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REVIEW ARTICLE

Quinazoline and its diverse array of therapeutic application:A review

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ABSTRACT

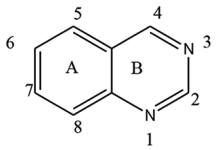
Heterocyclic chemistry being an important branch of chemistry includes many ring structures with heteroatoms such as nitrogen, oxygen, and sulfur. Quinazoline is an important nitrogen containing benzofused heterocycle and has several therapeutic actions such as antimalarial, antimicrobial, anticancer, and anticonvulsant. Quinazoline was first isolated from alkaloid vasicine. Vasicine, deoxyvasicine, tryptanthrin, and rutecarpine are some of the potent naturally occurring quinazolines. Substitutions on different positions of quinazoline ring lead to different activities. Detailed survey of activities of quinazoline such as anticancer, anticonvulsant, antifungal, antibacterial, and antidiabetic according to structure–activity relationship and marketed preparations containing quinazoline as an active moiety is described in this review.

Keywords: Anticancer, Anticonvulsant, Antifungal, Epidermal growth factor receptor, Quinazoline

INTRODUCTION

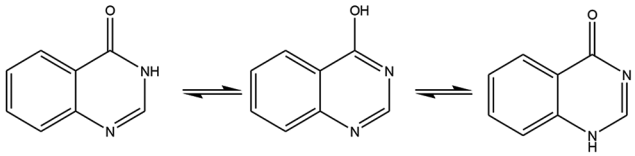
Heterocyclic chemistry is an important branch of chemistry. The majority of therapeutic agents contain one or more heterocycles. Rapid access to heterocyclic compound is possible due to advancement in synthetic processes. All heterocyclic compounds are of prime importance for medicinal chemist. All these chemical entities contribute for effective drug discovery and development process. In medicinal chemistry, fused rings such as quinoline and isoquinoline play an important role alongside heterocyclic rings such as pyrrole, pyridine, thiophene, and furan. Quinazoline is another essential fused heterocycle with a variety of therapeutic uses.[1]

Quinazoline is a benzofused ring system with two nitrogen present at 1st and 3rd position. According to IUPAC nomenclature rules, the numbering is started from nitrogen as a heteroatom.



(1).Quinazoline structure and numbering according to IUPAC nomenclature rules.

Quinazolinone is a ketonic form of quinazoline in which 4th position has carbonyl group. The resonating structure can be drawn as



(2).Resonating structures of Quinazoline

HISTORY OF DEVELOPMENT

Natural quinazolinones, which are commonly used in traditional folk medicine, are isolated from plants and microorganisms, while the main quinazolinone derivatives are obtained through a synthetic process involving a series of chemical reactions. Quinazolinones and quinazolines are

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the most valuable class of biologically active heterocyclic compounds. Quinazolinones, whether natural or synthetic, have prompted medicinal chemists to establish high selective and potent pharmacological activities due to their broad range of biological activities.

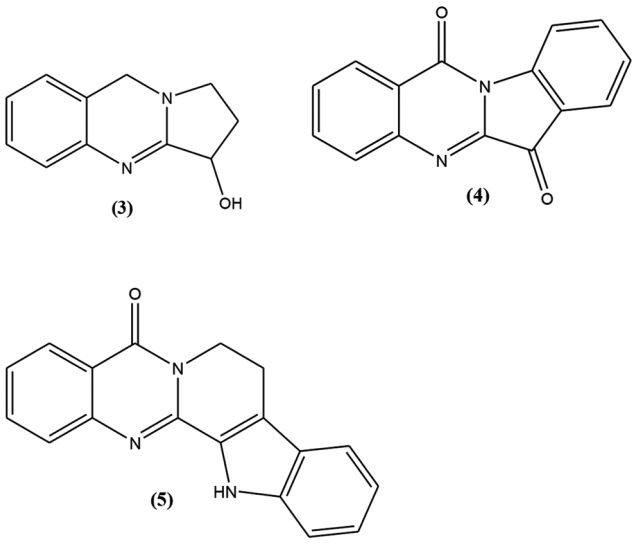
Several attempts to extract chemical constituents from plants were made during the 1980s period. Numerous heterocyclic compounds were discovered as a result of the research. In a similar fashion, quinazoline alkaloids were discovered. There are over 150 quinazoline alkaloids found in nature, which come from various biological families.[2]

