Chemistry & Biology Interface, 2018, 8, 2, 62-83

REVIEW PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Study of developments of biologically active Quinazolinones derivatives: A review

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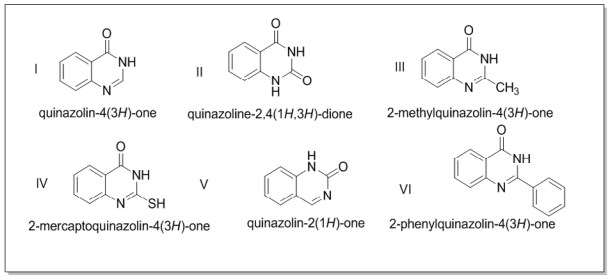
Received 12 February 2018; Accepted 5 April 2018

Abstract: Heterocyclic compounds possess diverse biological properties that have leads to intense study and research of these compounds. One of these compounds is Quinazolinone which has been found to exhibit various pharmacological activities. Quinazolinone having heterocyclic nucleus is a novel molecule which attract the chemist to search a new therapeutic molecule. The present review article covers several different Quinazolinone and their derivatives with various biological activities.

Keywords:

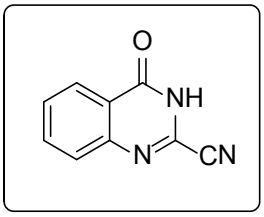
1.1 Introduction:

Organic cyclic compounds having one atom other than carbon in their ring formation are designated as "heterocyclic compounds". Now a day various heterocyclic compounds containing nitrogen, sulphur, oxygen and other hetero atoms are known. The organic compounds having heterocycle nucleus in central position perform biological activities in several agrochemical and pharmaceutical areas. Moreover heterocyclic compounds containing nitrogen atom are play a very important role in medicinal chemistry. Quinazoline as well as Quinazolinone are two nitrogen containing heterocyclic compounds,formed by fusion of benzene ring with pyrimidine and pyrimidinone moiety respectively. Quinazolinone motif can be classified into following six sub categories on the basis of position of the oxygen and the hydrogen of the nitrogen (NH) atom.



Among above six quinazolinone moieties, the quinazolin-4(3*H*)-ones are predominant either as intermediates of various synthetic drugs or as natural products in several proposed biosynthetic pathways. Both synthetic and naturally occurring organic compounds, having quinazolinone core exhibit diverse biological activities such as antimicrobial [1], anti-inflammatory [2], antitumor [3], anticonvulsant [4], anti-tubercular [5], anti-diabetic [6], anticancer [7], antimalarial [8], antihypertensive [9], antagonistic [10], diuretic [11], cellular phosphorylation inhibition [12] and kinase inhibitory activities [13].The quinazolin-(3*H*)-one unit mostly synthesized from anthranilic acid, various esters, isatoic anhydride, anthranilamide and anthranilonitrile however quinazolin-2(*H*)-one is a product of anthranilonitrile.

Several heterocyclic compounds containing quinazolinone nucleus have been isolated from various plant, animals and microorganisms. The first quinazolinone compound was synthesized in the late 1860s from anthranilic acid and cyanogen to give 2-cyanoquinazolinone[14].



2-cyanoquinazolin-4(*3H*)-one

About 200 naturally occurring quinazolinones alkaloids are known in present time [15]. Recently the interest behind the synthesis of quinazolinone derivatives is increasing among the biologist as well as chemist due to their excellent pharmacological activity and easy availability in nature.

Besides going deep inside the synthetic methodology for the synthesis of quinazolinone and its derivatives, here we effort to summarized the biological significance of quinazolinone and its derivatives. The review has been divided into three parts

(I) Quinazolinone based drug molecule in market

(II) Quinazolinone based molecule under clinical trial

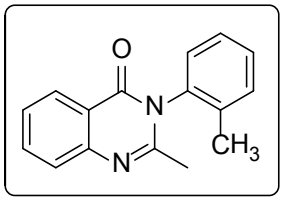
(III) Quinazolinone based biologically active molecules for different diseases discovered in last 10 years:

1.2 Quinazolinone based drug molecule in market:

Quinazolinone skeleton is a very well-known therapeutic agent, therefore a large number of quinazolinone based compounds have been synthesized and evaluated for broad spectrum of pharmacological activities. In present time, the rapid development shows that a large number of quinazolinone derivatives have been patented and available in the market which have diverse potential for several types of diseases. Some marketed drugs are summarized in this section.

1.2.1 Methaqualone:

It was first synthesized in 1951 and named as 2-methyl-3-(2-methylphenyl) quinazolin-4-(*3H*)-one**(1).** Methaqualone is a very popular drug, it possess both central and peripheral muscles relaxant activity and also exhibits sedative–hypnotic effects [16].

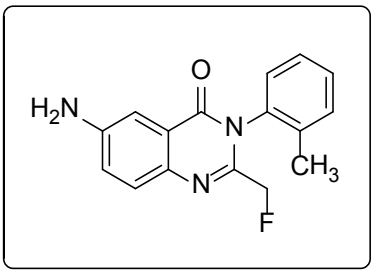


(1)

1.2.2 Afloqualone:

Itisamino&fluoroanalogueofMethaqualoneand

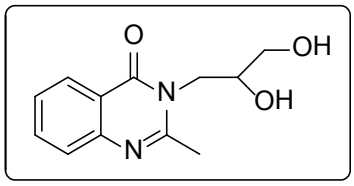
chemically named as 6-amino- 2-(fluoromethyl) - 3-(2-methylphenyl) quinazolin- 4(*3H*)-one **(2)**. It was developed first time in Japan in 1980. It also has sedative and muscle relaxant effects. It causes skin problems such as dermatitis through photosensitization [17, 18].



(2)

1.2.3 Diproqualone:

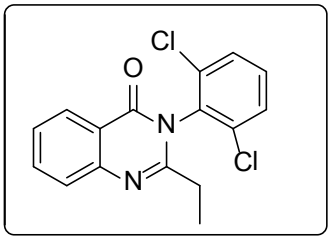
It is analogue of Methaqualone and chemically named as 3-(2,3-dihydroxypropyl)-2-methyl-quinazolin-4(*3H*)-one**(3)**. It was marketed first time in France and European countries. It is used for the treatment of osteoarthritis, rheumatoid arthritis, insomnia and neuralgia. This drug also iolytic, antihistamine and analgesic properties. It is not sold in the form of pure drug butonly as a camphosulfonate salt in combination mixture with other medicines such as ethenzamide[19].



(3)

1.2.4 Cloroqualone:

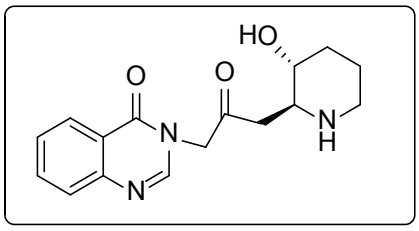
Cloroqualone is an analogue of Methaqualone developed in 1980 and chemically named as 3-(2,6-Dichlorophenyl)-2-ethyl-4-quinazolinone**(4)**. It has weaker sedative effect than Methaqualone. It was first time marketed in France and some European countries.It was sold either alone or in combination with other ingredients as a cough medicine. It has cough supressing effect [20-21].



(4)

1.2.5 Febrifugine:

Febrifugine alkaloid was extracted from leaves of *Dichroa febrifuga* in 1948 and it is also found in the garden plant Hydrangea. Its skeletal structure was reported after two years and chemically named as 3-[3-((2S, 3R)-3-Hydroxypiperidin-2-yl)-2-oxo propyl] quinazolin-4(*3H*)-one**(5)**. It has diverse effect on antimalarial activity [22].

