Synthesis of 1,2,3,4-Tetrahydropyrimidine Analogues from Active Methylene Compounds

ABSTRACT

By

MILAN CHANDRA DUTTA
DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

A THESIS
SUBMITTED
IN FULFILLMENT OF THE REQUIREMENT FOR THE
DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY

TO

NORTH-EASTERN HILL UNIVERSITY
SHILLONG-793022
MEGHALAYA (INDIA)
SEPTEMBER, 2009

Thesis

ABSTRACT

This thesis entitled, "Synthesis of 1,2,3,4-tetrahydropyrimidine analogues from active methylene compounds" has been divided into six chapters.

CHAPTER I

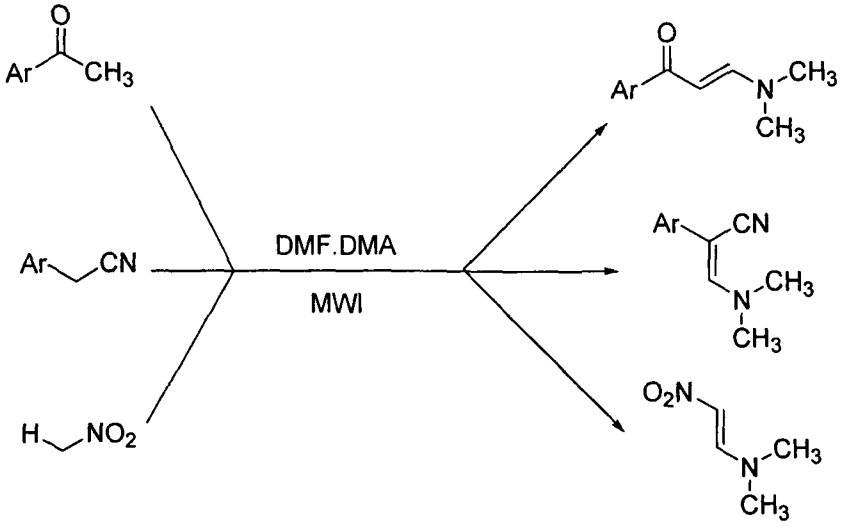
INRODUCTION

In this chapter a literature survey on the synthesis and biological properties of six-membered heterocyclic compounds containing two nitrogen atoms has been presented. We have also briefly highlighted the biological activities of bis-heterocyclic systems in general.

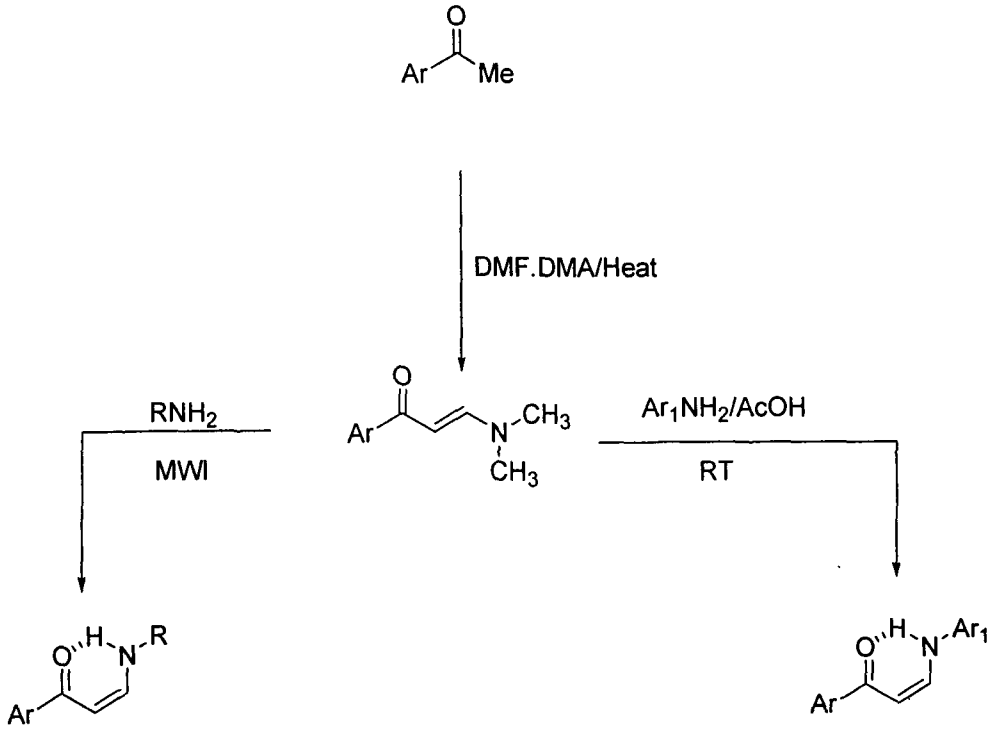
CHAPTER II

Formylation of active methylene compounds and their reactions with primary amines

This chapter presents the synthesis of starting materials required for the construction of the proposed heterocyclic systems. We have developed a facile route for the synthesis of enaminones from cheap and commercially available active proton compounds in two simple steps. The first step involves microwave irradiation of the required active proton compounds with DMF.DMA followed by the conversion of these formylated products to their respective enaminones in very short time and in good to excellent yields. A schematic presentation of the strategy developed is shown in **Schemes 1 & 2** The structures of the products synthesised have been established by their spectral and analytical data.



Scheme 1

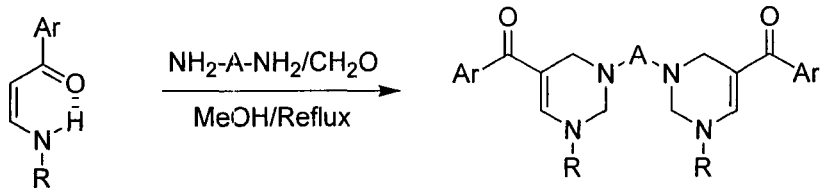


Scheme 2

CHAPTER III

A facile one-pot synthesis of Bis-Tetrahydropyrimidines from Enaminones

This chapter deals with the synthesis of bis-tetrahydropyrimidines from the respective enaminones. We have developed a facile one pot synthetic strategy for the synthesis of bis-tetrahydropyrimidines wherein we have been successful in constructing tetrahydropyrimidine rings and simultaneously linking two tetrahydropyrimidine rings by flexible aliphatic chain or rigid aromatic rings as shown in **Scheme 3**. The structures of the products have been established by their spectral and analytical data and the bilological activities of these dimeric molecules are under investigation.

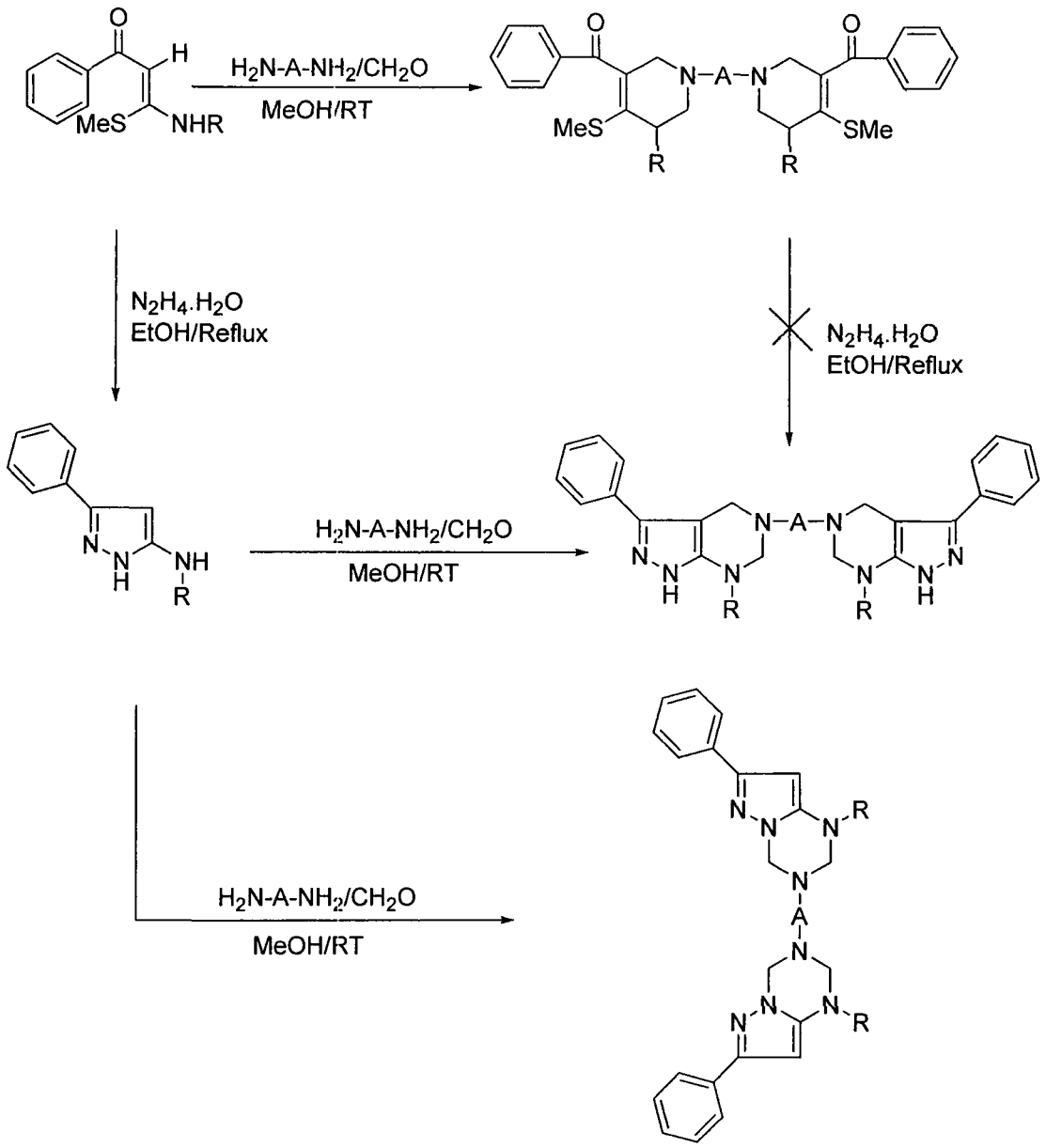


Scheme 3

CHAPTER IV

A facile one-pot synthesis of novel 1,2,3,4-tetrahydropyrimdines, Synthesis of Bis[(1-alkyl/aralkyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl]alkane and benzene, Bis [3-phenyl-7-methyl 4,5,6,7-tetrahydropyrazolo(3,4-*d*)pyrimidinyl]alkane and Bis[1-benzyl-7- phenyl-1,2,3,4-tetrahydropyrazolo(1,5-a)triazinyl]alkane & benzene.

In this chapter the synthesis of three different types of tetrahydropyrimidines are described. we have synthesized a series of hitherto unknown dimeric heterocyclic compounds in which we could successfully connect the two heterocyclic systems i.e 5-benzoyl-6-methylthio tetrahydropyrimidines, 3-phenyl-7-methyl pyrazolotetrahydropyrimidines and 1-benzyl-7-phenyl-pyrazolotriazines by a various aliphatic and aromatic linkers. **Scheme 4** depicts the synthetic strategy involved in the synthesis of the required heterocyclic compounds. The structures of all these products have been assigned based on their analytical and spectral data.

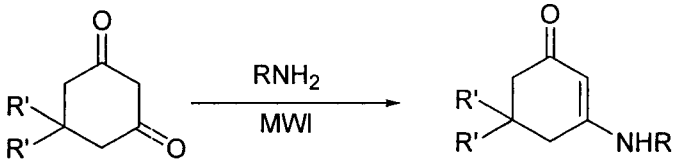

H2N-A-NH2/CH2O
MeOH/RT
N2H4.H2O
EtOH/Reflux
N2H4.H2O
EtOH/Reflux
H2N-A-NH2/CH2O
MeOH/RT
H2N-A-NH2/CH2O
MeOH/RT

Scheme 4

CHAPTER V

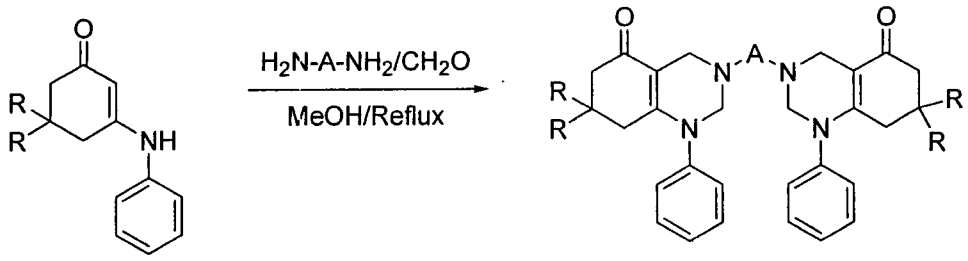
Synthesis of Fused Tetrahydropyrimidines (Hexahydroquinazolines) from cyclic Enaminones

In this chapter we have we have demonstrated a practical application of microwave assisted, solvent-free condensation of cyclic ketones with primary amines in domestic microwave oven to give enaminones derived from cyclohexanedione and dimedone in minutes and in very good to excellent yields (**Scheme 5**).



Scheme 5

The above mentioned enaminones have been used to synthesise a series of hitherto unknown bis-fusedtetrahydropyrimidines (1,2,3,4,7,8-hexahydroquinazolines-5-(6H)-ones) in good yields, wherein we have connected two-quinazoline rings through flexible aliphatic and rigid aromatic chains (**Scheme 6**).The structures of the dimeric molecules have been assigned unambiguously with the help of their analytical and spectral data.

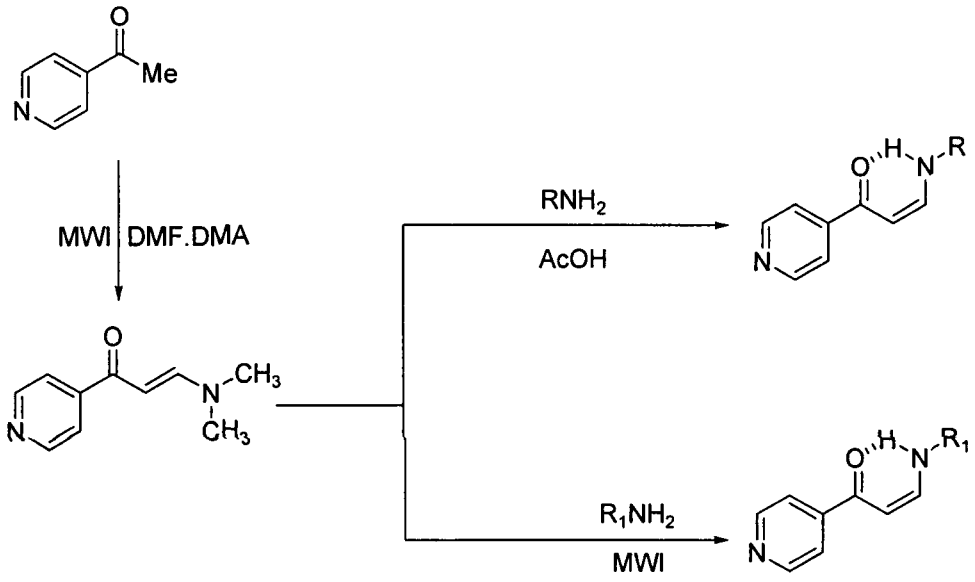


Scheme 6

CHAPTER VI

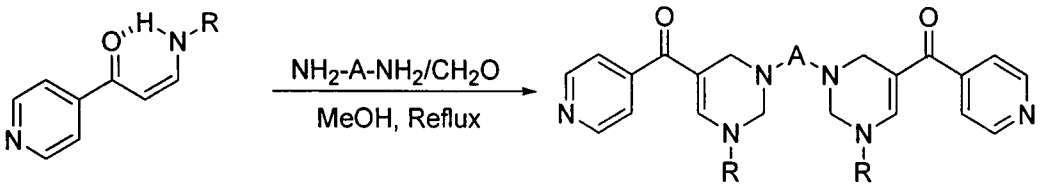
Synthesis of Novel Bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines)

The present chapter involves synthesis of appropriate enaminones from 4-acetylpyridine as shown in **Scheme 7**. The structures of the hitherto unknown enaminones were thoroughly investigated.



Scheme 7

We have synthesized a series of hitherto unknown bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines) in good yields, from the respective enaminones derived from 4-acetylpyridine wherein we have succeeded in replacing the nitro group at position 5 of the THP ring by another electron withdrawing group. The anti-bacterial properties of these bis-tetrahydropyrimidines are currently under investigation.



Scheme 8

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SEPTEMBER, 2009

DECLARARTION

I, Milan Chandra Dutta, 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.

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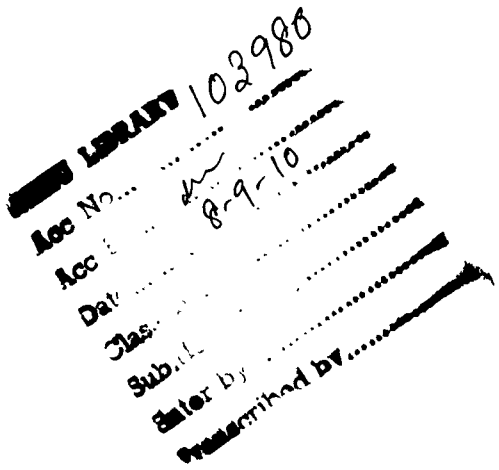

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CERTIFICATE

This is to certify that the thesis entitled, "*Synthesis of 1,2,3,4-Tetrahydropyrimidine Analogues from Active Methylene compounds*" submitted by Mr. Milan Chandra Dutta 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.

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DEDICATED

TO

MY

BELOVED PARENTS

&

GRAND MOTHER

Acknowledgement

I would like to express my deep sense of gratitude to my research guide Dr. J.N. Vishwakarma, Head, Organic Research Lab., Department of Chemistry, St Anthony's College Shillong, who has been my greatest source of inspiration and without whose encouragement, interest and guidance this research work would not have been possible.

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The research work described in this thesis was carried out in the Organic Research Lab., Department of chemistry, St Anthony's College, Shillong. It is indeed a great privilege to express my heartfelt thanks to Rev. Fr. Iaonnis Warpakma, SDB, Principal, St Anthony's College and Rev. Fr. Stephen Mavely, SDB for providing excellent infrastructure and facilities in the College which enabled me to carry out the research work smoothly. I specially thank Fr. Joseph Nellanatt, SDB for his keen interest and encouragement during the course of this investigation. I must also acknowledge the contributions of Fr. Joby Joseph, SDB and Fr. Steven Saji, SDB to this work.

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I wish to thank my laboratory colleagues: Kaushik Chanda, Asem Satyapati Devi and Madhushudan Saha and my classmates Dipanita, Juthika and Snigdha for their help, goodwill and encouragement. I would also like to thank all my other friends whose names I could not mention and with whom I have been associated all these years for their help and co-operation.

I am greatly indebted to my family members: my father for his unfailing faith in me, my mother for her unconditional love & affection and my brother Sarup, sister Aso for their continuous support, love and encouragement.

Above all I thank the almighty for keeping me in good health and for strengthening me day by day to overcome my difficulties and helping me in achieving my goal.

PREFACE

This thesis entitled, "Synthesis of 1,2,3,4-Tetrahydropyrimidine Analogues from Active Methylene compounds" presents development of novel green synthetic methodologies for an important class of synthons called enaminones. The synthetic potentials of these synthons have been exploited for the construction of novel bis-tetrahydropyrimidines and bis-fusedtetrahydropyrimidines. The thesis has been divided into six 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 deals with development of green synthetic methods for the formylation of active proton compounds and their conversion into enaminones. The chapter also lays emphasis on the superiority of the methodologies over the reported procedures.

Chapter III involves a brief literature survey on the synthesis and biological properties of tetrahydropyrimidines in general. It also highlights the importance of bis-heterocyclic compounds with reference to their biological properties compared to their monomeric units. This chapter presents a facile one-pot synthesis of hitherto unreported bis-tetrahydropyrimidines from enaminones described in chapter II.

Chapter IV deals with a short literature survey on the synthesis and biological properties of pyrazolopyrimidines and pyrazolotriazines followed by our synthetic strategies for a series of hitherto unreported bis-pyrazolotetrahydropyrimidines and bis-pyrazolotetrahydrotriazines in which heterocyclic systems have been linked through flexible aliphatic chains and rigid aromatic linkers.

Chapter V contains a literature reports on the synthesis and biological importance of fused pyrimidines and quinazolines followed by presentation of our work on the synthesis of a number of novel bis-fused-tertahydropyrimidines (bis-quinazolines) connected through flexible aliphatic and rigid aromatic chains. A plausible mechanism for the formation of the products has also been presented.

Chapter VI presents synthesis of novel enaminones derived from 4-acetylpyridine and their utilization to construct Bis-tetrahydroprimidines containing isonicotinoyl group in position 5 of the THP ring and linked to each other through a number of aliphatic as well as aromatic chains. This chapter also presents the importance of heterocyclic systems containing nicotinoyl and isonicotinoyl groups.

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

CONTENTS

CHAPTER I

INRODUCTION

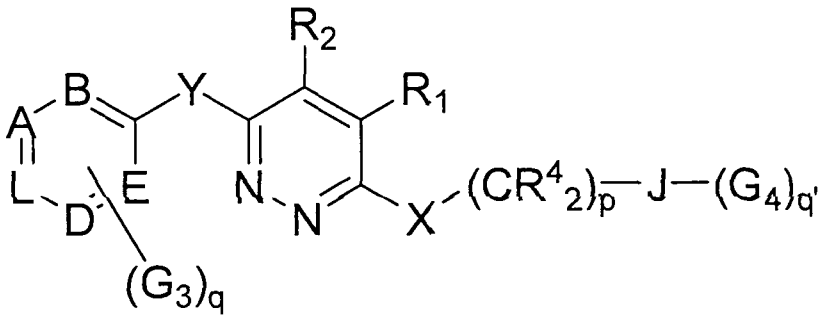
The necessity of more food with rapid increase in human population has lead to the horizontal and vertical growth of agriculture, as a result of which the agro-ecosystem has undergone dramatic change and has become more susceptible to the ravages of pests. Through centuries many control practices were developed for crop protection but the advent of organophosphorous and carbamate compounds completely changed the scenario. This led to the emergence of new problems like resistant pest strains, secondary pest out break, environmental pollution etc. This led to the need of such 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 compounds is in progress.

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

1.1 PYRIDAZINE BASED HETEROCYCLIC COMPOUNDS

Literature survey revealed that heterocyclic compounds containing pyridazine moiety have attracted much attention due to their potential 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 J. P. Dumas and coworkers have reported[6] the synthesis of a series of substituted and fused pyridazines, which were actually three sets of compounds having a general structural formula (**1**),



1

wherein **A, B, D, E** and **L**: nitrogen-containing heterocycle;

X and **Y**: a variety of linking units.

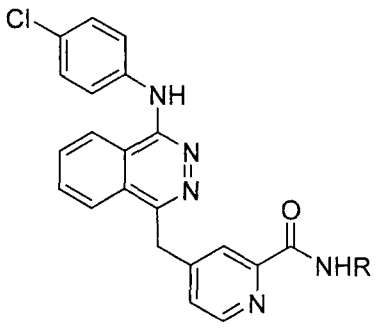
$\mathbf{R_1}$ and $\mathbf{R_2}$: independent substituents or together may be a ring defining bridge.

J: aryl, pyridyl, or cycloalkyl groups.

G: variety of defined substitutents

p,q and **q'**= 0,1,2.

The structures of a few compounds of the above-mentioned series are shown below;



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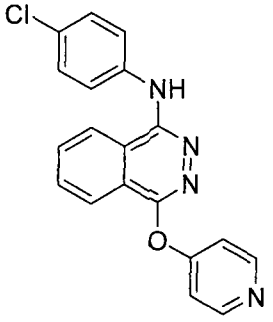

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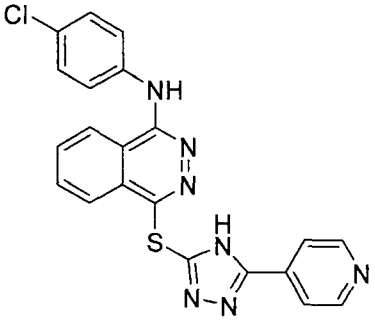

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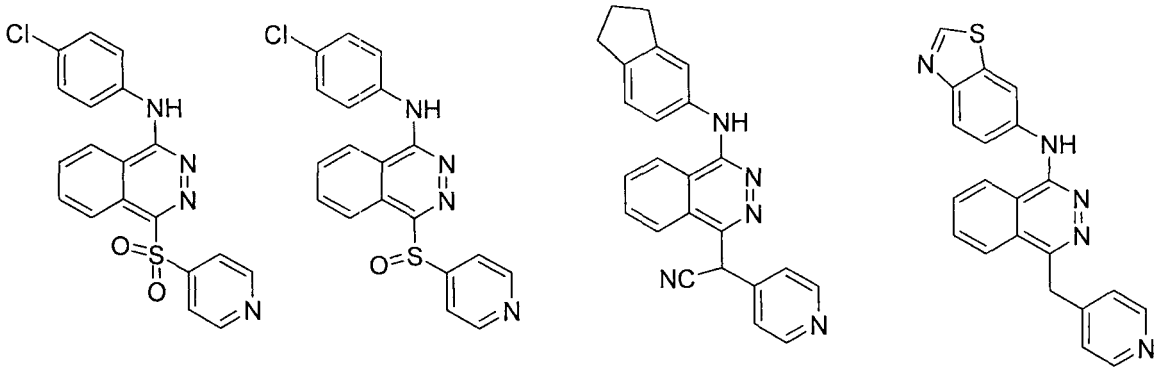
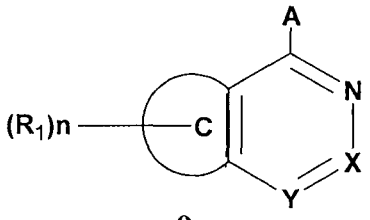


5 **6** **7** **8**

Pharmaceutical composition containing these molecules were tested on mammals having a condition characterized by abnormal angiogenesis. (Angiogenesis involves the development of capillaries from existing blood vessels, and is the principle mechanism by which organs, such as the brain and the kidney are vascularized. Angiogenesis can occur in embryonic development and in the adult. For example, during pregnancy, the female cycle, or wound healing. Some of the compounds synthesised by them were shown to possess angiogenesis inhibiting activity.

1.1.2 N. Watanabe et al. reported[7] the synthesis of another series of pyridazine analogues which were represented by the following general formula (**9**),



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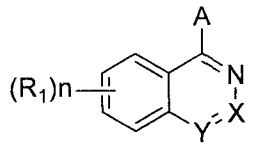
wherein ring **C**: 5 or 6 membered carbon chain ring and may contain a heteroatom,
n: 0 to 4, $\mathbf{R_1}$: halogen atom or lower alkyl, alkoxy, cycloalkyl, nitro or cyano group.
A: hydrogen/ halogen or $-NR^4R^5$ where R^4R^5 = Hydrogen, alkyl, acyl or aralkyl group.
X: NR^6 where R^6= alkyl, aralkyl or heteroalkyl group.

Y: -CO-, -CB- where **B**= hydrogen, halogen, NR^7R^8 where R^7R^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 (**10, 11, 12**) below were found to be of maximum importance.



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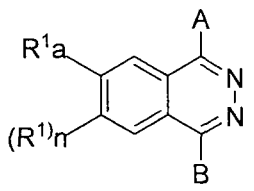

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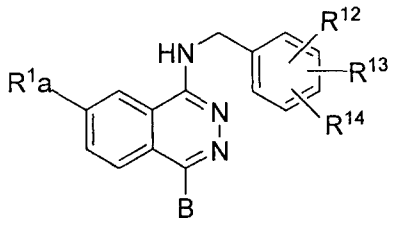

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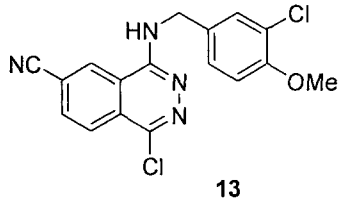
Of the above three series of compounds, compounds of structure **12** were found to be the most useful. The structures of a few active compounds of this series and their salts are shown below.



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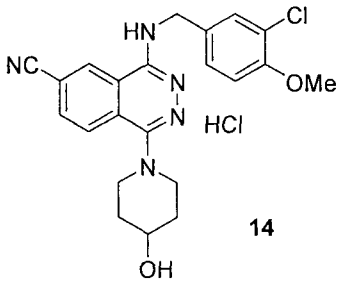

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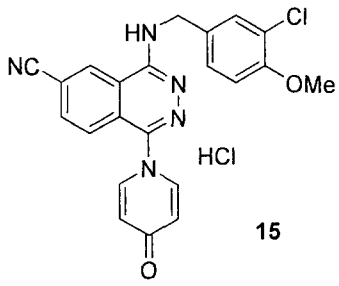

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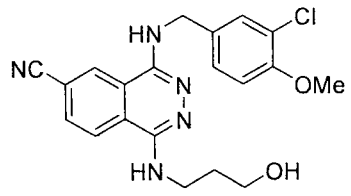

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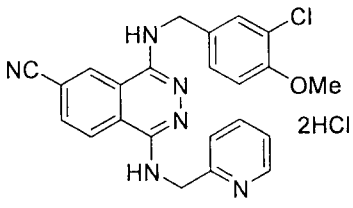

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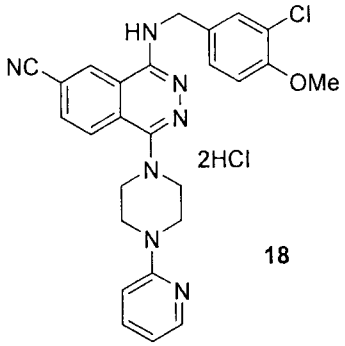

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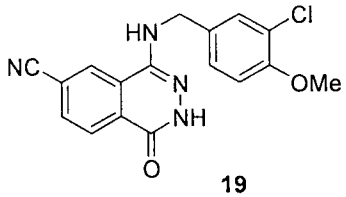

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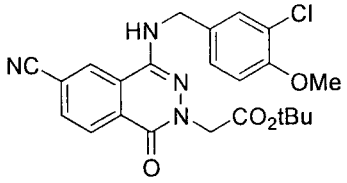

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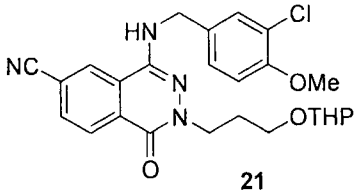

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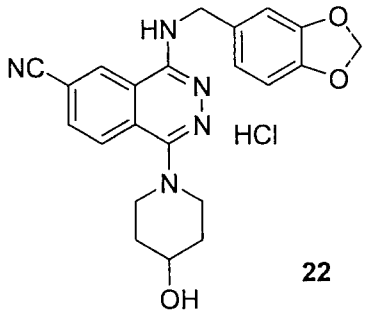

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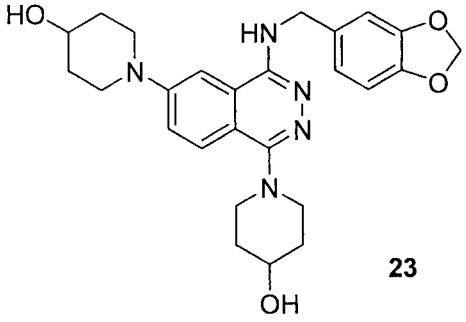

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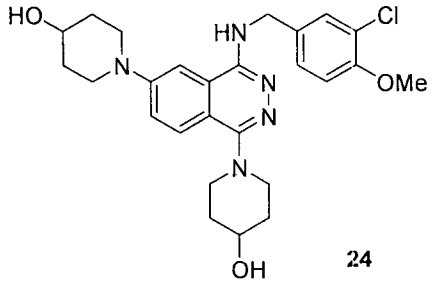

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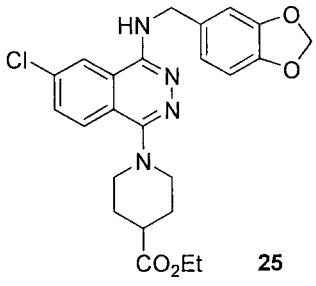

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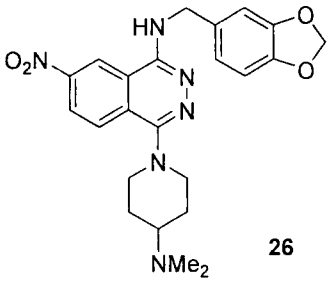

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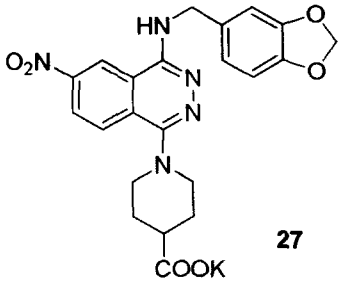

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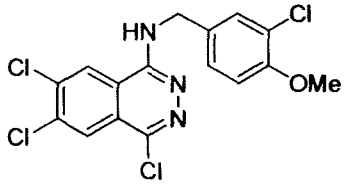

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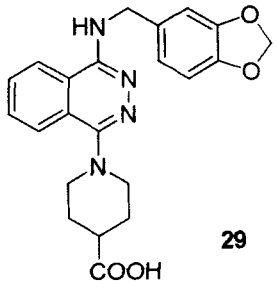
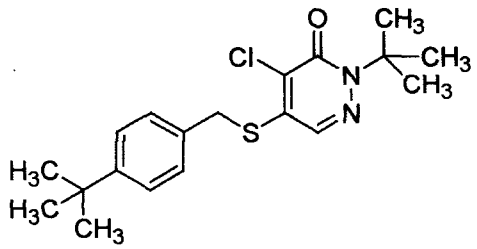


29

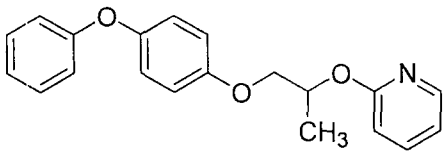
These molecules were found to be useful as preventive and therapeutic agents for diseases for which a cGMP-PDE inhibiting action is efficacious, for example, ischemic heart diseases such as angina pectoris, myocardial infarct and chronic and acute cardiac failure, pulmonary hypertension, arteriosclerosis and bronchial asthma. 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 (**30**) which has been shown to possess pesticidal activity[8]



30

1.1.3 Further, S Nakamura has reported[9] that a pesticidal composition comprising the above compound **30** along with 4-phenoxyphenyl 2-(2-pyridyloxy)propylether (**31**) as active ingredients can be used for controlling pests which are difficult to control satisfactorily by each of the above compound solely.



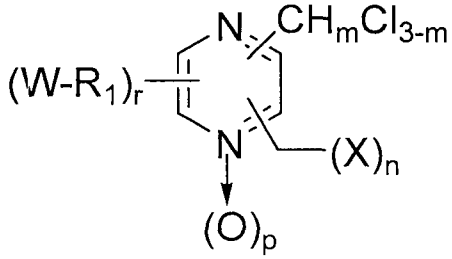
31

The above composition was found to be effective against arthropods (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).

1.2 PYRAZINE BASED HETEROCYCLIC COMPOUNDS

Substituted pyrazines in general and halogenated pyrazines in particular have been known to possess important pesticidal properties. They have been used in agricultural sector for controlling a wide range of pests. A few such molecules and their derivatives are described in the following sections.

1.2.1 R. D. Wilcox and coworkers have reported[10] the synthesis and activity of a series of novel pyrazine derivatives. These compounds were represented by the general formula (**32**),



32

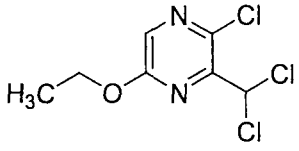
Wherein **W**: oxygen or a sulfur atom, a sulfinyl group or a sulfonyl group.

$\mathbf{R_1}$: alkyl, cycloalkyl, aryl, alkaryl group or aralkyl group.

X: bromo or chloro

m: 0, 1, 2; **p** and **r**: 0 or 1.

The structures of a few molecules of the above-mentioned series are listed below



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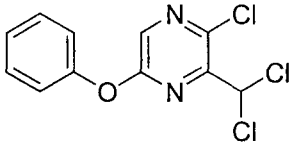

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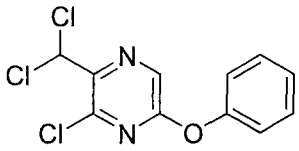

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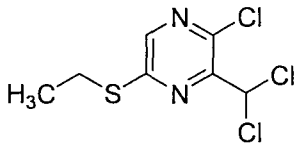

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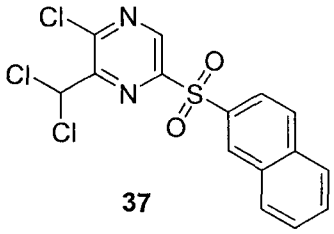
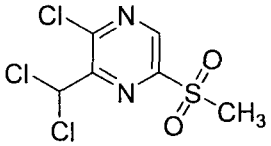


37



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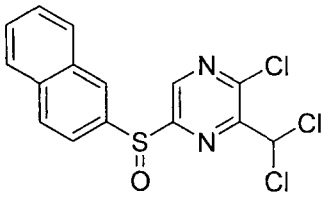

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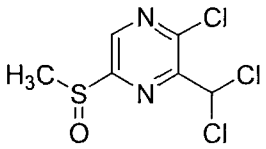

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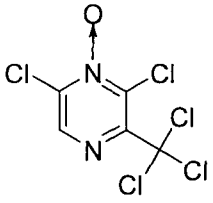

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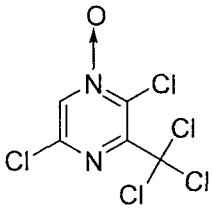
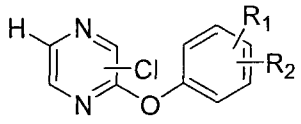


42

These chlorinated methylpyrazines, their corresponding ethers, thio ethers and N-oxide showed good pesticidal property and were useful as anthelmentics, fungicides, insecticides, micro biocides and the like. These compounds and their derivatives

were employed to control plant related fungi, such as that causing rice blast by their administration to the microorganisms and their habitat. Other fungal or bacterial organisms that acts as pests, such as *Staphylococcus aureus*, *Trichophyton mentagrophytes*, *Candida albicans*, *Cercosphora beticola*, and so forth, are similarly controlled by the compounds hereof. They were also found to be effective in the control of certain arthropods such as the two-spotted spider mite. As an anthelmentic they were found to be useful for the control of mouse tapeworm. These compounds can also be used to control trash fish or other aquatic pests.

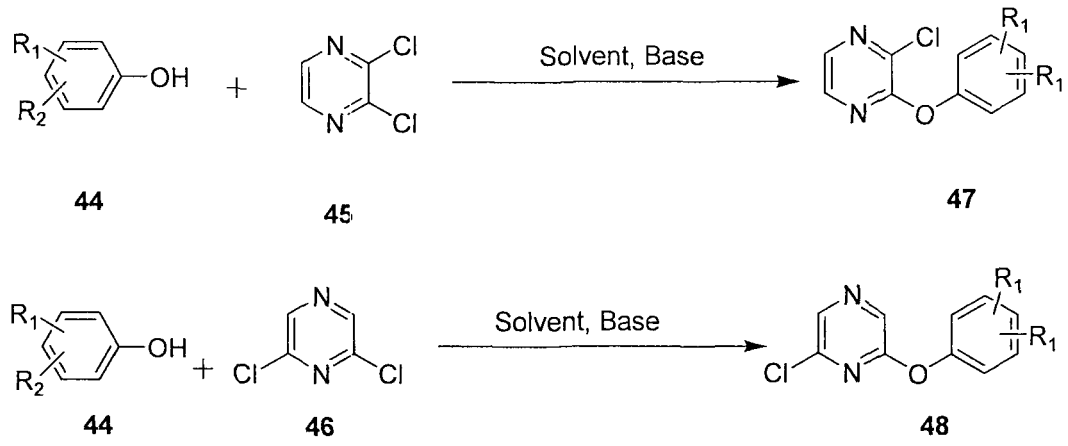
1.2.2 Shyam Sunder and coworkers have reported[11] the synthesis and activities of substituted 2-chloro-3-phenoxypyrazines and 2-chloro-6-phenoxypyrazines of general formula **43**.



43

wherein $\mathbf{R_1}$, $\mathbf{R_2}$: Hydrogen, lower alkyl/alkoxy, nitro, amino, cyano, trifluoromethyl, acetyl, methylthio, methylsulfinyl /sulfonyl, aminosulfonyl, phenoxy or halogen or alternatively $\mathbf{R_1}$, $\mathbf{R_2}$: $-O-CH_2-O-$

These compounds were prepared from suitably substituted phenols **44** by the reaction with 2, 3-dichloropyrazine or 2, 6-dichloropyrazine (**45**, **46**) in a solvent, (generally a lower alkanol such as ethanol or isopropanol) in the presence of a suitable base (such as sodium hydroxide). Other suitable base/solvents are sodium hydroxide/isopropanol, sodium ethoxide/ethanol and potassium hydroxide/ethanol. The reactants are mixed and the resulting mixture refluxed for sufficient time to obtain the desired products as depicted in **Scheme 1**.



Scheme 1

An alternative method of preparing the compounds is by using sodium metal in organic solvents such as benzene or toluene. In this method the appropriate phenol, sodium metal and organic solvents are refluxed until the phenate is formed, where upon 2,3-dichloropyrazine or 2,6-dichloropyrazine is added and the resulting mixture refluxed for a time sufficient to obtain the desired products **47** and **48**.

These compounds so prepared were tested for their antiviral activity against 0.05 ml of Rhinovirus type 1A (RV-1A), Rhinovirus type 2A (RV-2A), or Cox sackie A2 virus (Cox A21) in culture medium. The tissue-culture test data indicated that all the tested compounds were active against at least one of the three-tested virus. These compounds were administered in the form of composition comprising the compound in a mixture with a pharmaceutically acceptable carrier.

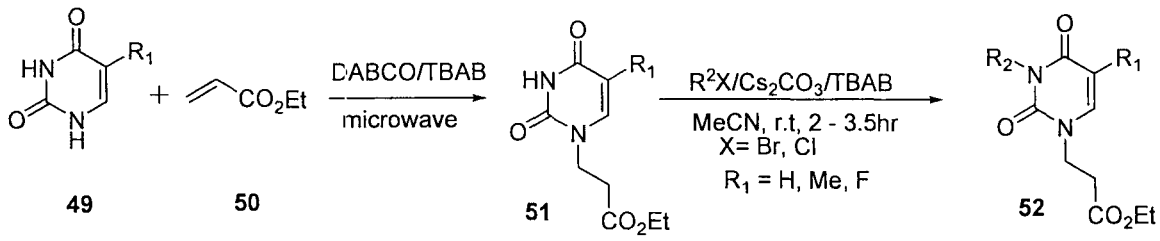
1.3 PYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

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 with different biological properties. Several groups have studied the chemistry and pharmacological properties of pyrimidine derivatives[12-17]. Pyrimidines are associated with various therapeutic activities such as antiviral[18] antitumor[19] antibacterial[20, 21]

antihypertensive[22], neuropeptide Y (NPY) antagonist activity[23], diuretics[24], antimalarial[25] etc. Several synthetic strategies have been reported for the preparation of derivatives[26-32].

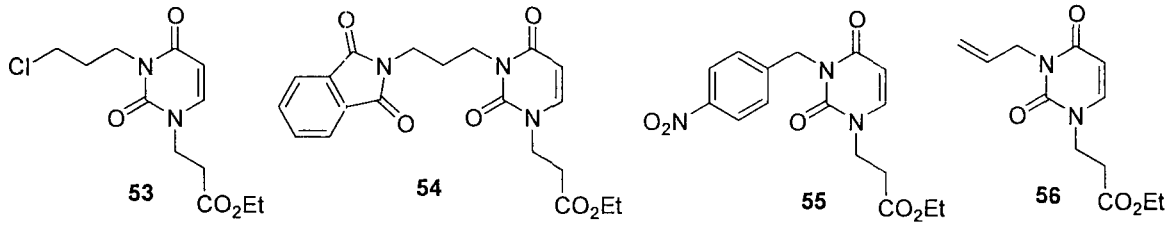
Some of these are discussed in the following sections.

1.3.1 A. K. Nezhad and coworkers reported[33-34] the synthesis of novel unsymmetrical 1, 3-dialkylpyrimidine derivatives via N3-alkylation of 1-alkylpyrimidines with carbon electrophiles in the presence of catalytic amount of TBAB and Cs_2CO_3 in MeCN at room temperature (**Scheme 2**).



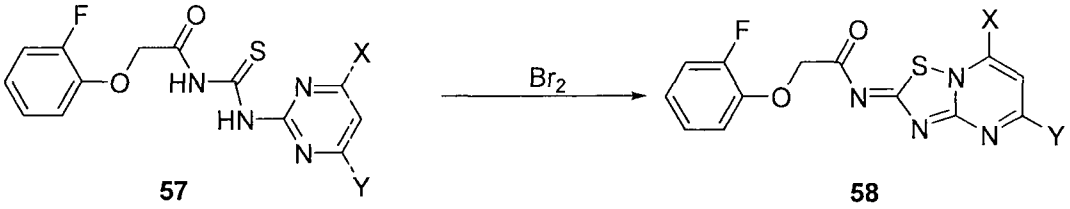
Scheme 2

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



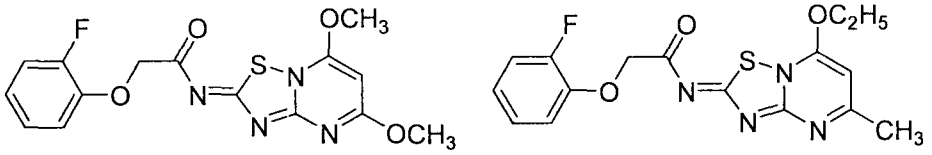
These *N*1, *N*3-substituted pyrimidines have required scaffold to be considered as intercalating and alkylating agents, which play a critical role in cancer chemotherapy.

1.3.2 S. Y. Ke and coworkers have reported[35] the synthesis of a series of *o*-fluorophenoxy acetylimino-2*H*-1,2,4-thiadiazolo[2,3-*a*]pyrimidine derivatives (**58**) from **57** using bromine as oxidant (**Scheme 3**).



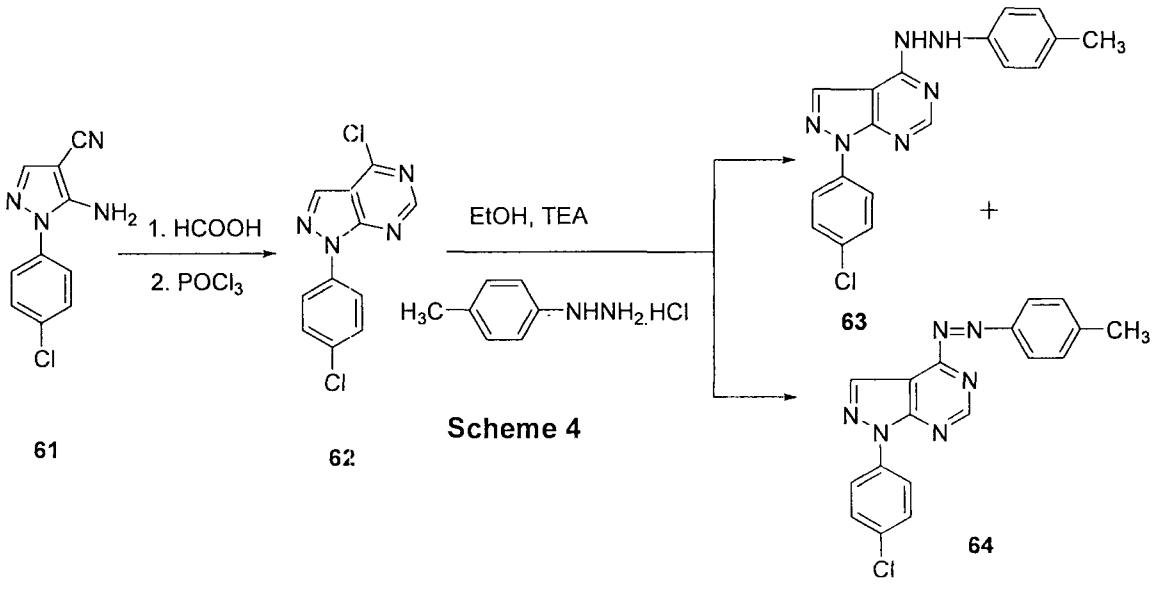
Scheme 3

For example, **59** and **60**. Some of these compounds showed good herbicidal activity.

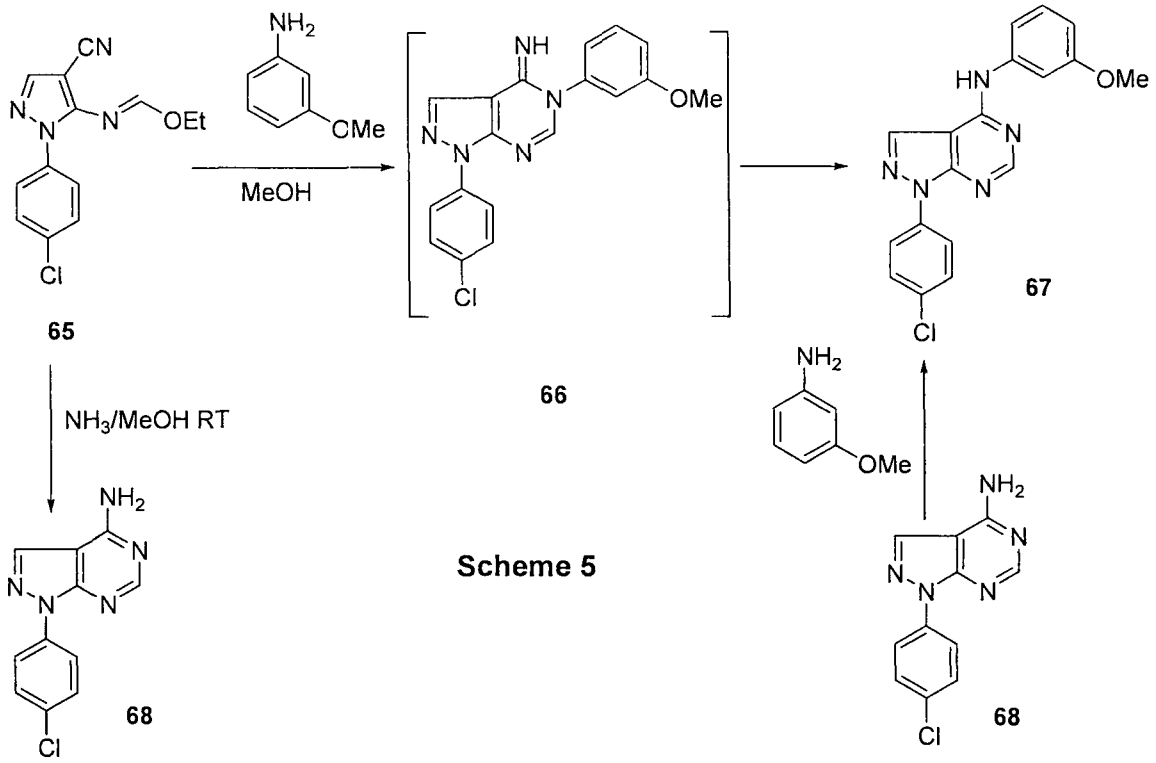


59 **60**

1.3.3 Ana M.F. Oliveira-campos and coworkers reported[36] the synthesis of the 4-substituted pyrazolo[3,4-*d*]pyrimidines as shown below (**Scheme 4, Scheme 5**).



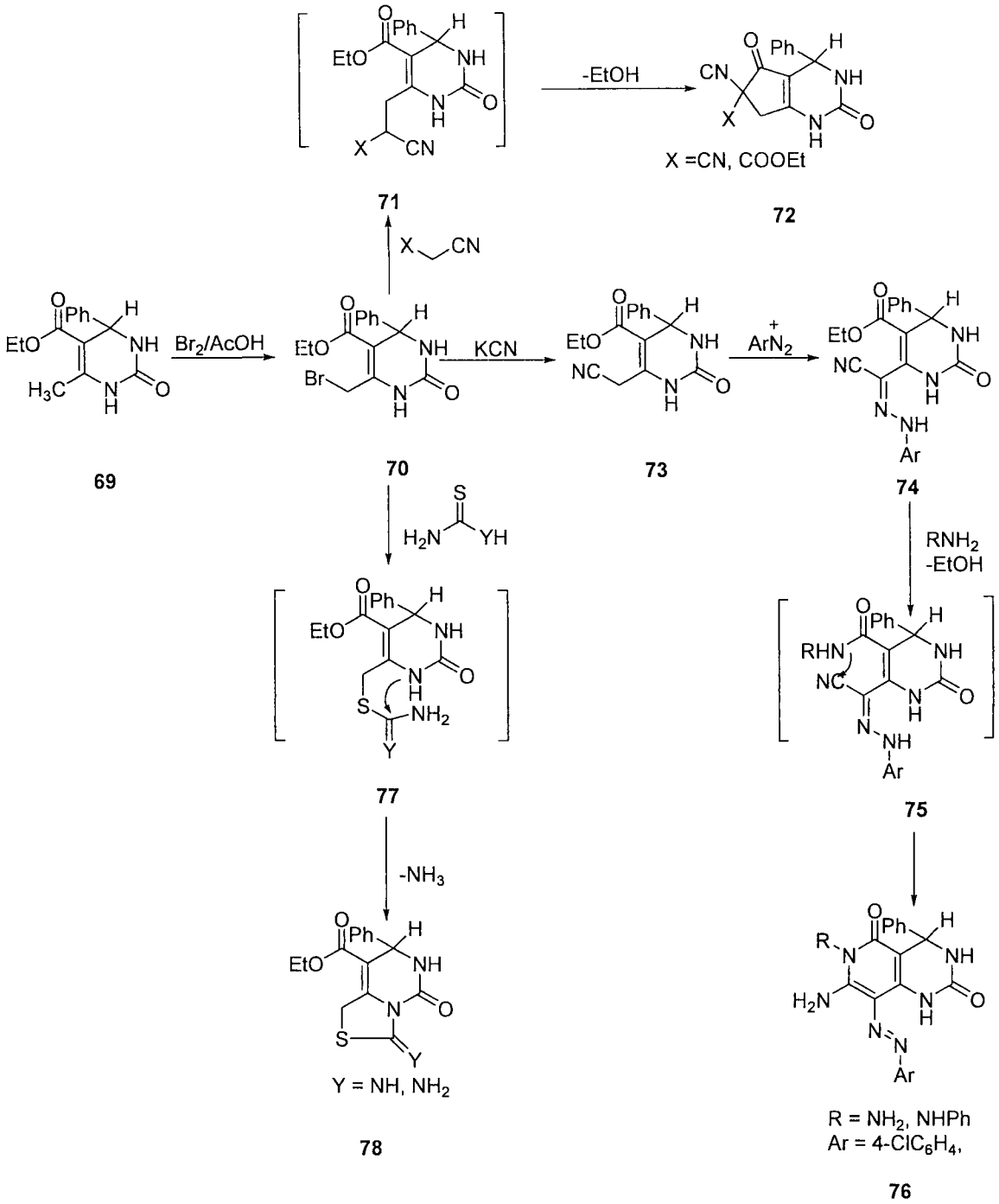
Scheme 4



Scheme 5

These compounds were tested for their antifungal activities.

1.3.4 N.A. kheder used the versatile 6-Bromomethylpyrimidine (**70**) as a building block for the synthesis of Cyclopenta [*d*] pyrimidine, pyrido[4, 3-*d*]pyrimidine and thiazolo [3, 4-*c*]pyrimidine[37] as shown in the (**Scheme 6**).

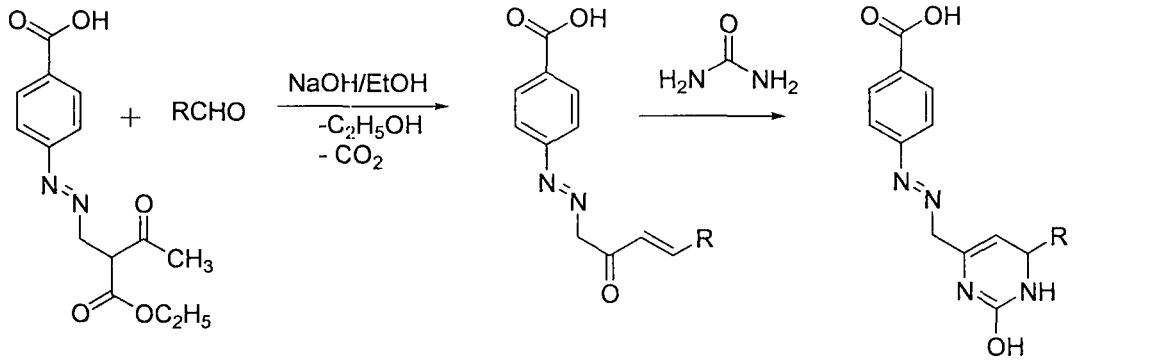


Scheme 6

The versatile synthon ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (**70**), was obtained via bromination of ethyl 6-methyl-2-

oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**69**) in acetic acid. Treatment of the compound **70** with malononitrile or with ethylcyanoacetate afforded the corresponding hexahydrocyclopentanal[*d*]pyrimidine derivatives **72**. 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 (**73**), which couples smoothly with 4-chlorobenzenediazonium chloride to give the corresponding hydrazone **74**. When the hydrazone was treated with hydrazine hydrate or phenyl hydrazine, it afforded the corresponding pyrido[4,3-*d*]pyrimidine derivatives **76**. It also reacts with thiourea, thiosemicarbazide to afford the corresponding thiazolo[3,4-*c*]pyrimidine (**78**).The antimicrobial activity of selected samples of the synthesized compounds was tested and showed moderate activities.

1.3.5 V. H. Shah and coworkers have reported[38] the synthesis of pyrimidine derivatives from their corresponding chalcones by reacting them with urea as shown in the (**Scheme 7**).

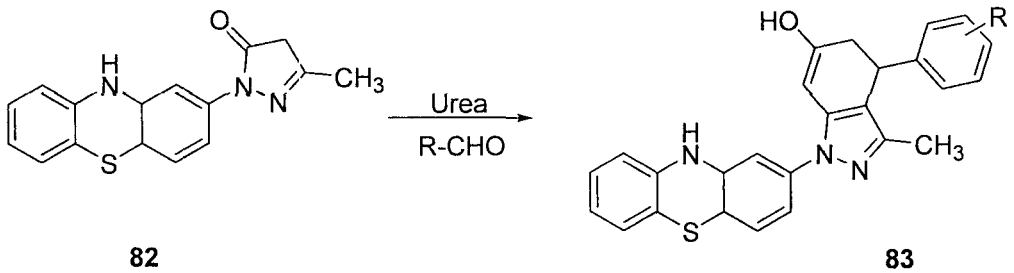


79 **80** **81**

R = Phenyl, subst Phenyl, Furyl

Scheme 7

Some of these compounds exhibited promising antitubercular activities against mycobacterium tuberculosis. They also reported[39] the synthesis of some pyrimidine derivatives containing the phenothiazine nuleus of the type **83** (**Scheme 8**).

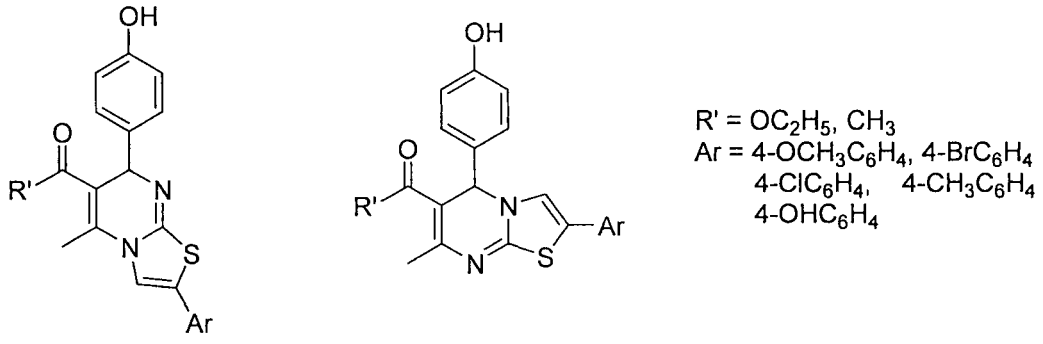


82 **83**

Scheme 8

These were also tested for their antitubercular activities.

1.3.6 C. Hu and coworkers synthesized[40] a series of 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives of the type **84** and **85**. Some of the compounds showed good activity as AchE inhibitor.



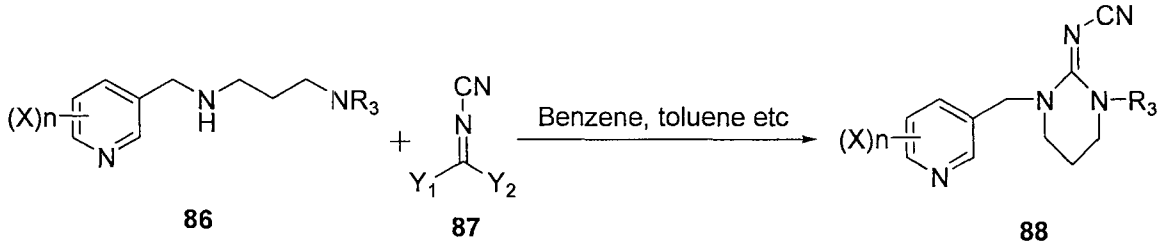
84 **85**

1.4 TETRAHYDROPYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

Tetrahydropyrimidines (THPs) are the most important of the three cyclic 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 uses are described in the following sections.

1.4.1 Laurenz Gsell has reported[41] the synthesis of substituted pyridyl methyl cyanoiminotetrahydropyrimidine (**88**) by the reaction of compounds **86** and **87** in appropriate solvents (**Scheme 9**),



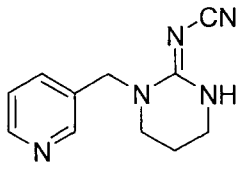
86 **87** **88**

Scheme 9

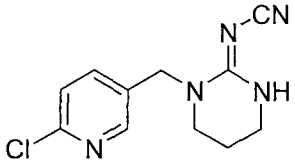
wherein R_3: H or alkyl groups, **X**= Halogen, **n** = 0, 1, 2 or 3

Y_1=Y_2 leaving groups such as $-SCH_3$, $-O-CH_3$, $-O-C_6H_5$.

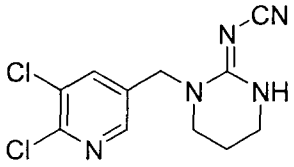
Similarly compounds **89, 90** and **91** have been synthesized by the above general method.



89



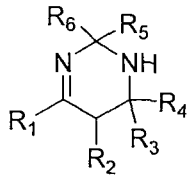
90



91

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.

1.4.2 Bernardus A. Oude Alink has reported[42] the synthesis of substituted 2,3,4,5-tetrahydropyrimidines and their derivatives of the general formula **92**.

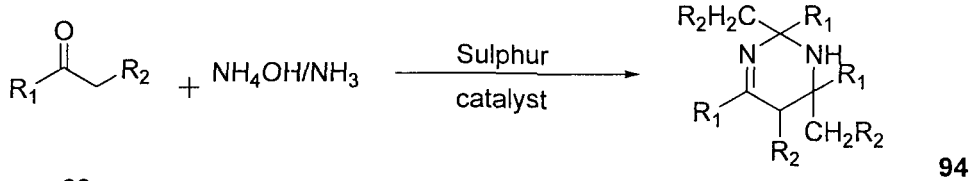


92

wherein $\mathbf{R_1}$-$\mathbf{R_6}$: hydrogen, alkyl, aryl, aralkyl, cycloalkyl, heterocyclic substituted derivatives thereof.

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

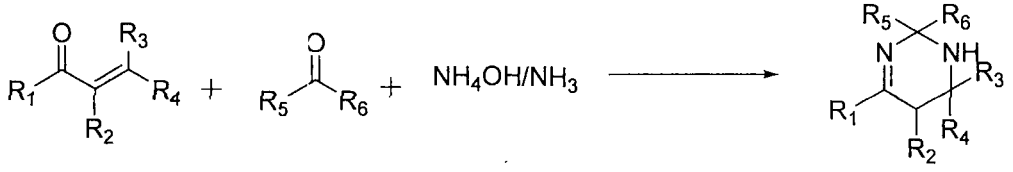
1.4.2a By the reaction of carbonyl compounds **93** (ketone or aldehyde) with NH_3 / NH_4OH and a sulphur-containing catalyst (eg CS_2) (**Scheme 10**).



93 **94**

Scheme 10

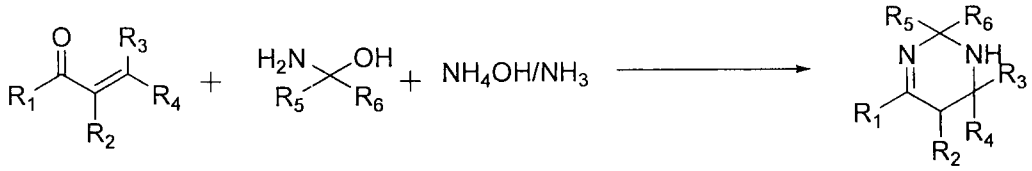
1.4.2b The reaction of an α, β-unsaturated ketones **95** and a carbonyl compound **96** and NH_3 / NH_4OH without a catalyst (**Scheme 11**).



95 **96** **97**

Scheme 11

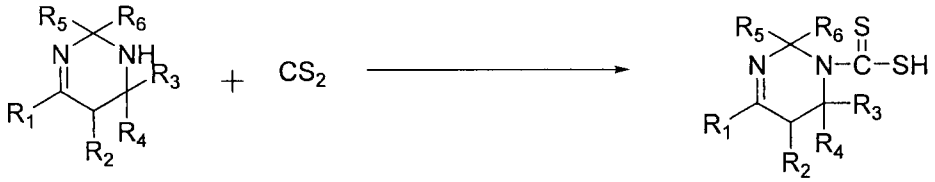
1.4.2c By the reaction of an α, β-unsaturated ketone **95**, 1-aminoalcohol **98** and NH_3 / NH_4OH without a catalyst (**Scheme 12**).



95 98 97

Scheme 12

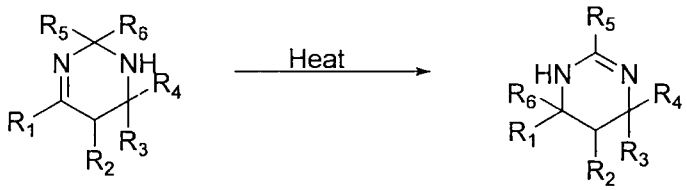
This THP **97** was further used as intermediates for the preparation of N-dithiocarboxylates. Reaction of the substituted 2,3,4,5-tetrahydropyrimidines (**97**) with carbon disulfide yielded 1:1 adducts **99** (**Scheme 13**).



97 99

Scheme 13

These adducts were efficient corrosion inhibitors in acid systems. Tetrahydropyrimidines where R_6 was hydrogen were isomerised to obtain 1,4,5,6-tetrahydropyrimidines (**100**) (**Scheme 14**).

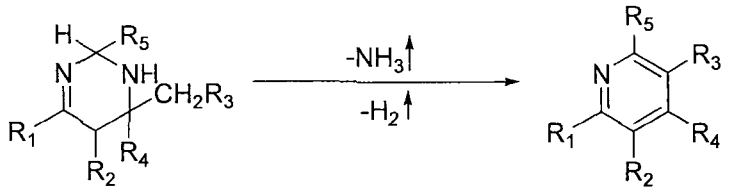


97 100

Scheme 14

THPs where the C_2 position contains at least one hydrogen and one of the groups attached to carbon 4 has at least a methylene group could be converted to substituted pyrimidines (**102**) by the liberation of ammonia (**Scheme 15**). These compounds

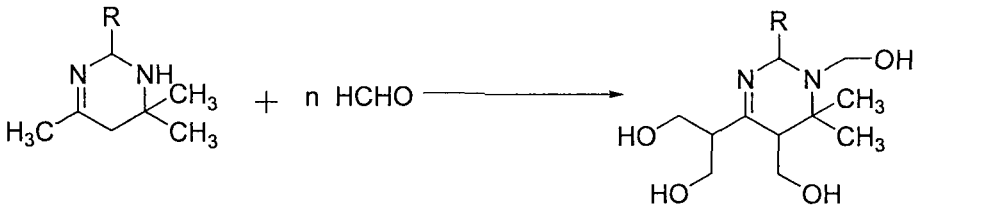
were useful as bactericides. In general the above series of compounds were found to be useful as biocides, anti-oxidants, oxygen-scavengers and as corrosion inhibitors.



101 **102**

Scheme 15

1.4.3 Oude Alink and coworker reported[44] the reaction of the tetrahydropyrimidines (**103**) with various stoichometric quantities of formaldehyde leading to the formation of a mixture of compounds called polyols of tetrahydropyrimidines (**104**) (**Scheme 16**).

