CHAPTER VI

SUMMARY
SUMMARY

In the present investigations, the author has synthesised different types of bridgehead nitrogen heterocyclic systems, containing a thiazole, thiadiazole, thiazine and thiadiazine nucleus fused to another heterocyclic ring, namely triazino-indole, s-triazole, imidazole, s-tetrazine or spiro-alkane tetracine. In addition the synthesis of heterocyclic systems in which thiazolo-quinoxaline is fused to triazino-indole or thiadiazino-quinoxaline is fused to s-triazole nucleus and a pyrazole ring is fused to thiazolo-s-tetrazine nucleus have also been achieved.

Another two condensed bridgehead nitrogen heterocyclic systems in which a thiazole or thiadiazole nucleus is fused to two other biologically active heterocyclic nuclei, pyrazolo/imidazolo and s-triazole nuclei resulting in the synthesis of pyrazolo [3',4':4,5]thiazolo[3,2-b]-s-triazole and imidazo [2,1-b]-1,3,4-thiadiazolo[4,3-d]-s-triazole have also been reported. (CHARTS 1-10)

In the first series the synthesis of thiazolo [3',2':2,3]-as-1,2,4-triazino [5,6-b]indoles (VI) and their isomeric compounds thiazolo [2',3':3,4]-as-1,2,4-triazino [5,6-b] indoles (VIII) have been achieved.

The synthesis of 9-methoxy-2,3-dihydro thiazolo [3',2':2,3]-as-triazino [5,6-b] indole (XI), 2,3-dihydro-10-methoxy-4H-(1,3) thiazino[3',2':2,3]-as-1,2,4-triazino[5,6-b]indole (XIII), 11-methoxy quinoxaline [2',3':4,5]thiazolo [3,2-b] indolo [2,3-e]-as-1,2,4-triazine (XV) and their angular isomers 9-methoxy-2,3-dihydro thiazolo [2',3':3,4]-as-triazino [5,6-b]indole (XII) 2,3-dihydro-10-methoxy-1H-[1,3] thiazino [2',3':3,4]-as-1,2,4-triazino [5,6-b]indole (XIV), and 1-methoxy
quinoxaline [2',3':4,5] thiazolo [2,3-c]indolo [2,3-e]-as-1,2,4-triazine (XVI) have also been achieved.

2,3-Dihydro-6-methoxy-5H-as-triazino [5,6-b]indole-3-thione (IV) obtained by the reaction of 7-methoxyisatin (II) with thiosemicarbazide and subsequent cyclization of the intermediate 7-methoxyisatin-3-thiosemicarbazone (III) with alkali, on condensation with α-haloketones gave 3-aroymethyl-thio-6-methoxy-5H-as-1,2,4-triazino [5,6-b]indole hydrohalides (V). The ketones (V) on PPA catalysed cyclization furnish 3-aryl-9-methoxythiazolo [3',2':2,3]-as-1,2,4-triazino [5,6-b]indoles (VI), the linear product and not 1-aryl-9-methoxythiazolo [2',3':3,4]-as-1,2,4-triazino [5,6-b]indoles (VIII) the angular isomer. The unequivocal synthesis of the angular isomer (VIII) has been sought and accomplished by the reaction of 7-methoxyisatin-3-thiosemicarbazone (III) with α-haloketones, followed by cyclization of the intermediate (VII) with POCl₃.

(CHART-1)

