**5.1 Introduction**

Quinazoline is a fused bicycle compound earlier known as benzo-1,3-diazine was first prepared in the laboratory by Gabriel\(^1\) in 1903, although one of its derivatives was known much earlier.\(^2\) The name quinazoline (German: Chinazolin) was first proposed for this compound by Weddige,\(^3\) on observing that this was isomeric with the compounds cinnoline and quinoxaline. Paal and Bush\(^4\) suggested the numbering of quinazoline ring system, which is currently used. The other less commonly used names for this ring system are ‘phenmiazine’ and 5, 6- benzopyrimidine. However, the name quinazoline is now universally accepted.

Of the many derivatives of quinazoline system known so far, keto-quinazolines are also called as quinazolinones, these are the most important class of compounds. Depending upon the position of the keto or oxo group, these compounds may be classified into two types: 2-(1H) quinazolinones and 4-(3H) quinazolines. These systems exhibit lactam-lactim tautomerism and undergo hydroxy group replacement reactions. 2-Cyano-4(3H)-quinazolinone was the first quinazolinone derivative to be synthesized.\(^5\)

**5.1.1. Brief Account of reactivity of 4-(3H) Quinazolinones**

Reactions associated with tautomeric nature of the quinazolinones are often quite complex and generally unpredictable. The recorded chemical investigation on the subject is voluminous. The amide linkages in quinazolinones should not be looked on as predominantly the keto or the enol form but as true keto-enol tautomers, showing reaction characteristic of both the forms.
Quinazolinones are always high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. Simple 4-(3H) quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4-(3H) quinazolinones form stable monohydrochlorides, chloroplatinate, chloroaurates and picrates and their metal salts of silver, mercury, zinc, copper, sodium and potassium.

**Stability of the ring system**

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

**Aromatisation**

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

**Alkylation**

The position of alkylation of quinazolinones is similar to all the aromatic nitrogen heterocyclic systems in which a hydroxyl group is found.
ortho or para to the nitrogen position. Such compounds exist in tautomeric mixture, the two structures being inter-convertible by the shift of one proton and one pair of electrons. In alkaline solution the ions of such compounds exist as resonance hybrids of the two major forms differing only by the position of two pairs of electrons. Thus in alkylation of such hydroxyl derivatives of pyridine, pyrimidine and similar heterocycles, the entering group may become attached to either the nitrogen atom, thus giving for instance, an N-alkyl-pyridine or to the oxygen atom, giving an alkoxy pyridine. Alkylating agent$^9$ and the conditions of alkylation but not the hetercyclic nucleus, were the factors determining the course of alkylation.

*Nitration*

4-(3H) Quinazolinone on boiling with nitric acid undergoes substitution to give 6-nitro-4- (3H) quinazolinone. On further nitration it has been observed that the second nitro group enters the 8-position to give 6,8-dinitro derivatives. 2-Substituted-4-(3H) quinazolinones were also found to behave similarly, under such conditions.$^{10-13}$

*Reduction*

2,3-Dihydro-3-methyl- 4-(1H) quinazolinone (10) could be obtained on reduction of 3-methyl-4-(3H) quinazolinone with Lithium Aluminium Hydride (LiAlH$_4$) in benzene.$^{14}$
Reactivity of the 2-methyl group

The methyl group in 2-position of 4-(3H) quinazolinone system was found to be quite reactive since it is linked to an azomethine carbon and condenses with aldehydes to give the styryl compounds. These studies, interestingly, revealed that quite a few of such quinazolinone derivatives possess a wide variety of pharmacological activities.

5.1.2. Methods of synthesis of 4-(3H) Quinazolinones

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

Condensation of anthranilic acid with acid amides

When anthranilic acid is heated in a open container with excess of formamide at 120 °C, water is expelled and a nearly quantitative (90%) conversion to 4-(3H) quinazolinones is achieved.

Condensation of acetanilides with urethanes

A number of attempts have been made to condense a urethane derivative with aniline to give 4-(3H) quinazolinone, directly. Urethane and acetanilide, heated for 3 hours with phosphorus pentoxide in toluene, give 2-methyl-4-(3H) quinazolinone.
Condensation of N-acylanthranilic acids with primary amines

4-(3H) Quinazolinones may also be synthesized directly from the corresponding N-acylanthranilic acid by heating with ammonia or substituted amines. Bogert and Steiner\(^\text{19}\) have prepared 2-methyl-3-alkyl-6-nitro- 4-(3H) quinazolinones from N-acyl-5-nitroanthranilic acid and a variety of primary amines.

