Chapter-4

Synthesis, characterization and biological activity of 2-thioxo-2,3,4,6,7,8-haxahydro-1H-quinazolin-5-one and hydrazine-4,6,7,8-tetrahydro-3H-quinazolin-5-one derivatives

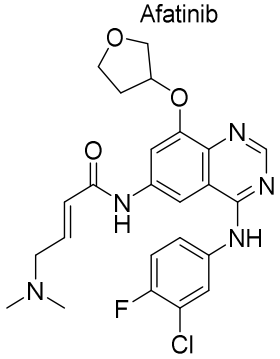
There are many fused heterocyclic rings like quinazoline and quinazolinone have been studied for their expanded applications in the field of pharmaceutical chemistry. Quinazoline and quinazolinone are reported for their diversified biological activities. The compounds with different substitutions bring together to knowledge of a target with understanding of the molecule types that might interact with the target receptors. Quinazolines and quinazolinones are considered as an important chemical for the synthesis of various physiological significance and pharmacological utilized molecules. Quinazolines and quinazolinone are a large class of biologically active compounds that exhibited broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and other activities. Being considered as advantaged scaffold, the alteration is made with different substituent.

4.1 Introduction

Quinazolines and quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties[1]. Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoan, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules (Figure 1). Based on the various reported drugs, there is an attempt to expand the huge potentiality and focused on the various biological activities of quinazolines and quinazolinones[2].

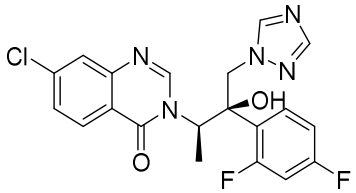
Quinazoline and quinazolinone compounds and their uses

Afatinib



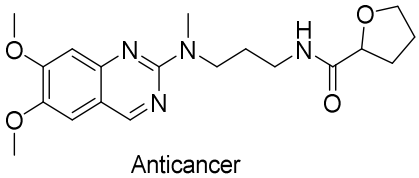
Tyrosine kinase inhibitor

Albaconazole



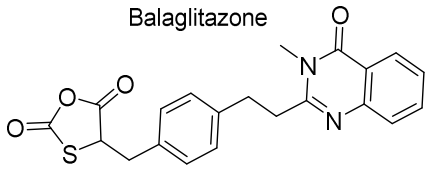
Antifungal

Alfuzocin



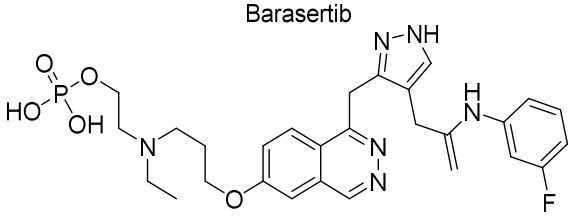
Anticancer

Balaglitazone



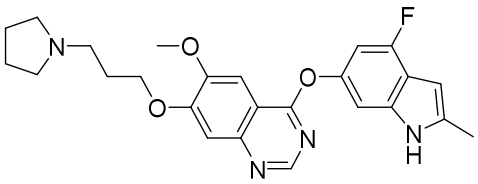
Antidiabetic and hypolipidimic

Barasertib



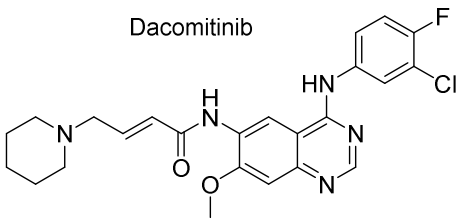
Acute mycloid leukemia

Cediranib



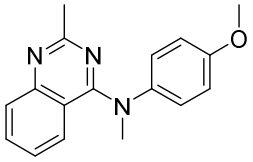
Hematological cancer, liver metastases

Dacomitinib



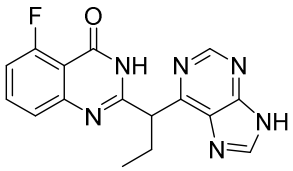
Anticancer

Verubulin



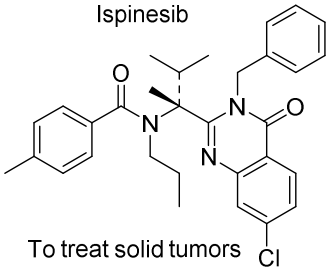
Anticancer

GS1101 (CAL101)



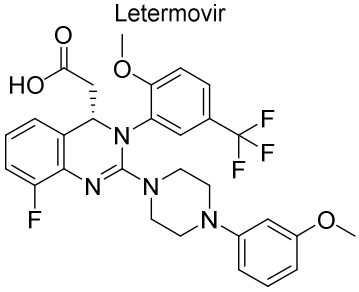
Antihaematological cancer

Ispinesib



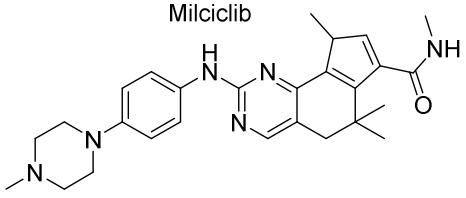
To treat solid tumors

Letermovir

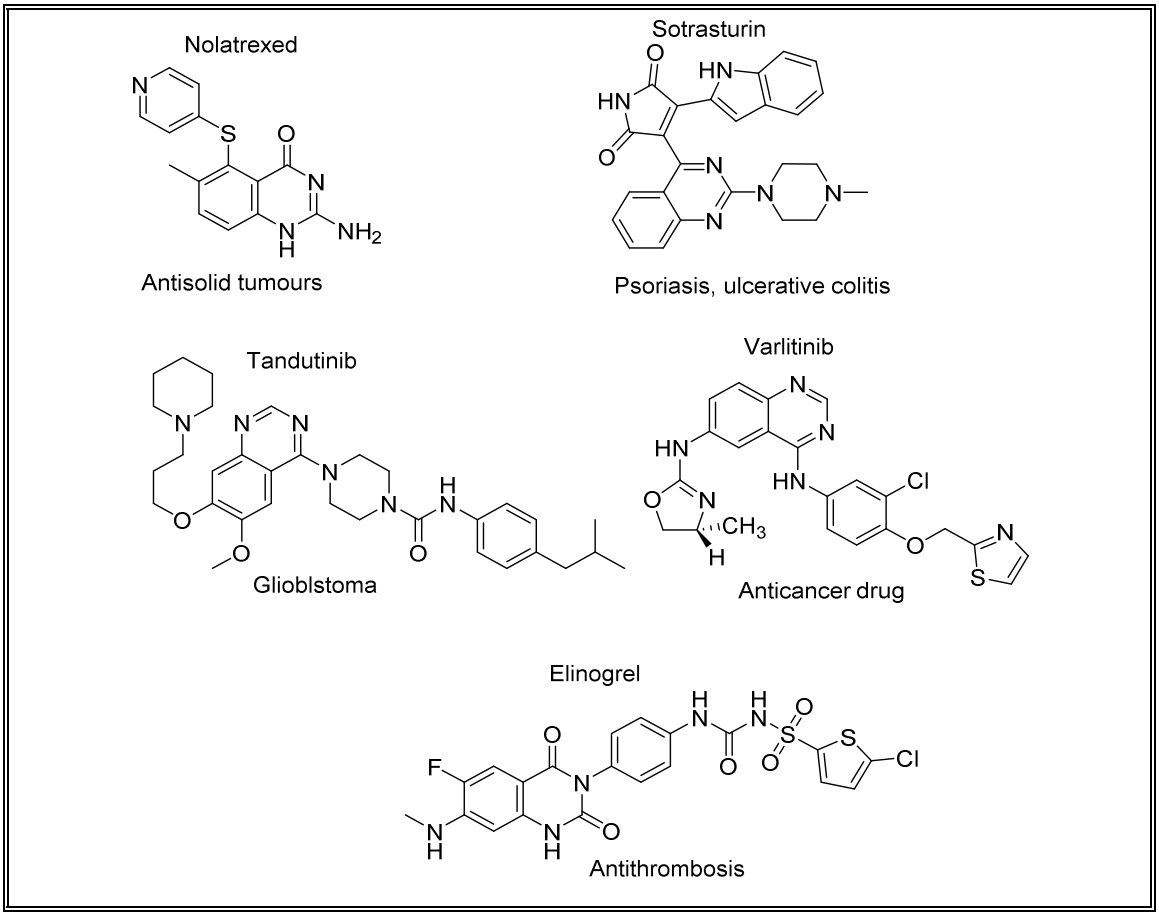


Human cytomegalovirus

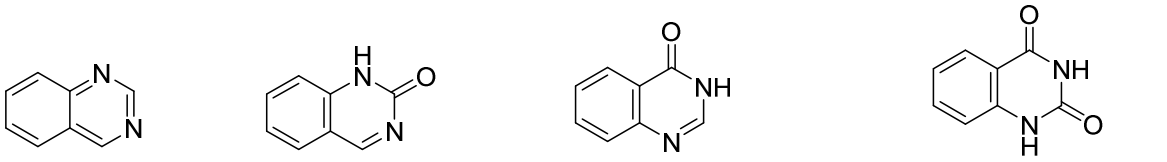
Milciclib



Anticancer



Five catagories of Quinazolinones will be classified, based on the substitution patterns of the ring system[3]. These are 2-substituted-4(3H)-quinazolinones, 3-substituted-4(3H)-quinazolinones, 4-substituted-quinazolines, 2,3-disubstituted-4(3H)-quinazolinones, and 2,4-disubstituted-4(3H)-quinazolinones. Depending upon the position of the keto or oxo group, these compounds may be classified into three types[4]. Out of the three (2(1H)quinazolinones, 4(3H)quinazolinones and 2,4(1H,3H)quinazolinedione) quinazolinone structures, 4(3H)-quinazolinones are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways (see Scheme 1).

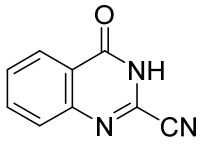


Scheme 1

This is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, isatoic anhydride, anthranilamide, and anthranilonitrile) while the 2(1H)-quinazolinone is predominantly a product of anthranilonitrile or benzamides with nitriles[4].

4.2. History

In 1869 Griess prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline, by the reaction of cyanogens with anthranilic acid. The bicyclic product was called bicyanoamido benzoyl and used this name until 1885[5]. The preparation of the quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel in 1903. The name was proposed by Widdege. Other names such as phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine, and 1,3-diazanapthaline have occasionally been used. The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected in the reactions of quinazoline. The properties of substitute's quinazolines depend largely on (a) the nature of the substituents, (b) whether they are in the pyrimidine ring or in the benzene ring, and (c) whether or not complete conjugation is present in the pyrimidine ring[6-8] (see Scheme 2).



4-oxo-3,4-dihydroquinazoline-2-carbonitrile

Scheme 2

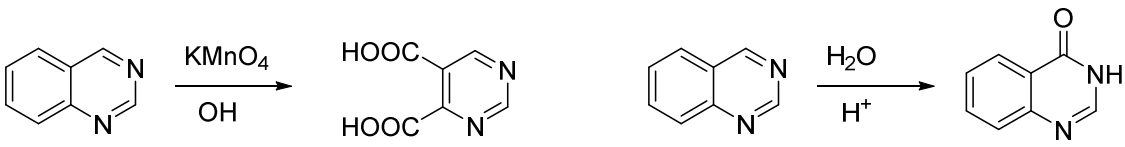
4.3 Chemical Properties of Quinazolines

The chemistry of quinazoline was reviewed by Williamson in 1957 and then by Lindquist in 1959 and brought up to date by Armarego in 1963.

Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. o-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.

4.3.1 Hydrolysis, Oxidation and Reduction

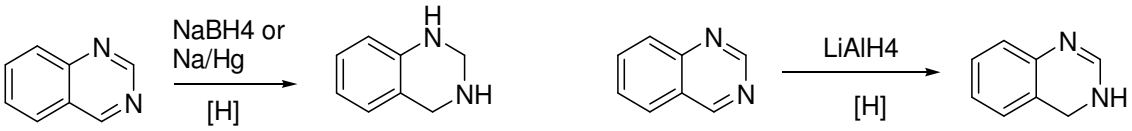
Catalytic hydrogenation of quinazoline stopped after the absorption of one molecule of hydrogen and gave 3,4-dihydro quinazoline (see Scheme 3).



Scheme 3

4.3.2. Reduction

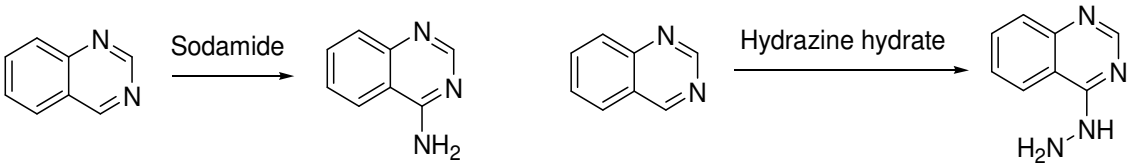
Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4-tetrahydroquinazoline (see Scheme 4).



Scheme 4

4.4 Nucleophilic and Electrophilic Substitution Reactions

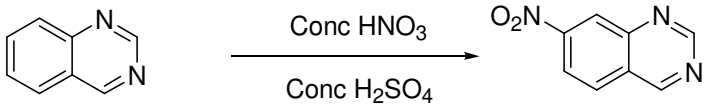
The two known nucleophilic substitution reactions of quinazoline are sodamide and hydrazine most probably proceed via the intermediate addition products, and gave 4-amino and 4-hydrazine quinazoline (see Scheme 5).



Scheme 5

4.4.1. Electrophilic Substitution Reaction of Quinazoline

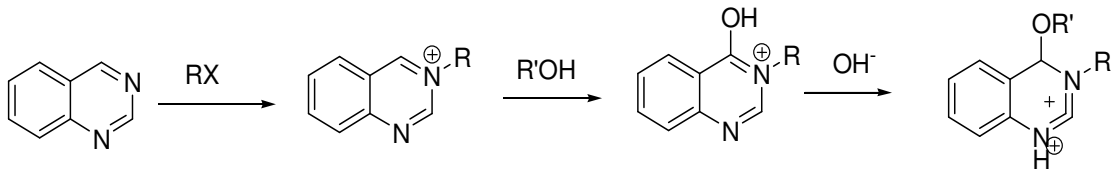
Nitration is the only known electrophilic substitution reaction of quinazoline. The expected order of reactivity is at positions 8 > 6 > 5 > 7 > 4 > 2. Quinazoline gives 6-nitroquinazoline with fuming nitric acid in concentrated H_2SO_4. No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present (see Scheme 6).



Scheme 6

4.4.2 Alkylation Reactions

Alkylation of quinazoline takes place on N atom, 3-methyl, 3-ethyl-3-alkyl, and 3-benzylquinazolinium salts that readily take up a molecule of alcohol to form the corresponding 4-alkoxy-3-alkyl-3,4- dihydroquinazolinium salts. These salts gave the pseudo bases, 3-alkyl-3,4-dihydro-4-hydroxy quinazolines on treatment with strong alkali (see Scheme 7).



Scheme 7

4.4.3 Addition Reactions

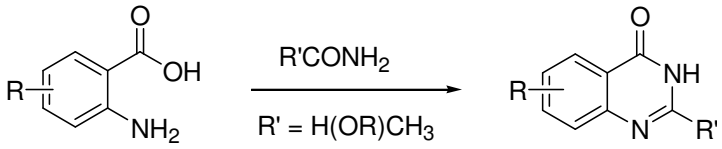
Quinazoline is highly reactive towards anionic reagents which attack on position 4. Sodium bisulphate, hydrogen cyanide, acetone, 2-butanone, acetophenone, and cyclohexanone add across the 3,4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl, and phenyl magnesium halides and phenyl lithium also add across the 3,4-double bond to give the corresponding 4- substituted 3,4-dihydroquinazolines.

4.5 Synthesis of Quinazoline Compounds

Various methods were reported for the synthesis of oxoquinazolines.

4.5.1 Niementowski's Synthesis

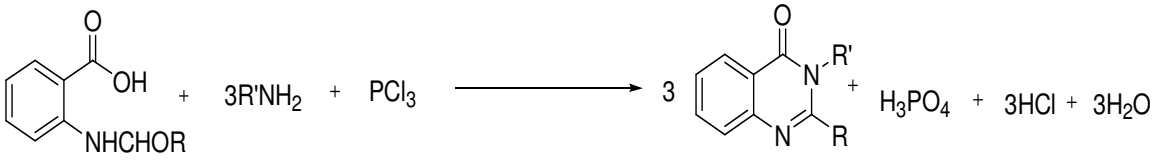
Compound 3 or 4-substituted anthranilic acid when reacted with formamide at 125-130°C gave 3,4-dihydro-4-oxoquinazoline (see Scheme 8).



Scheme 8

4.5.2 Grimmel, Guinther and Morgan's Synthesis

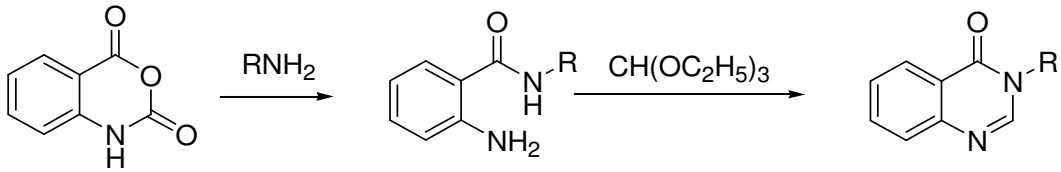
The o-amino benzoic acids, when heated with an amine together with phosphorous trichloride in toluene for two hours, gave 2,3-disubstituted3,4-dihydro-4-oxoquinazolines (see Scheme 9).



Scheme 9

4.5.3 From Isatoic Anhydride

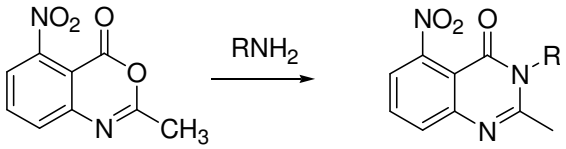
Isatoic anhydride was readily reacted with amines to dihydro-4-oxoquinazolines by refluxing ethyl orthoformate for 1-6 hours without isolating the intermediate amides (see Scheme 10).



Scheme 10

4.5.4 From 3,1,4-Benoxazones (Acylanthranils) and Amines

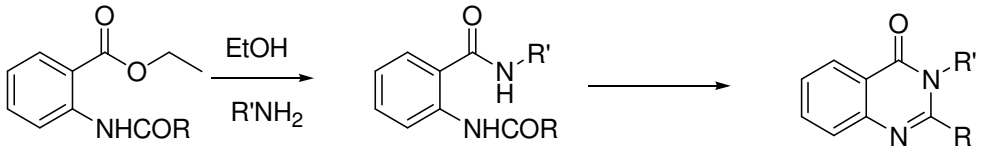
3,1,4-Benoxazones react with amines to give 3,4-dihydro-4- oxoquinazolines. Primary aliphatic amines and anilines react with 2-methyl-5-nitro-4-oxoquinazolines (see Scheme 11).