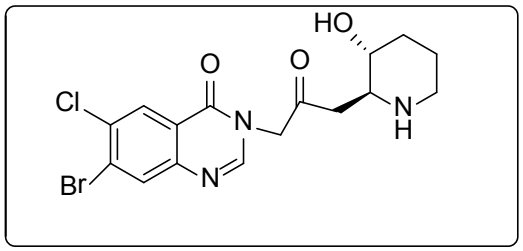


(5)

1.2.6 Halofuginone:

This alkaloid is synthetic halogen derivative of Febrifugine and isolated from Chinese herb *Dichroa febrifuga*. Its chemical name is 7-bromo-6chloro-3-[3-((2S,3R)-3-hydroxypiperidin-2-yl)-2-oxopropyl] quinazolin-4(*3H*)-one **(6)**. Halofuginone is used as a coccidiostat in veterinary medicine as well as in treatment of scleroderma. It plays significant role in inhibition of T helper 17 cells,immune cells and other autoimmune diseasebut it does

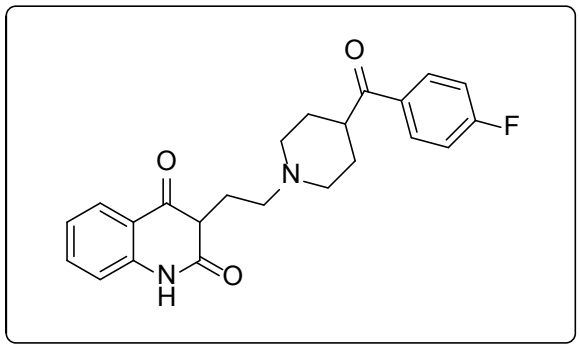
not affect other kinds of T cells which are involved in normal immune function. It exhibits diverse effect for the treatment of autoimmune disorders [23-24].



(6)

1.2.7 Ketanserin:

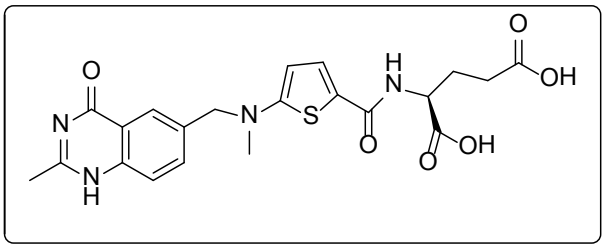
Ketanserin is chemically known as 3-[2-(4-(4-fluorobenzoyl) piperidin-1-yl) ethyl]-*1H*-quinazoline-2,4-dione **(7)**. It is used in treatment of chronic vascular hypertension and have significant role in blocking of actions of serotonin, therefore it is called as serotonin receptor antagonists. It is also responsible for inhibition of platelets accumulation [25].



(7)

1.2.8 Raltitrexed:

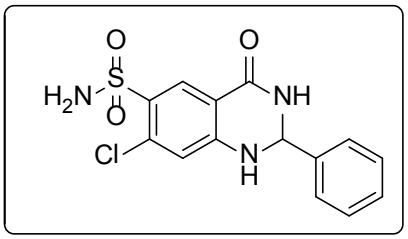
Its brand name is Tomudex and chemically called as *N*-[(5-(methyl [(2-methyl-4-oxo-1, 4-dihydroquinazolin-6-yl) methyl]amino)-2-thienyl) carbonyl]-L-glutamic acid**(8)**. It is chemically similar to folic acid; hence its drug name is folate antimetabolites. In 1998, Raltitrexed is used in treatment of colorectal cancer and manufactured by AstraZeneca. It is used in prevention of synthesis of thymidylate synthase as well as dihydrofolate reductase enzyme. It prevents formation of DNA and RNA by preventing the production of pyrimidine nucleotides which are required for the growth and survival of both normal cells and cancer cells [26-27].



(8)

1.2.9 Fenquizone:

The brand name and chemical name of Fenquizone are Idrolone and 7-chloro-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline-6-sulfonamide**(9)** respectively. Its structure is similar to thiazides and thiazides like diuretics sulphonamides.It is used in the treatment of oedema and hypertension [28].

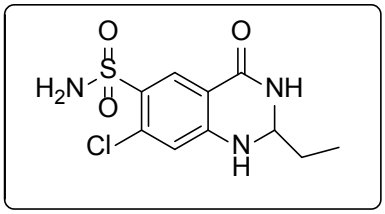


(9)

1.2.10 Quinethazone:

Quinethazone is a recently introduced oral diuretic agent in which a cyclic carbamyl group has replaced the cyclic sulphamyl group present in the thiazides. Its brand name is Hydromox chemically known as 7-chloro-2-

ethyl-4-oxo-1,2,3,4- tetrahydroquinazoline-6-sulfonamide**(10)**. It is used in treatment ofhypertension. Its adverse effects contain dizziness, dry mouth, nausea, and low potassium level [29].



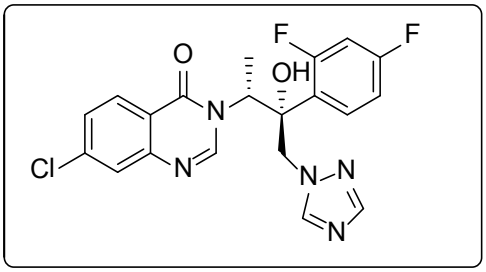
(10)

1.3 Quinazolinone based molecule under clinical trial:

In present time several quinazolinone derivatives are under clinical trials, which are summarized below.

1.3.1 Albaconazole

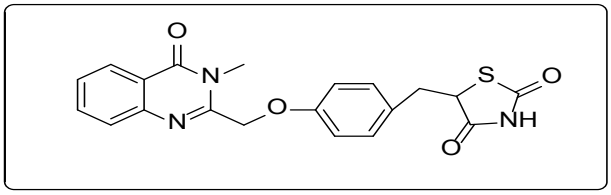
Albaconazole in phase 2 clinical trial, exhibited good pharmacokinetic properties and excellent tolerability and chemically named as 7-chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1H,1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4(*3H*)-one**(11)**. In this compound triazole moiety has diverse effects for fungal diseases and whole molecule has greater potential for broad spectrum antibacterial activity [30-31].



(11)

1.3.2 Balaglitazone:

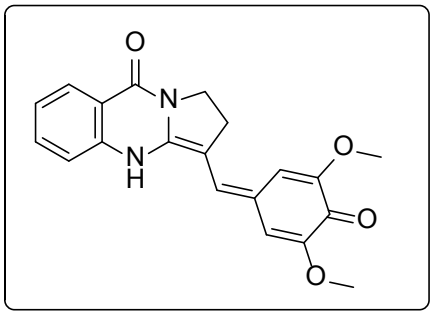
It is chemically known as 5-[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl) methoxy] phenyl]methyl]-2,4-thiazolidinedione**(12)**. It is approved for type 2 diabetes, antagonists for peroxisome Proliferator–Activator Receptor γ(PPARγ) and plays significant role in maintenance of glucose level in blood through insulin sensitization activity. Whereas, it's adverse effects such as oedemas, infarctions, and increased fracture rates, limit its applicability [32].



(12)

1.3.3 Isaindigotone:

Isaindigotone is a naturally occurring alkaloid which is commonly used in traditional Chinese medicine. It is chemically known as3-[(3,5-dimethoxy-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]-2,4-dihydro-*1H*-pyrrolo[2,1b] quinazolin-9-one**(13)**. Isaindigotone is used as an inhibitor of cholinesterase's (ChEs) and self-induced b-amyloid (Ab) aggregation [33-34].

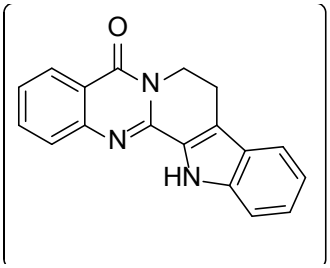


(13)

1.3.4 Nolatrexed:

Nolatrexed drug is under clinical trial and chemically known as 2-Amino-6-methyl-5-(4-pyridylthio)-*1H*-quinazolin-4-one**(14)**. It is

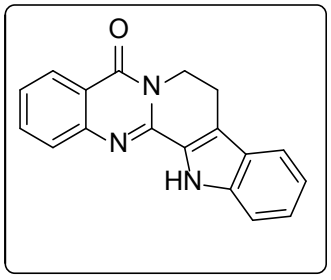
a lipophilic inhibitor of thymidylate synthase enzymeand responsible for removal of the problems produce through classical antifolates [35-36].