5.1.3. Biological importance of 4-(3H) Quinazolinones

The quinazolinone skeleton is a frequently encountered heterocycle in medicinal chemistry literature with applications including antibacterial,\(^\text{20}\) analgesic,\(^\text{21}\) anti-inflammatory,\(^\text{22,23}\) antifungal,\(^\text{24}\) antimalarial,\(^\text{25}\) antihypertensive,\(^\text{26}\) CNS depressant,\(^\text{27}\) anticonvulsant,\(^\text{28}\) antihistaminic & local anaesthetic,\(^\text{29}\) antiparkinsonism,\(^\text{30}\) antiviral and cancer activities.\(^\text{31}\) Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones and 3-arylquinazoline-2,4(1H,3H)-diones\(^\text{32}\) as antimycobacterial agents, quinazolinone derivatives\(^\text{33}\) are used as antitubercular agents. In the last few decades quinazoline heterocycles got much importance due to their wide range of biological properties like local anesthesia,\(^\text{34}\) active towards blood pressure\(^\text{35}\) and anti-tumor agents.\(^\text{36-39}\) Moreover, quinazoline nucleus has been found in certain alkaloids\(^\text{40}\) they display valuable pharmaceutical activities.\(^\text{41-44}\)
In recent years considerable attention have been paid for the synthesis of quinazoline derivatives, when a simple and 2-substituted-4-(3H)quinazolinone is heated with an equivalent amount of phosphorous pentachloride in phosphorous oxychloride, the corresponding 4-chloroquinazoline is obtained. If a methyl group is present at 3-position, prohibiting the usual tautomerism, the methyl group is lost during the chlorination. Based on this factor, the general methods of synthesis are described as condensation of anthranilic acid with acid amides which is heated in an open container with excess of formamide at 120 °C, water is expelled and a nearly quantitative (90%) conversion to 4(3H)-quinazolinones is achieved. But these methods suffering from some drawbacks like multiple steps in their chemical transformations that have been taken hours or even days to be completed. In view of these facts the use of dehydrating agent like sulphuric acid can offer numerous benefits for performing synthesis of benzoquinazoline compounds including reduced pollution, easy workup and increased reaction rates. Owing to the immense importance and varied bioactivities exhibited by quinazoline derivatives, efforts have been made from time to time to generate libraries of these compounds. Pursuant to the above observations which encouraged us to synthesize some new benzoquinazoline derivatives for potential biological activity.
5.2 Methods of synthesis of benzoquinazolines

Gang Liu et al.⁴⁹ have recently developed a new synthesis method for the target compounds N-aryl heterocyclic substituted-4-aminoquinazoline compounds from 4-chloroquinazoline and aryl heterocyclic amines under microwave irradiation using 2-propanol as solvent (Scheme-1). The new method requires short reaction time, it is very easy and mild and environmentally friendly. To the best of our knowledge, this is the first report on the synthesis of new quinazoline compounds containing heterocycle moieties using microwave irradiation.

Scheme- 1

John E. Oatis Jr, and John B. Hynes developed a method for the synthesis of benzoquinazoline derivatives. The target compound, 10-thia-5,8-deazafolic acid (2a), was prepared as shown in (Scheme I). The sodium salt of diethyl 4-mercaptobenzoyl-L-glutamate (3) was generated according
to the literature procedure and then reacted with 2-amino-6-bromomethyl-4-hydroxyquinazoline (4). The resulting diethyl ester (5) was purified by column chromatography and then saponified in dilute NaOH to yield the free acid 2a.