Scheme 11

4.5.5. From Ethyl 2-Acetamido-5-nitrobenzoate

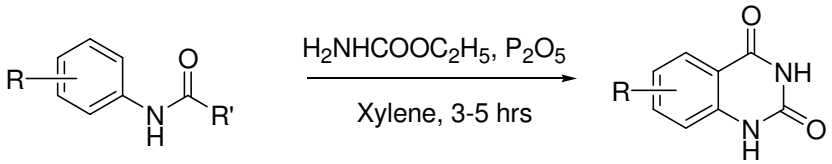
Ethyl 2-acetamido-5-nitrobenzene and alcoholic ammonia when heated gave 3,4-dihydro-methyl-6-nitro-4-oxoquinazoline (see Scheme 12).



Scheme 12

4.5.6 Sen and Ray's Synthesis

Boiling a solution of normal or isobutyrylanilides with urethane and phosphorous pentoxide in xylene gave 2-propyl and 2-isopropyl-3,4-dihydro-4- oxoquinazolines (see Scheme 13).



R = Me, OMe, OEt,; R' = Me, Et, Pr, Iso-Pro, Ph

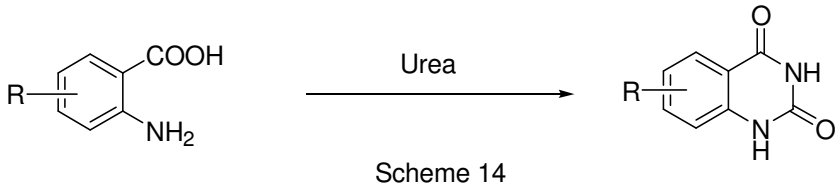
Scheme 13

4.6 Methods for the Synthesis of Quinazoline and Quinazolinone Derivatives (Benzoylene Urea)

Some methods were reported for the synthesis of quinazolines and quinazolinones are as follows.

4.6.1 From Anthranilic Acid and Urea

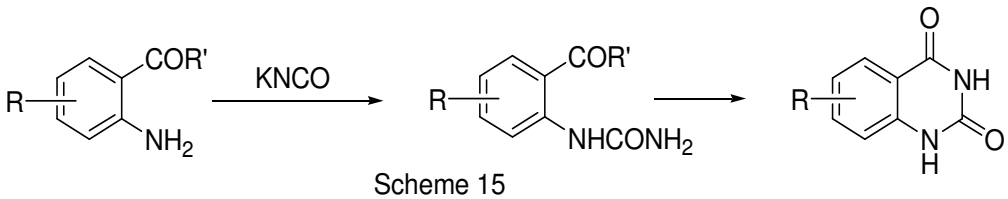
The fusion of anthranilic acid with urea gave 1,2,3,4-tetrahydro-2,4-dioxoquinazoline (see Scheme 14).



Scheme 14

4.6.2 From o-Ureidobenzoic Acid

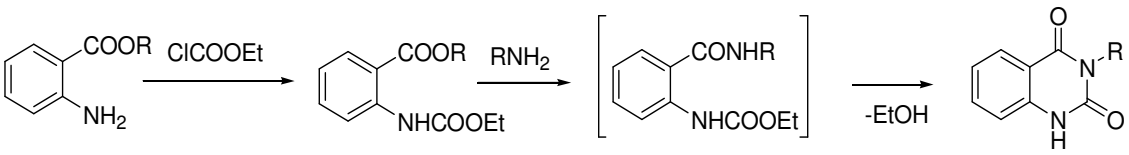
The o-ureidobenzoic acids are prepared from the corresponding anthranilic acid and potassium cyanate. The ureido acids are then easily cyclized to the respective 1,2,3,4-tetrahydro-2,4-dioxoquinazolines by heating with acid or alkali (see Scheme 15).



Scheme 15

4.6.3 From o-Ethoxy Carbonyl aminobenzoic Esters or Amides

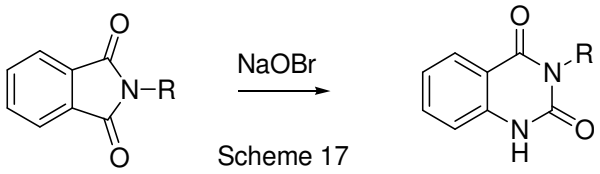
When o-ethoxycarbonylaminobenzamide and its 4-methyl derivatives are heated over their melting points, then they lose water and form 1,2,3,4-tetrahydro-2,4-dioxoquinazoline (see Scheme 16).



Scheme 16

4.6.4 From Phthalic Acid Derivatives

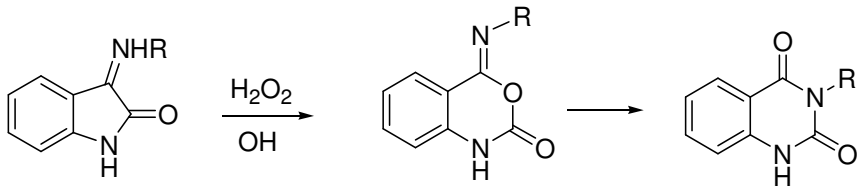
The derivatives of phthalic acid used for the preparation of dioxoquinazoline necessitate rearrangement of the Hoffmann Curties or Lossan type. Reaction of phthalamide or phthalimide, N-methyl, and N-ethyl phthalimide with alkali hypobromite gives the 1,2,3,4-tetrehydro 2,4-dioxoquinazoline (see Scheme 17).



Scheme 17

4.6.5 From Isatins

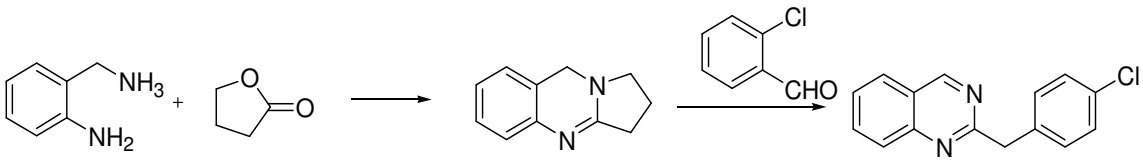
α-Isatinoxime rearranges to 1,2,3,4- tetrahydro-2,4-dioxoquinazoline on heating with dilute sodium hydroxide; β-imino derivatives of isatin, on the other hand, require oxidation with hydrogen peroxide in alkaline solution in order to form the dioxoquinazoline (see Scheme 18).



Scheme 18

4.6.6 From 2-Aminobenzylamine

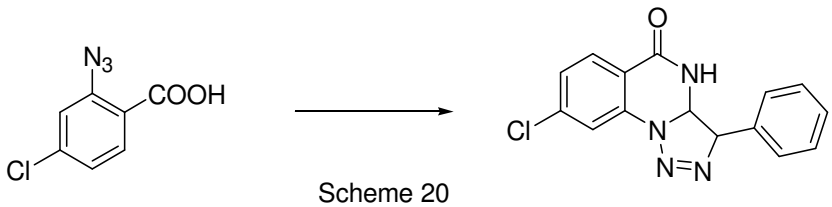
The 2-aminobenzylamine reacts with butyrolactone which involves forming intermediate compound and further condensed with benzaldehyde to give 3-(2-chlorobenzylidene)-1,2,3,9-tetrahydropyrrolo-2- quinazoline (see Scheme 19).



Scheme 19

4.6.7 From 2-Azido-4-chlorobenzoic Acid

The 2-azido-4-chlorobenzoic acid reacts with benzyl nitrile and formed 7-chloro-3-phenyl-[1, 2, 3]triazolo[1,5-a]quinazoline-5-one[9] (see Scheme 20).



Scheme 20

Condensation of o-iodobenzaldehydes with amidine hydrochlorides under ligand-free copper catalyzed Ullmann N-arylation conditions afforded the corresponding quinazolines[10]. Treatment of benzoxazine with hydrazine hydrate in ethanol prepared 3-amino-2-phenyl quinazolin-4-(3H)- one, which upon condensation with aldehydes gives

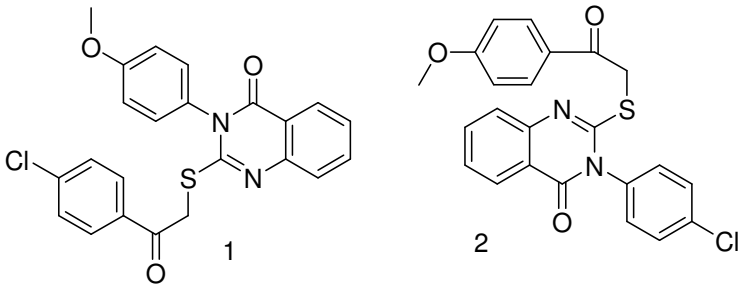
the corresponding 3-arylidenoamino derivatives. Cyclization of these derivatives using mercaptosuccinic acid afforded 1,3- thiazolidin-4-one ethanolic acid, which after esterfication with N-hydroxyphthalimide or N-hydroxysuccinamide via acid chlorides produced the respective ethanolic esters[11]. A series of quinoxalin-2(1H)-one-3-hydrazone derivatives were synthesized via condensation of 3-hydrazinoquinoxalin-2(1H)-one with the corresponding ketones under microwave irradiation and gave hydrazones in high yield in less reaction time compared to conventional method[12]. The (hydroxyimino)(2-phenyl(1,2,3,4-tetrahydroquinazolin-2-yl))methane and (hydroxyimino)(2-(2-thienyl)(1,2,3,4-tetrahydroquinazolin-2-yl))methane were synthesized by the condensation of 2-(hydroxyimino)-1-phenylethan-1-one and 2-(hydroxyimino)-1-(2-thienyl) ethan-1-one with 2- aminobenzylamine (2-ABA). Complexes of these ligands with Co3+ were prepared with a metal:ligand ratio of 1:2[13]. The [4+2]cycloaddition between 2,4-diphenylpyrimidine, ortho-quinodimethane and dimethyl acetylenedicarboxylate leads to 2,4-diphenylquinazoline-6,7-dicarboxylate. 2,4-Diphenylfuro[3,4-g]quinazoline-6,8-dione is also obtained by basic hydrolysis of compound, followed by the closure of the resulting diacid in acetic anhydride [14]. A series of triazoloquinazolinones and benzimidazoquinazolinones has been achieved under microwave irradiation by the reaction of aromatic aldehydes with 5-amino-1(H)-1,2,4-triazole (or 2-aminobenzimidazole) and dimedone in DMF[15].

4.7 Biological Importance of Quinazoline Derivatives

The quinazoline and quinazolinone skeleton is frequently encountered in medicinal chemistry. The various substituted quinazolines and quinazolinones are having significant antihypertensive, antineoplastic, antidepressant, and antipsychotic activities whereas some derivatives of quinazoline and quinazolinones are found to be effective agents such as analgesic, antipsychotic, antiarrhythmic, sedative hypnotics, antibacterial, anti-inflammatory, antifungal, antimalarial, anticonvulsant, anticoccidial, anti-Parkinsonism, cancer and other activities[6-8].

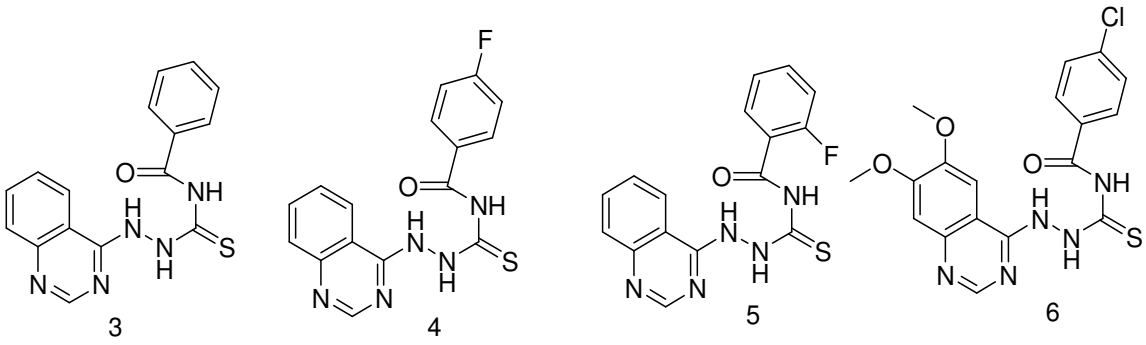
4.7.1 Quinazolinones as Anticancer Activity

Some new 3-substituted quinazolin-4(3H)-ones and 3,4-dihydro-quinazolin-2(1H)-one derivatives are reported that compounds 2-[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl)quinazolin-4(3H)one (1) and 3-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3H)-one (2) as broad-spectrum antitumors show effectiveness toward numerous cell lines that belong to different tumor subpanels[16] (see Scheme 21).



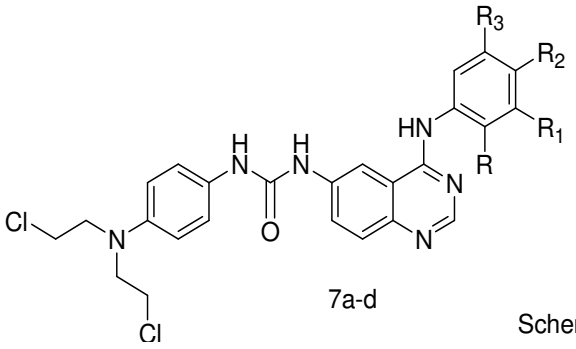
Scheme 21

A series of novel quinazoline derivatives (3-6) containing thiosemicarbazide moiety and evaluate their biological activity as antitumor agents[17]. The therapeutically important candidates are shown in (see Scheme 22).



Scheme 22

A series of phenyl N-mustard-quinazoline derivatives (7a–d) were evaluated for their antitumor activity[18] (see Scheme 23).

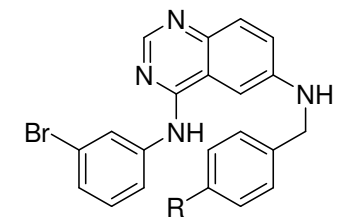


Compd	R	R_1	R_2	R_3
7a	H	OCH_3	OCH_3	OCH_3
7b	F	Cl	H	H
7c	H	Cl	F	H
7d	H	C≡CH	H	H

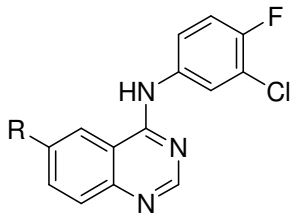
7a-d

Scheme 23

A series of few 4,6-di-substituted-(diaphenylamino)quinazolines derivatives (8a-b) were evaluated for antitumor activity was considered as potent EGFR inhibitors[19]. A series of quinazoline derivatives (9a-c) were evaluated for their function as EGFR inhibitors by applying radioiodination. All these compounds were further evaluated for potential SPECT activity for molecular imaging of breast cancer[20] (see Scheme 24).



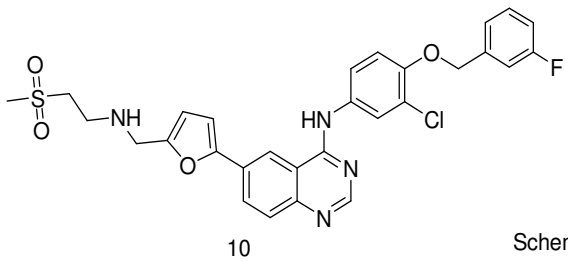
(8a-b) R = 8a -OH; 8b -Cl



(9a-c) R 9a -$NHCO(CH_2)_2Br$;
9b -$NHCO(CH_2)_2I$; 9c -NH_2

Scheme 24

A series of novel 6-furanylquinazoline derivatives (10-13) were subsequently evaluated for their biological activity as a potent ErbB-1/ErB-2 tyrosine kinase inhibitor[21] (see Schemes 25 and 26).



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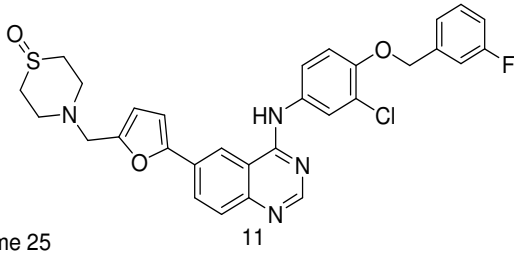
Scheme 25



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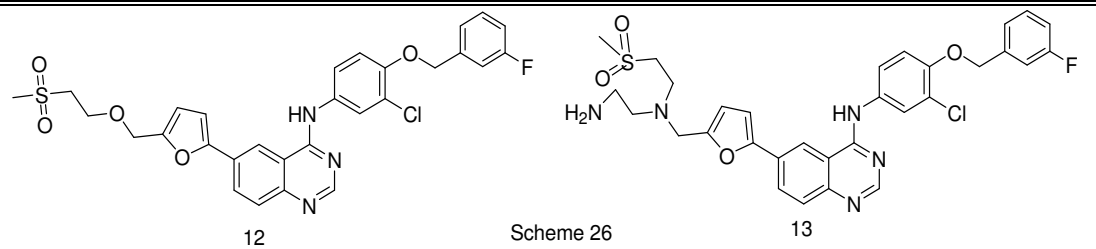
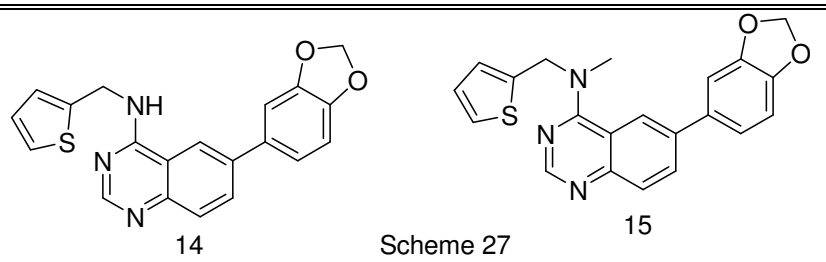
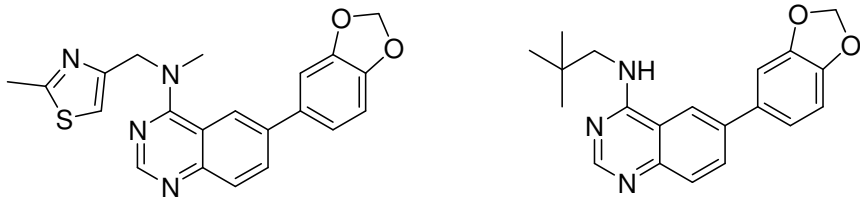


12 Scheme 26 13

A series of quinazoline derivatives (14-17) were evaluated for their activity as potent inhibitors of specific isoforms of Cdc2-like kinases (Clk) and dual specificity tyrosinephosphorylation regulated kinases (Dyrk)[22] (see Schemes 27 and 28).



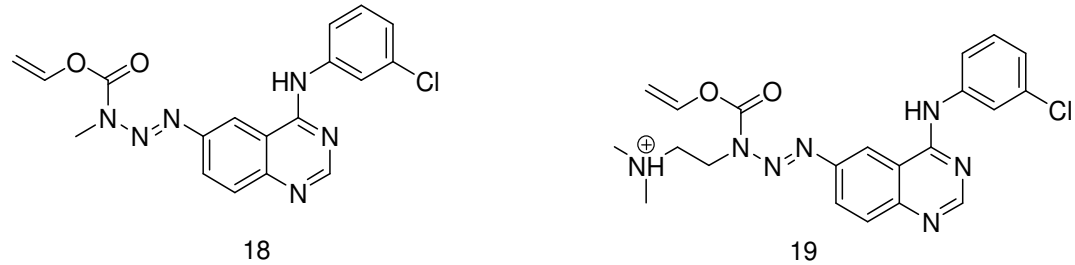
14 Scheme 27 15



16 17

Scheme 28

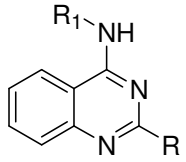
New combi-triazenes (18, 19) for targeting solid tumors express the epidermal growth factor receptor (EGFR) or its closest homologue HER2 (see Scheme 29).