(14)

1.3.5 Rutaecarpine:

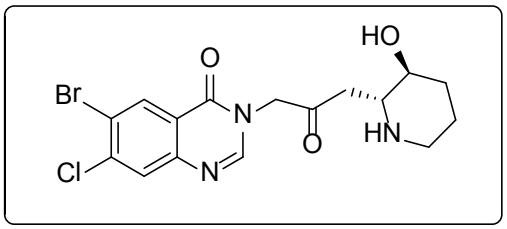
Rutaecarpine is an indolopyridoquinazolinone alkaloid that has been isolated from fruit of various plants and trees of the Rutaceae family, such as Evodia ruraecarpa and chemically known as 8,13-Dihydroindolo[2',3':3,4] pyrido[2,1-b]quinazolin-5(*7H*)-one**(15)**. This drug is under clinical trial and used for treatment of gastrointestinal disorders, headache, dysentery and inflammation related disorders. It also has cytotoxic, anti-platelet aggregation, vasorelaxation, and anti-anoxic activities [37-38].



(15)

1.3.6 Tempostatin:

Tempostatin is chemically known as 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidyl]-2-oxopropyl]quinazolin-4-one**(16)**. Tempostatin plays vital role in inhibition of cancer cells growth by preventing the production of new blood vessels [39].



(16)

1.4 Quinazolinone based biologically active molecules in different diseases discovered in last 10 years:

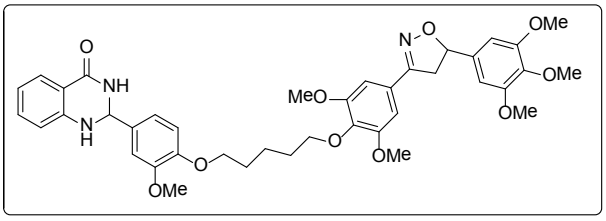
Several diseases that exist in present time among human mass are the result of advancement in life- style, indicates about an urgent need of development of new drug. Quinazolinone moiety is a part of various bioactive natural as well as synthetic compounds and plays a vital role in medicinal chemistry. In last decade, the development of the structural design of these compounds for selective and potent pharmacological activities remains highly desirable. In this section, we have discussed the new quinazolinone containing biologically active compoundsdeveloped in last 10 years, in different diseases.

1.4.1 Anticancer activity:

Cancer one of the serious health problemsin front of humanpopulation both in developed as well as developing countries.Cancer is a term used for diseases in which abnormal cells divide without any control and may attack other tissues also. Cancer is a devastating diseaseand it can spread to other parts of the body through the blood and lymph systems. In present scenario numbers of people suffering from cancer are increasing day by day and necessitatethe need of good protection from cancer with reducedadverse effects. [40] A large number of chemotherapeutic molecules have been developed in last few years which are used for the treatment of cancer that includes DNA-alkylating agents and antimitotic

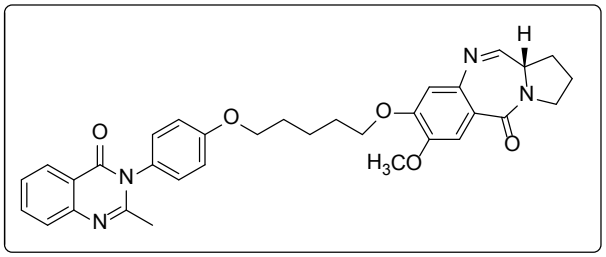
agents. Quinazolinones are among the most beneficial heterocyclic compound from both synthetic and medicinal chemistryaspects. Most of the researchers involved in synthesis ofquinazolinone and evaluation of its anticancer property. The structural designs of new hybrid quinazolinones moiety have attracted a great deal of attention because of their diverse chemical reactivity and excellent anticancer activities [41-46].

Kamal and co-workers [47]have designed and synthesized a series of novel hybrid quinazolinone derivatives **(1),**exhibited significantanticancer activity against 18 human cancer cell lines with GI_{50}values less than 1 μM.



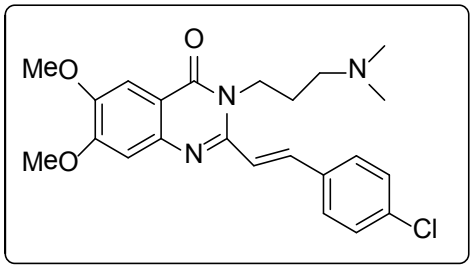
(1)

Kamal *et al*[48]have also synthesized new hybrid quinazolinone derivative **(2)**.Itwas tested against a panel of 60 human cancer cells in the National Cancer Institute, Bethesda. It possess significant activity against cancer cell lines with GI_{50} values of <0.1 1 μM.



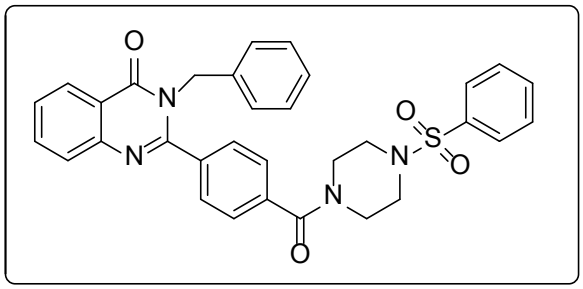
(2)

Zhang and his co-workers [49] have developed derivatives of quinazolinone **(3)**,which exhibited selective and exclusiveinhibition activity in p53 mutant cancer cell lines with IC_{50} value 6.96 ± 0.36against HepG2 but low toxicity to wild-type p53 cancer cell A375 and normal lung fibroblast WI-38 cells.



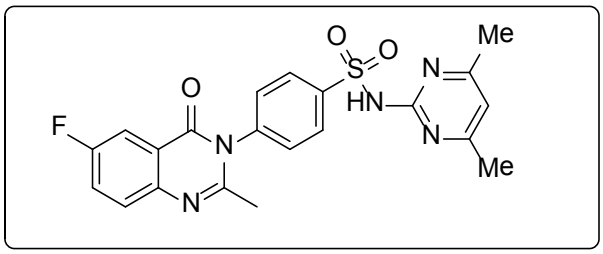
(3)

Rhee and his co-workers [50] have synthesized a novel quinazolinone derivative **(4)** has been evaluated its cytotoxic activities against five human tumor cell lines. This compound exhibit excellentactivity with IC_{50} value 2.9 ± 0.01, 8.6 ± 0.1, 2.5± 0.1, 4.2 ± 0.4, 2.6 ± 0.8μMagainst HeLa, HCT29, DU145, MDA-MB231, HL-60 cell lines respectively.



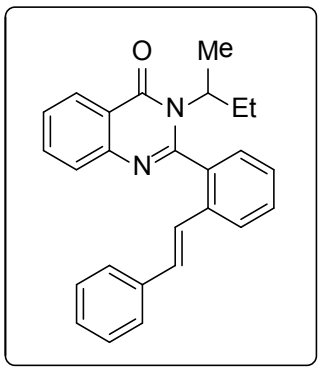
(4)

Zayed and his co-workers [51]have synthesized novel hybrid fluorinated quinazolinone sulphonamide **(5)**. The newly synthesized compound (5) was tested foritsanticancer activity against three cell line lung cancer cells, breast cancer cells and normal kidney cell] by using MTT assay and found to exhibit good anticancer activity with an IC_{50} value of 2.51 μM on the NCI cell line. The reference compound (methotrexate) however exhibited an IC_{50} value of 2.4 μM.



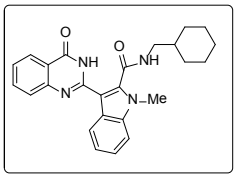
(5)

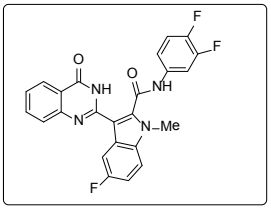
Shafiee and his co-workers [52] have prepared a new quinazolinone derivative **(6)** and it was tested against human breast cancer cell lines including human breast adenocarcinoma (MCF-7 andMDA-MB-231) and human ductal breast epithelial tumor (T-47D). The compound (6) contains sec-butyl group, show the excellent activity profile (IC_{50}< 5 μM) against all cell lines, being 2-fold more potent than the standard drug, etoposide.



(6)

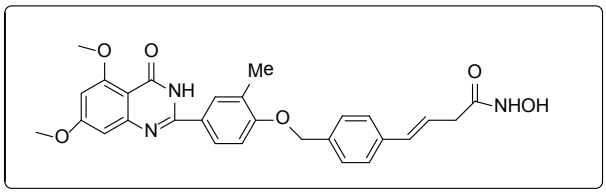
Dalimba *et al* [53] have prepared a new hybrid indole-quinazolinone compounds **(7)** and **(8)** with active amide group. The synthesized molecules have been analysed for their antiproliferative activity against two human cancer cell lines and **(7)** and **(8)** show best anti-cancer activity with IC_{50}39.6 ± 4.1, 42.4 ± 2.8 μM against MCF-7 and 17.8 ± 0.6, 15.8 ± 0.6μM against HepG2 cell lines respectively.





