CHAPTER - 2

STUDIES ON QUINAZOLINONE DERIVATIVES
2.1 - INTRODUCTION
INTRODUCTION:-

Heterocyclic Compound containing two nitrogen atoms represent an important group of organic compounds because many of them exhibit significant biological activity. Quinazolines have drawn much attention because of their wide applications as antimicrobial and Pharmaceutical activities. Quinazoline derivatives are used for the production of some commercial dyes and pigment, both natural and man made fiber, is known.

Quinazoline have attracted an interest in medicinal chemistry as Dihydrofolate reductase (DHFR) inhibitor, Trimetrexate. (1)

Antihypertensive agents such as prazosin, tetrazosin, doxazosin, alfuzosin and bunazosin. Anilinoguainazolines in particular are potent inhibitors of Growth Factor Receptor (GFR) tyrosine kinase and have found clinical applications in epidermal and Vascular Endothelia GFR targets. Iressa and Erlotinib are some examples. Quinazolinones are classes of fused heterocyclic that are of considerable interest because of the diverse range of their biological properties viz. anticancer, anti-inflammatory, anticonvulsant, anti-hypertensive and anti-microbial activities.

Quinazolinones is a building block for approximately 120 naturally occurring alkaloids isolated till date foam a number of familes of the plant Kingdom, from animals and microorganism. Methaqualone (2) was synthesized in 1951 and knows as sedative-hypnotic effects. Anti hypertensive, Metalazone.(3)
One of the most important cytotoxic natural products based on the quinazolinone moiety is the human DNA topoisomerase-I poison in Lutonin and its derivatives.\(^{19}\)

Quinazolina is a bicyclic compound consisting of a pyrimidine system fused at 5,6-position with benzene ring. Quinazoline is known as 1,3- diazonaaphthalene represented by structure (4). It has also been given names like phenmiazine, benzo-1,3-diazino or 5,6-benzo pyridine.\(^{20-21}\)

Quinazoline was first prepared by Gabriel in 1903\(^{22}\). Quinazoline is a solid, m.p. 48°C and can be recrystallised from ether. It is soluble in water and most organic solvents. It is basic in nature (pka-1.4).\(^{23}\)

Among many derivatives of quinazoline system known so far, an attempt is to synthesize some keto-quinazolines also known as Quinazolinones, are the most important
compounds. Depending upon the position of Keto or exo group, these compounds may be classified into two types, there are two structural isomers of Quinazolinone, 2-quinazolinone (5) and 4-quinazolinone (6).

The structure (6) is also known as 4 (3H)-quinazolinone which are most prevalent either as intermediate or as natural products in many proposed biosynthetic pathways. This is partly due to the structure being derived from the anthranilates (anthralinic acid, anthranilamide and anthranilonitrile). The 4(3H)-Quinazolinones are an important class of fused heterocyclic with a wide range of biological activities such as anti-cancer, anti-inflammatory, anti-malarial, anti-convulsant, and anti-hypertensive etc.

The nucleus of 4-(3H) – quinazolinone ring (6) is planer. The C_2-C_4 in 4-Quinazolinone are equal to 1.47 Å. The benzene ring C-C bond distances in two molecules are between 1.38 Å to 1.47 Å which are close to the standard value 1.40Å from benzene ring. There are C-C single bonds between two Sp^2-hybridised carbon atoms. (Standard value 1.47 Å). The C=N bond length in molecule are found to be 1.24 Å and C-N single bond length vary between 1.35 to 1.42 Å. The C_{(9)}-N_{(1)} bond in 4-quinazolinone shows some double bond character. The C=O length are 1.27 Å. (stand. value 1.22). The optimize benzene ring C-H bond length are 1.08 Å. In 4-Quinazolinone all C-C-C angles of benzene ring lie between 119.02° to 120.82°. The C-N-C bond angle at N_{(1)} 121° at N_{(5)} is 118.40°.

**Preparation of 4-(3H)-Quinazolinone**: -
Quinoxalinones are synthesized by a number of methods. Oxidation of quinazoline itself with two equivalents of hydrogen peroxide at room temperature in 2N acid gives a high yield of 4(3H)-quinazolinone.\(^{31}\)

\[
\begin{align*}
\text{COOH} & \quad \text{RCONH}_2 \\
\text{NH}_2 & \quad \text{NH} \\
\text{OH} & \quad \text{R} \\
\text{NH}_2 & \quad \text{AcONH}_2
\end{align*}
\]

4-(3H)-quinazolinones (8) are most conveniently obtained by the Niementowski reaction,\(^{32}\) anthranilic acid (7) is fused with an aliphatic amide.

Rad. Moghadam and Mohseni synthesized 2-substituted quinazolin-4 (3H)-ones under microwave conditions. This protocol involves the condensation of anthranilic acid, ammonium acetate and the orthoesters, which gives access to the 2-substituted-4(3H)-quinazolinone\(^{33}\).

\[
\begin{align*}
\text{COOH} & \quad + \text{RCONH}_2 & \quad \text{R} & \quad \text{O} \\
\text{NH}_2 & \quad \text{OET} & \quad \text{OET} & \quad \text{OET} + \text{AcONH}_2 & \quad 210 \text{ W, 5 min}
\end{align*}
\]
2-aminoquazolin 4(3H)-ones (13) are synthesized by the reaction of diphenylcyano carbonimidate (9) with methyl anthranilate (10) treated with sodium hydride in dioxane afforded the o-phenyl-isourea (11) in 50% yield after 16 h at room temperature. Addition of (12) to a saturated solution of the appropriate amine afforded the 3- substituted -4-oxo-3,4 dihydro-1H-ylidenc-cyanamide.\textsuperscript{34}

\[
\begin{align*}
\text{(9)} & \quad \text{CNC} \quad \text{O} \\
\text{PhO} & \quad \text{OPh} \\
\end{align*}
\]

\[
\begin{align*}
\text{(10)} & \quad \text{NaH} \quad \text{Dioxane} \\
\text{NH} & \quad \text{CH}_2\text{O}_2\text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{(11)} & \quad \text{NH}_2 \text{or Bn NH}_2 \quad \text{i - ProH} \\
\text{PhO} & \quad \text{CNC} \\
\end{align*}
\]

Abdel-Jalil et.al. reported that the condensation of aryl, alkyl and heteroaryl aldehydes in refluxing ethanol in the presence of CuCl\textsubscript{2} genarates a Schiff base intermediate (15) which is, in turn converted into the 2-substituted-quinazolinones.\textsuperscript{35}

\[
\begin{align*}
\text{(12)} & \quad \text{HCl, NaOH} \quad \text{DMSO} \\
\end{align*}
\]

\[
\begin{align*}
\text{(13)} & \quad \text{(14)} \quad \text{RCHO, EtOH} \quad 70^\circ\text{C}, 3h \\
\text{(15)} & \quad \text{NH}_2 \text{or Bn NH}_2 \quad \text{CuCl}_2, \text{EtOH} \quad 70^\circ\text{C}, 3h \\
\text{(16)} & \quad \text{R} \\
\end{align*}
\]
3-Amino-2-phenyl quinazolin-4(3H)-one (18) has been synthesized by the treatment of hydrazine hydrate with 2-phenyl-4H-3, 1-benzoazine-4-one (17) using NaY Zeolite as solid support under microwave irradiation. The compound on reaction with various aldoses afforded corresponding imino-sugars.\(^{36}\) (19)

![Diagram](image1)

(17)

(18)

(19)

An efficient and facile method for the synthesis of 2-substituted 2,3-dihydro-quinazolin-4(1H)-ones (20) forms anthranilamide with aledhydes or ketones in the presence of cerium (iv) ammonium nitrate in water by grinding technique.\(^{37}\)

![Diagram](image2)

(20)
The ethoxy (4H)-3, 1-benzoxazine -4-one (21) reacts with ammonium acetate gave the quinazolin-4-one (22) and with hydrazine hydrate in boiling ethanol to give 3-aminoquinazolinone.\(^{38}\) (23)

\[
\begin{align*}
\text{(21)} & \xrightarrow{\text{NH}_2\text{OAC}} \text{Oil bath, 190' 2h} & \text{(22)} \\
\end{align*}
\]

4-phenyl-quinazolinones (26) were synthesized by a palladium catalyzed reaction of o-amine (24) benzamide with benzyl alcohol (25). This protocol involves N-benzylation benzylic C-H-amidation and dehydrogenation in water. Which may play an important role in the smooth generation of the (\(\eta^3\)-benzyl) palladium species by the activation of the hydroxyl group of benzyl alcohol.\(^{39}\)

\[
\begin{align*}
\text{(24)} & + \text{TPPMS (10 mol\%)} \xrightarrow{\text{Pd (OAc)}_2 (5 \text{ mole\%})} \text{(25)} \\
\text{H}_2\text{O, 120}^\circ\text{C, 16 h} & \text{Sealed tube} \\
\end{align*}
\]
One pot synthesis of 4-(3H)-quinazolinone N-nucleoside (27) analogues under microwave irradiation by using montmorillonite K10 as catalyst and solid support in solvent free conditions has been reported.\textsuperscript{40}
2-phenylamino-6, 8-dibromo4H-3, 1-benzoxazinone has been reacted with hydrazine hydrate/amines/amides and yielded 4(3H)-quinazolinone.⁴¹ (28)