18 19

Scheme 29

A series of novel quinazoline derivatives (20a-c) showed potent ALK5 inhibitory activity[23] (see Scheme 30).

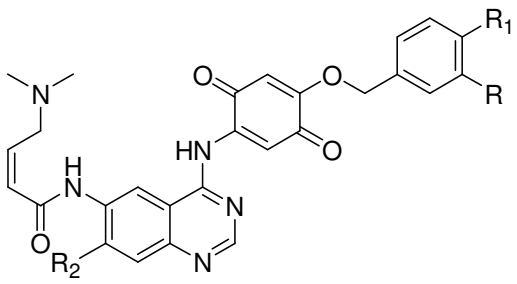


20 a-c

	R	R1
20a	6-Methyl-2-pyridinyl	Pyridine-4-yl
20b	6-Methyl-2-pyridinyl	1H-indazol-5-yl
20c	6-Methyl-2-pyridinyl	4-Pyrimidnyl

Scheme 30

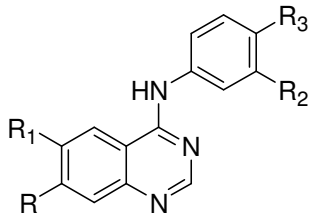
Quinazoline-based (21a-b) anticancer molecule is dual irreversible kinase inhibitors[24] (see Scheme 31). A series of quinazoline derivatives (22a-b) were evaluated for their biological activity against tyrosine kinase (EGFR)[25] (see Scheme 32).



21 a-b

Scheme 31

	R	R_1	R_2
21a	F	H	OCH_3
21b	F	F	OCH_3

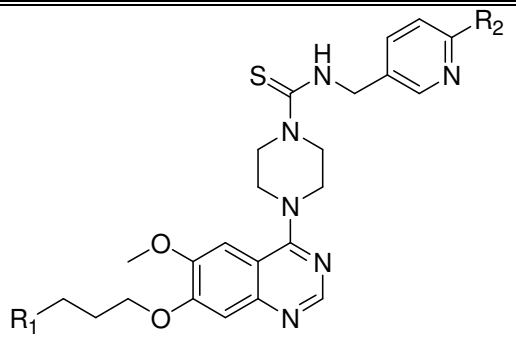


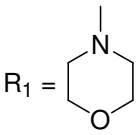
22 a-b

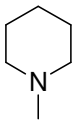
Scheme 32

	R	R_1	R_2	R_3
22a	OCH_3	OCH_3	H	Br
22b	NO_2	H	F	H

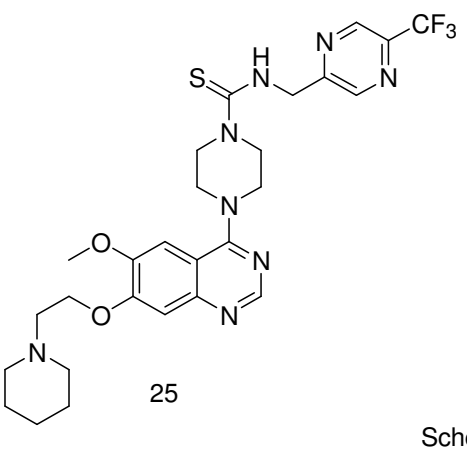
A series of 4-piperazin-1-yl-quinazoline template based aryl and benzyl thiourea derivatives (23-26) showed potent, selective, and orally bioavailable antagonist of platelet-derived growth factor (PDGF) receptor[26] (see Schemes 33 and 34).



23 R_1 =  , $R_2 = CF_3$

24 R_1 =  , R_2 = Cl

Scheme 33



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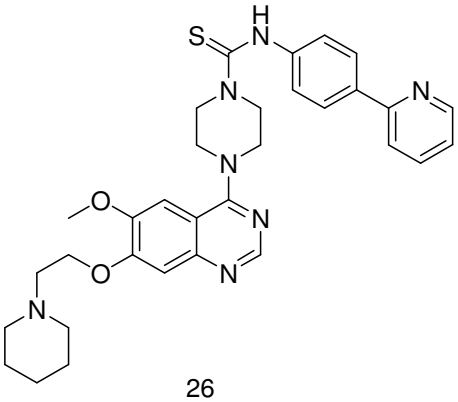
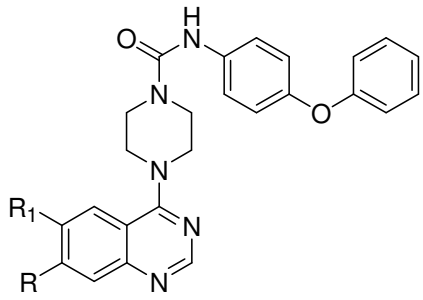


26

Scheme 34

A series of 4-[4-(N-substituted(thio)carbamoyl)-1-piperazinyl]-6,7-dimethoxyquinazoline derivatives (27a-b) were evaluated for their potential antagonizing activity against Platelet-Derived Growth Factor Receptor (PDGF)[27] (see Scheme 35).



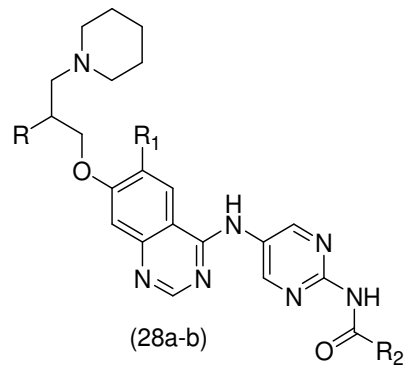
(27 a-b)

	R	R1
27a	OEt	OMe
27b	COOMe	H

Scheme 35

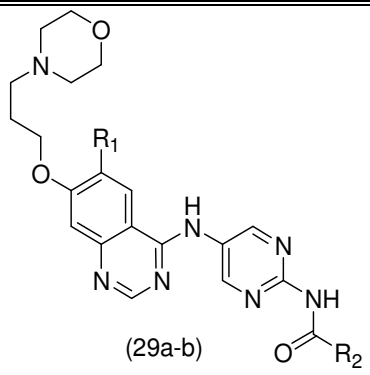
A series of quinazoline derivatives (28a-b and 29a-b) showed potent inhibitory activity against Aurora kinase[28] (see Scheme 36). A series of 1-acetanilide-4-aminopyrazole

substituted quinazoline derivatives (30a-c) were subsequently evaluated for their inhibitory activity against Aurora B kinase as potent antitumour agents[29] (see Scheme 37).



(28a-b)

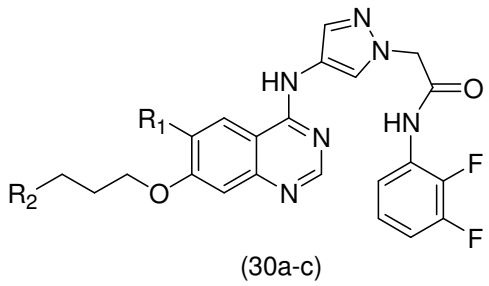
	R	R_1	R_2
28a	H	OCH_3	3-Cl-C_6H_4
28b	OH	OCH_3	C_6H_5



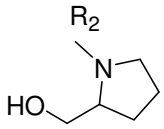
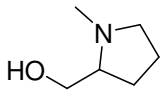
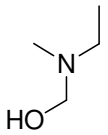
(29a-b)

	R_1	R_2
29a	OCH_3	3-Cl-4F-C_6H_3
29b	OCH_3	3-Cl-C_6H_4

Scheme 36

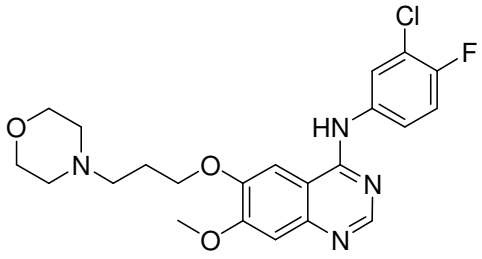


(30a-c)

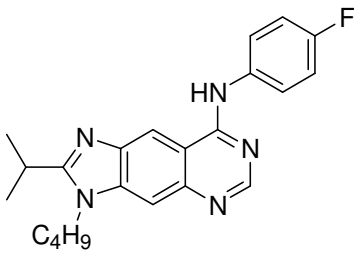
	R_1	R_2
30a	H	
30b	OCH_3	
30c	OCH_3	

Scheme 37

Some quinazolines were evaluated as antitumor agents, the biological activity of some 2,3-di-substituted 8-arylamino-3H-imidazo[4,5-g]quinazoline derivative (31 and 32) as a potent antitumor agent. Compound 32 possessed the highest activity on the A549 cell line[30] (see Scheme 38).



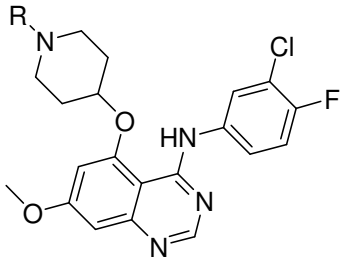
(31)



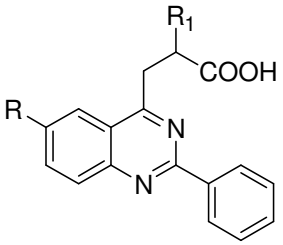
(32)

Scheme 38

A series of novel C-5 substituted anilinoquinazoline derivatives and evaluated their activity as an inhibitor of epidermal growth factor receptor tyrosine [31]. Few novel 4,6-disubstituted quinazoline derivatives (33-36) showed good anti-inflammatory and anticancer activity (cytotoxic) against U937 leukemia cell lines[32] (see Scheme 39).



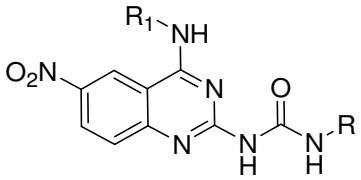
(33a-b) 33a R = CH_3; 33b R= H



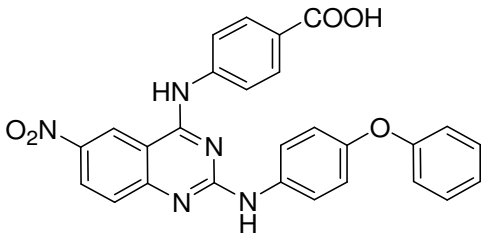
34 R = I; R_1 = CH_3; 35 R=H, R_1 = CH_3; 36 R=I, R_1 = $CH_2C_6H_5$

Scheme 39

A series of quinazoline derivatives (37 and 38) have strong inhibition on human Pin1[33] (see Scheme 40).



(37a-c)

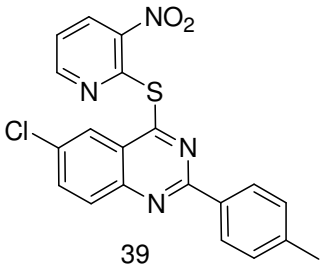


38

37a	3,4-Cl-C_6H_3	4-COOH-C_6H_4
37b	4-CF_3-C_6H_4	4-COOH-C_6H_4
37c	3-CF_3-C_6H_4	4-COOH-C_6H_4

Scheme 40

A series of quinazoline derivatives (39-42) were evaluated for their biological activity as potential antitumor agents[34] (see Schemes 41 and 42).



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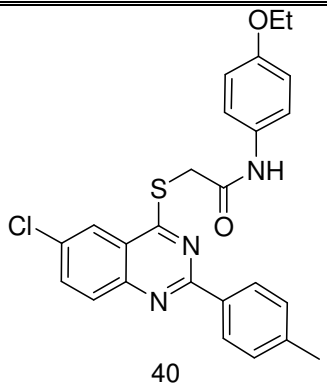

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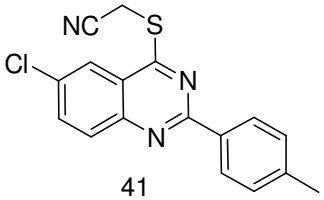
Scheme 41



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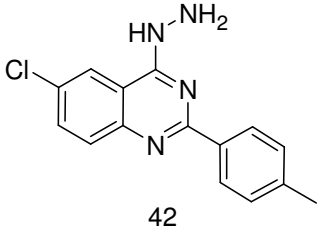


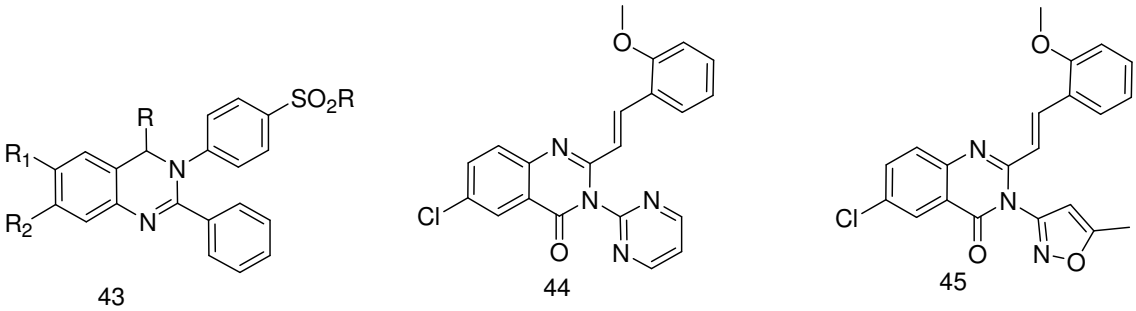
42

Scheme 42

HEPG2 human liver cell line was proved to be sensitive toward compounds 39, 40, and 41 with IC_{50} concentration range of 4.17–5.99 μg/mL. Regarding HELA cervix cell line, higher sensitivity was observed with compounds 39, 41 and 42 with IC_{50} concentration range of 3.56–5.39 μg/mL. With regard to broad-spectrum antitumor activity, compounds 42, 41, and 39 showed IC_{50} of 3.35–5.59 μg/mL against the three cell lines. Microwave-assisted synthesis and the SAR studies of modified 9-oxo-thia-zolo[5,4-f] quinazoline-2-carbonitriles allowed identification of new amidine and imidate derivatives as potent and dual CDK1/GSK-3 inhibitors. Combination of lead optimization and molecular modeling studies allowed a dual CDK1/GSK-3 inhibitor with submicromolar values[35]. Novel 2,3-disubstituted quinazoline-4(3H)-ones (43) were screened for cytotoxicity and for antiviral activity against influenza A[36]. The 6-Arylbenzimidazo [1,2-c]quinazoline derivatives were act as a tumor necrosis factor alpha (TNF- α) production inhibitors. These compounds were tested for their in vitro ability to inhibit the lipolysaccharide (LPS)

induced TNF-α secretion in the human promyelocytic cell line HL-60. The compound 6-

Phenyl-benzimidazo[1,2-c]quinazoline, coded as G1, resulted as the most potent inhibitor and with no significant cytotoxic activity. Thus, 6-arylbenzimidazo [1,2-c]quinazoline derivatives may have a potential as anti-inflammatory agents[37]. Docking studies of few synthesized 6,7-dialkoxy-4-anilinoquinazoline derivatives which showed EGFR-TK inhibitory activity were conducted[38]. The 3-(3-methylisoxazol-5-yl) and 3-(pyrimidin- 2-yl)-2 styrylquinazolin-4(3H)-ones (44, 45) were prepared by refluxing in acetic acid the corresponding 2-methylquinazolinones with the benzoic aldehyde and tested for their in vitro antileukemic activity against L-1210 (murine leukemia), K-562 (human chronic myelogenous leukemia), and HL-60 (human leukemia) cell lines showing in some cases good activity[39] (see Scheme 43).



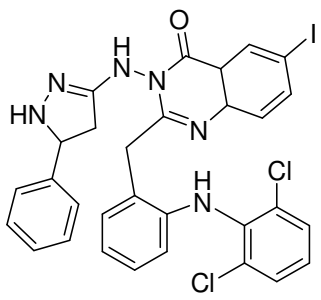
Scheme 43

4.7.2 Quinazolinones as Antibacterial Activity

A series of new 2-[2-(2,6-dichlorophenyl) amino] phenyl methyl-3-[(5-substitutedphenyl)-1,5-dihydro-1H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H)ones compounds (46) were tested for their antibacterial activity *in vitro* by measuring zone of inhibition in mm against different strains like two gram positive bacteria, namely, *Staphylococcus aureus* and *Bacillus subtilis*, and two gram negative bacteria, namely,

Escherichia coli and *Certium* at two different concentrations 100 μg/mL and 50 μg/mL[40].

Quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6, and DK-7) by treating 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide with the different substituted phenols. The synthesized compounds were evaluated for antibacterial activity by cup plate method by measuring inhibition zone. The compound DK-2 (47) showed more potent antibacterial activity than the standard drug ampicillin[41]. A series of quinazolines derivatives were evaluated for their biological activity on various bacterial cultures[42] (see Schemes 44 and 45).



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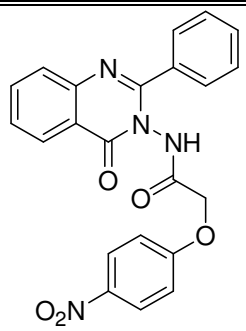

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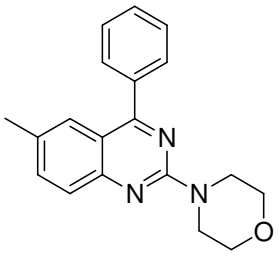
Scheme 44



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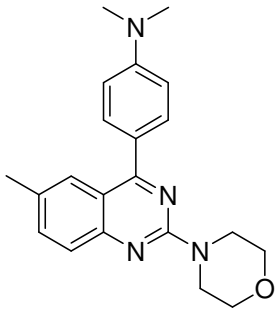

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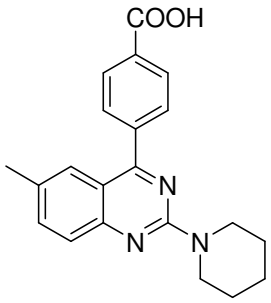
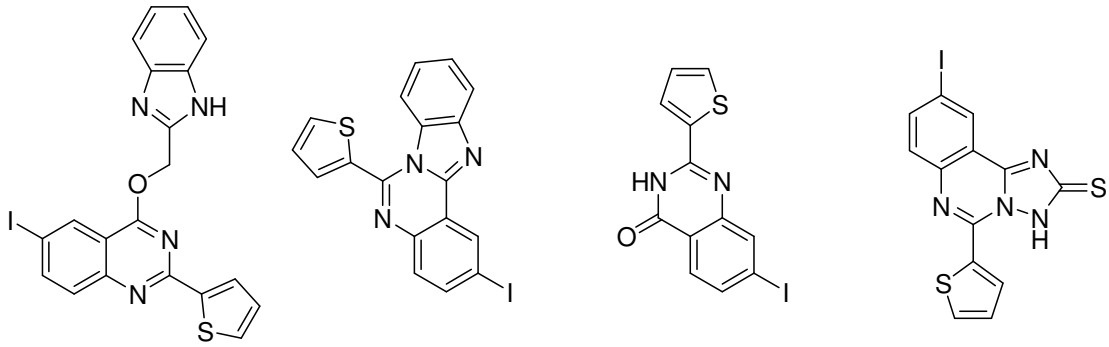


50

Scheme 44

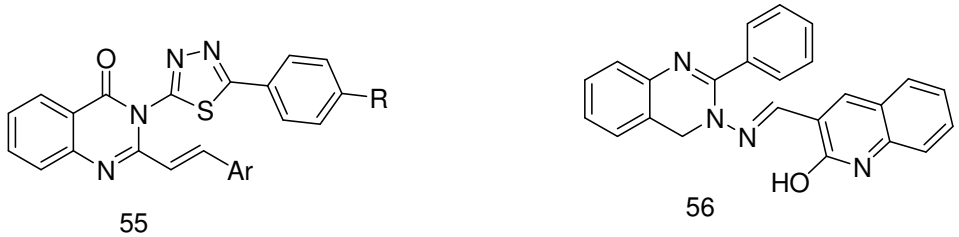
Compounds 49 and 50 showed comparative activity against *K. pneumoniae* as compared to ciprofloxacin. Compound 48 exhibited greater activity against *S. sonnei, E. faecalis,* and *P. aeruginosa* as compared to ciprofloxacin. A series of some novel substituted iodoquinazoline derivatives are evaluated for their antimicrobial activity[43]. Compounds 52 and 53 showed remarkable activity towards the gram negative bacteria *E. coli*, whereas compounds 51, 52, and 54 showed potent activity against *S. aureus, B. subtilis, S. Cerevisiae, and C. albicans* (see Scheme 46).



