CHAPTER-1
CHAPTER 1

INTRODUCTION TO THE MALARIA AND CHEMISTRY OF QUINAZOLINONES.

1.1. Historical background:

1.1.1 Introduction:

**Malaria = The Disease:** Malaria has been one of mankind’s most dreaded, crippling and uneradicatable diseases since pre-historic times. The disease is caused by the bite of the female anopheles mosquito on the human beings. There are several species of mosquitos known today and the anopheles mosquito is one of them. Incidentally, the male anopheles mosquito does not show any tendency to feed on vertebrate /human blood. The anopheles mosquito is a nocturnal feeder whereas the other species “Aedes aegypti” mosquito is a day feeder causing Dengue and Yellow fevers. In fact, the name malaria is derived from the Latin name “mala aria” meaning bad air. It was Dr. Ronald Ross who (when he was posted as a British army officer at Hyderabad, India, under a treaty signed between the British Indian Government and the then Nizam of Hyderabad) proved that malaria was transmitted by an insect Vector and that the parasite was carried in the stomach and salivary glands of the female anopheles mosquito. For this discovery, Dr. Ronald Ross was honoured with Nobel prize in Medicine in 1902 and was Knighted by the British Government.
Life cycle of malaria parasite: Malaria parasites have a very complex life cycle and can exist in many different forms (sporozoite, schizont, merozoite, trophozoite, and gametocyte). When a human being is bitten by an Anopheles mosquito, the parasite is introduced in its sporozoite form. This rapidly invades the liver where it matures first into a schizont and then into a merozoite. The merozoite form of the parasite leaves the liver and then invades red blood cells (erythrocytes). Within erythrocytes, the merozoite is sequentially transformed into a trophozoite, then into a schizont and finally back to a merozoite which ruptures out of the erythrocyte to moculate other erythrocytes. Within the erythrocyte, some merozoites also develop into gametocytes which are taken up by mosquitos, whereby they are matured back into infective sporozoites-thereby initiating the infective process all over again. This circuitous life cycle, shown in the figure drawn below, offers a number of targets for anti-malarial drugs.
Control and treatment of malaria: There are three potential ways to control malaria. Namely, elimination of the vector, drug therapy and vaccination. Elimination of the vector is probably the simplest and most effective method to check the onset of the disease. To achieve this, the adult female anopheles mosquito must be killed and all breeding areas destroyed. This can be done by application of insecticides and draining of all stagnant / still waters. One of the most effective insecticides has been DDT (Dichloro Diphenyl Trichloroethane). Dr. Paul Muller received the Nobel Prize in 1948 in Medicine for discovering that DDT kills the malaria carrying Anopheles mosquito. DDT is long lasting and, unfortunately, it is not easily
biodegradable. It accumulates in the environment. While being long lasting is beneficial from the point of view of mosquito control, it also means that DDT has a tendency to get into food chain and affects both animals and human beings.

In fact, the use of DDT has been banned in most of the advanced countries of America and Europe. Unfortunately, the areas of the world where malaria is endemic (such as Africa, the Indian sub-continent and countries of the far-east) are economically poor and cannot (1) afford newer insecticides (2) give proper funding to drain all stagnant areas & run a strong public hygiene programme and (3) provide good medical facilities such as hospitals, Doctors, Paramedical Staff and drugs to treat their citizens. In fact, the above mentioned three points form the basis and charter of the National Malaria Control Programme (NMCP) of the Government of India, Ministry of Health & Family Welfare, New Delhi. As a matter of fact, as a small post-script to the well-stated polices and not-so-easily implementable programmes of various health agencies of different Governments of Asia & Africa, it may be stated that “it is important to avoid anopheles mosquitoes by using (a) long sleeves and trousers (b) repellent creams and sprays (c) screened windows & doors (d) mosquito nets (e) repellent coils, vaporizable liquids & jet mats”.

The second most important method to control malaria is drug therapy i.e. treating the disease with chemicals (that will act as drugs) that destroy the parasite in its various stages and forms in human beings. In the following paragraphs, a small account is given of the chemicals / drugs that
have been used to treat malaria. The drugs are described in a chronological order with their chemical structures.

