CHAPTER-2

REVIEW OF LITERATURE AND RESEARCH ENVISAGED
A number of methods are reported in literature for the synthesis of Quinazolin 4(3H)-ones. A few of them are reported here:

- Niementowski synthesis$^{16-19}$. When anthranilic acid is heated with formamide at 120° it gives 4(3H)-quinazolone. This reaction has been applied to numerous substituted anthranilic acids and amides, thioamides and amidines.

\[
\text{COOH} \quad + \quad \text{HCONH}_2 \quad \xrightarrow{120^\circ \quad 2 \text{ hrs}} \quad \text{CONH} \quad + \quad \text{H}_2\text{O}
\]

- \textit{o}-Acylaminobenzamides afford 4-quinazolones when heated above their melting points.

\[
\text{NHCOR} \quad \xrightarrow{} \quad \text{NR'}R
\]

- Acetyl anthranilic acid reacts with ammonia and amines to give 4-quinazolones. Acetylanthranils can easily be prepared by heating anthranilic acid or a substituted anthranilic acid with an acid anhydride.

\[
\text{H}_2\text{N} \quad \xrightarrow{\text{Heat}} \quad \text{N} \quad \xrightarrow{\text{RNH}_2/\text{exothermic}} \quad \text{N}
\]

- Acetanilides when heated with urethane and phosphorous pentoxide it gives 2-methyl-4-hydroxyquinazoline.

\[
\text{NHCOC}_3 \quad + \quad \text{H}_2\text{N}-\text{COEt} \quad \xrightarrow{\text{P}_2\text{O}_5 \text{ in xylene} \quad 130-140^\circ} \quad \text{N}
\]
• Anthranilic acid heated with a nitrile gives 4(3H)-quinazolinone.

\[
\begin{align*}
&\text{NH}_2 \\
&\text{COOH} \\
&\text{RCN} \rightarrow \\
&\text{NH}_2 \\
&\text{CONHCOR} \\
&\text{R} \\
&\text{N} \\
&\text{O}
\end{align*}
\]

• Heating anthranilic acid or N acyl anthranilic acid with a nitrile to gives 4(3H)-quinazolinones.

\[
\begin{align*}
&\text{NH}_2 \\
&\text{COOH} \\
&\text{RCN} \xrightarrow{200-220^\circ \text{Sealed tube}} \\
&\text{NH}_2 \\
&\text{CONHCOR} \\
&\text{R} \\
&\text{N} \\
&\text{O}
\end{align*}
\]

• Two methods closely allied to the above involve the heating of anthranilonitrile with an acid anhydride and the hydrolysis of an N-acylanthranilonitrile.

\[
\begin{align*}
&\text{NH}_2 \\
&\text{CN} \\
&\text{AC}_2 \text{O} \rightarrow \\
&\text{NHCOCH}_3 \\
&\text{RCN} \xrightarrow{\text{Heat}} \\
&\text{NHCOCH}_3 \\
&\text{CONHCOR} \\
&\text{R} \\
&\text{N} \\
&\text{O}
\end{align*}
\]

Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)
- o-acylaminobenzaldehydes and o-acylamino arylketones give quinazolines when heated with ammonia under pressure or in fused ammonium acetate.

- When acid chloride, RCOCl, (viz., Hippuroyl chloride, mandeloyl chloride, Styryl chloride) is treated with anthranilic acid or dibromoanthranilic acid on ice bath and then at room temperature, benzoazinone is obtained which gives quinazolinone when it is refluxed with hydroxylamine hydrochloride.\(^2\)

- The other route to get quinazoline is by the use of o-nitrobenzaldehydes as starting material. Quinazoline is readily reduced to 3,4-dihydroquinazoline.\(^3\)

- Quinazoline may be prepared by the action of ammonia on acylated o-Aminobenzaldehyde or o-Aminoacetophenones.\(^4\)
MEDICINALLY IMPORTANT QUINAZOLIN 4(3H)-ONES

Antimicrobial activity

- Bhargava and Singh\textsuperscript{23} synthesized a series of 5-Nitro-3-aryl-2-substituted thio-4(3H)-quinazolinones. They observed that substitution of chloro, ethoxy at 4- position in the aryl improved the activity of these compounds.

\[ \text{R} = 2\text{-nitrobenzyl, N-methyl phenyl, carboxamido methyl, Ar = phenyl, 4-chlorophenyl etc.} \]

- N-Acetyl sulphonamide grouping at position 2 were more active than those with N,N-dimethylamino or morpholino/piperidino at position 2. A series of 2,3,6-trisubstituted-4-quinazolylsulphonyl-thioureas were synthesized\textsuperscript{24} and evaluated for antibacterial activity.

\[ \text{R} = \text{Me, Et, Br, n-Br, phenyl, R}^1 = \text{H, I} \]

- Verma\textsuperscript{25} synthesized a series of 2-Methyl/ styrlyl- 3-aryl- 4(3H)-quinazolinones and screened them against \textit{B. megaterium, E. coli, S. aureus} and \textit{Salmonella typhosa}.

\[ \text{R} = \text{4-COOMe, 3-COOMe, Ar=2-furyl} \]

- Fungicidal action of 2- Amino-4(3H)-quinazolinones has been reported by Bullock and Shreeran\textsuperscript{26}.
• 2-Thienylvinyl- 4(3H)- quinazolinones also exhibited same activity\textsuperscript{27}.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CH=CH} \\
\text{S}
\end{array}
\]

R = H, NH\textsubscript{2}NHPh, NHCONH\textsubscript{2}

• Joshi and Joshi\textsuperscript{28} synthesized quinazolinones with thiosemicarbazide, triazole and triazolo thiazine moities at position 3. Only quinazolinones with thiosemicarbazide moiety possessed measurable antifungal activity against all the three fungi at 20% conc.

\[
\begin{array}{c}
\text{O} \\
\text{N} \quad N \quad X \\
\text{Me}
\end{array}
\]

X = CH\textsubscript{2}CONHNHC\textsubscript{2}H\textsubscript{2}, triazole, triazolo, thiazine
R=H, Br, Cl, R\textsubscript{1} = H, Br, I, Cl

• 3-Aryl-2-(β-arylsulphonyl hydrazinomethyl)-4(3H)-quinazolinones were reported by Abdel Aleem and Abdal Ghaffer\textsuperscript{29}.

\[
\begin{array}{c}
\text{O} \\
\text{N} \quad \text{Ar} \\
\text{CH\textsubscript{2}HNNO\textsubscript{2}S} \\
\text{S}
\end{array}
\]

• Chaurasia \textit{et al.}\textsuperscript{30} synthesized benzothiazoyl quinazolinone and found them active against \textit{Aspergillus niger} and \textit{Drechslera australiensis}.

\[
\begin{array}{c}
\text{O} \\
\text{N} \quad \text{S} \\
\text{R\textsubscript{1}} \\
\text{R\textsubscript{2}}
\end{array}
\]

R = CH\textsubscript{2}CH\textsubscript{2}NEt\textsubscript{3}, R\textsubscript{1} = 4-Cl, 6-OME, S-Cl, R\textsubscript{2}=Cl, H
• Some new 4(3H) - quinazolinone was reported by Bahadur and Saxena\textsuperscript{31}.

\[
\begin{align*}
\text{R, } R^1 &= \text{H, Br, } R^2 = \text{H, 4-Cl, 3-Me, 4-Me, 4-OMe, } R^3 = \text{H} \\
\end{align*}
\]

• Antibacterial activity was also shown by quinazolinones with a 5-Mercapto-1,3,4-triazolyl group at 2\textsuperscript{nd} position\textsuperscript{32}.

\[
\begin{align*}
\text{R= 4-Me, } C_6H_5NHCOCH_3 \\
\end{align*}
\]

• Sengupta and Bhattacharya\textsuperscript{33} synthesized some substituted 2-Phenyl-3-arylquinazole-4-ones found them is be potent antibacterials.

\[
\begin{align*}
\text{R, } R^3, R^4 &= \text{H, } R^4 = \text{COOH, } R^4 = \text{Br} \\
\end{align*}
\]

• Synthesis of 2-Methyl/phenyl-3-[4'-substituted phenoxy) phenyl]-6,8-substituted-4(3H)-quinazolinones was carried out\textsuperscript{14} and these compounds were found to be more potent against Bacillus Subtilis than Sarcinia lutea.

\[
\begin{align*}
\text{R=Ph, Me, } R^4 = \text{4-Cl, Me, F, 2-Me, H, } R^2, R^3 = \text{H, Br} \\
\end{align*}
\]
• Shanker et al. observed that substitution of sulfonamido moiety at methyl of position 2 resulted in active compounds against all the tested micro-organism.

\[
\begin{align*}
\text{R} & = 4\text{-Me} \\
\text{X} & = \text{CH}_2
\end{align*}
\]

• Verma et al. further synthesized similar type of compound in which morpholino/piperidino moiety was incorporated at \( N^3 \)-aryl.

