FUNCTIONALIZATION AND HETEROANNULATION OF QUINAZOLONE NUCLEUS-SYNTHESIS, STRUCTURE ELUCIDATION AND BIOACTIVITY EVALUATION

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PAKISTAN

FEBRUARY 2008

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Dissertation

submitted to the University of Peshawar in partial fulfilment for the requirements for the Degree of Doctor of Philosophy in Chemistry

INSTITUTE OF CHEMICAL SCIENCES

UNIVERSITY OF PESHAWAR

PAKISTAN

FEBRUARY 2008

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INSTITUTE OF CHEMICAL SCIENCES

UNIVERSITY OF PESHAWAR

PAKISTAN

It is recommended that this dissertation prepared by Mr. Rasool Khan entitled "Functionalization and Heteroannulation of Quinazolone Nucleus-Synthesis, Structure Elucidation and Bioactivity Evaluation" be accepted as fulfilling this part of the requirements for the degree of

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DEDICATED

TO

MY PARENTS & LATE SISTER

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ACKNOWLEDGEMENTS

All praises be to **ALLAH** alone, the most compassionate, the most beneficent and ever merciful, who gave me the power to do, the sight to observe and mind to think and judge.

It gives me great contentment to express my heartfelt gratitude to my research supervisor Prof. Dr. Mohammad Arfan for his astute guidance, invaluable suggestions and keen criticisms while carrying out the present work. His enduring passion and moral support helped me out to overcome all the difficulties that I encountered during this endeavour. It is my privilege to thank Dr. Shazia Anjum, Assistant Professor, International Centre for Chemical and Biological Sciences, H.E.J. Research Institute of Chemistry, University of Karachi for her constant encouragement and ardent interest shown during the progress of the work. I am indebted to my co-supervisor, Prof. Dr. M. Iqbal Choudhary *H.I, S.I, T.I;* Director (acting),H.E.J. Research Institute of Chemistry, University of Karachi for his all possible help, support and encouragement.

I owe tremendous debt to Dr. Imtiaz Ahmad, Prof. Dr. Imdad-ullah Mohammadzai, and Dr. Ikhtiar Khan for their moral help and support. I would like to extend my thanks to my friends Shabir Ahmad, Ziarat Shah Afridi, Fazal Mabood Mohammad Imran, Dr. Zia-ullah Khattack, Dr. Manzoor Ahmad and to the research group fellows, Hazrat Amin, Mumtaz Ali, Jamal Rafique, Sayed Ishaq Ali Shah and Mehdi Shah. Thanks are due to Zulfiqar and Maqsood Jan (Lab. Staff, Organic Chemistry section, Institute of Chemical Sciences, University of Peshawar), and Tanweer and Shehzad (Lab. Staff HJRIC, University of Karachi). I am also thankful to Sajid Khan for his help and support in composing the thesis.

Finally, no words can articulate the feelings towards my parents, who have contributed and sacrificed a lot for me to accomplish this stage and will always remain a sole source of inspiration in my life to achieve higher goals.

RASOOL KHAN

ABSTRACT

The research work documented in this dissertation presents the synthesis and bioactivity evaluation of some quinazolin-4(3*H*)-one based heterocyclic compounds. Part first is concerned with the synthesis and synthetic methods both reported and newly designed and developed, while the second part is about the bioassays evaluation of the synthesized quinazolin-4(3*H*)-ones. 2-Aryl -4*H*-3,1-benzoxazin-4-one and methyl-N-acylanthranilates were prepared as starting materials for further transformations into a series of various 2,3-disubstituted quinazolin-4(3*H*)-ones.

Keeping in view the extensive applications of 2-aryl -4*H*-3,1-benzoxazin-4-one as precursor in the quinazolin-4(3*H*)-ones chemistry, a new, cheaper and facile one-pot method for the synthesis of 2-aryl -4*H*-3,1-benzoxazin-4-one was developed making use of readily available substituted benzoic acids. A faster and high- yielding microwave-assisted, solvent free method was also developed for the synthesis of methyl-2-[(trifluoroacetyl) amino] benzoate.

Both the 2-aryl -4*H*-3,1-benzoxazin-4-one and methyl-N-acylanthranilates synthesized were then utilized for the synthesis of 3-amino, 2-alkyl/aryl quinazolin-4(3*H*)-ones and 2,3-disubstituted quinazolin-4(3*H*)-ones. Consequently, a series of fifteen (**19-33**) 3-amino- 2-alkyl/aryl substituted quinazolin-4(3*H*)-ones and a series of twenty seven (**46-62**) 2,3-disubstituted quinazolin-4(3*H*)-ones were synthesized.

The necessity of development of new, cheaper and faster methods was realised and as a result, a simpler and less tedious three component one-pot method for the synthesis of ten (**22-31**) 3-amino, 2-aryl quinazolin-4(3*H*)-ones was developed starting from the available substituted benzoic acid.

As a consequence of the effect of substituents on the reactivity of 2-aryl -4*H*-3,1-benzoxazin-4-ones, three structurally novel quinazolin-4(3*H*)-ones (**34-36**) were synthesized from substituted 2-phenyl-4*H*-3,1-benzoxazin-4-ones. It was found that phenyl group substituted at position 2 failed to give any product. Reasons for the observed effect on the reactivity are proposed.

Keeping in view the importance of the nature and position of substituents in drug discovery, a series of (**37-62**) 2, 3-disubstituted quinazolin-4(3*H*)-ones were synthesized employing three different methods. The effect of substituents on the reactivity and the

plausible reaction mechanisms were explored. Nine open chain products as side products (**63a-i**) were isolated in addition to 2, 3-disubstituted quinazolin-4(3*H*)-ones. The reaction conditions were further tuned to afford side products as the main single products of these reactions and thus a series of nine open chain diamides (**63a-i**) were obtained and characterized successfully. The open chain products were then cyclized into the corresponding 2, 3-disubstituted quinazolin-4(3*H*)-ones under solvent free conditions using microwave irradiation. The open chain products were also transformed into structurally diverse products beside their conversion into 2, 3-disubstituted quinazolin-4(3*H*)-ones, hence N-[2-(hydrazinocarbonyl) phenyl] benzamide (**63 g**) synthesized was allowed to react with salicyldehyde to afford N-(2- {[(2E)-2- (2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide (**63 h**). Cyclization did not take place which support the hypothesis of diversity of reactivity of the open chain diamides (**63a-j**). X-ray structure of N-(2-{[(2E)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide not only proved the formation of the open chain diamides but also confirmed the diverse reactivity of the intermediate and showed that the diamides are not the reaction intermediates but rather stable reaction products which on prolonged heating and reflux (i.e., under the thermodynamic control) cyclized into 2, 3-disubstituted quinazolin-4(3*H*)-ones.

Keeping in view the importance of quinazolin-4(3*H*)-ones Schiff bases, a series of quinazolin-4(3*H*)-ones Schiff bases (**64-84**) were synthesized. Working on the synthesis of quinazolin-4(3*H*)-ones Schiff bases, three methods, i.e. $AlCl_3$/ $ZnCl_2$ catalyst, catalyst free and H_2SO_4 mediated synthesis were optimized and compared with each other for yield and reaction time. This study revealed that H_2SO_4 mediated synthesis was found better compared to other methods. A microwave- assisted, solvent and catalyst free method was also developed and optimized for the synthesis of quinazolin-4(3*H*)-one Schiff bases and was found more effective and environmentally friendly compared to the acids catalyzed methods.

2-Aminobenzohydrazide (**90**) has been widely used as a starting material in the synthesis of various bioactive heterocyclic compounds. An expeditious method for the synthesis of 2-aminobenzohydrazide from methylanthranilate and hydrazine hydrate using microwave irradiation was developed. The 2-aminobenzohydrazide was further

used for the synthesis of 3-(alkyl/arylideneamino)-2, 2-alkyl/aryl-2, 3-dihydroquinazolin-4 (1*H*)-ones (**91-105**). Here again, three different methods were optimized and compared. In the first attempt, 2-aminobenzohydrazide was allowed to react with various ketones and aldehydes over silica gel under solvent free conditions. A series of 3-(alkyl/arylideneamino)-2, 2-alkyl/aryl-2, 3-dihydroquinazolin-4 (1*H*)-ones (**91-96, 98-100**) were obtained. This method was found to be convenient and effective for all tried aliphatic ketones; however, it showed limitations in case of aromatic aldehydes and ketones. Liquid aromatic aldehydes and ketones reacted while solid aromatic aldehydes and ketones failed to give any product. A *para*-toluensulfonic acid catalysed method was used for the first time. However, this method was found to be effective but resulted in lower yields in case of aromatic aldehydes and ketones while failed in case of aliphatic ketones. Moreover, H_2SO_4 mediated method was optimized and was found to be efficient and high yielding compared to the two earlier stated methods. Applicability of this method was, however, again found limited to aromatic aldehydes and ketones. While aliphatic aldehydes failed to react using any of the three methods. Solvent and catalyst free microwave-assisted method for the synthesis 3-(arylideneamino) - 2-aryl-2, 3-dihydroquinazolin-4 (1*H*)-ones (**85, 95-104**) was developed. It was found to be faster, high yielding and environmentally friendly in comparison to all the three methods. Moreover its applications was also found limited to aromatic carbonyl systems only since both the aliphatic ketones and aldehyes failed to give the desired products.

Acetamidines have diverse synthetic applications and biological significance.Limited literature is available on the synthesis of acetamidines while no literature is reported on quinazolin-4(3*H*)-ones based acetamidines. In this quest, a series of twelve (**105-114**) novel unsymmetrical quinazolin-4(3*H*)-ones based acetamidines were synthesized. It was discovered in the present work that ethyl (1*E*)-*N*-(2-phenyl/methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoates tautomerize in the acidic media to the most stable amide tautomer and for this reason, no isolation of the ethanimidic acid ethylester has been reported. In further search, a more simple method for the synthesis of ethyl (1*E*)-*N*-(2-phenyl/methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoates was developed where no tautomeric conversion to the imide form occurred. Two new ethyl (1*E*)-*N*-(2-phenyl/methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoates (**105, 106**) were prepared. The

ethyl (1*E*)-*N*-(2-phenyl/methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoates synthesized were condensed with activated aromatic amines and a series of novel unsymmetrical quinazolin-4(3*H*)-ones based acetamidines (**107-114**) was synthesized. A more robust method for the synthesis of unsymmetrical quinazolin-4(3*H*)-ones based acetamidines was developed by the condensation of amides and aromatic amines. Besides high yielding, the method utilized amides as starting materials that are easily accessible. The method could find applications in the synthesis of diverse amidines.

Further working on synthesis of 2-alkyl/aryl- quinazoli-4(3*H*)-ones, a series of eleven quinazolinones (**117-126**) was synthesized by the cyclocondensation of methyl anthranilate and alkyl/aryl cyanides.

Oxidative deamination of *N*-amino- 2-alkyl/aryl- quinazoli-4(3*H*)-ones using aqueous $KMnO_4$ as deaminating agent was designed. After successful results, the reactions were tried under microwave irradiation and thus, a much cheaper and faster method for the oxidative deamination of *N*-amino- 2-alkyl/aryl quinazoli-4(3*H*)-ones was developed for the first time.

A new microwave-assisted method for the synthesis of 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones was developed and consequently, a series of three (**127-129**) 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones was synthesized. The method, however, was found to be of limited synthetic applications as substitution on position 2 of phenyl group in the 3-amino 2-aryl -quinazolin-4(3*H*)-ones failed to give 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones.

In the second part of the present work, majority of the synthesized compounds were screened for antifungal, antibacterial, antileishmanial, antioxidant and cytotoxic activities. Antiglycation and inhibition of enzymes including butylcholinesterase, acetylcholinesterase, tyrosinase and thermolysine were also studied.

Among the compounds screened for antifungal activities, compounds **23, 45** and **122** were found active against *T. Longifugus*, compounds **68** and **50** were active against *C. Albicans*. Compounds **112, 33, 89, 117, 39, 114, 9, 7, 29, 28 8, 96 97** and **98** were more active against *C. Albicans* than the standered drug amphotericine B. Compound **35** was found to be strongly active against *b. Subtilis*, *S.Aurea*, *E.Coli* and *S. Typhi* than the standerd drug Imepenium. Compounds **27** and **69** were found more potent against

S.Aurea than *the* standard drug used. Compound **12** was more active than the standard drug against *S. Typhi.*

Compounds **45, 78** and **86** showed strong antiliesmanial activities. Compound **29** was found to be highly cytoxic having **LD 50** 28.09 (µg/mL). Compounds **45** and **69** were found highly active against butylcholinesterase.

Compounds **76, 69, 19** and **56** showed highest tyrosinase inhibitory activities and compound **29** showed highest antiglycation activity. Compounds **55, 66, 19, 56** and **89** were found strongly thermolysine inhibetors.

LIST OF ABBREVIATIONS

µL	Micro liter
^{13}C-NMR	Carbon-13-nuclear magnetic resonance
^{1}H-NMR	Hydrogen-1-nuclear magnetic resonance
Ac_2O	Acetic anhydride
AChE	Acetylcholine esterase
Ar	Aryl
bend	Bending vibration
Bu	Butyl
BuhE	Butylcholine esterase
DCC	Dicyclohexyl carbodiimide
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethy sulfoxide
Dppf	Diphenylphosphinoferrocene
DPPH	1,1-diphenyl-2-picryl hydrazide
DTNB	5,5-dithiobis[2-nitrobenzoic acid]
EDG	Electron donating group
EI-MS	Electron Impect-Mass spectrometer
Et	Ethyl
Et_3N	Triethyl amine
$EtNiPr_2$	Di isopropyl ethylamine
EWG	Electron withdrawing group
FAB-MS	Fast atom bombardment-Mass spectrometer
Hz	Hertz
IC_{50}	Inhibitory concentration
IR	Infra red
J	Coupling constant
LAH	Lithium aluminium hydride
LDA	Lithium di isopropyl aluminium hydride

LTA	Lead tetra acetate
M.P.	Melting point
M.W	Microwave
m/z	Mass to charge ratio
Me	Methyl
MIC	Minimum inhibitory concentration
NH_4OAc	Ammonium acetate
$NO^{\cdot}$	Nitroperoxide radical
OD	Optical density
PBS	Phosphate buffer solution
Pd/C	Palladium on charcoal
PPE	Polyphosphate ethylester
PPh_3	Triphenyl phosphine
Psi	Pound per square inch
TsOH	*Pera*-toluene sulfonic acid
Py	Pyridine
Q	Quinazolinyl
R	Alkyl
r.t.	Room temperature
SEM	Slandered error of mean
Str.	Stretching vibration
TCA	Trichloroacetic acid
TEA	Triethanol amine
TFAA	Trifloroacetic anhydride
TFE	Trifloroethanol
THF	Tetrahydrofuran
ν	Wave number

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CHAPTER-1

INTRODUCTION

1.1. Quinazolin-4(3*H*)-one Heterocycles

Quinazolin-4(3*H*)-one ring system (Fig. 1) has been comprehensively studied because of its diverse therapeutic and chemical applications and is a core structure present in almost 180 natural products isolated both from plants and animals [1,2].

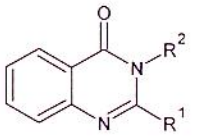
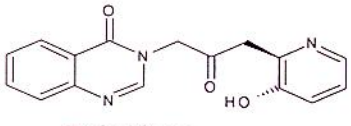


Fig.1: General Structure of Quinazolin-4(3*H*)-ones

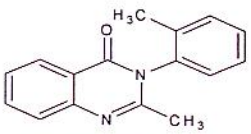
Quinazolin-4(3*H*)-one is a class of organic natural and synthetic compounds possessing a wide range of biological activities such as anticancer (including topoisomerase I and II, kinesin spindle proteins, thymidylate synthase, and tubulin polymerization inhibition), anti-inflamatory activities and cardiovascular activities[3]. Compounds belonging to this class have also exhibited cardiotonic, antihistamintic, antifungal, antiviral, and antimalarial [4] and hypothermic [5] activities. Beside this, some of these quinazolin-4(3*H*)-ones have shown psychotropic, hypnotic and a range of other CNS effects [6] such as CNS depressant, CNS stimulant, tranquilizing, antidepressant and anticonvulsant effects [7a, b]. In addition, quianzolin-4(3*H*)-one core scaffold has been widely utilized as a drug like template in medicinal chemistry and considered as a privileged structure [8].

Interest in the medicinal chemistry of quinazolin-4(3*H*)-one derivatives was stimulated in the early 1950's with the elucidation of a quinazolin-4(3*H*)-one alkaloid, namely,3-[-keto-(3-hydroxy-2-piperdyl)-propyl]-4-quinazolone [Febrifugine, Fig. 2] from an Asian plant, *Dichroa febrifuga*, which is an ingredient of a traditional Chinese herbal remedy; effective against malaria. In a quest to find additional potential quinazolin-4(3*H*)-one based drugs, various substituted quinazolin-4(3*H*)-ones have been synthesized, which led to the synthesis of the derivative 2-methyl-3-tolyl-quinazolin-4-(3*H*)-one [Methaqualone, Fig. 2]. Synthesis of methaqualone as the first sedative

hypnotic and anticonvulsant agent [9] triggered further interest of chemists to synthesize more quinazolin-4(3*H*)-one based heterocyclic compounds. In nutshell, a plethora of literature is now available on the chemistry and biology of this class of organic compounds.



Febrifugen



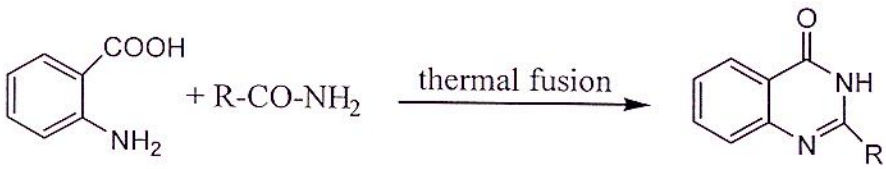
Methaqualone

Fig. 2: Bioactive quianzolin-4(3*H*)-ones alkaloids Febrifugen and Methaqualone

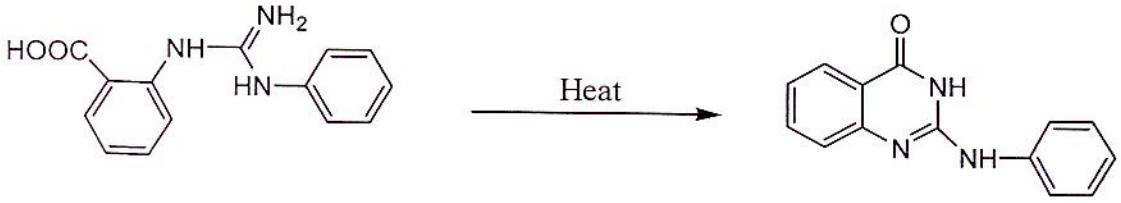
Quinazolin-4(3*H*)-one being a core structure present in many bioactive natural products, the 2,3-disubstituted quinazolin-4(3*H*)-ones find applications in the total synthesis of complex quinazolin-4(3*H*)-one based natural products.[9] 3-Aminoquinazolin-4(3*H*)-ones are also widely used as aziridinating agents for the regio- and stereoselective aziridination of double bond.[10-12]

1.2. Synthesis of Quinazolin-4(3*H*)-one Ring System

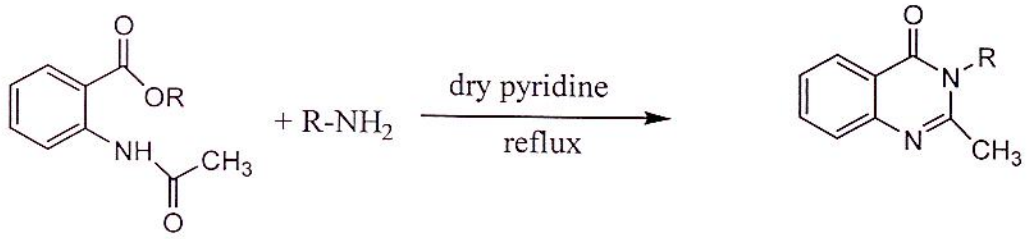
The synthesis of quinazolin-4(3*H*)-one ring system can be traced back to Korner's investigation in 1887, when he prepared 2-phenylquinazoline-4(3*H*)-one by the treatment of N-benzoyl *ortho*-anilamide with potassium hydroxide [13]. The first well-defined synthesis of quinazolin-4(3*H*)-ones was reported by Niementowski *via* direct thermal fusion of anthranilic acid and amide [Scheme 1.1] [14] while Wheeler *et al.*,[15] accessed the same nucleus by the cyclization of *ortho*- carboxyphenylthiourea and *ortho*-guanidino benzoic acid [Scheme 1.2]. Similarly, N-acetylanthranilate on reaction with urea or free amine gave substituted quinazolin-4(*H*)-ones [16] [Scheme 1.3].



Scheme 1.1: Synthesis of quinazolin-4(3*H*)-one by direct fusion of anthranilic acid and an amide



Scheme 1.2: Wheeler's approach to synthesis of quinazolin-4(3*H*)-ones



Scheme 1.3: Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones from N-acetyl anthranilate.

The chemistry of quinazolin-4(3*H*)-ones is although well documented in a comprehensive review by Connoloy *et al.*,[17] that covers most of the synthetic approaches to the quinazolin-4(3*H*)-one ring synthesis. An updated, concise report on the various synthetic approaches is, however, presented here. Several synthetic approaches for the construction of quinazolin-4(3*H*)-one ring system are reported in the literature. Some of the synthetic methods are discussed bellow and classified on the basis of synthetic methodologies followed and starting material used.

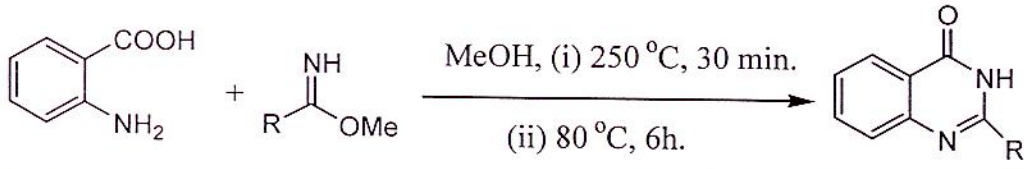
1.2.1. Classical methods

Anthranilic acid and their derivatives have been the precursors of choice in many classical methods. In addition to it, other simple starting materials like substituted aniline, *ortho*- nitrobenzoic acids, acyl azide isocynates and others have also been reported for the preparation of quinazolin-4(3*H*)-ones.

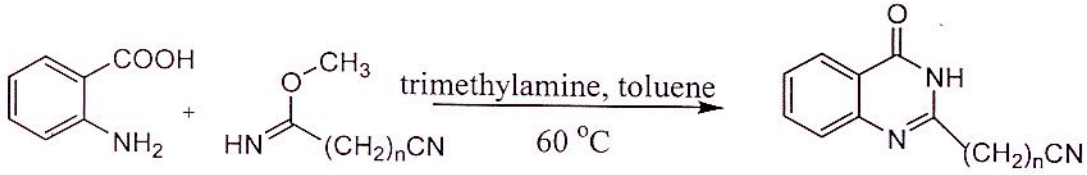
1.2.1.1. Synthesis from anthranilic acid and its derivatives

Anthranilic acid is the key starting material used for the synthesis of quinazolin-4(3*H*)-ones ring system and most of the published literature has utilized it either directly or indirectly for the synthesis of quinazolin-4(3*H*)-ones under various reaction conditions. Some of the most commonly practiced methods for the synthesis of quinazolin-4(3*H*)-one ring systems using anthranilic acid as a precursor are discussed here.

The synthesis of quinazolin-4(3*H*)-one *via* direct condensation of anthranilic acid and an imidate ester in refluxing methanol was independently reported by Ried *et al.* [18-22][Scheme 1.4] and Connolly *et al.*, [23] [Scheme1.5].

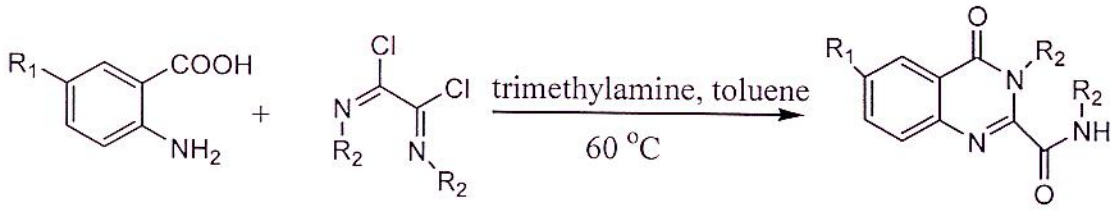


Scheme1.4: Ried *et al.*, approach for the synthesis of quinazolin-4(3*H*)-one



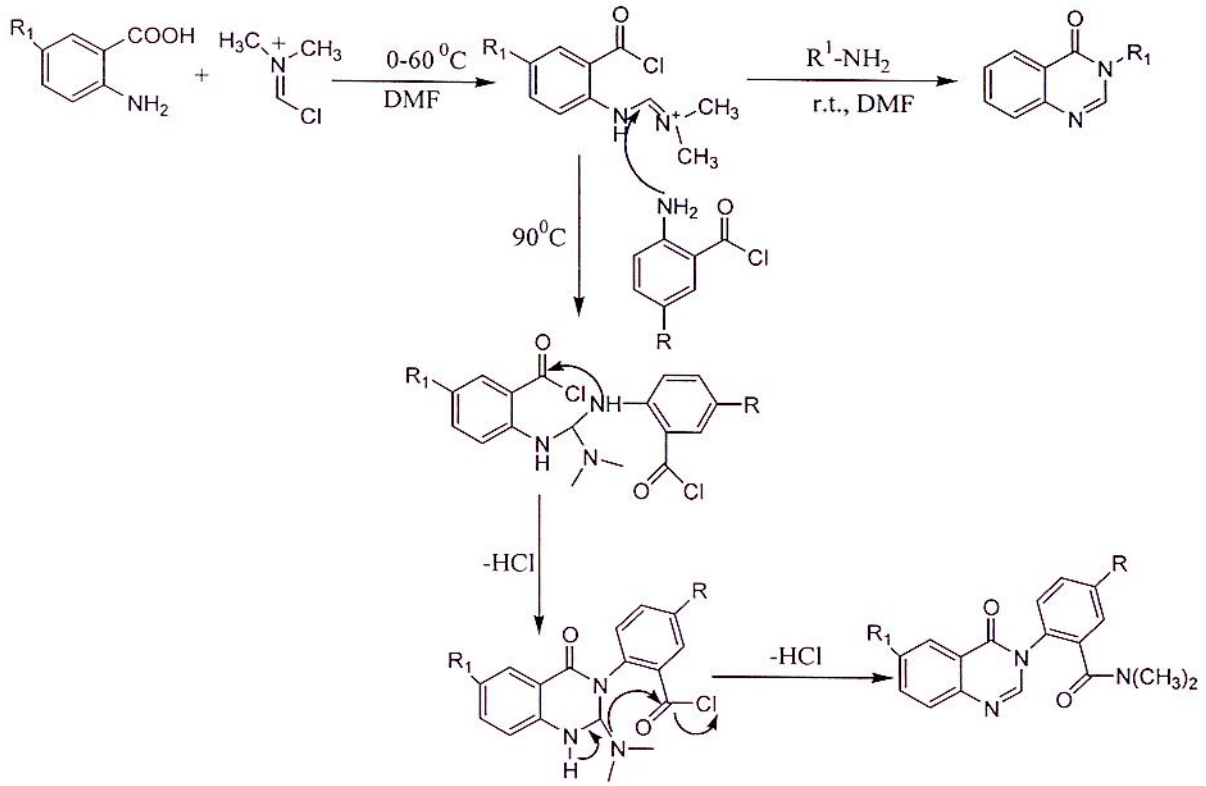
Scheme1.5: Connolly *et al.* approach to synthesis of quinazolin-4(3*H*)-one

A regioselective synthesis of thermodynamically stable 2, 3-disubstituted quinazolinone was investigated by Länger and Döring [24, 25] using oxalic acid bis (imidolyl chloride) and triethylamine in toluene at 60 °C [Scheme 1.6].



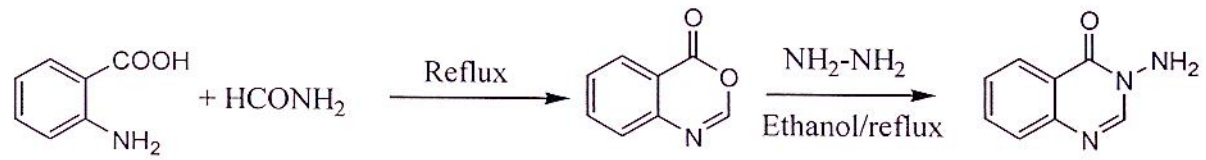
Scheme1.6: Länger and Döring approach to synthesis of quinazolin-4(3*H*)-one.

Perumal *et al.*, [26] investigated a novel route for the synthesis of 3-substituted quinazolin-4(3*H*)-one utilizing Vilsmeir reagent for the first time in the quinazolin-4(3*H*)-ones chemistry. It was proposed that anthranilic acid on reaction with Vilsmeir reagent give the corresponding methyleniminum salt of anthranilic acid chloride which on reaction with primary amines in suitable basic media (DMF) at room temperature afforded 3-substituted quinazolin-4(3*H*)-one. While at high temperature, it reacted with *ortho*-aminobenzoyl chloride and gave diacid chloride salt. The letter one is mechanistically interesting cyclization followed by intermolecular migration of the dimethylamino group is implicated in [Scheme1.7].



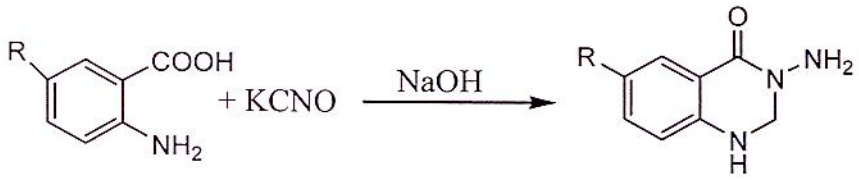
Scheme1.7: Perumal *et al.*, approach to synthesis of quinazolin-4(3*H*)-one.

An alternative protocol for the construction of quinazolin-4(3*H*)-one nucleus in good yield was devised by Vigril and Dai [27] involving initial conversion of anthranilic acid in to benzoxazinone on refluxing with triethyl orthoformate followed by reacting with primary aliphatic or aryl amines to give 3-substituted quinazolin-4(3*H*)-ones in good yield [Scheme 1.8]. This method, however, is associated with a draw back because the benzoxazinone on reaction with primary amines give mixture of products and thus, lowers the yields in addition to formation of a side product as diamiade. The diamide, however, on further dehydrative cyclization converted in to the corresponding quinazolin-4(3*H*)-ones.



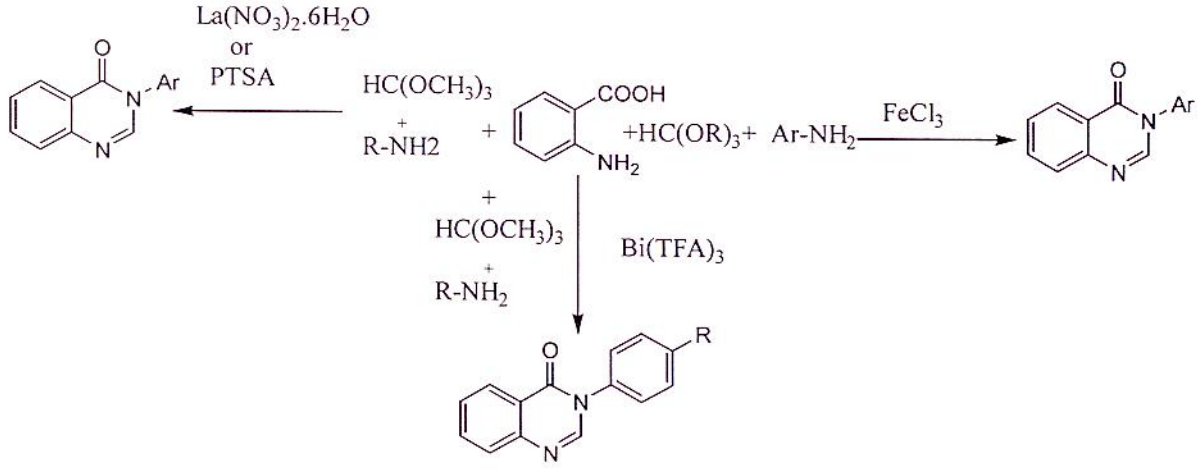
Scheme1.8: Virgil *et al.*, approach to the synthesis of quinazolin-4(3*H*)-one

Hammen and Allen [28 a, b] have synthesized quinazolin-4(3*H*)-ones and quinazolin-2, 4-diones by treatment of anthranilic acid and potassium cyanate followed by cyclization [Scheme1.9]. This is an efficient chemoselective method for the synthesis of 3-amino-2-substituted quinazolin-4(3*H*)-ones.



Scheme1.9: Hamman *et al.*, approach to the synthesis of quinazolin-4(3*H*)-one

Khosropour *et al.*, Adheven *et al.*, and Narasimhulu *et al.*, have independently described three component, one-pot synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones. [29-31] Anthranilic acid, suitable *ortho*- esters and primary aliphatic or aromatic amines were used under various catalytic conditions resulting in substantial yields of the products [Scheme 1.10].

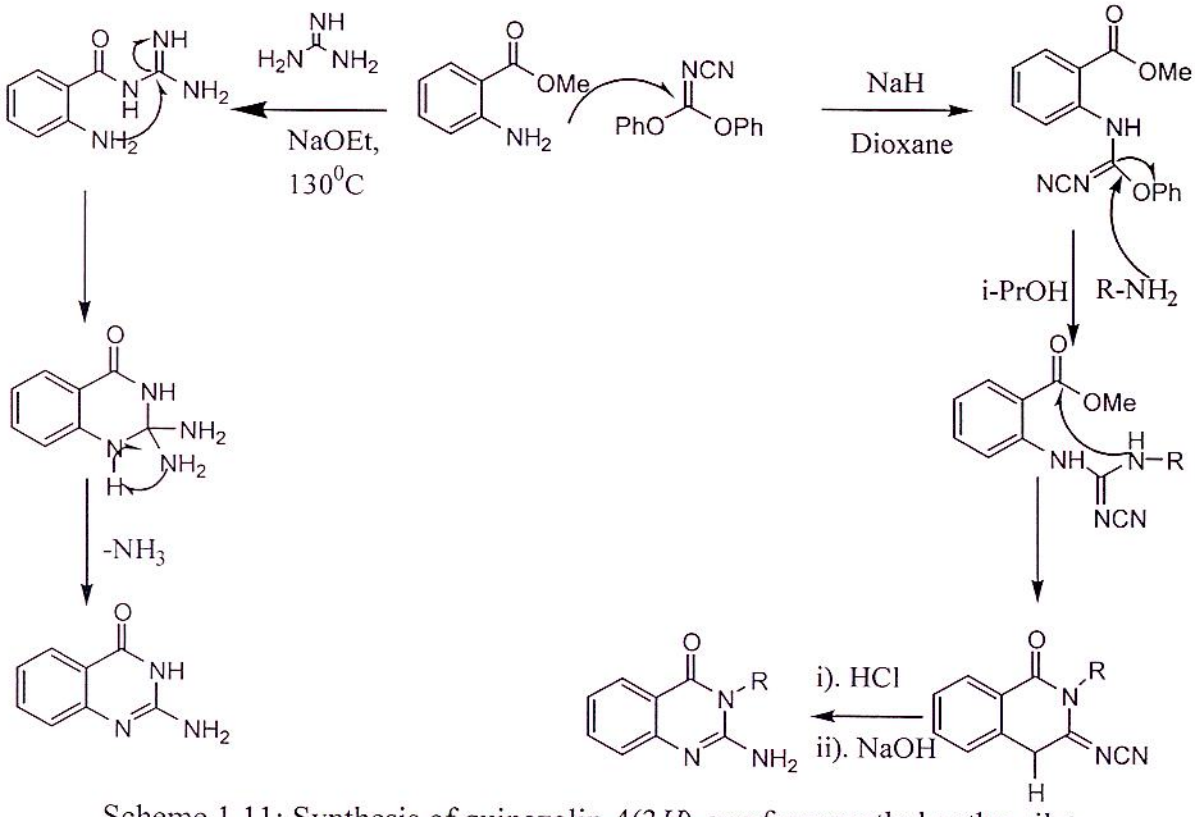


Scheme 1.10: Solvent free three components one-pot synthesis of quinazolin-4(3*H*)-one

1.2.1.2 Synthesis of quinazolin-4(3*H*)-ones from methyl anthranilate

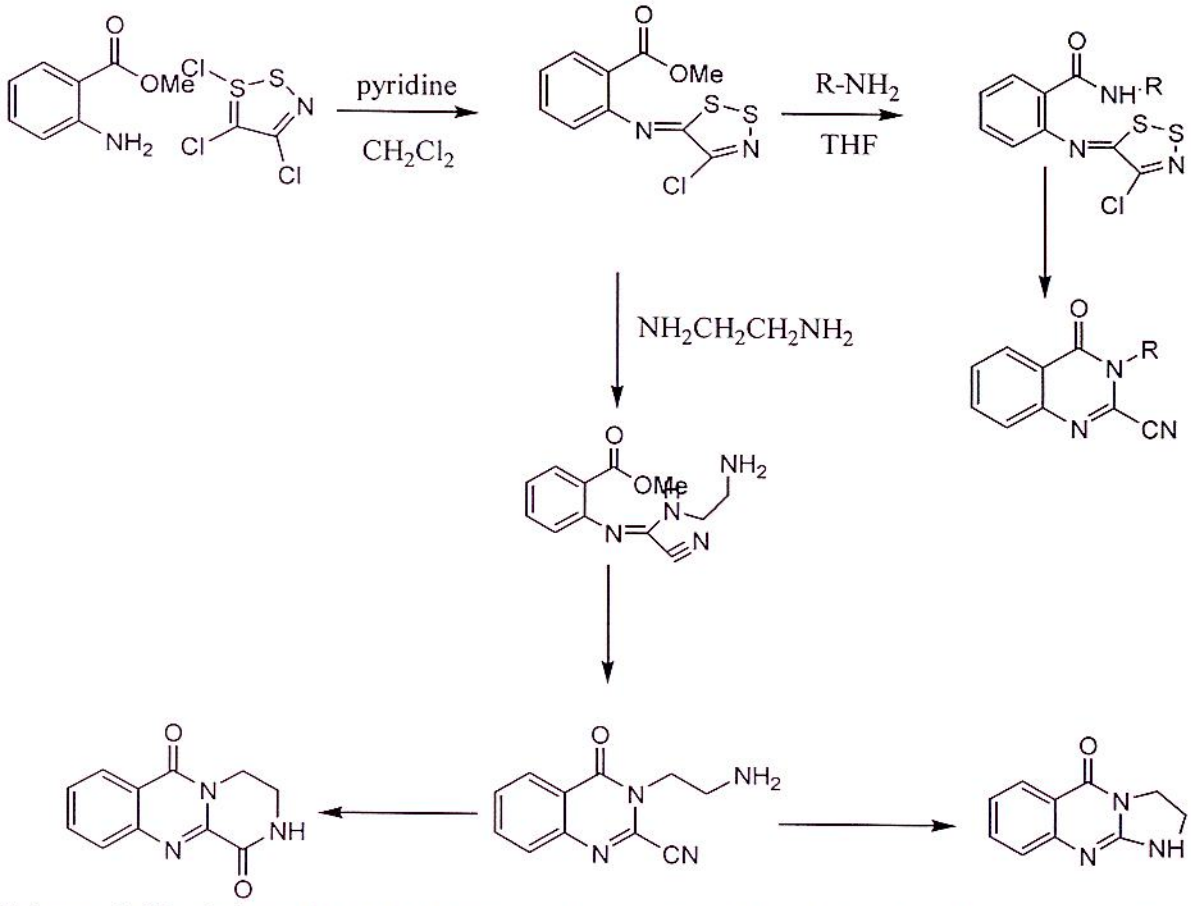
Methyl anthranilate and other anthranilic acid esters find wide applications in the synthesis of quinazolin-4(3*H*)-one scaffold. Garratt *et al.*, [32] described the synthesis of 2-aminoquinazolin-4(3*H*)-ones by the reaction of methyl anthranilate and diphenylcyanocarbodiamide using sodium hydride as a catalyst *via* *o*-phenylisourea intermediate followed by treatment with a suitable primary amine yielding 3-substituted-

4-oxo-3, 4-dihydro-1*H*-yliden-cyanamide. This further upon acid hydrolysis with HCl followed by treatment with NaOH yielded 2-aminoquinazolin-4(3*H*)-one. While in an alternative method, Hess *et al.*, [33]explored the reactivity of methyl anthranilate and guanidine in basic media for the synthesis of 2-aminoquinazolin-4(3*H*)-one by refluxing methyl anthranilate with excess of guanidine base in the presence of sodium ethoxide base [Scheme 1.11].



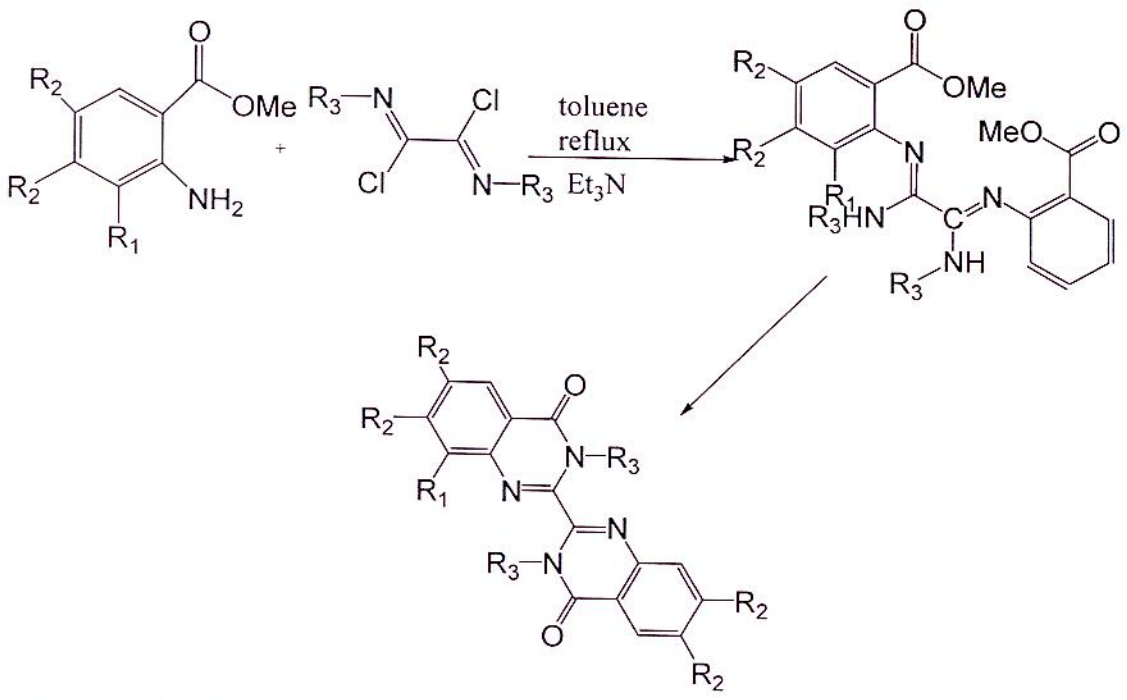
Scheme 1.11: Synthesis of quinazolin-4(3*H*)-one from methyl anthranilate

Appel's salt (4, 5-dichloro-1, 2, 3-dithiazoloium chloride) finds wide applications in organic synthesis and was for the first time utilized in the synthesis of 2-cyano, 3-alkyl-quinazolin-4(3*H*)-one by Kim. *et al.*[34] The reaction went through the initial formation of intermediate, which further reacted with a primary amine yielding the corresponding 2-cyano- 3-alkyl-quinazolin-4(3*H*)-one *via* desulfurization. This study was further extended through replacement of cyano group by a nucleophile as well as its condensation with 1, 2-diaminoethane. 3,4-dihydro-2,4-pyrazino[2,1,b] quinazolin-1,6-dione or 2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one was formed *via* internal replacement of cyano group [Scheme 1.12].



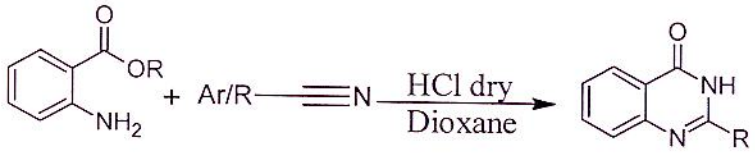
Scheme 1.12: Quinazolin-4(3*H*)-ones by the reaction of methyl anthranilate and appel's salt.

2, 2-Bisquinazolin-4(3*H*)-ones in low yields were prepared by reacting substituted methyl anthranilate and bis (phenylimidoyl) chloride in (2:1) molar ratio [Scheme 1.14].[35] The mechanism involves initial condensation followed by two-fold cyclization by internal nucleophilc attack of the amidine nitrogen on the ester group. This procedure offers an efficient and convenient route for the synthesis of new types of dimeric N-heterocyclic systems [Scheme1.13]. This reaction is opposite to the condensation of anthranilic acid and bis (phenylimidoyl) chloride as explained in [Scheme 1.6], where 1:1 molar ratio gave simple substituted quinazilin-4(3*H*)-ones.



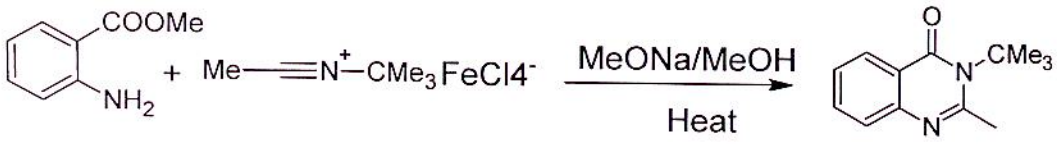
Scheme1.13: Dimeric quinazolin-4(3*H*)-ones from methyl anthranilate and imidolyl chloride

Anthranilates on reaction with both aryl and alkyl nitriles in the presences of dry HCl yield the corresponding 2-substituted quinazolin-4(3*H*)-one [36]. [Scheme1.14].This method, however, is associated with water sensitivity of both the starting esters and nitrile.



Scheme1.14: Synthesis of 2-substituted quinazolin-4(3*H*)-one *via* cyclocondensation of *ortho*-aminoester with alkyl/aryl cyanide.

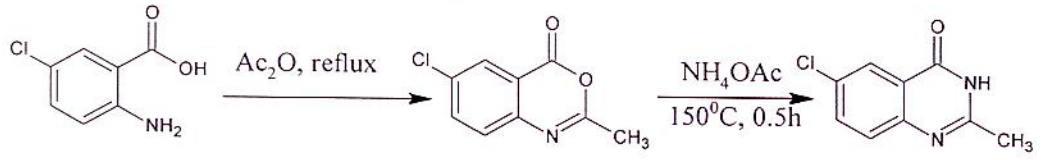
N-t-butyl amidine esters prepared from N-t-butyl acetonitrilium tetrachloroferate and methyl anthranilate on heating in strong basic media such is sodium methoxide yielded the corresponding quinazolin-4(3*H*)-ones [Scheme 1.15] [37].



Scheme 1.15: Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones via N-t-butyl acetonitrilium tetrachloroferate.

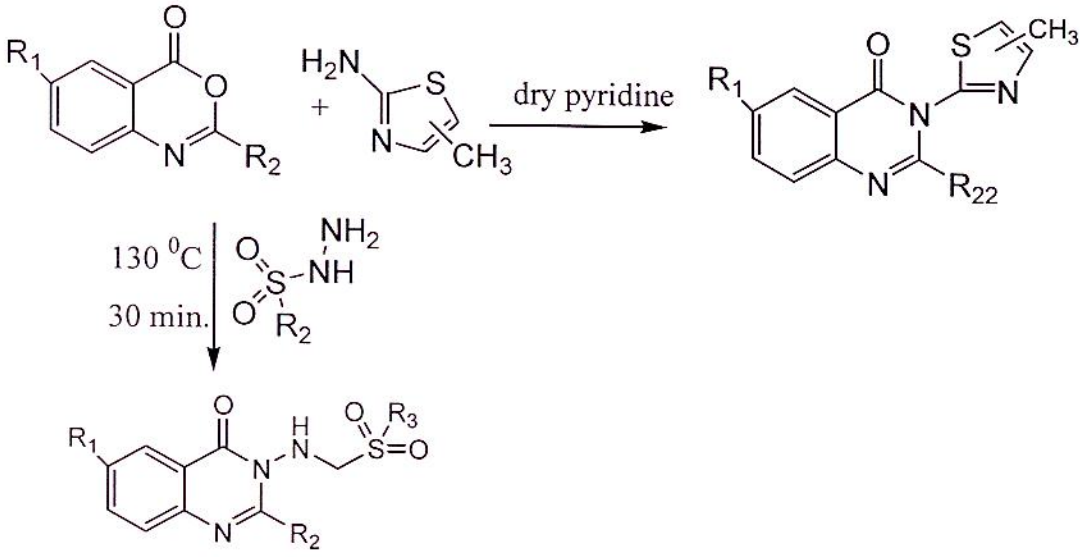
1.2.1.3. Synthesis from Benzoxazinone

Substituted benzoxazinones are important synthetic precursors for the synthesis of many heterocyclic compounds including the 2, 3-disubstituted quinazolin-4-(3*H*)-one ring system [38, 39]. Due to simple reaction procedure, most of the available literature is about the direct insertion reaction of primary amine into benzoxazinone in suitable high boiling solvent like, DMF, DMSO, pyridine, toluene, xylene and benzene[40-45]. Jiang *et al.*, [46] presented a simple and facile synthesis of quinazolin-4-(3*H*)-one by the initial treatment of 5-chloroanthranilic acid and acetic anhydride that resulted in benzoxazinone. The benzoxazinones further upon stirring with ammonium acetate at elevated temperature gave substituted quinazolin-4(3*H*)-one [Scheme 1.16]



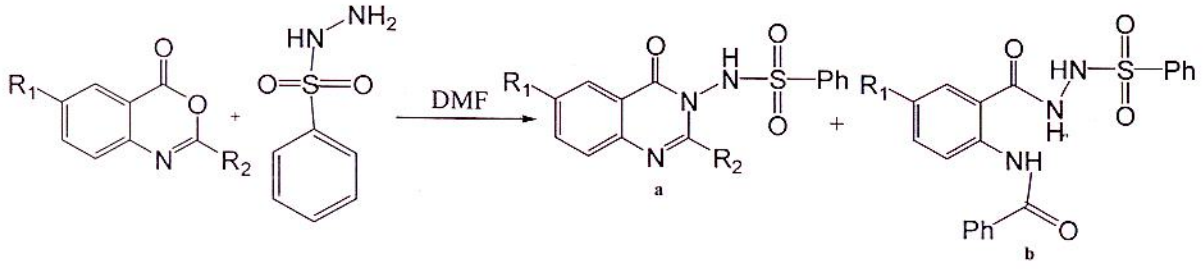
Scheme 1.16: Jiang *et al.*, approach to the synthesis of quinazolin-4(3*H*)-ones.

Parkanyi *et al.*, [47] and Zhou *et al.*, [48] have reported the synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-one in substantial yield by reacting benzoxazinone with amino-substituted thiazoles in boiling pyridine and a variety of substituted alky/aryl sulfonyl hydrazides.[Scheme 1.17].



Scheme 1.17: Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-one *via* reaction of 2-substituted benzoxazinones and primary amine.

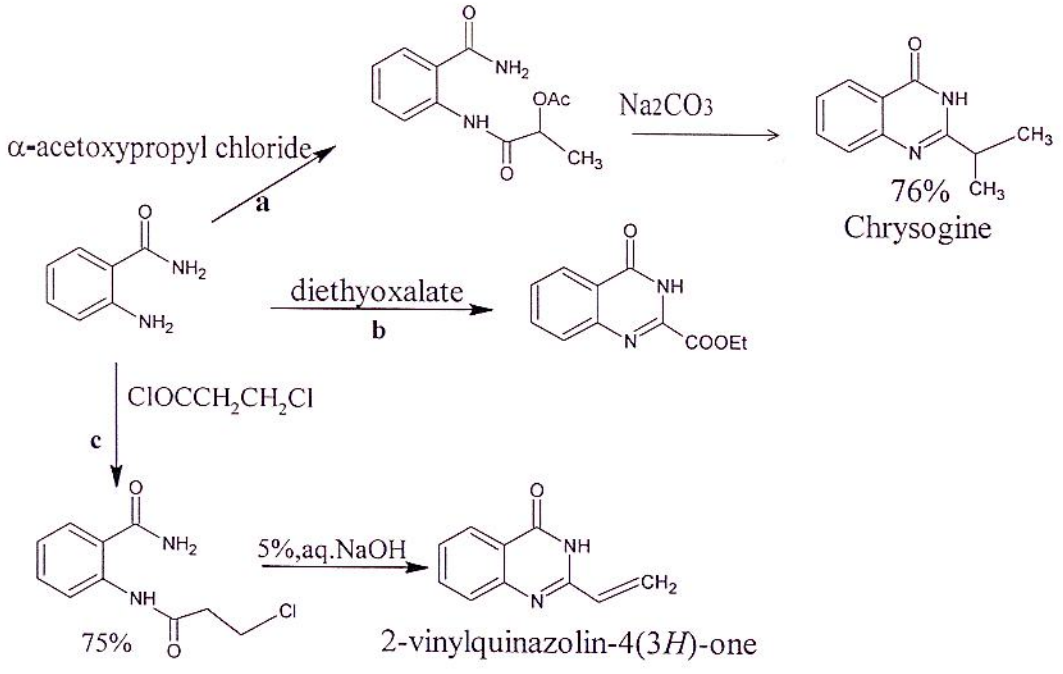
Considering the structure of benzoxazinone nucleus, two sites are available for nucleophilic attack, which can lead to the opening of the heterocyclic part of benzoxazinone. In most of the cases, re-closure of the heterocyclic part of the molecule provides a new compound with interesting chemical properties [49]. Competition between the two mentioned sites towards nucleophilic attack depends on different parameters such as the size of the nucleophile, the nucleophilicity of the nucleophile and the nature of the substituted nucleophile with respect to the two rings of the benzoxazinone. In general, benzoxazinones offer good opportunities for synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones. Sufficient literature is available on the utility of benzoxazinones for the synthesis of novel 2, 3-disubstituted quinazolin-4(3*H*)-ones [50]. During the course of investigation of the reactions of benzoxazinones with suitable primary amines, some open chain products have been investigated. Thus, a hypothesis was established that these reactions proceed *via* an open chain diamide as intermediate, which upon subsequent dehydration at elevated temperature or in the presence of dehydrating agent cyclized to the corresponding 2, 3-disubstitued quinazolin-4(3*H*)-ones [Scheme 1.18]



Scheme 1.18: Formation of open chain diamide intermediate

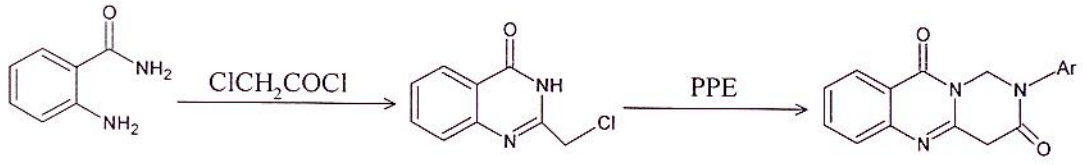
1.2.1.4. Synthesis of Quinazolin-4(3*H*)-ones Using Anthranilamide

The use of anthranilamide in the synthesis of quinazolin-4(3*H*)-one is known since 1887, when Körnor [13] reported the synthesis of 2-phenylquinazolin-4(3*H*)-one by cyclization of N-benzoyl *ortho*-anilamide with potassium hydroxide prepared from anthranilamide and benzoyl chloride in aq. NaOH. Bergman *et al.*, [51-53] has utilized the condensation of anthranilamide and 3-chloropropionyl chloride or with α-acetoxypropionyl chloride for the total synthesis of chrysogine and 2-vinylquinazolinone [Scheme 1.19]. While Baker and Almaula [54, 55] have reported the synthesis of 2-carboethoxyquinazolin-4(3*H*)-one by the condensation of anthranilamide and diethyl oxalate [Scheme 1.19].



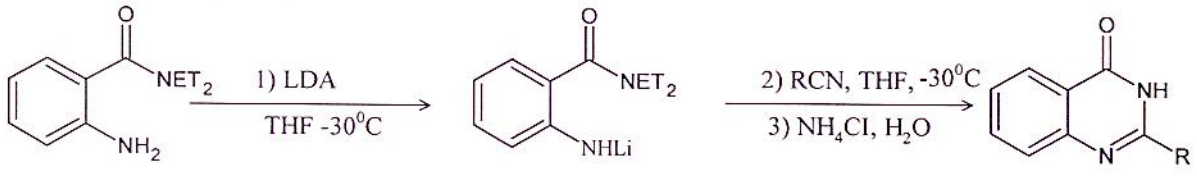
Scheme 1.19: Synthesis of chrysogine and 2-vinyl-quinazolinone from N-acylanthranilamide.

Redy et al., [56] have reported the use of polyphosphate ethylester (PPE) to achieve the synthesis of 2-chloromethylquinazolin-4(3H)-one in 71 % yield starting from anthranilamide. The 2-chloromethylquinazolin-4(3H)-one was further manipulated to acomplish 2-aryl-2Hpyrazino [2,1-b]quinazoline-3,6(1H,4H)-diones [Scheme 1.20].



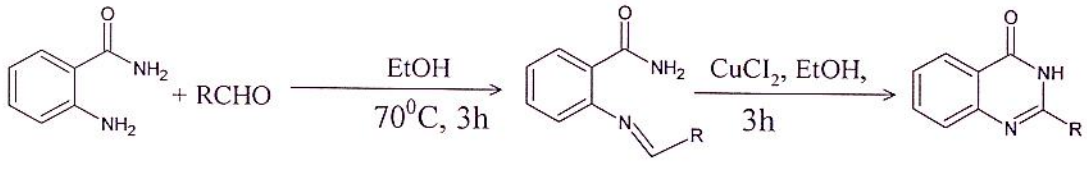
Scheme 1.20: Redy *et al.*, approach to the synthesis of 2-aryl-2*H*-pyrazino [2, 1-b] quinazolin-3, 6 (1*H*, 4*H*)-diones.

Couture *et al.*, [57] has reported a novel procedure for the synthesis of 2-aryl/alkyl quinazolin-4(3*H*)-ones by lithiation of 2-(diethylaminocaboxyl) anilide, followed by reacting with aryl/alkylnitrile [Scheme1.21]



Scheme1.21: Synthesis of 2-aryl/alkyl quinazolin-4(3*H*)-ones via lithation of anthranilamide.

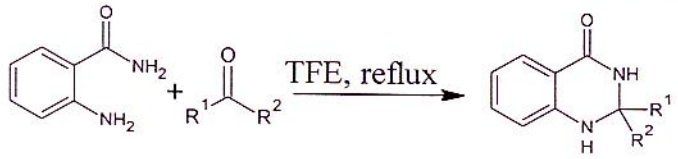
Similarly, the direct condensation of anthranilamide and aldehyde in refluxing ethanol followed by catalytic cyclization has been reported by abdel-jalil *et al.*, [58] [Scheme 1.22].



Scheme 1.22: Abdel-jalil *et al.*, approach to the synthesis of quinazolin-4-(3*H*)-one.

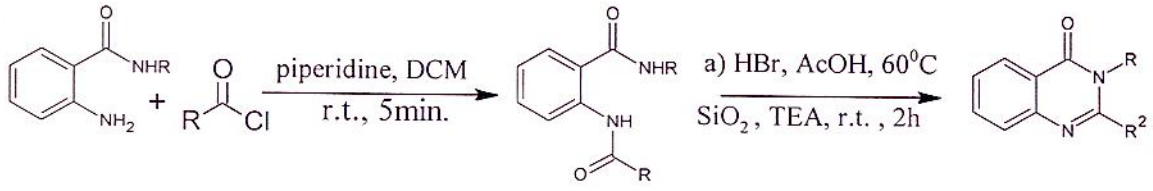
2,3-Dihydro-4(1*H*) quinazolinone derivatives are important bicyclic heterocycles and have attracted the attention of the chemists due to their wide range of biological activities such as anticancer [59], diuretic [60] and antibacterial activities [61], etc. Furthermore,

2, 3-dihydro-4(1*H*)-quinazolinones can be easily oxidized by NaHSO or DDQ to 4(3*H*)-quinazolinones [62-63]. Condensation of anthranilamide with structurally diverse ketones or aldehydes catalyzed by bases or acids has been widely utilized for the synthesis of 2, 3-dihydro-4(1*H*)-quinazolinones [64-66]. Zhan Qiao *et al.*, [67, 68] have developed a facile way to access 2, 3-dihydro-4(1*H*)-quinazolinones by treating anthranilamide with structurally diverse ketones or aldehydes in the presence of triflouroacetic acid (TFE) [Scheme 1.23].



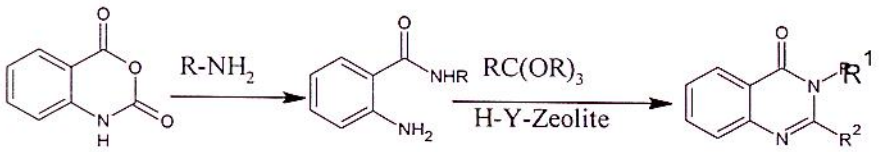
Scheme 1.23: Zhan Qiao *et al.*, approach to the synthesis 2, 3-dihydro-4(1*H*)-quinazolinones.

Chen *et al.*, [69] have developed a green, simple and practical method for the synthesis of 2, 3-dihydro-2-aryl-4(1*H*)-quinazolinones from *ortho*-anthranilamide and aldehyde using $Sc(OTF)_3$ as a catalyst while Kshirsagar *et al.*, [70] have reported an efficient method for the synthesis of 2,3-disubstituted quinazolin-4(3*H*)-ones [Scheme1.24] by reacting anthranilamide with an acid halide at room temperature in suitable basic media followed by the cyclization of the resulting product at elevated temperature using acetic acid or at room temperature on stirring over SiO_2.



Scheme 1.24: Jiu. XeChen *et al.*, approach to the synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones.

2H-3,1-benzoxazine-2,4(1H)-dione, a very active phosphodiesterase inhibitor was used as a starting material for the synthesis of 2,3 disubstituted quinazolin-4(3H)-one heterocycles by by Bakavoli et al., [71]. In this method, 2-amino-N-alkylbenzamide intermediate was prepared from 2H-3,1-benzoxazine-2,4(1H)-dione and suitable primary amine. 2-amino-N-alkylbenzamide on reaction with trialkylorthoacetate leads to the formation of 2, 3 disubstituted quinazolin-4(3H)-one via ring closing mechanism



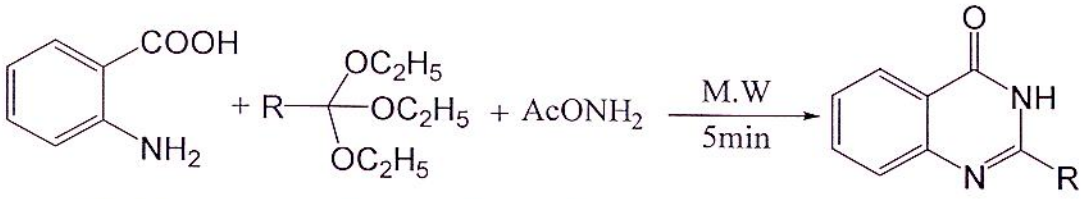
Scheme 1.25: B. Bakavoli *et al.* approach to the synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-one.

1.3. Microwave Approaches to Synthesis of Quinazolin-4(3*H*)-ones

Use of microwave is relatively new and a fast growing area in organic synthesis. Microwave methods were introduced in organic chemistry during the mid of 1980's and got very steady growth till the mid of 1990's. But after 1990's, considerable interest was developed in microwave – assisted chemistry and the number of publications have significantly increased in this area of chemistry [72].

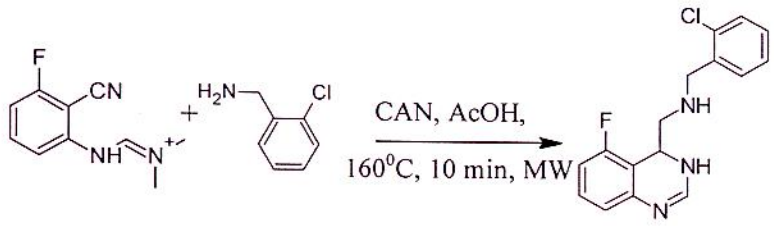
In the beginning, domestic microwave oven was the main source for carrying out organic transformations; however, achievements in the field of microwave chemistry have resulted in the invention of microwave synthesizers having higher accuracy and efficiency. The use of microwave technology in organic synthesis has been comprehensively reviewed by Lidstörm [73].

Due to both biological and synthetic importance of quinazolin-4(3*H*)-ones, increased interest has developed towards development of rapid, cheaper and cleaner synthetic methods for both already known and new quinazolin-4(3*H*)-ones heterocycles. In this quest, successful attempts have been made to synthesize quinazolin-4(3*H*)-ones nucleus. Moghdam *et al.*, have successfully synthesized 2, 3-disubstituted quinazolin-4(3*H*)-ones from the reaction of anthranilc acid, *ortho* ester and ammonium acetate under microwave conditions [74, 75] [Scheme 1.26].



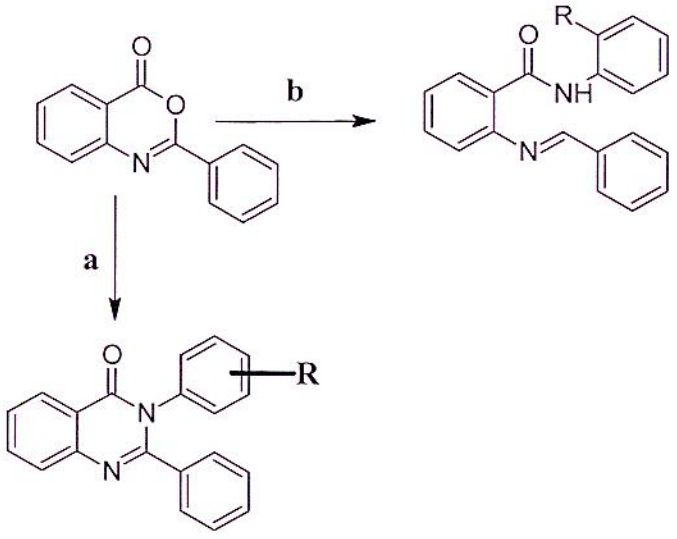
Scheme 1.26: Microwave- assisted synthesis of quinazolin-4(3*H*)-one nucleus.

Yoon *et al.*, [76] have prepared 4-aminoquinazoline from N, N-dimethylaminobenzamide with benzyl amine using ceric ammonium nitrate (CAN) under microwave irradiation [Scheme 1.27].



Scheme 1.27: Yoon *et al.* approach for the synthesis of quinazolin-4(3*H*)-ones

Dandia *et al.*, [77] reported the synthesis of some 2, 3 disubstituted quinazolin-4(3*H*)-ones from the reaction of benoxazine-4-one generated *in situ* under microwave irradiations. They observed that the substitution pattern affects the ring closing step as in case of *ortho* -substituted phenyl group they failed to obtaine 2, 3 disubstituted quinazolin-4(3*H*)-ones [schem1.28].

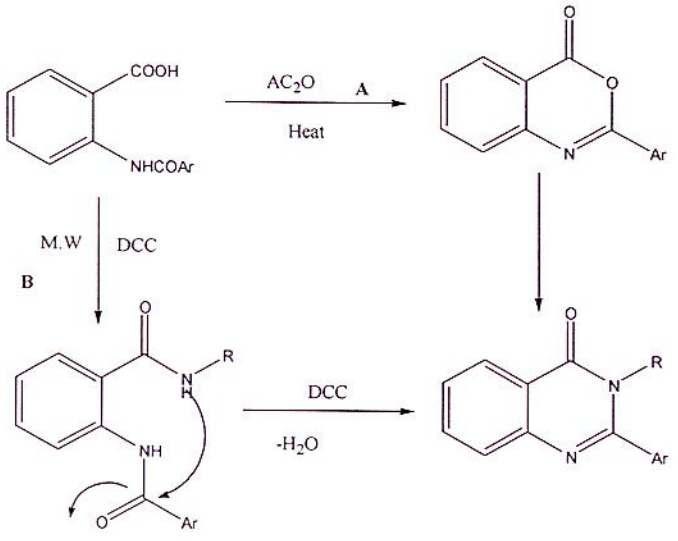


a. Microawave irradiation, cyclization takes place when R is not at *ortho*- position.

b. Reaction failed to cyclize in the presence of *ortho* substituent

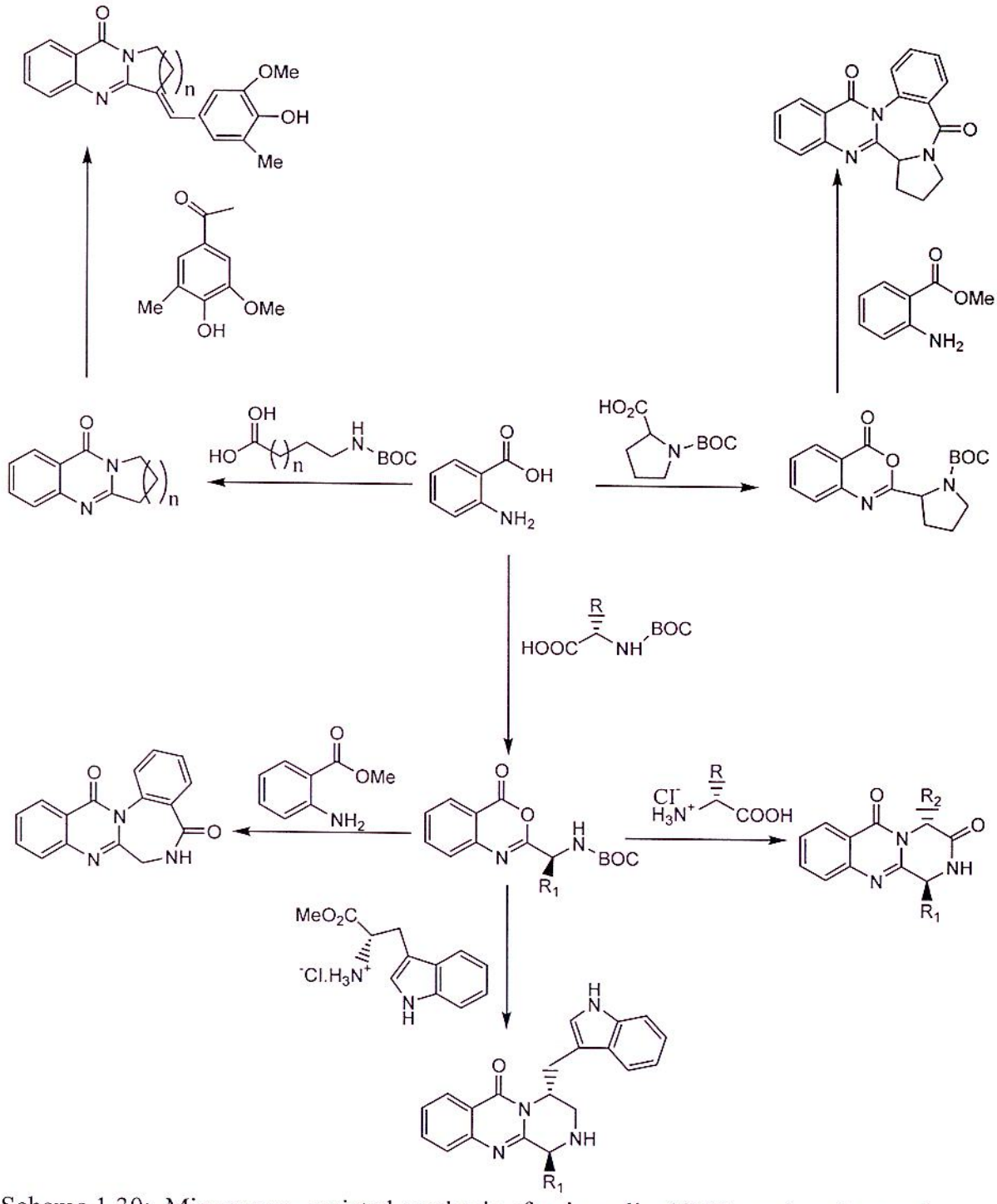
Scheme 1.28: Microwave - assisted synthesis of quinazolin-4(3*H*)-one from benzoxazinone

Kidwai [78] reported two different routes for the synthesis of several substituted quinazolin-4(3*H*)-ones under microwave conditions i.e. irradiating *ortho*-(benzoyl/phenyl)-aminobenzoic acid and primary amine in the presence of a coupling reagent, dicyclohexylcarbodiimide (DCC) and an alternate procedure by irradiating 2-arylbenzoxazinone and suitable primary amine over acidic alumina. [Scheme1.29]



Scheme 1.29: Microwave- assisted synthesis of quinazolin-4(3*H*)-one using coupling reagents

Liu [79] used microwave methodology for the first time in the synthesis of quinazolin-4(3*H*)-ones based natural products. In addition to synthesis of various substituted quinazolin-4(3*H*)-ones based heterocycles they have also reported novel one-pot microwave – assisted procedure for the synthesis of the pyrazino [2, 1-b] quinazoline-3, 6-dione, quinazolinobenzodiazepine, pyrrolo[2,1-b] quinazoline and quinazolinocarboline alkaloids [Scheme1.30].

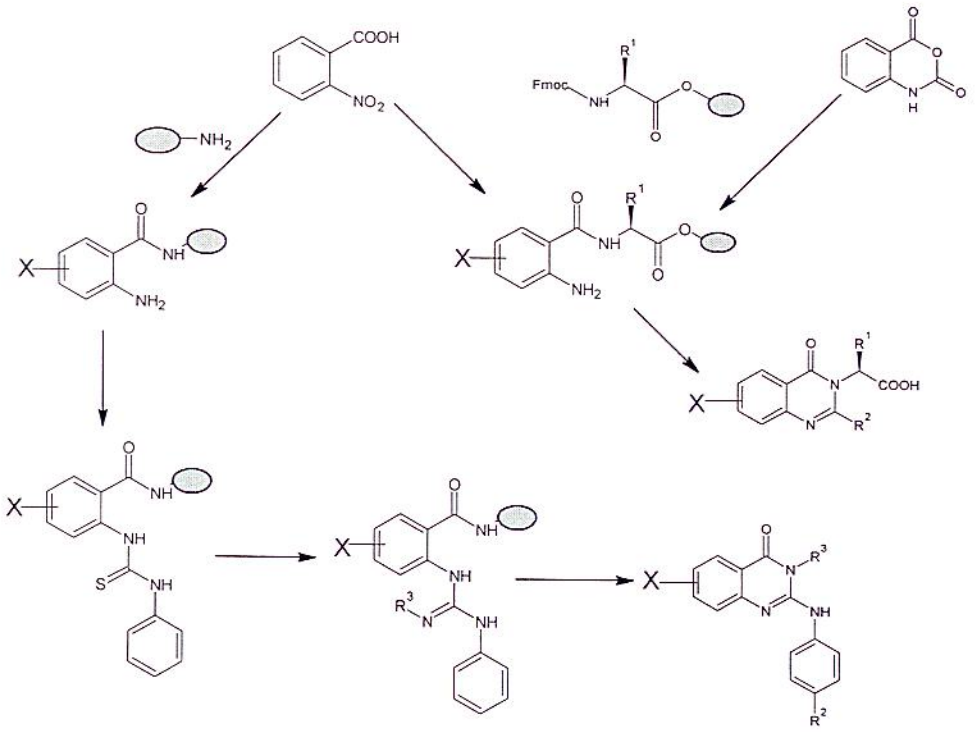


Scheme 1.30: Microwave- assisted synthesis of quinazolin-4(3*H*)-one based natural products

1.4. Solid Phase Synthesis

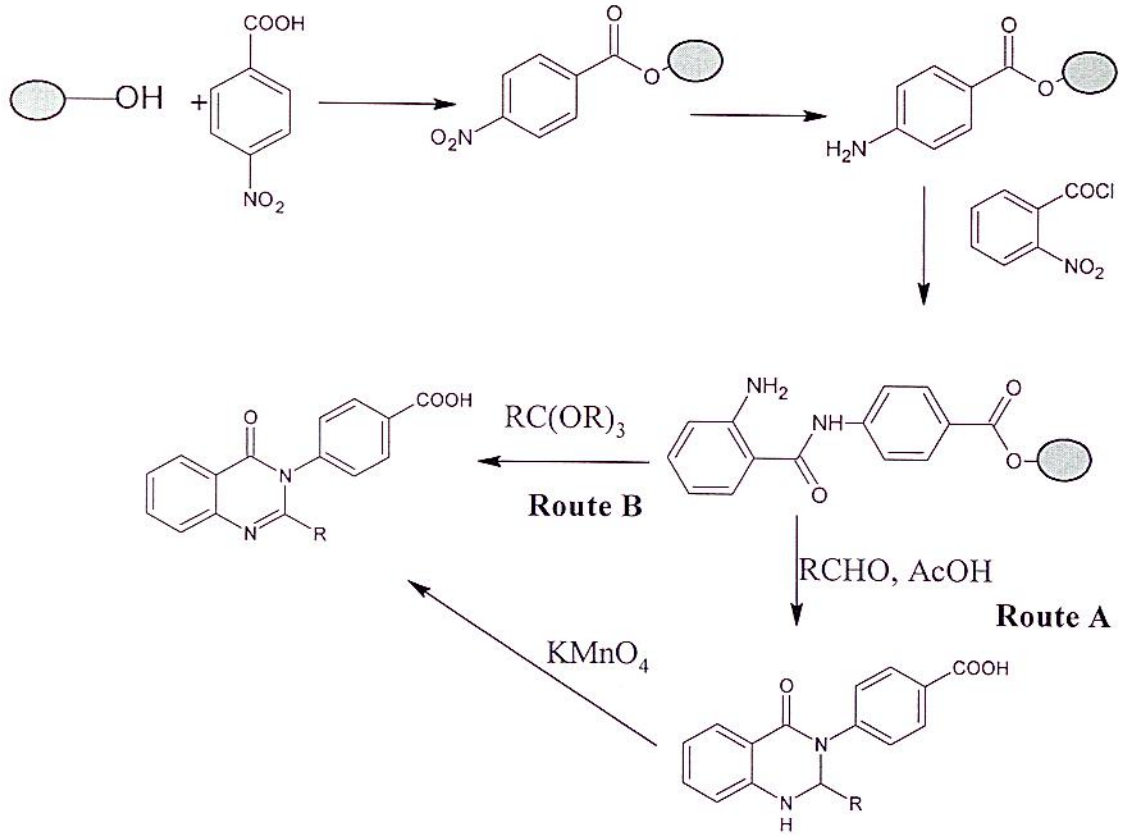
During the recent decades, combinatorial chemistry has proven to be a highly powerful tool in drug discovery and has, therefore, become popular among medicinal chemists [80]. This new technique has encouraged chemists to evolve new synthetic approaches suitable for the preparation of combinatorial libraries. This has led to the development of new solid-phase strategies for the synthesis of quinazolin-4(3*H*)-ones derivatives. Vogal and Marzinzik have reviewed literature on the solid phase synthesis of quinazolines and quinazolones [81].

A traceless and chemoselective approach for the synthesis of quinazolin-4(3*H*)-one was devised by Houghten *et al.*, [82] using *para*-methyl benzhydryl amine (MBHA) as resin to which *ortho*-nitrobenzoic acid was linked. Reduction of the nitro group resulted in amine which was condensed with phenylisothiocynate. The product was further treated with a primary amine in the presence of Mukaiyama's reagent and was finally cyclized to the corresponding 4(3*H*)-quinazolinone [Scheme1.31].



Scheme 1.31: Houghten *et al.*, Solid phase synthesis of 2, 3 disubstituted quinazoli-4(3*H*)-ones.

