GREEN SYNTHETIC APPROACH TO OCTAHYDROQUINAZOLINES AND BIS-OCTAHYDROQUINAZOLINES AND STUDY OF THEIR BIOLOGICAL ACTIVITIES

By

MADHUSUDHAN SAHA
DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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Chemistry

DECLARATION

I, **Madhusudhan Saha**, hereby declare that the subject matter of the thesis is the record of the work done by me, that the contents of this thesis did not form basis of the award of any previous degree to me or to the best of my knowledge to anybody else, and that the thesis has not been submitted by me for any research degree in any other university/ institute.

This is being submitted to the North-Eastern Hill University for the award of degree of Doctor of Philosophy in Chemistry.

Madhusudhan Saha
(Candidate)

Dr. J.N. Vishwakarma

Joint-Supervisor

Dr. J.N. Vishwakarma.
Organic Research Lab.
Department of Chemistry.
St. Anthony's College.
Shillong-793001 (India)

Dr. R.L. Nongkhlaw
Supervisor

[illegible]
Department of Chemistry
NEHU, Shillong

Professor B. Myrboh
Head
Department of Chemistry
North-Eastern Hill University, Shillong

विभागाध्यक्ष
Head
रसायन विज्ञान विभाग
Chemistry Department
पुर्वोत्तर पर्वतीय विश्वविद्यालय
North Eastern Hill University
शिलांग / Shillong - 793022

NORTH-EASTERN HILL UNIVERSITY

Permanent Campus, Shillong – 793 022 (Meghalaya)

CERTIFICATE

This is to certify that the thesis entitled, *"Green Synthetic Approach to octahydroquinazolines and bis-octahydroquinazolines and study of their biological activities"* submitted by Shri Madhusudhan Saha for the degree of Doctor of Philosophy of the North-Eastern Hill University, Shillong, embodies the record of original investigation carried out by him under our supervision. He has been duly registered, and the thesis presented is worthy of being considered for the Ph.D. degree in Chemistry.

The work described in this thesis is original and has not been submitted for any other degree or diploma in this or any other university.

Dr. J.N. Vishwakarma
Joint-supervisor

Dr. J.N. Vishwakarma.
Organic Research Lab.
Department of Chemistry.
St. Anthony's College.
Shillong-793001 (India)

Dr. R.L. Nongkhlaw
Supervisor

Lecturer
Department of Chemistry
NEHU, Shillong.

Countersigned

Professor B. Myrboh
Head, Department of Chemistry

विभागाध्यक्ष
Head
रसायन विज्ञान विभाग
Chemistry Department
पुर्वोत्तर पर्वतीय विश्वविद्यालय
North Eastern Hill University
शिलांग / Shillong - 793022

DEDICATED

TO

MY

BELOVED PARENTS

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Above all I thank the almighty for keeping me in good health and strengthening me in achieving my goal.

PREFACE

This thesis entitled “green Synthetic approach to octahydroquinazolines and bis octahydroquinazolines and Study of their Biological activities” presents development of novel green synthetic methodologies of biologically important octahydroquinazolines and bis-octahydroquinazolines from a important class of synthons called enaminone and bis-enaminones. The thesis has been divided into five chapters.

Chapter I of the thesis describes a brief background of the work and a brief literature survey on the biological importance of the relevant heterocyclic systems. The chapter also deals with the fact that in many cases bis-heterocycles are more potent than their monomeric analogues.

Chapter II involves a brief literature survey on the synthesis of enaminones and their conversion into quinazolines. This chapter describes our green synthetic strategies for a series of hitherto unreported 1,2,3,4,5,6,7,8-octhydroquinazolines and bis 1,2,3,4,5,6,7,8-octhydroquinazolines in which the quinazoline systems have been linked through flexible aliphatic chains and rigid aromatic linkers. This chapter is divided into three parts. Part-I deals with the synthesis of 1-methyl-3-alkyl/aryl/aralkyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines & bis 1-methyl-3,3′-(alkane/arene)diyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines.Part-II deals with the synthesis of 1-benzyl-3-alkyl/aryl/aralkyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines & bis 1-benzyl-3,3′-(alkane/arene)diyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-

octahydroquinazolines. Part-III deals with the synthesis of 1-phenylethyl-3-alkyl/aryl/aralkyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines & bis 1-phenylethyl-3,3′-(alkane/arene)diyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines.

Chapter III deals with a short literature survey on the superiority of some dimeric heterocycles than their monomeric counterpart followed by synthesis of 1,1′-(alkanediyl) bis (5-oxo-3-alkyl/aryl/aralkyl-1,2,3,4,5,6,7,8-octahydroquinazoline from bis enaminones.

Chapter IV involves brief literature survey on the change in the potency as inhibitors of the molecule with the modification of substituents at different position of the quinazoline moiety. This chapter presents a facile one-pot synthesis of hitherto unreported 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline & 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxooctahydroquinazoline.

Chapter V contains a short literature reports on the anti microbial activities of quinazolines followed by antibacterial and anti fungal studies of some synthesised quinazolines and bis octahydroquinazolines

Each chapter is framed into introduction, Results and discussions and experimental section. The entire documentation in this thesis is supported by appropriate references at the end of each chapter. The reference of the published work of the present investigation is cited in the respective chapter.

My bio-data followed by a list of publications is attached at the end.

CONTENTS

CHAPTER I

INTRODUCTION

Green chemistry also called sustainable chemistry is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. In 1990 the Pollution Prevention Act was passed in the United States. This act helped create a *modus operandi* for dealing with pollution in an original and innovative way. It aims to avoid problems before they happen.

As a chemical philosophy, green chemistry applies to organic chemistry, inorganic chemistry, biochemistry, analytical chemistry, and even physical chemistry. While green chemistry seems to focus on industrial applications, it does apply to any chemistry choice. Click chemistry is often cited as a style of chemical synthesis that is consistent with the goals of green chemistry. The focus is on minimizing the hazard and maximizing the efficiency of any chemical choice.

The twelve principles laid down by Paul T Anastas and John C. Warner help to explain what the definition means in practice. The principles cover such concepts as:

- the design of processes to maximize the amount of raw material that ends up in the product;
- the use of safe, environment-benign substances, including solvents, whenever possible;
- the design of energy efficient processes;
- the best form of waste disposal: not to create it in the first place.

The 12 principles are:

1. It is better to prevent waste than to treat or clean up waste after it is formed.

2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

The Nobel Prize Committee recognized the importance of green chemistry in 2005 by awarding Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock the Nobel

Prize for Chemistry for "the development of the metathesis method in organic synthesis." The Nobel Prize Committee states, "This represents a great step forward for 'green chemistry', reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment."

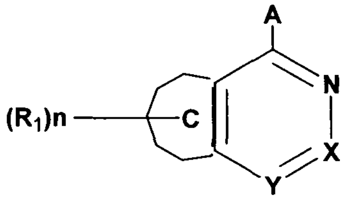
Bacteria, fungi and other microrganism that cannot be seen with our naked are extremely dangerous to human health. Some of the bacteria and fungi are harmful and can make men fall sick and are life threatening. Bacteria and fungi are a kind of parasite that depend on host and multiplies. Most of the short term diseases and few long term diseases are caused by bacteria. They live in human body, start to multiply and damage human immune system. It is better to take appropriate action against bacterial infection as it may cause serious damage to human body. Bacteria and fungi can be furious at the last stage that it can take away human life. Apart from these there are other insects and pests which spoil crop pose and direct challenge to human life. These challenges led to the chemist to develop antimicrobials and plant protecting agents which would readily degrade after a certain period of time and thus would not lead to environmental pollution, also would not remain for long enough to have some effect on the non target organisms. This property was found in a few heterocyclic compounds and the search for newer types of such compound is in progress.

The importance of heterocyclic compounds in medicinal and pharmaceutical chemistry is enormous due to their biological activities. Heterocyclic compounds containing two nitrogen atoms such as pyridazines, pyrimidines, pyrazines and quinazolines are known to possess important biological properties. A few such examples are mentioned hereunder.

1.1 PYRIDAZINE BASED HETEROCYCLIC COMPOUNDS

A brief survey on the recent reports on the work done on heterocyclic compounds containing pyridazine moiety revealed that substituted pyiridazine have attracted much attention due to their potential pesticidal, therapeutic and other biological properties[1-5]. They have subsequently been derivatized extensively and tested for their properties. A few such molecules are discussed in the following sections.

1.1.1 N.Watanabe and co-workersreported[6] the synthesis of series of pyridazine analogues which were represented by the following general formula (**1**).



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Ring **C**: 5 or 6 membered carbon chain ring and may contain a heteroatom,

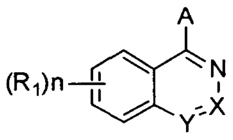
n: 0 to 4, **R**$_1$: halogen atom or lower alkyl, alkoxy, cycloalkyl, nitro or cyano group.

A: hydrogen/ halogen or -NR^{4}R^5 where R^{4}R^5 = Hydrogen, alkyl, acyl or aralkyl group.

X: NR^6 where R^6= alkyl, aralkyl or heteroalkyl group.

Y: -CO-, -CB- where **B**= hydrogen, halogen, NR^{7}R^8 where R^{7}R^8= alkyl, acyl or aralkyl groups. Pharmacologically acceptable salts of the compound of this series were tested for inhibitory activity against cyclic GMP phosphodiesterase (cGMP-PDE).

Of the above structural formula three series of compounds having general structures (**2, 3, and 4**) below were found to be of maximum importance.



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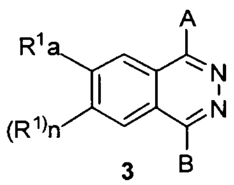

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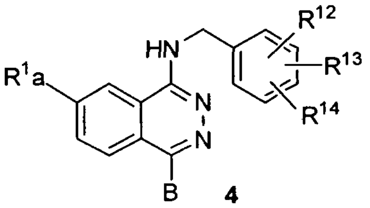

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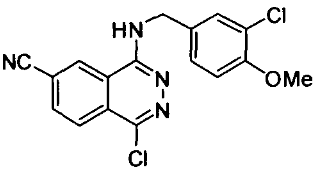
Of the above three series of compounds, compounds having the structure **4** were found to be most useful. The structures of a few active compounds of this series and their salts are shown below.



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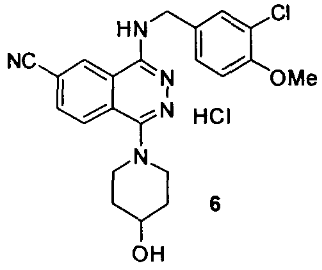

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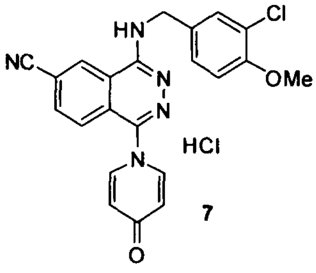

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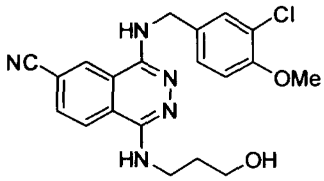

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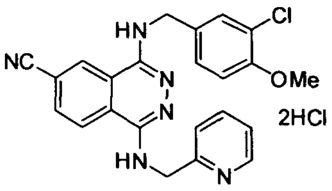

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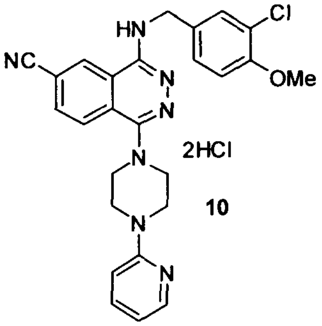

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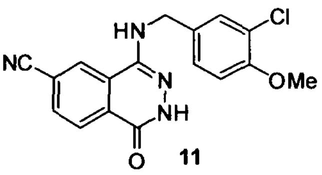

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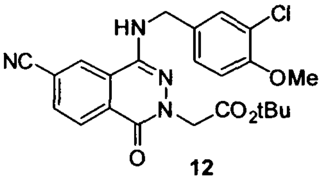

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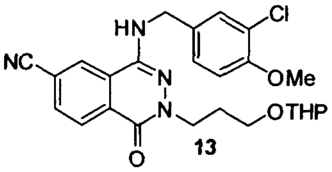

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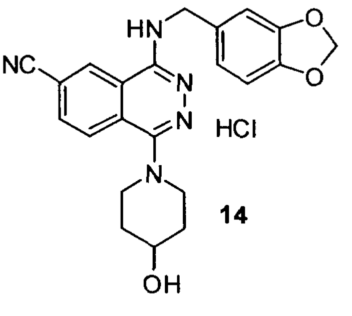

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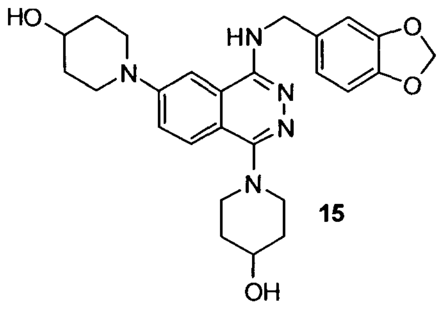

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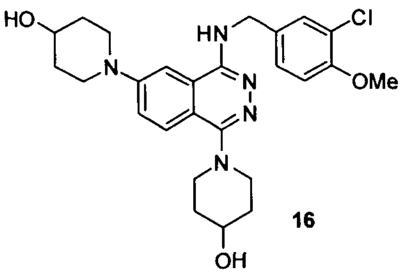

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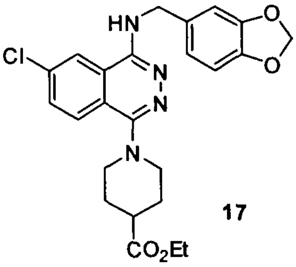

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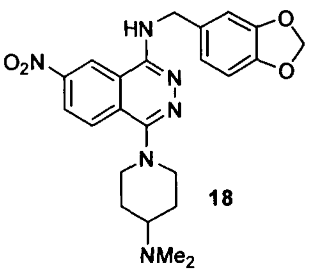

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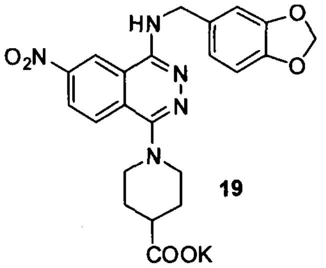

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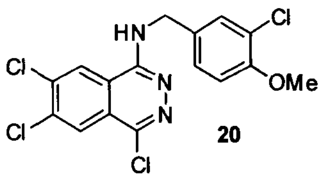

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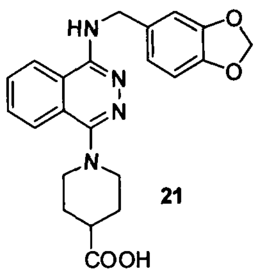

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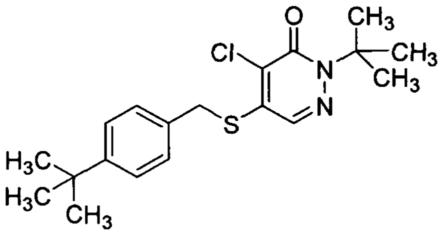
These molecules were found to be useful as preventive and therapeutic agents for diseases for which a cGMP-PDE inhibiting action is efficacious, for example, ischemic heart diseases such as angina pectoris, myocardial infarct and chronic and acute cardiac failure, pulmonary hypertension, arteriosclerosis and bronchial asthma[6]. However these compounds had problems of solubility, in vivo dynamics and toxicity and hence are not on market.

Other pyridazine based active compounds include 2-tert-butyl-5-(4-tert-butylbenzylthio)-4-chloropyridazin-3-(*2H*)-one (**22**) which has been shown to possess pesticidal activity.[7]



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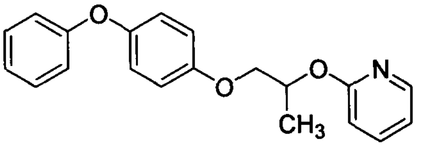
1.1.2 In extension, S Nakamura has reported[8] that a pesticidal composition comprising the above compound (**22**) along with 4-phenoxyphenyl 2-(2-pyridyloxy) propylether (**23**) as active ingredients can be used for controlling pests which are difficult to control satisfactorily by each of the above compound solely.



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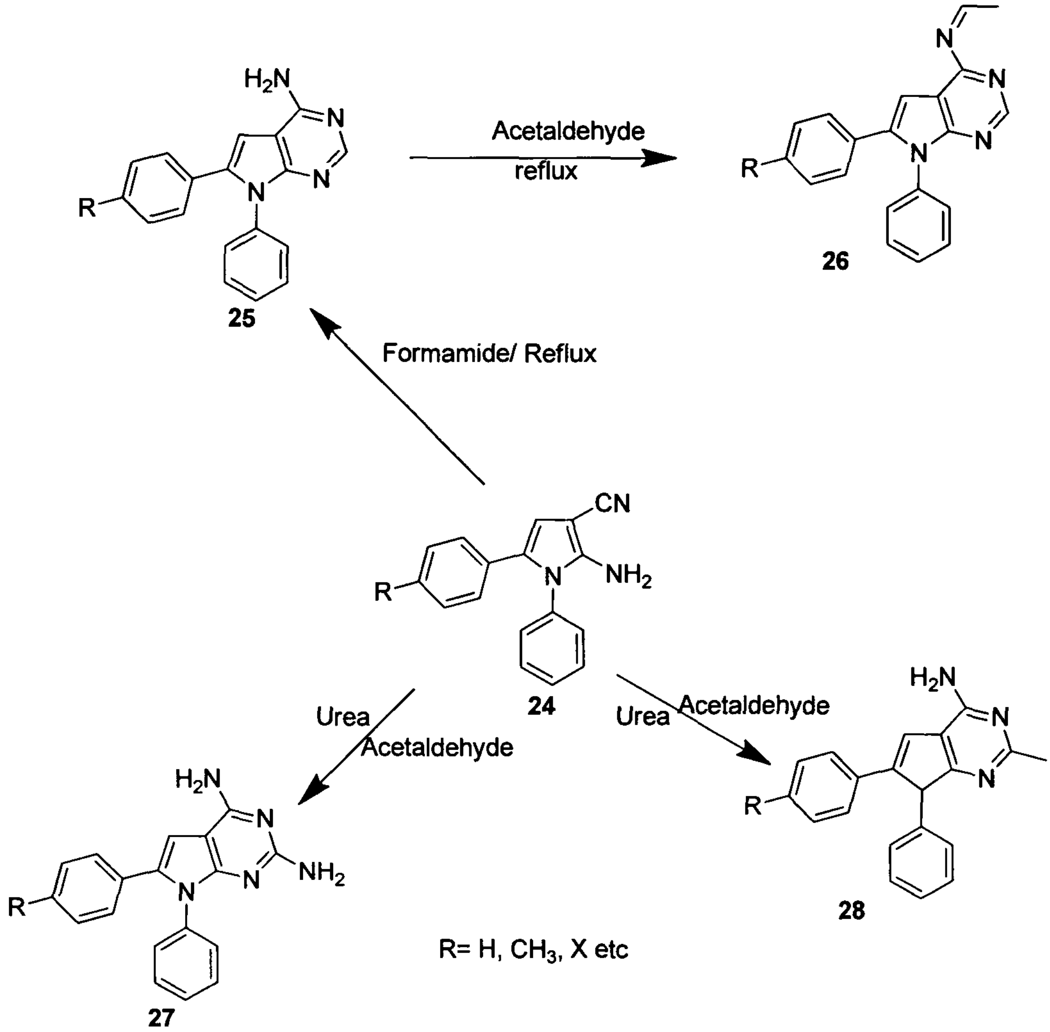
The above composition was found to be effective against arthropods[8]. (esp insects). A few of those insects are Hemipteran pests like *Sogatella furcifera* (white-backed rice planthoppers), Aphids like *Aphis gossypii* (cotton aphid), *Myzus persicae* (green peach aphid). Lepidopteran pest such as Pyralidae e.g. *Chilo suppressalis* (rice stem borer), *Cnaphalocrocis medinalis* (rice leafroller), *Mamestra brassicae* (cabbage armyworm), Coleopteran pests such as corn root worms e.g. *Diabrotica virgifera virgifera* (western corn rootworm). Acarina such as Tetranychidae (spide mites) e.g. *Tetranychus urticae* (two-spotted spider mite) and Nematoda such as *Pratylenchus coffeae* (coffee root-lesion nematode) *Pratylenchus vulnus* (walnut root-lesion nematode) *Heterodera glycines* (soyabean cyst nematode).[8]

1.2 PYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

Literature survey reveals that most of the compounds having pyrimidine nucleus posses pharmacological action.[9-11] A wide spectrum of biological activities like anti-inflamatory[12], antibacterial[13], antifungal[14], antitubercular[15], analgesic, hypothermic[16] are found to be associated with compounds having pyrimidine moiety. The pyrimidine nucleus is present in a wide range of bioactive natural products and its nucleus is also present in vitamin B_2 and Folic acid. Pyrimidines have been subjected to a large number of different modifications in order to obtain derivatives having different biological properties. Pyrimidine derivatives play a vital role in many biological processes[17], the ring system being present in nucleic acids, several vitamins, coenzymes, uric acid, purines and some marine microorganisms (e.g. *Sponge*).[18] Many synthetic members of pyrimidine are also important as synthetic drugs (e.g. *Barbituric acid derivatives)* and chemotherapeutic agents (e.g. *Sulfadiazine).* Several synthetic strategies have been reported for the preparation of pyrimdine derivatives, some of these are discussed in the following sections.

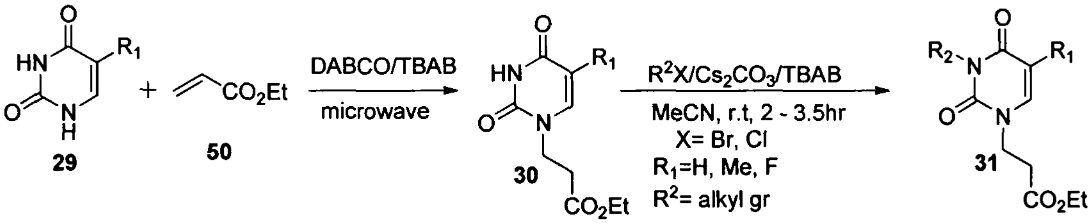
1.2.1 Khalid Mohammed Hassan Hilmy and co-workers reported[19] the synthesis of new pyrrolopyrimidine derivatives as potent antibacterial and antifungal agents by refluxing pyrrole derivative with formamide, urea/acetaldehyde under acidic condition **(Scheme 1)**



Scheme 1

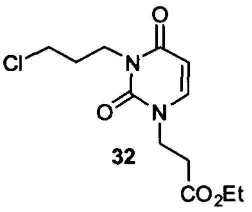
Some of these compounds showed good antbacterial and antifungal activity.

1.2.2 A. K. Nezhad[21] and co-workers reported the synthesis of novel unsymmetrical 1, 3-dialkylpyrimidine derivatives via N 3-alkylation of 1-alkylpyridines with carbon electrophiles in the presence of catalytic amount of TBAB and Cs_2CO_3 in MeCN at room temperature (**Scheme 2**).



Scheme 2

Some of the N-3 alkylated N-1 substituted pyrimidine nucleobases synthesized by them are shown below.



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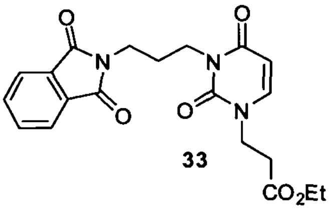

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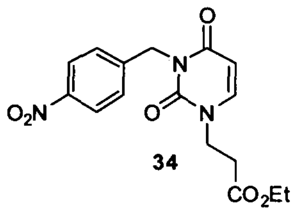

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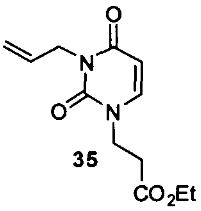
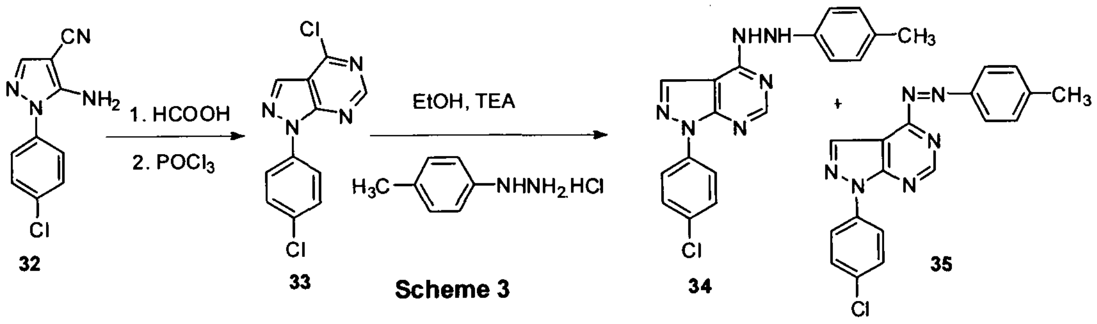


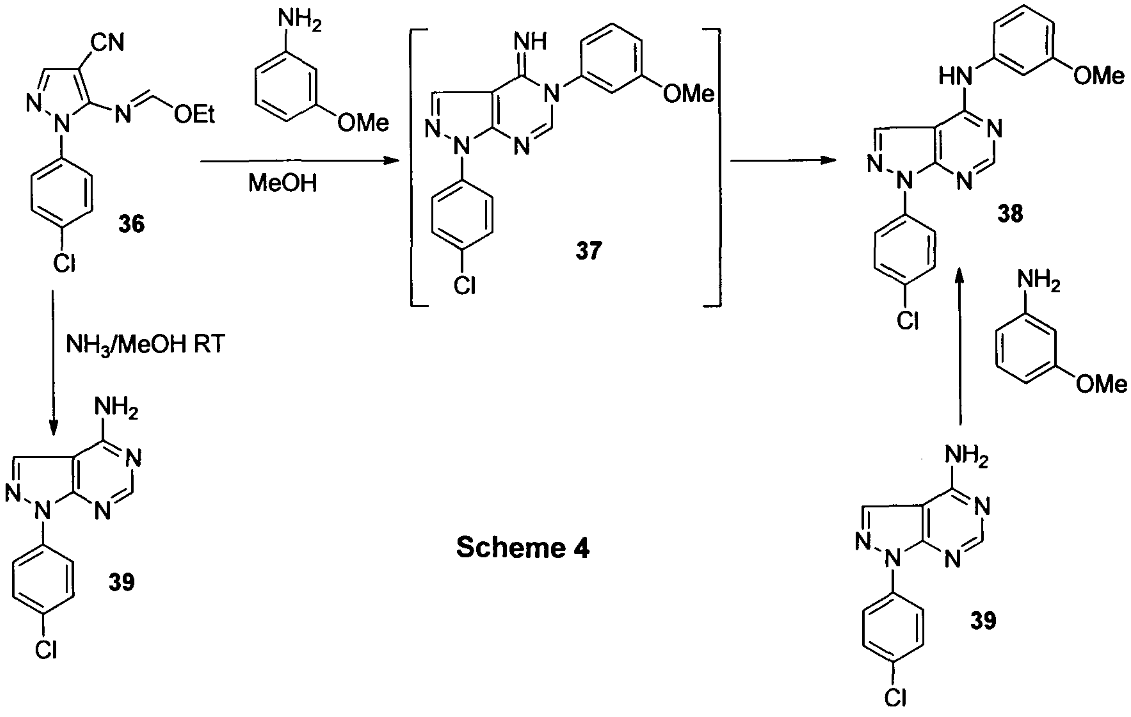
35

This N-1, N-3 substituted pyrimidines have required scaffold to consider as intercalating and alkylating agents[20], which plays a critical role in cancer chemotherapy[21].

1.2.3 Ana M.F. Oliveira-campos and co-workers reported[22] the synthesis of the 4-substituted pyrazolo [3, 4-d] pyrimidines as shown below (**Scheme 3, Scheme 4**).



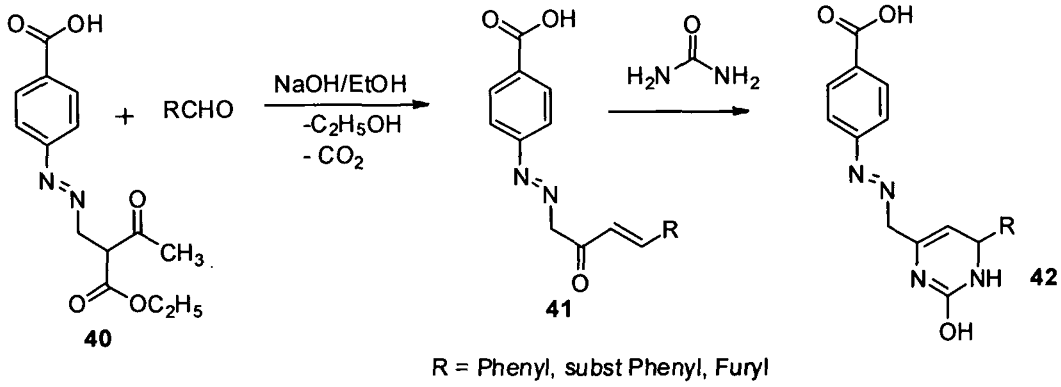
Scheme 3



Scheme 4

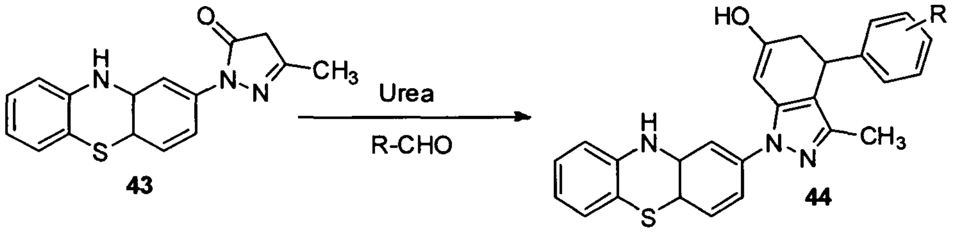
These compounds were tested for their antifungal activities[22].

1.2.4 V. H. Shah and co-workers have reported[23] the synthesis of pyrimidine derivatives from their corresponding chalcones by reacting them with urea (**Scheme 5**).



Scheme 5

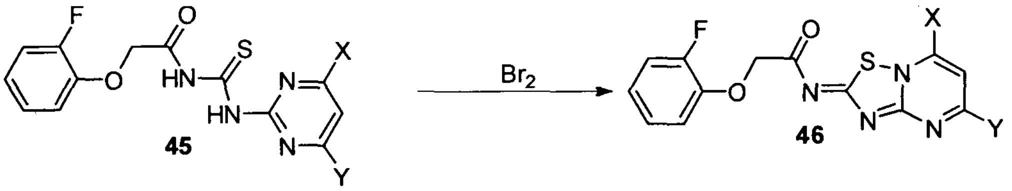
Some of these compounds exhibited promising antitubercular activities against Mycobacterium tuberculosis[23]. They also reported the synthesis of some pyrimidine derivatives containing the phenothiazine nucleus of the type **44** (**Scheme 6**).



Scheme 6

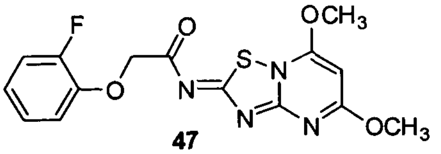
These were also tested for their anti tubercular activities[24].

1.2.5 S. Y. Ke and co-workers have reported the synthesis of a series of o-fluoro phenoxy acetylimino-2*H*-1, 2, 4-thiadiazolo [2,3-a] pyrimidine derivatives (**46**) from **45** using bromine as oxidant (**Scheme** 7).

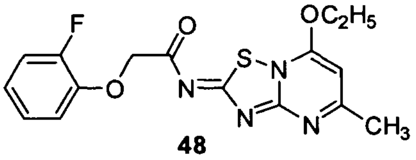


Scheme 7

For example, **47** and **48** some of these compounds showed good herbicidal activity[25]



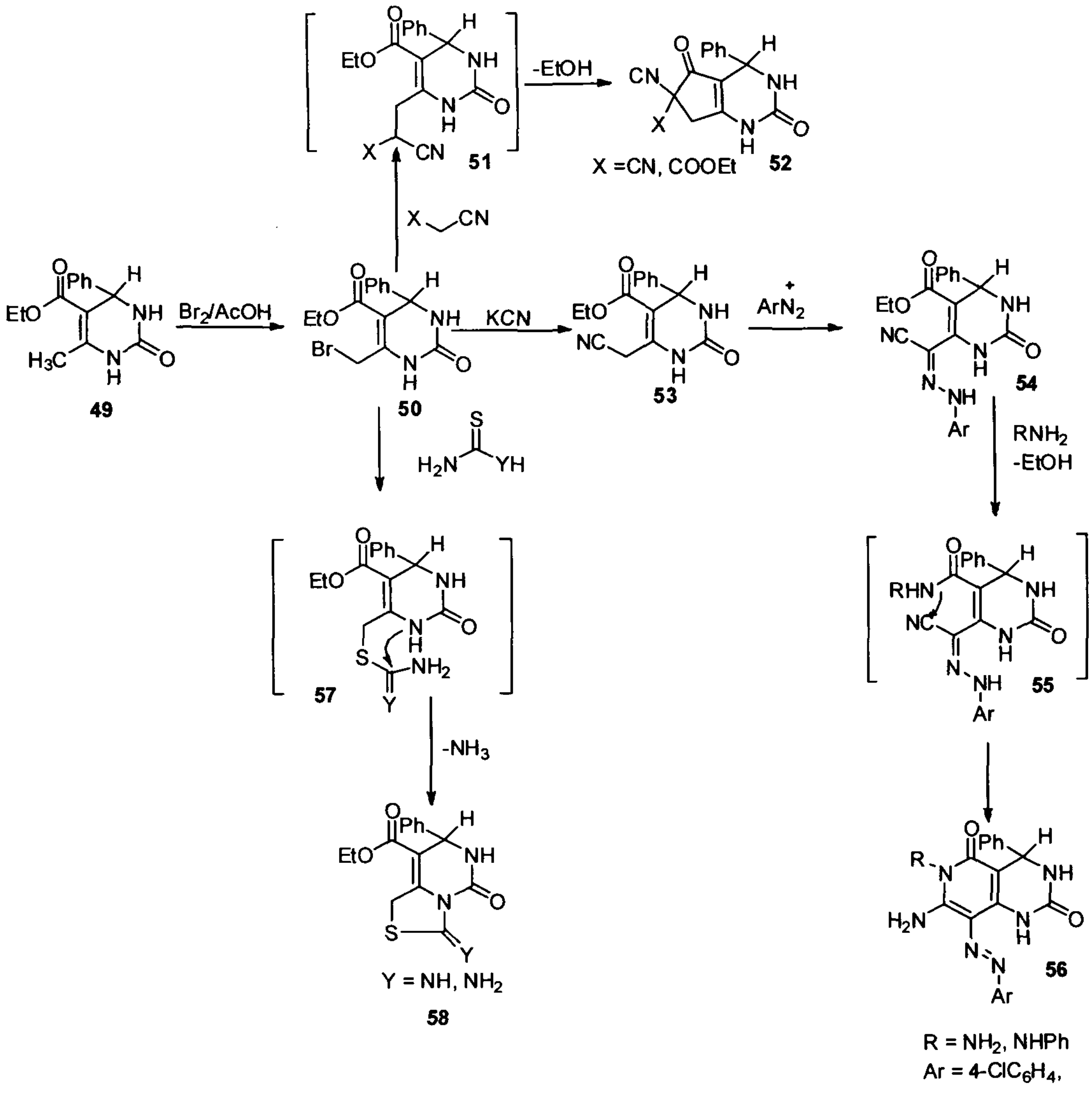
47



48

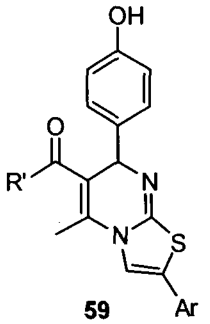
1.2.6 N.A. kheder used the versatile 6-Bromomethylpyrimidine (**50**) as a building block for the synthesis of cyclopenta [d] pyrimidine, pyrido [4, 3-d] pyrimidine and thiazolo [3, 4-c] pyrimidine as shown in the (**Scheme 8**).

The versatile synthon ethyl 6-(bromomethyl) –2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (**50**), was obtained via bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**49**) in acetic acid. Treatment of **50** with malononitrile or with ethylcyanoacetate afforded the corresponding hexahydrocyclopentanal [d] pyrimidine derivatives (**52**). 6-bromomethyl pyrimidine underwent nucleophyllic substituition reaction on treatment with potassium cyanide to afford ethyl 6-cyanomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**53**), which couples smoothly with 4-chlorobenzenediazonium chloride to give the corresponding hydrazone (**54**). When the hydrazone was treated with hydrazine hydrate or phenyl hydrazine, it afforded the corresponding pyrido-[4,3-d]-pyrimidine derivatives (**56**). It also reacts with thiourea, thiosemicarbazide to afford the corresponding thiazolo-[3,4-c]-pyrimidine (**58**).The antimicrobial activity of selected samples of the synthesized compounds was tested and showed moderate activities[26] .

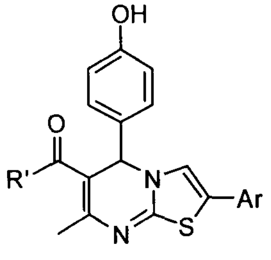


Scheme 8

1.2.7 C. Hu and co-workers synthesized a series of 5H-thiazolo [3,2-a] pyrimidine derivatives of the type **59** and **60**.



59

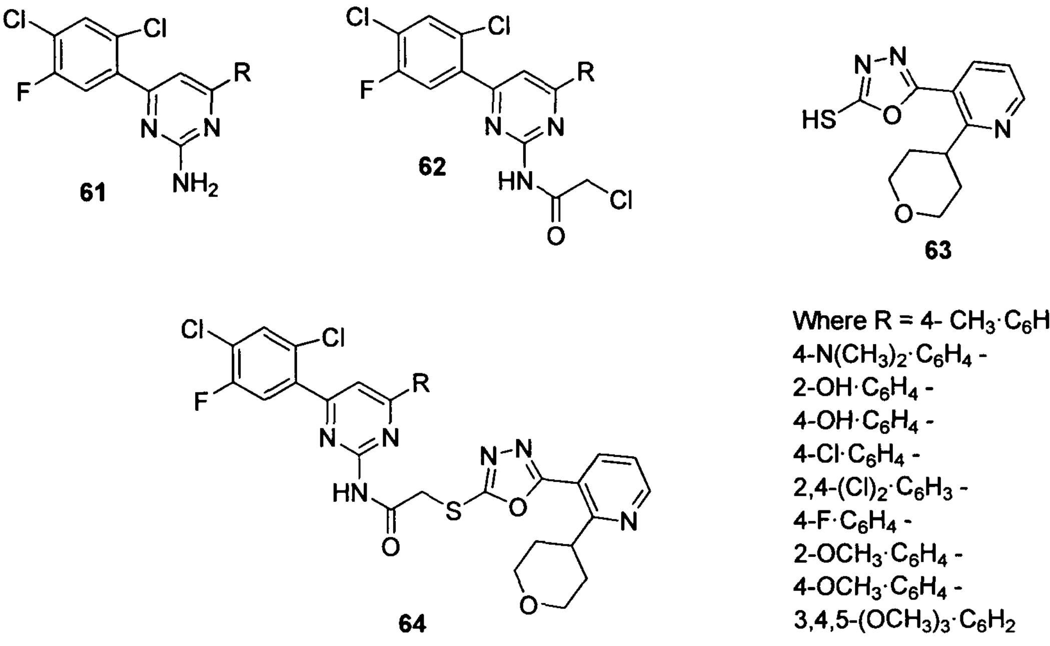


60

R' = OC_2H_5, CH_3
Ar = 4-$OCH_3C_6H_4$, 4-BrC_6H_4
4-ClC_6H_4, 4-$CH_3C_6H_4$
4-OHC_6H_4

Some of the compounds showed good activity as AchE inhibitor[27].

1.2.8: T.A.Naik and co-workers reported the synthesis of novel pyrimidine derivatives of the type **(61)** & **(62)** by refluxing nitrogen containing fragment like urea, guanidine, thiourea etc with acetyl acetone. These further reacted with **63** to give pyrimidine derivative **(64)** which has interesting biological properties[28] **(Scheme 9)**



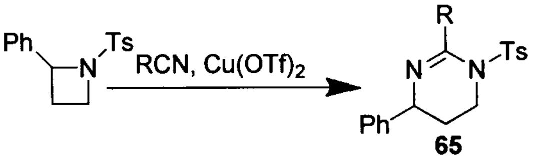
Where R = 4- $CH_3 \cdot C_6H_4$ -
4-$N(CH_3)_2 \cdot C_6H_4$ -
2-$OH \cdot C_6H_4$ -
4-$OH \cdot C_6H_4$ -
4-$Cl \cdot C_6H_4$ -
2,4-$(Cl)_2 \cdot C_6H_3$ -
4-$F \cdot C_6H_4$ -
2-$OCH_3 \cdot C_6H_4$ -
4-$OCH_3 \cdot C_6H_4$ -
3,4,5-$(OCH_3)_3 \cdot C_6H_2$

Scheme 9

1.3 TETRAHYDROPYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

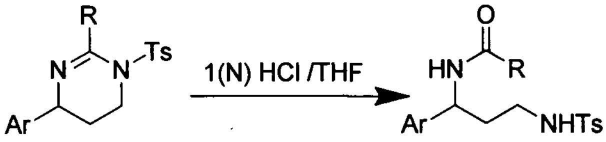
Tetrahydropyrimidines (THPs) are one of the most important heterocycles since these compounds have been found to be of minimal toxicity to men, domesticated animals and fish and selectively display remarkable control on pests, they have been produced in large numbers and various derivatives have been made. A few such molecules with reference to their preparation and properties are described in the following sections.

1.3.1 Manas K. Ghorai and co-workers reported[29] a highly efficient strategy for Cu $(OTf)_2$-mediated S_N^2 type nucleophilic ring-opening followed by [4+2] cycloaddition reactions of a number of 2-aryl-N-tosylazetidines with nitriles to afford a variety of substituted tetrahydropyrimidines **(65)** in excellent yields. The resulting tetrahydropyrimidines could easily be transformed into synthetically important 1,3-diamines by acid-catalyzed hydrolysis. The strategy has been extended to the synthesis of enantiomerically pure tetrahydropyrimidines from enantiopure disubstituted azetidines. The reaction proceeds through an S_N^2 type mechanism as proposed. The 1,3-diamines of the type produced are useful intermediates in organic synthesis. Moreover, the diamines **(65a-d)** are important structural units present in a number of peptidomimetic inhibitors of the HIV-1 protease, used for the treatment of AIDS. **(Scheme 9a)**



R = CH_3, Ph, CH_2Ph, 4-EtC_6H_4

Hydrolysis of Tetrahydropyrimidine with 1 (N) HCl

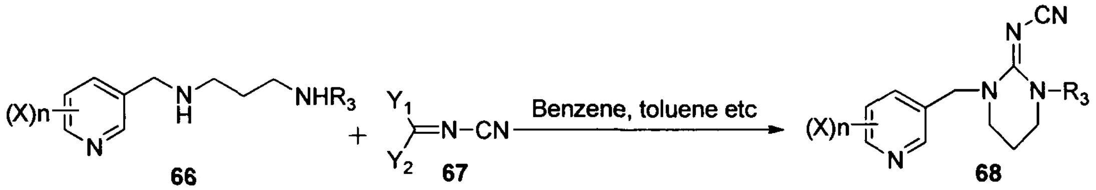


65 **65 a-d**

a, Ar = Ph, R= CH_3
b, Ar = Ph, R= Ph
c, Ar = 2-Cl-C_6H_4, R= CH_3
d, Ar = 4Cl-C_6H_4, R= CH_3

Scheme 9a

1.3.2: Laurenz Gsell has reported[30] the synthesis of substituted pyridyl methyl cyanoiminotetrahydropyrimidine (**68**) by the reaction of compounds having the structures **66** and **67** in appropriate solvents (**Scheme 10**).

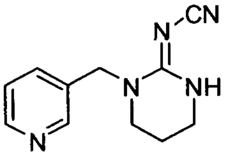


R_3: H or alkyl groups, **X**= Halogen, **n** = 0, 1, 2 or 3

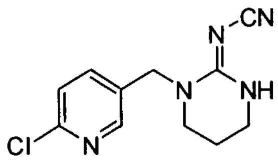
Y_1=Y_2 leaving groups such as –SCH_3, -OCH_3, -OC_6H_5.

Scheme 10

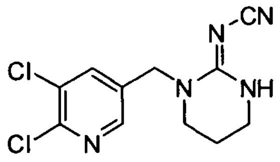
Similarly, THPs **69**, **70** and **71** have been synthesized by the above general method.



69



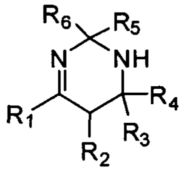
70



71

These compounds were found to be useful in controlling insects and pests of rice crops, while being well tolerated by plants and having low toxicity to warm blooded animals[30].

1.3.3 Bernardus and co-workers have reported[31] the synthesis of substituted 2,3,4,5-tetrahydropyrimidines and their derivatives of the general formula **72**.

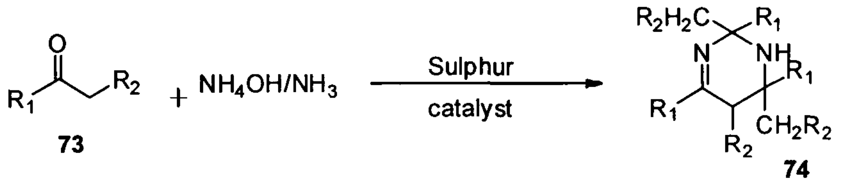


72

R_1-R_6: hydrogen, alkyl, aryl, aralkyl, cycloalkyl, heterocyclic substituted derivatives thereof.

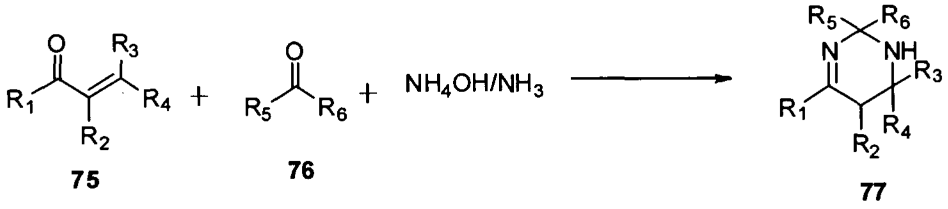
A few methods for the preparation of the tetrahydropyrimidines are described below

1.3.3a By the reaction of carbonyl compounds **73** (ketone or aldehyde) with NH_3 / NH_4OH and a sulphur-containing catalyst (eg CS_2) (**Scheme 11**).



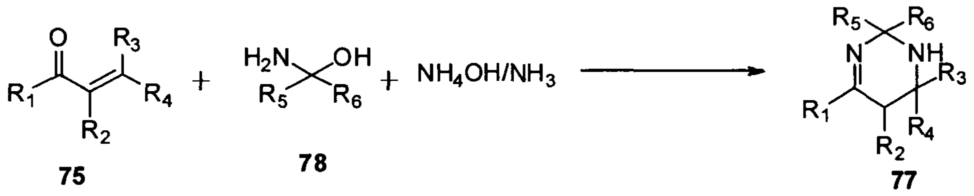
Scheme 11

1.3.3b The reaction of an α, β-unsaturated ketone (**75**) and a carbonyl compound (**59**) and NH_3 / NH_4OH without a catalyst (**Scheme 12**).



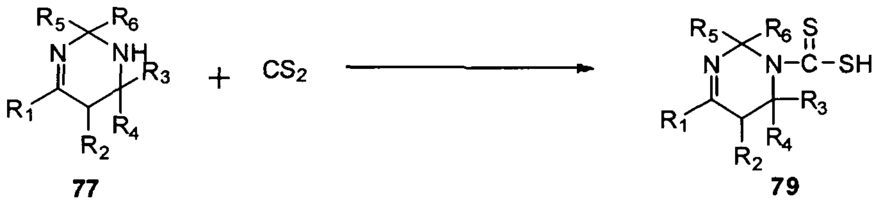
Scheme 12

1.3.3c By the reaction of an α, β-unsaturated ketone (**75**), 1- aminoalcohol (**78**) and NH_3 / NH_4OH without a catalyst (**Scheme 13**).



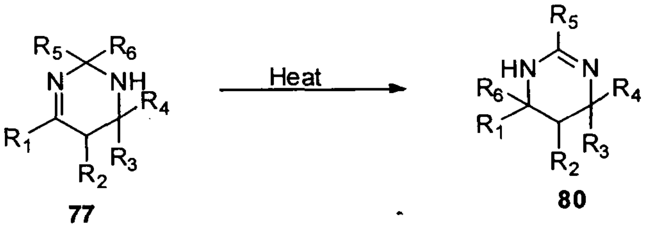
Scheme 13

This THP (77) was further used as intermediates for the preparation of N-dithiocarboxylates. Reaction of the substituted 2, 3, 4, 5-tetrahydropyrimidines (77) with carbon disulfide yielded 1:1 adducts (79) (**Scheme 14**)



Scheme 14

These adducts were efficient corrosion inhibitors in acid systems. Tetrahydropyrimidines where R_6 was hydrogen were isomerised to obtain 1, 4, 5, 6-tetrahydropyrimidines (**80**) (**Scheme 15**).

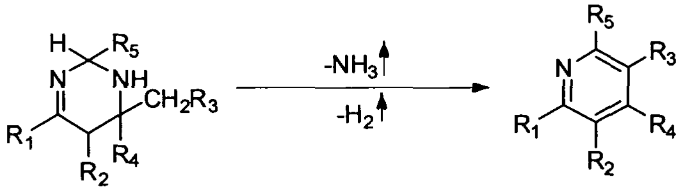


77

80

Scheme 15

THPs where the C_2 position contains at least one hydrogen and one of the group attached to carbon 4 has at least a methylene group could be converted to substituted pyrimidines (**82**) by the liberation of ammonia (**Scheme 16**). These compounds were useful as bactericides. In general the above series of compounds were found to be useful as biocides, anti-oxidants, oxygen-scavengers and as corrosion inhibitors[7].

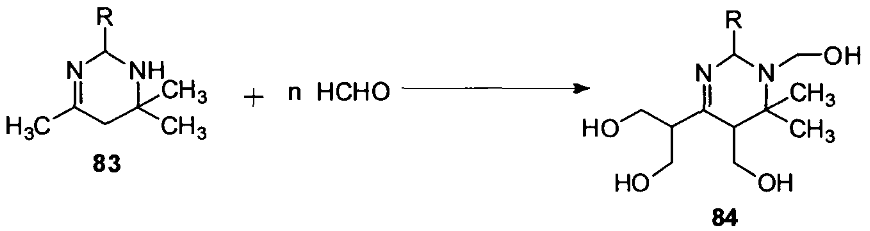


81

82

Scheme 16

1.3.4 Bernardusagain reported[32] the reaction of the tetrahydropyrimidines (**83**) with various stoichiometric quantities of formaldehyde leading to the formation of a mixture of compounds called polyols of tetrahydropyrimidines (**84**) (**Scheme 17**)



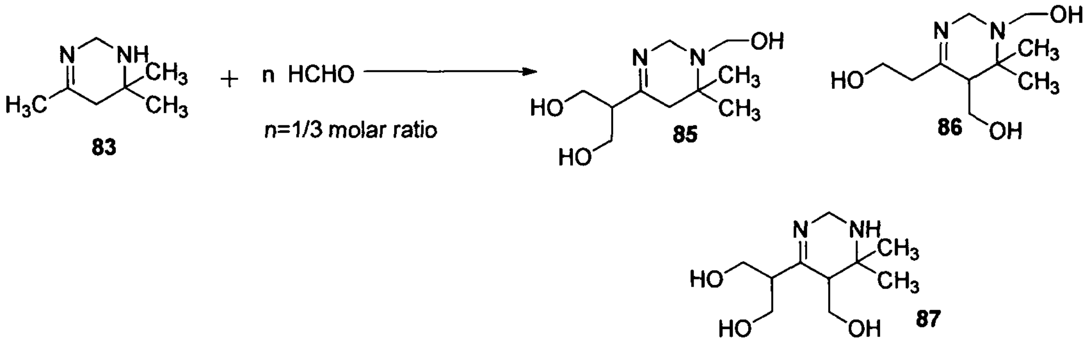
83

84

Scheme 17

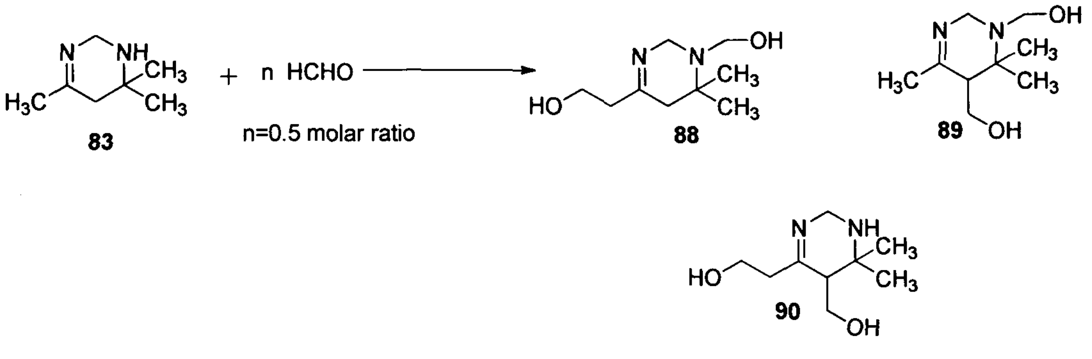
When **n** is less than 4, then a mixture of products with the $-CH_2OH-$ group located at one or more of the four possible sites 3, 5 and 6 were obtained.

For example, when 4,4,6-trimethyl 2,3,4,5-tetrahydropyrimidine was reacted with one third molar ratio of formaldehyde a mixture of products **85, 86** and **87** containing three methylol groups were obtained (**Scheme 18**)



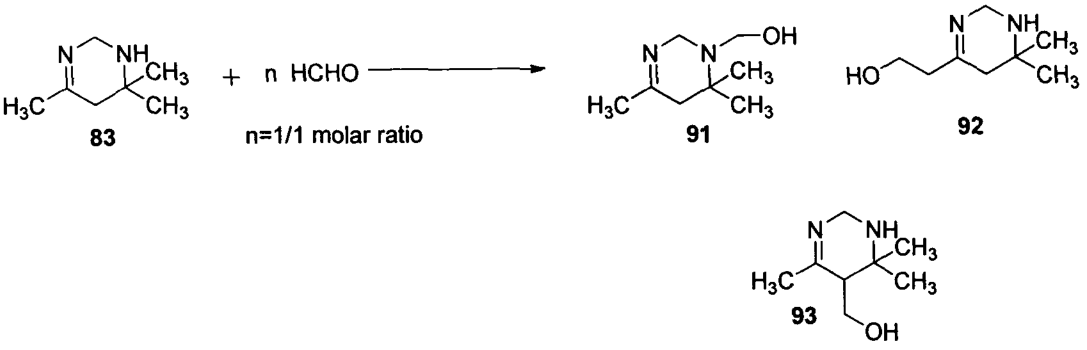
Scheme 18

When the same reaction was carried out with 0.5 molar ratio of formaldehyde the products obtained were **88, 89** and **90** (**Scheme 19**).



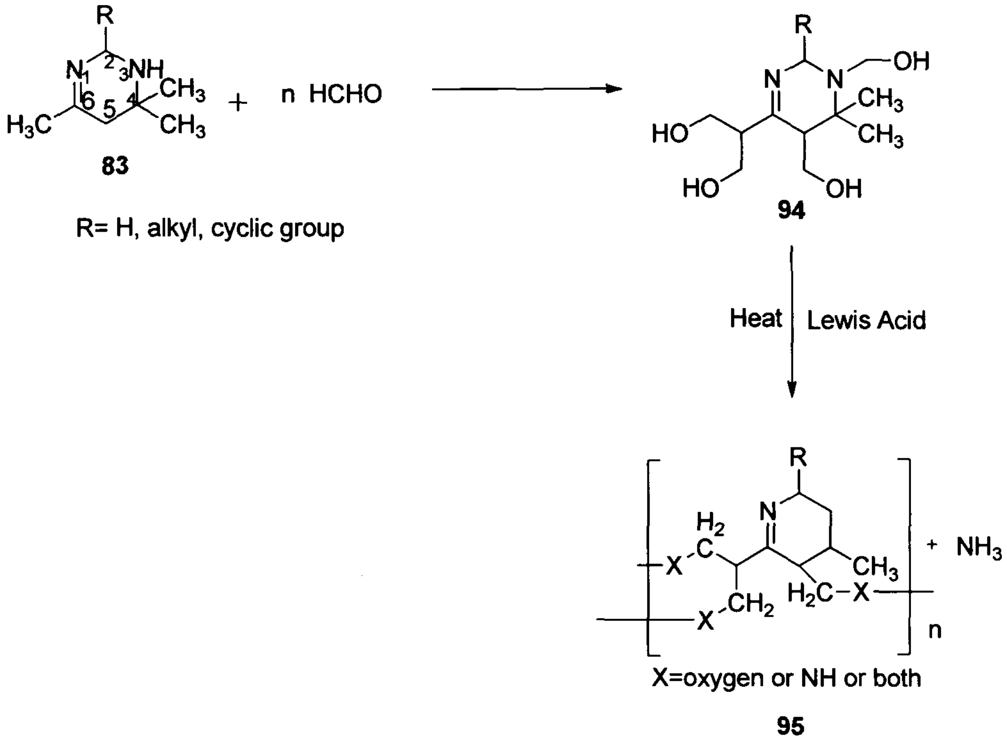
Scheme 19

Similarly when the reaction was carried out with 1 molar ratio of formaldehyde three possible products were obtained **91, 92** and **93** (**Scheme 20**)



Scheme 20

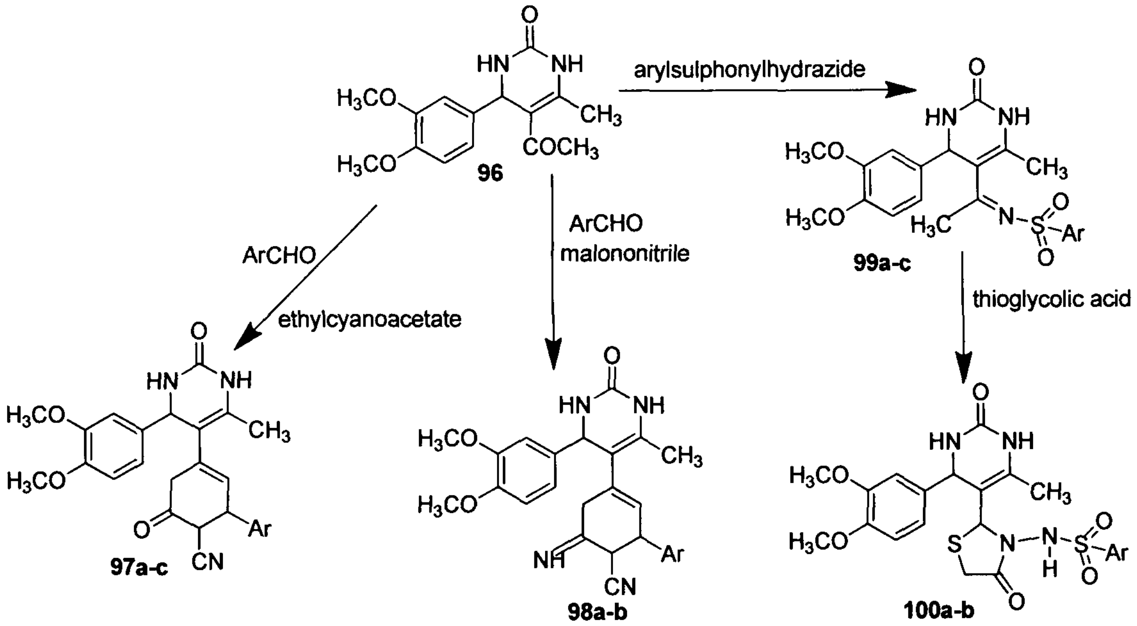
These compounds when heated in the presence of Lewis acid such as $FeCl_3$, $AlCl_3$, etc polymerized to form a compound having the general structure (**95**) by the liberation of ammonia (**Scheme 21**)



Scheme 20

The polyols of tetrahydropyrimidines and their respective polymers were found to be useful as corrosion inhibitors.

1.3.5 Omar AbdEi-Fattah and co-workers reported[33]the convenient synthesis of functionalized chalcones, pyridine and thiazolidinone derivatives incorporating pyrimidine moiety as a common structural subunit. The starting material namely: 5-acetyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine (**96**) allowed to react with appropriate aromatic aldehydes namely: *p*-hydroxybenzaldehyde, 4-hydroxy-3-methoxybenzaldehyde (vaniline) and *o*-hydroxybenzaldehyde (salicylaldehyde) in presence of ammonium acetate and ethyl cyanoacetate in butanol to afford compounds **97a-c** (**Scheme 21**). By the same method compounds **98a, 98b** were achieved by heating of compound **96** and appropriate aromatic aldehydes namely: *o*-hydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde in presence of excess of ammonium acetate and malononitrile in butanol. Furthermore compound **96** reacted with arylsulfonylhydrazides namely: benzenesulfonylhydrazid and toluenesulfonyl- hydrazide to give **99a, 99b** (**Scheme21**). Cyclocondensation of **99a, 99b** with thioglycolic acid in dry benzene gave the corresponding thiazolidinone derivatives **100a, 100b** (**Scheme 21**).

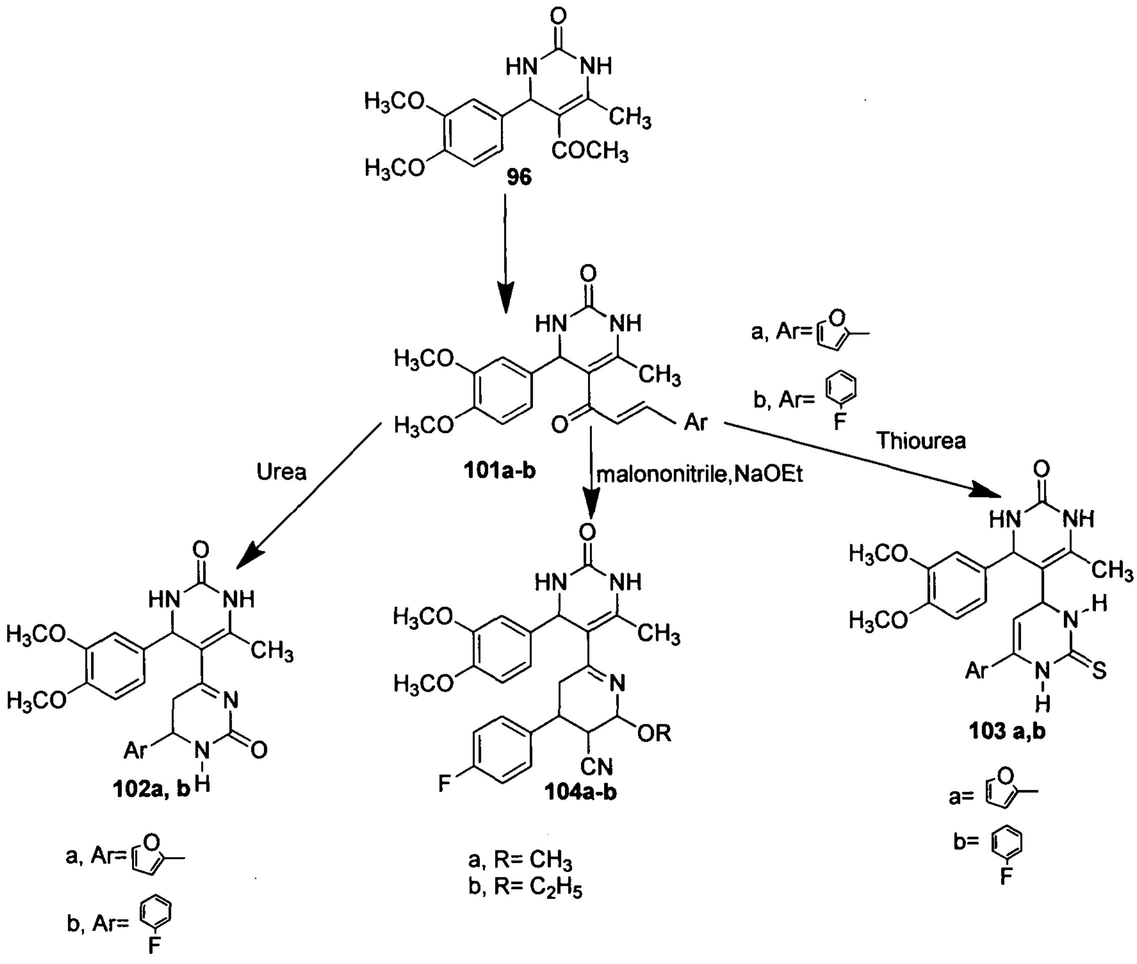


Ar= aryl group

Scheme-21

Condensation of compound **96** with different aldehydes namely: 5-methyl-furan-2-carboxyaldehyde and *p*-florobenzeldehyde in the presences of 20% NaOH solution at 60 °C afforded the corresponding **101 a, b (Scheme 22)**.

Moreover, condensation of compounds **101a, b** with urea in boiling ethanolic hydrochloric acid gave **102 a, b (Scheme 22)**. Similarly compounds **101 a, b** reacted with thiourea in boiling ethanolic potassium hydroxide solution to give compounds **103 a, b (Scheme 22)**. In this work, new compounds containing 2-alkoxypyridine moieties have been designed for their biological activity, particularly for antitumor properties. The preparation of 2-alkoxycyanopyridines in goodyields was reported *via* Micheal addition of malononitrile to, α, β-unsaturated carbonyl system. Herein, 5-chalconyl pyrimidine derivative **101b** was condensed with malononitrile in either sodium ethoxide/ethanol or sodium methoxide/ethanol to yield the corresponding 2-alkoxypyridines **104 a, b (Scheme 22)**.