51 52 53 54

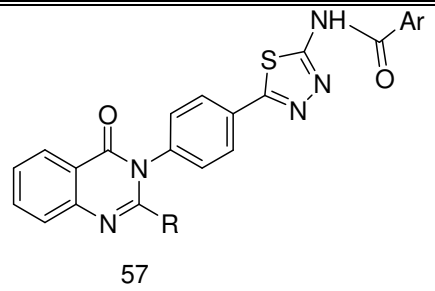
Scheme 46

The 3-[5-(4-substituted phenyl)-1,3,4-thiadiazole-2- yl]-2-styryl quinazoline-4(3H)-ones (55) reported their antibacterial and antifungal activity[44]. The 6,7,8,9-tetrahydro-5(H)-5-nitrophenylthiazolo[2,3-b]-quinazolin-3(2H)-one derivatives showed antimicrobial activity[45]. The 3-[(2-hydroxy-quinolin-3-ylmethylene)-amino]-2-phenyl-3H-quinazolin-4-one (56) and its metal (II) complexes were reported for their antimicrobial activity[46]. Some quinazoline derivatives (57) act as potential antimicrobial agents[47] (see Schemes 47 and 48).



55 56

Scheme 47



R = 2-chlorophenyl, Ar = different aryl groups

57

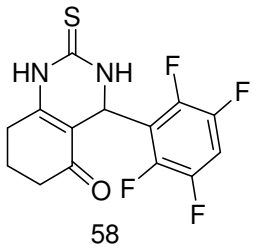
Scheme 48

Condensing 2-methyl/phenyl/chloro methyl disubstituted benzooxazine-4-one and 1-(2-aminoethyl)-4-substitutedbenzylidene-2-phenyl-1H-Imidazoles-5(4H)-one gave imidazolo-quinazoline-4-one derivatives. These compounds have shown promising antibacterial and antifungal activity[48]. The antibacterial activities of substituted quinazolines against bacterial strains *E. coli, P. aeruginosa, B. subtilis* and *S. aureus* were investigated. The sensitivity of the gram positive bacteria to the tested quinazolines was higher than that of gram negative bacteria. The most effective of quinazoline structure series were condensed [1,2,4]triazolo quinazolines and 10H-[1,2,4]triazino[5,4-b]quinazolin-10-ones[49].The 6-bromo-2-alkyl/aryl-3-{[phenyl(phenyldiazenyl)methylene]amino} quinazolin-4(3H)-ones were exhibited antimicrobial activities[50].

4.7.3 Quinazolinones as Antifungal Activity

Octahydroquinazoline (58) was obtained by a modification of the Biginelli reaction with phenacyl bromide and bromomalononitrile to furnish thiazolo [2,3-b] quinazoline and they found the interaction of compound with formamide, formic acid, and phenyl isothiocyanate yielded the corresponding pyrimidinothiazolo [2,3-b] quinazolines and exhibited antifungal activity against *Candida albicans*[51]. A series of few novel S-

substituted-6-fluoro-4-alkyl (aryl) thioquinazoline derivatives (59a-c) were evaluated for their pharmacological activity as antifungal[52] (see Scheme 49).



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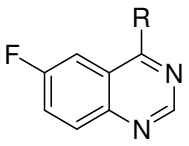


(59a-c)

	R
59a	$SCH_2CH=CH_2$
59b	$SCH_2CH_2CH_3$
59c	SCH_2CH_3

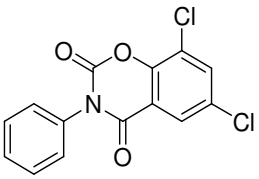
Scheme 49

All of these compounds exhibited good antifungal activity, especially compound 59c, having a wide spectrum of bioactivity; it shows potent inhibitory activity on the growth

of most of the fungi with EC_{50} values ranging from 8.3 to 64.2 μg/mL.

4.7.4 Antitubercular Activity

Some quinazolinones were reported as potent chemotherapeutic agents in the treatment of tuberculosis (TB). For example 3-aryl-6,8-dichloro-2H-1,3-benzoxazine-2,4(3H)-diones (60) and 3-arylquinazoline-2,4(1H,3H)-diones (61) are as anti-TB agents and quinazolinone derivatives as anti-TB agents. A series of 2-alkylthio-6-iodo-3-substituted-quinazolin-4-one derivatives were screened for their in vitro anti-TB activity against Mycobacterium tuberculosis strain HRv[53]. A series of quinazoline derivatives (62a-d) were evaluated for their pharmacological activity as anti-TB[54] (see Scheme 50).



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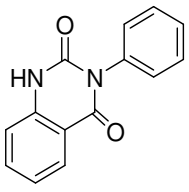

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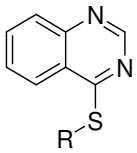


(62a-d)

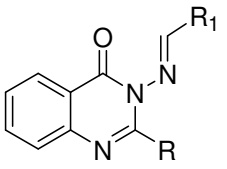
	R
62a	C_2H_5
62b	C_3H_7
62c	C_4H_9
62d	$CH(CH_3)_2$

Scheme 50

1,4-Disubstituted 3-[3'-(2'-phenyl-4'-oxo-quinazolinyl)]-2-azetidinones showed antifertility activity[55]. 6-substituted-2-phenyl-3-(5-substitutedmercapto-1,3,4-thiadiazole-2yl)quinazoline-4-(3H)-ones showed anti-TB activity[56]. Most of the synthesized compounds exhibited anti-TB activity against the strains of Mycobacterium tuberculosis, *M. avium, M. fortuitum, M. kansasii,* and *M. intracellulare*. The modification process with various hydrophobic chains clearly suggests the existence of hydrophobic pocket in the active site of the target of various strains of Mycobacterium spp., which eventually raise the therapeutic efficacy.

4.7.5 Quinazoline as Antiviral Agents

A series of Schiff bases of some 2-phenyl quinazoline-4(3)H-one derivatives are evaluated for their activity as antiviral agents[57] (see Scheme 51).



(63a-c)

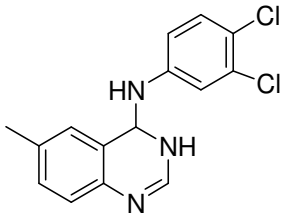
	R	R_1
63a	C_6H_5	2-OH-C_6H_4
63b	C_6H_5	4-MeO-C_6H_4
63c	C_6H_5	C_6H_5

Scheme 51

Compound 63a exhibited antiviral activity against herpes simplex virus-1 (KOS), herpes simplex virus-2(G), herpes simplex virus-1 (TK- KOS ACV), and vaccinia virus in HEL cell culture at selectivity index of 100, 100, 100, and 125, respectively, whereas

cytotoxicity was observed at 100 μg/mL. Compounds 63b and 63c demonstrated good

activity against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), and vaccinia virus. The protein kinase inhibitory activity and anticytomegaloviral activity showed few quinazoline (64) compounds[58]. Quinazolinones act as anti-HIV activity whereas compounds 3-amino-2-methyl mercaptoquinazolin-4(3H)-one (65) were synthesized by condensing the acidic imino group of isatin with formaldehyde and secondary amines and evaluated for antiHIV activity against HIV-1 III B in MT-4 cells[59] (see Scheme 52).



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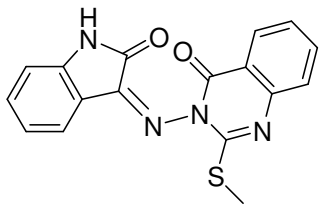


65

Scheme 52

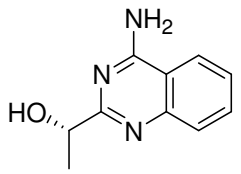
4.7.6 Quinazolinones as Antimutagenic Activity

The (S)-4-aminoquinazoline alcohols (66) were prepared from enantiomerically pure from (S)-quinazolinone alcohols. Mutagenic and antimutagenic properties of the (S)-4-aminoquinazoline alcohols were investigated by using Salmonella typhimurium and E. coli WP2uvrA tester strains at 0.01, 0.1, and 1 lg/plate concentrations. (S)-4-aminoquinazoline alcohols were found to be genotoxically safe at the tested concentrations. Among the tested (S)-4-aminoquinazoline alcohols, the best

antimutagenic activity was obtained with a methyl derivative at 0.1 μg/plate dose[60].

4.7.7 Quinazolinones as Anticoccidial Activity

A series of 3-(2-(2-methoxyphenyl)-2-oxoethyl) quinazolinone derivatives (67) are anticoccidial agents by modifying the quinazoline ring of febrifugine against Eimeriatenella in the chicken at a dose of 9 mg/kg. 3-(2-(2-Methoxyphenyl)-2-oxoethyl) quinazolinone derivatives (68) possess high anticoccidial activity and may serve as a lead compound for the development of anticoccidial drugs in the future[61]. A series of 4-(2-methoxyphenyl)-2-oxobutylquinazoline (69) derivatives are reported for their anticoccidial activity[62] (see Schemes 53 and 54).



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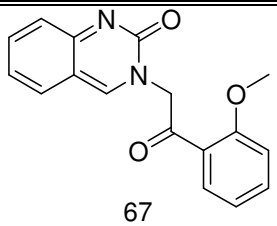
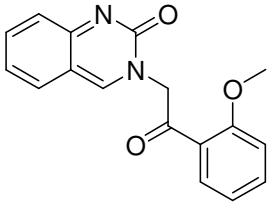


67

Scheme 53



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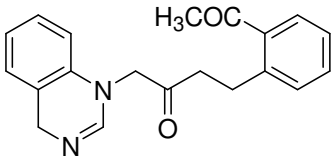

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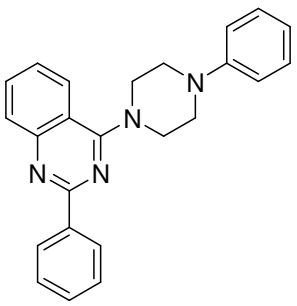
Scheme 54

4.7.8 Anti-Inflammatory and Analgesics Agents

A series of quinazoline derivatives (70, 71) showed potent analgesic and anti-inflammatory activity. All these compounds demonstrated potent activity as anti-inflammatory analgesic more than the reference compound indomethacin[63] (see Scheme 55).



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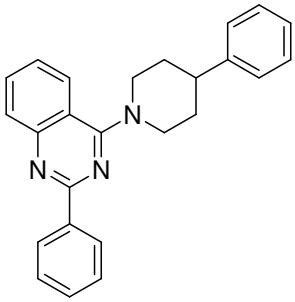
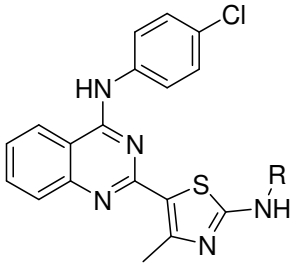


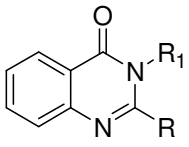
71

Scheme 55

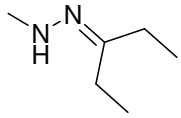
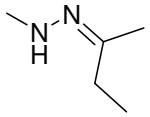
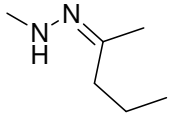
A series of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one (72) derivatives which became good inhibitors of NF κB and AP-1 mediated transcription activation[64]. A series of 3-phenyl-2-substituted-3Hquinazolin-4-one (73a-c) derivatives were evaluated for their pharmacological activity as analgesic and anti-inflammatory agents[65] (see Scheme 56).



(72a-b) 72a R= CH_3
72b R= 3Cl-C_6H_4



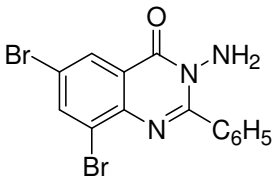
(73a-c)

	R	R_1
73a	C_6H_5	
73b	C_6H_5	
73c	C_6H_5	

Scheme 56

A series of some novel 2,3-disubstituted quinazolinone derivatives by condensing 2-methyl/2-phenyl/6-bromo-2-methyl/6-bromo-2-phenyl/6,8-dibromo-2-methyl/6,8-

dibromo-2-phenyl benzoxazines with compounds containing amino group were evaluated for their analgesic activity and they reported that compound (74) shows promising analgesic activity compared to standard drug Diclofenac sodium[66]. Various 2-(substituted phenyl methylene imino) amino acetyl methylene-3-(2''-substituted indol-3''-yl)-halo substituted-4(3H) quinazolinone and 2-(substituted phenyl amino methylene acetyl-4'-oxo-1'-thiazolidinyl-3-(2''-substituted indol-3''-yl)4(3H)-quinazolinones reported that compound (75) exhibited good anti-inflammatory activity[67] (see Scheme 57).



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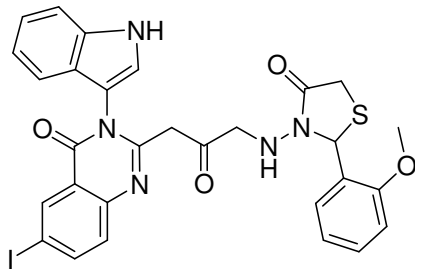

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Scheme 57

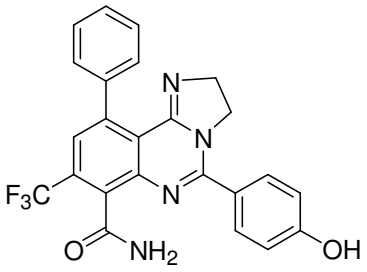
A series of novel 8/10-trifluoromethyl-substitutedimidazo [1,2-c] quinazolines are evaluated in vivo for their anti-inflammatory activity and in silico to recognize the hypothetical binding motif with the cyclooxygenase isoenzymes (COX-1 and COX-2) employing GOLD (CCDC, 4.0.1 version) software and found that compounds (76 and 77) show good anti-inflammatory activity against standard: indomethacin[68] (see Scheme 58).

A series of 5-(4-chlorophenyl)-9-iodo-3-substituted-1,2,4-triazolo[4,3-c]quinazoline and 2-(4-chlorophenyl)-6- iodo-4-substituted-quinazoline were evaluated as antiinflammatory agents. The result revealed that some compounds have activity comparable to indomethacin[69]. A number of substituted oxoquinazolines were reported for their analgesic and antibacterial activity[70]. A series of novel 3-(6-substituted-1,3-benzothiazole-2-yl)-2-[{(4-substitutedphenyl)amino}methyl]quinazolines-4(3H)-ones and quinazolines-4-one derivative were investigated for their anti-inflammatory and antibacterial activity[71]. A series of some 2-[(E)-2-furan-2-yl-vinyl]-quina-zolin-4(3H)-ones incorporated into pyrazoline, isoxazoline, pyrimidine, or pyrimidine-thione ring

systems at position 3 of the quinazoline ring. These compounds showed antimicrobial activity and anti-inflammatory activity[72].

4.7.9 Quinazoline as Antidepressant and Anticonvulsant

A series of novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones (78a-c) derivatives were evaluated for their activity as antidepressant agents[73] (see Scheme 59).



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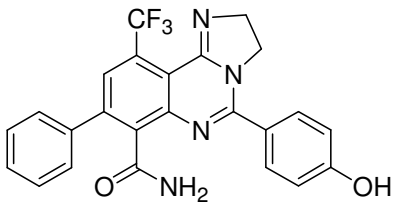

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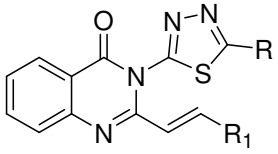
Scheme 58

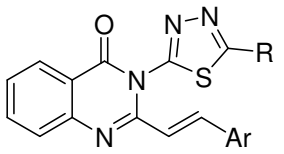


(78a-c)

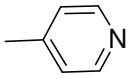
	R	R_1
78a	C_6H_5	C_6H_5
78b	4-Cl-C_6H_4	C_6H_5
78c	4-Cl-C_6H_4	p-$OCH_3C_6H_3$

Scheme 59

All the compounds showed anticonvulsant activity in MES screen; however, compound 78a showed potency similar to standard drug (phenytoin, carbamazepine) without any neurotoxicity A series of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-one. (79a-c) derivatives were evaluated for their activity as CNS depressant and anticonvulsant agents[74] (see Scheme 60).

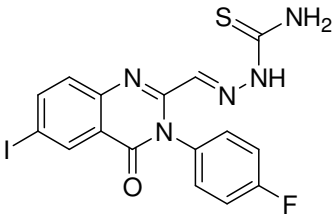


(79a-c)

	R	Ar
79a	C_6H_5	p-ClC_6H_4
79b	p-$OCH_3C_6H_4$	p-ClC_6H_4
79c	p-ClC_6H_4	

Scheme 60

Compounds with the above substituents showed potent CNS depressant activity. Compound 79a showed anticonvulsant activity at 0.5 and 4 h in different test models, whereas 79c showed anticonvulsant activity at 4 h in MES screen and at 0.5 and 4 h in subcutaneous PTZ screen. The 3-aryl-4(3H)-quinazolinone-2-carboxaldehydes, their corresponding Schiff's base, and thiosemicarbazone derivatives reported (80-82) as anticonvulsants[75] (see Scheme 61).



