CHAPTER - 2

section 2.1  Application of selected heterocycles
Section 2.2  Aim and work plan of the research
Section - 2.1: Applications of the selected heterocycles

The molecular modification of known pharmacodynamic compounds is a main kind of research in the field of chemotherapy. The structural modification can be carried out by substituting one group (s) by other group(s), adding new group(s), saturating the compound by adding hydrogens or by modifying the acidity or basicity. In each case a complex Structure Activity Relation is obtained. These relations are identical and serve as a guiding factors in mapping the structural features of the compounds with analogous activities.

A brief description regarding the applications of the heterocyclic moieties, (N-methyl piperazine, morpholine, thiaiazole and azetidinone) present in the final compounds has been made herein to explain the suitability and importance of the proposed research work.

N - METHYL PIPERAZINE

N- methyl piperazine derivatives exhibit potent biological activities such as- antiinflammatory, antiviral, antiulcer, antifilarial, neuroleptic, antipsychotic, local anaesthetic, antimalarial, antihistaminic, antiallergic, CNS depressant, sedative, antihypertensive, anthelmintic, neuroleptic etc.

The piperazine derivatives lacking the carboethoxy group but having methyl group at position - 4 also showed promising activity against microfilaria. 1-ethyl carbamyl -4- methyl piperazine hydrochloride and 1- di-isopropyl carbamyl -4- methyl piperazine display potential microfilarial activity. In dogs only the compound which produced measurable reductions in microfilaria in tolerated dose was 1-diethyl carbamyl -4- methyl piperazine hydrochloride.82-86

A series of trans and cis 2-aryl -2,3- dihydro -3- piperazinylmethyl -1,5-benzothiazepine 4(5H)- one (44) and their related compounds were synthesised and found to be potent antiulcer agents with gastric antisecretary and gastric mucosal blood increas-
ing activity.\textsuperscript{87}

\[
\text{(44)}
\]

4- [Methyl -1- (4-nitrophenyl) -amino phenyl thiocarbamide ] -piperazine (45) is an experimental antifilarial\textsuperscript{88} drug currently being evaluated in man.

\[
\text{(45)}
\]

1- Piperazino -3- phenyl indan derivative (46) has been synthesised and shown neuroleptic activity\textsuperscript{89} similarly to chlorpromazine.

\[
\text{(46)}
\]

4- Amino -6- chloro -2- piperazinopyrimidines (47) displayed with selective affinity for \(\alpha_2\) Adrenoceptors.\textsuperscript{90}
Clozapine analogues (48) have been synthesised and showed antipsychotic activity.\textsuperscript{91}

Substituted piperazine (49) and N-alkyl troponyl piperazine (50) displayed induced hypokinesia in rats\textsuperscript{92}.

Amides and sulphonamides of 5-and 6-amino-2-3-bis (4-alkyl-1-piperazinyl) quinoxalines (51) were synthesised and found to be antiamoebic activity.\textsuperscript{93}
Several alkyl piperazines (52) and (53) were found as dopamine antagonists in the isolated rabbit ear artery preparation\textsuperscript{94}.

\[
\begin{align*}
\text{(52)} \\
\text{CH} = \text{CH} - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{(53)} \\
\text{CH}_3 - \text{N} - \text{C} - \text{CH}_2 - \text{CH}_2 - \text{Cl}
\end{align*}
\]

Mezilamine or [5-(methylthio)-4-(piperazinopyrimidines) (54) were synthesised and shown to be dopamine antagonists and potential antipsychotic drugs\textsuperscript{95}.

\[
\begin{align*}
\text{(54)} \\
\text{Cl} - \text{SCH}_3 - \text{N} - \text{CH}_3
\end{align*}
\]

2- Piperazine carboxanilides (55) have been synthesised and found to be local anaesthetic activity\textsuperscript{96}.

\[
\begin{align*}
\text{(55)} \\
\text{R} = \text{H} / \text{alkyl} \\
\text{R}_1, \text{R}_2, \text{R}_3 = \text{alkyl}
\end{align*}
\]
1,4- Disubstituted piperazines (56) were synthesised and tested for anthelmintic, antiviral, amoebiasis, antimalarial, schistosomiasis and antiinflammatory activities.

![Chemical Structure](image)

R=CH₃
X=Cl / Br / NO₂

Several piperazines derivatives (57) and (58) have been synthesised which exhibited CNS depressant activity.

![Chemical Structure](image)

R= alkyl, cycloalkyl, aralkyl, aryl and heterocyclic group
A= CH₂CO, CH₂CH₂O(CH₂)₂, O(CH₂)₄, S(CH₂)₂, NH(CH₂)₂

![Chemical Structure](image)

R=H / alkyl

A=Ar-CO—CH₂—CH₂—N

![Chemical Structure](image)
A novel type of substituted piperazine (59-61) with high antiserotonin potency were synthesised and shown to be high antihistamine, antiallergic, CNS depressant and lower acute toxicity$^{100}$.