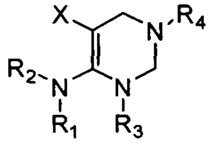


Scheme-22

1.4 1,2,3,4-TETRAHYDROPYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

Our literature survey on the synthesis and biological activity of Tetrahydropyrimidines in general and 1,2,3,4-tetrahydropyrimidines in particular at this stage revealed that so far only 5-nitro-1,2,3,4-tetrahydropyrimidines have been extensively synthesized and studied. They are known to possess important pesticidal and insecticidal properties. A few such nitro tetrahydropyrimidines their preparation and biological activities are described in the following sections.

1.4.1 H. Uneme and coworkers[34] reported the synthesis and activity of a series of tetrahydropyrimidines and their salts whose general structure can be represented as (**104**).



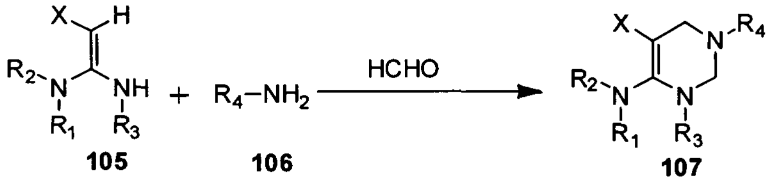
104

R_1, R_2, R_3, R_4: hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

X: electron withdrawing group or a salt thereof.

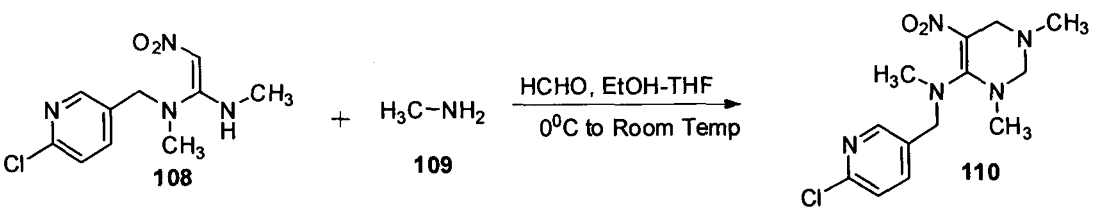
These compounds were prepared by mainly three methods, which can be summarized as under.

1.4.1a by the reaction of a compound (**105**) with an amine (**106**) and formaldehyde (R_1-R_4 has the same meaning as above) (**Scheme 23**).



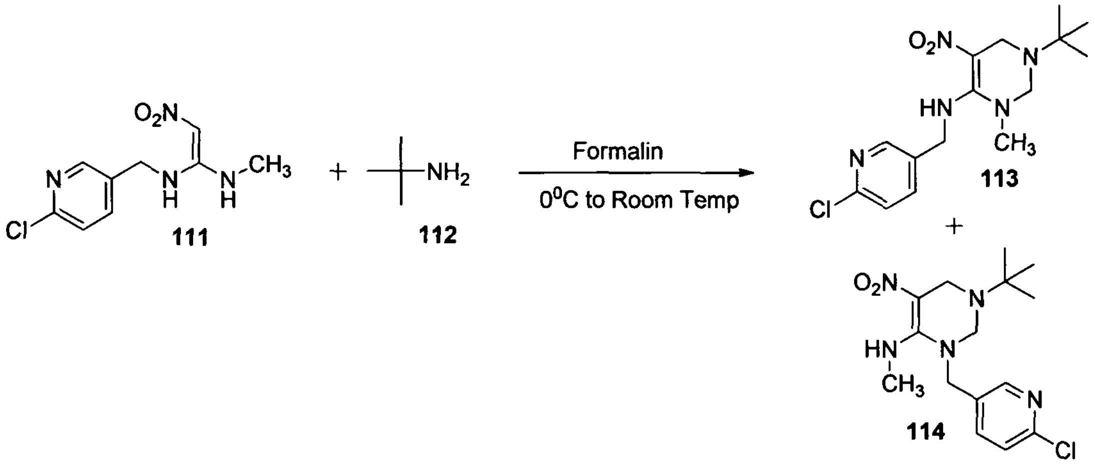
Scheme 23

For example, when to a mixture of 1-[N- (6-chloro-3-pyridylmethyl)-N-methylamino]-1-methylamino-2-nitroethylene (**108**) and 40% aqueous methylamine (**109**) was added 37% formalin dropwise over 20 minutes with cooling in ice and further stirred at room temperature for overnight. Subsequent work up and column purification yielded 4-[N- (6-chloro-3-pyridylmethyl)-N-methylamino]-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydropyrimidine (**110**) (**Scheme 24**).



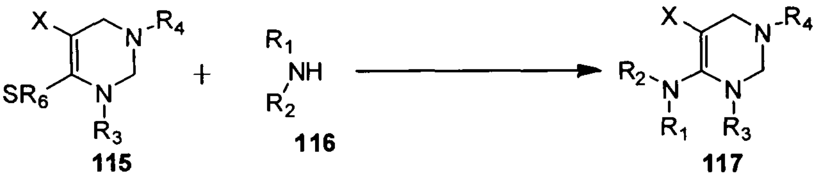
Scheme 24

Similarly, when to a mixture of 1-(6-chloro-3-pyridylmethylamino)-1-methylamino nitroethylene (**111**) and t-butylamine (**112**) in acetonitrile, 37% formalin was added dropwise with cooling and further stirred for 3.5 hours at room temperature, workup and subsequent purification yielded a mixture of 1-t-butyl-4-(6-chloro-3-pyridylmethylamino)-3-methyl-5-nitro-1,2,3,6-tetrahydropyrimidine (**113**) and 1-t-butyl-3-(6-chloro-3-pyridylmethyl)-4-methylamino-5-nitro-1,2,3,6-tetrahydropyrimidine (**114**) (**Scheme 25**).



Scheme 25

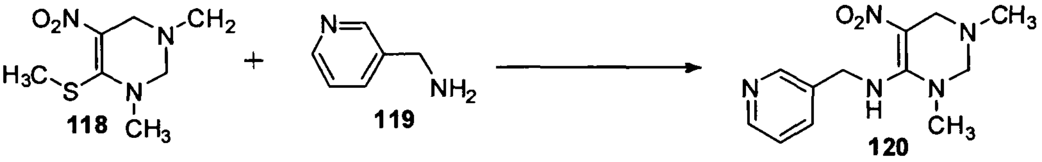
1.4.1b Reaction of compound (**115**) with an amine (**116**) as shown below (**Scheme 26**).



Scheme 26

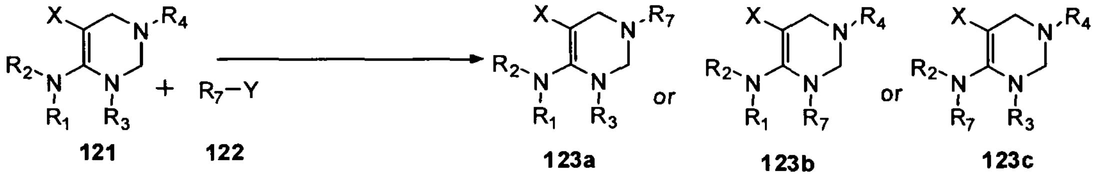
Where substituents have their usual meaning and R_6 means a lower alkyl group

For example, when 1,3-dimethyl-4-methylthio-5-nitro-1,2,3,6-tetrahydropyrimidine (**118**) was stirred with 3-pyridylmethylamine (**119**) in acetonitrile at room temperature for 5 hours, subsequent work up and purification yielded 1,3-dimethyl-4-(pyridylmethylamino)-5-nitro-1,2,3,6-tetrahydropyrimidine (**120**) (**Scheme 27**).



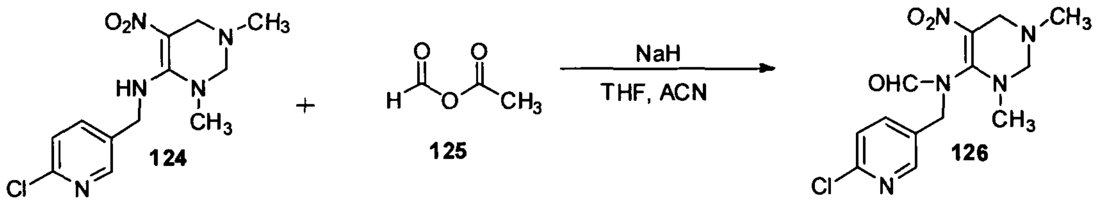
Scheme 27

1.4.1c By reacting a compound of the formula (**121**) where out of the groups R_1 to R_4 at least one means a H atom and the rest alkyl group, with (**122**) wherein $\mathbf{R_7}$ means a hydrocarbon group that may be substituted or a heterocyclic group, which may be substituted, and **Y** means a halogen atom or an alkylsulfonyloxy, arylsulfonyloxy or acyloxy group, which may be substituted by a halogen (**Scheme 28**).



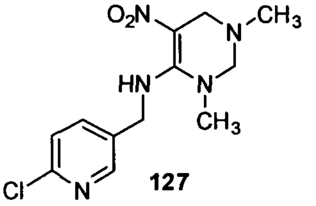
Scheme 28

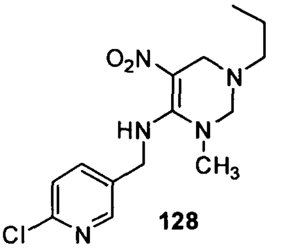
To a mixture of 4-(6-chloro-3-pyridylmethylamino)-1,3-dimethyl-5-nitro-1, 2, 3, 6-tetrahydropyrimidine (**124**) in THF and acetonitrile, sodium hydride was added in small portions, followed by aceticformicanhydride (**125**) in THF and continued stirring at room temperature for 3 hours. Subsequent work up and purification yielded 4-[N-(6-chloro-3-pyridylmethyl)-N-formylamino]-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydropyridine (**126**) (**Scheme 29**).



Scheme 29

Altogether 60 compounds were prepared in this series and their antiviral activity tested, out of which the structure of the preferable compounds are given below. The most preferable compound in the entire series was 1-benzyl-3-[(6-chloropyridin-3-yl) methyl]-N-methyl-5-nitro-1,2,3,6-tetrahydropyrimidin-4-amine (**134**).


127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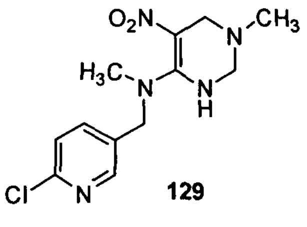
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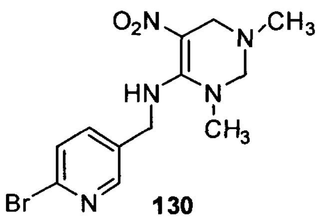
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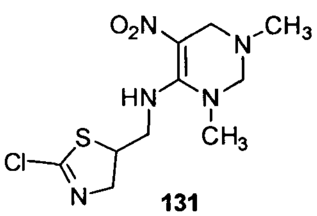
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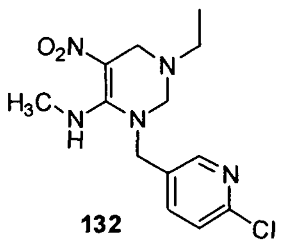
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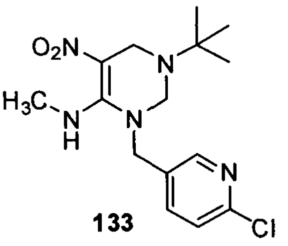
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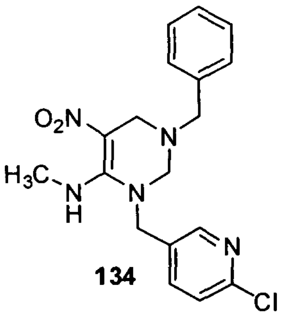
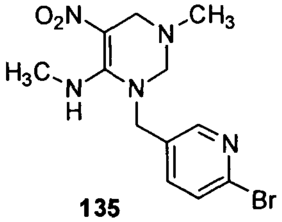
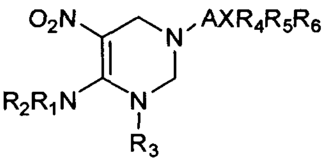

134


135

1.4.2 Stephen McCann and co-workers have reported[35] the synthesis of tetrahydropyrimidines of the type **136**

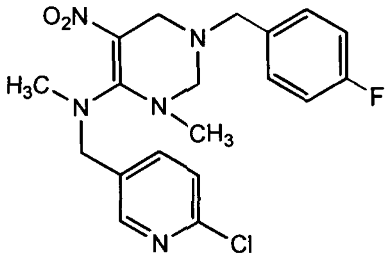

136

X: Si, Ge; **A**: Alkylene, alkenylenes

R_1-R_6: alkyl, alkenyl; **R_2-R_3**: ethyl, propyl and each group substituted with methyl.

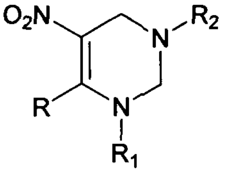
The tetrahydropyrimidines of the above series were found to be very good anthropocides.

Tetrahydropyrimidines were also prepared by Tomi Haga and coworkers[46], they reported the synthesis of 6-[N-(6-chloro-3-pyridylmethyl)-N-methylamino]-3-(4-fluorobenzyl)-1-methyl-5-nitro-1,2,3,4-tetrahydropyrimidine (**137**) which was used as noxious organism controlling agent for example, to control Laodelphax straitellus at 800 ppm with 100% mortality rate[46].



137

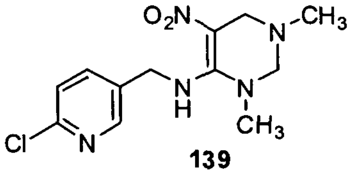
1.4.3 F. Wu and coworkers have also reported[36] the synthesis of tetrahydropyrimidines of the general structure (**138**).



138

R: NHCH$_2$Y; **R$_1$**=Low alkyl group; **R$_2$**=Alkenyl, aralkyl, haloalkyl groups;

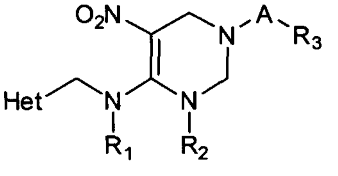
Y: 2-choloro-5 Pyridyl. For example 4- (2-Chloro-5-pyridylmethyl)amino-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydropyrimidine (**139**).



139

This compound was found to control Nepholettix ciccticeps on rice with 100% mortality vs 70% for sumethion. As insecticides these compounds had excellent control effect against insects pest having acquired resisting property. They were reported to have low toxicity against warm-blooded animal, fishes, crustacea, etc., reduced in residual property and having high safety to plants[47].

1.4.4 B. W. Kruger and his coworkers synthesized[37] and tested many 1,2,3,4-tetrahydropyrimidines (**140**)



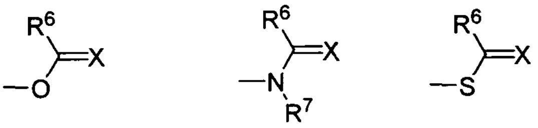
140

Het: substituted pyridyl or thiazolyl; **R_1-R_2**: C_1-C_4alkyl,

R_1-R_2: form a saturated 5 or 6 membered ring together with the adjacent carbon atoms which optionally contains N or O as further hetero atom.

A: cycloalkylene, straight chain or Branched alkylene having at least 2 carbon atoms which is optionally substituted by phenyl, Halogen, OH, CN or radical NR^4R^5 where R^4 and R^5 represents H, C_{1-4} alkyl, phenyl, N-alkyl or N-phenyl,

R_3: represents one of the radicals below

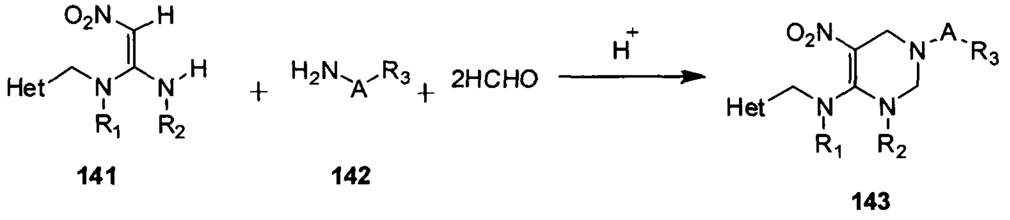


R_6: alkyl, aryl, aralkyl, heteroalkyl, alkoxy etc.

X: O, S, and **R^7**: H or C_{1-4} alkyl.

These compounds were prepared by basically three methods, they are

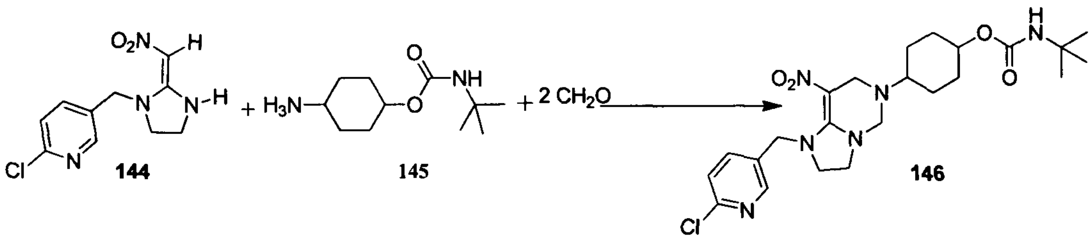
1.4.4a Reacting nitromethylene derivative (**141**) with amines (**142**) in the presence of at least twice the molar amount of formaldehyde in the presence of acidic catalyst and appropriate diluents (**Scheme 30**).



Scheme 30

Where R_1, R_2, Het, A and R_3 have their usual meaning. Particularly preferred compounds were those in which Het represents 2-Chloro-5-methylpyridine or 2-chloro-5-methyl-thiazole and R_1, R_2 represents methyl, ethyl and together with adjacent atoms represents 1, 3, 5-trimethyl-2-methylene-hexahydropyrimidine.

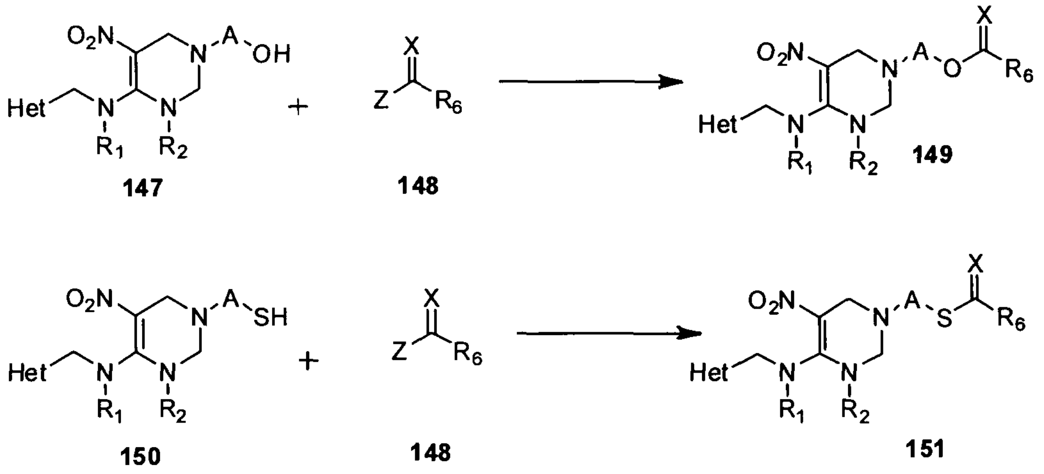
If for example, 3-(2-Chloropyridin-5-yl-methyl)-2-nitromethylene-imidazoline (**144**), 4-t-butylcarbamoyloxy-cyclohexylamine (**145**) and at least twice the molar amount formaldehyde are used as starting material, the corresponding reaction can be represented by the following equation (**Scheme 31**).



Scheme 31

The starting materials used are available or can be prepared by known methods, suitable diluent are water and organic solvents which are inert in the reaction (preferably aliphatic and aromatic) optionally hydrocarbons, such as pentane, hexane, cyclohexane, petrolium ether, benzene etc. The reactions are carried out in the presence of acid catalysts. Acids, which do not oxidize such as hydrochloric acid, hydrobromic acid, phosphoric acid and lower carboxylic acid such as acetic acid and propionic acid, have proved to be particularly useful. In general the reactions are carried out at temperatures between –20°C to 120°C preferably between 0°C and 80°C. In general the process was carried out under atmospheric pressure; however, it can also be carried out under elevated or reduced pressure.

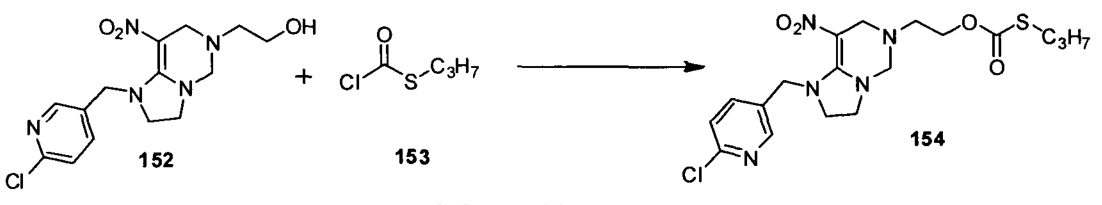
1.4.4b When **R_3** represents a radical then they were prepared by (**Scheme 32**).



Scheme 32

Where **Z** represents a leaving group, other terms have their usual meaning.

For example, when 6,7-dihydro-6-(2-hydroxy ethyl)-8-nitro-(5*H*)-3-(2-chloropyridine-5-yl-methyl)-imidazolino-(2,3-f)-pyrimidine (**152**) and thiopropyl chloroformate (**153**) are used as starting materials, the reaction can be represented by the following equation (**Scheme 33**).



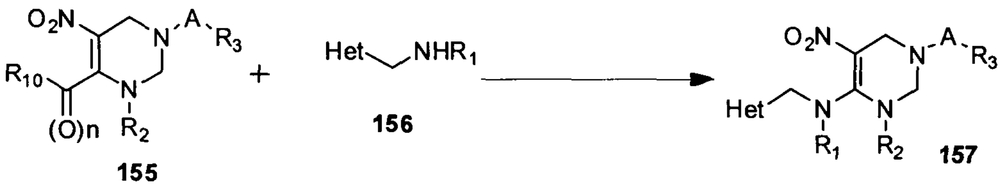
Scheme 33

The starting materials are available or can be prepared by known methods. The two reactants are preferably reacted using diluents in the presence of a basic reaction auxiliary. All inert organic solvents or a mixture of two solvents are suitable for use as diluents. However ethers, such as tetrahydrofuran and dioxane are preferred. Basic reaction auxiliaries which can be employed are all suitable acid-binding agents, such as amines, in particular tertiary amines, as well as alkali metal compounds and alkaline earth metal compounds for examples the hydroxides, oxides and carbonates of lithium, sodium, potassium, magnesium etc further more other basic compounds such as trimethyl amine, tribenzyl amine, tributyl amine, N-methylpiperidine, N-methyl imidazole, N-methyl morpholine etc were used however hydroxides of sodium and potassium or tertiary amines, such as triethylamine, tribenzyl amine or trihexylamine are preferably used.

The reaction time is approximately 0.5 to 48 hours. The reactions were carried out at temperature between +10°C to +200°C, preferably between +20°C and +150°C (particularly at room temperature or the boiling point of the diluents used).

After the completion of the reaction, the reaction mixtures are concentrated in vacuo (by approximately 50%) the residue is treated with aqueous acid, and the compounds are worked up in the manner known per se. The products obtained can be purified in the customary manner by recrystallization, distillation in vacuo or column chromatography.

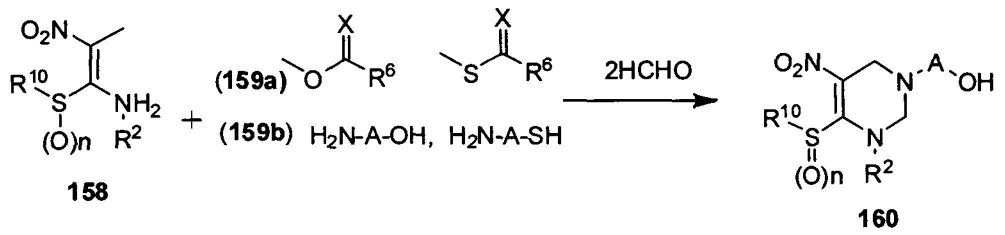
1.4.4c: (b) When R_1 and R_2 together with the adjacent atoms do not cyclize then they are prepared by (**Scheme 34**).



Scheme 34

R_{10}: C_1-C_4 alkyl or phenyl, **n**: 0, 1 or 2 and rest have their usual meaning.

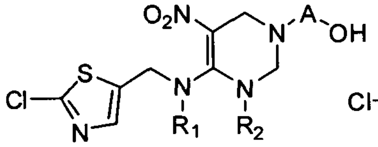
The above reaction was also carried out according to the method described in the process (**b**) under the conditions indicated therein. However the starting materials of the above reaction was prepared by reacting compounds of the formula (**158**) with radicals (**159a**) or amino alcohols (**159b**) in the presence of at least twice the molar amount of formaldehyde, if appropriate in the presence of acid catalysts and in the presence of diluents as shown below (**Scheme 35**).



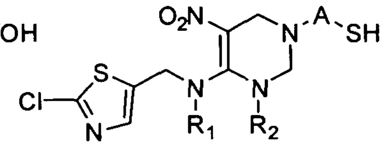
Scheme 35

Here $\mathbf{R^2}$, $\mathbf{R^{10}}$, **A** and **n** have the above-mentioned meanings.

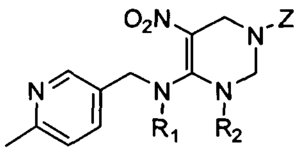
Other nitromethylene derivatives that were prepared are shown below.



161

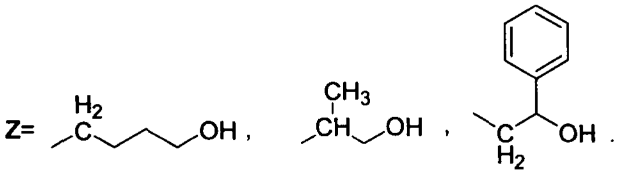


162



163

Wherein $\mathbf{R^1}$, $\mathbf{R^2}$ and **A** have the above mentioned meaning and



These compounds were found to be useful for combating pests (pests refers to animal pests, in particular insects, mites and nematodes which are harmful to plants or higher animals). The active compounds are suitable for combating animal pests, preferably arthropods, in particular insects, arachnids and nematodes, encountered in agriculture. In forestry, in the protection of stored products and of materials, and in the hygiene field and have good plant tolerance and favourable toxicity to warm-blooded animals. They are active against normally sensitive and resistant species and against all or some stages of their development.

For use as insecticides, acaricides and nematicides, the active compounds can be present in their commercially available formulations and in the use forms prepared from these formulations, as a mixture with other active compounds, such as insecticides, attractants, sterilizing agents, acaricides, nematicides, fungicides, growth regulating substances or herbicides. The insecticides include, for example, phosphates carbamates, carboxylates, chlorinated hydrocarbons, phenylureas, and substances produced by microorganisms inter alia. The active compounds can also be present as a mixture with synergistic agents (synergistic agents are compounds which increase the action of the active compounds, without it being necessary for the synergistic agent added to be active itself).

The active compound concentration of the use forms can be from 0.0000001 to 95% by weight of active compound, preferably between 0.0001 and 1% by weight. The compounds are employed in a customary-manner appropriate for the use forms.

These compounds were also found to be particularly suitable for treating vegetative and generative propagation material, such as for example, seeds of cereals, maize, vegetables and the like, or onions, nursery plants and the like.

When used against hygiene pests and pests of stored products, the active compounds are distinguished by an excellent residual action on wood and clay as well as a good stability to alkali on limed substrates, The active substances can be applied as such, in the form of their formulations by further dilution, such as ready to-use solutions, They are applied in the customary manner, for example by pouring, spraying, atomizing or scattering. These active compounds can be applied before or after emergence of the plants, can be incorporated into the soil before sowing.

The amount of active compound applied can vary within a substantial range. It depends essentially on the nature of the desired effect. In general, the application rates are between 10g and 10kg of active compound per hectare of soil surface, preferably between 50g and 5 Kg per ha.

Depending on their particular physical and /or chemical properties, the active compounds can be converted into customary formulation such as solutions, emulsions, suspensions, powders, foams, pastes, granules, aerosols, natural and synthetic substances impregnated with active compound, very fine capsule in polymeric substances and in coating compositions for seed, and further in formulations used with burning equipment, such as fumigating cartridges, fumigating cans, fumigating coils and the like, as well as ULV cold mist and warm mist formulations.

While having a favourable toxicity to warm-blooded species, the active compounds are also suitable for combating animal pests (ectoparasites), such as arthropods, preferably insects and arachnid (ectoparasites), which occur in animal keeping and livestock breeding, in domestic animals, productive livestock, Zoo animals, laboratory animals, experimental animals and pets. In this context, they are active against all or individual stages of development of the pests and against resistant and normally sensitive species of the pests.

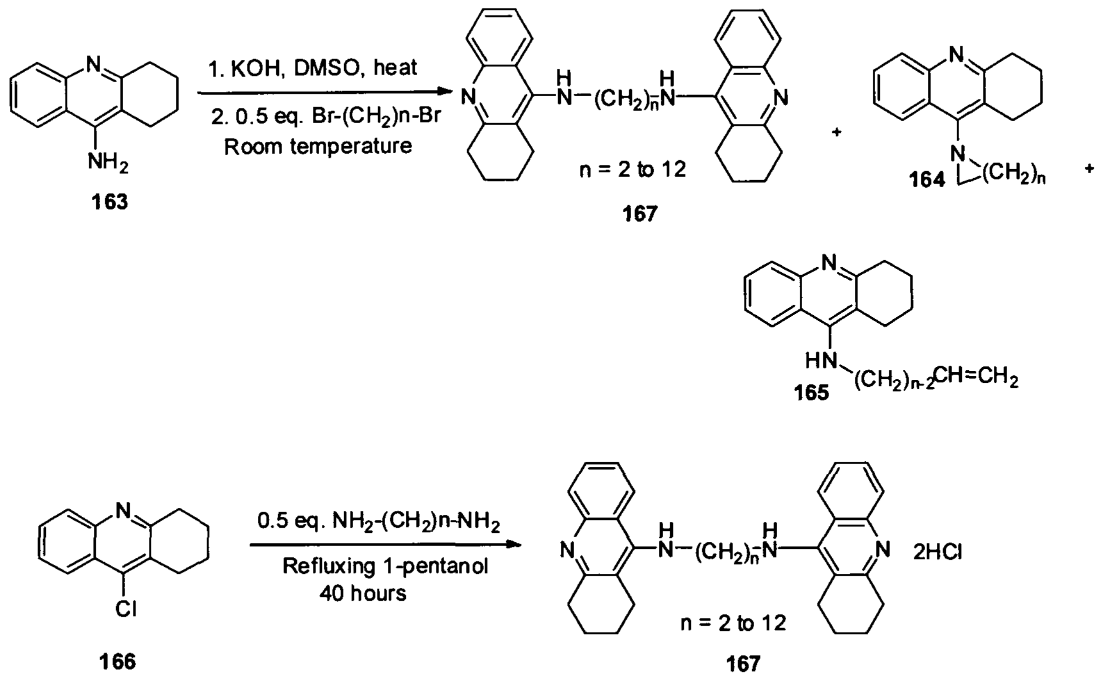
In these cases the active compounds are administered directly or in the form of suitable preparations, enterally, parenterally, dermally, nasally, by environment treatment, or with the aid of active compound-containing shaped articles such as, strips, plates, bands, collars, ear marks, limb bands, marking devices.

Some of the compounds were also found to control Nepholettix ciccticeps on rice with 100% mortality vs 70% for sumethion. As insecticides they had excellent control effect against insects pest having acquired resisting property, having low toxicity against warm blooded animal, fishes, crustacea, etc., reduced in residual property and having high safety to plants[38].

1.5 BIS -HETEROCYCLIC COMPOUNDS

Our literature survey at this stage revealed that synthetic study of bis-heterocyclic compounds have become an important field of research for finding new biologically active molecules. Recent reports have revealed that bis-heterocyclic compounds possess important pesticidal properties[39-41] and also antibacterial properties[42]. It is also evident from one of the reports that bis heterocyclic compounds possess better antimalarial activity than their monomer units, they are also known to possess antiproliferative and anti tumor activities[43]. Following these reports we envisaged that molecules with two tetrahydropyrimidines rings linked through flexible aliphatic chains or through rigid aromatic chains could have enhanced biological activities. Our literature surveys also revealed that bis-1,2,3,4-tetrahydropyrimidines are unknown in the literature except for our preliminary report[44] and hence their biological properties remain unexplored. It is worth mentioning here, at this stage, that bis-heterocycles are well documented in the literature. They have found numerous applications such as electrical materials[45], chelating agents and metal ligands[46] and as biologically active molecules[47] preferably, antitumor[48] and antimicrobial[49], based on the DNA binding affinity and enzyme inhibiting actions. These activities have been reported to be enhanced when different functionalities or substitutions are present on the two heterocyclic rings in the bis-compounds[50, 51], and in some cases they are known to possess more potent biological activities than their monomeric heterocycles as described below.

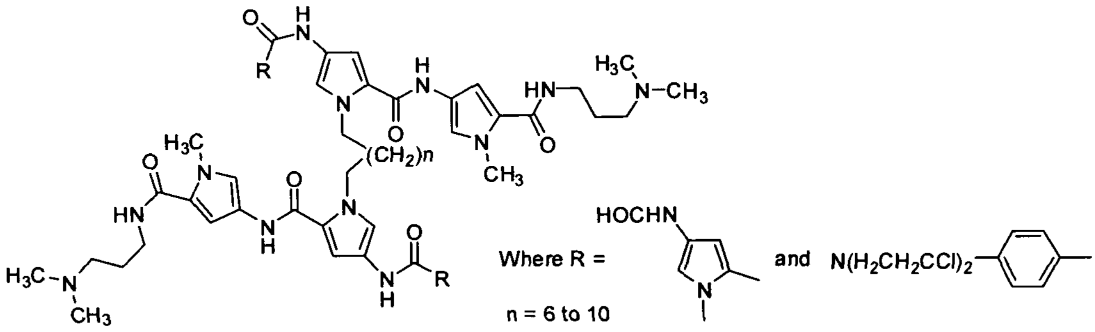
1.5.1 P.R. Carlier and co-workers have also reported[52] the synthesis and evaluation of alkylene-linked dimers of Tacarine (9-amino-1, 2, 3, 4-tetrahydroacridine) (**163**). The reaction of tacarine with dibromo alkanes gave the desired bis product in low yields (epecially when n = 2 to n = 6). To overcome this difficulty Carlier and coworkers explored reaction of 9-chloro-1, 2, 3, 4-tetrahydroacridine with diamines. This method was found to be successful and the optimun temperature proved to be refluxing 1-pentanol at atmospheric pressure for 40 hours (**Scheme 35**).



Scheme 35

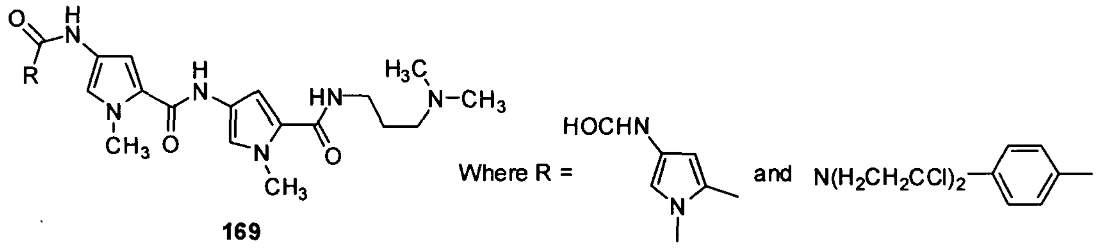
These dimeric compounds (**167**) particularly the heptylene-linked tacarine dimer was found to be 149 fold more potent and 250 fold more selective for acetylcholinesterase (AchE) than tacarine. This dimer also exhibited 24 fold reversing scopolamine-induced memory impairments and thus could be a promising drug candidate for palliative treatment of senile dementia of the Alzheimer's disease.

1.5.2 Y.H. Chen and coworkers[53] have designed and synthesized a novel class of bis (mustard) cross-linked Lexitropsins (**168**).



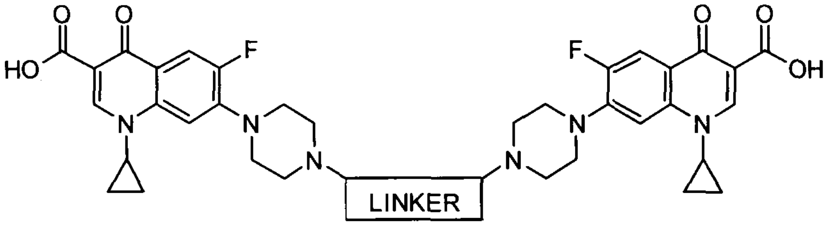
168

The activity of these dimers were compared to that of their monomer counter parts (**169**) and it was found that suitably cross-linked Lexitropsins demonstrated much greater binding strength than then their respective monomers to the alternating AT polymer where the antiparallel side by side bidentate binding is possible.

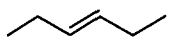
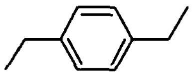
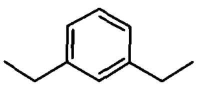
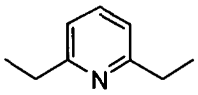
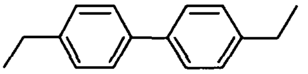


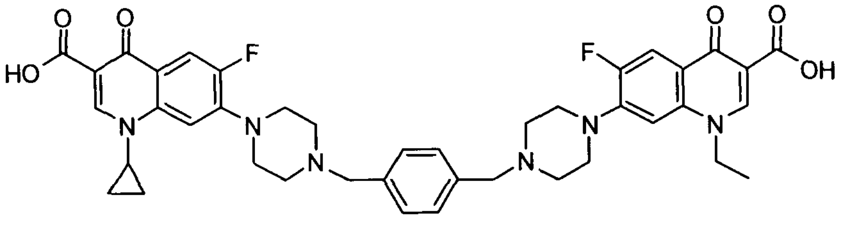
169

1.5.3 R. J. Kern and co-workers have reported[54] the synthesis of a series of symmetric (**170**) and asymmetric (**171, 172**) piperazinyl-linked dimers of the fluoroquinolone class of antibiotics.

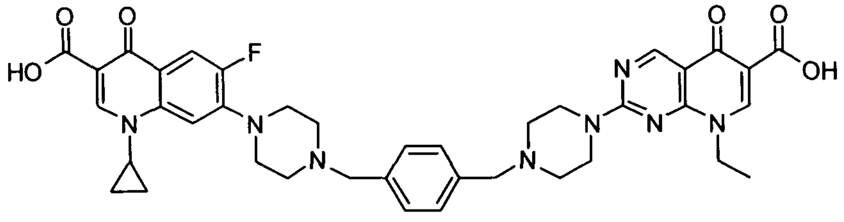


170

		Minimun inhibitory concentration MIC, microgram/mL		
		SA1199	SA1199-3	SA1199B
1		0.03	0.06	0.03
2		0.125	0.125	0.125
3		0.06	0.06	0.125
4		<0.03	<0.03	<0.03
5		4	8	8
6	Ciprofloxacin monomer	0.125	1	8



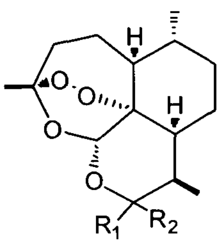
171



172

It was found that some specific piperazinyl-linked dimers of the FQ class of antibiotics display increased antibacterial potency against drug-resistant strains of *S. aureus*, including FQ resistant strains possessing N or A efflux-mediated and topoisomerase IV substitution mediated resistance mechanism.

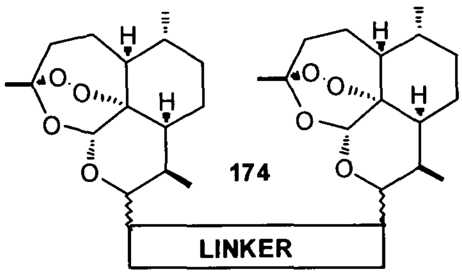
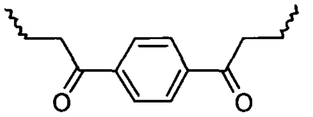
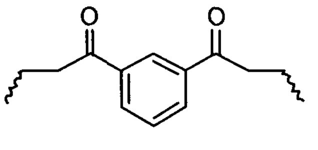
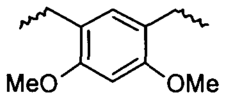
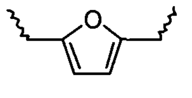
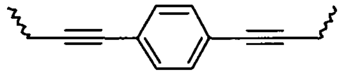
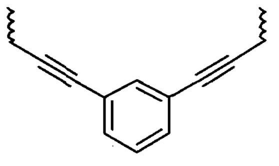
1.5.4 Gary. H. Poshner and co-workers have synthesized[55] dimeric derivatives of natural trioxane artemesinin (**173**), which is a herbal extract of the Chinese worm wood *artemesia annua* and have been used for centuries to treat fever including malaria related fever (the unusual seven membered C-O bridged by O-O peroxide unit is thought to be the central of its biological activity).



artemisinin, $R_1 = R_2 = O$

173

This involved connecting the two trioxanes through an aromatic linker group such as furan or a benzene ring (174).

Dimer	 174	Antimalarial IC_{50} (nM)
1		1.9
2		1.9
3		1.3
4		3.2
5		30
6		36
7	Artemisinin	9.7 ± 1.8

These compounds were tested against their standard assay for chloroquine-sensitive *plasmodium falciparium* (NF54) parasites. They found that the benzomethylenelinked dimers, the aryl dimer and the furan dimer were considerably more potent antimalarial agents than artemesinin itself. (IC_{50} values for the compound were 1.3-3.2 nM, compared with 9.7nM for artemisinin). Some of these compounds were also potent antiproliferative and antitumour agents

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CHAPTER-II

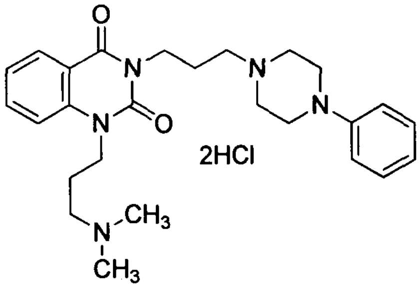
Introduction

Quinazolines and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals and are now known for a wide range of biological properties[1-8]including anti-inflammatory[9,10], anti-tumoral[11] anticonvulsant[12,13] hypnotic[14], sedative[14], antibacterial, antidiabetic, and several other useful and interesting properties. Quinazolines are one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals. The quinazoline antibacterials have emerged as an area of immense interest because of their broad spectrum of in vitro activity and their in vivo chemotherapeutic efficiency[16].

The rapid rise in bacterial resistance to the traditional antibiotics such as Penicillins and tetracyclines has encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity. Further derivatives of quinazolines are of considerable interest because of their pharmacological properties[17] such as protein tyrosine kinase inhibitor[18], cholecystokinin inhibitor etc.

2.1 The preparation and properties of a few such molecules are described in the following sections

2.1.1 Herbert J Havera synthesized a series of 1,3 -disubstituted 2,4(1*H*, 3*H*)-quinazolinediones from 3-substituted 2,4(1*H*, 3*H*)-quinazolinediones by treatment with sodium hydride and the desired alkyl halide in xylene. These compounds showed varying degrees of vasodilation and antihypertensive activity without significant blockade of α –adrenergic receptors.



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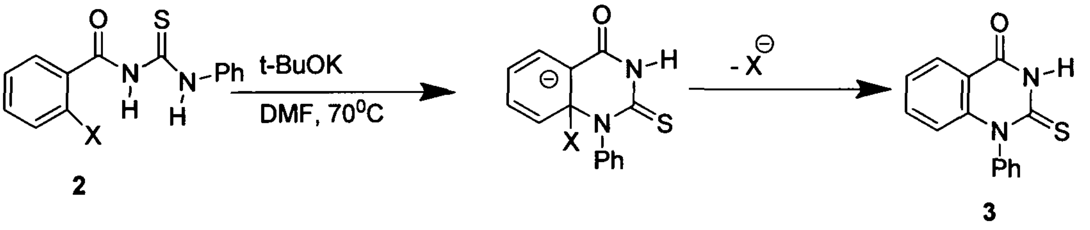
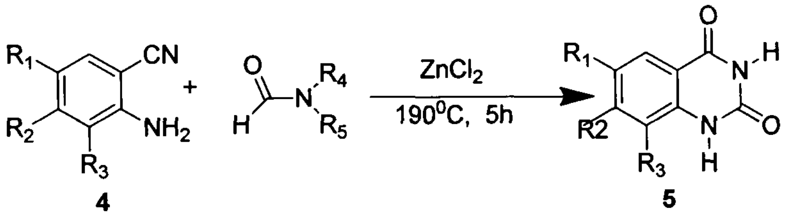
1-[3-(N,N-dimethylamino)propyl]-3-[3-(4-Phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione (**1**) of the above series was found to be more potent than papaverine in inducing vasodilation and induced a prolonged decrease in systolic blood pressure of hypertensive rats upon oral administration[19].

2.1.2 W. Russel Bowman and co-workers reported[20] the synthesis of 1*H*-quinazoline-4-ones (**3**) using intramolecular aromatic nucleophilic substitution reaction of 1-(2-bromobenzoyl)-3phenylthiourea 3-phenylureas (**2**) (**Scheme 1**)



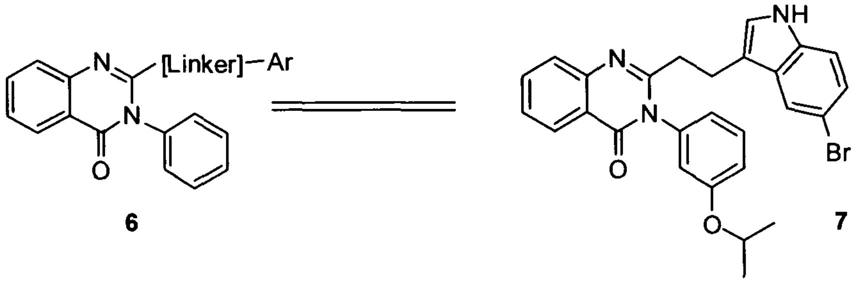
Scheme 1

2.1.3 Li Jiarong and co-workers reported[21] facile synthesis quinazoline-2,4(1H, 3H)-diones(**5**) by condensation of aromatic o-aminonitriles (**4**) with DMF or N,N-dimethylformamide in presence of $ZnCl_2$ at 190-200^{0}C in a sealed reactor.(**Scheme 2**). They reported number of substituted quinazolines, however for their utter surprise when the same o-aminonitriles carried out cyclo condensation with N, N-dimethylacetamide it did not result the desired quinazoline.



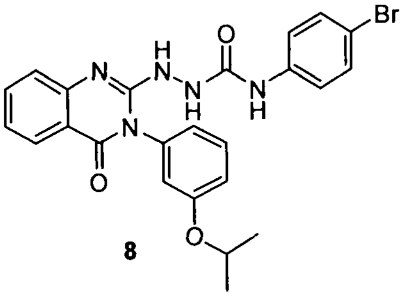
Scheme 2

2.1.4 Melvin J. Yu and co-workers have reported[22] that compound exemplified by 2-[2-(5-bromo-1*H*-indolyl-3-yl) ethyl]-3-[3-(1-methylethoxy) phenyl]-4(3*H*)-quinazolinone (7) (**Scheme 3**) represented a structurally novel series of non-peptide cholecystokinin B receptor ligands (CCK-B). It is postulated that CCK-B is involved in a variety of neurological disorder such as anxiety, pain and panic disorder.



Scheme 3

A series of analogs were prepared with methyl substituents on the Ethylene Bridge as well as congeners with different linkers (**6**). It was found that for derivatives with one to three methylene units separating the indole and quinazoline rings, maximal receptor binding activity was found when the distance separating the two-heteroaromatic system is defined by an ethyl group (7).



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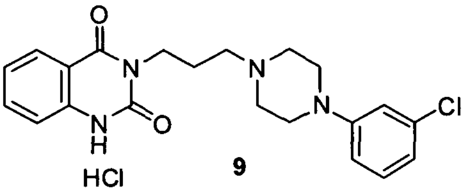
2.1.5 Further to it Janak K padia and co-workers, found that introduction of -NH- as a linker (**8**) dramatically enhanced binding affinity and selectivity for CCK-B receptors[23]. Quinazolines are also known to possess antimicrobial[24], anticonvulsant[25], sedative and hypertensive activity. Shin Hayao and co-workers have synthesized a series of 3 - (4-aryl-1-piperazinylalkyl)-2, 4 (1*H*, 3*H*) quinazolinedione (**9**), which were subsequently tested, and they showed varying degrees of sedative and hypotensive activity.



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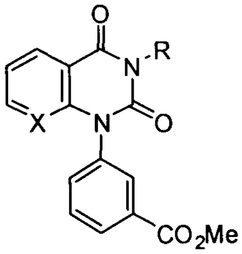
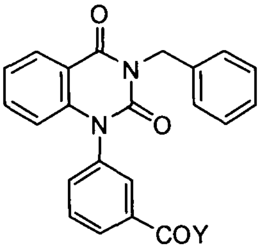
The above compound (**9**) of the said series was found to be a potential psychosedative, and its activity in experimental animals was comparable to that of Chlorpromazine[26].

2.1.6 There have also been reports of quinazoline showing antidepressant and anti-inflammatory activities J. A. Lowe and coworkers did a structure activity relationship of a series of quinazolinediones and azaquinazolinediones of the type (**10**) and (**11**) Which were found to possess potent inhibitory activity toward the calcium-independent phosphodiesterase enzyme (CaIPDE)[27] which proved to be useful in chronic diseases such as depression and inflammation.



10

X= C,N
R=H,Et,CH_2Ph,CH_2cyclopentyl
CH_2norbornyl



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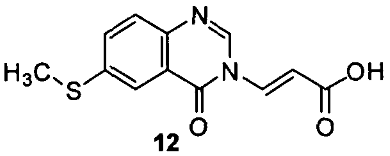
Y= OH, NHMe

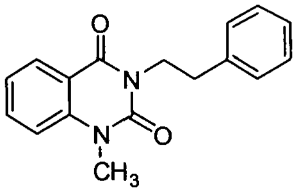
2.1.7 Quinazolines are also known to possess antiallergic activity, Ronald A. LeMahieu and coworkers prepared a series of substituted (E)-3-(4-oxo-4H-quinazoline-3-yl)-2-propenoic acid and evaluated in the rat passive cutaneous anaphylaxix (PCA) test for antiallergic activity. Alkoxy, alkylthio and isopropyl substituents at the 6 or 8 positions provided highly potent compounds of which



12

(E)-3-[6-(methylthio)-4-oxo-4*H*-quinazoline-3-yl]-2-propenoic acid (**12**) was found to be the most potent. It was further observed that conversion to the Z-isomer, reduction of the side chain double bond, or reduction of the quinazoline ring resulted in substantial loss of activity[28].

2.1.8 More than 40 alkaloids comprising of a 4(3*H*) quinazoline moiety were isolated from natural sources, for example D. L. Dreyer and co-workers have reported the isolation of two simple natural alkaloids, 1-methyl-3- (2'-phenylethyl)-1*H*, 3*H*-quinazoline-2, 4-dione (**13**) and 1-methyl-3- [2'-(4'-methoxyphenyl) ethyl]-1*H*, 3*H*-quinazoline-2, 4-dione (**14**) from the seed husk of *Zanthoxylum arborescens*



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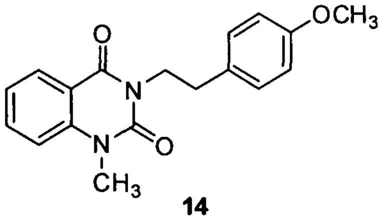
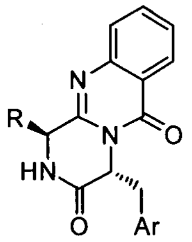


14

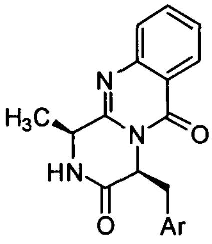
2.1.9 Atsushi Numata and co-workers have found that a strain of Aspergillus Fumigatus isolated from the gastrointestinal tract of the saltwater fish Pseudolabrus Japonicus, produces the novel metabolites fumiquinazolines (general structure **15** and **16**) which exhibit moderate cytotoxicity against the cultured P-388 Lymphocytic Leukaemia cells.[30]



15

Fumiquinazoline F($R=CH_3$)

Ar=3-indolyl



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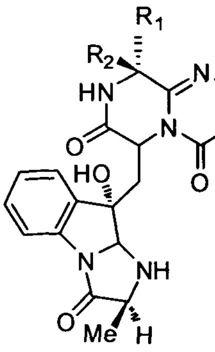
Fumiquinazoline G

For e.g



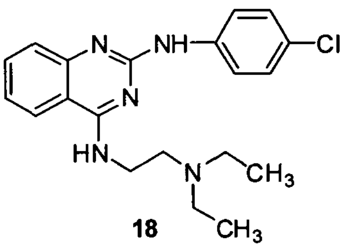
1) R_1=Me,R_2=H

2) R_1=H, R2=Me

17

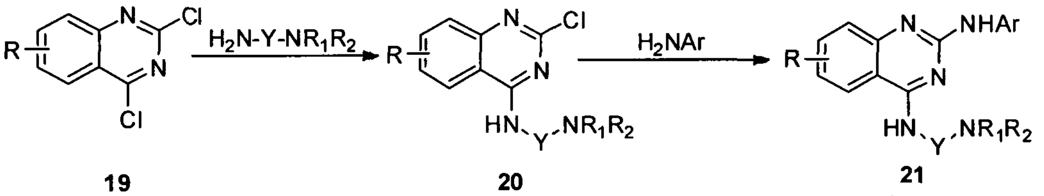
Later Numata and co-workers could isolate seven fumiquinazolines from the same strain showing similar toxicity[31].

2.1.10 Quinazoline are also reported to posses antimalarial activity. F.H.S. Curd and co-workers while working on Chlorguanide discovered that certain N^4-[(dialkylamino) alkyl]-N^2 –phenyl-2, 4-quinazolinediamines possessed strong antimalarial effects against *plasmodium galencium* in chicks. Among them N^2- (4-chlorophenyl)-N^4-[2-(diethylamino) ethyl]-2,4-quinazolinediamine (**18**) were found to be most promising.[32]



18

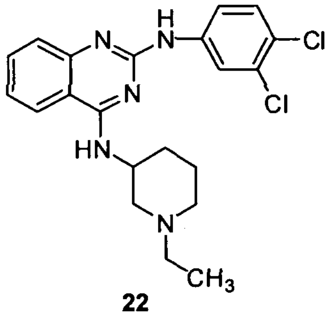
2.1.11 Edward F. Elsalger and co-workers synthesized a series of N^2 (and N^4)-aryl-N ^{4}(and N^2)-[(dialkylamino) alkyl]-2,4-quinazolinediamines. Condensation of appropriate 2,4-dichloroquinazolines (**19**) (prepared by chlorination of corresponding 2,4-(1*H*, 2*H*)-quinazolinediones with $POCl_3$or PCl_5) with the requisite N, N-dialkylalkylenediamine in appropriate solvents. (under this condition only the chlorine in 4-position is replaced) gave the corresponding 2-chloro-N-[(dialkylamino)alkyl]-4-quinazolinamines (**20**) which were condensed with appropriate arylamine in alcohol (in presence or absence of HCl) to yield the desired N^4-[(dialkylamino)alky]-N^2-Phenyl-and heterocyclic 2,4-quinazolinediamines (**21**) (**Scheme 4**).



R= H, Cl, NO_2
R_1,R_2 =alkyl groups
Ar=Aryl groups
Y= Alkyl,subst alkyl,Cycloalkyllinke

Scheme 4

All these compounds were tested against a normal drug sensitive strain of *p. berghei* in mice by parental route. Many compounds showed good results of which N^2- (3,4-dichlorophenyl)-N^4- (1-ethyl-3- piperidinyl) 2,4-quinazolinediamine **(22)** was selected for preclinical toxicity studies.



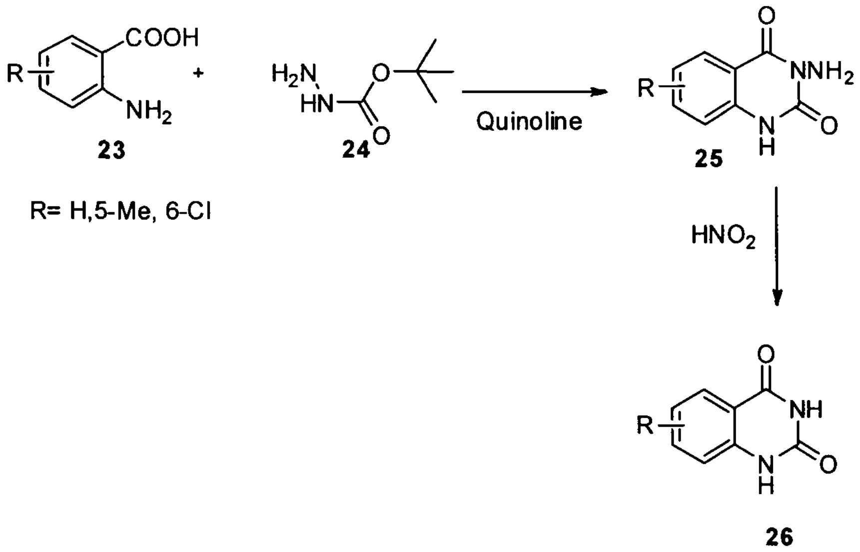
22

Unfortunately the above compound and several of its derivatives were shown to be phototoxic and plans to study it in humans were abandoned.[33] quinazolines are also known to posses antifungicide and diuretic properties[34].

2.2 METHODS OF PREPARATION OF QUINAZOLINES

A number of methods have been described for the preparation of quinazolines and their derivatives. The main synthetic routes to such compounds utilize 2-aminobenzoic acid or its derivatives **(23)**.

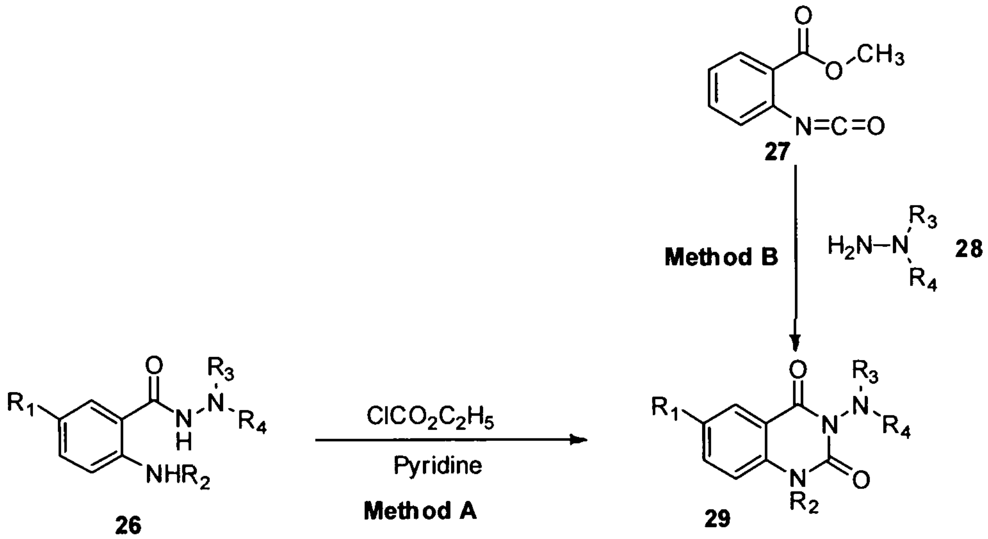
2.2.1 Iraj Lalezari and C.A. Stein have reported a simple one step synthesis of 3-amino-2,4(1*H*,3*H*)-quinazolinediones and its derivatives **(21)** by the reaction of anthranilic acids **(19)** and t-butyl carbazates **(20)** in refluxing quinoline.**(Scheme 5)**



Scheme 5

The compounds so formed were successfully deaminated by nitrous acid to afford the corresponding quinazolinediones[35] (**26**).

2.2.2 M. J. Kornet and co-workers have reported the synthesis of a number of 3-amino-2, 4(1H, 3H)-quinazolinediones by two different methods depending on the availability of starting materials. In the method A, o-aminobenzoyl-hydrazines (**26**) was reacted with ethylchloroformate in dry pyridine which gave (**29**) in moderate yields. The intermediate (**26**) were obtained from the reaction of isatoic anhydride and hydrazines.

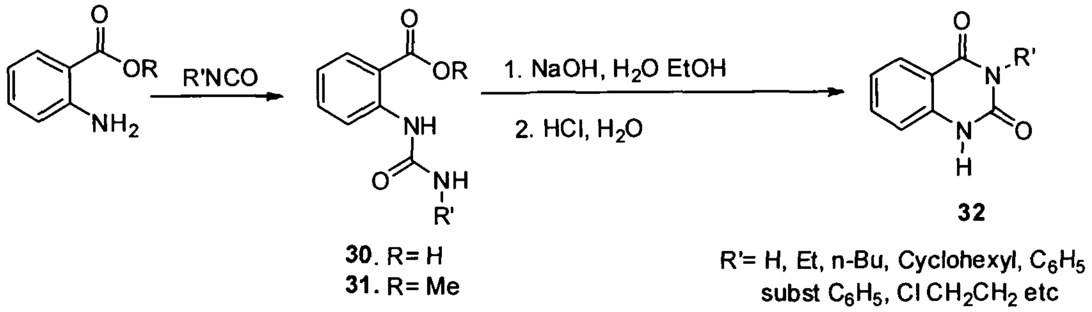


R_1= H, CH_3, NO_2, Cl
R_2= H, CH_3
R_3=R_4= CH_3, $(CH_2)_5$, $O(CH_2CH_2)_2$

Scheme 6

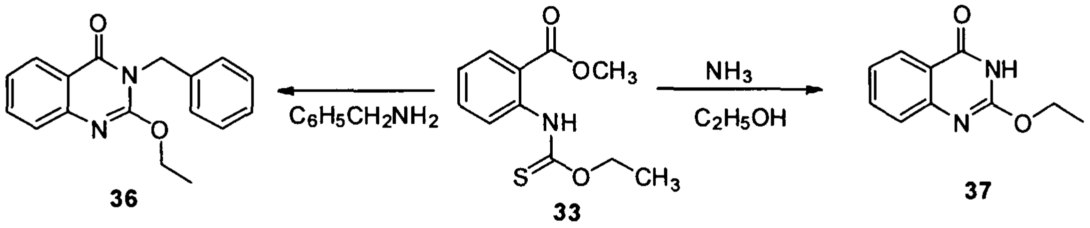
In the method **B**, compounds (**29**) (R_1=H) were synthesized from 2-methoxycarbonylphenyl isocyanate (**27**) and 1,1-di substituted hydrazines (**28**) in toluene. Both methods were monitored by TLC and indicated the formation of uncharacterized intermediate which lead to cyclized products[36] (**scheme 6**).

2.2.3a Papadopoulos reported a simple room temperature treatment of 2-(3-arylureido) benzoic acid (**30**) and methyl 2-(3-alkyl, or 3-arylureido)-benzoates (**31**) with aqueous-ethanolic sodium hydroxide to yield 3-substituted 2, 4 (1*H*, 3*H*) - quinazolinediones (**32**) [37](**Scheme 7**)

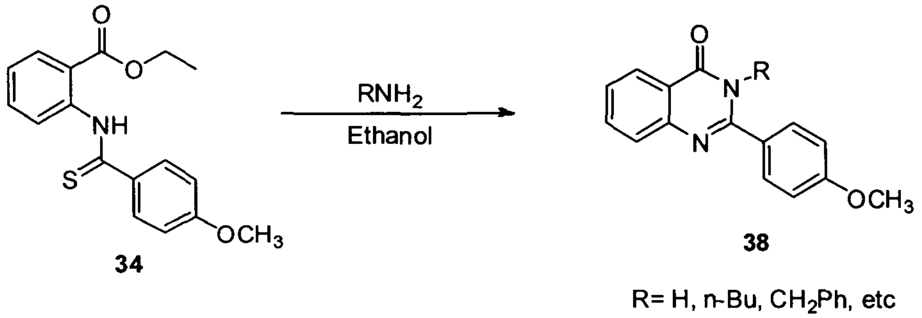


Scheme 7

2.2.3b Papadopoulos later reported the reaction of three derivatives of isothiocyanate. They were (1) Ethyl-N (2-methoxycarbonylphenyl) thiocarbamate (**33**), (**Scheme 8**). (2) N-(2-ethoxycarbonylphenyl)-4-methoxythiobenzamide (**34**), (**Scheme 9**) and (3) 2-(4-methoxyphenyl)-4*H*-3,1-benzothiazin-4-one (**35**) (**Scheme 10**). These three compounds are expected to react with nucleophillic reagent containing a primary amino group at both carbonyl and thiocarbonyl groups to form 2,4-disubstituted 4(3*H*)-quinazolinones as shown below in the following schemes.