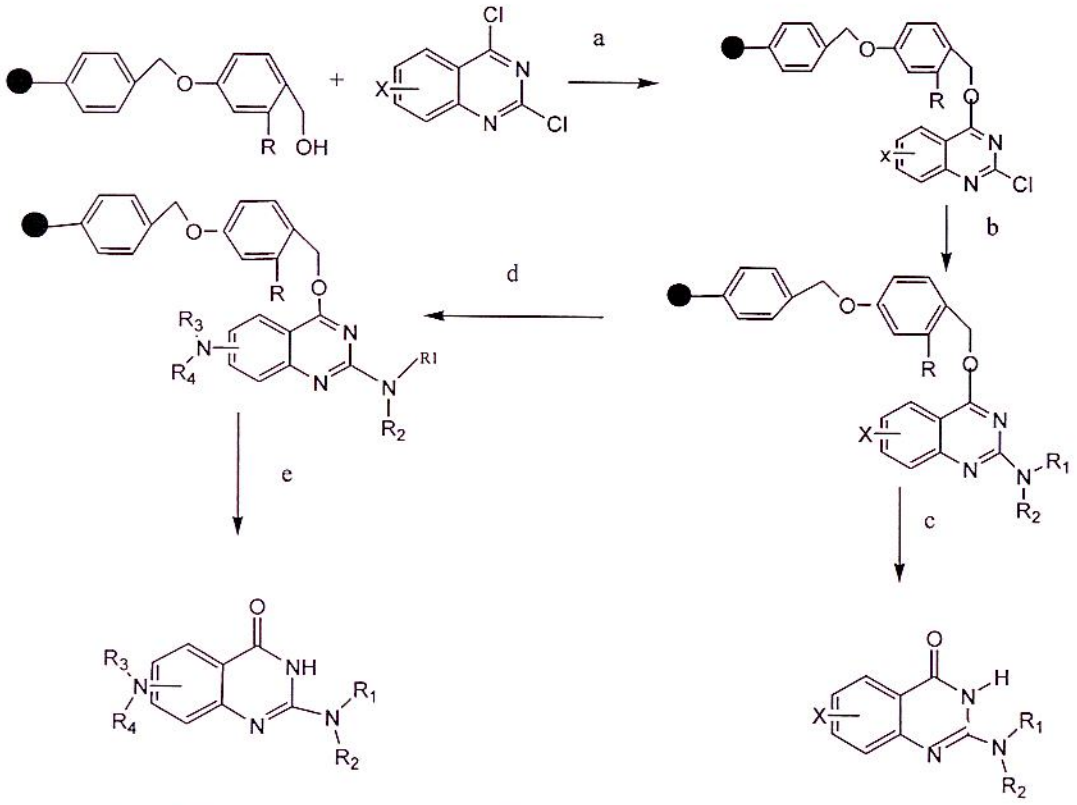
Zhang *et al.*, and Makino *et al.*, [83] separately described the synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones using polymer-supported anthranilamide as precursor. Zhang *et al.*, reacted polymer-supported anthranilamide with aldehyde or ketone and obtained 1, 2-dihydroquinazolin-4-one, which upon oxidation with $KMnO_4$ gave 2, 3-disubstituted quianzolin-4(3*H*)-one. [Scheme1.32, route B]. This method was, however, not applicable to the molecules susceptible to $KMnO_4$ oxidation and therefore, Makino *et al.*, synthesized 2, 3-disubstituted quianzolin-4(3*H*)-one by reacting polymer-supported anthranilamide with alkylorthoformate under milder acidic conditions [Scheme 1.33, route. B] in sufficient purity and substantial yield.



Scheme 1.32: Solid phase synthesis of 2, 3 disubstituted quinazoli-4(3*H*)-ones.

Weber *et al.*, [84] have recently reported a new regioselective approach to the solid phase synthesis of 2, 6- and 2, 7-diaminoquinazolin-4(3*H*)-one [Scheme1.33]. This method involves coupling of 2, 4, 6- and 2, 4, 7- trichloroquinazoline to a solid support *via* benzyl alcohol type linker and subsequent displacement of the chlorine at C-2 position by an amine followed by cleavage of the product from the resin, while a second

amino group was introduced *via* palladium-catalyzed amination followed by the cleavage of product from the linker.



Reagents and conditions: (a) n-BuLi, -20 °C., r. t., 16h. (b) HNR_1R_2, DMF, 80-100 °C, 3h.

(c) TFA/DCM, r.t., 2h. (d) HNR_3R_4, pd-complex, NaOtBu, o-xylene, 100 °C, 24h.

(e) TFA/DCM, r.t., 2h.

Scheme 1.33: Csaba Weber *et al.*, Solid phase synthesis of quinazolin-4(3*H*)-one

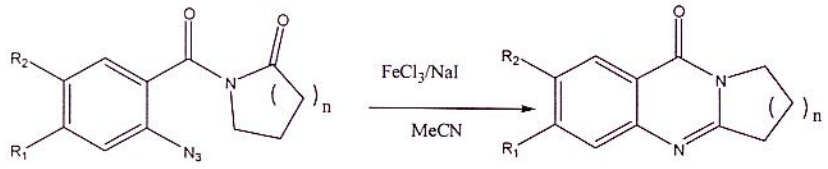
1.5. Miscellaneous Approaches

Here are some methods enlisted for the synthesis of quinazoilin-4(3*H*)-one ring system, where the starting materials are other than anthranilic acid, ester, benzoxazinone and anthranilamide. A brief survey of these methods is discussed.

1.2.4.1. Synthesis *via* coupling of azide and carbonyl compounds

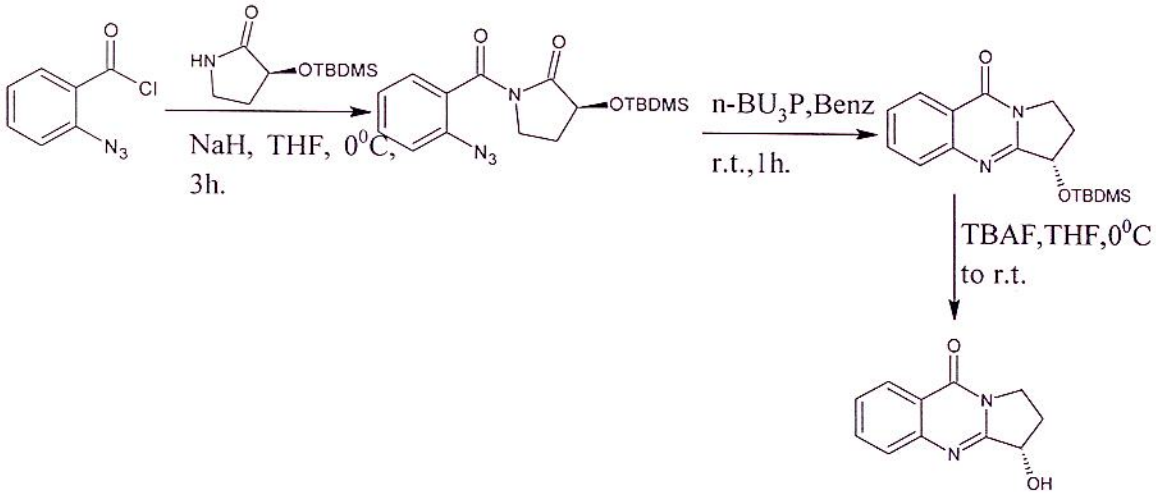
Kawal *et al.*, [85] have established an efficient intermolecular azido-reductive cyclization for the preparation of pyrrolo[2,1-b] quinazolin-4(3*H*)-one ring system using $FeCl_3$/NaI for the reduction of azide group for the first time. This new reductive

cyclization affords an alternative method for the synthesis of pharmacologically active fused ring quinazolin-4(3*H*)-ones and deoxyvascinone a quinazolinone natural product [Scheme 1.34].



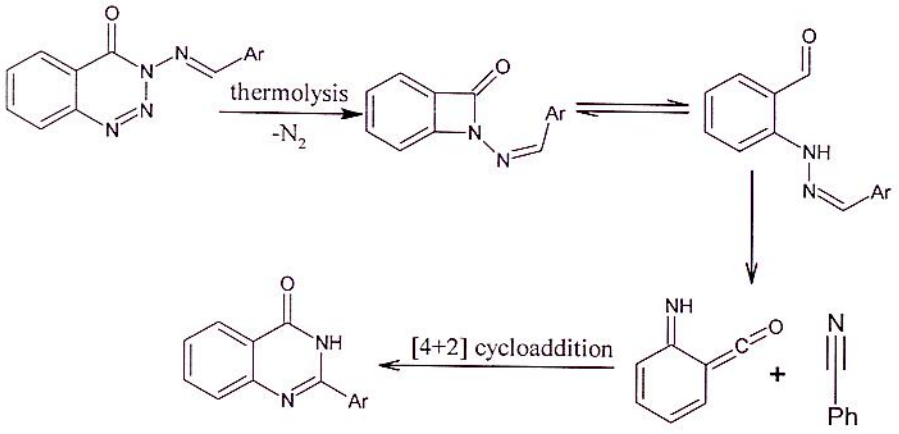
Scheme 1.34: Synthesis of annulated quinazolin-4(3*H*)-one via reductive cyclization using $FeCl_3$/NaI.

Euguchi *et al.*, [86] explored the interamolecular aza-Wittig reaction for the total synthesis of optically active *l*-Vasicinone by condensation of protected chiral synthone, (3S)-3-hydroxy-γ-lactame with *ortho*-azidobenzoyl chloride using sodium hydride in THF [Scheme 1.35].



Scheme 1.35: Euguchi *et al.*, approach to the synthesis of fused quinazolin-4(3*H*)-one ring system

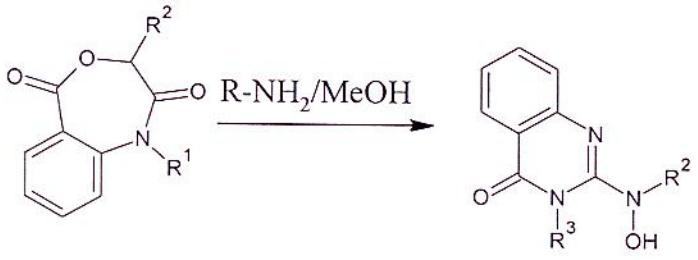
Smalley *et al.*, [87] prepared a series of 2-arylquinazolin-4(3*H*)-one by thermolysis of substituted benzotriazine-4-ones at elevated temperature in paraffin. The cyclization is believed to occur *via* 1, 3-hydrogen shift followed by loss of aryl cyanide, subsequent [4+2] cycloaddition with the iminoketene resulted in the formation of 2-arylquinazolinone[Scheme 1.36].



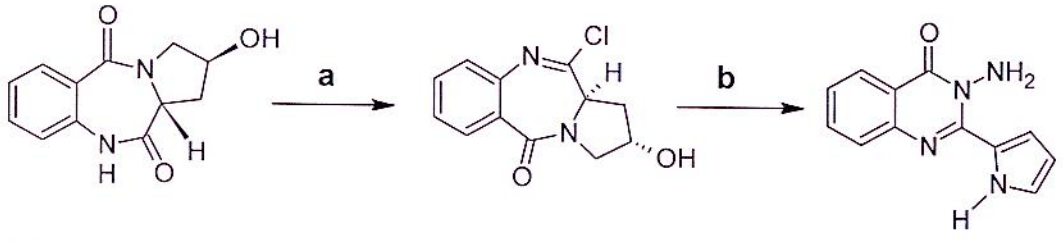
Scheme 1.36: Synthesis of 2-arylquinazolin-4(3*H*)-one from benzotriazine-4-one

1.2.4.2. Synthesis of quinazolin-4(3*H*)-one from benzodiazipines and benzoxazepinediones

Uskovokic *et al.*, [88] have reported the synthesis of 2-(α-hydroxy-alkyl)-3-N-methylquinazolinone from 4, 1- benzoxazepinediones [Scheme 1.37], while Fabis *et al.*, [89] have reported a straightforward method for the synthesis of 3-amino-2(1*H*-pyrrol-2-yl)-quinazolin-4(3*H*)-one *via* rearrangement of the 1, 4- benzoxazepinediones [Scheme 1.38].



Scheme 1.37: Synthesis of quinazolin-4(3*H*)-one from 4, 1- benzoxazepinediones

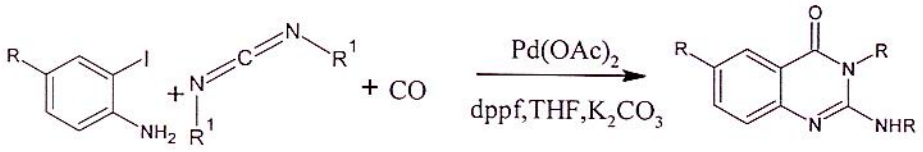


(a). $SOCl_2$/ pyridine, r. t., reflux. (b). Hydrazine hydrate, EtOH, r. t.

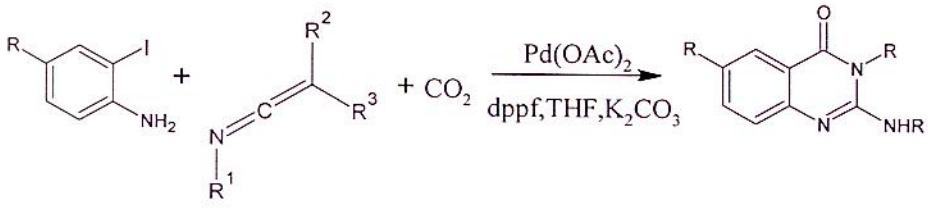
Scheme 1.38: Synthesis of quinazolin-4(3*H*)-one from 1, 4- benzoxazepinediones

1.2.4.3. Synthesis of quinazolin-4(3*H*)-ones by cyclocarbonization of *ortho*-iodoaniline

The synthesis of quinazolin-4(3*H*)-ones by reacting carbodiimides or ketenamines with *ortho*-iodoaniline and carbon monoxide under pressure in the presence of palladium acetate and diphenylphosphino ferrocene (dppf) was reported by Larksarp *et al.*,[90] [Scheme 1.39 & Scheme 1.38].

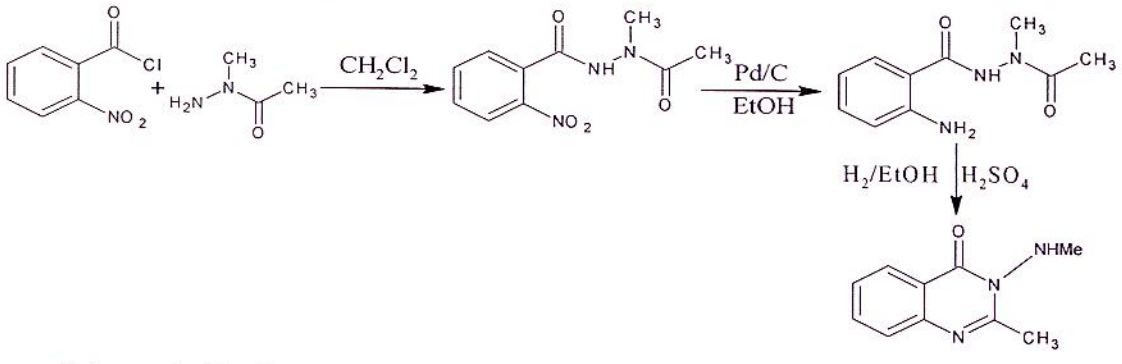


Scheme 1.39: Synthesis of quinazolin-4(3*H*)-ones using carbodiimides



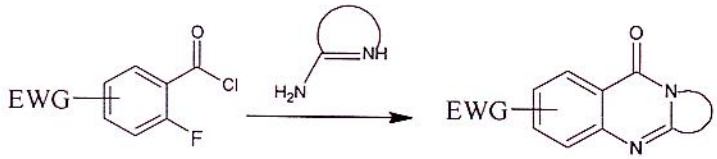
Scheme 1.40: Synthesis of quinazolin-4(3*H*)-ones using ketenamines

Peet *et al.*,[91] have described the synthesis of 2, 3-disubstitued quinazolin-4(3*H*)-one from *ortho*-nitrobezoyl chloride. In this procedure, *ortho*- nitrobezoyl chloride on reaction with 1-acetyl-1-methyl hydrazine under acidic condition gave *ortho*-nitrobenzoic acid produced *N*-acetyl-*N*-methyl hydrazide. The nitro group after reduction undergoes cyclization and yields the corresponding quinazolin-4(3*H*)-one. However, this method is low yielding [Scheme 1.41].



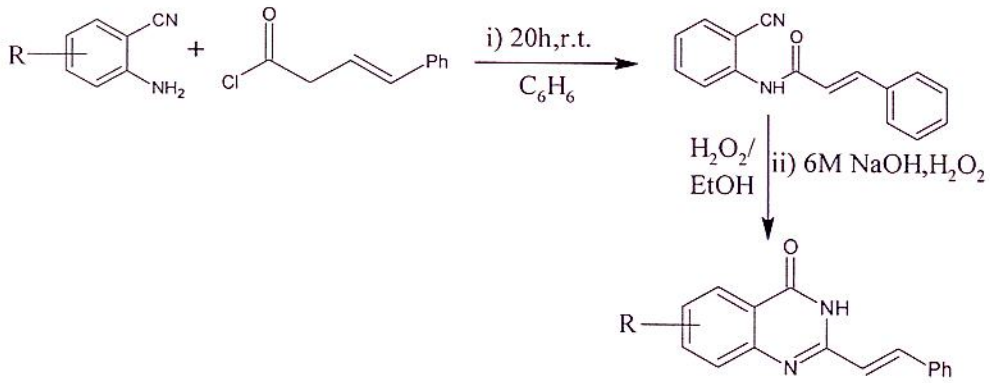
Scheme 1.41: Synthesis of 3-methylamino-2-methyl-quinazolin-4(3*H*)-ones via *ortho*- nitrobezoyl chloride

Smith *et al.*, [92] have developed one-pot synthesis of quinazolin-4(3*H*)-ones by cyclocondensation of 2-fluoro-substituted benzoyl chloride and 2-amino-*N*-heterocycles [Scheme 1.42].



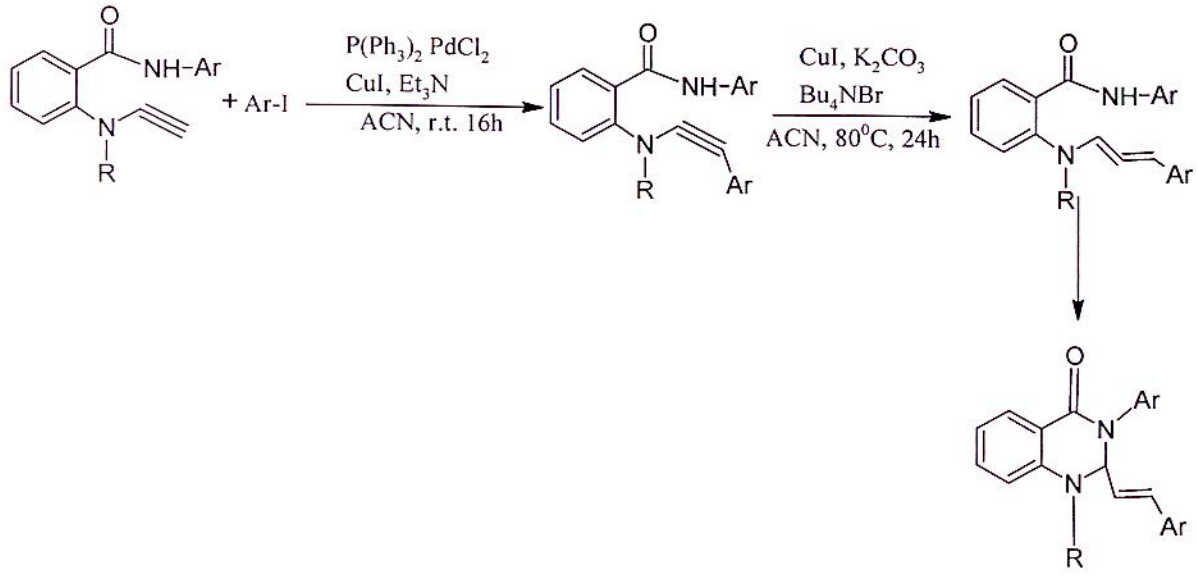
Scheme 1.42: Synthesis of quinazolin-4(3*H*)-ones from 2-fluoro-substituted bezoyl chloride.

Substituted *ortho*-aminobenzonitrile on reaction with cinamoyl chloride/ acyl halide followed by oxidative cyclization with hydrogen peroxide give 2-styrylquinazolin-4(3*H*)-one [93-96] [Scheme 1.43].



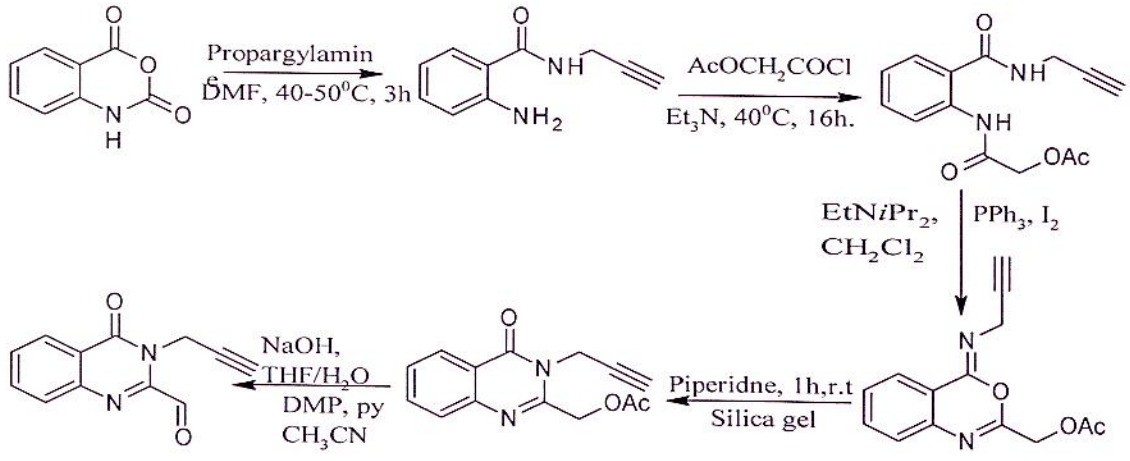
Scheme 1.43: Synthesis of quinazolinones from 2-aminobenzonitrile

Kundu and Chaudhuri [97] developed the first novel synthesis of quinazolin-4(3*H*)-one by employing copper catalyzed cyclization of substituted 2-[N-alkyl (benzyl)-N-(prop-2-ynyl) aminobenzamide [Scheme 1.44].



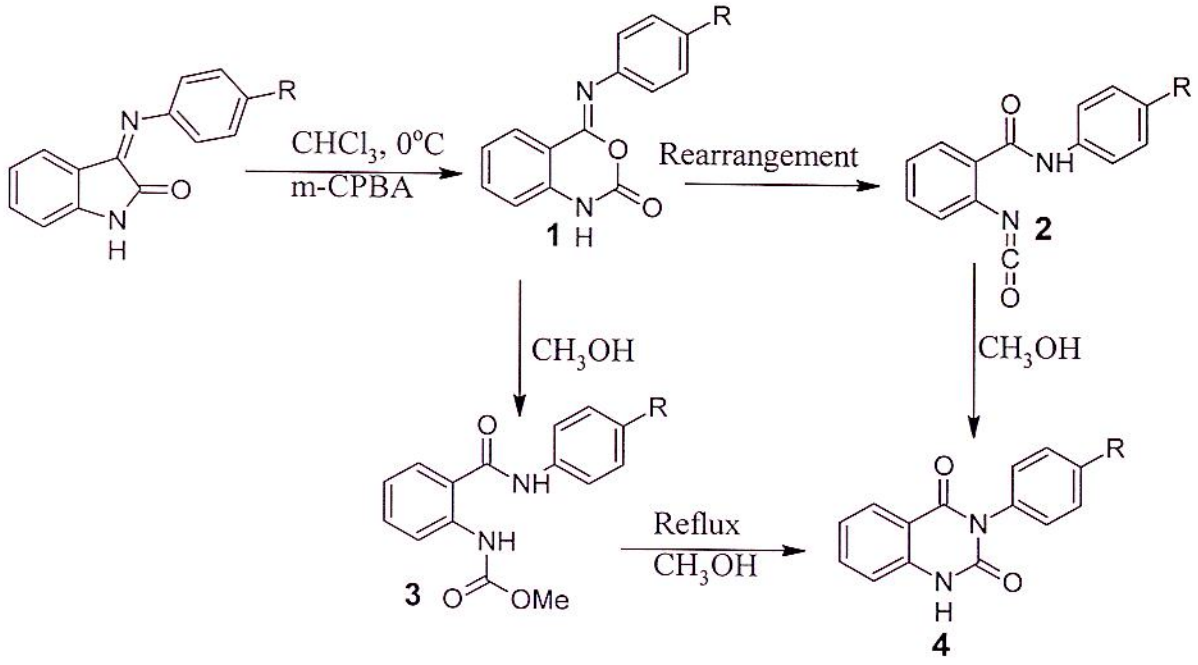
Scheme 1.44: Quinazolin-4(3*H*)-one *via* copper-catalyzed cyclization

Mazurkiewiez [98] has reported the synthesis of 4-oxo-3-prop-2-yn-1-yl-3, 4-dihydroquinazoline-2-carbaldehyde by reacting 2*H*-3,1-benzoxazine-2,4(1*H*)-dione with propargylamine. The resulting product was converted to its amide derivative. The amide was transformed into 4*H*-3, 1-benzoxazin-4-imine using triphenyl phosphine and iodine (huing's base) which then upon rearrangement over silica gel gave the corresponding quinazolin-4(3*H*)-ones. [Scheme 1.45]



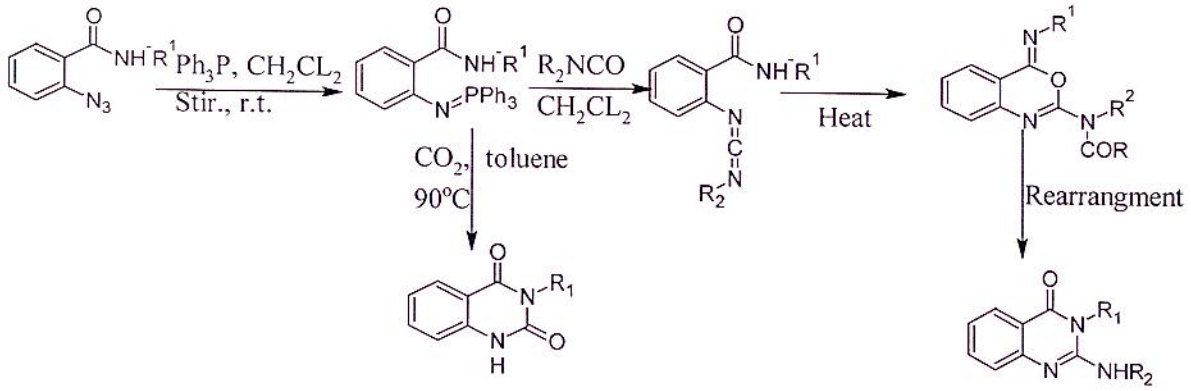
Scheme 1.45: Mazurkiewiez approach for synthesis 4-oxo-3-prop-2-yn-1-yl-3, 4-dihydroquinazoline-2-carbaldehyde

3-Arylimino-2-indolinones on reaction with *meta*-chloroperoxybenzoic acid at 0°C gave the corresponding benzoxazinone. The benzoxazinone upon ring opening with methanol resulted in the carbamate derivative or gave the isocyante carboxamide upon Baeyer- Villager type rearrangement. Both the carbamate and isocynate carboxamide cyclized to quinazolin-2, 4-dione upon simple reflux.[99] [Scheme 1.46]



Scheme 1.46: Synthesis of quinazolin-4(3*H*)-one *via* isocynate carboxamide intermediate

Iminophosphorane prepared from *ortho*-azidobenzamide through Staüdinger reaction followed by Aza-Wittig reaction [100] afforded 2,3-disubstituted quianzolin-4-(3*H*)-ones and quinazolin-2,4-diones [Scheme 1.47].



Scheme1.47: Synthesis of quinazolin-4(3*H*)-one from *ortho*-azidobenzamide

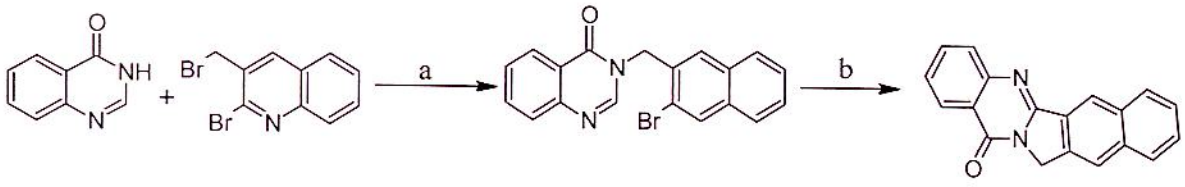
1.6. Synthetic Applications of Quinazolin-4(3*H*)-ones

1.6.1. A precursor to naturally occurring quinazolin-4(3*H*)-one based alkaloids

Following are some of the examples of naturally occurring quinazolin-4(3*H*)-ones alkaloids where simple quinazolin-4(3*H*)-ones are utilized as starting materials in their synthesis.

1.6.1.1. Luotinine

Harayama *et al.*, [101] reported single step total synthesis of Luotinine using quinazolin-4(3*H*)-ones with 70% yield. [Scheme 1.48]

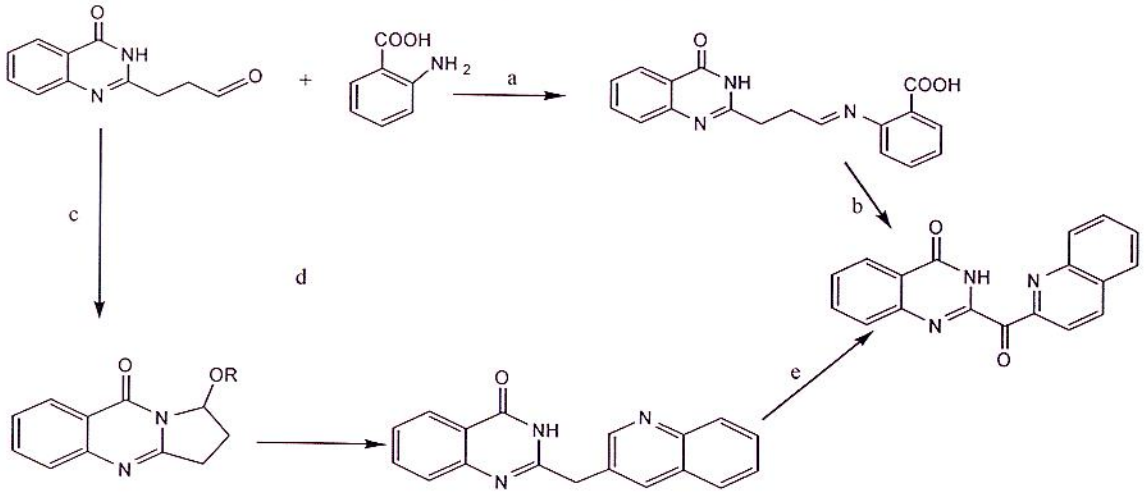


Scheme 1.48: Synthesise of Luotinin from quinazolin-4(3*H*)-one

(a). t-BuOK, DMF, r. t, 1.5h. (92%) (b). Pd $(OAc)_2$,tricyclohexylphosphine (Cy_3 P), KOAc, DMF, reflux, 30 min. (86%).

1.6.1.2. Luotinine F

Nomura *et al.*, [102] have reported a facile total synthesis of Luotinine F starting from 3-(4-oxo-3, 4-dihydroquinazolin-2-yl) propanal [Scheme 1.49].



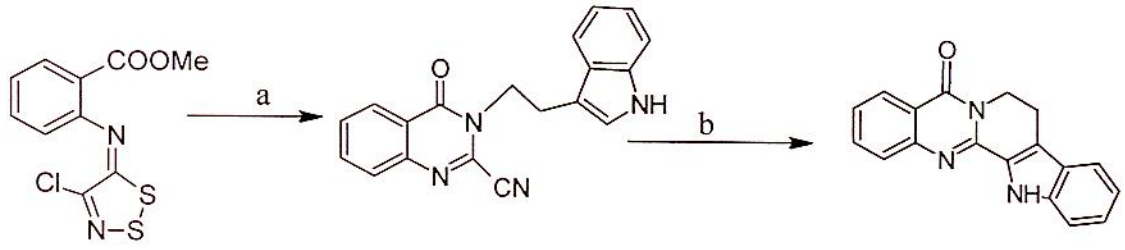
Reagents and conditions: a &b. biosynthetic pathway

(c)Friedländer condensation and Yamazaki's CrO3-H5IO6 oxidation reaction sequence, (d) *o*-aminobenzaldehyde, KOH, EtOH, reflux, 15 h (62%), (e) CrO3, H5IO6, DMF, rt, 1 h (96%).

Scheme1.49: Luotinin F from 3-(4-oxo-3, 4-dihydroquinazolin-2-yl) propanal

1.6.1.3. Rutaecarpine

Kim *et al.*, [103, 104] developed an efficient general approach for the synthesis of rutaecarpine and its analogues starting from the reaction of methyl anthranilate with 4, 5-dichloro-1, 2, 3-dithiazolium chloride (Appel's salt) [Scheme 1.50].

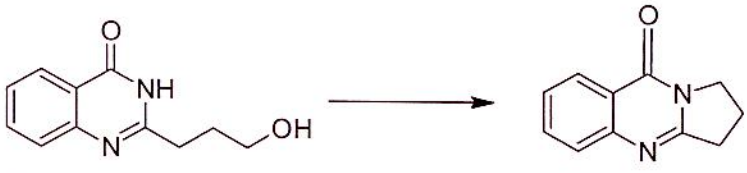


(a) CH_2Cl_2, pyridine, r. t., 3h. (b) TFAA, dry. HCl, 120-130 °C, 3 h

Scheme1.50: Synthesis of rutaecarpine

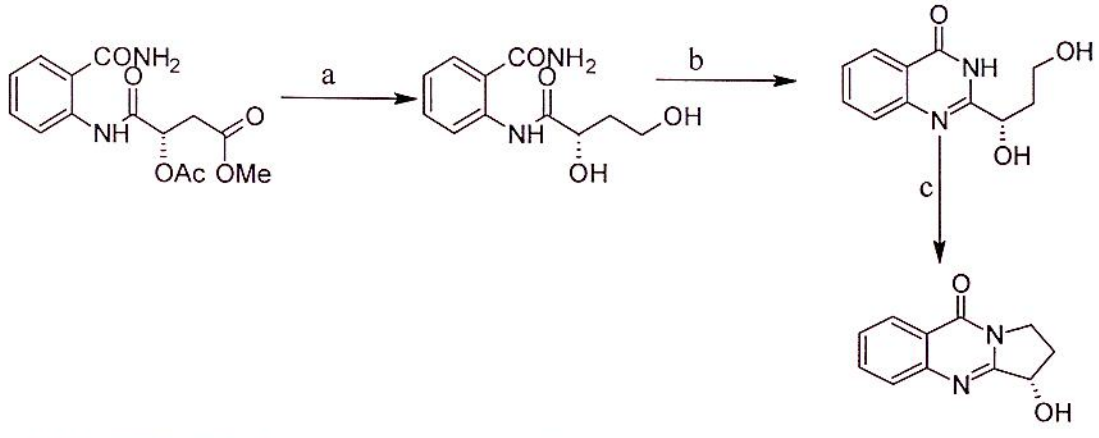
1.6.1.4. Deoxyvasicinone

Pegamine, a natural product synthesized anthranilamide and succinic anhydrides via esterification followed by reduction afford pegamine which further upon reductive cyclization results in formation of Deoxyvasicinone [Scheme 1.51].



Scheme 1.51: Syntehsis of Deoxyvasicinone.

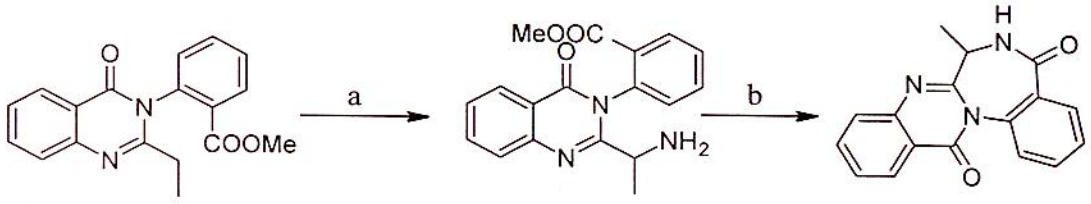
(-)-Vasicinone, is another quinazolin-4-(3*H*)-one alkaloid synthesized as illustrated in [Scheme 1.52].



(a, b) LAH, THF, 90 min., aqueous workup (92%); followed by reductive cyclization
(c) PPh_3, DEAD, THF, r.t., 1 h (90%).
Scheme 1.52: Syntehsis of (-)-Vasicinone.

1.6.1.5. Cirumdatine (F)

Bergman *et al.*, [105] reported total synthesis of Cirumdatin (F) starting from a substituted quinazolin-4(3*H*)-one [Scheme 1.53].

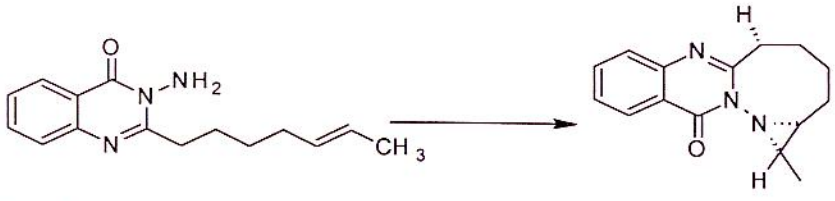


(a) (i)Br_2, NaOAc, HOAc, 60 ^{0}C. (ii) NaN_3, H_2O, ^{i}PrOH. (iii) H_2(220Psi), 5% Pd/C,EtOH,r.t. Acetonitrile, reflux.

Scheme 1.53: Synthesis of Cirumdatin (F)

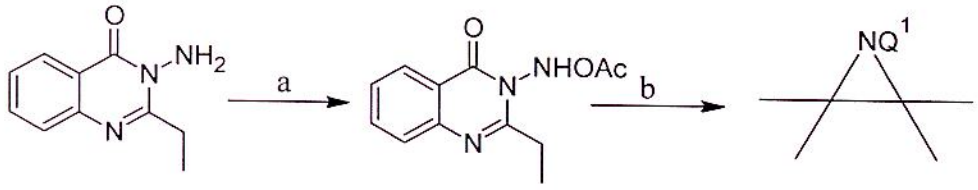
1.6.1.6. 3-*N*-Aminoquinazolin-4(3H)-one as aziridinating agents

It was shown in the work carried out by Rees *et al.*, that oxidation of a variety of N-aminoheterocylic compounds by lead tetra acetate(LTA) in the presences of alkenes gave aziridines.[106-108] Oxidation of 3-aminoquinazolinone by LTA in dilute dichloromethane solution resulted in an aziridine [109][Scheme 1.54].



Scheme 1.54: Lead tetra acetate catalysed aziridination of internal olefin.

It was shown that 3-acetoxyaminoquinazolin-4(3*H*)-one intermediate is formed by LTA oxidation of 3-aminoquinazolin-4(3*H*)-one, which then brings about aziridination of an alkene added subsequently to the reaction mixture [110] [Scheme 1.55].

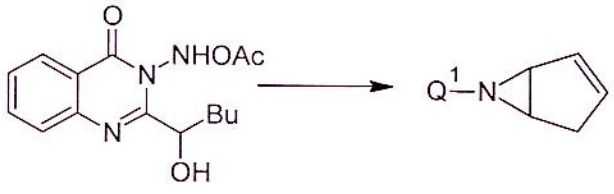


Q= quinazolin-4(3*H*)-one nucleus

(a). LTA, CH_2Cl_2, -20°C, (b). Alkene

Schem 1.55: Aziridination of 3-acetoxyaminoquinazolin-4(3*H*)-one

Aziridination of cyclopentadiene and cycloheptadiene with 3-acetoxyamino-2-[(S)-1-hydroxy-2, 2-dimethylpropyl] quinazolin-4(3*H*)-one (Q^1NHOAc) in the presence of titanium (IV) *tert*-butoxides gave the corresponding aziridines. This is highly diastereoselective reaction.[111] [Scheme. 1.56].

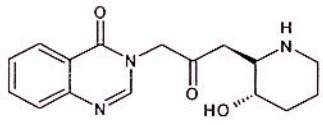


Schem 1.56: Diastereoselctive aziridination of cyclopentadiene

Chemistry of aziridination of alkenes with 3-aminoquinazolinones has been covered in much detail in a comprehensive review by Atkinson.[112]

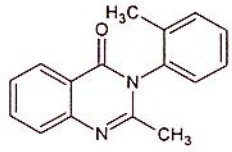
1.2. Bioactivities of Quinazolin-4(3*H*)-one Ring System

Quinazolin-4(3*H*)-ones, both synthesized as well as isolated from natural sources play vital role in the biological world. Quinazolin-4 (3*H*)-ones and the derivatives thereof are now known to have a wide range of biological properties, including hypnotic, sedative, analgesic, anti-convulsant, anti-tussive, anti-bacterial, anti-diabetic, anti-inflammatry, anti-tumor, protein tyrosine kinase inhibitor, cholecystokinin inhibitor, antimicrobial, anticonvulsant, sedative, antidepressant and anti-inflammatory as well as antiallergic and several other useful and interesting biological properties. Interest in the medicinal chemistry of quinazolinones was stimulated in early 1950's with the isolation of an active quinazolin-4(3*H*)-one based antimalarial drug, Febrifugin (**1**) from an Asian plant *Dichroa febrifuga*.



(1)

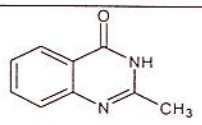
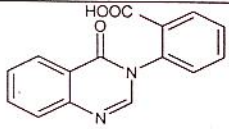
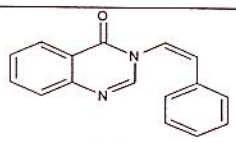
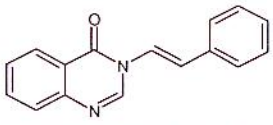
The first synthetic quinazolinone based drug was methaqualone (**2**), synthesized in 1951 and is an active sedative and hypnotic agent.

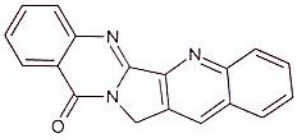
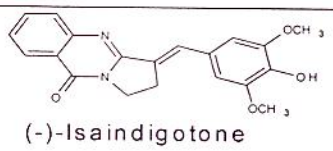
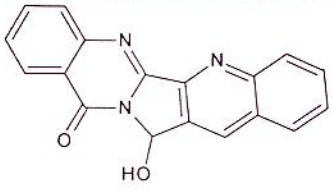
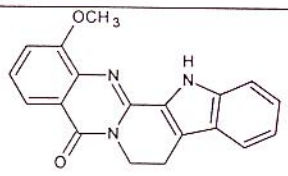
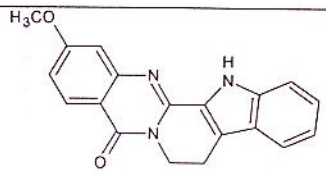


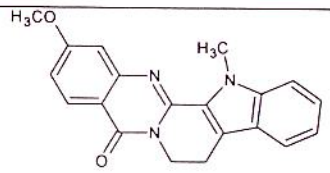
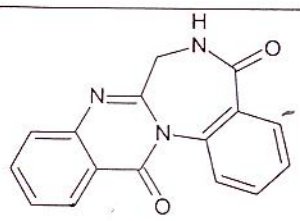
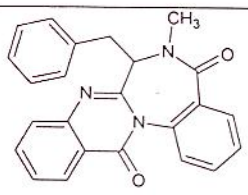
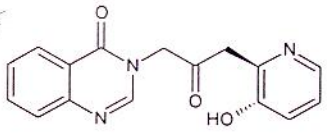
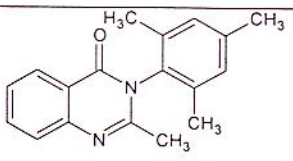
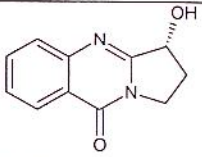
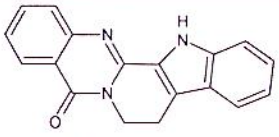
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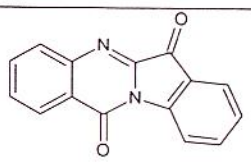
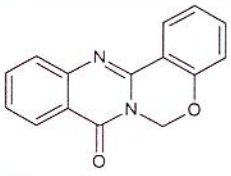
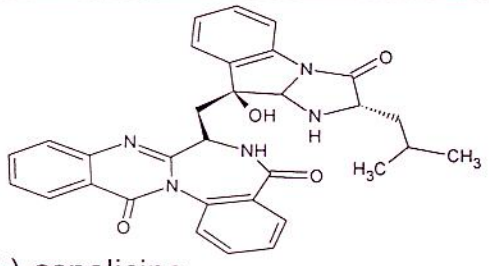
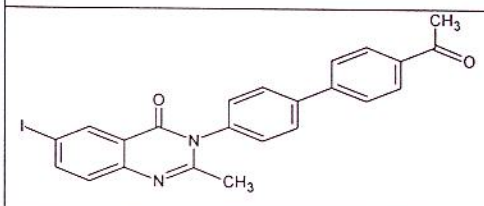
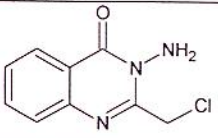
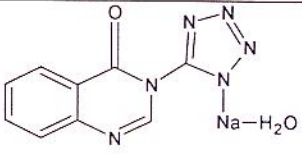
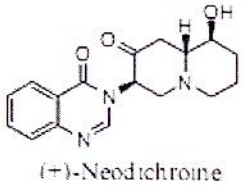
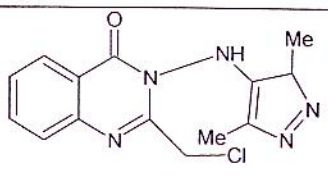
It is important to note that the quinazolin-4 (3*H*)-ones alkaloids are a class of natural and synthetic compounds with very diverse structures and hence, at present approximately fifty quinazolin-4(3*H*)-one derivatives with a wide variety of biological activities are available for clinical uses. Some bioactive quinazolin-4(3*H*)-ones are listed in Table 1.1.

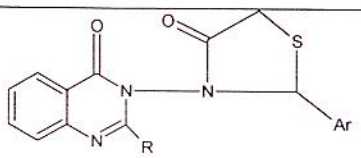
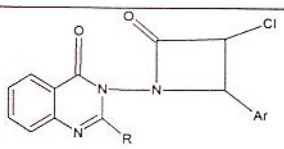
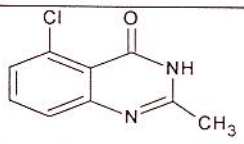
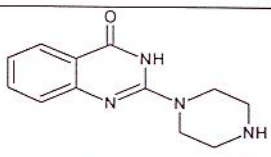
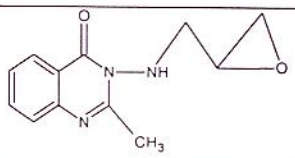
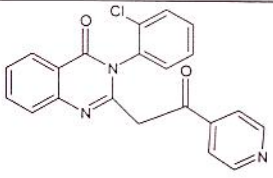
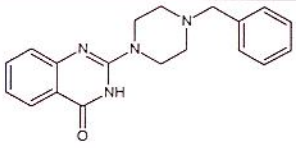
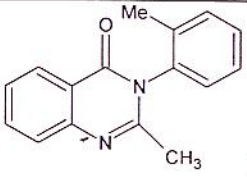
Table1.1: Some most common bioactive quinazolin-4(3*H*)-ones

Structure/name	**Source**	**Activity**	**Ref.**
 2-methylquinazolin-4(3*H*)-one	*Bacillus Cereus*	Low acute toxicity in mice	113
 2-(4-oxoquinazolin-3(4*H*)-yl)benzoic acid	*Isatis indigotica*	Anti-endotoxic	114
 3-[(*Z*)-2-phenylvinyl]quinazolin-4(3*H*)-one (Z)- Bogorin	*Glycomis chlorosparma*	Cytotoxic, antifungal	115
 3-[(*E*)-2-phenylvinyl]quinazolin-4(3*H*)-one	*Glycomis chlorosparma*	Cytotoxic, antifungal	116

(E)-Bogorin			
 Luotonine-F	*Peganum nigellastrum*	Antitumor	117
 Luotonine-A	*Peganum nigellastrum*	Antitumor, cytotoxic	118
 (-)-Isaindigotone	*Isatis indigotica*	Super oxide scavenger (anti-oxidant)	119-121
 Loutonine-B	*Isatis indigotica*	Cytotoxic towords murine leukemia P-388 cell line	122
 1-methoxyrutaecarpine	*Zanthoxylum integrifolium*	Antiplatlet aggregation activity	123
 2-methoxyrutaecarpine	*Aealiopsis tobouensis*	Antimalarial	124

 2-methoxy-13-methyl-ruteacarpine	*Aealiopsis tobouensis*	Antimalarial	125
 sclerotigenine	*Penicillium sclerotigenum*	Anti-insatin	126
 Benzomalvine	*Penicillinum culture*	Legend for neurokinin-1-receptor	127-129
 Febrifugine	*Dichroa febrifuga*	Antimalarial	130
	Synthetic	Sedative hypnotic	131
 (-)-Vascinone	*Adhatoda vasica*	Antitumor, bronchiodilator, hypnotic, anthelmintic, antianaphylactic	132-133
 Rutecarpine	Several members of *rutaceae* family	Analgesic,antiematic, antihypertensive, uterotonic, anti-inflamatory, cycloxygense inhibitor	134-135

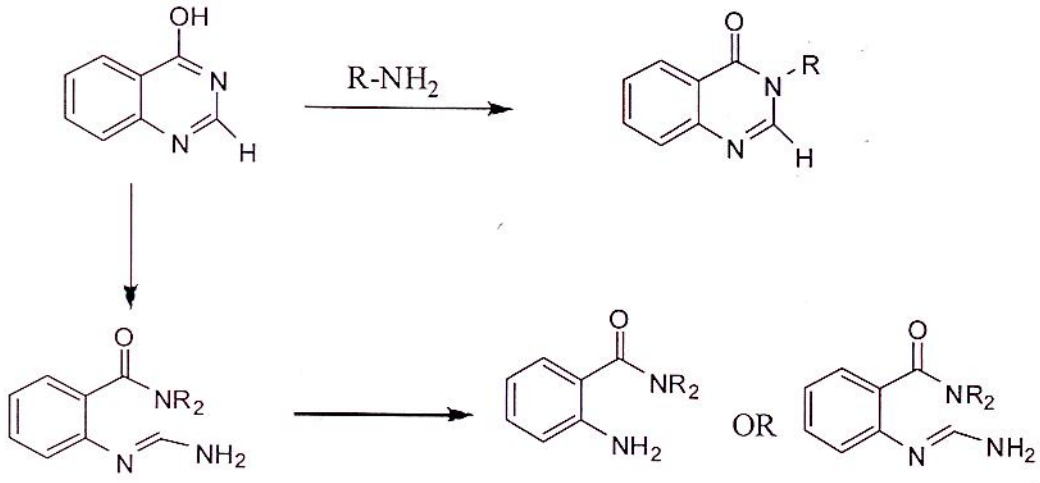
 Tryptanthrin		Antibiotic	134-135
		Antifertility	134-135
 (-)-aspelicine	*Aspergillus alliaceus*		136 [a,b]
	Synthetic	Pyruvic acid oxidation inhibitor	137
	Synthetic	Antifungal	138
	Synthetic	Antialergic	139
 (+)-Neodichroine	*Dichroa febrifuga*	Antimalerial	140
	Synthetic	CNS depressant	138

	Synthetic	CNS depressant, anti-Parkinson	141
	Synthetic	CNS depressant, anti-Parkinson	141
	Synthetic	Polymerase inhibitor	142
	Synthetic	Antihyperglycemic	143
	Synthetic	Acetylcholinesterase inhibitor	144
	Synthetic	Neurotoxic	145
	Synthetic	Hypoglycaemic	146
 Methaqualone	Synthetic	Sedative, hypnotic	9

1.8. Stability of Quinazolin-4(3*H*)-one Ring System

Quinazolin-4(3*H*)-one ring system is relatively stable towards oxidation, reduction and hydrolysis but some reactions can cause ring fission, for example, 4-hydroxyquinazolinone undergoes ring opening at 150 °C, which re-closed with primary amine forming 3-substituted, 4-oxo-3, 4-dihydroquinazolin but on treatment with

secondary amines lead to the formation of *ortho*-amino benzoyl derivatives [147][Scheme 1.57]



Scheme1.57: Stability of quianzolin-4(3*H*)-one ring System

1.7. Aims of the Present Work

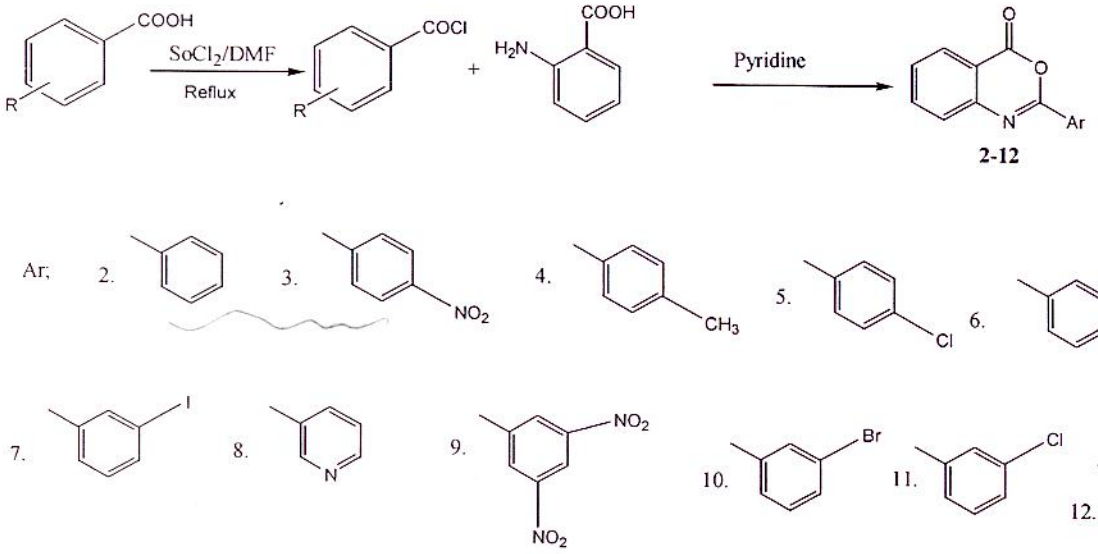
Keeping in view the diverse biological activities of the quinazolin-4(3*H*)-one pharmacophore, the aims of the present work were two-fold. Firstly, the research work aimed at synthesis of various new and known 2, 3-substituted quinazolin-4 (3*H*)-one derivatives *via* the new and known synthetic methods. Secondly, development of new cheaper and environmentally friendly synthetic methodologies for the synthesis of 4 (3*H*)-quinazolin-4(3*H*)-one was another objective of this research. The work documented here is comprised of two parts. The part A of this dissertation is about the synthesis and chemistry of quinazolin-4 (3*H*)-one while, part B presents biological activities data obtained for the compounds synthesized in this research.

1.8. Plan of Work

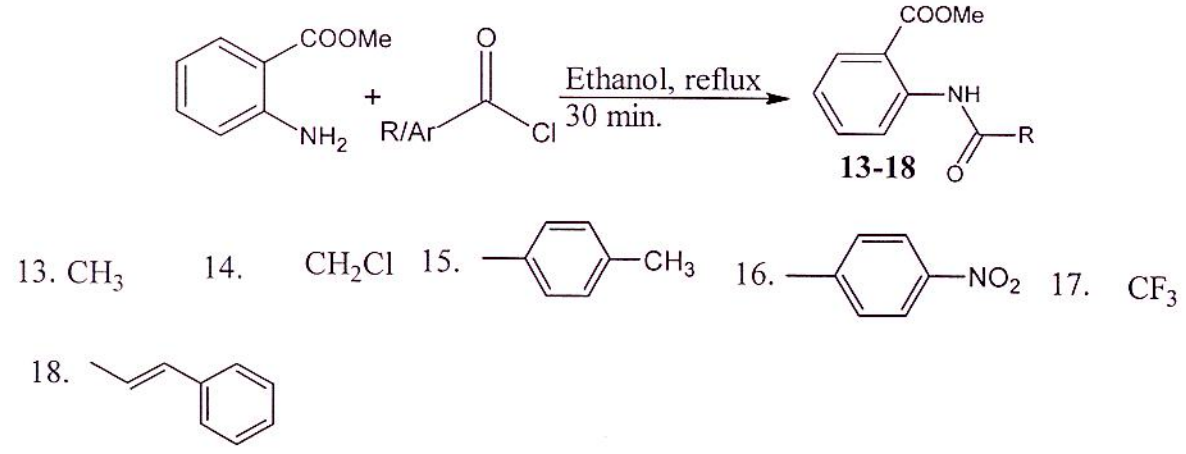
The plan of the synthetic experimental work is explained by the synthetic strategies adopted and is outlined below.

- Synthesis of 2-aryl -4*H*-3,1-benzoxazin-4-one **(2-12)** and methyl N-acyl anthranilates **(13-18)** as precursors and the development of simple, one-pot synthetic method for the synthesis of 2-ary benzoxazinones [Scheme 1.58, 1.59].

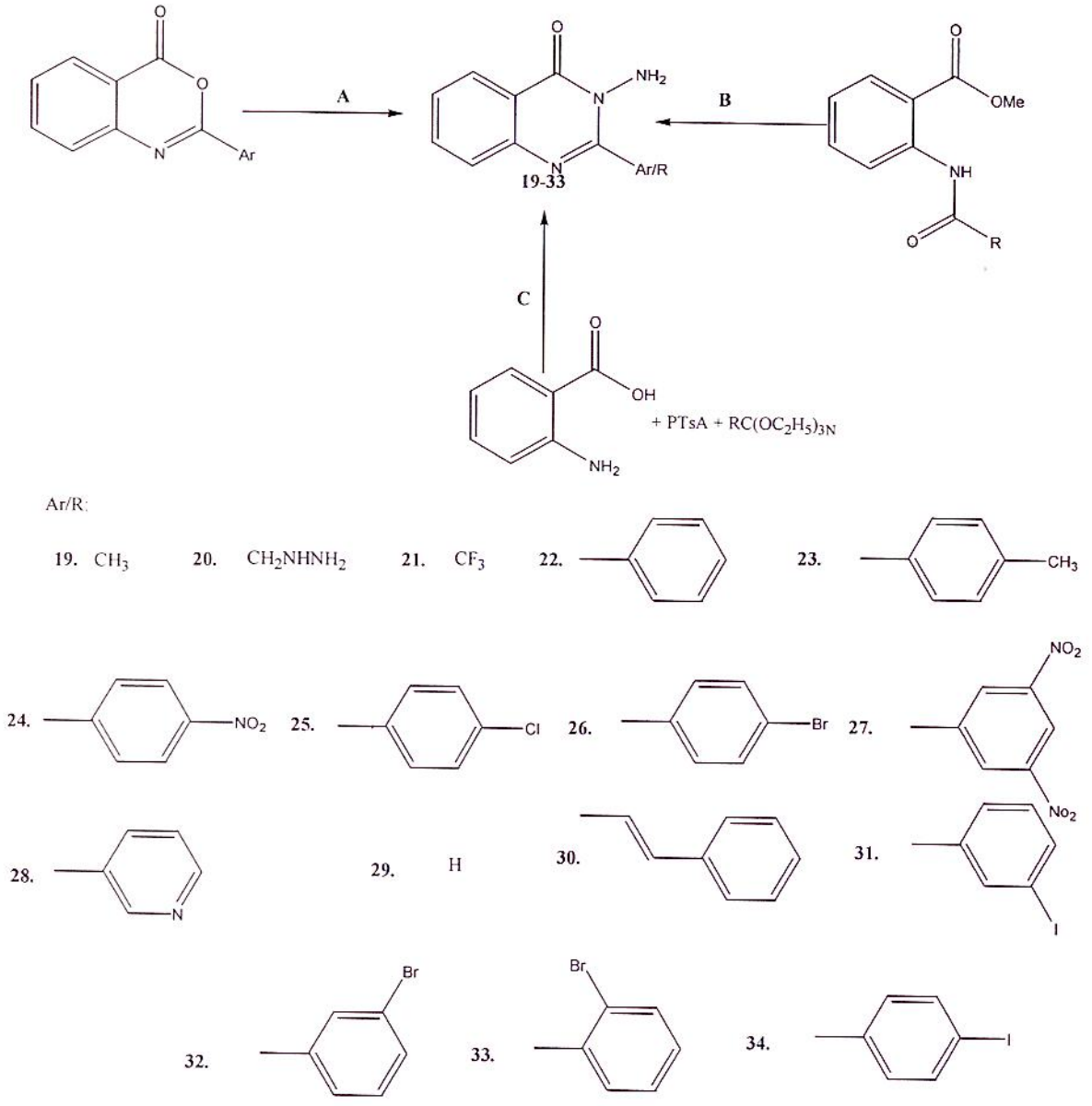
- Synthesis of 2-alkyl/aryl- 3-aminoquinazolin-4 (3*H*)-ones **(19-33)** and development of three components one-pot synthetic method for the same [Scheme 1.60, 1.61].
- Synthesis of novel quinazolinone based compounds from the reactions of 2-phenyl-benzoxazinones and effect of substituents on the reactivity 2-ary-benzoxazinones [Scheme 1.62].
- Synthesis of 3-(2-hydroxyethyl)-2-alkyl/arylquinazolin-4(3*H*)-ones (41-45) and other new and reported 2,3-disubstituted quinazolin-4(3H)-ones [Scheme 1.63].
- Synthesis and characterization of some open chain products **(63a-g)** during the synthesis 2, 3-disubstitued quinazolin-4(3*H*)-ones and transformation of the open chain products into 2,3-disubstituted quinazolin-4(3*H*)-ones under microwave irridiation and thermal method [Scheme 1.64].
- Transformation of the open chain products into structurally novel compounds (**63h**, **63j**) and their X-ray confirmations [Scheme 1.65].
- Synthesis of 2-alky/aryll-3-{[(1*E*)-arylmethylene] amino}quinazolin-4(3*H*)-one and development of a new simple and facile methods for their synthesis [Scheme 1.66].
- Synthesis of 2-Alky/aryl-3-{[(1*E*)-alkyl/arylmethylene] amino} -2, 3-dihydroquinazolin-4(1*H*)-ones and the development of new simple and facile methods for the synthesis of same series.[Scheme1.67].
- Synthesis of novel unsymmetrical quinazolinone based acetamidines and the establishment of a new method for their synthesis [Scheme 1.68, 1.69, 1.70].
- Synthesis of 2-alkyl/aryl quinazolin-4(3*H*)-ones and the development of a novel, efficient and green method for the synthesis 2-alkyl/aryl quinazolin-4(3*H*)-ones. [Scheme 1.71].
- Use of spectroscopic techniques including IR, NMR, EI-MS, FAB-MS and X-ray crystallography for structural determination.
- Bioactivity evaluation of the synthesized compounds in search of biologically active molecules.



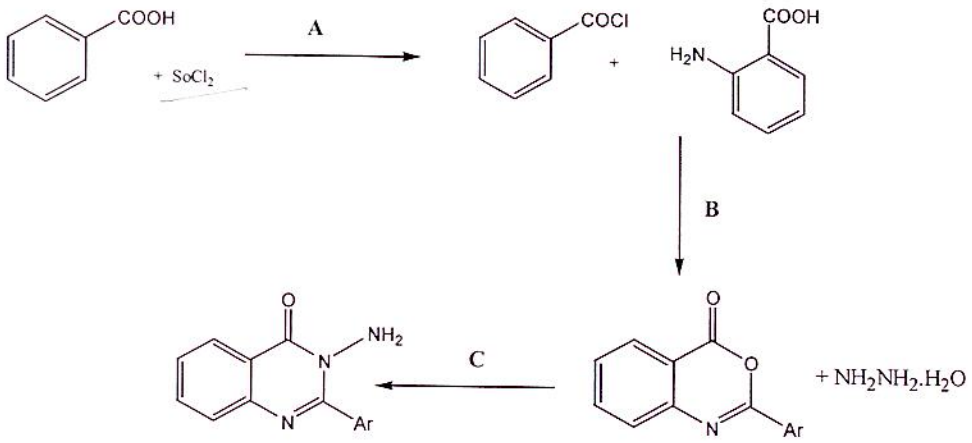
Scheme 1.58: Synthetic plan for 2-aryl benzoxizinones



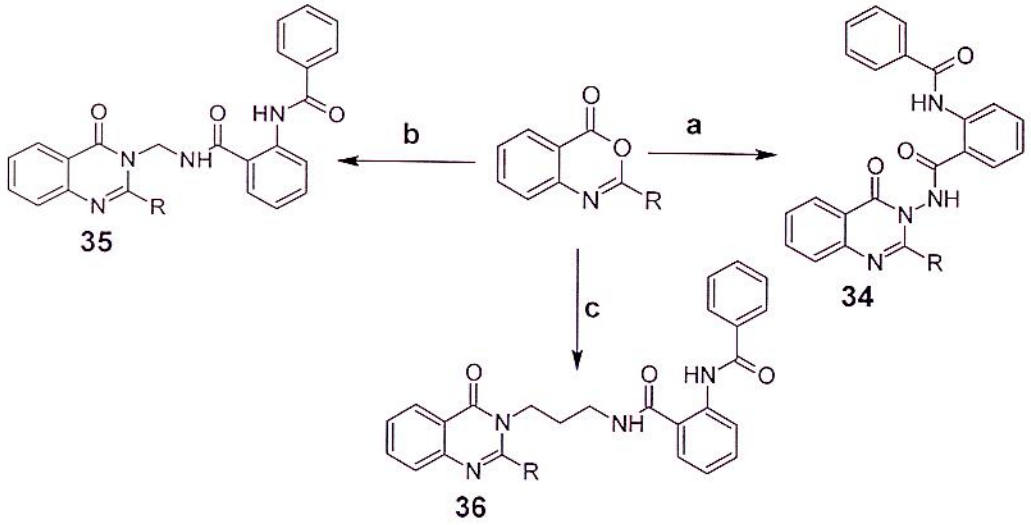
Scheme 1.59: Synthetic plan for N-acyl anthranilate methyl esters



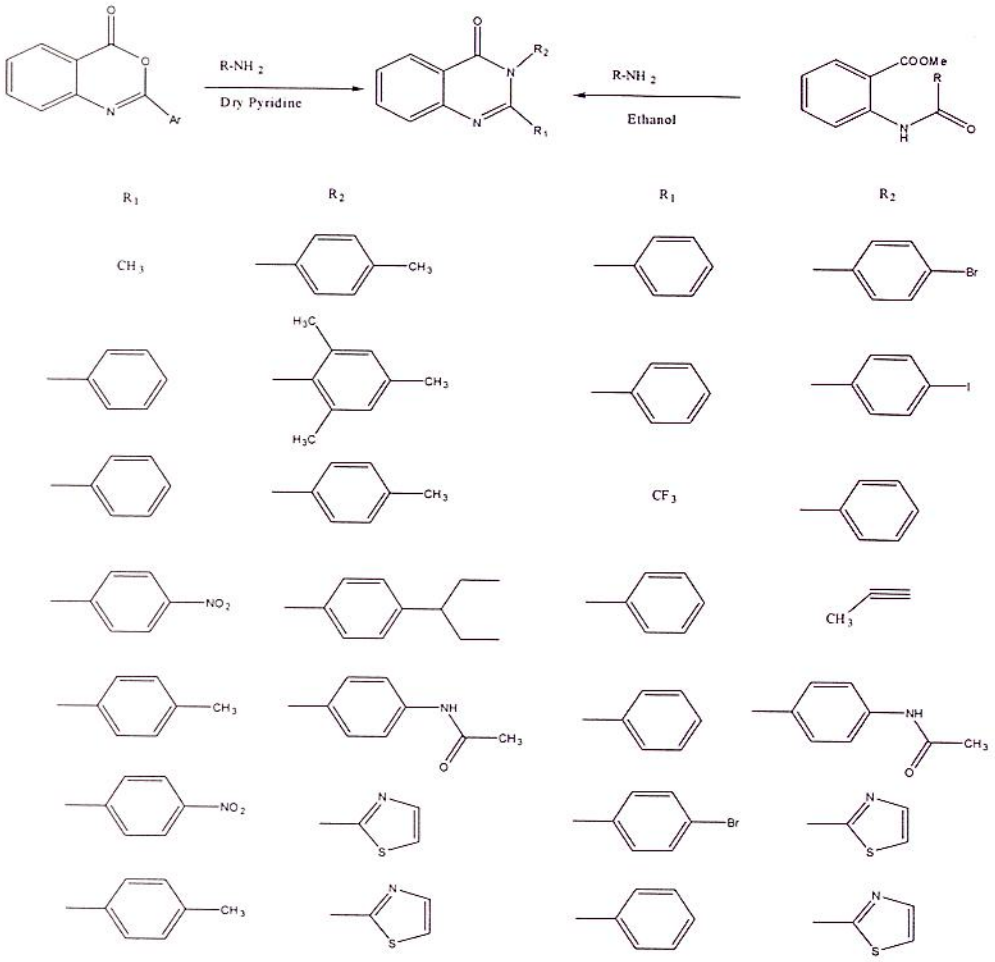
Scheme 1.60: Synthetic plan for 2-alkyl/aryl, 3-aminoquinazolin- 4(3*H*)-ones



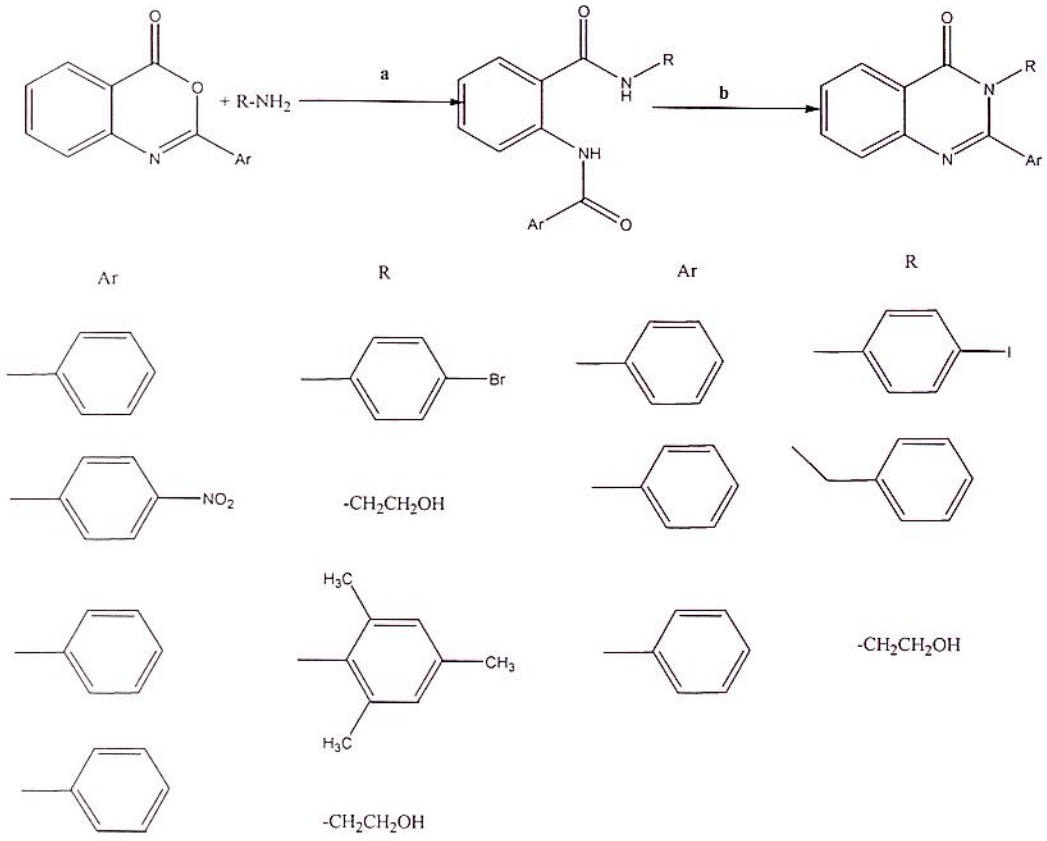
Scheme 1.61: One-pot synthesis of 2-aryl-3-aminoquinazolin-4(3H)-ones



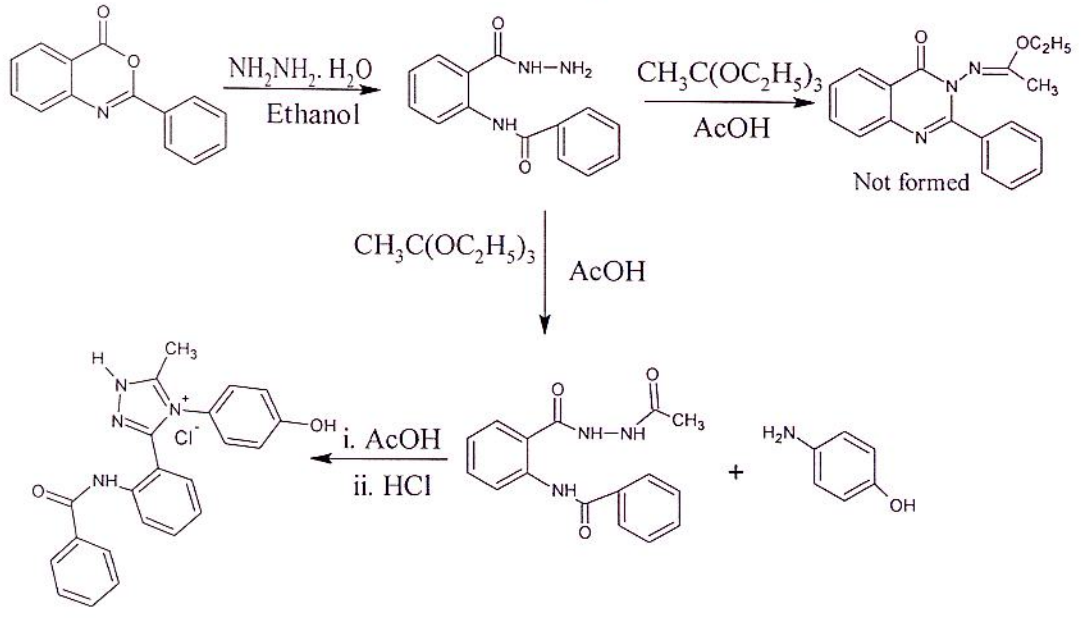
Scheme 1.62: Synthetic plan for novel 2-phenyl- 3-substituted quinazolin-4(*3H*)-ones



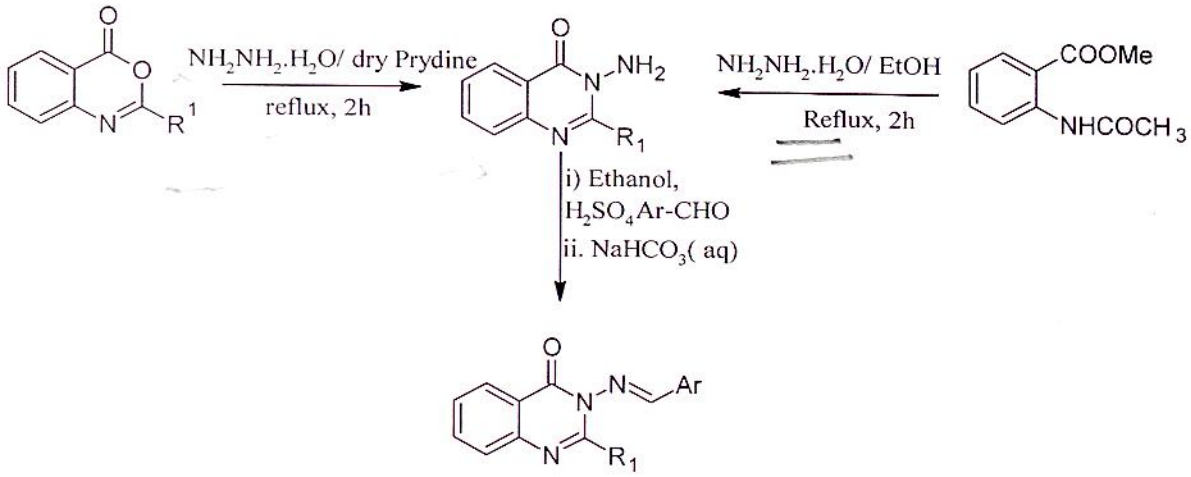
Scheme 1.63: Synthetic plan for 2,3-disubstituted quinazolin-4(3*H*)-ones



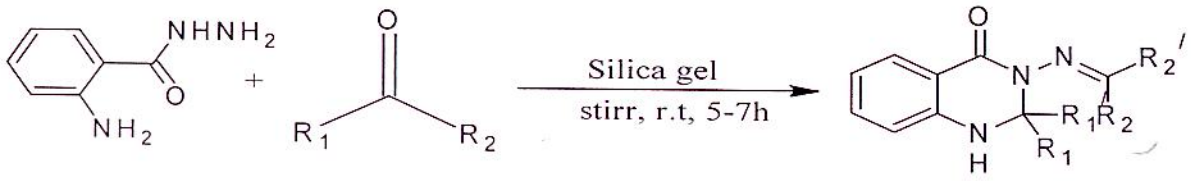
Scheme 1.64: Synthetic plan for diamide open chain products and their subsequent cyclization to 2,3-sisusbtituted quinazolin-4(*3H*)-ones



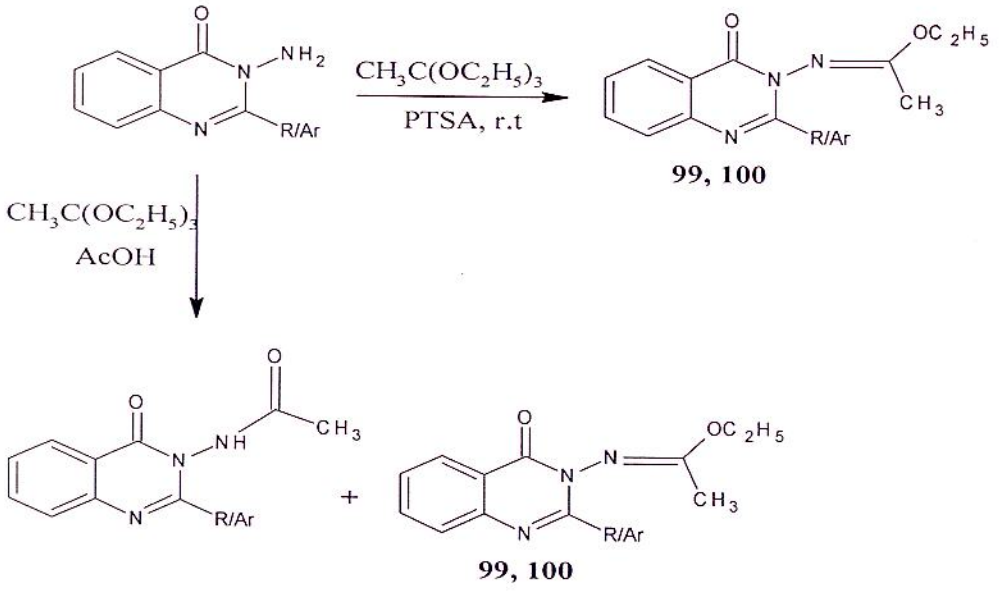
Scheme 1.65: Synthetic plan for the novel Triazolonium chloride salt



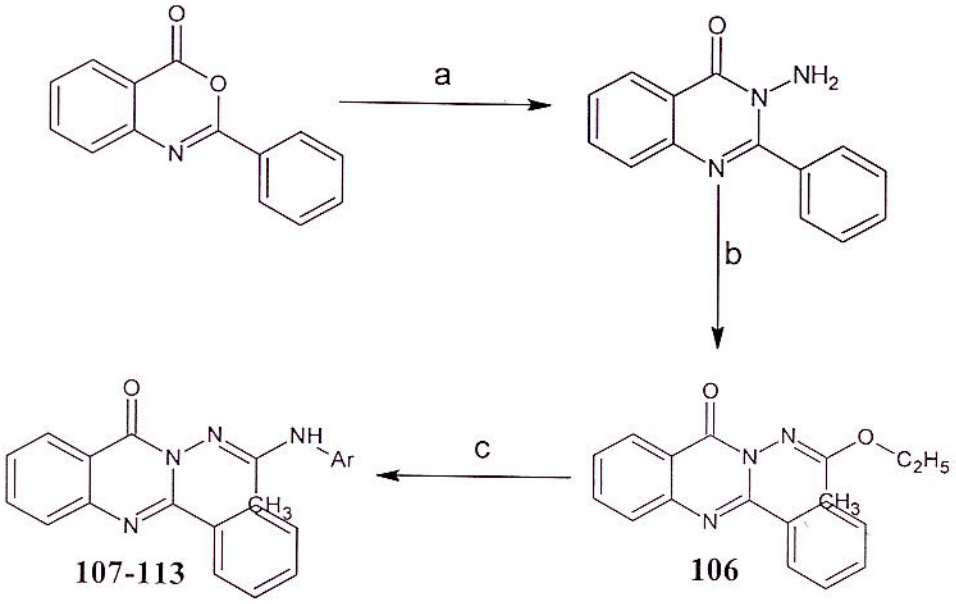
Scheme 1.66: Synthetic plan for 2-alkyl/aryl-3-{[(1*E*)-arylmethylene] amino}quinazolin-4(3*H*)-ones



Scheme 1.67: Synthetic plan for 2-Alky/aryl-3-{[(1*E*)- alkyl/arylmethylene] amino}-2, 3-dihydroquinazolin-4(1*H*)-ones.