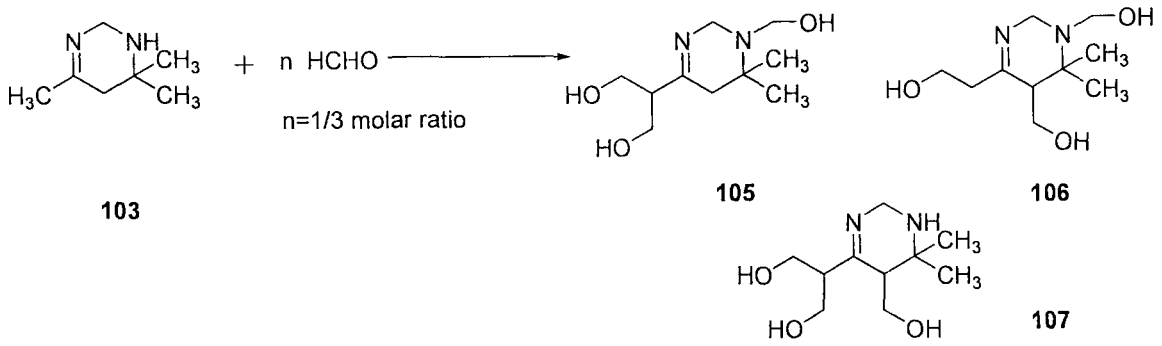


103 **104**

Scheme 16

When **n** is less than 4, 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.

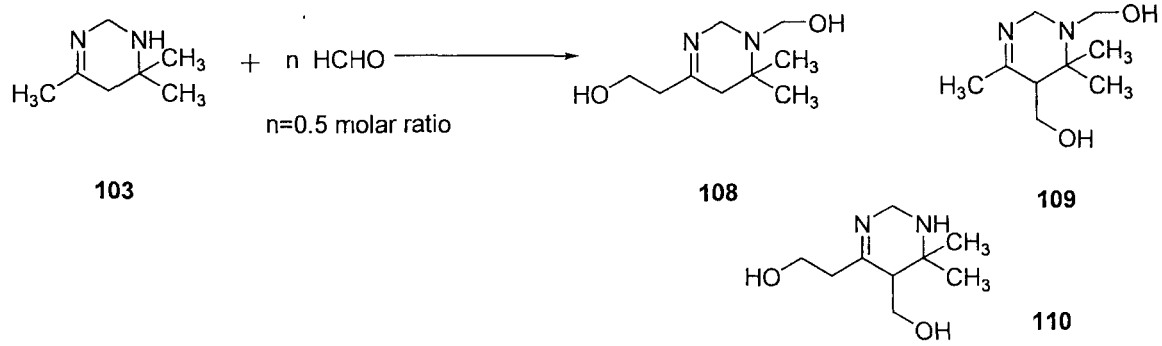
For example, when 4,4,6-trimethyl-2,3,4,5-tetrahydropyrimidine was reacted with one third molar ratio of formaldehyde a mixture of products **105, 106** and**107** containing three methylol groups were obtained (**Scheme 17**).



103 105 106 107

Scheme 17

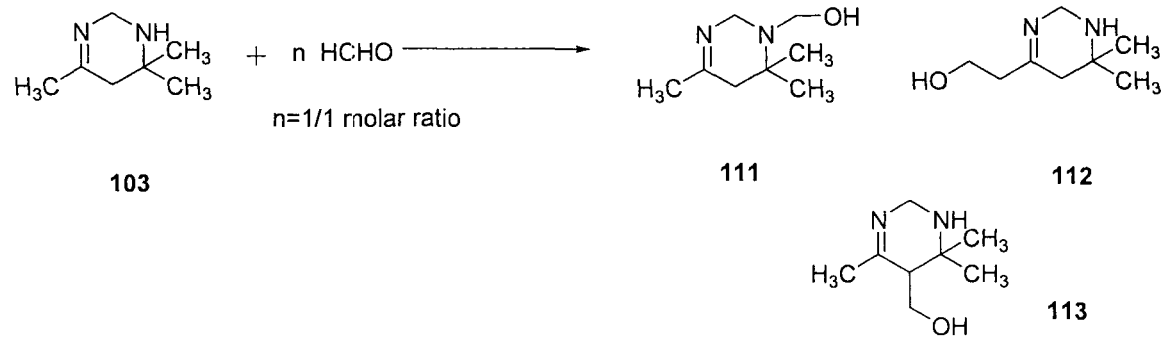
When the same reaction was carried out with 0.5 molar ratio of formaldehyde the products that were obtained were **108, 109** and **110** (**Scheme 18**).



103 108 109 110

Scheme 18

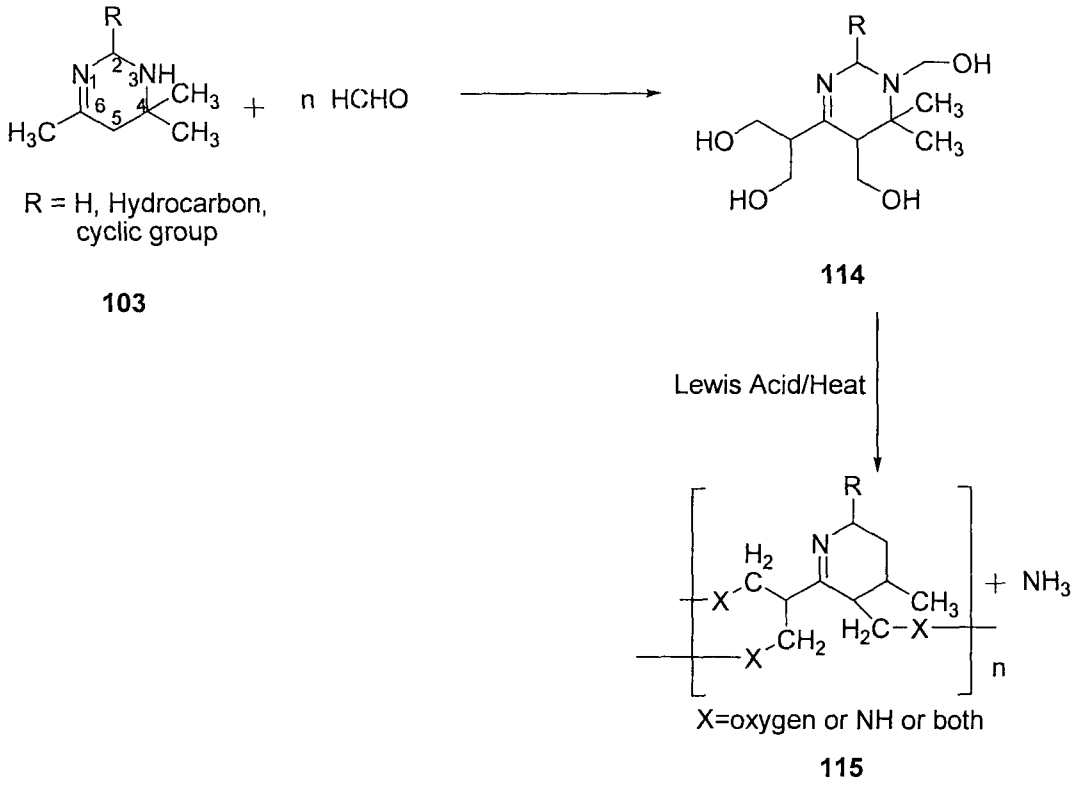
Similarly, when the reaction was carried out with 1 molar ratio of formaldehyde three possible products **111, 112** and **113** were obtained (**Scheme 19**).



103 111 112 113

Scheme 19

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 **115** with the liberation of ammonia. (**Scheme 20**)



Scheme 20

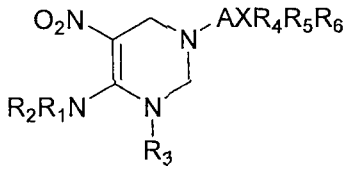
The polyols of tetrahydropyrimidines and their respective polymers were found to be useful as corrosion inhibitors.

1.5 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.

1.5.1 Stephen McCann and coworkers have reported[45] the synthesis of tetrahydropyrimidines of the type **116**,

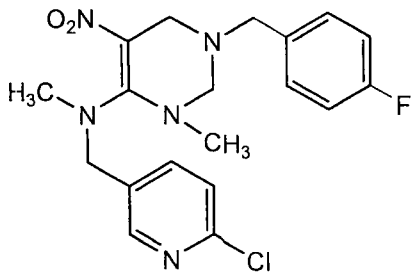


116

wherein **X**: Si, Ge; **A**: alkylene, alkenylenes

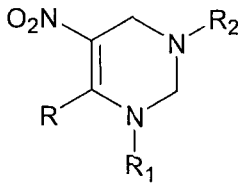
$\mathbf{R_1}$-$\mathbf{R_6}$: alkyl, alkenyl; $\mathbf{R_2}$-$\mathbf{R_3}$: ethyl, propyl and each group substituted with methyl. The tetrahydropyrimidines of the above series were found to be very good anthropocides

Takahiro and coworkers also prepared Tetrahydropyrimidines. They reported[46] the synthesis of 6-[N-(6-chloro-3-pyridylmethyl)-N-methylamino]-3-(4-fluorobenzyl)-1-methyl-5-nitro-1,2,3,4-tetrahydropyrimidine (**117**) which was used as noxious organism controlling agent for example, to control Laodelphax straitellus at 800 ppm with 100% mortality rate.



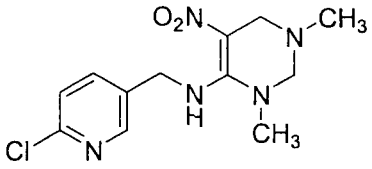
117

1.5.2: F. Uu and coworkers have also reported[47] the synthesis of tetrahydropyrimidines of the general structure **118**,



118

wherein **R**: $NHCH_2Y$; $\mathbf{R_1}$=low alkyl group; $\mathbf{R_2}$=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 (**119**).

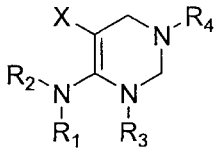


119

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 animals, fishes, crustacea, etc., reduced in residual property and high safety to plants[47].

1.5.3 H. Uneme and coworkers reported[48] the synthesis and activity of a series of tetrahydropyrimidines and their salts whose general structure can be represented by **120**,



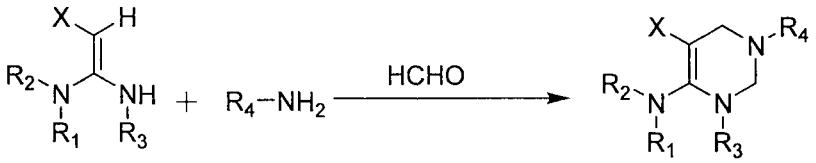
120

wherein $\mathbf{R_1}$, $\mathbf{R_2}$, $\mathbf{R_3}$, $\mathbf{R_4}$: 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.

1.5.3a By the reaction of **121** with an amine **122** and formaldehyde (R_1-R_4 has the same meaning as above) (**Scheme 21**).

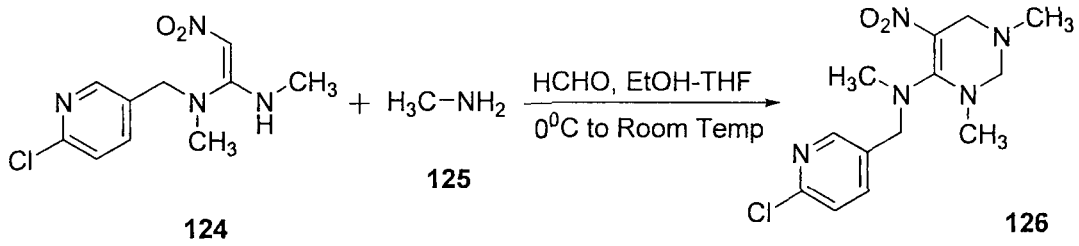


121 **122** **123**

Scheme 21

For example, when to a mixture of 1-[N- (6-chloro-3-pyridylmethyl)-N-methylamino]-1-methylamino-2-nitroethylene (**124**) and 40% aqueous methylamine

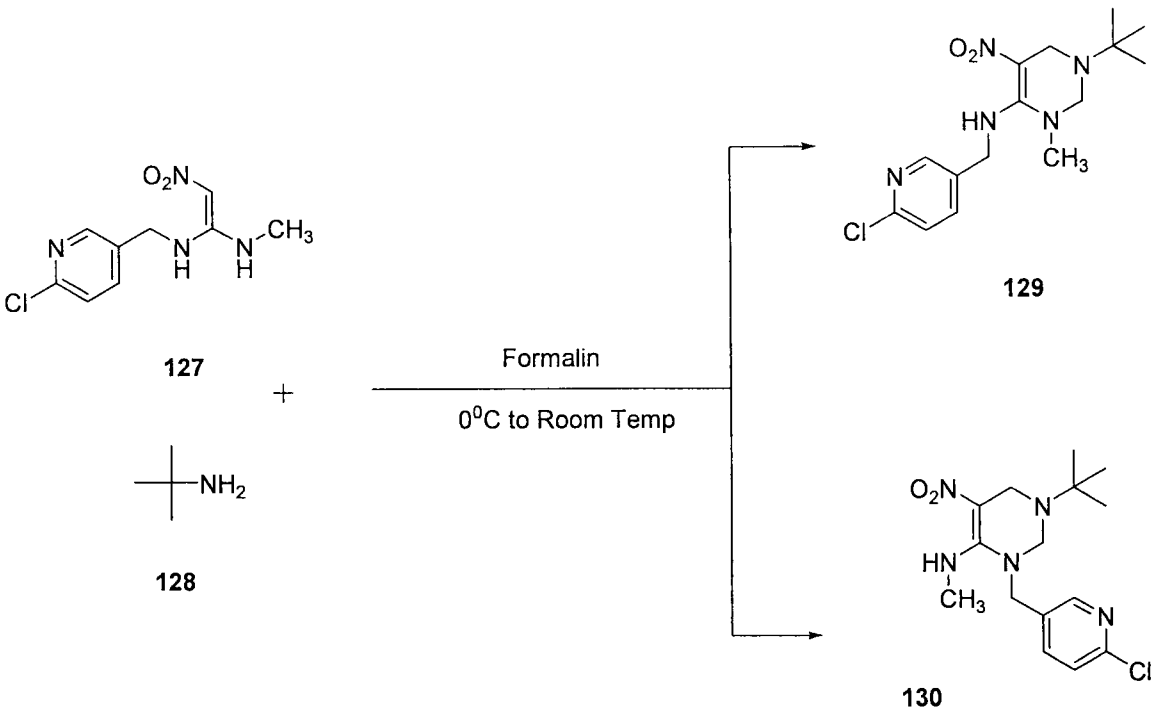
(**125**) was added 37% formalin dropwise over 20 minutes with cooling in ice and further stirred at room temperature overnight. Subsequent work up and column purification yielded 4-[N-(6-chloro-3-pyridylmethyl)-N-methylamino]-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydro- pyrimidine (**126**) (**Scheme 22**).



124 **125** **126**

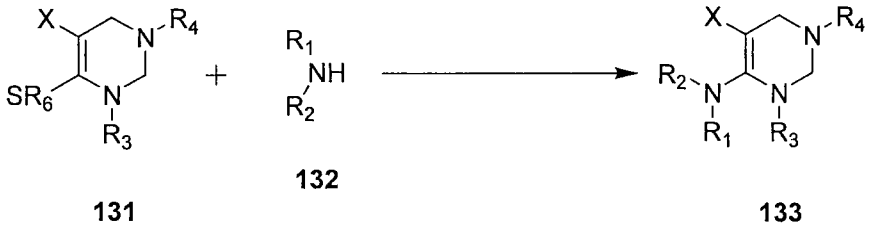
Scheme 22

Similarly, when to a mixture of 1-(6-chloro-3-pyridylmethylamino)-1-methylamino nitroethylene (**127**) and t-butylamine (**128**) in acetonitrile, 37% formalin was added dropwise with cooling and further stirred for 3.5hr 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 (**129**) and 1-t-butyl-3-(6-chloro-3-pyridylmethyl)-4-methylamino-5-nitro-1,2,3,6-tetrahydropyrimidine (**130**) (**Scheme 23**).



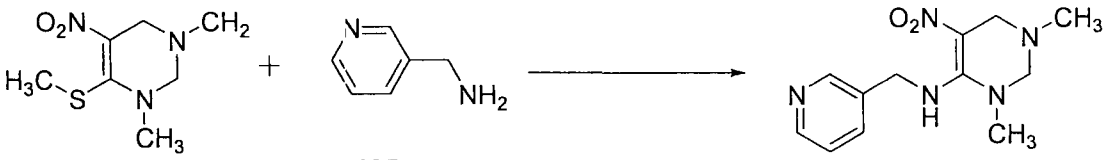
Scheme 23

1.5.3b By reacting compound **131** with an amine **132** as shown in **Scheme 24,**



Scheme 24

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 (**134**) was stirred with 3-pyridylmethylamine (**135**) 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 (**136**) (**Scheme 25**).

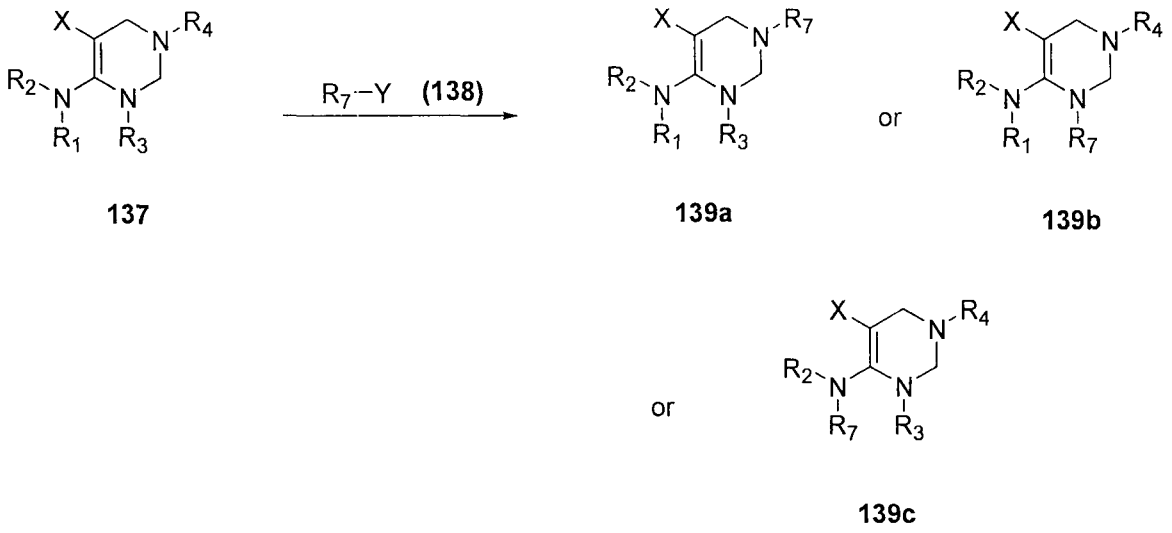


134 135 136

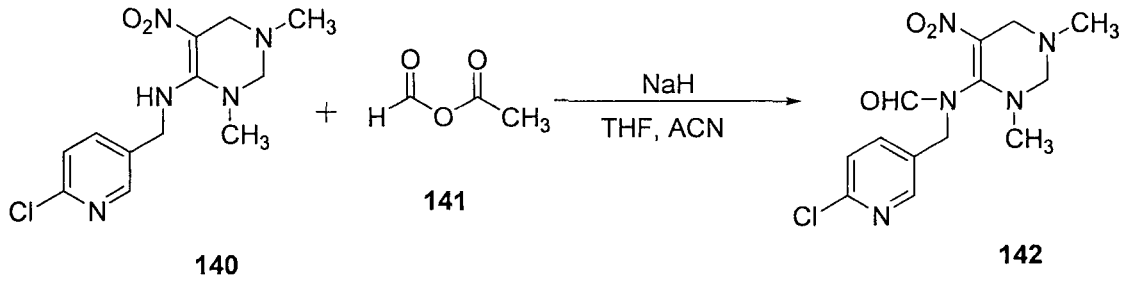
Scheme 25

1.5.3c By reacting a compound of the formula **137** (where of the groups R_1 to R_4 at least one means a H atom and the rest alkyl group) with **138**, 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 26**).

To a mixture of 4-(6-chloro-3-pyridylmethylamino)-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydropyrimidine (**140**) in THF and acetonitrile, sodium hydride was added in small portions, followed by aceticformicanhydride (**141**) 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-tetrahydropyrimidine (**142**) (**Scheme 27**).

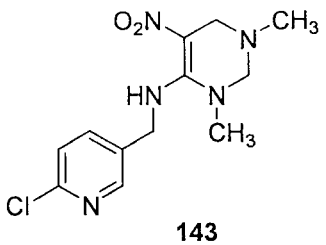


Scheme 26

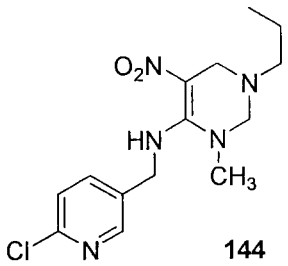


Scheme 27

Altogether 60 compounds were prepared in this series and their antiviral activity tested, out of which the structures 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 (**150**).



143



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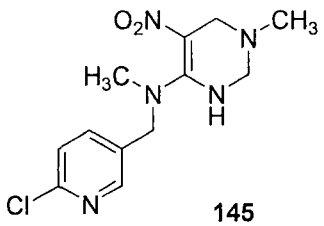
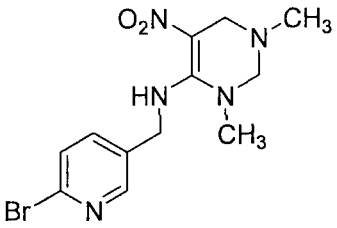
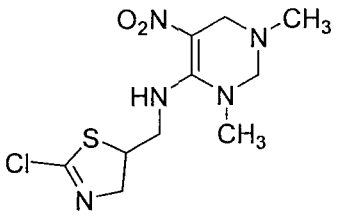


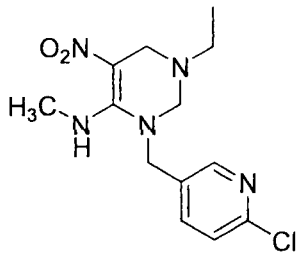
145



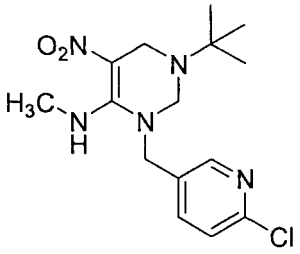
146



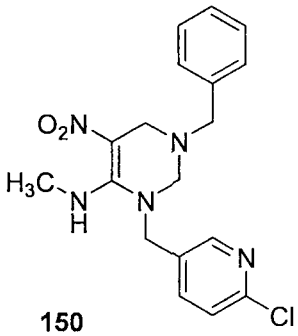
147



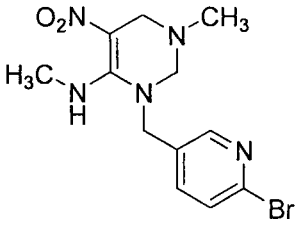
148



149

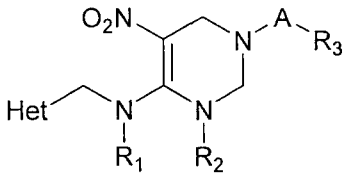


150



151

1.5.4 B. W. Kruger and his coworkers synthesized[49] and tested many 1,2,3,4-tetrahydropyrimidines of the general structure **152**,



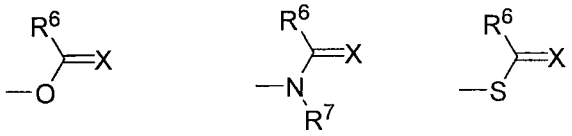
152

wherein **Het** : substituted pyridyl or thiazolyl; $\mathbf{R_1}$-$\mathbf{R_2}$: C_1-C_4alkyl,

$\mathbf{R_1}$-$\mathbf{R_2}$: 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,

$\mathbf{R_3}$: represents one of the following groups

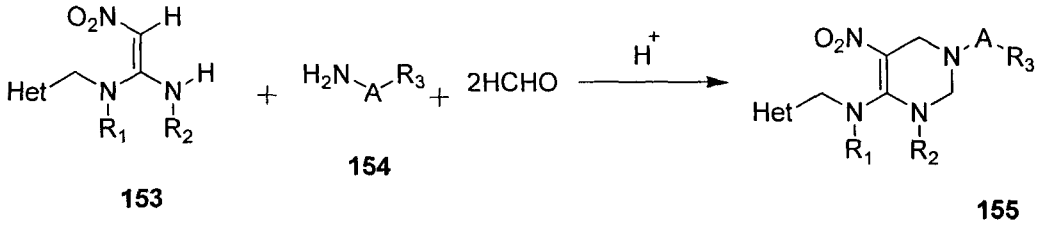


$\mathbf{R_6}$: alkyl, aryl, aralkyl, heteroalkyl , alkoxy etc.

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

These compounds were prepared by basically three methods, they are

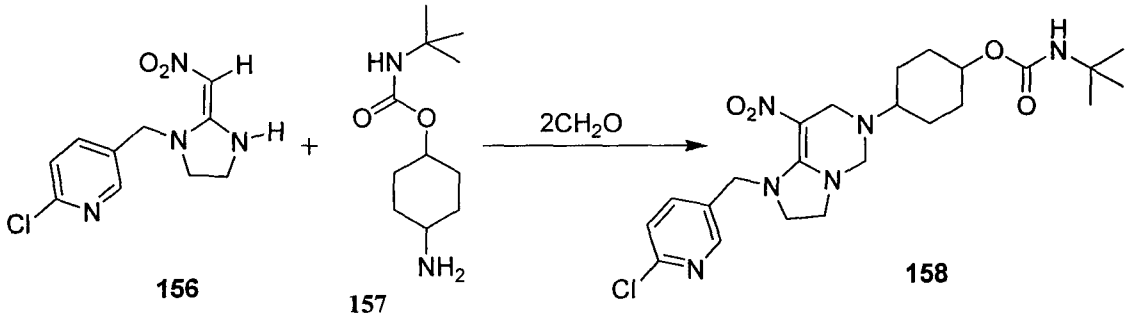
1.5.4a: (a) Reacting nitromethylene derivative (**153**) with amines (**154**) in the presence of at least twice the molar amount of formaldehyde in the presence of acidic catalyst and appropriate diluents (**Scheme 28**), Where $\mathbf{R_1}$, $\mathbf{R_2}$, **Het, A** and $\mathbf{R_3}$ have their usual meaning. Particularly preferred compounds were those in which **Het** represents 2-Chloro-5- methylpyridine or 2-chloro-5-methyl-thiazole and $\mathbf{R_1}$, $\mathbf{R_2}$ represents methyl, ethyl and together with adjacent atoms represents 1,3,5-trimethyl-2-methylene-hexahydropyrimidine.



153 154 155

Scheme 28

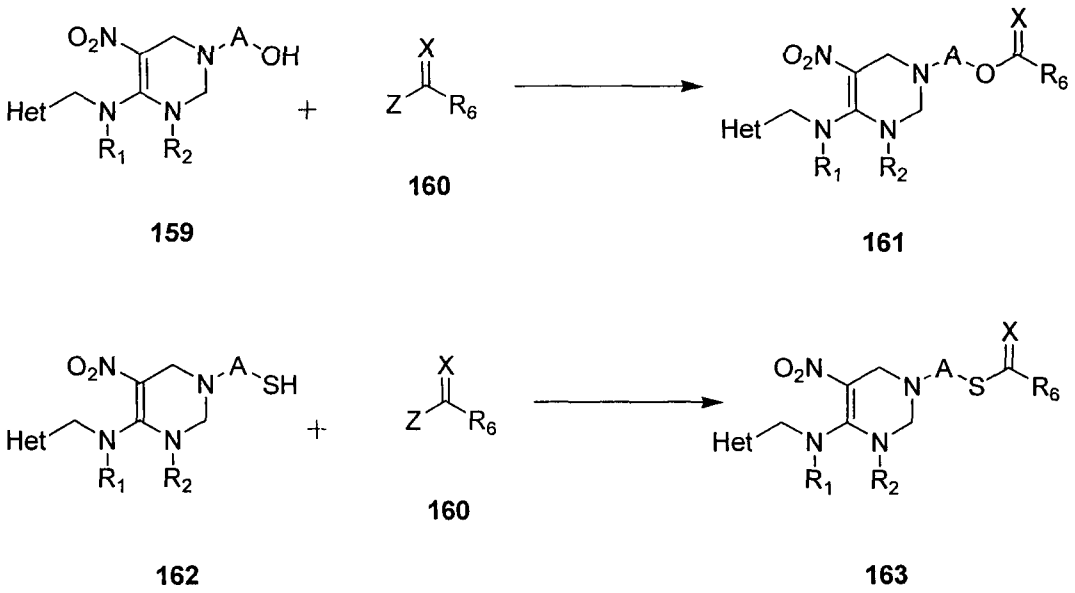
If, for example, 3-(2-chloropyridin-5-yl-methyl)-2-nitromethylene-imidazoline (**156**), 4-t-butylcarbamoyloxy-cyclohexylamine (**157**) and at least twice the molar amount formaldehyde are used as starting materials, the corresponding reaction can be represented by the following equation (**Scheme 29**). 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, pet ether, benzene etc. The reactions are carried out in the presence of acid catalysts. Acids, which do not oxidize such as hydrochloric acid and 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.



156 157 158

Scheme 29

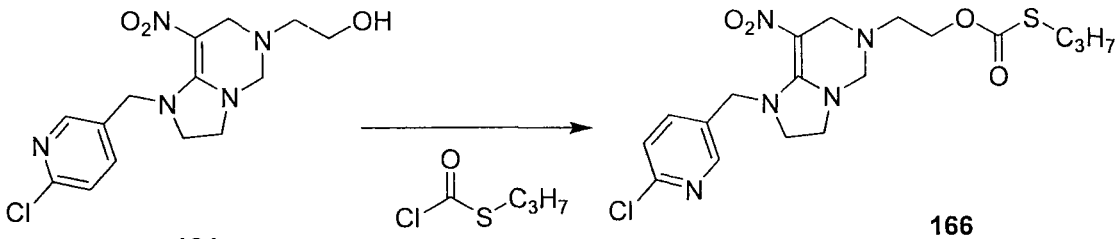
1.5.4b (b) When R_3 represents a radical, they were prepared as shown in **Scheme 30,**



Scheme 30

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

For example, when 6,7-dihydro-6-(2-hydroxyethyl)-8-nitro-(5*H*)-3-(2-chloropyridine-5-yl-methyl)-imidazolino-(2,3-*f*)-pyrimidine (**164**) and thiopropyl chloroformate (**165**) are used as starting materials, the reaction can be represented by the following equation (**Scheme 31**).



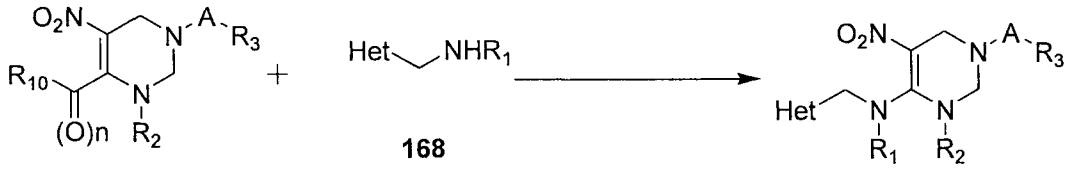
Scheme 31

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 at 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.

1.5.4c (b) When R_1 and R_2 together with the adjacent atoms do not cyclize then they are prepared by as shown in **Scheme 32**,

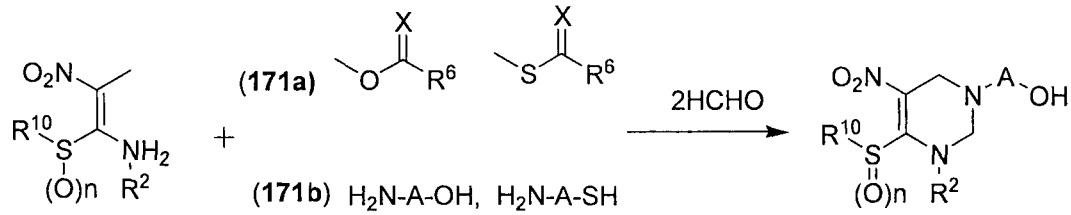


167 **168** **169**

Scheme 32

wherein $\mathbf{R_{10}}$: 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 (**170**) with radicals (**171a**) or amino alcohols (**171b**) 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 33**).

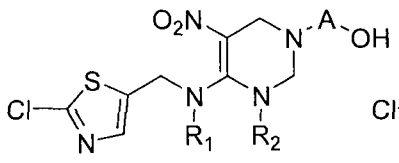


170 **172**

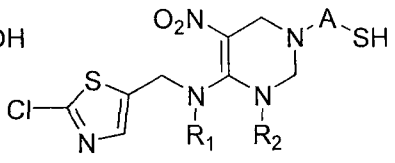
Scheme 33

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

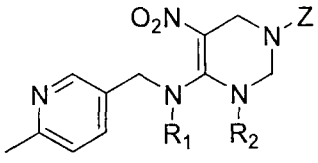
Other nitromethylene derivatives that were prepared are shown below,



173

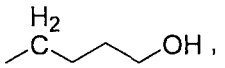
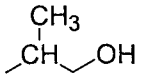
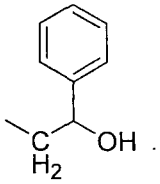


174



175

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

Z=  ,  ,  .

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 favorable toxicity to warm-blooded animals. They are active against normally sensitive and resistant species and against all or some stages of their development.

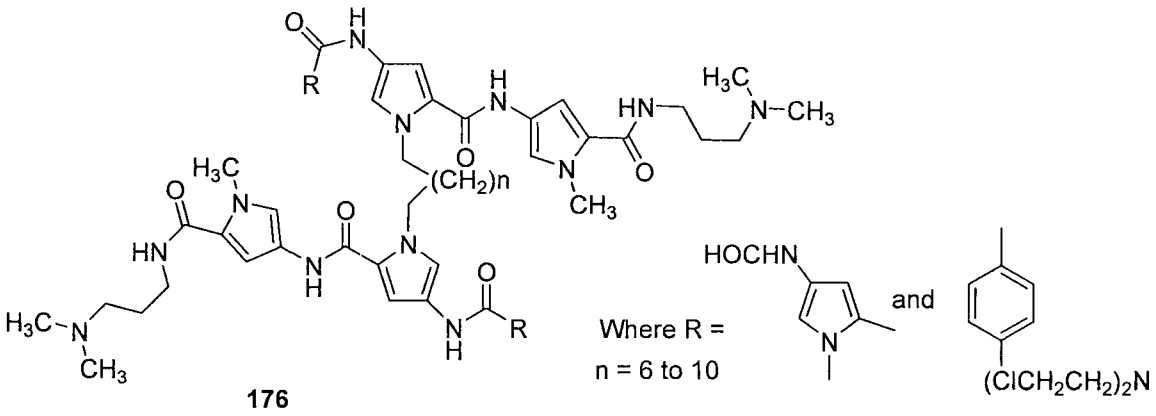
The active compound concentration of the use forms can be from 0.0000001 to 95% by weight of active compound, preferably between 0.0001 and 1% by weight. The compounds are employed in a customary-manner appropriate for the use form. These compounds were also found to control Nephotettix cincticeps on 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.

1.6 BIS-HETEROCYCLIC COMPOUNDS

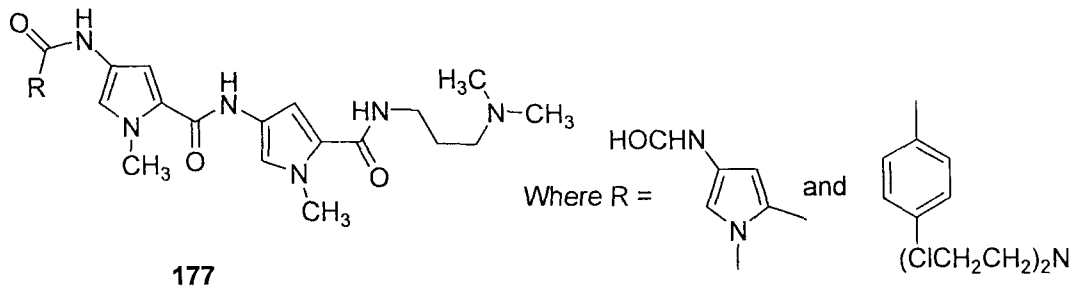
Literature reports have also highlighted the fact that many dimeric molecules have been synthesized and some of these dimers have been found to be biologically more active then their monomer counter parts. The following paragraphs describe some of these molecules.

1.6.1 Y.H. Chen and coworkers have designed and synthesized[50] a novel class of bis (mustard) cross-linked Lexitropsins (**176**).



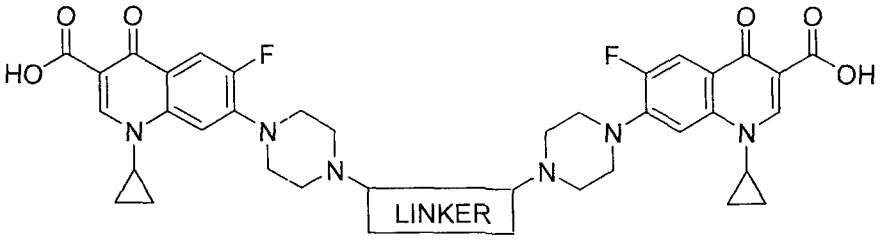
176

The activity of these dimers were compared to that of their monomer counter parts **177** and it was found that suitably cross-linked Lexitropsins demonstrated much greater binding strength than their respective monomers to the alternating AT polymer where the antiparallel side by side bidentate binding is possible.

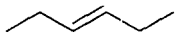
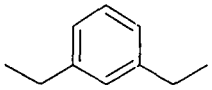
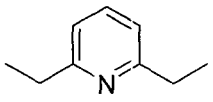
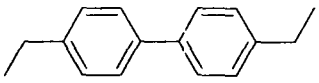


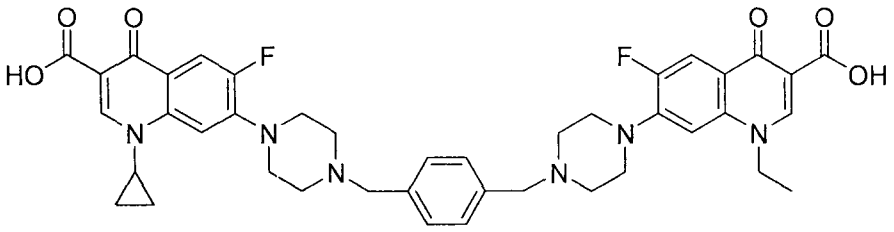
177

1.6.2 R. J. Kern and coworkers have reported[51] the synthesis of a series of symmetric compounds of the type **178** and asymmetric compounds of the type **179** and **180** that are piperazinyl-linked dimers of the fluoroquinolone class of antibiotics.

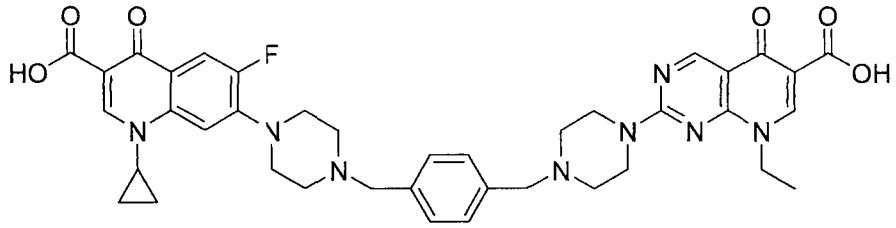


178

		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



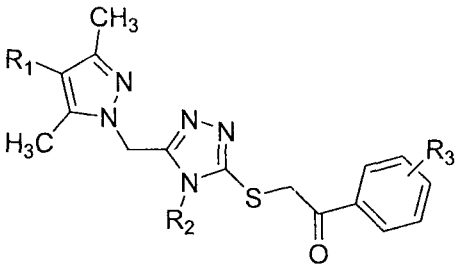
179



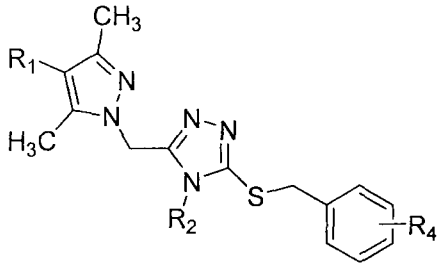
180

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 NorA efflux-mediated and topoisomerase IV substitution mediated resistance mechanism.

1.6.3 F. Q. He and coworkers have reported[52] the synthesis of bis-heterocyclic pyrrodiazole derivatives containing pyrazole **181** and **182**. Some of these compounds exhibited certain herbicidal activities against barnyard grass and rape.



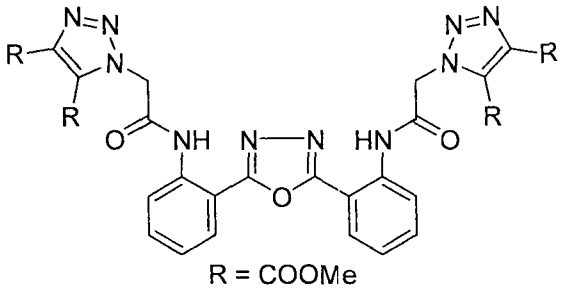
181



182

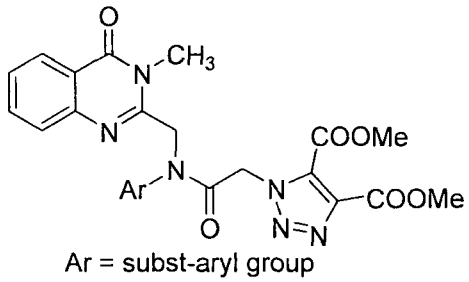
Where R_1 = H, NO_2 R_2 = Ph, CH_3
R_3 = H, 2,4-Cl_2, 2-F, 4-(Cl, Br, CH_3, OMe)
R_4 = 2-F, 2,4-Cl_2

1.6.4 P. S. N. Reddy and coworkers have reported[53] the synthesis of bis-heterocycles of the type (**183**) and (**184**).



R = COOMe

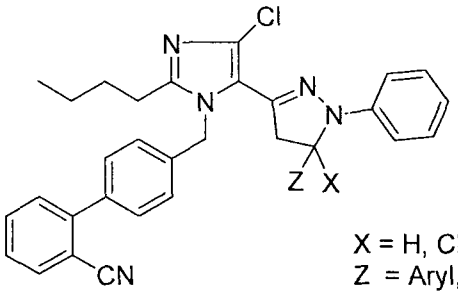
183



Ar = subst-aryl group

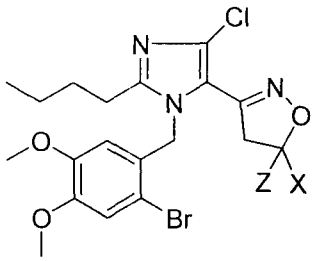
184

1.6.5: K. M. Lokanatha Rai and coworkers have reported[54,55] the synthesis of a series of bis-heterocycles of the type **185** and **186**.



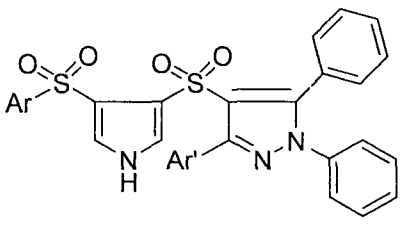
X = H, CH_3
Z = Aryl,subst alkyl or Ester groups.

185



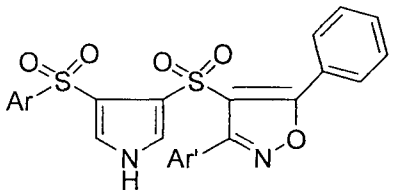
186

1.6.6 V. Padmavathi and coworkers have reported[56] the synthesis of sulfone linked bis-heterocycles, pyrrole together with pyrazole or isoxazole units of the type **187** and **188**.



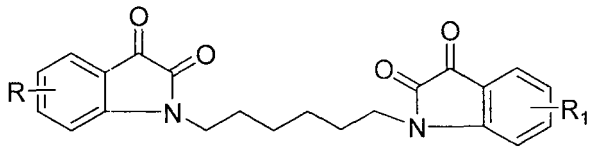
Ar, Ar' = Ph or subst Ph

187

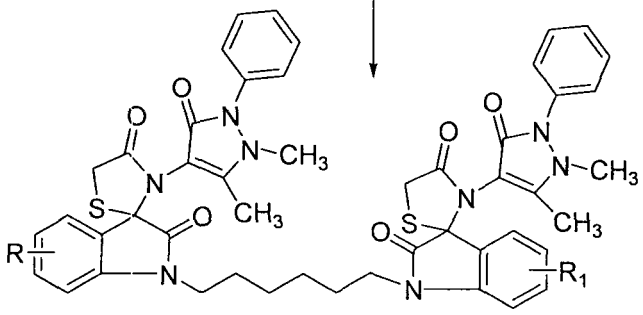


188

1.6.7 S. C. Jain and coworkers have reported[57] the synthesis of some unsymmetrical bis-indol-2, 3-dione(**189**), which were further used for the synthesis of bis-spiroindoles (**190**) (**Scheme 34**).



189

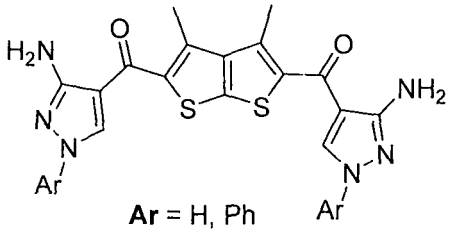


R, R_1 = CH_3, H or F

190

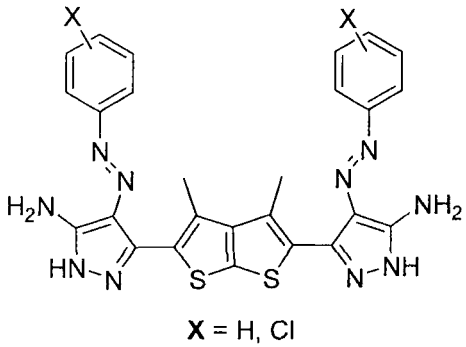
Scheme 34

1.6.8 Y. N. Mabkhoot has reported the synthesis[58] of a series of bis-heterocycles having the structures **191** and **192** containing thieno-[2,3-*b*]-thiophene linking unit.



Ar = H, Ph

191

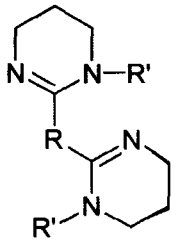


X = H, Cl

192

Our literature reports conclude that dimers of 1,4,5,6-tetrahydropyrimidines have also been prepared (although not thoroughly studied) and have been used for various purposes. Their preparation and uses are discussed in the following paragraphs.

1.6.9 Henry and Thomson reported[59] 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 dicarboxyllic preferably at 350^{0}F to 400^{0}F to gave tetrahydropyrimidine derivative of the structure (**193**) given below. The water molecules formed are removed azeotropically using benzene, toluene or xylene.

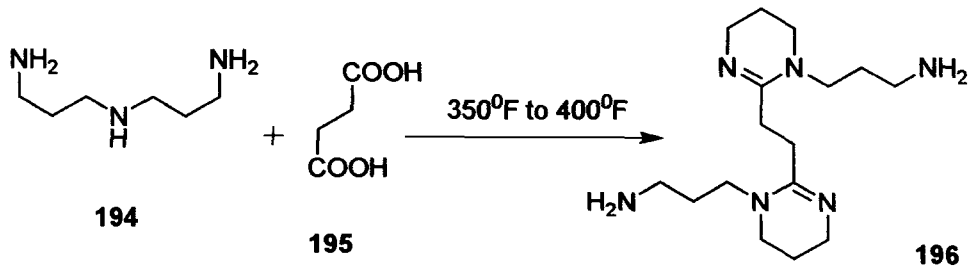


193

wherein **R**: hydrocarbon radical containing at least 2 carbon atoms.

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

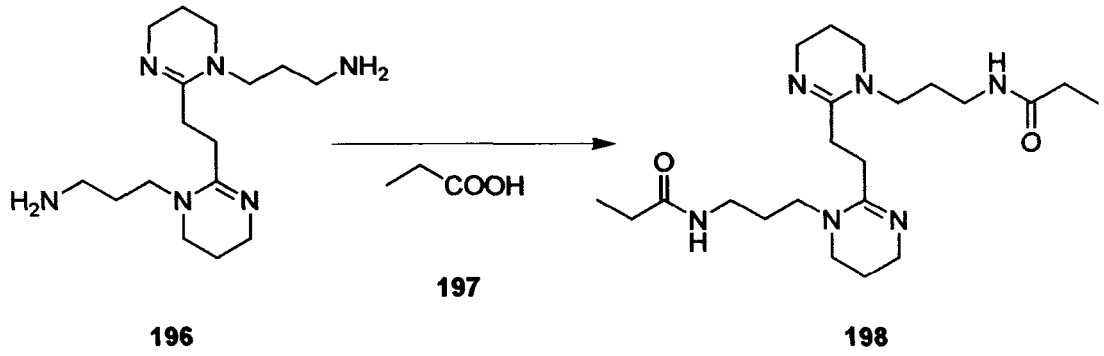
1.6.9a For example, the condensation of two mols of 3,3'-imino-bis-propylamine (**194**) with 1 mol of succinic acid (**195**) gave the corresponding bis-tetrahydropyrimidine having IUPAC nomenclature as 3,3'-(2,2'-(ethane-1,2-diyl)bis(5,6-dihydropyrimidine-2,1(4*H*)-diyl))dipropan-1-amine (**196**) (**Scheme 34**).



194 **195** **196**

Scheme 34

Further the compound **196** when reacted with carboxylic acid (**197**) (for e.g. 2mols of priopionic acid) gave the product **198** having amide linkage (**Scheme 35**).

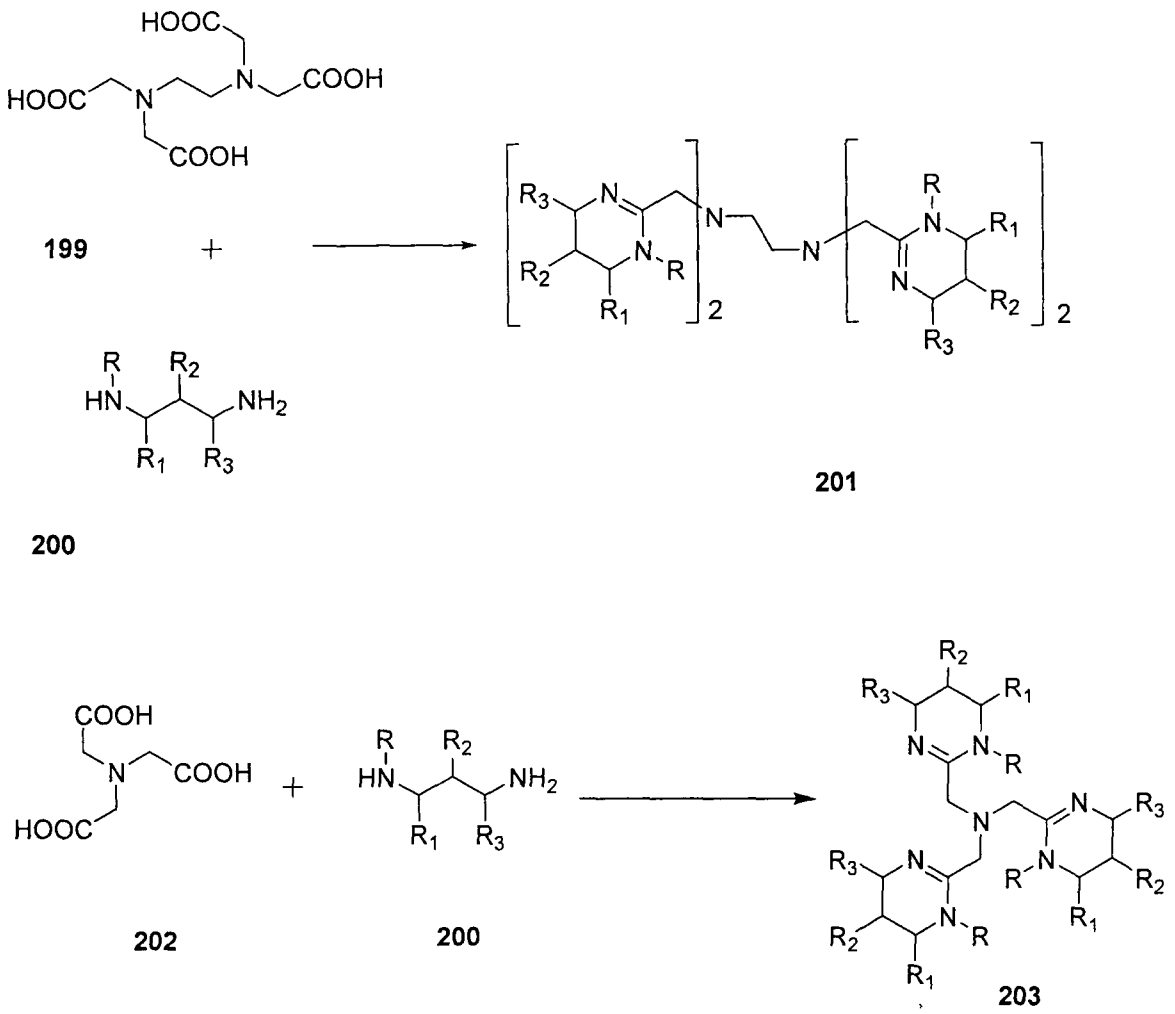


196 **197** **198**

Scheme 35

These bis tetrahydropyrimidines **196** and **198** 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.

1.6.9b 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 (**200**) group with ethylenediaminetetraceticacid (EDTA)(**199**) or nitrilotriacetic acid (**202**) at a temperature of 150^{0}C to 250^{0}C for 10 to 100 hours[60] (**Scheme 36**).



Scheme 36

wherein **R, R_1, R_2, R_3, R_4**: H-atom or alkyl.

1.7 Literature survey at this stage revealed that compounds having **bis-1,2,3,4-tetrahydropyrimidine** ring are unknown in the literature and hence their biological properties remain unexplored. Prompted by the above results we undertook to design and synthesize the hitherto unknown bis-1,2,3,4-tetrahydropyrimidines from active methylene compounds. The work described herein deals with the synthesis of such

bis-1,2,3,4-tetrahydropyrimidine rings. The work also describes the construction of the **bis-fused tetrahydropyrimidines, bis-pyrazolotetrahydropyrimidines, bis-triazinyl tetrahydropyrimidines**, as well as different synthons involved in the construction of the rings.

1.8 References.

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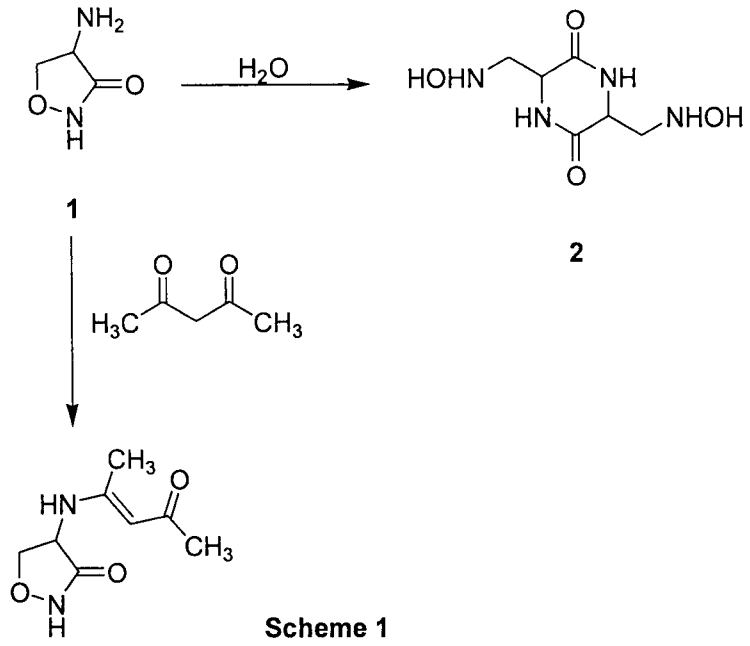
CHAPTER II

Formylation of active methylene compounds and their reactions with primary amines

Introduction

Enaminones are potential intermediates for the synthesis of a variety of heterocyclic systems like oxazoles, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, tetrahydrophenanthridines, pyranones, pyridine derivatives[1-3] etc.

2.1 Unlike enamines, which have been reported to be unstable in aqueous solutions[4-9], 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[10]. Cycloserine (**1**) is known to be unstable and has a tendency to form a dimer (**2**) as shown in **Scheme 1**. Preventing the formation of dimer would increase the stability both on the shelf and in physiological media.



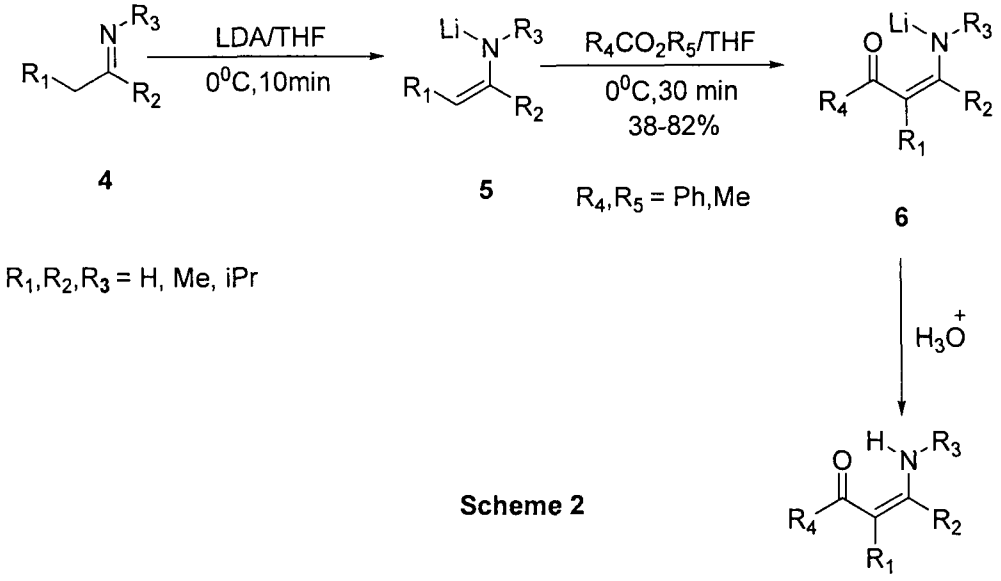
Scheme 1

Since the formation of the dimer (**2**) 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 (**3**), which was the condensation product of cycloserine and acetyl acetone and was found to be an efficacious prodrug of increased stability under aqueous conditions.

2.1.1 There are also reports of the potential use of enaminones for biological purpose. Scheone and co-workers have prepared[11] several enaminones and evaluated them for hypoglycaemic effectiveness, but their compounds gave poor activity.

2.2 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.

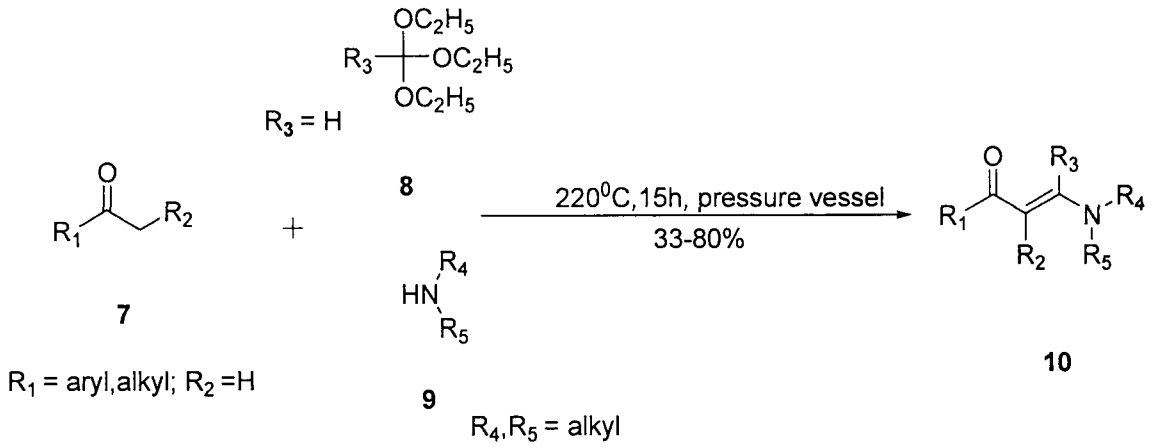
2.2.1 The reaction of α- metallated imines with esters under mild conditions leads to the formation of enaminoketones (also called unsymmetrical diketones)



Scheme 2

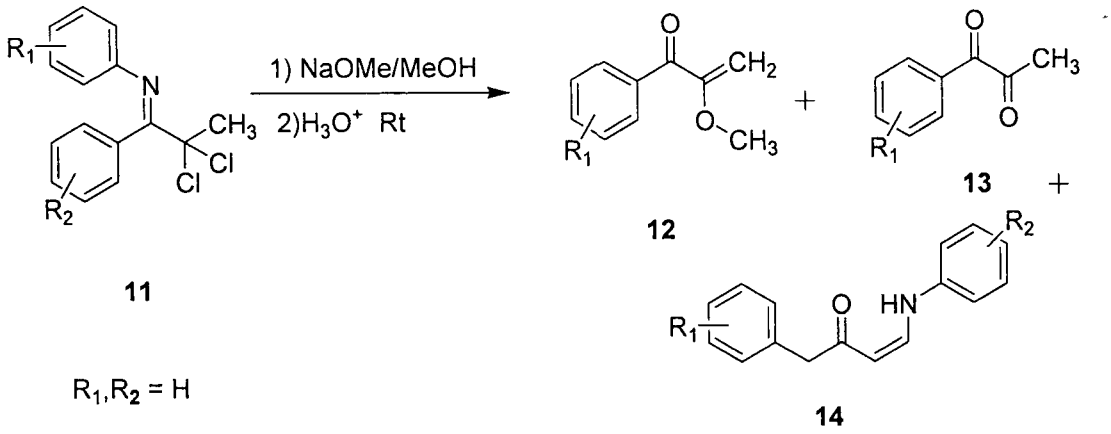
When imine anions **5** prepared from imines **4** (**Scheme 2**, by standard method) is allowed to react with esters at 0^0C in THF for 30 minutes, enaminoketones **6** were obtained. A two-fold excess of base is required for the reaction to go to completion indicating that a second equivalent of lithum derivative preferentially metallates the imine nitrogen atom of compound **6** as soon as it forms. The anionic form of **6** prevents it from further nucleophilic attack by the imine anions[12].

2.2.2 β-amino-α,β-unsaturated ketones (**10**) (β-acylenamines) were obtained in a mannich reaction by heating a mixture of ketone **7**, triethylorthoformate (**8**), and secondary amine **9** 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 E configuration[13] (**Scheme 3**).



Scheme 3

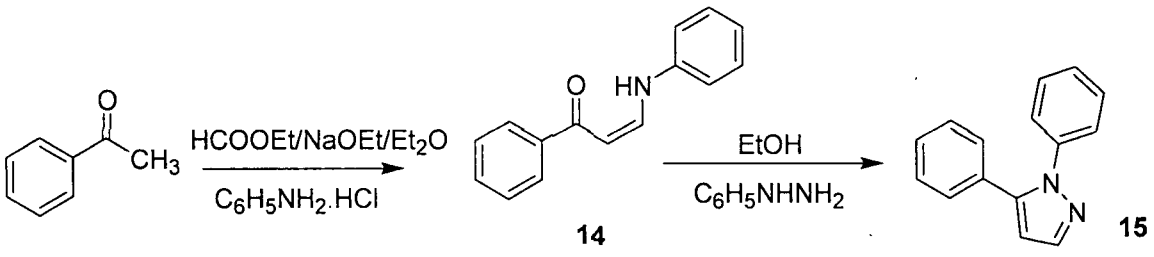
2.2.3 When *N*-1-(2,2′-dichloro-1-phenylpropylidene)aniline (**11**) was treated with 2N sodium methoxide in MeOH and refluxed overnight and the reaction mixture was hydrolysed with excess of aqueous 2N HCl overnight, the ethereal extract gave after evaporation, an oil from which a yellow solid material precipated on standing. The filtrate contained two compounds, namely, 2-methoxy-1-phenyl-2-propen-1-one (**12**) and 1-phenyl-1,2-propane dione (**13**). The solid product was identified as 3-anilino-1-phenyl-2-propen-1-one (**14**) (**Scheme 4**).



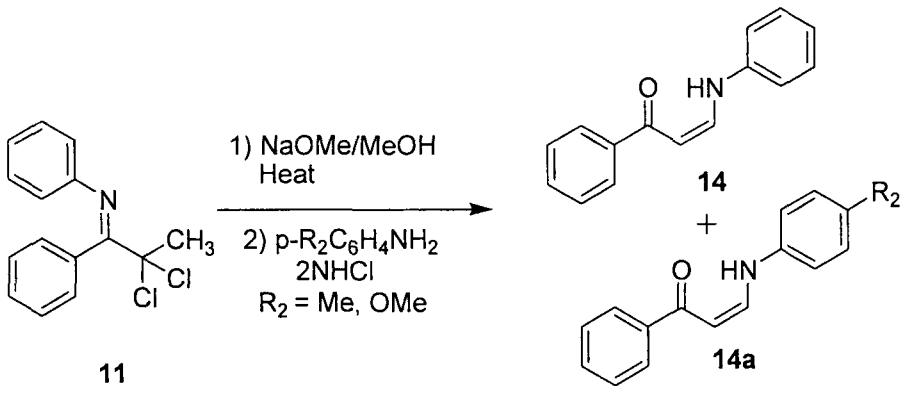
Scheme 4

The structure elucidation of enaminoketone **14** was supported by the synthesis of the authentic materials.

2.2.4 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 (**14**), an additional confirmation of the formation of **14** was the conversion of **14** into 1,5-diphenylpyrazole (**15**) by reacting with phenyl hydrazine[14] (**Scheme 5**).



Scheme 5

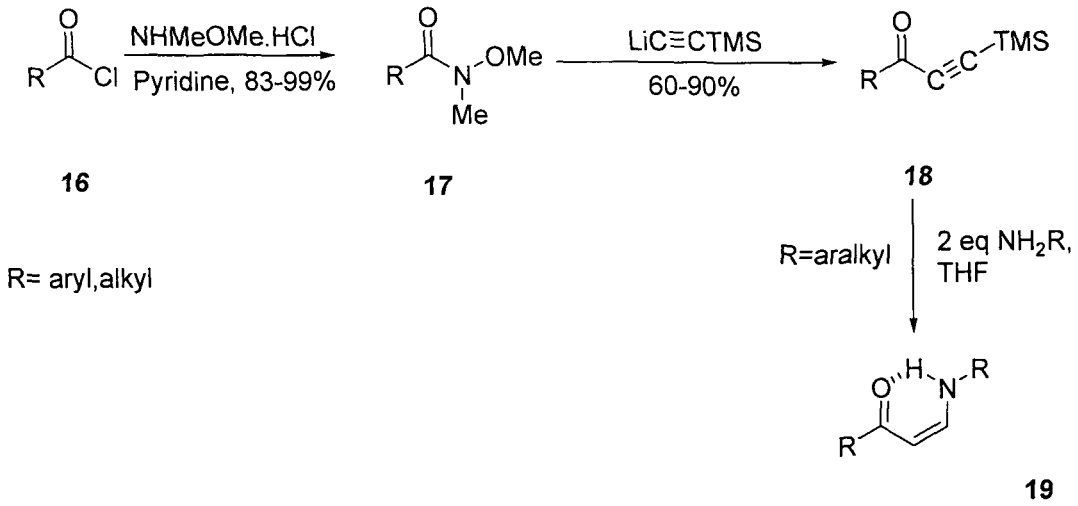


Scheme 6

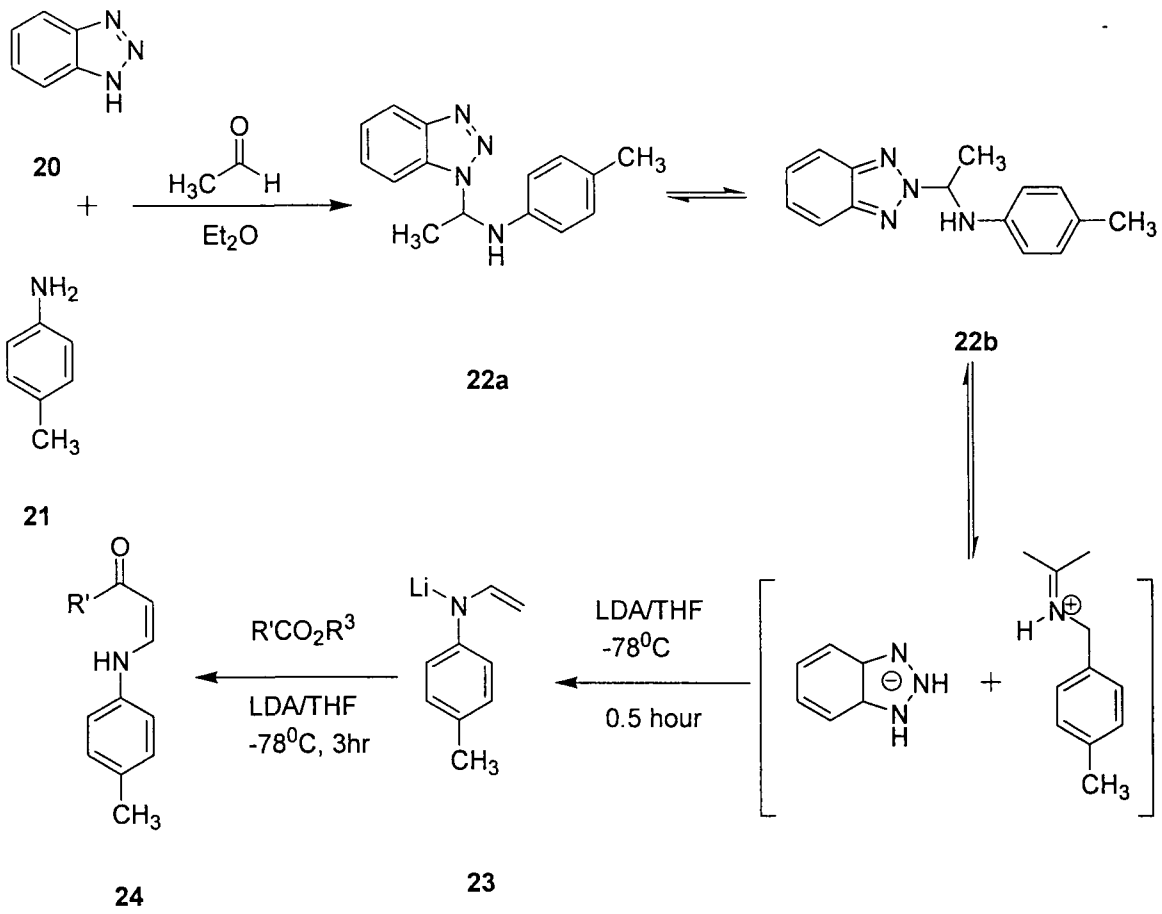
2.2.5 In order to check whether or not the transformation of α-halo ketimines in to β-ketoenamines is a result of an intramolecular process, the reaction mixture on N-phenyl α, α-dichloroketimine with sodium methoxide in methanol was hydrolysed with 2N HCl in the presence of p-toluidine. The solid isolated from this hydrolysis procedure consisted of a mixture of 3-anilino-1-phenyl-2-propen-1-one (18%) and 3-p-toluidino-1-phenyl-2-propen-1-one (25%), Similarly, when hydrolysis was carried out in the presence of p-anisidine, the solid fraction was a mixture of **14** and **14a** in 25% and 15% yields respectively[15] (**Scheme 6**).