Kumar et al. Synthesized 2, 3-disubstituted-quinazolinone (31) from (4H)-3, 1-benzoxazinones (29) and compound (30)
Jiang et al. involve the treatment of 5-chloroanthranilic acid (32) with acetic anhydride to afford the benzoxazinone (33) stirring with ammonium acetate at an evaluated temperature afforded, 6-chloro-2-methylquinazolin-4(3H)one.\(^\text{43}\) (34)

\[ \begin{align*}
\text{(32)} & \quad \text{Cl} \quad \text{O} \quad \text{OH} \quad \text{Ac}_2\text{O} \quad \text{reflux} \\
\text{(33)} & \quad \text{Cl} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{NH} \quad \text{OAc} \quad 150^\circ\text{C}, 0.5\text{H} \\
\text{(34)} & \quad \text{Cl} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{NH} \quad \text{OAc} \quad 150^\circ\text{C}, 0.5\text{H}
\end{align*} \]

**Physical Properties:**

Quinazolinone is a white crystalline solid with high melting points 215-216\(^\circ\text{C}\).\(^\text{44}\) For 2-methylquinazolinone, m.p. is 238-240\(^\circ\text{C}\).\(^\text{45}\) Quinazolinones are insoluble in aqueous alkali. They are generally soluble in dilute acids but sometimes soluble in concentrated acids. Simple 4 (3H)-quinazolinones although insoluble in dilute acids, are soluble in 6N HCL acid and forms stable mono hydrochloride, chloro palatinate etc.\(^\text{46}\)

The quinazolinone ring system is exceedingly stable in Oxidation, reduction, hydrogenation reactions and other treatment designed to break the ring. There is no report of degradation of quinazolinone by simple chemical oxidation. The IR Spectra of 4(3H)-
quinazolinone shows N-H band at 3482 cm\(^{-1}\), The four C-H bands at 3099-3066 cm\(^{-1}\), C-C-stretching band at 1583 cm\(^{-1}\) to 1000 cm\(^{-1}\), The C=O bands appears at 1706 cm\(^{-1}\), The C-N band in 4-quinazolinone at 1423, 852. 4-(3H)-quinazolinone shows a \(^{1}\)H-NMR signal in CDCl\(_3\) at \(\delta_H\) 7.5 to 8.5.

**CHEMICAL REACTIONS :-**

Quinazolinone have strong lactam-lactam tautomeric interaction.\(^{47}\) The tautomeric state of 2-methyl 4 (3H)-quinazolinone are given in Fig.1

The significance of this tautomeric interaction can also be seen when a 4-(3H)-quinazolinone containing a methyl in the 3-position is subjected to chlorination with POCl\(_3\), the methyl group is lost and chlorination proceeds.\(^{48}\) and when methyl group is present at 2-position the tautomeric effect is extended generating a exomethylene carbon,
this compound can be condensed with aldehyde producing 2-styryl-4(3H)-quinazolinones. The significance of these extended tautomeric effects is that they enhance reactivity of the substituted -4(3H)-quinazolinone.\textsuperscript{49}

**Aromatisation**- When a simple and 2-substituted -4 (3H)-quinazolinone (35) is heated with an equivalent amount of PCl\textsubscript{5} in presence of POCl\textsubscript{3}, the corresponding 4-chloroquinazoline (36) is obtained.

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{CH}_3
\end{array}
\quad \xrightarrow{\text{PCI}_5, \Delta, \text{POCl}_3} \quad \begin{array}{c}
\text{Cl} \\
\text{N}
\end{array}
\]

(35) \quad (36)

**Alkylation**- The position of alkylation of quinazolinone is mimilar to all the aromatic nitrogen heterocyclic system in which a hydroxyl group is found on ortho or para to the nitrogen position. Alkylation of 2-substituted quinazolin-4 (3H)-ones by reaction with sodium hydride in dimethyl formamide followed by alkylation O- and N-alkyl derivatives. The extent of alkylation at the different sites was reasonably explained in terms of steric properties of the 2-substituents.\textsuperscript{50}

**Nitration**: 4-(3H)- quinazolinone (37) on boiling with nitric acid undergoes substitution to give 6-nitro-4(3H)-quinazolinone (38) on further nitration it has been observed that the second nitro group enters at the 8-position to give, 6, 8- dinitro derivative. (39). 2-substituted -4 (3H)-quinazolinones were also found to behave similarly under, such conditions.\textsuperscript{51-54}
**Reduction :-**

2, 3-Dihydro-3-methyl-4 (1H)-quinazolinone -4 (3H)-quinazolinane (40) with Lithium Aluminium Hydride (LiAlH₄) in benzene.⁵⁵

![Chemical Structure of 40 and 41](image)

**Reactivity of 2-Methyl group :-**

The methyl Group in 2-position of 4 (3H)-quinazolinone system was found to be quite reactive since it is linked to an azomethine carbon and condenses with aldehydes to give styryl compounds.⁵⁶-⁵⁷

**Biological Activity and its importance :-**

The 4 (3H)-Quinazolinones are an important class of fused heterocyclic with a wide range of biological activities such as, antimicrobial, anti bacterial, antifungal, anti-inflammatory, anti-convulsant, anti-hypertensive, anti-malarial, anti-HIV, anti-cancer etc. agents. Quinazolinone derivatives are used in a number of dyes. They are also found applications in industry as sensitizers, co-polymer etc. In Agriculture quinazolinone derivatives are used as Herbicides, Insectisides, Bacteriacides etc.

**Antimicrobial Activity :-**

"Antimicrobial Activity may be defined as activity tending to destroy microbes, prevent their development or inhibit their pathogenic action."⁵⁸

Antimicrobial agents is defined as ay compound that selectively destroys or inhibits the growth of micro organism.⁵⁹
The antimicrobial activity of quinazolinones and its derivatives which can deal with the increasing resistance by microbes and also having significant antimicrobial activity for the effective treatment of various types of microbial diseases.\textsuperscript{60}

'Hosakera D. Revanasiddappa et al.' Synthesized a series of Quinazolinone compounds, having antimicrobial activity against the bacteria E.coli and S. aureus and fungi, Aspergillus niger and A. flavus.\textsuperscript{61}

A series of 3-thiazole substituted 2-styryl-4 (3H)-quinazolinone (42) derivatives have been reported as antimicrobial agents.\textsuperscript{62}

\begin{center}
\includegraphics[width=0.5\textwidth]{image1}
\end{center}

The compound 3-(substituted amide)-2-phenyl quinazol-4-one (43) showed antimicrobial activity against the bacteria E. coli and S. aureus and fungi, A. niger.\textsuperscript{63}

\begin{center}
\includegraphics[width=0.5\textwidth]{image2}
\end{center}

A series of 3-substituted quinazolinone (44) were reported as antimicrobial agents against the bacteria, B. subtilis E. coli and fungi. A niger and A. flavus.\textsuperscript{64}
The compound [5-(3-phenyl/methyl methin-2-phenyl -4-oxo (3H)-quinazolin) -2-(4"-chlorophenyl/3, 5"-dinitrophenyl/2"-nitrophenly)]-1,3,4-oxadiazoles (45) were reported as antimicrobial agents.\(^6\)

\[
\text{Ar} = \text{Phenyl, Cl} - \text{C}_6\text{H}_4 \\
\text{Br} - \text{C}_6\text{H}_4, \text{OCH}_3\text{C}_6\text{H}_4
\]

\[
(44)
\]

A series of N-(1-substituted-2-oxindolin-3-ylidene)-4-oxo-2-phenyl quinzalin-4(3H)-carboxamide (46) have showed anti-microbial activity against the bacteria Staphylococcus aureus, Escherichia coli and fungi A. niger and C. albicans.\(^6\)

\[
(45)
\]

\[
(46)
\]
The compound 2, 3-diphenyl-4(3H)-one (47) have anti-microbial activity against the bacteria E. coli and S. aureus and fungi. A. niger and C. albicans.\(^{67}\)

![Image of compound 47](image_url)

2-Aryl/alkyl, 3-amino-quinazolin-4-(3H)-ones (48) have been reported as anti-microbial agents.\(^{68}\)

![Image of compound 48](image_url)

\[ Ar = C_6H_5, p-C_6H_4NO_2 = P – C_6H_4CH_3 etc. \]

The compound 2- methyl-3-(3-methyl-5-oxo-4, 5-dihydro-1H-pyrazol-4-yl)- diazenyl quinazolin -4 (3H)-one (49) have antimicrobial activity against the bacteria E. coli and S. aureus and fungi. A. niger, C. albicans.\(^{69}\)

![Image of compound 49](image_url)
The compound 5-[3-(4-chlorophenyl)-4-oxo-6-iodo-3H-quinazolin-2-yl] thio] pyridozone-3,4,6–trione (50) showed antimicrobial activity against the bacteria E. coli, S. aureus and Fungi C. albicans.\(^7\)

Navin B. Patel et al. Synthesized a series of 2,3–disubstituted quinazolin-4 (3H)-ones are reported as antimicrobial agents.\(^\text{71}\)

A series of 2-methyl-3-(1,3,4-thiadiazolyl]-4-(3H)-quinazolinones (51) have screened antimicrobial activity against the bacteria S. aureus, B. subtilis and fungi A. niger and C. albicans.\(^\text{72}\)

![Compound 51](image)

3-aryl-4(3H)-quinazolinone-2-carboxaldehydes, (52) their corresponding Schiff bases have showed anti-microbial activity.\(^\text{73}\)

![Compound 52](image)

The compound 2-methyl-3-{4[2-,\ldots-tetrazol-5 yl - ethylamino] phenyl} -3H-quinazolin-4-one (53) have antimicrobial activity against the bacteria S. aureus E. coli and Fungi C. albicans and A. niger.\(^\text{74}\)

![Compound 53](image)
The compound 3-amino-2-(pyridin-3-yl)-4-quinazolinones (54) were reported as antimicrobial agents.\textsuperscript{75} The compound showed antimicrobial activity against the bacteria B. subtilis, Salmonella typhi and Fungi Aspergillus. Sp...

