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Synthesis of 1 Quinazolin-4-Ones Derivative for Anti-Microbial Activity

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ABSTRACT-

Heterocyclic compounds have been found to occur widely in nature and have proved to be of an immense significance to life. These compounds have attracted the attention of chemists and biologists due to their varied nature of physicochemical and pharmacological properties. A vast number of them are pharmacologically active and are in regular clinical use and proved to be potent drug. Their practical applications range from clinical use to field as diverse as agriculture, photography, biocide formulation and polymer science. The range of known compounds is virtually limitless, encompassing an impressive spectrum of physical, chemical and biological properties.

Structure activity relationship studies of quinazolinone ring system revealed in various literatures suggest position 2, 6 and 8 are very much important for structure activity studies and position 3 should be attached to different heterocyclic rings for better chemotherapeutic activity

The mechanisms of action of specific chemotherapeutic agents are taken up in more detail when individual drugs and groups of drugs are discussed later in this chapter. A few general observations are offered at this point. It is important to know something about the mechanisms of drug action because such knowledge helps in explaining the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.

1. INTRODUCTION

Heterocyclic compounds play a vital role in biological processes and are wide spread in natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in heme and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocyclic designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocyclic compounds have enormous potential as the most promising molecules as lead structures for the design of new drugs.

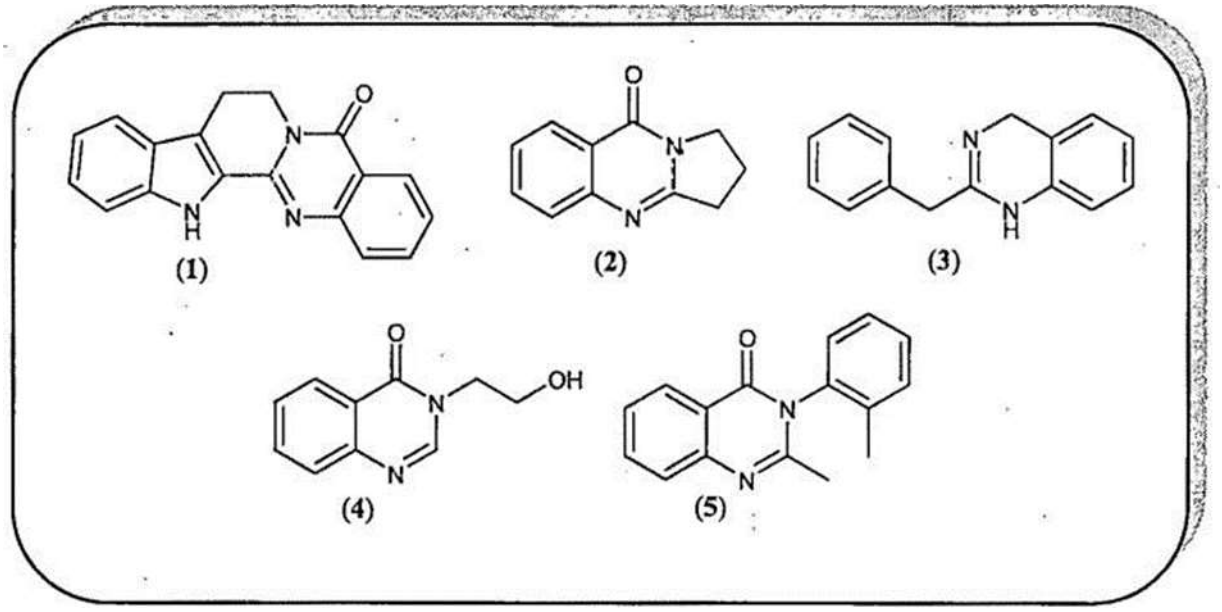
Heterocyclic compounds have been found to occur widely in nature and have proved to be of an immense significance to life. These compounds have attracted the attention of chemists and biologists due to their varied nature of physicochemical and pharmacological properties. A vast number of them are pharmacologically active and are in regular clinical use and proved to be potent drug. Their practical applications range from clinical use to field as diverse as agriculture, photography, biocide formulation and polymer science. The range of known compounds is virtually limitless, encompassing an impressive spectrum of physical, chemical and biological properties. Extensive application of these compounds in medicine has led to the chemistry of these materials to expand exponentially in the past few decades, so much so that virtually a limitless series of structurally novel compounds with a broad spectrum of reactivity and stability has been developed.

The great expansion in medicinal research in past has contributed much to the unparalleled progress of medicine during that period. Improved and basically more meaningful biological test procedures and methods of diagnosis have provided better guidance in drug discovery by pointing out suggestive observations which could be used in the design of new prophylactic and therapeutic agents. The growth of molecular biology with its chemical insight into experimental biology has contributed to more significant pharmacological theories. The elucidation of the structure of many metabolites, and of polypeptides, enzymes, polynucleotides and other biopolymers has also made possible a more rational study of the chemical mode of action of such compounds, and their interaction with drugs. Medicinal chemistry has taken advantage of these investigations, and of the refinement of pertinent chemical theories, to establish itself firmly as an interdisciplinary science. It has become the acknowledged meeting ground of modem organic and physical chemistry, and of biochemistry in the application of these fields to drugs, with its own literature and procedures.

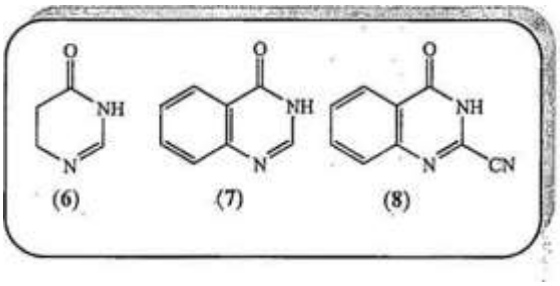
Today a large number of diseases are cured or at least controlled by drug therapy. The fight against bacterial and fungal infections has been largely won and significant progress has been made in treating disturbed mental, cardiovascular, gastrointestinal condition. To boast, it can be claimed that certain form of cancers can be cured by chemotherapy.

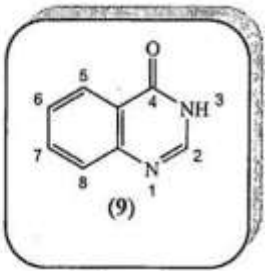
1.1 Quinazolin-4-ones: A Bioactive Heterocycle

Quinazolin-4-ones-a bioactive Heterocycle Quinazolin-4-ones is a building block for approximately 150 naturally occurring alkaloids such as rutaecarpine (1), deoxyvasicinone (2), glycosminine (3), eehinozolinone (4), and drugs like methaqualone (5) [1] isolated date from a number of families ofthe plant kingdom, animals and microorganisms [2].



The ortho-fusion of benzene nucleus with pyrimidone ring (6) gives rise to a class of heterocyclic compounds containing 1, 3-benzodiazine ring system (7). As early as 1869, Griess [3] built up this ring system (8) for the first time by reaction of cyanogens with anthranilic acid to give a compound named as bicyanoamidobenzene and used until 1885 when structure was known with some certainty.





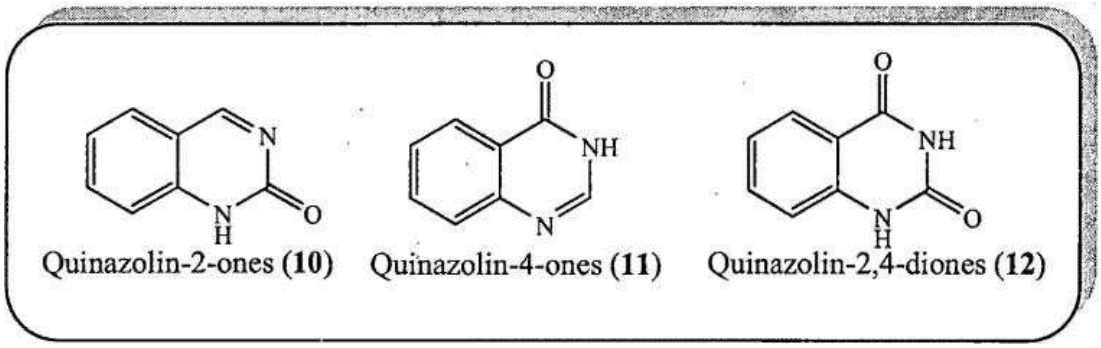
1.2 Numbering System of Quinazolin-4-ones

Quinazolin-4-ones is also known as phenmiazine, benzylene-amidine, 1,3- diazanaphthalene or benzo-l,3-diazine or 5,6-benzo-pyrimidine. The term phenmiazine was used by Wildman [4], The numbering shown in the structure (9) was suggested by Paal and Busch [5], and is One in the current use [6].

Quinazolin-4-ones will be classified into the following five categories, based on the substitution patterns of the ring system [7].

- 2-Substituted- Quinazolin-4-ones
- 3-Substituted- Quinazolin-4-ones
- 4-Substituted-quinazolmes
- 2,3-Disubstituted- Quinazolin-4-ones
- 2,4-Disubstituted- Quinazolin-4-ones

Depending upon the position of the keto or oxo group, these compounds may be classified into three types.