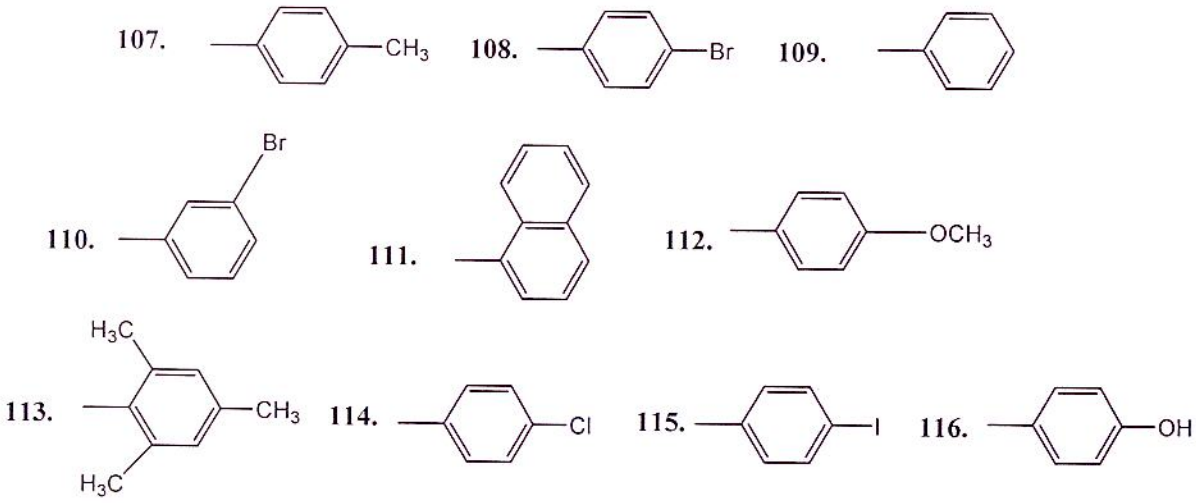


Scheme 1.68: Synthetic plan for imidate esters

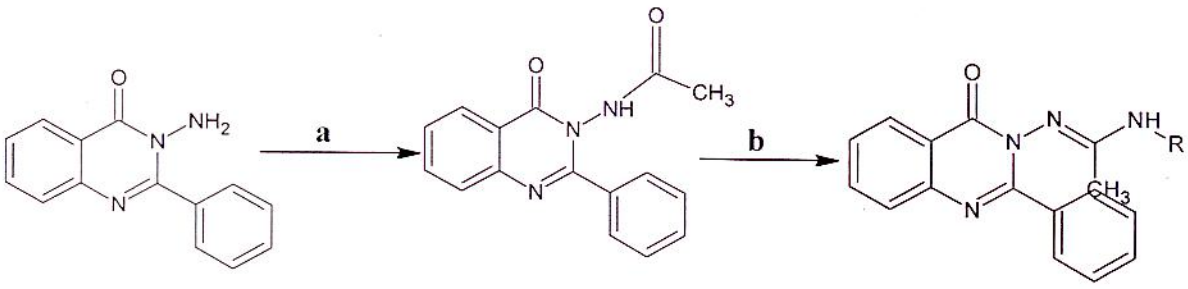


a.(i) $N_2H_4.H_2O$, py, reflux, (ii) HCl digestion
b. CH3C(OC2H5), PTSA, stirr, r.t.
c. Acetic acid, Ar-NH_2,

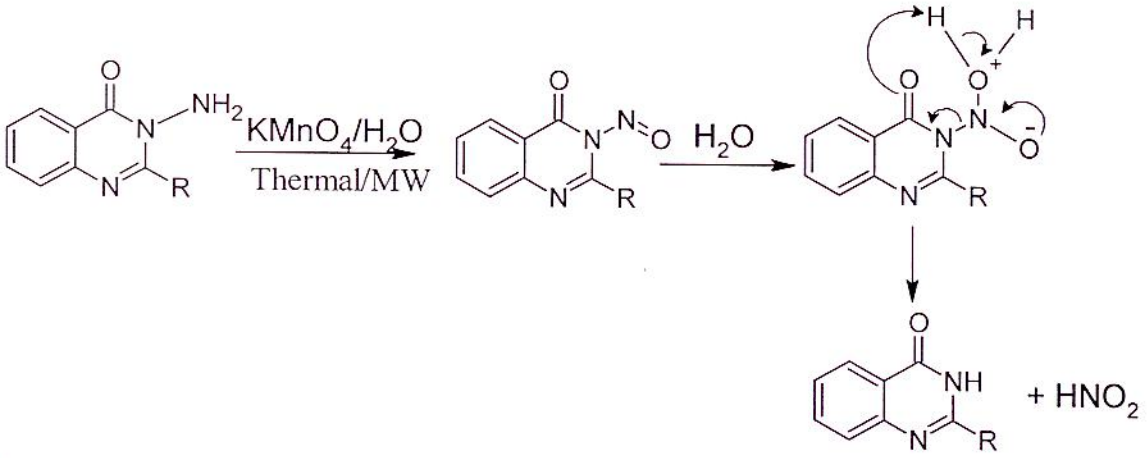
Ar=



Scheme 1.69: Synthetic plan for novel unsymmeterical quianzolin-4(3H)-one based acetamidines



Scheme 1.70: Synthetic plan of a new method for the unsymmetrical quinazolin-4(3H)-one based acetamidines



R=

117. CH_3 **118.** H_2C— **119.** —CH_3 **120.** —Cl

121. —Br **122.** —NO_2 **123.** H_2C— **124.** —OH

125. $-CH_2-C(=O)-O-C_2H_5$ **126.** C_2H_5

Scheme 1.71: Synthetic plan of a novel method for the synthesis of 2-alkyl/aryl quinazolin-4(3*H*)-ones (**117-126**).

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CHAPTER – 2

RESULTS AND DISCUSSION

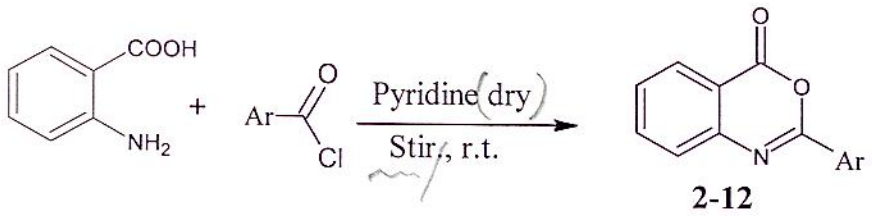
2.1. SECTION-A: Synthesis, Structure Elucidation, Method Development and Mechanism- Synthesis of the Starting Materials and 4(3*H*)-Quinazolinones

2.1.1. 2-Aryl 4*H*-3, 1-benzoxazin-4-one (2-12) and methyl *N*-acyl anthranilates (13-18)

4*H*-3, 1-benzoxazin-4-one derivatives are an important class of heterocyclic compounds [1-3] due to their interesting applications in biological world as well as in synthetic chemistry. Like other heterocyclic compounds, they too have medicinal importance. For example, they are used as precursors in the synthesis of several clinically used quinazolin-4(3*H*)-ones [4, 5]. Benzoxazinones and *N*-acyl derivatives of anthranilic acid have both been widely exploited as intermediates in the synthesis of quinazolin-4(3*H*)-one scaffold [6-8].

In the present work, a series of 2-aryl-4*H*-3, 1-benzoxazin-4-ones (**2-12**) and methyl-*N*-acyl anthranilates (**13-18**) were prepared which were then used as starting materials to synthesize new 2, 3-disubstituted quinazolin-4(3*H*)-ones.

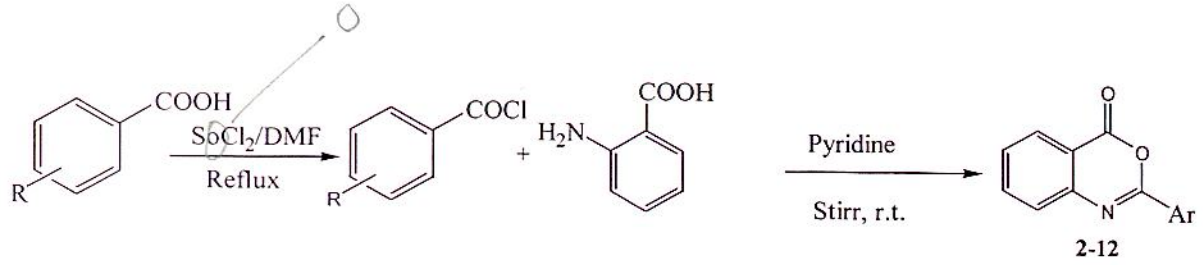
In the first step, 2-aryl 4*H*-3, 1-benzoxazin-4-ones (**2-12**) were synthesized by stirring magnetically anthranilic acid and substituted benzoyl chloride in dry pyridine for appropriate time at or below room temperature. The product formed was washed with saturated $NaHCO_3$ and recrystallized [Scheme 2.1].



2-12

Scheme 2.1: General route for the synthesis of 2-aryl-4(*H*)-3, 1-benzoxazin-4-ones (**2-12**)

The extensive use of 2-aryl-4*H*-3, 1-benzoxazin-4-one in the synthesis of heterocyclic compounds [1-3] further prompted us to investigate and develop a simple and convenient method to access 2-aryl-4*H*-3, 1-benzoxazin-4-ones.Consequently, a new direct one-pot simple and efficient method was established [Scheme 2.2].

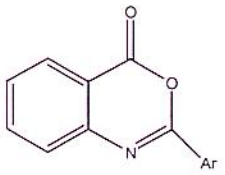


2-12

Scheme 2.2: Direct one-pot synthesis of 2-aryl-4(*H*)-3, 1-benzoxazin-4-ones (**2-12**)

In the next step, a series 2-aryl-4*H*-3, 1-benzoxazin-4-one [Table 2.1] was synthesized from the readily available inexpensive starting materials, i.e. substituted benzoic acids, through *in situ* preparation of acid chlorides, by refluxing substituted benzoic acids in slight excess of freshly distilled thionyl chloride containing few drops of DMF as a catalyst for 2-3 h. The mixture was then allowed to cool down to room temperature and added portion- wise to a well-stirred solution of anthranilic acid in dry pyridine under anhydrous and inert atmosphere.

Table 2.1: List of the synthesized 2-aryl-4(*H*)-3, 1-benzoxazin-4-ones (**2-12**) through Scheme 2.2.

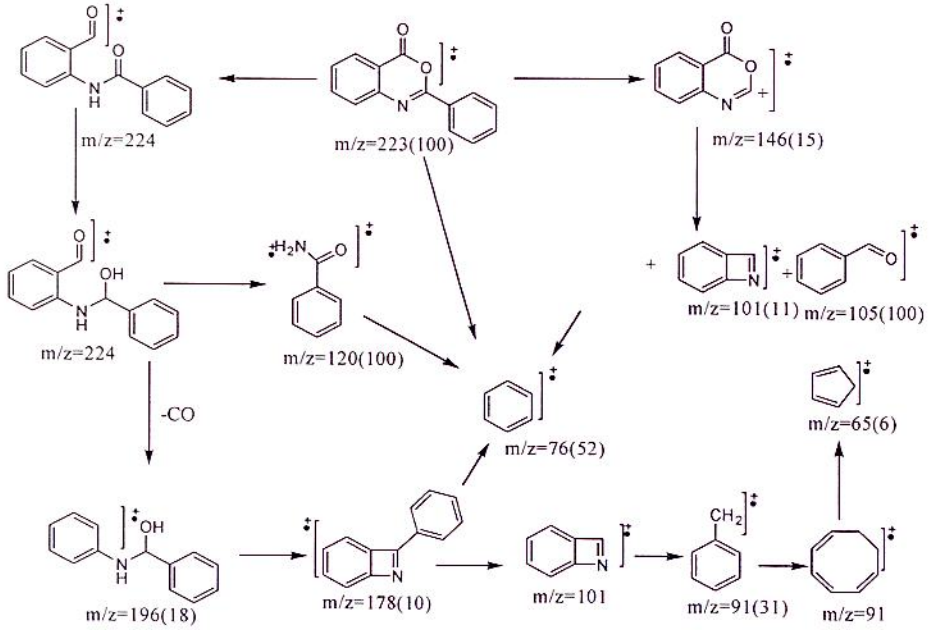


2-12

Compd #	**Ar**	**M.p.(°C)**	**Yield (%)**
2	C_6H_5	108-110	93
3	*p*-$C_6H_4NO_2$	202-204	89
4	*p*-$C_6H_4CH_3$	144	92
5	*p*-C_6H_4Cl	158-160	89
6	*p*-C_6H_4Br	184	87
7	*m*-C_6H_4 I	130	93
8	C_5H_4N(3-pyridinyl)	207	90
9	3,5$(NO)_2.C_6H_3$	125-126	82
10	*m*-C_6H_4Br	118-120	61
11	*m*- C_6H_4Cl	128-130	77
12	*o*-Br C_6H_4	180-182	67

The newly developed method was found effective and applicable for the synthesis of a range of 2-aryl-4*H*-3, 1-benzoxazin-4-one due to easy availability of substituted benzoic acids. As the reported methods are limited to the use of aromatic acid halides and anthranilic acid as starting materials for the synthesis of 2-aryl-4*H*-3, 1-benzoxazin-4-ones. Hence, the unstabality of acid halides makes their use as reagent limited and are difficult to be handled.

The structures of all the synthesized 2-aryl-4*H*-3, 1-benzoxazin-4-one (**2-12**) were confimed on the basis of physical data including IR, ^{1}H-NMR [Table 2.2a], EI-MS [Table 2.2b] and FAB-MS (+ve and –ve). In addition to IR and ^{1}H-NMR, Mass fragmentation pattern was found more helpful in assigning structure to these compounds. A typical mass fragmentation pattern was observed in the whole series, with a common base peak at m/z: 146 in the whole series confirm the loss of aryl substituent at postion **2** and an intense peak at *m/z*: 105 in the whole series observed were assigned to the loss of benzaldehyde fragment. Similarly, a peak at M-44 was attributed to the loss of lactonic group (-COO-) as CO_2. A representative mass fragmentation pattern for 2-phenyl-4*H*-3, 1-benzoxazin-4-one **2** is given [Scheme 2.3].



Scheme 2.3: Mass fragmentation pattern of 2-phenyl-4*H*-3, 1-benzoxazin-4-one

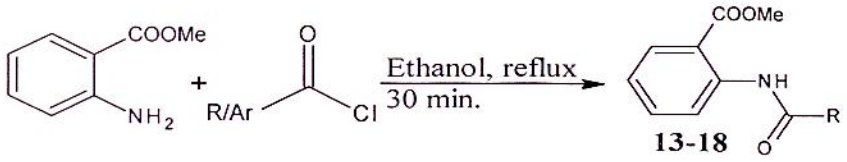
Table 2.2a: ^{1}H-NMR Spectroscopic data of 2-aryl-4*H*-3, 1-benzoxazin-4-ones (**2-12**)

Entry	Compd #	^{1}H-NMR data
1	**2**	(400 MHz, $CDCl_3$): δ 8.26 (d,1H, *J*=8), 7.82 (m, 4H), 7.56 (m, 4H)
2	**3**	(400 MHz, $CDCl_3$), *δ*: 8.34 (d, 2H, *J* = 9, Ar-H's), 8.02 (d, 1H, *J* = 9, Ar-H's), 7.98 (m, 3H, Ar-H's), 7.81(t, 1H, *J*=8.7), 7.39(t, 1H, *J*=8.5).
3	**4**	(300 MHz, $CDCl_3$), *δ*: 8.21(d, 1H, *J*=8.6), 8.11(d, 1H, *J*=8.7), 7.97(d, 2H, *J*=8), 7.82(t, 1H, *J*=8.4), 7.44(t, 1H, *J*=8.0), 7.18(d, 2H, *J*=8.4), 2.36(s, 3H, CH_3)
4	**5**	(300 MHz, $CDCl_3$), *δ*: 8.23 (d, 1H, *J* = 9), 8.15 (d, 1H, *J*=9), 7.94 (d, 2H, *J* = 8), 7.8 (t, 1H, *J*=8.5), 7.51-7.42 (m, 3H)
5	**6**	(300 MHz, $CDCl_3$), *δ*: 8.23 (d, 1H, *J* =8.9), 8.12(d,1H,*J*=8.7), 7.93 (dd, 2H, $J_{1,2}$ = 8.7, $J_{3,4}$ = 9.5), 7.81 (t, 1H, *J*=9.2), 7.66(m, 2H), 7.45 (d, 1H, *J* = 8.3)
6	**7**	(400 MHz, $CDCl_3$), *δ*: 8.27 (d, 1H, *J*=8), 8.17 (m, 2H), 8.1(d,1H, *J*=9.5), 7.89 (t, 1H, *J*=8.4), 7.80 (d, 1H, *J*=9), 7.45 (t, 1H, *J*=8.5), 7.35 (t, 1H, *J*=9.6).
7	**8**	(400 MHz, $CDCl_3$) δ: 9.31 (s, 1H, Ar-H), 9.14 (d, 1H, *J*=8.9), 8.27 (d, 1H, *J*=8), 8.19 (d, 2H, *J*=8.2), 8.07 (t, 1H, *J*=8), 7.93 (t, 1H, *J*=8), 7.44 (t, 1H, *J*=8.7)
8	**9**	(300 MHz, $CDCl_3$) δ: 9.8 (s, 1H), 9.21 (s, 2H), 8.2 (d, 1H, *J*=7.37), 8.10 (d, 1H, *J*=8.09), 7.81 (t, 1H, *J*=7.6), 7.47 (t, 1H, *J*=8.07)
9	**10**	(400 MHz, $CDCl_3$), *δ*: 8.6 (s, 1H), 8.2 (d, 1H, *J*=8), 8.15 (d, 1H, J=8.2), 8.07 (d, 1H, *J*=8.2), 7.6(d, 1H, *J*=8.5), 7.46 (t, 1H, *J*=8.2), 7.37 (t, 1H, *J*=8.4)
10	**11**	(300 MHz, $CDCl_3$), *δ*: 8.31 (s, 1H), 8.25-8.20 (m, 2H), 8.15 (d, 1H, *J*=9.7), 7.80-7.60 (t, 1H, *J*=8.5), 7.48 (t, 1H, *J*=9), 7.41-7.37 (m, 2H).
11	**12**	(300 MHz, $CDCl_3$): δ 8.23 (d, 1H, *J* =8.9), 8.17 (d,1H, *J*=8.7), 7.93 (d, 1H, *J*3,4 = 9.5), 7.81 (t,1H, *J*=9.2), 7.66 (d, 1H, *J*=9), 7.60 (t, 1H, *J*=8.6), 7.45 (t, 1H, *J* = 8.3), 7.21 (t, 1H, *J*=9.3)

Table 2.2b: Mass spectral data of 2-aryl-4*H*-3, 1-benzoxazin-4-one s (**2-12**)

Entry	Compd #	Mass spectral data
1	**2**	m/z: 223 (M^+ 100), 196 (7), 178(11), 146 (15), 120 (13), 119(4), 105 (100), 91(11), 77 (83), 65(3), 51 (18)
2	**3**	m/z: 268 ($M.^+$, 28), 253 (44), 236 (7), 235 (15), 207 (48), 179 (19), 178 (27), 167 (9), 105 (91), 104 (17), 102 (32), 92 (10), 77 (39), 76 (100), 63 (17), 51 (20)
3	**4**	m/z: 237 ($M.^+$,92), 146 (21), 120 (18), 119 (100), 91 (38), 76 (10), 65 (10)
4	**5**	m/z: 259 (M^{+2}, 3), 257 ($M.^+$, 8), 243 (10), 241 (61), 215 (2), 213 (5), 146 (24), 139 (5), 113 (4), 111 (13), 76 (91), 50 (5)
5	**6**	m/z: 303(M^{+2}, 48), 301(M^+, 56), 287(4), 285(40), 259(12), 257(16), 182(4), 181(11), 180(6), 168(9), 166(13), 146(81), 120(20), 118(22), 105(92), 92(11), 76(100), 63(25), 57(29), 51(42);
6	**7**	EI-MS m/z: 349 ($M.^+$, 89), 335 (11), 307 (19), 222 (67), 204 (76), 131 (17), 120 (27), 119 (31), 105 (100), 104 (9), 92 (71), 80 (24), 76 (57), 67 (10), 54 (18)
7	**8**	m/z: 224 (M^+, 89), 209 (27), 182 (15), 147 (43), 132 (5), 120 (19), 105 (100), 92 (59), 79 (71), 76 (18), 63 (5), 54 (11)
8	**9**	m/z: 313 (94), 299 (35), 268 (7), 221 (5), 168 (12), 120 (18), 105 (100), 92 (37), 76 (11), 75 (3), 63 (7), 54 (3)
9	**10**	m/z: 303 (M^{+2}, 15), 301 ($M.^+$, 62), 300 (4), 29 (46), 257 (44), 222 (10), 182 (4), 181 (11), 180 (6), 168 (10), 166 (13), 145 (79), 120 (18), 119 (14), 118 (25), 105 (92), 104 (4), 92 (11), 53 (7), 54 (34), 53 (7), 52 (14), 51 (42)
10	**11**	259 (M^{+2}, 86), 257 (100), 243 (21), 241(12), 215 (2), 214 (4), 213 (5), 207 (24), 152 (4), 140 (6), 138 (36), 120 (6), 119 (13), 102 (7), 90 (4), 77 (5), 76 (48), 50 (4)
11	**12**	m/z: 303 (M^{+2}, 48), 301 (M^+, 56), 287 (4), 285 (40), 259 (12), 257 (16), 182 (4), 181 (11), 180 (6), 168 (9), 166 (13), 146 (81), 120 (20), 118 (22), 105 (92), 92 (11), 76 (100), 63 (25), 57 (29), 51 (42)

Methyl *N*-acyl anthranilates are also widely used as starting materials in the synthesis quinazolin-4(3*H*)-one scaffold. Therefore, in the next set of experiments, a series of methyl *N*-aceyl anthranilate was synthesized by stirring suitable acid halide and methyl anthranilate in dry pyridine or by refluxing methyl anthranilate and suitable acid halide in boiling ethanol [Scheme 2.4].

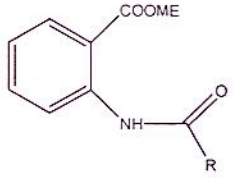


13-18

Scheme 2.4: General route for synthesis of methyl-N-acyl anthranilates (**13-18**)

Structure assignment was accomplished with the help of physical data including IR, 1H-NMR, EI-MS and FAB-MS. A series of methyl *N*-acyl anthranilates (**13-18**) [Table 2.3] was synthesized by simple stirring and reflux of suitable acid halide/acid anhydride with methylanthranilate [Scheme 2.3].

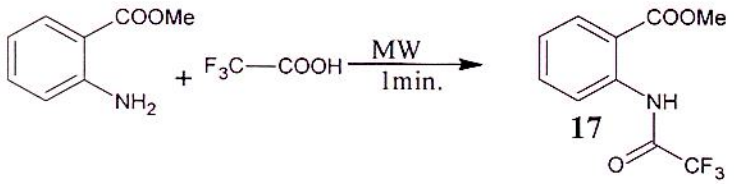
Table2.3: Synthesized methyl N-acylanthranilates (13-18)



13-18

Entry	Compd #	R	M.p.(°C)	Yield (%)
1	**13**	CH_3	193	96
2	**14**	CH_2Cl	101	88
3	**15**	*p*-$C_6H_4CH_3$	140	92
4	**16**	*p*-$NO_2C_6H_4$	181-183	66
5	**17**	CF_3	157	97
6	**18**	C_6H_5CH=CH-	84-86	90

A new microwave- assisted method for the synthesis of methyl 2-[(trifluoroacetyl) amino] benzoate **17** was developed by direct irradiation of methyl anthranilate and trifloro acetic acid [Scheme 2.5] using domestic microwave oven. The direct synthesis of amide from carboxylic acid has never been described in the literature. Attempts were made to extend the method to other aliphatic carboxylic acids but failed to obtain the desired products.



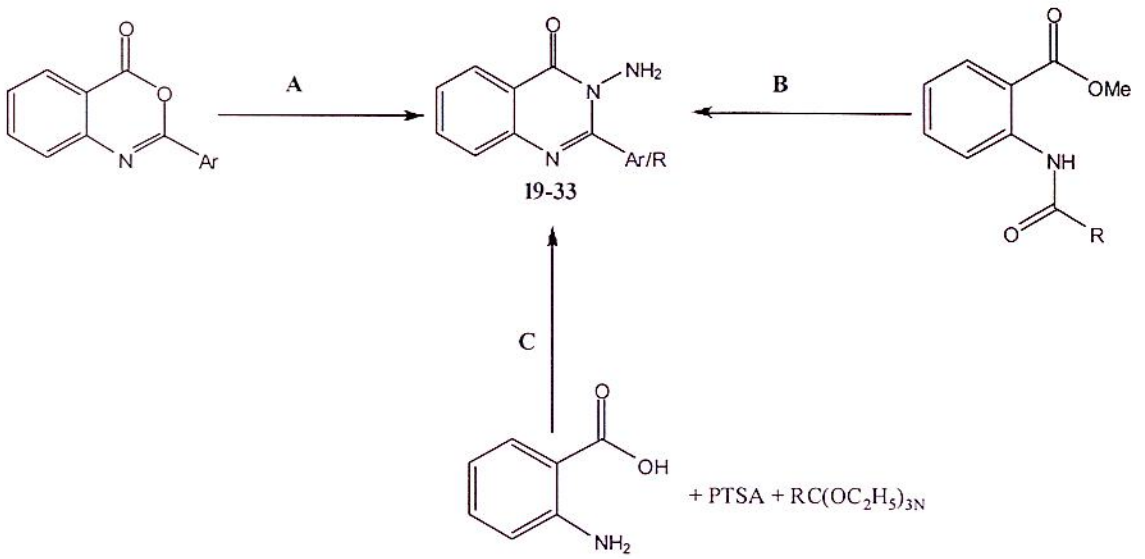
Scheme 2.5: Microwave- assisted synthesis of methyl 2-[(trifluoroacetyl) amino] benzoate (**17**).

2.1.2. 2-Alky/aryl-3-aminoquinazolin-4(3*H*)-ones (19-40)

2-Alky/aryl-3-aminoquinazolin-4(3*H*)-ones are an important class of quinazolin-4(3*H*)-ones heterocycles because of both biological and synthetic applications. Amino group at 3- position can act as a useful moiety to synthesize structurally diverse quinazolin-4(3*H*)-one based heterocycles. Consequently, an effort was made to develop an efficient, faster and easy method for the synthesis 2-alky/aryl-3-aminoquinazolin-4(3*H*)-ones. In this quest three reported methods [9-14] were used for the synthesis 2-alky/ aryl-3-amino quinazolin-4(3*H*)-ones with the modifications wherever required.

In the first attempt, 2-aryl-4*H*-3, 1-benzoxazin-4-one and Methyl *N*-acylanthranilates; used as starting compounds [Table 2.1& 2.2] were refluxed with hydrazine hydrate in appropriate solvent i.e. dry benzene or pyridine for the synthesis of 2-alky/aryl- 3-aminoquinazolin-4(3*H*)-ones [Scheme 2.6] and consequently, a series containing both new and reported 2-alky/aryl- 3-aminoquinazolin-4(3*H*)-ones was synthesized [Table 2.4]. Methyl -N- acetylanthranilate and their analogues ware successfully converted to 2-substituted, 3-aminoquinazolin-4(3*H*)-ones (**19-24**) by simples reflux with hydrazine hydrate in absolute ethanol in meaningfull yields [Scheme 2.6]. This method, however, failed in case of sterically hindered molecules. Therefore, an alternative method using 2-aryl-4*H*-3, 1-benzoxazin-4-one was found more suitable wherein 2-aryl-4*H*-3, 1-benzoxazin-4-one with suitable aromatic or aliphatic amines were refluxed and stirred in high boiling solvents such as pyridine, toluene or xylene. To circumvent the limitation faced in the above two methods, a recently reported method by Narasimhulu *et al.*, [15] was explored. A three component one-pot method using anthranilic acid, triethylorthoacetate and PTSA or $FeCl_3$ as a catalyst after necessary modification in the reported method was used to prepare 3-amino-2-alkyl/aryl–(4H)-quinazolinones (**19-33**). Reports from the previous workers show applicability of this method to position 3-

substituted quinazolin-4(3*H*)-one only while we have investigated and optimized this method for the synthesis of both 2,3-disubstituted quinazolin-4(3*H*)-ones. It was further found that not all the reactions go to completion at room temperature.The reaction completed only upon heating. Additionally, this method was also extended to some compounds, which have not been prepared previously using this protocol. [Scheme 2.6 - route **C**]



A. Hydrazine hydrate, Py. or benzene, reflux, 6-8 h.

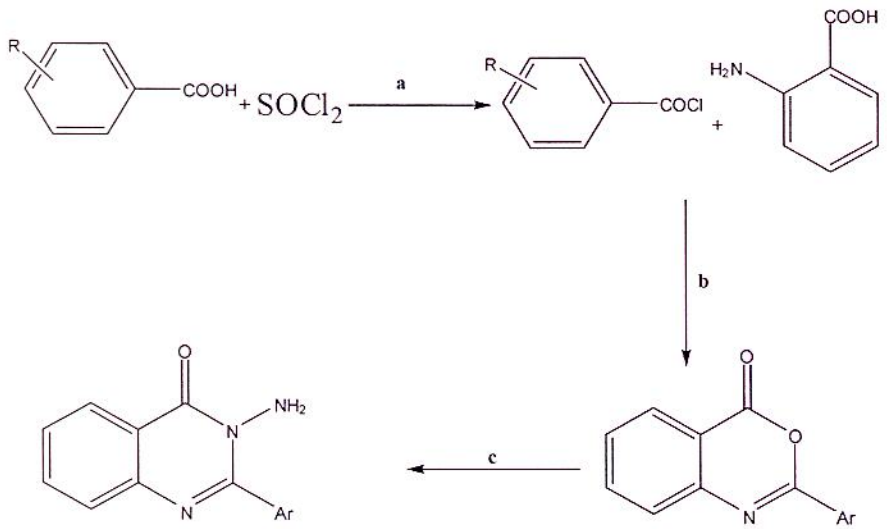
B. Hydrazine hydrate, ethanol, reflux, 2 h.

C. Anthranillic acid, PTSA, Triethyl ortho acetate, r.t., 15-30min.

Scheme 2.6: Synthesis of 2-alkyl/aryl- 3-aminoquinazolin-4(3*H*)-ones

One of the basic aims of this work was to develop an efficient methods for the synthesis of 2-Alky/aryl- 3-aminoquinazolin-4(3*H*)-ones. Therefore, the work was further extended in search of an efficient method for the synthesis of a range of 2-alky/aryl- 3-amino quinazolin-4(3*H*)-ones. Consequently, another efficient three component one-pot synthesis for a series of 2-alky/aryl- 3-amino quinazolin-4(3*H*)-ones was developed. Through this method, 2, 3-disubstituted quinazolin-4(3*H*)-ones were synthesized by *in-situ* preparation of aromatic acid halide(s) and 2-aryl-4*H*-3, 1-benzoxazin-4-ones [Scheme 2.7]. Thus, in a typical reaction procedure, a substituted benzoic acid was refluxed with slight excess of freshly distilled thionyl chloride containing few drops of DMF as catalyst for 2 h. The reaction mixture was cooled to room temperature and then

added portion wise to the well stirred solution of anthranilic acid in dry pyridine followed by addition of hydrazine hydrate.The contents were further refluxed for 2-3 h. Upon completion of the reaction, the mixture was poured into ice-cold water.The solid collected was further washed with $NaHCO_3$ solution. This method was found to be more effective copared to the literature reported step-wise method because of minimum loss of product during reaction quenching and work up steps. A variety of 2-aryl- 3-aminoquinazolin-4(3*H*)-ones (**22-31**) could be synthesized because of the cheaper and easier availablity of substituted benzoic acids compared to substituted benzoyl chlorides. In conclusion the intent of developing new method was successfully achieved by developing a much convenient, faster and cost effective method for the synthesis of 2-aryl - 3-aminoquinazolin-4(3*H*)-ones from economical and accessible substituted benzoic acids.

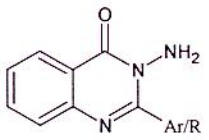


22-31

a. DMF, reflux, 2-3h., **b.** Pyridine dry, stirr, r. t, 15-30 min., **c.** Hydrazine hydrate, reflux, 2h.

Scheme 2.7: Direct three components one-pot synthesis of 2-aryl- 3-amino quinazolin-4(3*H*)-ones.

Table 2.4: 2-Alkyl/aryl- 3-aminoquinazolin-4(3*H*)-ones

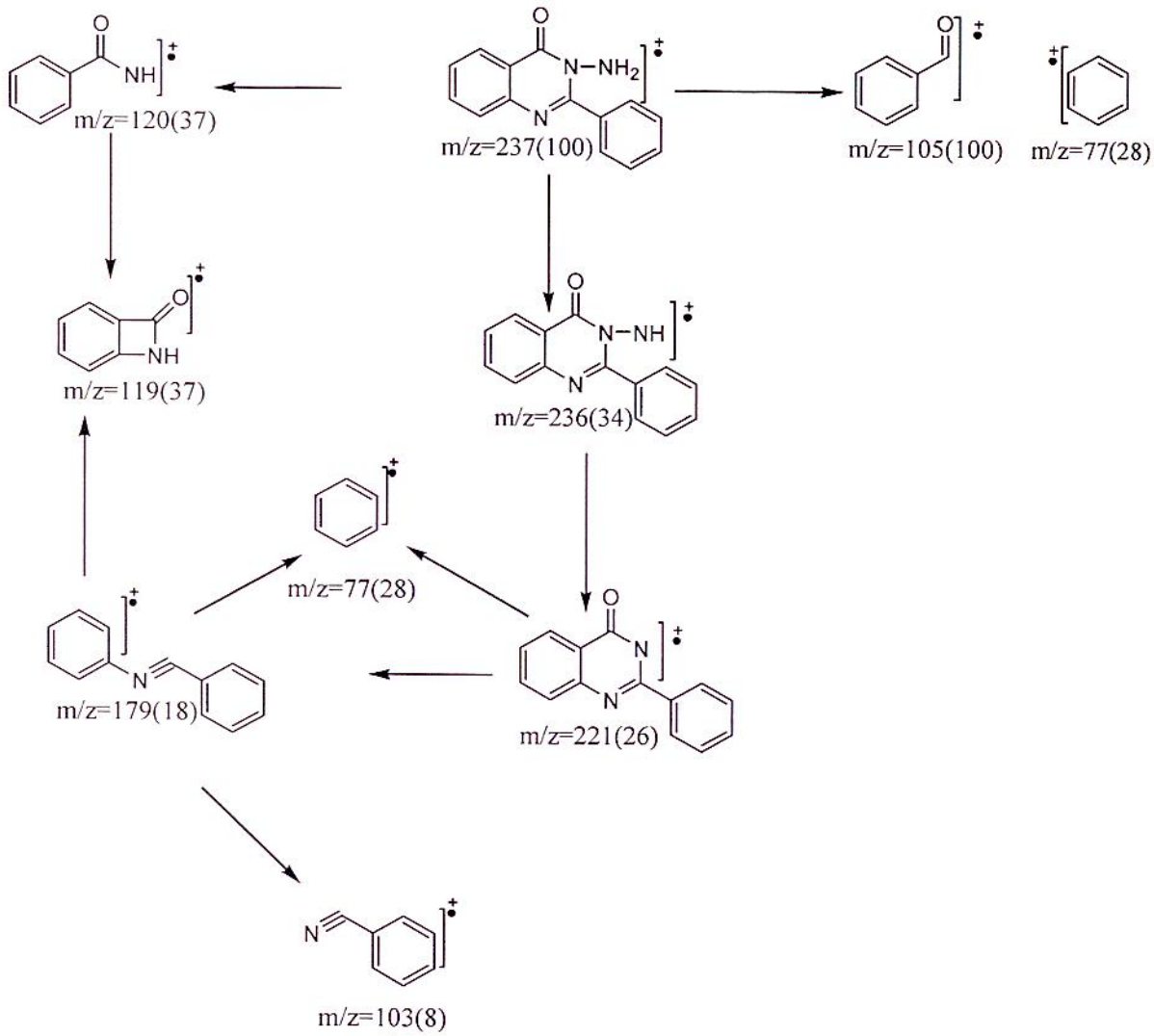


19-33

Compd #	R	M.p(°C)	Solubility	Yield (%)
19	CH_3	143	MeOH, $CHCl_3$	91
20	CH_2NHNH_2	136-138	MeOH, $CHCl_3$	79
21	CF_3	134	MeOH, $CHCl_3$	94
22	C_6H_5	236-238	MeOH, $CHCl_3$	86
23	4-C_6H_4 CH_3	165	MeOH, $CHCl_3$	85
24	4-$C_6H_4NO_2$	202	MeOH,	91
25	4-C_6H_4Cl	189-190	MeOH, $CHCl_3$	90
26	4-C_6H_4Br	170-172	MeOH, $CHCl_3$	78
27	3,5-$(NO_2)_2C_6H_3$	225-226	DMSO	72
28	C_5H_4N	207	DMF	72
29	3-I- C_6H_4	150	MeOH, $CHCl_3$	58
30	3-Br- C_6H_4	140	MeOH, $CHCl_3$	71
31	2- Br-C_6H_4	148	MeOH, $CHCl_3$	66.7
32	H	145-147	$CHCl_3$	94
33	C_6H_5CHCH	152-154	$CHCl_3$	82

Structures of all the synthesized compounds were established on the basis of their physical data. IR showed the presence of amine by its characteristic absorption bands in 3200-3300 cm^{-1} (-NH_2 group), while strong absorption band in 1600-1700 cm^{-1} (-C=O) indicated the presence of ketonic group. Presence of a broad and weak intensity band at δ 4-5 ppm (-NH_2) in ^{1}H-NMR spectra further confirmed the presence of free amine group [Table 2.5]. Characteristic absorption band at δ 7-9 ppm and *J* value were helpful in determining the nature and number of aromatic protons [Table 2.5a], while the presence of M-16 peak in the EI-MS spectrum [Table 2.5 b] confirmed the labile nature of N-NH_2. Mass fragmentation was observed to follow similar pattern for the entire series and

was proved more helpful in the structure determination. A representative mass fragmentation pattern of 2-phenyl- 3-aminoquinazolin-4(3*H*)-one is given in the [Scheme 2.8].



Scheme 2.8: Mass fragmentation pattern of 2-phenyl- 3-amino quinazolin-4 (3*H*)-one

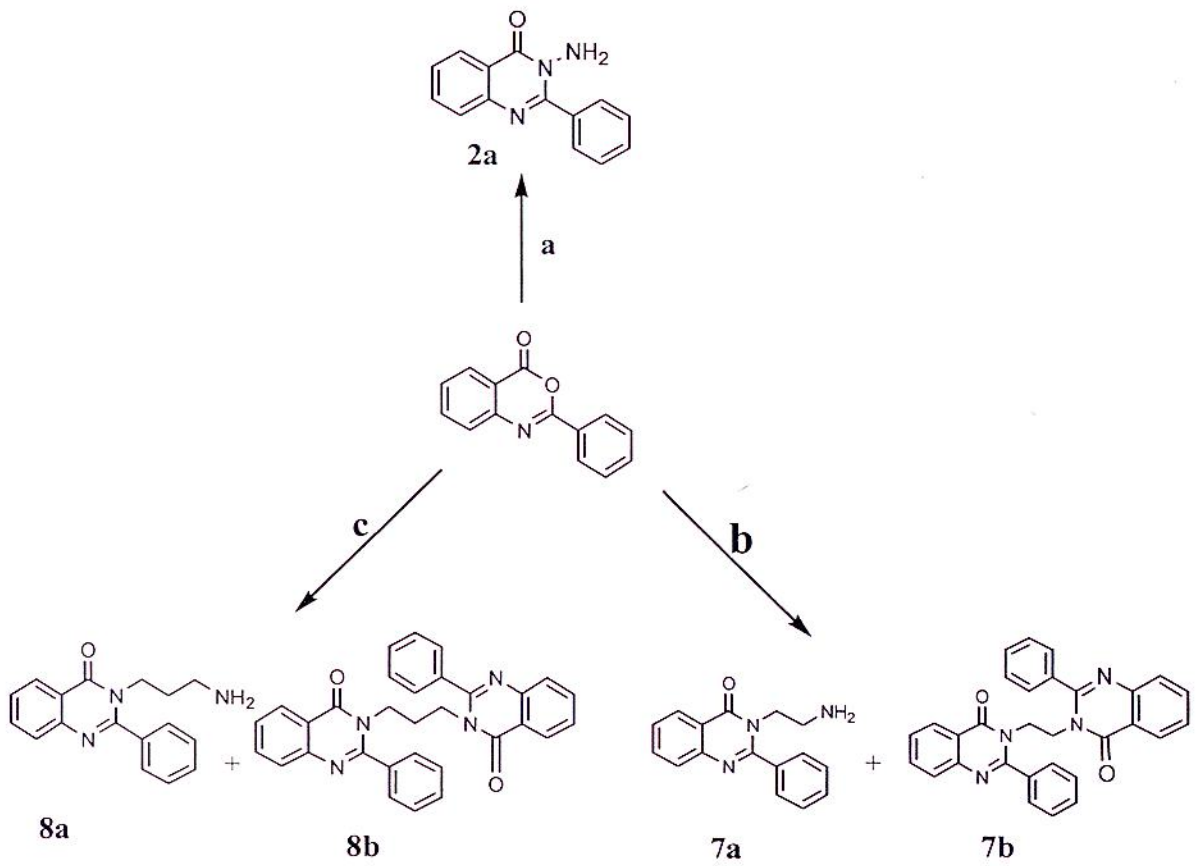
(22)

Table 2.5: ^{1}H-NMR spectral data of 3-amino-2- alkyl/aryl -quinazolin-4(3*H*)-ones

Entry	Compd.	^{1}H-NMR spectral data
1	**19**	(300MHz, $CDCl_3$), δ; 8.08 (d, 1H, *J*=8), 7.76 (t, 1H, *J*=10), 7.58 (d, 1H, *J*=10), 7.46 (t, 1H, *J*=10), 5.79 (s, 2H), 2.56 (s, 3H).
2	**20**	(300 MHz, $CDCl_3$), δ; 8.26 (d, 1H, *J*=9), 7.73 (t, 1H, *J*=9), 7.63 (d, 1H, *J*=9), 7.48 (t, 1H, *J*=9), 4.8 (b, s, 5H, NH), 3.47 (s, 2H, CH_2)
3	**21**	(300 MHz, $CDCl_3$), δ; 8.32 (d, 1H, *J*=9), 7.85 (t, 2H, *J*=8), 7.65 (m, 1H), 4.89 (s, b, 2H)
4	**22**	(300 MHz, $CDCl_3$), δ; 8.35 (d, 1H, *J*=8), 7.82 (m, 4H), 7.56 (m, 3H), 4.43 (s, 2H)
5	**23**	(300 MHz, $CDCl_3$), δ; 8.35 (d,1H, *J*=8), 7.93 (d, 2H, *J*=8), 7.64 (m, 3H), 7.45 (d, 1H, *J*=8), 7.15 (q, 1H, *J*=8), 4.08 (s, 2H), 2.348(s, 3H, CH_3)
6	**24**	(300 MHz, $CDCl_3$): δ 8.34 (d, 3H, *J*=9), 8.02 (d, 2H, *J*=9), 7.81 (s, 2H), 7.59 (m, 1H), 4.89 (b, s, 2H, N-H):
7	**25**	(300 MHz, $CDCl_3$), *δ*: 8.30 (d, 1H, *J*=6), 7.79-7.77 (m, 4H), 7.57-7.44 (m, 3H), 5.05(b, s, 2H).
8	**26**	(300MHz,$CDCl_3$) δ; 8.83 (d, 1H, *J*=8), 7.93-7.87 (q, 2H, $J_{1,2}$=8, $J_{3,4}$=8, $J_{1,3}$=1.6, $J_{2,4}$=1.6), 7.64-7.43 (m, 3H), 7.15-7.1 (q, 1H, $J_{1,3}$=1.64, $J_{2,4}$=1.4, $J_{1,2}$=8), 4.08 (s, b, 2H, N-H)
9	**27**	(300 MHz, $CDCl_3$), *δ*: 9.4 (S, 1H), 8.91 (S, 2H), 8.41 (d, 1H, *J*=8), 8.02(t, 1h, *J*=8), 7.63(d, 1H, *J*=9,4), 7.51(t, 1H, *J*=8), 5.13(s, 2H, NH_2)
10	**28**	(300 MHz, $CDCl_3$): 9.4 (s, 1H, Ar-H), 8.9 (d, 1H, *J*=14.5), 8.53 (d, 1H, *J*=14), 8.27 (d, 1H, *J*=9), 7.81-7.78 (m, 2H), 7.71 (t, 1H, *J*=14.5), 7.56 (m, 1H), 5.06 (b ,s, 1H)
11	**29**	(300 MHz, $CDCl_3$): δ 8.3 (d, 1H, *J*=7.6), 8.27 (s, 1H), 8.10 (t, 1H, *J*=14.5), 7.8 (d, 1H, *J*=8.5), 7.75 (m, 2H), 7.58 (t, 1H, *J*=8), 7.4 (t, 1H, *J*=15), 4.89 (b, s, 1H, NH_2)
12	**30**	(300 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.23 (d, 1H, *J*=9), 8.10 (d, 1H, *J*=8), 7.96 (t, 1H, *J*=8.5), 7.64 (d, 1H, *J*=9), 7.56 (t, 1H, $J_{1,2}$=8), 7.48 (d,1H, *J*=8.5), 7.39 (t,1H, *J*=9.3), 4.08 (s, b, 2H, N-H)
13	**31**	(300 MHz, $CDCl_3$): δ 8.87 (d, 1H, *J*=9.3), 8.53 (d, 1H, *J*=9.5), 8.31 (t, 1H, *J* =8.7), 8.27 (d, 1H, *J*=9), 7.81 (d,1H, *J*=8.7), 7.78-7.71 (m, 2H), 7.51 (t, 1H, *J*=9), 4.52 (s, b, 2H, N-H)
14	**32**	(300 MHz, $CDCl_3$): δ 9.7 (s,1H), 8.3 (d, 1H, *J*=8), 7.78-7.71 (m, 2H), 7.51 (t, 1H, *J*=8), 4.88 (s, b, 2H)
15	**33**	(300 MHz, $CDCl_3$): δ 8.42 (d,1H, *J*=8.28), 8.05 (d, 1H, *J*=6.99), 7.75-7.71 (m, 2H), 7.61 (d, 1H, *J*=13), 7.59 (d, d, 1H, *J*=7.7), 7.53-7.50 (m, 2H), 7.29 (d, 2H, *J*=7.9), 5.63 (d, 1H, *J*=13), 4.54 (s, 2H, NH_2)

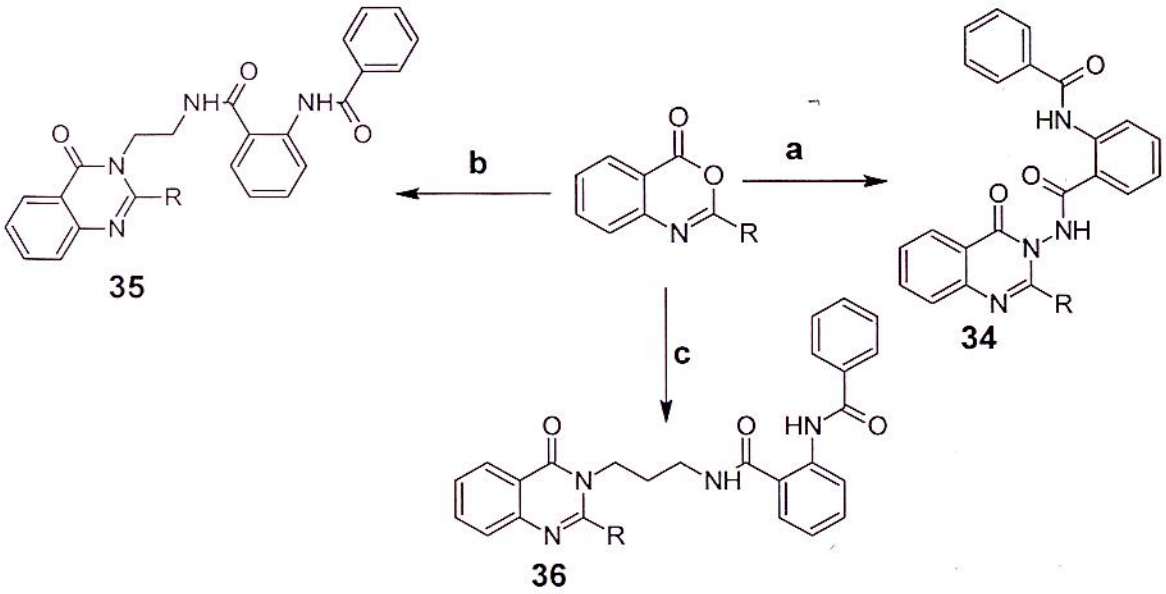
While attempting access to 4-quinazolinones, 2-phenyl-4*H*-3, 1-benzoxazin-4-one was treated with the three diamines, namely, hydrazine hydrate (80 %), ethylene diamine and 1,3-diaminopropane in dry benzene . This surprisingly furnished structurally novel

compounds in quantitative yields [Scheme 2.10] instead of the expected quinazolin-4(3*H*)-ones [scheme 2.9]. The reported literature [16-20] on quinazolin-4(*3H*)-one nucleus describes the formation of 3-amino-2-phenylquinazolin-4(3*H*)-one, 3-(3-aminopropyl)-2-(phenyl) quinazolin-4(3*H*)-one and 3-(2-aminethyl)-2-(phenyl) quinazolin-4(3*H*)-one along with formation of 1,3-bis(2-phenyl-4(3*H*)-quinazolinyl) propane and 1,2-bis (2-phenyl-4 (3*H*)-quinazolinyl) ethane by reacting 2-phenyl-(*4H)*-3, 1-benzoxazine-4-one with hydrazine hydrate, 1,3 diaminopropane and 1,2-diaminoethane respectively [Scheme2.9]. In our hands, however, novel and structurally interesting 4 (*3H*)-quinazolin-4 (3*H*)-one derivatives were obtained from the reaction 2-phenyl-4 (*H*)-3,1-benzoxazin-4-one (**2**) and an appropriate diamine under reflux in dry benzene or pyridine[Scheme 2.10].



a. Hydrazine monohydrate,pyridine,reflux
b. Ethylenediamine, pyridine,reflux
c.Propylendiamine,pyridnie,reflux

Scheme 2.9: Possible compounds resulting from reaction of 2-phenyl-4*H*-3,1-benzoxazin-4-one



R=C_6H_5

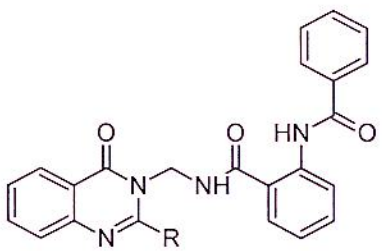
Scheme 2.10: Novel quinazolin-4(3*H*)-ones based compounds from 2-phenyl-3-oxo-quinazolin- 4 (3*H*)-one (**34-36**).

A: $NH_2NH_2.H_2O$ (80%), benzene, reflux, 2h.

B: $NH_2CH_2CH_2NH_2$, reflux, dry benzene, reflux, 2h.

C: $NH_2CH_2CH_2CH_2NH_2$, reflux, dry benzene, 2h.

Table 2.6: Novel quinazolin-4(3*H*)-one derivatives (**34-36**)



34-36

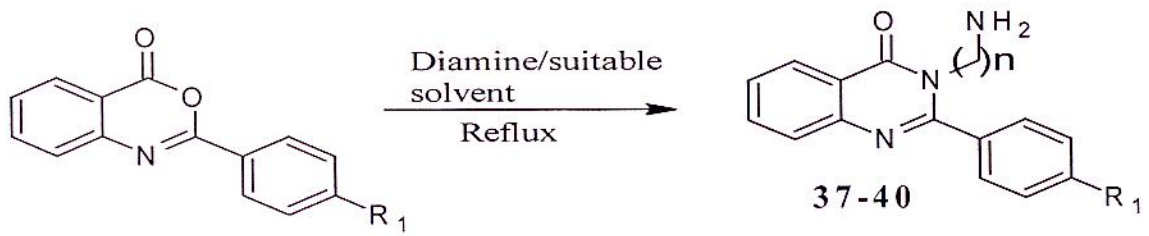
Entry	Compd #	N	M.P.(^{0}C)	Yiled (%)
1	**34**	0	164-166	85
2	**35**	2	237	75
3	**36**	3	90	81

Table 2.7: ^{1}H-NMR spectral data of compounds **34-36**

Entry	Compd #	^{1}H-NMR spectral data
1	**34**	300 MHz, $CDCl_3$): δ 11.8 (s, 2H, NH), 8.83 (d, 2H, *J*=8.4, Ar-H), 8.08 (3H, d, d, *J*=7.6, *J*=8.06), 7.58-7.498 (m, 9H, Ar-H), 7.45 (m, 2H, Ar-H), 7.139(t, 2H, *J*=7.737).
2	**35**	(300 MHz, $CDCl_3$): δ 12.19 (s, 2H, N-H), 8.72 (d, 2H, *J*=9), 8.02 (d, 2H, *J*=9), 7.99 (d, 4H, *J*=9), 7.557.45 (m, 8H), 6.89 (t, 2H, *J*=6), 4.57 (t, 2H, *J*=6), 3.73 (t, 2H, *J*=6).
3	**36**	(300 MHz, $CDCl_3$): δ 11.8 (s, 2H, NH), 8.61 (d, 2*H*, J=7), 8.02 (d, 2H, *J*=9), 7.99 (d, 4H, *J*=9), 7.557.45 (m, 8H), 6.89 (t, 2H, *J*=6), 4.01(t, 2H, 5.3), 3.58(t, 2H, J=6), 2.12(m, 2H)

In order to compare the method for the synthesis of these novel compounds with the reported method, we further observed the formation of the literature reported products when the reaction mixture was digested with H_2SO_4 or HCl. Thus, slight change in the already reported method [16-20] led us to the formation of entirely structurally different products (**34-36**) which are reported for the first time. The compound **34** was prepared by refluxing 2-phenyl-4*H*-3, 1-benzoxazin-4-one (**2**) with hydrazine in dry benzene. After washing with cold water and then recrystallization from ethanol, it afforded compound **34** with 85 % yield. The other analogues of this molecule i.e., compounds **35** and **36** were prepared by reacting 2-aryl-4*H*-3, 1-benzoxazin-4-one with 1, 2-diaminoethane and 1, 3-diaminopropane, respectively under the same reaction condition.

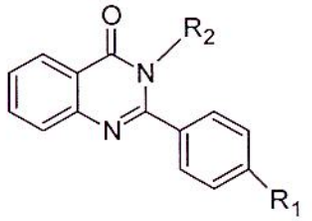
These results obtained further prompted us to synthesize a series of analogues of these compounds starting from the 2-aryl substituted-4*H*-3, 1-benzoxazin-4-one.We failed to obtain any of the structural analogues of compounds **34-36** and instead 3-(2-aminoethyl/propyl)-2-(aryl)quinazolin-4(3*H*)-one **37- 40** [Scheme 2.11] were obtained.



37-40

Scheme 2.11: Synthesis of compounds **37-40**

Table 2.8a: 2-Aryl- 3-alkylaminoquinazolin-4(*3H*)-ones (**37-40**)



37-40

Entry	Compd #	R_1	R_2	Reaction solvent	Yield (%)	M.P. (^{0}C)
1	**37**	CH_3	$-CH_2CH_2NH_2$	Toluene	80	190-192
2	**38**	CH_3	$-CH2CH_2CH_2NH_2$	Pyridine	91	238-239
3	**39**	Br	$-CH2CH_2CH_2NH_2$	Benzene	76	245-247
4	**40**	Cl	$-CH_2CH_2NH_2$	Pyridine	38	80

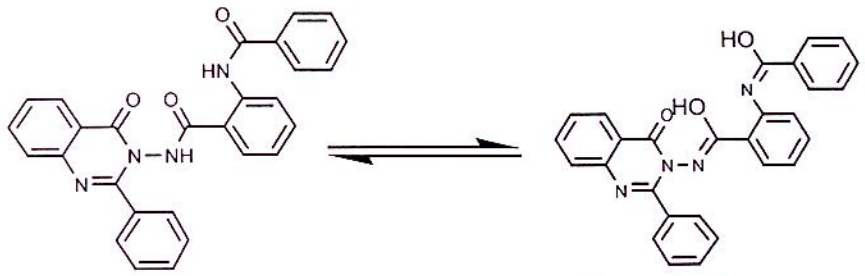
Table 2.8b: ^{1}H-NMR 2-Aryl- 3-alkylaminoquinazolin-4(*3H*)-ones (**37-40**)

Entry	Compd#	^{1}H-NMR spectral data
1	**37**	(300 MHz, $CDCl_3$): δ 8.86 (d, 1H, *J*=8, ArH), 8.63 (d, 1H, *J*=6, Ar-H), 7.83-7.76 (m, 3H, Ar-H), 7.57-7.52 (t, 1H, *J*=7, Ar-H),7.31 (d, 2H, J=9, Ar-H), 7.18 (t,1H, *J*=7, Ar-H), 4.10 (t, 2H, *J*=6, CH_2), 3.52 (t, 2H, *J*=6), 2.49(s,3H, CH_3), 1.18(s, 2H, N-H)
2	**38**	(300MHz, $CDCl_3$): δ 8.86 (d,1H, *J*=8), 8.63 (d,1H, *J*=6), 7.83-7.76 (m, 3H), 7.57-7.52 (t, 1H, *J*=7), 7.31 (d, 2H, *J*=9), 7.18 (t, 1H, *J*=7), 5.6 (t, 2H, NH), 3.33 (t, 2H, *J*=6), 2.72 (t, 2H, *J*=9), 1.79-1.61 (m, 2H)
3	**39**	(300 MHz, $CDCl_3$): δ 8.55 (d, 1H, *J*=9), 7.75-7.71 (m, 2H), 7.65-7.48 (m, 3H), 7.36-7.23 (m, 2H), 5.63 (b, t, 2H), 3.32 (t, 2H, *J*=6), 3.23-3.20 (m, 2H), 2.77 (t, 2H, *J*=7).
4	**40**	(300 MHz, $CDCl_3$): δ 8.22 (d, 1H, *J*= 7.16), 7.71 (t, 1H, *J*=7.428), 7.592 (t, 1H, J=8.02), 7.529 (d, 1H, J=8), 7.429-7.391 (m, 2H), 7.347 (t,1H, J=7.52), 7.26 (s, 1H), 4.172 (t, 2H, J=6.7), 3.104 (t, 2H, J=6.2), 1.64 (b, s, 2H)

In the light of these results, we decided to look into the effect of substituents on the reactivity of 2-aryl-4*H*-3, 1-benzoxazin-4-one towards the diamines. We found that both electron withdrawing and donating groups were present Thus, 2-aryl-4*H*-3-benzoxazin-4-one were allowed to react with 1,3-diaminopropane . 3-(3-Aminopropyl)-2-(4-methylphenyl) quinazolin-4(3*H*)-one (**38**) and 3-(3-aminopropyl)-2-(4-bromophenyl) quinazolin-4(3*H*)-one (**39**) were synthesised while no structural analogue of (**34-36**) was

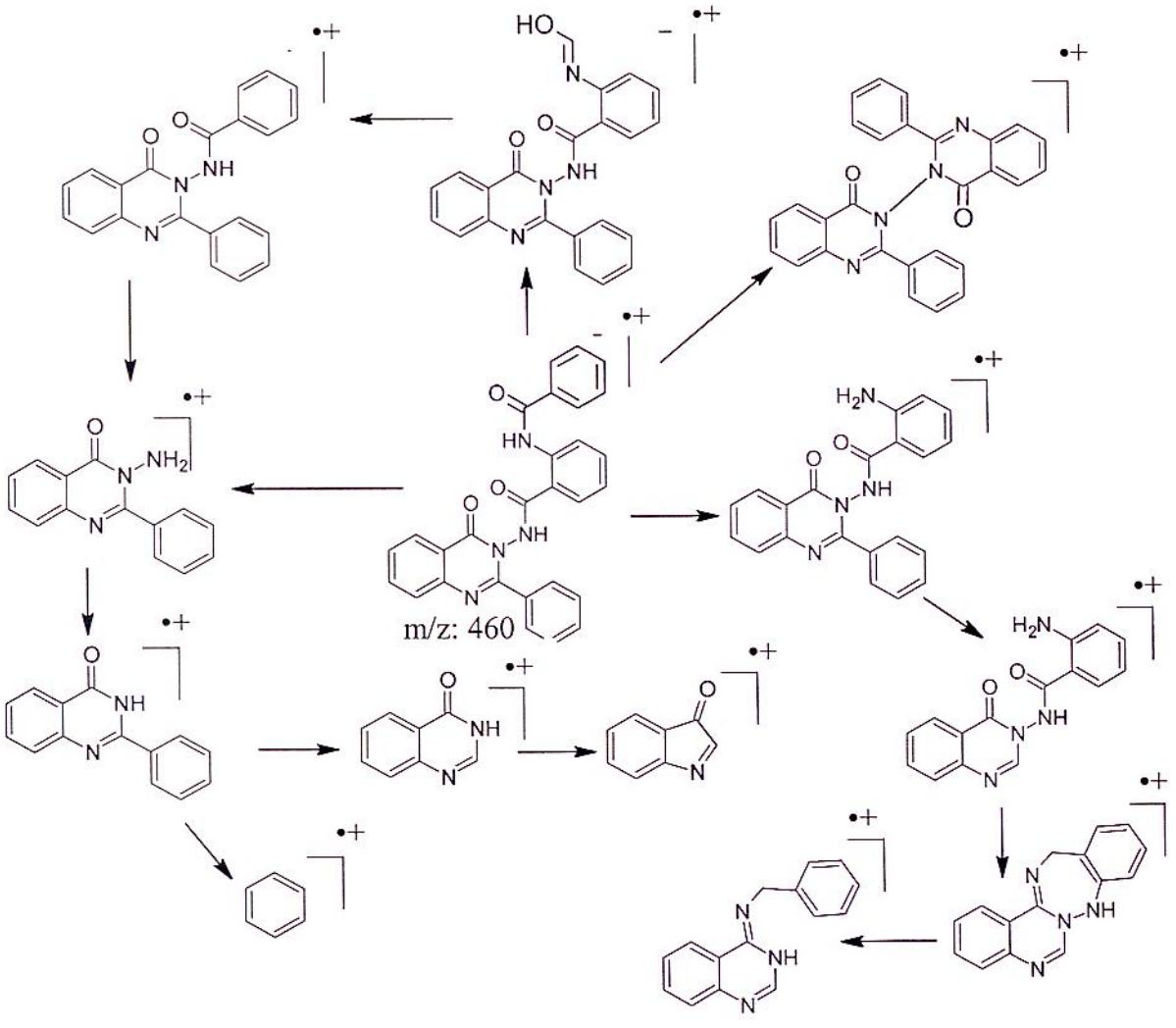
obtained. It supports the fact that the reactivity is controlled by steric factor and not by the electronic effects of the substituents.

Structures of compounds **(34-36)** synthesized were determined from their spectroscopic data including EI-MS, FAB-MS (+ve, -ve), ^{1}H -NMR, and IR. A medium intensity band appeared at 3318 cm^{-1} in the IR spectrum showed the presence of an amide bond, while a well developed broad band corresponded to amide N-H signal observed at 11.80 ppm (D_2O exchangeable) in ^{1}H-NMR spectrum of **(34).** These observations not only confirm the presence of amide (–NH-CO-) group in the compounds **(34-36)** but also indicated the acidic nature of the amide hydrogen in theses compounds. This means that these compounds exist in the form of amide-iminol tautomers [Scheme-2.12]. The presence of weak and D_2O exchangeable signal at 12.19 ppm confirmed the amide moiety in **35,** while triplets at 4.89 (-CH_2-), 4.57 (-CH_2) and multiplet at 2.15 (-CH-CH_2-CH_2-) were assigned to the presence of an aliphatic carbon chain. FAB (+ve, -ve) and EI-MS were found helpful in determining molecular mass and fragmentation pattern [Scheme 2.13]. The later was found very helpful in determining the structures of the compounds. Further, proof for the structure assignments of these compounds was obtained from the acid hydrolysis of these compounds. Thus, 2-aminobenzoyl-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzamide (**34**) upon acid hydrolysis in H_2SO_4 solution resulted in 3-amino-2-phenylquinazolin-4(3*H*)-one, anthranilic acid and benzoic acid [Scheme. 2.14]. All the three products resulting from acid hydrolysis were separated by solvent-solvent extraction using saturated $NaHCO_3$ solution and were then separated and purified using column chromatography.The resulting products were characterized using Mass and ^{1}H-NMR spectroscopy as well as by comparison with standard anthranilic acid and benzoic and also with the help of mixed melting point. The disappearance of base peak at m/z: 460 in EI-Ms and also peak at 11 ppm in ^{1}HNMR after acid hydrolysis of amide clearly indicated the amide bond in the compound **(34).** The amide hydrolysis in strong acidic media was observed, while a weakly acidic media like acetic acid and 10-15 % HCl did not cause the hydrolysis. This indicated the stability of the product in weakly acidic media. The amide was also stable in strong basic medium like saturated NaOH solution.

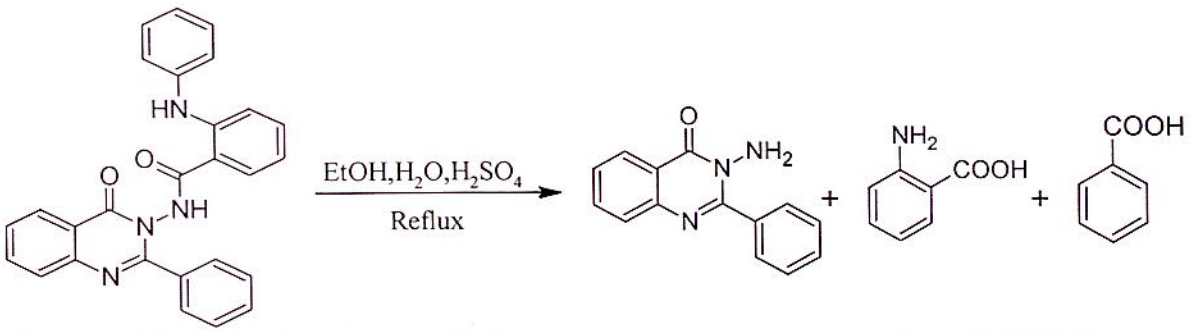


Imide form Iminol form

Scheme 2.12: Imide-Iminol tautomerism showing the stability of 2-aminobenzoyl-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzamide (**34**)



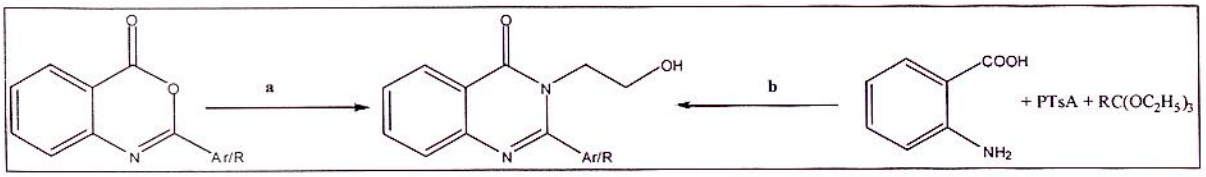
Scheme 2.13: Mass fragmentation pattern of 2-aminobenzoyle-N-(4-oxo-2-phenylquinazolin-3(*4H*)-yl) benzamide (**34**)



Scheme 2.14: Acid hydrolysis of 2-Aminobenzoyle-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzamide (**34**).

2.1.3. 3-(2-Hydroxyethyl)-2-substituted quinazolin-4-(3*H*)-ones (41-45)

Echinazolinone, 3-(2-Hydroxyethyl) quinazolin-4-(3*H*)-one (**44**) is a very powerful antifungal compound isolated from the *Echinops echinatus* [21, 22]. Therefore, it was decided to synthesize a series of 3-(2-hydroxyethyl)-2-substituted quinazolin-4-(3*H*)-ones. [Table 2.9]. 3-(2-Hydroxyethyl) quinazolin-4-(3*H*)-ones (Echinazolinone) (**44**) and (**45**) were synthesized by a cheaper method under solvent free conditions by modification of method reported by Narasimhulu *et al.*,[15] [Scheme.2.15]. The compounds were synthesized in excellent yields compared to the reported method for the synthesis of Echinazolinone[22]. Compounds (**41-43**) were synthesized by refluxing 2-aryl substituted-4*H*-3, 1-benzoxazin-4-one and monoethanolamine in dry benzene or toluene [Scheme 2.15]. Structures of all the 3-(2-hydroxyethyl)-2-substituted quinazolin-4-(3*H*)-ones synthesized were confirmed from the IR, ^{1}H-NMR and Mass spectra including both FAB-MS (+ve, -ve) and EI-MS. The presence of a broad band at 3400-3500 cm^{-1}, while the same group was confirmed from the D_2O replicable at δ 2.32-3.5 ppm in the ^{1}H-NMR spectra confirm the presence of (OH) group in the entire series [Table 2.10]. Mass fragmentation followed a regular pattern giving M-28 peak due to loss of (CO), which is a typical fragment results in the fragmentation of primary alcohol.



41-45

Scheme 2.15: Synthesis of 2-aryl/alkyl- 3-hydroxyethyl quinazoline-4(3*H*)-ones

a: Monoethanolamine, dry pyridine, reflux, 3-5h.
b: Monoethanolamine, $RC(OC_2H_5)_2$, TsOH, r. t. 1-2h

Table 2.9: 2-Alky/aryl- 3-{2-hydroxyethyl} quinazolin-4(3*H*)-ones

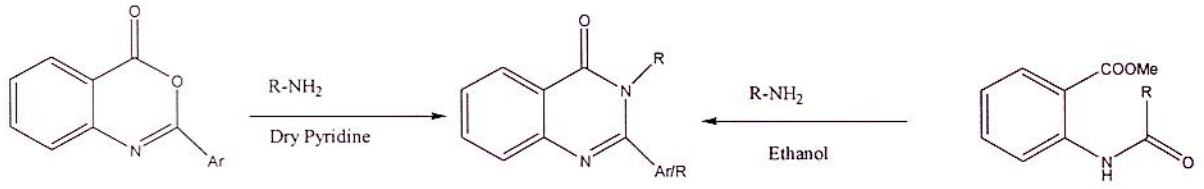
Entry	Compd #	R	M.P (^{0}C)	Solubility	Yield (%)
1	**41**	C_6H_5	164-166	$CHCl_3$	85
2	**42**	$C_6H_4.NO_2$	228	CH_3OH	87
3	**43**	$C_6H_4.CH_3$	178-180	$CHCl_3$	87
4	**44**	H	164	$CHCl_3$	89
5	**45**	CH_3		$CHCl_3$	86

Table 2.10: ^{1}H-NMR data of 2-Alky/aryl- 3-{2-hydroxyethyl} quinazolin-4(3*H*)-ones

Entry	Compd.#	^{1}H-NMR spectral data
1	**41**	^{1}H-NMR (300 MHz, CD_3OD) δ: 8.622 (d, 1H, *J*=8.25), 7.997 (d, 2H, *J*=8.19), 7.795 (d, 1H, *J*=7) 7.6-7.51 (m, 4H), 7.22-7.17 (t, 1H, *J*=8.14), 3.74-3.70 (t, 2H, *J*=5.7), 3.545-3.506 (t, 2H, *J*=5.7), 3.299 (s, 1H)
2	**41**	^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, 1H, *J*=8.28), 8.305 (t, 2H, *J*=8.8), 8.1325 (t, 2H, 8.6), 7.632-7.495 (m, 3H), 3.724 (t, 2H, *J*=5), 3.53 (t, 2H, *J*=5.2), 3.31(b, s, 1H, OH)
3	**43**	^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.3 (d, 1H, *J*=8.2), 8.15 (d, 2H, *J*=8), 7.8 (t, 1H, *J*=8.6), 7.52-7.48 (m, 2H), 7.27 (d, 2H, *J*=8), 3.7 (t, 2H, *J*=5), 3.55 (t, 2H, *J*=5.5), 2.49 (b, s, 1H), 2.32 (s, 3H, CH_3) .
4	**44**	^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.18 (d, 1H, *J*=8.04), 8.05 (s, 1H), 7.72-7.67 (t, 1H, *J*=8.4), 7.615 (d, 1H, *J*=7.8), 7.452-7.398 (t, 1H, *J*=8.16), 4.1506-4.1184 (t, 2H, *J*=4.8), 3.99-3.975 (t, 2H, 4.5), 2.978 (b, s, 1H)
5	**45**	^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.190 (d, 1H, *J*=8), 7.38-7.682 (t, 1H, *J*=7.9), 7.631 (d, 1H, *J*=7.3), 7.446-7.396 (t, 1H, *J*=7.7), 4.316-4.282 (t, 2H, *J*=5.07), 4.026-3.992 (t, 2H, *J*=5.26), 3.22 (b, s, 1H), 2.72 (s, 3H).

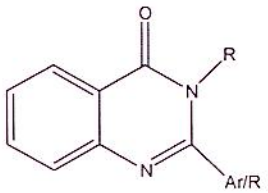
2.1.4. 2, 3-Disubstituted quinazolin-4(3*H*)-ones (46-54)

In search for more potent bioactive compounds, it was considered of interest to synthesize a range of 2-alkyl/aryl-3-alkyl/aryl-quinazolino-4(3*H*)-ones. Methyl -*N*-acyl anthranilates and 2-aryl substituted-4*H*-3, 1-benzoxazin-4-one were used as starting materials.and suitable primary amines in suitable solvent were employed in these reactions [Scheme 2.16].



Scheme 2.16: Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones (**46-54**)

Table 2.11: 2, 3-Disubstituted quinazolin-4(3*H*)-ones (**46-54**)

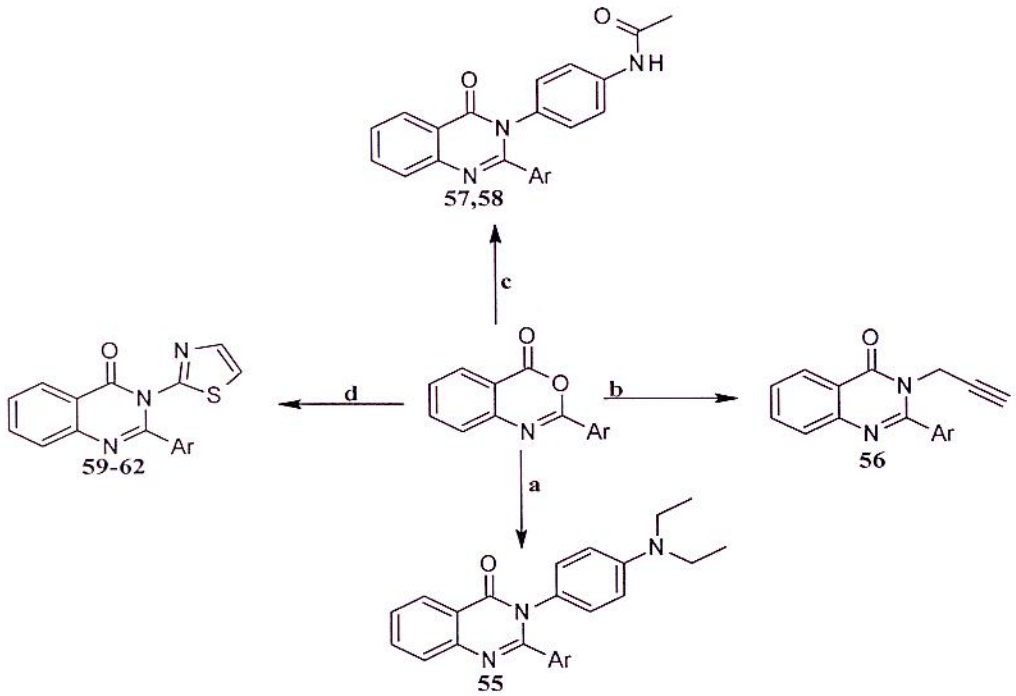


Entry	Compd #	R^1	R^2	M.P(^{0}C)	Yield (%)
1	**46**	CH_3	p-$CH_3C_6H_4$	197-199	67
2	**47**	CH_3	2-$CH_3C_6H_4$	200-202	94.6
3	**48**	CH_3	2,4,6$(CH_3)_3$ C_6H_2	89-100	96.1
4	**49**	C_6H_5	4-Br-C_6H_4	228-230	41
5	**50**	C_6H_5	2,4,6$(CH_3)_3$ C_6H_2	210-213	73
6	**51**	C_6H_5	4-I-C_6H_4	233-235	88
7	**52**	C_6H_5	C_6H_4-CH_2	155-157	89
8	**53**	C_6H_5	4-CH_3-C_6H_4	186-188	73
9	**54**	CF_3	C_6H_5	135	91

In this search, methyl-*N*-acylanthranilate was found of limited application in case of synthesis of sterically strained molecules. In most cases, the reactions failed to proceed when bulky amines were used. The reason could be attributed to the steric strain developed due to the *N*-acyl group which decreases the reactivity of ester part of methyl-

N-acylanthranilate towards the bulky nucleophile. These results led us to focus on the use of 2-aryl-4*H*-3, 1-benzoxazin-4-one as the reaction substrates. A series of 2, 3-disubstiuted quinazolin-4(3*H*)-ones [Scheme 2.17, Table 2.11] was synthesized by refluxing the 2-aryl-4*H*-3, 1-benzoxazin-4-one with the amine in a suitable high boiling point solvent. Methaqualone (**47**), a well known sedative and hypnotic drug and compound **48** were synthesized, adopting the procedure reported by Narasimhulu *et al.* [15].

Structures of the compounds **46-62** were established on the basis of spectroscopic data including IR, ^{1}H-NMR [2.12b], EI-MS and FAB-MS (+ve, -ve). The presence of strong absorption band at 1600-1700 cm^{-1} in the IR spectra indicated the presence of -C=O group while a medium intensity peak in the 1550-1600 cm^{-1} showed the presence of -C=N group. Mass fragmentation pattern was found very helpful in determining the structures. Common fragments at m/z: 145 and 105 were found in the whole series.



Scheme2.17: Synthesis of 2-aryl, 3-substituted quinazolin-4(3*H*)-ones (**55-62**)

a: 4-(*N,N*-diethylamino)-aniline, dry toluene, reflux, 5h

b: Propargylamine, dry benzene, reflux, 3h.

c: 4-Aminoacetanilide

d: 2-Aminothiazole, dry pyridine, reflux, 7h.

