CHAPTER II

AIM, SCOPE & PLAN OF THE WORK
Condensed Heterocyclic Systems containing thiazole, thiadiazole and thiadiazine nuclei have attracted worldwide attention of a large number of chemists, pharmacologists and biologists on account of the significant therapeutic and biological properties associated with them. Interest in the synthesis of thiazole or related nuclei and their derivatives was greatly developed especially with the discovery of penicillines, tetramisole, phenothiazines, chlorothiazide, acetazolamide etc., the well known products of high therapeutic importance. Applications of such compounds (derivatives of thiazole, thiazole and thiadiazine) are manifold and versatile, as is evident from the account given in the Chapter-I. They are used as antitubercular, amoebicidal, anticonvulsants, anthelmintics, fungistatics, bacteriostatics, antidepressants, platelet aggregation inhibitors, vulcanization accelerators and antineoplastic agents etc. They have also gained prominence for their use as intermediates in the synthesis of photographic sensitizers which have become not only an integral component of modern photography but also have revolutionized the whole science of this art, bringing a remarkable success to it.

Janssen and Coworkers\(^3\), during a routine screening programme as an anthelmintic in chickens, reported that 6-(2-thienyl)-5,6-dihydroimidazo[2,1-b]thiazole (I), the metabolite of 2-acetylimino-3-[2-hydroxy-2-(2-thienyl)-ethyl]-thiazoline (thiazothienol) (II), possessed more activity than compound (II). Further studies on imidazothiazole systems led to the discovery of tetramisole (6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazole (III) as a potential anthelmintic. Ruddi\(^5\) made similar observations while studying the biological properties of 2-benzyl-5,6-dihydroimidazo[2,1-b] thiazole-3(2H)-one (IV) and its cleavage product, 5-benzyl-3-([β-aminoethyl]-thiazoladin-2,4-dione hydrochloride (V).
Imidazo[2,1-b]thiazole (IV) was found to be more active than its cleavage product, 5-benzyl-3-(β-aminoethyl)-thiazolidin-2,4-dione (V).

\[ \text{I} \hspace{2cm} \text{II} \hspace{2cm} \text{III} \]

Compounds I & IV, being more potent than the corresponding uncyclized compounds II & V respectively, suggest that the condensed thiazole systems possess more activity. In view of the prodigious range of activities of the systems mentioned above, it is considered worthwhile to undertake investigations in the synthesis of bridgehead nitrogen heterocyclic systems containing thiazole, thiadiazole and thiadiazine nuclei.

In the present investigations, the synthesis of twenty one different condensed heterocyclic systems, namely, thiazolo[3',2': 2,3]-astriazino [5,6-b] indole, thiazolo[2',3': 3,4]-as-triazino[5,6-b]indole, thiazino[3',2': 2,3]-as-triazino[5,6-b]indole, thiazino[2',3': 3,4]-as-triazino[5,6-b]indole, quinoxalino[2',3': 4,5]thiazolo[3,2-b]indolo[2,3-e]-as-
triazine, quinoxalino [2',3': 4,5]thiazolo[2,3-d]indolo[2,3-e]-as-triazine, thiazolo [3,2-b]-s-triazole, thiazolo[2,3-c]-s-triazole, pyrazolo [3',4':4,5]thiazolo[3,2-b]-s-triazole, s-triazolo[3,4-b]-1,3,4-thiadiazine, s-triazolo[3',4':2,3]-1,3,4-thiadiazino[5,6-b]quinoxaline, imidazo [2,1-b]-1,3,4-thiadiazolo [2,3-c]-s-triazole, s-triazolo[3,4-b]-1,3,4-thiadiazolo[3,2-b] imidazo[4,5-b]quinoxaline, bis-(s-triazolo[3,4-b]-1,3,4-thiadiazolo[3,2-b] imidazo[4,5-b]cyclohexane]-5a,6a-diene, imidazo [2,1-b]-1,3,4-thiadiazole, thia
piperidine-4',7(8H)-[6H]pyrazolo[3,4-d] thiazolo[3,2-b]-s-tetrazine, have been accomplished. The fusion of two biologically active heterocyclic rings was expected to yield a compound more potent than either of the individual ones. This may help in finding out, as to what extent, if any, the attachment of an additional therapeutically active ring adds to the importance of thiazole or related nuclei (thiadiazole, thiadiazine) in chemotherapy. The synthesis of thiazolo-triazino-indole, thia
dzino-triazino-indole, s-triazolo-thiadiazine, imidazo-thiadiazole, imidazo-thiadiazolo-s
triazole, thiazolo-s-triazole, pyrazolo-thiazolo-s-triazole were undertaken to find out the effect on biological activity when a thiazole ring is replaced by thiazine, thia
diazole, thia
diazine or imidazole nucleus or when a pyrazole nucleus is fused to thiazolo-s-triazole moiety.