![Chemical structures](59-61)

Alkyl derivatives of 1-phenyl piperazine (62) and 4-diphenyl methyl piperazine (63) have been synthesised and found to have a CNS depressant and stimulant activity respectively$^{101}$.

![Chemical structures](62-63)
2- Diethyl amino ethyl -4- methyl piperazino-1- carboxylate (64) has been synthesised and reported as antiviral activity against an influenza infection in mice\textsuperscript{102}.

\[
\text{CH}_3\cdots\text{N}\cdots\text{COO}\cdots\text{CH}_2\cdots\text{CH}_2\cdots\text{N} (\text{C}_2\text{H}_5)_2
\]

(64)

1- Substituted -4- (1,2- diphenyl ethyl) - piperazine derivatives (65) have been synthesised and found to be analgesic activity\textsuperscript{103,104}

\[
\text{CH}_2\cdots\text{CH}\cdots\text{N} \cdots \text{N-} \text{R}
\]

(65) \quad R= \text{alkyl} / \text{aryl}

1- (3,4- Dimethoxy benzyl) -4- phenyl piperazine (66) have been prepared and found to be most potent inhibitory effect against epinephrine as adrinolytic and antihistaminic effect\textsuperscript{105}.

\[
\text{H}_3\text{CO}\cdots\text{CH}_2\cdots\text{N} \cdots \text{N-} \text{Ph}
\]

(66)
2-Phenyl-4-methyl piperazine (67) has been synthesised and shown to be anticonvulsant activity against seizures induced by electroshock\textsuperscript{106}.

![Diagram of 2-Phenyl-4-methyl piperazine (67)]

The compound (68) has been synthesised and found to be effective as a sedative\textsuperscript{107}.

![Diagram of Compound 68]

Various benzyl piperazines have adrenolytic antihistamine and potent inhibitory effect against epinephrine\textsuperscript{108}. Several bicyclic homologues of methyl substituted piperazine (69) were reported as potent local anaesthetic, anticholinergic, spasmylytic, antihistamine and diuretic\textsuperscript{109}. Substituted 2-phenoxy propionic acid and butyric acid derivatives (70) were reported to possess moderate hypocholesterinic activity in lowering of serum cholesterol in guinea pigs\textsuperscript{110}.

![Diagram of Compound 69 and 70]

- $R_1 = p$-$H_2N\text{C}_6\text{H}_4\text{CO}_2\text{CH}_2\text{CH}_2$,
- $(\text{C}_6\text{H}_5)_2\text{CH}$, $(\text{C}_6\text{H}_5)_2$
- $R_2 = \text{CH}_3$
- $R_1 = \text{CH}_2\text{CH}=\text{CH}_2$
Diethyl carbamazine, 1-diethyl carbamyl 4-methyl piperazine (71), medizine(72), hydroxizine(73), dibozane(74) are reported as antihistamine, sedative, antihypertensive and anthelmintic against filaria such as Loa-loa, Wuchereria brancrofti, Wuchereria malayi and Onchocera volvulus respectively.
Several methyl substituted piperazine derivatives with phenothiazine such as perazine (75), prochlorperazine (76), trifluoperazine (77), butaperazine (78), triethyl parazine (79) and thioperazine (80) were reported as psychotherapeutic drugs.\textsuperscript{113}

\begin{align*}
(75) & \quad R_1 = \text{H}; \quad R_2 = \text{CH}_3 \\
(76) & \quad R_1 = \text{CO-(CH}_2)_2\text{-CH}_3; \quad R_2 = \text{CH}_3 \\
(77) & \quad R_1 = \text{Cl}; \quad R_2 = \text{CH}_3 \\
(78) & \quad R_1 = \text{S-CH}_2\text{-CH}_3; \quad R_2 = \text{CH}_3 \\
(79) & \quad R_1 = \text{CH}_3; \quad R_2 = \text{CH}_3 \\
(80) & \quad R_1 = \text{SO}_2\text{-N(CH}_3)_2; \quad R_2 = \text{CH}_3
\end{align*}

Pipecurium (81) is another piperazine compound with an androstane nucleus displays as a potent neuromuscular blocking drug of long duration of action.\textsuperscript{114}
Many clinically used piperazines viz. 1- methyl- 4- (3,4,5- trimethoxy benzoyloxy)- methyl homopiperazine (dilzap); 4-bis [3-(3,4,5- trimethoxybenzoyloxy)- propyl]- homopiperazine; N-methyl-N'- [4- chloro- benzhydryl] -piperazine (chlorocyclizine) (82) and N-methyl -N'-(2- chlorobenzhydryl)- piperazine function as antihypertensive\textsuperscript{112,115}, coronary vasodilator\textsuperscript{112}, antihistaminic\textsuperscript{112,115} and parasympatholytic drug\textsuperscript{116}.

\[ \text{(82)} \]

2-Diethylamino ethyl 4- methyl piperazine 1- carboxylate (83) was screened for its antiviral activity against an influenza A (PR8) infection in mice\textsuperscript{117,118}.

\[ \text{(83)} \]

1,4- Disubstituted piperazines (84) have been used as antiparasitic agents\textsuperscript{119}.