Quinazoline was first isolated from natural source in the form of alkaloid. In 1988, first quinazoline alkaloid was isolated from vasicine (*Adhatoda vasica*). Vasicine **(3)** is known for its mucolytic properties. It also possesses activities such as cardiac depressant and uterine stimulant. Deoxyvasicine was identified against Alzheimer's disease. S-vasicinone, vasicine, and deoxyvasicinone were isolated from the seeds of *Peganum harmala*.[3]

Tryptanthrin**(4)** is a well-known alkaloid isolated which has insecticidal activity against larvae of the house longhorn beetle. Tryptanthrin suppresses the growth and induces neuronal differentiation in neuroblastoma cells. Alkaloid tryptanthrin was first isolated from the traditional Chinese medicine (Qingdai) in 1985. In 2013, studies tryptanthrin inhibited the growth of the neuroblastoma cells in a dose- and time-dependent manner and induced cell cycle arrest at the G0/G1 phase.[2,4]

Rutaecarpine **(5)**, another alkaloid with indole ring, was obtained from *Evodia rutaecarpa* which has numerous activities such as cardioprotective, antitumor, and anti-inflammatory. It exhibited weak cytotoxic activity against the human cells but effective against monocytic leukemia THP-1 cell line as well as protective effects toward murine liver cancer.

In 1992 and 1995, fumiquinazolines were isolated from the fungus *Aspergillus fumigatus*. They exhibited promising cytotoxic activity toward P388 murine leukemia as well as potent topo-II inhibition. Fumiquinazolines showed weak antifungal activity toward *Candidaalbicans* but it did not show any



activity on cancer cell line. Indolquinazolinones are mainly found in *Polygonum tinctorium, Strobilanthes cusia*, *Isatis tinctoria,* Calanthe, Couroupota, Strobilanthus, and Wrightia. Pyrrole quinazolinones, which are mostly vasicinone and deoxyvasicinone derivatives, are found in the families of Zygophyllaceae (*P. harmala* L., Nitraria), Acanthaceae (Adhatoda), Malvaceae (*Sida* L.), Crassulaceae (*Sedum*), Papilionaceae (*Galega* L.), and Scrophulariaceae (*Linaria*). Luotonin A is a pyrrole quinazolinone alkaloid first isolated in 1997 from the Chinese herbal medicinal plant *Peganum nigellastrum* that works as a human topoisomerase-I poison.[4] Quinazolinones have been isolated from *Fusarium lateritium* Nees, *Bacillus cereus* 041381, *Penicillium paneum* SD-44, and *Salicornia herbacea* in microorganisms.

SPECTRUM OF ACTIVITY

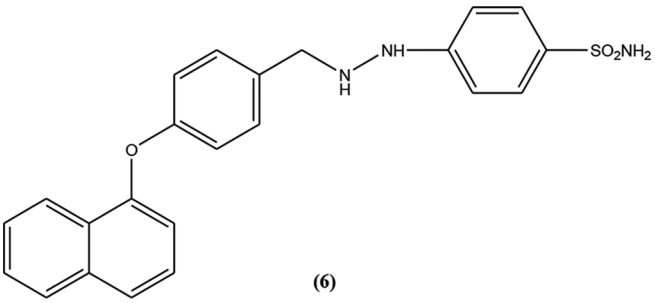
Naturally occurring quinazoline alkaloids as well as synthetic compounds, both have an integral value in medicinal chemistry and in agricultural industry. Quinazoline provides various privileged structures and they can be used to target various receptors. The diverse array of activity of quinazoline in therapeutic categories such as antimalarial,[5] antimicrobial,[6] antitubercular,[7] anticonvulsant,[8] anticancer, antihypertensive, antidiabetic, anti-inflammatory, anti-cholinesterase, cellular phosphorylation inhibition, dihydrofolate reductase

inhibition, kinase inhibitory activities, inhibitors of tubulin polymerization, diuretic, antipsychotic, dopamine agonist, and anti-HIV.[9] Agricultural application of quinazoline compounds includes plant growth promoter and fungicidal.