2.2.6 When trimethyl silyl ethynylketones (**18**) was reacted with 2 equivalents of benzyl amine in THF, the corresponding enaminone **19** was formed in good yield [16](**Scheme 7**).

2.2.7 Treatment of *N*-[1-(4-methylphenylamino)ethyl]benzotriazole (**22**) obtained from the condensation of benzotriazole (**20**), aldehyde and aromatic amine **21** with 2 equivalents of LDA in THF at -78^{0}C for 0.5 hour followed by reaction with esters at -78^{0}C for 3 hours gave the enaminone **24** in high to moderate yields. (**Scheme 8**)


NHMeOMe.HCl
Pyridine, 83-99%
LiC≡CTMS
60-90%
TMS
16
17
18
R= aryl,alkyl
R=aralkyl
2 eq NH2R,
THF
19

Scheme 7

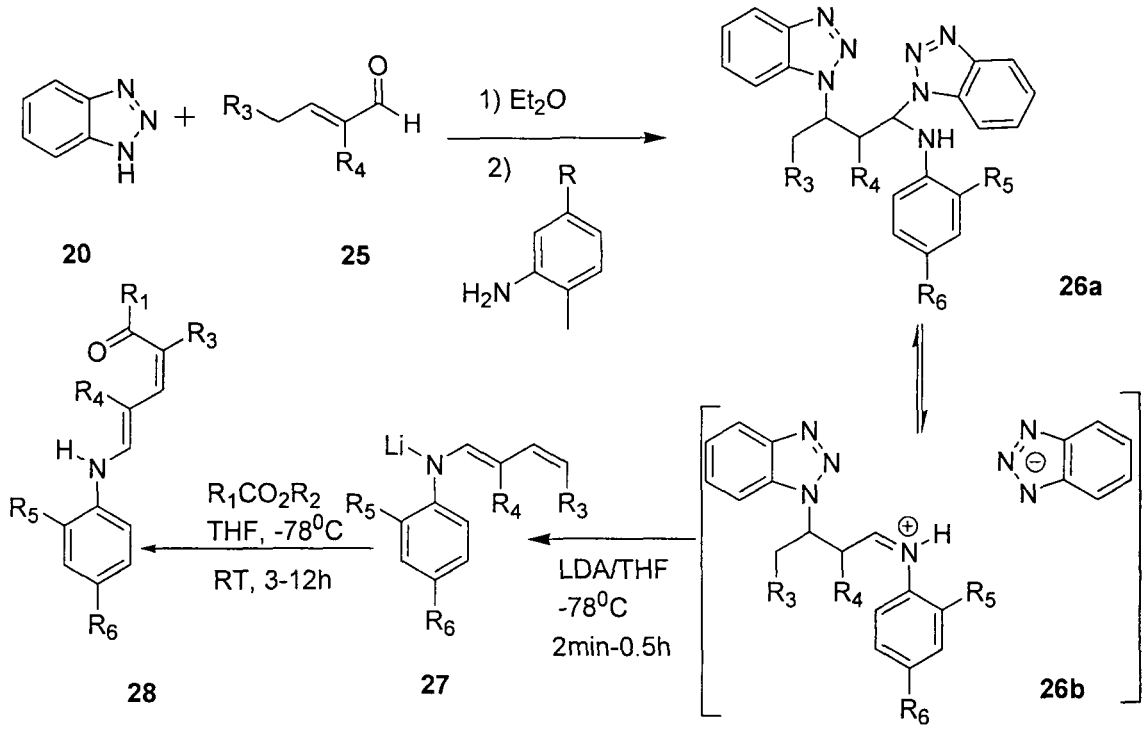


Scheme 8

N-[1-(4-Methylphenylamino)ethyl benzotriazole (**22**) exists in solution as a mixture of 1-benzotriazolyl (**22a**) and 2-benzotriazolyl isomer (**22b**). It is envisaged that the reaction proceeds by the deprotonation of secondary amine with concomitant elimination of benzotriazole followed by further deprotonation giving the N-metalated amine **23**. Addition of esters furnishes the mesomerically stabilized enaminones **24**. The J value *CH=CH* 7.8 to 8.3 suggests that the compound is in Z configuration.

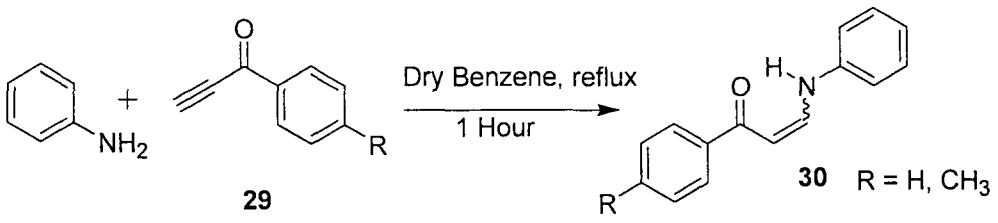
2.2.8 This general method was also applied to the generation of dienaminone derivatives by reaction of benzotriazole **20** (2.0 equivalent) and α,β-unsaturated

aldehyes **25** (1.0 equivalent) and a primary aryl amine giving 1,3-bis (benzotriazolyl) - substituted arylamines **26**. On further treatment with 3.0 equivalent of LDA in THF at -78^{0}C followed by reaction with esters gave dienones **28**. The reaction pathway was envisaged as shown in the (**Scheme 9**). The bis-compounds have a tendency towards facile ionization in solution to form intermediates which can be deprotonated sequentially giving access to the lithiated dienamines, which in turn react with electrophilic esters to give dienaminones[17].



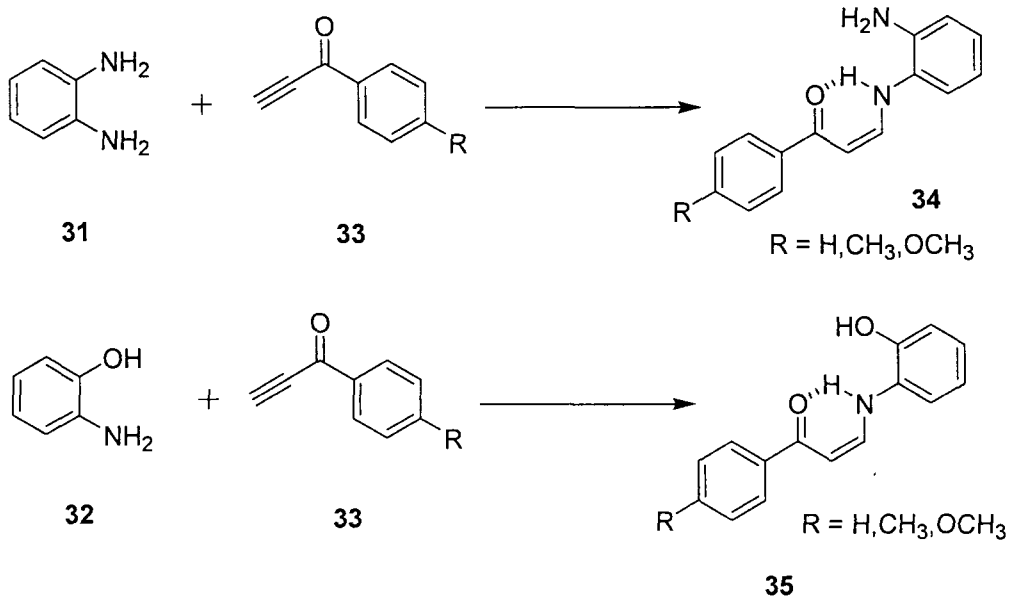
Scheme 9

2.2.9 Reaction of primary amines with ethynyl phenyl ketones **29** in presence of dry benzene gave an equilibrium mixture of cis and trans enamines **30** whose composition is solvent dependent (**Scheme 10**).



Scheme 10

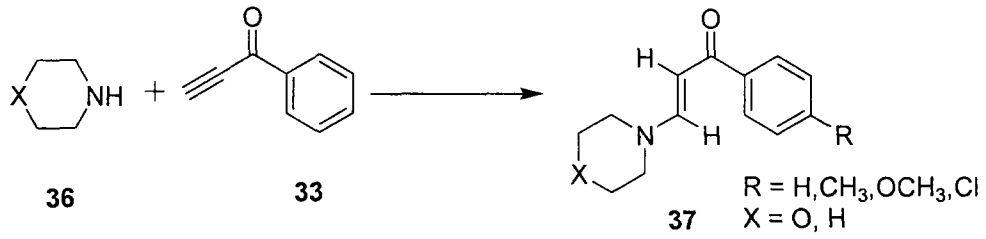
2.2.10 Similarly the reaction of *o*-phenylenediamine (**31**) and *o*-aminophenol (**32**) with aryl ethynyl ketones gave the corresponding cis-β-aminovinylketones **34** and **35** (The cis-stereochemistry of the double bond follows from the coupling constant J= 8Hz) (**Scheme 11**).



Scheme 11

However, the reaction of secondary amines (morpholine and piperidine) **36** to activated acetylenes **33** leads to the formation of trans-isomer **37** due to the opposing dipoles of the activating group and the C-N bond, and also by the absence of non-

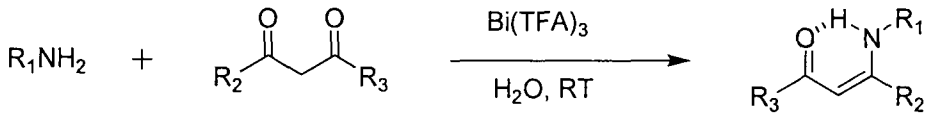
bonded interaction between the activating groups and the dialkylamino group[18] (**Scheme 12**).



36 33 37

Scheme 12

2.2.11 Enaminones have also been prepared by lewis acid catalysed reaction in water. A catalytic amount of bismuth trifluoroacetate (5 mole %) and the required amine when added to a stirred solution of 1,3-dicarbonyl compound **38** in water gave the required enaminones **39** (**Scheme 13**).



38 39

Scheme 13

This method was successfully applied to enamination of β-diketone (linear and cyclic) and β-ketoesters. In all cases the amine attack took place only at the methyl ketone, carbonyl for diketones and ketoesters. $Bi(TFA)_3$ is slightly soluble in water and can be separated by filteration, washed with DCM dried at 80°C under pressure and re-used in 3- runs without any loss of activity[19].

However, the above methods suffer from limitations such as a multi-step reaction sequence, high temperatures, low yields and longer reaction times etc.

2.2.12 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[20-21]. These techniques require open vessels with little or no solvent and are free of the risk of explosion. MORE chemistry reactions 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[22].

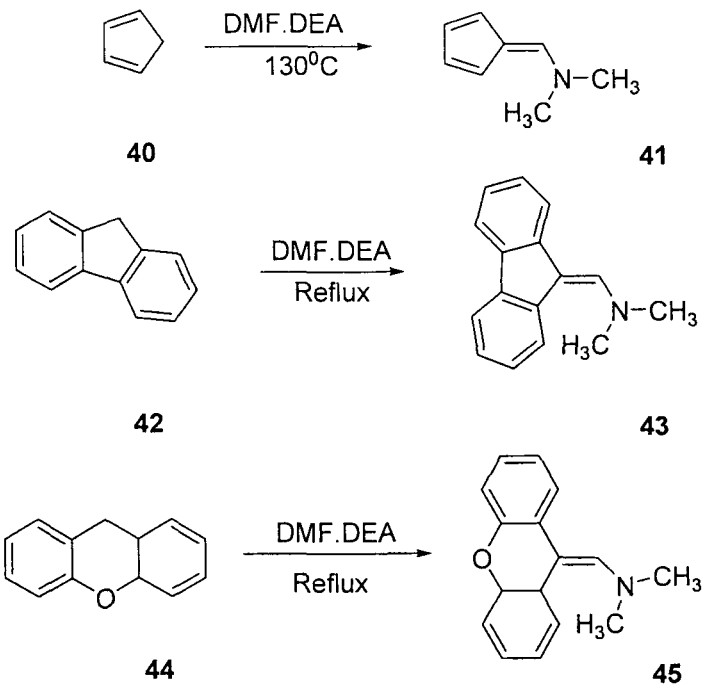
Prompted by the above we took up the synthesis of enaminones via formylated active methylene compounds.

Objectives:

1) Synthesis of formylated active methylene compounds
2) Conversion of some of the active methylene compounds so prepared to our required enaminones

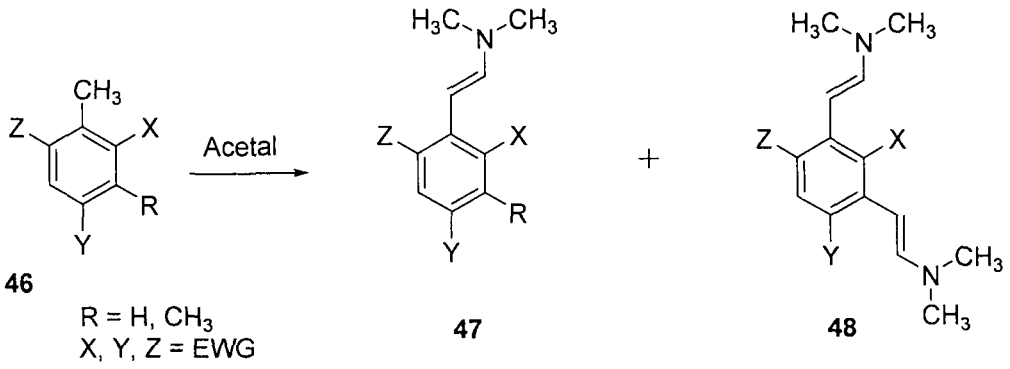
2.3 Our literature survey at this stage revealed that few formylated active methylene compounds are known[23-25]. The preparations of some of these compounds are given in the following sections.

2.3.1 Meerwein and coworkers[26a] reported the reaction of cyclopentadiene with N,N- dimethylformamide diethyl acetal (DMF.DEA) to yield 6-aminofluvene. The reaction proceeded at 130^0C to give the product in 32% yield. Later fluorene and xanthene were also converted to their enamines with tris (dimethylamino) methane (**Scheme 14**).



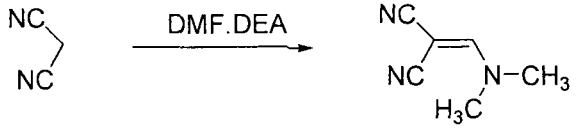
Scheme 14

The reaction of substituted toluene with formamide acetals gave enamines and dienamines depending on the number of methyl groups (**Scheme 15**).



Scheme 15

Meerwein et al. first reported[26b] the reaction of malononitrile and dimethylformamide diethylacetal to give the enamines as shown in **Scheme 16**. Later other enamines were prepared from other active methylene compounds.

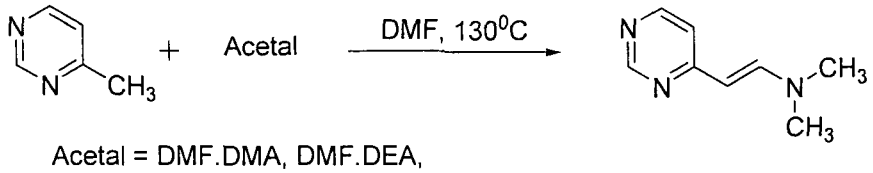


49 50

Scheme 16

The formylation needed reflux temperature for the less active methylene groups while the more active methylene group gets formylated at room temperature.

2.3.2 Bredreck et al. reported[27] the synthesis of enaminones by reaction of 4-methyl pyrimidine with various acetals (**Scheme 17**).

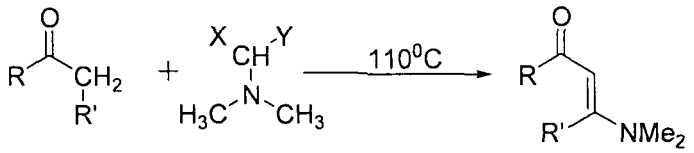


51 Acetal = DMF.DMA, DMF.DEA, Bis(dimethylamino)t-butoxymethane.

52

Scheme 17

2.3.3 P. F. Schuda and coworkers have reported[28] the synthesis of enamines from various ketones by reacting them with acetals at 110°C (**Scheme 18**).

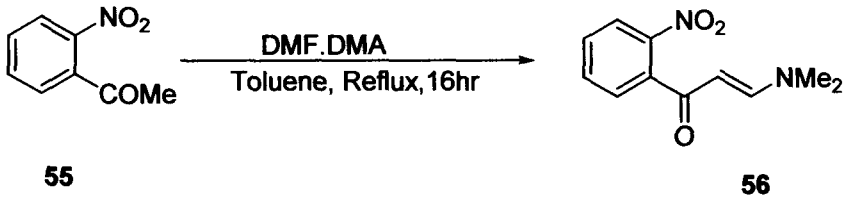


53 X=Y=OMe, X=Y=NMe_2 X=NMe_2 Y=OtBu 54

Scheme 18

2.3.4 S. S. Tseng and coworkers have also reported[29] the synthesis of enamines from various substituted acetophenones by reacting them with acetals at 120^0C.

2.3.5 V. M. Paradkar and coworkers have reported[30] the synthesis of enamines from nitro acetophenone in refluxing toluene (**Scheme 19**).

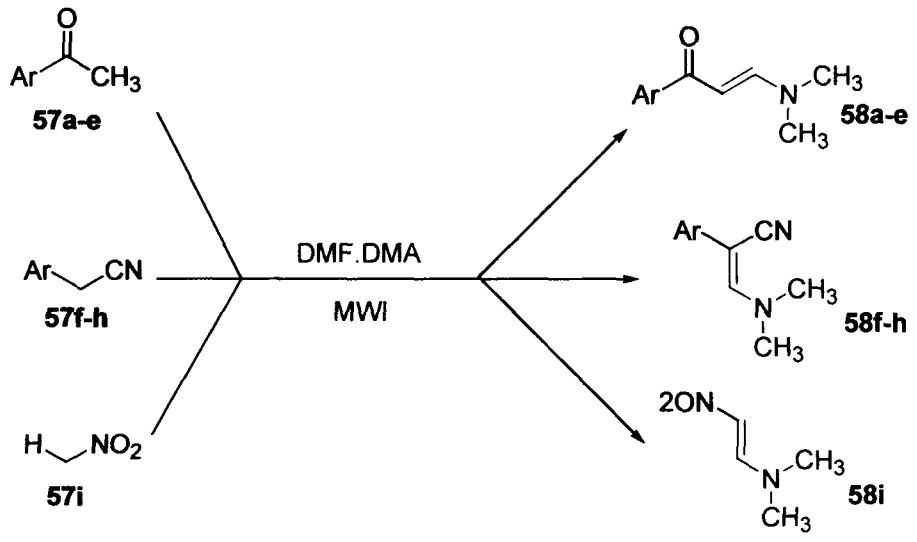


55 **56**

Scheme 19

But all their preparations involve thermal conditions, longer reaction time, toxic solvents and poor yields.

2.4 Prompted by the above, we took up the formylation of some active methylene compound using dimethylformamide-dimethylacetal (DMF-DMA) under microwave and the results of our studies are described herein (**Scheme 20**).



Scheme 20

2.5 Results and discussions.

When a mixture of acetophenone (5 mmol) and DMF-DMA (10 mmol) was irradiated in a domestic microwave oven at 300 watt for 22 min, the reaction was found to be complete (monitored by TLC). Work-up of the reaction mixture gave the desired compound **58a** in 70% yield. The structure of **58a** was established with the help of physical and the spectral data. The reaction followed similar trend with substituted acetophenones and the formylated ketones **58b-e** were obtained in 73-92% overall yields. The ^{1}HNMR spectra of **58a-e** exhibited a doublet due to the vinylic proton at C-2 between δ 5.69-5.88 with *J* 12.2-14.4 Hz while the proton at C-3 appears along with the aromatic protons. The coupling constant values suggest that these molecules exist in E-form. The six proton of the two methyl group of NMe_2 group appear as a single singlet at 3.10 except in **58d** and **58e** in which they appear as two singlets at δ 3.08 and 3.28 and δ 2.96 and 3.09, respectively for three protons each. This exclusive observation in case of **58d** could be attributed to the presence of nitro group in the para position of the benzene ring, which would decrease the electron density at the carbonyl carbon. This decreased electron density at the carbonyl carbon would facilitate delocalization of the lone pair of electrons of nitrogen atom of NMe_2 resulting in double bond character in C_3- N bond thus making the protons of the methyl group non-equivalent. The appearance of the two singlets due to the methyl group protons of NMe_2 in **58e** is probably due to the dominance of -I effect of the methoxy group over its +R effect.

The methodology could successfully be applied for the synthesis of formylated acetoniriles and compound **58f-h** could be obtained in 83-95% yields. In the ^{1} H

NMR spectra of **58f-h,** the vinylic protons appear between δ 6.86-7.09 while the six protons of NMe_2 give a singlet between 3.26-3.30 ppm.

The strategy proved to be equally useful for the construction of **58i** (97% yield) derived from nitro methane. The ^1H NMR spectrum of **58i** showed two doublets at 6.73 ppm (*J* 11.7 Hz) and 8.30 (*J* 11.7 Hz) ppm for the vinylic protons, which suggest that the alkene exists in *E* form. The six NMe_2 protons give two singlets at 2.90 and 3.23 ppm for three protons each.

Table 1 Characterization data of 3-dimethylamino-1-arylprop-2-en-1-ones (58a-e), 3-dimethylamino-2-arylacrylonitriles (58f-h) and 2-dimethylamino-1-nitroethene (58i).

Comp	Ar	power(watt)	Time(min)	yield(%)	Mp(^{0}C)
58a	C_6H_5	300	22	70	88-90 (88-90)[24]
58b	4-ClC_6H_4	180	20	88	82-83 (81-83)[24]
58c	4-BrC_6H_4	300	13	92	80-81
58d	4-$NO_2C_6H_4$	100	8	90	144-146
58e	4-$MeOC_6H_4$	300	15	73	95-97
58f[25]	C_6H_5	300	15	95	80-81
58g	4-ClC_6H_4	300	7	83	87-89
58h	4-$MeOC_6H_4$	300	22	83	85-86
58i	—	100	2	97	105-106 (104)[30]

2.6 Experimental.

Melting points were recorded by the open capillary method and are uncorrected. The IR spectra on KBr disc were recorded on a perkin-Elmer 983 spectrometer. ^{1}H NMR (90MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^{1}H NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and the coupling constant (Hz) are reported and TMS is used as the internal standard. The FAB mass spectra were recorded on a Joel SX 102/DA-6000 mass spectrometer/data system using Argon/Xenon (6KV, 10mA) as the FAB gas. Microwave irradiation was carried out in a Samsung domestic microwave oven, CE2733G, operating at 2450 MHz.

2.7 General procedure.

2.7a *Synthesis of 3-dimethylamino-1-arylprop-2-en-1-ones (58a-e).*

A mixture of the ketone **57** (5 mmol) and DMF-DMA (10 mmol) was taken in a 100ml conical flask and the content was irradiated in a domestic microwave oven for an appropriate length of time (Table 1). After the completion of the reaction (monitored by TLC), the excess of DMF-DMA and methanol formed were removed

under reduced pressure and the residue left was triturated with hexane to give pure desired compound **58a-e** in 70-90% overall yields. The products were crystallized from ethyl acetate/hexane mixture.

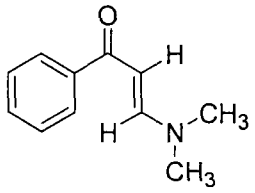
General procedure.

2.7b *Synthesis of 3-dimethylamino-2-arylacrylonitriles (58f-h).*

The reaction of pheylacetonitriles (**57f-h**) with DMF-DMA was carried out as mentioned above producing pure **58f-h** in 83-95% overall yields, which were crystallized from methanol. An identical experimental procedure yielded 2-dimethylamino-1-nitroethene (**58i**) in 97% yield, the crystallization of which was effected in methanol.

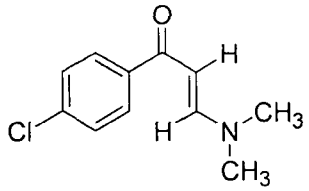
Individual description of the compounds.

(E)-3-(dimethylamino)-1-phenylprop-2-en-1-one 58a.



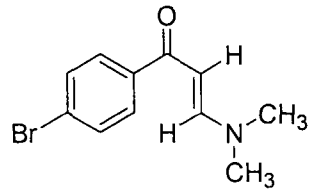
This compound was obtained as an off white solid, IR (KBr): 1596, 1619, 1640, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 6H, 2 CH_3), 5.87 (d, 1H, J=12.2Hz – C*H*=CH-N), 7.42-8.42 m, 6H); *Anal. Calcd. for* $C_{11}H_{13}NO$ (175.23): C, 75.40; H, 7.48; N, 7.99%. *Found*: C, 75.15; H, 7.44; N, 7.96%.

(E)-1-(4-chlorophenyl)-3-(dimethylamino) prop-2-en-1-one 58b.



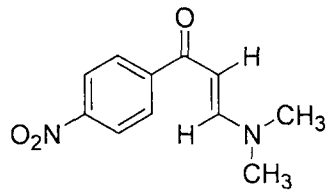
This compound was obtained as an off white solid, IR (KBr): 1546, 1580, 1644 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 6H, 2 CH_3), 5.83 (d, 1H, J=12.2Hz –C*H*=CH-N), 7.20-7.80 (m, 2H), 7.83-8.36 (m, 3H); *Anal. Calcd. for* $C_{11}H_{12}$ Cl NO (209.67): C, 63.10; H, 5.77; N, 6.68%. *Found*: C, 63.21; H, 5.73; N, 6.64%.

(E)-1-(4-bromophenyl)-3-(dimethylamino) prop-2-en-1-one 58c.



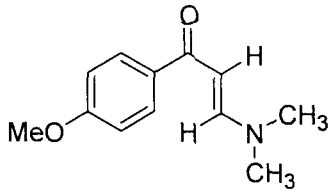
This compound was obtained as an off white solid, IR (KBr): 1541, 1574, 1586, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.06 (s, 6H, 2 CH_3), 5.76 (d, 1H, J=14.4Hz – C*H*=CH-N), 7.36-8.26 (m, 5H); MS, m/z 254 [M+]; *Anal. Calcd. for* $C_{11}H_{12}$ BrNO (254.12): C, 51.99; H, 4.76; Br, 31.44; N, 5.51%. *Found*: C, 51.85; H, 4.79; N, 5.55%.

(E)-3-(dimethylamino)-1-(4-nitrophenyl) prop-2-en-1-one 58d.



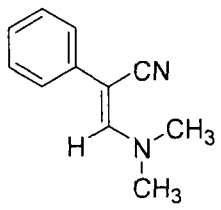
This compound was obtained as a white solid, IR (KBr): 1553, 1603, 1643 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.08 (s, 3H, CH_3), 3.28 (s, 3H, CH_3), 5.88 (d, 1H, J=12.5Hz, –C*H*=CH-N), 7.95-8.75 (m, 5H); *Anal. Calcd. for* $C_{11}H_{12}N_2O_3$ (220.22): C, 59.99; H, 5.49; N, 12.72%. *Found*: C, 59.95; H, 5.53; N, 12.76%.

(E)-3-(dimethylamino)-1-(4-methoxyphenyl) prop-2-en-1-one 58e.



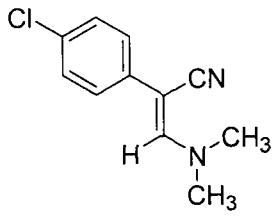
This compound was obtained as an off white solid, IR (KBr): 1580, 1602, 1638 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.96 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.72 (d, 1H, J=12.2Hz, –C*H*=CH-N), 6.90 (d, 2H), 7.79 (d, 1H J=12.2 Hz, –CH=C*H*-N), 7.90 (d, 2H); *Anal. Calcd. for* $C_{12}H_{15}NO_2$ (205.25): C, 70.22; H, 7.37; N, 6.82%. *Found*: C, 70.01; H, 7.42; N, 6.79%.

(Z)-3-(dimethylamino)-2-phenylacrylonitrile 58f.



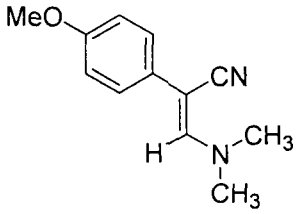
This compound was obtained as an off white solid, IR (KBr): 1572, 1592, 1622, 2177 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.26 (s, 6H, 2 CH_3), 7.09 (s, 1H, C=C*H*), 7.20-7.33 (m, 5H); *Anal. Calcd. for* $C_{11}H_{12}N_2$ (172.23): C, 76.71; H, 7.02; N, 16.27%. *Found*: C, 76.92; H, 7.07; N, 16.19%.

(Z)-2-(4-chlorophenyl)-3-(dimethylamino) acrylonitrile 58g.



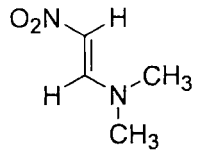
This compound was obtained as an off white solid, IR (KBr): 1561, 1590, 1630, 2184 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.29 (s, 6H, 2 CH_3), 7.09 (s, 1H, C=C*H*), 7.29-7.69 (m, 4H); MS, m/z 206 [M^+]; *Anal. Calcd. for* $C_{11}H_{11}ClN_2$ (206.67): C, 63.93; H, 5.36; N, 13.35%. *Found*: C, 63.75; H, 5.45; N, 13.42%.

(Z)-3-(dimethylamino)-2-(4-methoxyphenyl) acrylonitrile 58h.



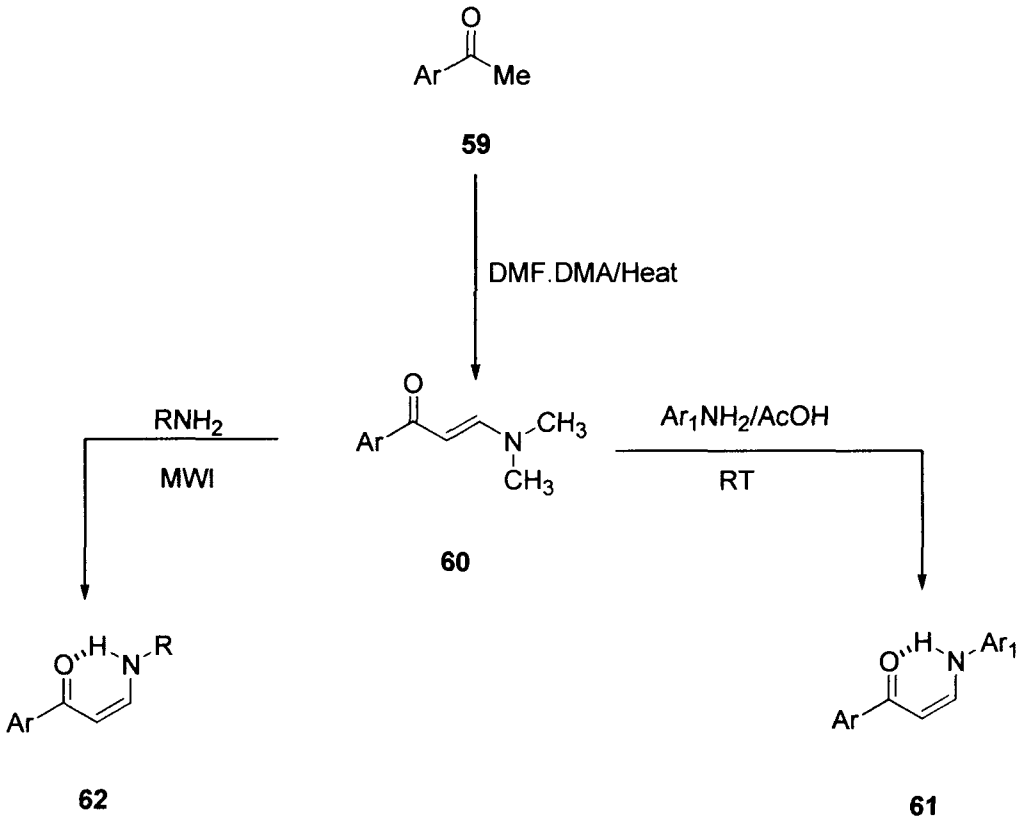
This compound was obtained as a pale yellow solid, IR (KBr): 1510, 1619, 2180 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.30 (s, 6H, 2 CH_3), 3.86 (s, 3H, OCH_3), 6.86 (s, 1H, C=CH), 7.06 (d, 2H), 7.43 (d, 2H); MS, m/z 202 [M^+]; *Anal. Calcd. for* $C_{12}H_{14}N_2O$ (202.25): C, 71.26; H, 6.98; N, 13.85%. *Found*: C, 71.05; H, 7.03; N, 13.77%.

(E)-N, N-dimethyl-2-nitroethenamine 58i.



This compound was obtained as a light brown solid, IR (KBr): 1538, 1634 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.90 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.73 (d, 1H, J=11.7 Hz, N–C*H*=CH), 8.30 (d, 1H, J=11.7 Hz, N–CH=C*H*); ^{13}C NMR ($CDCl_3$): δ 38.1, 45.5, 112.3, 151.2; *Anal. Calcd. for* $C_4H_8N_2O_2$ (116.12): C, 41.37; H, 6.94; N, 24.12%. *Found*: C, 41.31; H, 6.99; N, 24.20%.

2.7 For the synthesis of our required heterocyclic systems[31-36], we required enaminones of the types **61** and **62** (**Scheme 15**). The literature survey at this stage revealed that only a few compounds of this series are known[15-18], which have been obtained in poor yields. We herein report a facile general route to the title compounds by the reaction of 3-dimethylamino-1-arylprop-2-en-1-ones **60** with aromatic and aliphatic amines (**Scheme 21**).



Ar/Ar_1: Ph, 4-MePh, 4-MeOph, 4-ClPh, 4-BrPh;
R: Me, $PhCH_2$

Scheme 21

Table II — Preparation of 3-(alkyl/aralkyl/aryl) amino-1-arylprop-2-en-1-ones 61a-j and 62a-f

Compd	Ar	Ar_1/R	Reaction Time (hr/min)	Yield (%)	m.p. (°C) (lit. m.p.)
61a	C_6H_5	C_6H_5	4	92	141-42 (141)[15]
61b	C_6H_5	4-MeC_6H_4	2.5	92	157-59 (156-58)[16]
61c	C_6H_5	4-$MeOC_6H_4$	1	91	147-48 (147)[15]
61d	C_6H_5	4-BrC_6H_4	5	85	177
61e	4-$MeOC_6H_4$	C_6H_5	1.5	81	159-60 (133-34)[18]
61f	4-$MeOC_6H_4$	4-MeC_6H_4	1	91	151-52
61g	4-ClC_6H_4	4-MeC_6H_4	3.5	92	202-03
61h	4-MeC_6H_4	4-MeC_6H_4	3	98	185-86
61i	4-MeC_6H_4	C_6H_5	3	98	161-62 (165-66)[18]
61j	3-$MeOC_6H_4$	4-$MeOC_6H_4$	1	65	121-22
62a	C_6H_5	CH_3	30	85	130-31
62b	4-MeC_6H_4	CH_3	35	75	115 -16
62c	4-ClC_6H_4	CH_3	35	90	99-100
62d	4-$MeOC_6H_4$	$C_6H_5CH_2$	14	75	65-66
62e	4-MeC_6H_4	$C_6H_5CH_2$	10	84	112-13
62f	C_6H_5	$C_6H_5CH_2$	13	90	81 (81-82)[16]

2.8 Results and Discussions.

When 3-dimethylamino-1-phenylprop-2-en-1-one was stirred with an equimolar amount of aniline in acetic acid at room temperature, work-up of the reaction mixture yielded a pale yellow solid (92%), which was characterized as 3-anilino-1-phenylprop-2-en-1-one[15] **61a** on the basis of physical and spectral data (**Table II**). The reaction was found to be general between **60** and other primary aromatic amines to give the respective **61b-j** in 65-98% overall yields. These enaminones were found to exist in *Z*-form due to intra-molecular H-bonding as suggested by the coupling constant values ($J_{CH=CH,}$ 7.6-7.8Hz). The reaction of **60** with alkyl/aralkylamines under similar reaction conditions failed to give 3-alkylamino- or 3-aralkylamino-enaminones **62** and ended up in the formation of a complex mixture from which isolation of the desired product was not possible. However, when the reaction of **60** with alkyl or aralkylamines was carried out in refluxing ethanol, work-up of the reaction mixture resulted in the formation of the desired enaminones **62a-f** in 64-85% overall yields. But these reactions took very long time to go to completion (20-80 hr). Interestingly, when the reactions were carried out in domestic microwave oven, they went to completion giving enaminones **62a-f** in much better yields (75-90%) with shorter reaction time. However, it is important to note that **60** failed to react with primary aromatic amines in refluxing ethanol as well as under microwave irradiation. The structures of **62a-f** were established with the help of physical and spectral data. In the ^{1}H NMR spectra of 3-methylamino-1-phenylprop-2-en-1-one (**62a**), the N-Me protons appear as a doublet at 3.07 ppm due to their coupling with N-H proton which itself appears as a multiplet due to its coupling with C-3 vinylic proton. The vinylic proton at C-2 gives a doublet (J=6.9) at 5.70 ppm while the proton at C-3 appears as a double-doublet at 6.93 ppm. On D_2O shake, the signal due to N-Me protons collapses into a singlet as expected and the multiplet due to C-3 proton gets reduced to a doublet. Similar ^{1}H NMR spectra were obtained for enaminones **62b-f**. Compounds **62a-f** was also found to be in *Z*-form as indicated by the coupling constant values ($J_{CH=CH}$, 6.9-8.08Hz). The 1H NMR and D_2O exchange

spectra of 3-Methylamino-1-(4-methylphenyl)prop-2-en-1-one (**62b**) is shown in pages 79 and 80.

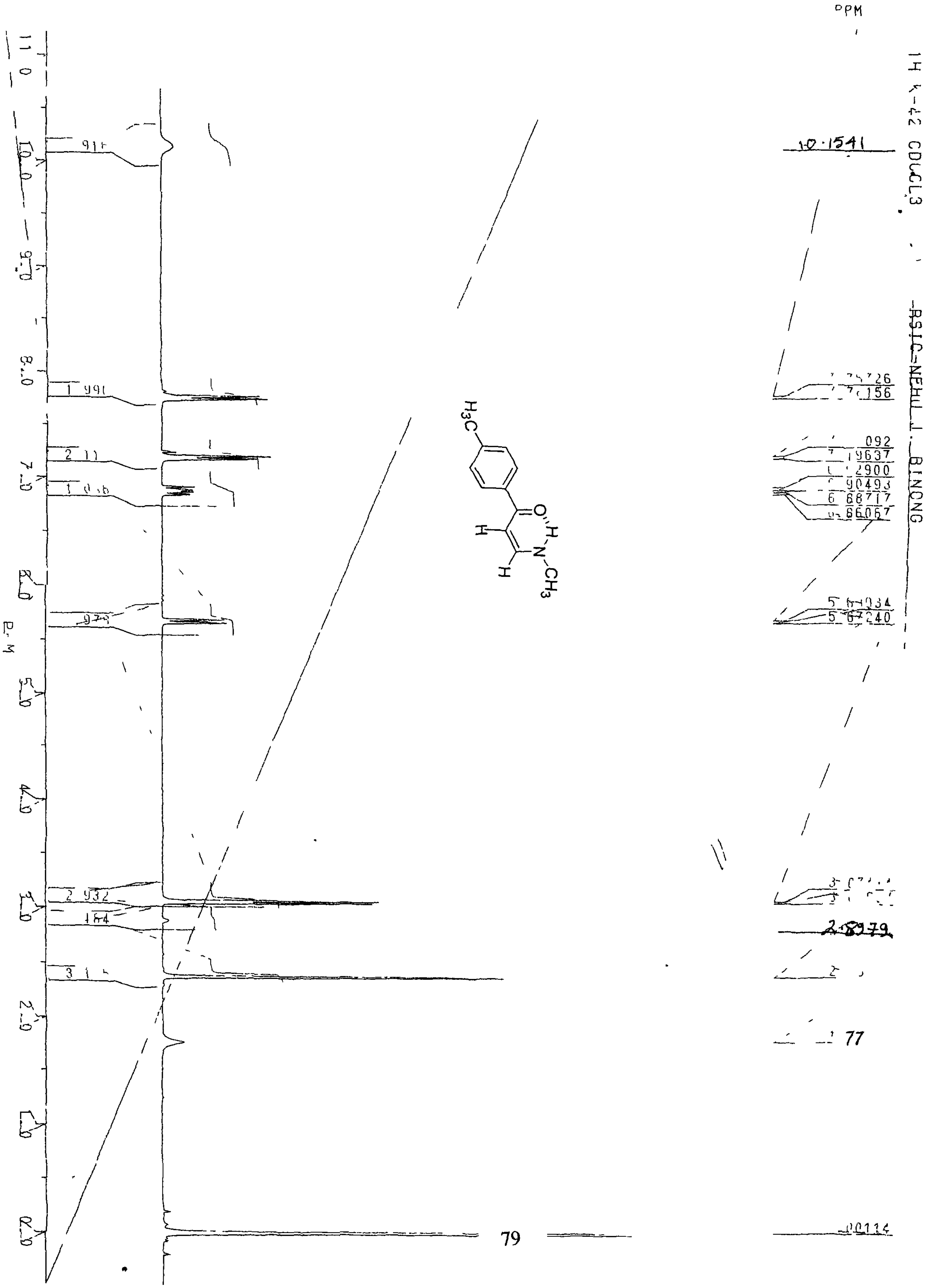
2.9 Conclusion.

In conclusion, we have developed a facile route for the synthesis of enaminones from cheap and commercially available active proton compounds in two simple steps. The first step involves microwave irradiation of the required active proton compounds with DMF.DMA followed by the conversion of these formylated products to their respective enaminones in very short time and in good to excellent yields.

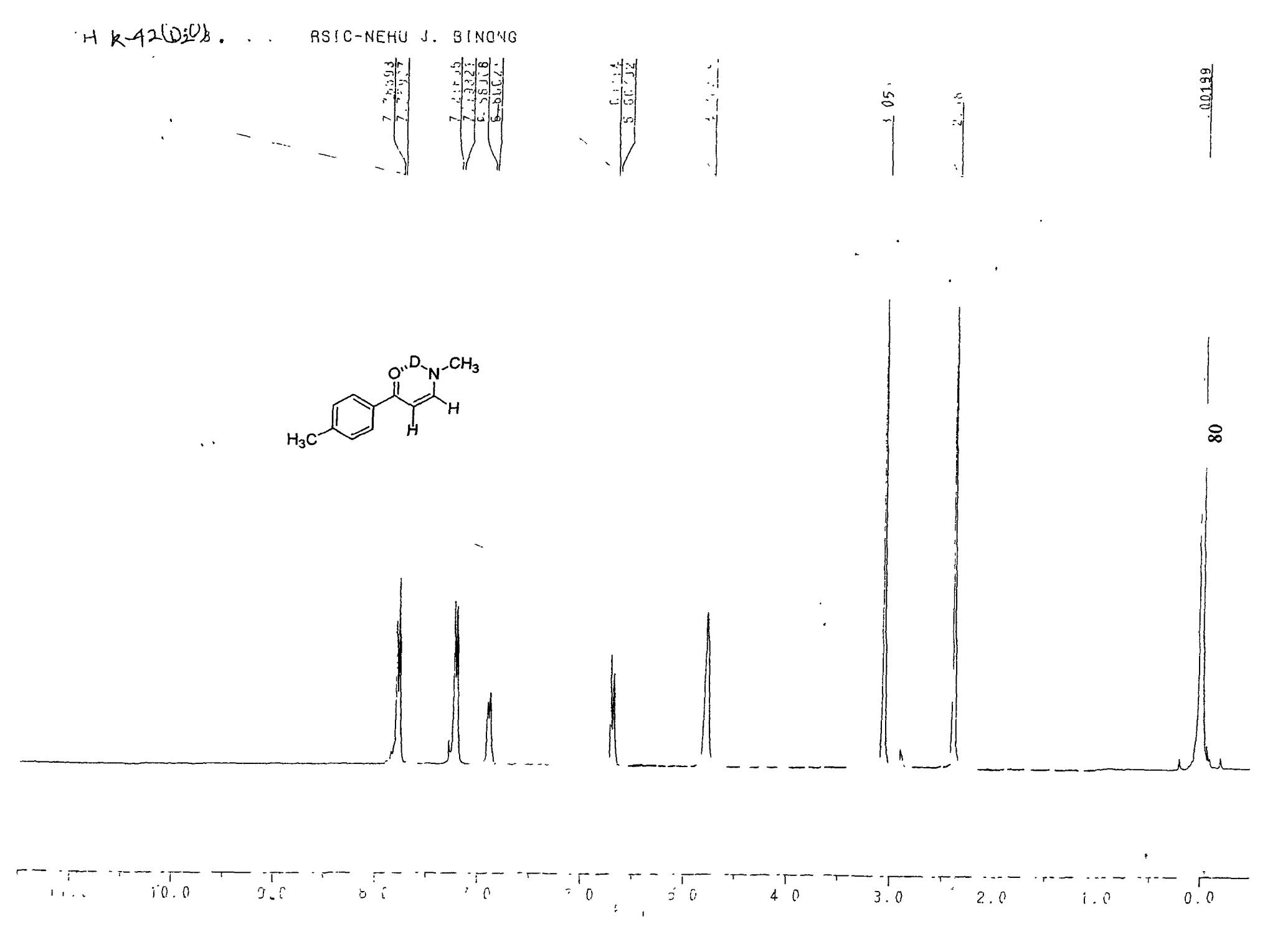
2.10 General Procedure.

2.10a *Synthesis of 3-arylamino-1-arylprop-2-en-1-ones (61a-j).*

To a solution of **60** (2 mmoles) in acetic acid (3-4 ml), appropriate amine (2 mmoles) was added and the resulting mixture was stirred at room temperature. After 15-20 min, precipitation occurred. The stirring was continued and on its completion (monitored on TLC), the mixture was poured into ice-cold water and precipitate formed was filtered, washed with water and dried to yield the title compounds **61a-j**. All the compounds were crystallized from methanol and the spectral data of the unknown compounds are given below.


PPM
1H K-42 CDCL3
10.1541
2.8979

H K-42(D2O) . . . RSIC-NEHU J. BINONG



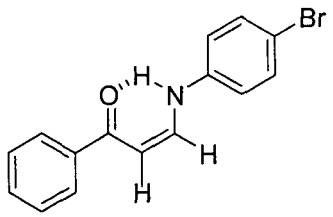
2.10b ***Synthesis of 3-alkyl/aralkylamino-1-arylprop-2-en-1-ones (62a-c).***

A mixture of **60** (1 mmole) and methylamine (3 mmoles) taken in a 5 ml conical flask was irradiated in a domestic microwave oven at 100 watt for appropriate time. After the completion of the reaction (monitored on TLC), chloroform (3 ml) was added and the organic layer was washed with water (2×2 ml), dried over anhydrous Na_2SO_4 and the solvent removed to get the desired enaminones **62a-c**, which were crystallized from hexane-ether mixture.

2.10c ***Synthesis of 3-aralkylamino-1-arylprop-2-en-1-ones (62d-f).***

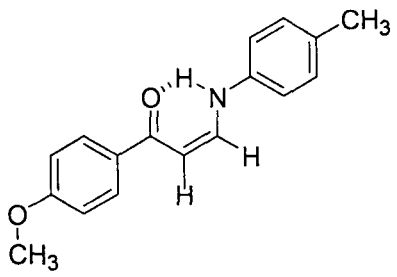
A mixture of **60** (1 mmole) and benzyl amine (1.5 mmoles) was taken in a 5-ml conical flask and the mixture was irradiated in a domestic microwave oven at 300 watt for appropriate time. At the end of the reaction (monitored on TLC), the flask was cooled and the mass was triturated with hexane to give the desired products **62d-f**, which were crystallized from hexane-ether mixture.

3-(4-Bromoanilino)-1-phenylprop-2-en-1-one 61d.



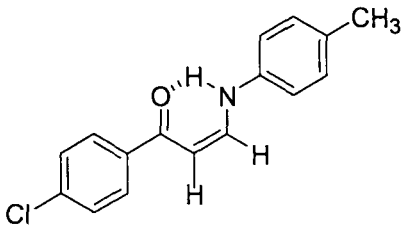
This compound was obtained as a yellow solid, IR (KBr): 1617, 1635, 1674, 3278, 3456 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.08 (d, 1H, J= 8.49Hz), 7.05 (m, 2H), 7.44-7.60 (m, 6H), 7.91-7.93 (m, 2H), 12.11 (br d, 1H, J= 12.5Hz, exchangeable with D_2O); MS: m/z 303 [MH^+]; *Anal. Calcd. for* $C_{15}H_{12}BrNO$ (302.17): C, 59.62; H, 4.00; N, 4.64%. *Found*: C, 59.41; H, 4.03; N, 4.59%.

3-(4-Toluidino)-1-(4-methoxyphenyl)prop-2-en-1-one 61f.



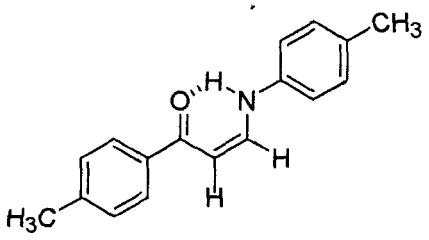
This compound was obtained as a yellow solid, IR (KBr): 1575, 1602, 1616, 3430 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H), 3.86 (s, 3H), 5.96 (d, 1H, J= 7.8Hz), 6.93-7.01 (m, 4H), 7.12-7.15 (m, 2H), 7.47 (dd, 1H, J= 7.8, 12.6Hz), 7.90-7.94 (m, 2H), 12.07 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; N, 5.24%. *Found*: C, 76.21; H, 6.45; N, 5.20%.

3-(4-Toluidino)-1-(4-chlorophenyl)prop-2-en-1-one 61g.



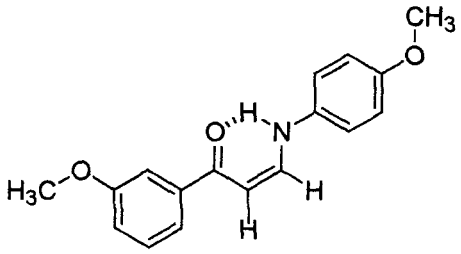
This compound was obtained as a yellow solid, IR (KBr): 1576, 1588, 1636, 3441 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H), 5.93 (d, 1H, J= 7.2Hz), 7.02 (d, 2H, J=7.8Hz), 7.16 (d, 2H, J=7.9Hz), 7.41 (d, 2H, J=8.1Hz), 7.60-7.70 (m, 1H), 7.83 (d, 2H, J=8.1Hz), 12.13 (br d, 1H, exchangeable with D_2O); MS: m/z 273 [MH^+]; *Anal. Calcd. for* $C_{16}H_{14}ClNO$ (271.74): C, 70.72; H, 5.19; N, 5.15%. *Found*: C, 70.91; H, 5.21; N, 5.11%.

3-(4-Toluidino)-1-(4-methylphenyl)prop-2-en-1-one 61h.



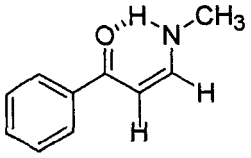
This compound was obtained as yellow solid, IR (KBr): 1575, 1606, 1629, 3439 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.42 (s, 3H), 6.10 (d, 1H), 6.90-7.70 (m, 7H), 7.80-8.15 (m, 2H), 12.00 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{17}H_{17}NO$ (251.32): C, 81.24; H, 6.82; N, 5.57%. *Found*: C, 81.18; H, 6.85; N, 5.61%.

3-(4-Methoxyanilino)-1-(3-methoxyphenyl)prop-2-en-1-one 61j.



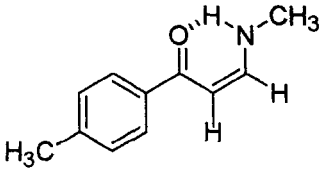
This compound was obtained as a yellow solid, IR (KBr): 1588, 1599, 1626, 3443 cm^{-1}; ^1H NMR ($CDCl_3$ 90MHz): δ 3.80 (s, 3H), 3.87 (s, 3H), 5.95 (d, 1H), 6.88-7.07 (m, 5H), 7.26-7.44 (m, 4H), 12.18 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{17}H_{17}NO_3$ (283.32): C, 72.07; H, 6.05; N, 4.94%. *Found*: C, 72.18; H, 6.09; N, 4.91%.

3-Methylamino-1-phenylprop-2-en-1-one 62a.



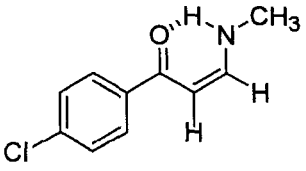
This compound was obtained as white solid, IR (KBr): 1597, 1603, 1635, 3268 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.07 (d, 3H, J=4.9Hz), 5.70 (d, 1H, J=6.9Hz), 6.93 (dd, 1H, J=6.9, 12.5Hz), 7.38-7.44 (m, 3H), 7.85-7.91 (m, 2H), 10.22 (br d, 1H, exchangeable with D_2O); MS: m/z 162 [MH^+]; *Anal. Calcd. for* $C_{10}H_{11}NO$ (161.2): C, 74.51; H, 6.88; N, 8.69%. *Found*: C, 74.43; H, 6.93; N, 8.62%.

3-Methylamino-1-(4-methylphenyl)prop-2-en-1-one 62b.



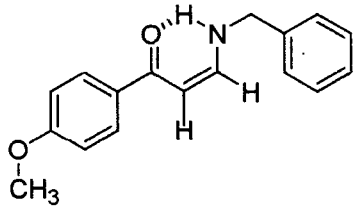
This compound was obtained as an off white solid, IR (KBr): 1580, 1606, 1630, 3265, 3384, 3443 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.38 (s, 3H), 3.06 (d, 3H, J=5.4Hz), 5.68 (d, 1H, J=8.1Hz), 6.90 (dd, 1H, J=8.1, 12.5Hz), 7.20 (d, 2H), 7.77 (d, 2H), 10.15 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{11}H_{13}NO$ (175.23): C, 75.40; H, 7.48; N, 7.99%. *Found*: C, 75.49; H, 7.52; N, 7.96%.

3-Methylamino-1-(4-chlorophenyl)prop-2-en-1-one 62c.



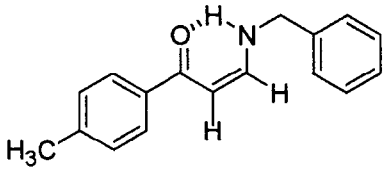
This compound was obtained as a whitish solid, IR (KBr): 1588, 1636, 3245, 3430 cm^{-1}; ^1H NMR ($CDCl_3$): δ3.08 (d, 3H, J=5.1Hz), 5.64 (d, 1H, J=6.9Hz), 6.93 (dd, 1H, J=6.9, 12.6Hz), 7.37 (d, 2H, J=8.1Hz), 7.80 (d, 2H, J=8.1Hz), 10.22 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{10}H_{10}ClNO$ (195.65): C, 61.39; H, 5.15; N, 7.16%. *Found*: C, 61.28; H, 5.11; N, 7.21%.

3-Benzylamino-1-(4-methoxyphenyl)prop-2-en-1-one 62d.



This compound was obtained as light brown solid, IR (KBr): 1582, 1601, 1634, 3278, 3443 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.84 (s, 3H), 4.44 (d, 2H, J=6.5Hz), 5.73 (d, 1H, J=8.3Hz), 6.89-6.92 (m, 3H), 7.29-7.35 (m, 5H), 7.86 (d, 2H, J=8.2Hz), 10.48 (br d, 1H, exchangeable with D_2O); MS: m/z 268 [MH^+]; *Anal. Calcd. for* $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; N, 5.24%. *Found*: C, 76.22; H, 6.44; N, 5.20%.

3-Benzylamino-1-(4-methylphenyl)prop-2-en-1-one 62e.



This compound was obtained as light brown solid, IR (KBr): 1580, 1606, 1631, 3279, 3439 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.45 (s, 3H), 4.52 (d, 2H, J=5.4Hz), 5.90 (d, 1H, J=8.1Hz), 7.00-7.70 (m, 8H), 7.85-8.15 (m, 2H), 11.00 (br d, 1H, exchangeable with D_2O); MS: m/z 252 [MH^+]; *Anal. Calcd. for* $C_{17}H_{17}NO$ (251.32): C, 81.24; H, 6.82; N, 5.57%. *Found*: C, 81.05; H, 6.78; N, 5.54%.

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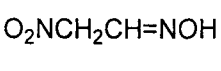
CHAPTER III

A facile one-pot synthesis of Bis-Tetrahydropyrimidines from Enaminones

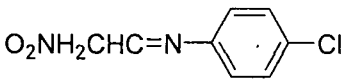
Introduction

Our literature survey reveals that tetrahydropyrimidines are known in the literature [1-7] and is one of the most important nitrogen containing heterocycles. Due to their biological activities they have attracted considerable attention. The synthesis of a few such heterocycles is discussed in the following sections.

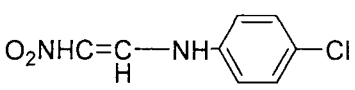
3.1 H. D. Urbarnska while working on the formation of heterocyclic systems from primary nitroparaffins, formaldehyde and amines extended the work to methazonic acids[8] (**1**). Methazonic acid is an oxime as well as a primary nitroparaffin and is unstable leading to the formation of several products. To avoid the instability of methazonic acid it was converted to another derivative **2** by reacting it with p-chloroaniline. Spectroscopic properties reveal the revision of originally proposed Schiff's base structure **2S** to a nitroenamine with resonance structures **2E** (enamine) and **2Sz** (Schiff's base zwitterion), and this is confirmed by the NMR spectra.



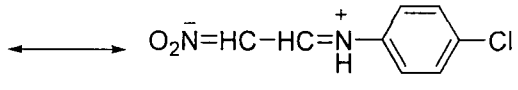
1



2S

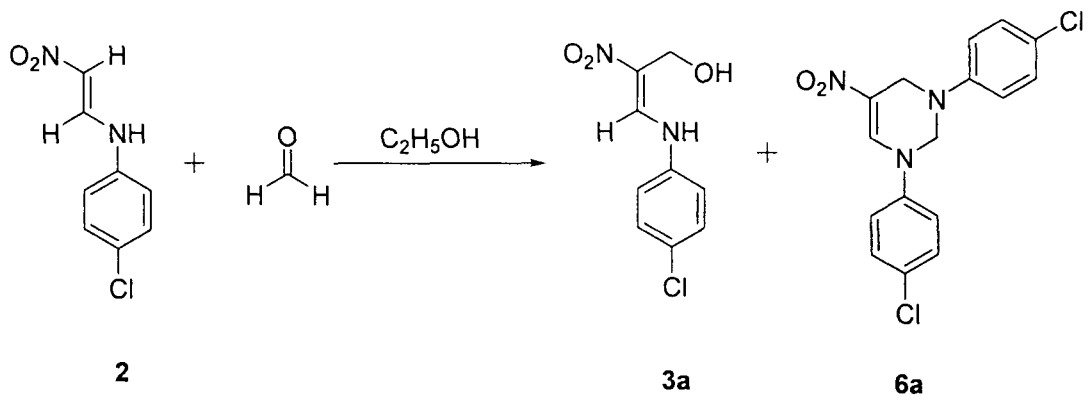


2E



2Sz

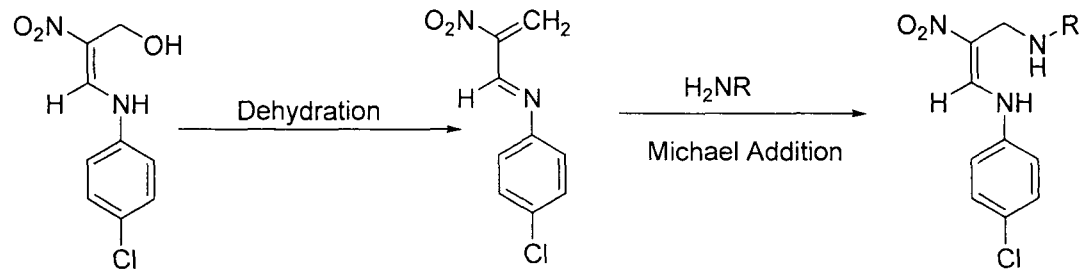
Nitroolefins do not normally undergo aldol reaction with formaldehyde, but the enamine function could modify this behaviour. Indeed, **2** reacted with formaldehyde in aqueous ethanol to yield carbinol (**3a**) together with a little of the 1,2,3,4-tetrahydropyrimidine (THP) **6a** as shown in **Scheme 1**.



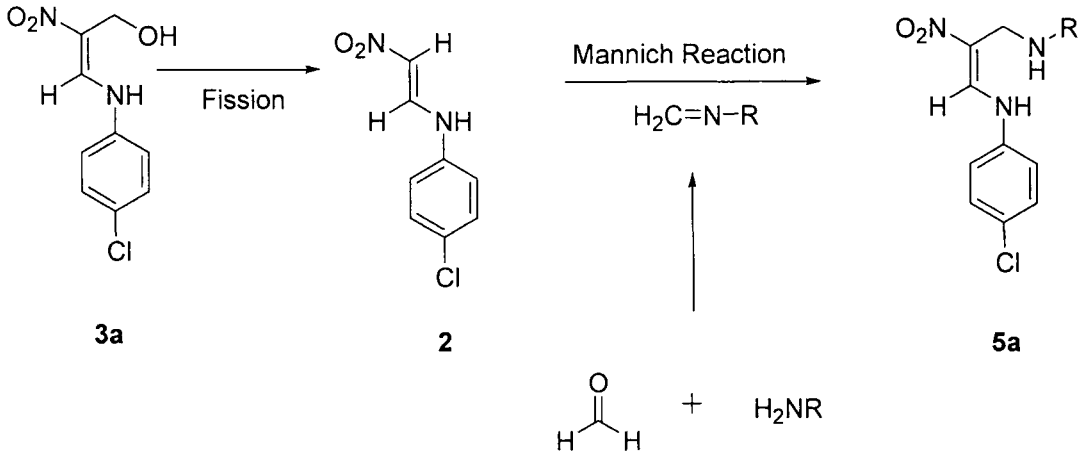
2 **3a** **6a**

Scheme 1

The formation of the cyclic product **6a** can be explained by partial hydrolysis of **3a** to give p-chloroaniline, which then reacts with another **3a** and formaldehyde. Although direct evidence is not available, diamine **5a** is probably an intermediate. The conversion of **3a** to **5a** may involve either dehydration followed by Michael addition or fission of **3a** to **2** followed by a Mannich reaction (**Scheme 2**).

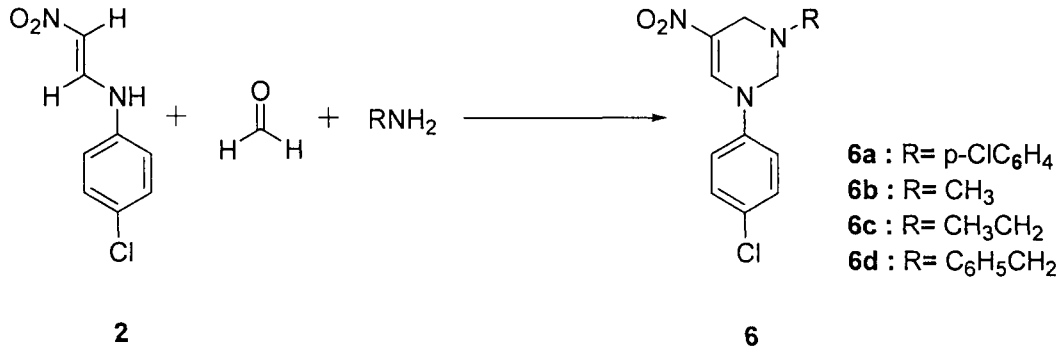


3a **4** **5a**



Scheme 2

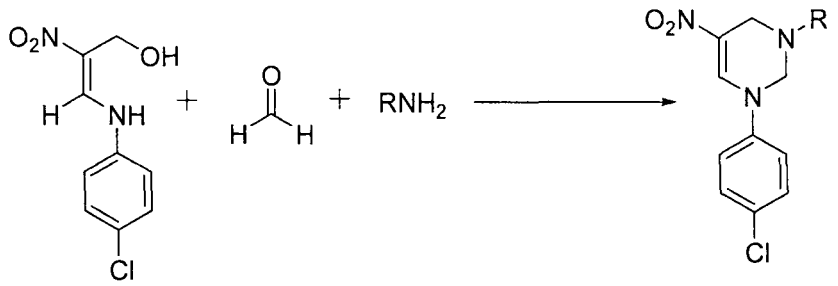
Treatment of nitroolefin **2** with formaldehyde and the appropriate primary amine gave four 5-nitro-1,2,3,4-tetrahydropyrimidines **6a** to **6d** (**Scheme 3**).



Scheme 3

The yield was highest when the molar proportion of **2**, formaldehyde, and the amine were 1:3:2. These reactions may be of Mannich type or they may involve the

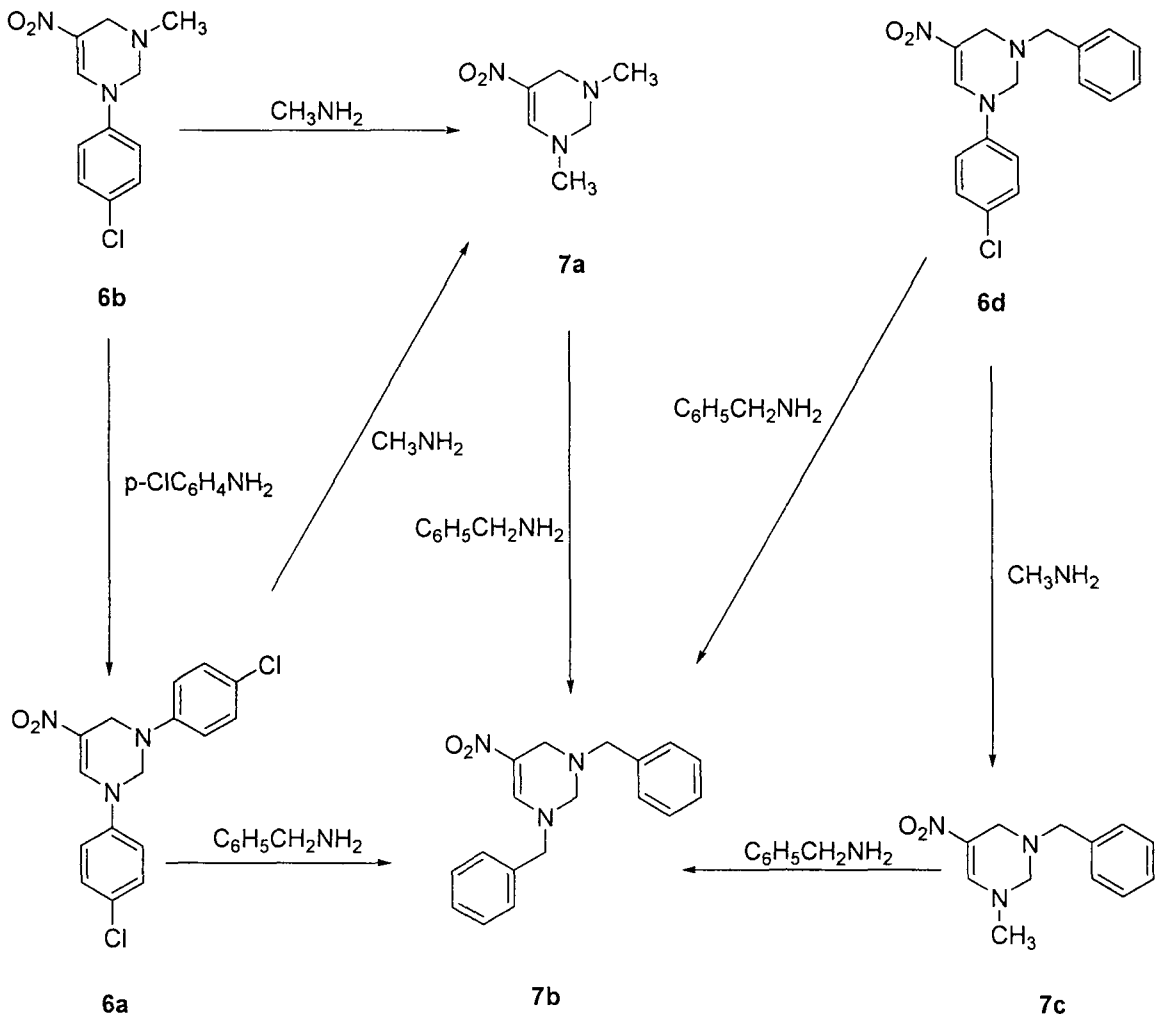
formation of the carbinol **3a**. As expected **3a** also reacts with formaldehyde and the amine in the proportions 1:2:2 to give the products **6** (**Scheme 4**).



