Fused pyrimidines, generally known as quinazolines (and their derivatives) have attracted considerable attention because of their great practical importance and biological activities, due to which their chemistry is fundamentally interesting to heterocyclic chemists. Their derivatives are of considerable interest because of their pharmacological properties\(^1\) such as protein tyrosine kinase inhibitor\(^2\), cholecystokinin inhibitor etc.

5.1 Preparation and properties of a few such molecules are described in the following sections.

5.1.1 Melvin J. Yu and coworkers have reported\(^3\) that compound exemplified by 2-[2-(5-bromo-1\textsubscript{H}-indolyl-3-yl)ethyl]-3-[3-(1-methylethoxy)phenyl]-4(3\textsubscript{H})-quinazolinone (2) (Scheme 1) represented a structurally novel series of non-peptide cholecystokinin B receptor ligands (CCK-B). It is postulated that CCK-B is involved in a variety of neurological disorders such as anxiety, pain and panic disorder.

![Scheme 1](image)
A series of analogues were prepared with methyl substituents on the ethylene bridge as well as congeners with different linkers (1). It was found that for derivatives with one to three methylene units separating the indole and quinazoline rings, maximal receptor binding activity was found when the distance separating the two-heteroaromatic system was defined by an ethyl group (2).

Further Janak K Padia and coworkers, found that introduction of -NH- as a linker (3) dramatically enhanced binding affinity and selectivity for CCK-B receptors⁴. Quinazolines are also known to possess antimicrobial⁵, anticonvulsant⁶, sedative and hypertensive activity. Shin Hayao and co-workers have synthesized a series of 3-(4-aryl-1-piperazinylalkyl)-2,4(1H, 3H)-quinazolinedione, which were subsequently tested, and they showed varying degrees of sedative and hypotensive activity.

The above compound 3-[3-(4-\textit{m}-chlorophenyl-1-piperazinyl) propyl]-2,4(1H,3H)-quinazolinedione (4) of the afore-mentioned series was found to be a potential
psychosedative and its activity in experimental animals was comparable to that of chlorpromazine.²

5.1.3 Herbert J Havera synthesized⁸ a series of 1,3-disubstituted-2,4(1H, 3H)-quinazolininediones from 3-substituted 2,4(1H, 3H)-quinazolininediones by treatment with sodium hydride and the appropriate alkyl halide in xylene. These compounds showed varying degrees of vasodilation and antihypertensive activity without significant blockade of α-adrenergic receptors.

5.1.4 There have also been reports of quinazoline showing antidepressant and anti-inflammatory activities. J. A. Lowe and coworkers studied⁹ the structure-activity relationship of a series of quinazolininediones and azaquinazolininediones of the type ⁶ and ⁷, which were found to possess potent inhibitory activity towards the calcium-independent phosphodiesterase enzyme (CaIPDE) thus proving to be useful in chronic diseases such as depression and inflammation.

![Chemical Structure](image)

1-[3-(N,N-dimethylamino)propyl]-3-[3-(4-phenyl-1-piperazinyl)propyl]-2,4(1H,3H)-quinazolininedione (5) of the above series was found to be more potent than papaverine in inducing vasodilation and induced a prolonged decrease in systolic blood pressure of hypertensive rats upon oral administration.
5.1.5 Quinazolines are also known to possess antiallergic activity. Ronald A. LeMahieu and coworkers prepared a series of substituted \((E)\)-3-(4-oxo-4'H-quinazoline-3-yl)-2-propenoic acid and evaluated for passive cutaneous anaphylaxis (PCA) test in rats for antiallergic activity. Alkoxy, alkylthio and isopropyl substituents at the 6 or 8 positions provided highly potent compounds. Of the above series that exhibited oral activity in the PCA test, \((E)\)-3-[6-(methylthio)-4-oxo-4'H-quinazoline-3-yl]-2-propenoic acid (8) was found to be the most potent. It was further observed that conversion to the Z-isomer, reduction of the side chain double bond, or reduction of the quinazoline ring resulted in substantial loss of activity.

5.1.6 More than 40 alkaloids comprising of a 4(3H) quinazoline moiety were isolated from natural sources. For example, D. L. Dreyer and coworkers have reported the isolation of two simple natural alkaloids, 1-methyl-3-(2'-phenylethyl)-
1H,3H-quinazoline-2,4-dione (9) and 1-methyl-3-[2'-(4'-methoxyphenyl)ethyl]-1H,3H-quinazoline-2,4-dione (10) from the seed husk of Zanthoxylum arborescens.

5.1.7 Atsushi Numata and coworkers have found\textsuperscript{12} that a strain of Aspergillus Fumigatus isolated from the gastrointestinal tract of the saltwater fish Pseudolabrus Japonicus, produces the novel metabolites fumiquinazolines (general structure 11 and 12) which exhibit moderate cytotoxicity against the cultured P-388 Lymphocytic Leukemia cells. Later Numata and coworkers could isolate\textsuperscript{13} seven fumiquinazolines from the same strain showing similar toxicity.
5.1.8 Quinazolines are also reported to possess antimalarial activity. F. H. S. Curd and coworkers while working on chlorguanide discovered\textsuperscript{14} that certain $N^4$-[(dialkylamino) alkyl]-$N^2$-phenyl-2,4-quinazolinediamines possessed strong antimalarial effects against \textit{plasmodium galencium} in chicks. Among them $N^2$-(4-chlorophenyl)-$N^4$-[2-(diethylamino) ethyl]-2,4-quinazolinediamine (14) was found to be most promising.