ACTIVITIES

Anticancer activity

Cancer is the global health challenge. It is identified by uncontrolled growth of cells. There are numerous causing factors thus have high mortality rate.[10]
Quinazoline is the most identified anticancer agents. Inhibition of vascular endothelial growth factor and vascular epidermal growth factor receptor (VEGFR) is the proposed mechanism followed by quinazoline. These agents are competitive inhibitors of ATP. The ATP-binding site has adenine region having two H-bond interactions with N-1 and N-6 amino group of adenine ring. Targeting one of the hydrogen bonds for inhibition is a strategy for anticancer activity. Hydrophobic channel – It is not used by ATP and may be exploited for inhibitor specificity.
Phosphate-binding region – This is used for improving inhibitor selectivity.[9] in 1997, luotonin is an alkaloid isolated from *Peganum nigellastrum* and to be founded with cytotoxic activity.[11]
2,3-disubstituted quinazoline core acts as EGFR inhibitor. Furan ring at 2nd position and urea, thiourea, thiosemicarbazide, phenyl hydrazine, hydroxylamine, para-amino benzoic acid, sulfonamide, and imine substitutions at 3rd position of quinazoline show optimum activity**(6)**.[12]
Sulfonamide functionalities have potential effect on solid tumors.[13] Anilinoquinazoline and with sulfonamide substitution at 6th position have remarkable activity against breast cancer cell line. Similarly, benzothiazole-quinazoline has highly promising antiproliferative activity on HL-60 as well as LoVo cell lines **(7)**.[14]



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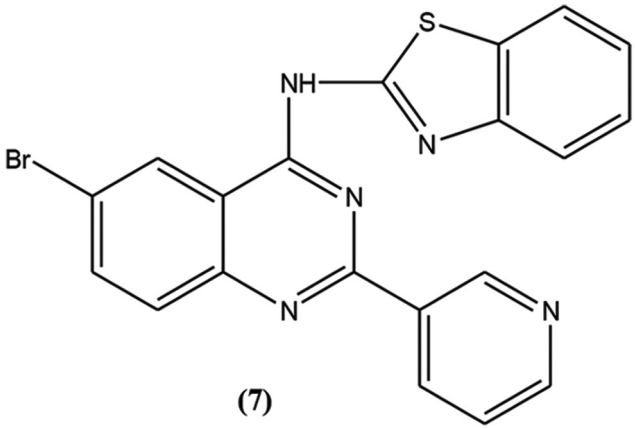

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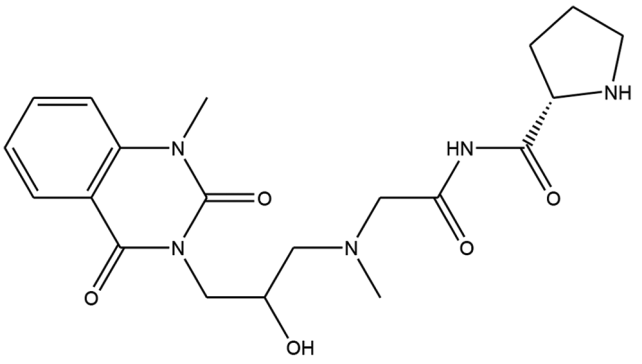
Antifungal activity

The high rate of morbidity and mortality in immune compromised patients such as patients receiving antineoplastic chemotherapy, organ transplantation, or AIDS is due to invasive fungal infection. *Candida*, *Cryptococcus*, and *Aspergillus* are predominant fungi causing such infections. Azoles, polyenes, and echinocandins are representative of present antifungal therapy but none of them fully satisfy the patient's need. The present antifungal agents also destroy the vital probiotics of human immune systems. Therefore, new antifungal agents are desired. Chitin synthase is an important enzyme involved in biosynthesis of chitin present in fungi cell. Fungal species are prone to cause frequent and severe infections in patients. Thus, resistance development of fungal strain is inevitable. Quinazolines are considered as better alternative for antifungal treatment.[15]
Quinazoli-2,4-dione has antifungal activity against *C. albicans* and *A. fumigatus*. 2-Substituted quinazoline compounds have antifungal activity **(8,9)**. Arylamine substitutions at 2nd position are more potent than alkylamine compounds. Likewise, electron-donating substitutions are more favorable than electron withdrawing in case of activity.[16]



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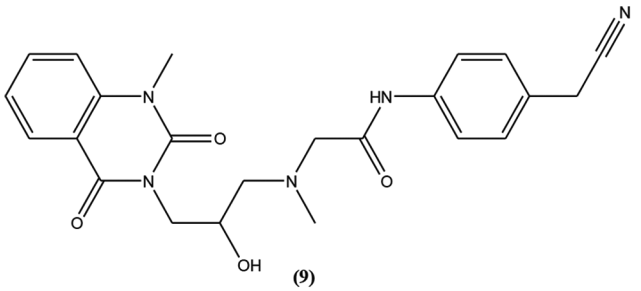