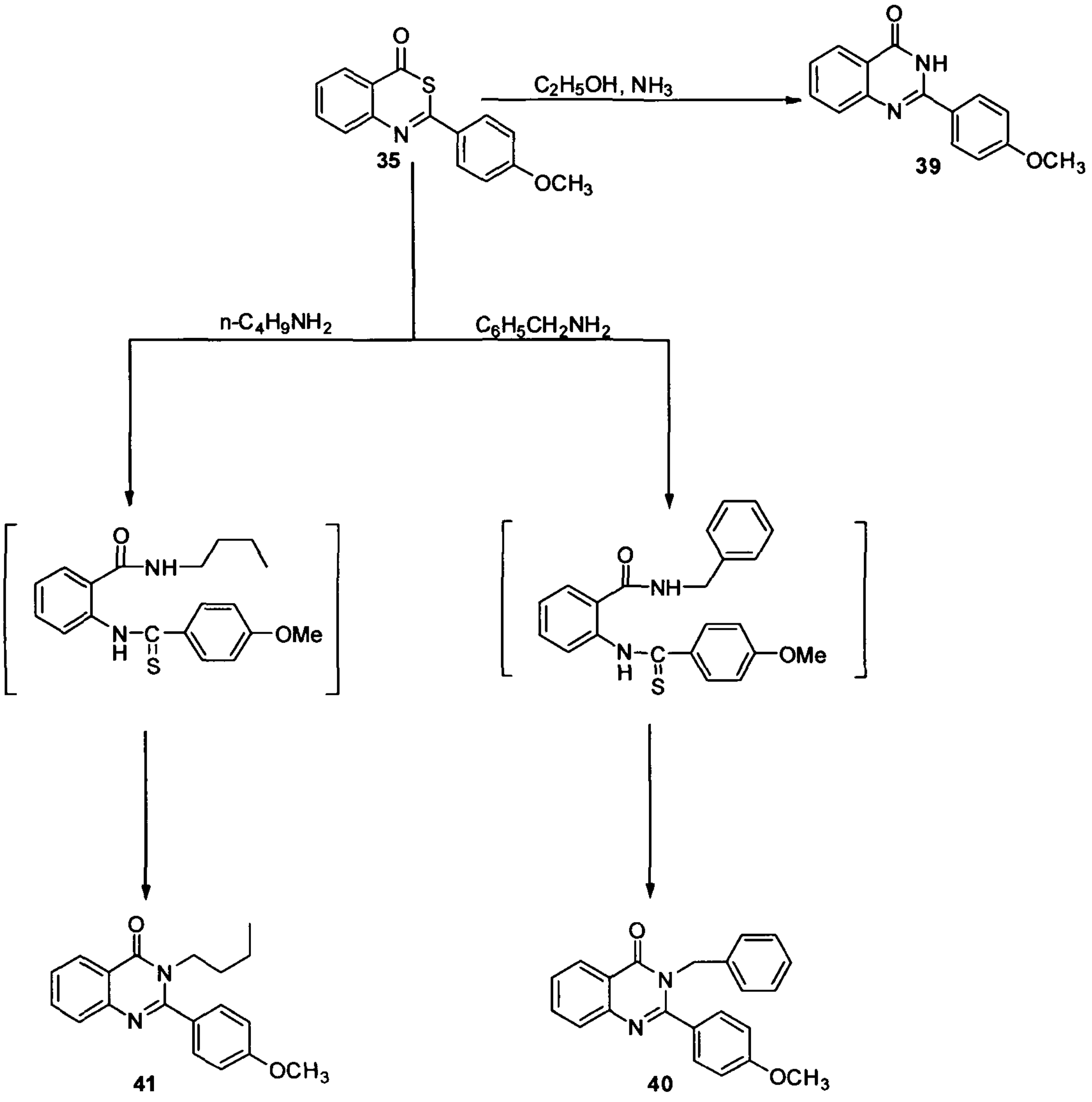


Scheme 8



Scheme 9

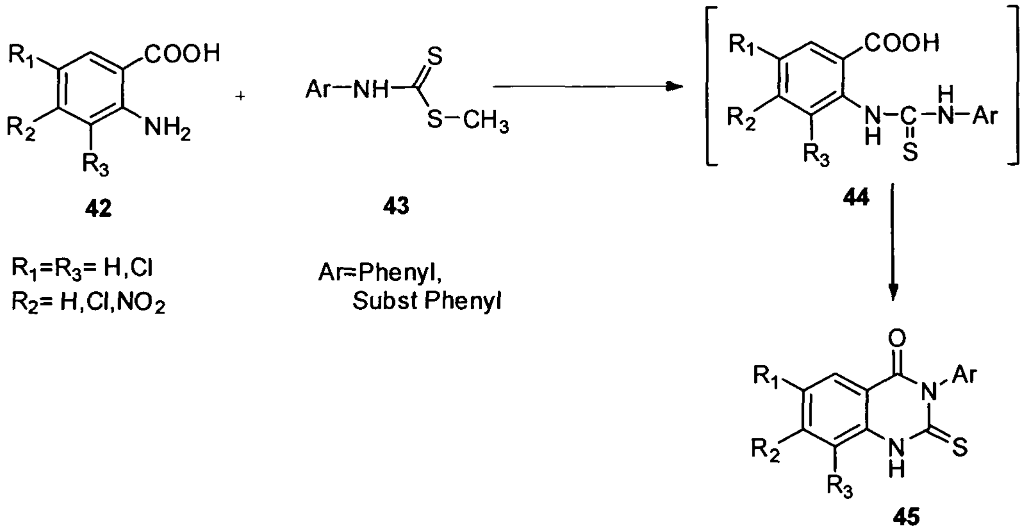
When Benzothiozinone (35) was heated with ethanolic ammonia at 100^{0}C or refluxed with benzyl amine compound (39) and (40) was obtained. Similarly when it was heated with n-butylamine on a steam bath compound (41) was obtained.



Scheme 10

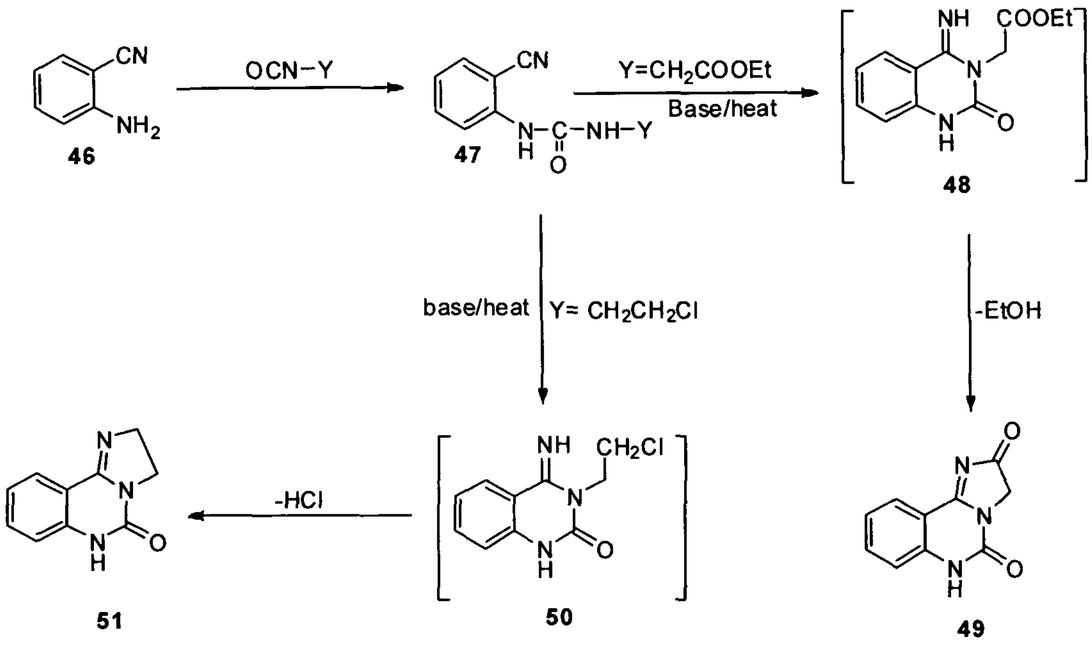
The formation of Quinazolinones (40) and (41) by the above reaction very likely involves the intermediate formation of thoiamides (indicated by square brackets) ^{38}.

2.2.4 E. Melendez and co-workers have also reported the synthesis of 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines (**45**) from N-aryldithiocarbamates (**43**) and anthranilic acid (**42**) by refluxing in DMF. The crude product was isolated by precipitation of the mixture in water[39] (**Scheme 11**).



Scheme 11

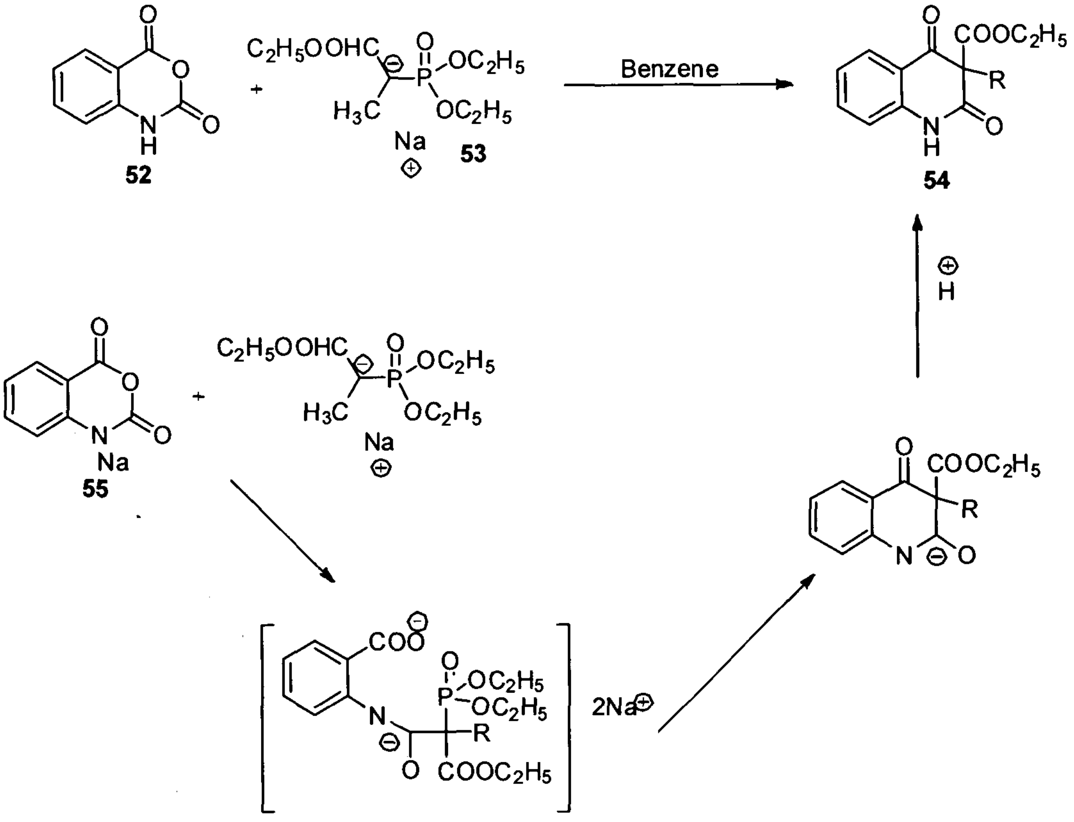
2.2.5 Papadopoulos reported a two step synthesis of 2,6-dihydro imidazo[1,2-c]-quinazoline-5-(3*H*)one (**51**) by the reaction of anthranilonitrile (**46**) with 2-chloroethyl isocyanate. This reaction proceeded by the formation of an intermediate 2-[3-(2-chloroethyl) ureido]-benzonitrile (**50**) which upon heating or treatment with a base undergoes a double cyclization to form 2,6-dihydroimidazo[1,2-c]-quinazoline-5-(3*H*)one[40] (**51**)(**Scheme 12**)



Scheme 12

Later he further reported the synthesis of imidazo-[1,2-c]-quinazoline-2,5-(3*H*,6*H*) dione (**49**) by the reaction of anthranilonitrile with ethylisocyanoacetate. The reaction proceeded in the similar manner via the formation of 2-(3-ethoxycarbonylmethylureido) benzonitrile (**48**), which undergo double cyclization to form imidazo compound[41](**49**) (**Scheme 12**).

2.2.6 Minami and co-workers reported[42] the synthesis of quinazolines from isatoic anhydride as per the scheme below (**Scheme 13**)



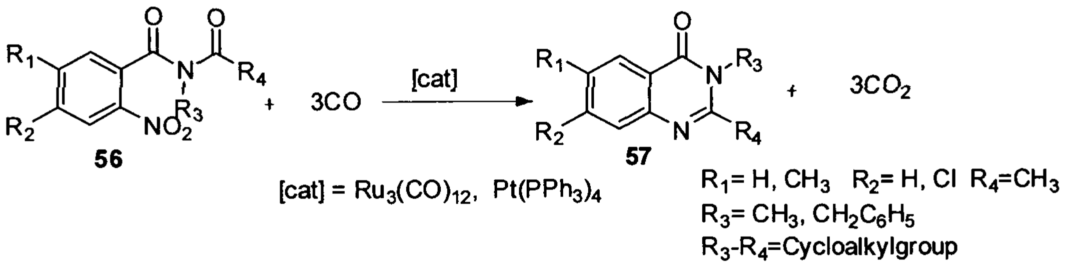
Scheme 13

The reaction of isatoic anhydride (**52**) with an ethyl-2-diethylphosphonopropanoate carbanion (**53**) in refluxing benzene gave 3-ethoxycarbonyl-3-methyl-2,4 (1*H*,3*H*)-quinolinedione (**54**) in poor yield.

However similar treatment of N-sodioisatoic anhydride (**55**) (prepared in situ from (**52**) and sodium hydride) in a mixed solvent gave (**54**) in good yields [42].

There are also reports of quinazoline being prepared from 2-carbomethoxy phenyl isocyanate[25], N-arylnitrilium salts[26], and 4*H*-3, 1-benzoxazinones[27]. Recently, the solid phase synthesis of 2,4-(1*H*, 3*H*)-quinazolinediones has been reported [28]. The direct ortho substitution of N- (tert- butoxycarbonyl) aniline by a lithium reagent was also described.

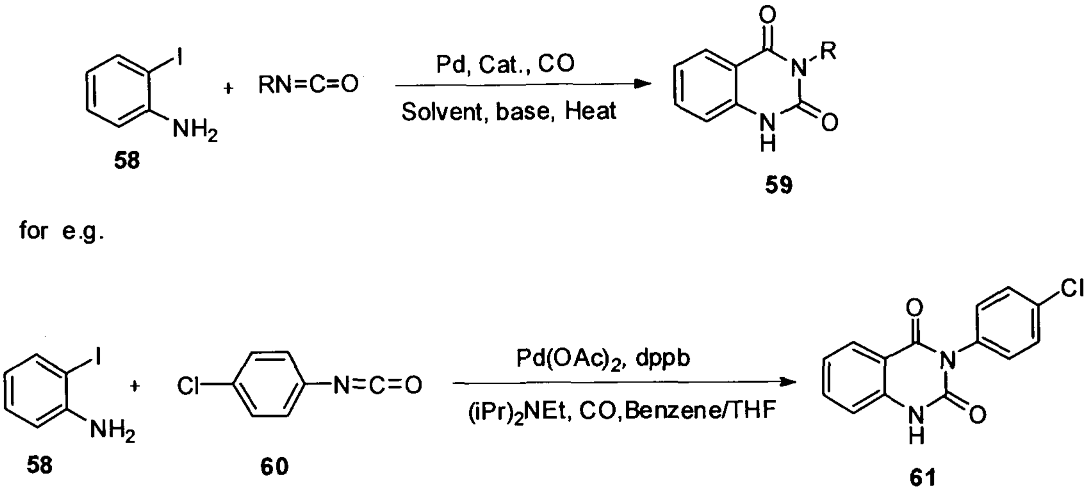
2.2.7 Transition metals were utilized in the preparation of these compounds; Akazone et al[43]reported the first Ruthenium catalysed synthesis of 4(3*H*)-quinazoline derivatives (57) by the reductive N-Heterocyclization of N-(2-nitro benzoyl) amides (56) under carbonmonoxide pressure. (Scheme 14)



Scheme 14

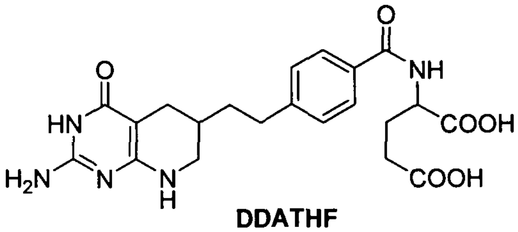
It was also reported that a combination of $PdCl_2$-$(PPh_3)_2$ and $SnCl_2$ was used for the intermolecular reductive N-heterocyclization of 2-nitrobenzamide to give the corresponding quinazolines[44].

2.2.8 Encouraged by the usefulness of 4(3*H*)-quinazoline derivatines, Larksarp and coworker examined the utility of palladium catalysts for the preparation of benzo[e]-1,3-oxazin-4-one derivatives from o-iodophenols with heterocumulenes and carbon monoxide they explored the preparation of the title compounds by palladium catalysed cyclocarbonylation reactions of o-iodoanilines (58) with heterocumulenes. They reported the synthesis of 4(3*H*)-quinazolinone derivatives (61) by treatment of o-iodoanilines with heterocumulenes such as isocyanates (57), carbodiimides and ketenimines in the presence of a palladium catalyst under carbon monoxide pressure[45] (**Scheme 15**).



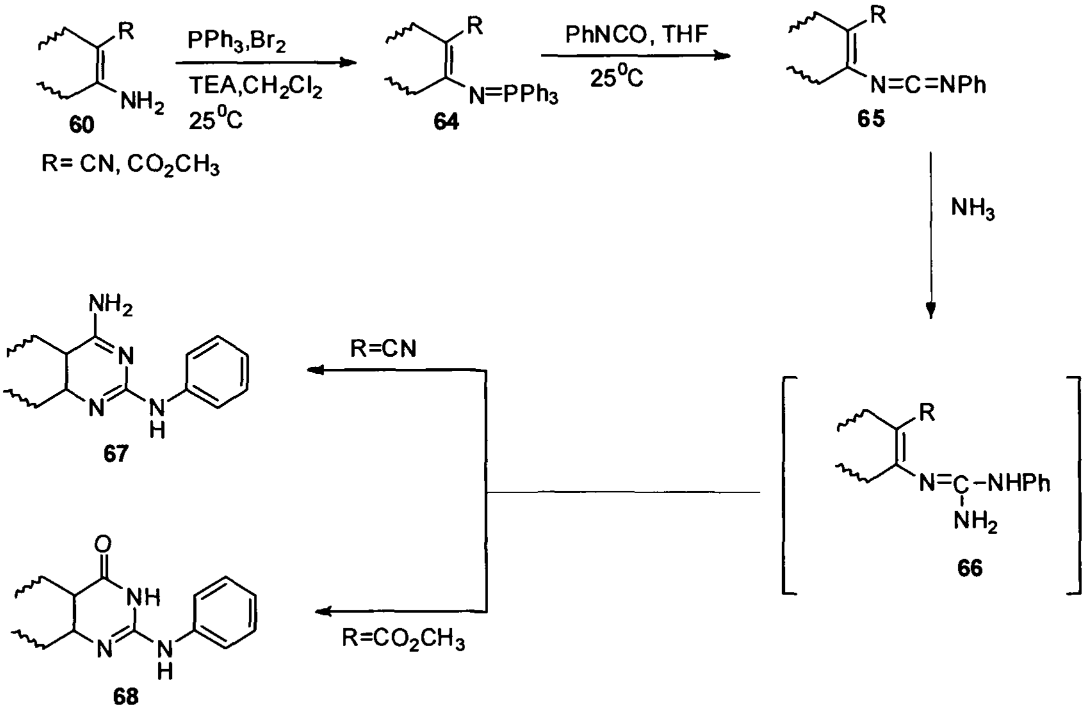
Scheme 15

2.2.9 E.C. Taylor and co-workers while working on development of synthetic strategies for the preparation of 5, 10-dideazatetrahydrofolic acid (**DDATHF, 62**) and its analogs, developed a facile pyrimidine annulation process, which took place under mild conditions and was found to be general for o-aminonitriles and o-aminoesters.



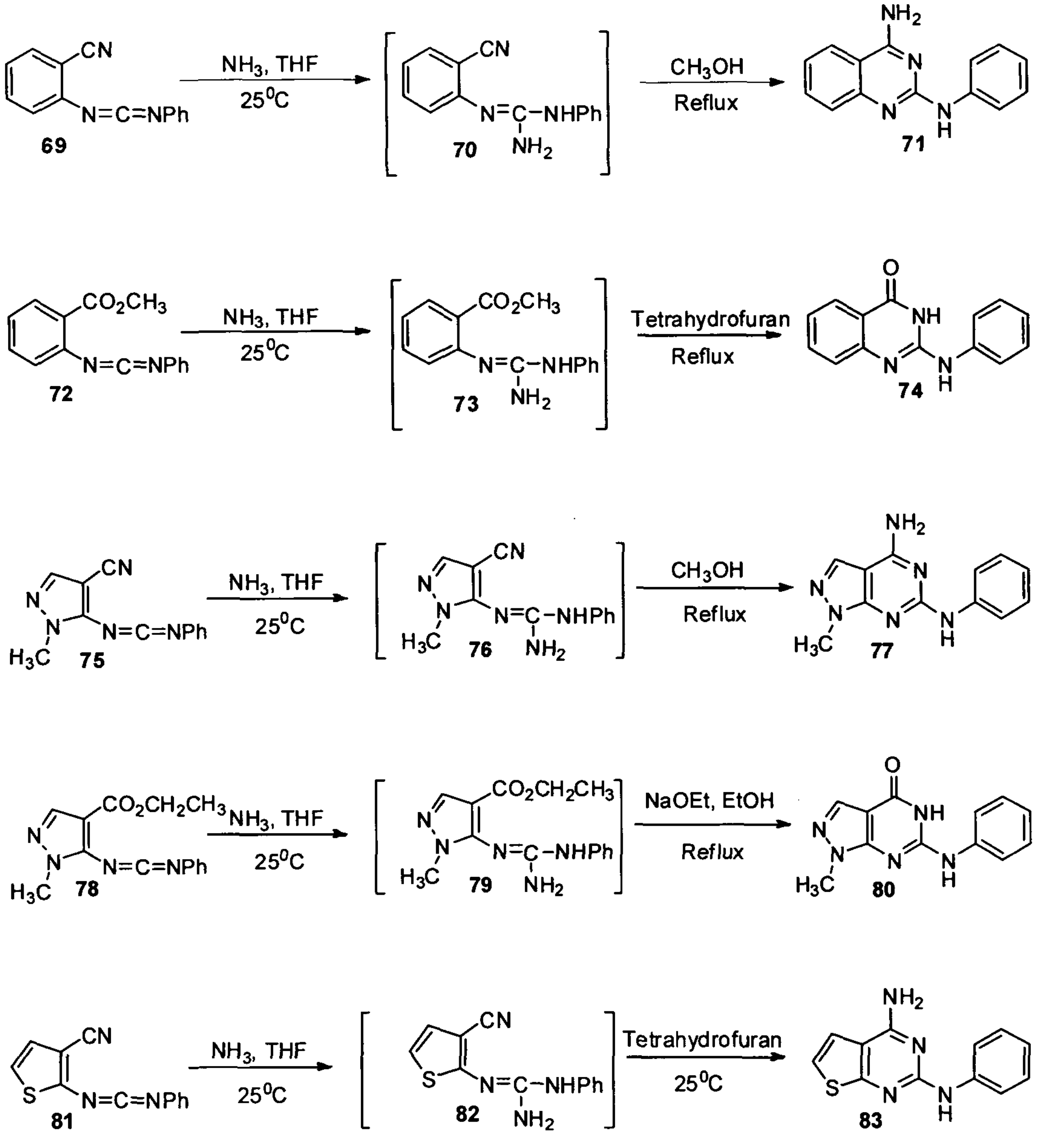
DDATHF

Treatment of o-aminoesters and o-aminonitriles (**63**) with dibromotriphenylphosphorane (generated *in situ* by slow addition of bromine to a cold solution of triphenyl phosphine in methylene chloride) resulted in formation of the corresponding iminophosphoranes (**64**). The iminophosphoranes undergo Aza Wittig reactions with isocyanates to give carbodiimides (**65**). (In case of iminophosphoranes derived from o-aminoesters. Wamhoff and co-workers found that the initially formed carbodiimides underwent a pericyclic rearrangement in alcoholic solvents to give 2-alkoxy fused pyrimidines. It was envisaged that this rearrangement was probably the consequence of the severe reaction conditions (80^{0}C, 4-8Hrs) employed for the carbodiimide synthesis, and the latter intermediate might be isolable under milder conditions. Thus the aza-wittig reactions of imino phosphoranes with phenyl isocyanate were carried out at room temperature, which permitted islolation of the corresponding carbodiimides in good yields.)



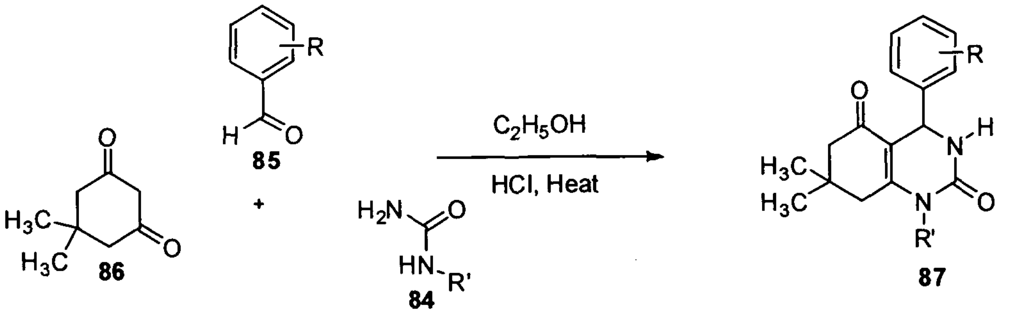
Scheme 16

Addition of ammonia to the resulting highly reactive carbodiimides (**65**) generated intermediate guanidino-substituted intermediates (**66**), which underwent intramolecular cyclization across the *ortho*-situated electrophyllic nitrile or ester functionalities to give the fused pyrimidines (**67** and **68**) (**Scheme 17**) (in some cases heating was required for cyclization as shown below) [46].



Scheme 17

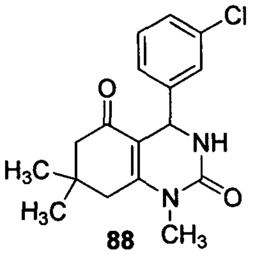
2.2.10 In 2003 Selma Sarac and co-workers synthesized a series of 4-aryl-7, 7-dimethyl-1, 2,3,4,5,6,7,8-octahydroquinazoline-2, 5 diones (**87**) and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2, 5 diones (**87**) according to the Biginelli reaction. This involved one-pot condensation of urea (**84**) (or N-methyl urea), aromatic aldehyde (**85**) and 5, 5-dimethyl-1, 3-cyclohexanedione (**86**) under strongly acidic conditions (**Scheme 18**)

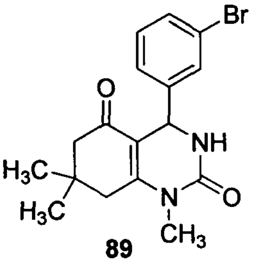


R : H, Cl, Br, CH_3, OCH_3
R' : H, CH_3

Scheme 18

These compounds were further tested for their Calcium antagonist activity. The in vitro tests were carried out on isolated rat ileum and lamb carotid artery. Compound (**88**) i.e 4-(3-Chlorophenyl)-1, 7, 7-trimethyl-3, 4, 7, 8-tetrahydroquinazoline-2, 5 (1*H*, 6*H*)-dione,


88

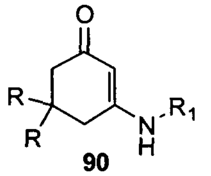

89

and (**89**) i.e 4-(3-Bromophenyl)-1,7,7-trimethyl-3, 4,7,8-tetrahydroquinazoline-2, 5(1*H*, 6*H*)-dione were found to be the most active derivatives on isolated rat compared to standard nicardipine. On isolated aortic strip of lamb the calcium antagonist activity of compound (**88**) was found to be as high as nicardipine (which was used as reference) [47].

2.3 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines

However, synthesis of 5-oxo-1,2,3,4,5,6,7,8-Octahydroquinazolines[48] is least attended to and to the best of our knowledge Bis-(5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines) are unknown, hence their biological properties remain unexplored. Prompted by the above findings our research group have recently reported a facile synthetic methodology for1-alkyl/aryl-3-alkyl/aralkyl/aryl-5-oxo1,2,3,4,5,6,7,8-octahydroquinazolines and 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-oxo1,2,3,4,5,6,7,8-octahydroquinazolines[49]. In continuation with the efforts on the synthesis of tetrahydropyrimidines [50-52] our group decided to develop a facile one-pot strategy for bis-1,2,3,4,7,8-hexahydroquinazolines-5(6*H*)-ones in which the two quinazolines are linked through flexible aliphatic chains or through rigid aromatic aromatic rings.

For the synthesis of our required quinazolines we required compounds of the type **90**

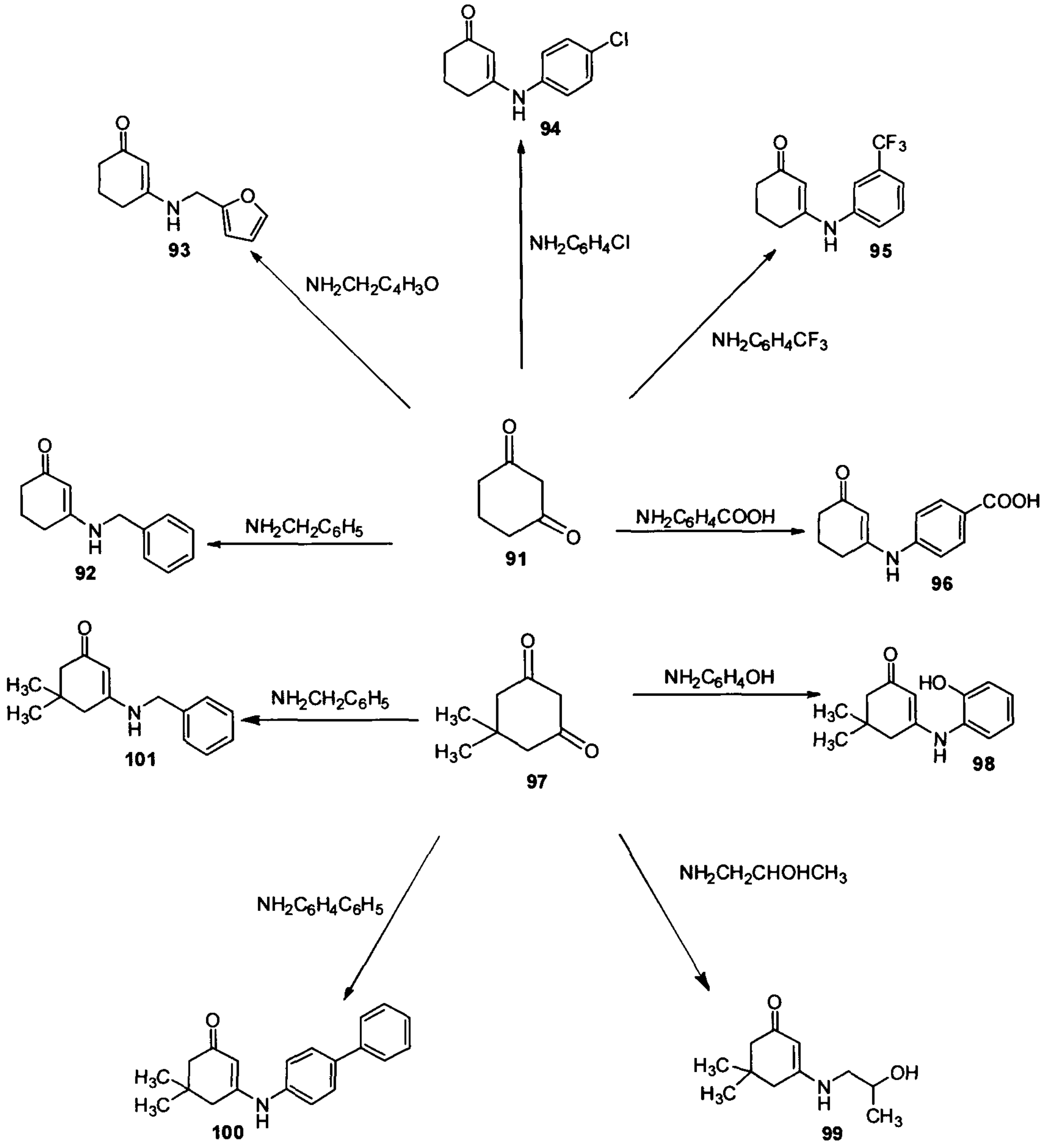


90

R= H, CH_3
R_1= Alkyl, Aryl,Aralkyl

2.4 METHODS OF PREPARATION OF ENAMINONES

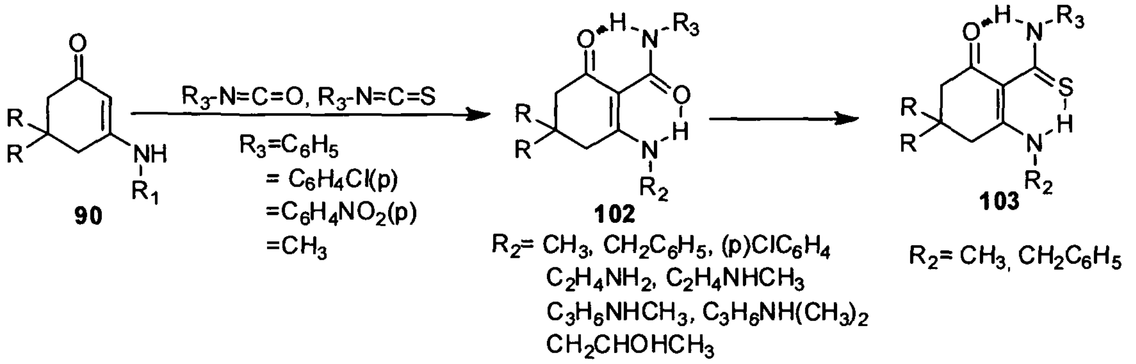
Literature survey at this stage revealed that Enaminones (**90**) have been prepared by many methods and have been also used as synthons for the synthesis of other heterocyclic compounds. A few of these methods and their uses are described in the following paragraphs



Scheme 19

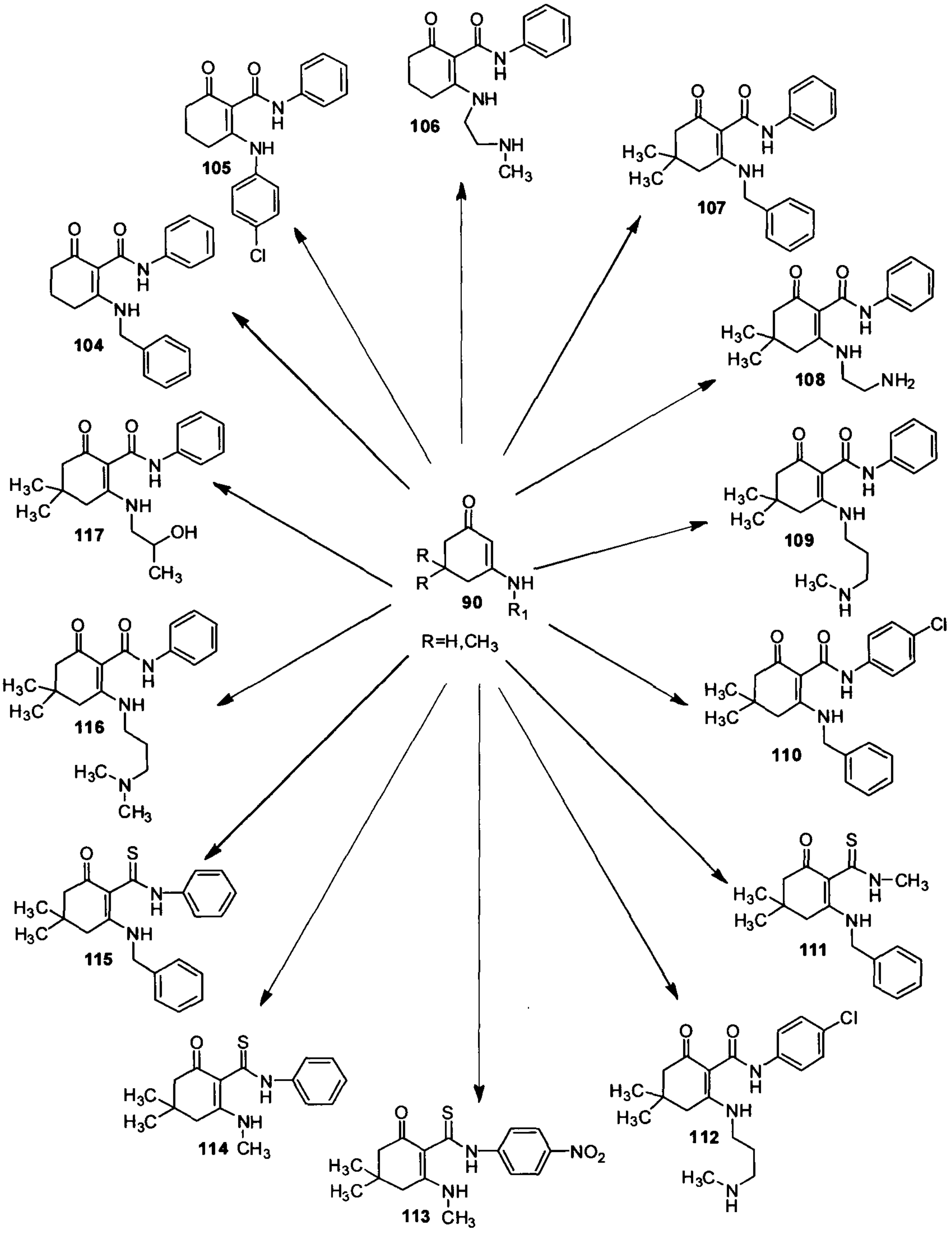
2.4.1 Ivo Jirkovsky reported[53] the synthesis of a series of N-substituted 3-amino-2-cyclohexen-1-ones and 3-amino-5,5-dimethyl-2-cyclohexen-1-ones (**92-101**) by the reaction of dimedone (**97**) or 1,3-cyclohexanedione (**91**) with various primary amines in dry benzene by azeotropic removal of water using Dean Stark apparatus (**Scheme 19**).

The secondary amines prepared from cyclic dione (**Scheme 19**) reacted with phenyl isocyanates, phenylisothiocyanates and methylisothiocyanate under fusion condition to yield substituted 2-amino-6-oxo-N-phenyl-1-cyclohexene-1-carboxamide (**102**) and corresponding thiocarboxamides (**103**)(**Scheme 20**).



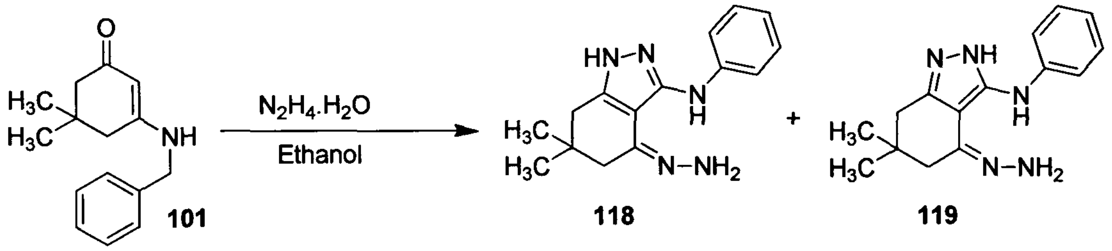
Scheme 20

A large number of compounds (**104-117**) have been prepared as shown in (**scheme 20a**). These reactions did not proceed in boiling tetrahydrofuran, benzene, toluene or xylene. These reactions were carried out without solvent at 115-145^0 C, the reactions were rapid, clean, quantative and the products were *cis* vinylogous ureas cross-conjugated with the original *trans*- enaminoketone.



Scheme 20a

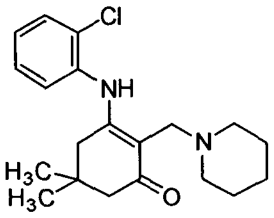
Reaction of 3-benzylamino-5,5-dimethyl-2-cyclohexen-1-one (**101**) with hydrazine hydrate in boiling ethanol gave a yellowish crystalline compound, from spectral data and considering the factor that hydrazones are more stable than enehydrazine the two structures that are most favourable are shown below (**118, 119**) (**Scheme 21**).



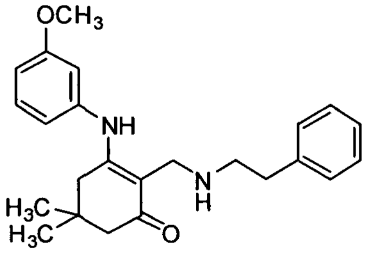
Scheme 21

Of the above two structure, **118** with one endocyclic double bond in the six-membered ring is favoured by the strain theory ^{54}.

2.4.2 Kase and co-workers mentioned in an abstract that (5,5-dimethyl-3- [(o-chlorophenyl) amino]-2-(N-piperidinylmethyl)-cyclohex-2-en-1-one (**120**), below and (5,5-dimethyl-3-[(m-methoxyphenyl) amino]-2-(N-methyl-N-phenethylaminomethyl)-cyclohex-2-en-1-one, (**121**), possessed analgesic, papaverine-like and anticonvulsant actions[55].

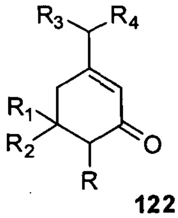


120



121

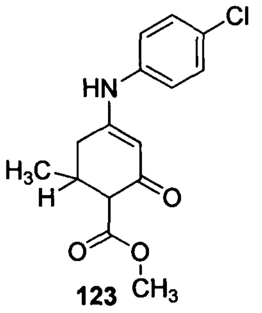
2.4.3 K. R. Scott and his group have reported the synthesis of a new series of novel enaminones of the type (**122**) below



122

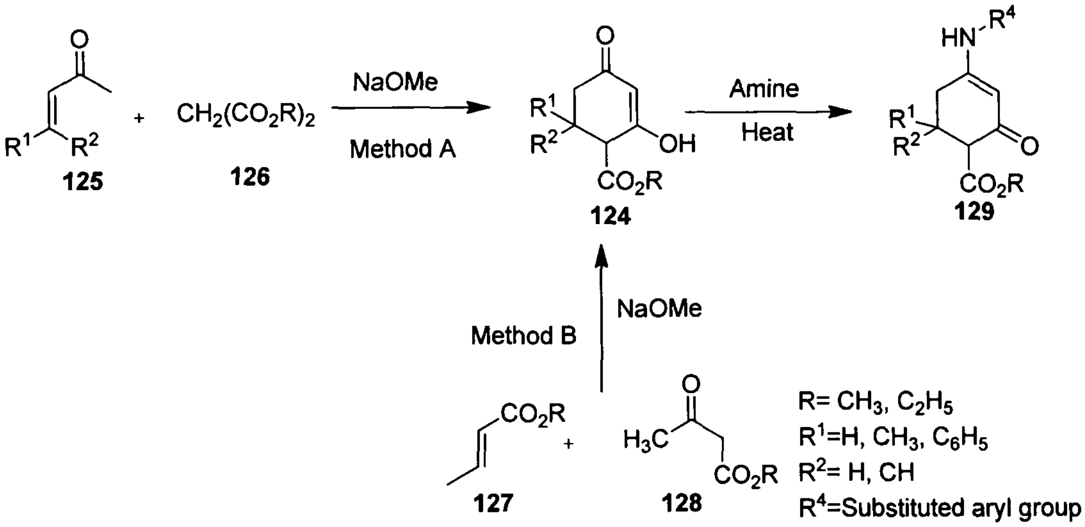
Where R=an Ester, H or an Amide
R_1 and R_2= H or CH_3
R_3= H
and R_4 =aryl, subst aryl, ether,alkyl etc

From cyclic β-dicarbonyl precursors by condensing them with morpholine, pyrrolidine, phenethylamine, hydrazine, substituted benzylamines and substituted anilines. These compounds were subsequently evaluated for anticonvulsant activity in avariety of anticonvulsant models by the National Institute of Neurological and Communicative Disorders and Stroke. Several of these compounds exhibited potent anticonvulsant activity with remarkable lack of neurotoxicity. The most active analog Methyl 4-[(p-Chlorophenyl) amino]-6-methyl-2-oxo-cyclohex-3-en-1-oate (**123**)



123

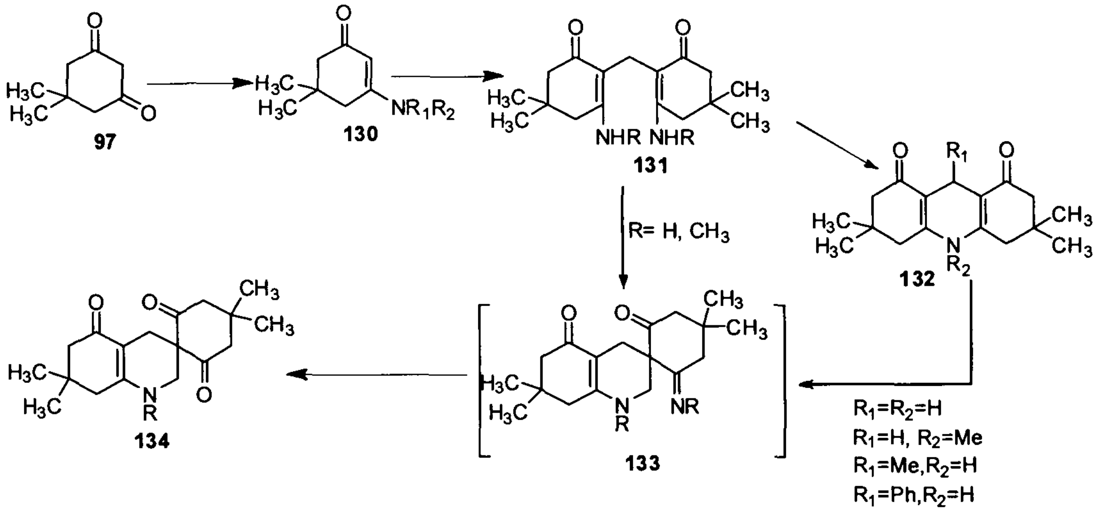
The cyclic enaminone esters (**123**) were synthesised from β- Hydroxy keto esters (**124**), which were in turn synthesised by Michael addition of a vinyl ketone to a malonic ester, followed by a ring closing claisen condensation (method **A**), or by a base-catalysed condensation of a crotonate ester (**127**) and acetoacetate (**128**) (method **B**) (**Scheme 22**).



Scheme 22

The β-hydroxy keto esters (**124**) were refluxed with 1 equivalent of the appropriate amino compound, under various conditions to provide the desired product (**129**). In most cases the reaction proceeded effectively in the presence of toluene. In case of hydrazines and anilines a much lower temperature was employed, most probably due to lower pK_a of aniline (4.63 for aniline) derivatives compared to benzylamine analogues (9.33 for benzylamine)[56-57].

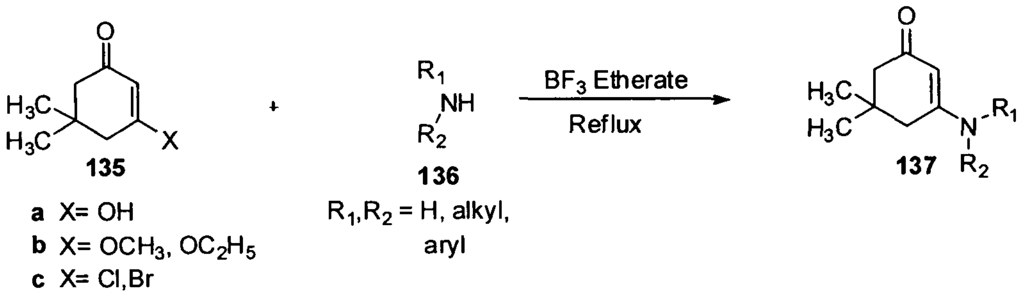
2.4.4 J. V. Greenhill and co-workers have prepared enaminones (**130**) from dimedones (**97**) by reacting it with ammonia or methylamine (**Scheme 23**). Under suitable & mild conditions the enaminones (**130**) reacted with formaldehyde to give the respective methylene bisenaminone derivative (**131**). The enaminones are readily hydrolysed back to dimedone in dilute mineral acid, but when methylene bis enaminone derivative was attempted to hydrolyse in the same way, acid insoluble, fluorescent compounds were formed which were identified as acridine derivatives (**132**)[58-59].



Scheme 23

Treatment of the enaminones or the methylene bis-enaminones with aqueous formaldehyde in dilute hydrochloric acid at room temperature gave good yields of unexpected spiro compound (134). The spiro compounds might reasonably arise from an internal mannich reaction of the methylene bisenaminones to give the unstable structures (133), which would readily hydrolyse to the diketones (134).

2.4.5 Marcel Azarro and co-workers[60] have also synthesized enaminones with low boiling amines such as methylamine, ethylamine, isopropylamine, and n-butyl amine. They used a synthetic route via a Lewis acid/amine complex, which used borontrifluoride diethyletherate instead of titanium tetrachloride due to easier handling.To freshly distilled boron trifluoride ethyl etherate in benzene the appropriate amine (136) (from pressure bottles in case of gaseous amines) was added. To this was added a solution of dimedone in benzene and refluxed for 4-6 hrs where by the expected product (137) was obtained in good yield. The use of Lewis acid brought in three advantages. Firstly the complexation of low boiling amines, the acid catalysis of the reaction and the equilibrium shifts towards the enaminone formation by the complexation of the water formed. If excess of BF_3 etherate is used then it leads to the mixture of enaminone and the vinylogous esters [60](**1b**) (**Scheme 24**).



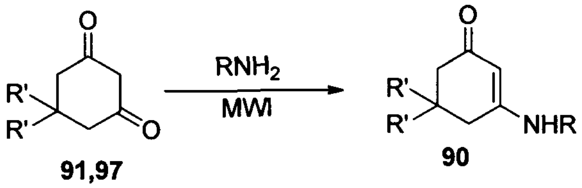
Scheme 24

However, all the above methods used for the synthesis of enaminones have some specific disadvantages. Some involve thermal conditions, longer reaction times, reagents in gaseous form (from pressure bottles etc) especially in case of low boiling amines, toxic solvents (like benzene etc) and dry conditions etc (azeotropic removal of water etc).

PART-I

2.5 Synthesis of 1-Methyl-3-alkyl/aryl/aralkyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines & 3,3′-(alkane/arene) diyl bis-1-methyl--5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines .

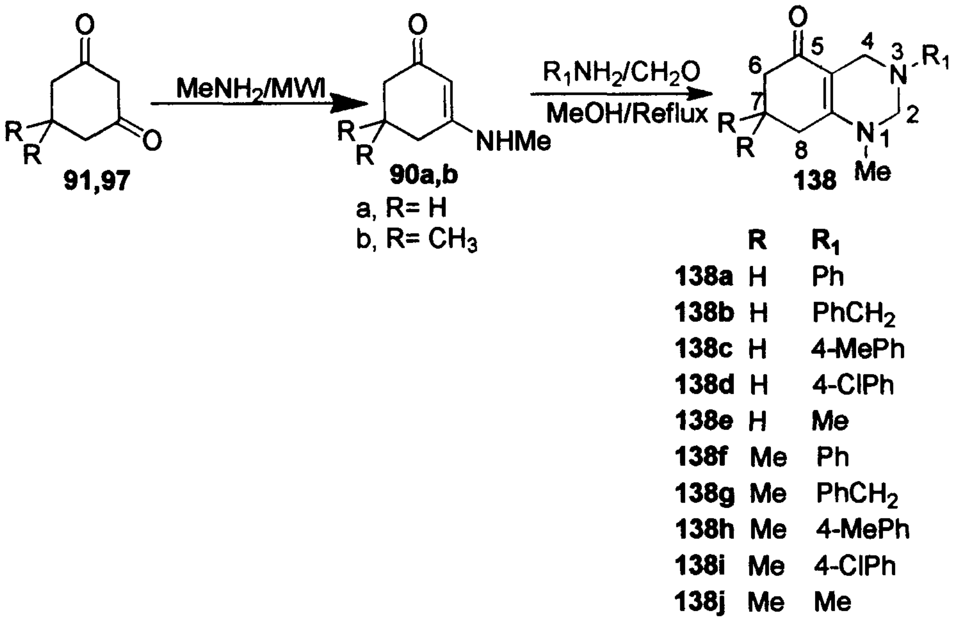
The growing interest in microwave-assisted reactions[61-64] prompted research group from our laboratory to take up the synthesis of enaminones **(90)** by the condensation of cyclohexan-1,3-dione & 5,5-dimethyl cyclohexan-1,3-dione **(91,97)** with appropriate primary amines under microwave irradiation. (**Scheme 25**).



a, R' = H; b, R'= CH_3
R= C_6H_5,4-ClC_6H_5, CH_3, $C_6H_5NH_2$

Scheme 25

These enaminones **(90a,b)** prepared by the reported procedures[65] as one equivalent of 1,3-cyclohexandione/3,3-dimethyl-1,3-cyclohexandione mixed with one equivalent of methylamine(40% aqueous solution) irradiated in microwave at 180 watt for 2-3 minutes to give a deep brown viscous mass, immediately applied pump to remove the water formed then cooled on trituration with hexane it gives light yellowish solid mass of desired enaminones **(90a,b)** and were used as synthons for the constructions quinazolines. Thus when enaminones **(90a,b)** were reacted with formaldehyde and primary amines in methanol, it lead to the formation of hitherto unknown 1,3-substituted-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and 1,3-substituted-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines **(138)**. as per the **scheme 26** given below.



	R	R_1
138a	H	Ph
138b	H	$PhCH_2$
138c	H	4-MePh
138d	H	4-ClPh
138e	H	Me
138f	Me	Ph
138g	Me	$PhCH_2$
138h	Me	4-MePh
138i	Me	4-ClPh
138j	Me	Me

Scheme 26

2.5.1 Results and Discussion

Thus, when 3-methylaminocyclohexenone **90a** was treated with aniline and formaldehyde under the influence of microwaves, a product was obtained in 61% yields which was characterized as 1-methyl-3-phenyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline **138a** on the basis of analytical and spectral data. The reaction of **90a** with other primary amines and formaldehyde behaved in a similar manner and octahydroquinazolines **138b-e** were isolated in 57-84% yields. The infrared spectra of **138a-e** showed strong peaks in the region of 1540 to 1636 cm^{-1} due to extensively delocalized double bonds and carbonyl groups [65]. In the ^1H NMR spectra of **138a-e**, the methylene protons at C-2 resonated near 4.50 ppm except in **138b** and **138e** where they appeared in the vicinity of 3.80 ppm. This lowering in chemical shift could be attributed to the absence of delocalization of N-3 lone pair of electrons. Probably a similar explanation could be extended for the appearance of CH_2 protons at C-4 close to 4.15 ppm except in **138b** and **138e** where they were found to resonate near 3.50 ppm. While CH_2 protons at C-7 appeared as multiplets in the range of 1.90-2.00 ppm, those at C-6 and C-8 resonated close to 2.40 and 2.30 ppm respectively.

The methyl protons at N-1 gave singlets close to 2.90 ppm. The Reactions of **90b** with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-methyl-3-alkyl/aralkyl/aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines **138f-j** were isolated in 75-89% yields, whose structures could be established with the help of analytical and spectral data. The infrared spectra of **138f-j** showed strong peaks in the region of 1540 to 1609 cm^{-1}. The ^1H NMR spectra of tetrahydropyrimidine rings of **138f-j** were found to have a similar pattern as those of **138a-e.** However, the six methyl protons at C-7 appeared as sharp singlets around 1.00 ppm and the CH_2 protons at C-6 and C-8 resonated in ranges of 2.25-2.99 and 2.18-2.24 ppm respectively. The aromatic protons resonated in their usual range; the structures of all the compounds are well supported by their mass spectra.

The plausible mechanism of the formation of octahydroquinazolines can be explained in the light of Mannich reaction as shown below

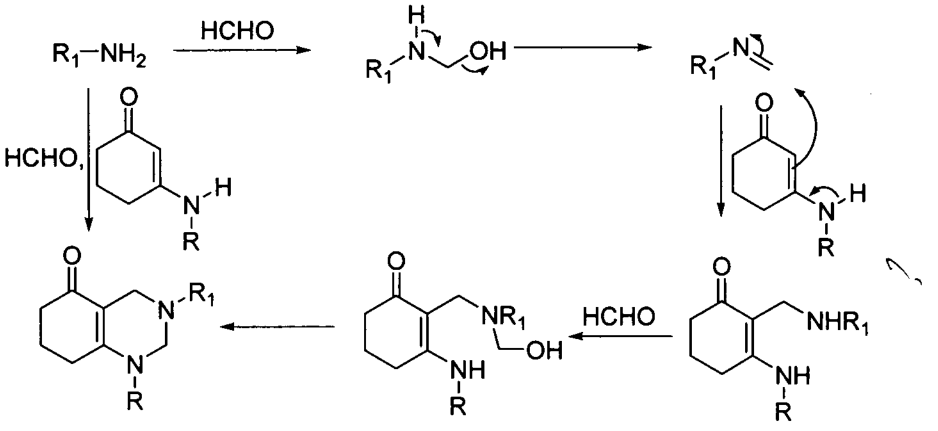


Table I Synthesis of 1,3-substituted-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and 1,3-substituted-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines.