3 **6**

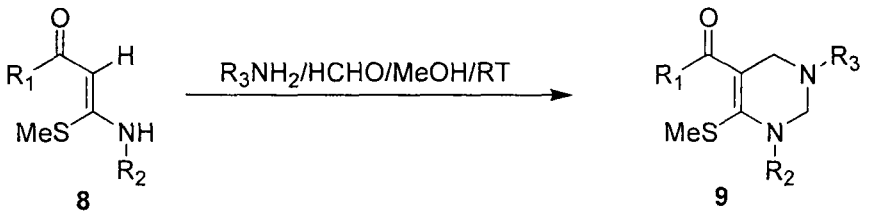
Scheme 4

3.1.1 It was observed that if more than 2 molar of amine was used, trans amination products **7** were formed in addition to **6**. It was observed that one or both the substituents were replaced in boiling ethanol depending upon the temperature and amine used. Although Urbanska and coworkers did not examine the transaminating ability of amines, they noted that 1,3 benzyl amino derivatives were formed when benzyl amine was used (**Scheme 5**). Thus, when **6b** and **6d** were heated in boiling ethanol (basified with triethylamine) **7a** and **7c** were obtained by semi disproportionation. However, when **6a** was refluxed with methylamine and benzylamine both amines were displaced giving **7a** and **7b** as shown in **Scheme 5**.


O2N
N
CH3
Cl
6b
CH3NH2
7a
6d
p-ClC6H4NH2
CH3NH2
C6H5CH2NH2
C6H5CH2NH2
CH3NH2
6a
C6H5CH2NH2
7b
C6H5CH2NH2
7c

Scheme 5

3.1.2 A few years back researchers from our group in connection with the investigation on the synthetic applications of 3-(aryl/benzyl) amino-3-methylthio-1-arylprop-2-en-1-one (**8**) and also in construction of tetrahydropyrimidine ring using formaldehyde and primary amines reported[9] the synthesis of 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-aroyl-6-methylthio -1,2,3,4- tetrahydropyrimidines (**Scheme 6**).



8 **9**

8	R_1	R_2
a	C_6H_5	$C_6H_5CH_2$
b	4-MeC_6H_4	$C_6H_5CH_2$
c	4-$MeOC_6H_4$	C_6H_5
d	4-ClC_6H_4	C_6H_5

9	R_1	R_2	R
a	C_6H_5	$C_6H_5CH_2$	4-$MeOC_6H_4$
b	4-MeC_6H_4	$C_6H_5CH_2$	$C_6H_5CH_2$
c	4-$MeOC_6H_4$	C_6H_5	$C_6H_5CH_2$
d	4-ClC_6H_4	C_6H_5	4-ClC_6H_4
e	4-ClC_6H_4	C_6H_5	4-MeC_6H_4
f	4-ClC_6H_4	C_6H_5	4-$MeOC_6H_4$
g	4-ClC_6H_4	C_6H_5	C_2H_5
h	4-ClC_6H_4	C_6H_5	CH_3

Scheme 6

When a mixture of **8a**, formaldehyde and p-anisidine in the ratio (1:2:1) was stirred in methanol at room temperature, subsequent work up, yielded a white solid which was characterized to be 1-benzyl-3-(4-methoxyphenyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidine (**9a**) in 74% yield. The reaction was found to be

general with other alkyl, aralkyl, arylamines and with corresponding **8b-d** to give the respective products **9b-h** in 71-91% overall yields. These THPs were found to be quite stable at room temperature and could be easily recrystallized from methanol.

3.1.3 Further, envisaging that the absence of the thiomethyl group in position 6 of the pyrimidine ring could alter the biological activities of the molecules, our group has also reported the synthesis of 1-(aralkyl/aryl)-3-(alkyl/aralkyl/aryl)-5-aroyl-1,2,3,4-tetrahydropyrimidines[10] (**scheme 7**).

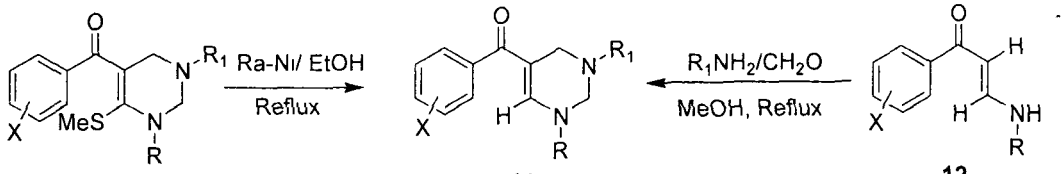
In order to achieve the synthesis of 1-(aralkyl/aryl)-3-(alkyl/aralkyl/aryl)-5-aroyl-1,2,3, 4-tetrahydropyrimidine (**11**) initially dethiomethylation of **10** was carried out. Compound **10a** was dissolved in ethanol and refluxed with Raney-Nickel (four times by weight) for 20 hours. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered and the residue was washed with ethanol. Ethanol was then removed under reduced pressure to give a paste, which was re-dissolved in chloroform. The solution was washed with water, dried over anhydrous sodium sulphate and the solvent was distilled off to give a white solid, which was recrystallized from hexane-ether mixture to yield **11a** in 50% yield. The structure was established on the basis of spectral and analytical data. De-thiomethylation of **10b** and **10c** proceeded smoothly under identical condition giving the corresponding **11b** and **11c** in 52% and 55% yields respectively

It is clear from the above scheme that this process has its limitations due to the fact that it involves the preparation of the tetrahydropyrimidine, followed by dethiomethylation of the tetrahydropyrimidine moiety to get the desired product.

In order to achieve the synthesis of the required tetrahydropyrimidines (THPs) in a single step, an alternative synthetic strategy was designed starting from enaminones of the type **12.** To examine the efficacy of the strategy, enaminones **12a-j** were synthesized and then reacted with primary amine and formaldehyde.

Thus, when a mixture of **12a**, formaldehyde and benzylamine (1:2:1) was refluxed in methanol for 6 hours, subsequent work up gave 1,3-dibenzyl-5-(4-methylbenzoyl)-1,2,3, 4-tetrahydropyrimidine in 79% yields. The reaction proceeded in the same manner with other alkyl, aralkyl, and aryl amines and with corresponding **12b-j** to give the respective products **11b-t** in 50-83% yields, except in **11d** and **11n**, which were obtained in 41 and 35%, yields respectively. The structures of the products were established on the basis of spectral and analytical data.

3.2 Our literature survey at this stage revealed that synthetic studies of small 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[11-13] and also antibacterial properties[14]. It is also evident from one of the reports that bis heterocyclic compounds possess better antimalarial activities than their monomer units, they are also known to possess antiproliferative and anti tumor activities[15]. Following these reports, we envisaged that molecules with two tetrahydropyrimidine rings linked through flexible aliphatic chains or through rigid aromatic chains could have enhanced biological activities. Our literature survey also revealed that bis-1,2,3,4-tetrahydropyrimidines are unknown in the literature except for our preliminary report[16] 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[17], chelating agents and metal ligands[18] and as biologically active molecules[19] preferably, antitumor[20] and antimicrobial[21], based on the DNA binding affinity and enzyme inhibiting actions. These activities have been reported to be enhanced when



10 11 12

	X	R	R_1
a	4-Me	$PhCH_2$	$PhCH_2$
b	4-Cl	Ph	Et
c	4-MeO	Ph	$PhCH_2$

	X	R	R_1
a	4-Me	$PhCH_2$	$PhCH_2$
b	4-Cl	Ph	Et
c	4-MeO	Ph	$PhCH_2$
d	4-MeO	Ph	Ph
e	H	Ph	Ph
f	H	Ph	$PhCH_2$
g	H	Ph	Me
h	H	4-MePh	Ph
i	H	4-MePh	$PhCH_2$
j	H	$PhCH_2$	Ph
k	H	$PhCH_2$	$PhCH_2$
l	4-Me	Ph	Ph
m	4-Cl	Ph	Ph
n	4-Cl	Ph	Me
o	4-Cl	4-MePh	$PhCH_2$
p	4-Cl	4-MePh	Ph
q	4-Cl	Ph	$PhCH_2$
r	4-MeO	4-MePh	$PhCH_2$
s	3-MeO	Ph	Ph
t	3-MeO	Ph	$PhCH_2$

	X	R
a	4-Me	$PhCH_2$
b	4-Cl	Ph
c	4-MeO	Ph
d	3-MeO	Ph
e	H	Ph
f	H	4-MePh
g	H	$PhCH_2$
h	4-Me	Ph
i	4-Cl	4-MePh
j	4-MeO	4-MePh

Scheme 7

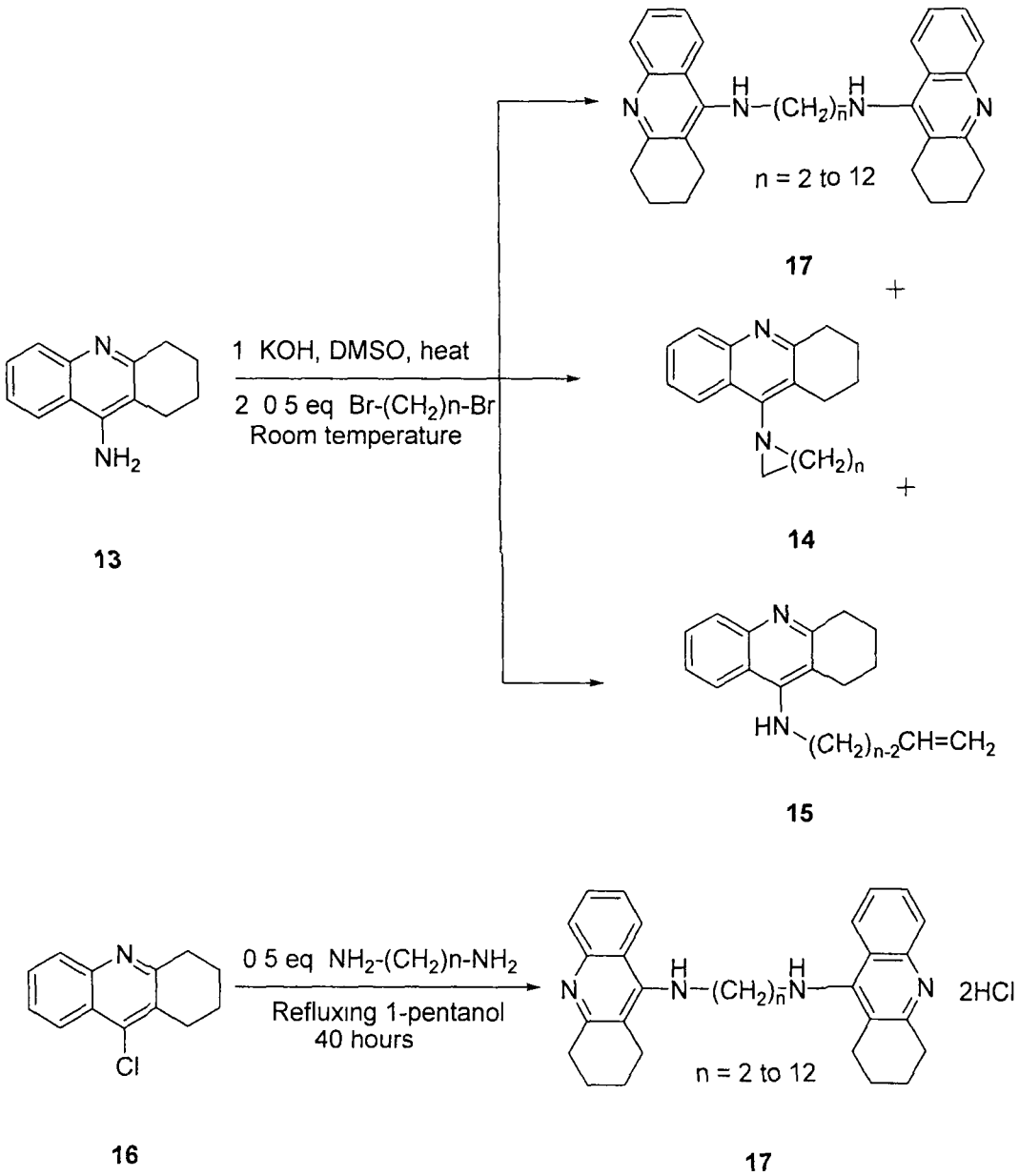
different functionalities or substitutions are present on the two heterocyclic rings in the bis-compounds[22, 23], and in some cases they are known to possess more potent biological activities than their monomeric heterocycles as described below.

3.2.1 P.R. Carlier and coworkers have also reported[24] the synthesis and evaluation of alkylene-linked dimers of tacarine (**13**). The reaction of tacarine with dibromo alkanes gave the desired bis product in low yields (epecially when n = 2 to n = 6). To over come 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 in 1-pentanol under atmospheric pressure for 40 hours (**Scheme 8**).

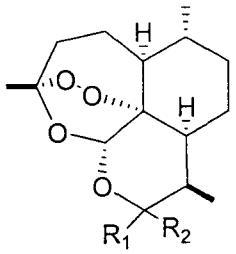
These dimeric compounds **17** particularly the heptylene-linked tacarine dimer was found to be 149 fold more potent and 250 fold more selective for acetylcholinesterase (AchE) than tacarine. This dimer also exhibited 24 fold reversing scopolamine-induced memory impairments and thus could be a promising drug candidate for palliative treatment of senile dementia of the Alzheimer's disease.

3.2.2 Gary. H. Poshner and coworkers have synthesized[25] dimeric derivatives of natural trioxane Artemesinin (**18**), 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).
This involved connecting the two trioxanes through an aromatic linker group such as furan or a benzene ring structure **19** (**Table I**).
These compounds were tested against their standard assay for chloroquine-sensitive *plasmodium falciparium* (NF54) parasites. They found that the benzomethylene-linked 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.



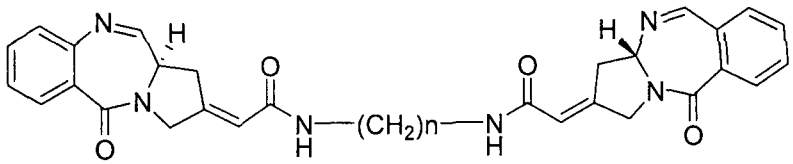
Scheme 8



artemisinin, $R_1 = R_2 = O$

18

3.2.3 J. W. Lown and coworkers have reported[26] the synthesis of bi-functional DNA alkylating C_2-linked pyrrolo[2,1-*c*][1,4]benzodiazepines (**20**).



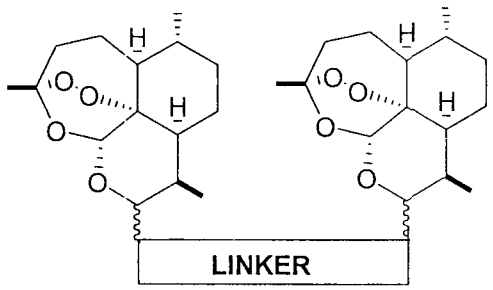
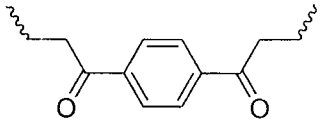
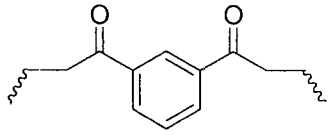
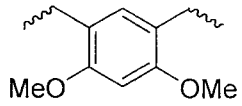
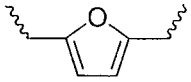
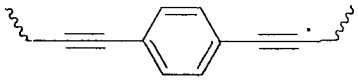
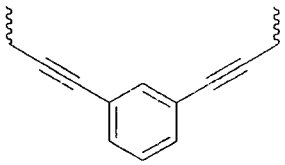
n = 3,4,5

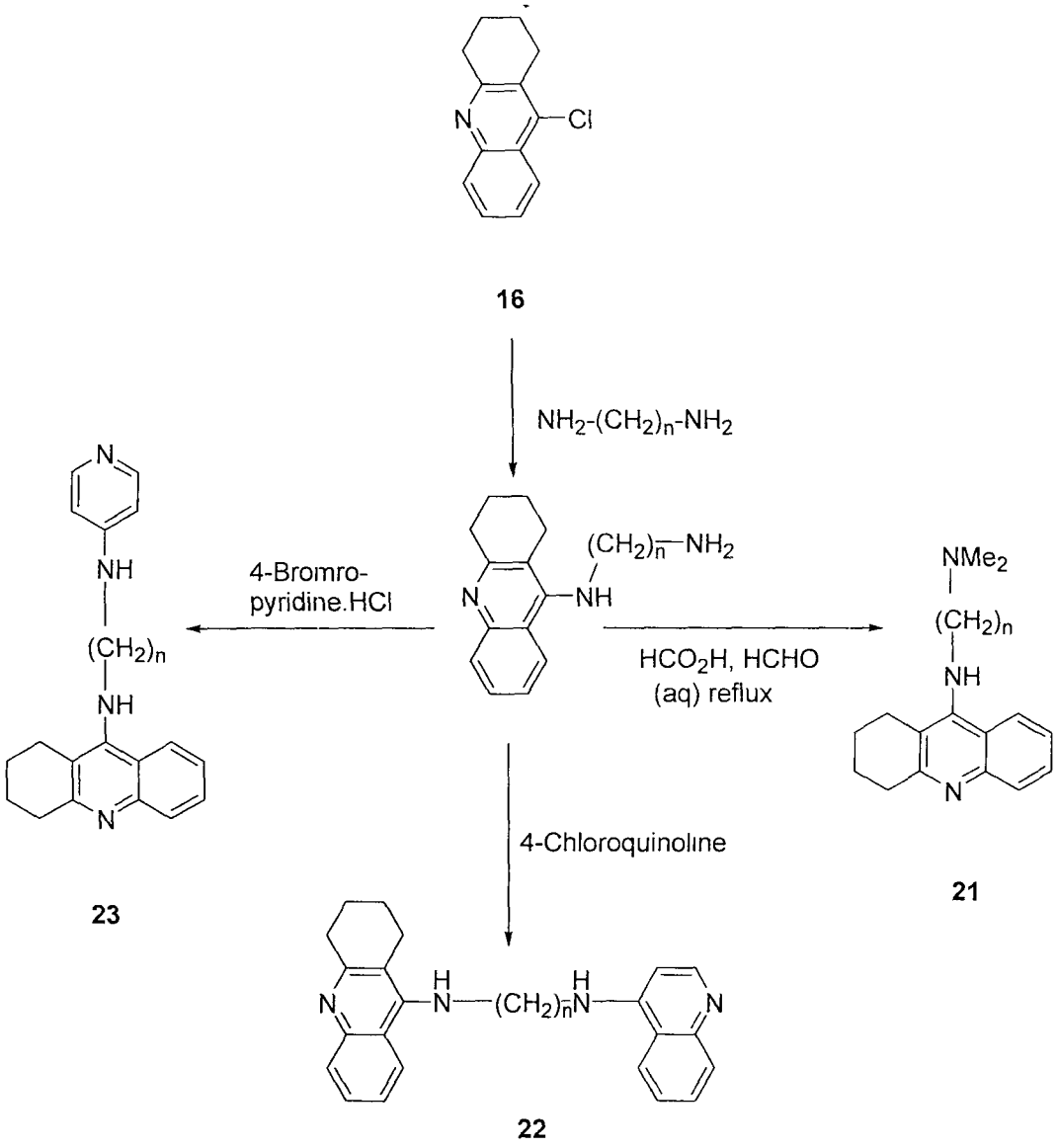
20

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

3.2.4 P. R. Carlier and coworkers also reported[27] the synthesis of heterodimers **21**, **22** and **23** of tacarine, which were tested for optimal binding to the AChE peripheral site (**Scheme 9**). These heterodimers showed improvements in inhibitory potency and selectivity with relative to tacarine itself.

Table –I Dimeric derivatives of natural trioxane artemesinin (1-6)

Dimer		Antimalarial IC_{50} (nM)
	 **19**	
1		1.9
2		1.9
3		1.3
4		3.2
5		30
6		38
7	Artemisinin	97 ± 18



Scheme 9

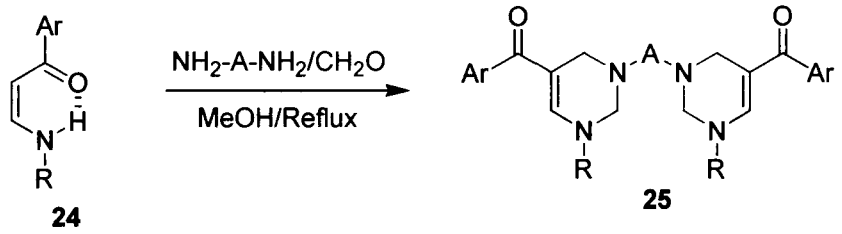
3.3 Prompted by the absence of literature reports on bis-1,2,3,4-tetrahydropyrimidines and potent biological activities of bis-heterocycles and in continuation with the on going strategy for the synthesis 1,2,3,4-tetrahydropyrimidines in our lab, we thus devised a facile one-pot synthesis of [alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(*2H*)-

diyl)bis](arylmethanones) and [1,4-phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(*2H*)-diyl]bis(phenylmethanone) and the result of the investigations are described herein (**Scheme 10**).

3.4 Results and Discussions.

Thus, when a mixture of enaminone **24a**, ethylenediamine and formaldehyde (2:1:4) was refluxed in methanol, work up of the reaction mixture gave **25a** in 79% yield. The structure of which was proposed to be [ethane-1,2-diyl-bis(3-phenyl-3,6-dihydropyrimidine-1,5(*2H*)-diyl)]bis(phenylmethanone), on the basis of spectra and analytical data. The reaction of **24a** with diamines (A=-$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -C_6H_4-) and formaldehyde took place under similar conditions to give the respective bis-tetrahydropyrimidines **25b-d** in 54-70% overall yields. Similarly the reaction of **24b-f** with appropriate diamines (**Scheme 8**) and Formaldehyde proceeded smoothly under identical conditions yielding the respective products **25e-g**, **25h**, **25i-k**, and **25l**and **25m** in moderate to high yields. The infrared spectra of **25a-m** showed strong peaks in the region of 1543-1626 cm^{-1} due to extensively delocalized double bonds and carbonyl groups. In the ^{1}HNMR spectra of **25a-m**, two singlets due to methylene protons at C-2 and C-6 appeared between 3.96-5.08 ppm and 3.64-4.43 ppm respectively. The benzylic methylene protons in **25e-g** and **25i-k** gave singlets in the range of 3.61-3.66 ppm whereas N-Me protons of **25m** appeared as a singlet at 2.94 ppm. The protons corresponding to the ethylene chain are observed as singlets resonating between 2.53-2.79 ppm for compounds **25a**, **25e**, **25h**, **25i** and **25I**. In the case of **25b**, **25f** and **25j** the NCH_2 protons of propylene chain exhibited triplets in the range of 2.41-2.68 ppm of propylene chain exhibited triplets in the range of 2.41-2.68 ppm while the CH_2 protons of position 2 of the chain gave multiplets between 1.48-1.79 ppm. In compounds **25c**, **25g**, **25k** and **25m**, the NCH_2 protons of the butylene chain appeared as multiplets in the range

.



24 25

Comp	Ar	R	Comp	Ar	R	A
24a	C_6H_5	C_6H_5	**25a**	C_6H_5	C_6H_5	$-(CH_2)_2-$
	C_6H_5	C_6H_5	**25b**	C_6H_5	C_6H_5	$-(CH_2)_3-$
	C_6H_5	C_6H_5	**25c**	C_6H_5	C_6H_5	$-(CH_2)_4-$
	C_6H_5	C_6H_5	**25d**	C_6H_5	C_6H_5	$-C_6H_4-$
24b	C_6H_5	$CH_2C_6H_5$	**25e**	C_6H_5	$CH_2C_6H_5$	$-(CH_2)_2-$
	C_6H_5	$CH_2C_6H_5$	**25f**	C_6H_5	$CH_2C_6H_5$	$-(CH_2)_3-$
	C_6H_5	$CH_2C_6H_5$	**25g**	C_6H_5	$CH_2C_6H_5$	$-(CH_2)_4-$
24c	$4\text{-}ClC_6H_5$	C_6H_5	**25h**	$4\text{-}ClC_6H_4$	C_6H_5	$-(CH_2)_2-$
24d	$4\text{-}ClC_6H_5$	$CH_2C_6H_5$	**25i**	$4\text{-}ClC_6H_4$	$CH_2C_6H_5$	$-(CH_2)_2-$
	$4\text{-}ClC_6H_5$	$CH_2C_6H_5$	**25j**	$4\text{-}ClC_6H_4$	$CH_2C_6H_5$	$-(CH_2)_3-$
	$4\text{-}ClC_6H_5$	$CH_2C_6H_5$	**25k**	$4\text{-}ClC_6H_4$	$CH_2C_6H_5$	$-(CH_2)_4-$
24e	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	**25l**	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	$(CH_2)_2-$
24f	C_6H_5	CH_3	**25m**	C_6H_5	CH_3	$-(CH_2)_4-$

Scheme 10

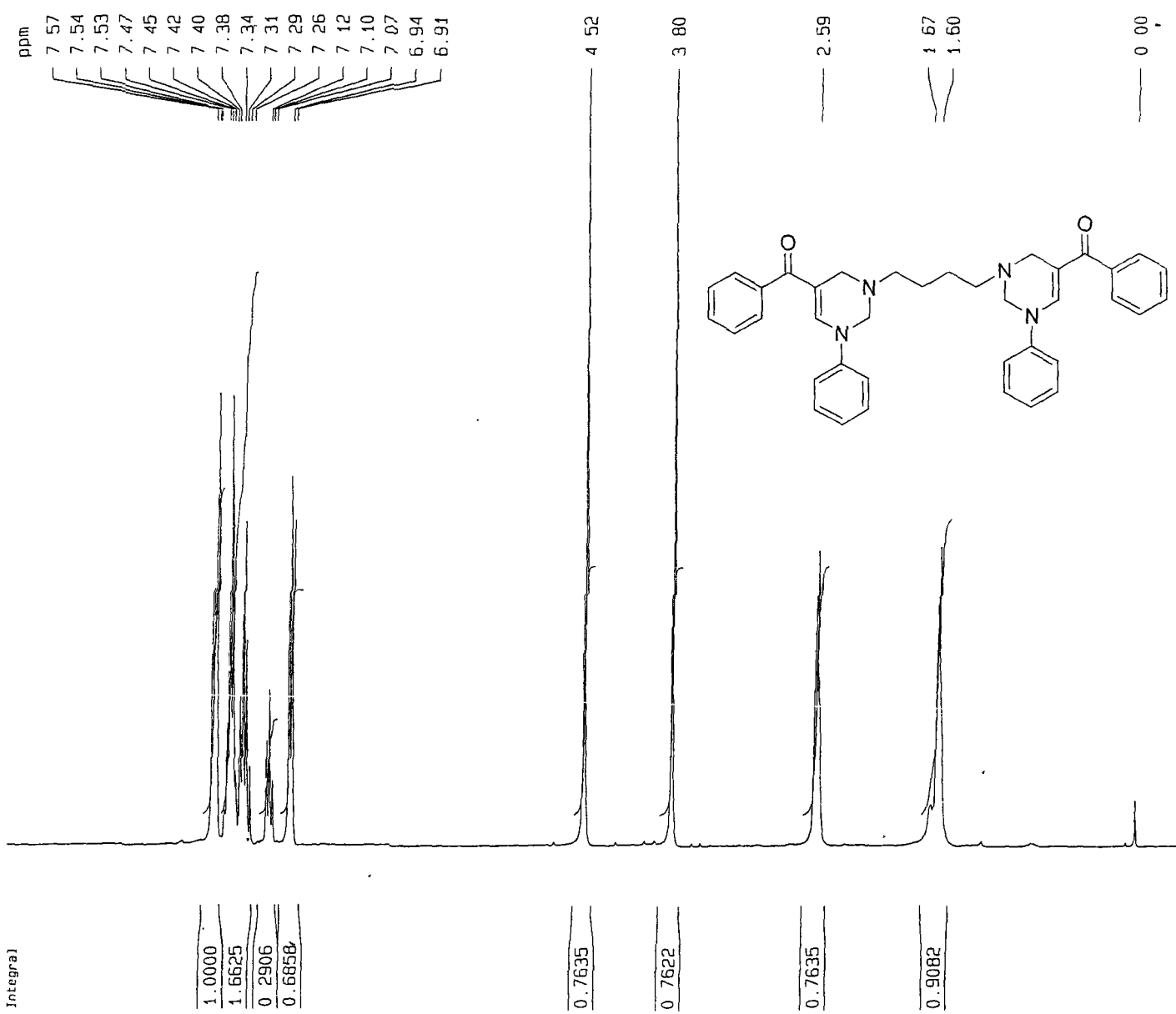
of 2.34-2.59 ppm, while the CH_2 protons of the position 2 and 3 of the chain gave multiples in the range of 1.33-1.65 ppm. The proton at C_4 was highly desheilded and its signal remained buried among the aromatic protons in the range of 6.73-7.57 ppm with the exception of **25m** in which it was visible as a singlet (for two protons) at 7.03 ppm. The ^1H NMR and ^{13}C NMR Spectra of [butane-1,4-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)] bis (phenylmethanone) **25c** are shown in pages 106 and 107.

3.5 Conclusion.

In conclusion we have developed a facile one pot synthetic strategy for the synthesis of bis-tetrahydropyrimidines wherein we have been successful in constructing tetrahydropyrimidine rings and simultaneously linking two tetrahydropyrimidine rings by flexible aliphatic chain or rigid aromatic rings. The bilological activities of these dimeric molecules are under investigation.

3.6 Experimental.

Melting points were recorded by the open capillary method and are uncorrected. The infrared spectra were recorded on a perkin-Elmer 983 spectrometer. ^1H NMR (90MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution ^1H NMR and ^{13}C NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and the coupling constant (Hz) are reported in the standard fashion with reference to TMS as internal references. The FAB mass spectra (MS) were recorded on a Joel SX 102/DA-6000 mass spectrometer using Argon as the FAB gas and *m*-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL III instrument.



Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	32
DS	0
SWH	8680 556 Hz
FIDRES	0 264910 Hz
AQ	1 8874868 sec
RG	128
DW	57 600 usec
DE	6 00 usec
TE	298 0 K
D1	1 00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	6 88 usec
PL1	-3 00 dB
SFO1	300 1321300 MHz

F2 - Processing parameters

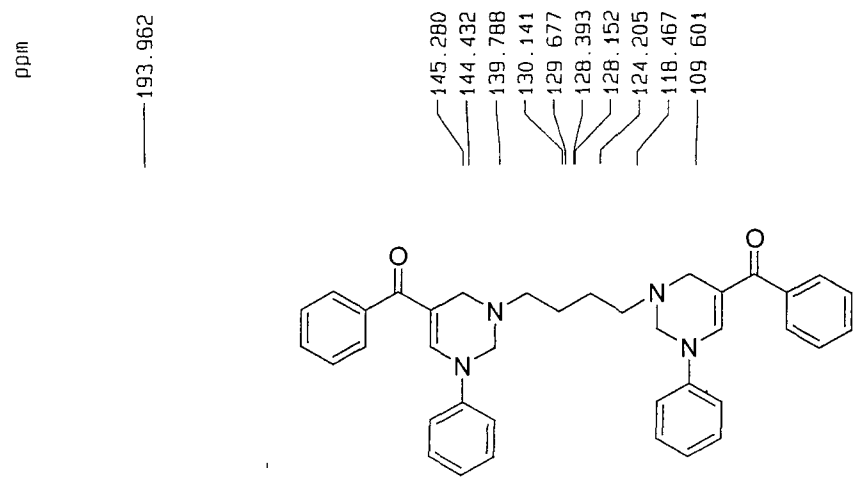
SI	16384
SF	300 1300064 MHz
WDW	EM
SSB	0
LB	0 10 Hz
GB	0
PC	1 20

1D NMR plot parameters

CX	20 00 cm
F1P	9 274 ppm
F1	2783 32 Hz
F2P	-0 619 ppm
F2	-185 80 Hz
PPMCM	0 49464 ppm/cm
HZCM	148 45605 Hz/cm

K-90

K-90
C13CPD



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PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 18832 393 Hz
FIDRES 0 287360 Hz
AQ 1 7400308 sec
RG 16384
DW 26 550 usec
DE 6 00 usec
TE 300 0 K
D1 2 00000000 sec
d11 0 03000000 sec
d12 0 00002000 sec

========== CHANNEL f1 ==========
NUC1 13C
P1 10 00 usec
PL1 -3.00 dB
SFO1 75 4760200 MHz

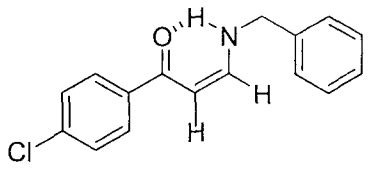
========== CHANNEL f2 ==========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3 00 dB
PL12 20.00 dB
PL13 20 00 dB
SFO2 300 1312005 MHz

F2 - Processing parameters
SI 32768
SF 75 4677516 MHz
WDW EM
SSB 0
LB 3 00 Hz
GB 0
PC 1 40

1D NMR plot parameters
CX 20 00 cm
F1P 215 000 ppm
F1 16225 57 Hz
F2P -5 000 ppm
F2 -347 34 Hz
PPMCM 11 00000 ppm/cm
HZCM 830 14526 Hz/cm

The starting materials **24a**[28], **24b**[29], **24c**[30] and **24e-f**[31] were prepared by our reported procedures. The unknown starting material **24d** was also prepared by our reported procedures[31] and its analytical and spectral data are given below.

(2Z)-3-(benzylamino)-1-(4-chlorophenyl)prop-2-en-1-one 24d.



This compound was obtained as a white solid in 74% yield, mp 83-84^{0}C; IR (KBr): 1585, 1615, 1657, 3430 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ4.46 (d, 2H, J=6.2Hz), 5.71 (d, 1H, C_2-H, J=7.4Hz), 6.99-7.05 (dd, 1H, C_3-H, J=7.4 & 12.5Hz), 7.27-7.38 (m, 7H), 7.79-7.82 (m, 2H), 10.63 (broad m, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_{16}H_{14}NO$ (271.75): C, 70 72; H, 5.19; N 5.15. *Found:* C, 70.51; H, 5.16; N, 5.21%.

[Alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(*2H*)-diyl)]bis (arylmethanones) (25a-c), and (25e-m) and [1, 4-phenylenebis(3-phenyl-3, 6-dihydropyrimidine-1,5 (*2H*)-diyl)]bis(phenylmethanone) (25d).

3.7 General procedure.

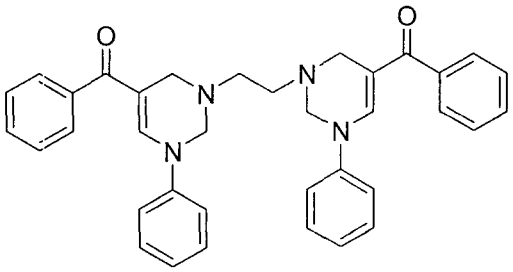
A mixture of diamine (1 mmol) and formaldehyde (4 mmol) in 2 ml methanol was stirred at room temperature for 10 minutes. To this was added a solution of enaminone **24** (2 mmol) in 5-6 ml methanol and the resulting mixture was refluxed for 4-5 hours in case of **25a-d, 25h** and **25l** and 20-24 hours in case of **25e-g, 25i-k** and **25m**. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled in ice water and the precipitated product was collected by

filtration, washed with cold methanol (3x1ml) and dried to give analytically pure **25a-d**, **25h** and **25l,** which were recrystallized from methanol.

In case of **25e-g, 25i-k** and **25m** where no precipitation occurred, the solvent was removed by distillation and the residue dissolved in $CHCl_3$ (5 ml). The solution was then washed with water (3x3ml), dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude bis-tetrahydropyrimidines which were purified by passing through a neutral alumina column using ethyl acetate as eluent to give the pure products.

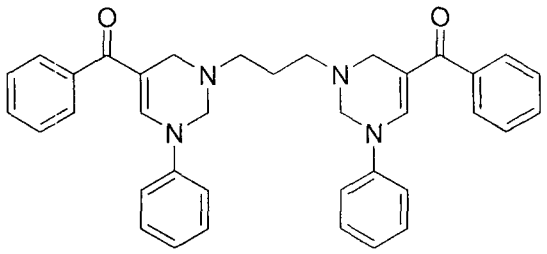
Individual description of the compounds.

[Ethane-1,2-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(*2H*)-diyl)] bis(phenyl-methanone) 25a.



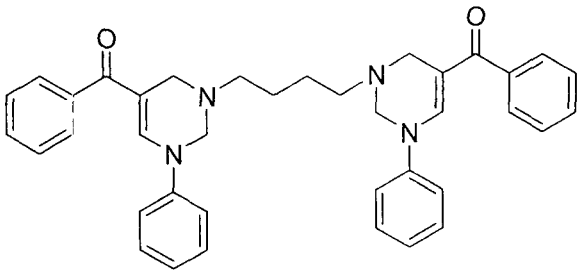
This compound was obtained as a white solid in 79% yield, mp 230^{0}C (decomp); IR (KBr): 1564, 1580, 1613 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 2.63 (s, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.44 (s, 4H, 2 CH_2), 6.73-6.95 (m, 7H), 7.12-7.35 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 47.1, 50.2, 68.0, 108.5, 118.0, 123.9, 127.7, 127.8, 129.3, 129.8, 139.2, 143.8, 144.8, 193.4; *Anal. Calcd. for* $C_{36}H_{34}N_4O_2$ (554.68): C, 77.95; H, 6.18; N, 10.10%. *Found:* C, 77.71; H, 6.31; N, 10.22%.

[Propane-1,3-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)] bis(phenyl-methanone) 25b.



This compound was obtained as a white solid in 59% yield, mp 165-67 ^{0}C; IR (KBr): 1563, 1580, 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 2H), 2.68 (t, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.51 (s, 4H, 2 CH_2), 6.90-7.28 (m, 6H), 7.31-7.82 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 26.3, 47.8, 50.3, 67.9, 109.5, 118.4, 124.2, 128.0, 128.3, 129.6, 130.0, 139.7, 144.3, 145.2, 193.8; *Anal. Calcd. for* $C_{37}H_{36}N_4O_2$ (568.71): C, 78.14; H, 6.38; N, 9.85%. *Found:* C, 77.92; H, 6.26; N, 9.98%.

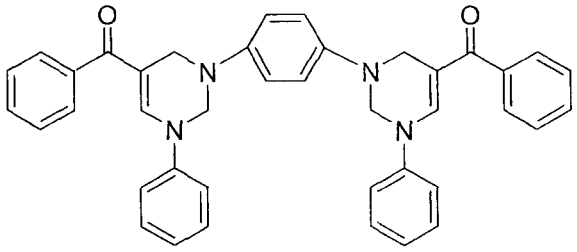
[Butane-1,4-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)] bis(phenyl-methanone) 25c.



This compound was obtained as a pale yellow solid in 70 % yield, mp 176-177 ^{0}C; IR (KBr): 1563, 1577, 1618 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 4H 2 CH_2), 2.59 (m, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.52 (s, 4H, 2 CH_2), 6.91-7.12 (m, 6H), 7.26-7.57 (m, 16H); ^{13}C NMR ($CDCl_3$): δ 25.6, 47.5, 52.5, 68.2, 109.6, 118.5, 124.2, 128.2, 128.4,

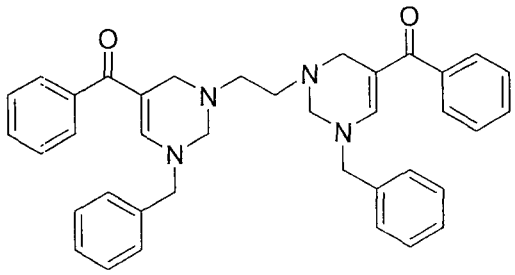
129.7, 130.1, 139.8, 144.4, 145.2, 193.9; *Anal. Calcd. for* $C_{38}H_{38}N_4O_2$ (582.73): C, 78.32; H, 6.57; N, 9.61%. *Found:* C, 78.60; H, 6.46; N, 9.46%.

[1,4-Phenylenebis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)] bis(phenyl-methanone) 25d.



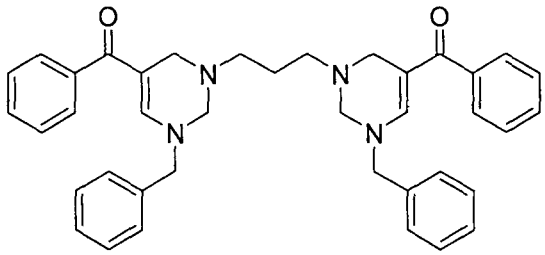
This compound was obtained as a yellow solid in 54% yield, mp 118-120^{0}C; IR (KBr): 1507, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.43 (s, 4H, 2 CH_2), 5.08 (s, 4H, 2 CH_2), 6.84-7.55 (m, 26H); ^{13}C NMR ($CDCl_3$): δ 47.3, 66.2, 110.6, 118.6, 119.3, 121.5, 124.5, 125.7, 128.2, 128.4, 129.8, 130.3, 142.9, 146.0, 193.8; *Anal. Calcd. for* $C_{40}H_{34}N_4O_2$ (602.72): C, 79.71; H, 5.69; N, 9.30%. Found: C, 79.98; H, 5.80; N, 9.18%.

[Ethane-1,2-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)] bis (phenyl-methanone) 25e.



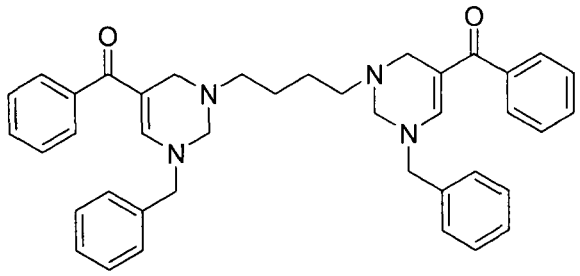
This compound was obtained as a pale yellow solid in 75% yield, mp 103-104^{0}C; IR (KBr): 1541, 1580, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.96 (s, 4H, 2 CH_2), 4.23 (s, 4H, 2 CH_2), 7.17-7.49 (m, 22 H); MS: m/z 583 [MH+]; *Anal. Calcd. for* $C_{38}H_{38}N_4O_2$ (582.73): C, 78.32; H, 6.57; N, 9.61%. *Found:* C, 78.61; H, 6.66; N, 9.48%.

[Propane-1,3-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis (phenyl - methanone) 25f.



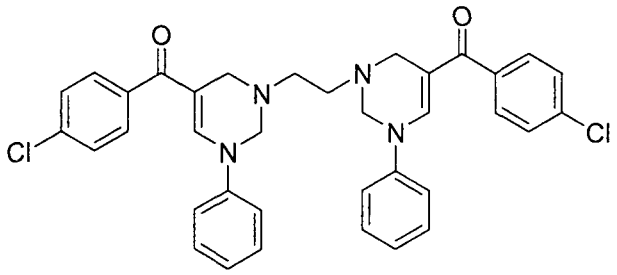
This compound was obtained as a pale yellow gum in 70 % yield; IR (KBr): 1543, 1573, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.49 (m, 2H), 2.42 (t, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.88 (s, 4H, 2 CH_2), 4.22 (s, 4H, 2 CH_2), 7.16-7.49 (m, 22H); ^{13}C NMR ($CDCl_3$): δ 25.8, 47.7, 50.8, 58.1, 65.7, 107.1, 127.5, 128.6, 128.9, 129.2, 129.7, 130.5, 135.7, 140.2, 150.3, 192.6; *Anal. Calcd. for* $C_{39}H_{40}N_4O_2$ (596.76): C, 78.49; H, 6.76; N, 9.39%. *Found:* C, 78.30; H, 6.64; N, 9.30%.

[Butane-1,4-diylbis(3-benzyl-3,6-dihydropyrimidine-1, 5(2*H*)-diyl)]bis (phenyl-methanone) 25g.



This compound was obtained as a pale yellow solid in 80 % yield, mp 99-100^{0}C; IR (KBr): 1551, 1580, 1617 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (m, 4H 2 CH_2), 2.36 (m, 4H, 2 CH_2), 3.66 (s, 4H, 2 CH_2), 3.90 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.19-7.29 (m, 6H), 7.31-7.45 (m, 10H), 7.48-7.51 (m 6H); MS: m/z 611[MH+]; *Anal. Calcd. for* $C_{40}H_{42}N_4O_2$ (610.79): C, 78.66; H, 6.93; N, 9.17%. *Found:* C, 78.39; H, 7.06; N, 9.25%.

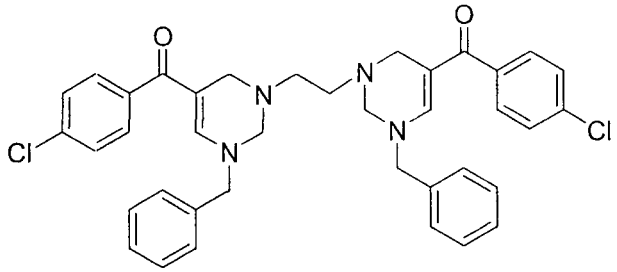
[Ethane-1,2-diylbis(3-phenyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl)methanone] 25h.



This compound was obtained as a pale yellow solid in 64 % yield, mp 176-177^{0}C; IR (KBr): 1544, 1570, 1613 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.79 (s, 4H, 2 CH_2), 3.81 (s, 4H, 2 CH_2), 4.61 (s, 4H, 2 CH_2), 6.90-6.93 (m, 4H), 7.10-7.15 (m, 3H), 7.31-7.46 (m, 8H), 7.49-7.57 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 47.4, 50.7, 68.6, 108.8, 116.4, 118.5, 118.9,

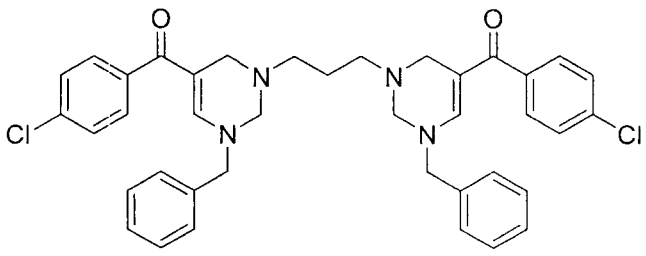
124.5, 128.8, 128.6, 129.7, 144.2, 145.1, 192.4; *Anal. Calcd. for* $C_{36}H_{32}Cl_2N_4O_2$ (623.57): C, 69.34; H, 5.17; N, 8.98%. *Found:* C, 69.62; H, 5.25; N, 8.85%.

[Ethane-1,2-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl) methanone] 25i.



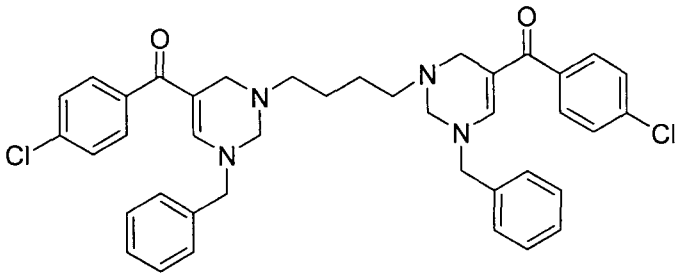
This compound was obtained as a white solid in 83 % yield, mp 95-96^{0}C; IR (KBr): 1547, 1575, 1611 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 3.96 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.16-7.44 (m, 20 H); MS: m/z 652 [MH+], 654 [MH^++2], 656 [MH^++4]; *Anal. Calcd. for* $C_{38}H_{36}Cl_2N_4O_2$ (651.62): C, 70.04; H, 5.57; N, 8.60%. *Found*: C, 70.24; H, 5.41; N, 8.49%.

[Propane-1,3-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl) methanone] 25j.



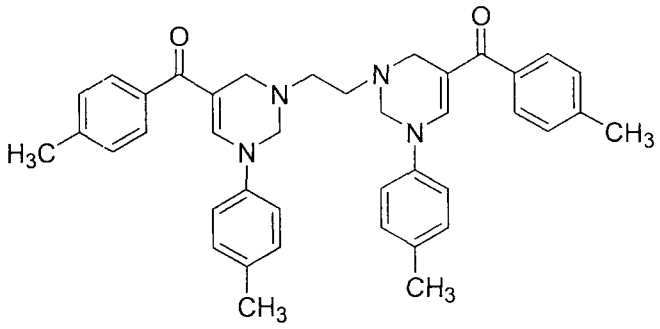
This compound was obtained as a pale yellow solid in 70 % yield, mp 105-106^{0}C IR (KBr): 1543, 1575, 1613 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 1.48 (m, 2H), 2.41 (t, 4H, 2 CH_2), 3.61 (s, 4H, 2 CH_2), 3.89 (s, 4H, 2 CH_2), 4.30 (s, 4H, 2 CH_2), 7.08-7.53 (m, 20H); MS: m/z 666 [MH+], 668 [MH$^+$+2], 670 [MH$^+$+4]; *Anal. Calcd. for* $C_{39}H_{38}Cl_2N_4O_2$ (665.65): C, 70.37; H, 5.75; N, 8.42%. *Found:* C, 70.10; H, 5.61; N, 8.56%.

[Butane-1,4-diylbis(3-benzyl-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-chlorophenyl) methanone] 25k.



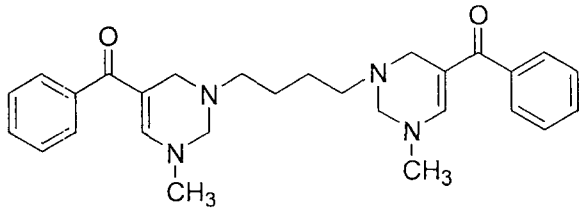
This compound was obtained as a pale yellow solid in 80 % yield; mp 105^{0}C; IR (KBr): 1555, 1575, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (m, 4H, 2 CH_2) 2.34 (m, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 3.93 (s, 4H, 2 CH_2), 4.25 (s, 4H, 2 CH_2), 7.17-7.45 (m, 20H); MS: m/z 680 [MH+], 682 [MH$^+$+2], 684 [MH$^+$+4]; *Anal. Calcd. for* $C_{40}H_{40}Cl_2N_4O_2$ (679.68): C, 70.68; H, 5.93; N 8.24%. *Found:* C, 70.95; H, 5.93; N, 8.10%.

[Ethane-1,2-diylbis(3-(4-methylphenyl)-3,6-dihydropyrimidine-1,5(2*H*)-diyl)]bis-[(4-methylphenyl)methanone] 25l.



This compound was obtained as a white solid in 65 % yield, mp 225-226^{0}C; IR (KBr): 1575, 1590, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 6H, 2 CH_3), 2.38 (s, 6H, 2 CH_3), 2.79 (s, 4H, 2 CH_2), 3.82 (s, 4H, 2 CH_2), 4.59 (s, 4H, 2 CH_2), 6.80-6.83 (m, 4H), 7.10-7.26 (m, 9H), 7.42-7.51 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.1, 21.8, 47.9, 51.1, 69.1, 109.0, 119.1, 128.9, 129.2, 130.6, 134.5, 137.4, 140.8, 142.5, 145.7, 194.2; *Anal. Calcd. for* $C_{40}H_{42}N_4O_2$ (610.79): C, 78.66; H, 6.93; N, 9.17%. *Found:* C, 78.42; H, 6.79; N, 9.02%.

[Butane-1,4-diylbis(3-methyl-3,6-dihydropyrimidine-1, 5(2*H*)-diyl)] bis(phenyl-methanone) 25m.



This compound was obtained as a yellow solid in 80 % yield, mp 148-149^{0}C; IR (KBr): 1552, 1582, 1626 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.65 (m, 4H, 2 CH_2), 2.58 (m, 4H,

2 CH_2), 2.94 (s, 6H, 2 CH_3), 3.66 (s, 4H, 2 CH_2), 3.96 (s, 4H.2 CH_2), 7.03 (s, 2H, 2 CH), 7.38-7.49 (m, 10H); MS: m/z 459 [MH+]; *Anal. Calcd. for* $C_{28}H_{34}N_4O_2$ (458.60): C, 73.33; H, 7.47; N 12.22%. *Found:* C, 73.60; H, 7.62; N, 12.36%.

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CHAPTER IV

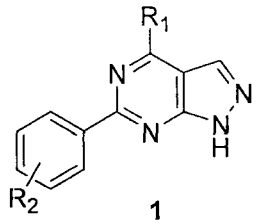
A facile one-pot synthesis of novel 1,2,3,4-tetrahydropyrimdines, Synthesis of Bis[(1-alkyl/aralkyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl]- alkane and benzene, Bis [3-phenyl-7-methyl 4,5,6,7-tetrahydropyrazolo(3,4-*d*)pyrimidinyl]alkane and Bis[1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo(1,5-a)triazinyl]alkane & benzene.

Introduction

Several pyrazolo[3,4-*d*]pyrimidines and their mercapto analogues are known to possess important biological properties[1-5]. Some substituted pyrazolo[1,5-*a*]pyrimidines have also been reported to act as unique phosphodiesterase inhibitors. It was also shown that some phenylpyrazolo[1,5-*a*]pyrimidines were found to be potent antagonist of human CRF_1 (Corticotropin releasing factor-1) that, in turn, are expected to have utility in treatment of stress related diseases[5b].

4.1 The synthesis and biological properties of few such molecules are described in the following sections.

4.1.1 Baker and Kozma have reported[6] the synthesis of a series of 4-hydroxy/amino-6-(substituted)-phenylpyrazolo[3,4-*d*]pyrimidines (**1**). The compounds **1** were prepared by the reaction of 5-amino-1*H*-pyrazole-4-carbonitrile (**2**) or 5-amino-1*H*-pyrazole-4-carboxamide (**3**) with substituted benzamidines to form 6-phenyl-pyrazolo[3,4-*d*]pyrimidines of the type **5** and **6**. This reaction proceeded smoothly at 200°C and the products could be readily purified. The method appeared to be quite general since, benzamidines substituted with either the electron withdrawing nitro group or the electron-donating hydroxyl group could be used.



1

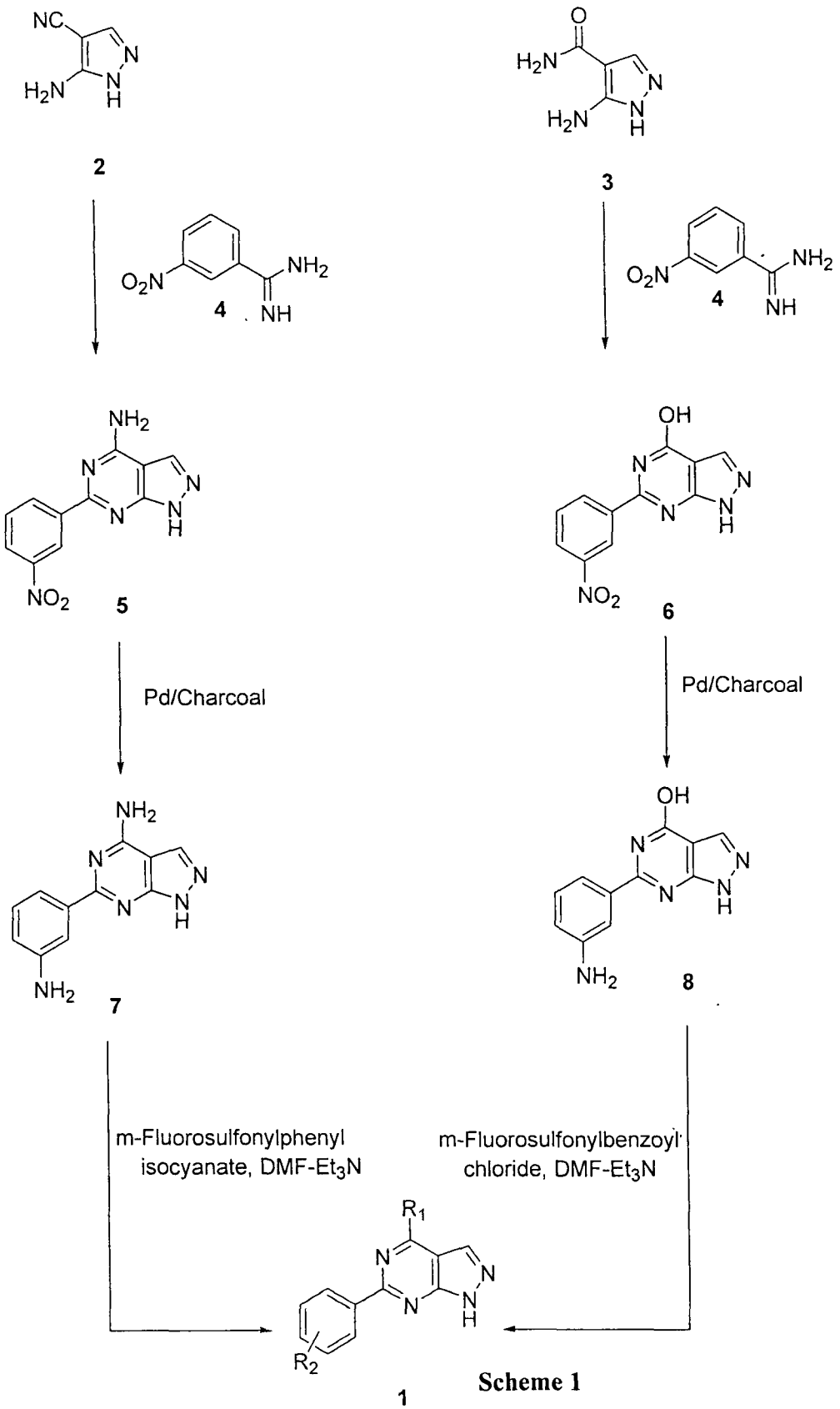
R_1 = OH, NH_2
R_2 = *m* or p-$NHCOC_6H_4SO_2F$
m or p-$NHCONHC_6H_4SO_2F$

The nitro groups of **5** and **6** were catalytically reduced to give the amines **7** and **8**. The final compounds were then prepared by reaction with *m*-fluorosulfonylphenylisocyanate or with appropriate fluorosulfonylbenzoyl chloride in DMF-triethyl amine[7] (**Scheme1**).

It was found that 4-hydroxy-6-phenylpyrazolo[3,4-*d*]pyrimidines with *m*-fluoro sulfonyl-benzamido (**9**) or *p*-fluorosulfonyl benzamido (**10**) groups on the meta position are active-site-directed irreversible inhibitors of xanthine oxidase.

Replacement of 4-OH group by amino groups in **9** or **10** (**Scheme 1a**) leads to loss of irreversible inhibition, but no loss of reversible inhibition occurs. They also reported the Structure activity relationship (SAR) of the other molecules synthesized.

4.1.2 O'Brien et al reported[8] the synthesis of a series 3-substituted 5,7-dimethylpyrazole[1,5-*a*]pyrimidines. The parent compound i.e 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines was synthesised according to the procedure of Makisumi [9] by condensation of 3-aminopyrazole (**11a**) and 3-amino-4-carbethoxy-pyrazole (**11b**) with acetylacetone which yielded the corresponding 5,7-dimethylpyrazolo[1, 5-*a*]pyrimidine (**12a**) and 3-carbethoxy derivative (**12b**).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N
N
H
2
O
H_2N
N
H_2N
N
H
3
O_2N
NH_2
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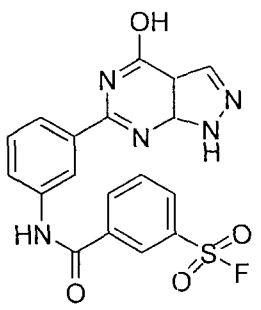
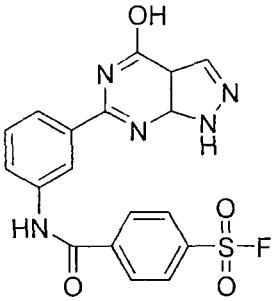
NH_2
N
N
N
N
H
NO_2
5
OH
N
N
N
N
H
NO_2
6
Pd/Charcoal
Pd/Charcoal
NH_2
N
N
N
N
H
NH_2
7
OH
N
N
N
N
H
NH_2
8
m-Fluorosulfonylphenyl
isocyanate, DMF-Et_3N
m-Fluorosulfonylbenzoyl
chloride, DMF-Et_3N
R_1
N
N
N
N
H
R_2
1

Scheme 1

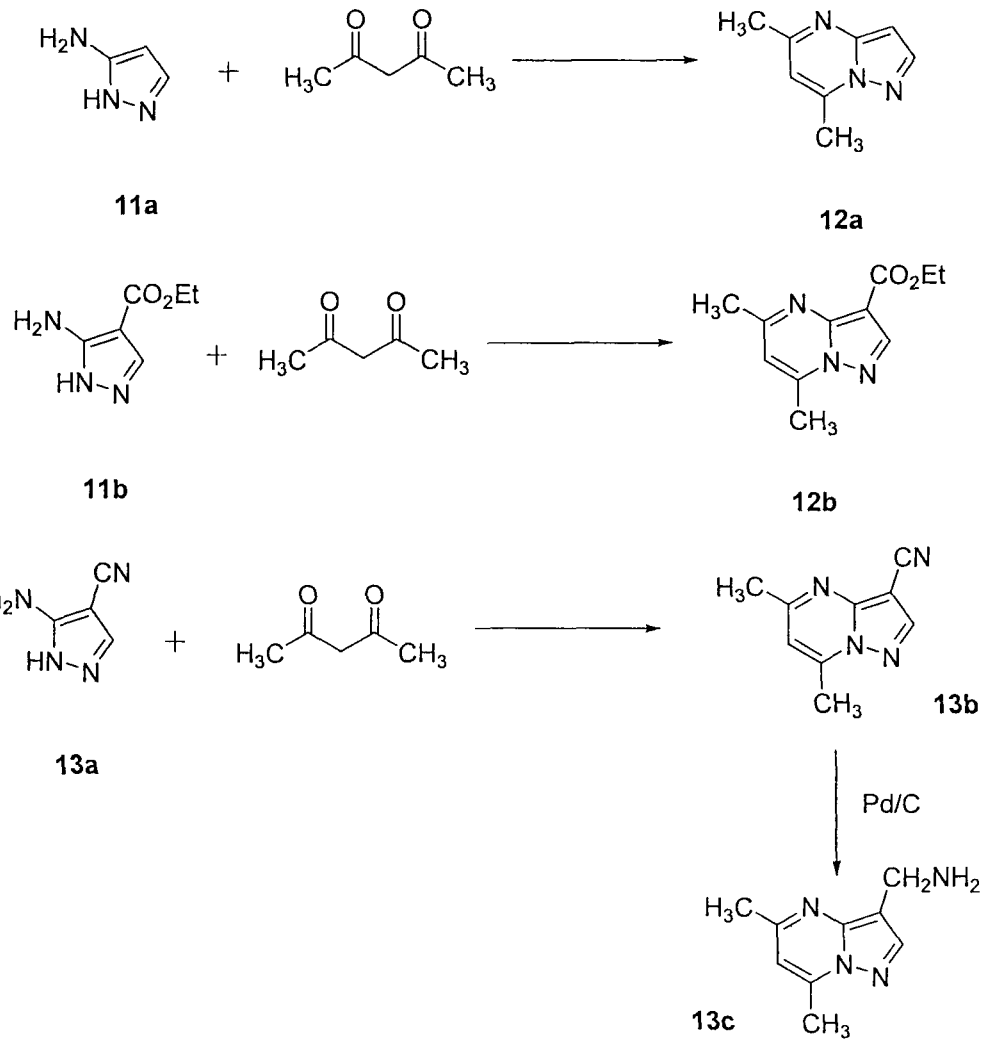


9



10

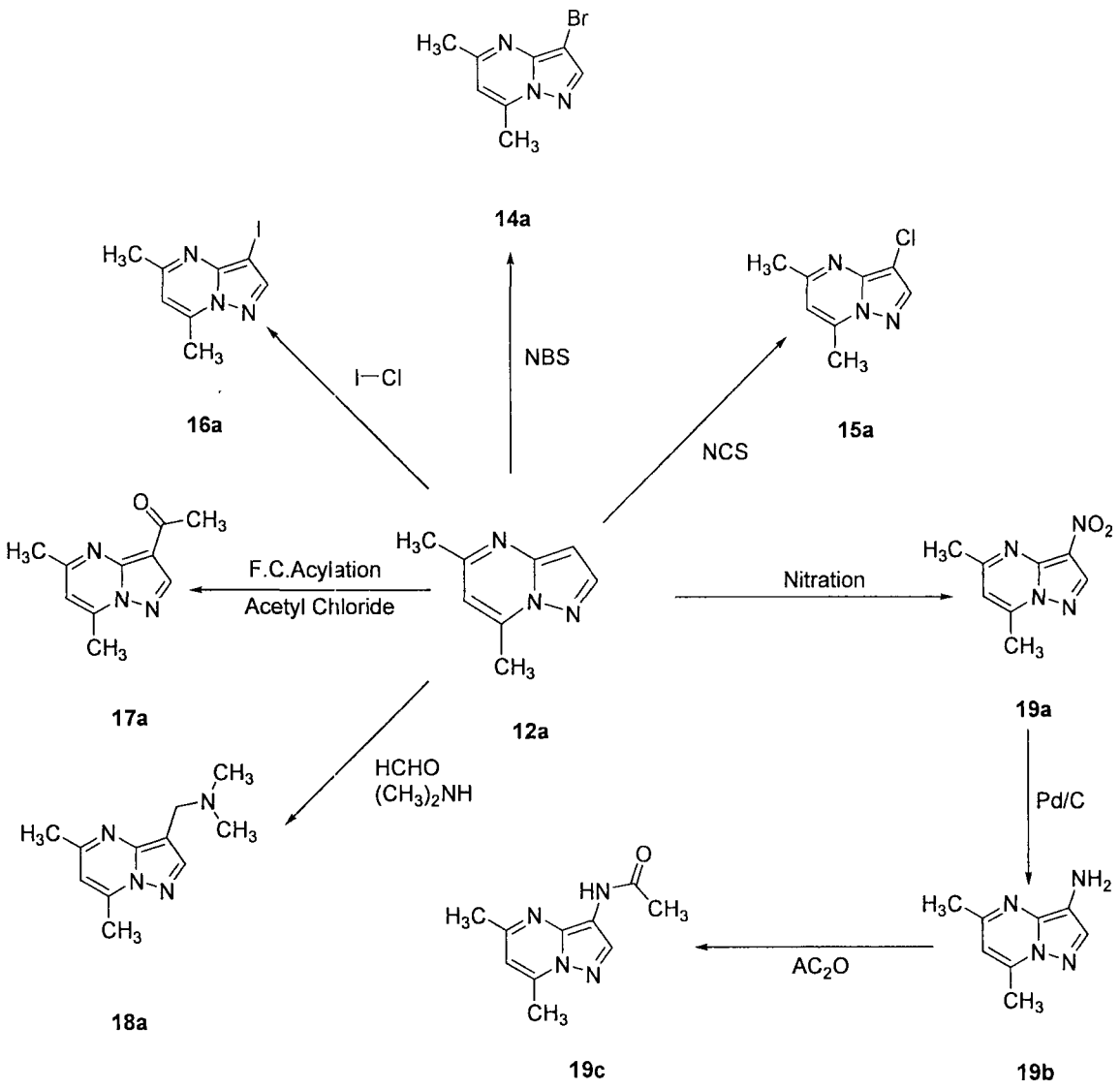
Scheme 1a



Scheme 2

Similar condensation of 3-amino-4-cyanopyrazole (**13a**) yields the 3-cyanoderivative **13b** in good yield. The catalytic reduction of 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**13b**) with palladium on charcoal catalyst affords 3-aminomethyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**13c**), which was isolated as hydrochloride (**Scheme 2**).

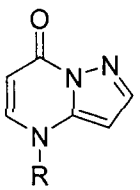
4.1.3 The electrophilic substitution of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**12a**) gave the 3-substituted products as shown below (**scheme 3**). When **12a** was brominated with NBS, 3-bromo-5,7-dimethylpyrazolo-[1,5-*a*] pyrimidine (**14a**) was obtained. Similarly chlorination with NCS afforded the 3-chloro compound **15a**. Reaction of **12a** with iodine monochloride yielded the corresponding 3-iodocompound **16a**. Friedel-Craft acylation with acetyl chloride gave the 3-acetyl derivative **17a**. Mannich reaction with dimethylamine and formaldehyde gave 3-dimethylaminomethyl-5,7-dimethylpyrazolo[1,5-*a*] pyrimidine(**18a**). In a similar fashion nitration of **12a** was accomplished with nitrating mixture (sulphuric acid and fuming nitric acid) at moderate temperature to yield the corresponding 5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**19a**). The nitro derivative was catalytically reduced over palladium on charcoal to yield 3-amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**19b**). This compound was highly colored due to air oxidation and was converted to 3-acetamido-5,7-dimethylpyrazolo[1,5- *a*]pyrimidine (**19c**) (**Scheme 3**). Electrophilic substitution at position 3 was not unexpected as O'Brien and coworkers examined the ^{13}C NMR spectra of the closely related pyrazolo[1,5-*a*]pyrimidine ring system and the study revealed that position 3 appears at a high-field resonance position which has been correlated with ease of electrophilic substitution[10]. These compounds so prepared were evaluated for their ability to inhibit Phosphodiesterase (PDE). It was found that 3-bromo, 3-chloro, 3- iodo and 3-acetyl derivatives were found to be more potent than Theophylline in their ability to inhibit these 3,3'-cAMP phosphodiesterases.