![Structure of 3-amino-2-(pyridin-3-yl)-4-quinazolinones (54)](image)

The compound 2-[2-(2,6-dichlorophenyl)amino]-phenylmethyl-3-[4-[2-(substituted phenyl)-4-oxo-thiazolidin-3-yl] phenyl sulfonamide-1-yl]-6-bromo quinazolin-4(3H)-one showed antimicrobial activity against S. aureus, E.coli and Fungi A. niger and A. clavatus.\textsuperscript{76}

A series of some new quinazolinone derivatives(55) were reported antimicrobial agents, showing anti bacterial, antifungal and cytotoxic activity.\textsuperscript{77}

![Structure of 2-[2-(2,6-dichlorophenyl)amino]-phenylmethyl-3-[4-[2-(substituted phenyl)-4-oxo-thiazolidin-3-yl] phenyl sulfonamide-1-yl]-6-bromo quinazolin-4(3H)-one](image)

A series of amino acid/peptide deriv\(\text{atives}\) of 2-hydroxy-5-(6-iodo-2-methyl-4-oxo-3,4-dihydro-3-quinazolinyl) benzoic acids (56) were reported as anti microbial agents,
showed anti bacterial and anti-fungal activity against B. subtilis, S. aureus and C. albicans, A. niger.\(^7\)

\[
\begin{align*}
\text{X} & \equiv \text{O-Me} \\
\text{O} & \equiv \text{NH} \\
\text{N} & \equiv \text{OH} \\
\text{I} & \equiv \text{CH}_3
\end{align*}
\]

A series of 6-iodo-2-phenyl quinazolinone-4(3H)-ones. (57) derivatives were screened for antimicrobial activity against C. albicans, P. aeruginosa.\(^7\)

\[
\begin{align*}
\text{I} & \equiv \text{OH} \\
\text{N} & \equiv \text{NH}
\end{align*}
\]

Charan singh H. Gill et at. synthesized a series of new quinazoliones (58) having antimicrobial activity against the bacteria B. subtilis, S. aureus and Fungi A. niger and C. albicans.\(^8\)

\[
\begin{align*}
\text{R}_1 & = \text{H, Cl} \\
\text{R}_2 & = \text{H} \\
\text{R}_3 & = \text{H CH}_3 \\
\text{R} & = \text{H, Cl}
\end{align*}
\]
The compound 6,8-disubstituted - 2 - (phenyl/methyl) - 3 - [4- (3-methyl – 5-pyrazolinon-1-yl)-carbonyl] phenyl/methyl/benzyl]-4(3H)quinazolinone (59) were reported as antimicrobial agents.\(^8\)

![Chemical Structure 59](image59.png)

A series of Quinazolin-4(3H)-ones (60) showed anti-microbial activity against the bacteria, B. subtilis, S. typhi and fungi A. fumigates, A. Alternata.\(^8\)

![Chemical Structure 60](image60.png)

The 6-(4-substituted-benzylidene-2-methyle/phenyl-5-imidazo-linone-1-yl]-2-methyle-4(3H)-quinazolinone have been reported as antimicrobial agents.\(^8\)

D. channe Gowda et.al. synthesized a series of urea/thiourea/acetamide/-sulphonomide derivatives of Quinazolinones conjugated lysine have been reported as anti-microbial agents.\(^8\)

The compounds triazolo-[4,3-a]-quinazolin-7-one, [1,2,4,5)-tetrazin[4,3-a]-quinazolin-8-ones, have antimicrobial activity against E. coli, S. pneumoniae, B. subtilis and fungi C. albicans, A. flavus.\(^8\)
**Anti-Bacterial Agents :-**

A series of Quinazolinone conjugate peptides were reported as anti-bacterial activity against the bacteria E.coli. B. subtilis. 4(4-oxo-3,4-dihydro quinazolin 2 yl)\(^8^6\)

The compound 2-(4-nitrophenyl)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acet amide (61) have antibacterial activity against S. aureus and E. coli.\(^8^7\)

![Image of compound 61](image_url)

The compound 2-methyl-3-(2-methylphenyl) quinazolin-4(3H)-ones (62) have showed anti bacterial activity against. S. aureus and E. coli.\(^8^8\)

![Image of compound 62](image_url)

A series of 3-(5-phenyl-1,3,4 -oxadiazole-2-yl) – 2 - (substituted styryl) -quinazoline- 4(3H)-ones (63) showed anti bacterial activity against the bacteria B. subtilis, E. coli, S. aureus and P. vulgaris.\(^8^9\)

![Image of compound 63](image_url)
The compound 1-amino-5-[6-bromo-3,4-dihydro 2-phenyl-4-oxo quinazolin-3yl) methyl-1,3,4-triazin-2-thiol (64) showed antibacterial activity.\textsuperscript{90}

![Chemical structure](image1)

(64)

3-[Arylideneamino]-2-methyl[1, 2, 4] triazolo [5, 1b] quinazolin-9(3H)-ones (65) were reported as Antibacterial agents.\textsuperscript{91}

![Chemical structure](image2)

(65)

2-phenyl-6-iodo-4(3H)-quinazolinones (66) have been reported as anti bacterial agents.\textsuperscript{92}

![Chemical structure](image3)

(66)

The N-1,2,4-triazolylquinazolinones (66) showed antibacterial activity.\textsuperscript{93}
**Antifungal Agents:**

The 2- [4{3-chloro phenyl) piperazine – 1 -yl] methyl] - 3-[8-hydroxy quinolin -5-yl]-3(H)-quinazolin-4-ones (68) ligands were reported as antifungal agents.\(^9^4\)

3-(2\(^1\)-substitutedarylidineimino-1,3-thiazol-4-yl)amino-2-methyl-mono-substituted quinazolin-4(3H)-ones (69) have been reported as Antifungal agents.\(^9^5\)

The fluorinated 2, 3-disubstituted quinazolin-4(3H)-ones have been reported as antifungal agents.\(^9^6\)

3-Alkylquinazolin-4-one derivatives (70) have been reported as antifungal agents.\(^9^7\)
The quinazolone derivatives of nalidixic acid have been reported as anti-fungal agents.\textsuperscript{98}

**Anti-inflammatory and Analgesic Agents**

A series of novel 2-phenyl-3,6,7-trisubstituted quinazolin-4 (3H)-ones (71) showed anti-inflammatory activity.\textsuperscript{99}

\[ \text{R} = \text{Et, n-Pr, Allyl} \]

3-\{4[6-aryl-2-oxo-1,2,5,6-tetrahydropyrimidin-4-yl]-phenyl\}-6,8-dibromo-2-phenyl-3H-quinazolin-4 ones (72) have showed anti-inflammatory and analgesic activity.\textsuperscript{100}

\[ \text{X} = \text{H, F, Cl, Br} \]

\[ \text{R} = \text{Et, n-Pr, Allyl} \]

6-bromo-2-methyl-3-(substituted phenyl)-(3H)-quinazolin-4-ones (73) showed anti-inflammatory activity.\textsuperscript{101}
A series of 2-[(E)-2-substitutedphenyl) ethenyl] -3- (2/4methylphenyl) quinazolin-4(3H)-ones were reported as anti-inflammatory agents.\textsuperscript{102}

The compounds substituted 4-(4-oxo-2-phenyl quinazolin-3(4H)-yl) N-aryl-methylene benzene sulfonamide derivatives (74) have been reported as Antiinflammatory and Analgesic agents.\textsuperscript{103}

\[
\text{NPhSO}_2\text{NR}_2\text{O}R_1\quad \text{(75)}
\]

2-substituted methyl-3-substituted phenylquazolinone derivatives (75) showed anti-inflammatory activity on tested animals.\textsuperscript{104}
3-{(1-alkyl/arylaminomethyl-2-oxo-1,2-dihydroindole-3-ylidene) amino} -2-methyl-6-quinazolin-4 (3H)-ones (76) showed analgesic and anti-inflammatory activity.\textsuperscript{105}

A series of 2,3-disubstituted Quinazolinone (77) derivatives have anti-inflammatory and analgesic activity.\textsuperscript{106}

A series of 6- Bromo Quinazolinone (78) derivatives have been reported as anti inflammatory and analgesic agents.\textsuperscript{107}

A series of novel 2-phenyl -3-substituted quinazolin-(3H)-ones (79) showed good analgesic activity.\textsuperscript{108}
3-(4-chlorophenyl)- 6 – iodo – 4 – oxo - 3,4 - dihydro quinazolinones having, oxazolone, imidazolidine etc. were reported as potential anti-inflammatory and analgesic activity.\textsuperscript{109}

N-cyclopropyl-4-methyl-3-[6-(4-methyl piperazin-1-yl)-4-oxoquinazolin-3(4H)-benzaimdes (AZD6703) were reported as a clinical $\text{P}^3\text{MAPKinase}$ inhibitor for the treatment of inflammatory diseases.\textsuperscript{110}