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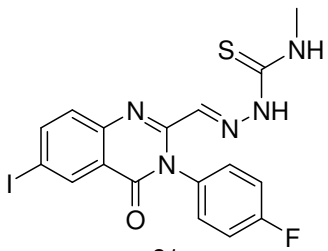

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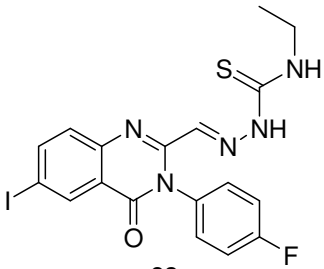

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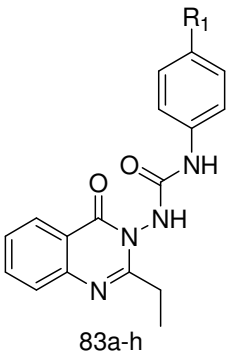
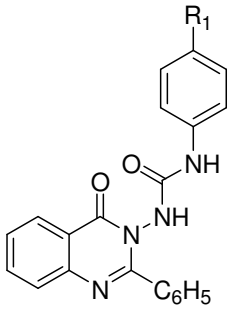
Scheme 61

Several 1-(4-substitutedphenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea derivatives (83a-h and 84a-h) were screened for their anticonvulsant activity by MES and scPTZ-induced seizure models in mice and found that these compounds were active in the MES screen whereas some compounds were found to be active in the scPTZ screen[76] (see Scheme 62).



83a-h

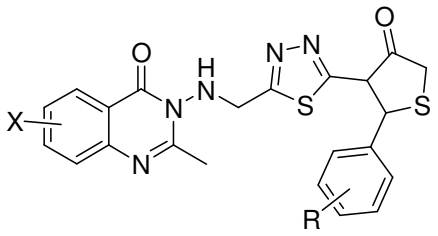


84a-h

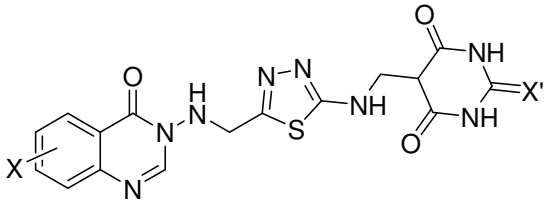
	R_1
84a	H
84b	NO_2
84c	$p(CH_3)$
84d	OEt
84e	Cl
84f	Br
84g	I
84h	OCH_3

Scheme 62

Two regioisomer series, 2-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/3-aryl-5-methyl-4-thiazolidinones (85) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-yl mercaptoacetylamino)-5-methyl-4-thiazolidinones were reported for their anticonvulsant activity[77]. Substituted quinazolinonyl-2-Oxo/thiobarbituric acid derivatives showed anticonvulsant activity against MES and scPTZ models[78]. A series of halogenated derivatives, 3-methyl, 3-ethyl and 3-phenyl-6-mono, and 6,8-disubstituted-3H-quinazolin-4-one derivatives exhibited anticonvulsant activity and phenobarbitone sodium was used as a reference drug[79]. Some thiadiazolyl and thiazolidinonyl quinazoline-4(3H)-ones (86) screened them for anticonvulsant activity against MES induced convulsions in animal models[80] (see Scheme 63).



85 X= H, R=H or p-OCH_3

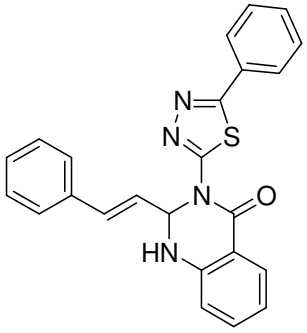


86 X=H or Cl, X' = O

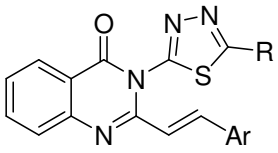
Scheme 63

A series of novel 3-[5-substituted phenyl-1,3,4 thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-one is screened for antidepressant activities with the help of the forced swim pool

method and found that compound (87) was most active against antidepressant activity[73]. The 3-[5-substituted-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones (88) and their antidepressant activity were screened with the help of forced swim pool method[73] (see Scheme 64).



87

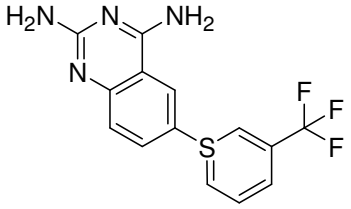


88 Ar = C_6H_5, R= pOCH_3

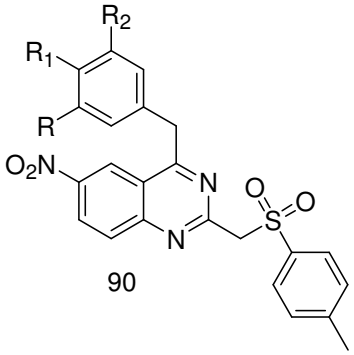
Scheme 64

4.7.10 Quinazolinones as Antimalarial Agents

The 2,4-diamino-6-[(aryl)thio]quinazoline compounds were known to their antimalarial properties wherein the 4-amino group was replaced by hydrazine and hydroxyamino moieties and they found that such changes reduce markedly the antimalarial properties of this series. The compound (89) was tested against a normal drug-sensitive strain of Plasmodium berghei in mice by the parenteral route[81]. A series of quinazoline derivatives (90) were evaluated for their antiplasmodial activity[82] (see Scheme 65).



89

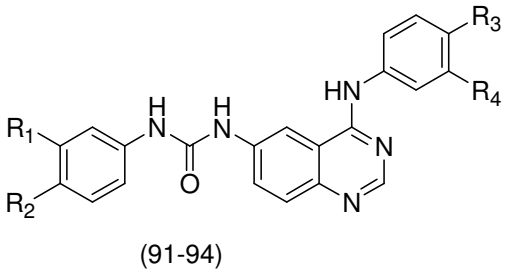


90

	R	R_1	R_2
90a	CF_3	H	H
90b	H	F	H
90c	Cl	H	H

Scheme 65

Compounds 90a and 90c show a high potential activity (resp., W2 IC_{50} values = 0.95 and 1.3 μM) in comparison with chloroquine and doxycycline. A series of new 6-ureido-4-anilinoquinazolines (91-94) were evaluated for their potent activity as antimalarial agents[83] (see Scheme 66).



(91-94)

91 R_1 = H, R_2 = Cl, R_3 = H, R_4 = F;

92 R_1 = Cl, R_2 = CH_3, R_3 = H, R_4 = F;

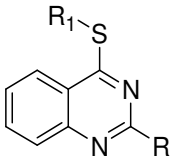
93 R_1 = CF_3, R_2 = Cl, R_3 = H, R_4 = CF_3

94 R_1 = CF_3, R_2 = Cl, R_3= OCH_3, R_4 = OCH_3

Scheme 66

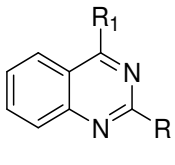
A series of 4-thiophenoxy-2-trichloromethyquinazolines derivatives (95a-b) were evaluated for their antiplasmodial activity against the human malarial parasite Plasmodium falciparum was determined[84]. Compounds 95a and 95b showed good activity against K1 Plasmodium falciparum (IC_{50} = 1.9 μM and 0.9 μM, resp.), whereas IC_{50} value of chloroquine is 0.5 μM. A series of (96a-d) in 4-aryl- 2-trichloromethylquinazolines (96a-d) were evaluated for their antiplasmodial activity[85]

(see Scheme 67). Compounds with the above substituents exhibited favourableantiplasmodial activity on THP1 and HepG2 human cell lines.



(95a-b)

	R	R_1
95a	CCl_3	S-C_6H_5
95b	CCl_3	S-C_6H_5-4-Cl



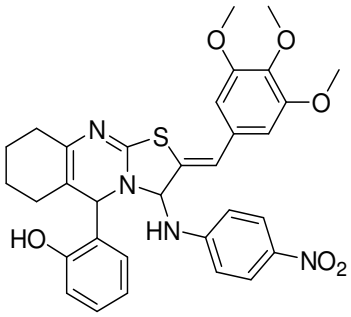
96a-d

	R	R_1
96a	CCl_3	4-F-C_6H_4
96b	CCl_3	4-Cl-C_6H_4
96c	CCl_3	4-OMe-C_6H_4
96d	CCl_3	2-Naphthyl

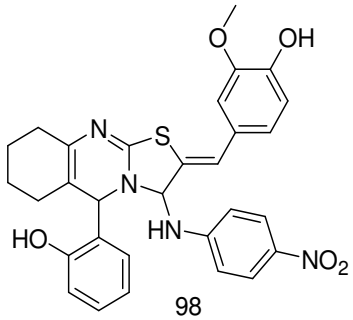
Scheme 67

4.7.11 Quinazolinones as Antioxidant Activity

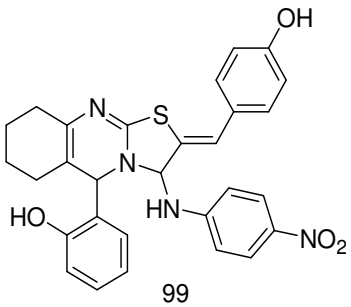
A series of novel thiazoloquinazoline derivatives by condensation of different aromatic aldehydes with 4-nitro aniline are screened for antioxidant activity by DPPH radical assay, nitric oxide scavenging activity, and hydrogen peroxide scavenging activity and reported that synthesized compounds (97-99) were found to be the most potent antioxidant activity[86] (see Scheme 68).



97



98



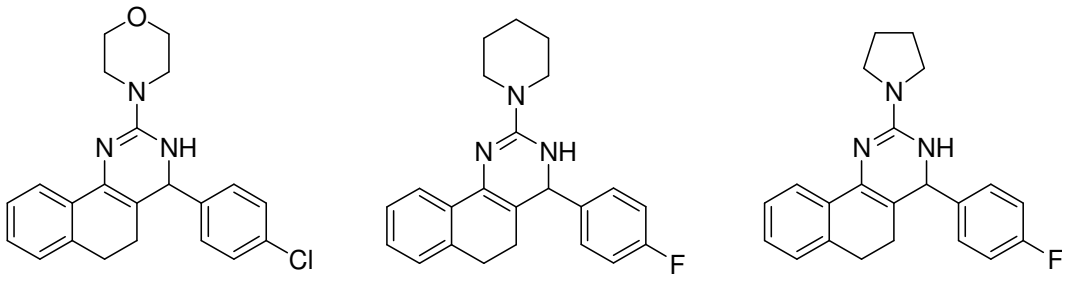
99

Scheme 68

4.7.12 Antileishmanial Agents

Compounds of both synthetic and natural origin comprising a diverse group of chemical structure have been reported as antileishmial agents. These include mostly nitrogen heterocyclic such as quinolines, purine, pyrimidine, acidine, phenothiazines, bisbenzamides, pyrazolol, pyridine, benzothiazole and imidazolines[87]. The 4-(substituted-benzylidine)-2-substituted-5,6-dihydrobenzo[h]quinazoline and 4-(substituted

benzylidine)-2-substituted-3,4,5,6-tetrahydrobenzo[h]quinazoline from 2-(substituted-benzylidine)tetralone and several substituted guanidine sulfates are evaluated for their in vitro antileishmanial activity and they reported that compounds (100-102) show promising antileishmanial activity against Leishmania donovani[88] (see Scheme 69).

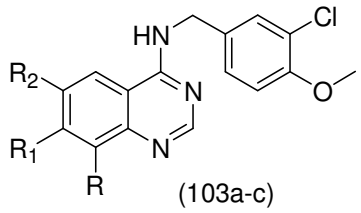


100 101 102

Scheme 69

4.7.13 Quinazoline as Neuroprotective Agents

Few quinazoline derivatives (103a-c) were evaluated for their activity as potent and highly selective PDE5 inhibitors to be employed for male erectile dysfunction[89] (see Scheme 70).

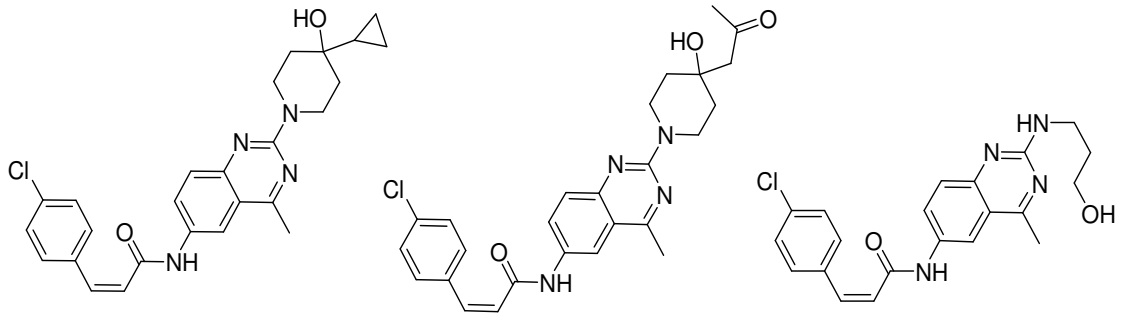


	R	R_1	R_2
103a	C_3H_7	OCH_3	$NHCOCF_3$
103b	CH_2CH_2OH	OCH_3	$NHCOCH_3$
103c	CH_2CH_2OH	OCH_3	$NHCOC_2H_5$

Scheme 70

4.7.14 Quinazoline as Antiobesity Agents

A series of quinazoline derivatives (104-106) are to be considered as an antagonist for melanin concentrating hormone receptor 1 (MCHR1)[90] (see Scheme 71).



104 105 106

Scheme 71

4.7.15 Antihypertensive Agents

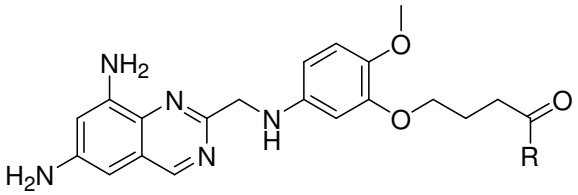
A series of 3-benzyl-2-substituted-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-ones have been synthesized by the cyclocondensation of 3-amino-2- benzylamino-3H-quinazolin-4-one. The compounds were evaluated for their *in vivo* antihypertensive activity. All the test compounds exhibited significant antihypertensive activity; 3-benzyl-2-methyl-3H-[1,2,4]triazolo[5,1-b]quinazolin-9-one exhibited antihypertensive activity more than the reference drug prazocine[91].

4.7.16 Anti-H1-Antihistaminic Agents

A series of 1-substituted-4-benzyl-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-ones were synthesized by the cyclization of 2-hydrazino-3-benzyl-3H-quinazolin-4-one. When tested for their *in vivo* H_1-antihistaminic activity on guinea pigs, all the test compounds protected the animals from histamine induced bronchospasm significantly[92].

4.7.17 Quinazoline as Antiprotozoan Agents

A series of quinazoline derivatives (107a-b) were evaluated for their activity as a potent inhibitor of trypanosomacruzi dihydrofolate reductase[93] (see Scheme 72).



107a R = OEt;
107b = OMe

Scheme 72

Heterocyclic compound containing quinazoline and quinazolinone nucleus plays most important role in the field of medicinal chemistry. It shows wide range of activities for medication purpose. A large number of quinazoline compounds have been synthesized and evaluated for their different biological activities. Some marketed quinazoline and quinazolinone nucleus containing drugs have different types of pharmacological activities. The quinazoline and quinazolinone based pharmaceuticals are becoming very important class of therapeutic agents and are likely to replace many obtainable organic based pharmaceuticals in the very near future. The quinazoline and quinazolinone based pharmaceuticals will be created on a large scale by different research development processes and will become available commercially for therapeutic uses. The biological profiles of this new generation of quinazoline and quinazolinone represent much progress with regard to the older compounds. This study gets an efficient way of understanding about the target pharmacophore relationship which can further aid the process of drug design developments. This study may also accelerate the designing processes to generate a larger number of therapeutically active molecules. The molecular treatment of potentially lead molecules is still a major line of approaches for the discovery and development of new drug molecules[94-99]. Combination of two or more moieties into one is a general procedure of handling and this can probably result in the raise of biological activities and deduction of untoward side effects.

4.8 Current work

The original Biginelli protocol for the preparation of the DHMPs consisted of heating a mixture of the three components (aldehyde, β-keto ester and urea) in ethanol containing a

catalytic amount of hydrochloric acid. This procedure leads in one step-one pot to the desired DHPMs. The major drawback associated with this protocol is the low yields, particularly for substituted aromatic and aliphatic aldehydes[100].

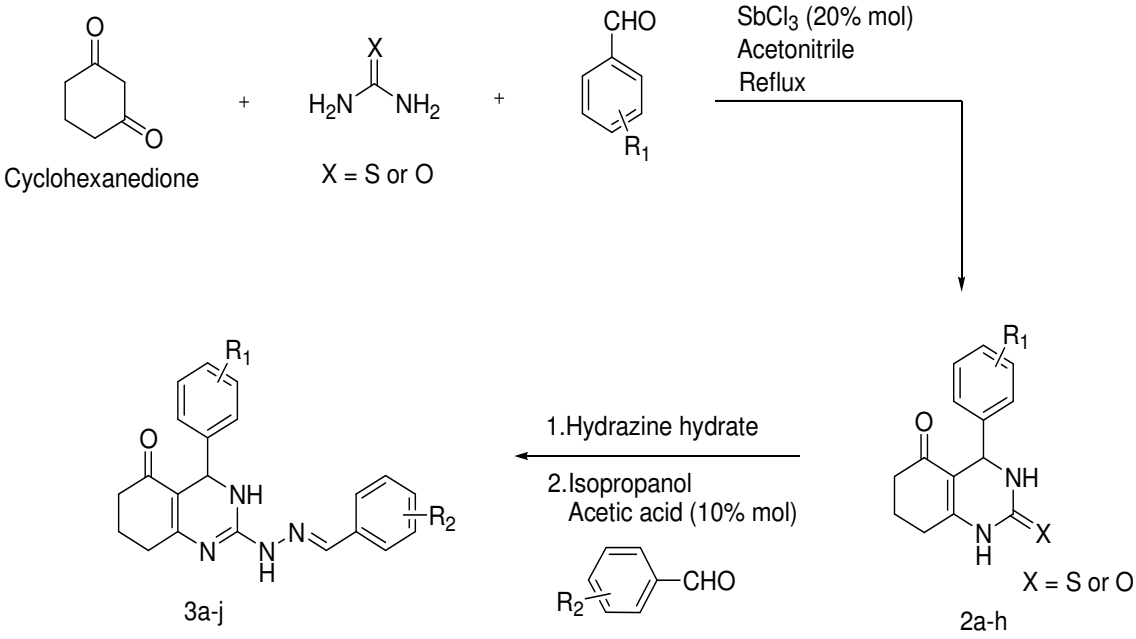
The synthesis of 2-thioxo-quinazolines **(2a-h)** by using Biginelli reaction and antimony(III)chloride ($SbCl_3$)[101] as catalyst provides better results with more sterically hindered substrates with good yield. $SbCl_3$ is inexpensive, easy to handle on large scale. Antimony(III)chloride ($SbCl_3$) catalyst was significantly more effective than other acid catalyst in the Biginelli reaction of cyclic β-diketones and it provides better results with more sterically hindered substrates with good yields. Reaction scheme is reported in **section 4.9**.

Synthesized compounds were evaluated against bacterial and fungal pathogenic strains and results are summarized in **section 4.14.1** as a MIC value.