The bark of Cinchona tree, grown in Peru and named after the Countess of Cinchona who was the wife of the Peruvian Viceroy, was introduced in Europe in the early 17th century as a cure for fevers. Later, it was realized to be a specific remedy for malaria. Quinine, isolated from the Cinchona bark in 1820, replaced the crude preparation and continued to be the major antimalarial drug till 1942. The world’s supply of Cinchona bark for producing quinine was met by Java and neighbouring countries. This was cut off from the Germans during World War I and from the Allies during World War II. Due to enormous military importance of malaria and its treatment, intense activity was initiated for the development of anti-malarial drugs. Mepacrine was produced in Germany in 1926 and extensively field tested by the Allies during World War II. Chloroquine was produced in USA soon after as a less toxic alternative to mepacrine; it had already been synthesised and used by Germans in 1934 as “Rosochin”. Chloroguanide was introduced in 1945 by the British as a well tolerated clinical curative.

None of the above drugs were found to be capable of preventing relapses of vivax malaria. Paraquine was the first 8-aminoquinoline to be tested in Germany in the 1920s. However, no attention was paid to it because of its poor Schizontocide action. This class of drugs was retested during World War II as radical curative and Primaquine emerged as the most desirable drug. Pyrimethamine was produced in 1951 under a planned post-war research programme for antimalarial drugs. The only important
additions of the recent years are Mefloquine, Atoraquone and Artimisinin for resistant falciparum malaria.
The most recent additions to the drug therapy of malaria are artemisinin and its derivatives. Isolated from “Artimisia annua” (quinghao), Chinese herbalists have been using this material since 168 B.C. Artemisinin and the derivatives, artemether and the synthetic arteflene, are active by virtue of the endoperoxide.

Finally, a word about vaccination against malaria. **Thus far, no vaccine has been developed that is effective against malaria “in vivo”**.
Quinazolinones:

There are biologically active molecules whose framework includes a six-membered ring containing two nitrogen atoms fused to a phenyl ring. Most of these molecules are based on the quinazolinone framework. The major sub-classes of quinazolinones fall into the following categories of:

- Quinazoline (I)
- 3H-Quinazolin-4-one (II)
- 1H-Quinazoline-2,4-dione (III)
- 1H-Quinazolin-2-one (IV)
- 2-Mercapto-3H-quinazolin-4-one (V)
- 2-Methyl-3H-quinazolin-4-one (VI)

1.2. Brief Account of reactivity of 4(3H)-Quinazolinones (II):

Reactions associated with tautomeric nature of the amide linkages in quinazolinones should not be looked on as predominantly the keto (II) or the
enol (VII) form but as true keto-enol tautomers, showing reaction characteristic of both the forms. (Scheme-1.1).

Quinazolinones are always high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. Simple 4(3H)-quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4(3H)-quinazolinones form stable monohydrochlorides, chloroplatinate, chloroaurates and picrates and their metal salts of silver, mercury, zinc, copper, sodium and potassium.

1.2.1. Stability of the ring system:

The ring system in quinazolinone is exceedingly stable in oxidation, reduction, hydrolysis reactions and other treatment designed to break the ring. There is no report of degradation of quinazolinone by simple chemical oxidation.

1.2.2. Aromatisation:

When a simple and 2-substituted- 4(3H)-quinazolinone (VIII) is heated with an equivalent amount of phosphorous pentachloride in phosphorous oxychloride, the corresponding 4-chloroquinazoline (IX) is obtained. If a methyl group is present at 3-position, prohibiting the usual
tautomerism, the methyl group is lost during the chlorination [1]. (Scheme-1.2).

1.2.3. Alkylation:

The position of alkylation of quinazolinones is similar to all the aromatic nitrogen heterocyclic systems in which a hydroxyl group is found ortho or para to the nitrogen position. Such compounds exist in tautomeric mixture (X), the two structures being inter-convertible by the shift of one proton and one pair of electrons. In alkaline solution the ions of such compounds exist as resonance hybrids of the two major forms differing only by the position of two pairs of electrons, as shown. Thus in alkylation of such hydroxyl derivatives of pyridine, pyrimidine and similar heterocycles, the entering group may become attached to either the nitrogen atom, thus giving for instance, an N-alkylpyridine or to the oxygen atom, giving an alkoxy pyridine [2]. (Scheme-1.3).

1.2.4. Nitration:

4(3H)-Quinazolinone (XII) on boiling with nitric acid undergoes substitution to give 6-nitro-4 (3H)-quinazolinone (XIII). On further nitration
it has been observed that the second nitro group enters the 8-position to give 6,8-dinitro derivatives (XIV). 2-Substituted-4(3H)-quinazolinones were also found to behave similarly, under such conditions [3-6]. (Scheme-1.4).

1.2.5. Reduction:

2-Hydro-3-methyl- 4(1H)-quinazolinone (XVI) could be obtained on reduction of 3-methyl-4(3H)-quinazolinone (XV) with lithium aluminium hydride (LiAlH₄) in benzene [7]. (Scheme-1.5).
**Table 1.1:** Some important derivatives of quinazolinones.