Scheme 3

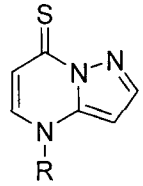
4.1.4 Due to the structural resemblance of pyrazolopyrimidines (**20** and **21**) to hypoxanthine (**22**), which plays a central role in the ATP production of S. *mansoni*[11] Robins and coworkers[12] synthesized several 7-hydroxypyrazolo[1,5-*a*]pyrimidines, 7-mercaptopyrazolo[1,5-*a*]pyrimidines, 4-alkylpyrazolo[1,5-*a*]pyrimidin-7-ones and

the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidine7-thiones. The 7-hydroxypyrazolo[1,5-*a*]pyrimidines were prepared by basically three methods



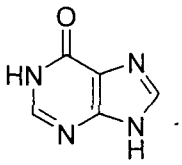
20

1, R = H,
2, R = alkyl



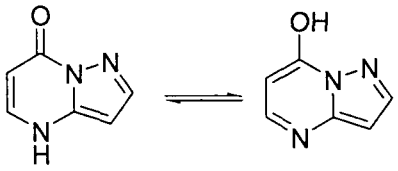
21

1, R = H
2, R = alkyl



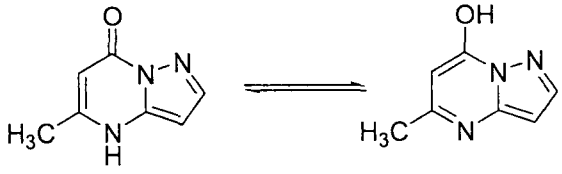
22

4.1.4a Method a. Condensation of the appropriate 3-aminopyrazole with sodium salt of ethylformylacetate[13] provided the desired 7-hydroxypyrazolo[1,5-*a*]pyrimidines **(23) (Scheme 4)**.



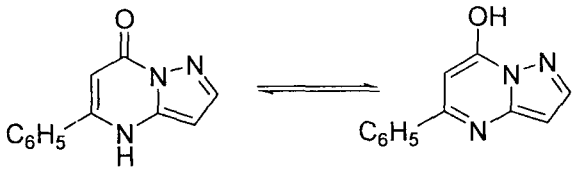
23a **23b**

4.1.4b Method b. The 7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidines **(24)** were obtained by the reaction of the required 3-aminopyrazole with ethyl acetoacetate by using acetic acid (according to the general procedure of Makisumi) **(24) (Scheme 4)**.



24a **24b**

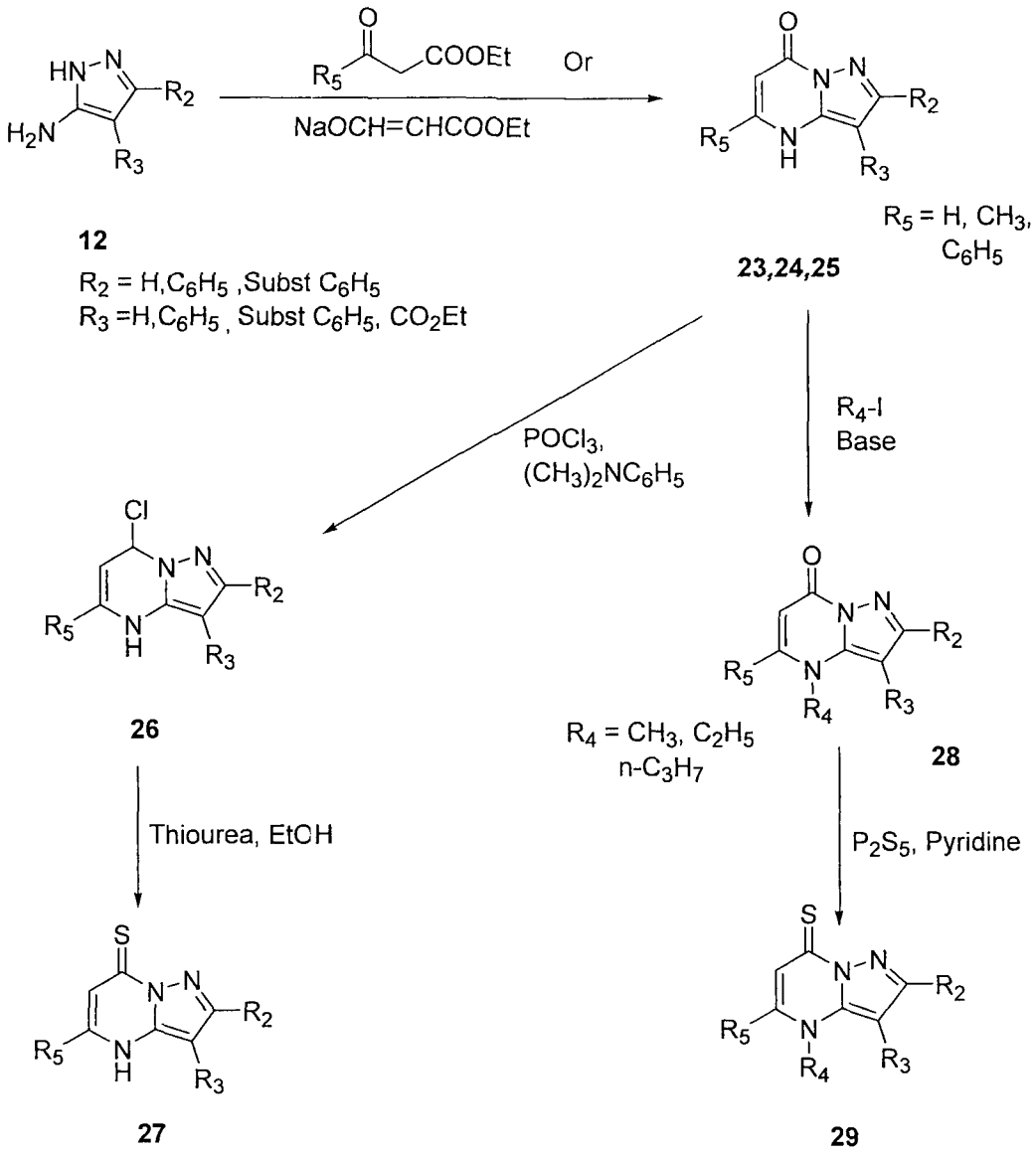
4.1.4c Method c.Similarly, the reaction of 3-aminopyrazoles with ethyl benzoylacetate in acetic acid afforded 7-hydroxy-5-phenylpyrazolo[1,5-*a*]pyrimidines(**25**) as described by Checchi et al[14] **(Scheme 4)**.



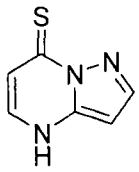
25a **25b**

4.1.5 Chlorination of the 7-hydroxypyrazolo[1,5-*a*]pyrimidines (**23, 24, 25**) with phosphorous oxychloride in the presence of N,N-dimethylaniline gave the corresponding 7-chloropyrazolo[1,5-*a*]pyrimidines (**26**), which upon treatment with thiourea in ethanol resulted in the formation of the corresponding 7-mercaptopyrazolo[1,5-*a*]pyrimidines (**27**). Alkylation of the 7-hydroxypyrazolo[1,5-*a*]pyrimidines with the appropriate alkyl iodide gave the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidine-7-ones (**28**). Treatment of the 4-alkylpyrazolo-[1, 5-*a*]pyrimidine-7-ones with phosphorous pentasulfide in pyridine yielded the corresponding 4-alkylpyrazolo[1,5-*a*]pyrimidine-7-thiones (**29**) (**Scheme 4**).

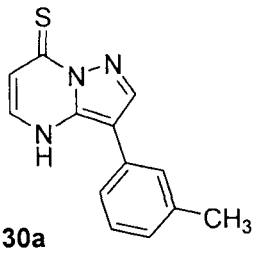
These three series of compounds were tested for antichistosomal activity against *Schistosoma mansoni*. Of the three series the greatest degree of activity in vitro was found with the 7-mercaptopyrazolo[1,5-*a*]pyrimidines (**27**). Compounds **30** and **30a (Scheme 4a)** of this series were found to be lethal at 10μg/ml after exposure of only 1hr. The 7-hydroxypyrazolo[1,5-*a*]pyrimidines were in general not active. However none of the compounds were active against *S.masoni* in vivo.


COOEt
Or
R5
NaOCH=CHCOOEt
R2
R3
H2N
HN
N
O
H
12
R2 = H,C6H5 ,Subst C6H5
R3 =H,C6H5 , Subst C6H5, CO2Et
23,24,25
R5 = H, CH3, C6H5
POCl3,
(CH3)2NC6H5
R4-I
Base
Cl
26
R4 = CH3, C2H5
n-C3H7
28
Thiourea, EtOH
P2S5, Pyridine
S
27
29

Scheme 4



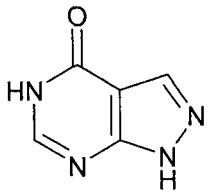
30



30a

Scheme 4a

4.1.6 Allopurinol (pyrazolo[3,4-*d*]pyrimidon-4-one, **31**) was synthesized and first reported by Robins[15] and shortly thereafter by Schmidt and Druey[16].



31

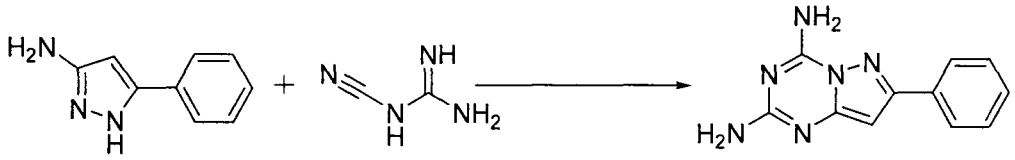
Fiegelson et al. first showed[17] that derivatives of the pyrazolo[3,4-*d*]pyrimidine ring system were potent inhibitors of xanthine oxidase. Roland K. Robins, Darrell E. O'Brien, J. P. Miller and their respective coworkers have reported[18] a detail structure-activity relationship of various types of pyrazolopyrimidines and pyrimidinones and their binding to xanthine oxidase. Allopurinol (**31**) despite having certain disadvantages[21] is one of the drugs of choice, worldwide, for the treatment of hyperuracemia and gouty arthritis.

4.2 PYRAZOLO TRIAZINES

The pyrazolo[1,5-*a*]1,3,5-triazines have attracted a lot of interest in the recent past and have become a widely studied cyclic heterocycles. It has been of some interest biologically, because of its isomeric resemblance to purines [20,21].

4.3 The preparations, reactions and biological properties of some of these molecules are discussed in the following sections.

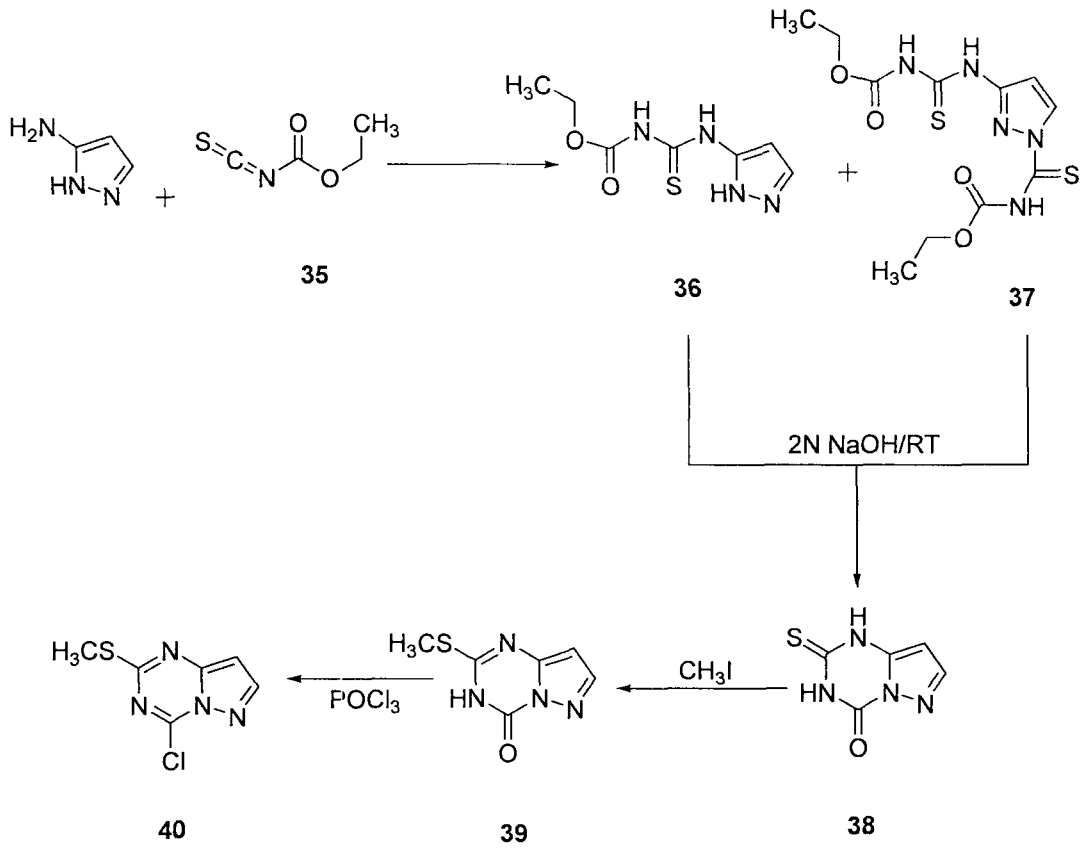
4.3.1 The first derivative of the pyrazolo-triazine ring system was 2,4-diamino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**34**) and was prepared by the ring closure of 3-amino-5-phenylpyrazole (**32**) with cyanoguanidine[22] (**33**) (**Scheme 5**).



32 **33** **34**

Scheme 5

4.3.2 In 1973 Darrell and coworkers [23] investigated the pyrazolo[1,5-*a*]-1,3,5-triazine ring system. They used 3-aminopyrazole as a starting material for the synthesis of certain pyrazolo[1,5-*a*]-1,3,5-triazines (**Scheme 6**). Treatment of 3-aminopyrazole with ethoxycarbonyl isothiocyanate gave *N*-carbethoxy-*N'*-(pyrazol-3-yl) thiourea (**36**) and small amount of *N*-carbethoxy-*N'*-(1-carbethoxythiocarbamoylpyrazol-3-yl) thiourea (**37**).



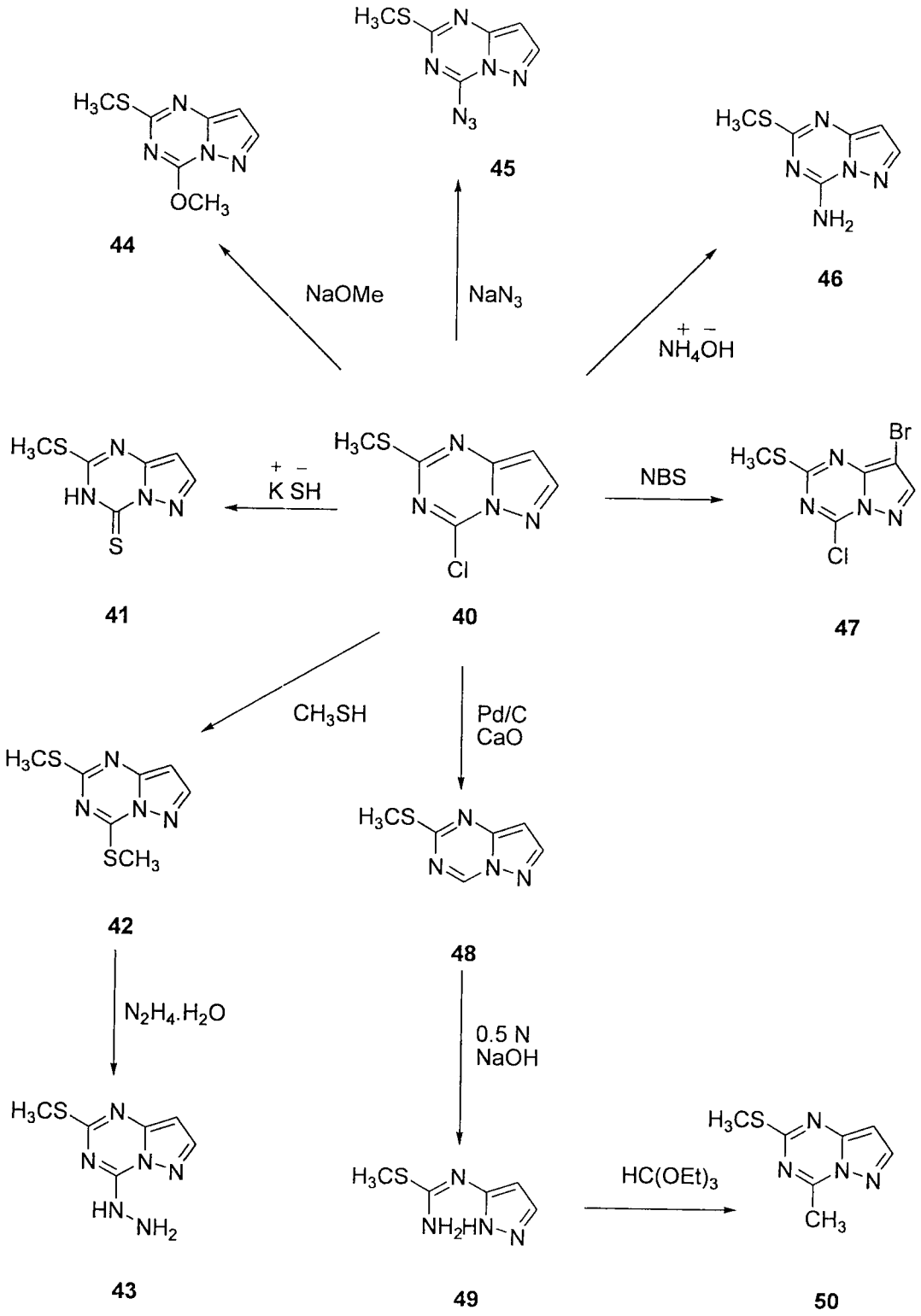
Scheme 6

Both **36** and **37** when treated with 1N sodium hydroxide solution at room temperature afforded 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**38**). Methylation of **38** with Methyliodide gave 2-Methylthio 4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**39**). Treatment of **39** with $POCl_3$ afforded 4-Chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**40**). This chloro derivative was the most versatile intermediate in the preparation of other derivatives of pyrazolo-triazine ring system as shown in (**Scheme 7**).

4.3.2a Treatment of **40** with Potassium hydrosulfide gave the corresponding 2-methylthio-4-thioxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**41**). Similarly reaction of **40** with methane thiol in the presence of a base gave 2,4-bismethylthiopyrazolo [1,5-*a*]-1,3,5-triazine (**42**), which further reacted with hydrazine hydrate at room

temperature to give 4-hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**43**). 4-methoxy-2-methylthio pyrazolo[1,5-*a*]-1,3,5-triazine (**44**) was obtained by reaction of sodium methoxide with **40**. Reaction of **40** with sodium azide yielded 4-azido-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**45**). The Corresponding 4-amino-2-methylthiopyrazolo[1,5-a]-1,3,5-triazine (**46**) was prepared from the corresponding chloro derivative (**40**) and aqueous ammonia at room temperature.

4.3.2b Electrophilic substitution of the pyrazolo[1,5-*a*]-1,3,5- triazine ring system took place at the 8 positions, thus when **40** was reacted with N-bromosuccinimide in refluxing ethanol 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**47**) was obtained. Reductive dehalogenation of the chloroderivative (**40**) with palladium on charcoal catalyst in the presence of calcium oxide afforded 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**48**). This when treated with 0.5N NaOH at room temperature resulted in opening of the 1,3,5-triazine ring to yield S-methyl-N-(pyrazol-3-yl) thiourea (**49**), which acts as starting material for preparation of 4-alkyl derivatives of the ring system. **49** can be cyclised back to afford 4-methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**50**) by refluxing with triethylorthoformate (**Scheme 7**).

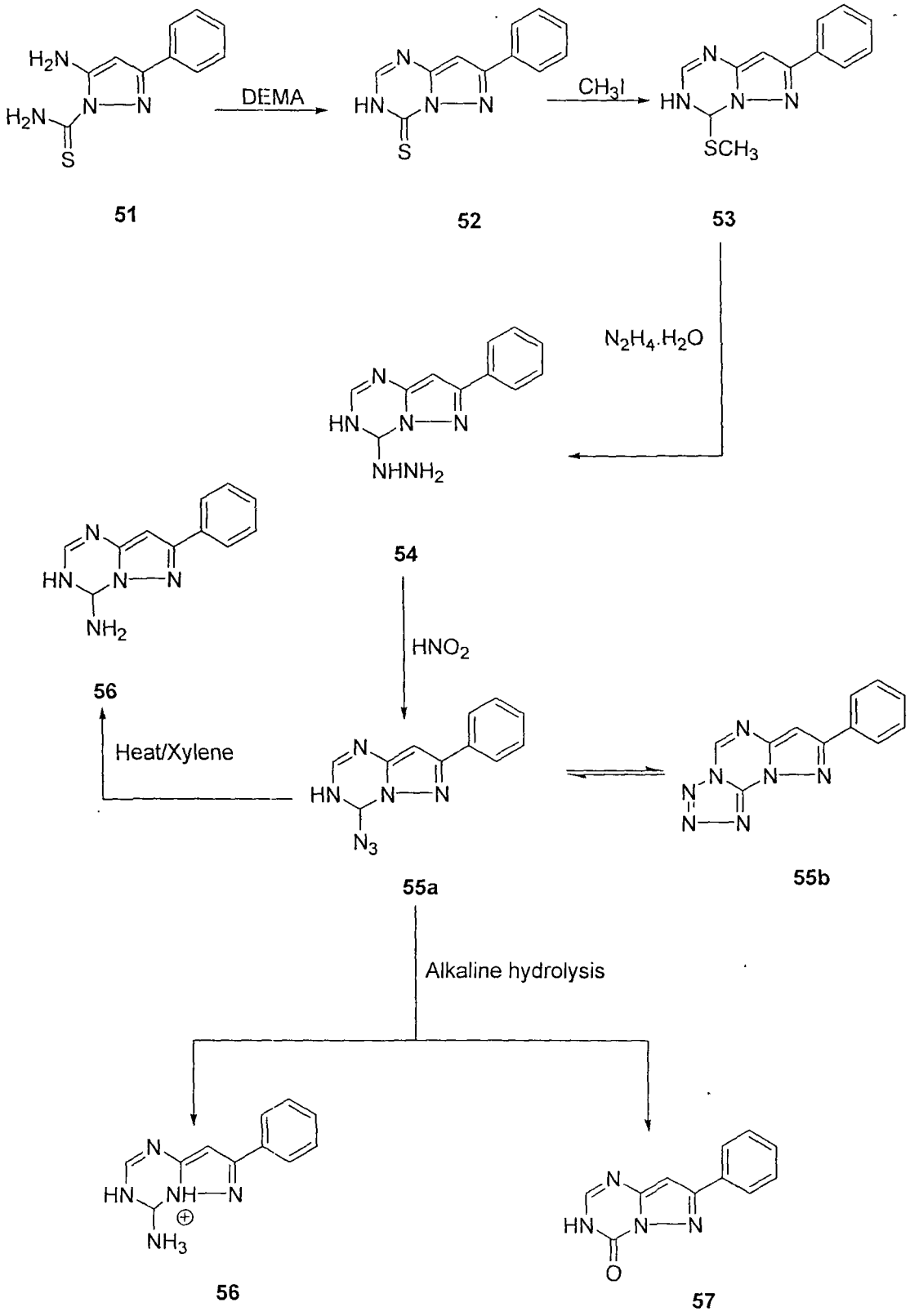

H3CS
N3
45
OCH3
44
NaOMe
NaN3
NH2
46
NH4OH
HN
S
41
K SH
Cl
40
NBS
Br
47
CH3SH
Pd/C
CaO
SCH3
42
48
N2H4.H2O
0.5 N
NaOH
HN
NH2
43
NH2HN
49
HC(OEt)3
CH3
50

Scheme 7

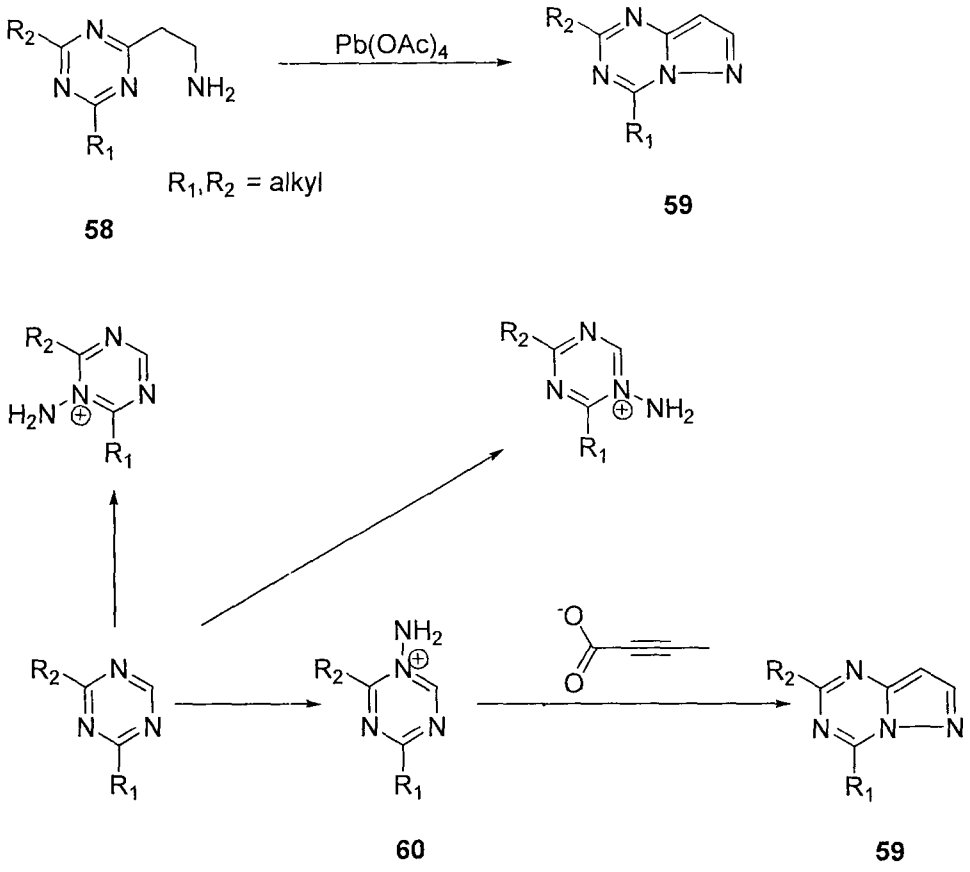
4.3.3 Kobe and coworkers studied[24] the chemistry of 4-hydrazino-7-phenylpyrazolo [1,5-*a*]-1,3,5-triazines (**54**). Condensation of 3-amino-5-phenyl-2-thiocarbamoyl pyrazole (**51**) with diethoxymethylacetate (DEMA) yielded 4-mercapto-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine **(52),** which was alkylated with methyliodide to give 4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine(**53**). Reaction of **53** with hydrazine hydrate gave the desired hydrazino analogue (**54**) (**Scheme 8**).

The reaction of **54** with nitrous acid gave 8-phenyltetrazolo[1,5-*e*]pyrazolo[1,5-*a*]-1,3,5-triazine (**55b**), which was found to be in equilibrium with 4-azido-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**55a**). The equlibrium of tetrazolo **55b** and azido **55a** was studied by ^{1}H NMR and an attempt was made to determine if substituents in the pyrazole nucleus could sufficiently stablize the tricyclic tetrazolo form (**55b**) over bicyclic azido form (**55a**). Thermal degradation of **55** in an aprotic solvent gave 4-amino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**56**) indicating the involvement of a nitrene mechanism in the decomposition process. Heating **55** in aqueous base gave both **56** and the hydroxy analogue 7-Phenylpyrazolo[1,5-*a*]-1,3,5-triazine-4(3*H*)one (**57**) further substantiating the existence of a nitrene intermediate with a competing nucleophilic displacement of the azido group by the hydroxyl group (**Scheme 8**).

4.3.4 Novinson and coworkers while working[25] on the preparation of 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines (**59**) have tried two approaches. The first one was by using 2,4-dialkyl-1,3,5-triazine derivatives. 6-aminoethyl-2,4-dialkyl-1,3,5-triazines (**58**) could be possibly cyclized using lead tetraacetate, in analogy to the synthesis of pyrazolo[1,5-*a*]pyridines as reported by Kirchner[26] (**Scheme 9**). Or by the reaction of 1-amino-2, 4-dialkyl pyridinium salts (**60**) with methyl propiolate (**Scheme 9**)[27]. In both cases two isomers would be possible if the two-alkyl groups were not the same.


DEMA
CH3I
N2H4.H2O
HNO2
Heat/Xylene
Alkaline hydrolysis
51
52
53
54
55a
55b
56
56
57

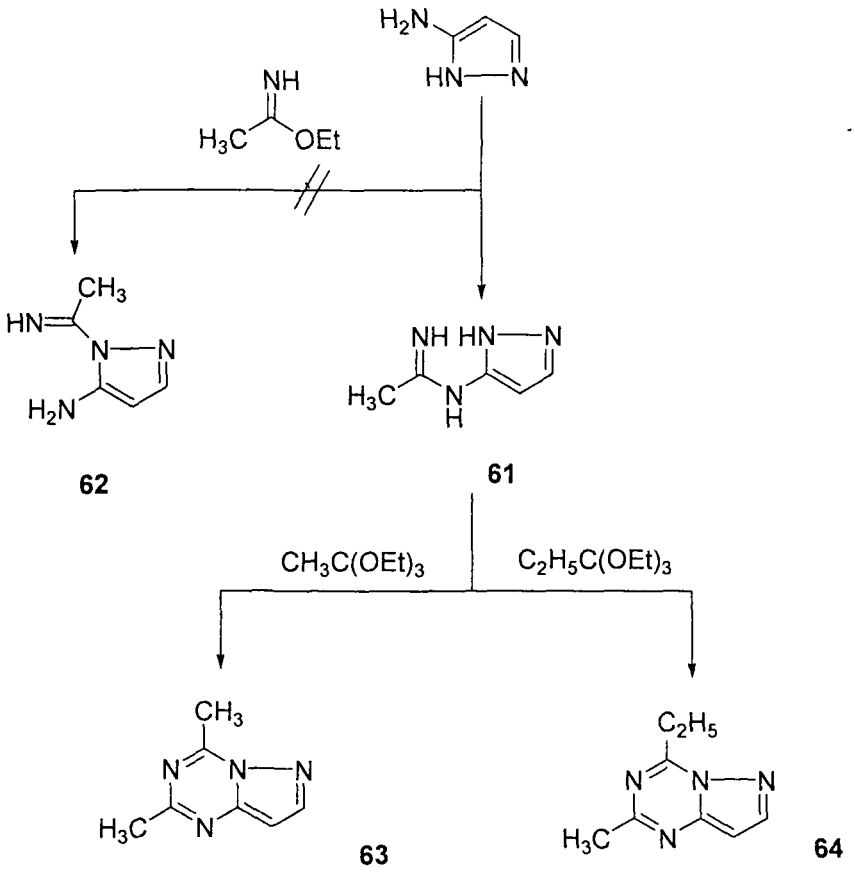
Scheme 8



Scheme 9

4.3.4a Novinson et al. took the alternative approach[28] and built the ring system from 3-aminopyrazole whereby they modified the classical Pinner reaction. It was observed that when 3-aminopyrazole was reacted with ethylacetimidate, *N*-(pyrazol-3-yl)acetamidine (**61**) was obtained rather than the isomeric 2-acetamidoyl-3-aminopyrazole (**62**). When **61** was cyclized with triethyl orthoacetate (**Scheme 10**) 2,4-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine (**63**) was obtained. In analogous manner, *N*-(pyrazolo-3-yl) acetamidine (**61**) was condensed with triethyl orthopropionate to yield 4-ethyl-2-methyl-pyrazolo[1,5-*a*]-1,3,5-triazine (**64**).

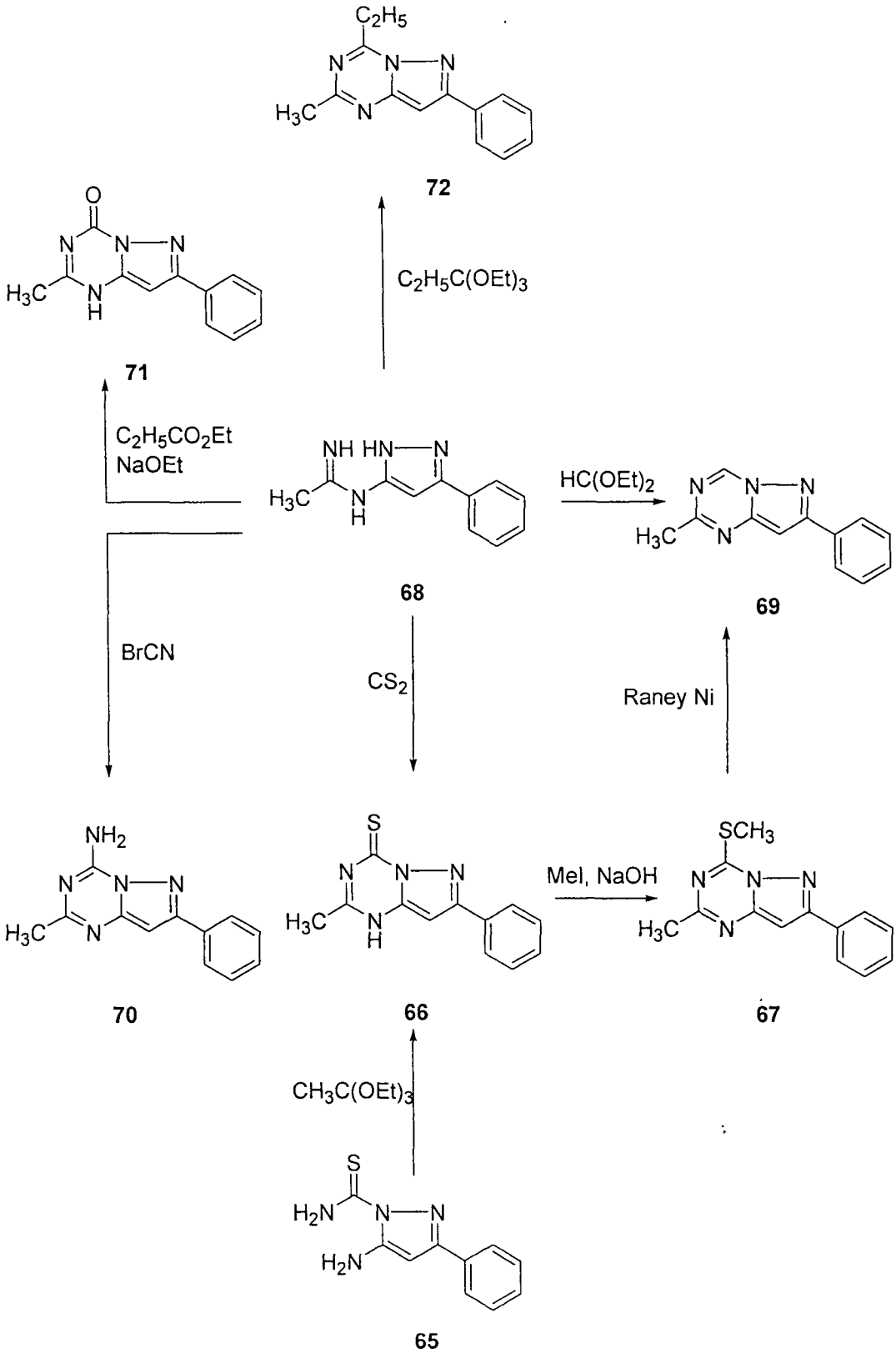
4.3.4b When 3-amino-2-thiocarbamoyl-5-phenylpyrazole (**65**) was refluxed with triethyl orthoacetate (**Scheme11**), 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-3*H*-4-thione (**66**) was obtained.



Scheme 10

This thione **66** was readily alkylated by methyl iodide to afford 2-methyl-4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**67**). The 4-methylthio group of 67 was dethiated with raney nickel to yield 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**69**). Alternatively when *N*-(5-phenylpyrazol-3-yl)acetamidine (**68**) was refluxed with triethylorthoformate, it directly gave **69**. When **68** was condensed with cyanogenbromide 4-amino-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**70**) was obtained. Compound **68** was condensed with diethylcarbonate in the presence of ethanolic sodium methoxide to yield 2-methyl-7-phenylpyrazole[1,5-*a*]-1,3,5-3*H*-4-

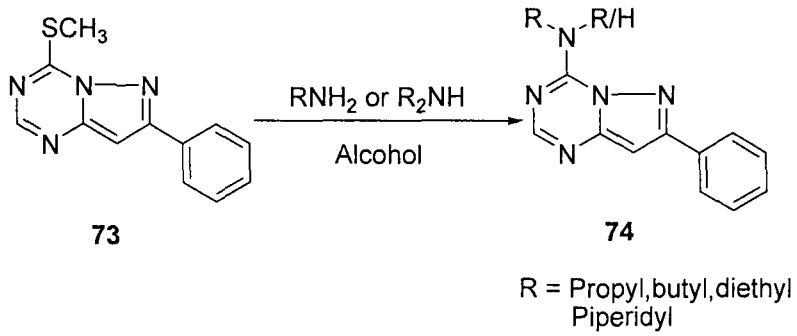
one (**71**). Similarly 4-ethyl-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**72**) was synthesized by cyclizing **68** with triethylorthopropionate as shown in the (**Scheme11**). The unique feature of this two-step synthetic approach was that it was a convenient method of preparing fused triazines based on available pyrazoles rather than the less accessible dialkyltriazines.


C2H5
H3C
72
C2H5C(OEt)3
71
C2H5CO2Et
NaOEt
HC(OEt)2
68
69
BrCN
CS2
Raney Ni
NH2
S
SCH3
MeI, NaOH
70
66
67
CH3C(OEt)3
H2N
65

Scheme 11

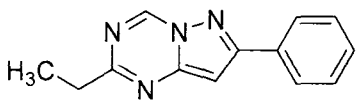
4.3.5 Harris and coworkers[29] have listed eight diseases where inhibitors of cAMP phosphodiesterase could be potential therapeutic agents. These are (1) asthama, (2) diabetes mellitus, (3) female fertility, (4) male infertility, (5) psoriasis, (6) thrombosis, anxiety and (7) hypertension, the data in support of these conclusions have also been summarized by them.

4.3.6 Encouraged by the good in vitro potency of their pyrazolo derivatives, as inhibitors of cAMP phosphodiesterase, K. Senga and coworkers[30] envisaged that the structure-activity relationship might carry over to pyrazolo[1,5-*a*]-1,3,5-triazines. They synthesized a series of various pyrazolo[1,5-*a*]-1,3,5-triazines and studied them as inhibitors of cAMP phosphodiesterase isolated from various sources such as Bovine brain, bovine heart and rabbit lung. In most cases the starting materials used were prepared earlier. Treatment of 7-phenyl-4-(methylthio)pyrazolo[1,5-*a*]-1,3,5-triazine[24] (**73**) with various primary and secondary amines in alcohol gave the 7-phenyl-4-(alkylamino) pyrazolo[1,5-*a*]-1,3,5-triazines (**74**) (**Scheme 12**).



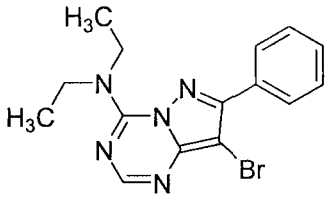
Scheme 12

A number of compounds were prepared and a few were found to be superior to theophylline for example 2-ethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**75**).



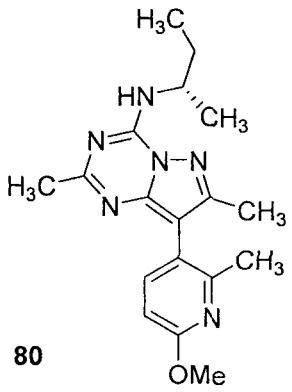
75

The most active compound was 8-bromo-4-(diethylamino)-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**79**) which was found to be 185 times more potent than theophylline as an inhibitor[30] of PDE isolated from rabbit lung.



79

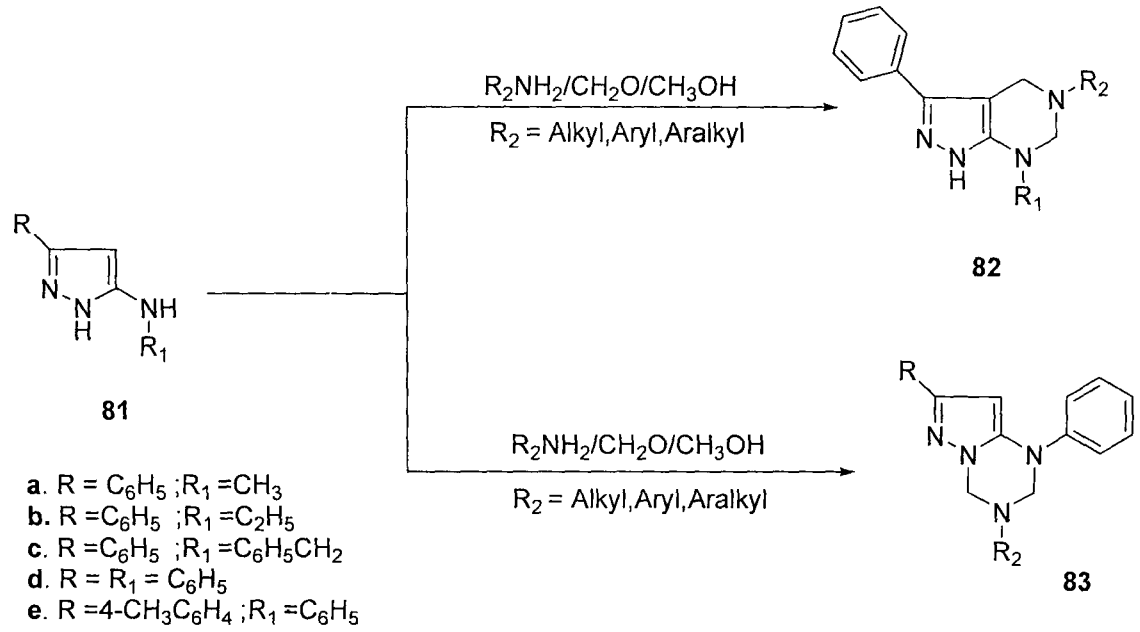
4.3.7 Recently Paul J. Gilligan and coworkers have reported[31] the synthesis and structure-activity relationship of 8-(pyrid-3-yl)pyrazolo[1,5-*a*]-1,3,5-triazines as potent, orally bioavailable corticotropin releasing factor Receptor-1 (CRF_1) Antagonists. These CRF_1 receptor antagonists may be potential anxiolytic or antidepressant drugs. The best molecule of the series was N-sec butyl-8-(6-methoxy-2-methylpyridin-3-yl)-2,7-dimethylpyrazolo[1,5-*a*]-1,3,5-triazin-4-amine (**80**) which has been advanced to clinical trials.



80

4.3.8 Researchers of our group have reported the synthesis of substituted 4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines and 1,2,3,4-tetrahydropyrazolo[1,5-a]triazine derivatives[32] by employing the previously reported[33] 3(5)-alkyl/arylamino pyrazoles

as bifunctional nucleophiles in tetrahydropyrimidine annelation with formaldehyde and primary amines (**Scheme 13**).

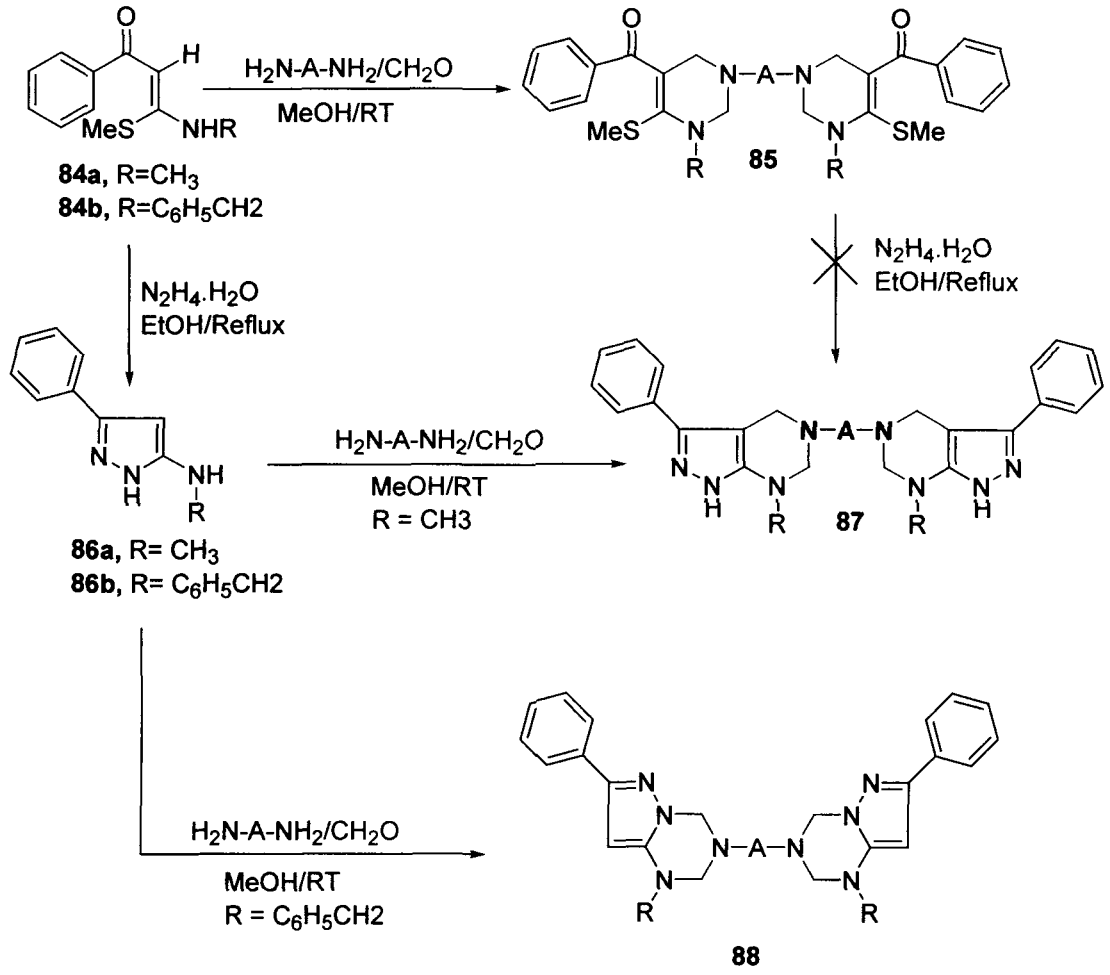


Scheme 13

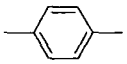
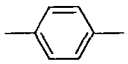
It was observed that the reaction of *N*-methyl-3-phenyl-1*H*-pyrazol-5-amine (**81a**) with formaldehyde and benzyl amine yielded a crystalline solid, which was characterized as 3-phenyl-5-benzyl-7-methyl-4,5,6,7-tetrahydro-1(2*H*)-pyrazolo [3,4-*d*]pyrimidine (**82**). The reaction was found to be general in all cases where R=aryl and R_1= alkyl or aralkyl groups. However in cases where R and R_1 both were aryl or substituted aryl, eg, when 3(5)-anilinopyrazole (**81d**) was reacted with benzylamine and formaldehyde under identical conditions, the product isolated was characterized as 1,7-diphenyl-3-benzyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazine (**83**) instead of the corresponding pyrazolo pyrimidine. The triazine was apparently formed by cyclization on the pyrazole ring nitrogen instead of at C-4 position. The difference in the reactivity of 3(5)-alkylamino and the corresponding arylaminopyrazoles to give **82** and **83** respectively can be rationalized in terms of

reduced nucleophilicity of C-4 position in case where both R and R_1 were aryl. Because of increased delocalization of the non-bonding electron pair of the arylamino nitrogen over the aryl group rather than the pyrazole ring, while the nitrogen lone pair in the alkylamino group in alkyl and aralkyl case is completely delocalized over the pyrazole ring, thus facilitating ring closure at the C-4 position.

4.4 However, to the best of our knowledge, bis-pyrazolotetrahydropyrimidines are unknown in the literature and hence their biological properties remain unexplored. Prompted by the above observation and in continuation with our on-going programme on the development of novel synthetic strategies for tetrahydropyrimidines[34-36], we undertook the present investigation and the results of our studies are reported herein.


H2N-A-NH2/CH2O
MeOH/RT
84a, R=CH3
84b, R=C6H5CH2
85
N2H4.H2O
EtOH/Reflux
86a, R= CH3
86b, R= C6H5CH2
H2N-A-NH2/CH2O
MeOH/RT
R = CH3
87
H2N-A-NH2/CH2O
MeOH/RT
R = C6H5CH2
88

Scheme 14

Compd	R	A
85a, 87a	CH_3	$-(CH_2)_2-$
85b, 87b	CH_3	$-(CH_2)_4-$
85c	CH_3	
85d, 88a	$CH_2C_6H_5$	$-(CH_2)_2-$
85e, 88b	$CH_2C_6H_5$	$-(CH_2)_4-$
85f, 88c	$CH_2C_6H_5$	

4.5 Results and Discussions.

When mixture of N, S-acetal (**84a**)[37], ethylenediamine and formaldehyde (2:1:4) in methanol was stirred at room temperature, work up of the reaction mixture yielded an off white solid in 72% yield, which was characterized as 1,2-bis(1-methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl) ethane (**85a**). The reaction was found to be general with other diamines and with corresponding **84** to give the respective **85b-f** in 52-72% overall yields. The structures of these products were confirmed on the basis of analytical and spectral data. Thus, the IR spectra of **85a-f** showed strong absorption bands in the range 1603-1639cm^{-1} due to carbonyl group stretching frequencies. The ^1H NMR spectra showed singlets due to methylene protons at C_2 and C_4 of the tetrahydro pyrimidine ring in the range of δ 3.80-4.55 and δ 3.40-4.12 respectively. The singlets due to NMe protons in **85a-c** appeared as singlets in the range of δ3.00-3.10 while the benzylic methylene protons in **85d-f** gave singlets in the range of δ 3.65-4.30. In the spectra of **85a** and **85d** the signals due to the protons of ethylene chain appeared as singlets at δ 2.80 and δ 2.56 ppm respectively, whereas the NCH_2 protons of butylenes chain in compounds **85b** and **85e** gave muliplets in the range of δ 2.35-2.52. The signals corresponding to the methylene protons at C_2 and C_3 of the butylenes chain of **85b** and **85e** are observed

as the multiplets resonating between δ 1.40-1.62 ppm. The singlets due to the protons of methylthio group appeared between δ 1.90-1.98, while the aromatic protons gave multiplets in the usual range.

Further reaction of **85** with hydrazine hydrate to achieve the synthesis of **87** resulted in the formation of a complex reaction mixture from which isolation of the desired product was unsuccessful. This is probably due to the cleavage of the tetrahydropyrimidine ring in the presence of this nucleophilic reagent under experimental conditions. We then turned our attention to another strategy involving the conversion of **84** into pyrazole[33] **86** and then **86** into the desired bis-pyrazolo tetrahydropyrimidines **87** (**Scheme 14**).

Thus, when a mixture of 3(5)-methylaminopyrazole **86a**, ethylenediamine and formaldehyde (2:1:4) was stirred at room temperature in methanol for 5 hour, work up of the reaction mixture gave **87a** in 53% yields, the structure of which was proposed to be 1,2,-bis(3-phenyl-7-methyl-4,5,6,7-tetrahydropyrazole[3,4-*d*]pyrimidinyl) ethane on the basis of analytical and spectral data. Similarly, **86a** reacted with butylenediamine and formaldehyde under identical conditions to give **87b** in 55% yield. However, the reaction of **86a** with *p*-phenylenediamine and formaldehyde gave an intractable reaction mixture from which no product could be isolated. Interestingly, when 3(5)-benzylaminopyrazole **86b** was reacted with ethylenediamine and formaldehyde under identical conditions, the product isolated (51%) was characterized as 1,2-bis(1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo [1,5-*a*]triazinyl)ethane (**88a**) instead of the corresponding bis-pyrazolopyrimidinylethane. The reaction of **86b** was found to follow a similar course of reaction with others diamines giving **88b** and **88c** in 50 and 55% yields respectively. The bis-pyrazolotriazinyl derivatives **88** were distinguished from the corresponding bis-pyrazolopyrimidinyl derivatives by the presence of a signal due to H-8 between δ 5.72-6.05 (2 s, 2x1H) in their ^{1}H NMR spectra. In addition the band due to NH in the IR spectra of **87a-b** was found absent in those of **88a-c**. The

difference in the reactivities of 3(5)-methylaminopyrazole **86a** and the corresponding benzyl amionopyrazole **86b** to give **87** and **88** respectively could be explained in terms of decreased nucleophilicity of C_4 position in **86b** because of reduced delocalization of the lone pair of electron of the benzylamino nitrogen due to hyperconjugation of CH_2 of benzyl group, while the nitrongen lone pair in methylamino group of **86a** is completely delocalized over pyrazole ring, thus facilitating ring closure through C_4 position.

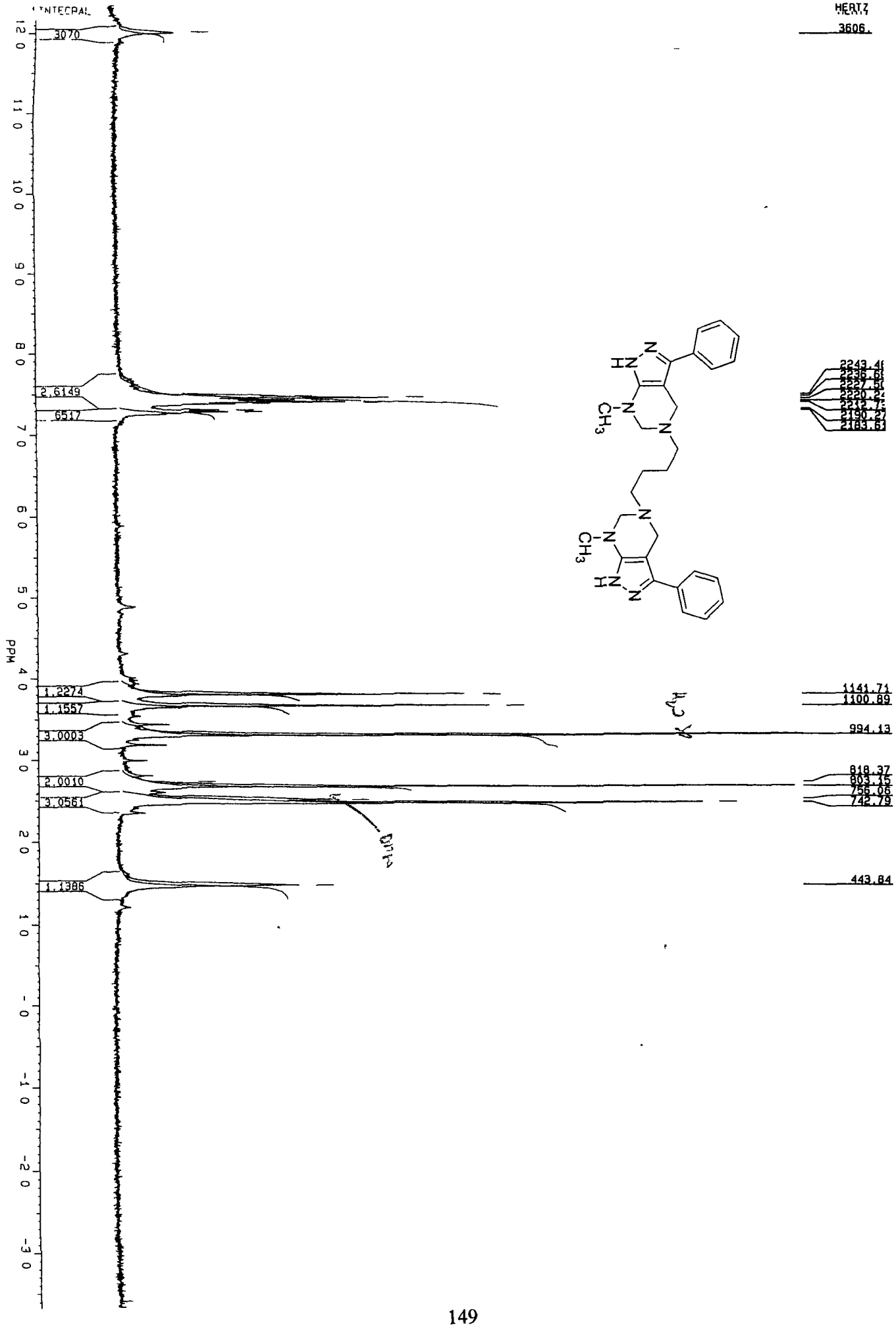
The ^1H NMR and Mass Spectra of 1,4-bis(3-phenyl-7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinyl)butane (**87b**) and 1,4-bis (1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl) butane (**88b**) are shown in pages 149-152.

4.6 Conclusion.

In conclusion, we have synthesized a series of hitherto unknown dimeric heterocyclic compounds in which we could successfully connect the two heterocyclic moiety i.e 5-benzoyl-6-methylthio tetrahydropyrimidines, 3-phenyl-7-methyl pyrazolotetrahydropyrimidines and 1-benzyl-7-phenyl-pyrazolotriazines by a various aliphatic and aromatic linkers.

4.7 Experimental Section

Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 983 spectrometer. ^1H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High resolution ^1H NMR and ^{13}C 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 fashion with reference to TMS as internal reference. FAB-mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon


INTEGRAL
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3070
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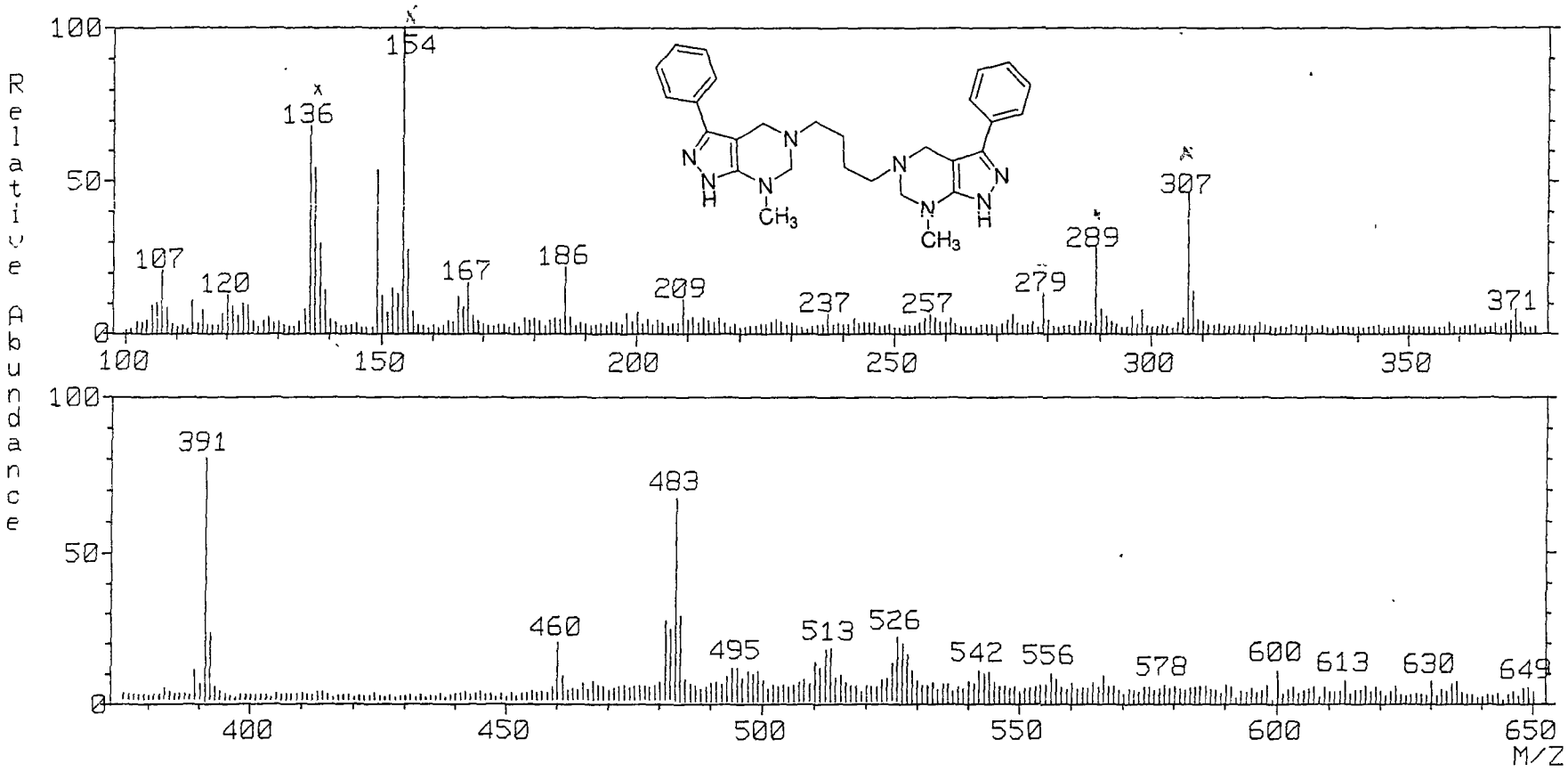
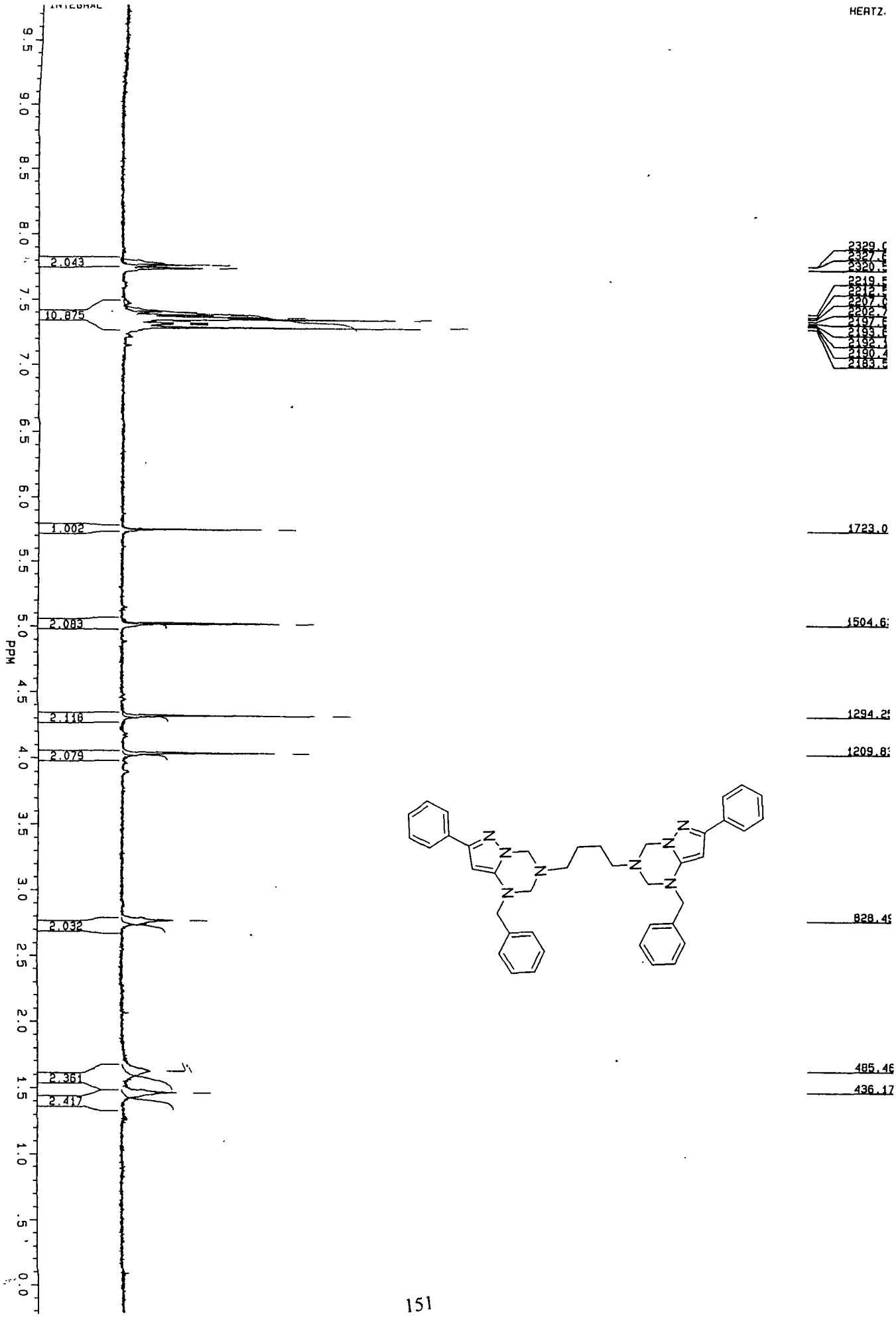
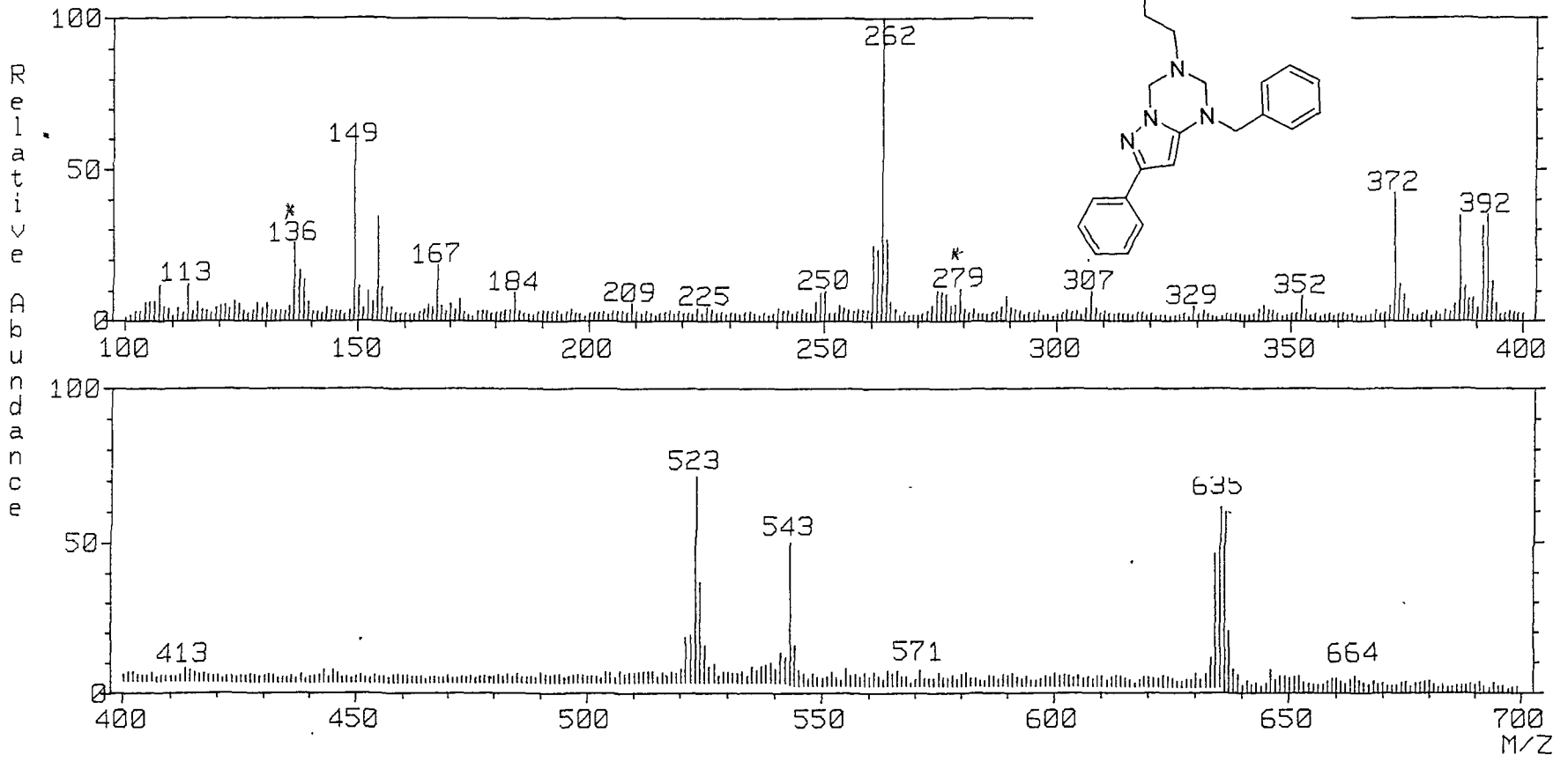
6517
1.2274
1.1557
3.0003
2.0010
3.0561
1.1386
PPM
1141.71
1100.89
994.13
818.37
803.15
756.06
742.79
443.84

MASS SPECTRUM Data File: 4EFB27E 27-FEB- 4 10:14
Sample: C-5 DR J N VISHWAKARMA SHILLONG #6950
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 18.2883 Lv 0.00
Scan# (1 to 2)




INTEGRAL
HERTZ
2.043
10.875
1.002
2.083
2.118
2.079
2.032
2.361
2.417
PPM
1723.0
1504.6
1294.2
1209.8
828.4
485.4
436.17

MASS SPECTRUM Data File: 4EFB27B :50
SamPle: C-2 DR J N VISHWAKARMA SHILLONG #6950
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 262.0000 Int. E
Scan# (3 to 4)



as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were performed on a Vario-EL III instrument.