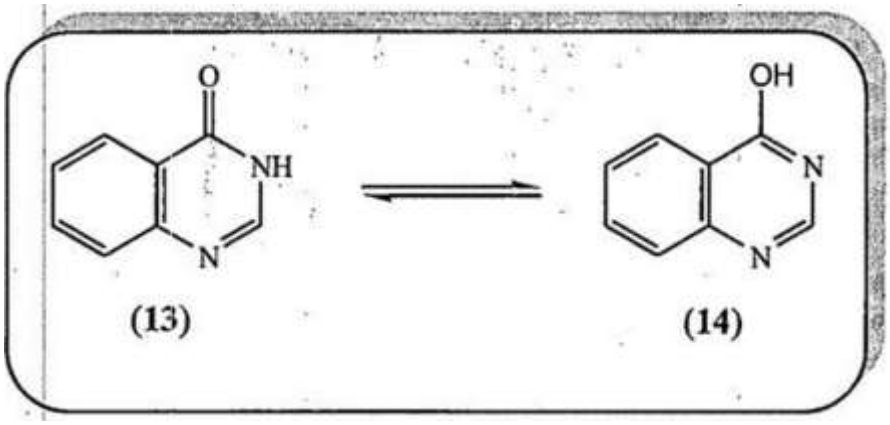
Out of the three quinazolinone structures, quinazolin-4-ones (11) are most prevalent, either as intermediates or as natural products in many proposed biosynthetic pathways. This is partly due to the structure being derived from the anthranilates (anthranilic acid or various esters, isatoicanhydride, anthranilamide and anthranilonitrile) while the quinazolin-2-ones (12) is predominantly a product of anthranilonitrile or benzamides with nitriles [8].

1.3 Chemistry

The chemistry of the quinazolin-4-ones alkaloids is well documented in a number of comprehensive reviews and monographs. Quinazolin-4-ones derivatives are of considerable interest because of their pharmacological properties; e.g., protein tyrosine kinase inhibitor, eholeeystokin inhibitor, antimicrobial, anticonvulsant, sedative and hypnotensive, antidepressant and anti-inflammatory as well as antiallergy. Some of these have interesting biological properties such as antimalarial activity, biofungicide and diuretic properties.

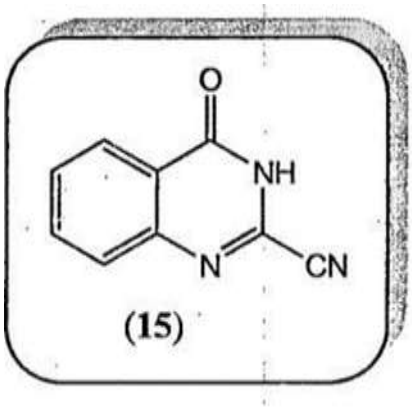
Structure activity relationship studies of quinazolinone ring system revealed in various literatures suggest position 2, 6 and 8 are very much important for structure activity studies and position 3 should be attached to different heterocyclic rings for better chemotherapeutic activity [9].

Quinazoline having a hydroxyl group in the 2 or 4 position are tautomeric with the corresponding tautomeric with keto-dihydroquinazolines [10]. Thus 4- hydroxyquinazoline, 4-keto-3,4-dihydroquinazoline, is commonly named 4(3*H)*- quinazolone, or simply 4-quinazoline. It was further simplified that 4- hydroxyl quinazoline (13) an|d 4-quihazoline or 4(3//)-quinazoline(14) is ;a tautomeric mixture of the lactum and the. lactim form. Various data' [11,12] indicate that 4-hydroxyquinazolini exists as an equilibrium mixture of (13) and (14) in which the form (13) is the nJost favored. Because of tautomerism, the quinazolones are high melting insoluble solid, extremely stable to heat, light and air. These are also resistant to chemical oxidation, reduction, hydrolysis and substitution on the benzene ring. They are readily soluble in alkali and form stable salt.



1.4 Synthetic Aspects of Quinazolin-4-ones

The first quinazolin-4-ones were synthesized [13] in the late 1860s from anthranilie acid and cyanogens to give 2-cyano quinazolin-4-ones (15). Interest in the medicinal chemistry of quinazolin-4-ones derivatives was stimulated in the early 1950s with the elucidation of a quinazolin-4-ones alkaloid, 3-[3-keto-y-(3-hydroxy-2-piperidyl)- propyl]- 4-quinazolone febrifugine (16) [14], from an Asian plant *Dichroa febrifuga*, which is! an ingredient of a traditional Chinese herbal remedy, effective against malaria.



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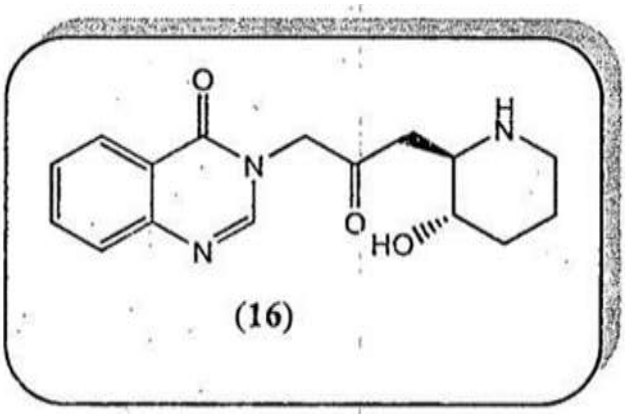
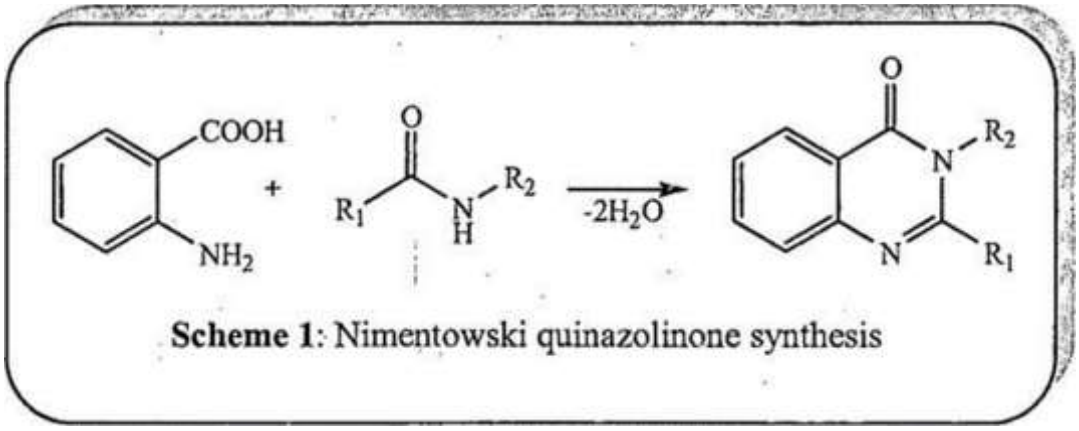


(16)

The topical synthetic methodologies such as iminophosphorane mediated synthesis (aza-wittig methodology), microwave-assisted synthesis, solid phase synthesis, and application of different catalyst etc., will be discussed retrospectively focusing on the pathways to quinazolin, quinazolin-4-ones and their derivatives.

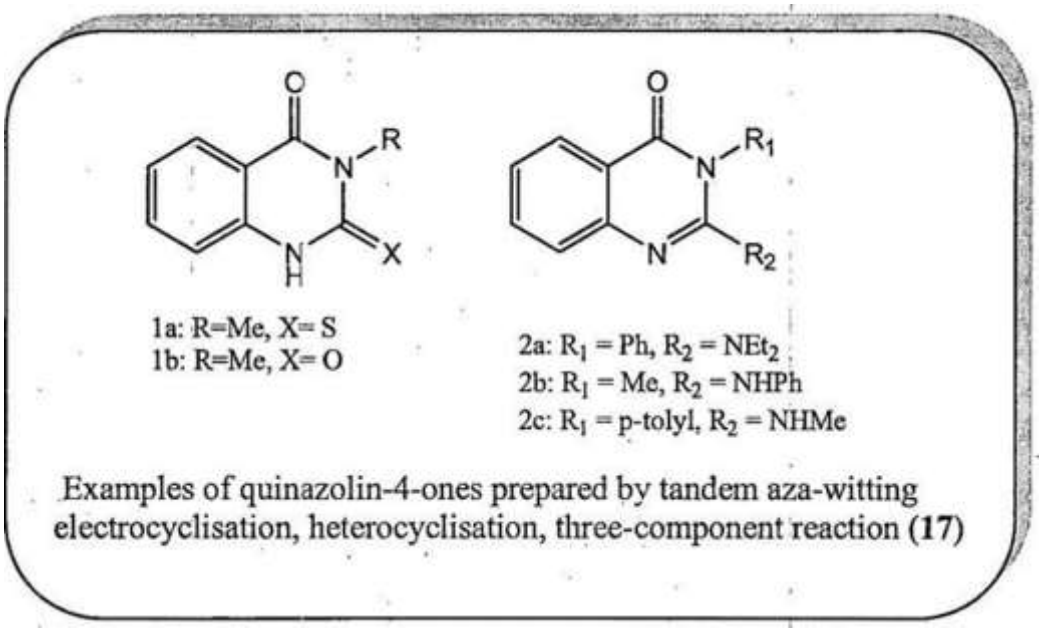
1.4.1 Niementowaski quiinazolin-4-ones synthesis

Niementowaski quinazolin-4-ones synthesis Was discovered by Stefan Niementowaski (1866-1925) [15], obtained quinazolin-4-ones by condensation of anthranilic acid and amides (Scheme 1). The original work was published in 1895 [16] and the utility of the reaction has been reviewed [17], The reactions have been modified to use anthranilic acid esters and isatoic anhydride [18].