5.1.9 Edward F. Elsalger and coworkers synthesized\textsuperscript{15} a series of $N^2$ (and $N^4$)-aryl-$N^4$(and $N^3$)-[(dialkylamino) alkyl]-2,4-quinazolinediamines. Condensation of
appropriate 2,4-dichloroquinazolines (15) (prepared by chlorination of corresponding 2,4-(1H, 2H)-quinazolinediones with POCl$_3$ or PCl$_3$) with the requisite $N, N$-dialkylalkylenediamine in appropriate solvents. (under this condition only the chlorine in position-4 is replaced) gave the corresponding 2-chloro-$N$-[(dialkylamino)alkyl]-4-quinazolinamines (16) which were condensed with appropriate arylamine in alcohol (in presence or absence of HCl ) to yield the desired $N^4$-[(dialkylamino)alkyl]-$N^2$-phenyl-and heterocyclic 2,4 quinazolinediamines (17) (Scheme 2).

Scheme 2
All these compounds were tested against a normal drug sensitive strain of *P. berghei* in mice by parental route. Many compounds showed good results of which *N*-^2-(3,4-dichlorophenyl)-N-^4-(1-ethyl-3-piperidinyl) 2,4-quinazolinediamine (18) was selected for preclinical toxicity studies.

![Chemical Structure](image)

Unfortunately, the above compound and several of its derivatives were shown to be phototoxic and plans to study it in humans were abandoned. Quinazolines are also known to possess antifungicide and diuretic properties\(^{16}\).

### 5.2 METHODS OF PREPARATION OF QUINAZOLINES

A number of methods have been described for the preparation of quinazolines and their derivatives. The main synthetic routes to such compounds utilize 2-aminobenzoic acid or its derivatives (19).

#### 5.2.1 Iraj Lalezari and C.A. Stein have reported\(^{17}\) a simple one step synthesis of 3-amino-2,4(1*H*,3*H*)-quinazolinediones and its derivatives (21) by the reaction of anthranilic acids (19) and t-butyl carbazates (20) in refluxing quinoline (**Scheme 3**). The compounds so formed were successfully deaminated by nitrous acid to afford the corresponding quinazolinediones (22).
5.2.2 M. J. Komet and co-workers have reported\(^\text{18}\) the synthesis of a number of 3-amino-2,4(1\(H,3\(H\))-quinazolininediones by two different methods depending on the availability of starting materials. In method A, \(o\)-aminobenzoylhydrazines (23) was reacted with ethylchloroformate in dry pyridine, which gave 26 in moderate yields. The intermediate 23 were obtained from the reaction of isatoic anhydride and hydrazines. In method B, compounds 26 \((R_1=H)\) were synthesized from 2-methoxycarbonylphenyl isocyanate (24) and 1,1-disubstituted hydrazines (25) in toluene. Both methods were monitored by TLC and indicated the formation of uncharacterized intermediate which lead to the cyclized products (Scheme 4).

5.2.3a Papadopoulos reported\(^\text{19}\) a simple room temperature treatment of 2-(3-arylureido) benzoic acid (27) and methyl 2-(3-alkyl, or 3-arylureido)-benzoates (28)
with aqueous-ethanolic sodium hydroxide to yield 3-substituted 2,4-(1H,3H)-quinazolinediones (29) (Scheme 5).

Scheme 4

Scheme 5
5.2.3b Papadopoulos later reported the reaction of three derivatives of isothiocyanate. They were (1) Ethyl-\(N\)-(2-methoxycarbonylphenyl)thiocarbamate (30), (Scheme 6). (2) \(N\)-(2-ethoxycarbonylphenyl)-4-methoxythiobenzamide (31), (Scheme 7) and (3) 2-(4-methoxyphenyl)-4\(H\)-3,1-benzothiazin-4-one (32) (Scheme 8). These three compounds are expected to react with nucleophilic reagents containing a primary amino group at both carbonyl and thiocarbonyl to form 2,4-disubstituted-4(3\(H\))-quinazolinones as shown below.

1) 

\[
\begin{align*}
&\text{Scheme 6} \\
33 & \xleftrightarrow{C_6H_5CH_2NH_2} \text{Ethanol} \\
30 & \xrightarrow{NH_3} \text{C}_2\text{H}_5\text{OH} \\
34 &
\end{align*}
\]

Similarly 2) 

\[
\begin{align*}
&\text{Scheme 7} \\
31 & \xrightarrow{RNH_2, \text{Ethanol}} \text{C}_2\text{H}_5\text{OH} \\
35 & \text{R} = \text{H, n-Bu, CH}_2\text{Ph, etc}
\end{align*}
\]

When benzothiozinone (32) was heated with ethanolic ammonia at 100\(^\circ\)C or refluxed with benzyl amine compound 36 and 37 were obtained. Similarly when it was heated with n-butylamine on a steam bath, compound 38 was obtained. The
formation of quinazolinones (37 and 38) by the following reactions very likely involves the intermediate formation of thioamides.
5.2.4 E. Melendez and coworkers have also reported the synthesis of 3-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines (42) from N-aryldithiocarbamates (40) and anthranilic acid (39) by refluxing in DMF. The crude product was isolated by precipitation of the mixture in water (Scheme 9).

\[
\begin{align*}
\text{R}_1 &= \text{R}_3 = \text{H}, \text{Cl} \\
\text{R}_2 &= \text{H}, \text{Cl}, \text{NO}_2 \\
\text{Ar} &= \text{Phenyl, Subst Phenyl}
\end{align*}
\]

Scheme 9

5.2.3c Papadopoulos reported a two step synthesis of 2,6-dihydroimidazo[1,2-c]-quinazoline-5-(3\(H\))one (48) by the reaction of anthranilonitrile (43) with 2-chloroethyl isocyanate. This reaction proceeded by the formation of an intermediate 2-[3-(2-chloroethyl)ureido]-benzonitrile (44) which upon heating or treatment with a base undergoes a double cyclization to form 2,6-dihydroimidazo[1,2-c]quinazoline-5-(3\(H\))one (48) (Scheme 10).