4.8 General procedure.

4.8a *Bis-[(1-alkyl/aralkyl)-5-benzoyl-6-methylthio-1,2,3,4-tetrahydro pyrimidinyl) alkane and benzene (85a-f).*

A mixture of diamine (1 mmol) and formaldehyde (4 mmol) in 2 ml methanol was stirred at room temperature for 10 minutes. To this was added a solution of enaminone **84** (2 mmol) in 5-6 ml methanol and the resulting mixture was stirred for 3-8 hours in case of **85b**, **85c, 85e, 85f** and 22-30 hours in case of **85a** and **85d**. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled in ice-cold water and the precipitated product was collected by filtration, washed with cold methanol (3x1 ml) and dried to give analytically pure **85a-f**, which were recrystallized from methanol.

4.8b *Bis (3-phenyl-7-methyl 4,5,6,7-tetrahydropyrazolo[3,4-d] pyrimidinyl] alkanes (87a-b).*

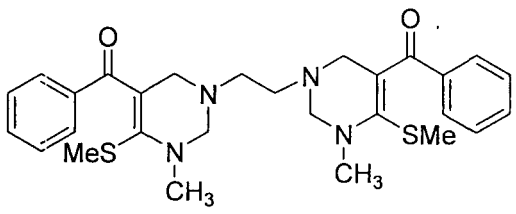
A mixture of diamine (1 mmol) and formaldehyde (4 mmol) in 2 ml methanol was stirred at room temperature for 10 minutes. To this was added a solution of aminopyrazole **86a** (2 mmol) in 5-6 ml methanol and the resulting mixture was stirred for 3-8 hours. After the completion of the reaction (monitored by TLC) the solvent was distilled off, the residue dissolved in chloroform, the solution washed with water (3x3ml), dried over anhydrous Na_2SO_4 and the solvent evaporated to give crude bis pyrazolotetrahydropyrimidines **87a-b**, which were purified by passing through neutral alumina column using ethyl acetate as eluant.

4.8c ***Bis (1-benzyl -7-phenyl -1,2,3,4-tetrahydropyrazolo[1, 5-a]triazinyl) alkane & benzene (88a-c).***

A mixture of diamine (1 mmol) and formaldehyde (4 mmol) in 2 ml methanol was stirred at room temperature for 10 minutes. To this a solution of aminopyrazole **86b** (2 mmol) in 5-6 ml methanol was added and the resulting mixture was further stirred for 3-8 hours. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled in ice water and the precipitated product was collected by filtration, washed with cold methanol (3x1 ml) and dried to give analytically pure **88a-c**, which were recrystallized from methanol.

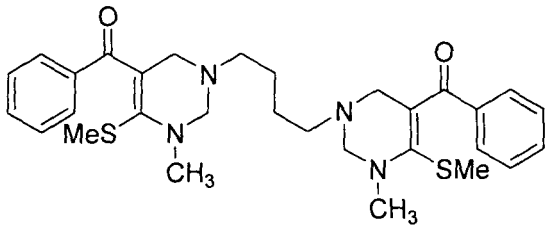
Individual description of the compounds.

1,2-Bis (1-methly-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl) ethane 85a.



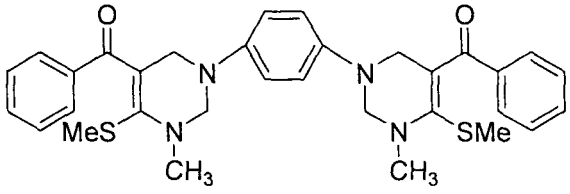
This compound was obtained as a white solid in 72% yield, mp159-160^{0}C; IR (KBr): 1455, 1554, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 6H, 2 CH_3), 2.80 (s, 4H, 2CH_2), 3.10 (s, 6H, 2 CH_3), 3.58 (s, 4H, 2 CH_2), 3.98 (s, 4H, 2 CH_2), 7.35-7.48 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.61, 40.04, 52.16, 53.74, 72.94, 115.28, 127.76, 128.33, 130.66, 142.04, 152.71, 195.73; Mass: m/z 523 [MH^+]; *Anal. Calcd. for* $C_{28}H_{34}N_4O_2S_2$ (522.73): C, 64.34; H, 6.56; N, 10.72%. *Found*: C, 64.11; H, 6.51; N, 10.79%.

1,4-Bis (1-methyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl) butane 85b.



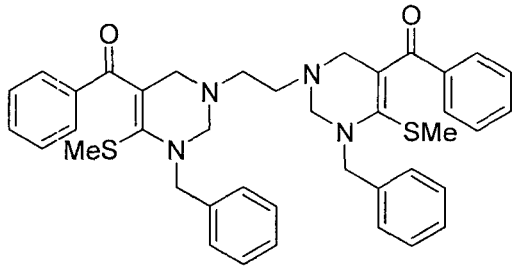
This compound was obtained as a white solid in 66% yield, mp116-118^{0}C; IR (KBr): 1542, 1603 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58-1.62 (m, 4H), 1.90 (m, 6H, 2 CH_3), 2.42-2.52 (m, 4H), 3.05 (s, 6H, 2 CH_3), 3.45 (s, 4H, 2 CH_2), 3.8 (s, 4H, 2 CH_2), 7.28-7.40 (m, 6H), 7.59-7.64 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.47, 25.49, 40.09, 53.65, 53.86, 72.50, 115.83, 127.75, 128.35, 130.66, 142.02, 152.71, 195.82; Mass: m/z 551 [MH$^+$]; *Anal .Calcd. for* $C_{30}H_{38}N_4O_2S_2$ (550.78): C, 65.42; H, 6.95; N, 10.17%. *Found*: C, 65.63; H, 6.89; N, 10.22%.

1,4-Bis (1-methly-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)benzene 85c.



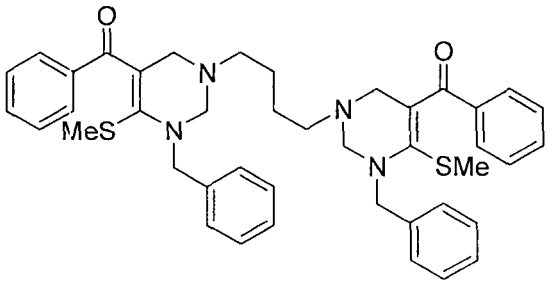
The compound was obtained as a white solid in 56% yield, mp 210-211^{0}C; IR (KBr): 1510, 1555, 1625 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 6H, 2 CH_3), 3.00 (s, 6H, 2CH_3), 4.12 (s, 4H, 2 CH_2), 4.45 (s, 4H, 2 CH_2), 7.19-7.29 (m, 3H), 7.30-7.43 (m, 7H), 7.65-7.70 (m, 4H); Mass: m/z 571 [MH$^+$]; *Anal .Calcd. for* $C_{32}H_{34}N_4O_2S_2$ (570.77): C, 67.34; H, 6.00; N, 9.82%. *Found*: C, 67.08; H, 6.04; N, 9.76%.

1,2-Bis (1-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl)ethane 85d.



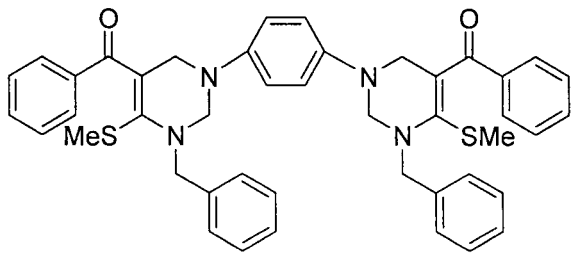
This compound was obtained as a white solid in 52% yield, mp101-102^{0}C; IR (KBr): 1522, 1634 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 6H, 2 CH_3), 2.56 (s, 4H, 2CH_2), 3.45 (s, 6H, 2 CH_2), 3.75 (s, 4H, 2 CH_2), 4.55 (s, 4H, 2 CH_2). 7.22-7.45 (m, 16H), 7.68-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.79, 52.14, 54.48, 55.12, 69.57, 117.36, 127.37, 127.66, 127.89, 128.52, 128.76, 131.08, 141.41, 151.64, 195.84; Mass: m/z 675 [MH^+]; *Anal. Calcd. for* $C_{40}H_{42}N_4O_2S_2$ (674.92): C, 71.18; H, 6.27; N, 8.30%. *Found*: C, 71.42; H, 6.22; N, 8.36%.

1,4-Bis (1-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl) butane 85e.



This compound was obtained as a white solid in 60% yield, mp149-159^{0}C; IR (KBr): 1562, 1639 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.40-1.50 (m, 4H, 2 CH_2), 1.90 (s, 6H, 2CH_3), 2.35-2.40 (m, 4H, 2 CH_2), 3.40 (s, 4H, 2 CH_2), 3.65 (s, 4H, 2 CH_2), 4.55 (s, 4H, 2CH_2), 7.25-7.41(m, 16H), 7.69-7.72 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.66, 25.21, 53.89, 54.32, 55.19, 69.46, 117.86, 127.69, 127.87, 128.51, 128.70, 131.05, 138.13, 141.42, 151.60, 195.96; Mass: m/z 703 [MH^+]; *Anal. Calcd. for* $C_{42}H_{46}N_4O_2S_2$ (702.97): C, 71.76; H, 6.60; N, 7.97%. *Found*: C, 72.02; H, 6.64; N, 8.04%.

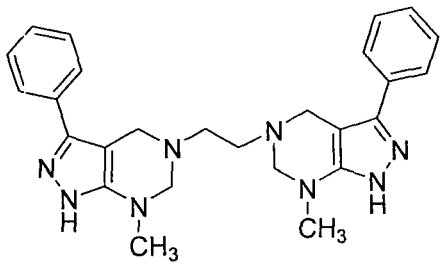
1,4-Bis (1-benzyl-5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidinyl) benzene 85f.



This compound was obtained as a white solid in 70% yield, mp 197-198^{0}C; IR (KBr): 1516, 1568, 1629 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 6H, 2 CH_3), 4.00 (s,

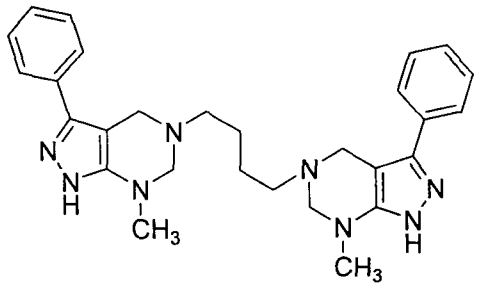
4H, $2CH_2$), 4.30 (s, 4H, 2 CH_2), 4.52 (s, 4H, 2 CH_2), 7.28-7.45 (m, 20H), 7.75-7.79 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.37, 50.49, 54.91, 67.00, 117.40, 126.94, 127.54, 127.97, 128.29, 128.59, 128.83, 131.37, 137.71, 140.92, 141.94, 152.63, 195.84; Mass: m/z 723 [MH^+]; *Anal. Calcd .for* $C_{44}H_{42}N_4O_2S_2$ (722.96): C, 73.10; H, 5.86; N, 7.75%. *Found*: C, 73.31; H, 5.90; N, 7.69%.

1,2-Bis (3- phenyl -7-methyl-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinyl) ethane 87a.



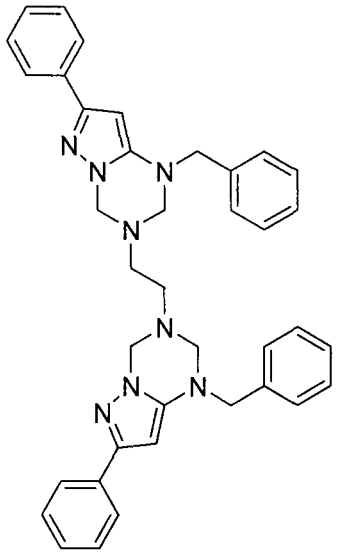
The compound was obtained as a white solid in 53% yield, mp 248-250^{0}C; IR (KBr): 1445, 3170 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50 (s, 2H, 2 CH_2), 2.73 (s, 6H, $2CH_3$), 3.75 (s, 4H, 2 CH_2), 3.90 (s, 4H, 2 CH_2), 7.25-7.65 (m, 10H), 12.05 (br m 2H, 2 NH, exchangeable with D_2O): ^{13}C NMR ($CDCl_3$): δ 36.79, 49.34, 52.11, 71.69, 98.65, 125.35, 126.40, 127.45, 128.81, 129.90; Mass: m/z 455 [MH^+]; *Anal .Calcd. for* $C_{26}H_{30}N_8$ (454.57): C, 68.70; H, 6.65; N, 24.65%. *Found*: C, 68.95; H, 6.70; N, 24.53%.

1,4-Bis (3- phenyl -7-methyl-4, 5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidinyl)butane 87b.



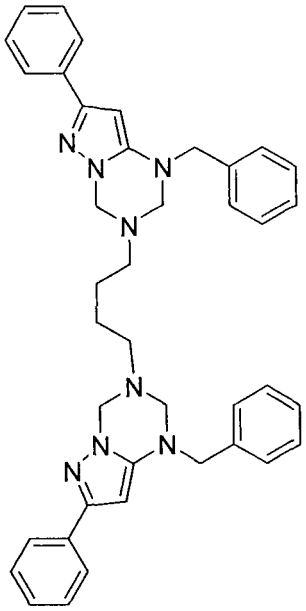
The compound was obtained as a white solid in 55% yield, mp 214-216^{0}C; IR (KBr): 1363, 3416 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41-1.55 (m, 4H, 2 CH_2), 2.41-2.55 (m, 4H, 2 CH_2), 2.73 (s, 6H, 2 CH_3), 3.65 (s, 4H, 2 CH_2), 3.85 (s, 4H, 2 CH_2), 7.25-7.55 (m, 10H), 12.00 (br m 2H, 2 NH, exchangeable with D_2O); Mass: m/z 483 [MH^+]; *Anal. Calcd. for* $C_{28}H_{34}N_8$ (482.62): C, 69.68; H, 7.10; N, 23.22%. Found: C, 69.42; H, 7.16; N, 23.33%.

1,2-Bis (1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl) ethane 88a.



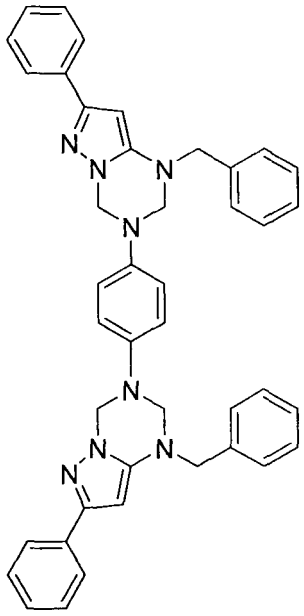
This compound was obtained as a white solid in 51% yield, mp 225-226^0 C; IR (KBr): 1399, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.90 (s, 4H, 2 CH_2), 3.98 (s, 4H, 2 CH_2), 4.25 (s, 4H, 2 CH_2), 4.99 (s, 4H, 2 CH_2), 5.72 (s, 2H, 2 C_8-H), 7.24-7.37 (m, 16H), 7.70-7.73 (m, 4H); Mass: m/z 607 [MH^+]; *Anal. Calcd. for* $C_{38}H_{38}N_8$ (606.76): C, 75.22; H, 6.31; N, 18.47%. Found: C, 75.48; H, 6.26; N, 18.56%.

1,4-Bis (1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl) butane 88b.



This compound was obtained as a white solid in 50% yield, mp 132-133^{0}C; IR (KBr): 1576, 1637 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.35-1.45 (m, 4H, 2 CH_2), 2.69-2.82 (m, 4H, 2 CH_2), 4.05 (s, 4H, 2 CH_2), 4.33 (s, 4H, 2 CH_2), 5.03 (s, 4H, 2 CH_2), 5.75 (s, 2H, 2 C_8-H), 7.23-7.45 (m, 16H), 7.70-7.80 (m, 4H); Mass: m/z 635 [MH^+]; *Anal. Calcd. for* $C_{40}H_{42}N_8$ (634.82): C, 75.68; H, 6.67; N, 17.65%. *Found*: C, 75.40; H, 6.73; N, 17.54%.

1,4-Bis (1-benzyl-7-phenyl-1,2,3,4-tetrahydropyrazolo[1,5-*a*]triazinyl) benzene 88c.



The compound was obtained as a white solid in 55% yield, mp154-156^{0}C; IR (KBr): 1454, 1515, 1576 cm $^{-1}$; ^{1}H NMR ($CDCl_3$): δ 4.59 (s, 4H, 2 CH_2), 4.83 (s, 4H, 2CH_2), 5.85 (s, 4H, 2 CH_2), 6.05 (s, 2H, 2 C_8-H), 7.45-7.80 (m, 21H), 8.09-8.12 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 53.93, 65.06, 65.67, 83.75, 120.59, 125.40, 127.55, 128.47, 128.64, 133.71, 136.45, 143.21, 148.49, 150.49; Mass: m/z 655 [MH^+]; *Anal. Calcd. for* $C_{42}H_{38}N_8$ (654.81): C, 77.04; H, 5.85; N, 17.11%. *Found*: C, 77.30; H, 5.80; N, 17.21%.

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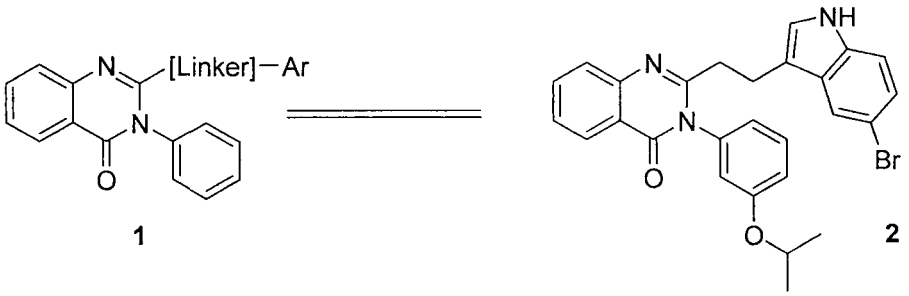
CHAPTER V

Synthesis of Fused Tetrahydropyrimidines (Hexahydroquinazolines) from cyclic Enaminones

Fused pyrimidines, generally known as quinazolines (and their derivatives) have attracted considerable attention because of their great practical importance and biological activities, due to which their chemistry is fundamentally interesting to heterocyclic chemists. Their derivatives are of considerable interest because of their pharmacological properties[1] such as protein tyrosine kinase inhibitor[2], cholecystokinin inhibitor etc.

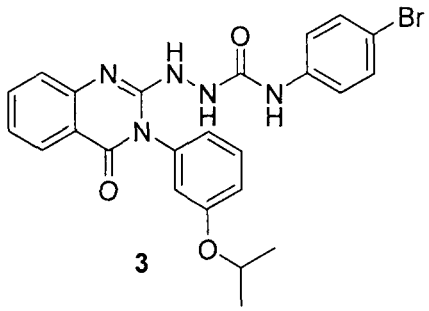
5.1 Preparation and properties of a few such molecules are described in the following sections.

5.1.1 Melvin J. Yu and coworkers have reported[3] that compound exemplified by 2-[2-(5-bromo-1*H*-indolyl-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3*H*)-quinazolinone (**2**) (**Scheme 1**) 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 disorders such as anxiety, pain and panic disorder.



Scheme 1

A series of analogues were prepared with methyl substituents on the ethylene bridge as well as congeners with different linkers (**1**). 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 was defined by an ethyl group (**2**).



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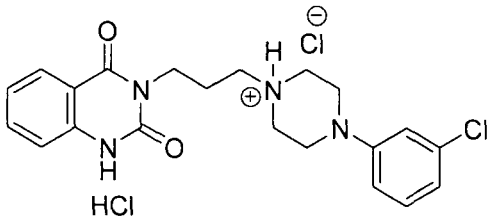
5.1.2 Further Janak K Padia and coworkers, found that introduction of -NH- as a linker (**3**) dramatically enhanced binding affinity and selectivity for CCK-B receptors[4]. Quinazolines are also known to possess antimicrobial[5], anticonvulsant[6], sedative and hypertensive activity. Shin Hayao and co-workers have synthesized a series of 3-(4-aryl-1-piperazinylalkyl)-2,4(1*H*, 3*H*)-quinazolinedione, which were subsequently tested, and they showed varying degrees of sedative and hypotensive activity.

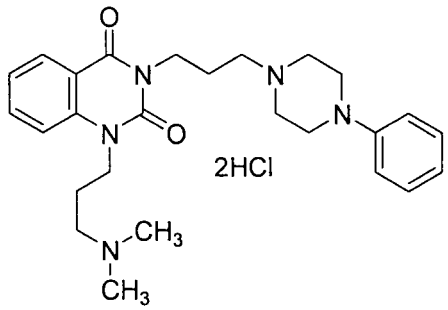


4

The above compound 3-[3-(4-*m*-chlorophenyl-1-piperazinyl) propyl]-2,4(1*H*,3*H*)-quinazolinedione (**4**) of the afore-mentioned series was found to be a potential

psychosedative and its activity in experimental animals was comparable to that of chlorpromazine[7].

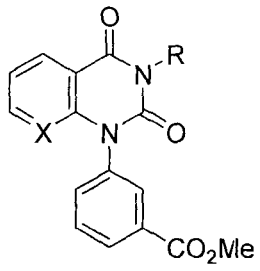
5.1.3 Herbert J Havera synthesized[8] a series of 1,3-disubstituted-2,4(1*H*, 3*H*)-quinazolinediones from 3-substituted 2,4(1*H*, 3*H*)-quinazolinediones by treatment with sodium hydride and the appropriate alkyl halide in xylene. These compounds showed varying degrees of vasodilation and antihypertensive activity without significant blockade of α-adrenergic receptors.



5

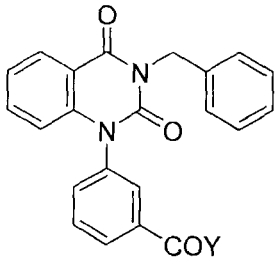
1-[3-(*N*,*N*-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1*H*,3*H*)-quinazolinedione (**5**) of the above series was found to be more potent than papaverine in inducing vasodilation and induced a prolonged decrease in systolic blood pressure of hypertensive rats upon oral administration.

5.1.4 There have also been reports of quinazoline showing antidepressant and anti-inflammatory activities. J. A. Lowe and coworkers studied[9] the structure-activity relationship of a series of quinazolinediones and azaquinazolinediones of the type **6** and **7**, which were found to possess potent inhibitory activity towards the calcium-independent phosphodiesterase enzyme (CaIPDE) thus proving to be useful in chronic diseases such as depression and inflammation



6

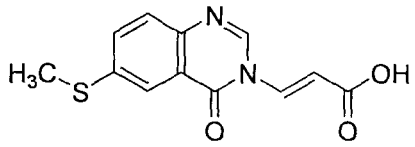
X= C,N
R=H,Et,CH_2Ph,CH_2cyclopentyl
CH_2norbornyl



7

Y= OH, NHMe

5.1.5 Quinazolines are also known to possess antiallergic activity. Ronald A. LeMahieu and coworkers prepared[10] a series of substituted (*E*)-3-(4-oxo-4*H*-quinazoline-3-yl)-2-propenoic acid and evaluated for passive cutaneous anaphylaxix (PCA) test in rats for antiallergic activity. Alkoxy, alkylthio and isopropyl substituents at the 6 or 8 positions provided highly potent compounds.

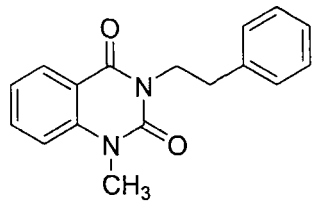


8

Of the above series that exhibited oral activity in the PCA test, (*E*)-3-[6-(methylthio)-4-oxo-4*H*-quinazoline-3-yl]-2-propenoic acid (**8**) 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.

5.1.6 More than 40 alkaloids comprising of a 4(3*H*) quinazoline moiety were isolated from natural sources. For example, D. L. Dreyer and coworkers have reported[11] the isolation of two simple natural alkaloids, 1-methyl-3-(2′-phenylethyl)-

1*H*,3*H*-quinazoline-2,4-dione (**9**) and 1-methyl-3-[2′-(4′-methoxyphenyl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione (**10**) from the seed husk of *Zanthoxylum arborescens*.



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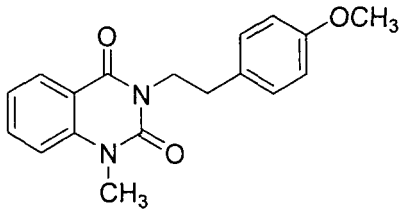

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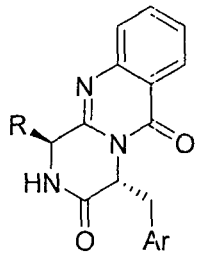
5.1.7 Atsushi Numata and coworkers have found[12] that a strain of *Aspergillus Fumigatus* isolated from the gastrointestinal tract of the saltwater fish *Pseudolabrus Japonicus*, produces the novel metabolites fumiquinazolines (general structure **11** and **12**) which exhibit moderate cytotoxicity against the cultured P-388 Lymphocytic Leukemia cells.

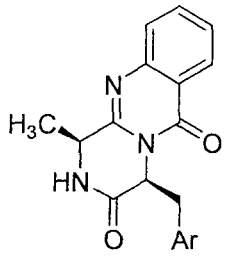
Later Numata and coworkers could isolate[13] seven fumiquinazolines from the same strain showing similar toxicity.



11

Fumiquinazoline F(R =CH_3)

Ar =3-indolyl



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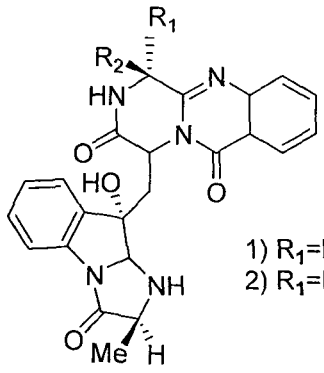
Fumiquinazoline G

For e.g

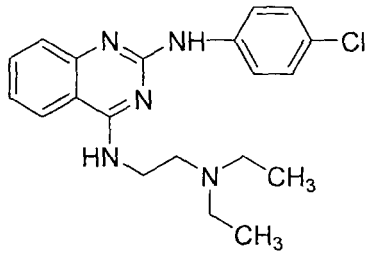


1) R_1=Me,R_2=H
2) R_1=H, R_2=Me

13

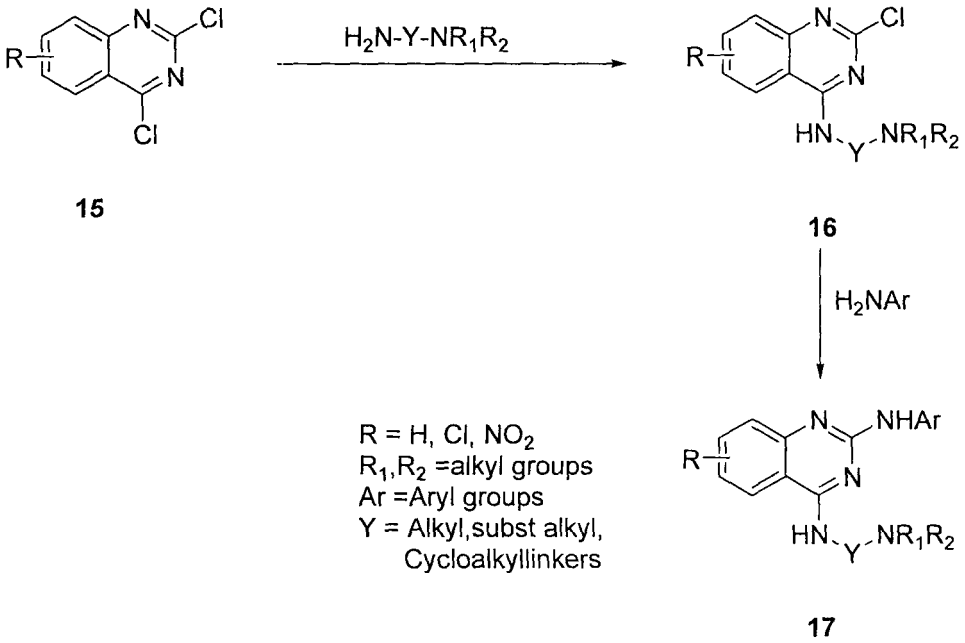
5.1.8 Quinazolines are also reported to possess antimalarial activity. F. H. S. Curd and coworkers while working on chlorguanide discovered[14] that certain N^4-[(dialkylamino) alkyl]-N^2-phenyl-2,4-quinazolinediamines possessed strong antimalarial effects against *plasmodium galencium* in chicks. Among them N^2-(4-chlorophenyl)-N^4-[2-(diethylamino) ethyl]-2,4-quinazolinediamine (**14**) was found to be most promising.

5.1.9 Edward F. Elsalger and coworkers synthesized[15] a series of N^2 (and N^4)-aryl-N^4(and N^2)-[(dialkylamino) alkyl]-2,4-quinazolinediamines. Condensation of



14

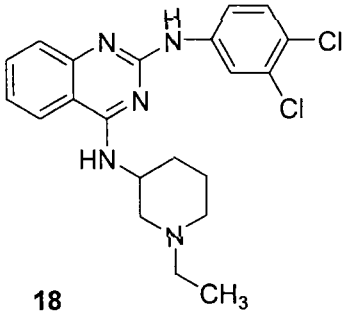
appropriate 2,4-dichloroquinazolines (**15**) (prepared by chlorination of corresponding 2,4-(1*H*, 2*H*)-quinazolinediones with $POCl_3$ or PCl_5) with the requisite *N*, *N*-dialkylalkylenediamine in appropriate solvents. (under this condition only the chlorine in position-4 is replaced) gave the corresponding 2-chloro-*N*-[(dialkylamino)alkyl]-4-quinazolinamines (**16**) 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 (**17**) (**Scheme 2**).



15 16 17

Scheme 2

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 (**18**) was selected for preclinical toxicity studies.



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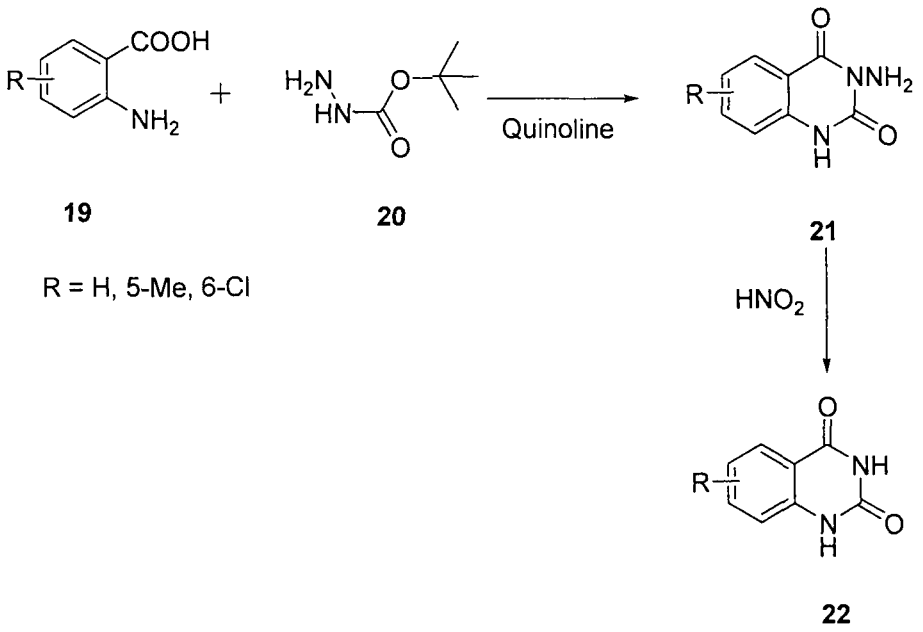
Unfortunately, the above compound and several of its derivatives were shown to be phototoxic and plans to study it in humans were abandoned. Quinazolines are also known to posses antifungicide and diuretic properties[16].

5.2 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 (**19**).

5.2.1 Iraj Lalezari and C.A. Stein have reported[17] a simple one step synthesis of 3-amino-2,4(*1H,3H*)-quinazolinediones and its derivatives (**21**) by the reaction of anthranilic acids (**19**) and t-butyl carbazates (**20**) in refluxing quinoline (**Scheme 3**). The compounds so formed were successfully deaminated by nitrous acid to afford the corresponding quinazolinediones (**22**).

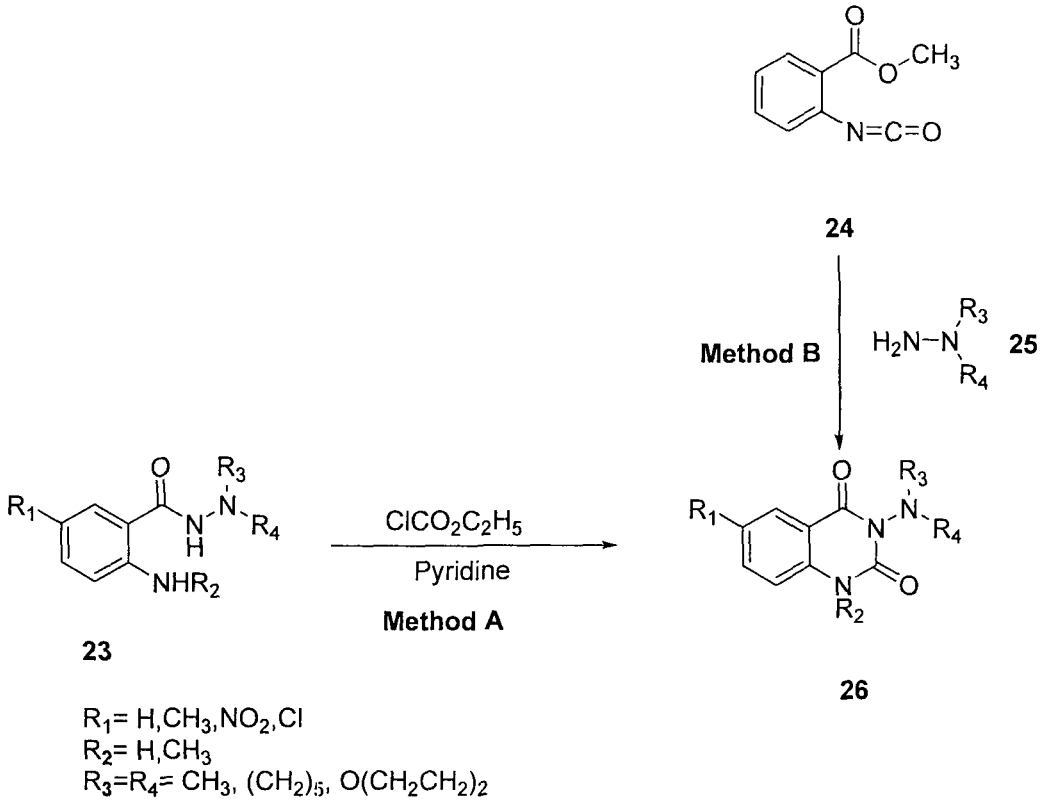


Scheme 3

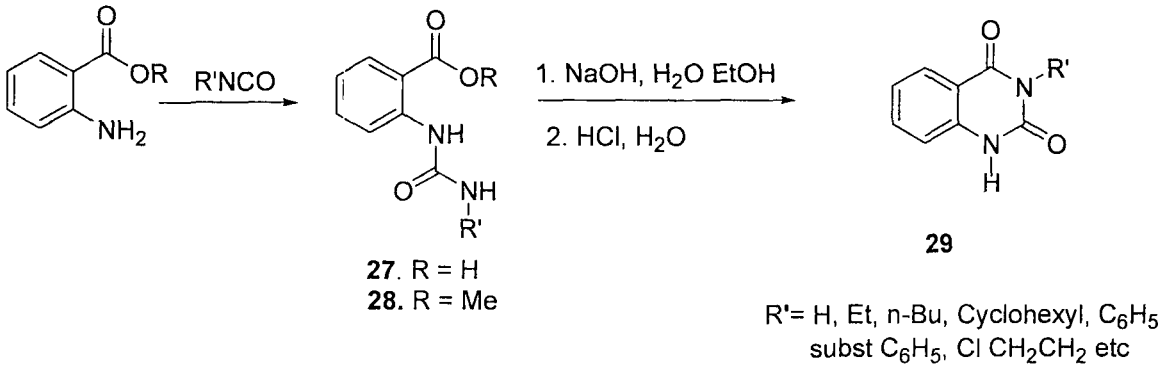
5.2.2 M. J. Kornet and co-workers have reported[18] the synthesis of a number of 3-amino-2,4(1*H*,3*H*)-quinazolinediones by two different methods depending on the availability of starting materials. In method A, *o*-aminobenzoylhydrazines (**23**) was reacted with ethylchloroformate in dry pyridine, which gave **26** in moderate yields. The intermediate **23** were obtained from the reaction of isatoic anhydride and hydrazines. In method **B**, compounds **26** (R_1=H) were synthesized from 2-methoxycarbonylphenyl isocyanate (**24**) and 1,1-disubstituted hydrazines (**25**) in toluene. Both methods were monitored by TLC and indicated the formation of uncharacterized intermediate which lead to the cyclized products (**Scheme 4**).

5.2.3a Papadopoulos reported[19] a simple room temperature treatment of 2-(3-arylureido) benzoic acid (**27**) and methyl 2-(3-alkyl, or 3-arylureido)-benzoates (**28**)

with aqueous-ethanolic sodium hydroxide to yield 3-substituted 2,4-(1*H*,3*H*)-quinazolinediones (**29**) (**Scheme 5**).



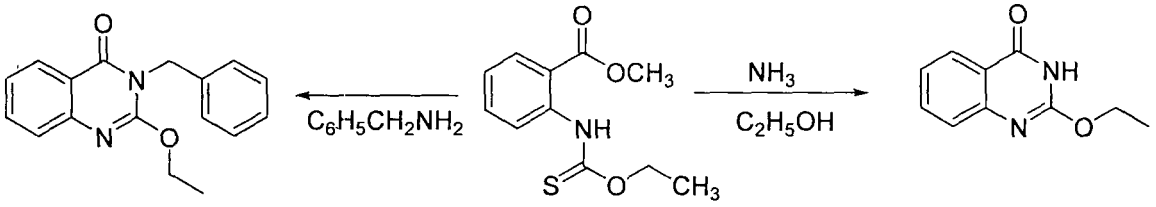
Scheme 4



Scheme 5

5.2.3b Papadopoulos later reported[20] the reaction of three derivatives of isothiocyanate. They were (1) Ethyl-*N*-(2-methoxycarbonylphenyl)thiocarbamate (**30**), (**Scheme 6**). (2) *N*-(2-ethoxycarbonylphenyl)-4-methoxythiobenzamide (**31**), (**Scheme 7**) and (3) 2-(4-methoxyphenyl)-4*H*-3,1-benzothiazin-4-one (**32**) (**Scheme 8**).These three compounds are expected to react with nucleophilic reagents containing a primary amino group at both carbonyl and thiocarbonyl to form 2,4-disubstituted-4(3*H*)-quinazolinones as shown below

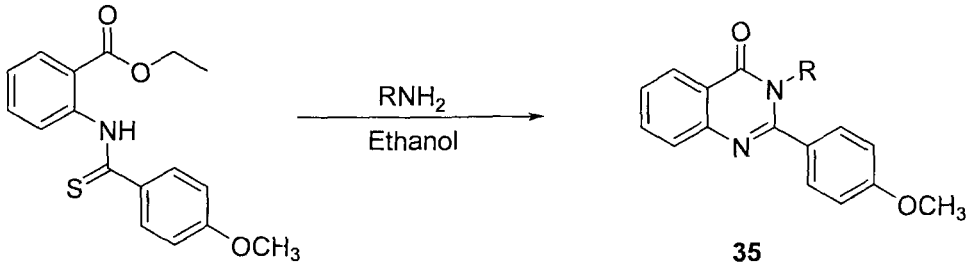
1)



33 **30** **34**

Scheme 6

Similarly 2)



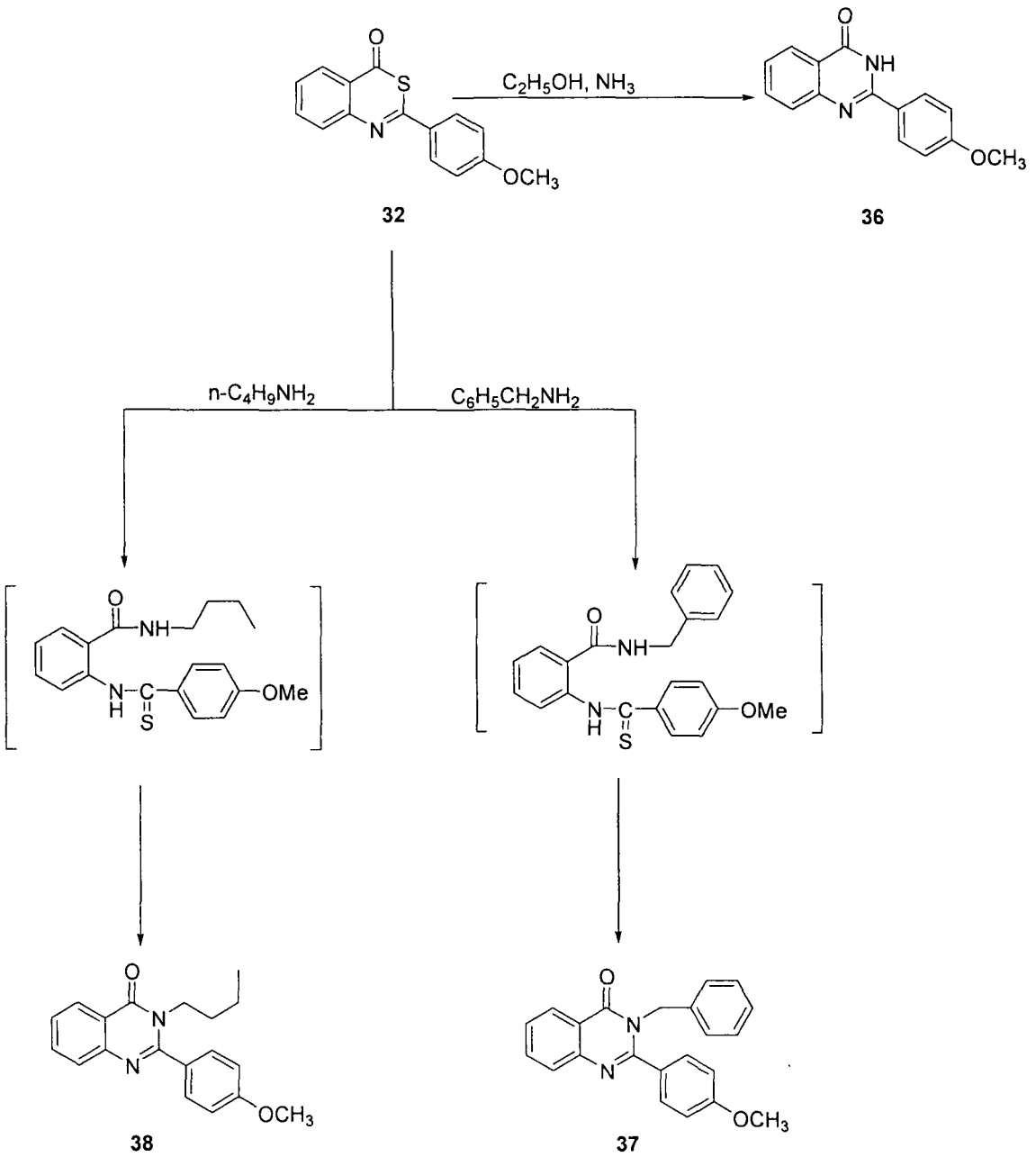
31 **35**

R = H, n-Bu, CH_2Ph, etc

Scheme 7

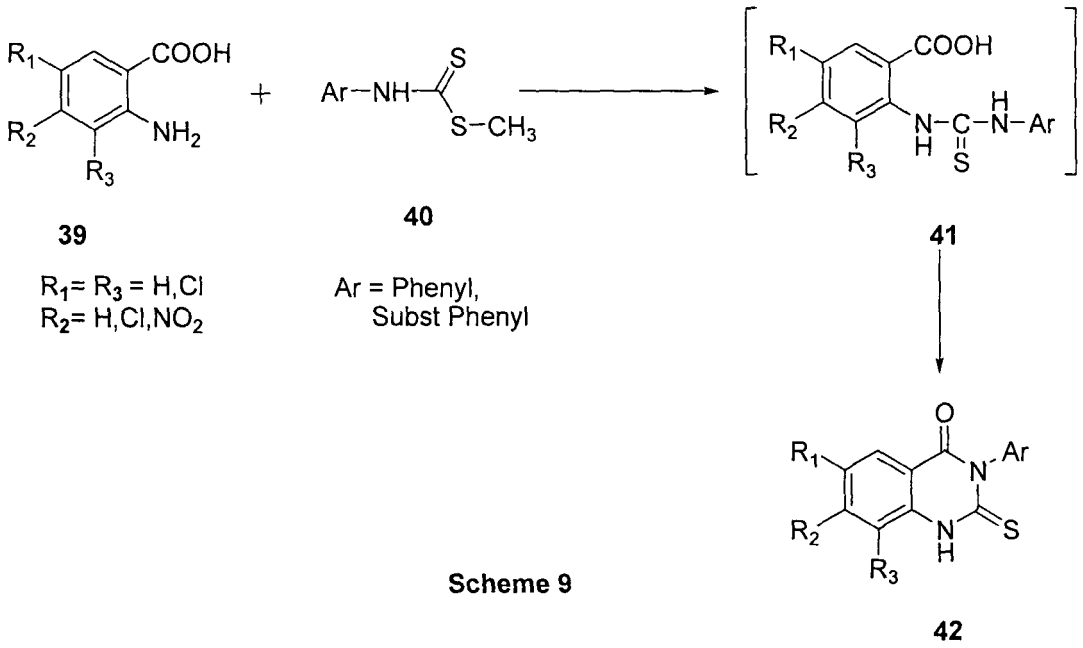
When benzothiozinone (**32**) was heated with ethanolic ammonia at 100^0C or refluxed with benzyl amine compound **36** and **37** were obtained. Similarly when it was heated with n-butylamine on a steam bath, compound **38** was obtained. The

formation of quinazolinones (**37** and **38**) by the following reactions very likely involves the intermediate formation of thioamides.



Scheme 8.

5.2.4 E. Melendez and coworkers have also reported[21] the synthesis of 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines (**42**) from *N*-aryldithiocarbamates (**40**) and anthranilic acid (**39**) by refluxing in DMF. The crude product was isolated by precipitation of the mixture in water (**Scheme 9**).



39

R_1= R_3 = H,Cl
R_2= H,Cl,NO_2

40

Ar = Phenyl,
Subst Phenyl

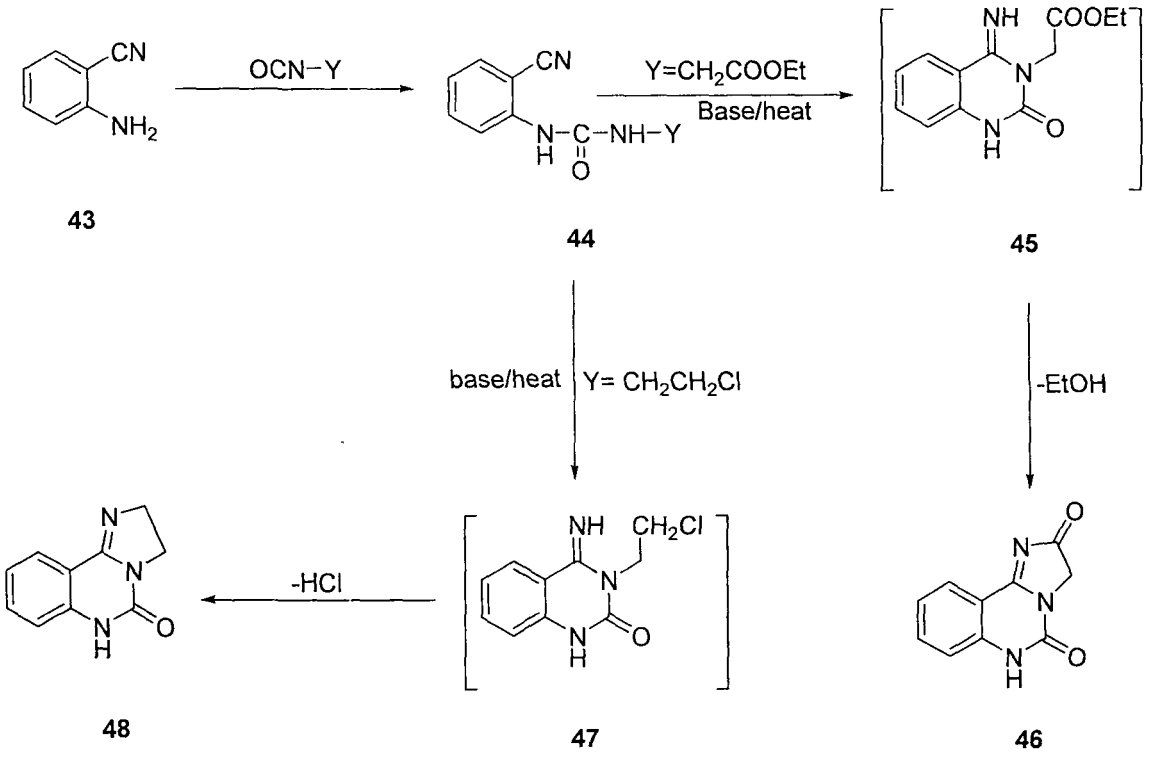
41

42

Scheme 9

5.2.3c Papadopoulos reported[22] a two step synthesis of 2,6-dihydroimidazo[1,2-*c*]-quinazoline-5-(3*H*)one (**48**) by the reaction of anthranilonitrile (**43**) with 2-chloroethyl isocyanate. This reaction proceeded by the formation of an intermediate 2-[3-(2-chloroethyl)ureido]-benzonitrile (**44**) 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 (**48**) (**Scheme 10**).

Later he further reported[23] the synthesis of imidazo[1,2-*c*]quinazoline-2,5-(3*H*,6*H*) dione (**46**) by the reaction of anthranilonitrile with ethylisocyanoacetate. The reaction proceeded in the similar manner via the formation of 2-(3-ethoxycarbonylmethylureido) benzonitrile (**44**), which undergo double cyclization to form imidazo compound **46** (**Scheme 10**).



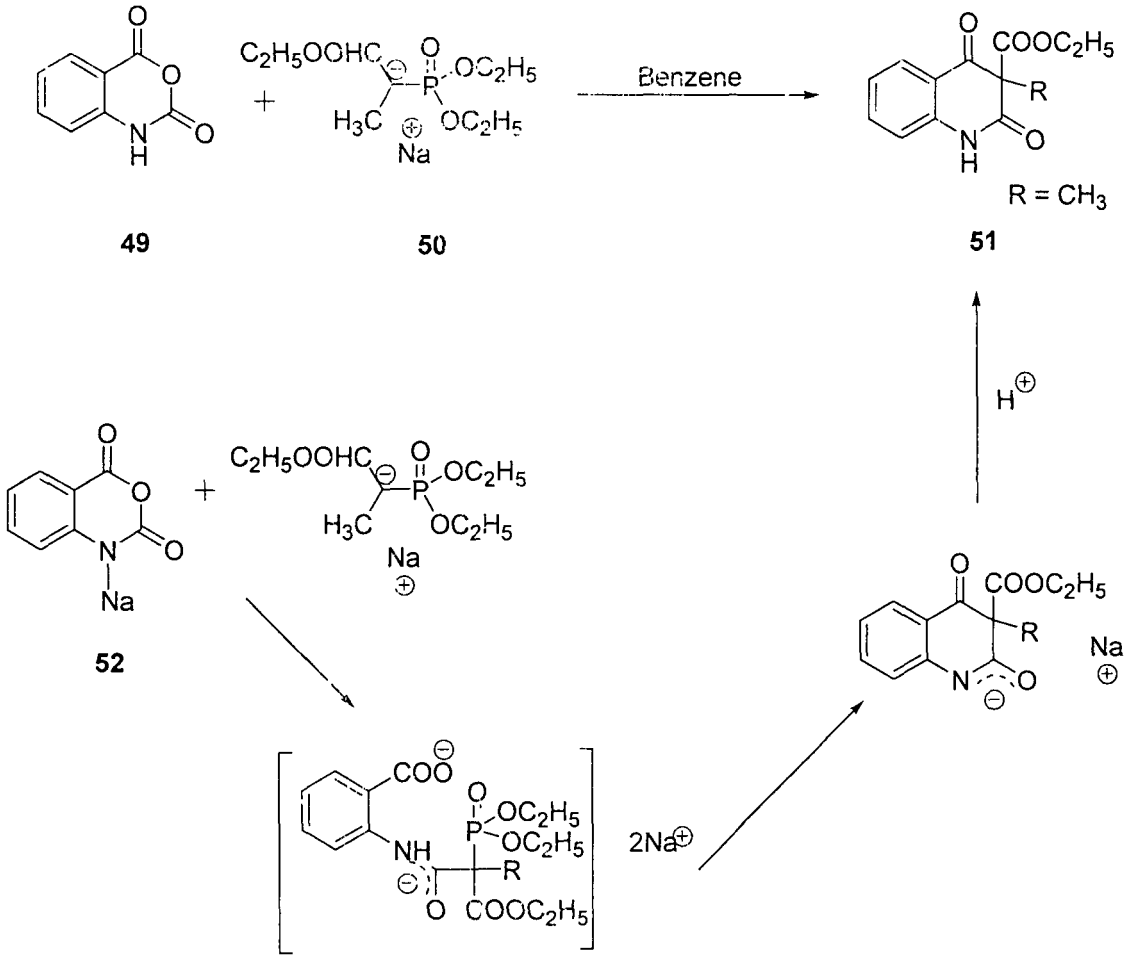
Scheme 10

5.2.5 Minami and coworkers reported[24] the synthesis of quinazolines from isatoic anhydride as per the scheme below (**Scheme 11**). The reaction of isatoic anhydride (**49**) with an ethyl-2-diethylphosphonopropanoate carbanion (**50**) in refluxing benzene gave 3-ethoxycarbonyl-3-methyl-2,4(1*H*,3*H*)-quinolinedione (**51**) in poor yield.

However similar treatment of *N*-sodioisatoic anhydride (**52**) (prepared in situ from **49** and sodium hydride) in a mixed solvent gave **51** in good yields [24].

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

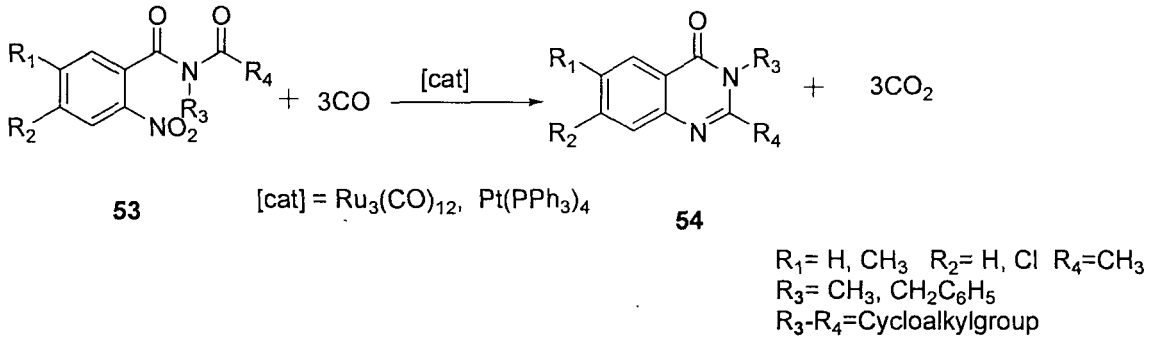
direct ortho substitution of *N*-(tert- butoxycarbonyl) aniline by a lithium reagent was also described.



Scheme 11

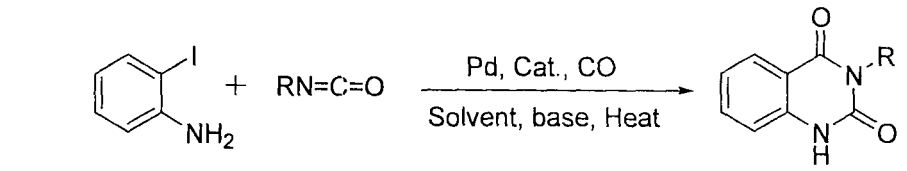
5.2.6 There are also reports of the use of transition metals in the preparation of these compounds. Akazone et al. reported[29] the first Ruthenium catalysed synthesis of 4(3*H*)-quinazoline derivatives (**54**) by the reductive N-Heterocyclization of *N*-(2-

nitro benzoyl)amides (**53**) under carbonmonoxide pressure (**Scheme 12**). 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[30].



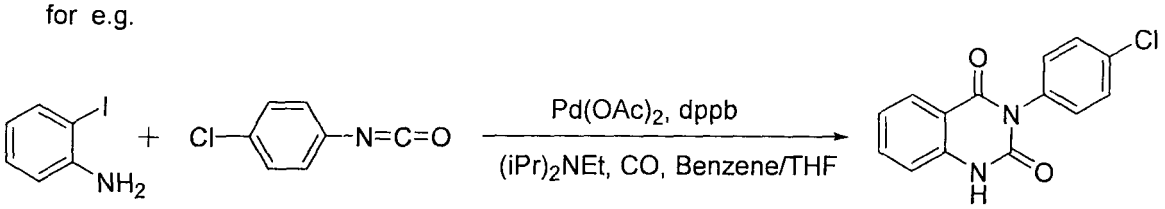
Scheme 12

5.2.7 Encouraged by the usefulness of 4(3*H*)-quinazoline derivatines, Larksarp and coworker examined[31] 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 (**55**) with heterocumulenes. They reported the synthesis of 4(3*H*)-quinazolinone derivatives (**58**) 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 (**Scheme 13**).



55 56

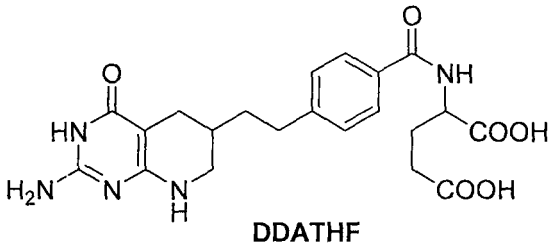
for e.g.



55 57 58

Scheme 13

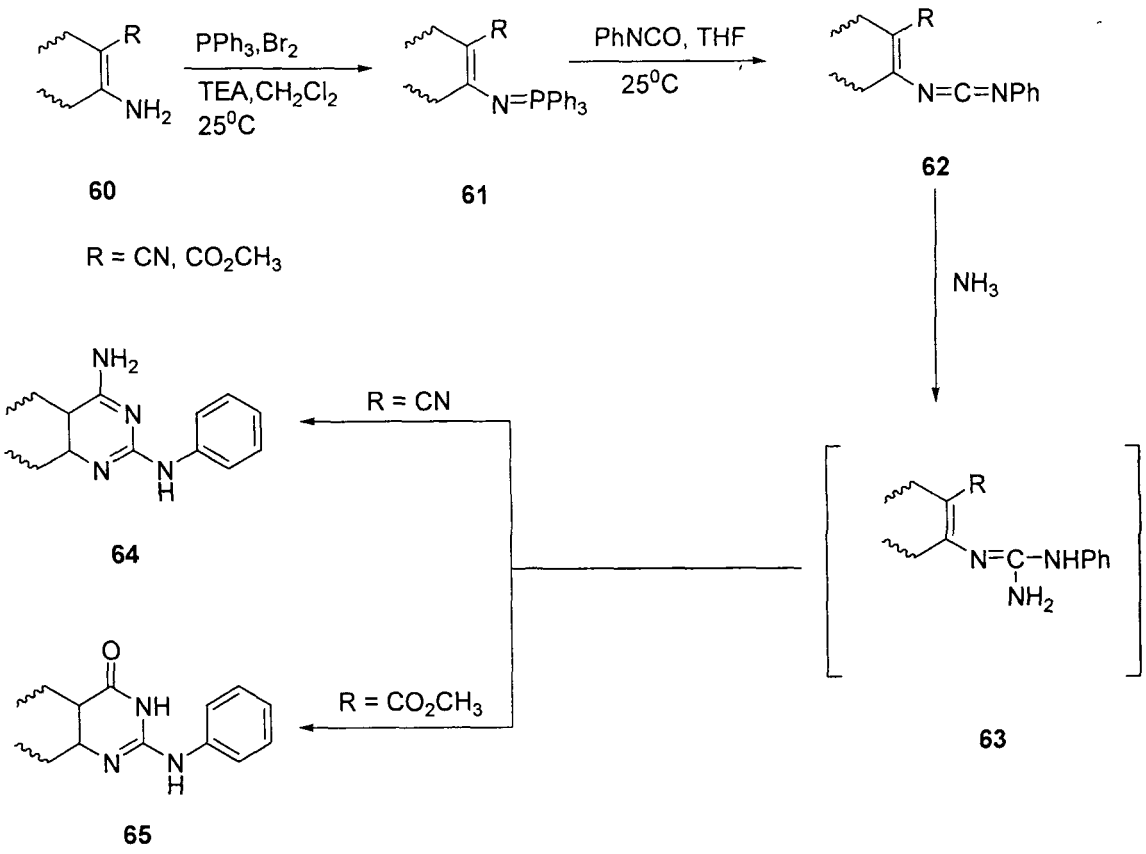
5.2.8 E.C. Taylor and coworkers while working[32] on the development of synthetic strategies for the preparation of 5,10-dideazatetrahydrofolic acid (**DDATHF, 59**) and its analogues, developed a facile pyrimidine annulation process, which took place under mild conditions and was found to be general for *o*-aminonitriles and *o*-aminoesters.



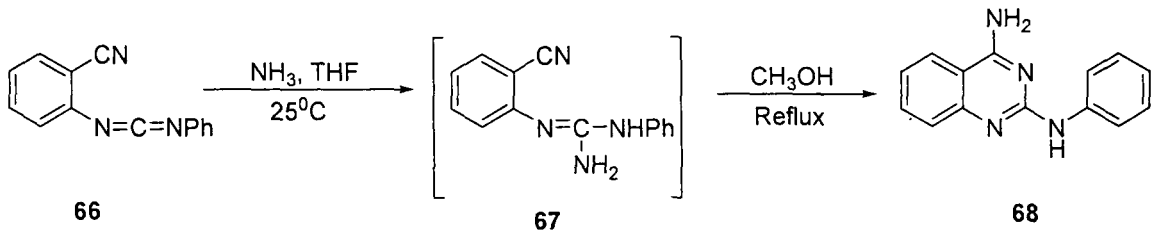
DDATHF

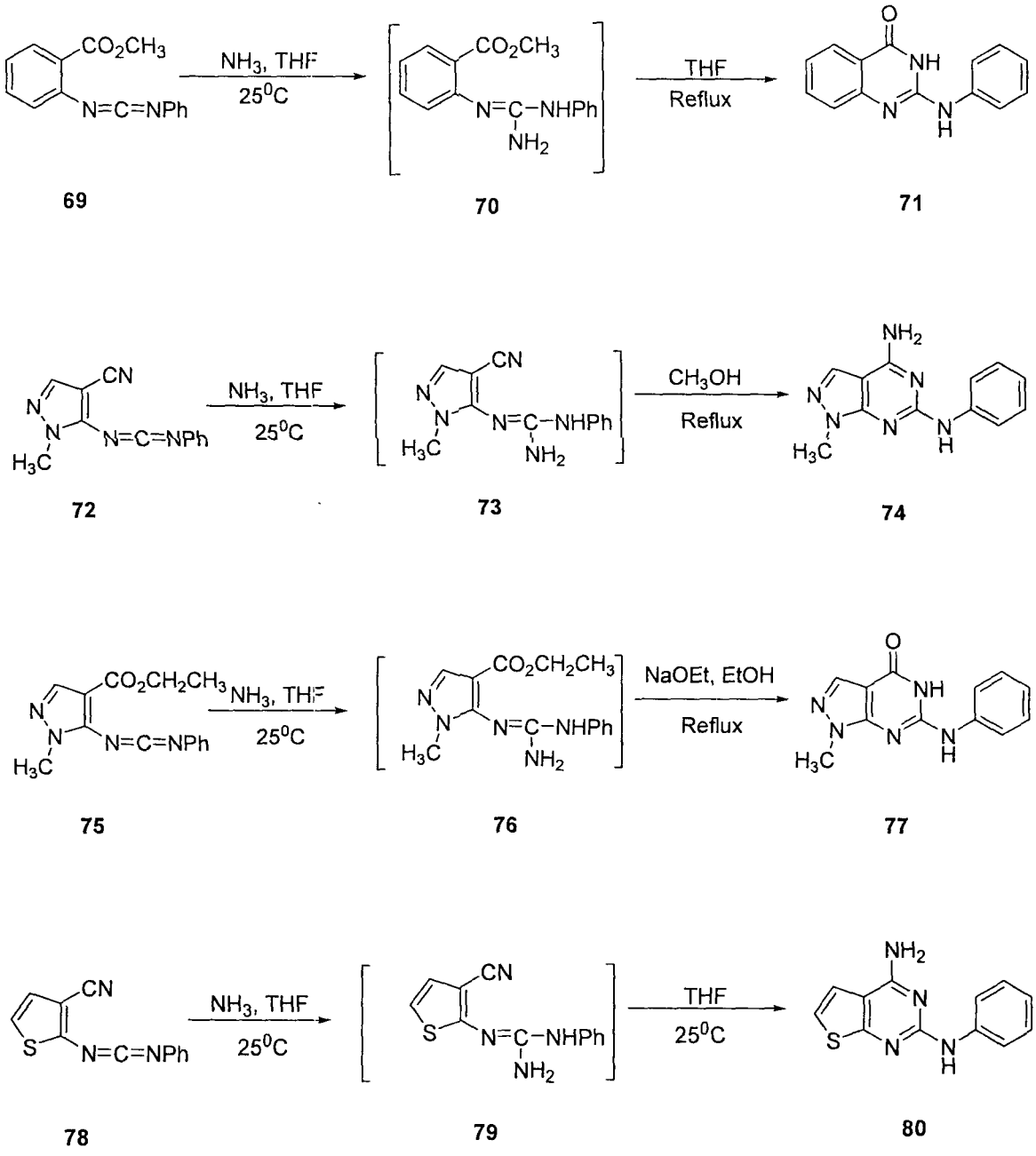
Treatment of *o*-aminoesters and *o*-aminonitriles **60** with dibromotriphenylphosphorane (generated *in situ* by slow addition of bromine to a cold solution of triphenyl phosphine in methylene chloride) resulted in the formation of the corresponding iminophosphoranes **61**. The iminophosphoranes undergo aza

Wittig reactions with isocyanates to give carbodiimides **62**. 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 (80^0C, 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. Addition of ammonia to the resulting highly reactive carbodiimides **62** generated guanidino-substituted intermediates **63**, which underwent intramolecular cyclization across the *ortho*-situated electrophilic nitrile or ester functionalities to give the fused pyrimidines **64** and **65** (**Scheme 14**) .in some cases heating was required for cyclization as shown in **Scheme 15**.


