CHAPTER 1
GENERAL INTRODUCTION

Synthesis of various condensed triazoles, tetrazolopyrimidines and pyrroloquinazolines have been extensively reviewed in this chapter.

1.1 Condensed [1,2,4]triazoles:

Several condensed triazoles with a variety of valuable pharmacological activities\(^1,2,3\) have been found in the literature. This has spurred the interest in the preparation and pharmacological evaluation of triazolopyrrolopyrimidines. A number of routes have been proposed for the synthesis of condensed [1,2,4]triazoles. The synthesis of various condensed [1,2,4]triazoles have been classified into the following categories.

(i) Using one carbon donor moiety
(ii) Using C-N donor moiety
(iii) Formation of N-N bond
(iv) Formation of C-N bond
(v) Annellation of [1,2,4]triazole onto other heterocycles
(vi) Via rearrangement reactions

(i) Using one carbon donor moiety:

The most commonly used method for the synthesis of condensed [1,2,4]triazoles is through the cyclization of 2-hydrazino derivatives with one carbon donor synthons like carbocyclic acids, esters, orthoesters, amides, acid chlorides, anhydrides, cyanogen yields, carbon disulfide and isothiocyanate (Scheme-1).

![Scheme-1](attachment:image.png)
Condensation of 3-aryl-2-hydrazinoquinazolin-4-ones (1) with carboxylic acids such as formic acid, acetic acid and propionic acid yielded corresponding [1,2,4]triazolo[4,3-a]quinazolines (2) (Scheme-2).

When 2-hydrazinopyrimidinone derivatives (3) were reacted with orthoesters in boiling acetic acid, triazolopyrimidines (4) were obtained (Scheme-3). A synthesis of 5-substituted[3,4-c]-s-triazoloquinoxazolines (6) has been proposed by Postovaskii et al from 2-substituted-4-hydrazinoquinazolines (5) and triethylorthoformate (Scheme-4).
In the same manner 2-substituted-6-chloro-4-hydrazinoquinazolines (7) on cyclization with triethylorthoformate gave 5-substituted-9-chlorotriazoloquinazolines (8) (Scheme-5).

![Scheme-5](image)

When 2-hydrazinoquinazolin-4(3H)-ones (9) were reacted with a variety of orthoesters, linear triazolo[3,4-b]quinazolin-5(10H)-ones (10) were obtained (Scheme-6).

![Scheme-6](image)

Cyclization of 2-chloro-3-hydrazinoquinoxaline (11) by triethylorthoformate afforded 4-chloro[1,2,4]triazolo[4,3-α]quinoxaline (12) (Scheme-7).

![Scheme-7](image)

2-Methyl-4-hydrazinoquinazoline (13) on reaction with carbon disulfide gave 3-mercapto triazoloquinazoline (14) (Scheme-8).
Cyclocondensation of 5,6-diphenyl[1,2,4]triazin-3-ylhydrazine(15) with isocyanate gave carbamoyl derivatives(16), aminotriazolotriazine(17) or mercaptotriazolotriazine(18) depending upon the reaction conditions (Scheme-9).

3-Amino-5-aryl[1,2,4]triazolo[4,3-b]pyridazine (20) was obtained by cyclocondensation of 3-hydrazino-6-phenylpyridazine(19) with cyanogen bromide(Scheme-10). Kottke et al have proposed the another method involving the synthesis of 3-pyridyl-s-triazolo[5,1-b]quinazolin-9(3H)-ones(22) by refluxing 3-amino-2-(pyridylamino)-4(3H)-quinazolinones(21) with formic acid (Scheme-11).
Reaction of 2-(acetyl)hydrazino-3-aminoquinazolin-4(3H)-one (23) with triethylorthoformate afforded 1-(acetylamino)-1H,5H-[1,2,4]triazolo[3,2-b]quinazolin-5-ones (24) (Scheme-12). When 2-anilino-3-aminoquinazolin-4(3H)-one (25) treated with triethylorthoformate, [1,2,4]triazolo[1,5-b]quinazolin-9(3H)-one (26) was formed (Scheme-13).
Treatment of 3,4-diamino-6-phenyl-4,5-dihydro[1,2,4]triazine (27) with isothiocyanates gave fused triazoles (28) (Scheme-14).