4.9 Reaction Scheme

The key intermediates for the synthesis of 2-(aryl-methylenehydrazone)-quinazolin-5-one **(3a-j)** are shown in the scheme as mentioned below. Hexahydro-1H-quinazolin-5-ones **(2a-h)** were prepared by Biginelli reaction of 1,3-cyclohexandione, urea/thiourea and aldehydes in acetonitrile in the presence of antimony(III)chloride as acid catalyst. Antimony(III)chloride gave us excellent yield compare to other acid catalysts such as concentrated hydrochloric acid, sulfuric acid and TMSCl. The best results were obtained with a 0.2:1:1:1.5 ratio of antimony(III)chloride, aldehydes, cyclic ketone and urea/thiourea for the synthesis of compounds **(2a-h)**. Compounds **(2a-h)** on reflux with hydrazine hydrate for 10 hours formed the hydrazides which were reacted *insitu* with the substituted aldehydes in isopropanol and acetic acid as catalyst yielded the desired 2-(aryl-methylenehydrazone)-quinazolin-5-one **(3a-j)**. The reaction scheme is as below.

Scheme. Synthesis of hexahydro-1H-quinazolin-5-ones (2a-h) and 2-(aryl-methylenehydrazone)-quinazolin-5-one (3a-j)



4.10 Experimental

General Procedures. All the reagents were obtained commercially and used with further purification. All melting points were taken in open capillaries and are uncorrected. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was run using TLC aluminum sheets silica gel $60F_{254}$(Merck). Elemental analysis (% C, H, N) was carried out by EURO EA 3000 CHN elemental analyzer. IR spectra were recorded on a shimadzu FTIR 8401 spectrophotometer in KBR. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using solvent peak as internal standard. Mass spectra were scanned on a shimadzu LCMS 2010 spectrometer.

4.11 Physical data

Table-I. Analytical IR spectral data of hexahydro-1H-quinazolin-5-ones (2a-h) and 2-(aryl-methylenehydrazone)-quinazolin-5-one (3a-j)

Sr. no.	R_1	R_2	m.p. (°C)	Yield (%)
2a	4-Cl	-	256-257	92
2b	4-F	-	276-278	90

2c	2-Cl	-	239-241	94
2d	H	-	220-223	92
2e	4-CF_3	-	152-153	84
2f	2-CF_3	-	145-146	83
2g	4-Br	-	198-199	85
2h	2-Br	-	193-194	86
3a	4-Cl	4-Cl	170-173	90
3b	4-Cl	2-Cl	177-179	92
3c	2-Cl	4-Cl	189-191	89
3d	2-Cl	2-Cl	197-199	93
3e	4-F	4-Cl	161-162	87
3f	4-F	2-Cl	155-156	85
3g	4-Br	4-Cl	210-211	88
3h	4-Br	2-Cl	201-202	91
3i	2-Cl	2-OH 4-Boc piperazine	183-184	85
3j	4-Cl	2-OH 4-Boc piperazine	179-180	86

*All compounds gave analysis for C, H and N in the range of ±0.4.

4.12 Spectral discussion

Compound **2a** show intense peaks at 3311 cm^{-1} in IR spectra for (NH), 1705 cm^{-1} for carbonyl (C=O) and 1177 for thioxo (C=S) streatching. In the mass spectra molecular ion peak is in agreement with the molecular weight of the compound. Elemental analysis data have been found to be in conformity with the assigned structure. ^{1}H NMR spectrum of **2a** showed a double doublet at δ 7.2 and 7.35 ppm for aromatic (4H) protons and two broad singlet at δ 8.90 and 10.0 ppm for two NHs. Furthermore, the ^{13}C NMR of compound **2a** showed the signal at δ 173.9 ppm which is corresponding to C-2 (C=S group).

The IR spectra of compound **3a** show intense peak at around 3345 cm^{-1} for (NHs), 1689 cm^{-1} for (C=O). ^{1}H NMR spectra of **3a** showed double doublets at δ 7.3, 7.36, 7.42 and 7.8 ppm for two pera substituted aromatic (8H) protons and two broad singlet at δ 8.05 and 10.1 ppm indicating the presence of two NH protons, in addition to the signals corresponding to six methylene protons at δ 1.7-2.5 ppm. Singlet at around δ 8.12 ppm indicates for azomethine proton, and at around δ 5.3 ppm indicates for C-5 proton. Data from the elemental analysis and mass spectrum is also in agreement with the assigned

structure. The ^{13}C NMR of compound **3a** revealed that the signal corresponding to the thione was absent and a resonance of –N=**C**-N- carbon atom (C-2) at δ 152.34 ppm was indicated to the chemical shift of the corresponding carbon atom. The signal at δ 192.63 corresponding to the (C=O) and at δ 147 ppm corresponds to azomethine carbon. The signal at δ 49.23 ppm indicates for C-5 carbon.

4.12.1 Mass spectral study

Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. The molecular ion peak was found in agreement with molecular weight of the respective compound. Characteristic M^{+2} ion peaks with one-third intensity of molecular ion peak were observed in case of compounds having chlorine atom. The compounds having chlorine atom showed this characteristic peak. Fragmentation pattern can be observed to be particular for this kind of compounds and the characteristic peaks obtained for each compound. Various characteristic peaks obtained for each compound in this series.

4.12.2 IR spectral study

Various functional groups present in molecule were identified by characteristic frequency obtained for them. Presence of carbonyl group can be confirmed by IR spectra because carbonyl stretching frequency was observed for carbonyl group present in the moiety. C=O group (N-CO-) and C=O groups of ester were observed between 1650-1750 cm^{-1}. Peaks were identified for aromatic and alkyl group as per their characteristics. In case of compounds having different substations on aromatic ring, characteristic frequencies were observed depending on the functional group present i.e. hydroxyl, chloro, fluoro etc.

4.12.3 ^{1}H NMR spectral study

Numbers of proton identified from NMR spectrum and their chemical shift (ppm) were in agreement of structure of molecule. ^{1}H NMR spectrum of **2a** showed a double doublet at

δ 7.2 and 7.35 ppm for aromatic (4H) protons and two broad singlet at δ 8.90 and 10.0 ppm for two NHs. Furthermore, the ^{13}C NMR of compound **2a** showed the signal at δ 173.9 ppm which is corresponding to C-2 (C=S group). Singlet at around δ 8.12 ppm indicates for azomethine proton, and at around δ 5.3 ppm indicates for C-5 proton. The ^{13}C NMR of compound **3a** revealed that the signal corresponding to the thione was absent and a resonance of –N=**C**-N- carbon atom (C-2) at δ 152.34 ppm was indicated to the chemical shift of the corresponding carbon atom. The signal at δ 192.63 corresponding to the (C=O) and at δ 147 ppm corresponds to azomethine carbon. The signal at δ 49.23 ppm indicates for C-5 carbon.

4.12.4 Elemental analysis

Elemental analysis showed calculated and found percentage values of carbon, hydrogen and nitrogen in support of structure of synthesized compounds. The spectral and elemental analysis data are given below for individual compounds.

4.12.5 Spectral data of synthesized compounds (2a-h and 3 a-j)

General procedure for preparation of 2-thioxo-quinazolines (2a-h): To a mixture of 1,3-cyclohexanedione (1mmol), thiourea (1.5 mmol), substituted aldehydes (1mmol) and antimony(III)chloride (20 mol %), acetonitrile (5ml) was added and content was refluxed for 8 hours. After completion of the reaction as monitored by TLC, the reaction mixture is poured into ice-cold water and stirred for 10-15 minutes. The content of the flask were then filtered and washed with cold water (20 ml) to remove excess thiourea. The solid so obtained was the corresponding 2-thioxo-quinazolines (**2a-h).** It was then recrystallized by hot methanol to get the pure product.

4-(4-Chloro-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2a): White solid, (yield 92%), m.p. 256-257°C, Anal.Calcd for $C_{14}H_{13}ClN_2OS$: C 57.43, H 4.48, N 9.57% Found: C 57.41, H 4.45, N 9.51%. IR (KBr, cm^{-1}): 3311 (br, NH's), 3040, 3010 (ArC-H), 2960 (alkyl C-H), 1614 (C=C), 1705 (C=O), 1177 (C=S), 735 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72-1.8 (m, 2H, CH_2), 1.95-2.0 (m, 2H, CH_2), 2.18-2.28 (m, 2H, CH_2), 5.42 (bs, 1H, CH), 7.2 (dd, 2H, Ar-H), 7.35 (dd, 2H, Ar-H), 8.90 (bs, 1H, NH), 10.0 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-*d_6*) δ: 20.45 (CH_2), 26.2 (CH_2), 38.8 (CH_2), 49.22 (CH), 111.7, 126.3, 127.2, 128.3, 128.8, 133.5, 142.1, 155.2 (Ar-C), 173.9 (C=S), 194.8 (C=O), MS: (M+1) 293.04.

4-(4-Fluoro-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2b): Cream solid, (yield 90%), m.p. 276-278°C, Anal.Calcd for $C_{14}H_{13}FN_2OS$: C 60.85, H 4.74, N 10.14% Found: C 60.78, H 4.70, N 10.09%. IR (KBr, cm^{-1}): 3305 (br, NH's), 3040, 3010 (ArC-H), 2960 (alkyl C-H), 1617 (C=C), 1686 (C=O), 1174 (C=S), ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73-1.81 (m, 2H, CH_2), 1.93-1.98 (m, 2H, CH_2), 2.13-2.23 (m, 2H, CH_2), 5.46 (bs, 1H, CH), 7.19 (dd, 2H, Ar-H), 7.31 (dd, 2H, Ar-H), 8.85 (bs, 1H, NH), 9.89 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-*d_6*) δ: 20.45 (CH_2), 26.2 (CH_2), 38.18 (CH_2), 49.4 (CH), 111.7, 126.3, 127.2, 128.3, 128.8, 133.5, 142.1, 155.2 (Ar-C), 173.7 (C=S), 192.8 (C=O), MS: (M+1) 277.2

4-(2-Chloro-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2c): Off-white solid, (yield 94%), m.p. 239-241°C, Anal.Calcd for $C_{14}H_{13}ClN_2OS$: C 57.43, H 4.48, N 9.57% Found: C 57.49, H 4.45, N 9.51%. IR (KBr, cm^{-1}): 3310, 3229 (br, NH's), 3040, 3010 (ArC-H), 2960 (aliphatic C-H), 1614 (C=C), 1698 (C=O), 1179 (C=S), 735 (C-Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.72-1.8 (m, 2H, CH_2), 1.95-2.0 (m, 2H, CH_2), 2.2-2.3 (m, 2H, CH_2), 5.32 (bs, 1H, CH), 7.10-7.39 (m, 4H, Ar-H), 7.90 (bs, 1H, NH), 9.89 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-*d_6*) δ: 20.45 (CH_2), 26.2 (CH_2), 38.8 (CH_2), 49.4 (CH), 111.7, 126.3, 127.2, 128.3, 128.8, 133.5, 142.1, 155.2 (Ar-C), 173.8 (C=S), 192.8 (C=O), MS: (M+1) 293.04.

4-Phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2d): Light yellow solid, (yield 92%), m.p. 220-223 °C, Anal.Calcd for $C_{14}H_{14}N_2OS$: C 65.09, H 5.46, N 10.84% Found: C 65.11, H 5.55, N 10.89%. IR (KBr, cm^{-1}): 3300 (br, NH's), 3010, 3024 (ArC-H), 2960 (aliphatic C-H), 1692 (C=O), 1611 (C=C), 1185 (C=S). ^{1}H NMR (400

MHz, DMSO-d_6): δ 1.83-1.9 (m, 2H, CH_2), 2.1-2.2 (m, 2H, CH_2), 2.4-2.5 (m, 2H, CH_2), 5.34 (bs, 1H, CH), 7.10-7.39 (m, 5H, Ar-H), 7.80 (bs, 1H, NH), 9.69 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 19.3 (CH_2), 27.6 (CH_2), 29.8 (CH_2), 53.4 (CH), 111.9, 126.7, 127.1, 128.3, 143.4, 156.2 (Ar-C), 174.4 (C=S), 193.9 (C=O), MS: (M+1) 259.09.

2-Thioxo-4-(4-trifluoromethyl-phenyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2e): Brown solid, (yield 84%), m.p. 152-153, Anal.Calcd for $C_{15}H_{13}F_3N_2OS$: C 55.21, H 4.02, N 8.58% Found: C 55.18, H 4.06, N 8.63%. IR (KBr, cm^{-1}): 3290 (broad, NH's), 1697 (C=O), 1189 (C=S).

2-Thioxo-4-(2-trifluoromethyl-phenyl)-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2f): Light brown solid, (yield 83%), m.p. 145-146, Anal.Calcd for $C_{15}H_{13}F_3N_2OS$: C 55.21, H 4.02, N 8.58% Found: C 55.26, H 3.98, N 8.55%. IR (KBr, cm^{-1}): 3312 (broad, NH's), 1705 (C=O), 1181 (C=S).

4-(4-Bromo-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2g): Off-white solid, (yield 85%), m.p. 198-199, Anal.Calcd for $C_{14}H_{13}BrN_2OS$: C 49.86, H 3.89, N 8.31% Found: C 49.89, H 3.85, N 8.26%. IR (KBr, cm^{-1}): 3322 (broad, NH's), 1710 (C=O), 1172 (C=S).

4-(2-Bromo-phenyl)-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (2h): Off-white solid, (yield 86%), m.p.193-194, Anal.Calcd for $C_{14}H_{13}BrN_2OS$: C 49.86, H 3.89, N 8.31% Found: C 49.91, H 3.92, N 8.35%. IR (KBr, cm^{-1}): 3320 (broad, NH's), 1708 (C=O), 1176 (C=S).

General procedure for preparation of 2-(aryl-methylenehydrazone)-quinazolin-5-one (3a-j): To a corresponding compound (**2a-h)** (1 mmol), hydrazine hydrate (1.1 mmol) was added; content was refluxed for 10 hours. After completion of the reaction as monitored by TLC, isopropanol (5ml) was added followed by corresponding aldehydes (1 mmol) and acetic acid (10 mol %), content was refluxed for 12-18 hours. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and washed with isopropanol (5 ml). The solid so obtained was the corresponding (**3a-j**). It was then recrystallized by hot isopropanol to get the pure product.

2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(4-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3a): Yellow solid, (Yield 90%), m.p. 170-173°C, Anal.Calcd for

$C_{21}H_{18}Cl_2N_4O$: C 61.03, H 4.39, N 13.56% Found: C 61.01, H 4. 34, N 13.50%. IR (KBr, cm^{-1}): 3445, (NH), 2965 (ArC-H), 1689 (C=O), 1602 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.7-1.9 (m, 2H, CH_2), 2.2-2.3 (m, 2H, CH_2), 2.4-2.5 (m, 2H, CH_2), 5.3 (d, 1H, CH), 7.3 (dd, 2H, Ar-H), 7.36 (dd, 2H, Ar-H), 7.42 (dd, 2H, Ar-H), 7.8 (dd, 2H, Ar-H), 8.05 (bs, 1H, NH), 8.12 (s, 1H, azomethine proton), 10.1 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.59 (CH_2), 26.19 (CH_2), 36.18 (CH_2), 49.23 (CH), 108.76, 128.0, 128.18, 128.37, 128.54, 131.4, 133.1, 134.7, 144.0, 152.3 (Ar-C), 147.0 (azomethine carbone) 192.63 (C=O), MS: (M+Na) 435.1.

2-[N'-(2-Chloro-benzylidene)-hydrazino]-4-(4-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3b): Light yellow solid, (Yield 92%), m.p. 177-179°C, Anal.Calcd for $C_{21}H_{18}Cl_2N_4O$: C 61.03, H 4.39, N 13.56% Found: C 61.07, H 4. 44, N 13.60%. IR (KBr, cm^{-1}): 3334, (br, NH's), 2965 (ArC-H), 1692 (C=O), 1607 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.7-1.87 (m, 2H, CH_2), 2.18-2.28 (m, 2H, CH_2), 2.3-2.4 (m, 2H, CH_2), 5.31 (d, 1H, CH), 7.1 (dd, 2H, Ar-H), 7.15 (dd, 2H, Ar-H), 7.3-7.5 (m, 4H, Ar-H), 7.95 (bs, 1H, NH), 8.07 (s, 1H, azomethine proton), 10.0 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.57 (CH_2), 26.09 (CH_2), 36.08 (CH_2), 49.3 (CH), 108.2, 128.3, 128.1, 128.39, 128.54, 131.46, 133.15, 134.75, 144.4, 147.2, 152.31 (Ar-C), 192.9 (C=O), MS: (M+Na) 435.1.

2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(2-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3c): Light brown solid, (yield 89%), m.p. 189-191°C, Anal.Calcd for $C_{21}H_{18}Cl_2N_4O$: C 61.03, H 4.39, N 13.56% Found: C 60.98, H 4.33, N 13.55%. IR (KBr, cm^{-1}): 3405 (NH), 2965,2933 (ArC-H), 1652(C=O), 1603 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.67-1.77 (m, 2H, CH_2), 2.11-2.22 (m, 2H, CH_2), 2.25-2.37 (m, 2H, CH_2), 5.3 (d, 1H, CH), 7.05-7.22 (m, 4H, Ar-H), 7.4 (dd, 2H, Ar-H), 7.5 (m, 2H, Ar-H), 7.99 (bs, 1H, NH), 8.13 (s, 1H, azomethine proton), 10.07 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.50 (CH_2), 26.11 (CH_2), 36.17 (CH_2), 49.0 (CH), 108.7, 128.0, 128.1, 128.33, 128.59, 131.8, 133.0, 134.99, 144.07, 147.99, 152.13 (Ar-C), 192.66 (C=O), MS: (M+Na) 435.1.

2-[N'-(2-Chloro-benzylidene)-hydrazino]-4-(2-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3d): Brown solid, (yield 93%), m.p. 197-199°C, Anal.Calcd for $C_{21}H_{18}Cl_2N_4O$: C 61.03, H 4.39, N 13.56% Found: C 60.98, H 4.33, N 13.55%. IR (KBr,

cm^{-1}): 3340, (br, NH's), 2987 (ArC-H), 1698 (C=O), 1601 (C=C). ^1H NMR (400 MHz, DMSO-d_6): δ 1.76-1.84 (m, 2H, CH_2), 2.02-2.14 (m, 2H, CH_2), 2.31-2.39 (m, 2H, CH_2), 5.34 (d, 1H, CH), 7.1-7.24 (m, 4H, Ar-H), 7.4-7.7 (m, 4H, Ar-H), 8.12 (bs, 1H, NH), 8.03 (s, 1H, azomethine proton), 9.98 (bs, 1H, NH), ^{13}C NMR (400 MHz, DMSO-d_6) δ: 20.37 (CH_2), 26.26 (CH_2), 36.27 (CH_2), 49.13 (CH), 108.17, 128.02, 128.21, 128.38, 128.53, 131.44, 133.12, 134.77, 144.02, 147.03, 152.15 (Ar-C), 192.4 (C=O), MS: (M+Na) 435.1.

2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(4-fluoro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3e): Brown solid, (yield 87%), m.p. 161-162°C, Anal.Calcd for $C_{21}H_{18}ClFN_4O$: C 63.56, H 4.57, N 14.12% Found: C 63.58, H 4.53, N 14.16%. IR (KBr, cm^{-1}): 3350, (br, NH's), 1730 (C=O).

2-[N'-(2-Chloro-benzylidene)-hydrazino]-4-(4-fluoro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3f): Brown solid, (yield 85%), m.p. 155-156°C, Anal.Calcd for $C_{21}H_{18}ClFN_4O$: C 63.56, H 4.57, N 14.12% Found: C 63.62, H 4.58, N 14.08%. IR (KBr, cm^{-1}): 3344, (br, NH's), 1722 (C=O).