![Scheme 1](image)

Initial attempts to prepare the oxygen analogue 2b, by direct alkylation of diethyl 4-hydroxybenzoyl-L-glutamate with (4) or its N-trimethylacetyl derivative 6, yielded complex reaction mixtures. Therefore, the route shown in (Scheme II) was employed to synthesize this target compound. Methyl 4-hydroxybenzoate reacted smoothly with 6-bromomethyl-4-hydroxy-2-trimethylacetamidoquinazoline (6) in the
presence of cesium bicarbonate\textsuperscript{50} to yield compound (7). Stepwise deprotection, first with acid and then with base, afforded the key intermediate, 2-amino-6-(4-carboxyphenoxy)methyl)-4-hydroxyquinazoline (8). The direct conversion of 7 to 8 in base resulted in a substantially reduced yield. The glutamic acid moiety was then introduced via the solid-phase peptide synthesis technique\textsuperscript{51,52} yielding 10-oxa-5,8-deazafolic acid (2b).
The synthesis of 5,8,10-deazafoolic acid (2c) commenced with compound (4) which was converted to its triphenylphosphonium salt (9) with triphenylphosphine as shown in (Scheme III). Generation of the corresponding ylide with sodium ethoxide followed by coupling with diethyl 4- formylbenzoyl-L-glutamate (8) yielded approximately equal amounts of the cis and trans olefins (10) in high yield. This mixture was then reduced catalytically to give diethyl 5,8,10-deazafolate (11). Finally, hydrolysis in dilute NaOH yielded the desired compound, 2c.
The discovery of a novel condensation reaction between 2-hydroxy-1-naphthaldehyde (IV) and guanidine led to the preparation of several previously unreported 3-substituted benzo [f]quinazoline derivatives (Chart I). Heating a mixture of IV and guanidine carbonate in n-octanol led to the formation of 3-aminobenzo[f] quinazoline (V). Hydrolysis of V with 6 N hydrochloric acid afforded a sparingly soluble hydrochloride salt, which gave 3-hydroxybenzo [f] quinazoline (VI) on neutralization. Thiation of VI with phosphorus pentasulfide in pyridine furnished 3-mercaptobenzo [f] quinazoline (VII).

1-Cyano-2-naphthylamine (VIII)\(^{53}\) was found to be an excellent starting material for the synthesis of 1-substituted benzo [f] quinazolines (Chart II). For the preparation of VIII, 2-aminonaphthalene-1-sulfonic acid was treated with acetic anhydride in pyridine, and the resulting pyridinium
salt of 2-acylamino-1-naphthalenesulfonic acid was converted into 2-acylamino-1-bromonaphthalene by bromination in aqueous acetic acid.\textsuperscript{54} Treatment of the latter with cuprous cyanide in dimethylformamide\textsuperscript{55} yielded 2-acylamino-1-cyanonaphthalene from which VIII was readily obtained upon removal of the N-acetyl blocking group by brief alkaline hydrolysis.\textsuperscript{56,53}

In an alternative approach, 1-bromo-2-naphthylamine was acetylated, and the resulting 2-diacetylamino-1-bromonaphthalene was converted into VIII by reaction with cuprous cyanide in dimethylformamide, followed by alkaline hydrolysis. Condensation of VIII with formamide afforded 1-aminobenzo [f]quinazoline (IX). Overnight treatment of IX with excess nitrous acid in acetic or hydrochloric acid at room temperature gave only a moderate yield of 1-hydroxybenzo [f] quinazoline (X). Thiation of X with phosphorus pentasulfide in pyridine afforded 1-mercaptobenzo[f] quinazoline (XI).

The unsubstituted parent member of the series, benzo [f] quinazoline (I), was obtained on dethiation of XI with Davison sponge nickel in refluxing ethanol.\textsuperscript{57}
5.3 Biologically active Benzoquinazoline derivatives

Gefitinib or ZD-1839
(Iressa®; AstraZeneca)

Vandetanib or ZD-6474
(Zactima®; AstraZeneca)

Erlo tinib or OSI-774
(Tarceva®; Genentech/OSI/P)

Lapatinib or GW-572016
(Tykerb®; GlaxoSmithKline)

Anti cancer drugs
5.4 present work

A simple, efficient and general method has been developed for the synthesis of new substituted 4-amino-benzoquinazoline derivatives 3(a-p) from 4-hydroxy benzoquinazoline with various amines by using sulphuric acid as a dehydrating agent afforded the products in excellent yield when compared to 4-chlorobenzo quinazoline with various amines under reflux condition using 2-propanol as solvent. In the present study, we performed the synthesis and biological evaluation of some libraries of these compounds. We explored the possibility of synthesizing Benzo[g]quinazolin-4-yl-(4-chloro-phenyl)-amine libraries. The whole work is summarized in (Scheme-1).