2,3-Dihydro-6-methoxy-5H-as-triazino [5,6-b] indole-3-thione (IV) on condensation with 1,2-dibromoethane, 1,3-dibromopropane and 2,3-dichloroquinoxaline gives the linear cyclized products 9-methoxy-2,3-dihydro thiazolo [3',2':2,3]-as-triazino [5,6-b] indole (XI), 2,3-dihydro-10-methoxy-4H-[1,3]thiazino [3',2':2,3]-as-1,2,4-triazino [5,6-b] indole (XIII) and 11-methoxyquinoxalino [2',3':4,5] thiazolo [3,2-b]indolo[2,3-e]-as-1,2,4-triazine (XV) respectively and not the angular isomers 9-methoxy-2,3-dihydrothiazolo [2',3':3,4]-as-triazino [5,6-b] indole (XII), 2,3-dihydro-10-methoxy-1H-[1,3]thiazino [2',3':3,4]-as-1,2,4-triazino [5,6-b] indole (XIV) and 1-methoxy quinoxalino [2',3':4,5] thiazolo [2,3-c] indolo [2,3-e]-as-1,2,4-triazine
(i) H₂SO₄; (ii) NH₂NHCSNH₂; (iii) KOH; (iv) & (vi) RC₆H₄COCH₂Br; (v) PPA; (vii) POC₁.

CHART-1
The unequivocal synthesis of the latter (XIV, XII and XVI) have been accomplished by the reaction of 7-methoxyisatin-3-thiosmicarbazone (III) with 1,2-dibromoethane, 1,3-dibromopropane and 2,3-dichloroquinoxaline respectively.

(CHART-2)
In thiazolo-s-triazole series, the synthesis of both isomers, namely thiazolo [3,2-b]-s-triazoles (XX) and thiazolo [2,3-c]-s-triazoles (XXII) have been achieved. 3-(2',5'-dichlorophenyl)-5-mercapto-s-triazole (XVIII) on condensation with α-haloketones followed by the cyclization of the intermediate ketone (XIX) with PPA gives 2-(2',5'-dichlorophenyl)-5-aryl thiazolo [3,2-b]-s-triazoles (XX) and not the isomeric thiazolo [2,3-c]-s-triazoles (XXII). Unequivocal synthesis of the latter (XXII) has been achieved through POCl₃ cyclization of 2-(2',5'-dichlorobenzoyl hydrazino)-4-aryl-thiazolehydrobromide (XXI) which is in turn obtained by the reaction of 1-(2',5'-dichlorobenzoyl)-3-thiosemicarbazide (XVII) with α-haloketones.

(CHART-3)
In the third series the synthesis of 6-(3,4,5-trimethoxy phenyl)-3-(aryl)-cis-3,3a-dihydropyrazolo [3',4':4,5] thiazolo [3,2-b]-s-triazoles (XXV) has been achieved by the condensation of 3-(3,4,5-trimethoxy phenyl)-5-mercapto-s-triazole (XXIII) with chloroacetic acid and aldehyde in the presence of acetic anhydride, anhydrous sodium acetate and glacial acetic acid to furnish 6-arylidene-2-(3,4,5-trimethoxyphenyl) thiazolo [3,2-b]-s-triazol-5(6H)-ones (XXIV) followed by condensation with 2,4-dinitrophenyl hydrazine/hydrazine hydrate. The structures (XXV) were supported by IR and ¹H NMR spectral data.
i) KOH, ii) BrCH₂CH₂Br, iii) Br(CH₂)₃Br, iv) 2,3-Dichloroquinoxaline, NaOAc.
i. NaOH; ii & iv. p-R-C,H₄-COCH₂Br; iii. PPA; v. POCl₃

CHART-3
The appearance of two doublets (J=7.8 Hz) at δ 7.18 and 7.76 corroborates the cyclic structure and cis configuration.

(CHART-4)