Table 2.12: 2-Aryl- 3-aryl/heteroaryl quinazolin-4(3H)-ones (**55-61**)

Entry	Compd #	Ar	M.P(^{0}C)	Yield (%)
1	**55**	4-Nitrophenyl	235-237	81
2	**56**	Phenyl	173-175	86
3	**57**	4-Methylphenyl	179-180	83
4	**58**	Phenyl	228	89
5	**59**	4-Nitrophenyl	231	97
6	**60**	4-Bromoylphenyl	289	76
7	**61**	4-Methylphenyl	212-214	78
8	**62**	Phenyl	186-189	71

Table 2.13: ^{1}H-NMR 2-Aryl/alkyl- 3-aryl/heteroaryl quinazolin-4(3*H*)-ones (**47-62**)

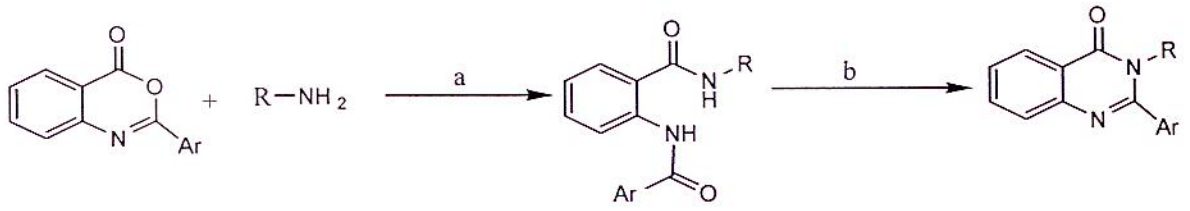
1	**46**	(300 MHz, $CDCl_3$) δ: 8.7 (d, 1H, *J*=9), 8.02 (s, 2H, J=8), 7.59-7.42 (m, 7H), 7.21 (d, 2H, J=9), 7.024 (t, 1H, J=7), 2.34 (s, 3H, CH_3)
2	**47**	(400 MHz, $CDCl_3$) δ: 8.36 (d, 1H, *J*=8.2), 7.96 (d, 1H, *J*=8), 7.83 (t,1H, *J*=8.2), 7.76 (t,1H, *J*=7.9), 7.63 (t,1H, *J*=8), 7.48 (d, 1H, *J*=8.5), 7.35 (t, 1H, *J*=7.69), 7.31 (d, 1H, *J*=8.03), 2.54 (s, 3H, CH_3), 2.23 (s, 3H, Ar-CH_3).
3	**48**	(400 MHz, $CDCl_3$) δ: 8.57 (d, 1H, *J*=8), 7.97 (d, 1H, *J*=8), 7.85 (t,1H, *J*=7.6), 7.63 (t, 1H, *J*=8.2), 6.93 (s, 2H, Ar-H), 2.51(s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.11 (s, 6H, Ar-CH_3)
4	**49**	(300 MHz, $CDCl_3$) δ: 8.40 (d, 1H, *J*=8.2), 8.01 (d, 1H, *J*=13), 7.93-7.79 (m, 2H), 7.65(t, 1H, *J*=8), 7,58 (t, 1H, *J*=8.7), 7.49-7.40 (m, 6H)
5	**50**	(300 MHz, $CDCl_3$): δ 8.7 (d, 1H, *J*=8), 8.02 (d, 1H, *J*=8), 7.95 (d, 2H, *J*=8), 7.63-7.42 (m, 5H), 7.28 (t, 1H, *J*=8), 6.96 (s, 2H), 2.3 (s, 3H), 2.2 (s, 6H)
6	**51**	(300 MHz, $CDCl_3$): δ 8.4 (d, 1H, *J*=7.8), 7.98 (d, 2H, *J*=15), 7.85-7.81 (t, 1H, *J*=8), 7.6-7.54 (m, 4H), 7.5-7.45 (m, 3H), 7.3-7.28 (d, 2H, *J*=11.5)
7	**52**	(300 MHz,$CDCl_3$):δ 8.82 (d, 1H, *J*=8), 8.042 (d, 2H, *J*=8), 7.53-7.47 (m, 5H), 7.35-7.31 (m, 5H), 7.09 (t, 1H, *J*=8), 4.63 (s, 2H, CH_2)
8	**53**	(300 MHz, $CDCl_3$): δ 8.70 (d, 1H, *J*=8), 8.02 (d, 1H, *J*= 8), 7.57-7.45 (m, 7H), 7.21 (d, 2H, *J*=9), 7.02 (t, 1H, *J*=8), 2.34 (s, 3H, CH_3)
9	**54**	(300MHz, $CDCl_3$) δ: 8.31(d,1H, *J*=7.7), 8.01(d,1H, *J*=8), 7.82(d, 2H, *J*=8), 7.71(t, 1H, *J*=8.1), 7.61(t, 1H, *J*=8), 7.53(t,1H, *J*=8)
10	**55**	(300MHz, $CDCl_3$): δ 8.39 (d, 1H, *J*=8), 8.32 (d, 2H, *J*=8), 8.0 (d, 1H, *J*=7.8), 7.85 (t, 1H, *J*=7.9), 7.59 (d, 1H, *J*=8.2), 7.51 (t, 1H, *J*=8.6), 7.30 (d, 2H, *J*=11.76), 7.10 (d, 2H, *J*=10.8), 3.33-3.27 (q, 4H, *J*=5.7), 1.29 (t, 6H, *J*=5.9)

11	**56**	(300 MHz, $CDCl_3$): δ 8.83 (d, 1H, *J*=6), 8.03-8.01 (d, 2H, *J*=6), 7.57-7.47 (m, 5H), 7.13 (t, 1H, *J*=6), 4.25 (d, 2H, *J*=3), 2.29 (t, 2H, *J*=3); IR (KBr): 2910 (C-H), 2120 (b, m), 1599 (C=N), 1453 (C-C, bend), 1252 (C-C, str.), 896 (broad, medium), 761 (sharp)
12	**57**	(300MHz, $CDCl_3$): δ 8.56 (d, 1H, *J*=6), 7.77 (d, 2H, *J*=9), 7.67 (d, 2H, *J*=6), 7.45 (d, 2H, *J*=9), 7.18 (d, 2H, *J*=6), 7.07 (t, 3H, *J*=6), 2.3 (s, 3H), 2.05 (s, 3H)
13	**58**	(300MHz, $CDCl_3$) δ: 11.2 (b, s, 1H), 8.39 (d, 1H, *J*=8), 8.01 (d, 2H, *J*=7.9), 7.82-7.75 (m, 3H), 7.55-7.52 (m, 2H), 7.50-7.42 (m, 5H), 2.49 (s, 3H)
14	**59**	(300MHz, $CDCl_3$) δ: 8.3 (d, 3H, *J*=8.3), 7.55-7.51 (m, 2H), 7.01 (d, 1H, *J*=4), 6.70 (d, 1H, *J*=3.5)
15	**60**	(300 MHz, $CDCl_3$): δ 8.87 (d, 1H, *J*=6), 8.23 (d, 1H, *J*=6), 8.21 (d, 1H, *J*=8), 7.92 (d, 2H, *J*=9), 7.65 (t, 2H, *J*=6), 7.52 (d, 1H, *J*=9), 7.02 (d, 1H, *J*=3), 6.8 (d, 1H, *J*=4)
16	**61**	(300MHz, $CDCl_3$): δ 8.96 (d, 1H, *J*=9), 8.29 (d, 1H, *J*=9), 8.17 (t, 1H, *J*=6), 7.94 (d, 2H, *J*=9), 7.68 (m, 1H,), 7.53 (s, 1H), 7.33-7.223 (m, 3H), 7.12 (d, 1H, *J*=3), 6.8(d, 1H, *J*=3), 2.45 (s, 3H)
17	**62**	(300MHz, $CDCl_3$): δ 8.99 (d, 1H, *J*=9), 8.47 (d, 1H, *J*=9), 8.04-8.019 (m, 2H), 7.65-7.56 (m, 4H), 7.89 (t, 1H, *J*=9) 7.20 (d, 1H, *J*=4), 6.88 (d, 1H, *J*=3)

2.1.5. 2-(Aroylamino)-*N*-alkyl/arylbenzamides (63a-g) (Open Chain diamides)

Research on quinazolin-4(3*H*)-ones describes the formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones from 2-aryl-4*H*-3, 1-benzoxazin-4-one and aromatic or aliphatic amines as described in schemes 2.16 and 2.17. While in the present search, using 2-aryl-4*H*-3, 1-benzoxazin-4-one as precursors for the synthesis of 2, 3-diarylquinazolin-4(3*H*)-one, some open chain products were isolated and characterized along with the formation of 2,3-disubstituted quinazolin-4(3*H*)-ones [Scheme 2.18]. The products synthesized were characterized and identified to be diamides [Table 2.14]. They proved helpful in deducing the mechanism of the formation of 2, 3-disubstituted quinazolin-4-(3*H*)-ones from 2-aryl-4*H*-3, 1-benzoxazin-4-one. These products were also then converted in to the corresponding 2,3-disubstituted quinazolin-4(3*H*)-ones using microwave irradiation and thermal fusion at high temperature under solvent and catalyst free condition. Thus, a new solvent and catalyst free method for the synthesis of 2,3-disubstituted quinazolin-4-(3*H*)-ones from 2-(arylamino)-*N*-(4-alkyl/aryl)benzamide was devised. Therefore, efforts were focused on the selective synthesis of diamides as selective reaction products and consequently, a series of diamides were synthesized by modification of the literature

method [21-24] for the synthesis of 2, 3-disubstituted quinazolin-4-(3*H*)-ones and the effect of structure on reactivity in these reactions was explained. It is important to note that the formation of diamides and their further cyclization to the 2, 3-disubstituted quinazolin-4(3*H*)-ones is affected by the structure of 2-aryl-4*H*-3, 1-benzoxazin-4-one as well as the structure of amine used. The formation of diamides was observed as side product in case of substituted amine, while in most cases, where bulky amines were allowed to react with 2-aryl-4*H*-3, 1-benzoxazin-4-one; diamide was the only product synthsized. The reason thus could be attributed to the steric hinderance exerted by the bulky substituent in cyclization of the diamides. Structures of the diamides synthesized were established on the base of spectroscopic data including IR, ^{1}HNMR, FAB-MS and EI-MS. The appearance of broad bands at 3200-3300 cm^{-1} confirmed the presence of amide carobyl (NH-CO) groups. On the other hand, a weak broad signal, (D_2O exchangeable) centred at 10-11 ppm in ^{1}H-NMR spectrum confirmed the presence of an amide (-CO-NH) group. Interesting information from the mass fragmentation pattern was the appearance of (M-18) peak for all the compounds. This indicates that the open chain diamide cyclize to the corresponding 2, 3-disubstituted quinazolinones upon dehyradtion at elevated temprature.



63a-g

a) Pyridine or benzene, reflux, 3-5 h. **b**) Thermal fusion or MW irridiatios

Scheme 2.18: Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones via diamide intermediates

Table 2.14(a): 2-(Aroylamino)-*N*-alkyl/arylbenzamides (**63a-g**)

Compd #	Ar	R	M.P (^{0}C)	Yield (%)
63a	Phenyl	4-Bromophenyl	238	41
63b	Phenyl	4-Iodophenyl	253-255	78
63c	4-Nitrophenyl	2-Hydroxyethyl	228-231	93
63d	Phenyl	Benzyl	155-157	89
63e	Phenyl	Mesityl	210-213	83
63f	Phenyl	2-Hydroxyethyl	185	59
63g	Phenyl	NH_2	165	91

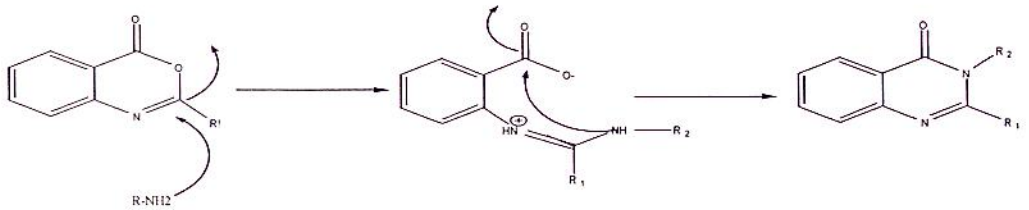
Table 2.14(b): ^{1}H-NMR spectral data of 2-(Aroylamino)-*N*-alkyl/arylbenzamides (**63a-g**)

Entry	Compd #	^{1}H-NMR spectral data
1	**63a**	^{1}HNMR (300MHz, $CDCl_3$) δ: 10.21 (s, 2H, NH), 8.45 (d, 1H, *J*=8.2), 8.21 (d, 1H, *J*=13), 7.93-7.79 (m, 3H), 7.65 (t, 1H, *J*=8), 7, 58 (t, 1H, *J*=8.7), 7.49-7.40 (m, 6H).
2	**63b**	^{1}HNMR (300MHz, $CDCl_3$) δ: 10.9 (s, 2H, NH), 8.4(d, 1H, *J*=8), 7.9 (d, 2H, *J*=7.9), 7.83 (t, 1H, *J*=8), 7.7-7.5 (m, 4H), 7.45-7.40 (m, 3H), 7.3 (d, 2H, *J*=8.5).
3	**63c**	^{1}HNMR (300MHz, $CDCl_3$) δ: 12.52 (s, N-H), 12.48 (s, N-H), 8.77 (s, 1H, *J*=8.4), 8.65 (d,1H, *J*=8.4), 8.28 (d, 2H, *J*=8.8), 8.135 (d, 1H, *J*=8.8), 7.64 (d, 1H, *J*=7.6), 7.514 (t, 1H, *J*=8.25), 7.139 (t, 1H, *J*=7.6), 3.734 (t, 2H, *J*=5), 3.53 (t, 2H, *J*=5.2), 3.31 (b, s, 1H, OH)
4	**63d**	^{1}HNMR (300MHz, $CDCl_3$): δ 12.108 (s, 2H, N-H), 8.82 (d, 1H, *J*=8), 8.042 (d, 2H, *J*=8), 7.53-7.47 (m, 5H), 7.35-7.31 (m, 5H), 7.09 (t, 1H, *J*=8), 4.63 (s, 2H, CH_2).
5	**63e**	^{1}HNMR (300MHz, $CDCl_3$): δ 10.2 (s, 2H, N-H), 8.7 (d, 1H, *J*=8), 8.02 (d, 1H, *J*=8), 7.95 (d, 2H, *J*=8), 7.63-7.42 (m, 4H), 7.28 (t, 1H, *J*=8), 6.96 (s, 2H), 2.3 (s, 3H), 2.2 (s, 6H).
6	**63f**	^{1}HNMR (300MHz, CD_3OD) δ: 12.186 (s, N-H), 12.04 (s, N-H), 8.622 (d, 1H, *J*=8.25), 7.997 (d, 2H, *J*=8.19), 7.795 (d, 1H, *J*=7) , 7.6-7.51 (m, 4H), 7.22-7.17 (t, 1H, *J*=8.14), 3.74-3.70 (t, 2H, *J*=5.7), 3.545-3.506 (t, 2H, *J*=5.7), 3.299 (s, 1H).
7	**63g**	^{1}HNMR (300MHz, CD_3OD) δ 8.10.7 (m, 2H), 7.91(d, 1H, *J*=8.355), 7.685 (m, 5H), 7.317 (t, 1H, *J*=7.113), 7.052(t, 1H, *J*=8.4), 6.67 (d, 1H, *J*=7.2). 4.61(S, 2H, NH_2)
8	**63h**	^{1}HNMR (400MHz, CD_3OD) δ: 11.19 (s, 2H, -CO-NH), 11.10(S, 1H, OH) 9.17(s, 1H), 8.612 (d,1H, *J*= 8.4), 7.936 (d, 1H, *J*=7.28), 7.807(d.d, 2H, $J_{1,2}$=8.5, $J_{3,4}$= 8.68), 7.68 (m, 3H), 7.49 (t, 1H, *J*=8.016), 7.21(d, 1H, *J*=8.1), 7.118(t, 2H, J=7.56), 6.97 (d, 1H, *J*=8.1), 6.93 (t, 1H, *J*=8.4).
9	**63i**	^{1}HNMR (300MHz, CD_3OD) δ: 7.92 (d, 1H, *J*=7), 7.905 (t, 1H, *J*=6.9), 7.65-7.607 (m, 2H), 7.576-7.507 (m,5H), 7.296 (d.d, 2H, *J*=6.36), 6.94-6.915(m, 2H), 2.56(s, 3H, CH_3)

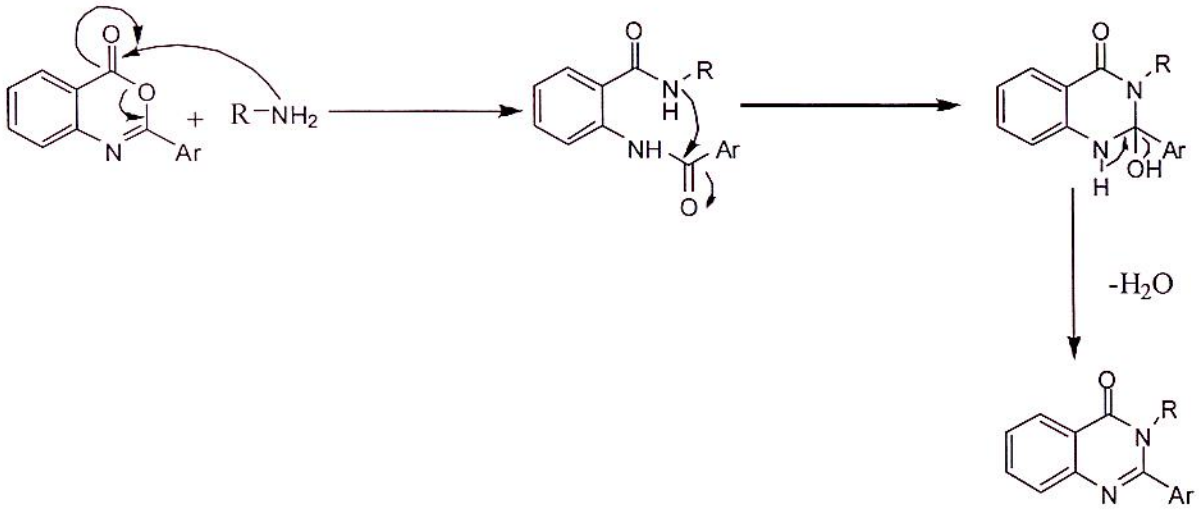
2.1.6. Mechanism of formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones from benzoxazinones

From the aforemaintionad observations and results (i.e. the formation and isolation of open chain diamides), it was realised that the formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones from the 2-aryl-4*H*-3, 1-benzoxazin-4-one is actually a two step process [Scheme 2.18]. The steps involed are: initial formation of the diamides (**63a-g**) as stable intermediate products, and their subsequent conversion into the 2, 3-disubstituted quinazolin-4(3*H*)-ones via ring closure reaction in a high boiling solvent.

In the light of these results, a plausible mechanism for the formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones from the 2-aryl-4*H*-3, 1-benzoxazin-4-one was investigated and propsed. The reported literature belives that the mechanism of formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones starts by reaction of substituted benzoyl chloride with anthranilic acid followed by reaction with primary alkyl/aryl amine. This led to the formation of amidine salt as an intermediate and finally gives the target 2, 3-disubstituted quinazolinoes [21-24] [Scheme 2.20]. While from our results, it is clear that open diamide is the stable reaction intermediate and no imidine salt as shown in [Scheme 2.20] supposed to be the reaction intermediate. Thus, the formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones *via* amidine salt intermediate can be ruled out. It was also found that dimides **63a-g** are stable reaction products in most cases of sterically strained aromatic amines and also when solvent containing water were used where the presence of moisture in the reaction solvent prevented the cyclization and dehydration step. In conclusion, it was decided that 2-aryl-4*H*-3, 1-benzoxazin-4-one when allowed to react with primary amine results in the formation of diamide intermediate, which then upon dehydration cyclise to the corresponding 2, 3-disubstituted quinazolin-4(3*H*)-ones as shown in the scheme 2.21.

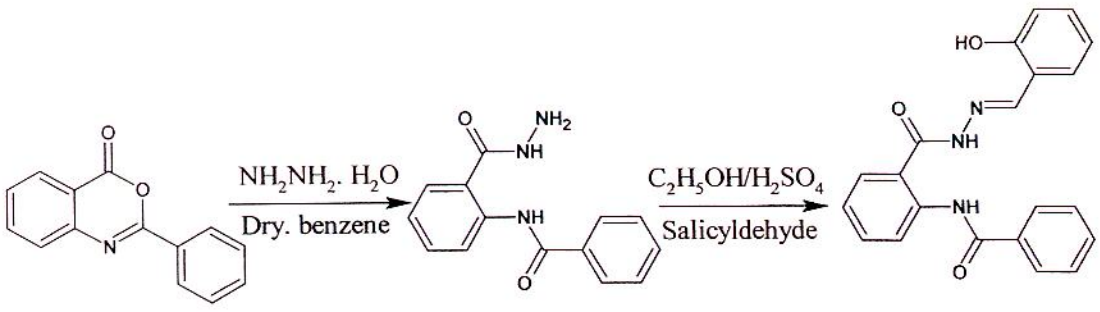


Scheme 2.19: Reported mechanism of formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones *via* imidate salt intermediate [21-24]



Scheme 2.20: Mechanism of formation of 2, 3-disubstituted quinazolin-4(3*H*)-ones *via* diamide intermediate

The study was further extended and the synthesis of open chain product, *N*-[2-(hydrazinocarbonyl) phenyl] benzamide (**63 g**) was accomplished along with the formation of 3-amino, 2-phenyl quinazoli-4(3*H*)-one by reacting 2-aryl-4*H*-3, 1-benzoxazin-4-one and hydrazine hydrate in boiling benzene. While *N*-[2-(hydrazinocarbonyl) phenyl] benzamide (**63 g**) was the only reaction product in boiling ethanol. On further reaction of compound (**63 g**) with the salicyldehyde in boiling ethanol, interestingly a novel open chain Schiff's base i.e. *N*-(2-{[(2*Z*)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide (**63 h**) was obtained [Scheme 2.18b]. The structure of compound (**63h**) was confirmed by the characteristic absorption peaks of amide in IR region, D_2O exchangeable amide proton peak in the ^{1}H-NMR region and further confirmation was done on the basis of molecular ion peak in EI-MS, FAB-MS and Mass fragmentation pattern. It is important to note that the compoud (**63h**) did not cyclize further under the selected reaction conditions.



63g **63h**

Scheme 2.21: Synthesis of *N*-(2-{[(2E)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} henyl) benzamide. **(63h)**

In addition to spectroscopic proof of the structure, crystals of the *N*-(2-{[(2*E*)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide were obtained and the absolute structure [Fig.3] was determined with the help of X-ray crystallography, which confirmed the formation and reactivity of the open chain products [fig.3 & fig. 4]

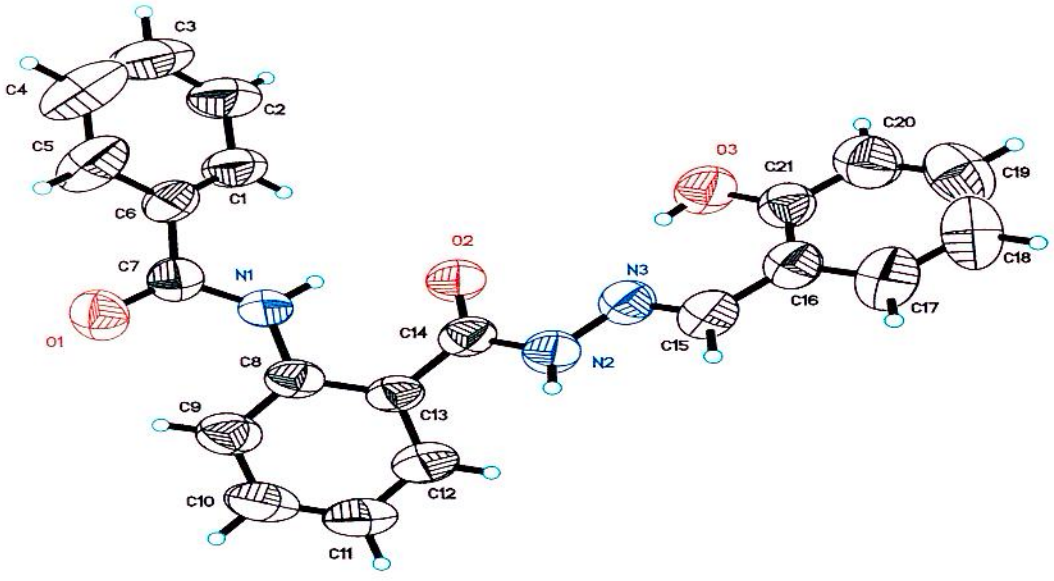


Fig. 3: *ORTEP* drawing of *N*-(2-{[(2*E*)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide **(63h)**

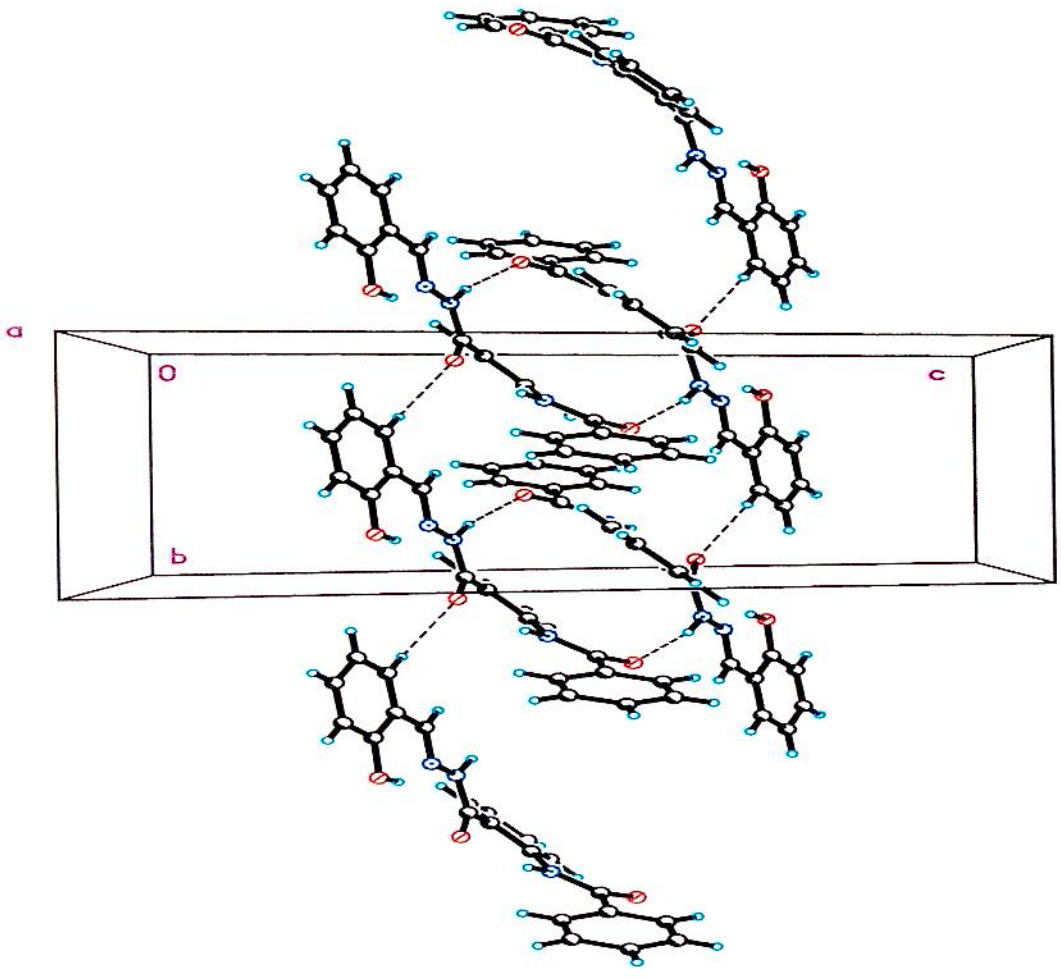
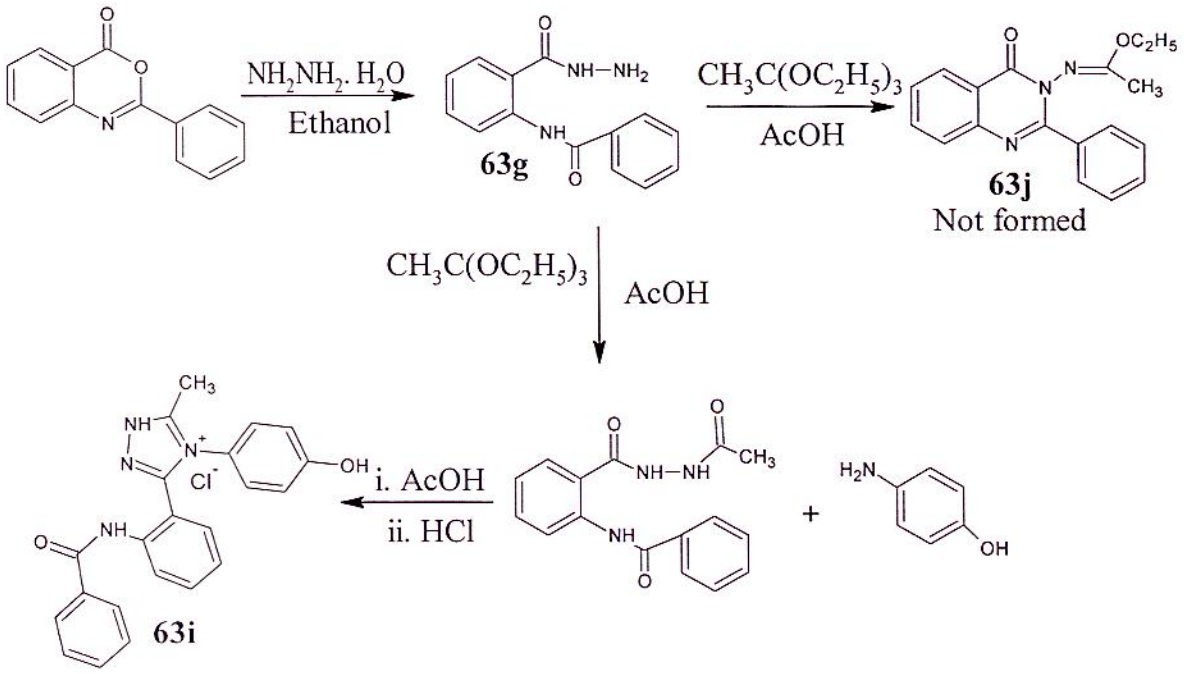


Fig. 4: ORTEP drawing of *N*-(2-{[(2E)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide showing the stability *via* hydrogen bonding **(63h)**.

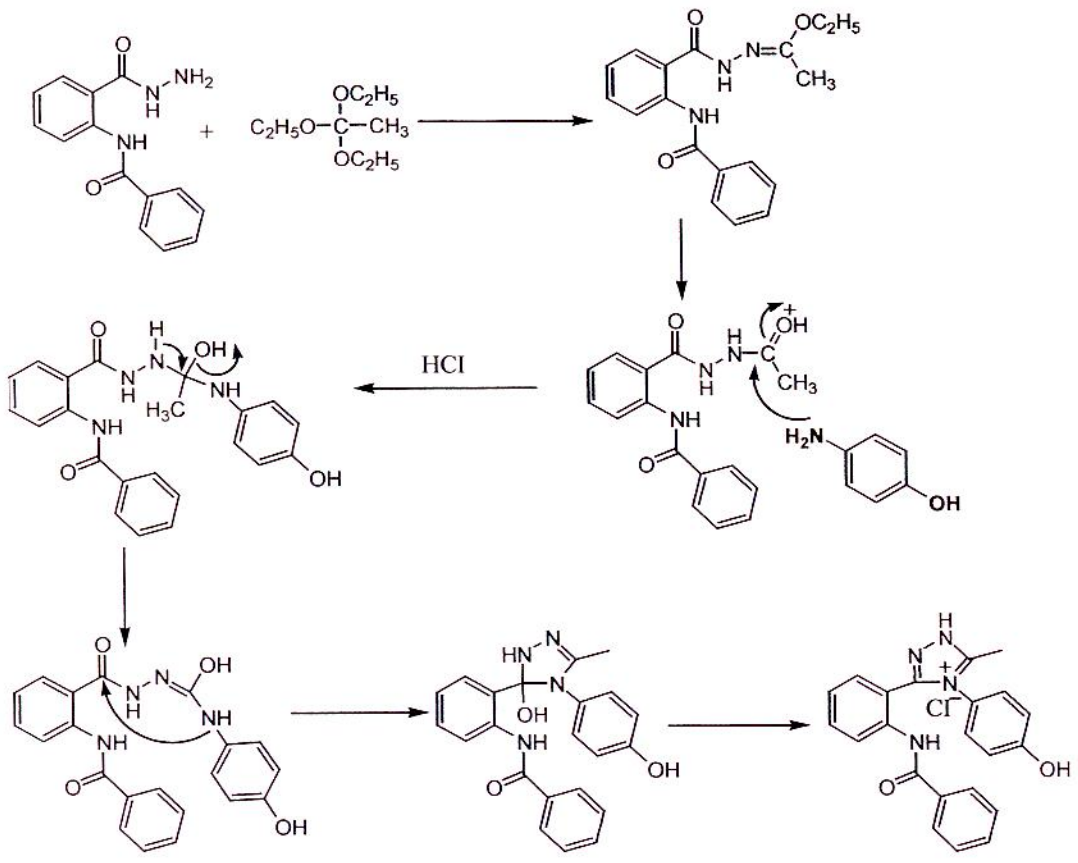
Another important and surprising finding made during this study was in the reaction of the compound (**63 g)** with triethyl orthoacetate. Instead of the desired quinazolinone product (**63 j**), an acetylation took place at the hydrazino-amine group. Further, reaction of the acetylated product with 4-aminophenol yielded surprisingly a novel triazole, 3-[2-(benzoylamino) phenyl]-4-(4-hydroxyphenyl)-5-methyl-1*H*-1, 2, 4-triazol-4-ium chloride (**63 i**) [Scheme 2.19]. The synthesis of this 1, 2, 4-triazol-4-ium ring has never been reported elsewhere previously. Structure of compound (**63 i**) was established from the data obtained from IR, ^{1}H-NMR and MS. The structure of compound (**63 i**) was further supported by the crystallographic data of *N*-{2-[4-(4-hydroxyphenyl)-5-methyl-4*H*-1, 2, 4-triazol-3-yl] phenyl} benzamide hydrochloride [Fig.

5]. In conclusion the diverse reactivity of open chain diamides was explored in detail and some novel compounds were synthesized.



Scheme 2.22: Route for the synthesis of 3-[2-(benzoylamino) phenyl]-4-(4-hydroxyphenyl)-5-methyl-1*H*-1, 2, 4-triazol-4-ium chloride

The proposed mechanism for formation of *N*-{2-[4-(4-hydroxyphenyl)-5-methyl-4*H*-1, 2, 4-triazol-3-yl] phenyl} benzamide hydrochloride is given in Scheme 2.19 b. Protonation of the acetamide carbonyl oxygen is followed by nucleophilic attack by the 4-aminophenol which led to the formation of acetamidine type intermediate. This further undergoes dehydration in the acidic medium which subsequently cyclizes through internal nucleophilic attack and then another dehydration step resulting in the 1, 2, 4 triazol-4-ium chloride.



Scheme 2.23: Proposed mechanism for formation of 3-[2-(benzoylamino) phenyl]-4-(4-hydroxyphenyl)-5-methyl-1*H*-1, 2, 4-triazol-4-ium chloride **(63i)**

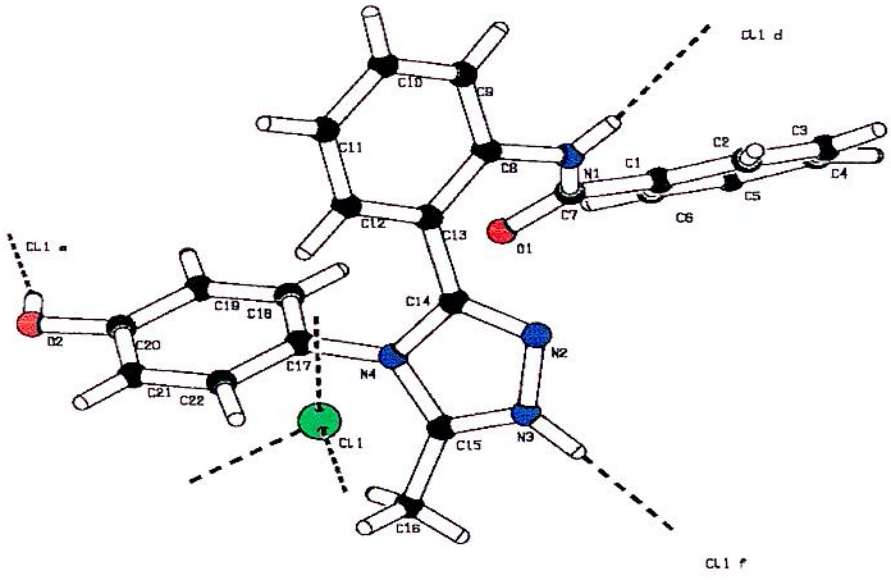


Fig: 5. ORTEP *II* drawing of 3-[2-(benzoylamino) phenyl]-4-(4-hydroxyphenyl)-5-methyl-1*H*-1, 2, 4-triazol-4-ium chloride **(63i)**

2.2. SECTION B: Synthesis, Structure Elucidation, Method Development and Mechanism of Quinazolin-4(3H)-one Schiff's Bases

2.2.1. 3-[(Alkyl/arylidene)amino]-2-(alkyl/aryl)-quinazolin-4(3*H*)-one (Quinazolin-4(3*H*)- one Schiff's bases)

Schiff's bases find extensive applications in chemistry [25-27] due to their intresting physical properties [28-30] and important biological activities.[31, 32] Studies on the synthesis of Schiff's bases have received more attention in heterocyclic chemistry because of their high synthetic utility and have found extensive usage in the synthesis of a wide variety of heterocyclic compounds. [33-40]

Hydrazine derived Schiff's bases have shown antibacterial activity [41]. The antibacterial activities of quinazolin-4(3*H*)-ones Schiff's bases have been reported recently [42]. Search for potential antibiotic drugs is one of the primary tasks of the present day medicinal chemists of increasing resistance of the pathogenic bacteria. Large number of nitrogen containing heterocycles have been recently studied for their antibacterial and anti-mycobacterial effects e.g. 3, 5-dinephthyl-2-pyrazolines [43], 2-phenyl-5,5-dialkylimidazolinones[44], 4-amino-5-aryl-1,2,4-triazoles [45] triazolo or tetrazolo pyrrolopyrimidines and benzimidazoles [46] 1,3-benzoxazinediones [47] quinazolines and quinoxalines [48].

The antibacterial and CNS activities of 3-arylidenamino-2-phenyl quinazolin-4(3*H*)-ones and 3-(2'-aryl-4'-thiazolidin-3'-yl)-2-phenyl quinazolin-4(3*H*)-one were compared and increased activity was shown by the one with thiazolidinone ring. Keeping in view the biological importance of quinazolin-4(3*H*)-ones derivatives, Shanker *et al.*, linked four memberd azetidinone and five memberd thiazolidinone with quinazolin-4(3*H*)-ones. The resulting compounds i.e. 3-[2-alkyl-4(3*H*)-oxo-3-quinazolinyl]-2-aryl-4-thiazolidinones and 1-[2-alkyl-4(3*H*) oxoquinazolinyl]-4-aryl-chloro-2-azetidinones were studied for their anti-Parkinsonian activity and against tumour, rigidity, ptosis and hypokinesia showing very good activities. Even, some compounds showed better activities than L-dopa; a clinical drug. 2-Styrylquinazolin-4(3*H*)-one have exhibited growth inhibitory activity against leukemia cells. 2-Carboethoxyquinazolin-4(3*H*)-one have shown anti-allergic, anti-helmintics and anti-tubercular activities [49].

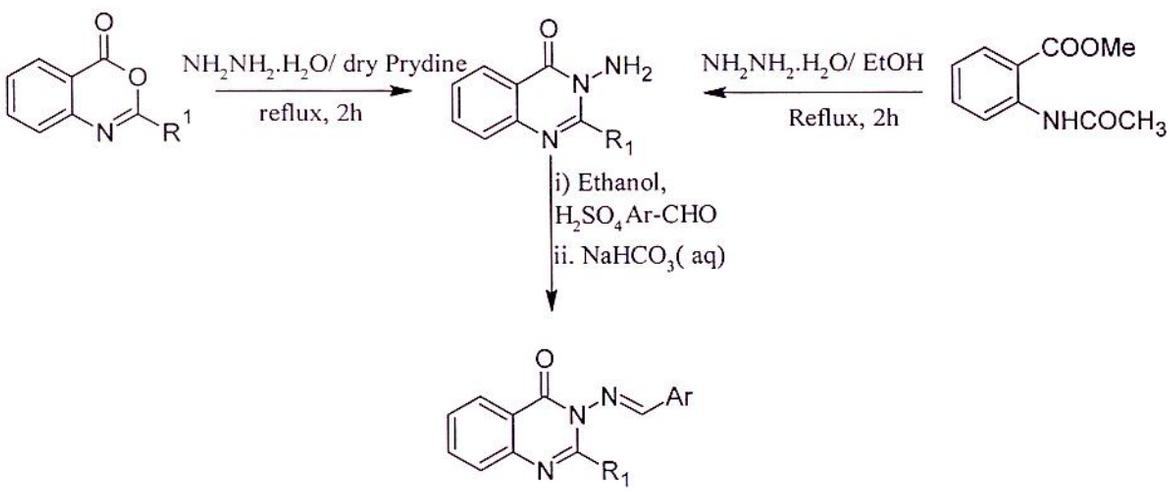
In view of their useful biological activities, quinazolin-4(3*H*)-ones Schiff's bases are of great interest to medicinal and synthetic chemists. The present work was thus aimed at the synthesis of structurally diverse 3-[(Alkyl/arylidene) amino]-2-(alkyl/aryl)-quinazolin-4(3*H*)-ones and development of new, efficient, better yielding and cost effective synthetic methods. Published literature [50, 51] reports the synthesis of quinazolin-4(3*H*)-ones Schiff's bases using hydrochloric acid and acetic acid as catalysts in refluxing ethanol. These catalysts are, however, not suitable catalysts because they cause hydrolysis of the resulting products. Hydrolysis not only decreases the yields (39-60 %) [52] but also make the reactions reversible and the starting materials remain in the reaction mixture along with the products because of the unfavourable chemical equilibrium .This also makes the separation and purification tedious and further, the reaction does not complete over a longer period of time. In the present work, the following three methods were tried for the synthesis of 3-[(Alkyl/arylidene) amino]-2-(alkyl/aryl)-quinazolin-4(3*H*)-ones (quinazolin-4(3*H*)-ones Schiff's bases) i.e.

1. $ZnCl_2$/ $AlCl_3$ catalysed synthesis
2. Simple reflux in absolute ethanol
3. H_2SO_4 catalysed synthesis

In the first attempt, 3-amino- 2-alkyl/ary quinazolin-4(3*H*)-one was allowed to react with substituted aromatic aldehydes in high boiling solvent such as nitrobenzene or toluene using $ZnCl_2$ or $AlCl_3$ as catalysts. This method was found low yielding and limited to few aldehydes i.e. salicyldehyde, benzaldehyde, while sterically bulky aldehydes like nephthaldehyde failed to react under these conditions. Further, the removal of high boiling solvent after completion was tedious and responsible for reducing the yield of the products.

In the next attempt, 3-amino- 2-substituted quinazolin-4(3*H*)-one(s) were allowed to react with substituted aromatic aldehydes in boiling ethanol in the absence of a catalyst. This method also turned out to be unsatisafactory as all the aldehydes except benzaldehye, slicyldehyde and chlorobenzaldehyde failed to react. Moreover, low yields were another major drawback. Therefore, the work was further continued in search of a better method. 3-Amino- 2-substituted quinazolin-4(3*H*)-ones were next allowed to react with substituted aromatic aldehydes in boiling ethanol catalysed with few drops of

H_2SO_4. Thus, in a typical reaction procedure, aromatic aldehydes were stirred at room temperature for 15-30 min in ethanol containing small aliquit of H_2SO_4. To the mixture, was then added ethanolic solution of 3-amino- 2-aryl/alkyl quinazolin-4(3*H*)-ones drop-wise and the mixture was refluxed for appropriate time. After completion of reaction, the excess of ethanol was removed under reduced pressure and the remaining mixture was poured into ice cold water. The product precipitated was filtered, washed with $NaHCO_3$ solution and recrystallized from ethanol-water mixture. This method was found better compared to earlier two methods both for high yield and shorter reaction time. Moreover, a range of aromatic aldehydes containing electron withdrawing or electron donating groups and also sterically hindered aldhehydes were found to react under the reaction conditions. The three methods were compared for yield & reaction time and reactivity of aldehydes [Table 2.15]. Therefore, the above mentioned method was used for further synthesis of quinazolin-4(3*H*)-ones Schiff's bases. All the products were obtained in almost pure form after neutralization of the reaction mixture with aqueous $NaHCO_3$ [Scheme 2.23, Table 2.16].



Scheme.2.24: General route for the synthesis of quinazolin-4(3*H*)-ones Schiff's bases

Table 2.15: Yield and reaction time comparison of the synthesized Schiff's bases

Entry	Compd #	R_1	Ar	Method	Yield (%)	Time
1	**64**	CH_3	C_6H_5	A	47	7h.
				B	67	5h
				C	86	30min
2	**66**	CH_3	2-HO- C_6H_4	A	53	7H
				B	61	5H
				C	76	30 min
3	**65**	CH_3	4-NO_2- C_6H_4	A	51	11h.
				B		No reaction
				C	61	8h
4	**71**	CH_3	2-hydroxynaphthyl	A		No reaction
				B		No reaction
				C	74.86	2h.

Methods:

A: $AlCl_3$ or $ZnCl_2$, nitrobenzene, reflux.

B: ethanol, reflux

C: H_2SO_4, ethanol, reflux.

Table 2.16: List of the synthesized quinazolin-4(3*H*)-ones Schiff's bases

Entry	Compd #	R_1	R_2	M.P(^{0}C)
1	**64**	CH_3	C_6H_5	178-180
2	**65**	CH_3	4-NO_2.C_6H_4	210
3	**66**	CH_3	2-OH- C_6H_4	218-220
4	**67**	CH_3	4-F- C_6H_4	163-164
5	**68**	CH_3	4-$(CH_3)_2$N- C_6H_4	166-168
6	**69**	CH_3	4-CH_3O- C_6H_4	189-191
7	**70**	CH_3	4-CH_3- C_6H_4	185-187
8	**71**	CH_3	2-Hydroxy naphthyl	196-197
9	**72**	CH_3	2-Chloro-6-nitrophenyl	281-283
10	**73**	CH_3	3,4-Dihydroxyphenyl	293
11	**74**	C_6H_5	4-$(CH_3)_2$N- C_6H_4	163
12	**75**	C_6H_5	4-CH_3O- C_6H_4	159
13	**76**	C_6H_5	2-OH- C_6H_4	220-24
14	**77**	C_6H_5	3-Cl- C_6H_4	179-180
15	**78**	C_6H_5	2-Hydroxy naphthyl	258.9-260
16	**79**	4-$NO_2C_6H_4$	2-Hydroxy naphthyl	312-315
17	**80**	4-$NO_2C_6H_4$	4-F- C_6H_4	241-243
18	**81**	PhCHCH-	C_6H_5	152
19	**82**	PhCHCH-	4-NO_2.C_6H_4	212
20	**83**	CH_3	3-Cl- C_6H_4	179-180
21	**84**	4-I-C_6H_4	2-Hydroxy-5-methoxyphenyl	193-195

The products obtained in this case were almost pure and were further purified whereever needed. This method was found faster, high yielding and cleaner compared to those where weaker acids and Lewis acids were used as catalysts. While in another attempt, TsOH was used as a catalyst in boiling toluene where reactions occurred but were sluggish and low yielding. As far as the reactivity based on the nature of aldehydes was concerned, aliphatic aldehydes were found totally non-reactive and similarly, both aliphatic and aromatic ketones failed to react under the conditions described. It was

further observed during the present study that aromatic aldehydes having electron donating groups were more reactive than aldehydes with electron withdrawing groups. Also, decreased reactivity was observed when the reactions were catalyzed with portic acids, while under uncatalyzed conditions, no significant difference in reactivity was observed. Hence, from these results it can be inferred that formation of a carbocation is involved as a reaction intermediate when protic acids are used as catalysts which definitely gain stability due to the presence of electron donating group. Microwave-assisted method was then explored for the synthesis of quinazolin-4(3*H*)-one Schiff's bases. Thus, a solvent and catalyst free microwave method for the synthesis of quinazolin-4(3*H*)-one Schiff's bases was optimized and established. High yields and much shorter time compared to the thermal solution phase catalytic methods were achieved under the microwave-assisted procedure [Table 2.21]. In a typical experimental procedure, equimolar quantities of aromatic aldehyde and 3-aminoquinazolinone were charged in a container placed in a domestic microwave oven (1200W, 2450MHZ). All reactions were completed within 3-9 min time under solvent free conditions; however, silica gel or dowex $_{50}$ was used as a solid support in few cases.

The probable mechanism is believed to involve the initial formation of carbocation intermediate which is then attacked by $-NH_2$ nucleophile followed by dehydration leading to the formation of the target Schiff's bases.

Table 2.17 (a): Comparative data of quinazolin-4(3*H*)-one Schiff's bases synthesis by sulphuric acid catalyzed (A) and microwave-assisted (B) methods.

Entry	**Comp #**	**Method**	**Yield (%)**	**Time**
1	**64**	A B	84 91	5h 3 min
2	**65**	A B	61 83	8h 3 min
3	**70**	A B	60 92	5h 3 min
4	**71**	A B	75 96	2h 2min
5	**72**	A B	88 99	2h 5min.
6	**76**	A B	67 85	2h. 2 min.
7	**77**	A B	78 98	2h. 3min.

8	**78**	A B	88 93	2h. 5min
9	**79**	A B	87 89	5h 3 min
10	**82**	A B	83 89	5h 5 min
11	**83**	A B	71 91	2h 7min

Method A: 3-Aminoquinazolin-4(3*H*)-one + aromatic aldehyde, H_2SO_4, ethanol, reflux, 5-7h

Method B: 3-Aminoquinazolin-4(3*H*)-one + aromatic aldehyde, M.W, 3-9 min

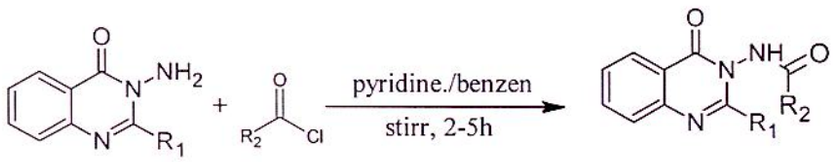
Table 2.17 (b): ^{1}H-NMR spectral data of 2-alky/aryl-3-{[(1*E*)-arylmethylene] amino} quinazolin-4(3*H*) -ones (64-84)

Entry	Compd.#	1H-NMR data
1	**64**	^{1}HNMR (500MHz, DMSO-d^6): δ ppm 8.51 (s,1H), 7.707 (d, 1H, *J*=8), 7.519 (d, 1H, *J*=7.5), 7.39-7.32 (m,1H), 7.215 (t, 1H, *J*=8.5, $J_{2,3}$=9), 7.145 (t, 1H, *J*=7.5), 7.094 (t, s, 1H, J=7.5), 2.153 (s, 3H)
2	**65**	^{1}HNMR (300MHz): δ ppm 9.33 (s, 1H), 8.432 (d, 2H, *J*=9), 8.335 (d, 2H, *J*=9), 8.257 (d,1H, *J*=9), 7.884 (t,1H, *J*=8.7), 7.69 (d, 1H, *J*=9), 7.642 (t, 1H, *J*=9), 2.57 (s, 3H)
3	**66**	^{1}HNMR(300MHz, $CDCl_3$) δ ppm: 10.7 (b, s, 1H), 8.99 (s, 1H), 8.289 (d, 1H, *J*=7.8), 7.79-7.69 (m, 2H), 7.508- 7.438 (q, 2H, *J*=7.4), 7.38 (d, 1H, *J*=7.6), 7.07 (d, 1H, *J*=8), 7.026-6.97 (t, 3H, *J*=8). 2.71(s, 3H, CH_3)
4	**67**	^{1}HNMR (500MHz, CD_3OD) δ ppm : 9.01 (s,1H), 8.27 (d, 1H, *J*=5), 7.907 (t, 2H, *J*=8.6), 7.749 (t,1H, *J*=10), 7.65 (d,1H, *J*=8), 7.465 (t,1H, *J*=7.5), 7.19 (t, 2H, *J*=8.5), 2.6 (s, 3H)
5	**68**	^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 9.82 (s, 1H, weak), 8.62 (d, 1H, *J*=8), 7.9 (d, 1H, *J*=10), 7.51-7.42 (m, 2H), 7.19 (d, 2H, *J*=10), 6.95 (d, 2H, *J*=8), 2.94 (s, 6H, N-CH_3), 2.54 (s, 3H, CH_3) .
6	**69**	^{1}HNMR (500MHz, $CDCl_3$) δ ppm: 8.83 (s,1H), 8.27 (d, 1H, *J*=6), 7.85 (d, 2H, *J*=9), 7.74 (t,1H, *J*=7), 7.65 (d,1H, *J*=7), 7.46 (t,1H, *J*=9), 6.99 (d, 2H, *J*=9), 3.87 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3)
7	**70**	^{1}HNMR (500MHz, $CDCl_3$) δ ppm: 8.8 (s,1H), 8.28 (d, 1H, *J*=9), 7.844 (d, 2H, *J*=8.9), 7.724 (d,1H, *J*=7), 7.655 (d,1H, *J*=7.2), 7.46-7.41 (t,1H, *J*=9), 7.00 (d, 2H, *J*=9), 2.6 (s,3H), 2.21 (s, 3H)
8	**71**	^{1}HNMR (300MHz, $CDCL_3$) δ ppm: 12.17 (s,1H), 9.88 (s,1H), 8.33 (d,1H, *J*=9), 8.025 (d, 1H, *J*=8), 7.96 (d,1H, *J*=9), 7.82 (t, 3H, *J*=10), 7.585-7.482 (m, 2H), 7.43 (t,1H, *J*=9), 7.288 (s, 1H), 2.71 (s, 3H)
9	**72**	^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.28 (d, 1H, *J*=8.2), 8.07-8.03 (m, 2H), 7.98 (d,1H, *J*=8), 7.9-7.7(m, 3H, Ar-H),

		(2.57(s, 3H, CH_3)
10	**73**	^{1}HNMR (300MHz, CD_3OD) δ ppm: 10.02 (S, 2H,OH), 8.7 (s,1H), 8.27 (d, 1H, *J*=8), 8.01-7.97 (m, 3H), 7.91 (d, 1H, *J*=7.86), 7.29 (s,1H, *J*=8), 7.10 (d,1H, *J*=8), 2.54 (s, 3H, CH_3)
11	**74**	^{1}HNMR (300MHz, CD_3OD) δ ppm: 9.82 (s, 1H), 8.62 (d,1H, *J*=8), 7.96-7.85 (m, 2H), 7.72-7.65 (m, 3H), 7.51-7.43 (m, 5H), 6.95 (d, 2H, *J*=8), 2.95 (s, 6H).
12	**75**	^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 9.3 (b, s,1H), 8.34 (d, 1H, *J*=9), 8.25-8.20 (m, 2H), 7.78-7.74 (m, 2H), 7.67-7.62 (m, 4H), 7-53-7.45 (m, 4H), 3.86 (s, 3H).
13	**76**	^{1}HNMR (300MHz, CD_3OD) δ ppm: 11.2 (s,1H), 9.8 (s,1H), 8.35 (d,1H, *J*=8.4), 8.21-8.18 (m, 2H), 7.8-7.75 (m, 3H), 7.7-7.64 (m, 3H), 7.48 (d,1H, *J*=8), 7.23-7.13 (m, 3H).
14	**77**	^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 9.3 (s, 1H), 8.35 (d, 1H, *J*=7.8), 8.23-8.21 (m, 2H), 7.96-7.94 (m, 3H), 7.7-7.58 (m, 5H), 7.48 (d, 1H, *J*=8), 6.67 (s, 1H).
15	**78**	^{1}HNMR (300MHz, CD_3OD) δ ppm: 11.6 (s,1H), 10.5 (s, 1H), 8.38 (d, 1H, *J*=9), 8.28 (d,1H, *J*=9), 8.05 (d, 2H, *J*=9), 7.55-7.49 (m, 5H), 7.39-7.29 (m, 4H), 7.04 (s, 1H), 6.79 (t, 1H, *J*=9)
16	**79**	^{1}HNMR (400MHz, CD_3OD) δ ppm: 11.2 (b, s,1H), 9.8 (s,1H), 8.6 (d, 2H, *J*=9.5), 8.47 (d,1H, *J*=9.8), 8.45 (d,1H, *J*=9.5), 8.43 (d,1H, *J*=9.5), 8.4 (d,1H, *J*=10), 8.1-7.9 (m, 2H), 7.97 (d,1H, *J*=9.7), 7.83-7.64 (m, 3H), 7.56 (d, 1H, *J*=10), 7.3 (d,1H, *J*=10)
17	**80**	^{1}HNMR (300MHz, CD_3OD) δ ppm: 9.6 (s, 1H), 8.56 (d, 2H, *J*=9.2), 8.48 (d, 2H, *J*=9), 8.41 (d, 1H, *J*=9), 8.01-7.78 (m, 3H), 7.68-7.65 (m, 3H), 7.54(d, 1H, *J*=9).
18	**81**	^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 9.12 (s,1H), 8.34 (d,1H, *J*=8.3), 8.12 (d,1H, *J*=8), 7.90-7.83 (m, 3H), 7.80 (d, 2H, *J*=8.5), 7.74-7.68 (m, 2H), 7.67 (d, 1H, *J*=9), 7.58 (t, 2H, *J*=9), 7.40-7.34 (m, 3H), 7.50 (d, 1H, *J*=14)
19	**82**	^{1}HNMR (400MHz, CD_3OD) δ ppm: 9.21 (s,1H), 8.6 (d, 2H, *J*=11), 8.30 (d,1H, *J*=8.3), 8.20 (d, 2H, *J*=8.7), 8.03 (d, 1H, *J*=7.9), 7.99 (d, 2H, *J*=9.2), 7.90 (d,1H, *J*=8.1), 7.74-7.69 (m, 3H), 7.7 (d, 1H, *J*=12), 5.6 (d, 1H, *J*=12)
20	**83**	^{1}HNMR (300MHz,$CDCL_3$) δ ppm: 8.83 (s, 1H), 8.46 (d, 1H, *J*=8), 8.00 (d, 1H, *J*=8), 7.55-7.46 (m, 2H), 7.406 (t,1H, *J*=8), 7.34-7.27 (m, 2H), 6.89 (s,1H), 3.41(s, 3H, CH_3)
21	**84**	^{1}HNMR (300MHz, $CDCl_3$) δ ppm 10.08 (s,1H), 9.76 (s,1H), 8.73 (d,1H, *J*=8.3), 8.61 (d, 2H, *J*=8.3), 8.46 (d, 2H, *J*=7.9), 8.27-8.22 (m, 2H), 7.81-7.79 (m,1H), 7.25-7.21 (m, 2H), 6.91 (d,1H, *J*=3.1), 4.38 (q, 2H, *J*=7.3), 1.41 (t, 3H, *J*=7.3)

Research on quinazolin-4(3*H*)-one nucleus have shown that substitution on 3-position enhances the activities, thus the free amino group on 3-position was condensed

with acid halides yielding the corresponding imide products [Scheme 2.24]. This was achieved by making slight modification in the reported method [53]. In case of N-acetylation, e.g., acetyl chloride and 2-methyl 3-aminoquinazolinone were stirred at room temperature. The product got precipitated upon cooling and was obtained in high purity and was further washed with hexane solvent to remove the last traces of the unreacted acetyl chloride. Benzoyl chloride failed to react under the uncatalyzed conditions, however, when benzoyl chloride was refluxed with 2-methyl 3-aminoquinazolinone in dry pyridine for 6 h, substantial yield was obtained. The same reaction was carried out in aqueous NaOH below room temperature. The product was found to be a mixture of the acetylated product and benzoic acid obviously formed as a result of hydrolysis of the benzoyl chloride under the alkaline condition. Bbenzoic acid was removed by washing the mixture with saturated $NaHCO_3$ solution. Similarly, chloro-acetyl chloride reacted in refluxing benzene and even in the absences of solvent [2]



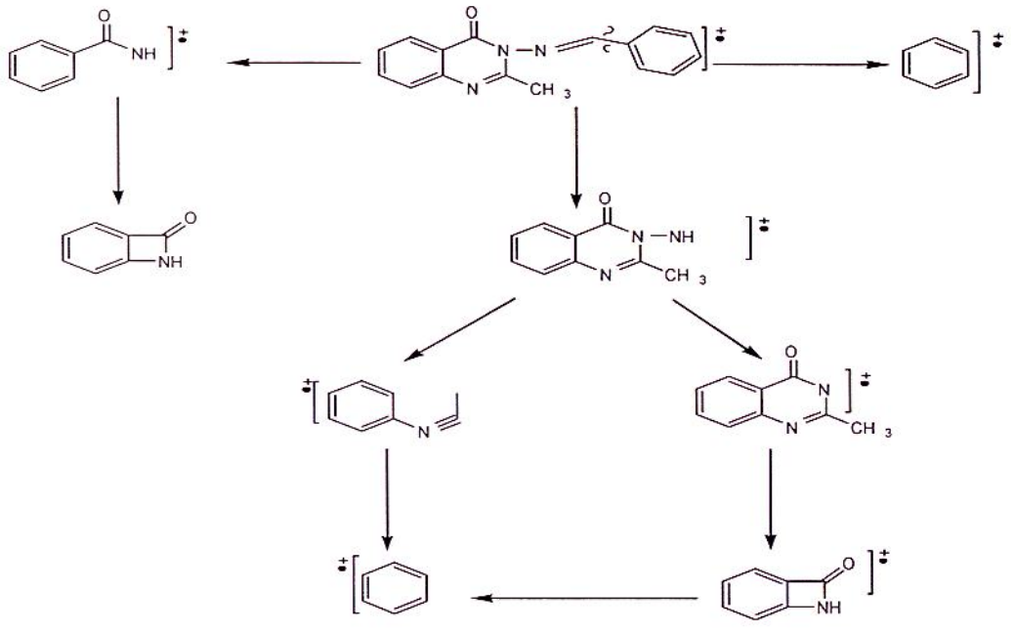
Scheme 2.25: Synthesis of quinazolinone-N-aryl/alkylimides

Table 2.18 (a): List of quinazolinone-N-aryl/alkylimides

Entry	Compd #	R_1	R_2	M.P (^oC)
1	**85**	CH_3	CH_3	172-174
2	**86**	CH_3	C_6H_5	102-103
3	**87**	CH_3	CH_2Cl	196-199
4	**88**	C_6H_5	CH_2Cl	174-178
5	**89**	$NO_2C_6H_4$	CH_2Cl	211-213

Structures of all the synthesized compounds were established on the basis of spectral data including IR, ^{1}H-NMR, EI-MS, FAB-MS (+ve, -ve) and ^{13}C-NMR wherever ever needed. Mass fragmentation pattern was found more helpful in assigning the structures. Strong peak appeared at m/z: 145, 106 and 105 were the characteristic fragments through out the whole series. A typical mass fragmentation pattern of a

representative compound is given in the [Scheme 2.25]. The appearance of a singlet at δ 8-10 ppm in the ^{1}H-NMR spectrum confirmed the –N=CH proton while the number and kind of aromatic protons were confirmed from the peak intensities and characteristic coupling constants of the aromatic hydrogens[Table 2.18 b]. The confirmation of C=N and C=O groups were ascertained from their characteristics weak and strong absorptions bands at 1600-1700 cm^{-1} in the IR spectrum.



Scheme 2.26: Fragmentation pattern of quinazolin-4(3*H*)-ones Schiff's bases

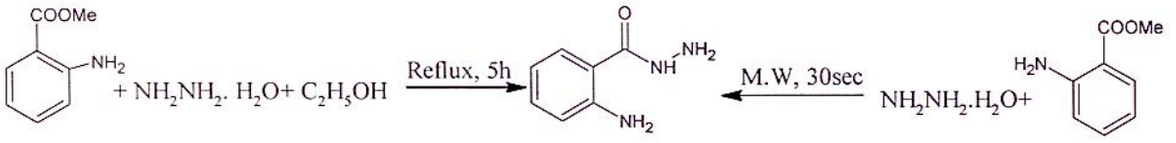
Table 2.18 (b): 1H-NMR spectral data *N*-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl) alky/arylamide (**85-89**)

Entry	Compd.#	1H-NMR data
1	85	^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 11.3 (b, s, 1H), 8.214 (d, 1H,*J*=10), 8.021 (d, 1H, *J*=10), 7.902(t, 1H, *J*= 7.4), 7.582 (t, 1H, J=7.45), 2.87(s, 3H, CH_3), 2.48 (s, 3H, CH_3)
2	86	^{1}HNMR (300MHz,$CDCl_3$) δ ppm: 11.85(S,1H), 8.37(d,1H, *J*=7.8), 8.12-7.96 (m, 5H), 7.64 (d, 1H, J=7.4), 7.41-7.27 (m, 2H), 2.34 (s,3H, CH_3)
3	87	^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 11.3 (s, b, 1H), 8.21 (d, 1H, *J*=9), 8.15 (d, 1H, *J*=10), 7.9-7.87 (t, 1H, *J*=10, *J*=8.5), 7.58-7.55 (t, 1H, *J*=10, *J*=8.5), 3.84 (s, 2H), 2.54 (s, 3H)
4	88	^{1}HNMR (300 MHz, $CDCl_3$) δ ppm: 9.81(s, 1H), 8.23 (d, 1H, *J*=8), 7.823-7.79 (m, 2H), 7.60 (t, 1H, *J*=7.8), 7.60 (d, 1H, *J*=7.6), 7.54-7.41 (m, 1H), 7.46 (t, 1H, *J*=7.4), 7.39-7.34 (m, 2H), 3.84 (s, 2H)
5	89	^{1}HNMR (300 MHz, CD_3OD) δ ppm: 10.54 (s, 1H), 8.37(d, 1H, J=8), 8.237 (d, 2H, *J*=8), 7.95 (d, 2H, *J*=7.6), 7.80 (t, 1H, *J*=7.6), 7.607 (d, 1H, *J*=8), 7.53 (t, 1H, *J*=7.4), 3.93 (s,2H)

2.2.2. Synthesis of [(3-alkyl/arylidene) amino]-2-(alkyl/aryl)-2, 3-dihydroquinazolin- 4(1*H*)-one

2-Aminobenzoylhydrazines have been extensively utilized in the synthesis of a variety of bioactive hetrerocycles [54-57]. The cyclization of 2-aminobenzoylhydrazine is a thoroughly studied field of heterocyclic chemistry. A large variety of potential pharmacophoric heterocycles can be produced in this way, depending upon the reaction conditions and reagents [58].

2-Aminobenoylhydrazide **90** has been synthesized from isotoic anhydride and hydrazine hydrate via ring opening reaction [59]. In the first trial, we chose the reaction of methylanthranilate and hydrazine hydrate, but this method gave a mixture of two products i.e., 2-aminobenzoylhydrazide and bis- N-aminobenzoylhydrazide. Next, microwave-assised method was tried in a catalyst and solvent free condition [Scheme-2.26].This method is not reported in the literature and afforded selectively 2-amino benzohydrazide **90** in 99 % yield.



Scheme-2.27: Synthesis of 2-aminobenzohydrazide (**90**) via thermal and microwave method.

2-Aminobenzohydrazide (**90**) synthesized, was then allowed to react with various available ketones and aldehyedes under different experimental conditions to synthesize 3-(alkyl/aryllideneamino)-2- alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones **91-104**. There are only few specific reports on the synthesis 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzoylhydrazides [60, 61] and 2-alkyl/aryl dihydroquinazolin-4(3*H*)-one from benzamide [62, 63].

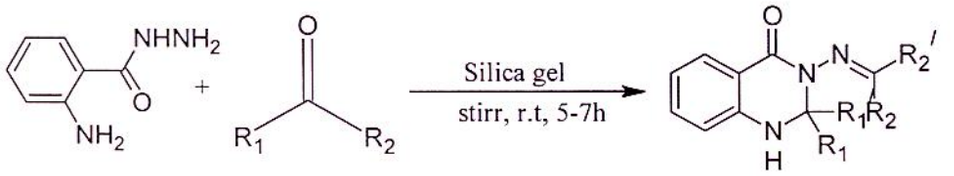
Because of diverse reactivity of 2-aminobenzoylhydrazide, several products were initially reported with erroneous structures and were later on corrected. Reddy *et al.*, has erroneously reported the formation of open chain Schiff's bases and triazipine moiety from the reaction of 2-aminobenzoylhydrazide and benzylidenanilines.[64] These results were later on corrected by Peet *et al.* [65a,b] They reported the formation of 2-aryl-3-

arylidineaminoquinazolin-4(3*H*)-ones from the same reactions. In this connection, Fülöp *et al.*, [65c] has investigated the reaction products of 2-aminobenzoylhydrazide and 3-(alkyl/aryllideneamino)-2-alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones (Schiff's bases) in detail and have also investigated the stereochemical detail. In this work, we allowed various aldehydes and ketone to react with 2-aminobenzoylhydrazide for the synthesis of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones.since, there is no clear and concise reported method for the synthesis of these compounds. Therefore, the search for simple, facile and widely applicable method for the synthesis of these compounds was started. Interest in catalytic reactions is increasing rapidly in search of new effective, cheaper and environmentally friendly synthetic method. The use of silica gel supported $FeCl_3$ has recently been reported in the literature for the construction of the quinazolin-4(3*H*)-one ring system [67]. Attention, therefore, was focused on the catalytic synthesis of a series of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones (**86-97**) and search for the applicability of various catalysts for the synthesis of these compounds. 2-Amiobezoylhydrazide was used as precursors for the synthesis of comounds **86-97**. Different reaction conditions were tried. Three different methods were optimized for the synthesis of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-one i.e. **i)** Silica gel supported solvent free method, **ii)** H_2SO_4 catalysed synthesis and **iii)** Solvent and catalyst free microwave-assisted synthesis. Appreciable differences in the reactivity were observed in this study. Both aliphatic and aromatic aldehydes showed different degree of reactivity under different reaction conditions.

i). Silica gel supported synthesis for 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones (86-97)

Synthesis of 2, 2-dimethyl-2, 3-dihydroquinazoline-4(1*H*)-thiones was reported by Wagner *et al.*, [88] via condensation of 2-aminothiobenzamide and acetone under milder condition. While silica gel catalysed synthesis of 2,2-dimethyl-3-phenyl-2,3-dihydroquinazoline-4(1*H*)-thiones was first reported by Kubicov *et al.*,[89] via condensation of 2-amino-N-phenylthiobenzamides with acetone under the catalysis by silica gel.

The use of silica supported $FeCl_3$ has recently been investigated in the literature for the construction of the quinazolin-4(3*H*)-ones ring system.[67] While we attempted the use of silica gel for the synthesis of a range of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-one [Table 2.19]. Cyclocondensation of 2-aminobenzohydrazide with selected ketones or aldehydes by stirring over silica gel [Scheme 2.27] under solvent free condition. This method was found very well for all the aliphatic ketones and some liquid aromatic aldehydes. Aliphatic aldehydes and solid aldehydes and ketones failed to react with 2-aminobenzohydrazide under the same conditions. Further, it was found that increase in temperature caused a decrease in the rate of reaction and eventually completely blocked the reactivity. Since, the extent of adsorption decreases on heating, thus no reaction favoured when the reaction mixture was heated. Encouraging results from silica gel supported method further prompted us to investigate other catalysts for same conversion and these reactions were also carried out using TsOH and $ZnCl_2$ as catalysts, TsOH was found good catalyst next to silica gel, however, silica is cheaper and give highest yield compared to TsOH. On the other hand, PTSA reduced the time required for completion of reaction from several hours to 2-3 h but found inactive in case of acetone and 3-pentanone.



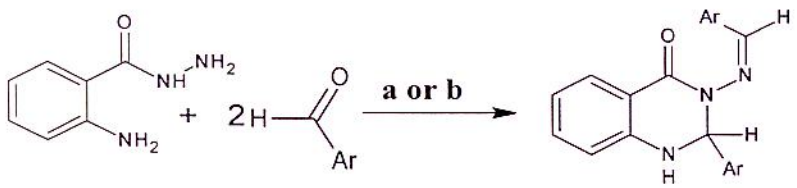
Scheme2.28: Silica gel catalysed synthesise of quinazolin-4(3*H*)-ones **91-96**

Table 2.19: Silica gel catalyzed 3-(alkyl/aryllideneamino)-2- alkyl/aryl -2, 3-dihydroquinazolin-4 (1*H*)-ones (**91-96**)

Entry	**Compd #**	**R_1**	**R_2**	**M.P (^{0}C)**	**Yield (%)**
1	**91**	CH_3	CH_3	245-248	92
2	**92**	C_2H_5	C_2H_5	142-144	50
3	**93**	C_2H_5	CH_3		
4	**94**	--	--	108-110	76
6	**95**	C_6H_5	H	185-187	69.3
7	**96**	2-OH-C_6H_4	H	208-210	86.2

(i) H_2SO_4 catalysed synthesis 3-(aryllideneamino)-2- aryl -2, 3-dihydroquinazolin-4(1*H*)-ones

This method was adopted for the synthesis of 3-(arylideneamino)-2-aryl -2, 3-dihydroquinazolin-4(1*H*)-one by refluxing aromatic aldehyde and 2-aminobenzohydrazide **90** in absolute ethanol containing few drops of H_2SO_4. A series of 3-(aryllideneamino)-2, aryl -2, 3-dihydroquinazolin-4(1*H*)-ones [Table 2.20] was synthesized. This method, however, failed in case of aliphatic ketones. It highly important to explain here, that for the synthesis of 3-(alkylideneamino)-2, alkyl-2, 3-dihydroquinazolin-4(1*H*)-one(s) silica gel was found the best catalyst and H_2SO_4 was totally found undesired for these reactions.While on the other hand, silica gel failed with exception of few for the synthesis of 3-(aryllideneamino)-2, aryl -2, 3-dihydroquinazolin-4(1*H*)-one and Ethanol/H_2SO_4. In another attempt, Ethanol/ TsOH system was used for the same series of reaction and was found a good system. In this method, again the desired products were collected in 3-5 h. by refuxing 2-aminobenzohydrazide **90** and aromatic aldehyde(s) in refluxing ethanol containing TsOH as catalyst. It is important to highlight here that no appreciable change in the percentage yield was observed in both the methods used; however, these methods are described for the first time.



Scheme2.29: H_2SO_4 or TsOH mediated synthesis of 3-(arylideneamino)-2, aryl -2, 3-dihydroquinazolin-4 (1*H*)-ones (**95-103**)

Method **a.** (i) H_2SO_4/ EtOH, reflux, 2-3h (ii) Aq.$NaHCO_3$

b. TsOH/EtOH, stirr, 2-5h, r.t or reflux

Table 2.20: H_2SO_4 or TsOH Catalysed synthesis of 3-(alkyl/arylideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones (**95-103**)

Entry	Compd #	Ar	M.P(°C)	Yield (%)
1	**95**	C_6H_5	185-168	69.3
2	**96**	2-HO- C_6H_4-	208-210	86.2
3	**97**	2-Hydroxynaphthyl	170-172	67.34
4	**98**	4-MeO-C_6H_4-	208	88.74
5	**99**	4-Cl-C_6H_4-	176-178	47.82
6	**100**	2-Cl-C_6H_4-	188-189	49.43
7	**101**	2-HO,5-OC_2H_5- C6H3-	131-133	52.59
8	**102**	3-Indolyl-	139-140	69.0
9	**103**	2-HO,5-CH_3-C_6H_3	176-179	68.0

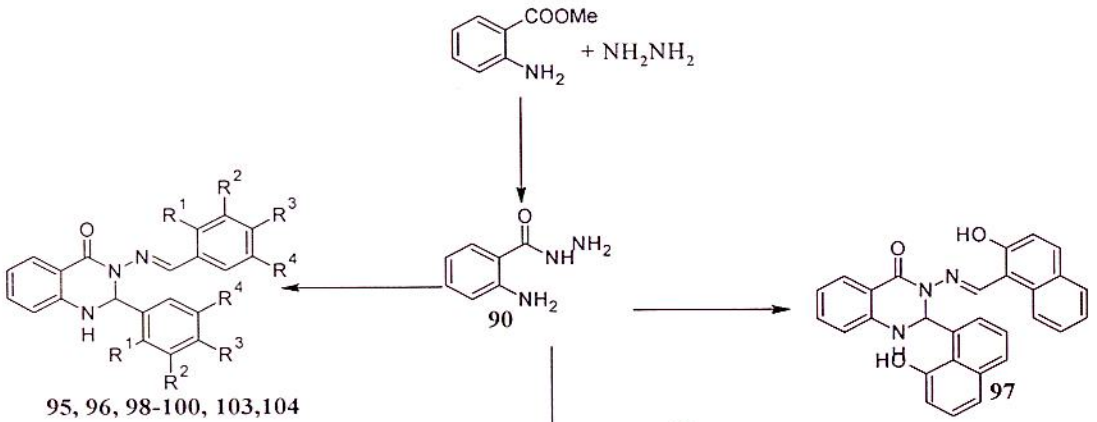
2.2.4. Microwave- assisted synthesis of 3-(alkyl/arylideneamino)-2- alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones

Conventionally, 2, 3-dihydro-4(1*H*)-quinazolinones are elaborated by the condensation reaction of anthranilamide with structurally diverse ketones or aldehydes catalyzed by bases or acids [68]. However, some alternative new methodologies have also been employed, for example, reductive cyclization of 2- nitrobenzamides with various carbonyl compounds promoted by either Lewis acids $ZnCl_2$ or $TiCl_4/Zn$ [69] or lanthanide metallic samarium (Sm/I_2) [70] .Recently, a facile synthesis of 2,3-dihydro-4(1*H*)-quinazolinones was reported . In a typical procedure, 2, 3-dihydro-4(1*H*)-quinazolinones were obtained by treating anthranilamide with structurally diverse ketones or aldehydes (3.0 equiv.) in the refluxing trifluoroethanol (TFE).[71]

In recent years, microwave irradiation has been utilized extensively as a clean source of energy for the synthesis of organic compounds [72].The rapid heating induced by such radiation avoids harsh classical conditions and the decomposition of the reagents, leading to the formation of products under mild reaction conditions, thus increasing the yield. Some important reviews have been published in recent years, covering a large number of microwave induced reactions. [73]

In our investigations on the synthesis of quinazolin-4(3*H*) ones Schiff's bases and 3-(alkyl/arylideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones, suitable 3-amino-2-alkyl/aryl quinazolin-4(3*H*)-ones and aromatic aldehyde(s) were irradiated in a microwave oven for 2-6 min under solvent and catalyst free conditions.

In the present work, a new method for the synthesis of 3-(aryllideneamino)-2, aryl -2, 3-dihydroquinazolin-4(1*H*)-one [Table 2.21] with the help of microwave irradiation using domestic microwave oven is described [Scheme 2.30]. The method was found much cheaper, environmentally friendly and a faster practical method compared to the thermal methods. However, the method developed was of limited use as it is applicable only to aromatic aldehydes.The method failed to give the desitrd products in case of aliphatic aldehydes and ketones. It is thereore concluded that although the microwave-assisted method is much faster and high yielding than the conventional H_2SO_4 or TsOH catalysed method, but id limited to 3-(arylideneamino)-2- aryl -2, 3-dihydroquinazolin-4(1*H*)-one and can not be used for the synthesis of 3-(alkylideneamino)-2, alkyl-2, 3-dihydroquinazolin-4(1*H*)-ones[Table 2.20]. It was further concluded that the conventional H_2SO_4 or TsOH catalysed methods are inappropriate for the synthesis of 3-(alkylideneamino)-2- alkyl-2, 3-dihydroquinazolin-4(1*H*)-ones and only silica gel mediated solvent free method or simple refluxing in boiling ethanol were found appropriate for the synthesis of 3-(alkylideneamino)-2, alkyl-2, 3-dihydroquinazolin-4(1*H*)-ones. The present comparative study thus highlights the applicability of all the three methods in the synthesis of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-one(s).