In the present protocol it has been found possible to highlight comparative study on the yield ratio and characterization of some 4-substituted analogues of benzoquinazoline derivatives. These observations have encouraged us to synthesize some new products containing the benzoquinazoline moiety hoping to obtain new compounds with potential biological activity. All the reactions involved are highly efficient to give the desired compounds in high yield and high purity. Subsequently, this adopted procedure is simple, rapid and eco-friendly due to easy experimental procedures. The versatility of this methodology can be extended to develop a stream-lined approach to other drug like heterocycles in a combinatorial fashion.
Scheme-1

\[
\text{COOH} \quad \xrightarrow{\text{NH}_2\text{CHO}} \quad \text{NH}_2\text{CHO} \quad \xrightarrow{4-5 \text{ hrs, } \triangle} \quad \text{CONH}
\]

\[
\text{Cl} \quad \xrightarrow{\text{POCl}_3/\text{PCl}_5} \quad \text{OH}
\]

\[
\text{R} = -\text{H}, -2\text{CH}_3, -3\text{CH}_3, -4\text{CH}_3, -4\text{OCH}_3, -2\text{Cl}, -4\text{Cl}, -2,6\text{-di-CH}_3, -3,4\text{-di-CH}_3, -2,4\text{-di-F}, -2,5\text{-di-F}, -3,4\text{-di-Cl}.
\]
5.5 Materials and methods

Chemicals were purchased from Merck, Fluka and Aldrich Chemical Companies. The melting points of the products were determined by open capillary tubes and are uncorrected. The IR spectra were recorded on *Nicolet 5700 FT-IR* spectrophotometers using KBr pellets. Wave numbers are expressed in cm\(^{-1}\). The \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on *Bruker-Avance 300MHz* spectrophotometer using CDCL3-\(d_6\) as solvent and TMS as internal standard reference, chemical shifts are expressed in parts per million. The mass spectra were recorded on *Shimadzu-2010A* spectrophotometer. The elemental analyses were recorded on *Here’s CHN rapid analyzer*. Completion of the reaction was checked by TLC on silica gel 60 F\(_{254}\) (Merck) detected by UV light (254 nm) and iodine vapors.

5.6 Experimental Procedure

**General procedure for the synthesis of 4-Benzooquinazolone (1)**

3 amino 2-naphthoicacid (1.87 g, 0.01 mole) was heated with excess of formamide (5 mL) for 4 h at 120-125 °C. Further 5 mL of ethyl alcohol were added and the reaction mixture was refluxed and progress of the reaction was monitored by TLC, consequent heating was continued up to 12 h. After completion of the reaction, the mixture was poured in to ice cold water and kept aside for some time. The solid product separated on cooling was filtered, washed with water and recrystallized from ethanol.
General procedure for the synthesis of 4-Chlorobenzoquinazoline (2)

4-Benzoquinazoline (1.46 g, 0.01 mole), phosphorus pentachloride (3 g, 0.014 mole) and phosphorus oxychloride (12 mL) were refluxed for two hours at 115-118 °C. The phosphorus oxychloride was removed by distillation at reduced pressure. The residue was extracted three times with ether. The undissolved material was mixed with ether and poured into ice cold water, and several ether extracts were made. Thus obtained ether extracts were freed from acid with sodium bicarbonate and dried. The product from the ether extract was recrystallized from hexane.

Method-A

General procedure for the synthesis of substituted 4-amino benzoquinazoline derivatives (3)

4-Chloro benzoquinazoline (0.82 g, 0.005 mole), various amines (0.01 mole) and (0.561 g, 0.01 mole) potassium hydroxide in 10 mL propanol was stirred under reflux for 12 h and left overnight. The work-up was carried out as the mixture is poured into ice cold water. The solid product that precipitated were filtered off, dried and recrystallized from hexane.

Method-B.

General procedure for the synthesis of substituted 4-amino benzoquinazoline derivatives (3)

A mixture of Benzo[g]quinazoline-4-ol (1.96 g, 0.01 mole), various amines (0.01 mole) and potassium hydroxide (0.561g, 0.01 mole) in 10 mL of propanol containing 2 mL of Conc H₂SO₄. The reaction mixture was
refluxed for 12 h at 120-125 °C, kept aside at room temperature and poured in to crushed ice. The solid product that precipitated were filtered off and recrystallized from the suitable solvent to afford the substituted benzoquinazoline derivatives.