3- Methyl -5-nitro-6 (N-alkyl/aryl piperazino) -2,4- diones (85) were synthesised and found to be less leishmanicidal\textsuperscript{120}.
N- heterocyclyl alkyl or N- [(polycyclyl) - alkyl] -N'- substituted piperazines have been synthesised and found to be insecticidal activity\textsuperscript{121}. 1-[(1-phenyl-2-pyrrolidonyl)-methyl]-piperazine have been synthesised and found to be antiischemics and anticonvulsant activity\textsuperscript{122}. 1-4-bis (3',4',5'-trimethoxybenzoyl) -2-[(substituted carbonyl and carbamoyl oxy)]-methyl]-piperazines have been prepared and showed antagonists activity\textsuperscript{123}. N-[(2-oxopyrrolidin-1-yl)-acetyl]-piperazine derivatives have been synthesised and used for the treatment of senile dementia, psychosis, or amnesia\textsuperscript{124}.

N,N'- disubstituted piperazines have been prepared and found to be plant fungicidal activity and dysuria\textsuperscript{125}. New -N- substituted piperazine derivatives have been
synthesised and found to be improving functional disorder of brain\textsuperscript{126}. N-N'-bis-(acyl acyl)-piperazines have been synthesised and found to be anticancer adjuvants\textsuperscript{127}. 
Morpholine

The morpholine molecule and its derivatives are known to be biological active. Several morpholine derivatives have been used as a medicinal agent. Some morpholine derivatives have been synthesised and found to possess analgesic, CNS depressant, antiinflammatory, antiallergic, antimicrobial, anthelmintic, antiviral, anaesthetic and plant growth promoting properties\textsuperscript{128-134}.

Phenothiazine and phenidimetrazine (86) and (87) are the morpholine derivatives that are claimed to possess fewer peripheral adrenergic effects as compared to amphetamine in relation to their central anorexic action\textsuperscript{135-136}.

![Chemical structure of morpholine derivatives](image)

Some N-[2- (phenoxy/chloro/bromo/nitro phenoxy)- acetyl]- morpholines (88) have been synthesised and found to possess antiinflammatory, CNS depressant, antiallergic plant growth promoting, antimicrobial and anthelmintic properties.\textsuperscript{137-139}

![Chemical structure of morpholine derivative](image)

The compound (89) were prepared and found to be agrochemical fungicides\textsuperscript{140}.
3-Phenyloctahydro pyrido-2, 1-c and 1:4 oxazine hydrochloride (90) have been synthesised which was shown to possess a depressant action on the central nervous system\textsuperscript{141}.

(S-) -3 [(Benzyloxy)-methyl]-morpholine hydrochloride (91) have been synthesised and found to be non stimulant appetite suppressant property\textsuperscript{142}. 
Morpholinyl anthracyclines (92) and (93) are new analogues which were 100 to 1000 times more potent than doxorubicin against tumor in cell culture or in mice.
6- Morpholino -4, 4 - diphenyl -3- heptatone (94) was found to be a potent analgesic activity\(^\text{144}\).

\[
\begin{align*}
\text{CH}_2\text{-CH-N} & \\
\text{CH}_3
\end{align*}
\]

(94)

The diguanide morpholine (95) enjoyed a short vogue as a prophylactic against influenza\(^\text{145}\).

\[
\begin{align*}
\text{O} & \\
\text{N-C-NH-C-NH}_2 & \\
\text{NH} & \quad \text{NH}
\end{align*}
\]

(95)

2-O-ethoxy phenoxy methyl morpholine (vivalan) (96) is very active antidepressant drug\(^\text{146}\).

\[
\begin{align*}
\text{OC}_2\text{H}_5 & \\
\text{OCH}_2 & \\
\text{N}
\end{align*}
\]

(96)

2- (Morpholino)- acetyl amino-5- methyl-1,3,4- thiadiazole (97) has been synthesised and shown to be antiinflammatory agent\(^\text{147}\).
4- (N- morpholino)- phenyl thiosemicarbazide substituted isattins (98) have shown antibacterial and antiviral activities\textsuperscript{48}.

Several 2- cyano-3- (methoxy substituted phenyl)- acrylamides represented by the structures (99) and (100) have been synthesised and found to be useful herbicides\textsuperscript{149,150}.