\[
\text{RNCS} \rightarrow \text{Ph} \begin{array}{c} \text{N} \text{NH} \text{NH}_2 \end{array} \begin{array}{c} \text{Ph} \text{N} \text{NH} \text{NH} \text{R} \end{array}
\]

**Scheme-14**

3-Amino-4(3H)-aminobenzofuranopyrimidine (29) was cyclized using acetic anhydride in the presence of the catalytic amount of sulfuric acid to afford triazolobenzofuranopyrimidine (30) (Scheme-15). Padmanabhan et al. have used urea as synthon to cyclize 2,3-diaminoquinazolin-4(3H)-one (31) in order to obtain triazoloquinazolin-2,5-dione (32) (Scheme-16).

\[
\text{CH}_3\text{CO}_2\text{H} \rightarrow \text{H}_2\text{SO}_4 \begin{array}{c} \text{N} \text{NH} \text{NH}_2 \end{array} \begin{array}{c} \text{N} \text{NH} \text{NH}_2 \end{array}
\]

**Scheme-15**

Cyclocondensation of 3-amino-2-hydrazinoquinazolin-4(3H)-one (33) with triethylorthoformate, CS\textsubscript{2} or ethylchloroformate afforded [1,2,4]triazoloquinazolines (34) (Scheme-17).

6
Synthesis of 3-phenyl[1,2,4]triazolo[4,3-c]quinazoline (36) was reported from 2-phenyl-4-(benzoylhydrazino)quinazoline (35) and phosphorous oxychloride (Scheme-18).

Cyclization of 3-substituted-2-hydrazinoquinazolin-4-ones (37) by acetic anhydride or acetyl chloride provided 1-methyl-4-aryltriazolo[4,3-a]quinazolin-5-ones (38) (Scheme-19).

The same type of 3,6,8-trisubstituted triazoloquinazolones (40) were synthesized by treating hydrazino derivative (39) with carboxylic acids (Scheme-20). Methyl[1,2,4]triazolo[4,3-
cquinazoline\textsuperscript{25} (42) was synthesized from 2-methyl-4-hydrazinoquinazoline (41) and mono or dicarbonyl compounds (Scheme-21).

\[\text{Scheme-20}\]

Treatment of 2,5,6-trisubstituted-4-hydrazinothieno[2,3-d]pyrimidines (43) with triethylorthoformate afforded corresponding s-triazolo[4,3-c]thieno[3,2-e]pyrimidines\textsuperscript{26,27,28} (44) (Scheme-22).

\[\text{Scheme-21}\]

(ii) Using C-N donor moiety:

In this type of cyclization substrates capable of donating C-N moieties such as nitriles, iminoethers, imidohalides, amides etc. have been utilized with N-aminoazaheterocycles.

Phadke et al\textsuperscript{29} have synthesized [1,2,4]triazolo[1,5-a]pyrimidines (46) by the cyclization on
of 2(1H)-pyridone(45) with amides in the presence of zinc chloride (Scheme-23).

N-Aminotriazinone(47) was reacted with diphenylcarbodiimide under neutral condition to yield [1,2,4]triazino[4,3-b][1,2,4]triazoles (48) (Scheme-24).

1,6-Diaminopyridin-2-thione(49) on treatment with nitriles gave [1,2,4]triazolo[1,5-a]pyrimidine derivatives (50) (Scheme-25). Pendre et al. have synthesized 6-phenyl-1,3-dimethyl-(1H)-[1,2,4]triazolo[4,3-b][1,2,4]triazole(52) by refluxing N-aminotriazol-2-thione (51) with benzonitrile in tert-butanol containing potassium tert-butoxide (Scheme-26).
(iii) Formation of N-N bond:
In such type of reactions 2-amidoximeazaheterocycles were cyclized thermally, photochemically or under acidic conditions.

Pyrazolotriazole (54) was prepared by stirring a mixture of oxime(53) in the presence of p-toluenesulfonyl chloride, triethylamine and tetrahydrofuran (Scheme-27).

