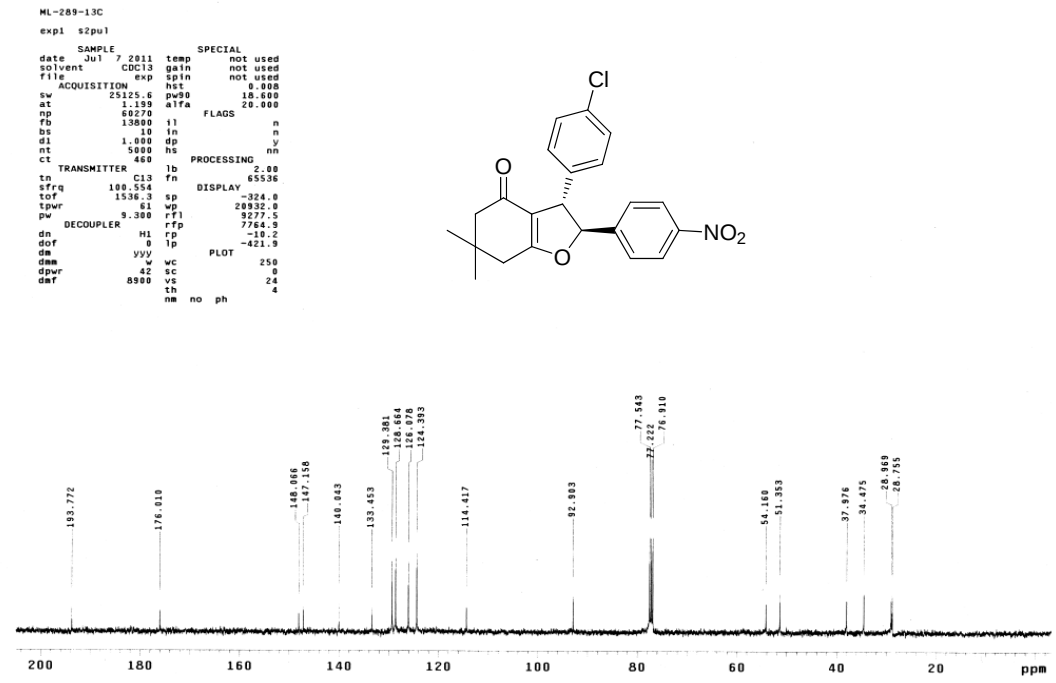
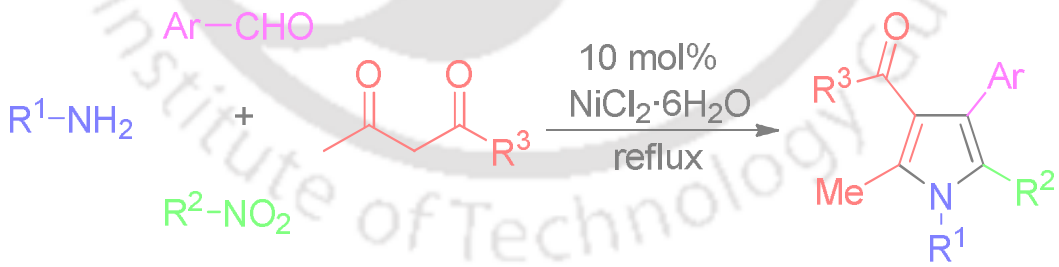


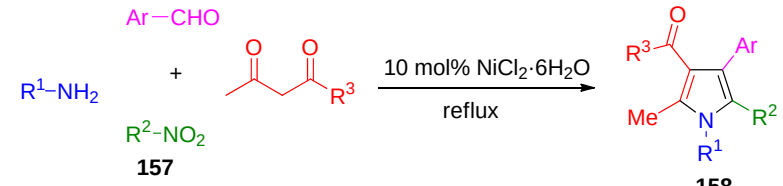
Figure 37.

Synthesis of *tetra*-substituted pyrroles by four-component coupling reaction in the presence of $NiCl_2 \cdot 6H_2O$



In the chapters II-V, we have already described successful synthesis of nitrogen- and oxygen containing heterocyles through MCRs using either β-ketoesters[100,114] or 1,3-dicarbonyl compounds.[126,143] Therefore, we interested further whether the same starting materials can be exploited for the synthesis of substituted pyrrole derivatives or not. Pyrrole and its derivatives are naturally occurring compounds and some of their synthetic strategies have been reviewed recently.[144] They also display a wide range of biological activities such as antibacterial, antiviral, anticonvulsant, anticancer and antioxidant.[145] Some of them are promising lead molecule for cholesterol lowering agent. In addition, they are also useful in building blocks which are extensively used in material science.[146] The synthesis of pyrroles and their derivatives are usually achieved by employing well-known Hantzsch[147] or Knorr[148] or Paal Knorr[149] reaction. Recently, *tetra* substituted pyrrole derivatives were reported by Jana *et al.* by employing four-component reaction catalyzed by $FeCl_3$[34] or palladium mediated Suzuki coupling based MCRs.[150] Recently, Menendez and his co-workers reviewed[151] the synthesis of pyrroles and their derivatives through multicomponent reactions.

Nickel salts are commonly used in coupling reaction.[152] A few years ago, we have shown that anhydrous $NiCl_2$ is a useful and effective Lewis acid catalyst for chemoselective thioacetalization of aldehydes[153a] and for deprotection of tetrahydropyranyl ether as well as *tert*-butyldimethylsilyl ether using a combination of catalytic amount of $NiCl_2{\cdot}6H_2O$ and 1,2-ethanthiol.[153b] Recently, other research groups have shown the efficacy of anhydrous $NiCl_2$ for multicomponent reactions.[154] We envisioned that nickel(II) chloride hexahydrate can be explored further as useful catalyst for the synthesis of highly substituted pyrroles. Herein, we wish to report a simple and useful synthetic protocol for the synthesis of *tetra*-substituted pyrroles by employing $NiCl_2{\cdot}6H_2O$ as a catalyst through one-pot four-component condensation reaction of aromatic aldehydes, benzylamines, β-ketoesters or 1,3-diketone and nitroalkanes as shown in Scheme 52.



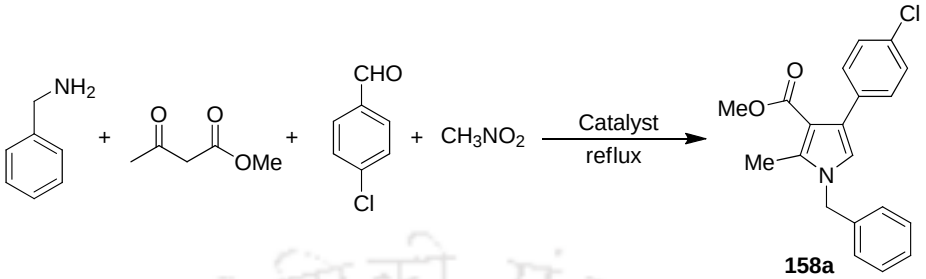
R^1 = Ph/ $PhCH_2$/ cyclohexyl/ furfuryl /chiral amines
R^2 = Me/ Et
R^3 = Me/ OMe/ OEt/ $OC(CH_3)_3$/ O-allyl

Scheme 52.

With this goal in mind, a mixture of methylacetoacetate (1 mmol) and benzylamine (1 mmol) and $NiCl_2{\cdot}6H_2O$ (0.1 mmol) in 1 mL of nitromethane in a 25 mL round bottomed flask was stirred at room temperature. After 10 minutes of stirring, the reaction mixture was solidified and then, 4-chlorobenzaldehyde was added into it. Finally, the reaction flask was kept for refluxing with constant stirring in a pre-heated oil-bath. After completion of the reaction checked by TLC, the reaction mixture was brought to room temperature and the excess nitromethane was removed in a rotary evaporator. After usual work-up procedure and purification through a column chromatography, the desired product **158a** was obtained in 78% yield. The desired product was characterized by recording IR, ^{1}H NMR, ^{13}C NMR spectra and elemental analysis. Appearance of a strong absorption peak at 1696 cm^{-1} in the IR spectrum indicates the presence of carbonyl group ester C=O and. In ^{1}H NMR spectrum, the characteristic signals at δ 2.47 (s, 3H, Me), 3.68 (s, 3H, OMe), 5.07 (s, 2H, C5-2H) and 6.57 (s, 1H, C6-H) as well as the peaks at δ 11.7 (Me), 50.7 (OMe), 110.9(C6), and 166.1 of C=O in the ^{13}C NMR spectrum confirmed the formation of tetrasubstituted pyrrole **158a**.

The efficacy of the other catalysts were also scrutinized by carrying out similar set of reactions in the presence of other catalysts such as $Fe_2(SO_4)_3$, $ZnCl_2$, $NiCl_2$ and $NiCl_2{\cdot}6H_2O$ under identical conditions and the results are summarized in Table 16. Among them, $NiCl_2{\cdot}6H_2O$ is found to be the most effective catalyst for the synthesis of *tetra*-substituted pyrrole derivatives. In the above transformation, nitroalkane plays a dual role namely of a solvent as well as a reactant.

Table 16 Optimization of reaction conditions for the synthesis of *tetra*-substituted pyrrole[a]



158a

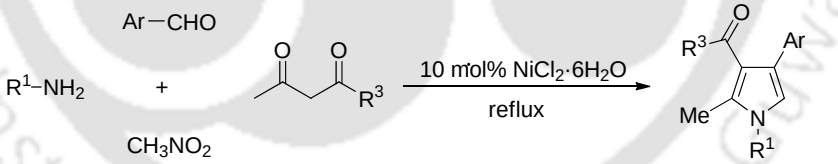
Entry	Catalyst	Catalytic amount (mol %)	Time (h)	% Yield[b]
1	$Fe_2(SO_4)_3$	10	12	40
2	$ZnCl_2$	10	12	45
3	$NiCl_2$	10	12	49
4	$NiCl_2.6H_2O$	5	13	60
5	$NiCl_2.6H_2O$	10	10	78
6	$NiCl_2.6H_2O$	15	10	77

[a]The reactions were performed using 1 mmol scale with benzylamine, methylacetoacetate and 4-chlorobenzaldehyde respectively in 1 mL of nitromethane under reflux conditions. [b]Isolated yield.

After optimization of the reaction conditions, the next reaction was carried out with a mixture of benzylamine, methylacetoacetate, benzaldehyde and nitromethane in presence of 10 mol% of $NiCl_2.6H_2O$ under identical reaction conditions and afforded the desired product **158b** in 72% yield (Table 17, entry 2). Encouraged by these successful result, the reactions were examined with various aromatic aldehydes containing substituents such as Me, MeO, NO_2, F, and Br in the aromatic ring with benzylamine and methylacetoacetate in the presence of same amount of catalyst under similar reaction conditions and the products (**158c-g**) were obtained in good yields (Table 17, entries 3-7). The same methodology was further extended with heteroaromatic aldehydes namely 2-formylthiophene and furan-2-carbaldehyde respectively and the desired products **158h** and **158i** (Table 17, entries 8 and 9) were isolated in 58% and 55% yield respectively. Further, the scope of the present protocol was elongated with other amines such as cyclohexylamine, 4-methylbenzylamine and furfurylamine with methylacetoacetate and 4-chlorobenzaldehyde. All these reactions went smoothly and also provided the products **158j-l** (Table 17, entries 10-12) in good yields under similar reaction conditions.

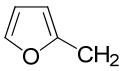
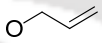
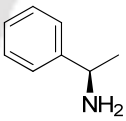
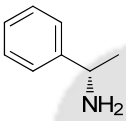
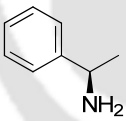
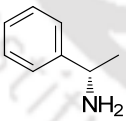
Similarly, the reactions were also verified with different β-ketoesters namely ethylacetoacetate, *tert*-butylacetoacetate, allylacetoacetate with benzylamine and 4-chlorobenzaldehyde respectively and the required products **158m-o** (Table 17, entries 13-15) were isolated in good yields. Finally, the reactions were also examined with acetylacetone, benzylamine and 4-chlorobenzaldehyde or 4-bromobenzaldehyde in a similar manner and the desired products **158p** and **158q** (Table 17, entries 16 and 17) were isolated in 56 % and 60 % yield respectively. It was observed that aniline also reacts with acetylacetone and benzaldehyde under identical conditions and the product **158r** was obtained in 52% yield (Table 17, entries 18). Further, the scope of reaction was also verified with chiral benzyl amines such as (*R*)-1-phenylethanamine or (*S*)-1-phenylethanamine under similar conditions and the preferred product **158s** and **158t** were isolated in 76% and 72% yield (Table 17, entry 19 and 20) respectively. Similarly, the reaction of chiral (*R*)-1-phenylethanamine, ethylacetoacetate and 4-fluorobenzaldehyde gave the product **158u** in 75 % yield (Table 17, entry 21). Similarly, an aldehyde containing electron-withdrawing group such as *o*-nitrobenzaldehyde also provides the product **158v** in 65 % yield (Table 17, entry 22) on reaction with (*S*)-1-phenylethanamine and ethylacetoacetate in a similar manner.

Table 17 Synthesis of *tetra*-substituted pyrrole derivatives from various aromatic aldehydes, β-ketoesters amines and nitroalkanes



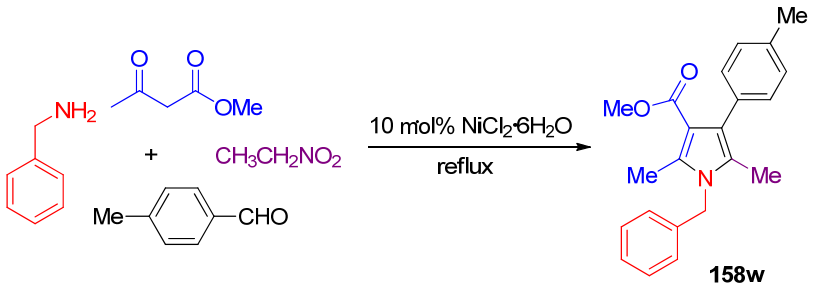
158

Entry	R_1	Ar	R^3	Time/h	Product[a]	%Yield[b]
1	$C_6H_5CH_2$	4-Cl- C_6H_4	OMe	8	**158a**	78
2	$C_6H_5CH_2$	C_6H_5	OMe	9	**158b**	72
3	$C_6H_5CH_2$	4-Me- C_6H_4	OMe	8	**158c**	75
4	$C_6H_5CH_2$	4-OMe- C_6H_4	OMe	8	**158d**	65
5	$C_6H_5CH_2$	4-NO_2- C_6H_4	OMe	9	**158e**	70
6	$C_6H_5CH_2$	4-F- C_6H_4	OMe	8	**158f**	76
7	$C_6H_5CH_2$	4-Br- C_6H_4	OMe	8	**158g**	73

8	$C_6H_5CH_2$	2-Thiophen	OMe	12	**158h**	58
9	$C_6H_5CH_2$	2-furan	OMe	11	**158i**	55
10	C_6H_{11}	4-Cl- C_6H_4	OMe	9	**158j**	74
11		4-Cl- C_6H_4	OMe	10	**158k**	72
12	4-$MeC_6H_4CH_2$	4-Cl- C_6H_4	OMe	9	**158l**	70
13	$C_6H_5CH_2$	4-Cl- C_6H_4	OEt	10	**158m**	78
14	$C_6H_5CH_2$	4-Cl- C_6H_4	$OC(CH_3)_3$	11	**158n**	76
15	$C_6H_5CH_2$	4-Cl- C_6H_4		12	**158o**	75
16	$C_6H_5CH_2$	4-Cl- C_6H_4	Me	8	**158p**	56
17	$C_6H_5CH_2$	4-Br-C_6H_4	Me	9	**158q**	60
18	C_6H_5	C_6H_5	Me	10	**158r**	52
19		4-Me- C_6H_4	OMe	6	**158s**	76
20		4-Me- C_6H_4	OMe	7	**158t**	72
21		4-F- C_6H_4	OEt	8	**158u**	75
22		2-NO_2-C_6H_4	OEt	10	**158v**	65

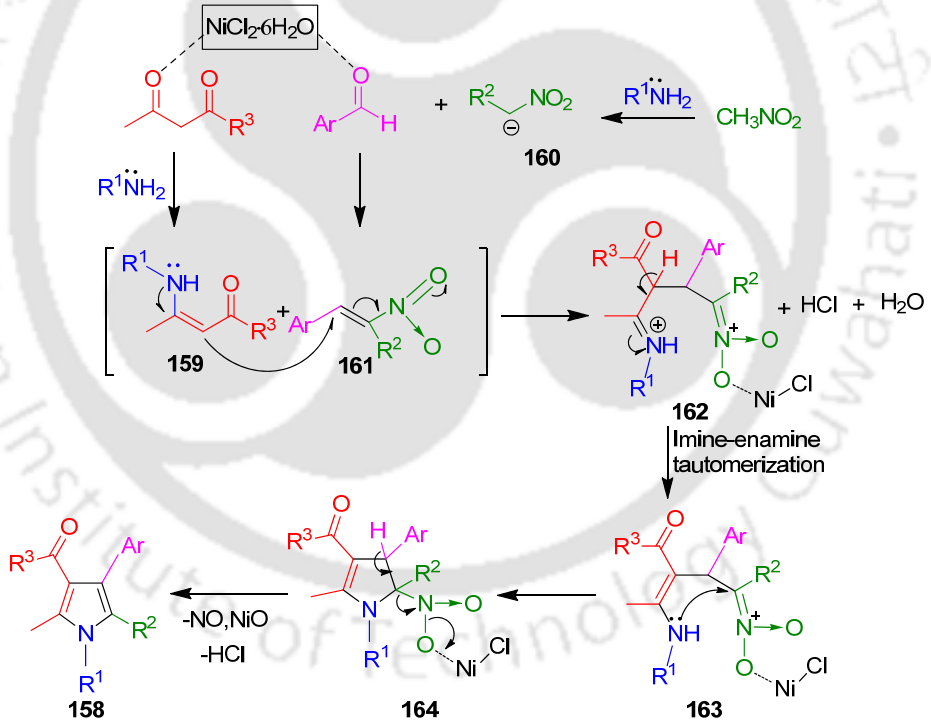
[a]The reactions were performed using 1 mmol of amines, 1 mmol of β-ketoesters or 1,3-diketone, and 1 mmol of aromatic aldehydes in 1mL nitromethane under reflux conditions. [b]Isolated yield.

The scope of the present protocol was further scrutinized with other nitroalkane namely nitroethane with benzylamine, methylacetoacetate and 4-methyl benzaldehyde and the product **158w** was obtained in 60% yield (Scheme 52). These successful results clearly indicate that the present protocol is also extendable to a wide variety of substrates. All the products were characterized from ^{1}H NMR, ^{13}CNMR spectra as well as from elemental analysis. The spectral data of compounds **158c**, **158d**, **158g, 158k and 158n** are given in Figure 40-44 in Experimental Section.



Scheme 53.

The formation of various *tetra*-substituted pyrroles can be rationalized as follows: Initially, amine reacts with β-ketoester to produce enamine **159** in the presence of Lewis acid $NiCl_2{\cdot}6H_2O$. We assume that nitroalkane reacts with benzylamine to generate carbanion **160** which reacts with the $NiCl_2{\cdot}6H_2O$ activated aromatic aldehyde to form nitrostyrene **161**,[155] as shown in Scheme 54.



Scheme 54. Plausible mechanism for the formation of substituted pyrrole derivatives

Subsequently, the enamine **159** reacts with nitrostyrene **161** to provide Michael adduct **162**. The intermediate **162** undergoes concomitant cyclization with the elimination of NiO, NO and HCl to provide the final product **158**, since the intermediate "enamine **159'** can react[35] as a 'di-nucleophile.' We have noted that pH of the reaction mixture is ~ 2-3

during reaction time, which indicates the generation of HCl in the medium. To prove the mechanism, we have carried out an experiment with a mixture of β-ketoester, benzylamine, aromatic aldehyde and nitromethane in presence of 10 mol % NiO. We have obtained tetrasubstituted pyrrole derivative **158b** in 70% yield. From this observation we may believe that generated NiO coming out from the reaction is further participating in the catalytic cycle for the formation of the product However, the detailed mechanism is under investigation which will be disclosed in full article.

In addition, the structure of compound **158k** was further confirmed by single XRD crystallographic data and the ORTEP diagram of substituted pyrrole **158k** is shown in Figure 38.

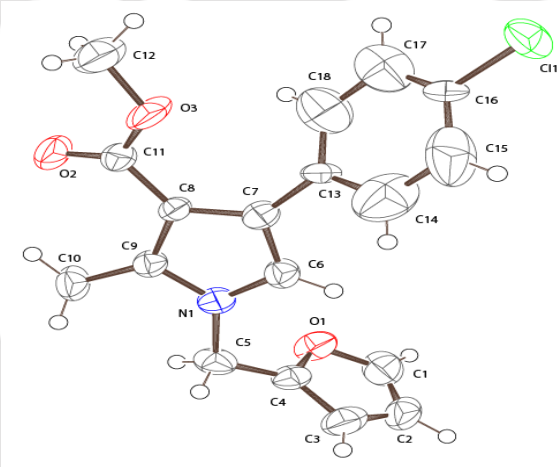


Figure 38. ORTEP diagram of compound of **158k** (CCDC 848584)

In order to support the mechanism, the product NiO which is coming out from $NiCl_2$ was characterized through x-ray diffraction (XRD) analysis. A representative XRD pattern of the product NiO is shown in Figure 39.

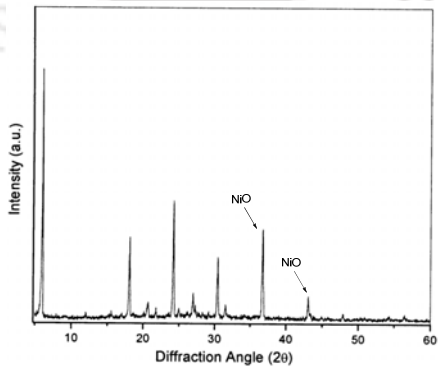
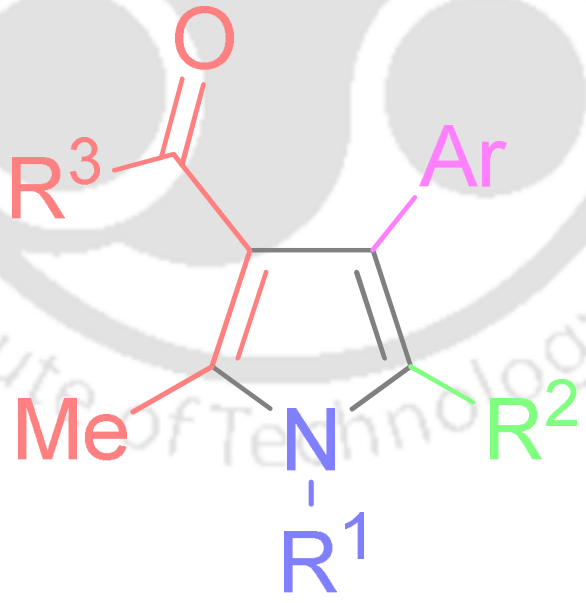


Figure 39. XRD pattern

It is noted that major XRD peaks for the NiO lie in the diffraction angle (θ range of 20°- 50°) in x-ray diffractogram. The sharp crystalline peaks appearing at 2θ ~36.18° and 43.2° may be attributed to [1 1 1] and [2 0 0] reflections of NiO.[156a] On the other hand, additional peaks have also been noted distinctly at 2θ ~20.67°, 24.24°, 24.95° and 30.46° with progressively diminishing intensity. These peaks may be related to Ni and or NiO based complex(es) present in traces in the compounds. The presence of $NiCl_2$ in the compounds could not be noticed because the finger print XRD peaks of $NiCl_2$ (expected at 2θ ~15°) is absent in the XRD.[156b] To be more conclusive for proving the mechanism, an effort is undergoing to isolate the "by product" of the reaction under study.

In this chapter, we have successfully demonstrated four-component reaction for the synthesis of *tetra*-substituted pyrroles starting from amines, β-ketoesters or 1,3-dicarbonyl compounds, aromatic aldehydes or heteroaromatic aldehydes and nitroalkanes using $NiCl_2{\cdot}6H_2O$ as catalyst in moderate to good yields. The reaction proceeds through the formation of enamine and nitrostyrene followed by Michael addition and subsequently, it undergoes intramolecular cyclization to afford pyrroles derivatives.