**Anti-Convulsant agents :-**

The anticonvulsant activity of quinazolinone derivatives was attributed to its ability to bind the non-competitive site of $\alpha$-amino-hydroxy-methyl-4-isoxazolepro Pionic acid (AMPA) receptors.\textsuperscript{111}

A series of 2,3,8-trisubstituted-4 (3H)-quinazolinone (80) derivatives have anticonvulsant activity.\textsuperscript{112}

\begin{center}
\includegraphics[width=0.5\textwidth]{image1.png}
\end{center}

A series of 6-bromo/3-(substituted-benzylamino)-2-phenyl-quinazolin-4(3H) ones (81) were reported as anti-convulsant agents.\textsuperscript{113}

\begin{center}
\includegraphics[width=0.5\textwidth]{image2.png}
\end{center}
The compound 3-N1-(4-Dimethyl amino benzyldene semicarbazone)-2-phenyl -3H-quinazolin-4-one (82) showed anticonvulsant activity.\(^{114}\)

![Chemical Structure of Compound 82](image)

A series of quinazolinone derivatives, methaqualone analoges (83) were reported as anticonvulsant agents.\(^{115}\)

![Chemical Structure of Compound 83](image)

**Anti-Viral Agents :-**

The compound 2- phenyl -3 -(4-trifluro-methyl benzalamino)-4 (3H)-quinazolinone (84) have been reported as anti-viral agents.\(^{116}\)

![Chemical Structure of Compound 84](image)
2-Phenyl-3-disubstituted quinazolin-4(3H)-ones (85) have antiviral activity against Herpes simplex virus type.\textsuperscript{117}

\[
\begin{align*}
\text{\textbf{(85)}}
\end{align*}
\]

2-Aryl or 2-methyl-3-(substituted-Benzalamino)-4(3H)-quinazolinone derivatives (86) were reported as anti-viral agents.\textsuperscript{118}

\[
\begin{align*}
\text{\textbf{(86)}}
\end{align*}
\]

The compound 4-(6,8-dibromo-4-oxo-2-phenyl quinazolin-3(4H-1-yl)-N-(4, 5-dimethyloxazol-2-yl) benzene-sulphonamide (87) inhibited the replication of avian influenza (H5N1) virus have been reported.\textsuperscript{119}
**Anti-Oxidant Agents :-**

The compound 6, 8- dibromo-2-phenyl-3-[4-phenyl-thiazol-2-yl]-quinazolin-4 (3H)-ones (88) exhibited anti-oxidant activity.\(^1\)\(^{20}\)

![Chemical Structure](image)

\(R_1 = \text{phenyl thiazolyl.}\)

The compound 2-\{[2-(4-chlorophenyl)-4-oxo-quinazolin-3-(4H)-yl] amino\}-N-(substituted phenyl)-acetamides have shown significant anti-oxidant activity.\(^1\)\(^{21}\)

A series of 6-iodo-2-propyl-4(3H)-quinazolinone and its fused heterocycles were reported as anti-oxidant agents.\(^1\)\(^{22}\) The compound 6, 8-dihalo subs-3-(2-(7-substituted oxy-4-methyl-2-oxoquinazolin-1(3H)-yl- ethyl)-2 substituted-4(3H)-ones have shown anti oxidant activity.\(^1\)\(^{23}\) A series of 2, 3- disubstituted quinazolin-4(3H)ones have been reported as anti-oxidant Agents.\(^1\)\(^{24}\)

**Anti Tubercular and Anti Tumor Agents :-**

A1. Deeb et al. Synthesized some 2-alkylthio-6-iodo-3-substituted-quinazolin-4-one derivatives (89) have anti tubercular activity.\(^1\)\(^{25}\)

![Chemical Structure](image)

\(R_1 = \text{allyl}\)

\(R_2 = \text{Br}.\)
2-substituted 4-methyl-4-ethyl-4, 5-dihydro-benzo [h][1,2,4] triazolo [1, r-c] quinazolines were reported as anti tumor agents.\textsuperscript{126}

A series of 4 (3H)-quinazolinones have been reported as anti tumor agents on Hela cell line.\textsuperscript{127}

The compound 4(3H)-quinazolinone derivatives (90) with dithiocarbamate side chain have been reported as anti tumor agent.\textsuperscript{128}

\[
\text{\textsuperscript{(90)}}
\]

7-amino quinazoline derivatives have been reported as anti tumor agents.\textsuperscript{129} Oral anti tumaral effect of 3,4 –dihydro quinazoline derivatives on solid tumor have been reported.\textsuperscript{130}

**Anti- malarial Agents :-**

A series of 4-Quinazolinone (91) compound were reported as anti malarial agents.\textsuperscript{131}

Febrifugine (93) was isolated as anti-mali (91) ents. In the Chinese herb Chang Sha.\textsuperscript{132}
Bhargave et al. have synthesized a series of 6-bromo-2-(N, N-disubstituted carbamoyl methylthio)-3-aryl (or alkyl) 4 (3H)-quinazolinone. (93) Some derivative showed antimalarial activity.\textsuperscript{133}

![Chemical structure of 6-bromo-2-(N, N-disubstituted carbamoyl methylthio)-3-aryl (or alkyl) 4 (3H)-quinazolinone](image)

Certain 4(3H)-quinazolinones have been reported as antimalarial activity.\textsuperscript{134}

4-Thiophenoxy-2-trichloro methyl. Quinazolines display in vitro selective antiplasmodial activity against the human malarial Parasite Plasmodium falciparum.\textsuperscript{135}

**Anticancer Agents:**

N-(3-chloro-4-fluorophenyl)-2-(chloromethyl)-7-fluoro-3,4-dihydro quinazolin-4-amino hydrochloride (94) have anticancer activity.\textsuperscript{136}

![Chemical structure of N-(3-chloro-4-fluorophenyl)-2-(chloromethyl)-7-fluoro-3,4-dihydro quinazolin-4-amino hydrochloride](image)
A series of 3- (arylidene amino)-2-phenyl quinazoline-4(3H) one derivatives have been reported as anticancer agent. A series of 2,3-disubstituted 4 (3H)-quinazolinone derivatives are reported as anticancer agents. The compound 2-[[bis-(chlorophyl) amino] methyl]-6, 8 dinitro-1-(4-substituted ethyl)-1H-quinazolin-4-one derivatives have anti cancer activity. 2, 4- Diamine-quinazolines were reported as inhibitors of β–catenine/Tcf-4 for the treatment of colorectal cancer.

**Sedative-Hypnotic :-**

Methaqualone (2-methyl-3-o-tolyl-4(3H) quinazolinone) have hypnotic activity. 1-4 (-substituted-phenyl)-3-(4-oxo-2-propyl-4H-quinazolin-3-yl)-urea (H1-H12) derivative showed potent sedative-hypnotic and CNS depressant activity.

6-Fluoro-2-methyl-3-(p-bromophenyl)-4(3H)-quinazolinone (95) have been reported as hypnotic agents.

![Chemical structure](image)

**Anti hypertensive Agents :-**

The compound 2-butyl-6-methyl-3-[(z)-tetrazol-5-yl) biphenyl-4-y1] methyl]-quinazolin-4(3H)-one having anti hypertensive activity and show cardiovascular activity also.

The thia diazolyl quinazolones have been reported as anti-hypertensive agents.

**In Industry :-**

**Dyes :-**
The compounds 7-bromo-6-chloro-3-[3-(2R,3S)-3-hydroxy-2-piperidyl]-2-oxopropyl]-4(3H)-quinazolinone (96) have been reported as organic marine dyes.  

![Chemical structure of 96](image)

A series of disperse dyes based on 2-methyl-3-[3'-amino phthalimido]-4(3H)-quinazolinone (97) were synthesized and used for dyeing nylon 66 and polyester.

![Chemical structure of 97](image)

2-phenyl-3-{4-[N-(4-aminophenyl) carbamoyl]-phenyl}-quinazolin-4 (3H)-one-6-sulphonic acid (98) based mono azo reactive dye and their dying performance on silk, cotton, wool, fibers have been reported.

![Chemical structure of 98](image)
A series of 4-Oxoquinazoline (99) have been reported as dyes.\textsuperscript{148}

\[
\text{(99)}
\]

2-Bis-styryl-6-aryla-zo-4-oxoquinazoline-found as dyes.\textsuperscript{149} Phenyl Pyrazolones substituted 3-(4-aminophenyl)-2-phenyl quinazolin-4(3H)-one derivatives. have been reported as dye\textsuperscript{150} for dying silk, wool etc.

**Miscellaneous Activities :-**

**Insecticidal Agents :-**

The compound 4-phenyl-2,3-dihydro-6-(β-naphtylamino-ethyl) -10-iodo [1,2,4]-triazino[2,3-c]-quinazolin-5-one (100) have been reported as potent insecticidal agents.\textsuperscript{151}
1-[2-phenyl-4-oxo(3H)-quinazolin-3-(benzo-yl/2-methyl methane carbonyl]-3-methyl-5(4H)-pyrazolones (101) have been reported as insecticidal agents against Callosobruchus chinensis with legume grains as host.¹⁶⁵

![Chemical structure](image)

(101)

A series of 3-[4(3H)-Quinazolinone-2-yl) thiomethyl]-1,2,4-triazole-5-thiols have insecticidal activity against the adult stage of blow fly. (chrysomyia albiceps.)¹⁵²

2-hydrazino-3-(4-substituted phenyl)-quinazolin-4(3H)-one with appropriate aryl isothiocyanate, have been reported as insecticidal agents.¹⁵³
Herbicidal Agents :-

A series of 2-styryl quinazolin-4(3H)-one and 4-chloro-2-styryl quinazoline derivatives (102) have been reported as inhibitor of photosynthetic electron transport (PET) in Spinach chloroplasts. (spinacia oleracea L.).