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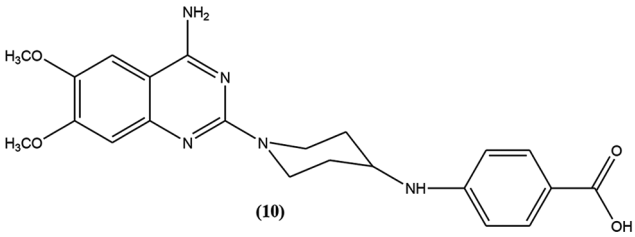

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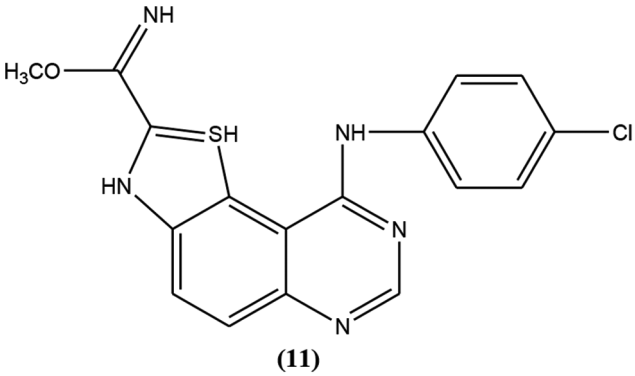

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Antibacterial activity

The abrupt and widespread rise in bacterial antibiotic resistance is a major problem. Perhaps, the most important issue in bacterial infections is the worldwide development of antibiotic resistances in normal Gram-positive coccal pathogens. The most important of these species are *Streptococcus pneumoniae*, *Enterococcus* resistant to vancomycin, and *Staphylococcus aureus* resistant to methicillin (as well as vancomycin). The mechanism of the action of quinazoline as an antibacterial agent involves inhibition of bacterial topoisomerase. Topoisomerase is having a key role in proliferation of cell and synthesis of genetic material of bacteria like DNA.[17] 2,3-disubstituted as well as 2,4-disubstituted quinazolines have antibacterial activity. Many of the quinazolines are familiar to indigenous traditional system of medicine.A pyrrole alkaloid like deoxyvasicinone isolated from *Adhatoda vasica* (Acanthaceae) has fused 4(3H)-quinazolinone structure having antimicrobial activity.[6]

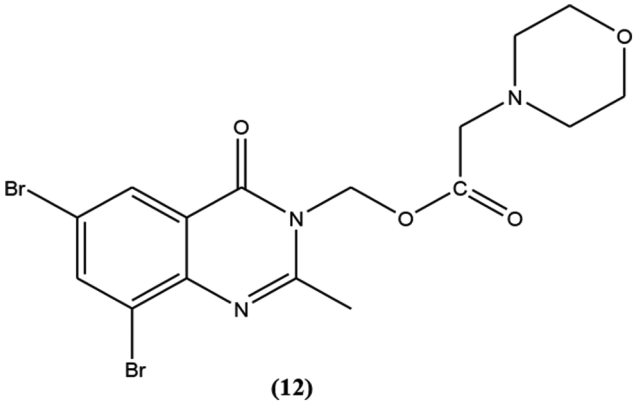
Dihydrofolate reductase inhibition is done by 2,4-diamino quinazolines **(10)**.4-amino quinazolines inhibit synthesis of DHFR and formation of RNA in case of *E. coli* and *S. aureus* **(11)**. Larger substitutions are more active than smaller alkyl substitutions.[18]

Anti-inflammatory activity

There is a lot of evidence from clinical trials that lowering blood pressure with Angiotensin-converting enzyme inhibitors. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-converting enzyme blockers (ARBs) are the classes of antihypertensive agent like beta-blockers (BBs) and calcium channel blockers in the treatment of hypertension. Nonsteroidal anti-inflammatory drugs (NSAIDs) act through blocking the release of these chemicals by inhibition of cyclooxygenase. NSAIDs are known to cause a variety of side effects, including damage to the mucosa of the gastrointestinal tract (GIT), bleeding, intolerance, and renal toxicity. There is also a need for safer and more active NSAIDs and analgesics.

