

**DIMEDONE ANNULATED MULTI-COMPONENT ASSEMBLY
PROCESS (MCAP): AN EXPEDITIONARY APPROACH
TOWARDS SYNTHESIS AND BIOLOGICAL EVALUATION OF
SIX-MEMBERED HETEROCYCLES AND ENAMINONES**



Ph.D Thesis

By

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**INSTITUTE OF CHEMICAL SCIENCES
UNIVERSITY OF PESHAWAR, PAKISTAN**

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PROCESS (MCAP): AN EXPEDITIONARY APPROACH
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In

Organic Chemistry

By

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It is recommended that this dissertation prepared by **Mr. Ihsan Ali** entitled “**Dimdone Annulated Multi-component Assembly Process (MCAP): An Expeditionary Approach Towards Synthesis and Biological Evaluation of Six-memebered Heterocycles and Enaminones**” be accepted as fulfilling this part of the requirements for the degree of “**Doctor of Philosophy in Organic Chemistry**”.

RESEARCH SUPERVISOR

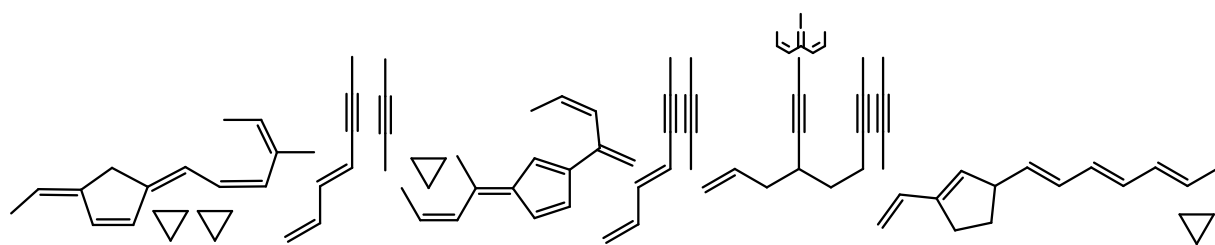
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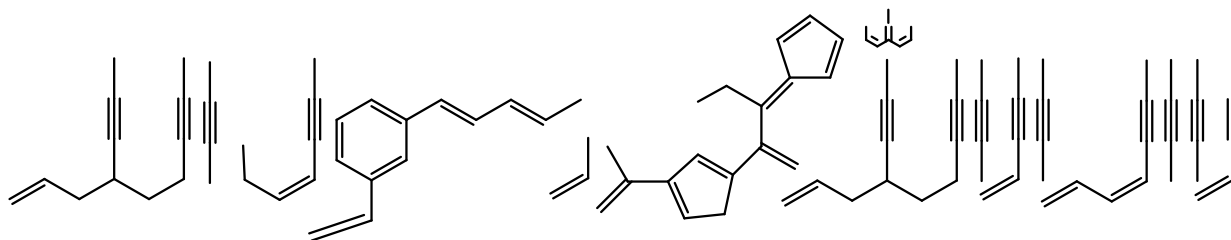
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In the name of ALLAH, the most Beneficent, the most merciful



There is no god but ALLAH; Muhammad (Peace be upon him) is His prophet.

DEDICATION

TO

MY LOVING PARENTS

Whose inspiration towards knowledge served me

As beacon of light

And to my

Brothers and Sisters

for their sweet feelings who always

pray for my bright future and success

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Hassan Ali

Multicomponent reactions (MCRs) are convergent reaction, in which three or more substrates of variable complexity react to form a product, where basically all or most of atoms contribute to the newly formed product. The control of selectivity, for example chemo- and regioselectivities, is among the most important objectives in organic synthesis with special emphasis on six-membered functionalized heterocyclic frame work frequently available in a variety of antihypertensive and other drugs. For MCRs, the issue of selectivity is of particular significance due to the high probability of several potential parallel reaction pathways leading to different product classes.

- A piece of research findings presented in this dissertation refers to the development and standardization of dimedone annulated multi-component assembly process that has resulted into production of multi-functional six-membered aza- and oxa-heterocyclic compounds beside enaminones.
- This single-step multi-component assembly process offers a convenient route to generate structural diversity into heterocyclic frame work which may ensure interesting biological and pharmacological properties.
- Subsequently, these heterocyclic compounds and enaminones possessing interesting multi-functional motifs have been screened for different kinds of biological properties. As expected, majority of these compounds have exhibited interesting biological and pharmacological properties.
- Apparently, this synthetic protocol has been partially modified but otherwise derived from the well-known Hantzsch Condensation of four or three components (as the case may be) namely dimedone, appropriately substituted aromatic aldehyde, β -keto ester and either a substituted 1,3-dicarbonyl system or ammonium acetate gives an easy excess to a diverse range of highly substituted six-membered aza- and/or oxa-heterocycles often known as polyhydroquinolines (PHQs) and xanthenes respectively.
- As regards optimization of experimental conditions for this protocol, choice of a suitable weak base or acid catalyst, appropriate protic solvent, mode of activation energy source such as heating or microwave irradiation beside adjustment of molar ration of dimedone to other partners remained the main players to control acceptable yields of the desired products.

- As far locally synthesized compounds, initially fifteen known PHQs derivatives besides five new compounds **2(a-t)** have been obtained and fully characterized using morpholine and I_2 / Al_2O_3 as a binary catalytic system under microwave irradiation (table 2.1). Furthermore, in order to further this synthetic scheme, compound **2a** was structurally modified to hydrophobic alkyl ethers **3(a-c)** through alkylation of phenolic component.
- Polyhydroacridines-1,8-diones (PHAs) unit is frequently available in previously reported anti-malarial, antibacterial and anticancer drugs. The reported synthetic protocol for these compounds was further modified using solid-phase synthetic process (tables 2.20 & 2.22) that involved green chemistry. Unlike reported compounds, these compounds **4(a-g)** were tested for analgesic, anti-inflammatory and leishmanicidal activities but all remained inert to these assays.
- Substituted 1,4-dihydropyridine is an important class of anti-hypertensive drugs available in the market and several inconvenient methods of their synthesis are available in the literature. We have synthesized and carefully characterized these known compounds through a highly convenient and green protocol (table 2.16). This procedure involves microwave irradiation with shortest possible reaction time beside good to excellent isolated yields.
- Inspired by isolation in minute quantity of structurally interesting intermediate trapped during the synthesis of xanthenes **7(a-j)** through a well-known Knoevenagel Condensation followed by Michael Addition reaction, it was extended to a series of such compounds **6(a-l)** after modification in experimental conditions. Later on, these compounds were subjected to various biological assays as highlighted in the following paragraph.
- This part of the dissertation demands special attention because the intermediates trapped in the afore-mention procedure were subjected to cyclodehydration that resulted into the formation of substituted xanthenes **7(a-j)** reported in **table. 3.9**. This protocol involves use of moderate recyclable acid catalyst Amberlite IR-120H, acetonitrile as highly coordinating organic solvent under reflux conditions. This procedure has been developed in our laboratory and gave high yielding desired products.

- β -Enaminones are interesting synthetic intermediates and have been widely employed in organic synthesis. In particular, they have been used as synthons of a wide variety of bioactive heterocycles, as well as pharmaceutical compounds having diverse biological potential. Due to their wide range of activity and importance, several methods have been developed but inherit procedural demerits. We have modified the reported protocol using PPA-SiO₂ as a catalyst under solvent free conditions and produced a series of functionalized β -Enaminones **8(a-k)**, (table 4.3) by condensing dimedone with either substituted aromatic or aliphatic amines in variable isolated yields. Use of chiral aliphatic amines has resulted into a few novel chiral β -Enaminones **8(g-j)**. Their biological studies are in process but cannot be included in the thesis at this stage.
- Part-B of the dissertation involves screening of the locally synthesized substituted and poly-functionalized six-membered heterocyclic compounds. Among them, polyhydroquinoline derivatives **2(a-p)** were tested for anti-inflammatory, anti-epileptic, analgesic, cytotoxicity, and muscles relaxant activities, besides Protein Tyrosine Phosphatase 1B (PTP1B) inhibition. Based on computational study, compounds **2g** (39.19±0.02), and **2m** (37.42±0.04) exhibited significant PTP1B activities while compounds **2b**, **2f**, **2i**, and **2n** remained inactive
- As regards analgesic activity of PHQ derivatives **2(a-p)** and **3(a-c)** and, variable effects were observed. For instance, among the tested compounds, **3i**, **3h**, **2f** and **2e** demonstrated the maximum analgesic activity. Similarly, the above series **2(a-f)** and **3(a-c)** of synthetic compounds were tested for anti-inflammatory activity by employing carrageenan induced paw edema model. Among the tested compounds **2d**, **3b** and **2g** exhibited significant anti-inflammatory. However, a moderate anti-inflammatory effect was observed with **3c** and **2d**, while rest of the compounds was devoid of anti-inflammatory potential. Surprisingly, none of these PHQs derivatives showed muscles relaxant, anti-epileptic and cytotoxicity activities.
- During the development and standardization of multi-component assembly process leading to the formation of six-membered heterocyclic compounds, an intermediate (**4a**)

possessing interesting structural features was isolated. Later on, a series of these precursors **4(a-l)** possessing variable substituents were synthesized and screened for cytotoxicity and leishmanicidal activities. Among the tested series **4(a-l)**, compounds **4(b-f)** showed potent leishmanicidal activity against *Leishmania major* (DESTO) promastigotes, while the same series failed to reveal any cytotoxicity.

- Similarly, employing afore-mentioned one-step multi-component assembly process, another series **5(a-j)** of six-membered oxa-heterocyclic compounds was synthesized and screened for cytotoxicity and leishmanicidal activities. Among them compounds **5(b-f)** exhibited potent leishmanicidal activity against *Leishmania major* (DESTO) promastigotes, while the same series did not show any cytotoxic effect.

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Standard abbreviations and acronyms

S. No	Symbol	Name
1.	MCRs	Multicomponent reaction
2.	DHP	1,4-Dihydropyridines
3.	PHQs	Polyhydroquinolines
4.	PHAs	Polyhyroacridine-1,8-diones
5.	Dimedone	5,5-dimethylcyclohexane-1,3-dione
6.	4-HC	Four component Hantzsch reaction
7.	3-HC	Three component Hantzsch reaction
8.	Ar	Aryl
9.	EDG	Electron donating group
10.	EWG	Electron withdrawing group
11.	b	Broad
12.	d	Doublet
13.	dd	Doublet of doublet
14.	m	Multiplet
15.	q	Quartet
16.	t	Triplet
17.	brs	Broad singlet
18.	m.p	Melting point
19.	Hz	Hertz
20.	DMF	Dimethyl Formamide
21.	DMSO	Dimethyl sulfoxide

22.	THF	Tetrahydrofuran
23.	R _f	Retention time
24.	TLC	Thin layer Chromatography
25.	TEBA chloride	Tri Ethyl Benzyl Ammonium Chloride
26.	bend	bending
27.	def	deformation
28.	EtOH	Ethanol
29.	IR	Infrared
30.	UV	Ultraviolet
31.	PTP1B	Protein tyrosine phosphatase
32.	MTT	3-[4,5-dimethylthiazol- 2-yl]-2, 5-diphenyltetrazolium bromide
33.	NSAIDs	non-steroidal anti-inflammatory drugs
34.	SEM	Standard error of mean
35.	PBS	Phosphate Buffered Saline
36.	PG	Prostaglandin
37.	min	Minutes
38.	h	Hours
39.	Mol. F	Molecular formula
40.	Mol. W	Molecular weight

Part A

Chapter 1

General Introduction

1.1. General introduction

Part of the pleasant quality of organic synthesis involves heterocyclic scaffolds¹, because there is the almost unlimited variety of possible target structures that lurks in the shadow, waiting to be made. There are the vast organic reactions that help to change one molecule into another. In addition to utilize these reactions for synthetic purposes, there is the remarkable range of reagents, catalysts, reaction background and advance techniques that should be assembled sequentially. Finally, in advance organic syntheses the formations of C-heteroatom and C-C bonds have been appeared essentially important. A great number of helpful methods available are still giving goods results under mild condition which mainly involve, generation of carbanion either from organometallic compounds, or from compounds containing ‘activated’ or methylene groups. Some of the procedures are the Grignard reaction, claisen ester condensation, aldol, Michael reaction and those reactions which involve nucleophilic displacement at saturated carbon atom as in the alkylation of ketone². But instead these conventional synthetic technique, combinatorial synthetic methodology, microwave assisted synthesis and recent development in molecular biology, the speed of novel authenticated medicines introduction has abridged obviously over the precedent two decades. The majority medicines in use are small synthetic organic molecules that often contain a heterocyclic ring. Though, the varieties of easily available functionalized heterocyclic building blocks for the synthesis of structurally diverse libraries are rather limited³. Therefore, the progresses in new rapid and clean synthetic routes towards libraries of such compounds are of absolutely important to medicinal and synthetic chemists. Undoubtedly, the most efficient strategies involve multicomponent reactions (MCRs), which have emerged as a powerful tool for the rapid introduction of molecular diversity^{4,5}.

1.2. Multicomponent Reactions

In conventional synthetic approach to molecule possessing heterocyclic rings are formed in a step wise procedure. Subsequent steps construct the aliphatic molecular frame work around the aromatic template or steps are taken to introduce the appropriately synthetic sequence. Though these approaches admirably serve most purposes, often they are plagued by serious shortcomings for the preparation of closely related natural products or synthetic analogs with even the simplest aromatic modification often necessitates an independent total synthesis. In the past decade, many research groups have intended for the understanding of the concept of Ideal Synthesis (Fig. 1) by the development of multi-step, single operation processes for construction of complex molecule in which several bonds are formed in a chain of events and without the requirement of isolating the intermediates. Reactions that meet these criteria, normally referred to as tandem reactions⁶, permit the inexpensively and environment friendly synthesis of an extensive choice of organic molecules⁷.

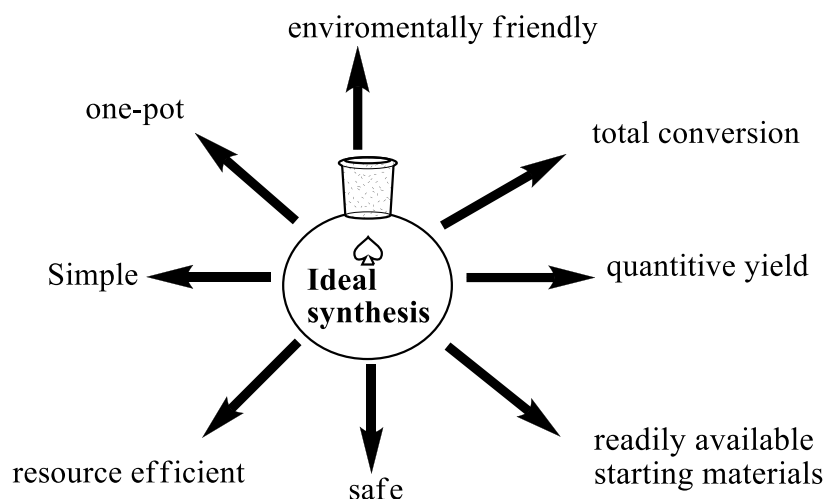
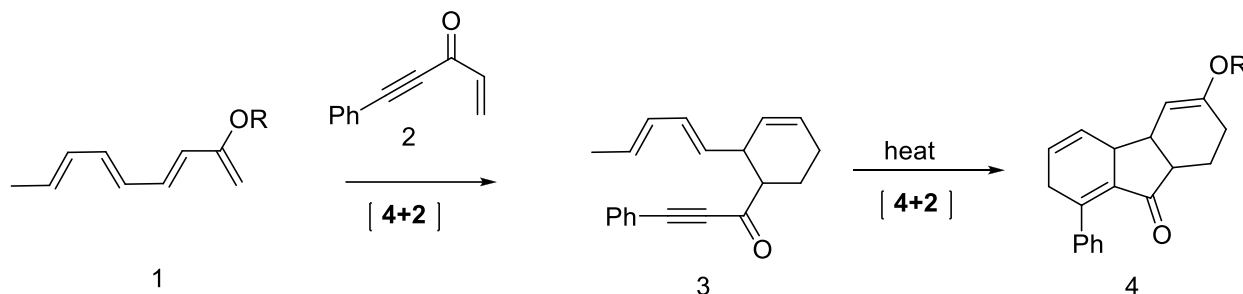


Fig. 1. General aspects of ideal synthesis

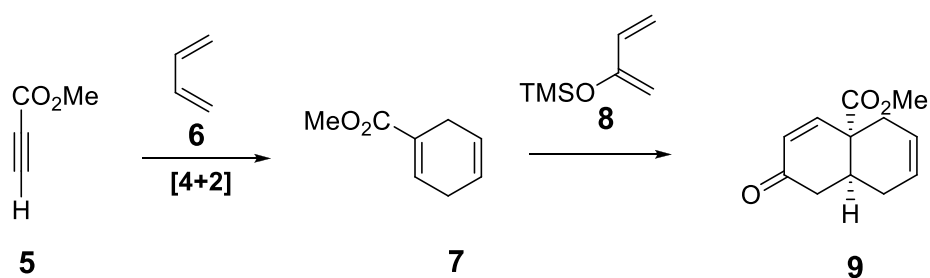
As recommended by Denmark, a difference can be made among the three categories of tandem reactions: i) cascade or domino reactions; ii) consecutive reactions; iii) sequential

reaction^{7,8}. In a tandem cascade reaction, for the next steps reaction cause the structural change. However, these reactions did not require the addition of further reagents or modification in condition because the intermediates cannot be isolated⁹⁻¹¹.



Scheme 1. Tandem consecutive reaction

Tandem consecutive reactions are different from cascade reactions in that the intermediate is an isolable thing. The intermediate undergo the second reaction step, but extra endorsement in the form of energy is required. For example as shown in scheme 1, the second Diels-alder cyclization has been promoted by heating in the same reaction flask while the intermediate **3** formed can be isolated¹².

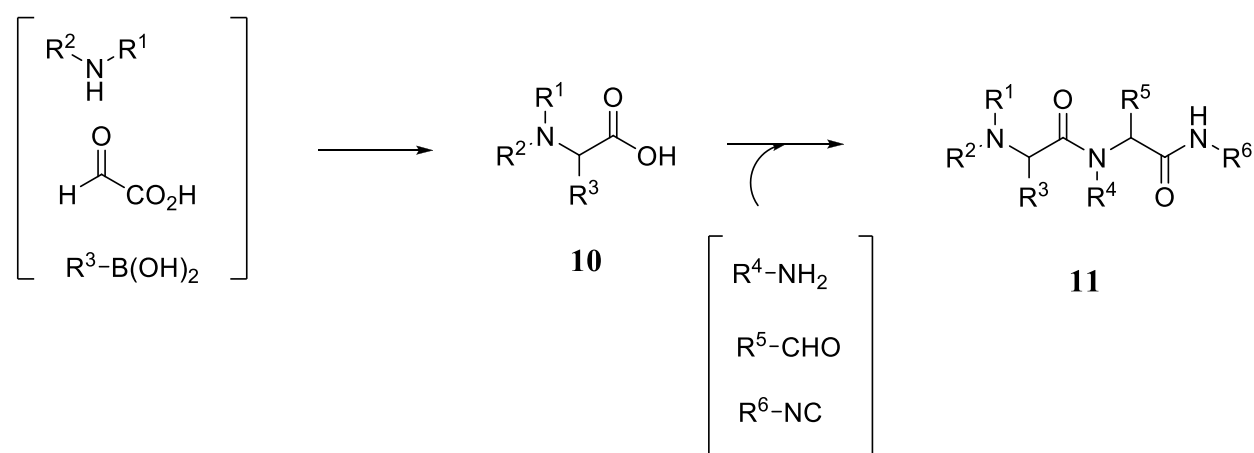


Scheme 2. Diels-alder cyclization

In tandem sequential reactions, the functionalities formed in the initial reaction step should allow the intermediate to employ in the coming step. However, for such tandem process to precede an additional component are required¹³ (Scheme 2). So multi-component assembly process are defined as the chemical alteration utilizing more than two starting material as the

input for product formation. Since several substrates are put together, indeed, there is also the possibility of generating manifold analogs. This diversity and accessibility to a large number of compounds, combined with high-throughput screening techniques, means that MCRs represent a very important tool in modern drug discovery processes¹⁴.

Different classification way of MCRs is feasible, for example classifications on the basis of number of component involved, three or four component reaction, mechanism, and also according to variability¹⁵.



Scheme 3. Petasis-Ugi reaction

On the other hand, the Petasis-Ugi like MCRs reactions shown in scheme 3 have high variability¹⁶ are of high exploratory power, because both high complexity and broad diversity are generated in this procedure¹⁷. On the basis of mechanism of MCRs, three different types are often distinguished in the literature:

- Type I, when all the participating reactions are reversible.
- Type II, when the majority of the reactions are reversible, but the final product is formed irreversibly.
- Type III, when practically all of the reactions are irreversible.

Type I MCRs are usually reactions of carbonyl compounds, amines and weak acids. The product formation is in low purity and yield since all steps of the reaction are in equilibrium. However, the product formation can be improved by using a bifunctional substrate. The primarily formed products then can subsequently be transformed into product ;(type II MCRs). The equilibrium is shifted towards the product side because the final step is irreversible. The yield and purity of the product in such MCRs are usually high. Similarly, in the isocyanides based MCRs there is also an irreversible step, as the carbon of the isocyanide moiety is formally oxidized to C^{IV}. In the case of type III MCRs, mostly occurs in nature while only a few examples are known in preparative organic chemistry¹⁸.

Table 1. MCRs clasified by reaction mechanism

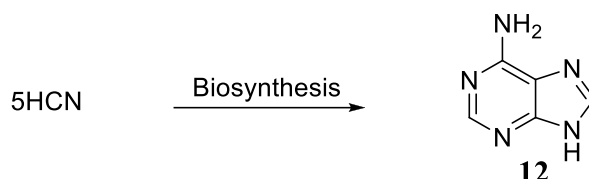
MCR type	general reaction equation
I	$A + B \rightleftharpoons C \rightleftharpoons D \dots O \rightleftharpoons P$
II	$A + B \rightleftharpoons C \rightleftharpoons D \dots O \longrightarrow P$
III	$A + B \longrightarrow C \longrightarrow D \dots O \longrightarrow P$

The exact multi component reactions must be distinguished as of the tandem, cascade, and domino or zipper reactions¹⁹ where one starting substrate having several functionalities that react in several consecutive steps, e. g.: Type I. These one-pot, multi step synthesis procedures rely on a high conversion of $A + B \rightleftharpoons P^1$ that will allow to add a third reactant C, eventually under different reaction conditions whereas true MCRs are run under the same conditions by adding the starting materials at the same time.

1.3. History of Multicomponent Reactions

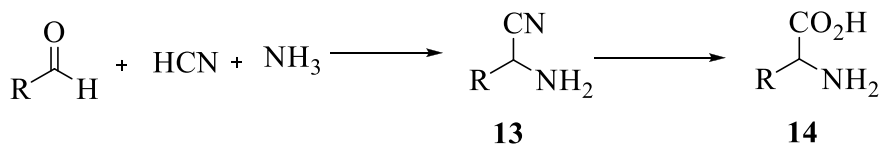
The MCRs concept is not mysterious in nature. It seems that adenine **12**, one of the main

constituents of DNA and RNA was prebiotically created by the condensation of five molecules of HCN, an abundant component of prebiotic impression, in a reaction catalyzed by NH_3 (Scheme 4). Similarly, the other nucleic bases have been generated involving HCN and H_2O MCR reactions.



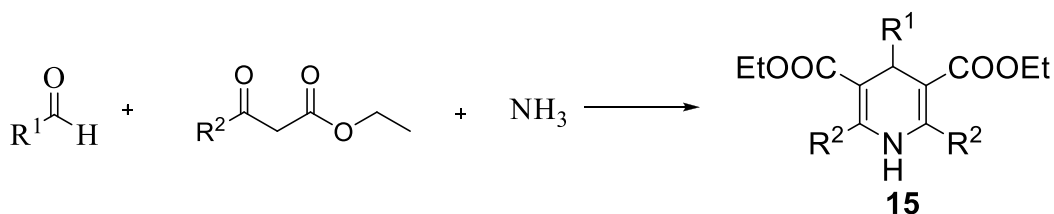
Scheme 4. Biosynthesis of adenine

The history of MCRs date back to the year 1850, when Strecker reaction (S-3CR) describing the development of α -amino cyanides from ammonia, carbonyl compounds, and HCN has been introduced²⁰ (Scheme 5).



Scheme 5. Strecker synthesis of amino acids (1850 by Strecker)

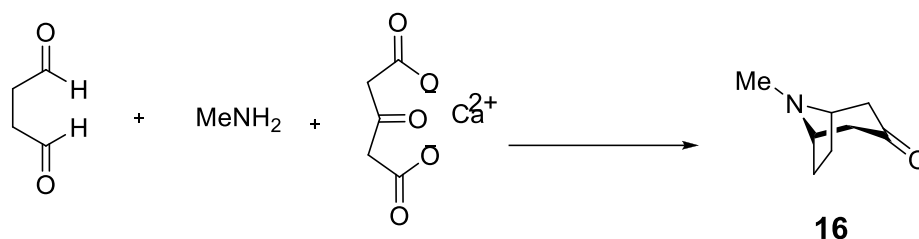
The dramatic progress of multicomponent chemistry can be credited to the job of Hantzsch in 1882. He reported symmetrically substituted dihydropyridine **15** from ammonia, aldehyde, and two equivalent of β -ketoesters²¹.



Scheme 6. Hantzsch dihydropyridine synthesis

The earliest application of MCRs in natural product synthesis was achieved some 25

years later, in 1917, by Robinson. He prepared alkaloid tropinone **16** by using a three-component reaction based on Mannich-type reactions (M-3CR)^{22,23}.



Scheme 7. Robinson synthesis of tropinone

Passerini reported the first MCR involving isocyanides (IMCR) in 1921 (P-3CR)²⁴, and over the years these reactions have become increasingly important highlighted in several publications. MCR which leads to α -amino acids is the Bucherer-Bergs reaction (BB-4CR), which was first reported in 1929²⁵. The others discoveries made in the area of multi-component reactions have been summarized in figure 2.

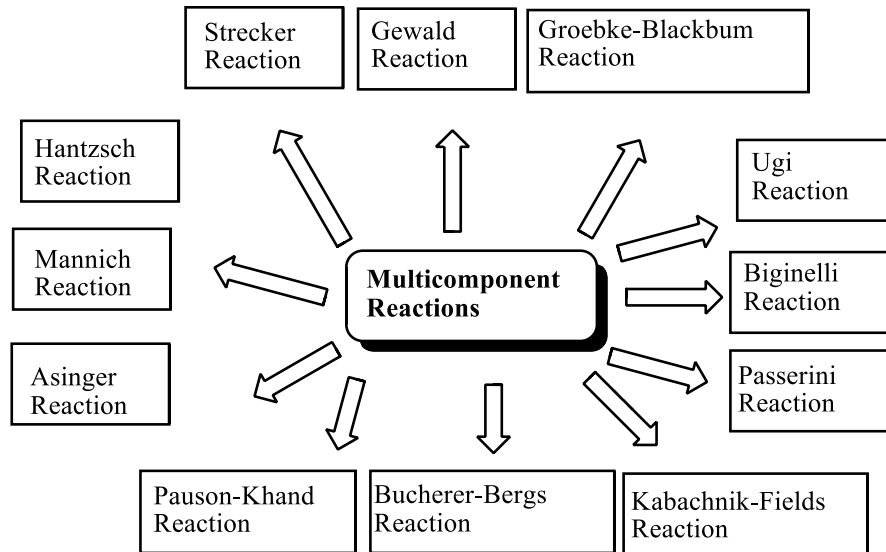


Fig. 2. Naming multicomponent reactions

In recent years, many novel MCRs including Michael addition-initiated three component domino sequences²⁶, Knoevenagel/hetero-Diels-Alder-based MCRs²⁷, radical chain MCRs²⁸,

transition metal-catalyzed Pauson-Khand MCRs²⁸, as well as Petasis MCRs²⁹⁻³¹, have been added to the chemist's armamentarium and successfully applied to all fields of organic synthesis.

Finally, MCRs can be classified according to the functional groups involved in the reaction. Examples are imine based MCRs, carbene based MCRs and isocyanide based MCRs (IMCRs). One of the most famous MCRs, the Hantzsch dihydropyridine synthesis four-component (H-4CR), belongs to both imine and 1,3-dicarbonyl based MCRs.

1.4. Chemistry of 1, 3-dicarbonyl compounds

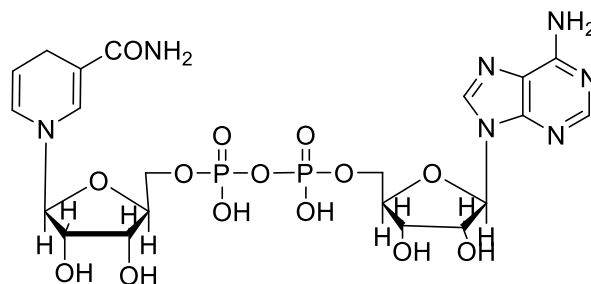
1,3-Dicarbonyls are one of the most popular and intriguing functional groups in organic chemistry. Owing mostly to their CH₂ flanked between two carbonyl atoms, these peculiar species, referred to as active methylene, undergo or induce a broad range of transformations. Due to the others reactive sites and the active methylene of 1,3-dicarbonyl systems towards many other substrates involved in a variety of synthetic pathways, including Knoevenagel condensations, Michael, Mannich reactions, cyclodehydration, cycloadditions and metal-promoted transformation. The acidity of the C-H bonds in these compounds is due to a combination of the inductive electron-withdrawing effect of the unsaturated groups and resonance stabilization of the anion formed by removal of a proton. Not all groups are equally effective in 'activating a neighboring CH₂. Nitro is the most powerful of the common groups and thereafter the series follows the approximate order NO₂>COR>SO₂R>CO₂R>CN>C₆H₅³²⁻³³.

Carboxylic ester and carbonyl groups are certainly the most important activating groups in synthesis. Removal of a proton from the α-carbon atom of a carbonyl compounds with base gave the corresponding enolate anion and it is these anions, which are involved in base-catalyzed condensation reaction of carbonyl compounds such as the aldol condensation and in bimolecular nucleophilic displacements. Out of the 1,3-dicarbonyls reaction path ways towards synthesis of

diverse heterocyclic scaffold through multicomponent assembly process, Hantzsch reactions, (three component and four component) have been exploited in a variety of reagents.

1.5. Variation and recent advances in Hantzsch multicomponent reaction (1,3-Dicarbonyls based MCRs)

The chemistry of dihydropyridine (basic skeleton **18**) initiate more than 122 year back after the finding of aurther Hantzsch²³. Initially, further investigation on Hantzsch discovery was relatively slow, however it picked up very quick because of their structural similarity to reduced Nicotinamide Adenine Dinucleotide (NADH) (**17**), which is an established “hydrogen transferring agent” in life processes³⁴. In 1970 and in coming years several new compounds having the dihydropyrans basic nucleus were entered into their clinical use as antihypertensive agents, out of which some have qualified the clinical trials (**Chart 1**).



17

The importance of the chemistry and pharmacology of DHP heterocyclic scaffold can be realized from the appearance of vast number of articles describing its synthetic and biological applications. Due to the considerable and continuous significant role of DHPs chemistry in organic chemistry as synthetic intermediates and in pharmaceutical chemistry providing pharmacophors. Much attention has been focused on the synthesis of various DHPs, by varying one or either two components in Hantzsch reaction.

1.5.1. Structure variation in the aldehyde component of Hantzsch reactions

Aldehyde is one of the major constituent in Hantzsch multicomponent reaction. Hantzsch originally used the acetaldehyde and formaldehyde²³. Latter on almost all types of aldehydes (aliphatic³⁵, aromatic^{36,37}, spioraldehydes and a variety of heterocyclic aldehydes,^{37,38} and aldehydes bearing biphenyl-2'-tetrazole Substitution³⁹) have been reported in this reaction. To name a few of them are the pyridine carboxaldehyde including cinchonidinaldehyde based on aldehydes. The aldehydes variations have been extended to aldose^{40,42} and some of other smaller sugar derivatives to obtain sugar based Hantzsch pyridine via C-nucleoside of Hantzsch bases.

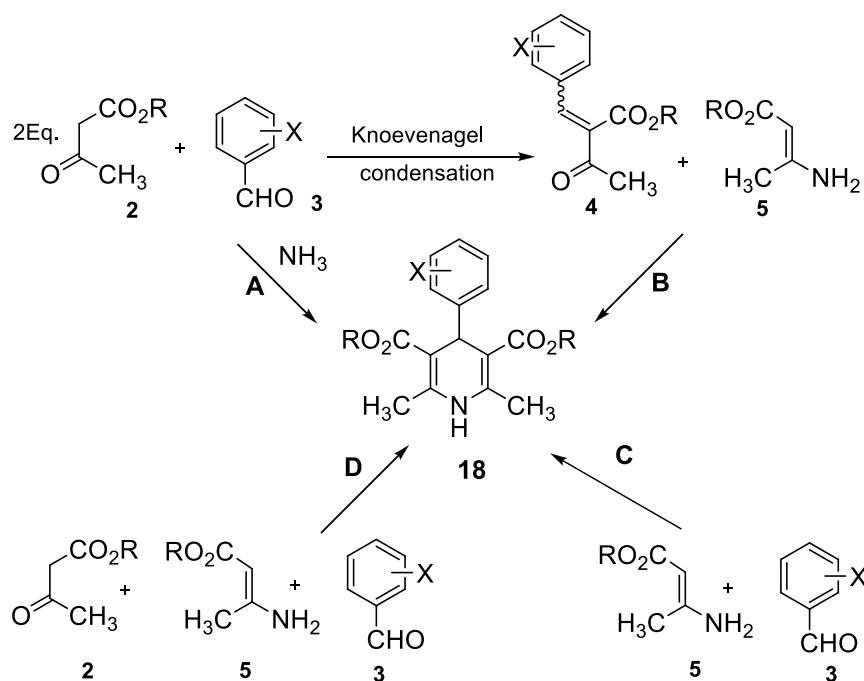


Fig. 3. The common variation in the synthesis of DHPs

1.5.2. Variation in the active methylene component of Hantzsch reaction

The 1,3-diketones, i- cyanoacetophenone or ii- phenylthioacetophenone are used in place of acetoacetic ester. In all these reactions, always symmetrical Hantzsch bases were obtained⁴⁰⁻⁴⁴.

The α -haloketones have also been successfully utilized as activating methylene unit for the synthesis of various DHPs. However the scope and generality of Hantzsch reaction become more widened when cyclic ketone particularly, dimedone appeared in the literature. Not all few active methylene variant has given in chart 1. The use of α -haloketones has fairly extended the scope of this reaction^{45,47}.

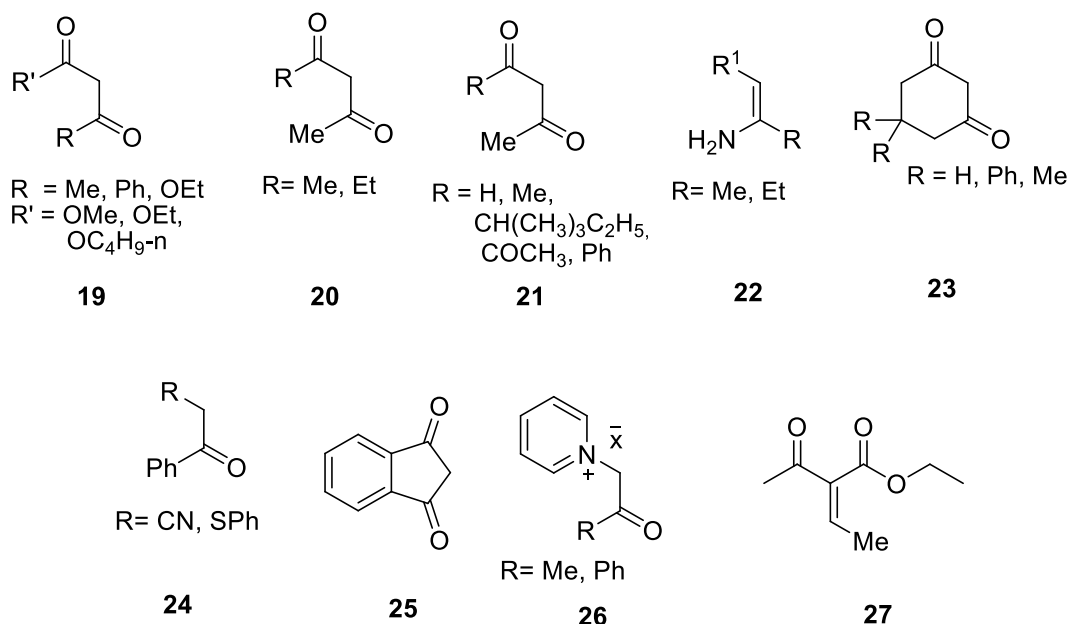


Chart 1. Various types of active methylene used in Hantzsch reaction

1.6. Dimedone as a versatile reagent for the synthesis of heterocyclic scaffolds

Dimedone (**28**) is an aliphatic compound having 1, 3- group flanked by a methylene group and exist in a tautomeric trans-enolized form where intermolecular hydrogen bonding is not possible⁴⁸. The inherent structural features in **28** have created various reactive centers: C-1, C-2, and to a less extent C-6 in addition to C-3 in or 3-O (Fig. 4). Such phenomenon attracted much attention for using it as a synthetic reagent for the characterizations of aldehydes, since its discovery, by the formation of readily crystalizable derivatives. Determination of formaldehyde in textiles has been done by a colorimetric method by using **28**⁴⁹. Moreover, dimedone is an

excellent precursor for partially hydrogenated fused heterocycles⁵⁰, where two of the carbon-atoms of dimedone are part of the backbone of the formed heterocycles. Its structural features and its reactivity to form more functionalized derivatives have led to the construction of a wide range of fused or spiral biheterocycles⁵¹.

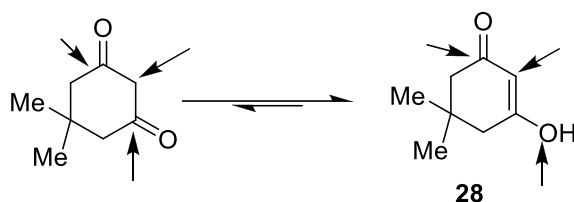


Fig. 4. Indication of the most reactive sites of dimedone (**28**)

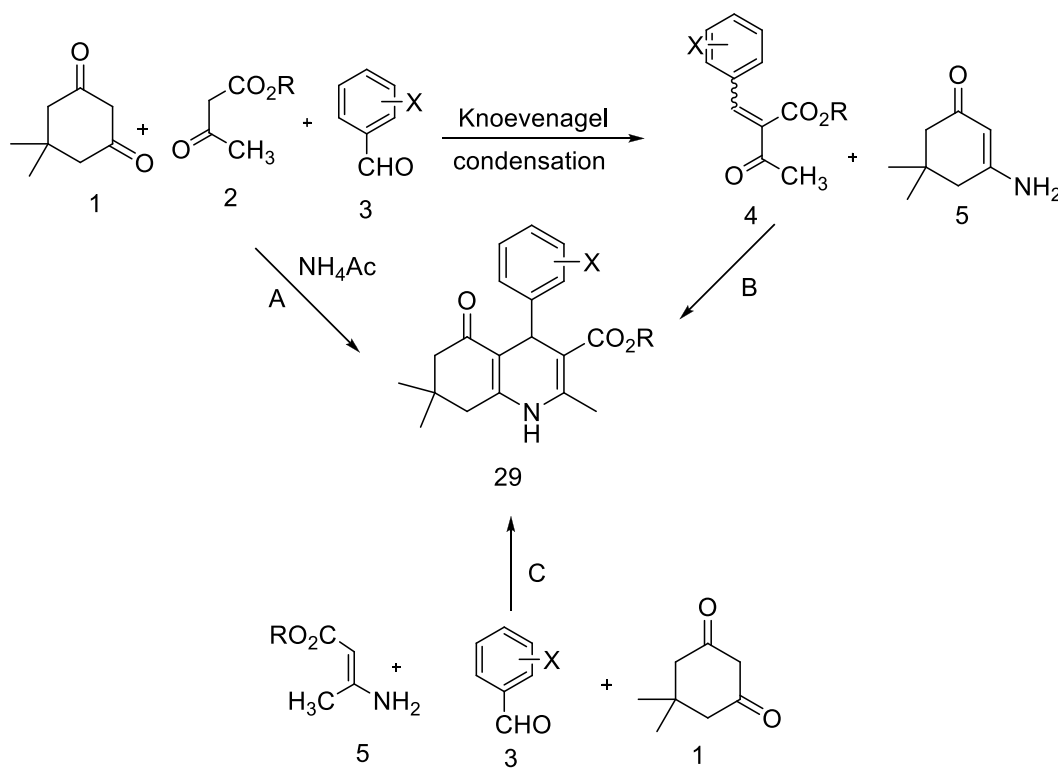


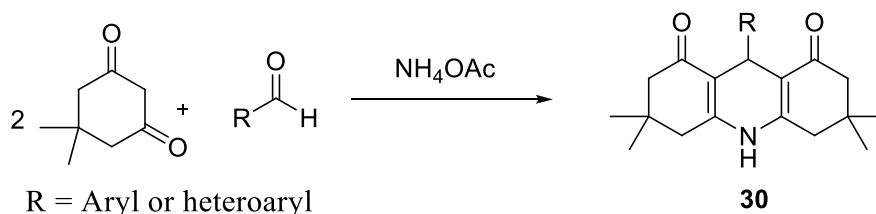
Fig. 5. The most common variation used for the synthesis of polyhydroquinolines

The polyhydroquinolines (PHQs) are known to affect several physiological functions like the therapy of “Alzheimer’s disease” and in tumor treatment with the highest value^{52,53}. Due to

the physiological and therapeutical role and its importance in the design of biologically important heterocycles, several efficient methods for the synthesis of PHQs and DHPs derivatives, based on microwave irradiation, expensive reagent and catalysts have been developed. To mention few of them are sulfonated β -cyclodextrine⁵⁴, Melamine trisulfonic acid⁵⁵, $\text{Cu}(\text{OTf})_2/\text{MWI}$ ⁵⁶, $\text{Yb}(\text{PFO})_3$ ⁵⁷, $\text{TFA}/\text{THF}/\text{MWI}$ ⁵⁸ and Organocatalysts⁵⁹.

1.7. Reported synthetic strategies of polyhydroacridine-1,8-diones derivatives

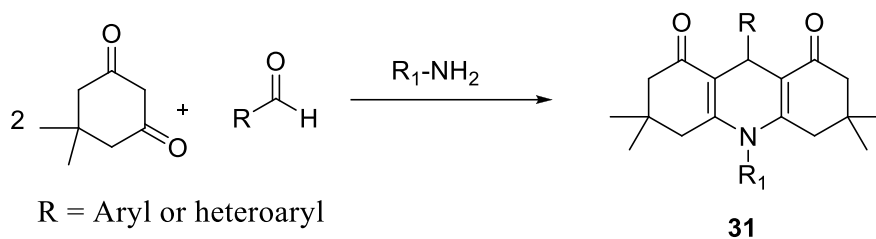
Polyhydroacridine-1,8-diones are multifunctionalized 1,4-dihydropyridine type entity. 1,4-Dihydropyridines (1,4-DHPs) are well known compounds as of their biological activities⁴⁰, variation on the DHP ring, such as diverse substituent or heteroatom⁴⁰, have allowed the study of the wide-ranging structure and activity association. In this background, polyhydroacridine-1,8-diones are also progressively more receiving attention due to their resemblance in properties with those of 1,4-dihydropyridines. The synthesis of polyhydroacridine-1,8-diones by the reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone) with different aldehydes and ammonium acetate (Scheme 8) by heating in conventional solvents⁶⁰, by solvent-free straight heating⁶¹, by microwave-assisted synthesis⁶², by reactions in aqueous media using ammonium chloride, or $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ or *L*-proline as catalysts⁶³, and by using ionic liquids⁶⁴ have been reported.



Scheme 8. Synthesis of polyhydroacridines-1,8-diones

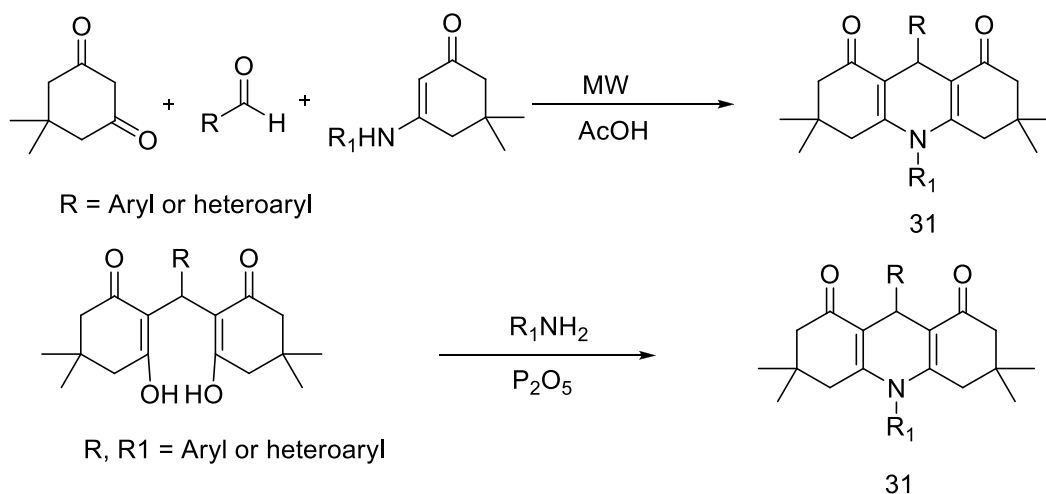
The synthesis of *N*-aryl-polyhydroacridine-1,8-diones by the reaction of 5,5-dimethylcyclohexane-1,3-dione (dimedone) with different aldehydes and amines (Scheme 9) using microwave irradiations^{62,65}, reactions in aqueous media employing *p*-dodecyl benzene sulfonic

acid⁶⁶, sodium dodecyl sulfate (SDS)⁶⁷ or L-proline⁶⁸ and ionic liquids^{69,70} as catalysts have been reported.

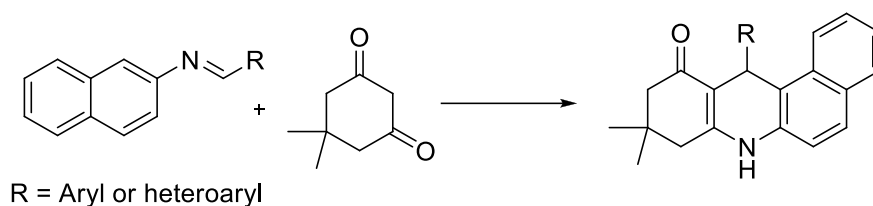


Scheme 9. Synthesis of *N*-aryl-polyhydroacridine-1,8-diones

Tu *et. al.*⁷¹ and Nikolaeva *et. al.*⁷² have also reported the synthesis of *N*-aryl-polyhydroacridine-1,8-diones by the reaction of enaminoketones with aldehydes in 20% P_2O_5 solution and isopropyl alcohol as solvent. Shchekotikhin *et al.*⁷³ have reported microwaves synthesis of the same reaction in acetic acid (Scheme 10). *N*-substituted-polyhydroacridine-1,8-diones can also be obtained from the reaction of methylene-bis(5,5-bimethylcyclohexane-1,3-dione) with amines^{74,75} (Scheme 10). The reactions of various Schiff bases with 1,3-diketones to afford *N*-substituted polyhydroacridine-1,8-diones are also well documented⁷⁶⁻⁷⁸ (Scheme 11).



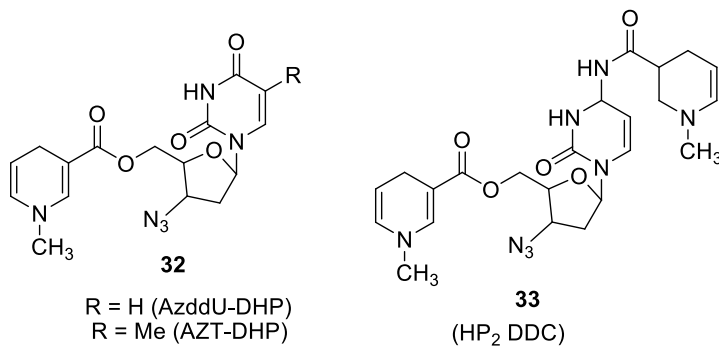
Scheme 10. Synthesis of *N*-substituted-polyhydroacridine-1,8-diones



Scheme 11. Synthesis of N-substituted-polyhydroacridine-1,8-diones from Schiff's bases

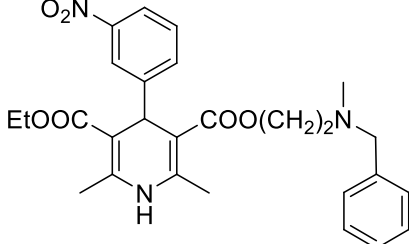
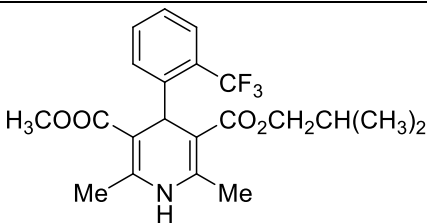
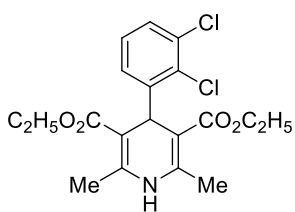
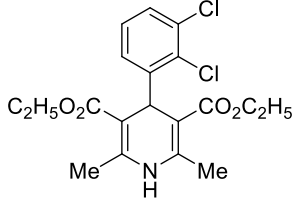
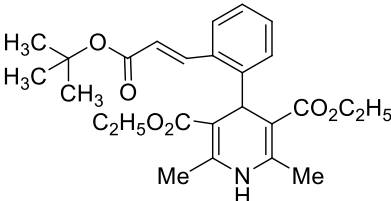
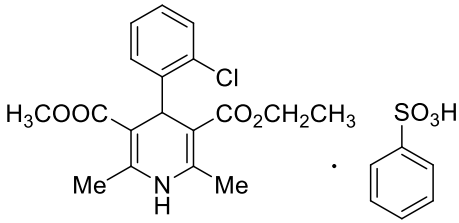
1.8. Pharmacological application of nitrogen heterocycles (DHPs)

The chemistry of 1, 4-dihydropyridine and its derivatives has been studied from century ago because there were proofs to be attractive due known pharmacological group of heterocyclic scaffold, such as nifedipine and Nicardipine which are clinical medicine since 1975 (Table 2). These compounds are routinely used in the treatment of a varieties of cardiovascular disorders, such as hypertension, cardiac arrhythmias or an- gina^{79,80} (such as Benidipine and Lacidipine),⁸¹ and calcium agonists (such as BAY K 8644,)³⁵. DHPs have also been explored to possess anti-tumor³⁷, anti-inflammatory⁸², anticonvulsant activity⁸³, antitubercular activity^{84,85}. The 1,4-dihydropyridine has also recently been introduced as a neuroprotectant and cognition enhancer lacking neuronal-specific calcium antagonist properties^{86,87}. In addition to these activities, their biological activity profile is further extended as anti-HIV agents⁸⁸ by preparing/ condensing these molecules with already clinically used HIV agents e.g. 3'-azido-2',3'- dideoxyuridine DHP (AzddU-DHP)⁸⁹ **32** and 3'-azido- 3'-deoxythymidine DHP (AZT-DHP)⁹⁰ **33**. Other nucleoside dihydropyridine⁹¹, 2',3'-dideoxycytidine (DDC) derivative (HP 2 DDC⁹² and among non peptidic dimeric, 4-aryl-1,4-dihydropyridine⁹³ are reported as HIV protease inhibitors⁹⁴. Mukherjee *et. al.*⁹⁵ reported DHPs derivatives to be associated with contraceptive activities. Marco-Contelles *et. al.*⁹⁶ described acetylcholinesterase inhibitory and neuroprotective activities of fused DHPs (tacipyrines) for the treatment of Alzheimer's disease.

**Table 2.** Pharmacological activity of 1,4-dihydropyridine analogs

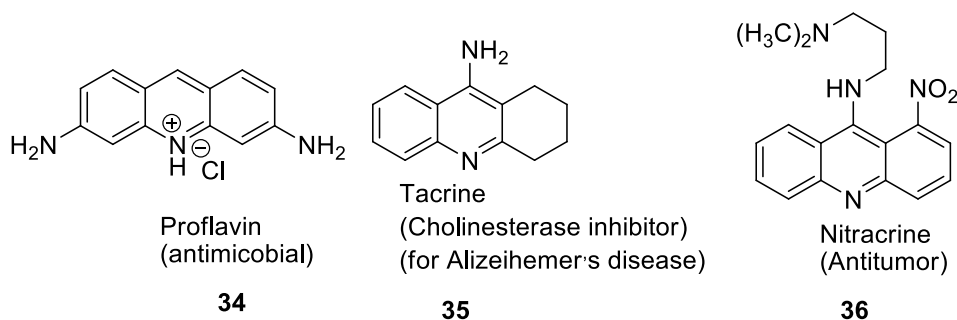
S.No.	Structure	Drug name
1.		Anti-hypertensive, Nifedipine (1977)
2.		Calcium antagonist (Bay K 8644)
3.		Nitrendipine
4.		Nitrendipine

(Continued)

5.		Nicardipine
6.		Nisoldipine (Germany 1990)
7.		Felodipine (Sweden 1988)
8.		Felodipine (Sweden 1988)
9.		Lacidipine (Lacipil or Lacirex, Glaxo, UK, 1991)
10.		Amlodipine Besylate (Istin, Pfizer, USA, 1990)

Similarly, among nitrogen heterocycles, acridine analogs are equally important. During 20th century Proflavin **34** was used as a topical antibacterial and antifungal agent⁹⁷. In the 1940's and to the present day, the acridine (e.g., quinacrine, pyronaridine and acranil) have been used as

anti-malarial drugs⁹⁸. The first acridine-based therapeutic agents specifically designed for cancer treatment were developed during the 1970's. These efforts led to the development of m-amsacrine, 9-anilinoacridine introduced into clinical use in 1976⁹⁹. Acridine has been clinically utilized in combination or as a single agent with other antineoplastic drugs in the treatment of acute lymphocytic¹⁰⁰, acute myeloid^{101,102} and leukemias¹⁰³. Asulacrine is an inhibitor of topoisomerase II, which has shown potential against breast and lung cancer^{104,105}. Nitracrine (Ledakrin) is another acridine antineoplastic agent used in mammary ovarian tumors and in inhibition of RNA synthesis¹⁰⁶.



1.9. Present work

In the light of literature survey as mentioned above, Hantzsch multicomponent reaction has enormous utility in both organic syntheses and pharmaceutical industries. The great synthetic potential of MCRs involving the specific reactivity of easily accessible 1,3-dicarbonyl derivatives are a constant stimulant for synthetic work. Therefore, the following objectives were concluded for the project.

- To outline the synthetic potential of tandem MCRs involving the specific reactive sites, of 1,3-dicarbonyl particularly the dimedone. In addition, to expedite more recent application for the development of new and highly functionalized small organic molecules having synthetic and biological importance.

- Synthesis of six-membered heterocyclic compounds from the easily available 1,3-dicarbonyls compounds having interesting structure from biological point of views through Hantzsch multicomponent reaction is the major domain of the present work.
- Finding of the of best nitrogen donor for the formation nitrogen containing heterocycles among the various inorganic salt is also under consideration.
- Synthesis of symmetrical and unsymmetrical nitrogen heterocycles is another domain of the present project.
- To develop a convenient, solvent free and energy saving protocol for the synthesis of dihydropyridine and polyhydroquinoline analogs.
- The libraries of the synthesized compounds having diverse structural features will be screened for their biological activities where our research group is engaged in for explorative synthetic work.

Part A

Synthesis and characterization of Aza-heterocycles

- **Polyhydroquinolines (PHQs)**
- **1,4-Dihydropyridine (DHPs)**
- **Polyhydroacridine-1,8-diones (PHAs)**

2.1. Results and discussion

Multi-component assembly processes offer convenient procedures for the introduction of many points of structural diversity into heterocyclic compounds, prepared in a straight forward manner in single synthetic step. These features in combination with the extremely fast reaction kinetics of microwave-assisted organic synthesis provide new methods for the rapid and efficient synthesis of heterocyclic compounds. These methods employed in the synthesis of libraries of desired heterocyclic compounds suitable for biological evaluation and structure activity relationship (SAR) studies. Among the various classes of organic compounds, heterocycles constitute the largest group of organic compounds and are becoming ever more important in all aspects of pure and applied chemistry. Similarly, the heterocycles like polyhydroquinolines (PHQs), 1,4-Dihydropyridines and acridinrdiones are the synthetic analogous of renowned class of dihydropyridine drugs.

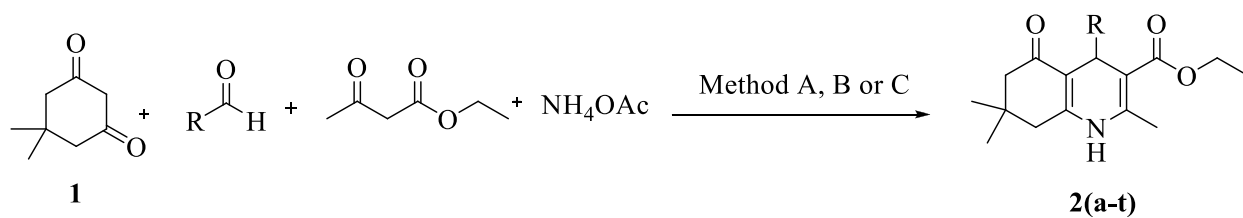
This chapter deals with the study of results and discussion along with experimental procedures for the multicomponent synthesis of polyhydroquinoline derivatives, their reaction with alkyl halides, acridine-1,8-diones (PHAs) and 1,4-dihydropyridine (DHPs) analogs.

Unfortunately, some of the reported methods did not worked in our hands. Therefore, the new protocols were applied for the targeted class of N-heterocyclic scaffold synthesis via dimedone annulated multicomponent assembly process. For the synthesis of polyhydroquinoline derivatives three methods under microwaves irradiation were adapted, in which variant catalysts were used. In the first method morpholine was used as catalyst, while in the second and third method morpholine supported on alumina and I_2/Al_2O_3 was used as catalyst under microwave irradiations respectively. Under these conditions, a significant acceleration of the reaction was achieved as indicated by the scale time which is fastest in the first method as compared to the

second and third method (Table 2.1). However, by using I_2/Al_2O_3 combination slight difference was observed in the reaction time. In these new developed protocols, the adjustment of the reactants ratio has contributed an important role in the product formation. Various known and new polyhydroquinolines have been synthesized by this Hantzsch type four component reaction (4H-C) from good to excellent yield.

2.2. Synthesis and characterization of polyhydroquinoline derivatives

The polyhydroquinoline derivatives have been synthesized from dimedone (**1**), various aromatic aldehydes, ethylacetoacetate and ammonium acetate via four component Hantzsch (4H-C) type unsymmetrical reaction using morpholine as an organocatalyst under conventional method and microwave irradiation. The reaction scheme describes three methods for the formations of polyhydroquinolines are given below (Scheme 2.1).



Method A: Morpholine, Solvent free, MW, 450 W, 1.0-1.6 min.

Method B: Morpholine/ Al_2O_3 , Solvent free, MW, 450 W, 1.2-3 min.

Method C: I_2/Al_2O_3 , Solvent free, MW, 450 W, 2-4 min.