• Rao et al. synthesized a number of 3-Aryl quinazolinones. Out of them compound these two totally controlled Curvularia lunata and Fusarium oxysporum at a dose level of 800\( \mu \)g/ml.

\[
\begin{align*}
\text{R} & = \text{NMe}_2, \text{NEt}_2, \text{piperidino}, \text{morpholino}. \\
\text{R}^1 & = \text{H}, 2\text{-NO}_2, 3\text{-Me}, 3\text{-OMe}, \text{R}^1\text{=NO}_2, \text{Me}, \text{R}^2 = \text{H}, \text{Br} \\
\text{R}^3 & = 4\text{-Me}, 2\text{-Me}, 4\text{-NO}_2, \text{R}^2\text{=H}, \text{Br}
\end{align*}
\]

• 5-\{N-[6,8-Dibromo-2-methyl-4(3H)-oxo-quinazolinyl] acetamides–N-substituted dithiocarbamates were reported by Shankar et al. in 1985.

\[
\begin{align*}
\text{NR}^1\text{R}^2 & = \text{anilino, } p\text{-toludino, } p\text{-anisidino, } p\text{-phenitidino etc.}
\end{align*}
\]
• Lakhan and Rai\textsuperscript{40} synthesized a number of 2-[(Dialkylamino)-alkylthio]-3-aryl, or alkyl-6,8-disubstituted-4(3H)-quinazolinone. Diisopropyl amino ethyl substituent at position 2, were found to be more active against \textit{S. aureus} than \textit{E. coli}.

\[
\begin{array}{c}
\text{O} \\
\text{R}^3 \\
\text{N} \\
\text{R}^2 \\
\text{R}^4 \\
\text{S(CH}_2)_2RR'
\end{array}
\]

R, R\textsuperscript{1}= H, Et, isopropyl, R\textsuperscript{2}= Et, substituted phenyl, R\textsuperscript{3}, R\textsuperscript{4}=H, Br.

• Takahashi and Yamane\textsuperscript{41,49} synthesized 2-(3',4'-Dimethoxy styryl)-3-phenylquinazolinones and found them to inhibit \textit{E. coli in vitro}.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CH}=\text{CHR}
\end{array}
\]

R = 3, 4- (OMe)\textsubscript{2}Ph, R\textsuperscript{1}= H, Cl, Br

• Bactericidal activities of thiadiazoloquinazolinone were reported by Khalil and Habib\textsuperscript{42}.

\[
\begin{array}{c}
\text{O} \\
\text{NNNHCH}_2 \\
\text{N} \\
\text{N} \\
\text{Me} \\
\text{NHR}
\end{array}
\]

R=Bu, Ph, CH\textsubscript{3}C\textsubscript{6}H\textsubscript{5}, p- Cl-C\textsubscript{6}H\textsubscript{4}

• Ahmed \textit{et al.}\textsuperscript{43} synthesized some quinazolin containing oxadiazolin-5-thiones in 1988.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CHR}^1 \\
\text{N} \\
\text{R}^2
\end{array}
\]

R=ph, 2-Cl C\textsubscript{6}H\textsubscript{5}, R\textsuperscript{1}= H, Me, R\textsuperscript{2}= H, Et\textsubscript{2}NCH\textsubscript{2}, Morpholinimethyl.
Kulkarni and Ali\textsuperscript{44,51} synthesized 2-Methyl-6,8-substituted-3-[substituted-aminoacetyl]-4(3H)-quinazolinones and screened them against \textit{Bacillus subtilis} and \textit{Staphylococcus aureus}.

\[ \text{NR=phenyl piperazo, } R^1 = \text{H, Br, } R^2 = \text{I} \]

Fungicidal action has also been inhibited by some 3- (5-Methyl-3- isoxazolyl)-2-styryl quinazolin-4(3H)-ones against \textit{Paecilomyces variotii}\textsuperscript{45}.

\[ R = \text{Ph, OMeC}_2\text{H}_5, \text{NMMeC}_2\text{H}_5, \text{NO}_2\text{C}_2\text{H}_5, \text{ClC}_6\text{H}_4 \text{etc.} \]

Cyclohexylidenehydrazide and 4-aza-1-thiaspiro[4,5] decan-3-one derivatives of 3-phenyl-4(3H)-quinazolinone were reported by Karali \textit{et al.}\textsuperscript{46}.

\[ R^1 \text{ and } R^2 = \text{CH}_3, \text{Cl, H} \]

In 1985, Lemura and coworkers\textsuperscript{47} prepared a series of 2,3-Disubstituted quinazolin-4-one.
- Saxena and Khan\textsuperscript{48} synthesized 2-Alkylhydrazino-quinazolin-4(3H)-one in 1997.

\[ \text{R} = \text{CH}_3, \text{n-C}_6\text{H}_{13}, \text{C}_6\text{H}_5, \text{Ar} = \text{Ph}, \text{p-ClC}_6\text{H}_4, \]

- In 1990, 2-Methyl 6,8-substituted-3- [substituted amino acetyl]-4(3H)- quinazolinone were being reported\textsuperscript{50}.

\[ \text{R} = \text{H}, \text{Br}, \text{I}, \text{R}^1 = \text{H}, \text{Br} \]

- Achaiah and Reddy\textsuperscript{52} synthesized a few quinazolinones with chromone moiety in 1991.

\[ \text{R} = \text{Me}, \text{Ph}, \text{R}^1 = \text{H}, \text{Me}, \text{R}^2 = \text{H}, \text{Cl}, \text{Me} \]

- Antimicrobial\textsuperscript{53}, antiinflammatory and diuratic\textsuperscript{50} activities of schiff bases of 3-Amino-2-methyl quinazolin-4(3H)-ones were being reported by Mishra \textit{et al}.

\[ \text{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)} \]
• Some novel 4(3H)-quinazolinone derivatives were reported by Said et al.54.

\[ R=H, \text{ Halogen or nitro, } R^1=H, R^2= \text{ hydroxy / acetox} \]

• Synthesis of 2-(4-Aryl-2-pyrazolin-3-yl)-3-aryl-4(3H)-quinazolinone were carried out by Reddy et al.55.

\[ R = \text{ substituted phenyl, } R^1=H, 2-\text{Me, 2-Cl, 4-Me, 4-Br} \]

• In 1993, Krintzberger and his coworkers56 prepared a series of 2-Guanidino-3-substituted quinazolin-4-ones and studied them for antibacterial activity.

• Singh et al.57 synthesized 6- (4'-Substituted benzylidene-2 methyl/ phenyl-5'-imidazolinon-1'-yl)-2 methyl-4 (3H) quinozolinones.

• Mishra et al.58 synthesized a few 2-Methylquinazolin-4(3H) ones in 1995.

\[ X = H, \text{ Br. } \text{ Ar} = o-C_6H_4COOH, p-C_6H_4COOH, p-C_6H_4SO_3H, p-C_6H_4NO_2, \text{ etc.} \]
• Mishra *et al*. synthesized 2-Methyl-quinazolin-4(3H)-one in 1995.

\[
\begin{align*}
X & = H, X' = Br, Ar = m-C_6H_4COOH, p-C_6H_4COOH, o-C_6H_4OH
\end{align*}
\]

• In 1996, Gaur *et al.* synthesized some novel 2-Substituted methyl-3-(4-substituted Sulphonamide phenyl) quinazolin-4(3H)-one.

\[
\begin{align*}
\text{N} & \quad \text{SO}_2\text{NHR}
\end{align*}
\]

• Oliver and coworkers in 1996 prepared some imidazole quinazolines-4-ones and 3-substituted- quinazolin-4(3H)-ones.

• Kumar and coworkers, in 1997 reported the synthesis of a series of 2,6,8-trisubstituted 3-(2-thiazolyl)-quinazolin-4-ones.

• Same group of authors again synthesized some 2-Substituted aryl 6,8-disubstituted quinazolin-4-ones in 1997.