<table>
<thead>
<tr>
<th>S.No</th>
<th>IUPAC Name</th>
<th>Structure</th>
</tr>
</thead>
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<tr>
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</tr>
<tr>
<td>XVIII</td>
<td>Gefitinib</td>
<td><img src="image2" alt="Gefitinib Structure" /></td>
</tr>
<tr>
<td>XIX</td>
<td>Erlotinib</td>
<td><img src="image3" alt="Erlotinib Structure" /></td>
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<tr>
<td>XX</td>
<td>Alfuzosin</td>
<td><img src="image4" alt="Alfuzosin Structure" /></td>
</tr>
<tr>
<td>XXI</td>
<td>Trimethotrexate</td>
<td><img src="image5" alt="Trimethotrexate Structure" /></td>
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<td>Bunazosin</td>
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<tr>
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<td>Afloqualone</td>
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<tr>
<td>XXX</td>
<td>Febrifugine</td>
<td><img src="image4" alt="Febrifugine" /></td>
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</table>

1.3. Synthesis of Quinazolinone derivatives:

Most of the methods employed for the synthesis of 4(3H)-quinazolinones make use of anthranilic acid, anthranilamide or one of their functional derivatives as the starting materials. Based on this factor, the general methods of synthesis are:

1.3.1. Condensation of anthranilic acid with acid amides:

When anthranilic acid (XXXI) is heated in a open container with excess of formamide at 140-145 °C, water is expelled and a nearly
quantitative (90%) conversion to 4(3H)-quinazolinones (II) [8] is achieved. (Scheme-1.6).

![Scheme-1.6](image)

1.3.2. Condensation of acetanilides with urethanes:

A number of attempts have been made to condense a urethane derivative with aniline to give 4(3H)-quinazolinone, directly. Urethane (XXXIII) and acetanilide (XXXII) heated for 3 hours with phosphorus pentoxide in toluene, give 2-methyl-4(3H)-quinazolinone (VI) [9]. (Scheme-1.7).

![Scheme-1.7](image)

1.3.3. Condensation of N-acylanthranilic acids with primary amines:

4(3H)-Quinazolinones may also be synthesized directly from the corresponding N-acylanthranilic acid by heating with ammonia or substituted amines. Bogert and Steiner [10] have prepared 2-methyl-3-alkyl-
6-nitro-4(3H)quinazolinones (XXXVI) from N-acyl-5-nitroanthranilic acid (XXXIV) and a variety of primary amines. (Scheme-1.8).

\[
\begin{align*}
&\text{O} \quad \text{NH} \\
&\text{OH} \\
&\text{NH} \\
&\text{O} \\
&\text{N} \quad \text{CH}_3
\end{align*}
\]

\[\text{XXXIV} \quad \text{XXXV} \quad \text{XXXVI} \]

....Scheme – 1.8

1.3.4. 2 – (4,5 – Dihydro – (1H) – pyrazol – 5 – yl) – 4 (3H) quinazolinone.

El – Shahed et.al. reported [11] the preparation of 3 – amino -2 – (3-p-tolyl) -4, 5 – dihydro-(1H)pyrazol- 5-yl) – 4(3H)quinazolinone (XXXIX). The reaction of β-(4 – methyl benzoyl) acryloyl chloride (XXXVII) with anthranilic acid (XXXI) followed by cyclization of the resulting anilide by acetic anhydride yielded 2-(4-methylbenzoylvinyl) – 4H – 3,1, - benzoazin -4 – one (XXXVIII) which was treated with hydrazine hydrate to obtain XXXIX .(Scheme-1.9).
1.3.5. **2 – Piperazinyl /pyrrolidine /piperidine – 4(3H) quinazolinone.**

2-Piperaziny-4(3H)-quinazolinones showed very prominent anti-hyperglycemic activity. In fact, some of the derivatives have reduced blood glucose level in streptozotocin and sucrose loaded rat models[12]. These compounds were synthesized by halogenations of quinazoline – 2,4 – dione (XXXX) with POCl₃ to yield 2,4 – dichloroquinzoline (XXXI), which was regioselectively hydrolyzed to 2 - chloro -4 (3H)quinazolinone (XXXXII) and then treated with cyclic secondary amines to yield 2 – piperazinyl/pyrrolidine/piperidine- 4(3H) – quinazolinone (XXXXIII), (Scheme-1.10).
1.3.6. 2-(3, 4, - Dihydro - 2(1H) - isoquinolin) - 4 (3H)quinazolinones.