![Diagram](102)

The compound 3-methyl-4-oxo-3,4- dihydroquinazolin-5-sulfonamide was used to prepare a highly herbicidal sulfonil urea derivatives. (103)

![Diagram](103)

CNS Activity :-

1-(4-substituted-phenyl)-3-(4-oxo-2-propyl)-4H-quinazolin-3-yl)-urea(104) have been reported as anti-CNS agent. (104)
5-cyclohexyl-5-methyl-2-sulfanyl-3,4,5,6-tetrahydro benzo[h] Quinazolin-4-one have been reported as Psychotropic Activity.\textsuperscript{157}

**Antineoplastic and antimoamine oxidase :**

3-allyl-4-oxo-2-thioxo-1,2,3,4,5,6-Hexahydro spiro (Benzo) [h] Quinazoline-5, 1-cyclohexanes have been reported as antineoplastic and Antimonoamine oxidase active.\textsuperscript{158}

2-substituted 4-ethyl-4-methyl-4, 10-dihydro benzo[h]-[1,2,4] triazolo [1,5-c] quinazolin-11 (5H)-ones were reported as antineoplastic and antimonoaime oxidase agents.\textsuperscript{159}

**Antihyperlipidemic :**

The antihyperlipidemic and antihyper cholestcrolemic activities of quinazolinone derivatives are reported.\textsuperscript{160}

A series of 6,8-dibroma-2-methyl-4(3H)quinazolinone (105) have been reported as Antihypercholesterolomic agents.\textsuperscript{161}

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

\textbf{(105)}

**Antiulcer Agent :**

2-[5-substituted-H-benzo(d)imidazol-2-yl sulfinyl] methyl-3-substituted quinazolin-4 (3H)-ones (106) have antiulcer activity against pylorus ligation induced, aspirin induced ulcer in rat model.\textsuperscript{162}

\[
\begin{align*}
&\text{O} & \text{R} & \\
&\text{N} & \text{R} & \text{O} \\
&\text{N} & \text{CH}_2 & \text{S} \\
&\text{NH} & \\
&\text{N} & \\
&\text{CH}_3 & \\
&\text{R}_1 & \\
\end{align*}
\]

\textbf{(106)}

\text{\text{R} = 2 - pyridyl, 3 - pyridyl 2 - pyroline}
**H₁-Antihistaminic Agent** :-

A series of 3-([CN,N-Dialkylamino) alkyl-6-halo-2-thio-4(3H)-Quinazolinone (107) have been reported as H₁-Antihistaminic agents.¹⁶³

5-chloro-2-methyl-3-(5-methyl-thiazol-2-yl)-4 (3H)-quinazolinones have been reported as Anticancer and antiviral agents.¹⁶⁴ A series of radiiodinated quinazolinone derivatives have been reported as useful in alkaline phosphatase-mediated cancer diagnosis and therapy. ¹⁶⁵ 2-Aryl or 2-methyl-3-(substituted-Benzalamino)-4-(3H)-quinazolinone derivatives as Antiviral agents.¹⁶⁶ A series of 4(3H)-quinazolinone were reported as anti-convulsant agents.¹⁶⁷ 6-7-bis (arylthio)-quinazoline-5,8- diones and Furo [2,3-f]-quinazolin-5-ols. have been reported as antifungal agents.¹⁶⁸
2.2 - EXPERIMENTAL
2.2 Experimental :-

All the melting points of the compounds were determined in open capillary tubes and are uncorrected. The I.R. spectra were recorded in KBr on Perkin- Elemer 137-Spectrophotometer. The $^1$H-NMR (CDCl$_3$) Spectra were recorded on a Varian EM 360 Spectrophotometer. The chemical shift values are expressed in $\delta$ppm, downfield from TMS, which was used as internal standard. Elemental analysis for C, H and N were carried out by Coleman-Carbon, hydrogen and Nitrogen analyzers.

2.2.1 Synthesis of Starting Materials:--

2.2.1.1 5-Bromo and 3, 5- dibromoanthranilic acids $^{169}$

20.0 g (0.15 mole) of anthranilic acid was dissolved in 250 ml. of glacial acetic acid and the solution was cooled below 150 °C. To this, 9.5 ml of liquid bromine was added, when the mixture was converted into a thick mass of white glistening crystals consisting of hydro bromides of mono-and dibromoanthranilic acids. The product was filtered and washed with benzene. It was then boiled with 500ml. of boiling water containing 25ml.of concentrated hydrochloric acid and filtered under suction. The insoluble residue was further extracted twice with 500ml. of boiling water and it consisted of 3, 5-dibromoanthranilic acid, nearly one third of the product. The filtrate, on cooling yielded abundant precipitate of the 5-bromoanthranilic acid. It was recrystallised from hot water, yield 14g (65%), m.p. 219-222° C (Lit m.p. 219-220° C).

3, 5-Dibromoanthranilic acid was crystallized from ethanol, yield 9.0g (30%), m.p. 232 °C (Lit.$^{170}$ m.p. 235° C).

2.2.1.2 5 - Iodoanthranilic acid $^{171}$:-

55 gm. (0.4mole) of anthranilic acid was dissolved in 500ml. of water and 40ml. of concentrated hydrochloric acid, and the solution was cooled to 20°C. In a beaker a solution of iodine monochloride in hydrochloric acid was prepared by diluting 70ml. of concentrated hydrochloric acid with 250ml. of cooled water, the water was cooled to 5°C temperature by adding sufficient amount of crushed ice, and during 2 minutes with
stirring 65.5g (0.4mole) of iodine monochloride was added in it. The iodine monochloride solution at 5°C was stirred rapidly into the anthranilic acid solution at 20°C. 5-iodoanthranilic acid was separated out almost immediately as a granular, tan to violet precipitate, the reaction temperature rose to 18-22°C. The mixture was stirred for an hour, while warming to room temperature, filtered, and washed with three 50ml. portions of cold water, pressed as dry as possible and then dried at 90-100°C, m.p. 185-190°C (decomp). yield, 85%.

5-iodoanthranilic acid was purified, by recrystallisation of its ammonium satl as follows. To 50g. of the acid in a 250ml. beaker, 100ml hot water was added in it and the acid was dissolved by stirring in 40ml. of concentrated ammonia at 60°C. Sodium hydro sulphite was added in about 0.5g. Portions until no further bleaching action was observed, about 2.5g of decolorizing charcoal was added, and after stirring, the mixture was filtered. The filtrate was washed with 5ml. of boiling water.

The combined filtrates and washing were transferred to a 250ml. of beaker, allowed to cool slowly without agitation until crystals formation was appeared completed, then cooled to 5°C. The Crystalline ammonium salt was then removed by suction filtration, washed with 10ml. of ice-water, sucked as dry as possible, and spread in a thin layer on a glass tray and allowed to dry in air at 35-50°C, yield 70%. The ammonium salt was dissolved in three parts of hot water; ammonia was added if necessary to effect complete solution at 60°C, the solution was again treated with sodium hydrosulphite and 1.5-2.0g of decolorizing charcoal, filtered hot, and the 5- iodoanthranilic acid was precipitated by adding HCL in 3 to 5ml. portions, stirred thoroughly after each addition, until the reaction mixture was just faintly acid to Congo red. Ice was then added until the temperature was reduced to 20°C and the precipitated acid was filtered, washed freely with cold water, and dried at 100-110°C. 5-Iodoanthranilic acid was almost quantitatively precipitated from its ammonium salt solution and obtained as a yellow powder, m.p. 192-195°C ( decomp), (Litt. M.p. 185-190°C).

2.2.2 Synthesis of 2- Methyl-6, 8-Substituted -4 (3H)-quinazolinones:-

**General procedure :-**

(0.1mole) of substituted anthranilic acids and 4.7g (0.1mole) of acetamid were dissolved in acetic acid in a 250ml. round bottom flask and the reaction mixture was refluxed at 120°-130°C for 2hr. followed by further heating at 170°-180°C for 2hr. The excess of acetamid was distilled off under reduced pressure. The residue was dissolved in ether. The solid obtained was filtered, dried and recrystallised from ethanol; water mixture. The physical and analytical data are recorded in (Table-1)

**2.2.3- Synthesis of 3-(3-chloropropanoyl)-2-methyl-6, 8-substituted-4(3H)-quinazolinones :-**

**General Procedure :-**

3- chloropropanoyl chloride 18.9g (0.15mole), 2-methyl-6, 8-substituted-4(3H)-quinazolinone 16.0g (0.1mole) in dry benzene. (100ml) was placed in a 250ml. round bottom flask and the reaction mixture was refluxed on a steam bath for 4-5hrs. The excess solvent was distilled off under reduce pressure to get solid material. The solid was washed with water and on recrystallisation from ethanol. 3-(3-chloropropanoyl)-2-methyl-6,8-substituted-4 (3H)-quinazolinone crystals are recorded in (Table-2)

**2.2.4 Synthesis of 2-methyl-6, 8-substituted-3-[substituted-amino-propanoyl]-4 (3H)-Quinazolinone :-**

**General Procedure :-**

A mixture of 3-(3-chloropropanoyl)-2-methyl-6,8-substituted-4-(3H)-quinazolinone (0.1mole), Secondary amine (0.15mole), (methyl piperazine and Phenyl piperazine) and triethyl amine 20.2g. (.2mole) was refluxed in dry benzene for 6-8 hrs. Triethyl amine hydrochloride was separated out and filtered. The filtrate was concentrated under reduced pressure to get solid material and filtered. It was recrystallised from ethanol (75%), 2-Methyl-6, 8-substituted-3-[substituted-amino-propanoyl]-4-(3H)-quinazolinone was obtain-ned. yield. (70%).
The similar procedure was adopted in the preparation of the following compounds, viz.