Scheme 2.1 Synthesis of polyhydroquinoline derivatives

Table 2.1 Synthesis of polyhydroquinoline derivatives **2(a-t)** using methods (A-C) under microwave irradiation

Entry	R	Compd.	Methods (A, B, C)* (Time, min)	Yield (%)		
				A	B	C
1.	4-OH-C ₆ H ₄ -	2a	1.6 2.0 3.0	90	81	89
2.	C ₆ H ₅ -	2b	1.6 2.0 ---	85	82	---
3.	3-OH-C ₆ H ₄ -	2c	1.6 2.5 4.0	70	78	71
4.	2,4-Cl- C ₆ H ₄ -	2d	--- 2.4 2.5	---	71	76
5.	4-N,N-(CH ₃) ₂ - C ₆ H ₄ -	2e	1.5 3.0 4.0	73	68	59
6.	4-OCH ₃ -C ₆ H ₄ -	2f	1.4 2.1 2.8	68	60	58
7.	3- NO ₂ - C ₆ H ₄	2g	1.6 2.7 3.6	64	64	71
8.	4-NO ₂ - C ₆ H ₄ -	2h	1.5 --- 4.0	60	---	69
9.	4-F-C ₆ H ₄ -	2i	1.4 2.0 2.0	92	90	90
10.	2-Cl- C ₆ H ₄	2j	--- --- 3.5	---	---	80
11.	4-Cl- C ₆ H ₄ -	2k	1.3 --- 2.4	90	---	92
12.	2-pyridyl	2l	1.0 2.7 ---	85	81	---

(Continued)

Entry	R	Compd.	Methods (A, B, C) (Time, min)	Yield (%)		
				A	B	C
13.	3-pyridyl	2m	1.0 3.0 ---	72	80	---
14.	4-pyridyl	2n	1.0 2.0 2.0	91	81	91
15.	2-OCH ₂ CH ₃ - C ₆ H ₅ -	2o	1.2 --- 4.0	90	---	62
16.	4-OH, 3-OCH ₃ - C ₆ H ₃ -	2p	1.6 3.0 4.0	77	58	67
17.	Terephthaldehyde	2q	1.6 --- ---	56	---	---
18.	3-OCH ₃ , 4- OCH ₃ - C ₆ H ₃ -	2r	--- 2.7 4.0	---	66	68
19.	2-OCH ₃ , 3- OCH ₃ - C ₆ H ₃ -	2s	1.6 --- ---	57	---	----
20.	4-OCH ₂ CH ₃ - C ₆ H ₄ -	2t	1.2 2.7 3.8	92	80	82
21	2-OH- C ₆ H ₃ -	NP	---	---	---	---
22	2-OH-3-OCH ₃ - C ₆ H ₃ -	NP	---	---	---	---

Reaction conditions; The reaction was carried out by mixing of dimedone (0.95 mmol), respective aldehyde (1 mmol), ethylacetoacetate (1.2 mmol) and ammonium acetate (1.2 mmol) using the following methods.

(---) = Not attempted;

NP = Not desired product

***Method A:** Morpholine, Solvent free, MW, 450 W 1.0-1.6 min.

***Method B:** Morpholine/Al₂O₃, Solvent free, MW, 450 W, 2-3 min.

***Method C:** I₂/Al₂O₃, Solvent free, MW, 450 W, 2-4 min.

2.2.1. Morpholine catalyzed synthesis of polyhydroquinoline derivatives (Method A)

Morpholine has been used in various reaction transformations like in sequential Michael and Aldol reactions of aromatic aldehyde with 2'-hydroxy acetophenone with excellent yields^{107,108}. It is a weak base ($pK_b = 5.51$) and commercially available catalyst.

The reaction of dimedone (**1**), *p*-hydroxybenzaldehyde, ethylacetoacetate and ammonium acetate (Entry 1), was used for the optimization of polyhydroquinoline to check the scope and generality of the morpholine as catalyst. Initially, the reaction was carried out in the absence of catalyst in ethanol, which yielded a dimedone-aldehyde adduct. However, on addition of 5 mol % morpholine as catalyst under reflux for 6 hours the target molecule (**2a**) was formed in 70% yield. When excess of morpholine was used as solvent as well as catalyst, the reaction failed to form the desired product even at refluxed temperature (**2a**) (Entry 3, Table 2.2). When the reaction was carried at room temperature using morpholine as catalyst the targeted molecule was obtained in good yield in 20 minutes. This method has been reported by Majid M. Heravi *et. al.*¹⁰⁹. But when we carried the model reaction under microwave irradiation without catalyst the reaction goes to completion within 6 minutes in 78% of product formation (**2a**) (Entry 5 Table 2.2).

Table 2.2. Optimization of the reaction condition using morpholine as catalyst under microwave irradiation (**Method A**)

Entry*	Solvent	Catalyst	Temperature	Time	Yield ^b (%)	Lit
1.	Ethanol	None	Reflux	6 h	NP ^a	---
2.	Ethanol	Morpholine	Reflux	3 h	70	---
3.	Morpholine	---	Reflux	8 h	NP ^a	---
4.	None	Morpholine	r. t	20 min	76	[109]
5.	----	---	MW, 450 W	6 min	78	---
6.	None	Morpholine	MW, 450 W	80 sec	90	---

1-6 represent model reaction under microwave irradiation; ^aNP = No desired product; ^bisolated product.

However, the time of the reaction dramatically reduced to second scales (80 seconds) by using morpholine as catalyst (10 mol%) under microwaves irradiation, (entry 6 Table 2.2). We made the process more facile and docile. The product formation is also almost twofold and the reaction time is in second scale.

2.2.1.1. Effect of loading morpholine as catalyst

The optimization process was kept continued to check the effect of the catalyst by increasing its amount in order to determine the optimum catalysis level of morpholine. It was observed that the yield of compound (**2a**) decreased with increase in the amount of morpholine in model reaction. The compound **2a** was obtained in 80%, 90%, 77% and 60% in loading of morpholine as catalyst, 5 , 10, 15 and 20 mol% (Entry 1-4, Table 2.3). It has been observed that 10 mol% is the optimum amount of the catalysis to push the reaction in the forward direction.

Table 2.3. Effect of the amount of morpholine as catalyst

Entry*	amount of catalyst (mol %)	Time(sec)	yield (%)
1.	5	100	80
2.	10	90	90
3.	15	100	77
4.	20	100	60

***Reaction conditions;** The model reaction was carried out under MW, 450 W and solventless condition

The change in ratio of four components also paly an important role in the formation of desired product. The best results were obtained while, using (0.95: 1.2: 1.0: 1.5) ratio of dimedone, ethyl acetoacetate, aldehydes and ammonium acetate respectively. It was also found that even slight excess of dimedone in reaction mixture yielded polyhydroacridine-1,8-dione in substantial amount. After optimization it was concluded that morpholine (10 mol %) is the

sufficient and optimum value for catalysis of polyhydroquinoline synthesis through multicomponent assembly process.

By exploitation of the morpholine activity as a small organ-catalyst through the Hantzsch reaction in the model reaction, the optimized reaction condition was extended to the condensation of other aldehydes with 1,3-diketone, β -keto ester and ammonium acetate under microwave irradiation in the same power. The nature of electron withdrawing and electron rich substituents afforded the desired product without any obvious effect. The use of terephthalaldehyde allowed the presence of two polyhydroquinoline on the benzene ring; (**2q**). Out of the twenty compounds seventeen different aldehydes has been checked for the synthesis of various derivatives of polyhydroquinolines by this method as summarized in table 2.1.

2.2.2 Morpholine/ Al_2O_3 catalyzed synthesis of polyhydroquinoline derivatives (Method B)

After the successful application of morpholine as an organo-catalyst for the sequential Hantzsch reaction, the strategy was then turned toward solid-phase organic synthesis (SPOS) which is generally popular in the medicinal chemistry community, for lead optimization. Therefore, first the morpholine 10 mol% was adsorbed on solid support neutral alumina (1 g) and then the reaction carried out under microwaves as shown in table 2.1 (**method B**). Without further optimization of the catalyst amount which was not required, therefore, the model reaction was carried out using 10 mol% of morpholine adsorbed on 0.5 gm of neutral alumina and was used as catalyst. Fourteen compounds were synthesized by using method B, which indicates that this method also tolerate the EDG as well as electron rich substituents on aromatic ring of the aldehydes (Table 2.1, Method B).

2.2.3. I₂/Al₂O₃ catalyzed synthesis of polyhydroquinoline derivatives (Method C)

In the continuation to search convenient procedure and more solid phase organic catalyst for the synthesis of polyhydroquinolines, the catalytic ability of molecular iodine was exploited previously adsorbed on neutral Al₂O₃. The catalyst was prepared by adsorbing 0.2 mmol of iodine on 0.5 g of neutral alumina according to the method reported by Ira Saxena *et al*¹¹⁰.for Bignilli reaction with slight modification. However, during optimization it has been observed that 0.5 mmol absorbed on 0.5 g of I₂ can give the best result in case of Hantzsch reaction as shown in table 2.4.

Different entries of the same model reaction were performed to determine the optimum amount of I₂/Al₂O₃ as catalyst. By changing the amount of catalyst from 0.2 mmol/0.2 g to 0.5 mmol/ 0.5 g, the desired compound **2a** was obtained in high yield (88%) in latter value (Entry 2, Table 2.4). However, further increased in the amount of catalyst has adverse effect on the formation of product (Entry 3, Table 2.4). Conclusively, this method was safer in term of product formation as compared to using morpholine without solid support (Method A).

When the amount of catalyst under microwave irradiation was optimized and the others aromatic aldehydes containing different substitutes on aromatic ring were allowed to react with dimedone, ethyl acetoacetate and ammonium acetate to afford different derivatives of polyhydroquinolines under the same reaction condition. It has been observed that this method also tolerate different functionalities on aromatic ring like Pyridyl, halides, nitro, hydroxyl and methoxy (Table 2.1, Method C). By using method C, fifteen derivatives of polyhydroquinolines were synthesized.

Table 2.4. Effect of the amount of I₂/Al₂O₃ as catalyst (**Method C**)

Entry*	I ₂ /Al ₂ O ₃	Time (min)	Yield ^b (%)
1.	0.2 mmol/0.5 g	3	70
2.	0.5 mmol/0.5 g	4	88
3.	1.0 mmol/0.5 g	3	83

*1-3 represent model reaction under MW 450 W; ^bisolated product

It can be assumed safely, that microwave assisted synthesis of polyhydroquinolines derivatives using the above three mentioned methods are superior over already reported methods. Several functional groups such as hydroxyl, methoxy groups, halides electron rich and electron deficient aldehydes and aryl aldehydes (hetero) worked well and remain stable under the reaction conditions. These methods do not involve the use of toxic solvents, hence are environmentally sound processes, and should preferably be facile for the synthesis of biologically active molecules. Ultimately, we can say, the combination of solid supported catalyst with microwave irradiation brought an elegant solution for the problem of the notoriously slower reactions compared to those in solution phase.

The presence of certain functional groups on the ortho position of benzaldehyde did not led to the formation of desired product. Therefore, a failure was observed when salicylaldehyde and substituted salicylaldehyde was used to give similar product. Thus, reaction with salicylaldehyde (Entry 21) and substituted salicylaldehyde (Entry 22) under the three mentioned procedure did not give the desired heterocycles.

All the synthesized PHQs were subjected to spectroscopic analysis for their structure confirmation (IR, ¹H, ¹³C-NMR, EIMS, CHN analysis) and their physical parameters. The physical data of the polyhydroquinoline derivatives has given in table 2.5.

Table 2.5. Physical data of the polyhydroquinoline derivatives **2(a-t)**

S.#	Compd.	Aldehyde	Physical appearance	Rf* value	m.p. (°C)	
					Observed	Reported
1.	2a	4-OH-C ₆ H ₄ -	White solid	0.41	230-232	231-233 ¹¹¹
2.	2b	C ₆ H ₅ -	Light yellow solid	0.61	205-207	202-204 ¹¹¹
3.	2c	3-OH-C ₆ H ₄ -	Off white solid	0.42	220-222	220-222 ¹¹²
4.	2d	2,4-Cl- C ₆ H ₄ -	Off white solid	0.58	214-216	216-218 ¹¹³
5.	2e	4-N,N-(CH ₃) ₂ -C ₆ H ₄ -	Yellow crystals	0.51	226-228	230-232 ¹¹¹
6.	2f	4-OCH ₃ -C ₆ H ₄ -	Light yellow solid	0.53	254-256	258-260 ¹¹²
7.	2g	3- NO ₂ - C ₆ H ₄	Off white crystals	0.62	178-180	174-176 ¹¹¹
8.	2h	4-NO ₂ - C ₆ H ₄ -	Off white crystals	0.64	243-245	244-246 ¹¹¹
9.	2i	4-F-C ₆ H ₄ -	White crystals	0.60	182-184	184-186 ¹¹⁴
10.	2j	2-Cl- C ₆ H ₄	white solid	0.63	205-207	206-208 ¹¹¹
11.	2k	4-Cl- C ₆ H ₄ -	White solid	0.65	244-246	245-247 ¹¹⁵
12.	2l	2-pyridyl	Yellow crystals	0.57	133-135	new
13.	2m	3-pyridyl	Light yellow crystals	0.54	68-70	66-67 ¹¹⁵
14.	2n	4-pyridyl	Light yellow crystals	0.51	102-104	----
15.	2o	2-ethoxy- C ₆ H ₅ -	Off white crystals	0.60	168-172	new
16.	2p	Vanillin	Off white crystals	0.43	212-214	209-211 ¹¹¹
17.	2q	Terephthaldehyde	Yellow solid	0.45	308-312	new
18.	2r	3,4-dimethoxy-C ₆ H ₃ -	yellow crystals	0.51	200-202	197-199 ¹¹³
19.	2s	2,3-dimethoxy-C ₆ H ₃ -	White crystals	0.51	---	new
20.	2t	4-ethoxy- C ₆ H ₄ -	White crystals	0.62	193-196	new

*n-Hexane: Ethyl acetate (3:7) on Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at $\lambda=254\text{nm}$

2.3. Spectral discussion of polyhydroquinolines (PHQs) 2(a-t)

2.3.1. IR study of polyhydroquinoline derivatives

All the synthesized compounds were confirmed from the functional group frequency in the IR spectral data. The OH weak stretching bands often appeared in their typical range 3400-3300 cm^{-1} for compounds **2a**, **2b**, and **2p**. The fundamental absorption for the N-H indicates in the 3300-3200 cm^{-1} in all compounds, which was also confirmed from C-N stretching in the range 1400-1300 cm^{-1} . The aliphatic part of the basic nucleus was confirmed from C-H just below 3000 cm^{-1} and C-H bending above 1400 cm^{-1} . The major functional groups fundamental absorption bands are displayed in table 2.6.

Table 2.6. *FT IR Spectral data of polyhydroquinoline derivatives **2(a-t)**

Compd.	Ar	NH	COOC**	C=O*	C=C	C-O	C-N
2a	4-OH-C ₆ H ₄ -	3227	1701	1674	1604	1166	1377
2b	C ₆ H ₅ -	3228	1697	1670	1608	1191	1379
2c	3-OH-C ₆ H ₄ -	3273	1692	1674	1606	1207	1379
2d	2,4-Cl- C ₆ H ₄ -	3234	1700	1678	1602	1184	1366
2e	4-N,N-(CH ₃) ₂ -C ₆ H ₄ -	3286	1681	1681	1641	1149	1381
2f	4-OCH ₃ -C ₆ H ₄ -	3279	1696	1677	1601	1156	1391
2g	3- NO ₂ - C ₆ H ₄	3281	1712	1685	1540	1143	1376
2h	4-NO ₂ - C ₆ H ₄ -	3310	1686	1648	1526	1140	1368
2i	4-F-C ₆ H ₄ -	3271	1705	1645	1600	1211	1379
2j	2-Cl- C ₆ H ₄	3281	1701	1678	1598	1140	1378
2k	4-Cl- C ₆ H ₄ -	3270	1691	1671	1595	1093	1394
2l	2-pyridyl	3290	1672	1629	1597	1222	1323

(Continued)

Compd.	Ar	NH	COOC**	C=O*	C=C	C-O	C-N
2m	3-pyridyl	3294	1698	1665	1605	1141	1367
2n	4-pyridyl	3165	1691	1680	1600	1166	1315
2o	2-ethoxy - C ₆ H ₅ -	3221	1690	1680	1590	1161	1307
2p	4-OH, 3-OCH ₃ - C ₆ H ₃ -	3288	1695	1643	1587	1145	1345
2q	Terephthaldehyde	3278	1703	1686	1606	1147	1371
2r	3, 4-dimethoxy- C ₆ H ₃ -	3319	1706	1684	1614	1160	1379
2s	2,3-dimethoxy - C ₆ H ₃ -	3296	1693	1693	1600	1168	1369
2t	4-ethoxy- C ₆ H ₄ -	3205	1701	1680	1601	1169	1367

* $\nu(\text{Cm}^{-1})$ **ester, *Ketonic

2.3.2. ¹H NMR Spectral data of polyhydroquinolines 2(a-t)

In the ¹H NMR spectrums of polyhydroquinoline derivatives the number of protons and their chemical shifts were found to support the structure of the synthesized compounds. The characteristic peak which requires comments is the appearance of the C-H proton at C-4 in the range 4.82-5.08 ppm as singlet in all compounds. The appearance of broad singlet in the range 5 to 7 ppm for NH shows that the dihydropyridine ring formed due to the annulations reaction. In compounds **2i**, **2m**, and **2n** also appears signals between 7.0-8.0 ppm relating to the proton of the pyridine ring, showing the characteristic multiplicity depending on the position of the nitrogen atom in the pyridine ring. In case of compound **2g** and **2h** the aromatic proton appeared at 7.98 and 7.92 ppm due to the deshielding effect of nitro group on aromatic ring. The quartet appeared at 3.71 to 4.05 ppm and triplet at 1.91 to 1.12 ppm is due to ester group. The two methyl group attached to C-7 gives singlet in the most downfield regions as shown in table 2.7 and the sample spectra of compound **2t** and **2q** have been given in figures 2.1, 2.2.

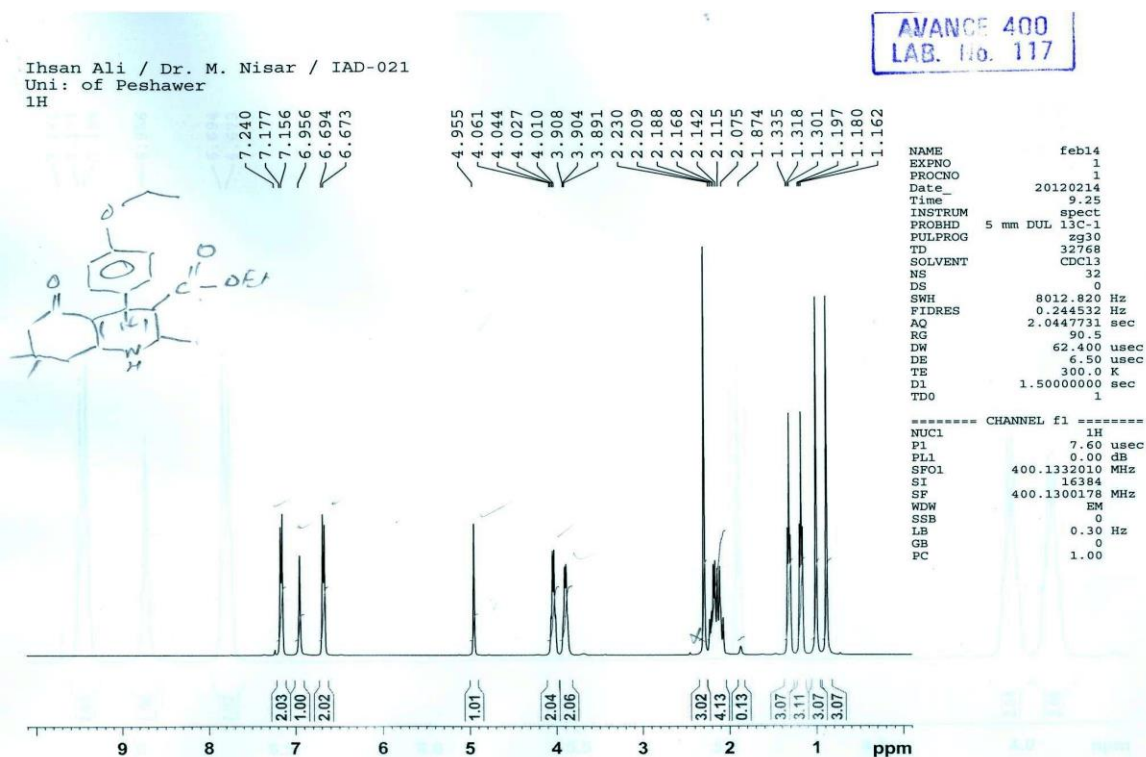
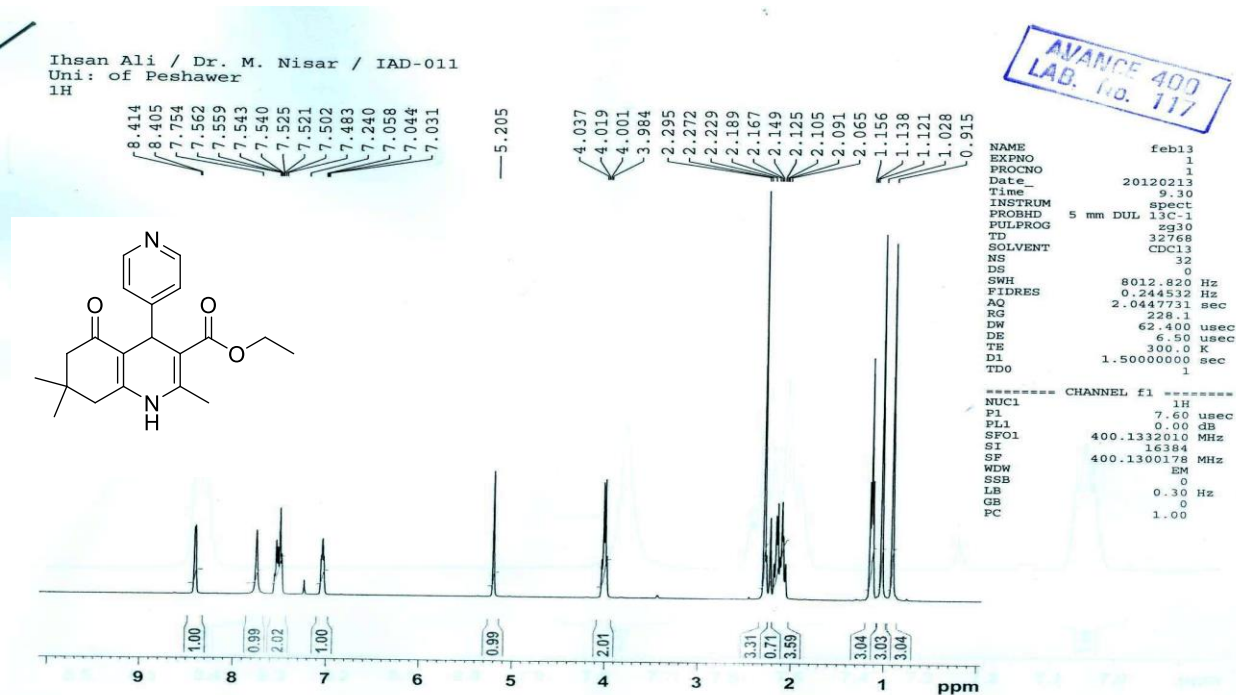
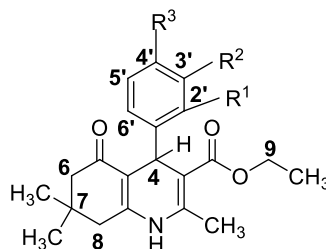

 Fig 2.1. Sample ^1H NMR spectrum of compound 2t.

 Fig. 2.2. Sample ^1H NMR spectrum of compound 2q.

Table 2.7. ^1H NMR spectral data of polyhydroquinolines derivatives **2(a-t)**

Compd.	$\delta(\text{ppm})$, Integration, multiplicity and coupling constants(J)												
	H-4'	H-2'	H-6'	H-3'	H-5'	CH, C-4	OCH ₂ C-9	=C-CH ₃	2CH ₂ C-6,8	CH ₃ Ester	2CH ₃ C-7	NH	R
2a	---	7.14 (2H, d, $J = 8.4$ Hz)		6.63 (2H, d, $J = 8.4$ Hz)		4.96 (1H, s)	4.04 (2H, q, $J = 7.2$ Hz)	2.35 (3H, s)	2.20-2.16 (4H, m)	1.19 (3H, t, $J = 7.2$ Hz)	1.05 (3H, s) 0.90 (3H, s)	5.59 (s, 1H)	R ³ = OH 4.96 (s, 1H)
2b	7.06-7.29 (5H, m)					5.02 (1H, s)	4.02 (2H, q, $J = 6.9$ Hz)	2.33 (3H, s)	2.27-2.14 (4H, m)	1.17 (3H, t, $J = 7.2$ Hz)	1.04 (3H, s) 0.90 (3H, s)	6.14 (1H, s)	R = H
2c	6.51 (1H, d, $J = 7.2$ Hz) H-4' 7.14 (1H, s) H-2' 6.49 (1H, d, $J = 6.6$ Hz) H-6'				6.96 (1H, t, $J = 7.8$ Hz)	4.90 (1H, s)	4.05 (2H, q, $J = 9.6$ Hz)	2.30 (3H, s)	2.54-2.01 (4H, m)	1.92 (3H, t, $J = 7.2$ Hz)	1.11 (3H, s) 1.06 (3H, s)	6.73 (1H, s)	R ² = OH 5.06 (s, 1H)
2d	7.81 (1H, d, $J = 8.8$ Hz) H-3' 7.71-7.67 (2H, m) H-5', H-6'					4.81 (1H, s)	4.09 (2H, q, $J = 6.9$ Hz)	2.83 (3H, s)	2.41-2.18 (4H, m)	1.23 (3H, t, $J = 6.8$ Hz)	1.06 (3H, s) 1.03 (3H, s)	6.54 (1H, s)	R ² = R ³ = Cl
2e	7.14 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.57 (d, $J = 8.7$ Hz, 2H, Ar-H),					4.92 (1H, s)	4.05 (2H, q, $J = 6.9$ Hz)	2.32 (3H, s)	2.23-2.14 (4H, m)	1.20 (3H, t, $J = 6.9$ Hz)	1.04 (3H, s) 0.93 (3H, s)	5.99 (1H, s)	R ³ = N(CH ₃) ₂ 4.96 s, 6H)

(300 or 400 MHz)

(Continued)

Compd.	δ (ppm), Integration, multiplicity and coupling constants(J)												
	H-4'	H-2'	H-6'	H-3'	H-5'	CH, C-4	OCH ₂ C-9	=C-CH ₃	2CH ₂ C-6,8	CH ₃ Ester	2CH ₃ C-7	NH	R
2f	---	7.20 (2H, d, <i>J</i> = 8.7 Hz)		6.71 (2H, d, <i>J</i> = 8.7 Hz)		4.97 (1H, s)	4.02 (2H, q, <i>J</i> = 7.2 Hz)	2.33 (3H, s)	2.30-2.04 (4H, m)	1.18 (3H, t, <i>J</i> = 7.2 Hz)	0.93 (3H, s) 0.91 (3H, s)	6.11 (s, 1H)	R ³ = OCH ₃ 3.70 (s, 3H)
2g	7.92 (1H, m) H-2' 7.90 (1H, m) H-4' , 7.70 (2H, d, <i>J</i> = 7.8 Hz) H-5',H-6'					4.84 (1H, s)	4.09 (2H, q, <i>J</i> = 7.2 Hz)	2.35 (3H, s)	2.34-2.12 (4H, m)	1.17 (3H, t, <i>J</i> = 7.2 Hz)	1.19 (3H, s) 1.14 (3H, s)	6.79 (1H, s)	R ² = NO ₂
2h	---	7.98 (2H, d, <i>J</i> = 8.8 Hz)		7.61 (2H, d, <i>J</i> = 8.8 Hz)		5.28 (1H, s)	4.02 (2H, q, <i>J</i> = 7.2 Hz)	2.38 (3H, s)	2.37-2.14 (4H, m)	1.19 (3H, t, <i>J</i> = 6.9 Hz)	1.13 (3H, s) 1.06 (3H, s)	6.80 (1H, s)	R ³ = NO ₂
2i	---	7.22 (2H, m)		6.84 (2H, m)		5.00 (1H, s)	4.02 (2H, q, <i>J</i> = 7.2 Hz)	2.32 (3H, s)	2.26-2.14 (4H, m)	1.16 (3H, t, <i>J</i> = 7.2 Hz)	1.03 (3H, s) 0.89 (3H, s)	6.45 (1H, s)	R ³ = F
2j	7.46-7.29 (2H, m) H-3',4',5',6'					5.08 (1H, s)	4.01 (2H, q, <i>J</i> = 7.2 Hz)	2.40 (3H, s)	2.28-2.11 (4H, m)	1.21 (3H, t, <i>J</i> = 7.2 Hz)	1.07 (3H, s) 0.99 (3H, s)	6.12 (1H, s)	R ¹ = Cl
2k	---	7.36 (2H, d, <i>J</i> = 8.8 Hz)		7.19 (2H, d, <i>J</i> = 8.8 Hz)		5.79 (1H, s)	4.06 (2H, q, <i>J</i> = 7.2 Hz)	2.42 (3H, s)	2.36-2.20 (4H, m)	1.17 (3H, t, <i>J</i> = 7.2 Hz)	1.01 (3H, s) 0.93 (3H, s)	6.41 (1H, s)	R ³ = Cl
2l	7.04 (1H, d, <i>J</i> = 10.8 Hz) H-4 , 7.48-7.56 (2H, m) H-5',6'			8.41 (1H, m) H-3'		5.20 (1H, s)	4.01 (2H, q, <i>J</i> = 7.2 Hz)	2.29 (3H, s)	2.26-2.06 (4H, m)	1.13 (3H, t, <i>J</i> = 7.2 Hz)	1.02 (3H, s) 0.91 (3H, s)	7.75 (1H, s)	R ¹ = 2-pyridyl

(300 or 400 MHz)

(Continued)

Compd.	*δ(ppm), Integration, multiplicity and coupling constants(J)												
	H-4´	H-2´	H-6´	H-3´	H-5´	CH, C-4	OCH ₂ C-9	=C-CH ₃	2CH ₂ C-6,8	CH ₃ Ester	2CH ₃ C-7	NH	R
2m	8.32 (1H t, J=8.2 Hz)	8.47 (1H, s) 7.18 (2H,m)		7.72-7.24 (1H, m)		5.01 (1H, s)	4.03 (2H, q, J = 7.2 Hz)	2.29 (3H, s)	2.27-2.05 (4H, m)	1.15 (3H, t, J =7.2 Hz)	1.01(3H, s) 0.83 (3H, s)	7.13 (1H, s)	R ² =3-pyridyl
2n	---	8.39 (2H, d, J = 4.4 Hz)		7.25 (2H, d, J = 8.7 Hz)		5.01 (1H, s)	4.04 (2H, q, J = 7.2 Hz)	2.35 (3H, s)	2.29-2.09 (4H, m)	1.16 (3H, t, J =7.2 Hz)	1.02(3H, s) 0.86 (3H, s)	7.61 (1H, s)	R ³ =4-pyridyl
2o	6.95 (1H, d, J = 6.0Hz)	7.24 (1H, d, J= 6.0 Hz) H-6´		6.70-6.63 (2H, m) H-5´, H-3´		5.05 (1H, s)	3.97-3.81 (4H, m)	2.32 (3H, s)	2.23-1.94 (4H, m)	1.23 (3H, t, J = 6.8 Hz)	0.95 (3H, s) 0.81 (3H, s)	7.62 (s,1H)	R ¹ =O CH ₂ CH ₃ 1.08 (3H, t, J =7.2 Hz
2p	---	6.84 (1H, s) 6.61(2H, s)				4.87 (1H, s)	4.04 (2H, q, J = 7.2 Hz)	2.32 (3H, s)	2.45-2.14 (4H, m)	1.13(3H, t, J =6.8 Hz)	1.02 (3H, s) 0.95 (3H, s)	6.11 (s, 1H)	R ³ = OH, 5.50 (s,1H), R ² = OCH ₃ 3.77 (s, 3H)
2q	7.06 (4H, s)					4.99 (2H, s)	3.97 (4H, q, J = 6.9 Hz)	2.95 (6H, s)	2.36-2.02 (8H, m)	1.10 (6H, t, J = 6.9 Hz)	1.04 (6H, s) 1.02 (6H, s)	5.97 (s, 2H)	R ³ = dimmer
2r	---	6.99 (1H, s) 6.80 (1H, d, J = 8.3Hz)		6.73 (1H, d, J = 8.3 Hz)		5.62 (1H, s)	4.04 (2H, q, J = 7.3 Hz)	2.41 (3H, s)	2.18-2.34 (4H, m)	1.21 (3H, t, J = 6.8 Hz)	1.01 (3H, s) 0.97 (3H, s)	6.12 (s,1H)	R ³ = R ² = OCH ₃ 3.88 (s, 6H)
2s	7.34- 7.13 (1H, m)	7.08-6.91 (2H, m) H-5´, H-6´				4.82 (1H, s)	4.02 (2H, q, J = 7.2 Hz)	2.25 (3H, s)	2.11-2.09 (4H, m)	1.20 (3H, t, J = 6.8 Hz)	1.07 (3H, s) 0.99 (3H, s)	6.01 (s, 1H)	R ¹ = R ² = OCH ₃ 4.22 (s, 6H)
2t	---	7.17(2H, d, J= 8.4 Hz)		6.69 (2H, d, J = 8.4 Hz)		5.95 (1H, s)	4.04 (2H, q, J = 6.9 Hz)	2.23 (3H, s)	2.20-2.11 (4H, m)	1.31 (3H, t, J = 6.9 Hz)	1.00(3H, s) 0.88(3H, s)	6.95 (s, 1H)	R ³ = OCH ₂ CH ₃ 3.90 (2H, t, J = 6.8 Hz) 1.19 (3H, t, J = 6.8Hz

2.3.3. ^{13}C NMR Spectral data of polyhydroquinolines 2(a-t)

The ^{13}C NMR spectra of the polyhydroquinoline derivatives exhibited signals in the aliphatic, aromatic and carbonyl regions including signals corresponding to the heterocyclic ring. The ketonic carbonyl carbon resonates at 194.4-198.5 ppm while the ester carbonyl carbon appeared at 167 -169.6 ppm, which are its typical region as shown in the table 2.8. The heterocyclic ring having four quaternary carbons and one tertiary carbon (C-4) confirmed the formation of the desired basic nucleus of polyhydroquinolines. These compounds show the signal for C-3 and C-4' at lower values (105-107 and 110-112 ppm) than those expected for typical olefin carbon atoms while C-2 and C-8' appear at higher values (150 ppm) and C-4 appears between 30.1-36.1 ppm. These differences have been accounted for by the strong push-pull effect of the groups linked to the olefin double bonds. The two methyl carbon, C-7' and C-7'' exhibited signals in the typical aliphatic region at 28.1 and 27.1 ppm respectively. The methylene carbon signals corresponding to C-6, C-8 and C-10 was also assigned from DEPT 135 data between 50.1, 40.1 and 60.1ppm respectively. The aromatic part of the polyhydroquinolines derivatives have shown signals in the typical aromatic region as shown in the following table 2.8.

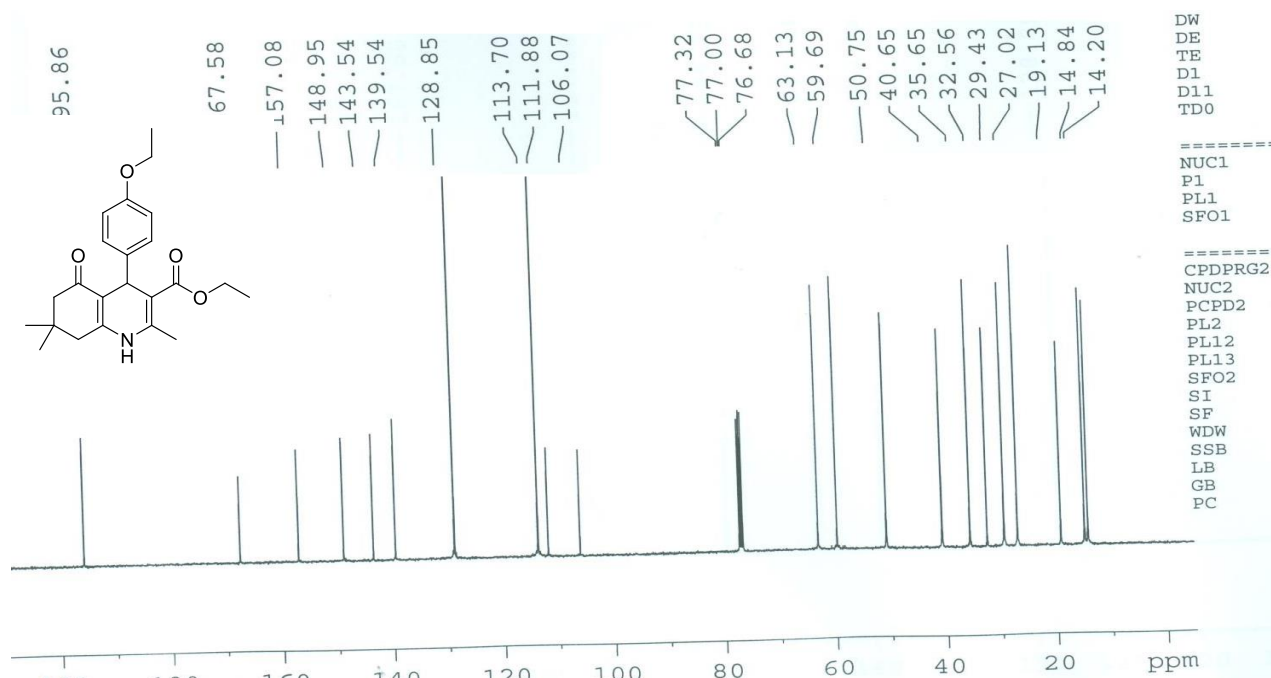
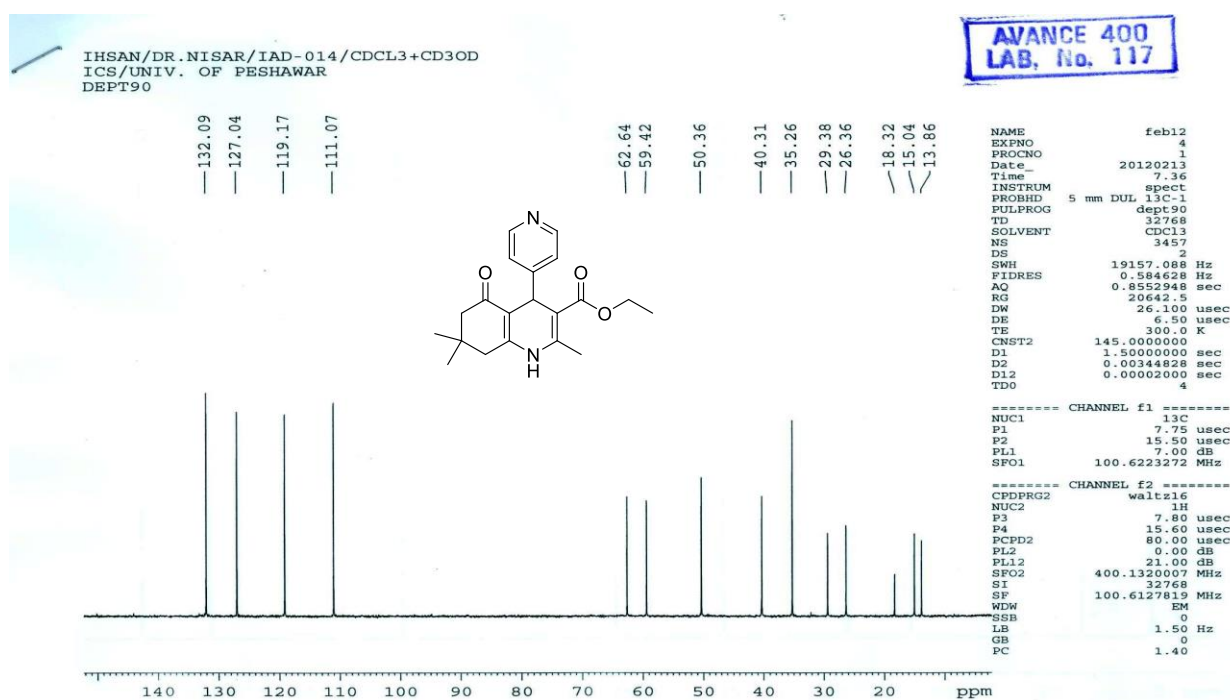
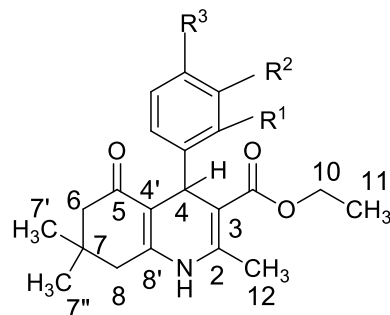
Fig. 2.3. Sample ^{13}C NMR spectrum of 2tFig.2.4 . Sample ^{13}C NMR spectrum of 2n

Table 2.8. ^{13}C NMR spectral data of polyhydroquinolines derivatives **2(a-t)**

Compd.	C=O*	C=O**	C-2	C-8'	C-4'	C-3	C-10 CH ₂	C-6 CH ₂	C-8 CH ₂	C-7	C-4 CH	C-7' C-7''	C-11, C-12	Aromatic carbons	R
2a	198.5	169.5	156.5	152.5	112.5	107.2	60.8	51.8	41.0	36.9	29.6	28.5 27.0	18.5 14.5	140.1, 131.9, 129.9, 115.5,	R ³ =OH
2b	195.4	167.4	148.1	147.0	112.1	106.0	59.7	50.7	41.0	36.5	32.4	29.4 27.1	19.3 14.1	143.4, 127.9, 127.8, 125.9, 124.5	R=H
2c	198.4	169.4	158.0	152.5	112.1	106.5	60.8	51.3	41.1	37.6	33.4	28.6, 27.1,	18.3 14.5	150.2, 146.0, 139.9, 129.6, 115.9	R ² =OH

(75 or 100 MHz) *Ketonic ** ester

Continued

Carbons	¹³ C NMR spectral data of polyhydroquinolines derivatives														
	C=O*	C=O**	C-2	C-8'	C-4'	C-3	C-10 CH ₂	C-6 CH ₂	C-8 CH ₂	C-4 CH	C-7	C-7' C-7''	C-11, C-12	Aromatic carbons	R
2d	198.5	169.6	157.5	152.1	112.5	107.8	60.3	52.5	41.3	36.4	33.5	28.0 27.0	18.5 14.5	145.6, 140.9, 139.8, 129.5, 120. .2, 115.7,	R ¹ = R ³ =Cl
2e	198.5	169.6	152.2	150.7	112.5	107.0	60.8	51.5	41.5	36.7	33.4	29.6 27.1	18.5 14.5	145.4, 138.2, 129.5, 114.2,	R ³ = -N(CH ₃) ₂ 41.1
2f	195.5	167.4	157.7	147.8	112.3	106.3	59.7	50.7	41.0	35.6	32.4	29.1 27.2	19.3 14.2	143.0, 139.5 128.9, 113.2	R ³ =OCH ₃ 55.1
2g	195.6	169.2	157.0	152.6	113.1	104.5	59.3	59.3	40.1	39.6	32.4	28.3 27.1	17.5 13.5	147.0, 138.6, 120.9, 119.1	R ² =NO ₂
2h	196.8	167.9	158.1	153.8	114.7	102.4	62.7	58.6	41.4	39.8	33.8	28.2 27.5	18.8 14.8	148.1, 139.5, 128.7, 121.8, 120.2	R ³ =NO ₂
2i	195.6	167.3	162.8	159.6	111.9	105.9	59.8	50.7	41.9	35.9	32.6	29.4 27.0	19.2 14.1	148.3, 143.5, 142.9, 129.4, 129.3, 114.6	R ³ =F
2j	196.1	167.9	150.0	143.2	110.5	102.1	56.5	51.7	45.8	42.1	31.5	27.8 26.6	18.5 13.9	140.1, 129.1, 127.1, 126.0. 124.8, 115.1	R ¹ =Cl
2k	195.7	167.5	151.9	147.6	112.0	105.9	59.8	50.6	40.8	35.9	31.6	29.4 , 27.5	19.5 14.0	143.5, 142.9, 132.4, 129.3, 114.2	R ³ =Cl
2l	195.5	167.3	149.3	149.4	110.5	104.2	59.6	50.6	40.8	39.7	32.8	28.6 28.1	19.1 14.1	148.4, 145.1, 135.6, 124.5,	R ¹ = 2-pyridyl
2m	195.3	167.0	149.3	149. .3	104.7		59.8	50.6	40.5	35.0	32.6	29.3 27.1	18.9 14.2	148.9, 146.6, 143.4, 136.2	R ² = 3-pyridyl

Compd.	¹³ CNMR spectral data of polyhydroquinolines derivatives (1-20)														
	C=O (ketone)	C=O (Ester)	C-2	C-8'	C-4'	C-3	C-10 CH ₂	C-6 CH ₂	C-8 CH ₂	C-4 CH	C-7	C-7' C-7''	C-11, C-12	Aromatic carbons	R
2n	195.4	166.9	155.7	149.4	110.4	104.0	59.9	50.6	40.7	36.5	32.6	29.3 27.0	19.0 14.1	149.3, 149.0, 145.1, 123.4	R ³ =4-pyridyl
2o	196.1	168.4	157.3	150.2,	109.5	103.6	59.4	50.3	40.4	35.2	32.1	29.3 26.3	18.3 13.8	150.1, 144.1, 133.2, 132.0, 127.0, 119.1,	R ¹ =O CH ₂ CH ₃ 62.6,15.0
2p	198.5	169.5	152.3	148.2	112.4	106.9	60.8	51.5	41.1	37.2	33.4	29.7 27.0	18.5 14.6	145.7, 145.6, 140.7, 121.3, 115.6, 113.1	R ³ =OH, R ² =OCH ₃ 56.3
2q	198.4	169.4	152.6	146.1	112.2	106.5	60.8	51.5	41.0	37.1	33.4	29.5 27.2	20.8 18.5	128.5, 128.3,	R ³ =is dimmer
2r	194.8	167.0	150.2	148.6	109.6	101.7	59.8	50.5	40.9	35.8	32.1	28.7 27.5	18.1 14.5	148.6, 147.3, 143.8, 140.2	R ² = R ³ =OCH ₃ 60.0, 55.9
2s	195.3	167.8	152.8	148.6	110.6	105.5	59.7	50.8	41.2	34.3	32.6	28.8 27.8	19.4 14.1	147.8, 142.4, 139.5, 123.5, 122.5, 111.2	R ¹ = R ² =OCH ₃ 60.1, 55.6
2t	195.8	167.5	157.0	148.9	111.8	106.0	59.6	50.7	40.6	35.6	32.5	29.4 27.0	19.1 14.2	143.5, 139.5, 128.8,, 113.7	R ³ =O CH ₂ CH ₃ 63.1, 14.8

2.3.4. EIMS and CHN elemental analysis data of polyhydroquinoline derivatives 2(a-t)

The structures of synthesized compounds were confirmed from EIMS spectral data and elemental analysis of carbon, hydrogen and nitrogen. The instrumental data in both techniques were in full agreement with theoretical data as displayed in the following table 2.9.

Table 2.9. CHN and EIMS data of polyhydroquinoline derivatives 2(a-t)

Compd.	Mol. F	Calcd (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt EIMS (M+%)
		C	H	N	C	H	N		
2a	C ₂₁ H ₂₅ NO ₄	70.96	7.09	3.04	70.91	7.00	3.14	355.4	355.1 (100.0)
2b	C ₂₁ H ₂₅ NO ₃	74.31	7.42	4.13	74.39	7.31	4.32	339.4	339.0 (28.5)
2c	C ₂₁ H ₂₅ NO ₄	70.96	7.09	3.04	70.99	7.11	3.18	355.4	355.1 (42.1)
2d	C ₂₁ H ₂₃ Cl ₂ NO ₃	61.77	5.68	17.37	61.79	5.56	17.40	407.1	407.1 (46.8)
2e	C ₂₃ H ₃₀ N ₂ O ₄	72.22	7.91	7.32	72.32	7.98	7.55	382.1	382.2 (30.9)
2f	C ₂₂ H ₂₇ NO ₄	71.52	7.37	3.79	71.60	7.29	3.85	369.1	369.3 (52.4)
2g	C ₂₁ H ₂₄ N ₂ O ₅	65.61	6.29	7.29	65.66	6.31	7.38	384.1	384.2 (67.1)
2h	C ₂₁ H ₂₄ N ₂ O ₅	65.61	6.29	7.29	65.70	6.11	7.61	384.1	384.2 (49.1)
2i	C ₂₁ H ₂₄ FNO ₃	70.57	6.77	5.32	70.66	6.59	6.70	357.1	357.3 (66.7)
2j	C ₂₁ H ₂₄ ClNO ₃	67.46	6.47	3.75	67.50	6.35	3.81	373.1	373.2 (53.7)
2k	C ₂₁ H ₂₄ ClNO ₃	67.46	6.47	3.75	67.49	6.41	3.79	373.1	373.2 (62.5)

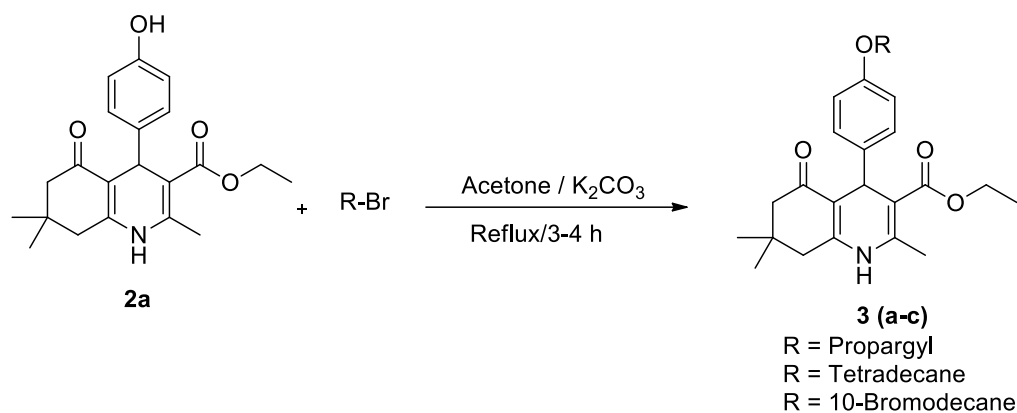
(Continued)

Compd.	Mol. F	Calcd (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt EIMS (M+%)
		C	H	N	C	H	N		
2l	C ₂₀ H ₂₄ N ₂ O ₃	70.56	7.11	8.23	70.50	7.01	8.30	340.4	341.2 (24.1)
2m	C ₂₀ H ₂₄ N ₂ O ₃	70.56	7.11	8.23	70.60	7.09	8.29	340.4	340.0 (33.7)
2n	C ₂₀ H ₂₄ N ₂ O ₃	70.56	7.11	8.23	70.59	7.12	8.28	340.4	340.9 (20.1)
2o	C ₂₃ H ₂₉ NO ₄	72.04	7.62	3.65	72.00	7.56	3.70	383.18	383.2 (98.7)
2p	C ₂₂ H ₂₇ NO ₅	68.55	7.06	3.63	68.50	7.01	3.68	385.19	385.2 (48.7)
2q	C ₃₆ H ₄₄ N ₂ O ₆	71.97	7.38	4.66	71.92	7.31	4.69	600.3	600.1 (21.8)
2r	C ₂₃ H ₂₉ NO ₅	69.15	7.32	3.51	69.16	7.28	3.49	399.2	399.3 (99.7)
2s	C ₂₃ H ₂₉ NO ₅	69.15	7.32	3.51	69.12	7.34	3.50	399.2	399.0 (92.0)
2t	C ₂₃ H ₂₉ NO ₄	72.04	7.62	3.65	72.01	7.59	3.69	382.2	383.2 (100.0)

(M+%): % Abundance

2.4. Reaction of polyhydroquinoline (2a) with alkyl halides

The new polyhydroquinolines derivatives, (entry 23-25) compounds **3(a-c)** were synthesized by the reaction polyhydroquinoline derivative (**2a**) (0.5 mmol) with respective alkyl halides (0.5 mmol) in the presences of K₂CO₃ (1.25 mmol, 2.5 eq.) using acetone as solvent according to scheme 2.2. The reaction mixture was refluxed for 3-4.5 h and the progress of reaction was monitored by TLC. The crude product was purified by column chromatography using ethyl acetate and n-hexane solvent system.



Scheme 2.2. Synthesis polyhydroquinoline analogs **3 (a-c)** from compound **2a**

The other reactive sites like NH and CH₂ adjacent to ketone group do not react with alkyl halides even using sodium hydride in THF, a stronger base than potassium carbonate. Therefore, clean alkylation takes place at phenolic oxygen only. The synthesized compounds were confirmed from their physical data and spectroscopic analysis like IR, NMR, EIMS and elemental analysis. The physical data is given in table 2.10.

Table 2.10. Physical data of the polyhydroquinoline derivatives **3(a-c)**

S.#	Comp	R	Physical appearance	R _f * value	m.p.	
					Observed	Reported
23	3a	Propargyl	yellowish powder	0.51	155-160	New
24	3b	Tetradecane	Light yellow solid	0.55	130-133	New
25	3c	10-Bromodecane	Light yellow solid	0.52	170-172	New

**n*-Hexane : Ethyl acetate (1:1) on Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at λ=254nm

2.4.1. Characterization of ethyl 2,7,7-trimethyl-5-oxo-4-(4-(prop-2-ynoxy)phenyl)1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**3a**)

The target molecule **3a** was fully characterized from spectroscopic data. In the IR spectral data the formation of compound **3a** was confirmed from the disappearances of OH peak at 3433 cm⁻¹ in the substrate **2a**. The presence of fundamental absorbance in the range of 3200-3300 cm⁻¹

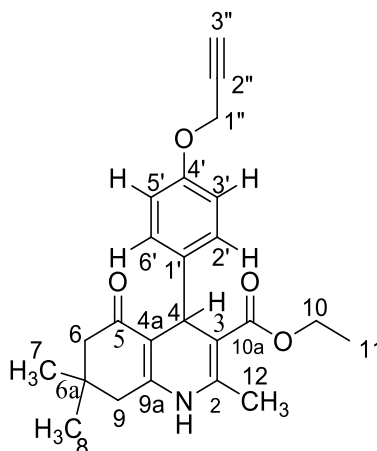
confirmed the presence of NH in the heterocyclic ring which was also ensured from the C-N stretching between 1300 and 1400 cm^{-1} . The major group frequencies are given in the following table 2.11.

Table 2.11. *IR Spectral data of polyhydroquinoline derivatives **3(a-c)**

Comp	NH	SP ² C-H	SP ³ C-H	COOC**	C=O*	C=C	C-H Bend	C-O	C-N
3a	3276	3074	2929	1680	1662	1595	1479	1107	1145
3b	3375	3082	2961	1721	1680	1620	1456	1243	1127
3c	3204	3070	2945	1741	1686	1585	1486	1273	1187

* $\nu(\text{Cm}^{-1})$ **ester *Ketonic

The structure of compounds **3a** was confirmed from ^1H NMR spectrum. For ethyl 2,7,7-trimethyl-5-oxo-4-(4-(prop-2-ynyloxy)phenyl)1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**3a**) characteristic signals were observed for the Propagyl group. The appearance of doublet for the OCH_2 at 4.58 ppm and terminal acetylenic proton at 2.47 ppm of the propagyl group confirmed the formation of the target molecules **3a**. All the other confirmatory peaks and aromatic rings protons with J value were observed to be in accordance with the substrates **2a**, as shown in table 2.12.

Table 2.12. ^1H NMR data of compound **3a**

$\delta(\text{ppm})$	Multiplicity	Integration	coupling constants J (Hz)	Assignment
7.18	d	2H	8.7	Ar-H
6.79	s	2H	8.7	Ar-H
5.84	s	1H	---	NH
4.98	s	1H	---	CH (C-4)
4.58	d	2H	2.4	CH_2 (C-1'')
4.04	q	2H	7.2	CH_2 (C-10)
2.47	t	1H	2.4	CH (C-3'')
2.36	s	3H	---	CH_3 (C-12)
2.27-2.15	m	4H	---	2CH_2 (C-6,9)
1.17	t	3H	7.2	CH_3 (C-11)
1.04	s	3H	---	CH_3 (C-7)
0.90	s	3H	---	CH_3 (C-8)

The formation of compound **3a** was also further established from the ^{13}C NMR spectral data. The appearance of additional signals for terminal acetylenic carbon at 78.2 (C-3''), for quaternary carbon C-2'' at 81.2 ppm and tertiary carbon CH (C-1'') at 67.7 ppm clearly showed the formation of target molecule. The other confirmatory signals in their respective region were

found almost at required range as for the starting material **2a**. The carbonyl carbons appeared at their typical region at 196.4 ppm. The spectral data has been presented in table 2.13.

Table 2.13. ^{13}C NMR spectral data of compound **3a**

Assignment	$\delta(\text{ppm})$	Assignment	$\delta(\text{ppm})$	Assignment	$\delta(\text{ppm})$
C-5	196.4	C-4a	112.3	C-9	41.4
C-10a	168.4	C-3	107.0	C-6a	37.5
C-2	151.1	C-2''	81.2	C-4	32.2,
C-9a	149.5	C-3''	78.2	C-7	29.4
C-4'	150.3	C-10	61.2	C-8	27.2
C-1'	140.8	C-1''	67.7	C-12	19.3
C-3'	129.4	C-6	51.1	C-11	14.1
C-5'	1114.1				

2.4.2. Characterization of ethyl 2,7,7-trimethyl-5-oxo-4-(4-(tetradecyloxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**3b**)

The structure of compound **3b** was confirmed from its ^1H NMR spectral data. The appearance of additional peaks for long chain alkyl group clearly revealed the formation of desired product. The significant peaks of which are; the singlet for 22 protons at 1.23 ppm in the most down field region, triplet for the terminal CH_3 of alkyl group and multiplet for the CH_2 at alpha carbon to ethereal linkage fully confirmed the formation of **3b** as indicated in the following figure 2.5. The other signals resonate in their typical region and were found in agreement with that for the substrate **2a**. To mention some of them are the brs at 6.46 ppm for NH, while the two methyl group of cyclohexanone exhibited in the most downfield at 1.17 and 1.18 ppm as singlet.

The characteristic peak for CH at C-4 exhibited at 4.95 ppm as singlet. The aromatic protons appeared in their typical aromatic regions as shown in the following figure 2.5.