In another series, the synthesis of some bridgehead nitrogen heterocyclic systems, namely, s-triazolo [3,4-b]-1,3,4-thiadiazine (XXVII, XXVIII, XXXIV, XXX), s-triazolo [3,4-b]-1,3,4-thiadazole (XXXI, XXXII, XXXIII) and s-triazolo [3',4':2,3]-1,3,4-thiadiazino [5,6-b]quinoxaline (XXX) have been carried out. 3-isopropyl-4-amino-5-mercapto-s-triazole (XXVI) obtained by reaction of isobutyric acid with thiocarbohydrazide on reaction with chloroacetic acid, α-haloketone, benzoin, bromoacetaldehyde diethyl acetal and 2,3-dichloroquinoxaline yielded in one step the cyclized products 3-isopropyl-7H-s-triazolo [3,4-b]-1,3,4-thiadiazino-6(5H) one (XXVII), 6-(p-chlorophenyl)-3-isopropyl-7H-s-triazolo [3,4-b]-1,3,4-thiadiazine (XXXIV), 3-isopropyl-6,7-diphenyl-5H-s-triazolo [3,4-b]-1,3,4-thiadiazine (XXVIII), 3-isopropyl-7H-s-triazolo [3,4-b]-1,3,4-thiadiazine hydrobromide (XXIX) and 3-isopropyl-s-triazolo [3',4':2,3]-1,3,4-thiadiazino [5,6-b]quinoxaline (XXX).

The reaction of (XXVI) with carbon disulphide in presence of alc. KOH, aromatic carboxylic acids in presence of POCl₃ and aromatic carboxyaldehydes in presence of dry benzene furnished cyclized products, 3-isopropyl-s-triazolo [3,4-b]-1,3,4-thiadiazolo-6 (5H) thione (XXXI), 6-aryl-3-isopropyl-s-triazolo [3,4-b]-1,3,4-thiadiazoles (XXXII) and 6-aryl-5,6-dihydro-3-isopropyl-s-triazolo [3,4-b]-1,3,4-thiadiazoles (XXXIII) respectively.

(CHART-5)

In another series synthesis of 6-bromo-7-aryl-3-(3,4,5-trimethoxyphenyl)-imidazo [2,1-b]-1,3,4-thiadiazolo [2,3-c]-s-triazoles
(i) ClCH₂COOH, anhyd. NaOAc, ArCHO, Ac₂O, gl. AcOH;
(ii) 2,4-dinitrophenyl hydrazine/hydrazine hydrate

CHART-4
R = isopropyl

(i) ClCH₂COOH, NaOAc; (ii) ArCOCH₂X, (iii) PhCHOHCOPh, KOH;
(iv) 2,3-Dichloroquinoxaline, NaOAc; (v) CS₂, KOH; (vi) ArCOOH, POCl₃;
(vii) ArCHO;
(viii) Bromoacetaldehyde diethyl acetal

CHART 5

R = isopropyl

(i) ClCH₂COOH, NaOAc; (ii) ArCOCH₂X, K₂CO₃; (iii) PhCHOHCOPh, KOH;
(iv) 2,3-Dichloroquinoxaline, NaOAc; (v) CS₂, KOH; (vi) ArCOOH, POCl₃;
(vii) ArCHO; (viii) Bromoacetaldehyde diethyl acetal
(XXXVIII), 3-(3,4,5-trimethoxyphenyl)-s-triazolo[3,4-b][1,3,4]-thiadiazolo [3,2-b]imidazo[4,5-b]quinoxaline (XXXIX) and 3,9-di-(3,4,5-trimethoxy phenyl)-6,14-dioxo-bis-(s-triazolo[3,4-b][1,3,4]-thiadiazolo[3,2-b]-imidazo[4,5-b]-cyclohexane]-5a,6a-diene) (XL) have been accomplished. Condensation of 3-(3,4,5-trimethoxy phenyl)-4-amino-5-mercapto-s-triazole (XXXV) with cyanogen bromide yielded 6-amino-3-(3,4,5-trimethoxyphenyl)-s-triazolo[3,4-b][1,3,4]-thiadiazole (XXXVI), which on reaction with α-haloketones, 2,3-dichloroquinoxaline and chloranil furnished 7-ary1-3-(3,4,5-trimethoxyphenyl)-imidazo[2,1-b]-1,3,4-thiadiazolo[2,3-c]-s-triazole (XXXVII), 3-(3,4,5-trimethoxy phenyl)-s-triazolo[3,4-b][1,3,4]-thiadiazolo[3,2-b]imidazo[4,5-b] quinoxaline (XXXIX) and 3,9-di-(3,4,5-trimethoxyphenyl)-6,14-dioxo- bis-(s-triazolo[3,4-b][1,3,4]-thiadiazolo[3,2-b]-imidazo[4,5-b]-cyclohexane]-5a,6a-diene (XL) respectively. Bromination of compd (XXXVII) gives compound (XXXVIII).