IIIa. 2-Methyl-6,8-dihydro-3[methyl piperazino-propanoyl]-4(3H)-quinazolinone.

IIIb. 2- Methyl-6 hydro, 8-bromo-3 [methyl piperazino-propanoyl]-4 (3H)-quinazolinone.

IIIc. 2-Methyl-6-hydro, 8-iodo-3[methyl piperazino-propanoyl]-4 (3H)-quinazolinone.

IID. 2-Methyl-6-bromo, 8-hydro-3-[methyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

IIId. 2-Methyl-6- 8-dibromoo-3[methyl piperazino-propanoyl]-4(3H)-quinazolinone.

IIIe. 2-Methyl-6- 8-dibromoo-3[methyl piperazino-propanoyl]-4(3H)-quinazolinone.

IIIf. 2- Methyl-6-bromo, 8-iodo-3- [methyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

IIIg. 2-Methyl-6, 8-dihydro-3-[phenyl piperazino-propanoyl]-4 (3H)-quinazolinone.

IIIh. 2-Methyl-6-hydro, 8-bromo-3-[phenyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

IIII. 2-Methyl-6hydro, 8-iodo-3-[phenyl piperazino-propanoyl]-4(3H)-quinazolinone.

IIIj. 2- Methyl-6bromo, 8-hydro-3- [phenyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

IIIk. 2-Methyl-6, 8-dibromo-3-[phenyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

III. 2-Methyl-6-bromo, 8-iodo-3-[phenyl piperazino-propanoyl]-4 (3H)-Quinazolinone.

The physical and analytical data are given in Table-3 and the spectral data are recorded in Table-4.
Table-1

2-Methyl-6,8-substituted-4 (3H)-quinazolinone

![Chemical Structure]

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>R</th>
<th>R₁</th>
<th>Molecular Formula</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Ia</td>
<td>H</td>
<td>H</td>
<td>C₉H₈N₂O</td>
<td>238</td>
<td>75%</td>
<td>67.5 (66.8)</td>
</tr>
<tr>
<td>Ib</td>
<td>H</td>
<td>Br</td>
<td>C₉H₇N₂OBr</td>
<td>242</td>
<td>70%</td>
<td>45.18 (45.2)</td>
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<tr>
<td>Ic</td>
<td>H</td>
<td>I</td>
<td>C₉H₇N₂OI</td>
<td>248</td>
<td>65%</td>
<td>37.76 (36.80)</td>
</tr>
<tr>
<td>Id</td>
<td>Br</td>
<td>H</td>
<td>C₉H₇N₂OBr</td>
<td>240</td>
<td>66%</td>
<td>45.18 (45.10)</td>
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<tr>
<td>Ie</td>
<td>Br</td>
<td>Br</td>
<td>C₉H₆N₂OBr₂</td>
<td>250</td>
<td>60%</td>
<td>34.06 (34.50)</td>
</tr>
<tr>
<td>If</td>
<td>Br</td>
<td>I</td>
<td>C₉H₆N₂OBrI</td>
<td>249</td>
<td>59%</td>
<td>29.67 (30.40)</td>
</tr>
</tbody>
</table>
Table 2

3-(3-chloro propanoyl) -2- Methyl-6, 8-substituted-4 (3H) - Quinazolinone

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Molecular Formula</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis (%)</th>
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</thead>
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<td></td>
<td></td>
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<td>C</td>
</tr>
<tr>
<td>IIa</td>
<td>H</td>
<td>H</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; Cl</td>
<td>230</td>
<td>68%</td>
<td>57.6 (57.2)</td>
</tr>
<tr>
<td>IIb</td>
<td>H</td>
<td>Br</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;BrCl</td>
<td>232</td>
<td>67%</td>
<td>43.90 (44.00)</td>
</tr>
<tr>
<td>IIc</td>
<td>H</td>
<td>I</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;ICl</td>
<td>228</td>
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<td>38.40 (39.10)</td>
</tr>
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<td>IIId</td>
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<td>H</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;BrCl</td>
<td>231</td>
<td>65%</td>
<td>43.90 (44.20)</td>
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<tr>
<td>IIe</td>
<td>Br</td>
<td>Br</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>240</td>
<td>62%</td>
<td>35.46 (35.26)</td>
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<tr>
<td>IIIf</td>
<td>Br</td>
<td>I</td>
<td>C&lt;sub&gt;12&lt;/sub&gt;H&lt;sub&gt;9&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;BrICl</td>
<td>239</td>
<td>60%</td>
<td>31.78 (32.0)</td>
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</table>
Table-3

2-Methyl-6,8-substituted-3-[substituted-amino-propanoyl]-4(3H)-
Quinazolinone-

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R₁</th>
<th>NR₂</th>
<th>Molecular Formula</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
<th>Elemental Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>IIIa</td>
<td>H</td>
<td>H</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₂N₄O₂</td>
<td>231</td>
<td>75%</td>
<td>64.96</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(63.35)</td>
</tr>
<tr>
<td>IIIb</td>
<td>H</td>
<td>Br</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₁N₄O₂Br</td>
<td>285</td>
<td>70%</td>
<td>51.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.10)</td>
</tr>
<tr>
<td>IIIc</td>
<td>H</td>
<td>I</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₁N₄O₂I</td>
<td>245</td>
<td>65%</td>
<td>46.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(46.62)</td>
</tr>
<tr>
<td>IIId</td>
<td>Br</td>
<td>H</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₁N₄O₂Br</td>
<td>288</td>
<td>70%</td>
<td>51.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.15)</td>
</tr>
<tr>
<td>IIIe</td>
<td>Br</td>
<td>Br</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₀N₄O₂Br₂</td>
<td>258</td>
<td>62%</td>
<td>43.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(43.68)</td>
</tr>
<tr>
<td>IIIf</td>
<td>Br</td>
<td>I</td>
<td>Methylpiperazino</td>
<td>C₁₇H₂₀N₄O₂BrI</td>
<td>244</td>
<td>61%</td>
<td>39.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(38.60)</td>
</tr>
<tr>
<td>IIIg</td>
<td>H</td>
<td>H</td>
<td>Phenylpiperazino</td>
<td>C₂₂H₂₃N₄O₂</td>
<td>225</td>
<td>69%</td>
<td>70.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(71.00)</td>
</tr>
<tr>
<td>IIIh</td>
<td>H</td>
<td>Br</td>
<td>Phenylpiperazino</td>
<td>C₂₂H₂₃N₄O₂Br</td>
<td>228</td>
<td>67%</td>
<td>58.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(58.42)</td>
</tr>
<tr>
<td>IIIi</td>
<td>H</td>
<td>I</td>
<td>Phenylpiperazino</td>
<td>C₂₂H₂₃N₄O₂I</td>
<td>215</td>
<td>60%</td>
<td>52.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(52.40)</td>
</tr>
</tbody>
</table>
The analytical values for C, H and N were with in \( \pm 0.4\% \) of the calculated values which are in parentheses.