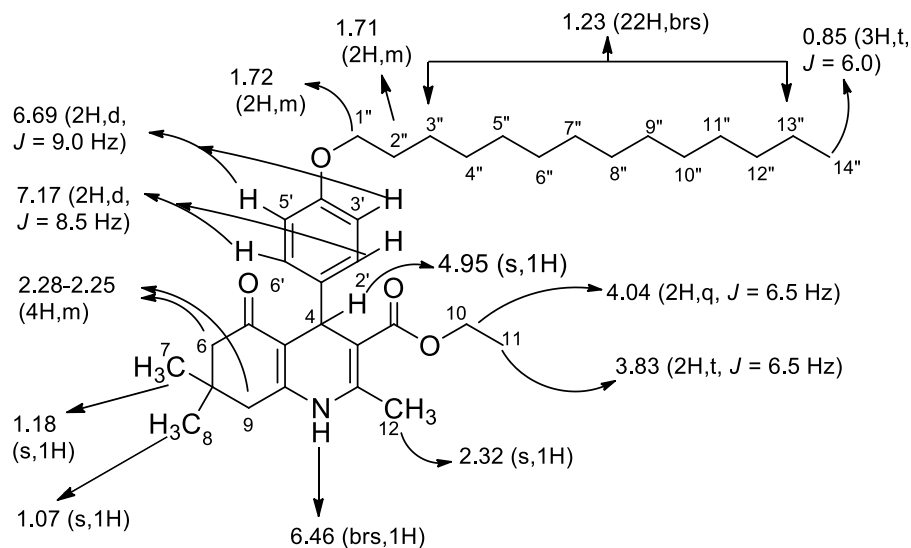


Fig. 2.5. Displaying of ¹H NMR spectral data of compound **3b**

The structure of compound **3b** was further concluded from the ¹³C-NMR spectral data. In which signals were found in different regions for their respective carbons i.e. carbonyl, aromatic aliphatic and aromatic region. The carbonyl carbon resonates at their typical position 195.6 ppm. The most off field signal for the terminal CH₃ group appeared at 14.0 ppm. Out of these signals other confirmatory peaks are for methylene carbon at the C-1'' appeared at high value at 67 ppm due to the ether linkage. The other signals for CH₂ of long alkyl group were exhibited between 22-29 ppm in the typical aliphatic region. The appearance of signals for aromatic carbons and four quaternary carbons (C-4, C-4a, C-8, and C-8a) also confirmed the formation of the target molecule **3b** as displayed in the figure 2.6.

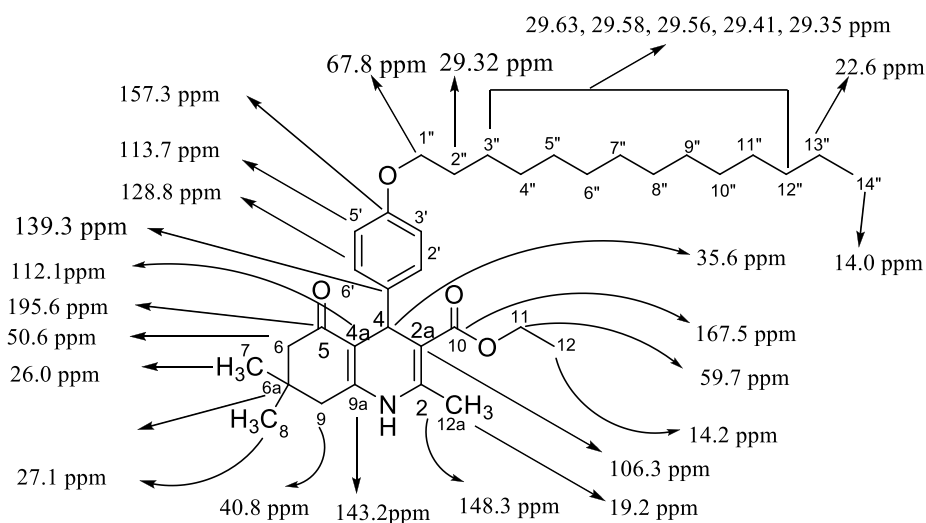


Fig. 2.6. Displaying of ¹³C NMR spectral data of compound **3b**

2.4.3. Characterization of ethyl 4-(4-(10-bromodecyloxy)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**3c**)

The target compound **3c** was characterized from their spectroscopic data, the IR spectra showed that absorption band for the OH group at 3343 cm⁻¹ of the starting material **2a** disappeared which indicate the alkylation site. All the other characteristics functional groups bands like carbonyls, NH, C=C aromatic and C-H aliphatic were found in their respective region and has been summarized in table 2.10.

The compound **3c** was further confirmed from the comparison of ¹H NMR spectral data with that of substrate **2a**. The disappearance of OH signals and appearance of multiples signals in the most downfield region shows alkylation. The appearance of triplet at 3.39 ppm for CH₂ (C-10'') indicate that alkylation occur at one side. The exhibition of multiplet for CH₂ at C-1'' 3.84 revealed the presence of ether linkage as shown in the fig 2.7.

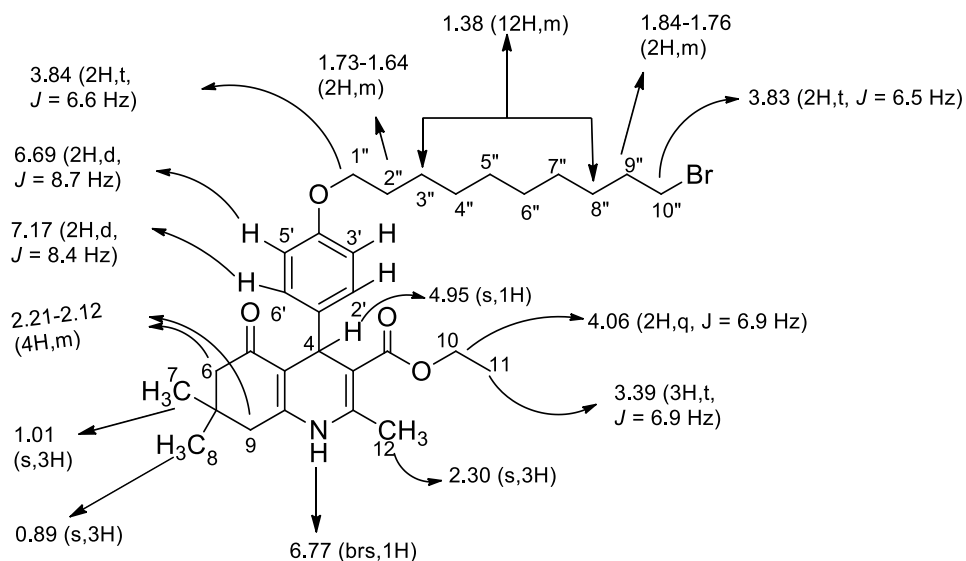


Fig. 2.7. Displaying of the ^1H NMR data of compound **3c**

2.4.4. CHN and EIMS analysis of polyhydroquinoline derivatives **3(a-c)**

The novel derivatives of compound **2a** were further supported from their CHNS analysis and EIMS spectral data as summarized in table 2.14. All the elemental calculation and EIMS were found in full agreements with experimental data.

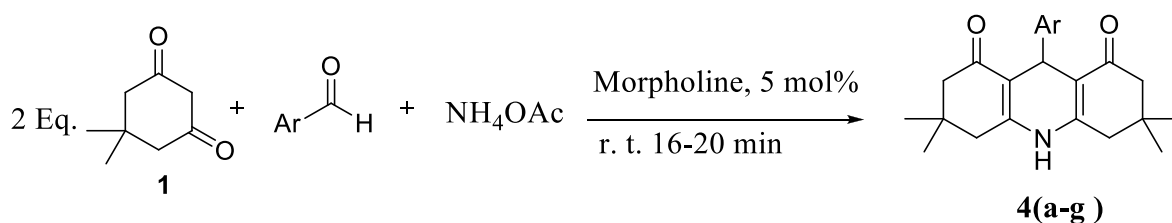
Table 2.14. CHN and EIMS data of polyhydroquinoline derivatives **3(a-c)**

Compd	Mol. F	Calcd (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt EIMS (M+%)
		C	H	N	C	H	N		
3a	$\text{C}_{24}\text{H}_{27}\text{NO}_4$	73.26	6.92	3.56	73.19	6.88	3.61	393.1	393.2 (98.7)
3b	$\text{C}_{35}\text{H}_{53}\text{NO}_4$	76.18	9.68	2.54	76.12	9.60	2.60	551.4	551.3 (60.8)
3c	$\text{C}_{31}\text{H}_{44}\text{BrNO}_4$	64.80	7.72	2.44	64.78	7.70	2.51	573.2	573.1 (36.7)

(M+%) = (M+%) = % abundance

2.5. Synthesis and characterization of polyhydroacridine-1,8-diones derivatives 4(a-g)

During optimization of reaction conditions for the synthesis of polyhydroquinoline in method A (as described in section 2.2) a side product was isolated in considerable amount and carefully characterized as polyhydroacridine-1,8-dione. Due to this chemical modification which leads toward polyhydroacridine-1,8-diones as a multifunctional type heterocycles having likeness with 1,4-dihydropyridine (a well known class of drug) allow the study to the extended structure. In this context the polyhydroacridine-1,8-diones derivative were prepared by using twofold of dimedone (**1**) with substituted aromatic aldehyde using morpholine as catalyst under solvent free condition, at room temperature. The reaction goes to completion in minutes scale time according to scheme 2.3.



Scheme 2.3. Synthesis of polyhydroacridine-1,8-diones derivatives

Table 2.15. Morpholine catalyzed synthesis of polyhydroacridine-1,8-diones derivatives **4(a-g)** and its physical data

Entry	Compd.	Ar	Time (mint)	Yield* (%)	Physical State	R _f *	m.p. (°C)	
							Observed	Lit.
26.	4a	C ₆ H ₅ -	16	76	White solid	0.58	272-274	277 ⁶¹
27.	4b	4-Cl-C ₆ H ₄ -	17	90	white solid	0.51	288-290	294 ⁶¹
28.	4c	3-OH-C ₆ H ₄ -	18	80	White crystals	0.49	>300	---

(Continued)

Entry	Compd.	Ar	Time (mint)	Yield* (%)	Physical State	R _f *	m.p. (°C)	
							Observed	Lit.
29.	4d	4-OH- C ₆ H ₄ -	20	77	White solid	0.46	286-288	---
30.	4e	4-F-C ₆ H ₄ -	16	78	White solid	0.53	290-291	---
31.	4f	4-NO ₂ - C ₆ H ₄ -	20	70	White solid	0.59	295-296	300 ¹²²
32.	4g	3-NO ₂ -C ₆ H ₄	18	77	Off white crystals	0.58	>300	296 ¹²³

Reaction condition; Morpholine 5%, at room temperature under solvent free condition, *Isolated yield. *TLC Solvent system, R_f: Hexane: Ethyl acetate 1: 3. On Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at $\lambda=254$ nm

2.5.1. Solvent Effect

In order to investigate solvent effect, the reaction of dimedone (**1**), benzaldehyde and ammonium acetate was chosen as the model reaction (Scheme 2.3). Initially, the model reaction was carried out without catalyst. In this case the major product isolated was dimedone aldehyde adduct. In order to study the solvent effect the model reaction was carried in different medium (Table 2.16). Among the tested solvents, such as ethanol, methanol, water, chloroform and acetonitrile, the later gave the best result.

Surprisingly, the target molecule **4a** was formed in 16 minutes in high yield, when the reaction was carried out at room temperature while using morpholine (5 %) (Entry 7, Table 2.16). The reaction gave a yellow product in 90% (Table 2.16).

Table 2.16. Optimization of reaction condition

Entry	Solvent	Catalyst	Temperature (°C)	Time	Yield (%)
1	Ethanol	Morpholine	Reflux	5 h	40
2	Methanol	Morpholine	Reflux	8 h	65
3	Ethanol	---	Reflux	7 h	70
4	Water	---	Reflux	3 h	45
5	CHCl ₃	Morpholine	Reflux	5 h	60
6	CH ₃ CN	Morpholine	Reflux	3 h	50
7	Solvent free	Morpholine (5 mol %)	R. T	20 min	92

1-7 = represents the same model reaction for the formation **4a**; ^aIsolated yeild

2.5.2. Effect of loading of morpholine as catalyst

Encouraged by the obtained results, shown in the table 2.16, it was necessary to determine the optimum amount of loading of the catalyst. By changing the amount of the catalyst from 2 to 5 and 10 mol%, the yield of the product **4a** was found 71, 90, 84% respectively. It was concluded that only 5 mol% of morpholine was sufficient as an optimum catalytic amount to push the reaction forward with maximum yield of the target compound (Table 2.17).

Table 2.17. Effect of the amount of morpholine as catalyst

Entry*	Catalyst (mol%)	Time (min)	Yield ^b
1.	2	30	71
2.	5	20	90
3.	10	16	84

2.5.3. Effect of ammonium salts

The optimization process was proceeded to investigate the best nitrogen donor among various inorganic salts. The model reaction was examined in different reaction conditions by

using different salts. Ammonium carbonate and ammonium acetate gave best results in term of isolated product. It has been concluded that the ammonium carbonate and ammonium acetate are less toxic solid source of ammonia. In case of ammonium acetate gives the best result was obtained at room temperature and solvent free condition while using 5 mol % morpholine as a catalyst (Entry 10, Table 2.18).

Table 2.18. Effect of different ammonium salts over the synthesis of polyhydroacridine-1,8-diones derivatives

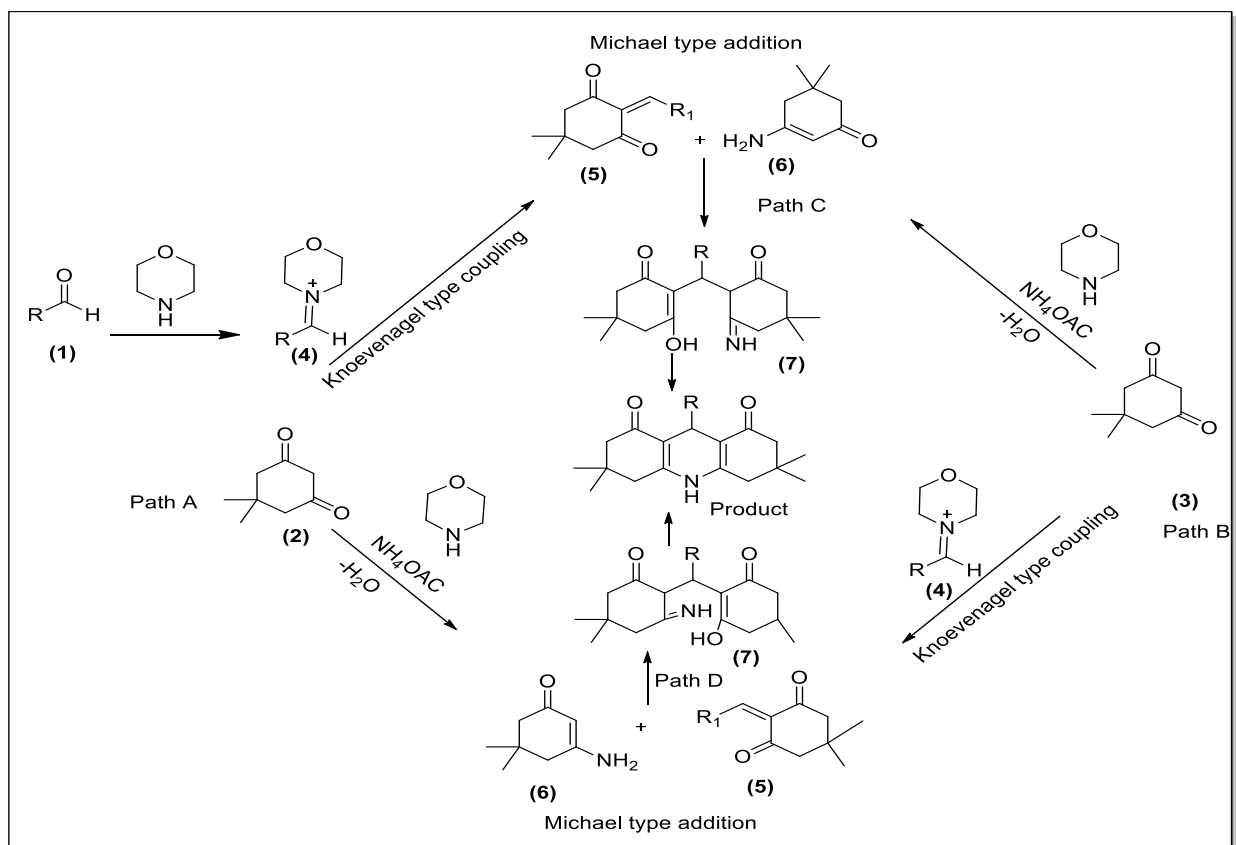
Entry	Ammonium salt	Solvent	Temperature (°C)	Time (h)	Yield* (%)
1	NH ₄ Cl	Ethanol	Reflux	5	0
2	NH ₄ Cl	Water	Reflux	5	0
3	(NH ₄) ₂ CO ₃	Ethanol	Reflux	4	80
4	(NH ₄) ₂ CO ₃	Water	Reflux	4	82
5	(NH ₄) SO ₄	Ethanol	Reflux	5	0
6	NH ₄ NO ₃	Ethanol	Reflux	5	40 ^b
7	(NH ₄) ₂ [Ce(NO ₃) ₆]	Ethanol	Reflux	5	0
8	(NH ₄) ₂ [Ce(NO ₃) ₆]	Water	Reflux	5	10
9	(NH ₄) ₂ CO ₃	Solvent free	R. T	I	51
10	CH ₃ CO ₂ NH ₄	Solvent free	R. T	16 min	92

*Isolated yield; ^bMixture of products was formed

The optimized reaction condition was applied to the condensation of other aldehyde with 1,3-diketone and ammonium acetate at room temperature. The effect of the nature of substituents on the aromatic ring showed no obvious effect in terms of yield under the reaction condition. The aromatic aldehydes containing electron withdrawing groups (such as halides, NO₂ group) or electron-donating groups (such as OCH₃, OH group) were employed. They reacted well to gave the corresponding polyhydroacridine-1,8-dione derivatives. The structures of the entire synthesized compounds were confirmed by IR, ¹H-NMR, EIMS and elemental analysis.

2.6. Proposed mechanism for the formation of polyhydroacridine-1,8-diones derivatives

The tentative mechanism for the formation of polyhydroacridine-1,8-diones shown in scheme 2.4. There is evidence in the literature that morpholine (weak base, $pK_b = 5.51$) can catalyze Knoevenagel condensation as well as Michael addition.^{109,119} In this context in the Hantzsch reaction, morpholine is supposed to facilitate the Knoevenagel condensation for the formation of **5** in path A and path B and the Michael addition for the formation of 1,5-dicarbonyl intermediate **7** in path C and D.



Scheme 2.4. Proposed mechanism for the formation of polyhydroacridine-1,8-diones derivatives

2.7. Spectral discussion of polyhydroacridine-1,8-diones derivatives

2.7.1. IR data of polyhydroacridine-1,8-diones derivatives 4(a-g)

In the IR spectra of the synthesized polyhydroacridine-1,8-diones, the fundamental absorption

for the N-H exhibited between 3340-3200 cm^{-1} , which indicates that annulations occurs. The presence of N-H was further confirmed from the appearance of C-N stretching in the range of 1400-1300 cm^{-1} . The aromatic C-H and C=C stretching bands appears in their respective typical region above 3000 and 1600 respectively. All the others groups were identified from their functional group frequencies in the target molecules. The major functional group fundamental absorption bands are displayed in the table 2.19.

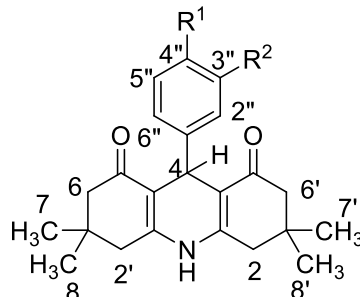
Table 2.19. IR data of polyhydroacridine-1,8-diones derivatives **4(a-g)**

Compd.	$\nu(\text{Cm}^{-1})$							
	OH	NH	C _{sp2} -H	C _{sp3} -H	C=O*	C=C	C-H**	C-N
4a	---	3238	3078	2967	1670	1602	1487	1361
4b	---	3343	3067	2957	1656	1602	1481	1297
4c	3414	3248	3058	2960	1674	1607	1466	1354
4d	3465	3242	3069	2950	1664	1612	1471	1361
4e	---	3310	3041	2954	1657	1587	1464	1369
4f	---	3340	3081	2953	1651	1593	1468	1379
4g	---	3340	3066	2987	1672	1618	1484	1342

*Ketonic, **C-H; Bending.

2.7.2. ^1H NMR Spectral data of polyhydroacridine-1,8-diones derivatives **4(a-g)**

The ^1H NMR spectra showed a singlet corresponding to the NH proton at 6.9-6.7 ppm, while in case of compound **4f** and **4g** it appeared at 8.2 and 8.4 ppm due to nitro group on the phenyl ring. The confirmatory peak appeared at 5.1-5.0 ppm as singlet confirmed the presence of H-4 proton. The methyl groups (C-7, 7' and C-8, 8') resonate as singlets at d 1.1- 1.0 ppm and 1.0-0.9 ppm respectively. All the aromatic protons appear in its typical region with corresponding multiplicity as shown in table 2.20.

Table 2.20. ^1H NMR spectral data of polyhydroacridine-1,8-diones derivatives **4(a-g)**

Protons	4a R ¹ = R ² = H	4b R ¹ = Cl, R ² = H	4c R ¹ = H, R ² = OH	4d R ¹ = OH, R ² = H	4e R ¹ = F, R ² = H	4f R ¹ = NO ₂ , R ² = H	4g R ¹ = H, R ² = NO ₂
H-4''	7.58-7.31 (m, 5H)	---	7.48-7.31 (m, 3H) 7.18 (s, 1H, C-2'')	---	---	---	---
H-3''		7.34 (d, <i>J</i> = 8.4 Hz, 2H)		6.99 (d, <i>J</i> = 8.5Hz, 2H)	7.37 (d, <i>J</i> = 8.4 Hz, 2H)	7.98 (d, <i>J</i> = 7.2 Hz, 2H)	8.01 (s, 1H,C- 3'')7.67 (m, 3H)
H-5''		7.23 (d, <i>J</i> = 8.4 Hz, 2H)		6.85 (d, <i>J</i> = 8.5Hz, 2H)	6.96 (d, <i>J</i> = 8.4 Hz, 2H)	7.47 (d, <i>J</i> = 8.2 Hz, 2H)	
H-2''							
H-6''							
NH	6.91 (brs, 1H)	6.81 (brs, 1H)	6.90 (brs, 1H)	6.79 (brs, 1H)	6.89, (brs, 1H	8.21 (brs, 1H)	8.41 (brs, 1H
C-4	5.17 (s, 1H)	5.41 (s, 1H)	5.09 (s, 1H)	5.04 (s, 1H	5.19 (s, 1H)	5.09 (s, 1H)	5.02(s, 1H)
C-2, C-2'	2.38-2.26 (dd, 4H)	3.31- 2.16 (m, 8H)	2.37- 2.26 (dd, 4H)	2.40- 2.25 (dd, 4H)	2.39- 2.27 (dd, 4H	2.33- 2.25 (dd, 4H)	2.34- 2.26 (dd, 4H)
C-6, C-6'	2.20-2.19 (dd, 4H)		2.19-2.09 (m, 4H,	2.20-2.0 (m, 4H)	2.23-2.03 (dd, 4H)	2.13-2.02 (dd, 4H)	2.19-2.01 (dd, 4H)
C-7,C-7'	1.05 (s, 6H)	1.12 (s, 6H)	1.10 (s, 6H)	1.08 (s, 6H)	1.11 (s, 6H)	1.01 (s, 6H)	1.01 (s, 6H)
C-8, C-8'	0.98 (s, 6H)	1.05 (s, 6H,	1.09 (s, 6H)	0.97 (s, 6H)	0.97 (s, 6H)	0.88 (s, 6H)	0.91 (s, 6H)
R	---	---	5.60 (s, 1H, OH)	5.67 (s, 1H, OH)	---	---	---

2.7.3. CHN and EIMS data of polyhydroacridine-1,8-diones derivatives 4(a-g)

All the synthesized compounds showed the elemental analysis and EI-MS data in agreement with the calculated data as summarized in table 2.21.

Table 2.21. CHN and EIMS data of polyhydroacridine-1,8-diones derivatives 4(a-g)

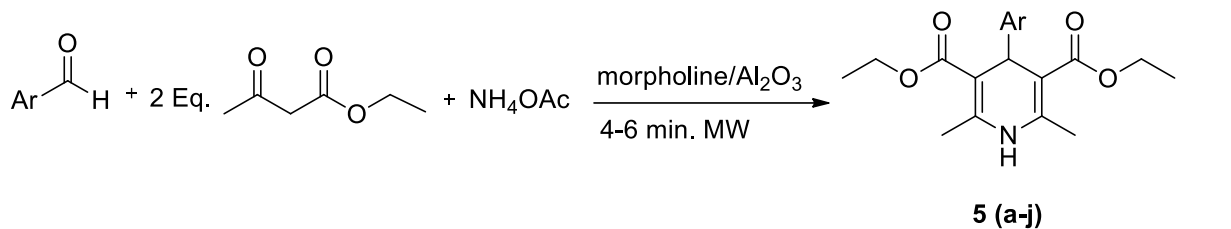
Compd.	Mol. F	Calcd (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt EIMS (M+%)*
		C	H	N	C	H	N		
4b	C ₂₃ H ₂₆ ClNO ₂	71.96	6.83	3.65	71.81	6.80	3.69	383.1	383.2 (67.9)
4c	C ₂₃ H ₂₇ NO ₃	75.59	7.45	3.83	75.50	7.38	3.99	365.1	365.2 (81.4)
4d	C ₂₃ H ₂₇ NO ₃	75.59	7.45	3.83	75.54	7.48	3.89	365.1	365.2 (76.6)
4e	C ₂₃ H ₂₆ FNO ₂	75.18	7.13	3.81	75.14	7.10	3.89	382.1	367.2 (78.2)
4f	C ₂₃ H ₂₆ N ₂ O ₄	70.03	6.69	7.10	70.11	6.61	7.25	394.1	394.2 (37.9)
4g	C ₂₃ H ₂₆ N ₂ O ₄	70.03	6.69	7.10	70.09	6.67	7.20	394.1	394.2 (41.7)

*(M+%)= % abundance

2.8. Synthesis and characterization of 1,4-dihydropyridine derivatives (DHPs) 5(a-j)

During optimization of the reaction conditions for the synthesis of polyhydroquinoline derivatives using method A as described in section 2.3, the 1,4-dihydropyridine was traced as side product under reflux condition. This result turn our attention towards synthesis of 1,4-dihdropyrinde. When the reaction was carried out using twofold of ethylacetoacte, aldehydes and ammonium acetate in the presence of morpholine/Al₂O₃ (0.5 g containing 10 mol% morpholine) as catalyst under microwave irradiation, the product 1,4-dihydropyridine were obtained within 4-6 min

in good to excellent yield. The biologically demanding class, 1,4-dihydropyridine were then cleanly synthesized according to scheme 2.5.



- | | | | | | |
|---------------|---|---------------|---|---------------|--|
| 33. 5a | Ar = C ₆ H ₅ - | 34. 5b | Ar = 4-pyridyl | 35. 5c | Ar = 3-pyridyl |
| 36. 5d | Ar = 2-pyridyl | 37. 5e | Ar = 4-NO ₂ -C ₆ H ₄ - | 38. 5f | Ar = 4-Cl-C ₆ H ₄ - |
| 39. 5g | Ar = 3-OH-C ₆ H ₄ | 40. 5h | Ar = 4-OH-C ₆ H ₄ - | 41. 5i | Ar = 4-OCH ₃ -C ₆ H ₄ - |
| 42. 5j | Ar = 4-NO ₂ -C ₆ H ₃ | | | | |

Scheme 2.5. Synthesis of 1,4-dihydropyridine derivatives **5(a-j)**

2.8.1. Effect of loading morpholine/Al₂O₃ as catalyst over the synthesis of DHPs

Interestingly, when model reaction was carried in ethanol as solvent and morpholine/alumina as catalyst no product formation was detected even at reflux temperature for 7 h (Entry 1, Table 2.22). Therefore further exploration of solvent effect was not necessary in this study. The model reaction was then carried out in the solvent free condition using morpholine as catalyst. In this case the product formed in poor yield within 4 min (Entry 2, Table 2.22). The model reaction was carried out at different rate. Initially the reaction was carried out by loading 0.2 g of catalyst. The product form was 50 % in 5 minutes. When the amount of catalyst was increased up to 0.5 g containing 10 mol% of morpholine the product formation dramatically increased up to 86%. On further increase of the amount of catalyst has adverse effect, which indicates that 0.5 g containing 10 mol% morpholine is the optimum amount of catalyst for this reaction as shown in the Table 2.22.

Table 2.22. Effect of loading morpholine/ Al_2O_3 as catalyst over the synthesis of DHPs

Entry ^a	Catalyst Morpholine / Al_2O_3 (g)	Solvent	Time ^b (min)	Yield ^c (%)
1.	0.5	Ethanol	7 h	NP
2.	0.5	Solvent free	4	10
3.	0.25	Solvent free	4	50
4.	0.5	Solvent free	4	86
5.	1.0	Solvent free	5	80
6.	1.5	Solvent free	5	60

^aReaction conditions: from 1-6 is the same model reaction under solvent free condition, MW 450 W. ^bThe progress of reaction was monitored by TLC (ethyl acetate: n-hexane 3:1). ^cIsolated yield; ^dPure morpholine not doped on Al_2O_3 .

At optimized condition different aldehydes were made to react with ethylacetoacetate and ammonium acetate, in order to check the generality of the present protocol. It was observed that this method is superior over some of the literature procedure (Table 2.23). This protocol tolerates many functional groups in the aromatic ring like halogen, methoxy, hydroxyl, nitro and hetero atom aldehyde. Short reaction times, environmentally soundness solventless, easy reaction work up are the additional advantages of the present method. In case of liquid aldehydes like benzaldehyd, 2-pyridyl, 3-pyridiyl and 4-pyridyl, the products were purified by recrystalization using binary solvent system (aqueous ethanol) while in case of solid aldehydes column chromatography was used.

The structures of all the synthesized compounds were ascertained by comparison of physical data with reported data and spectroscopic analysis like IR, ^1H NMR, and EIMS spectral data.

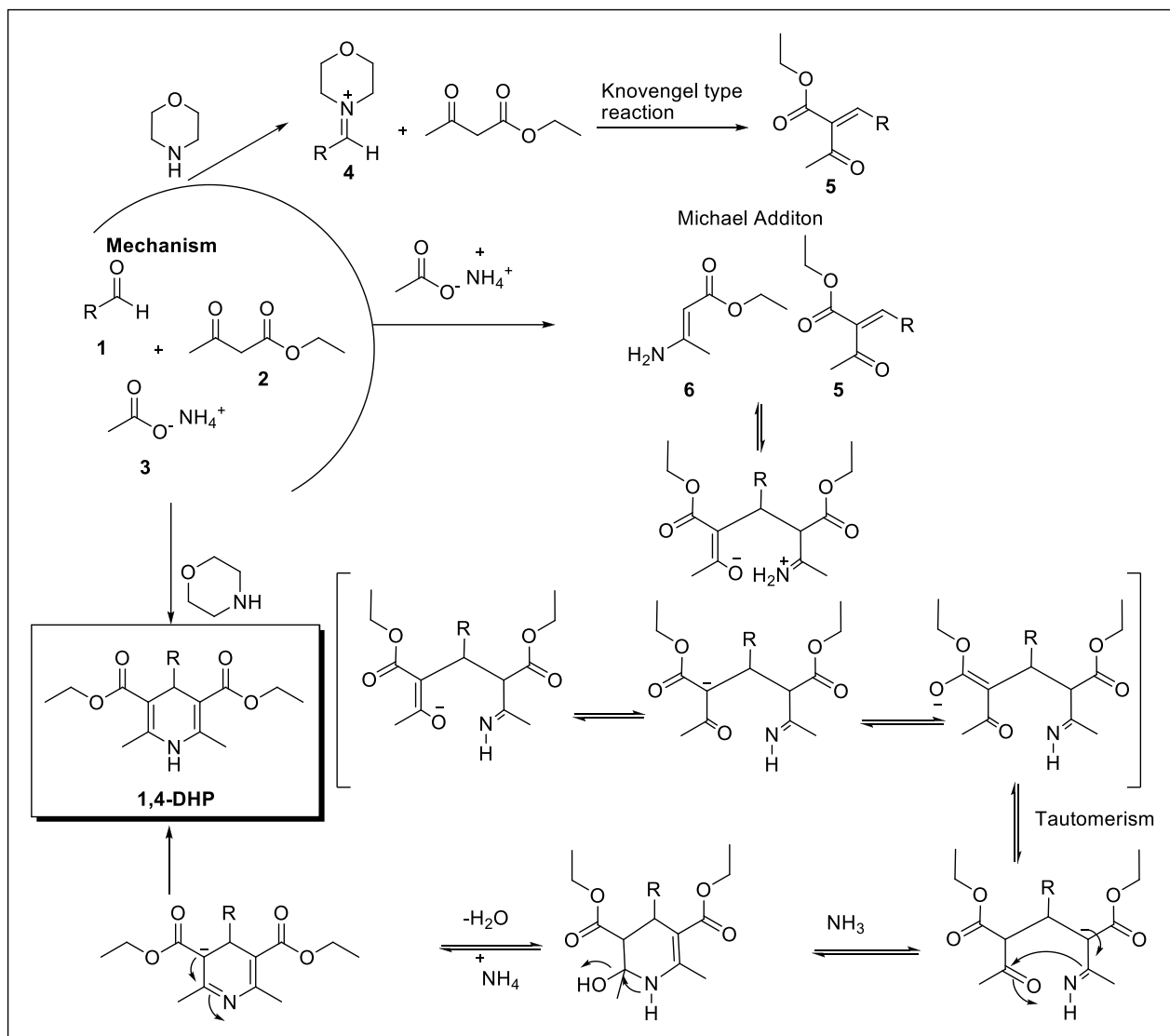
Table 2.23. Morpholine/ Al_2O_3 catalyzed synthesis of 1,4-DHPs derivatives **5(a-j)**, and its physical data and FT IR data

Compd.	Ar	a*	Yield (%)	Physical state	R_f^b	m.p. ($^{\circ}\text{C}$)		IR $\nu(\text{Cm}^{-1})$	
						Observed	Lit.	NH	C=O**
5a	C_6H_5-	4.0	82	Yellow solid	0.57	154-156	156 ¹²⁰	3323	1728
5b	4-pyridyl	4.0	80	Yellow solid	0.55	180-182	180 ¹¹⁶	3231	1709
5c	3-pyridyl	4.0	85	Yellow solid	0.58	192-194	192 ¹¹⁶	3265	1701
5d	2-pyridyl	4.5	79	Orange solid	0.60	193-195	194 ¹¹⁶	3264	1697
5e	4- NO_2- C_6H_4-	4.5	72	Yellow solid	0.62	130-133	127 ¹²⁰	3373	1721
5f	4-Cl- C_6H_4-	4.0	90	White solid	0.62	141-144	143 ¹²⁰	3317	1701
5g	3-OH- C_6H_4	6	70	Yellow solid	0.47	181-182	182 ¹¹⁶	3289	1700
5h	4-OH- C_6H_4-	4.5	76	White solid	0.45	188-190	185 ¹²¹	3321	1703
5i	4-OCH ₃ - C_6H_4-	4.2	60	Orange solid	0.63	195-196	194 ¹²⁰	3280	1694
5j	3- NO_2- C_6H_3	4.5	66	Brown solid	0.64	168-170	171 ¹²¹	3320	1680

*a Time (mint) morpholine/ Al_2O_3 (0.5gm), MW= 450W; R_f^b : TLC solvent system: n-Hexane: Ethyl acetate, 4:3, On Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at $\lambda=254\text{nm}$. **ester

2.8.2. Proposed Mechanism of Hantzsch Reaction (formation of DHPs)

1,3-Dicarbonyl compounds have many synthetic applications and is an exceptional synthetic platforms due to the presences of four contiguous reaction sites. Addition of a second carbonyl makes the adjacent proton much more acidic, so it can be removed by weaker bases. The resultant anion produced by deprotonation is more stable when two carbonyl oxygen are present due to conjugation of the enolate. The key steps in formation of 1,4-dihydropyridine is Knoevenagel type coupling followed by Michael addition. The proposed mechanism for the morpholine catalyzed synthesis of 1,4-dihydropyridne has been shown in the following scheme 2.5.



Scheme.2.6. Proposed mechanism for the synthesis of 1, 4-dihydropyridine basic nucleus

2.9. Spectral data of 1,4-DHPs derivatives

2.9.1. IR data of 1,4-DHPs derivatives 5(a-j)

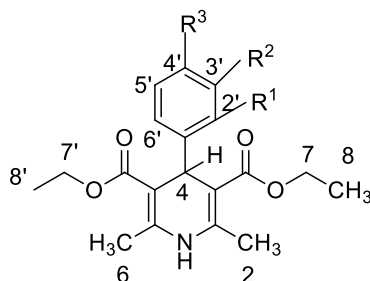
The structure of 1,4-dihydropyridine derivatives were confirmed from their IR spectral data. The various functional groups like ester, NH, C=C, and C-H were identified by their characteristic frequencies obtained for them. The confirmatory band of carbonyl group was observed in the range 1680-1721 cm^{-1} . Another characteristics band showing the N-H stretching of

secondary amine was observed at 328-3373 cm^{-1} suggesting the formation of desired products (Table 4.16).

2.9.2. ^1H NMR Spectral data of 1,4-DHP derivatives 5(a-j)

The ^1H NMR spectra of the DHPs revealed a brs corresponding to the NH proton in the range of 5.68- 6.55 ppm, while in case of compound **5d** at 8.57 ppm due to pyridyl ring. The confirmatory singlet resonated at 4.87-5.27 ppm corresponding to the H-4 proton. The methyl groups on C-2 and C-6 of the 1,4-DHP rings exhibited as singlets at 2.2-2.3 ppm. The ^1H NMR spectra of compounds **5b**, **5c**, and **5d** also show signals between 7.0-8.5 ppm corresponding to the protons of the pyridyl ring, showing the characteristic multiplicity depending on the position of the nitrogen atom in the ring. In case of compounds **5e**, endowed with a *p*-nitrophenyl ring, the aromatic protons appear at 8.20 and 7.57 ppm. The ^1H NMR data has been displayed in table 2.24.

Table 2.24. ^1H NMR spectral data of 1,4-DHPs derivatives **5(a-j)**



Com	* δ (ppm), Integration, multiplicity and coupling constants(J)									
	H-4'	H-2'	H-6'	H-3'	H-5'	NH	C-4	C-7, 7'	C-2,6	C-8,8'
5a	7.27-7.09 (m, 5H, Ph-ring)					5.68 (brs, 1H)	4.96 (s 1H)	4.10 (m, 4H)	2.30 (s, 6H)	1.19 (t, J = 14.1, 6H)
5b	---	7.42 (d, J = 6Hz, 2H)	8.43 (d, J = 6Hz, 2 H)			6.35 (brs,1 H)	5.06 (s,1H)	4.08(q, J = 7.2, 4H)	2.35 (s, 6H)	1.19 (t, J = 7.2, 6H)

(Continued)

5c	8.38 (d, $J = 4.8$ Hz, 1H)	8.48 (d, $J = 2.1$ Hz, 1H)	7.71-7.67 (m, 2H)	6.55 (brs, 1H)	5.07 (s, 1H)	4.12-4.07 (m, 4H)	2.37 (s, 6H)	1.21 (t, $J = 7.1$ 6H)
5d	8.23 (d, $J = 5.8$ Hz, 1H) C-3' 7.72-7.59 (m, 3H, Ar-H) C-4'-6'			8.57 (br s, 1H)	5.27 (s, 1H)	4.13-4.05 (m, 4H)	2.29 (s, 6H)	1.24 (t, $J = 7.1$ 6H)
5e	---	7.57 (d, $J = 8.2$ Hz, 2H)	8.20 (d, $J = 8.2$ Hz, 2H)	5.96 (br s, 1H)	4.94 (s 1H)	4.15-4.08 (m, 4H)	2.34 (s, 6H)	1.24 (t, $J = 7.1$ 6H)
5f	---	6.98 (d, $J = 7.8$ Hz, 2H)	7.20 (d, $J = 7.8$ Hz, 2H)	5.97 (brs, 1H)	4.99 (s 1H)	4.15-4.02 (m, 4H)	2.34 (s, 6H)	1.24 (t, $J = 7.2$, 6H)
5g	7.12-6.89(m, 3H), 6.88 (s, 1H)			5.87 (brs, 1H)	5.02 (s 1H)	4.17-2.09 (m, 4H)	2.33 (s, 6H)	1.27 (t, $J = 7.00$, 6H)
5h	---	7.18 (d, $J = 8.5$ Hz, 2H)	6.72 (d, $J = 8.8$ Hz, 2H)	5.85 (brs, 1H)	4.89 (s 1H)	4.12 (q, $J = 7.2$ Hz, 4H)	2.31 (s, 6H)	1.22 (t, $J = 7.00$, 6H)
5i	---	7.13 (d, $J = 8.02$ Hz, 2H)	7.02 (d, $J = 8.02$ Hz, 2H)	5.65 (brs, 1H)	4.99 (s 1H)	4.09 (q, $J = 7.20$ Hz, 4H)	2.31 (s, 6H)	1.22 (t, $J = 7.10$, 6H)
5j	8.23 (s, 1H, Ar-H), 8.10 (d, $J = 8.04$ Hz, 1H, Ar-H), 7.48 (m, 2H, Ar-H)			6.19 (brs, 1H)	5.00 (s 1H)	4.11 (q, $J = 7.02$ Hz, 4H)	2.39 (s, 6H)	1.23 (t, $J = 7.02$, 6H)

*(300 or 400 MHz)

2.9.3. CHN and EIMS data of 1,4-DHPs derivatives 5(a-j)

All the synthesized compounds shows the elemental analysis and EI-MS data in agreement with the calculated data as summarized in table 2.25.

Table 2.25. CHN and EIMS data of 1,4-DHP derivatives **5(a-j)**

Comp	Mol. F	Calcd (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt EIMS M+1)
		C	H	N	C	H	N		
5a	C ₁₉ H ₂₃ NO ₄	69.26	7.04	4.25	69.22	7.01	4.29	329.14	329.0 (33.4)
5b	C ₁₈ H ₂₂ N ₂ O ₄	65.44	6.71	8.48	65.52	6.62	8.54	330.38	331.0 (8.4)
5c	C ₁₈ H ₂₂ N ₂ O ₄	65.44	6.71	8.48	65.57	6.70	8.55	330.38	331.0 (10.7)
5d	C ₁₈ H ₂₂ N ₂ O ₄	65.44	6.71	8.48	65.40	6.63	8.58	330.38	330.9 (12.2))
5e	C ₁₉ H ₂₂ N ₂ O ₆	60.95	5.92	7.48	60.90	5.89	7.54	374.39	374.2 (26.5)
5f	C ₁₉ H ₂₂ ClNO ₄	62.72	6.09	3.85	62.70	6.01	3.88	363.12	363.2 (33.7)
5g	C ₁₉ H ₂₃ NO ₅	66.07	6.71	4.06	66.09	6.66	4.09	345.39	345.3 (19.8)
5h	C ₁₉ H ₂₃ NO ₅	66.07	6.71	4.06	66.11	6.62	4.10	345.39	345.10 (39.1)
5i	C ₂₀ H ₂₆ NO ₄	69.95	7.34	4.08	69.96	7.30	3.99	343.42	343.1 (89.2)
5j	C ₁₉ H ₂₂ N ₂ O ₆	60.95	5.92	7.48	60.96	5.94	7.40	374.39	374.1 (33.3)

(M+%) (% abundance)

2.10. Experimental Section

2.10.1. General information

A microwave (CEM Discover system, model 908010, USA) was used for the synthesis of PHQ derivatives. The aldehydes and other chemicals were purchased from Sigma Aldrich and organic solvents from Fischer scientific. Electrothermal melting point apparatus (England) was used to determine melting points and not calibrated. The ¹H NMR spectra were recorded on Bruker (300 or 400 or 500 MHz, CDCl₃) and ¹³C NMR NMR spectra were also recorded on Bruker (75, or 100 or 125 MHz, CDCl₃) using TMS as internal standard. IR spectroscopy was performed using Thermo-Scientific, Nicolet 380 FTIR. CHN analyses were performed on a Carlo Erba Strumentation-Mod-1106 Italy. Electron impact mass spectra (EI MS) were recorded on Finnigan

MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

2.11. General procedure for the synthesis of polyhydroquinoline derivatives 2(a-t) under microwave irradiation

Method A

In a china dish mixture of dimedone (0.95 mmol), respective aldehyde (1 mmol), ethyacetate (1.2 mmol), ammonium acetate (1.2 mmol) and morpholine (0.08 ml, 10 mol%) was irradiated by microwaves (CEM Discover system, model 908010, USA) for few seconds. The acquired solid was treated with 3-5 ml of CH₃CN and 6 ml of H₂O. The crude product was then filtered. The pure product was obtained either by recrystallization from ethanol or by column chromatography in ethyl acetate: *n*-hexane in variable ratio.

Method B

The dimedone (0.95 mmol), respective aldehyde (1 mmol), ethyacetate (1.2 mmol), ammonium acetate (1.2 mmol) and morpholine/Al₂O₃ (1 gm containing 10 mol% morpholine) were mixed in china dish and was kept under microwave irradiation for 2-3 minutes. The resultant solids were allowed to cool at room temperature and then dissolved in 10 x 3 ml ethyl acetate. The catalyst was filtered out. The organic layer was washed with water (10 ml), followed by brine solution and dried with MgSO₄ (Anhy). The excess of ethyl acetate was evaporated under vacuum in order to get the crude product. The crude product was purified by column chromatography using ethyl acetate: *n*-hexane solvent system.

Method C

The dimedone (0.95 mmol), respective aldehyde (1 mmol), ethyacetate (1.2 mmol), ammonium acetate (1.2 mmol), and iodine/Al₂O₃ (impregnated on 0.5 g of neutral alumina) were

mixed in china dish and irradiated with microwave irradiation for 3-4 minutes. The reaction mixture was allowed to cool. The solid catalyst was filtered out and 30 ml of ethyl acetate was added to the mixture. The organic layer was washed with water in order to destroy the excess of ammonium acetate and dried with MgSO_4 . The excess of organic solvent was evaporated under vacuum. The pure product was obtained after column chromatography using ethyl acetate and n-hexane solvent system.

2.12. Spectroscopic and physical data of polyhydroquinoline derivatives 2(a-t)

The structures of the all synthesized compounds were ascertained from their spectroscopic data as given below.

Ethyl 4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2a)

The title compound was synthesized by using the above mentioned methods A, B, and C in excellent yields of 90, 81 and 89% respectively.

White solid; mp 230-232 °C; **IR** (neat, ν_{max} , cm^{-1}): 3433, 3227, 3199,

3074, 2992, 1674, 1443; **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.14 (d, J =

8.4 Hz, 2H, Ar-H), 6.63 (d, J = 8.4 Hz, 2H, Ar-H), 5.59 (s, 1H, -CH),

4.96 (s, 1H, OH), 4.04 (q, J = 7.2 Hz, 2H, $-\text{OCH}_2\text{-CH}_3$), 2.35, (s, 3H,

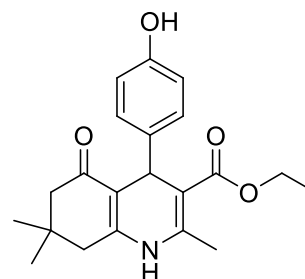
C- CH_3), 2.20-2.16 (m, 4H, 2- CH_2 -), 1.19-1.148 (t, J = 7.2 Hz, 3H, CH_2CH_3), 1.05 (s, 3H, C- CH_3),

0.90 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ; 198.5 (C=O), 169.5 (C=O ester), 156.5, 152.3,

145.6, 140.1, 139.9, 115.4, 112.5, 107.2, 60.8, 51.5, 41.0, 36.9, 33.9, 27.0, 18.5, 14.5; **EIMS** (m/z ,

%): 355.1 (100.0) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4$ (355.4): C, 70.96; H, 7.09; N, 3.04; Found:

C, 70.91; H, 7.00; N, 3.14.



Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2b)

This compound was synthesized by using the above general procedure A, and B.

Light yellow solid; Yield: Method A: 85%; Method B: 82%;

mp: 205-207 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3228, 3219, 3082, 2962, 1697,

1481; **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.06-7.29 (m, 5H, Ar-H), 6.14

(s, 1H, NH), 5.02 (s, 1H, -CH), 4.02 (q, $J = 6.9$ Hz, 2H, $-\text{OCH}_2\text{-CH}_3$),

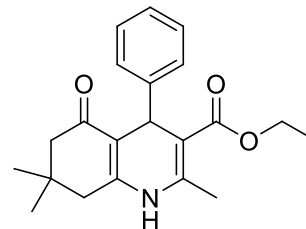
2.33(s, 3H, $=\text{C-CH}_3$), 2.27-2.14 (m, 4H, 2 x CH_2), 1.17 (t, $J = 6.9$ Hz, 3H, $\text{CH}_3\text{-CH}_2\text{O}$), 1.04 (s, 3H,

C- CH_3), 0.90 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ; 195.4, 167.4, 148.1, 147.0, 143.4,

127.9, 127.8, 125.9, 124.5, 112.1, 106.0, 59.7, 50.7, 32.6, 29.4, 27.1, 19.3, 14.1; **EIMS** (m/z , %):

339.0 (28.5) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_3$ (339.4): C, 74.31; H, 7.42; N, 4.13; Found: C,

74.39; H, 7.31; N, 4.32.

**Ethyl 4-(3-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2c)**

The target molecule has been synthesized according to the general procedures mentioned above. Yield; method A: 70%; Method B; 78%; Method C: 71%; Off

white solid; mp: 220-222 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3392, 3273, 3076,

2956, 1671; **^1H NMR** (CD_3OD , 300 MHz): δ ; 6.96 (t, $J = 7.8$ Hz, 1H,

Ar-H), 6.73 (s, 1H, NH), 6.70 (s, 1H, Ar-H) 6.51 (d, $J = 7.2$ Hz, 1H, Ar-

H), 6.49 (d, $J = 6.6$ Hz, 1H, Ar-H), 4.90 (s, 1H, Ar-CH), 5.06 (s, 1H, OH),

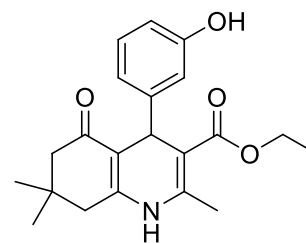
4.05 (q, $J = 7.2$ Hz, 2H, $-\text{OCH}_2\text{-CH}_3$), 2.54-2.01 (m, 4H, 2- CH_2 -), 2.30 (s, 3H, C- CH_3), 1.92 (t, $J =$

7.2 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$); 1.15 (s, 3H, C- CH_3), 1.06 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ;

198.4, 169.4, 158.0, 152.5, 150.2, 146.0, 139.9, 129.6, 115.9, 112.1, 106.5, 60.8, 51.5, 41.1, 37.6,

33.4, 27.9, 27.1, 18.5, 14.5; **EIMS** (m/z , %): 355.1 (42.1) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4$

(355.4): C, 70.96; H, 7.09; N, 3.04. Found: C, 70.99; H, 7.11; N, 3.18.



Ethyl 4-(2,4-dichlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2d)

The mentioned compound has been prepared by using methods B and C as described above. Yield: Method A: 71%; Method B: 76%; Off white solid;

mp: 214-216°C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3291, 3203, 3088, 1702, 1605,

1100, 859; **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.85 (d, $J = 8.4$ Hz, 1H,

Ar-H), 7.72-7.67 (m, 2H, Ar-H), 6.54 (s, 1H, NH), 4.81 (s, 1H, Ar-

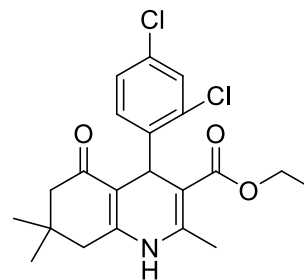
CH), 4.09 (q, $J = 6.9$ Hz, 2H, OCH_2CH_3), 2.83 (s, 3H, $=\text{C}-\text{CH}_3$), 2.61-

2.38 (m, 4H, 2 x CH_2), 1.23 (t, $J = 6.8$ Hz, 3H, $\text{CH}_3-\text{CH}_2\text{O}$), 1.06 (s, 3H, $\text{C}-\text{CH}_3$), = 0.93 (s, 3H, C-

CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ; 198.5, 169.6, 157.5, 152.1, 145.6, 145.6, 140.9, 139.8, 129.5,

120.2, 115.7, 107.8, 60.3, 51.8, 41.2, 36.9, 33.5, 28.0, 27.0, 18.5, 14.5; **EIMS** (m/z , %): 407.1 (46.8)

$[\text{M}^++1]$; Anal. Calcd for $\text{C}_{21}\text{H}_{23}\text{Cl}_2\text{NO}_3$ (407.1): C, 61.77; H, 5.68; N, 17.37. Found: C, 61.79; H, 5.56; N, 17.40.



Ethyl 4-(4-(dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2e)

This compound has been synthesized by all the three methods

A, B, and C as mentioned above. Yield: Method A: 73%; Method B:

68%; Method C: 59%; Yellow solid; mp: 226-228 °C; **IR** (neat, $\nu_{\max}$,

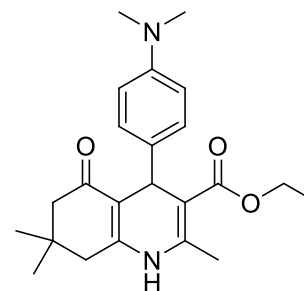
cm^{-1}): 3286, 3080, 2972, 1681, 1381; **^1H -NMR** (CDCl_3 , 300 MHz): δ ;

7.14 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.57 (d, $J = 8.7$ Hz, 2H, Ar-H), 5.99 (s,

1H, NH), 4.92 (s, 1H, -CH), 4.05 (q, $J = 6.9$ Hz, 2H, $-\text{OCH}_2-\text{CH}_3$), 2.83 (s, 6H, $-\text{N}(\text{CH}_3)_2$), 2.32 (s,

3H, $=\text{C}-\text{CH}_3$), 2.23-2.14 (m, 4H, 2 x CH_2), 1.20 (t, $J = 6.9$ Hz, 3H, $\text{CH}_3-\text{CH}_2\text{O}$), 1.04 (s, 3H, C-

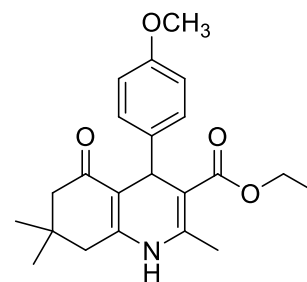
CH_3), 0.93 (s, 3H, $\text{C}-\text{CH}_3$); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ; 198.5, 169.6, 152.2, 150.7, 145.4,



138.2, 129.5, 114.2, 112.5, 107.0, 60.8. 51.5, 41.5, 41.1, 36.7, 33.4, 29.6, 27.1, 18.5, 14.5; **EIMS** (m/z , %): 382.2 (39.9) [$M^+ + 1$]; Anal. Calcd for $C_{23}H_{30}N_2O_4$ (382.5): C, 72.22; H, 7.91; N, 7.32; Found: C, 72.32; H, 7.98; N, 7.55.

Ethyl 4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2f)

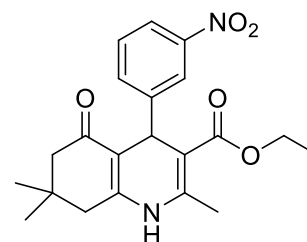
The target molecule was prepared from multicomponent Hantzsch by using the above general three methods. Yield: Method A: 68%; Method B: 60%; Method C: 58%; Light yellow solid; mp: 254-256°C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3208, 3011, 2918, 1678, 1451; **^1H NMR** (CDCl_3 , 300 MHz): δ 7.20 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.71 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.11 (s, 1H, NH), 4.97 (s, 1H, Ar-CH-), 4.02 (q, $J = 7.2$ Hz, 2H, $-\text{OCH}_2-$ CH₃), 3.70 (s, 3H, OCH₃), 2.32 (s, 3H, $=\text{C}-\text{CH}_3$), 2.30-2.04 (m, 4H, 2 x CH₂), 1.18 (t, $J = 7.2$ Hz, 3H, CH₃-CH₂O), 0.93 (s, 3H, C-CH₃), 0.91 (s, 3H, C-CH₃); **^{13}C NMR** (CDCl_3 , 75 MHz): δ 195.5, 167.4, 157.7, 147.8, 143.0, 139.5, 128.9, 113.2, 112.3, 106.3, 59.7, 55.0, 50.7, 41.0, 35.6, 32.6, 29.4, 27.1, 19.3, 14.2; **EIMS** (m/z , %): 369.3 (52.4) [$M^+ + 1$]; Anal. Calcd for $C_{22}H_{27}NO_4$ (369.1): C, 71.52; H, 7.37; N, 3.79; Found: C, 71.60; H, 7.29; N, 3.85.



Ethyl 2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2g)

This compound was also synthesized by using all the three methods A, B, and C.

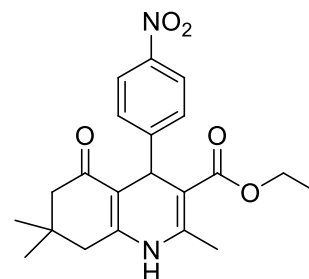
Yield: Method A: 64%; Method B: 64%; Method C: 71%; Off white solid; mp: 179-181 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3295, 3087, 2935, 1718, 1607, 1540, 1013; **^1H NMR** (CDCl_3 , 300 MHz): δ 7.92 (m, 1H, Ar-H), 7.89 (m, 1H, Ar-H), 7.70 (d, $J = 7.8$, 1H, Ar-H), 7.40 (t, $J = 7.8$, 1H, Ar-H), 6.79 (s, 1H, NH), 4.84 (s, 1H, -CH), 4.09 (q, $J = 7.2$



Hz, 2H, -OCH₂-CH₃), 2.35 (s, 3H, C-CH₃), 2.34-2.12 (m, 4H, 2-CH₂-), 1.19 (s, 3H, C-CH₃), 1.14 (s, 3H, C-CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ; 195.6, 169.2, 157.0, 152.6, 147.0, 138.6, 120.9, 119.1, 113.1, 104.5, 59.3, 40.1, 39.6, 32.4, 28.3, 27.1, 17.5, 13.5; EIMS (m/z, %): 384.2 (67.1) [M⁺+1]; Anal. Calcd for C₂₁H₂₄N₂O₅ (384.1): C, 65.61; H, 6.29; N, 7.29; Found: C, 65.66; H, 6.31; N, 7.38.

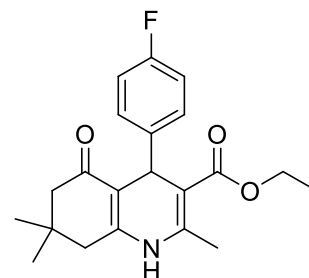
Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2h)

Using the above general procedure method A, the compounds **5h** has been obtained in 86% yield. Off white crystals; mp: 243-245 °C; IR (neat, ν_{max}, cm⁻¹): 3310, 2989, 1686, 1648, 1526, 1140; ¹H NMR (CDCl₃, 300 MHz): δ; 7.98 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.61 (d, *J* = 8.8 Hz, 2H, Ar-H), 6.80 (s, 1H, NH), 5.28 (s, 1H), 4.02 (q, *J* = 7.2 Hz, -OCH₂-CH₃, 2H), 2.40 (s, 3H, C-CH₃), 2.37-2.14 (m, 4H, 2-CH₂), 1.19 (t, *J* = 7.2 Hz, 3H, C-CH₃), 1.13 (s, 3H, C-CH₃), 1.06 (s, 3H C-CH₃), 0.97(s, 3H C-CH₃). ¹³C NMR (CDCl₃, 75 MHz): δ; 196.8, 167.9, 158.1, 153.8, 148.1, 139.5, 128.7, 121.8, 120.2, 114.7, 102.4, 62.7, 58.6, 41.4, 39.8, 33.8, 28.2, 27.5. 18.8, 14.8; EIMS (m/z, %): 384.2 (49.1) [M⁺+1]; Anal. Calcd. for C₂₁H₂₄N₂O₅ (384.1): C, 65.61; H, 6.29; N, 7.29. Found: C, 65.70; H, 6.11; N, 7.61.



Ethyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2i)

This compound has been synthesized by using the above general procedure A, B and C in exallent yield 92,%, 90% and 90% respectively. White solid; mp: 182-184°C; IR (neat, ν_{max}, cm⁻¹): 3271, 3180, 3071, 2962, 1705, 1485; ¹H NMR (CDCl₃, 300 MHz): δ; 7.22 (m, 2H, Ar-H), 6.84 (m, 2H, Ar-H), 6.45 (s, 1H, NH), 5.00 (s, 1H, -CH), 6.45 (s, 1H, NH), 5.00 (s, 1H), 4.04 (q, *J* = 7.2, 2H, -OCH₂-CH₃), 2.32 (s, 3H, =C-CH₃), 2.26-2.14 (m, 4H, 2 x CH₂), 1.16 (t, *J* =



7.2 Hz, 3H, CH₃-CH₂O), 1.03 (s, 3H, C-CH₃), 0.89 (s, 3H, C-CH₃). ¹³C NMR (CDCl₃, 75 MHz): δ; 195.6, 167.3, 162.8, 159.6, 148.3, 143.5, 142.9, 129.4, 129.3, 114.6, 111.9, 105.9, 59.8, 50.7, 40.9, 35.9, 32.6, 29.4, 27.0, 19.2, 14.1; **EIMS** (*m/z*, %): 357.3 (66.7) [M⁺+1]; Anal. Calcd for C₂₁H₂₄FNO₃ (357.1): C, 70.57; H, 6.77; N, 5.32; Found: C, 70.66; H, 6.70; N, 5.39.

Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2j)

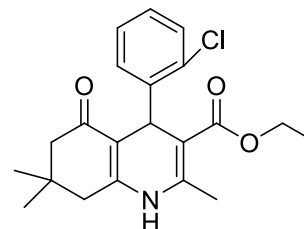
The title compounds has been prepared by using the above general procedure method C.

White solid; Yield 80%; mp 205-207 °C; **IR** (neat, ν_{max}, cm⁻¹): 3177,

3058, 2948, 1719, 1641, 1614, 1517, 1197, 1054; **¹H NMR**

(CDCl₃, 300 MHz): δ; 7.61 (s, 1H, NH), 7.467.29 (m, 4H, ArH), 6.12

(s, 1H, NH), 5.08 (s, 1H, Ar-CH), 4.01, (q, *J* = 7.2 Hz, -OCH₂-CH₃,



2H), 2.40 (s, 3H, C-CH₃), 2.28 -2.11 (m, 4H, 2 x CH₂), 1.21 (t, *J* = 7.2 Hz, 3H, CH₃), 1.07 (s, 3H,

CH₃), 0.99 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ; 196.1, 167.9, 150.0, 143.2, 40.1, 129.1,

127.1, 126.0, 124.8, 115.1, 110.5, 102.1, 56.5, 51.7, 45.8, 42.1, 32.5, 31.1, 27.8, 26.6, 18.5, 13.9.

EIMS (*m/z*, %): 373.2 (53.7) [M⁺+1]; Anal. Calcd for C₂₁H₂₄ClNO₃ (373.1): C, 67.46; H, 6.47; N, 3.75. Found: C, 67.50; H, 6.35; N, 3.81.

Ethyl 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2k)

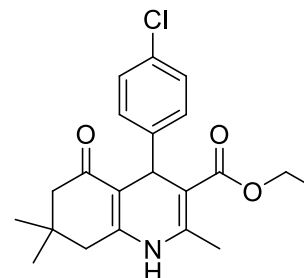
The title compound has been synthesized by using the above general protocol in Method A and C. Yield: Method A; 9%; Method C: 92%; White Powder;

Yield 94 %; mp 244-246 °C; **IR** (neat, ν_{max}, cm⁻¹): 3270, 3150,

3070, 2966, 1691, 1450; **¹H NMR** (CDCl₃, 300 MHz): δ; 7.36 (d, *J*

= 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.41 (s, 1H, NH), 5.79 (s,

1H, Ar-CH-), 4.06 (q, *J* = 7.2, 2H, -OCH₂-CH₃), 2.42 (s, 3H, C-



CH₃), 2.36-2.20 (m, 4H, 2 x CH₂), 1.17 (t, *J* = 7.2 Hz, 3H, CH₃-CH₂O), 1.01 (s, 3H, C-CH₃), 0.93

(s, 3H, C-CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ; 195.7, 167.5, 151.9, 147.6, 143.5, 142.9, 132.4, 129.3, 128.9, 114.2, 112.0, 105.9, 59.8, 50.6, 40.8, 35.9, 31.6, 29.4, 27.5, 19.5, 14.0; EIMS (m/z, %): 373.2 (62.5) [M⁺+1]; Anal. Calcd for C₂₁H₂₄ClNO₃ (373.19); C, 67.46; H, 6.47; N, 3.75. Found: C, 67.49; H, 6.41; N, 3.79.

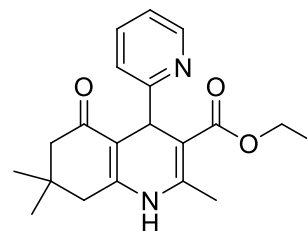
Ethyl 2,7,7-trimethyl-5-oxo-4-(pyridin-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2l)

The title novel compound was synthesized according to the Method A and B as mentioned above under the heading general procedure for the synthesis of polyhydroquinolines derivatives.

Yield: method A: 85%; Method B: 81%; Yellow crystals; Yield 85%;

mp: 133-135 °C; IR (neat, ν_{max}, cm⁻¹): 3292, 3190, 3066, 1689, 1067,

¹H NMR (CDCl₃, 400 MHz): δ; 8.41 (d, J=3.6Hz, 1H, Ar-H), 7.75 (s, 1H, NH), 7.48-7.56 (m, 2H, Ar-H), 7.04 (t, J = 10.8 Hz, 1H, Ar-H),



5.20 (s, 1H, Ar-H), 4.00 (q, J = 7.2 Hz, -OCH₂-CH₃), 2.29 (s, 3H, =C-CH₃), 2.26-2.06 (m, 4H, 2 x CH₂), 1.13 (t, J = 7.2 Hz, 3H, CH₃-CH₂O), 1.02 (s, 3H, C-CH₃), 0.91 (s, 3H, C-CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ; 195.5, 167.3, 164.5, 149.4, 148.4, 145.1, 135.6, 124.5, 121.4, 110.5, 104.2, 59.6, 50.6, 40.8, 39.7, 32.8, 28.6, 28.1, 19.1, 14.1; EIMS (m/z, %): 341.2 (24.1) [M⁺+1]; Anal. Calcd for C₂₀H₂₄N₂O₃ (340.4): C, 70.56; H, 7.11; N, 8.23. Found: C, 70.50; H, 7.01; N, 8.30.

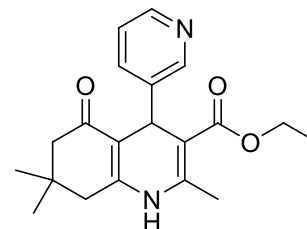
Ethyl 2,7,7-trimethyl-5-oxo-4-(pyridin-3-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2m)

This molecule was prepared according the general procedure method A and B as mentioned above with 72% and 80% yield.

Light yellow crystals; mp 68-70 °C; IR (neat, ν_{max}, cm⁻¹): 3294,

3180, 3059, 2933, 1672, 1072; ¹H NMR (CDCl₃, 300 MHz): δ; 8.47

(brs, 1H,), 8.32 (t, J = 8.2 Hz, 1H, Ar-H), 8.08 (s, 1H, Ar-H), 7.72

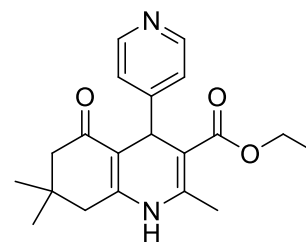


(m, 1H, Ar-H), 7.18 (m, 1H, Ar-H), 7.13 (s, 1H, NH,) 5.01, (s, 1H, Ar-CH), 4.03 (q, J = 7.2 Hz, -

OCH₂-CH₃), 2.29 (s, 3H, =C-CH₃), 2.27-2.05 (m, 4H, 2 x CH₂), 1.15 (t, J = 7.2 Hz, 3H, CH₃-CH₂O), 1.01 (s, 3H, C-CH₃), 0.83 (s, 3H, C-CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ ; 195.3, 167.0, 149.3, 148.9, 146.6, 143.4, 136.2, 123.1, 111.1, 104.7, 59.8, 50.6, 40.5, 35.0, 32.6, 29.3, 27.1, 18.9, 14.2; EIMS (m/z , %): 340.0 (33.7) [M^+ +1]; Anal. Calcd for C₂₀H₂₄N₂O₃ (340.4): C, 70.56; H, 7.11; N, 8.23. Found: C, 70.60; H, 7.09; N, 8.29.

Ethyl 2,7,7-trimethyl-5-oxo-4-(pyridin-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2n)

The mentioned compound was synthesized by using all the above mentioned procedures A, B, and C. Yield: Method A: 91%; Method B: 87%; Method C; 90%; Light yellow crystals; mp: 102-104 °C; IR (neat, $\nu_{\max}$, cm⁻¹): 3166, 3087, 2964, 1667, 1002; ¹H NMR (CDCl₃, 400 MHz): δ ; 8.39 (d, J = 4.4 Hz, 2H, ArH), 7.25 (d, J = 4Hz 1H, ArH), 7.61 (s, 1H, NH), 5.02



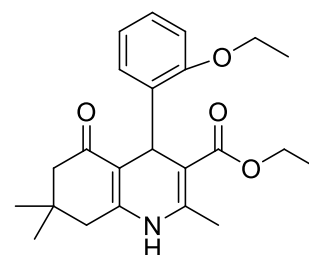
(s, 1H, Ar-CH), 4.03 (q, J = 7.2 Hz, -OCH₂-CH₃), 2.35 (s, 3H, =C-CH₃), 2.29-2.09 (m, 4H, 2 x CH₂), 1.14 (t, J = 7.2 Hz, 3H, CH₃-CH₂O), 1.02 (s, 3H, C-CH₃), 0.86 (s, 3H, C-CH₃); ¹³C-NMR (CDCl₃, 100 MHz): δ ; 195.4, 166.9, 155.7, 149.3, 149.0, 145.1, 123.4, 110.4, 104.0, 59.9, 50.6, 40.7, 36.5, 32.6, 29.3, 27.0, 19.0, 14.1; EIMS (m/z , %): 340.9 (20.1) [M^+ +1]; Anal. Calcd. for C₂₀H₂₄N₂O₃ (340.4): C, 70.56; H, 7.11; N, 8.23; Found: C, 70.59; H, 7.12; N, 8.28.

Ethyl 4-(2-ethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2o)

The target molecules has been obtained by using the above protocol Method A and C in 90% and 62% yields respectively. Off white crystals; mp: 168-172 °C;

IR (neat, $\nu_{\max}$, cm⁻¹): 3200, 3221, 3066, 2954, 1680, 1031; ¹H NMR (CDCl₃, 400 MHz): δ ; 7.62 (s, 1H, NH), 7.24 (d, J = 6 Hz, 1H, Ar-H),

6.95 (t, J = 6.8 Hz, 1H, Ar-H), 6.70-6.63 (m, 2H, Ar-H), 5.05 (s, 1H,



CH), 3.97-3.81 (m, 4H, (2 x OCH₂-CH₃), 3.32 (s, 3H, C=CH₃), 2.23-1.94 (m, 4H, 2 x CH₂-), 1.23 (t,

$J = 6.8$ Hz, 3H, OCH_2CH_3), 1.08 (t, $J = 7.2$ Hz, 3H, OCH_2CH_3), 0.95 (s, 3H, C- CH_3), 0.81 (s, 3H, C- CH_3); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz): δ ; 196.1, 168.4, 157.3, 150.2, 150.1, 144.1, 144.0, 133.2, 132.0, 127.0, 119.1, 109.5, 103.6, 62.6, 59.4, 50.3, 40.4, 40.3, 35.2, 35.0, 32.1, 29.3, 26.3, 18.3, 15.0, 13.8; **EIMS** (m/z , %): 383.2 (98.7) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_4$ (383.18): C, 72.04; H, 7.62; N, 3.65. Found: C, 72.00; H, 7.56; N, 3.70.

Ethyl 4-(4-hydroxy-3-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2p)

The preparation of this compound was also tested by all the above described methods

White solid; Yield: Method A: 77%; Method B: 58%, Method C: 67%;

mp: 212-214 °C; **IR** (neat, ν_{max} , cm^{-1}): 3455, 3270, 3362, 3074, 2904,

1703, 1024; $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ ; 6.84 (s, 1H, Ar-H) 6.61

(s, 2H, Ar-H) 6.11 (s, 1H, NH), 5.50, (s, 1H, OH), 4.87 (s, 1H, CH-) 4.

04 (q, $J = 7.2$ Hz, 2H, $-\text{OCH}_2\text{CH}_3$), 3.77 (s, 3H, OCH_3), 2.32 (s, 3H,

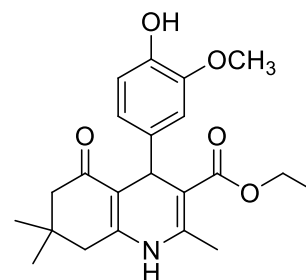
$=\text{C}-\text{CH}_3$) 2.45-2.14 (m, 4H, 2 x CH_2), 1.13 (t, $J = 7.2$ Hz, 3H, $\text{CH}_3-\text{CH}_2\text{O}$), 1.02 (s, 3H, C- CH_3),

0.95 (s, 3H, C- CH_3); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ ; 198.5, 169.5, 152.3, 148.2, 145.7, 145.6,

140.7, 121.3, 115.6, 113.1, 112.4, 106.9, 60.8, 56.3, 51.5, 41.1, 37.2, 33.4, 29.7, 27.0, 18.5, 14.6;

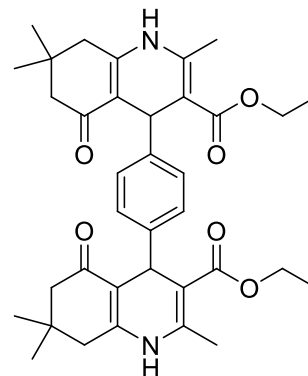
EIMS (m/z , %): 386.0 (48.7) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_5$ (385.19): C, 68.55; H, 7.06; N,

3.63; Found: C, 68.50; H, 7.01; N, 3.68.



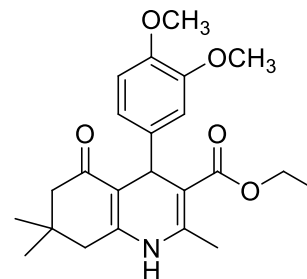
Diethyl-4,4'-(1,4-phenylene)bis(2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate) (2q)

The target novel compound was synthesized by the above mentioned method A. Yellowish solid; Yield: 60 %; mp: 308-312 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3392, 3288, 3061, 2951, 1697, 1033; **^1H NMR** (CDCl_3 , 300 MHz): δ : 7.06 (s, 4H, Ar-H), 5.97 (s, 2H, 2xNH), 4.99 (s, 2H, 2xAr-CH), 3.97 (q, $J = 6.9$ Hz, 4H, 2 x $\text{OCH}_2\text{-CH}_3$), 2.95 (s, 6H, 2 x C=CH_3), 2.36-2.02 (m, 8H, 4 x CH_2), 1.10 (t, $J = 6.9$ Hz, 6H, 2 x CH_2CH_3), 1.04 (s, 6H, 2 x C- CH_3), 1.02 (s, 6H, 2 x C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ : 198.4, 169.4, 152.6, 146.1, 128.5, 128.3, 112.2, 106.5, 61.5, 60.8, 51.5, 41.0, 37.1, 33.4, 29.5, 27.2, 20.8, 18.5; **EIMS** (m/z , %): 600.1 (21.8) (M^+); Anal. Calcd for $\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_6$ (600.30): C, 71.97; H, 7.38; N, 4.66. Found: C, 71.92; H, 7.31; N, 4.69.



Ethyl-4-(3,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2r)

The title compound was obtained by using the above described method B and C yielded in 66 and 68% respectively. Yellow solid; mp: 229-231 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3319, 3023, 2968, 1706, , 1619, 498,1408, 1213, 1107; **^1H NMR** (CDCl_3 , 300 MHz): δ : 6.99 (s, 1H, Ar-H), 6.80 (d, $J = 8.3$ 1H, Ar-H), 6.74 (d, $J = 8.3$ Hz, 1H, Ar-H), 6.12 (s, 1H, NH), 5.62 (s, 1H, CH), 4.04 (q, $J = 7.3$ Hz, 2H, OCH_2CH_3), 3.88 (s, 6H, OCH_3), 2.41 (s, 3H,C- CH_3), 2.18-2.34 (m, 4H, 2 x CH_2), 1.21 (t, $J = 7.3$ Hz, 3H, OCH_2CH_3), 1.01 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ : 194.8, 167.0, 150.2, 148.6, 147.3, 143.8, 140.2, 120.2, 111.3, 109.6, 101.7, 61.0, 59.8, 55.9, 50.5, 40.9,35.8, 32.1, 28.7, 27.5, 18.1, 14.5; **EIMS** (m/z , %): 399.0 (92.0) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{NO}_5$ (399.2): C, 69.15; H, 7.32; N, 3.51; Found: C, 69.16, H, 7.28 N, 3.49.



Ethyl 4-(2,3-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2s)

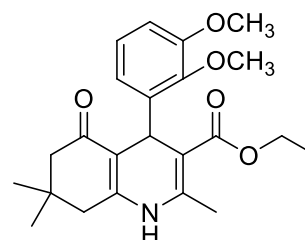
This compounds was synthesized by using the above mentioned general procedure Method

A. Light yellow crystals; Yield 57 %; mp 200-202 °C; **IR** (neat,

$\nu_{\max}$, cm^{-1}): 3296, 3018, 2962, 1693, 1024; **^1H NMR** (CDCl_3 , 300

MHz): δ ; 7.34-7.13 (m, 1H, Ar-H), 7.08-6.91 (m, 2H, Ar-H), 6.01

(s, 1H, NH), 4.82 (s, 1H, CH-), 4.02 (q, $J = 7.2$ Hz, 2H, $-\text{OCH}_2-$



CH_3), 4.22 (s, 6H, $2 \times \text{OCH}_3$), 2.25 (s, 3H, $=\text{C}-\text{CH}_3$), 2.11-2.09 (m, 4H, $2 \times \text{CH}_2$), 1.20 (t, $J = 7.2$

Hz, 3H, $\text{CH}_3-\text{CH}_2\text{O}$), 1.07 (s, 3H, C- CH_3), 0.99 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ;

195.3, 167.8, 152.8, 148.6, 147.8, 142.4, 139.5, 123.5, 122.5, 111.2, 110.6, 105.5, 60.1, 59.6, 55.6,

50.8, 41.2, 34.3, 32.6, 28.8, 27.8, 19.4, 14.1; **EIMS** (m/z , %): 399.3 (99.7) [$\text{M}^+ + 1$]; Anal. Calcd for

$\text{C}_{23}\text{H}_{29}\text{NO}_5$ (399.2): C, 69.15; H, 7.32; N, 3.51; Found: C, 69.12; H, 7.34; N, 3.50.

Ethyl 4-(4-ethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (2t)

The target molecule has been synthesis according the above

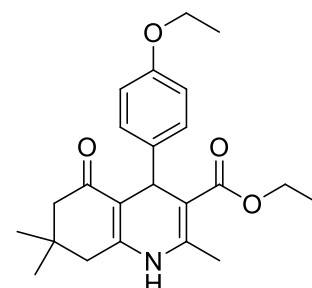
mentioned Methods A, B, and C in excellent yields 92, 80, 92%

respectively. White crystals; 211-213 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3205, 3170,

3062, 2930, 1701, 1009; **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.17, (d, $J = 8.4$

Hz, 2H, Ar-H), 6.95 (s, 1H, NH), 6.69 (d, $J = 8.4$, 2H, Ar-H), 5.95 (s, 1H,

Ar-CH), 4.04 (q, $J = 6.9$ Hz, 2H, OCH_2-CH_3), 3.90 (t, $J = 6.8$ Hz, 3H, Ar- OCH_2CH_3), 2.23 (s, 3H,



C- CH_3) 2.20-2.11 (m, 4H, $2 \times \text{CH}_2$ -), 1.10 (t, $J = 6.8$ Hz, 3H, CH_3CH_2); 1.19 (d, 3H, CH_3CH_2), 1.00

(s, 3H, C- CH_3), 0.88 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): δ ; 195.8, 167.5, 157.0, 148.9,

143.5, 139.5, 128.8, 113.7, 111.8, 106.0, 63.1, 59.6, 50.7, 40.6, 35.6, 32.5, 29.4, 27.0, 19.1, 14.8,

14.2; **EIMS** (m/z , %): 383.2 (100.0) [$M^+ + 1$]; Anal. Calcd for $C_{23}H_{29}NO_4$ (382.21): C, 72.04; H, 7.62; N, 3.65; Found: C, 72.01; H, 7.59; N, 3.69.

2.13. General procedure for the reaction of Ethyl 1-(4-hydroxyphenyl)-3, 6, 6-trimethyl-8-oxo-1,4,5,6,7,8-hexahydronaphthalene-2-carboxylate (2a) with alkyl halides (23-25)

The compound (2a) (0.5 mmol) and potassium carbonate (1.25 mmol) was dissolved in 25 ml acetone (HPLC grade) in a 50 ml round bottom flask already charged with magnetic bar. This was stirred for 15 min. at 40 °C. The alkyl halide (1.2 mmol, 1.2 equivalents) was then added drop wise within 5 min. The reaction mixture was allowed to stir for 4-5 h at 60 °C. The progress of the reaction was monitored by TLC (Ethyl acetate: n-hexane, 3:1). After disappearance of the substrates the acetone was evaporated under vacuum. In order to destroy the excess of potassium carbonate 2x10 ml of water was added and 3x10 ml of dichloromethane. The organic layer was separated and dried with anhydrous $MgSO_4$, washed with brine and concentrated under vacuum. The crude product was purified by column chromatography by using 20% ethyl acetate and *n*-hexane.

2.14. Spectroscopic data of polyhydroquinoline derivatives 3(a-c)

Ethyl 2,7,7-trimethyl-5-oxo-4-(4-(prop-2-ynoxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3a)

The title compound, a novel derivative of polyhydroquinoline was synthesized according to the above mentioned general procedure 2.12 from the reaction Propargyl

bromide and substrate 5a. Yellow powder; Yield: 68 %; mp: 155-

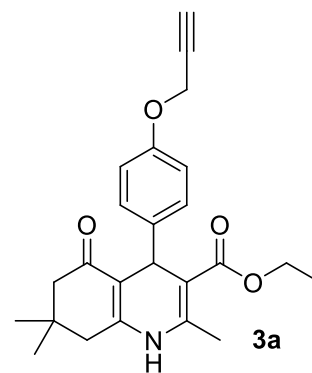
160 °C; **IR** (neat, ν_{max} , cm^{-1}): 3276, 3074, 2929, 2285, 1680, 1479;

^1H NMR ($CDCl_3$, 300 MHz): δ ; 7.18 (d, J = 8.7 Hz, 2H, Ar-H), 6.76

(d, J = 8.7 Hz, 2H, Ar-H), 5.84 (s, 1H, NH), 4.98 (s, 1H, Ar-CH),

4.58 (d, J = 2.4 Hz, 1H, Ar-O-CH₂-C $\equiv$), 4.04 (q, J = 7.2 Hz, 2H, -

OCH₂-CH₃), 2.47 (d, J = 2.4 Hz 1H, acetylene-H), 2.36 (s, 3H, =C-CH₃), 2.27-2.15 (m, 4H, 2 x



CH₂), 1.17 (t, $J = 7.2$ Hz, 3H, CH₃-CH₂O); 1.04 (s, 3H, C-CH₃), 0.90 (s, 3H, C-CH₃); ¹³C NMR (CDCl₃, 75 MHz): δ ; 196.4, 168.4, 151.1, 149.5, 150.3, 129.4, 114.1, 112.3, 107.0, 81.2, 78.2, 61.2, 57.7, 51.1, 41.4, 37.5, 32.2, 29.4, 27.2, 19.3, 14.1; EIMS (m/z , %): 393.2 (98.7) [$M^+ + 1$]; Anal. Calcd for C₂₄H₂₇NO₄ (393.19); C, 73.26; H, 6.92; N, 3.56; Found: C, 73.19; H, 6.88; N, 3.61.

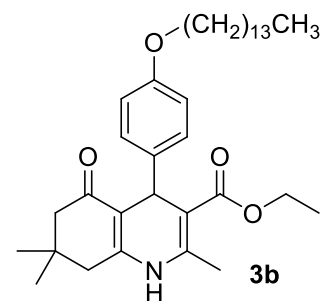
Ethyl-2,7,7-trimethyl-5-oxo-4-(4-(tetradecyloxy)phenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (3b)

Following the above general procedure 2.12, the substrate **5a** (1 mmol) and 1-bromotetradecane, (1.2 mmol) gave the title compound **3b**.

Yellow solid; Yield: 71%; mp: 130-133 °C; IR (neat, $\nu_{\max}$, cm⁻¹): 3175, 3082, 2929, 1721, 1680, 1565, 1456, 1243, 1127, 1079;

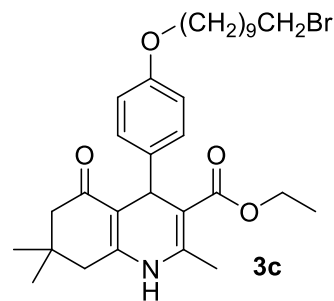
¹H NMR (CDCl₃, 500 MHz): δ ; 7.17 (d, $J = 8.5$ Hz, 2H, Ar-H) 6.69 (d, $J = 9.0$ Hz, 2H, Ar-H), 6.46 (s, 1H, NH), 4.95 (s, 1H, Ar-CH), 4.04 (q, $J = 7.0$ Hz, 2H, -OCH₂-CH₃) 3.83 (t, $J = 6.5$ Hz, 2H, O-CH₂-CH₂-), 2.32

(s, 3H, C-CH₃), 2.28-2.13 (m, 4H, 2 x CH₂), 1.72 (m, Hz, 2H, O-CH₂-CH₂-CH₂-), 1.69 (m, Hz, 2H, O-CH₂-CH₂-CH₂-), 1.19, (m, 22H, (CH₂)₁₁) 1.02 (s, 3H, C-CH₃), 0.90 (s, 3H, C-CH₃) 0.85, (t, $J = 7.2$ Hz, 3H, CH₂-CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ ; 195.6, 167.5, 157.3, 148.3, 143.2, 139.3, 128.8, 113.7, 112.1, 106.3, 67.8, 59.7, 50.6, 40.9, 35.6, 32.6, 31.8, 29.6, 29.5, 29.51, 29.41, 29.35, 29.32, 27.1, 26.0, 22.6, 19.2, 14.2, 14.0; EIMS (m/z , %): 551.3 (60.8) [$M^+ + 1$]; Anal. Calcd for C₃₅H₅₃NO₄ (551.40); C, 76.18; H, 9.68; N, 2.53; Found: C, 76.12; H, 9.60; N, 2.60.



Ethyl 4-(4-(10-bromodecyloxy) phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolines-3-carboxylate (3c)

Light yellow solid; Yield: 70%; mp: 170-172 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3204, 3070, 2945, 1741, 1686, 1595, 1486, 1273, 1187, 1039, 778, 698; **^1H NMR** (CDCl_3 , 300 MHz): δ : 7.17 (d, $J = 8.4$ Hz, 2H, Ar-H) 6.76 (s, 1H, NH) 6.69 (d, $J = 8.7$ Hz, 2H, Ar-H), 4.95 (s, 1H, Ar-CH), 4.02 (q, $J = 6.9$ Hz, 2H, $-\text{OCH}_2-\text{CH}_3$), 3.82 (t, $J = 6.6$ Hz, 2H, $\text{O}-\text{CH}_2-\text{CH}_2-$), 3.37 (t, $J = 6.9$ Hz, 2H, $-\text{CH}_2-\text{Br}$), 2.30 (s, 3H, C- CH_3), 2.21-2.12 (m, 4H, 2 x CH_2), 1.86-1.76 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{Br}$), 1.73-1.68 (m, 2H, $\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$), 1.38-1.15 (m, 12H, $(\text{CH}_2)_6$) 1.01 (s, 3H, C- CH_3), 0.89 (s, 3H, C- CH_3); **^{13}C NMR** (CDCl_3 , 125 MHz): δ : 195.7, 167.5, 157.8, 148.5, 143.7, 139.5, 128.7, 113.7, 113.1, 107.3, 67.9, 59.6, 50.7, 41.9, 36.6, 32.6, 31.1, 30.5, 0.4, 30.2, 30.1, 29.9, 29.8, 28.1, 27.0, 24.5, 23.1; **EIMS** (m/z , %): 573.1 (36.7) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{35}\text{H}_{53}\text{NO}_4$ (573.20); C, 64.80; H, 7.72; N, 2.44; Found: C, 75.12; H, 8.07; N, 2.91. EIMS: m/z (%) 573.1 (36.7); Anal. Calcd for $\text{C}_{31}\text{H}_{44}\text{BrNO}_4$ (573.2) C, 64.80; H, 7.72; N, 2.44; Found: C, 64.78; H, 7.70; N, 2.51.

**2.15. General procedure for the synthesis of polyhydroacridine-1,8-diones derivatives 4(a-g)**

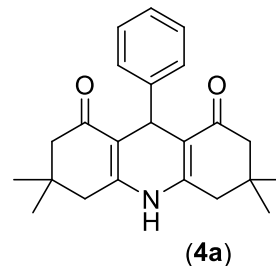
In a typical reaction, the mixture of dimedone **1** (2 mmol) and aldehyde **2** (1 mmol) and ammonium acetate (1.5 mmol) in the presence of morpholine as catalyst (5 mol%) was stirred in 25 ml round-bottomed flask until the completion of reaction. The reactants consumption was detected by TLC. The reaction mixture was poured into the ice cold water and the yellow precipitate solid was washed with additional water (10 ml) and purified by recrystallization from ethanol to afford the

required purity of polyhydroacridine-1,8-diones derivatives. The product was confirmed by the IR, ^1H -NMR and EI-MS spectral data.

2.16. Spectroscopic and physical data of PHAs 4(a-g)

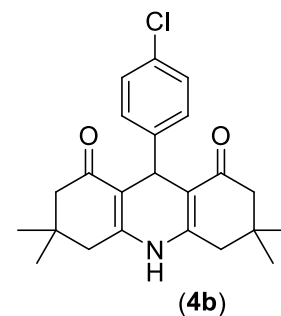
9-(4-phenyl)-3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (26)

Off white solid; Yield: 76%; mp: 272-274 °C; **IR** (neat, ν_{max} , cm^{-1}): 3238, 3078, 2967, 1670, 1602, 1487, 1361, 1187; **^1H NMR** (CDCl_3 , 400 MHz): δ ; 7.58-7.31(m, 5H, Ar-H), 6.91 (brs, 1H, NH), 5.17 (s, 1H, CH), 2.38-2.26 (dd, 4H, 2 CH_2), 2.20-2.19 (dd, 4H, 2 CH_2), 1.05 (s, 6H, 2 CH_3), 0.98 (s, 6H, 2 CH_3); **EIMS** (m/z , %): 349.2 (57.3) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{NO}_2$ (349.4): C, 79.05; H, 7.79; N, 4.01; Found: C, 79.17; H, 7.59; N, 4.12.



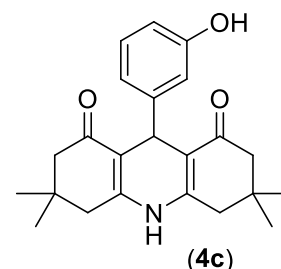
9-(4-Chlorophenyl)- 3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (27)

Off white solid; Yield: 90%; mp: 288-290 °C; **IR** (neat, ν_{max} , cm^{-1}): 3343, 3067, 2957, 1656, 1602, 1481, 1297, 1147; **^1H NMR** (CDCl_3 400 MHz): δ ; 7.34 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.23 (d, $J = 8.4$ Hz, 2H, Ar-H) 6.81 (s, 1H, NH), 5.41 (s, 1H, CH), 3.31- 2.16 (m, 8H, 4 CH_2), 1.12 (s, 6H, 2 CH_3), 1.05 (s, 6H, 2 CH_3); **EIMS** (m/z , %): 383.2 (67.9) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{23}\text{H}_{26}\text{ClNO}_2$ (383.1): C, 71.96; H, 6.83; N, 3.65; Found: C, 71.81; H, 6.80; N, 3.69.



9-(3-Hydroxyphenyl)- 3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (28)

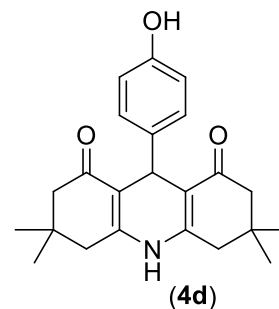
white crystals; Yield: 80%; mp: >300 °C; **IR** (neat, ν_{max} cm^{-1}) ; 3414, 3248, 3058, 2960, 1674, 1607, 1466, 1354, 1146; **^1H NMR** (CDCl_3 , 400 MHz): δ ; 7.48-7.31 (m, 3H, Ar-H), 7.18 (s, 1H, Ar-H) 6.91 (brs, 1H,



NH), 5.60 (s, 1H, OH), 5.09 (s, 1H, CH), 2.37-2.26 (dd, 4H, 2CH₂), 2.19-2.09 (m, 4H, 2CH₂), 1.10 (s, 6H, 2CH₃), 1.09 (s, 6H, 2CH₃); **EIMS** (*m/z*, %): 365.2 (81.4) [*M*⁺+1]; Anal. Calcd for C₂₃H₂₇NO₃ (365.1): C, 75.59; H, 7.45; N, 3.83. Found: C, 75.50; H, 7.38; N, 3.99.

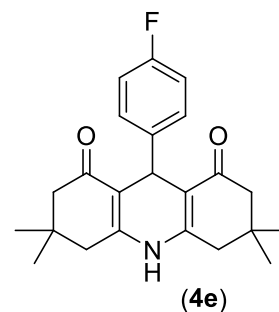
9-(4-Hydroxyphenyl)- 3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (29)

white crystals; Yield:77%; mp: 286-288 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3465, 3242, 3069, 2950, 1664, 1612, 1471, 1361, 1188; **¹H NMR** (CDCl₃ 400 MHz): δ ; 6.99 (d, *J*= 8.5Hz, 2H, Ar-H), 6.85 (d, *J*= 8.5Hz, 2H, Ar-H), 6.79 (brs, 1H, NH), 5.56 (s, 1H, OH), 5.04 (s, 1H, CH), 2.40- 2.25 (dd, 4H, 2CH₂), 2.20-2.0 (m, 4H, 2CH₂), 1.08 (s, 6H, 2CH₃), 0.97 (s, 6H, 2CH₃); **EIMS** (*m/z*, %): 365.2 (76.6) [*M*⁺+1]; Anal. Calcd for C₂₃H₂₇NO₃ (365.1): C, 75.59; H, 7.45; N, 3.83; Found: C, 75.54; H, 7.48; N, 3.89.



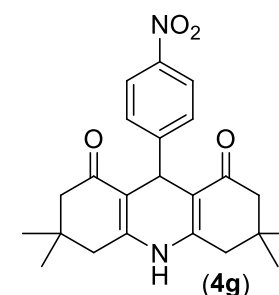
9-(4-Fluorophenyl)- 3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (30)

White crystals; Yield:78%; mp: 290-291 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3310, 3041, 2954, 1657, 1587, 1464, 1369, 1186; **¹H NMR** (CDCl₃, 400 MHz): δ ; 7.37 (d, *J*= 8.4Hz, 2H, Ar-H), 6.96 (d, *J*= 8.4Hz, 2H, Ar-H), 6.89 (brs, 1H, NH), 5.19 (s, 1H, CH), 2.39-2.27 (dd, 4H, 2CH₂), 2.23-2.03 (m, 4H, 2CH₂), 1.11 (s, 6H, 2CH₃), 0.97 (s, 6H, 2CH₃); **EIMS** (*m/z*, %): 367.2 (78.2) [*M*⁺+1]; Anal. Calcd for C₂₃H₂₆FNO₂ (367.1): C, 75.18; H, 7.13; N, 3.81; Found: C, 75.14; H, 7.10; N, 3.89.



9-(4-Nitrophenyl)-3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (31)

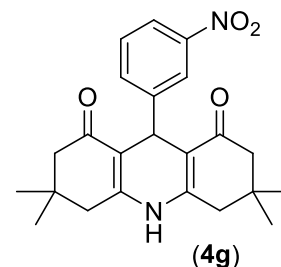
Yellow solid; Yield: 70%; mp: 295-296 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3340, 3081, 2953, 1651, 1593, 1468, 1379, 1219; **¹H NMR** (CDCl₃, 400 MHz): δ ; 8.21(brs, 1H, NH), 7.98 (d, *J* = 7.2 Hz, 2H, ArH), 7.47 (d, *J*= 8.2



Hz, 2H), 5.09 (s, 1H, CH), 2.33-2.25 (dd, 4H, 2CH₂), 2.13-2.02 (dd, 4H, 2CH₂), 1.01 (s, 6H, 2CH₃), 0.88 (s, 6H, 2CH₃); **EIMS** (*m/z*, %): 394.2 (37.9) [*M*⁺ +1]; Anal. Calcd for C₂₃H₂₆N₂O₄: (394.19): C, 70.03; H, 6.69; N, 7.10. Found: C, 70.11; H, 6.61; N, 7.25.

9-(3-Nitrophenyl)- 3,3,6,6-Tetramethyl-1,8-dioxodecahydroacridine (32)

Yellowish white crystals; Yield: 78%; mp: >300 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3329, 3066, 2987, 1672, 1618, 1484, 1342, 1223, **¹H NMR** (CDCl₃, 400 MHz): δ ; 8.41 (s, 1H, NH) 8.01 (s, 1H, Ar-H) 7.85 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.67 (m, 3H, Ar-H), 5.02 (s, 1H, CH), 2.34-2.26 (dd, 4H, 2CH₂), 2.19-2.01 (dd, 4H, 2CH₂), 1.02 (s, 6H, 2CH₃), 0.91 (s, 6H, 2CH₃); **EIMS** (*m/z*, %): 394.2 (41.7) [*M*⁺ +1]; Anal. Calcd for C₂₃H₂₆N₂O₄ (394.19): C, 70.03; H, 6.69; N, 7.10; Found: C, 70.09; H, 6.67; N, 7.20.



2.17. General procedure for the synthesis of 1,4-dihydropyridine derivative

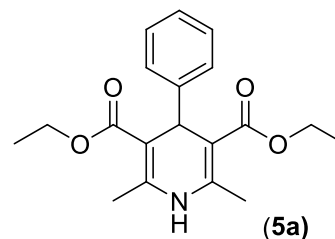
Aldehyde (1.0 mmol), ethylacetoacetate (1.2 mmol), ammonium acetate (1.2 mmol) and morpholine/Al₂O₃ (1.0 g containing 10 mol% morpholine) were mixed in china dish and kept under microwave irradiation (450 W) for specified time as mentioned in the result discussion section (Table 2.18). The progress of the reaction was monitored by TLC using ethyl acetate: n-hexane (4:1) solvent system. After the reactants had consumed, the mixture was allowed to cool to room temperature. The reaction mixture was dissolved in dichloromethane or ethyl acetate (30 ml) and the solid was filtered out. The excess ammonium acetate was destroyed by washing with water (10 ml). The organic layer was dried with Sodium sulphate (anhyd). The organic layer was evaporated under vacuum. The crude product obtained was either purified by recrystallization from binary solvent system (aqueous ethanol and ethyl acetate or dichloromethane) or column chromatography.

2.18. Spectroscopic and physical data of DHPs 5(a-j)

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (33)

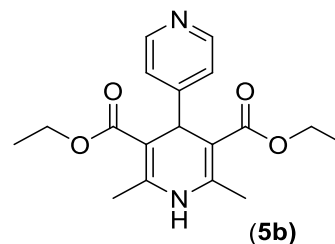
The title compound was synthesized from the reaction of ethylacetoacetate, benzaldehyde and ammonium acetate according to the above mentioned procedure under microwaves in 4.0 minutes.

Pale yellow solid; Yield: 82%; mp: 154-156 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3323 (N-H str), 3045(Ar-H), 2956, (C-H str), 1728 (C=O ester), 1640 (C=C str), 1483(C-H bend), 1381(C-N), 901 (Ar-H); **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.27-7.09 (m, 5 H, Ar-H), 5.68 (brs, 1 H, NH) 4.96 (s 1H, CH), 4.11-4.01 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.30 (s, 6H, 2CH_3), 1.19 (t, $J = 14.1$ (6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 329.0 (33.4) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_4$ (329.14): C, 69.26; H, 7.04; N, 4.25; Found: C, 69.22; H, 7.01; N, 4.29.



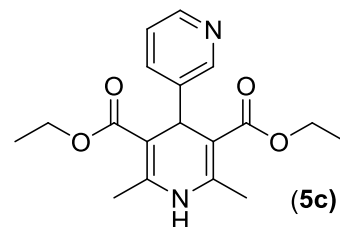
Diethyl 2,6-dimethyl -4-(4-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (34)

Using the above general procedure the target molecules was synthesized under microwave in 4.0 minute from the reaction 4-pyridyl carboxaldehyde. Pale yellow solid; Yield: 80 %; mp: 180-182 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3231 (N-H str), 3065 (Ar-H), 2926 (C-H str), 1709 (C=O ester), 1619 (C=C str), 1483 (C-H, Bend), 1389 (C-N), 991 (Ar-H); **^1H NMR** (CDCl_3 , 400 MHz): δ ; 8.43 (d, $J = 6\text{Hz}$, 2 H, Ar-H), 7.42 (d, $J = 6\text{Hz}$, 2 H, Ar-H), 6.35 (brs, 1 H, NH) 5.06 (s 1H, CH), 4.08 (q, $J = 7.2$, 4H, $2\text{OCH}_2\text{CH}_3$), 2.35 (s, 6H, 2CH_3), 1.19 (t, $J = 7.2$, 6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 331.0 (8.4) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ (330.38): C, 65.44; H, 6.71; N, 8.48; Found: C, 65.52; H, 6.62; N, 8.54.

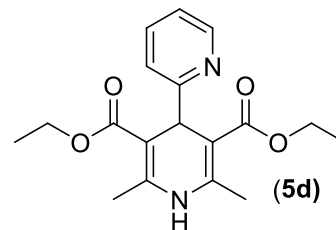


Diethyl 2,6-dimethyl -4-(3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (35)

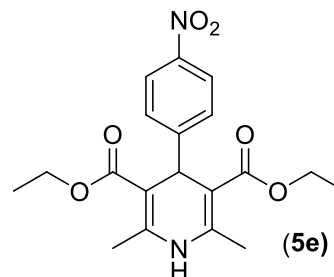
Pale yellow solid; Yield: 85 %; mp: 192-194 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3265 (N-H str), 3071 (Ar-H), 2946, (C-H str), 1701 (C=O ester), 1611 (C=C str), 1471 (C-H bend), 1385 (C-N), 988 (Ar-H); **^1H NMR** (CDCl_3 , 400 MHz): δ ; 8.48 (d, $J = 2.1\text{Hz}$, 1H, Ar-H), 8.38 (d, $J = 4.8\text{ Hz}$, 1H, Ar-H), 7.71-7.67 (m, 2H, Ar-H), 6.55 (brs, 1H, NH), 5.07 (s 1H, CH), 4.12-4.07 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.37 (s, 6H, 2CH_3), 1.21 (t, $J = 7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 331.0 (10.7) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ (330.38): C, 65.44; H, 6.71; N, 8.48; Found: C, 65.57; H, 6.70; N, 8.55.

**Diethyl 2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (36)**

Orange solid; Yield: 79 %; mp: 193-195 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3264 (N-H str), 3086 (Ar-H), 2966, (C-H str), 1697 (C=O ester) 1601 (C=C str), 1467 (C-H bend), 1390 (C-N), 908 (Ar-H). **^1H NMR** (CDCl_3 , 300 MHz): δ ; 8.57 (brs, 1H, NH), 8.23 (d, $J = 5.8\text{ Hz}$, 1H), 7.72-7.59 (m, 3H, Ar-H), 5.27 (s 1H, CH), 4.13-4.05 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.29 (s, 6H, 2CH_3), 1.24 (t, $J = 7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 330.9(12.2) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_4$ (330.38): C, 65.44; H, 6.71; N, 8.48; Found: C, 65.40; H, 6.63; N, 8.58.

**Diethyl 2,6-dimethyl-4-(4-Nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (37)**

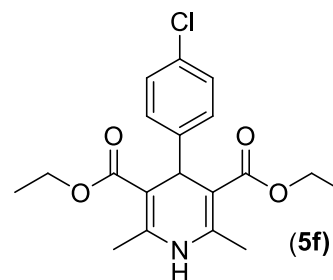
Yellow solid; Yield: 72 %; mp: 130-133 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3373 (N-H str), 3076 (Ar-H), 2986 (C-H str), 1721 (C=O ester) 1611 (C=C str), 1487 (C-H bend), 1393 (C-N) 978 (Ar-H). **^1H NMR** (CDCl_3 , 300 MHz): δ ; 8.20 (d, $J = 8.2\text{ Hz}$, 2H,



ArH), 7.57 (d, $J = 8.2\text{Hz}$, 2H, Ar-H), 5.96 (brs, 1H, NH) , 4.94 (s 1H, CH), 4.15-4.08 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.39 (s, 6H, 2CH_3), 1.23 (t, $J = 7.1$, 6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 374.2 (26.5) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4$ (374.20): C, 60.95; H, 5.92; N, 7.48; Found: C, 60.90; H, 5.89; N, 7.54.

Diethyl 2,6-dimethyl-4-(4-Chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (38)

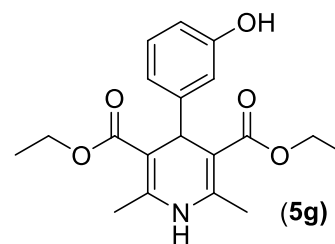
White solid; Yield: 90 %; mp: 141-144 °C; **IR** (neat, ν_{max} , cm^{-1}): 3317 (N-H str), 3075 (Ar-H), 2959 (C-H str), 1701 (C=O ester) 1617 (C=C str), 1437 (C-H bend), 1329 (C-N) 998 (Ar-H). **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.20 (d, $J = 7.8\text{ Hz}$, 2H, Ar-H), 6.98 (d, $J = 7.8\text{ Hz}$, 2H, Ar-H), 5.97 (brs, 1H, NH), 4.99 (s 1H, CH),



4.15-4.02 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.34 (s, 6H, 2CH_3), 1.24 (t, $J = 7.2$, 6H, $\text{CH}_3\text{CH}_2\text{O}$); **EIMS** (m/z , relative abundance, %): 363.2 (33.7) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{ClNO}_4$ (363.12): C, 62.72; H, 6.09; N, 3.85; Found: C, 62.70; H, 6.01; N, 3.88.

Diethyl 2,6-dimethyl-4-(3-Hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (39)

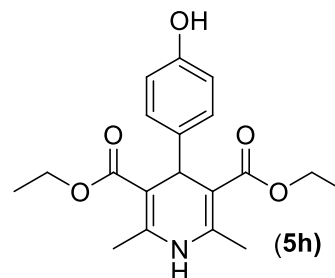
Yellow solid; Yield: 70 %; mp: 181-182 °C; **IR** (neat, ν_{max} , cm^{-1}): 3483, (OH), 3289 (N-H str), 3084 (Ar-H), 2967 (C-H str), 1700 (C=O ester) 1639 (C=C str), 1459 (C-H bend), 1385 (C-N) 950 (Ar-H); **^1H NMR** (CDCl_3 , 300 MHz): δ ; 7.12-6.89 (m, 3H, Ar-H), 6.88 (s, 1H, Ar-H), 5.87 (brs, 1H, NH), 5.21 (s, 1H, OH), 5.02 (s 1H, CH), 4.17-2.09 (m, 4H, $2\text{OCH}_2\text{CH}_3$), 2.33 (s, 6H, 2CH_3), 1.27 (t, $J = 7.00$, 6H, $\text{CH}_3\text{CH}_2\text{O}$);



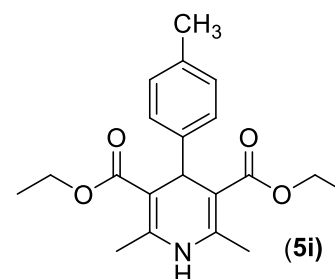
EIMS (m/z , relative abundance, %): 345.3 (19.8) [$\text{M}^+ + 1$] Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_5$ (345.39): C, 66.07; H, 6.71; N, 4.06; Found: C, 66.09; H, 6.66; N, 4.09.

Diethyl 2,6-dimethyl-4-(4-Hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (40)

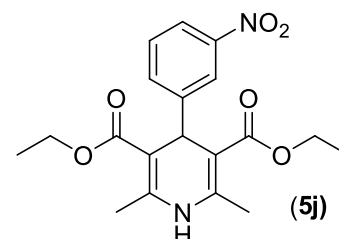
White solid; Yield: 76 %; mp: 189-191 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3488 (OH), 3321 (N-H str), 3080 (Ar-H), 2971 (C-H str), 1703 (C=O ester) 1616 (C=C str), 1476 (C-H bend), 1375 (C-N) 951 (Ar-H). **^1H NMR** (CDCl_3 , 300 MHz): δ : 7.18 (d, J = 8.5 Hz, 2H, Ar-H), 6.72 (d, J = 8.8 Hz, 2H, Ar-H), 5.85 (brs, 1H, NH), 5.32 (s, 1H, OH), 4.89 (s 1H, CH), 4.12 (q, J = 7.2 Hz, 4H, $2\text{OCH}_2\text{CH}_3$), 2.31 (s, 6H, 2CH_3), 1.22 (t, J = 7.00, 6H, $\text{CH}_3\text{CH}_2\text{O}$) **EIMS** (m/z , relative abundance, %): 345.1 (39.1) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_5$ (345.39): C, 66.07; H, 6.71; N, 4.06; Found: C, 66.11; H, 6.62; N, 4.10.

**Diethyl 2,6-dimethyl-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (41)**

Orange solid; Yield: 60%; mp: 195-196 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3280 (N-H str), 3073 (Ar-H), 2976 (C-H str), 1694 (C=O ester) 1606 (C=C str), 1487 (C-H bend), 1343 (C-N); **^1H NMR** (CDCl_3 , 300 MHz): δ : 7.13 (d, J = 8.02 Hz, 2H, Ar-H), 7.02 (d, J = 8.02 Hz, 2H, Ar-H), 5.65 (brs, 1H, NH), 4.99 (s 1H, CH), 4.09 (q, J = 7.20 Hz, 4H, $2\text{OCH}_2\text{CH}_3$), 2.31 (s, 6H, 2CH_3), 2.27 (s, 3H, Ar- CH_3), 1.22 (t, J = 7.00, 6H, $\text{CH}_3\text{CH}_2\text{O}$) **EIMS** (m/z , relative abundance, %): 343.1(89.2) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_4$ (343.12): C, 69.95; H, 7.34; N, 4.08; Found: C, 69.96; H, 7.30; N, 3.99.

**Diethyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (42)**

Brown solid; Yield: 66 %; mp 168-170 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3250 (N-H str), 3087 (Ar-H), 2967 (C-H str), 1698 (C=O ester) 1598 (C=C str), 1483 (C-H bend), 1349 (C-N); **^1H NMR** (CDCl_3 , 300 MHz): δ : 8.23 (s, 1H, Ar-



H), 8.10 (d, $J=8.04$ Hz, 1H, Ar-H), 7.48 (m, 2H, Ar-H) 6.19 (brs, 1H, NH), 5.00 (s 1H, CH), 4.11 (q, $J = 7.02$ Hz, 4H, 2OCH₂CH₃), 2.39 (s, 6H, 2CH₃), 1.23 (t, $J = 7.02$, 6H, CH₃CH₂O); **EIMS** (m/z , relative abundance, %): 374.1 (33.3) [M^++1]; Anal. Calcd for C₁₉H₂₂N₂O₆ (374.39): C, 60.95; H, 5.92; N, 7.48; Found: C, 60.96; H, 5.94; N, 7.40.

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Chapter 3

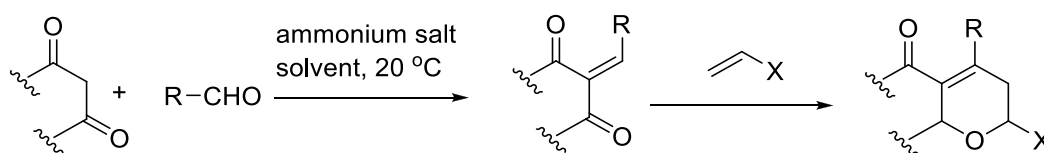
Synthesis and characterization of Oxa-heterocycles

- **2,2'-(Arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene)**
- **1,8-Dioxo-octahydroxanthenes**

3.1 Introduction

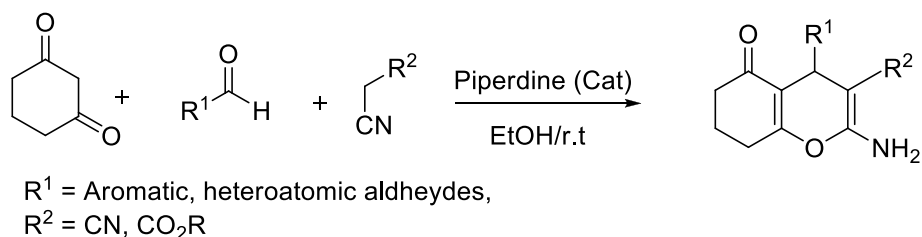
The economic and ecological pressure coupled with associated biological screening is not a very new problem, which is playing progressively more important role in the growth of modern synthetic methods for the therapeutically important heterocyclic molecules¹. In this respect, exploitation of the chemistry of 1,3-dicarbonyls throughout the multicomponent reaction (MCRs), domino reaction or multicomponent reaction in the sense in which one component is used in twofold ratio incorporating multiple functionalities. The cycloaddition and dehydrogenation reactions have fascinated the chemical community². In a series of communications, the cycloadditions reaction of carbonyl compound with conjugated dienes, known as the hetero-Diels-Alder reaction, the Domino-Knoevenagel, Hetero-Diels Alder, reaction, multicomponent assembly process based on Michael addition led to a variety of heterocyclic scaffolds. Hantzsch pyrrole synthesis has been one of the keystone reactions in organic chemistry for the construction of six-membered rings containing an oxygen atom³.

In the Domino-Knoevenagel hetero-Diels Alder reaction, a highly reactive alkenes moiety is first formed *in situ* through a Knoevenagel condensation between an aldehydes and a cyclic or acyclic 1,3-dicarbonyl compound. In the subsequent step, the resulting 1-oxa-1,3-butadiene can undergo a cycloadditions with a dienophile such as enol ether or an enamine to afford functionalized dihydropyrans (Scheme 1). In this sequence, ammonium salts are used as mild catalysts at room temperature in a wide range of solvents⁴⁻⁷.



Scheme 1. The Domino-Knoevenagel Hetero-Diels Alder reaction

In the presence of catalytic amount of piperidine, variation of the Hantzsch reaction for the synthesis of 4*H*-pyran derivative of 1,4-dihydropyran has been planned at Bayer AG⁸ from 1,3-diketo compound (Scheme 2).



Scheme 2. Synthesis of xanthene derivatives

The 1,3-Dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophonic species in a large variety of synthetic transformations. Among them the oxygen containing six-membered heterocycles and their corresponding synthetic intermediate like bis-dimedone has gain attention in the recent years⁸.

3.2 Reported strategies for the synthesis of dimedone incorporated dibenzopyran (xanthenes) and bisdimedone intermediates

Out of the 1,3-dicarbonyl compounds, dimedone is a well-known reagent for the characterization of aldehydes by giving bis(dimedonyl)methane **2**, that can be cyclized into the corresponding xanthene derivatives **3** by the action of acids such as sulfuric⁹⁻¹¹, hydrochloric acid and *p*-DBSA¹² in water. TEBA chloride was used to catalyze the reaction to afford **2**, which were cyclized to the xanthenes by the action of PTSA in water^{13,14}. The condensation of **1** and aromatic aldehydes in ethylene glycol gave the xanthenes derivatives¹²⁻¹⁵ **3**.

A variety of aldehydes including those derived from heterocyclic compounds such as theophyllin-7-acetaldehyde and 2-formylfuro[3,2-*b*]pyrrolo-5-carboxylates afforded **2**, which on

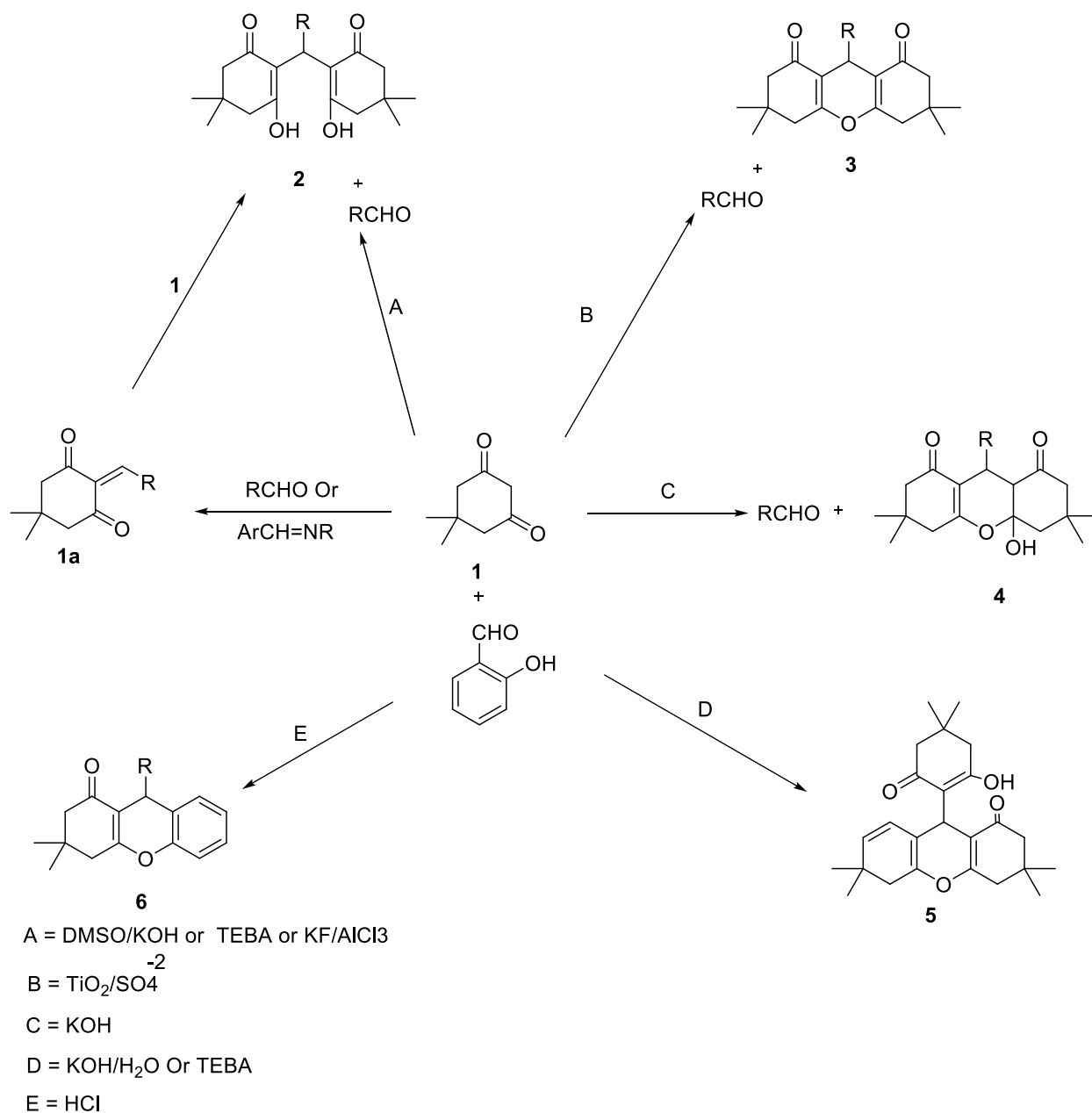
boiling with dilute hydrochloric acid afforded the xanthenes¹⁵⁻¹⁷ **3**. Better yield of **2** were obtained when a mixture of dimedone, benzaldehyd, acetic anhydride, and sodium acetate was MW irradiated for 5 min. This proved that the reaction proceeded through the intermediate **1a** of an aldehyde-dimedone adduct, which in a fast step added to another molecule of dimedone via Michael addition to give **3**¹⁷.