5.7 Results and discussion

Reaction sequence for the benzoquinazoline compounds is outlined in (Scheme 1). Physical and analytical data of the synthesized compounds are reported in (Table-1). Comparative study of yield ratio is summarized in (Table-2). The newly synthesized compounds were confirmed by its spectral analysis. In the IR spectra -NH absorption comes around 3440-3460 cm\(^{-1}\) besides the C=\(\text{N}\) absorption around 1612-1625 cm\(^{-1}\). The \(^1\)H NMR spectra showed downfield shift of NH peaks around \(\delta\) 4.2-4.6 ppm. The aromatic protons resonated as multiplet in the region of \(\delta\) 6.47-8.12 ppm. In \(^{13}\)C NMR the aromatic carbons of various environments present in all the compounds appeared as signals in the range of 113.1–149.4 ppm. In the present protocol method-A suffered from some drawbacks like multiple steps in their chemical transformations that have been taken hours or even days to be completed. To overcome this problem we have introduced sulphuric acid as a dehydrating agent in method-B for the synthesis of substituted 4-amino benzoquinazoline derivatives in high yields. This method offer numerous benefits for performing synthesis of benzoquinazoline libraries including reduced pollution, easy workup and increased reaction rates.
The compounds are reported to give yields about 65-75% with high purity monitored by TLC and the structures of all derivatives 3(a-e) are supported by spectral data. The X-ray analysis of the compound(s) is under progress. The IR, $^1$H NMR, $^{13}$C NMR and mass spectra are in agreement with the proposed structures (Table-3).

(3a) *Benzo[g]quinazolin-4-yl-(4-chloro-phenyl)-amine*

Colorless solid, m.p; 214-215°C; IR (KBr):

$\nu$ (cm$^{-1}$) 3440 (-NH), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s, 1H, NH), 6.47 - 8.12 (m, 11H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine); GCMS: $m/z$ [M$^+$]=305: Anal. Calcd. For C$_{18}$H$_{12}$ClN$_3$: C 70.71, H 3.96, Cl 11.59, N 13.74 %. Found: C 70.72, H 3.95, Cl 11.61, N 13.75 %.

(3b) *Benzo[g]quinazolin-4-yl-o-tolylamine*

Colorless solid, m.p; 217-219°C; IR (KBr):

$\nu$ (cm$^{-1}$) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s, 1H, NH), 2.38 (s, 3H, CH$_3$); 6.47 - 8.12 (m, 11H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 20.82, 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine); GCMS: $m/z$ [M$^+$]= 285: Anal. Calcd. For C$_{19}$H$_{15}$N$_3$: C 79.98, H 5.30, N 14.73 %. Found: C 79.97, H 5.31, N 14.74 %.
Chapter 5

Chemistry of Benzoquinazolines

(3c) Benzo[g]quinazolin-4-yl-o-Phenyl-amine

Colorless solid, m.p; 232-234°C; IR (KBr): 
\[\nu (\text{cm}^{-1}) 3440 (-\text{NH}), 1625 (\text{C} = \text{N}), 1510 (\text{C} = \text{C}) ;\]
\[^1\text{H} \text{NMR} (\text{CDCl}_3, 300\text{MHz}): \delta \text{ ppm} = 4.2 \text{ (s, 1H, NH)}, 6.47 - 8.12 \text{ (m, 11H, Ar-H)} ;\]
\[^{13}\text{C} \text{NMR} (75 \text{ MHz CDCl}_3, \delta \text{ ppm}): 128.32-136.82(\text{Ar-C}), 160–170 (\text{C} = \text{N of Pyrimidine}) ;\]
GCMs: \[m/z [\text{M}^+]= 271:\]
Anal. Calcd. For C\textsubscript{18}H\textsubscript{13}N\textsubscript{3}: C 79.68, H 4.83, N 15.49 %. Found: C 79.66, H 4.85, N 15.48 %.