(CHART-6)

In another series, the synthesis of imidazo[2,1-b]-1,3,4-thiadiazoles (XLII) and thiadiazolo[2',3':2,1]imidazo[4,5-b]quinoxaline (XLIV) have been achieved. 2-Amino-5-p-hydroxyphenyl-1,3,4-thiadiazole (XL), obtained by treating-(p-hydroxybenzoyl)-3-thiosemicarbazide with conc. sulphuric acid, on reaction with α-haloketones and 2,3-dichloroquinoxaline furnished 2,6-diaryl imidazo[2,1-b]-1,3,4-thiadiazoles (XLII) and 2-(p-hydroxyphenyl)thiadiazolo[2',3':2,1]imidazo[4,5-b]quinoxaline (XLIV) respectively. The synthesis of 2,6-diaryl-5-bromo-imidazo[2,1-b]-1,3,4-thiadiazole (XLIII) have been achieved by bromination of (XLII) in the presence of glacial acetic acid.
(i) CNBr (ii) Chloranil, anhydrous NaOAc, AcOH; (iii) 2,3-Dichloroquinoxaline, anhyd. NaOAc; (iv) R-C₆H₄-COCH₂Br; (v) Br₂, AcOH.
In another series, synthesis of spiro[cycloheptane-1,7'(8'H)[6H]-cis-3',3'a dihydropyrazolo[3',4':4,5]thiazolo-[3,2-b]-s-tetrazines (XLVIII) have been achieved.

1',2',4',5'-tetraazaspiro[5,6]dodecane-3'-thione (XLV) obtained by the reaction of cycloheptanone with thiocarbohydrazide, on condensation with chloroacetic acid and aldehyde in presence of gl. acetic acid afforded 7'-arylidene-6'(7'H)-oxospiro[cycloheptane-1,3'(4'H)-[2H]thiazolo[3,2-b]-s-tetrazines (XLVII). The condensation of (XLVII) with 2,4-dinitrophenyl hydrazine yielded in one step the cyclized products, cis-3',3'a-dihydro-2'-{2'',4''-dinitrophenyl}-3-aryl-spiro[cycloheptane-1,7'(8'H)-[6H]pyrazolo[3',4':4,5]thiazolo-[3,2-b]-s-tetrazines (XLVIII).

In next series, synthesis of cis-8,8a-dihydropyrazolo[3',4':4,5]thiazolo [2,3-b]-s-triazolo [3,4-b][1,3,4]thiadiazole (LIII) have been achieved.

Condensation of 3-{(p-chlorophenyl)-6-{(p-nitrophenyl)-s-triazolo[3,4-b][1,3,4]thiadiazole (L), obtained by the condensation of 4-amino-5-mercaptop-3-{(p-chlorophenyl)-s-triazole (IL) with p-nitrobenzoic acid in presence of POCl₃, with thioglycollic acid yielded 3-{(p-chlorophenyl)-8a-{(p-nitrophenyl) thiazolo[2,3-b]-s-triazolo[3,4-b] [1,3,4]-thiadiazol-6(7H)-one (LI) which on condensation with aldehydes yielded 7-aryl-8a-{(p-nitrophenyl)-3-{(p-chlorophenyl)-thiazolo [2,3-b]-s-triazolo[3,4-b][1,3,4]thiadiazol-6(7H)-ones (LII). On further condensation of (LII) with 2,4-dinitrophenyl hydrazine/hydrazine hydrate yielded, 9a-{(p-nitrophenyl)-8-aryl-3-{(p-chlorophenyl)-cis-8,8a-dihydropyrazolo...
(i) \( R-C_6H_4-COCH_2Br \); (ii) \( \text{Br}_2, \text{AcOH} \); (iii) 2,3-dichloroquinoxaline, anhyd. \( \text{NaOAc} \)
i) ClCH₂COOH, anhyd. NaOAc
ii) ArCHO, anhyd NaOAc, gl. AcOH
iii) 2, 4-DNP, NaOAc
[3',4':4,5]thiazolo [2,3-b]-s-triazolo[3,4-b][1,3,4] thiadiazoles (LIII) in one step.