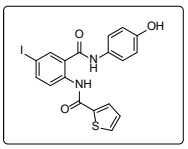
(7) **(8)**

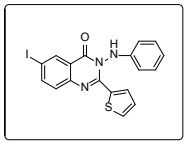
Chen and his co-workers [54] have reported new hybrid quinazolinone derivatives **(9)**. This synthesized compound exhibit *in vitro* antiproliferative activity when treated against human acute myelogeneous leukemia (AML). It was found that it reduces the expression of Myc by Western blot analysis. These results show that compound **(9)**is a mostpotent with an IC_{50} value of 5.09 μM against proliferation of A549 cells.

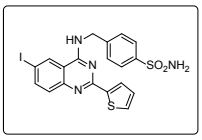


(9)

El-Subbagh*et al*[55] have prepared a new derivatives of 2-thieno-4(*3H*)-quinazolinone and evaluated its biological activity. The compound **(10), (11)** and **(12)** are antitumor agents with GI_{50} values of 12.7, 10.3, 16.9 μM, respectively. These threequinazolinone analogs **(10), (11)** and **(12)** could be considered as useful templates for future development to obtain more potent antitumor agents.





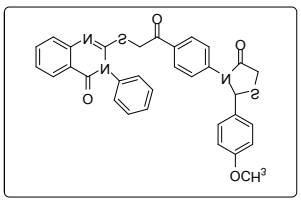


(10) **(11)** **(12)**

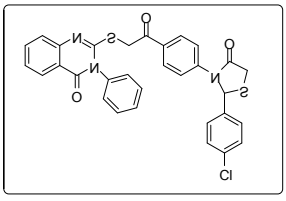
1.4.2 Antibacterial activity:

The development of constant growth of bacterial resistance against the traditional antibiotics such as penicillin and tetracycline has motivated a continuing search for new classes of heterocyclic compounds with novel modes of anti-bacterial activity. One of the most frequently known heterocyclic molecules in medicinal chemistry is 4(*3H*)-quinazolinone with wide applications including antibacterial and anti-insecticidal activities. The literature survey revealed that antimicrobial activities of quinazolinone motifs increase by substituting different heterocyclic ring at the third position. The quinazolinone nucleus containing compounds have a broad spectrum of *in-vitro* and their *in-vivo* chemotherapeutic activity [56-59].

Dave e*t al*[60] have synthesized some new quinazolinone nucleus containing compounds. The antibacterial activities of all synthesized compounds have beenevaluated against gram-positive bacteria(*Bacillus subtilis* and *Staphylococcus aureus*) and gram-negative bacteria (*E. coli* and *Klebsiella promioe*) at a concentration of 50µg/mL by agar cup plate method. A tetracycline is used as a standard compound for comparison. The compound **(13)** and **(14)**were found more toxic than tetracycline for microbes however other compounds are less toxic than tetracycline.

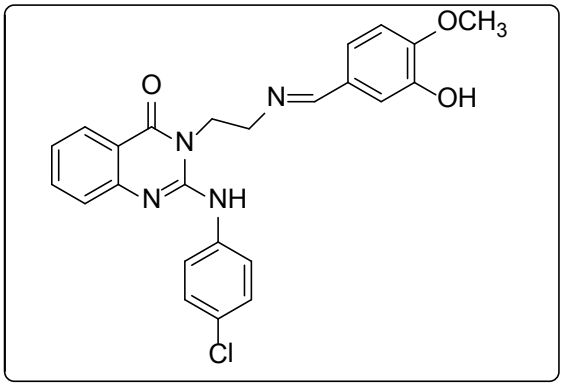


(13)



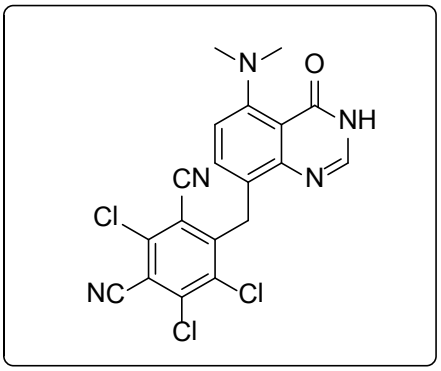
(14)

Song and his co-workers [61] were able to conveniently develop a new quinazolinone nucleus containing compound **(15)**. The biological activity of synthesized compoundwas preliminary evaluated in vitro and it was show good antibacterial activities against tobacco and tomato bacterial wilts compared with the commercial plant bactericide thiodiazole copper with EC_{50} value 49.26$^{\mu g/ml}$.



(15)

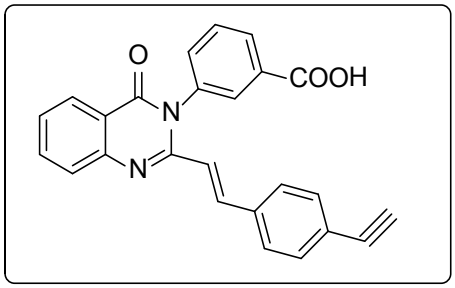
Lin and his co-workers [62] have designed and synthesized new quinazolinone nucleus containing compound and evaluated its antimicrobial activities against four strains of gram-positive bacteria(*Staphylococcus aureus*and *Bacillus cereus*)and gram-negative bacteria(*Escherichia coli* and *Pseudomonas aeruginosa*). The synthesized compound **(16)** exhibited significant activity towards Gram-positive bacterial, Gram-negative bacterial. The MIC (0.8–3.3lg/mL) and MBC (2.6–7.8lg/mL) value for this compound are very nearest to those of norfloxacin, chlorothalonil, and fluconazole which indicate that the compound **(16)** is stronger antimicrobial agent.



(16)

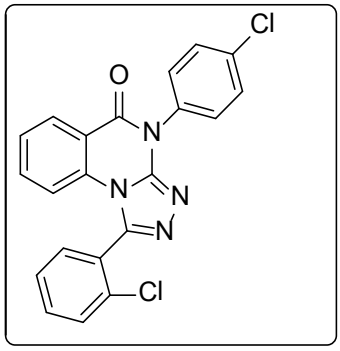
Bouley*et al* [63] were able to develope

a new hybrid quinazolinone derivatives **(17)** and evaluate their biological activity whichexhibit exquisite antibacterial activity (MIC =0.03 µg/mL) and may have favourable pharmacodynamics.



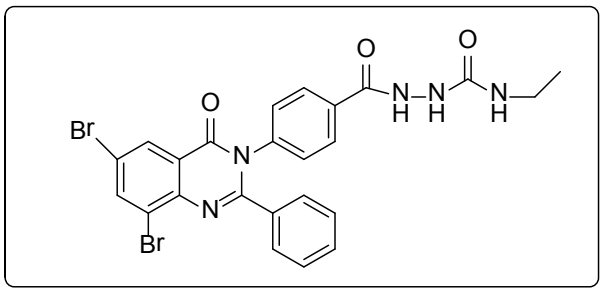
(17)

Nizamuddin and his co-workers [64]were able to develope novel quinazolin-(3H)-one with triazole nucleus derivatives **(18)** and evaluated its activity against both Gram positive (*B. subtilis*) and Gram-negative (*E. coli*, *P. aeruginosa*). The MIC value 1.56 μg/mL obtained was compared with standard compound ciprofloxacin that means the compound (18) is morepotent than standard drug against *S. pneumonia*.



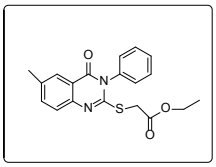
(18)

Ahmed*et al* [65] were able to conveniently prepare new quinazolinone derivatives and screened them for antibacterial activity, tested against Gram-positive bacteria (*Staphylococcus aureus*, *Legionella monocytogenes* and *Bacilluscereus*) and Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*), using paper discdiffusion technique. The synthesized compound **(19)** was found to exhibit themostpotent *in vitro* anti-microbial activity with the MICsof1.56, 3.125,1.56,25,25and25 μg/m Lagainst *E. coli, S. typhimurium, L. monocytogenes, S. aureus, P. aeruginosa,* and *B. cereus* respectively.