Spiro quinazolinone is reported for superior anti-inflammatory activity with lesser adverse effects on GIT.[19] In response to infection and other cellular stress, signaling of molecules like mitogen-activated protein kinase are activated. It's worth noting that 2-substituted quinazoline derivatives have anti-allergic, analgesic, phosphodiesterase (PDE) 2, PDE 5 inhibitory, and anti-inflammatory properties, whereas 2, 3-disubstituted quinazolin-4- derivatives with substitute on the benzene ring at positions 6 and 8 are having anti-histaminic and COX-II inhibitory

properties. Likewise, 2, 4-disubstituted quinazoline derivatives with substitution on the benzene ring at position-6 possess NOS-II inhibitors, NFKB inhibitors, tumor necrosis factor inhibitors, interleukin-6 inhibitors, and combined type 3 and 4 PDE inhibitors with both bronchodilatory and anti-inflammatory properties exhibit remarkable anti-inflammatory activity. 1,3-disubstituted quinazolin-2,4-diones have anti-inflammatory activity. While, 2,3-disubstituted quinazolinone with 6th and 8th position substituted has remarkable antihistaminic and Cox inhibitory action **(12,13)**.[20]



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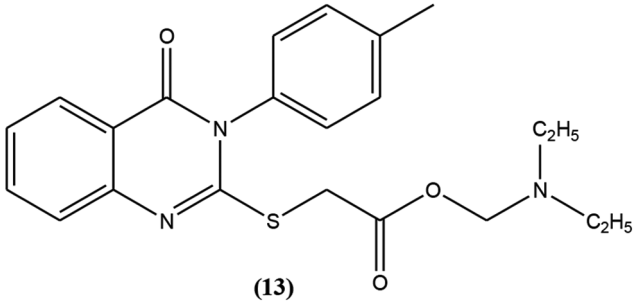

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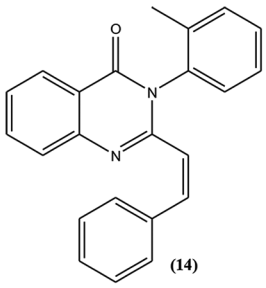
Anticonvulsant and central nervous system (CNS) depressant activity

Epilepsy is characterized by episodic neuronal discharge and seizures.[21] Gamma-aminobutyric acid (GABA) is the inhibitory neurotransmitter; hence, inhibition of GABA or increase in excitatory neurotransmitter can cause abnormal CNS activities. The treatment approach is blockade of receptors of glutamate such as NMDA, AMPA, and KAINATE which is targeted.[22] Many 4(3H)-quinazolinone derivatives represent an important category among heterocyclic compounds of medicinal interest. Other derivatives of 4(3H)-quinazolinones possess a wide range of biological activities, especially on the CNS.

4(3H)-Quinazolinone derivatives as anticonvulsant agents the search for new antiepileptic drugs with reduced toxicity and lower side effects are continuous.[23] 4(3H)-Quinazolinone represents a very good nucleus for the preparation of some new sedative/hypnotic and anticonvulsant agents, it was found that the 3H-quinazolin-4-one has been reported to possess different pharmacological effects, namely, sedative-hypnotic and anticonvulsant ones. 2-styrylquinazolin-4(3H)-ones **(14,15)** is also reported as moderate potent antiepileptic compounds with lesser adverse effects.[8]



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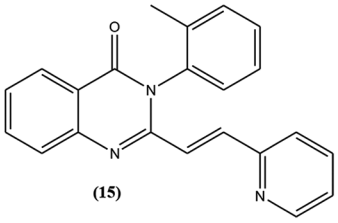

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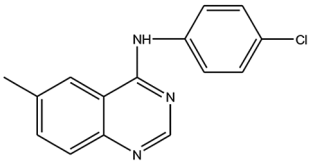
Antiviral activity

Substituted quinazolines are also active against viruses such as varicella zoster, adenovirus, and HCMV. Adenovirus is a double-stranded DNA virus having wide spectrum of infections and illness. 3-hydroxy-2,4-quinazolinediones is reported against adenovirus. Similarly, 1,2,3-triazole linked 3-hydroxy compounds is also reported for its antiviral activity against DNA viruses such as adenovirus and herpes simplex virus. The literature also shows that substitution at N1 position leads to favorable activity against DNA virus. Incorporation of electron-withdrawing groups such as NO_2, CN, and F at para position of alkyl group can improve the activity against vaccinia virus.[24,25]