In addition to the systems mentioned above, the synthesis of condensed heterocyclic systems namely quinoxalino-thiazolo-indolotriazine and s-triazolo-thiazidino-quinoxaline have been carried out in order to study the effect on biological activity, if any, when a thiazolo-
quinoxaline is fused to s-triazole nucleus. Synthesis of various condensed heterocyclic systems and their biological screening would provide a rational approach to the study of structure-activity relationship.

It was one of the primary aims of the author to study the orientation of cyclization when there was the possibility of the formation of the isomeric products during cyclization. The orientation of the cyclized product was secured by the unequivocal synthesis.

In the first series, the synthesis of 7,8-dichloro-3-arylthiazolo[3',2':2,3]-as-triazino[5,6-b]indole, 7,8-dichloro-1-aryl thiazolo[2',3':3,4]-as-triazino[5,6-b]indole, 7,8-dichloro-2,3-dihydro thiazolo[3',2':2,3]-as-triazino[5,6-b]indole, 7,8-dichloro-2,3-dihydrothiazolo[2',3':3,4]-as-triazino[5,6-b]indole, 8,9-dichloro-4H-2,3-dihydro[1,3]thiazino[3',2':2,3]-as-triazino[5,6-b]indole, 8,9-dichloro-1H-2,3-dihydro[1,3]thiazino[2',3':3,4]-as-triazino[5,6-b]indole, 9,10-dichloroquinoxalino[2',3':4,5]thiazolo[3,2-b]indolo[2,3-e]-as-triazine and 2,3-dichloroquinoxalino[2',3':4,5]thiazolo[2,3-d]indolo[2,3-e]-as-triazine have been carried out.

2,3-Dihydro-7,8-dichloro-5H-as-triazino[5,6-b]indole-3-thione, on condensation with α-haloketones give 3-aroylmethylthio-7,8-dichloro-5H-as-triazino[5,6-b]indole hydrobromide which on polyphosphoric acid cyclization furnishes 3-aryl-7,8-dichlorothiazolo[3',2':2,3]-as-triazino[5,6-b]indole, the linear isomer and not 1-aryl-7,8-dichlorothiazolo[2',3':3,4]-as-triazino[5,6-b]indole, the angular isomer. The unequivocal synthesis of the angular isomer has been achieved by the condensation of 5,6-dichloroisatin-3-thiosemicarbazone with α-haloketones followed by the cyclization of the resulting intermediate with POCl₃, to furnish 1-aryl-7,8-dichlorothiazolo[2',3':3,4]-as-triazino[5,6-b]indole.

Similary the reaction of 2,3-dihydro-7,8-dichloro-5H-as-
triazino[5,6-b]indole-3-thione with 1,2-dibromoethane, 1,3-dibromopropane, and 2,3-dichloroquinoxaline gives the cyclized products, 7,8-dichloro-2,3-dihydrothiazolo [3',2':2,3]-as-triazino-[5,6-b]indole, 2,3-dihydro-8,9-dichloro-4H-[1,3]thiazino[3',2':2,3]-as-triazino[5,6-b]indole and 9,10-dichloroquinoxalino[2',3':4,5] thiazolo[3,2-b]indolo[2,3-e]-as-triazine and not the angular isomers 7,8-dichloro-2,3-dihydrothiazolo[2',3':3,4]-as-triazino[5,6-b]indole, 8,9-dichloro-1H-2,3-dihydro[1,3]thiazino[2',3':3,4]-as-triazino[5,6-b]indole and 2,3-dichloroquinoxalino[2',3':4,5]thiazolo[2,3-c]indolo[2,3-e]-as-triazine.