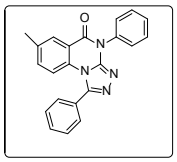


(19)

Alanazi*et al* [66] have reported a series of new quinazolinone nucleus containing compounds**(20)**, **(21)** and **(22).**The antimicrobial screening of these compounds revealed that compounds **(20), (21)** and **(22)** are the most active against *Staphylococcus aureus* ATCC 29213 with minimum inhibitory concentration (MIC) of 16, 32 and 32 μg/mL respectively, However compound **(22)** possessed antimicrobial activities against all tested strains with the lowest MIC compared with other tested compounds.



(20)



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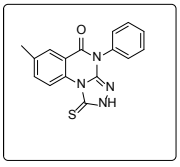


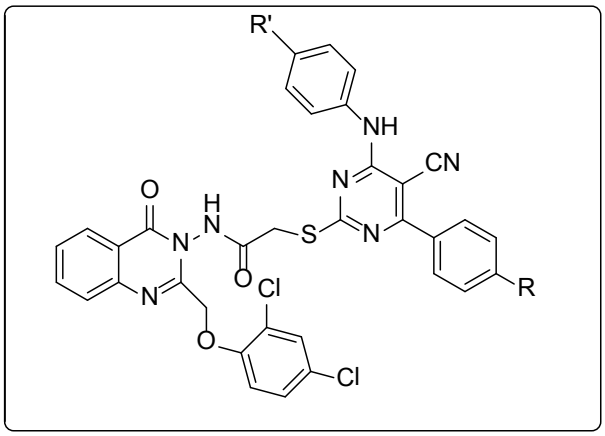
(22)

1.4.3 Anti-inflammatory activity:

The inflammation is a biological response to a series of biochemical reactions whose majorfunction is protection of the body from infection and resolution of tissue damage caused byinjury.It reflects the response of the organism

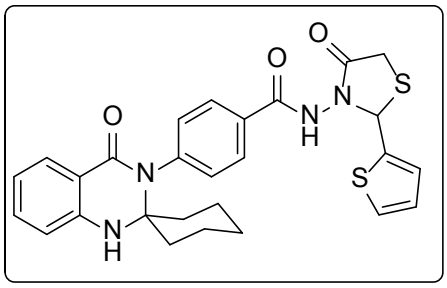
to various stimuli and is related to many disorders such as arthritis, asthma and psoriasis which require prolonged or repeated treatment. [67-68] However the non-steroidal anti-inflammatory drugs (NSAIDs) havingvarious adverse effects such as gastrointestinal mucosal damage, bleeding, intolerance and renal toxicity.A growing interest and discovery of new, selective and promising inhibitors with an improved security and efficacy profile has motivated the researcher & scientific community towards design and development of new anti-inflammatory and anti-allergic agents, based upon quinazolinone nucleus [69].

Awadallah and his co-workers [70]have synthesized a series of hybrid quinazolinone-pyrimidines derivatives **(23), (24), (25)** and **(26)**. The derivatives of pyrimidinyl quinazolinone wereevaluated using the carrageenan-induced rat paw oedema model for their anti-inflammatory activity. The synthesized compounds exhibited most anti-inflammatory activity because it has an anilino group in position 4.



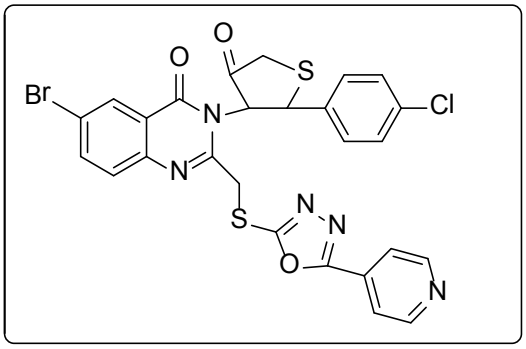
(23)R= Cl; R'= OH
(24)R= OH; R'= H
(25)R= OH; R'= Cl
(26)R= O H; R'= OH

Amin*et al* [71] have synthesized a new quinazolinone derivative **(27)**. The inflammatory activity of synthesized compound have been evaluated and compared with indomethacin and tramadol reference drugs. After result discussion, the compound **(27)** was found to be most potent towards inflammation and it shown excellent activity with value 56.2 ± 9.9 ml which nearest to indomethacin drugs.



(27)

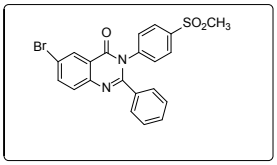
Kumar*et al* [72] have prepared new anti-inflammatory agent based upon the quinazolinone nucleus. The biological activity of synthesized compound **(28)** has been evaluated and it is found to exhibit 36.3 inhibition of oedema. This compound show equal anti-inflammatory activity like standard drug phenyl butazone at the dose of 25, 50 and 100 mg/kg p.o.



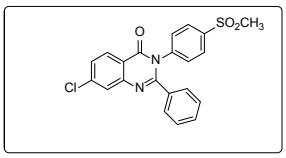
(28)

Manivannan and his co-workers [73] were able to design and synthesize new quinazolinone derivatives **(29), (30), (31)** and **(32).** The synthesized compounds were evaluated for cyclooxygenase inhibitions by ovine COX assay and carrageenan-induced rat paw oedema assay. The compounds **(29), (30), (31)** and

(32) having methyl sulfonyl group possess potent anti-inflammatory activity with 49±1.16, 45±0.82, 46±1.36 and 54±1.83 percentage oedema inhibition by using indomethacin as standard drug in 4 hrs.



(29)



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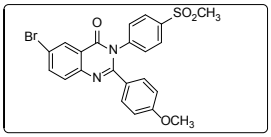

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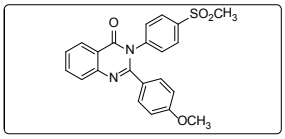
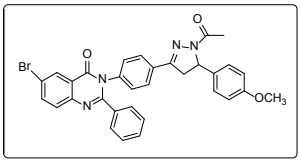


(32)

Mohammed and his co-workers [74] have also reported two series of 2-phenyl-4(*3H*) quinazolinone derivatives**(33)** and **(34)**. The biological activities of all synthesized compounds were evaluated through carrageenan-induced rat paw edema assay. Among the all molecules some of the compounds **(33)** and **(34)**show considerable potent anti-inflammatory activity in experimental rats with 46±1.26, 43±1.82 percentage oedema assay in comparing to indomethacin as reference drug in 3hrs.



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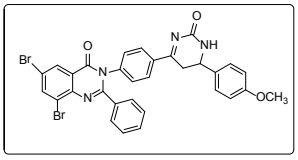
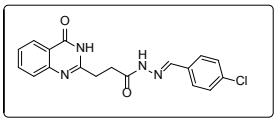


(34)

Gowda*et al* [75] have synthesized a series of quinazolinone derived Schiff base derivatives and evaluated for anti-inflammatory agents in vitro. Author found the excellent anti-inflammatory activity for synthesized compounds **(35), (36), (37)** and **(38)**.



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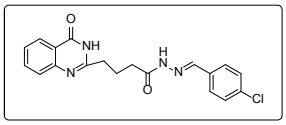

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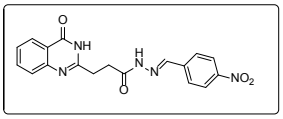

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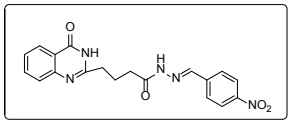
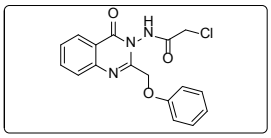


(38)

Georgey*et al* [76] have reported newly synthesized quinazolinone derivatives **(39)** and **(40)**. The anti-inflammatory activities of synthesized compounds were evaluated using ibuprofen as standard drug and applying the method of carrageenan rat paw oedema. The compound **(39)** show moderate anti-inflammatory activity (66.7% protection) however compound **(40)** is found to have slight increase in activity (79.84% protection) than the reference drug (75.13% protection).The anti-inflammatory activity of **(39)** &**(40)**increased by the insertion of anti-inflammatorydrugs (naproxen, ibuprofen, diclofenac)through an ester link to form several compoundswhere thepercentage inhibition of oedema is ranging from (67-94.5%).



