CHAPTER I

INTRODUCTION

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 pharmacaeutical 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. They have subsequently been derivatized extensively and tested for their properties. A few such molecules are discussed in the following sections.
J. P. Dumas and coworkers have reported the synthesis of a series of substituted and fused pyridazines, which were actually three sets of compounds having a general structural formula (1),

\[
\begin{array}{c}
\text{A} \quad \text{B} \quad \text{Y} \quad \text{X} \quad \text{CR}_2^4 \quad \text{J} \quad \text{G}_4 \qquad \text{q'} \\
\text{E} \quad \text{D} \quad \text{L} \\
\text{G}_3 \quad \text{q}
\end{array}
\]

wherein A, B, D, E and L: nitrogen-containing heterocycle; X and Y: a variety of linking units. R\(_1\) and R\(_2\): independent substituents or together may be a ring defining bridge. J: aryl, pyridyl, or cycloalkyl groups. G: variety of defined substituents p, q and q\(^{'}\) = 0, 1, 2.

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

\[2\]  \[3\]  \[4\]
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\textsuperscript{7} the synthesis of another series of pyridazine analogues which were represented by the following general formula (9),

\begin{equation}
\text{9}
\end{equation}

wherein ring C: 5 or 6 membered carbon chain ring and may contain a heteroatom,
\( n \): 0 to 4, \( R_1 \): halogen atom or lower alkyl, alkoxy, cycloalkyl, nitro or cyano group.
\( A \): hydrogen/ halogen or \(-NR^4R^5\) 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, NR²R₈ where R²R₈= 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.

![Structural formulas](image)

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.

![Active compounds](image)
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.

Further, S Nakamura has reported 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.
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 the synthesis and activity of a series of novel pyrazine derivatives. These compounds were represented by the general formula (32),

![Chemical Structure](image-url)
Wherein W: oxygen or a sulfur atom, a sulfinyl group or a sulfonyl group.
R₁: 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

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 \textit{Staphylococcus aureus}, \textit{Trichophyton mentagrophytes}, \textit{Candida albicans}, \textit{Cercospora 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\textsuperscript{11} the synthesis and activities of substituted 2-chloro-3-phenoxypyrazines and 2-chloro-6-phenoxypyrazines of general formula 43.

\[
\begin{array}{c}
\text{H} \\
\text{N} \\
\text{N} \\
\text{\textit{Cl}} \\
\text{\textit{R}_1} \\
\text{\textit{R}_2}
\end{array}
\]

43

wherein \(\text{R}_1, \text{R}_2\): Hydrogen, lower alkyl/alkoxy, nitro, amino, cyano, trifluoromethyl, acetyl, methylthio, methylsulfinyl/sulfonyl, aminosulfonyl, phenoxy or halogen or alternatively \(\text{R}_1, \text{R}_2\): \(-\text{O}-\text{CH}_2-\text{O}-\)

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.
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, whereupon 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 B₂ 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. Pyrimidines are associated with various therapeutic activities such as antiviral, antitumor, antibacterial.
anti-hypertensive\textsuperscript{22}, neuropeptide Y (NPY) antagonist activity\textsuperscript{23}, diuretics\textsuperscript{24}, antimalarial\textsuperscript{25} etc. Several synthetic strategies have been reported for the preparation of derivatives\textsuperscript{26-32}. Some of these are discussed in the following sections.

1.3.1 A. K. Nezhad and coworkers reported\textsuperscript{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\textsubscript{2}CO\textsubscript{3} in MeCN at room temperature (Scheme 2).

![Scheme 2](attachment:image.png)

Some of the N3-alkylated N1-substituted pyrimidine nucleobases synthesized by them are shown below.

![Nucleobases](attachment:nucleobases.png)

These N1, N3-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\textsuperscript{35} the synthesis of a series of \textit{o}-fluorophenoxy acetylimino-2\textit{H}-1,2,4-thiadiazolo[2,3-\textit{a}]pyrimidine derivatives (58) from 57 using bromine as oxidant (Scheme 3).