The Knoevenagel condensation, Michael addition and cyclodehydration of dimedone with aliphatic or aromatic aldehydes in the solid state by grinding without catalyst or with $\text{KF}/\text{Al}_2\text{O}_3$ as catalyst at room temperature was limited to give **2** ($\text{R} = \text{alkyl or aryl}$)^{19,20}. Similarly, the $\text{HClO}_4\text{-SiO}_2$ catalyzed²¹ the reaction to give **2**. When the reaction was carried out on solid state using $\text{TiO}_2/\text{SO}_4^{2-}$ super acid or silica sulfate^{20,21}, PPA-SiO_2 neat or in acetonitrile²¹ $\text{NH}_2\text{SO}_3\text{H}$ and SDSFe^{3+} -montmorillonite²² as catalysts, it afforded the respective xanthenes **3**. $\text{InCl}_3 \cdot 4\text{H}_2\text{O}$ promoted the preparation of xanthenediones in ionic liquids, whereas in absence of the catalyst both **2** and **3** were formed^{32,24}. Similarly $[\text{bmim}][\text{BF}_4]$ in the presence of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ gave xanthenediones in high yield. However, when a combination of trimethylchlorosilane (TMSCl) and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ afforded ring-opened derivatives of xanthenediones with high efficiency²⁴, whereas TMSCl in MeCN/DMF gave the xanthenes²⁵ **3**. An efficient approach to the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxooctahydroxanthene **3** using $p\text{-DBSA}$ as a catalyst in water was carried out under ultrasonic irradiation²⁶.

Coupling of **1** with urea and aldehydes gave the xanthenes **3** ($\text{R} = \text{Ar}$) rather than the quinazoline²⁷ **4**. Azomethines behaved like synthetic equivalents of benzaldehyd in the reaction with **1**²⁸. Reaction of **1** with aromatic azomethine gave **3** ($\text{R} = \text{Ar}$) via intermediate formation of **2**. Thus reaction of **1** with aromatic aldehydes was found to be dependent on the substituent on the aromatic ring. Dimedone with benzaldehyd in the presence of potassium hydroxide gave a

mixture of benzal dimedone **1a** and 9-phenyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione **3** (R = Ph)²⁸⁻³⁰ (Scheme 3). The presence of functional groups on the ortho position of benzaldehyd led to the formation of different types of heterocyclic compounds. Thus, reaction with salicylaldehyde³¹ under acidic condition gave **6**, whereas in aqueous potassium hydroxide or TEBA in water³² the product was **5** (R=H). The reaction of substituted salicylaldehydes with dimedone catalyzed by KF/Al₂O₃ gave **5** (R=Me)³³. The reaction with m-methoxybenzaldehyde gave **3**³⁴ and with 2,6-dichlorobenzaldehyde gave **4**, which existed as two enantiomeric pairs of diastereomers³⁵. Compound **6** was obtained from the condensation of **1** with o-hydroxybenzyl alcohol in the presence of hexamethylphosphoramide (HMPA)³⁶.

Treatment of dimedone with sodium hydride followed by β -bromostyrene and CuI in HMPA at 120 °C gave **2** (R=Bn) that was cyclized to **3** upon treatment with H₂SO₄³⁷. Dimedone **1** did not change in DMSO at temperatures up to 150 °C, but at 180 °C, methylation took place with the formation of **3** (R = Me)³⁸. When the reaction was carried out in the presence of KOH, **2** (R = Me) was isolated in low yield which by fractional crystallization readily underwent cyclization to **3**; KOH inhibited heterocyclization of **2**³⁸.



Scheme 3 Syntheses of dimedone incorporated dibenzopyran (xanthenes) and bisdimedone

Currently, Shivaji S. Pandit *et. al*³⁹ has reported the use of the hypervalent iodine diacetoxy iodobenzene (DIB) and Mohammad Ali Bigdeli⁴⁰, DABCO-bromine as an acid catalyst in aqueous media for the preparation of xanthene **3** from the one pot condensation of

dimedone with various aromatic aldehydes. The other catalysts in the latest literature are P_2O_5/SiO_2 ,⁴¹ different ionic liquids (ILs) such as, [BMIM][BF₄], [CMIM][HSO₄], [NMP][HSO₄], [BMIM][HSO₄], [(CH₂)₄SO₃HMIM][HSO₄], [BMIM][H₂PO₄]⁴², ZrO(OTf)₂⁴³, and Bronsted acidic imidazolium salts containing perfluoroalkyl tails⁴³ for the synthesis of 1,8-Dioxo-Octahydroxanthenes. While the open chain dimedone containing compound 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) many improved catalyst has been reported like urea under ultrasound⁴⁴, and in water⁴⁵.

3.3 Application of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydroxanthenes

Among the oxygen containing heterocycles several class of O-heterocycles with trivial name exist, 2H-pyran, 4H-pyran, 2H-chromen, flavonoid, coumarine, dihydrocoumarine, and xanthene. Among them xanthene and their derivatives having interesting structural framework on one or either side of pyran ring constitute a significant class of organic compounds. Pyran ring is the basis of the pyranoses. Xanthene itself is used as a fungicide in both agriculture and to fight fungal infections in animals. But its main function is as a fundamental structure of chromospheres particularly luminescent dyes. Xanthene and its derivatives have got importance in various dyes including fluorenes, pyronins, succineins, sacchareins, rosamines, rhodamines, rhodols and fluorones and as pH sensitive fluorescent materials for visualization of biomolecules⁴⁶.

Furthermore, 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydroxanthenes have found wide utility in medicinal and pharmaceutical chemistry with a variety of biological applications that include antiviral⁴⁷, antibacterial⁴⁸, anti-inflammatory activities, anti-depressants and antimalarial agents⁴⁹. Xanthenediones a closely

constitutes a structural unit in a number of natural products that have prominent position in medicinal chemistry^{50,51} and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring^{49,52}.

3.4 Present work

Bis-dimedone, (2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexane-1-one) and 1,8-dioxo-octahydroxanthene derivatives as building blocks for synthesis of carbohydrates, naturally occurring alkaloids and others heterocycles. Besides these applications, in the view of biological activities it was planned to synthesize some of outline bis-dimedone and oxa-heterocyclic derivatives. Synthesis of these compounds was based on the following principles.

- Utilization of the easily accessible 1,3-dicarbonyls compounds for the synthesis of synthetically and biologically important non-heterocycles and heterocyclic compounds.
- Modification in the literature method or development of new catalyst is also under consideration in this project. To achieve this goal solid supported catalyst will be tested which is an attractive alternate to the conventional Lewis acid and triflates.
- Attempt will be made to convert the synthesized non-heterocyclic compounds ((2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexane-1-one) in to their respective O-heterocycles.
- After the successful completion of synthesis, 2,2'-(arylmethylene)bis (3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-Dioxo-Octahydroxanthene derivatives will be screened for their biological activities with special emphasis on antileishmanicidal.

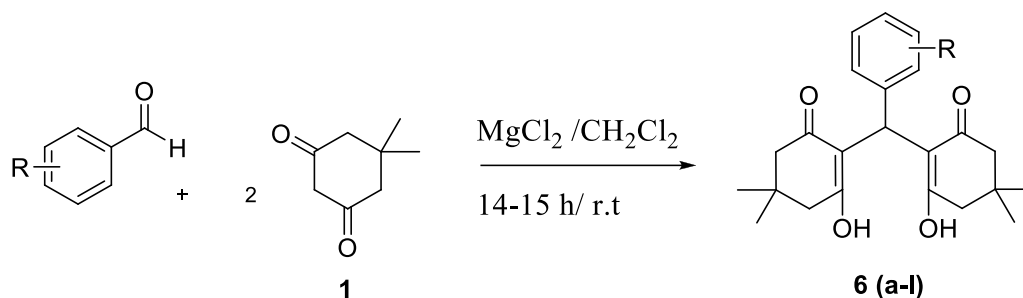
3.5 Results and discussion

This section deals with the results and discussion as well as the experimental protocol of MgCl_2 catalyzed preparation of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **6(a-l)**. The cyclized heterocycles 1,8-dioxo-octahydroxanthene was synthesized by using Amberlite IR-120H as a solid acid catalyst.

3.6 Synthesis and characterization of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **6(a-l)**

The 2,2'-(Arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) a versatile synthetic intermediate has been synthesized by a surprisingly cheap catalyst magnesium chloride at room temperature using CH_2Cl_2 as solvent in good yield (Scheme 3.1). This methodology has extraordinary advantages over the reported protocol not only because of cheap catalyst, but that, magnesium comprises the essential element of numerous generally used capable catalysts and engages at normal oxidation state in bioactivities of living organisms involving its bio-friendlier reliability. Due to these enthralling facial appearances, several current reports on the utility of magnesium compounds as catalysts^{53,54} are available. So far the catalysis capacity of magnesium cation has not been examined for the synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydroxanthenes. It seems reasonable to expect that Mg^{2+} cations dissolved in less coordinative ionic medium would have the ability of chemical activity. To deal with the solubility problems, recently, Kurosh Rad-Moghadam and Seyyedeh Cobra Azimi⁵⁵ have reported $\text{Mg}(\text{BF}_4)_2$ doped in $[\text{BMIm}][\text{BF}_4]$ as homogenous ionic liquid catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes. Obviously, this method involves the expensive reagents, preparation of ionic liquid catalyst and tedious work up. Since

our concern is the solubility issues, that is, catalytic amount of Mg ions are expected in solvent to facilitate the reaction towards product, therefore, initially the reaction was carried out at room temperature for 24 h. It was soluble in organic solvent dichloromethane and 1,8-dioxooctahydroxanthene will be obtained at room temperature. Unexpectedly, 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) has been obtained in good yield (scheme 3.1). In this context the reaction condition were optimized. At room temperature no cyclized product was obtained while on heating at 80 °C and DMF (4 ml) as solvent the xanthenes were obtained in 4 h. So the 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) a synthetically versatile compound has been prepared at room temperature by using 25 mol % of MgCl_2 and dichloromethane as solvent by vigorous stirring for the specified time as displayed in table 3.1. The ratio of catalyst in comparison to substrates is high but this is probably due to the less solubility of MgCl_2 in organic solvent.



Scheme 3.1. Synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)

Table 3.1 MgCl₂ catalyzed synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives (**3a-l**) and its physical data

Entry	Compd.	R	Time (h)	Yield %	Solvent system**	R _f	m.p. (°C)	
							Observed	Lit.
43	6a	---	15	60	3:7	0.42	88-90	---
44	6b	H	14	68	3:7	0.39	191-192	194-196 ⁵⁶
45	6c	4-F-	14.5	80	3:7	0.40	185-187	---
46.	6d	4-Cl-	14	83	3:7	0.41	144-146	146-147 ⁵⁵
47	6e	4-OH-	14	78	4:7	0.36	194-196	192-194 ⁴⁴
48	6f	4-OCH ₃ -	14.5	70	3:7	0.45	139-141	140-141 ⁵⁶
49	6g	3-NO ₂ -	15	72	3:7	0.49	122-124	120-122 ⁴⁴
50	6h	4-NO ₂ -	14	77	3:7	0.52	194-196	191-193 ⁴⁴
51	6i	3-OH-	14	78	1:1	0.53	197-199	----
52	6j	4-OH, 3-OCH ₃ -	15	60	1:2	0.38	126-128	122-124 ⁵⁵
53	6k	4-CH ₃ -	14	78	3:7	0.45	130-133	132-134 ⁵⁷
54	6l	2-furfuryl	14	58	3:7	0.63	102-014	---

* **Reaction conditions**; MgCl₂, (25 mol %), solvent CH₂Cl₂, and room temperature. ** on Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at λ=254nm (Ethyl acetate : Hexane)

3.6.1. Optimization of reaction condition

After exploiting the properties of 1,3-dicarbonyl as an active methylene the 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives were successfully synthesized in one pot. The next step was the optimization of reaction condition and evaluation

of the role of solvent and catalyst on yield of desired product. Initially, the model reaction was carried out without catalyst for 24 h at room temperature (entry 1, table 3.2). In the absences of catalyst aldheyde-dimedone addduct was isolated. When catalyst at different ratio, was used it was concluded that 25 mol % is sufficient for the catalysis of reaction towards the product (Run 6, Table 3.2). However, increases of the catalyst from 25 mol % to 30 mol% equivalent have shown adversed effect on the yield of the product and reaction time as shown in table 3.2.

Table 3.2. Effect of loading of catalyst over synthesis of 2,2'-(arylmethylene)bis(3-hydroxyl-5,5-dimethyl-2-cyclohexene-1-one)

Run	Catalyst (mol %)	Time (h)	Yield* (%)
1.	---	24	NP
2.	5	16	51
3.	10	16	60
4.	15	14	68
5.	20	14	76
6.	25	14	77
7.	30	16	71

^aReaction condition: Model reaction of benzaldehyde (0.5mmol), dimedone (1 mmol), MgCl₂, (25 mol %) as catalyst, and CH₂Cl₂ was used as medium . *isolated yield

In order to determine solvent effect, the model reaction was carried out in different solvents like acetonitrile, DMF, ethanol, methanol and halogenated solvents (CHCl₃ and CH₂Cl₂). Among the tested solvents the role halogenated solvents is more important because aprotic solvent can stop the dehydration and trap the product it desired. The following table presents the effect of solvent on yield of product

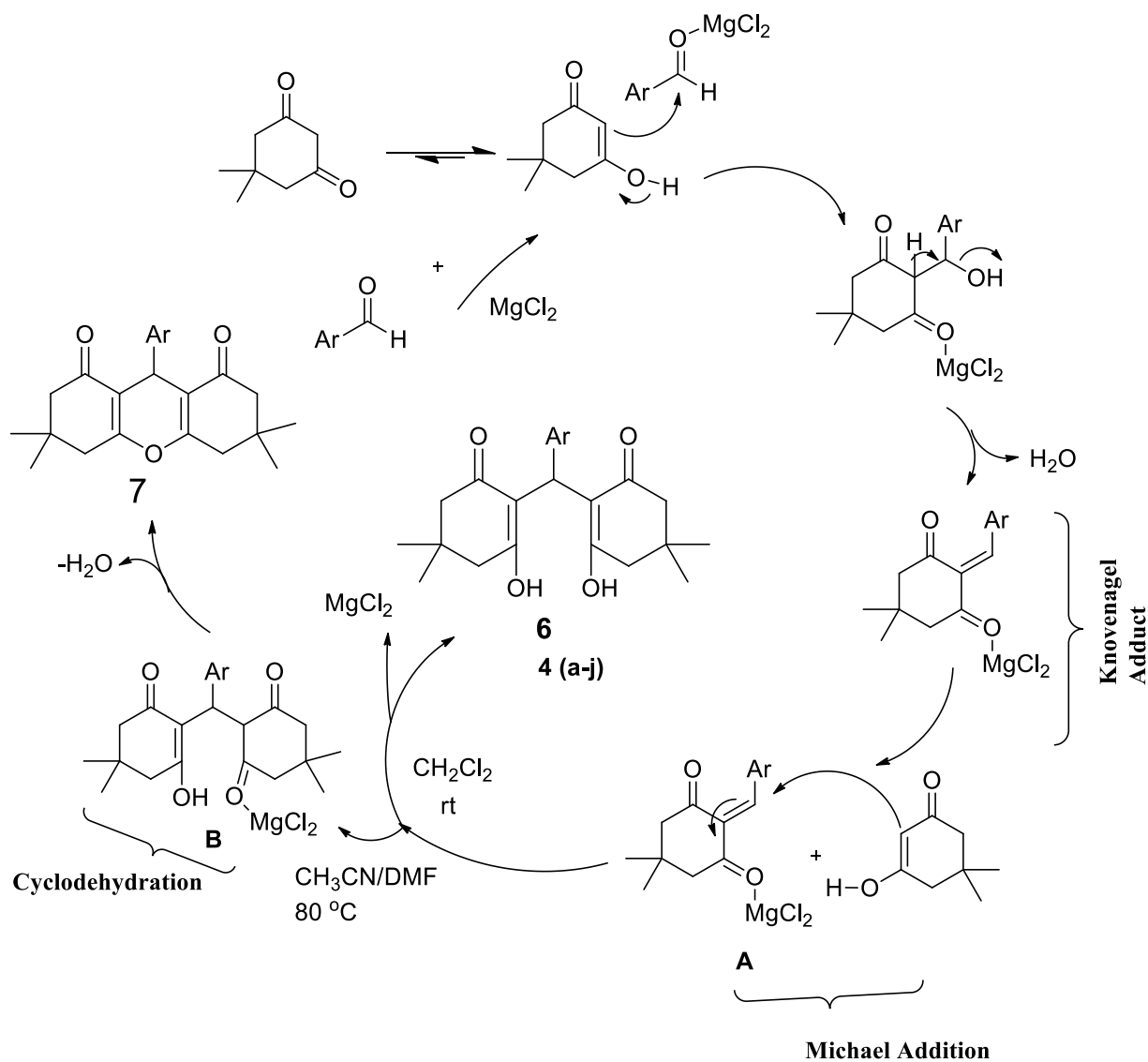
Table 3.3 Solvent effect over the synthesis of 2,2'-(arylmethylene)bis(3-hydroxyl-5,5-dimethyl-2-cyclohexene-1-one)

Entry	Solvent	Temperature	Catalyst mmol)**	Time (h)	Yield
1.	Acetonitrile	R. T	25	16	40
2.	Methanol	R. T	25	16	60
3.	Ethanol	R. T	25	17	50
4.	DMF	R. T	25	16	60
5.	CHCl ₃	R. T	25	14	66
6.	CH ₂ Cl ₂	R. T	25	14	72
7.	CH ₂ Cl ₂	R. T	none	14	NP ^c
8.	CH ₂ Cl ₂	80 °C	25	1 h	mixture ^d

^a**Reaction condtions;** 1-8 = Model reaction of benzaldehyde (0.5mmol), dimedone (1 mmol), and MgCl₂, (5.2 equivalent) as catalyst. ^{**} the amount of catalyst (MgCl₂) ^bThree consecutive reaction at different amount of catalyst NP^c = Not desired product. ^dMixture of 2,2'-(arylmethylene)bis(3- hydroxy-5,5- dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydroxanthenes confirmed by TLC and EIMS spectra

3.6.2. Proposed mechanism for the MgCl₂ catalyzed synthesis of 1,8-dioxo-octahydro-xanthene and 2,2'-(arylmethylene)bis(3-hydroxyl-5,5-dimethyl-2-cyclohexene-1-one)

On the basis of observation made during synthetic work, a tentative mechanism is proposed for the catalytic activity of MgCl₂ as shown in scheme 3.2. The aldehydes dimedone adduct which is also known as Knoevenagel adduct formed is expected to undergo Michael Addition with another dimedone molecule to form intermediate **A** under the influence of MgCl₂. The product **6** formed in the dichloromethane due to the heterogeneous nature of reaction, which does not facilitate the formation of complex with MgCl₂. As mentioned in the result discussion section that under DMF/CH₃CN cyclized product **7** has been obtained, this is probably due to homogenization with solvent which helps better complexation.



Scheme 3.2. Proposed mechanism for the formation of bisdimedone **6** and 1,8-dioxooctahydroxanthene **7**

3.7. Spectral discussion of bis-dimedone derivatives 6(a-l)

3.7.1. IR spectral study of bis-dimedone derivatives 6(a-l)

Various functional groups present in molecule were identified by their corresponding group frequency. For 2,2'-(arylmethylene)bis(3- hydroxy-5,5- dimethyl-2-cyclohexene-1-one), a feature band of carbonyl group was observed in the range of $1690\text{--}1798\text{ cm}^{-1}$ while the OH stretching band often appeared at $3450\text{--}3600\text{ cm}^{-1}$. The C-H asymmetrical Str due to aliphatic parts of molecule were observed at $2900\text{--}2989\text{ cm}^{-1}$. The fundamental group frequencies like, C=C aromatic, C-C and C-H bending were observed in their respective range as shown in the following table 3.4.

Table 3.4. IR Spectral data of Bis dimedone derivatives **6(a-l)**.

Compd.	$\nu(\text{Cm}^{-1})$								
	OH	SP ² C-H	SP ³ C-H	** C=O	C=C	*C-H	C-C	Others	
6a	3630	---	2993	1795	1575	1367	871	---	---
6b	3670	3013	2916	1683	1595	1361	896	---	---
6c	3656	3083	2930	1780	1606	1368	891	C-F	697
6d	3585	3010	2952	1787	1639	1373	891	C-Cl	710
6e	3690	3030	2961	1798	1650	1382	991	Ph-OH	3378
6f	3490	3061	2972	1790	1637	1402	870	---	---
6g	3497	3028	2942	1797	1608	1411	969	---	---
6h	3577	3068	2960	1795	1624	1387	1005	---	---
6i	3663	3066	2988	1698	1598	1380	996	Ph-OH	3278
6j	3651	3078	2948	1738	1628	1389	953	Ph-OH	3398
6k	3610	3078	2969	1780	1607	1388	1002	---	---
6l	3450	---	2989	1690	1544	1359	945	---	---

*(Bending), **Ketonic

3.7.2. ¹H NMR spectral study of 2,2'-(arylmethylene)bis(3- hydroxy-5,5- dimethyl-2 cyclo-hexene-1-one)derivatives **6(a-l)**

In the ^1H NMR spectrum of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **6(a-l)**, the integration ratio (number of protons) and their chemical shifts were found to support the structure. In case of compound **6a** the characteristic signal appeared as singlet at 3.13 ppm for methylene CH_2 . The multiplet observed at 2.26-2.29 ppm was assigned to protons at C-5,5' and C-6,6'. The four methyl groups resonated as singlet at 1.02 and 1.08 ppm respectively. The ^1H NMR spectrums of **6(b-k)** is less or more the same. The momentous features are the appearance of singlets for chelating OH at 12.17-11.95 ppm in almost all compounds, indicate that cyclodehydration failed to occur. The methylene groups gave multiplet in most of the compounds at 2.36-2.01 ppm. The appearance of singlet between 3.01-5.42 ppm was assigned to methine proton at C-4, which is a confirmatory peak.

The aromatic ring protons were observed at 6.95-8.15 ppm and J value were found to be in accordance with substitution pattern on phenyl ring.

In case of compound **6l** the appearance of singlets at 7.26, 6.30, and 5.95 ppm was assigned to the protons in the furfuryl ring. The confirmatory peaks resonated at 12.17 ppm was assigned to chelating OH group and 5.41 as singlet to proton at C-4. The representative spectra of **6b** and **6f** is given below

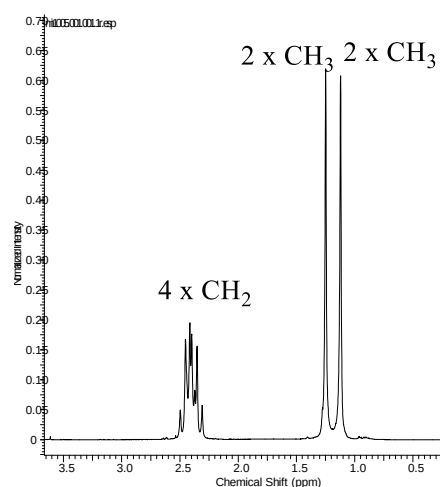


Fig 3.1. Representative signals of CH_2 & CH_3 in the ^1H NMR spectra

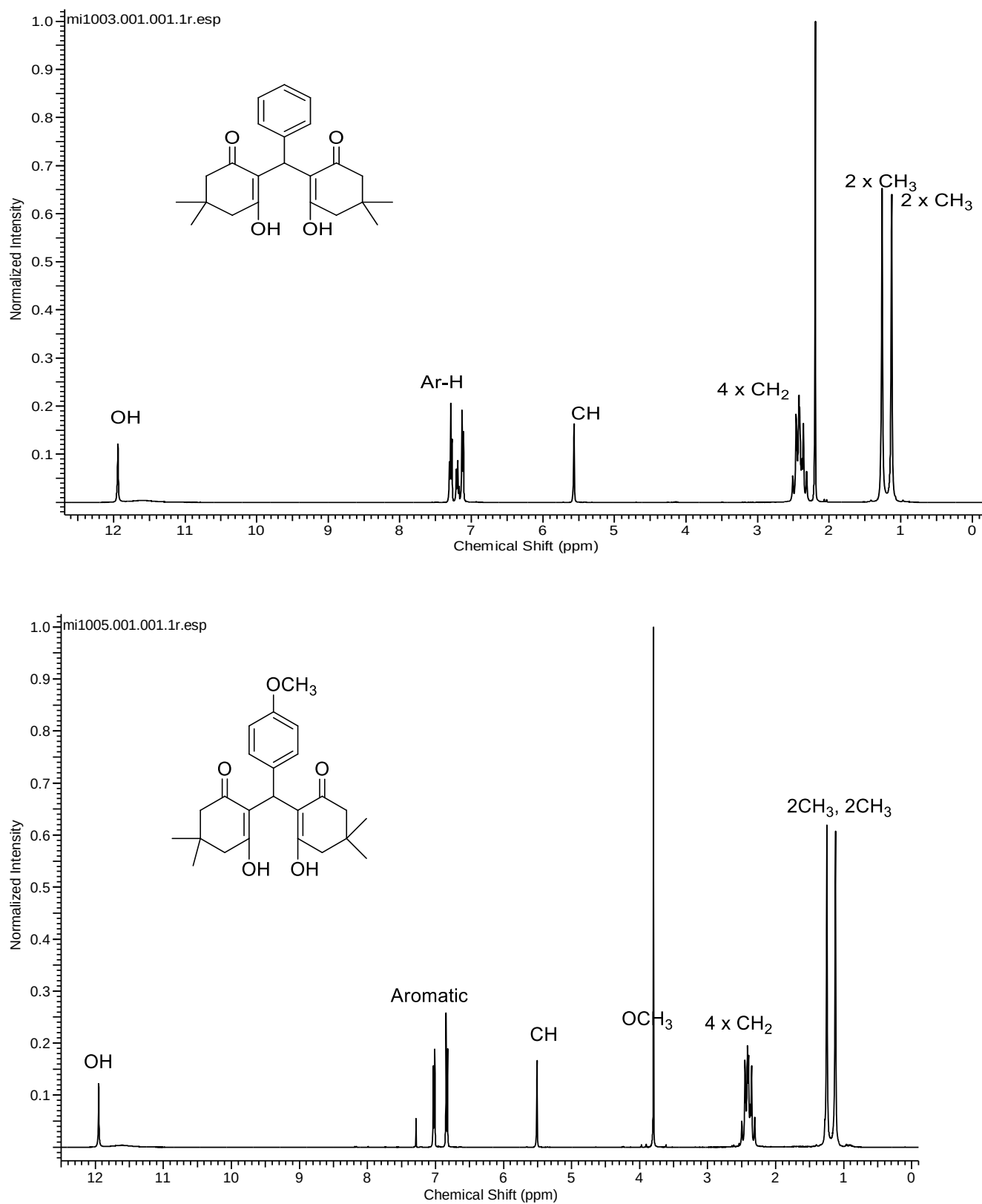
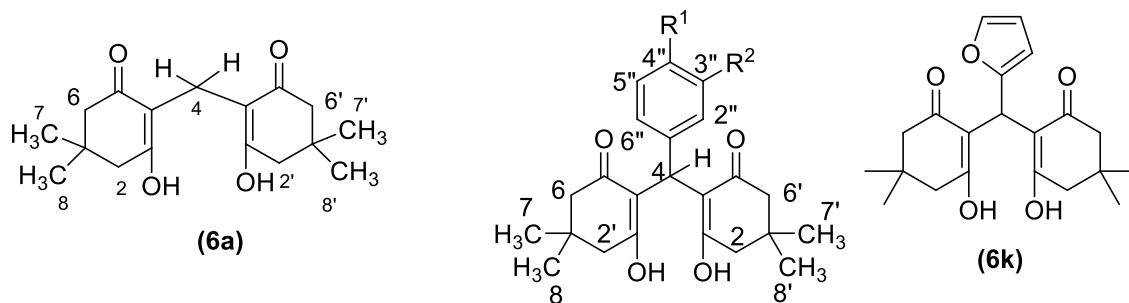


Fig 3.2. Representative ^1H NMR spectrum of **6b** and **6f** in CDCl_3

Table 3.5. ^1H NMR spectral data of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **6(a-l)**

Compd.	$\delta(\text{ppm})$, Integration, multiplicity and coupling constants(J)									
	H-4'	H-2'	H-6'	H-3'	H-5'	OH	C-4	C-2, 2' C-6,6'	C-7,7' C-8,8'	R
6a	---					12.1 (s, 2H)	3.13 (s, 1H)	2.26-2.29 (m, 8H)	1.02 (s, 6H) 1.08 (s, 6H)	---
6b	7.12 – 7.41 (m, 5H)					11.95 (s, 2H)	5.58 (s, 1H)	2.60–2.38 (m, 8H)	1.38 (s, 6H) 1.23 (s, 6H)	---
6c	7.18–7.16 (d, J = 8.4 Hz, 2H)		6.93 (d, J = 8.4 Hz, 2H)		11.91 (s, 2H)	5.46 (s, 1H)	2.43–2.23 (m, 8H)	1.13 (s, 6H) 1.02 (s, 6H)	---	
6d	-- -	7.19 (d, J = 8.4 Hz, 2H)	6.97 (d, J = 8.4 Hz, 2H)		11.80 (s, 2H)	5.41 (s, 1H)	2.42–2.21 (m, 8H)	1.11 (s, 6H) 1.08 (s, 6H)	---	
6e	-- -	6.65 (d, J = 8.4 Hz, 2H)	7.45 (d, J = 8.4 Hz, 2H)		11.81 (s, 2H)	5.39 (s, 1H)	2.40–2.21 (m, 8H)	1.13 (s, 6H) 1.04 (s, 6H)	R ¹ =OH 5.18, 1H)	
6f	-- -	6.85 (d, J = 7.8 Hz, 2H)	7.14 (d, J = 7.8 Hz, 2H)		11.98 (s, 2H)	5.49 (s, 1H)	2.44–2.24 (m, 8H)	1.23 (s, 6H) 1.14 (s, 6H)	R ¹ =OCH ₃ 3.71(s,3H)	
6g	7.99 -7.94 (m, 2H) 7.40 -7.30 (m, 1H), 7.18 (s, 1H)					11.91 (s, 2H)	5.45 (s, 1H)	2.44–2.25 (m, 8H)	1.21 (s, 6H) 1.06 (s, 6H)	R ² =NO ₂
6h	-- -	8.06 (d, J = 7.8 Hz, 2H)	7.15 (d, J = 7.8 Hz, 2H)		11.84 (s, 2H)	5.46 (s, 1H)	2.43–2.16 (m, 8H)	1.23 (s, 6H) 1.10 (s, 6H)	R ¹ =NO ₂	
6i	7.12 (m, 3H, Ar-H); 6.93 (s 1H, Ar-H)					12.02 (s, 2H)	4.93 (s, 1H)	2.51–2.36 (m, 8H)	1.16(s, 6H) 1.26(s, 6H)	R ² =OH 5.55(s,1H)
6j	6.74 (d, J = 6.2 Hz, 1H, Ar-H), 6.69 (t, J = 6.6Hz, 2H, Ar-H)					11.92 (s, 1H)	5.42 (s,1H)	2.27–2.48 (m, 8H)	1.17 (s, 6H) 1.03 (s, 6H)	R ¹ =OCH ₃ 3.69
6k	-- -	7.02 (d, J = 8.0 Hz, 2H)	6.90 (d, J = 8.0 Hz, 2H)		11.89 (s, 2H)	5.42 (s,1H)	2.40–2.20 (m, 8H)	1.15 (s, 6H) 1.02 (s, 6H)	R ¹ =CH ₃ 2.23(s,3H)	
6l	7.26 (m, 1H, CH),6.30 (m, 1H, CH) 5.95 (m, 1H, CH)					12.17 (s, 2H)	5.41 (s,1H)	2.36 (brs, 8H)	1.18 (s, 6H) 1.09 (s, 6H)	2-furfuryl

(300 or 400 MHz)

3.7.3. ^{13}C NMR spectral study

The ^{13}C NMR spectra further strengthened the structure of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) which displayed signals in the aliphatic, aromatic and carbonyl regions. For the basic skeleton as indicated in the structure, six quaternary carbons signals and one tertiary carbon (C-9) confirmed the formation of the desired molecules. The most downfield carbonyl carbon appeared at 192-190 ppm and the quaternary carbon C-1, 1'' having hydroxyl group appeared at 189-190 ppm confirmed that cyclodehydration has failed to occur. Another confirmatory signal for such class of compound is the appearance of tertiary carbon C-4 at between 30 and 32 ppm. In the most off field region the two methyl groups C-7' and C-7'' attached to the C-7 resonates signals in the typical aliphatic region at 28.1 and 27.1 respectively. The aromatic ring carbons were visible in the typical aromatic region as presented in the table 3.6. The representative spectrum for **3b** is given below.

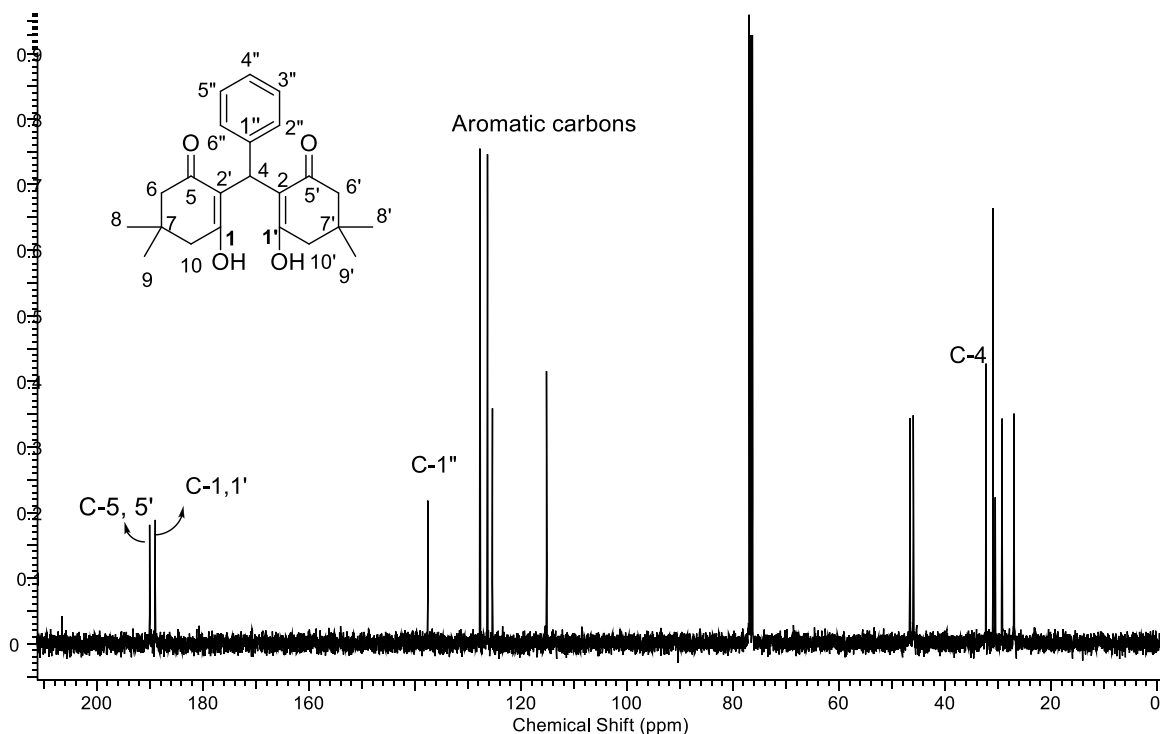
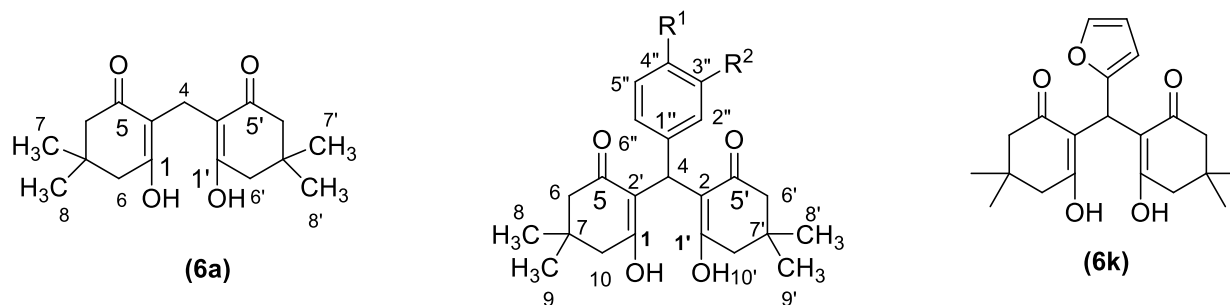


Fig. 3.3. Representative ^{13}C -NMR spectrum of compound **6b**

Table 3.6 ^{13}C NMR spectral data of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **6(a-l)**

^{13}C NMR spectral data											
Compd.	R	C-5,5'	C-1,1'	C-2,2'	C-6,6'	C-10,10'	C-4	C-7,7'	C-8'-8	C-9,9'	Aromatic
6 a		189.1	188.60	46.09	47.2	---	30.90	26.5	27.08		
6 b	----	190.9	190.1	118.1	43.5	43.5	26.5	25.8	24.5	23.1	139.3, 124.3, 124.2, 12.4
6 c	R ¹ = F	190.6	189.0	116.2	47.7	46.6	32.5	26.8	27.6	23.0	138.3, 134.5, 133.5, 120.1
3 d	R ¹ = Cl	190.1	189.8	115.3	47.9	46.7	32.4	23.0	28.7	27.7	139.2, 136.5, 132.3, 119.9
6 e	R ¹ = OH	190.2	189.8	115.4	47.5	47.0	31.2	29.0	28.7	27.5	140.2, 132.5, 129.4, 120.4
6 f	R ¹ = OCH ₃ 56.91	191.0	190.4	115.7	48.5	47.2	30.9	28.4	27.1	26.9	139.6, 133.5, 130.3, 120.7

(Continued)

¹³C NMR spectral data of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives 6(a-l)

Compd.	R	C-5,5'	C-1,1'	C-2,2'	C-6,6'	C-10,10'	C-4	C-7,7'	C-8'-8	C-9,9'	Aromatic
6h	R ¹ = NO ₂	191.0	189.8	114.7	49.5	47.3	31.1	29.8	27.6	26.5	140.2, 132.5, 129.3, 122.8
6i	R ² = OH	191.4	189.9	119.8	47.1	44.3	32.4	30.4	27.1	23.2	158.1, 134.5, 133.2, 132.4, 132.2
6j	R ¹ = (OCH ₃), 55.86	189.0	188.7	111.5	47.8	47.4	31.8	31.1	29.8	27.5	147.1, 143.2, 135.1, 124.1, 118.8, 118.5
6k	R ¹ = CH ₃ 20.56	190.0	189.1	110.6	48.5	48.3	30.6	30.9	26.8	25.7	139.6, 138.6 133.8, 131.4, 118.7
6l	2-furfuryl	192.0	190.6	110.2	49.2	47.2	29.9	28.9	25.7	23.9	154.2 (=C-O-C) 112.1, 110.5, 106.7

3.7.4. CHN and Mass spectral study

The structure of synthesized 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives were further confirmed jointly by elemental analysis and EIMS spectra data. The calculated and observed data was in agreement as displayed in table 3.7.

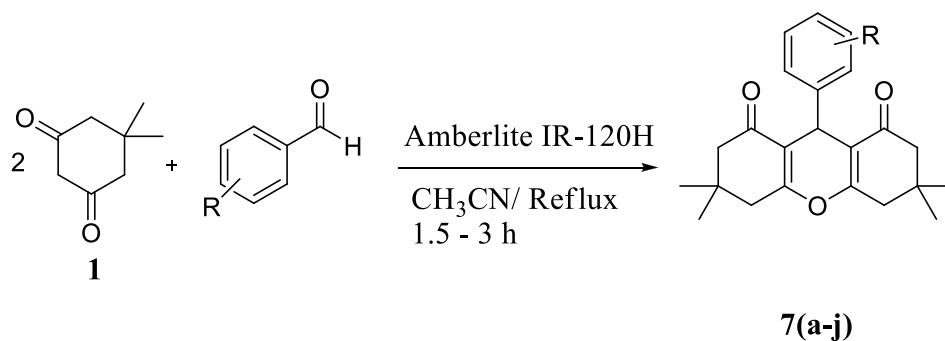
Table 3.7. CHN and EIMS data of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **6 (a-l)**

Compd.	R	Calcd (%)		Observed (%)		Mol. F	Mol. Wt (Calcd)	*M. Wt. Observed (M+%)
		C	H	C	H			
6a	H	69.84	8.27	69.89	8.19	C ₁₇ H ₂₄ O ₄	292.14	292.3(100.0)
6b	C ₆ H ₅ -	74.97	7.66	75.10	7.56	C ₂₃ H ₂₈ O ₄	368.20	368.3 (60.1)
6c	4-F-C ₆ H ₄ -	71.48	7.04	71.50	7.09	C ₂₃ H ₂₇ FO ₄	386.10	386.2 (80.2)
6d	4-Cl-C ₆ H ₄ -	68.56	6.75	68.61	6.67	C ₂₃ H ₂₇ ClO ₄	402.16	402.3 (86.1)
6e	4-OH-C ₆ H ₄ -	71.85	7.34	71.80	7.42	C ₂₃ H ₂₈ O ₅	384.19	384.2 (90.1)
6f	4-OCH ₃ - C ₆ H ₄ -	72.34	7.59	72.39	7.62	C ₂₄ H ₃₀ O ₅	398.21	398.3 (100.0)
6g	3-NO ₂ -C ₆ H ₄ -	66.81	6.58	66.85	6.63	C ₂₂ H ₂₇ NO ₆	413.18	413.2 (37.1)
6h	4-NO ₂ -C ₆ H ₄ -	66.81	6.58	66.90	6.63	C ₂₂ H ₂₇ NO ₆	413.18	413.2(49.2)
6i	3-OH-C ₆ H ₄	71.85	7.34	71.90	7.51	C ₂₃ H ₂₈ O ₅	384.19	384.3 (90.1)
6j	4-OH,3- OCH ₃ -C ₆ H ₄ -	69.54	7.30	69.66	7.27	C ₂₄ H ₃₀ O ₆	414.20	414.3 (26.40)
6k	4-CH ₃ -C ₆ H ₄ -	75.36	7.91	75.41	7.87	C ₂₄ H ₃₀ O ₄	382.21	382.2 (91.2)
6l	2-furfuryl	70.37	7.31	70.40	7.27	C ₂₁ H ₂₆ O ₅	358.18	358.2 (68.2)

*Molecular weight (M+%) (Relative abundance)

3.8 Synthesis and characterization of 1,8-dioxo-octahydroxanthene derivatives 7(a-j)

After the successful utilization of dimedone as an active methylene component for the synthesis of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one), the study was extended towards synthesis of 1,8-dioxo-octahydroxanthenes. The 1,8-dioxo-octahydroxanthene derivatives were synthesized by the condensation and cyclodehydration reaction of dimedone **1** with aromatic aldehydes in acetonitrile in the presences of Amberlite IR-120H as a solid acid catalyst at reflux temperature for 1.5-3 h. This a novel one-pot combination using Amberlite IR-120H as catalyst and acetonitrile as solvent not only preserves the simplicity but also consistently gave the corresponding product in good to excellent yield (shown in table 3.8). The scope and generality of this one-pot synthesis of 1,8-dioxooctahydroxanthene derivatives through the Knoevenagel and Michael addition reaction is illustrated with different substituted aromatic aldehydes in scheme 3,3.



Scheme 3.3. Synthesis of 1,8-dioxo-octahydroxanthene derivatives using Amberlite IR-120H

Table 3.8 Amberlite IR-120H catalyzed synthesis of 1,8-dioxo-octahydoroxanthene derivatives and its physical data **7(a-j)**

Entry	Compd.	R	Time (h)	Yield %	R _f **	m.p. (°C)	
						Observed	Lit.
55	7a	3-NO ₂ -	3	80	0.47	168–170	168–170 ²⁹
56	7b	4-F-	1.5	94	0.51	218-222	---
57	7c	4-Cl-	1.5	90	0.51	228-230	230-232 ⁵⁷
58.	7d	4-OH-	3	75	0.41	243-245	246–248 ²⁹
59	7e	4-NO ₂ -	3	70	0.45	222-225	221-222 ⁵⁷
60	7f	4-N(CH ₃) ₂	3	79	0.45	230-234	224–226 ²⁹
61	7g	4-OH, 3-OCH ₃ -	2.9	86	0.40	214-215	226-228 ²⁹
62	7h	4-OCH ₃ -	2.5	73	0.52	250-254	239-240 ⁵⁷
63	7i	H	1.5	72	0.56	199-202	198-200 ⁵⁷
64	7j	2-furfuryl	2	82	0.51	75-78	---

^aReaction conditions: Dimedone (**1**) (2 mmol), aromatic aldehyde (1 mmol) and Amberlite IR-120H (200 mg) were refluxed in acetonitrile for the specified time. The reaction was monitored by TLC. After completion of reaction the catalysts was filtered out and the crude product was crystallized from ethanol or purified by column chromatography using ethyl acetate: *n*-Hexane. **TLC Solvent system R_f: Ethyl acetate: *n*-Hexane; 3:7, on Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at λ=254nm

3.8.1. Optimization of reaction condition

Several reaction condition parameters were optimized to improve the yield of the target molecules. The reaction involving *m*-nitro benzaldehyde, (entry **1**) with dimedone was used to check standardization of reaction condition and to identify the role of Amberlite IR-120H as

catalyst. Initially, the reaction (run 1) was performed in the absence of catalyst and solvent. No desired product was detected even after heating at 90 °C. With amberlite IR-120H no cyclised product was detected (run 2, table 3.9). However, when catalytic amount of Amberlite IR-120H (100 mg/0.5 mmol of dimedone) was added and reaction was carried out at room temperature for 24 h, bis dimdone (open chain form) derivative was obtained (run 3 table 3.9). The desired product **7a** was obtained at reflux temperature with excellent yield (80%) (run 4, table 3.9). In order to find out the optimum conditions in respect of medium, the model reaction was checked in different solvents (run 5-8). Among the tested solvents like water, ethanol, chloroform and acetonitrile, the later gave the best result in term of isolated desired product.

Table 3.9 Catalytic efficiency of Amberlite IR-120H in various solvents over synthesis of 1,8-dioxo-octahydroxanthene

Run	Solvent	Catalyst	Temp (°C)	Time (h)	Yield ^d (%)
1.	---	---	90	7	NP
2.	CH ₃ CN	---	90	6	NP
3.	CH ₃ CN	Amberlite IR-20H	R.T	24	NP
4.	Water	Amberlite IR-20H	reflux	7	mixture
5.	Ethanol	Amberlite IR-20H	reflux	8	59
6.	CHCl ₃	Amberlite IR-20H	reflux	7	40
7.	CH ₃ CN	Amberlite IR-20H	reflux	3	80

***Note:** Run 1-7 represents same model reaction, carried out in different solvent using Amberlite IR-120H in 200 mg/1.0 mmol of dimedone. ^a Isolate yield. NP = not the desired product.

Continuing the optimization of reaction condition in respect of loading catalyst, the reaction was carried out with different amount of Amberlite IR-120H. It was evaluated with different

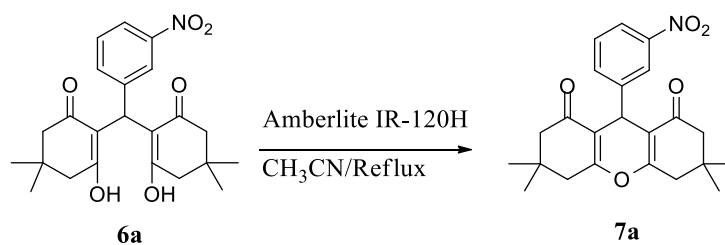
loading, 100, 150, 200 and 250 mg/1.0 mmol of dimedone. By increasing the amount of Amberlite IR-120H up to 200 mg/mmol, the yield of the product **7a** was improved up to 90 % (run 3, table 3.10). However, it has been found out that further increase in the amount of catalyst has adverse effect on the yield of product. (Table 3.10).

Table 3.10. Effect of loading of catalyst over synthesis 1,8-dioxo-octahydroxanthene (**7a**)

Run	Amberlite IR-120H (mg)	Time (h)	Yield* (%)
1.	100	3	51
2.	150	2	60
3.	200	2	90
4.	250	3	80

*isolated yield

Another strong evidence for the role of Amberlite IR-120H as catalyst in the mentioned reaction came into insight when 2,2'-(3-nitrophenylmethylene) bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (**6g**) was heated at reflux temperature in CH₃CN the desired compound **7a** obtained. It indicated that catalyst has played a vital role in the cyclodehydration steps for the formation of 1, 8-dioxo-octahydroxanthene derivatives. Among the solvent the role of CH₃CN was also important in the trapping of desired product (scheme 3.4).



Scheme 3.4 Synthesis of 9-(3'-nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (**7a**)

The recyclability of the catalyst was also checked by performing three consecutive model reactions. The already used catalyst was washed with additional 15 ml of ethyl acetate and dried at 130 °C for 30 mins before further use. In the three consecutive model reactions Amberlite IR-120H showed the same reactivity as fresh one without any significant loss in its activity. (Fig 3.4).

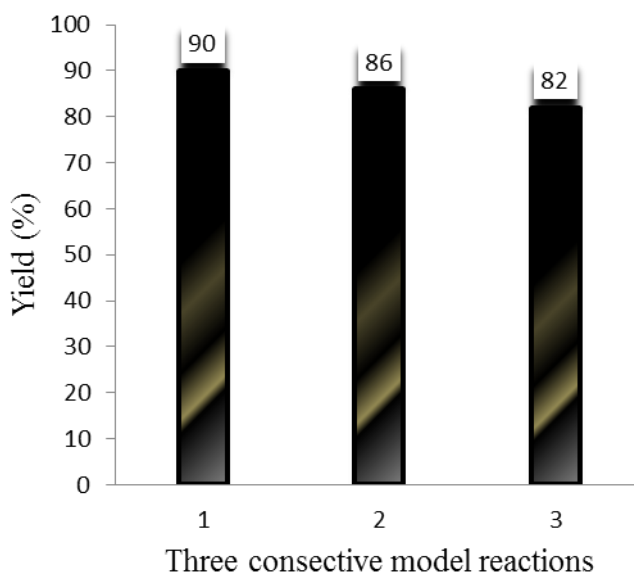
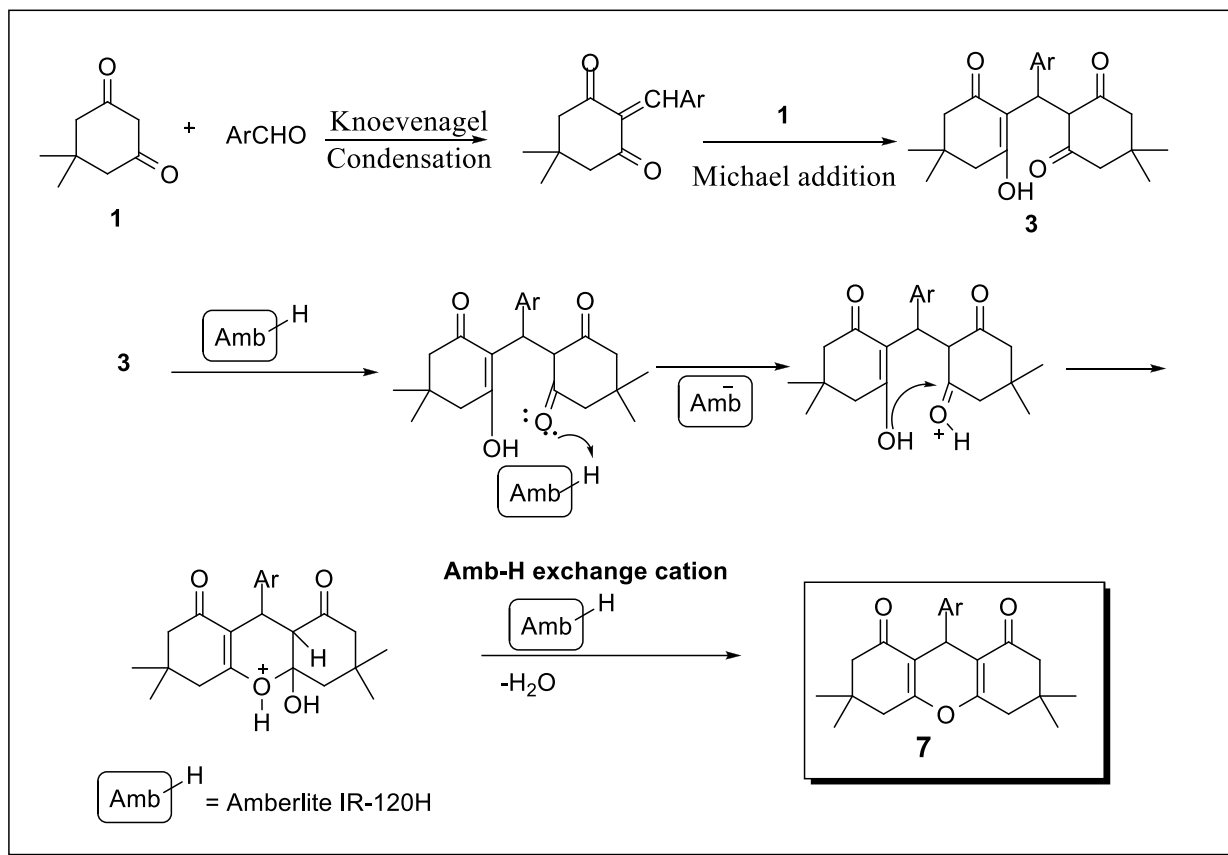


Fig. 3.4. Recyclability of Amberlite IR-120H as catalyst in the synthesis of **7a**

3.9. Proposed mechanism for the formation of 1,8-dioxo-octahydroxanthene

Amberlite IR-120H is a styrene divinylbenzene copolymers having sulphonic group with total cation exchanger efficiency 1.8 meq/1 ml. It is commercially available in the form of amber beads. It has been used for condensation reaction of various aromatic aldehydes with 1,3-diketone (Dimedone) to afford 1,8-dioxo-octahydroxanthene. The proposed mechanism showed that the product development occurs through Knoevenagel condensation, Michael addition and cyclodehydration of dimedone with various aldehydes as shown below.



Scheme 3.5. Proposed mechanism for the Amberlite IR-120H mediated reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**) with aromatic aldehydes (**2**)

The structure of the entire products was established from their spectral data (IR, ^1H , ^{13}C -NMR, EIMS and elemental analysis).

3.10 Spectral discussion of 1,8-dioxo-octahydroanthene derivatives 7(a-j)

3.10.1 IR spectral study

The various functional groups like carbonyls, C-H aromatic, C-H bending and in some cases where phenol OH were present were confirmed by their characteristic frequency in the IR spectra. The confirmatory band of carbonyl group was appeared in the range of $1643\text{--}1690\text{ cm}^{-1}$. In case of **7d** and **7g** OH stretching band appear at $3300\text{--}3426\text{ cm}^{-1}$. The C-H asymmetrical and bending

frequencies were clearly observed just below 3000 and 900-1043 cm^{-1} respectively. The spectral data has been summarized in table 3.11.