(iv) Formation of C-N bond:
Condensed [1,2,4]triazoles have also been constructed by oxidative cyclization of previously prepared 2-azinehydrozones with various oxidizing agents. Dehydrative cyclization of 2-acylhydrazinones under thermal condition or in the presence of cyclizing agent like polyphosphoric acid, phosphorous oxychloride, triethylamine etc have been successfully used for the synthesis of condensed [1,2,4]triazoles.

Compound(55) on cyclization using bromine in acetic acid gave triazolopyridine (56) (Scheme-28).
Triazolotriazine (58) was obtained by the treatment of hydrazone (57) with lead tetraacetate in methylene chloride (Scheme-29).

Cyclocondensation of ethyl(2-hydrazinothiazol-4-yl)acetate (59) with phosphorous oxychloride yielded thiazolo[2,3-c]-s-triazole (60) (Scheme-30).

2-(N-Benzoyl)hydrazinopyrimidine (61) was cyclized in dimethylformamide to get 5-amino-6-cyano-3,7-diphenyl-s-triazolo[4,3-a]pyrimidine (62) (Scheme-31).
1-((Acylamino)-2-(methylthio)pyrimidine hydroiodide (63) was refluxed with two equivalent of (alkyl)ammonium acetates in acetic acid to form 3H,5H-[1,2,4]triazolo[1,5-a]pyrimidines (64) (Scheme-32). Cyclocondensation of pyrimidine (65) with thiosemicarbamide yielded triazolopyrimidine of the type (66) (Scheme-33).

Desulfurization of pyrimidine derivative (67) with semicarbazide afforded polysubstituted [1,2,4]triazolo[4,3-a]pyrimidine-3-one (68) (Scheme-34). 1-Substituted[1,2,4]-triazolo[3,4-c]-1,4-benzoxazines (70) were obtained by treating 2-chloro-1,4--benzoxazine-3-ones (69) with acylhydrazines (Scheme-35).
Use of cyanamide in aqueous acetic acid followed by treatment with potassium hydroxide (50%, w/v) gave triazoloquinazoline (72) from N-methylantranilhydrazine(71) (Scheme-36).
(v) Annellation of $[1,2,4]$triazole onto other heterocycles:

Triazoles such as aminotriazoles and mercaptotriazoles have been annellated onto the appropriate substrate to form condensed $[1,2,4]$triazoles.

Pentan-2,4-dione (73) and 3,5-diamino$[1,2,4]$triazole (74) were cyclocondensed in presence of aqueous potassium hydroxide to yield $[1,2,4]$triazolopyrimidine (75) (Scheme-37).

\[
\begin{align*}
&\text{H}_3\text{C} \quad \text{C} = \text{O} \\
&\text{CH}_2 + \quad \text{H}_2\text{N} \quad \text{N} \rightarrow \text{NH}_2 \\
&\text{H}_3\text{C} \quad \text{C} = \text{O} \quad \text{H}_2\text{N} \quad \text{N} \rightarrow \text{NH}_2 \\
73 & \quad 74 & \quad \text{aq KOH} & \quad 75
\end{align*}
\]

Scheme-37

3-Amino-4(H)-$[1,2,4]$triazole (76) and $\alpha$-cyanoketene-$\beta$-thioacetal yield (77) were reacted to obtain $[1,2,4]$triazolopyridine (78) (Scheme-38).

\[
\begin{align*}
&\text{N} \quad \text{N} \\
&\text{N} \quad \text{NH}_2 + \quad \text{H}_3\text{CS} \quad \text{C} = \text{C} \quad \text{COCH}_3 \\
&\text{N} \quad \text{N} \quad \text{NH}_2 + \quad \text{H}_3\text{CS} \quad \text{C} = \text{C} \quad \text{CN} \\
76 & \quad 77 & \quad 78
\end{align*}
\]

Scheme-38

Treatment of 3-amino-4H-$[1,2,4]$triazole (79) with 4-methoxyphenylmethylene malononitrile (80) afforded s-triazolo[3,4-b]pyrimidine (81) (Scheme-39).
Cyclocondensation of 2-amino-3-triazolylthiophenes (82) by alkanoic acid, alkyl nitriles, orthoesters or carbon disulfide afforded 5,8,9-trisubstituted[1,2,4]triazolo[1,5-c]thieno[3,2-e]pyrimidine (83) (Scheme-40).