Anti-HCMV activity is shown by 4-anilino substituted quinazoline compound **(16,17)** and which can be evaluated by performing inhibition studies of viral kinase pUL97 which is considered as target for antiviral activity. Thus, inhibition of viral



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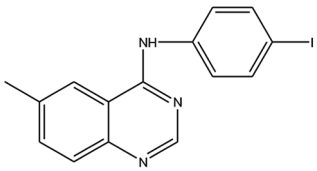

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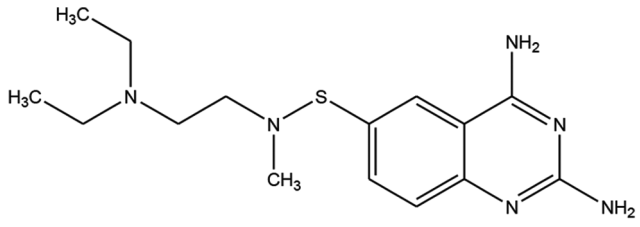
protein is the mode of action shown by 4-anilino substituted quinazolines. 4,5,7,8-substituted fluorescent quinazoline has antiviral activity against HCMV.[26]

Antimalarial activity

Malaria is a tropical parasitic disease that affects billions of people worldwide. It remains the world's most dangerous disease, despite the fact that the number of cases and deaths associated with it has reduced in recent years. Malaria is caused by plasmodial species and transmitted by host-like mosquitoes in human. It is known for destruction of RBCs and can be occurring recurrently. Due to the emergence of resistance, *Plasmodium falciparum* strains to the older medications such as quinine and chloroquine, artemisinins and ACT with fixed-dose combinations are the first-line treatment for falciparum malaria in almost all regions where malaria is endemic. Despite the fact that artemisinins are effective and fast-acting antimalarials, their widespread use in the treatment of *P. falciparum* malaria patients increases the possibility of drug resistance.[27] There is a constant need to develop newer drugs with newer mode of action.

Quinazolinone with 3-aryl and 2-styryl substitutions shown activity against plasmodial species.[28] Amines or acetamide moieties substitution at 2nd and 4th position enhances the antimalarial activity **(18,19,20)**.[29]



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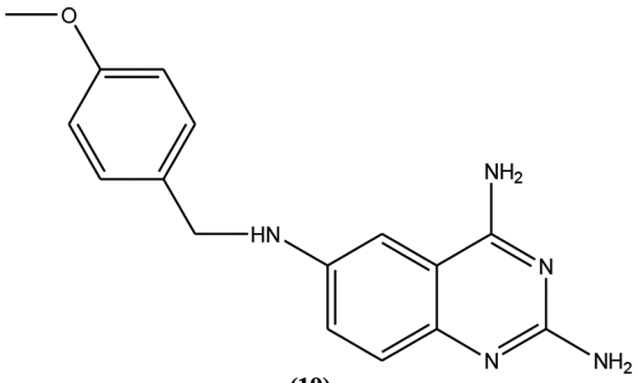

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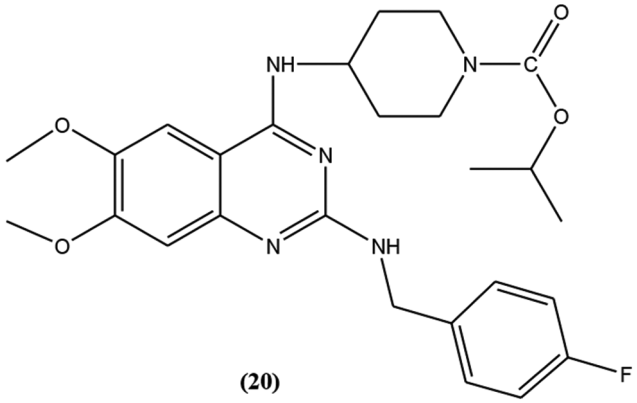

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Antidiabetic activity –α-Glucosidase inhibitor

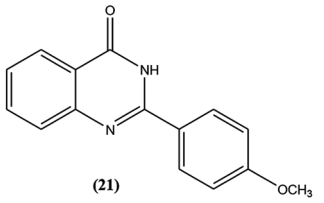
As per the definition of the WHO, diabetes is a chronic disease where pancreas is not capable to produce enough quantity of insulin or when the body cannot use produced insulin effectively.