Table 3.11 FT IR Spectral data of 1,8-dioxo-octahydroxanthene derivatives **7(a-j)**

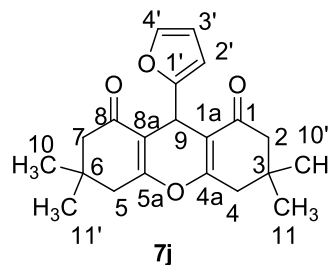
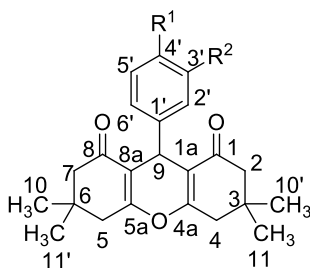
Compd.	R	$\nu(\text{Cm}^{-1})$						
		=C-H	C-H	C=O	C=C	C-O	Others	
7a	3-NO ₂ -C ₆ H ₄ -	3025	2954	1676	1620	1124	C-N	1454
7b	4-F-C ₆ H ₄ -	3010	2956	1680	1602	1195	-C-F	694
7c	4-Cl-C ₆ H ₄ -	3060	2955	1685	1605	1198	C-Cl	585
7d	4-OH-C ₆ H ₄ -	3086	2970	1670	1600	1208	Ar-OH	3344
7e	4-NO ₂ -C ₆ H ₄ -	3065	2958	1686	1606	1197	----	---
7f	4-N(CH ₃) ₂ -C ₆ H ₄ -	3020	2967	1643	1589	1195	---	---
7g	4-OH,3-OCH ₃ -C ₆ H ₄ -	3038	2938	1676	1627	1134	Ar-OH	3426
7h	4-CH ₃ -C ₆ H ₄ -	3032	2915	1647	1597	1203	---	---
7i	C ₆ H ₅ -	3047	2954	1674	1611	1143	----	----
7j	2-furfuryl	---	2921	1690	1561	1149	---	---

3.10.2 ¹H NMR spectral study

In the ¹H NMR spectrum of 1,8-dioxo-octahydroxanthene the most prominent signals to support the structure and confirm the formation of heterocyclic ring is the disappearance of peaks from 12.17-11.95 ppm. It ensured that 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) formed during reaction have been transformed in to 1,8-dioxo-octahydroxanthene. The singlet resonated at 4.41-5.44 ppm is due to the proton at C-9, which ensured the Knoevenagel condensation took placed. The methylene group at C-2 and C-7 appeared as singlet at 2.43-2.46 ppm, almost at the same pattern in all compounds, while

methylene at C-4, and 5 resonated as multiplet between at 2.54-2.01 due to ABq, system. The appearance of singlet in the typical aliphatic region between 0.97-1.18 δ ppm is due to the methyl protons attached to C-3 and C-6. The aromatic protons were visible in their typical regions (8.01-6.57 ppm) with appropriate splitting pattern and integration ratio depending on the substituents on aromatic ring. In case of compound **7j** the multiplet exhibited at 7.35 ppm is due to H-4'. The other tow multiplet is due to H-2' and H-3' in accordance to their coupling pattern. The confirmatory peaks for compound **7j** appeared at 4.64 ppm due to the proton at C-9.the methyl and methin carbon also resonated at its corresponding region as presented in the table

3.12

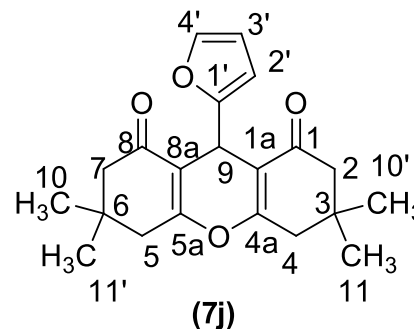
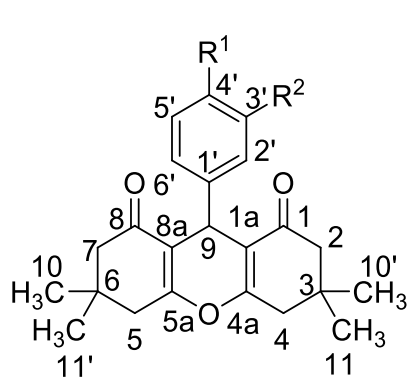
Table 3.12 ^1H NMR spectral data of 1,8-dioxo-octahydroxanthene derivatives **7(a-l)**

Compd.	* δ (ppm), Integration, multiplicity and coupling constants(J)								
	H-4'	H-2'	H-6'	H-3'	H-5'	C-9	C-7,2	C-5 and C-4	C-10,10' C-11,11'
7a	7.96-7.99 (m, 2H)		7.78 (m, 1H)	---	7.39 (m,1 H)	4.81 (s,1H)	2.48 (s,4H)	2.20, 2.12 dd (J = 16.5, 16.0, Hz, 4H)	0.97 (s, 6H) 1.09 (s, 6H)
7b	---	7.241-7.218 (t, J = 8.4Hz, 2H)		6.88-6.85 (t, J = 9.0Hz,2H)		4.70 (s,1H)	2.44 (s,4H)	2.17(ABq, J = 16.6,Hz, 4H)	0.96 (s, 6H) 1.08 (s, 6H)
7c	---	7.02 (d, J = 8.4Hz, 2H)		6.99 (d, J = 8.4Hz, 2H)		5.45 (s, H,	2.44 (s, 4H)	2.18, 2.13 (ABq, J = 16.6,Hz, 4H)	1.07 (s, 6H) 1.08 (s, 6H)
7d	---	6.98 (d, J = 8.5 Hz, 2H)		7.70 (d, J = 8.5 Hz, 2 H)		4.35 (s,1H,	2.43 (s, 4H)	2.28, 2.23 (ABq, J = 13.5,Hz, 4H)	1.41 (s, 6H) 1.35 (s, 6H)
7e	---	8.01 (d, J = 8.6 Hz, 2H)		7.42 (d, J = 8.6 Hz, 2H)		4.78 (s,1H,	2.46 (s, 4H)	2.15, 2.13 ABq, J = 16.0Hz, 4H)	0.95 (s, 6H) 1.08 (s, 6H)
7f		6.57 (d, J = 7.0 Hz, 2H,		6.56 (d, J = 7.0 Hz, 2H)		4.50 (s, 1H)	2.40 (s, 4H)	2.34, 2.18 ABq, J = 16.6Hz, 4H)	0.97 (s, 6H) 1.06 (s, 6H)
7g	---	7.08 (s, 1H, Ar-H), 6.78 (d, J = 9.2 Hz, 1H, Ar-H), 6.57 (t, J = 10.5 Hz, 1H, Ar-H)				4.66 (s, 1H)	2.45 (s, 4H)	2.54-2.15 (ABq, J = 16.2 Hz, 4H)	1.07 (s, 6H) 1.15 (s, 6H)
7h		7.19 (d, J = 10.5 Hz, 2H)		6.74 (d, J = 11.0 Hz, 2H)		4.69 (s, 1H)	2.45 (s, 4H)	2.25-2.15 (ABq, J = 16.7Hz,4H)	0.99 (s, 6H) 1.09 (s, 6H)
7i	7.29-7.08 (m, 5H, Ar-H)					4.41 (s, 1H)	2.46 (s, 4H)	2.25-2.14 (ABq, J = 16.6Hz,4H)	1.13 (s, 6H) 1.07 (s, 6H)
7j	7.35 (m, 1H, H-4'), 6.31 (m, 1H, H-2') 6.14 (m, 1H, H-3'),					4.64 (s, 1H)	2.41 (s, 4H)	2.21 (s, 4H)	1.15 (s, 6H) 1.04 (s, 6H)

*500 and or 600 MHz

3.10.3 ^{13}C NMR spectral study

The structure of 1,8-dioxo-octahydoroxanthene derivatives **6(a-j)** were further confirmed from their ^{13}C NMR spectra. The obvious difference between the 2,2'-(arylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydoroxanthene derivatives **7(a-j)** is the disappearance of signals at 189-190 ppm and appearance of additional signal at near 162 ppm for **C-5a, 4a** ensured that cyclodehydration has occurred. The carbonyl carbons exhibited at its typical region 196-195 ppm. The two quaternary carbons resonated at 115-113 ppm. The methyl and methine carbon also resonated at its corresponding region as indicated in the table 3.13.

Table 3.13 ^{13}C NMR spectral data of 1,8-dioxo-octahydoroxanthene derivatives **7(a-j)**

^{13}C NMR spectral data of 1,8-dioxo-octahydoroxanthene derivatives 7(a-j)										
Compd.	C-8,1	C-5a, 4a	C-8a, 1a	C-7,2	C-5,4	C-9	C-6,3	C-11,11'	C-10,10'	Aromatic carbons
7a	196.9	162.9	115.7	50.6	40.8	32.2	32.0	29.1	27.2	146.2, 135.7, 128.7, 122.4, 121.6, 120.5
7b	196.3	162.2	117.7	50.7	40.8	32.1	31.2	29.2	27.2	160.2, 139.9, 122.5, 120.7
7c	196.5	163.5	115.3	49.9	41.8	32.3	31.3	29.5	27.3	136.7, 131.5, 128.3, 128.1,
7d	194.3	162.5	115.5	50.0	42.4	32.7	31.8	29.6	27.8	138.72, 134.76, 129.5, 129.2
7e	196.1	162.9	114.5	50.5	40.8	32.3	32.2	29.2	27.2	151.4, 148.4, 129.3, 123.4

Continued

¹³C NMR spectral data of 1,8-dioxo-octahydoroxanthene derivatives 7(f-j)

Compd.	C-8,1	C-5a, 4a	C-8a, 1a	C-7,2	C-5,4	C-9	C-6,3	C-11,11'	C-10,10'	Aromatic carbons
7f	196.3	162.4	113.6	53.5	40.5	32.2	32.2	29.2	27.2	151.4, 129.7, 128.4
7g	196.6	162.0	115.8	50.7	40.8	32.2	31.3	29.3	27.2	145.4, 144.0, 136.4, 120.3
7h	196.5	163.0	113.4	50.7	40.8	32.3	30.9	29.2	27.3	157.9, 136.4, 129.3, 115.7,
7i	196.3	162.2	115.6	50.7	40.8	32.2	31.8	29.2	27.3	144.0, 128.3, 126.3
7j	195.2	163.1	111.3	50.2	40.1	30.3	29.2	28.3	26.2	140.0 (C-4'), 110.1 (C-3'), 109.9 (C-2'), 101.5 (C-1')

3.10.4 Elemental analysis and mass spectral study

The mass spectra of the synthesized compound were recorded on Finnigan MAT-311A, Germany. The entire compound showed matched mass spectra with calculated values as displayed in the following table 3.14. The elemental analysis was performed on a Carlo Erba Strumentation-Mod-1106 Italy and also found in relation with theoretical value.

Table 3.14 CHN and EIMS data 1,8-dioxo-octahydoroxanthene derivatives **7(a-j)**

Compd.	Mol. F	Calcd (%)		Observed (%)		Mol. Wt (Calcd)	M.Wt. EIMS (M+%)
		C	H	C	H		
7a	C ₂₃ H ₂₅ NO ₅	69.87	6.37	69.92	6.30	395.17	395.2 (74.1)
7b	C ₂₃ H ₂₅ FO ₃	74.98	6.84	75.02	6.78	368.18	368.2 (98.2)
7c	C ₂₃ H ₂₅ ClO ₃	71.77	6.55	71.70	6.58	384.15	384.2 (100.0)
7d	C ₂₃ H ₂₆ O ₄	75.38	7.15	75.30	7.10	366.18	366.2 (34.9)
7e	C ₂₃ H ₂₅ NO ₅	69.86	6.37	69.80	6.39	395.18	395.2 (67.1)
7f	C ₂₅ H ₃₁ NO ₃	76.30	7.94	76.38	8.09	393.23	393.3 (21.6)
7g	C ₂₄ H ₂₈ NO ₄	72.70	7.12	73.00	7.09	396.19	396.3 (12.2)
7h	C ₂₄ H ₂₈ O ₄	75.76	7.42	75.70	7.46	380.20	380.2 (91.2)
7i	C ₂₃ H ₂₆ O ₃	78.83	7.48	78.80	7.44	350.19	350.1 (95.3)
7j	C ₂₁ H ₂₄ O ₄	74.09	7.11	74.04	7.17	340.17	340.3 (29.7)

The fragmentation pattern and EIMS Spectra of compound **7a** is given below, which confirmed the formation of the target molecule.

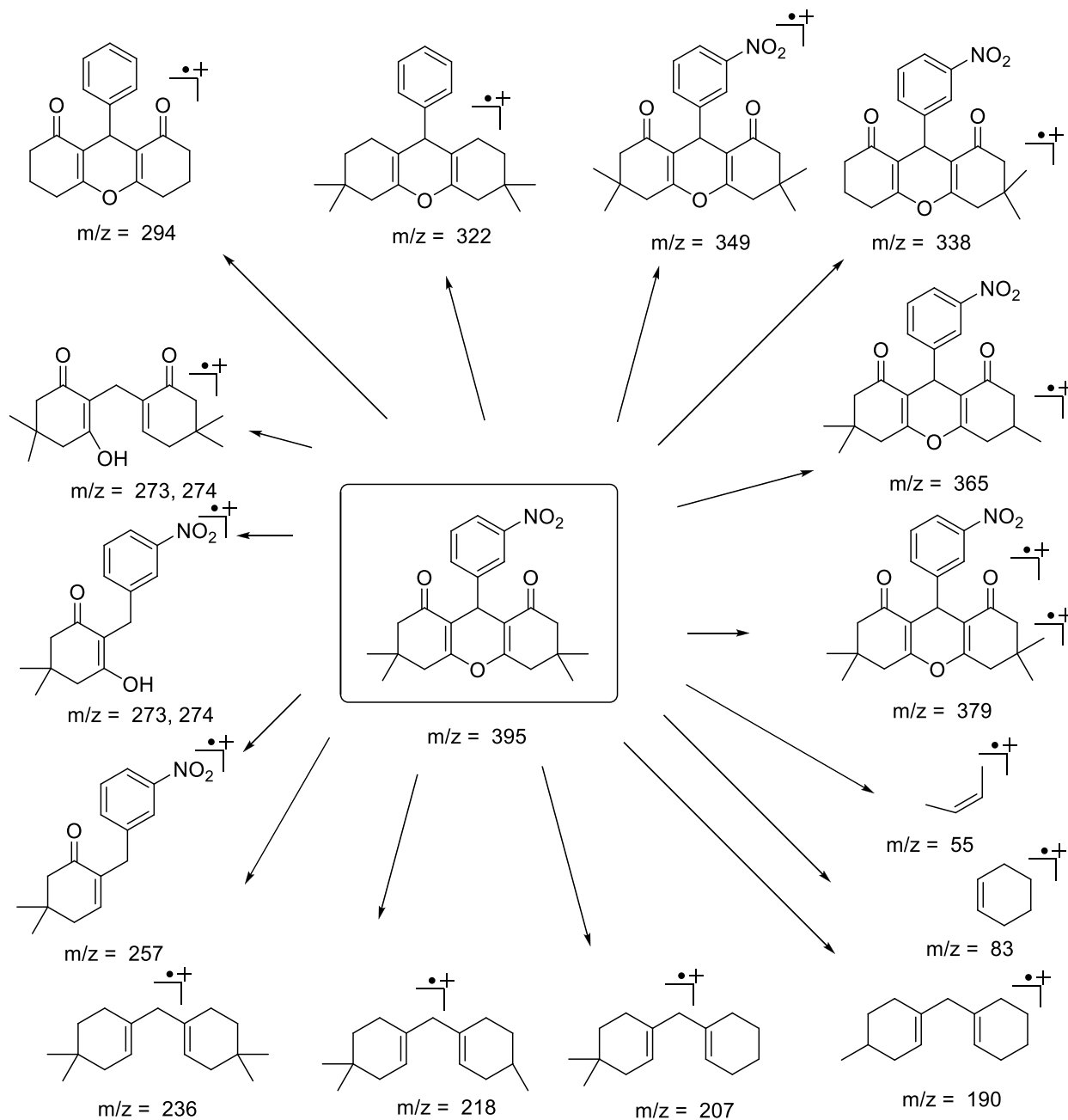


Fig 3.5. Mass fragmentation pattern for **7a**

3.11 Experimental

3.11.1 Instrumentation

The commercially available solvents were used after employing standard method of purification. All the glass wares with standard quick fit joints were used throughout the work after cleaning and drying at 120 °C. 4-Chlorobenzaldehyde was purchased from ACROS ORGANICS and other aromatic aldehyde were Merck or Sigma Aldrich. The 5,5-dimethyl-1,3-cyclohexane commercially known as Dimedone was purchased from TCI Chemical supplier located in Karachi (Pakistan). Melting points of the synthesized compounds were determined in an open capillary tube by using electro thermal melting point apparatus (England) and were uncorrected. Structures of purified products were determined by ^1H (400, 300, 500 and 600 MHz for different samples in CDCl_3) and ^{13}C -NMR using TMS as internal standard. IR vibration frequencies were measured using Thermo-Scientific, Nicolet 380 FTIR while the CHN analysis was performed on a Carlo Erba Strumentation-Mod-1106 Italy.) Electron impact mass spectra (EI MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

3.12 General procedure for the synthesis of 2,2'-(arylmethylene)bis(3- hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives 6 (a-l)

The mixture of 5,5-dimethyl-1,3-cyclohexanedione (Dimedone, 2 equiv.), respective aldehydes (1 equiv.) and MgCl_2 (5.2 mmol, 500 mg) as catalyst in dichloromethane (8 time w/v) was stirred at room temperature till the completion of reaction. The reaction progress was monitored by TLC (Ethyl acetate: *n*-Hexane 3:7). After sufficient amount of product formation and decreased in concentration of starting materials or completion of reaction as observed on

TLC, the reaction was stopped. The mixture was poured into ice cold water washed with brine, dried over anhydrous Na_2SO_4 and concentrated the organic layer as crude product. The column chromatography was used to obtain suitable pure product for spectroscopic service in order to confirm the structure of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives **6(a-l)**. The spectral data of the synthesized molecules are given below.

2,2'-methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**6a**)

The title compound **3a** was synthesized by using the above mentioned general procedure from paraformaldehyde and dimedone.

White solid; yield: 60%; mp: 88-90 °C; **IR** (neat, ν_{max} , cm^{-1}): 3630

(OH, str), 2993 (C-H, str), 1795 (C=O), 1575 (C=C), 1367 (C-H, bend),

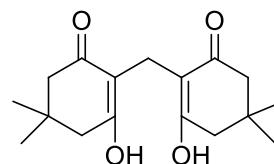
871 (C-C); **^1H NMR** (CDCl_3 , 300 MHz): δ ; 3.13 (s, 1H, CH) 2.26-2.29

(m, 8H, 4 $\times$ CH_2); 1.02 (s, 6H, 2 $\times$ CH_3); 1.08 (s, 6H, 2 $\times$ CH_3); **^{13}C**

NMR (CDCl_3 , 75MHz): δ ; 189.1 (2C=O), 188.60 (2C=C-OH), 46.09 (2 CH_2), 47.2 (2 CH_2),

30.90 (CH_2), 30.82 (2 CMe_2), 27.08 (2 CH_3), 26.5 (2 CH_3); **EIMS** (m/z , %): 292.3 (100.0) ($\text{M}^+ + 1$);

Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_4$ (292.14): C, 69.84; H, 8.27; Found: C, 69.89; H, 8.19.



2,2'-(phenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**6b**)

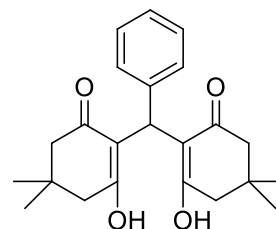
Yellow solid; Yield: 68%; mp: 191-192 °C; **IR** (neat, ν_{max} , cm^{-1}): 3670 (OH, str), 3013 (C-H, aromatic) 2916 (C-H, str), 1683 (C=O), 1595 (C=C), 1361 (C-H,

bend), 896 (C-C); **^1H NMR** (CDCl_3 , 300 MHz): δ ; 11.95 (s, 2H,

OH), 6.82–6.51 (m, 5H, ArH), 5.58 (s, 1H, CH), 2.60-2.38 (m, 8H, 4

$\times$ CH_2), 1.38 (s, 6H, 2 CH_3), 1.23 (s, 6H, 2 CH_3); **^{13}C NMR** (CDCl_3 ,

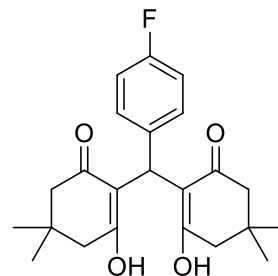
75MHz): δ ; 190.9 (2C=O), 190.1 (2C=C-OH) 139.3, 124.3, 124.2, 118.1, 43.5, 43.5, 26.5, 25.8,



24.5, 24.4, 23.12; **EIMS** (m/z , %): 368.3 (60.1) ($M^+ + 1$); Anal. Calcd for $C_{23}H_{28}O_4$ (368.20) C, 74.97; H, 7.66; Found: C, 75.10; H, 7.56;

2,2'-(4-Fluorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6c)

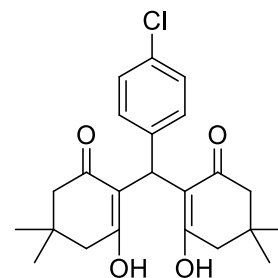
The mentioned molecule was obtained from p-Fluorobenzaldehyde and dimedone by using the general procedure 3.12. White solid; Yield: 80%; mp: 185-187 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3656 (OH, str), 3083 (C-H, aromatic), 2930 (C-H, str), 1780 (C=O), 1606 (C=C), 1368 (C-H, bend), 891 (C-C), 697 (C-F); **^1H NMR** ($CDCl_3$, 300 MHz): δ : 11.91 (s, 2H, OH); 7.18-7.16 (d, J = 8.4 Hz, 2H, Ar-H), 6.93 (d, J = 8.4 Hz, 2H, Ar-H), 5.46 (s, 1H, CH), 2.43-2.23 (m, 8H, 4 x CH_2), 1.13 (s, 6H, 2 x CH_3), 1.02 (s, 6H, 2 x CH_3);



^{13}C NMR ($CDCl_3$, 75MHz): δ : 190.6 (2C=O), 189.0 (C=C-OH), 138.3, 133.5, 139.6, 120.1 (aromatic carbons), 116.2 (2-C=C-OH), 47.7 (2 CH_2), 46.67 (2 CH_2), 32.57 (CH), 23.08 (2 CH_3), 28.80 (2 CH_3), 27.60 (2 CH_3); **EIMS** (m/z , %): 386.2 (80.2) ($M^+ + 1$); Anal. Calcd for $C_{23}H_{27}FO_4$ (386.1): C, 71.48; H, 7.04; Found: C, 71.50; H, 7.09.

2,2'-(4-chlorophenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6d)

White crystals; Yield: 77%; mp: 144-146 °C; **IR** (neat, $\nu_{\max}$, cm^{-1}): 3585 (OH, str), 3010 (C-H, aromatic) 2952 (C-H, str), 1787 (C=O), 1639 (C=C), 1373 (C-H, bend), 891 (C-C), 710 (C-Cl); **^1H NMR** ($CDCl_3$, 300 MHz): δ : 11.80 (s, 2H, OH), 7.19 (d, J = 8.4 Hz, 2H, Ar-H), 6.97 (d, J = 8.4 Hz, 2H, Ar-H), 5.41 (s, 1H, CH), 2.42-2.21 (m, 8H, 4 x CH_2), 1.11 (s, 6H, 2 x CH_3), 1.08 (s, 6H, 2 x CH_3); **^{13}C NMR** ($CDCl_3$, 75MHz): δ : 190.1 (2C=O), 189.8 (C=C-OH), 139.2, 132.3, 130.3, 119.9 (aromatic carbons),



115.3 (2-C=C-OH), 47.9 (2CH₂), 46.7 (2CH₂), 32.4 (CH), 23.0 (2CMe₂), 28.7 (2CH₃), 27.7 (2CH₃); **EIMS** (*m/z*, %): 402.3 (86.1) (M⁺ + 1); Anal. Calcd for C₂₃H₂₇ClO₄ (402.16): C, 68.56; H, 6.75; Found: C, 68.61; H, 6.67.

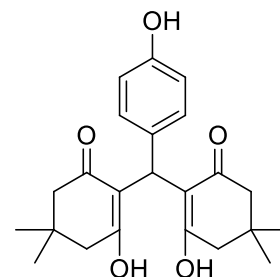
2,2'-(4-hydroxyphenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (6e)

The title compound was synthesised from p-hydroxy benzaldehyde and 5,5- dimethyl-2-cyclohexene-1,3-dione by using the mentioned general procedure 3.12. White solid; Yield: 80 %; mp: 194-196 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹):

3690 (OH, str), 3378 (phenolic OH) 3030 (C-H, aromatic) 2961(C-H, Str), 1798 (C=O), 1650 (C=C), 1382 (C-H, bend), 991 (C-C);

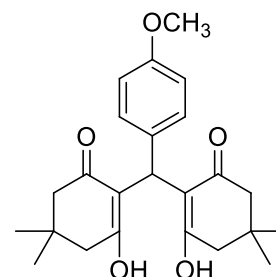
¹H NMR (CDCl₃, 300 MHz), δ : 11.81 (s, 2H, OH), 7.45 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.65 (d, *J* = 8.4 Hz, 2H, Ar-H), 5.39 (s, 1H, CH),

2.40-2.21 (m, 8H, 4 x CH₂), 1.13 (s, 6H, 2 x CH₃), 1.04 (s, 6H, 2 x CH₃); **¹³C NMR** (CDCl₃, 75MHz): δ ; 190.20 (2C=O), 189.86 (C=C-OH), 140.2, 132.5, 129.4, 120.4 (aromatic carbons), 115.4 (2-C=C-OH), 47.5 (2CH₂), 47.0 (2CH₂), 31.27 (CH), 29.0 (2CMe₂), 28.7 (2CH₃), 27.5 (2CH₃); **EIMS** (*m/z*, %): 384.2 (90.1) (M⁺ + 1); Anal. Calcd for C₂₃H₂₈O₅ (384.19): C, 71.85; H, 7.34; Found: C, 71.80; H, 7.42.



2,2'-(4-methoxyphenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (6f)

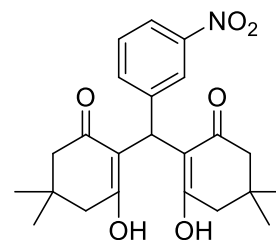
White solid; Yield: 70%; mp: 139-141°C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3490 (OH, str), 3061 (C-H, aromatic) 2972(C-H, Str), 1790 (C=O), 1637 (C=C), 1402 (C-H, Bend), 870 (C-C); **¹H NMR** (CDCl₃, 300 MHz): δ ; 11.98 (s, 2H, OH), 7.14 (d, *J* = 7.8 Hz, 2H, Ar-H), 6.85 (d, *J* = 7.8 Hz, 2H, Ar-H),



5.49 (s, 1H, CH), 3.71 (s, 1H, OCH₃), 2.44-2.24 (m, 8H, 4 x CH₂), 1.23 (s, 6H, 2 x CH₃), 1.14 (s, 6H, 2 x CH₃); ¹³C NMR (CDCl₃, 75MHz): δ; 191.0 (2C=O), 190.4 (C=C-OH), 139.6 133.5, 130.3, 120.7 (aromatic carbons), 115.7 (2-C=C-OH), 56.9 (OMe), 48.5 (2CH₂), 47.2 (2CH₂), 30.9 (CH), 28.4 (2CMe₂), 27.1 (2CH₃), 26.93 (2CH₃); EIMS (m/z, %): 398.3 (100.0) (M⁺+1); Anal. Calcd for C₂₄H₃₀O₅ (398.21): C, 72.34; H, 7.59; Found: C, 72.39; H, 7.62.

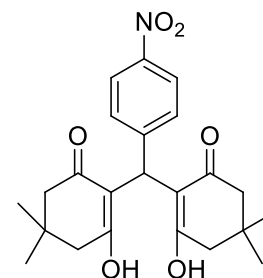
2,2'-(3-nitrophenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (6g)

White solid; Yield: 72%; m.p: 122-124 °C; IR (neat, ν_{max}, cm⁻¹): 3497 (OH, str), 3028 (C-H, aromatic), 2942 (C-H, str), 1797 (C=O), 1608 (C=C), 1411 (C-H, bend), 969 (C-C); ¹H NMR (CDCl₃, 300 MHz): δ; 11.91 (s, 2H, OH), 7.99-7.94 (m, 2H, Ar-H), 7.40-7.30 (m, 1H, Ar-H), 7.18 (s, 1H, Ar-H), 5.45 (s, 1H, CH), 2.44-2.25 (m, 8H, 4 x CH₂), 1.21 (s, 6H, 2 x CH₃), 1.06 (s, 6H, 2 x CH₃); ¹³C NMR (CDCl₃, 75MHz): δ; 191.1 (2C=O), 189.2 (C=C-OH), 148.1 140.5, 132.1, 129.7, 122.20 (aromatic carbons), 113.8 (2-C=C-OH), 47.9 (2CH₂), 47.5 (2CH₂), 32.8 (CH), 31.4 (2CMe₂), 29.1 (2CH₃), 27.2 (2CH₃); EIMS (m/z, %): 413.2 (37.1) (M⁺ + 1); Anal. Calcd. For C₂₂H₂₇NO₆ (413.18): C, 66.81; H, 6.58; N, 3.39. Found: C, 66.85; H, 6.63; N, 3.57.



2,2'-(4-nitrophenylmethylene)bis(3-hydroxy-5,5- dimethyl-2-cyclohexene-1-one) (6h)

White solid; Yield: 84%; mp: 195-197 °C; IR (neat, ν_{max}, cm⁻¹): 3577 (OH, str), 3068 (C-H, aromatic), 2960 (C-H, str), 1795 (C=O), 1624 (C=C), 1387 (C-H, bend), 1005 (C-C); ¹H NMR (CDCl₃, 300 MHz): δ; 11.84 (s, 2H, OH), 8.06 (d, J = 7.8 Hz, 2H, Ar-H), 7.15 (d, J = 7.8 Hz, 2H, Ar-H), 5.46

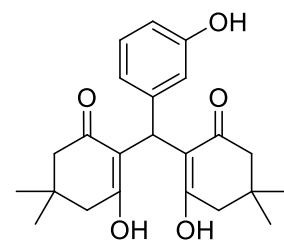


(s, 1H, CH), 2.43-2.16 (m, 8H, 4 x CH₂), 1.23 (s, 6H, 2 x CH₃), 1.10 (s, 6H, 2 x CH₃); ¹³C NMR (CDCl₃, 75MHz): δ; 191.0 (2C=O), 189.8 (C=C-OH), 140.2, 132.5, 129.3, 122.8, 120.7 (aromatic carbons), 114.7 (2-C=C-OH), 49.5 (2CH₂), 47.3 (2CH₂), 29.8 (CH), 29.1 (2CMe₂), 27.6 (2CH₃), 26.5 (2CH₃); **EIMS** (*m/z*, %): 413.2 (49.2) (M⁺+1); Anal. Calcd for C₂₂H₂₇NO₆ (413.18): C, 66.81; H, 6.58; N, 3.39; Found: C, 66.90; H, 6.63; N, 3.47.

2,2'-(3-hydroxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6i)

White solid; Yield: 78%; mp: 197-199 °C; **IR** (neat, $\nu_{\max}$, cm⁻¹): 3663

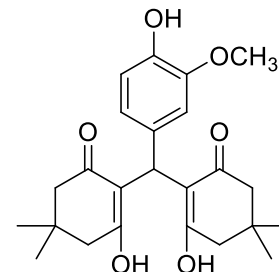
(OH, str), 3278 (Phenolic OH) 3066 (C-H, aromatic) 2988 (C-H, str), 1698 (C=O), 1598 (C=C), 1380 (C-H, bend), 996 (C-C); ¹H NMR (CDCl₃, 300 MHz): δ; 12.02 (s, 2H, OH), 7.12 (m, 3H, Ar-H), 6.93 (s, 1H, Ar-H), 5.55 (s, 1H, OH), 3.93 (s, 1H, CH), 2.51-2.36 (m, 8H, 4 x



CH₂), 1.26 (s, 6H, 2 x CH₃), 1.16 (s, 6H, 2 x CH₃); ¹³C NMR (CDCl₃, 75MHz): δ; 191.4 (2C=O), 189.9 (C=C-OH), 158.1, 134.5, 133.2, 132.4, 132.2 (aromatic carbons), 119.8 (2-C=C-OH), 44.3 (2CH₂), 47.1 (2CH₂), 32.4 (CH), 30.4 (2CMe₂), 27.1 (2CH₃), 23.2 (2CH₃); **EIMS** (*m/z*, %): 384.3 (100.1) (M⁺ +1); Anal. Calcd for C₂₃H₂₈O₅ (384.19): C, 71.85; H, 7.34; Found: C, 71.90; H, 7.51.

2,2'-(4-hydroxy-3-methoxyphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6j)

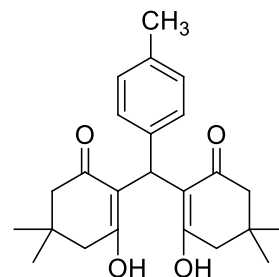
White Solid; Yield: 60; mp: 194-196 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3651 (OH, str), 3398 (Phenolic OH) 3078 (C-H, aromatic) 2948 (C-H, str), 1838 (C=O), 1628 (C=C), 1389 (C-H, bend), 953



(C-C); **¹H NMR** (CDCl₃, 300 MHz): δ ; 11.97 (s, 2H, OH), 11.92 (s, 1H, OH), 6.74 (d, J = 6.2 Hz, 1H, Ar), 6.69 (t, J = 6.6 Hz, 2H, Ar-H), 6.43 (s, 1H, OH), 5.42 (s, 1H, CH), 3.69 (s, 3H, OCH₃), 2.27–2.48 (m, 8H, 4 x CH₂), 1.17 (s, 6H, 2 x CH₃), 1.03 (s, 6H, 2 x CH₃); **¹³C NMR** (CDCl₃, 75 MHz): δ ; 189.0 (2C=O), 188.7 (C=C-OH) 147.1, 143.2, 118.8, 135.1, 124.1, 118.5 (aromatic carbons), 111.5 (2C=C-OH), 55.8 (OCH₃), 47.8 (2CH₂), 47.4 (2CH₂), 31.8 (CH), 31.1 (2CMe₂), 29.8 (2CH₃), 27.5 (2CH₃); **EIMS** (m/z , %): 414.3 (26.40) (M^+ + 1); Anal. Calcd for C₂₄H₃₀O₆ (414.20): C, 69.54; H, 7.30; Found: C, 69.66; H, 7.27.

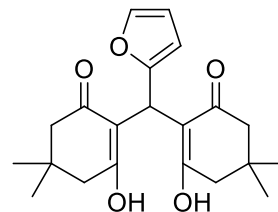
2,2'-(4-methylphenylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6k)

White solid; Yield: 60%; mp: 136-138 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3610 (C=C-OH, str), 3078 (C-H, aromatic), 2969 (C-H, str), 1780 (C=O), 1607 (C=C), 1388 (C-H, bend), 1002 (C-C); **¹H NMR** (CDCl₃, 300 MHz): δ ; 11.89 (s, 2H, OH), 7.02 (d, J = 8.0 Hz, 2H, Ar-H), 6.90 (d, J = 8.0 Hz, 2H, Ar-H), 5.42 (s, 1H, CH), 2.40-2.20 (m, 8H, 4 x CH₂), 2.23 (s, 3H, CH₃), 1.15 (s, 6H, 2 x CH₃), 1.02 (s, 6H, 2 x CH₃); **¹³C NMR** (CDCl₃, 75 MHz): δ ; 190.0 (2C=O), 189.1 (C=C-OH), 139.6, 138.6, 133.8, 131.4, 118.7 (aromatic carbons), 110.6 (2-C=C-OH), 48.5 (2CH₂), 48.3 (2CH₂), 30.6 (CH), 26.9 (2CMe₂), 26.8 (2CH₃), 25.7 (2CH₃) 20.5 (CH₃); **EIMS** (m/z , %): 382.2 (91.2) (M^+ + 1); Anal. Calcd for C₂₄H₃₀O₄ (382.21): C, 75.36; H, 7.91; Found: C, 75.41; H, 7.87.



2,2'-(furan-2-ylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (6l)

White solid; Yield: 60%; mp: 102-104 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3450 (C=C-OH, str), 2989 (C-H, str), 1690 (C=O), 1544



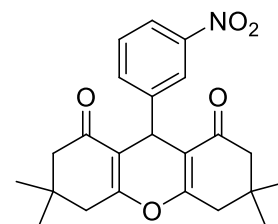
(C=C), 1359 (C-H, bend), 945 (C-C); $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ ; 12.17 (s, 2H, OH); 7.26 (s, 1H, CH), 6.30 (s, 1H, CH), 5.95 (s, 1H, CH), 5.41 (s, 1H, CH), 2.36 (brs, 8H, 4 x CH_2), 1.18 (s, 6H, 2 x CH_3), 1.09 (s, 6H, 2 x CH_3); $^{13}\text{C NMR}$ (CDCl_3 , 75MHz): δ ; 192.0 (2C=O), 190.6 (C=C-OH), 154.2 (=C-O-C), 112.1, 110.5, 110.2, 106.7 (aromatic carbons), 49.7 (2 CH_2), 49.2 (2 CH_2), 27.9 (2 CMe_2), 26.9 (2 CH_3), 25.7 (2 CH_3); **EIMS** (m/z , %): 358.2 (68.2) ($\text{M}^+ + 1$); Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5$ (358.18): C, 70.37; H, 7.31; Found: C, 70.40; H, 7.27.

3.13 General procedure for the preparation of 1,8-dioxo-octahydroxanthene derivatives 7(a-j)

The mixture of *p*-chlorobenzaldehyde (1 mmol), dimedone (2 mmol), Amberlite IR-120H (200 mg) in acetonitrile (10 ml) was subsequently refluxed for about 1.5-3 h. The disappearance of the starting materials was ascertained by TLC (*n*-hexane: Ethyl acetate as eluents). After completion, the reaction mixture was cooled and filtered out the catalyst. The reaction mixture was then fractionated with dichloromethane (3 x 10 ml). The dichloromethane layer was dried with MgSO_4 (anhydrous) and evaporated under vacuum. The residue was crystallized by ethanol to afford the pure compound. The products were fully characterized by IR, $^1\text{H NMR}$, $^{13}\text{C NMR}$, EIMS and CHNS analysis the data as given below

9-(3'-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (7a)

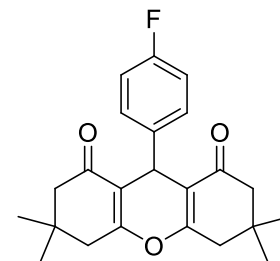
White crystals; Yield: 80%; mp: 168-170 °C; **IR** (neat KBr, ν_{max} , cm^{-1}); 3025 (C-H, aromatic) 2954, 2872 (C-H, str), 1776 (C=O), 1620, 1521 (C=C), 1350 (C-H, bend), 1124 (C-O), 1001 (C-C); $^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ ; 7.99 (s, 1H, Ar-H), 7.969-7.963 (m, 1H,



Ar-H), 7.78 (d, $J = 6.5$ Hz, 1H, Ar-H), 7.39 (m, 1H, Ar-H), 4.81 (s, 1H, CH), 2.48 (s, 4H, 2CH₂), 2.20, 2.12 (dd, $J = 16.5, 16.0$ Hz, 4H, 2CH₂), 1.09 (s, 6H, 2CH₃), 0.97 (s, 6H, 2CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ ; 196.9 (2C=O), 162.9 (=C-O-), 146.2, 135.7, 128.7, 122.4, 121.6, (aromatic carbons), 115.7 (=C-C=O), 50.6 (2CH₂), 40.82 (2 x CH₂), 32.2 (CH), 32.0 (2CMe₂), 29.1 (2CH₃), 7.2 (2CH₃); EIMS (m/z , %): 395.2 (74.1) [$M^+ + 1$]; Anal. Calcd for C₂₃H₂₅NO₅ (395.17): C, 69.87; H, 6.37; Found: C, 69.92; H, 6.30.

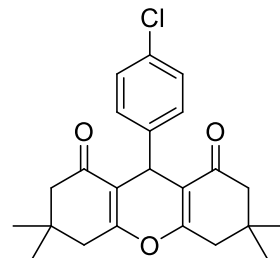
9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (7b)

White solid; Yield: 94%; mp: 218-222 °C; IR (neat KBr, $\nu_{\max}$, cm⁻¹) 3010 (C-H, aromatic), 2956 (C-H, str), 1680 (C=O), 1602, 1506 (C=C), 1359 (C-H, bend), 1195 (C-O), 1002 (C-C), 694 (C-F); ¹H NMR (CDCl₃, 600 MHz): δ ; 7.241-7.218 (t, $J = 8.4$ Hz, 2H, Ar-H), 6.88-6.85 (t, $J = 9.0$ Hz, 2H, Ar-H), 4.70 (s, 1H, CH), 2.44 (s, 4H, CH₂), 2.19, 2.16 (ABq, $J = 16.6$ Hz, 4H, CH₂), 1.08 (s, 6H, 2CH₃), 0.96 (s, 6H, 2CH₃); ¹³C NMR (CDCl₃, 200 MHz): δ ; 196.3 (2C=O), 162.2 (=C-O-), 160.2, 139.9, 130.4, 129.6, 122.5, 120.7 (aromatic carbons), 117.7 (=C-C=O), 50.7 (CH₂), 40.8 (2CH₂), 32.1 (CH), 31.2 (2CMe₂), 29.2 (2CH₃), 27.2 (2CH₃); EIMS (m/z , %): 368.2(98.1) [$M^+ + 1$]; Anal. Calcd for C₂₃H₂₅FO₃ (368.18); C, 74.98; H, 6.84; Found: C, 75.02; H, 6.78.



9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (7c)

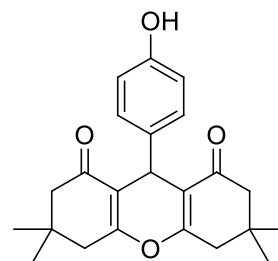
White solid; Yield: 90%; mp: 228-230 °C; IR (neat KBr, $\nu_{\max}$, cm⁻¹) 3060 (C-H, aromatic), 2955 (C-H, str), 1685 (C=O), 1605, 1510 (C=C), 1360 (C-H, bend), 1198 (C-O), 1010 (C-C) 585 (C-Cl);



¹H NMR (CDCl₃, 500 MHz): δ ; 7.02 (d, J = 8.4Hz, 2H, Ar-H), 6.99 (d, J = 8.4Hz, 2H, Ar-H), 5.45 (s, 1H, CH), 2.44 (s, 4H, 2CH₂), 2.18, 2.13 (ABq, J = 16.6, Hz, 4H, 2CH₂), 1.08 (s, 6H, 2CH₃), 1.07 (s, 6H, 2CH₃); **¹³C NMR** (CDCl₃, 125 MHz): δ ; 196.5 (2C=O), 163.5 (=C-O-), 136.7, 131.5, 128.3, 128.17 (aromatic carbons), 115.3 (=C-C=O), 49.9 (2CH₂), 41.8 (2CH₂), 32.3 (CH), 31.3 (2CMe₂), 29.5 (2CH₃), 27.3 (2CH₃); **EIMS** (m/z , %): 384.2 (76.8) [M^+ +1]; Anal. Calcd for C₂₃H₂₅ClO₃ (384.15): C, 71.77; H, 6.55; Found: C, 71.70; H, 6.58.

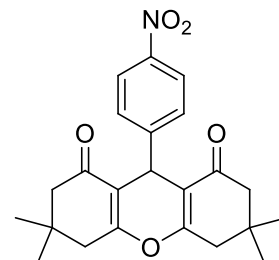
9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (7d)

White solid; Yield: 75%; mp: 242-244 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹); 3344 (Ph-OH), 3086 (C-H, aromatic), 2970 (C-H, str), 1670 (C=O), 1600, 1517 (C=C), 1390 (C-H, bend), 1208 (C-O), 1043 (C-C); **¹H NMR** (CDCl₃, 500 MHz): δ ; 6.98 (d, J = 8.5 Hz, 2H, Ar-H), 6.70 (d, J = 8.5 Hz, 2H, Ar-H), 4.90 (s, 1H, OH), 4.35 (s, 1H, CH), 2.43 (s, 4H, 2CH₂), 2.28, 2.23 (ABq, J = 13.5 Hz, 4H, 2CH₂), 1.41 (s, 6H, 2CH₃), 1.35 (s, 6H, 2CH₃); **¹³C NMR** (CDCl₃, 125 MHz): δ ; 194.3 (2C=O), 162.5 (=C-O-), 138.7, 134.7, 129.5, 129.2, (aromatic carbons), 115.5 (=C-C=O), 50.0 (2CH₂), 42.4 (2CH₂), 32.7 (CH), 31.8 (2CMe₂), 29.6 (2CH₃), 27.8 (2CH₃); **EIMS** (m/z , %): 366.2 (34.9) [M^+ +1]; Anal. Calcd for C₂₃H₂₆O₄ (366.18): C, 75.38; H, 7.15; Found: C, 75.30; H, 7.10.



9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione(7e)

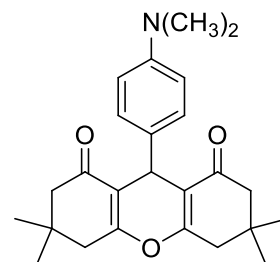
White solid; Yield; 70%; mp: 222-225 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹); 3065 (C-H, aromatic), 2958 (C-H, str), 11869 (C=O), 1606, 1523 (C=C), 1392 (C-H, bend), 1197 (C-O), 997 (C-C); **¹H NMR** (CDCl₃, 400



MHz): δ ; 8.01 (d, $J = 8.6$ Hz, 2H, Ar-H), 7.42 (d, $J = 8.6$ Hz, 2H, Ar-H), 4.78 (s, 1H, CH), 2.46 (s, 4H, 2CH₂), 2.15, 2.13 (ABq, $J = 16.0$ Hz, 4H, 2CH₂), 1.08 (s, 6H, 2CH₃), 0.95 (s, 6H, 2CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ ; 196.1 (2C=O), 162.9 (=C-O-), 151.4, 148.4, 129.3, 123.4 (aromatic carbons), 114.5 (=C-C=O), 50.5 (2CH₂), 40.8 (2CH₂), 32.3 (CH), 32.2 (2CMe₂), 29.2 (2CH₃), 27.2 (2CH₃). EIMS (m/z , %): 395.2 (67.1) [M + H]; Anal. Calcd for C₂₃H₂₅NO₄ (395.18): C, 69.86; H, 6.37; N, 3.54; Found: C, 69.80; H, 6.39; N, 4.20.

9-(4'-N,N-Dimethylphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione(7f)

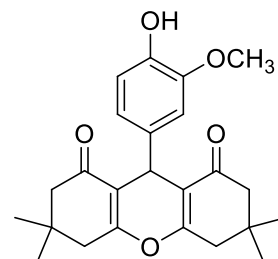
White solid; Yield: 70%; mp; 230-234 °C; IR (neat KBr, $\nu_{\max}$, cm⁻¹); 3020 (C-H, aromatic), 2967 (C-H, str), 1643 (C=O), 1589 (C=C), 1359 (C-H, bend), 1195 (C-O), 1039 (C-C).; ¹H NMR (CDCl₃, 500 MHz): δ ; 6.57 (d, $J = 7.0$ Hz, 2H, Ar-H), 6.56 (d, $J = 7.0$ Hz, 2H, Ar-H),



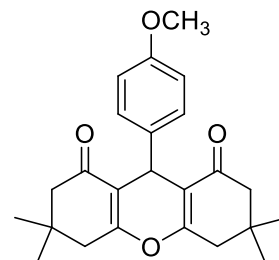
4.50 (s, 1H, CH) 3.06 (s, 6H, N(CH₃)₂), 2.40 (s, 4H, 2CH₂), 2.34, 2.18 (ABq, $J = 16.6$ Hz, 4H, 2CH₂), 1.06 (s, 6H, 2CH₃), 0.97 (s, 6H, 2CH₃); ¹³C NMR (CDCl₃, 125 MHz): δ ; 196.3 (2C=O), 162.4 (=C-O-), 151.4, 129.7, 128.4, (aromatic carbons), 113.6 (=C-C=O), 53.5 (2 x CH₂), 40.5 (2 x CH₂), 32.2 (CH), 32.2 (2x CMe₂), 29.2 (2CH₃), 27.2 (2CH₃). EIMS (m/z , %): 393.3 (21.6) [M⁺ + 1]; Anal. Calcd for C₂₅H₃₁NO₃ (393.23): C, 76.30; H, 7.94; N, 3.56; Found: C, 76.38; H, 8.09; N, 3.52.

9-(4'-hydroxy-3'-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione (7g)

White solid; Yield: 77%; mp: 214-215 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3302 (Ph-OH), 3038 (C-H, aromatic), 29389 (C-H, str), 1676 (C=O), 1627, 1517 (C=C), 1355 (C-H, bend), 1134 (C-O), 1029 (C-C); **^1H NMR** (CDCl_3 , 500 MHz): δ : 7.08 (s, 1H, Ar-H), 6.78 (d, $J = 9.2$ Hz, 1H, Ar-H), 6.57 (t, $J = 10.5$ Hz, 1H, Ar-H), 5.44 (s, 1H, OH) 4.66 (s, 1H, CH) 3.75 (s, 3H, OCH_3), 2.45 (s, 4H, 2CH_2), 2.25, 2.15 (ABq, $J = 16.2$ Hz, 4H, 2CH_2), 1.15 (s, 6H, 2CH_3), 1.07 (s, 2H, 2CH_3); **^{13}C NMR** (125 MHz, CDCl_3): δ : 196.6 ($2\text{C}=\text{O}$), 162.0 ($=\text{C}-\text{O}-$), 145.4, 144.0, 136.4, 120.3 (aromatic carbons), 115.81 ($=\text{C}-\text{C}=\text{O}$), 55.5 (OCH_3) 50.7 (2CH_2), 40.8 (2CH_2), 32.2 (CH), 31.3 (2CMe_2) 29.3 (2CH_3), 27.2 (2CH_3); **EIMS** (m/z , %): 396.3 (12.2) [$\text{M}^+ + 1$]; Anal. Calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_4$, (396.19): C, 72.70; H, 7.12; Found: C, 73.00; H, 7.09.


9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (7h)

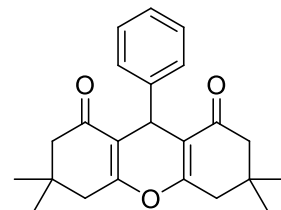
White solid; Yield: 72%; mp: 250-254 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3032 (C-H, aromatic) 2915 (C-H, str), 1647 (C=O), 1597 (C=C), 1393 (C-H, bend), 1203 (C-O), 998 (C-C); **^1H NMR** (CDCl_3 , 500 MHz): δ : 7.19 (d, $J = 10.5$ Hz, 2H, Ar-H), 6.74 (d, $J = 11.0$ Hz, 2H, Ar-H), 4.69 (s, 1H, CH) 3.73 (s, 3H, OCH_3), 2.45 (s, 4H, 2CH_2), 2.25-2.15 (ABq, $J = 16.7$ Hz, 4H, 2CH_2), 1.09 (s, 6H, 2CH_3), 0.99 (s, 2H, 2CH_3); **^{13}C NMR** (CDCl_3 , 125 MHz): δ : 196.5 ($2\text{C}=\text{O}$), 162.0 ($=\text{C}-\text{O}-$), 157.9, 136.4, 129.3, 115.7 (aromatic carbons), 113.4 ($=\text{C}-\text{C}=\text{O}$), 55.1 (OCH_3) 50.7 (2CH_2), 40.8 (2CH_2), 32.2 (CH), 30.9 (2CMe_2) 29.2 (2CH_3), 27.3 (2CH_3);



EIMS (m/z , %): 380.2 (91.2) [$M^+ + 1$]; Anal. Calcd for $C_{24}H_{28}O_4$ (380.2): C, 75.76; H, 7.42; Found: C, 75.70; H, 7.46.

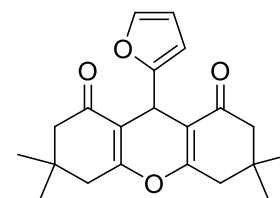
3,3,6,6-Tetramethyl-9-phenyl-1,8-dioxo-octahydroxanthene (7i)

Yellowish white solid; Yield: 82%; mp: 199-202 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3047 (C-H, aromatic) 2954 (C-H, str), 1674 (C=O), 1611, 1510 (C=C), 1386 (C-H, bend), 1143 (C-O), 1041 (C-C); **^1H NMR** ($CDCl_3$, 500 MHz): δ ; 7.29-7.08 (m, 5H, Ar-H), 4.41 (s, 1H, CH), 2.46 (s, 4H, 2CH₂), 2.25-2.14 ABq, $J = 16.6$ Hz, 4H, 2CH₂), 1.13 (s, 6H, 2CH₃), 1.07 (s, 6H, 2CH₃); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ ; 196.3 (2C=O), 162.2 (=C-O-), 144.0, 128.3, 126.3 (aromatic carbons), 115.6 (=C-C=O), 50.7 (2 x CH₂), 40.8 (2 x CH₂), 32.2 (CH), 31.8 (2 x CMe₂), 29.2 (2CH₃), 27.3 (2CH₃); **EIMS** (m/z , %): 350.1 (95.3) [$M^+ + 1$]; Anal. Calcd for $C_{23}H_{26}O_3$ (350.19): C, 78.83; H, 7.48; Found: C, 78.80; H, 7.44.



9-(Furan-2-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (7j)

Yellow solid; Yield: 62%; mp: 75-78 °C; **IR** (neat KBr $\nu_{\max}$, cm^{-1}): 2921 (C-H, str), 1690 (C=O), 1561 (C=C), 1401 (C-H, bend), 1149 (C-O), 1003 (C-C); **^1H NMR** ($CDCl_3$, 500 MHz): δ ; 7.35 (m, 1H, H-4'), 6.31 (m, 1H, H-2'), 6.14 (m, 1H, H-3'), 4.64 (s, 1H, CH), 2.41 (s, 4H, 2 x CH₂) 2.21 (s, 4H, 2 x CH₂), 1.15 (s, 6H, 2CH₃), 1.04 (s, 6H, 2CH₃); **^{13}C NMR** ($CDCl_3$, 125 MHz): δ ; 195.2 (2C=O), 163.1 (=C-O-), 140.0 (C-4'), 111.3 (C-8a,1a) 110.1 (C-3'), 109.9 (C-2'), 101.5 (C-1'), 50.2 (2 x CH₂), 40.1 (2 x CH₂), 30.3 (CH), 29.2 (2 x CMe₂), 28.3 (2CH₃), 26.2 (2CH₃); **EIMS** (m/z , %): 340.3 (29.7) [$M^+ + 1$]; Anal. Calcd for $C_{21}H_{24}O_4$ (340.17): C, 74.09; H, 7.11; Found: C, 74.04; H, 7.17.



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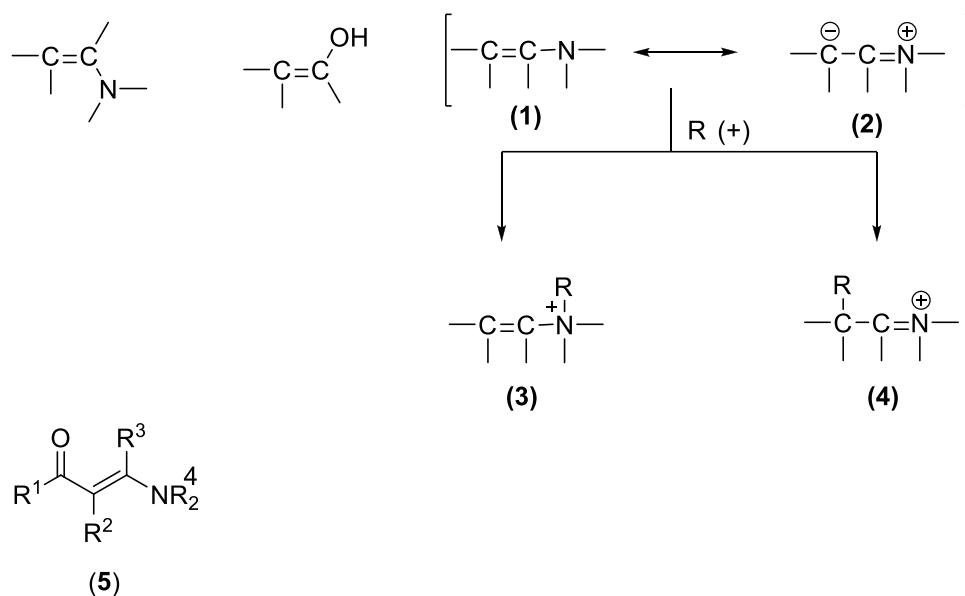
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Chapter 4
Synthesis and characterization of β -enaminones
(A Non-heterocyclic derivatives of dimedone)

4.1. Introduction

Enaminones are chemical compounds including an amino group coupled with C=C to carbonyl group. These are the resourceful synthetic intermediates that combine the ambident electrophilicity of enone with the ambident nucleophilicity of enamine just like enol. The enaminones motif are stable because the carbonyl group, conjugate with enamine and therefore, can be easily synthesized, purified and stored under normal atmospheric condition¹. The term "enamine" was first introduced by Wittig and Blumenthal² as the nitrogen analogues of the term "enol". The general structure is represented as (5) (Scheme 1).



Scheme 1. Mesomeric structure of β -enaminones

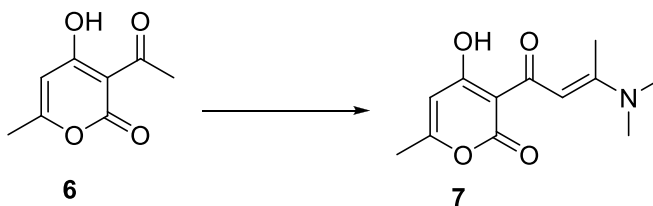
Since the electron pair on the nitrogen atom can overlap the π electrons of double bond therefore, enamines are capable of existing in two mesomeric forms **1** and **2**. The electrophilic attack may occur either at the nitrogen atom of the enamine to give an enammonium cation (**3**) or at the carbon atom of the enamine to give an iminium cation (**4**). Since the enaminones (**5**) are readily obtainable versatile reagent and having interesting chemistry in the transformation of

molecules to therapeutically important cascades, therefore several synthetic approaches have been developed in the recent year.

4.2. Reported synthetic approach to enaminones

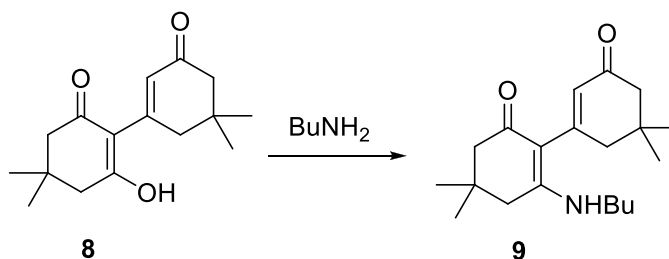
4.2.1. Condensation reactions

In general enaminones can be synthesized by the condensation reaction of active methylene ketones (both cyclic and acyclic) with dialkylamino dimethyl acetal in solvents like DMF, toluene³, ethanol⁴, or without solvent. For example the fungicidal known as dehydroacetic acid **6** react with N,N-dimethylacetamide dimethyl acetal yielded 72% of the enaminone⁵ **7** as shown in scheme 2.



Scheme 2. Synthesis of enaminone **7** from dehydroacetic acid **6**

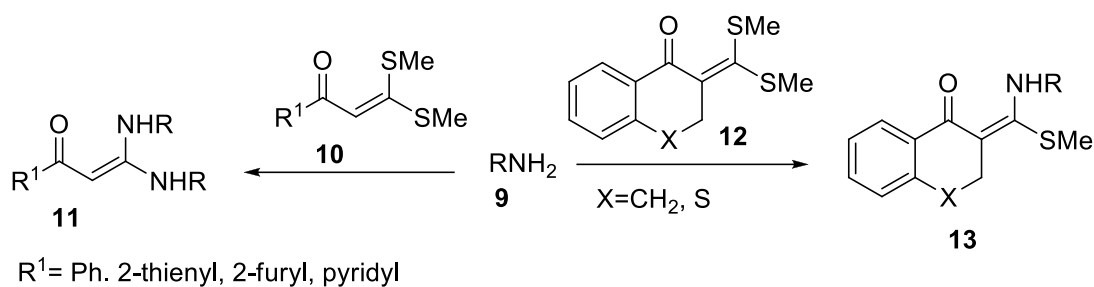
In another example the enaminone **9** is formed from the reaction of **8** with n-butyl amine in xylene under reflux condition⁶ (Scheme 3).



Scheme 3. Dimedone derivatives of β -enaminone **9**

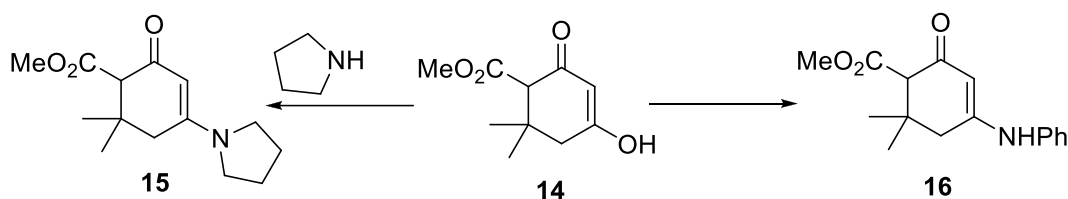
Singh *et. al.*⁷ and Kohra *et. al.*⁸ have reported the reaction of lithioamino anions with α -oxoketene dithioketals **12** and **10** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst afforded the concerned

enaminones **11** and **13** respectively, in good to excellent yield.



Scheme 4. Synthesis of β -enaminones derivatives

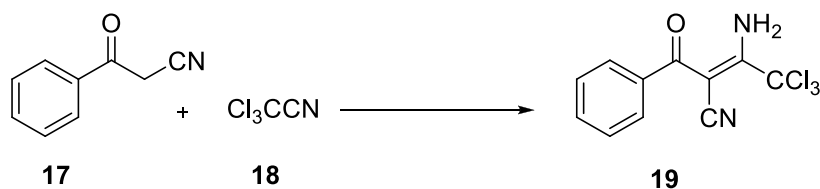
Cyclic ketones react with amine to yield enaminones, the reaction of the cyclohexane dione derivative **14** with pyrrolidine affording **15** and with benzyl amine giving **16**⁹ (Scheme 5).



Scheme 5. Pyrrolidine and benzyl amine derivatives of enaminones

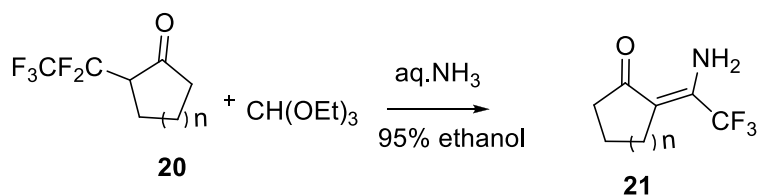
4.2.2. Addition reactions and cleavage of heterocycles

The addition reactions and cleavage of heterocycles have been extensively utilized as a route to enaminones¹⁰. To mention some of them is the reaction of benzoyl acetonitrile **17** with trichloroaceto-nitrile **18** has been reported to yield the enaminone **19**¹¹ (scheme 6).