When 5-amino-1H-[1,2,4]triazoles (84) were treated with ethylethoxycrotonate (85), triazolopyrimidone of the type (86) were obtained (Scheme-41).
Kawasima et al. have reported that compounds (88) were formed when [1,2,4]triazoles (87) were reacted with β-ketoesters and sodium methoxide in methanol. Compounds (88) were refluxed with mesitylene to form 1H-pyrazolo[3,2-c][1,2,4]triazoles (89) (Scheme-42).

When 3-mereapto-s-triazoles (90) were cyclocondensed with alkyl-4-haloacetate, alkylthiazolo[3,2-b]-s-triazol-5-ylacetate derivatives (91) were formed (Scheme-43).

Thioureidotriazolothiols (92) were refluxed in N,N-dimethylformamide to obtain triazolo[3,4-b][1,3,4]thiadiazole derivatives (93) (Scheme-44).
N-Aminotriazol-4-thione (94) was reacted with aromatic aldehydes to give benzylidine derivative (95) which on reaction with phenacyl bromide derivative gave thiazolothiadiazinium bromide (96) (Scheme-45).

Cyclization of 4-amino-5-aryl[1,2,4]triazole-3-thione (97) with phenacyl chloride yielded 7H-3-aryl-6-phenyltriazolo[3,4-b][1,3,4]thiadiazine (98) (Scheme-46).
(vi) Rearrangement of heterocycles:

Hydrazine and its derivatives were employed to form an intermediate such as acyclic amidrazones, which were cyclized to furnish condensed [1,2,4]triazoles.

Triazoloquinazolines (100) were obtained by reaction of corresponding acyl benzoxazinones (99) with thiosemicarbazide (Scheme-47).

Pyran-1,5-dione (101) and thiosemicarbazide were reacted to afford condensed pyridotriazole (102) (Scheme-48).
Scheme 48
1.2 Condensed [1,2,3,4]tetrazolopyrimidines:

In a view of wide range of biological activities exhibited by condensed [1,2,3,4]-tetrazolopyrimidines there has been a spate of activities amongst the medicinal chemists for their synthesis\textsuperscript{55,56}. Tetrazolopyrrolopyrimidines are the isosters of wellknown tetrazoloquinazolines. The following routes for the synthesis of condensed tetrazolopyrimidines have been reviewed.

(i) Nucleophilic substitution of chloropyrimidines.
(ii) Condensation of preformed 5-aminotetrazoles with $\beta$-keto compounds.
(iii) Cyclocondensation of tetrazolylanilines and their analogous.
(iv) Azido-tetrazole tautomerism.

(i) Nucleophilic Substitution of Chloropyrimidines:

Chloropyrimidines easily undergo nucleophilic substitution reaction on the treatment with nucleophilic reagents such as hydrazine hydrate, metal azide, secondary amines etc. Various chloropyrimidines were reacted with hydrazine hydrate to give hydrazinopyrimidines which on diazotization afforded condensed tetrazolopyrimidines. Chloropyrimidines have also been used with metal azides for the direct synthesis of condensed tetrazolopyrimidines.