Later he further reported the synthesis of imidazo[1,2-c]quinazoline-2,5-(3\(H,6H\)) dione (46) by the reaction of anthranilonitrile with ethylisocyanoacetate. The reaction proceeded in the similar manner via the formation of 2-(3-ethoxycarbonylmethylureido) benzonitrile (44), which undergo double cyclization to form imidazo compound 46 (Scheme 10).
5.2.5 Minami and coworkers reported\textsuperscript{24} the synthesis of quinazolines from isatoic anhydride as per the scheme below (Scheme 11). The reaction of isatoic anhydride (49) with an ethyl-2-diethylphosphonopropanoate carbanion (50) in refluxing benzene gave 3-ethoxycarbonyl-3-methyl-2,4(1H,3H)-quinolinedione (51) in poor yield. However similar treatment of N-sodioisatoic anhydride (52) (prepared in situ from 49 and sodium hydride) in a mixed solvent gave 51 in good yields\textsuperscript{24}.

There are also reports of quinazoline being prepared from 2-carbomethoxy phenyl isocyanate\textsuperscript{25}, N-aryl nitritium salts\textsuperscript{26}, and (4H)-3,1-benzoxazinones\textsuperscript{27}. Recently, the solid phase synthesis of 2,4-(1H, 3H)-quinazolinediones has been reported\textsuperscript{28}. The
direct ortho substitution of \( N -(\text{tert- butoxy carbonyl}) \) aniline by a lithium reagent was also described.

\[
\begin{align*}
\text{O} & \quad \text{COOC}_2\text{H}_5 \\
\text{C}_2\text{H}_5\text{OOHC} & \quad \text{R} \quad \text{OOC}_2\text{H}_5 \\
\text{H}_3\text{C} & \quad \text{OC}_2\text{H}_5 \\
\text{Na} &
\end{align*}
\]

\( \text{Benzene} \)

\[
\begin{align*}
\text{O} & \quad \text{COOC}_2\text{H}_5 \\
\text{C}_2\text{H}_5\text{OOHC} & \quad \text{R} \quad \text{OOC}_2\text{H}_5 \\
\text{H}_3\text{C} & \quad \text{OC}_2\text{H}_5 \\
\text{Na} &
\end{align*}
\]

\( R = \text{CH}_3 \)

\( \text{H}^{\oplus} \)

Scheme 11

5.2.6 There are also reports of the use of transition metals in the preparation of these compounds. Akazone et al. reported the first Ruthenium catalysed synthesis of \( 4(3H)\)-quinazoline derivatives (54) by the reductive N-Heterocyclization of \( N -(2-\)
nitro benzoyl)amides (53) under carbonmonoxide pressure (Scheme 12). It was also reported that a combination of PdCl₂ (PPh₃)₂ and SnCl₂ was used for the intermolecular reductive N-heterocyclization of 2-nitrobenzamide to give the corresponding quinazolines³⁰.

![Scheme 12](image)

5.2.7 Encouraged by the usefulness of 4(3H)-quinazoline derivatines, Larksarp and coworker examined¹¹ the utility of palladium catalysts for the preparation of benzo[e]-1,3-oxazin-4-one derivatives from o-iodophenols with heterocumulenes and carbon monoxide they explored the preparation of the title compounds by palladium catalysed cyclocarbonylation reactions of o-iodoanilines (55) with heterocumulenes. They reported the synthesis of 4(3H)-quinazolinone derivatives (58) by treatment of o-iodoanilines with heterocumulenes such as isocyanates (57), carbodiimides and ketenimines in the presence of a palladium catalyst under carbon monoxide pressure (Scheme 13).
5.2.8 E.C. Taylor and coworkers while working\textsuperscript{32} on the development of synthetic strategies for the preparation of 5,10-dideazatetrahydrofolic acid (DDATHF, 59) and its analogues, developed a facile pyrimidine annulation process, which took place under mild conditions and was found to be general for \( o \)-aminonitriles and \( o \)-aminoesters.

Treatment of \( o \)-aminoesters and \( o \)-aminonitriles 60 with dibromotriphenylphosphorane (generated \textit{in situ} by slow addition of bromine to a cold solution of triphenyl phosphine in methylene chloride) resulted in the formation of the corresponding iminophosphoranes 61. The iminophosphoranes undergo aza
Wittig reactions with isocyanates to give carbodiimides 62. In case of iminophosphoranes derived from o-aminoesters, Wamhoff and co-workers found that the initially formed carbodiimides underwent a pericyclic rearrangement in alcoholic solvents to give 2-alkoxy fused pyrimidines. It was envisaged that this rearrangement was probably the consequence of the severe reaction conditions (80°C, 4-8hrs) employed for the carbodiimide synthesis, and the latter intermediate might be isolable under milder conditions. Thus the aza-Wittig reactions of imino phosphoranes with phenyl isocyanate were carried out at room temperature, which permitted isolation of the corresponding carbodiimides in good yields. Addition of ammonia to the resulting highly reactive carbodiimides 62 generated guanidino-substituted intermediates 63, which underwent intramolecular cyclization across the ortho-situated electrophilic nitrile or ester functionalities to give the fused pyrimidines 64 and 65 (Scheme 14). In some cases heating was required for cyclization as shown in Scheme 15.
Scheme 14
Scheme 15

5.2.9 In 2003 Selma Sarac and coworkers synthesized a series of 4-aryl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5 diones (84) and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5 diones (84) according to the Biginelli
reaction. This involved one-pot condensation of urea 81 (or N-methyl urea), aromatic aldehyde 82 and 5,5-dimethyl-1,3-cyclohexanedione (83) under strongly acidic conditions (Scheme 16).