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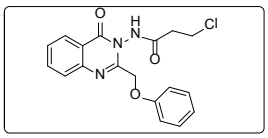


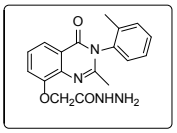
(40)

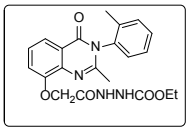
1.4.4 Anticonvulsant activity:

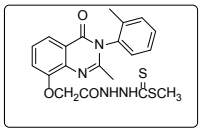
Epilepsy is a chronic neurological disorders characterized by neuronal hyperexcitability and neuronal firing.An international campaign against epilepsyconducted by World Health Organization (WHO) in partnershipwith International Bureau for Epilepsy (IBE) and

International League against Epilepsy (ILAE) recommends that around 1% of worldpopulation at any time is suffering with this neurological disorder [77]. A large number of anticonvulsants are used for the treatment of this type of disorder known as antiepileptic drugs. In current time many newer drugs (such as pregabalin, stiripentol, zonisamide,tiagabine, lamotrigine, levetiracetam, topiramatephenobarbital, phenytoin, carbamazepine and valproic acid) are used for the treatment of this disorder [78]. About 70% of people with epilepsy attain some improvement, with satisfactory seizure control, by the available antiepileptic drugs. However their therapeutic efficacy is overcome bysome undesirable side effects such as headache, nausea,hepatotoxicity, anorexia, ataxia, drowsiness, gastrointestinaldisturbances, and hirsutism [79]. That is why; it has becomevery necessary to search for new chemical moiety for the treatment of epilepsy with less toxicity and fewer side-effects. In quinazolinone moiety the presence of aromatic or aliphatic group at position 2 and a substituted aromatic ring at position 3 are essentialrequirements for anticonvulsant as well as CNS activities. Furthermore, these drugs reduce the above mentioned side-effects carried by the conventional treatment.

El-Azab and his co-workers [80] have synthesized a series of new 2,3,8-trisubstituted-4(*3H*)-quinazolinone derivatives and evaluated them for their anticonvulsant activity in mice. The results of this study demonstrated that compounds**(41), (42)** and **(43)** exhibitbest anticonvulsant activitywith relatively low neurotoxicity and low toxicity in the median lethal dose test as compared with the reference drugs. The **(41), (42)** and **(43)** have ED_{50}, (98, 160 and 150 mg/kg) TD_{50} (267, 246 and 287 mg/kg) and LD_{50}1000, (418, 501 mg/kg)respectively against valproate and Methaqualone.

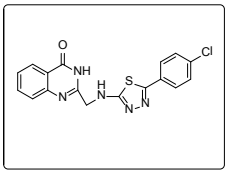


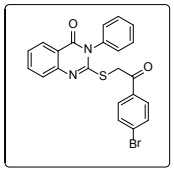


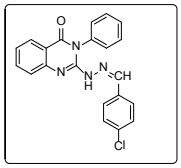


(41) **(42)** **(43)**

Georgey*et al* [81] have reported a number of 2-substituted and 2, 3-disubstituted quinazolinone analogues. The anticonvulsant activity of synthesized compounds were evaluated and compared to diazepam and phenobarbital standards.The result suggested that the compounds **(44), (45)** and **(46)** have good anticonvulsant activity and low neural toxicity.

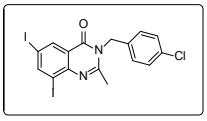


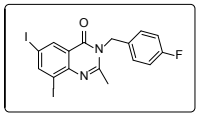


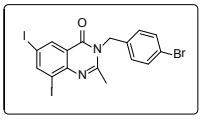


(44) **(45)** **(46)**

Zayed and his co-workers [82] were able to conveniently develope a series of 6,8-diiodo-2-methyl-3-substituted-quinazolin-4(*3H*)-ones derivatives. The anticonvulsant activities of novel synthesized compounds were evaluated by the maximal electroshock-induced seizure and subcutaneous pentylenetetrazole tests. The results suggested that compound **(47), (48)** and **(49)** have good anticonvulsant activity and much lower toxicity compared with reference drugs. The compound **(47), (48)** and **(49)** exhibit 100% PTZ protection and 100% MES protection against Methaqualone and valproate.

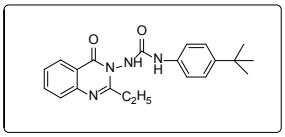






(47) **(48)** **(49)**

Kashaw*et al* [83] have reported several new derivatives of 1-(4-substituted-phenyl)-3-(4-oxo-2-phenyl/ethyl-4H-quinazolin-3-yl)-urea and screened them for their anticonvulsant activity. The effect of compound **(50)** and **(51)** have shown good anticonvulsant activity at 100 mg/kg body weight however other compound show activity at 300 mg/kg body weight.



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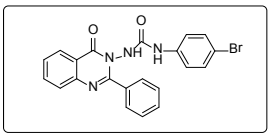
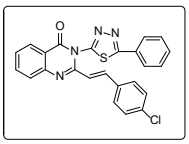


(51)

Jatav and his co-workers [84] have prepared a series of novel 3-[5-substituted phenyl-1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(*3H*)-ones derivatives. The anticonvulsant activity of synthesized compounds were evaluated using maximal electroshock (MES) induced seizures and subcutaneous pentylenetetrazole (scPTZ) induced seizure models in mice. The compound **(52), (53)** and **(54)** have shown anticonvulsant activity in one or more test models. The **(52)** and **(53)** showed anticonvulsant activity at 0.5 and 4 h in both testModels (MES and scPTZ screen), whereas **(54)** showed anticonvulsant activity at 4 h in MES screen and at 0.5 and 4 h in scPTZ screen. Three compounds namely **(52), (53)** and **(54)**exhibited anticonvulsant activity in scPTZ screen at both 0.5 and 4 h.



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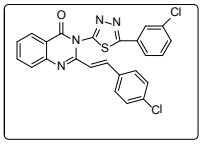

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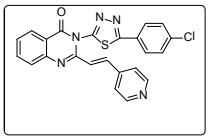


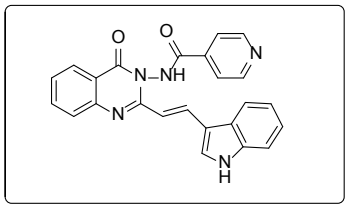
(54)

1.4.5 Antitubercular activity:

Tuberculosis (TB) is a major and challenging health problem world-wide. It is a chronic infectious disease caused by *Mycobacterium tuberculosis* but other species *Mycobacterium bovis* and *Mycobacterium africanum* responsible for disease condition. The current survey revealed that TB has re-emerged as one of the leading causes of death across the world (nearly 3 million deaths annually) [85]. It is mostly asymptomatic and becomes serious when impairment of immunity arises due to conditions like malnutrition, diabetes, malignancy and AIDS. In last few decades, incidence of TB continued to rise year by year in despite of availability of several drug molecules [86].

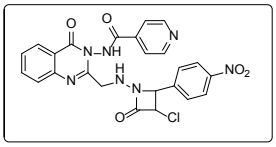
When the emergence of multidrug-resistant (MDR-TB) and the extremely-drug resistant (XDR-TB) get together, it will predictably become even tougher to treat TB in the near future. In last few years, the World Health Organization confirmed Tuberculosis "a global healthemergency". Inpresenttime,therearesome clinical drugs such as rifampicin and isoniazid, no longer being effective against MDR and XDR TB strains of *Mycobacterium tuberculosis* [87]. It is therefore an urgentmission to discover and design novel quinazolinone derivatives as antitubercular drugs that can work ondifferent biological targets and can produce desirable changes by new inhibitorymechanisms.

Babu and his co-workers [88] were effort to design and developed a series of new 2-styrylquinazolinone derivatives. In anti-tubercular screening, compound **(55)** was found to be highly active against both H37Rv strain and MDR strain (DKU 156) with MIC values of 0.625 and 0.3125 μg/mL, respectively.