Compound	R	R_1	Yield %	Time(sec)/Power(watt)	M.P^{0}C
138a	H	Ph	61	120/100	Gum
138b	H	$PhCH_2$	84	120/180	Gum
138c	H	4-MePh	63	120/300	Gum
138d	H	4-ClPh	57	180/300	132
138e	H	Me	70	120/180	Gum
138f	CH_3	Ph	80	120/180	140
138g	CH_3	$PhCH_2$	85	120/180	142
138h	CH_3	4-MePh	89	120/180	132
138i	CH_3	4-ClPh	75	180/180	174
138j	CH_3	Me	78	120/180	Gum

The ^{1}HNMR and Mass spectra of **3-phenyl-5-oxo-1,7,7-trimethyl-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline** (138a) is given in the following pages

```
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Solvent    : CDCl3
Spectrum   : 1H Spectrum
Instrument : AS-I-10
Analyst    : Jingal
Date       : 09.08.2007
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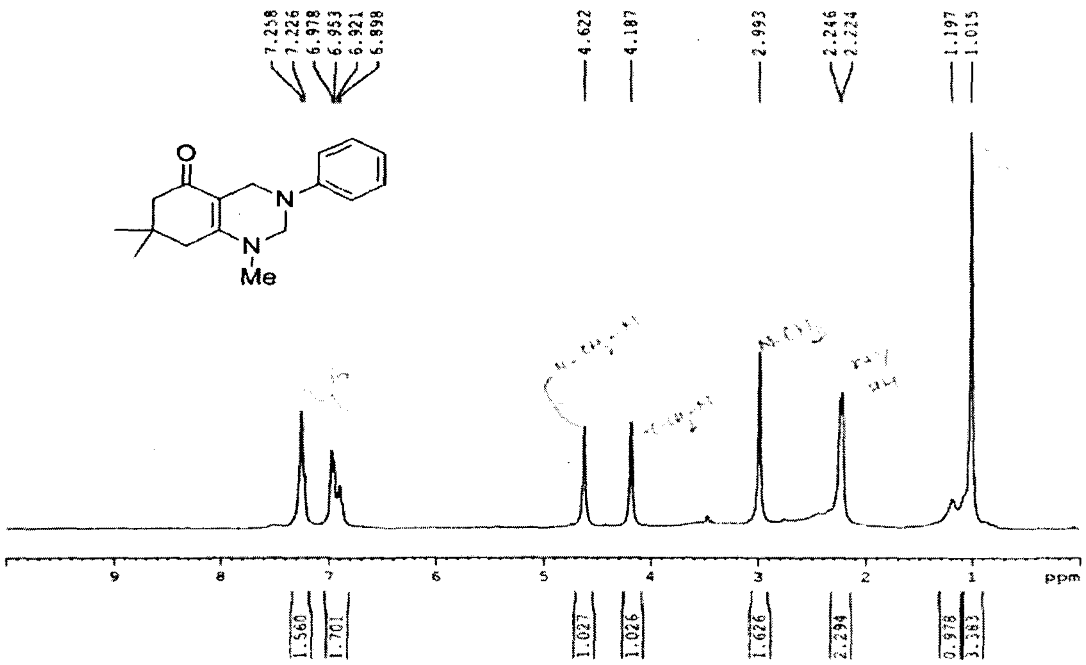

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DE                           6.00 u
TE                            0.0 K
D1                     2.00000000 s
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MCWRK                  0.01500000 s

======== CHANNEL f1 ========
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PL1                          1.00 dB
SFO1                  300.1325511 M

F2 - Processing parameters
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LB                           0.50 H
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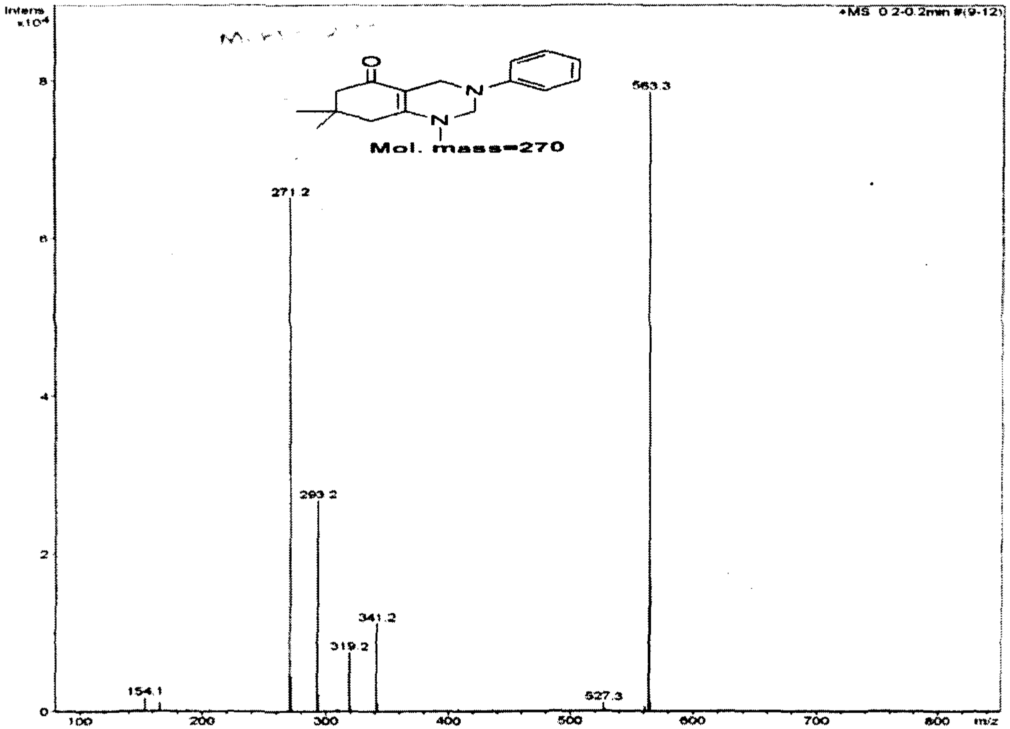
Sample Name 05(948-90 A)/MS-5

Method (+ve) MS Method_Low m

Analysed by CHETAN

Date 09-08-2007



Bruker Daltonics DataAnalysis 3.4 Instrument micrOTOF-Q Page 1 of 1

2.5.2 Experimental

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard pattern with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Microwave irradiation was carried out in a CEM Discover Benchmate microwave digester Enaminones **90a** and **90b** were synthesized by our reported procedure[65].

2.5.3 Synthesis of 1,3-substituted-1,2,3,4,7,8-octahydroquinazolines (138a-e) and 1,3-substituted-7,7-dimethyl-1,2,3,4,7,8-octahydroquinazolines (138f-j).

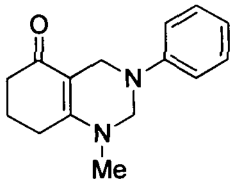
General procedure.

A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone **90a, b** (1 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (monitored by tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **138a-j** in 57-89 % yields.

Thus we have demonstrated a practical application of microwave assisted, solvent-free condensation of cyclic ketones with primary amines in microwave digester in very good to excellent yields.

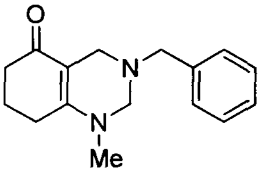
The IR and NMR spectral data of 1,3-substituted-1,2,3,4,7,8-Octahydroquinazolines (**138a-e**) and 1,3-substituted-7,7-dimethyl-1,2,3,4,7,8-Octahydroquinazolines (**138f-j**) are given below.

1-Methyl-3-phenyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (138a)



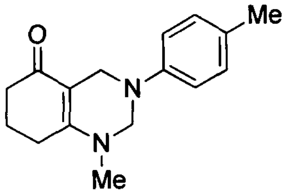
This compound was obtained as brown gum in 61% yield; IR (KBr): 1542 (νC=C), 1605 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.95-2.00 (m, 2H, C$_7$-H), 2.33 (t, 2H, J=6.3 Hz, C$_8$-H), 2.45 (t, 2H, J=6.3 Hz, C$_6$-H), 2.96 (s, 3H, N-CH$_3$), 4.18 (s, 2H, C$_4$-H), 4.57 (s, 2H, C$_2$-H), 6.87-6.98 (m, 3H, aromatic), 7.17-7.28 (m, 2H, aromatic); MS: m/z 243.2 (MH$^+$). Anal. Calcd for $C_{15}H_{18}N_2O$ (242.32): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.39; H, 8.16; N, 10.41%.

1-Methyl-3-benzyl-5-oxo-1, 2, 3, 4, 5 ,6 7, 8-octahydroquinazoline (138b)



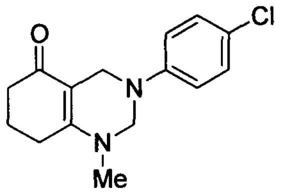
This compound was obtained as brown gum in 84% yield; IR (KBr): 1559 (νC=C), 1636 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.90-2.01 (m, 2H, C$_7$-H), 2.31 (t, 2H, J=6.0 Hz, C$_8$-H), 2.45 (t, 2H, J=6.3 Hz, C$_6$-H), 2.89 (s, 3H, N-CH$_3$), 3.58 (s, 2H, N$_3$-CH$_2$), 3.66 (s, 2H, C$_4$-H), 3.85 (s, 2H, C$_2$-H), 7.26-7.39 (m, 5H, aromatic); MS: m/z 257.2 (MH$^+$). Anal. Calcd for $C_{16}H_{20}N_2O$ (256.34): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.91; H, 7.80; N, 10.99%.

1-Methyl-3-tolyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (138c)



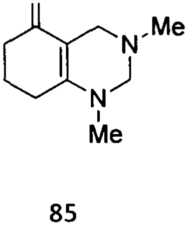
This compound was obtained as light brown gum in 63% yield; IR (KBr): 1548 (νC=C), 1611 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.87-2.00 (m, 2H, C_7-H), 2.28 (s, 3H, Ar-CH_3), 2.33 (m, 2H, C_8-H), 2.43 (m, 2H, C_6-H), 2.94 (s, 3H, N-CH_3), 4.15 (s, 2H, C_4-H), 4.55 (s, 2H, C_2-H), 6.87-6.91 (m, 4H, aromatic); MS: m/z 257.2 (MH^+). Anal. Calcd for $C_{16}H_{20}N_2O$ (256.34): C, 74.97; H, 7.86; N, 10.93. Found: C, 74.89; H, 7.82; N, 10.88%.

1-Methyl-3-(4-chlorophenyl)-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (138d)



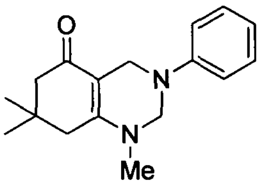
This compound was obtained as brown solid in 57% yield; mp 132^{0}C; IR (KBr): 1542 (νC=C), 1611 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.96 (m, 2H, C_7-H), 2.40 (t, 2H, J=6.0 Hz, C_8-H), 2.43 (t, 2H, J=6.6 Hz, C_6-H), 2.99 (s, 3H, N-CH_3), 4.14 (s, 2H, C_4-H), 4.54 (s, 2H, C_2-H), 6.89 (d, 2H, J=8.8 Hz, aromatic), 7.19 (d, 2H, J=8.8 Hz, aromatic); MS: m/z 277.2 (MH^+). Anal. Calcd for $C_{15}H_{17}ClN_2O$ (276.76): C, 65.10; H, 6.19; N, 10.12. Found: C, 65.25; H, 6.14; N, 10.06%.

1, 3-Dimethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (138e)



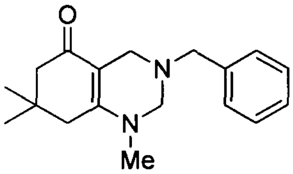
This compound was obtained as light brown gum in 70% yield; IR (KBr): 1636 (νC=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90-2.02 (m, 2H, C_7-H), 2.32 (t, 2H, J=6.0 Hz, C_8-H), 2.44 (t, 2H, J=6.6 Hz, C_6-H), 2.90 (s, 3H, N_3-CH_3), 2.97 (s, 3H, N_1-CH_3), 3.42 (s, 2H, C_4-H), 3.82 (s, 2H, C_2-H); MS: m/z 181.1 (MH^+). Anal. Calcd for $C_{10}H_{16}N_2O$ (180.25): C, 66.63; H, 8.95; N, 15.54. Found: C, 66.81; H, 8.89; N, 15.61%.

1, 7, 7-Trimethyl-3-phenyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (138f).



This compound was obtained as yellow solid in 80% yield; mp 140°C; IR (KBr): 1540 (νC=C), 1599 (νC=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01 (s, 6H, C_7-CH_3), 2.22 (s, 2H, C_8-H), 2.25 (s, 2H, C_6-H), 2.99 (s, 3H, N_1-CH_3), 4.18 (s, 2H, C_4-H), 4.62 (s, 2H, C_2-H), 6.90-6.97 (m, 3H, aromatic), 7.22-7.25 (m, 2H, aromatic) ; MS: m/z 271.2 (MH^+). Anal. Calcd for $C_{17}H_{22}N_2O$ (270.37): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.70; H, 8.15; N, 10.32%.

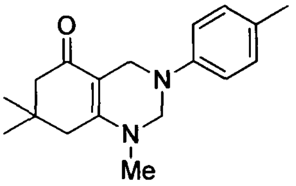
1, 7, 7-Trimethyl-3-benzyl-5-oxo-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline (138g).



This compound was obtained as brown solid in 85% yield; mp 142°C; IR (KBr): 1566 (νC=C), 1609 (νC=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.10 (s, 6H, C_7-CH_3), 2.19 (s, 2H, C_8-H), 2.32 (s, 2H, C_6-H), 2.93 (s, 3H, N_1-CH_3), 3.67 (s, 2H, C_4-H), 3.77 (s, 2H, N_3-CH_2), 3.99 (s, 2H, C_2-H), 7.28-7.37 (m, 5H, aromatic); MS: m/z 284.8 (MH^+).

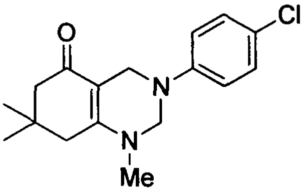
Anal. Calcd for $C_{18}H_{24}N_2O$ (284.40): C, 76.02; H, 8.51; N, 9.85. Found: C, 76.16; H, 8.47; N, 9.90%.

1, 7, 7-Trimethyl-3-tolyl-5-oxo-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline (138h).



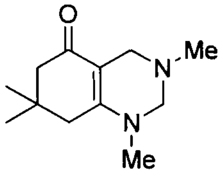
This compound was obtained as brown solid in 89% yield; mp 132^{0}C; IR (KBr): 1540 (νC=C), 1594 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.02 (s, 6H, C_7-CH_3), 2.22-2.39 (m, 7H, C_8-H + C_6-H + Ar-CH_3), 2.97 (s, 3H, N_1-CH_3), 4.16 (s, 2H, C_4-H), 4.59 (s, 2H, C_2-H), 6.87 (d, 2H, J=8.1Hz, aromatic), 7.05 (d, 2H, J=8.1Hz, aromatic); MS: m/z 284.8 (MH^+) Anal. Calcd for $C_{18}H_{24}N_2O$ (284.40): C, 76.02; H, 8.51; N, 9.85. Found: C, 75.92; H, 8.59; N, 9.80%.

1,7,7-Trimethyl-3-(4-chlorophenyl)-5-oxo-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline (138i).



This compound was obtained as yellow solid in 75% yield; mp 174^{0}C; IR (KBr): 1540 (νC=C), 1600 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 6H, C_7-CH_3), 2.12-2.24 (m, 4H, C_8-H + C_6-H), 2.99 (s, 3H, N_1-CH_3), 4.15 (s, 2H, C_4-H), 4.60 (s, 2H, C_2-H), 6.87 (d, 2H, J= 8.1Hz, aromatic), 7.19 (d, 2H, J= 8.1Hz, aromatic); MS: m/z 305.1 (MH^+) Anal. Calcd for $C_{17}H_{21}N_2OCl$ (304.81): C, 66.99; H, 6.94 N, 9.19. Found: C, 66.80; H, 6.99; N, 9.23%.

1,3,7,7-Tetramethyl-5-oxo-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline (138j).

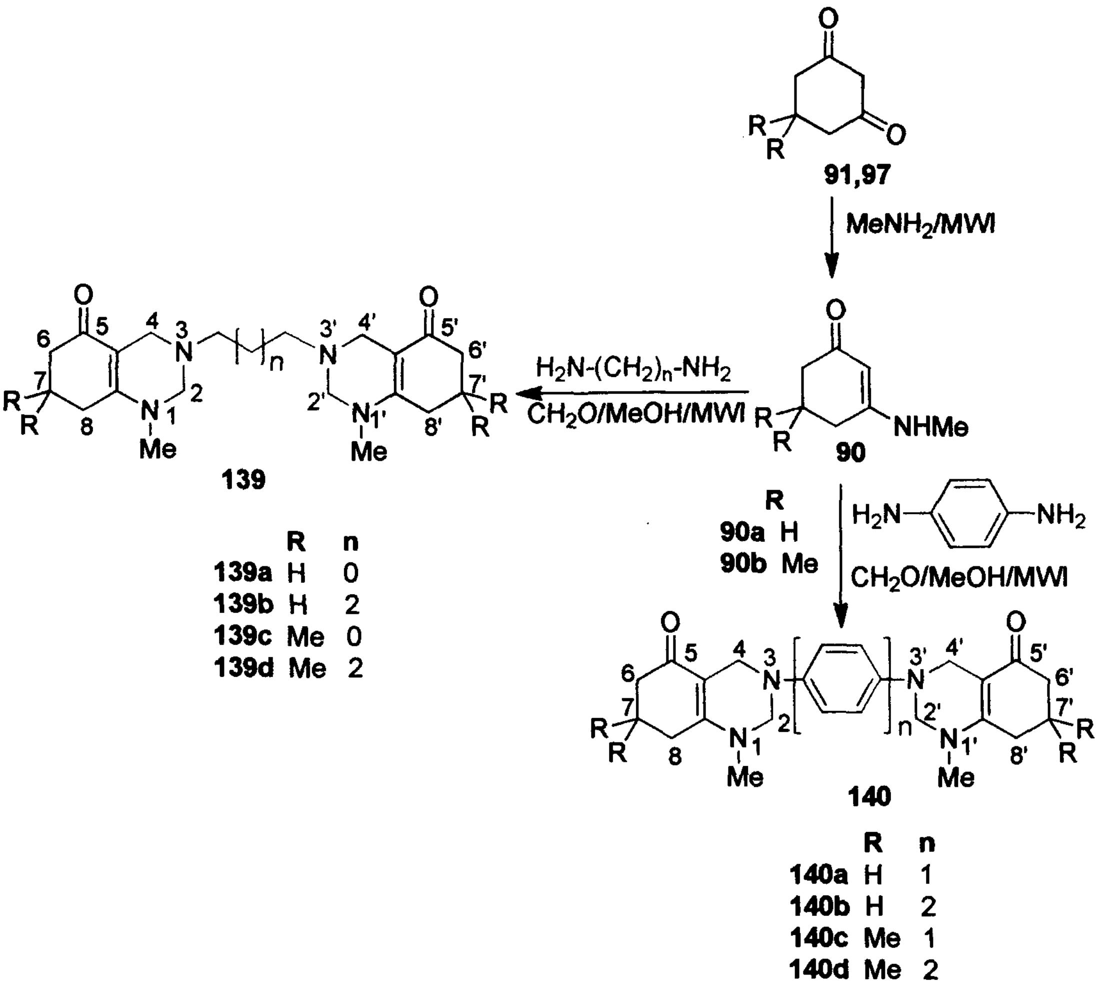


This compound was obtained as brown gum in 78% yield; IR (KBr): 1560 (νC=C), 1595 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.08 (s, 6H, C_7-CH_3), 2.18 (s, 2H, C_8-H), 2.28 (s, 2H, C_6-H), 2.41 (s, 3H, N_3-CH_3), 2.95 (s, 3H, N_1-CH_3), 3.45 (s, 2H, C_4-H), 3.86 (s, 2H, C_2-H); MS: m/z 209.2 (MH^+). Anal. Calcd for $C_{12}H_{20}N_2O$ (208.30): C, 69.19; H, 9.68; N, 13.45. Found: C, 69.05; H, 9.65; N, 13.53%.

The present work describes an efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown 1,3-substituted-1,2,3,4,7,8-octahydroquinazolines and 1,3-substituted-7,7-dimethyl-1,2,3,4,7,8-octahydroquinazolines from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

2.5.4 Synthesis of 3,3′-(alkane/arene) diyl bis-1-methyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines .

The enaminone **(90a,b)** and were used as synthons for the constructions bis quinazolines Thus when enaminones **(90a,b)** were reacted with formaldehyde and diamines in methanol, it lead to the formation of hitherto unknown 1-Methyl-3,3'-(alkane/arene) diyl bis-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines where the two quinazoline rings connected by both flexible aliphatic linker as well as rigid aromatic linker **(139 & 140)** as per the **scheme 27** given below.



	R
90a	H
90b	Me

	R	n
139a	H	0
139b	H	2
139c	Me	0
139d	Me	2

	R	n
140a	H	1
140b	H	2
140c	Me	1
140d	Me	2

Scheme 27

2.5.5 Results and Discussion

Encouraged by the successful synthesis of octahydroquinazolines **138a-j**, we then turned our attention to the synthesis of bis-octahydroquinazolines. Thus, when enaminone **90a** was reacted with 1,2-diaminoethane and formaldehyde under the influence of microwaves in methanol, a product **139a** was isolated in 55% yield, the structure of which was established to be 3,3′-(ethane-1,2-diyl) bis-5-oxo (1-methyl-1,2,3,4,7,8-octahydroquinazoline based on analytical and spectral data. The compound **90a** gave the corresponding product **138b** under identical conditions on reaction with 1,4-diaminobutane and formaldehyde. We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains. Subsequently, with the intention to connect the two octahydroquinazoline rings through aromatic linkers, enaminones **90** were reacted with aromatic diamines and formaldehyde to give **140** in 55-60% yields, the structures of which could be established with the help of spectral and analytical data. The infrared spectra of **139 a-d** and **140 a-d** showed strong peaks in the range of 1516-1669 cm^{-1} due to extensive delocalization of the enaminone moiety. The ^1H NMR spectra of these dimers were found to have the same pattern as in the monomeric octahydroquinazolines except that the signals due to CH_2 protons of ethylene linkers appeared at 2.68 ppm while those in butylene appeared in the ranges of 2.45-2.46 and 1.55-2.17ppm. The dimeric structures of **139a-d** and **140a-d** were further supported by their mass spectra.

The plausible mechanism of the formation of bis-octahydroquinazolines can be explained in the light of Mannich reaction as shown in the following page.

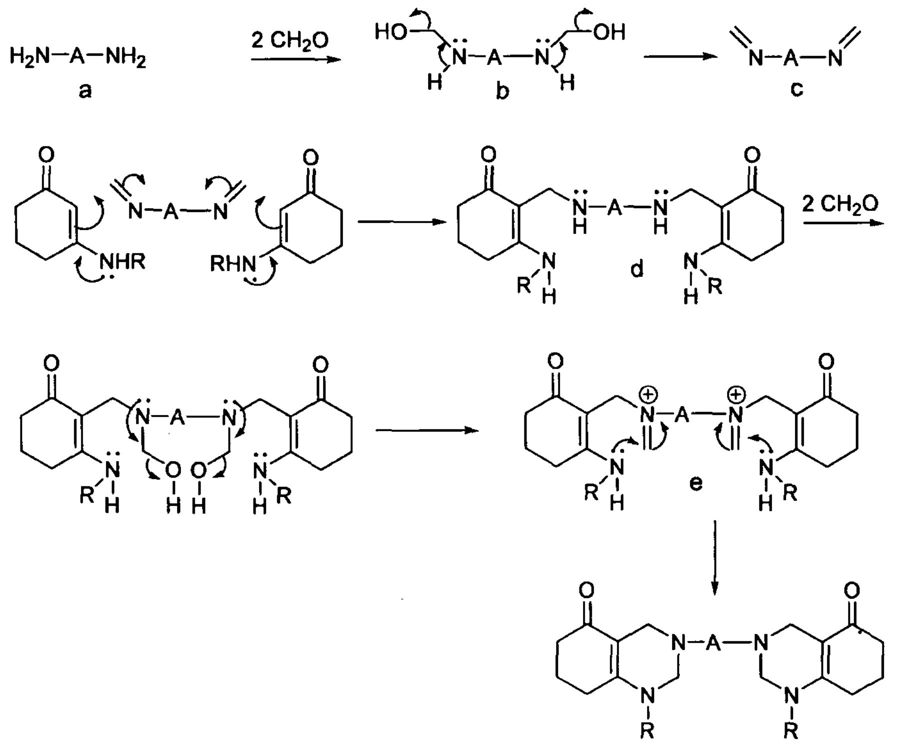
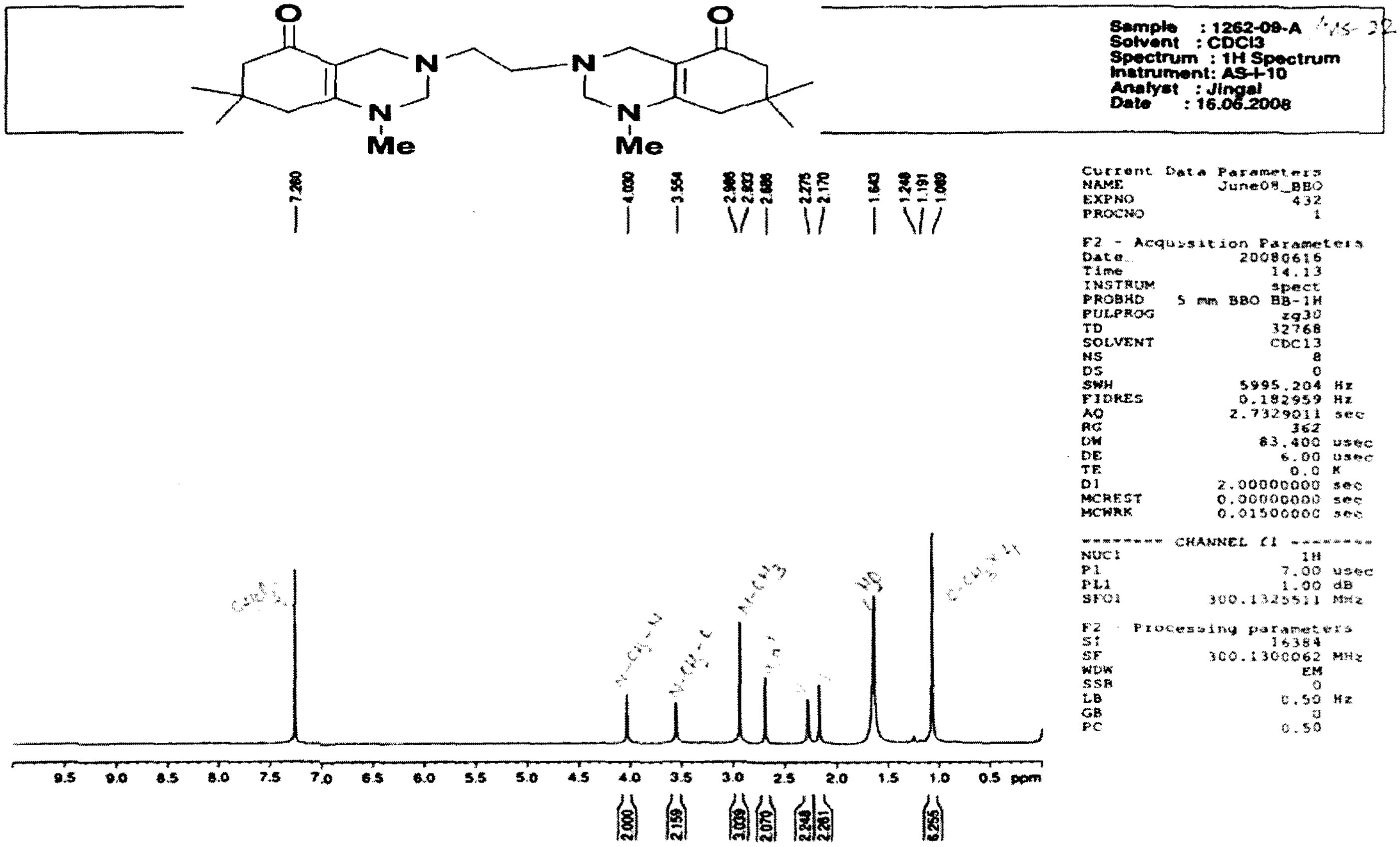


Table 2 Synthesis of 3,3'-(alkane/arene) diyl bis-1-methyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines .

Compound	R	linker	Yield %	Time(sec)/Power(watt)	M.P^{0}C
139a	H	$-CH_2-CH_2-$	55	180/300	Gum
139b	H	$-(CH_2)_4-$	56	120/180	Gum
139c	CH_3	$-CH_2-CH_2-$	60	120/300	Gum
139d	CH_3	$-(CH_2)_4-$	58	180/300	Gum
140a	H	$-C_6H_4-$	60	180/300	Gum
140b	H	$-(C_6H_4)_2-$	55	180/300	Gum
140c	CH_3	$-C_6H_4-$	56	120/180	Gum
140d	CH_3	$-(C_6H_4)_2-$	57	120/180	Gum

The ^{1}HNMR and Mass spectra of **3, 3′-(ethane-1,2-diyl) bis (1-methyl -5-oxo 1,7,7-trimethyl-1,2,3,4,7,8-octahydroquinazoline)** is given in the following pages



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Instrument: AS-I-10
Analyst : Jingal
Date : 16.06.2008

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AO               2.7329011 sec
RG                       362
DW                  83.400 usec
DE                    6.00 usec
TE                     0.0 K
D1              2.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                      7.00 usec
PL1                     1.00 dB
SFO1             300.1325511 MHz

F2 - Processing parameters
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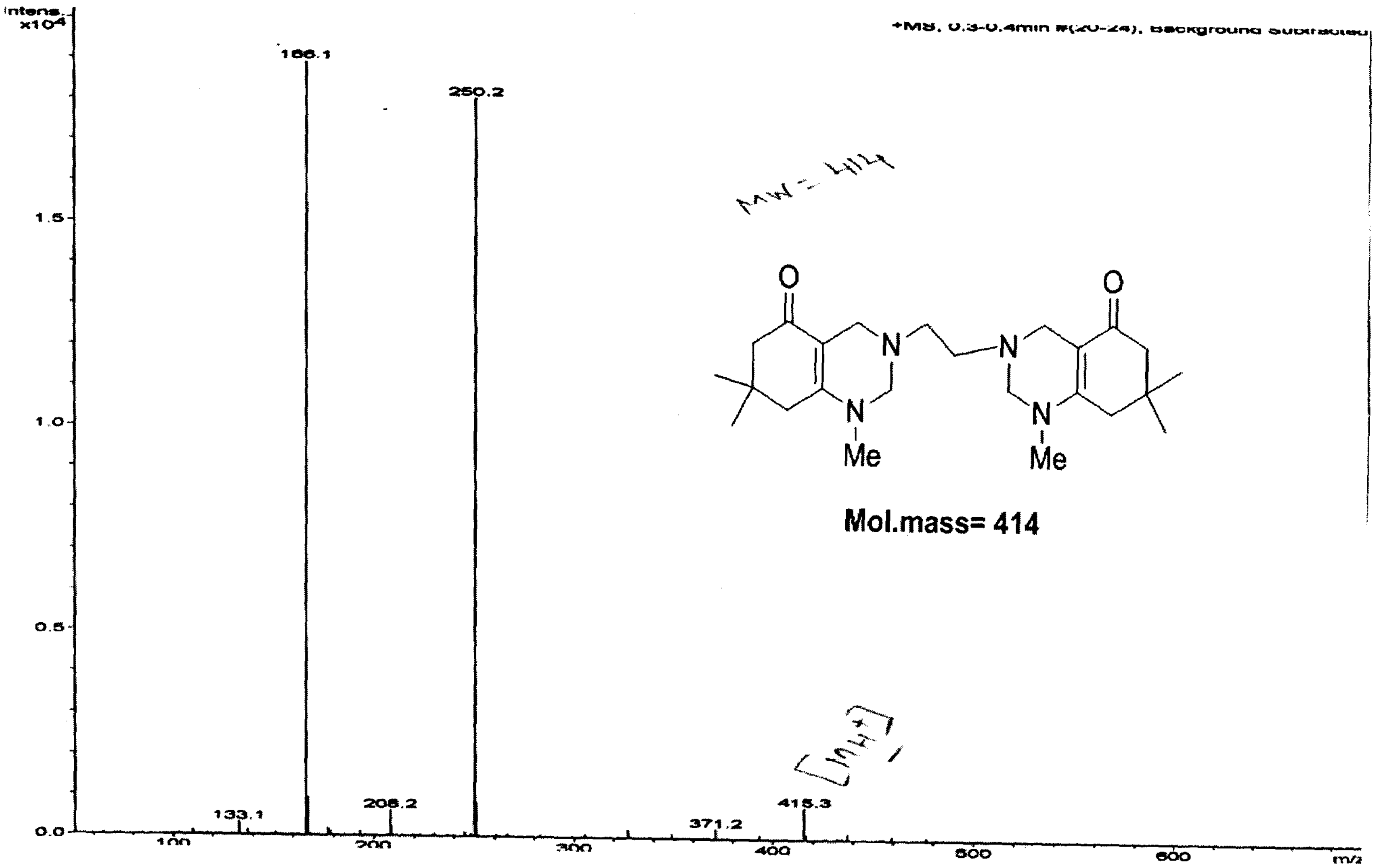
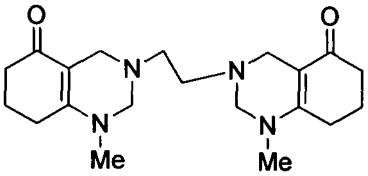
Intens.
x10⁴
1.5
1.0
0.5
0.0
+MS, 0.3-0.4min #(20-24), Background Subtracted
166.1
250.2
133.1
208.2
371.2
415.3
100
200
300
400
500
600
m/z
MW = 414
[M+H]+
O
O
N
N
N
N
Me
Me
Mol.mass= 414

2.5.6 General Procedure: A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1.5 mL methanol was shaken at room temperature for 5 minutes. To this mixture, a solution of enaminone **90** (1 mmol) in 5 mL methanol was added in one lot and the resulting mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (monitored by tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) yielding **139 &140** in 55-60% yields.

In conclusion, we have demonstrated a practical application of microwave assisted, condensation of cyclic ketones with diamines using very minimum quantity of solvent in domestic microwave oven in very good to excellent yields.

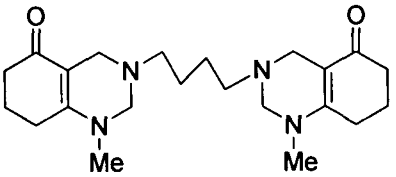
2.5.7 Description of individual compounds

3,3′-(Ethane-1,2-diyl) bis (5-oxo-1-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline) (139a)



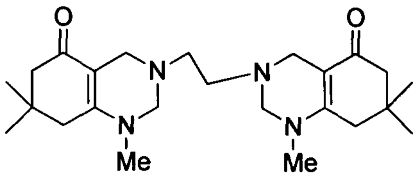
This compound is obtained as dark brown gum; yield 55%; IR (KBr): 1543(νC=C), 1668 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90-1.92 (m, 4H, C_7-H + $C_{7'}$-H), 2.27 (t, 4H, J=6.3 Hz, C_8-H + $C_{8'}$-H), 2.42 (t, 4H, J=6.0 Hz, C_6-H + $C_{6'}$-H), 2.68 (s, 4H, -CH_2-CH_2-), 2.93 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 3.47 (s, 4H, C_4-H + $C_{4'}$-H), 3.98 (s, 4H, C_2-H + $C_{2'}$-H), MS: m/z 359.2 (MH^+). Anal. Calcd for $C_{20}H_{30}N_4O_2$ (358.48): C, 67.01; H, 8.44; N, 15.63. Found: C, 67.21; H, 8.40; N, 15.69%.

3,3′-(Butane-1,2-diyl) bis (5-oxo-1-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline) (139b)



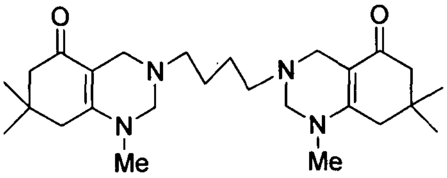
This compound is obtained as dark brown gum; yield 56%; IR (KBr): 1538 (νC=C), 1653 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.52-1.58 (m, 4H, C$_7$-H + C$_{7'}$-H), 1.95 (t, 4H, J=6.0 Hz, C$_8$-H + C$_{8'}$-H), 2.22-2.27 (m, 4H, -CH$_2$C*H*$_2$C*H*$_2$CH$_2$-), 2.45 (t, 4H, J=6.0 Hz, C$_6$-H + C$_{6'}$-H), 2.95 (s, 6H, N$_1$-CH$_3$ + N$_{1'}$-CH$_3$), 3.43 (s, 4H, -C*H*$_2$CH$_2$CH$_2$C*H*$_2$-), 3.88 (s, 4H, C$_4$-H + C$_{4'}$-H), 4.98 (s, 4H, C$_2$-H + C$_{2'}$-H); MS: m/z 387.1 (MH$^+$). Anal. Calcd for $C_{22}H_{34}N_4O_2$ (386.53): C, 68.36; H, 8.87; N, 14.49. Found: C, 68.21; H, 8.22; N, 14.60%.

3, 3′-(Ethane-1,2-diyl) bis(5-oxo-1,7,7-trimethyl--1,2,3,4,5,6,7,8-octahydroquinazoline) (139c)



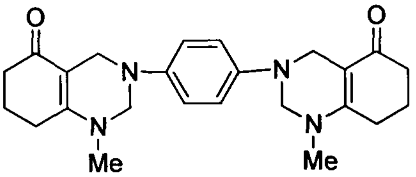
This compound is obtained as dark brown gum; yield 60%; IR (KBr): 1557 (νC=C), 1669 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.06 (s, 12H, C$_7$-CH$_3$ + C$_{7'}$- CH$_3$), 2.17 (s, 4H, C$_8$-H + C$_{8'}$-H), 2.27 (s, 4H, C$_6$-H + C$_{6'}$-H), 2.68 (s, 4H, -CH$_2$-CH$_2$-), 2.99 (s, 6H, N$_1$-CH$_3$ + N$_{1'}$-CH$_3$), 3.55 (s, 4H, C$_4$-H + C$_{4'}$-H), 4.03 (s, 4H, C$_2$-H + C$_{2'}$-H); MS: m/z 415.3 (MH$^+$). Anal. Calcd for $C_{24}H_{38}N_4O_2$ (414.58): C, 69.53; H, 9.24; N, 13.51. Found: C, 69.35; H, 9.28; N, 13.59%.

3, 3′-(Butane-1,2-diyl) bis(5-oxo-1,7,7-trimethyl--1,2,3,4,5,6,7,8-octahydroquinazoline) (139d)



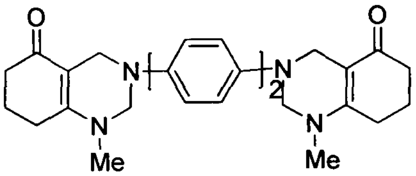
This compound is obtained as dark brown gum; yield 58%; IR (KBr): 1557 (νC=C), 1650 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 12H, C_7-CH_3 + $C_{7'}$-CH_3), 1.55 (s, 4H, $-CH_2C\mathit{H}_2C\mathit{H}_2CH_2-$), 2.16 (s, 4H, C_8-H + $C_{8'}$-H), 2.26 (s, 4H, C_6-H + $C_{6'}$-H), 2.40 (s, 4H, $-C\mathit{H}_2CH_2CH_2C\mathit{H}_2-$), 2.89 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 3.47 (s, 4H, C_4-H + $C_{4'}$-H), 3.91 (s, 4H, C_2-H + $C_{2'}$-H); MS: m/z 443.3 (MH^+). Anal. Calcd for $C_{26}H_{42}N_4O_2$ (442.64): C, 70.35; H, 9.56; N, 12.66. Found: C, 70.21; H, 9.51; N, 12.61%.

3, 3′-(phnylenene-1,4-diyl) bis(5-oxo-1-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline) (140a)



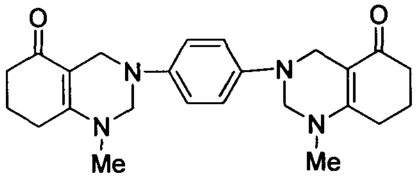
This compound is obtained as dark brown gum; yield 60%; IR (KBr): 1516 (νC=C), 1541 (νC=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.84-1.94 (m, 4H, C_7-H + $C_{7'}$-H), 2.38 (t, 4H, J=6.0 Hz, C_8-H + $C_{8'}$-H), 2.52 (t, 4H, J=1.8 Hz, C_6-H + $C_{6'}$-H), 2.97 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 4.14 (s, 4H, C_4-H + $C_{4'}$-H), 4.54 (s, 4H, C_2-H + $C_{2'}$-H), 6.90-6.96 (m, 4H, aromatic); MS: m/z 407.1 (MH^+). Anal. Calcd for $C_{24}H_{30}N_4O_2$ (406.52): C, 70.91; H, 7.44; N, 13.78. Found: C, 70.75; H, 7.50; N, 13.69%.

3, 3′-(biphnyl-4, 4’-diyl) bis (5-oxo-1-methyl--1,2,3,4,5,6,7,8-octahydroquinazoline) (140b)



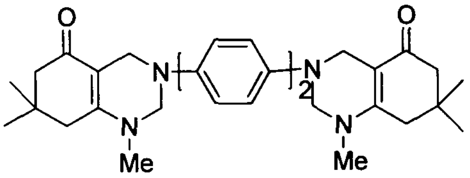
This compound is obtained as dark brown gum; yield 55%; IR (KBr): 1533 (νC=C), 1609 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.86-1.90 (m, 4H, C_7-H + $C_{7'}$-H), 2.21 (t, 4H, J=6.3 Hz, C_8-H + $C_{8'}$-H), 2.51 (t, 4H, J=1.8 Hz, C_6-H + $C_{6'}$-H), 2.94 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 4.05 (s, 4H, C_4-H + $C_{4'}$-H), 4.47 (s, 4H, C_2-H + $C_{2'}$-H), 6.68-6.88 (m, 8H, aromatic); MS: m/z 483.7 (MH^+). Anal. Calcd for $C_{30}H_{34}N_4O_2$ (482.62): C, 74.66; H, 7.10; N, 11.61. Found: C, 74.47; H, 7.15; N, 11.66%.

3, 3′-(phnylenene-1,4-diyl) bis (5-oxo-1,7,7-trimethyl--1,2,3,4,5,6,7,8-octahydroquinazoline) (140c)



This compound is obtained as dark brown gum in 56% yield; IR (KBr) 1548 (νC=C), 1647 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.01 (s, 12H, C_7-CH_3 + $C_{7'}$-CH_3), 2.17 (s, 4H, C_8-H + $C_{8'}$-H), 2.25 (s, 4H, C_6-H + $C_{6'}$-H), 2.95 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 4.10 (s, 4H, C_4-H + $C_{4'}$-H), 4.53 (s, 4H, C_2-H + $C_{2'}$-H), 6.87-6.91 (m, 4H, aromatic), MS: m/z 463.4 (MH^+) Anal. Calc. for $C_{28}H_{38}N_4O_2$ (462.63): C, 72.69; H, 8.28; N, 12.11. Found: C, 72.51; H, 8.24; N, 12.17%

3, 3′-(biphenyl-4, 4′-diyl) bis (5-oxo-1-methyl--1,2,3,4,5,6,7,8-octahydroquinazoline) (140d)



This compound is obtained as dark brown gum; 57% yield; IR (KBr): 1533 (νC=C), 1609 (νC=O) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.02 (s, 12H, C_7-CH_3 + $C_{7'}$-CH_3), 2.20 (s, 4H, C_8-H + $C_{8'}$-H), 2.25 (s, 4H, C_6-H + $C_{6'}$-H), 3.00 (s, 6H, N_1-CH_3 + $N_{1'}$-CH_3), 4.21 (s, 4H, C_4-H + $C_{4'}$-H), 4.63 (s, 4H, C_2-H + $C_{2'}$-H), 6.95-7.05 (m, 4H, aromatic), 7.43-7.48 (m, 4H, aromatic); MS: m/z 539.3 (MH^+). Anal. Calcd for $C_{34}H_{42}N_4O_2$ (538.72): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.64; H, 7.81; N, 10.47%.

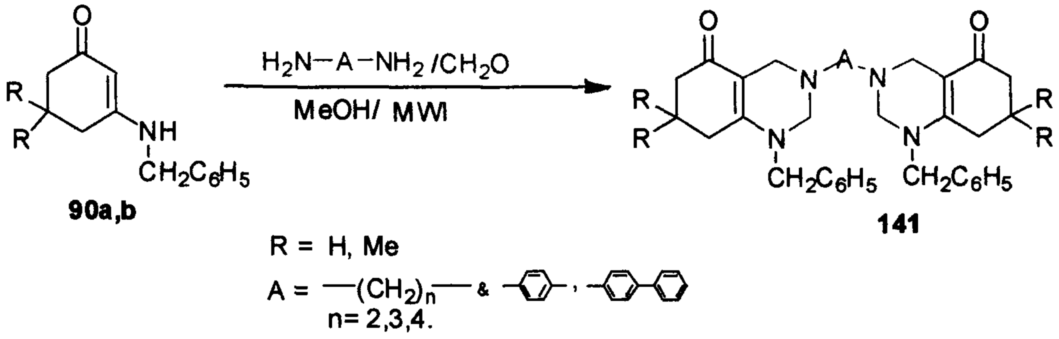
2.5.8: Conclusion

The present work in chapter (part-I) describes an efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis-octahydroquinazolines from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

PART-II

2.6 A Facile Microwave Assisted One-Pot Strategy for the synthesis of bis-1-benzyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline.

Keeping in view the importance of fused pyrimidine rings in medicine, as antimalarials and other biological properties and the biological importance of 1,2,3,4,5,6,7,8-octahydro-quinazoline-2,5-diones as calcium antagonist and potential antibacterials in continuation of our studies on the synthesis octahydroquinazolines, we herein this part of the chapter wish to report the synthesis of hitherto unreported bis-octahydroquinazolines bearing benzyl group in position 1 of the ring under microwave irradiation (**Scheme 28**).

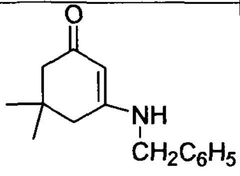
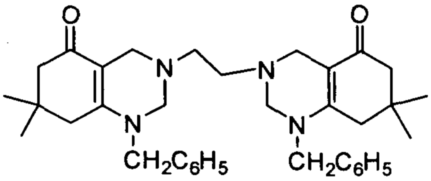
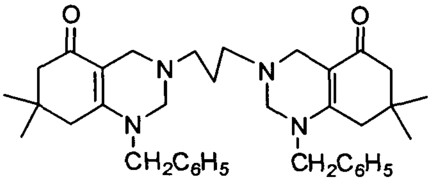


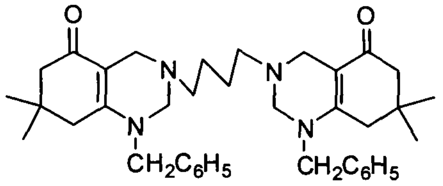
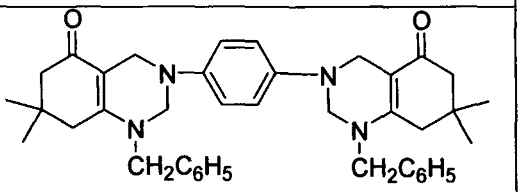
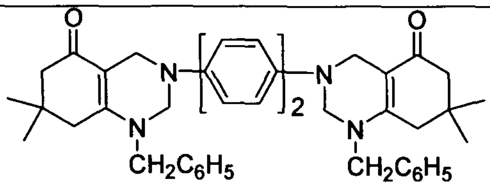
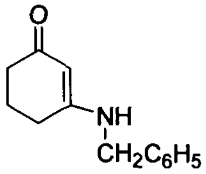
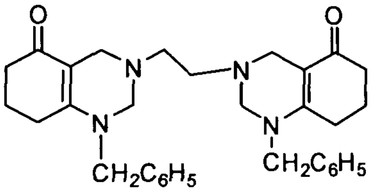
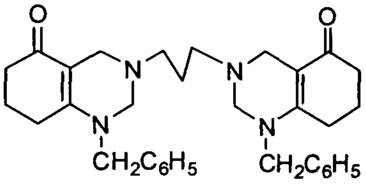
Scheme 28

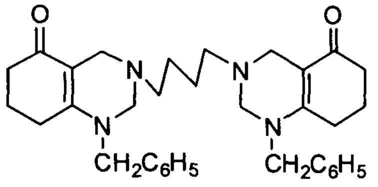
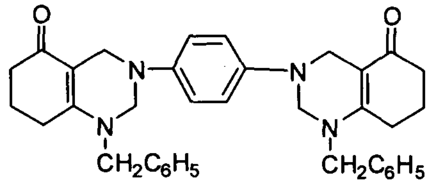
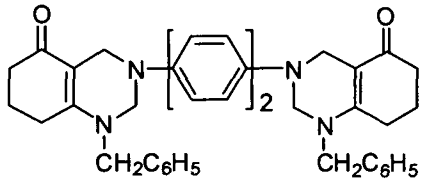
2.6.1 Results and Discussion

Thus when a mixture of 3-benzylcyclohex-2-en-1-one (**90a**), ethylenediamine and formaldehyde (2:1:4) in methanol was subjected to MWI, work- up of the reaction mixture followed by chromatographic purification yielded to a solid in 65% yield, which was characterized as 3,3′-(Ethane-1,2-diyl) bis (1-benzyl-5-oxo-7,7-dimethyl-1,2,3,4,7,8-octahydroquinazoline (**141a**) with the help of spectral and analytical data. The reaction was found to be general with other diamines and with corresponding enaminones **90a-b** to give the respective **141a-j** in 45-78% overall yields. The structures of the rest of the compounds were also established on the basis of spectral and analytical data. Thus, the infrared spectra of **141a-j** showed strong peaks in the range of 1513 to 1670 cm^{-1}due to highly delocalized double bonds and carbonyl group stretching frequencies of enaminone functionalities. In the ^1H NMR spectra of **141a & 141f** the NCH_2 protons of ethylene chain appeared as singlets at 2.61 ppm and 2.62 ppm respectively whereas the NCH_2 protons of propylene chain **141b & 141g** appeared as multiplets near 2.45 ppm and 2.29 ppm and that of C_2 protons of propylene chain appeared as multiplets around1.25 and 1.92 ppm respectively. Likewise in **141c & 141h** protons at C_1 and C_2 of butylene chain appeared as multiplets between 2.40-2.81 ppm and 1.38-1.96 ppm respectively.The protons at C_2 and C_4 of quinazoline ring resonated in the range of 4.44-4.47ppm and 3.92-4.44 ppm respectively.The methyl protons at C_7 of quinazoline ring in **141a-e** appeared as singlets in the range of 1.04-1.06ppm. The protons at C_7 of quinazoline ring in **141f-j** appeared as multiplets in the range of 1.77-1.96 ppm.The aromatic protons resonated in their usual range of 6.84-7.39 ppm.

Table III. Synthesis of 3,3′-(alkane/arene)diyl bis-1-benzyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines (141a-j)

Entry	Enaminones	conditions	bis- quinazolines
1		$H_2N\text{-}(CH_2)_2\text{-}NH_2, CH_2O/$ MeOH/180Watt 2 Minutes	 **141a**
2	**90a**	$H_2N\text{-}(CH_2)_3\text{-}NH_2, CH_2O/$ MeOH/180Watt 3 Minutes	 **141b**

3	**90a**	H_2N-$(CH_2)_4$-NH_2,CH_2O/ MeOH/180Watt 3 Minutes	 **141c**
4	**90a**	H_2N-C_6H_4-NH_2,CH_2O/ MeOH/450Watt 3 Minutes	 **141d**
5	**90a**	H_2N-$(C_6H_4)_2$-NH_2,CH_2O MeOH/450Watt 4 Minutes	 **141e**
6		H_2N-$(CH_2)_2$-NH_2,CH_2O/ MeOH/450Watt 4 Minutes	 **141f**
7	**90b**	H_2N-$(CH_2)_3$-NH_2,CH_2O/ MeOH/450Watt 5 Minutes	 **141g**

8	**90b**	$H_2N-(CH_2)_4-NH_2,CH_2O/$ MeOH/450Watt 5 Minutes	 **141h**
9	**90b**	$H_2N-C_6H_4-NH_2,CH_2O/$ MeOH/450Watt 5 Minutes	 **141i**
10	**90b**	$H_2N-(C_6H_4)_2-NH_2,CH_2O$ MeOH/450Watt 4 Minutes	 **141j**

The ^{1}HNMR and Mass spectra of Starting material and few compounds along with the structures are given in the following pages

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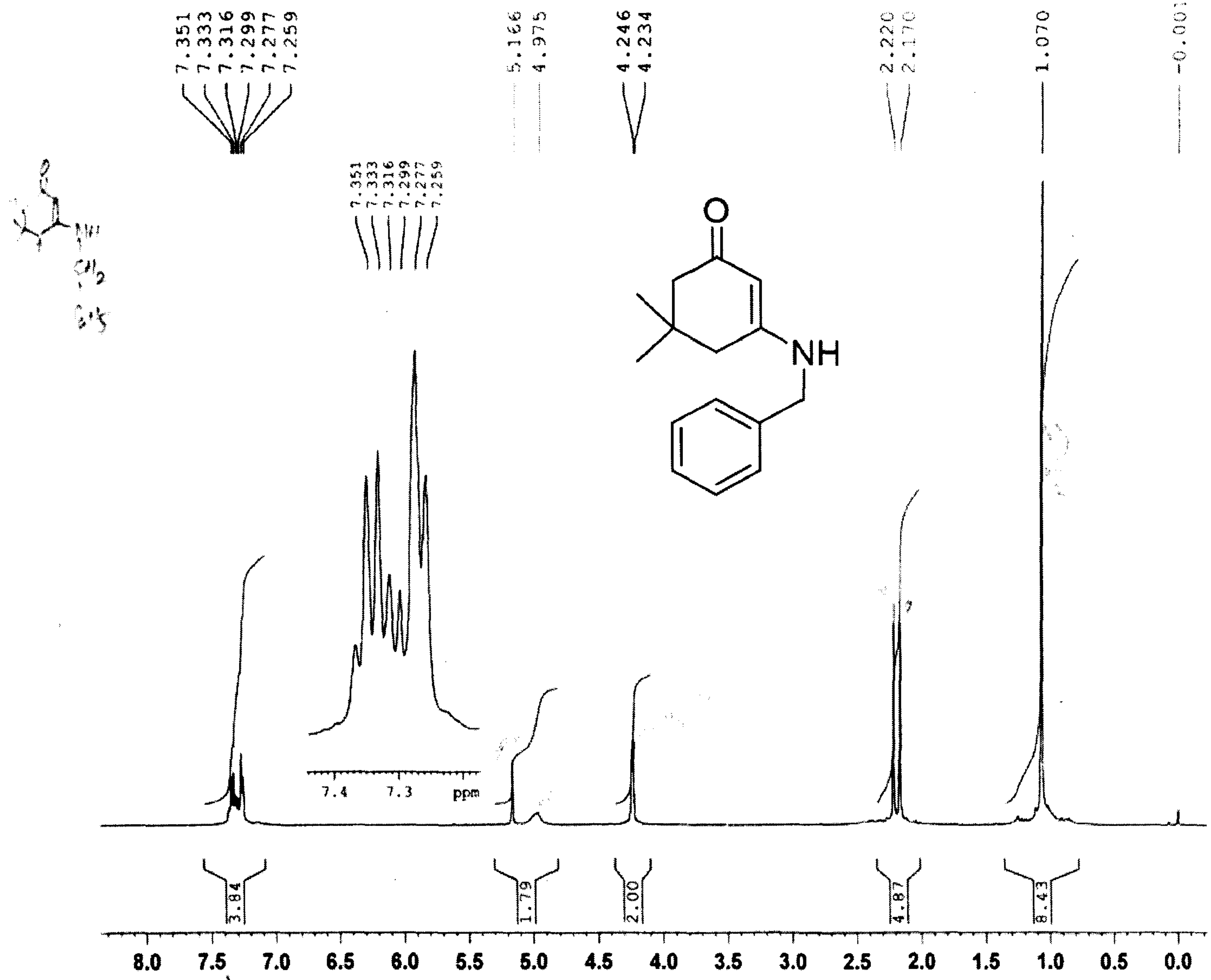

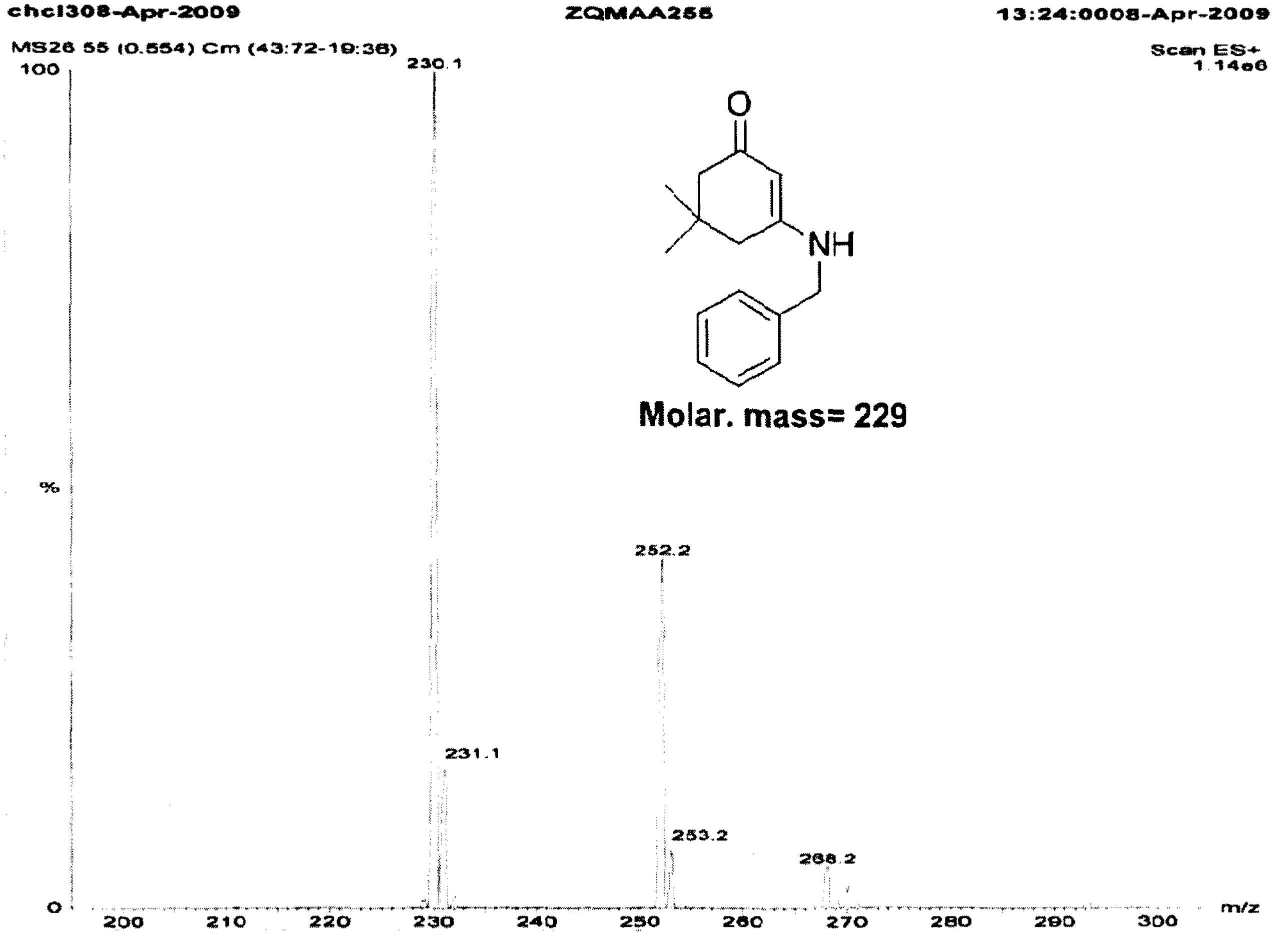
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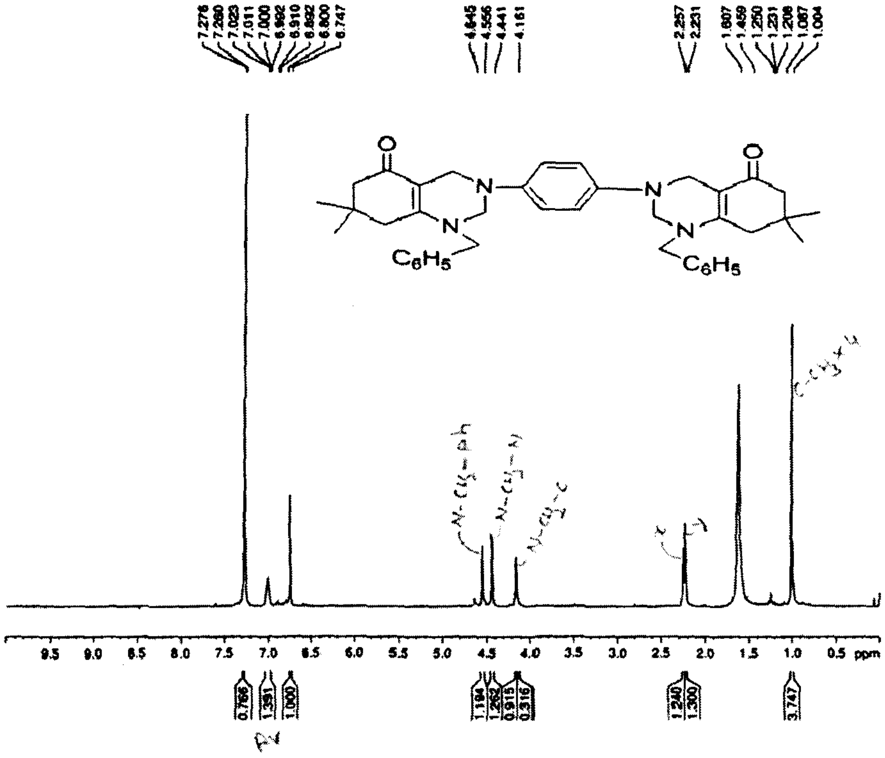
Analyst : Chinar
Date : 19.06.2008



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PROCNO                 1

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GB                     0
PC                  0.50
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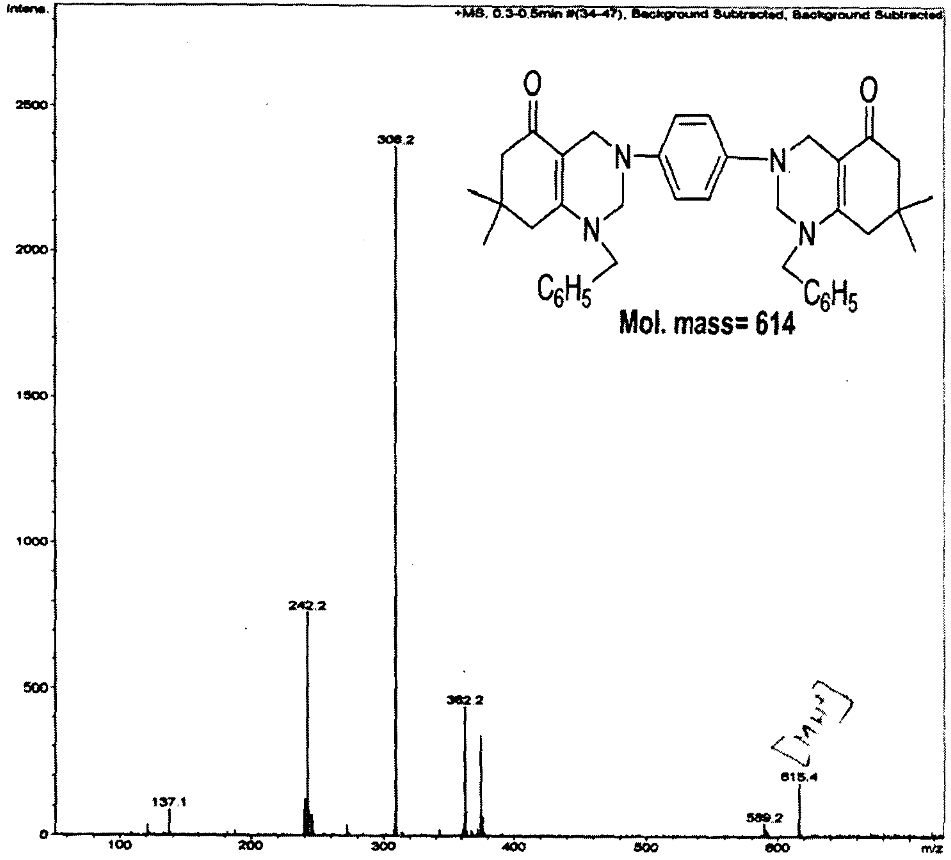
Method	(+ve) MS Method_Low.m	**Date**	20-06-2008



2.6.2 Experimental

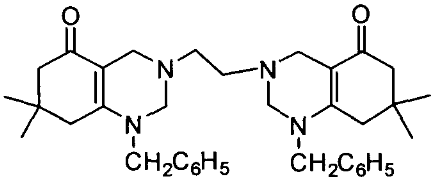
Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard pattern with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Microwave irradiation was carried out in a CEM Discover Benchmate microwave digester. Enaminones **90a** and **90b** were synthesized by our reported procedure [65].

General Procedure: Synthesis of bis 3,3′-(alkane/arene) diyl bis-1-benzyl-5-oxo-7,7-(unsubstituted/substituted)-1,2,3,4,5,6,7,8-octahydroquinazolines (141a-j)

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% solution) in 1.5mL methanol was shaken at room temperature for 5 minutes. To this a solution of enaminones **90** (1 mmol) was added in a 5-6 ml methanol and irradiated in a Microwave digester for 2-3 minutes. After the completion of the reaction (monitored by TLC), methanol was removed under reduced pressure to give a gum, which is subjected to column chromatography (Silica gel, EtoAC) to isolate **141a-j** in 45-78% yields.

2.6.3 Description of individual compounds

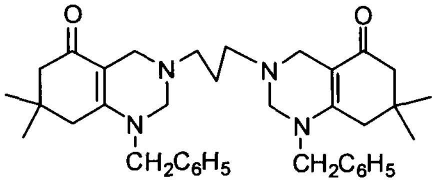
3,3′-(Ethane-1,2-diyl)bis(1-benzyl-5-oxo-7,7-dimethyl-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141a).



141a

3,3′-(Ethane-1,2-diyl)bis(1-benzyl-7,7-dimethyl-1,2,3,4,7,8-hexahydroquinazoline-5(6H) one (2a). This compound was obtained as pale yellow solid in 65% yield; mp 78 ^{0}C; IR (KBr): 1560,1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 12H), 2.19 (s, 4H), 2.31 (s, 4H), 2.61 (s, 4H), 3.55 (s, 4H), 4.02 (s, 4H), 4.43 (s, 4H), 7.16-7.39 (m, 10H); MS: m/z 567.4 (MH$^+$). Anal. Calcd. for $C_{36}H_{46}N_4O_2$ (566.37): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.15; H, 8.22; N, 9.83%.

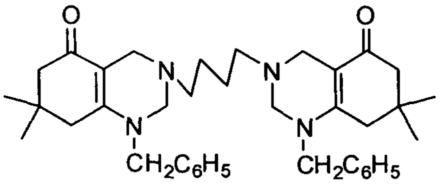
3,3′-(Propane-1,2-diyl) bis-(1-benzyl-5-oxo-7,7-dimethyl-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141b).



141b

This compound was obtained as pale yellow gum in 45% yield: IR (KBr): 1524, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ1.05 (s, 12H), 1.25-1.28 (m, 2H), 2.20 (s, 4H), 2.31 (s, 4H), 2.45-2.49 (m, 4H), 3.51 (s, 4H), 3.92 (s, 4H), 4.44 (s, 4H), 7.18-7.37 (m, 10H); MS: m/z 581.4 (MH$^+$). Anal. Calcd. for $C_{37}H_{48}N_4O_2$ (580.80): C, 76.51; H, 8.33; N, 9.65. Found: C, 76.66; H, 8.30; N9.69 %.

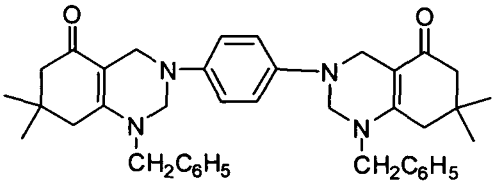
3,3′-(Butane-1,2-diyl) bis-(1-benzyl-5-oxo-7,7-dimethyl-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141c).



141c

This compound was obtained as pale yellow solid in 78% yield, mp 87^{0}C; IR (KBr): 1517, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.05 (s, 12H), 1.38-1.40 (m, 4H), 2.20 (s, 4H), 2.31 (s, 4H), 2.32-2.40 (m, 4H), 3.52 (s, 4H), 3.94 (s, 4H), 4.44 (s, 4H), 7.18-7.37 (m, 10H); MS: m/z 595.4 (MH$^+$). Anal. Calc. for $C_{38}H_{50}N_4O_2$ (594.83): C, 76.73; H, 8.47; N, 9.42. Found: C, 76.82; H, 8.45; N, 9.39 %.

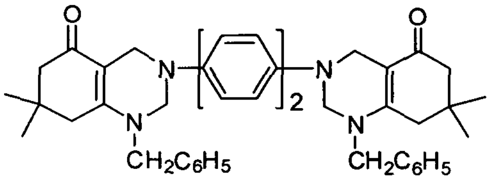
3,3′-(Phenylene-1,4-diyl) bis-(1-benzyl-5-oxo-7,7-dimethyl-1, 2, 3,4 ,5 ,6, 7, 8octahydroquinazoline) (141d).



141d

This compound was obtained as pale yellow solid in 52% yield; mp 170 ^{0}C; IR (KBr): 1513,1560 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.04 (s, 12H), 2.23 (s, 4H), 2.26 (s, 4H), 4.16 (s, 4H), 4.44 (s, 4H), 4.56 (s, 4H), 4.65 (s, 4H), 7.26-7.28 (m, 14H); MS: m/z 615.4 (MH$^+$). Anal. Calcd. for $C_{40}H_{46}N_4O_2$ (614.82): C, 79.46; H, 6.67; N, 8.83. Found: C, 78.27; H, 7.49; N, 9.15%.

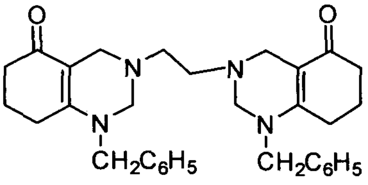
3,3′-(Biphenyl-4,4′-diyl) bis-(1-benzyl-5-oxo-7,7-dimethyl-1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141e).



141e

This compound was obtained as pale yellow solid in 65% yield; mp 185 ^{0}C; IR (KBr):1545, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 12H), 2.21(s, 4H), 2.50 (s, 4H), 3.52 (s, 4H), 3.93 (s, 4H), 4.45 (s, 4H), 7.21-7.38 (m, 18H); MS: m/z 691.4 (MH$^+$). Anal. Calc. for $C_{46}H_{50}N_4O_2$ (690.91): C, 79.97; H, 7.29; N, 8.11. Found: C, 76.86; H, 7.32; N, 8.11%.

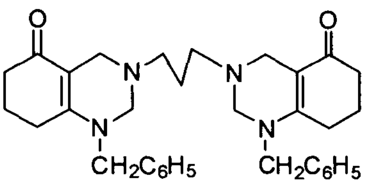
3,3′-(Ethane-1,2-diyl) bis-(1-benzyl-5-oxo -1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141f).



141f

This compound was obtained as pale yellow gum in 42% yield; IR (KBr): 1560, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.92-1.96 (m, 4H), 2.29-2.32 (m, 4H), 2.44-2.47 (m, 4H), 2.62 (s, 4H), 3.52(s, 4H), 3.98 (s, 4H), 4.43(s, 4H), 7.15-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.51, 25.88, 29.68, 35.68, 47.64, 52.38, 70.26, 77.03, 103.76, 126.32, 129.07, 136.78, 159.01, 193.85; MS: m/z 511.3 (MH$^+$). Anal. Calc. for $C_{32}H_{38}N_4O_2$ (510.67): C, 75.26; H, 7.50; N, 10.97. Found: C, 75.35; H, 7.50; N, 10.92%.

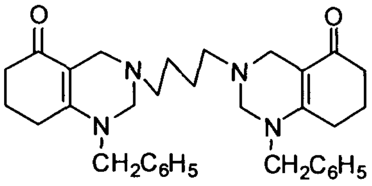
3,3′-(Propane-1,2-diyl) bis-(1-benzyl-5-oxo -1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141g).



141g

This compound was obtained as pale yellow gum in 39% yield; IR (KBr): 1560,1659 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58-1.63 (m, 4H), 1.92-1.95 (m, 4H) 2.13-2.16 (m, 2H), 2.29-2.32 (m, 4H), 2.46 (s, 4H), 3.35 (s, 4H), 3.88 (s, 4H), 4.44(s, 4H), 7.17-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.51, 25.76, 30.94, 35.67, 48.30, 51.55, 69.50, 77.04, 104.37, 126.31, 127.78, 129.05, 136.82, 158.83, 193.75; MS: m/z 525.4 (MH^+). Anal. Calc. for $C_{33}H_{40}N_4O_2$ (524.70): C, 75.54; H, 7.68; N, 10.68. Found: C, 75.65; H, 7.71; N, 10.66%.

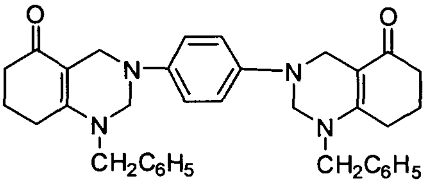
3,3′-(Butane-1,2-diyl) bis-(1-benzyl-5-oxo -1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141h).



141h

This compound was obtained as pale yellow gum in 45% yield; IR (KBr): 1552,1601,1670 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.68-1.69 (m, 4H) 1.94-1.96 (m, 4H), 2.11 (s, 4H) 2.29 (s, 4H), 2.78-2.81 (m, 4H), 3.44-3.48 (m, 4H), 3.90 (s, 4H), 4.44 (s, 4H), 7.17-7.37 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.53, 25.70, 30.94, 35.69, 47.95, 52.31, 69.65, 77.04, 104.30, 126.35, 127.78, 129.03, 136.85, 158.84, 193.79; MS: m/z 539.7 (MH^+). Anal. Calc. for $C_{34}H_{42}N_4O_2$ (538.72): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.92; H, 7.84; N, 10.37%.

3,3′-(Phenylene-1,4-diyl) bis-(1-benzyl-5-oxo -1, 2, 3,4 ,5 ,6. 7, 8-octahydroquinazoline) (141i).

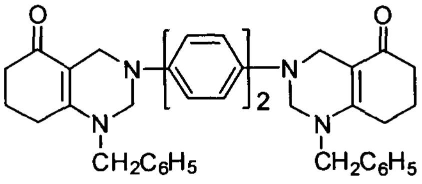


141i

This compound was obtained as pale yellow gum in 52% yield; IR (KBr): 1527, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.93-1.95 (m, 4H), 2.34-2.37 (m, 4H), 2.42-2.44 (m, 4H), 4.09 (s, 4H), 4.47(s, 4H), 4.52 (s, 4H), 6.96-7.37 (m, 14H); ^{13}C NMR ($CDCl_3$):

δ 21.49, 25.87, 29.70, 35.71, 46.08, 52.25, 68.41, 77.02, 105.06, 119.12, 126.21, 127.73, 129.01, 136.43, 159.62, 193.56; MS: m/z 559.4 (MH$^+$). Anal. Calc. for $C_{36}H_{38}N_4O_2$ (558.71): C, 77.30; H, 6.86; N, 10.03. Found: C, 77.28; H, 6.89; N, 10.07 %.

3,3′-(Biphenyl-4,4′-diyl) bis-(1-benzyl-5-oxo -1, 2, 3,4 ,5 ,6, 7, 8-octahydroquinazoline) (141j).



141j

This compound was obtained as pale yellow gum in 48% yield; IR (KBr): 1547, 1608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.76-1.89 (m, 4H), 2.29-2.32 (m, 4H), 2.38-2.39 (m, 4H), 4.19 (s, 4H), 4.44 (s, 4H), 4.58 (s, 4H), 6.84-7.39 (m, 18H); ^{13}C NMR ($CDCl_3$): δ 21.48, 25.89, 29.70, 35.71, 45.52, 52.26, 67.56, 77.03, 105.03, 117.82, 126.28, 127.23, 129.04, 136.41, 147.32, 159.70, 193.66; MS: m/z 635.8 (MH$^+$). Anal. Calc. for $C_{42}H_{42}N_4O_2$ (634.8): C, 77.30; H, 6.86; N, 10.03. Found: C, 79.61; H, 6.61; N, 8.80%

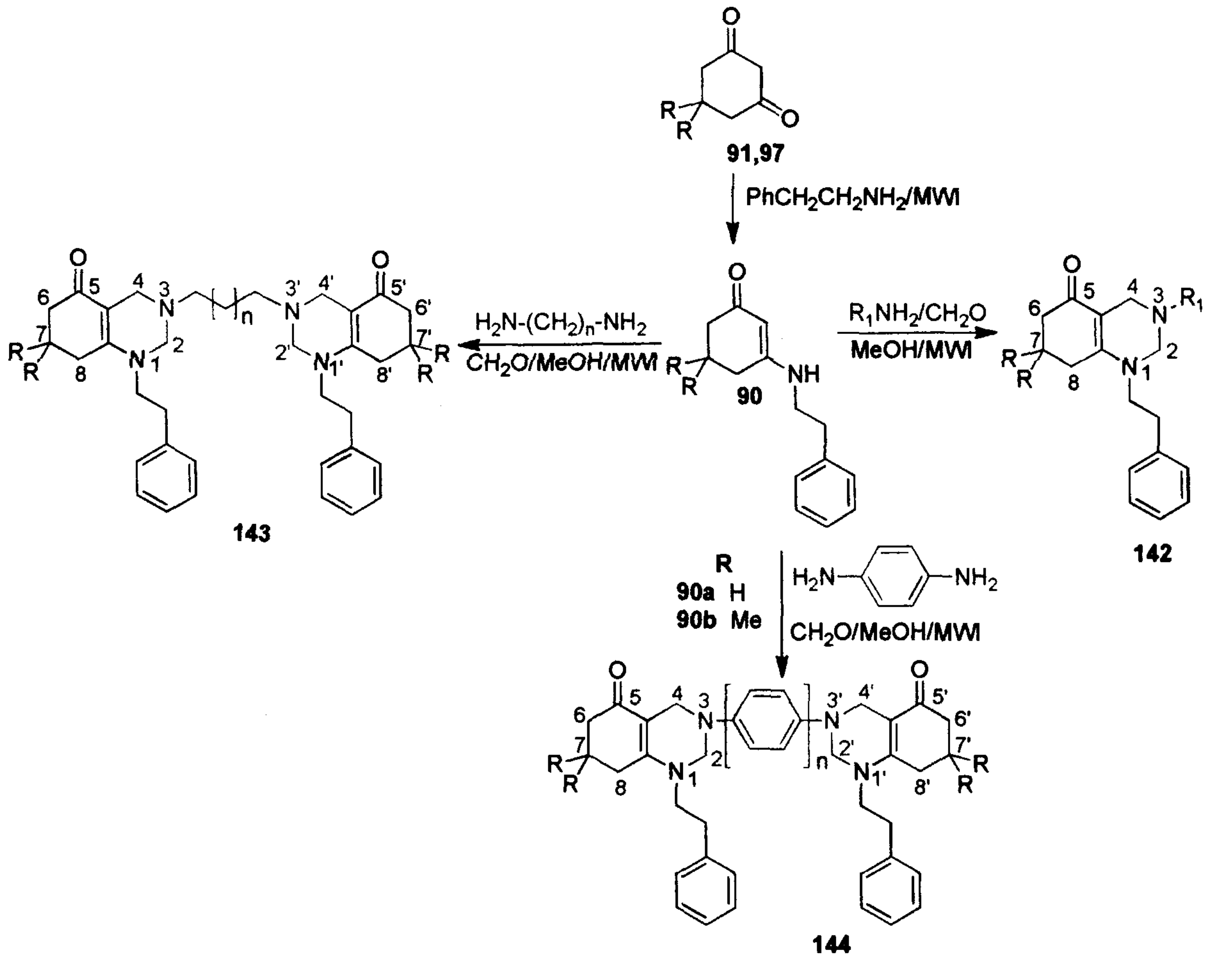
2.6.4 Conclusion:

This part of the chapter describes an efficient, simple, fast and environment-friendly methodology for synthesizing hitherto unreported bis-octahydroquinazolines from easily accessible starting materials.

PART-III

2.7 Microwave Assisted One-pot Synthesis of Novel 1-Phenylethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines & 3,3′-(alkane/arene) diyl bis-1-phenylethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines

Quinazolines have attracted considerable attention because of their great pharmacological importance and biological activities. Keeping in view the biological properties of octahydroquinazolines [47,66,] we have recently reported [67-68] the synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines bearing phenyl, benzyl and methyl groups in position 1 of the ring and bis-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines bearing phenyl, benzyl and methyl group in position 1 of the ring. The biological properties of these molecules are under investigation. We now wish to report herein a short MW assisted synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin and bis 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolin bearing phenylethyl group in position 1 of quinazoline ring to see the impact this group incorporated in position 1 on biological properties of these molecules. **(Scheme 29)**



Scheme 29

2.7.1 Results and Discussion

Thus, when 3-phenylethylaminocyclohexenone **90 a** was treated with methylamine and formaldehyde under the influence of microwaves, a product was obtained in 78% yields which was characterized as 1-phenylethyl-3-methyl-5-oxo-1,2,3,4,7,8-octahydroquinazoline **142a** on the basis of analytical and spectral data. The reaction of **90a** with other primary amines and formaldehyde behaved in a similar manner and octahydroquinazolines **142b-e** were isolated in 55-78% yields. The infrared spectra of **142a-e** showed strong peaks in the region of 1553 to 1615 cm^{-1} due to extensively delocalized double bonds and carbonyl groups [7]. In the ^1H NMR spectra of **142a-e**, the methylene protons at C-2 resonated near 3.85 ppm except in **142b** where they appeared in the vicinity of 4.57 ppm but in 3d it appeared near 3.45 ppm. This increment in chemical shift could be attributed to the presence of delocalization of N-3 lone pair of electrons with phenyl ring. Methylene protons at C-2 for 3f-j resonated at higher δ value than the corresponding 3a-e which may be due to presence of electronic donating methyl groups at C-7 in 3f-j. Probably a similar explanation could be extended for the appearance of CH_2 protons at C-4 close to 3.43 ppm except in **142b** and **142d** where they were found to resonate near 4.14 ppm and 2.96 ppm respectively. While CH_2 protons at C-7 appeared as multiplets in the range of 1.52-1.83 ppm, those at C-6 and C-8 resonated close to 2.40 and 2.30 ppm respectively. The methylene protons at N-1 gave multiplets close to 2.84-3.36 ppm whereas the adjacent methylene protons gave multiplets close to2.40-2.69 ppm. The reactions of **90b** with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-phenylethyl-3-alkyl/aralkyl/aryl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines **142f-j** were isolated in 62-85% yields, whose structures could be established with the help of analytical and spectral data. The infrared spectra of **142f-j** showed strong peaks in the region of 1526 to 1623 cm^{-1}. The ^1H NMR spectra of tetrahydropyrimidine rings of **142f-j** were found to have a similar pattern as those of **142a-e.** However, the six methyl protons at C-7 appeared as sharp singlets around 0.90 ppm and the CH_2 protons at C-6 and C-8 resonated in ranges of 1.99-2.17 and 2.10-2.25 ppm respectively.

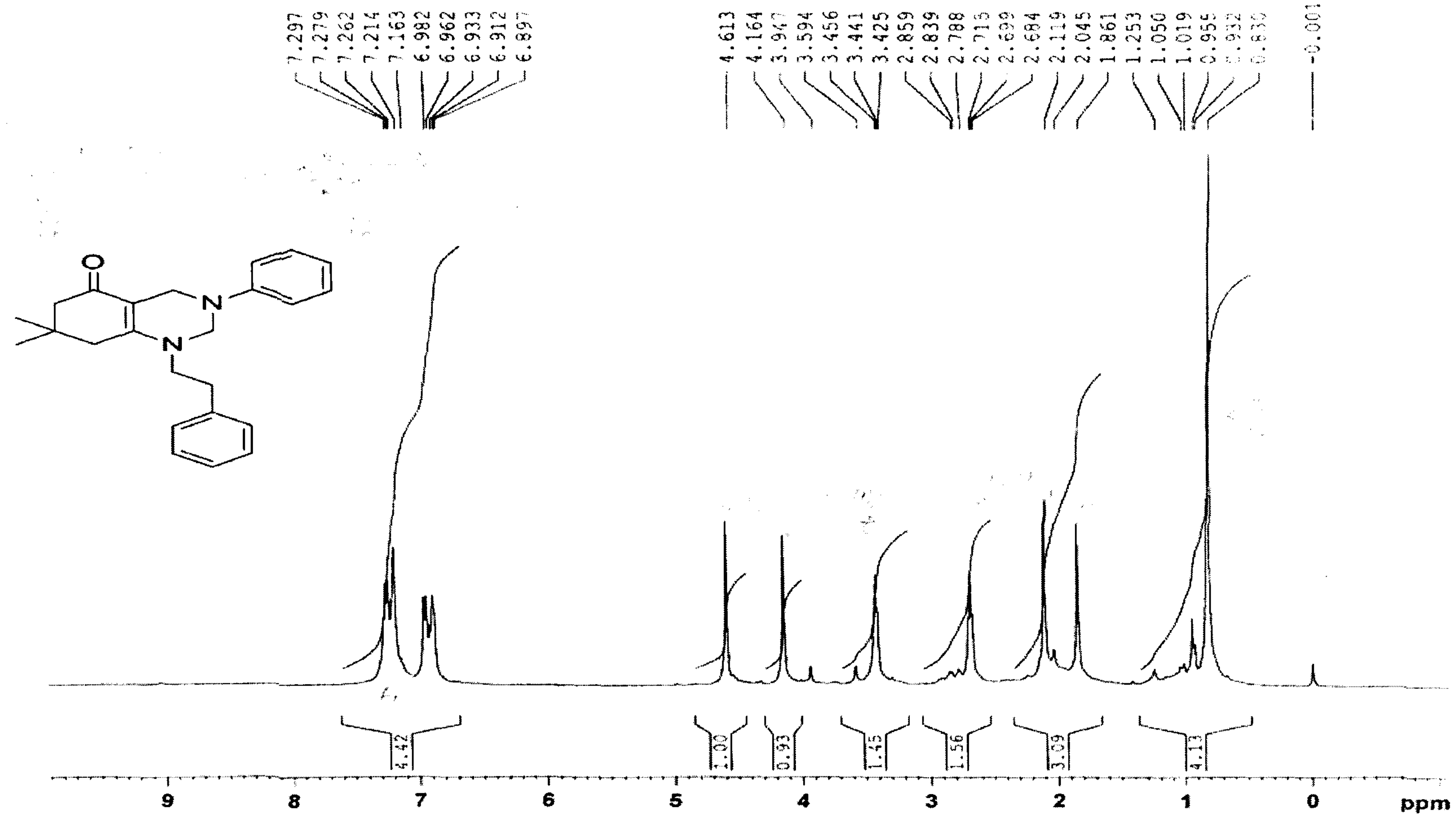
Encouraged by the successful synthesis of octahydroquinazolines **142a-j**, we then turned our attention to the synthesis of bis-octahydroquinazolines. Thus, when enaminone **90a** was reacted with 1,2-diaminoethane and formaldehyde under the influence of microwaves in methanol, a product **143a** was isolated in 71 % yield, the structure of which was established to be 3,3′-(Ethane-1,2-diyl)bis(1-phenylethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines based on analytical and spectral data. The reaction was found to be general with other diamines and with corresponding 2a-b to give the respective product 4b-f in 51-68% overall yields (Table2). We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains **143**a-f and through aromatic linkers **144a-d**. The structures of which could be established with the help of spectral and analytical data. The infrared spectra of **143a-f** and **144a-d** showed strong peaks in the range of 1538-1669 cm^{-1} due to extensive delocalization of the enaminone moiety and carbonyl group. The ^{1}H NMR spectra of these dimers were found to have the same pattern as in the monomeric octahydroquinazolines except that the signals due to NCH$_2$ protons of ethylene linkers appeared at 2.61-2.73 ppm while those in propylene resonated in the range of 2.04-2.47 ppm and in butylene appeared in the ranges of 2.14-2.34 ppm. The structures of **143a-d** and **144a-d** were further supported by their ^{13}C and mass spectra.

2.7.2 Table IV Synthesis of quinazolines 142a-j, 143a-d and 144a-d

Compd	R	R$_1$	n	MW Irradiation (watt/sec)
142a	H	-CH$_3$	-	180/120
142b	H	-C$_6$H$_5$	-	180/180
142c	H	-C$_6$H$_4$-CH$_3$	-	180/150
142d	H	-C$_6$H$_4$-Cl	-	180/130
142e	H	-CH$_2$-C$_6$H$_5$	-	180/150
142f	-CH$_3$	-CH$_3$	-	180/120
142g	-CH$_3$	-C$_6$H$_5$	-	180/90
142h	-CH$_3$	-C$_6$H$_4$-CH$_3$	-	180/90
142i	-CH$_3$	-C$_6$H$_4$-Cl	-	180/120
142j	-CH$_3$	-CH$_2$-C$_6$H$_5$	-	180/90
143a	H	-	0	180/180

143b	H	-	1	180/210
143c	H	-	2	180/120
143d	$-CH_3$	-	0	180/120
143e	$-CH_3$	-	1	180/150
143f	$-CH_3$	-	2	180/180
144a	H	-	1	180/210
144b	H	-	2	180/180
144c	$-CH_3$	-	1	180/180
144d	$-CH_3$	-	2	180/180

The ^{1}HNMR and Mass spectra of few compounds along with the structures are given in the following pages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7.279
7.262
7.214
7.163
6.982
6.962
6.933
6.912
6.897
4.613
4.164
3.947
3.594
3.456
3.441
3.425
2.859
2.839
2.788
2.715
2.699
2.684
2.119
2.045
1.861
1.253
1.050
1.019
0.955
0.932
0.830
-0.001
O
N
N
4.42
1.00
0.93
1.45
1.56
3.09
4.13
9
8
7
6
5
4
3
2
1
0
ppm

Analysis Info

Method	MS Method broad (+ve).m	Analysed by	Aniket
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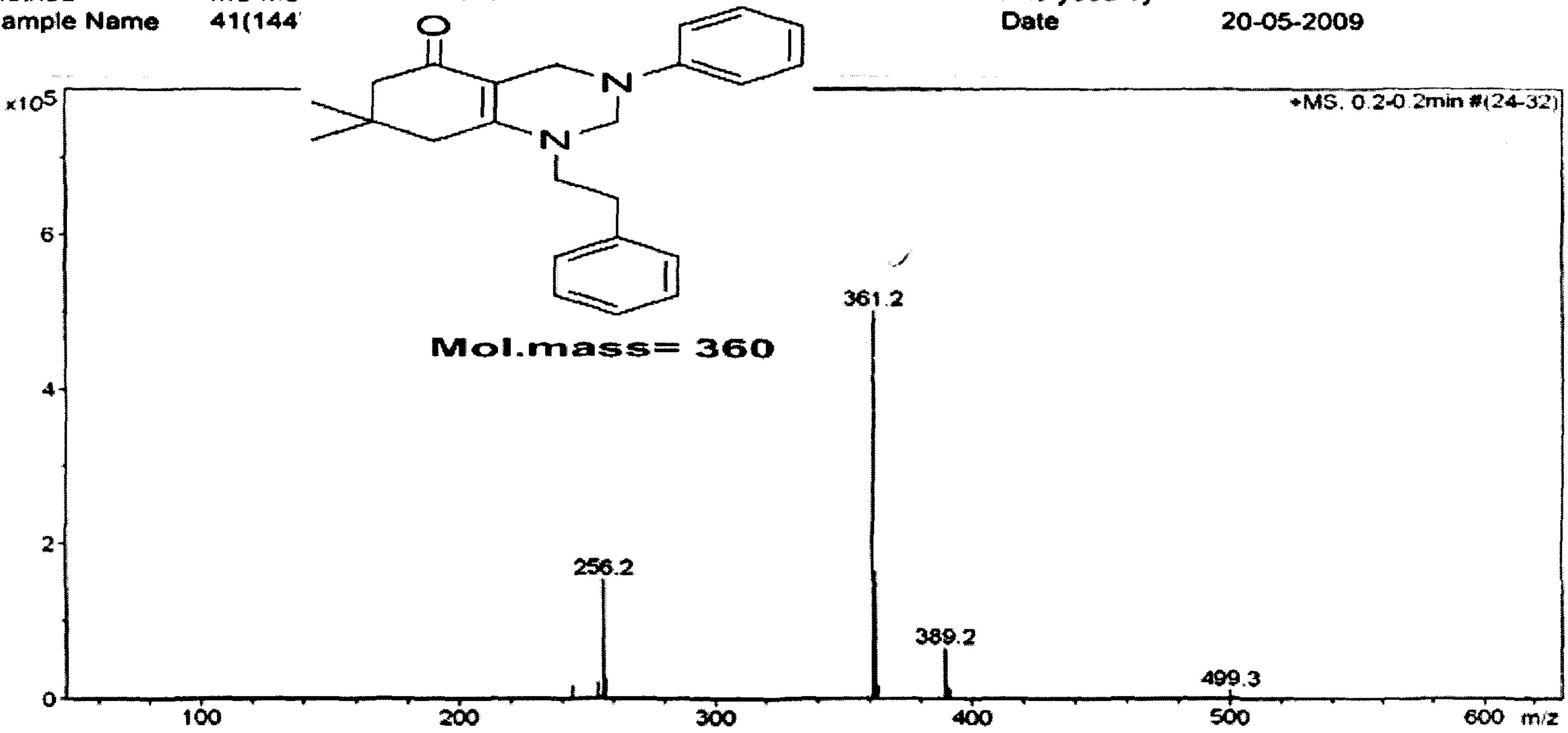

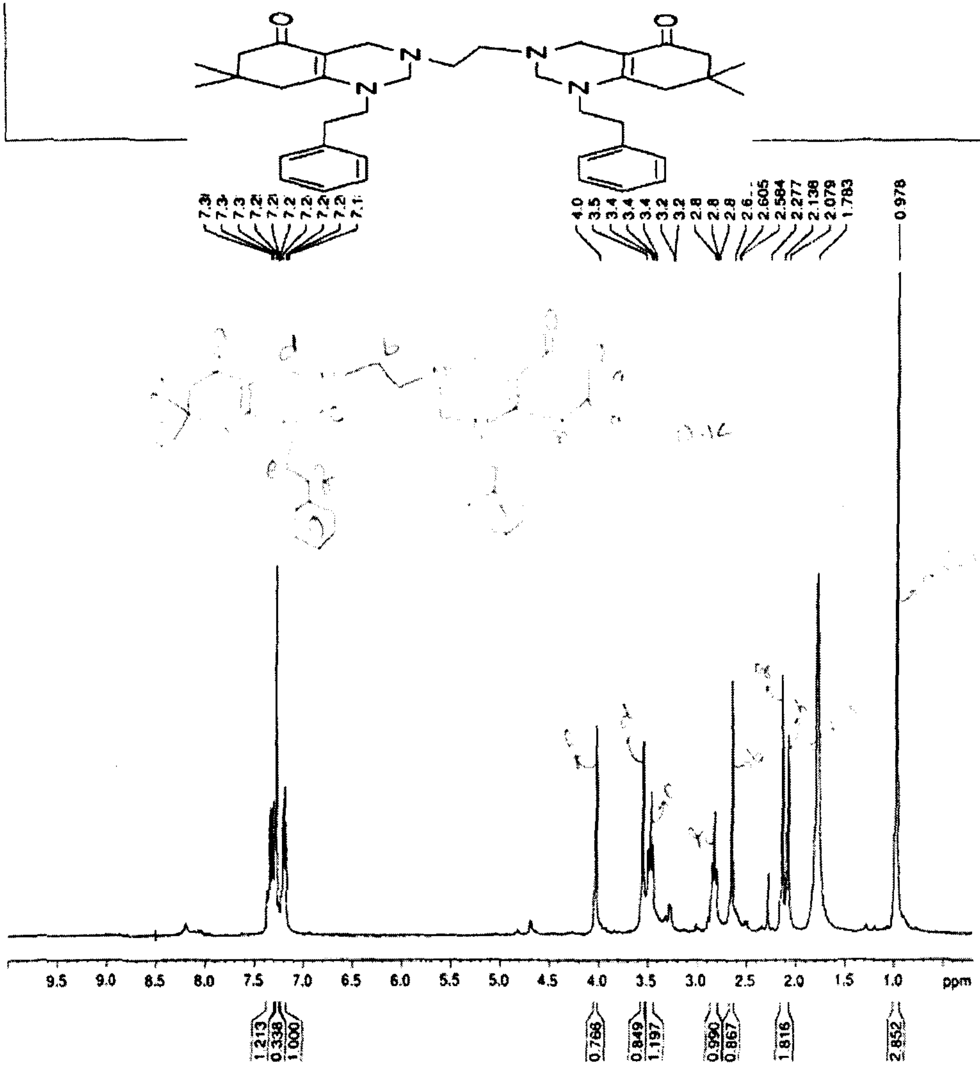

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Spectrum : 1H Spectrum
Instrument: AS-I-10
Analyst : Rajendra
Date : 21.05.2009

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EXPNO                  520
PROCNO                   1

F2 - Acquisition Parameters
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TD                   16384
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NS                      16
DS                       2
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FIDRES            0.365918 Hz
AQ               1.3664756 sec
RG                     256
DW                  83.400 usec
DE                    6.00 usec
TE                     0.0 K
D1              2.00000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    7.00 usec
PL1                   1.00 dB
SFO1           300.1325511 MHz

F2 - Processing parameters
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SF             300.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.20 Hz
GB                       0
PC                    0.50
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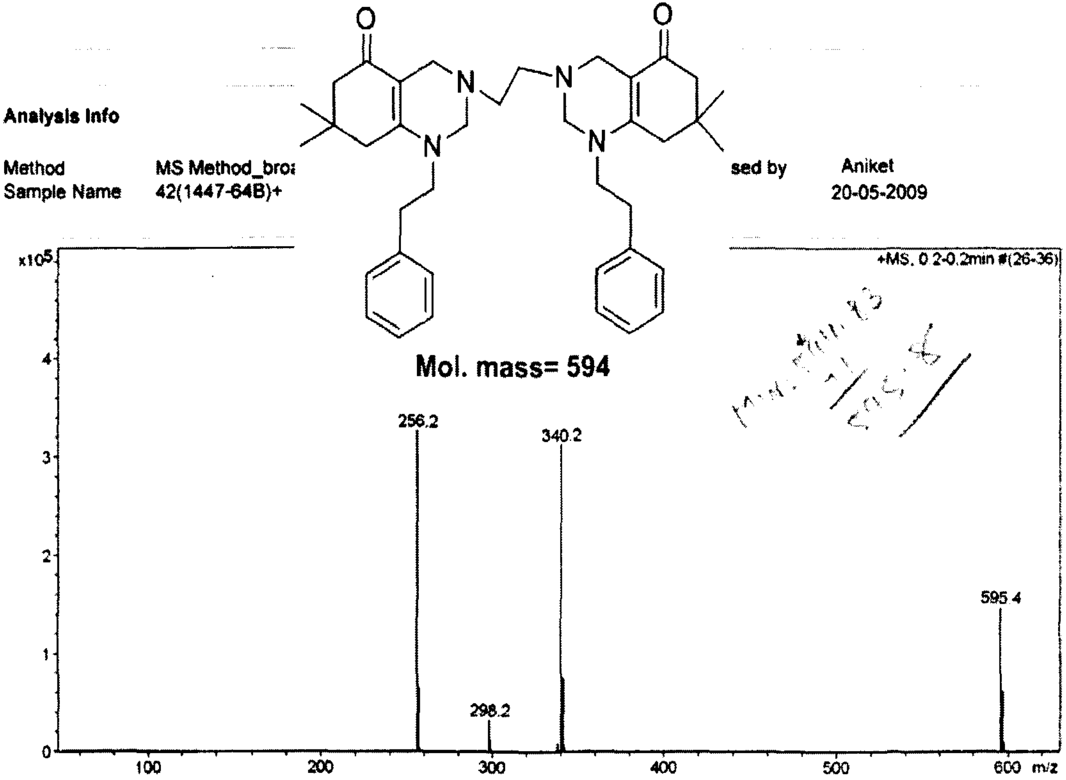
Analysis Info

Method MS Method_bro

Sample Name 42(1447-64B)+

sed by Aniket

20-05-2009



Mol. mass= 594

M.W. : 594.83
+1
595.8

In

Bruker Daltonics DataAnalysis 3.4

2.7.3 Experimental

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^{1}H NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the standard pattern with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument. Microwave irradiation was carried out in a CEM Discover Benchmate microwave digester. Enaminones **90**a and **90**b were synthesized by our reported procedure [65].

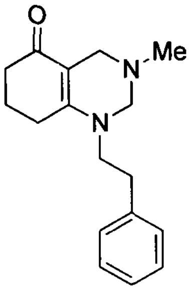
Synthesis of 1,3-substituted-1, 2, 3,4 ,5 ,6 7, 8-octahydroquinazolines (142 a-e) and 1,3-substituted-7,7-dimethyl-1,2,3,4,7,8-octahydroquinazolines (142f-j).

2.7.4: General procedure:

A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone **90a, 90b** (1 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **142a-j** in 55-85 % yields.

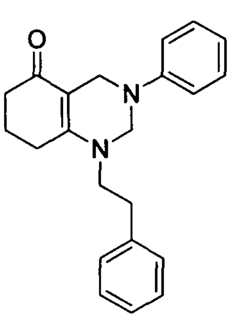
2.7.5 Description of individual compounds

1-Phenylethyl-3-methyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142a).



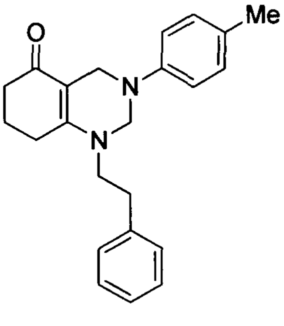
This compound was obtained as grey a solid in 78% yield, mp 53^{0}C; IR (KBr): 1557, 1603 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ1.52-1.58 (m, 2H), 1.83 (s, 2H), 2.08 (s, 2H), 2.24 (s, 2H), 2.24 (s, 2H), 2.40 (s, 2H), 2.84 (s, 2H), 3.43 (s, 2H), 3.85 (s, 2H), 7.19-7.31 (m, 5H)); ^{13}C NMR (CDCl$_3$): δ 21.40, 25.35, 35.62, 35.73, 41.60, 50.09, 70.89, 103.88, 126.93, 128.78, 128.82, 137.95, 158.27, 193.62; MS: m/z 271.9 (MH$^+$). Anal. Calc. for $C_{17}H_{22}N_2O$ (270.17): C, 75.52; H, 8.20; N, 10.36. Found: C, 75.71; H, 8.15; N, 10.39%.

1-Phenylethyl-3-phenyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142b).



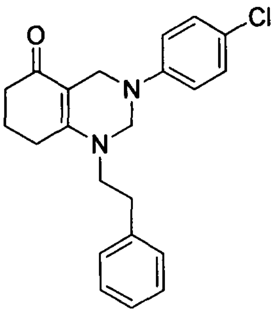
This compound is obtained as pale yellow gum in 75% yield: IR (KBr): 1557, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.69-1.75 (m, 2H), 2.04-2.07 (m, 2H), 2.22-2.25 (m, 2H), 2.91-2.95 (m, 2H), 3.40-3.48 (m, 2H), 4.14 (s, 2H), 4.57 (s, 2H), 6.88-7.28 (m, 10H); ^{13}C NMR (CDCl$_3$): 21.29, 25.44, 35.66, 36.61, 45.26, 45.49, 50.75, 67.54, 104.44, 117.67, 120.86, 126.88, 128.78, 128.78, 128.84, 128.96, 137.99, 159.71, 193.41; MS: m/z 332.8 (MH$^+$). Anal. Calc. for $C_{22}H_{24}N_2O$ (332.19): C, 79.48; H, 7.28; N, 8.43. Found: C, 79.33; H, 7.32; N, 8.37 %.

1-Phenylethyl-3-tolyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142c).



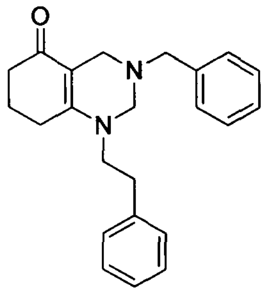
This compound is obtained as pale yellow gum in 55% yield: IR (KBr): 1559, 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.64-1.67 (m, 2H), 1.86 (s, 2H), 2.15 (s, 2H), 2.67-2.72 (s, 2H), 3.36-3.39 (m, 2H), 3.99 (s, 2H), 6.79-7.18 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 20.50, 21.29, 25.43, 30.94, 35.55, 35.64, 36.61, 45.26, 45.71, 50.77, 67.97, 104.47, 125.09, 126.87, 128.50, 129.78, 159.67, 193.40; MS: m/z 347.8 (MH^+). Anal. Calc. for $C_{23}H_{26}N_2O$ (346.2): C, 79.73; H, 7.56; N, 8.09. Found: C, 79.82; H, 7.52; N, 8.13 %.

1-Phenylethyl-3-(4-chlorophenyl)- 5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142d).



This compound is obtained as grey solid in 58% yield, mp 158°C; IR (KBr): 1563, 1615 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.71-1.77 (m, 2H), 2.17 (s, 2H), 2.26 (s, 4H), 2.93-2.96 (m, 2H), 3.45-3.48 (m, 2H), 7.20-7.30 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 17.73, 21.36, 25.44, 30.94, 35.63, 36.64, 45.26, 108.01, 126.44, 128.50, 128.88, 138.92, 166.34, 194.07; MS: m/z 367.81 (MH^+). Anal. Calc. for $C_{22}H_{23}ClN_2O$ (366.15): C, 72.02; H, 6.32; N, 7.64. Found: C, 72.17; H, 6.28; N, 7.70 %.

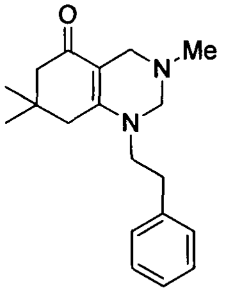
1-Phenylethyl-3-benzyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142e).



It was obtained as brown gum in 75% yield: IR (KBr): 1553, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80-1.83 (m, 2H), 2.20-2.26 (m, 2H), 2.72-2.75 (m, 2H), 3.36-3.39 (m, 2H), 3.55 (s, 2H), 3.64 (s, 2H), 3.86 (s, 2H), 7.12-7.33 (m,10H); ^{13}C NMR ($CDCl_3$):

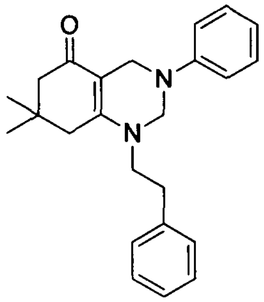
21.39, 25.36, 35.69, 48.72, 50.88, 57.93, 68.32, 104.00, 126.88, 127.44, 128.46, 128.78, 128.98, 137.80, 138.02, 158.74, 193.63 MS: m/z 347.1 (MH$^+$). Anal. Calc. for $C_{23}H_{26}N_2O$ (346.2): C, 79.73; H, 7.56; N, 8.09. Found: C, 79.91; H, 7.53; N, 8.15 %.

1-Phenylethyl-3,7,7-trimethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142f).



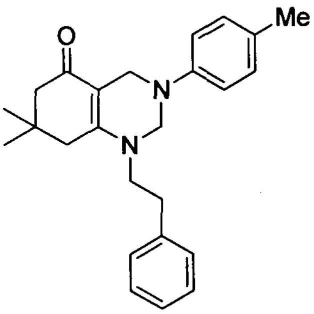
This compound is obtained as pale yellow solid in 73% yield, m.p 75^{o}C IR (KBr): 1559, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (s, 6H), 1.99 (s, 3H), 2.06 (s, 2H), 2.33 (s, 2H), 2.74-2.78 (t, 2H, J=5.4Hz), 3.38-3.41 (m, 5H), 3.81 (s, 2H), 7.11-7.28 (m, 5H); MS: m/z 299.1 (MH$^+$). Anal. Calc. for $C_{19}H_{26}N_2O$ (298.2): C, 76.47; H, 8.78; N, 9.39. Found: C, 76.35; H, 8.73; N, 9.45 %.

1-Phenylethyl-3-phenyl-7,7-dimethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142g).



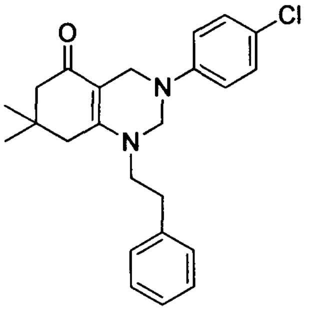
This compound is obtained as pale yellow solid in 69% yield, mp 85^{0}C; IR (KBr): 1559, 1604cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.89 (s, 6H), 1.99 (s, 3H), 2.06 (s, 2H), 2.33 (s, 2H), 2.74-2.78 (t, 2H, J=5.4Hz), 3.38-3.41 (m, 5H,), 3.81 (s, 2H), 7.11-7.28 (m, 5H); MS: m/z 361.2 (MH$^+$). Anal. Calc. for $C_{24}H_{28}N_2O$ (360.22): C, 79.96; H, 7.83; N, 7.77. Found: C, 79.85; H, 7.87; N, 7.74 %.

1-Phenylethyl-3-tolyl-7,7-dimethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydro-quinazoline (142h).



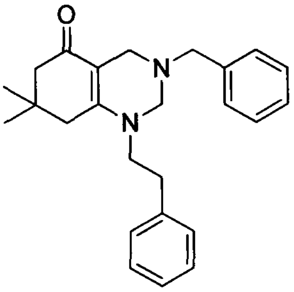
This compound is obtained as pale yellow solid in 85% yield, mp 89^{0}C; IR (KBr): 1526, 1623cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.84 (s, 6H), 2.07 (s, 3H), 2.17 (s, 2H), 2.25 (s, 2H), 2.68-2.71 (t,2H, J=5.1Hz), 3.41-3.44 (t, 2H, J=5.1Hz), 4.13 (s, 2H), 4.57 (s, 2H), 6.87-7.27 (m, 9H); ^{13}C NMR (CDCl$_3$): δ 20.48, 28.65, 30.92, 31.90, 32.00, 35.65, 39.11, 45.24, 49.28, 50.27, 68.29, 118.16, 126.80, 128.71, 128.93, 130.46, 138.05, 146.40, 157.94, 192.88; MS: m/z 375.1 (MH$^+$). Anal. Calc. for $C_{25}H_{30}N_2O$ (374.24): C, 80.17; H, 8.07; N, 7.48. Found: C, 80.02; H, 8.11; N, 7.51 %.

1-Phenylethyl-3-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (142i).



This compound is obtained as pale yellow solid in 62% yield, mp 95^{0}C; IR (KBr): 1530, 1623cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.96 (s, 6H), 2.05 (s, 2H), 2.14 (s, 2H), 2.77-2.81 (t, 2H, J=5.1Hz), 3.42-3.51 (t, 2H, J=5.1Hz), 3.60 (s, 2H), 3.95 (s, 2H), 7.06-7.30 (m, 9H); ^{13}C NMR (CDCl$_3$): δ 28.66, 32.00,32.47, 35.96, 39.13, 47.37, 49.24, 50.72, 55.72, 69.83, 102.21, 126.22, 126.95, 128.46, 128.71, 137.94, 139.84, 157.14, 193.21; MS: m/z 395.6 (MH$^+$). Anal. Calc. for $C_{24}H_{27}ClN_2O$ (394.18): C, 72.99; H, 6.89; N, 7.09. Found: C, 73.15; H, 6.84; N, 7.05 %.

1-Phenylethyl-3-benzyl-7,7-dimethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline (142j).



This compound is obtained as brown gum in 76% yield; IR (KBr): 1559, 1602 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.99 (s, 6H), 2.09 (s, 2H), 2.15 (s, 2H), 2.74-2.78 (t, 2H, J=7.2Hz), 3.37-3.44 (t, 2H, J=7.2Hz), (3.60 (s, 2H), 3.66 (s, 2H), 3.93 (s, 2H), 7.15-7.36 (m, 10H); MS: m/z 375.2 (MH$^+$). Anal. Calc. for $C_{25}H_{30}N_2O$ (374.24): C, 80.17; H, 8.07; N, 7.48. Found: C, 80.03; H, 8.05; N, 7.51%.

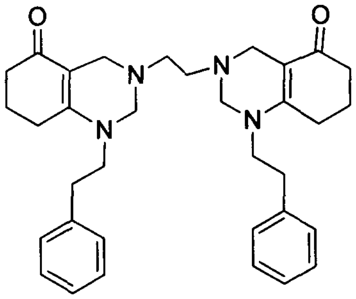
2.7.6 Synthesis of bis-quinazolines 143a-f & 144a-d

General procedure:

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1.5 mL methanol was shaken at room temperature for 5 minutes. To this mixture, a solution of enaminone **2** (1 mmol) in 5 mL methanol was added in one lot and the resulting mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (monitored by tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) yielding **143a-f & 144a-d** in 51-79% yields.

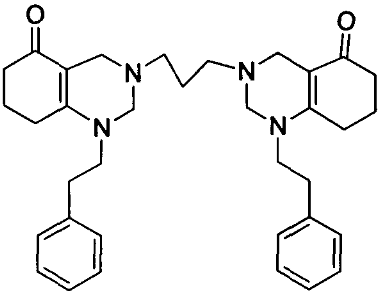
2.7.7 Description of the individual compounds

3,3′-(Ethane-1,2-diyl) bis (1-phenylethyl -5-oxo-1,2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (143a).



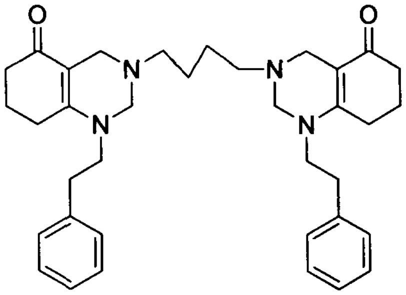
This compound is obtained as brown gum in 71% yield; IR (KBr): 1597, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.73-1.94 (m, 4H), 2.16-2.29 (m, 8H), 2.54 (s, 4H), 2.73 (s, 4H), 3.36 (s, 4H), 3.44 (s, 4H), 3.93 (s, 4H), 7.09-7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.36, 25.32, 35.56, 35.75, 47.31, 50.97, 51.28, 70.41, 103.05, 126.95, 128.72, 128.77, 128.84, 137.91, 159.91,159.06,193.74; MS: m/z 539.7 (MH$^+$). Anal. Calc. for $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.96; H, 7.81; N, 10.46 %.

3,3′-(Propane-1,3-diyl) bis (1-phenylethyl-5-oxo-1,2,3, 4, 5, 6, 7, 8-octahydroquinazoline) (143b).



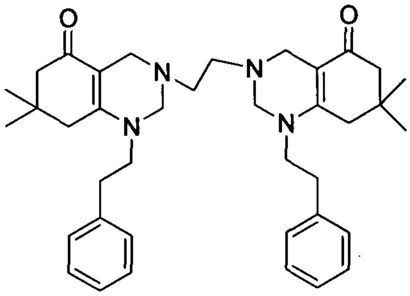
This compound is obtained as brown gum in 68% yield; IR (KBr): 1560, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.66-1.75 (m, 4H), 2.06-2.10 (m, 8H), 2.44-2.47 (m, 4H), 2.73-2.76 (m, 4H), 3.37-3.40 (m, 8H), 3.81 (s, 4H), 7.09-7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.34, 25.33, 25.77, 29.69, 35.61, 35.72, 48.18, 51.00, 51.56, 69.57, 103.80, 126.92, 128.82, 137.98, 158.82, 193.61; MS: m/z 553.7 (MH$^+$). Anal. Calc. for $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.14. Found: C, 76.20; H, 8.09; N, 10.08%.

3,3′-(Butane-1,4-diyl) bis (1-phenylethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (143c).



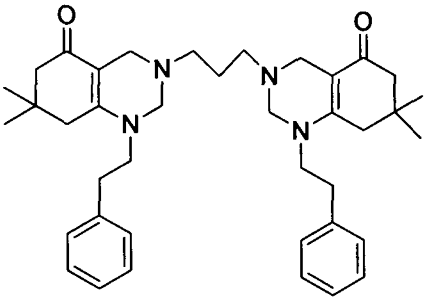
This compound is obtained as brown gum in 59% yield; IR (KBr): 1587, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50 (s,4H), 1.73-1.76 (m, 4H), 2.10-2.19 (m, 8H), 2.34 (s, 4H), 2.73-2.77 (m, 4H), 3.37 (s, 8H), 4.19 (s, 4H), 7.12-7.26 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 21.37, 25.34, 25.46, 30.94, 35.63, 35.73, 47.84, 50.97, 53.50, 69.84, 103.84, 126.91, 128.79, 128.81, 137.99, 158.77, 193.61; MS: m/z 567.8 (MH^+). Anal. Calc. for $C_{36}H_{46}N_4O_2$ (566.36): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.50; H, 8.24; N, 10.08 %.

3,3′-(Ethane-1,2-diyl) bis (1-phenylethyl-7,7-dimethyl -5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (143d).



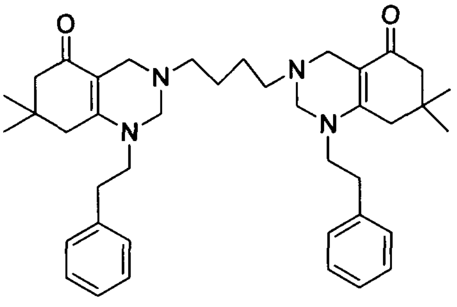
This compound is obtained as yellow solid in 65% yield, mp 90^{0}C; IR (KBr): 1547, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 12H), 2.08 (s, 4H), 2.14 (s, 4H), 2.61 (s, 4H), 2.80-2.85 (t, 4H, J=6.9Hz), 3.47-3.94 (t, 4H, J=6.9Hz), 3.55 (s, 4H), 4.03 (s, 4H), 7.18-7.36 (m, 10H); MS: m/z 595.8 (MH^+). Anal. Calc. for $C_{38}H_{50}N_4O_2$ (594.39): C, 76.73; H, 8.47; N, 9.42. Found: C, 76.52; H, 8.51; N, 9.47 %.

3,3′-(Propane-1,3-diyl) bis (1-phenylethyl-7,7-dimethyl -5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (143e).



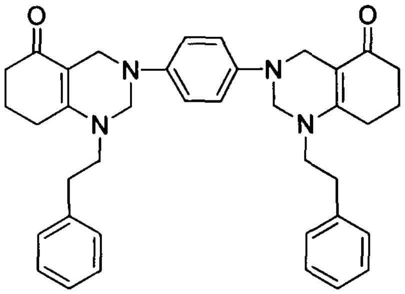
This compound is obtained as brown gum in 75% yield; IR (KBr): 1556, 1651cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.98 (s, 12H), 1.74-1.78 (m, 2H), 2.04 (s, 4H), 2.12 (s, 4H), 2.50-2.55 (t, 4H, J=7.2Hz), 2.80-2.84 (t, 4H, J=7.2Hz), 3.44 (s, 4H), 3.59 (s, 4H), 3.95 (s, 4H), 7.18-7.35 (m,10H); MS: m/z 609.1 (MH$^+$). Anal. Calc. for $C_{39}H_{52}N_4O_2$ (608.41): C, 76.93; H, 8.61; N, 9.20. Found: C, 76.76; H, 8.65; N, 9.16 %.

3,3′-(Butane-1,4-diyl) bis (1-phenylethyl-7,7-dimethyl -5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (143f).



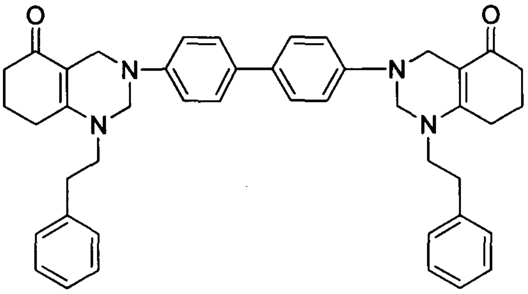
This compound is obtained as brown solid in 72% yield, mp 68^{0}C; IR (KBr): 1557, 1604 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.97 (s, 12H), 1.58 (s, 4H), 1.98 (s, 4H), 2.14 (s, 4H), 2.47 (s, 4H), 2.81-2.85 (t, 4H, J=6.9Hz), 3.45-3.50 (m, 8H), 7.18-7.37 (m, 10H); MS: m/z 623.4 (MH$^+$). Anal. Calc. for $C_{40}H_{54}N_4O_2$ (622.42): C, 77.13; H, 8.74; N, 8.99. Found: C, 77.01; H, 8.78; N, 8.96 %.

3,3′-(1,4-Phenylene) bis (1-phenylethyl-5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydroquinazoline) (144a).



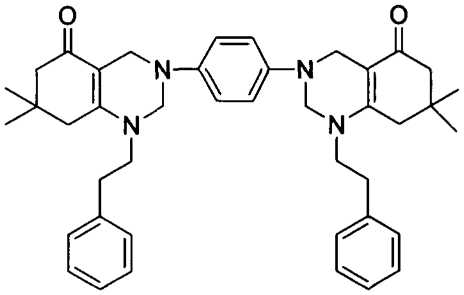
This compound is obtained as brown solid in 51% yield, mp 95^{0}C; IR (KBr): 1557,1632 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25-1.28 (m, 4H), 2.06 (s, 4H), 2.26 (s, 4H), 2.69 (s, 4H), 3.42-3.45 (m, 4H), 3.92 (s,4H), 4.17 (s, 4H), 6.93-7.26 (m, 14H); MS: m/z 587.8 (MH$^+$). Anal. Calc. for $C_{38}H_{42}N_4O_2$ (586.33): C, 77.78; H, 7.21; N, 9.55. Found: C, 77.97; H, 7.24; N, 9.50 %.

3,3′-(Biphenyl-4,4′-diyl) bis (1-phenylethyl -5-oxo-1, 2, 3, 4, 5, 6, 7, 8-octahydro-quinazoline) (144b).



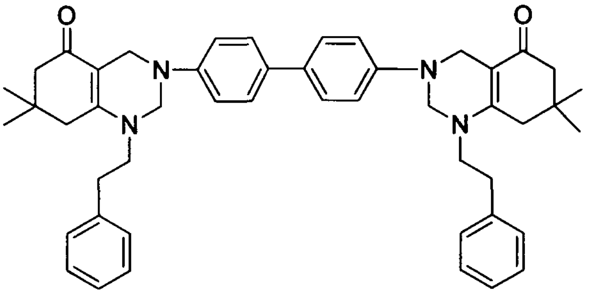
This compound is obtained as brown gum in 61% yield; IR (KBr): 1545, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25-1.28 (m, 4H), 2.06 (s, 4H), 2.26 (s, 4H), 2.69 (s, 4H), 3.42-3.45 (m, 4H), 3.92 (s, 4H), 4.17 (s,4H), 6.93-7.26 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 17.17, 21.35, 25.44, 29.70, 35.57, 36.62, 45.27, 107.99, 126.45, 128.50, 128.63, 128.88, 138.90, 166.46, 194.04; MS: m/z 662.8 (MH$^+$). Anal. Calc. for $C_{44}H_{46}N_4O_2$ (662.36): C, 79.73; H, 6.99; N, 8.45. Found: C, 79.55; H, 7.02; N, 8.40 %.

3,3′-(1,4-Phenylene) bis (1-phenylethyl-7,7-dimethyl -5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline) (144c).



This compound is obtained as brown solid in 65% yield, mp 88^{0}C; IR (KBr): 1549, 1605 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.86 (s, 12H), 1.88 (s, 4H), 2.11 (s, 4H), 2.65-2.69 (t, 4H, J=7.8Hz), 3.39-3.43 (t, 4H, J=6.4Hz), 4.09 (s, 4H), 4.59 (s,4H) 7.21-7.27 (m, 14H); MS: m/z 643.3 (MH$^+$). Anal. Calc. for $C_{42}H_{50}N_4O_2$ (642.39): C, 78.47; H, 7.84; N, 8.72. Found: C, 78.61; H, 7.89; N, 8.75 %.

3,3′-(Biphenyl-4,4′-diyl) bis (1-phenylethyl-7,7-dimethyl -5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) (144d).



This compound is obtained as brown solid in 79% yield, mp 88^{0}C; IR (KBr): 1538, 1609 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.92 (s, 12H), 2.11 (s, 4H), 2.37 (s, 4H), 3.25-3.29 (t, 4H, J=7.2Hz), 3.41-3.46 (m, 4H), 4.17 (s, 4H), 4.62 (s, 4H), 6.91-7.48 (m,18H); ^{13}C NMR (CDCl$_3$): δ 13.64, 22.20, 28.02, 28.28, 28.87, 29.20, 31.43, 31.75, 38.89, 41.17, 45.73, 48.78, 49.52, 70.49, 103.24, 128.29, 128.44, 155.35, 192.80; MS: m/z 719.7 (MH$^+$). Anal. Calc. for $C_{48}H_{54}N_4O_2$ (718.42): C, 80.19; H, 7.57; N, 7.79. Found: C, 80.05; H, 7.54; N, 7.82 %.

2.7.6 Conclusion:

The part of the chapter describes an efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis- octahydroquinazolines from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

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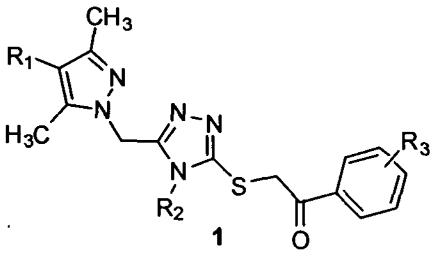
Chapter-III

Synthesis of 1,1'-(alkanediyl) bis (5-oxo-3-alkyl/aryl/aralkyl-1,2,3,4,7,8-octahydroquinazoline)

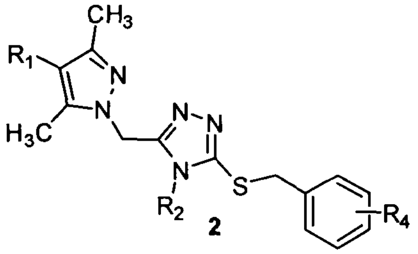
Introduction

Literature reports have highlighted the fact that many molecular hybrids have been synthesized and some of these compounds have been found to be biologically more active than their monomer counter parts. The following paragraphs describe some of these molecules.

3.1.1: F. Q. He and co-workers have reported[1] the synthesis of bis-heterocyclic pyrrodiazole derivatives containing pyrazole (**1** and **2**). Some of these compounds exhibited certain herbicidal activities against barnyard grass and rape.



1



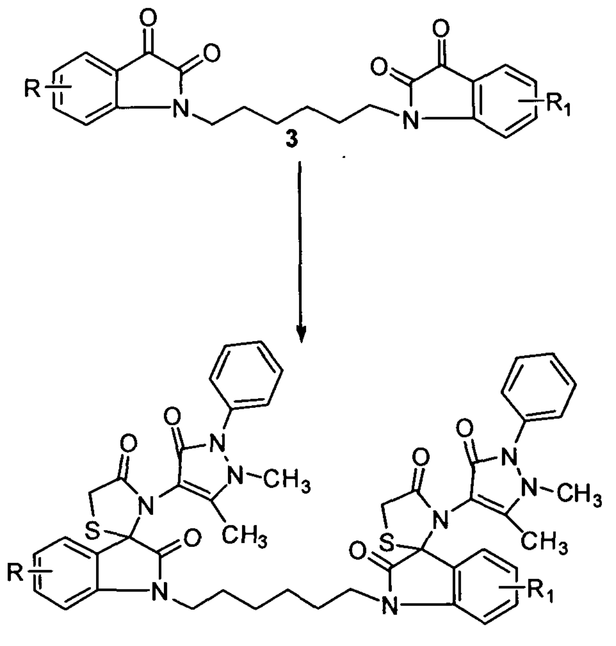
2

Where R_1 = H, NO_2 R_2 = Ph, CH_3

R_3 = H, 2,4-Cl_2, 2-F, 4-(Cl, Br, CH_3, OMe)

R_4 = 2-F, 2,4-Cl_2

3.1.2 S.C. Jain and co-workers have reported[2] the synthesis of some unsymmetrical bis-indol-2, 3-dione (**3**), which was further used for the synthesis of bis-spiroindoles (**4**).

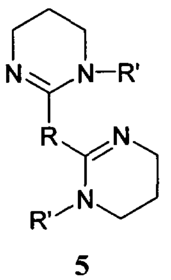


3

R, R_1 = CH_3, H or F

4

3.1.3a Henry and Thomson reported[3] that condensation of 2 mmols of an alkylene polyamine having at least one primary amino group separated from another primary or secondary amino group by 3 carbon atoms with one mole of dicarboxylic preferably at 350°F to 400°F to give tetrahydropyrimidine derivative of the structure (5) given below. The water molecules formed are removed azeotropically using benzene, toluene or xylene.

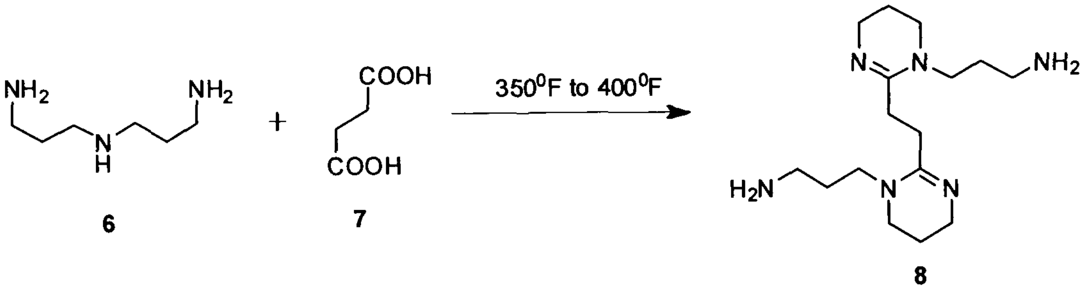


5

R: hydrocarbon radical containing at least 2 carbon atoms.

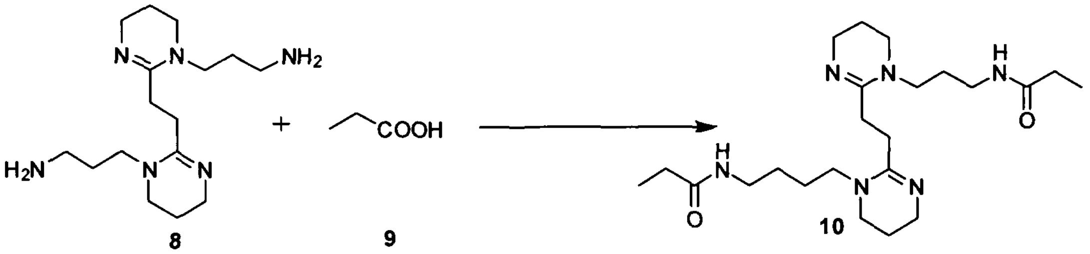
R': hydrogen, a hydrocarbon or a substituted hydrocarbon radical.

3.1.3b For example, the condensation of two moles of 3,3'-imino-bis-propylamine (**6**) with 1 mole of succinic acid (**7**) gave the corresponding bis-tetrahydropyrimidine (**8**) whose IUPAC name was 3,3'-(2,2'-(ethane-1,2-diyl)bis(5,6-dihydropyrimidine-2,1(4H)-diyl))dipropan-1-amine (**Scheme 1**).



Scheme1

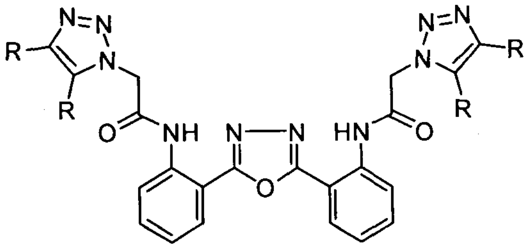
Further the compound **8** when reacted with carboxylic acid (**9**) (for e.g. 2mols of priopionic acid) gave the product having amide linkage. (**10**) (**Scheme 2**).



Scheme 2

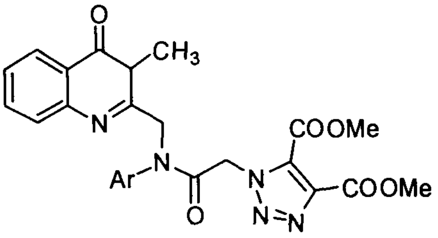
These bis tetrahydropyrimidines (**8**, **10**) were used for stabilizing hydrocarbon distillate (for example, fuel oil, burner oil, range oil, diesel oil, marine oil, slushing oil, turbine oil) by preventing sediment formation (or dispersing them when formed), preventing discoloration, oxidation inhibitor, rust or corrosion preventative, and detergent properties. In lubricating oil the additive may function as pour point depression, viscosity index improver, antifoaming agent, oil ness additive etc. In gasoline, naphtha, aromatic solvents, kerosene, jet fuel etc it acts as corrosion inhibitor along with above mentioned properties[3].

3.1.4 P.S.N. Reddy and co-workers have reported[4] the synthesis of bis-heterocycles of the type (**11**) and (**12**).



R = COOMe

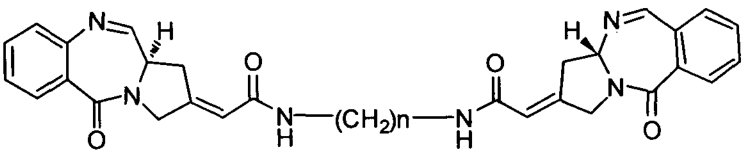
11



Ar = subst-aryl group

12

3.1.5 J.W. Lown and co-workers have reported[5] the synthesis of bi-functional DNA alkylating C_2-linked pyrrolo [2, 1-c][1, 4] benzodiazepines (**13**).

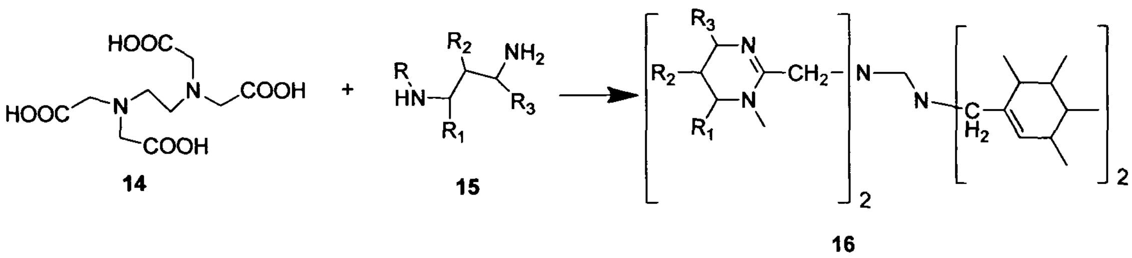


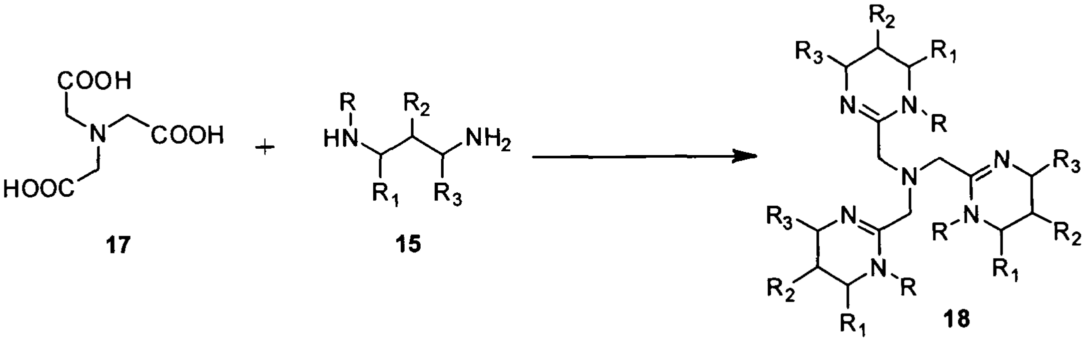
n = 3,4,5

13

These were synthesized in order to probe DNA cross-linking efficiency and structural requirements for the optimum interstrand cross-linking as well as cytotoxicity.

3.1.6 1,4,5,6-tetrahydropyrimidinyl substituted compounds were also found to be useful as ash-less bases and rust inhibitors, these bis or tris THP are prepared by reacting a C_3 to C_{50} amine containing 1,3-diaminopropane (**15**) group with ethylenediaminetetraceticacid (EDTA)(**14**) or nitrilotriacetic acid (**17**) at a temperature of 150^0C to 250^0C for 10 to 100 hours[7] (**Scheme 3**).





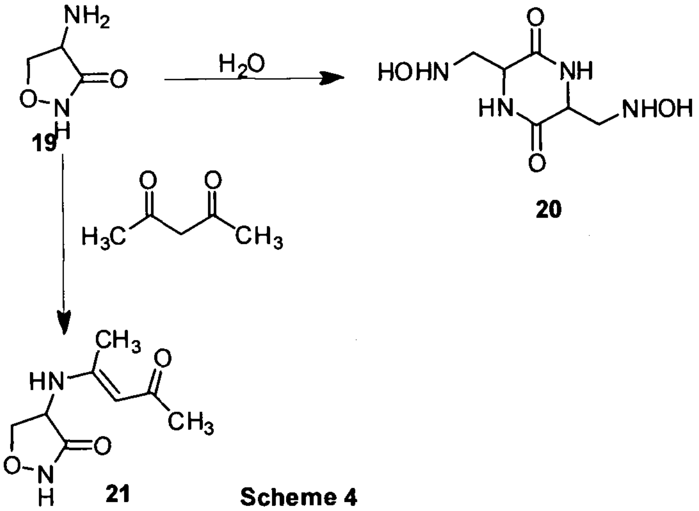
R, R$_1$, R$_2$, R$_3$, R$_4$: H-atom or alkyl group.

Scheme 3

3.2 Synthesis of enaminones

Enaminones are potential intermediates for the synthesis of a variety of heterocyclic systems like oxazoles, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, tetrahydrophenanthridines, pyranones, pyridine derivatives[7-9]etc.

3.2.1 Unlike enamines, which have been reported to be unstable in aqueous solutions[10-15], enaminones, obtained from β-dicarbonyl compounds are quite stable and have been employed as prodrugs with variable results. For example, acetyl acetone has been used to prepare a prodrug of Cycloserine [16]. Cycloserine (**19**) is known to be unstable and has a tendency to form a dimer (**20**) as shown **Scheme 1.** Preventing the formation of dimer would increase the stability both on the shelf and in physiological media.

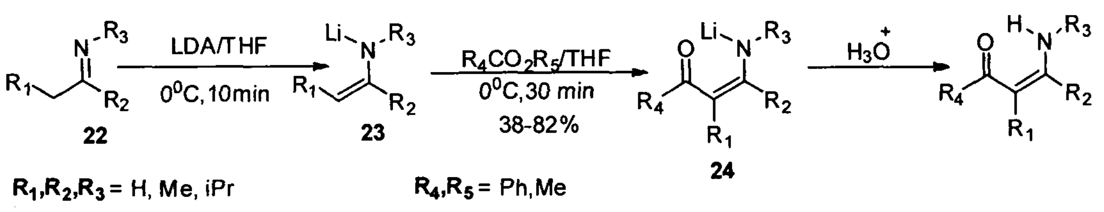


Scheme 4

Since the formation of the dimer (**20**) requires a reaction of the amino group of cycloserine, functionalization of this amino group was the easiest and most direct approach to retarding the dimer formation. Stirring a mixture of cycloserine and acetylacetone for 2 days gave *(R)*-4-[(1-methyl-3-oxo-1-butenyl)-amino]-3-isoxazolidinone (**21**), which was the condensation product of cycloserine and acetyl acetone and was found to be an efficacious prodrug of increased stability under aqueous conditions.

3.2.2 There are also reports of the potential use of enaminones for biological purpose, Scheone and coworkers[17] have prepared several enaminones and evaluated them for hypoglycaemic effectiveness, but their compounds gave poor activity.

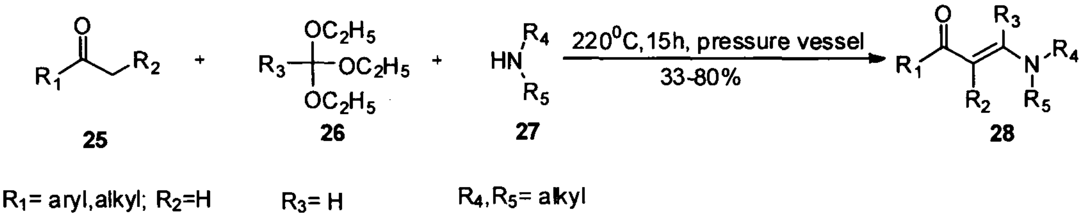
3.2.3 A number of synthetic strategies for the synthesis of enaminones are known in the literature. A few recent methods are discussed in the following sections.The reaction of α- metallated amines with esters under mild conditions leads to the formation of enaminoketones (also called unsymmetrical diketones)



Scheme 5

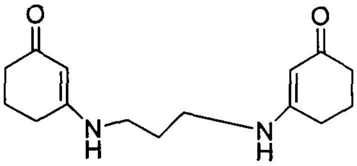
When imine anions **23** prepared from imines (**22**) (**Scheme 5**, by standard method) is allowed to react with esters at O°C in THF for 30 minutes, enaminoketones (**24**) were obtained. A twofold excess of base is required for the reaction to go to completion indicating that a second equivalent of lithum derivative preferentially metallates the imine nitrogen atom of compound **24** as soon as it forms .The anionic form of **24** prevents it from further nucleophillic attack by the imine anions[18].

3.2.4 β-amino-α,β unsaturated ketones (**28**) (β-acylenamines) were obtained in a mannich reaction by heating a mixture of ketone (**25**), triethylorthoformate (**26**), and secondary amine (**27**) in a pressure vessel. Triethylorthoacetate can also be used with good results, but the method failed with symmetrical ketones like acetone and cyclohexanone. Coupling constant *J CH=CH* (12Hz) suggests the trans configuration[19] (**Scheme 6**).



Scheme 6

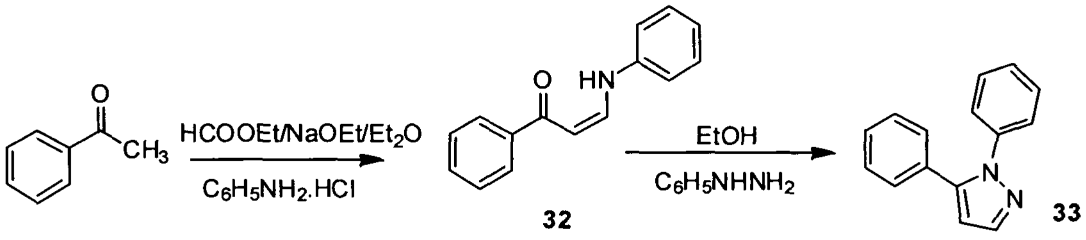
3.2.5 When N-1-(2, 2'-dichloro-1-phenylpropylidene) aniline (**29**) was treated with 2N sodium methoxide in MeOH and refluxed for overnight and the reaction mixture was hydrolysed with excess of aqueous 2N HCl for overnight, the etheral extract gave after evaporation, an oil from which a yellow solid material precipated on standing. The filtrate contained two compounds, namely, 2-methoxy-1-phenyl-2-propen-1-one (**30**) and 1-phenyl-1, 2-propane dione (**31**). The solid product was identified as 3-anilino-1-phenyl-2-propen-1-one (**32**) (**Scheme 7**).



Scheme 7

The structure elucidation of enaminoketone (**32**) was supported by the synthesis of the authentic materials.

3.2.6 Reaction of ethyl formate and acetophenone with sodium ethoxide in ethereal medium gave the sodium salt of benzoylacetaldehyde, which was condensed with aniline hydrochloride (and p-anisidine hydrochloride) to yield β ketoenamines (**32**), an additional confirmation of the formation of (**32**) was the conversion of (**32**) into 1,5-diphenylpyrazole by reacting with phenyl hydrazine[20] (**33**) (**Scheme 8**).

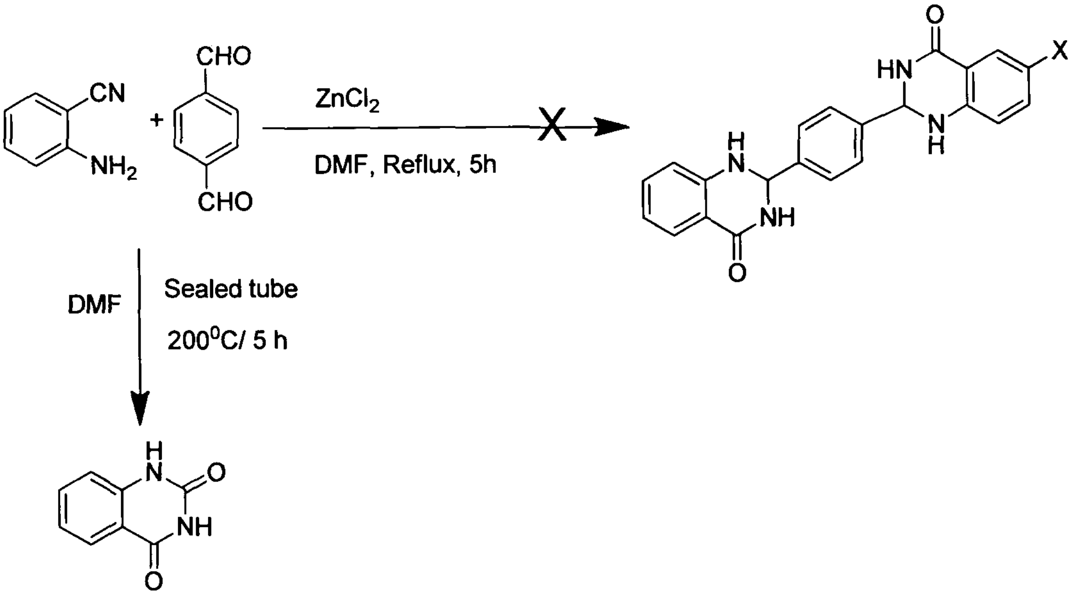


Scheme 8

In order to prepare bis quinazolines of our interest we needed the starting material bis-enaminones, which we easily prepared by following our previous strategy.

Microwave assisted organic reactions have blossomed into an important tool; with a variety of applications, particularly after the development of Microwave- induced Organic Reaction Enhancement (MORE) chemistry techniques[21-22]. These techniques require open vessels with little or no solvent and are free of the risk of explosion. MORE chemistry reaction lead to extremely faster, cleaner than conventional reaction and lead to higher atom economy (less chemical waste). Because of short time requirement, ease of workability and eco-friendliness, microwaves provide an alternative to environmentally unacceptable procedures using toxic and expensive reagents[23].

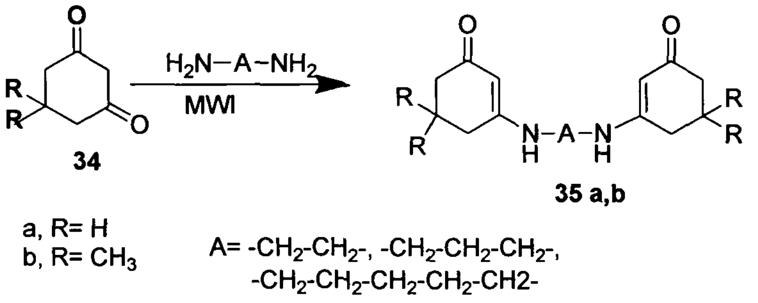
3.2.7 Li Jiarong and co-workers in continuation to their previous research of cyclocondensation of aromatic *o*-aminonitriles with ketones under the catalysis of $ZnCl_2$, a new conversion to form 1,2-dihydroquinazoline-4(3*H*)-one derivatives was found coexisting with the normal Friedlalinder-type quinoline annulation.[25] Thus, they thought similar 1,2-dihydroquinazoline-4(3*H*)-ones could be afforded by the reaction of *o*-aminonitriles with aromatic aldehydes through this conversion. To their surprise, the reaction of 2-aminobenzonitrile with terephthalaldehyde in the sealed reactor under the catalyst of $ZnCl_2$ (0.1 mol %) at 200 °C afforded a white product instead of the expected symmetrical bisdihydroquinazolin-4(3*H*)-one and this product was characterized as quinazoline-2,4(1*H*,3*H*)-dione [26]on the basis of its spectra and analytical data. Moreover, its structure was further confirmed by X-ray crystallographic diffraction and compared with the authentic sample. In fact, the reactant, terephthalaldehyde, could be completely recovered from the reaction mixture. Thus, they speculated DMF was involved in the reaction. To their delight, **33** were obtained as the only product with the same reaction in the absence of terephthalaldehyde (**Scheme 9**). To obtain the optimal reaction conditions, a variety of catalysts were first investigated for detecting the catalytic activities of different metal ions for the product of **33**. The data indicated that $ZnCl_2$ is the most effective.



Scheme 9

3.3 Synthesis of bis-enaminones:

Bis enaminones (**35a,b**) prepared by the reported procedures[27] as two equivalent of 1,3-cyclohexandione/ 3,3-dimethyl-1,3-cyclohexandione mixed with one equivalent of diamines irradiated in microwave digester at 180 watt for 2-3 minutes to give a deep brown viscous mass, immediately applied pump to remove the water formed then cooled on trituration with methanol it gives light yellowish solid mass of desired bis-enaminone (**35a,b**) and are filtered off and were used as synthons for the construction of bis quinazolines (**Scheme 10**)