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

1.3.3 Ana M.F. Oliveira-campos and coworkers reported\textsuperscript{36} the synthesis of the 4-substituted pyrazolo[3,4-\textit{d}]pyrimidines as shown below (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 as shown in the (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 hexahydrocyclopentan[d]pyrimidine derivatives 72. 6-bromomethyl pyrimidine underwent nucleophilic substitution 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).

\[ \text{Scheme 7} \]
Some of these compounds exhibited promising antitubercular activities against mycobacterium tuberculosis. They also reported the synthesis of some pyrimidine derivatives containing the phenothiazine nuleus of the type 83 (Scheme 8).

These were also tested for their antitubercular activities.

1.3.6 C. Hu and coworkers synthesized a series of $S\text{-thiazolo}[3,2-\alpha]\text{pyrimidine}$ derivatives of the type 84 and 85. Some of the compounds showed good activity as AchE inhibitor.

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 the synthesis of substituted pyridyl methyl cyanoiminotetrahydropyrimidine (88) by the reaction of compounds 86 and 87 in appropriate solvents (Scheme 9),

\[
\begin{align*}
\text{86} & \quad \text{87} \\
\text{88}
\end{align*}
\]

wherein \(R_3: \text{H or alkyl groups}, \ X= \text{Halogen}, \ n = 0, 1, 2 \text{ or } 3\)

\(Y_1=Y_2 \) leaving groups such as \(-\text{SCH}_3, -\text{O-CH}_3, -\text{O-C}_6\text{H}_5\).

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

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 the synthesis of substituted 2,3,4,5-tetrahydropyrimidines and their derivatives of the general formula 92.
wherein \( R_1-R_6 \): hydrogen, alkyl, aryl, aralkyl, cycloalkyl, heterocyclic substituted derivatives thereof.

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

1.4.2a By the reaction of carbonyl compounds 93 (ketone or aldehyde) with \( \text{NH}_3 / \text{NH}_4\text{OH} \) and a sulphur-containing catalyst (eg \( \text{CS}_2 \)) (Scheme 10).

\[
\begin{align*}
\text{R}^1,\text{R}^2,\text{NH},\text{OH} / \text{NH}_3 & \xrightarrow{\text{Sulphur catalyst}} \text{R}^1,\text{R}^2,\text{NH}^+\text{R}^3,\text{CH}_2\text{R}^4,\text{R}^5,\text{R}^6
\end{align*}
\]

Scheme 10

1.4.2b The reaction of an \( \alpha, \beta \)-unsaturated ketones 95 and a carbonyl compound 96 and \( \text{NH}_3 / \text{NH}_4\text{OH} \) without a catalyst (Scheme 11).

\[
\begin{align*}
\text{R}^1,\text{R}^2,\text{O} & \xrightarrow{\text{NH}_4\text{OH}/\text{NH}_3} \text{R}^1,\text{R}^2,\text{NH} \quad \text{NH}_4\text{OH}/\text{NH}_3 \quad \text{NH}^+\text{R}^3,\text{R}^4
\end{align*}
\]

Scheme 11

1.4.2c By the reaction of an \( \alpha, \beta \)-unsaturated ketone 95, 1-aminoalcohol 98 and \( \text{NH}_3 / \text{NH}_4\text{OH} \) without a catalyst (Scheme 12).
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).

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).

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.

\[
\begin{align*}
\text{Scheme 15}
\end{align*}
\]

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).

\[
\begin{align*}
\text{Scheme 16}
\end{align*}
\]

When \(n\) is less than 4, a mixture of products with the \(-\text{CH}_2\text{OH}\) 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).
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).

Similarly, when the reaction was carried out with 1 molar ratio of formaldehyde three possible products 111, 112 and 113 were obtained (Scheme 19).
These compounds when heated in the presence of Lewis acid such as FeCl₃, AlCl₃, etc. polymerize to form a compound having the general structure 115 with the liberation of ammonia. (Scheme 20)

\[
\begin{align*}
R & = \text{H, Hydrocarbon, cyclic group} \\
\text{Scheme 20}
\end{align*}
\]

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 the synthesis of tetrahydropyrimidines of the type 116,

wherein \( X: \) Si, Ge; \( A: \) alkylene, alkenylenes
\( R_1-R_6: \) alkyl, alkenyl; \( R_2-R_3: \) ethyl, propyl and each group substituted with methyl.
The tetrahydropyrimidines of the above series were found to be very good anthropocides