(3d) Benzo[g]quinazolin-4-yl-m-Tolyl-amine

Colorless solid, m.p; 227-229°C; IR (KBr): \[\nu (\text{cm}^{-1}) 3440 (-\text{NH}), 2925 (\text{C-H}), 1625 (\text{C} = \text{N}), 1510 (\text{C} = \text{C}) ;\]
\[^1\text{H} \text{NMR} (\text{CDCl}_3, 300\text{MHz}): \delta \text{ ppm} = 4.2 \text{ (s, 1H, NH)}, 2.38 \text{ (s, 3H, CH}_3\); 6.47 - 8.12 \text{ (m, 11H, Ar-H)} ;\]
\[^{13}\text{C} \text{NMR} (75 \text{ MHz CDCl}_3, \delta \text{ ppm}): 20.82, 128.32-136.82(\text{Ar-C}), 160–170 (\text{C} = \text{N of Pyrimidine}) ;\]
GCMs: \[m/z [\text{M}^+]= 285:\]
Anal. Calcd. For C\textsubscript{19}H\textsubscript{15}N\textsubscript{3}: C 79.98, H 5.30, N 14.73 %. Found: C 79.97, H 5.31, N 14.74 %.

(3e) Benzo[g]quinazolin-4-yl-(3-fluoro-phenyl)-amine

Colorless solid, m.p; 212-214°C; IR (KBr): \[\nu (\text{cm}^{-1}) 3440 (-\text{NH}), 1625 (\text{C} = \text{N}), 1510 (\text{C} = \text{C}) ;\]
\[^1\text{H} \text{NMR} (\text{CDCl}_3, 300\text{MHz}): \delta \text{ ppm} = 4.2 \text{ (s, 1H, NH)}, 6.47 - 8.12 \text{ (m, 11H, Ar-H)} ;\]
\[^{13}\text{C} \text{NMR} (75 \text{ MHz CDCl}_3, \delta \text{ ppm}): 128.32-136.82(\text{Ar-C}), 160–170 (\text{C} = \text{N of Pyrimidine}) ;\]
GCMs: \[m/z [\text{M}^+]= 289:\]
Anal. Calcd. For C\textsubscript{18}H\textsubscript{12}FN\textsubscript{3}: C 74.73, H 4.18, F 6.57, N 14.52 %. Found: C 74.75, H 4.20, F 6.56, N 14.51 %.
(3f) Benzo[g]quinazolin-4-yl-p-tolyl-amine

Colorless solid, m.p: 223-225\(^0\)C; IR (KBr): \(\nu\) (cm\(^{-1}\)) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C) ; \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) ppm = 4.2 (s, 1H, NH), 2.38 (s, 3H, CH\(_3\)); 6.47 - 8.12 (m, 11H, Ar-H); \(^{13}\)C NMR (75 MHz CDCl\(_3\), \(\delta\) ppm): 20.82, 128.32-136.82(Ar-C), 160-170 (C=N of Pyrimidine); GCMS: \(m/z\) [M\(^+\)] = 332: Anal. Calcd. For C\(_{21}\)H\(_{24}\)N\(_4\): C 75.87, H 7.28, N 16.85 %. Found: C 75.87, H 7.28, N 16.85 %.

(3g) Benzo[g]quinazolin-4-yl-(2-Chloro-phenyl)-amine

Colorless solid, m.p: 207-208\(^0\)C; IR (KBr): \(\nu\) (cm\(^{-1}\)) 3440 (-NH), 1625 (C=N), 1510 (C=C) ; \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) ppm = 4.2 (s, 1H, NH), 6.47 - 8.12 (m, 11H, Ar-H) ; \(^{13}\)C NMR (75 MHz CDCl\(_3\), \(\delta\) ppm): 128.32-136.82(Ar-C), 160-170 (C=N of Pyrimidine); GCMS: \(m/z\) [M\(^+\)] = 305: Anal. Calcd. For C\(_{18}\)H\(_{12}\)ClN\(_3\): C 70.71, H 3.96, Cl 11.59, N 13.74 %. Found: C 70.71, H 3.96, Cl 11.59, N 13.74 %.

(3h) Benzo[g]quinazolin-4-yl-(2,3-dimethyl-phenyl)-amine

Colorless solid, m.p: 216-219\(^0\)C; IR (KBr): \(\nu\) (cm\(^{-1}\)) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C) ; \(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) ppm = 4.2 (s, 1H, NH), 2.38 (s, 3H, CH\(_3\)), 6.47 - 8.12
(m, 10H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 20.82, 128.32-
136.82(Ar-C), 160–170 (C=N of Pyrimidine); GCMS: $m/z [M^+]$= 299: Anal.
Calcd. For C$_{20}$H$_{17}$N$_3$: C 80.24, H 5.72, N 14.04 %. Found: C 80.24, H 5.72,
N 14.04 %.