Scheme 10

3.3.1 Results and Discussion

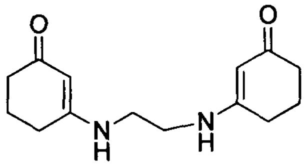
Thus, when a mixture of 1,3-cyclohexanedione (**34a**) and diamine (2:1) was irradiated in a microwave digester for 2 min, work-up of the reaction mixture yielded the desired condensation product **35c-e** in 75-85% yield, which was characterized on the basis of analytical and spectral data. Condensation of dimedone (**34b**) with diamines could be achieved under similar conditions giving **35f-h** in 85-91% overall yields. The reaction of dimedone with ethylene went to completion when a mixture (2:1) of the two was subjected to microwave irradiation. In conclusion, we have demonstrated a practical application of microwave assisted, solvent-free condensation of cyclic ketones with diamines in microwave digester in very good to excellent yields.

3.3.2 General procedure.

A mixture of 1, 3-diketone (2 mmole) and diamine (1 mmole) in a 10 ml conical flask placed in a beaker was irradiated in a microwave digester. After the completion of the reaction (monitored by TLC), water formed during the reaction was distilled under reduced pressure to give a solid mass, which was triturated with methanol, filtered and then recrystallized from appropriate amount of methanol to give the bis-enaminones **35c-h**. The products were identified by IR and NMR spectroscopy and also by comparing their melting points with those of the authentic products.

The description of individual bis- enaminones given below

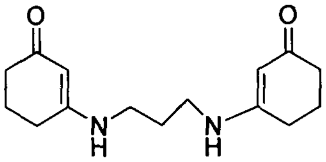
3,3ꞌ-(ethane-1,2-diyl bise (azandiyl) bis (cyclohexan-2-enone) (35c)



This compound was obtained as pale yellow solid in 85% yield; mp 178 ^{0}C; IR (KBr): 1533, 1600, 3257, 3245 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.26-1.30 (m, 6H), 3.02-

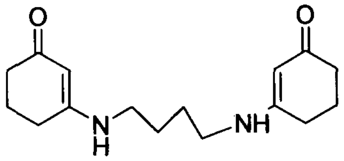
3.04 (m, 4H), 3.56-3.61 (m, 8H), 5.40 (s, 2H); MS: m/z 249.4 (MH^+). Anal. Calcd. for $C_{14}H_{20}N_2O_2$ (248): C, 67.71; H, 8.12; N, 11.28.

3,3'-(propane-1,3-diyl bis(azandiyl) bis (cyclohexan-2-enone) (35d)



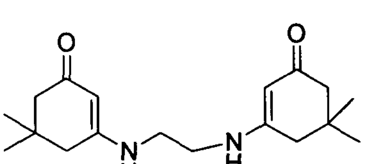
This compound was obtained as pale yellow solid in 78% yield; mp 145 ^0C; IR (KBr): 1537, 1560, 3257, 32445 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54-1.67 (m, 6H), 2.84-2.89 (m, 4H), 3.14-3.18 (m, 4H), 3.56-3.61 (m, 6H), 5.40 (s, 2H); MS: m/z 263.5(MH^+). Anal. Calcd. for $C_{15}H_{22}N_2O_2$ (262.35): C, 68.67; H, 8.45; N, 10.68.

3,3'-(butane-1,4-diyl bis (azandiyl) bis (cyclohexan-2-enone) (35e)



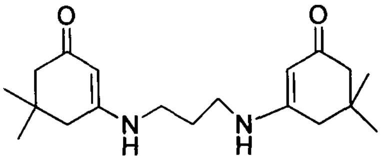
This compound was obtained as pale yellow solid in 75% yield; mp 202 ^0C; IR (KBr): 1531, 1566, 3247, 3243 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26-1.28 (m, 4H), 1.30-1.32 (m, 4H), 3.02-3.08 (m, 6H), 3.56-3.61 (m, 8H), 5.40 (s, 2H); MS: m/z 277.5(MH^+). Anal. Calcd. for $C_{16}H_{24}N_2O_2$ (276.37): C, 69.53; H, 8.75; N, 10.14.

3, 3'-(ethane-1,2-diyl bis (azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35f)



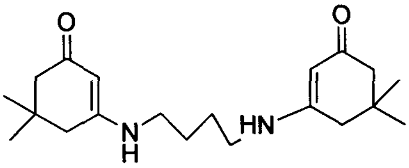
This compound was obtained as pale yellow solid in 91% yield; mp 153^0C; IR (KBr): 1541, 1593, 3257, 3445 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01-1.08 (m, 14H), 2.24 (s, 4H), 2.50-2.55 (m, 4H) 3.56 (s, 4H), 5.46(s, 2H); MS: m/z 305.9 (MH^+). Anal. Calcd. for $C_{18}H_{28}N_2O_2$ (304.22): C, 71.02; H, 9.27; N, 9.20.

3, 3'-(propane-1,3-diyl bis(azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35g)



This compound was obtained as pale yellow solid in 82% yield; mp 173 ^{0}C; IR (KBr): 1545, 1600, 3276, 3456, cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34-1.42 (m, 12H), 1.26 (s, 4H), 2.24 (s, 4H), 2.50 (s, 4H) 3.56 (s, 4H), 5.45 (s, 2H); MS: m/z 319.3(MH$^+$). Anal. Calcd. for $C_{19}H_{30}N_2O_2$ (318.23): C, 71.66; H, 9.50; N, 8.80.

3,3'-(butane-1,4-diyl bis(azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35h)

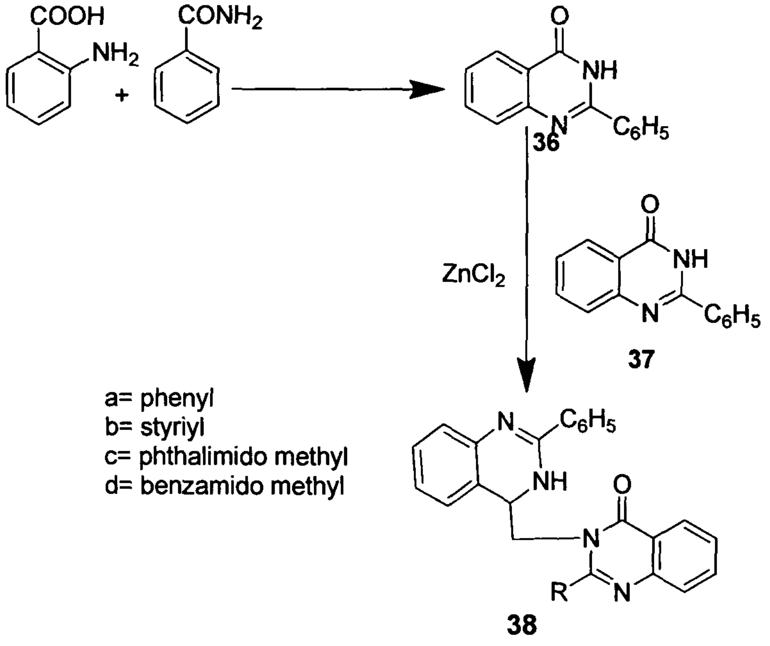


This compound was obtained as pale yellow solid in 85% yield; mp 168 ^{0}C; IR (KBr): 1537, 1560, 3331, 3343 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01-1.04 (m, 12H), 1.26-1.28 (m, 4H), 3.02-3.04 (m, 8H), 3.52 (s, 4H), 5.40 (s, 2H); MS: m/z 333.6 (MH$^+$). Anal. Calcd. for $C_{20}H_{32}N_2O_2$ (332.25): C, 72.25; H, 9.70; N, 8.43.

3.4: Synthesis of bis quinazolines:

Our literature survey has revealed that Bis-quinazolines compounds are a relatively new and important in the field of research for finding new biologically active molecules. Recent reports have revealed that bis-quinazolines compounds possess pesticidal propertiesand also antibacterial, antimalarial, antiproliferative and antitumor activities. Envisaging that the presence of two quinazoline ring in the same molecule connected by flexible aliphatic chain at 1,1′ position could enhance the activity of the molecule. Bis-enaminones were reacted with formaldehyde and various diamines and the result of which are discussed herein.

3.4.1 Anjani K. Tiwari and co-workers rported[28] the synthesis of bis quinazoline of the type (**38**) by condensation of 2-phenyl-4(3*H*)-quinazolone and 2-aryl-3-amino-4(3*H*)-quinazolones (**37**) in presence of anhydrous $ZnCl_2$catalyst where they have connected the two quinazoline rings at 4 and 3 positions through secondary amine linkage. The brief procedure is given below Synthesis of 3-(0-phenyl-quinazolin-4-yl-amino)-2-(phenyl/styryl/benzamidomethyl/phthalimidomethyl)-4(3*H*)-quinazolones (**38a-d**)The target compounds (**38a-d**) were synthesized by heating equimolar quantities of 2-phenyl-4(3H)-quinazolone and 2-aryl-3-amino-4(3H)-quinazolone (**37**) containing anhydrous zinc chloride (1.0 g) at 130 to 140 ^{0}C for 4 h. During heating, the contents were stirred occasionally. Subsequently, the hot melt was cooled to room temperature, treated with diluted hydrochloric acid (w100 ml) and then stirred vigorously. The solid was filtered off and washed with cold water. After removing water, it was dissolved in ethanol and treated by charcoal. The solvent was evaporated in vacuo and the crystalline product was washed with ethanol and dried (**Scheme 11**).

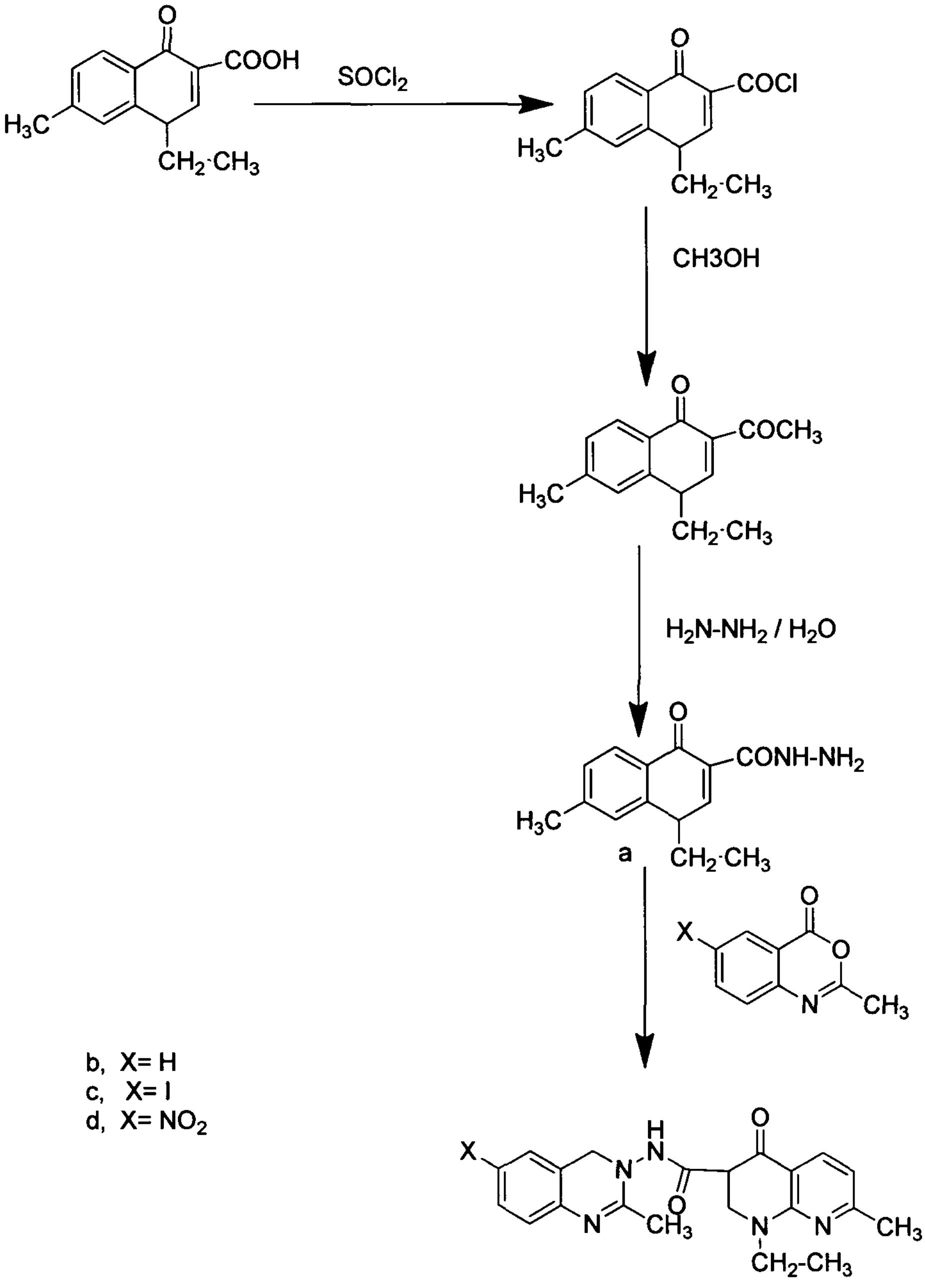


Scheme 11

The bis-quinazoline derivatives so prepared found to be active against many bacterial and fungal strains.

3.4.2 G. Grover and co-workers in the process of synthesis of biheterocycles[29] carrying the biodynamic heterocyclic systems at position 3, a series of new nalidixic acid derivatives having quinazolones moiety were synthesised to achieve enhanced biological activity and wide spectrum of activity. Nalidixic Acid was first converted into its acid chloride using thionyl chloride as an acylating agent at laboratory temperature later it was converted to methyl ester. Nalidixoyl chloride formed vigorously reacts with methanol to give a methyl ester of nalidixic acid. The ester on addition of hydrazine hydrate furnished nalidixic acid hydrazide. Appropriate anthranilic acid was refluxed with acetic anhydride to form Benzoxazine/ Acetanthranil. 5-iodo-derivative of anthranilic acid was prepared and also utilised to obtain 6-iodo-benzoxazine/Acetanthranil. Also, 6-nitro benzoxazine/Acetanthranil was obtained by nitration of acetanthranil using conc. H_2SO_4 and fuming HNO_3. Equimolar proportions of the appropriate synthesised acetanthranils and nalidixic acid hydrazide in the presence of ethanol were refluxed to synthesise quinazolones. Elemental analysis and IR spectra confirmed nalidixic acid hydrazide formation. The structures of the compounds obtained have been established on the basis of Spectral (IR, ^1H NMR and mass) data. The current study also involves in vitro antimicrobial screening (using Agar dilution and Punchwell diffusion method) of synthesised quinazolone derivatives bearing nalidixic acid moiety on randomly collected microbial strains. The derivatives **39a, b & d** showed marked inhibitory activity against enteric pathogen like Aeromonas hydrophila, acausative agent of diarrhoea in both children as well as adults. Among the respiratory pathogens included in study, derivative d was found to be active against *Streptococcus pyogenes.* No significant inhibitory activity was seen by any of synthesised derivatives against *Coagulase negative Staphylococcus.* Derivative **39a** was found to show very high activity against the *Candida colonies* and derivative **39d** was also found to exhibit inhibitory activity against *Candida albicans;* a normal flora of the human body which plays an important role in causing opportunistic infections inimmunocompromised hosts.

Proteus vulgaris, a gram-negative bacteria included in our study was found to be inhibited by derivative **39b.**

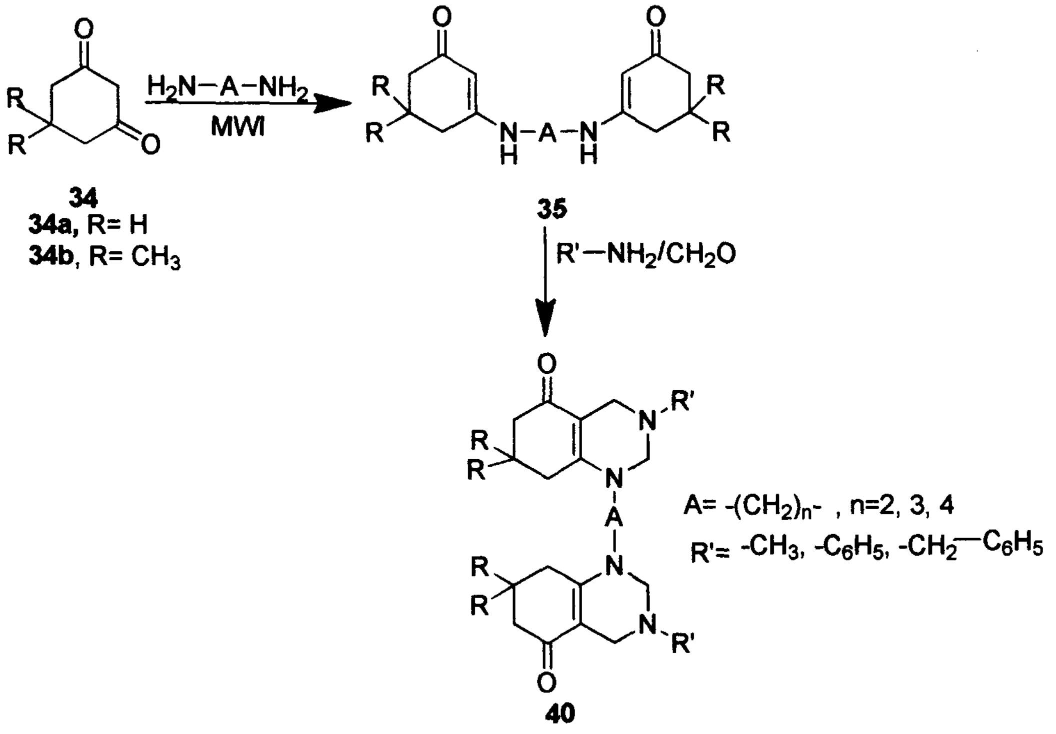


39 b, c, d

Scheme 12

3.4.3 Synthesis of 1,1′-(alkanediyl) bis (3-alkyl/aryl/aralkyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines (40a-r).

Prompted by the above observation and in continuation with our on-going programme on the development of novel synthetic strategies for bis-octahydroquinazolines, we undertook the present investigation to synthesis bis-octahydroquinazolines in which we have connected two quinazoline moiety at 1,1′ position unlike previous chapter where we connected two quinazoline ring at 3,3′ position and the results of our studies are reported herein (**Scheme 12**).



Scheme 12

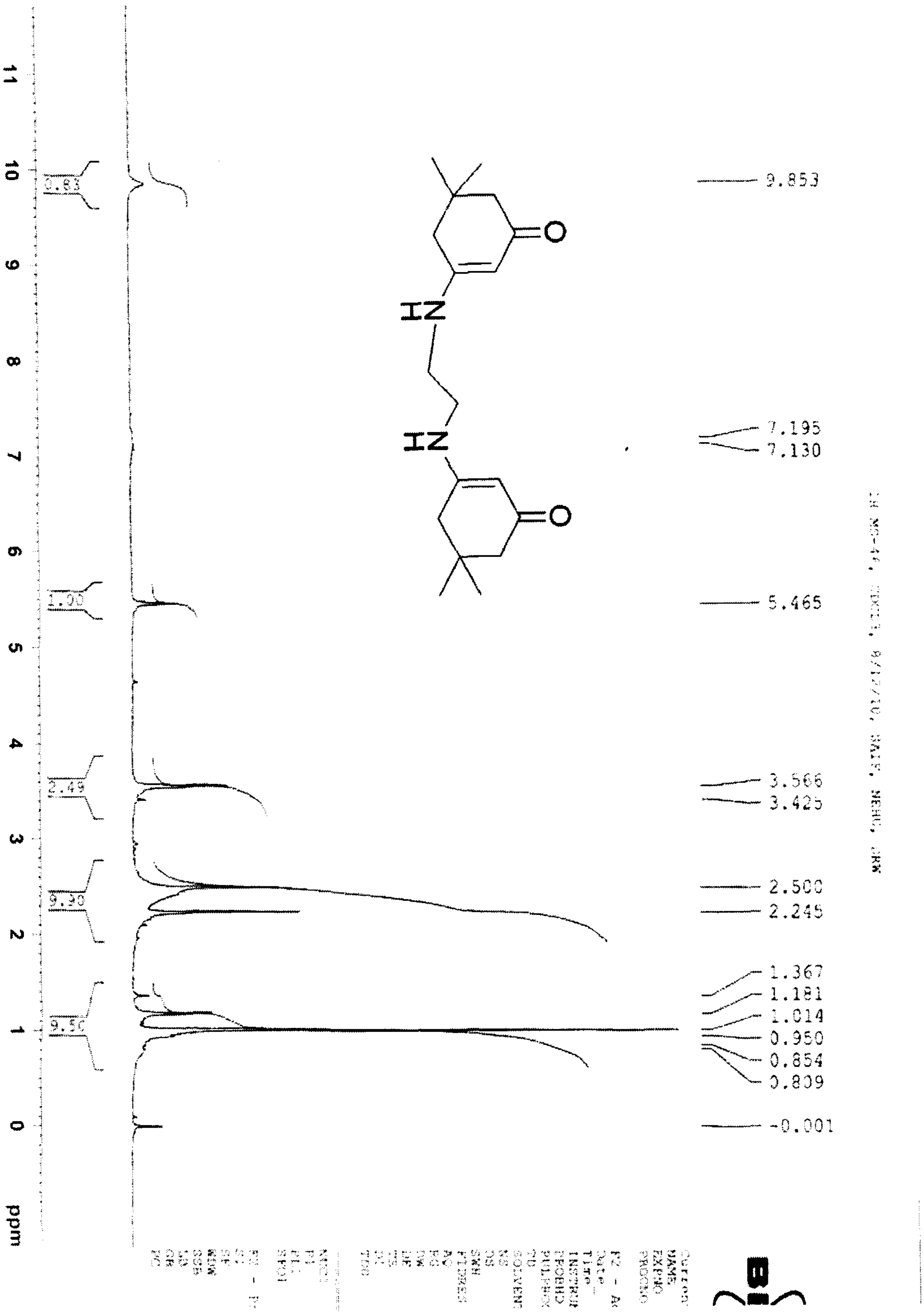
3.4.4: Results and Discussion

Thus, when 3,3′-(ethane-1,2-diyl bis (azandiyl) bis (cyclohexan-2-enone) **35a** was treated with methylamine and formaldehyde refluxed in methanol, a product was obtained in 61 % yields which was characterized as 1,1′-(ethane-1,2-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline **40a** on the basis of analytical and spectral data. The reaction of **35** with other primary amines and formaldehyde behaved in a similar manner and bis-octahydroquinazolines **40b-r** were isolated in 52-73% yields. The infrared spectra of **40a-r** showed strong peaks in the region of 1553 to 1653 cm^{-1} due to extensively delocalized double bonds and carbonyl groups[7]. In the ^1H NMR spectra of **40a-h**, the methylene protons at C-7 appeared as multiplets near 1.89-1.96 ppm except in **40e** and **40f** where they appeared in the vicinity of 1.01-1.18 ppm . The methyl protons at C-7 for **40i-r** gave sharp singlets around 1.05 ppm. Methylene protons at C-2 for **40i-r** resonated at higher δ value than the corresponding **40a-h** which may be due to presence of electronic donating methyl groups at C-7 in **40i-r**. The CH_2 protons at C-8 resonate close to 2.3 ppm except in **40f** and **40h** where they were found to resonate near 1.88 ppm and 1.95 ppm respectively. The rest methylene protons in the quinazoline ring resonated in the region of 3-4 ppm respectively, the aromatic protons appeared in the usual region. The ^{13}C spectra of the molecules showed a sharp signal near 193 ppm due to the carbonyl carbon, the sp^2 hybridised carbon of quinazoline ring along with that of benzene gave signal in the region of 102-156 ppm. The aliphatic carbons appeared in their usual range in the ^{13}C spectrum further all the compounds were verified by their mass spectrum.

Table: Synthesis of 1,1′-(alkanediyl) bis (3-alkyl/aryl/aralkyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines (3a-r).

Comd	R	A	R′	Reflux(hrs)	M.P.°C	Yield%
40a	H	$-CH_2-CH_2-$	$-CH_3$	12	Gum	61
40b	H	$-CH_2-CH_2-$	$-C_6H_5$	14	106	57
40c	H	$-CH_2-CH_2-$	$-CH_2-C_6H_5$	11	115	52
40d	H	$-CH_2-CH_2-CH_2-$	$-CH_3$	15	Gum	56
40e	H	$-CH_2-CH_2-CH_2-$	$-C_6H_5$	17	Gum	58
40f	H	$-CH_2-CH_2-CH_2-$	$-CH_2-C_6H_5$	13	Gum	56
40g	H	$-CH_2-CH_2-CH_2-CH_2-$	$-CH_3$	11	Gum	73
40h	H	$-CH_2-CH_2-CH_2-CH_2-$	$-C_6H_5$	9	Gum	65
40i	H	$-CH_2-CH_2-CH_2-CH_2-$	$-CH_2-C_6H_5$	9	Gum	71
40j	$-CH_3$	$-CH_2-CH_2-$	$-CH_3$	7	Gum	53
40k	$-CH_3$	$-CH_2-CH_2-$	$-C_6H_5$	9	245	61
40l	$-CH_3$	$-CH_2-CH_2-$	$-CH_2-C_6H_5$	8	205	71
40m	$-CH_3$	$-CH_2-CH_2-CH_2-$	$-CH_3$	12	186	73
40n	$-CH_3$	$-CH_2-CH_2-CH_2-$	$-C_6H_5$	10	Gum	58
40o	$-CH_3$	$-CH_2-CH_2-CH_2-$	$-CH_2-C_6H_5$	11	Gum	65
40p	$-CH_3$	$-CH_2-CH_2-CH_2-CH_2-$	$-CH_3$	8	140	70
40q	$-CH_3$	$-CH_2-CH_2-CH_2-CH_2-$	$-C_6H_5$	8.5	Gum	57
40r	$-CH_3$	$-CH_2-CH_2-CH_2-CH_2-$	$-CH_2-C_6H_5$	7	125	73

The ^{1}HNMR, ^{13}C and Mass Spectra of a starting material and few compounds along with the structures are given in the following pages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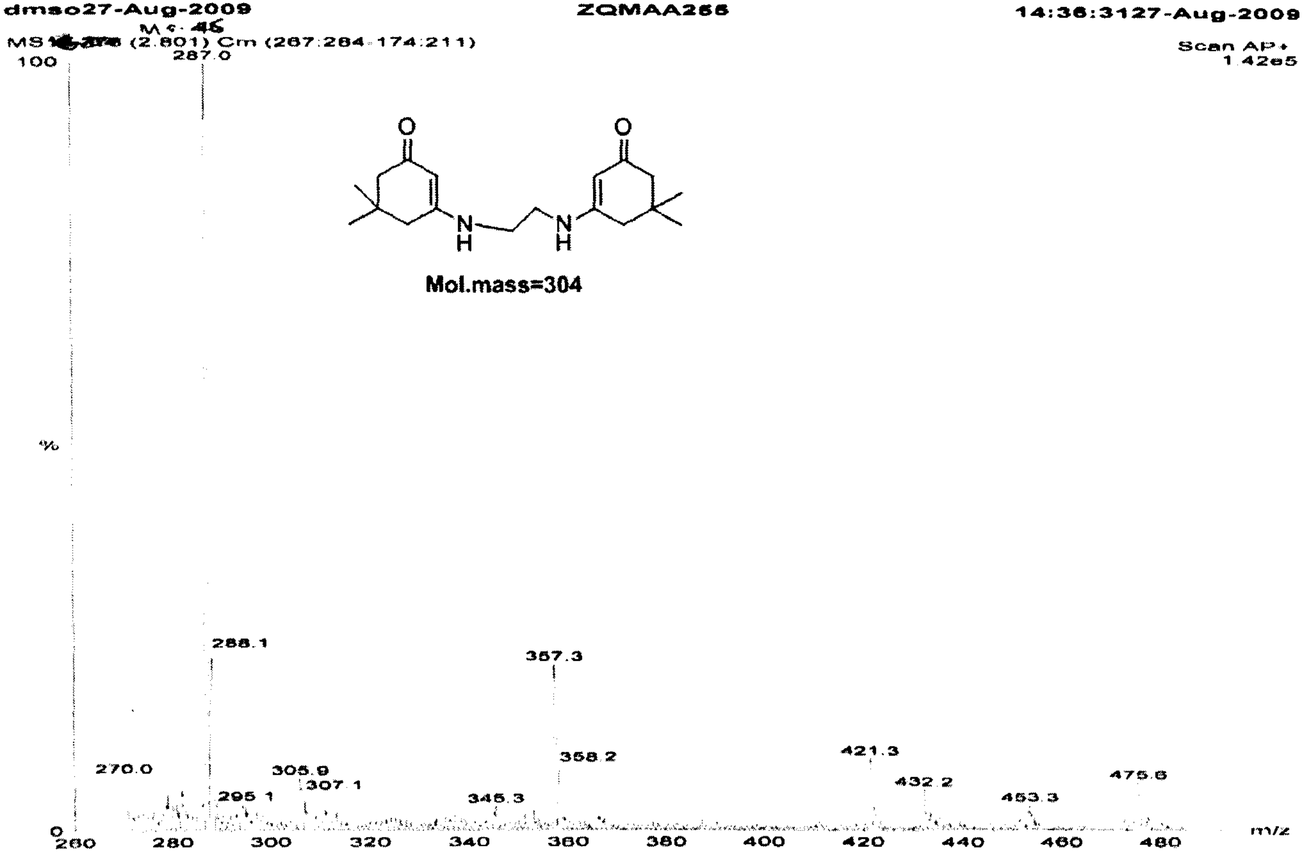
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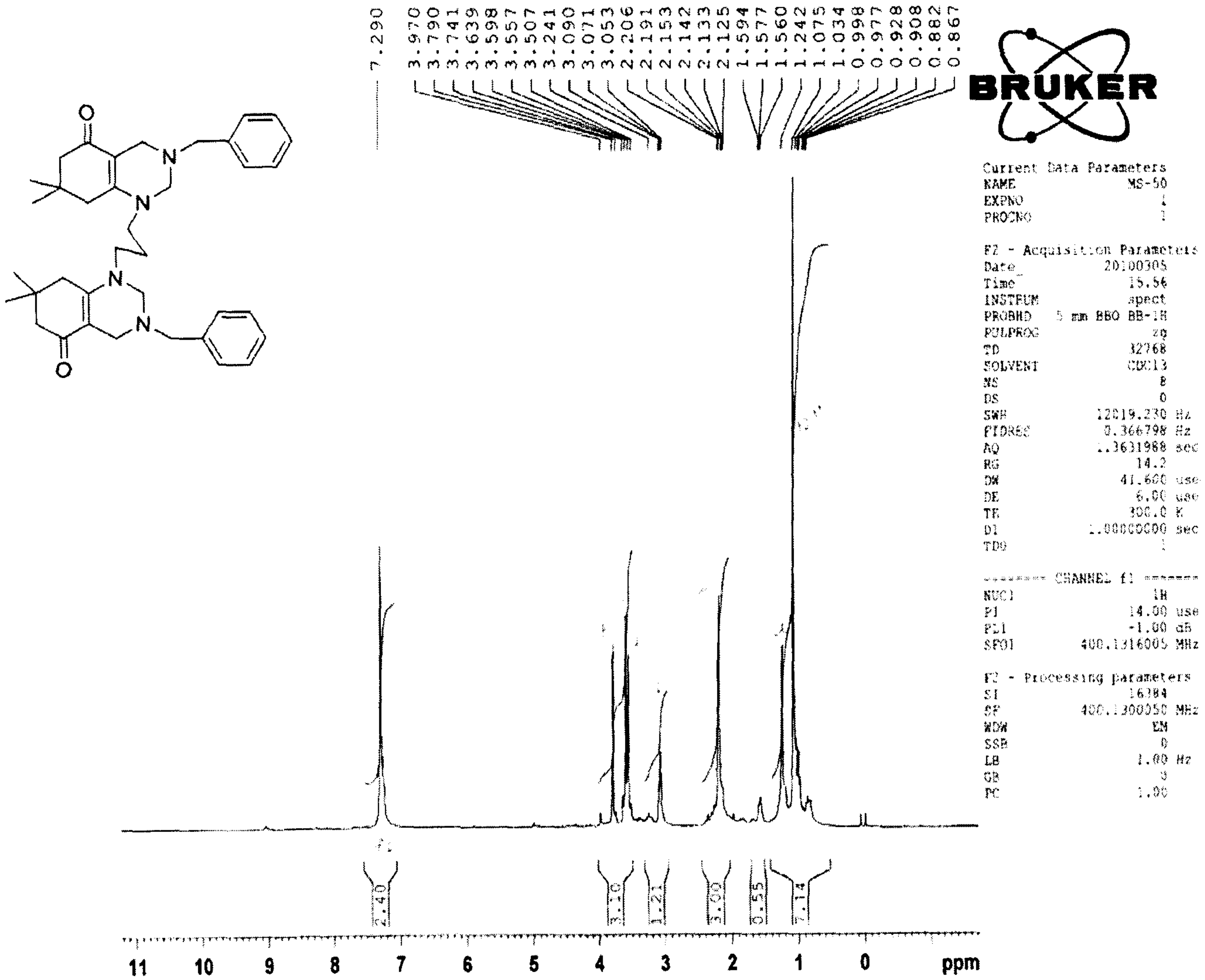

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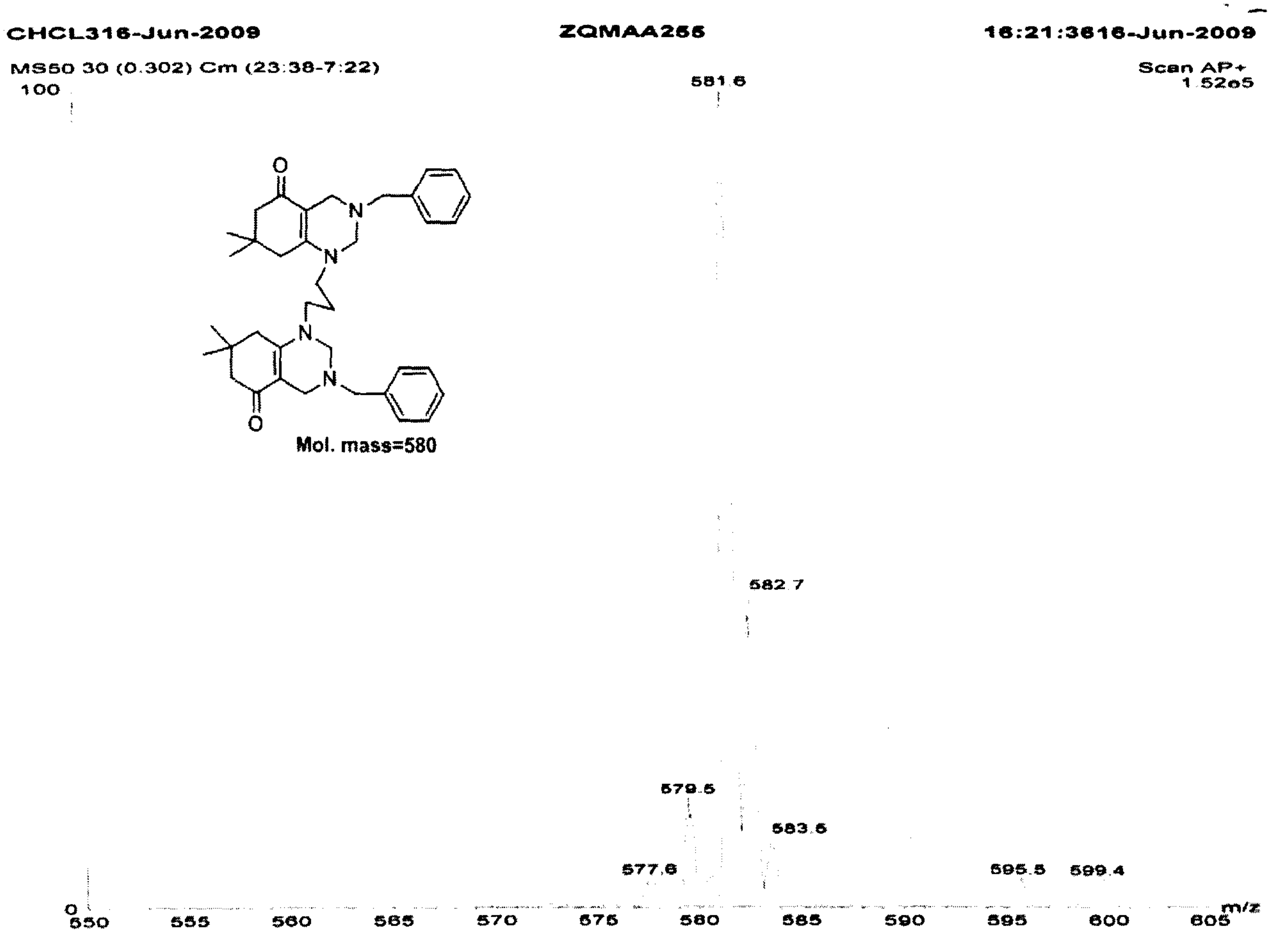
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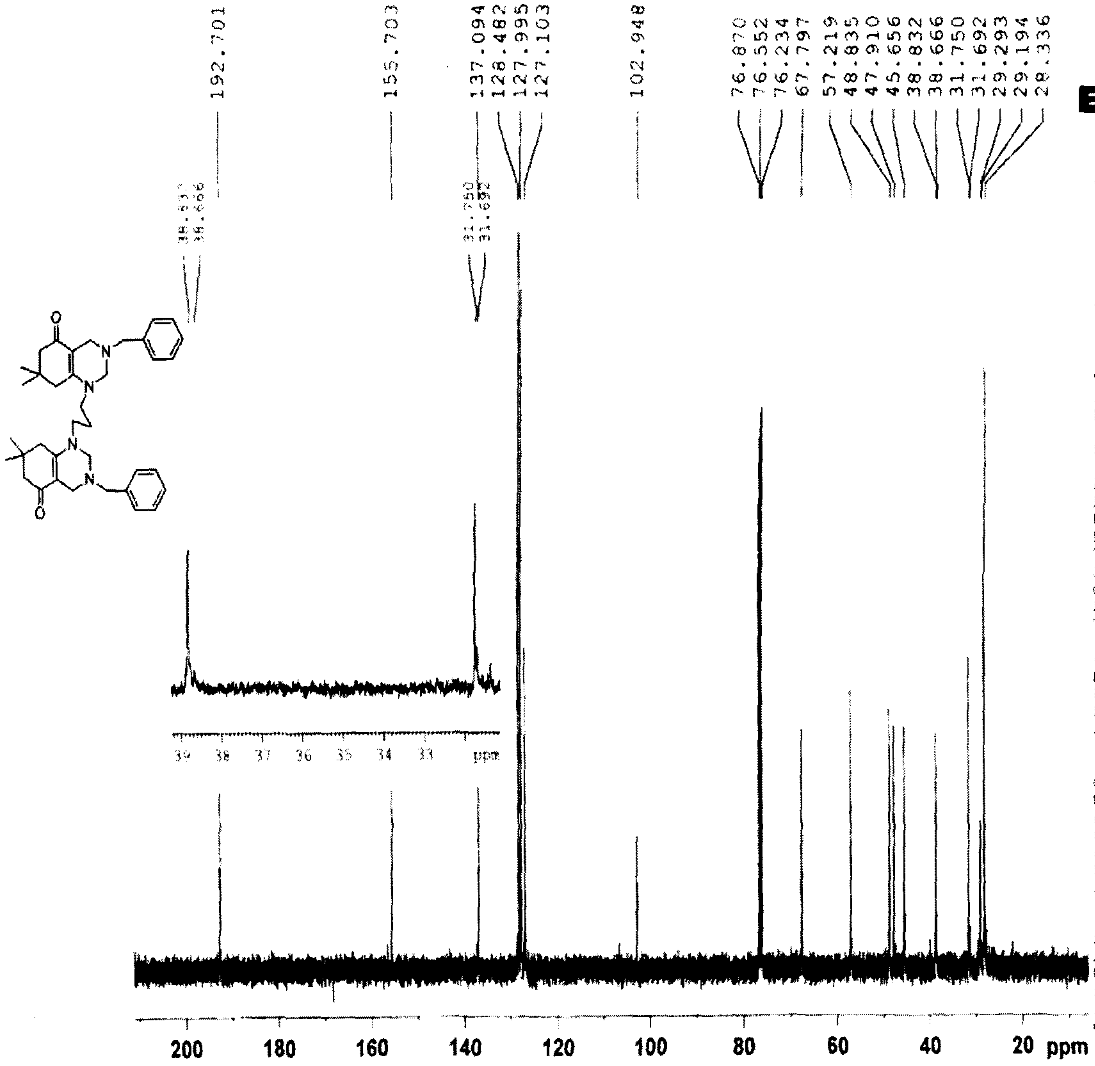

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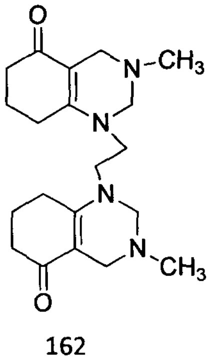
3.4.5 Experimental

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-983 spectrometer.^{1}H NMR(90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H NMR and ^{13}C NMR (300MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to TMS as internal reference. FAB- Mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 using Argon as the FAB gas and m-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL-III instrument. Microwave irradiation was carried out in CEM Discover Benchmate microwave digester. Bis-enaminones **35a-f** were synthesized by condensation of diketone (**34a, 34b**) with diamines (2:1) in microwave at 180 watt in 2-4 minutes. Due to less solubility of the bis-enaminones in methanol and other solvents at room temperature the bis-quinazolines were synthesized by refluxing in methanol at 65^{0}C.

General procedure A mixture of primary amine (2 mmol) and formaldehyde (4 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of bis-enaminone **35** (1 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was refluxed at 65^{0}C for 7-15 hours. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **40a-r** in 51-73 % yields.(**Scheme 12**)

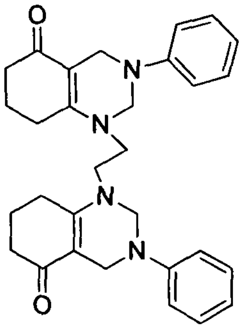
3.4.6 Description of the individual compounds:

1,1′-(ethane-1,2-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40a)



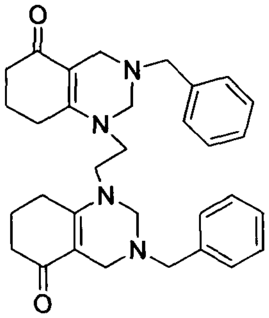
This compound was obtained as light brown gum in 61% yield,: IR (KBr): 1552, 1609 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.96-2.02 (m, 4H), 2.31-2.45 (m, 14H), 3.38 (s, 8H), 3.83 (s, 4H); ^{13}C NMR (CDCl$_3$): δ 21.46, 25.57, 35.63, 41.47, 41.70, 47.99, 50.28, 105.90, 157.10, 193.89; MS: m/z 359.2 (MH$^+$). Anal. Calc. for $C_{20}H_{30}N_4O_2$ (358.24): C, 67.01; H, 8.44; N, 15.63%.

1,1′-(ethane-1,2-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40b)



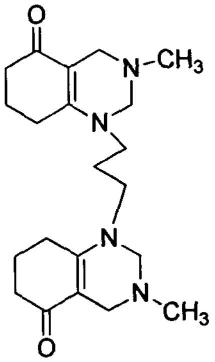
This compound was obtained as yellow solid in 57% yield, m.p 106^{0}C: IR (KBr): 1557, 1603 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.86-1.89 (m, 4H), 2.29-2.32 (t, 4H,J=6.4Hz), 3.20-3.24 (m, 4H), 4.04-4.08 (m, 4H), 4.45-4.54 (m, 4H), 4.84-4.89 (m,4H), 6.84-7.02 (m, 6H), 7.19-7.28 (m,4H); MS: m/z 483.4 (MH$^+$). Anal. Calc. for $C_{30}H_{34}N_4O_2$ (482.27): C, 74.66; H, 7.10; N, 11.61. Found: C, 74.51; H, 7.06; N, 11.63 %

1,1′-(ethane-1,2-diyl) bis-5-oxo-3-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40c)



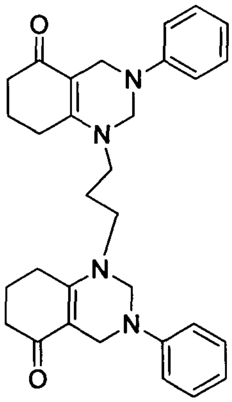
This compound was obtained as yellow solid in 52% yield, m.p 115^{0}C: IR (KBr): 1554, 1653 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.89-1.92 (m, 4H), 2.24-2.32 (m, 8H), 3.11 (s, 4H), 3.50 (s, 4H), 3.60 (s, 4H), 3.70 (s, 4H), 7.26-7.34 (m, 10H); MS: m/z 511.8 (MH$^+$). Anal. Calc. for $C_{32}H_{38}N_4O_2$ (510.30): C, 75.26; H, 7.50; N, 10.97. Found: C, 75.35; H, 7.54; N, 10.90 %

1,1'-(propane-1,3-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40d)



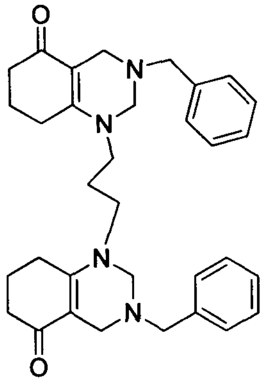
This compound was obtained as pale yellow gum in 56 % yield: IR (KBr): 1553, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.93-1.98 (m, 6H), 2.38-2.40 (m, 4H), 2.45-2.56 (m, 4H), 3.86-3.91 (m, 4H), 4.24 (s, 4H); ^{13}C NMR (CDCl$_3$): δ 21.17, 25.14, 35.38, 39.08, 39.29, 39.50, 39.71, 39.92, 40.13, 40.34, 41.27, 45.91, 49.87, 157.86, 193.06; MS: m/z 373.1 (MH$^+$). Anal. Calc. for $C_{21}H_{32}N_4O_2$ (372.25): C, 67.71; H, 8.66; N, 15.04%.

1,1'-(propane-1,3-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40e)



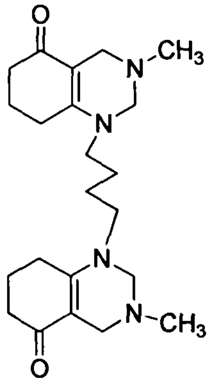
This compound was obtained as brown gum in 58% yield: IR (KBr): 1573, 1653 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03-1.09 (m, 4H), 1.14-1.25 (m, 2H), 2.12-2.20 (m, 8H) 3.15-3.18 (m, 4H), 4.11 (s, 4H), 4.47 (s, 4H), 6.89-6.93 (m, 6H), 7.23-7.26 (s,4H); ^{13}C NMR ($CDCl_3$): δ 28.14, 29.19, 31.75, 38.82, 44.73, 45.63, 48.78, 67.53, 103.88, 117.17, 120.70, 128.70, 128.85, 147.96, 156.83, 192.64; MS: m/z 497.5 (MH^+). Anal. Calc. for $C_{31}H_{36}N_4O_2$ (496.28): C, 74.97; H, 7.31; N, 11.28%

1,1′-(propane-1,3-diyl) bis-5-oxo-3-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40f)



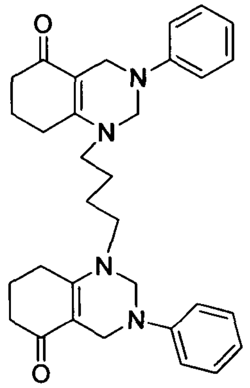
This compound was obtained as yellow gum in 56% yield: IR (KBr): 1560, 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.01-1.18 (m, 4H), 1.54-1.57 (m, 2H), 2.08-2.15 (m, 8H), 3.48-3.83 (m, 12H), 7.24 (s,10H); ^{13}C NMR ($CDCl_3$): δ 21.42, 25.47, 28.93, 35.62, 46.15, 48.93, 57.90, 67.97, 104.97, 127.58, 128.49, 128.94, 129.18, 137.52, 158.08, 193.75; MS: m/z 525.6 (MH^+). Anal. Calc. for $C_{33}H_{40}N_4O_2$ (524.32): C, 75.54; H, 7.68; N, 10.68 %

1,1′-(butane-1,4-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40g)



This compound was obtained as yellow gum in 73 % yield: IR (KBr): 1560, 1602 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.89-1.96 (m, 8H), 2.43 (s, 6H) 2.80-2.85 (m, 4H), 2.87-2.99 (m, 4H), 3.79-3.83 (m, 4H), 4.31 (s, 4H), 4.84 (s, 4H); MS: m/z 387.1 (MH^+). Anal. Calc. for $C_{22}H_{34}N_4O_2$ (386.53): C, 68.36; H, 8.87; N, 14.49 %

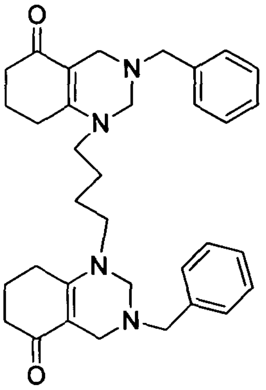
1,1′-(butane-1,4-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40h)



This compound was obtained as yellow gum in 65 % yield:: IR (KBr): 1545, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.32-1.36 (m, 4H), 1.62-1.68(m, 4H), 2.23-2.40(m, 4H)

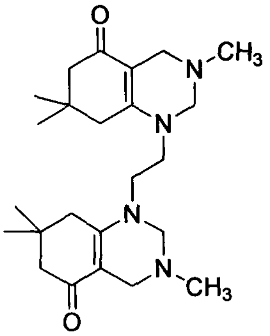
2.73-2.75 (m, 4H), 3.03(s, 4H), 3.79(s, 4H), 4.31 (s, 4H), 6.94-7.27(m, 10H); MS: m/z 511.6 (MH^+). Anal. Calc. for $C_{32}H_{38}N_4O_2$ (510.32): C, 75.26; H, 7.50; N, 10.97 %

1,1′-(butane-1,4-diyl) bis-5-oxo-3-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40i)



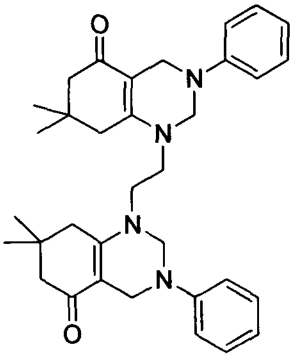
This compound was obtained as yellow gum in 71 % yield: IR (KBr): 1527, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26-1.30 (m, 4H), 1.88-1.99 (m, 4H) 2.23-2.42 (m, 8H), 3.03 (s, 4H), 3.50 (s, 4H), 3.57 (s,4H), 3.74 (s,4H), 7.19-7.24 (m,10H); MS: m/z 539.1 (MH^+). Anal. Calc. for $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40 %

1,1′-(ethane-1,2-diyl) bis-5-oxo-3,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40j)



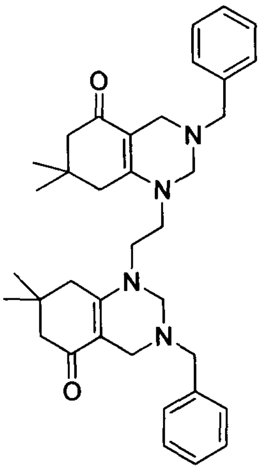
This compound was obtained as yellow gum in 53 % yield:: IR (KBr): 1557, 1608 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07(s, 12H), 2.28(s, 4H), 2.39(s, 4H), 3.36-3.42(m, 10H), 3.84(s, 4H), 5.30(s, 4H); ^{13}C NMR ($CDCl_3$): δ 28.79, 32.23, 39.50, 41.42, 41.69, 48.04, 49.26, 53.43, 53.43, 71.46, 104.53, 155.44, 193.47; MS: m/z 415.4 (MH^+). Anal. Calc. for $C_{24}H_{38}N_4O_2$ (414.3): C, 69.53; H, 9.24; N, 13.51%

1,1′-(ethane-1,2-diyl) bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40k)



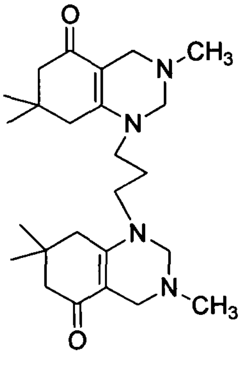
This compound was obtained as yellow solid in 61 % yield, m.p 245^{0}C; IR (KBr): 1578, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 12H), 1.87 (s, 4H), 2.12-2.24 m, 4H), 2.59 (s, 4H), 5.06 (s, 4H), 5.42 (s, 4H), 7.05 (s, 4H), 7.73 (s, 6H); MS: m/z 539.1 (MH^+). Anal. Calc. for $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.93; H, 7.80; N, 10.46 %

1,1′-(ethane-1,2-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40l)



This compound was obtained as yellow solid in 71 % yield, m.p 205^{0}C; IR (KBr): 1557, 1606 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.07 (s, 12H), 2.17 (s, 4H), 2.59-2.88 (m, 8H), 3.16 (s, 4H), 3.51 s, 4H), 3.82 (s, 4H), 5.33 (s, 4H), 7.02-7.30 (m, 10H); ^{13}C NMR (CDCl$_3$): δ 28.27, 31.61, 38.75, 39.12, 39.33, 39.53, 39.74, 39.95, 47.49, 47.77, 47.84, 57.15, 68.14, 127.06, 127.96, 128.32, 136.91, 192.72; MS: m/z 567.5 (MH$^+$). Anal. Calc. for $C_{36}H_{46}N_4O_2$ (566.36): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.15; H, 8.13; N, 9.86%

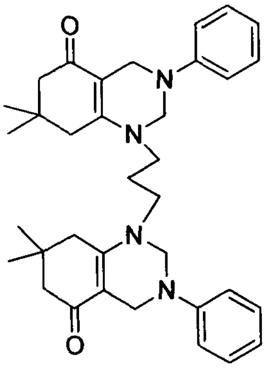
1,1′-(propane-1,3-diyl) bis-5-oxo-3,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40m)



This compound was obtained as yellow solid in 73 % yield, m.p 186^{0}C; IR (KBr): 1533, 1578 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.07-1.61 (s, 18H), 1.88-1.91 (s, 4H), 2.20-2.21 (m, 4H), 3.21 (s, 6H), 3.49-3.52 (m, 4H), 5.15 (s, 4H); MS: m/z 529.9 (MH$^+$).

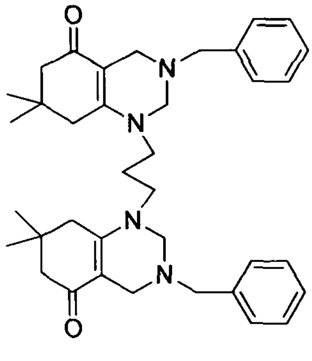
Anal. Calc. for $C_{25}H_{40}N_4O_2$ (428.32): C, 70.06; H, 9.41; N, 13.07. Found C, 70.21; H, 9.43; N, 13.02 %

1,1′-(propane-1,3-diyl) bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40n)



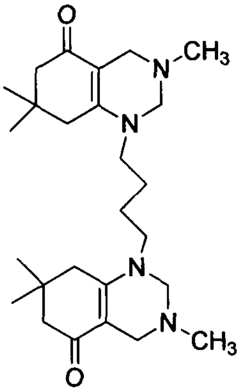
This compound was obtained as light brown gum in 58 % yield; IR (KBr): 1560, 1599 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07 (s, 12H), 1.18(s, 4H), 2.06-2.21 (m, 6H), 3.09-3.13 (m, 4H), 4.04 (s, 4H), 4.57 (s, 4H), 6.84-6.86 (m, 6H), 7.16-7.20 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 28.59, 29.36, 29.54, 29.70, 30.96, 31.93, 32.27, 39.33, 45.13, 46.19, 48.71, 68.18, 104.19, 117.72, 121.40, 129.40, 148.29, 158.38, 192.89; MS: m/z 553.6 (MH^+). Anal. Calc. for $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.14. %

1,1′-(propane-1,3-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40o)



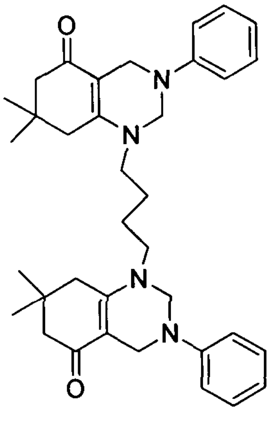
This compound was obtained as light brown gum in 65 % yield; IR (KBr): 1560, 1599 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.07 (s, 12H), 1.24 (s, 4H), 1.56-1.59 (t, 2H J=6.8Hz), 2.15 (s, 4H), 3.05-3.09 (m, 4H), 3.50-3.63 (m, 8H), 3.79 (s, 4H), 7.29 (s,10H); ^{13}C NMR (CDCl$_3$): δ 28.33, 29.19, 29.29, 31.69, 31.75, 38.66, 38.83, 45.65, 47.91, 48.83, 57.21, 67.79, 102.94, 127.10, 127.99, 128.48, 137.09, 155.70, 192.70; MS: m/z 581.6 (MH$^+$). Anal. Calc. for $C_{37}H_{48}N_4O_2$ (580.38): C, 76.51; H, 8.33; N, 9.65%

1,1′-(butane-1,4-diyl) bis-5-oxo-3,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40p)



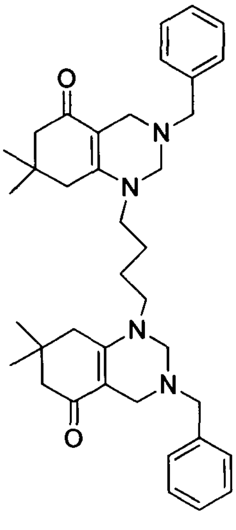
This compound was obtained as light brown solid in 70 % yield, m.p 140^{0}C; IR (KBr): 1557, 1603 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.08 (s, 12H), 1.57 (s, 4H), 2.40 (s, 6H), 3.24 (s, 4H), 3.44 (s, 4H), 3.87 (s, 4H); ^{13}C NMR (CDCl$_3$): δ 26.92, 28.79, 30.94,32.23, 39.30, 41.50, 48.49, 49.26, 49.83, 70.83, 102.82, 155.97; MS: m/z 443.6 (MH$^+$). Anal. Calc. for $C_{26}H_{42}N_4O_2$ (442.3): C, 70.55; H, 9.56; N, 12.66. Found: C, 70.41; H, 9.51; N, 12.70 %

1,1′-(butane-1,4-diyl)bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40q)



This compound was obtained as light brown gum in 57 % yield; IR (KBr): 1559, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 12H), 1.95-2.29 (m, 8H), 3.01-3.18 (m, 8H), 4.08 (s, 4H), 4.45 (s, 4H), 6.81-6.96 (m, 6H), 7.15-7.29 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 27.92, 28.35, 29.16, 30.94, 31.84, 39.21, 45.15, 48.15, 48.15, 48.67, 49.23, 49.31, 67.80,117.69, 120.75, 129.44, 148.60, 157.59, 192.91; MS: m/z 566.8 (M^+). Anal. Calc. for $C_{36}H_{46}N_4O_2$ (566.78): C, 76.29; H, 8.18; N, 9.89%

1,1′-(butane-1,4-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40r)



This compound was obtained as light yellow solid in 73 % yield, m.p 125^{0}C; IR (KBr): 1559, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 12H), 1.77 (s, 4H), 2.14-2.25

(m, 8H), 3.10 (s, 4H), 3.59-3.63 (m, 8H), 3.86 (s, 4H), 7.27-7.32 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 26.88, 28.82, 30.94, 32.24, 39.39, 48.33, 48.48, 49.30, 57.57, 68.07, 102.75, 127.51, 128.45, 128.96, 137.77, 156.50,193.14; MS: m/z 595.6 (MH^+). Anal. Calc. for $C_{38}H_{50}N_4O_2$ (594.39): C, 76.73; H, 8.47; N, 9.42. Found: C, 76.60; H, 8.51; N, 9.39 %

3.4.6 Conclusion

The present chapter describes an efficient, simple, strategy for the synthesis of hitherto unknown bis-octahydroquinazolines in which the two quinazoline ring connected at 1,1′ positon from easily accessible starting materials in good yields with promising pharmacological and biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

3.4.7 References

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Chapter-IV

Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline & 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline.

Introduction

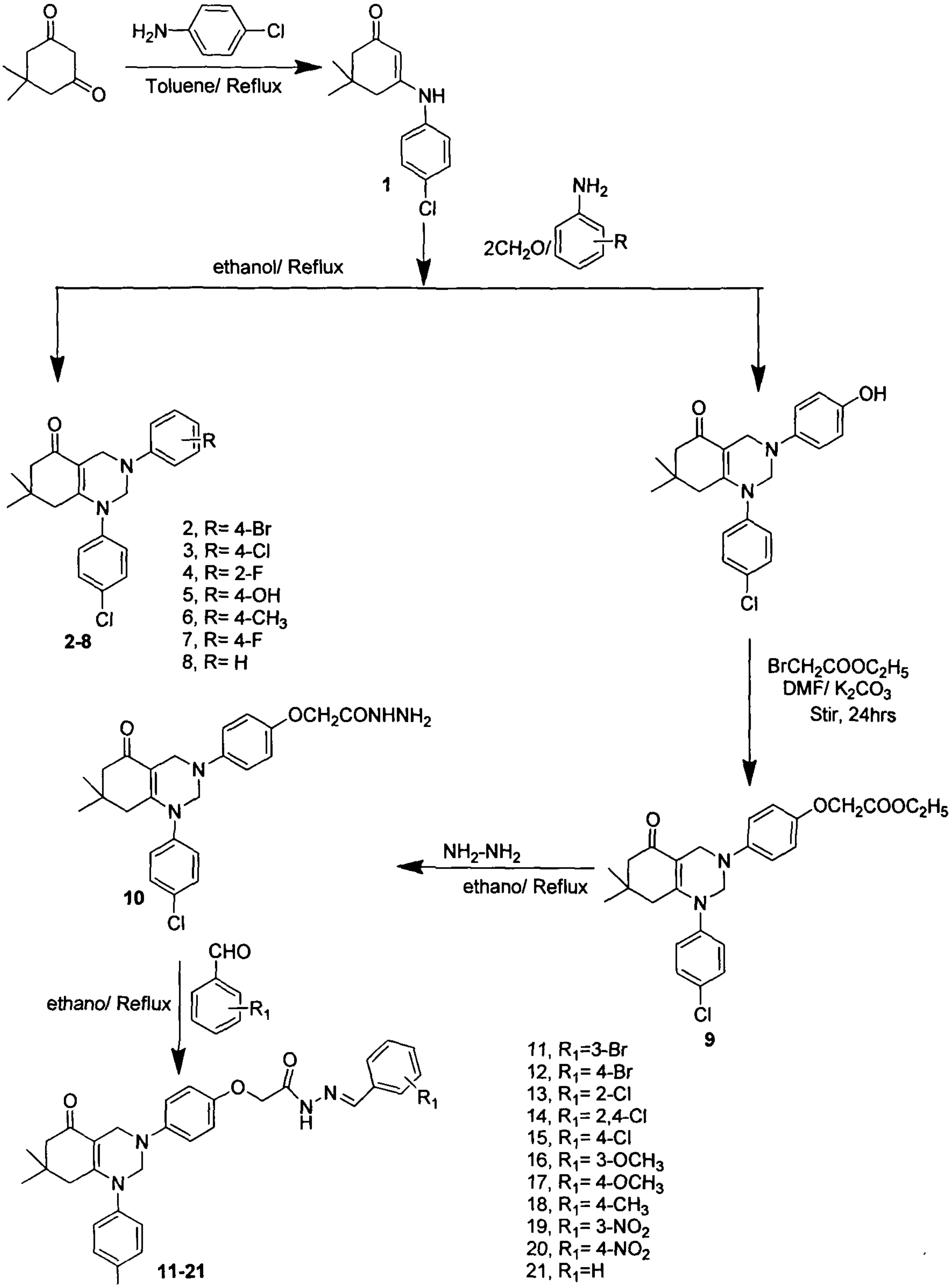
Literature report reveals that with the modification of substituents at different position of the quinazoline moiety there is change in the potency as inhibitors of the molecule. Some of the reports are highlited below

4.1.1 O.I. El-Sabbagh and co-workers have reported[1] the synthesis of octahydroquinazolines varying substituents at 3-position of the quinazoline moiety and studied their antihypertensive activity. All octahydroquinazoline derivatives were prepared which structurally related to the antihypertensive clinically used α_1-blocker prazosin. Several novel 1-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxo-3-(substitutedphenyl) quinazoline derivatives (**2–21**) structurally similar to prazosin, were prepared using Mannich reaction of 3-(4-chlorophenylamino)-5,5-dimethyl-2-cyclohexenone (**1**) with different aromatic amines in the presence of formaline. The structures of the quinazoline derivatives were established using elemental and spectral analyses. Compounds **18**, **20** and **21** were found to possess a high hypotensive effect through their expected α_1-blocking activity like the clinically used drug prazosin but with the advantage of being not causing reflex tachycardia and having prolonged duration of action when tested in adrenaline-induced hypertension in anaesthetized rats.

Condensation of 5, 5-dimethyl-1, 3-cyclohexanedione with 4-chloroaniline was conducted by heating the reactants at reflux in toluene to afford 5, 5-dimethyl-3-(4-chlorophenylamino)-2-cyclohexenone (**1**). The novel 5-oxo-octahydroquinazolines (**2–8**) were then obtained by heating at reflux equimolar amounts of enaminone (**1**) and the primary aromatic amines with two equivalents of formaldehyde in ethanol containing catalytic amount of glacial acetic acid.

These quinazolines (**2–8**) were formed through Mannich reaction either at C-2 or arylamino group of the enaminone system. The former would be kinetically favorable being irreversible followed by ring formation using excess formaldehyde. The structures of 5-oxo-octahydroquinazolines (**2–8**) were established using elemental and spectral analyses. IR spectral data showed the disappearance of the NH absorption band at 3250 cm^{-1} of the starting enaminone. ^1H NMR proved the disappearance of both singlet at $\delta = 7.85$ ppm due to NH group and also the vinylic proton singlet at $\delta = 5.65$ ppm of the starting enaminone. Moreover, the formation of the 5-oxo-octahydroquinazoline was confirmed through appearance of two characteristic singlets around $\delta = 4.26$ and 4.87 ppm for the two methylene groups at 4- and 2-positions of the quinazoline skeleton.

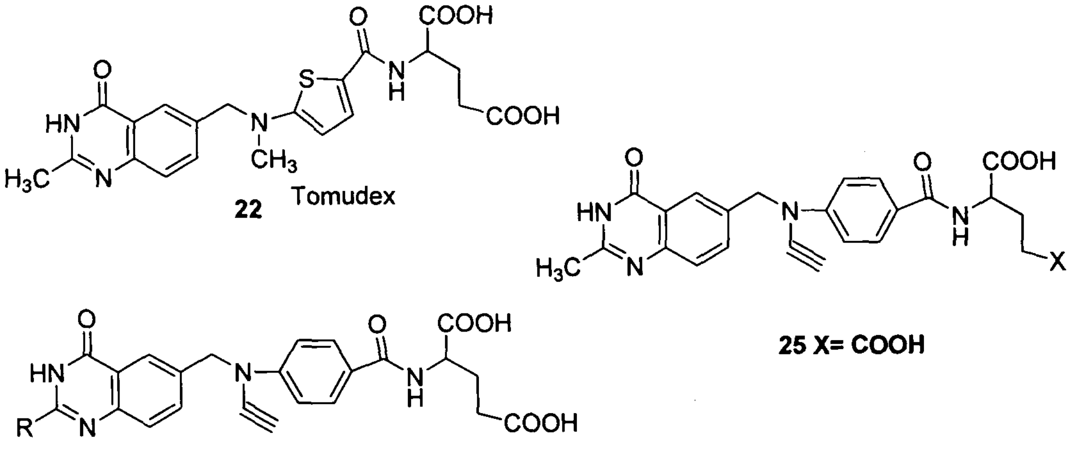
The novel ester (**9**) was prepared by stirring equimolar amounts of 3-(4-hydroxyphenyl)-5-oxo-octahydroquinazoline (**6**) and ethyl bromoacetate in dimethylformamide (DMF) containing K_2CO_3 at room temperature for 24 hr. The ester **9** was allowed to condense with hydrazine hydrate through refluxing the reactants in ethanol for 2 h to afford the novel hydrazide **10** in 72% yield. The chemical structures of ester **9** and hydrazide **10** were established using elemental analysis and different spectroscopic methods. Condensation of the hydrazide key intermediate **10** with aromatic aldehydes in equimolar amounts was conducted through heating the reactants in ethanol containing 10 drops of glacial acetic acid for 2 h to give the novel hydrazone derivatives **11–21**. **(Scheme 1)**


H2N–C6H4–Cl
Toluene/ Reflux
1
NH
Cl
NH2
2CH2O/
R
ethanol/ Reflux
OH
2-8
2, R= 4-Br
3, R= 4-Cl
4, R= 2-F
5, R= 4-OH
6, R= 4-CH3
7, R= 4-F
8, R= H
BrCH2COOC2H5
DMF/ K2CO3
Stir, 24hrs
OCH2CONHNH2
10
NH2-NH2
ethano/ Reflux
OCH2COOC2H5
9
CHO
ethano/ Reflux
R1
11-21
11, R1=3-Br
12, R1= 4-Br
13, R1= 2-Cl
14, R1= 2,4-Cl
15, R1= 4-Cl
16, R1= 3-OCH3
17, R1= 4-OCH3
18, R1= 4-CH3
19, R1= 3-NO2
20, R1= 4-NO2
21, R1=H

Scheme 1

All novel 5-oxo-octahydroquinazolines (**2**–**21**) were screened[1] to study their effect on the arterial blood pressure whereas compounds **2**, **4**, **5**, **9**–**17** and **19** which did not produce any effect were excluded. On the other hand, compounds **3**, **6**, **7**, **8**, **18**, **20** and **21** which showed an effect on the arterial blood pressure were subjected to study their α-blocking activity using prazosin as a reference drug. The results presented and illustrated and showed that compounds **18**, **20** and **21** produced significant ($P < 0.05$) decrease in both SABP and DABP with rapid onset of action (after 5 min) meanwhile such compounds caused non-significant decrease in the HR. Compounds **18**, **20** and **21** rapidly reversed the vasopressor effect of adrenaline into depressor response after 30 min which were sustained for 1 hour. Thus, these compounds can be considered as rapidly acting α_1-blockers like prazosin but with advantageous of being did not cause reflex tachycardia and having prolonged duration of action.

4.1.2 Tomudex (ZD1694, **22**), a new quinazoline based inhibitor of thymidylate synthase (TS), has recently been introduced in a number of European territories for the treatment of advanced colorectal cancer[2]. It is a highly potent cytotoxic agent in vitro and shows in vivo antitumor activity in a range of preclinical models 3 without the unacceptable kidney toxicity associated with its predecessor, CB 3717 (**23**). In international phase III studies in patients with previously untreated advanced colorectal cancer, the efficacy and acceptable safety profile of Tomudex was confirmed. Response rates, time to progression, and survival are consistent with the published literature for 5-fluorouracil and leucovorin. In addition there were reductions in the incidence of certain potentially serious adverse events and benefits in terms of improvements in quality of life, performance status, and weight gain. All the evidence suggests that the high cytotoxicity of Tomudex (**22**) is due to rapid intracellular localization via the reduced folate carrier protein (RFC) and then extensive metabolism by folylpolyglutamate synthetase (FPGS) to polyglutamates which are retained within cells and are 60- 70 times more potent as inhibitors of TS.6 Tumor cells however may be resistant to classical folate-based antimetabolites through reduced expression of FPGS7 or upregulation of the polyglutamatehydrolyzing en- zyme ç-glutamyl hydrolase. This fact has prompted the search for a complementary class of agents which would not be substrates for FPGS and hence insensitive to ç-glutamyl hydrolase but would also still rely on the RFC for cellular uptake. This requirement for RFC of the Sirotnak group that in murine tumor models compounds with favorable kinetic parameters for the RFC may offer a tumor-selective advantage. Agents with this biochemical profile should therefore be active in tumors expressing (1) low levels or modified FPGS expression and (2) high levels of ç-glutamyl hydrolase and which are therefore resistant to folate-based antimetabolites that require polyglutamation for their cytotoxicity. The lack of prolonged drug retention through polyglutamation may also allow for greater control over the duration of TS inhibition. A compound not subjected to metabolic activation through polyglutamation needs to have a high intrinsic potency as a TS inhibitor. As a starting point modifications to the quinazoline antifolate ICI198583 **(24)**10 (the more soluble, less toxic C2-methyl analogue of CB 3717) were undertaken. The combined effect of the incorporation of 7-methyl and 2¢-fluoro substituents gave the analogue ZM214888 **(25)**, a compound showing enhanced inhibition of TS and an overall retention of growth inhibition in cell lines. Moreover, the cytotoxicity of **(25)** results entirely from the parent monoglutamate since 7-methyl-substituted N10-propargyl quinazoline antifolates are not substrates for FPGS. Molecular modelling studies based on an analysis of the X-ray structures of *E. coli* TS enzyme ternary complexes of CB 371714,15 and its tetraglutamate derivative suggested that tighter binding inhibitors may be available in this class of compounds through extension of the glutamate moiety into the dipeptide region of the ternary complex. This work describes the synthesis and biological activities of new analogues of ZM214888 that were prepared to explore the hypotheses that has resulted in compounds with improved TS and growth inhibitory properties leading to the next generation of antitumor TS inhibitors, which are not substrates for FPGS but which still require RFC-mediated uptake into cells. **(Scheme 2)**