Hiedo et al\textsuperscript{57,58} have reacted 2-substituted-4-chloro-5,6,7,8-tetrahydroquinazolines (103) with hydrazine hydrate to give 2-substituted-4-hydrazino-5,6,7,8-tetrahydroquinazolines (104) which on diazotization with sodium nitrite in hydrochloric acid gave 5-substituted-7,8,9,10-tetrahydro[1,5-c]quinazolines (105). Compounds (105) were also obtained by the direct reaction of chloro derivatives (103) with sodium azide in refluxing alcohol (Scheme-49). 5,7-Disubstitutedtetrazolo[1,5-a]quinazolines (108)\textsuperscript{59} were prepared by the reaction of 2-chloro-4,7-disubstitutedquinazolines (106) with sodium azide. In another variation compounds (106) were reacted with hydrazine hydrate to give hydrazino derivatives (107) which were converted to tetrazoloquinazolines (108) by diazotization (Scheme-50).
4-Chloropyrimidines fused to heterocycles such as substituted-4-chlorothieno[2,3-d]pyrimidines (109) underwent nucleophilic substitution reaction with sodium azide to give substitutedtetrazolo[1,5-c]thieno[3,2-e]pyrimidines (111). 4-Chloroderivatives also underwent hydrazinolysis to give 4-hydrazino derivatives (110) which on diazotization yielded the same thienotetrazolopyrimidines (111) (Scheme-51). 2,4-Dichloroquinazoline (112) on treatment with sodium azide in acetone yielded a mixture of 5-azidotetrazolo[a]quinazoline (113) and 5-azidotetrazolo[c]quinazoline (114) (Scheme-52).
Cyclocondensation of appropriate 2-chloroquinazolin-4(3H)-ones (115) with sodium azide provided tetrazolo[1,5-a]quinazolin-5-ones (116) (Scheme-53).
5-Substituted tetrazolo[1,5-c]quinazoline (118) was obtained by cyclocondensation of 2-substituted-4-chloropyrimidine (117) with sodium azide (Scheme-54).

2-Aryl-4-chloroquinazoline (119) and sodium azide were reacted to form 5-aryl-tetrazolo[1,5-c]quinazoline (120) (Scheme-55). Various N-substituted tetrazolo[1,5-a]-
quinazolones (122) were obtained by condensation of N-substituted-2-chloroquinazolones (121) and sodium azide (Scheme-56).

Treatment of 2,4-dichloroquinazoline (123) with sodium azide in dimethyl sulfoxide yielded a mixture of tetrazolo[1,5-b]quinazoline (124) and quinazolin-2,4-(1H,3H)-dione (125) but not the desired 5-chlorotetrazolo[1,5-c]quinazoline (Scheme-57). Reaction of 5-piperidinotetrazolo[a]quinazoline (126) with hydrazine hydrate in alcohol gave 5-hydrazinotetrazolo[a]quinazoline (127) which on diazotization afforded 5-azidotetrazolo[a]quinazoline (128) (Scheme-58).
When 2-substituted-4-hydrazinoquinazolines (129) were diazotized with sodium nitrite in hydrochloric acid, 5-substituted tetrazolo[1,5-c]quinazolines (130) were formed (Scheme-59).
Diazotization of 2-hydrazinoquinazolin-4(3H)-one (132) followed by methylation with dimethylsulphate gave 4-methyltetrazolo[1,5-a]quinazolin-5-ones (131) (Scheme-60).

In another variation, 2-hydrazino-3-substitutedquinazolin-4(3H)-ones (133) were diazotized to give 4-substitutedtetrazolo[1,5-a]quinazolin-5-ones (134) (Scheme-61). Dihydrotetrazolo[1,5-a]quinazolinones, thiones and imines (136) were synthesized by Bowie et al using corresponding 2-hydrazino-3,4-dihydroquinazoline derivatives (135) with sodium nitrite in hydrochloric acid (Scheme-62).
Secondary aminosubstituted tetrazolo[1,5-c]quinazolines (138) were synthesized by diazotization of 2-secondary aminosubstituted-4-hydrazinoquinazolines (137) (Scheme-63). 2-Hydrazino-4-substituted quinazoline (139) on diazotization yielded tetrazoloquinazolines (140) (Scheme-64).
Fused hydrazinopyrimides such as 4-hydrazinopyrido[3',2':4,5]thieno[3,2-d]-pyrimidines (141) on diazotization provided tetrazolopyridothienopyrimidine (142) (Scheme-65). Diazotization of 4-hydrazino-5H-pyrimido[5,4-b]indole (143) with sodium nitrite in acetic acid gave corresponding tetrazolopyrimidoindole (144) (Scheme-66).

Treatment of 4-hydrazinofuro[2,3-d]pyrimidines (145) with sodium nitrite in acetic acid gave furo[3,2-e]tetrazolo[1,5-c]pyrimidines (146) (Scheme-67).
Treatment of 2-hydrazino derivative (R=H, 147a) on diazotization gave tetrazolo[1,5-a]quinazoline (148) whereas similar reaction of 2-hydrazino derivative (R=Me, 147b) afforded corresponding tetrazolo[5,1-b]quinazoline (149) (Scheme-68).