These compounds were further tested for their calcium antagonist activity. The in vitro tests were carried out on isolated rat ileum and lamb carotid artery. 4-(3-chlorophenyl)-1,7,7-trimethyl-3,4,7,8-tetrahydroquinazoline-2,5 (1H, 6H)-dione (85) and 4-(3-bromophenyl)-1,7,7-trimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (86) (Scheme 16a) were found to be the most active derivatives on isolated rat ileum compared to standard nicardipine. On isolated aortic strip of lamb the calcium antagonist activity of compound 85 was found to be as high as that of nicardipine (which was used as reference).

![Scheme 16](image-url)
5.3 However, synthesis of 5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines is least attended to and to the best of our knowledge bis-(5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines) are unknown, hence their biological properties remain unexplored. Prompted by the above findings we have recently reported a facile synthetic methodology for 1-alkyl/aryl-3-alkyl/aralkyl/aryl-5-oxo1,2,3,4,5,6,7,8-octahydroquinazolines and 1-aralkyl/aryl-3-alkyl/aralkyl/aryl-5-oxo1,2,3,4,5,6,7,8-octahydroquinazolines. In continuation with our efforts on the synthesis of tetrahydropyrimidines we decided to develop a facile one-pot strategy for bis-1,2,3,4,7,8-hexahydroquinazolines-5(6H)-ones in which the two quinazolines are linked through flexible aliphatic chains or through rigid aromatic aromatic rings.

For the synthesis of our required quinazolines we required compounds of the type 87.
5.4 METHODS OF PREPARATION OF ENAMINONES

Literature survey at this stage revealed that Enaminones (87) have been prepared by many methods and have also been used as synths for the synthesis of other heterocyclic compounds. A few of these methods and their uses are described in the following sections.

5.4.1 Ivo Jirkovsky reported the synthesis of a series of \( N \)-substituted 3-amino-2-cyclohexen-1-ones and 3-amino-5,5-dimethyl-2-cyclohexen-1-ones (89-97) by the reaction of dimedone (83) or 1,3 cyclohexanedione (88) with various primary amines in dry benzene by azeotropic removal of water using Dean Stark apparatus (Scheme 17). The secondary amines prepared from cyclic dione (Scheme 17) reacted with phenyl isocyanates, phenylisothiocyanates and methylisothiocyanate under fusion condition to yield substituted 2-amino-6-oxo-\( N \)-phenyl-1-cyclohexene-1-carboxamide (98) and corresponding thiocarboxamides (99) (Scheme 18).
Scheme 17
Scheme 18

A large number of compounds (100-113) have been prepared as shown in (Scheme 18a). These reactions did not proceed in boiling tetrahydrofuran, benzene, toluene or xylene. These reactions were carried out without solvent at 115-145°C, the reactions were rapid, clean, quantitative and the products were cis vinylogous ureas cross-conjugated with the original trans-enaminoketone.
Scheme 18a
Reaction of 3-benzylamino-5,5-dimethyl-2-cyclohexen-1-one (97) with hydrazine hydrate in boiling ethanol gave a yellowish crystalline compound, which could have the two possible structures 114 and 115 (Scheme 19).

Scheme 19

Of the above two structures, 114 with one endocyclic double bond in the six-membered ring is favoured by the strain theory.

5.4.2 Kase and coworkers reported that (5,5-dimethyl-3-[(o-chlorophenyl)amino]-2-(N-piperidinylmethyl)-cyclohex-2-en-1-one (116) and (5,5-dimethyl-3-[(m-methoxyphenyl)amino]-2-(N-methyl-N-phenethylaminomethyl)-cyclohex-2-en-1-one (117) possessed analgesic, papaverine-like and anticonvulsant actions.
5.4.3 K. R. Scott and his group have reported\textsuperscript{42,43} the synthesis of a new series of novel enaminones having a general formula 118, from cyclic $\beta$-dicarbonyl precursors by condensing them with morpholine, pyrrolidine, phenethylamine, hydrazine, substituted benzylamines and substituted anilines. These compounds were subsequently evaluated for anticonvulsant activity in a variety of anticonvulsant models by the National Institute of Neurological and Communicative Disorders and Stroke. Several of these compounds exhibited potent anticonvulsant activity with remarkable lack of neurotoxicity. The most active analogues was methyl 4-[(p-chlorophenyl) amino]-6-methyl-2-oxo-cyclohex-3-en-1-oate (119).

The cyclic enaminone esters 119 were synthesised from $\beta$-hydroxy keto esters 120, which were in turn synthesised by Michael addition of a vinyl ketone to a malonic ester, followed by a ring closing claisen condensation (method A), or by a base-catalysed condensation of a crotonate ester 123 and acetoacetate 124 (method B) (Scheme 20). The $\beta$-hydroxy keto esters (120) were refluxed with 1 equivalent of the appropriate amino compound, under various conditions to provide the desired product 125. In most cases the reaction proceeded effectively in the presence of toluene. In case of hydrazines and anilines a much lower temperature was employed,
most probably due to lower pKₐ of aniline (4.63 for aniline) derivatives compared to benzylamine analogues (9.33 for benzylamine).