Scheme 6. Synthesis of β -enaminones by addition reaction

Another interesting example found in the literature¹² is the reaction of cyclopentanone derivatives **20** in the presence of aqueous ammonia to give enaminone **21**, with 60–65% yield (Scheme 7).



Scheme 7. Synthesis of cyclopentanone derivative β -enaminones

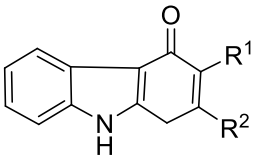
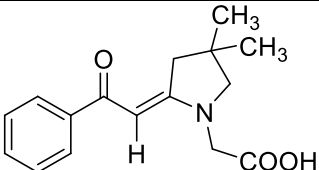
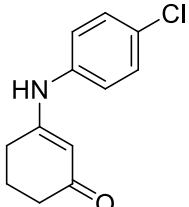
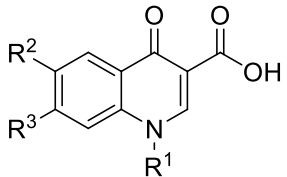
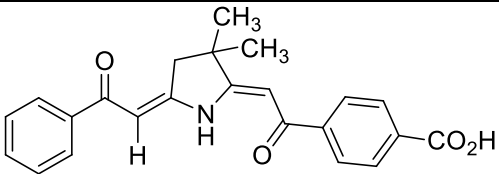
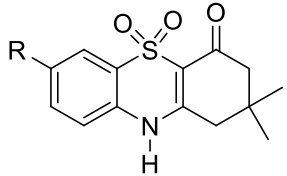
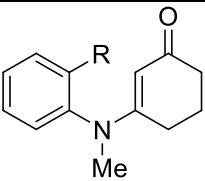
The straight forward method is the direct condensation of the 1,3-dicarbonyl with amine at reflux temperature with azeotropic removal of water molecule¹³. The recent routes are subsequently reported for the transformation of 1,3-ketone compounds (dimedone) into their respective enaminones are $\text{P}_2\text{O}_5/\text{SiO}_2$ ¹⁴, $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}/\text{MgSO}_4$ ¹⁵, NaAuClO_4 ¹⁶, $\text{Bi}(\text{TFA})_3$ ¹⁷, $\text{HClO}_4 \cdot \text{SiO}_2$ ¹⁸, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ¹⁹, $\text{Sc}(\text{OTf})_3$ ²⁰, ionic liquid $[\text{EtNH}_3]\text{NO}_3$ ²¹, iodine²², $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ ²³ and Silica supported $\text{Fe}(\text{HSO}_4)_3$ ²⁴ other synthetic approaches that lead toward β -enaminone are from isoxazoles reductive cleavage²⁵, the use of expensive catalyst like $[\text{BMIM}]\text{BF}_4$ ²⁶, cyclization of amino acids²⁷ and copper mediated aminolysis of dithioacetals²⁸.

4.3. Biological applications of enaminones

Enaminones have wide range of synthetic versatility in the preparation of naturally occurring alkaloids²⁹ and therapeutically active nitrogen containing heterocycles^{30, 31} particularly, antiepileptic³², anticonvulsant³³, anti-inflammatory³⁴, antitumor activities and cardiovascular effects^{35, 36}. Kordik and Reitz^{36b} have reported that an iodo-enaminone, **2a** (Table 4.1) was required for derivatives related to a CNS-active series. Haight *et. al.* reported the enaminones

derivative as HIV protease inhibitor ritonavir^{36b}. Some of the pharmacological activities are summarized in table 4.1.

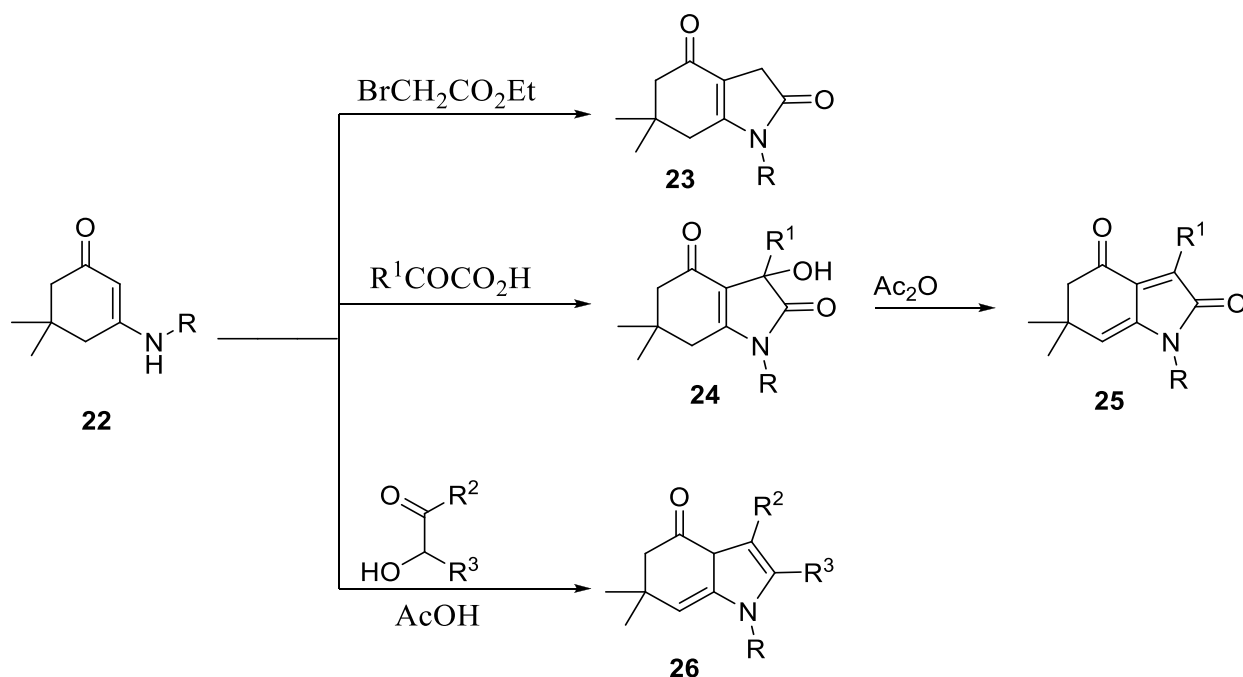
Table 4.1. Pharmacological activities of enaminones

S.No	Enaminones	Pharmacological activity
1.		Cardio-tonic murrayaquinone ³⁶
2.		Anti-anflamotry ⁶
3.		Anticonvulsant ³³
4.		Antibacterial ³⁸
5.		Antimalarial ^{38,39}
6.		Anticonvulsant ⁴⁰
7.	 2a = R = I 2b = R = Cl	CNS-Active ^{36b}

4.4. Synthetic applications of dimedone derived β -enaminones

4.4.1. Synthesis of indole

Condensation of the β -enaminone **22** (R=Ph) with ethyl bromoacetate gave hexahydroindolone **23**⁴¹, whereas with pyruvic acid gave the indole derivatives **24**, (R¹=Me) and **25** as the major and minor products, respectively. The two diastereomers of **24** (R = dichlorophenyl) were separated, when 2,3 dichlorophenyl enamine **22** was used whose dehydration with acetic anhydride afforded **25**. Reaction of phenylglyoxalic acid with enaminone **22** gave indole **26**⁴² (Scheme 8).

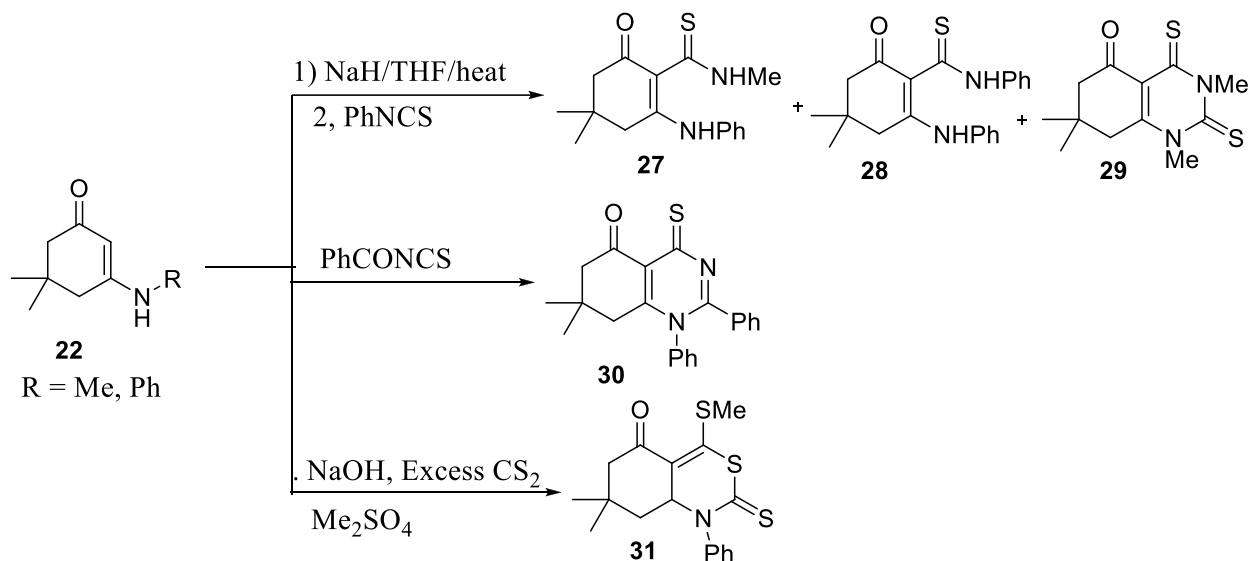


Scheme 8. Synthesis of indolones and indole derivatives from enaminones

4.4.2. Synthesis of miscellaneous heterocycles

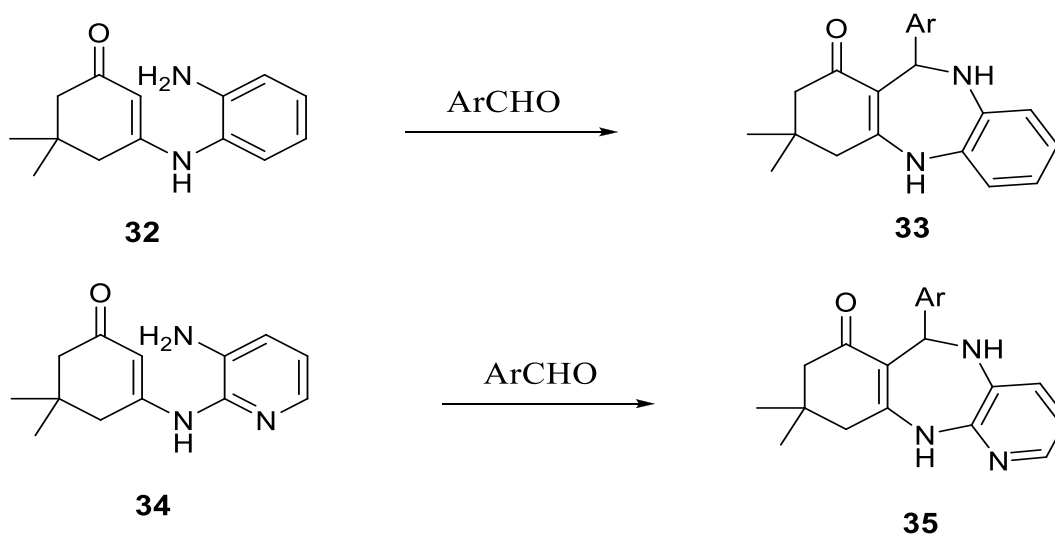
When the enaminone **22** (R=Me) reacted with sodium hydride in THF under reflux followed by phenyl isothiocyanate, afforded a mixture of product of which enaminone (R = Ph) **27**, **28**, and quinazoline derivative **29** were isolated. Contrarily, reaction of enaminone **22** (R=Ph)

with benzoyl isothiocyanate afforded the quinazoline **30** as a single product⁴³ as shown in scheme 9. Reaction of N-aryl-enamine **22** with excess of carbon disulfide in the presences of sodium hydroxide followed by dimethylsulfate afforded benzo[3,1] thiazines **31**⁴⁴.



Scheme 9. Miscellaneous heterocycles from β -enaminones

The seven membered heterocycles diazepines **33** and **35** have been reported by the cyclization of enaminone **32**, **34** with aromatic aldehydes⁴⁵ (scheme 10).



Scheme 10. Synthesis of diazepines from β -enaminones

4.5. Present work

Enaminones are useful building blocks in organic synthesis which can be further transformed into valuable bioactive nitrogen heterocycles, natural therapeutic agents and alkaloids. They are also used as precursors for the synthesis of various types of compounds like N-substituted carbazolones, peptides, quinolines, azocompounds, α , β -aminoacids that severe important role in asymmetric catalysis via chelating agent.

Owing to the significant role of enaminones in organic synthesis and in the chemistry of life, the study was extended towards the synthesis of 1,3-dicarbony (dimedone) derivative β -enaminones with the following objectives.

1. Functionailization of the 5,5-dimethyl-cyclohexane-1,3-dione, a well known dicarbonyls with various aromatic and aliphatic amines for the preparation of β -enaminones to get the synthetically versatile reagents.
2. Some of the drugs like molecules available in the market have been forced to react with dimedone either by solid support catalyst or through microwave irradiations.
3. Modifications in the literature protocols and application of new solid supported catalyst like PPA-SiO₂ have been applied in order to achieve regioselectivities in the targets molecules.

4.6. Results and Discussion

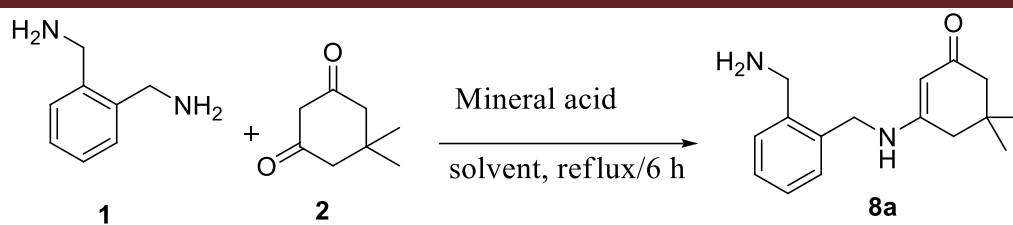
The chemistry of β -enaminones has attracted the attention of organic synthetic chemist as well as medicinal chemist for the last half century because of the typical push-pull system. In which the amine group pushes and the carbonyl pulls electrons density, which consequently gives enough stability to the molecule for their preparation. The greener, environmentally sound and solid supported catalyst has got much attention in the past few decades⁴⁶. Unfortunately, there are few examples found in the literature using solid supported catalyst,⁴⁷⁻⁴⁹ microwave⁵⁰⁻⁵² and ultrasound⁵³ for synthesis of β -enaminones. The Lewis acids catalyzed reaction methods and some of the reported protocols generally face the problem of unsatisfactory yield, tedious work up, low selectivity and toxic solvent.

To overcome these difficulties, initial work was to search the best catalyst for the synthesis of β -enaminones. It was planned to utilize acid catalytic system; a) Mineral acid catalysts b). Polyphosphoric acid supported on silica gel (PPA-SiO₂) as catalyst for the synthesis of β -enaminones.

4.7. Synthesis and characterization of β -enaminones

4.7.1 Mineral acid catalyzed synthesis of β -enaminones

First of all, a number of mineral acids e.g., HCl, CH₃COOH and sulfuric acid were screened as catalysts using the reaction of 1,2-phenylenedimethanamine (0.5 mmol) with dimedone (0.5 mmol) as a model reaction. These acids catalyzed the reaction towards the product **8a** but took longer reaction time with unsatisfactory yield as summarized in table 4.2.



Scheme 4.1. Mineral acid catalyzed synthesis of enaminones derivative

The increasing of reaction time and quantity of mineral acid up to few drops has showed adverse effect on the yield of target molecules. 4 Å molecular sieves were used for azeotropic removal of water from the reaction mixture to favors the reaction in forward direction, but the yield was still unsatisfactory.

Table 4.2. Mineral acid catalyzed synthesis of β -enaminones

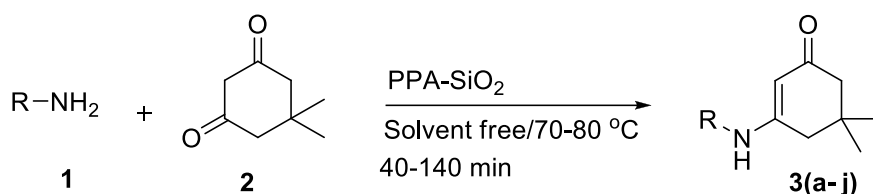
Entry	Solvent	Mineral acid	Time (h)	Product	Yield (%)
1.	Ethanol	HCl	7	8a	50
2.	Ethanol	AcOH	8	8a	57
3.	Ethanol	H ₂ SO ₄	6	8a	58
4.	Methanol	AcOH	6	8a	40

4.7.2 Polyphosphoric acid-silica (PPA-SiO₂) catalyzed synthesis of β -enaminones

In the consequences of the above observations, i.e. not an ideal synthesis, our attention was switched over towards solid supported catalyst. In order to achieve the goal of development of an ideal synthetic route for the synthesis of β -enaminones, a solid supported catalyst was prepared (PPA-SiO₂). PPA-SiO₂ was obtained by absorbing poly phosphoric acid (2.4 g) on silica gel (5 g) in chloroform (100 ml) at 50 °C and with vigorous stirring for 2 h. The catalyst was then completely dried at first under rotary evaporator and then under vacuum oven at 100 °C for 3.5 h. It was prepared from the reaction of silica gel with poly phosphoric acid according to the

literature protocol with slight modification⁵⁴. It has been used in some organic reactions, such as: conversion of carbonyl compounds into oxathioacetals and dithioacetals⁵⁴, synthesis of amidoalkyl naphthols⁵⁵, and for the preparation 1,8-dioxo-octahydroxanthenes derivatives⁵⁶.

The reaction pathway for the synthesis of β -enaminones has given in scheme 4.2. The β -enaminones **8(a-j)** were obtained by the treatment of different amines (aliphatic & aromatic) with dimedone in the presence of PPA-SiO₂ as catalyst at 70-80 °C under solvent free condition.



Scheme 4.2 Synthesis of β -enaminones (the non-heterocyclic derivatives of dimedone)

Table 4.3 Synthesis of β -enaminones by using PPA-SiO₂ as catalyst under solvent free condition **8(a-j)**

^a Entry	Comp	R	Time (min)	Yield ^b (%)
65.	8a	1,2-phenylene-dimethanamine	40	89
66.	8b	C ₆ H ₅ -	40	68
67.	8c	4-OCH ₃ C ₆ H ₅ -	45	77
68.	8d	4-CH ₃ C ₆ H ₅ -	40	74
69.	8e	4-BrC ₆ H ₅ -	40	88
70.	8f	4-NO ₂ C ₆ H ₅	55	80
71.	8g	(1S,2S)-(+)-1-amino-1-phenyl-1,3-propanediol	60	71
72.	8h	D-Threo-2-Amino-1-(4-nitrophenyl)-1,3-propanediol	60	70
73.	8i	4-(methyl)cyclohexane carboxylic acid	140	48
74.	8j	2-(1-(methyl)cyclohexyl) acetic acid	140	50

^a**Reaction conditions:** all the reaction were carried under solvent free condition by heating the reaction flask in oil bath at 70-80°C at loading 110 mg/ mmol of PPA-SiO₂ as catalyst. The progress of reaction was monitored by TLC (ethyl acetate: n-hexane 5:1). ^bIsolated yield.

In order to check the scope and generality of the PPA-SiO₂ as catalyst a comparative study was carried out under different solvents versus solvent free using the same model reaction entry 2 (Table 4.3).

4.7.2.1. Optimization of reaction condition (solvent effect)

Various parameters were studied in the optimization of reaction condition, to improve the yield of desired product. Initially, solvent effect was optimized. The model reaction was carried out in different solvents such as H₂O, CH₃OH, C₂H₅OH, CH₃CN, CH₃ and THF. In ethanol and methanol product (**3b**) formed in acceptable amount but took longer reaction time. Among the aprotic solvent the product formation was observed only in acetonitrile and chloroform as shown in table 4.4. However, the reaction carried out in the solvent free condition significantly improved not only the yield of the desired product but also took lesser time than under solution condition (as shown below in table 4.4).

Table 4.4 Comparative study of the reaction between 1,2-phenylenedimethanamine and dimedone using PPA-SiO₂ as catalyst in solvents versus the solvent free method

Run	Solvent	Temperature (°C)	Time (min)	Yield ^a (%)
1.	Water	80	140	Incomplete
2.	Methanol	Reflux	130	70
3.	Ethanol	Reflux	140	71
4.	Acetonitrile	Reflux	140	48
5.	Chloroform	Reflux	130	56
6.	THF	Reflux	140	Traces
7.	Solvent free	70 °C	40	88

^aIsolated yield; **amount of catalyst; 100 mg/1.0 mmol

4.7.2.2. Effect of loading PPA-SiO₂ as catalyst over the synthesis of β -enaminones

After optimization of reaction condition in respect of solvent the next step was the determination of the optimum amount of catalyst. In this context, the model reaction was carried out by varying the loading amount of catalyst to 50, 80, 110, 130 and 150 mg. It was observed that the rate of reaction and yield of the product increased with the increase of catalyst. It was noted that the optimum amount of catalyst turned out to be 110 mg/mmol of dimedone to obtain best result in term of product. However, above 110 mg, the catalyst showed no significant effect on the yield of the product (Table 4.5).

Table 4.5 Effect of PPA-SiO₂ loading as catalyst over the synthesis of β -enaminones

Entry	Catalyst (mg)	Time ^b (min)	Yield ^c (%)
1.	50	60	50
2.	80	50	64
3.	110	40	89
4.	130	45	86
5.	150	45	82

Reaction conditions: 1,2-phenylenedimethanamine (1.0 mmol, 136 mg) and dimedone (1.0 mmol, 140 mg) and PPA-SiO₂ heated under oil bath solvent free condition. ^bThe progress of reaction was monitored by TLC (ethyl acetate : n-hexane 5:1). ^cIsolated yield.

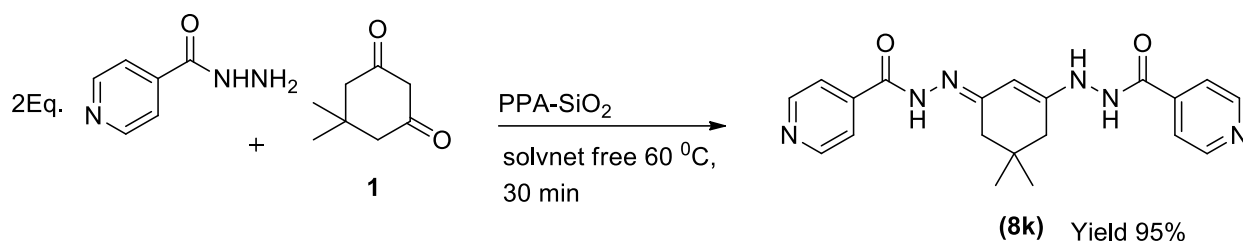
Table 4.6. Physical data of the β -enaminone derivatives **8(a-k)**

Compd.	R	Physical appearance	R _f [*]	m.p. (°C)	
				Observed	reported
8a	1,2-phenylenedimethanamine	Light yellow solid	0.46 ^b		New
8b	C ₆ H ₅ -	Yellow powder	0.35 ^a	185-186	183-185 ⁵⁷
8c	4-OCH ₃ C ₆ H ₅ -	Yellow solid	0.51 ^a		192-194 ⁵⁷
8d	4-CH ₃ C ₆ H ₅ -	Yellow solid	0.60 ^a	202-205	199-201 ⁵⁷
8e	4-BrC ₆ H ₅ -	Yellow crystals	0.51 ^a	160-162	159-163 ⁵⁷
8f	4-NO ₂ C ₆ H ₅	Light yellow solid	0.53 ^a	188-190	191-193 ⁵⁷
8g	1-(4-nitrophenyl)propane-1,3-diol	Yellow solid	0.41 ^b	205-208	New
8h	1-phenylpropane-1,3- diol	Yellow solid	0.40 ^b	230-234	New
8i	4-(methyl)cyclohexane-carboxylic acid	White crystals	0.30 ^b	270-272	New
8j	2-(1-(methyl)cyclohexyl) acetic acid	White crystals	0.32 ^b	288-290	New
8k	(E)-N'-(3-(2-isonicotinoylhydrazinyl)-5,5-dimethylcyclohex-2-enylidene)isonicotinohydrazide	whit solids	0.30 ^b	181-183	New

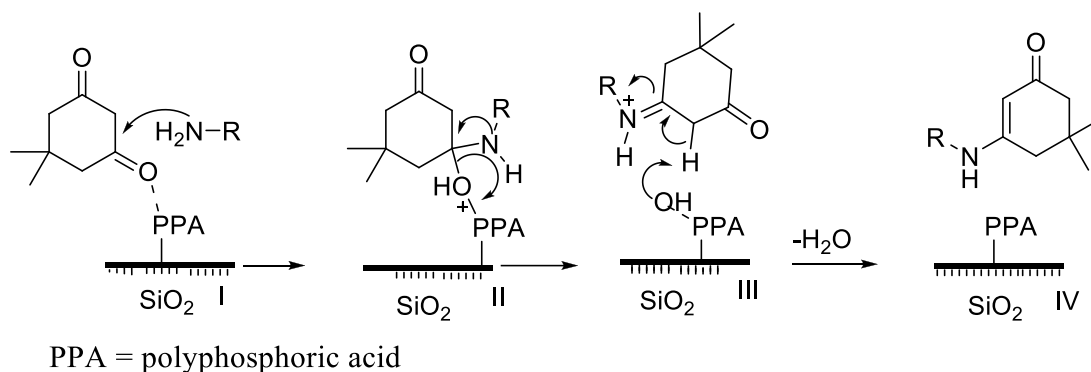
*Solvent system: ^an-Hexane: Ethyl acetate (1:5), ^bMethanol: Chloroform (1:7), on Silica gel-60 F₂₅₄ (Merck), Visualized under UV-lamp at $\lambda=254\text{nm}$. The yellow spot of compound **8i** and **8j** was also detected by spraying of 2% vanillin in isopropanol solution on developed TLC and heating for 2 min on hot plate.

Interestingly, both aliphatic and aromatic amines gave the single desired product in good to excellent yield under neat condition using PPA-SiO₂ as catalyst. However, variation in the product was observed when isonicotinohydrazide was made to react with dimedone as shown in

the scheme 4.3. Considering the reactivity of hydrazide the reaction was carried out at room temperature for 3 h. A mixture of products was obtained. That was probably β -enaminones (substituted on one carbonyl carbon of the 1,3-diketone) and the isolated product **8k**. But when the ratio was varied to 2:1 (isonicotinohydrazide and dimedone) and carried out under thermal condition at 60 °C, a single product **8k** in 95 % yield was isolated in 30 min (scheme 4.3).



Scheme 4.3. Synthesis of (**3k**)



Scheme 4.4. Suggested mechanism for the formation of an enaminone using PPA-SiO₂

The structure of all the synthesized compounds was confirmed from the IR, ¹H NMR, ¹³C NMR, EIMS and CHN analysis data.

4.8. Spectral discussion of β -enaminones

4.8.1 IR Spectral study of β -enaminones **8(a-j)**

The formation of the β -enaminones, **8(a-j)**, compound **8k** was confirmed from their respective group frequencies in the FT-IR spectra. The sharp stretching observed in the region 3200-3450 cm^{-1} was due to the N-H in the entire synthesized compound. The characteristic peak appeared in the region between 3000 and 31000 cm^{-1} was due to the C-H bond of the aromatic ring as well as the C-H at C-2 in almost all compounds. The principal bands between 1700-1600 cm^{-1} was due to the typical Ketonic group. The two typical peak appeared in the region above 1600 and 1500 cm^{-1} was assigned to aromatic C=C bond. The C-H bending of the aliphatic was observed in the region 1454-1200 cm^{-1} . The IR spectral data of the enaminones **8(a-k)** has presented in table 4.7.

Table 4.7. IR spectral data of β -enaminones **8(a-j)** and hydrazinyl enaminones **8k**,

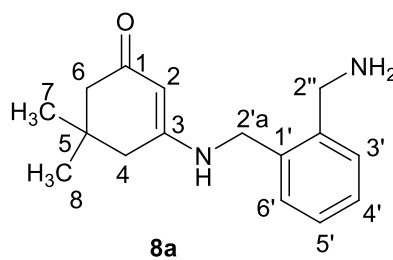
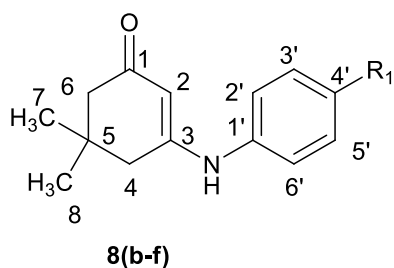
Compd.	Amine	$\nu(\text{Cm}^{-1})$					
		NH	C _{SP2} -H	C _{SP3} -H	C=O	C=C	OH
8c	1,2-phenylenedimethan-amine	3288	3027	2931	1650	1593	---
8b	C ₆ H ₅ -	3265	3034	2949	1657	1578	---
8c	4-OCH ₃ C ₆ H ₅ -	3205	3010	2957	1640	1568	---
8d	4-CH ₃ C ₆ H ₅ -	3254	3021	2951	1645	1588	---
8e	4-BrC ₆ H ₅ -	3204	3031	2921	1687	1576	---
8f	4-NO ₂ C ₆ H ₅	3272	3062	2941	1638	1538	---
8g	1-(4-NO ₂ phenyl)propane-1,3-diol	3214	3018	2924	1648	1559	3608, 3540
8h	1-phenylpropane-1,3-diol	3198	3010	2952	1644	1589	3590, 3540

(Continued)

8i	4-(methyl)-cyclohexane carboxylic acid	3251	---	2937	1683	1516	---
8j	2-(1-(methyl) cyclohexyl) acetic acid	3310	---	2927, 2848	1708, 1643	1581,	---
8k	Isonicotinohydrazide	3262	3021	2938	1674	1558	---

4.8.2. ^1H NMR spectral discussion of β -enaminones 8(a-k)

The ^1H NMR chemical shift values were found in complete accordance with the structure of the target molecules. The salient features in the structure which require comments are; the presence of allylic proton H-2 at 4.95-5.75 ppm as singlet in almost all compound. It showed the absence of any significant allylic interaction, which ensured the formation of β -enaminones instead of Schiff base formation. Another momentous feature was the methyl signals which appeared as isochronous in most of the synthesized compound at 0.98-1.08 ppm. The methylene protons of C-4 and C-6 were very broad and appeared as ABq but in case of compound **3b** as singlet at 2.14 ppm and 2.03 ppm respectively, due the $\text{o-CH}_2\text{NH}_2$ group on aromatic moiety. The appearance of aromatic proton and its splitting pattern were found in accordance with the structure of the molecules, as summarized in table 4.10. In case of compounds **3a** and **3b** the aromatic protons resonated as multiplet at 7.14-7.51 ppm and 7.08-7.04 ppm respectively, because of ortho and meta coupling. In compounds **3c**, **3d**, **3e** and **3f** the aromatic protons appeared as doublet to substituents at para position (Table 3.8).

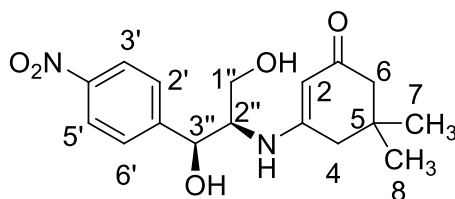
Table 4.8. ^1H NMR spectral data of β -enaminones **8(a-f)**

Protons	8a o-CH ₂ NH ₂	8b R ¹ = H	8c R ¹ = OCH ₃	8d R ¹ = CH ₃	8e R ¹ = Br	8f R ¹ = NO ₂
H-4'		7.14–7.51 (m, 5H)	----	----		---
H-2'	---		6.90 (d, <i>J</i> = 7.5 Hz, 2H)	7.30 (d, <i>J</i> = 7.2 Hz, 2H)	7.36 (d, 2H, <i>J</i> = 8.6 Hz)	7.99-7.871 (m, 2H, ArH))
H-6'	7.08-7.04 (m, 4H)					7.58-7.55 (m, 2H,
H-3'			6.41 (d, <i>J</i> = 7.5 Hz, 2H)	6.81 (d, <i>J</i> = 7.2 Hz, 2H)	6.92 (d, 2H, <i>J</i> = 8.6 Hz)	(m, 2H,
H-5'						)
NH	3.23 (brs, 1H)	6.49 (brs, 1H)	7.12 (brs, 1H)	6.54 (brs, 1H)	6.71 (brs, 1H)	6.59 (brs, 1H)
C-2 (CH)	4.96 (s, 1H)	5.70 (s, 1H)	5.01 (s, 1H)	4.95 (s, 1H)	5.20 (s, 1H)	5.50 (s, 1H)
C-6 (CH₂)	2.14 (s, 2H)	2.41-2.26 (m, 4H, 2CH ₂),	2.13-2.27 (m, 4H, 2CH ₂),	2.42-2.21 (m, 4H, 2CH ₂),	2.31 (ABq, 4H)	2.36 (s, 2H)
CH₂ C-4	2.03(s, 2H)					2.26 (s, 2H)
2 x CH₃, C,7,8.	0.93 (s, 6H)	1.02 (s, 6H)	1.03 (s, 6H)	1.01 (s, 6H)	0.98 (s, 6H)	1.12 (s, 6H),
o-CH₂NH₂	4.14 (s, 2H) 8.4, (brs, 2H)	---	---	---	---	---
R¹	--	----	3.67, (s, 3H)	2.12 (s, 3H)	---	---

D- Thero-3-(1,3-dihydroxy-1-(4-nitrophenyl)propan-2-ylamino)-5,5-dimethylcyclohex-2-enone (8g)

The structure of the D-Thero-3-(1,3-dihydroxy-1-(4-nitrophenyl)propan-2-ylamino)-5,5-dimethylcyclohex-2-enone was established with the help of ^1H NMR spectral data. The presence of singlet for H-2 at 5.12 ppm corresponding to deshielded allylic proton. The aromatic protons resonated at higher chemical shift at 8.11 ppm and 7.47 ppm respectively, due to the additional deshielding effect of the nitro group on aromatic moiety. The two hydroxyl group resonated at 3.06 as singlet. The triplet at 3.30 ppm corresponded to the protons at C-3'' and C-2'' due the splitting pattern with proton at C-1''. The proton at C-2'' showed lack of splitting pattern and appeared as brs probably due to its trans position (Table 4.9).

Table 4.9. ^1H NMR data of D-Thero-3-(1,3-dihydroxy-1-(4-nitrophenyl)propan-2-ylamino)-5,5-dimethylcyclohex-2-enone



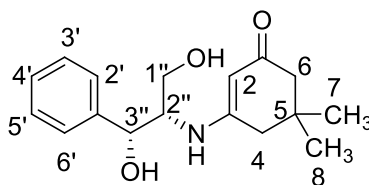
$\delta(\text{ppm})$	multiplicity	Integration	coupling constants J (Hz)	Assignment
8.11	d	2H	$J = 8.8 \text{ Hz}$	Ar-H (C-2'-6')
7.47	d	2H	$J = 8.8 \text{ Hz}$	Ar-H (C-3'-5')
5.12	s	1H	---	CH (C-2)
3.06	s	2H	---	2xOH (C-3'', 1'')
3.30	t	2H	$J = 2.8 \text{ Hz}$	CH (C-3'', 2'')
3.12	brs	2H	---	$\text{CH}_2(\text{C-1}'')$
2.15	d	2H	$J = 16.0 \text{ Hz}$	$\text{CH}_2(\text{C-6})$
2.01	s	2H	$J = 17.2 \text{ Hz}$	$\text{CH}_2(\text{C-4})$
0.92	s	3H	---	$\text{CH}_3(\text{C-7})$
0.77	s	3H	---	$\text{CH}_3(\text{C-8})$

(400 MHz, CDCl_3)

Characterization of 3-((1R,2S)-1,3-dihydroxy-1-phenylpropan-2-ylamino)-5,5-dimethylcyclohex-2-enone

The formation of the novel compound 3-((1R,2S)-1,3-dihydroxy-1-phenylpropan-2-ylamino)-5,5-dimethylcyclohex-2-enone was confirmed from their momentous peaks appeared in the ^1H NMR Spectrum. The singlet resonated at 5.80 ppm was assigned to allylic proton at C-2, brs at 6.34 ppm was due to NH. The hydroxyl group resonated at 5.18 ppm and 5.07 ppm due to the S configuration at their respective carbons. The protons at C-1'', C-2'' and C-3'' appeared at 4.13-3.81 ppm as brs which is not differentiable due to cis configuration. The aromatic proton resonated at their typical position with appropriate spin splitting pattern as shown in the following table.

Table 4.10. ^1H -NMR Spectral data of 3 ((1R,2S)-1,3-dihydroxy-1-phenylpropan-2-ylamino)-5,5-dimethylcyclohex-2-enone

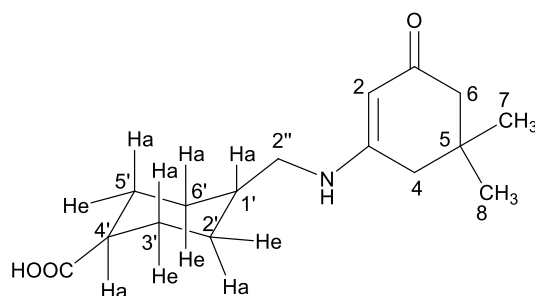


$\delta(\text{ppm})$	multiplicity	Integration	J (Hz)	Assignment
7.37-7.19	m	5H	---	Ar-H
6.34	brs	1H		NH
5.80	s	1H	---	(C-2)
5.18	S	1H	---	OH (C-1'')
5.07	s	1H	---	OH(C--3'')
4.13-3.81	brs	4H	---	(C-1'', C-2'', 3'')
2.47-2.21	m	4H	---	(C-6, C-4)
0.94	s	3H	---	(C-7)
0.67	s	3H	---	(C-8)

Characterization of 4-((5,5-dimethyl-3-oxocyclohex-1-enylamino)methyl)cyclohexane carboxylic acid (**8i**)

In case of compound **8i** the ^1H NMR spectrum showed the characteristic signal at 4.76 ppm for the allylic H-2 and a brs at 6.93 ppm for the NH, Which ensured the formation of β -enaminone functionality. The proton at C-4/C-6 appeared at 2.82-2.78 ppm as ABq type signals. The two protons at C-2'' resonated at 2.16 ppm as multiplet due to the electron withdrawing group in the neighborhood. The multiplet appeared at 2.10 ppm was assigned the proton at C-4. Another multiplet resonated at 1.93 ppm corresponded to the protons at carbon C-3 and C-5, because equatorial protons may be more deshielded than axial protons. The set of multiplets resonated at 1.77-1.31 ppm and 1.27-0.93 ppm corresponding to the protons at C-2 and C-6 (Table 4.11).

Table 4.11. ^1H NMR Spectral data of 4-((5,5-dimethyl-3-oxocyclohex-1-enylamino)methyl)-2-methylcyclohexanecarboxylic acid (**8i**)

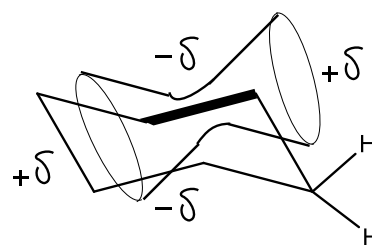


$\delta(\text{ppm})$	multiplicity	Integration	J (Hz)	Assignment
6.93	brs	1H	---	NH
4.76	s	1H	---	(C-2)
2.82-2.78	s	4H	---	(C-6, C-4)
2.16	m	2H	---	C-2''
2.10	m	1H	---	(C-4')
1.93	m	4H	---	(C-3', C-5')
1.77, 1.31	m	2H,	---	C-6'
1.47	m	1H	---	C-1'
1.23, 1.27	m	2H	---	(C-2')
1.18	s	6H	---	C-7, C-8

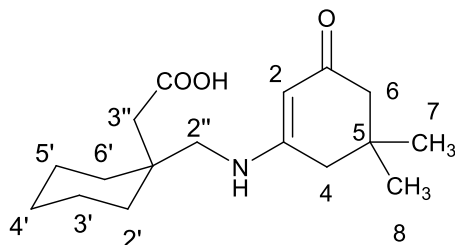
Characterization of 2-(1-((5,5-dimethyl-3-oxocyclohex-1-enylamino)methyl)cyclohexyl)acetic acid (8j)

The structure of the target molecule was confirmed from the characteristic signals in the ^1H NMR spectrum. The characteristic peaks for allylic proton at C-2 appear at 5.49 ppm as singlet, while the NH as brs singlet at 7.52 ppm, confirmed the formation of this novel enaminones derivatives. The most deshielded signal at 3.35 ppm and 2.45 ppm corresponded to the C-3'' and C-2'' respectively, due to strong electron withdrawing group in the neighborhood. The two equatorial protons at C-6' and C-2' resonated at higher frequency (2.40 ppm and 2.34 ppm) then the axial protons (1.47 ppm). The two set of multiplets for three protons in the region 1.47-1.34 ppm corresponding to the protons at C-3', C-4' and C-5' where equatorial protons may be more deshielded than axial protons.

The explanation for this shift effect is based on the anisotropy cones shown in the figure, Where the equatorial protons reside in the deshielding ($+\delta$) region of the C-C anisotropy, and the axial in the $-\delta$ region. In other words that additional contributing effect may based on the supposition that a C-H is



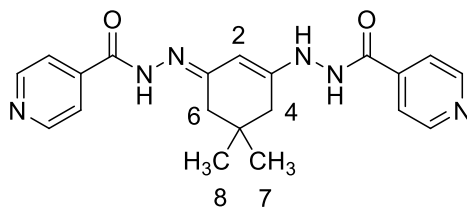
a stronger sigma donor than a C-C Bond, which leads to increased electron density on the axial protons (anti to two C-H bonds) hence $-\delta$). The methyl group resonated at 1.05 ppm as singlet also confirmed that the bulky group present in the neighbor prevents it from splitting. The protons at C-4/C-6 also resonated at their typical position as indicated in the following table 4.12.

Table 4.12. ^1H NMR Spectral data of 2-(1-((5, 5- dimethyl-3-oxocyclohex-1-enylamino) methyl)cyclohexyl)acetic acid (**8j**)

$\delta(\text{ppm})$	multiplicity	Integration	J (Hz)	Assignment
7.52	brs	1H	---	NH
5.49	s	1H	---	Allylic-H at C-2)
3.35	brs	2H	---	(C-3'')
2.45	s	2H	---	CH ₂ at C- 2''
2.40	ABq	2H	---	(C-6)
2.34	ABq	2H	---	(C-4)
2.40 and 2.34	m	4H,	---	(C-2'-C-6')
1.47, 1.37-1.34	m	6H	---	C-4', C-3', C-5')
1.05	s	6H	---	(C-7, 8)

Characterization of (E)-N'-(3-(2-isonicotinoylhydrazinyl)-5,5-dimethylcyclohex-2-enylidene)isonicotinohydrazide

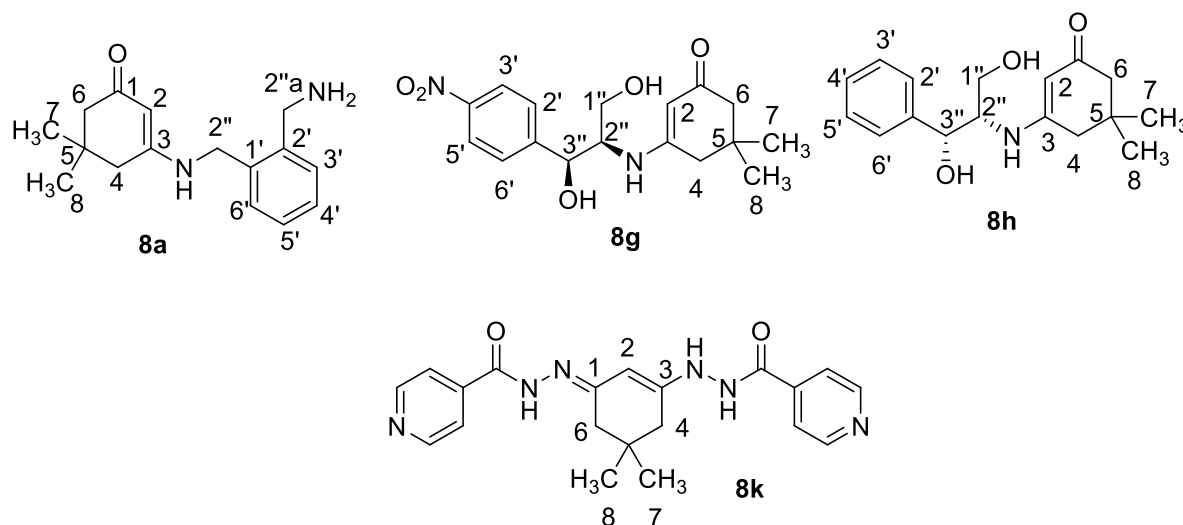
The structure of the new molecule was confirmed from the ^1H -NMR spectral data. The appearance of allylic proton at 5.81ppm as singlet confirmed the formation of enaminone. The appearance of brs in the most deshielded region, 10.84 ppm ensured the presence of an amidic NH group. The aromatic protons were equivalent and appeared as doublet at 8.52 ppm with $J= 4.2$ Hz and 7.76 ppm with $J=4.5$ Hz. The frequency is slightly higher due to the pyridyl nitrogen on aromatic ring. The other protons like methyl and protons at C4/C-6 resonated at their typical position as indicated in the following table 4.13.

Table 4.13. ^1H NMR Spectral data of (E)-N'-(3-(2-isonicotinoylhydrazinyl)-5,5-dimethylcyclohex-2-enylidene)isonicotinohydrazide (**8k**)

$\delta(\text{ppm})$	multiplicity	Integration	J (Hz)	Assignment
10.84	brs	3H	---	NH
8.52	d	4H	J = 4.2	Aromatic H
7.76	d	4H	J = 4.5	(C-2', 6')
5.81	s	1H	---	(C-2)
2.40	s	4H	---	(C-4, 6)
1.04	s	6H	---	(C-7,8)

4.9.3 ^{13}C NMR spectral data of β -enaminones derivatives **8(a-k)**

The formation of novel β -enaminones derivatives were further confirmed from the ^{13}C NMR spectral data. Two comments require; first is the appearance of a signal for the allylic carbon in the regions 165.1-149.7 ppm. Secondly, the appearance of signals for carbonyl carbons at their typical regions 197.8- 196.8 ppm and amidic carbonyl at 164.8 ppm for compound **8k** fully confirmed the formation of the targets molecules. The other signals were also considered like the appearance of quaternary carbon C-5, at 32.2-32.5 ppm. The aromatic carbons resonated at their typical regions as shown in the following table 4.14. In case of compound **8k** the aromatic carbons resonated 121.7 ppm. The signals for the methyl carbon resonated at the most downfield regions 28-27 ppm in almost all compounds.

Table 4. 14. ^{13}C NMR spectral data of enaminones derivates **8a**, **8g**, **8h**, **8k**

Carbons	^{13}C NMR spectral data of enaminones derivatives									
	C=O*	C-3	C-2	C-6 CH ₂	C-2''	C-4 CH ₂	C-5	C-7 C-8	Aromatic carbons	Others
8g	196.8	163.1	102.2	49.7	62.1	42.3	33.6	27.3 26.5	148.4, 147.1, 139.5, 138.5, 132.5, 130.0	68.1 (C-3'') 60.7(C-1'')
8h	197.1	165.6	94.3	48.7	60.1	43.3	32.6	27.9 27.5	149.4, 147.1, 126.5, 123.3	69.15(C-3'') 59.5(C-1'')

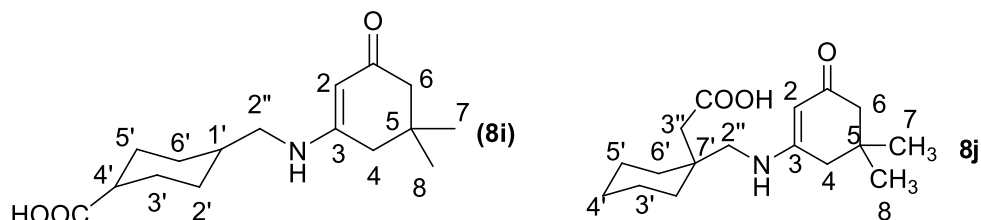
Ketonic while in case of **8k** amidic

(75 or 100 MHz)

The structure of compounds **8i** and **8j** was further supported by its C-13 Spectrum. The signals resonated at 193.6, 195.5 ppm was assigned to ketonic carbonyl carbon and 176.7, 175.9 ppm was due to carboxylic acid carbonyl carbon. The other characteristic peaks which confirmed the formation of desired β -enaminones were the appearance of signals for quaternary carbons, and allylic carbon at 162.9 and 168.5 respectively. In both compounds the tertiary allylic carbon

resonates in at 93.6 and 109.5 respectively. The signals for quaternary carbon 5 appeared at 32.1 and 32.7 ppm. The methyl group resonated at their typical aliphatic region 27-28 ppm as shown in the following table 4.15.

Table 4.15 ^{13}C NMR spectral data of β -enaminones derivatives **8(i-j)**



Carbons	^{13}C NMR spectral data of β -enaminones derivatives										
	C=O*	COOH	C-3	C-2	C-6 CH ₂	C-2''	C-4 CH ₂	C-5	C-4'	C-7 C-8	Others
8i	193.6	176.7	162.9	93.6	50.2	48.2	44.1	32.1		27.9 27.8 35.5	38.6 (C-1') 29.5 (C-3',5') 28.2 (C-6',2')
8j	195.5	175.9	168.5	109.5	51.6	48.1	43.8	32.7	C-1' 40.3	28.3 28.0	40.6 (C-3'') 25.4 (C-6',2') 22.6, 21.4, (C-4', 5',3')

*Ketonic while in case of **3k** amidic

(75 or 100 MHz)

4.9.4. EIMS and elemental analysis study of β -enaminones derivatives **8(a-k)**

The EI- mass spectra of the synthesized β -enaminones were found almost similar to calculated values as displayed in the following table 4.16. The elemental analysis were performed on a Carlo Erba Strumentasion-Mod-1106 Italy and also found in relation with theoretical value.

Table 4.16. CHN and EIMS data of β -enaminones **8(a-k)**

Compd.	Mol. F.	Calcd. (%)			Observed (%)			Mol. Wt (Calcd)	M.Wt. EIMS* (M+%)
		C	H	N	C	H	N		
8a	C ₁₆ H ₂₂ N ₂ O	74.38	8.58	10.84	74.45	8.50	10.89	258.17	258.15 (8.51)
8b	C ₁₄ H ₁₇ NO	78.10	7.96	6.51	78.17	7.91	6.56	215.13	216.2 (100.0)
8c	C ₁₅ H ₁₉ NO ₂	73.44	7.81	5.71	73.39	7.77	5.73	384.15	245.0 (46.8)
8d	C ₁₅ H ₁₉ NO	78.56	8.35	6.11	78.58	8.32	6.15	229.15	229.2 (91.3)
8e	C ₁₄ H ₁₆ BrNO	57.16	5.48	4.76	57.10	5.39	4.80	293.03	293.1 (90.8)
8f	C ₁₄ H ₁₆ N ₂ O ₃	64.60	6.20	10.76	64.59	6.18	10.81	260.29	260.3 (47.1)
8g	C ₁₇ H ₂₂ N ₂ O ₅	61.07	6.63	8.38	61.01	6.59	8.43	334.37	335.1 (20.8)
8h	C ₁₇ H ₂₃ NO ₃	70.56	8.01	4.84	70.49	8.05	4.90	289.37	290.0 (74.9)
8i	C ₁₆ H ₂₅ NO ₃	68.79	9.02	5.01	68.73	9.00	5.10	279.18	279.1 (53.5)
8j	C ₁₇ H ₂₇ NO ₃	69.59	9.28	4.77	69.55	9.20	4.70	293.21	292.9 (13.7)
8i	C ₂₀ H ₂₂ N ₆ O ₂	63.48	5.86	22.21	63.40	5.80	22.18	378.18	378.1 (100.0)

4.10. Experimental Section

4.10.1. Preparation of PPA/SiO₂ catalyst

The catalyst PPA/SiO₂ was prepared by the reported method¹ with slight modification. The round-bottom flask, already dried at 120 °C was charged with a magnetic bar, Polyphosphoric acid (2.5 g), CHCl₃ 120 ml and was stirred for 1h at 50 °C. SiO₂ [(100-200 mesh), 5.1 g] was added and the stirring was continued for next 1h. The excess of chloroform was evaporated under vacuum using rotary evaporator. The solids obtained were dried under vacuum oven for 4 h at 120 °C.

4.10.2. General procedure for the synthesis of β -enaminones derivatives

The mixture aromatic or aliphatic amines **1** (1 mmol), 5,5-dimethyl cyclohexane-1,3-dione (Dimedone) **2** (1 mmol) and PPA-SiO₂ (110 mg/mmol) was stirred at 70-80 °C for the specified time shown in the table 1. The product formation was monitored by TLC. After completion of reaction the catalyst was filter from reaction condition in warmed condition and washed with ethyl acetate 20 ml. The mixture was kept at room temperature; the solid obtained was filtered. The pure product was obtained in most cases by recrystalization in binary solvent system using 95% ethanol or dichloromethane and hexane at different ratio. Some of the product was also purified by using column chromatography. The products were ascertained by IR, ¹H NMR, ¹³C NMR, mass spectroscopy and CHNS analysis.

4.11. Spectral and physical data of β -enaminones**3-(2-(aminomethyl)benzylamino)-5,5-dimethylcyclohex-2-enone (65)**

The mentioned compound was prepared by the above procedure from the reaction of 1,2-diamionmethane and 1,3-diketone in 40 minutes at 70-80 °C using the same catalyst.

Yellowish Solid; Yield: 89%; mp: 152-154 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}):

32088 (NH), 3027 (C-H, aromatic), 2931 (C-H, str), 1650 (C=O), 1593

(C=C), 1234 (C-C, bend); **^1H NMR** (CDCl_3 , 300 MHz): 8.31 (s, 2H,

NH_2), 8.41 (brs, 1H, NH), 7.08-7.04 (m, 4H, Ar-H), 4.96 (s, 1H, CH),

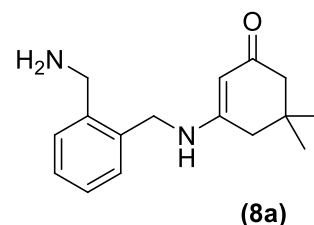
4.14 (s, 2H, $\text{CH}_2\text{-NH}_2$), 2.14 (s, 2H, CH_2), 2.03 (s, 2H, CH_2), 0.93 (s,

6H, 2 CH_3); **^{13}C NMR** (CDCl_3 , 75 MHz): 197.8 (C=O), 165.1 ($-\text{NH-C}=\text{C}-$), 137.3, 128.0, 127.7,

127.3, 126.5, (aromatic carbons), 94.9 (C = CH), 48.9 (CH_2), 46.5 (CH_2), 44.1 (CH_2), 42.7

(CH_2), 32.6 (2 CMe_2), 27.9 (2 CH_3); **EIMS** (m/z , %): 258.15 (8.51) ($\text{M}^+ + 1$); Anal. Calcd for

$\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}$ (258.17): C, 74.38; H, 8.58; N, 10.84; Found: C, 74.45; H, 8.50; N, 10.89.

**5,5-dimethyl-3-(phenylamino)cyclohex-2-enone (65)**

The title compound was synthesized by using the above general protocol from the reaction of aniline and dimedone under thermal condition at 70 °C for 40 min using PPA- SiO_2 as catalyst. Yellowish solid; Yield: 68%; mp: 187-188 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3265 (NH),

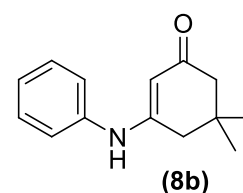
3034 (C-H, aromatic), 2949 (C-H, str), 1657 (C=O), 1578 (C=C), 1244

(C-C, bend); **^1H NMR** (CDCl_3 , 300 MHz): 7.45-7.14 (m, 5H), 6.49

(brs, 1H, NH), 5.70 (s, 1H) (s, 1H, CH), 2.41-2.26 (m, 4H, 2 CH_2), 1.02

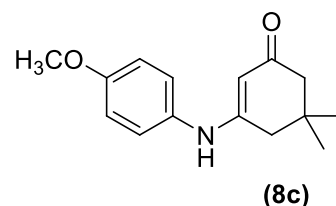
(s, 6H, 2 CH_3); **EIMS** (m/z , %): 216.2 (100.0) ($\text{M}^+ + 1$); Anal. Calcd.

for $\text{C}_{14}\text{H}_{17}\text{NO}$ (215.13): C, 78.10; H, 7.96; N, 6.51. Found: C, 78.17; H, 7.91; N, 6.56.

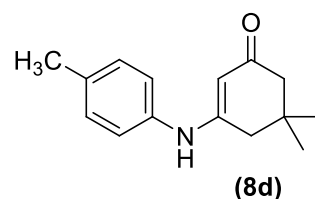


3-(4-methoxyphenylamino)-5,5-dimethylcyclohex-2-enone (67)

The target molecule was achieved by using the above mentioned method from the reaction p-methoxy aniline with dimedone using PPA-SiO₂ as solid catalyst under thermal condition for 45 min. White solids: Yield: 77 %; mp: 190-192 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3205 (NH), 3010 (C-H, aromatic), 2957 (C-H, str), 1640 (C=O), 1568 (C=C), 1372 (C-C, bend); **¹H NMR** (CDCl₃, 300 MHz): 6.90 (d, J = 7.5 Hz, 2H, Ar-H), 6.41 (d, J = 7.5 Hz, 2H, Ar-H), 7.12 (brs, 1H, NH), 5.01 (s, 1H, CH), 3.67 (s, 3H, OCH₃), 2.43-2.27 (m, 4H, 2CH₂), 1.03 (s, 6H, 2CH₃); **EIMS** (m/z , %): 245.0 (46.8) (M^+ +1); Anal. Calcd for C₁₅H₁₉NO₂ (245.1); C, 73.44; H, 7.81; N, 5.71: Found: C, 73.39; H, 7.77; N, 5.73.

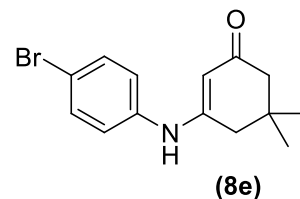
**5,5-dimethyl-3-(p-tolylamino)cyclohex-2-enone (68)**

The target molecule was prepared from the reaction of p-toulidine with dimedone in 40 minutes in the presences of PPA-SiO₂ as catalyst under heating at 70-80 °C according the general procedure mentioned above. White solid; Yield: 74%; mp: 201-202 °C; **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3254 (NH), 3021 (C-H, aromatic), 2951 (C-H, str), 1645 (C=O), 1588 (C=C), 1254 (C-C, bend); **¹H NMR** (CDCl₃, 400 MHz): 7.30 (d, J = 7.2 Hz, 2H, Ar-H), 6.81 (d, J = 7.2 Hz, 2H, Ar-H), 6.54 (brs, 1H, NH), 4.95 (s, 1H, CH), 2.42-2.21 (m, 4H, 2CH₂), 1.01 (s, 6H, 2CH₃); **EIMS** (m/z , %): 229.2 (91.3) (M^+ +1); Anal. Calcd for C₁₅H₁₉NO (229.15): C, 78.56; H, 8.35; N, 6.11: Found: C, 78.58; H, 8.32; N, 6.15.