4-[3'-(1'- Unsubstituted/substituted-5- phenyl)- pyrazolinyl morpholines found remarkable antimicrobial activity\textsuperscript{151} against pathogenic bacteria and fungi \textit{Escherichia coli}, \textit{Streptococcus aureus} and \textit{Tricophyton mentagrophytes}. .
The morpholine derivatives (101) was synthesised and found to be potential antinociceptive agent\textsuperscript{152}.

\[
\begin{array}{c}
\text{O} \\
\text{OH} \\
\text{N} \\
\text{CH₃} \\
\end{array}
\]

(101)

Some morpholine derivatives (102) were found to be more potent analgesic, antinflammatory and antimicrobial agents\textsuperscript{64}.

\[
\begin{array}{c}
\text{O} - \text{CH (R)} - \text{C} - \text{N} \\
\end{array}
\]

(102) \hspace{1cm} R=H / CH₃

The pharmacological significance of morpholino oxadiazole derivative (103) has reported as potent CNS, cardiovascular and antiinflammatory agent\textsuperscript{153}.

\[
\begin{array}{c}
\text{NO₂} \\
\text{N} \\
\text{CH₂} - \text{N} \\
\text{NO₂} \\
\text{C} - \text{O} - \text{C=S} \\
\end{array}
\]

(103)

3- Ethyl-6,7- dihydro-2- methyl-5- morpholino- methyl- indole-4-(5H)- one hydrochloride (104) (molindone hydrochloride) an unique antipsychotic indoleamine is useful in the treatment of chronic schizophrenia\textsuperscript{154}.
(1- Ethyl - 3, 3- diphenyl) -4- (2- morpholino ethyl) -2- pyrrolidinone hydrochloride hydrate (105) (doxapram hydrochloride) is used to stimulate respiration\textsuperscript{155} in patients with post-anaesthetic respiratory depression and to hasten arousal during the period.

4-[3-(4- Butoxy phenoxy) - propyl]- morpholine hydrochloride (106) (promaxin hydrochloride) is too irritating for opthalmic use but an effective topical local anesthetic with few toxic reaction. It was used for relief of pain and itching due to insect bites, minor, wounds and haemorrhoids\textsuperscript{156}. 

\begin{equation}
\text{CH}_3-(\text{CH}_2)_3-O-\text{Ph}-O-(\text{CH}_2)_3-N^+\text{Cl}^-
\end{equation}
4-(N-heteroyl/diphenyl/aminoacetyl/propionyl)- morpholines (107) have been synthesised and found to be anthelmintic and antimicrobial activities\textsuperscript{157}.

\[
\begin{array}{c}
\text{HET} \\
\begin{array}{c}
\text{R} \\
\text{N-CH-C-N}
\end{array}
\end{array}
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

(107)

\[ R = \text{H} / \text{CH}_3 \]

\text{HET} \quad \text{N} = \text{benzotriazol / phenothiazine / diphenylamine}

1-Oxa-7-azaspiro [4,5]- decanes and triazolylmethyl- morpholines have been synthesised and found to be NK-1 receptor antagonists for treating mania or hypomania\textsuperscript{156}.

1-oxa-7-azaspiro [4,5]- deca

nes and triazolylmethyl- morpholines have been synthesised and found to be NK-1 receptor antagonists for treating aggressive behavior disorder\textsuperscript{159}.

N-[(2-Substituted aryloxy) propanoyl]-piperazines and N-[(2-substituted aryloxy)-acetyl]-morpholine have been synthesised and found to be antiallergic activity\textsuperscript{37,38}.

N- (1-Formamido-2,2,2-trichloroethyl)-morpholine has been synthesised and found to be fungicidal activity\textsuperscript{160}.

Morpholine moiety containing modomycin derivatives have been synthesised and found to be antitumor agents\textsuperscript{161}. 
Some -2- (2'-aryl -6,8- substituted quinoline- 3-yl-methyl) -3- substituted amino methyl benzimidazoles (108) have been found to exhibit pronounced amoebicidal activity.\textsuperscript{162}

![Chemical structure](image)

(108) \( R = \text{Morpholino}; R_1 = H; R_2 = H \)
Thiadiazoles

The -N-C-S linkage present in thiadiazoles makes them of versatile biological interest as pesticides and chemotherapeutic agents. Thiadiazoles are reported as antibacterial\textsuperscript{163-165} antifungal\textsuperscript{166,167} insecticides\textsuperscript{168} pesticides\textsuperscript{169,170} herbicide\textsuperscript{171} CNS depressant, sedative, anticonvulsant, antiinflammatory and hypoglycemic agents\textsuperscript{172}.