(3i) Benzo[g]quinazolin-4-yl-(2,4-difluoro-phenyl)-amine

Colorless solid, m.p; 231-233$^0$C; IR (KBr): $\upsilon$
(cm$^{-1}$) 3440 (-NH), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s,
1H, NH), 6.47 - 8.12 (m, 10H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 128.32-136.82(Ar-C), 160–170 (C=N of
Pyrimidine); GCMS: $m/z [M^+]$= 271: Anal. Calcd. For C$_{18}$H$_{13}$N$_3$: C 79.68, H
4.83, N 15.49 %. Found: C 79.66, H 4.85, N 15.48 %.

(3j) Benzo[g]quinazolin-4-yl-(2,5-difluoro-phenyl)-amine

Colorless solid, m.p; 216-218$^0$C; IR (KBr): $\upsilon$
(cm$^{-1}$) 3440 (-NH), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s, 1H,
NH), 6.47 - 8.12 (m, 10H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine);
GCMS: $m/z [M^+]$= 307: Anal. Calcd. For C$_{18}$H$_{11}$F$_2$N$_3$: C 70.35, H 3.61, F
12.36 N 13.67 %. Found: C 70.37, H 3.62, F 12.35 N 13.68 %.

(3k) Benzo[g]quinazolin-4-yl-(4-fluoro-phenyl)-amine

Colorless solid, m.p; 218-221$^0$C; IR (KBr): $\upsilon$
(cm$^{-1}$) 3440 (-NH), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s,
(3l) Benzo[g]quinazolin-4-yl-(2-fluoro-phenyl)-amine

Colorless solid, m.p; 217-220°C; IR (KBr): $\nu$ (cm$^{-1}$) 3440 (-NH), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s, 1H, NH), 6.47 - 8.12 (m, 11H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine); GCMS: $m/z$ [M$^+$]= 289: Anal. Calcd. For C$_{18}$H$_{12}$FN$_3$: C 74.73, H 4.18, F 6.57, N 15.49 %. Found: C 74.73, H 4.18, F 6.57, N 15.49 %.

(3m) Benzo[g]quinazolin-4-yl-(2,6-dimethyl-phenyl)-amine

Colorless solid, m.p; 239-243°C; IR (KBr): $\nu$ (cm$^{-1}$) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 4.2 (s, 1H, NH), 2.38 (s, 3H, CH$_3$), 6.47 - 8.12 (m, 11H, Ar-H); $^{13}$C NMR (75 MHz CDCl$_3$, $\delta$ ppm): 20.82, 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine); GCMS: $m/z$ [M$^+$]= 299: Anal. Calcd. For C$_{20}$H$_{17}$N$_3$: C 80.24, H 5.72, N 14.04 %. Found: C 80.26, H 5.73, N 14.06 %.

(3n) Benzo[g]quinazolin-4-yl-(4-methoxy-phenyl)-amine

Colorless solid, m.p; 224-225°C; IR (KBr): $\nu$ (cm$^{-1}$) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C); $^1$H NMR (CDCl$_3$, 300MHz): $\delta$ ppm = 3.78 (s, 3H, OCH$_3$), 4.2
(s, 1H, NH), 6.47 - 8.12 (m, 11H, Ar-H); \(^{13}\text{C} \text{NMR (75 MHz CDCl}_3, \delta \text{ppm): 56.12,128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine)}; \text{GCMS: } m/z \ [M^+] = 301: \text{Anal. Calcd. For C}_{19}\text{H}_{15}\text{N}_3\text{O: C 75.73, H 5.02, N 13.94, O 5.31 \%}. \text{Found: C 75.73, H 5.02, N 13.94, O 5.31 \%.}