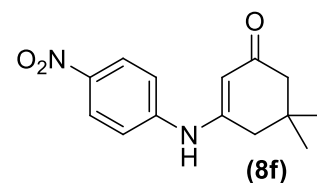


3-(4-bromophenylamino)-5,5-dimethylcyclohex-2-enone (69)

The mentioned compound was synthesized according to the above mentioned procedure from the reaction p-bromo-aniline and dimedone. Off white solid; Yield: 74%; mp: 215-217 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3204 (NH), 3021 (C-H, aromatic), 2951 (C-H, str), 1687 (C=O), 1576 (C=C), 1376 (C-C, bend); **^1H NMR** (CDCl_3 , 400 MHz): 7.36 (d, J = 8.6 Hz, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 2H, Ar-H); 6.71 (brs, 1H, NH), 5.20, (s, 1H, CH), 2.31 (AB-q, 4H, 2CH_2), 0.98 (s, 6H, 2CH_3); **EIMS** (m/z , %): 293.1(90.8) ($\text{M}^+ + 1$); Anal. Calcd. For $\text{C}_{14}\text{H}_{16}\text{BrNO}$ (293.03): C, 57.16; H, 5.48; N, 4.76. Found: C, 57.10; H, 5.39; N, 4.80.

**5,5-dimethyl-3-(4-nitrophenylamino)cyclohex-2-enone (70)**

Using the above mentioned general procedure for the synthesis of β -Enaminones the title compounds has been synthesized from p-nitro aniline and dimedone. Yellow solid; Yield: 67%; mp: 194-195 °C: **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3272 (NH), 3062 (C-H, aromatic), 2941 (C-H, str), 1638 (C=O), 1538 (C=C), 1329 (C-C, bend); **^1H NMR** (CDCl_3 , 300 MHz): 7.99-7.871 (m, 2H, ArH), 7.58-7.55 (m, 2H, Ar-H), 6.59 (brs, 1H, NH), 5.50, (s, 1H, CH), 2.36 (s, 2H, CH_2), 2.26 (s, 2H, CH_2), 1.12 (s, 6H, 2CH_3); **EIMS** (m/z , %): 260.3 (47.1) ($\text{M}^+ + 1$); Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ (260.29): C, 64.60; H, 6.20; N, 10.76; Found: C, 64.59; H, 6.18; N, 10.81.



3-((1S,2R)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-ylamino)-5,5-dimethylcyclohex-2-enone (71)

The reaction of D-Threo-2-Amino-1-(4-nitrophenyl)-1,3-propanediol with dimedone give the target molecules according to the general procedure mentioned above in 71 minutes.

Yellowish Solid; Yield: 60%; mp: 176-177 °C: **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3608 (OH), 3540

(OH), 3214 (NH), 3018 (C-H, aromatic), 2924 (C-H, str),

1648 (C=O), 1559 (C=C), 1229 (C-H, bend); **^1H NMR**

(CDCl_3 , 400 MHz): 8.11 (d, $J = 8.8$ Hz, 2H, Ar-H, C-2',6')

7.47 (d, $J = 8.8$ Hz, 2H, Ar-H, C-3'-5'), 5.12 (s, 1H, CH,

C-2), 3.06 (s, 2H, OH), 3.30 (t, $J = 2.8$ Hz, 2H, C-3'', 2'') 3.12 (s, 2H, C-1''), 2.15 (d, $J = 16.0$ Hz

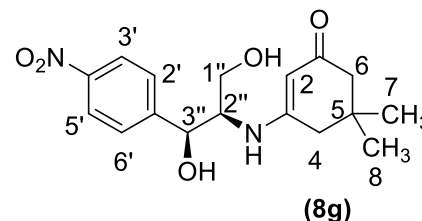
C-6), 2.01 (d, $J = 17.2$ Hz C-4), 0.92 (s, 3H, CH_3), 0.77 (s, 3H, CH_3); **^{13}C NMR** (CDCl_3 , 100

MHz); δ : 197.1 (C=O), 165.6 (NH-C=), 149.4, 147.1, 126.5, 123.3 (aromatic carbons), 94.3

(C=CH), 69.15 (CH-OH), 60.1 (CH-NH), 59.5 (CH_2 -OH), 48.7 (CH_2), 43.3 (CH_2), 32.6

(2CMe_2), 27.9 (2CH_3), 27.5 (2CH_3); **EIMS** (m/z , %): 335.1 (20.8) ($\text{M}^+ + 1$); Anal. Calcd for

$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_5$ (334.37): C, 61.07; H, 6.63; N, 8.38; Found: C, 61.01; H, 6.59; N, 8.43.



3-((1R,2S)-1,3-dihydroxy-1-phenylpropan-2-ylamino)-5,5-dimethylcyclohex-2-enone (72)

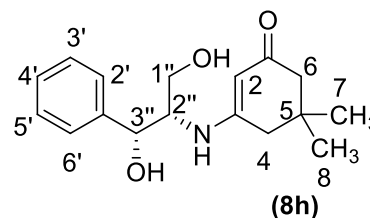
Using the above general procedure the target molecule was prepared from the reaction of (1S,2S)-(+)-1-amino-1-phenyl-1,3-propanediol with dimedone.

Yellowish solid; Yield: 60%; mp: 103-105 °C: **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3590 (OH),

3540 (OH), 3198 (NH), 3010 (C-H, aromatic), 2952 (C-H, str),

1644 (C=O), 1589 (C=C), 1249 (C-C, bend); **^1H NMR** (CDCl_3 ,

400 MHz): 7.37-7.19 (m, 5H, Ar-H), 6.34 (brs, 1H, NH), 5.80



(s, 1H, CH, C-2), 5.18 (s, 1H, OH), 5.07 (s, 1H, OH), 4.13-3.81 (m, 4H, C-1'', C-2'', 3''), 2.47-2.21 (m, 4H, 2CH₂, C-2,6), 0.94 (s, 3H, CH₃), 0.67 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 100 MHz): 196.8 (C=O), 163.1 (NH-C=), 148.4, 147.1, 139.5, 138.5, 132.5, 130.0 (aromatic carbons), 102.2 (C=CH), 68.1 (CH-OH), 62.1 (CH-NH), 60.7 (CH₂-OH), 49.7 (CH₂), 42.3 (CH₂), 33.6 (2CMe₂), 27.3 (CH₃), 26.5 (CH₃); **EIMS** (*m/z*, %): 290.0 (74.9) (M⁺ +1); Anal. Calcd for C₁₆H₂₂NO₃ (289.37); C, 70.56; H, 8.01; N, 4.84; Found: C, 70.49; H, 8.05; N, 4.90.

4-((5,5-dimethyl-3-oxocyclohex-1-enylamino)methyl)cyclohexanecarboxylic acid (73)

The reaction of amino acid (Transexamic acid) and dimedone gave the target molecule according the general procedure mentioned above in 140 min. White crystals; Yield: 48%; mp:

270-272 °C: **IR** (neat KBr, $\nu_{\max}$, cm⁻¹): 3251 (NH), 2937

(C-H, str), 1683 (C=O), 1516 (C=C), 1240 (C-O), 1149 (C-C, bend); ¹H NMR (CDCl₃, 400 MHz); δ : 6.93 (s, 1H, NH); 4.76 (s, 1H, CH), 2.82-2.78 (m, 4H, 2H, 2CH₂), 2.16

(m, 2H, CH₂NH), 2.10 (m, 1H, CH, C-4'), 1.93, (m, 4H,

2CH₂, C-3',C-5'), 1.77, 1.31, (m, 2H, CH₂, C-6'), 1.47, (m, 1H, C-1'), 1.27, 0.94, (m, 2H, CH₂,

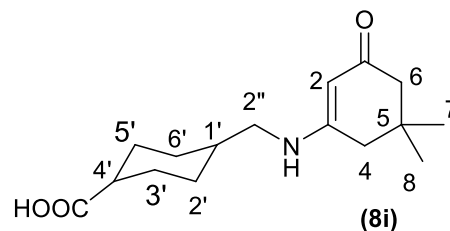
C-2'), 0.91 (s, 3H, CH₃), 0.87 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ : 193.6 (C=O), 176.7

(Carboxylic acid carbon), 162.9 (NH-C=), 93.6 (C=CH), 50.2 (CH₂-C=O), 48.2(CH₂-NH), 42.5

(CH), 42.0 (CH₂), 35.7 (CH), 29.5 (CH₂), 28.7 (2CMe₂), 27.9 (CH₃), 27.8. (CH₃); **EIMS** (*m/z*,

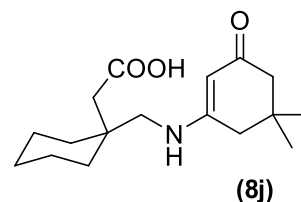
%): 279.1(53.5) (M⁺ +1); Anal. Calcd for C₁₆H₂₅NO₃ (279.18); C, 68.79; H, 9.02; N, 5.01:

Found: C, 68.73; H, 9.00; N, 5.10.

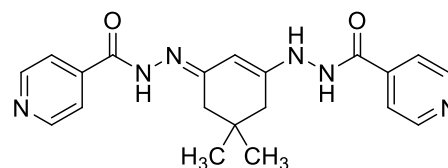


2-(1-((5,5-dimethyl-3-oxocyclohex-1-enylamino)methyl)cyclohexyl)acetic acid (74)

Using the above general procedure the target molecule was synthesized by the reaction of 2-(1-(methyl) cyclohexyl)acetic acid with dimedone in 140 minute under thermal condition at 80 °C. White crystals; Yield: 50 %; mp: 155-158 °C; **IR** (neat KBr, $\nu_{\max}$, cm^{-1}): 3310 (NH), 2927, 2848 (C-H, str), 1708 (C=O, carboxylic, 1643 (C=O, ketonic), 1581 (C=C), 1373 (C-H, bend); **^1H NMR** (CDCl_3 , 400 MHz); δ : 7.52 (brs, 1H, NH), 5.43 (s, 1H, CH), 3.19 (s, 2H, CH_2NH), 2.45 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 2.20 (s, 2H, CH_2), 1.4-1.3 (m, 10H, 5 CH_2), 1.05 (s, 3H, CH_3), 1.03 (s, 3H, CH_3). **^{13}C NMR** (CDCl_3 , 100 MHz): δ : 195.5 (C=O), 175.9 (COOH), 168.5 (NH-C=), 109.5 (C=CH), 51.6 (CH_2), 48.1(CH_2 -NH), 43.8 (CH_2), 41.1, 1.40.6 (CH_2), 36.6 (CH_2), 32.7 (CH_2), 28.3 (2 CMe_2), 25.8 (2 CH_3), 25.4 (2 CH_3), 22.6 (CH_2), 21.4 (CH_2); **EIMS** (m/z , %): 292.9 (13.7) ($\text{M}^+ + 1$); Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_3$ (293.2): C, 69.59; H, 9.28; N, 4.77; Found: C, 69.55; H, 9.20; N, 4.70.

**(E)-N'-(3-(2-isonicotinoylhydrazinyl)-5,5-dimethylcyclohex-2-enylidene)isonicotinohydrazide (75)**

Using the above general procedure for the synthesis of β -enaminones the title compound was obtained in excellent yield within 30 min. Yellow solid; Yield: 90 %; mp: 181-183 °C; (neat KBr $\nu_{\max}$, cm^{-1}): 3262 (NH), 3021 (C-H, aromatic), 2938 (C-H, str), 1674 (C=O), 1558 (C=C), 1267 (C-O); **^1H NMR** (CDCl_3 , 400 MHz): 10.84 (brs, 2H, NH), 8.52 (d, $J = 5.6$ Hz, 4H, Ar-H), 7.76 (d, $J = 6$ Hz, 4H, Ar-H), 5.81 (s, 1H, CH), 2.40 (s, 4H, 2 CH_2), 1.04 (s, 6H, 2 CH_3); **^{13}C NMR** (CDCl_3 , 100 MHz): 164.8 (2NH-C=O), 149.7 (NH-C=), 121.7 (aromatic carbons), 90.1 (C=CH), 48.9 (CH_2), 40.3 (CH_2), 32.2 (2 CMe_2), 27.4 (2 CH_3); **EIMS** (m/z , %): 378.1(100.0) ($\text{M}^+ + 1$); Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}_2$ (378.18); C, 63.48; H, 5.86; N, 22.21; Found: C, 63.40; H, 5.80; N, 22.18.



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PART B

Chapter 5 **Biological Evaluation**

5.1. Introduction

The studies of heterocyclic compounds have now become a separate field of pharmaceutical chemistry with a long history of contribution, present society and future prospects. Today life is totally dependent on the heterocyclic compounds. It takes starts with nitrogenous bases like purine/primidine and in case of disease, is cured from medicines, many of which are heterocyclic in nature. It also provides reagents and synthetic methods into the related fields such as biochemistry, material sciences and polymer chemistry.

Preliminary bioassay screening plays a very crucial role in the drug development program. It provides an opportunity for bioactivities and thus helps in the selection of leads like compounds for secondary screening of detailed pharmacological evaluations. Certainly, new or modified therapeutic agents always possess through the preliminary bioassay system with an acceptable safety profile.

The series of synthesized compounds like polyhydroquinoline derivates, 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydro-xanthenes have been screened for the following biological activities using standard protocols.

1. Protein tyrosine phosphatase 1B (PTP1B) inhibitors of polyhydroquinoline derivatives
2. Cytotoxicity of polyhydroquinolines derivatives
3. Analgesic activity of polyhydroquinolines derivatives
4. Muscles relaxant activity of polyhydroquinolines derivatives
5. Anti-epileptic activity of polyhydroquinolines derivatives
6. Anti-inflammatory activity of polyhydroquinolines derivatives
7. Cytotoxicity studies of 2,2'-(arylmethylene)bis(3- hydroxy-5,5- dimethyl-2-cyclohexene-1-one)

Leishmanicidal studies 2,2'-(arylmethylene)bis(3- hydroxy-5,5- dimethyl-2-cyclohexene-1-one)

9. Cytotoxicity of 1,8-dioxo-octahydroxanthene derivatives
10. Leishmanicidal studies 1,8-dioxo-octahydroxanthene derivatives

The detail description of each bioassay is as below.

5.2. Protein tyrosine phosphatase 1B (PTP1B) inhibition activity of polyhydroquinoline derivatives

Protein tyrosine phosphatase (PTPs) plays critical role during tyrosine phosphorylation such as cell growth, metabolic activities, cell to cell adhesion, cell-matrix contacts, immunological response and cell proliferation and differentiation.^{1,2} It is an intracellular non-receptor type PTP, which is regarded to be well-validated remedial goal for drug advancement. The genetic and biochemical investigation confirmed the control of insulin- and leptin-receptor⁵. Various investigations have exposed that PTP1B-knockout mice confirmed increased sensitivity to insulin, enhanced glycemic control, and resistant to diet-induced obesity³. Recently, PTP1B inhibition is used as a significant and therapeutic strategy for targeting obesity and type 2 diabetes. Due to well documented genetic and biochemical evidences regarding PTP1B to numerous human infections, significant efforts have been made to develop PTP1B inhibitors^{4,9}. Permeability and selectivity are the major challenges in developing well-validated therapeutic target for new drug as PTP1B inhibitors¹⁰. Various laboratories have reported the PTP inhibitor but these are mostly substantiated either due to their structural features large (MW > 500) or hydrophilic molecules containing multiple acid, peptide groups as well inconvenient synthetic route^{7,10-13}.

In the current investigation an efforts have been made to screen out PHQs derivative as a new class of PTP1B inhibitors owing to its therapeutic and synthetic potential¹⁴, which clearly indicate the remarkable potential of novel PHQ derivate as source of valuable drugs.

Furthermore, the permeability problems of carboxylic acid containing compounds are well documented³. Therefore, the polyhydroquinolines having ester moiety are expecting to be more cell-membrane permeable than the corresponding acid. In addition, we speculate that there is also the possibility of cleavage of ester group of polyhydroquinoline in the cell by enzymes to provide more potent PTP inhibitor. Execution of this synthetic plan in the laboratory may afford numerous opportunities to engage biological receptors connected with nitrogen heterocyclic moieties as well as with carbonyls of the polyhydroquinoline and may impart interesting biological properties thus leading to discovery of useful therapeutic agents.

5.2.1. Procedure for protein tyrosine phosphatase 1B (PTP1B) inhibition

The enzymatic assay was performed at normal temperature in 96-well plates in DMG buffer with pH 7.0. The reaction was started by addition of the enzyme. The final concentration of enzymes was 10 or 100 mM for PTP1B. The initial rate of PTP catalyzed hydrolysis of p-nitrophenol phosphate (pNPP) was measured by following the absorbance change at 405nm. IC₅₀ value was determined under fixed p-NPP at concentration of 1 mM. All the assays were carried out in duplicate or triplicate and the average results were presented as IC₅₀ values.

5.2.2. Molecular Docking simulations

FRED 2.1¹⁵ was used in this study to dock the OMEGA pre-generated multi-conformer library mentioned above. FRED 2.1 strategy was to exhaustively dock/score all possible

positions of each ligand in the binding site. The exhaustive search was based on rigid rotations and translations of each conformer within the binding site defined by a box. FRED filtered the poses ensemble by rejecting the ones that clash with the protein (PTP1B) or that did not have enough contacts with the protein. The final poses could then be scored or re-scored using one or more scoring functions. In this study, the smooth shape-based Gaussian scoring function (shapegauss) was selected to evaluate the shape complementarity between each ligand and the binding pocket. Default FRED protocol was used except for the size of the box defining the binding sites. In an attempt to optimize the docking-scoring performance, an exhaustive docking with shapegauss applying the "Optimization" mode was performed.

The "Optimization" modes involve a systematic concrete body optimization of the top ranked poses from the exhaustive docking. Three different boxes were explored for LOX (PDB ID: 2BGD). Three different simulations were carried out with an added value of 8 Å around the reference ligand.

5.3. Result and discussion (polyhydroquinolines as tyrosine phosphatase 1B (PTP1B) inhibitors)

Except compounds **2b**, **2f**, **2i**, **2n**, rest of the compounds exhibited promising PTP1B inhibitory activity (Table 5.1). The computational study was carried out to identify molecular binding mode and mechanism behind the enzyme inhibitory activities of the polyhydroquinoline derivatives. The surface of enzyme was found to compose of active pockets. (Figure 5.1). These active sites of PTP1B consist of amino acid side chain. Among these amino acids the most important were Ser 216, Arg221, Tyr46 and Phe182. Due to salvation in active pockets most of the surrounding was composed of amino acids instructing positive electrostatic potential.

However Asp181 was responsible for negative electrostatic found as a minor patch (Figure 5.3) inside the active pocket of PTP1B. Most of the compounds showed considerable inhibitory effect against PTP1B. Compound **2m** (IC_{50} of 37.58 ± 0.02) was the most active

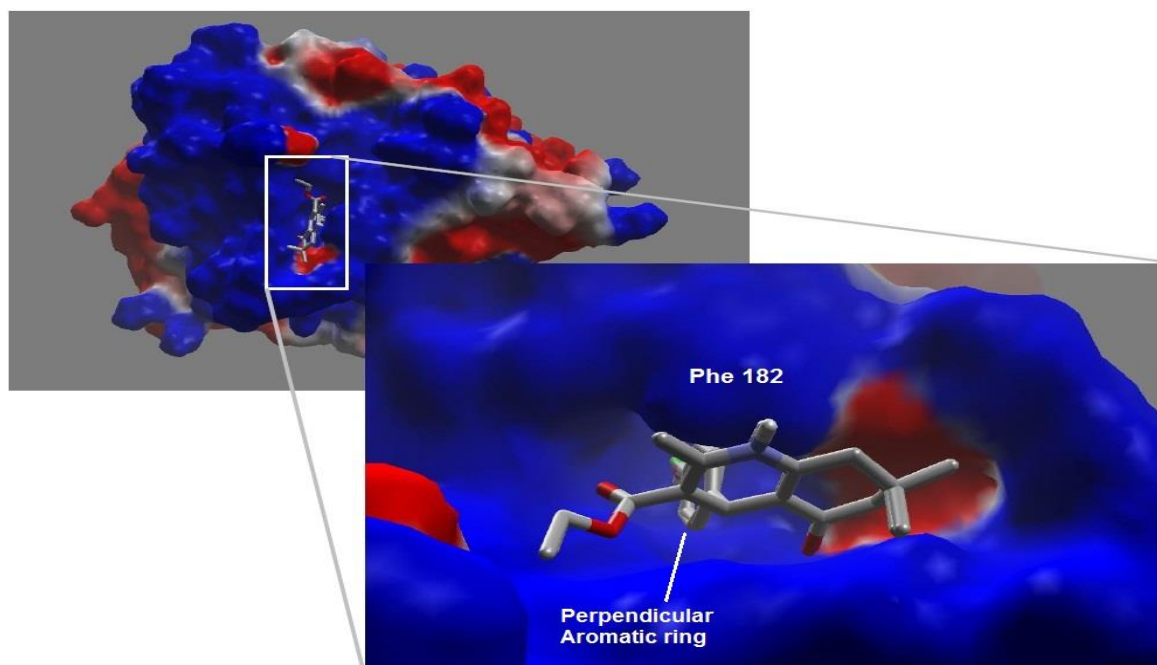


Fig. 5.1. Electrostatic surface of PTP1B Blue color indicates positive electrostatic surface, red color regions indicates negative electrostatic surface and white region depicts non-polar (hydrophobic) surface of the enzyme. Perpendicular aromatic ring (having R_1 , R_2 and R_3 groups) of all compounds are partially hidden behind the slit made up of Phe 182 amino acid side chain. All of the compounds revealed favorable steric and electrostatic matching with active site of PTP1B.

compound, followed by compound **2g**, (IC_{50} of $41.19 \pm 0.02 \mu M$) **2h** (IC_{50} of 60.56 ± 0.02) and **2a** (IC_{50} of μM 60.82 ± 0.02), respectively. Detailed computational insights revealed the similar molecular binding mode of all active compounds (Figure 5.2 and 5.3). The major reason behind significant enzyme inhibitory effects of the active molecules is the presence of smaller but polar group on aromatic moiety of PHQs. It has been observed in case of **2m**, the OH group at para

position involved in the formation of enzyme-inhibitor complex. The three important simultaneous hydrogen bonding interactions of OH group with significant amino acid side chains were recognized.

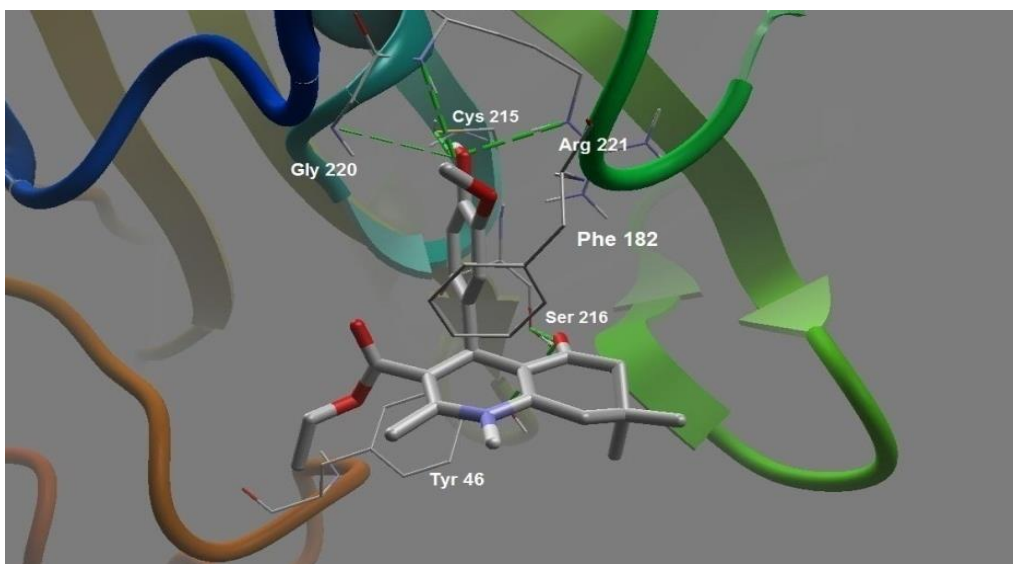


Fig. 5.2. Binding mode of compound **2m** inside catalytic site of PTP13.

Hydrogen atoms(except polar ones) were omitted for clarity.

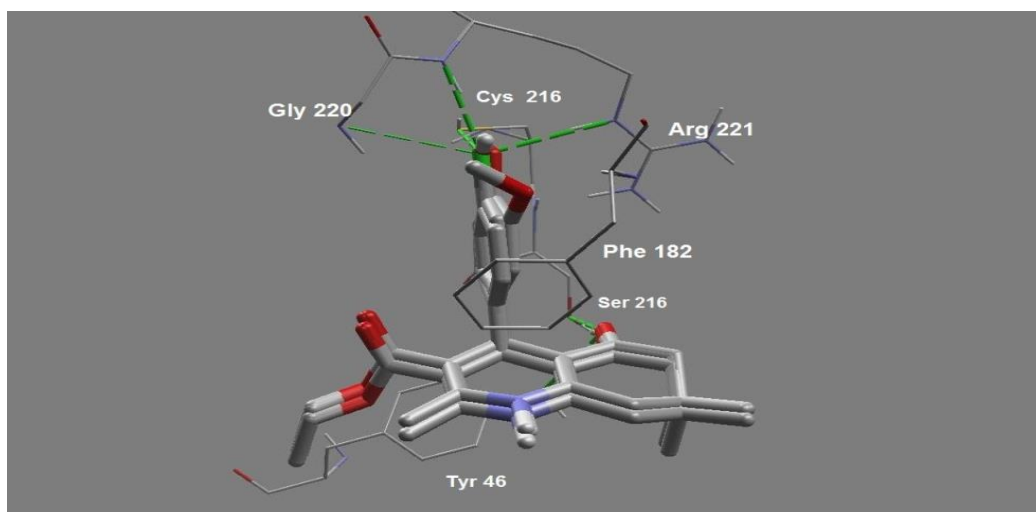


Fig.5.3. Binding modes of compound **2a**, **2h**, and **2m**. All poses of the compounds seem to be superimposed on each other. It clearly depicts similar bonding interactions between the enzyme and inhibitors.

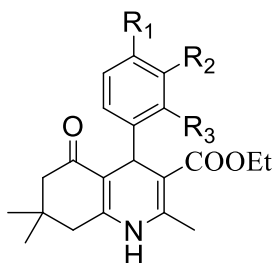
The most important amino acid that involved in enzyme inhibition was Arg221. Encouragingly, among the various amino acid side chains Arg221 was found in favorable contact with hydroxyl moiety of the compound **2m**. It was observed that guanidine a (3.08 °A) and amide (3.00 °A) has two hydrogen bonding interactions.

In addition, hydroxyl also revealed hydrogen bonding with Gly220 (3.17 °A) and Cys215 (3.34 °A), being other significant amino acid side chains of PTP1B. In case of compound having methoxy (OCH₃) group, hydrogen bonding was determined between methoxy group and Phe182 (2.84). Beside hydrogen bonding other interaction which reinforced the macromolecular complex are the hydrophobic interactions involving Ph182 (2.84). Furthermore, the carbonyl moiety, (SP² hybridized oxygen) as a part of cyclohexanone have vital role as hydrogen bonding acceptor. The phenyl parts showed as hydrophobic interactions played an important role in the stabilization of inhibitor-enzyme interactions. The important amino acids that involved in hydrogen bonding with carbonyl of cyclohexanone group are the Tyr46 (2.92) and Ser 216 (2.89). In addition, ethoxy group revealed hydrophobic interactions with Val48. The active compounds (**2a**, **2g** and **2h**), also represented similar binding mode and interaction as in the case of molecule **2m**, except additional interactions due to presence of methoxy group on aromatic ring. It is the major factor behind highest potency of the compound **2m**.

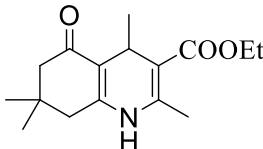
Form the point of view of structure activity; it can be assumed that molecules having less polar or bulky groups at R₁ position were mostly responsible for lower inhibitory activity. The geometry of the entire molecules was sterically favorable towards Phe182. In active molecules no electrostatic or steric clashes were observed besides from favorable interactions. Conclusively we can say that smaller but polar groups are required to be attached at position ortho, meta and

para position of the aromatic ring, located at C-4 position of PHQs derivatives will be potent inhibitor. Another assumption was the use of the corresponding ester moiety in the polyhydroquinoline can act as a pro-drug. These compounds will be more cell-membrane permeable than their corresponding acid, and can be cleaved in the cell by enzymes to lessen the active PTP inhibitor.

Table 5.1. Enzyme inhibitory activity of polyhydroquinoline derivatives



Product	R ₁	R ₂	R ₃	IC ₅₀ (μM)
2a	OH	H	H	60.82±0.02
2b	H	H	H	>200
2c	H	OH	H	71.24±0.05
2d		H	H	90.27±0.02
2e	4-N(CH ₃) ₂	H	H	112.38±0.03
2f	-OCH ₃	H	H	>200
2g	F	H	H	39.19±0.02
2h	Cl	H	H	55.40±0.04
2i	2-Pyridyl	H	H	123.35±0.01
2j	H	3-Pyridyl	H	129.71±0.03

2k	H	H	4-Pyridyl	87.97±0.04
2l	H	H	2-OCH ₂ CH ₃	>200
2m	OH	OCH ₃	H	37.42±0.04
2n		H	H	>200
2o	H	OCH ₃	OCH ₃	75.87±0.01
2p	4-OCH ₂ CH ₃	H	H	92.49±0.02
Ursolic acid				2.7±0.02

5.4. Cytotoxicity studies of polyhydroquinolines derivatives

5.4.1 Procedure for cytotoxicity assay (in vitro)

The in vitro cytotoxicity assay was carried out by using mice hepatocytes according to the literature procedure¹⁶. The tested compound was incubated for 24 h, and lastly the MTT assay was employed to the determination of the cell viability. For MTT assay, cells were maintained in RPMI-1640 medium containing 10% FBS, 110 µg/ml penicillin sodium salts, 2 mg/ml sodium bicarbonate solution, and 100 µg/ml streptomycin sulfate. Initial seeding of the 8.6×10^3 mice hepatocytes, was carried out in 96-well plates. The cells were treated with test compounds at various concentrations as well as with vehicle (0.2% MSO) and then incubated for 48 h followed by performing MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay.

5.5. Analgesic activity of polyhydroquinoline derivatives

Pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage. Numerous progresses have been made in

the understanding of pathogenesis and as a result, important growth has taken place in the development of novel anti-inflammatory drugs¹⁷. The major causes of pain and inflammation are the human morbidity and motarality^{18,19}. The excessive inflammation also contributes to many acute and chronic human diseases^{20,21}. Inflammatory response is characterized by the abundant productions of nitric oxide (NO) and prostaglandin E2 (PGE2), and of cytokines, such as tumor necrosis factor²².

Currently used non-steroidal anti-inflammatory drugs (NSAIDs) have limitations for therapeutic use since they cause GIT disorder²³ and renal side effects that are inseparable from their pharmacological activities²¹. Therefore, these events highlight the need of the synthesis of such compounds devoid of such side effects which has become an important goal for medicinal chemists in recent years.

5.5.1. Procedure for analgesic activity

The polyhydroquinolines **2(a-f)** and **3(a-c)** were tested for their analgesic effect. The acetic acid induced writhing pain model was used for this experiment. BALB/c mice were divided in various groups (n=6). Normal saline was administering (i.p, 10 ml/kg) to the negative control group and diclofenac sodium (i.p. 10 mg/kg) was injected to the positive control group, while the rest of groups were treated with 2.5 and 5 mg/kg of each compound. After 30 min of saline, diclofenac sodium and compounds administration, the animals were treated i.p. with 1% acetic acid. The number of abdominal constrictions (writhes) was counted after 5 min of acetic acid injection for the period of 10 min²⁴. The compounds were also tested using hot plate model pain paradigm.

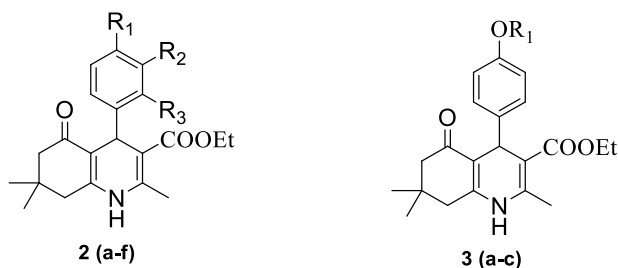
5.5.2. Statistical analysis

The results obtained were expressed as mean $\pm$ SEM (Standard error of mean) of six animals. For statistical analysis, ANOVA was followed by post hoc Dennett's test for multiple comparisons. Effects were considered to be significant at the $P < 0.05$ level.

5.5.3. Result and discussion on analgesic activity of polyhydroquinoline derivatives

The tested molecules demonstrated variable analgesic effect, as presented in table 5.2. The maximum analgesic effect was observed with **3c** and **3b** followed by **2f** and **2e** in acetic acid induced writhing test. In case of hot plat no analgesic effect was observed by any of tested compound.

The chemical induced and thermal induced pain animal models were extensively used for evaluation of analgesic potential of any substance. In case of chemical induced pain model acetic acid was well known chemical for induction of pain, while hot plat experiment was used for thermal induced pain. The compound with inhibiting induced writhing potential was generally considered as peripheral analgesic, the latency time enhancing effect in hot plate is considered as central analgesic (Table 5.2).

Table 5.2. Analgesic effect of various synthetic polyhydroquinoline derivatives in acetic acid induced writhing pain model

Compd.	R ₁	R ₂	R ₃	Dose	Writhing
Mean Writhing					
				2.5 mg/kg	5 mg/kg
2a	OH	H	H	33.54±1.22**	25.87±2.43**
2b	F	H	H	30.87±2.77**	22.65±2.54***
2c		H	H	66.34±1.87	65.09±2.65
2d	H	NO ₂	H	20.54±1.96**	19.09±1.65***
2e	NO ₂	H	H	27.87±1.54**	20.98±2.76***
2f	OCH ₃	OCH ₃	H	40.87±2.75**	28.87±1.98**
3a	Propagyl	---	---	55.32±2.87*	50.34±1.88*
3b	Tetradecane	---	---	20.54±1.87***	18.98±1.76***
3c	10-Br-decane	---	---	22.54±2.55***	18.09±2.65***
Saline				10 ml/kg	72.34±
Diclofenac Sodium				10 mg/kg	12.43±***

^aValues represents the number of writhing, after 30 min of treatment with saline (10 ml/kg), diclofenac sodium (10 mg/kg) and compounds (2.5 and 5 mg/kg). Data presented as mean ± S.E.M (n=6). * P< 0.05, ** P<0.01, *** P<0.001, all compared with control.

In the current research activity the tested substance failed to increase the latency time in hot plate pain model, while some of the compound significantly protected the acetic acid induced writhing in animal. The induction of pain by acetic acid injection was due to the stimulation of

local peritoneal receptors which lead to the release of prostaglandin (PG). The release of PG was responsible for induction of pain²⁵. Now the protection induced writhing by our tested compounds was attributed to the PG release inhibition property. So our tested compounds were peripheral analgesic not central ones (Fig 5.4).

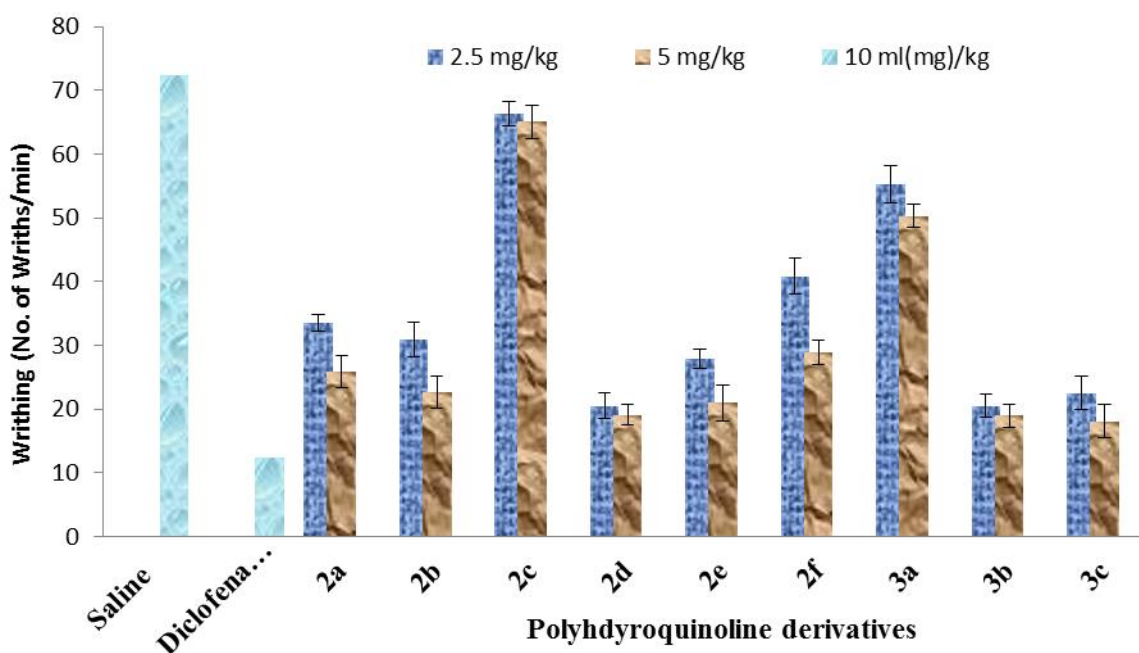


Fig. 5.4. Graphical representation of analgesic activities of polyhydroquinoline derivatives in comparison with standard diclofenac and saline

5.6. Anti-inflammatory activity of polyhydroquinoline derivatives

The anti-inflammatory activity was performed on rat of either sex (150 - 250 g). The animals were randomly divided in various groups each of six animals²⁵. Group I was treated with normal saline (10 ml/kg), group II with diclofenac sodium (10 mg/kg), rest of the groups were treated with synthetic compounds **2(a-f)** and **3(a-c)** at the dose of 2.5 and 5 mg/kg. After thirty minutes of the above intraperitoneal administration, carrageenan (1%, 0.05 ml) was injected

subcutaneously in the sub plantar tissue of the right hind paw of each rat. The inflammation was measured using plethysmometer (LE 7500 plan lab S.L) immediately after injection of carrageenan and then 1,2,3,4 and 5 h. The average foot swelling in drug treated animal as well as standard was compared with that of control and the percent inhibition (anti-inflammatory activity) of edema was determined using the formula.

Percent inhibition = $A-B/A \times 100$, where A represent edema volume of control and B as paw edema of tested group.

5.6.1. Results and discussion on anti-inflammatory effect of polyhydroquinolines

The synthetic compounds were tested for anti-inflammatory effect at the same dose using carrageenan induced paw edema. Among the tested compounds **2d**, **3b** and **3c** exhibited significant anti-inflammatory effect as presented in Table 5.3. A moderate anti-inflammatory effect was observed with **3c** followed by **2b** and **2d**, while the rest of compounds were devoid of anti-inflammatory potential as displayed in Fig 5.5 and 5.6.

Carrageenan-induced paw edema is a well-established animal model to assess the anti-inflammatory effect of natural products as well as synthetic chemical compounds. Edema formation due to carrageenan in paw is a biphasic event, during 1–5 h; the initial phase (1 h or 1.5 h) is predominately a non-phagocytic edema followed by a second phase (2-5) h with increased edema formation that remained up to 5 h^{24,25}. The inflammation at initial phase was directly attributed to histamine, serotonin or bradykinin²⁶. The late phase or second phase edema has been shown to be the result of overproduction of prostaglandin. Our tested compounds significantly protected the induced paw edema from the 1st h and remained significant up to 5th h,

the maximum effect was demonstrated at the 3rd h of treatment. The results suggested a tentative mechanism that the anti-inflammatory effect was due to inhibition of histamine, serotonin or prostaglandin.

Table 5.3. Anti -inflammatory effect of various synthetic compounds in carrageenan induced odema model

Comp	Dose	1 h	2 h	3 h	4 h	5h
2d	2.5 mg/kg	3.23± 2.65	4.65± 2.76	4.98± 2.09	4.07± 2.22	3.88± 1.99
	5 mg/kg	5.34± 2.98	6.98± 1.09*	7.10± 1.45*	6.99± 2.87*	6.84± 2.76*
3b	2.5 mg/kg	10.31± 2.98*	13.54± 2.98*	15.98± 2.98*	15.60± 2.98*	14.88± 2.98*
	5 mg/kg	15.54± 1.65*	16.65± 1.78*	16.98± 1.03*	16.89± 1.68*	16.10± 2.65*
3c	2.5 mg/kg	14.54± 2.34*	15.34± 2.04*	15.90± 1.90*	15.78± 1.87*	15.50± 3.90*
	5 mg/kg	18.56± 1.98*	18.89± 2.09*	19.40± 2.88*	19.30± 2.98*	19.05± 2.56*
Control	10 ml/kg	-	-	-	-	-
Diclofenac	10 mg/kg	66.45± 0.76***	72.67± 0.54***	78.09± 0.09***	75.98± 0.98***	74.87± 0.54***

^aValues are reported as mean ± S.E.M. for group of six animals. The data was analyzed by ANOVA followed by Dennett's test. Asterisks indicated statistically significant values from control. * $P < 0.05$, ** $P < 0.01$

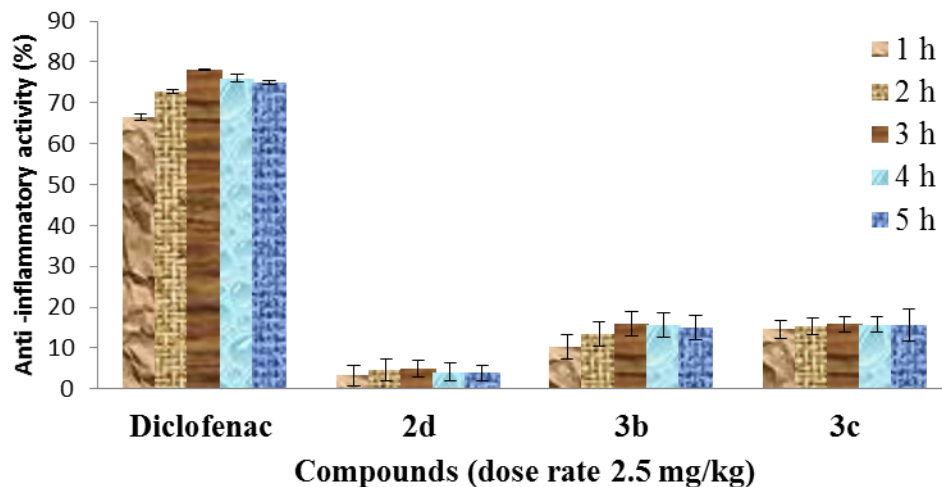


Fig. 5.5. Graphical representation of Anti-inflammatory activity of polyhydroquinolines (at dose rate 2.5/Kg)

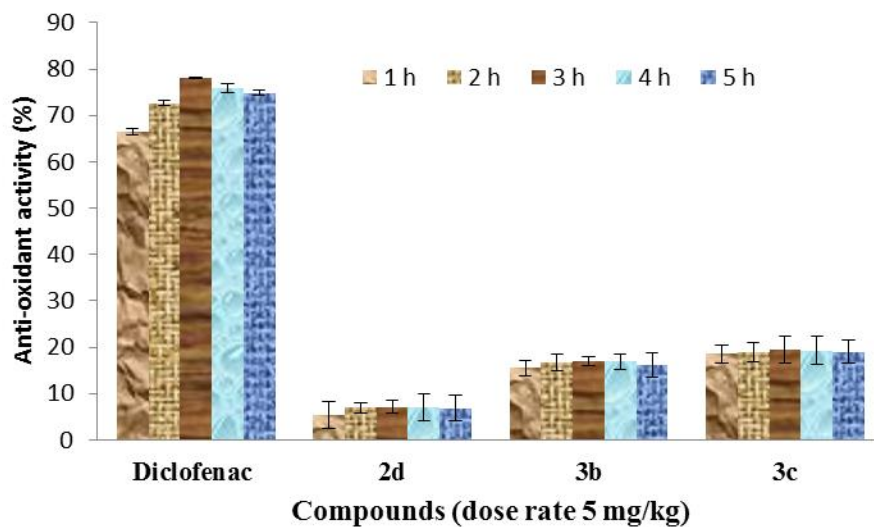


Fig.5.6. Graphical representation of anti-inflammatory activity of polyhydroquinolines derivatives (at dose rate 5 mg./Kg)

5.7. Muscles relaxant activity of polyhydroquinolines derivatives**5.8. Anti-epileptic activity of polyhydroquinolines derivatives**

The polyhydroquinoline derivatives have shown negative muscles relaxant and anti-epileptic activities.

5.9. Cytotoxicity studies of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)

The detailed experimental procedure has been described in section 5.4.1. Interestingly, none of the compounds shows significant cytotoxicity effect as showed in table 5.5.

5.10. Leishmanicidal studies

Leishmaniasis is one of the most devastating of parasitic diseases. It occurs in all continents except Australia¹⁶. It is mostly zoonotic in nature, but also exists in an anthroponotic mode of transmission in some parts of Europe and Asia. According to WHO, about 350 million people in the world are at risk of acquiring leishmaniasis²⁷. On the basis of symptomatology leishmaniasis occurs in visceral (VL), cutaneous (CL), mucocutaneous (MCL) and diffuse (DCL) forms^{28,29}. *Leishmania major* and *L. tropica* cause the cutaneous form of the disease which is a stigmatizing and disfiguring disease^{30,31}. If remains without treatment, it becomes visceral disease, which is highly fatal. More than 500,000 casualties, have been caused by *Leishmania (L.) chagasi/infantum* in Latin America and southern Europe and by *Leishmania (L.) donovani* in Africa, India, Pakistan and Middle East³³. The systemic pentavalent antimonials still remain the recommended drugs for treatment in most endemic countries, but these have unpleasant and serious side effect such as renal, neural, cardiac toxicity^{31,32,34}. Treatment of CL

or VL with antimonials is even more difficult in human immunodeficiency virus (HIV)-infected individuals and is associated with frequent relapses because these drugs require healthy immune system for optimal anti-parasitic activity. Conclusively, the therapy of Leishmaniasis is still complicated, with a limited therapeutic arsenal, very poisonous drugs, and resistance cases³⁵.

Therefore, the development of new, effective molecules for chemotherapy is one of the urgent tasks of current research. The present work was designed with the assumption that 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 1,8-dioxo-octahydro-xanthene derivatives Xanthenes and their derivatives having interesting structural framework constitutes a significant class of organic compound can contribute as a potential leishmanicidal compounds. Its nucleus comprises structural features of a broad range of natural products³⁶. The xanthenes nucleus is often come upon as a structural component of compounds possessing biological activity as anticoagulant, spasmolytic, anticancer, anti-anaphylactin^{37,38} agents. Also, they can be used as cognitive enhancers for the treatment of neurodegenerative disease including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus³⁹. Some xanthenes derivatives could also be used as photoactive materials⁴⁰.

Our concern for testing the synthesized 1,8-dioxo-octahydroxanthenes arose also from the fact that these compounds are affordable and could be cheaply obtained in large quantities through a one pot synthesis, which is critical for any drug developed against a neglected tropical disease.

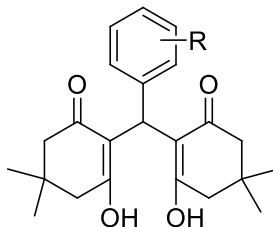
5.11. Procedure for Leishmanicidal activity (in vitro)

For leishmanicidal activity *Leishmania major* (PS28/DESTO) promastigotes were cultured at 22–25°C in RPMI-1640 (Sigma) as reported earlier¹⁶. Medium was supplemented with 10% heat inactivated (56°C for 30 min) fetal bovine serum (FBS). The culture of promastigotes at logarithmic phase was sediment down at 800 rpm, counted with the help of improved Neubauer chamber under the microscope and three times washed with saline in the same condition. The final density of 2×10^6 cells/ml was achieved by diluting the parasites with fresh culture medium. In a 96-well micro titer plate, 180 μ l of medium was added in the first row and 100 μ l of medium was added in others wells. The compounds to be screened were dissolved to a final concentration of 1.0 mg in 0.1 ml of PBS (Phosphate Buffered Saline, pH 7.4 containing 0.5% MeOH, 0.5%DMSO). One row was used for control (DMSO) which received medium while one for standard drugs (Pentamidine and ampicilline to a final concentration of 1.0 mg/mL was added separately as positive control). Plate was incubated at 22–24°C for 72 h. Results are the replicates of three different experiments. The 50% inhibitory concentrations (IC₅₀) were calculated by EZ-Fit 5.03 Perrella Scientific Software.

5.12. Results and Discussion on Leishmanicidal activity of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one)

The entire synthesized compound showed no significant cytotoxicity (Shown in Table 5.5). It is a positive signal from this oxygen containing heterocyclic scaffold for further exploration and safety of cells in case of any *in vivo* activity. All the synthesized compounds were further tested for their leishmanicidal activity These compounds showed significant

leishmanicidal activity except few like compound **6a**, **6b**, **6j**, **6l**, which were found inactive. The result displayed in table 5.5 indicated that polar group substituted compounds at Para position on aromatic rings, showed promising activity. Halogen substituted derivatives showed best activities in comparison to the rest of compounds for example compound **6c** having fluorine at Para position showed activity with (IC_{50} $\mu\text{g/ml}$) 2.9 ± 0.003 while compound **6d** having chlorine show with (IC_{50} $\mu\text{g/ml}$) 7.2 ± 0.005 . These are the most potent among the tested compounds. Apart from halogens, other polar groups like hydroxyl and methoxy substituents at para position Compound **6e** (16.4 ± 0.001), **6f** (31.7 ± 0.05) also exhibited significant activities. Interestingly, alkyl group at para position (compound **6l** inactive) and amino groups (compound **6j** 97.3 ± 0.004), at Para position showed no activity, which indicated negative effect of alkyl groups on leishmanicidal activities. Similarly, substitution at position 3 of aromatic ring showed considerable activities but less pronounced than Para substituted derivatives Compound **7** (39.2 ± 0.001), compound **6i** (49.2 ± 0.001). All compounds showed no considerable cytotoxicity, which showed preliminary safety of the test compounds for further refinement and development of new lead compounds.

Table 5.4. Cytotoxicity and leishmanicidal activity of 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **6(a-l)**

Compd.	R	Leishmanicidal activity (IC ₅₀ µg/ml)	Cytotoxicity (IC ₅₀ , µg/ml)
6a	--	>100	>100
6b	H	98.7±0.001	>100
6c	4-F	2.9±0.003	>100
6d	4-Cl	7.2±0.005	>100
6e	4-OH	16.4±0.001	>100
6f	4-OCH ₃	31.7±0.05	>100
6g	3-NO ₂	39.2±0.001	>100
6h	4-NO ₂	27.1±0.003	>100
6i	3-OH	49.2±0.001	>100
6j	4-N(CH ₃) ₂	97.3±0.004	>100
6k	3-Cl	25.67±0.003	>100
6l	4-CH ₃	>100	>100
Pentamidine		2.56	-

5.13. Cytotoxicity studies 1,8-dioxo-octahydroxanthene derivatives

For procedures see section 5.2 of this chapter. The negative result of the cytotoxicity of 1,8-dioxo-octahydroxanthene derivatives has displayed in table 5.6, which indicates its safety profile for the cell in further in vivo pharmacological investigation.

5.14. Procedure for Leishmanicidal studies 1,8-dioxo-octahydroxanthene derivatives

The experimental procedure has been given in section 5.11.

5.14.1. Results and discussion on Cytotoxicity and Leishmanicidal activity of 1,8-dioxo-octahydroxanthene derivatives

The *in vitro* cytotoxicity assay was carried out by using mice hepatocytes according to the reported protocol¹⁶. The entire synthesized compound showed no significant cytotoxicity (Shown in Table 2). This was a positive signal form this interesting oxygen heterocyclic scaffold for further exploration as biological active and safety for cells in case of any *in vive* activity. The entire synthesized compounds were further discovered for their leishmanicidal activity according to the assumption that xanthenes derivatives have attractive skeleton on either side of the pyran ring which may act as potent leishmanicidal agents.

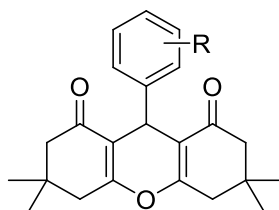
The ten 1,8-Dioxo-octahydroxanthene **7(a-j)** were evaluated in vitro for activity against *Leishmania major* (DESTO) promastigotes previously cultured at 22-25 °C, in the presence of the standard leishmanicidal agent Pentamidine as described previously

Growth inhibition as represented by % value. The data of growth inhibition of all synthesized compounds has been described in table 2. Compounds, **7(b-h)** inhibited parasitic growth, while **7f**, **7i**, **7j**, were found inactive. The data pointed out that chloro- and flouro derivatives had greater leishmanicidal activity than the corresponding hydroxylated and /or methoxylated compounds or N-alkylated. One of the NO₂- (**3e**) showed significant activity while the second one (**3a**) was inactive.

From structure-activity point of view, some trends were observed. Halogen substituted derivatives showed best activities in comparison to the rest of other compounds **3b**, **3c**. Fluorinated aryl moiety showed most potent activity. It is a well-established fact that halogen has

significant effect on both distribution and the energy of LUMOs that probably appeared to be more toxic against parasites than their parent compounds. Other polar groups like hydroxyl (4-OH) **3d**, (4-OH), **3g** (3-OCH₃) and nitro groups at Para position **3e** (4-NO₃) also exhibited excellent activities. Similarly, substitution at position 3 of aromatic ring showed considerable activities but less pronounced than para substituted derivatives. No substitution on aromatic ring **3i** observed inactive. We can say that the negative results of the cytotoxicity and potent Leishmanicidal activity preserve this class of heterocyclic scaffold for further refinement as well as development of lead compounds.

Table 5.5. Leishmanicidal activity and Cytotoxicity assay of 1,8-Dioxo-octahydroxanthene derivatives, **7(a-j)**.



Compd.	Ar	Leishmanicidal activity (IC ₅₀ , µg/ml)	Cytotoxicity (IC ₅₀ , g/ml)
7a	3-NO ₂	88.3±0.02	>100
7b	4-F-	3.1±0.02	>100
7c	4-Cl	6.7±0.03	>100
7d	4-OH	8.3±0.01	>100
7e	4-NO ₃	39.1±0.01	>100
7f	4-OH, 3-OCH ₃	11.4±0.01	>100
7g	4-N(CH ₃) ₂	>100	>100
7h	4-OCH ₃	50.7±0.01	>100
7i	H	>100	>100
7j	2-Furfuryl	>100	>100

All the synthesized compounds showed no considerable cytotoxicity which is a positive signal towards safety for cell, form this interesting oxygen heterocyclic scaffold for further exploration in case of any *in vive* biological activity. Six compounds showed potential in vitro leishmanicidal activity. Conclusively, it appeared that smaller group substituted particularly halogens at para position in the aromatic ring might be responsible for the leishmanicidal activity along with either side of the pyran ring. Broad mechanism support studies are essential to have a say to the better understanding of the mechanism of action of these compounds.

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Conclusion

Modern organic research synthesis focuses on the discovery and the formation of selective multiple bond-forming transformation allowing the creation of several covalent bonds in a single step. Hence, the number of steps required to obtain a target molecule is reduced. In this context, 1,3-dicarbonyl compounds are exceptional synthetic platform due to the presence of four contiguous reaction sites. This functional group density allows cascades of elemental steps from simple substrates leading to the selective formation of elaborated molecular architectures. More than twelve commercial, clinically important drugs have been manufactured and used worldwide by utilizing the multicomponent reaction assembly process, specifically based on Hantzsch reaction. These features in combination with the extremely fast reaction kinetics of microwave-assisted organic synthesis provide new methods for the rapid and efficient synthesis for pharmaceutical and synthetically versatile heterocyclic and non-heterocyclic compounds.

The modified protocol for Hantzsch reaction has been exploited for the selective synthesis of aza-heterocycles under microwave irradiation. Morpholine remains the attractive catalyst in term isolated product. Among the nitrogen heterocyclic compound polyhydroquinoline (PHQs) **2(a-t)**, polyhydroacridine-1,8-diones (PHAs) **4(a-g)** and 1,4-dihydropyridine (DHPs) **5(a-j)** derivatives were synthesized from dimedone, substituted aromatic aldehydes, ethyl acetoacetate and ammonium acetate in good to excellent yield. This simple procedure is applicable to a wide variety of aromatic and heterocyclic aldehydes with EDG as well as EWG.

By continuing the utilization of the 1,3-dicarbonyl chemistry a series of versatile synthetic intermediates, called bisdimedone derivatives **6(a-l)** were synthesized from dimedone with various substituted aldehydes. The reaction was catalyzed by MgCl_2 at room temperature. In conclusion we have identified MgCl_2 as an efficient catalyst for the Knoevenagel followed by Michael addition reaction. The synthesis of oxa-heterocyclic molecules (1,8-dioxo-octahydro-xanthenes) **7(a-j)** were successfully obtained by using Amberlite IR-120H as a recyclable solid acid in the acetonitrile as solvent in good to excellent yield.

β -Enaminone a resourceful precursor for different size of heterocyclic compounds and alkaloids have been synthesized by using PPA-SiO_2 as a heterogeneous catalysts. It has been explored as a powerful catalyst for synthesis a series of dimedone derived β -enaminones **8(a-k)**

Conclusion

under solvent free condition at 70-80 °C. This method was applicable to a wide range of aromatic and aliphatic amines to gave the desired product respectable yield.

After the successful completion of development of simple synthesis protocols for dimedone incorporating reaction, the next step was the biological and pharmacological activities the resultant compounds. In this context, polyhydroquinoline derivative were screened for their Protein tyrosine phosphatase 1B (PTP1B) inhibition property guided by computational chemistry. Among them compound **2m** (IC_{50} of 37.58 ± 0.02) was the most active compound, followed by compound **2g**, (IC_{50} of 41.19 ± 0.02 μM) **2h** (IC_{50} of 60.56 ± 0.02) and **2a** (IC_{50} of μM 60.82 ± 0.02), respectively, while compounds **2b**, **2f**, **2i**, and **2n**, were found inactive while others exhibiting promising PTP1B inhibitory activity. Interestingly, all the synthesized compounds showed negative cytotoxicity.

Polyhydroquinoline derivatives exhibited variable analgesic effect. In case of hot plat method no analgesic effect was observed. However, in acetic acid induced writhing test maximum analgesic effect was observed with **3i**, **3h**, **2f** and **2e**.

The polyhydroquinoline derivatives **2(a-p)** and **3(a-c)** were tested for anti-inflammatory effect. Among the tested compounds **2d**, **3h** and **3g** exhibited significant anti-inflammatory. A moderate anti-inflammatory effect was observed with **2d**, and **3c** while the rest of compounds were devoid of anti-inflammatory potential. However, the PHQs derivatives failed to show muscles relaxation activity and Anti-epileptic activity.

The versatile intermediates 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) **6(a-l)** and oxa-heterocyclces (1,8-dioxo-tetrahydroxanthene) derivatives **7(a-j)** were tested for the cytotoxicity and leishmanicidal activities. The compounds **6(b-f)** in 2,2'-(arylmethylene)bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) series and **7(b-f)** in 1,8-dioxo-tetrahydroxanthene derivatives showed potential leishmanicidal activity against *Leishmania major* (DESTO) promastigotes.