2,5- Disubstituted -1,3,4-thiadiazoles \textbf{(109)} are reported as good antibacterial agent\textsuperscript{173}.

\begin{center}
\includegraphics[width=0.5\textwidth]{109.png}
\end{center}

\textbf{(109)} \hspace{1cm} \text{Ar = phenyl/ sub.phenyl}

2- Arylamino-5- aryloxymethyl -1,3,4- thiadiazoles \textbf{(110)} and 2-aryloxy methyl -5-phenyl -1,3,4- thiadiazolo-[3,2-a] -1,3,5 - triazine -7- thiones - \textbf{(111)} are reported as potential antifungal agents\textsuperscript{174}.

\begin{center}
\includegraphics[width=0.5\textwidth]{110.png}
\end{center}

\textbf{(110)} \hspace{1cm} \text{Ar = phenyl/ sub.phenyl}

2- Substituted -1,3,4 - thiadiazolo-[2,3-c] -1,2,4 - triazino-[5,6-b]- indoles \textbf{(112)} and 3,6,9 - triaryl -2- thioazolo-[4,5-d] -1,3,4- thiadiazolo-[2,3-b]-pyrimidines are also reported as antifungal agents\textsuperscript{175,176}.
R = H/OH/OCH₃/CH₃/Cl
5-[(3-Substituted isoxazolo(4,5-d)pyrimidin-4-yl)-oxymethyl]-2-(p-substituted phenyl amino-1,3,4-thiadiazoles) and 5-(2',4'-diphenoxymethyl)-2-(2'-aryl-5'H-4'-thiazolidinone)-1,3,4-thiadiazoles (113) are found to display antibacterial activity\textsuperscript{177,178}.

R = H/OH/OCH₃/NO₂/Cl
2-Amino-5-(4'-hydroxyalkoxyl 2',4'-dialkoxyl-5'-nitroaryl)-thia-3,4-diazoles (114) and 2-anilino-5-[4'-(substituted anilino)]-methyl-1,3,4-thiadiazoles(115) are found to exhibit antimicrobial activity\textsuperscript{179,180}.

R = H/CH₃/C₃H₅
2-(4-Chlorophenoxy)methyl-1,3,4-thiadiazolo[5,1-b]-imidazole-6-ones (116) and N-(2-mercapto acetyl)-5-amino (substituted aryl)-1,3,4-thiadiazolyl hydrazines are reported as good pesticides\textsuperscript{181,182}.

2 - 2-Dialkylphosphate/thiophates of 2-amino-5-(2,4-dichlorophenyl)-1,3,4-thiadiazoles (117) are found to act as potential insecticides\textsuperscript{183}.

2-(Substituted acetyl)-amino-5-alkyl-1,3,4-thiadiazoles (118) are reported as CNS depressant\textsuperscript{184}.
2-Amino-5-substituted-1,3,4-thiadiazoles (119) are found to exhibit CNS depressant, sedative and anticonvulsant activity.\textsuperscript{185}

\begin{center}
\begin{align*}
\text{R} &= \text{acetyl/sub.acetyl} \\
\end{align*}
\end{center}

2-Arylamino-5-[(p-3-aryl-4-oxoquinazolin-3-yl)-methylamino]phenyl]-1,3,4-thiadiazoles (120) are found to display hypoglycemic activity.\textsuperscript{186}

\begin{center}
\begin{align*}
\text{R} &= \text{cyclohexyl, furan, or } \text{phenyl} \\
\end{align*}
\end{center}

8-[5'-Aryl-1',3',4'-thiadiazol-2'-yl]-aminomethyl]-7-hydroxyl-acetoxy-4-methyl coumarins (121) have been synthesised and found to display antifungal activity against \textit{Aspergillus niger} and \textit{Helminthosporium oryzae}.\textsuperscript{187}
2-Aryl-3-[5'-o-hydroxy phenyl-1',3',4'-thiadiazol-2'-yl]-5H-methyl-4-thiazolidinones (122) have been synthesised and were screened for their antibacterial activity against *Streptococcus aureus*, *Escherchia coli* and antifungal activity *Aspergillus niger* and *Candida albicans*.

5-Aryl-2,3-dihydro-3-oxo-2-phenyl-1,2,4-thiadiazoles (123) have been synthesised and found to possess herbicidal and fungicidal activities.
Some 3-substituted -6- aryl amino -1,2,4- triazole -[3,4 -b] -1,3,4- thiazole (124) has been synthesised and screened for their fungicidal activity against Helminthosporium oryzae and Cephalosporium sacchari [190].

2,5 - Disubstituted -1,3,4 - thiazole (125) derivatives have been synthesised and shown antimicrobial activity [191].

2- (2 - Arylethyl) -5- phenylamino -1,3,4 - thiazole (126) are found to exhibit antiamoebic activity [192].
2- Arylideneamino -5- (N^{10} - phenothiazinomethyl) -1,3,4 - thiadiazoles
T-15807
(127) have been synthesised and screened for their antifungal activity^{71}.

(127) \( R_1 = R_2 = H / \text{alkyl} / \text{aryl} \)
Azetidinines

Staudinger\textsuperscript{193} before 1912, initiated work on the chemistry of the 2-azetidinones or β-lactams. Interest in these compounds was largely lost until 1943, when it was suggested that the Penicillin might contain azetidinone ring. Since then, a great deal of work has been done on these compounds.