Scheme 1: Nimentowski quinazolinone synthesis

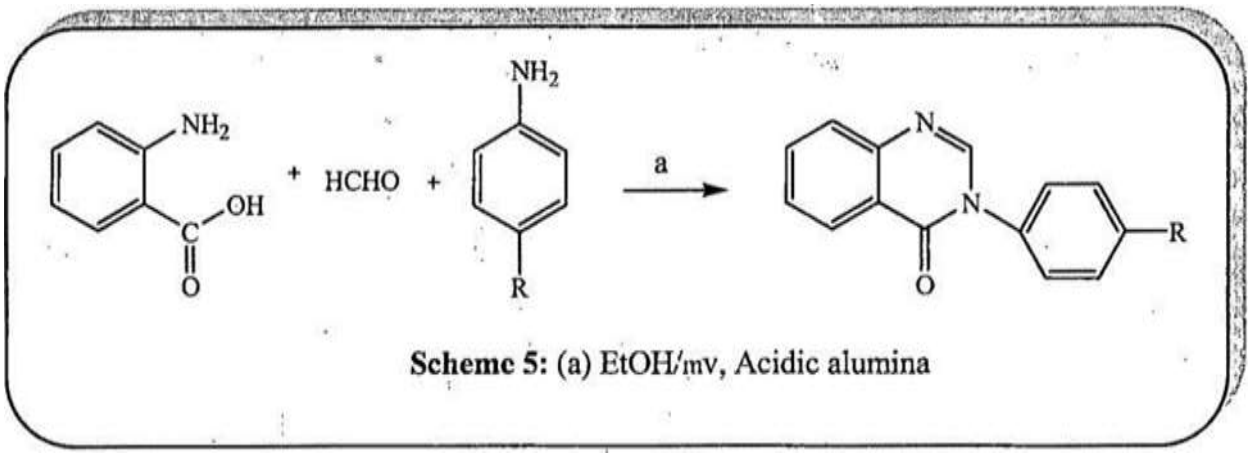
Microwave-assisted synthesis



Examples of quinazolin-4-ones prepared by tandem aza-witting electrocyclisation, heterocyclisation, three-component reaction **(17)**

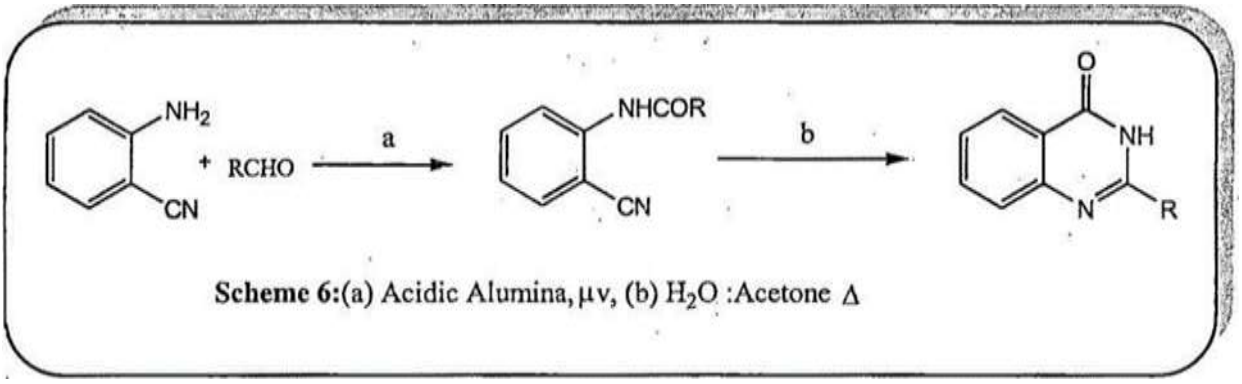
A number of microwave-assisted methods have been recently reported for the synthesis of 2-substituted quinazolin-4-ones analogs by the use of anthranilie acid, anthranilamide, isatoic anhydride, and 3,1-benzoxazinones as appropriate precursors.

Mishra [26] reported solid supported microwave synthesis of some 3- substituted~4-(2/f) quinazolinones, which has been carried out by the reaction of anthranilie acid, formaldehyde and primary aromatic amines. The reactions were conducted in presence of acidic alumina where formaldehyde entered into cycloaddition to yield the quinazolin-4-ones derivatives (Scheme 5). The reactions completed within 2- 4 minutes with 82-94% of yields in microwave reactions while it took 5-7 hours for completion affording only 56-68% of the yields in conventional reactions.



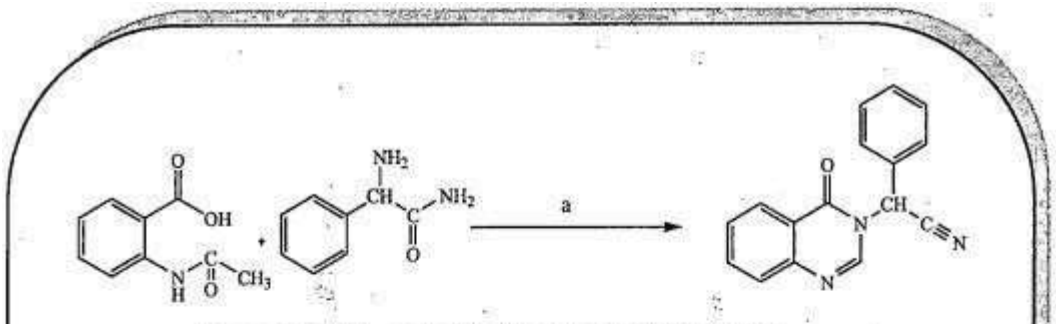
Scheme 5: (a) EtOH/mv, Acidic alumina

Kidwai and Priya [27] synthesized 2-substituted-3/7-quinazolin-4-ones using sodium perborate (Scheme **6**). The key step is the microwave prompted reaction sequence combining 2-aminobenzonitril and aromatic/Heteroaromatic aldehyde providing efficient access to intermediate for the synthesis of the final compound. SPB (sodium perborate) in water and acetone system is proved as selective catalyst of hydration for cyanides.

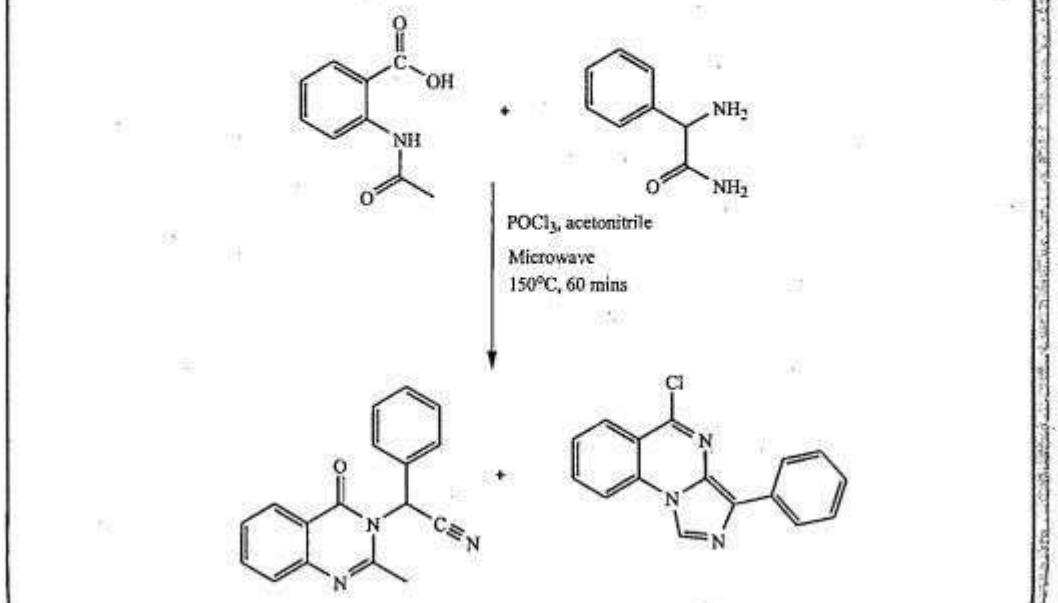


Scheme 6:(a) Acidic Alumina, μv, (b) H_2O :Acetone Δ

Guo *et at,* [28] developed a new method for one step synthesis of imidazo[L5-a]- quinazoline (Scheme 7 and Scheme **8**). In this method, the cyclization of TV- acylanthranilic acid with 2-amino acetamide or 2-amino-acetonitrile in the presence of POCI**3** afforded the 5-chlorOimidazo-[l,5-a]-quinazolines under microwave irradiation. The yield of imidazoquinazoline was improved by introducing an electron-withdrawing group at the 5-position of 2-acetamidobenzoic-acid.



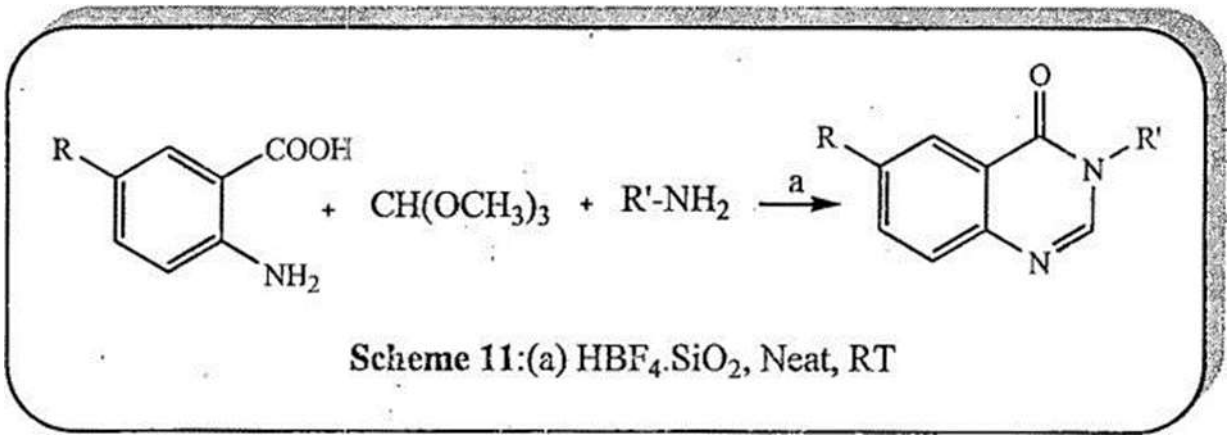
Scheme 7: (a) PCl_3, acetonitrile, Microwave, 160 °C, 30 mints