Takahiro and coworkers also prepared Tetrahydropyrimidines. They reported the synthesis of 6-[\( N-(6\)-chloro-3-pyridylmethyl)-\( N\)-methylamino]-3-(4-fluorobenzyl)-1-methyl-5-nitro-1,2,3,4-tetrahydropyrimidine (117) which was used as noxious organism controlling agent for example, to control Laodelphax straetellus at 800 ppm with 100% mortality rate.
1.5.2: F. Uu and coworkers have also reported\textsuperscript{47} the synthesis of tetrahydropyrimidines of the general structure \textbf{118},

\begin{center}
\includegraphics[width=0.2\textwidth]{117.png}
\end{center}

wherein $R$: NHCH$_2$Y; $R_1$=low alkyl group; $R_2$=Alkenyl, aralkyl, haloalkyl groups; $Y$: 2-choloro-5 Pyridyl. For example 4- (2-Chloro-5-pyridylmethyl)amino-1,3-dimethyl-5-nitro-1,2,3,6-tetrahydropyrimidine (\textbf{119}).

\begin{center}
\includegraphics[width=0.2\textwidth]{119.png}
\end{center}

This compound was found to control Nepholettix cicecticeps 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.

1.5.3 H. Uneme and coworkers reported the synthesis and activity of a series of tetrahydropyrimidines and their salts whose general structure can be represented by

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_3 & \quad \text{R}_4
\end{align*}
\]

wherein \( \text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4 \): hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

\( \text{X} \): 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 (\( \text{R}_1-\text{R}_4 \) has the same meaning as above) (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).

![Scheme 22](image)

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

where substituents have their usual meaning and R₆ 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).
1.5.3c By reacting a compound of the formula 137 (where of the groups R₁ to R₄ at least one means a H atom and the rest alkyl group) with 138, wherein R₇ 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).
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).
1.5.4 B. W. Kruger and his coworkers synthesized and tested many 1,2,3,4-tetrahydropyrimidines of the general structure 152,
wherein Het: substituted pyridyl or thiazolyl; R₁-R₂: C₁-C₄ alkyl,
R₁-R₂: 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 NR₄R₅ where
R₄ and R₅ represents H, C₁-₄ alkyl, phenyl, N-alkyl or N-phenyl,
R₃: represents one of the following groups

\[ \begin{align*}
R_6 & = \text{alkyl, aryl, aralkyl, heteroalkyl, alkoxy etc.} \\
X & = \text{O, S, and R}^7 : \text{H or C}_{1-4} \text{ alkyl.}
\end{align*} \]

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 \( R_1, R_2, \text{Het}, A \) and \( R_3 \)
have their usual meaning. Particularly preferred compounds were those in which \( \text{Het} \)
represents 2-Chloro-5- methylpyridine or 2-chloro-5-methyl-thiazole and \( R_1, R_2 \)
represents methyl, ethyl and together with adjacent atoms represents 1,3,5-trimethyl-
2-methylene-hexahydropyrimidine.
If, for example, 3-(2-chloropyridin-5-yl-methyl)-2-nitromethylene-imidazoline (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 \(-20^\circ C\) to \(120^\circ C\) preferably between \(0^\circ C\) and \(80^\circ C\). In general the process was carried out under atmospheric pressure, however, it can also be carried out under elevated or reduced pressure.
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-$y$)-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,

\[
\begin{align*}
\text{O}_2\text{N} & \text{ } \text{ } \text{O}_2\text{N} \\
\text{R}_{10} & \text{ } \text{ } \text{R}_{10} \\
\text{R}_2 & \text{ } \text{ } \text{R}_2 \\
\text{ Het} & \text{ } \text{ } \text{Het} \\
\text{NHR} & \text{ } \text{ } \text{NHR} \\
\text{ (O)n} & \text{ } \text{ } \text{ (O)n} \\
\text{167} & \text{ } \text{ } \text{168} & \text{ } \text{ } \text{169}
\end{align*}
\]

Scheme 32

wherein $R_{10}$: 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).