A large number of antibiotics contain azetidinone moiety\textsuperscript{194,195}. The reactivity of azetidinones influences largely on substitution\textsuperscript{196,197}. 2-Azetidinones and its derivatives possess variety of therapeutic activities\textsuperscript{198,199}.

4- Aryl -1- [2′-4′- bis-(ethyl amino) -s- triazine -6′-yl-amino] -3- chloro-2-azetidinones (128) have been synthesised and exhibited highest antimicrobial activity against the various strains of bacteria and fungi\textsuperscript{200}.

![Chemical structure of 128]

(128) \hspace{1cm} R = alkyl /aryl

4- Oxothiazolidines, 4-oxoazetidines, malonanilic acid hydrazines and pyrazoline derivative of phenothiazine (129) have been synthesised and tested for their antimicrobial activity. These compounds exhibit moderate to good antibacterial and tuberculostatic activities\textsuperscript{201}. 


\[
\begin{align*}
\text{X} & \quad \text{N} \\
\text{X} & \quad \text{X} \\
\text{CO-CH}_2-\text{NH-} & \quad \text{N-} \\
\text{--CHR} & \quad \text{O} \\
\text{Cl} & 
\end{align*}
\]

(129) \hspace{1cm} R = \text{Different alkyl group} \\
X = \text{Br}

\[N^{10} - \text{ Arylidenehydrazidophenothiazine and their 4-thiazolidinones and 2-azetidinones (130) have been synthesised and exhibited antibacterial and antifungal activities}^{202}.\]

\[
\begin{align*}
\text{X} & \quad \text{X} \\
\text{CO-} & \quad \text{NH-} \quad \text{N-} \\
\text{--CHR} & \quad \text{O} \\
\text{Cl} & 
\end{align*}
\]

(130) \hspace{1cm} R = \text{alkyl / aryl} \\
X = \text{Cl / Br /NO}_2

1- [2- \text{Alkyl -4(3H)-oxoquinazolinyl}] -4- \text{aryl -3- chloro -2- azetidinones have been synthesised and found to be antiparkansonia activity against hypokinesia and catatonia}^{203}.

4- \text{Aryl -3- chloro -1- (4- phenyl - 2- oxozolyl) -azetidine -2-ones (131) and 1"- [4" - aryl (2',4'- bithiazol)-2'-yl] 4" - aryl - 2" azetidinones (132) are found to display antibacterial activity}^{204,205}.\]
1-[5'- (Substituted phenoxy methyl)-1,3,4- thiaiazol -2'-yl] -4-
substituted -2- azetidinones (133) and 1- [5'- aryl -1,3,4- thiaiazol -2'-yl] -3- chloro -4-
substituted -2- azetidinones (134) were reported and showed potential antifungal agents.\textsuperscript{206,207}
4-Aryl -1- (phenothiazinoamidyl) -2- azetidiones (135) and 5- aryl -2-
[spiro-(1,3 - dithiolone)-2,4 - (3' - chloro-2' - azetidinon)-1' -yl]-1,3,4 -oxa/thiadiazoles
(136) are found to exhibit antiinflammatory activity\textsuperscript{208}.

\begin{center}
\includegraphics[width=0.2\textwidth]{135.png}
\end{center}

\begin{center}
(135)
\end{center}

\begin{center}
\includegraphics[width=0.2\textwidth]{136.png}
\end{center}

\begin{center}
(136) \hspace{1cm} R = phenyl / sub. phenyl
\end{center}

Benzothiazolosulphonamidoazetidin -2- ones (137) are reported to exhibit
antimicrobial activity against pathogens \textit{Bacillus subtilis}, \textit{Streptococcus aureus},
\textit{Escherchia coli} and \textit{Penicillium aeruginosa} \textsuperscript{209}.

\begin{center}
\includegraphics[width=0.4\textwidth]{137.png}
\end{center}

\begin{center}
(137) \hspace{1cm} X = CH\textsubscript{3} / OCH\textsubscript{3} / NO\textsubscript{2} / Cl / Br
\end{center}
1,3,7,9 - Tetrabromo -10 [\(\alpha\)-{2-(2-hydroxy phenyl)-3- chloro -4- oxo-1-azetidinylamino}-acetyl]- phenothiazines (138) are found to display tuberculostatic activity.  

![Chemical Structure](image1.png)

(138) \(X = \text{CH}_3 / \text{OCH}_3 / \text{OH} / \text{NO}_2 / \text{Cl}\)

3-chloro -2-oxo-4- (substituted phenyl)- azetidine -1-yl- thioure as (139) are found to exhibit antiparkinsonian activity.