Scheme 8: (a) $POCl_3$, acetonitrile, Microwave, 150 °C, 60 mints

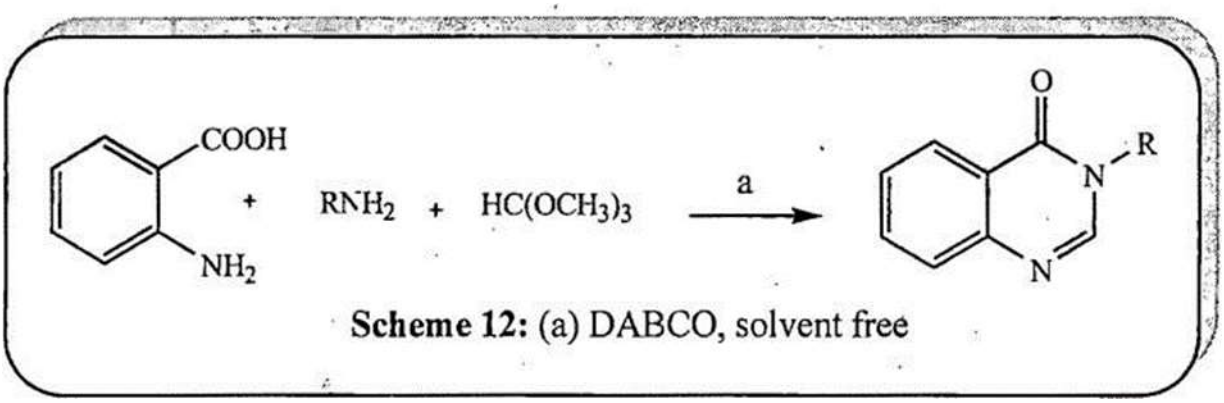
1.4.2 Solvent Free Reaction Using Heterogeneous Catalyst

Laxminarayana *et al,* [31] developed a simple and efficient synthesis of 4(3/f)- quinqzolinones by coupling of substituted anthranalic acid, triethyorthoformate and substituted amines using HBF4.SiO2 as a heterogeneous catalyst under solvent free conditions (Scheme 11). The reaction proceeded with in few minutes with excellent yields. The simple experimental procedure and reusability of the catalyst are significant advantages of this protocol.



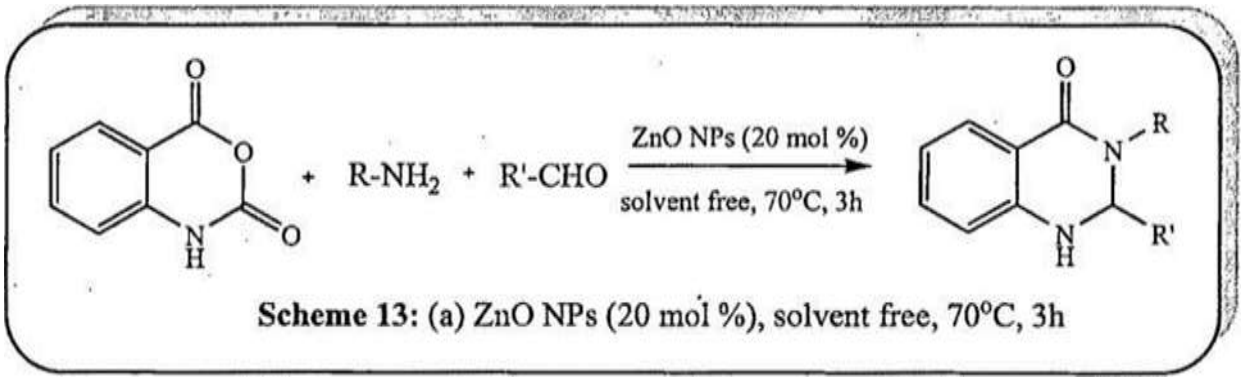
Scheme 11:(a) $HBF_4.SiO_2$, Neat, RT

Heravi *et al,* [32] have synthesized quinazolin-4-ones in high to excellent yields through one-pot condensation of anthranilic acid, trimethyl orthoformate and primary amines in the presence of DABCO (l,4-diazabicyclo[2,2,2]octane) under solvent free conditions (Scheme 12).



Scheme 12: (a) DABCO, solvent free

Yavari *et al.,* [33] have developed three-component one-pot cyclocondensation reaction of isatoic anhydride with amines and aldehydes using ZnO nanopartieles under solvent-free conditions to afford the corresponding 2,3-disubstituted quinazolin-4-ones in good yields **(Scheme 13);**



Scheme 13: (a) ZnO NPs (20 mol %), solvent free, 70°C, 3h

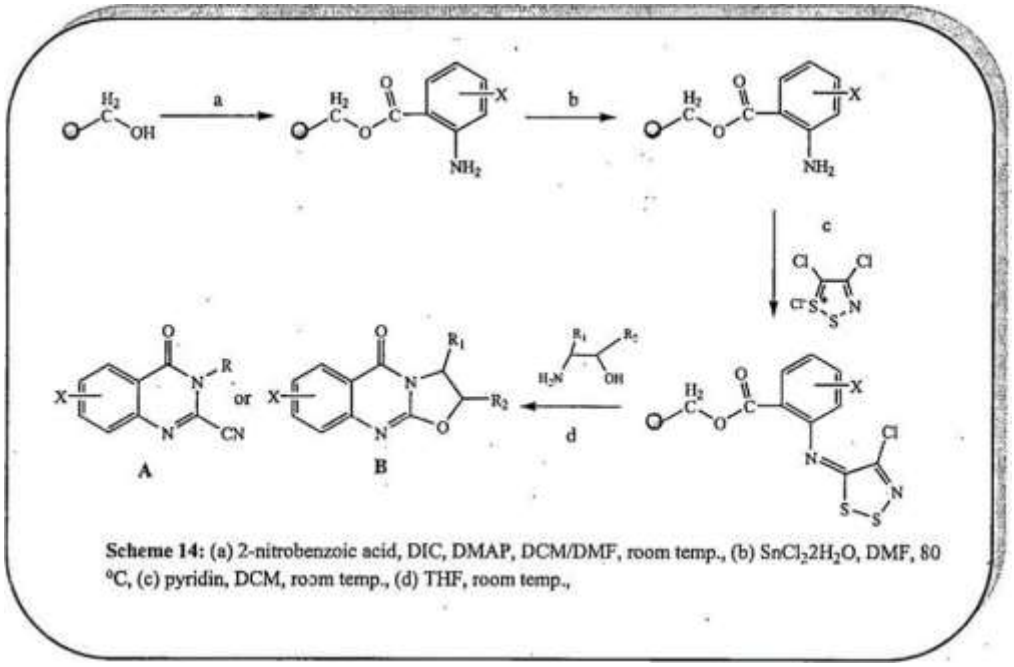
1.4.3 Solid Phase Synthesis

Solid-phase heterocyclic chemistry has been reviewed recently by Krchnak and Holladay [34]. Application of this methodology for synthesis of quinazolin-4-ones compounds is increasing rapidly.

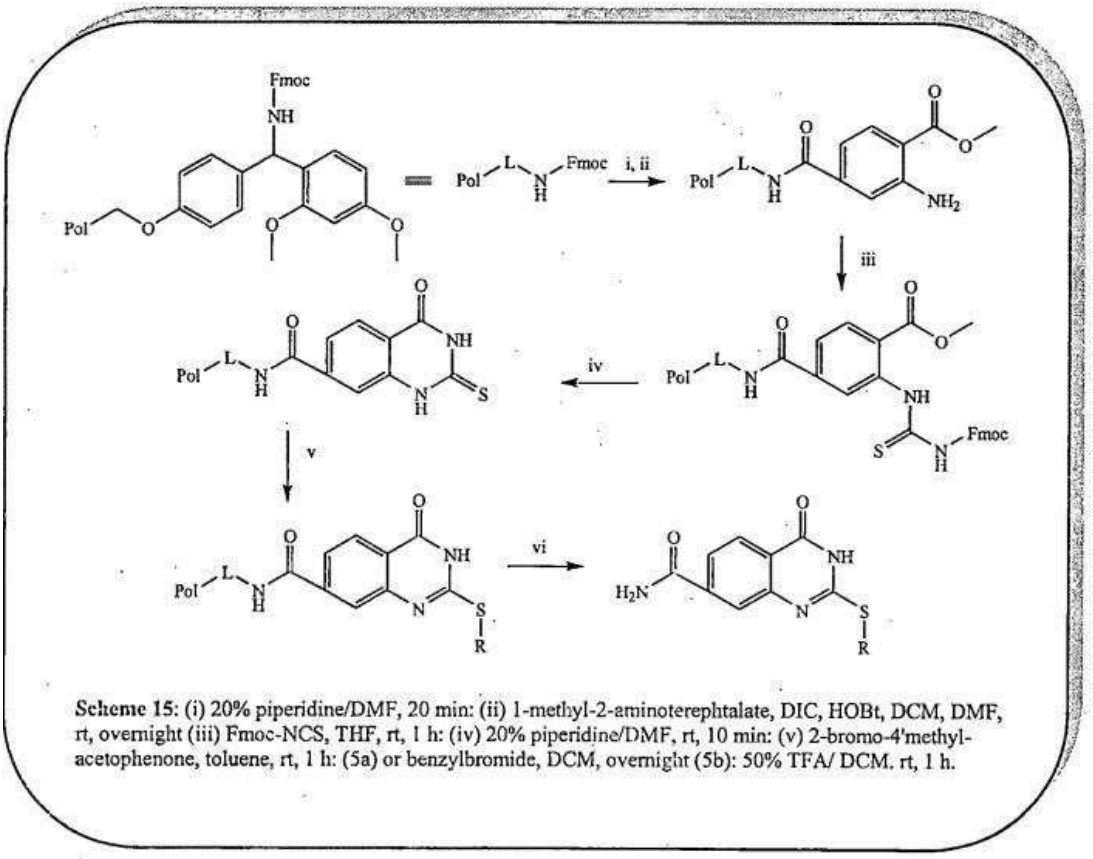
Gong *et al.,* [35] reported four step synthesis of 2-cyano quinazolin-4-ones in 35- 60% overall isolated yields and 2,3-dihydrooxazolo[2,3-b]quinazolin-5-ones in 20-71% four-step overall isolated yields utilizing polymer-bound anthranilic acid derivatives. Further 6-amino-2-cyano quinazolin-4-ones were also synthesized in 30-44% six-step overall isolated yields by making use of anthranilic acid derivative resin via dithiazole resins **(Scheme 14).**