![Chemical Structure]

5.4.4 J. V. Greenhill and co-workers have prepared enaminones (126) from dimeredone (83) by reacting it with ammonia or methylamine (Scheme 21). Under suitable, mild conditions the enaminones 126 reacted with formaldehyde to give the respective methylene bis-enaminone derivative 127. The enaminones are readily hydrolysed back to dimeredone in dilute mineral acid, but when methylene bis...
enaminone derivative was attempted to hydrolyse in the same way, acid insoluble, fluorescent compounds were formed which were identified as acridine derivatives.

![Chemical Structures](image.png)

**Scheme 21**

Treatment of the enaminones or the methylene bisenaminones with aqueous formaldehyde in dilute hydrochloric acid at room temperature gave good yields of unexpected spiro compound (130). The spiro compounds might reasonably arise...
from an internal mannieh reaction of the methylenebisaminones to give the unstable structures (129), which would readily hydrolyse to the diketones (130).

5.4.5 Marcel Azarro and coworkers have also synthesized\textsuperscript{46} enaminones with low boiling amines such as methylamine, ethylamine, isopropylamine, and n-butyl amine. They used a synthetic route via a Lewis acid/amine complex, which used boron trifluoride diethyletherate instead of titanium tetrachloride due to easier handling.

To freshly distilled boron trifluoride ethyl etherate in benzene the appropriate amine (132) (from pressure bottles in case of gaseous amines) was added. To this was added a solution of dimedone in benzene and refluxed for 4-6 hrs whereby the expected product (133) was obtained in good yield. The use of Lewis acid brought in three advantages, for example the complexation of low boiling amines, the acid catalysis of the reaction and the equilibrium shifts towards the enaminone formation by the complexation of the water formed. If excess of BF\textsubscript{3} etherate is used then it leads to the mixture of enaminone and the vinylogous esters (131b) (Scheme 22).

\[ \text{BF}_3 \text{Etherate} \]

\[ \begin{align*} 
131 & \quad \text{NH} \\
132 & \quad \text{Refux} \\
133 & \quad \text{R}_1, \text{R}_2 \\
& \text{X= OH} \\
& \text{b X= OCH}_3, \text{OC}_2 \text{H}_5 \\
& \text{c X= Cl,Br} \\
& \text{R}_1, \text{R}_2 = \text{H, alkyl, aryl} \\
\end{align*} \]

Scheme 22

However, all the above methods used for the synthesis of enaminones have some specific disadvantages. Some involve thermal conditions, longer reaction times,
reagents in gaseous form (from pressure bottles) especially in case of low boiling amines, toxic solvents (like benzene) and dry conditions (azeotropic removal of water).

5.4.6 The growing interest in microwave-assisted reactions\textsuperscript{47-50} prompted us to take up the synthesis of enaminones (87) by the condensation of 1,3-diketones (83,88) with appropriate primary amines under microwave irradiation and the results of our investigation are reported herein (Scheme 23).

\[ \text{Scheme 23} \]

\begin{align*}
\text{R}^\prime &= \text{H, CH}_3 \\
\text{R} &= \text{C}_6\text{H}_5, \text{4-ClC}_6\text{H}_5, \text{CH}_3, \text{C}_6\text{H}_5\text{NH}_2
\end{align*}

5.5 Results and Discussions

Thus, when a mixture of 1,3-cyclohexanedione (88) and aniline (1:1) was irradiated in a domestic microwave oven for 2 min, work-up of the reaction mixture yielded the desired condensation product 87a in 93% yield (Table I), which was characterized as 3- anilinocyclohex-2-en-1-one on the basis of analytical and spectral data. Condensation of 4-chloroaniline and benzyl amine with cyclohexanedione proceeded in a similar manner and the corresponding enaminones 87b and 87d were obtained in 88 and 98% yields, respectively. Synthesis of 87c involved treatment of the ketone with two equivalents of methylamine (40% aqueous solution).
Condensation of dimedone with primary amines could be achieved under similar conditions giving 87e-h in 93-98% overall yields. The reaction of dimedone with methylamine went to completion when a mixture (1:3) of the two was subjected to microwave irradiation.

In conclusion, we have demonstrated a practical application of microwave assisted, solvent-free condensation of cyclic ketones with primary amines in domestic microwave oven in very good to excellent yields.

These enamimones 87 were further used as synthons for the construction of fused tetrahydropyrimidine (quinazoline) rings as shown in Scheme 24.
Table I—Synthesis of cyclic enaminones

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R₁</th>
<th>Yield (%)</th>
<th>Time (sec)/Power (watt)</th>
<th>M.p.°C (lit. m.p.) (solvent of cryst.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>87a</td>
<td>H</td>
<td>C₆H₅</td>
<td>93</td>
<td>60/300</td>
<td>173-74 (176-78&lt;sup&gt;51&lt;/sup&gt;) (MeOH)</td>
</tr>
<tr>
<td>87b</td>
<td>H</td>
<td>4-ClC₆H₄</td>
<td>88</td>
<td>270/180</td>
<td>190-91 (190-91.5&lt;sup&gt;43&lt;/sup&gt;) (Hexane-EtOAc)</td>
</tr>
<tr>
<td>87c</td>
<td>H</td>
<td>Me</td>
<td>83</td>
<td>15/100</td>
<td>68-69 (67-67.5&lt;sup&gt;52&lt;/sup&gt;) (Hexane-Benzene)</td>
</tr>
<tr>
<td>87d</td>
<td>H</td>
<td>C₆H₅CH₂</td>
<td>98</td>
<td>60/300</td>
<td>125-26 (125-27&lt;sup&gt;43&lt;/sup&gt;) (EtOAc)</td>
</tr>
<tr>
<td>87e</td>
<td>Me</td>
<td>C₆H₅</td>
<td>94</td>
<td>90/300</td>
<td>183-84 (181-83&lt;sup&gt;42&lt;/sup&gt;) (Hexane-Benzene)</td>
</tr>
<tr>
<td>87f</td>
<td>Me</td>
<td>4-ClC₆H₄</td>
<td>93</td>
<td>780/300</td>
<td>206-08 (208-10&lt;sup&gt;43&lt;/sup&gt;) (EtOAc)</td>
</tr>
<tr>
<td>87g</td>
<td>Me</td>
<td>Me</td>
<td>98</td>
<td>270/180</td>
<td>152-53 (153-54&lt;sup&gt;46&lt;/sup&gt;) (Hexane-EtOAc)</td>
</tr>
<tr>
<td>87h</td>
<td>Me</td>
<td>C₆H₅CH₂</td>
<td>98</td>
<td>120/300</td>
<td>131-32 (130-31&lt;sup&gt;10&lt;/sup&gt;) (Hexane-EtOAc)</td>
</tr>
</tbody>
</table>
Thus when enaminones 87 were reacted with formaldehyde and primary amines in methanol, it lead to the formation of hitherto unknown 1,3-substituted-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines and 1,3-substituted-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines (134).