(55)

Myangar *et al* [89] have reported a series of new hybrid 2-[(4'-oxo-3'-chloro-2'-phenylazetidin-1'-ylamino)-methyl]-3-[N-isonicotinamide-yl]-quinazolin-4-one. The biological screening of these synthesized compounds indicates that the compound **(56)** and **(57)** are most potent antitubercular agent. Compound **(56)** containing 4-nitro substituent showed better activity (50 μg/ml) and compound **(57)**displayed good activity (50–62.μg/ml) which is attributed due to 4-chloro groups.



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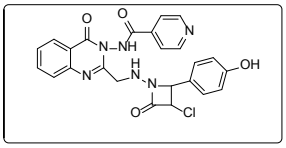
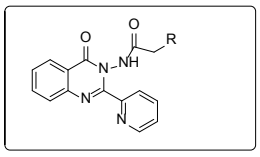


(57)

Monica kachroo and his co-workers [90] have synthesized a series of new hybrid 2-(substituted)-N-(4oxo-2-(pyridine-2-yl) quinazolin-3(*4H*)-yl acetamide **(58)** and 2-(substituted)-N-(4oxo-2-(pyridine-3-yl) quinazolin-3(*4H*)-yl acetamide**(59)** derivatives. All the synthesized compounds were screened for *in-vitro* antitubercular activity by Microplate Alamar Blue Assay (MABA) method. Almost all derivatives have shown moderate antitubercular activity (MIC at 50µg/ml**)** as compared to the standards which show activity at 3.125µg/ml.



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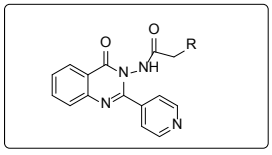

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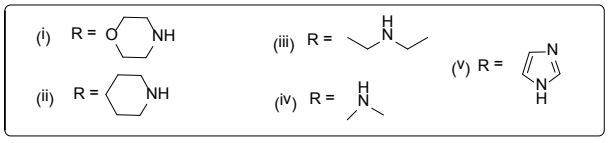
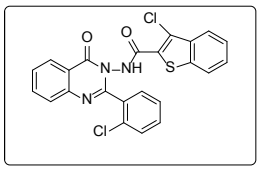


Subramaniam *et al* [91] have prepared a novel series of 3-chloro-*N*-(4-oxo-2-arylquinazolin-3(4*H*)-yl)-1-benzothiophene-2-carboxamide. The antitubercular activities of synthesized compounds are screened against *Mycobacterium tuberculosis* H_{37}Rv strain by microplate alamar blue method. The result of newly developed compound **(60)** and **(61)** are show good antitubercular activity.The antitubercular activity of the synthesized compounds revealed that the compounds **(60)** and **(61)** were active at a concentration of 50µg/ml against *Mycobacterium tuberculosis*.



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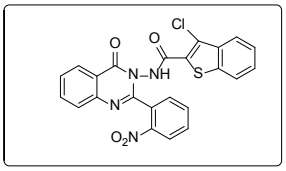
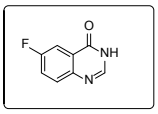
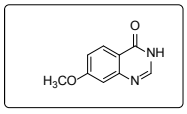
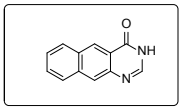


(61)

1.4.6 Antifungal activity:

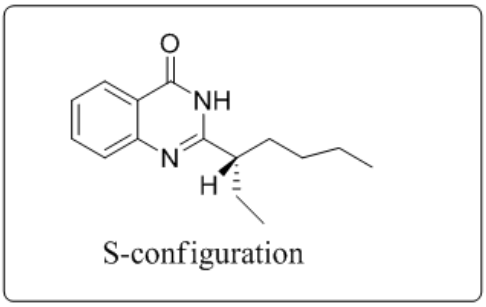
Fungi are important opportunistic pathogens of human being as well as plant kingdom. In case of humans, *Cryptococcus neoformans*, species of *Candida*and *Aspergillus* are responsible for causing both superficial and invasive infections [92-93]. On other hand, the phytopathogenic fungi play significant role incontaminating food with toxic compounds, reducing yields and lowering product quality of agriculture. Several fungi are harmful for plant such as *Fusarium oxysporumf. sp. albedinis*,*Fusarium oxysporum f. sp.canariensis* and *Verticillium dahliaeKleb* causes Bayoud disease [94-95]. Now a days different type of commercial plant fungicides, such as carbendazim, metalaxyl, isoprothiolane, triadimefon, thiabendazole, benomyl, thiophanate methyl, are beingused for controllingvarious fungal plant diseases in current agricultural system. However, many shortcomings have generated with wide use of these fungicides such as the increase of the fungal resistanceand fungicide residues, which are dangerous to mankind and animals. Hence, it has become necessary to find out new and efficacious drugs to solve these problems. Quinazolinone is a very common chemical entity

and it plays major role in medicinal chemistry. Therefore, the synthesis of quinazolinone and its derivatives produce considerable interests in the search of better antifungal agents [96-97].
Lazrek and his co-worker [98] were able to prepare a series of hybrid Quinazolin-4-(3H)-ones derivatives throughmicrowave irrradiation. *In vitro* antifungal activity of synthesized compounds were screened against tree plant fungi; *Fusarium oxysporum f. sp. albedinis, Fusarium oxysporum f. sp. canariasis* and *Verticillium dahliae Kleb*. The results demonstrated that Compounds **(62), (63)** and **(64)**displaygood antifungal activity.

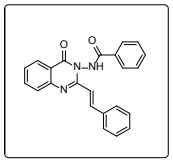
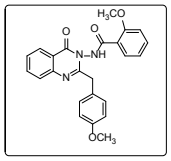
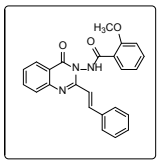
(62) **(63)** **(64)**

Xu*et al* [99] have isolated the derivatives of quinazolinone fromthe n-butyl alcohol extract of the marine-derived bacterium *Bacillus cereus* and screened their antifungal activity against *Candida albicans*. The results revealed that compound **(65)** was displays excellent antifungal activity.



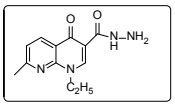
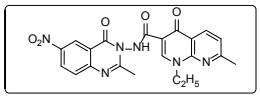
(65)

Zhang*et al* [100] have designed and synthesized a novel hybrid quinazolinone derivative and screened their antifungal activity by selecting four phytopathogenic fungi such as *P. Capsici*, *C. Gloeosporioides, V. Mali*, *A. Alternate*using minimum inhibitory concentration (MIC) method. The results demonstrated that compound **(66), (67)** and **(68)** exhibit broad spectrum of antifungal activities.

(66) **(67)** **(68)**

Grover*et al* [101] have reported a series of new nalidixic acid derivatives having quinazolinonemotif to achieve enhanced biological activity. The antifungal activities of synthesized compounds **(69)** and **(70)** were evaluated. The results revealed that compound **(69)** display high activity against *Candida colonies* as well as compound **(70)** show inhibitory activity against *Candida albicans*.

(69) **(70)**

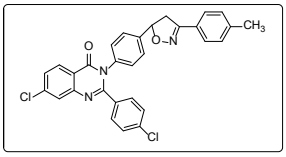
1.4.7 Anti-hypertension activity:

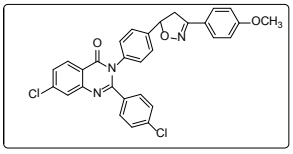
In last decade, hypertension has become one of the most life threatening health problems across the globe. Cardiac diseases cause more premature deaths than all other non-communicable and communicable diseases as it affects all vital organs of the body. Generally high blood pressure is very harmful for arterial diseases.In year 2000, WHO figured outthe total number of adults suffering from hypertension was 972 million and this may rise by about 60% to a total of 1.56 billion by 2025 [102-103].

Various derivatives of quinazolinone analogous such as Prazosin, terazosin, doxazosin, bunazosin, tiodazosin, trimazosin and alfuzosin are available in the market. These are used for the treatment of various arterial diseases. Quinazolinone derivatives are found to exhibit

diverse pharmacological activities such as antihypertensive, anti-hyperlipidemic and anti-cardiovascular etc.Under the consideration of this, an attempt has been made to explore quinazolinones as potential antihypertensive agents [104-105].