Highly efficient solid-phase synthesis is amenable to high throughput/eombinatorial synthesis by Krchnak *et. at,* [36], Solid-phase synthesis of thiazolo-[2,3,b]-quinazolines under mild conditions was developed using resin-bound 2- amino-terephthalamic acid, Fmoc-NCS, and bromoketones **(Scheme 15).** Primary amines immobilized to an acid-cleavable backbone amide linker were acylated with 1-methyl-2- aminoterephtalate. Following cleavage of the methyl ester, Fmoc-NCS

was used to form a resin bound thiourea. Bromo ketones were subsequently added to form an aminothiazole ring and the cyclisation was performed using DIC/HOBt to afford thiazolo-[2,3,b]-quinazolines.



Scheme 14: (a) 2-nitrobenzoic acid, DIC, DMAP, DCM/DMF, room temp., (b) $SnCl_2 2H_2O$, DMF, 80 °C, (c) pyridin, DCM, room temp., (d) THF, room temp.,



Scheme 15: (i) 20% piperidine/DMF, 20 min: (ii) 1-methyl-2-aminoterephtalate, DIC, HOBt, DCM, DMF, rt, overnight (iii) Fmoc-NCS, THF, rt, 1 h: (iv) 20% piperidine/DMF, rt, 10 min: (v) 2-bromo-4'methyl-acetophenone, toluene, rt, 1 h: (5a) or benzylbromide, DCM, overnight (5b): 50% TFA/ DCM. rt, 1 h.

Drugs vary considerably in their range of effectiveness. Many are narrow spectrum drugs-that is, they are effective only against a limited variety of pathogens. Others are broad spectrum drugs and attack many different kinds of pathogens. Drugs may also be classified based on the general microbial group they act against: antibacterial, antifungal, antiprotozoan, and antiviral. Some agents can be used against more than one group; for example, sulfonamides are active against bacteria and some protozoa.

Chemotherapeutic agents can be synthesized by microorganism or manufactured by chemical procedures independent of microbial activity. A number of the most commonly employed antibiotics are natural-that is, totally synthesized by one of the few bacteria or fungi. In contrast, several important chemotherapeutic agents are completely synthetic. The synthetic antibacterial drugs in table-1 are the sulfonamides, trimethoprim, chloramphenicol, ciprofloxacin, isoniazid and dispone. Many antiviral and antiprotozoal drugs are synthetic. An increasing number of antibiotics are semisynthetic.

Semisynthetic antibiotics are natural antibiotics that have been chemically modified by the addition of extra chemical groups to make them less susceptible to inactivation by pathogens. Ampicillin, carbenicillin and methicillin are good examples.

1.6.1.2 Mechanism of action of antimicrobial agents:

The mechanisms of action of specific chemotherapeutic agents are taken up in more detail when individual drugs and groups of drugs are discussed later in this chapter. A few general observations are offered at this point. It is important to know something about the mechanisms of drug action because such knowledge helps in explaining the nature and degree of selective toxicity of individual drugs and sometimes aids in the design of new chemotherapeutic agents.

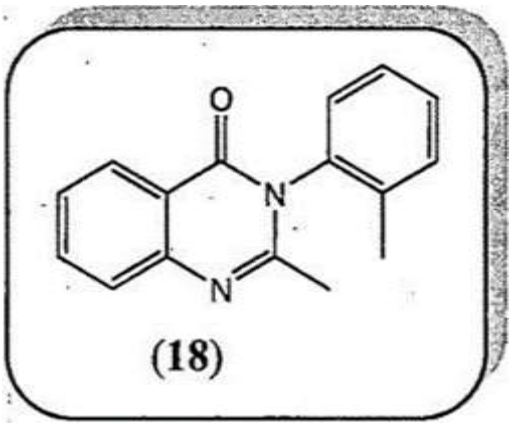
Antimicrobial drugs can damage pathogens in several ways. As can be seen in table- 2, which summarizes the mechanisms of the antibacterial drugs listed in table-1. The most selective antibiotics are those that interfere with the synthesis of bacterial cell walls (e.g., penicillins, cephalosporins, vancomycin, and bacitracin). These drugs have a high therapeutic index because bacterial cell walls have a unique structure not found in euearyotic cells.

Streptomycin, gentamicin, chloramphenicol. Tetracycline, erythromycin and many other antibiotics inhibit protein synthesis by binding with the procaryotic ribosome. Because these drugs discriminate between procaryotic and eukaryotic ribosomes, their therapeutic index is fairly high, but not as favorable as that of cell wall synthesis inhibitors. Some drugs bind to the 30S (small) subunit, while others attach to the 50S (large) ribosomal subunit. Several different steps in the protein synthesis mechanism can be affected: aminoacyl-tRNA binding, peptide bond formation, mRNA reading, and translocation. For example, fusidic acid binds to EF-G and blocks translocation, whereas mucopirocin inhibits isoleucyl-tRNA synthetase.

The antibacterial drugs that inhibit nucleic acid synthesis or damage cell membranes often are not as selectively toxic as other antibiotics. This is because procaryotes and eucaryotes do not differ as greatly with respect to nucleic acid synthetic mechanisms or cell membrane structure. Good examples of drugs that affect nucleic acid synthesis or membrane structure are quinolones and polymyxins. Quinolones inhibit the DNA gyrase and thus interfere with DNA replication, repair and transcription. Polymyxins act as detergents or surfactants and disrupt the bacterial plasma membrane.

1.5 Pharmacological importance: Quinazolin-4-ones derivatives

In a quest to find additional potential quinazolin-4-ones based drags, various substituted quinazolin-4-ones have been synthesized [37]. Methaqualone (18) was synthesized for the first time in 1951 and it is the most well known synthetic quinazolin-4-ones drag, famous for its sedative-hypnotic effects. The introduction of methaqualone and its discovery as a. hypnotic triggered the research activities towards the isolation, synthesis and the studies on the pharmacological properties of the quinazolin-4-ones and related compounds. The quinazolin-4- ones skeleton is a frequently encountered heterocycles in medicinal chemistry literature with applications including antibacterial, analgesic, anti-inflammatory, antifungal, antimalarial, CNS depressant, anticonvulsant, anticoccidial, anti-parkinsonism, and cancer activities. Little number of quinazolin-4-ones was reported as potent chemotherapeutic agents in the treatment of tuberculosis [8].



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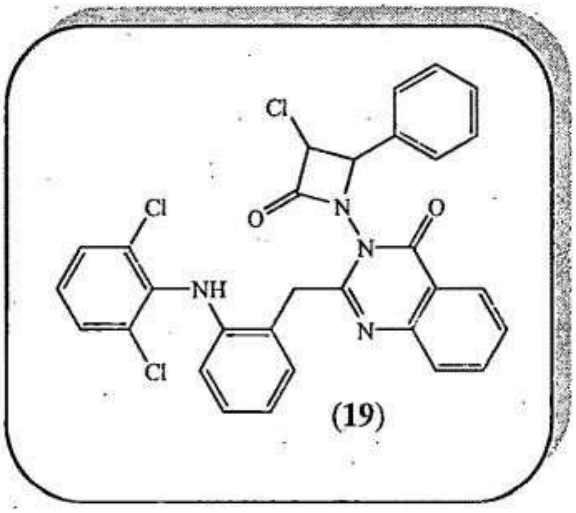
1.5.1 Antimicrobial activity

Patel *et al.,* [38] synthesized a series of 2-oxo-azetidinyl-quinazolin-4(3*H*)-ones (19) and screened for *in vitro* antimicrobial activity. They found synthesized compounds with good antimicrobial activity.



