CHAPTER : I

GENERAL INTRODUCTION
Quinazoline (A) is a benz-1,3-diazine. Quinazoline containing a 2- or 4-hydroxy substituent (B, C) forms a distinct class. Both these compounds are reported to exist mainly in the keto form in the solid state and in solution (1). They are reported to exhibit properties of both the keto and enol forms (2, 3, 67). Similarly 2-mercaptoquinazol-4-one (D) can exist in two forms.
The work reported in the present thesis is on the study of synthesis of various 2-mercapto-3-arylquinazol-4-ones.

1:1 Some natural quinazolones:

Among the important quinazoline alkaloids a special mention may be made of arborine(I)(4), febrifugine(II) and peganine or vasicine(III)(5 to 7). The plant *glycosmis arborea correa* is the main source of arborine(8). This plant is reported to have been used as a febrifuge. Febrifugine, isolated from the roots of *Dichroa febrifuga* lourd, was considered a very interesting alkaloid due to its high antimalarial activity. Only its high toxicity has precluded its practical use(9 to 12).

(I) Arborine

(II) Febrifugine

(III) Vasicine
Some important synthetic quinazol-4-ones:

Quinazol-4-ones substituted both in the benzene as well as the hetero ring are known to possess a variety of physiological properties. Analogues of febrifugine have been prepared and tested for antimalarial activity(13). Some of the 2-(dialkylaminoalkyl)quinazol-4-ones have also been tested for this property(14). Considering the importance of the quinazoline ring system in an antimalarial like febrifugine and vasicine, Narang and coworkers have synthesised 2- and 3-substituted-quinazol-4-ones and 3,4-dihydro-quinazol-4-onyl-2-mercaptoacetanilides to study their antimalarial and antibacterial activities(15 to 18). Several 2-methyl-3-aryl-, 2-mercapto-3-aryl-, and 2(γ-trichloro-β-hydroxy) propyl-3-arylquinazol-4-ones have been synthesised with a view to study their pesticidal properties(19). Gujral and Saxena tested some 2-alkyl-3-phenyl-4(3H)-quinazolones and found them active as ataractic agents(20) while Buzas and Hoffman synthesised 2-alkyl-3-substituted-4(3H)-quinazolones as potential hypnotics and analgesics(21).

It has been reported that quinazoline sulfonamides possess a high diuretic activity. 7-chloro-6-sulfamyl-2-ethyl-3H-1,2-dihydroquinazol-4-one(IV) has been marketed
under the name 'Quinethazone'(22). Some of the 2,3-disubstituted quinazol-4-ones have been reported to possess a high hypnotic activity(23,24). 2-Methyl-3-0-tolylquinazol-4-one(V) has been patented under the name 'Methaqualone' or 'Malsedin'(23 to 25).

(IV) Quinethazone

(V) Malsedin

(VI) Chlorothiazide
The chemistry of quinazol-4-ones has been studied by a number of workers and a number of methods for their syntheses are reported and reviewed (26 to 55). The outlines of these methods can be classified as under.

**Type - I**

\[
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{N} \\
\end{array}
\quad \xrightarrow{\text{reaction}}
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{N} \\
\end{array}
\]

Thus this above type includes the condensation of

(i) an anthranilic acid with an acid amide (26 to 30);
(ii) an anthranilic acid with a cyanide (28) and
(iii) an anthranilic acid with a compound containing a \(-\text{N} = \text{C}\) system (32 to 34).

**Type - II**

\[
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{N} \\
\end{array}
\quad \xrightarrow{\text{reaction}}
\begin{array}{c}
\text{C} \\
\text{N} \\
\text{N} \\
\end{array}
\]
This type includes the condensation of

(i) an N-acylanthranilic acid with an aromatic amine in presence of phosphorus trichloride (19, 35 to 37);

(ii) an N-acylanthranilic acid with acetic anhydride followed by a reaction with an amine (38, 40, 41);

(iii) an N-acylanthranilic acid with an amine in a sealed tube (42) and

(iv) an N-acylanthranilic acid with formamide (43).

Type-III

![Chemical structure diagram]

The above type includes the condensation of

(i) an acetanilide with urethane in presence of phosphorus pentoxide (44 to 46); and

(ii) a benzanilide imidochloride with urethane and subsequent cyclisation (47).
This includes the condensation of

(i) an anthranilic acid with an acid chloride and subsequent cyclisation of the N-acylantranilamide obtained(48) and

(ii) an anthranilamide with acetic anhydride(31,49).

Besides these, many other methods for the syntheses of quinazol-4-ones are reported(50 to 55).

1:4 Properties of quinazol-4-ones:

Quinazol-4-ones are high melting solids. They are soluble in aqueous alkali and form solid hydrochlorides. Aqueous and alcoholic solutions of 1,2-disubstituted quinazol-4-ones show flourescence. Except 1,2-disubstituted they are stable towards oxidation, hydrolysis and reduction(3). With phosphorus oxychloride 2R-3H-quinazol-4-one gives a 2R-4-chloroquinazoline(56,57). The chlorine at 4-position
of a quinazoline nucleus can be replaced by an amino, hydrazino, mercapto or alkoxy group(3,58,59). Quinazol-4-one undergoes electrophilic substitution like nitration and halogenation(59 to 61). 2-Methylquinazol-4-one exhibits reactions characteristics of active methyl group(62,63). A quinazol-4-one undergoes O- and N-methylation depending upon the reaction conditions(38,64,65). 2-Benzyl-3H-quinazol-4-one with benzaldehyde gives 2-(β-phenyl) styryl-3H-quinazol-4-one(66).