Synthesis of *tetra*-substituted pyrroles by four-component coupling reaction in the presence of $NiCl_2 \cdot 6H_2O$

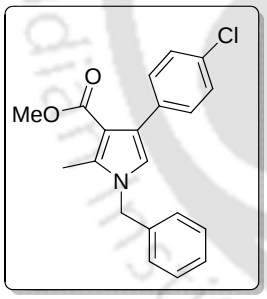


Experimental Section

*General procedure for the synthesis of tetra-substituted pyrroles derivatives **158**:*

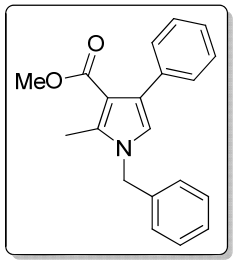
To a mixture of an amine (1 mmol) and β-ketoester (1 mmol) in nitromethane (1 mL) was added with 10 mol% $NiCl_2{\cdot}6H_2O$ and kept for stirring at room temperature. The solid precipitate appeared after 10 minutes and then aromatic aldehyde (1 mmol) was added into it. Subsequently, the reaction mixture was kept for refluxing in a heated oil-bath with constant stirring. After completion of the reaction as monitored by TLC, the reaction mixture was brought to room temperature and the excess nitromethane was removed in a rotary evaporator. Then, the crude residue was dissolved in 25 mL of dichloromethane and the solid particle was removed by filtration. The precipitate was further washed with 2 mL of dichloromethane. The filtrate was washed with water and dried over anhydrous sodium sulfate. The organic extract was concentrated and the crude residue was finally purified through a silica gel column chromatography. The final product was obtained by eluting with ethyl acetate and hexane mixture (5:95).

Methyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158a**)



Oily liquid, (0.265 g 78%), **IR** (KBr): 3030, 2948, 2845, 1696, 1520, 1435, 1282, 1212, 1203, 1185, 1142, 1060 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.68 (s, 3H), 5.07 (s, 2H), 6.57 (s, 1H), 7. 06 (d, J = 6.8 Hz, 2H), 7.29 (brs, 4H), 7.37-7.31 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 50.7, 110.9, 120.8, 125.2, 126.6, 127.9, 128.0, 129.1, 130. 6, 132.3, 134. 5, 136.7, 136.9, 166.1**. Anal. Calcd** for $C_{20}H_{18}ClNO_2$ (339.81) C, 70.69; H, 5.34; N, 4.12; found C, 70.59; H, 5.28; N, 4.06.

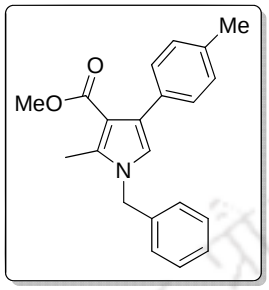
Methyl 1-benzyl-2-methyl-4-phenyl-1H-pyrrole-3-carboxylate (**158b**)



Oily liquid, (0.220 g 72%), **IR** (KBr): 3030, 2926, 1698, 1604, 1525, 1496, 1451, 1435, 1410, 1284, 1204, 1185, 1144, 1124, 1066, 1028 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.67 (s, 3H), 5.07 (s, 2H), 6.59 (s, 1H), 7.07 (d, J = 7.6 Hz, 2H), 7.26-7.23 (m, 2H), 7.32 (t, J = 7.2 Hz, 4H), 7.38-7.36 (m 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.0, 50.7, 110.9, 120.8, 126.3, 126.7, 127.8, 127.9, 129.1, 129.3, 135.9,

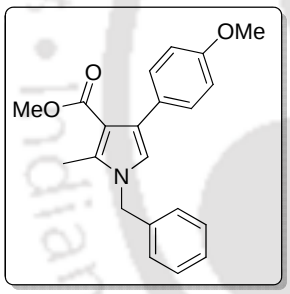
136.7, 136.9, 166.5. **Anal. calcd** for $C_{20}H_{19}NO_2$ (305.37) C, 78.66; H, 6.27; N, 4.59; found C, 78.59; H, 6.19; N, 4.48.

Methyl 1-benzyl-2-methyl-4-p-tolyl-1H-pyrrole-3-carboxylate (**158c**)



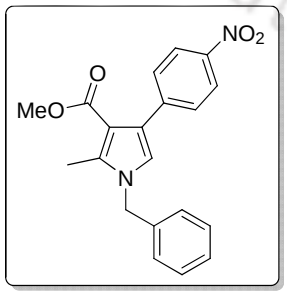
Oily liquid, (0.240 g 75%), **IR** (KBr): 3028, 2926, 1698, 1526, 1437, 1283, 1203, 1188, 1143, 1065 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.46 (s, 3H), 3.68 (s, 3H), 5.06 (s, 2H), 6.56 (s, 1H), 7.06 (d, J = 6.8 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.27(d, J = 8.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 21.3, 29.50, 50.7, 110.9, 120.6, 126.3, 126.7, 127.9, 128.5, 129.0, 129.1, 132.9, 135.8, 136.5, 136.9, 166.5. **Anal. calcd** for $C_{21}H_{21}NO_2$ (319.39) C, 78.97; H, 6.63; N, 4.39; found C, 78.88; H, 6.54; N, 4.31.

Methyl 1-benzyl-4-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158d**)



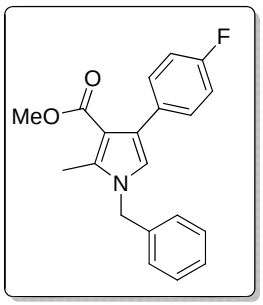
Oily liquid, (0.218 g 65%), **IR** (KBr): 2946, 2835, 1696, 1606, 1523, 1438, 1288, 1245, 1204, 1179, 1143, 1066, 1033 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.68 (s, 3H), 3.82 (s, 3H), 5.06 (s, 2H), 6.55 (s, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.06 (d, J = 7.6 Hz, 2H), 7.35-7.28 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 50.6, 55.4, 110.8, 113.2, 120.4, 125.9, 126.6, 127.9,128.4, 129.0, 130.3, 136.5, 136.9, 158.3, 166.5. **Anal. calcd** for $C_{21}H_{21}NO_3$ (335.39) C, 75.20; H, 6.31; N, 4.18; found C, 75.11; H, 6.22; N, 4.12.

Methyl 1-benzyl-2-methyl-4-(4-nitrophenyl)-1H-pyrrole-3-carboxylate (**158e**)



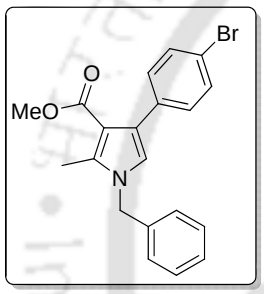
Oily liquid, (0.245 g 70%), **IR**(KBr): 2928, 2340, 1705, 1508, 1437, 1342, 1294, 1176, 1141, 1050 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 3.70 (s, 3H), 5.09 (s, 2H), 6.69 (s, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.38-7.29 (m, 3H), 7.51 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 29.8, 50.8, 110.8, 121.6, 123.1, 124.3, 126.6, 128.2, 129.2, 129.6, 136.3, 137.7, 143.1, 146.2, 165.8. **Anal. calcd** for $C_{20}H_{18}N_2O_4$ (350.36) C, 68.56; H, 5.18; N, 8.00; found C, 68.48; H, 5.10; N, 7.91.

Methyl 1-benzyl-4-(4-fluorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158f**)



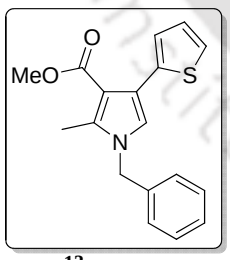
Yellow solid, (0.245 g 76%); M.p. 75°C; **IR** (KBr): 3027, 2946, 2846, 1698, 1523, 1438, 1284, 1215, 1204, 1187, 1143, 1061 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.48 (s, 3H), 3.68 (s, 3H), 5.06 (s, 2H), 6.56 (s, 1H), 7.02 (t, J = 8.8 Hz, 2H), 7.07 (d, J = 6.8 Hz, 2H), 7.28-7.35 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.8, 50.7, 110.9, 114.5, 114.7, 120.7, 125.5, 126.7, 128.4, 129.1, 130.8, 130.9, 132.0, 136.8, 166.3. **Anal. calcd** for $C_{20}H_{18}FNO_2$ (323.36) C, 74.29; H, 5.61; N, 4.33; found C, 74.11; H, 5.55; N, 4.26.

Methyl 1-benzyl-4-(4-bromophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158g**)



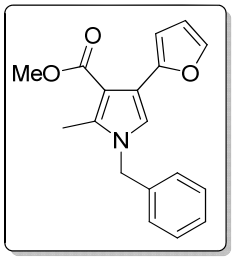
Oily liquid, (0.280 g 73%), **IR**(KBr): 3035, 2985, 2930, 1696, 1530, 1485, 1428, 1385, 1285, 1206, 1185 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.67 (s, 3H), 5.06 (s, 2H), 6.57 (s, 1H), 7.06 (d, J = 6.8Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 6.8 Hz, 1H), 7.34 (t, J = 6.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 50.7, 110.8, 120.3, 120.7, 125.2, 126.7, 128.2. 129.1. 130.8, 130.9, 134.9, 136.7, 137.1, 166.2. **Anal. calcd** for $C_{20}H_{18}BrNO_2$ (384.26) C, 62.51; H, 4.72; N, 3.65; found C, 62.45; H, 4.66; N, 3.56.

Methyl 1-benzyl-2-methyl-4-(thiophen-2-yl)-1H-pyrrole-3-carboxylate (**158h**)



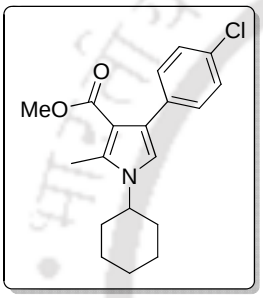
Oily liquid, (180 g 58%); **IR** (KBr): 2925, 2851, 1698, 1528, 1497, 1438, 1410, 1371, 1266, 1186, 1124, 1105, 1075 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 3.67 (s, 3H), 4.96 (s, 2H), 6.64 (s, 1H), 6.92 (dd, J = 3.2, 5.2 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 7.06 (dd, J = 1.2, 3.6 Hz, 1H), 7.11 (d, J = 5.2 Hz, 1H), 7.16-7.27 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.8, 29.9, 50.8, 111.1, 118.6, 121.5, 123.9, 125.9, 126.7, 126.9, 128.1, 129.1, 136.6, 137.1, 137.3, 166.1. **Anal. calcd** for $C_{18}H_{17}NO_2S$ (311.39) C, 69.43; H, 5.50; N, 4.50found C, 69.36; H, 5.41; N, 4.42.

Methyl 1-benzyl-4-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (**158i**)



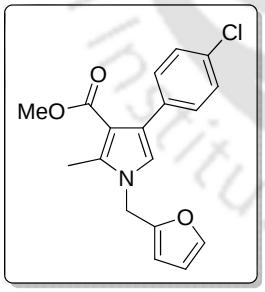
Oily liquid, (162 g 55%), **IR** (KBr): 2925, 2853, 1701, 1604, 1523, 1492, 1439, 1364, 1280, 1207, 1189, 1130, 1078 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 3.75 (s, 3H), 4.99 (s, 2H), 6.34 (dd, J = 2.0, 3.2 Hz, 1H), 6.66 (dd, J = 0.8, 3.2 Hz, 1H), 6.87 (s, 1H), 6.98 (d, J = 6.8 Hz, 2H), 7.17-7.31(m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.9, 29.9, 50.9, 107.2, 109.8, 111.3, 115.9, 120.7, 126.6, 127.8, 128.0, 129.1, 136.7, 136. 9, 140. 5, 149.7, 165.9**. Anal. calcd** for $C_{18}H_{17}NO_3$ (295.33) C, 73.20; H, 5.80; N, 4.74; found C, 73.09; H, 5.71; N, 4.65.

Methyl 4-(4-chlorophenyl)-1-cyclohexyl-2-methyl-1H-pyrrole-3-carboxylate (**158j**)

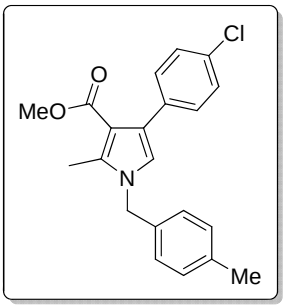


Oily liquid, (0.245 g 74%), **IR** (KBr): 2930, 2855, 1698, 1522, 1436, 1412, 1277, 1200, 1155, 1133, 1083 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31-1.40 (m, 2H), 1.48-1.58 (m, 4H), 1.69 (d, J = 13.2 Hz, 2H), 1.77 (d, J = 13.6 Hz, 2H), 1.94 (d, J = 12 Hz, 1H), 2.47 (s, 3H), 3.58 (s, 3H), 6.54 (s, 1H), 7.20 (brs, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.4, 25.5, 26.0, 29.9, 34.1, 50.6, 55.5, 109.9, 116.3, 124.9, 127.8, 130.5, 131.9, 135.0, 136.0, 166.5. **Anal. calcd** for $C_{19}H_{22}ClNO_2$ (331.83) C, 68.77; H, 6.68; N, 4.22; found C, 68.68; H, 6.59; N, 4.13.

Methyl 4-(4-chlorophenyl)-1-(furan-2-ylmethyl)-2-methyl-1H-pyrrole-3-carbocxylate (**158k**)



Pale yellow solid, (0.237 g 72%), M.p. 98°C, **IR** (KBr): 2925, 2854, 1698, 1527, 1488, 1438, 1415, 1283, 1193, 1147, 1089, 1070, 1014 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.59 (s, 3H), 4.91 (s, 2H), 6.17 (dd, J = 0.8, 7.2 Hz, 1H), 6.26 (dd, 1.6, 3.2 Hz, 1H), 6.49 (s, 1H), 7.19 (brs, 4H), 7.66 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.6, 29.9, 43.7, 50.7, 108.7, 110.7, 120.2, 125.2, 127.8, 130.6, 132.1, 134.4, 136.7, 143.1, 149.6, 166.1. **Anal. calcd** for $C_{18}H_{16}ClNO_3$ (329.77) C, 65.56; H, 4.89; N, 4.25; found C, 65.48; H, 4.78; N, 4.18.

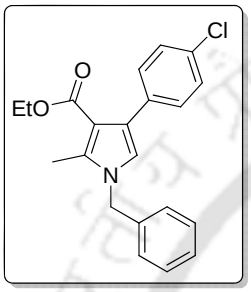


Methyl 1-(4-methylbenzyl)-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate(**158l**)

Oily liquid, (0.247 g 70 %), **IR** (KBr): 2925, 2851, 1703, 1518, 1486, 1437, 1415, 1282, 1198, 1188, 1143, 1089, 1014

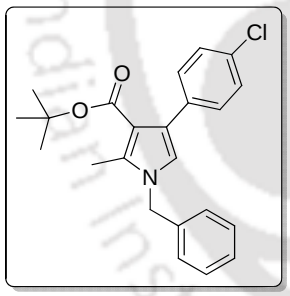
cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.67 (s, 3H), 2.80 (s, 3H), 4.01 (s, 3H), 5.34 (s, 2H), 6.88 (s, 1H), 7.29 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 7.2 Hz, 2H), 7.62 (brs, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 21.2, 22.9, 29.9, 50.0, 110.7, 120.7, 125.2, 126.8, 127.9, 129.8, 130.6, 132.1, 133.7, 134.6, 136.9, 137.8, 166.3. **Anal. calcd** for $C_{21}H_{20}ClNO_2$ (353.84) C, 71.28; H, 5.70; N, 3.96; found C, 71.21; H, 5.61; N, 3.88.

Ethyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158m**)



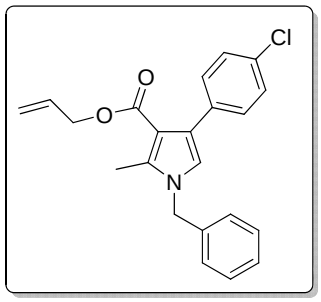
Oily liquid, (275 g 78%), **IR** (KBr): 3031, 2979, 2928, 1694, 1525, 1489, 1422, 1382, 1280, 1203, 1183, 1144, 1089, 1015 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 3H), 2.46 (s, 3H), 4.15 (q, J = 7.2 Hz, 2H), 5.04 (s, 2H), 6.55 (s, 1H), 7.05 (d, J = 7.2 Hz, 2H), 7.25-7.35 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$):δ 11.7, 14.3, 50.7, 59.6, 111.1, 120.7, 125.2, 126.7, 127.8, 128.0, 129.1, 130.8, 132.1, 134.6, 136.8, 136.9, 165.8. **Anal. calcd** for $C_{21}H_{20}ClNO_2$ (353.84) C, 71.28; H, 5.70; N, 3.96; found C, 71.21; H, 5.58; N, 3.87.

Tert-butyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158n**)



Oily liquid, (290 g 76%), **IR**(KBr): 2976, 2929, 1690, 1525, 1488, 1454, 1421, 1391, 1365, 1289, 1173, 1142, 1089, 1015 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37 (s, 9H), 2.44 (s, 3H), 5.03 (s, 2H), 6.53 (s, 1H), 7.07 (d, J = 7.2 Hz, 2H), 7.28 (brs, 4H), 7.29-7.35 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.6, 28.4, 50.7, 79.9, 109.9, 112.7, 120.3, 125.1, 126.8, 127.8, 128.0, 129.1, 130.8, 131.9, 134.9, 136.9, 165.2. **Anal. calcd** for $C_{23}H_{24}ClNO_2$ (381.89) C, 72.34; H, 6.33; N, 3.67; found C, 72.26; H, 6.27; N, 3.58.

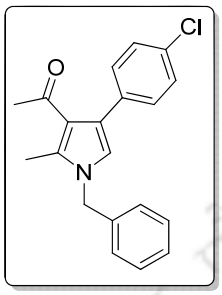
Allyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158o**)



Oily liquid, (0.274 g 75%), **IR** (KBr) ν_{max} 3027, 2932, 1697, 1524, 1486, 1451, 1420, 1277, 1203, 1182, 1143, 1091, 1056, cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 4.61 (d, J = 4.8 Hz, 2H), 5.03 (s, 2H), 5.11 (d, J = 11.6 Hz, 2H), 5.78-5.88 (m, 1H), 6.55 (s, 1H), 7.05 (d, J = 7.6 Hz, 2H), 7.24-7.34 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.8, 50.7, 64.5, 110.8, 117.7, 120.8, 125.3, 126.7, 127.8, 128.0, 129.1, 130.7, 132.1,

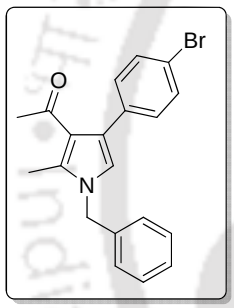
132.7, 134.5, 136.7, 137.1, 165.4. **Anal. calcd** for $C_{22}H_{20}ClNO_2$ (365.85) C, 72.22; H, 5.51; N, 3.83; found C, 72.13; H, 5.42; N, 3.76.

1-(1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrol-3-yl)ethanone (**158p**)



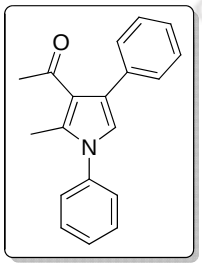
Oily liquid, (0.181 g 56%), **IR**(KBr): 3048, 3035, 1665, 1504, 1408, 1212, 1203 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.44 (s, 3H), 5.06 (s, 2H), 6.54 (s, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.29-7.37 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.7, 31.2, 50.4, 110.0 120.3, 122.2, 126.0, 126.8, 127.9, 128.3, 129.0, 129.5, 135.2, 136.4, 136.7, 197.6. **Anal. calcd** for $C_{20}H_{18}ClNO$ (323.82) C, 74.18; H, 5.60; N, 4.33; found C, 74.11; H, 5.48; N, 4.24.

1-(1-benzyl-4-(4-bromophenyl)-2-methyl-1H-pyrrol-3-yl)ethanone (**158q**)



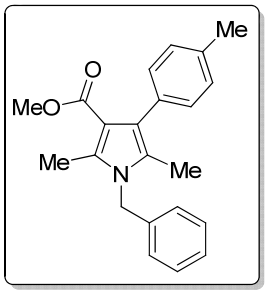
Oily liquid, (0.220 g 60%), **IR** (KBr):3045, 3030, 1668, 1506, 1410, 1215, 1205 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.42 (s, 3H), 5.05 (s, 2H), 6.53 (s, 1H), 7.07 (d, J = 6.8 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.8, 31.3, 50.5, 120.4, 120.9, 122.1, 124.8, 125.6, 126.8, 128.0, 129.1, 129.5, 131.0, 131.5, 135.4, 135.6, 136.5, 197.4. **Anal. calcd** for $C_{20}H_{18}BrNO$ (368.27) C, 65.23; H, 4.93; N, 3.80; found C, 65.16; H, 4.86; N, 3.76.

1-(2-methyl-1,4-diphenyl-1H-pyrrol-3-yl)ethanone (**158r**)



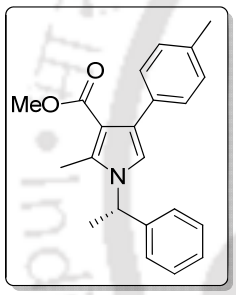
Oily liquid, (143 g 52%), **IR** (KBr): 3055, 3025, 1648, 1506, 1406, 1220 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.39 (s, 3H), 6.66 (s, 1H), 7.29-7.37 (m, 7H), 7.42-7.45 (m, 1H), 7.48-7.52 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.1, 31.3, 120.9, 122.6, 125.2, 126.4, 128.4, 128.6, 129.6, 130.7, 132.9, 134.7, 135.7, 138.8, 197.4. **Anal. calcd** for $C_{19}H_{17}NO$ (275.34) C, 82.88; H, 6.22; N, 5.09; found C, 82.78; H, 6.13; N, 4.98.

(R)-methyl 2-methyl-1-(1-phenylethyl)-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**158s**)



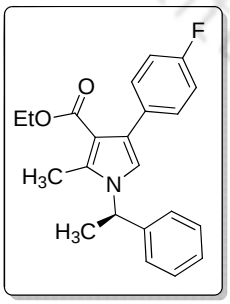
Oily liquid, (253 g 76%); $[\alpha]_D^{25} = -58.8$ (*c* 1.5, $CHCl_3$); **IR** (KBr): 2990, 2984, 2851, 1701, 1527, 1437, 1412, 1277, 1214, 1189, 1149, 1118, 1079, 1027 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.74 (d, *J* = 7.2 Hz, 3H), 2.28 (s, 3H), 2.36 (s, 3H), 3.58 (s, 3H), 5.27 (q, *J* = 6.8 Hz, 1H), 6.63 (brs, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 7.06 (d, *J* =8.0 Hz, 2H), 7.16-7.25 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.5, 21.2, 22.2, 50.5, 55.2, 110.7, 116.9, 125.9, 127.6, 128.5, 128.9, 129.0, 133.2, 135.6, 136.5, 142.2, 166.5. **Anal calcd** for $C_{22}H_{23}NO_2$ (333.42) C, 79.25; H, 6.95; N, 4.20; found C, 79.05; H, 6.82; N, 4.05.

(S)-methyl 2-methyl-1-(1-phenylethyl)-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**158t**)



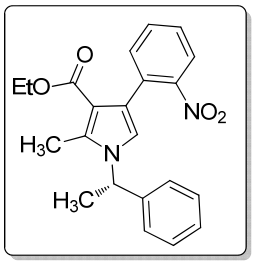
Oily liquid, (240 g 72%); $[\alpha]_D^{25} = +58.1$ (*c* 1.5, $CHCl_3$); **IR** (KBr): 2986, 2982, 2850, 1700, 1525, 1435, 1409, 1276, 1212, 1185, 1115, 1075, 1024 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.80 (d, *J* = 7.2 Hz, 3H), 2.35 (s, 3H), 2.43 (s, 3H), 3.66 (s, 3H), 5.36 (q, *J* = 6.8 Hz, 1H), 6.71 (brs, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.23-7.32 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.8, 21.5, 22.5, 50.8, 55.4, 11.9, 117.1, 126.1, 127.9, 128.7, 129.2, 129.3, 133.4, 135.9, 136.7, 142.5, 166.8. **Anal calcd** for $C_{22}H_{23}NO_2$ (333.42) C, 79.25; H, 6.95; N, 4.20; found C, 79.10; H, 6.84; N, 4.08.