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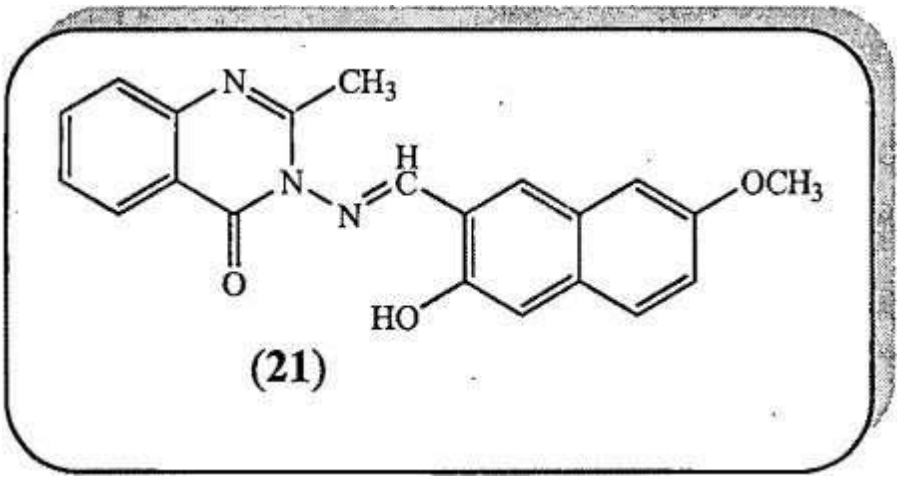

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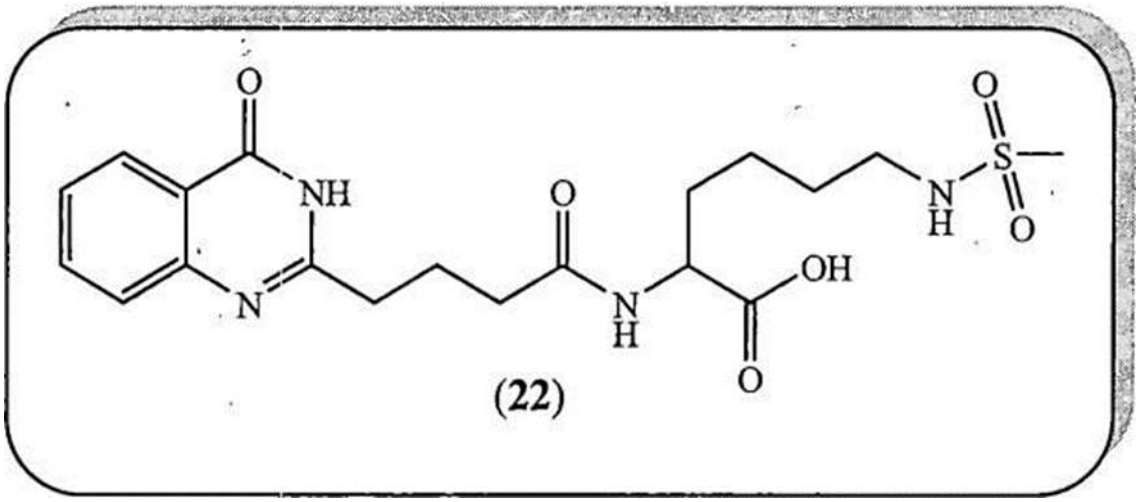
1.5.2 Antibacterial activity

Gowda *et al.,* [41] synthesized a series of urea / thiourea / acetamide /sulphonamide derivatives of quinazolinones conjugated lysine (22) and screened for their antibacterial studies and structure activity relationship has been developed. Antibacterial activity of the synthesized compounds were tested against different strains of both gram positive bacteria namely *B. substilis* and gram negative bacteria like *E. coli*, *P. fluorescens*, *Xanthomonas campestris pvs.* and *Xanthoinonasoryzae.*

The activity profile revealed that the compounds containing urea and thiourea functionalities along with fluoro group have exerted a highly potent activity. Thus, the title compounds represent a novel class of potent antimicrobial agents.



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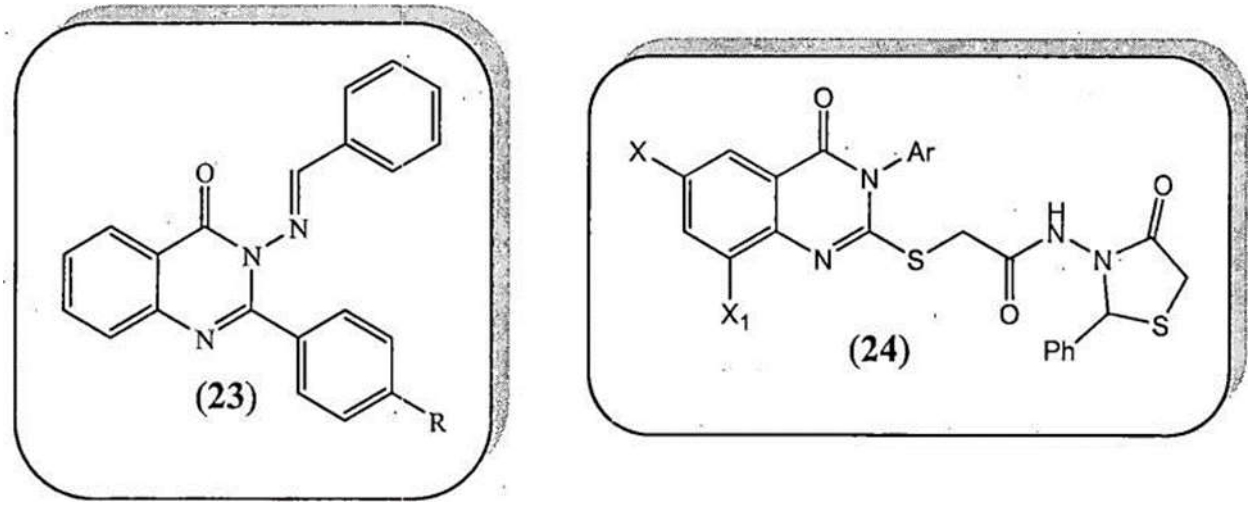
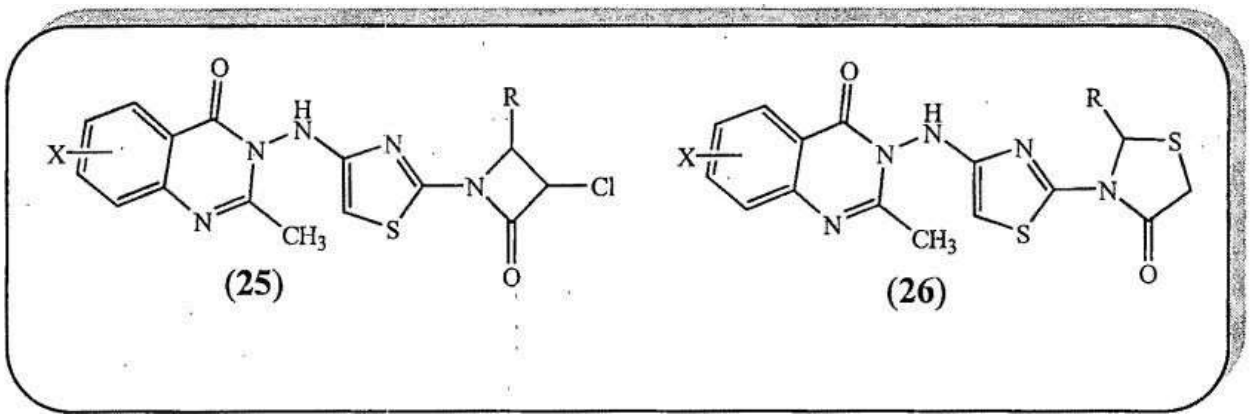
Rajsekaran *et al.,* [42] investigated various quinazolinone amines clubbed with five membered heterocyclic aldehyde to obtain 2,3-substituted quinazolin-4(3*H*)-ones (23) with potent antibacterial activity against *S. aureus, B. subtilis, E. coli* and *K. pneumonia* and *in vitro* antioxidant activity.



Shiradkar *et. al.,* [43] synthesized 2-(5-amino-[l,3,4]thiadiazol-2-ylmethylsulfanyl)-6,8- disubstituted-3-phenyl-3*H*-quinazolin-4-one (24) and evaluated for their preliminary *in vitro* antibacterial activity against *S. aureus, E. coli, P. aeruginosa* and *S. typhosa*. All compounds were also screened for antitubercular activity against *Mycobacterium tuberculosis H37Rv* strain by MABA assay method. The results demonstrate that the activity against mycobacteria was related more to antibacterial activity than to changes in the lipophilicity of the compounds.

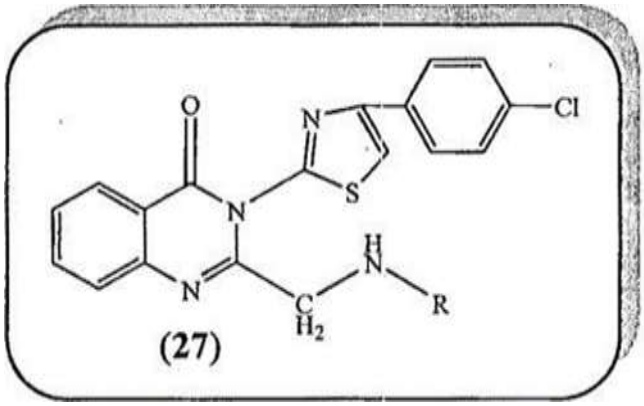
1.5.3 Antifungal activity

Rajput *et al,* [44] synthesized 3-(2'-substitutedarylidineimino-1',3'-thiazol-4'-yl)amino-2- methyl-monosubstituted quinazolin-4(3*H*)-ones, 3-[2'-(3'-chloro-2'-oxo-4'-substitutedaryl-r- azetidinyl)-1'-,3'-thiazol-4'-yl]-amino-2- methylmono substituted quinazolin-4-(3*H*)-ones (25), and 3-[2,-(substitutedaryl-4,-thiazolidinon-3,-yl)-1',3'-thiazol-4l-yl]-amino-2-methylmono substituted quinazolin-4(3*H*)-ones (26) were synthesized and reported as antifungal agent.

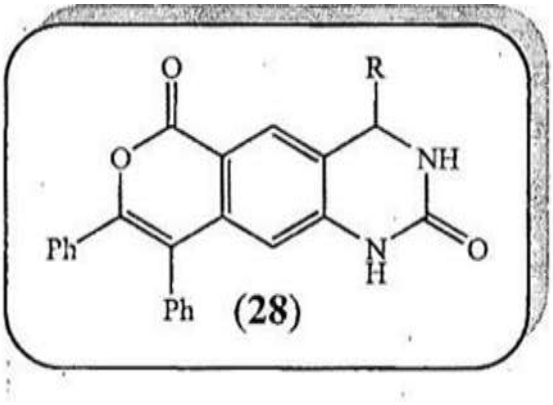


1.5.4 Antitubercular activity

Pattan *et al.,* [45] synthesized a new series of N-3[4-(4-chlrophenyl thiazole-2-yl)-2- amino methyl]-qu:inazoline-4(3*H*)-one (27) and screened for their antitubercular activity using *H37Rv* strain on L. J. medium. All the compounds have showed moderate to promising antitubercular activity.