• Synthesis of some new heterocyclic system bearing 2-Phenyl-6-iodo-4(3H)-quinazolinones of the following structure were reported by Abdul-Hamide.

\[
\begin{align*}
R & = \text{CH}_3, \text{Ph}
\end{align*}
\]
• Abdul Rahman and Taha\textsuperscript{66} in the same year reported the synthesis of a series of 2,3-Disubstituted quinazolines.

\[
\text{O} \quad \text{N} \quad \text{R}^1
\]
\[
\text{CH} = \text{CH} - \text{CO} \quad \text{Ph}
\]

• In 1997, Tamany \textit{et al.}\textsuperscript{67} synthesized certain analogs of 2-Phenyl-3-substituted quinazolin-4(3H)-ones.

\[
\text{O} \quad \text{N} = \text{NCH} \quad \text{Ph}
\]

• Further a new series of quinazolin-4(3H)-ones synthesized by Mishra \textit{et al.}\textsuperscript{68}.

\[
\text{Ar} \quad \text{N} \quad \text{Ar}
\]
\[
\text{CH}_2\text{Ph}
\]

$\text{Ar}= m\text{-C}_6\text{H}_4\text{OH}, \text{C}_6\text{H}_4\text{, } o\text{-C}_6\text{H}_4\text{COOH etc.}$

• Banerjee \textit{et al.}\textsuperscript{69} synthesized Methyl-3-aryl-2-thio-2,4(1H,3H)-quinazolinindiones.

\[
\text{O} \quad \text{N} \quad \text{Ar}
\]
\[
\text{S} \quad \text{CH}_3
\]

$\text{Ar}= 3\text{-Cl, HCH}_2\text{C}_6\text{H}_5, -\text{HCH}_2\text{OC}_6\text{H}_4, -\text{C}_6\text{H}_4\text{CH}_3$

• In 1998, Kovalenko\textsuperscript{70} prepared some novel 2,3-Disubstituted quinazolines.

\[
\text{O} \quad \text{N} \quad \text{CHRCONHR}^1
\]

\[
\text{R}
\]

\textsuperscript{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)}
• In 1998 Shivarama et al.\textsuperscript{71} synthesised a series of 2-(Nitrofurylvinyl)-3-substituted arylquinazolines.

\[
\begin{array}{c}
\text{O} \\
\mid \\
\text{N} \\
\mid \\
\text{CH=CH} \\
\mid \\
\text{O} \\
\mid \\
n\text{NO}_2 \\
\end{array}
\]

• Aziza et al.\textsuperscript{72} in the same year prepared a series of 2-Ethyl-6-iodo-3-substituted quinazolines.

\[
\begin{array}{c}
\text{O} \\
\mid \\
\text{N} \\
\mid \\
\text{CH}_2\text{COR} \\
\mid \\
\text{C}_2\text{H}_5 \\
\end{array}
\]

• Abdul Rahman in 1998 reported\textsuperscript{73} the synthesis of several 2,3-Disubstituted quinazolines-4-ones.

• Arti et al.\textsuperscript{74} in 1998, prepared a series of 2-Methylbenzylamino quinazolin-4(3H)-ones.

• A series of novel 6,8-Disubstituted-2 aryl- quinazolin- 4(3H)-ones were reported by Kumar et al.\textsuperscript{75} in 1998.

• In the same year Patnaik and coworkers\textsuperscript{76} synthesized a few analogs of 3-Aryl-2-(4-arylthiazol-2-yl-amino methyl)quinazolin-4-ones.

• Pandey and coworkers\textsuperscript{77} in 1999, synthesized some Schiff's and Mannich bases of Isatin derivative with 3-Amino-2-methylthio quinazolin-4(3H)-ones and reported their antibacterial, antifungal and anti-HIV activities.

• In 1999, Pei-pei et al.\textsuperscript{78} reported the SAR of a series of 2-Substituted quinazolines and their \textit{in vitro}.

• Pandey and his coworkers\textsuperscript{79} in 1999 synthesized a series of 2-Furyl vinyl-3-aryl quinazolin-4(3H)-ones.
• Shivarama et al.\textsuperscript{80} synthesized N-1,2,4-Triazolyl quinazolinones in 1999.

\[ R=\text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7, \text{C}_6\text{H}_{11} \]

\[ R'=\text{CH}_3 \]

• Recently Udupi et al.\textsuperscript{81} synthesized some quinazolinones of following types as antibacterial, antitubercular and anti-inflammatory agents.

• In 1999, Ibrahim\textsuperscript{82} synthesized various 2,3-Disubstituted quinazolin-4-ones by introducing chloro group at 6 and 7 positions. These compounds were found to exhibit potent activity.

• Kovalenko\textsuperscript{83} in 1999, synthesized some 2,3,6,8-Tetra substituted quinazolin-4(3H)-ones.
- In 1999, Ramasarma and coworkers\textsuperscript{84} reported the synthesis of some novel oxoquinazolyl thiosemicarbazones.

- Ahluwalia and coworker\textsuperscript{85} also prepared a series of substituted quinazolines.

- In 2000, Bhatt \textit{et al.}\textsuperscript{86} synthesized manich bases of 7-Nitro-2- methyl-4(3H)-quinizolinone.

\[
\begin{align*}
\text{Ar} &= 2\text{-chlorophenyl, 4-nitrophenyl, phenoxy methyl, 4\text{-chlorophenyl,}} \\
&\text{2\text{-hydroxyphenyl, etc.}}
\end{align*}
\]

- 2-(2-Aryl vinyl)-7-substituted-quinazolin-4(3H)-one were reported by Meligie \textit{et al.}\textsuperscript{87}.

\[
\begin{align*}
\text{O} &\text{X} \\
\text{O} &\text{X} \\
\text{O} &\text{X} \\
\text{O} &\text{X}
\end{align*}
\]
Srivastava et al. synthesized some 2-Methyl-3-(arylthiocarbamido) quinazol-4-ones and 2-methyl-3-(aryl-idencarboxamido) quinazol-4-ones in 1999.

Kant and Saksena in 2003, prepared a series of 2,3-Disubstituted quinazolines.

Selvam et al. group prepared some 2,6-Disubstituted quinazoline-4-ones by incorporating sulphonamide at 3-position.

Anticonvulsant Activity

Jackman and coworkers in 1960, prepared some 2-Methyl-3-(o-tolyl) quinazolin-4(3H)-ones and 2-methyl-3-(o-chlorophenyl) quinazolin-4(3H)-ones. These compounds were reported to possess sedative, hypnotic and anticonvulsant activities.
• Anticonvulsant and anti-tumor properties of Orthonol-(2-methyl-3-α-tolyl)-4(3H)-quinazolinone was reported by Zilbermint. \(^{92}\)

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

• 2-Mercapto-3-(4-carboxyanilino) and 2-mercapto-3-dimethylamino-4(3H)-quinazolinones was reported by Kirchner and Zalay. \(^{93}\)

\[
\begin{align*}
\text{O} & \text{N} \\
R^1 & \text{H, SH} \\
R^2 & \text{H, C}_6\text{H}_5, C_6\text{H}_5\text{COOH, NMe}_2
\end{align*}
\]

• Sedative and anticonvulsant activities were also shown in a large number of 2-Methyl-3aryl-4(3H)-quinazolinone substituted at position 5, 6, 7, and 8. \(^{94-96}\)

\[
\begin{align*}
\text{R} & \text{= 2-Me, 2-Et, R}^1, R^2, R^3, R^4 = \text{H, Cl, NO}_2, \\
\text{NH}_2 & \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{R} & \text{=H, 7-NH}_2, 7-\text{Me, R}^1 = 6-\text{Me, 4, 5-Me, 4-} \\
\text{Ome, 4-Cl, 2-Me} & \text{R}^1 = \text{H, 2-Me, R}^2 = 4-\text{Cl, 3-Cl, 3-OMe,} \\
& \text{4-OMe}
\end{align*}
\]

• Numerous compounds (8) related to methaqualone (9) exhibited anticonvulsant activity. \(^{97}\) 8\(_i\) showed greater activity than methaqualone against maximal electroshock seizures compound 8\(_{II}\) exhibited pronounced anticonvulsant activity but showed greater toxicity than 8\(_i\).
Glasser et al. synthesized and screened a series of 2-Thioquinazoline-4-ones for CNS activity in mice with a dosage ranging from 10-600 mg/kg.

Barthwal et al. reported some quinazolinone 1,3,4-Oxadiazoles as anticonvulsants.
• Misra et al.\textsuperscript{100,102} reported that 2-Phenyl/methyl 3 or 4-(benzimidazol-2-yl) phenyl-6, 8-substituted/unsubstituted quinazolin 4(3H)-ones at a dose level of 100 mg/kg.

\[ R = \text{Br, I, } R^1 = \text{Br, H} \]

• Shukla and Saxena\textsuperscript{101} were synthesised 2-(Substituted) phenoxy methyl-3 heterocyclic substituted-4-(3H)-quinazolones.

\[ R = 4-\text{Me, 2-Cl, 4-NO}_2; \quad R^1, R^2 = \text{H, Br}; \quad Z = 2\text{-thiazolyl, 2-pyridyl} \]

• Further, 2-Phenoxy methyl-3-N-substituted amino carbonyl methyl-8-substituted-4(3H)-quinazolinone were synthesized by Shukla et al.\textsuperscript{103}.

\[ R^1 = \text{H, 2-Me, 2-Cl}; \quad R^2 = \text{morpholinyl, thiazolyl, piperidinyl} \]

• Husain and Singh\textsuperscript{104} synthesized some 2-Aryloxymethyl-3-substituted carboxymethyl-6, 8-disubstituted-4(3H)-quinazolinone. These compound showed 20-60% protection against pentylenetetrazole induced seizures in mice.

\[ \text{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)} \]
$R^1 = \text{isobutyl}, R^2 = \text{morpholinyl}$

- Presence of piperazine moiety at position 2 enhanced the activity against electroshock seizures and pentylene tetrazole seizure as reported by Lata et al.\textsuperscript{105} in 3-Aryl-2-(1'-arylpiparazin-4'-yl-carboxamide methyl)-mercapto quinazolinones.