A new type of tetrazoles such as 7-substituted-(1H,9H)-tetrazolo[5,1-b]quinzaolin-9-ones (151) were synthesized by diazotization of 2-hydrozino-3-aminoquinazolin-4(3H)-ones (150) (Scheme-69).
(ii) Condensation of preformed 5-aminotetrazoles with β-keto compounds:

5-Aminotetrazoles were condensed with compounds having -C(\(\text{C.CH-OH}\))CO- functional group to give tetrazolo[a]pyrimidine derivatives.

Cyclocondensation of 5-aminotetrazole (152) with β-oxoesters (153) furnished tetrazolo[a]pyrimidines (154) (Scheme-70).

Gerhard et al\(^{84}\) have synthesized condensed tetrazolopyrimidines (157) by condensing 2-hydroxymethylenecyclohexanone or cycloheptanone (156) with 5-aminotetrazole (155) (Scheme-71).
(iii) Cyclocondensation of tetrazolylanilines and their analogous:

Cyclocondensation of tetrazolylanilines and their analogous such as 2-amino-tetrazolylypyrimidine or 2-amino-tetrazolylythiophenes afforded corresponding condensed tetrazolopyrimidines.

2-Tetrazolylanilines(158) were cyclized on the treatment of bubbled COCl$_2$ in benzene to give tetrazolo[1,5-c]quinazolines (159) (Scheme-72). The same type of cyclization was carried out by reacting 2-tetrazolylanilines(160) in the presence of carbonyl compounds(161) to give tetrazolo[1,5-c] pyrimidines (162) (Scheme-73).

\[ \text{Scheme-72} \]

\[ \text{Scheme-73} \]

Treatment of 5-bromotetrazolylaniline(163) with benzoyl chloride in pyridine provided tetrazolo[1,5-c]quinazolines (164) (Scheme-74).
Tetrazolo[1,5-c]quinazoline (167) was prepared from 5-(2-aminophenyl)tetrazole (165) and 4-(N-N-dimethylamino)benzaldehyde (166) (Scheme-75).

2-Tetrazolyl-5-substitutedanilines (168) were reacted with various carbonyl compounds to provide 5,6-dihydrotetrazolo[1,5-c]quinazolines (169) (Scheme-76). In the same manner 4-amino-5-tetrazolylpyrimidine (170) with substituted aldehydes gave 5,6-dihydropyrimido[5,4-e]tetrazolo[1,5-c]pyrimidines (171) (Scheme-77).
2-Amino-3-tetrazolylthiophenes (172) on acetylation followed by dehydrative oxidation yielded tetrazolo[1,5-c]thieno[3,2-e]pyrimidines (173) (Scheme-78).

(iv) Azido-tetrazole tautomerism:

In a suitable solvent some azides were found to be present in equilibrium with tetrazoles. Azido-tetrazole equilibrium was established between azidotetrazolo[1,5-a]quinazoline (174) and bistetrazoloquinazoline (175) in dimethyl formamide (Scheme-79).
The equilibrium was also established between tetrazolo[1,5-a]quinazoline (177) and 2-azidoquinazoline (176) when compound (176) was treated with acetyl acetone and ethanol in presence of triethylamine (Scheme-80).
1.3 Pyrroloquinazolines:

Vasicine(178), the oldest and best known quinazoline alkaloid contains pyrroloquinazoline ring system. Chemically vasicine is 3-hydroxy-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline(178). Vasicine was extracted from *Adhatoda vasica* knees (*Acanthaceae*)\(^9\). Latter it was found in *paganum harmala* (*Zygophyllaceae*) and in number of other species. Structure elucidation of vasicine was accomplished by Spath et al\(^94\) and the same authour reported the first synthesis of vasicine, in which methyl-4-amino-2-hydroxybutyrate(179) was condensed with 2-nitrobenzyl chloride(180) to give 1-(2-nitrobenzyl)-3-hydroxypyrrolidin-2-one(181) which after reduction cyclized readily to vasicine (Scheme-81).