Comp.	R_1	R_2	R_3	R_4
95.	H	H	H	H
96.	OH	H	H	H
98.	H	H	OCH_3	H
99.	H	H	Cl	H
100.	Cl	H	H	H
103.	OH	H	H	OCH_3
104.	Cl	H	H	NO_2

Scheme 2.30: Microwave- assisted synthesis and its comparison with the classical methods

Table 2.21: Microwave -assisted synthesis of 3-(arylideneamino)-2- aryl -2, 3-dihydroquinazolin-4(1*H*)-ones (**85-104**).

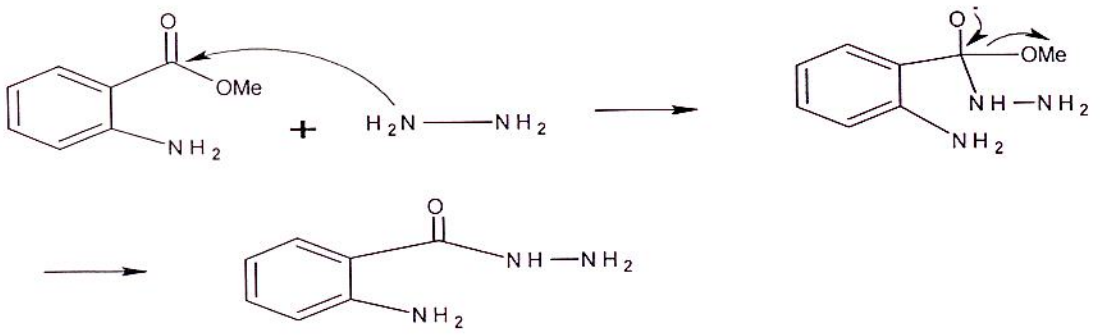
Entry	Compd #	Reaction Time	Yield (%)
1	**85**	1 min	99
2	**91**	No reaction	
3	**92**	No reaction	
4	**95**	2min	91
5	**96**	2min	93
6	**97**	3min	97
7	**98**	2min	97
8	**99**	3min	97
9	**100**	2min	95
10	**102**	3min	99
11	**103**	3min	97
12	**104**	3min	95

2.2.5. Mechanism and structure determination

Structural elucidation of all the synthesized 3-(alkyl/arylideneamino)-2- alkyl/aryl -2, 3 dihydroquinazolin-4(1*H*)-ones **91-103** was accomplished from their IR, NMR and mass spectral data. All these compounds have 3-(arylideneamino)-2-phenylquinazolin-4 (3*H*)-one as the basic skeletal structure.

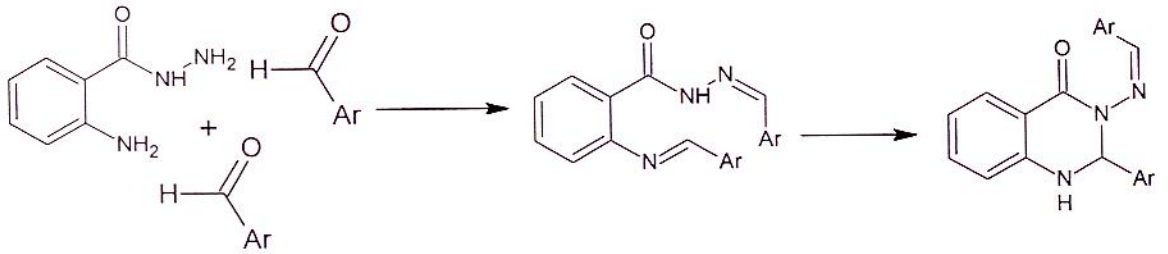
The presence of medium intensity band at 3200-3300 cm^{-1} in the IR region shows the presence of secondary amine. The presence of the secondary amine (N-H) was further confirmed from the medium intensity, broad, D_2O exchangeable peak at 8-9 ppm in the ^{1}H-NMR spectra. Further, the functional group was confirmed from the IR data i.e. C=O (sharp, intense peak at 1600-1800 cm^{-1}), C=N (medium intensity, sharp peak at 1500-1580 cm^{-1}) .The presence of sharp peaks at 1370-1400 $cm^{-1}$and at 980-100 cm^{-1}, 700-800 cm^{-1} confirmed the presence of aromatic C=C bond conjugation in addition to C-H bend and aromatic C-H bending, respectively. Further, number and types of aromatic hydrogens were confirmed from the *ortho* coupling with *J*=7-9 Hz and *meta* coupling (*J*=2-3 Hz). ^{1}H-NMR spectral data of 3-(alkyl/arylideneamino)-2- alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-ones is given the table 2.22 and table 2.23. The molecular formulae of the compounds were established from the mass spectra including FAB-MS (+ve, -ve) and EI-MS.

Mass fragmentation pattern in EI-MS was found most helpful in structural determination, since the basics quinazolin-4(3*H*)-ones skeleton is same in all the compounds and furthermore the labile nature of N-N bond made the fragmentation pattern clearer and easy to interpret. The intense peak at m/z 106,105 clearly indicated the formation of benzaldehyde in the mass fragmentation. The possible mechanism of the formation of 3-(alkyl/aryllideneamino)-2, alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-one(s) is believed to involve the intial formation of *N*'-[(1*Z*)-alkyl/arylmethylene]-2-{[(1*Z*)-alkyl/arylmethylene] amino} benzohydrazide via the condensation of 2-aminobenzohydrazide and aldehyde or ketone, following internal nucleophilic cyclization [Scheme 2.32]



(1)

Scheme 2.31: Mechanism of 2-aminobenzohydrazide formation



Scheme 2.32: Mechanism of formation of 3-(alkyl/arylideneamino)-2- alkyl/aryl -2, 3-dihydroquinazolin-4(1*H*)-one from 2-amino benzohydrazide

Table 2.22: 1H-NMR spectral data of 2-Alky/-3-{[(1*E*)-alkyl/methylene] amino}-2, 3-dihydroquinazolin-4(1*H*)-one (**91-94**)

Entry	Compd.#	1H-NMR data
1	**91**	^{1}HNMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 (d, 1H, *J*=8), 7.29 (t, 1H, *J*=8), 6.839 (t, 1H, *J*=7.5), 6.618 (d, 1H, *J*=8), 4.161 (s, b, 1H), 2.15 (s, 6H, CH_3), 1.878 (s, 6H, CH_3).
2	**92**	^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 7.89 (d, 1H, *J*=7.37), 7.29-7.25 (t,1H, *J*=8.09), 6.83 (t, 1H, *J*=7.5), 6.61(d, 1H, *J*=8.012), 4.8 (b, s, w, 1H), 2.31-2.25 (m, 4H), 2.10-1.85 (m, 4H), 1.08 (t, 3H, *J*=11), 1.03 (t, 3H, *J*=11.7), .98 (t, 6H, *J*=14).s
3	**93**	^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (d, 1H, *J*=7.38), 7.91 (t, 1H, *J*=8), 7.34 (t, 1H, *J*=7.38), 6.89 (d, 1H, *J*=7.35), 5.18 (s, 1H, N-H), 2.25 (q, 2H, $J_{1,3}$=4.8, $J_{2,4}$=5.2), 2.18-1.97 (m, 5H), 1.60 (s, 3H), 1.23 (t, 3H, *J*=5.2), 1.09 (t, 3H, *J*=5.4)
4	**94**	^{1}H-NMR (300 MHz, CD_3OD) δ (ppm): 8.21 (d, 1H, *J*=8.6), 7.85 (t, 1H, *J*=9), 7.19 (t, 1H, *J*=8.6), 6.87 (d, 1H, *J*=8.6), 5.21 (s, 1H, N-H), 2.81-2.68 (m, 4H), 2.19-1.92 (m, 4H), 1.87-1.592 (m,12H)
5	**95**	^{1}HNMR (300 MHz, CD_3OD) δ ppm: 10.54 (s, 1H), 8.37(d, 1H, J=8), 8.237 (d, 2H, *J*=8), 7.95 (d, 2H, *J*=7.6), 7.80 (t, 1H, *J*=7.6), 7.607 (d, 1H, *J*=8), 7.53 (t, 1H, *J*=7.4), 3.93 (s,2H)

2.3. SECTION-C: Synthesis, Structure Elucidation, Method Development and Mechanism of Quinazolin-4(3H)-one Acetamidines

2.3.1. Unsymmetrical quinazolin-4(3*H*)-ones based acetamidines

The chemistry of amidine is known for more than a century, and the amidine functionality finds its presences in many natural products and is also a critical part of many biological systems. Substituted amidines bind to sigma receptor in the brain and, therefore, are useful for the treatment psychotic mental illness, hypertension and for the treatment or prevention of anxiety. [74, 75 a-e]

This class of compounds have also exhibited effects upon the perfused heart and the heart lung preparation. A minority of the amidines are comprised of a second group that have exhibited marked positive inotropic and chronotropic effects including a high affinity for σ receptor suggesting that σ receptors plays an important role in mediating antipsychotic activity. [76 a, b]

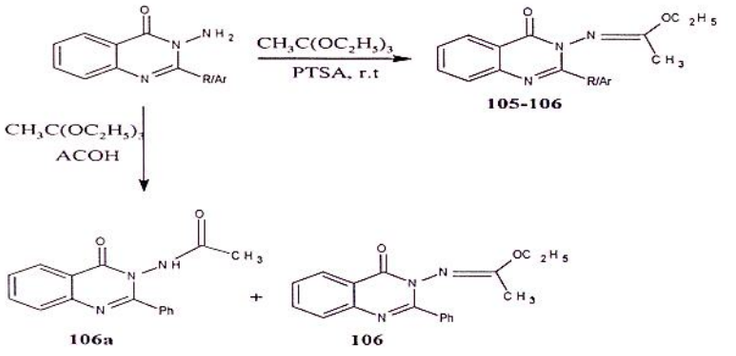
Structure - activity relationship has shown the effect of substituent changes on sigma receptor affinity in the amidine series in comparison to corresponding guanidines. Changing guinadine functionality with acetamidine generally increases sigma receptor affinity. Unsymmetrical acetamidines have shown threefold greater affinity for sigma receptor than the symmetrerical ones. [77 a, b]

On the other hand, a large number of studies have proven quinazolin-4(3*H*)-one nucleus as a versatile pharmacophore and its derivatives have exhibited diverse biological functions such as anti-microbial, hypnotic, analgesic, anti-allergic, anticonvulsant, antimalarial, and many others.[78]

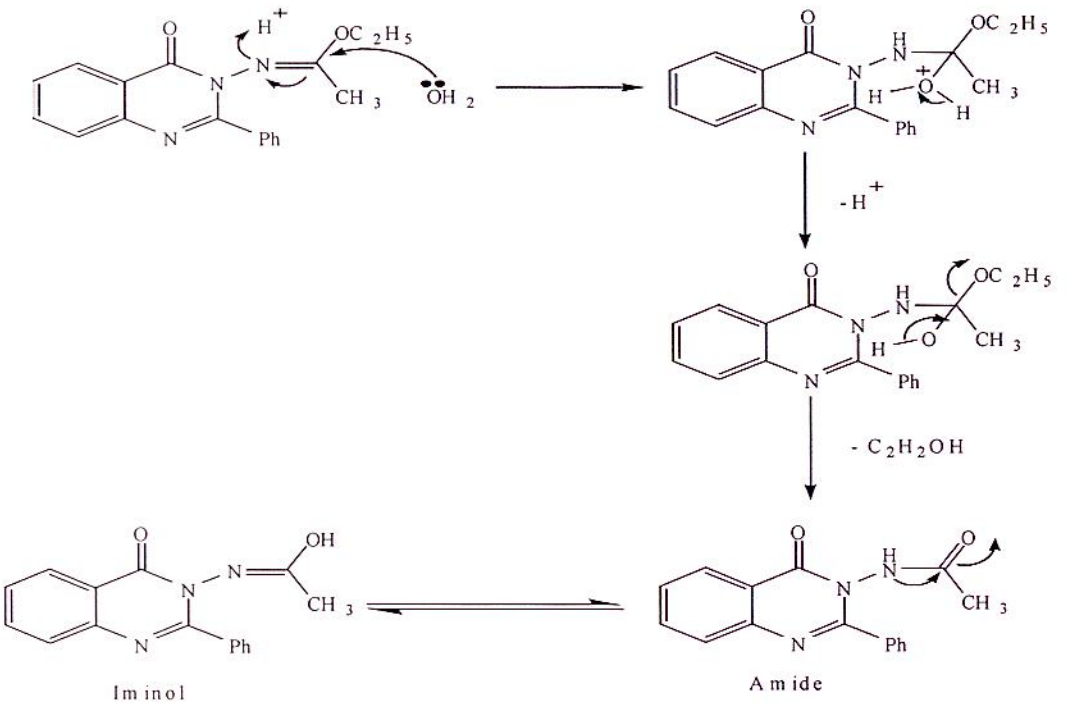
In recent years, the emphasis of heterocyclic chemistry has been focused on the synthesis of bi-hetrocyclic structures that are conjugated molecules consisting of more than one privileged class of compounds [79]. Since, the chemistry of both quinazolin-4(3*H*)-ones and acetamidines is well explored, while there is no literature information available about quinazolin-4(3*H*)-one based acetamidines, it was, therefore, felt worthwhile to synthesize some new unsymmetrical quinazolin-4(3*H*)-one based acetamidines with the aim to be used as precursors for synthesis of other novel heterocyclic skeletons as pharmacologically active molecules.

In this quest, ten novel N-(4-oxo-phenyl-3(4*H*)-quinazolinyl)-N-(substituted aryl) acetamidines were successfully synthesized in meaningfull yields by necessary modifications in the method reported by Taylor and Ehrhat [80]. 2-Phenyl-4H-3,1-benzoxazinone-4-one (PBO) was prepared as described earlier in the literature [81] . PBO was reacted with hydrazine to obtain the corresponding imidate ester in a very good yield. The target compounds, acetamidines were then synthesized by treating the imidate esters with active aromatic amines.

Tayoler *et al.*, [80] have reported the synthesis of acetamidines via the *in situ* preparation of imidate ester by initial reaction of primary amine with triethyl ortho acetate in acetic acid medium but have not isolated the intermediate esters formed in these reactions. Further, they have reported that the synthesis of symmetrical acetamidine is much easier than the unsymeterical ones. It was, therefore, decided to isolate and characterise the intermediate products. Surprisingly, a mixture of two products **106, 106a** were collected as intermediate products i.e. the formation of imidate ester **106** along with an amide **106a** intermediate product [Scheme 2.33]. It was also observed that the amide **106a** was formed in larger amount than the imidate esters **106** while on prolong heating, the amide **106a** was the sole product. It was realized in the present studies that the formation of amide **106a** might result by the acetic acid mediated acetylation of the amino group. Therefore, in a separate reaction, the 3-amino- 2-phenyl quinazolin-4(3*H*)-ones were allowed to react with acetic acid but no product was formed. Thus, it can be concluded that the protonation of imine nitrogen in compound **106** in the acidic medium followed by hydrolysis give the corresponding amide. The amide (**106a**) is stabe due to amide-iminole tautomerism [Scheme 2.34].



Scheme 2.33: Synthesis of imidate esters -condition optimization



Scheme 2.34: Acid hydrolysis of compound **106** and tautmeric stability of hydrolysed product **106a**

It was further realised to develop a method that would afford the imidate esters (**105-106**) selectively. An efficient, facile, selective and high yielding method was developed using *para*-toluene sulfonic acid (TsOH) as a catalyst in much shorter time at room temperature [Scheme 2.33b]. Thus, 2-methyl/phenyl -3-aminoquinazolin-3(4*H*)-one in excess of triethyl ortho-acetate was stirred at room temperature using 5 equivalents of TsOH as a catalyst under argon atmosphere and the imidate esters (**105** and **106)** were collected in a pure crystalline form as single products.

Structures of the amide and imidate esters **105, 106** were elucidated from the IR, EI-MS, FAB-MS, and ^{1}H-NMR spectroscopic data. The presence of characteristic amide peak at 3200-3400 cm^{-1} was observed in IR spectrum of the amide while a weak D_2O exchangeable peak for the amide proton was found in ^{1}H-NMR centred at 10-11 ppm. Structure of the imidate ester was confirmed from the characteristic triplet and quartet for -O-CH_2CH_3 group in addition to the supporting data obtained from other spectroscopic techniques. Since, imidate esters have not been isolated and literature have described their in situ preparation and have been used directly in the next step without characterization. It was, therefore, felt of interest to focus more on their synthesis and

characterization. Therefore, attempts were made on growing crystals and consequently colourless crystals were grown of the compound **105**. The structure of **105** was unambiguously established by X-ray crystallography. The 3D *ORTEP* model generated fron the X-ray crystallographic data of the imidate ester **105** is given in the Fig.6. Detailed X-ray crystal data is given in the appendex II.

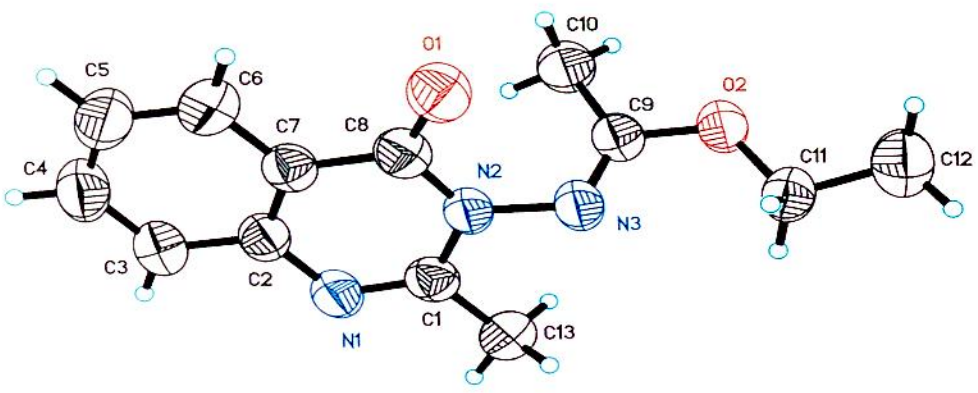


Fig.6: *ORTEP* model of the ethyl (1*E*)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoate (105)

The imidate ester **106** synthesized was then allowed to react with aromatic amines for the synthesis of quinazolin-4(3*H*)-ones based acetamidines. Here, again necessary modifications were made in the method published by Taylor *et al.*[80] for the synthesise of quinazolin-4(3*H*)-ones based acetamidines. Thus, the imidate ester (**106**) was thermally fused with active aromatic amines followed by addition of glacial acetic acid and the contents refluxed for 3-5h. Consequently, a series of novel unsymmetrical acetamidines (**107-11**) were synthesised in meaningfull yields [Table 2.23]. A possible mechanism of the quinazolin-4(3*H*)-ones based on acetamidine from imidate ester is believed to involve the initial nucleophillic attack of aromatic amine on imidate carbon followed by elimination of ethoxy anion as shown in [Scheme 2.38a]

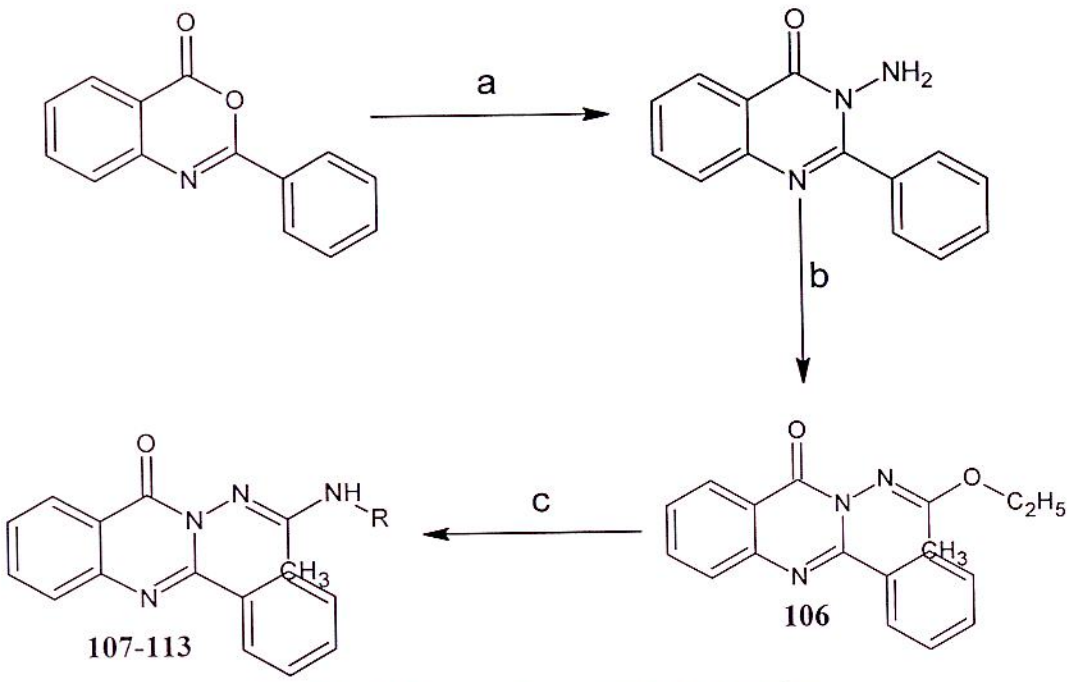
The chemistry of acetamidines although is more than 100 years old, but still there is limited literature available on the synthetic methods. In our search, of the formation of amide along with imidate esters [Scheme 2.34], it was considered of interest to use the quinazolin-4(3*H*)-ones amide (**106a**) as a precursor for the synthesis of quinazolin-

4(3*H*)-ones based acetanmidine, thus 2-phenyl-3-aminoacetyl quinazolin-4(3*H*)-one (**106a**) was synthesized by stirring acetyl chloride and 3-amino-2-phenylquinazolin-4(3*H*)-one in dry pyridine at room temperature. Compound (**106a**) was then condensed with aromatic amine at high temperature for 10-15 min followed by addition of acetic acid and further reflux for 3-5 h. Consequently, a new method [scheme 2.36] was developed for the synthesis of novel unsymmetrical quinazolinone based acetamidines (**107-113**).

Further, it was observed that aromatic amine substituted with electron donating group gave the corresponding acetamidine while an electron withdrawying group on aromatic amine failed to yield the corresponding acetamidines. The reason for which could be attributed to the amide-iminol tautomerism which decreases the reactivity of carbonyl carbon [Scheme 2.33]

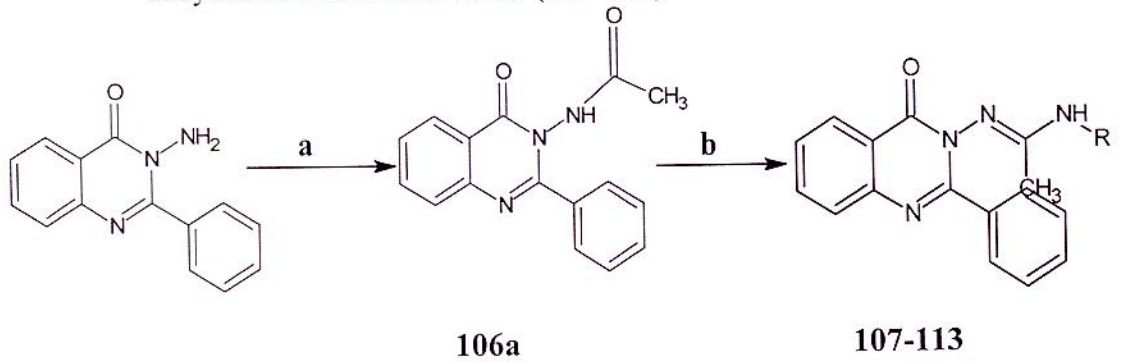
The newly developed method [scheme 2.36] seems to be cheaper, faster and more selective compared to the reported one for acetamidines [80]. The mechanism of formation of acetamidine from compound (**106a**) is believed to proceed *via* initial formation of carbocation intermediate [Scheme 2.38b].The carbocation upon reaction with aromatic amine followed by dehydration results in the formation of acetamidine.

IR, Mass [EI and FAB), ^{1}H-NMR were used for the structural determination. Mass fragmentation pattern was found more helpful in the structure determination of these compounds and typical fragmentation pattern is shown in [Scheme 2.37].



a.(i) $N_2H_4.H_2O$, py, reflux, (ii) HCl digestion
b. CH3C(OC2H5), PTSA, stirr, r.t.
c. Acetic acid, Ar-NH_2,

Scheme 2.35: General route to the synthesis of quinazolin-4(3*H*)-ones based unsymmetrical aceatmidines (**107-113**)



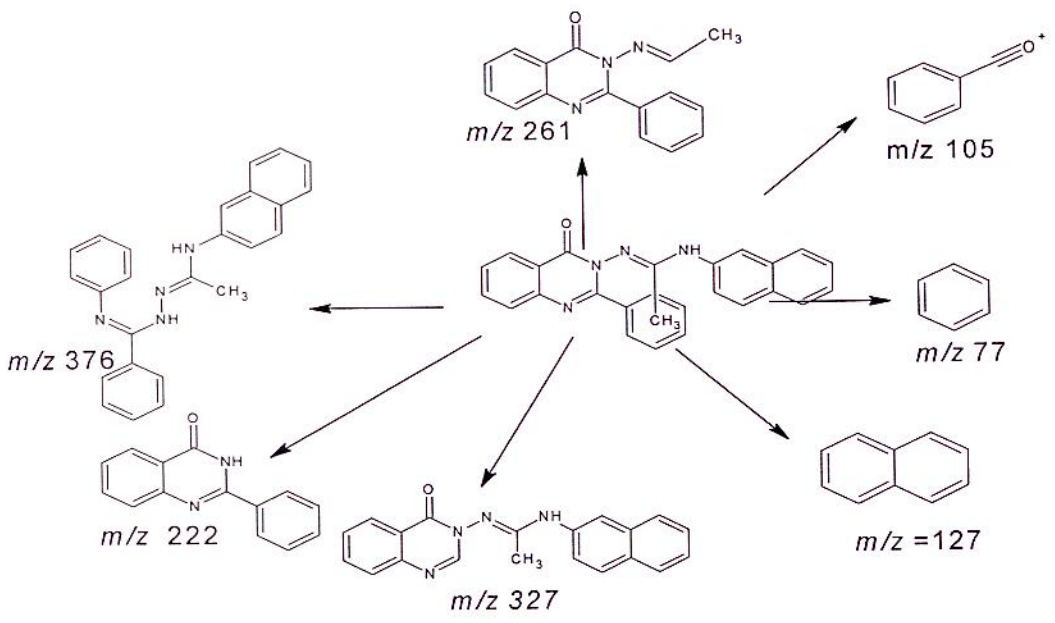
106a **107-113**

a. Acetyl chloride, dry pyridine, r.t., **b.** Aromatic amine, acetic acid,

Scheme 2.36: Synthesis of quinazolin-4(3*H*)-ones based unsymmetrical acetamidines (**107-113**) from amide (**106a**)

Table 2.23 (a): Melting points and yields the synthesized acetamidines **107-116**

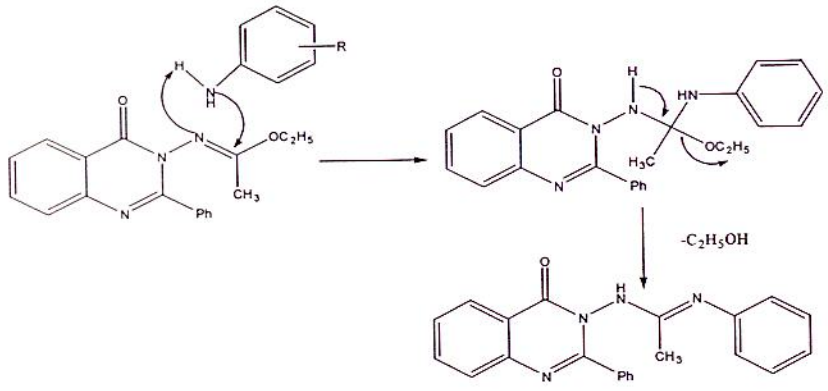
Entry	Compd #	R	M.P (°C)	Yield (%)
1	**107**	4-methylphenyl	227-219	69
2	**108**	4-Bromophenyl	244-246	90
3	**109**	Phenyl	233-236	57
4	**110**	3-Bromophenyl	222-225	60
5	**111**	Naphthyl	218-220	66
6	**112**	4-methoxyphenyl	224-226	62
7	**113**	2,4,6 Trimethylphenyl	165-168	60
8	**114**	4-Chlorophenyl	252-255	80
9	**115**	4-Iodophenyl	248-250	81
10	**116**	4-hydroxyphenyl	255-258	77



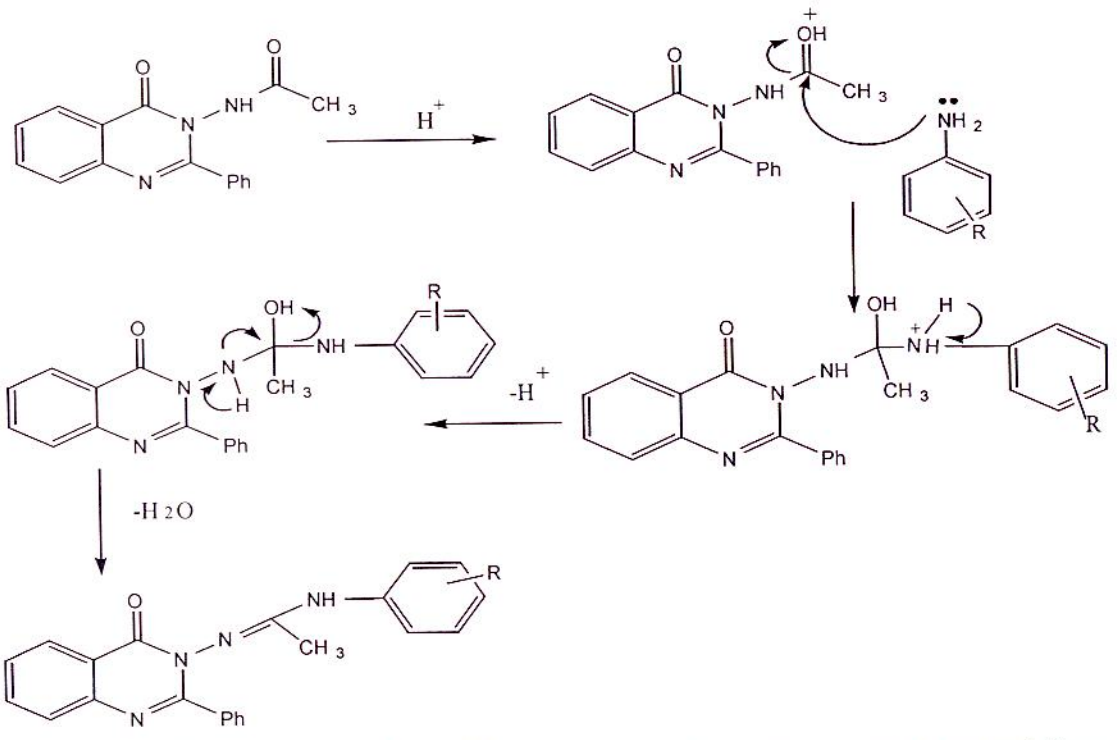
Scheme 2.37: Typical mass fragmentation pettern of quinazolin-4(3*H*)-one based acetamidines **111**

Table 2.23 (b): ^{1}H-NMR Spectral data of acetamidines **107-116**

Entry	Comp#	^{1}HNMR data
1	**107**	^{1}HNMR (300MHz, $CDCl_3$):δ (ppm) : 10.9 (b, s, 1H, N-H), 8,47 (d, 1H, *J*=7.8), 7.96 (m, 3H, Ar-H), 7.61 (m, 5H, Ar-H), 7.12 (q, 4H, Ar-H), 2.38 (s, 3H,), 2.16 (s, 3H)
2	**108**	^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.92 (s,1H, NH), 7.916 (d, 3H, *J*=6.98), 7.77 (d, 2H, *J*=8), 7.638-7.453 (m, 6H), 7.127-7.077 (t,1H, *J*=7.5), 7.0 (d,1H, *J*=7.64), 2.37 (s, 3H, CH_3)
3	**109**	^{1}HNMR (300MHz, DMSO-d_6) δ: 11.05 (b, s, 1H, N-H), 8.09 (d, 1H, *J*=8), 7.3 (d, 2H, *J*=8), 7.88-7.83 (m, 4H), 7.76 (t, 1H, *J*=8), 7.61-7.57 (m, 3H), 7.07(d, 2H, *J*=8), 6.97 (t, 1H, *J*=8), 2.34 (s, 3H, CH_3)
4	**110**	^{1}HNMR (300MHz, DMSO-d_6), δ (ppm): 11.05 (b, s, 1H, N-H), 8.09 (d, 1H, *J*=8), 7.93 (d, 2H, *J*=8), 7.88 (s,1H), 7.76 (d, 1H, *J*=8), 7.61 (m, 6H), 7.07 (t,1H, *J*=8), 6.97 (d,1H, *J*=8), 2.34 (s, 3H, CH_3).
5	**111**	^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.53 (s, 1H, N-H), 7.95 (d, 1H, *J*=8), 7.83 (t, 1H, *J*=8.3), 7.78 (t, 2H, *J*=8), 7.71(d, 2H, *J*=7.6), 7.65-7.61(m, 6H), 7.43-7.39 (m, 2H), 7.27 (t.1H, *J*=8.3), 7.12 (d, 1H, *J*=7.89), 2.35 (s, 3H)
6	**112**	^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.9 (b, s, 1H, N-H), 7.96 (m, 4H, Ar-H), 7.61 (m, 5H, Ar-H), 7.12 (m, 4H, Ar-H), 3.8 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3).
7	**113**	^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 11.01 (b, s, 1H), 8.14 (d, 1H, *J*=8), 8.0-7.6 (m, 6H), 7.3 (d, 1H, *J*=8), 6.93 (d, 1H, *J*=8.34), 6.8 (s, 2H), 2.2 (s, 3H), 2.1 (s, 6H), 2.0 (s, 3H).
8	**114**	^{1}HNMR(300MHz, $CDCL_3$), δ (ppm); 9.01 (s, 1H), 8.36(d, 1H, J=8.3), 8.23 (d, 2H, *J*=8.6), 8.02(t, 1H, J=9), 7.771 (d, 1H, J=8.6), 7.68-7.63 (m,1H), 7.39 (d, 1H, *J*=9), 7.34 (t, 1H, *J*=9), 7.15 (d, d, 2H, *J*=8,3), 6.95 (d, 2H, J=8.1), 2.23 (s, 3 H, CH_3).
9	**115**	^{1}HNMR (300 MHz, $CDCl_3$), δ (ppm): 10.5 (b, s, 1H, NH), 8.43 (d, 1H, *J*=8), 8.02-7.97 (m, 2H), 7.71-7.69 (m, 2H), 7.63-7.59 (m, 3H), 7.532-7.51(m, 2H), 7.365(t, 1H, *J*=7.8), 7.15 (d, 2H, *J*=8.1), 2.23 (s, 3H, CH_3)
10	**116**	^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 11.03 (b, s, 2H, NH), 7.92 (d,1H, *J*=9.6), 7.80 (d, 2H, *J*=8.7), 7.767(t, 1H, J=8.6), 7.61 (d, 1H, *J*=8.6), 7.58-7.53 (m, 1H), 7.748-7.35 (m, 3H), 7.29 (d, 2H, *J*=7.9), 6.97 (d, 2H, *J*=8.23), 2.01 (s, 3H, CH_3).



Scheme 2.38a: General mechanism of formation of quinazolinone based acetamidines from imidate ester (**106**)



Scheme 2.38b: General mechanism of formation of quinazolinone based acetamidines from amide ester (**106a**)

2.4. SECTION-D: Deamination of N-Aminoquinazolin-4(*3H*)-ones and Synthesis of 3-Isoindolo-2-yl-2-Substituted Quinazolin-4(*3H*)-ones

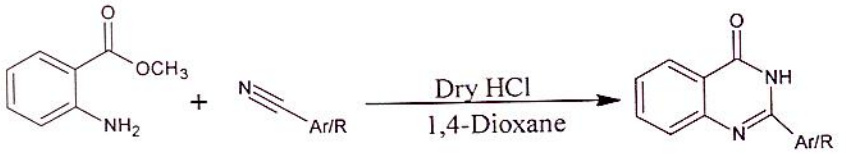
2.4.1. 2-Alkyl/arylquinazolin-4(*3H*)-ones by deamination of 3-N-aminoquinazolin-4(*3H*)-ones

Reported literature describes the synthesis of 2-aryl/alkyl-4 (3*H*) quinazolin-4(3*H*)-ones **(111-120)** by employing Nimentowski reaction, a condensation between anthranilic acid and alkanamide [83]. Other methods involve reaction of arencarboximides with isotoic anhydride [84] and stirring ammonium acetate with benzoxazinone at elevated temperature [85]. The labile nature of N-N bond has been utilized for the preparation of 2-alkyl/aryl-substituted-4(3*H*)-quinazolinone via neat pyrolysis of 2-*p*-tolyl-3-benzylidene aminopyrido [2, 3-*H*] quinazolin-4(3*H*)-one above its melting point [86]. Procedures for N-N bond cleavage using dissolving metal reagents have been reported [87]. 2-Ethylquinazolin-4(*3H*)-one has been prepared by reduction of *N*-quinazolinyl aziridine using lithium or sodium in liquid ammonia [88] via diazotization [89] Reddy *et al.* reacted 2-aryl-3,4-dihydro-*5H*-1,3,4-benzotriazepin-5-ones with $KMnO_4$ in acetone under reflux; ring contraction resulted in formation of 2-arylquinazoliolin-4(*3H*)-ones [92].The reported methods are associated with drawbacks such as expensive reagents, expensive and hazardous solvents, longer reaction times and formation of side products [91].

The developments of new green synthetic strategies are having high demand today for obvious reasons. The use of water and ionic liquids as solvents is preferred over other volatile and toxic solvents. Moreover, domestic microwave synthetic methods are not only environmentally friendly but are also cheap, less tedious and need much shorter reaction times for reaction completion. Literature on microwave chemistry has tremendously increased after 1990 and most of the conventional methods stoichiometricaly driven organic reactions are being replaced with catalytic, microwave and other environmentally friendly methods.Although more sophisticated but costly microwave synthesizers are now available, the use of domestic microwave oven in organic synthesis has been used in several standard research papers [92].

In the present study, a series of 2-alkyl/arylquinazolin-4(3*H*)-ones was synthesized using two different methods i.e. cyclocondensation of methyl anthranilate and alkyl/arylcyanide and the newly developed aqueous $KMnO_4$ mediated deamination of

2-alkyl/aryl-3-aminoquianzolin-4(3*H*)-ones under both conventional thermal reflux and microwave irradiations. In the first method, dry HCl was passed over a mixture of methyl anthranilate and alkyl/arycyanide in dry dioxane at room temperature [Scheme 2.39] for 7-12 h.with continuous stirring. Aafter reaction completion, the mixture was neutralized with 5-10 % aq.$NaHCO_3$ solution and the product was then extracted with dichloromethane.



Scheme 2.39: Synthesis of 2-alkyl/arylquinazolin-4(3*H*)-ones via cyclocondensation

This method was found low yielding and also formation of side product was observed due to the reactivity of secondary amine in the acidic medium with methylesters, the side product, however, formed was found sensitive to hydrolysis and was decomposed in to the target 2-ethylquinazolin-4(3*H*)-ones upon refluxing in aq. H_2SO_4 or aq. HCl in ethanol. It is, however, important to state here that the side products were not observed in case of arylcyanides. The work was, therefore, further continued in search of a better method for the synthesis of 2-alkyl/arylquinazolin-4(3*H*)-ones and thus, a novel method for the synthesis of 2-alkyl/arylquinazolin-4(3*H*)-ones *via* oxidative deamination of 2-alkyl/aryl- 3-aminoquinazolin-4(3*H*)-ones was developed.

We, therefore, in our method of $KMnO_4$ mediated oxidative deamination have used water as solvent under conventional thermal condition and have also extended the procedure to microwave-assisted technique obtaining some very interesting results [Scheme 2.40]. To our knowledge, this is the first facile, cheaper and environmentally benign thermal and microwave-assisted deamination method of an amino group attached to nitrogen as a part of quinazolin-4(3*H*)-ones ring system. The method will be equally useful for deamination of any *N*-aminoheterocyclic system.

Compounds **117-126** were prepared by refluxing N-amino quinazolin-4(3*H*)-ones in aqueous $KMnO_4$ for appropriate time. The encouraging syntheses of aryl/alkylquinazolinone-4(*3H*)-ones in aqueous $KMnO_4$ media by conventional heating further prompted us to carry out these reactions using microwave irradiation [Scheme

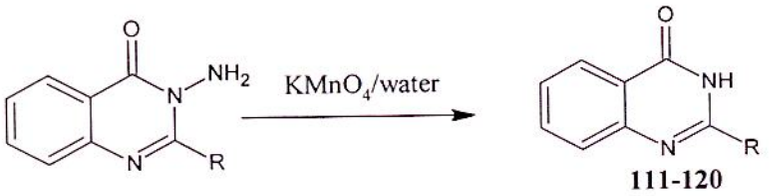
2.40]. All reactions were successfully carried out under microwave irradiation using water as solvent in shorter time periods and with improved yields [Table 2.24] in comparison to the conventional heating method.

Mixture of substrate and $KMnO_4$ in aqueous medium in 100 ml conical flask was irradiated in domestic microwave oven (1000 W) with short pulses of 10-15 seconds at a time. After each pulse, the reaction vessel was cooled before another pulse was supplied. Continuous irradiation resulted in spill over with complete loss of water leading to reaction failure. The spill over also occurred when the mixture was irradiated without using heat sink, in the form of a separate beaker containing water. The oxidative deamination may involve $KMnO_4$ mediated oxidation of the amino group to a nitroso group which is followed by hydrolytic cleavage of the *N*-nitroso bond [Scheme 2.44]. Reddy *et al.*, [93] have explained the ring contraction and formation of the 2-arylquinazolin-4(*3H*)-ones under thermal condition using acetone as a medium through a proposed mechanism [Scheme 2.42]. Their proposed reaction mechanism envisages the formation of three reaction intermediates one after another, *viz* diaziridine, 2-arylquinazolin-4(*3H*)-one and diquinazolinylhyrazine followed by decomposition of the hydrazine intermediate through loss of N_2. The authors have proposed the formation and actual isolation of the second reaction intermediate as the basis for their proposed mechanism. Assuming that their proposed third reaction intermediate, i.e., diquinazolinylhydrazine is acceptable when dry acetone is used as medium; the same mechanism will be highly unlikely in aqueous medium in our opinion. Therefore, the more plausible reaction mechanism followed in our reported method is $KMnO_4$ mediated oxidative transformation of the $N\text{-}NH_2$ into N-NO followed by water promoted hydrolytic removal of the nitroso group as shown in [Scheme 2.42].

Table 2.24: Deammination of aminoquinazolinones in aqueous $KMnO_4$ using thermal (A) and microwave irradiations (B) methods

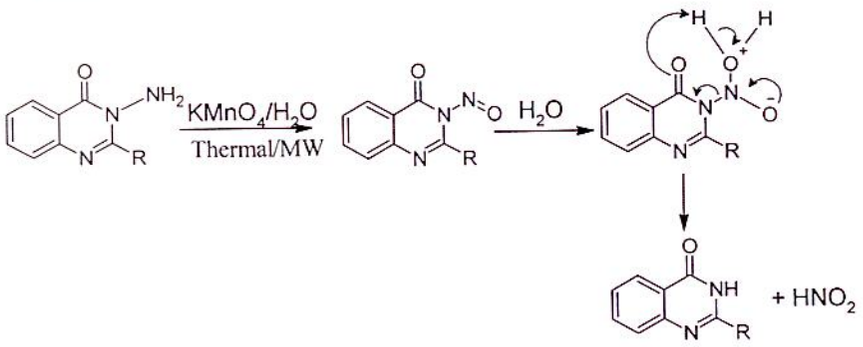
Entry	Compd. #	R	Method	Reaction Time	Yield (%)	M.P(^{0}C)
1	**117**	CH_3	A	4 h	73	240
			B	10 min	81	
2	**118**	C_6H_5	A	3 h	70	238
			B	12 min	90	
3	**119**	4-$CH_3C_6H_4$	A	4 h	73	240-42
			B	10 min	81	
4	**120**	4-ClC_6H_4	A	4 h	72	303
			B	12 min	85	
5	**121**	4-BrC_6H_4	A	4 h	69	170-72
			B	13 min	80	
6	**122**	4-$NO_2C_6H_4$	A	5 h	67	360
			B	12 min	80	
7	**123**	$C_6H_4CH_2$	A	3 h	70	255
			B	10 min	88	
8	**124**	4-HOC_6H_4	A	4 h	80	126
			B	10 min	83	
9	**125**	$CH_2CO_2C_2H_5$	A	4 h	65	155-57
			B	10 min	83	
10	**126**	C_2H_5	A	4 h	80	234
			B	8 min	91	

In conclusion, we have developed simple and environmentally friendly thermal and microwave irradiation methods for deamination of 2-alkyl/aryl 3-aminoquinazolinone 2-alkyl/aryl quinazolin-4(3*H*)-ones applicable to other analogous systems, making use of a cheaper readily available oxidant and medium as potassium permanganate and water respectively. The microwave -assisted procedure has the added advantage of very high yields in much shorter times over the thermal method.

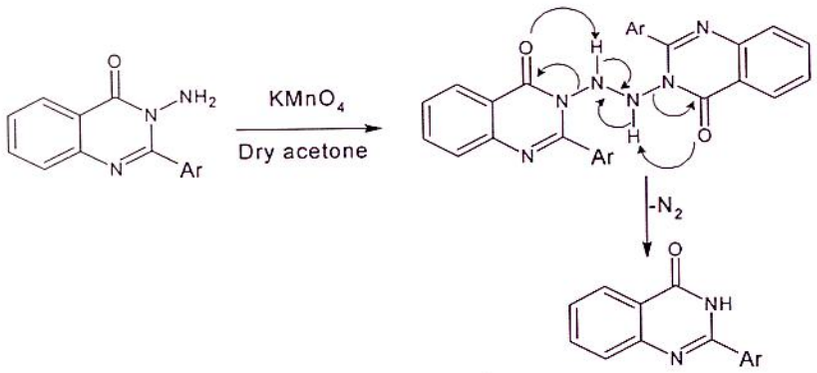


111-120

Scheme 2.40: Water-promoted oxidative deamination of N-amino quinazolin-4(3*H*)-ones



Scheme 2.41: Proposed mechanism of deamination



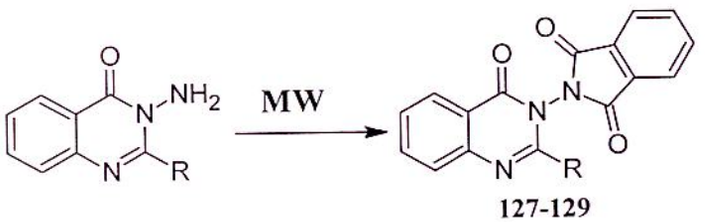
Scheme 2.42: Mechanism proposed by Reddy *et al*

2.4.2. 3-Isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones

3-Heteroaryl –quinazolin-4(3*H*)-ones are important class of quinazolin-4(3*H*)-ones derivatives as potent antimicrobial agents. [94-95] The synthesis of 3-heteroaryl – quinazolin-4(3*H*)-ones and related compound is reported via condensation of 3-aminoquinazolin-4(3*H*)-ones and different oxo cyclic compounds in glacial acetic acid [96] and in refluxing chloroform [97].These methods are very low yielding i.e. 22 %, and 30-50 % respectively. In the present study, two new methods i.e. direct thermal fusion at elevated temperature and microwave irradiation were optimized for the synthesis of 3-

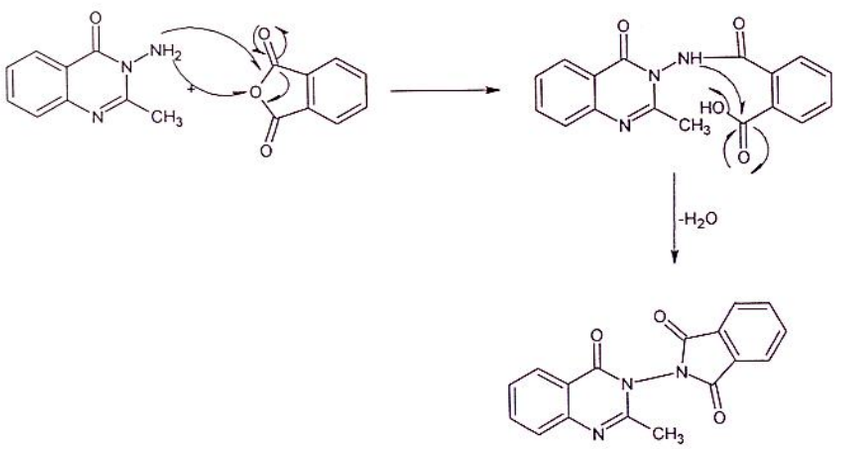
isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones [Scheme 2.43]. In the first method, phthalic anhydride and 3-aminoquinazolin-4(3*H*)-ones were condensed at 150 ^{0}C for 30 min. After completion of the reaction, the product was recrystallized from ethanol. In the next step, 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-ones were synthesized by irradiation of 3-aminoquinazolinone and phthalic anhydride in domestic microwave oven for 8-12 min. Both the methods were found high yielding and faster compared to the already reported method in the solution phase ref.

Structural assignment was done on the basis of ^{1}HNMR, IR, EI-MS and FAB-MS. ^{1}HNMR Spectral data is given in Table 2.27 Mechanistically, the reaction is believed to take place via the initial opening of phthalic anhydride and formation of an imide intermediate which then upon cyclization via internal nucleophilic attack by nitrogen is followed by the loss of water molecule [Scheme 2.44] to give the target 3-isoindolo-2-yl-2-substituted quinazolin-4(3*H*)-one in substantial yield [Table 2.25].



127-129

Scheme 2.43: Micowave- assisted solvent and catalyst free synthesis of **127-129**



Scheme 2.44. Mechanism of formation of 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-isoindole-1,3 (2*H*)-dione

Table 2.25: Microwave- assisted synthesis of 2-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl)-1*H*-isoindole-1, 3(2*H*)-dione **(127-129)**

Entry	Compd. #	R	M.P (^{0}C)	Time (min.)	Yield (%)
1	**127**	H	176-178	12min	91
2	**128**	CH_3	167-169	8min	99
3	**129**	Phenyl	68-70	13min	97

Table 2.26: Synthesis of 2-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl)- 1*H*-isoindole-1, 3(2*H*)-diones via thermal fusion method **(127-129)**

Entry	Compd. #	R	M.P(^{0}C)	Time (min.)	Yield (%)
1	**127**	H	176-179	30	83
2	**128**	CH_3	167-169	30	85
3	**129**	Phenyl	68-70	30	91

Table 2.27: 1HNMR spectral data of of 2-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl)- 1*H*-isoindole-1,3(2*H*)-diones **(127-129)**

Entry	Compd.#	^{1}HNMR data
1	**127**	^{1}HNMR (300 MHz) δ (ppm): 10.23 (s, 1H), 8.29 (d, 1H, *J*=7.57), 8.01(1, 2H, *J*=8.73), 7.89 (t, 1H, 8.2), 7.78 (t, 1H, 7.7), 7.6 (t, 2H, *J*=8.56), 7.55-7.51(t, 1H, *J*=8.23)
2	**128**	^{1}HNMR (300 MHz) δ (ppm): 8.21 (d, 1H, *J*=7.83), 8.0196-7.99 (dd, 2H, *J*=8.57), 7.89 (d, 2H, *J*=8.565), 7.822-7.767 (t, 1H, *J*=8.2), 7.717 (d, 1H, *J*=7.7), 7.5-7.452 (t, 1H, *J*=7.3), 2.48 (s, 3H, CH_3)
3	**129**	^{1}HNMR (300 MHz) δ (ppm): 8.24 (d, 1H, *J*=8.2), 8.21 (d, 2H, *J*=7.8), 7.99 (dd, 2H, *J*=8.67), 7.85 (t, 1H, *J*=8.56), 7.73 (d, 1H, 8.2), 7.67 (t,1H, *J*=8.7), 7.62 (m, 2H), 7.59 (t, 2H, *J*=8), 7.56 (t, 1H, *J*=8.6)

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CHAPTER – 3

EXPERIMENTAL SECTION

MATERIAL

All the starting materials used were of analytical grade. Organic liquids and solvents were further purified using standard methods of purifications where needed[1]. TLC was performed on precoated silica gel $60F_{254}$ TLC plates (Merck). Column chromatography (silica gel) and recrystalization was used for purification. Melting points were measured in open capillaries using Gallen kamp melting point apparatus and were uncorrected .IR spectra were recorded on KBr disc with using bio rad-win IR. Mass spectra were recorded on MAT-312 and NMR spectra were recorded on 300 and 400 MHz bruker NMR spectrophotometer.

SECTION A: Synthesis of 2-Aryl-4(*H*)-3,1-benzoxazinones and Methyl-*N*-acylanthranilates

3.1. 2-Aryl-4(*H*)-3, 1-benzoxazin-4-one (2-12)

Method A: Synthesis of 2-aryl-4(*H*)-3, 1-benzoxazine-4-one from aromatic acyl-chloride-General Procedure

To the well stirred solution of anthranilic acid in dry pyridine at room temperature was added a substituted benzoyl chloride drop- wise with continuous stirring at or below room temperature, until a precipitate appeared. The precipitate formed was filtered, washed with saturated aqueous $NaHCO_3$ solution, dried and finally recystallized from suitable solvent to obtain the desired 2-aryl-4(*H*)-3, 1-benzoxazine-4-ones (**2-12**).

Method B: Direct one-pot Synthesis of 2-aryl-4(*H*)-3, 1-benzoxazine-4-one – General Procedure

Substituted benzoic acid in freshly distilled thionyl chloride was boiled under reflux for 2-5 h and the mixture was then allowed to cool below room temperature and added drop-wise to a well- stirred solution of anthranilic acid in dry pyridine. The stirring was further continued till the product precipitated. The mixture was added to a saturated solution of $NaHCO_3$ and shaken. The product precipitated out and filtered, washed with $NaHCO_3$ solution followed by distilled water, dried and recrystallized from water-ethanol

mixture to give the corresponding 2-aryl-4(*H*)-3, 1-benzoxazine-4-one (**2-12**) in 80-96 % yield.

3.1.1. Typical synthesis of 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one (2) via method A

Anthranilic acid (2.0 mg, 0.006 mol) was stirred in 10 mL dry pyridine for 15 min. To the stirred solution was then added drop -wise 3.5 mL benzoyl chloride with continuous stirring for the next 30 min at room temperature. The product precipitated was filtered, washed with saturated $NaHCO_3$ followed by distilled water, dried and recrystallized from water -ethanol mixture. Yield 93 % , m. p. 108-110°C; IR (KBr) υ_{max}: 2922 (C-H, str.), 1759 (C=O, str.), 1602 (C=N, str.), 1557 (C=C, str.), 1470 (C-H, bend), 1309 (C-H, bend), 1224 (C-O, str.), 1172 (C-C, str.): EI-MS m/z: 223 (M^+ 100), 196 (7), 178(11), 146 (15), 120 (13), 119(4), 105 (100), 91(11), 77 (83), 65(3), 51 (18): ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.26 (d,1H, *J*=8), 7.82 (m, 4H), 7.56 (m, 4H)

3.1.2. 2-(4-Nitrophenyl)-4*H*-3, 1-benzoxazin-4-one (3)

4-Nitrobenzoic acid= 1.2 g, 0.007 mol

Freshly distilled $SOCl_2$ = 10 mL

Anthranilic acid= 0.5 g., 0.0036 mol

Pyridine (dry) = 15mL

Yield 89 %, m. p.202-204 °C: IR (KBr) υ_{max} cm^{-1}: 1709 (C=O, str.), 1600 (C=N, str.), 1471 (C=C-C, str.), 1344 (C-O, str.), 1233 (C-C, str.), 747, 690, 669 (C-H, bend, arom.):EI-MS m/z: 268 (M^+, 28), 253 (44), 236 (7), 235 (15), 207 (48), 179 (19), 178 (27), 167 (9), 105 (91), 104 (17), 102 (32), 92 (10), 77 (39), 76 (100), 63 (17), 51 (20), ^{1}HNMR (400 MHz, $CDCl_3$), *δ*: 8.34 (d, 2H, *J* = 9, Ar-H's), 8.02 (d, 1H, *J* = 9, Ar-H's), 7.98 (m, 3H, Ar-H's), 7.81(t, 1H, *J*=8.7), 7.39(t, 1H, *J*=8.5).

3.1.3. 2-(4-Methylphenyl)-4*H*-3, 1-benzoxazin-4-one (4)

4-Methylbenzoic acid (3.9g, 0.029 mol)

Thionyl chloride=10mL

Anthranilic acid= 2 g., 0.0155 mol

Yield : 92 %, m. p. 144°C; IR (KBr) υ_{max} cm^{-1}: 3262 (C-H, str), 1725 (C=O, str), 1516 (C=N, str), 1464 (C=C-C, str), 1264 (C-O, str), 1198 (C-C, str): EI-MS m/z: 237 ($M.^+$,92), 146 (21), 120 (18), 119 (100), 91 (38), 76 (10), 65 (10), ^{1}HNMR (300 MHz,

$CDCl_3$), δ: 8.21 (d, 1H, J=8.6), 8.11 (d, 1H, J=8.7), 7.97 (d, 2H, J=8), 7.82 (t, 1H, J=8.4), 7.44 (t, 1H, J=8.0), 7.18 (d, 2H, J=8.4), 2.36 (s, 3H, CH_3).

3.1.4. 2-(4-Chlorophenyl)-4*H*-3, 1-benzoxazin-4-one (5)

4-Chloro benzoic acid = 0.029 mol

Thionyl chloride = 10 mL

Anthranilic acid= 2 g., 0.0155 mol

Yield: 89 %, M.p:158-160 °C; IR (KBr) υ_{max} cm^{-1}: 3039 (C-H, str.), 1716 (C=O, str.), 1557 (C=N, str.), 1470 (C=C, str.), 1224 (C-O, str.), 1173 (C-C, str.), 765 (C-Cl, str.): EI-MS m/z: 259 (M^{+2}, 3), 257 ($M.^{+}$, 8), 243 (10), 241 (61), 215 (2), 213 (5), 146 (24), 139 (5), 113 (4), 111 (13), 76 (91), 50 (5); ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 8.23 (d, 1H, J = 9), 8.15 (d, 1H, J=9), 7.94 (d, 2H, J = 8), 7.8 (t, 1H, J=8.5), 7.51-7.42 (m, 3H).

3.1.5. 2-(4-Bromophenyl)-4*H*-3, 1-benzoxazin-4-one (6)

4-Bromobenzoic acid= 6g, 0.029 mol.

Thionyl chloride=10 mL.

Anthranilic acid= 2 g., 0.0155 mol.

Yield 87 %, m. p. 184 °C.; IR (KBr) υ_{max} cm^{-1}: 3021 (C-H, str.), 1726 (C=O, str.), 1602 (C=N, str.), 1546 (C=C, srt.), 1415 (C-H, bend), 1309 (C-O, Str.), 1172 (C-C, str.); EIMS m/z: 303(M^{+2}, 48), 301(M^{+}, 56), 287(4), 285(40), 259(12), 257(16), 182(4), 181(11), 180(6), 168(9), 166(13), 146(81), 120(20), 118(22), 105(92), 92(11), 76(100), 63(25), 57(29), 51(42); ^{1}HNMR (300 MHz, $CDCl_3$), δ: 8.23 (d, 1H, J =8.9), 8.12(d,1H,J=8.7), 7.93 (dd, 2H, $J_{1,2}$ = 8.7, $J_{3,4}$ = 9.5), 7.81 (t, 1H, J=9.2), 7.66 (m, 2H), 7.45 (d, 1H, J = 8.3).

3.1.6. 2-(3-Iodophenyl)-4*H*-3, 1-benzoxazin-4-one (7)

3-Iodobenzoic acid= 4 g., 0.016 mol.

Thionyl chloride= 10 mL.

Anthranilic acid= 2 g., 0.0155 mol.

Yield: 93%, m. p. 130 °C: IR (KBr) υ_{max} cm^{-1}: 2928 (C-H, Str.), 1689 (C=O, str.), 1716 (C=N, str.), 1584 (C=C, str.), 1484 (C-H, bend), 1309 (C-H, bend, conju.), 1211 (C-O, str), 1178 (C-C, str); EI-MS m/z: 349 ($M.^{+}$, 89), 335 (11), 307 (19), 222 (67), 204 (76), 131 (17), 120 (27), 119 (31), 105 (100), 104 (9), 92 (71), 80 (24), 76 (57), 67 (10), 54

(18); ^{1}HNMR (400 MHz, $CDCl_3$), δ: 8.27 (d, 1H, J=8), 8.17 (m, 2H), 8.1(d,1H, J=9.5), 7.89 (t, 1H, J=8.4), 7.80 (d, 1H, J=9), 7.45 (t, 1H, J=8.5), 7.35 (t, 1H, J=9.6).

3.1.7. 2-Pyridin-3-yl-4*H*-3, 1-benzoxazin-4-one (8)

Nicotinic acid= 2 g., 0.106 mol.

Thionyl chloride= 10 mL

Anthranilic acid= 2 g., 0.0155 mol

Yield: 90 %, m. p. 207 ^{0}C; IR (KBr) υ_{max} cm^{-1}: 3039 (C-H, str.), 1724 (C=O, str.), 1622 (C=C, str.), 1557 (C=N, str.), 1415 (C-H, bend.), 1245 (C-O, str.), 1172 (C-C, str.), EI-MS m/z: 224 (M^+, 89), 209 (27), 182 (15), 147 (43), 132 (5), 120 (19), 105 (100), 92 (59), 79 (71), 76 (18), 63 (5), 54 (11) :^{1}HNMR (400 MHz, $CDCl_3$) δ: 9.31 (s, 1H, Ar-H), 9.14 (d, 1H, J=8.9), 8.27 (d, 1H, J=8), 8.19 (d, 2H, J=8.2), 8.07 (t, 1H, J=8), 7.93 (t, 1H, J=8), 7.44 (t, 1H, J=8.7).

3.1.8. 2-(3, 5-Dinitrophenyl)-4*H*-3, 1-benzoxazin-4-one (9)

3, 5-Dinitrobenzoicacid= 3.4 g, (0.016 mol)

Thionyl chloride= 10 mL

Anthranilic acid= 2 g., 0.0155 mol

Yield: 82 %, m.p. 125-126 ^{0}C: IR (KBr) υ_{max} cm^{-1}: 2931 (C-H, str), 1754 (C=O, str), 1617 (C=N, str), 1587 (C=C, str): EI-MS m/z: 313 (94), 299 (35), 268 (7), 221 (5), 168 (12), 120 (18), 105 (100), 92 (37), 76 (11), 75 (3), 63 (7), 54 (3): ^{1}HNMR (300 MHz, $CDCl_3$) δ: 9.8 (s, 1H), 9.21 (s, 2H), 8.2 (d, 1H, J=7.37), 8.10 (d, 1H, J=8.09), 7.81 (t, 1H, J=7.6), 7.47 (t, 1H, J=8.07).

3.1.8. 2-(3-Bromophenyl)-4*H*-3, 1-benzoxazin-4-one (10)

3-Bromobenzoic acid = 2 g., (0.00995 mol)

Thionyl chloride =10 mL

Anthranilic acid = 2 g, 0.0155 mol

Yield: 61 %, m.p. 118-120 ^{0}C; IR (KBr) υ_{max} cm^{-1}: 2978 (C-H, str), 1697 (C=O, str.), 1617 (C=C, str.), 1415 (C-H, bend.), 1224 (C-O,str.), 865 (C-Br, str.): EI-MS m/z: 303 (M^{+2}, 15), 301 ($M.^+$, 62), 300 (4), 29 (46), 257 (44), 222 (10), 182 (4), 181 (11), 180 (6), 168 (10), 166 (13), 145 (79), 120 (18), 119 (14), 118 (25), 105 (92), 104 (4), 92 (11), 53 (7), 54 (34), 53 (7), 52 (14), 51 (42); ^{1}HNMR (400 MHz, $CDCl_3$), δ: 8.6 (s, 1H), 8.2 (d,

1H, *J*=8), 8.15 (d, 1H, *J*=8.2), 8.13 (d, 1H, *J*=8), 8.07 (d, 1H, *J*=8.2), 7.6(d, 1H, *J*=8.5), 7.46 (t, 1H, *J*=8.2), 7.37 (t, 1H, *J*=8.4).

3.1.9. 2-(3-Chlorophenyl)-4*H*-3, 1-benzoxazin-4-one (11)

3-Cholorobenzoicacid = 2 g., 7.78 mmol

Thionyl chloride= 10 mL

Anthranilic acid = 2 g., 0.0155 mol (15.5 mmol)

Yield: 77.6 %, m. p. 128-130 °C; IR (KBr) υ_{max} cm^{-1}: 2827 (C-H, str), 1656 (C=O, str.), 1574 (C=N, C=C, str.), 1309 (C-H, bend. Arom.), 680 (C-Cl, str.): EI-MS (m/z): 259 (M^{+2}, 86), 257 (100), 243 (21), 241(12), 215 (2), 214 (4), 213 (5), 207 (24), 152 (4), 140 (6), 138 (36), 120 (6), 119 (13), 102 (7), 90 (4), 77 (5), 76 (48), 50 (4); ^{1}H-NMR (300 MHz, $CDCl_3$), δ: 8.31 (s, 1H), 8.25-8.20 (m, 2H), 8.15 (d, 1H, *J*=9.7), 7.80-7.60 (t, 1H, *J*=8.5), 7.48 (t, 1H, *J*=9), 7.41-7.37 (m, 2H).

3.1.10. 2-(2-Bromophenyl)-4*H*-3, 1-benzoxazin-4-one (12)

2-Bromobenzoic acid= 2 g., 0.0066 mol

Thionyl chloride = 10 mL

Anthranilic acid= 2 g., 0.015 mol.

Yield: 66.78%, m. p. 180-182 °C: IR (KBr) υ_{max} cm^{-1}: 1751(C=O, str), 1648(C=N, str), 1550(C=C, str), 1401(C=C-C, str), 1230(C-O, str), 1150(C-C, str): EI-MS m/z: 303 (M^{+2}, 48), 301 (M^{+}, 56), 287 (4), 285 (40), 259 (12), 257 (16), 182 (4), 181 (11), 180 (6), 168 (9), 166 (13), 146 (81), 120 (20), 118 (22), 105 (92), 92 (11), 76 (100), 63 (25), 57 (29), 51 (42); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.23 (d, 1H, *J* =8.9), 8.17 (d, 1H, *J*=8.7), 7.93 (d, 1H, *J*3,4 = 9.5), 7.81 (t,1H, *J*=9.2), 7.66 (d, 1H, *J*=9), 7.60 (t, 1H, *J*=8.6), 7.45 (t, 1H, *J* = 8.3), 7.21 (t, 1H, *J*=9.3).

3.2. Synthesis of methyl-N-acylanthranilates (13-18)

General Procedure

A mixture of methyl anthranilate (3 mL) and suitable acid halide in slight excess were refluxed for half an hour. The reaction mixture was poured into ice-cold water containing few drops of pyridine where the product precipitated out on vigorous stirring. The product was filtered, washed with distilled water, dried and recrystallized from suitable solvent.

3.2.1. Typical procedure for the synthesis of Methyl N-acetyl anthranilate (13)

Methyl anthranilate (3 g, 0.0196 mol) and excess of acetyl chloride (10 mL) were refluxed for 15 minutes with continuous stirring. The reaction mixture was then poured in to ice-cold water containing few drops of pyridine. The product precipitated was filtered, dried and recystalized from absolute ethanol. Yield: 96 %, m.p. 193 °C; IR (Nujal) υ_{max} cm^{-1}: 3270 (broad, N-H, str.), 2958 (CH_3,.str.), 2856 (CH_3. str.), 1702 ($COOCH_3$, str.), 1602 (NH-CO-CH_3, str.), 1453 (=CH_2, Arom.), 1365 (CH, bend), 1264 (C-C, str.), 1141 (C-C, str), 763 (arom. bend): EI-MS m/z: 193 (M^+, 25), 151 (61), 119 (100), 92 (34), 65 (19), 51 (4): ^{1}H-NMR (500 MHz, DMSO.d^6): δ 10.5 (s, 1H), 8.2 (d, 1H, *J*=8), 7.8 (d, 1H, *J*=7), 7.5 (t, 1H, *J*=10), 3.86 (s, 3H, CH3), 2.10 (s, 3H).

3.2.2. Methyl 2-[(chloroacetyl) amino] benzoate (14)

Methyl anthranilate= 3 g., 0.0196 mol

Chloroacetyl chloride= 5 mL.

Yield: 88 %, m. p. 101 °C; IR (KBr) υ_{max} cm^{-1}: 3256 (N-H, str.), 2912 (C-H, str), 2852 (=C-H, str.), 1690 (C=O, str), 1560 (C=O, str), 1543 (C=N, str), 1444 (C-H, bend), 1376 (C-H, str.), 1270 (C-N, str), 1197 (C-C, str), 697 (C-Cl, str), 960, 758, 661 (Arom, C-H, bend); EI-MS m/z: 227 (m^+,9), 178 (10), 151 (19), 146 (100), 132 (15), 119 (71), 104 (5), 92 (58), 90 (68), 77 (51), 51 (23): ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 11.8 (s, b, 1H), 8.69 (d, 1H, *J*=8), 8.06 (d,1H, *J*=8), 7.1 (t, 1H, *J*=9), 4.19 (s, 2H, CH_2), 3.94 (s, 3H, CH_3)

3.2.3. Methyl 2-[(4-methylbenzoyl) amino] benzoate (15)

Methylanthranilate= 3 g., 0.0196 mol

4-methyl benzoyl chloride= 10 mL.

Yield: 92 %. m.p. 140 °C: IR (KBr) υ_{max} cm^{-1}: 3256 (N-H, str), 2912 (C-H, str), 1690 (C=O), 1598 (C=O), 1533 (C=C), 1444 (C-H, bend), 1270 (C-O), 1241 (C-N), 1197 (C-C); EI-MS m/z: 269 (M^+, 3), 254 (2), 226 (2), 120 (11), 119 (100), 105 (30), 91 (37), 65 (17); ^{1}H-NMR (300MHz,$CDCl_3$) : δ 11.9 (s, b, 1H), 8.92 (d, 1H, *J*=6), 8.03 (d, 2H, *J*=9), 7.94 (m, 2H), 7.5 (t, 1H, *J*=9), 7.30 (d, 2H, *J*=9), 7.11 (t, 1H, *J*=9), 3.94 (s, 3H), 2.41 (s, 3H, CH_3).

3.2.4. Methyl 2-[(4-nitrobenzoyl) amino] benzoate (16)

Methylanthranilate = 3 g., 0.0196 mol

P-Nitrobenzoyl chloride= 4 g., 0.021 mol

Yield: 66 %, m.p. 181-183 °C: IR (KBr) υ_{max} cm^{-1}: 3212 (N-H), 2964 (C-H), 1685 (C=O), 1590 (C=O), 1533 (C=C), 1444 (-N=O), 1376 (-N=O), 1270 (C-O), 1241 (C-N), 1197 (C-C): EI-MS m/z: 300 (M^+, 3), 270 (51), 224 (12), 151 (65), 120 (8), 105 (10), 92 (10), 76 (100), 51 (19): ^{1}HNMR (300 MHz, CDCl3): 8.34 (d, 3H, *J*=9), 8.02 (d, 2H, *J*=9), 7.81 (s, 2H), 7.59 (m, 1H), 3.9 (s, 3H).

3.2.5. Methyl 2-[(trifluoroacetyl) amino] benzoate (17)

A mixture of methyl anthranilate (1.0 g, 0.00653 mol) and triflouroacetic acid in a capped tube was put in to a Teflon cylinder container and microwave irradiated at three stages (20sec. each) for 60sec. After been cooled to room temperature, to the resulting mixture was added ice-cold water to precipitate the product which was then filtered, washed with cold water, dried and recrystallized from ethanol Yield: 97 %; m. p. 157 °C; IR (KBr) υ_{max} cm^{-1}: 3234 (N-H), 3011 (C-H), 1675 (C=O), 1567 (C=O), 1542 (C=C), 1296 (C-N, C=N), 1233 (C-C): EI-MS m/z: 247 (M^+, 51), 150 (60), 119 (98), 105 (100), 92 (44), 76 (5), 65 (20), 51 (3): ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 11.9 (s, b, 1H), 8.7 (d, 1H, *J*=8), 8.22 (d, 1H, *J*=8), 7.16 (t, 2H, *J*=8), 3.94 (s, 3H, CH_3).

3.2.6. Methyl 2-{[(2*Z*)-3-phenylprop-2-enoyl] amino} benzoate (18)

Methyl anthranilate (3.2 g, 0.021 mol) and cinnamoyl chloride (3.108 g., 0.021 mol) were stirrred for 30 min at room temperature. The reaction mixture was then poured into cold water. The precipitate formed was filtered, washed with cold water and recystallized from ethanol. Yield: 90 %, m.p.84-86 °C: IR (KBr) υ_{max} cm^{-1}: 3220 (N-H), 1678 (C=O), 1608 (C=O), 1515 (C=C, Conju.), 1259 (C-O,C-N), 1178 (C-C); EI-MS m/z: 281 (M^+, 39), 251 (19), 223 (27), 151 (69), 132 (43), 130 (31), 119 (100), 116 (85), 104 (45), 94 (37), 92 (34), 65 (21), 51 (4): ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 8.60 (d, 1H, *J*=6.7), 7.83 (t, 1H, *J*=6.5), 7.54-7.49 (m, 3H), 7.3-6.9 (m, 2H), 6.7 (d, 1H, *J*=12.87), 5.86 (b, s, 1H, -NH), 5.8-5.57 (d, 1H, *J*=14), 3.98 (s, 3H, CH_3).

3.3. Syntheis of 2 -alkyl 3-aminoquinazolin-4(3*H*)-ones (19-21)

3.3.1. 3-Amino-2-methylquinazolin-4(3*H*)-one (19)

Methyl N-acetyl anthranilate (2 g., 0.01mol) and hydrazine hydrate 80 % (10 mL) were boiled under reflux for 2 h., after completion of the reaction as indicated by TLC, the reaction mixture was then allowed to cool to room temperature and was poured in to ice cold water, the product precipitated on stirring was filtered, washed with saturated $NaHCO_3$ solution followed distilled water, dried and re crystallized from water to give the target compound. Yield: 91 %, m.p.143 °C; IR (KBr) υ_{max} cm^{-1}: 3297 (NH), 2954 (C-H), 1721 (C=O), 1590 (C=N), 1563 (C=C), 1225 (C-O,C-N), 1193 (C-C); EI-MS m/z: 175 (M^+, 100), 145 (82), 120 (5), 117 (12), 90 (11), 76 (25), 65 (3), 51 (15). ^{1}H-NMR (300MHz, $CDCl_3$), δ; 8.08 (d, 1H, *J*=8), 7.76 (t, 1H, *J*=10), 7.58 (d, 1H, *J*=10), 7.46 (t, 1H, *J*=10), 5.79 (s, 2H), 2.56 (s, 3H).

3.3.2. 3-Amino-2-(hydrazinomethyl) quinazolin-4(3*H*)-one (20)

Methyl 2-[(chloroacetyl) amino] benzoate = 1 g., 0.0044 mol.

Hydrazine hydrate 80 % = 5 mL.

Ethanol =10 mL.

Reflux time = 2 h.

Yield: 79 %, m. p. 136-138 °C: IR (KBr) υ_{max} cm^{-1}: 3525 (N-H), 3010 (N-H), 1645 (C=O), 1532 (C=N), 1471 (C=C), 1251 (C-N, C-O), 1196 (C-C); FAB-MS (-ve, +ve); m/z: 204, 206. EI-MS m/z: 205 (3), 175 (68), 165 (6), 149 (19), 123 (13), 109 (25), 97 (43), 85 (68), 83 (100), 71 (54), 57 (85), 52 (52). ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 8.26 (d, 1H, *J*=9), 7.73 (t, 1H, *J*=9), 7.63 (d, 1H, *J*=9), 7.48 (t, 1H, *J*=9), 4.8 (b, s, 5H, NH), 3.47 (s, 2H, CH_2)

3.3.3. 3-Amino-2-(trifluoromethyl) quinazolin-4(3*H*)-one (21)

Methyl 2-[(trifluoroacetyl) amino] benzoate = 2 g, 0.008 mol.

Hydrazine hydrate 80 % = 10 mL.

Ethanol =10 mL.

Reflux time =2 h.

Yield: 94 %, m. p. 134 °C: IR (KBr) υ_{max} cm^{-1}: 3208 (N-H), 1665 (C=O), 1601 (C=N), 1530 (C=C), 1251 (C-N, C-O), 1188 (C-C); EI-MS m/z: 229 (100), 124 (3), 200 (53),

180 (13), 130 (26), 120 (6), 90 (5), 77 (3). ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 8.32 (d, 1H, *J*=9), 7.85 (t, 2H, *J*=8), 7.65 (m, 1H), 4.89 (s, b, 2H)

3.4. Syntheis of 2-aryl- 3-amino quinazolin-4(3*H*)-ones (22-31)

Method A: Synthesis from 2-Aryl-4H-3, 1-benzoxazine-4-ones

A mixture of 2-aryl-4H-3, 1-benzoxazine-4-one and hydrazine mono haydrate (80 %) in benzene was refluxed for 2-5 h. After completion of the reaction as indicated by TLC, the product precipitated upon cooling and was further digested with dilute HCl solution for 1 h., and was then cooled to room temperature. The precipitate formed was filtered, washed with water and recrystallized from ethanol to give the target compound.

Method B: Direct one-pot synthesis starting from substituted benzoic acids

Substituted benzoic acid and excess of thionyl chloride containing few drops of DMF as catalyst were refluxed for 2 h under argon atmosphere. The reaction mixture was cooled to room temperature and was then added portion- wise to a vigorously stirred solution on anthranilic acid in dry pyridine at 0 °C. The stirring was further continued for 1-2 h at room temperature. Hydrazine hydrate (80 %, 5-10 mL) was added to the same mixture and refluxed for 3-7 h. After completion of the reaction, the reaction mixture was poured into ice cooled water containing few drops of HCl. The product precipitated was filtered, washed with water, dried and recrystallized from suitable solvent to get the target compounds (**22-31**).

3.4.1. 3-Amino-2-phenylquinazolin-4(3*H*)-one (22)

Yield: 86 %, m.p: 236-238 °C; IR (KBr) $\upsilon_{max:}$ 3207 (N-H), 1768 (C=O), 1602 (C=N), 1484 (C=C), 1245 (C-O, C-C); EI-MS m/z: 237 (100), 236 (34), 222 (26), 221(12), 208 (59), 180 (18), 179 (7), 152 (7), 119 (37), 105 (10), 103(8), 77 (28), 63 (5), 50 (14). ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 8.35 (d, 1H, *J*=8), 7.82 (m, 4H), 7.56 (m, 4H), 4.43 (s, 2H)

3.4.2. 3-Amino-2-(4-methylphenyl) quinazolin-4(3*H*)-one (23)

Yield: 85 %. m.p.165 °C; IR (KBr) $\upsilon_{maxs:}$ 3308 (N-H), 1665 (C=O), 1530 (C=N), 1251 (C-O, C-N), 769, 695, 660 (arom, C-H, bend); EI-MS m/z: 251 (M^+, 4), 138 (100), 222 (2), 200 (5), 146 (19), 120 (96), 91 (38), 82 (10), 65 (18), ^{1}H-NMR (300 MHz, $CDCl_3$), δ; 8.35 (d,1H, *J*=8), 7.93 (d, 2H, *J*=8), 7.64 (m, 3H), 7.45 (d, 1H, *J*=8), 7.15 (q, 1H, *J*=8), 4.08 (s, 2H), 2.348(s, 3H, CH_3)

3.4.3. 3-Amino-2-(4-nitrophenyl) quinazolin-4(3*H*)-one (24)

Yield: 91 %, m.p.202 °C: IR (KBr) υ_{max}: 3207 (NH), 3040 (CH), 1635 (C=O), 1529 (C=N), 1345 (C-H, bend), 1296 (C-O), 1233 (C=C), 840 (C-H, arom. Bend), 709 (C-H, bend), 671 (C-H, bend, arom.): EI-MS m/z: 282 (M^+, 81), 180 (30), 253 (40), 236 (44), 207 (43), 179 (19), 177 (27), 105 (10), 92 (10), 90 (26), 76 (100), 65 (13), 51 (19). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.34 (d, 3H, *J*=9), 8.02 (d, 2H, *J*=9), 7.81 (s, 2H), 7.59 (m, 1H), 4.89 (b, s, 2H, N-H):

3.4.4. 3-Amino-2-(4-chlorophenyl) quinazolin-4(3*H*)-one (25)

Yield: 90 %, m.p.189-190 °C; IR (KBr) υ_{max}: 3212 (N-H), 1769 (C=O), 1660 (C=N, C=C), 1245 (C-O, C-N), 1172 (C-C), 768 (C-Cl); EIMS m/z: 273 (M^{+2}, 50), 272 (53), 271 ($M.^+$, 100), 270 (86), 257 (4), 255 (13), 243 (100), 242 (61), 214 (4), 213 (5), 202 (24), 178 (73), 90 (3), 77 (5), 76 (8), 50 (4); ^{1}HNMR (300 MHz, $CDCl_3$), *δ*: 8.30 (d, 1H, *J*=6), 7.79-7.77 (m, 4H), 7.57-7.44 (m, 3H), 5.05(b, s, 2H).