2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(4-bromo-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3g): Brown solid, (yield 88%), m.p. 210-211°C, Anal.Calcd for $C_{21}H_{18}BrClN_4O$: C 55.10, H 3.96, N 12.24% Found: C 55.14, H 3.98, N 12.28%. IR (KBr, cm^{-1}): 3332, (br, NH's), 1744 (C=O).

2-[N'-(2-Chloro-benzylidene)-hydrazino]-4-(4-bromo-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one (3h): Brown solid, (yield 91%), m.p. 201-202°C, Anal.Calcd for $C_{21}H_{18}BrClN_4O$: C 55.10, H 3.96, N 12.24% Found: C 55.08, H 4.01, N 12.20%. IR (KBr, cm^{-1}): 3348, (br, NH's), 1724 (C=O).

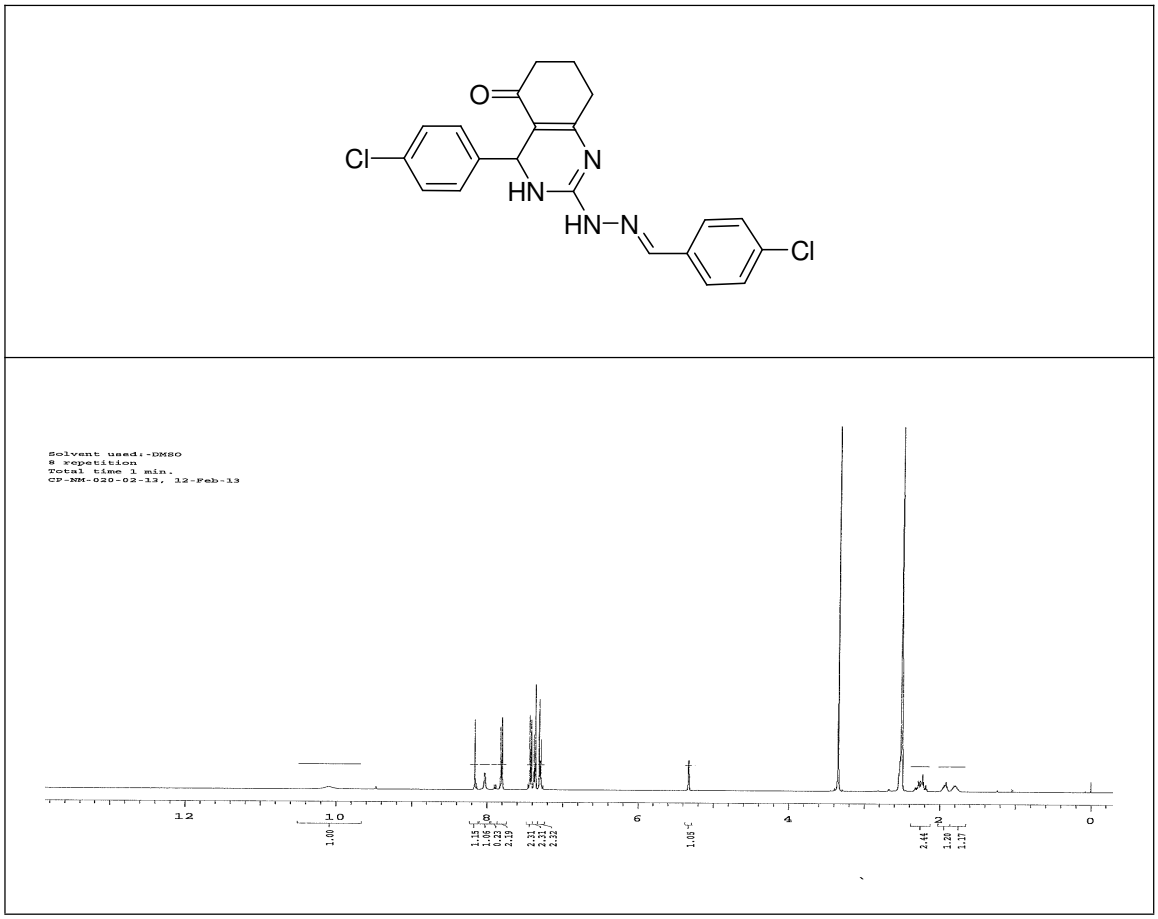
4-(4-{[4-(2-Chloro-phenyl)-5-oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl]-hydrazonomethyl}-3-hydroxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (3i):

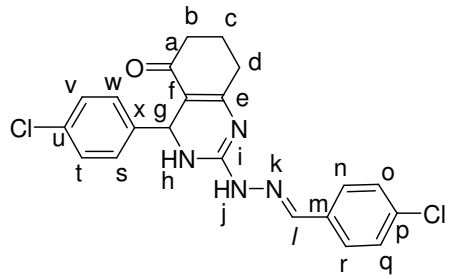
Off-white solid, (yield 85%), m.p. 183-184°C, Anal.Calcd for $C_{30}H_{35}ClN_6O_4$: C 62.22, H 6.09, N 14.51% Found: C 62.20, H 6.05, N 14.55%. IR (KBr, cm^{-1}): 3340, (br, NH's), 1736 & 1710 (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ 1.47-1.49 (s, 9H, $-C(CH_3)_3$), 2.07-2.17 (m, 2H, CH_2), 2.38-2.60 (m, 4H, CH_2), 2.96-3.03 (m, 4H, CH_2), 3.55-3.60 (m, 4H, CH_2), 5.84-5.85 (d, 1H, CH), 6.73-7.43 (m, 7H, Ar-H), 8.19 (s, 1H, azomethine proton), 8.66 (s, 1H, OH).

4-(4-{[4-(4-Chloro-phenyl)-5-oxo-3,4,5,6,7,8-hexahydro-quinazolin-2-yl]-hydrazonomethyl}-3-hydroxy-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (3j):

Off-white solid, (yield 86%), m.p. 179-180°C, Anal.Calcd for $C_{30}H_{35}ClN_6O_4$: C 62.22, H 6.09, N 14.51% Found: C 62.25, H 6.11, N 14.49%. IR (KBr, cm^{-1}): 3354, (br, NH's), 1726 & 1710 (C=O).

4.12.5.1 ^{1}H NMR spectrum of 3a





2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(4-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one

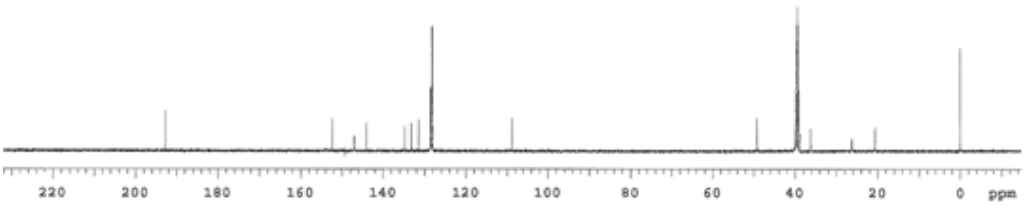
Compound-3a

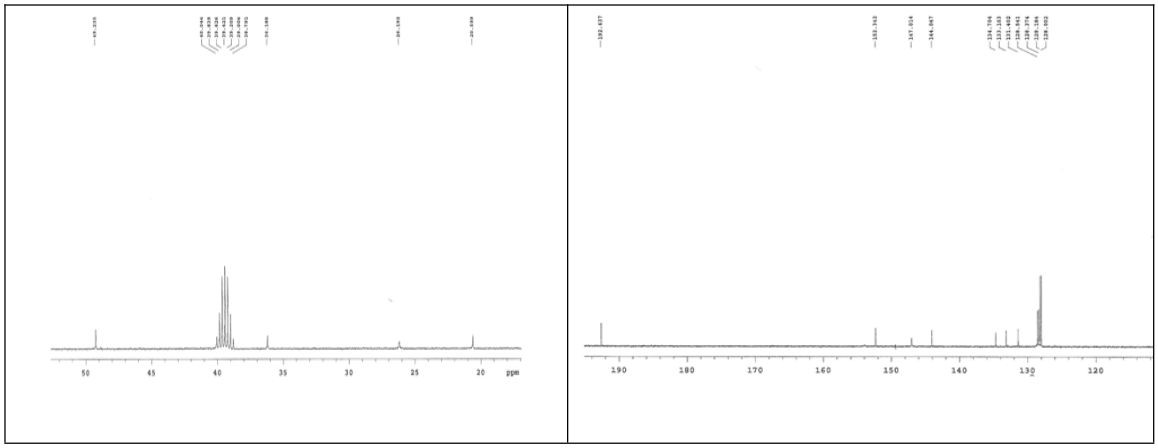
Assignment of ^{1}H NMR:

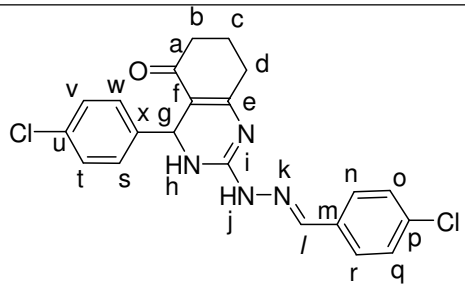
Sr.No.	Signal (δppm)	No. of Protons	Multiplicity	Assignment
1	1.7-1.9	2H	multiplet	c
2	2.2-2.3	2H	multiplet	d
3	2.4-2.5	2H	multiplet	b
4	5.3	1H	singlet	g
5	7.3	2H	double doublet	w,s

6	7.36	2H	double doublet	v,t
7	7.42	2H	double doublet	o,q
8	7.8	2H	double doublet	n,r
9	8.05	1H	broad singlet	j
10	8.12	1H	singlet	*l*

4.12.5.2 Carbon NMR spectrum of 3a







2-[N'-(4-Chloro-benzylidene)-hydrazino]-4-(4-chloro-phenyl)-4,6,7,8-tetrahydro-3H-quinazolin-5-one

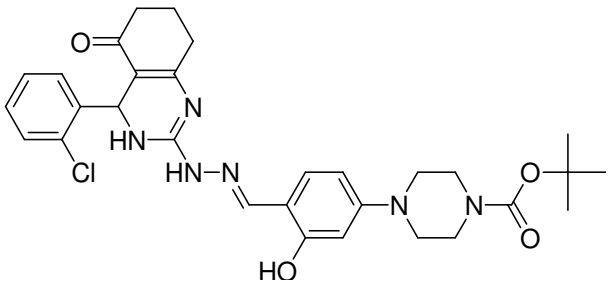
Compound-3a

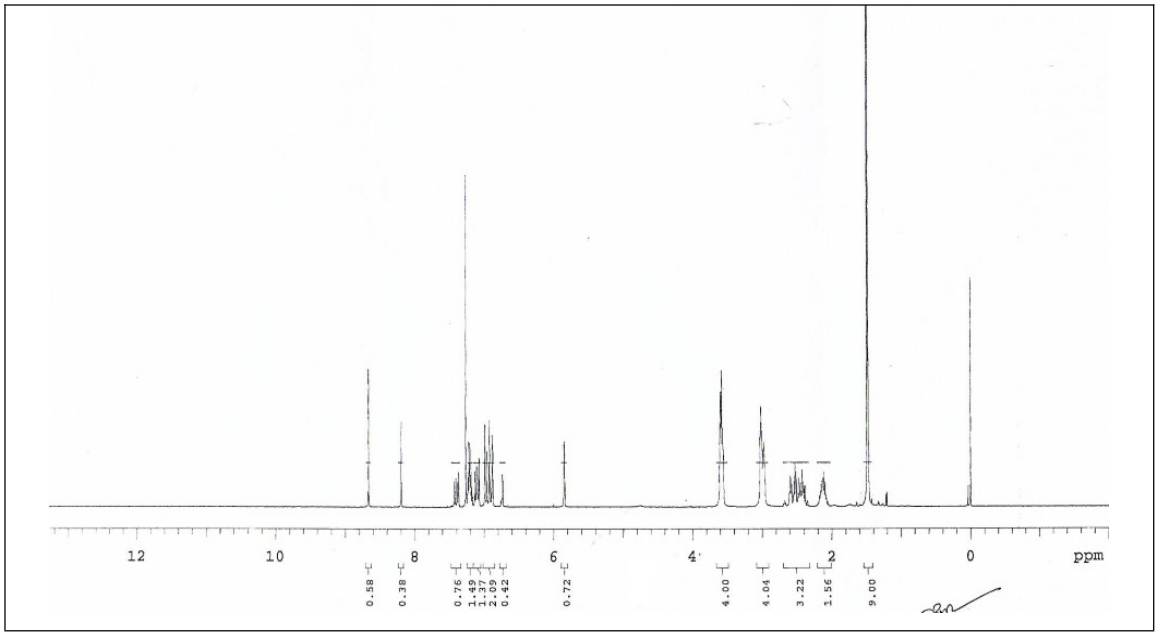
Assignment of ^{13}C NMR:

Sr.No.	Signal (δppm)	Assignment of carbon
1	20.59	c

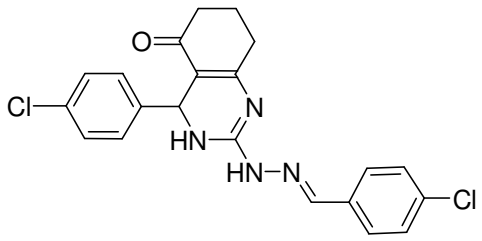
2	26.19	d
3	36.18	b
4	49.23	g
5	108.76	f
6	128.0	w,s
7	128.18	o,q
8	128.37	v,t
9	128.54	n,r
10	131.4	m
11	133.1	u
12	134.7	p
13	144.0	x
14	152.3	e
15	147.0	*l*
16	192.63	a

4.12.5.3 ^{1}H NMR spectrum of 3i



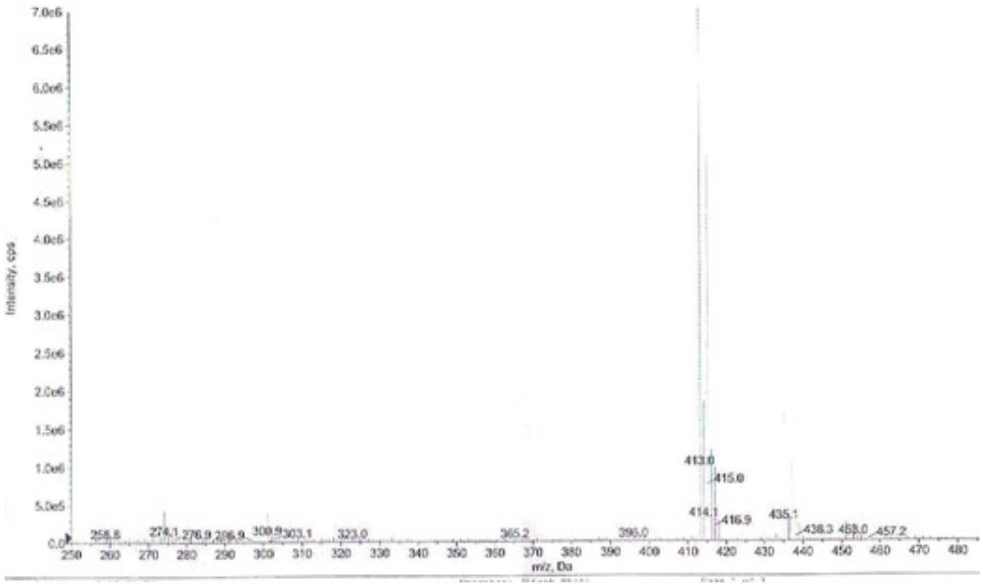


4.12.5.4 Mass spectrum of 3a

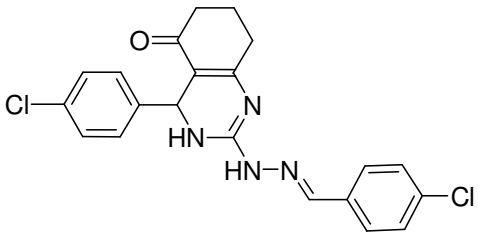


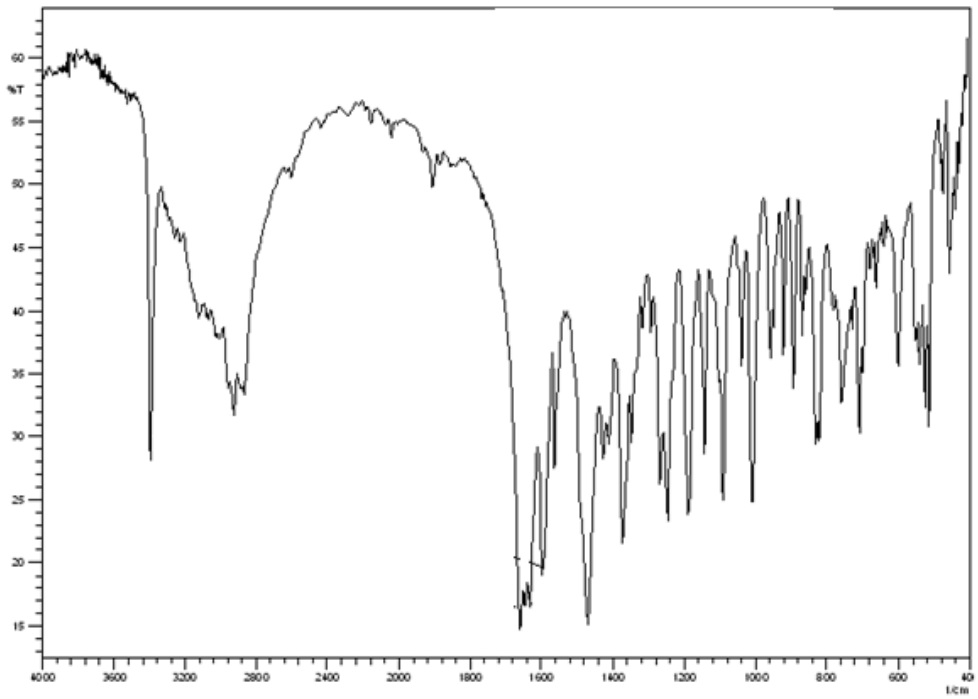
m/e = 412.09

Mass (m/z): 413.0 (M+1)



4.12.5.5 IR spectrum of 3a



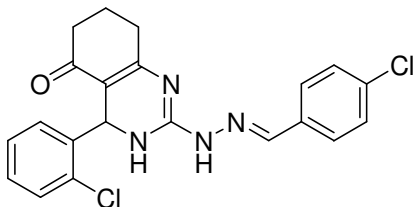


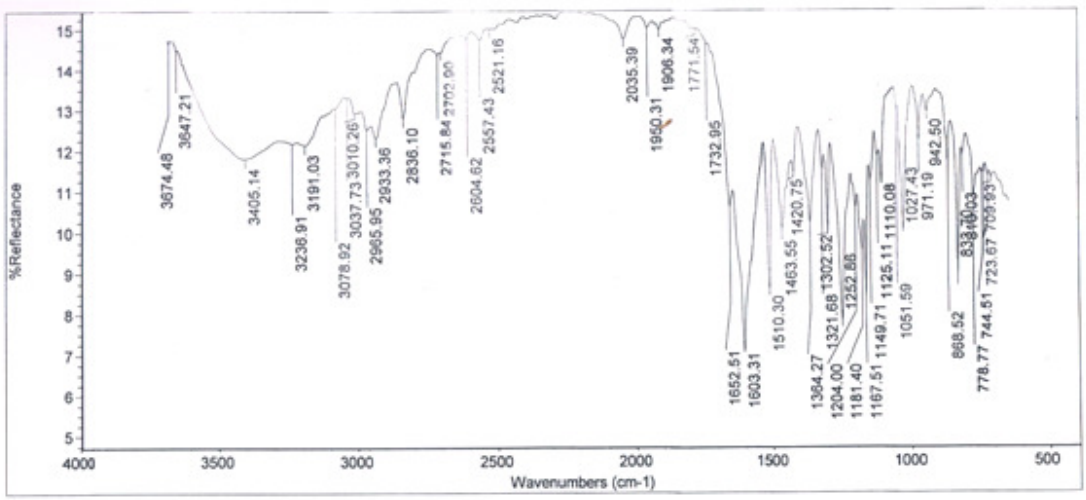
Instrument: SHIMADZU FTIR 8400 spectrophotometer,

Frequence range: 4000-400 cm^{-1} (KBr disc)

IR (KBr, cm^{-1}): 3445, (NH), 2965 (C-H), 1689 (C=O), 1602 (C=C)

4.12.5.6 IR spectrum of 3c





Instrument: SHIMADZU FTIR 8400 spectrophotometer,

Frequence range: 4000-400 cm^{-1} (KBr disc)

IR (KBr, cm^{-1}): 3405 (NH), 2965,2933 (C-H), 1652(C=O), 1603 (C=C)

4.13 Biological activity

Antimicrobial activity of the synthesized compounds:

The *in-vitro* antimicrobial activity of the synthesized compounds against two Gram (+ve) [*Staphylococcus aureus (S. aureus), Staphylococcus pyogenus (S. pyogenus)*] and two Gram (-ve) [*Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa)*] microorganism using broth dilution method.