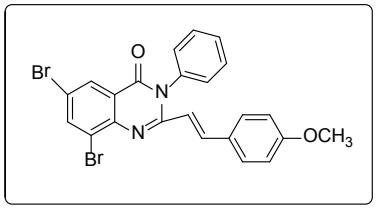
Rahman and his co-workers [106] have designed and synthesized a series of novel 7-substituted-3-(4-(3-(4-substitutedphenyl)-4,5-dihydroisoxazol-5-yl)phenyl)-2-substituted quinazolin-4(3*H*)-one derivatives. The biological activity of synthesized compounds were screened and the results demonstrated that the compound **(71)** and **(72)** exhibit potent antihypertensive activity through their anticipated $\alpha_1$adrenergic receptor blocking property, which is similar to its clinically used analogue, prazosin, without disturbing heart rate with prolonged period of action when evaluated in adrenaline induced hypertension in anaesthetized rats.





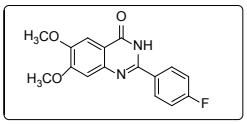
(71) **(72)**

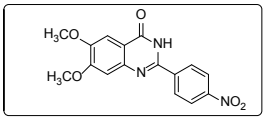
Zaranappa*et al* [107] have prepared a series of new 6,8-dibromo-3-phenyl-2-substituted quinazolin-4-(3*H*)-one derivatives. The newly synthesized compounds are screened for their antihypertensive activities. Among all compounds **(73)** was found to excellent antihypertensive activity in comparison to the standard compound.



(73)

Patel *et al*[108] have developed a new hybrid quinazolinone derivative **(74)** and **(75)** and screened their antihypertensive activity against α_1-adrenergic receptor blocking activity. The results revealed that compound **(74)** and **(75)** display better antihypertensive activity.



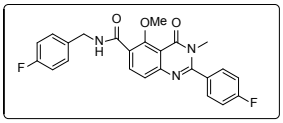


(74) **(75)**

1.4.8 Antiviral activity:

Previously, various diseases in human beings and plant were found to be caused by infection by virus. Several drugs viz. idoxuridine, trifluridine, cidofovir,saquinavir, atazanavir, lopinavir, brivudin and telbivudine are used for treatment of different viral diseases. The designing and devolvement of new quinazolinone based drug has become an area of keen interesting due to its antiviral activity against animal and plant viruses. [109-110].

Wang and his co-workers [111] were able to conveniently design and synthesized novel hybrids quinazolinone derivatives. The *in vitro* antiviral activities of newly developed compounds were evaluated. The results are demonstrated that compound **(76)** and **(77)** show good antiviral activity against HIV and TMV. Primary bioassay results indicated that most of the quinazolinones possess anti-HIV activity especially for compound 11b with 77.5% inhibition rate at 10 μM emerged as a new active lead. Most of the synthesized compounds were also found to exhibit good anti- TMV activity, of which compound 9a showed similar in vivo anti-TMV activity to commercial plant virucide Ribavirin.



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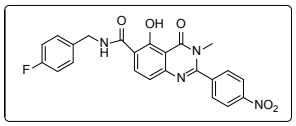
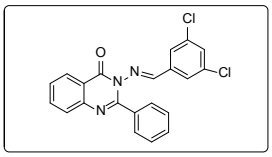


(77)

Gao*et al* [112] have reported a series of new 2-aryl- or 2-methyl-3-(substituted-benzalamino)-4(*3H*)-quinazolinone derivatives and evaluated their antiviral activities. The results found that the compounds **(78)** and **(79)** exhibits moderate good antiviral activity against TMV.



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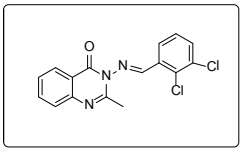
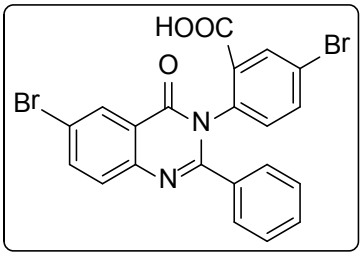


(79)

Selvam and his co-workers [113] have synthesized a series of quinazolinone derivatives. The antiviral activities of synthesized compounds were evaluated against HIV, HSV and vaccinia viruses. The compound **(80)**exhibited good antiviral activity against Herpes simplex and vaccinia viruses.

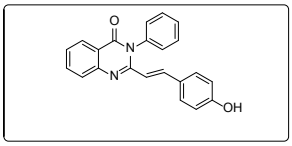


(80)

1.4.9 Antimalarial activity:

Malaria is one of the most common diseases in countries of Africa, Southeast Asia, and South America. It is a neglected parasitic diseasecaused by parasites of the genus Plasmodium spp. Female *Anopheles*mosquitoes play a very important role for the transmission of this disease through bites of animal body. *Plasmodium falciparum* and *Plasmodium vivax*are the prevalent species but the former is the most dangerous for human being. If infection of malaria cannot be prevented then it may cause death of living organisms. The drug therapy, responsible for cure and prevention of infection of malaria is available in market. Although several commercial drugs such as chloroquine and sulfadoxine–pyrimethamine are being used for treatment of malaria butvarious reports show that these parasites have developed at least partial resistance to almost every antimalarial drugs which are used in recent time. The good bioactivity and lesser side effects of quinazolinone based molecules promote the scientific community for the search of new antimalarial agents [114-117].

Birhan*et al* [118] have reported quinazolinone based series of chemical entities. The antimalarial activities of some 3-aryl-2-(substituted styryl)-4(3H)-quinazolinone derivatives were screened. All the evaluated compounds displayed significant antimalarial activities than the negative control group ($p < 0.05$). The results revealed that the compound **(81)** and **(82)** exhibit better antimalarial activities with mean percentage suppression of 72.86 and 67.60 % respectively.



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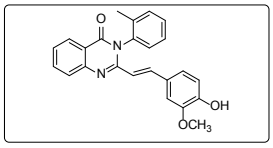


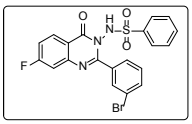
(82)

1.4.10 Anti-diabetic activity:

Diabetes is reduces the ability of body to convert glucose into energy. When we take the glucose in form of bread, rice, pasta, potatoes, corn, fruit, and milk products etc. then it transferred into blood and are used by cells for energy. The

hormone insulin is required for the transfer of glucose to cells *via* blood [119-120]. Insulin is secreted in the pancreas with the help of beta cells. When human afflicted by diabetes two types diseases are known. Type-1 diabetes in which the pancreas fails to produce sufficient quantity of insulin, however on the other hand, Type-2 diabetes in which the insulin produced is defective and cannot move glucose into the cells [121-122]. A vast number of antidiabetic agents have different mechanisms of action and variable efficacies are available in market but these drugs have many side effects. Many researchers have found that quinazolinone derivatives exhibit broad pharmacological activities and its drugs reduced the side effects. Owing this reason many biologists as well as chemists synthesized various derivatives of quinazolin-4(*3H*)-one and screened their anti-diabetic activity [123-124].

Rahman and his co-workers [125] were able to design and synthesize a series N-substituted-(4-oxo-2-substituted-phenylquinazolin-3-(*4H*)-yl), substituted benzene sulfonamide derivatives. The antidiabetic activities of synthesized compounds were evaluated by using a Glucometer-elite commercial test (Bayer), based on the Glucose oxidize method and the activity was compared with diazoxide. The compound **(83), (84), (85), (86)** and **(87)** show good antidiabetic activity.



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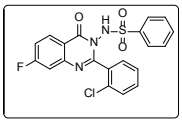
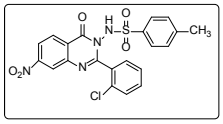
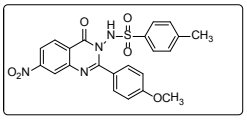


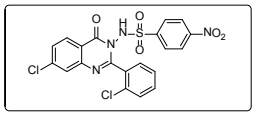
(84)



(85)



(86)



(87)

1.5 Conclusion:

The main aimof this review literature is to provide an overview of diverse pharmacological activities of quinazolinone moiety since last decade. In recent years newer quinazolinone nucleus based various compounds were designed and synthesized by biologists as well as chemists. This compounds exhibit excellent activity against pathogen and less toxicity. The curiosity of this work is to gather the literature reported by researchers on quinazolinone for its diverse pharmacological activities. At last, this review helps to find potential future directions on the growth of new potentquinazolinonesderivatives for various biological targets.

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