3.4.5. 3-Amino-2-(4-bromophenyl) quinazolin-4(3*H*)-one (26)

Yield: 78 %, m.p.170-172 °C; IR (KBr) υ_{max}: 3175 (N-H), 1750 (C=O), 1602 (C=N), 1546 (C=C), 1245 (C-N, C-O), 1189 (C-C), 756 (C-Br); EI-MS m/z: 317 (M^{+2}, 15.26), 316 (63), 315 (14.97), 304 (97), 302(94), 288 (46), 286 (40), 207 (44), 183 (16), 179 (27), 178 (20), 155 (13), 120 (21), 119 (55), 102 (39), 90 (34), 76 (100), 81 (18), 79 (8), 51 (42); ^{1}H-NMR (300MHz,$CDCl_3$) δ; 8.83 (d, 1H, *J*=8), 7.93-7.87 (q, 2H, $J_{1,2}$=8, $J_{3,4}$=8, $J_{1,3}$=1.6, $J_{2,4}$=1.6), 7.64-7.43 (m, 3H), 7.15-7.1 (q, 1H, $J_{1,3}$=14, $J_{2,4}$=14, $J_{1,2}$=8), 4.08 (s, b, 2H, N-H)

3.4.6. 3-Amino-2-(3, 5-dinitrophenyl) quinazolin-4(3*H*)-one (27)

Yield: 72 %, m. p. 225-226 °C; IR (KBr) υ_{max}: 3183 (N-H), 1666 (C=O), 1245 (C-O, C-N), 1172 (C-C), 768 (C-Cl): EI-MS m/z: 327 (M^+, 82), 312 (91), 299 (71), 168 (7), 105 (100), 74 (4), 76 (12), 51 (19): ^{1}HNMR (300 MHz, $CDCl_3$), *δ*: 9.4 (S, 1H), 8.91 (S, 2H), 8.41 (d, 1H, *J*=8), 8.02 (t, 1h, *J*=8), 7.63 (d, 1H, *J*=9,4), 7.51(t, 1H, *J*=8), 5.13 (s, 2H, NH_2)

3.4.7. 3-Amino-2-pyridin-3-ylquinazolin-4(3*H*)-one (28)

Yield: 72 %, m.p. 207 °C; IR (KBr) υ_{max}: 3218 (N-H), 1718 (C=O), 1645 (C=N, C=C), 1303 (C-O, C-N), 1249 (C-C), 780, 752, (C-H, Aroma.Bend) EI-MS m/z: 238 (M^+, 19), 223 (18), 222 (91), 209 (27), 146 (43), 120 (19), 105 (100), 102 (39), 90 (34), 79 (83), 76

(100), 81 (18), 51 (42): ^{1}H-NMR (300 MHz, $CDCl_3$): 9.4 (s, 1H, Ar-H), 8.9 (d, 1H, *J*=14.5), 8.53 (d, 1H, *J*=14), 8.27 (d, 1H, *J*=9), 7.81-7.78 (m, 3H), 7.71 (t, 1H, *J*=14.5), 7.56 (m, 1H), 5.06 (b ,s, 1H).

3.4.10. 3-Amino-2-(3-iodophenyl) quinazolin-4(3*H*)-one (29)

2-(3-Iodophenyl)-4H-3,1-benzoxazin-4-one (2 g), hydrazine hydrate (80 % , 5 mL) and benzene (15 mL). Yield: 58 %, m.p. 150 °C: IR (KBr) υ_{max}: 3251 (NH), 1786 (C=O), 1602 (C=N), 1401 (CH_2, bend. Arom.), 1315 (CH_2, bend), 1245 (C-O, bend), 837, 768, 675 (C-H, bend., arom.): EI-MS m/z: 363 (M^+, 13), 347 (100), 334 (19), 221 (5), 206 (43), 204 (79), 146 (27), 132 (5), 120 (19), 105 (100), 92 (73), 76 (57), 54 (3); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.3 (d, 1H, *J*=7.6), 8.27 (s, 1H), 8.10 (t, 1H, *J*=14.5), 7.8 (d, 1H, *J*=8.5), 7.75 (m, 2H), 7.58 (t, 1H, *J*=8), 7.4 (t, 1H, *J*=15), 4.89 (b, s, 2H, NH_2).

3.4.11. 3-Amino-2-(3-bromophenyl) quinazolin-4(3*H*)-one (30)

Yield: 71 %, m.p. 140 °C: IR (KBr) υ_{max}: 3240 (NH), 1676 (C=O), 1484 (C=N), 1401 (C-H, bend), 1245 (C-O), 1172 (C-C), 1076 (C-H, bend), 768 (C-Br), 675 (C-H, bend, arom.): EI-MS m/z: 317 (M^{+2}, 99), 316 (63), 315 (92), 314 (49), 301(6), 299 (4), 288 (46), 287 (46), 286 (40), 285 (40), 236 (12), 207 (44), 185 (5), 183 (16), 182 (4), 180 (10), 179 (27), 178 (19), 177 (8), 157 (8), 155 (13),152 (7), 150 (14), 120 (21), 119 (55), 118 (22), 105 (12), 103 (15), 102 (39), 97 (8), 91 (11), 81 (18), 77 (49), 76 (100), 71 (11), 63 (25), 56 (29), 51 (42); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.23 (d, 1H, *J*=9), 8.10 (d, 1H, *J* =8), 7.96 (t, 1H, *J*=8.5), 7.64 (d, 1H, *J*=9), 7.56 (t, 1H, $J_{1,2}$=8), 7.48 (d,1H, *J*=8.5), 7.39 (t,1H, *J*=9.3), 4.08 (s, b, 2H, N-H)

3.4.12. 3-Amino-2-(2-bromophenyl) quinazolin-4(3*H*)-one (31)

Yield: 66.7 %, m. p. 148 °C: IR (KBr) υ_{max}: 3241 (N-H), 1654(C=O), 1602 (C=N), 1546 (C=C), 1245 (C-N,C-O), 1189 (C-C), 782 (C-Br): EI-MS m/z: 317 (M^{+2}, 99), 316 (63), 315 (92), 314 (49), 301 (6), 299 (4), 288 (46), 287 (46), 286 (40), 285 (40), 236 (12), 207 (44), 185 (5), 183 (16), 182 (4), 180 (10), 179 (27), 178 (19), 177 (8), 157 (8), 155 (13), 152 (7), 150 (14), 120 (21), 119 (55),118 (22), 105 (12), 103 (15), 102 (39), 97 (8), 91 (11), 81 (18), 77 (49), 76 (100), 71 (11), 63 (25), 56 (29), 51 (42): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.87 (d, 1H, *J*=9.3), 8.53 (d, 1H, *J*=9.5), 8.31 (t, 1H, *J* =8.7), 8.27 (d, 1H, *J*=9), 7.81 (d,1H, *J*=8.7), 7.78-7.71 (m, 2H), 7.51 (t, 1H, *J*=9), 4.52 (s, b, 2H, N-H).

3.4.8. 3-Aminoquinazolin-4(3*H*)-one (32)

A mixture of anthranilic acid (1.2 m mol), triethylorthoformate (2.0 m mol), hydrazine hydrate (2.0 m mol) and *para*-toluene sulfonic acid (5.0 m mol) was stirred at room temperature for 30 min. After completion of the reaction as indicated by TLC, the reaction mixture was poured into water followed by extracting with dichloromethane (3x10 ml). The combined organic layer was washed with saturated $NaHCO_3$ solution, dried over anhydrous $NaSO_4$. Dichloromethane was evaporated under vacuum at 500 m.bar (room temperature). The solid left was dried and recrystallized from water- ethanol mixture. Yield 94 %, m.p. 145-147 °C; IR (KBr) υ_{max}: 3293 (N-H), 2924 (=C-H), 2854 (=C-H), 1667 (C=O), 11529 (C=C), 1247 (C-C), 1168 (C-C), 770, 694, 627(Arom, =C-H, bend); EI-MS m/z: 161 (M+,74), 132 (100), 105 (11), 104 (15), 90 (9), 77 (31), 76 (22), 64 (7), 63 (8), 51 (10): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.7 (s,1H), 8.3 (d, 1H, *J*=8), 7.78-7.71 (m, 2H), 7.51 (t, 1H, *J*=8), 4.88 (s, b, 2H) .

3.4.9. 3-Amino-2-[(*E*)-2-phenylvinyl] quinazolin-4(3*H*)-one (33)

Methyl 2-{[(2*Z*)-3-phenylprop-2-enoyl] amino} benzoate (2.25 g., 0.007998) and hydrazine monohydrate (5 ml.), in absolute ethanol (10 mL) were refluxed for 2 h. After completion of the reaction, the miture was poured into ice cold water and was stirred for few minutes. The product precipitated was filterd, dried and recrystallized from ethanol. Yield: 82 %, m. p. 152-154 °C: IR (KBr) υ_{max}: 3297 (NH), 1608 (C=O), 1515 (C=N), 1435 (CH_2, bend), 1259 (C-O), 1178 (C-C), 975 (C-H, arom. bend), 750 (C-H, bend), 698 (C-H, arom.bend): FAB-MS (+ve, -ve) m/z: 264, 262: EI-MS m/z: 263 (21, M^+), 261 (37), 247 (59), 246 (17), 184 (43), 171 (18), 169 (31), 166 (38), 159 (37), 145 (100), 120 (71), 105 (77), 91 (32), 77 (69), 65 (13): ^{1}H-NMR (300 MHz, CDCl3): δ 8.42 (d,1H, *J*=8.28), 8.05 (d, 1H, *J*=6.99), 7.75-7.71 (m, 2H), 7.61 (d, 1H, *J*=13), 7.59 (d, d, 1H, *J*=7.7), 7.53-7.50 (m, 2H), 7.29 (d, 2H, *J*=7.9), 5.63 (d, 1H, *J*=13), 4.54 (s, 2H, NH_2).

3.5. The Synthesis of Novel 3-N-Substituted Quinazolin-4(3*H*)-ones (34-36) from 2-Phenyl -4*H*-3,1- Benzoxazin -4-one

3.5.1. 2-Aminobenzoyl-N-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) benzamide (34).

To the hot stirred solution of 2-phenyl-4*H*-3, 1-benzoxazin-4-one (3.76 g, 28.8 m mole) in 30 mL dry benzene was added 2 mL of hydrazine hydrate monohydrate (98 %). The mixture was refluxed for 30 minutes; a white precipitated appeared on cooling was

filtered, washed with n-hexane followed by distilled water and recrystallized from ethanol. Yield: 85 %, m. p. 164-166 °C; IR (KBr) $\upsilon_{max\ (cm^{-1})}$: 3318 (N-H), 2952 (C-H), 1662 (C=O), 1599 (C=O), 1528 (C=N), 1492 (C=C-C), 1302 (C-N), 1255 (C-C=C), 757, 701, 996 (Arom. -C=C-C, bend.): FAB-MS (+ve, -ve); (461, 459): EI-MS m/z: 460 (M^+,2), 295 (3), 267 (5), 224 (100), 146 (25), 120 (13), 105 (100), 77 (79), ^{1}H-NMR (300 MHz, CDCl3): δ 11.8 (s, 2H, NH), 8.83 (d, 2H, *J*=8.4, Ar-H), 8.08 (3H, d, d, *J*=7.6, *J*=8.06), 7.58-7.498 (m, 9H, Ar-H), 7.45 (m, 2H, Ar-H), 7.139 (t, 2H, *J*=7.737).

3.5.2. 2-Aminobenzoyle-N-[3-(4-oxo-2-phenylquinazolin-3(4H)-yl) propyl]benzamide (35)

This compound was prepared from 2-phenyl-4*H*-3,1-benzoxazin-4-one (3.76 g, 28.8 m.mole) in 30 ml dry benzene and 2 ml ethylendiamin using the method as described for compound **34.** Yield; 75 %, m. p. 237 °C; IR (KBr) υ_{max}: 3407 (N=C-OH), 3254 (N-H), 2925 (C-H), 1726 (C=O), 1599 (C=O, C=N), 1492 (-C=C, conjugated), 1328 (C-O), 1255 (C-C): EI-MS m/z: 488 (M^+, 26), 470 (7), 411 (1), 264 (3), 249 (54), 248 (99), 247 (100), 235 (9), 224 (84), 223 (59), 222 (39), 205 (11), 189 (3), 179 (3), 145 (5), 120 (13), 119 (18), 105 (45), 91 (6), 77 (26), 60 (6).^{1}H-NMR (300 MHz, $CDCl_3$): δ 12.19 (s, 2H, N-H), 8.72 (d, 2H, *J*=9), 8.02 (d, 2H, *J*=9), 7.99 (d, 4H, *J*=9), 7.557.45 (m, 8H), 6.89 (t, 2H, *J*=6), 4.57 (t, 2H, *J*=6), 3.73 (t, 2H, *J*=6).

3.5.3. 2-Aminobenzoyle-N-[2- (4-oxo-2-phenylquinazolin-3 (4H) -yl) ethyl] benzamide (36)

This compound was prepared from 2-phenyl-4*H*-3, 1-benzoxazin-4-one **2** (3.76 g, 28.8 m mol) in 30 mL dry benzene and 1,2-diaminopropane (2 mL) using the method as described for compound **44.** Yield: 81%, m.p. 90 °C; IR (KBr) υ_{max}: 3451 (N=C-OH), 3234 (N-H), 1662 (C=O), 1528 (C=O, conjugated), 1444 (-C=C, conjugated) 1255 (C-N, C-O), 1164 (C-C), 757, 706, 669 (=C-H, Arom. bend.): EI-MS m/z: 502 (M^+, 31), 425 (5), 397 (6), 263 (10), 262 (27), 254 (9), 249 (38), 236 (31), 235 (100), 224 (78), 223 (51), 120 (33), 119 (10), 105 (89), 77 (38), ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.8 (s, 2H, NH), 8.61 (d, 2*H*, J=7), 8.02 (d, 2H, *J*=9), 7.99 (d, 4H, *J*=9), 7.557.45 (m, 8H), 6.89 (t, 2H, *J*=6), 4.01(t, 2H, 5.3), 3.58 (t, 2H, J=6), 2.12 (m, 2H).

3.5.4. 3-[2-(4-Methylphenyl) quinazolin-3(4*H*)-yl] ethane-1-amine (37)

A mixture of 2-(4-methylphenyl)-4H-3, 1-benzoxazin-4-one (1.7 g, 0.007 mol) and excess of 1,3-diaminoethaneane (0.967 mL, 0.0143 mol) in dry toluene (15 mL) was refluxed with continuous stirring for 6 h. After completion of the reaction as indicated by TLC, the reaction mixture was allowed to cool to room temperature and was poured into water. The product precipitated was filtered, washed with hexane followed by water, dried and recrystallized from benzene. Yield 80 %, m. p. 190-192 °C; IR (KBr) υ_{max}: 3421 (NH), 2951 (C-H), 1687 (C=O), 1522 (C=N), 1446 (C=C, arom), 1359 (C-H, arom. Bend), 1257 (C-O, C-N), 1229 (C-C): EI-M S (m/z): 279 (M^+,14), 263 (12), 235 (16), 222 (31), 221 (51), 194 (11), 208 (26), 163 (3), 145 (100), 137 (5), 120 (32), 119 (72), 91 (62), 65 (19), 57 (26), 56 (23): ^{1}H -NMR (300 MHz, $CDCl_3$): δ 8.86 (d, 1H, *J*=8, ArH), 8.63 (d, 1H, *J*=6, Ar-H), 7.83-7.76 (m, 2H, Ar-H), 7.57-7.52 (t, 1H, *J*=7, Ar-H),7.31 (d, 2H, J=9, Ar-H), 7.18 (t,1H, *J*=7, Ar-H), 4.10 (t, 2H, *J*=6, CH_2), 3.52 (t, 2H, *J*=6), 2.49(s,3H, CH_3), 1.18(s, 2H, N-H).

3.5.5. 3-(3-Aminopropyl)-2-(4-methylphenyl) quinazolin-4(3*H*)-one (38)

A mixture of 2-(4-methylphenyl)-4*H*-3, 1-benzoxazin-4-one (**4**) and 1,3diaminopropane (2 mL) in dry pyridine (15 mL) was refluxed with continuous stirring for 6 h. After completion of the reaction as indicated by TLC, the mixture was acidified with few drops of dilute HCl. The product precipitated out upon cooling was filtered, washed with hexane followed by water, dried over anhydrous sodiumsulfate and re crystallized from benzene.Yield 91 %, m. p. 238-239 °C; IR (KBr) υ_{max}: 3228 (N-H), 3005 (C-H), 1668 (C=O), 1504 (C=N), 1424 (C=C, conj.), 1311 (C-N), 1258 (C-C); EI-MS m/z: 293 (M^+,4), 267 (5), 238 (16), 202 (26), 163 (3), 137 (5), 120 (32), 119 (100), 91 (62), 65 (19), 57 (26), 56 (23); ^{1}H-NMR (300MHz, $CDCl_3$): δ 8.86 (d,1H, *J*=8), 8.63 (d,1H, *J*=6), 7.83-7.76 (m, 2H), 7.57-7.52 (t, 1H, *J*=7), 7.31 (d, 2H, *J*=9), 7.18 (t, 1H, *J*=7), 5.6 (t, 2H, NH), 3.33 (t, 2H, *J*=6), 2.72 (t, 2H, *J*=9), 2.34(s, 3H, CH_3), 1.79-1.61 (m, 2H).

3.5.6. 3-(3-Aminopropyl)-2-(4-bromophenyl) quinazolin-4(3*H*)-one (39)

This compound was prepared by refluxing 2-(4-bromophenyl)-4*H*-3, 1-benzoxazin-4-one and 1, 3- diaminopropane in boiling benzene with continuous stirring for 8 h. After completion of reaction as indicated by TLC, the reaction mixture was

allowed to cool bellow the room temperature. The product precipitated upon cooling was filtered, washed with hexane followed by water and dried over anhydrous sodiumsulfate and recrystallized from ethanol. Yield 76 %, m. p. 245-247 °C; IR (KBr) υ_{max}: 3250 (NH), 2880 (C-H), 1664 (C=O), 1534 (C=N), 1496 (C=C), 1304 (C-N), 1255 (C-C), 757 (C-Br); EI-MS m/z: 358 (M^{+2}, 3), 357 (M^{+}, 4), 333 (14), 331 (16), 303 (38), 301 (38), 288 (2), 223 (2), 184 (71), 183 (73), 156 (32), 154 (35), 148 (16), 145 (21), 120 (100), 119 (17), 105 (17), 92 (16), 77 (13), 76 (21), 57 (46), 56 (39): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.55 (d, 1H, *J*=8.37), 7.73-7.69 (m, 2H), 7.58 (d, 1H, *J*=7), 7.51(d, 1H, *J*=8.4), 7.466-7.349 (m, 2H), 7.031 (t, 1H, *J*=7.22), 3.321 (t, *J*=6, 2H), 3.225 (m, 2H), 2.77 (t, *J*=6.39, 2H), 1.1712-1.599 (m, 2H)

3.5.7. 3-(2-Aminoethyl)-2-(3-chlorophenyl) quinazolin-4(3*H*)-one (40)

2-(4-Chlorophenyl)-4*H*-3,1-benzoxazin-4-one (2 g, 0.00778 mol) and slight excess of diaminoethane (0.86 g, 0.0143 mol) in dry pyridine (10 mL) were refluxed for 4 h. The prosuct precipitated out upon cooling was filtered washed with water and recrystallized from ethanol. Yield: 38 %, m.p. 80 °C; EI-MS m/z: 301 (M^{+2}, 21), 299 (M^{+}, 15), 285 (12), 283 (7), 257 (71), 255 (63), 145 (100), 132 (7), 120 (21), 105 (97), 91 (57), 65 (7), 113 (71), 111 (57), 101 (31), 99 (27), 65 (4): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.22 (d, 1H, *J*= 7.16), 7.71 (t, 1H, *J*=7.428), 7.592 (s, 1H), 7.529 (d, 1H, *J*=8), 7.429-7.391 (m, 2H), 7.347 (t,1H, *J*=7.52), 7.26 (s, 1H), 3.39 (t, 2H, *J*=6.3), 2.72 (t, 2H, *J*=6.9), 1.79 (s, 2H, NH_2)

3.6. Synthesis of 3-(2-Hydroxyethyl)-2-alkyl/arylquinazolin-4(3*H*)-ones(41-45)

3.6.1. 3-(2-Hydroxyethyl)-2-phenylquinazolin-4(3*H*)-one (41)

A mixture of 2-phenyl-4*H*-3, 1-benzoxazine-4-one **2** (2 g, 0.008968 mol) and monoethanolamine (2 mL, 0.032 mol) in dry benzene was refluxed with continuous stirring under argon atmosphere for 6h. After completion of reaction as indicated by TLC the reaction mixture was allowed to cool bellow room temperature where the product upon cooling was precipitated out was filtered, washed with n-hexane followed by water, dried and recrystallized from ethanol. Yield 85 %, m.p: 164-166 °C; IR (KBr) υ_{max}: 3344 (O-H), 2280 (C-H), 1664 (C=O), 1496 (C=C), 1427 (C=C, conjugated), 1255 (C-C); EI-MS m/z: 266 (M^{+}, 25), 254 (11), 249 (7), 235 (10), 224 (40), 223 (43), 222 (14), 190 (6), 189 (39), 180 (4), 179 (22), 167 (3), 149 (6), 146 (28), 120 (16), 111 (7), 106 (12), 105

(100), 97 (11), 85 (11), 83 (10), 77 (81), 71 (16), 57 (25), 55 (13), 51 (14), 44 (100), 43 (15), 40 (5); ^{1}H-NMR (300 MHz, CD_3OD) δ: 8.622 (d, 1H, *J*=8.25), 7.997 (d, 2H, *J*=8.19), 7.795 (d, 1H, *J*=7) 7.6-7.51 (m, 4H), 7.22-7.17 (t, 1H, *J*=8.14), 3.74-3.70 (t, 2H, *J*=5.7), 3.545-3.506 (t, 2H, *J*=5.7), 3.299 (s, 1H).

3.6.2. 3-(2-Hydroxyethyl)-2-(4-nitrophenyl) quinazolin-4(3*H*)-one (42)

2-(4-nitrophenyl)-4*H*-3, 1-benzoxazin-4-one = 2 g

Mono ethanolamine = 2 mL

Dry benzene = 10 mL

Reflux time = 3 h.

Yield: 87 %; m.p. 228 °C; IR (KBr) υ_{max}: 3450 (O-H), 2924 (C-H), 1676 (C=O), 1640 (C=N), 1582 (C=C), 1347 (C-N, C-O), 1256 (C-C), 853, 768, 698 (arom. =C-H, bend); EI-MS m/z: 311 (M^+, 23), 295 (53), 280 (35), 266 (100), 254 (7), 226 (29), 146 (12), 122 (6), 120 (44), 119 (13), 105 (5), 104 (41), 15 (15), 76 (19), 75 (7), 64 (5), 50 (4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, 1H, *J*=8.28), 8.305 (t, 2H, *J*=8.8), 8.1325 (t, 2H, 8.6), 7.632-7.495 (m, 3H), 3.724 (t, 2H, *J*=5), 3.53 (t, 2H, *J*=5.2), 3.31(b, s, 1H, OH)

3.6.3. 3-(2-Hydroxyethyl)-2-(4-methylphenyl) quinazolin-4(3*H*)-one (43)

2-(4-methylphenyl)-4*H*-3, 1-benzoxazin-4-one = 2g

Mono ethanolamine=2mL, Benzene (dry) = 10 ml

Yield:87 %; m. p.178-180 °C; IR (KBr) υ_{max}: 3471 (O-H), 2934 (C-H), 1603 (C=O), 1534 (C=N), 1449 (C=C, conj.), 1304 (C-O), 1255 (C-C); EI-MS m/z: 280 (M^+,14), 264 (23), 249 (55), 235 (100), 222 (29), 195 (7), 146 (19), 105 (100), 92 (29), 76 (7), 64 (5), 50 (4): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.3 (d, 1H, *J*=8.2), 8.15 (d, 2H, *J*=8), 7.8 (t, 1H, *J*=8.6), 7.52-7.48 (m, 2H), 7.27 (d, 2H, *J*=8), 3.7 (t, 2H, *J*=5), 3.55 (t, 2H, *J*=5.5), 2.49 (b, s, 1H), 2.32 (s, 3H, CH_3) .

3.6.4. 3-(2-Hydroxyethyl) quinazolin-4(3*H*)-one (44)

A mixture of anthranilic acid (1.2 m mol), triethylorthoformate (2.0 m mol), monoethanolamine (2.0 m mol) and *pera*-toluene sulfonic acid (5 m mol) was stirred at room temperature under argon atmosphere for 1.5 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into 5 %, aq.$NaHCO_3$ and the product precipated was filtered. A second crop of the product was collected from the filtrate by extracting with dichloromethane. The product obtained was dried and recrystalized from

ethanol. Yield: 89 %; IR (KBr) υ_{max}: 3250 (N-H), 2825 (C-H), 1675 (C=O), 1589 (C=C), 1450 (C=C), 1275 (C-O), 1250 (C-C); EI-MS m/z: 190 (22), 171 (4), 160 (10), 159 (12), 147 (100), 146 (690, 145 (12), 130 (46), 129 (32), 119 (10), 105 (2), 102 (17), 92 (4), 77 (27), 76 (15), 51 (6): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.18 (d, 1H, *J*=8.04), 8.05 (s, 1H), 7.72-7.67 (t, 1H, *J*=8.4), 7.615 (d, 1H, *J*=7.8), 7.452-7.398 (t, 1H, *J*=8.16), 4.1506-4.1184 (t, 2H, *J*=4.8), 3.99-3.975 (t, 2H, 4.5), 2.978 (b, s, 1H).

3.6.5. 3-(2-Hydroxyethyl)-2-methylquinazolin-4(3*H*)-one (45)

Anthranilic acid =1.2 mmol.

Triethylorthoacetate =2 mmol.

Monoethanolamine =2mmol

Para-Toluene sulfonic acid = 5 mmol

Reaction time = 1h.

Yield: 89 %; IR (KBr) υ_{max}: 3250 (O-H), 1664 (C=O), 1534 (C=N, C=C), 1449 (C=C, conj.), 1304 (C-O), 1255 (C-C), 757, 700, 664 (arom. =C-H, bend); EI-MS m/z: 204 (M^+,28), 185 (9), 173 (13), 161 (59), 169 (100), 159 (7), 146 (5), 145 (10), 143 (13), 119 (7), 118 (7), 116 (9), 92 (2), 90 (5), 77 (13), 76 (8), 50 (3); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.190 (d, 1H, *J*=8), 7.38-7.682 (t, 1H, *J*=7.9), 7.631 (d, 1H, *J*=7.3), 7.446-7.396 (t, 1H, *J*=7.7), 4.316-4.282 (t, 2H, *J*=5.07), 4.026-3.992 (t, 2H, *J*=5.26), 3.22 (b, s, 1H), 2.72 (s, 3H).

3.7. Synthesis of 2, 3-disubstituted quinazolinone (46-62)

3.7.1. 2-Methyl-3-(4-methylphenyl) quinazolin-4(3*H*)-one (46)

A mixture of methyl-N-acetylanthranilate (2 g) and 4-methylaniline was boiled under reflux for 10 h. in absolute ethanol. After completion of reaction as indicated by TLC, ethanol was evaporated under reduced pressure and the mixture was allowed to cooled by adding ice cooled water the precipitate formed upon cooling was filtered, dried and recrystallized from ethanol. Yield 67 %, m.p. 197-199 °C; IR (KBr) υ_{max}: 2935 (C-H), 1664 (C=O), 1534 (C=N), 1449 (C=C, conjugated), 1204 (C-C); EI-MS m/z: 250 (M^+,5), 235 (34), 222 (19), 210 (2), 179 (10), 145 (18), 105 (64), 105 (100), 92 (19), 77 (67), 65 (13), 51 (12); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.27 (d, 1H, *J*=9), 8.02 (t, 1H, J=8), 7.69-7.59 (m, 2H), 7.21 (d, 2H, J=9), 7.024 (d, 2H, J=8.7), 2.53(s,3H, CH_3), 2.34 (s, 3H, CH_3).

3.7.2. 2-Methyl-3-(2-methylphenyl) quinazolin-4(3*H*)-one (47)

A mixtrure of anthranilic acid, triethylorthoacteate, *ortho*-toluidine and *para*-toluenesulfonic acid was stirred under argon atmosphere for 2 h. After completion of the reaction, the mixture was poured into ice-cold water. The product pricipated was filtered; wahed with $NaHCO_3$ solution. A second crop of the product was obtained by extracting the aqueous layer with dichoromethane. After evaporation of dichoromethane under reduced pressure both the solids were combined, dried and recrystallized from ethanol. Yield: 94.6 %, m.p. 200-202 °C; IR (KBr) υ_{max} (cm^{-1}): 1662 (C=O, str), 1523(C=N, str), 1388(C=C-C, str), 1199(C-O, str), 1154(C-C, str). 886, 852, 679 (C-H, bend, arom):EI-MS m/z: 250 (M^+, 28), 235 (53), 159 (100), 146 (13), 145 (92), 105 (78), 92 (34), 77 (51), 76 (15), 65 (5), 54 (3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.36 (d, 1H, *J*=8.2), 7.96 (d, 1H, *J*=8), 7.83 (t,1H, *J*=8.2), 7.76 (t,1H, *J*=7.9), 7.63 (t,1H, *J*=8), 7.48 (d, 1H, *J*=8.5), 7.35 (t, 1H, *J*=7.69), 7.31 (d, 1H, *J*=8.03), 2.25 (s, 3H, CH_3), 2.23 (s, 3H, Ar-CH_3).

3.7.3. 3-Mesityl-2-methylquinazolin-4(3*H*)-one (48)

This compound was prepared from trimethylaniline, anthranilic acid, triethylortho acetate and *para*-toluene sulphonic acid as decribed for compound **47**.

Yield: 96.1 %, m.p. 99-100 °C; IR (KBr) υ_{max} cm^{-1}: 1616 (C=O, str), 1532 (C=N, str), 1488 (C=C, str), 1388 (C=C-C, str), 1192 (C-O, str), 1125 (C-C, str), 848, 805, 677 (C-H, bend, arom):EI-MS m/z: 278 (M^+, 43), 277 (28), 263 (79), 159 (92), 145 (100), 120 (97), 118 (12), 105 (71), 92 (11), 91 (13), 76 (28), 65 (5), 54 (3); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.57 (d, 1H, *J*=8), 7.97 (d, 1H, *J*=8), 7.85 (t,1H, *J*=7.6), 7.63 (t, 1H, *J*=8.2), 6.93 (s, H, Ar-H), 2.51(s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.11 (s, 6H, Ar-CH_3).

3.7.4. 3-(4-Bromophenyl)-2-phenylquinazolin-4(3*H*)-one (49)

A mixture of compound 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one (1 g, 0.00448 mol) and 4-bromoaniline (0.78 g, 0.00448 mol) in dry pyridine (10mL) was refluxed for 6h with continuous stirring. After reaction completion the reaction mixture was allowed to cool to room temperature and acidified with dilute HCl. The solid precipitated was filtered, washed with water, dried and recrystallized from ethanol. Yield.41%, m. p. 228-230 °C; IR (KBr) υ_{max} cm^{-1}: 3066 (=C-H), 1603 (C=O), 1492 (C=C, conjugated), 1258 (C-C), 757 (C-Br); EI-MS m/z: 379 (M^{+2}, 14), 377 (M^+, 10), 301 (81), 221 (100), 208 (47), 180 (3), 157 (27), 105 (100), 92 (6), 77 (34), 65 (37), 57 (3): ^{1}H-NMR (300 MHz,

$CDCl_3$) δ: 8.40 (d, 2H, *J*=8.2), 8.01 (d, 1H, *J*=13), 7.93-7.79 (m, 2H), 7.65(t, 1H, *J*=8), 7,58 (t, 1H, *J*=8.7), 7.49-7.40 (m, 6H).

3.7.5. 3-Mesityl-2-phenylquinazolin-4(3*H*)-one (50)

A mixture of 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one **2** (1 g, 0.00448 mol) and 2, 4, 6-trimethylaniline (0.6 g, 0.00448 mol) in 10 mL dry benzene was refluxed for 8h with magnetic stirring. After completion of reaction, the reaction mixture was allowed to cool below room temperature. The solid precipitated out upon cooling was filtered, washed with hexane, dried and recrystallized from ethanol.Yield.73 %, m. p. 210-213 °C; IR (KBr) υ_{max} cm^{-1}: 2934 (C-H), 1641 (C=O), 1496 (C=C), 1255 (C-C); EI-MS m/z: 340 (M^+, 12), 254 (10), 222 (60), 146 (5), 135 (100), 120 (18), 105 (58), 92 (5), 76 (20), 65 (4); ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.7 (d, 1H, *J*=8), 8.02 (d, 2H, *J*=8), 7.95 (t, 1H, *J*=8), 7.63-7.42 (m, 5H), 6.96 (s, 2H), 2.3 (s, 3H), 2.2 (s, 6H) .

3.7.6. 3-(4-Iodophenyl)-2-phenylquinazolin-4(3*H*)-one (51)

This was prepared from 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one **2** (1 g, 0.00448 mol) and 4-iodoaniline (1 g, 0.00448 mol) in 10 ml dry benzene by the method as described for compound **35.** Yield 88 %, m. p. 231-235 °C; IR (KBr) υ_{max} cm^{-1}: 1664 (C=O), 1603 (C=N), 1534 (C=C, conjugated), 1257 (C-C), 565 (C-I): EI-MS m/z: 424 (12), 348 (3), 297 (3), 222 (96), 209 (10), 181 (5), 146 (11), 120 (11), 105 (100), 92 (14), 77 (24), 65 (5), 51 (7); ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.4 (d, 1H, *J*=7.8), 7.98 (d, 2H, *J*=15), 7.85-7.81 (t, 1H, *J*=8), 7.6-7.54 (m, 4H), 7.5-7.45 (m, 3H), 7.3-7.28 (d, 2H, *J*=11.5).

3.7.7. 3-Benzyl-2-phenylquinazolin-4(3*H*)-one (52)

This was prepared from 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one **2** (1 g, 0.00448 mol) and freshly distilled benzyl amine (0.015 mL, 0.00896 mol) in dry benzene (10 mL) by the method as described for compound **35.** Yield 89 %, m. p.155-157 °C; IR (KBr) υ_{max} cm^{-1}: 2929 (C-H), 1668 (C=O), 1519 (C=C, conjugated), 1305 (C=C-C); FAB-MS (-ve), 311, EI-MS m/z: 312 (M^+,), 252 (4), 223 (49), 195 (10), 139 (10), 120 (60), 105 (100), 92 (32); ^{1}H-NMR (300 MHz,$CDCl_3$):δ 8.82 (d, 1H, *J*=8), 8.042 (d, 2H, *J*=8), 7.53-7.47 (m, 5H), 7.35-7.31 (m, 5H), 7.09 (t, 1H, *J*=8), 4.63 (s, 2H, CH_2).

3.7.8. 3-(4-Methylphenyl)-2-phenylquinazolin-4(3*H*)-one (53)

This compound was prepared from 2-phenyl-4(*H*)-3, 1-benzoxazine-4-one **2** (1g, 0.00448 mol) and 4-methylaniline (0.015 mL, 0.00896 mol) in dry benzene (10 mL) by the method as described for compound **35.** Yield 73 %, m. p.186-188 °C; IR (KBr) υ_{max} cm^{-1} cm^{-1}: 2982 (C-H), 1664 (C=O), 1512 (C=C), 1448 (C=C-C), 1232 (C-C); EI-MS m/z: 312 (M^+, 3), 222 (18), 210 (4), 179 (8), 145 (18), 120 (36), 105 (100), 92 (19), 77 (73), 51 (13): ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.70 (d, 1H, *J*=8), 8.02 (d, 2H, *J*= 8), 7.57-7.45 (m, 6H), 7.21- 7.02 (m, 4H), 2.34 (s, 3H, CH_3).

3.7.8.3-Phenyl-2-(trifluoromethyl) quinazolin-4(3*H*)-one (54)

A mixture of methyl 2-[(trifluoroacetyl) amino] benzoate (1 g, 4.048 m mol) and freshly distilled aniline (0.5 g, 5.376 m mol) was refluxed in absolute ethanol (10 mL) for 3h. After completion of the reaction, ethanol was evaporated under reduced pressure and the the remaining mixture was poured into ice-cold water. The solid precipitated was filterd, washed with water and recystallized from ethanol. Yield: 91 %, m.p. 135 °C; EI-MS m/z: 290 (M^+,61), 221 (31), 213 (49), 200 (31), 196 (4), 172 (27), 145 (100), 132 (12), 120 (19), 105 (81), 77 (8), 76 (11), 65 (7), 54 (5): ^{1}HNMR (300MHz, $CDCl_3$) δ: 8.31(d,1H, *J*=7.7), 8.01-7.953 (m,3H), 7.82 (d, 4H, *J*=8), 7.61-7.53 (m,1H).

3.7.9. 3-[4-(Diethylamino) phenyl]-2-(4-nitrophenyl) quinazolin-4(3*H*)-one (55)

A mixture of 2-(4-nitrophenyl)-4H-3, 1-benzoxazine-4-one (0.25 g, 0.001016 mol) and 4-N,N-diethylamino aniline in slight excess(0.5ml) was refluxed in dry pyridine for 5 h. After completion, the reaction mixture was poured into ice-cold water containing few drops of HCl. Precipitate formed was filterted, dried and recrystallized from ethanol. Yield: 81 %, m. p. 235-237 °C: IR (KBr) υ_{max} cm^{-1}: 2927 (C-H), 1666 (C=O), 1601 (C-N, C=C), 1468 (C=C-C), 1442 (N=O), 1378 (N=O); EI-MS m/z: 414 (M^+,17), 398 (100), 370 (8), 297 (4), 250 (8), 218 (11), 205 (10), 164 (10), 119 (8), 91 (8), 76 (14), 55 (7); ^{1}HNMR(300MHz, $CDCl_3$): δ 8.39 (d, 2H, *J*=8), 8.32-8.02 (m, 3H), 7.59-7.51(m, 3H), 7.30 (d, 2H, *J*=8.76), 7.10 (d, 2H, *J*=9), 3.33-3.27 (q, 4H, *J*=5.7), 1.29 (t, 6H, *J*=5.9).

3.7.8. 2-Phenyl-3-prop-2-yn-1-ylquinazolin-4(3*H*)-one (56)

A mixture of 2-phenyl-4H-3, 1-benzoxazine-4-one **2** (0.05 g, 0.000228 mol) and propargyl amine (0.01 ml, 0.008 mol) was refluxed in dry benzene for 8 h. After completion of reaction the reaction mixture was cooled, benzene was evaporated under

reduced pressure and the product was collected as white solid. Yield: 86 %, m.p. 173-175 °C; IR (KBr) υ_{max} cm^{-1}: 2120 (-CCH), 1599 (C=O), 1505 (C=C), 1435 (C=C-C); EI-MS m/z: 246 (M^+ , 2), 222 (10), 196 (9), 179 (145), 120 (5), 105 (100), 77 (71), 76 (52), 65 (5), 51 (12). ^{1}HNMR (300 MHz, $CDCl_3$): δ 8.83 (d, 1H, *J*=6), 8.03-8.01 (d, 2H, *J*=6), 7.57-7.47 (m, 5H), 7.13 (t, 1H, *J*=6), 4.25 (d, 2H, *J*=3), 2.29 (s, 1H).

3.7.9. *N*-{4-[2-(4-Methylphenyl)-4-oxoquinazolin-3(4*H*)-yl] phenyl} acetamide (57)

2-(4-Methylphenyl)-4H-3, 1-benzoxazin-4-one (0.05 g, 0.00021097 mol), para-aminoacetanilde (0.03 g, 0.00021097 mol) in 10ml dry pyridne was refluxed for 5 h. Yield: 83 %, m. p.179-180 °C: IR (KBr) υ_{max} cm^{-1}: 3313 (NH), 2924 (CH),1667 (C=O), 1586 (C=O), 1447 (C-H, bend), 1322 (C-H, bend), 1248 (C-O), 1187 (C-C), 821, 754, 687 (C-H, arom.bemd): EI-MS m/z: 369 (M^+,2), 235 (42), 150 (99), 145 (12), 119 (100), 91 (22), 76 (7), 65 (3): ^{1}HNMR (300MHz, $CDCl_3$): δ 11.02(s, b, 1H), 8.56 (d, 1H, *J*=6), 7.77 (d, 2H, *J*=9), 7.67 (d, 2H, *J*=6), 7.45 (d, 2H, *J*=9), 7.18 (d, 2H, *J*=6), 7.07 (t, 3H, *J*=6), 2.3 (s, 3H), 2.05 (s, 3H).

3.7.10. N-[4-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) phenyl] acetamide (58)

2-phenyl-4H-3, 1-benzoxazine-4-one **2** (0.05g, 0.000228 mol) and para-aminoacetanild as described for described for compound **57**.

Yield: 89 %, m.p. 228 °C; IR (KBr) υ_{max} cm^{-1}: 3265 (NH), 3066 (CH), 1630 (C=O), 1611 (C=O), 1510 (C=N), 1447 (C-H, bend), 1322 (C-H, bend), 1248 (C-O), 1187 (C-C), 833, 821, and 640 (C-H, arom. bend): EI-MS m/z: 355 (M^+,12), 303 (12), 201 (100), 184 (37), 182 (30), 157 (29), 120 (43), 76 (24), 51 (9): ^{1}HNMR (300MHz, CDCl3) δ: 11.2 (b, s, 1H), 8.39 (d, 1H, *J*=8), 8.01 (d, 2H, *J*=7.9), 7.82-7.75 (m, 3H), 7.55-7.52 (m, 2H), 7.50-7.42 (m, 5H), 2.49 (s, 3H).

3.7.11. 2-(4-Nitrophenyl)-3-(1, 3-thiazol-2-yl) quinazolin-4(3*H*)-one (59)

A mixture of 2-(4-nitrophenyl)-4H-3, 1-benzoxazine-4-one (0.2 g, 0.000813 mol) and 2-aminothiazole (0.08 g,) was refluxed in dry pyridine as described for compound **55**. Yield: 97 %, m. p.231 °C; IR (KBr) υ_{max} cm^{-1}: 1645 (C=O), 1575 (C=N), 1520 (C=C,), 1301 (C-H, bend), 1245 (C-O), 1234 (C-C), 834, 756, 681 (C-H, arom. bend): EI-MS m/z: 350 (M^+, 67), 319 (23), 294 (15), 281 (12), 267 (93), 253 (18), 229 (11), 145 (83), 132 (11), 120 (71), 105 (100), ^{1}HNMR (300MHz, $CDCl_3$) δ: 8.28 (d, 1H, *J*=8.536),

8.127 (d, 2H, *J*=8.536 m), 8.063 (d, 1H, *J*=7.94), 7.632 (d, 2H, *J* =7.8), 7.492 (t, 1H, *J* =7.28), 7.125 (t, 1H, *J* =7.744), 7.01 (d, 1H, *J*=4), 6.70 (d, 1H, *J*=3.5).

3.7.12. 2-(4-Bromophenyl)-3-(1, 3-thiazol-2-yl) quinazolin-4(3*H*)-one (60)

2-(4-Bromophenyl)-4H-3, 1-benzoxazine-4-one (0,2 g, 0.0006623 mol) 2-aminothiazol (0.066 g) were refluxed in dry pyridine (10 mL)

Yield: 76 %, m. p. 289 °C: IR (KBr) υ_{max} cm^{-1}: 1686 (C=O), 1591 (C=N), 1520 (C=C,), 1301 (C-H, bend), 1245 (C-O), 1234 (C-C), 750 (C-Br), 834, 756, 681 (C-H, arom. Bend), EI-MS m/z: 385 (M^{+2},), 383 (M+, 2), 381 (2), 302 (100), 300 (99), 259 (38), 257 (41), 222 (10), 185 (77), 183 (81), 157 (41), 155 (45), 145 (46), 90 (37), 76 (54), 55 (2), 51 (7):^{1}HNMR (300 MHz, $CDCl_3$): δ 8.87 (d, 1H, *J*=6), 8.23 (d, 1H, *J*=6), 8.21 (d, 1H, *J*=8),7.92 (d, 2H, *J*=9), 7.65 (t, 2H, *J*=6), 7.52 (d, 1H, *J*=9), 7.02 (d, 1H, *J*=3), 6.8 (d, 1H, *J*=4).

3.7.13. 2-(4-Methylphenyl)-3-(1, 3-thiazol-2-yl)quinazolin-4(3*H*)-one (61)

A mixture of 2-(4-methylphenyl)-4H-3, 1-benzoxazine-4-one (0.05 g, 0.0002109 mol) and 2-aminothiazole (0.02 g,) was refluxed in dry pyridine as described for compound 55.

Yield: 78 %, m. p. 212-214 °C; IR (KBr) υ_{max} cm^{-1}: 1654 (C=O), 1591 (C=N), 1520 (C=C,), 1301 (C-H, bend), 1245 (C-O), 1234 (C-C), 834, 756, 681 (C-H, arom. Bend): EI-MS m/z: 319 (M^+, 2), 318 (12), 239 (43), 238 (100), 193 (7.5), 146 (19), 120 (18), 119 (100), 92 (6), 91 (41), 65 (10). ^{1}HNMR (300MHz, $CDCl_3$): δ 8.96 (d, 1H, *J*=9), 8.29-8.17 (m, 5H), 7.94 (d, 2H, *J*=9), 7.68 (d, 1H, *J*=3), 7.12 (d, 1H, *J*=3), 2.45 (s, 3H).

3.7.14. 2-Phenyl-3-(1, 3-thiazol-2-yl) quinazolin-4(3*H*)-one (62)

A mixture of 2-phenyl-4H-3, 1-benzoxazine-4-one (0.3 g, 0.001345 mol) and 2-aminothiazole (0.1345 g,) was refluxed in dry pyridine as described for compound 55.

Yield: 71 %, m.p.186-189 °C: IR (KBr) υ_{max} cm^{-1}: 1671 (C=O), 11601 (C=N), 1520 (C=C,), 1301 (C-H, bend), 1245 (C-O), 1234 (C-C), 834, 756, 681 (C-H, arom. bend): EI-MS m/z: 305 (M+,15), 274 (6), 262 (25), 248 (21), 228 (78), 222 (100), 208 (13), 191 (10), 146 (20), 119 (100), 91 (39), 65 (13): ^{1}HNMR (300MHz, $CDCl_3$): δ 8.99 (d, 1H, *J*=9), 8.47 (d, 1H, *J*=9), 8.04-8.019 (m, 2H), 7.65-7.56 (m, 4H), 7.89 (t, 1H, *J*=9) 7.20 (d, 1H, *J*=4), 6.88 (d, 1H, *J*=3).

3.8. Synthesis of 2, 3-Disubstituted Quinazolin-4(3*H*)-ones Via Diamide Intermediate

3.8.1. Synthesis of Diamdes (63a-f)

3.8.1.1. Typical synthesis of 2-(benzoylamino)-*N*-(4-bromophenyl) benzamide (63a)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol) and 4-bromoaniline (1.55 g, 0.00896 mol) in pyridine were refluxed for 1-2 h. After completion of reaction as indicated by TLC, the reaction mixture was poured into cold water. The product thus precipitated was filtered, washed with cold water, dried and recrystallized from ethanol to obtain the desired product. Yield.41 %, m. p. 238 °C; IR (KBr) υ_{max} cm^{-1}: 3244 (-NH), 1603 (C=O), 1492 (C=C, conjugated), 1258 (C-C), 757 (C-Br); FAB-MS m/z: (+ve, -ve): 397, 395; EI-MS m/z: 397 (M^{+2},4), 394.9 (M, 5), 224 (100), 173 (43), 171 (47), 146 (10), 120 (7), 106 (4), 105 (60), 92 (6), 77 (34), 65 (3), 51 (3); ^{1}HNMR (300MHz, $CDCl_3$) δ: 10.21 (s, 2H, NH), 8.45 (d, 1H, *J*=8.2), 8.21 (d, 1H, *J*=13), 7.93-7.79 (m, 3H), 7.65 (t, 1H, *J*=8), 7,58 (t, 1H, *J*=8.7), 7.49-7.40 (m, 6H).

3.8.1. 2. 2-(Benzoylamino)-*N*-(4-iodophenyl) benzamide (63b)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol), 4-iodoaniline (0.00896 mol) were refluxed in pyridine for 2h. Yiled 78 %, m. p. 253-255 °C; EI-MS m/z: 443 (18), 442 (71), 342 (6), 225 (16), 224 (96), 219 (100), 210 (8), 182 (6), 164 (10), 106 (4), 105 (37), 91 (10), 77 (26), 51 (5); ^{1}HNMR (300MHz,CDCl3) δ: 10.9 (s, 2H, NH), 8.4(d,1H, *J*=8), 7.9 (d, 2H, *J*=7.9), 7.83 (t, 1H, *J*=8), 7.7-7.5 (m, 4H), 7.45-7.40 (m, 3H), 7.3 (d, 2H, *J*=8.5).

3.8.1.3. *N*-(2-hydroxyethyl)-2-[(4-nitrobenzoyl) amino] benzamide (63c)

2-(4-Nitrophenyl)-4*H*-3, 1-benzoxazin-4-one (0.25 g, 0.00106 mol), monoethanol amine (1mL) in benzene were refluxed for 1h.Yield. 93 %, m. p. 228-231^{0}C; EI-MS m/z: 329 (M^+, 24), 314 (13), 300 (9), 299 (52), 298 (11), 271 (5), 270 (36), 269 (100), 268 (10), 162 (7), 150 (46), 146 (13), 120 (44), 119 (13), 104 (44), 92 (15), 76 (19); ^{1}HNMR (300MHz, $CDCl_3$) δ: 12.52 (s, N-H), 12.48 (s, N-H), 8.77 (s, 1H, *J*=8.4), 8.65 (d,1H, *J*=8.4), 8.28 (d, 2H, *J*=8.8), 8.135 (d, 1H, *J*=8.8), 7.64 (d, 1H, *J*=7.6), 7.514 (t, 1H, *J*=8.25), 7.139 (t, 1H, *J*=7.6), 3.734 (t, 2H, *J*=5), 3.53 (t, 2H, *J*=5.2), 3.31 (b, s, 1H, OH).

3.8.1.4. 2-(Benzoylamino)-*N*-benzylbenzamide (63d)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol) and benzylamine (0.00896 mol) in pyridine were refluxed for 1h. Yield. 89 %, m.p.155-157 ^{0}C; IR (KBr) υ_{max} cm^{-1}: 3250 (N-H), 2929 (C-H), 1668 (C=O), 1519 (C=C, conjugated), 13035 (C=C-C); FAB-MS (-ve), 329, EI-MS m/z: 330 (8), 312 (M^+,), 252 (4), 223 (49), 195 (10), 139 (10), 120 (60), 105 (100), 92 (32); ^{1}HNMR (300MHz, $CDCl_3$): δ 12.108 (s, 2H, N-H), 8.82 (d, 1H, *J*=8), 8.042 (d, 2H, *J*=8),7.53-7.47 (m, 5H), 7.35-7.31 (m, 5H), 7.09 (t, 1H, *J*=8), 4.63 (s, 2H, CH_2).

3.8.1.5. 2-(Benzoylamino)-*N*-mesitylbenzamide (63e)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol) and 2, 4, 6-trimethylaniline (1.2 g, 0.00896 mol) in pyridine were refluxed for 1h. Yield 30 % m.p. 210-213 °C; IR (KBr) υ_{max} cm^{-1}: 3216 (N-H), 2934 (C-H), 1641 (C=O), 1496 (C=C), 1255 (C-C); EI-MS m/z: 358(4), 340 (M^+, 12), 254 (10), 222 (60), 146 (5), 135 (100), 120 (18), 105 (58), 92 (5), 76 (20), 65 (4); ^{1}HNMR (300MHz, $CDCl_3$): δ 10.2 (s, 2H, N-H), 8.7 (d, 1H, *J*=8), 8.02 (d, 1H, *J*=8), 7.95 (d, 2H, *J*=8), 7.63-7.42 (m, 4H), 7.28 (t, 1H, *J*=8), 6.96 (s, 2H), 2.3 (s, 3H), 2.2 (s, 6H).

3.8.1.6. 2-(Benzoylamino)-*N*-(2-hydroxyethyl) benzamide (63f)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol) and excess of monoethanol amine (2 ml) in pyridine were refluxed for 2h.Yiled 59 %, m.p. 185°C; IR (KBr) υ_{max} cm^{-1}: 3344 (O-H), 3250 (N-H), 2280 (C-H), 1664 (C=O), 1496 (C=C), 1427 (C=C, conjugated), 1255 (C-C); EI-MS m/z: 284 (M^+ 10), 266 (25), 254 (11), 249 (7), 235 (10), 224 (40), 223 (43), 222 (14), 190 (6), 189 (39), 180 (4), 179 (22), 167 (3), 149 (6), 146 (28), 120 (16), 111 (7), 106 (12), 105 (100), 97 (11), 85 (11), 83 (10), 77 (81), 71 (16), 57 (25), 55 (13), 51 (14), 44 (100), 43 (15), 40 (5); ^{1}HNMR (300MHz, CD_3OD) δ: 12.186 (s, N-H), 12.04 (s, N-H), 8.622 (d, 1H, *J*=8.25), 7.997 (d, 2H, *J*=8.19), 7.795 (d, 1H, *J*=7) , 7.6-7.51 (m, 4H), 7.22-7.17 (t, 1H, *J*=8.14), 3.74-3.70 (t, 2H, *J*=5.7), 3.545-3.506 (t, 2H, *J*=5.7), 3.299 (s, 1H).

3.8.1.7. *N*-[2-(hydrazinocarbonyl) phenyl] benzamide (63g)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (2 g, 0.00896 mol) was refluxed in boiling benzene for 30 min. To the boilong solution was then added hydrazine monohydrate 80%

(5ml) at once. The product precipitated out in the hot solution was filtered after cooling and recrystallized from ethanol.

Yiled 87 %, m.p: 158-160 °C; EI-MS m/z: 255(M^+, 8.48), 237 (55.75), 222 (57), 133 (11), 132 (20), 121(6), 120(35.7), 105(100), 91(14), 90(42), 76(10), 65(20), 63(13), 51(7): ^{1}HNMR (300MHz, CD_3OD) δ 8.10.7 (m, 2H), 7.91(d, 1H, *J*=8.355), 7.685 (m, 5H), 7.317 (t, 1H, *J*=7.113), 7.052(t, 1H, *J*=8.4), 6.67 (d, 1H, *J*=7.2). 4.61(S, 2H, NH_2) IR?

3.8.18. *N*-(2-{[(2*Z*)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide (63h)

Salicyldehyde (0.1 ml, 0.0008196 mol.) in dry ethanol contaning 2-3 drops of sulfuric acid was haeted under reflux stirred magnetically for 30 min. To the hot solution was then added ethanolic solution of 2-Phenyl-4*H*-3, 1-benzoxazin-4-one (0.2 g, 0.00784 mol) and refluxed further with stirring for 1h under argon atmosphere. After completion, the reaction mixture was poured into ice cold water. The product precipitated was filtered, washed with 5% cold $NaHCO_3$ solution, dried and recrystallized from ethanol.

Yiled 81 %, m.p: 224-226 °C; FAB-MS m/z: (-ve 358); EI-MS m/z: 359 (M^+, 9), 248 (3), 240 (5), 225 (32.7), 224 (100), 223 (37), 136 (84), 1120 (21.8), 119 (29.8), 106 (7), 105 (94), 92 (5.6), 77 (39.8), 769 (3.9), 51 (4.8); ^{1}HNMR (400MHz, CD_3OD) δ: 11.19 (s, 2H, -CO-NH), 11.10(S, 1H, OH) 9.17(s, 1H), 8.612 (d,1H, *J*= 8.4), 7.936 (d, 1H, *J*=7.28), 7.807(d.d, 2H, $J_{1,2}$=8.5, $J_{3,4}$= 8.68), 7.68 (m, 3H), 7.49 (t, 1H, *J*=8.016), 7.21(d, 1H, *J*=8.1), 7.118(t, 2H, J=7.56), 6.97 (d, 1H, *J*=8.1), 6.93 (t, 1H, *J*=8.4).

3.8.18. 5-[2-(Benzoylamino) phenyl]-4-(4-hydroxyphenyl)-3-methyl-1*H*-1, 2, 4-triazol-4-ium chloride (63i)

2-Phenyl-4*H*-3, 1-benzoxazin-4-one (0.25 g, 0.00098 mol), triethylorthoacetate (1ml) and 1.0 ml. acetatic acid were refluxed for 2h. After completion of the reaction the mixture was cooled to room temperature and the solid precipated out was then thermally fused with *para*-aminophenol (0.1068 g, 0.00098 mol) to melt. To the molten solution was added 1-2ml. acetic acid and refluxed for 2h. After completion of reaction the reaction mixture was poured in 8M HCl solution and was allowed to stand for several hours. The product was precipitated out in pure crystalline form.

Yield 77 %, m.p. 225 °C: EI-MS m/z: 371 (M^+, 9), 370 (14), 294 (5), 293 (32), 167 (4), 106 (15), 105 (100), 93 (5), 78 (9), 77 (87), 65 (13), 63 (12), 51(10); ^{1}HNMR (300MHz, CD_3OD) δ: 7.92 (d, 1H, *J*=7), 7.905 (t, 1H, *J*=6.9), 7.65-7.607 (m, 2H), 7.576-7.507 (m,5H), 7.296 (d.d, 2H, *J*=6.36), 6.94-6.915(m, 2H), 2.56(s, 3H, CH_3).

3.8.2. Synthesis of 2, 3-disubstituted quinazolin-4(3*H*)-ones (22, 41, 42, 49, 50, 51 and 52) via cyclization of the diamides (63a-h)

3.8.2.1 General procedure for microwave -assisted cyclization of the diamides

0.1 g of 2-(Aroylamino)-*N*-alkyl/arylbenzamides (**63a-h**) was placed in an open mouth vial and was irridiated in a domestic microwave oven for 3-5 min with consective pulses of 30 sec durations. The products upon completion of the reaction were recrystallized from ethanol and compared with the ones synthesized via conventional method for their percantage yields.

3.9. SEZCTION B: Synthesis of 2-alky/aryl-3-{[(1*E*)-arylmethylene] amino} quinazolin-4(3*H*) -ones (64-84)

3.9.1. 2-Methyl-3-{[(1*E*)-phenylmethylene] amino} quinazolin-4(3*H*)-one (64)

3-Amino-2-methylquinazolin-4(3*H*)-one (0.87 g, 0.005 mol) and benzaldehyde (0.7 mL, 0.01 mol) in absolute ethanol were boiled under reflux for 5 h. After completion of reaction monitored by TLC, the excess of the solvent was evaporated under reduced pressure and the reaction mixture was allowed to cool. The solid precipitated upon cooling was filtered, washed with water followed by hexane and recrystallized from ethanol. Yield 86 %, m.p. 178-180 °C: IR (KBr) υ_{max} cm^{-1}: 3044 (CH), 1635 (C=O), 1602 (C=O,C=N), 1529 (C=C), 1344 (C-H, bend), 1233 (C-O), 1154 (C-C), 843, 777, 690 (C-H, bend, arom.) :EI-MS; m/z 263 (M^+,3), 175 (4), 161 (11), 160 (100), 119 (9), 117 (12), 90 (12), 77 (27), 76 (26), 63 (5), 51 (10): ^{1}HNMR (500MHz, DMSO-d^6): δ ppm 8.51 (s,1H), 7.707 (d, 1H, *J*=8), 7.519 (d, 1H, *J*=7.5), 7.39-7.32 (m,1H), 7.215 (t, 1H, *J*=8.5, $J_{2,3}$=9), 7.145 (t, 1H, *J*=7.5), 7.094 (t, s, 1H, J=7.5), 2.153 (s, 3H): ^{13}CNMR (300 MHz, $CDCL_3$), δ ppm: 166, 134, 132, 129, 127, 126, 77, 76, 23.

3.9.2. 2-Methyl-3-{[(1*E*)-(4-nitrophenyl) methylene] amino} quinazolin-4 (3*H*)-one (65)

3-Amino-2-methylquinazolin-4(3*H*)-one (0.5 g, 0.002857 mols) and *para*-nitrobenzaldehyde (0.43 g, 0.002857 mols) were refluxed in absolute ethanol for 8 h.

After reaction completion the excess of ethanol was evaporated under reduced pressure and the remaining mixture was poured into ice cold water. The product precipitated out was filtered, washed with water and recrystallized from water - ethanol to afford the title product. Yield.61 %, m. p 210 °C; IR (KBr) υ_{max} cm^{-1}: 2924 (CH), 1679 (C=O), 1660 (C=O, C=N), 1524 (C=C), 1344 (C-H, bend), 1233 (C-O), 1146 (C-C), 843, 777, 690 (C-H, bend, arom.): EI-MS; m/z: 308 (M^+,72), 186 (26), 175 (5), 161 (83), 160 (100), 159 (29), 146 (6), 145 (31), 144 (7), 143 (18), 132 (20), 131 (11), 119 (45), 118 (62), 117 (85), 116 (14), 104 (11), 102 (18), 92 (9), 90 (36), 89 (36), 82 (5), 77 (44), 76 (84), 75 (11), 63 (21), 50 (21): ^{1}HNMR (300MHz): δ ppm 9.33 (s, 1H), 8.432 (d, 2H, *J*=9), 8.335 (d, 2H, *J*=9), 8.257 (d,1H, *J*=9), 7.884 (t,1H, *J*=8.7), 7.69 (d, 1H, *J*=9), 7.642 (t, 1H, *J*=9), 2.57 (s, 3H): ^{13}CNMR ($CDCl_3$): δppm 166, 134, 132, 128, 128,127, 126, 126, 77, 77, 76, 23.

3.9.3. 3-{[(1E)-(2-hydroxyphenyl) methylene] amino}-2-methylquinazolin-4(3*H*)-one (66)

Salicyldehyde (1 mL, 0.0122 mol) in absolute ethanol containing 2-3 drops of concentrated HCl was stirred for 15min. To the stirred solution was added ethanolic solution of 3-amino-2-methylquinazolin-4(3*H*)-one (0.5 g, 0.002857 mols) and the mixture was refluxed for 2 h. After completion of reaction as indicated by TLC, excess of the solvent was evaporated under reduced pressure and the mixture was added into ice cold water. The solid thus precipitated was filtered washed with water and recrystallized from water- ethanol mixture. Yield 76 %, m. p. 218-220 °C: IR (KBr) υ_{max} cm^{-1}: 3436 (OH, broad), 3007 (CH), 1719 (C=O), 1646 (C=N), 1575 (C=C), 1432 (C-H, bend), 1247 (C-O), 1217 (C-N), 1181 (C-C): EI-MS; m/z: 279 (M^+, 48), 186 (4.5), 161 (80), 160 (100), 145 (20), 132 (18), 120 (21), 119 (22), 118 (31), 117 (44), 165 (10), 90 (18), 77 (28), 76 (28), 63 (15): ^{1}HNMR(300MHz, $CDCl_3$) δ ppm: 10.7 (b, s, 1H), 8.99 (s, 1H), 8.289 (d, 1H, *J*=7.8), 7.79-7.69 (m, 2H), 7.508- 7.438 (q, 2H, *J*=7.4), 7.38 (d, 1H, *J*=7.6), 7.07 (d, 1H, *J*=8), 7.026-6.97 (t, 3H, *J*=8). 2.71(s, 3H, CH_3)

3.9.4. 3-{[(1*E*)-(4-fluorophenyl) methylene] amino}-2-methylquinazolin-4(3*H*)-one (67)

4-Flourobenzaldehyde (0.058 g, 0.00021 mol) was dissolved in ethanol containing 2-3 drops of con.H_2SO_4 and stirred for 15 min at room temperature. To the stirred

solution was added drop- wise an ethanolic solution of amino-2-methylquinazolin-4(3*H*)-one (0.026 g, 0.000146mol) and was further refluxed for 3 h with continuous stirring. After completion of the reaction as monitored by TLC, excess of the solvent was evaporated under reduced pressure and the concentrated mixture was added to 10 % $NaHCO_3$ solution. The solid precipitate was filtered, washed with water and recrystallized from water- ethanol mixture. Yield 81 %, m. p. 163-164 °C; IR (KBr) υ_{max} cm^{-1}: 3044 (CH), 1725 (C=O), 1601 (C=N), 1313 (C-H, bend), 1259 (C-O), 1231 (C-C), 830 (C-F): EI-MS m/z: 281 (M^+, 36), 248 (1), 224 (2), 186 (6), 161 (41), 160 (100), 159 (13), 143 (9), 132 (10), 131 (6), 122 (5), 120 (13), 119 (22), 117 (31), 108 (8), 107 (7), 102 (6), 95 (12), 92 (7), 90 (16), 77 (21), 76 (42), 75 (10), 50 (11): ^{1}HNMR (500MHz, CD_3OD) δ ppm : 9.01 (s,1H), 8.27 (d, 1H, *J*=5), 7.907 (t, 2H, *J*=8.6), 7.749 (t,1H, *J*=10), 7.65 (d,1H, *J*=8), 7.465 (t,1H, *J*=7.5), 7.19 (t, 2H, *J*=8.5), 2.6 (s, 3H).

3.9.5. 3-{(1*E*)-[4-(dimethylamino) phenyl] methylene] amino}-2-methylquinazolin-4(3*H*)-one (68)

This was prepared from 4-N, N-dimethylamino benzaldehyde (), 2-methyl 3-aminoquianzolin-4(3H)-one (0.026 g, 0.00014857 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield 75 %, m.p. 166-168 °C; IR (KBr) υ_{max} cm^{-1}: 3068 (C-H), 1666 (C=O), 1601 (C=N),1425 (C-H, bend), 1259 (C-O), 1231 (C-N), 1174 (C-C): EI-MS m/z: 306 (10), 183 (57), 160 (87), 159 (100), 147 (34), 146 (18), 145 (4), 136 (2), 133 (19), 130 (11), 121 (18), 120 (56) 119 (23), 106 (68), 105 (100), 92 (9), 77 (10), 76 (7), 63 (11), 52 (13); ^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 9.82 (s, 1H, weak), 8.62 (d, 1H, *J*=8), 7.9 (d, 1H, *J*=10), 7.51-7.42 (m, 2H), 7.19 (d, 2H, *J*=10), 6.95 (d, 2H, *J*=8), 2.94 (s, 6H, N-CH_3), 2.54 (s, 3H, CH_3) .

3.9.6. 3-{[(1*E*)-(4-methoxyphenyl) methylene] amino}-2-methylquinazolin-4(3*H*)-one (69)

This was prepared from 4-methoxy benzaldehyde (), 2-methyl 3-aminoquianzolin-4(3H)-one (0.026 g, 0.00014857 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield.69 %, m. p. 189-191 °C; IR (KBr) υ_{max} cm^{-1}: 2906 (CH), 1668 (C=O), 1597 (C=N), 1445 (C-H, bend), 1364 (C-H, bend), 1314 (C-O), 1233 (C-C), 937, 813 (C-H,

arom.bend): FAB-MS (+ve) 294; EI-MS m/z: 293 (14), 186 (2), 175 (52),161 (39), 160 (100), 146 (39),133 (23), 120 (18), 119 (23),118 (26), 105 (10), 92 (14), 90 (18), 77 (29), 76 (31), 63 (8), 51(9), 50 (10): ^{1}HNMR (500MHz, $CDCl_3$) δ ppm: 8.83 (s,1H), 8.27 (d, 1H, *J*=6), 7.85 (d, 2H, *J*=9), 7.74 (t,1H, *J*=7), 7.65 (d,1H, *J*=7), 7.46 (t,1H, *J*=9), 6.99 (d, 2H, *J*=9), 3.87 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3)

3.9.7. 2-Methyl-3-{[(1*E*)-(4-methylphenyl) methylene] amino} quinazolin-4 (3*H*)-one (70)

This was prepared from 4-methyl benzaldehyde, 2-methyl 3-aminoquianzolin-4(3H)-one (0.026 g, 0.00014857 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield 60 %, m. p. 185-187 °C; IR (KBr) υ $_{max}$: 2919 (CH), 1716 (C=O), 1683 (C=N), 1370 (C-H, bend), 1280 (C-O), 920, 782 (C-H, arom. bend): EI-MS m/z: 277 (15), 186 (2), 175 (30), 160 (100), 146 (38), 133 (21), 119 (24), 118 (26), 105 (9), 92 (18), 90 (20), 77 (24), 76 (26), 63 (5), 50 (6): ^{1}HNMR (500MHz, $CDCl_3$) δ ppm: 8.8 (s,1H), 8.28 (d, 1H, *J*=9), 7.844 (d, 2H, *J*=8.9), 7.724 (d,1H, *J*=7), 7.655 (d,1H, *J*=7.2), 7.46-7.41 (t,1H, *J*=9), 7.00 (d, 2H, *J*=9), 2.6 (s,3H), 2.21 (s, 3H) .

3.9.8. 3-{[(1*E*)-(2-hydroxynaphthalen-1-yl) methylene] amino}-2-methylquinazolin-4(3*H*)-one (71)

This was prepared from 2-hydroxy nephthaldehyde (0.09 g, 0.00057 mol), 2-methyl 3-aminoquianzolin-4(3H)-one (0.1 g, 0.00057 mol) and 2-3 drops H_2SO_4 as catalyst using the method as described for compound 67.

Yield 74.86 %, m. p. 196-197 °C; IR (KBr) υ $_{max}$: 3342 (OH), 2935 (CH), 1719 (C=O), 1646 (C=N), 1512 (C=C), 1432 (C-H, bend), 1349 (C-H, bend), 1307 (C-O), 1217 (C-C), 876, 756, 682 (C-H, arom. bend): EI-MS m/z: 329 (M^{+}2), 170 (12), 169 (63), 161 (38), 160 (100), 141 (13), 127 (24), 126 (10), 119 (11), 118 (14), 117 (27), 115 (19), 114 (23), 90 (15), 77 (20), 76 (33), 63 (11), 51 (4); ^{1}HNMR (300MHz, $CDCL_3$) δ ppm: 12.17 (s,1H), 9.88 (s,1H), 8.33 (d,1H, *J*=9), 8.025 (d, 1H, *J*=8), 7.96 (d,1H, *J*=9), 7.82 (t, 3H, *J*=10), 7.585-7.482 (m, 2H), 7.43 (t,1H, *J*=9), 7.288 (s, 1H), 2.71 (s, 3H).

3.9.9. 3-{[(1*E*)-(2-chloro-6-nitrophenyl) methylene] amino}-2-methylquinazolin-4(3*H*)-one (72)

This was prepared from 2-chloro-6-nitrobenzaldehyde (0.04 g, 0.00216 mol), 2-methyl 3-aminoquianzolin-4(3H)-one (0.05 g, 0.00285 mol) and H_2SO_4 as catalyst using the method described for compound **67**. Yield: 88.3 %, m. p.281-283 °C; EI-MS m/z: 345 (M^{+2} 23), 343 (M^+, 15), 398 (5), 316 (12), 289 (13), 184 (12), 182 (13), 160 (36), 159 (100), 126 (45), 120 (10), 119 (12), 118 (7), 106 (87), 105 (100), 92 (17), 77 (39), 76 (87), 53 (12): ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 8.81 (s, 1H), 8.28 (d, 1H, *J*=8.2), 8.07-8.03 (m, 2H), 7.98 (d,1H, *J*=8), 7.9-7.7(m, 3H, Ar-H), (2.57(s, 3H, CH_3)

3.9.10. 3-{[(1*E*)-(3,4-dihydroxyphenyl)methylene]amino}-2-methylquinazolin-4(3*H*)-one(73)

This was prepared from 3, 4-dihydroxy benzaldehyde (0.02365 g, 0.0001714 mol), 2-methyl 3-aminoquianzolin-4(3H)-one (0.03 g, 0.0001714 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 40 %, m. p. 293 °C; IR (KBr) υ_{max}: 3436 (OH), 3342 (OH), 1719 (C=O), 1646 (C=N), 1512 (C=C), 1382 (C-H, bend), 1247 (C-O), 1154 (C-C), 826, 782, 752(C-H, arom. bend): EI-MS m/z: 295 (M^+, 21), 294 (34), 281 (45), 268 (14), 160 (86), 159 (100), 146 (51), 120 (19), 106 (21), 105 (100), 80 (14), 54(3): ^{1}HNMR (300MHz, CD_3OD) δ ppm: 10.02 (S, 2H,OH), 8.7 (s,1H), 8.27 (d, 1H, *J*=8), 8.01-7.97 (m, 3H), 7.91 (d, 1H, *J*=7.86), 7.29 (s;1H, *J*=8), 7.10 (d,1H, *J*=8), 2.54 (s, 3H, CH_3) .

3.9.11. 3-({(1*E*)-[4-(dimethylamino) phenyl] methylene} amino)-2-phenylquinazolin-4(3*H*)-one (74)

This was prepared from 4-N, Ndimethyl benzaldehyde (0.0342g, 0.00252mol), 2-phenyl 3-aminoquianzolin-4(3*H*)-one (0.03 g, 0.000126 mol) and 2-3 drops H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 67 %, m.p.163 °C; IR (KBr) υ_{max}: 2927 (CH), 1666 (C=O), 1601 (C=N), 1425 (C-H, bend), 1378 (C-H, bend), 1259 (C-O), 1174 (C-C), 830, 763, 688 (C-H, arom. bend): FAB-MS: (+ve, -ve) 369,367: EI-MS m/z: 223 (57), 222 (4), 146 (42), 145 (20),130 (6), 120 (17), 119 (10), 115 (9), 105 (100), 92 (9) , 77 (79), 69 (6), 51 (13): ^{1}HNMR (300MHz, CD_3OD) δ ppm: 9.82 (s, 1H), 8.62 (d,1H, *J*=8), 7.96-7.85 (m, 2H), 7.72-7.65 (m, 3H), 7.51-7.43 (m, 5H), 6.95 (d, 2H, *J*=8), 2.95 (s, 6H).

3.9.12. 3-{[(1*E*)-(4-methoxyphenyl) methylene] amino}-2-phenylquinazolin-4(3*H*) one (75)

This was prepared from 4-methoxybenzaldehyde (mol), 2-phenyl 3-aminoquianzolin-4(3*H*)-one (0.03 g, 0.0001714 mol) and H_2SO_4 as catalyst using the method described for compound 67.

Yield: 72%, m. p. 159 °C; IR (KBr) υ_{max}: 2906 (CH), 1668 (C=O), 1597 (C=N), 1364 (C-H, bend), 1233 (C-O), 1157 (C-C), 1000, 937, 813 (C-H, arom. bend): EI-MS m/z: 293 (M^+, 15), 279 (31), 269 (5), 267 (4), 263 (14), 135 (14), 133 (81), 160 (18), 159 (91), 122 (7), 121 (60), 105 (100), 92 (28), 79 (13), 67 (7), 53 (9): ^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 9.3 (b, s,1H), 8.34 (d, 1H, *J*=9), 8.25-8.20 (m, 2H), 7.78-7.74 (m, 2H), 7.67-7.62 (m, 4H), 7-53-7.45 (m, 4H), 3.86 (s, 3H).

3.9.13. 3-{[(1*E*)-(2-hydroxyphenyl) methylene] amino}-2-phenylquinazolin-4(3*H*)-one(76)

This was prepared from salicaldehyde (mol), 2-phenyl 3-aminoquianzolin-4(3*H*)-one (0.03 g, 0.0001714 mol) and H_2SO_4 as catalyst using the method described for compound 67. Yield: 67 %, m. p. 220-224 °C; IR (KBr) υ_{max}: 3436 (OH), 1664 (C=O), 1575 (C=N), 1512 (C=C), 1432 (C-H, bend), 1303 (C-O), 1247 (C-C), 876, 752, 982 (C-H, arom. bend): EI-MS (m/z): 341 (26), 340(17), 329 (18), 265 (18), 249 (31), 222 (68), 208 (14), 146 (31), 135 (17), 121 (79), 119 (81), 106 (10), 105 (100), 104 (28), 92 (14), 67 (05), 54 (4): ^{1}HNMR (300MHz, CD_3OD) δ ppm: 11.2 (s,1H), 9.8 (s,1H), 8.35 (d,1H, *J*=8.4), 8.21-8.18 (m, 2H), 7.8-7.75 (m, 3H), 7.7-7.64 (m, 3H), 7.48 (d,1H, *J*=8), 7.23-7.13 (m, 3H).

3.9.14. 3-{[(1*E*)-(3-chlorophenyl) methylene] amino}-2-phenylquinazolin-4(3*H*)-one(77)

This was prepared from 3-chlorobenzaldehyde (0.011g, 0.0001714mol), 2-phenyl 3-aminoquianzolin-4(3H)-one (0.03 g, 0.0001714 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 78 %, m. p. 179-180 °C: IR (KBr) υ_{max}: 1601 (C=O), 1529 (C=N), 1444 (C=C, aroma.), 1233 (C-C), 919, 840, 757 (C-H, arom. bend), 709 (C-Cl): EI-MS m/z: 362 (7), 359.8 (12), 325 (12), 313 (21), 298 (14), 249 (45), 222 (67), 221 (81), 208 (17), 120 (13), 106 (12), 105 (100) 92 (7), 67 (16), 54 (5): ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 9.3 (s,

1H), 8.35 (d, 1H, *J*=7.8), 8.23-8.21 (m, 2H), 7.96-7.94 (m, 3H), 7.7-7.58 (m, 5H), 7.48 (d, 1H, *J*=8), 6.67 (s, 1H).

3.9.15. 3-{[(1*E*)-(2-hydroxynaphthalen-1-yl)methylene]amino}-2-phenylquinazolin-4(3*H*)-one(78)

This was prepared from 3-hydroxynephthaldehyde (0.15g, 0.0008438 mol), 2-phenyl 3-aminoquianzolin-4(3*H*)-one (0.2 g, 0.0008438 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 77.65 %, m. p. 258.9-260 °C: IR (KBr) υ_{max}: 3436 (O-H), 1719 (C=O), 1575 (C=N), 1512 (C=C), 1480 (C=C-C), 1303 (C-H, bend), 1005, 826, 752 (C-H, arom. bend): EI-MS m/z: 391 (M,), 222 (5), 186 (23), 169 (9), 128 (15), 120 (22), 119 (10), 115 (13), 105 (100), 92 (16), 77 (85), 65 (10), 51 (15); ^{1}HNMR (300MHz, CD_3OD) δ ppm: 11.6 (s,1H), 10.5 (s, 1H), 8.38 (d, 1H, *J*=9), 8.28 (d,1H, *J*=9), 8.05 (d, 2H, *J*=9), 7.55-7.49 (m, 5H), 7.39-7.29 (m, 4H), 7.04 (s, 1H), 6.79 (t, 1H, *J*=9).