(27)



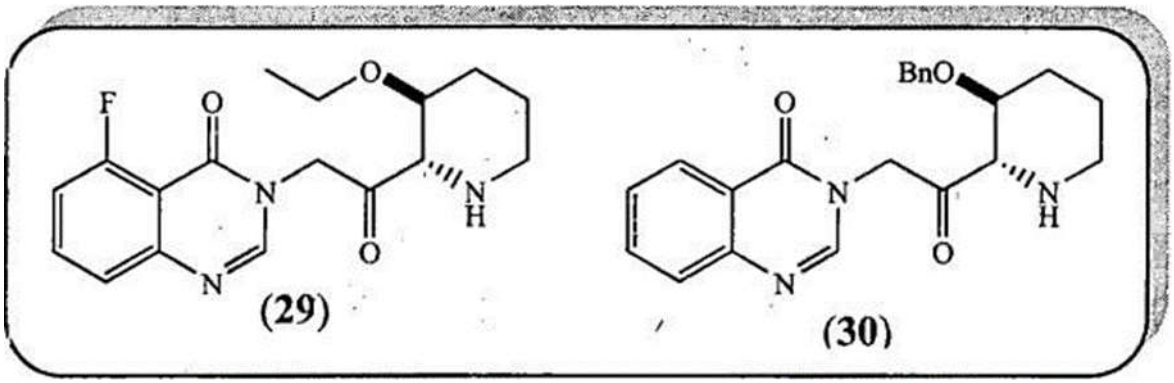
(28)

Rai *et al*., [46] synthesized a series of 4-aryl-8,9 diphenyl-1,4 dihydro,3*H*-7-oxa-l,3 diazaonthracene (28) and evaluated for their possible antitubercular activity against *H37Rv* strain using Lowenstein Jenison medium.

1.5.5 Antimalarial activity

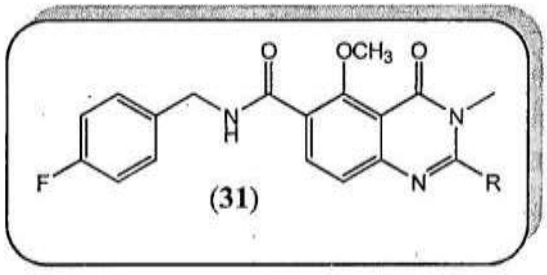
Zhu *et al.,* [47] have synthesized novel febrifugine analogues which possess excellent *in vivo* antimalarial activity and most of them become less toxic than the natural product.

Synthesized compounds were tested against *Plasmodium falciparum* clones W-2, a chloroquine resistant cell line for m *vitro* efficacy. All compounds were also evaluated for antimalarial efficacy and toxicity in mouse models. The ED50S (effective dose leading to 50% reduction in parasitemia), MCDs (minimum clearance dose), and MTDs (maximum tolerated dose) were determined. The therapeutic indices, which were obtained by using the MCDs as the effective parameters, were calculated. Some of the compounds: 3-[2-(3-ethoxypiperidin-2-yl)-2-oxoethyl]- 5-fIuoro-3*H* quinazolin-4-one (29) and 3-[2-(3-benzyloxypiperidin-2-yl)-2-oxoethyl]-3*H*-pyrido- [3,2-d]pyrimidin-4-one **(30)** possess a therapeutic index over ten time's superior to that of febrifugine and the commonly used antimalarial drug chloroquine.

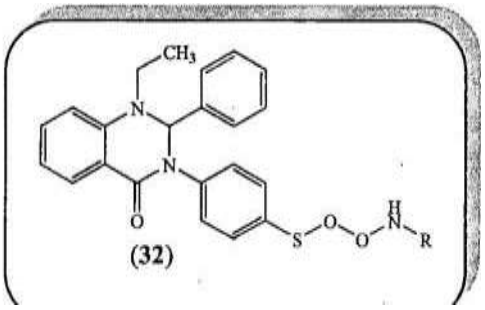


1.5.6 Anti HIV

Wang *et al,* [48] provides a practical method for the preparation of 5-hydroxy quinazolinones **(31)** and evaluated as novel HIV-1 inhibitors. The cytotoxicity of compounds was evaluated by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay method. Primary bioassay results indicated that most of the quinazolinones possess anti-HIV activity. Most of the synthesized compounds were also found to exhibit good anti-TMV activity.



(31)



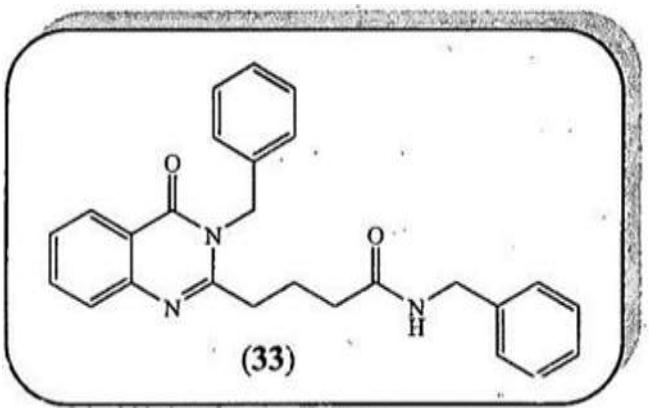
(32)

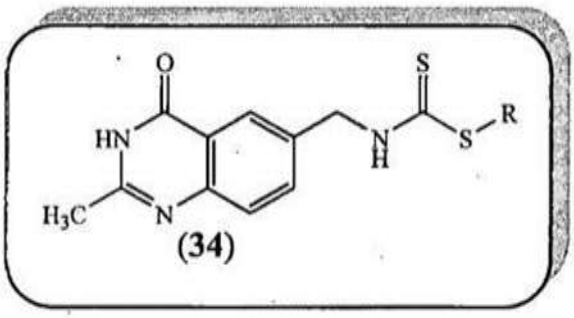
1.5.7 Anti-inflammatory activity

Amin *et al.,* [49] reported synthesis, biological evaluation and molecular docking of [(2*H*,3*H*)-quinazoline-2,10-cyclohcxan]-4(l*H*)-one (32) derivatives as anti-inflammatory and analgesic agents.

1.5.8 Cytotoxic Activity

Hassanzadeh *et al.* [50] reported synthesis of some 4(3*H*)-quinazolinone (33) and screened against HeLa cells. Cytotoxicity was determined by rapid colorimetric assay using MTT. The results indicated that the tested compounds did not show significant cytotoxicity alone and in combination with doxorubicin.

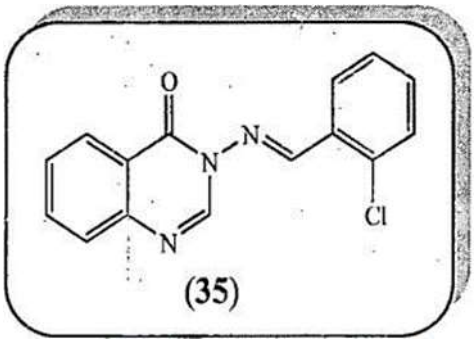




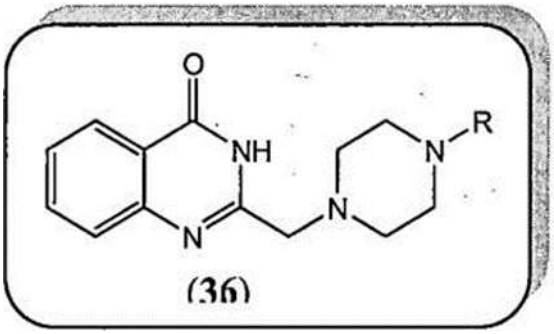
A series of N-((2-methyl-4(3*H*)-quinazolinone-6-yl)-methyl)-dithiocarbamates (34) were synthesized and evaluated for their cytotoxic activity against five human cancer cell lines by Cao *et al,* [51].

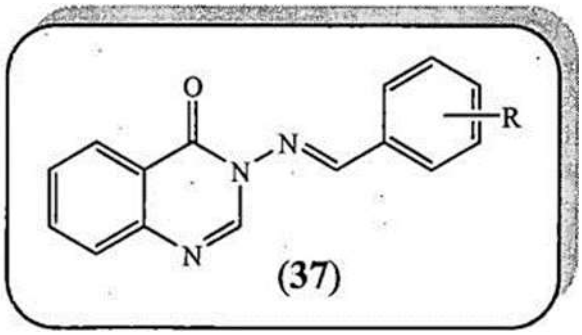
2.1.1.8. Anticancer activity'

Noolvi *et al,* [52] synthesized some 2-furano-4(3*H*)-quinazolinones (35), diamides (open ring quinazolines), quinoxalines. Among the synthesize compounds, seventeen compounds were screened for anticancer activity at a single high dose (10^{-5} M) in full NCI 60 cell panel. Among the selected compounds, 3-(2-chloro benzylideneamine)-2-(furan-2-yl) quinazoline-4(3*H*)-one was found to be the most active candidate of the series. Rational approach and QSAR techniquesenabled the understanding of the pharmacophoric requirement for quinazoline, diamides and quinoxaline derivatives and concluded that: (i) the quinazoline ring is satisfactory backbone for antitumor activity; (ii) the presence of 2-chloro benzylideneamine group at 3 position of quinazoline enhances the activity as hydrophobic region.