\[
\begin{align*}
\text{O}_2\text{N} & \text{ } \text{ } \text{O}_2\text{N} \\
\text{R}^{10} & \text{ } \text{ } \text{R}^{10} \\
\text{S} & \text{ } \text{ } \text{S} \\
\text{NH}_2 & \text{ } \text{ } \text{NH}_2 \\
\text{ (O)n} & \text{ } \text{ } \text{ (O)n} \\
\text{170} & \text{ } \text{ } \text{171a} + \text{171b} & \text{ } \text{ } \text{172}
\end{align*}
\]

Scheme 33

Here $R^2$, $R^{10}$, A and n have the above-mentioned meanings.
Other nitromethylene derivatives that were prepared are shown below,

![Chemical structures](173, 174, 175)

wherein $R^1$, $R^2$ and $A$ have the above mentioned meaning and:

$Z = \begin{align*}
\text{H}_2 & \quad \text{C}_\text{H}_2\text{OH}, \\
\text{CH}_3 & \quad \text{C}_\text{H}_2\text{OH}, \\
\text{CH}_3 & \quad \text{C}_\text{H}_2\text{OH}.
\end{align*}$

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 than their monomer counterparts. The following paragraphs describe some of these molecules.

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

The activity of these dimers were compared to that of their monomer counterparts 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.
1.6.2 R. J. Kern and coworkers have reported 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.
Minimun inhibitory concentration
MIC, microgram/mL

<table>
<thead>
<tr>
<th></th>
<th>SA1199</th>
<th>SA1199-3</th>
<th>SA1199B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td>2</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>0.06</td>
<td>0.125</td>
</tr>
<tr>
<td>4</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Ciprofloxacin monomer</td>
<td>0.125</td>
<td>1</td>
</tr>
</tbody>
</table>
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 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.
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 the synthesis of bis-heterocycles of the type (183) and (184).

1.6.5: K. M. Lokanatha Rai and coworkers have reported the synthesis of a series of bis-heterocycles of the type 185 and 186.
1.6.6 V. Padmavathi and coworkers have reported\textsuperscript{56} the synthesis of sulfone linked bis-heterocycles, pyrrole together with pyrazole or isoxazole units of the type 187 and 188.

1.6.7 S. C. Jain and coworkers have reported\textsuperscript{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).
Y. N. Mabkhoot has reported the synthesis of a series of bis-heterocycles having the structures 191 and 192 containing thieno-[2,3-b]-thiophene linking unit.
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\(^9\) that condensation of 2 mmols of an alkylene polyamine having at least one primary amino group separated from another primary or secondary amino group by 3 carbon atoms with one mole of dicarboxylic preferably at 350\(^{0}\)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.

\[
\begin{align*}
\text{R:} & \quad \text{hydrocarbon radical containing at least 2 carbon atoms.} \\
\text{R':} & \quad \text{hydrogen, a hydrocarbon or a substituted hydrocarbon radical.}
\end{align*}
\]

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(4H)-diyl))dipropan-1-amine (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).

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, oiliness 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 C₃ to C₅₀ amine containing 1,3-diaminopropane (200) group with ethylenediaminetetracetic acid (EDTA)(199) or nitrilotriacetic acid (202) at a temperature of 150°C to 250°C for 10 to 100 hours⁶⁰ (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.


41. L. Gsell, *USPAT 4948798*.
42. B. A. Oude Alink, *USPAT 4145545*.
44. B. A. Oude Alink and B. T. Outlaw, *USPAT 4343930*.
49. B. W. Kruger, H. Uhr, J. Kanellakopulos, E. R. Gesing, H. Wolf, A.-
   Turberg, N. Menecke, C. Erdelen, U. W. Wachendroff-Neumann, J.
   Hartwig, USPAT 5869491.
    2223.
52. F. Q. He, X. H. Liu, B. L. Wang and Z. M. Li, Heteroatom. Chemistry.,
53. A. Komaraiah, K. Ramakrishna, B. Sailu and P. S. N. Reddy, Arkivoc,
    2007 (xiv), 110.
    309.
    370.
56. T. Radhalakshmi, K. Mahesh, A. V. Nagendra Mohan and V. Padmavathi,
    (xv), 54.
58. Y. N. Mabkhoot, Molecules., 2009, 14, 1904.
60. B. W. Hotten, USPAT4157972.