(R)-ethyl4-(4-fluorophenyl)-2-methyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate(**158u**)



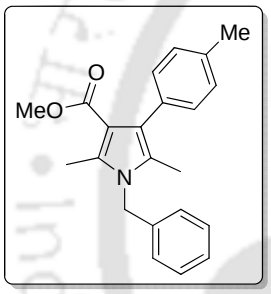
Oily liquid, (263 g 75%); $[\alpha]_D^{25} = -30.0$ (*c* 1.0, $CHCl_3$); **IR**(KBr): 2930, 2926, 2920, 1694, 1525, 1499, 1422, 1276, 1214, 1186, 1155, 1116, 1030, 1010 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.70 (d, *J* = 6.8 Hz, 3H), 2.35 (s, 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 5.25 (q, *J* = 7.2 Hz, 1H), 6.59 (brs, 1H), 6.91 (d, *J* = 8.8 Hz, 2H0, 6.97 (d, *J* = 7.6 Hz, 2H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.19-7.25 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.6, 14.2, 22.2, 55.2, 59.5, 111.0, 114.2, 114.5, 116.9, 125.1, 125.9, 127.7, 128.9, 130.8, 130.9, 136.6, 142.2, 165.9. **Anal calcd** for $C_{22}H_{22}FNO_2$ (351.41) C, 75.19; H, 6.31; N, 3.99; found C, 75.05; H, 6.19; N, 3.84.

(S)-ethyl 2-methyl-4-(2-nitrophenyl)-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**158v**)



Oily liquid, (0.245 g 65%); $[\alpha]_D^{25} = +32.1$ (*c* 1.5, $CHCl_3$); **IR** (KBr): 2988, 2934, 2886, 1685, 1536, 1455, 1405, 1275, 1220, 1195, 1155, 1085, 1045 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 6.8 Hz, 3H), 1.84 (d, *J* = 7.2 Hz, 3H), 2.44 (s, 3H), 4.00(q, *J* = 7.2 Hz, 2H), 5.40(q, *J* = 7.2 Hz, 1H), 6.76 (brs, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.28-7.37 (m, 5H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.5, 13.8, 22.3, 55.3, 59.4, 111.1, 116.9, 121.5, 123.8, 125.7, 127.4, 127.7, 129.0, 132.0, 132.1, 133.0, 137.2, 142.3, 149.9, 165.2. **Anal. calcd** for $C_{22}H_{22}N_2O_4$ (378.42) C, 69.83; H, 5.86; N, 7.40; found C, 69.72; H, 5.68; N, 7.28.

Methyl 1-benzyl-2,5-dimethyl-4-(p-tolyl)-1H-pyrrole-3-carboxylate (**158w**)



Yellow solid, (200 g 60%); M.p. 95°C; **IR** (KBr): 3055, 3025, 1648, 1506, 1406, 1220 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.04 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 3.61 (s, 3H), 5.11 (s, 2H), 6.95 (d, *J* = 6.8 Hz, 2H), 7.26 (d, *J* = 3.6 Hz, 2H), 7.31-7.35 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 10.4, 11.7, 21.3, 47.1, 50.4, 110.5, 122.6, 125.6, 126.2, 127.4, 128.9, 130.4, 133.4, 135.0, 135.3, 137.0, 166.4. **Anal. calcd** for $C_{22}H_{23}NO_2$ (333.42) C, 79.25; H, 6.95; N, 4.20; found C, 79.15; H, 6.78; N, 4.06.

*XRD for compound **158k***

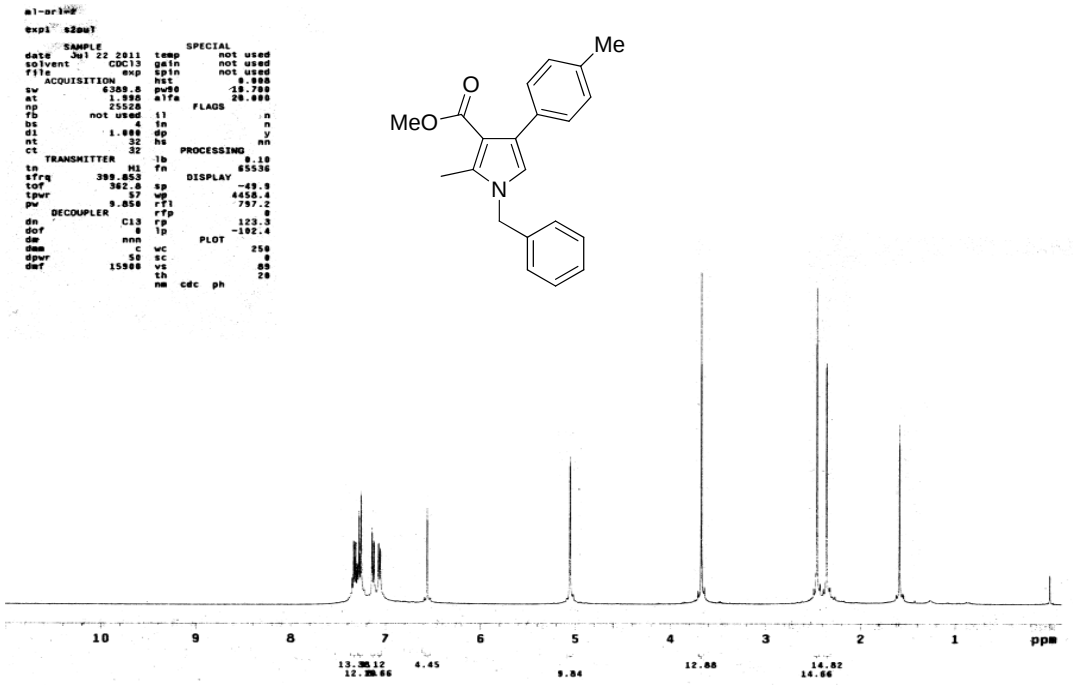
Complete crystallographic data of compound **158k** for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No.: 848584. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 18 Crystal data and structures refinement for the compounds **158k**, for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 158k**
Formula	$C_{18}H_{16}ClNO_3$
CCDC number	848584

Formula weight	329.77
T (K)	296 K
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
a (Å)	10.0966(19)Å
b (Å)	10.810(2)Å
c (Å)	15.854(3)Å
α (°)	93.481(16)º
β (°)	92.412(14)º
γ (°)	108.649(14)º
V (Å^3)	1633.0(5) Å^3
Z	4
D_{calcd} (g m^{-3})	1.341/cm^3
μ (mm^{-1})	0.248 mm^{-1}
F(0 0 0)	688.0
Reflection collected	7319
Unique reflections	2368
Goodness-of-fit (GOF)[a] on F^2	1.307
R [$I > 2\sigma(I)$]	[b]R_1 = 0.2540, [c]wR_2 = 0.4654
R indices (all data)	[b]R_1 = 0.1645, [c]wR_2 = 0.4033

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 1-benzyl-2-methyl-4-p-tolyl-1H-pyrrole-3-carboxylate* ***(158c)***



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 1-benzyl-2-methyl-4-p-tolyl-1H-pyrrole-3-carboxylate* ***(158c)***

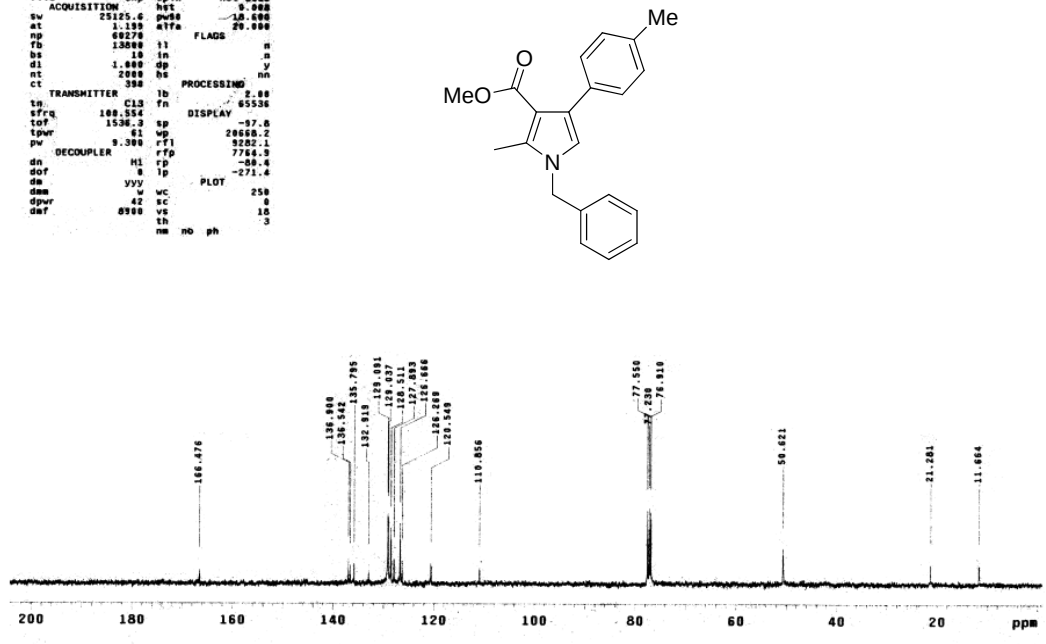
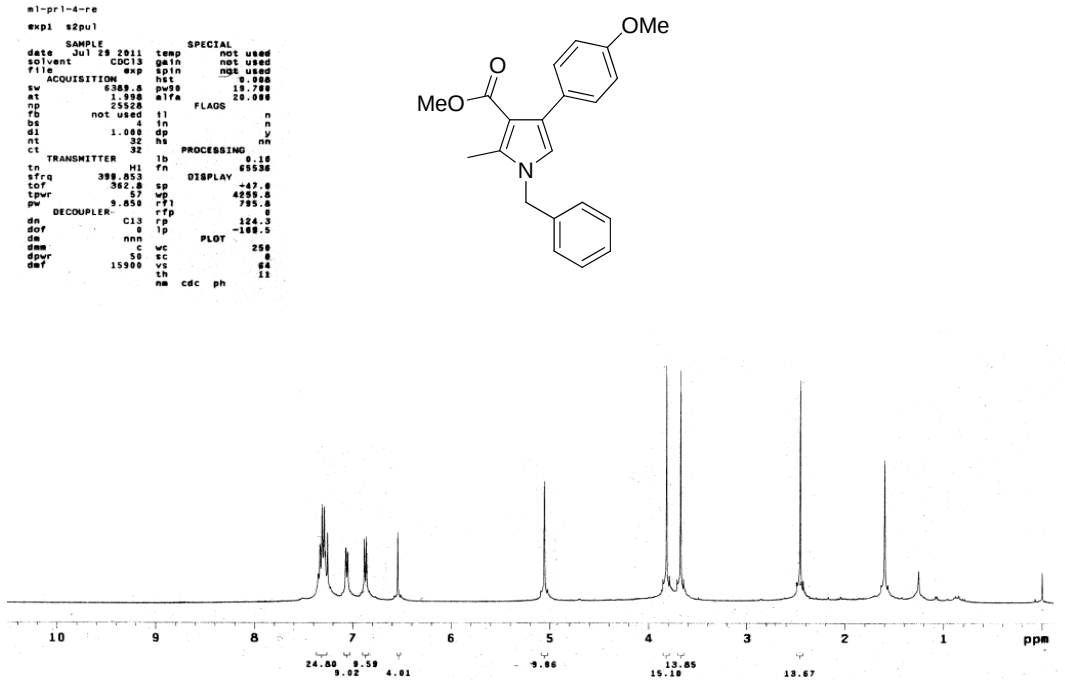


Figure 40.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 1-benzyl-4-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158d**)*



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 1-benzyl-4-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158d**)*

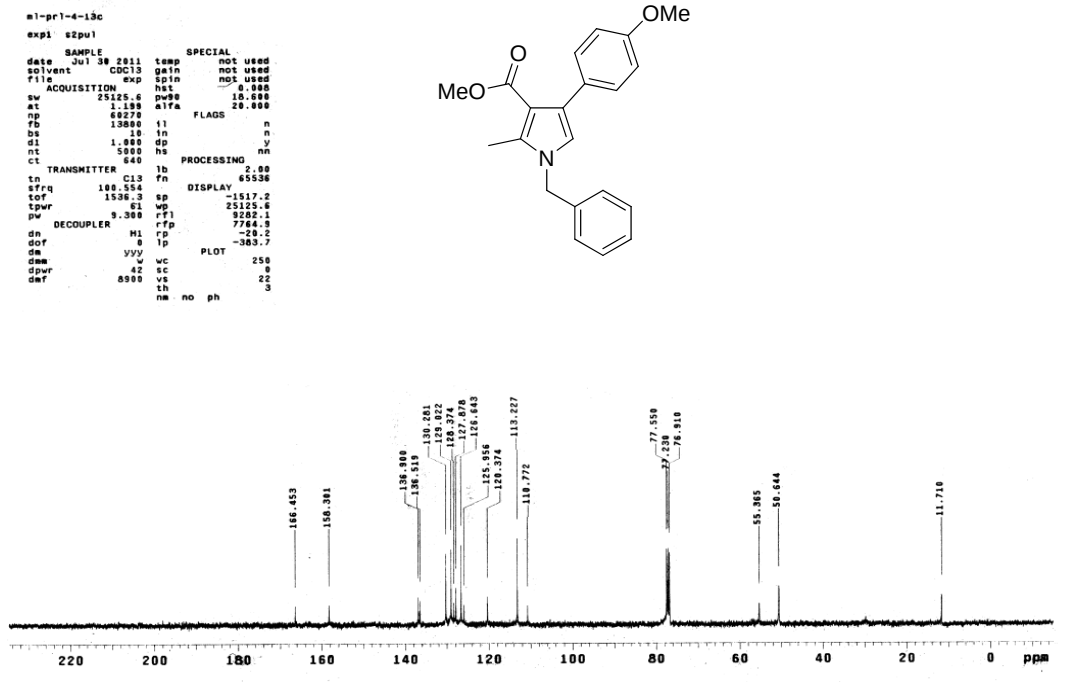
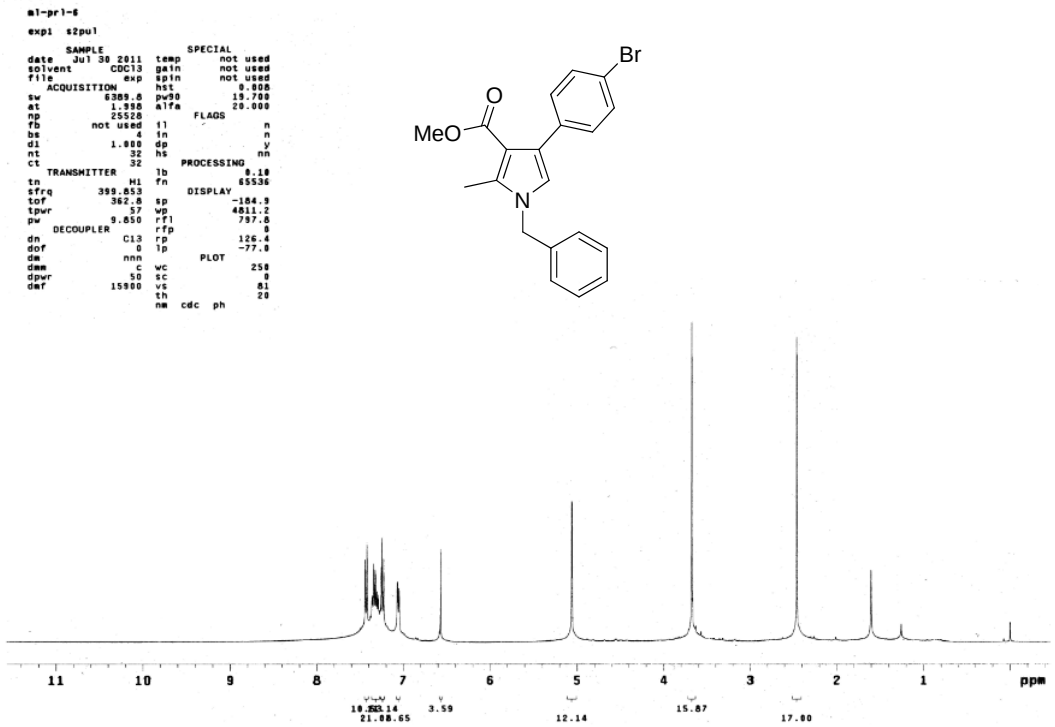


Figure 41.

^{1}H NMR (400 MHz, $CDCl_3$): *Methyl 1-benzyl-4-(4-bromophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158g**)*



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 1-benzyl-4-(4-bromophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158g**)*

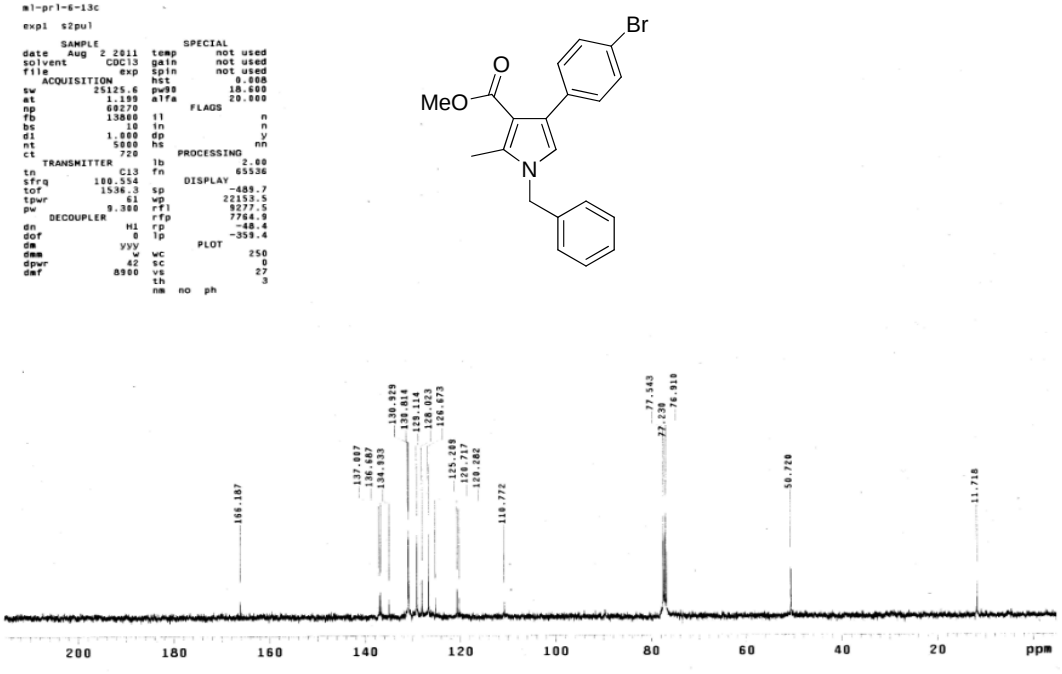
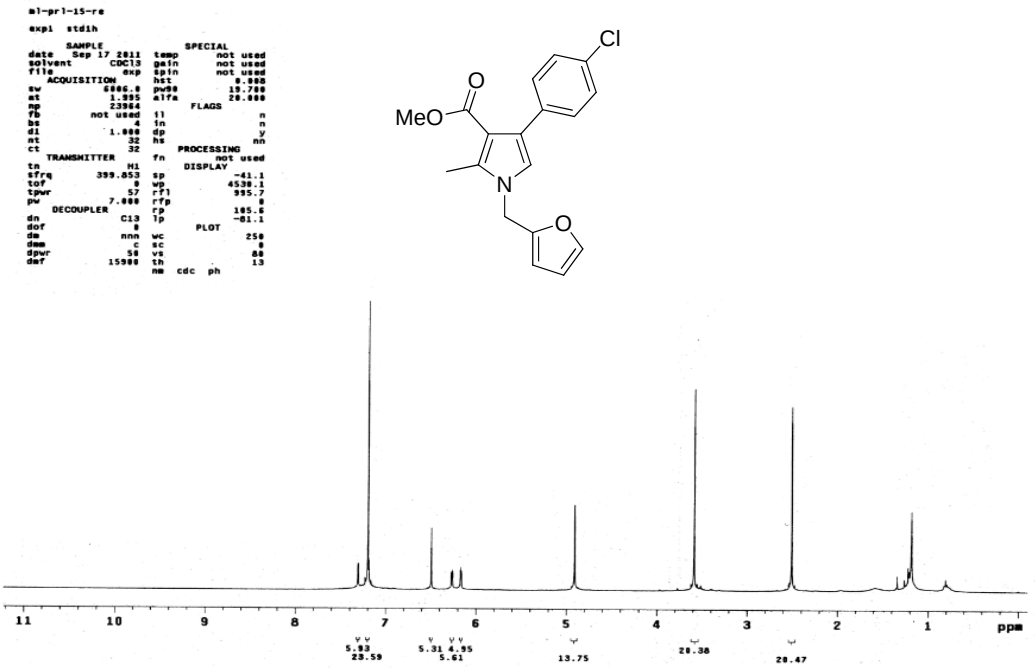


Figure 42.

^{1}H NMR (400 MHz, $CDCl_3$):*Methyl 4-(4-chlorophenyl)-1-(furan-2-ylmethyl)-2-methyl-1H-pyrrole-3-carboxylate (**158k**)*



^{13}C NMR (100 MHz, $CDCl_3$): *Methyl 4-(4-chlorophenyl)-1-(furan-2-ylmethyl)-2-methyl-1H-pyrrole-3-carboxylate (**158k**)*

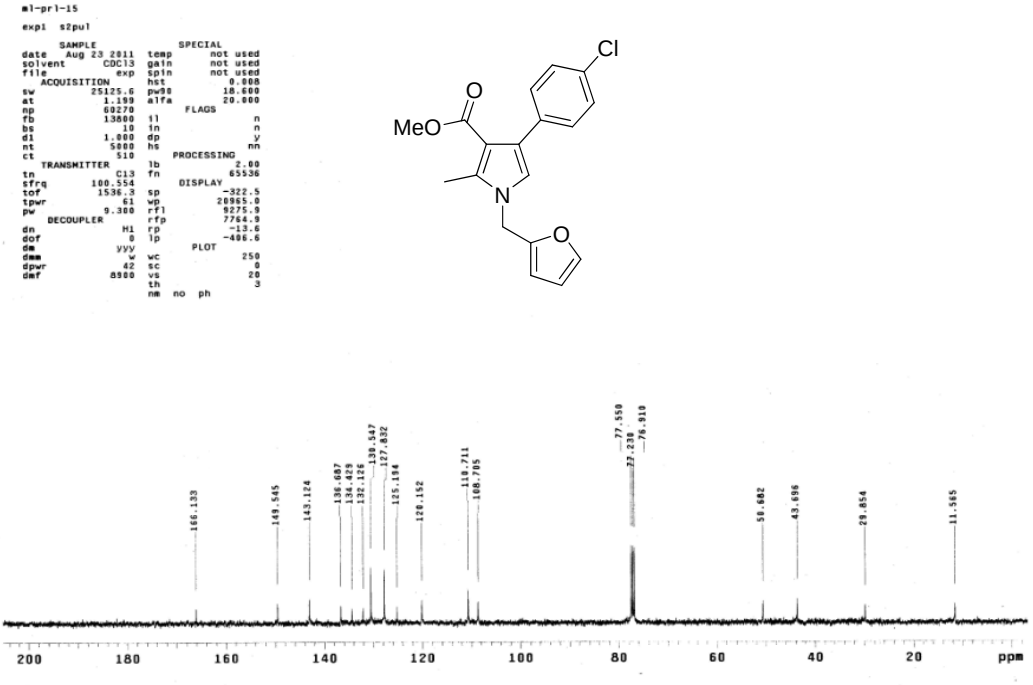
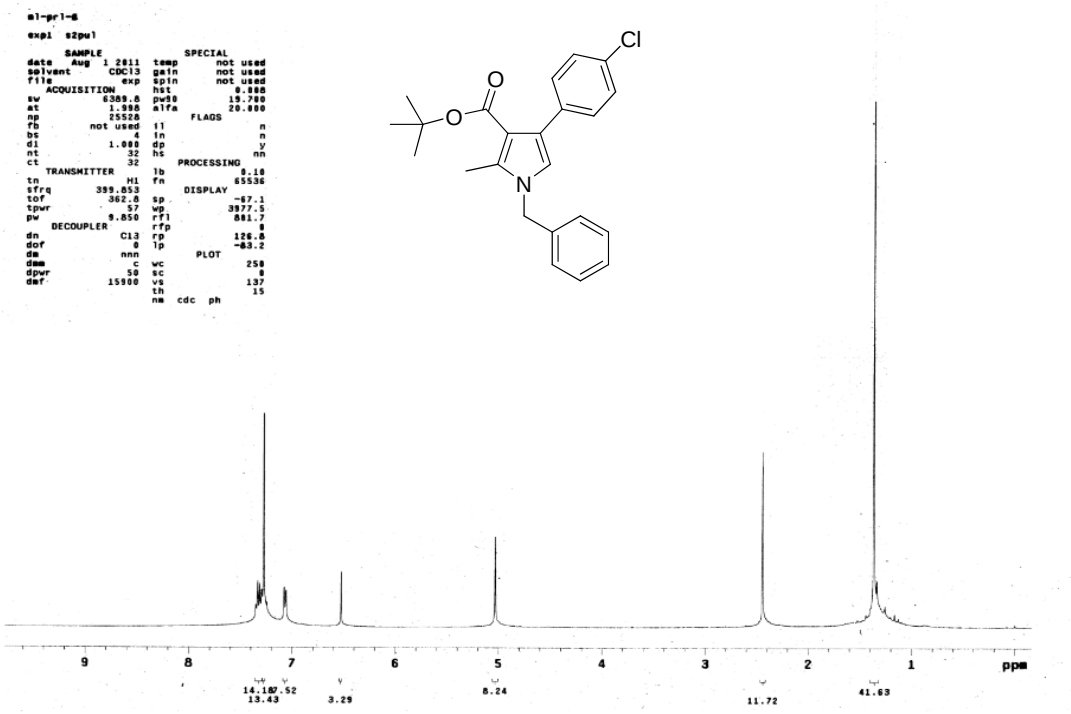


Figure 43.