1:5 Syntheses of quinazol-2:4-diones:

The quinazol-2:4-diones have been prepared by a number of workers. Some of the methods are as under.

Type - I

(A) This type includes condensation of

(i) an anthranilic acid with potassium cyanate 68 to 71 and

(ii) an anthranilate with a urethane(71).
This case consists of condensation of

(i) an anthranilic acid with urea and an arylurea (68 to 72);

(ii) an anthranilamide with urea(68) and

(iii) of two molecules of potassium anthranilate(73).

**Type - II**

![Chemical structure](image)

This type mainly consists of cyclisation of 2-ureidobenzoic acid(69).

**Type - III**

![Chemical structure](image)

In this method a quinazol-2:4-dione is obtained from isatoic diazide and ammonia(74).
Type - IV

This type consists of heating a diarylurea with potassium carbonate in presence of carbon dioxide under pressure(73).

Besides these, the other reported methods for the syntheses of quinazol-2:4-diones are mainly from arylamines by heating in presence of carbon dioxide under pressure(75).

1:6 Properties of quinazol-2:4-diones:

2:4-Dihydroxyquinazoline is tautomeric with 1:2:3:4-tetrahydroquinazol-2:4-dione. These compounds dissolve in aqueous alkalis. Methylation of their alkaline solution give N-methyl derivatives. Ethylation however give both N-ethyl and O-ethyl derivatives, as also the treatment of the silver salts with methyl iodide(76). With diazomethane they give the 3-methyl and then 1:3-dimethyl derivatives(77). But 4-hydroxyquinazoline gives both 4-methoxyquinazoline and 4-oxo-3-methyl-3:4-dihydroquinazoline(78).
The general methods for the syntheses of 2-mercaptoquinazol-4-ones starts with an anthranilic acid or its derivative. They can be summerised as below.

**Type - I A**

This type includes condensation of

(i) an anthranilic acid or its ester with potassium or ammonium thiocyanate (18, 79 to 86);

(ii) an anthranilic acid or its ester with ethylthiocyanatoformate (18, 80, 81);

(iii) an anthranilic acid with an alkyl, aralkyl or arylisothiocyanate (87 to 99);

(iv) an 2-aminobenzaldoxime with an alkyl or arylisothiocyanate (100, 101) and

(v) an isatin with an alkyl or arylisothiocyanate (100 to 103).
Type - I B

This type mainly consists of condensation of anthranilic acid with thiourea or an arylthiourea (97, 104).

Type - II

This type includes condensation of an anthranilamide with carbon disulphide (83, 84) or ammonium thiocyanate (83, 84).

Type - III
This type consists of cyclisation of 2-thioureidobenzyl alcohols(105).

1:8 Properties of 2-mercaptoquinazol-4-ones:

2-Mercaptoquinazol-4-ones are high melting solids. They are soluble in aqueous alkali and can be precipitated from such a solution on acidification. Their aqueous alkaline solutions are yellow in colour, while 2-mercapto-3-arylquinazol-4-ones containing a nitrogroup give a reddish alkaline solutions. They give colourless lead salts and yellow copper salts with their respective acetates.

1:9 Present work:

The present work deals with the syntheses of various unsubstituted and benz-bromo-substituted 2-mercapto-3-arylquinazol-4-ones(I). The syntheses was carried out by the known method of heating a mixture of an anthranilic acid and (i) an arylthiourea or (ii) an arylisothiocyanate. Thus anthranilic acid, 5-bromoanthranilic acid, 4-bromoanthranilic acid and 3:5-dibromoanthranilic acid were heated with phenyl-, p-tolyl-, p-anisyl-, p-nitrophenyl- and p-chlorophenylthioureas as well as with phenyl-, p-tolyl-, p-anisyl-, p-nitrophenyl- and p-chlorophenylisothiocyanates
to get the corresponding 2-mercapto-3-arylquinazol-4-ones(I).

\[
\begin{align*}
\text{(A)} & \quad R_1 \quad R_2 \quad R_3 \\
\text{(B)} & \quad \text{OR} \quad \Delta \\
\text{(C)} & \quad \text{(I)} \\
\end{align*}
\]

At: \quad R_1 = R_2 = R_3 = H \\
R_1 = -Br, R_2 = R_3 = H \\
R_2 = -Br, R_1 = R_3 = H \\
R_1 = R_3 = -Br, R_2 = H \\
and, Y = H, -CH_3, -OCH_3, -NO_2 and -Cl

The following reactions of 2-mercapto group were studied.  
(i) Oxidation of 2-mercapto-3-arylquinazol-4-ones(I) with aqueous potassium permanganate to the corresponding quinazol-
2:4-diones(II).

(ii) Its reaction with iodine in aqueous potassium iodide to get the disulphides(III).

(iii) Condensation with methyl iodide and 2:4-dinitrochlorobenzene to the corresponding thio ethers(IV and VI) and subsequent oxidation to the respective sulphones(V and VII).

(iv) Similar condensations with monochloroacetic acid and -bromoacetophenone gave(VIII and IX).

(v) Isomerisation to the corresponding 2-arylamino-6-keto-4:5-benzo-1:3-thiazines(X) by heating with concentrated sulphuric acid.