$I \quad R^1 = 3-\text{Me}, H, \; R^2 = H$
$II \quad R^1 = 4-\text{Me}, R^2 = H$
$III \quad R^1 = 4-\text{Cl}, R^2 = 3-\text{F}$

- Vaidya et al.\textsuperscript{106} synthesized 3,4-Dihydro-4-oxoquinazolines.

$R^1 = \text{O-CH}_3\text{C}_6\text{H}_4, \; m-\text{CH}_3\text{C}_6\text{H}_4, \; \text{O-FC}_6\text{H}_4$

- A series of 2, 3-Disubstituted-4(3H)-quinazolinone were synthesized by El-Nasser et al.\textsuperscript{107}.

$R^1R^2 = \text{H, Br}$
$R^3 = \text{H, Br, Cl, NO}_2$

Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)
• Des Pandey et al.\textsuperscript{108} synthesised 6,8-Dibrome-3-[(5-aryl-1,3,4-oxadiazol-2-yl)-
methyl]-2-methyl-4(3H)-quinazolinones and active against supramaximal
electroshock seizures in rats and metrazole induced seizures (MES) in mice.

\[
\begin{align*}
\text{R} &= 2-\text{ClPh}, 4-\text{OHPh} \\
\end{align*}
\]

• Wolfe et al.\textsuperscript{109} synthesized some new 2-Substituted-3-aryl-4(3H)-quinazolinone
and observed that compound with a single orthosubstituent at 3-aryl had the most
promising compound against the activity.

\[
\begin{align*}
\text{R} &= \text{Cl, Br, I, OMe, Me, F} \\
\end{align*}
\]

• A number of 6,8-Disubstituted-3-[5-(2-hydroxy-3[substituted phenyl] amino)
propyl]-thio-(1,3,4-thiadiazol-2-yl)-2-methyl-4(3H)-quinazolinone were
synthesized by Shrumali et al.\textsuperscript{110}.

\[
\begin{align*}
\text{R}^1, \text{R}^2 &= \text{H, Br, I, R}^3 = \text{H, Me, Cl} \\
\end{align*}
\]

• Ibrahim\textsuperscript{111} in 1998, synthesized a series of 3-Substituted 6,8-dichloro-2-phenyl-
4(3H)-quinazolinone. These compounds were found to possess good activity.

\[
\begin{align*}
\end{align*}
\]
• In the same year, Nawrocka and Stasko\textsuperscript{112} prepared a series of substituted quinazoline-4-ones. The pharmacological investigation of these compounds showed anticonvulsant activity as expected.

• Cyrilo and Gerhard\textsuperscript{113} in 2000, synthesized some Acetylenic quinazoline derivative with the aim of exhibiting good activity.

• Zappala \textit{et al.}\textsuperscript{114} synthesized the following compound.

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

**DRUGS ACTING ON CNS**

**Behavioural activity**

• A large number of fluorinated 2-Alkyl-3-aryl-4(3H)-quinazolinone were tested for their hypnotic, analgesic and behavioural activities\textsuperscript{115}.

\begin{center}
\includegraphics[width=0.5\textwidth]{compound2.png}
\end{center}

\[ R^1, R^2 = H, Me \]

• Joshi \textit{et al.}\textsuperscript{116} reported a novel series of Fluorinated 2-alkyl/phenyl-3-aryl-4(3H)-quinazolinone as depressant.

\begin{center}
\includegraphics[width=0.5\textwidth]{compound3.png}
\end{center}

<table>
<thead>
<tr>
<th>R</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>2-Me</td>
</tr>
<tr>
<td>SH</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>4-F</td>
</tr>
<tr>
<td>n-C\textsubscript{3}H\textsubscript{7}S</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>4-F</td>
</tr>
<tr>
<td>C\textsubscript{6}H\textsubscript{5}</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
- CNS depressant activity of 2-Alkyl -3-(3,5-dimethyl-4-hydroxy of 2-alkyl-3-
dihydroquinazolin-4-one are reported by Parikh et al.\textsuperscript{117}.

\[
\begin{align*}
\text{R}^1 & = \text{CH}_3, \quad \text{R}^2 = \text{CH}_3, \quad \text{R}^3 = \text{CH}_3 \\
\text{C}_2\text{H}_5 & = \text{CH}_3, \quad \text{H} = \text{CH}_3, \quad \text{C}_2\text{H}_7 = \text{CH}_3
\end{align*}
\]

- Some derivatives of 2-(N-Arylpiperazinocarbonyl methyl thio) 3-aryl-6-bromo-4(3H)-quinazolinones have been reported as psychotropic agents\textsuperscript{118}.

- Antidepressant activity of several 2-(Fluoromethyl)-3-aryl-4(3H)-quinazolines were reported by Junichi et al.\textsuperscript{119}.

\[
\begin{align*}
\text{R}^1 & = \text{H, Cl, R}^2 = \text{H, Cl, NO}_2, \text{NH}_2\text{NHAe, R}^3 = \text{H, Me, Cl, R}^4, \text{R}^5 = \text{H, Cl}
\end{align*}
\]

- Sato and Tsukamoto\textsuperscript{120} reported the CNS depressant and anti-inflammatory activity of quinazolinone acetamides.

\[
\begin{align*}
\text{R} & = \text{Heterocyclic amines}
\end{align*}
\]
• Bhargava and Prakash\textsuperscript{121} synthesized 5-Substituted-2-mercapto-3-aryl/alkyl-4(3H)-quinazolinone as CNS depressant and in addition they reported the antimicrobial activities.

\[
\text{R} = \text{aryl, } R_1, R_2 = \text{Isobutyl or benzyl group}
\]

• In 1978, Mukherji et al.\textsuperscript{122} synthesized some new series of N-[4(3H)-quinazolinone-3-yl] methyl morpholino, piperazine and malonyl urea as CNS depressant.

• Tewari et al.\textsuperscript{123} reported that 2-Aryl-3-(2-hydroxy-ethyl) 6,8-disubstituted 4(3H)-quinazolinone showed CNS depressant activity

\[
\text{Ar} = \text{C}_6\text{H}_5, \text{CH}_2\text{NCOCH}_3, R, R' = \text{H, Br, Cl, I}
\]

• Kausi\textsuperscript{124} reported a new series of CNS depressant and anticonvulsant.
- Pharmacological evaluation of some newer substituted 4(3H)-quinazolinones as CNS depressant and anticonvulsant agent are reported by Shukla and Saxena\textsuperscript{125}.

- Doichev \textit{et al.}\textsuperscript{126} studied the effect of following compound on the behaviour, stress reaction and oxygen consumption in model groups of albino mice.

- Tanabe and Seiyaku\textsuperscript{127} in 1985, synthesized some 2-Fluoromethyl-3-substituted phenyl-6-amino quinazolin 4(3H)-one, these compounds were found to possess CNS depressant activity.

- Chourasia and Sharma\textsuperscript{128} in 1982, prepared a series of 3-(2-Benzthiazolyl)-2, 6-disubstituted quinazolin-4(3H)-ones. These compounds were found to exhibit CNS depressant activity.
- Some 2-Methyl-3-(substituted phenyl)-6-substituted-4(3H)-quinazolinones showed potent tranquilizing, antidepressant and anticonvulsant activities. Substitution of the bromo group at position 6 did not produce any effect but iodo substituted derivative showed tranquilizing and antidepressant activities and were devoid of anticonvulsant activity\textsuperscript{129}.

\[
R = H, \text{ Br, I, } R^1 = \text{ Ac, COCH}_2\text{CH}_2\text{NR}^2
\]

- Hussain and Shukla\textsuperscript{130} claimed 3-(Benzylidene amine phenyl)-2-phenyl quanazolin 4(3H)-ones to be stimulant.

\[
\begin{array}{l}
R^1 \\
- \text{H} \\ 
- \text{OH} \\ 
- \text{H} \\ 
- \text{OH}
\end{array}
\quad
\begin{array}{l}
R^2 \\
- \text{4-OMe} \\ 
- \text{3-OMe} \\ 
- \text{4-OH} \\ 
- \text{3-OH} \\ 
- \text{4-OH}
\end{array}
\]

- CNS stimulant activity in 2-Carbamoyl methylthio and 2[(dimethylamino alkyl)thio]-3-alkyl/aryl-4(3H)-quinazolinone was reported by Lakhan and Singh\textsuperscript{131}.

\[
R = \text{CH}_3\text{CONH}_2, \text{ CH}_2\text{CH}_2\text{NMMe}_2
\]

- Following group of quinazolinones were reported as psychotropic agents\textsuperscript{132}.

\textsuperscript{129} Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)
• Certain analogs of 2-Substituted thio-3-substituted phenyl quinazolin-4(3H)-ones with chloro group at C-7 position were prepared by Lakhan and Singh\textsuperscript{133} in 1989. These compound were reported to possess CNS depressant activity.

\[ \text{R = H, Br, } X^1 = H \text{ or Br, } R = H \text{ or CH}_3, R^1 = C, \text{ Br or CH}_3 \]

• Saxena and Khan\textsuperscript{134} synthesized 2-Alkyl/aryl-3-(arylhydrazine) quinazolin 4(3H)-ones as CNS active agents.