Table 4

2-Methyl-6,8-substituted-3-[substituted-amino-propanoyl]-4(3H)-quinazolinone-

<table>
<thead>
<tr>
<th>Comp. No.</th>
<th>R</th>
<th>R₁</th>
<th>NR₂</th>
<th>I.R. (KBr.) ( \nu_{\text{max}} ) cm(^{-1} )</th>
<th>(^1)H-NMR (CDCl₃ δppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>H</td>
<td>H</td>
<td>Methylpiperazino</td>
<td>1630 (C=N), 1600 (C=C), 1660 (C=O)</td>
<td>( \delta 2.1(8H,m,2xCH₂-N-CH₂, 3.8 (3H,s,CH₃, N of)), 2.8 (2H,t,N-CH₂) )</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.4 (2H,t,C-CH₃), 7.3-8.0 (4H,m ArH) and 1.3 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>H</td>
<td>Br</td>
<td>Methylpiperazino</td>
<td>1629 (C=N), 1601 (C=C), 1665 (C=O)</td>
<td>2.1(8H,m,2xCH₂-N-CH₂), 3.8 (3H,s,CH₃), 2.8 (2H,t,N-CH₂) 2.4 (2H,t,CH₂-CO), 7.5 (3H,m ArH) and 1.3 (3H, s, CH₃)</td>
</tr>
<tr>
<td>IIIc</td>
<td>H</td>
<td>I</td>
<td>Methylpiperazino</td>
<td>1628 (C=N), 1598 (C=C), 1668 (C=O)</td>
<td>2.0(8H,m,2xCH₂-N-CH₂), 3.8 (3H,s,CH₃), 2.7 (2H,t,N-CH₂) 2.4 (2H,t,COCH₂), 7.3 (3H,m ArH) and 1.3 (3H, s, CH₃)</td>
</tr>
<tr>
<td>IIId</td>
<td>Br</td>
<td>H</td>
<td>Methylpiperazino</td>
<td>1629 (C=N), 1601 (C=C), 1664 (C=O)</td>
<td>2.1(8H,m,2xCH₂-N-CH₂), 3.7 (3H,s,CH₃), 2.8 (2H,t,N-CH₂) 2.4 (2H,t,COCH₂), 7.6 (3H,m ArH) and 1.4 (3H, s, CH₃)</td>
</tr>
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<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>IIIe</strong></td>
<td><strong>Br</strong></td>
<td><strong>Br</strong></td>
<td><strong>Methylpiperazino</strong></td>
<td>1627 (C=N), 1600 (C=C), 1670 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.1 (8H, m, 2xCH₂-N-CH₂), 3.8 (3H, s, CH₃), 2.8 (2H, t, N-CH₂) 2.4 (2H, t, COCH₂), 7.7 (2H, m, ArH) and 1.3 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIf</strong></td>
<td><strong>Br</strong></td>
<td><strong>I</strong></td>
<td><strong>Methylpiperazino</strong></td>
<td>1631 (C=N), 1598 (C=C), 1675 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2 (8H, m, 2xCH₂-N-CH₂), 3.8 (3H, s, CH₃), 2.8 (2H, t, N-CH₂) 2.3 (2H, t, COCH₂), 7.4 (2H, m, ArH) and 1.2 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIg</strong></td>
<td><strong>H</strong></td>
<td><strong>H</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1632 (C=N), 1604 (C=C), 1680 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 7.5-8.4 (9H, m, ArH), 2.4 (2H, t, CO-CH₂) and 1.5 (3H, s, CH₃) 2.7 (2H, t, N-CH₂)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIh</strong></td>
<td><strong>H</strong></td>
<td><strong>Br</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1630 (C=N), 1601 (C=C), 1682 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 7.7 (8H, m, ArH), 2.3 (2H, t, CO-CH₂), 2.7 (2H, t, N-CH₂), 1.5 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIi</strong></td>
<td><strong>H</strong></td>
<td><strong>I</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1629 (C=N), 1601 (C=C), 1681 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 7.8 (8H, m, ArH), 2.4 (2H, t, CO-CH₂), 2.8 (2H, t, N-CH₂), 1.6 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIj</strong></td>
<td><strong>Br</strong></td>
<td><strong>H</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1633 (C=N), 1600 (C=C), 1680 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 8.1 (8H, m, ArH), 2.4 (2H, t, CO-CH₂), 2.8 (2H, t, N-CH₂), 1.6 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>IIIk</strong></td>
<td><strong>Br</strong></td>
<td><strong>Br</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1630 (C=N), 1599 (C=C), 1679 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 8.2 (7H, m, ArH), 2.4 (2H, t, CO-CH₂) 2.8 (2H, t, N-CH₂), 1.6 (3H, s, CH₃)</td>
<td></td>
</tr>
<tr>
<td><strong>III</strong></td>
<td><strong>Br</strong></td>
<td><strong>I</strong></td>
<td><strong>Phenylpiperazino</strong></td>
<td>1628 (C=N), 1602 (C=C), 1678 (C=O)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.8 (8H, m, 2xCH₂-N-CH₂), 8.4 (7H, m, Ar-H), 2.4 (2H, t, CO-CH₂) 2.8 (2H, t, N-CH₂), 1.6 (3H, s, CH₃)</td>
<td></td>
</tr>
</tbody>
</table>
2.3 - RESULT AND DISCUSSION
Nientowski Cyclocondensation Reaction :-

The synthesis of 2-methyl-6,8-substituted-4 (3H)-Quinazolinones (I) has been accomplished by Nientowski cyclocondensation reaction of different substituted anthranilic acids with acetamide in acidic media. The compound (I) again condense with 3-chloropropanoyl chloride in dry benzene to give 3-(3-chloropropanoyl)-2-methyl-6,8-substituted -4 (3H)-Quinazolinone (II). The compound (II) reacts with different Secondary amines in presence of triethylamine in dry benzene to give corresponding, 2-Methyl-6,8-substituted-3-[substituted-aminopropanoyl]-4 (3H)-Quinazolinone  (III) (Scheme-2)
The Probable mechanism of scheme-2 may be given in the following steps –
(iii) -

$\text{R} \quad \text{CH}_3 \quad \text{N} - \text{C} - \text{CH}_2 - \text{CH} - \text{H} + \text{N} - \text{R}_2 \quad \text{Substitution/Elimination}$

(T.S.)

$\text{R} \quad \text{CH}_3 \quad \text{O} - \text{N} - \text{R}_1 \quad \text{Cl}$

- $\text{HCl}$

(III)
In scheme (2), First of all protonation of acetamide occurs in the presence of acetic acid, amino group of substituted anthranilic acid acts as nucleophile and attack at the carbonyl carbon of acetamide, followed by loss of water to give an intermediate. O-amidine (Ia). In intermediate (Ia), the-NH$_2$ group which acts as nucleophile, attacks at the carboxylic carbon of the intermediate to give (Ib), which is activated on protonation, followed by elimination of water results in the formation of compound (I). The second step involves, the nucleophilic attack of the ring-NH (as nucleophile) at the carbonyl carbon of chloropropanoyl chloride, followed by elimination of one molecule of HCl results in the formation of compound (II). In final step the compound (II) reacts with secondary amine to produce compound (III) with the elimination of HCl. The nucleophilic attack of the nitrogen of secondary amine at the carbon bearing chlorine results in the formation of compound (III).

2.3.1-2-Methyl-6,8-dihydro-3-[Methylpiperazino-propanoyl]-4(3H)-quinazolinone IIIa.

![Diagram of IIIa]

2-methyl-6,8-dihydro-3-[methylpiperazinopropanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl -6 , 8-dihydro-4(3H)-quinazolinone with methyl piperazine (secondary amine). The elemental analysis of the compound (IIIa) corresponds to the molecular formula. The IR (KBr, δ max, cm$^{-1}$) shows 1629(C=N), 1600 (C=C), 1660 (C=O). The $^1$H-NMR of the compound IIIa. shows δ ppm 2.1 (8H,m,piperazine), 3.8 (3H,s,CH$_3$-piperazine), 7.3-8.0 (4H,m,ArH) and 1.3 (3H,s,CH$_3$).
2.3.2. 2-methyl-6-hydro, 8-bromo-3-[methylpiperazino propanoyl]-4(3H)-Quinazolinone IIIb.

2-methyl-6hydro,8-bromo-3-[me (IIIb)perazino-propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 hydro, 8-bromo-4(3H)-quinazolinone and methyl piperazine. The molecular formula of the compound (IIIb) is C_{17}H_{21}N_{4}O_{2}Br. The elemental analysis of the compound (IIIb) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1630(C=N), 1601 (C=C), 1665 (C=O). The ¹H-NMR of the compound (IIIb). shows δ ppm 2.7 (8H,m,piperazine), 3.8 (3H,s,CH₃-piperazine), 7.5(4H,m,Ar-H) and 1.3 (3H,s,CH₃).

2.3.3. 2-Methyl-6hydro,8-iodo-3-[methylpiperazinopropanoyl]-4(3H)-Quinazolinone. IIIc

2-methyl-6hydro, 8-iodo-3-[methylpiperazino propanoyl]-4(3H)-quinazolinone IIIc was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 hydro, 8-iodo-4(3H)-
quinazolinone and methyl piperazine. The molecular formula of the compound (IIIc) is C₁₇H₂₁N₄O₂I. The elemental analysis of the compound (IIIc) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1628(C=N), 1598 (C=C), 1668 (C=O). The ¹H-NMR of the compound (IIIc) shows δ ppm 2.0 (8H,m,piperazine), 3.8 (3H,s,CH₃), 7.6(3H,m,ArH) and 1.3 (3H,s,CH₃).

2.3.4. 2-Methyl-6 bromo, 8-hydro-3-[methylpiperazinopropanoyl]-4(3H)-Quinazolinone. IIId.

2-methyl-6 bromo, 8-hydro-3-[methylpiperazinopropanoyl]-4(3H)-quinazolino-none was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 bromo, 8-hydro-4(3H)-quinazolinone and methyl piperazine. The molecular formula of the compound (IIId) is C₁₇H₂₁N₄O₂Br. The elemental analysis of the compound (IIId) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1629(C=N), 1601 (C=C), 1664 (C=O). The ¹H-NMR of the compound (IIId) shows δ ppm 2.1 (8H,m,piperazine), 3.7 (3H,s,CH₃-piperazine), 7.6(3H,m,ArH) and 1.4 (3H,s,CH₃).

2.3.5. 2-Methyl-6,8-dibromo-3-[methylpiperazinopropanoyl]-4(3H) Quinazolinone. IIIe
2-methyl-6, 8-dibromo-3-[methylpiperazino-propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6, 8-dibromo-4(3H)-quinazolinone. The molecular formula of the compound (IIIe) is C_{17}H_{20}N_{4}O_{2}Br_{2}. The elemental analysis of the compound (IIIe) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1627(C=N), 1600 (C=C), 1670 (C=O). The ¹H-NMR of the compound (IIIe) shows δppm 2.1 (8H,m,piperazine), 3.8 (3H,s,CH₃ piperazine), 7.7(2H,m,Ar.H) and 1.3 (3H,s,CH₃).