^{1}H NMR (400 MHz, CDCl$_3$): *Tert-butyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158n**)*



^{13}C NMR (100 MHz, CDCl$_3$): *Tert-butyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (**158n**)*

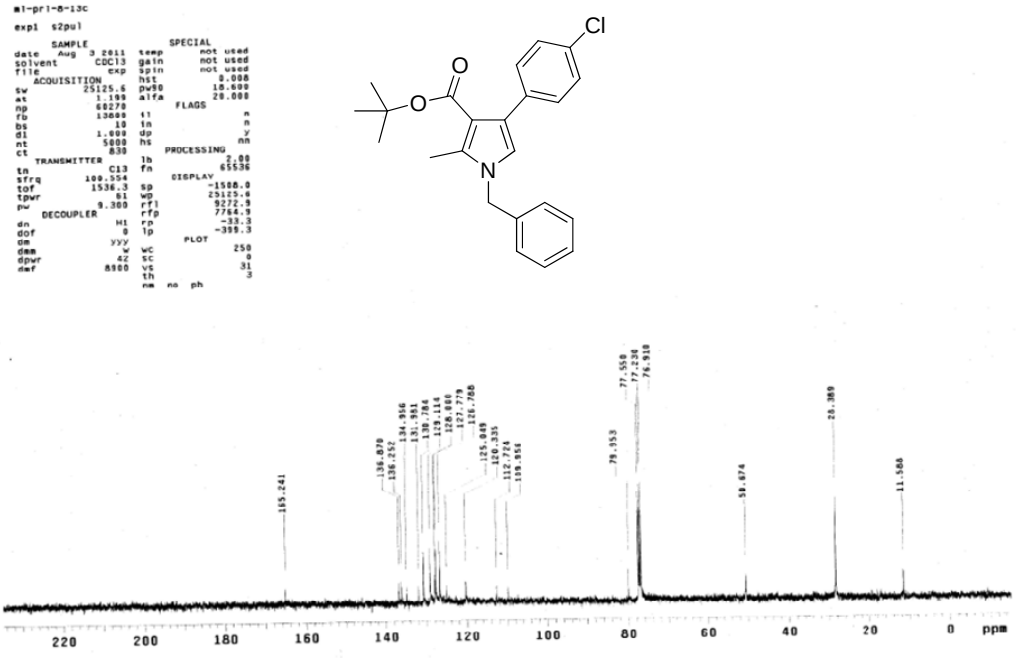


Figure 44.

References

References:

1. (a) B. M. Trost, *Science* **1991**, *254*, 1471–1477. (b) R. A. Sheldon, *Chem. Ind.* **1992**, 903–906. (c) B. M. Trost, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.
2. Jiménez-González, C.; Constable, D. J. C. *Green Chemistry and Engineering*, John Wiley & Sons, Inc.: New Jersey, USA, 2011.
3. (a) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; 1st ed.; Wiley-VCH: Weinheim, Germany, 2005. (b) Orru, R. V. A.; Ruijter, E. In *Synthesis of Heterocycles via Multicomponent Reaction I* & *II*, ed. Maes, B. U. W.; Springer: Heidelberg, Germany, 2010.
4. Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*, Oxford University Press: New York, USA, 1998.
5. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.
6. (a) Dömling, A.; Ugi, I. *Angew. Chem. Intl. Ed.* **2000**, *39*, 3168–3210. (b) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Eds.* **2005**, *44*, 1602–1634.
7. Ugi, I. *J. Prakt. Chem.* **1997**, *399*, 499–516.
8. Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246.
9. Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
10. Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26.
11. Schwartz, A. W.; Joosten, H.; Voet, A. B. *Biosystems* **1982,** *15*, 191–193.
12. Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27–45.
13. Vedejs, E.; Kongkittingam, C. A. *J. Org. Chem.* **2001**, *66*, 7355–7364.
14. (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126–129. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181–189.
15. (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 734–742. (b) Ugi, I.; Domling, A.; Werner, B. *J. Het. Chem.* **2000**, *37*, 647–658.
16. (a) Bonne, D.; Coquerel, Y.; Constantieux, T. Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, 21, 1085–1109. (b) Sanchez Duque, M. del M.; Allais, C.; Isambert, N.; Constantieux, T.; Rodriguez, J. *Top. Heterocycl. Chem.* **2010**, *23*, 227–277. (c) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980. (d) Langer, P. *Synthesis* **2002**, 441–459.

(e) Langer, P. *Chem. Eur. J.* **2001**, *7*, 3858–3866. (f) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V.; *Chem. Rev*. **1995**, *95*, 1065–1114.

17. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1–82.

18. Sambongi, Y.; Nitta, H.; Ichihashi, K.; Futai, M.; Ueda, I. *J. Org. Chem.* **2002,** *67*, 3499–3501.

19. Moseley, J. D. *Tetrahedron. Lett.* **2005**, *46*, 3179–3181.

20. (a) Mobinikhaledi, A.; Foroughifar, N.; Fard, M. A. B.; Moghanian, H.; Ebrahimi. S.; Kalhor, M. *Synth. Commun*. **2009**, *39*, 1166–1174. (b) Sapkal, S. B.; Shelke, K. F.; Shingate, B. B. Shingare, M. S. *Tetrahedron Lett*. **2009**, *50*, 1754–1756.

21. (a) Kumar, A.; Maurya, R. A. *Synlett*. **2008**, 883–885. (b) Wang, S. X.; Li, Z. Y.; Zhang, J. C.; Li, J. T. *Ultrason. Sonochem.* **2008**, *15*, 677–680.

22. Mekheimer, R. A.; Hameed, A. A.; Sadek, K. U. *Green Chem.* **2008**, *10*, 592–593.

23. Evans, C. G.; Gestwicki, J. E. *Org. Lett*. **2009**, *11*, 2957–2959.

24. Chebanov, V. A.; Saraev, V. E.; Desenko, S. M.; Chermenko, V. N.; Knyazeva, I. V.; Groth, U.; Glasnov, T. N.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 5110–5118.

25. Shaabani, A.; Rahmati, A.; Rezayan, A. H. Darvishi, M.; Badri, Z.; Sarvari, A. *QSAR Comb. Sci*. **2007**, *26*, 973–979.

26. (a) Michael, A. *J. Prakt.Chem.* **1887**, *35*, 349–356. (b) Michael, A. *J. Prakt. Chem.* **1894**, *49*, 20–29. (c) Tokoroyama, T. *Eur. J. Org. Chem.* **2010**, 2009-2016.

27. Kohler, E. P.; Potter, H. *J. Am. Chem. Soc.* **1935**, *57*, 1316–1321.

28. (a) Enders, D.; Wang, C.; Liebich, J. X.; *Chem.-Eur. J.* **2009**, *15*, 11058–11076. (b) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657–9672. (c) Vicario, J. L.; Badía, D.; Carrillo, L; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513–538.

29. Enders, D.; Lättgen, K.; Narine, A. A. *Synthesis* **2007**, 959–980.

30. Enders, D.; Saint-Dizier, A.; Lannou, M. I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29–49.

31. (a) Nising, C. f.; Stefan Bräse, S. *Chem. Soc. Rev*. **2012**, *41*, 988–999. (b) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR, Comb. Sci*. **2006**, *25*, 432-438.

32. Shanthi, G.; Perumal, P. T. *Tetrahedron Lett*. **2009**, *50*, 3959–3962.

33. Dey, S.; Pal, C.; Nandi, D.; Giri, V. S.; Zaidlewicz, M.; Krzeminski, M.; Smentek, L.; Hess, B. A.; Gawronski, J.; Kwit, M.; Babu, N. J.; Nangia, A.; Jaisankar, P. *Org. Lett.* **2008**, *10*, 1373–1376.

34. Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem*. **2010**, *75*, 1674–1683.

35. Zhong, C.; Liao, T.; Tuguldur, O.; Shi, X. *Org. Lett.* **2010**, *12*, 2064–2067.

36. (a) Simon, C.; Peyronel, J.; Rodriguez, J. *Org. Lett.* **2001**, *3*, 2145-2148. (b) Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. *Tetrahedron* **2007**, *63*, 4407–4413.

37. Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389–1399.

38. (a) Lieby-Muller, F.; Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Commun.* **2008**, 4207–4209. (b) Allais, C.; Constantieux, T.; Rodriguez, J. *Chem. Eur. J.* **2009**, *15*, 12945-12948.

39. Liu, Y.; Sun, J. -W. *J. Org. Chem.* **2012**. *77*, 1191–1197.

40. Shaabani, A.; Rezayan, A. H.; Keshipour, S.; Sarvary, A.; Ng, S. W. *Org. Lett.* **2009**, *11*, 3342–3345.

41. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360-416. (b) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.

42. De Souza, R. O. M. A.; Da Penha, E. T.; Milagre, H. M. S.; Garden, S. J.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem. Eur. J.* **2009**, *15*, 9799–9804.

43. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.

44. Nilsson, B. L.; Overman, L. E. *J. Org. Chem*. **2006**, *71*, 7706–7714.

45. Dondoni, A.; Massi, A.; Sabbatiny, S.; Bertolasi, V. *J. Org. Chem*. **2002**, *67*, 6979–6994.

46. (a) Huang, Y. J.; Yang, F. Y.; Zhu C. J. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387. (b) Yu, J. Shi, F. Gong, L. –Z. *Acc. Chem. Res.* **2011,** *44*, 1156 –1171.

47. (a) Jones, G. In Organic Reactions; Wiley: New York, 1967; Vol. 15, pp 204–599. (b) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 341–394. (c) List, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 1730–1734.

48. Freeman, F. *Chem. Rev*. **1981**, *80*, 329–350.

49. (a) Tietze, L. F.; Saling, P. *Synlett* **1992**, 281–282. (b) Borah, H. N.; Deb, M. L.; Boruah, R. C.; Bhuyan, P. J. *Tetrahedron Lett*. **2005**, *46*, 3391–3393.

50. (a) Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115–136.

51. (a) Ayoubi, S. A.-E.; Texier-Boullet, F.; Hamelin, J. *Synthesis* **1994**, 258–260. (b) Binev, I. G.; Binev, Y. G.; Stamboliyska, B. A.; Juchnovski, I. N. *J. Mol. Struct.* **1997**, *435*, 235–239. (c) Brufola, G.; Fringuelli, F.; Piermatti, O.; Pizzo, F. *Heterocycles* **1997**, *45*, 1715–1721.

52. Heravi, M. M.; Baghernejad, B.; Oskooie, H. A.; Hekmatshoar, R. *Tetrahedron Lett.* **2008**. *49*, 6101–6103.

53. Li, M.; Yang, W. L. Wen, L. R.; Li, F. Q. *Eur. J. Org. Chem.* **2008.** 2751–2758.

54. Babu, N. S.; Pasha, N.; Rao, K. T. V.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* **2008**, *49*, 2730–2733.

55. Balalaie, S.; Bararjanian, M.; Amani, A. M.; Movassagh, B. *Synlett.* **2006**, 263–266.

56. Khurana, J. M.; Nand, B.; Saluja, P.; *Tetrahedron*. **2010**, *66*, 5637–5641.

57. Banerjee, S.; Horn, A.; Khatri, H.; Sereda, G. *Tetrahedron Lett.* **2011**, *52*, 1878–1881.

58. Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y. *Org. Biomol. Chem*. **2010**, *8*, 3078–3082.

59. Chowdhury, S.; Nandi, G. C.; Samai, S.; Singh, M. S. *Org. Lett.* **2011**, *13*, 3762–3765.

60. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron* **2009**, *65*, 7129–7134.

61. Gao, S. J.; Tsai, C. H.; Yao, C. F. *Synlett.* **2009**, 949–954.

62. Khurana, J, M.; Magoo, D. *Tetrahedron Lett.* **2009**, *50*, 4777–4780.

63. Wang, R. Z.; Zhang, L. F.; Cui, Z. S. *Synth. Commun*. **2009**, 39, 2101–2107.

64. Das, B.; Laxminarayana, K.; Krishnaiah, M.; Srinivas, Y. *Synlett*. **2007**, 3107–3112.

65. (a) Nagarajan, A. S.; Reddy, B. S. R. *Synlett*. **2009**, 2002–2004. (b) Vasuki, G.; Kumaravel, K. *Tetrahedron Lett.* **2008**, *49*, 5636–5638.

66. Kumaravel, K.; Vasuki, G. *Green Chem*. **2009**, *11*, 1945–1947.

67. Mannich C.; Krosche, W. *Arch. Pharm.* **1912**, *250*, 647–667.

68. Syamala, M. *Org. Prep. Proced. Int*. **2005**, *37*, 103–171.

69. (a) Fox, M. A.; Whitesell, J. K. *Organic Chemistry 3rd ed*. John and Bartlett: Sudhury, **2003**. pp 851. (b)Jeyaraman, R.; Avila, S. *Chem. Rev.* **1981**. *81*, 149–174.

70. Metten, B.; Kostermans, M.; Van B. G.; Smet, M.; Dehaen, W. *Tetrahedron* **2006**, *62*, 6018–6028.

71. Shi, F. Luo, S. W.; Tao, Z. –L.; He, L.; Yu, J.; Tu, S. J.; Gong, L. –Z. *Org. Lett*. **2011**, *13*, 4680–4683.

72. (a) Shen, L.; Cao, S.; Liu, N. J.; Wu, J. J.; Zhu, L. J.; Qian, X. H. *Synlett.* **2008**, 1341–1344. (b) Safaei, S.; Mohammadpoor-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V. *Synlett.* **2011**, 2214–2222.

73. Shen, L.; Zhang, J.; Cao, S.; Yu, J. L.; Liu, N. J.; Wu, J. J.; Qian, X. H. *Synlett.* **2008**, 3058–3062.

74. Elbein, A. D.; Molyneux, R. In *Alkaloids, Chemical and Biological Perspectives*, Pelletier, S. W. Ed. John Wiley & Son: New York. 1987, Vol. 57.

75. Clarke, P. A.; Saytsev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209–5212.

76. (a) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398–8402. (b) A. T. Khan, Md. M. Khan, K. K. R. Bannuru, *Tetrahedron*, **2010**, *47*, 7762–7789.

77. Habib-Zahmani, H.; Hacini, S.; Charonnet, E.; Rodriguez, J. *Synlett*. **2002**, 1827–1830.

78. Wang, X. S.; Li, Q.; Wu, J. R.; Li, Y. L.; Yao, C. S.; Tu, S. J. *Synthesis* **2008**, 1902–1910.

79. (a) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Org. Lett*. **2007**, *9*, 1687–1690. (b) Sotoca, E.; Allais, C.; Constantieux, T.; Rodriguez, J. *Org. Biomol. Chem.* **2009**, *7*, 1911–1920. (c) Sotoca, E.; Constantieux, T.; Rodriguez, J. *Synlett.* **2008**, 1313–1316.

80. Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 131–163.

81. Cravotto, G.; Nano, G. M.; Palmisanob, G.; Tagliapietraa, S. *Tetrahedron: Asymmetry* **2001**, 12, 707–709.

82. Zhang, H.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1272–1275.

Chapter 2

83. (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (b) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod*. **2005**, *68*, 1556–1575.

84. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett*. **2000**, *2*, 3679–3681.

85. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19–32.

86. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1206–1210.

87. Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625–633.

88. Bin, H.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265–286.

89. (a) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.*, **2007**, *129*, 1480–1481. (b) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.*, **2003**, *125*, 4716–4617. (c) Takemiya, A, Hartwig, J. F. *J. Am. Chem. Soc.*, **2006**, *128*, 6042–6043. (d) Amat, M.; Bassas, O.; Perica`s, M. A.; Pasto, P.; Bosch, J. *Chem.Commun.* **2005**, 1327–1329. (e) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325–2328.

90. Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770–3772.

91. (a) Takasu, K.; Shindoh, N.; Tokuyama, H.; Ihara, M. *Tetrahedron.* **2006**, *62*, 11900–11907. (b) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773–5776.

92. (a) Murty, M. S. R.; Ram, R.; Yadav, J. S. *Tetrahedron. Lett.* **2008**, *49*, 1141–1145. (b) Carballo, R. M; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 3837–3840. (c) Dobbs, A. P.; Guesne, S. J. J. *Synlett* **2005**, 2101–2104.

93. Fusetero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286.

94. Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169–3171.

95. Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmipravha, T. R.; Mandal, G. C. *Tetrahedron Lett*. **1998**, *39*, 8163–8166.

96. (a) Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785–786. (b) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett*. **2002**, *43*, 2843–2846. (c) Bose, G.; Bujar Barua, P. M. Chaudhuri, M. K.; Kalita, D.; Khan, A. T. *Chem. Lett.* **2001**, 290–291. (d) Bose, G.; Mondal, E. ; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907–8909.

97. (a) Lin, Xu. F.; Cui, S. L.; Wang, Y. G. *Synth. Commun.* **2006**, *36*, 3153–3160. (b) Kavala, V.; Patel, B. K.; *Eur. J. Org. Chem.* **2005**, *2*, 441–451. (c) Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842–5845. (d) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177–4180. (e) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett*. **2001**, *42*, 7679–7681.

Chapter 3

98. (a) Khan, A. T.; Choudhury, L. H.; Parvin, T.; Ali, M. A. *Tetrahedron Lett.*, **2006,** *47*, 8137–8141, (b) Khan, A. T.; Choudhury, L. H.; Parvin, T. *Tetrahedron Lett.* **2007**, *63*, 5593–5601.

99. Khan, A. T.; Parvin, T.; Choudhury, L. H. *Eur. J. Org. Chem*. **2008**, 834–839.

100. Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett*. **2010**. *51*, 4419–4424.

101. Murai, K.; Nakatani, R.; Kita, Y.; Fujioka, H. *Tetrahedron* **2008**, *64*, 11034–11040.

102. Knabe, J.; Buech, H. P.; Bender, S. *Arch. Pharm*. **1995**, *328*, 59–66.

103. Atwal, K. S.; Bergey,, J. L.; Hedberg, A.; Moreland, S. *J. Med. Chem*. **1987**, *30*, 635–640.

104. Di Braccio, M.; Grossi, G.; Roma, G.; Vargiu, L.; Mura, M.; Marongiu, M. E. *Eur. J. Med. Chem.* **2001**, *36*, 935–949 and reference therein.

105. (b) Khan, A. T.; Khan, M. M.; *Tetrahedron Lett.* **2011,** *52*, 3455-3459. (c) Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010,** *51*, 4419–4424.

106. (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Oxford University Press, Oxford, 1999. (b) Desiraju, G. R. *Acc. Chem. Res.* **2002**, *35*, 565–573. (c) Steiner, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76.

107. (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289–296. (b) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543.

108. Lee, J. M.; Ahn, D.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K. Chang, S. *J. Am. Chem. Soc*. **2006**, *128*, 12954–12962.

109. (a) Schuster, T.; Bauch, M.; DUrner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179–181. (b) Thadani, A. N.; Stankovic, A. R.; Rawal, V. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5846–5850. (c) Feldman, K. S.; Campbell, R. F. *J. Org. Chem.* **1995**, *60*, 1924–1925.

110. (a) Pihko, P. M. *Angew. Chem., Int. Ed*. **2004,** *43*, 2062–2064. (b) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095.

111. Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett*. **2005**, *7*, 5657–5660.

112. Zu, L.; Wang, J.; Li, H.; Xie, H., Jiang, W. Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037.

113. (a) Kamata, K.; Hirano, T.; Kuzuya, S. Mizuno, N. *J. Am. Chem. Soc.* **2009**, *131*, 6997–7004. (b) Fackler, P.; Berthold, C.; Voss, F. Bach, T. *J. Am. Chem. Soc.* **2010**, *132*, 15911–15913.

Chapter 4

114. Khan, A. T.; Lal, M.; Basha R. S. *(Communicated).*

115. (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*, Butter-worths, London, 1963; (b) Feuer, G. *Progress in Medicinal Chemistry* ed. Ellis G. P. and West, G. P., North-Holland Publishing Company, New York, 1974.

116. Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517–520.

117. Cingolani, G.; Gualtteri F.; Pigin, M. *J. Med. Chem*. **1969**, *12*, 531–532.

118. Wu, J. Y. C.; Fong, W. F.; Zhang, J. X.; Leung, C. H.; Kwong, H. L.; Yang, M. S.; Li, D.; Cheung, H. Y. *Eur. J. Pharmacol.* **2003**, *473*, 9–17.

119. (a) Baraldi, P. G.; Manfredini, S.; Simoni, D.; Tabrizi, M. A.; Balzarini, J.; Clercq, E. D. *J. Med. Chem.* **1992**, *35*, 1877–1882. (b) Perrella, F. W.; Chen, S. F.; Behrens, D. L.; Kaltenbach, R. F.; Seitz, S. P. *J. Med. Chem*. **1994,** *37*, 2232–2237.

120. (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W.; Hughes, S. H.; Gragg, G. M. Boyd, M. R. *J. Med. Chem*. **1992,** *35*, 2735–2743. (b) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Waltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem*. **1993**, *36*, 4131–4138.

121. (a) Foye, W. O. *Principi di Chemico Farmaceutica; Piccin: Padora, Italy*, 1991. P 416. (b) Andreani, L. L.; Lapi, E. *Bull. Chim. Farm.* **1960**, *99*, 583–586. (c) Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H.; Yaoxue, X. B. *Chem. Abstr*. **1982**, *17*, 17. *Chem. Abstr*. **1982**, *96*, 135383e.

122. Ellis, G. P. In *The Chemistry of Heterocyclic Compounds Chromenes, Chromanes and Chromones*; In Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, NY, 1977; Chapter II, p 11.

123. Arnesto, D.; Horspool, W. M.; Martin, N.; Ramos, A.; Seaone, C. *J. Org. Chem.* **1989**, *54*, 3069–3072.

124. (a) Khurana, J. M.; Kumar, S. *Tetrahedron Lett.* **2009**, *50*, 4125–4127. (b) Heravi, M. M.; Sadjadi, S.; Haj, N. M.; Oskooie, H. A.; Bamoharram, F. F. *Catal. Commun.* **2009**, *10*, 1643–1646 and references therein; (c) Abdolmohammadi, S.; Balalaie, S. *Tetrahedron Lett.* **2007**, *48*, 3299–3303.

125. Murugan, R.; Sriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21–27.

Chapter 5

126. Khan, A. T.; Lal, M.; Ali, S.; Khan, M. M. *Tetrahedron Lett*. **2011**, *52*. 5327-5332.

127. C. –J. Li, T. –H. Chan, *Organic Reactions in Aqueous Media*, Willey: New York, **1997**.

128. B. C. Ranu, S. Banerjee, *Tetrahedron Lett*. **2007**, *48*, 141–143.

129. C. –J. Li, *Chem. Rev*. **2005**, *105*, 3095–3166.

130. (a) A. Kumar, M. K. Gupta, M. Kumar, *Tetrahedron Lett*. **2011**, *52*, 4521–4525. (b) C. S. McKay, D. C. Kennedy, J. P. Pezacki, *Tetrahedron Lett*. **2009**, *50*, 1893–1896.