![Chemical Structure](image2.png)

(139) \(X = \text{CH}_3 / \text{OCH}_3 / \text{Cl} / \text{OH}\)

Substituted - 2-oxo - 3 - chloro -3- (2-chlorophenoxy) - 4 - (arylindol - 3 -yl) - azetidines (140) are reported as CNS depressant and antiinflammatory agents.
1- [2 - Alkyl - 4 - (3H) - oxo-3-quinazolinyl] -4-aryl - 3 - chloro - 2 - azetidinones (141) are found to display antiparkinsonian, antitubercular and antirigidity activity.\textsuperscript{203}

1 -[5 - (N\textsuperscript{10} - phenothiazinomethyl) - 1',3'4' - thiadiazol - 2' -yl] -4 - substituted -2 - azetidinones (142) have been synthesised and screened for their antifungal activity.\textsuperscript{71}
Several new substituted carbazolyl-thiadiazol-3-chloro-2-oxo-azetidines (143) have been synthesised and showed antiinflammatory activity.\textsuperscript{212}
Section -2.2 : Aim and work plan of the research

The literature survey on structure activity relationship of N-methyl piperazinones, morpholines, thia diazoles and azetidinones has prompted the authoress to synthesis some new N-methyl piperazinylthiadiazoles, N-methyl piperazinyl-thiadiazoloazetidinones,morpholinothiadiazoles and morpholinothiadiazoloazetidinones and to assay their pharmacological activity such as antibacterial, antifungal, antiinflammatory, analgesic and anticonvulsant to get new compounds as a possible new age drugs.

Work plan of the research:

The work plan of the research has been divided into three parts :

Part-I : Synthesis of new heterocyclic compounds.

Part-II : Characterization of the compounds.

Part-III : Pharmacological activity of the synthesised compounds.

Part-I : Synthesis of the new heterocyclic compounds :

Four series of compounds have been synthesised by following the Scheme-1.

Series-1: 2- Arylidenlamino -5- (N⁴-methyl-N¹-piperazinylmethyl) -1,3,4-thiadiazoles:

The compounds of Series -1 (Compounds LS 4-13) have been synthesised through the Compounds LS 1-3 by following the first four steps of the Scheme-1.
SCHEME -1

\[ \text{CH}_3^4\text{N} \quad \text{N}^1\text{-H} \downarrow \quad \text{ClCH}_2\text{COOC}_2\text{H}_5 \]

\[ \text{CH}_3\text{-N} \quad \text{N}-\text{CH}_2\text{COOC}_2\text{H}_5 \]

**Compound LS-1**

\[ \downarrow \quad \text{H}_2\text{NNHCSNH}_2 \]

\[ \text{CH}_3\text{-N} \quad \text{N}-\text{CH}_2\text{CONHNHCSNH}_2 \]

**Compound LS-2**

\[ \downarrow \quad \text{H}_2\text{SO}_4 / \text{liq. NH}_3 \]

\[ \text{CH}_3\text{-N} \quad \text{N}-\text{CH}_2\cdot\text{C} \quad \text{C}-\text{NH}_2 \]

**Compound LS-3**

\[ \downarrow \]

\[ \text{CH}_3\text{-N} \quad \text{N}-\text{CH}_2\cdot\text{C} \quad \text{C}-\text{N}=\text{C} \quad \text{R}_1 \quad \text{R}_2 \quad \text{C}=\text{O} \]

**Compounds LS 4-13**

\[ \downarrow \quad \text{ClCH}_2\text{COCl/ Et}_3\text{N} \]

\[ \text{CH}_3\text{-N} \quad \text{N}-\text{CH}_2\cdot\text{C} \quad \text{C}-\text{N}\text{-C} \quad \text{R}_1 \quad \text{R}_2 \quad \text{Cl} \quad \text{O} \]

**Compound LS 14-23**

Where: \( R_1 = R_2 = \text{Aryl} / \text{sub. aryl} \)
<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-4</td>
<td>2-Benzylidenamino -5-(N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-5</td>
<td>2-(4-Dimethylamino benzylidenamino) -5- (N⁴-methyl-N¹-piperazinylmethyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-6</td>
<td>2-(2-Nitro benzylidenamino) -5- (N⁴-methyl-N¹-piperazinylmethyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-7</td>
<td>2- (2-Chloro benzylidenamino) -5- (N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-8</td>
<td>2- (4-Chloro benzylidenyamino)-5- (N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-9</td>
<td>2-(4-Methoxy benzylidenamino) -5- (N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-10</td>
<td>2-Cinnamylidenamino -5- (N⁴-methyl-N¹ piperazinylmethyl) -1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-11</td>
<td>2-(Furfurylidenamino) -5- (N⁴-methyl-N¹-piperazinylmethyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-12</td>
<td>2- (α-Methyl benzylidenamino) -5- (N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
<tr>
<td>LS-13</td>
<td>2-(α-Phenyl benzylidenamino) -5- (N⁴-methyl-N¹-piperazinyl methyl)-1,3,4-thiadiazole.</td>
</tr>
</tbody>
</table>
Series -2: N\textsuperscript{4}-methyl -N\textsuperscript{1}- piperazinylmethyl thiadiazoloazetidinones:

The compounds of Series -2 (Compounds LS 14-23) have been synthesised using the compounds of Series -1 as precursors by following the last step of the Scheme-1.