The synthesis of linear and angular isomers simultaneously were undertaken primarily for two reasons. Firstly, to study the orientation of cyclization of the intermediate 3-aroylmethylthio-7,8-dichloro-5H-as-triazino[5,6-b]indole hydrobromide obtained by the reaction of 2,3-dihydro-7,8-dichloro-5H-as-triazino[5,6-b]indole-3-thione with α-haloketones. 2,3-Dihydro-7,8-dichloro-5H-as-triazino[5,6-b]indole-3-thione, being unsymmetrical, its reaction with α-haloketones and subsequent cyclization of the intermediate is likely to give one or both isomers, depending upon the mode of cyclization.

Similarly the reaction of 2,3-dihydro-7,8-dichloro-5H-as-triazino[5,6-b]indole-3-thione with 1,2-dibromoethane, 1,3-dibromopropane and 2,3-dichloroquinoxaline is expected to yield one or both isomers in each case depending upon the mode of cyclization. In each case, only one isomer was obtained and their structures were established by unambiguous synthesis of the angular isomers. Secondly, their biological screening would help in deciding which system i.e. thiazolo[3',2':2,3]-as-triazino-[5,6-b] indole or thiazolo[2',3':3,4]-as-triazino[5,6-b]indole possesses more activity. This would also give an idea about
the effect, if, any, on the biological activity, when a thiazole ring is replaced by thiazine ring or when a quinoxaline ring is fused to thiazolo-triazino indole system.

The second series pertains to synthesis of two isomeric systems thiazolo [3,2-b]-s-triazole and thiazolo [2,3-c]-s-triazole. The synthesis of thiazolo-s-triazoles were opted with two objectives in mind, firstly to determine the direction of cyclization of 3-(m-hydroxyphenyl)-5-aroylethylthio-s-triazole, which being unsymmetrical, is likely to furnish one or both the isomers depending upon the mode of cyclization. Secondly the biological screening of thiazolo [3,2-b]-s-triazole and thiazolo [2,3-c]-s-triazole will reveal which isomer possesses more activity.

The third series pertains to synthesis of 6-o-nitrophenyl-2-(2,4-dinitrophenyl)-3-aryl-trans-3,3a-dihydropyrazolo[3',4':4,5]thiazolo [3,2-b]-s-triazoles and its 2H analogue. The condensation of 3-o-nitrophenyl-s-triazole-5-thione with chloroacetic acid and aromatic aldehydes in the presence of anhydrous sodium acetate, acetic anhydride and glacial acetic acid afforded 6-arylidene-2-o-nitrophenyl thiazolo [3,2-b]-s-triazolo-5(6H)-ones, which on treatment with 2,4-dinitrophenyl hydrazine and hydrazine hydrate yielded in one step, the cyclized product, 6-o-nitrophenyl-2-(2,4-dinitrophenyl)-3-aryl-trans-3,3a dihydropyrazolo[3',4':4,5] thiazolo [3,2-b]-s-triazoles and 6-o-nitrophenyl-2H-3-aryl-trans-3,3a dihydropyrazolo[3',4':4,5]thiazolo [3,2-b]-s-triazoles respectively.