22 Tomudex

23 R= NH2

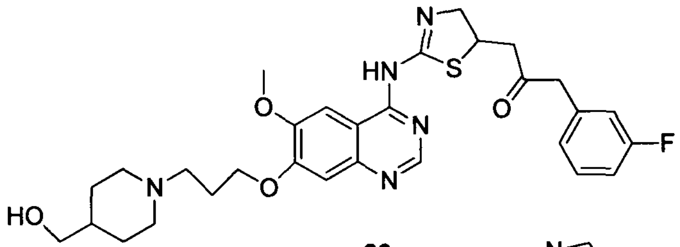
24 R= CH3

25 X= COOH

Scheme 2

4.1.3 The mitogenic action of EGF is mediated by ligand-induced autophosphorylation of the EGF receptor (EGF-R), which is commonly overexpressed in numerous human cancers. Inhibitors of receptor tyrosine kinase (RTK) activity could therefore be considered as effective potential antitumor agents. For this purpose, 4-aminoquinazoline derivatives were prepared[3] and evaluated for their ability to inhibit RTK activity and the autophosphorylation of EGF-R. In addition, these compounds were tested on A431 cell growth to estimate their antiproliferative effect. The results showed that the substituent at the 4-position of the quinazoline ring must be an aromatic amine carrying small lipophilic electron-withdrawing groups on the 3- (or 2-) position of the phenyl ring. This aromatic moiety might be far from the quinazoline provided that the linking group is conformationally restricted, such as with piperazine. Hydrophilic and non-aromatic substituents such as morpholine gave completely inactive compounds. Introduction of a bulk at the 2-position of the quinazoline ring in 2,4-diaminoquinazolines or tricyclic compounds led to inactive products. This study reports additional structure-activity relationships of a well-characterized series to develop new inhibitors of EGF-R-associated tyrosine kinase activity.

4.1.4 The synthesis of a novel series of quinazolines substituted at C-4 by five-membered ring aminoheterocycles is reported. Their in vitro structure-activity relationships versus Aurora A and B serine-threonine kinases are discussed. Fre'de'ric H. Jung and Co-workers reported[4] that quinazolines with a substituted aminothiazole at C4 possess potent Aurora A and B inhibitory activity and excellent selectivity against a panel of various serine-threonine and tyrosine kinases, as exemplified by compound **26**.They also found that the position and nature of the substituent on the thiazole play key roles in cellular potency. Compounds with an acetanilide substituent at C5 have the greatest cellular activity. The importance of the C5 position for substitution has been rationalized by initio molecular orbital calculations. Results showed that the planar conformation with the sulfur of the thiazole next to the quinazoline N-3 is strongly favored over the other possible planar conformation. Compound **26** is a potent suppressor of the expression of phospho-histone H3 in tumor cells in vitro as well as in vivo, where **26**, administered as its phosphate prodrug **27**, suppresses the expression of phospho-histone H3 in subcutaneously implanted tumors in nude mice.



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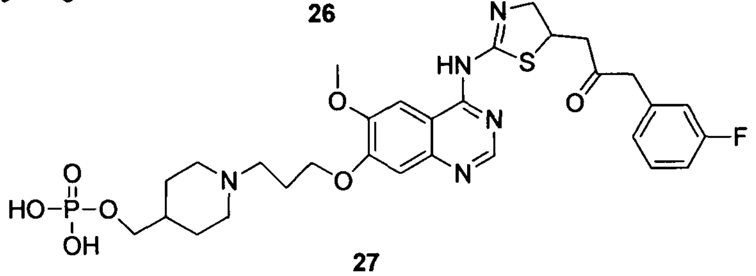

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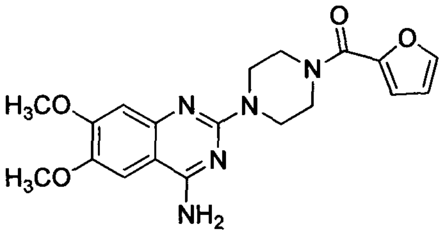
4.1.5 Regarding the structure and activity relationship of quinazolines reported in Foye's principles of medicinal chemistry[5] that prazosin (**28**), terazosin (**29**) and doxazosin (**30**) contain a 4-amino-6,7-dimethoxy quinazoline ring system attached to a piperazine nitrogen. The only structural differences are in the groups attached to the other nitrogen of the piperazine, and the difference in these groups affords dramatic differences in some of the pharmacokinetic properties of these agents. For example when the furan ring of prazosin is reduced to form the tetrahydro furan of terazosin, the compound becomes significantly more hydrophilic. The clinical parameters shows perhaps most significant are the long half-lives and durations of action for terazosin and doxazosin, which permit once a day dosing and generally lead to increased patient compliance (Table I).



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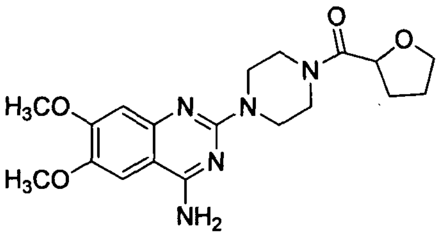

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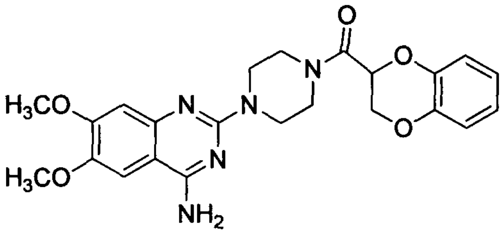


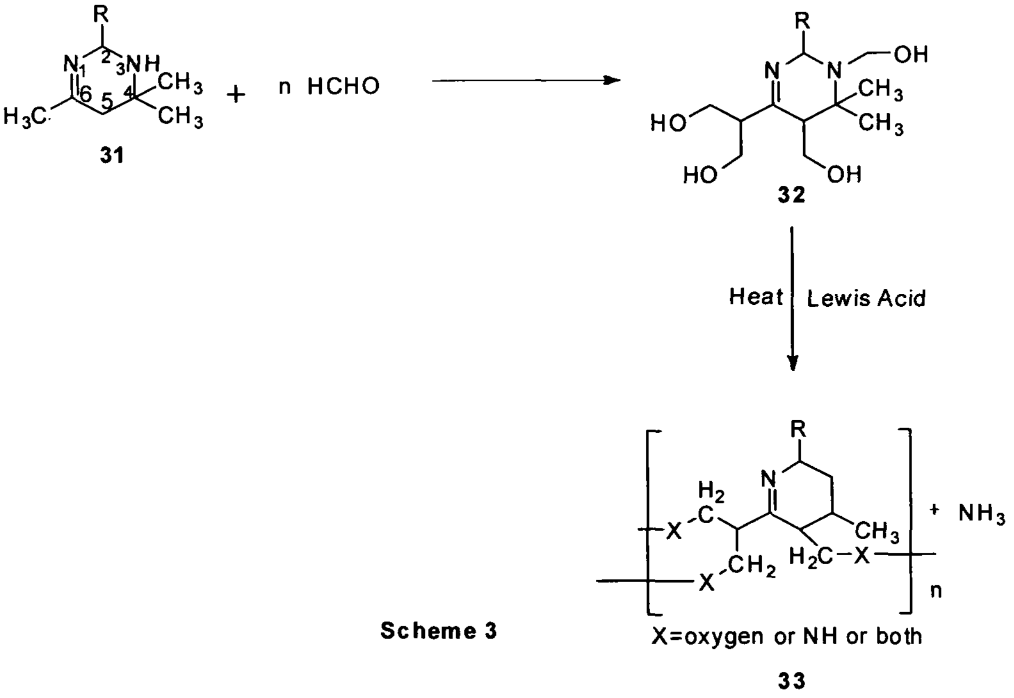
30

Table I

Drug	Trade name	Therapeutic dose	Half-life hours	Frequency of administration	Bioavailability %
Prazosin (**28**)	Minipres	2-20	2-3	BID-TID	45-65
Terazosin(**29**)	Hytrin	1-40	12	QD-BID	90
Doxazosin(**30**)	Cardura	1-16	22	QD-BID	65

Our literature survey at this stage reveals that there is dramatic change in the behaviour as well as change in the potency of the quinazoline compounds with hydrophilic groups at different positions. Further our observatios on tetrahydro pyrimidine shows that there is formation of mixture of compounds called polyols of tetrahydropyrimidines by the pyrimidine ring having hydroxyethyl group at 3, 5, 6 position of the ring.

4.1.6 Oude Alink and co-workers reported[6] hydroxy ethyl substituted compounds of tetrahydropyrimidine when heated in the presence of Lewis acid such as $FeCl_3$, $AlCl_3$, etc polymerized to form a compound having the general structure (**95**) by the liberation of ammonia (**Scheme 3**)

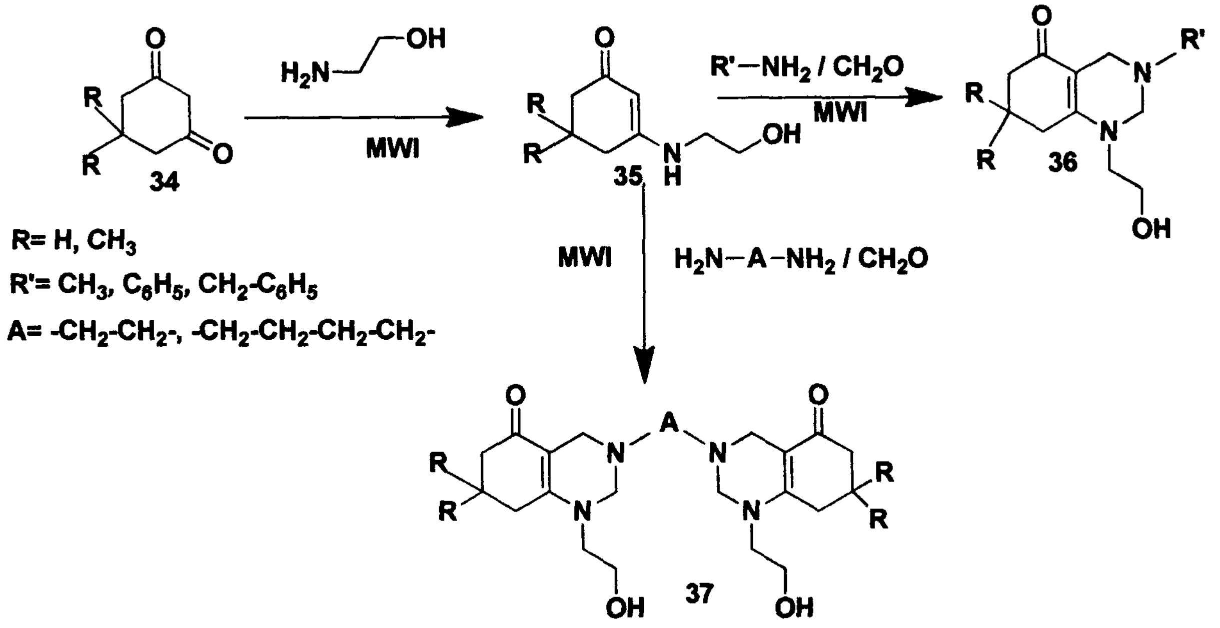


Scheme 3

The polyols of tetrahydropyrimidines and their respective polymers were found to be useful as corrosion inhibitors, and were used in fluid for drilling wells, in air drilling, used in Brine, acid Systems and as pickling inhibitors.

4.2 Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline & 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline.

Prompted by the above and in view of extending programme of synthesis of octahydrquinazoline we took up the synthesis of octahydroquinazolines with hydrophilic substituents. In continuation of our studies on the synthesis octahydroquinazolines we now wish to report herein a short MW assisted synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline and 3,3'-(alkanediyl) bis 1-(2-hydroxyethyl)- 5-oxo-1,2,3,4,5,6,7,8- octahydroquinazoline bearing 2-hydroxyethyl group in position 1 of quinazoline ring to see the impact of this hydrophilic group incorporated in position 1 on the biological properties of these molecules **(Scheme 4)**



Scheme 4

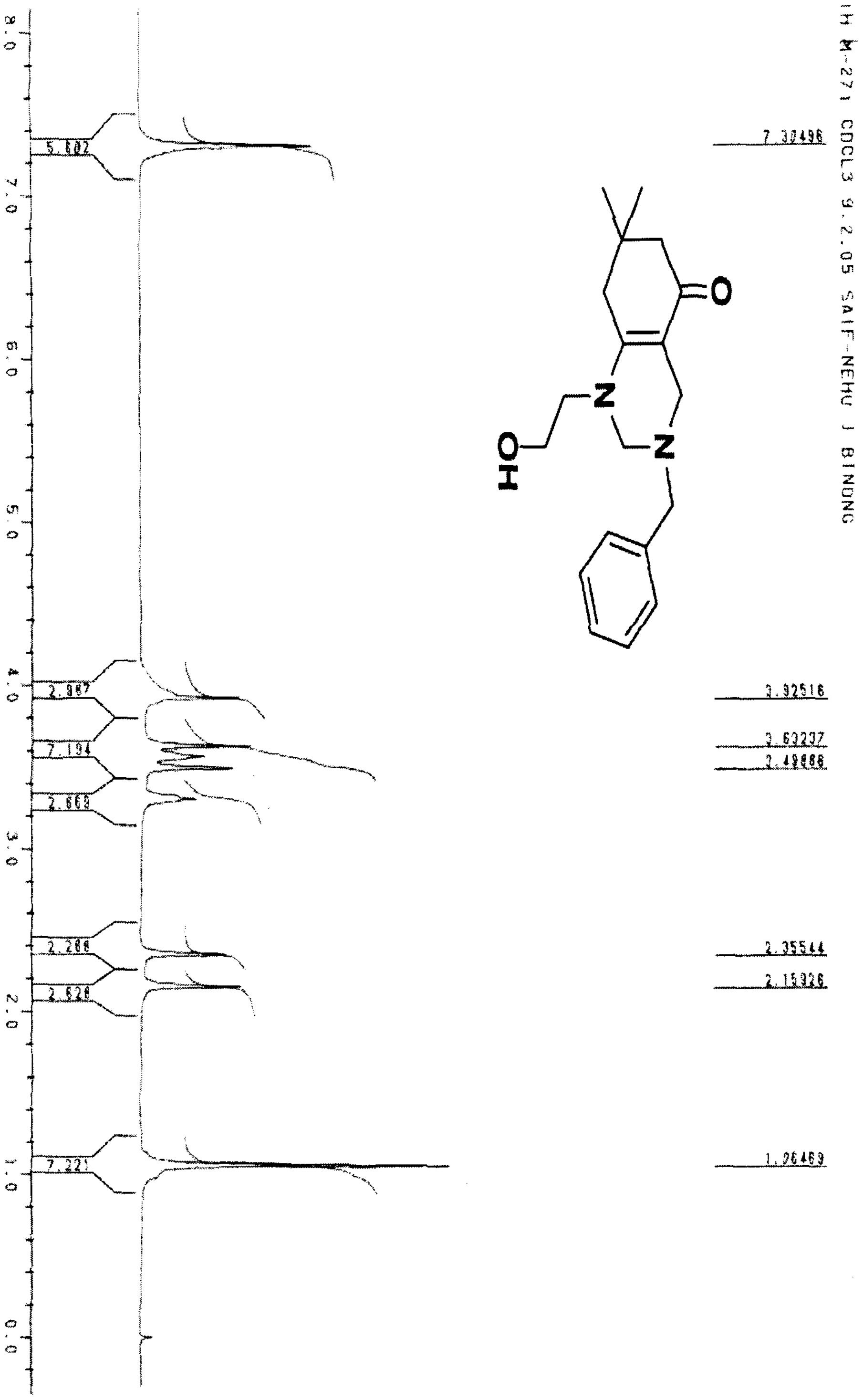
4.2.1 Results and Discussion

Thus, when a solution of 3-(2-hydroxyethyl) aminocyclohexenone **35a** was treated with methylamine and formaldehyde under the influence of microwaves, a product was obtained in 71% yields which was characterized as 1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline **36a** on the basis of analytical and spectral data. The reaction of **35a** with other primary amines and formaldehyde behaved in a similar manner and octahydroquinazolines **36b-d** were isolated in 51-79% yields. The infrared spectra of **36a-d** showed strong peaks in the region of 1530 to 1653 cm^{-1} due to extensively delocalized double bonds and carbonyl groups[7]. In the ^1H NMR spectra of **36a-h**, the methylene protons at C-7 appeared as multiplets in the range of 1.94-1.98 ppm. The methylene proton adjacent to -OH group resonated 3.60 ppm, the methylene protons at C-2 gave sharp singlet at 4.12 ppm whereas the CH_2 protons in **3d** appeared around 5.12 may be due to presence of two hydroxyethyl group at 1 and 3 position of quinazoline ring. The hydroxyl group gave broad singlet near 4.60 ppm which disappears with D_2O shake. The methyl protons attached to nitrogen in **36a** gave singlet at 2.40 ppm. The aromatic protons appeared in their usual range. The Reactions of **35b** with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (**36e-h**) were isolated in 61-75% yields, whose structures could be established with the help of analytical and spectral data. The infrared spectra of **36e-h** showed strong peaks in the region of 1533 to 1600 cm^{-1}. The ^1H NMR spectra of tetrahydropyrimidine rings of **36e-h** were found to have a similar pattern as those of **36a-d.** However, the six methyl protons at C-7 appeared as sharp singlets around 1.06 ppm whereas in **3f** it appeared at 1.01 ppm which may be due to the presence of phenyl group at N-3 position and the CH_2 protons at C-6 and C-8 resonated in ranges of 2.15-2.17 and 2.30-2.40 ppm respectively.

Encouraged by the successful synthesis of octahydroquinazolines **36a-h**, we then turned our attention to the synthesis of bis-octahydroquinazolines. Thus, when enaminone **35a** was reacted with 1,2-diaminoethane and formaldehyde under the influence of microwaves in methanol, a product **36a** was isolated in 65 % yield, the structure of which was established to be 3,3′-(ethanediyl) bis(1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) based on analytical and spectral data. The reaction was found to be general with other diamines and with corresponding **35a-b** to give the respective product **37a-d** in 51-79% overall yields. We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains **37a-d**. The structures of which could be established with the help of spectral and analytical data. The infrared spectra of **37a-d** showed strong peaks in the range of 1531-1653 cm^{-1} due to extensive delocalization of the enaminone moiety and carbonyl group. The ^1H NMR spectra of these bis- quinazolines were found to have the same pattern as in the monomeric octahydroquinazolines except that the signals due to NCH_2 protons of ethylene linkers appeared at 2.74-2.84 ppm while those in butylene appeared in the ranges of 2.54-2.86 ppm. The structure of some quinazolines and bis-quinazolines were further supported by their ^{13}C and mass spectra. The ^1HNMR, Mass and ^{13}C spectra of few compounds are given in the following pages.

Table Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36a-h) & 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a-d).

Compd	R	R′/A	Mol.formula	MWI-Power/ Time(Sec)	M.P.°C	Yield %
36a	H	$-CH_3$	$C_{11}H_{18}N_2O_2$	180watt/180	Gum	71
36b	H	$-C_6H_5$	$C_{16}H_{20}N_2O_2$	180watt/210	Gum	68
36c	H	$-CH_2-C_6H_5$	$C_{17}H_{22}N_2O_2$	180watt/120	Gum	59
36d	H	$-(CH_2)_2-OH$	$C_{12}H_{20}N_2O_3$	180watt/120	90	51
36e	$-CH_3$	$-CH_3$	$C_{13}H_{22}N_2O_2$	180watt/150	Gum	61
36f	$-CH_3$	$-C_6H_5$	$C_{18}H_{24}N_2O_2$	180watt/180	68	65
36g	$-CH_3$	$-CH_2-C_6H_5$	$C_{19}H_{26}N_2O_2$	180watt/210	95	75
36h	$-CH_3$	$-(CH_2)_2-OH$	$C_{14}H_{24}N_2O_2$	180watt/180	Gum	72
37a	H	$-CH_2-CH_2-$	$C_{22}H_{34}N_4O_4$	180watt/180	79	65
37b	H	$-(CH_2)_4-$	$C_{24}H_{38}N_4O_4$	180watt/180	88	79
37c	$-CH_3$	$-CH_2-CH_2-$	$C_{26}H_{42}N_4O_4$	180watt/150	Gum	51
37d	$-CH_3$	$-(CH_2)_4-$	$C_{28}H_{46}N_4O_4$	180watt/150	Gum	68


1H M-271 CDCL3 9.2.05 SAIF-NEHU J BINDNG
7.30496
3.92516
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1.26469
5.602
2.987
7.194
2.669
2.288
2.628
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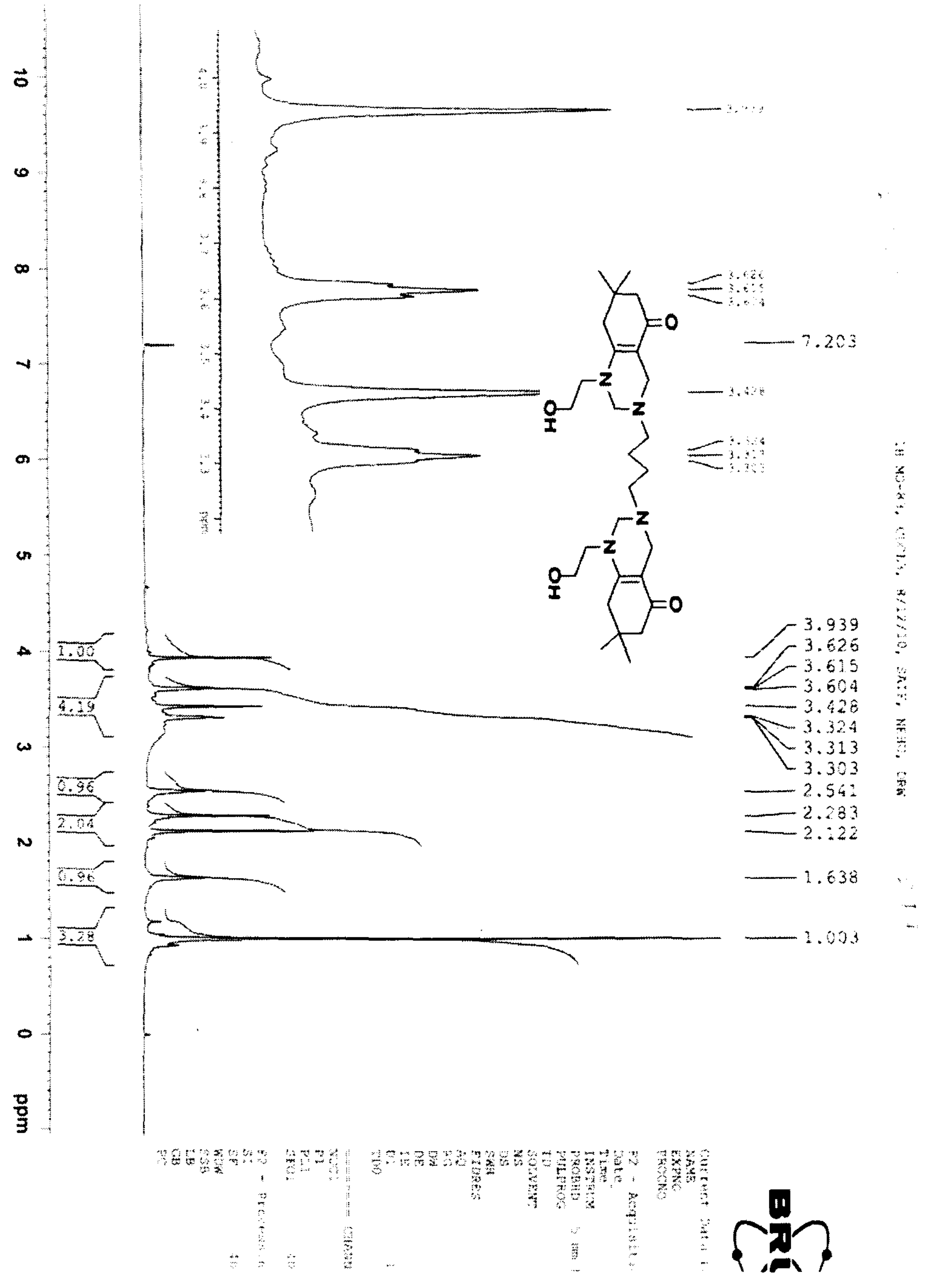

10
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ppm
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3.28
7.203
3.939
3.626
3.615
3.604
3.428
3.324
3.313
3.303
2.541
2.283
2.122
1.638
1.003
O
N
OH
Current Data Parameters
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Date_
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT
NS
DS
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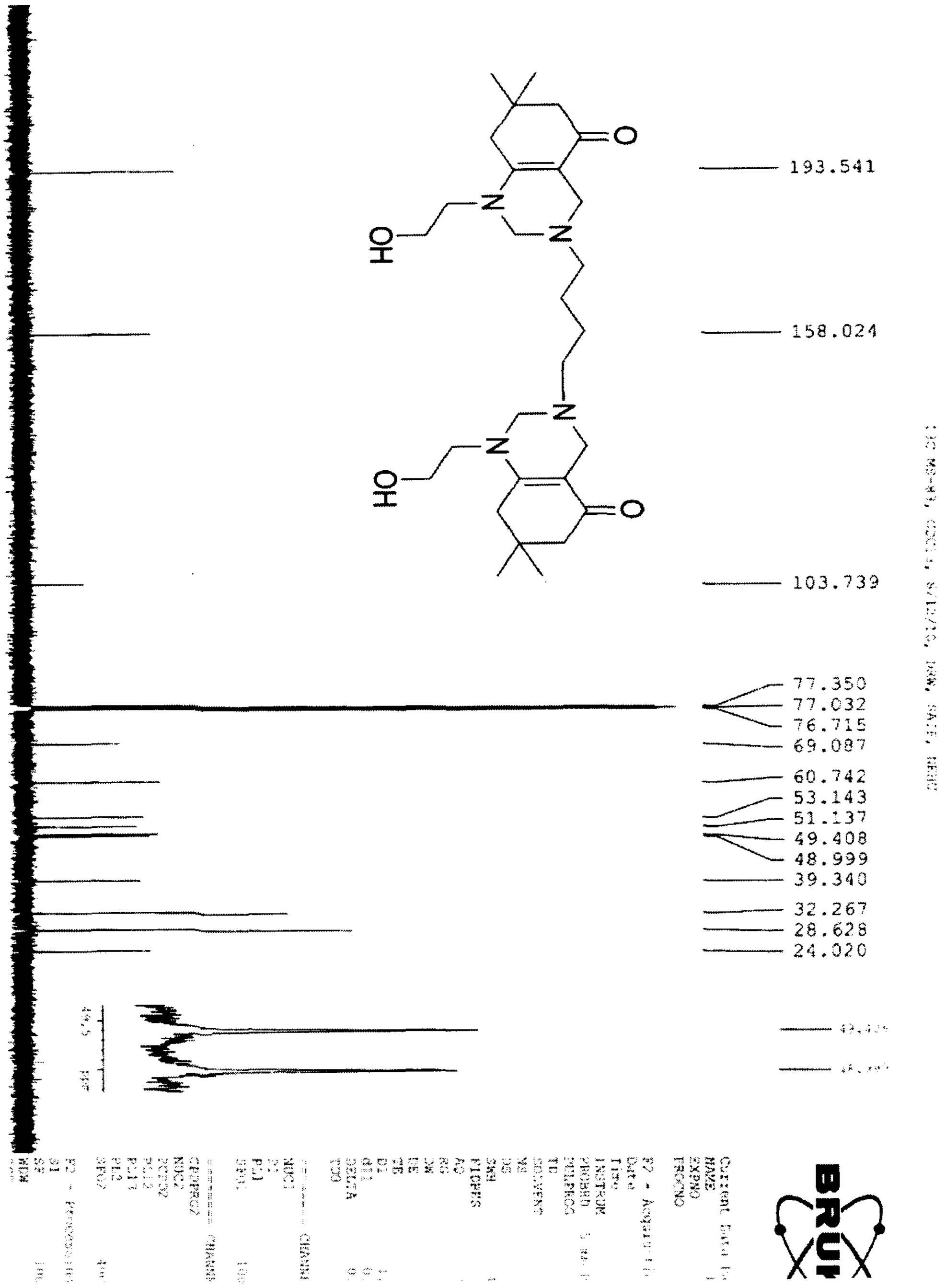
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53.143
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49.408
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Chloroform08-Dec-2010 ZQMAA255 12:51:5008-Dec-2010

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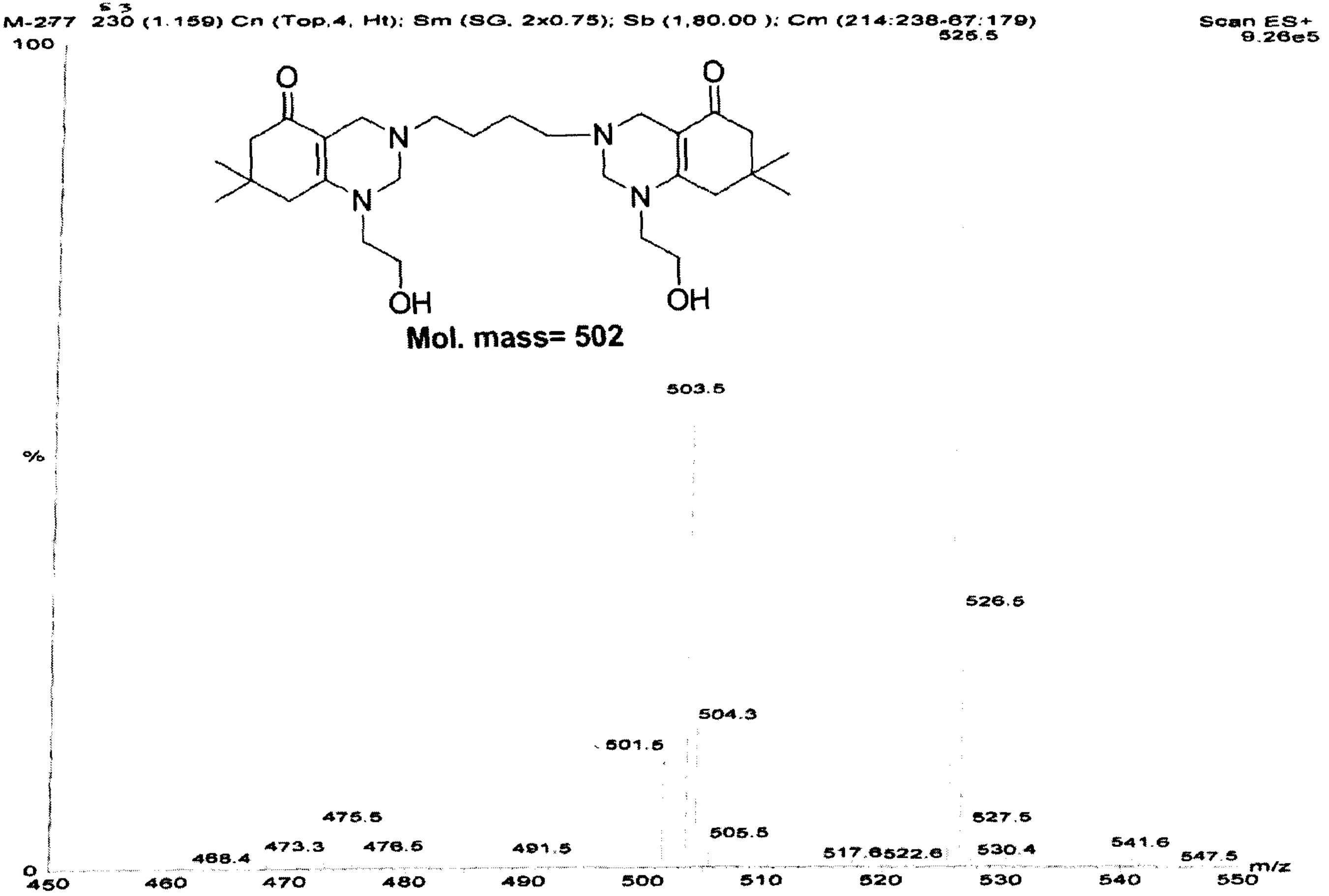


4.2.2 Experimental

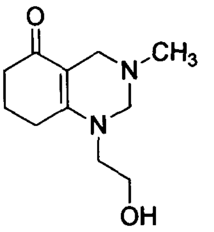
Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-983 spectrometer.^{1}H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H NMR and ^{13}C NMR (300MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to TMS as internal reference. FAB- Mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 using Argon as the FAB gas and m-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL-III instrument. Microwave irradiation was carried out in CEM Discover Benchmate microwave digester.

4.2.3 General procedure.

Equimolar mixture of 1,3-diketone (**34a,b**) and ethanolamine was irradiated in microwave at 180 watt, the reaction gets completed in 2-3 minutes monitored by tlc. The reaction mixture died off under reduced pressure in hot to give the enaminone (**35**) which was used without isolation. A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone (**35**) (1 mmol) in 4 ml methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **36a-h** in 51-79 % yields.

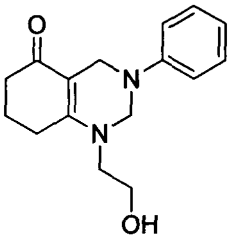
4.2.4 Individual description of the compounds

1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36a)



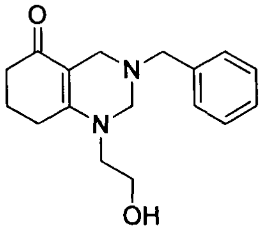
This compound was obtained as reddish brown gum with 71% yield; IR (KBr): 1530, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.95-197 (m, 2H), 2.30 (s, 4H), 2.40 (s, 4H), 2.60 (s, 2H), 3.35-3.42 (m, 4H), 3.65-3.70 (m, 2H), 3.90 (s, 2H), 4.60 (s, 1H); MS: m/z 211.2 (MH^+). Anal. Calc. for $C_{11}H_{18}N_2O_2$ (210.14): C, 62.83; H, 8.63; N, 13.32 %

1-(2-hydroxyethyl)-3-phenyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36b)



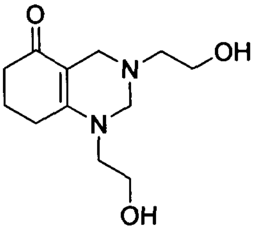
This compound was obtained as reddish brown gum with 68 % yield; IR (KBr): 1541, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.96-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.60 (t, 2H), 4.08 (s, 2H), 4.60 (s, 1H), 6.79-6.94 (m, 3H), 7.18-7.21 (m, 2H); MS: m/z 273 (MH^+). Anal. Calc. for $C_{16}H_{20}N_2O_2$ (272.15): C, 70.56; H, 7.40; N, 10.29%

1-(2-hydroxyethyl)-3-benzyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36c)



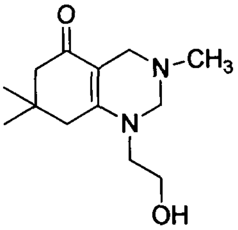
This compound was obtained as reddish brown gum with 59 % yield; IR (KBr): 1551, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.95-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.57-3.60 (m, 4H), 4.08 (s, 2H), 4.60 (s, 1H), 7.23-7.33 (m, 5H); MS: m/z 287 (MH^+). Anal. Calc. for $C_{17}H_{22}N_2O_2$ (286.17): C, 71.30; H, 7.74; N, 9.78%

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36d)



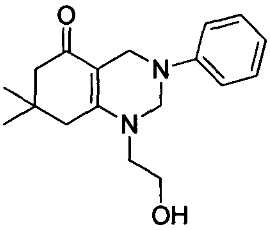
This compound was obtained as brownish solid in 51% yield, m.p 90°C; IR (KBr): 1529, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.94-1.97 (m, 2H), 2.27 (s, 2H), 2.53 (s, 2H), 3.38 (s, 2H), 3.45 (s, 2H), 3.62-3.70 (m, 6H), 4.03 (s, 2H),5.12 (s, 1H); MS: m/z 241 (MH^+). Anal. Calc. for $C_{12}H_{20}N_2O_3$ (240): C, 59.98; H, 8.39; N, 11.66 Found C, 59.84; H, 8.36; N, 11.68 %

1-(2-hydroxyethyl)-3,7,7-trimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36e)



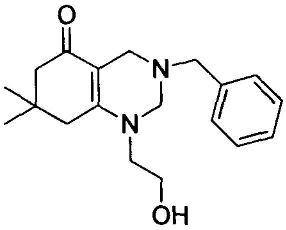
This compound was obtained as brown gum with 61 % yield; IR (KBr): 1541, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 6H), 2.16 (s, 2H), 2.34 (s, 2H), 2.40 (s, 3H), 3.37-3.39 (m, 4H), 3.66-3.70 (t, 2H), 3.82 (s, 2H), 4.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 46.62, 48.61, 40.48, 36.14, 31.24, 27.59; MS: m/z 239.8 (MH$^+$). Anal. Calc. for $C_{13}H_{22}N_2O_2$ (238.17): C, 65.51; H, 9.30; N, 11.75%

1-(2-hydroxyethyl)-3-phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36f)



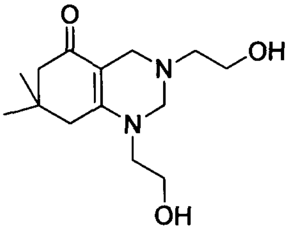
This compound was obtained as yellow solid in 65 % yield, m.p 68^{0}C; IR (KBr): 1584, 1599 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 6H), 2.17 (s, 2H), 2.39 (s, 2H), 3.41-3.44 (t, 2H), 3.60-3.63 (t, 2H), 4.13 (s, 1H), 4.61 (s, 1H), 4.65 (s, 2H); ^{13}C NMR ($CDCl_3$): 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 48.61, 46.62, 40.48, 36,14, 31.24, 27.59; MS: m/z 301.2 (MH$^+$). Anal. Calc. for $C_{18}H_{24}N_2O_2$ (300.18): C, 71.97; H, 8.05; N, 9.33. Found: C, 71.85; H, 8.00; N, 9.28 %

1-(2-hydroxyethyl)-3-benzyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36g)



This compound was obtained as yellow solid with 75 % yield, m.p 95^{0}C; IR (KBr): 1537, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.06 (s, 6H), 2.15 (s, 2H), 2.35 (s, 2H), 3.29-3.33 (t, 2H), 3.49 (s, 2H), 3.63 (t, 2H), 3.68 (s, 2H), 3.92 (s, 2H), 4.60 (1, 1H), 7.29-7.33 (m, 5H); MS: m/z 315.2 (MH$^+$). Anal. Calc. for $C_{19}H_{26}N_2O_2$ (314.20): C, 72.58; H, 8.33; N, 8.91. Found: C, 72.75; H, 8.27; N, 8.95 %

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline (36h)



This compound was obtained as brown gum with 72 % yield; IR (KBr): 1532, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.06 (s, 6H), 2.36 (s, 2H), 2.65 (t, 2H), 3.39 (s, 2H), 3.48-3.52 (m, 4H), 3.71 (s, 2H), 4.08 (1, 2H), 4.26 (s, 2H); MS: m/z 269 (MH$^+$). Anal. Calc. for $C_{14}H_{24}N_2O_3$ (268.12): C, 62.66; H, 9.01; N, 10.44%

4.2.5 Synthesis of 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a-b) and 3,3′-(alkanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37c-d):

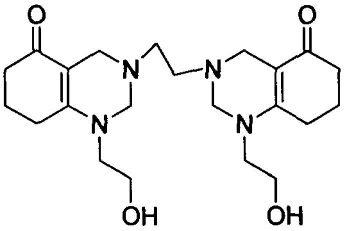
General procedure

Equimolar mixture of 1,3-diketone (**34a,b**) and ethanolamine was irradiated in microwave at 180 watt, the reaction gets completed in 2-3 minutes monitored by tlc.

The reaction mixture died off under reduced pressure in hot to give the enaminone **35**. A mixture of diamine (1mmol) and formaldehyde (4 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone **35** (2 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-3 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate **37a-d** in 51-79 % yields.

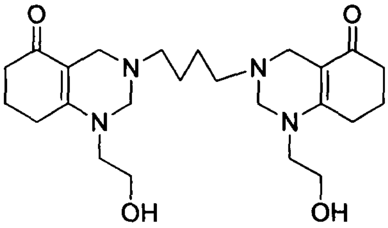
4.2.6 Individual description of the compounds

3,3'-(ethanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a)



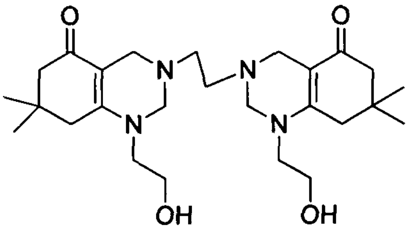
This compound was obtained as yellow solid in 65 % yield, m.p 75^{0}C; IR (KBr): 1533, 1584 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.94-1.97 (m, 4H), 2.28-2.31 (m, 4H), 2.59-2.61 (t, 4H), 2.74 (s, 4H), 3.41-3.44 (t, 4H), 4.14 (s, 4H), 3.90 (s, 2H), 4.60 (s, 2H); MS: m/z 419.2 (MH$^+$). Anal. Calc. for $C_{22}H_{34}N_4O_4$ (418.53): C, 63.13; H, 8.19; N, 13.39. Found: C, 63.34; H, 8.14; N, 13.33 %

3,3'-(butanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37b)



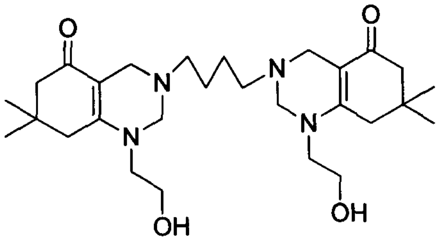
This compound was obtained as yellow solid in 79 % yield, m.p 88^{0}C; IR (KBr): 1531, 1653 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.84-1.87 (m, 4H), 2.02-2.04 (m, 4H), 2.84-2.86 (m, 4H), 2.94-2.96 (t, 4H), 3.47 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60 (s, 4H); MS: m/z 447.2 (MH$^+$). Anal. Calc. for $C_{24}H_{38}N_4O_4$ (446.29): C, 64.55; H, 8.58; N, 12.58. Found: C, 64.39; H, 8.54; N, 12.55 %

3,3'-(ethanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37c)



This compound was obtained as brown gum in 51 % yield; IR (KBr): 1558, 1600 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.03 (s, 12H), 1.90 (s, 4H), 2.65-2.67 (m, 4H), 2.84 (s, 4H), 2.94-2.96(t, 4H), 3.47(s, 4H), 4.14 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60(s, 2H); MS: m/z 475(MH$^+$). Anal. Calc. for $C_{26}H_{42}N_4O_4$ (418.53): C, 65.79; H, 8.92; N, 11.80%

3,3'-(butanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37d)



This compound was obtained as brown gum in 68 % yield; IR (KBr): 1536, 1606 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.03 (s, 12H), 1.63(s, 4H), 2.12 (s, 4H), 2.28 (s, 4H), 2.54(s, 4H), 3.30-3.32(t, 4H), 3.42 (s, 4H), 3.60-3.62 (t, 4H), 3.94 (s, 4H), 4.60(s, 2H); ^{13}C NMR ($CDCl_3$): δ 193.54, 158.02, 103.73, 69.74, 53.14, 51.13, 49.40, 48.99, 39.34, 32.26, 28.62, 24.02; MS: m/z 503.5(MH^+). Anal. Calc. for $C_{28}H_{46}N_4O_4$ (418.53): C, 66.90; H, 9.22; N, 11.15%

4.2.7 Conclusion

The present chapter describes an one pot efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis- octahydroquinazolines with hydrophillic group at position **1** of the quinazoline ring from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

4.2.8 References

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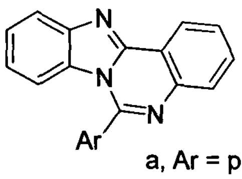
Chapter-V

Study of biological activities of octahydroquinazolines and bis-octahydroquinazolines

In the broad class of heterocyclic compounds, the nitrogen heterocycles play an important role. Among them, quinazolines are most important class of compounds and have received much attention from synthetic as well as medicinal chemists, because of the diverse range of their pharmacological properties [1–8] and also in several areas as materials in electronics, in electrochemistry as anticorrosive agents, as polymers or optical materials and fluorescent tags in DNA sequencing[9–12]. There are reports described benzimidazo and benzothiazoloquinazoline derivatives as cytotoxic compounds with potential antitumoral [13–17] and particularly, there is one report that describes the antitumor activity of benzimidazo quinazolines [17]. It was reported that benzimidazo quinazoline derivatives show various therapeutic activities, such as anticancer [14,16,17], antiviral [18,19], antimicrobial [20], anti-inflammatory [13,18] and anticonvulsants [21]. Based on the importance of these molecules, attention was attracted towards synthesis of novel quinazoline derivatives in order to find more potent biologically active molecules.

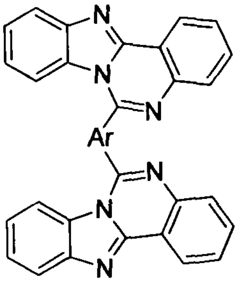
5.1 The preparation and biological activities of a few such molecules are described in the following sections.

5.1.1 Rondla Rohini and co-wokers reported the synthesis of Mono and bis-6 arylbenzimidazo quinazolines **(1a-d, 2a-e)** through oxidative cyclisation[22] of corresponding 2-o-arylideneaminophenyl benzimidazoles the antimicrobial activities of all synthesized quinazolines against different bacteria and fungi were evaluated. Among the compounds tested some of quinazolines were found to be superior in inhibiting all the bacterial and fungal strains.



1

a, Ar = phenyl
b, Ar = 2-pyridyl
c, Ar = 2-thienyl
d, Ar = 2-pyrrolyl



2

a, Ar = 1,2-phenyl
b, Ar = 1,3-phenyll
c, Ar = 1,4-phenyl
d, Ar = 2,6-pyridyl
e, Ar = 2,5-thienyl

All the quinazolines prepared herein were screened for their potential biological activities such as, antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus pyogenes* (Gram positive) and *Salmonella typhimurium*, *Escherichia coli*, *Klebsiella pneumonia* (Gram negative) bacterial strains by agar diffusion method [23,24] Ampicillin was used as a reference standard. Preliminary screening for ten quinazolines was performed at fixed concentrations of 1000 mg/ml. screening results are summarized in Table 1

Table 1 Zone of inhibition of newly synthesized mono, bis-benzimidazo[1,2-c]quinazolines against different bacteria and fungi.

Compound (1000 mg/ml)	Zone of inhibition (mm)								
	Gram-positive bacteria			Gram-negative bacteria			Fungi		
	S. aureus	*B. subtilis*	*S. pyogenes*	*S. typhimurium*	*E. coli*	*K. pneumonia*	*A. niger*	*C.albicans*	*T. viridae*
IIIa	18	14	13	12	18	16	10	10	9
IIIb	50	42	49	38	51	35	49	48	45
IIIc	51	45	50	40	50	36	51	48	46
IIId	25	21	18	15	20	12	13	11	6
IIIe	22	18	13	14	18	12	11	9	9
IVa	18	14	15	12	20	15	16	13	13
IVb	21	18	15	15	19	18	18	15	12
IVc	25	19	18	14	21	18	21	16	13
IVd	52	45	50	46	50	49	50	50	45

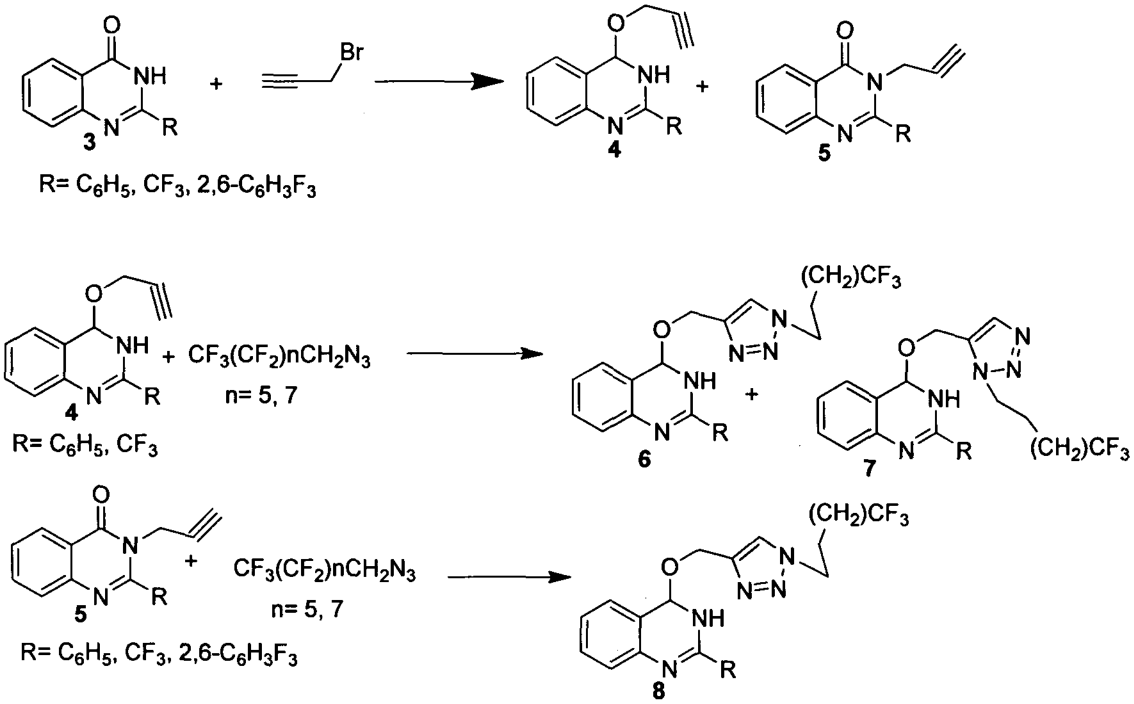
IVe	55	50	52	46	51	50	55	51	48
Std	48a	39a	35a	45a	40a	45a	45b	40b	41b

a Ampicillin.

b Ketoconazole.

All the above-mentioned quinazoline compounds were also examined for antifungal activity against *Aspergillus niger*, Candida albicans, *Trichoderma viridae* fungal strains. Ketoconazole was used as standard drug for the comparison of antifungal results. The fungal strains were grown and maintained on Sabouraud glucose agar plates. Preliminary screening for ten quinazolines was performed at fixed concentrations of 1000 mg/ml. The plates were incubated at 26^{0}C for 72 h and zones of inhibition formed were measured. The antifungal screening revealed that all the tested compounds IIIa–e and IVa–e showed moderate to good inhibition. The pyridyl and thienyl substituted quinazolines IIIb, IIIc and IVd; IVe showed same trend in the case of fungal strains. In general, the order of both antibacterial and antifungal activity of the quinazolines is IVe> IVd> IIIc> IIIb> IVc> IIId> IVb> IIIe> IVa> IIIa. A possible explanation for this result is that the antibacterial and antifungal activity of compounds may be depending on the basic skeleton of molecule as well as on the nature of substituents. Hence they[25] concluded that although all quinazolines itself were observed active the activity was further enhanced by the presence of basic bis benzimidazo quinazoline structure and as well as pyridyl, thienyl groups.

5.1.2 P. Mani Chandrika and coworkers reported[26] the synthesis of novel fluorous tagged triazol-4-yl substituted quinazoline derivatives and their biological evaluation, theoretical and experimental validation. The 2-substituted quinazol-4-ones 3 were initially propargylated using propargyl bromide in acetone and potassium carbonate under reflux conditions, obtained two isomers **4**, **5** in definite proportions. The ratio of each isomer is evaluated based on the substituent present in second position. The CF_3 substituent promoted O-propargylated isomer 4 and phenyl substituent favored N-propargylated isomer 5 as major products. However, the 2,6-difluorophenyl substituent gave exclusively N-propargylatedisomer 5. The role of CF_3 is consistent with the earlier reports whereas role of phenyl substituent is differed. The change in ratio and mode of formation of products may be due to change in reaction medium and base. Each isomer is separated and characterized. The isomers 4 and 5were independently reacted with perfluoroalkyl azides in THF using copper (I) iodide as catalyst to give perfluoroalkyl-1H,1,2,3-triazol-4-yl substituted O-, N-quinazoline derivatives 6a–d, 7a–b and 8a–f. Compound **4** gave product **6** as major and **7** as minor however compound **5** gave exclusive product **8.** The reaction is considered to take place via 1,3 dipolar cycloaddition of azide to alkyne, through a preformed copper acetylide complex formation The reactions are drawn in **Scheme**[26] **1** and products are tabulated in **Table 2.**



Scheme 1

Table 2 Triazol-4-yl substituted quinazoline derivatives

Entry	Compd no.	R
1	3a	C_6H_5
2	3b	CF_3
3	3c	2,6-$C_6H_3F_2$
4	4a	C_6H_5
5	5a	C_6H_5
6	4b	CF_3
7	5b	CF_3
8	4c	2,6-F2C6H3
9	5a	C_6H_5
10	5a	C_6H_5
11	6b	C_6H_5
12	7b	C_6H_5
13	6c	CF_3
14	6d	CF_3
15	8a	C_6H_5
16	8b	C_6H_5
17	8c	2,6-$C_6H_3F_2$
18	8d	2,6-$C_6H_3F_2$
19	8e	CF_3
20	8f	CF_3

Antimicrobial activity

In vitro antibacterial assay of the compounds 4a, 5a, 6a–d, 7b, 8a–f were done by dissolving in acetone and Screened for in vitro antibacterial activity against gram-positive (*Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis*) and gram-negative (*Pseudomonas aeruginosa, Escherichia coli*) bacteria. Compounds 6c and 7b showed significant activity against all the species of gram-positive and gram-negative bacteria except *E. coli.* Compounds 5a, 6a–b, 8a–b and 8d–f showed moderate activity and 4a, 6d and 8c showed the least activity. The regioisomer 3a found to be more active than compound 4a and 7b is more active than compound 6b against all the bacterial species. The compound 6c is identified as most active compound. The MIC values of the compounds were compared with those obtained with penicillin and streptomycin. Compound 6c and 7b are considered as interesting lead compounds.

In vitro antifungal activity assays

The in vitro antifungal activity of compounds 4a, 5a, 6a–d, 7b,8a–f were screened against the fungal strains, viz., *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36) and filamentous fungal cultures like *Rhizopus oryzae* (MTCC 262), *Aspergillus niger* (MTCC 1344), *Aspergillus flavus* (MTCC 277), *Candida rugosa* (NCIM 3462) by agar cup diffusion method. The strains were obtained from the Institute of Microbial Technology, Chandigarh. Compounds 5a, 8a, 8e showed promising activity against most of the fungi at 100 mg/ml. It is found that the inhibition diameter increases with concentration. Compound 6d is inactive against all the fungal cultures except for *C. albicans* (MTCC 227) and *C. rugosa* (NCIM 3462). The regioisomer 7b was found to be more active than 6b and 5a was more active than 4a. However, all the compounds 4a, 6d and 8c were inactive against all fungal cultures except for C. albicans up to a maximum concentration of 100 mg/ml. The compounds 5a and 8e are identified as most active compounds. The inhibitory zone diameters of the compounds are compared with those obtained with 50 mg/ml of standard amphotericin.

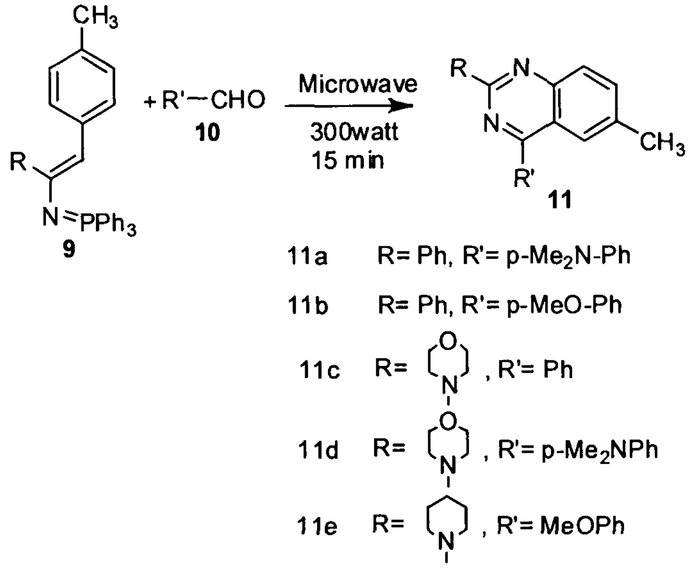
5.1.3 Jantova S and coworkers reported the in vitro antibacterial activity of ten series of substituted quinazolines the antibacterial activity of ten series of substituted quinazolines (157 derivatives) against bacterial strains *Escherichia coli* CCM 3988, *Pseudomonas aeruginosa* CCM 3955, *Bacillus subtilis* ATCC 6663 and *Staphylococcus aureus* CCM 3953 by microdilution assay was investigated. The sensitivity of the Gram positive bacteria to the tested quinazolines was higher than that of Gram negative bacteria. The most effective of ten quinazoline structure series were condensed [1,2,4] triazoloquinazolines and 10H-[1,2,4]triazino[5,4-

b]quinazolin-10-ones. Study of structure-activity relationship showed that the most effective derivatives were those carrying a unsubstituted benzene ring or one substituted with small substituents (Cl and CH_3) while having pyrimidine ring substituted with larger substituents, such as morpholine, phenyl or secondary amines. The most effective derivative 1-[(3-methylphenyl)amino]- 10H-[1,2,4]triazino[5,4-b]quinazolin-10-one had MIC values 5 mg/L for *E. coli*; 100 mg/L for *P. aeruginosa,* 10 mg/L for *S. aureus* and 1 mg/L for *B. subtilis.* 9-chloro-morpholin-4-yl [1,2,4]triazolo[4,3-c]quinazolin-3(4H)-thione demonstrated MIC value lower than ampicillin for *B. subtilis* and the same MIC value as ampicillin for *E. coli.*

Our literature survey at this stage reveals that infectious diseases caused by bacteria affect millions of people worldwide. Concerted and systematic programs to discover and develop new antibiotics have been driven to a considerable extent by the development of resistance by these organisms to the drugs commonly used against them.

The rapid rise in bacterial resistance to the traditional antibiotics such as Penicillins and tetracyclines has encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity. The quinazoline antibacterials have emerged as an area of immense interest because of their broad spectrum of in vitro activity and their in vivo chemotherapeutic efficiency. The design and synthesis of newer antimicrobials is an area of immense significance and continues to attract the attention of increasing number of medicinal chemists. Quinazolines exhibit a wide range of activity such as anthelmintic, [28] antimicrobial, CNS depressant,[29] neuroleptic,[30] hypnotic[31] and analgesic.[31]

5.1.3 Preet M. S. Bedi etal reported[32] the synthesised some novel series of 6-methyl-2-aryl/secondary amino-4- aryl-quinazoline (**11a-e**) by the reactions of N-imidoyl iminophosphoranewith aldehydes by microwave condensation order to study their antibacterial activities.