R
NH2
PPh3,Br2
TEA,CH2Cl2
25°C
N=PPh3
PhNCO, THF
25°C
N=C=NPh
60
61
62
R = CN, CO2CH3
NH3
NH2
N
N
H
R = CN
64
R
N=C-NHPh
NH2
63
O
NH
R = CO2CH3
65

Scheme 14


CN
N=C=NPh
NH3, THF
25°C
N=C-NHPh
NH2
CH3OH
Reflux
NH2
N
N
H
66
67
68

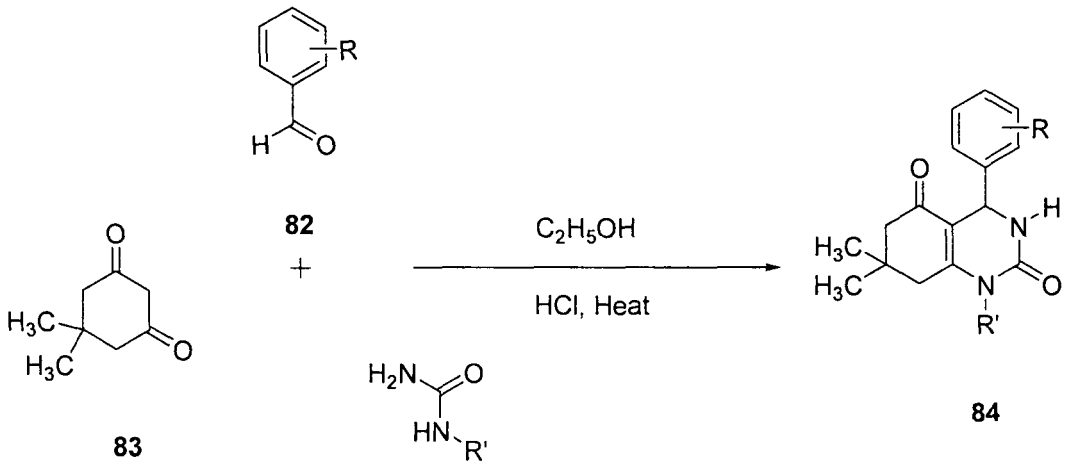


Scheme 15

5.2.9 In 2003 Selma Sarac and coworkers synthesized[33] a series of 4-aryl-7,7-dimethyl-1, 2,3,4,5,6,7,8-cctahydroquinazoline-2,5 diones (**84**) and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5 diones (**84**) according to the Biginelli

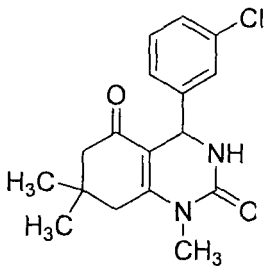
reaction. This involved one-pot condensation of urea **81** (or N-methyl urea), aromatic aldehyde **82** and 5,5-dimethyl-1,3-cyclohexanedione (**83**) under strongly acidic conditions (**Scheme 16**).

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. 4-(3-chlorophenyl)-1,7,7-trimethyl-3,4,7,8-tetrahydroquinazoline-2,5 (1*H*, 6*H*)-dione (**85**) and 4-(3-bromophenyl)-1,7,7-trimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1*H*,6*H*)-dione (**86**) (**Scheme 16a**) were found to be the most active derivatives on isolated rat ileum compared to standard nicardipine. On isolated aortic strip of lamb the calcium antagonist activity of compound **85** was found to be as high as that of nicardipine (which was used as reference).

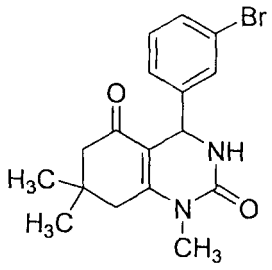


R : H, Cl, Br, CH_3, OCH_3
R' : H, CH_3

Scheme 16



85

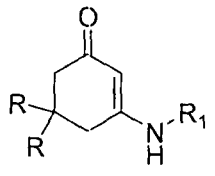


86

Scheme 16a

5.3 However, synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines[34] 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 we have recently reported a facile synthetic methodology for 1-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[35]. In continuation with our efforts on the synthesis of tetrahydropyrimidines [36-39] we 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 **87**.



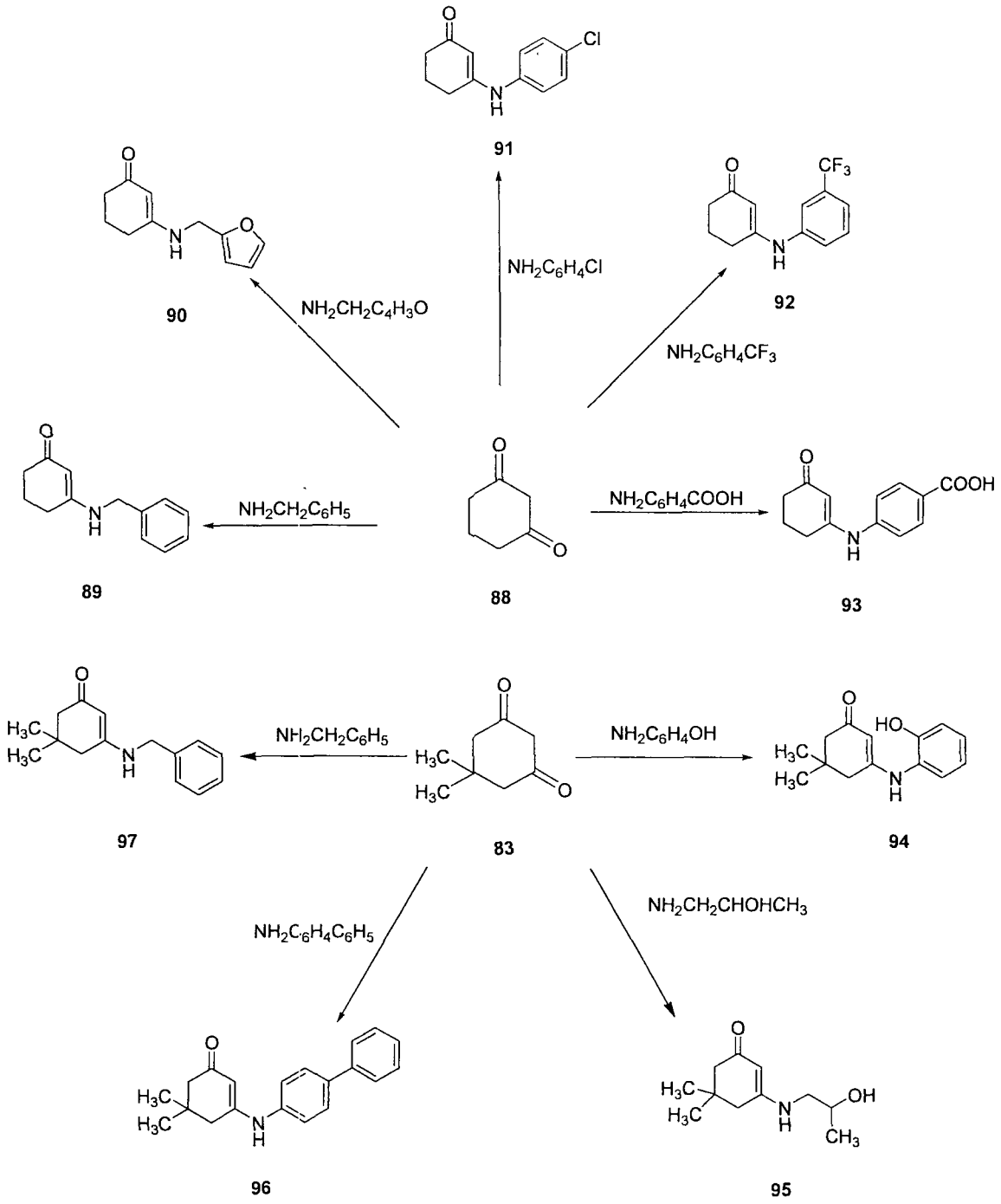
87

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

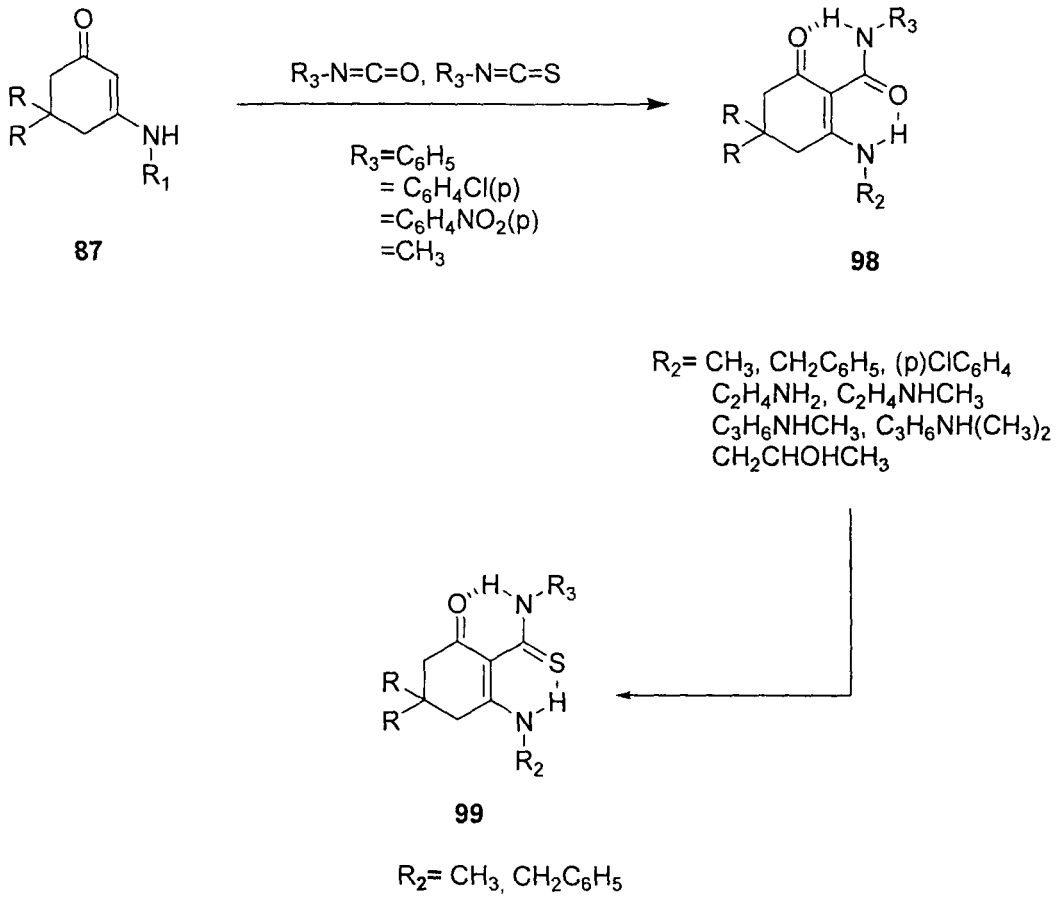
5.4 METHODS OF PREPARATION OF ENAMINONES

Literature survey at this stage revealed that Enaminones (**87**) have been prepared by many methods and have also been used as synthons for the synthesis of other heterocyclic compounds. A few of these methods and their uses are described in the following sections.

5.4.1 Ivo Jirkovsky reported the synthesis[40] of a series of *N*-substituted 3-amino-2-cyclohexen-1-ones and 3-amino-5,5-dimethyl-2-cyclohexen-1-ones (**89-97**) by the reaction of dimedone (**83**) or 1,3 cyclohexanedione (**88**) with various primary amines in dry benzene by azeotropic removal of water using Dean Stark apparatus (**Scheme 17**). The secondary amines prepared from cyclic dione (**Scheme 17**) reacted with phenyl isocyanates, phenylisothiocyanates and methylisothiocyanate under fusion condition to yield substituted 2-amino-6-oxo-*N*-phenyl-1-cyclohexene-1-carboxamide (**98**) and corresponding thiocarboxamides (**99**) (**Scheme 18**).

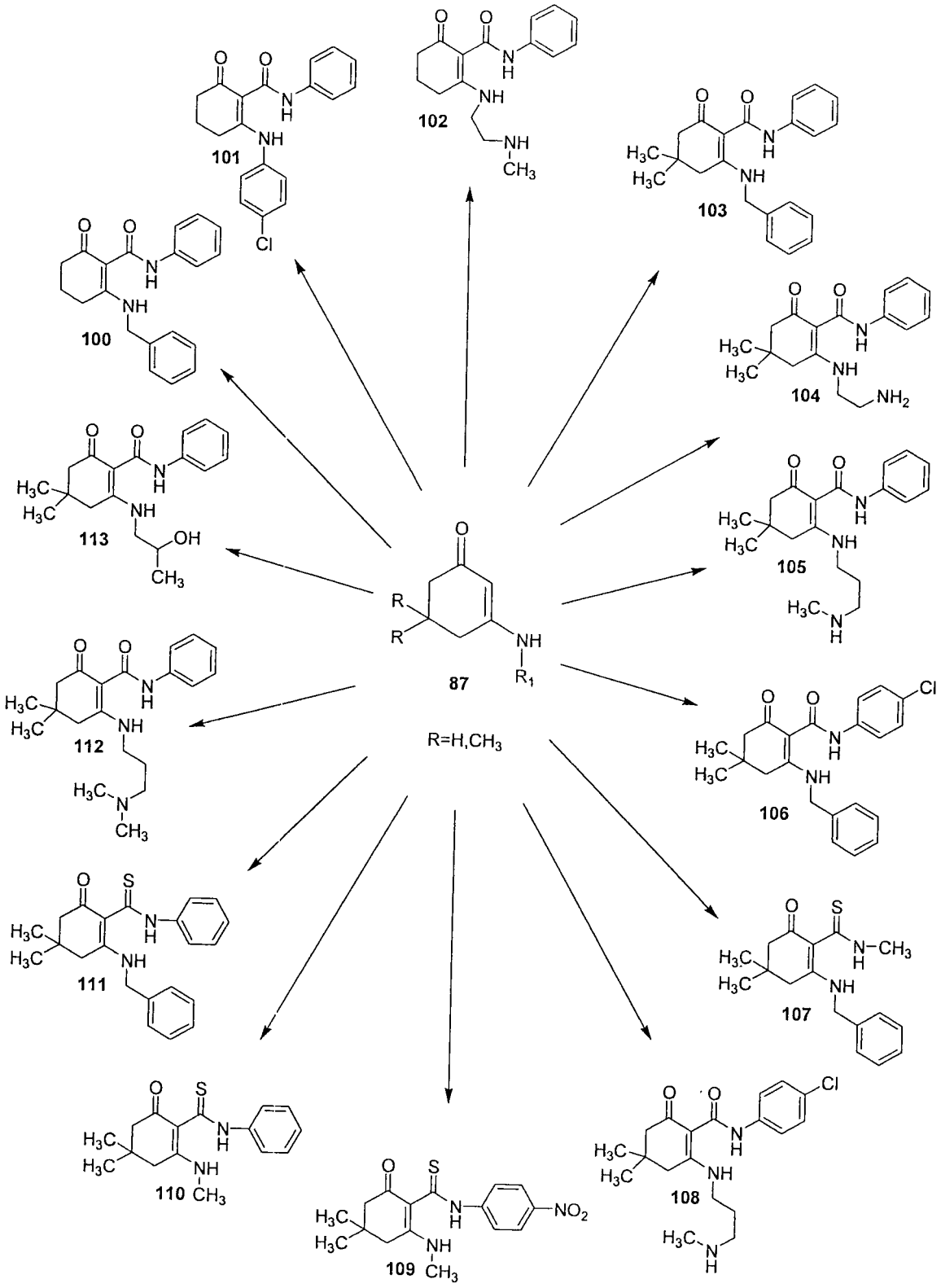

91
90
92
89
88
93
97
83
94
96
95
NH2C6H4Cl
NH2CH2C4H3O
NH2C6H4CF3
NH2CH2C6H5
NH2C6H4COOH
NH2C6H4OH
NH2C6H4C6H5
NH2CH2CHOHCH3

Scheme 17



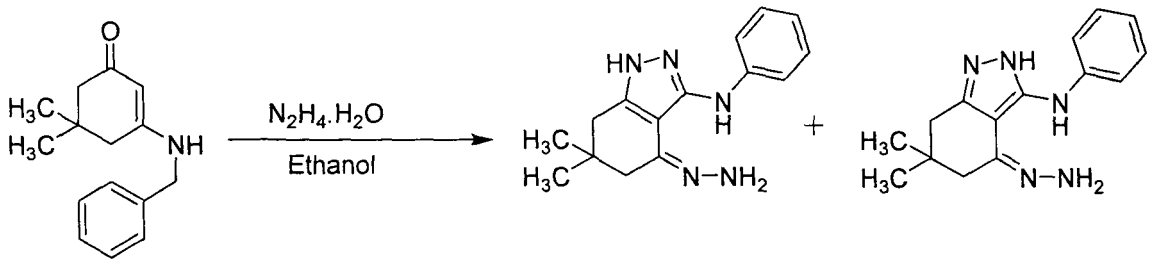
Scheme 18

A large number of compounds (**100-113**) have been prepared as shown in (**Scheme 18a**). 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 18a

Reaction of 3-benzylamino-5,5-dimethyl-2-cyclohexen-1-one (**97**) with hydrazine hydrate in boiling ethanol gave a yellowish crystalline compound, which could have the two possible structures **114** and **115** (**Scheme 19**).

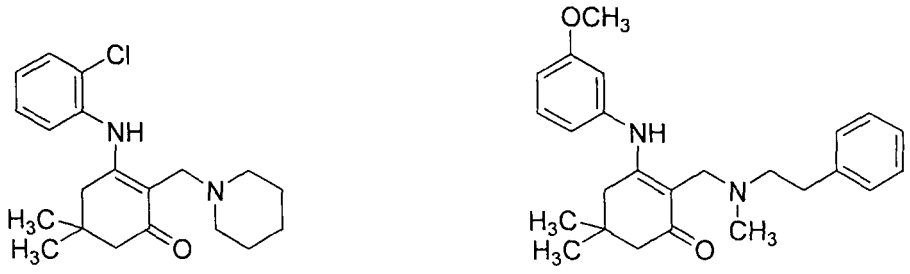


97 **114** **115**

Scheme 19

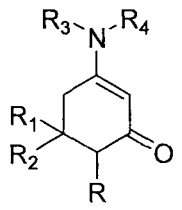
Of the above two structures, **114** with one endocyclic double bond in the six-membered ring is favoured by the strain theory.

5.4.2 Kase and coworkers reported[41] that (5,5-dimethyl-3-[(*o*-chlorophenyl)amino]-2-(*N*-piperidinylmethyl)-cyclohex-2-en-1-one (**116**) and (5,5-dimethyl-3-[(*m*-methoxyphenyl)amino]-2-(*N*-methyl-*N*-phenethylaminomethyl)-cyclohex-2-en-1-one (**117**) possessed analgesic, papaverine-like and anticonvulsant actions.



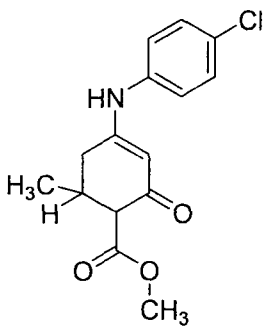
116 **117**

5.4.3 K. R. Scott and his group have reported[42,43] the synthesis of a new series of novel enaminones having a general formula **118**, 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 analogues was methyl 4-[(*p*-chlorophenyl) amino]-6-methyl-2-oxo-cyclohex-3-en-1-oate (**119**).



118

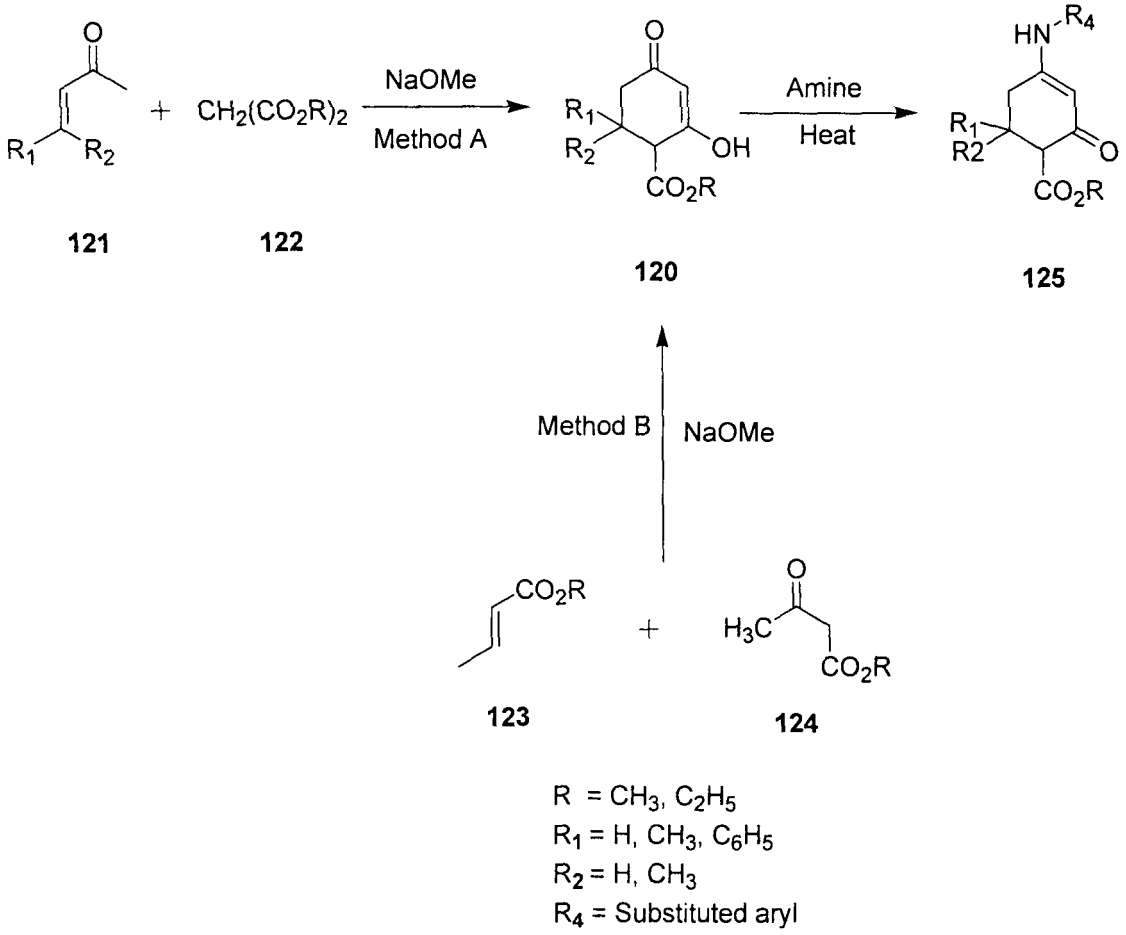
R = H, Ester or Amide
R_1 , R_2 = H or CH_3
R_3 = H
R_4 =aryl, subst aryl, ether,alkyl etc



119

The cyclic enaminone esters **119** were synthesised from β-hydroxy keto esters **120**, 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 **123** and acetoacetate **124** (method **B**) (**Scheme 20**). The β-hydroxy keto esters (**120**) were refluxed with 1 equivalent of the appropriate amino compound, under various conditions to provide the desired product **125**. 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).



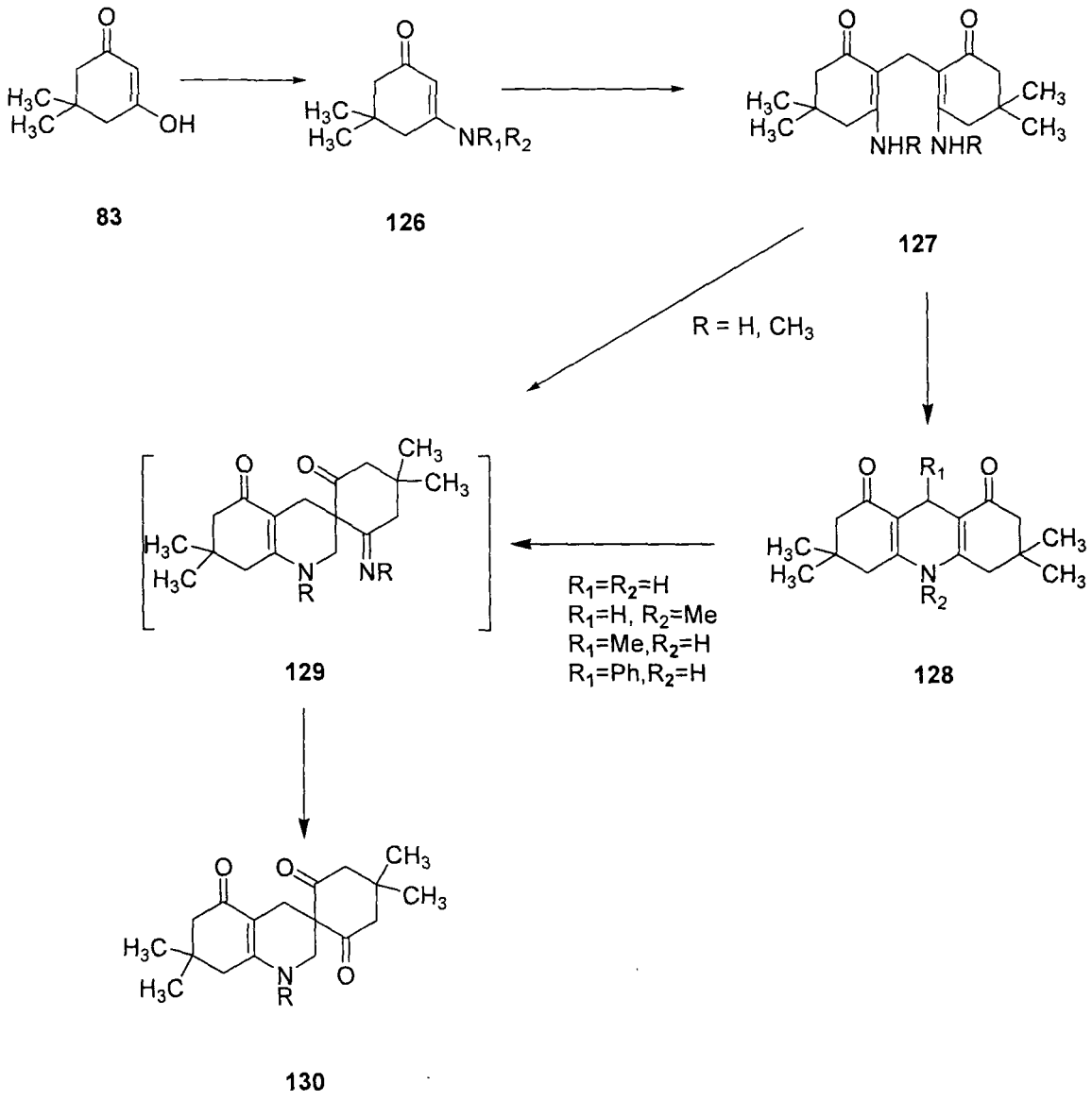
121 122 120 125

123 124

Scheme 20

5.4.4 J. V. Greenhill and co-workers have prepared[44,45] enaminones (**126**) from dimedone (**83**) by reacting it with ammonia or methylamine (**Scheme 21**). Under suitable, mild conditions the enaminones **126** reacted with formaldehyde to give the respective methylene bisenaminone derivative **127**. 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 **128**.



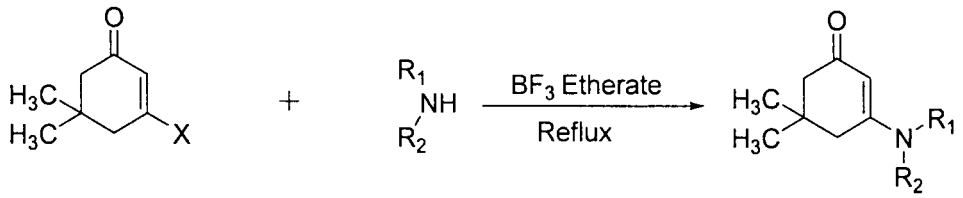
Scheme 21

Treatment of the enaminones or the methylene bisenaminones with aqueous formaldehyde in dilute hydrochloric acid at room temperature gave good yields of unexpected spiro compound (**130**). The spiro compounds might reasonably arise

from an internal mannich reaction of the methylenebisenaminones to give the unstable structures (**129**), which would readily hydrolyse to the diketones (**130**).

5.4.5 Marcel Azarro and coworkers have also synthesized[46] 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 **132** (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 whereby the expected product **133** was obtained in good yield. The use of Lewis acid brought in three advantages, for example 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 (**131b**) (**Scheme 22**).



131 **132** **133**

a X= OH
b X= OCH_3, OC_2H_5
c X= Cl,Br

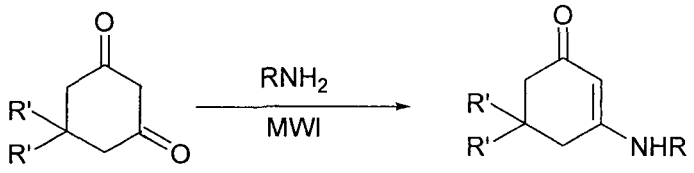
R_1,R_2 = H, alkyl, aryl

Scheme 22

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) especially in case of low boiling amines, toxic solvents (like benzene) and dry conditions (azeotropic removal of water).

5.4.6 The growing interest in microwave-assisted reactions[47-50] prompted us to take up the synthesis of enaminones **(87)** by the condensation of 1,3-diketones **(83,88)** with appropriate primary amines under microwave irradiation and the results of our investigation are reported herein (**Scheme 23**).



83,88 **87e-h**

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

Scheme 23

5.5 Results and Discussions

Thus, when a mixture of 1,3-cyclohexanedione (**88**) and aniline (1:1) was irradiated in a domestic microwave oven for 2 min, work-up of the reaction mixture yielded the desired condensation product **87a** in 93% yield (**Table I**), which was characterized as 3- anilinocyclohex-2-en-1-one on the basis of analytical and spectral data. Condensation of 4-chloroaniline and benzyl amine with cyclohexanedione proceeded in a similar manner and the corresponding enaminones **87b** and **87d** were obtained in 88 and 98% yields, respectively. Synthesis of **87c** involved treatment of the ketone with two equivalents of methylamine (40% aqueous solution).

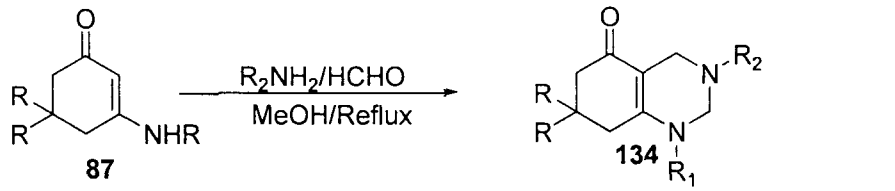
Condensation of dimedone with primary amines could be achieved under similar conditions giving **87e-h** in 93-98% overall yields. The reaction of dimedone with methylamine went to completion when a mixture (1:3) of the two was subjected to microwave irradiation.

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

These enaminones **87** were further used as synthons for the construction of fused tetrahydropyrimidine (quinazoline) rings as shown in **Scheme 24**.

Table I—Synthesis of cyclic enaminones

Compd	R	R_1	Yield (%)	Time (sec)/ Power (watt)	M.p.°C (lit. m.p.) (solvent of cryst.)
87a	H	C_6H_5	93	60/300	173-74 (176-78[51]) (MeOH)
87b	H	4-ClC_6H_4	88	270/180	190-91 (190-91.5[43]) (Hexane-EtOAc)
87c	H	Me	83	15/100	68-69(67-67.5[52]) (Hexane-Benzene)
87d	H	$C_6H_5CH_2$	98	60/300	125-26 (125-27[43]) (EtOAc)
87e	Me	C_6H_5	94	90/300	183-84(181-83[42]) (Hexane-Benzene)
87f	Me	4-ClC_6H_4	93	780/300	206-08(208-10[43]) (EtOAc)
87g	Me	Me	98	270/180	152-53(153-54[46]) (Hexane-EtOAc)
87h	Me	$C_6H_5CH_2$	98	120/300	131-32(130-31[40]) (Hexane-EtOAc)

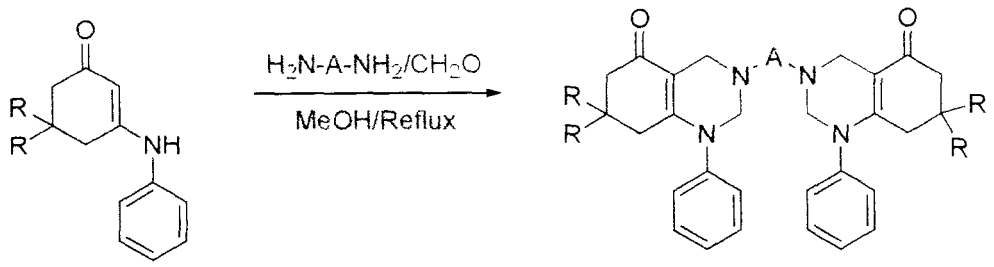


R= H,Me R_1= C_6H_5,$C_6H_5CH_2$ R_2= C_6H_5, $C_6H_5CH_2$, CH_3

Scheme 24

Thus when enaminones **87** 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 (**134**).

Our literature survey revealed that bis-heterocyclic compounds are a relatively new and important in the field of research for finding new biologically active molecules. Recent reports have revealed that bis heterocyclic compounds possess pesticidal properties[53-55] and also antibacterial[56], antimalarial, antiproliferative and antitumor activities[57]. Envisaging that the presence of two-quinazoline ring in the same molecule connected by flexible aliphatic chain or rigid aromatic chain could enhance the activity of the parent molecule, these enaminones were reacted with formaldehyde and various diamines and the result of which are discussed herein (**Scheme 25**).



87

135

R = H, CH_3

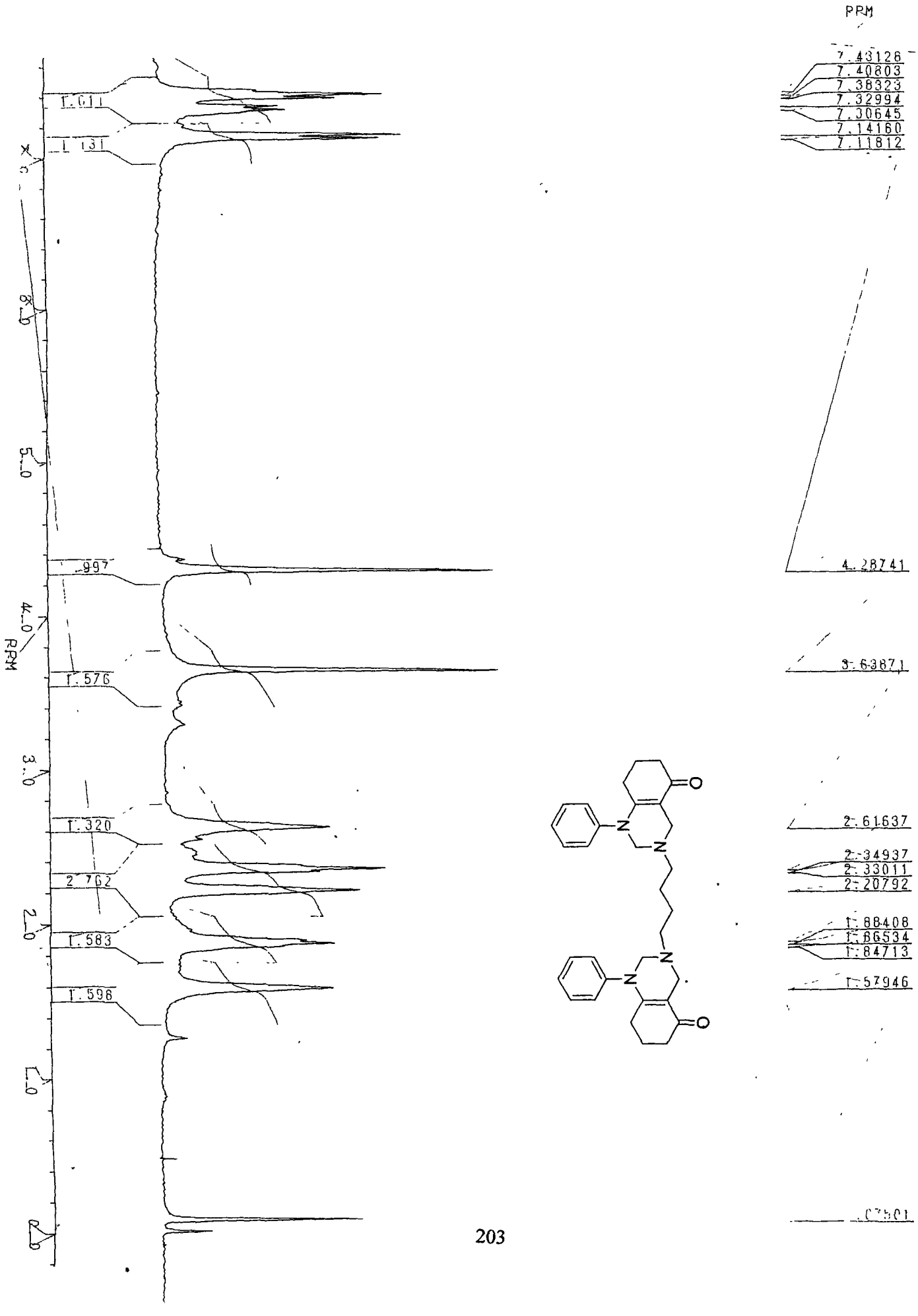
A = -(CH_2)n- -C_6H_5-
n = 2,3,4

Scheme 25

5.6 Results and Discussions.

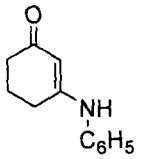
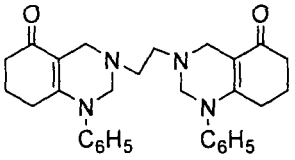
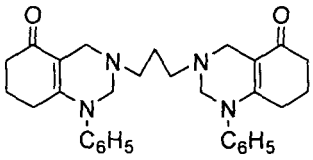
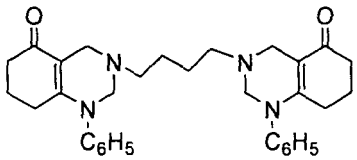
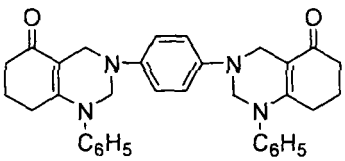
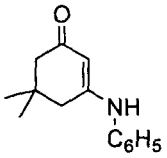
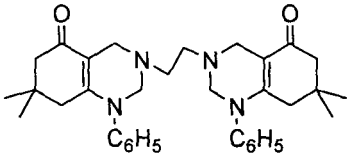
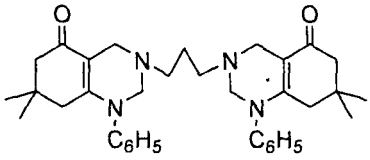
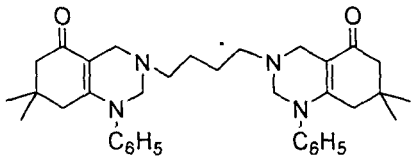
Thus, when a mixture of 3-anilinocyclohex-2-en-1-one (**87a**) (**Scheme 25**), ethylenediamine and formaldehyde (2:1:4) in methanol was refluxed, work-up of the reaction mixture followed by chromatographic purification yielded a solid in 58% yields, which was characterized as 3,3'-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one (**135a**). The reaction was found to be general with other diamines and with corresponding **87a-b** to give the respective **135b-h** in 58-88% overall yields. The structures of the bis-quinazolines were assigned on the basis of spectral and analytical data. Thus, the infrared spectra of **135a-k** showed strong peaks in the range of 1427 to 1619 cm^{-1} due to highly delocalised double bonds and carbonyl group stretching frequencies of enaminone functionalities. In the ^1H NMR spectra of **135a** & **135e** the NCH_2 protons of ethylene chain appeared as singlets at 2.83 ppm and 2.93 ppm respectively whereas the NCH_2 protons of propylene chain in **135b** & **135f** gave triplets in the range of 2.60-2.72 ppm. The protons at C_2 of propylene chain gave multiplets in the range of 1.59-1.88 ppm. Likewise in **135c** & **135g** the protons at C_1 & C_2 of butylene chains gave multiplets in the range of 2.56-2.90 and 1.46-1.88 ppm respectively. The protons at C_2 and C_4 of quinazoline ring resonated in the range of 4.24-4.99 and 3.64-4.56 ppm respectively. In **135a-d** the C_8 protons of the parent ring appeared as triplets between 2.10 & 2.30 ppm but in **135e-**

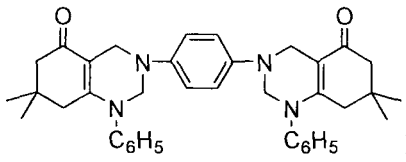
h they appeared as singlets between 1.99 & 2.10 ppm. The C_6 protons of the parent ring in **135a-d** appeared as triplets between 2.31 & 2.60 ppm but in **135e-h** they appeared as singlets between 2.13 & 2.26 ppm. The C_7 protons of the ring in **135a-d** resonated giving multiplets in the range of 1.58-2.06 ppm. The two-methyl protons at C_7 in **135e-h** gave singlets between 0.90 & 1.03 ppm. The aromatic protons resonated in their usual range of 6.91-7.93 ppm. A plausible mechanism for the formation of **2** from the cyclic enaminones **1** is worked out (**Scheme 26**). The ^1H NMR and ^{13}C NMR Spectra of 3,3'-(butane-1,4-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135c.are shown in pages 203-204.

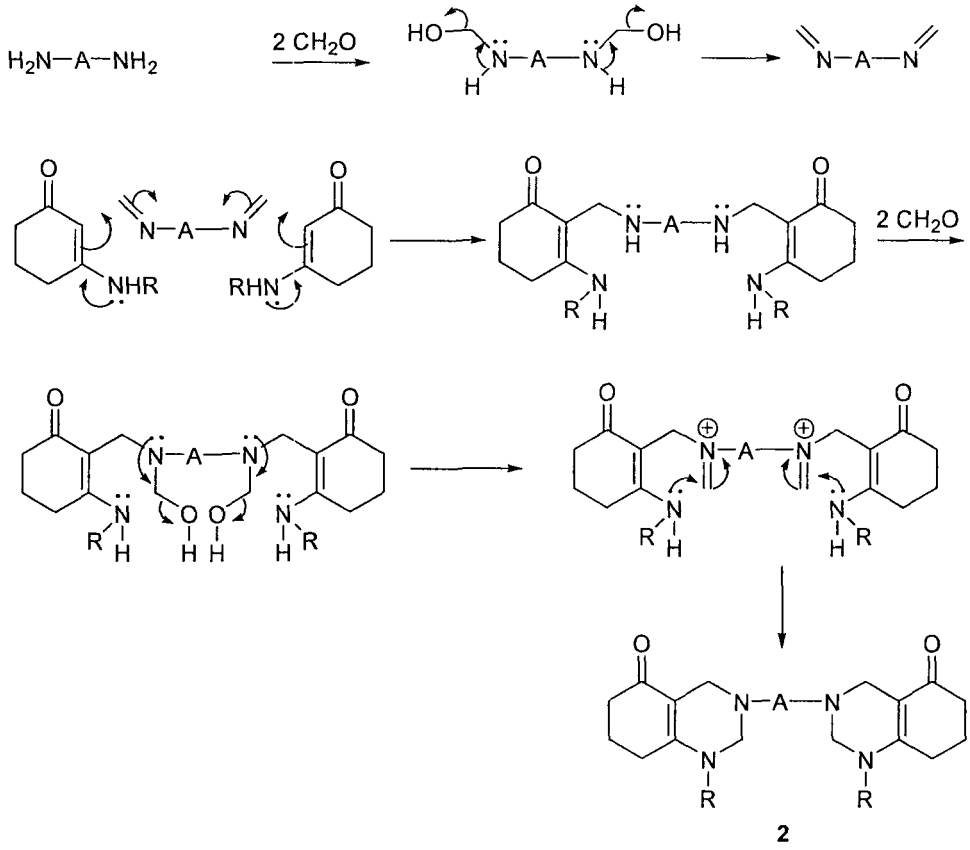

PRM
7.43126
7.40803
7.38323
7.32994
7.30645
7.14160
7.11812
4.28741
3.63871
2.61637
2.34937
2.33011
2.20792
1.88408
1.86534
1.84713
1.57946
1.611
1.131
.997
1.576
1.320
2.762
1.583
1.596
8.0
5.0
4.0
3.0
2.0
1.0
0.0
RPM

PPM
195.030
156.481
14.046
129.641
127.528
104.756
77.007
77.267
76.654
52.517
52.524
47.506
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
PPM

Table. Synthesis of Bisquinazolinones 135a-h

Entry	Enaminones 1	Conditions	Bisquinazolinones 2
1	 **87a**	H_2N-$(CH_2)_2$-NH_2, CH_2O, MeOH/Reflux, 27 h	 **135a**
2	**87a**	H_2N-$(CH_2)_3$-NH_2, CH_2O, MeOH/Reflux, 22 h	 **135b**
3	**87a**	H_2N-$(CH_2)_4$-NH_2, CH_2O, MeOH/Reflux, 24h	 **135c**
4	**87a**	H_2N-C_6H_4-NH_2, CH_2O, MeOH/Reflux, 24 h	 **135d**
5	 **87b**	H_2N-$(CH_2)_2$-NH_2, CH_2O, MeOH/Reflux, 22 h	 **135e**
6	**87b**	H_2N-$(CH_2)_3$-NH_2, CH_2O, MeOH/Reflux, 23 h	 **135f**
7	**87b**	H_2N-$(CH_2)_4$-NH_2, CH_2O, MeOH/Reflux, 8 h	 **135g**

8 **87b** H_2N-C_6H_4-NH_2, CH_2O, MeOH/Reflux, 20 h  **135h**



Scheme 26

5.7 Conclusions.

In conclusion, we have synthesized a series of hitherto unknown bisfused tetrahydropyrimidines (1,2,3,4,7,8-hexahydroquinazolines-5-(6*H*)-ones) in good

yields, from their respective cyclic-enaminones wherein we have succeeded in connecting two-quinazoline moiety via flexible aliphatic and rigid aromatic chain.

5.8 Experimental Section.

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 (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 fashion 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. Enaminones **87a** and **87b** were synthesized by our reported procedure [58].

5.9 General Procedure.

5.9.1 *Synthesis of cyclic enaminones (87a-h).*

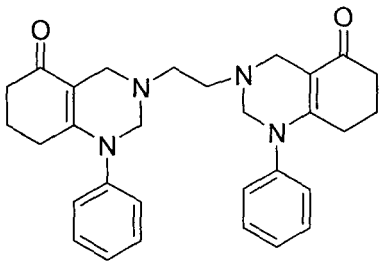
A mixture of 1,3-diketone (1 mmole) and primary amine (1 mmole) in a 10 ml conical flask placed in a beaker, was irradiated in a domestic microwave oven. After the completion of the reaction (monitored by TLC), water formed during the reaction was distilled under reduced pressure to give a solid mass, which was triturated with hexane, filtered and then recrystallized from appropriate solvent to give the enaminones **87a-h** (**Table I**). For **87c**, 2 mmoles of methylamine and for **87g**, 3 mmoles of methylamine (40% aqueous solution) were used. The products were identified by IR and NMR spectroscopy and also by comparing their melting points with those of the authentic products.

5.9.2 *Synthesis of bis-quinazolines (135a-h).*

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% solution) in 1.5 ml methanol was stirred at room temperature for 5 minutes. To this was added a solution of enaminones **87** (1 mmol) in 5-6 ml methanol and the resulting mixture was refluxed for specified period of time (table). After the completion of the reaction (monitored by TLC), methanol was removed under reduced pressure to give a gum, which on trituration with hexane and subsequent recrystallization in appropriate solvent gave compounds **135a**, **135e**, **135g** and **135h.** In case of compounds **135b, 135c, 135d** and **135f** the gum was chromatographed using neutral alumina and ethylacetate (eluant).

5.10 Individual description of the compounds.

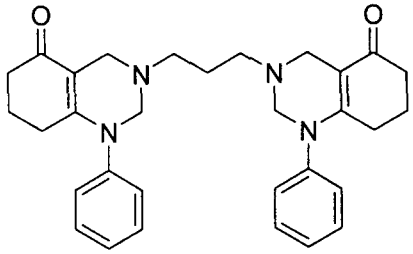
3,3′-(Ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135a.



This compound was obtained as a pale yellow solid in 58% yield; mp 182-184 ^{0}C (EtOAc); IR (KBr): 1493, 1566 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.70 (m, 4H, 2 CH_2), 2.12-2.28 (t, 4H, 2 CH_2), 2.31-2.60 (t, 4H, 2 CH_2), 2.83 (s, 4H, 2 CH_2), 3.73 (s, 4H, 2 CH_2), 4.43 (s, 4H, 2 CH_2), 7.07-7.87 (m, 10H); MS: m/z, 483 [MH^+]; *Anal. Calcd.*

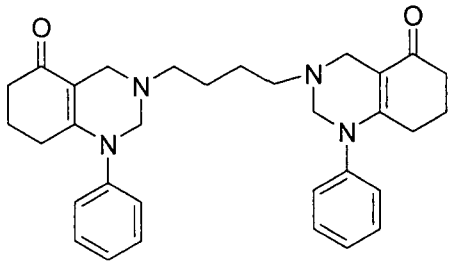
for $C_{30}H_{34}N_4O_2$ (482.27): C, 74.66; H, 7.10; N, 11.61%. *Found*: C, 74.41; H, 7.07; N, 11.66%.

3,3′-(Propane-1,3-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135b.



This compound was obtained as yellow gum in 70% yield; IR (CCl_4): 1493, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.84-1.85 (m, 4H, 2 CH_2), 1.86-1.88 (m, 2H), 2.18-2.20 (t, 4H, 2 CH_2), 2.32-2.36 (t, 4H, 2 CH_2), 2.67-2.72 (t, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.30 (s, 4H, 2 CH_2), 7.11-7.13 (m, 4H), 7.27-7.43 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 22.10, 26.07, 27.72, 36.55, 47.96, 50.95, 71.98, 104.83, 127.36, 127.50, 129.84, 143.02, 158.36, 194.94; MS: m/z, 497 [MH^+]; *Anal. Calcd. for* $C_{31}H_{36}N_4O_2$ (496.28): C, 74.97; H, 7.31; N, 11.28%. *Found*: C, 74.66; H, 7.33; N, 11.24%.

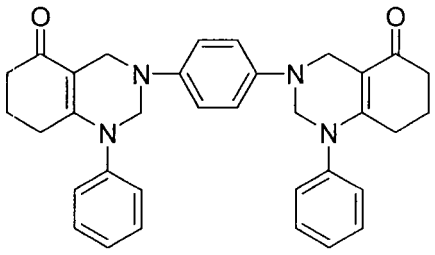
3,3′-(Butane-1,4-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135c.



This compound was obtained as yellow gum in 65% yield; IR (CCl_4): 1493, 1560 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58 (m, 4H, 2 CH_2), 1.85-1.88 (m, 4H, 2 CH_2), 2.21 (t, 4H, 2 CH_2), 2.33 (t, 4H, 2 CH_2), 2.62 (t, 4H, 2 CH_2), 3.64 (s, 4H, 2 CH_2), 4.29 (s, 4H, 2 CH_2), 7.12-7.14 (m, 5H), 7.30-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 22.08, 25.59, 27.71, 30.51, 47.59, 52.59, 72.19, 104.76, 124.61, 127.37, 129.31, 143,05, 158.48, 195.03; MS: m/z. 511 [MH^+]; *Anal. Calcd. for* $C_{32}H_{38}N_4O_2$ (510.29): C, 75.26; H, 7.50; N, 10.97%. *Found*: C, 75.50; H, 7.48; N, 10.92%.

3,3′-(1,4-Phenylene)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one

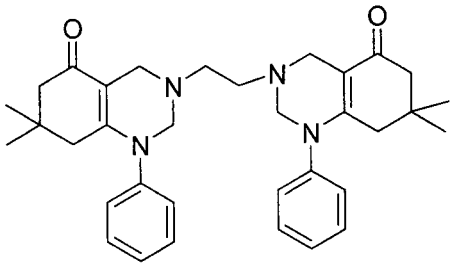
135d.



This compound was obtained as yellow solid in 71% yield; mp 191-193 ^0C; IR (KBr): 1427, 1507, 1566 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.70-2.06 (m, 4H, 2 CH_2), 2.10-2.30 (t, 4H, 2 CH_2), 2.33-2.60 (t, 4H, 2 CH_2), 4.56 (s, 4H, 2 CH_2), 4.99 (s, 4H, 2

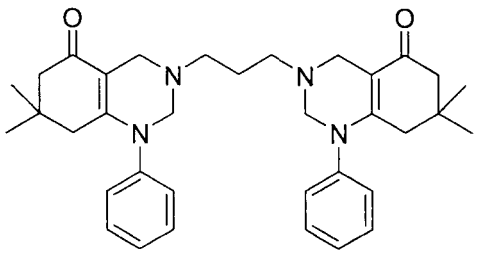
CH_2), 6.96-7.93 (m, 14H); MS: m/z, 531 [MH^+]; *Anal. Calcd. for* $C_{34}H_{34}N_4O_2$ · (530.27): C, 76.95; H, 6.46; N, 10.56%. *Found*: C, 76.70; H, 6.45; N, 10.51%.

3,3′-(Ethane-1,2-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135e.



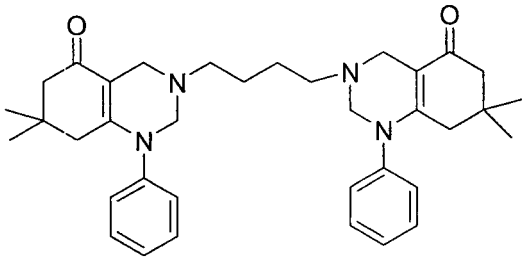
This compound was obtained as yellow solid in 88% yield; mp 193-194 ^{0}C ($CHCl_3$/Hexane); IR (KBr): 1493, 1566, 1619 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 12H, 4 CH_3), 2.10 (s, 4H, 2 CH_2), 2.23 (s, 4H, 2 CH_2), 2.93 (s, 4H, 2 CH_2), 3.80 (s, 4H, 2 CH_2), 4.50 (s, 4H, 2 CH_2), 7.03-7.76 (m, 10H); MS: m/z, 539 [MH^+]; *Anal. Calcd. for* $C_{34}H_{42}N_4O_2$ (538.33): C, 75.80; H, 7.86; N, 10.40%. *Found*: C, 76.05; H, 7.88; N, 10.44%.

3,3′-(Propane-1,3-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135f.



This compound was obtained as yellow gum in 68% yield; IR (CCl_4): 1427, 1493, 1566, cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.90 (s, 12H, 4 CH_3), 1.59-1.61 (m, 2H), 1.99 (s, 4H, 2 CH_2), 2.13 (s, 4H, 2 CH_2), 2.60-2.65 (m, 4H, 2 CH_2) 3.58 (s, 4H, 2 CH_2), 4.24 (s, 4H, 2 CH_2), 7.01-7.08 (m, 4H), 7.25-7.41 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 24.92, 27.28, 27.36, 31.64, 39.99, 46.40, 48.65, 48.96, 49.46, 70.92, 102.15, 126.38, 127.89, 129.39, 141.78, 155.62, 193.42; *Anal. Calcd. for* $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.15%. *Found*: C, 76.31; H, 7.98; N, 10.11%.

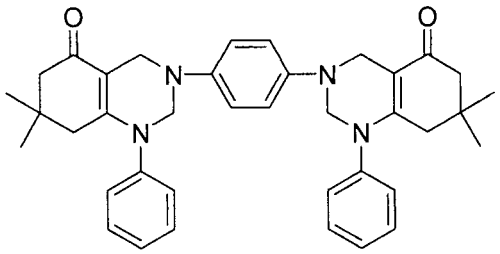
3,3′-(Butane-1,4-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135g.



This compound was obtained as a pale yellow solid in 59% yield; mp 168-169 ^0C (EtOAc); IR (KBr): 1440, 1566, 1613 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (s, 12H, 4 CH_3), 1.46-1.83 (m, 4H, 2 CH_2), 2.13 (s, 4H, 2 CH_2), 2.26 (s, 4H, 2 CH_2), 2.56-2.90 (m, 4H, 2 CH_2) 3.76 (s, 4H, 2 CH_2), 4.45 (s, 4H, 2 CH_2), 7.10-7.86 (m, 10H); MS: m/z, 567 [MH^+].

Anal. Calcd. for $C_{36}H_{46}N_4O_2$ (566.36): C, 76.29; H, 8.18; N, 9.89%. *Found*: C, 76.02; H, 8.21; N, 9.83%.

3,3'-(1,4-Phenylene)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6*H*)-one 135h.



This compound was obtained as yellow solid in 55% yield; mp 126-128 ^{0}C (MeOH/EtOAc); IR (KBr): 1507, 1566 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 12H, 4 CH_3), 2.00 (s, 4H, 2 CH_2), 2.23 (s, 4H, 2 CH_2), 4.27 (s, 4H, 2 CH_2), 4.89 (s, 4H, 2 CH_2), 6.91-6.96 (m, 8H), 7.27-7.36 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 28.08, 28.52, 32.82, 41.24, 45.96, 50.21, 52.59, 71.21, 104.63, 119.13, 127.53, 127.62, 129.88, 142.84, 157.52, 194.22; MS: m/z, 587 [MH^+]; *Anal. Calcd. for* $C_{38}H_{42}N_4O_2$ (586.33): C, 77.78; H, 7.21; N, 9.55%. *Found*: C, 77.52; H, 7.18; N, 9.61%.

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Chapter VI

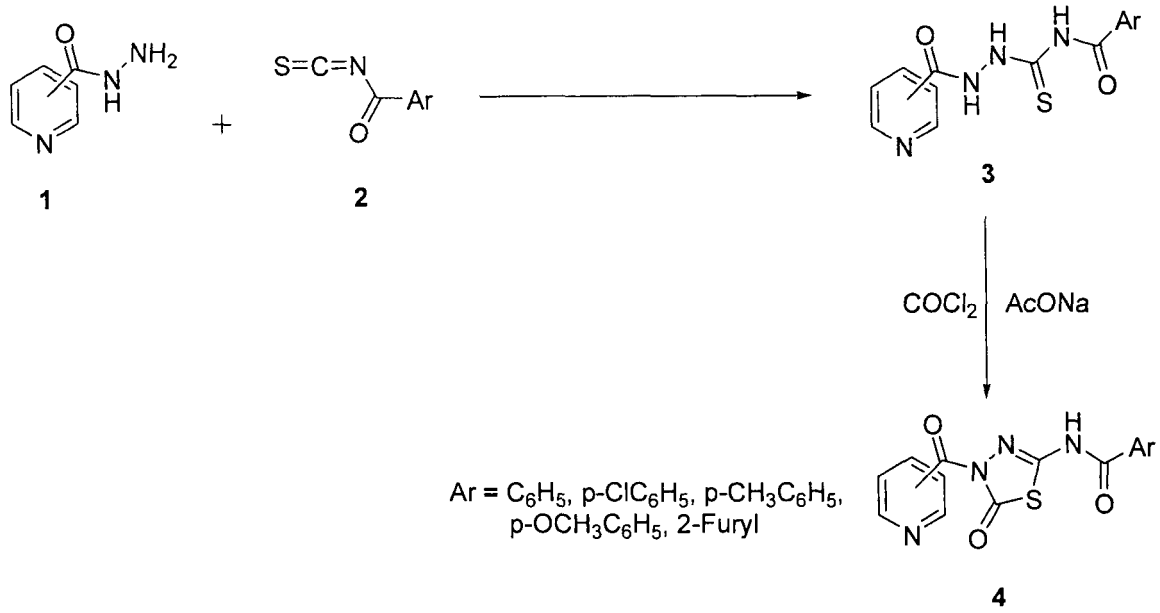
Synthesis of Novel Bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines)

Introduction

Heterocyclic compounds containing isonicotinoyl group are well documented in the literature[1-6]. Literature survey reveals that compounds containing isonicotinoyl groups have been synthesized and were tested for their chelating[7-10] and biological properties[11-14]. Isonicotinic acid hydrazide (isoniazid) is reported to be a well-acknowledged drug [15-16] and is one of the primary drugs used in combination with ethanbutol, rifampin, streptomycin and pyrazinamide to treat tuberculosis[17]. A large number of compounds containing the isoniazid moiety have been synthesized, tested and further studies are going on due to the increasing resistance of bacterial strains of certain type of antibiotics[18-19].

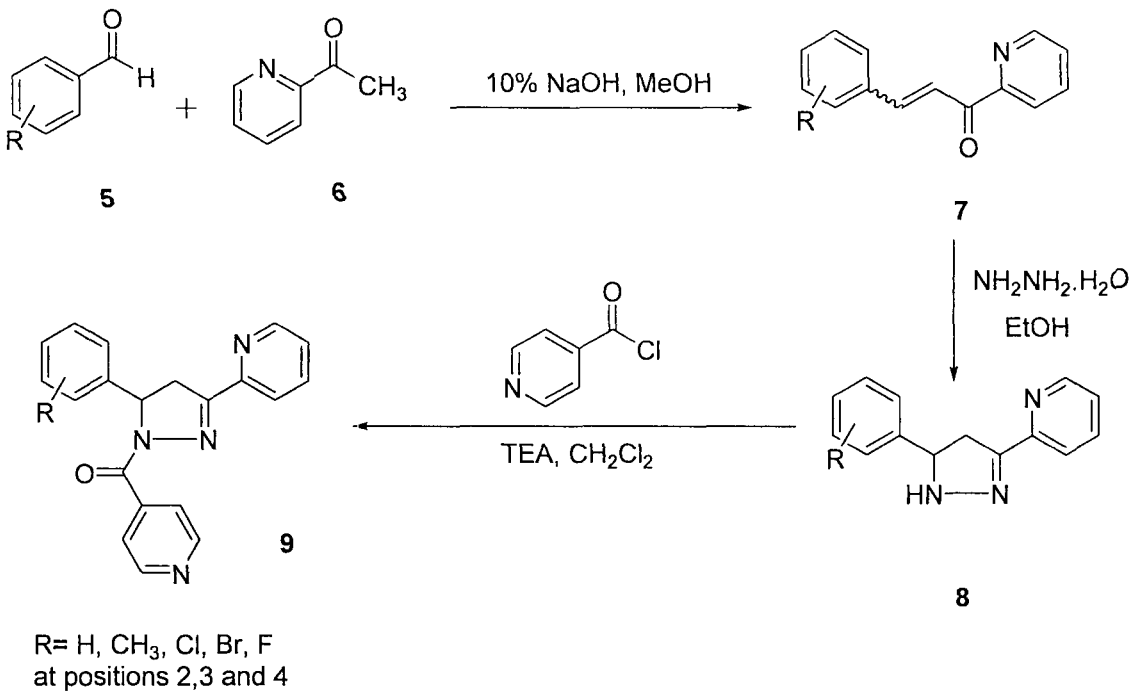
6.1 The synthesis and biological properties of a few such molecules are described in the following sections.

6.1.1 S. Schenone and coworkers have reported[20] the synthesis of a series of 1,3,4-thiadiazol-2(3*H*)-ones with a nicotinoyl/isonicotinoyl group in position 3 and an aroylamino substituent in position 5 of the ring as shown in **Scheme 1**. Reaction of nicotinoyl or isonicotinoyl hydrazide (**1**) with the relevant acylisothiocyanates (**2**) gave the corresponding acylthiosemicarbazides (**3**). Subsequent cyclization with phosgene, in the presence of sodium acetate led to the expected 1,3,4-thia-diazol-2(3*H*)-ones (**4**). These compounds were evaluated for antipyretic and anti-inflammatory activities. All the compounds exhibited anti-inflammatory activity and were devoid of antipyretic properties. It was also observed that the best results were obtained in the isonicotinyl compounds and the furoyl substituent showed superior influence over the benzoyl group.



Scheme 1

6.1.2 M. G. Mamolo and coworkers have also reported[21] the synthesis of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazole derivatives as shown in **Scheme 2.**

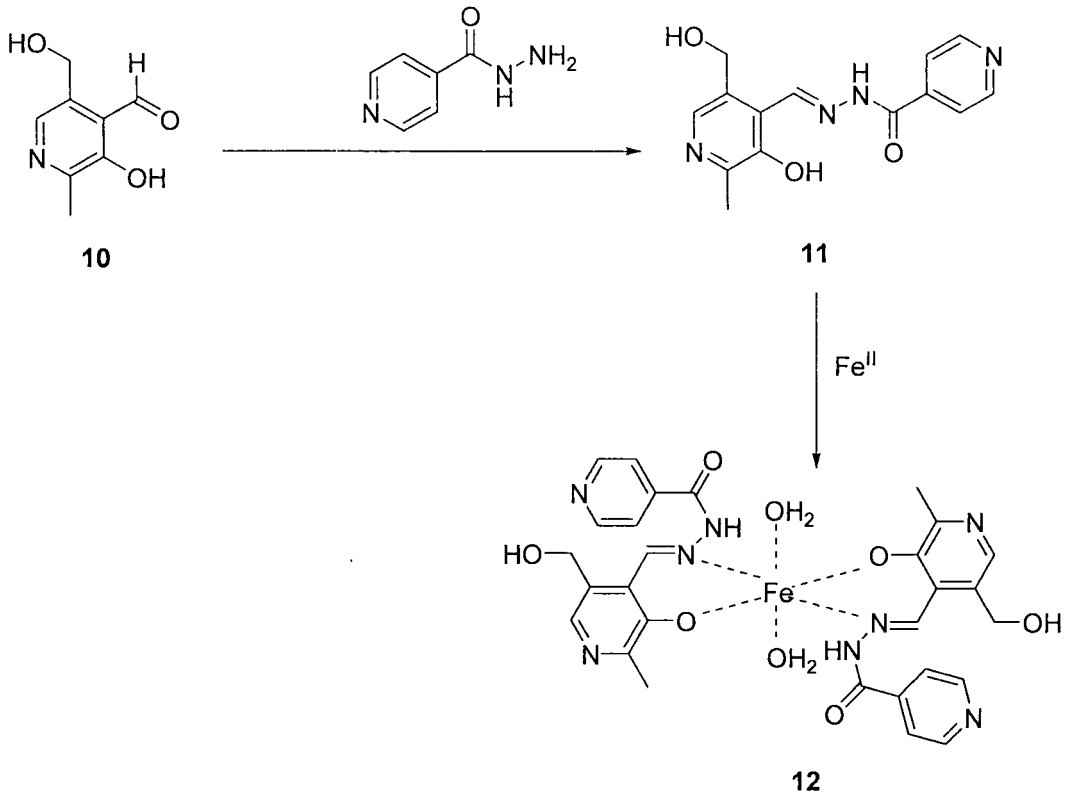


Scheme 2

The synthesis of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazoles (**9**) was carried out by reacting isonicotinoyl chloride with the corresponding 5-aryl-3-(pyridin-2-yl)-4,5-dihydro-1*H*-pyrazoles (**8**) which in turn were prepared from the corresponding 3-aryl-1-(pyridin-2-yl)-propenones (**7**) by treating them with hydrazine hydrate. The required propenones were synthesized by the reaction of the appropriate aromatic aldehyde (**5**) with 2-acetylpyridine (**6**). It was further observed that the pyrazoles (**8**) were quite unstable and in many cases the crude residue was further reacted to give the final compounds. These compounds were tested for their in vitro antimycobacterial activity. These compounds were tested for their antimycobacterial activity towards a strain of Mycobacterium tuberculosis $H_{37}Rv$ and towards a strain of M. tuberculosis H4, isolated from human bronchial aspirates. The activity of these compounds towards strains of *M. gordonae*, *M. bovis*, *Candida albicans*, *Escherichia coli* and *Staphylococcus epidermis* was also determined. These compounds showed interesting activity against a strain of *Mycobacterium tuberculosis* and a human strain of *M. tuberculosis* H4.

6.1.3 P. Ponka and coworkers have reported[22] the synthesis of a series of acylhydrazone by schiff base condensation of various acyl hydrazide (including isonicotinic acid hydrazide) with aromatic aldehydes like pyridoxal (**10**), salicylaldehyde (**13**) and 2-hydroxy-1-naphthaldehyde (**15**) to give various acyl hydrazones (**11, 14, 16**). (**Scheme 3**). Compounds of complex **12** types have shown varying abilities to promote the movement of iron across biological membrane.

Later Ponka and Buss reported[23] the hydrolysis of pyridoxal isonicotinoyl hydrazone (PIH) and its analogues. These PIH were synthesized by previously reported methods[24-28] and it was found that PIH analogues undergo significant amino acid-catalysed hydrolysis in cell culture medium and in serum, achieving equilibrium with their corresponding aldehydes and hydrazides with half-times of 1-8hrs.These along with other data led to the conclusion that PIH analogs effectively mobilize iron in vivo and in vitro, and could therefore be promising candidates for treatment of the secondary iron overload.