The fourth series describes the synthesis of some interesting heterocyclic systems, namely, s-triazolo[3,4-b][1,3,4] thiadiazine and s-triazolo[3',4':2,3][1,2,4]thiadiazino [5,6-b]quinoxaline. The reaction of 3-(m-hydroxyphenyl)-4-amino-5-mercapto-s-triazole with α-haloketone, benzoin and 2,3-dichloroquinoxaline furnish respectively in one step the
cyclized products, 3-m-hydroxyphenyl-6-substituted-7H-s-triazolo[3,4-b] [1,3,4]thiadiazine, 3-m-hydroxyphenyl-6,7-diphenyl-5H-s-triazolo[3,4-b] [1,3,4]thiadiazine and 3-m-hydroxyphenyl-5H-s-triazolo [3',4':2,3][1,3,4] thiadiazino [5,6-b] quinoxaline. The synthesis of s-triazolo-thiadiazines and s-triazolo-thiadiazino-quinoxaline were undertaken in order to study the effect on biological activity when a thiazole ring is replaced by a thiadiazine or quinoxaline ring is fused to triazolo-thiadiazine nuclues.

In the fifth series the synthesis of 3,9-di(o-chlorophenyl)-6,14-dioxo-bis-(s-triazolo [3,4-b] [1,3,4]thiadiazolo [3,2-fa] [imidazo [4,5-fa] cyclohexane]-5a,6a-diene), 3-(o-chlorophenyl)-s-triazolo[3,4-b] [1,3,4]thiadiazolo[3,2-b] imidazo[4,5-b]quinoxaline, 7-aryl-3-(o-chlorophenyl)imidazo[2,1-b] [1,3,4]thiadiazolo[2,3-c]-s-triazoles and their 6-bromo analogues have been achieved by the condensation of 4-amino-5-mercapto-3-(o-chlorophenyl)-s-triazole with cynogen-bromide to yield 6-amino-3-(o-chlorophenyl)-s-triazolo[3,4-b][1,3,4]thiadiazole followed by independent treatment with chloranil, 2,3-dichloroquinoxaline, α-haloketones (followed by bromination). The synthesis of imidazo thiadiazolo-s-triazoles were undertaken in order to study the effect on biological activity when an imidazole ring is fused to s-triazolo-thiadiazole moiety.

In the next series the synthesis of 2-α-naphthyl-thiadiazolo[2',3':2,1]imidazo[4,5-b]quinoxaline, 2-α-naphthyl-6-aryl-imidazo[2,1-b][1,3,4]-thiadiazole and their 5-bromo analogues have been achieved by the condensation of 2-amino-5-(α-naphthyl) thiadiazoles with 2,3-dichloro-quinoxaline and α-haloketones (followed by bromination) respectively. The synthesis of imidazo [2,1-b]-1,3,4-thiadiazoles together with their brominated products would reveal the effect of the introduction of bromine into the imidazole ring on the biological properties of imidazo-
In the seventh series of present investigation describes the synthesis of $2H$-imidazo [2,1-\textit{b}]pyrazolo [3,4-\textit{d}] thiazoles. Required compound 2-mercapto imidazoline on treatment with ethylchloroacetate and aldehydes in the presence of pyridine and piperidine gave 2-arylidene-5,6-dihydro-$5H$-imidazo[2,1-\textit{b}] thiazolidin-3-ones which on treatment with hydrazine hydrate and 2,4-dinitrophenyl hydrazine gave 3-substituted-
\textit{cis}-3,3\alpha-6,7-tetrahydro-$2H$-imidazo[2,1-\textit{b}]pyrazolo[3,4-\textit{d}]thiazoles and their 2-phenyl derivatives.

The eighth series is attributed to the facile synthesis of 3,3\alpha-dihydro-2,3-diaryl-6,7-dihydro-$5H$-pyrazolo$[3',4':4,5]$ thiazolo$[3,2-\textit{a}]$ pyrimidine, from 2-arylidene-6,7-dihydro-$5H$-thiazolo$[3,2-\textit{a}]$pyrimidine-$3(2\textit{H})$-one and arylhydrazines. Their synthesis and screening would reveal the effect on the biological activity when a pyrazole ring is fused to thiazolo-pyrimidine system.