Our literature survey revealed that bis-heterocyclic compounds are a relatively new and important in the field of research for finding new biologically active molecules. Recent reports have revealed that bis heterocyclic compounds possess pesticidal properties\(^{53-55}\) and also antibacterial\(^{56}\), antimalarial, antiproliferative and antitumor activities\(^{57}\). Envisaging that the presence of two-quinazoline ring in the same molecule connected by flexible aliphatic chain or rigid aromatic chain could enhance the activity of the parent molecule, these enaminones were reacted with formaldehyde and various diamines and the result of which are discussed herein (Scheme 25).

---

**Scheme 24**
5.6 Results and Discussions.

Thus, when a mixture of 3-anilinocyclohex-2-en-1-one (87a) (Scheme 25), ethylenediamine and formaldehyde (2:1:4) in methanol was refluxed, work-up of the reaction mixture followed by chromatographic purification yielded a solid in 58% yields, which was characterized as 3,3'-(ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one (135a). The reaction was found to be general with other diamines and with corresponding 87a-b to give the respective 135b-h in 58-88% overall yields. The structures of the bis-quinazolines were assigned on the basis of spectral and analytical data. Thus, the infrared spectra of 135a-k showed strong peaks in the range of 1427 to 1619 cm\(^{-1}\) due to highly delocalized double bonds and carbonyl group stretching frequencies of enamino functionalities. In the \(^1\)H NMR spectra of 135a & 135e the NCH\(_2\) protons of ethylene chain appeared as singlets at 2.83 ppm and 2.93 ppm respectively whereas the NCH\(_2\) protons of propylene chain in 135b & 135f gave triplets in the range of 2.60-2.72 ppm. The protons at C\(_2\) of propylene chain gave multiplets in the range of 1.59-1.88 ppm. Likewise in 135c & 135g the protons at C\(_1\) & C\(_2\) of butylene chains gave multiplets in the range of 2.56-2.90 and 1.46-1.88 ppm respectively. The protons at C\(_2\) and C\(_4\) of quinazoline ring resonated in the range of 4.24-4.99 and 3.64-4.56 ppm respectively. In 135a-d the C\(_8\) protons of the parent ring appeared as triplets between 2.10 & 2.30 ppm but in 135e-
h they appeared as singlets between 1.99 & 2.10 ppm. The C₆ protons of the parent ring in 135a-d appeared as triplets between 2.31 & 2.60 ppm but in 135e-h they appeared as singlets between 2.13 & 2.26 ppm. The C₇ protons of the ring in 135a-d resonated giving multiplets in the range of 1.58-2.06 ppm. The two-methyl protons at C₇ in 135e-h gave singlets between 0.90 & 1.03 ppm. The aromatic protons resonated in their usual range of 6.91-7.93 ppm. A plausible mechanism for the formation of 2 from the cyclic enaminoles 1 is worked out (Scheme 26). The ¹H NMR and ¹³C NMR Spectra of 3,3’-(butane-1,4-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135c are shown in pages 203-204.
Table. Synthesis of Bisquinazolinones 135a-h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enaminones 1</th>
<th>Conditions</th>
<th>Bisquinazolinones 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$N-(CH$_2$)$_2$-NH$_2$, CH$_2$O, MeOH/Reflux, 27 h</td>
<td><img src="image135a.png" alt="Structure 135a" /></td>
<td>135a</td>
</tr>
<tr>
<td>2</td>
<td>H$_2$N-(CH$_2$)$_3$-NH$_2$, CH$_2$O, MeOH/Reflux, 22 h</td>
<td><img src="image135b.png" alt="Structure 135b" /></td>
<td>135b</td>
</tr>
<tr>
<td>3</td>
<td>H$_2$N-(CH$_2$)$_4$-NH$_2$, CH$_2$O, MeOH/Reflux, 24 h</td>
<td><img src="image135c.png" alt="Structure 135c" /></td>
<td>135c</td>
</tr>
<tr>
<td>4</td>
<td>H$_2$N-C$_6$H$_4$-NH$_2$, CH$_2$O, MeOH/Reflux, 24 h</td>
<td><img src="image135d.png" alt="Structure 135d" /></td>
<td>135d</td>
</tr>
<tr>
<td>5</td>
<td>H$_2$N-(CH$_2$)$_2$-NH$_2$, CH$_2$O, MeOH/Reflux, 22 h</td>
<td><img src="image135e.png" alt="Structure 135e" /></td>
<td>135e</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$N-(CH$_2$)$_3$-NH$_2$, CH$_2$O, MeOH/Reflux, 23 h</td>
<td><img src="image135f.png" alt="Structure 135f" /></td>
<td>135f</td>
</tr>
<tr>
<td>7</td>
<td>H$_2$N-(CH$_2$)$_4$-NH$_2$, CH$_2$O, MeOH/Reflux, 8 h</td>
<td><img src="image135g.png" alt="Structure 135g" /></td>
<td>135g</td>
</tr>
</tbody>
</table>
5.7 Conclusions.