5 - Cyclopropyl – 1 – 2 (5-(cyclopropylamino)methyl ) – 3, 4,- dihydro – 2 (1H)- isoquinilinyl) -7- methoxy – 4(3H)quinazolinone (XXXXVI), is useful in the treatment of hypertension, myocardial infarction, male erectile dysfunction (MED) hyperlipidemia, cardiac arrhythmia, glaucoma and benign prostatic hyperplasia (BPH) [13]. It was prepared by reacting 2 – chloro – 5 – cyclopropyl methoxy -4 (3H)quinazolinone (XXXXIV), and N – (1, 2,3,4 – tetrahydro – 5 – iso quinolinyl) methyl) cyclopropanamine dihydrochloride (XXXXV), in the presence of diisopropyl ethylamine (DIPEA) in butanol gave (XXXXVI) (Scheme-1.11).
Ishida et.al reported [14] the synthesis of PARP inhibitor 2 – (3-(4-phenyl piperidin – 1-yl)cyclopent – 1 – enyl) – 4(3H) quinazolinone \((XXXVIII)\) via cyclization of 2-(3-(4-phenyl- piperidin – 1 – yl)cyclopent – 1-enecarbonyl)amino benzamide \((XXXVII)\) in dioxane with aq. NaOH (Scheme-1.12).

\[
\text{Dioxane} \rightarrow \text{Aq.NaOH}
\]

\[
(XXXVII) \rightarrow (XXXVIII)
\]

1.3.8. 2- (3 – (3,6 – dihydro - 2H – pyridine – 1- yl)propyl) – 4 \((3H)\) quinazolinones.

Junya et.al. reported [15] a different class of 4(3H) -quinazolinone analogues, 2 – (3-(4-4( - substituted phenyl) – 3,6 – dihydro- 2H – pyridine - 1- yl)propyl) -4(3H)quinazolinones \((LIII)\), as potent PARP-1 inhibitors, which represent attractive therapeutic candidates for neurodegenerative disorders such as cerebral ischemia or parkinsons disease. The amide compounds \((XXXXIX)\)
on the resins were subsequently treated with 4 – bromobuteryl chloride, followed by N – alkylation with several substituted amines to give the cycloamine derivatives (LII). Treating the resin with 1 N NaOH gave the desired quinazolinone derivatives (LIII) in 40-80% yield (Scheme-1.13).

1.3.9. 2 – (N – Morpholinomethyl) -4(3H) – quinazolinones.

Murugan et.al. reported [16] the synthesis of 2 – (N-Morpholinomethyl) – 3- (acetophenon – 4 - yl) - 4(3H)quinazolinones (LV). Reactions of 3-(5-acetyl-4-oxo-cyclohexa-1,5-dienyl)-2-chloromethyl-3H-quinazolin-4-one (LIV) with morpholine in the presence of potassium carbonate in dry methanol gave LV (Scheme-1.14).
1.3.10. $2 - (1 - \text{imidazol} - 1 - \text{yl} \text{ alkyl) } - 4 \ (3\text{H}) - \text{quinazolionones.}$

Bainian et.al. reported [17] $2 - (1 - \text{imidazol} - 1 - \text{yl} \text{ alkyl}) - 4(3\text{H})\text{quinazolinone (LIX)}$ analogs as useful for treating cellular proliferative diseases and disorders by modulating the activity of KSP (kinesin – like spindle protein). They were prepared in three steps starting from $2 - (1 - \text{amino} - 2 - \text{methylpropyl}) - 3 - \text{benzyl-} \ Z - \text{chloro} - 4(3\text{H})\text{quinazolinone (LVI).}$ Reaction of LVI with 2-bromo-1,1-dimethoxy-ethane gave (LVII), and benzoylation of the resultant secondary amine with benzoyl chloride yielded $N - (1 - (3 - \text{benzyl} - 7 - \text{chloro} - 3,4 - \text{dihydro} - 4 - \text{oxoquinazolin} - 2 \text{ yl}) - 2 - \text{methylpropyl}) - N - (2,2 - \text{dimethoxyethyl})\text{benzamide (LVIII).}$ The latter on deprotection followed by cyclocondensation with $\text{NH}_4\text{OAc}$ in refluxing acetic acid gave LIV (Scheme-1.15).
1.3.11. 2 – (3 – Pyrrolidin – 1 – yl benzyl) amino) – 4 (3H) quinazolinones.