• 2-Phenyl-3-[4-(N,N-disubstituted carbamoyl) phenylanino]-8-substituted 4(3H)-quinazolinone were synthesized by Nigam \textit{et al.}\textsuperscript{135} They reported that the compound where \( R^2 \) was H possessed both stimulant and depressant activities while compound where \( R^2 \) was Br exhibited stimulant action only.

\[ \text{R = H, Br, NR}^1 R^2 = \text{Morpholino, piperidine, n-methyl piperazino} \]

• In 1990, Nigam and Coworkers\textsuperscript{136} again synthesized some 2-Phenyl/3-[4-N,N-disubstituted amino carbonyl]phenyl]-8-substituted-4(3H) quinazoliniones was found to be the most active compound in this series.

---

Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)
R = H, Br, NR¹R² = Morphino, Piperidino, N-phenylpiperazino diethylamino

**Hypnotic**

- After the reporting of 2,3-Disubstituted 4(3H)-quinazolinone. Potential hypnotic agent in 1956 by Gujral et al.¹³⁷ prompted the medicinal chemists to explore on 4(3H)-quinazolinones.

- Laubach and Lamore¹³⁸ synthesized 2-Methyl-3-(4-chloro/bromo-2-methylphenyl)-4(3H)-quinazolinone.

- Some novel 4(3H)-quinazolinone was being reported by Olin et al.¹³⁹.
• In 1972, Hisano et al. synthesized 2-Heterocyclic substituted 4(3H)-quinazolinone derivative.

\[
\begin{align*}
R^1 &= \text{aryl, } R^2 = \text{H, CH}_3, R^3 = \text{H, } R^4 = \text{H etc.} \\
\end{align*}
\]

• The following compound was reported to exhibit sedative and muscle relaxant properties. These found to be potent tranquilizer with excellent reabsorption.\textsuperscript{141,142}

\[
\begin{align*}
\end{align*}
\]

• Rahman et al.\textsuperscript{143} synthesized some new 4(3H)-quinazolone analogs.

\[
\begin{align*}
R &= \text{C}_6\text{H}_4I, \text{CH}_3-\text{CH} = \text{CH} - , R^1 = \text{Cl, H etc.} \\
\end{align*}
\]

• 3-Amino-2-(hetero aryl) amino-4(3H)-quinazolinone synthesized by Kotlke et al.\textsuperscript{144}

\[
\begin{align*}
R^1 &= \text{Heteroaryl, } R^2, R^3 = \text{H, alkyl, alkoxy, halogen} \\
\end{align*}
\]
Analgesic and Muscle relaxant Activity

- Kacker and Zaheer\textsuperscript{145} synthesized 2,3-Disubstituted 4-quinazolinone as potential analgesia.

\[
\begin{align*}
\text{R}^1 &= -\text{CH}_3, -\text{C}_2\text{H}_5, \text{pyridine} \\
\text{R}^2 &= \text{Ph}, \text{o-tolyl}, \text{m-tolyl}, \text{o-nitrophenyl etc.}
\end{align*}
\]

- Shanker \textit{et al.}\textsuperscript{146} synthesized N\textsuperscript{4}[N-(6,8-dibromo-2-methyl-3-quinazolin-4(3H)-oxyl) acetamido]N\textsuperscript{1}-substituted sulfanilamides.

\[
\begin{align*}
\text{R} &= 5\text{-methoxy isoxazolyl, 2, 6-dimethoxy-4-pyrimidyl,} \\
&= 5\text{-methyl-2(1, 3, 4-thiadiazolyl), H.}
\end{align*}
\]

- A series of 3-\(\alpha\)-(5-Substituted marcaptoacetamido) and 3-\(\alpha\)-(N,N-disubstituted aminoacetamido)-6,8-dibromo-2-methyl-quinazolin-4-one were synthesized by Shanker \textit{et al.}\textsuperscript{147} in 1985.

\[
\begin{align*}
\text{R} &= \text{ter-butyl, 2-carboxyphenyl, sec-butyl}
\end{align*}
\]

- The following compound reported by Alagarsamy \textit{et al.}\textsuperscript{148} in 2000.
- Alagarsamy and Revathi\textsuperscript{149} prepared some novel 2-Phenyl-3-(substituted methyl amino)-quinazolin-4(3H)-ones and studied their analgesic, anti-inflammatory and antibacterial activity.

\[
\begin{align*}
\text{O} & \quad \text{N} - \text{NHCH}_2\text{R} \\
\text{N} & \quad \text{C}_6\text{H}_5
\end{align*}
\]

\[R = \text{N}, \quad \text{N}, \quad \text{N}, \quad \text{NH} \quad R = \text{N}^\text{Me}, \quad \text{N}^\text{Me}, \quad \text{N}^\text{C}_3\text{H}_5\]

- Paneerselvam and coworkers\textsuperscript{150} in 2003, synthesized a series of 2-Methyl-3,6-disubstituted quinoxolin-4-ones.

\[
\begin{align*}
\text{O} & \quad \text{N}^\text{R}_1 \\
\text{R}^2 & \quad \text{CH}_3
\end{align*}
\]

- In 2003, Kumar and coworkers\textsuperscript{151} reported the analgesic, anti-inflammatory, ulcerogenic and cyclooxygenase activities of a series of novel quinazolinyl pyrozolines.

\[
\begin{align*}
\text{O} & \quad \text{N}^\text{R}_1 \\
x & \quad \text{CH}_2\text{COCH}_2\text{R}
\end{align*}
\]

**Antiviral Activity**

- In 1982, Agnihotri and Shukla\textsuperscript{152} prepared some 2,3,-Disubstituted quinazolin-4(3H)-ones.

\[
\begin{align*}
\text{O} & \quad \text{N}^\text{R} \\
\text{C} & \quad \text{CH} = \text{CH} - \text{R}_1
\end{align*}
\]

\[\text{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)}\]
• Pandey and Raj\textsuperscript{153} synthesized a series of 2,3-Disubstituted quinazolines in 1985.

![Chemical structure of 2,3-Disubstituted quinazolines](image)

• Pandey \textit{et al.}\textsuperscript{154} observed that the presence of a cinnamoyl phenyl group at position 3 resulted in active compounds. These compounds showed 80\% inhibition of Ranikhet disease virus.

![Chemical structure of cinnamoyl phenyl group](image)

\text{R=4-OMe, 2-OH, 5-OMe.}

• Agrawal \textit{et al.}\textsuperscript{155} studied the antiviral and hypoglycemic activity of Substituted 2-phenyl-3-[2-substituted anilinothiazoyl-5-(N-mercaptophenyl)] quinolin-4-ones.

![Chemical structure of quinolin-4-ones](image)

\text{Ar = phenyl, tolyl, p-bromophenyl}

\text{R}^1 = \text{H or Br, } \text{R}^2 = \text{H or NO}_2, \text{R}^3 = \text{H or Br}

• Some new 1-(2-Aryl-4-oxo(3H)-quinazolyl)-3-aryl-5-phenyl-formazans were synthesized by Pandey and Negli\textsuperscript{156}.

![Chemical structure of 1-(2-Aryl-4-oxo(3H)-quinazolyl)-3-aryl-5-phenyl-formazans](image)
Antimycobacterial activity

- Rao and his coworkers\textsuperscript{157,158} reported antitubercular activity of a number of compounds give of the following types and these compound has minimum inhibitory concentration below 100\(\mu\)g/mL.

\[
\text{R}=\text{Me, Alkyl, } R^1=\text{4-Me, 4-Br, cyclohexyl}
\]

- Habib and Hazzaa\textsuperscript{159} synthesized of 2-Methyl-3-arylamino-4(3H)-6,8-disubstituted quinazolinones in 1981.

- In 1998, Desai and his coworkers\textsuperscript{160} prepared a series of substituted quinazolines.

- Karel and coworkers\textsuperscript{161} in 1999, synthesized some novel quinazoline derivative

Antimalarial Activity

- Bhargava and Chaurasiya\textsuperscript{162} synthesized 6,8-Dibromo-3-substituted 2-(N,N,-dialkyl or (N-piperidino)-carboxamidomethylthio-4(3H)-quinazolinone in 1962.

\[
\text{R}=\text{CH}_2\text{CONPhCH}_2\text{CHMe}_2, R^1=\text{H, 3-Me, 4-Me, 4-Cl, 4-Br etc.}
\]

- Bhargava and Shyam\textsuperscript{163} synthesized some new 4(3H)-quinazolinone in 1977.

- Singhal et al.\textsuperscript{164} synthesized new quinazolinone derivative and screened against \(P.\text{berghrei}\) and \(P.\text{gellinaceum}\) in mice.

\[\text{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)}\]
A series of 2-Aryloxymethyl-3-[4-nitrophenyl-sulfonyl] phenyl quinazolin-4(3H)-one were synthesized against *P. berghrei* in 1985\(^{165}\).

Lakhan *et al.*\(^{166}\) synthesized new series of quinazolinones, search for potent drugs in this category.