In conclusion, we have synthesized a series of hitherto unknown bisfused tetrahydropyrimidines (1,2,3,4,7,8-hexahydroquinazolines-5-(6H)-ones) in good
yields, from their respective cyclic-enaminones wherein we have succeeded in-
connecting two-quinazoline moiety via flexible aliphatic and rigid aromatic chain.

5.8 Experimental Section.

Melting points were recorded by open capillary method and are uncorrected. The IR
spectra were recorded on a Perkin-Elmer 983 spectrometer. $^1$H NMR (90 MHz)
spectra were recorded on Varian EM-390 spectrometer. High-resolution $^1$H NMR
and $^{13}$C NMR (300 MHz) spectra were recorded on Bruker ACF-300 spectrometer.
The chemical shifts (δ ppm) and the coupling constants (Hz) are reported in the
standard fashion with reference to TMS as internal reference. FAB-mass spectra
(MS) were measured on JEOL 3SX 102/DA-6000 Mass spectrometer using Argon
as the FAB gas and m-nitrobenzylalcohol as the matrix. Elemental analyses were
performed on a Vario-EL III instrument. Enaminones 87a and 87b were synthesized
by our reported procedure 58.

5.9 General Procedure.

5.9.1 Synthesis of cyclic enaminones (87a–h).

A mixture of 1,3-diketone (1 mmole) and primary amine (1 mmole) in a 10 ml
conical flask placed in a beaker, was irradiated in a domestic microwave oven. After
the completion of the reaction (monitored by TLC), water formed during the reaction
was distilled under reduced pressure to give a solid mass, which was triturated with
hexane, filtered and then recrystallized from appropriate solvent to give the
enaminones 87a–h (Table I). For 87c, 2 mmoles of methylamine and for 87g, 3
mmoles of methylamine (40% aqueous solution) were used. The products were
identified by IR and NMR spectroscopy and also by comparing their melting points
with those of the authentic products.
5.9.2 Synthesis of bis-quinazolines (135a-h).

A mixture of diamine (0.5 mmol) and formaldehyde (2 mmol, 40% solution) in 1.5 ml methanol was stirred at room temperature for 5 minutes. To this was added a solution of enaminones 87 (1 mmol) in 5-6 ml methanol and the resulting mixture was refluxed for specified period of time (table). After the completion of the reaction (monitored by TLC), methanol was removed under reduced pressure to give a gum, which on trituration with hexane and subsequent recrystallization in appropriate solvent gave compounds 135a, 135e, 135g and 135h. In case of compounds 135b, 135c, 135d and 135f the gum was chromatographed using neutral alumina and ethylacetate (eluant).

5.10 Individual description of the compounds.

3,3′-(Ethane-1,2-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135a.

![Chemical Structure](image)

This compound was obtained as a pale yellow solid in 58% yield; mp 182-184 °C (EtOAc); IR (KBr): 1493, 1566 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.70 (m, 4H, 2 CH\(_2\)), 2.12-2.28 (t, 4H, 2 CH\(_2\)), 2.31-2.60 (t, 4H, 2 CH\(_2\)), 2.83 (s, 4H, 2 CH\(_2\)), 3.73 (s, 4H, 2 CH\(_2\)), 4.43 (s, 4H, 2 CH\(_2\)), 7.07-7.87 (m, 10H); MS: m/z, 483 [MH\(^+\)]; Anal. Calcd.
for C$_{30}$H$_{34}$N$_4$O$_2$ (482.27): C, 74.66; H, 7.10; N, 11.61%. Found: C, 74.41; H, 7.07; N, 11.66%.

3,3'-(Propane-1,3-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135b.

This compound was obtained as yellow gum in 70% yield; IR (CCl$_4$): 1493, 1560 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 1.84-1.85 (m, 4H, 2 CH$_2$), 1.86-1.88 (m, 2H), 2.18-2.20 (t, 4H, 2 CH$_2$), 2.32-2.36 (t, 4H, 2 CH$_2$), 2.67-2.72 (t, 4H, 2 CH$_2$), 3.64 (s, 4H, 2 CH$_2$), 4.30 (s, 4H, 2 CH$_2$), 7.11-7.13 (m, 4H), 7.27-7.43 (m, 6H); $^{13}$C NMR (CDCl$_3$): $\delta$ 22.10, 26.07, 27.72, 36.55, 47.96, 50.95, 71.98, 104.83, 127.36, 127.50, 129.84, 143.02, 158.36, 194.94; MS: m/z, 497 [MH$^+$]; Anal. Calcd. for C$_{31}$H$_{36}$N$_4$O$_2$ (496.28): C, 74.97; H, 7.31; N, 11.28%. Found: C, 74.66; H, 7.33; N, 11.24%.