**Table-2.2: List of the compounds synthesised under Series -2**

<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-14</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- phenyl -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-15</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (4-dimethylamino phenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-16</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (2-nitro phenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-17</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (2-chloro phenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-18</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (4-chloro phenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-19</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (4-methoxy phenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-20</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (2- phenyl ethenyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-21</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4- (2-furyl) -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-22</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4-methyl -4-phenyl -3- chloro -2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-23</td>
<td>1-[5\textsuperscript{'-}(N\textsuperscript{4}-methyl-N\textsuperscript{1}-piperazinylmethyl)-1\textsuperscript{',}3\textsuperscript{',} 4\textsuperscript{-} thia diazol-2\textsuperscript{-}yl] -4, 4-diphenyl -3- chloro -2-oxo-azetidine.</td>
</tr>
</tbody>
</table>
Series-3: 2 - Arylidenlamino -5- morpholinomethyl-1,3,4-thiadiazole :

The compounds of Series -3 (Compounds LS 27-36) have been synthesised through the Compounds LS 24-26 by following the first four steps of Scheme -2.

Table- 2.3: List of the compounds synthesised under Series -3

<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-27</td>
<td>2- Benzylidenlamino -5- (N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-28</td>
<td>2- (4-Dimethylamino benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-29</td>
<td>2-(2-Nitro benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-30</td>
<td>2-(2-Chloro benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-31</td>
<td>2-(4-Chloro benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-32</td>
<td>2-(4-Methoxy benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-33</td>
<td>2- Cinnamylidenamino -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-34</td>
<td>2-Furfurylidenlamino -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-35</td>
<td>2-(α-Methyl benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
<tr>
<td>LS-36</td>
<td>2- (α-Phenyl benzylidenlamino) -5-(N- morpholinomethyl) -1,3,4- thiadiazole.</td>
</tr>
</tbody>
</table>
SCHEME - 2

\[ \text{Compound LS-24} \]
\[ \xrightarrow{\text{CICH}_2\text{COOC}_2\text{H}_5} \]
\[ \text{NH}_2\text{NHCSNH}_2 \]
\[ \xrightarrow{\text{H}_2\text{SO}_4 / \text{liq. NH}_3} \]
\[ \text{Compounds LS-26} \]
\[ \xrightarrow{R_1 \xrightarrow{\text{C}=O} R_2} \]
\[ \text{Compounds LS-27-36} \]
\[ \xrightarrow{\text{CICH}_2\text{COCl/ Et}_3\text{N}} \]
\[ \text{Compounds LS-37-46} \]

Where: \( R_1 = R_2 = \text{Aryl / sub. aryl} \)
Series -4 : N-morpholinomethyl thiadiazoloazetidinones :

The compounds of Series -4 (Compounds LS 37-46) have been synthesised using the compounds of Series-3 as precursors and by following the last step of the Scheme -2.

Table-2.4: List of the compounds synthesised under Series-4

<table>
<thead>
<tr>
<th>Compounds No.</th>
<th>Chemical name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS-37</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-phenyl-3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-38</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(4-dimethylamino phenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-39</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(2-nitro phenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-40</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(4-chloro phenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-41</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(4-chloro phenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-42</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(4-methoxy phenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-43</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(2-phenyl ethenyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-44</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-(2-furyl) -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-45</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] -4-methyl-4-phenyl -3- chloro-2-oxo-azetidine.</td>
</tr>
<tr>
<td>LS-46</td>
<td>1-5′-(N-morpholinomethyl) - 1′,3′,4′- thiazol -2′-yl] - 4, 4-diphenyl -3- chloro-2-oxo-azetidine.</td>
</tr>
</tbody>
</table>
PART-II: Characterization of the synthesised compounds:

The melting points of the compounds have been determined in an open capillary and are uncorrected. Rf values were determined by TLC on silica gel coated plates using iodine as a developer. All the compounds were analysed for C, H and N percentage. The IR and $^1$H NMR spectra of the representative compounds were recorded on a Shimadzu 8201 PC FTIR spectrophotometer in KBr discs ($\nu$ max recorded in cm$^{-1}$) and on Bruker WM/DRX at 200 MHz (chemical shift in $\delta$ ppm) in CDCl$_3$, using TMS as an internal standard respectively.

PART-III: Pharmacological activity of the synthesised compounds:

The synthesised compounds were screened for their antibacterial, antifungal, antiinflammatory, anticonvulsant and analgesic activities. Some of the compounds were found to display remarkable pharmacological activity.