**Antitumor activity**

Kunzel *et al.*\(^{167}\) synthesized 2-Phenyl-4(3H)-quinazolones and observed that compound at 100mg/kg dose showed the best cytostatic activity in mice.
• 2-Styrylquinazolin 4(3H)-ones were synthesized by Jiang et al.\textsuperscript{168}, which were found to inhibit tubulin polymerization and the growth of 1210 murine leukemia cells.

\[
\text{R=5,6,7,8-Cl, 6-Br, 6-F, 6-NH}_2, 6-\text{OMe}
\]

• Boyal and coworkers\textsuperscript{169} in 1993, reported the synthesis of some 2-Methyl-6-substituted quinazolines.

• Raffa and coworkers\textsuperscript{170} in 1999, reported the synthesis of some 3-(3-Phenylisoxazo-5-yl)-quinazoline derivative.

• In 2000, Parkanyi and Schmid\textsuperscript{171} synthesized 5-Chloro-2-methyl-3-(5-methylthiazol-2-yl)-4(3H)-quinazolinones.

\[
\text{R}^1=\text{Cl, R}^2, \text{R}^3, \text{R}^4=\text{H etc.}
\]

• In 2000, Mann Jen and coworkers\textsuperscript{172} synthesized some novel 2-Aryl-6,7-disubstituted quinazolin-4-ones.

• Murugan et al.\textsuperscript{173} synthesized 2-Substituted quinazolin-4(3H)-ones in 2003.
• In 2003, Dinakaran et al. synthesized 6-Bromo-2,3-disubstituted-4(3H)-quinazolinones.

• Synthesis and primary cytotoxicity evaluation of 3-\{[(3-Phenyl-4(3H)-quinazolinone-2-yl)mercapto-acetyl]hydrazono\}-1H-2-indolinones were reported by Gursoy and Karah.

• In 2004, Raffa et al. reported the cytotoxicity and inhibitory effect on tubulin polymerization of a new 3-Heterocyclo substituted 2-styrylquinazolinone.
R = phenyl, 2-pyridinyl, 3-methyl-2-pyridinyl etc.

- In 2004, Raffa et al.\textsuperscript{177} synthesized new 3-(5-Methylisoxazol-3-yl) and 3-(pyrimidin-2-yl)-2-styrylquinazolin-4(3H)-ones.

- In 2004, Raffa et al.\textsuperscript{178} synthesized new 3-(1-Phenyl-3-methyl-pyrazol-5-yl)-2-styrylquinazolin-4(3H)-ones.
Antihistaminic and antiulcer activity

- Lemathieu et al.\textsuperscript{179} reported 3- (4-oxo-3H-quinazolin-3-yl)-2-propionic acid as a new series of this category.

\[
\text{R} = \text{H, 6 or 8-OCH}_3, \text{6-OH, 6-SCH}_3 \text{ etc.}
\]

- In 1986, Lewis et al.\textsuperscript{180} synthesized sodium salt of 3 (1H-Tetrazol-5-yl) 4(3H)-quinazolinone.

- 2-[3-(1-Piperidinyl methyl-phenoxy)-propylamino]-4(3H)-quinazolinone was reported by Oshita et al.\textsuperscript{181} as a potent and selective histamine H\textsubscript{2}-receptor antagonist in guinea pig atria and gastric mucosa cell.

- Takahashi et al.\textsuperscript{182} synthesized 2-(Heterocyclylalkyl)-quinazolin-4-ones, which showed 40-96% inhibition of indomethacin-induced ulcer in mice at a 100mg/kg oral dose.
• Synthesis and histamine H₂-antagonist activity of 4(3H)-quinazolinone derivatives was being reported by Ogawa et al.¹⁸³.

\[
\begin{align*}
\text{NH} \\
\text{O} \\
\text{R} \\
\end{align*}
\]

\[R = \text{HN} = \text{CH}_2 \text{CH}_2 \text{SCH}_2 \text{CH}_2 \text{CH}_2 \text{C} \]

etc.

• Peet et al.¹⁸⁴ synthesized 3- (1H-Tetrazol-5-yl)- 4(3H)- quinazolinone sodium salt.

\[
\begin{align*}
\text{O} \\
\text{N} \\
\text{N} \\
\text{Na}_2 \text{H}_2 \text{O}
\end{align*}
\]

• In 1989, Lemura and coworkers¹⁸⁵ synthesized the following 2- (4-Substituted piperazinylmethyl)-3- substituted 4(3H)-quinazolinone.

\[
\begin{align*}
\text{O} \\
\text{N} \\
\text{CH}_2 \text{CH}_2 \text{OR}^1 \\
\text{CH}_2 \text{N} \text{R}
\end{align*}
\]

**Hypoglycemic activity**

• Gupta et al.¹⁸⁶ synthesized 2-Piperazino- 4(3H)-quinazolinone monoacetate and reported that they were effective blood sugar lowering agent exhibiting activity in male and female albino rats at dose ranging between 10- 100 mg/kg of body weight.

\[
\begin{align*}
\text{NH} \\
\text{N} \\
\text{NHCH}_2 \text{COOH}
\end{align*}
\]
• A series of N-(2-Aryl-6,8 disubstituted-4-quinazolin-3-yl)-N-arylsulphonyl urea synthesized by Husain and Srivastava\textsuperscript{187}.

\[
\begin{align*}
R^1 & = \text{NHCOMe, H, OMe, } R^1 = H, R^3 = \text{Br, H} \\
Ar & = \text{Ph, -CH = CHPh.}
\end{align*}
\]

• In 1982, Husain and Gupta\textsuperscript{188} reported the hypoglycemic activity of 2-(Substituted phenoxy)methyl)-3- (thiazole-2-yl) -4-quinazolones.

\[
\begin{align*}
R^1 & = H, CH_3, CH_2CH_3, \text{etc} \\
R & = p-CH_3, m-CH_3 \text{ etc} \\
X & = Cl, Br \text{ etc} \\
X^1 & = H, Br, I \text{ etc.}
\end{align*}
\]

• Agarwal et al.\textsuperscript{189} synthesized some Hitherto as known substituted-2-phenyl-3-[2-substituted anilinothiazolyl-5-(N-mercaptophenyl) quinazolin-4-ones.

\[
\begin{align*}
R^1 & = \text{Ph, 2-MeC_6H_4, 4-BrC_6H_4, 4- ClC_6H_4} \\
R^1, R^2, R^3 & = H \text{ etc.}
\end{align*}
\]

• Lakan et al.\textsuperscript{190} synthesized 2-(Substituted phenoxy)methyl)-3-(thiazol-2-yl)-4quinazolones. These compound caused 15 and 17% lowering of blood sugar level at 250 mg/ kg orally in rats.

\[
\begin{align*}
R & = 4-\text{Me, 3- Me, } R^1 = \text{Me, R}^2, R^3 = H
\end{align*}
\]

Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)
- Husain and Jamali\textsuperscript{191} also synthesized N\textsuperscript{1}{[(3-Aryl-4-oxo-quinazolin-2-yl)-methyl] amino} benzoyl{[-N\textsuperscript{4}-arylthiosemicarbazides} and 2-(arylamino)-5{-[(3-aryl-4-oxoquinazolin-2-yl)-methyl]amino}phenyl-1,3,4-thiadiazoles and oxadiazoles, expecting that the incorporation of thidiazole or oxadiazole moiety in quinazolone nucleus might enhance their activity.

\[ R=2\text{-}Me, 4\text{-}OMe, 4\text{-}NO_2, R^1=H, Me, OMe, Cl, Br \]

\[ R=2\text{-}Me, 4\text{-}OMe, 4\text{-}NO_2, R^1=H, Me, OMe, Cl, Br, Z=O, S \]

- Novel 2-[4-diethoxyphosphorylmethyl]phenyl 4(3H)-quinazolinone reported by Kurogi \textit{et al.}\textsuperscript{192} in 1996.

\[ E=(C_6H_5)_2 OH, Me, Et, Pr. \]
Antiparkinsonian activity

- 2,6,8-Trisubstituted quinazolinones and their corresponding 3-hydroxyquinazolones reported by Tiwari and Pandey\(^{193}\).

\[
\begin{align*}
\text{X} & = \text{-H, CH} = \text{CHC}_2\text{H}_5 \\
\text{R} & = \text{-CH}_2\text{NHCOC}_6\text{H}_5, \text{-CH} = \text{CHC}_2\text{H}_5
\end{align*}
\]

- Year 1975, saw a new pharmacological activity being reported for 4(3H)-quinazolinone\(^ {194}\).

\[
\begin{align*}
\text{R} & = \text{C}_6\text{H}_5\text{CONHCH}_2, \text{C}_6\text{H}_5\text{CH(OH)}, \text{C}_6\text{H}_5\text{CH=CH}_3 \\
\text{R}^1, \text{R}^2 & = \text{H, Br.}
\end{align*}
\]

- Kumar and Coworkers\(^ {195}\) synthesized some 3-(Substituted phenyl)-2-substituted methyl-4-oxo-quinazolines in 1981.

\[
\begin{align*}
\text{R} & = \text{C}_6\text{H}_5\text{CONHCH}_2, \text{C}_6\text{H}_5\text{CH(OH)}, \text{C}_6\text{H}_5\text{CH=CH}_3 \\
\text{R}^1, \text{R}^2 & = \text{H, Br.}
\end{align*}
\]

- Srivastava \textit{et al.}\(^ {196}\) synthesized 2-Methylamino substituted phenyl-3-substituted anilino-4(3H)-quinazolinones and observed the effect of bulky groups at position 2 on antiparkinsonian as well as on behavioural activities.

\[
\begin{align*}
\text{R} & = (\text{CH}_2)_2\text{Ph, CIC}_6\text{H}_4, \text{R}^1=\text{H}
\end{align*}
\]

- A series of 3-(2-Hydroxyethyl)-2-methyl quinazolinones was synthesized by Srivastava \textit{et al.}\(^ {197}\).
Srivastava et al. synthesized 3-[2-Alkyl - 4(3H)-oxo-3-quinazolinyl]-2-aryl-4-thiazolidinones and studied against tremor or rigidity, ptosis, hypokinesia and catatonia.