The next series describes the facile synthesis of trans-$3',3'\alpha$-dihydrospiro$[3\textit{H}-5,6$-dichloroindole-$3,5'$-pyrazolo$[3',4':4,5]$thiazolo-$2(1\textit{H})$-one,spiroheterocyclic system. Condensation of 5,6-dichloroisatin-3-imine with thioglycollie acid furnished $3'$-arylspiro $[3\textit{H}-5,6$-dichloro indole-$3,2'$-thiazolidine]-$2(1\textit{H}),4'(5'\textit{H})$-dione, which on condensation with aromatic aldehydes finished $5'$-arylidene derivatives followed by treatment with 2,4-dinitrophenylhydrazine and hydrazine hydrate independently.

In continuation of above series, the tenth series describes the synthesis of $6(7\textit{H})$-oxospiro $[\text{cyclododecane-1',3}(4\textit{H})-\text{[2H]}$-thiazolo$[3,2-\textit{b}]$-\textit{s}-tetrazine]obtained by the reaction of 1,2,4,5-tetraazaspiro $[5,11]$ heptadecane-3-thione with chloro acetic acid. 7-arylidene-$6(7\textit{H})$-oxospiro $[\text{cyclododecane-1'}3(4\textit{H})-\text{[2H]}$-thiazolo$[3,2-\textit{b}]$-\textit{s}-tetrazines]have been
prepared by the condensation of 6(7H)-oxospiro [cyclododecane-1',3,(4H)-[2H]-thiazolo[3,2-b]-s-tetrazines with aldehydes (aromatic). 7-arylidene 6(7H)-oxospiro[cyclodecane-1',3(4H)-[2H]-thiazolo[3,2-b]-s-tetrazines] on condensation with p-nitrophenylhydrazine furnish 3,3a-dihydro-2,3-diaryl spiro [cyclododecane-1',7(8H)-[6H]-pyrazolo[3',4':4,5]thiazolo[3,2-b]-s-tetrazines]. The synthesis and biological screening would help in revealing the effect on the biological activity when a pyrazole ring is fused to the thiazolo-s-tetrazine system.

In the next series the synthesis the 7'-p-chlorobenzylidene-6'(7'H)oxospiro-[2,6-di(o-hydroxyphenyl)piperidine-3',4(4'H)-[2H] thiazolo[3,2-b]-s-tetrazine has been achieved by condensation of spiro[2,6-di-(o-hydroxyphenyl) piperidine-3',4-1',2',4',5'-tetrahydro-s-tetrazine-6'-thione with chloro acetic acid to yield 6'(7'H)-oxospiro [2,6-di (o-hydroxyphenyl) piperidine-3',4(4'H)-[2H]thiazolo[3,2-b]-s-tetrazine, followed by treatment with p-chlorobenzaldehyde. Condensation of 7'-arylidene-6'(7'H)oxospiro-[2,6-di(o-hydroxyphenyl) piperidine-3',4(4'H)-[2H]thiazolo[3,2-b]-s-tetrazine with 2,4-dinitrophenyl hydrazine furnishes 3,3a-dihydro-2,3-diaryl-2',6'-di(o-hydroxyphenyl)spiropiperidine-4',7(8H)-[6H]pyrazolo[3,4-d]thiazolo[3,2-b]-s-tetrazine. Their synthesis and biological screening would help in revealing the effect on the biological activity when a pyrazole ring is fused to spiropiperidine-thiazolo-s-tetrazine system.

**Antibacterial Studies**

A few compounds from each series, on representative basis, have been screened against two gram-negative and one gram-positive bacteria with a view of achieving some relationship between chemical structures and bacteriostatic activity. The method used, antibacterial
results and conclusions derived therefrom, regarding structure-activity relationship are depicted in Chapter-IV.

**Antifungal Studies**

Since most of the compounds synthesized in the present investigations contain the group N-C-S, which is present in the structure of the well known fungicides$^{112}$, it was considered desirable to study on a representative basis, a few compounds from each series for their antifungal activities. Study of their antifungal activities was expected to lead to formulation of a relationship between structural change and antifungal action. The method used for assaying antifungal activity in regard to structure-activity relationship is discussed in Chapter-V.