131. R. D. H. Murray, J. Mendez, S. A. Brown, *The Natural Coumarins, Occurrence, Chemistry, and Biochemistry*; Wiley: New York, NY, **1982**, pp. 13.

132. K. C. Majumdar, S. K. Chattopadhyay, *Heterocycles in Natural Product Synthesis*, Wiley-VCH: Germany **2011**, pp. 99–152.

133. (a) M. L. King, C. C. Chiang, H. C. Ling, E. Fujita, M. Ochiai, A. T. McPhail, *J. Chem. Soc., Chem. Commun.* **1982**, 1150–1151. (b) A. Schoop, H. Greiving, A. Göhrt *Tetrahedron Lett.* **2000**, *41*, 1913–1916.

134. (a) H. Jiang, Y. Hamada, *Org. Biomol. Chem*. **2009**, *7*, 4173–4176. (b) J. Magolan, M. J. Coster, *J. Org. Chem.* **2009**, 74, 5083–5086.

135. (a) N. C. Veitch, R. J. Grayer, *Nat. Prod. Rep.* **2008**, *25*, 555–611. (b) T. Nakatsuka, Y. Tomimori, Y. Fukada, H. Nukaya, *Biorg. Med. Chem. Lett.* **2004**, *14*, 3201–3203. (c) T. Furuta, T. Kimura, S. Kondo, H. Mihara, T. Wakimoto, H. Nukaya, K. Tsuji, K. Tanaka, *Tetrahedron* **2004**, *60*, 9375–9379.

136. Q. -F. Wang, H. –K. Song, J. Chen, C. -G. Yan, *J. Comb. Chem*. **2009**, *11*, 1007–1010 and references therein.

137. (a) C. –R. Liu, B. –H. Zhu, Zheng, J. –C. Sun, X. –L. Xie, Z, Tang, Y. *Chem. Commun*. **2011**, *47*, 1342–1344. (b) X. Lin, Z. Mao, X. Dai, P. Lu, Y Wang, *Chem. Commun*. **2011**, *47*, 6620–6622.

138. (a) Q. –F. Wang, H. Hou, L. Hui, C. –G. Yan, *J. Org. Chem*. **2009**, *74*, 7403–7406. (b) E. Altieri, M. Cordaro, G. Grassi, F. Risitano, A. Scala, *Tetrahedron*. **2010**, *66*, 9493–9496. (c) Chuang, C. –P.; Chen, K. –P. *Tetrahedron*, **2012**, *68*, 1401-1406.

139. Y. Jiang, D. Ma, *Tetrahedron: Asymmetry* **2002**, *13*, 1033–1038.

140. W. Cao, W. Ding, J. Chen, Y. Chen, Q. Zang, G. Chen, *Synth. Commun.* **2004**, *34*, 1599–1608.

141. (a)Y. Ye, L. Wang, R. Fan, *J. Org. Chem.* **2010**, *75*, 1760–1763. (b) Z. Yang, M. Fan, R. Mu, W. Liu, Y. Liang, *Tetrahedron.* **2005**, *61*, 9140–9146. (c) G.- W. Wang, Y. –W. Dong, P. Wu, T. –T. Yuan, Y. –B. Shen, *J. Org. Chem*. **2008**, *73*, 7088–7095.

142. S. Martinet, A. Méou, P. Brun, *Magn. Reson. Chem.* **2007**, *45*, 182–184.

Chapter 6

143. Khan, A. T.; Lal, M. Basha, R. S. *(Communicated).*

144. Mal, D.; Shome, B.; Dinda, B. K. In *Heterocyles in Natural Product Synthesis*, Majumdar, K. C.; Chattopadhyay, S. K.; Eds.; Wiley-VCH: Weinheim, 2011; pp 187–220.

145. (a) Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafic, A.; Manettic, F. *Bioorg. Med. Chem.* **2004**, *12*, 1453–1458. (b) Protopopova, M.; Bogatcheva, E.; Nikonenko, B.; Hundert, S.; Einck, L.; Nacy, C. A.; *Med. Chem.* **2007**, *3*, 301–316. (c) Teixeira, C.; Barbault, F.; Rebehmed, J.; Liu, K.; Xie, L.; Lu, H.; Jiang, S.; Fan, B.; Maurel, F.; *Bioorg. Med. Chem*. **2008**, *16*, 3039–3048. (d) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q.; *J. Am. Chem. Soc*. **1999**, *121*, 54–62. (e) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem*. **1999**, *34*, 991–996.

146. (a) Lazerges, M.; Chane-Ching, K. I.; Aeiyach, S.; Chelli, S.; Peppin-Donnat, B.; Billon, M.; Lombard, C.; Maurel, F.; Jouini, M. *J. Solid State Electrochem*. **2009**, *13*, 231–238. (b) Kros, A.; van Hövel, S. W. F. M.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. *Sens. Actuators, B*, **2001**, *80*, 229–233. (c) Loudet, A.; Burgess, K. *Chem. Rev*. **2007**, *107*, 4891–4932. (d) Kiskan, B.; Akar, A.; Kizilcan, N.; Ustamehmetoglu, B. *J. Appl. Polym. Sci*. **2005**, *96*, 1830–1834.

147. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 1474–1483. (b) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2896–2899. (c) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. *I. Chem. Heterocycl. Compd.* **2004**, *40*, 1218-1219.

148. (a) Knorr, L. *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 1635–1642. (b) Manley, J.M.;Kalman,M. J.; Conway, B. G.; Ball, C. C.; Havens, J. L.; Vaidyanathan, R. *J. Org. Chem*. **2003**, *68*, 6447–6450. (c) Shiner, C. M.; Lash, T. D. *Tetrahedron* **2005**, *61*, 11628–11640.

149. (a) Pall, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371. (b) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–216. (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, *24*, 5277–5288.

150. Reddy, G. R.; Reddy, T. R.; Joseph, S. C.; Reddy, K. S.; Reddy, L. S.; Kumar, P. M.; Krishna, G. R.; Reddy, C. M.; Rambabu, D.; Kapavarapu, R.; Lakshmi, C.; Meda, T.; Priya, K. K.; Parsa, K. V. L.; Pal, M. *Chem. Comm.* **2011**, *47*, 7779–7781.

151. Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421.

152. (a) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 6180–6182. (b) Lee, K.; Counceller, C. M.; Stambuli. J. P. *Org. Lett*. **2009**, *11*, 1457–1459.

153. (a) Khan, A. T.; Mondal, E.; Sahu, P. R.; Islam. S. *Tetrahedron Lett*. **2003**, *44*, 919–922. (b) Khan, A. T.; Islam, S.; Choudhary, L. H.; Ghosh. S. *Tetrahedron Lett*. **2004**, *45*, 9617–9621.

154. (a) Samai, S.; Nandi, G. C.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5555–5558. (b) Zhang, X.-N.; Li, Y.-X.; Zhang, Z. –H. *Tetrahedron* **2011**, *67*, 7426–7430.

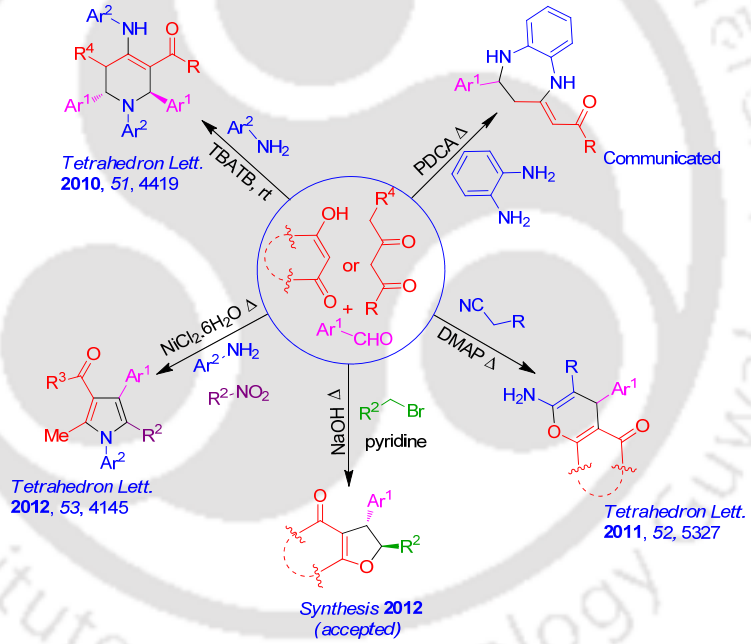
155. Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953,** *18*, 1–3.

156. (a) Srivastava, N. Srivastava, P. C. *Bull. Mater. Sci*. **2010**, *33*, 653-656. (b) Kang, D. –J.; Kim, S. G. *Korean J. Chem. Eng*. **2009**, *26*, 1800–1805.

Conclusion and Future Perspective

In conclusion, we have accomplished the synthesis of nitrogen containing heterocycles such as highly substituted piperidines, 1,5-benzodiazepiene derivatives and *tetra*-substituted pyrrole derivatives starting from β-dicarbonyl compounds using multicomponent reactions (MCRs). Similarly, the oxygen containing heterocyles pyran annulated heterocycles and *trans*-2,3-dihydrofuran derivatives by employing 1,3-dicarbonyl compounds using MCRs, which are the new additions in the area of synthetic organic chemistry.

Over all summary of the dissertation, we have shown the usefulness of 1,3-dicarbonyl compounds for the synthesis of nitrogen and oxygen heterocycles based on multicomponent reactions, which can be visualized easily in Figure below.



Figure

We would like to explore other reagents which can act as catalysts for multicomponent reactions (MCRs) for similar kind of transformations to synthesize new heterocycles. Subsequently, the investigation will be carried out in future for the synthesis of optically active compounds using chiral organocatalysts. Further, the synthesized compounds will be utilized for synthesizing complex heterocycles preferably second MCR approach. Moreover, we would like to do some biological study of these compounds in collaboration with other research groups.

LIST OF AUTHOR'S PUBLICATIONS AND COMMUNICATIONS

1. *'Bromodimethylsulfonium bromide (BDMS) catalyzed synthesis of imidazo[1,2-a]pyridine derivatives and their fluorescence properties'* Abu T. Khan, Sidick Basha R, **Mohan Lal** *Tetrahedron Lett.,* **2012**, *53* 2211–2217.

2. *'One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst'* Abu T. Khan, **Mohan Lal**, Shahzad Ali and Md. Musawwer Khan; *Tetrahedron Lett.,* **2011**, *52.* 5327-5332.

3. *'New three-component reaction: Synthesis of 1-[(alkylthio)(phenyl)methyl]-naphthalene-2-ol catalyzed by bromodimethylsulfonium bromide (BDMS)'* Abu T. Khan, Shahzad Ali, Ajaz A. Dar and **Mohan Lal** *Tetrahedron Lett.,* **2011,** *52,* 5157-5160.

4. *'Silica Supported Perchloric Acid ($HClO_4$-SiO_2): an Efficient Catalyst for One-pot Synthesis of Functionalized Tetrahydropyrimidine Derivatives'* Abu T. Khan, Md. Musawwer Khan, Deb Kumar Das and **Mohan Lal** *J. Heterocyclic. Chem,* **2011**, *accepted in press.*

5. 'VO(acac)$_2$/H_2O_2/NaI: a mild and efficient combination for the cleavage of dithioacetal derivatives of sugars' Abu T. Khan, Shahzad Ali, Sidick Basha R, Md. Musawwer Khan, **Mohan Lal**, *Carbohydrate Research,* **2011***, 346,* 2629–2632.

6. *'Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB)'* Abu T. Khan, **Mohan Lal**, Md. Musawwer Khan; *Tetrahedron Lett.* **2010**, *51*, 4419-4424.

7. *'Hydrogen-bond-mediated regioselective synthesis of 1,5-benzodiazepines using organocatalyst 2,6-pyridinedicarboxylic acid involving multicomponent reactions'* Abu T. Khan, **Mohan Lal**, Sidick Basha R (*will be Communicated soon).*

8. *'Pyridinium ylide mediated one-pot three-component regio- and diastereoselective synthesis of trans-2,3-dihydrofuran derivatives'* Abu T. Khan, **Mohan Lal**, Sidick Basha R *Synthesis* **2012***(acceped).*

9. *'Nickel(II) chloride hexahydrate ($NiCl_2{\cdot}6H_2O$) as an efficient and useful catalyst for one-pot four-component reaction: Synthesis of tetra-substituted pyrroles, a potential*

phosphodiesterase 4B inhibitor ' Abu T. Khan, **Mohan Lal**, Prasanta Ray Bagdi, Sidick Basha R, *Parameswaran Saravanan, Sanjukta Patra Tetrahedron Lett.* **2012,** *53*, 4145-4150.

10. '*Formation of unexpected α-amino amidine through three-component 'UGI condensation reaction'* Abu T. Khan, Sidick Basha R, **Mohan Lal**, Mohammad Hedayetullah Mir *RSC Adv.* **2012,** *2*, 5506–5509.

11. *'Bromodimethylsulfonium bromide (BDMS) catalyzed synthesis of 2,3-unsaturated-O-glycosides via Ferrier rearrangement'* Abu T. Khan, Sidick Basha R, **Mohan Lal** *ARKIVOC* **2013,** *ii, 1-12.*

LIST OF CONFERENCES AND SYMPOSIUMS

1. *Presented a poster titled 'Synthesis of 1,5-Benzodiazepines and Benzimidazole using Organocatalyst 2,6-Pyridinedicarboxylic acid by Three-Component Reaction' CHEMISTRY: FRONTIERAR AND CHALLENGES (CFC-2011),* held at Department of Chemistry Aligarh Muslim University, Aligarh India 5-6 March, **2011**.

2. Presented a poster titled *'Three-component synthesis of pyran annulated heterocyclic compounds using DBU as a catalyst'* in Frontiers in Chemical Sciences (FICS 2010), held at Indian Institute of Technology Guwahati, India, during December 3-4, **2010**.

3. Presented a poster titled '*Pyridinium ylide mediated one-pot three-component regio- and diastereoselective synthesis of trans-2,3-dihydrofuran derivatives'* RSC international symposium in advance Chemical Sciences (AICS 2012), held at Indian Institute of Technology Guwahati, India, on 31st January, **2012**.

4. Presented a poster titled *'Regio- and diastereoselective synthesis of trans-2,3-dihydrofuran derivatives involving one-pot three-component reactions and their biological,* National Symposium on Recent Trends in Chemical Science and Technology, RTCST 2012, held at Indian Institute of Technology Patna, India, during March 3-4, **2012**.

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Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB)

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ABSTRACT

Tetrabutylammonium tribromide (TBATB) has been found to be an efficient catalyst for the one-pot synthesis of highly substituted piperidines through a combination of 1,3-dicarbonyl compounds, aromatic aldehydes, and various amines in ethanol at room temperature. Atom economy, good yields, environmentally benign, and mild reaction conditions are some of the important features of this protocol.

Recently, multicomponent reactions (MCRs)[1] have been paid much attention by synthetic organic chemists from all over the world because the building of architecturally complex molecules with diverse range of complexity can easily be achieved from readily available starting materials. In most of the cases a single product was obtained from three or more different substrates by reacting in a well-defined manner through MCRs.[2] These time-efficient reactions are environmentally benign and atom economic. MCRs are cost-effective since the expensive purification processes as well as the protection–deprotection steps are non-existent.[3] The synthesis of heterocycles using MCRs is a domain of classical carbonyl condensation chemistry. Among various carbonyl compounds, 1,3-dicarbonyl derivatives represent important synthetic building blocks, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a large variety of synthetic transformations.[4] Thus, the high synthetic potential of these easily accessible reagents have found numerous applications, especially for the synthesis of complex heterocyclic molecules.[5]

The piperidines and their analogues are important heterocycles that are present in many naturally occurring alkaloids, biologically active synthetic molecules, and organic fine chemicals.[6] Some of them also act as pharmaceutical agents.[7] Compounds containing piperidine structural motif exhibit anti-hypertensive,[8] antibacterial,[9] antimalarial,[10] anticonvulsant, and anti-inflammatory activities.[11] Thus, the synthesis of highly substituted piperidines has gained considerable attention,[12] and a number of procedures have been developed using several approaches such as tandem cyclopropane ring-opening/Conia-ene cyclization,[13] imino Diels–Alder reactions,[14] aza-Prins-cyclizations,[15] intramolecular Michael reactions,[16] and intramolecular Mannich reaction onto iminium ions.[17] The functionalized piperidines have been reported using MCRs strategy by employing bromodimethylsulfonium bromide (BDMS),[18] $InCl_3$,[19] and L-proline/TFA.[10] However, the use of expensive and excess amount of catalysts are some of the disadvantages of the above-mentioned methods. Therefore, there is a need for highly efficient, versatile, and eco-friendly synthetic protocol to obtain these valuable compounds in good yields.

Chaudhuri et al. reported environmentally benign synthesis of tetrabutylammonium tribromide (TBATB) as a useful brominating reagent.[20] The efficacy of these organic ammonium tribromides was demonstrated for several organic transformations such as deprotection of dithioacetals,[21a] conversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[21b] and synthesis of α-bromo enones[21c] with various naturally occurring flavone derivatives.[21d] A wide variety of organic transformations were developed involving tetrabutylammonium tribromide (TBATB) by other authors.[22] Because of the unique properties of the reagent tetrabutylammonium tribromide (TBATB), it would be an efficient catalyst for the one-pot synthesis of the highly functionalized piperidines from the reaction of 1,3-dicarbonyl compounds, aromatic aldehydes, and amines. In this Letter, a one-pot MCR leading to highly functionalized piperidine derivatives along with their mechanistic aspects is reported (Scheme 1).

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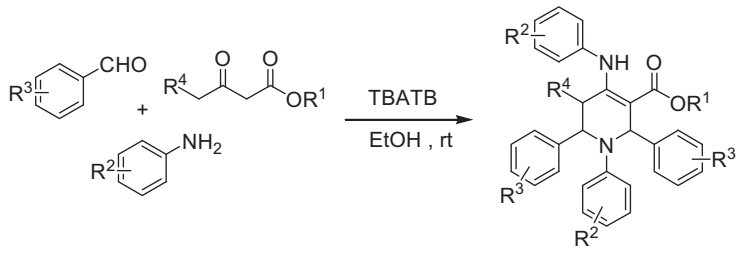


Scheme 1. Synthesis of functionalized piperidines.

Table 1
Optimization of reaction conditions for the synthesis of functionalized piperidine **1a**

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	CH_3CN	No catalyst	12	0
2	CH_3CN	10	12	66
3	EtOH	05	10	56
4	EtOH	10	10	78
5	EtOH	20	10	69
6	CH_2Cl_2	10	10	54
7	CH_3OH	10	12	68
8	Neat	10	5	51

[a] Isolated yield.

In the beginning of the study, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was treated with 10 mol % of TBATB at room temperature. The solid product was filtered and washed with ethanol to give functionalized piperidine **1a** in 66% yield. The product was characterized by its melting point, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis. A series of trial reactions were performed with a combination of 4-methylbenzaldehyde, aniline, and methyl acetoacetate to obtain the best result in terms of yield and reaction time for the formation of **1a** (Table 1). Several solvents were screened prior to concluding ethanol as the best solvent. In the neat reaction, the product was obtained in moderate yields (51%), and it is probably due to the lack of effective interaction of reactants with the catalyst.

Using the optimal reaction conditions, the reaction of benzaldehyde with aniline and methyl acetoacetate was studied and the product **1b** was obtained in good yields. The reactions of various aromatic aldehydes containing substituents in the aromatic ring such as OMe, Cl, Br, and NO_2 with aniline and methyl acetoacetate were performed under the same reaction conditions. The reaction time and the percentage yield of the products **1c–h** are shown in Table 2. However, in case of 3- and 4-nitrobenzaldehydes the products were obtained in low yield (Table 2, entries 7 and 8). This may be attributed to the formation of more stable imine having an extra conjugation in the presence of nitro group. This stable imine is less reactive and has less solubility in ethanol. Some of the aldehydes such as β-naphthaldehyde and *n*-butanal did not give their corresponding functionalized piperidines.

Several aliphatic and aromatic amines were examined to study the generality and scope of the present protocol. Various anilines with substituents such as Me, OMe, Br, and NO_2 were treated with 4-methylbenzaldehyde and methyl acetoacetate under identical reaction conditions. All these reactions underwent smoothly to provide the corresponding piperidine derivatives **1i–l**, in moderate to good yields (Table 2, entries 9–12). Similarly, aliphatic amines such as *n*-butylamine and benzylamine also yielded the corresponding piperidines **1m** and **1n**, respectively, in moderate yields. The present method failed to furnish the expected piperidine derivative with α-naphthylamine, which may be due to steric hindrance of the bulky naphthyl group.

Table 2
Synthesis of functionalized piperidines using TBATB in ethanol[23]

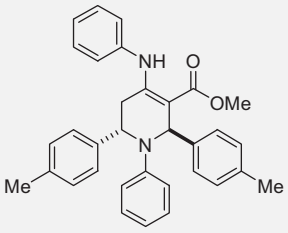
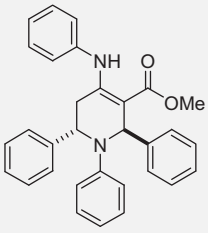
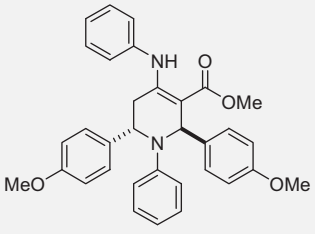
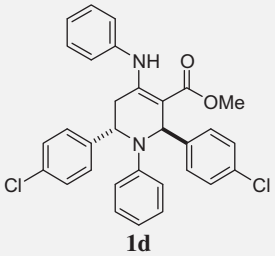
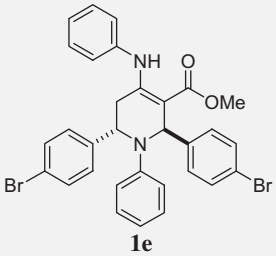
Entry	Product[a]	Time	Yield[b] (%)
1	 **1a**	8	78
2	 **1b**	24	74
3	 **1c**	8	80
4	 **1d**	10	82
5	 **1e**	8	80

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Table 2 (*continued*)

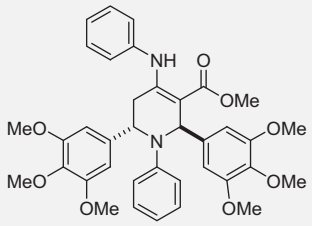
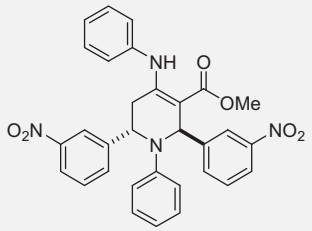
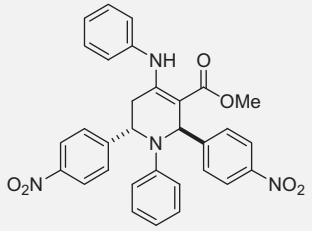
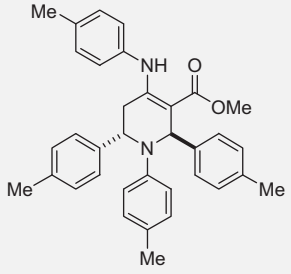
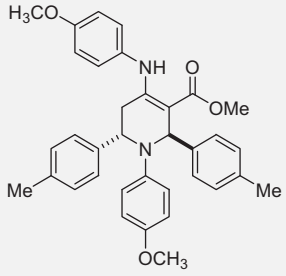
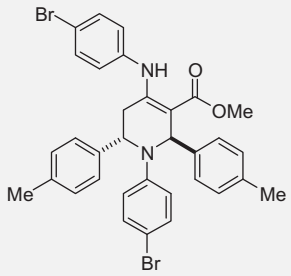
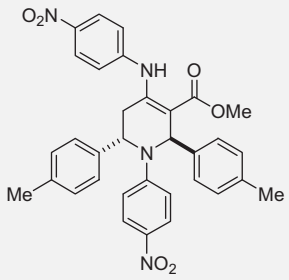
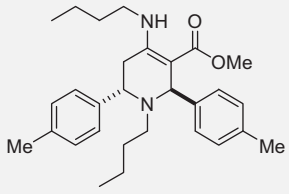
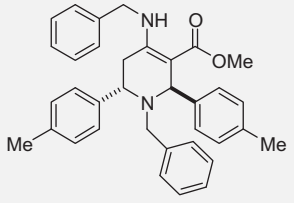
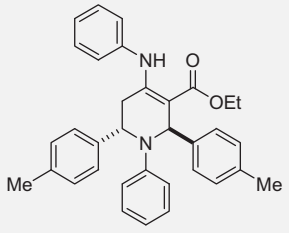
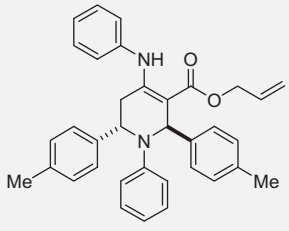
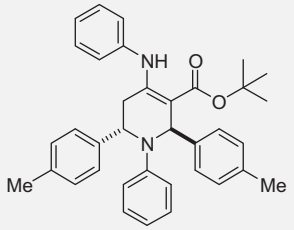
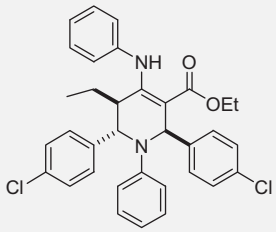
Entry	Product[a]	Time	Yield[b] (%)
6	 **1f**	30	60
7	 **1g**	36	30
8	 **1h**	26	28
9	 **1i**	12	75
10	 **1j**	9	72
11	 **1k**	8	63

Table 2 (*continued*)

Entry	Product[a]	Time	Yield[b] (%)
12	 **1l**	24	54
13	 **1m**	47	51
14	 **1n**	45	51
15	 **1o**	9	70
16	 **1p**	29	62
17	 **1q**	15	64

(*continued on next page*)

Table 2 (*continued*)

Entry	Product[a]	Time	Yield[b] (%)
18	 **1r**	30	31

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectrometry, and elemental analysis.
[b] Isolated yield.