3.9.16. 3-{[(1*E*)-(2-hydroxynaphthalen-1-yl) methylene] amino}-2-(4-nitrophenyl) quinazolin-4 (3*H*)-one (79)

This was prepared from 3-hydroxynephthaldehyde (0.012g, 0.0000709 mol), 2-phenyl 3-aminoquianzolin-4(3H)-one (0.02g, 0.0000709 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 86.5 %, m.p. 312-315 °C: IR (KBr) υ_{max}: 3342 (O-H), 1646 (C=O), 1523 (C=N), 1432 (C=C-C, arom.), 1247 (C-C, arom.), 876, 782 (C-H, arom.bend): EI-MS m/z: 438 (37), 412 (28), 427 (14), 422 (12), 393 (30), 317 (12), 306 (10), 294 (17), 266 (100), 254 (27), 226 (13), 172 (18), 170 (47), 157 (14), 143 (21), 132 (18), 106 (27), 105 (100),s 92 (37), 67 (7), 54 (6); ^{1}HNMR (400MHz, CD_3OD) δ ppm: 11.2 (b, s,1H), 9.8 (s,1H), 8.6 (d, 2H, *J*=9.5), 8.47 (d,1H, *J*=9.8), 8.45 (d,1H, *J*=9.5), 8.43 (d,1H, *J*=9.5), 8.4 (d,1H, *J*=10), 8.1-7.9 (m, 2H), 7.97 (d,1H, *J*=9.7), 7.83-7.64 (m, 3H), 7.56 (d, 1H, *J*=10), 7.3 (d,1H, *J*=10)

3.9.17. 3-{[(1*E*)-(4-fluorophenyl)methylene]amino}-2-(4-nitrophenyl)quinazolin-4(3*H*)-one(80)

This was prepared from 4-flourobenzaldehyde (0.03 g, 0.00010638 mol), 2-phenyl 3-aminoquianzolin-4(3*H*)-one (0.013g, 0.00010638 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 72.69 %, m. p. 241-243 °C: IR (KBr) υ_{max}:1601 (C=O), 1529 (C=N), 1444 (C=C, arom.), 1233 (C-C, arom.), 840,757, 671 (C-H, arom.): EI-MS m/z: 388 (M^+,12), 376 (5), 370 (12), 343 (10), 294 (14), 267 (11), 266 (81), 265 (90), 253 (16), 208 (8), 105 (100), 103 (69), 92 (37), 67 (12), 54 (3); ^{1}HNMR (300MHz, CD_3OD) δ ppm: 9.6 (s,1H), 8.56 (d, 2H, *J*=9.2), 8.48 (d, 2H, *J*=9), 8.41 (d,1H, *J*=9), 8.01-7.78 (m, 3H), 7.68-7.65 (m, 3H), 7.54(d, 1H, *J*=9).

3.9.18. 3-{[(1*E*)-phenylmethylene]amino}-2-[(*E*)-2-phenylvinyl]quinazolin-4(3*H*)-one(81)

3-Amino-2-[(*E*)-2-phenylvinyl]quinazolin-4(3*H*)-one (0.1 g, 0.000398 mol) and benzaldehyde (0.042 g, 0.000398 mol) were refluxed in absolute ethanole for 5h. After completion of the reaction, excess of ethanol was evaporated under reduced pressure and solid remining was recrystallized from water-ethanol mixture.

Yield: 82 %, m. p. 152 °C: IR (KBr) υ_{max}: 1663 (C=C), 1523 (C=N), 1408 (C=C-C), 1233 (C-C, arom.), 919. 840, 757 (C-H, aroam. bend): EI-MS m/z: 351 (M^+, 17), 248 (5), 247 (100), 171 (71), 159 (70), 147 (7), 146 (39), 120 (42), 105 (100), 103 (13), 92 (41), 65 (13), 51 (11), 28 (49): ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 9.12 (s,1H), 8.34 (d,1H, *J*=8.3), 8.12 (d,1H, *J*=8), 7.90-7.83 (m, 3H), 7.80 (d, 2H, *J*=8.5), 7.74-7.68 (m, 2H), 7.67 (d, 1H, *J*=9), 7.58 (t, 2H, *J*=9), 7.40-7.34 (m, 3H), 7.50 (d, 1H, *J*=14).

3.9.19. 3-{[(1*E*)-(4-nitrophenyl)methylene]amino}-2-[(*E*)-2-phenylvinyl]quinazolin-4(3*H*)-one(82)

3-Amino-2-[(*E*)-2-phenylvinyl]quinazolin-4(3*H*)-one (0.1g, 0.000398 mol) and benzaldehyde (0.042 g, 0.000398 mol) were refluxed in absolute ethanol for 5h after completion of reation, the reaction mixture was poured into ice cold water. The product precipitated was filtered, washed with water and recrystallized from ethanol.

Yield 83 %, m. p. 212 °C: IR (KBr) υ_{max}:1679 (C=O), 1524 (C=N), 1471 (C=C-C), 1344 (C-H, bend), 834, 777, 747 (C-H, bend, arom.): EI-MS m/z: 396 (M^+,36), 350 (28), 293 (5), 292 (17), 248(71), 245(56), 244(13), 235(41), 195 (12), 172 (83), 170 (42), 149 (53), 146 (12), 145 (91), 135 (49), 120 (31), 105 (100), 92 (42), 91 (41), 65 (14), 51 (10): ^{1}HNMR (400MHz, CD_3OD) δ ppm: 9.21 (s,1H), 8.6 (d, 2H, *J*=11), 8.30 (d,1H, *J*=8.3), 8.20 (d, 2H, *J*=8.7), 8.03 (d, 1H, *J*=7.9), 7.99 (d, 2H, *J*=9.2), 7.90 (d,1H, *J*=8.1), 7.74-7.69 (m, 3H), 7.7 (d, 1H, *J*=12), 5.6 (d, 1H, *J*=12).

3.9.20. 3-{[(1*E*)-(3-chlorophenyl)methylene]amino}-2-methylquinazolin-4(3*H*)-one(83)

This was prepared from 3-chlorobenzaldehyde (0.012 ml, 0.0001142 mol), 2-methyl 3-aminoquianzolin-4(3H)-one (0.02 g, 0.0001142 mol) and H_2SO_4 as catalyst using the method described for compound **67**.

Yield: 71 %, m. p. 179-180 °C: IR (KBr) υ_{max}: 1716 (C=O), 1557 (C=N), 1470 (C=C-C), 1415 (C=C, arom.), 1309 (C-H, bend. arom.), 765 (C-Cl): EI-MS m/z: 299 (M^{+2}, 3), 297.78 (M^+,12), 263 (7), 240 (2), 224 (50), 223 (98), 179 (4), 146 (23), 137 (3), 120 (20), 119 (18), 105 (100), 92 (10), 76 (64) 65 (8), 51 (10): ^{1}HNMR (300MHz,$CDCL_3$) δ ppm: 8.83 (s, 1H), 8.46 (d, 1H, *J*=8), 8.00 (d, 1H, *J*=8), 7.55-7.46 (m, 2H), 7.406 (t,1H, *J*=8), 7.34-7.27 (m, 2H), 6.89 (s,1H), 3.41(s, 3H, CH_3)

3.9.21. 3-{[(1*E*)-(2-hydroxy- 5-ethoxyphenyl) methylene]amino}-2-(3-iodophenyl) quinazolin-4(3*H*)-one (84)

5-Ethoxy-2-hydroxybenzaldehyde (0.228 g, 0.00137 mol) was dissolven in absolute ethanol (10 ml) conatining few drops of H_2SO_4 for 15 min. to the stirred solution was the added 3-amino-2-(4-iodophenyl) quinazolin-4(3H)-one (0.5g, 0.00137mol) and the mixture was refluxed for 5h. After completion, the reaction mixture was poured into icecold water. The product precipitated out was filtered washed with 5% $NaHCO_3$ aques solution dried and recrystallized from ethanol.

Yield: 61.3 %, m. p. 193-195 °C: FAB-MS m/z: 512, 510 (+ve, -ve); EI-MS m/z: 511 (M^+, 17), 510 (22), 467 (3), 384 (2), 347 (51), 375 (23), 173 (48), 170 (38), 159 (91), 145 (100), 132 (13), 120 (28), 105 (71), 92 (53), 79 (18), 76 (14), 65 (11), 52 (5): ^{1}HNMR (300MHz, $CDCl_3$) δ ppm 10.08 (s,1H), 9.76 (s,1H), 8.73 (d,1H, *J*=8.3), 8.61 (d, 2H, *J*=8.3), 8.46 (d, 2H, *J*=7.9), 8.27-8.22 (m, 2H), 7.81-7.79 (m,1H), 7.25-7.21 (m, 2H), 6.91 (d,1H, *J*=3.1), 4.38 (q, 2H, *J*=7.3), 1.41 (t, 3H, *J*=7.3) .IR?

3.10. Microwave- assisted Synthesis of 2-Alkyl/aryl-3-{[(1*E*) - arylmethylene] amino} quinazolin-4(3*H*)-ones (64, 65, 70, 71, 72, 76-79, 82 and 83)

General Procedure

2-Alkyl/aryl- 3-aminoquianzolin-4(3H)-ones were taken in a vial and placed a cylindrical capped Teflon container and was then irradiated in domestic microwave oven

for 3-10 min. The products were recrystallized from ethanol to afford 91-99 % of the desired products.

3.10.1. Typical procedure for the synthesis of 2-methyl-3-{[(1*E*)-(4-nitrophenyl) methylene] amino} quinazolin-4(3*H*)-one (65)

3-Amino-2-methylquinazolin-4 (3*H*)-one (0.01 g, 0.0571 m mol) and 4-nitrobenzaldehyde (0.0086 g, 0.0571m mol) were heated under microwave irradiation in domestic microwave oven for 3min at consecutive pulse rate of 30sec. The product was recrystallized from ethanol -water mixture: Yields and reaction times for all compounds synthesized via microwave irradiation are given in table 2.17 in Chapter 2.

3.11. Synthesis of *N*-(2-alkyl/aryl-4-oxoquinazolin-3(4*H*)-yl) alky/arylamide (85-89)

3.11.1. N-(2-methyl-4-oxoquinazolin-3(4H)-yl) acetamide (85)

A mixture of 3-amino-2-methylquinazolin-4(3*H*)-one (0.5 g, 0.00285 mol) and acetyl chloride was stirred in dry pyridine (10 mL) for 1 h. after completion of the reaction , the raection mixture was poured into ice cold water and the product precipitated was filtered, washed and recrystallized from ethanol. Yield: 91 %, m. p. 172-174 °C; IR (KBr) υ_{max}: 2954 (C-H), 1741 (C=)), 1706 (C=O), 1483 (C=C-C), 1462 (C-H, bend), 1238 (C-C), 1079, 1002, 971 (C-H, bend, arom.): EI-MS m/z: 217 (M^+.13), 175 (100), 160 (14), 46(73), 118 (9), 117 (19), 90 (18), 77 (23), 76 (29), 63 (9), 62 (11), 51 (13) ^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 11.3 (b, s, 1H), 8.214 (d, 1H,*J*=10), 8.021 (d, 1H, *J*=10), 7.902(t, 1H, *J*= 7.4), 7.582 (t, 1H, J=7.45), 2.87(s, 3H, CH_3), 2.48 (s, 3H, CH_3): ^{13}CNMR (300MHz, $CDCl_3$) δ (ppm): 169, 160, 158, 157, 144, 137, 135, 128, 127, 126, 120, 117, 21, 18.

3.11.2. N-(2-methyl-4-oxoquinazolin-3(4H)-yl) benzamide (86)

3-Amino-2-methylquinazolin-4(3*H*)-one (0.5 g, 0.00285 mol) was dissloved in dry pyridine (10 mL) and stirred, to the stirred solution was then added dropwise benzoylchloride (1 ml) and stirring was continued for the next 1 h. After completion, the reaction mixture was poured into water and was allowed to stand.The product separated out was filterd, washed with water and recrystallized from ethanol.Yield: 78 %, m. p.102-103 °C: IR (KBr) υ_{max}: 3165 (N-H), 2921 (C-H), 1735 (C=O), 1696 (C=O), 1499 (C=C), 1417 (C=C-C), 1377 (C-H, bend), 1256 (C-C=C): EI-MS m/z: 279 (M^+, 8), 167 (8), 149 (22), 122 (40), 106 (6), 105 (100), 84 (8), 77 (52), 76 (7), 71 (8), 66 (14), 57 (17), 56

(10), 52 (40): ^{1}HNMR (300MHz,$CDCl_3$) δ ppm: 11.85(S,1H), 8.37(d,1H, *J*=7.8), 8.12-7.96 (m, 5H), 7.64 (d, 1H, J=7.4), 7.41-7.27 (m, 2H), 2.34 (s,3H, CH_3); ^{13}CNMR (300MHz, $CDCl_3$) δ (ppm): 172, 134, 130, 129, 128, 77.6, 77, 76.

3.11.3. 2-Chloro-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide (87)

A mixture 3-amino-2-methylquinazolin-4(3*H*)-one (0.1 g, 0.00057 mol) and slight excess of chloacetylchloride (0.1 mL, 0.0013 mol) in 10ml dry benzene were refluxed under argon atmosphere with continuous stirring for 5h. After completion, the reaction mixture was cooled to room temperature and excess of solvent was evaporated under reduced pressure, the solid left behind was washed with water, dried and recrystallized from benzene.Yield 41.9 %, m.p. 196-199 °C: IR (KBr) υ_{max}: 3492 (N-H), 2929 (C-H), 1638 (C=O), 1598 (C=O), 1473 (C=C-C), 1280 (C-C=C), 774 (C-Cl): EI-MS m/z: 253 (M^{+2}, 13), 251 (M^{+}, 20), 202 (54), 175 (81), 161 (29), 159 (100), 146 (71), 118 (10), 117 (19), 90 (16), 77 (23), 76 (31), 62 (11), 51 (14): ^{1}HNMR (300MHz, $CDCl_3$) δ ppm: 11.3 (s, b, 1H), 8.21 (d, 1H, *J*=9), 8.15 (d, 1H, *J*=10), 7.9-7.87 (t, 1H, *J*=10, *J*=8.5), 7.58-7.55 (t, 1H, *J*=10, *J*=8.5), 3.84 (s, 2H), 2.54 (s, 3H).

3.11.4. 2-Chloro-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetamide (88)

3-Amino-2-phenylquinazolin-4(3*H*)-one (0.2 g, 0.0084 mol.) and chloacetylchloride (0.1 mL, 0.0013 mol) in 10mL dry benzene under argon atmosphere was refluxed with continuous stirring for 5h. The reaction mixture was cooled, benzene was evaporated under reduced pressure and the solid left behind was washed with water, dried and recrystallized from benzene. Yield 78.45 %, m.p. 174-178 °C: IR (KBr) υ_{max}: 3324 (N-H), 2929 (C-H), 1683 (C=O), 1598 (C=O), 1473 (C=C), 1344 (C-H, bend), 1280 (C-C=C), 970, 929, 858 (C-H, bend. arom), 774 (C-Cl): EI-MS m/z: 316 (M^{+2}, 19), 313.9 (M^{+}, 27), 265 (8), 264 (45), 236 (30), 208 (29), 179 (55), 152 (19), 119 (18), 105 (46), 102 (17), 90 (36), 77 (100), 76 (75), 58 (38), 51 (38), 51 (23): ^{1}HNMR (300 MHz, $CDCl_3$) δ ppm: 9.81(s, 1H), 8.23 (d, 1H, *J*=8), 7.823-7.79 (m, 2H), 7.60 (t, 1H, *J*=7.8), 7.60 (d, 1H, *J*=7.6), 7.54-7.41 (m, 1H), 7.46 (t, 1H, *J*=7.4), 7.39-7.34 (m, 2H), 3.84 (s, 2H).

3.11.5. 2-(4-Nitrophenyl)-4-oxoquinazolin-3(4*H*)-yl] carbamic chloride (89)

This was prepared by refluxing 3-amino-2-(4-nitrophenyl) quinazolin-4(3*H*)-one (0.03, 0.000106 mole) and chloroacetylchloride (0.1 mL, 0.0013 mol) in dry benzene (10

ml) as described for compounds **88**. Yield: 53 %, m.p. 211-213 °C: IR (KBr) $\upsilon_{max.}$ 3492 (N-H), 2934 (C-H), 1679 (C=O), 1598 (C=O), 1347 (C=C-C), 1166 (C-C=C), 1014, 970, 929 (C-H, arom. bend), 696 (C-Cl): EI-MS m/z: 361(M^{+2}, 13) 359 (M^{+}, 21), 324 (8), 310 (41), 282 (19), 266 (100), 254 (17), 145 (100), 133 (27), 106 (16), 105 (89), 90 (36), 77 (100), 76 (75), 58 (38), 51 (38), 51(23): ^{1}HNMR (300 MHz, CD_3OD) δ ppm: 10.54 (s, 1H), 8.37(d, 1H, J=8), 8.237 (d, 2H, *J*=8), 7.95 (d, 2H, *J*=7.6), 7.80 (t, 1H, *J*=7.6), 7.607 (d, 1H, *J*=8), 7.53 (t, 1H, *J*=7.4), 3.93 (s,2H).

3.12. Syntehsis of 2-aminobenzohydrazide (90)

Method A

Methyl anthranilate (2 g, 0.0132 mol) and 10ml hydrazine monohydrate (98%) in absolute ethanol (10 mL) was stirred under reflux for 5 h. After completion of the reaction, excess of solvent was evaporated under reduced presuusre and a solid was obtained. Alternatively, the reaction mixture after completion of the reaction was cooled below the room temprature in refrigerator. The product precipitated upon cooling was washed with water, dried and recrystallized from ethanol. Yield 89 %, m.p 110-112 °C.

Method B

Methyl anthranilate (2 g, 0.132 mol) and 1-2 mL hydrazine monohydrate (98 %) in saeled tube placed in a teflon container and was then heated under microwave irridation for 1min at consective pulses of 10 sec. After completion of the reaction the tube was cooled in cold water. The product after solidification was recrystallized from ethanol.

Yiled 99 %, m.p. 110 °C: IR (KBr) $\upsilon_{max.}$ 3306 (N-H), 1654 (C=O), 1462 (C=C-C), 1378 (C-H, bend), 1287 (C-N, C-O), 1002, 974, 877 (C-H, arom.bend): EI-MS m/z: 151 (M^{+},7), 136 (31), 121 (5), 120 (5), 105 (100), 92 (78), 79 (12), 76 (33), 68 (5), 54 (5): ^{1}HNMR (300 MHz, DMSO-d^6) δ (ppm): 9.47 (s, 1H, CONH), 7.43 (d, 1H, *J*=90), 7.147 (t,1H, *J*=9), 6.705 (d, 1H, *J*=9), 6.480 (t, 1H, *J*=9), 4.387 (s, 4H, NH_2): ^{13}CNMR (300 MHz, DMSO-d^6) δ (ppm): 168, 149, 131, 127, 116, 114, 113.

3.13. 2-Alky/-3-{[(1*E*)-alkyl/methylene] amino}-2, 3-dihydroquinazolin-4(1*H*)-one (91-94).

3.13.1. Method A: Silica gel mediated synthesis

2-Aminobenzohydrazide (1.47 g, 0.01 mol) was dissolved in excess of ketone (5-10 mL). To the solution was then added silica gel (2-3 g) as heterogenous catalyst, and stirred at room temperature for 10-12 h. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the residue was washed with acetone. The combined filtrates were then evaporated under reduced pressure.The product resulted was recrystallized from ethanol.

3.13.2. Method B: $ZnCl_2/FeCl_3$ mediated synthesis

2-Aminobenzohydrazide, suitable ketone/aromatic aldehyde and $ZnCl_2$ / $FeCl_3$ were stirred at slightly elevated temperature for 5-7 h. Upon completion of the reaction the reaction the mixture was filterd. The solvent was evaporated under reduced pressure. A second corp of the product was obtained from the residual concentrate by extracting with acetone, followed by evaporation of the solvent under reduced pressure. The products were recrystallized from water-ethanol mixture.

3.13.3. Method C: PTSA catalyzed synthesis

2-Aminobenzohydrazide, suitable ketone/aromatic aldehyde and TsOH were stirred at slightly elevated temperature for 15-30min. After completion of the reaction, the reaction content was poured into water. The solid precipated on cooling was filtered, dried and recrystallized from water-ethanol mixture.In case of no solid formation after pouring the reaction mixture in water, the aqueous layer was extracted with dichlomethane followed by evaporation of the organic solvent under reduced pressure and the residue was recrystallized from water-ethanol mixture.

3.13.4. 3-(Isopropylideneamino)-2, 2-dimethyl-2, 3-dihydroquinazolin-4(1*H*)-one (91)

2-Aminobenzohydrazide (0.5 g, 0.0033 mol) dissolved in excess of acetone was stirred on room temprature for overnight in the presence of silica gel. After completion of reaction, the reaction mixture was filtered through sintered glass funnel. Excess of the solvent was evaporated under reduced pressure and the solid left behind was washed with water and recrystallized from ethanol. Yield 92 %, m. p. 245-248 °C; IR (KBr) υ_{max}:

3306 (N-H), 2973 (C-H), 1627 (C=O), 1509 (C=N), 1489 (C=C), 1357 (C-H, bend), 1273 (C-N): EI-MS m/z: 231 (M^+, 30), 217 (15), 216 (100), 191 (6), 174 (3), 161 (17), 160 (89), 132 (4), 121 (4), 117 (10), 91 (5), 87 (4), 85 (22), 77 (3), 52 (19); ^{1}HNMR (300 MHz, $CDCl_3$) δ (ppm): 7.89 (d, 1H, *J*=8), 7.29 (t, 1H, *J*=8), 6.839 (t, 1H, *J*=7.5), 6.618 (d, 1H, *J*=8), 4.161 (s, b, 1H), 2.15 (s, 6H, CH_3), 1.878 (s, 6H, CH_3).

3.13.5. 2, 2-Diethyl-3-[(1-ethylpropylidene) amino]-2,3-dihydroquinazolin-4(1*H*)-one (92)

2-Aminobenzohydrazide (0.25 g 1.6 m mol) and excess of 3-pentanone were stirred at room temperature for 12 h over silica gel as catalyst. After completion of reaction as indicated by TLC, the reaction mixture was then shaken with excess acetone and filtered. The solvent was evaporated under reduced pressure and the resulting compound was purified on silica gel column using 10 % ethylacetate- n-hexane as eluting solvent. Yield: 50 %, m.p.142-144 °C; IR (KBr): υ_{max} 3306 (N-H, str.), 2973 (C-H), 1626 (C=O), 1509 (C=N), 1489 (C=C), 1457 (C=C-C), 1357 (C-H, bend), 1273 (C-N): FAB-MS (+ve, -ve), 288 (+ve), 286 (-ve): EI-MS; m/z: 287 (M^+, 6), 259 (12), 258 (74), 188 (38), 175 (26), 160 (10), 132 (11), 130 (9), 92 (13), 84 (100), 77 (13), 56 (72), 55 (10): ^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 7.89 (d, 1H, *J*=7.37), 7.29-7.25 (t,1H, *J*=8.09), 6.83 (t, 1H, *J*=7.5), 6.61(d, 1H, *J*=8.012), 4.8 (b, s, w, 1H), 2.31-2.25 (m, 4H), 2.10-1.85 (m, 4H), 1.08 (t, 3H, *J*=11), 1.03 (t, 3H, *J*=11.7), .98 (t, 6H, *J*=14).

3.13.6. 2-Ethyl-2-methyl-3-{[(1*E*)-1-methylpropylidene] amino}-2, 3-dihydroquinazolin-4(1*H*)-one (93)

2-Aminobenzohydrazide (0.25 g 1.6 m mol) and excess of 2-pentanone were stirred at room temperature for 12 h over silica gel as catalyst as described for compound **92**.

Yield: 78 %; m.p. 110 °C: EI-MS; m/z: 259 (M^+, 29), 258 (12), 245 (37), 243(10), 189 (62), 175 (81), 148 (12), 105 (100), 92 (23), 84 (81), 76 (27), 56 (13): ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (d, 1H, *J*=7.38), 7.91 (t, 1H, *J*=8), 7.34 (t, 1H, *J*=7.38), 6.89 (d, 1H, *J*=7.35), 5.18 (s, 1H, N-H), 2.25 (q, 2H, $J_{1,3}$=4.8, $J_{2,4}$=5.2), 2.18-1.97 (m, 5H), 1.60 (s, 3H), 1.23 (t, 3H, *J*=5.2), 1.09 (t, 3H, *J*=5.4) .

3.13.7. 3'-(Cyclohexylideneamino)-1'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one (94)

2-Aminobenzohydrazide (0.25 g 1.6 mmol) and slight excess of cyclohexanone were stirred at room temperature for 12 h over silica gel as catalyst as described for compound **92**. Yield: 92 %, m.p. 208-210 °C; EI-MS; m/z: 311(M^+, 57), 310 (31), 215 (89), 201(37), 186 (13), 185 (23), 112 (42), 105 (100), 96 (74), 76 (29), 52 (4): ^{1}H-NMR (300 MHz, CD_3OD) δ (ppm): 8.21 (d, 1H, *J*=8.6), 7.85 (t, 1H, *J*=9), 7.19 (t, 1H, *J*=8.6), 6.87 (d, 1H, *J*=8.6), 5.21 (s, 1H, N-H), 2.81-2.68 (m, 4H), 2.19-1.92 (m, 4H), 1.87-1.592 (m,12H)

3.14. Synthesis of 2-Aryl-3-{[(1*E*)-arylmethylene] amino}-2, 3-dihydroquinazolin-4(1*H*)-ones (95-104)

3.14.1. Method A: Thermal acid –catalyzed synthesis

Aromatic aldehyde was dissolved in absolute ethanol and few drops of H_2SO_4 was added as catalyst and stirred at room temperature for 15-30 min. To the stirred solution was then added ethanolic solution of 2-aminobenzohydrazide dropwise and the combined mixture was then refluxed for 2-3h with continous stirring. After completion of reaction, the solvent was removed under reduced pressure and the solid left was washed with saturated $NaHCO_3$ solution. The product was dried and recrystallized from water-ethanol mixture to obtain the desired products.

3.14.2. Method B: Microwave- assisted synthesis

Suitable aromatic aldehyde and 2-aminobenzohydrazide in (1:2 mol ratio) were taken in a vial placed in a teflon box and was irradiated in a microwave oven for 2-10min. The product after completion of the reaction was washed with water and recystallized from water-ethanol mixture.

3.14.3. Typical procedure for the synthesis of 2-phenyl-3-{[(1*E*)-phenylmethylene] amino}-2, 3-dihydroquinazolin-4(1*H*)-one (95) Via Method-A

A mixture 2-aminobenzohydrazide (0.2 g, 0.00132 mol) and redistilled benzyldehyde (0.3 g, 0.00264 mol) in 10ml dry methanol containing 2-3 drops H_2SO_4 Was heated under reflux for 3h. After reaction completion, the reaction mixture was allowed to cool and then poured into ice-cold water. The product precipitated out was filtered, dried and recrystallized from ethanol.

Yield: 69.3 %, m. p. 185-187 °C: IR (KBr) υ_{max}: 3250 (N-H), 1642 (C=O), 1520 (C=N), 1456 (C=C), 1395 (C-H, bend), 1250 (C-C), 1033, 966 (C-H, arom.bend): EI-MS m/z: 328 (10), 327 (8), 250 (12), 139 (11), 224 (24), 223 (60), 209 (23), 208 (100), 181 (8), 180 (32), 179 (5), 167 (6), 163 (6), 161 (9), 160 (16), 152 (16), 151 (6), 149 (13), 148 (10), 147 (67), 132 (5), 130 (9), 121 (6), 120 (31), 119 (21), 111 (7), 109 (5), 105 (21), 104 (17), 97) 10), 92 (13), 90 (10), 83 (9), 77 (27), 71 (11), 69 (10), 47 (10): ^{1}HNMR (300 MHz, $CDCl_3$) δ (ppm): 9.59 (s, b,1H), 8.10 (d, 1H, *J*=8), 7.602 (t, 2H, *J*=8), 7.47 (t, 2H, *J*=8), 7.37-7.30 (m, 10H), 6.28 (s, 1H).

3.14.4. 2-(2-Hydroxyphenyl)-3-{(1E)-(2-hydroxyphenyl) methyl}-2, 3-dihydroquinazolin-4 (1*H*)-one (96)

2-Aminobenzohydrazide (0.1 g, 0.66 mmol) and salicaldehyde (5.5 mL, 4.6 m mol) in absolute ethanole containing few drops of H_2SO_4 were stirred under reflux for 4 h. The reaction mixture was allowed to cool and then added to ice cold water. The product precipitated out was filtered washed with water, dried and recrystallized from ethanol.

Yield 86.2 %, m.p. 208-210 °C,; IR (KBr): 3794, 3364, 37943195, 2862, 2713, 2580, 2461, 1927, 1615, 1455, 1366, 1235, 1155, 1099, 1036.7, 950.8, 926.7, 906.5, 862.1, 749.3, 696.3, 650.9, 588.5, 526.5, 466.7, 424.3: EI-MS; m/z: 359 ($M^{+\cdot}$ 42), 240 (25), 239 (49), 199 (4), 197 (45), 196 (58), 180 (84), 167 (29), 147 (75), 146 (10), 121 (57), 120 (100), 105 (33), 92 (43), 78 (42), 77 (89), 76 (12), 65 (44), 51 (39): ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 10.12 (s, 1H), 9.51(s, 3H), 7.96 (d, 1H, *J*=8), 7.76 (d, 1H, J=8), 7.63 (d, 1H, *J*=8), 7.41-7.32 (m, 4H), 7.25 (t, 1H, *J*=7.68), 6.98-6.89 (m, 3H), 6.78-6.76 (d,1H, *J*=8.2), 6.29 (s,1H).

3.14.5. 2-(2-Hydroxynaphthyl)-3-[(1E-)-(2-hydroxynaphthyl)methyl]-2,3 dihydroquinazolin-4(1*H*)-one (97)

2-Aminobenzohydrazide (0.1 g, 0.66 m mol), and 2- hydroxynaphthaldehyde (0.23 g, 1.0 m mol) were stirred under reflux at in absolute ethanol containing 2-3 drops H_2SO_4. After completion of reaction the solution was poured in ice cold water. The product precipitated out was filtered, washed with water, dried and recrystallized from ethanol.

Yield 67.34 %, m. p. 170-172 °C: IR (KBr): 410, 434, 461, 542, 572, 623, 697, 752, 778,

811, 883, 958, 1090, 1167, 1247, 1304, 1393, 1463, 1515, 1600, 1666, 1856, 1946, 2333, 2654, 3007, 3055, 3188. EI-MS; m/z: 459 (M^+, 16), 290 (49), 277 (45), 274 (85), 260 (15), 176 (12), 158 (12), 144 (71), 128 (45), 120 (100), 105 (100), 92 (57), 65 (13), 77 (7), 51 (3); ^{1}HNMR (300MHz $CDCl_3$) δ (ppm): 13.1 (b,1H), 10.82 (s, 3H), 8.404 (d, 1H, *J*=8.1), 8.373 (d, 1H, *J*=8), 7.93 (d, 1H, *J*=9), 7.878 (t, 2H, *J*=9), 7.81(d, 1H, *J*=8.1), 7.73-7.68 (m, 3H), 7.57(m, 2H), 7.54(d, 1H, *J*=8.1), 7.51(t, 1H, *J*=8.7), 7.46(t, 1H, *J*=8.1), 7.36(d, 1H, *J*=9), 7.28 (t, 1H, *J*=9), 6.98 (d, 1H, *J*=8.7), 6.29 (S, 1H)

3.14.6. 3-[(4-Methoxybenzylidene)amino]-2-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (98)

2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and 0.27 g (1.98 m mol) *p*-anisaldehyde were stirred under reflux for 4 h in absolute ethanol containing 2-3 drops H_2SO_4. After completion, the reaction mixture was poured into ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol. Yield 88.74 %, m. p. 208-210 °C; IR (KBr) $V_{max:}$ 3243 (N-H), 3003 (C-H), 1634 (C=O), 1558 (C=N), 1489 (C=C), 1286 (C-N), 1225 (C-C), 1014, 962, 925 (C-H, arom. bend): EI-MS; m/z: 388 (M^+,3), 387 (14), 254 (28), 253 (74), 252 (30), 239 (17), 238 (100), 210 (22), 196 (5), 180 (9), 168 (10), 167 (30), 147 (46), 146 (20), 135 (23), 134 (25), 130 (26), 120 (51), 119 (43), 108 (10), 105 (26), 92 (33), 90 (16), 78 (10), 77 (42), 65 (12), 64 (12), 51 (13); ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 11.2 (s,1H), 8.107 (d, 1H, *J*=7.44), 7.60 (d, 2H, *J*=8), 7.47 (d, 2H, *J*=7.7), 7.37 (t, 1H, *J*=8), 6.89 (t, 1H, *J*=8), 6.84-6.81 (m, 4H), 6.66(d, 1H, *J*=8.1), 6.28 (s,1H), 5.05 (b, s,1H NH), 3.83 (s, 3H, CH_3), 3.74 (s, 3H, CH_3)

3.14.7. 2-(4-Chlorophenyl) -3- [(1E) - (4-chlorophenyl) methylene] 2, 3-dihydro quinazoline-4 (1*H*)-one (99)

2-Aminobenzo hydrazide (0.1 g, 0.66 m mol) and *p*-chlorobenzaldehyde 0.14 g (0.995m mol) were stirred under reflux for 4 h in ethanol containing 2-3 drops H_2SO_4. After completion the reaction mixture was poured in ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol.

Yield: 47.82 %, m.p. 176- 178 °C; IR (KBr): 510, 584, 667, 751, 789, 825, 908, 962, 1014, 1086, 1155, 1225, 1286, 1351, 1489, 1558, 1634, 1917, 2353, 2815, 3003, 3323; EI-MS; m/z: 400 (M^{+2}), 396 (M^+,4), 295 (5), 258 (28), 257 (30), 244 (35), 243 (15), 242

(100), 214 (23), 180 (18), 179 (12), 148 (16), 147 (90), 139 (38), 130 (16), 124 (19), 120 (24), 119 (43), 113 (6), 111 (17), 105 (24), 102 (13), 92 (29), 89 (46), 77 (35), 65 (9), 51 (9); ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 9.3 (s,1H), 6.994 (d,1H, *J*=8.1), 7.58 (d, 2H, *J*=9), 7.431 (t, 2H, *J*= 8.4), 7.396 (t, 2H, *J*=9), 7.36-7.34 (m, 3H), 7.33 (t,1H, *J*=7.8), 6.97 (t,1H, *J*=7.8), 6.75 (d,1H, *J*=9), 6.27 (s,1H).

3.14.8. 2-(2-Chlorophenyl)-3-[(1E)-(2-chlorophenyl)methylene],3-dihydro quinazolin-4(1*H*)-one (100)

2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and *ortho*-chlorobenzaldehyde (0.14 g ,0.995m mol) were stirred under reflux for 4 h in ethanol containing 2-3 drops H_2SO_4. After completion the reaction mixture was poured in ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol. m. p. 188-190 °C: Yield. 49.43 %. IR (KBr): 742, 966, 1033, 1144, 1250, 1395, 1456, 1520, 1642, 1955, 2301, 2429, 3043, 3250, 3649, 3737, 384: EI-MS; m/z: 396 (M^+,3), 259 (4), 258 (17), 257 (15), 244 (18), 242 (54), 214 (12), 180 (14), 152 (24), 148 (21), 146 (100), 138 (27), 121 (11), 120 (21), 119 (38), 105 (25), 102 (18), 92 (28), 89 (32), 77 (32), 76 (10), 75 (12), 65 (12), 51 (14); ^{1}HNMR (300MHz, CD_3OD) δ (ppm): 11.3 (s,1H), 7.97 (d,1H, *J*=8.1), 7.89 (d,1H, *J*=8.9), 7.83 (d,1H, *J*=9), 7.63 (t,1H, *J*=7.8), 7.43-7.41 (m, 3H), 7.36-7.29 (m, 4H), 6.9 (t,1H, *J*=7.8), 6.7 (d,1H, *J*=9), 5.46 (b, s, 1H)

3.14.9. 2-(2-Hydroxy-5-ethoxyphenyl)-3-[(1E)-(2-hydroxy-5-ethoxyphenyl) methylene] 2,3-dihydro quinazoline-4(1H)-one (101)

2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and 5-ethoxy salicyldehyde (0.16 g, 1 m mol) were stirred under reflux for 4 h in ethanol containing 2-3 drops H_2SO_4. After completion the reaction mixture was poured in ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol.Yield: 52.59 %, m.p. 131-133 °C; IR (KBr) $V_{max:}$ 3364 (N-H, O-H), 2995 (C-H), 1615 (C=O), 1486 (C=N), 1455 (C=C), 1366 (C-H, bend), 1235 (C-N, C-C), 1036, 950, 926 (C-H, arom. bend): EI-MS; m/z: 447 (M^+, 16), 299 (10), 288 (21), 287 (100), 286 (62), 285 (11), 270 (12), 269 (72), 268 (14), 267 (11), 257 (13), 242 (19), 241 (95), 240 (34), 229 (15), 213 (44), 211 (15), 197 (9), 185 (12), 184 (24), 162 (15), 161 (85), 147 (15), 146 (19), 136 (24), 133 (22), 132 (76), 127 (12), 121 (8), 120 (86), 119 (17), 115 (15), 105 (16), 104 (25), 92 (26), 90 (10), 77 (35), 76 (24), 65 (20), 63 (12), 52 (11), 51 (16); ^{1}HNMR (300MHz,

$CDCl_3$) δ (ppm): 11.2 (s,1H), 8.99 (s, 2H), 8.012 (d,1H, *J*=7.8), 7.4 (s, 1H), 7.305 (t, 1H, *J*=9.3), 6.94 (d,1H, *J*=8.1), 6.915 (d, 2H, *J*=7.8), 6.882 (t,1H, *J*=8.7), 6.85 (d,1H, *J*=8.7), 6.795 (d,1H, *J*=7.6), 6.62 (s,1H), 6.12 (S,1H), 4.17-4.068 (m, 4H), 1.49-1.43 (m, 6H) .

3.14.10. 2-(2-Indolylyphenyl)-3-[(1E)-(2indolylphenyl) methylene]2,3-dihydro quinazolin-4(*1H*)-one (102)

2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and indol 3- carboxaldehye (0.135 g) were stirred under reflux for 4 h in ethanol containing 2-3 drops H_2SO_4. After completion the reaction mixture was poured in ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol.Yield: 69 %, m.p.139-140 °C: IR (KBr) $V_{max:}$ 3432 (N-H), 1679 (C=O), 1524 (C=N, C=C), 1344 (C-H, bend), 1233 (C-N), 1009, 947, 777 (C-H, arom. Bend): EI-MS; m/z: 405 (M^+,11), 404 (37), 392 (37), 379 (69), 289 (45), 262 (100), 249 (83), 147 (79), 146 (39), 143 (21), 130 (57), 120 (41), 119 (7), 105 (100), 92 (76), 77 (8), 76 (12), 65 (19), 51 (12); ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 11.24 (s,1H), 8.35 (d,1H, *J*=7.89), 8.09 (d,1H, *J*=8.23), 7.95 (d,1H, *J*=8.3), 7.73 (d,1H, *J*=7.97), 7.67 (t,1H, *J*=7.8), 7.53 (d,1H, *J*=8.1), 7.5 (s,1H), 7.48 (t,1H, *J*=8.32), 7.40-7.34 (m, 3H), 6.89 (t, 1H, *J*=7.8), 6.80 (d,1H, *J*=8.23), 6.65 (s,1H), 6.43 (s,1H), 6.28 (S, 1H)

3.14.11. 2-(2-Hydroxy- 5-methylyphenyl) - 3- [(1E) - (2- hydroxyl- 5-methylphenyl) methylene] 2, 3-dihydroquinazolin-4(1*H*)-one (103)

This was praperad from 2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and 5-methyl, 2-hydroxy benzaldehyde (0.255 g, 0.66 m mol) were stirred under reflux for 4 h in ethanol containing 2-3 drops H_2SO_4. After completion the reaction mixture was poured in ice cold water. The product precipitated out was washed with water, dried and recrystallized from ethanol.

Yield: 68 %, m.p. 176-179 °C: IR (KBr) $V_{max:}$ 3364 (N-H, O-H), 2923 (C-H), 1645 (C=O), 1486 (C=N), 1455 (C=C), 1366 (C-H, bend), 1235 (C-N, C-C), 1036, 950, 926 (C-H, arom. Bend): EI-MS; m/z: 387 (14), 253 (100), 252 (74), 239 (17), 238 (28), 211 (7), 210 (23), 180 (8), 167 (30), 146 (47), 140 (3), 135 (23), 134 (25), 121 (19), 120 (51), 119 (43), 108 (11), 105 (100), 92 (33), 77 (42), 76 (7), 65 (12), 51 (13); ^{1}HNMR (300MHz, $CDCl_3$) δ (ppm): 9.45 (s,1H), 8.72 (s, 3H), 8.071 (d,1H, J=9), 7.96 (d, 1H, J=9), 7.75 (m, 2H), 7.45 (d, 1H, *J*=8.1), 7.38 (S, 1H), 7.301 (d, 1H, *J*=9), 6.92 (t,1H,

J=8.1), 6.682 (d,1H, *J*=8.1), 6.63 (s,1H, recemic), 6.60 (s,1H, recemic), 2.54 (s, 6H).

3.14.12. 2- (2-Chloro-5-nitroyphenyl) -3- [(1E)- (2- chloro- 5-nitrophenyl) methylene] 2, 3-dihydro quinazolin-4(1*H*)-one (104)

This was praperad from 2-Aminobenzohydrazide (0.1 g, 0.66 m mol) and 5-methyl, 2-hydroxy benzaldehyde (0.32 g, 0.66 m mol) were stirred under reflux in ethanol containing 2-3 drops H_2SO_4 as described for compound **103**.

Yield: 70 %: m.p. 240 °C:IR (KBr) $V_{max.}$ 3232 (N-H), 1634 (C=O), 1558 (C=N), 1286 (C-N), 1225 (C-C), 1014, 962, 908 (C-H, arom. bend): EI-MS; m/z: 499.89(M^{+2}), 486(M^{+},3), 329 (5.96), 304 (11.79), 303 (10), 289 (23.97), 288 (12), 287 (74), 241 (11), 213 (8), 177 (7), 147 (43), 123 (8.71), 83 (7), 78 (61), 69 (17), 63 (100), 61 (14), 57 (27), 55 (28): ^{1}HNMR (300MHz, $CDCL_3$) δ (ppm) 8.9 (s,1H), 8.63 (s,1H),8.32 (d, 1H, *J*=7.8), 8.01(s, 1H), 7.97 (d, 1H, *J*=7.6), 7.93 (d, 1H, *J*=8.1), 7.71-7.67(m, 2H), 7.41 (t, 1H, *J*=9.3), 7.128 (d, 1H, *J*=8.1), 7.102 (t, 1H, *J*=7.86), 6.87 (s,1H), 6.21(b,s,1H).

SECTION-C: Synthesis of Quinazolin-4(3*H*)-one Based Unsymmetrical Acetamidines

3.15.1. Ethyl(1*E*)-*N*-(2-methyl/phenyl-4-oxoquinazolin-3(4*H*)-yl)ethanimidoates (105-106)

3.15.2. Ethyl (1*E*)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoate (105)

Method A

3-Amino-2-methylquinazolin-4(3*H*)-one (0.17 g, 0.0009714 mol), PTSA (4.2 g, 0.0284 mol) and triethylorthoacetate (0.25 mL, 0.00145 mol) under argon atmosphere were stirred for 12 h. After completion of reaction as indicated by TLC, the reaction mixture was poured into water; the aqueous layer was then extracted with dichloromethane.After evaporation of dichloromethane under reduced pressure, the product collected was then purified on silica gel column to give colourless crystals of **105**. Yield: 76 %.

Method B

3-Amino-2-methylquinazolin-4(3*H*)-one (0.17 g, 0.0009714 mol), triethylortho acetate (0.25 mL, 0.00145 mol) and glacial acetic acid (1.0 mL) was reflux with continuous stirring for 5 h.after completion of reaction, the reaction mixture was poured into the ice cold water, the product separated as a white crystalline solid which was filtered, washed with water and recrystallized from ethanol.Yield: 67.44 % :m. p; 134 ^{o}C: FAB-MS (+ve, -ve): 246, 244: EI-MS (m/z); 245 (M^{+}, 35), 230 (27), 202 (14), 201 (11), 200 (100), 175 (40), 161(7), 160 (30), 146 (32), 145 (8), 119 (15), 118 (39) 104 (6), 92 (5), 91 (14), 90 (27), 77 (27), 76 (50), 65 (4), 63 (9), 51 (3): ^{1}H-NMR (300MHZ , $CDCl_3$): δppm 8.25 (d, 1H, *J*=8.1, Ar H), 7.735 (t, 1H, *J*=8.4, Ar H), 7.644 (d, 1H, *J*=7.5, Ar H), 7.451 (t, 1H, *J*=8.1, Ar H), 4.452 (q, 2H, *J*=5.7, OCH_2), 2.463 (s, 3H, CH_3), 1.858 (s, 3H, CH_3), 1.430 (t, 3H, *J*=6.7, CH_3)

3.15.3. Ethyl (1E)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) ethanimidoate (106)

Compound **106** was synthesized from 3-amino-2-phenyl-4(3H)-quinazolinone (0.2 g, 0.85 m mol), triethylorthoacetate (0.37 mL) using both methods A and B as described for compound 105. Yield: 83 %, m. p. 132-133 ^{o}C.; IR (KBr), ν_{max}: 3335 (b, 2^{0} N-H, str), 3233 (s ,=C-H, str), 2868 (s,C-H, str), 1840 (w, C=C, overtone), 1720 (s,C=O,str), 1659 (s,w,C=C,str), 1431 (m, s, C-C-H, bend), 1217 (m, s, C-O, str), 1172

(s, C-C, str), 813 (s, m, C-H, bend, arom. region), 765 (s, C-H, bend, arom. region), 685 (s, C-H, bend); EIMS m/z:307 (M+, 2), 279 (85), 237 (23), 202 (5), 105 (100), 77 (45), 51 (10): ^{1}HNMR (300MHz, $CDCl_3$): δ/ppm: 9.02 (d,1H, *J*=8), 8.175 (d, 2H, *J*=8), 7.92 (d,1H, *J*=7.8), 7.54 (m, 3H), 7.24 (m, 2H), 3.7 (q, 2H, *J*=5.4), 2.65 (s,3H), 1.24 (t, 3H, *J*=5).

3.16. Synthesis of quinazolin-4(3*H*) - one based unsymmetrical acetamidines- General procedures for synthesis of compounds 107-116

Method A

Ethanimidic acid, N-[4-oxo-2-phenyl-3(4*H*)-quinazolinyl]- ethyl ester (0.2 g, 0.65 m mol) and suitably substituted aromatic amine (0.65 m mol) in equimolar ratio were fused to melt, then added 1-2 mL of glacial acetic acid and refluxed for 4-5 h. After completion the reaction as monitored by TLC, the volatiles ware evaporated under reduced pressure and the remaining mixture was allowed to cool to room temperature. The solid formed upon cooling was then treated with 0.8M HCl-MeOH and recrystallized from ethanol to yield compounds **107-113** in 46-95% yields.

Method B

Equimolar amounts of *N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl) acetamide and aromatic amine were melt together upon fusion, the molten solution was then refluxed for 2-3 h after adding 1-2 mL acetic acid. After completion of the reaction as monitored by TLC, to the reaction mixture was addede 5-10 ml 0.8 M HCl solution and was allowed to cool, the precipitate thus appeared was filtered, wahed with cold water, and recrystallized from ethanole to afford 60-95% of the target compounds **107-116**.

3.16.1. (1*E*)-*N*-(4-methylphenyl)-*N*'-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (107)

Aromatic amine: *p*-toluidine (0.069 g, 0.65 mmol):

Yield: (69 %); m.p. 227-229 °C); IR (KBr), ν_{max}: 3233 (s ,=C-H, str), 2868 (s, C-H, str), 1840 (w, C=C, overtone), 1720 (s, C=O, str), 1659 (s, w, C=C, str), 1431 (m, s, C-C-H, bend), 1217 (m, s, C-O, str), 1172 (s, C-C, str), 813 (s, m, C-H, bend, arom.), 765 (s, C-H, bend, arom.), 685 (s, C-H, bend): MS (FAB, +ve, -ve) m/z; 369, 367; MS-EI (m/z); 368 (M+, 35), 340 (7), 324 (4), 291 (73), 135 (3), 132 (14),105 (100), 77 (81); ^{1}HNMR

(300MHz, $CDCl_3$):δ (ppm) : 10.9 (b, s, 1H, N-H), 8,47 (d, 1H, *J*=7.8), 7.96 (m, 3H, Ar-H), 7.61 (m, 5H, Ar-H), 7.12 (q, 4H, Ar-H), 2.38 (s, 3H,), 2.16 (s, 3H).

3.16.2. (1*E*)-*N*-(4-bromophenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (108)

Aromatic amine: *p*-bromoaniline (0.112g, 0.65mmol):

Yield: 90 %; m.p. 244-246 °C; IR (KBr) ν_{max}: 3240 (b, s, N-H, str), 3078 (=C-H, str), 3005 (s, -C-H, str), 1668 (s, C=O, str), 1599 (s, w, C=C, str), 1424 (m, -C-H, bend), 1311 (m,s, C-H, str), 1258 (s, m, C=C, str), 1095 (m, s, bend), 881 (m, C-H, bend), 694 (m, -C-Br, str.); EI MS m/z: 435 (M^{+2}, 11), 433 (10), 406 (3), 404 (3), 357 (18), 355 (18), 276 (2), 96 (3), 179 (6), 152 (1), 105 (100), 77 (89), 76 (9), 51 (13); ^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.92 (s,1H, NH), 7.916 (d, 3H, *J*=6.98), 7.77 (d, 2H, *J*=8), 7.638-7.453 (m, 6H), 7.127-7.077 (t,1H, *J*=7.5), 7.0 (d,1H, *J*=7.64), 2.37 (s, 3H, CH_3).

3.16.3. (1*E*)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)-*N*-phenylethanimidamide (109)

Aromatic amine: Aniline: Yield: 57 %; m. p. 233-236 °C; IR (KBr), ν_{max}: 3222 (b, N-H, str.), 3078 (=C-H, str.), 2992 (C-H, str.), 1680 (C=O, str.), 1614 (C=N, str.), 1574 (C=C, str), 1424 (=C-H, bend), 1311 (=C-H, bend), 1258 (C-C, str.), 881, 772, 752 (C-H, bend, arom); MS (FAB, +ve, -ve) m/z (340, 338), EI-MS m/z:`354 (M^+, 81), 339 (12), 328 (39), 313 (12), 277 (86), 264 (27), 261 (41), 222 (89), 209 (18), 181 (55), 133 (31), 105 (100), 103 (16), 77 (83), 58 (12), 54 (14); ^{1}HNMR (300MHz, DMSO-d_6) δ: 11.05 (b, s, 1H, N-H), 8.09 (d, 1H, *J*=8), 7.3 (d, 2H, *J*=8), 7.88-7.83 (m, 4H), 7.76 (t, 1H, *J*=8), 7.61-7.57 (m, 3H), 7.07(d, 2H, *J*=8), 6.97 (t, 1H, *J*=8), 2.34 (s, 3H, CH_3).

3.16.4. (1*E*)-*N*-(3-bromophenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (110)

Aromatic amine: 3-Bromoaniline: Yield 60 % ; m.p. 222-225 °C; IR (KBr), ν_{max}: 3301(N-H, str), 3078 (=C-H, str.), 2992 (C-H, str.) 1680(C=O, str.) 1614 (C=N, str.), 1579 (C=C, str.) 1424 (=c-H, bend), 1258 (C-C, str.), 1174 (C-C, str.), 982,846 (C-H, ben, Aroam.), 752 (C-Br, str.); EI-MS m/z: 435(M^{+2}, 11), 433 (10), 406 (3), 404 (3), 357 (18), 355(18), 276 (2), 196 (3), 179 (6), 152 (1), 105 (100), 77 (89), 76 (9), 51 (13): ^{1}HNMR (300MHz, DMSO-d_6), δ (ppm): 11.05 (b, s, 1H, N-H), 8.09 (d, 1H, *J*=8), 7.93 (d, 2H, *J*=8), 7.88 (s,1H), 7.76 (d, 1H, *J*=8), 7.61 (m, 6H), 7.07 (t,1H, *J*=8), 6.97 (d,1H, *J*=8), 2.34 (s, 3H, CH_3).

3.16.5. (1*E*)-*N*-(3-Nephthyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (111)

Aromatic amine: 2-Naphthylamine: Yield 66 %; m.p.218-220 °C; IR (KBr); ν_{max}: 3241 (N-H,str.), 2933 (C-H, str), 2866 (C-H, str.), 1651(C=O, str.), 1520 (C=c, str.), 1417 (C-H, bend), 1203 (C-C, str.), 975, 885, 780 (C-H, bend, arom.); EI-MS m/z: 404 (M^+, 23), 376 (8), 327 (42), 299 (4), 261(2), 230 (2), 222 (71), 168 (12), 127 (22) 105 (100), 77 (70): ^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.53 (s, 1H, N-H), 7.95 (d, 1H, *J*=8), 7.83 (t, 1H, *J*=8.3), 7.78 (t, 2H, *J*=8), 7.71(d, 2H, *J*=7.6), 7.65-7.61(m, 6H), 7.43-7.39 (m, 2H), 7.27 (t.1H, *J*=8.3), 7.12 (d, 1H, *J*=7.89), 2.35 (s, 3H).

3.16.6. (1*E*)-*N*-(4-methoxyphenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (112)

Aromatic amine: *p*-Anisidine: yield 62 %; m.p. 224-226 °C; IR (KBr);ν_{max}: 3312 (N-H, str.), 3116 (=C-H, str), 2924 (C-H, str.), 1167 (C=O, str), 1611 (C=C, str), 1586 (C=N, str.), 1447 (=C-H, str.), 1401 (=C-H, bend), 1322 (C-H, bend), 1304 (C-O, str.), 1248 (C-C, str.) 833, 745,678 (C-H, bend. Arom.); EI-MS m/z: 384 (M^+, 36), 356 (6), 307(49), 279 (2), 148 (9), 105 (100), 77 (74), 50 (10); ^{1}HNMR (300MHz, $CDCl_3$): δ (ppm): 10.9 (b, s, 1H, N-H), 7.96 (m, 4H, Ar-H), 7.61 (m, 5H, Ar-H), 7.12 (m, 4H, Ar-H), 3.8 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3).

3.16.7. (1*E*)-*N*-(2, 4, 6-timethylphenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (113)

Aromatic amine: 2, 4, 6-Trimethylphenylamine: yield 60 %; m.p.165-168 °C; IR (KBr); ν_{max}: 3241 (N-H, str.), 2940 (=C-H, str), 1670 (C=O, str.), 1630 (N=C, str.), 1611 (C=C, str), 1447 (=C-H, bend), 1401(C-H, bend), 1187 (C-C, str.), 821, 745, 640 (C-H, bend, arom.); EI-MS *m/z*: 396 (M^+,2), 319 (2), 177 (40), 135 (100), 120 (54), 104 (15), 91 (28), 77 (24), 65 (12): ^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 11.01 (b, s, 1H), 8.14 (d, 1H, *J*=8), 8.0-7.6 (m, 6H), 7.3 (d, 1H, *J*=8), 6.93 (d, 1H, *J*=8.34), 6.8 (s, 2H), 2.2 (s, 3H), 2.1 (s, 6H), 2.0 (s, 3H).

3.16.8. (1*E*)-*N*-(4-chlorophenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (114)

Aromatic amine: P-chlorophenyl: Yield 80 %: m. p. 252-255 °C; FAB-MS (+,-) 389,387; EI-MS: 390 (M^{+2}, 20), 388 (M^+, 54), 371(6), 362 (5), 360 (59), 344 (6), 314

(27), 313 (27), 312 (17), 311 (87), 154 (4), 152 (11), 111(8),106 (8), 105 (100), 77 (44), 75 (4), 51(5), 44 (8): ^{1}HNMR (300MHz, $CDCL_3$), δ (ppm); 9.01 (s, 1H), 8.36 (d, 1H, *J*=8.3), 8.23 (d, 2H, *J*=8.6), 8.02(t, 1H, *J*=9), 7.771 (d, 1H, *J*=8.6), 7.68-7.63 (m, 1H), 7.39 (d, 1H, *J*=9), 7.34 (t, 1H, *J*=9), 7.15 (d, d, 2H, *J*=8,3), 6.95 (d, 2H, *J*=8.1), 2.23 (s, 3 H, CH_3).

3.16.9. (1*E*)-*N*-(4-iodophenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (115)

Aromatic amine: *p*-iodophenyl: yield 81%: m.p. 248-250 °C; IR (KBr); $\nu_{max:}$ 3222 (N-H, str.), 3078 (C-H, str.), 1921(overtone), 1668 (C=O, str.), 1614 (C=C, str.), 1504 (C=N, str.), 1424 (C-H,bend), 1174 (C-C,str), 982, 846, 752 (C-H,bend, arom.); FAB-MS (+ve, -ve) 481,479; EI-MS: 480 (M, 20), 465 (54), 404 (6), 362 (5), 360 (59), 340 (6), 314 (27), 313 (27), 312 (17), 311 (87), 154 (4), 152 (11), 111(8), 106 (8), 105 (100), 77 (44), 75 (4), 51 (5), 44 (8).; ^{1}HNMR (300 MHz, $CDCl_3$), δ (ppm): 10.5 (b, s, 1H, NH), 8.43 (d, 1H, *J*=8), 8.02-7.97 (m, 2H), 7.71-7.69 (m, 2H), 7.63-7.59 (m, 3H), 7.532-7.51(m, 2H), 7.365(t, 1H, *J*=7.8), 7.15 (d, 2H, *J*=8.1), 2.23 (s, 3H, CH_3)

3.16.10. (1*E*)-*N*-(4-hydroxyphenyl)-*N'*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)ethanimidamide (116)

Aromatic amine: *pera* aninophenole Yield: 77 %, m.p. 255-258 °C; IR (KBr), $\nu_{max:}$ 3471 (O-H, str.), 3251 (N-H, str.), 2880 (C-H, str.), 1664 (C=O, str.), 1603 (C=N, Str.), 1540 (C=C, str.), 1449 (C-H, bend), 1255 (C-C, str.), 796, 757, 700 (C-H, bend. Arom); FAB-MS (+ve, -ve): (371, 369): EI-MS m/z: 370 (M^+,8.59), 369 (14), 293 (34), 106 (12), 105 (100), 93 (5), 78 (9), 77 (87), 65 (13), 51 (10); ^{1}HNMR (300 MHz, $CDCl_3$): δ (ppm): 11.03 (b, s, 2H, NH), 7.92 (d, 1H, *J*=9.6), 7.80 (d, 2H, *J*=8.7), 7.767(t, 1H, J=8.6), 7.61 (d, 1H, *J*=8.6), 7.58-7.53 (m, 1H), 7.748-7.35 (m, 3H), 7.29 (d, 2H, *J*=7.9), 6.97 (d, 2H, *J*=8.23), 2.01 (s, 3H, CH_3).

SECTION- D: 2-Alkyl/arylquinazolin-4(3*H*)-ones (117-126) and 2-(2-Substituted -4-Oxoquinazolin-3(4*H*)-yl)-1*H*-Isoindole-1, 3(2*H*)-Diones (127-129)

3.17. 2-Alkyl/arylquinazolin-4(3*H*)-ones (117-126)

3.17.1. 2-Alkyl/arylquinazolin-4(3*H*)-one preparation via oxidative deamination of N-aminoquinazolones

General experimental procedures for oxidative deamination of N-aminoquinazolinones

Method A

A mixture of appropriate 2-alkyl/aryl-aminoquinazolin-4(3*H*)-one (0.28 m mol) and $KMnO_4$ (1.12 m mol) in 10 ml water was refluxed for 3-5 h. After completion of the reaction, as monitored by TLC, the reaction mixture was hot filtered and the filtrate was allowed to cool. The product thus precipitated was filtered, dried and recrystallized from water- ethanol mixture to give the corresponding (**117- 126**) in 65-80 % yield (Table 2.24).

Method B

A mixture of appropriate 2-alkyl/aryl-aminoquinazolin-4(3*H*)-one (0.28 m mol) and $KMnO_4$ (1.12 m mol) in 10 ml water was placed in domestic microwave oven. An additional flask containing water was placed as a heat sink. The flask was irradiated for appropriate time (Table 2.24) at interval for 30 sec followed by 10 sec irradiation. After completion of reaction, the water was evaporated completely and the mixture was extracted with dichloromethane and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the corresponding products (**117-126**) in 80-91% yield.

3.17.1. Synthesis of 2-Alkyl/arylquinazolin-4(3*H*)-ones (117-126) by cyclocondensation of methylanthranilate and aryl/alky cyanides

A stream of dry hydrogen was passed through the mixture of methylanthranilate and suitable alky/aryl cyanide in dry 1, 4-dioxane solvent for 6-12h. After completion of the reaction as indicated by TLC, the reaction mixture was basified with 10% $NaHCO_3$. The product was extracted with DCM and dried over anhydrous $NaHSO_4$. Excess of solvent was evaporated under pressure and products were purified by recrystalization from water-ethanol mixture.

3.17.2. 2-Methylquinazolin-4(3*H*)-one (117)

This compound was prepared from 3-amino-2-methylquinazolin-4(3H)-one via both the methods A and B as described above.

IR (KBr): 3170 (NH), 3065 (C-H), 2925 (C-H), 1667 (C=O), 1603 (C=N), 1510 (C=C), 1471 (C=C arom.), 1451 (C=C, arom), 1240 (C-C), 1144 (C-O), 786 (C-C, bend, arom), 692 (C-C, bend, arom): FAB-MS *m/z*: 161 (M+1), 159 (M-1); EI-MS *m/z*: 160 (M^+, 100), 145 (21), 120 (19), 92 (23), 76 (10), 64 (11): ^{1}HNMR (400 MHz, $CDCl_3$,) δ ppm : 8.16 (d, 1H, *J*=7.6 Hz), 7.78 (t, 1H, *J*=7.1 Hz), 7.6 (d, 1H, *J*=7.8 Hz), 7.48 (t, 1H, *J*=7.1 Hz), 2.4 (s, 3H).

3.17.3. 2-Phenylquinazolin-4(3*H*)-one (118)

This compound was prepared from 3-amino-2-phenylquinazolin-4(3H)-one via both the methods A and B as described above.

IR (KBr): 3374 (NH), 3065 (C-H), 1668 (C=O), 1603 (C=N), 1563 (C=O), 1478 (C=C, arom), 1293 (C-O), 1240 (C-C), 820 (C-C, bend arom), 692 (C-C,bend, arom.): EI-MS *m/z*: 222 (M^+), 119 (100), 105 (23), 90 (30), 77 (63), 76 (18):^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 10.2 (s, 1H), 8.26 (d, 1H, *J*=8 Hz), 7.82 (m, 4H), 7.56 (m, 4H) .

3.17.4. 2-(4-Methylphenyl) quinazolin-4(3*H*)-one (119)

This compound was prepared from 3-amino-2-(4-methylphenyl)quinazolin-4(3*H*)-one via both the methods A and B as described above. IR (KBr) υ_{max} cm^{-1}: 3347 (NH), 2924 (C-H), 2796 (C-H), 1672 (C=O), 1610 (C=N), 1470 (C=N), 1373 (C-C, bend, arom.), 1231 (C-O), 1188 (C-C), 769 (C-C, bend, arom.), 681(C-C,bend, arom): EI-MS *m/z*: 236 (M^+, 57), 119 (100), 91 (25), 90 (25), 76 (13), 63 (14): ^{1}HNMR (, 400 MHz, $CDCl_3$) δ ppm: 10.11 (s, 1H), 7.92 (d, 1H, *J*=9 Hz), 7.69 (m, 3H), 7.20 (m, 4H), 2.348 (s, 3H, CH_3)

3.17.5. 2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (120)

This compound was prepared from 3-amino-2-(4-chlorophenyl)quinazolin-4(3*H*)-one *via* both the methods **A** and **B** as described above.IR (KBr) υ_{max} cm^{-1}: 3312 (N-H), 1705 (C=O), 1548 (C=N), 1378 (C-H, bend), 1250 (C-C): EI-MS *m/z*: 258 (M^{+2}, 12), 256 ($M.^+$, 52), 178 (4), 149 (13), 138 (9), 119 (100), 113 (3), 111(12), 102 (5), 94 (14), 91 (4), 90 (13), 77 (5), 76 (8), 57 (8): ^{1}HNMR (400 MHz, $CDCl_3$,) δ ppm: 9.80 (s, 1H), 8.28 (d,

1H, *J*=11 Hz), 8.04 (d, 2H, *J*=11.07 Hz), 7.82 (d, 1H, *J*=10 Hz), 7.75 (d, 1H, *J*=11 Hz), 7.54 (d, 2H, *J*=11 Hz), 7.42 (d, 1H, *J*=11.2 Hz) .

3.17.6. 2-(4-Bromophenyl) quinazolin-4 (3*H*)-one (121)

This compound was prepared from 3-amino-2-(4-bromophenyl)quinazolin-4(3*H*)-one via both the methods A and B as described above. IR (KBr) υ_{max} cm^{-1}: 1716 (C=O, str), 1602 (C=N, str), 1557 (C=C, str), 1470 (C=C-C, str), 1309 (C-O, str), 1224 (C-C, str), 767 (C-Br, str): EI-MS *m/z*: 302 (M^{+2}, 52), 301 (M^{+}, 36), 300 (58), 299 (37), 248 (3), 185 (3.7), 183 (3.6), 157 (4), 155 (3.9), 1120 (7), 119 (100), 102 (8), 92 (12), 90 (13), 76 (17), 75 (9), 69 (19), 57 (11): ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 7.95 (d, 1H, *J*=11 Hz), 7.81 (d, 1H, *J*=10.8 Hz), 7.76 (t, 2H, *J*=8.4 Hz), 7.59 (d, 1H, *J*=11.8 Hz), 7.53 (m, 2H).

3.17.7. 2-(4-Nitrophenyl) quinazolin-4(3*H*)-one (122)

This compound was prepared from 3-amino-2-(4-nitrophenyl)quinazolin-4(3*H*)-one *via* both the methods **A** and **B** as described above. IR (KBr) υ_{max} cm^{-1}: 3374 (N-H), 1667 (C=O), 1603 (C=N), 1478 (C=C), 1293 (C-C=C), 942, 820, 768 (C-H, arom. bend): EI-MS *m/z*: 267 (M^{+}, 12), 150 (82), 120 (44), 119 (100), 104 (65), 92 (53), 90 (20), 76 (60). ^{1}HNMR (400 MHz, $CDCl_3$,) δ ppm: 10.3 (s, 1H), 8.34 (d, 3H, *J*=9 Hz), 8 (d, 2H, *J*=9 Hz), 7.9 (d, 2H, *J*=9 Hz), 7.5 (m, 1H).

3.17.8. 2-Benzylquinazolin-4(3*H*)-one (123)

This compound was prepared from 3-amino-2-benzylquinazolin-4(3*H*)-one via both the methods A and B as described above. IR (KBr) υ_{max} cm^{-1} : 3347 (C-H), 1677 (C=O), 1603 (C=N), 1451(C=C-C), 1340 (C-H, bend), 1240 (, C-N,C-C), 942, 820, 768 (C-H, arom.bend): EI-MS *m/z*: 236 (M^{+}, 55), 235 (100), 207 (5), 119 (20), 92 (42), 77 (57): ^{1}HNMR (400 MHz, $CDCl_3$) δ ppm: 10.2 (s, 1H), 8.2 (d, 1H, *J*=7.8 Hz), 7.8 (d, 1H, *J*=8 Hz), 7.2 (dd, 1H, *J*=9 Hz), 7.6 (dd, 1H, *J*=8.5 Hz), 7.08 (d, 1H, *J*=14 Hz), 7.06 (d, 1H, *J*=16 Hz), 7.2 (dd, 2H, *J*=14 Hz), 7.25 (dd, 1H, *J*=16 Hz), 4.1(s, 2H).

3.17.9. 2-(4-Hydroxyphenyl) quinazolin-4(3*H*)-one (124)

This compound was prepared from 3-amino-2-(4-hydroxyphenyl)quinazolin-4(3*H*)-one *via* both the methods A and B as described above.IR (KBr) υ_{max} cm^{-1} : 3354 (N-H, O-H), 1685 (C=O), 1486 (C=N), 1455 (C=C), 1366 (C-H, bend), 1235 (C-N, C-C), 1036, 950, 926 (C-H, arom. Bend): EI-MS *m/z*: 252 (M^{+}, 100), 208 (8), 132 (12), 120 (8),

119 (90), 90 (10), 77 (5): ^{1}HNMR ($CDCl_3$, 400 MHz,) δ ppm: 10.00 (s, 1H), 8.28 (d, 1H, *J*=7.8Hz), 8.05 (d, 1H, *J*=8.5 Hz).

3.17.10. Ethyl (4-oxo-3,4-dihydroquinazolin-2-yl)acetate (125)

This compound was prepared from ethyl (3-amino-4-oxo-3,4-dihydroquinazolin-2-yl)acetate via both the methods A and B as described above.IR (KBr) υ_{max} cm^{-1} : 3352 (N-H), 1664 (C=O), 1530 (C=N), 1445 (C=C), 1328 (C-H, bend), 1235 (C-N, C-C), 1036, 950, 926 (C-H, arom. Bend): EI-MS *m/z*: 232 (M^+, 62), 160 (100), 119 (37), 89 (39), 77 (28), 60 (42), 55 (21).^{1}HNMR ($CDCl_3$, 400 MHz) δ ppm: 8.26 (d, 1H, *J*=7.8 Hz), 7.76 (m, 2H), 7.49 (t, 1H, *J*=7.1 Hz), 4.26 (q, 2H, *J*=7.36 Hz), 3.86 (s, 1H), 1.34 (t, 3H, *J*=7.17 Hz).

3.17.11. 2-Ethylquinazolin-4(3*H*)-one (126)

This compound was prepared from 3-amino-2-ethylquinazolin-4(3*H*)-one via both the methods A and B as described above IR (KBr) υ_{max} cm^{-1} : 3432 (N-H), 1591 (C=O), 1530 (C=N), 1483 (C=C-C), 1367 (C-H, bend), 1253 (C-N, C-C), 1009, 950, 898 (C-H, arom. Bend); EI-MS *m/z*: 174 (M^+, 92), 173 (100), 149 (14), 119 (33), 77 (7), 55 (12); ^{1}HNMR ($CDCl_3$, 400MHz,) δ ppm: 10.40 (s, 1H), 8.27 (d, 1H, *J*=7.8 Hz), 7.76 (t, 1H, *J*=8.2 Hz), 7.65 (d, 1H, *J*=8 Hz), 7.46 (t, 1H, *J*=8 Hz), 2.83 (q, 2H, *J*=15 Hz), 1.43 (t, 3H, *J*=7.6 Hz).

3.18. 2-(2-Substituted -4-oxo-quinazolin-3(4*H*)-yl)-1*H*-isoindole-1, 3(2*H*)-diones (127-129)

3.18.1. Typical procdure for the synthesis of 3-(1,3-dihydro-2*H*-isoindol-2-yl)quinazolin-4(3*H*)-one(127)

Method A: Synthesis via thermal fusion

A mixture of 2-methyl,3-aminoquinazolin-4(3*H*)-one (0.05 g, 0.00028 mol) and phthalic anhydride (0.042 g, 0.00028 mol) in 25 mL round bottom flsk were thermaly fused on hotplate at 150 °C for 30 min. On chilling the flask the product solidified, crude product was then recrystallized from water-ethanol mixture to obtaine the desired product yield. 83 %, m. p. 176-178 °C

Method B: Microwave assisted synthesis

3-Aminoquinazolin-4(3*H*)-one (.01 g, 0.000062 mole) and 2-benzofuran-1, 3-dione (0.01 g, 0.000062 mol) were irradiated in domestic microwave oven for 12 min.

the product after formation was purified over silica column using ethylacetate/hexane (1:9).

Yield: 93 %, m.p: 176-180 °C; EI-MS m/z: 291 (M^+, 8), 290 (25), 265 (10), 160 (21), 146 (51), 145 (100), 132 (45), 121 (12), ^{1}HNMR (300 MHz) δ (ppm): 10.23 (s, 1H), 8.29 (d, 1H, *J*=7.57), 8.01(1, 2H, *J*=8.73), 7.89 (t, 1H, 8.2), 7.78 (t, 1H, 7.7), 7.6 (t, 2H, *J*=8.56), 7.55-7.51(t, 1H, *J*=8.23)

3.18.2. 3-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-methylquinazolin-4(3*H*)-one(128)

3-Amino-2-methylquinazolin-4(3*H*)-one (0.01 g, 0.00005714 mol), and 2-benzofuran-1, 3-dione (0/0845 g, 0.00005714 mol) were irradiated in domestic microwave oven for 8 min.The product was recrystilized from water ethanol mixture.

Yield: 91 %, m.p: 167-169 °C; EI-MS m/z: 305 (M^+, 9), 26 2 (2), 166 (3), 149 (22), 123 (6), 122 (87), 105 (100), 104 (35), 92 (17), 77 (49), 76 (63), 65 (46), 51(36); ^{1}HNMR (300 MHz) δ (ppm): 8.21 (d, 1H, *J*=7.83), 8.0196-7.99 (dd, 2H, *J*=8.57), 7.89 (d, 2H, *J*=8.565), 7.822-7.767 (t, 1H, *J*=8.2), 7.717 (d, 1H, *J*=7.7), 7.5-7.452 (t, 1H, *J*=7.3), 2.48 (s, 3H, CH_3)

3.18.3. 3-(1,3-Dihydro-2*H*-isoindol-2-yl)-2-phenylquinazolin-4(3*H*)-one(129)

3-Amino-2-phenylquinazolin-4(3*H*)-one (0.2 g,0.000843 mol) and 2-benzofuran-1, 3-dione (0.1248 g, 0.000843 mol) in an open mouth Vaile was irradiated for 13 minutes, the product formed was recrystallized from dilute ethanol.

Yield: 99 %, m.p: 68-69 °C, EI-MS m/z: 367 (M^+, 13), 290 (37), 222 (57), 208 (73), 180 (14), 146 (89), 133 (11), 105 (100), 92 (48), 65 (12), 51 (13): ^{1}HNMR (300 MHz) δ (ppm): 8.24 (d, 1H, *J*=8.2), 8.21 (d, 2H, *J*=7.8), 7.99 (dd, 2H, *J*=8.67), 7.85 (t, 1H, *J*=8.56), 7.73 (d, 1H, 8.2), 7.67 (t,1H, *J*=8.7), 7.62 (m, 2H), 7.59 (t, 2H, *J*=8), 7.56 (t, 1H, *J*=8.6)

CHAPTER – 4

BIOACTIVITY EVALUATION

4.1. Summary

This chapter deals with the bioassay screening of the quinazolinones synthesized in the present study. Selected compounds were evaluated for antifungal, antibacterial, Antilieshmanial, antioxident, Brine Shrimp (Cytotoxicity), Urease Inhibition, ButylCholine Esterase Inhibition, AChE Inhibition, Tyrosinase inhibitory and Anti-glycation activities using reported methods. Structural activity relationships have been discussed.

4.2. Introduction

Due to the importance of Quinazolinones based heterocycles for their diverse biological activities such as inhibition of Topoisomerase I and II [1,2], Kinesin spindle protine (KSP) [3], and tubulin polymerization [Raffa,D.; Edler], thymidylate synthase [4], this class of heterocyclic compounds is also reported for their anti-inflamatory and cardiovascular activities. These compounds also reported as Cardiotonic, antihistamine, antifungal, antiviral, antimicrobacterail and antimalarial agents [5]. In addition to all these literature also describes psychotropic, hypnotic and a range of other CNS effects such as CNS depression, CNS stimulation, tranquilizing, antidepressant and anticonvulsant [6, 7]

Due to importance of this class of compounds much attention has been paid to the synthesis. We therefore beside the development of efficient and high-throughput methodologies for the pharmacologicaly interesting compounds and novel quinazolinones heterocycles have screened some of the synthesized compounds for various Bioactivities.

4.3. ESSAYS PROTOCOLS

4.3.1. Cytotoxicity

Brine shrimp (Artemisia salina leach) eggs were hatched in a shallow rectangular plastic dish (22×32 cm), filled with artificial sea water which was papered with a commercial salt mixture (Instant Ocean, aquarium system, Inc., Mentor, OH, USA) and double distilled water. An unequal partition was made in the plastic dish with the help of a perforated device. Approximately 50mg of the eggs were sprinkled in to a large compartment was opened to ordinary light. After two days nauplli were collected by a pipette from a light side. A simple of the test compound was prepared by 20mg of each

compound in 2ml methanol. From this stock solution, 400, 50 and 5µg/ml were transferred into 9 vials three for each dilution and one vial was kept as controlhaving 2ml of methanol only. The solvent of allowed to evaporate overnight. After two days, when shrimp larvae were ready, 1ml of sea water was added to each vial and 10 shrimps were added (30 shrimps/dilution) and the volume was makeup to 5ml with sea water in each vial. After 24h the number of survivors was counted. Data were analysed by a finney computer program to determine the LD_{50} [8, 9]

4.3.2. Antifungal Assay (*In Vitro*)

Antifungal activity was performed following agar tube dilution protocol [Paxton, 1991]. Crude extract and subsequent fractions were used in dose of 24 mg/mL and pure compounds 12 mg/mL of sterile DMSO, serving as stock solution. The agar dilution method is the most convenient method for routine testing of samples such as plant extracts. The method is suitable for testing non-sterile plant extracts, because aerobic organisms do not develop well under the solidified agar. However, the occasional culture that develops on the surface of the agar can be easily recognized. Non-polar extracts, essential oils, suspensions of solids or emulsions and antimicrobial substances, which do not diffuse through agar media, can be tested directly by incorporating them with the agar media as if they were aqueous solutions. This method has an advantage that unlike the diffusion method, no concentration gradient occurs during the testing procedure. More over, several different test microorganisms may be tested simultaneously on the same dilution, which makes the agar dilution method very efficient.

Antifungal activity was carried out against clinical specimen of human pathogens namely *Candida albicans* (ATCC 2091), *Candida glabarata* (ATCC 90030), *Aspergillus flavus* (ATCC 32611), *Trichophyton longifusis* (clinical isolate), *Mycosporum canis* (ATCC 11622) and *Fusarium solani* (ATCC 11712).

- **Sabouraud Dextrose Agar (SDA)**

Formula	**g/litre**
Mycological peptone	10.0
Glucose	
Agar	
pH	

15 g of SDA was dissolved in distilled water and volume was made to 1 liter, the mixture was heated for at least 10 minutes and then sterilized in autoclave (15 lbs/in^2 pressure and at 121° C temperature for 15 minutes).

Procedure

The culture of organisms was maintained on Sabouraud Dextrose Agar (SDA). Sabouraud Dextrose Agar (4 ml) was dispensed into screw cap tubes, which were then placed in autoclave at 121^0 C for 15 minutes and then temperature was brought to 50^0 C. The stock solution (66.6 µL) was then added to non-solidified SDA media, giving final concentration of 400 µg of extract per ml of SDA. Tubes were then allowed to solidify in slanting position at ambient temperature. Each tube was inoculated with a piece of inoculum (4 mm diameter), removed from 7 days old culture of respective fungi. For non mycelial growth, an agar surface streak was employed. Inhibition of fungal growth was observed after 7 days of incubation at 28±1^0 C. Media supplemented with DMSO and reference anti fungal drugs were used as negative and positive control respectively. Miconazole was used as standard antifungal drug for all pathogens except *C.albicans* for which Amphotericin-B was used as a standard drug. Growth in medium containing extracts was determined by measuring linear growth in mm and then percent growth inhibition was calculated with reference to negative control using formula:

$$\% \text{ Inhibition} = \frac{\text{Growth in sample tube (mm)}}{\text{Growth in control tube (mm)}} \times 100$$

Following scale was employed to measure activity of sample.

Table 4.1: Criteria for determining antifungal assay

Entry	Percent Inhibition	Activity
1	30-40	Low
2	50-60	Moderate
3	61-70	Good
4	Above 70	Significant

4.3.3. Antibacterial Assay (*In vitro*)

Antibacterial assay was carried out by agar well diffusion method [Atta-ur-Rehman *et al.*, 1999]. Pure compounds were used in dose of 1 mg/mL DMSO.