(CHART-9)

In another series, synthesis of spiropiperidine-4',7(8H)-[6H]pyrazolo [3,4-d]thiazolo [3,2-b]-s-tetrazines (LVIII) have been achieved.

Spiro [2,6-di-(m-nitrophenyl)piperidine-3',4-1',2',4',5'-tetrahydro-s-tetrazine-6'-thione (LV) obtained by the reaction of 2,6-di-(m-nitrophenyl) piperidine-4-one (LIV) with thiocarbohydrazide, on condensation with chloroacetic acid and aldehyde in presence of gl. acetic acid afforded 7'-arylidene-6'(7'H)-oxospiro[2,6-di-(m-nitrophenyl)piperidine-3',4(4'H)[2H]thiazolo [3,2-b]-s-tetrazine] (LVII). The condensation of (LVII) with 2,4-dinitrophenylhydrazine/hydrazine hydrate yielded in one step the cyclized products 3,3a-dihydro-3-aryl-2',6'-di-(m-nitrophenyl)spiropiperidine-4',7(8H)-[6H] pyrazolo[3,4-d]thiazolo [3,2-b]-s-tetrazines (LVIII).

(CHART-10)

The structures of the compounds synthesised in the present work have been characterized by IR, PMR and Mass spectral data in addition to elemetal analysis. In case, where there exists the possibility of obtaining more than one isomer during cyclization, the structural assignment of the isomer obtained has been firmly secured by unequivocal synthesis of one of the isomers.

A few compounds (on a representative basis) from each series have been screened against three bacteria (Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa) and the fungus
(i) \( \text{P-N}_2\text{O}_2\text{C}_6\text{H}_4\text{C}_0\text{0H}, \text{ POCl}_3 \)
(ii) \( \text{HSCH}_2\text{COOH} \);
(iii) \( \text{ArCHO, anhyd. NaOAc, gl. AcOH} \);
(iv) \( \text{2,4-dinitrophenyl hydrazine/hydrazine hydrate, anhyd. NaOAc, AcOH} \).

CHART 9

L: \( R = 2,4\)-DNP

Li: \( R = H \)

a: \( R = 2,4\)-DNP

b: \( R = H \)

\( \text{P-NO}_2\text{C}_6\text{H}_4\text{COOH, POCl}_3 \)
\( \text{HSCH}_2\text{COOH; ArCHO, anhyd. NaOAc, gl. AcOH; } \)
\( \text{2,4-dinitrophenyl hydrazine/hydrazine hydrate, anhyd. NaOAc, AcOH} \).
LVII

a: \( R = 2,4\text{-DNP} \)
b: \( R = H \)

(iv)

LVIII

i)

LVI

(ii)

LVLIV

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ii) ClCH\(_2\)COOH, NaOAc; iii) ArCHO, anhyd. NaOAc, gl. AcOH;
iv) 2,4-dinitrophenyl hydrazine/Hydrazine hydrate, anhyd. NaOAc, AcOH.

**CHART 10**

i) \( H_2NNCSNHNH_2 \)
ii) ClCH\(_2\)COOH, NaOAc; iii) ArCHO, anhyd. NaOAc, gl. AcOH;
iv) 2,4-dinitrophenyl hydrazine/Hydrazine hydrate, anhyd. NaOAc, AcOH.
(Candida albicans). From the biological screening data obtained, some broad generalizations, regarding structure-activity relationship have been derived.

Thirteen research papers embodying the above research work have been published/accepted/communicated in Journals of repute (List of publications attached).