The reaction was further examined for various 1,3-dicarbonyl compounds such as ethyl acetoacetate, allyl acetocetate, and *t*-butyl acetoacetate with 4-methylbenzaldehyde and aniline (Table 2, entries 15–18) in ethanol was catalyzed by 10 mol % TBATB. The desired piperidine derivative **1o–q** was obtained in good yields as shown in Table 2. This confirms that the alkoxy (–OR) moiety present in the ester functionality does not have any major role in determining the course of the reaction.

In addition, the reaction of ethyl butyrylacetate with 4-chlorobenzaldehyde and aniline was performed under identical reaction conditions to study the effect of an alkyl group at the β position of 1,3-dicarbonyl compound. The product of the reaction was a fully substituted piperidine **1r** in 31% yield. The low yield of product **1r** was due to the steric hindrance of alkyl group. We suggest that any enolizable alkyl group in the β position of 1,3-dicarbonyl compounds is sufficient for the formation of highly functionalized piperidines using MCRs (Scheme 2). The methods to prepare a large number of fully functionalized piperidine derivatives are under investigation.

All the products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra and by elemental analysis and well matched with the literature-reported compounds.[10,18,19] The structure as well as the relative stereochemistry of piperidine **1l** were confirmed by X-ray crystallographic analysis[24] (Figure 1).

The formation of piperidines through a Knoevenagel-type intermediate followed by [4+2] aza-Diels–Alder reaction has been proposed by various groups.[11,18,19] It was projected that β-keto ester reacts with amine to give enamine **5**, which reacts further with aldehyde to give a Knoevenagel-type product. This acts as a reactive diene and it undergoes aza-Diels–Alder reaction with imine **6** to give substituted piperidines. In support of this mechanism, the intermediate diene isolation was attempted with other reactive dienophiles such as dimethyl acetylenedicarboxylate and maleic anhydride, but in vain. Since no cycloaddition products were obtained, an alternate plausible mechanism for the product formation is proposed (see Scheme 3). TBATB reacts with ethanol which yields dry HBr[22e] and subsequently results in the formation of enamine **5** and imine **6** (Scheme 3). It is well known that enamine **5** would be a better nucleophile and the nucleophilic attack will take place preferentially on the activated imine **6** to give intermediate **7** through intermolecular Mannich-type reaction. The intermediate **7** reacts with aldehyde to give intermediate **8** by the elimination of a water molecule. There is a spontaneous tendency in the presence of HBr for tautomerization to give the intramolecular hydrogen bonded species either **9** or **10**. The tautomer **10** immediately undergoes intramolecular Mannich-type reaction to form intermediate **11**. The tautomer **9** would give a four-membered ring product **12**, which is unfavorable. The intermediate **11** tautomerizes to give the final piperidine derivative **1** due to conjugation with the ester group. In conclusion, the product formation is going through inter- and intramolecular Mannich-type reactions.

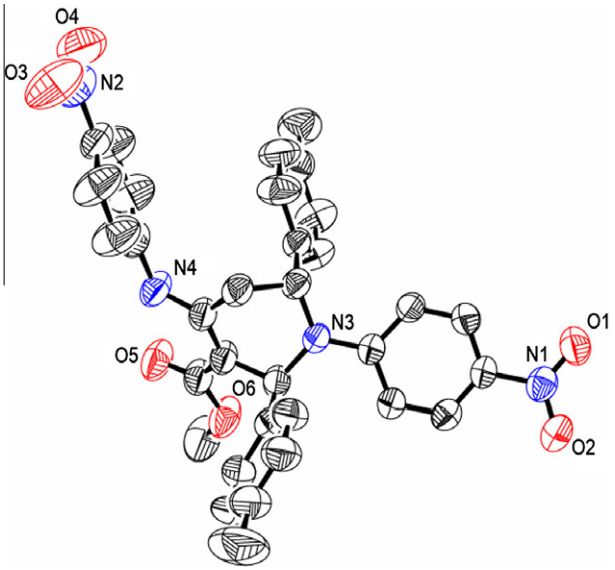
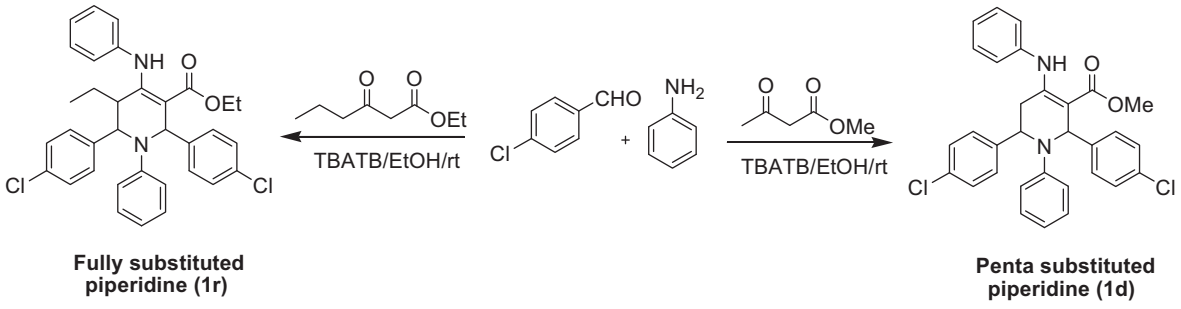
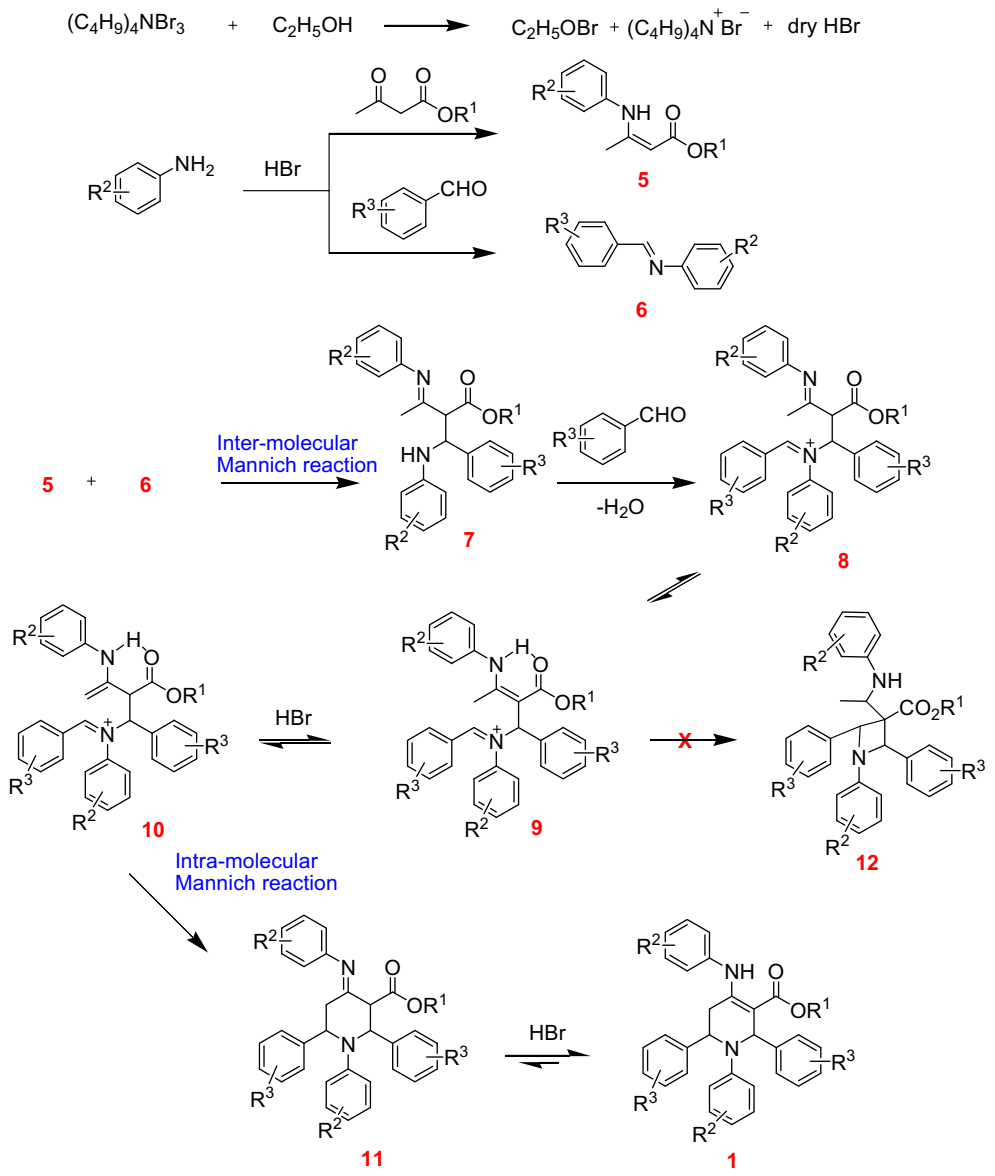


Figure 1. ORTEP diagram of **1l** (CCDC 775694).

In conclusion, we have found that the formation of highly functionalized piperidines is possible in the presence of TBATB as catalyst via one-pot five-component reaction at room temperature from readily available starting materials. Some advantages of this MCRs protocol are good yields, mild reaction conditions, environmentally benign catalyst, absence of tedious separation procedures, superior atom-economy, and low cost. In addition, mechanistic studies revealed another possibility for the formation of piperidines through double Mannich-type reactions.



Scheme 2. Criteria for the formation of piperidine derivatives.



Scheme 3. A plausible mechanism for the formation of highly substituted piperidine.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.069.

References and notes

1. (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*; Wiley: Weinheim, 2005; (b) Ugi, I. *Pure Appl. Chem.* **2001**, *73*, 187; (c) Nair, V.; Rajesh, C.; Vinod, A.; Bindu, U. S.; Streekenth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (d) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (e) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
2. (a) Tempest, P. A. *Curr. Opin. Drug Disc.* **2005**, *8*, 776; (b) Fujioka, H.; Murai, K.; Kubo, O.; Ohba, Y.; Kita, Y. *Org. Lett.* **2007**, *9*, 1687; (c) Evdokimov, N. M.; Kireev, A. S.; Yakovenko, A. A.; Antipin, M. Y.; Magedov, I. V.; Kornienko, A. *J. Org. Chem.* **2007**, *72*, 3443; (d) Wang, X. S.; Li, Q.; Wu, J. R.; Li, Y. L.; Yao, C. S.; Tu, S. J. *Synthesis* **2008**, 1902.
3. (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259; (b) Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765.
4. (a) Benetti, S.; Romagnoli, R.; De Risi, C.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065; (b) Langer, P. *Chem. Eur. J.* **2001**, *7*, 3858; (c) Langer, P. *Synthesis* **2002**, 441; (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957.
5. (a) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR. Comb. Sci.* **2006**, *25*, 432; (b) Sharma, G. V. M.; Reddy, K. L.; Lakshmi, P. S.; Krishna, P. R. *Synthesis* **2006**, 55; (c) Wang, L. M.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. *Tetrahedron* **2005**, *61*, 1539.
6. (a) Elbein, A. D.; Molyneux, R.. In Pelletier, S. W., Ed.; Alkaloids, Chemical and Biological Perspectives; John Wiley & Sons: New York, 1987; Vol. 57, (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435; (c) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.
7. Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679.
8. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19.
9. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1206.

10. Misra, M.; Pandey, S. K.; Pandey, V. P.; Pandey, J.; Tripathi, R.; Tripathi, R. P. *Bioorg. Med. Chem.* **2009**, *17*, 625.
11. Bin, H.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265.
12. (a) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480; (b) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716; (c) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042; (d) Amat, M.; Bassas, O.; Perica's, M. A.; Pasto, P.; Bosch, J. *Chem. Commun.* **2005**, 1327; (e) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325.
13. Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770.
14. (a) Takasu, K.; Shindoh, N.; Tokuyama, H.; Ihara, M. *Tetrahedron* **2006**, *62*, 11900; (b) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773.
15. (a) Murty, M. S. R.; Ram, R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 1141; (b) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org. Lett.* **2006**, *8*, 3837; (c) Dobbs, A. P.; Guesne, S. J. J. *Synlett* **2005**, 2101.
16. Fustero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283.
17. Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169.
18. Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398.
19. Clarke, P. A.; Saytsev, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209.
20. Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmipravha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163.
21. (a) Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785; (b) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, 2843; (c) Bose, G.; Barua, P. M. B.; Chaudhuri, M. K.; Kalita, D.; Khan, A. T. *Chem. Lett.* **2001**, 290; (d) Bose, G.; Mondal, E.; Khan, A. T.; Bordoloi, M. J. *Tetrahedron Lett.* **2001**, *42*, 8907.
22. (a) Lin, Xu. F.; Cui, S. L.; Wang, Y. G. *Synth. Commun.* **2006**, *36*, 3153; (b) Kavala, V.; Patel, B. K. *Eur. J. Org. Chem.* **2005**, *2*, 441; (c) Gopinath, R.; Haque, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842; (d) Gopinath, R.; Patel, B. K. *Org. Lett.* **2000**, *2*, 4177; (e) Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, *42*, 7679.
23. *General procedure for the synthesis of highly functionalized piperidines* **1**: To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of ethanol was added TBATB (0.1 mmol) and stirred at room temperature. After 20 min, aromatic aldehyde (2 mmol) was added to the reaction mixture and stirring was continued. After completion of the reaction, a thick precipitate was obtained. The solid product was filtered off and washed with ethanol. The pure product was characterized by conventional spectroscopic methods. *Spectral data for compound* (**1l**): yield 0.312 g, 54%. Yellow solid, mp 253–254 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.55 (s, 1H), 8.00 (d, 2H, J = 9.2 Hz), 7.97 (d, 2H, J = 9.6 Hz), 7.13 (s, 6H), 7.02 (d, 2H, J = 8.0 Hz), 6.54 (d, 2H, J = 9.6 Hz), 6.48 (s, 1H), 6.43 (d, 2H, J = 9.2 Hz), 5.27 (d, 1H, J = 3.2 Hz), 3.99 (s, 3H), 3.06 (dd, 1H, J = 15.2, 5.6 Hz), 2.94 (dd, 1H, J = 15.2, 2.4 Hz), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.3, 153.3, 151.9, 144.1, 138.3, 138.1, 137.9, 137.5, 137.2, 130.0, 129.7, 126.2, 126.1, 125.9, 125.1, 123.1, 112.3, 102.0, 58.5, 55.8, 52.0, 33.8, 21.3, 21.2; IR ν_{max} (KBr): 1658, 1587 cm^{-1}. Anal. Calcd for $C_{33}H_{30}N_4O_6$ (578.62): C, 68.50; H, 5.23; N, 9.68. Found: C, 68.39; H, 5.14; N, 9.88; HRMS (ESI): calcd for $C_{33}H_{30}N_4O_6$ $[M+H]^+$: m/z = 579.2244; found: 579.2244. *Spectral data for compound* (**1r**): yield 0.177 g, 31%. White solid, mp 239–241 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.78 (s, 1H), 7.38–7.43 (m, 4H), 7.34 (d, 2H, J = 8.4 Hz, 2H), 7.12–7.25 (m, 10H), 6.78 (d, 2H, J = 8.0 Hz), 5.99 (s, 1H), 4.86 (d, 1H, J = 4.0 Hz), 4.33–4.25 (m, 1H), 4.15–4.07 (m, 1H), 3.04 (m, 1H), 1.22 (t, 3H, J = 7.2 Hz), 0.77–0.85 (m, 1H), 0.67–0.76 (m, 1H), 0.18 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.2, 161.8, 151.2, 154.8, 139.9, 139.1, 132.7, 132.4, 129.6, 129.0, 128.9, 128.5, 128.4, 126.6, 126.3, 119.2, 116.2, 95.6, 63.8, 61.7, 60.0, 43.1, 22.2, 14.6, 12.1; IR ν_{max} (KBr): 1655, 1594 cm^{-1}. Anal Calcd for $C_{34}H_{32}N_2O_2Cl_2$ (571.54): C, 71.45; H, 5.64; N, 4.90. Found: C, 71.34; H, 5.53; N, 5.02.
24. Complete crystallographic data of **1l** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 775694. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst

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ABSTRACT

The one-pot three-component reaction for the synthesis of pyran annulated heterocycles is reported by condensing aromatic aldehydes, ethyl cyanoacetate, or malononitrile and C–H activated acidic compounds in the presence of catalytic amount of 4-(dimethylamino)pyridine (DMAP) in ethanol under reflux conditions. The significant features of the present protocol are simple, environmentally benign, high yields, non-aqueous work-up procedure, no chromatographic separation and recyclability of the catalyst.

Multicomponent reactions (MCRs) have gained considerable attention due to powerful bond forming efficiency in combinatorial and medicinal chemistry.[1] The nature of the catalyst and solvent[2,3a] also play a crucial role in the determination of the product and selectivity. Therefore, development of an inexpensive, mild, and reusable catalyst for MCRs remains of interest to the synthetic organic chemist. We have demonstrated effectiveness of various catalysts in organic synthesis using MCRs strategy.[3] We conceived that DMAP might be a better catalyst which can be explored further for multicomponent reactions for the synthesis of pyran annulated heterocycles. A few years ago, the importance and usefulness of 4-(dimethylamino)pyridine (DMAP) in organic synthesis has been reviewed as an efficient catalyst.[4]

Pyran annulated coumarins are widely distributed in nature[5a] and exhibit diverse physiological activities.[5b] Compounds having dihydropyran structural motif exhibit a wide range of biological activities, such as diuretic, analgesic, myorelaxant activity,[6] anticoagulant,[7] anticancer,[8] anti-tumoral,[9] and anti-HIV.[10] In addition, they are also useful for the treatment of neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, and Parkinson's disease.[11] Moreover, they are also used as cosmetics, pigments,[12] and useful as photoactive materials.[13] A considerable effort has been made for the synthesis of pyran annulated heterocyclic derivatives due to their wide applications. Recently, a few methods have been reported by employing three-component reaction using DBU,[14a] TBAB,[14b] diammonium hydrogen phosphate,[14c] heteropoly acids.[14d] Nevertheless, these protocols reported by others are quite useful, still there is further scope to develop a new methodology using a less expensive catalyst under mild reaction conditions and applicable to a wide range of substrates in great demand.

In this Letter, we report 4-(dimethylamino)pyridine (DMAP) catalyzed synthesis of pyran annulated heterocyles, which are obtained through one-pot three-component condensation reaction of aldehydes, ethyl cyanoacetate or malononitrile, and 4-hydroxycoumarin as well as condensation of aldehydes, malononitrile, and cyclic 1,3-diketones (Scheme 1).

For this study, a mixture of 4-chlorobenzaldehyde (1 mmol) and ethyl cyanoacetate (1 mmol) in ethanol was treated with DMAP (0.1 mmol) at room temperature. After consumption of starting aldehyde as checked by TLC, 4-hydroxycoumarin was added to the reaction mixture and kept for stirring under reflux conditions. After the completion of the reaction monitored by TLC, the reaction mixture was brought to room temperature and the solid precipitate was filtered off. The desired product **4a** was obtained in 61% yield, which was characterized by ^{1}H NMR, ^{13}C NMR, and by elemental analysis.

The reaction was optimized using different catalysts for obtaining the best yield of **4a** are summarized in Table 1. It was noted that 20 mol % of the DMAP in ethanol provides the best result in terms of yield and time. Under solvent-free conditions, the product was obtained in a moderate yield (56%).

After the optimization of the reaction conditions, the reaction of benzaldehyde with ethyl cyanoacetate and 4-hydroxycoumarin was carried out under the same reaction conditions and it afforded the product **4b** in 76% yield. The reaction of various other aromatic aldehydes having substituents such as Me, NO_2, OH,

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0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
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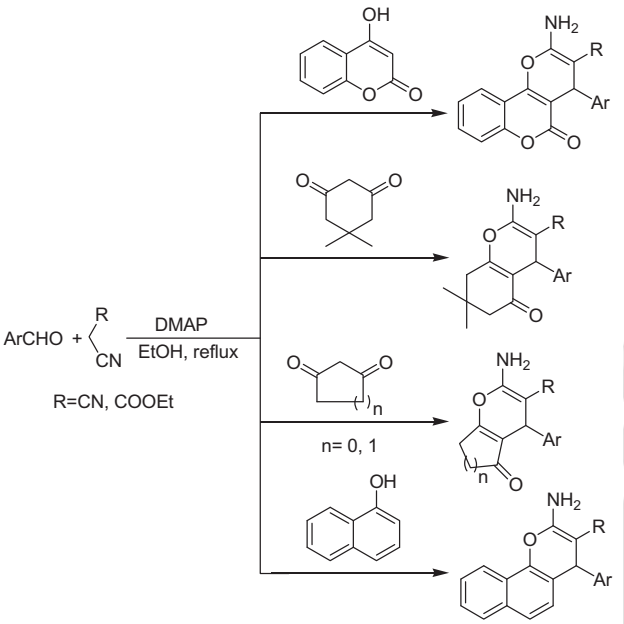


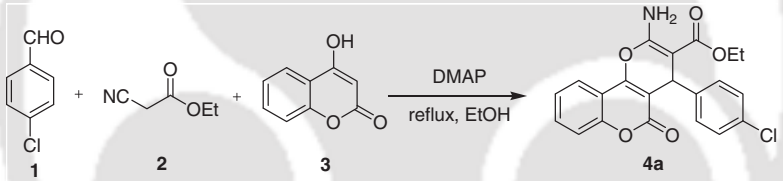
Scheme 1. Synthesis of pyran annulated heterocycles.

Cl, and Br were examined with ethyl cyanoacetate and 4-hydroxycoumarin using identical reaction conditions and resulted in products **4c–i** (Table 2, entries 3–9) in good yields. Similarly, the reaction of aromatic aldehydes with malononitrile and 4-hydroxycoumarin was also carried out using same mol % of DMAP under identical reaction conditions and the products **4j–k** were obtained in excellent yields.

The present protocol was extended using dimedone and the reaction of benzaldehyde, ethyl cyanoacetate, and dimedone was carried out under similar reaction conditions. The desired product **4l** was obtained in 94% yield. The reaction of other aromatic aldehydes substituted with Cl, Me, NO_2, and MeO was also performed with dimedone and ethyl cyanoacetate, the desired products **4m–p** were isolated in good yields (Table 3, entries 2–5). The reaction of 4-chloroaldehyde with malononitrile and dimedone was performed and the product **4q** was obtained in good yield.