Connolly et.al. reported [18] the preparation of 6,7-dimethoxy–2-(methyl-(3 – pyrrolidin –1– yl- benzyl)amino)–4(3H)quinazolinone (LXII) and 6,7 dimethoxy – 2 – (methyl – (2–methyl 1,2,3 – dihydro–1 H – isoindol–5–ylmethyl)amino)–4(3H)quinazolinone (LXIV), via amination of 2 – chloro – 6,7 – dimethoxy – 1 H – quinzalone – 4 – one with methyl – (2– methyl 1,2,3– dihydro – 1 H – isoindol 5–ylmethyl)amine (LXIII) and N – methyl – (3 – (pyrrolidin yl) benzyl)amine (LXI) with a yield of 60% ...(Scheme-1.16).
1.3.12. 2 – (4,5 – Dihydro(1,3, 4) thiazol – 2 yl- 4(3H) quinazolinone.

1.3.13. 2-((Piperazine – 1–sulfonyl) – phenyl) – 4(3H)quinazolinones.

Gursoy et al. reported [20] 2-((2-ethoxy – 5 – (piperazine – 1– sulfonyl)phenyl) – 8 – methoxy – 4(3H)quinazolinone (LXIX) inhibit growth of neoplastic cells and are useful for the treatment of patients having precancerous lesions [23]. It was prepared by the reaction of 2-((2-ethoxyphenyl) -8 – methoxy – 4(3H) – quinazolinone (LXVIII) with chlorosulfonic acid and subsequently reaction with piperazine. ...(Scheme-1.18).

[Chemical structures and reaction schemes are shown in the image.]

...(Scheme – 1.17)

...(Scheme – 1.18)
1.3.14. **Bis 2,2′ – (2,3-butanediyl) bis – 4 (3H) – quinazolinone.**

Smith et.al. reported [21] bis – 2,2′ – (2,3-butanediyl) bis – 4(3H) – quinazolinone (LXXXIX) in 71% crude yield by the reaction of diliothio reagent of 2 – ethyl – 4 (3H) – quinazolinone with iodine

...(Scheme-1.19).

\[
\begin{align*}
\text{(LXXVIII)} & \xrightarrow{i) 2.2 \text{ LDA,THF,-78} \text{ } ^{0}\text{C} \text{ ii) 2.2 } \text{I}_2, \text{iii) aq.}\text{NH}_4\text{Cl} \text{ (LXXXIX)}
\end{align*}
\]
Present work: It is obvious from the literature that quinazolinones posses a wide range of biological activities such as anti-bacterial, anti-microbial, anti-fungal, anti-cancer and anti-malarial types.

Keeping in view the importance of quinazolinones ring systems, the present thesis describes the synthesis and characterization of several quinazolinones based intermediates which may later on find application as potentially biologically active molecules or intermediates for the synthesis of more complicated derivatives. This thesis consists of five chapters:

CHAPTER – 1: This Chapter deals with the introduction to malaria and quinazolinones - their importance, nomenclature, physical, chemical properties and synthesis.

CHAPTER – 2: This chapter describes the synthesis and characterization of new compounds like N-substituted-2-styrylquinazolinones. The synthesis has been studied under two sets of conditions, namely, (i) Conventional conditions and (ii) Green conditions.

Chapter – 3: This Chapter is divided into three sections: namely, Section-A, Section-B and Section-C respectively.

Section-A: This Section describes the reaction of 2-mercapto-3H-quinazolin-4-one with chloroacetic acid and subsequent chemical reactions of the intermediary products.

Section-B: This Section describes the condensation of 2-mercapto-3H-quinazolin-4-one with phenacyl bromide and subsequent chemical reactions of the intermediary products.
**Section-C:** This Section describes the condensation of 2-mercapto-3H-quinazolin-4-one with 2-chloromethylpyridine hydrochloride and subsequent chemical reactions of the intermediary products.

**Chapter – 4:** This Chapter is divided into two sections: namely, Section-A and Section-B.

**Section-A:** This Section discusses the reactions of 2-mercapto-3H-quinazolin-4-one with 2-chloroacetic acid 2-bromopropionic acids and subsequent chemical reactions of the intermediary products leading to the formation of quinazolinobenzimidazole synthesis.

**Section-B:** This Section explains the condensation of 2-mercapto-3H-quinazolin-4-one with hydrazine hydrate and subsequent chemical reactions of the intermediary products leading to the formation of pyrazole derivatives.

**Chapter – 5:** This Chapter outlines the reactions of (4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylsulfanyl)-acetic acid hydrazide and condensation of the latter with carbonyl derivatives leading to the a variety of products which may be new chemical entities having useful biological properties.