2.3.6. **2 – Methyl – 6 - bromo, 8 - iodo - 3 [methylpiperazinopropanoyl]-4(3H) Quinazolinane, IIIf**

![Image](image_url)

2-methyl-6-bromo, 8-iodo-3-[methylpiperazino propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 bromo, 8-iodo-4(3H)-quinazolinone and methyl piperazine. The molecular formula of the compound (IIIf) is C_{17}H_{20}N_{4}O_{2}BrI. The elemental analysis of the compound (IIIf) corresponds to the
molecular formula. The IR (KBr, δ max, cm⁻¹) shows 1631 (C=N), 1598 (C=C), 1675 (C=O). The ¹H-NMR of the compound (IIIf) shows δ ppm 2.2 (8H, m, piperazino), 3.8 (3H, s, CH₃-piperazino), 7.4 (2H, m, ArH) and 1.2 (3H, s, CH₃).

2.3.7. 2-Methyl -6, 8-dihydro-3-[phenyl piperazino propanoyl]-4(3H) Quinazolinone. IIIg.

![Structure of IIIg](image)

2-methyl-6, 8-dihydro-3-[phenyl piperazino propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3(3-chloropropanoyl)-2-methyl-6, 8-dihydro -4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIg) is C₂₂H₂₄N₄O₂. The elemental analysis of the compound (IIIg) corresponds to the molecular formula. The IR (KBr, δ max, cm⁻¹) shows 1632 (C=N), 1604 (C=C), 1680 (C=O). The ¹H-NMR of the compound (IIIg) shows δ ppm 2.8 (8H, m, piperazino), 7.5-8.4 (9H, m, ArH) and 1.5 (3H, s, CH₃).

2.3.8. 2-Methyl -6 hydro, 8-bromo-3-[phenyl piperazino propanoyl]-4(3H) Quinazolinone. IIIh

![Structure of IIIh](image)
2-methyl-6hydro,8-bromo-3-[phenylpiperazino-propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 hydro, 8-bromo-4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIh) is C_{22}H_{23}N_{4}O_{2}Br. The elemental analysis of the compound (IIIh) corresponds to the molecular formula. The IR (KBr, δmax, cm\(^{-1}\)) shows 1630(C=N), 1601 (C=C), 1682 (C=O). The \(^1\)H-NMR of the compound (IIIh) shows δppm 2.8 (8H,m,piperazino), 7.7(9H,m,ArH) and 1.5 (3H,s,CH\(_3\)).

2.3.9 2 - Methyl -6hydro, 8-ido-3-[phenyl piperazino-propanoyl]-4(3H) Quinazolinone, IIIi

![Structure of IIIi](image)

2-methyl-6 hydro, 8-ido-3-[phenyl piperazine propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3(3-chloropropanoyl)-2-methyl-6 hydro, 8-ido-4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIi) is C_{22}H_{23}N_{4}O_{2}I. The elemental analysis of the compound (IIIi) corresponds to the molecular formula. The IR (KBr, δmax, cm\(^{-1}\)) shows 1629(C=N), 1601 (C=C), 1681 (C=O). The
$^1$H-NMR of the compound (IIIi) shows $\delta$ ppm 2.8 (8H, m, piperazino), 7.8(8H, m, ArH) and 1.6 (3H,s,CH$_3$).

2.3.10. 2-Methyl-6bromo, 8-hydro-3-[phenyl piperazino-propanoyl]-4(3H)-Quinazolinone, IIIj.

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

(IIIj)

2-methyl-6bromo,8-hydro-3-[phenylpiperazino-propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6 bromo, 8-hydro-4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIj) is C$_{22}$H$_{23}$N$_4$O$_2$Br. The elemental analysis of the compound (IIIj) corresponds to the molecular formula. The IR (KBr, $\delta_{\text{max}}$, cm$^{-1}$) shows 1633(C=N), 1600 (C=C), 1680 (C=O). The $^1$H-NMR of the compound (IIIj) shows $\delta$ ppm 2.8 (8H, m, piperazino), 8.1(8H, m, ArH) and 1.6 (3H,s,CH$_3$).

2.3.11. 2- Methyl - 6, 8 – dibromo -3-[phenyl piperazino-propanoyl]-4(3H)-Quinazolinone. IIIk.

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

(IIIk)
2-methyl-6, 8-dibromo-3-[phenyl-piperazino propanoyl]-4(3H)-quinazolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6, 8-dibromo -4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIk) is C_{22}H_{22}N_{2}O_{2}Br. The elemental analysis of the compound (IIIk) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1630(C=N), 1599 (C=C), 1679 (C=O). The ¹H-NMR of the compound (IIIk) shows δ ppm 2.8 (8H, m, piperazine), 8.2(7H, m, Ar-H) and 1.6 (3H,s,CH₃).

2.3.12. 2-Methyl – 6 - bromo, 8 – Iodo -3-[phenyl piperazino-propanoyl]-4(3H)-Quinazolinone, IIIl.

![III](image)

2-methyl-6-bromo,8-iodo-3-[phenyl piperazino-propanoyl]- 4(3H)- quina- zolinone was synthesized by the reaction of 3-(3-chloropropanoyl)-2-methyl-6-bromo, 8-iodo -4(3H)-quinazolinone and phenyl piperazine. The molecular formula of the compound (IIIl) is C_{22}H_{22}N_{4}O_{2}BrI. The elemental analysis of the compound (IIIl) corresponds to the molecular formula. The IR (KBr, δmax, cm⁻¹) shows 1628(C=N), 1602 (C=C), 1678
(C=O). The $^1$H-NMR of the compound (III) shows $\delta$ ppm 2.8 (8H, m, piperazine), 8.4(7H, m, ArH) and 1.6 (3H,s,CH$_3$).
References

1. Koos M. Biological significance of heterocyclic compounds, chem. papers, 1994, 48, 108
3. Dandia A. Singh R. & saravg P., J Fluorine chem., 126, 2005
(b) Wedge, S. R. etal. J. Cancer Res. 2005, 65, 4389
31. A. Albert, W. L. F. Armarego and E. spinner, J. Cham. soc., 1961, 2689
46. Soderbaum and Widman, Ber, 22, (1889), 1665.
52. Magidson and Golovchins Kaya, J. Gen Chem. USSR, 8,(1938), 1797.
60. Rakhi Rajput and Abinav Prasoon Mishra*, Inter. J. Res. Pharmaceutical and Biomedical Sciences, 3 (1), 2012, 82-89
70. Aldel S. El-Azad, A. A. Kadi et.at., Saudipharm. J. 2010, 9, 72-84
73. Aly MM, Mohamed YA., El Bayouki KM, Basyouni WM and A.
77. F. Hassanzadeh¹, E. Jafari¹, G. H. Hakimelahi¹,², et.al., Research in Pharmaceutical Sciences, May 2012, 7(2): 87-94.
87. Deepti Kohli¹*, S. Riaz Hashim, Sagar Vishal, Manish Sharma et. al., Int. J. Pharmacy and Pharmaceutical Sciences, 1(1), 2009, 163-169.
90. Ch. Rajveer¹*, B Stephen Rathinaraj* et.al., RJPBCS, 1(2); 2010, 366-371.


111. H. Georgey, S. Abbas et. al Molecules, 2008 13, 2557.


118. Xingwen Gao, Xujian Cai, Kai Yan, Baoag Song, Lili Gao and Zhuo Chen, Molecules, 2007, 12, 2621-642.


121. S. Rajasekaran*, G. K. Rao, P. N. Sanjay Pal², Qaseem Ahmad¹ and A. Jasmine, Indian J. Heterocycl Chem. 19 (2009), 191-192
136. Hong Ze Li, Hal-Yun He, Ywan Yuan Han¹ et.al molecules, 1420.3049, 2010.
138. G. A. Khodarahmi¹,², M. Rahmani Khajouei¹, G. H. Hakimelahi, D. Abedi et.al., RPS, 2012, 7(3), 151-158.


154. Josef Jampilek¹, Robert Musiol, Jacek Finster, Matus Pesko, James carroll et.al., Molecules, 2009 14, 4246-265.


157. N. P. Grigaryan\textsuperscript{1}, L.A. Tarzyan\textsuperscript{1}, A. I. Markosyan, et.al., Pharmaceutical Chem. J. 45(2) 2011.
158. A. I. Markosyan\textsuperscript{1}, S.A. Gabrielyan, F.G. Arseyan\textsuperscript{1}, and R. S. Sukasyan\textsuperscript{1}, Pharm. Chem. J. 44(8), 2010, 405-408.
159. A. I. Markosyan, S. A. Gabrielyon, F. G. Arseyan\textsuperscript{1} and R. S. Sukasyan\textsuperscript{1}, Pharm. Chem. J., 44(8), 2010, 405-408.
163. M. Bhagawan Raju\textsuperscript{1} K. K. Raju Sekhar* and G. Prasanthi\textsuperscript{2}, J. Pharmacy Res. 2010, 3(11), 2628-2630.
165. Kai Chen\textsuperscript{1}, Ketai Wang\textsuperscript{1}, Agop M. Kirichian\textsuperscript{1}, Ayman F. Al Aowad\textsuperscript{1}, Lakshmanan K. Iyer\textsuperscript{2}, S. James Adelstein, et.al./ www.mct.accjournals.org, on More. 19, 2012, Am. Association for cancer Research.
166. Xingwen Gao, Xue Juan Cai, Kai Yan, Baoan Song* et.al, Molecules 2007 12, 2621-2642.