![Scheme-81](image)

Spath and Platzer\(^104\) subsequently reported a second simpler synthesis starting from γ-butyrolactone(182). The γ-butyrolactone was brominated and hydrolyzed to afford γ-hydroxybutyrolactone(183) which on condensation with γ-aminobenzalamine(184) at 200°C gave vasicine (Scheme-82).
Southwick and Casnova prepared vasicine from 2-nitrotoluene using series of reaction sequences. A parallel series of reaction with only slight modification allowed preparation of the analogous 7-methoxyvasicine (185) from 3-methoxy-4-nitroanisole.

Leonard and Martell reported the condensation of γ-amino-α-hydroxy butyraldehyde (186) with 2-aminobenzaldehyde (187) to form vasicine (Scheme-83).

Finally a facile synthesis of vasicine was published in 1970 in the course of which condensation of 2-nitrobenzylchloride (188) with 3-hydroxypyrrolidone (189) afforded vasicine (Scheme-84).
Vasicinone (190) is an oxidation product of vasicine. Mehta et al. have reported that the total crude of alkaloids from *Adhatoda vasica* contains predominantly vasicine but that gradually converted to vasicinone due to autooxidation. Similarly pure vasicine undergoes autooxidation to vasicinone. Compound (190) has been isolated from the seeds and other part of *peeganum harmala* as well as *Linaria transiliensis*. Onaka reported a biometric type synthesis of vasicinone starting from anthranilic acid (191) and 2-methylbutyrolactam (192) (Scheme-85).

7-Hydroxyvasicine (193) was isolated by Spath et al. from the leaves of *Adhatoda vasica* and detected in the seeds of some species by Groger and Johne. Vasicinolone (194) was also isolated from *Adhatoda Vasica*.
Vasicol\textsuperscript{117} (195) was isolated from the roots of a vasica and was characterized as 2,3,4,9-tetrahydropyrrolo[2,1-b]quinazolin-3-3a(1H)-diol Siddiqui\textsuperscript{118} isolated a crystalline compound deoxyvasicine(196) from the seeds of \textit{Peganum harmala}.

\begin{center}
\textbf{195}
\end{center}

\begin{center}
\textbf{196}
\end{center}

Deoxyvasicine and its derivative \textsuperscript{119} (199) have been synthesized by condensation of anthranilic acid derivative(197) and 2-pyrrolidone(198) followed by reduction with Zn/HCl (Scheme-86).

\begin{center}
\textbf{197}
\end{center}

\begin{center}
\textbf{198}
\end{center}

\begin{center}
\textbf{199}
\end{center}

\textbf{Scheme-86}

Anisotine(200), Anisessine(201), Aniflorine(202), Deoxyaniflorine(203) and Sessiflorine(204) were also isolated in low yields from \textit{Anisotes sessiliflorus} C.B.Cl as well as \textit{Adhatoda vasica} \textsuperscript{120,121}. Vasicoline(205), Vasicolinone(206), and Adhatodine(207) were also found in \textit{adhatodavasica} \textsuperscript{122}.

38
No. | R₁ | R₂ | R₃
---|---|---|---
200 | H | H | H
201 | H | H | H
202 | OH | NMe₂ | OMe
203 | H | NMe₂ | OMe
204 | H | NMe | OMe

205 | R₁ = H₂ | R₂ = NMe₂ | R₃, R₄ = H
206 | R₁ = O | R₂ = NMe₂ | R₃, R₄ = H
207 | R₁ = H₂ | R₂ = H | R₃ = CO₂Me | R₄ = NHMe
From different parts of peganum harmala soviet coworkers have isolated the pyrroloquinazolines paganidine (208), isopeganidine (209) and peganol (210). E.C. Taylor et al have synthesized pyrroloquinazoline of the type (211) from anthranilonitrile, where as pyrrolo[1,2-a]quinazoline (212) was obtained by condensation of 2-quinazoline propionic acid with KCN followed by cyclization.

\[\text{CH}_2\text{CH}_3\]