The scope of presented protocol further investigated with other C–H activated acidic compounds such as 1,3-cyclopentadione and 1,3-cyclohexadione using 4-chlorobenzaldehyde and malononitrile under similar reaction condition and the results were summarized in Table 3 (entries 7–9). The reaction of 4-chloroaldehyde with malononitrile and α-naphthol was performed and the product **4u** was obtained in good yield. From the above observation, it is important to mention that the reaction was fast and also provided better yields using either aldehyde having electron withdrawing group viz. NO_2 or with malononitrile. All the products were charac-

Table 1
Optimization of reaction conditions



Entry	Catalyst	Solvent	Catalytic amount (mol %)	Time (h)	Yield[a] (%)
1	DMAP	Neat	20	3	56
2	Piperidine	EtOH	20	4	40
3	DMAP	EtOH	10	5	61
4	DMAP	EtOH	20	3	78
5	DMAP	EtOH	30	3	76
6	DMAP	MeOH	20	3	69
7	DMAP	Water	20	4	62

[a] Isolated yield.

Table 2
Synthesis of dihydropyrano[3,2-*c*]chromene derivatives using aromatic aldehydes, ethyl cyanoacetate or malononitrile, and 4-hydroxycoumarin catalyzed by DMAP[15]

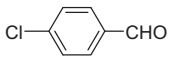
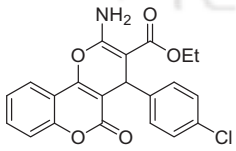
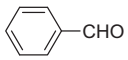
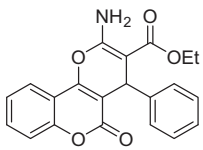
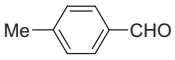
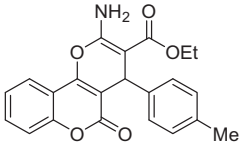
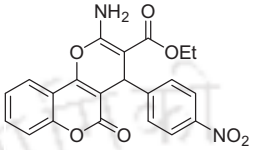
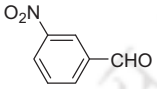
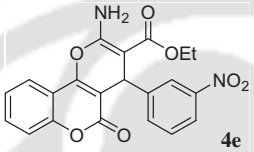
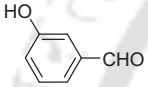
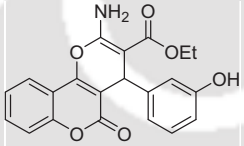
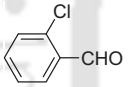
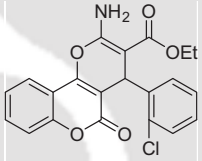
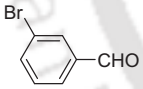
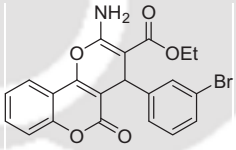
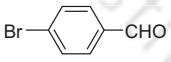
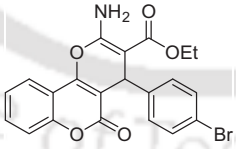
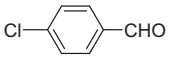
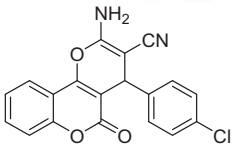
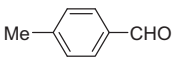
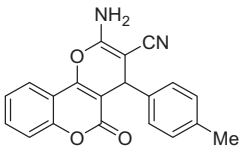
Entry	Aromatic aldehydes	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
1		 **4a**	2.5	78	194–195 [192–194][14a]
2		 **4b**	3.5	76	187–189

Table 2 (*continued*)

Entry	Aromatic aldehydes	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
3		 **4c**	4.0	76	114–117
4		 **4d**	1.5	82	241–244 [241–243][14a]
5		 **4e**	3.5	80	242–245 [247–250][14c]
6		 **4f**	3.0	67	208–210
7		 **4g**	5.0	64	209–212
8		 **4h**	4.5	81	196–198
9		 **4i**	4.0	80	142–144
10		 **4j**	[5]	94	264–266 [263–265][14d]
11		 **4k**	[10]	92	258–260 [253–255][14a]

[a] Isolated yield.

Table 3
Synthesis of chromene derivatives using diketones, ethyl cyanoacetate or malononitrile, and aromatic aldehydes catalyzed by DMAP[15]

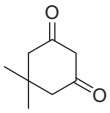
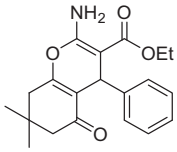
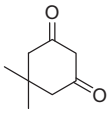
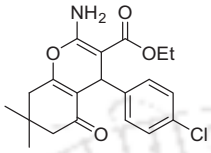
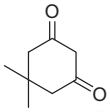
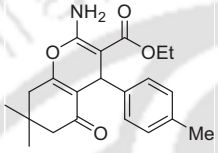
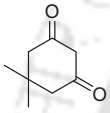
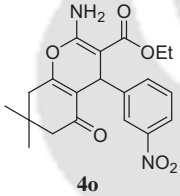
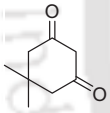
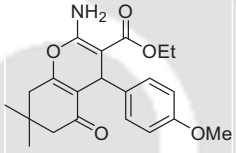
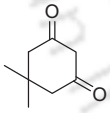
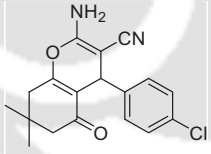
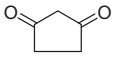
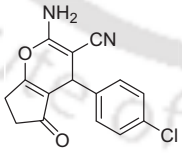
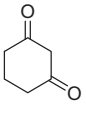
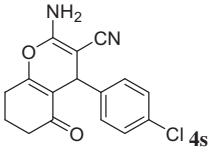
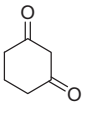
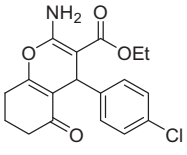
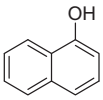
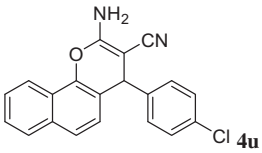
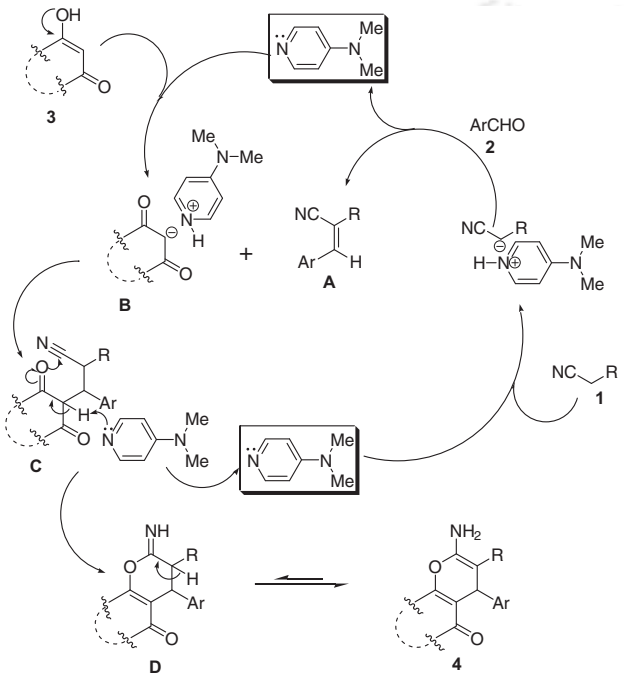
Entry	1,3-Diketones	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
1		 **4l**	3.5	94	144–146
2		 **4m**	5.0	92	139–142
3		 **4n**	4.5	91	151–152
4		 **4o**	1.5	91	154–156
5		 **4p**	3.5	91	131–134
6		 **4q**	[15]	94	213–215 [212–214][14e]
7		 **4r**	[10]	98	216–218
8		 **4s**	[10]	95	241–243
9		 **4t**	2.5	95	163–165

Table 3 (*continued*)

Entry	1,3-Diketones	Product	Time (h/[min])	Yield[a] (%)	Mp °C (lit.)
10		 **4u**	[20]	92	244–243

[a] Isolated yields.



Scheme 2. Plausible mechanism for the formation of pyran annulated heterocyclic compounds.

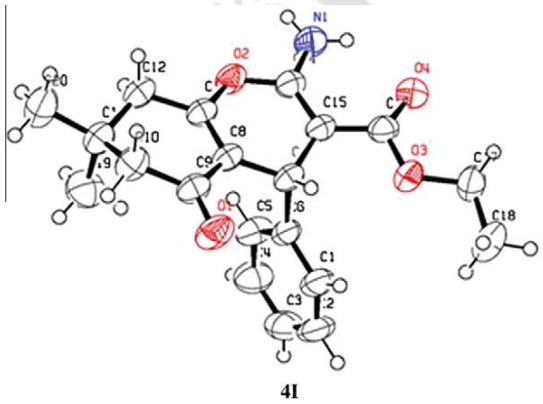


Figure 1. ORTEP diagram of **4l** (CCDC 828132).

terized by IR, ^{1}H NMR, and ^{13}C NMR spectra and by elemental analysis.

The formation of various pyran annulated heterocyclic compounds can be rationalized as follows. Initially, the Knovengel product **A** was formed by the reaction of aldehyde and alkyl nitrile in the presence of DMAP, which reacts with in situ generated carbanion from activated C–H acidic compounds to give intermediate **C**. The intermediate **C** was cyclized to **D** in the presence of DMAP. Finally, **D** tautomerized to give the desired product **4** as shown in Scheme 2.

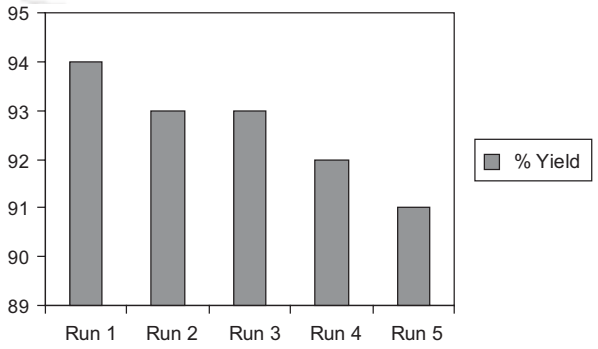


Figure 2. Reusability of the catalyst.

Moreover, the structure of compound **4l** was further confirmed by X-ray crystallographic analysis (Fig. 1).[16]

Further the role of catalyst was ascertained by the reaction of **A**, which is obtained from the reaction of 4-chlorobenzaldehyde and malononitrile in the presence of DMAP, with 4-hydroxycoumarin in the presence of DMAP and without DMAP. The product **4j** was obtained with DMAP within 5 min in 94% yield, whereas the same reaction without catalyst gave only 63% yield after 1 h of stirring under reflux conditions.

The reusability test was performed as follows: A mixture of 4-chlorobenzaldehyde (2 mmol), malononitrile (2 mmol), 4-hydroxycoumarin, and DMAP (0.4 mmol) was stirred in ethanol (8 mL) under reflux condition. After completion of the reaction, the solid precipitate was filtered using a Buchner funnel. The precipitate was washed with ethanol (0.5 mL). The filtrate containing catalyst was reused for similar scale of reaction for the same substrates. The procedure was repeated five times which is depicted in Figure 2.

In summary, we have devised a simple and efficient protocol for the synthesis of pyran annulated heterocycles using DMAP as catalyst via one-pot three-component condensation reaction of an aldehyde, ethyl cyanoacetate or malononitrile, and either 4-hydroxycoumarin or 1,3-cyclic ketones or 2-naphthol in excellent yields. The advantages offered by this DMAP versus known catalysts are (i) inexpensive, (ii) reusable, and (iii) no need chromatographic separation. The significant features of this protocol are good yields and applicable to the broad range of substrates especially the less reactive alkyl nitrile such as ethyl cyanoacetate also provides the desired pyran annulated heterocycles, which are not much studied earlier.

Acknowledgments

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Supplementary data

Supplementary data (X-ray crystallographic data (CIF files) of **4a** and **4l** and spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.019.

References and notes

1. (a) Zhu, J.; Bienayme, H. *Multicomponent Reactions*, 1st ed.; Wiley-VCH: Weinheim, Germany, 2005; (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; (c) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; (d) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.
2. Wang, X.-S.; Li, Q.; Wu, J.-R.; Li, Y.-L.; Yao, C.-S.; Tu, S.-J. *Synthesis* **2008**, 1902.
3. (a) Khan, A. T.; Khan, M. M.; Bannuru, K. K. R. *Tetrahedron* **2010**, *66*, 7762; (b) Khan, A. T.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 3455; (c) Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010**, *51*, 4419; (d) Khan, A. T.; Parvin, T.; Choudhury, L. H. *J. Org. Chem.* **2008**, *73*, 8398.
4. Murugan, R.; Sriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21.
5. (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butter-worths: London, 1963; (b) Feuer, G. Progress in Medicinal Chemistry In Ellis, G. P., West, G. P., Eds.; North-Holland Publishing Company: New York, 1974.
6. Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517.
7. Cingolani, G. M.; Gualtteri, F.; Pigin, M. *J. Med. Chem.* **1961**, *12*, 531.
8. Wu, J. Y. C.; Fong, W. F.; Zhang, J. X.; Leung, C. H.; Kwong, H. L.; Yang, M. S.; Li, D.; Cheung, H. Y. *Eur. J. Pharmacol.* **2003**, *473*, 9.
9. (a) Baraldi, P. G.; Manfredini, S.; Simoni, D.; Tabrizi, M. A.; Balzarini, J.; Clercq, E. D. *J. Med. Chem.* **1877**, *35*, 1992; (b) Perrella, F. W.; Chen, S. F.; Behrens, D. L.; Kaltenbach, R. F.; Seitz, S. P. *J. Med. Chem.* **1994**, *37*, 2232.
10. (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W.; Hughes, S. H.; Gragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735; (b) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Waltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westley, J. W. *J. Med. Chem.* **1993**, *36*, 4131.
11. (a) Foye, W. O. *Principi di Chemico Farmaceutica; Piccin: Padora, Italy*, 1991. P 416.; (b) Andreani, L. L.; Lapi, E. *Bull. Chim. Farm.* **1960**, *99*, 583; (c) Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H.; Yaoxue, X. B. *Chem. Abstr.* **1982**, *17*, 17. *Chem. Abstr.* **1982**, *96*, 135383e; (d) Bonsignore, L.; Loy, G.; Secci, D.; zCalignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517.
12. Ellis, G. P. In *The Chemistry of Heterocyclic Compounds Chromenes, Chromanes and Chromones*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, NY, 1977; p 11. Chapter II.
13. Arnesto, D.; Horspool, W. M.; Martin, N.; Ramos, A.; Seaone, C. *J. Org. Chem.* **1989**, *54*, 3069.
14. (a) Khurana, J. M.; Nand, B.; Saluja, P. *Tetrahedron* **2010**, *66*, 5637; (b) Khurana, J. M.; Kumar, S. *Tetrahedron Lett.* **2009**, *50*, 4125; (c) Heravi, M. M.; Sadjadi, S.; Haj, N. M.; Oskooie, H. A.; Bamoharram, F. F. *Catal. Commun.* **2009**, *10*, 1643. and references therein; (d) Abdolmohammadi, S.; Balalaie, S. *Tetrahedron Lett.* **2007**, *48*, 3299.
15. *General procedure for the synthesis of pyran annulated heterocyclic compounds*: Into a mixture of an aromatic aldehyde (1 mmol) and ethyl cyanoacetate or malononitrile (1 mmol) in 4 mL of ethanol was added the catalyst DMAP (0.025 g, 0.2 mmol) and kept for stirring at room temperature. The solid precipitate was formed immediately in case of malononitrile or it took 20–30 min. for ethyl cyanoacetate. Then C–H activated acidic compound (1 mmol) was added into the reaction mixture and it was kept for stirring under reflux conditions. After sometime, the reaction mixture was converted into clear solution. After the completion of the reaction, the solid precipitate came out under hot conditions at the stipulated time mentioned in the Table 2 and Table 3. The reaction mixture was brought to room temperature and the solid precipitate was filtered off to obtain the desired product. *Ethyl 2-amino-4-(3-hydroxyphenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carboxylate Ethyl 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate* (***4l***): Yield 0.320 g, 94%. Solid, mp 144–146 °C. IR ν_{max} (KBr): 3403, 3290, 2956, 1667, 1614, 1524, 1371 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 3H), 1.10 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.19 (q, J = 16.4 Hz, 2H), 2.42 (s, 2H), 3.98-4.07 (m, 2H), 4.70 (s, 1H), 6.17 (brs, 2H), 7.10 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.6 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 27.5, 29.2, 32.4, 33.9, 40.8, 50.9, 59.8, 80.9, 116.9, 126.2, 127.9, 128.4, 145.9, 158.5, 161.5, 169.3, 196.5 ; Anal. Calcd for $C_{20}H_{23}NO_4$ (341.40): C, 70.36; H, 6.79; N, 4.10. Found C, 70.29; H, 6.71; N, 4.01.
16. Complete crystallographic data of **4l** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 828132, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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Synthesis of *tetra*-substituted pyrroles, a potential phosphodiesterase 4B inhibitor, through nickel(II) chloride hexahydrate catalyzed one-pot four-component reaction

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This work is dedicated to my mentor, Professor Dr. R. R. Schmidt on the occasion of his 77th birthday

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ABSTRACT

A wide variety of *tetra*-substituted pyrrole derivatives were synthesized through one-pot four-component condensation reaction of aromatic aldehydes, benzylamines, β-ketoesters, and nitroalkanes in the presence of 10 mol % $NiCl_2{\cdot}6H_2O$ in good yields. Some of them exhibit properties as potential inhibitors of phosphodiesterase 4B (PDE4B) through docking studies.

In recent times, multicomponent reactions (MCRs) have been extensively utilized in organic synthesis, combinatorial and medicinal chemistry due to their simplicity and high selectivity, good yield, superior atom-economy, high variability, less time consuming and avoidance of costly purification processes.[1]

Pyrrole and its derivatives are naturally occurring compounds and some of their synthetic strategies have been reviewed recently.[2] They also display a wide range of biological activities such as antibacterial, antiviral, anticonvulsant, anticancer, and antioxidant.[3] Some of them are promising lead molecule for cholesterol lowering agent. In addition, they are also useful in building blocks which are extensively used in material science.[4] The synthesis of pyrroles and their derivatives is usually achieved by employing well-known Hantzsch[5] or Knorr[6] or Paal Knorr[7] reaction. Recently, *tetra*-substituted pyrrole derivatives were reported by Jana and co-workers by employing four-component reaction catalyzed by $FeCl_3$[8] or palladium mediated Suzuki coupling based MCR.[9] Menendez and his co-workers reviewed[10] recently the synthesis of pyrroles and their derivatives through multicomponent reactions (MCRs). Phosphodiesterase (PDE) are enzymes that play vital roles in regulating the cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), secondary messengers that mediate several biological processes with response to extracellular signals.[11] The inhibition of PDE leads to higher levels of cyclic nucleotides. They also have therapeutic potential such as anti-inflammators, anti-asthmatics, vasodilators, antidepressants, antithrombiotics and cognitive function enhancers.[12,13] The existing therapies serve as symptomatic treatment and PDE inhibitors prevent progression of several diseases and provide better relief for symptoms.[14] Due to their wide range of biological activities, the synthesis of these compounds under different reaction conditions is highly desirable.

Nickel salts are commonly used in coupling reaction.[15] A few years ago, we had demonstrated anhydrous $NiCl_2$ as an useful Lewis acid for chemoselective thioacetalization of aldehydes[16a] and deprotection of tetrahydropyranyl ether as well as *tert*-butyldimethylsilyl ether using a combination of catalytic amount of $NiCl_2{\cdot}6H_2O$ and 1,2-ethanthiol.[16b] Recently, other research groups have shown the efficacy of anhydrous $NiCl_2$ for multicomponent

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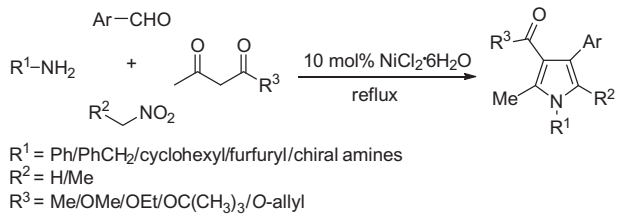


Scheme 1. Synthesis of *tetra*-substituted pyrrole derivatives.

reactions (MCRs).[17] As a part of our ongoing research interest to find out new catalysts on MCRs for the synthesis of various heterocyclic compounds[18], we perceived nickel(II) chloride hexahydrate might be a useful catalyst for the synthesis of highly substituted pyrroles. Herein, we wish to report a simple and useful synthetic protocol for the synthesis of *tetra*-substituted pyrroles by employing $NiCl_2{\cdot}6H_2O$ as a catalyst through one-pot four-component condensation reaction of aromatic aldehydes, benzylamines, β-ketoesters or 1,3-diketone, and nitroalkanes as shown in Scheme 1.

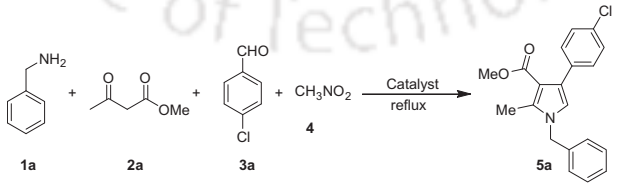
With this goal in mind, a mixture of methylacetoacetate (1 mmol), benzylamine (1 mmol) and $NiCl_2{\cdot}6H_2O$ (0.1 mmol) in of nitromethane (1 mL) was stirred at room temperature with 4-chlorobenzaldehyde to give the desired product **5a** in 78% yield. The efficacy of the other catalysts was also scrutinized by carrying out similar set of reactions in the presence of other catalysts such as $Fe_2(SO_4)_3$, $ZnCl_2$, $NiCl_2$ and $NiCl_2{\cdot}6H_2O$ under identical conditions and the results are summarized in Table 1. Among them, $NiCl_2{\cdot}6H_2O$ is found to be the most effective catalyst for the synthesis of *tetra*-substituted pyrrole derivatives. In the above transformation, nitroalkane plays a dual role of a solvent as well as a reactant.

After optimization of the reaction conditions, the next reaction was carried out with a mixture of benzylamine, methylacetoacetate, benzaldehyde and nitromethane in presence of 10 mol % of $NiCl_2{\cdot}6H_2O$ under identical reaction conditions and it afforded the desired product **5b** in 72% yield (Table 2, entry 2). Due to these successful results, various aromatic aldehydes having substituents such as Me, MeO, NO_2, F, and Br in the aromatic ring were examined with benzylamine and methylacetoacetate in the presence of the same amount of catalyst in similar reaction conditions and the products **5c–g** (Table 2, entries 3–7) were obtained in good yields. The same methodology was further extended with heteroaromatic aldehydes namely 2-formylthiophene and furan-2-carbaldehyde, respectively and the desired products **5h** and **5i** (Table 2, entries 8 and 9) were isolated in 58% and 55% yields, respectively. Further, the scope of the present protocol was elongated with other amines such as cyclohexylamine, 4-methylbenzylamine, and furfurylamine with methylacetoacetate and 4-chlorobenzaldehyde. All these reactions went smoothly and also provided the products **5j–l** (Table 2, entries 10–12) in good yields under similar reaction conditions. Similarly, the reactions were also verified with different β-ketoesters namely ethylacetoacetate, *tert*-butylacetoacetate, allylacetoacetate with benzylamine and 4-chlorobenzaldehyde, respectively and the required products **5m–o** (Table 2, entries 13–15) were isolated in good yields. Finally, the reactions were also studied with acetylacetone, benzylamine, and 4-chlorobenzaldehyde or 4-bromobenzaldehyde in a similar manner and the desired products **5p** and **5q** (Table 2, entries 16 and 17) were isolated in 56% and 60% yields, respectively. It was observed that aniline also reacts with acetylacetone and benzaldehyde under identical conditions and the product **5r** was obtained in 52% yield (Table 2, entries 18). Further, the scope of the reaction was also verified with chiral benzyl amines such as (*R*)-1-phenylethanamine or (*S*)-1-phenylethanamine under similar conditions and the preferred products **5s** and **5t** were isolated in 76% and 72% yields (Table 2, entry 19 and 20) respectively. Similarly, the reaction of (*R*)-1-phenylethanamine, ethylacetoacetate, and 4-fluorobenzaldehyde gave the product **5u** in 75% yield (Table 2, entry 21). Similarly, an aldehyde containing electron-withdrawing group such as *o*-nitrobenzaldehyde also provided the product **5v** in 65% yield (Table 2, entry 22) on reaction with (*S*)-1-phenylethanamine and ethylacetoacetate in a similar manner.