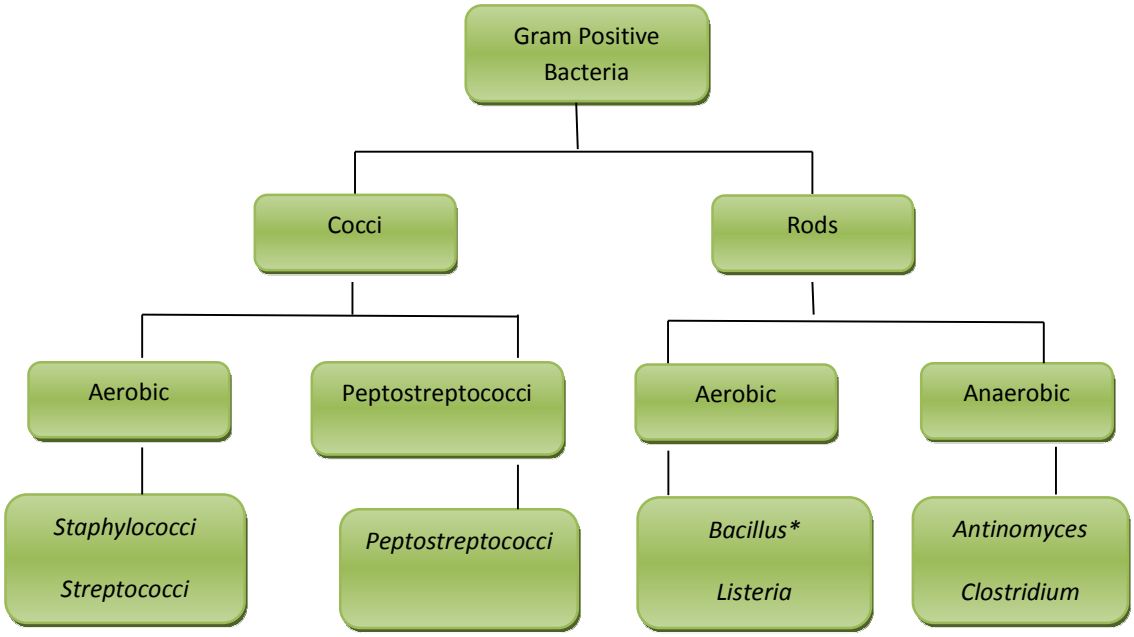
Bacteria were among one of the first life forms appear on the earth. It is present in most habitats on the planet. Bacteria were present in soil, water, deep in earth, live bodies of

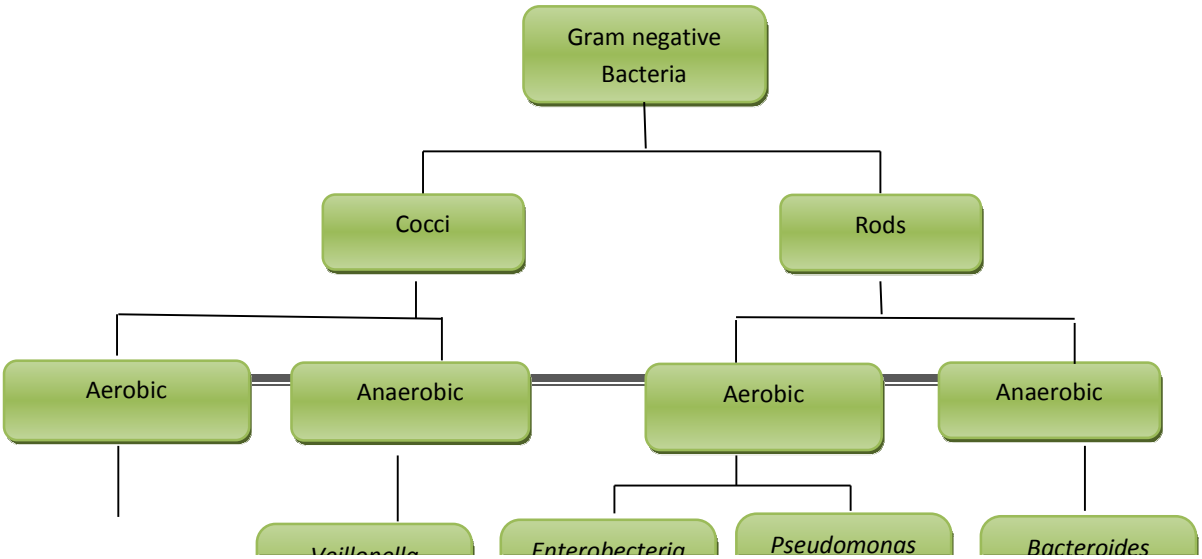
plants and animals etc. MICs are used for the *in vitro* activity of antimicrobials and such an information obtained from the studies have been utilized to measure MIC of the compounds, which give a definitive answer when a borderline result is obtained by other methods of testing or incase of disc diffusion methods are inappropriate.

Classification of bacteria:

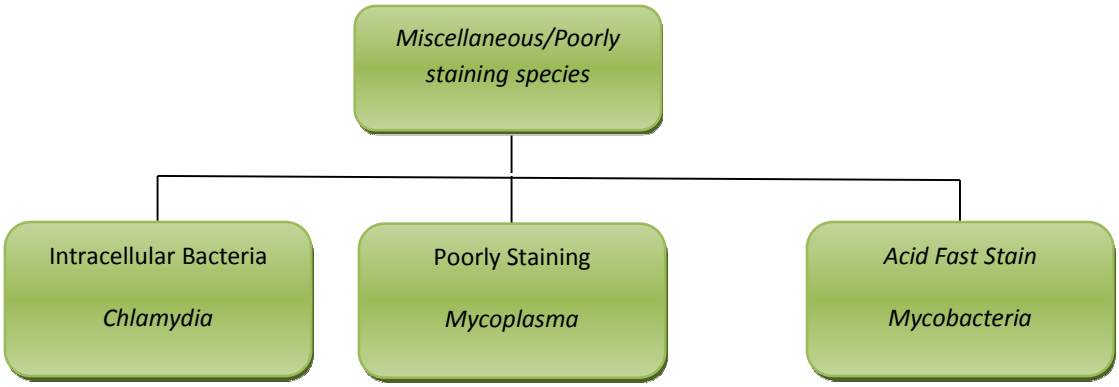
- Bacterial morphology (rod and cocci shape)
- Staining properties of the organism (Gram positive and negative)
- O_2 growth requirement of the species utilized (aerobic and anaerobic)

Based on the staining properties the chart is given below:





Miscellaneous bacteria:



Bacteria used for study of antibacterial activity:

Some of the bacteria which have been used for antibacterial activity along with their shapes, occurance and diseases spread by them are list below:

Bacteria	Shape	Occurrences	Disease
Serratia marcescens	Rod shaped	• Respiratory and urinary tracts of hospitalized	• Pneumonia and other respiratory disease • Urinary tract infections

		adults • Gastrointestional system of child	• Bloodstream infections, including endocarditis • Septicarthritis, osteomyelitis and endocarditis
Escherichia coli	Rod shaped	• Lower intestine of warm-blooded organisms	• Mild to severe and bloody diarrhea, mostly without fever
Pseudomonas aeruginosa	Rod shaped	• Soil • Water • Skin	• Blood stream, urinary track infection • Surgical site infection • Lung infection
Staphylococcus aureus	Round shaped	• Skin • Nose • Respiratory track	• Wound, skin and deep tissue infections • Pneumonia, septicaemia and endocarditis • Staphylococcal scalded skin syndrome (SSSS) • Toxic shock syndrome • Food poisoning
Bacillus subtilis	Rod shaped	• Upper layers of the soil • Human faeces	• Food poisoning • Nausea • Vomiting • Diarrhoea

The synthesized compounds were screened for their antibacterial and antifungal activities using ampicillin, chloramphenicol and griseofulvin as standard drugs.

Experimental:

Equipment and chemicals:

Sterilized pipettes, Erlenmeyer flask, sterilized sugar tubes, control microorganisms, sterilized double distilled water, Nutrient Broth (NB), cotton plug and test tube stand.

Stock solutions: Stock solution were prepared in DMSO

Microorganism cultures:

The microorganisms were grown in nutrient broth dissolved in 50 ml double distilled water followed by incubating them for 24 hours at 35˚C.

Broth dilution method:

Appropriate volume of 2% Nutrient Broth was transferred to the sugar tubes for sterilization purpose using autoclave. Then, the desired concentration of the compound (μM) was achieved in each sugar tubes by adding appropriate volume of the stock solution. Now, each of the microorganism culture (10 μL) was added to each of the previously prepared sugar tubes of the test compounds.

Interpretation:

If the dilution inhibits the growth, a whole experiment was repeated with the next dilution i.e. half the concentration of the test compound than the early one. This procedure was repeated till the faint turbidity by the inoculums itself was observed and the said concentration is termed as Minimum Inhibitory Concentration (MIC).

The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method. Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 CFU [Colony Forming Unit] per milliliter by comparing the turbidity. The strains employed for the activity were procured from [MTCC – Micro Type Culture Collection] Institute of Microbial Technology, Chandigarh.

Results and discussion:

The compounds **(2a-h)** and **(3a-j)** were screened for their antibacterial activity against *Escherichia coli (E.coli), Pseudomonas aeruginosa (P.aeruginosa)*, *Staphylococcus aureus (S.aureus), Streptococcus pyogenes (S.pyogenes)* as well as antifungal activity

against and *Candida albicans (C.albicans)*. DMSO was used as vehicle to get desired concentration of compounds to test upon microbial strains. The lowest concentration, which showed no visible growth after spot subculture was considered as MIC for each compound. The standard antibiotics used for comparison in the present study were Ampicillin for evaluating antibacterial activity as well as Griseofulvin for antifungal activity. The protocols are summarized in 4.13.1.

An examination of the data (summarized in 4.13.1) reveals that amongst all the synthesized compounds **(2a-h)** and **(3a-i),** compounds **3a** and **3c** exhibited excellent activity against Gram positive bacteria *Staphylococcus aureus (S.aureus)*. Compounds **2a** and **3a** exhibited excellent activity against Gram negative bacteria *Escherichia coli (E.coli)* as compared to standard antibiotic Ampicillin.

Antifungal study revealed that compounds **2a**, **2b** and **3a** are more potent as compared to standard fungicidal Griseofulvin against *Candida albicans (C.albicans)*.

4.13.1: Antimicrobial activity of compounds **2a-h** and **3a-j**

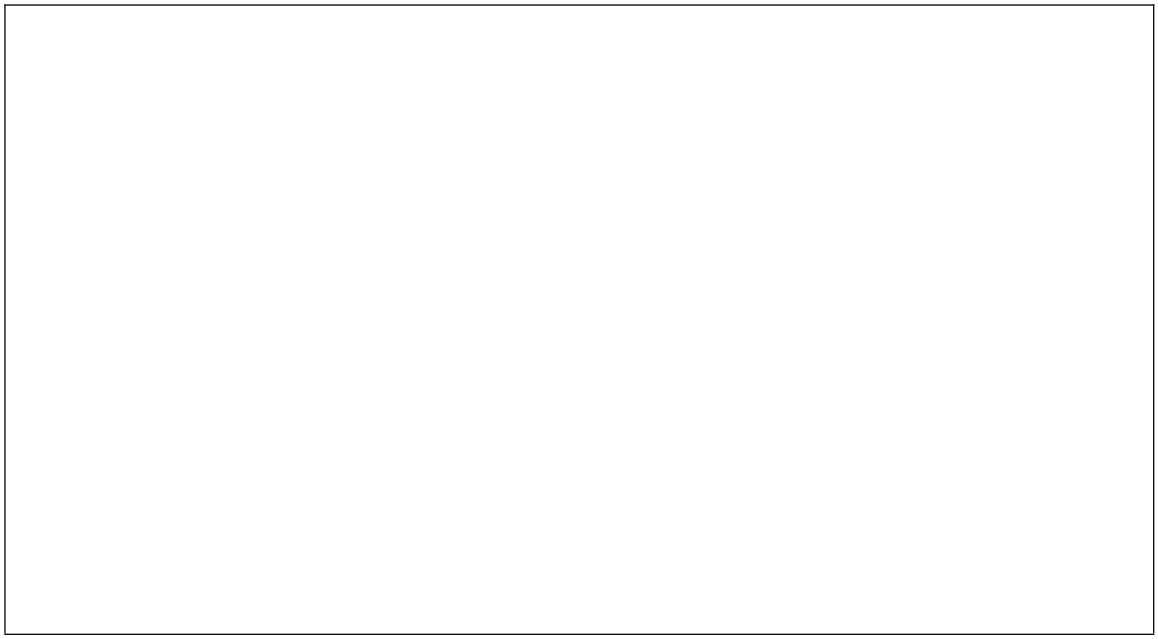
Comp.No.	Minimal inhibitory concentration µg/ml				
	Gram-negative bacteria		Gram-positive bacteria		Fungi
	E.coli	***P.aeruginosa***	***S.aureus***	***S.pyogenus***	***C.albicans***
2a	62.5	250	200	250	**250**
2b	200	100	250	200	**250**
2c	100	100	200	125	500
2d	200	250	250	200	1000
2e	200	200	250	200	>1000

2f	250	200	500	200	1000
2g	100	250	250	100	1000
2h	250	200	500	150	>1000
3a	62.5	250	62.5	100	**250**
3b	200	100	200	200	>1000
3c	100	100	62.5	125	1000
3d	200	250	250	200	1000
3e	150	200	250	125	1000
3f	200	250	250	200	1000
3g	250	200	500	150	>1000
3h	100	100	500	125	1000
3i	200	150	500	150	>1000
3j	250	200	500	125	1000
Ampicillin	100	--	250	100	--
Chloramphenicol	50	50	50	50	--
Griseofulvin	--	--	--	--	500

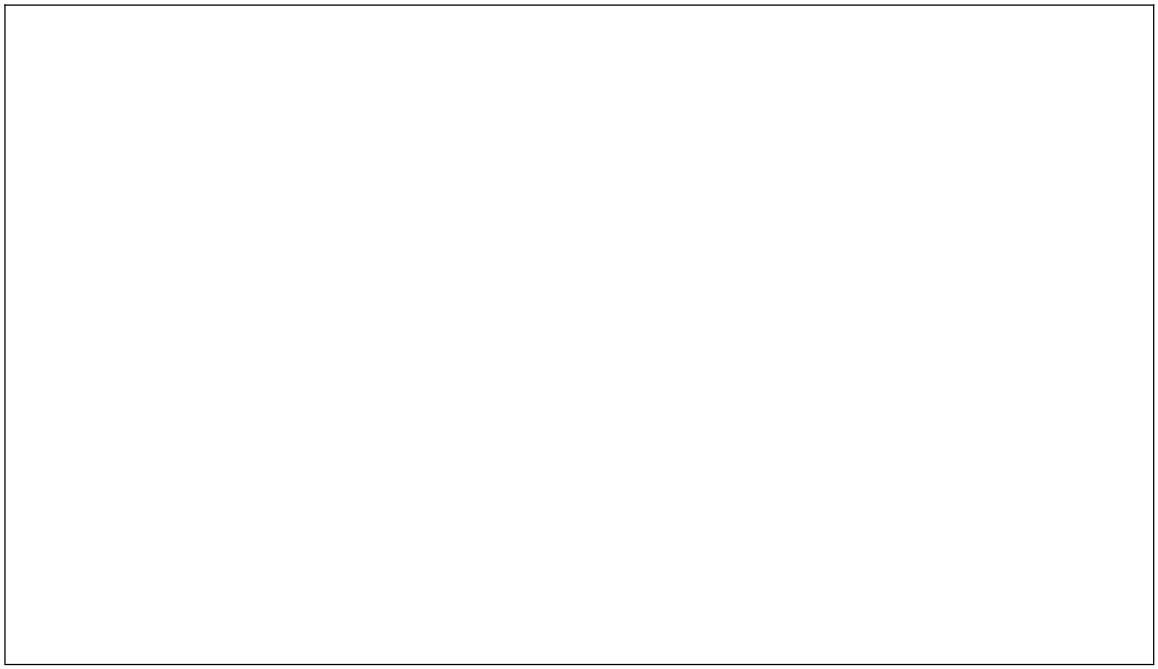
(--) No inhibition zone

For better understanding of comparative biological activity of the synthesized compounds the graphical chart for the compounds (2a-h) and (3a-j) are given below.

Graphical chart of antimicrobial activity of compounds (2a-h):



Graphical chart of antimicrobial activity of compounds (3a-j):



Conclusion

A series of some derivatives **(3a-j)** have been synthesized with high yield via *insitu* approach from compounds **(2a-h)**. Also, compounds **(2a-h)** can be prepared by multicomponent reaction between 1,3-cyclohexanedione, urea/thiourea and aldehydes with high yield using antimony(III)chloride as a catalyst.

It can be concluded from (section 4.13.1) that compound **3a** and **3c** is highly active against Gram positive bacteria *Staphylococcus aureus (S.aureus),* compounds **2a** and **3a** exhibited excellent activity against Gram negative bacteria *Escherichia coli (E.coli)* as compared to standard antibiotic Ampicillin.

Antifungal study revealed that compounds **2a**, **2b** and **3a** are more potent as compared to standard fungicidal Griseofulvin against *Candida albicans (C.albicans)*.

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