The antibacterial activity of all the synthesized compounds were determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards against Gram positive microorganisms *Bacillus subtilis* MTCC 121, *Bacillus cereus* MTCC 1272, *Staphyloccocus aureus* MTCC 1430, *Enterococcus faecalis* MTCC 439 and Gram negative microorganisms *Escherichia coli* MTCC 42, *Pseudomonas aeruginosa* MTCC 1034, *Proteus vulgaris* MTCC 744, *Klebsiella pneumoniae* MTCC 109 and *Shigella sonnei* MTCC 2957 at 50lg/mL concentration, using dimethyl sulfoxide (DMSO) as solvent. The bacteria were subcultured on Mueller Hinton Agar medium. Standard antibacterial ciprofloxacin was also screened under similar conditions for comparison. Solvent control was also maintained under similar conditions. The Petri dishes were incubated at 37^0C for 48h to know the bacterial growth inhibition developed around the hole and was measured in millimetre for particular test solution with particular organism. It has been observed that the test compounds (11a–e) exhibited interesting antibacterial activity, however with a degree of variation. Results reveal that compounds 11d and 11e showed significant activity against *K. pneumoniae* as compared to ciprofloxacin. Moreover, the introduction of p-methoxy phenyl group in compound 11b, decreases its antibacterial activity against Gram positive and Gram negative bacterial strains.

However compound 11b did not show any activity against Gram positive S. aureus. Antibacterial data indicated that compound 11c showed maximum activity against S. sonnei as compared to the standard and exhibited significant activity against E. faecalis and P. aeruginosa as compared to ciprofloxacin. It is interesting to note that by the introduction of morpholino and piperidino moieties in compounds 11d and 11e, increases their antibacterial activity against Gram positive and Gram negative bacterial strains. Compound 11d was superior in action against *S. aureus, E. faecalis* and *K. pneumoniae* overthe standard ciprofloxacin, where as compound 6e containing piperidino moiety showed maximum activity against *K. pneumoniae* as compared to ciprofloxacin. Solvent DMSO did not show any antibacterial activity. Therefore the results of antibacterial screening of compounds revealed that quinazolines having morpholino and piperidino heterocycles showed significant activity comparable to standard drug against Gram positive and Gram negative bacterial strains. The other chemical moiety found to be favourable towards antibacterial activity was p-dimethylamino phenyl followed by pmethoxy phenyl in the quinazoline ring system.

5.2 Prompted by the above interesting biological and good in vitro properties of substituted quinazolines and non availability of any reports of biological properties of 5-Oxo octahydroquinazoline we undertook the antimicrobial investigation of some novel representative 5-Oxoctahydroquinazolines and bis 5-Oxo octahydroquinazolines the results of our studies are reported herein.

5.2.1 NEED FOR TESTING ANTIBACTERIAL EFFECT

It is important to study about the antibacterial agents which are effective against these bacteria because *Staphylococcus aureus* can cause a range of illnesses from minor skin infections, such as pimples, impetigo, boils, cellulitis folliculitis, furuncles, carbuncles, scalded skin syndrome and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, Toxic shock syndrome (TSS), and septicemia. Its incidence is from skin, soft tissue, respiratory, bone, joint, endovascular to wound infections. It is still one of the four most common causes of nosocomial infections, often causing postsurgical wound infections. Methicillin was the first antibiotic in this class to be used (it was introduced in 1959), but only two years later, the first case of methicillin-resistant *S. aureus* (MRSA) was reported in England. Vancomycin-resistant *S. aureus* (VRSA) is a strain of *S. aureus* that has become resistant to the glycopeptides. The first case of vancomycin-intermediate *S. aureus* (VISA) was reported in Japan in 1996; but the first case of *S. aureus* truly resistant to glycopeptide antibiotics was only reported in 2002. Three cases of VRSA infection has been reported in the United States as of 2005.

Staphylococcus epidermidis is usually non-pathogenicbut patients with a compromised immune system and are often at risk for developing an infection. These infections can be both nosocomial and community acquired, but they are more of a threat to hospital patients. *S. epidermidis* causes biofilms to grow on plastic devices place within the body. This occurs most commonly on intravenous catheters and on medical prostheses. Infection can also occur in dialysis patients or anyone with a implanted plastic device that may be contaminated. Another disease it causes is Endocarditis. This occurs most often in patients with defective heart valves. In some other cases sepsis can occur in hospital patients.

Bacillus subtilis is less pathogenic; it may contaminate food & sometimes causes food poisoning *B. subtilis* produces the proteolytic enzyme subtilisin. *B. subtilis* spores can survive the extreme heating that is often used to cook food, and it is responsible for causing *ropiness* — a sticky, stringy consistency caused by bacterial production of long-chain polysaccharides . An opportunistic pathogen of immunocompromised individuals,

Pseudomonas aeruginosa typically infects the pulmonary tract, urinary tract, burns, wounds, and also causes other blood infections. It is the most common cause of infections of burn injuries and of the external ear (otitis externa), and is the most frequent colonizer of medical devices. *Pseudomonas* can, in rare circumstances, cause community-acquired pneumonias, as well as ventilator-associated pneumonias, being one of the most common agents isolated in several studies. Pyocyanin is a virulence factor of the bacteria and has been known to cause death in *C. elegans* by oxidative stress. However, research indicates that salicylic acid can inhibit pyocyanin production. One in ten hospital-acquired infections is from *Pseudomonas*. Cystic fibrosis patients are also predisposed to *P. aeruginosa* infection of the lungs. *P. aeruginosa* may also be a common cause of "hot-tub rash" (dermatitis), caused by lack of proper, periodic attention to water quality. The most common cause of burn infections is *P. aeruginosa*. *Pseudomonas* is also a common cause of post-operative infection in radial keratotomy surgery patients. The organism is also associated with the skin lesion ecthyma gangrenosum. With plants, *P. aeruginosa* induces symptoms of soft rot with *Arabidopsis thaliana* (Thale cress) and *Lactuca sativa* (Lettuce). It is a powerful pathogen with *Arabidopsis* and with some animals.

E.coli is a Gram negative rod-shaped bacterium that is commonly found in the lower intestine of warm-blooded organisms (endotherms).It is used as model organism in microbiological studies. Most *E. coli* strains are harmless, but some can cause serious food poisoning in humans. The harmless strains are part of the normal flora of the gut, and can benefit their hosts by producing vitamin K and by preventing the establishment of pathogenic bacteria within the intestine. Virulent strains of *E. coli* can cause gastroenteritis, urinary tract infections, and neonatal meningitis. In rare cases, virulent strains are also responsible for haemolytic-uremic syndrome (HUS), peritonitis, mastitis, and septicemia. *E. coli* can harbor both heat-stable and heat-labile enterotoxins.The latter, termed LT, contains one A subunit and five B subunits arranged into one holotoxin, and is highly similar in structure and function to cholera toxins. Non-pathogenic strain of E.coli is used as probiotic agent in medicine, mainly for the treatment of various gastroenterological diseases, including inflammatory bowel disease. *E. coli* are extremely sensitive to streptomycin or gentamicin.

Pseudomonas aeruginosa is a highly prelevant opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* consists in its low antibiotic susceptibility. This low susceptibility is attributable to a concerted action of multidrug efflux pumps with chromosomally-encoded antibiotic resistance genes and the low permeability of the bacterial cellular envelopes. Besides intrinsic resistance, *P. aeruginosa* easily develop acquired resistance either by mutation in chromosomally-encoded genes, or by the horizontal gene transfer of antibiotic resistance determinants. Development of multidrug resistance by *P. aeruginosa* isolates requires several different genetic events that include acquisition of different mutations and/or horizontal transfer of antibiotic resistance genes. Hypermutation favours the selection of mutation-driven antibiotic resistance in *P. aeruginosa* strains producing chronic infections, whereas the clustering of several different antibiotic resistance genes in integrons favours the concerted acquisition of antibiotic resistance determinants. Some recent studies have shown that phenotypic resistance associated to biofilm formation or to the emergence of small-colony-variants may be important in the response of *P. aeruginosa* populations to antibiotics treatment.

Streptococcus pyogenes is a Gram-positive facultative anaerobic bacterium. It is non-motile and does not produce spores. *Steptococus pyogenes* has the potential to cause both mild and severe diseases. It has ability to destroy red blood cells; this hemolysis is attributed to toxins formed by Group A streptococci called streptolysins. Streptolysins can destroy not only red blood cells, but also the white blood cells responsible for fighting off bacteria and disease, as well as other body cells. *Streptococcus pyogenes* can be considered an opportunistic pathogen. It is part of the normal flora of the respiratory tract in many people, but usually does not cause complications until the person's natural defenses to disease compromised. *Streptococcus pyogenes* is somewhat unique in that it does not cause just one disease, but is capable of causing many different diseases. These diseases range from mild, like strep throat and impetigo; *Streptococcus pyogenes* is the most common bacterial cause of sore throat. A painful, red throat with white patches on your tonsils is characteristic of pharyngitis, otherwise known as strep throat. It is usually accompanied by swollen lymph nodes, fever, and headache. Occasionally nausea, vomiting, and abdominal pain also accompany it. A doctor through a throat culture or a rapid strep test can diagnose strep throat.

Bacillus megaterium is a rod-shaped, gram positive, endospore forming, species of bacteria used as a soil inoculants in agriculture and horticulture. Bacterium is arranged into the streptobacillus form. *Bacillus megaterium* is a rod shaped bacteria and one of the largest eubacteria found in soil. *Bacillus megaterium* is able to survive in some extreme conditions such as desert environments due to the spores it forms, *Bacillus megaterium* produces penicillin amidase used for making penicillin. It produces enzymes for modifying corticosteroids, as well as several amino acid dehydrogenases.

Alkaligenes faecalis is a gram negative, rod-shaped, motile bacterium that is commonly found in environment, it was originally named for its first discovery in feces. It is opportunistic pathogen, it is generally considered pathogenic when an opportunistic infection does occur. It generally caused urinary tract infection. .*Alkaligenes faecalis* has been used for the production of non-standard amino acids. *A. faecalis* is normally found in soil, water, and environments in association with humans.

Proteus mirabilis is a gram-negative, facultative anaerobic bacteria. This rod shaped bacterium has the ability to produce high levels of urease, urease hydrolyzes urea to ammonia (NH_3) and therefore makes urine more alkaline. Increase in alkalinity leads to the formation of calcium carbonate crystals, which may leads to renal failure. It can also cause wound infections, septicemia & pneumonias. *Proteus mirabilis* is generally susceptible to most antibiotics apart from tetracycline; however 10%–20% of *P. mirabilis* strains are also resistant to first generation cephalosporin and ampicillins.

Alcaligenes is a genus of Gram-negative, pathogenic, opportunistic bacteria. *Alcaligenes* are found in various locations, including soil and aquatic environments, *Alcaligenes denitrificans*, has been known to inhibit the growth of certain types of algae. They may also be found in the respiratory tracts of cystic fibrosis patients, where they cause clinical symptoms of pulmonary disease

Bacillus circulans is Gram positive, motile & aerobic bacteria. It is used in industries for the production of L-glutamic acid. Although it is not a major pathogen, *Bacillus circulans* has been reported to cause infections such as endocarditis.

Shigella flexneri is a gram negative, non-motile, non spore forming, rod shaped bacteria, very closely related to *Escherichia coli* that can cause diarrhea in humans called shigellosis. The diarrhea is often bloody which usually resolves in 5 to 7 days. Shigellosis can usually be treated with antibiotics. The antibiotics commonly used are ampicillin, trimethoprim/sulfamethoxazole (also known as Bactrim or Septra), nalidixic acid and the fluoroquinolone, ciprofloxacin.

Study of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration was studied using cup plate method as repoted by Yadav and Bhise[33]. The antibacterial activity and MIC was studied against different strains of bacteria, viz. *Bacillus megaterum, Bacillus subtilis, E. coli* and *Staphylococcus epidermidis* by agar diffusion method in particular, cup-plate method. They determined the MIC Chitosanis which is deacetylated product formed by treatment of chitin with concentrared (50%) caustic alkali. Again the antimicrobial effect and MIC of special type of fibres produced in Isofahan Polyacryl plant on three species[34] of *Staphylococcus aureus, Staphylococcus epidermidis and S lugdemensis*

5.2.2: A. Bactericidal Study

I. Materials

1. Bacterial strains used for antibacterial property studies

i. *Staphylococcus aureus*(MTCC902):Kingdom:Bacteria, Phylum :Firmicutes,Class:Cocci, Order : Bacillales , Family :Staphylococcaceae

ii. *Staphylococcus epidermidis* (MTCC 435),

iii. *Bacillus subtilis* (MTCC2389) : Family: Bacillaceae

iv. *Pseudomonas aeruginosa* (MTCC425): Class: Gamma Proteobacteria, Order: Pseudomonadales, Family: Pseudomonadaceae

v. *Escherichia coli k12* (MTCC302): Order: Enterobacterials, Family: Enterobacteriaceae

vi. *Streptococcus pyogenes* (MTCC1927)

vii. *Bacillus megaterium* (MTCC1684) Domain: Bacteria, Phylum: Firmicutes, Class: Bacilli, Order: Bacillales, Family: Bacillaceae, Genus: Bacillus

viii. *Alkaligene faecalis* (MTCC126)

ix. *Proteus mirabilis* (MTCC425)

x. *Alkaligene denitrificans*(MTCC299)

xi. *Bacillus circulans* (MTCC3161)

xii. *Cloustridium sporogenes* (MTCC1349)

xiii. *Shiegella flexneri* (MTCC3105)

All the strains were obtained from the Institute of Microbial Technology, Chandigarh.

II a. Medium for bacterial culture (broth): Specified by M.T.C.C.

MATERIAL	AMOUNT
Beef extract	1.0 g/L
Yeast extract	2.0 g/L
Peptone	5.0 g/L
Sodium chloride	5.0 g/L
Distilled water	1 L

b. Solid medium for plating

Hard agar medium: above broth +15g/L agar

Soft agar medium: +7 g/L agar agar

c. Antibiotic control: **Rifampicin** (1mg/mL)

5.2.3 Revival of Lyophilized Cultures:

The lyophilized culture supplied by M.T.C.C was inoculated into the nutrient broth and incubated at 37° C for 24 hours.

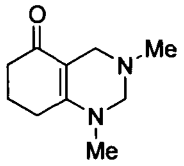
5.2.4 Cup plate method to study antibacterial property:

In this method a layer of hard agar medium was made on the Petri plates. Now a layer of soft agar media was poured onto it. The media was allowed to solidify and punched to make wells. Now the solvent (DMSO), antibiotic control and the test sample (synthesized chemical) at different concentration was loaded in separate wells (20µl in each well). The plates were incubated at 24 hours. Then the zone of inhibition was measured.

5.2.5 Determination of Minimum Inhibitory concentration (MIC):

The MIC was taken as the minimum concentration of antibiotic at which zone of inhibition was observed. The plates were incubated in incubators at 37 ± 1 °C for bacteria and 28 ± 1 °C for fungi (BOD incubator). The MICs were recorded by visual observations after 24 h (for bacteria) and 72–96 h (for fungi) of incubation. Rifampicin is used as standard drug (positive control) and DMSO is used as negative control.

Out of eighty novel quinazoline and bis quinazolines prepared in the previous four chapters antimicrobial studies were carried out with the following representative quinazolines and bis quinazolines.



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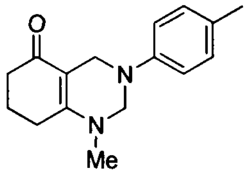

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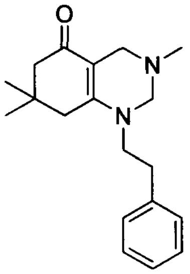

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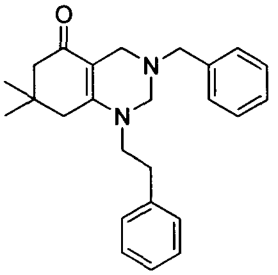

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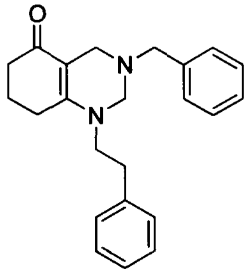

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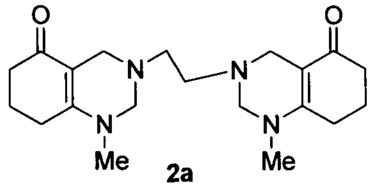
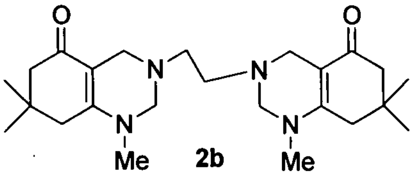

2a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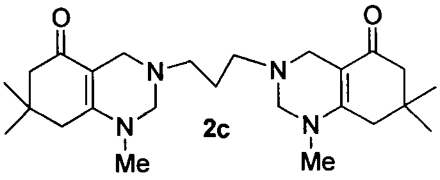
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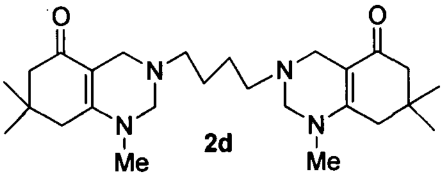
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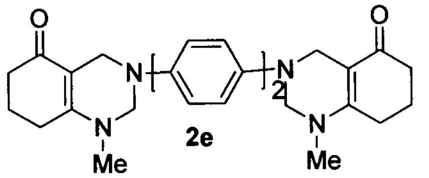
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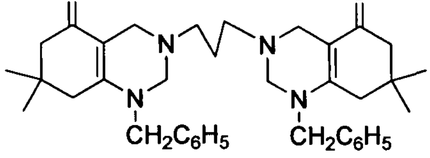
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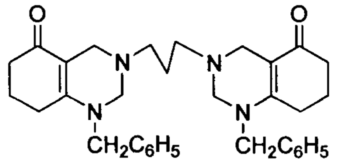
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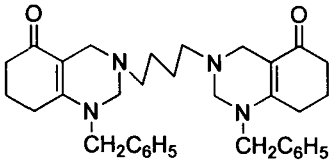
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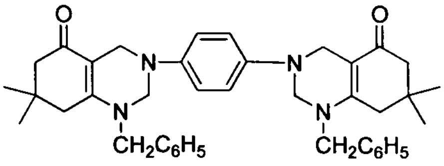
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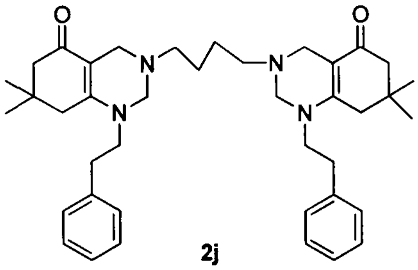
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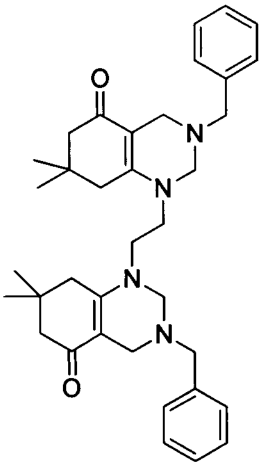

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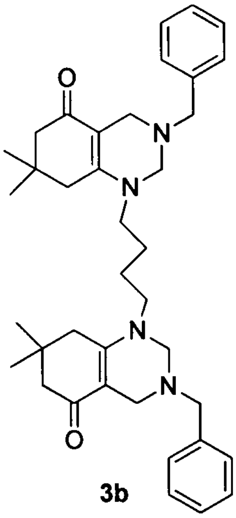

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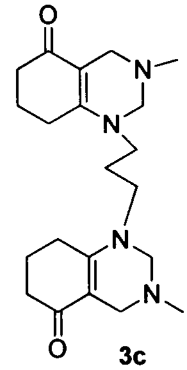

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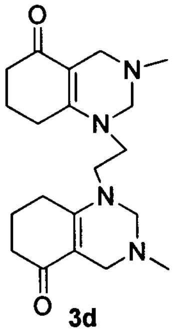
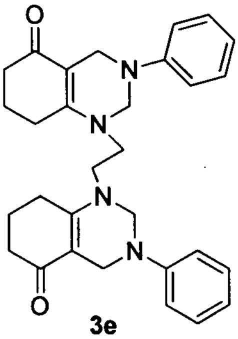


3d



3e

Fig 1 Zone of inhibition caused by compound**1d** in *B.megaterium* culture. C: antibiotic control. S: Solvent control. Wells 1-4: 7.5mg/ml;3.75mg/mL;0.93mg/ml of compound loaded.

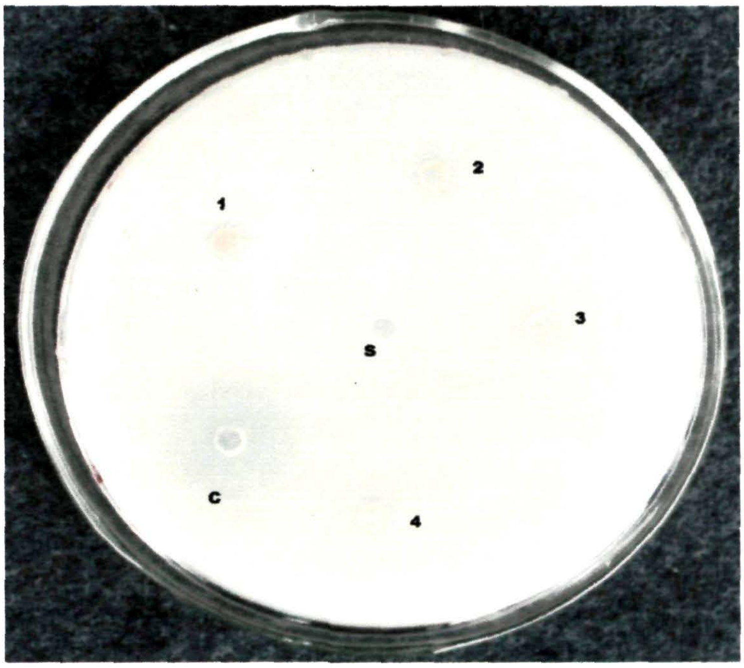


Fig 2 Test for determination of MIC ofcompound **2e** on *S.epidermidis* culture. C: Antibiotic control. S: Solvent control. Wells 1-4: 3.5 mg/mL; 1.75 mg/ml; **0.87 mg/ml (MIC)**; 0.43 mg/ml of compound loaded.

5.3 RESULTS AND DISCUSSION

5.3.1 Observation-1

Anti-bacterial Affect

Among the different quinazoline of Chapter-2 tested for their susceptibility to different bacterial strain only for four of them shows the positive results.

Compound name	Microorganisms used for study	Gram stain	Zone of inhibition of compound at different dilution.			Zone of inhibition of antibiotic
			1:1	1:2	1:4	
1a	*Staphylococcus aureus*	Positive	-	-	-	20mm
	Stretococcus pyogenes	Positive	-	-	-	15mm
1b	*Staphylococcus aureus*	Positive	-	-	-	20mm
	Stretococcus pyogenes	Positive	-	-	-	15mm
2a	*Staphylococcus aureus*	Positive	-	-	-	20mm
	Stretococcus pyogenes	Positive	-	-	-	15mm
2b	*Staphylococcus aureus*	Positive	-	-	-	20mm
	Stretococcus pyogenes	Positive	-	-	-	15mm

2e	*Escherichia coli*	Negative	-	-	-	20mm
	Staphylococcus aureus	Positive	-	-	-	16mm
	Bacillus subtilis	Positive	-	-	-	13mm
	Proteus mirabilis	Negative	-	-	-	19mm
	Bacillus megaterium	Positive	5mm	2mm	1mm	24mm
	Staphylococcus epidermidis	Positive	4mm	2mm	1mm	15mm
2f	*Streptococcus pyogenes*	Positive	-	-	-	16
	Alkaligene faecalis	Positive	-	-	-	13
	Staphylococcus aureus	Positive	-	-	-	17
2c	*Bacillus subtilis*	Positive	5.5mm	3.5mm	2.5mm	20mm
	Streptococcus pyogenes	Positive	-	-	-	15mm
	Alkaligene denitrificans	Negative	-	-	-	20mm
	Escherichia coli	Negative	4mm	1mm	0.5mm	26mm
	Pseudomonas aeruginosa	Negative	-	-	-	10mm
	Shigella flexneri	Negative	-	-	-	14mm

5.3.2 Anti-bacterial Affects of quinazolines on *Staphylococcus epidermidis*

The largest zone of inhibition was found for Compound **2e** (4mm) at 3.5mg/ml concentration. This was significantly smaller than the zone of inhibition for antibiotic control (Rifampicin), which is 15mm at 1mg/ml concentration. This compound was also found to have inhibitory affect at lower concentration. The Minimum inhibitory concentration (MIC) was found to be 0.87mg/ml.

5.3.3 Anti-bacterial affect of quinazoline on *Bacillus megaterium*

The largest zone of inhibition was found for Compound **2e** (5mm) at 3.5mg/ml concentration, which was significantly smaller as compared to the zone of inhibition of antibiotic control (24mm) at 1mg/ml concentration. This compound is also found to have inhibitory affect at low concentration. The MIC of the molecule is found to have 0.87mg/ml.

5.3.4 Anti-bacterial affect of quinazoline on *Bacillus subtilis*

This Compound **2c** at concentration of 3.5mg/ml showed the largest zone of inhibition (5.5mm) in terms of diameter. This is significantly smaller as compared to the diameter of zone of inhibition of antibiotic control at 1mg/ml concentration. This Compound also has good antibacterial affect at other concentrations. The MIC of the molecule found to have 1.75mg/ml.

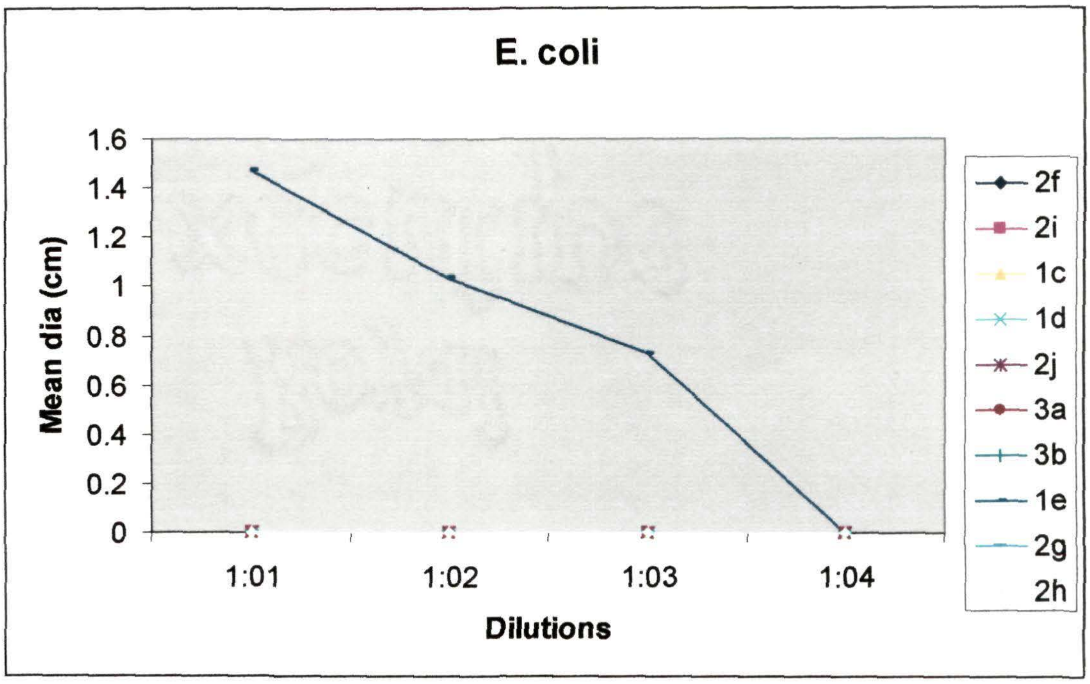
5.3.5 Anti-bacterial affect of quinazoline on *Escherichia coli*

The largest zone of inhibition in terms of diameter was found for the Compound **2c** (4mm) at 3.5-mg/ml concentrations. This value is significantly smaller as compared to the zone of inhibition caused by the antibiotic (26) at 1mg/ml concentration. This molecule also shows the anti bacterial affect at low concentration. The MIC of the molecule is found to be 3.5mg/ml.

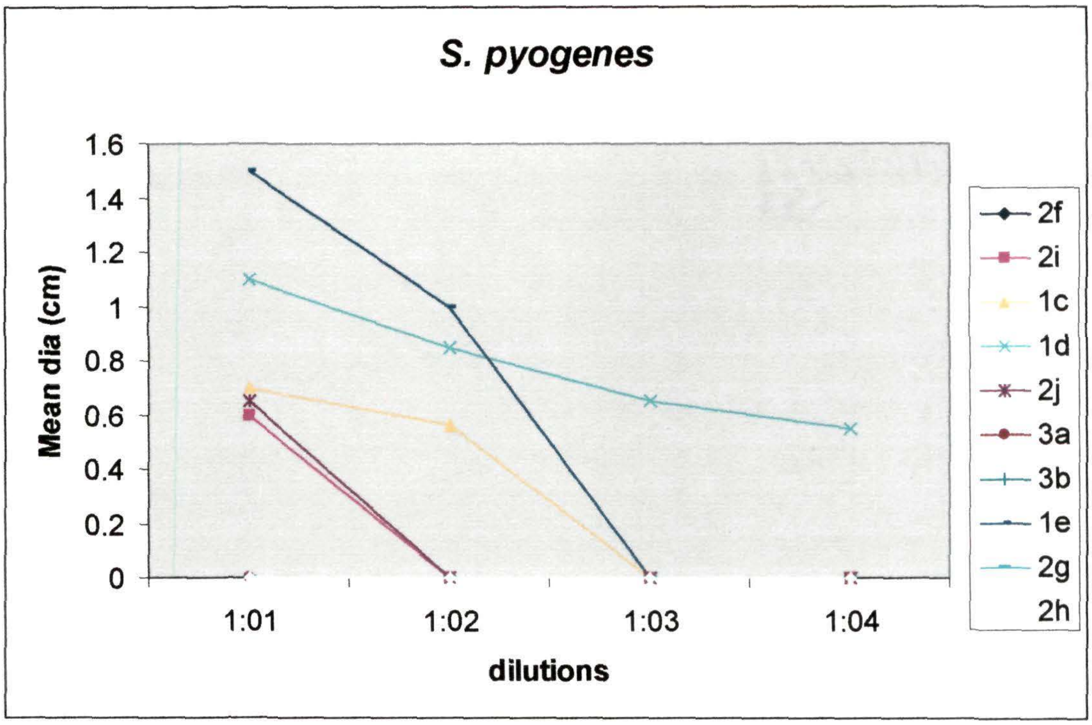
5.3.6 Observation-2

Antibacterial activity of some representative quinazolines in graphical representation.

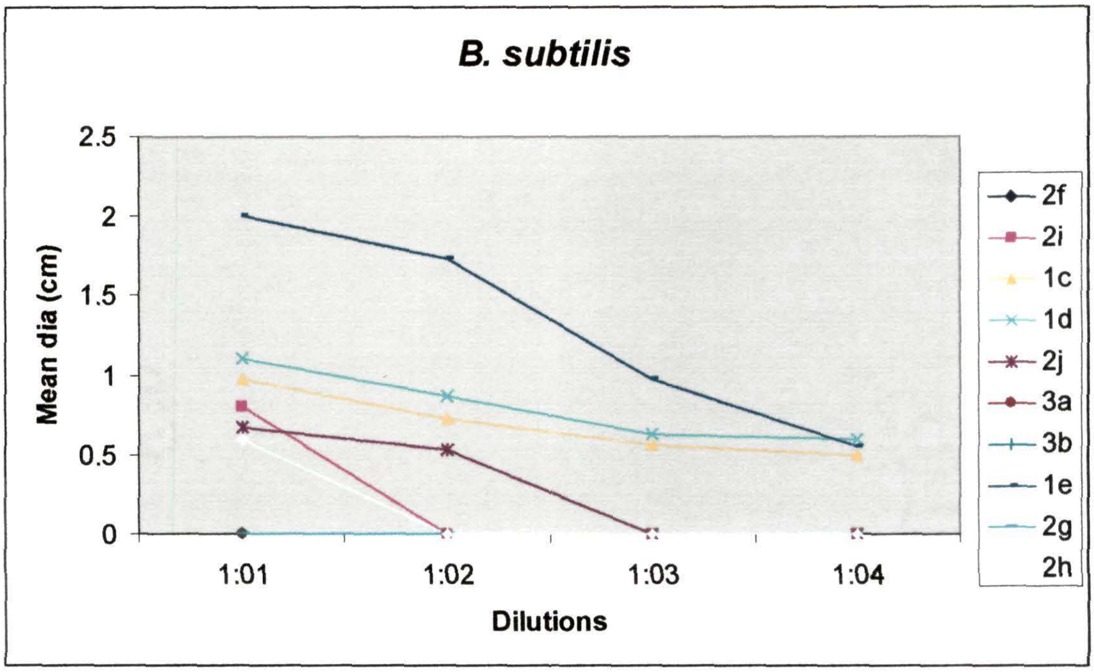
a) ***Escherichia coli* K12**: compound **1e** showed inhibitory effects on *E. coli* as: Dilutions1:1-1.47cm, 1:2-1.03 cm, 1:3-0.73 cm. Therefore it showed minimum bactericidal activity at 1:3 dilutions. The other compounds did not show any bactericidal activity against *E. coli.*



- ***b) Alcaligens faecalis***: The compounds did not show any inhibitory effects on *A. faecalis.*
- ***c) Streptococcus pyogens***: compound **2i** showed inhibitory effects on *S. pyogens* as: Dilution1:1-0.6 cm. Compound **1c** showed inhibitory effects as: Dilutions1:1-0.7 cm and 1:2-0.56 cm. Ligand **1d** showed inhibitory effects as: Dilutions1:1-1.1 cm, 1:2-0.85 cm, 1:3-0.65 cm and 1:4-0.55 cm. Compound **2j** showed inhibitory effects as: Dilutions1:1-0.65 cm. Compound **1e** showed inhibitory effects as: Dilutions1:1-1.5 cm and 1:2-1 cm. Therefore it showed minimum bactericidal activity at 1:4 dilutions for Compound **1d**.



d) ***Bacillus subtilis***: Compound **2f** showed inhibitory effects on *B. subtilis* as: Dilution 1:1-0.6 cm. Compound **2i** showed inhibitory effects as: Dilutions1:1-0.8 cm. Ligand 1c showed inhibitory effects as: Dilutions1:1-0.97 cm,1:2-0.73 cm, 1:3-0.56 cm and 1:4-0.5 cm. Compound **1d** showed inhibitory effects as: Dilutions1:1-1.1 cm, 1:2-0.87 cm, 1:3-0.63 cm and 1:4-0.6 cm. Compound **2j** showed inhibitory effects as: Dilutions1:1-0.67 cm and 1:2-0.53 cm. Compound **1e** showed inhibitory effects as: Dilutions1:1-2 cm,1:2-1.73 cm,1:3-0.97 cm and 1:4-0.55 cm. Therefore it showed minimum bactericidal activity at 1:4 dilution for Compound **1c.**



The compound **1e** showed maximum inhibition against all the bacterial species, except *Alcaligens faecalis*. It was the only compound which showed bactericidal activity against the Gram negative bacterium *E.coli.*

The compound **1d** was the next to show bactericidal activity against only Gram positive bacteria under study. But this activity was found to be less than that of **1e.**

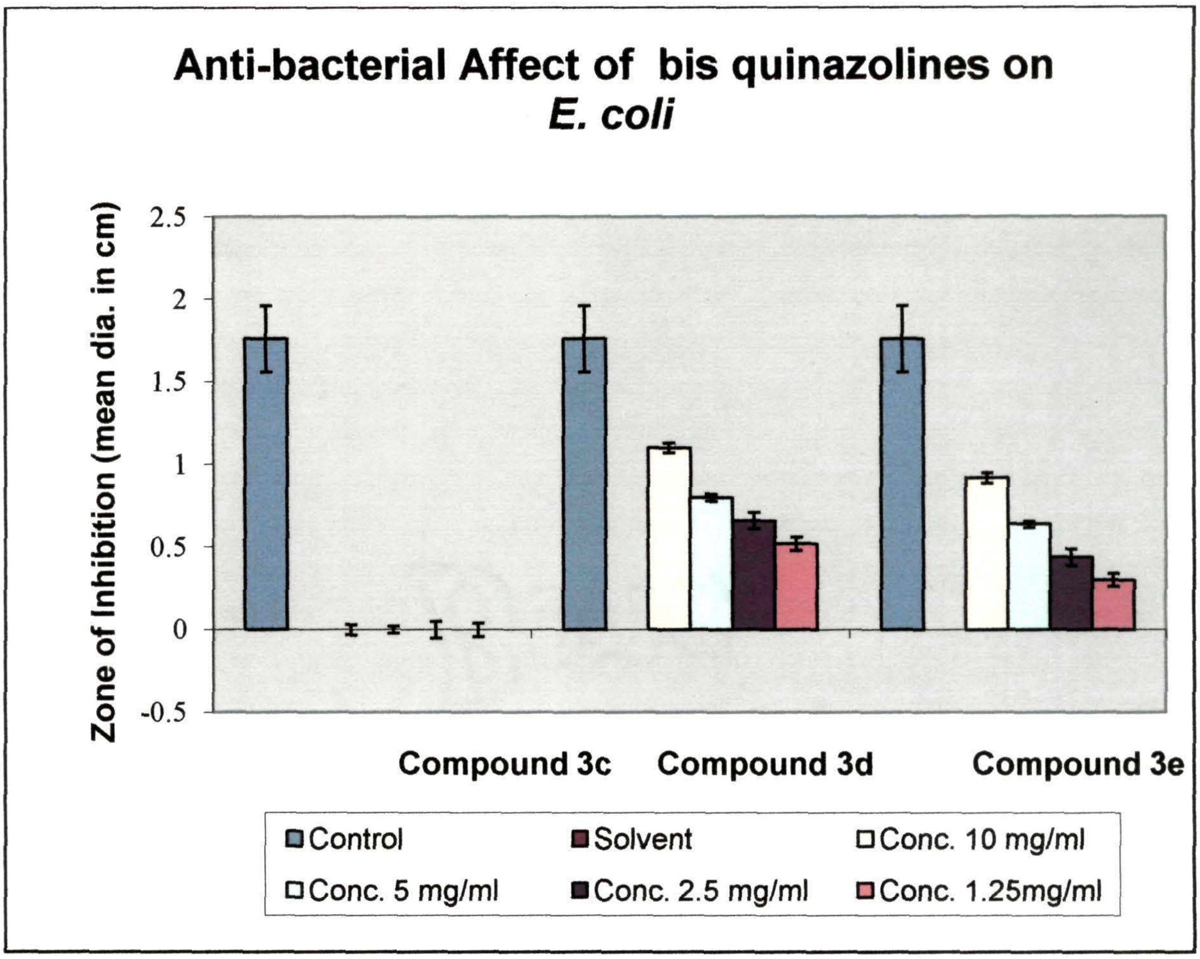
This was followed by the compound **1c** which showed a still lower bactericidal activity than the aforementioned.

For *S. pyogens*, the compound **2j** followed by **2i** was found to show the next level of bactericidal activity. But, for *B. subtilis*, **2i** was followed by **2j**.

The compound **2h** showed activity against *B. subtilis* only, after **2j**. The rest of the compounds, i.e., **2f**, **3a** and **2g** did not show any bactericidal activity against any of the bacterial strains under study.

5.3.7 Observation-3

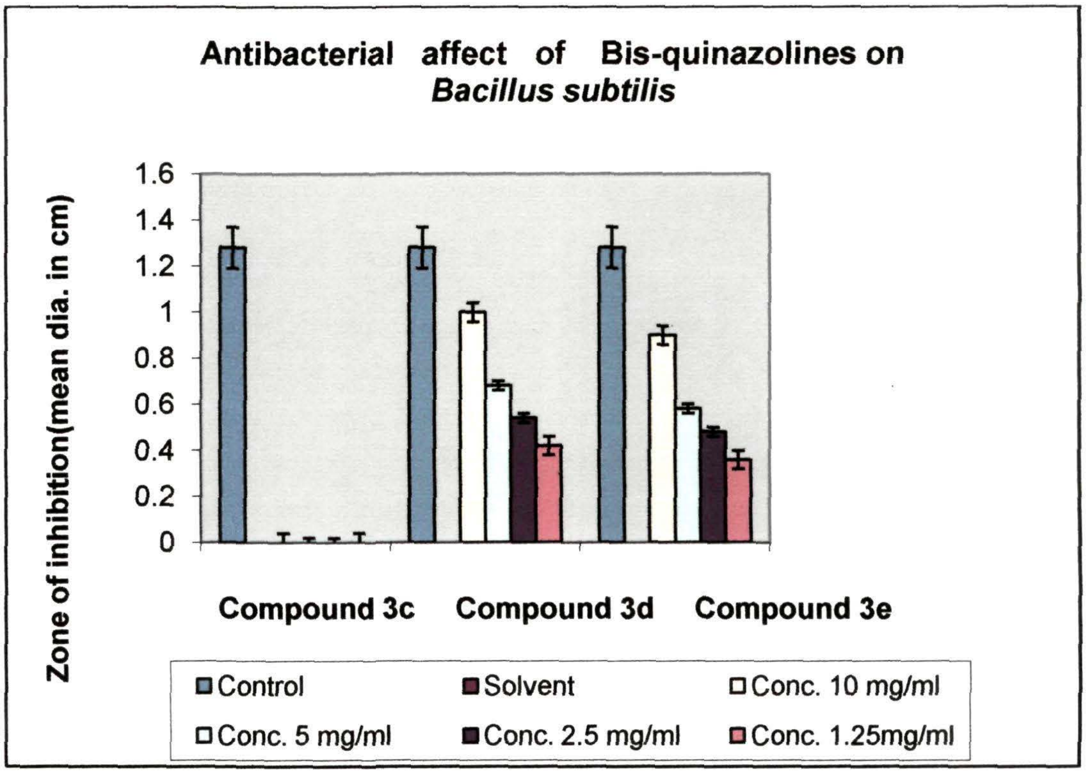
Anti-bacterial Affect of bis-quinazoline 3c, 3d and 3e on *E. coli*



The largest mean diameter (1.1±0.03 cm) of zone of inhibition was due to the 1,1′-(ethan-1,2-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (Compound **3d**) at 10 mg/ml concentration. However, this was significantly smaller than the mean diameter (1.76 ± 0.08 cm) of zone of inhibition measured in the antibiotic control. Compound **3d** also had inhibitory affect at lower concentrations. The minimum inhibitory concentration (MIC) of this Compound was 0.31 mg/ml.

The Compound **3e** (1,1′-(propan-1,3-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline) at 10 mg/ml concentration caused a zone of inhibition of 0.92±0.05 cm mean diameter. This value was significantly lower than the value (1.36±0.11cm) recorded due to the antibiotic control. This value is not significantly different from the zone of inhibition of the Compound **3d** at 10mg/ml concentration .This compound also showed antibacterial properties at lower concentration. The MIC of this molecule was 1.25 mg/ml.

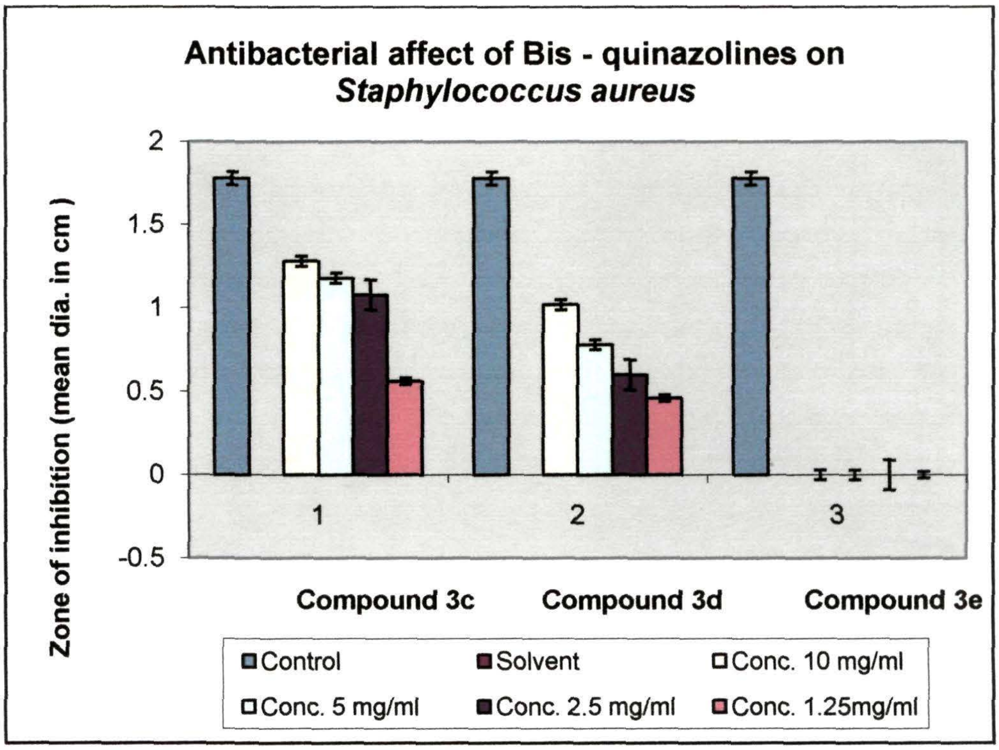
5.3.8 Anti-bacterial Affect of bis-quinazoline 3c, 3d and 3e on *Bacillus subtilis*



The largest zone of inhibition in terms of mean diameter was found for Compound **3d** (1.0 ± 0.0 cm) at 10mg/ml concentration. This was significantly smaller than the zone of inhibition for antibiotic control (1.28 ± 0.05). Molecule **3d** was also found to have inhibitory affect at lower concentrations. The MIC of the molecule was found to be 0.31mg/ml

The compound **3d** showed the largest zone of inhibition (0.9 ±0.04) at concentration 10 mg/ml. This value was found to be significantly less than the value for the antibiotic control (1.82 ± 0.14). However this value is not significantly different from the Zone of inhibition of compound **3d** at the concentration 10mg/ml. At lower concentrations also it was active against the bacteria. The minimum inhibitory concentration of this Compound was found to be 0.63 mg/ml.

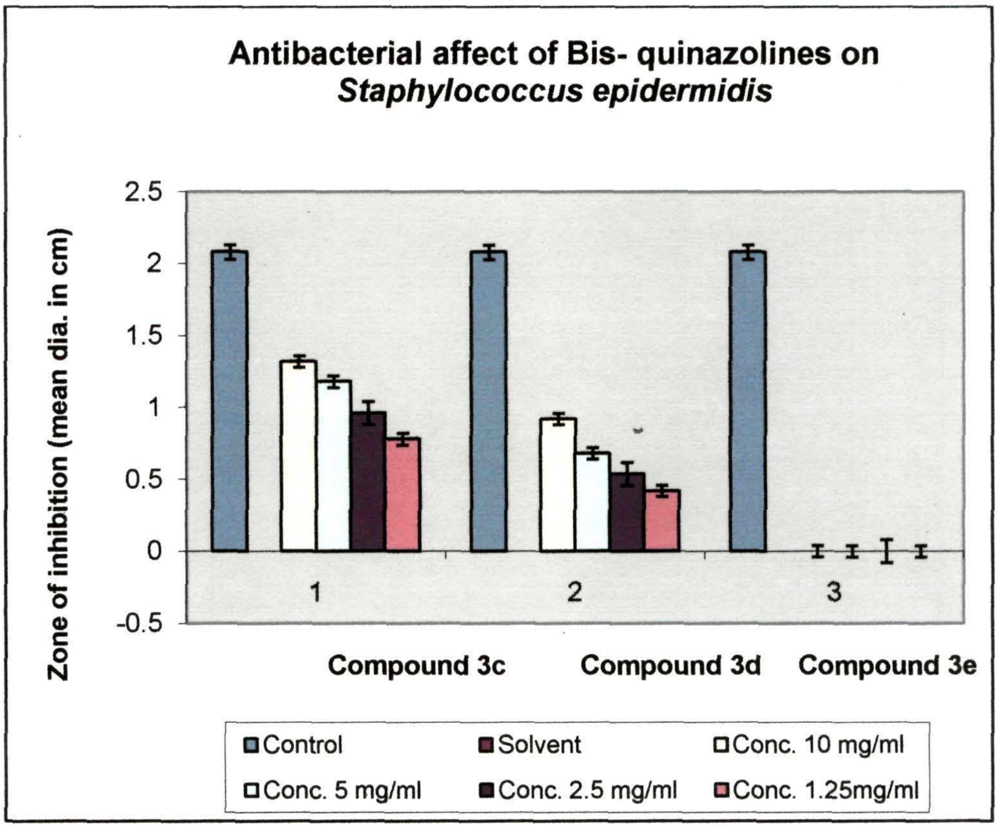
5.3.9 Anti-bacterial Affect of bis-quinazoline 3c, 3d and 3e on *Staphylococcus aureus*



The Compound **3c** (1,1′-(propan-1,3-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline) at concentration of 10mg/ml showed the largest zone of inhibition (1.28± 0.22 cm) in terms of mean diameter . This was significantly smaller than the zone of inhibition for the antibiotic control (2.94 ± 0.07 cm). It had inhibitory effect at other concentrations also. The MIC of this molecule was found to be 1.25 mg/ml.

For Compound **3d** the mean diameter of the largest zone of inhibition was 1.02 ± 0.03 cm which was for the concentration 10mg/ml. This value was significantly smaller than the value for antibiotic control (1.78 ± 0.04 cm) and not significantly different from the zone of inhibition for Compound **3c** at concentration 10mg/ml. Antibacterial property was present at other concentrations. The minimum inhibitory concentration of this molecule was 0.63 mg/ml.

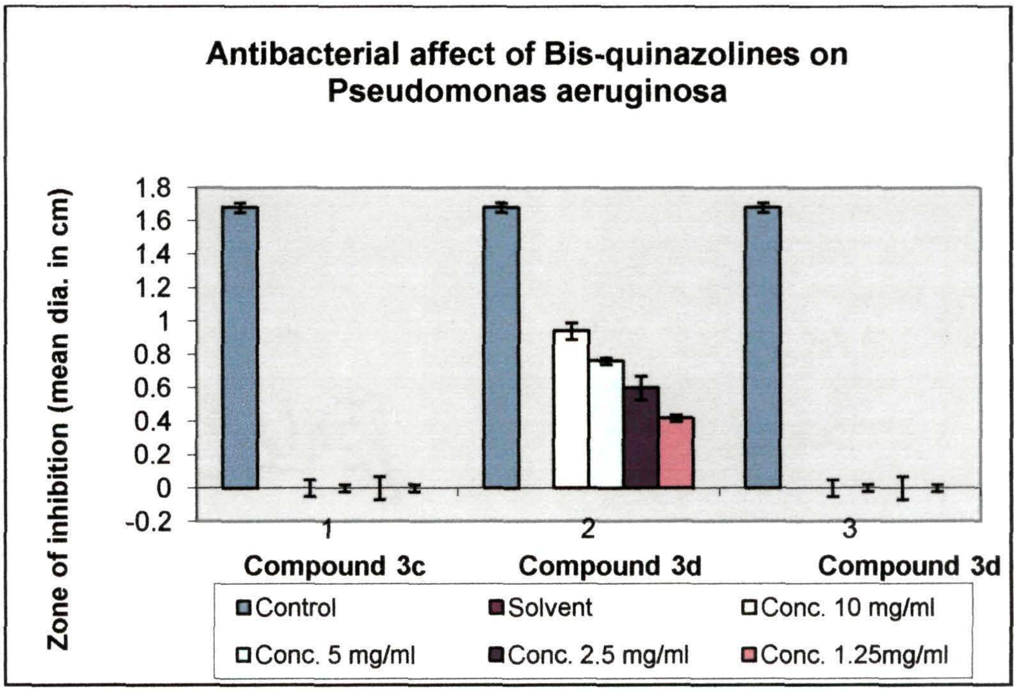
5.3.10 Anti-bacterial Affect of bis-quinazoline 3c, 3d and 3e on *Staphylococcus epidermidis*



The largest zone of inhibition in terms of mean diameter was found for the Compound **3c** (1.32 ± 0.33 cm) at the concentration of 10 mg/ml .This value was significantly smaller than the value of zone of inhibition of antibiotic control (3 ± 0.07 cm) . Zone of inhibition was observed for lower concentrations also. The minimum inhibitory concentration of Compound **3c** was 0.63 mg/ml.

The largest mean diameter of the zone of inhibition for Compound **3d** is 0.92 ± 0.02 cm .This value is significantly less than the value of antibiotic control (2.08 ± 0.11 cm) and not significantly less from the mean diameter of zone of inhibition of Compound **3c** at the concentration of 10 mg/ml. The MIC of the molecule was 0.31 mg/ml.

5.3.11: Anti-bacterial Affect of bis-quinazoline 3c, 3d and 3e on *Pseudomonas aeruginosa*



The Compound **3d** was the only one to show antibacterial property against *Pseodomonas aeruginosa.* The largest mean diameter of the zone of inhibition (0.94± 0.05 cmShaker incubator.) was observed at concentration 10 mg/ml. This was not significantly different from the zone of inhibition of antibiotic control (0.88 ±0.03 cm). At lower concentration of the compound, zone of inhibition was observed. The MIC was 0.63 mg/ml.

5.4 Antifungal Study

5.4.1 Materials

Fungal strains used for the antifungal property studies

- i. *Candida albicans* (MTCC-227)
- ii. *Penicillium citreonigrum* (MTCC-160)
- iii. *Aspergillus niger* (MTCC-281)

All the strains obtained from Institute of Microbial Technology, Chandigarh

5.4.2 a) Medium preparation for fungal culture: specified by M.T.C.C.

MATERIAL	AMOUNT
Potato (scrubbed and diced)	200.0g/L
Dextrose	20.0g/L
Agar	15.0g/L
Distilled water	1.0L

b. **Antibiotic control: Nystatin (1mg/mL)**

5.4.3 Cup plate method to study antifungal property:

In this method the pathogen spore suspension was prepared in 5ml of sterile distilled water. The suspension of 2ml was spread over the potato dextrose agar (PDA) plates uniformly after it solidifying. Five different wells are bored using the gel puncher. Now the solvent (DMSO), antibiotic control and the test sample (synthesized compound) at different concentration was loaded in separate wells (20μl in each well). The plates were incubated at 48 hours. Then the zone of inhibition caused by the synthetic compound was measured using millimeter scale.

5.4.4 Materials used

a) **Apparatus**

1. Petri plates (9cm diameter)
2. Conical flask.
3. Gel puncher.
4. Incubator.
5. Autoclave.
6. Laminar flow hood.
7. Shaker incubator.
11. Eppendroff tube.
12. Micropipette.

b) **Reagents**

1. Lyophilized culture of bacteria and fungi.
2. Nutrient broth (Sterilized).
3. DMSO (Solvent)
4. Distilled water.
5. Ethanol.
6. Antibiotic control (Rifampicin & Nystatin).

Name of the Molecule	Fungal strain used for study	Zone of inhibition of compound at different dilution.			Zone of inhibition of antibiotic
		1:1	1:2	1:4	(Nystain)
1a	*Candida albicans*	-	-	-	16mm
	Penicillium citreonigrum	-	-	-	15mm
	Aspergillus niger	-	-	-	15mm
1b	*Candida albicans*	-	-	-	15mm
	Penicillium citreonigrum	-	-	-	13mm
2a	*Aspergillus niger*	-	-	-	15mm
	Candida albicans	-	-	-	16mm
	Penicillium citreonigrum	-	-	-	12mm
2b	*Candida albicans*	-	-	-	13mm
	Penicillium citreonigrum	-	-	-	14mm

5.4.5 Conclusion Among the representative quinazoline tested for antifungal property none of them were found to be active against the fungal strains used during the study.

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BIO-DATA

Name	Madhusudhan Saha
Father's Name	Shri Jyotish Chandra Saha
Address for correspondence	Department of Chemistry Don Bosco College, Tura, West Garo Hills Meghalaya-794002, India
Email	ms.19.chem@gmail.com
Date of Birth	27/10/1969. **Sex** Male
Nationality	Indian. **Languages known** English, Bengali, Hindi.

Academic Qualifications

Exam Passed	**Year**	**Board/University**	**Percentage**
M.Sc (Organic Chemistry)	1993	North Eastern Hill University	66.11
B.Sc (Chemistry)	1991	North Eastern Hill University	59.00
PU (Sc)	1988	North Eastern Hill University	50.00
HSLC	1985	Meghalaya Board of School Education.	53.33

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