Antibacterial activity was studied against various human pathogens including *Escherichia coli* (ATCC 25922), *Bacillus subtilus* (ATCC 6633), *Shigella flexenari* (clinical isolate), *Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853) *and Salmonella typhi* (ATCC 19430).

In this bio assay, three types of media were used viz. solid medium (nutrient agar), semi-solid medium (soft agar) and liquid medium (nutrient broth).

- **Solid medium (Nutrient agar)**

  Nutrient agar 28 g

  Distilled water 1 L (q.s)

Nutrient agar was dissolved in distilled water and volume was made up to 1 liter. It was then placed in auto clave at 121^0 C for 15 minutes. Media was then cooled to 40^0 C and poured in sterile petri dishes and media was then allowed to solidify at room temperature.

- **Semi solid medium (Soft agar)**

  Soft agar 0.8 g

  Distilled water 100 mL (q.s)

Soft agar was dissolved in distilled water and volume was made up to 100 mL. It was then dispensed in 7 mL quantity to screw capped test tubes. These test tubes were placed in auto clave at 121^0 C for 15 minutes and then referigerated.

- **Liquid medium (Nutrient broth)**

  Nutrient broth 0.8 g

  Distilled water 100 mL (q.s)

Nutrient broth was dissolved in distilled water and volume was made up to 100 mL. Prepared broth was dispensed in 3 mL quantity to screw capped test tubes, which were placed in auto clave at 121^0 C for 15 minutes and then refrigerated.

Procedure

The culture of bacterial organisms was maintained on stock culture agar.A colony of bacterial culture was inoculated in nutrient broth and incubate at 37 ± 1° C for 24 hours. Next day soft agar was melted and cooled to 40 ^{0} C and then added 100 µL of bacterial culture, shaken well and then poured it on nutrient agar containing plate. The plate was rotated to make even distribution of culture and allowed to solidify the lawn. Wells (6 mm diameter) were made in medium in each plate using a sterile metallic borer with centers at least 24 mm apart. Samples (3 mg/ml of DMSO) were then added in respective well using sterilized dropping pipettes. Other wells supplemented with DMSO and reference anti bacterial drug served as negative and positive control, respectively. Plates were then incubated at 37 ±1 ^{0} C for 24 hours. Activity was determined by measuring diameter of zones depicting inhibition (mm). Antibacterial potential of sample was then determined as per criteria mentioned in Table 2.8. Percent growth inhibition was calculated with reference to the positive control.

Table 4.2: Criteria for determining antibacterial assay

Entry	Diameter	Activity
1	Below 9 mm	No activity
2	9-12 mm	Non-Significant
3	13-15 mm	Low
4	16-18 mm	Good
5	Above 18 mm	Significant

The synthesized compounds were screened for antibacterial activity against the *Escherichia coli*, *Proteus mirabilis, Pseudomonas aeroginosa, Salmonella typhi, Shigella boydii and Bacillus cerous, Corynebacterium diptheirae, Staphylococcus aeureus, and Streptococcus pyogenes* by using literature protocol [3a,b]. In the agar well diffusion method, wells were duged in the media with the help of a sterile metallic borer with contres at least 24 mm part. Two to eight hours old bacterial inoculums containing

approximately 10^4-10^6 colony forming units (CFU)/ml were spread on the surface of nutrient agar with the help of a sterile cotton swab. Cotton swab was rotated firmly against the upper inside well of the tube to express excess fluid, Entire agar surface of the plate was streaked with the swab three times turning the plate 60^0 between each streaking. Recommended concentration of the test sample (2mg/ml of DMSO) was then added in their respective wells. Other wells supplemented with DMSO and reference antibacterial drugs serving as negative and positive controls, respectively. The plates were incubated immediately at 37 ° C for 14-19 h or later in necessary; Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

4.3.4. Leishmanicidal Bioassay (*in vitro*)

Parasites cultivated in bulk were aseptically sedimented down at 3000 rpm, counted with the help of improved incubator chamber under the microscope and diluted with fresh medium to a final concentration of 2.0×10^6 parasites ml^{-1}.

The compounds to be checked were dissolved in appropriate solvent and then diluted to a final concentration of 1.0 mg/ml of PBS (phosphate buffer saline, PH 7.4 containing 0.5% MeOH). 5% DMSO) was added as negative control, while glucantime, amphotericin B, pentamidine and ampiciline to a final concentration of 1.0mg/ml was added as positive control. The plate was then incubated at 21-22^{0}C in dark for 3-5 days during which control organism multiply 3-6 times. The culture was examined microscopilly on an improved neubauer chamber and IC_{50} values of the compounds possessed antileishminial activity were calculated.[11, 12]

4.3.5. Tyrosinase inhibition assay

Tyrosinase inhibition assay were performed in 96-well micro plate format using SpectraMax 340 microplate reader (Molecullar Device, CA, USA) according to the method reported by hearing (1987).[13] the compounds were screened for the *ortho*-diphenolase inhibitory activity of Tyrosinase using L-DOPA as substrate. All the active inhibitors from the preliminary screening were subjected to IC_{50} studies. Compounds were dissolved in methanol to a concentration of 2.5%. 30 unites of the mashroom tyrosinase (28 nM from sigma chemical co., USA) first preincubated with compound in 50nM Na-phosphate buffer (PH 6.8) for 10 minutes at 25^{0}C, then the L-DOPA (0.5mM)

was added to the reaction mixture and the enzyme reaction was monitored by measuring the change in the absorbance at 475 nm (at 37^0C) sue to the formation of the DOP Achrome for 10 min. the present inhibition of the enzyme was calculated as follow, by using MS Excell®™ 2000(Microsoft cop. USA) based program developed for this purpose:

Percent inhibition= [ABS $_{Blank}$- ABS $_{Sample}$/ ABS $_{Blank}$] ×100

Where:

ABS $_{Blank}$= absorbance for the blank

ABS $_{sample}$= absorbance for the sample

After screening the compounds median inhibitory concentration (IC_{50}) was also calculated. All the studies have been carried out at least in triplicate and the results represents the mean± S.E.M (Standard error of the mean). Kojic acid was used as standard inhibetor for the tyrosinase.

4.3.6. Cholinesterase Inhibition Assays [14, 15]

The standard operational assay protocol was employed to determine the AChE and BChE inhibition activities of natural products, by the spectrophotometric method of Ellman *et al.*, (1961). Enzymes and reagents such as electric-eel AChE (EC 3.1.1.7), horse-serum BChE (E.C 3.1.1.8), acetylthiocholine iodide, butyrylthiocholine chloride, 5, 5′-dithiobis [2-nitrobenzoic acid] (DTNB), and galanthamine were purchased from Sigma (St. Louis, MO, USA). All other chemicals were of molecular biology grade.

Acetylthiocholine iodide and butyrylthiocholine chloride were used as the substrates to assay AChE and BChE activities, respectively. The reaction mixture contained 150 μL of sodium phosphate buffer (100 mM) (pH 8.0), 10 μL of DTNB, 10 μL (0.2 mM) of test-compound solution and 20 μL of AChE or BChE solution, which were mixed and incubated for 15 minutes at 25^o C. The reaction was then initiated with the addition of 10 μL acetylthiocholine or butyrylthiocholine, respectively. The hydrolysis of acetylthiocholine and butyrylthiocholine were monitored by the formation of yellow 5-thio-2-nitrobenzoate anion resulting from the reaction of DTNB with thiocholine, catalyzed by acetylthiocholine and butyrylthiocholine, respectively at a wavelength of 412 nm (15 min.). Test compounds and the positive control (galanthamine)

were dissolved in EtOH. As the extinction coefficient of the yellow anion is known, the rate of enzymatic reaction was finally determined by applying the Ellman equation.

$$\text{Rate (mols / L / min.)} = \frac{\text{Change in absorbance / min.}}{13,600}$$

All the inhibition studies were conducted in 96-well micro-titer plates using Spectra Max-340 (Molecular Devices, CA, USA). Concentration of compounds that inhibited the hydrolysis of substrates (acetylthiocholine and butyrylthiocholine) by 50 % (IC_{50}) was determined by monitoring effect of various concentrations of the compound on inhibition values. The IC_{50} (inhibitor concentration that inhibits 50 % activity of AChE and BChE) values were then calculated using the EZ-Fit Enzyme Kinetics program.

4.3.7. Urease inhibition bioassay

Urease assay and inhibition Reaction mixtures comprising 25 µL of enzyme (Jack bean Urease) solution and 55 µL of buffers containing 100 mM urea were incubated with 5 µL of test compounds (1 mM concentration) at 30 °C for 15 min in 96-well plates. Urease activity was determined by measuring ammonia production using the indophenol method as described by Weatherburn.[16] Briefly, 45 µL each of phenol reagent (1% w/v phenol and 0.005% w/v sodium nitroprusside) and 70 µL of alkali reagent (0.5% w/v NaOH and 0.1% active chloride NaOCl) were added to each well. The increasing absorbance at 630 nm was measured after 50 min, using a microplate reader (Molecular Device, USA). All reactions were performed in triplicate in a final volume of 200 µL. The results (change in absorbance per min) were processed by using SoftMax Pro software (Molecular Device, USA). All the assays were performed at pH 8.2 (0.01 M $K_2HPO_4.3H_2O$, 1 mM EDTA and 0.01 M $LiCl_2$). Percentage inhibitions were calculated from the formula $100- (OD_{testwell}/OD_{control}) \times 100$. Thiourea was used as the standard inhibitor of Urease

4.3.8. Antiglycation Bioassay[22-25]

BSA (Bovine Serum Albumin) as 10 mg/ml dissolved in 67 mM phosphate buffer (pH: 7.4)

Glucose as 50mg/ml of Buffer;

- 3mM Sodium Azide in required quantity of Buffer to inhibit bacterial growth

- Using 3 mM concentrations of new compounds along with standard inhibitors
- Incubating the prepared sample (60 µl) in the incubator for a week at 37^0C.
- After incubation in 96 well plates for a week, samples are taken out and cooled at room temperature.
- Then 6µl of 100 % TCA (Trichloro acetic acid) is added to each well, supernatant containing unbounded glucose, inhibitor and interfering Substances are removed after agitation and centrifugation at 14000 rpm for 4 minutes, pellets are obtained at the bottom of the wells.
- Then solvent is removed from each well and 60 µl of PBS (pH: 10) is added to dissolve the pellets and to serve screening.
- The comparison of fluorescence intensity at 370 nm Excitation and Emission at 440nm is obtained by using Spectrofluorimeter.
- Rutin is used as the standard inhibitor with 82.5 % inhibition at 3mM concentration.

Calculations:

% Inhibition =100 – (OD (test) / OD (blank) × 100

4.3.9. Antioxidant Bioassay

A: Nitric Oxide radical scavenging assay

To 10µl of test compound(s) in DMSO was added 20µl BPS(Phosphate Buffer Solution) followed by addition of 70 µl Sodium Nitroprisside and was incubated for 30 minutes, after shaking the mixture 50 µl Sulfanilic acid solution was added , shaked wel and end point was measured. Vitamin C was used as positive control and DMSO as blank. The percent Radical scavenging ability was measured using the formula:

% Inhibition = {O.D (test)/ O.D (blank) ×100}-100

Where: O.D = Optical density or Absorption maximum

B: DPPH radical scavenging assay

Test sample (s) was dissolved in DMSO and allowed to react with ethanolic solution of 1,1-Diphenyl-2-picrylht\ydrazyl radical(DPPH) for 30 min. at 37 ^{0}C. After incubation the decrease in absorption was measured at 515nm using microplate reader. The percent redical scavenging ability was determined in comperasion with DMSO treated control group.

4.4.0. RESULTS AND DISCUSSION

4.4.1. Antifungal bioassay

There are reports describing the antifungal activities [18] of the 2, 3-disubstituted quinazolin-4(3*H*)-ones, a representative antimicrobial agent in clinical use is methaqualone [17], therefore, some selected quinazolin-4(3*H*)-ones synthesized were tested against five fungi i.e. *Aspergillus Flavus*, *T. Longifusus, C. Albicans, M. Canis* and *F. Solani*. The results are illustrated in [Table 4.1 and 4.2]. Compounds showed weak to moderate activities against the tested fungi. Compounds **23, 42, 45** and **122** showed moderate activities against the fungus *T. Longifusus*. Compound Rsh-72 showed good activity against *C. Albicans* and compounds **68, 72** and **124** showed significant activity against *Aspergillus Flavus*, while all other compounds were found inactive. Similarly, compounds **23, 42, 56** and **122** were found less active against *F. Solani* while all other compounds were found inactive.

All compounds exhibited variable activities against different fungal strains. Almost all compounds showed negligible activities against *C. albicans* and *C. glebrata* while weak to good activities were shown by some tested compounds against *T. lonifusus*, *A. flavus, M .canis* and *F. solani.* Compounds **114** and **70** were found completely inactive against all the fungi.

Structural activity relationship reveals that substitution at both 2 & 3 positions play an important role in their antifungal activities. It was found that bromo group enhanced the activity as the compound **42** containing 4-bromophenyl showed significant activity against *T. longifusus*, while the same compound showed weak activity against *M. canis* and *F. solani.* Similarly, pronounced activities were found due to the presence of ethylester group on position 2 against *T. longifusus* and weak activities against *M. canis* and *F. solani*. It was found that the activities further increased due to the presence of heteroaryl (2,3-thiazolo) group at 3 position as compound **55** showed significant activities against *M. canis* and *F. solani* and showed weak activity against *T. longifusus* and *C. glabrata*. The detailed activities by various compounds are given in the [Table 4.1]

The systemic fungal infections are on the increase much recently due to the non susceptibility of commonly used antifungal agent such as fluconazol. Resistance to

standard antifungal agents in *Candida* sp. and *Aspergillus Fumigatus* have led to the over production of multi drug transporters. *C. albicans* is the most active fungi for Candidiasis thereby encompasses infections that range from superficial, such as oral thrush and vaginitis, to systemic and potentially life-threatening diseases. *Candida* infections of the latter category are also referred to as candidemia and are usually confined to severely immunocompromised persons such as cancer, transplant and AIDS patients, whereas superficial infections of skin and mucosal membranes by *Candida* causing local inflammation and discomfort is common in many human populations. On the other hand, quinazolin-4(3*H*)-ones are reported for specific inhibition of CDRI in *C. albicans*. Therefore, some of the compounds were specifically tested for inhibitory activity against *C. albicans*, all compounds showed moderate to good activities against the fungus compared to the standard antifungal Amphotericine B (20 μg/ml), compound **117** showed highest activity, compound **31** was also found very active, while all the rest were found moderately active [Table 4.2]

Structural activities relation ship shows that methyl side chain is more important and increase the activities as found in case of compounds **114** which showed the highest activity among the entire series. It was also observed from the inhibition of quianzolinoine based acetamidines **103, 112** and **111** which showed moderate but significant inhibition against *C. albican* due to presence of CH_3, while limited effect was observed due to subtituent on the phenyl group as in case of **111** and **112**.Slight increases in the inhibition rate was observed due the presence of Iodo group and thus Iodo group was found to increase activity compared to chlorogroup.The graphs (Fig. 7-Fig. 13) showed the extent of inhibition by active compounds agianst *C. albican* in comparison to the standard drug amphotericine.

Table 4.3: Results of antifungal bioassays

Entery	Compd.	*T.Longifugus*	*C.Albicans*	*A.Flavus*	*M.Canis*	*F.Solani*	*C.Glebrata*
1	**67**	20	0	0	50	0	20
2	**68**	20	0	50	20	0	0
3	**56**	20	0	0	50	50	20
4	**34**	20	0	0	50	0	0
5	**122**	50	0	0	20	20	0
6	**58**	20	0	0	20	0	0
7	**42**	40	20	0	50	0	0
8	**45**	50	0	0	20	20	0
9	**114**	00	0	0	00	0	0
10	**23**	50	0	0	20	30	0
11	**70**	00	0	0	00	0	0
12	**72**	20	0	50	20	0	0
13	**124**	20	0	40	00	0	0
14	**22**	00	0	0	00	0	0
SD	**A**	**B**	**C**	**D**	**E**	**F**	**G**

A = Miconazol = 70 µg /ml, **B** = Miconazol = 110 µg /ml, **C** = Amphotericim = 20 µg /ml, **D** = Miconazol = 98 µg /ml, **E** = Econazol Miconazol = 73.2 µg /ml,

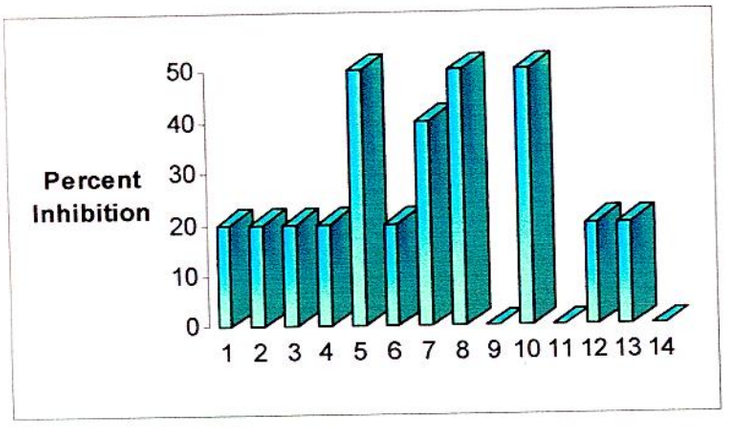


Fig 7: Anti fungal activity of various compounds against *T. Longifugus*

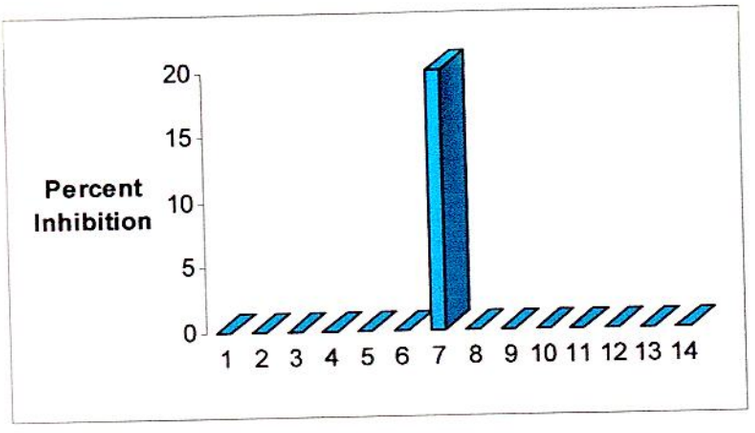


Fig 8: Anti fungal activity of various compounds against *C.Albicans*

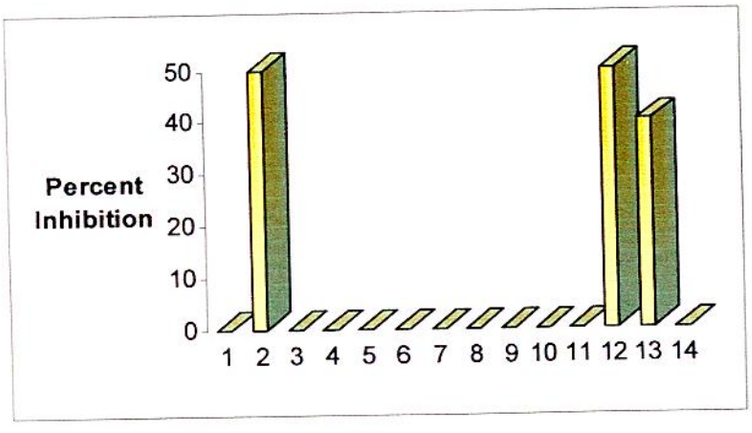


Fig 9: Anti fungal activity of various compounds against *A. Flavus*

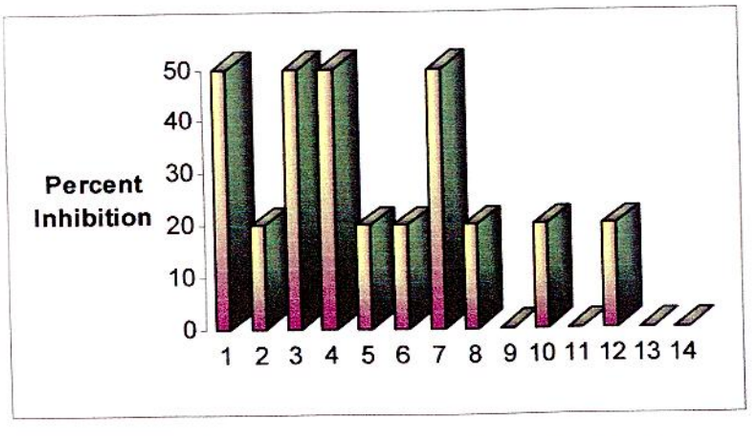


Fig 10: Anti fungal activity of various compounds against *M.Canis*

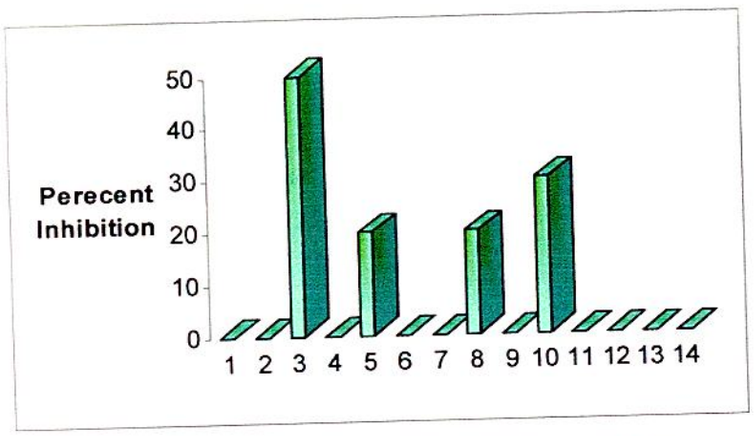


Fig 11: Anti fungal activity of various compounds against *F.Solani*

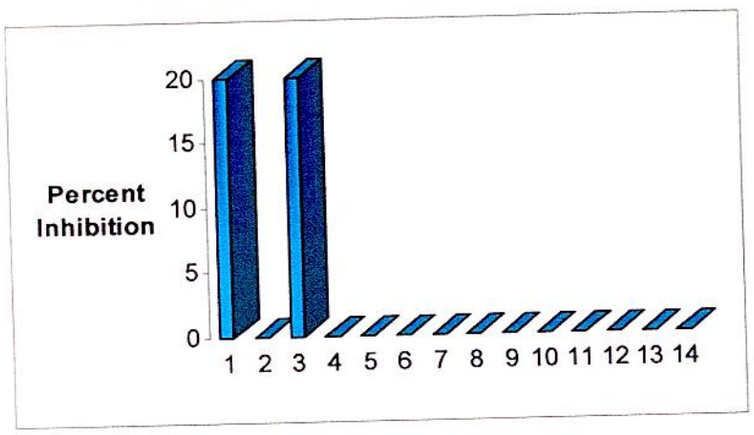


Fig 12: Anti fungal activity of various compounds against *C.Glaberata*

Table 4.4: Results of antifungal bioassay against *C.Albicans*

Entry	Compd.	*C. albicans*
1	**104**	20
2	**112**	22
3	**47**	20
4	**48**	20
5	**18**	19
6	**33**	22
7	**111**	20
8	**89**	23
9	**117**	24
10	**39**	21
11	**23**	18
12	**45**	21
13	**114**	29
14	**9**	23
15	**7**	22
16	**29**	27
17	**28**	24
18	**8**	23
19	**O1**	20
20	**O3**	20
21	**96**	23
22	**O5**	25
23	**98**	29
24	**99**	27
25	**SD Amphotericine B.**	20

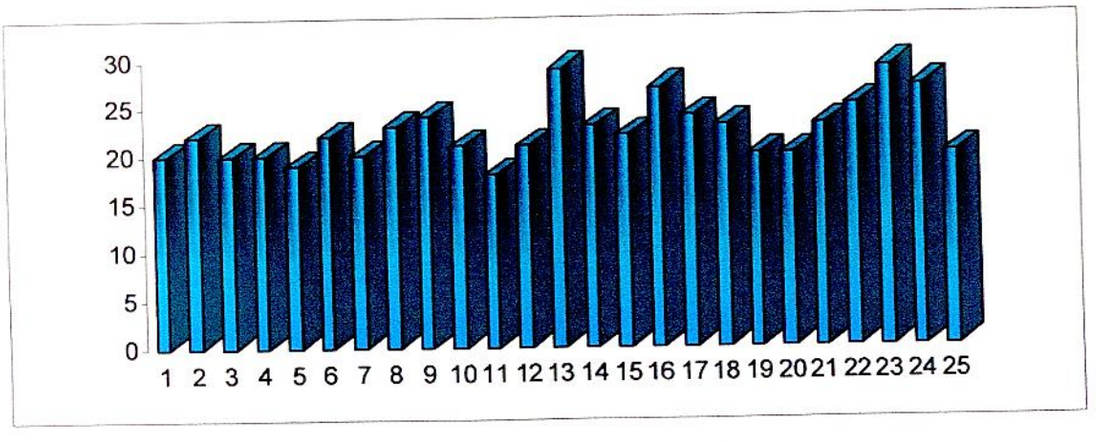


Fig 13: Anti fungal activity of various compounds against *C. albicans*

4.4.2. Antibacterial assay

In view of wide spread resistant strains of microorganisms, there is an urgent need for the development of new antimicrobial agents to treat the patients infected with multidrug resistant bacteria.

The extensive research in the field of antibiotics has lead to the development of a large number of antibiotics including cephalosporins, penicillin's, aminoglycosides, tetracyclines, carbenems, monobactam, streptogramins, macrolides, and dihydrofolate reduces inhibitor. Methaquolon is representative antibiotic of quinazolin-4(3*H*)-one. This encouraged us to search for antibacterial compounds among various quinazolinone derivatives. Some of the synthesised quinazolinones were tested for *in- vitro* antibacterial activity against gram +Ve and gram –Ve bacteria.

Among the tested compounds was founds highly active against *B.subtilis* (+ve), *S. Aureuy, E-coli and S. Typhi (-ve)*, was compound **35** which showed highest activity against *S.Areu*. The same compoing showed moderate activities against *B.subtilis, E.Coli,* and *S.typhi*. The compound 35 was found highly active against *S.typhi* and moderately active against *B.substilis, S.Aureu* and *E.coli. S*imilarly, compounds **35** and **27** showed very good activities against *S.Aureu,* while all the rest of the synthesized compounds were either found inactive or very weakly active against the tested bacteria. Further, a series of the compounds synthesized were tested against *B. Pumis (-ve)* and *S. Aureus (-ve*).Compounds **33, 55, 93** and **111** were found highly active against *B. Pumis (-ve)* while **30** showed significant activity against *S. Aureus (-ve*) while other compounds showed weak to moderate activities and some were found completly inactive. [Table 4.3]

Structural activity relationship showed that methyl group increases the activity as was observed in case of compound **114.** The acetamidine was also found to enhance activity in some case as found in **111,** which showed good activity against B. pumis

Table 4.5: Antibacterial activities at concentration 1mg/ml

Entery	**Compd.**	**Gram-positive**		**Gram-negative**			
1		*B.Subtilis*	*S.Aurea*	*E.Coli*	*S.Flexenari*	*P.Aeruginosa*	*S.Typhi*
2	**37**	-	10	-	12	-	-
3	**37**	-	13	-	-	-	-
4	**35**	40	40	44	-	-	46
5	**27**	16	20	16	13	-	16
6	**19**	-	-	-	-	-	10
7	**22**	12	16	15	-	-	23
8	**56**	-	11	-	10	-	-
9	**70**						
10	**69**	14	18	14	11	-	11
11	**68**	12	17	11	-	-	-
12	**121**	10	14	10	-	-	-
13	**89**	10	11	-	9	12	11
14	**67**	13	--	10	--	--	--
15	**114**	14					
16	**45**	15					
17	**7**	15	13	10			
18	**SD***	26	17	25	24	17	21

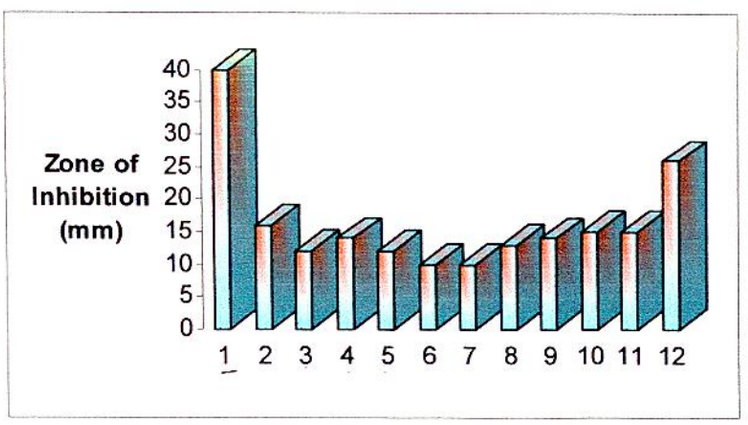


Fig 14: Anti bacterial activities of compounds against *B.Subtilis*

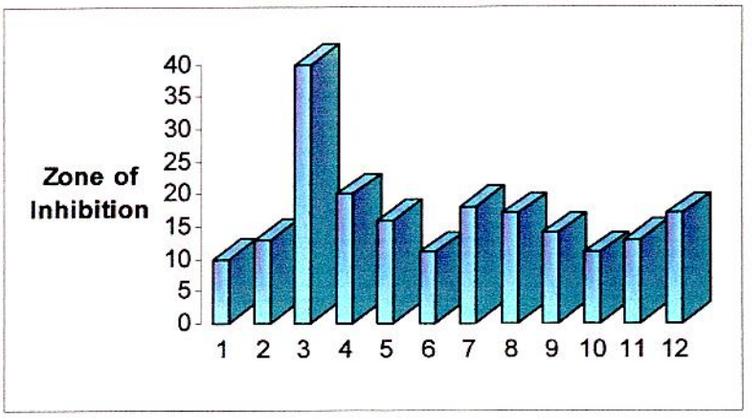


Fig 15: Anti bacterial activities of compounds against *S. Aureus*

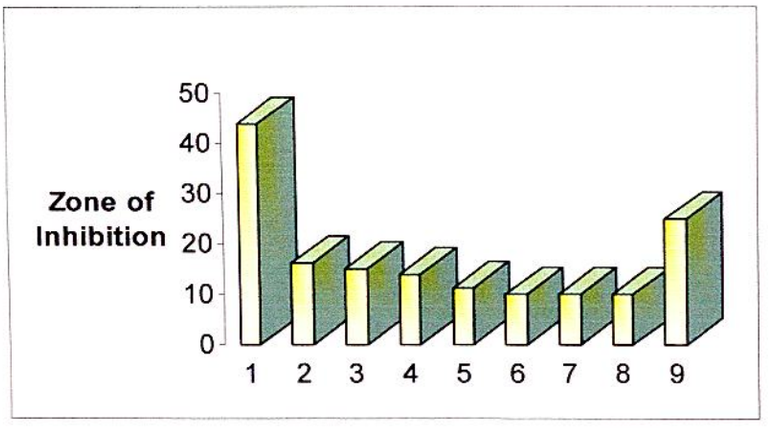


Fig 16: Anti bacterial activities of compounds against *E .Coli*

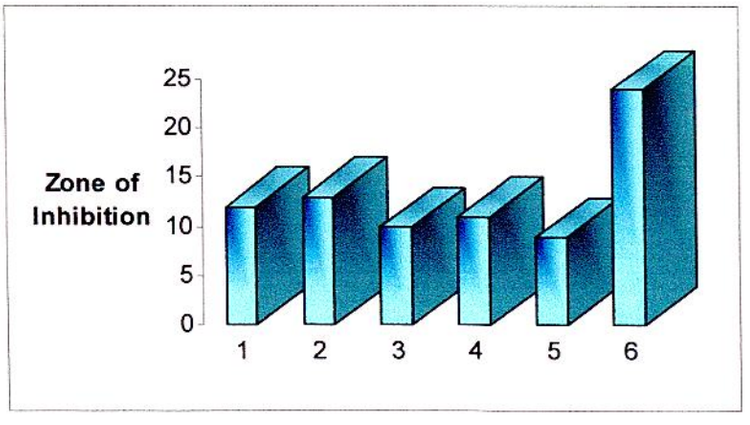


Fig 17: Anti bacterial activities of compounds against *S.Flexenari*

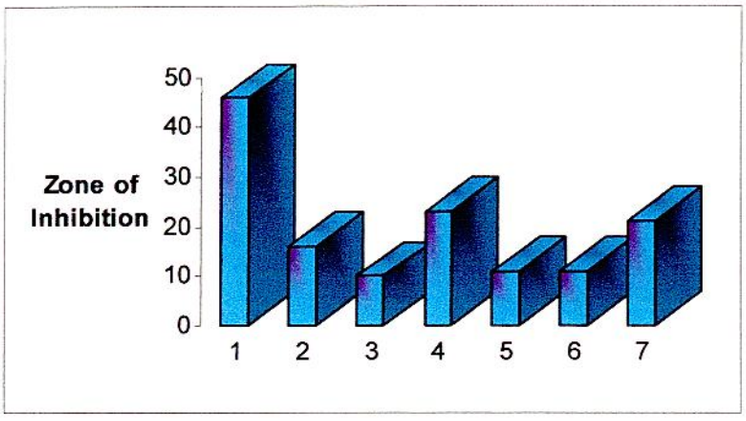


Fig 18: Anti bacterial activities of compounds against *S. Typhi*

Table 4.6: Results of antibacterial bioassay at concentration 1mg/ml

Entry	**Compd #**	***Bacillus pumis***	***Staphylococcus aureus***
1	**33**	26	22
2	**108**	17	0
3	**30**	18	21
4	**23**	16	0
5	**45**	20	0
6	**58**	21	20
7	**114**	23	18
8	**96**	20	17
9	**97**	20	0
10	**98**	20	16
11	SD^1	21	15
12	SD^2	35	27

SD^1 = Imipenium

SD^2 = Gentamycien.

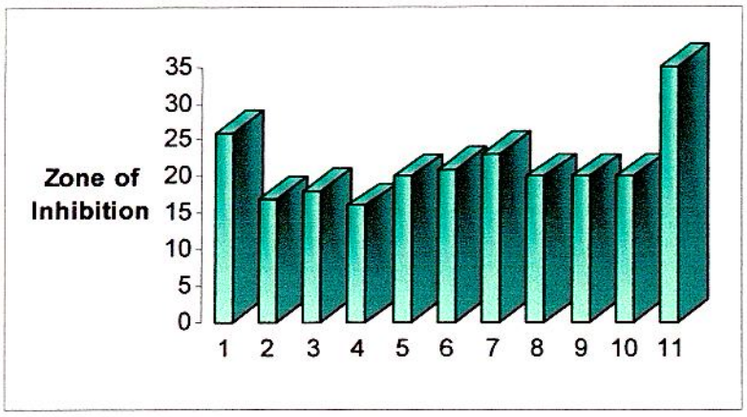


Fig 19: Anti bacterial activities of compounds against *Bacillus pumis*

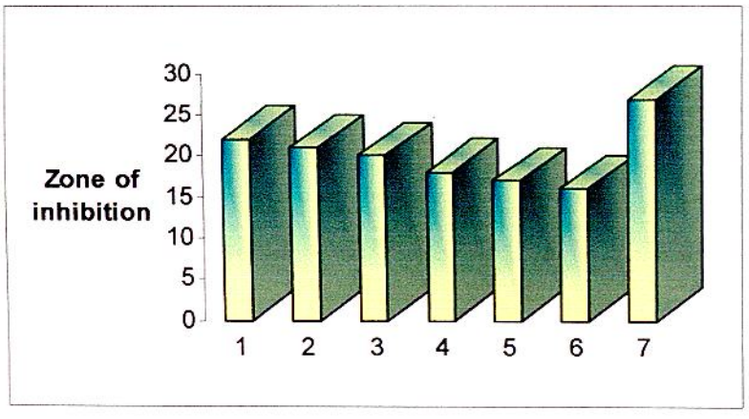


Fig 20: Anti bacterial activities of compounds against *Staphylococcus aureus*

4.4.3. Antleishmanial Activity

Several reports describing the Antleishmanial activity of the nitrogen containing compounds.This prompted us to test some of the syntehsised quinazolinones for their antileishminial activity since literature do not describe antileishminial acitivities of this class of compounds.

A total of 18 compounds were tested. The activity was tested at 100 μg/ml levels according to the literature method. Amphotericine B was used as standard drug having IC_{50}=50 μg/ml. Among the tested compounds, **45** showed the highest activity with IC_{50}=48 μg/ml. presence of chlorine as substituent which was found to enhance the antileishmanial activity as can be seen in case of compounds **86**, IC_{50}=55μg/ml, **78** IC_{50}=67.4 μg/ml while all the other compounds showed moderate activities [Table 4.5]

Structural activity relationship reveals that phenolic substitutents increased the activity while benzylic group at 3-position markedly increased activity and in this contest

compound **45** was found highly active than the standard leishmanicidal drug used. Since, there is no literature available on the lieshminicidal activities of quinazolinone derivatives thus, it is concluded from the present study that a suitable potential candidate against leishmania disease can be explored in this class of heterocyclic compounds.

Table 4.7: Results of antilieshmanial bioassay

Entry	Compd #	IC_{50}(µg/ml)
1	**16**	72
2	**23**	71
3	**24**	71
4	**34**	71
5	**35**	71
6	**38**	95
7	**43**	98
8	**45**	48
9	**56**	71
10	**58**	93
11	**66**	7100
12	**67**	7100
13	**68**	94
14	**69**	82.1
15	**78**	67.4
16	**86**	55.9
17	**114**	89.4
18	**124**	71

4.4.4. Antioxidant Activity

Some of the synthesised compounds were tested for their anti oxidant activity using both (NO and DPPH) radical scavenging assay.Most of the compounds showed weak to made rate activity. The combined results are given in [Table 4.6 and 4.7]. Only compound 19 showed significant activities. This is due to more NO radical scavenging ability. This could be attributed to the presence of phenolic moiety in the compound **19**. The next more potent compound found was **24**, while rest of the screened compounds showed marginal or no antioxidant activity.

The same series of the compounds was also tested for DPPH radical scavenging ability and bit diversity was observed for their NO radical seavenging ability. Compound **24** was found most potent among the tested compounds having 67.1% DPPH radical

scavenging ability, while compounds **7, 61** and **69** were found moderately active and rest of the compounds were found inactive completely.

From structural activity relationship, it is concluded that the presence of phenolic group made significant contribution to the anti-oxidant activities. The results are also summarized in graphs.

Table 4.8: NO· Radical scavenging activities at 0.5 m M concentration

Entry	**Compd #**	**%RSA**
1	**7**	37.6
2	**19**	74.1
3	**20**	--
4	**24**	70
5	**28**	--
6	**43**	--
7	**58**	--
8	**61**	36.7
9	**66**	--
10	**69**	36.99
11	**114**	

Table 4.9: DPPH. Radical scavenging activities at 0.5 m M concentration

Entry	**Compd %**	**%RSA**
1	**7**	36
2	**19**	67.1
3	**20**	-
4	**24**	38.66
5	**28**	-
6	**43**	-
7	**58**	-
8	**64**	-
9	**66**	-
10	**68**	-
11	**69**	36.9
12	**114**	-

4.4.5. Results of cytotoxicity bioassays

A range of the synthesised quinazolinones was subjected for brine-shrimp lethality bioassay using the protocol of Meyer *et al*. The compounds **32, 36** showed strong cytotoxicity. Compound **70** was found moderately cytotoxic while all other were found inactive [Table 4.8]

Table 4.10: Results of cytotoxicity bioassay

Entry	Compd #	LD 50 (µg/ml)
1	7	--
2	19	--
3	19	99.6
4	20	--
5	22	98
6	32	28.09
7	34	99
8	38	--
9	41	--
10	42	99
11	42	--
12	43	-
13	44	--
14	45	--
15	45	99
16	46	--
17	52	--
18	56	--
19	58	98
20	60	57
21	64	89
22	66	--
23	67	--
24	68	--
25	68	--
26	69	98.7
27	70	53
28	77	--
29	78	--
30	89	--
31	114	--
32	115	98
33	122	--
34	124	99

4.4.6. *In vitro* Urease Inhibition

A range of the synthesised compounds were screened for urease inhibition studies [Table 4.9]. All the tested compounds showed weak uraese inhibition activities or were found inactive compared to the standard drug thiourae. Among the tested compounds, **56** was found active. However, the acticity was found very low comared to the standard thiourae.

Table 4.11: Results of Urease inhibition bioassays

Entry	Compd #	Conc.	%Inhibition
1	SD*		IC_{50} 21.10±0.310
2	**16**	0.2	--
3	**19**	0.2	31.5
4	**24**	0.1	--
5	**28**	0.2	38.6
6	**31**	0.2	21.9
7	**32**	0.1	34.0
8	**33**	0.05	23.9
9	**38**	0.2	32.2
10	**43**	0.2	--
11	**44**	0.1	--
12	**45**	0.1	--
13	**45**	0.2	--
14	**53**	0.1	8.5
15	~~**56**~~ 53	0.2	37
16	**56**	0.2	40.1
17	**58**	0.1	--
18	**59**	0.1	--
19	**66**	0.1	16.4
20	**67**	0.2	20
21	**68**	0.1	19
22	**69**	0.1	--
23	**69**	0.1	5
24	**76**	0.1	--
25	**78**	0.1	
26	**79**	0.05	37.3
27	**89**	0.2	43.3
28	**114**	0.2	23.3
29	**115**	0.2	21.9
30	**124**	0.1	39.2

4.4.7. Cholinesterase inhibition

A range of the synthesized compounds were screened for *in vitro* inhibition of both acetylcholine esterase and butylcholine esterase inhibition activities. The results are summarised in the [Table 4.10 and 4.11]. The tested compounds were found weakly active or inactive against acetylcholine esterase (Table 5.8), while most of the compounds showed moderate butylcholine esterase inhibitory activities [Table 4.10]. Compounds **45** and **69** were found highly active against butylcholine esterase with (IC_{50}= 17.5 ± 0.8) and (IC_{50}= 2.32 ± 0.1), respectively. The compound **69** was found more potent than the standard drug used. Structural activity relationship shows that phenolic substituent at position 3 significantly increased the activity, thus compound **69** having phenolic substituent at 3 position was found 3.66 times more active than the standard butylcholinesterase inhibitor. Another important contribution was made by the benzylic substituent at position 3 and thus compound **45** was found more potent than the standard inhibitor. Structurally, novel quianzolinone derivatives prepared i, e. **59, 57** and **58** showed moderate activities at concentration of 0.1µg/ml, with the highest activity shown by compound **58**, which indicate that Methylene Bridge is responsible for increase in inhibition but increasing the methylene chain than two carbons decrease the inhibition as was found in case of compound **57**. Compound **57** contains active sites and can be explored after derivitization in search of potential inhibitors. The diverse activities are due to different substituents at both position 2 & 3.

The same series of compounds was also tested for their inhibition against acetylcholinesterase. Among the whole series, only five compounds were found weakly active [Table 4.11]

Table 4.12: Butylcholinesterase inhibition bioassay

Entry	Compd #	Conc.	% inhibition
1	**16**	0.2	--
2	**19**	0.2	26.4
3	**24**	0.2	22.6
4	**31**	0.2	37
5	**32**	0.2	45.8
6	**34**	0.2	12.4
7	**38**	0.2	5
8	**43**	0.2	31
9	**44**	0.2	24
10	**45**	0.2	90.7(IC_{50}=7.5±0.8)
11	~~45~~ 47	0.2	26
12	**54**	0.2	19.1
13	**56**	0.2	45
14	**58**	0.1	34.9
15	**60**	0.1	47.5
16	**61**	0.1	68
17	**66**	0.2	--
18	**67**	0.2	23.7
19	**68**	0.2	29.5
20	**69**	0.05	33.1
21	**69**	0.2	93.3((IC_{50}=2.32±0.1)
22	**76**	0.2	47.8
23	**77**	0.2	32.8
24	**78**	0.2	62
25	**79**	0.2	
26	**85**	0.1	57
27	**89**	0.2	16.5
28	**114**	0.2	68
29	**115**	0.2	25.5
30	**124**	0.2	17.2
SD* (standard drug)	Galathamine		IC_{50} 8.5±0.01

Table 4.13: Results of Acetylcholinesterase inhibition bioassay

Entry	Compd #	Conc.	% inhibition
1	**16**	0.2	--
2	**19**	0.2	-
3	**24**	0.2	--
4	**31**	0.2	--
5	**32**	0.2	--
6	**38**	0.2	--
7	**41**	0.2	--
8	**43**	0.2	--
9	**44**	0.2	35
10	**45**	0.2	-- X
11	**45**	0.2	--
12	**54**	0.2	--
13	**56**	0.2	8.6
14	**58**	0.1	--
15	**60**	0.1	-- X
16	**60**	0.1	--
17	**66**	0.2	--
18	**67**	0.2	--
19	**68**	0.2	--
20	**69**	0.05	-- X
21	**69**	0.2	17.6
22	**76**	0.2	5.9
23	**77**	0.2	00
24	**78**	0.2	--
25	**79**	0.2	7.0
26	**85**	0.1	--
27	**86**	0.2	--
28	**114**	0.2	--
29	**115**	0.2	--
30	**124**	0.2	--
SD*	Galathamine		IC_{50} 8.5±0.01

4.4.8. Tyrosinase inhibitory assays

Tyrosinase also known as polyphenol oxidase (PPO), is a multifunctional copper-containing enzyme, widely distributed in plant and animals.It catalyses the *o*-hydroxylation of monophenols and also the oxidation of *o*-diphenols to *o*-quinones. Thyrosinase is believed to be a key enzyme for the biosynthesis of melanin in both plants and animals.Therefore, it is considered to be clinically useful for the treatment of various dermatological disorders associated with melanin hyperpigmentation and also important in cosmetics for whitening and depigmentation after sunburn. In addition, it is believed to be involved in the molting process of insect and adhesion of marine organism[20]. In insects, several functions of this enzyme have been reported in the generation of o-diphenols and quinines for pigmentation, wound healing, parasite encapsulation and sclerotization and the enzyme in alternative target site for the control of insect past. Tyrosinase is responsible for the enzymatic browning reactions in damaged fruits during post-harvest handling and processing. It is also important in fruit pulp manufacturing in food industry. In addition, tyrosinase inhibitors are becoming important constituents of cosmetic products that relate to hyperpigmentations. Therefore, there is a need of concerted effort to search for naturally occurring tyrosinase inhibitors from plants, because plants constitute a rich source of bioactive chemicals[21]. It was thus realised to search for tyrosinase inhibitors in the quinazolinones derivatives which have not explored in the literature published about bioactivities of quinazolinones. In the present study, a series of quinazolinones have been studied for their inhibition pattern and structure activity relationship against Tyrosinase. Most of the compounds showed weak to moderate activities while some of the tested compounds were found inactive against Tyrosinase.

Structural activities showed that chlorosubstitution on the aromatic ring at position 3 is responsile for increase in the activities. Compounds **69** showed significant activities, in addition to the nephtholic substituent at position three was found active as compound **76** containing nephtholic group at position 3 which was found significantly active having IC_{50} 41.6 μM. Compounds **19, 74** and **53** showed moderate activities, while the rest of compounds showed weak activities. Results are recorded in Table 4.12. Compound 76 was found the most active. Compounds **19, 74** and **53** were found

moderately active while all other tested compounds were found either weakly active or completely inactive in the present studies.

Table 4.14: Results of Tyrosinase inhibitory activities at 0.5 m M concentration

Entry	Compd #	% inhibition
1	**16**	--
2	**19**	41.6 μM
3	**24**	--
4	**32**	44%
5	**34**	--
6	**38**	33.9%
7	**41**	--
8	**42**	34.88%
9	**43**	48.37%
10	**44**	--
11	**45**	--
12	**53**	--
13	**56**	46.6 μM
14	**58**	--
15	**61**	41.86%
16	**67**	27.6%
17	**68**	48%
18	~~**68**~~ 65	27.9%
19	**69**	37.3 μM
20	**76**	41.6μM
21	**77**	344 μM
22	**79**	--
23	**86**	48%
24	**107**	--
25	**109**	--
26	**112**	--
27	**113**	--
28	**115**	--
29	BHA	44.2(± 0.3)
30	Kojic acid	16.67(± 0.5)

4.4.9. Antiglycation Bioassays

Glycation of protein is non-enzymatic reaction of amino groups of protein with glucose and other reducing sugars which causes the structural and functional modifications of tissue protein.

Glycation of protein (Millard's Reaction), is also known as Browning reaction due to the formation of brown colour products called Advanced Glycation End products (AGEs), which are fluorescent materials.

Hyperglycemia, the clinical hallmark of poorly controlled diabetes, is known to cause rapid protein glycation and production of Advanced Glycation End products (AGEs)

Many studies have been conducted to study the significant role of glycation in the progress of normal aging and pathogenic age related diseases such as diabetic complications i.e. retinopathy, neuropathy and cataract formation, atherosclerosis, end stage renal diseases, rheumatoid arthritis and neurodegenerative diseases.

In the present study, it was considered important to explore quinazolinone derivatives for their antiglycation activities. Some of the compounds were found weakly active while other were inactive at all. Compound **32** was the most active among the whole series having significant inhibition (68.54 %). It is thus concluded that in thorough search for anti glycation active compounds, quinazolinone derivatives seem to be more important and could result in potential active compounds. Results of the antiglycation activities of a series of quianzolinone derivatives are given in [Table 4.13]

Table 4.15: Results of antiglycation bioassays

Entry	Compd #	% inhibition
1	**16**	07
2	**32**	68.54
3	**38**	--
4	**43**	14
5	**44**	29
6	**45**	05
7	**58**	--
8	**61**	14
9	**66**	24.56
10	**68**	--
11	**69**	23.44
12	**77**	--
13	**77**	05
14	**86**	--
15	**89**	--

4.4.10. Thermolysine inhibition assay

Quinazolinon ring system shows a diverse range of biological activities and for this reason is thoroughly explored heterocyclic system in medicinal chemistry. Their thermoycine inhibitory activities are, however, not explored in the literature. Keeping in mind their biological and clinical applications, a series of quinazolinone derivatives was evaluated for their thermolycine inhibition and intresting results were collected. Some of the compounds were found highly active [Table 4.11] and showed very much significant IC_{50} values while other showed weak activities and IC_{50} could not calculated for them.

Table 4.16: Results of thermolysine inhibition bioassay

Entry	Code	IC_{50} values (in mM)
1	**19**	0.054897
2	**20**	low activity[a]
3	**21**	0.037862
4	**22**	IN[b]
5	**24**	3,118
6	**25**	12,743
7	**26**	low activity[a]
8	**30**	0,00125
9	**36**	low activity[a]
10	**38**	low activity[a]
11	**44**	low activity[a]
12	**45**	IN[b]
13	**48**	IN[b]
14	**51**	very low activity[a]
15	**61**	0.076851
16	**62**	low activity[a]
17	**68**	1,8321
18	**74**	0.042035
19	**77**	4,002
20	**78**	low activity[a]
21	**85**	low activity[a]
22	**86**	Low[a]
23	**87**	low activity[a]
24	**91**	$2,4774 \times 10^{-4}$
25	**95**	Low[a]
26	**106**	122.637
27	**111**	25876110,74
28	**119**	low activity[a]
29	**120**	362468613444,037
30	**125**	low activity[a]
31	**126**	very low activity[a]

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Appendix 1: Crystal data and structural refinement of *N*-(2-{[(2E)-2-(2-hydroxybenzylidene) hydrazino] carbonyl} phenyl) benzamide.

Crystal data

$C_{21}H_{17}N_3O_3$

$M_r = 359.38$

Monoclinic, *C2/c*

$a = 21.191\ (17)$ Å

$b = 8.308\ (7)$ Å

$C = 22.333\ (18)$ Å

B = 113.093 (16)°

$V = 3617\ (5)$ Å^3

$Z = 8$

$F_{000} = 1504$

$D_x = 1.320$ Mg m^{-3}

Mo *Kα* radiation

$\lambda = 0.71073$ Å

Cell parameters from 1173 reflections

$\theta = 1.9–26.0°$

$\mu = 0.09$ mm^{-1}

$T = 298\ (2)$ K

Cell measurement pressure: ? kPa

Block, colourless

0.43 × 0.42 × 0.12 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer

Radiation source: fine-focus sealed tube

Monochromator: graphite

9402 measured reflections

3530 independent reflections

1574 reflections with $I > 2\sigma(I)$

Detector resolution: 83.66 pixels mm^{-1}

T = 298(2) K

ω scan

Absorption correction: multi-scan SADABS(Bruker, 2000)

T_{min} = 0.962, T_{max} = 0.989

R_{int} = 0.066

θ_{max} = 26.0°

θ_{min} = 1.9°

h = −26 25

k = −7 10

l = −27 27

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)]$ = 0.058

$wR(F^2)$ = 0.144

S = 0.98

3530 reflections

256 parameters

3 restraints

? constraints

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Hydrogen site location: inferred from neighbouring sites

H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0576P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = <0.001

$\Delta\rho_{max}$ = 0.15 e $Å^{-3}$

$\Delta\rho_{min}$ = −0.14 e $Å^{-3}$

Extinction correction: none

Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit S are based on F^2, conventional *R*-factors *R* are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating *R*-factors(gt) *etc.* and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on F, and R– factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.45445 (11)	0.3597 (2)	−0.05898 (9)	0.0835 (6)
O2	0.44845 (10)	0.0703 (2)	0.13243 (8)	0.0779 (6)
O3	0.36293 (12)	−0.2097 (3)	0.21629 (10)	0.0874 (7)
H3A	0.3878 (14)	−0.183 (4)	0.1971 (14)	0.107 (13)*
N1	0.46302 (13)	0.2377 (3)	0.03463 (12)	0.0648 (6)
H1A	0.4423 (12)	0.210 (3)	0.0590 (11)	0.076 (10)*
N2	0.49542 (13)	−0.1750 (3)	0.13780 (11)	0.0681 (7)
H2A	0.5169 (14)	−0.238 (3)	0.1210 (14)	0.108 (12)*
N3	0.45158 (12)	−0.2387 (3)	0.16313 (10)	0.0652 (6)
C1	0.34063 (16)	0.4007 (4)	0.02319 (15)	0.0877 (9)
H1	0.3710	0.3755	0.0652	0.105*
C2	0.2760 (2)	0.4574 (5)	0.0127 (2)	0.1238 (14)
H2	0.2634	0.4721	0.0478	0.149*
C3	0.2306 (2)	0.4919 (4)	−0.0487 (3)	0.1169 (13)

H3	0.1869	0.5292	−0.0557	0.140*
C4	0.2494 (2)	0.4717 (4)	−0.0989 (2)	0.1216 (15)
H4	0.2184	0.4936	−0.1410	0.146*
C5	0.3149 (2)	0.4185 (4)	−0.08851 (15)	0.0988 (11)
H5	0.3280	0.4080	−0.1234	0.119*
C6	0.35999 (15)	0.3815 (3)	−0.02718 (13)	0.0610 (7)
C7	0.42971 (15)	0.3260 (3)	−0.01908 (14)	0.0632 (8)
C8	0.52890 (15)	0.1701 (3)	0.05674 (12)	0.0607 (7)
C9	0.57928 (17)	0.2234 (3)	0.03672 (15)	0.0787 (9)
H9	0.5695	0.3050	0.0059	0.094*
C10	0.64372 (18)	0.1567 (4)	0.06212 (18)	0.0892 (10)
H10	0.6770	0.1940	0.0481	0.107*
C11	0.66005 (16)	0.0365 (4)	0.10769 (16)	0.0844 (9)
H11	0.7040	−0.0072	0.1250	0.101*
C12	0.60973 (17)	−0.0180 (3)	0.12719 (14)	0.0748 (8)
H12	0.6202	−0.0996	0.1581	0.090*
C13	0.54421 (14)	0.0450 (3)	0.10229 (12)	0.0579 (7)
C14	0.49196 (15)	−0.0158 (3)	0.12497 (11)	0.0624 (7)
C15	0.45143 (15)	−0.3908 (4)	0.17016 (11)	0.0689 (8)
H15	0.4790	−0.4551	0.1563	0.083*
C16	0.40886 (15)	−0.4642 (3)	0.19952 (11)	0.0663 (8)

C17	0.40993 (19)	−0.6294 (4)	0.20810 (13)	0.0897 (10)
H17	0.4369	−0.6928	0.1931	0.108*
C18	0.3720 (2)	−0.7015 (4)	0.23827 (17)	0.1112 (13)
H18	0.3736	−0.8125	0.2441	0.133*
C19	0.3317 (2)	−0.6074 (6)	0.25980 (16)	0.1117 (12)
H19	0.3060	−0.6555	0.2803	0.134*
C20	0.32907 (17)	−0.4442 (5)	0.25141 (14)	0.0948 (10)
H20	0.3013	−0.3822	0.2659	0.114*
C21	0.36732 (16)	−0.3716 (4)	0.22158 (12)	0.0688 (8)

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.1149 (18)	0.0716 (13)	0.0855 (13)	0.0198 (11)	0.0625 (14)	0.0091 (10)
O2	0.0862 (15)	0.0743 (13)	0.0886 (13)	0.0240 (11)	0.0508 (12)	0.0094 (10)
O3	0.1040 (19)	0.0867 (16)	0.0860 (15)	0.0276 (13)	0.0528 (15)	0.0126 (11)
N1	0.0631 (17)	0.0649 (14)	0.0753 (16)	0.0142 (12)	0.0367 (15)	0.0120 (12)
N2	0.0812 (19)	0.0644 (18)	0.0695 (15)	0.0160 (13)	0.0411 (15)	0.0043 (12)

N3	0.0788 (18)	0.0694 (16)	0.0530 (13)	0.0128 (12)	0.0317 (13)	0.0041 (11)
C1	0.068 (2)	0.121 (3)	0.077 (2)	0.0272 (19)	0.0329 (19)	0.0153 (18)
C2	0.083 (3)	0.175 (4)	0.129 (3)	0.047 (3)	0.058 (3)	0.040 (3)
C3	0.062 (3)	0.110 (3)	0.159 (4)	0.018 (2)	0.023 (3)	0.011 (3)
C4	0.115 (4)	0.102 (3)	0.102 (3)	0.039 (2)	−0.008 (3)	−0.005 (2)
C5	0.118 (3)	0.093 (2)	0.069 (2)	0.042 (2)	0.018 (2)	0.0007 (17)
C6	0.068 (2)	0.0519 (16)	0.0578 (17)	0.0086 (13)	0.0188 (16)	−0.0016 (13)
C7	0.079 (2)	0.0503 (16)	0.0662 (18)	0.0068 (14)	0.0348 (18)	−0.0026 (14)
C8	0.061 (2)	0.0547 (16)	0.0707 (18)	0.0016 (14)	0.0303 (16)	−0.0082 (13)
C9	0.074 (2)	0.0647 (19)	0.106 (2)	0.0012 (16)	0.044 (2)	−0.0015 (16)
C10	0.074 (3)	0.079 (2)	0.133 (3)	−0.0033 (18)	0.060 (2)	−0.010 (2)
C11	0.056 (2)	0.087 (2)	0.106 (2)	0.0067 (17)	0.028 (2)	−0.0089 (19)
C12	0.069 (2)	0.0743 (19)	0.079 (2)	0.0115 (16)	0.0259 (18)	−0.0071 (15)
C13	0.056 (2)	0.0598 (17)	0.0598 (16)	0.0094 (14)	0.0244 (15)	−0.0049 (13)

C14	0.067 (2)	0.067 (2)	0.0544 (16)	0.0160 (15)	0.0256 (15)	−0.0010 (13)
C15	0.089 (2)	0.065 (2)	0.0530 (16)	0.0151 (15)	0.0276 (16)	−0.0017 (14)
C16	0.081 (2)	0.070 (2)	0.0458 (15)	0.0061 (15)	0.0235 (16)	−0.0005 (13)
C17	0.130 (3)	0.069 (2)	0.0632 (18)	0.0018 (18)	0.031 (2)	−0.0022 (15)
C18	0.165 (4)	0.083 (2)	0.081 (2)	−0.029 (3)	0.043 (3)	0.004 (2)
C19	0.130 (4)	0.127 (3)	0.087 (2)	−0.032 (3)	0.051 (3)	0.002 (2)
C20	0.103 (3)	0.112 (3)	0.072 (2)	−0.001 (2)	0.038 (2)	0.0051 (19)
C21	0.074 (2)	0.078 (2)	0.0516 (16)	0.0059 (16)	0.0218 (16)	0.0071 (14)

Geometric parameters (Å, °)

O1—C7	1.231 (3)	C8—C9	1.382 (4)
O2—C14	1.229 (3)	C8—C13	1.400 (3)
O3—C21	1.350 (3)	C9—C10	1.373 (4)
O3—H3A	0.828 (10)	C9—H9	0.9300
N1—C7	1.346 (3)	C10—C11	1.370 (4)
N1—C8	1.403 (3)	C10—H10	0.9300
N1—H1A	0.855 (10)	C11—C12	1.377 (4)

N2—C14	1.349 (3)	C11—H11	0.9300
N2—N3	1.370 (3)	C12—C13	1.380 (4)
N2—H2A	0.869 (10)	C12—H12	0.9300
N3—C15	1.274 (3)	C13—C14	1.476 (4)
C1—C6	1.350 (3)	C15—C16	1.442 (4)
C1—C2	1.379 (4)	C15—H15	0.9300
C1—H1	0.9300	C16—C17	1.385 (4)
C2—C3	1.362 (5)	C16—C21	1.396 (4)
C2—H2	0.9300	C17—C18	1.372 (4)
C3—C4	1.341 (5)	C17—H17	0.9300
C3—H3	0.9300	C18—C19	1.376 (5)
C4—C5	1.385 (5)	C18—H18	0.9300
C4—H4	0.9300	C19—C20	1.367 (4)
C5—C6	1.363 (4)	C19—H19	0.9300
C5—H5	0.9300	C20—C21	1.374 (4)
C6—C7	1.489 (4)	C20—H20	0.9300
C21—O3—H3A	106 (2)	C11—C10—H10	119.3
C7—N1—C8	129.3 (2)	C9—C10—H10	119.3
C7—N1—H1A	119.6 (19)	C10—C11—C12	118.2 (3)
C8—N1—H1A	110.9 (18)	C10—C11—H11	120.9
C14—N2—N3	118.5 (2)	C12—C11—H11	120.9

C14—N2—H2A	119 (2)	C11—C12—C13	122.0 (3)
N3—N2—H2A	120 (2)	C11—C12—H12	119.0
C15—N3—N2	118.0 (2)	C13—C12—H12	119.0
C6—C1—C2	120.4 (3)	C12—C13—C8	118.9 (3)
C6—C1—H1	119.8	C12—C13—C14	120.2 (3)
C2—C1—H1	119.8	C8—C13—C14	120.8 (2)
C3—C2—C1	120.3 (4)	O2—C14—N2	121.5 (3)
C3—C2—H2	119.8	O2—C14—C13	123.5 (3)
C1—C2—H2	119.8	N2—C14—C13	115.0 (2)
C4—C3—C2	119.5 (4)	N3—C15—C16	120.5 (3)
C4—C3—H3	120.3	N3—C15—H15	119.7
C2—C3—H3	120.3	C16—C15—H15	119.7
C3—C4—C5	120.4 (4)	C17—C16—C21	118.4 (3)
C3—C4—H4	119.8	C17—C16—C15	120.2 (3)
C5—C4—H4	119.8	C21—C16—C15	121.4 (3)
C6—C5—C4	120.2 (3)	C18—C17—C16	121.3 (3)
C6—C5—H5	119.9	C18—C17—H17	119.4
C4—C5—H5	119.9	C16—C17—H17	119.4
C1—C6—C5	119.2 (3)	C17—C18—C19	119.1 (4)
C1—C6—C7	123.1 (3)	C17—C18—H18	120.4
C5—C6—C7	117.6 (3)	C19—C18—H18	120.4

O1—C7—N1	123.1 (3)	C20—C19—C18	120.9 (4)
O1—C7—C6	121.7 (3)	C20—C19—H19	119.5
N1—C7—C6	115.2 (2)	C18—C19—H19	119.5
C9—C8—C13	119.0 (3)	C19—C20—C21	120.1 (3)
C9—C8—N1	123.1 (3)	C19—C20—H20	120.0
C13—C8—N1	117.9 (2)	C21—C20—H20	120.0
C10—C9—C8	120.4 (3)	O3—C21—C20	116.5 (3)
C10—C9—H9	119.8	O3—C21—C16	123.3 (3)
C8—C9—H9	119.8	C20—C21—C16	120.2 (3)
C11—C10—C9	121.4 (3)		
C14—N2—N3—C15	174.5 (2)	C9—C8—C13—C12	1.9 (4)
C6—C1—C2—C3	1.2 (6)	N1—C8—C13—C12	−176.8 (2)
C1—C2—C3—C4	−0.6 (6)	C9—C8—C13—C14	−180.0 (2)
C2—C3—C4—C5	−0.9 (6)	N1—C8—C13—C14	1.4 (3)
C3—C4—C5—C6	2.0 (6)	N3—N2—C14—O2	−3.7 (4)
C2—C1—C6—C5	−0.1 (5)	N3—N2—C14—C13	175.8 (2)
C2—C1—C6—C7	177.9 (3)	C12—C13—C14—O2	143.3 (3)
C4—C5—C6—C1	−1.4 (5)	C8—C13—C14—O2	−34.8 (4)
C4—C5—C6—C7	−179.6 (3)	C12—C13—C14—N2	−36.1 (3)
C8—N1—C7—O1	0.9 (4)	C8—C13—C14—N2	145.7 (2)
C8—N1—C7—C6	−179.0 (2)	N2—N3—C15—C16	177.0 (2)

C1—C6—C7—O1	−154.8 (3)	N3—C15—C16—C17	−178.8 (2)
C5—C6—C7—O1	23.3 (4)	N3—C15—C16—C21	−0.6 (4)
C1—C6—C7—N1	25.0 (4)	C21—C16—C17—C18	−0.9 (4)
C5—C6—C7—N1	−156.9 (2)	C15—C16—C17—C18	177.3 (3)
C7—N1—C8—C9	20.4 (4)	C16—C17—C18—C19	0.6 (5)
C7—N1—C8—C13	−161.0 (2)	C17—C18—C19—C20	0.1 (6)
C13—C8—C9—C10	−1.3 (4)	C18—C19—C20—C21	−0.5 (5)
N1—C8—C9—C10	177.3 (3)	C19—C20—C21—O3	−178.7 (3)
C8—C9—C10—C11	0.0 (5)	C19—C20—C21—C16	0.2 (4)
C9—C10—C11—C12	0.7 (5)	C17—C16—C21—O3	179.3 (2)
C10—C11—C12—C13	−0.1 (4)	C15—C16—C21—O3	1.1 (4)
C11—C12—C13—C8	−1.2 (4)	C17—C16—C21—C20	0.4 (4)
C11—C12—C13—C14	−179.4 (2)	C15—C16—C21—C20	−177.7 (2)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1A···O2	0.85 (3)	1.97 (2)	2.707 (4)	144 (2)
O3—H3A···N3	0.83 (3)	1.85 (3)	2.597 (4)	149 (3)
C9—H9···O1	0.93	2.34	2.901 (5)	118
N2—H2A···O1^{i}	0.87 (3)	1.99 (3)	2.837 (4)	164 (3)
C4—H4···O3^{ii}	0.93	2.60	3.399 (5)	145

C17—H17···O2^{iii}	0.93	2.46	3.291 (5)	149

Symmetry codes: (i) $x+3/2, y+1/2, z$; (ii) $-x+1/2, -y+1/2, -z$; (iii) $x, y-1, z$.

All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Data collection: *SMART* (Bruker, 2000); cell refinement: *SAINT* (Bruker, 2000); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997a); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997a); molecular graphics: *SHELXTL* (Sheldrick, 1997b); software used to prepare material for publication: *SHELXTL*, *PARST* (Nardelli, 1995) and *PLATON* (Spek, 2003).

Appendix II. Crystal data and structure refinement of ethyl (1*E*)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) ethanimidoate (**106**)

Crystal data

$C_{13}H_{15}N_3O_2$

$M_r = 245.28$

Monoclinic, $P2(1)/n$

$a = 8.5247\ (18)$ Å

$b = 13.259\ (3)$ Å

$D_x = 1.277$ Mg m^{-3}

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 1368 reflections

$\theta = 2.3–26.0°$

$\mu = 0.09$ mm^{-1}

c = 11.313 (2) Å

β = 93.871 (4)°

V = 1275.8 (5) Å^3

Z = 4

F_{000} = 520

T = 298 (2) K

Block, colourless

0.44 × 0.27 × 0.18 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer

Radiation source: fine-focus sealed tube

Monochromator: graphite

Detector resolution: 83.66 pixels mm^{-1}

T = 298(2) K

ω scan

Absorption correction: multi-scan SADABS (Bruker,2000)

T_{min} = 0.962, T_{max} = 0.984

6994 measured reflections

2515 independent reflections

1489 reflections with $I > 2\sigma(I)$

R_{int} = 0.032

θ_{max} = 26.0°

θ_{min} = 2.3°

h = −9 10

k = −15 16

l = −13 12

Refinement

Refinement on F^2

Hydrogen site location: inferred from neighbouring sites

Least-squares matrix: full

H-atom parameters constrained

$R[F^2 > 2\sigma(F^2)] = 0.054$

$w = 1/[\sigma^2(F_o^2) + (0.0769P)^2 + 0.127P]$ where $P = (F_o^2 + 2F_c^2)/3$

$wR(F^2) = 0.157$

$(\Delta/\sigma)_{max} = <0.001$

$S = 1.02$

$\Delta\rho_{max} = 0.20$ e Å^{-3}

2515 reflections

$\Delta\rho_{min} = -0.18$ e Å^{-3}

172 parameters

Extinction correction: none

Primary atom site location: structure-invariant direct methods

Secondary atom site location: difference Fourier map

Refinement of F^2 against ALL reflections. The weighted *R*-factor *wR* and goodness of fit S are based on F^2, conventional *R*-factors *R* are based on F, with F set to zero for negative F^2. The threshold expression of $F^2 > 2\text{sigma}(F^2)$ is used only for calculating *R*-factors(gt) *etc.* and is not relevant to the choice of reflections for refinement. *R*-factors based on F^2 are statistically about twice as large as those based on F, and R– factors based on ALL data will be even larger.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*Y*	*Z*	U_{iso}*/U_{eq}

O1	0.0989 (2)	0.71587 (13)	0.93593 (14)	0.0719 (5)
O2	0.13012 (19)	0.65168 (12)	1.28597 (12)	0.0629 (5)
N1	0.3481 (2)	0.45918 (14)	0.88296 (16)	0.0578 (5)
N2	0.2066 (2)	0.56693 (13)	1.00239 (15)	0.0517 (5)
N3	0.1312 (2)	0.57393 (15)	1.10987 (15)	0.0581 (5)
C1	0.2817 (3)	0.47710 (17)	0.98056 (19)	0.0534 (6)
C2	0.3416 (3)	0.53473 (18)	0.79718 (19)	0.0542 (6)
C3	0.4226 (3)	0.5197 (2)	0.6952 (2)	0.0702 (7)
H3	0.4745	0.4591	0.6841	0.084*
C4	0.4254 (4)	0.5938 (2)	0.6120 (2)	0.0800 (9)
H4	0.4821	0.5841	0.5455	0.096*
C5	0.3454 (3)	0.6830 (2)	0.6250 (2)	0.0755 (8)
H5	0.3489	0.7331	0.5677	0.091*
C6	0.2609 (3)	0.69804 (19)	0.7219 (2)	0.0652 (7)
H6	0.2042	0.7574	0.7293	0.078*
C7	0.2598 (3)	0.62450 (17)	0.80925 (18)	0.0518 (6)
C8	0.1790 (3)	0.64219 (18)	0.9167 (2)	0.0549 (6)
C9	0.1904 (3)	0.64045 (17)	1.18077 (19)	0.0534 (6)
C10	0.3241 (3)	0.71031 (19)	1.1664 (2)	0.0708 (7)
H10A	0.4001	0.6781	1.1203	0.106*
H10B	0.3721	0.7275	1.2430	0.106*

H10C	0.2862	0.7705	1.1268	0.106*
C11	0.0022 (4)	0.5858 (2)	1.3129 (2)	0.0670 (7)
H11A	−0.074 (3)	0.5932 (18)	1.252 (2)	0.072 (8)*
H11B	0.062 (2)	0.4976 (14)	1.3415 (14)	0.039 (5)*
C12	−0.0522 (4)	0.6198 (2)	1.4293 (2)	0.0936 (10)
H12A	−0.1376	0.5779	1.4507	0.140*
H12B	−0.0869	0.6886	1.4229	0.140*
H12C	0.0330	0.6148	1.4889	0.140*
C13	0.2838 (3)	0.39919 (18)	1.0745 (2)	0.0664 (7)
H13A	0.3394	0.3408	1.0494	0.100*
H13B	0.1779	0.3808	1.0889	0.100*
H13C	0.3356	0.4255	1.1459	0.100*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0699 (11)	0.0698 (12)	0.0779 (11)	0.0157 (10)	0.0191 (9)	0.0010 (9)
O2	0.0666 (11)	0.0702 (11)	0.0535 (9)	−0.0082 (9)	0.0158 (8)	−0.0109 (8)
N1	0.0621 (13)	0.0581 (12)	0.0542 (11)	−0.0001 (10)	0.0101 (10)	−0.0085 (10)
N2	0.0541	0.0538	0.0481	−0.0051 (9)	0.0110 (9)	−0.0060 (9)

	(12)	(12)	(10)			
N3	0.0612 (13)	0.0642 (12)	0.0506 (10)	−0.0091 (10)	0.0160 (9)	−0.0106 (9)
C1	0.0511 (14)	0.0536 (14)	0.0553 (13)	−0.0057 (12)	0.0011 (11)	−0.0063 (11)
C2	0.0519 (14)	0.0613 (15)	0.0497 (12)	−0.0083 (12)	0.0066 (11)	−0.0076 (11)
C3	0.0838 (19)	0.0737 (17)	0.0546 (14)	0.0018 (15)	0.0147 (13)	−0.0088 (13)
C4	0.092 (2)	0.096 (2)	0.0538 (15)	−0.0013 (18)	0.0213 (14)	−0.0051 (15)
C5	0.085 (2)	0.084 (2)	0.0585 (15)	−0.0063 (17)	0.0112 (14)	0.0086 (14)
C6	0.0666 (16)	0.0668 (16)	0.0623 (15)	0.0008 (13)	0.0050 (13)	0.0070 (13)
C7	0.0479 (13)	0.0559 (14)	0.0515 (13)	−0.0048 (11)	0.0032 (11)	−0.0068 (11)
C8	0.0480 (14)	0.0581 (15)	0.0591 (14)	−0.0010 (12)	0.0065 (11)	−0.0064 (12)
C9	0.0526 (14)	0.0573 (14)	0.0506 (13)	0.0017 (12)	0.0069 (11)	−0.0045 (11)
C10	0.0689 (17)	0.0733 (17)	0.0714 (16)	−0.0164 (14)	0.0135 (13)	−0.0126 (13)
C11	0.0656 (17)	0.0811 (19)	0.0562 (15)	−0.0120 (15)	0.0166 (14)	−0.0023 (14)

C12	0.101 (2)	0.106 (2)	0.0758 (18)	0.001 (2)	0.0240 (17)	−0.0007 (17)
C13	0.0761 (18)	0.0608 (15)	0.0629 (14)	−0.0041 (14)	0.0085 (13)	0.0037 (12)

Geometric parameters (Å, °)

O1—C8	1.220 (3)	C5—H5	0.9300
O2—C9	1.336 (2)	C6—C7	1.389 (3)
O2—C11	1.446 (3)	C6—H6	0.9300
N1—C1	1.296 (3)	C7—C8	1.456 (3)
N1—C2	1.393 (3)	C9—C10	1.485 (3)
N2—C1	1.382 (3)	C10—H10A	0.9600
N2—C8	1.400 (3)	C10—H10B	0.9600
N2—N3	1.416 (2)	C10—H10C	0.9600
N3—C9	1.274 (3)	C11—C12	1.495 (4)
C1—C13	1.481 (3)	C11—H11A	0.93 (3)
C2—C7	1.391 (3)	C11—H11B	1.307 (18)
C2—C3	1.398 (3)	C12—H12A	0.9600
C3—C4	1.362 (4)	C12—H12B	0.9600
C3—H3	0.9300	C12—H12C	0.9600
C4—C5	1.378 (4)	C13—H13A	0.9600

C4—H4	0.9300	C13—H13B	0.9600
C5—C6	1.366 (3)	C13—H13C	0.9600
C9—O2—C11	117.48 (18)	N2—C8—C7	113.4 (2)
C1—N1—C2	117.55 (19)	N3—C9—O2	118.6 (2)
C1—N2—C8	123.26 (18)	N3—C9—C10	129.6 (2)
C1—N2—N3	116.90 (17)	O2—C9—C10	111.83 (19)
C8—N2—N3	118.90 (18)	C9—C10—H10A	109.5
C9—N3—N2	113.73 (18)	C9—C10—H10B	109.5
N1—C1—N2	122.97 (19)	H10A—C10—H10B	109.5
N1—C1—C13	119.9 (2)	C9—C10—H10C	109.5
N2—C1—C13	117.15 (19)	H10A—C10—H10C	109.5
C7—C2—N1	122.93 (19)	H10B—C10—H10C	109.5
C7—C2—C3	118.8 (2)	O2—C11—C12	106.6 (2)
N1—C2—C3	118.3 (2)	O2—C11—H11A	106.4 (16)
C4—C3—C2	120.0 (2)	C12—C11—H11A	112.5 (15)
C4—C3—H3	120.0	O2—C11—H11B	107.8 (8)
C2—C3—H3	120.0	C12—C11—H11B	101.0 (7)
C3—C4—C5	120.9 (2)	H11A—C11—H11B	121.6 (18)
C3—C4—H4	119.5	C11—C12—H12A	109.5
C5—C4—H4	119.5	C11—C12—H12B	109.5
C6—C5—C4	120.1 (2)	H12A—C12—H12B	109.5

C6—C5—H5	119.9	C11—C12—H12C	109.5
C4—C5—H5	119.9	H12A—C12—H12C	109.5
C5—C6—C7	119.9 (2)	H12B—C12—H12C	109.5
C5—C6—H6	120.1	C1—C13—H13A	109.5
C7—C6—H6	120.1	C1—C13—H13B	109.5
C6—C7—C2	120.2 (2)	H13A—C13—H13B	109.5
C6—C7—C8	120.5 (2)	C1—C13—H13C	109.5
C2—C7—C8	119.2 (2)	H13A—C13—H13C	109.5
O1—C8—N2	121.1 (2)	H13B—C13—H13C	109.5
O1—C8—C7	125.5 (2)		
C1—N2—N3—C9	116.0 (2)	N1—C2—C7—C6	178.4 (2)
C8—N2—N3—C9	−74.7 (3)	C3—C2—C7—C6	−0.8 (3)
C2—N1—C1—N2	−0.2 (3)	N1—C2—C7—C8	1.1 (3)
C2—N1—C1—C13	179.5 (2)	C3—C2—C7—C8	−178.2 (2)
C8—N2—C1—N1	7.7 (3)	C1—N2—C8—O1	172.7 (2)
N3—N2—C1—N1	176.38 (19)	N3—N2—C8—O1	4.2 (3)
C8—N2—C1—C13	−172.1 (2)	C1—N2—C8—C7	−9.8 (3)
N3—N2—C1—C13	−3.4 (3)	N3—N2—C8—C7	−178.33 (17)
C1—N1—C2—C7	−4.0 (3)	C6—C7—C8—O1	5.5 (4)
C1—N1—C2—C3	175.3 (2)	C2—C7—C8—O1	−177.2 (2)
C7—C2—C3—C4	2.5 (4)	C6—C7—C8—N2	−171.9 (2)

N1—C2—C3—C4	−176.8 (2)	C2—C7—C8—N2	5.5 (3)
C2—C3—C4—C5	−1.9 (4)	N2—N3—C9—O2	−178.56 (18)
C3—C4—C5—C6	−0.4 (4)	N2—N3—C9—C10	0.3 (4)
C4—C5—C6—C7	2.1 (4)	C11—O2—C9—N3	1.0 (3)
C5—C6—C7—C2	−1.4 (4)	C11—O2—C9—C10	−178.1 (2)
C5—C6—C7—C8	175.9 (2)	C9—O2—C11—C12	−175.0 (2)

All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.