Enzyme Inhibitory

- Joshi et al. synthesized substituted 2-Methyl-3-(o-dialkylaminopropyl)-4-quinazolones and 2-methyl-3-(morpholino aminopropyl)-4-quinazolones.

- Misra et al. investigated the MAO inhibitory action in 2-Methyl-3(4-hydrazinocarbonyl methylene-oxyphenyl)-4-quinazolones using rat liver homogenate.
• Several substituted styryl quinazolones were synthesized and tested for their ability to inhibit the oxidative deamination of Kynuramine by mono amine oxidase from the rat brain.\textsuperscript{201}

• Sathi \textit{et al.}\textsuperscript{202} investigated the MAO inhibiting activity of substituted quinazolinone series and observed that all quiaxolinones inhibited MAO to a considerable extent.

• 2-Piperidino/morpholino methyl-3-(substituted phenyl)-4(3H)-quinazolinones were synthesized by Bahadur \textit{et al.}\textsuperscript{203}.

• A series of 2-Mercapto acetyl-N-(4-aryl/oxy) phenyl ureido-3-aryl-4(3H)-quinazolinone were synthesized by Singh \textit{et al.}\textsuperscript{204}.
Antiinflammatory Activity

- In 1977, Koizumi and his coworkers\textsuperscript{205} prepared a series of 2, 6-Disubstituted quinazolin-4-ones.

- Five quinazolines with sulfanilamide grouping moiety at N\textsuperscript{3} were synthesized by Shanker et al.\textsuperscript{206}.

- 3-α-(N, N-Disubstituted aminoacetamido)-6,8-dibromo-2-methyl-quinazolin-4-ones which exhibited appreciable degree of anti-inflammatory activity\textsuperscript{207}.
- Quinazolinones, substituted by oxadiazole moiety at N via a methylene group were also found to this type of activity\textsuperscript{208}.

\[
\begin{align*}
\text{R} &= 4\text{-Hydroxy phenyl, 2-chlorophenyl, 4-chloromethoxyphenyl, } R^1, R^2 = H, \text{ Br}
\end{align*}
\]

- Sadanandan \textit{et al.}\textsuperscript{209} synthesized various 3-Substituted phenyl 4(3H)-quinazolinones in 1987.

\[
\begin{align*}
\text{R} &= 3\text{-Cl, 2-OMe, 2-OH} \\
R^1 &= 2\text{-Cl, 2-Me} \\
NR^2 &= \text{Phenylpiperazino, Homopiperidino, Morpholino}
\end{align*}
\]

- In oximidazoline substituted quinazolinones exhibited protection (29.3-56.4\%) against carrageenin-induced mice paw edema\textsuperscript{210}.

\[
\begin{align*}
\text{R} &= \text{Me, } R^1, R^2, R^3 = H, \text{ etc.}
\end{align*}
\]

- Kamal and Sattur in 1988, reported\textsuperscript{211} the synthesis of some 1,5,7-Triubstituted 1,2,4-triazoloquinazolines. These compounds showed both analgesic and anti-inflammatory activities.
• Nigam et al.\textsuperscript{212} in 1991, synthesized some 3-substituted aryl-2,6-disubstituted quinazolines.

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \\
\text{N} \\
\text{R} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{O} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{R}^1 \\
\text{phenyl} \\
\end{array}

• Hitkari et al.\textsuperscript{213} in 1995, synthesized some 6-Substituted-2-alkyl-3-(4-aminobenzene sulphonamide)-quinazolin-4-ones.

\[
\begin{array}{c}
\text{O} \\
\text{R}^1 \\
\text{N} \\
\text{R} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{O} \\
\text{S} \\
\end{array}
\begin{array}{c}
\text{SO}_2\text{NH} \\
\text{Ph} \\
\text{NH}_2 \\
\end{array}

• Saravanan and coworkers\textsuperscript{214} in 1998, prepared some 2,3-Disubstituted 6-bromo quinazolin-4-ones.

\[
\begin{array}{c}
\text{Br} \\
\text{N} \\
\text{R} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{CH}_2 \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{CH}_2\text{COR} \\
\text{O} \\
\end{array}
\begin{array}{c}
\text{CH}_2 \\
\end{array}

• Rity et al.\textsuperscript{215} in 1998, prepared certain analog of 2-Methyl-substituted quinazolin-4-ones.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{CH}_3 \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{R} \\
\end{array}
\begin{array}{c}
\text{phenyl} \\
\end{array}

• Ramasarma et al.\textsuperscript{216} in 1999, prepared a series of 3-(Thiadiazolylamino)-2,6,8-trisubstituted quinazolin-4-ones.

\[
\begin{array}{c}
\text{O} \\
\text{X} \\
\text{N} \\
\text{N} \\
\text{R} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{S} \\
\text{R}^2 \\
\end{array}
\begin{array}{c}
\text{X} \\
\end{array}
\begin{array}{c}
\text{X} \\
\end{array}
\begin{array}{c}
\text{N} \\
\text{N} \\
\end{array}
\begin{array}{c}
\text{R}_1 \\
\end{array}
\begin{array}{c}
\text{R}_2 \\
\end{array}
\begin{array}{c}
\text{R} \\
\end{array}
\end{array}
Cardiovascular Activity

- Agrawal et al.\textsuperscript{217} synthesized the following various quinazolinone derivative and tested their in vivo activity in dogs.

\[
\begin{align*}
\text{R} & = \text{Me}, \text{R}^1 = \text{Et}, \text{R}^2 = \text{I}, \text{R}^4 = \text{H} & \text{R} & = \text{Et, Pr, R}^1, \text{R}^2 = \text{H, Br, I}
\end{align*}
\]

- Sato and Vehida\textsuperscript{218} described sympatholytic activity of 2-Thio-quinazolinones at 15 \(\mu\text{g/kg}\) (i.v.).

- A series of 3-[4-{3-(4-Aryl-1-piperazinyl)-iso-propanoxy}] phenyl]-4(3H)-quinazolinone were synthesized by Botras and Saad\textsuperscript{219}.

\[
\begin{align*}
\text{R} & = \text{H, Me, R}^1 = \text{H, Me}
\end{align*}
\]

- 2-Methyl-3-[imino(substituted phenyl)]-4(3H)-quinazolinone is being reported by Ashok et al.\textsuperscript{220}.

\[
\begin{align*}
\text{R} & = 2,6-\text{Cl}_2, 2,4-\text{Cl}_2, -2\text{F}, -4\text{F}, 2-\text{Cl}
\end{align*}
\]
Anthelmintic activity

- Husain et al.\textsuperscript{221} reported that the presence of quinazolinone nucleus induced anthelmintic activity in the following compounds.

\[
\begin{align*}
\text{R} & = \text{Ph, 4-ClPh, 4-BrPh, \alpha-naphthyl, 2-tolyl, 3-onisyl, H and S-Cl} \\
\text{R'} & = \text{H and Me} \\
\text{R} & = \text{H, 2-Me, 4-Me} \\
\text{R'} & = \text{Ph, 2-ClPh, 4-OHPh, 2-furyl} \\
\text{R} & = \text{H and Me}
\end{align*}
\]

- Tiwari and Mishra\textsuperscript{222} synthesized (Quinazol-4(3H)-one mercapto acetyl urea and mandelyl quinazol-4(3H)-ones) in 1975.

\[
\begin{align*}
\text{R} & = p\text{-chlorophenyl, Phenyl} \\
\text{R'} & = p\text{-anisyl, } p\text{-phenetidyl, } o\text{-tolyl, benzyl etc.}
\end{align*}
\]

- A series of 2-(o-Arylidene amino phenyl)-3-(5-alkyl-1,3,4-thiadiazol-2-yl)-quinazolin-4-ones has been synthesized by Shukla et al.\textsuperscript{223}.