3,3'-(Butane-1,4-diyl)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135c.
This compound was obtained as yellow gum in 65% yield; IR (CCl₄): 1493, 1560 cm⁻¹; ¹H NMR (CDCl₃): δ 1.58 (m, 4H, 2 CH₂), 1.85-1.88 (m, 4H, 2 CH₂), 2.21 (t, 4H, 2 CH₂), 2.33 (t, 4H, 2 CH₂), 2.62 (t, 4H, 2 CH₂), 3.64 (s, 4H, 2 CH₂), 4.29 (s, 4H, 2 CH₂), 7.12-7.14 (m, 5H), 7.30-7.43 (m, 5H); ¹³C NMR (CDCl₃): δ 22.08, 25.59, 27.71, 30.51, 47.59, 52.59, 72.19, 104.76, 124.61, 127.37, 129.31, 143.05, 158.48, 195.03; MS: m/z. 511 [MH⁺]; Anal. Calcd. for C₃₂H₃₈N₄O₂ (510.29): C, 75.26; H, 7.50; N, 10.97% Found: C, 75.50; H, 7.48; N, 10.92%.

3,3'-((1,4-Phenylene)bis(1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one

135d.

This compound was obtained as yellow solid in 71% yield; mp 191-193 °C; IR (KBr): 1427, 1507, 1566 cm⁻¹; ¹H NMR (CDCl₃): δ 1.70-2.06 (m, 4H, 2 CH₂), 2.10-2.30 (t, 4H, 2 CH₂), 2.33-2.60 (t, 4H, 2 CH₂), 4.56 (s, 4H, 2 CH₂), 4.99 (s, 4H, 2
CH$_2$), 6.96-7.93 (m, 14H); MS: m/z, 531 [MH$^+$]; Anal. Calcd. for C$_{34}$H$_{34}$N$_4$O$_2$·(530.27): C, 76.95; H, 6.46; N, 10.56%. Found: C, 76.70; H, 6.45; N, 10.51%.

3,3'-(Ethane-1,2-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135e.

![Chemical structure 135e]

This compound was obtained as yellow solid in 88% yield; mp 193-194 °C (CHCl$_3$/Hexane); IR (KBr): 1493, 1566, 1619 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.03 (s, 12H, 4 CH$_3$), 2.10 (s, 4H, 2 CH$_2$), 2.23 (s, 4H, 2 CH$_2$), 2.93 (s, 4H, 2 CH$_2$), 3.80 (s, 4H, 2 CH$_2$), 4.50 (s, 4H, 2 CH$_2$), 7.03-7.76 (m, 10H); MS: m/z, 539 [MH$^+$]; Anal. Calcd. for C$_{34}$H$_{42}$N$_4$O$_2$ (538.33): C, 75.80; H, 7.86; N, 10.40%. Found: C, 76.05; H, 7.88; N, 10.44%.

3,3'-(Propane-1,3-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135f.

![Chemical structure 135f]
This compound was obtained as yellow gum in 68% yield; IR (CCl₄): 1427, 1493, 1566, cm⁻¹; ¹H NMR (CDCl₃): δ 0.90 (s, 12H, 4 CH₃), 1.59-1.61 (m, 2H), 1.99 (s, 4H, 2 CH₂), 2.13 (s, 4H, 2 CH₂), 2.60-2.65 (m, 4H, 2 CH₂) 3.58 (s, 4H, 2 CH₂), 4.24 (s, 4H, 2 CH₂); 7.01-7.08 (m, 4H), 7.25-7.41 (m, 6H); ¹³C NMR (CDCl₃): δ 24.92, 27.28, 27.36, 31.64, 39.99, 46.40, 48.65, 48.96, 49.46, 70.92, 102.15, 126.38, 127.89, 129.39, 141.78, 155.62, 193.42; Anal. Calcd. for C₃₅H₄₄N₄O₂ (552.35): C, 76.05; H, 8.02; N, 10.15%. Found: C, 76.31; H, 7.98; N, 10.11%.

3,3'-(Butane-1,4-diyl)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135g.

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

This compound was obtained as a pale yellow solid in 59% yield; mp 168-169 °C (EtOAc); IR (KBr): 1440, 1566, 1613 cm⁻¹; ¹H NMR (CDCl₃): δ 1.03 (s, 12H, 4 CH₃), 1.46-1.83 (m, 4H, 2 CH₂), 2.13 (s, 4H, 2 CH₂), 2.26 (s, 4H, 2 CH₂), 2.56-2.90 (m, 4H, 2 CH₂) 3.76 (s, 4H, 2 CH₂), 4.45 (s, 4H, 2 CH₂), 7.10-7.86 (m, 10H); MS: m/z, 567 [MH⁺].

Anal. Calcd. for C₃₆H₄₆N₄O₂ (566.36): C, 76.29; H, 8.18; N, 9.89%. Found: C, 76.02; H, 8.21; N, 9.83%.
3,3'-(1,4-Phenylene)bis(7,7-dimethyl-1-phenyl-1,2,3,4,7,8-hexahydroquinazolin-5(6H)-one 135h.

This compound was obtained as yellow solid in 55% yield; mp 126-128 °C (MeOH/EtOAc); IR (KBr): 1507, 1566 cm⁻¹; ¹H NMR (CDCl₃): δ 0.93 (s, 12H, 4 CH₃), 2.00 (s, 4H, 2 CH₂), 2.23 (s, 4H, 2 CH₂), 4.27 (s, 4H, 2 CH₂), 4.89 (s, 4H, 2 CH₂), 6.91-6.96 (m, 8H), 7.27-7.36 (m, 6H); ¹³C NMR (CDCl₃): δ 28.08, 28.52, 32.82, 41.24, 45.96, 50.21, 52.59, 71.21, 104.63, 119.13, 127.53, 127.62, 129.88, 142.84, 157.52, 194.22; MS: m/z, 587 [MH⁺]; Anal. Calcd. for C₃₈H₄₂N₄O₂ (586.33): C, 77.78; H, 7.21; N, 9.55%. Found: C, 77.52; H, 7.18; N, 9.61%.
5.11 References