Murahari *et al.,* [53] synthesized 2-(piperazin-l-ylmethyl) quinazolin-4(3*H*)-one **(36)** and were evaluated for their anti-cancer activity by MTT assay method.



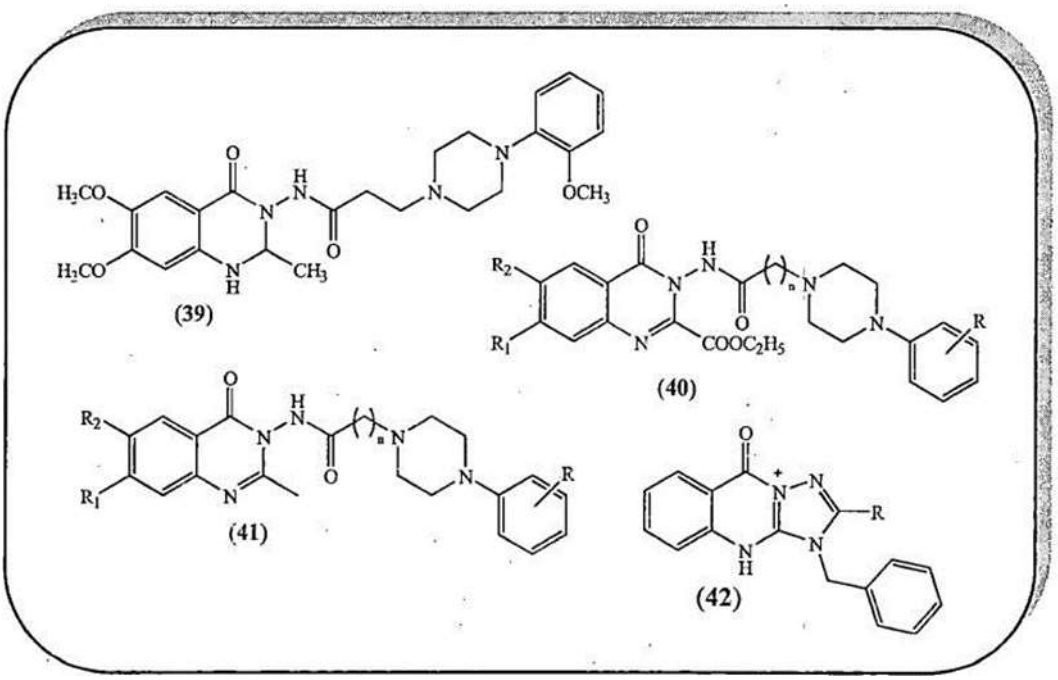


Das *et al,* [54] synthesized some 3-(arylideneamino)-phenylquinazoline-4(3*H*)-ones (37) and were evaluated for their anti-cancer activity.

2.1.1.9 Antihypertensive

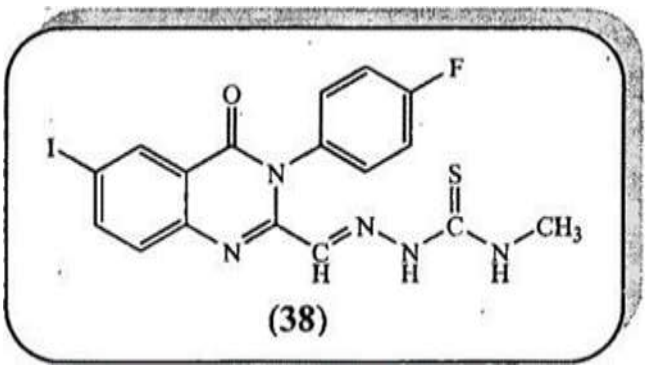
Three series of new 2-[(4-substituted piperazin-l-yl) methyl]quinazolin-4(3*H*)-ones(39), ethyl 6,7-dimethoxy-4-oxo-3-[2-(4-substituted-piperazin-lyl) acetamido/ propanamido]-3,4- dihydroquinazoline-2-carboxylates **(40)** and their 2-methyl analogues **(41)** were designed and synthesized by Abouzid *et al.*, [55], The final compounds were evaluated for their *in vivo* hypotensive activity in normotensive cats.

Alagarsamy *et al.*, [56] reported synthesis of 3-benzyl-2-substituted-3 *H* /-(l,2,3)-triazolo (5,l-b)-quinazolin-9-ones **(42).** The title compounds were evaluated for their *in vivo* antihypertensive activity using spontaneously hypertensive rats (SHR). The results of antihypertensive activity study indicate that all the test compounds were found to reduce blood pressure (BP) significantly.



2.1.10 Anticonvulsant, analgesic, cytotoxic and antimicrobial Activities

Aly *et al.*, [57] synthesized novel 3-aryl-4(3*H*)-quinazolinone-2-carboxaldehydes **(38),** their corresponding Schiffs base and thiosemicarbazone derivatives and reported compounds as potential anticonvulsant, analgesic, cytotoxic as well as their antimicrobial activities.



2.2 Quinazolin-4-ones Derivatives under Clinical Trial

Several quinazolin-4-ones alkaloids are known to elicit a wide variety of biological responses. This has spurred the preparation and pharmacological evaluation of a great number of quinazolin-4-ones derivatives and intensive research in the quinazolin-4-ones area is still in active progress. There are many quinazolin-4-ones derivatives which are under different phases of trial

i.e. Pre-clinical trial, Phase I trial, Phase II trial, Phase III trial or Phase IV trial [58]. Tiyptanthrin

(43) (indolo [2,l-b]quinazolin-6,12-dione), is a natural product that was obtained from a Chinese plant, *Strobilanthes cusia*. It has broad-spectrum biological activities including anti-tuberculosis property. Tryptanthrin demonstrated MIC of 1 pg/ml against MTB in BACTEC assay. It showed MIC values of 0.5-1.0 pg/ml against MDR-TB strains. Preclinical evaluation of tryptanthrin has been conducted [59].

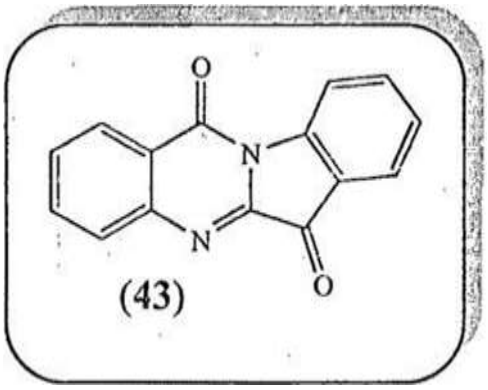
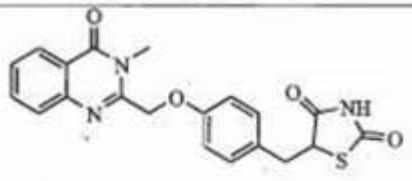
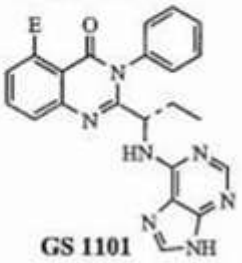
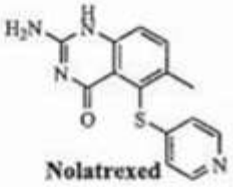
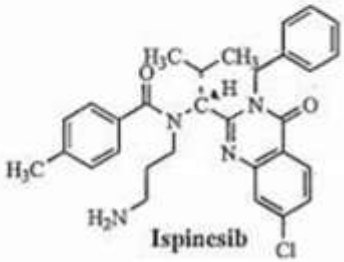
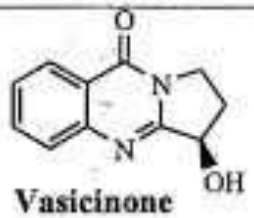
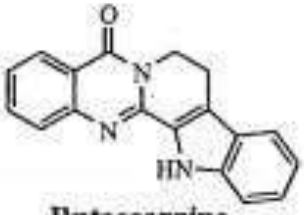
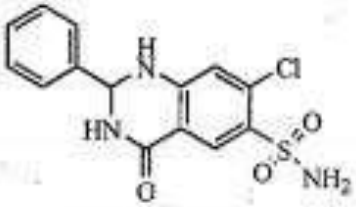
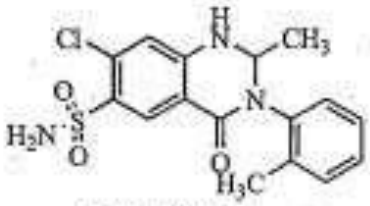


Table 2.1 Natural/Synthetic quinazolin-4-ones of Therapeutic Importance

No.	Natural/Synthetic quinazolin-4-ones	Activity
1	 **Balaglitazone**	partial PPAR-γ agonist
2	 **GS 1101**	an oral small molecule inhibitor of the delta isoform of PI3-kinase (p110delta), for the treatment of hematological cancer
3	 **Nolatrexed**	thymidylate synthase inhibitor, for use in the treatment of solid tumors
4	 **Albaconazole**	For the oral treatment of superficial fungal infections.
5	 **Ispinesib**	KSP inhibitor that was found to be more selective for KSP over other members of the It effectively induced tumor regression in several preclinical models. Ispinesib was chosen for further development as an antimitotic agent

No.	Natural/Synthetic Quinazolin-4-ones	Activity
6	 **Vasicinone**	Antitumor, bronchodilating, anthelminitic, antinaphylactic
7	 **Luotonin**	Antitumor
8	 **Rutaecarpine**	Strong analgesic, antiemetic, antihypertensive, uterotonic
9	 **Ketanserin**	serotonin receptor antagonist
10	 **Fenquizone**	It is a diuretic, part of the class of low-ceiling sulfonamide diuretics. Fenquizone is used primarily in the treatment of treatment of oedema and hypertension
11	 **Metolazone**	Diuretic, antihypertensive

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