\[
\begin{align*}
\text{R} & = 4\text{-NO}_2, 2\text{-NO}_2, 3\text{-NO}_2, 4\text{-Cl, 3-NO}_2, 2\text{-NO}_2 \\
\text{R'} & = \text{H, CH}_3, \text{C}_2\text{H}_5
\end{align*}
\]

\[
\begin{align*}
\text{R} & = 4\text{-Cl, 3-NO}_2, 2\text{-NO}_2 \\
\text{R'} & = \text{C}_2\text{H}_5, \text{C}_3\text{H}_7
\end{align*}
\]
The following compound synthesized in 1983\textsuperscript{224} showed cestocidal activity. SAR studies showes methyl group at position 2 in 4(3H)-quinazolinone gave optimum activity where as substitution by phenyl group altered the activity. Substitution by piperazine nucleus enhance the activity. Replacement of piperazine by pyrrolidine or morpholine residue made the compound active.

\[
\begin{align*}
\text{a} & \quad R = \text{CH}_3, R_1^1, R_2^1 = \text{H}, \text{Br}, \text{I}, R_3^1 = \text{OMe} \\
\text{b} & \quad R = 3\text{-nitro-4(4\text{-methylpiperazino})phenyl, } R_1^1, R_2^1, R_3^1 = \text{H} \\
\text{c} & \quad R = 3\text{-nitro-4-(pyrrolidino)phenyl, } R_1^1, R_2^1, R_3^1 = \text{H} \\
\text{d} & \quad R = 3\text{-nitro-4-(morpholino)phenyl, } R_1^1, R_2^1, R_3^1 = \text{H}
\end{align*}
\]

Shukla and Srivastava\textsuperscript{225} synthesized a series of 2-Methyl-phenyl-3-aminoacetoxy-6, 8-substituted quinazolinone in 1985.

\[
\begin{align*}
R = \text{piperazino, } R_1^1 = \text{C}_6\text{H}_5, R_2^1, R_3^1 = \text{Br}
\end{align*}
\]

In the same year Shukla and Srivastava\textsuperscript{226} demonstrated that substitution of the 4-(3-Phthalimido, acetamido, and propionamido) phenyl group at position 3 in the quinazolinone nucleus also exhibited the activity.

\[
\begin{align*}
R = \text{C}_6\text{H}_5, R_1^1, R_2^1 = \text{Br} \\
R = \text{CH}_3, R_1^1, R_2^1 = \text{H}
\end{align*}
\]
• Shukla and Rastogi\textsuperscript{227} synthesized some analogs of quinazolinone

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{CH}_2\text{NR}
\end{array}
\]

\[\text{R} = 4(4\text{-chlorophenyl})-1\text{-piperazinyl, piperidino, 4-methyl-1-piperazinyl etc.}\]

• 2-Methyl-3-(substituted) amino-4-quinazolinones were synthesized by Gupta et al.\textsuperscript{228}.

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{OCH}_2\text{NHNNH} \\
\text{Ph}
\end{array}
\]

\[\text{R, } \text{R'}=\text{H, Br}\]

• Several 3-[4-[3-(2,3,4-Substituted) phenyl-1-oxo(2,3-substituted propane)] phenyl]-2-phenyl/methyl 6,8-substituted-4(3H) quinazolinones were synthesized to evaluate their cestocidal activity \textit{in vivo} against \textit{H.nana} infection in rats\textsuperscript{229}.

\[
\begin{array}{c}
\text{N} \\
\text{Ph} \\
\text{C} \\
\text{CH} \\
\text{CH} \\
\text{C} \\
\text{Br} \\
\text{Br} \\
\text{Ph}
\end{array}
\]

\[\text{R}^1=\text{H, } \text{R}^2=\text{OH}\]

• Compound with a (Benzylidene amino) phenyl group at position 3 were also synthesized by Shukla et al.\textsuperscript{230}

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{N} \\
\text{CH} \\
\text{N} \\
\text{C} \\
\text{R}
\end{array}
\]

\[\text{R} = 3\text{-NO}_2, \text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2=\text{H, R}^3 = \text{I}\]

\[\text{R} = 2\text{-OH, R}^1 = \text{C}_6\text{H}_5, \text{R}^2, \text{R}^3 = \text{Br}\]

\[\text{R} = 3\text{-NO}_2, \text{R}^1 = \text{C}_6\text{H}_5, \text{R}^2=\text{H, R}^3 = \text{I}\]

\[\text{R} = 2\text{-OH, R}^1 = \text{C}_6\text{H}_5, \text{R}^2, \text{R}^3 = \text{Br}\]
- 2-Methyl/phenyl-3-(4-substituted phenyl imino-4-oxothiazolidine-3-yl phenyl)-6, 8-disubstituted (3H)-quinazolin-4-ones have been synthesized by Srivastava et al.\textsuperscript{231} and evaluate for their anthelmintic activity.

\textbf{Antihypertensive activity}

- Kotto and coworkers\textsuperscript{232} in 1965 prepared a series of 2-Substituted amino-5,6,7,8-substituted quinazolin-4-ones with the aim of producing highly active compound. These compounds exhibited antihypertensive activity by inhibiting the angiotensin converting enzyme.

- In 1986, Cheen and Ming\textsuperscript{233} synthesized some 1,3,4- Triazole quinazolin- 4-ones speculating antihypertensive properties. The compound 2,9-dimethyl -1,3,4-triazoloquinazolin- 4(3H)-one was found to be the most active antihypertensive agent in the series.

\textbf{Antifertility Activity}

- Shukla and Saxena\textsuperscript{234} synthesized some substituted quinazolinone-4-ones in 1979.

\textit{Department of Pharmaceutical Sciences, Dr. H. S. Gour Vishwavidyalaya, Sagar (M.P.)}
Bronchodilators

- 6-Alkylbenzimidazo [1,2-C]- quinazolinone as bronchodilators have been reported from the same laboratory in 2000\textsuperscript{235}.
RESEARCH ENVISAGED AND PLAN OF WORK

4(3H)-quinazolinone and its derivatives have been reported to exhibits anticonvulsant, antimicrobial, sedative, tranquilizer, analgesic, anesthetic, anticancer, antihypertensive, anti-inflammatory, diuretic and muscle relaxant properties\(^{236-239}\). 2-methyl-3-\(\alpha\)-toly-4(3H)-quinazolinone (Methaqualone) is the most frequently prescribed quinazolinones derivative as a safe sedative-hypnotic and anticonvulsant drug\(^{240,241}\).

![Methaqualone structure](image)

In spite of the fact that literally thousands of quinazolinone related to methaqualone have been synthesized and tested for CNS depressant and anticonvulsant activity, none of the anticonvulsant drug currently in use contains the 4(3H)-quinazolinone ring system because a persistent problem with such molecules arises from the fact that, to date, nearly every derivative tested in combined neurotoxicity and anticonvulsant screening has exhibited neurotoxic value (TD\(_{50}\)) that are less than, or only slightly higher than ED\(_{50}\) observed in typical anticonvulsant test i.e. protection against maximal electro shock (MES) induced seizures. Consequently, the protective index (PI), corresponding to the value TD\(_{50}/\) ED\(_{50}\), is too low to provide sufficient differential between dosage effecting CNS depression and those leading to protection against seizures. Our attention was drawn to an earlier discovery\(^{242,243}\) that \(-\text{CH}_3\) is not necessary for the activity and that substitution of R \((-\text{CH}_3\) at 2\(^{\text{nd}}\) position indeed exhibits protection against MES induced seizures. Thus, it appears to us that considerable scope is there for synthesizing novel molecules which may have anticovvulsant activity. In this line we thought of introducing \(-\text{CH}=$CH-Ar in place of \(-\text{CH}_3\) at 2\(^{\text{nd}}\) position of 4(3H)-quinazolinone.

![Diagram](image)

**Target for CNS depressant**

**Target for anticonvulsant and antimicrobial activity**

---

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The work was planned on the following lines.

1. Detailed review of literature of various series of 4(3H)-quinazolinone in the area of anticonvulsant and CNS neurotoxicity and antimicrobial activity.

2. Synthesis of title compounds comprises of following two steps:
   I. Synthesis of 2-amino-5-aryl 1,3,4-thiadiazoles
   II. Synthesis of title compounds using these 1,3,4-thiadiazoles

3. Characterization and purification of the molecules.
   I. Recrystalisation of the prepared compounds
   II. Determination of melting point
   III. Thin Layer Chromatography
   IV. Elemental analysis (Nitrogen and Sulphur)
   V. Infrared Spectroscopy: To ascertain the presence of characteristic functional groups
   VI. Nuclear Magnetic Resonance spectroscopy
   VII. Mass spectroscopy: To determine molecular weight

4. Pharmacological testing of the synthesized molecules for following biological activity.
   I. Anticonvulsant activity in maximal electroshock (MES) and subcutaneous pentyleneetrazole (scPTZ) screens.
   II. Neurotoxicity Screening

5. QSAR analysis of the synthesized compounds with relation to its biological activity:
   I. Calculation of various parameters like electronic, spatial, and thermodynamic etc. using QSAR standard software
   II. Multiparameter (MLR) analysis using standard software like SYSTAT or other statistical softwares.
   III. Selection of appropriate QSAR equation.