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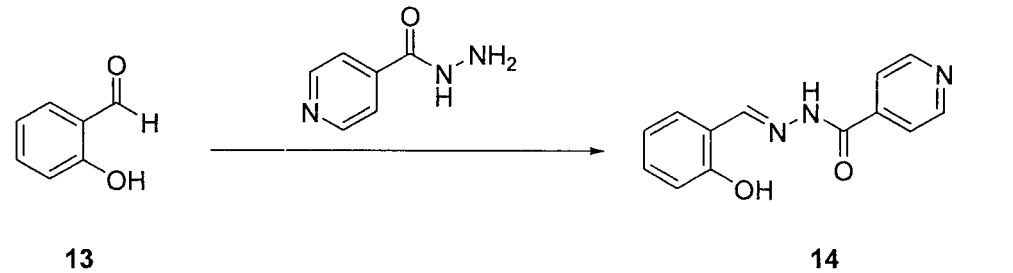

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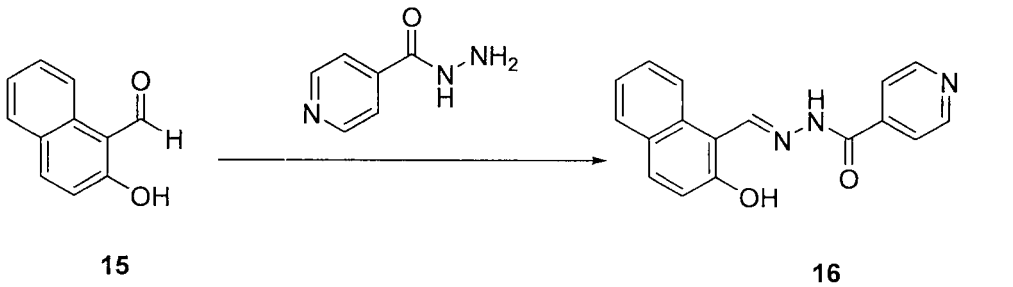
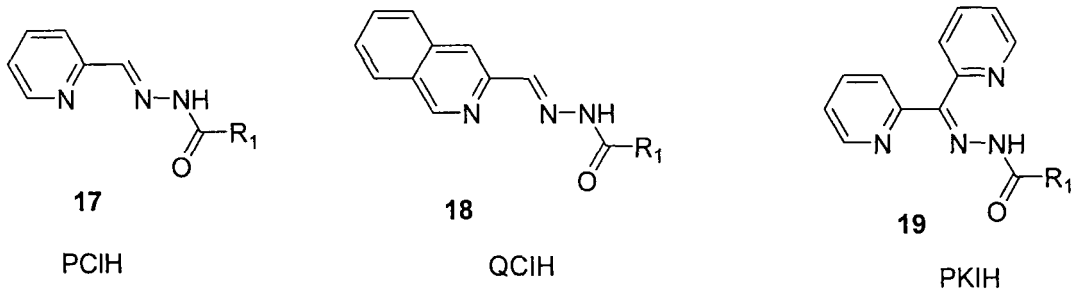
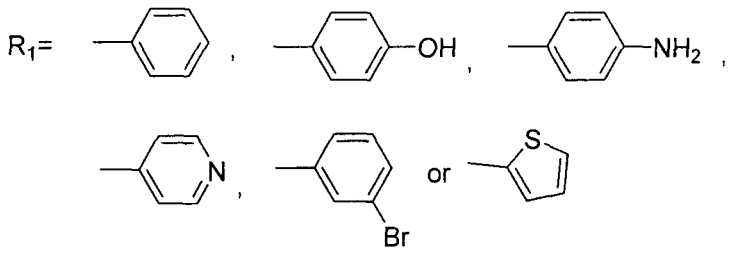


15 16

Scheme 3

6.1.4 In an attempt to develop chelators as potent anti-tumor agents, D. R. Richardson and coworkers reported[29] the synthesis of two series of novel ligands based on the very active 2-pyridylcarboxaldehyde isonicotinoyl hydrazone (PCIH) group. They replaced the aldehyde moiety of the PCIH series (**17**) with more lyophylic 2-quinoline carboxaldehyde or di-2-pyridylketone moieties giving 2-quinolinecarboxaldehyde isonicotinoyl hydrazone (QCIH) series (**18**) and di-2-pyridylketone isonicotinoyl hydrazone (PKIH) series (**19**).



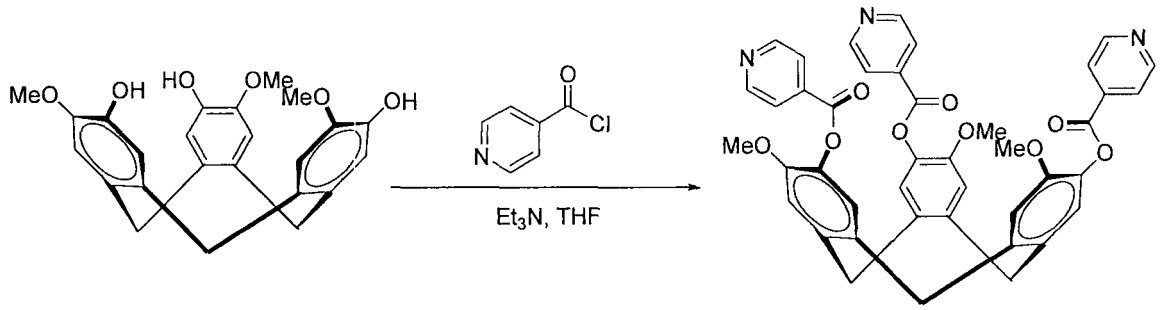


The PCIH (**17**) and QCIH (**18**) analogues were synthesized by Schiff base condensation with either 2-pyridylcarboxaldehyde or 2-quinolinecarboxaldehyde and their respective acid hydrazide [30]. The PKIH series (**19**) were synthesized by condensing 2-di-pyridyl ketone with the acid hydrazide[31]. They examined the structure-activity relationship of the 18 ligands belonging to the three related groups of novel aroyl hydrazone chelators as shown above. It was observed that despite each of these analogs having similar Fe-binding site, the activity of these chelators differed substantially. The PCIH group of ligands had high Fe chelation activity but low antiproliferative effects. The QCIH group had little Fe chelation or

antiproliferative activity, and some of the PKIH series were amongst the most effective Fe chelators and antiproliferative agents.

Later Des R. Richardson and coworkers reported[32] the measurement of redox activity of iron in the presence of the di-2-pyridyl ketone isonicotinoyl hydrazone series of chelators using a variety of assays. The results of the investigation demonstrated that the antiproliferative activity of these chelators relates to intracellular iron chelation, followed by the stimulation of iron-mediated free radical generation via the so-formed complex.

6.1.5 M. J. Hardie and coworkers reported[33] the synthesis of a range of new multidentate bridging ligands/ molecular hosts by appending nitrogen-containing heterocycles to either cyclotricatechylene or cyclotriguaiacylene cores. For example, they reported the synthesis of tris(isonicotinoyl)cyclotriguaiacylene (**21**) which was prepared by stirring cyclotriguaiacylene (**20**) and nicotinoyl hydrochloride at room temperature in THF (**Scheme 4**).

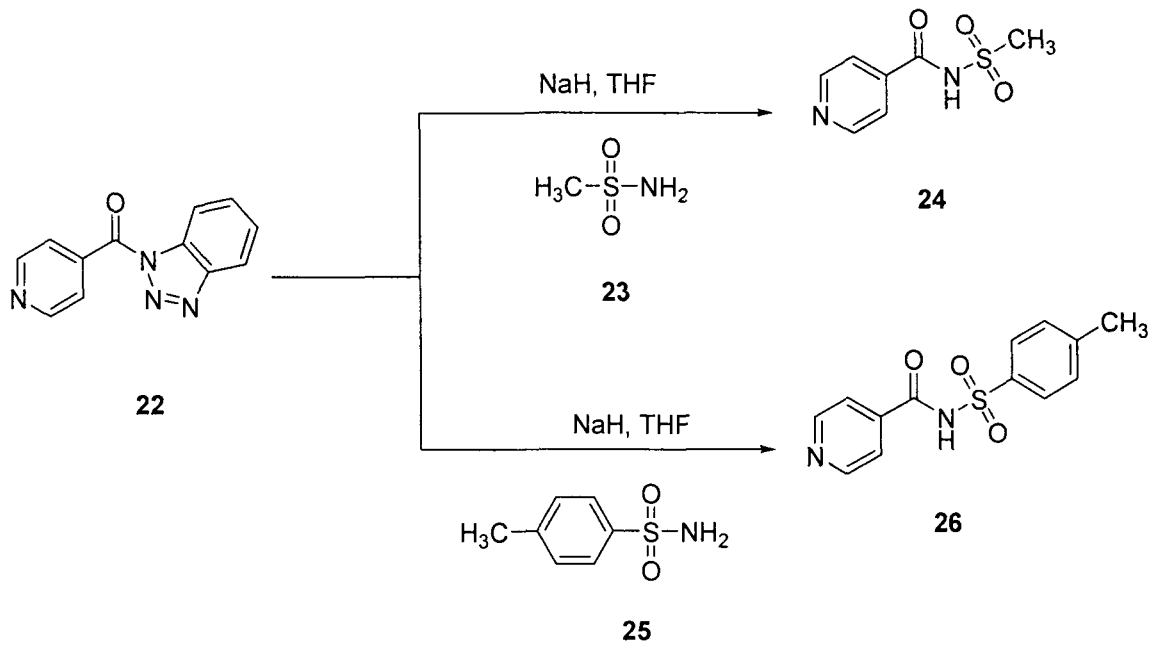


20 21

Scheme 4

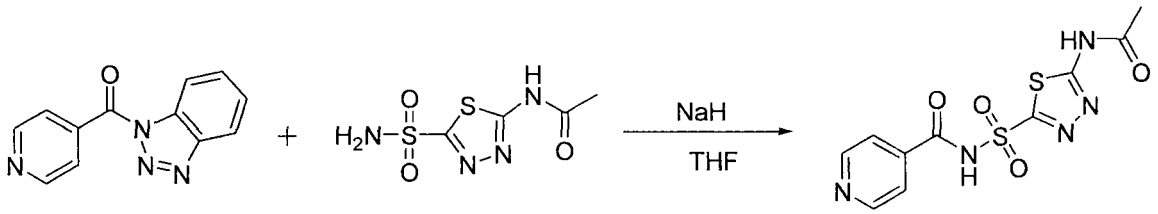
6.1.6 Alan R. Katrirtzky and coworkers have reported[34] the synthesis of N-acylsulfonamides. These preparations were carried out by reacting N-acylbenzotriazoles (**22**) with sulfonamides (methylsulfonamide (**23**), p-

tolylsulfonamide (**25**) and acetazolamide (**28**)) in THF in the presence of NaH for 90 minutes. Removing THF gave the sodium salt of the corresponding N-acylsulfonamides, which on acidification with 2N HCl solution gave N-acylsulfonamides in good yield. For example, N-isonicotinoylmethanesulfonamide (**24**) and N-isonicotinoyl-4-methylbenzenesulfonamide (**26**) were synthesized as shown in **Scheme 5**.



Scheme 5

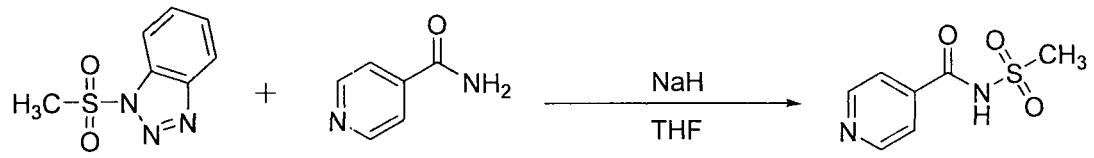
They also reported the synthesis of N-acylsulfonamides derived from acetazolamide. For example, *N*-{5-[(isonicotinoylamino)sulfonyl]-1,3,4-thiadiazol-2-yl}acetamide (**28**) was synthesized as shown in **Scheme 6**.



22 27 28

Scheme 6

They also reported the synthesis of N-acylsulfonamides by utilizing sulfonylbenzotriazole (**29**) and amides (reverse reaction). The reverse synthesis of *N*-isonicotinoylmethanesulfonamide (**24**) is shown in **Scheme 7**.



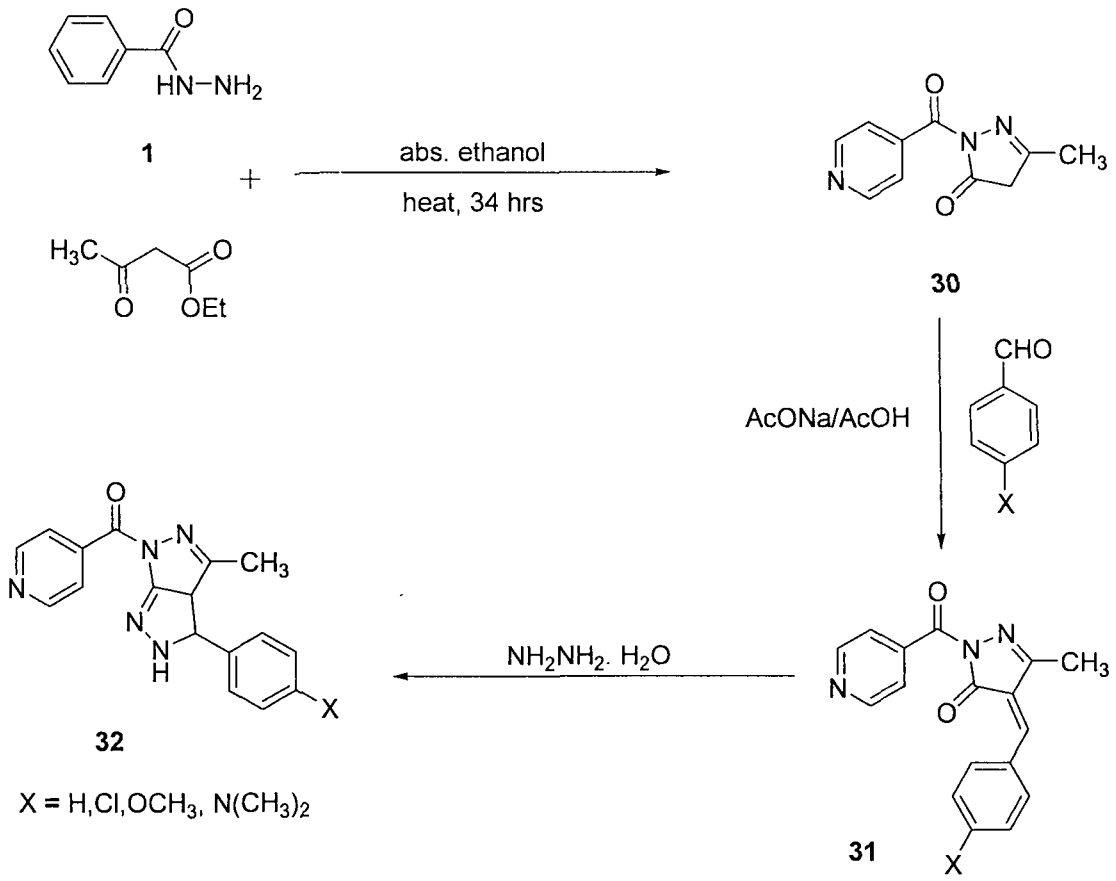
29 24

Scheme 7

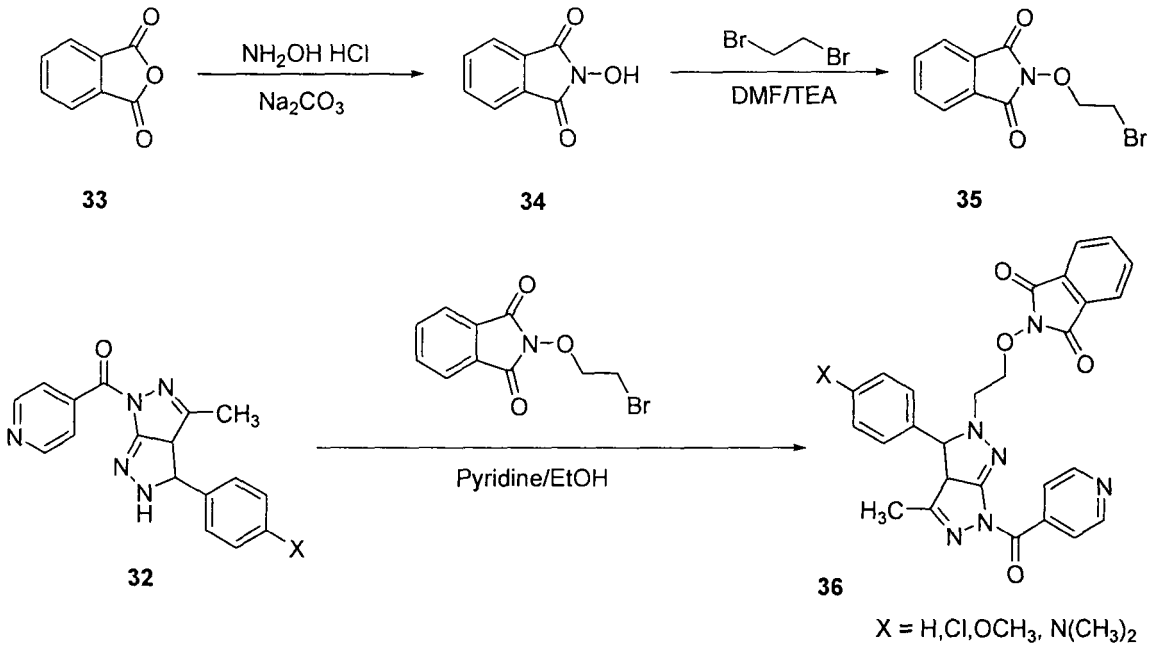
6.1.7 Considering the importance of isonicotinic acid hydrazide (isoniazid) [35], pyrazoles [36-40] and alkoxyphthalamides[41-43] in industrial and pharmacological fields. G.L.Talesara and coworkers reported[44] the synthesis and pharmacological studies of some 1-isonicotinoyl-3-methyl-4-(4-substituted phenyl)-3a,4-dihydropyrazolo[3,4-*c*]pyrazoles and their ethoxyphthalamide derivatives, where they undertook the synthesis of some new combinatorial molecules, incorporating above moieties with the aim to increase their biological activities. When isoniazid (**1**) was reacted with ethylacetoacetate in absolute alcohol 2-isonicotinoyl-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**30**) was obtained. This was then reacted with various 4-substituted benzaldehydes to obtain their corresponding arylidene derivatives (**31**), which were then subjected to reaction with hydrazine hydrate. This led to a cyclocondensation

reaction yielding 4-(4-chlorophenyl/4-methoxyphenyl/4-*N,N*-dimethylaminophenyl/phenyl)-1-isonicotinoyl-3-methyl-3a,4-dihydropyrazolo[3,4-*c*]-pyrazole (**32**) (**Scheme 8**). These compounds were tested for their antimicrobial activity against one-gram positive *B. Subtilis* and three-gram negative strains, *P. mirabilis*, *E. coli* and *K. pneumoniae*. For comparative study two standard drugs ciprofloxacin and roxithromycin were used. *Candida albicans* (MTCC227) and *Aspergillus fumigatus* (MTCC2550) were used as the testing fungal strains. Amphotericin B and flucanazole were used as standard drugs. However, the overall activity profile of the compounds were found to be moderate to poor.

With an aim to increase the antimicrobial activity of these molecules they (Talesara et al.) fused the ethoxyphthalimide moiety with the pyrazolo[3,4-*c*]pyrazole ring system. Thus, when compound **32** was reacted with phthalimidoxyethyl bromide (**35**) in ethanol in the presence of pyridine, 2-*N*-ethoxyphthalimido-6-isonicotinoyl-4-methyl-3-(4-substituted phenyl)-3,3a-dihydro pyrazolo[3,4-*c*]pyrazoles (**36**) were obtained (**Scheme 9**).


HN–NH2
1
abs. ethanol
heat, 34 hrs
H3C
O
OEt
CH3
30
AcONa/AcOH
CHO
X
NH2NH2. H2O
31
32
X = H,Cl,OCH3, N(CH3)2

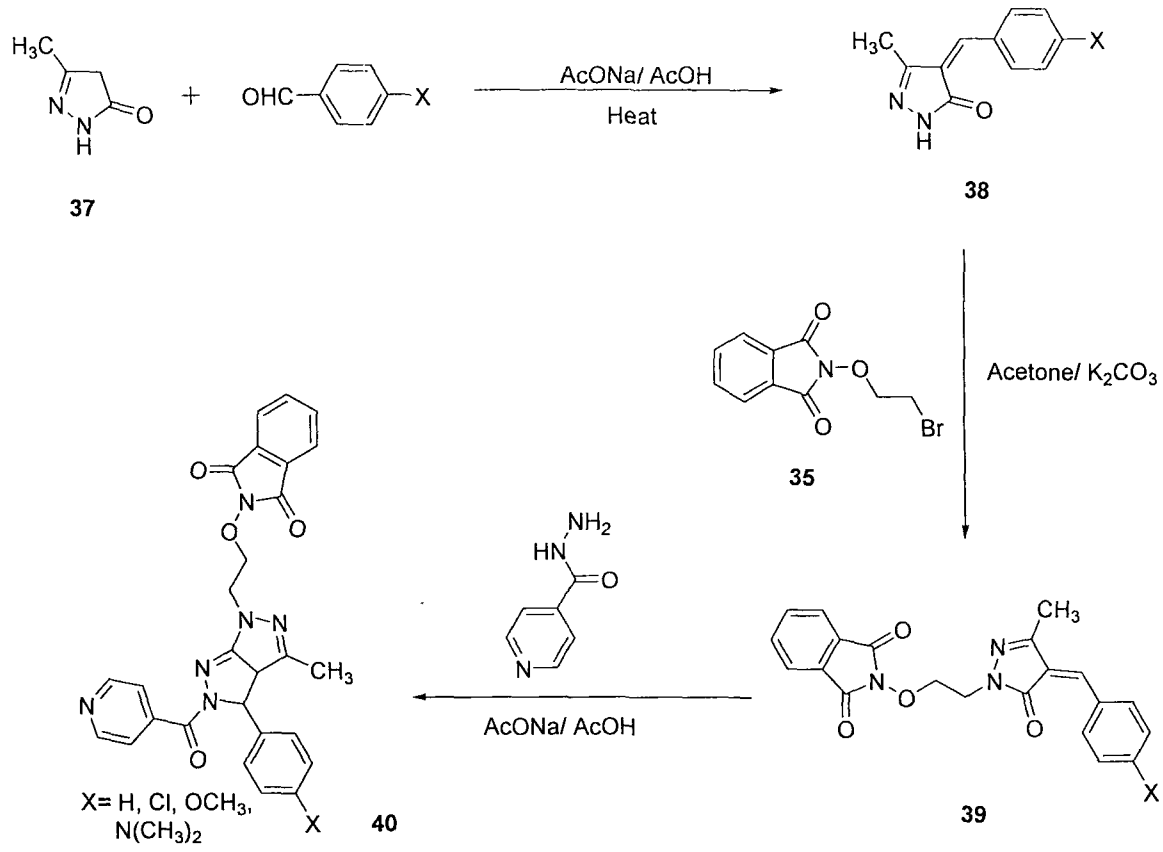
Scheme 8



Scheme 9

These compounds **36** showed comprehensive fungus-inhibiting properties than bacterial. Two compounds showed strong activity against *P. mirabilis*, *B. subtilis*, *C. albicians* and *A. fumigatus* while moderate to good activity against *K. pneumoniae* and *E.coli.* The antiproliferative activity was measured against murine leukemia cells (L1210/0) and human T-lymphocyte cells (Molt 4/C8, CEMO/0 cells). However none of the compounds exhibited antitumor cell activity at a reasonably low concentration. They also reported the antiviral activity of these compounds but none of the compounds was able to inhibit the cytopathic effects of influenza A or B at subtoxic concentration or at the highest concentration (100μg/mL) tested.

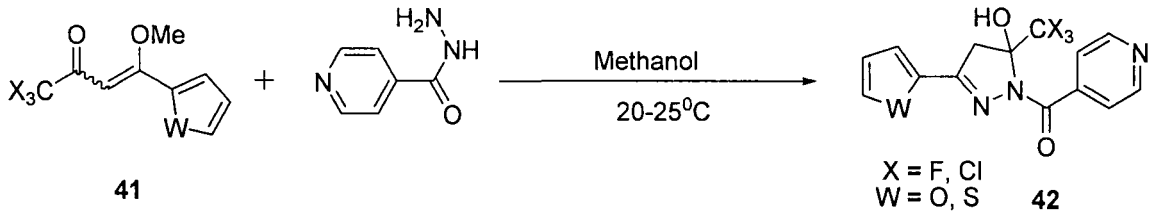
Later G.L.Talesara and coworkers reported[45] the synthesis of 6-*N*-ethoxyphthalimido-2-isonicotinoyl-4-methyl-3-(4-substituted phenyl)-3,3a-dihydro pyrazolo[3,4-*c*]pyrazoles (**40**) (**Scheme 10**).



Scheme 10

They used 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**37**) as starting material which was prepared by the reaction between ethylacetoacetate and hydrazine hydrate in absolute alcohol. Compound **37** on condensation with substituted benzaldehydes in the presence of sodium acetate as a base gave the corresponding 5-methyl-4-substituted benzylidene-2,4-dihydro-3*H*-pyrazol-3-one (**38**). These, when reacted with phthalimidoxyethyl bromide (**35**) in acetone using K_2CO_3 as a base afforded 1-*N*-ethoxyphthalimido-3-methyl-4-(4-substituted benzylidene) pyrazol-5-one (**39**). Compound **39** was cyclized with isoniazid in the presence of sodium acetate and acetic acid to yield 6-*N*-ethoxyphthalimido-2-isonicotinoyl-4-methyl-3-(4-substitutedphenyl)-3,3a-dihydropyrazolo[3,4-*c*]pyrazoles (**40**).

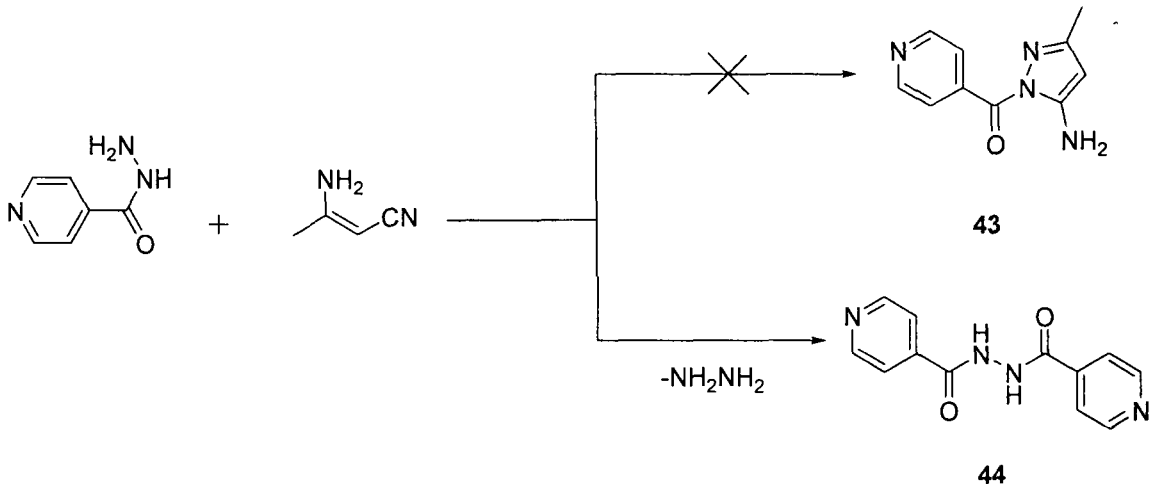
6.1.8 H.G. Bonacorso and coworkers have reported[46] the synthesis of a novel series of heteroaroyl-2-pyrazolines trihalomethyl and substituted heteroaryl as non-condensed heteropolycyclic systems. The regiospecific cyclocondensation reaction of 1,1,1-trifluoro(chloro)-4-methoxy-4-(2-furyl)-3-buten-2-ones and 1,1,1-trifluoro(chloro)-4-methoxy- 4-(2-thienyl)-3-buten-2-ones (**41**) with isonicotinic acid hydrazides in anhydrous methanol under mild conditions at room temperatures yielded 3-(2-furyl)- or 3-(2-thienyl)-5-hydroxy-5-trifluoro(chloro)methyl-4,5-dihydro-1*H*-1-(isonicotinoyl)pyrazoles (**42**) (**Scheme 11**).



41 42

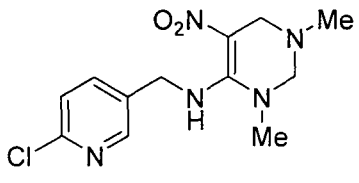
Scheme 11

6.1.9 J. Quiroga and coworkers[47] in continuation of their study on the preparation of amino derivatives of pyrazoles, by the reaction of β- aminoacrylonitriles with compounds containing hydrazine moiety, reported the reaction of isoniazid with β-aminoacrylonitrile in the presence of sodiumacetate trihydrate in ethanol under refluxing conditions. Under these conditions, N,N′-bis-(isonicotinoyl)hydrazine (**44**) was obtained with the elimination of a hydrazine molecule instead of the expected pyrazole (**43**) (**Scheme 12**).

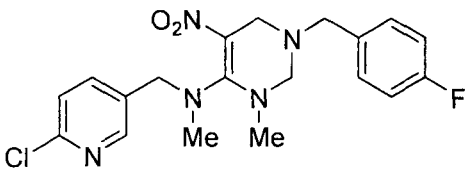


Scheme 12

Prompted by the above literature reports and also by the potential biological activities of 5-nitro-1,2,3,4-tetrahydropyrimidine derivatives of the type **45**[48] and **46**[49] and in continuation with our work on the synthesis of bis-heterocycles (especially tetrahydropyrimidines)



45



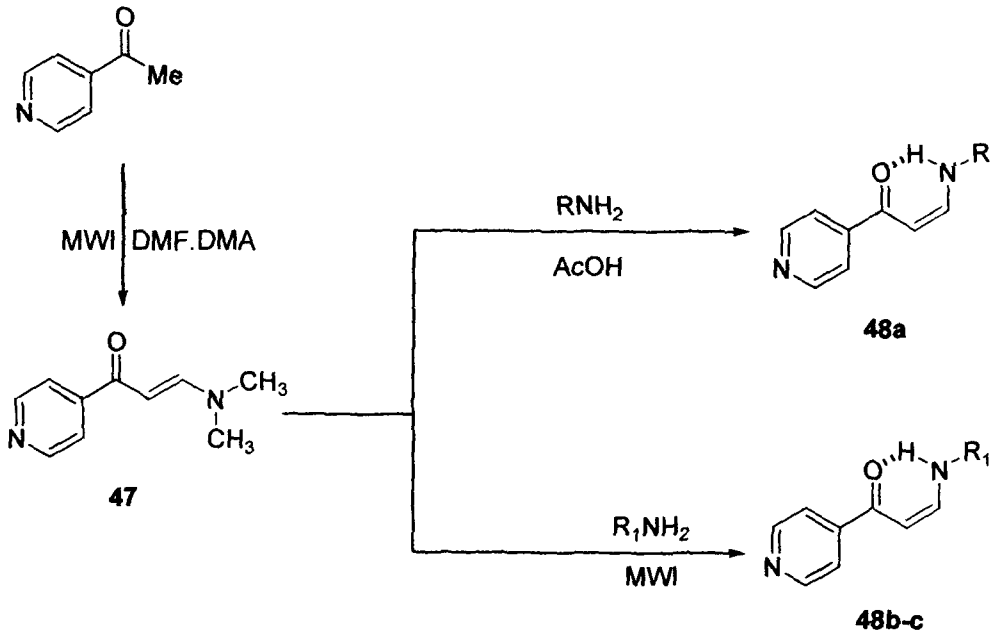
46

we envisaged that the presence of another electron withdrawing group in position 5 of the tetrahydropyrimidine ring could have an important impact on the biological activities of these molecules. Our literature survey revealed that 1,2,3,4-tetrahydropyrimidine and bis-(1,2,3,4-tetrahydropyrimidines) bearing isonicotinoyl group in position 5 of the ring are unknown in the literature to the best of our

knowledge and hence their biological properties remain unexplored.

Furthermore, bis-compounds have received considerable importance as being model for main chain polymers[50-54]. It is also reported that many biologically active natural and synthetic products have molecular symmetry[55]. As a result, a number of organic chemists are shifting their attentions to the synthesis of bis-heterocycles[56-59]. Prompted by the above facts, we undertook to develop synthetic methodologies for bis-(5-isonicotinyl-1,2,3,4-tetrahydropyrimidines) and the results of our studies are reported herein.

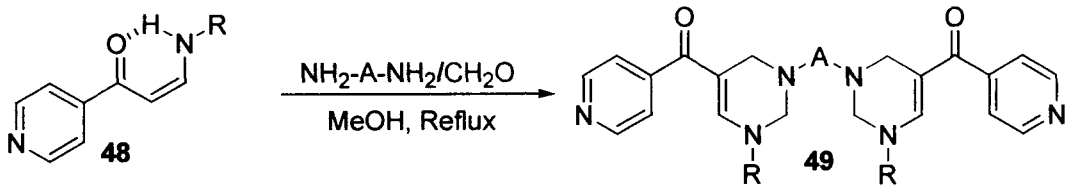
6.2 In order to synthesize the proposed bis-1,2,3,4-tetrahydropyrimidine bearing isonicotinyl group in position 5 of the ring, we required enaminones of the type **48** which could be derived from 4-acetylpyridine (**Scheme 13**).



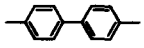
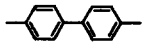
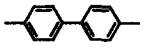
Scheme 13

Their synthesis could be achieved by first reacting 4-acetylpyridine with DMF-DMA following previously reported procedure[60] to yield the formylated product **47** and then converting **47** into **48** by a procedure[61] developed in our laboratory. The structures of **48** as 3-(phenyl/benzyl/methyl)amino-1-isonicotinoylpropenones were established with help of spectral and analytical data. The enaminones **48a-c** exist exclusively in Z-form as indicated by the highly deshielded N-H proton (10.76-12.25 ppm) signals due to hydrogen bonding and the low coupling constants of the vinylic protons (J=6 Hz).

6.3 These heteroaroyl enaminones (**48**) thus synthesized were used as synthons for the construction of the required bis-1,2,3,4-tetrahydropyrimidines as shown in **Scheme 14**.



48	R
a	Ph
b	Bn
c	Me

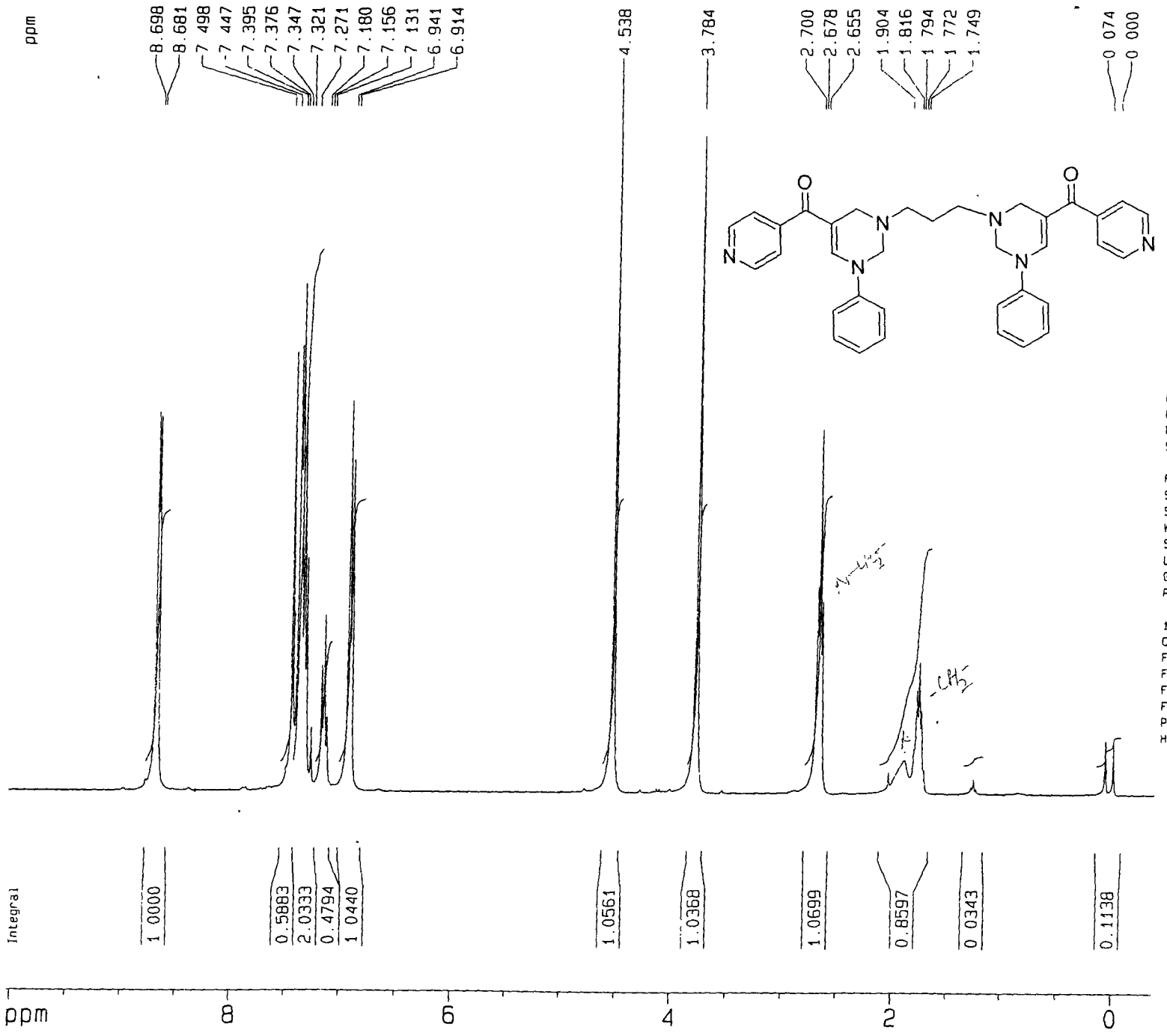
49	R	A
a	Ph	$-CH_2CH_2-$
b	Ph	$-CH_2CH_2CH_2-$
c	Ph	$-CH_2CH_2CH_2CH_2-$
d	Ph	
e	Ph	
f	Bn	$-CH_2CH_2-$
g	Bn	$-CH_2CH_2CH_2-$
h	Bn	$-CH_2CH_2CH_2CH_2-$
i	Bn	
j	Bn	
k	Me	$-CH_2CH_2-$
l	Me	$-CH_2CH_2CH_2-$
m	Me	$-CH_2CH_2CH_2CH_2-$
n	Me	
o	Me	

Scheme 14

6.4 Results and discussions.

Thus, when **48a** (2 mmol) was reacted with a mixture of ethylenediamine (1 mmol) and formaldehyde (4 mmol) in methanol, expected product **49a** was obtained in 55% yields, the structure of which was established to be [3,3'-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) based on

spectral and analytical data. The reaction of **48a** with other diamines (A= -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -C_6H_4-) and formaldehyde led to the formation of the respective products **49b-d** in 60-65% yields. Likewise, **48b** and **48c** reacted with diamines and formaldehyde under similar conditions giving the expected products **49e-i** in good yields. The infrared spectra of **49a-o** showed strong peaks in the region of 1500 to 1630 cm^{-1} due to extensively delocalised double bonds and carbonyl groups. In the ^1H NMR spectra of **49a-o**, the α and β protons of pyridine ring appear as doublets in the vicinity of 8.60 and 7.30 ppm respectively. The signal of C_6-H proton of the THP ring remains buried with the aromatic protons except in case of **49k-o**, where it was found resonating at 6.97 ppm. The signals due to benzylic CH_2 protons in **49f-j** were found in the range of 3.65-3.90 ppm. The protons at C-4 of the THP ring resonated just below 4.00 ppm except in cases where phenyl or biphenyl group is attached to N-3, while those bonded to C-2 were more de-shielded and resonated in the vicinity of 4.50 ppm The N-CH_2 protons of the linker chain of **49a-c, e-g, i-k** resonated between 2.40 to 2.80 ppm, while other CH_2 protons of the linker chains appeared as multiplets close to 1.75ppm. In the ^{13}C NMR spectra of the THPs, the most striking signal was due to carbonyl carbon close to 190 ppm. The ^1H NMR and ^{13}C NMR Spectra of [3,3'-(propane-1,3-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) **49b** are shown in pages 239-240.



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PROCNO	1

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PULPROG	zg
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FIDRES	0 192661 Hz
AQ	2 5952756 sec
RG	143 7
DW	79 200 usec
DE	6 00 usec
TE	298 0 K
D1	1 00000000 sec

========== CHANNEL f1 ==========

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P1	6 88 usec
PL1	-3 00 dB
SFO1	300 1325027 MHz

F2 - Processing parameters

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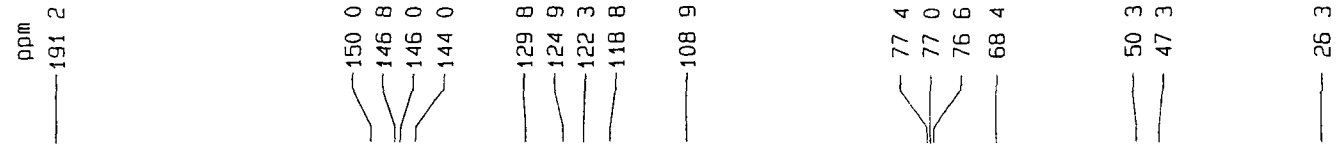
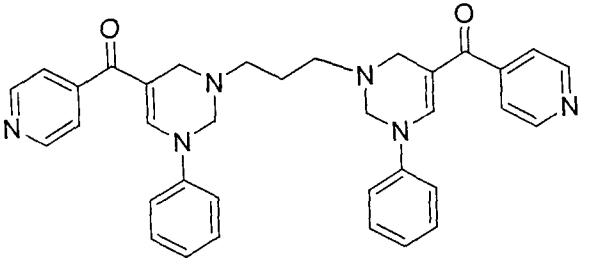
SF	300 1300027 MHz
WDW	EM
SSB	0
LB	0 10 Hz
GB	0
PC	1 20

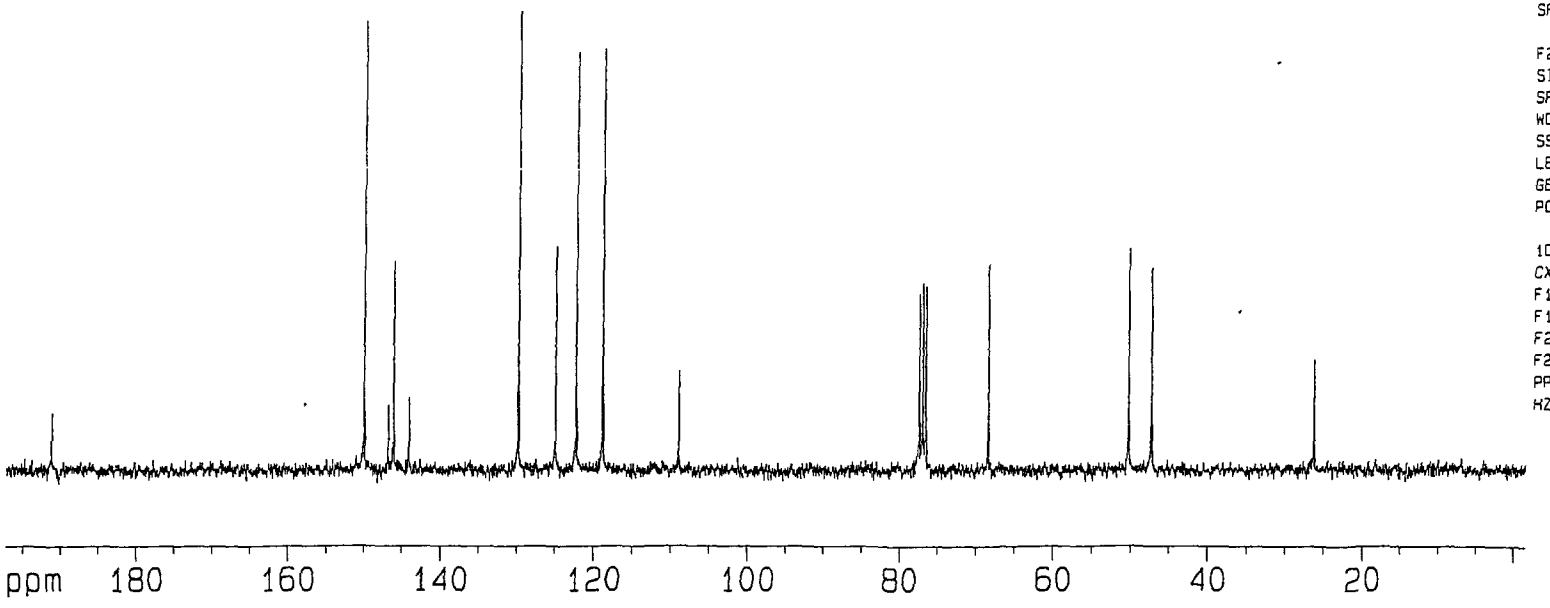
1D NMR plot parameters

CX	20 00 cm
F1P	10 034 ppm
F1	3011 46 Hz
F2P	-0 386 ppm
F2	-115 88 Hz
PPMCM	0 52100 ppm/cm
HZCM	156 36691 Hz/cm

M-214







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SWH	19960 080 Hz
FIDRES	0 609133 Hz
AQ	0 8208884 sec
RG	11585 2
DW	25 050 usec
DE	6 00 usec
TE	315 0 K
D1	2 00000000 sec
d11	0 03000000 sec

========== CHANNEL f1 ==========

NUC1	13C
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PL1	-3 00 dB
SFO1	75 4767751 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	100 00 usec
PL2	-3 00 dB
PL12	20 00 dB
SFO2	300 1319936 MHz

240

F2 - Processing parameters

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SF	75 4677528 MHz
WDW	EM
SSB	0
LB	3 00 Hz
GB	0
PC	1 50

1D NMR plot parameters

CX	20 00 cm
F1P	197 306 ppm
F1	14890 26 Hz
F2P	-1 670 ppm
F2	-126 00 Hz
PPMCM	9 94880 ppm/cm
HZCM	750 81323 Hz/cm

M-214

6.5 Conclusion.

In conclusion, we have synthesized a series of hitherto unknown bis-(5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines) in good yields, from the respective enaminones derived from 4-acetyl pyridine, wherein we have succeeded in replacing the nitro group at the 5-position of the THP ring by another electron withdrawing group. The anti-bacterial properties of these bis-tetrahydropyrimidines are currently under investigation.

6.6 Experimental Section.

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 and ^{13}C 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 fashion 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. Enaminones **48** were synthesized by our reported procedure [61].

6.7 General procedure

6.7.1 *Synthesis of 3-phenylamino-1-pyridin-4-ylpropenone* (48a).

To a solution of enaminone **47** (1 mmol) in 2 ml acetic acid aniline (1 mmol) was added and the resulting mixture was stirred at room temperature for 45 hours when a solid product precipitated out. After the completion of the reaction (monitored by TLC), the mixture was poured over chilled water and the precipitated product was collected by filtration, washed repeatedly by water to ensure complete removal of acid and dried to give practically pure **48a** in 82% yields. It was recrystallised from hexane-ethyl acetate mixture.

6.7.2 *Synthesis of 3-benzylamino-1-pyridin-4-ylpropenone* (48b).

To a solution of enaminone **47** (1 mmol) in 3 ml ethanol was added benzylamine (1.2 mmol) and the resulting mixture was refluxed for 48 hours. After the completion of the reaction (monitored by TLC), ethanol was distilled off to give a gum, which on trituration with hexane yielded practically pure **48b** in 61% yield. It was recrystallised from hexane-ethylacetate mixture.

Alternatively this compound **48b** could also be synthesized under microwave irradiation. A mixture of enaminone **47** (1 mmol) and benzylamine (1.5 mmol) was taken in a 5-mL conical flask and the resulting mixture was irradiated in domestic microwave oven at 300 watt for an appropriate time. At the end of the reaction (monitored by TLC), the flask was cooled and the mass was triturated with hexane to give the desired product **48b**, which was recrystallized from hexane-ethylacetate mixture.

6.7.3 *Synthesis of 3-methylamino-1-pyridin-4-ylpropenone* (48c).

To a solution of enaminone **47** (1 mmol) in 3 ml ethanol was added an aqueous solution of methylamine (3 mmol, 40% solution) and the resulting mixture was stirred at 50^0C for 40 hours. After the completion of the reaction (monitored by TLC), ethanol was distilled off to give a brown gum, which was dissolved in chloroform (3 ml). This solution was washed with water (2x2 ml), dried over anhydrous sodium sulphate and chloroform distilled off to give the product **48c** in 52% yields. It was further purified by column chromatography (silica gel, 20% ehylacetate-hexane).

Alternatively **48c** could also be synthesized under microwave irradiation. A mixture of **47** (1 mmol) and methylamine (3 mmoles) was taken in a 5ml conical flask and the resulting mixture was irradiated in domestic microwave oven at 100 watt for appropriate time. After the completion of the reaction (monitored by TLC),

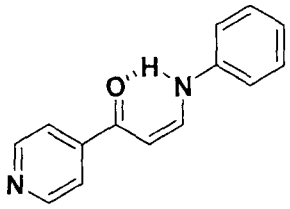
chloroform (3 ml) was added and the organic layer was washed with water (2x2 ml), dried over anhydrous Na_2SO_4 and the solvent removed to obtain the enaminone **48c** which was further purified by column chromatography (silica gel, 20% ethylacetate-hexane).

6.8 *Synthesis of Bis-tetrahydropyrimidines (49a-o).*

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol) in 1 ml of methanol was stirred at room temperature for 5-10 minutes. To this was added a solution of the enaminone **48** (1 mmol) in 4 ml of methanol and the resulting solution was refluxed for 4-12 hours. On completion of the reaction (monitored by TLC), the solvent was distilled off. The residue was dissolved in 3 ml of chloroform and the solution washed with water (2x2 ml), dried over anhydrous Na_2SO_4 and chloroform distilled off to give a gum from which the product **49** was isolated by column chromatography (silica gel, ethylacetate) in 40-65% yields.

6.9 Individual description of the compounds.

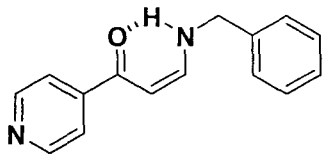
(Z) 3-phenylamino-1-pyridin-4-ylpropenone 48a.



This compound was obtained as a yellow solid, mp 149-150^{0}C; IR (KBr): 1566, 1639, 3032, 3217 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.02 (d, 1H, J=6Hz), 7.13-7.16 (m, 3H), 7.36-7.41 (m, 2H), 7.61 (dd, 1H, J=6Hz, 12Hz), 7.73 (d, 2H, J=6Hz), 8.76(d, 2H,

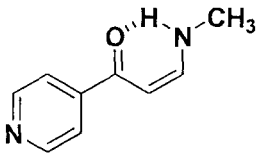
J=6Hz), 12.25 (br d, 1H, exchangeable with D_2O J=12Hz); MS: (m/z) 224 [M+], 225 [MH+]; *Anal. Calcd.* for $C_{14}H_{12}N_2O$ (224.26); C, 74.98; H, 5.39; N, 12.49%. *Found*: C, 74.75; H, 5.50; N, 12.42%.

(E) 3-benzylamino-1-pyridin-4-ylpropenone 48b.



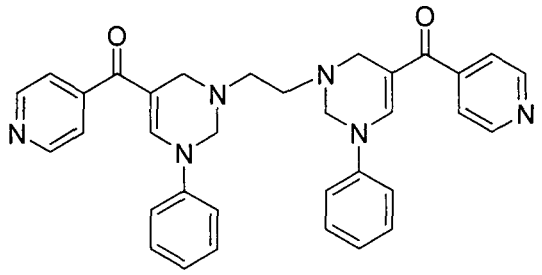
This compound was obtained as a light brown solid, mp 113-115^{0}C; IR (KBr): 1566, 1639, 3025, 3443 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.49 (d, 2H, J= 6Hz), 5.74 (d, 1H, J=6Hz), 7.10 (dd, 1H, J=6 Hz, 12.9 Hz), 7.27-7.39 (m, 5H), 7.66 (d, 2H, J=5.7Hz), 8.68 (d, 2H, J=5.7Hz), 10.76 (br d, 1H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$): δ 52.9, 90.6, 120.7, 127.3, 128.0, 128.9, 137.1, 146.1, 150.3, 155.2, 187.7; MS: m/z 238 [M^+], 239 [MH^+]; *Anal. Calcd. for* $C_{15}H_{14}N_2O$ (238.28): C, 75.61; H, 5.92; N, 11.76%. *Found*: C, 75.85; H, 6.01; N, 11.82%.

(Z) 3-methylamino-1-pyridin-4-ylpropenone 48c.



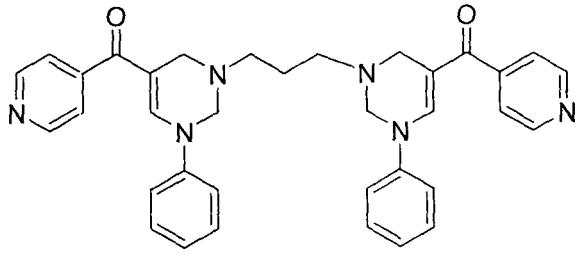
This compound was obtained as light brown gum, IR (KBr): 1527, 1566, 1639, 3005, 3244 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.15 (d, 3H, J=6Hz), 5.90 (d, 1H, J=7.5Hz), 7.30 (dd, 1H, J=7.5, 12Hz), 7.95 (d, 2H, J=6Hz), 9.10 (d, 2H, J=6Hz), 11.01 (br d, 1H, exchangeable with D_2O); *Anal. Calcd. for* $C_9H_{10}N_2O$ (162.19): C, 66.65; H, 6.21; N, 17.27%. *Found*: C, 66.51; H, 6.28; N, 17.36%.

[3,3′-(Ethane-1,2-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49a.



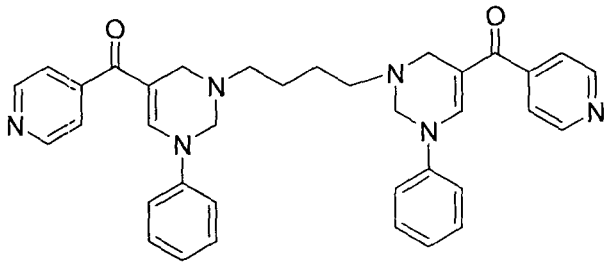
This compound was obtained as a white solid in 55% yield, mp 189-191^{0}C; IR (KBr): 1541, 1596, 1649 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.80 (s, 4H), 3.83 (s, 4H), 4.64 (s, 4H), 6.92 (d, 4H), 7.15-7.20 (m, 2H), 7.27-7.51 (m, 10H), 8.69 (d, 4H); MS: m/z 557 [MH^+]; *Anal. Calcd. for* $C_{34}H_{32}N_6O_2$ (556.66): C, 73.36; H, 5.79; N, 15.10%. *Found*: C, 73.55; H, 5.73; N, 15.02%.

[3,3′-(Propane-1,3-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49b.



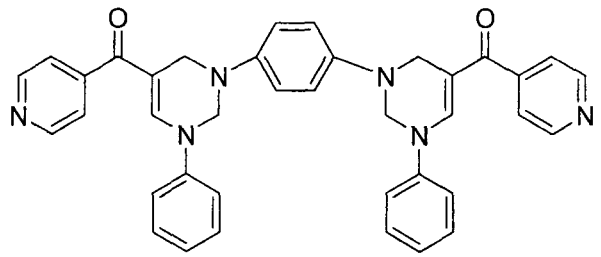
This compound was obtained as a white solid in 65% yield, mp 193-195^{0}C; IR (KBr): 1495, 1568,1641 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.75-1.82 (m, 2H), 2.68 (t, 4H), 3.78 (s, 4H), 4.54 (s, 4H), 6.93 (d, 4H) 7.13-7.18 (m, 2H), 7.27-7.50 (m, 10H), 8.69 (d, 4H); ^{13}C NMR ($CDCl_3$): δ 26.3, 47.3, 50.3, 68.4, 108.9, 118.6, 122.3, 124.9, 129.8, 144.0, 146.0, 146.8, 150.0, 191.2; *Anal. Calcd. for* $C_{35}H_{34}N_6O_2$ (570.68): C, 73.66; H, 6.01; N, 14.73%. *Found*: C, 73.81; H, 6.09; N, 14.81%.

[3,3′-(Butane-1,4-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49c.



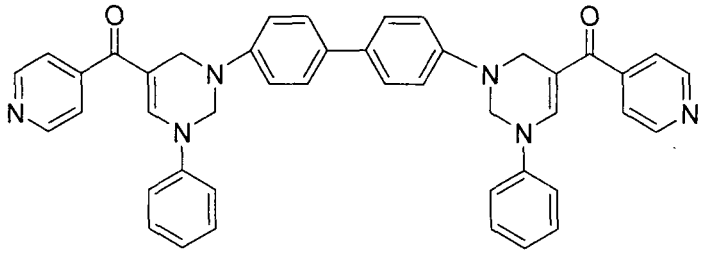
This compound was obtained as light yellow solid in 60% yield, mp 153-154^{0}C; IR (KBr): 1498, 1568, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60-1.61 (m, 4H), 2.59-2.60 (m, 4H), 3.79 (s, 4H), 4.54 (s, 4H), 6.93 (d, 4H), 7.14-7.18 (m, 2H), 7.27-7.45 (m, 10H), 8.69 (d, 4H); MS: m/z 585 [MH$^+$]; *Anal. Calcd. for* $C_{36}H_{36}N_6O_2$ (584.71): C, 73.95; H, 6.21; N, 14.37%. *Found*: C, 73.83; H, 6.25; N, 14.32%.

[3,3'-(1,4-Phenylene)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49d.



This compound was obtained as a yellow solid in 62% yield, mp 168-170^{0}C; IR (KBr): 1563, 1619, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.39 (s, 4H), 5.08 (s, 4H), 6.87-6.93 (m, 4H), 7.15-7.46 (m, 16H), 8.68 (d, 4H, J=5.4Hz); MS: m/z 605 [MH^+]; *Anal. Calcd. for* $C_{38}H_{32}N_6O_2$ (604.7): C, 75.48; H, 5.33; N, 13.90%. *Found*: C, 75.31; H, 5.38; N, 13.84%.

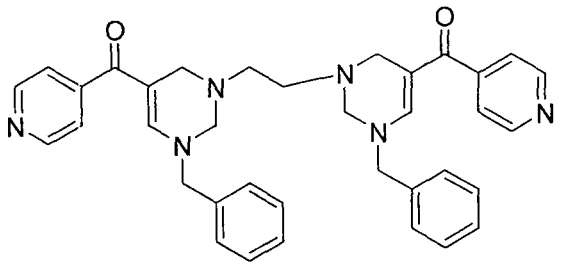
[3,3'-(Biphenyl-4,4'-diyl)bis(1-phenyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis- (pyridin-4-ylmethanone) 49e.



This compound was obtained as a brown solid, yield 50%, mp 230^{0}C (decomp); IR (KBr): 1567, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.51 (s, 4H), 5.19 (s, 4H), 6.94-7.00

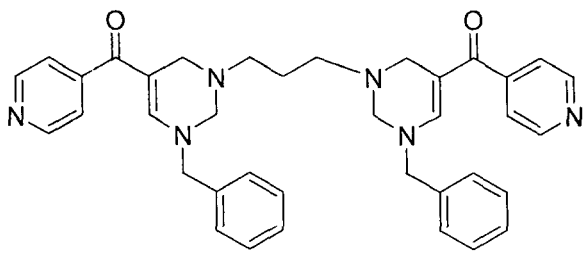
(m, 12H), 7.16-7.89 (m, 12H), 8.68 (d, 4H, J=4.8Hz); ^{13}C NMR ($CDCl_3$): δ 45.2, 65.0, 104.2, 119.2, 120.5, 122.3, 124.6, 125.1, 126.3, 127.0, 129.7, 142.8, 146.2, 149.5, 151.0, 189.5; *Anal. Calcd. for* $C_{44}H_{36}N_6O_2$ (680.8): C, 77.63; H, 5.33; N, 12.34%. *Found*: C, 77.47; H, 5.39; N, 13.28%.

[3,3'-(Ethane-1,2-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl))bis-(pyridin-4-ylmethanone) 49f.



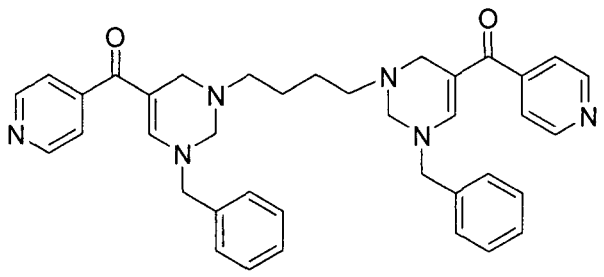
This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1561, 1656 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 4H), 3.63 (s, 4H), 3.98 (s, 4H), 4.27 (s, 4H), 7.18-7.32 (m, 16H), 8.65 (d, 4H); ^{13}C NMR ($CDCl_3$): δ29.5, 46.9, 50.5, 58.2, 67.3, 104.9, 121.0, 122.3, 127.6, 128.4, 129.0, 147.3, 150.5, 189.7; *Anal. Calcd. for* $C_{36}H_{36}N_6O_2$ (584.71): C, 73.95; H, 6.21; N, 14.37%. *Found*: C, 73.99; H, 6.26; N, 14.41%.

[3,3'-(Propane-1,3-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49g.



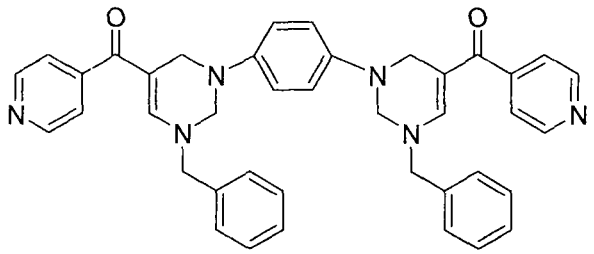
This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1563, 1656 cm^{-1}; ^1H NMR ($CDCl_3$); δ 1.42-1.52 (m, 2H), 2.40 (t, 4H), 3.61 (s, 4H), 3.86 (s, 4H), 4.27 (s, 4H), 7.17-7.19 (m, 6H), 7.32-7.37 (m, 10H), 8.63 (d, 4H); ^{13}C NMR ($CDCl_3$): δ 25.6, 47.0, 50.4, 51.8, 58.1, 66.4, 105.0, 121.0, 122.2, 127.4, 128.5, 128.9, 147.3, 149.6, 189.5; *Anal. Calcd. for* $C_{37}H_{38}N_6O_2$ (598.74): C, 74.22; H, 6.40; N, 14.04%. *Found*: C, 74.05; H, 6.43; N, 14.11%.

[3,3'-(Butane-1,4-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49h.



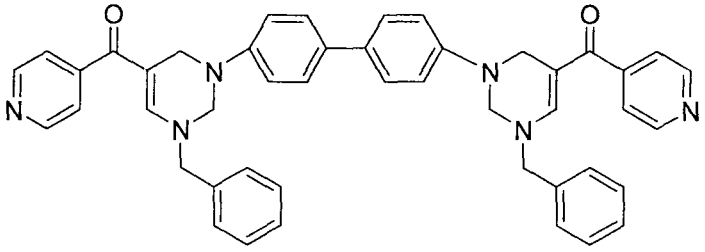
This compound was obtained as a light brown gum in 50% yield, IR (KBr): 1563, 1659 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25-1.33 (m, 4H), 2.34-2.41 (m, 4H), 3.64 (s, 4H), 3.93 (s, 4H), 4.27 (s, 4H) 7.15-7.35 (m, 16H), 8.67 (d, 4H); MS: m/z 612 [M^+]; *Anal. Calcd. for* $C_{38}H_{40}N_6O_2$ (612.76): C, 74.48; H, 6.58; N, 13.71%. *Found*: C, 74.31; H, 6.54; N, 13.77%.

[3,3′-(1,4-Phenylene)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis(pyridin-4-ylmethanone) 49i.



This compound was obtained as a brown solid in 40% yield, mp188-190^{0}C; IR (KBr): 1566, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.27 (s 4H), 4.30 (s, 4H), 4.52 (s, 4H), 6.74 (s, 4H), 7.05-7.15 (rn, 6H), 7.21-7.35 (m, 10H), 8.66 (d, 4H); MS: m/z 632 [M^+], 633 [MH^+]; *Anal. Calcd. for* $C_{40}H_{36}N_6O_2$ (632.75): C, 75.93; H, 5.73; N, 13.28%. *Found*: C, 75.72; H, 5.69; N, 11.32%.

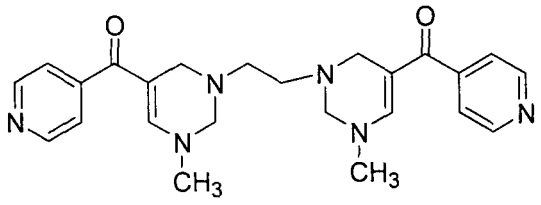
[3,3′-(Biphenyl-4,4'-diyl)bis(1-benzyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis- (pyridin-4-ylmethanone) 49j.



This compound was obtained as a brownish solid in 45% yield, mp 225^{0}C(decomp); IR (KBr): 1565, 1653 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 4.32 (s, 4H), 4.38 (s, 4H), 4.64 (s, 4H), 6.90 (s, 4H), 7.09-7.15 (m, 6H), 7.26-7.41 (m, 14H), 8.66 (d, 4H): Mass (m/z)

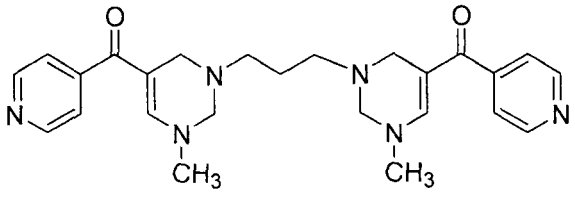
708, 709 [MH+]; *Anal. Calcd. for* $C_{46}H_{40}N_6O_2$ (708.85): C, 77.94; H, 5.69; N, 11.86%. *Found*: C, 77.74; H, 5.64; N, 11.90%.

[3,3'-(Ethane-1,2-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49k.



This compound was obtained as a light brown gum in 45% yield, IR (KBr): 1565, 1654 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.64 (s, 4H), 3.02 (s, 6H), 3.35 (s, 4H), 3.41 (s, 4H), 6.85 (s, 2H), 7.40 (d, 4H), 8.66 (d, 4H); ^{13}C NMR ($CDCl_3$): δ 40.00, 45.11, 53.52, 70.05, 84.82, 106.25, 122.36, 149.60, 151.50, 189.93; *Anal. Calcd. for* $C_{24}H_{28}N_6O_2$ (432.52): C, 66.65; H, 6.53; N, 19.43%. *Found*: C, 66.81; H, 6.57; N, 19.50%.

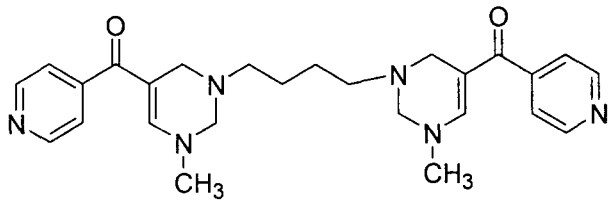
[3,3'-(Propane-1,3-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49l.



This compound was obtained as a light brown gum in 55% yield, IR (KBr): 1560, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.74-1.78 (m, 2H), 2.64 (t, 4H), 2.98 (s, 6H), 3.31 (s,

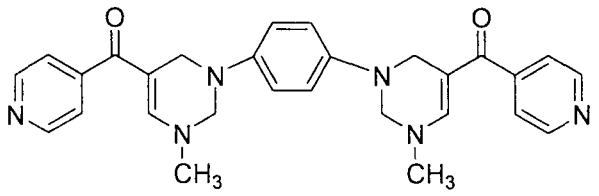
4H), 3.48 (s, 4H), 6.97 (s, 2H), 7.33 (d, 4H), 8.66 (d, 4H); ^{13}C NMR ($CDCl_3$): δ 26.13, 41.21, 46.53, 50.95, 68.86, 104.95, 122.33, 149.63, 150.25, 151.20, 189.20; *Anal. Calcd. for* $C_{25}H_{30}N_6O_2$ (446.54): C, 67.24; H, 6.77; N, 18.82%. *Found*: C, 67.15; H, 6.75; N, 18.91%.

[3,3'-(Butane-1,4-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49m.



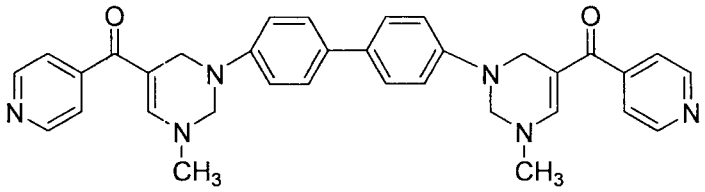
This compound was obtained as a light brown gum in 60% yield, IR (KBr): 1563, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.58-1.73 (m 4H), 2.38-2.57 (m, 4H), 2.96 (s, 6H), 3.74 (s, 4H), 3.95 (s, 4H), 6.96 (s, 2H), 7.32 (d, 4H), 8.70 (d, 4H); MS: m/z 461 [MH^+]; *Anal. Calcd. for* $C_{26}H_{32}N_6O_2$ (460.57): C, 67.80; H, 7.00; N, 18.25%. *Found*: C, 67.98; H, 7.06; N, 18.21%.

[3,3'-(1,4-Phenylene)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis-(pyridin-4-ylmethanone) 49n.



This compound was obtained as a light brown solid in 40% yield, mp 235^{0}C; IR (KBr): 1615, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.01 (s, 6H), 4.25 (s, 4H), 4.59 (s, 4H), 6.95-6.99 (m, 6H), 7.32-7.33 (m, 4H), 8.64-8.70 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 40.7, 45.1, 66.6, 105.2, 118.8, 121.9, 142.6, 146.9, 149.4, 151.7, 188.40; *Anal. Calcd. for* $C_{28}H_{28}N_6O_2$ (480.56): C, 69.98; H, 5.87; N, 17.49%. *Found*: C, 69.85; H, 5.90; N, 17.61%.

[3,3′-(Biphenyl-4,4'-diyl)bis(1-methyl-1,2,3,4-tetrahydropyrimidine-5,3-diyl)]bis- (pyridin-4-ylmethanone) 49o



This compound was obtained as an off white solid in 40% yield, mp 235^{0}C; IR (KBr) 1563, 1654 cm^{-1}; ^{1}HNMR ($CDCl_3$): δ 3.02 (s 6H), 4.36 (s, 6H), 4.67 (s, 6H), 6.95-7.07 (m, 6H), 7.26-7.38 (m, 4H), 7.45-7.51 (m, 4H), 8.65-8.66 (m, 4H); Mass (m/z) 556 [M+], 557 [MH+]; *Anal. Calcd. for* $C_{34}H_{32}N_6O_2$ (556.66): C, 73.36; H, 5.79; N, 15.10%. *Found:* C, 73.21; H, 5.82; N, 15.29%.

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