The scope of the present protocol was further scrutinized with other nitroalkane namely nitroethane with benzylamine, methylacetoacetate, and 4-methyl benzaldehyde and the product **5w** was obtained in 60% yield (Scheme 2). These successful results clearly indicate that the present protocol is also extendable to a wide variety of substrates.

The formation of various *tetra*-substituted pyrroles can be rationalized as follows: Initially, amine reacts with β-ketoester to produce enamine **A** in the presence of Lewis acid $NiCl_2{\cdot}6H_2O$. We assume that nitroalkane reacts with benzylamine to generate carbanion **B** which reacts with the $NiCl_2{\cdot}6H_2O$ activated aromatic aldehyde to form nitrostyrene **C**,[20] as shown in Scheme 3. Subsequently, the enamine **A** reacts with nitrostyrene **C** to provide Michael adduct **D**. The intermediate **D** undergoes concomitant cyclization with the elimination of NiO, NO, and HCl to provide

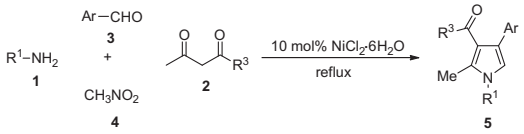
Table 1
Optimization of reaction conditions for the synthesis of *tetra*-substituted pyrrole[a]



Entry	Catalyst	Catalytic amount (mol %)	Time (h)	Yield[b] (%)
1	$Fe_2(SO_4)_3$	10	12	40
2	$ZnCl_2$	10	12	45
3	$NiCl_2$	10	12	49
4	$NiCl_2{\cdot}6H_2O$	5	13	60
5	$NiCl_2{\cdot}6H_2O$	10	10	78
6	$NiCl_2{\cdot}6H_2O$	15	10	77

[a] The reactions were performed using 1 mmol scale with benzylamine (**1a**), methylacetoacetate (**2a**) and 4-chlorobenzaldehyde (**3a**) respectively in 1 mL of nitromethane under reflux conditions.
[b] Isolated yield.

Table 2
Synthesis of *tetra*-substituted pyrrole derivatives from various aromatic aldehydes, β-ketoesters amines and nitroalkanes[19]



Entry	R_1	Ar	R^3	Time/h	Product[a]	Yield[b] (%)
1	$C_6H_5CH_2$	4-Cl-C_6H_4	OMe	8	**5a**	78
2	$C_6H_5CH_2$	C_6H_5	OMe	9	**5b**	72
3	$C_6H_5CH_2$	4-Me-C_6H_4	OMe	8	**5c**	75
4	$C_6H_5CH_2$	4-OMe-C_6H_4	OMe	8	**5d**	65
5	$C_6H_5CH_2$	4-NO_2-C_6H_4	OMe	9	**5e**	70
6	$C_6H_5CH_2$	4-F-C_6H_4	OMe	8	**5f**	76
7	$C_6H_5CH_2$	4-Br-C_6H_4	OMe	8	**5g**	73
8	$C_6H_5CH_2$	2-Thiophen	OMe	12	**5h**	58
9	$C_6H_5CH_2$	2-Furan	OMe	11	**5i**	55
10	C_6H_{11}	4-Cl-C_6H_4	OMe	9	**5j**	74
11		4-Cl-C_6H_4	OMe	10	**5k**	72
12	4-Me$C_6H_4CH_2$	4-Cl-C_6H_4	OMe	9	**5l**	70
13	$C_6H_5CH_2$	4-Cl-C_6H_4	OEt	10	**5m**	78
14	$C_6H_5CH_2$	4-Cl-C_6H_4	$OC(CH_3)_3$	11	**5n**	76
15	$C_6H_5CH_2$	4-Cl-C_6H_4		12	**5o**	75
16	$C_6H_5CH_2$	4-Cl-C_6H_4	Me	8	**5p**	56
17	$C_6H_5CH_2$	4-Br-C_6H_4	Me	9	**5q**	60
18	C_6H_5	C_6H_5	Me	10	**5r**	52
19		4-Me-C_6H_4	OMe	6	**5s**	76
20		4-Me-C_6H_4	OMe	7	**5t**	72
21		4-F-C_6H_4	OEt	8	**5u**	75
22		2-NO_2-C_6H_4	OEt	10	**5v**	65

[a] The reactions were performed using 1 mmol of amines (**1**), 1 mmol of β-ketoesters (**2**) or 1,3-diketone, and 1 mmol of aromatic aldehydes (**3**) in 1 mL nitromethane under reflux conditions.
[b] Isolated yield.

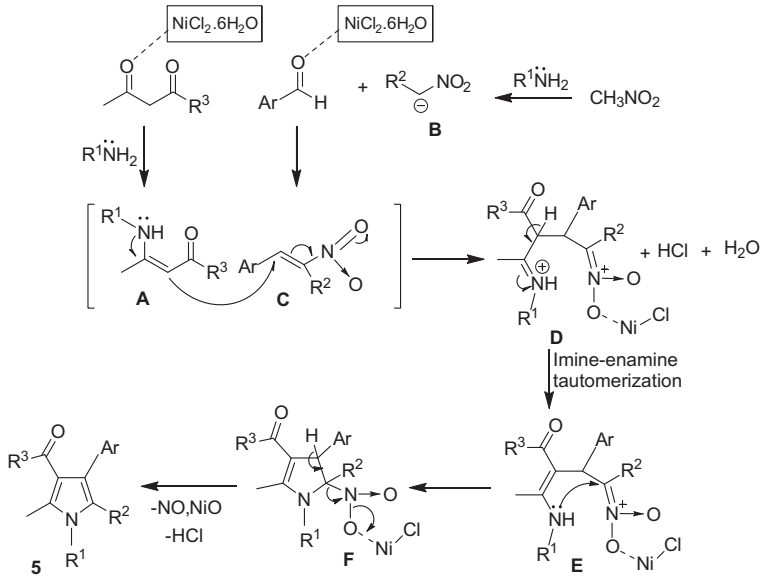
Scheme 2. Synthesis of fully substituted pyrrole.

the final product **5**, since the intermediate 'enamine **A'** can react[21] as a 'di-nucleophile.' The pH of the reaction mixture was 2-3 during reaction time indicating the generation of HCl in the medium. To prove the mechanism, we have carried out an experiment with a mixture of β-ketoester, benzylamine, aromatic aldehyde, and nitromethane in the presence of 10 mol % NiO. We have obtained tetra-substituted pyrrole derivative **5b** in 70% yield. From this observation we believe that the NiO generated in the reaction is further participating in the catalytic cycle for the formation of the product.

The structure of compound **5k** was confirmed by single XRD crystallographic data[22] and the ORTEP diagram of substituted pyrrole **5k** is shown in Fig. 1.

In support of the mechanism, the by product, NiO was characterized through X-ray diffraction (XRD) analysis. A representative XRD pattern of the product NiO is given in Supplementary data.

Structure-based docking study is a viable method for the identification of hits and enriching the lead identification phase of the pharmaceutical industry.[23] The synthesized compounds especially



Scheme 3. Plausible mechanism for the formation of substituted pyrrole derivatives.

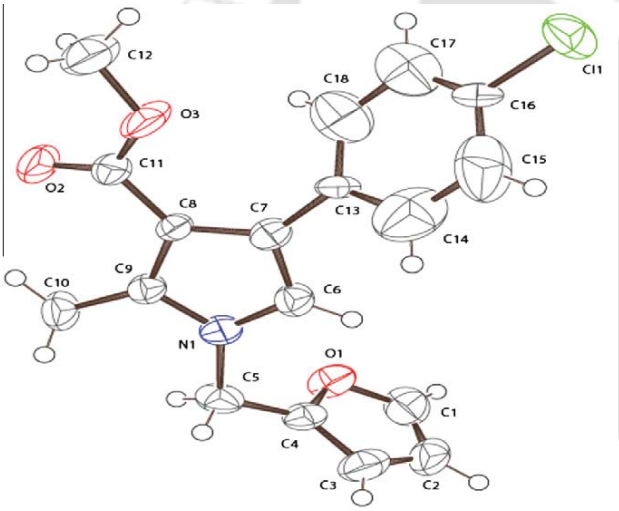


Figure 1. ORTEP diagram of compound of **5k** (CCDC 848584).

the top hits formed hydrogen bond with hydroxyl group of Tyr233 and also a conserved π interaction with Phe446 as shown in Table 3. The interactions were also stabilized by the hydrophobic residues of the active site pocket mainly Ile410 and Phe446. The best hit, **5b** had similar interaction mode and hydrophobic contacts with Pro396 and Phe414 also contributed to the binding as shown in Fig. 2 (predicted free energy of binding: −0.29 kcal/mol). The compounds bound near to the invariant Gln443 which could be exploited to design non-selective PDE inhibitors.

The docking provides insight into designing selective inhibitors for PDE4 which are provided in Table 4. The contact residues of the synthesized derivatives from the docking studies are analyzed for their conservation within PDE family used in the current study. Significant differences observed in the contact residues are: (i) Tyr403 whose counterpart are Histidine, Glutamine, Serine and Alanine in PDE1, PDE3, PDE5, PDE7, and PDE9, respectively; (ii) Met431 whose counterpart are Threonine, Phenyalanine, Aspartate, Leucine, and Phenyalanine in PDE1, PDE3, PDE5, PDE7 and PDE9, respectively.

Partial differences are also observed in the contact residues as shown in Table 4 which can be exploited to design selective inhibitors.

The compounds bound near to the invariant Gln443 which could be exploited to design non-selective PDE inhibitors. Design of lead molecules interacting with Asn395, Pro396, and Thr407 can be designed for dual inhibitors against PDE family and lead molecules with strong interactions towards Tyr403 and Met431 can be designed to selectively inhibit PDE4 family.

Table 3
Compounds with comparable inhibition efficiency of reference compound (PDB ligand ID: 20A)

Entry	Product	Score	Poseview H-bond	Poseview π-interaction	Poseview hydrophobic contact residues
1	**5b**	−8.29	Y233-O1	F446[2]	**I410**, F414, **F446**, P396, N395, Y403
2	**5f**	−8.22	Y233-O1	F446[2]	N395 P396, **I410**, F414, **F446**
3	**5h**	−8	Y233-O1	F446[2]	**I410**, F414, **F446**
4	**5r**	−7.99		F446[2]	N395, Y403, T407, M431, **I410**, F414, **F446**
5	**5a**	−7.97	H234-O	F446	Y233, L393, N395, **I410**, **F446**
6	**5c**	−7.96		F446	Y233, N395, **I410**, F414, S442, **F446**
7	**5j**	−7.9		F446[2], F414	**I410**, N395, F414, **F446**
8	**5q**	−7.87		F446[2]	M431, **I410**, F414, **F446**
9	**5m**	−7.84		F446[3]	M431, **I410**, **F446**
10	**20A**	−7.76	Q443	F446	**I410**, M431, **F446**
11	**5g**	−7.72		F446[3]	M431, **I410**, **F446**

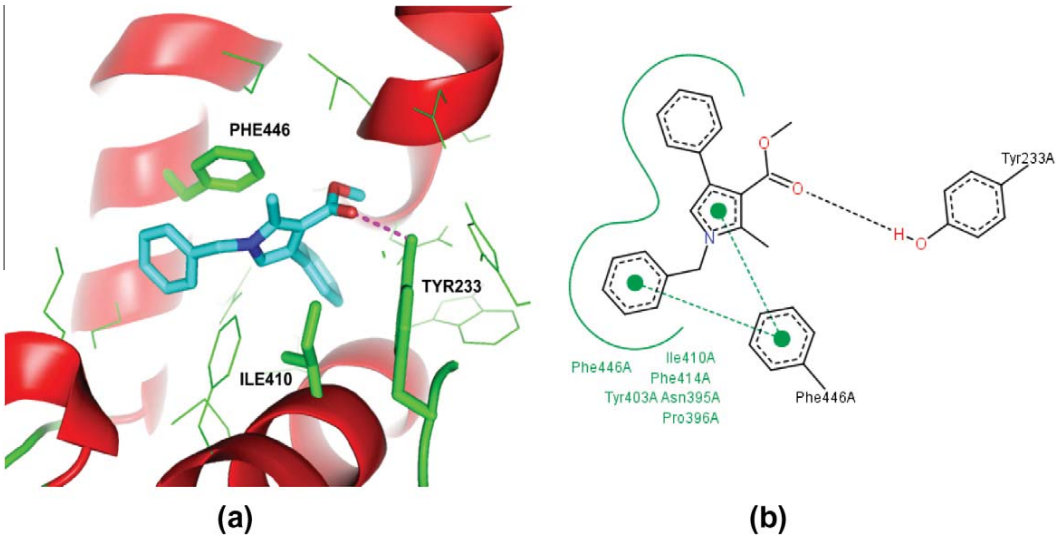


Figure 2. Interaction mode of the best hit (**5b**) with PDE4B in (a) 3D and (b) 2D view.

Table 4
Contact residues of synthesized pyrrole derivatives from the docking studies provide insight to design selective inhibitors for PDE4

PDE Type	PDB Id	Contact residues of synthesized derivatives								
PDE4B*	3D3P	**Y233**	N395	P396	Y403	T407	**I410**	F414	M431	**F446**
PDE1	1TAZ		H		H		L		T	
PDE3	1SO2		G		H				F	
PDE5	1UHO		A	I	Q	A	V		D	
PDE7	1ZKL				S	S	V		L	
PDE9	2HD1	F		E	A	A	L	Y	F	
PDE4B2B	1FOJ									
PDE4D	1MKD									
PDE4D2	1OYN									

*Numbering according to the PDE4B (PDB Id: 3D3P) (Residues interacting with the synthesized derivatives in the docking studies are highlighted in bold and corresponding identical residue in other family are not shown).

In summary, we have demonstrated the use of a four-component reaction for the synthesis of *tetra*-substituted pyrroles starting from amines, β-ketoesters or 1,3-dicarbonyl compounds, aromatic aldehydes or heteroaromatic aldehydes, and nitroalkanes using $NiCl_2{\cdot}6H_2O$ as catalyst in moderate to good yields. The reaction proceeds through the formation of enamine and nitrostyrene followed by Michael addition and subsequently, it undergoes intramolecular cyclization to afford pyrroles derivatives. The binding study of the synthesized pyrrole derivatives indicates their potential as inhibitors of phosphodiesterase 4B (PDE4B) enzymes.

Acknowledgments

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Supplementary data

Supplementary data (X-ray crystallographic data (CIF files) of **5k**, spectral data of all compounds and copies of ^1H and ^{13}C NMR spectra of products and interaction mode) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.133.

References and notes

1. (a) Zhu, J. *Bienaymé, H*; Multicomponent Reactions, Wiley-VCH: Weinheim, 2005; (b) Orru, R. V. A.; Ruijter, E. In *Synthesis of Heterocyles via Multicomponent Reactions*; Maes, B. U. W., Ed.; Springer-Verlag: Berlin, 2010; Vol. 1 & 11,. Vol. I & II.
2. Mal, D.; Shome, B.; Dinda, B. K. In *Heterocyles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, 2011; pp 187–220.
3. (a) Biava, M.; Porretta, G. C.; Deidda, D.; Pompei, R.; Tafic, A.; Manettic, F. *Bioorg. Med. Chem.* **2004**, *12*, 1453–1458; (b) Protopopova, M.; Bogatcheva, E.; Nikonenko, B.; Hundert, S.; Einck, L.; Nacy, C. A. *Med. Chem.* **2007**, *3*, 301–316; (c) Teixeira, C.; Barbault, F.; Rebehmed, J.; Liu, K.; Xie, L.; Lu, H.; Jiang, S.; Fan, B.; Maurel, F. *Bioorg. Med. Chem.* **2008**, *16*, 3039–3048; (d) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62; (e) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J. M. *Eur. J. Med. Chem.* **1999**, *34*, 991–996.
4. (a) Lazerges, M.; Chane-Ching, K. I.; Aeiyach, S.; Chelli, S.; Peppin-Donnat, B.; Billon, M.; Lombard, C.; Maurel, F.; Jouini, M. *J. Solid State Electrochem.* **2009**, *13*, 231–238; (b) Kros, A.; van Hövel, S. W. F. M.; Nolte, R. J. M.; Sommerdijk, N. A. J. M. *Sens Actuators, B* **2001**, *80*, 229–233; (c) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891–4932; (d) Kiskan, B.; Akar, A.; Kizilcan, N.; Ustamehmetoglu, B. *J. Appl. Polym. Sci.* **2005**, *96*, 1830–1834.
5. (a) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474–1483; (b) Kaupp, G.; Schmeyers, J.; Kuse, A.; Atfeh, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2896–2899; (c) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Compd.* **2004**, *40*, 1218.
6. (a) Knorr, L. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1635–1642; (b) Manley, J. M.; Kalman, M. J.; Conway, B. G.; Ball, C. C.; Havens, J. L.; Vaidyanathan, R. *J. Org. Chem.* **2003**, *68*, 6447–6450; (c) Shiner, C. M.; Lash, T. D. *Tetrahedron* **2005**, *61*, 11628–11640.

7. (a) Pall, C. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 367–371; (b) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–216; (c) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, *24*, 5277–5288.
8. Maiti, S.; Biswas, S.; Jana, U. *J. Org. Chem.* **2010**, *75*, 1674–1683.
9. Reddy, G. R.; Reddy, T. R.; Joseph, S. C.; Reddy, K. S.; Reddy, L. S.; Kumar, P. M.; Krishna, G. R.; Reddy, C. M.; Rambabu, D.; Kapavarapu, R.; Lakshmi, C.; Meda, T.; Priya, K. K.; Parsa, K. V. L.; Pal, M. *Chem. Comm.* **2011**, *47*, 7779–7781.
10. Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402–4421.
11. Conti, M.; Beavo, J. *Annu. Rev. Biochem.* **2007**, *76*, 481–511.
12. Bender, A. T.; Beavo, J. A. *Pharmacol. Rev.* **2006**, *58*, 488–520.
13. Card, G. L.; England, B. P.; Suzuki, Y.; Fong, D.; Powell, B.; Lee, B.; Luu, C.; Tabrizizad, M.; Gillette, S.; Ibrahim, P. N.; Artis, D. R.; Bollag, G.; Milburn, M. V.; Kim, S. H.; Schlessinger, J.; Zhang, K. Y. *Structure* **2004**, *12*, 2233–2247.
14. Rotella, D. P. *Nat. Rev. Drug Discov.* **2002**, *1*, 674–682.
15. (a) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182; (b) Lee, K.; Counceller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, *11*, 1457–1459.
16. (a) Khan, A. T.; Mondal, E.; Sahu, P. R.; Islam, S. *Tetrahedron Lett.* **2003**, *44*, 919–922; (b) Khan, A. T.; Islam, S.; Choudhary, L. H.; Ghosh, S. *Tetrahedron Lett.* **2004**, *45*, 9617–9621.
17. (a) Samai, S.; Nandi, G. C.; Singh, M. S. *Tetrahedron Lett.* **2010**, *51*, 5555–5558; (b) Zhang, X.-N.; Li, Y.-X.; Zhang, Z.-H. *Tetrahedron* **2011**, *67*, 7426–7430.
18. (a) Khan, A. T.; Lal, M.; Ali, S.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 5327–5332; (b) Khan, A. T.; Das, D. K.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 4539–4542; (c) Khan, A. T.; Khan, M. M. *Tetrahedron Lett.* **2011**, *52*, 3455–3459; (d) Khan, A. T.; Khan, M. M.; Bannuru, K. K. R. *Tetrahedron* **2010**, *66*, 7762–7772; (e) Khan, A. T.; Lal, M.; Khan, M. M. *Tetrahedron Lett.* **2010**, *51*, 4419–4424.
19. *General Procedure for the Synthesis of Pyrrole*: To a mixture of an amine (1 mmol) and β-ketoester (1 mmol) in nitromethane (1 mL) was added 10 mol % $NiCl_2{\cdot}6H_2O$ and kept for stirring at room temperature. The solid precipitate appeared after 10 minutes and then aromatic aldehyde (1 mmol) was added into it. Subsequently, the reaction mixture was kept for refluxing in a heated oil-bath with constant stirring. After completion of the reaction as monitored by TLC, the reaction mixture was brought to room temperature and the excess nitromethane was removed in a rotary evaporator. Then, the crude residue was dissolved in 25 mL of dichloromethane and the solid particle was removed by filtration. The precipitate was further washed with 2 mL of dichloromethane. The filtrate was washed with water and dried over anhydrous sodium sulfate. The organic extract was concentrated and the crude residue was finally purified through a silica gel column chromatography. The final product was obtained by eluting with ethyl acetate and hexane mixture (5:95). *Spectral data: Methyl 4-(4-chlorophenyl)-1-(furan-2-ylmethyl)-2-methyl-1H-pyrrole-3-carboxylate* (**5k**): Yield = 0.237 g (72%), yellow solid, mp 98 °C, IR (KBr) ν_{max} 2925, 2854, 1698, 1527, 1488, 1438, 1415, 1283, 1193, 1147, 1089, 1070, 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.51 (s, 3H), 3.59 (s, 3H), 4.91 (s, 2H), 6.17 (dd, J = 0.8, 7.2 Hz, 1H), 6.26 (dd, 1.6, 3.2 Hz, 1H), 6.49 (s, 1H), 7.19 (br s, 4H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6, 29.9, 43.7, 50.7, 108.7, 110.7, 120.2, 125.2, 127.8, 130.6, 132.1, 134.4, 136.7, 143.1, 149.6, 166.1. Anal. calcd for $C_{18}H_{16}ClNO_3$ (329.77) C, 65.56; H, 4.89; N, 4.25%; found C, 65.48; H, 4.78; N, 4.18%. *Allyl 1-benzyl-4-(4-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate* (**5o**): Yield = 0.274 g (75%), oily liquid, IR (KBr) ν_{max} 3027, 2932, 1697, 1524, 1486, 1451, 1420, 1277, 1203, 1182, 1143, 1091, 1056, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3H), 4.61 (d, J = 4.8 Hz, 2H), 5.03 (s, 2H), 5.11 (d, J = 11.6 Hz, 2H), 5.78–5.88 (m, 1H), 6.55 (s, 1H), 7.05 (d, J = 7.6 Hz, 2H), 7.24–7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 50.7, 64.5, 110.8, 117.7, 120.8, 125.3, 126.7, 127.8, 128.0, 129.1, 130.7, 132.1, 132.7, 134.5, 136.7, 137.1, 165.4. Anal. calcd for $C_{22}H_{20}ClNO_2$ (365.85) C, 72.22; H, 5.51; N, 3.83%; found C, 72.13; H, 5.42; N, 3.76%. *(R)-methyl 2-methyl-1-(1-phenylethyl)-4-(p-tolyl)-1H-pyrrole-3-carboxylate* (**5s**): Yield = 0.253 g (76%), oily liquid, $[\alpha]_D^{20}$ −58.8° (c 1.5, $CHCl_3$); IR (KBr) ν_{max} 2990, 2984, 2851, 1701, 1527, 1437, 1412, 1277, 1214, 1189, 1149, 1118, 1079, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.74 (d, J = 7.2 Hz, 3H), 2.28 (s, 3H), 2.36 (s, 3H), 3.58 (s, 3H), 5.27 (q, J = 6.8 Hz, 1H), 6.63 (br s, 1H), 6.99 (d, J = 7.6 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.16–7.25 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5, 21.2, 22.2, 50.5, 55.2, 110.7, 116.9, 125.9, 127.6, 128.5, 128.9, 129.0, 133.2, 135.6, 136.5, 142.2, 166.5. Anal. calcd for $C_{22}H_{23}NO_2$ (333.42) C, 79.25; H, 6.95; N, 4.20; found C, 79.05; H, 6.82; N, 4.05.
20. Gairaud, C. B.; Lappin, G. R. *J. Org. Chem.* **1953**, *18*, 1–3.
21. Zhong, C.; Liao, T.; Tuguldur, O.; Shi, X. *Org. Lett.* **2010**, *12*, 2064–2067.
22. Complete crystallographic data of **5k** (CCDC no. is 848584) for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).
23. Lyne, P. D. *Drug Discov. Today* **2002**, *7*, 1047–1055.