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R}
\end{array}
\]

\[208\quad \text{R}=\text{OH}\]

\[209\quad \text{R}=\text{H}\]

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

\[210\]

2-Aminobenzylamine or anthranilamide (213) were cyclized by 5-chloropentanone (214) and the product obtained was treated with LiAlH\(_4\) to give pyrroloquinazoline (215) (Scheme-87).
The condensed product of succinilamine(216) and anthranilic acid(217) was cyclized with acid anhydride to yield 1,4-dihydro-4-oxo-2-quinazolinepropionic acid(218) which was further cyclized in Ac2O and dimethylformamide to give pyrrolo[1,2-a]quinazolin-1,5-(2H, 3H)-diones (219) (Scheme-88).

3-Benzoylpropionic acid(220) and 5-chloroanthranilamide(221) with PTSA in o-dichlorobenzene were reacted to prepare 1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinazolin-5-ones (222) (Scheme-89).
The reaction of quinazoline propionic acid esters(223) with KCN in 1,2-dimethoxyethane gave pyrroloquinazolines(224) (Scheme-90).

The synthesis of pyrrolo[1,2-a]quinazolin-5(4H)-ones (225) involved cyclization of intermediates(226) formed from reaction of 2-bromoethyl-3-phenylquinazolin-4(3H)-one with active methylene compound in THF and sodium ethoxide(Scheme-91).
Anjello et al. have reported the cyclocondensation of 2-(2-methyl-3-carbethoxy-1H-pyrrolyl)aniline (227) with carboxylic acids, benzaldehyde or nitrous acid (228) to obtain pyrrolo[1,2-c]quinazoline (229) (Scheme-92).

\[
\text{\textbf{scheme-92}}
\]

2,3,3a,4-Tetrahydropyrrolo[1,2-a]quinozoline-1,5-diones (231) were prepared by acid catalysed cyclization of anthranilamide derivative (230) (Scheme-93). Treatment of substituted anthranilamides (232) with butyrolactone (233) in presence of catalyst BF₃ yielded 5H-pyrrolo[1,2-a]quinazolines (234) (Scheme-94).

\[
\text{\textbf{scheme-93}}
\]

\[
\text{\textbf{scheme-94}}
\]
Methylantranilate (235) and pyrrolinone (236) were reacted to give pyrroloquinazoline (237) (Scheme-95).

\[ \text{Methylantranilate} \quad \xrightarrow{\text{reaction}} \quad \text{Pyrroloquinazoline} \]

When 2-hydroxyhalohexanone (238) was reacted with amlonitrile or anthranilic acid derivatives (239) 5-amino or 5-oxopyrroloquinazolines (240 & 241) were obtained according to the scheme-96.

\[ \text{2-hydroxyhalohexanone} \quad \xrightarrow{\text{reaction}} \quad \text{5-amino or 5-oxopyrroloquinazolines} \]

scheme-95

scheme-96
Quinazolium salt (245) were reacted with 2-alkynoate (246) to give pyrrolo[1,2-c]quinazolines of the type (247) (Scheme-98).

Susse and Dave et al. have synthesized 5-oxo or 5-aminopyrroloquinazolines (250a & b) by condensing anthranilic acid derivative or anthranilonitrile with 2-bromo-1-substitutedalkyldenepropanedinitriles (249) in propanol (Scheme-99).
Bandurco et al. have reported the synthesis of pyrrolo[1,2-c]quinazolines (252) by cyclocondensation of 4-methylquinozolines (251) with ethylbromo acetate (Scheme-100).

5-Amino-1-oxo-1,2-dihydropyrrolo[1,2-a]quinazolin-3-carbonitriles (255) were arised from the reaction between compound (253) and malononitrile (254) (Scheme-101). The reaction of N-benzoyl-3,4-dihydro-4-quinazolinecarbonitrile (256) with nucleophile such as acetylenedicarboxylate (257) provided the corresponding pyrrolo[1,2-c]quinazoline (258) (Scheme-102).
The Witting type condensed product (259) of pyrrolidinosubstituted phenone phospheranes was cyclized thermally to afford trans pyrrolo[1,2-a]quinazolines (260) (Scheme-103).