(3o) Benzo[g]quinazolin-4-yl-(2,4-dichloro-phenyl)-amine

Colorless solid, m.p; 206-209°C; IR (KBr): \( \nu \) (cm\(^{-1}\)) 3440 (-NH), 1625 (C=N), 1510 (C=C); \(^1\text{H} \text{NMR (CDCl}_3, 300MHz): \delta \text{ppm} = 4.2 \) (s, 1H, NH), 6.47 - 8.12 (m, 10H, Ar-H); \(^{13}\text{C} \text{NMR (75 MHz CDCl}_3, \delta \text{ppm): 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine)}; \text{GCMS: } m/z \ [M^+] = 340: \text{Anal. Calcd. For C}_{18}\text{H}_{11}\text{Cl}_2\text{N}_3: C 63.55, H 3.26, Cl 20.84,N 12.35 \%. \text{Found: C 63.57, H 3.25, Cl 20.83,N 12.37 \%.}

(3p) Benzo[g]quinazolin-4-yl-(3,4-dimethyl-phenyl)-amine

Colorless solid, m.p; 227-228°C; IR (KBr): \( \nu \) (cm\(^{-1}\)) 3440 (-NH), 2925 (C-H), 1625 (C=N), 1510 (C=C); \(^1\text{H} \text{NMR (CDCl}_3, 300MHz): \delta \text{ppm} = 4.2 \) (s, 1H, NH), 2.38 (s, 3H, CH\(_3\)); 6.47 - 8.12 (m, 11H, Ar-H); \(^{13}\text{C} \text{NMR (75 MHz CDCl}_3, \delta \text{ppm): 20.82, 128.32-136.82(Ar-C), 160–170 (C=N of Pyrimidine)}; \text{GCMS: } m/z \ [M^+] = 299: \text{Anal. Calcd. For C}_{20}\text{H}_{17}\text{N}_3: C 80.24, H 5.72, N 14.04 \%. \text{Found: C 80.26, H 5.73, N 14.05 \%.}
Table 1

Physical and analytical data of the Benzoquinazoline derivatives 3(a-p)

![Chemistry of Benzoquinazolines](image)

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>Method 1 Reaction time (Hr)</th>
<th>Method 2 Reaction time (Hr)</th>
<th>m.p. (°C)</th>
<th>Mol. Formula/ Mol. Wt</th>
<th>Elem. Analysis (Cal./Found)</th>
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<td>Yield (%)</td>
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<td></td>
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<tr>
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<td>2-CH_{3}</td>
<td>18 / 55.87</td>
<td>15 / 59.84</td>
<td>217-219</td>
<td>C_{19}H_{12}N_{2} 285</td>
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<tr>
<td>3 c</td>
<td>H</td>
<td>16 / 66.47</td>
<td>14 / 68.46</td>
<td>232-234</td>
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<td>79.66</td>
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<td>3-CH_{3}</td>
<td>15 / 62.20</td>
<td>12 / 65.00</td>
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<td>C_{19}H_{12}N_{2} 285</td>
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</tr>
<tr>
<td>3 e</td>
<td>3-F</td>
<td>17 / 63.43</td>
<td>15 / 64.48</td>
<td>212-214</td>
<td>C_{19}H_{12}F_{2}N_{3} 289</td>
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<tr>
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<td>4-CH_{3}</td>
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<td>14 / 67.49</td>
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<td>12 / 65.49</td>
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<td>14 / 54.20</td>
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<td>C_{20}H_{12}N_{2} 299</td>
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* Products were characterized by IR, NMR, MS and elemental analysis

* Isolated yields

* Melting points are uncorrected
### Table- 2

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<th>Entry</th>
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</table>
Spectrum 1: IR Spectrum of compound (3a) (Code-BZ-QN)

Spectrum 2: $^1$H NMR (300MHz) Spectrum of compound (3a)
Chapter 5

Chemistry of Benzoquinazolines

Spectrum 3: $^1$H NMR (300MHz) Spectrum of compound (3a) D$_2$O

Spectrum 4: $^{13}$C NMR (75MHz) Spectrum of compound (3a)
Spectrum 5: Mass Spectra of compound (3a)

Spectrum 6: IR Spectrum of compound (3d)
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Spectrum 7: $^1$H NMR (300MHz) Spectrum of compound (3d)

Spectrum 8: $^{13}$C NMR (75MHz) Spectrum of compound (3d)
Spectrum 9: $^1$H NMR (300MHz) Spectrum of compound (3d)
Spectrum 10: Mass Spectra of compound (3d)
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Chemistry of Benzoquinazolines
5.8 References


35. (a) Paal and Busch, *Chem. Ber.*, 1889, **22**, 2683.

(b) Gabriel and Colman, *German Patent.*, 161401.