Two main types of diabetes are type 1 and type 2 diabetes. The destruction of insulin-producing cells in the pancreas, mainly due to autoimmune responses, is a characteristic of type 1 diabetes. The absolute insulin deficiency manifested in Type 1 diabetes. Type 2 diabetes, however, has two defects: Insulin failure and resistance to insulin. The prevalence of diabetes in type 2 amounts to 90%–95%. The ongoing diabetes crisis indicates that the diabetes is very prevalent.[30]

α-Glucosidase is an enzyme that plays an important role in the digestion of carbohydrates. For hydrolysis of the carbohydrates, α-Glucosidase is necessary as only the blood circulation monosaccharides can be absorbed into the gut. Since it played a key role in the digestion of carbohydrates and the treatment of glycoproteins, the therapeutic goal for drug

development in diseases such as diabetes, obesity, cancer, and the treatment of HIV is considered relevant. α-Glucosidase has been introduced as a therapeutic target for the treatment of type 2 diabetes in this aspect, as enzyme inhibition slows carbohydrate digestion and monosaccharide absorption. 2-Substituted quinazoline is studied for glucosidase inhibitory activity which found that substitution on benzene ring at para position will led to the antidiabetic activity **(21,22)**.[31]

1,2,3-triazole is another important moiety which has pharmacological activities such as anticancer, antioxidant, and anticonvulsant. Similarly, the alpha-glucosidase inhibition by 1,2,3-triazole cannot be denied. Quinazoline attached with triazole ring attached will absolutely lead to increase in potency **(23)**.[32]



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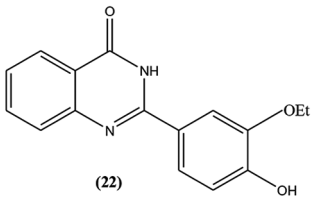

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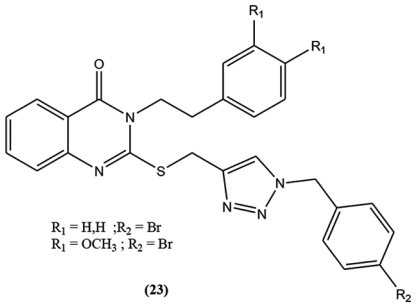

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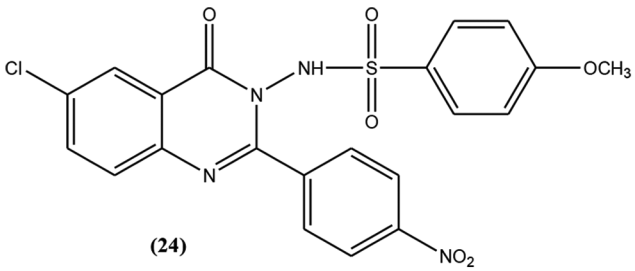
Antihypertensive and diuretic activity

Hypertension is well known as a significant public health issue that affects both middle-aged and older people.[9] There is a lot of evidence from clinical trials that lowering blood pressure with angiotensin-converting enzyme inhibitors (ACEIs) is one of the drug classes. Inflammation and injury are associated with release of chemicals like prostaglandin, leukotriene, histamine etc. All antihypertensive drugs, including CCBs and thiazide-type diuretics, will minimize the risks of hypertension. In most outcome trials, thiazide-type diuretics were used to treat hypertension.[33] These types of diuretics are associated with severe adverse effects such as hypokalemia, hypomagnesemia, glucose tolerance, and azotemia which cannot be fully eliminated by other therapies also.

Other treatment approaches like vasodilator have an adverse effect of interfering with insulin releasing activity and cause hyperglycemia. 2-phenyl-N-substituted benzene sulfonamide derivatives **(24)** were established and evaluated for antihypertensive and diuretic activity.[34]

Carbonic anhydrases are enzymes that catalyze the conversion of CO_2 to bicarbonate and other hydrolytic reactions. Drugs that function as diuretics, antiepileptics, antiglaucoma, antiobesity, and antitumor agents may all benefit from CA inhibition. Targeting pathogen produced enzymes may lead to new anti-infectives. Highly isoform selective CA inhibitors (CAIs) were discovered thanks to successful structure-based drug design campaigns, which could lead to a new generation of drugs targeting these common enzymes.[35] Substituted iodinated quinazoline tails with benzene sulfonamide **(25)** act as carbonic anhydrase inhibitor. It has wide application as CAI because it inhibits CA-I and CA-II prominently.[36]



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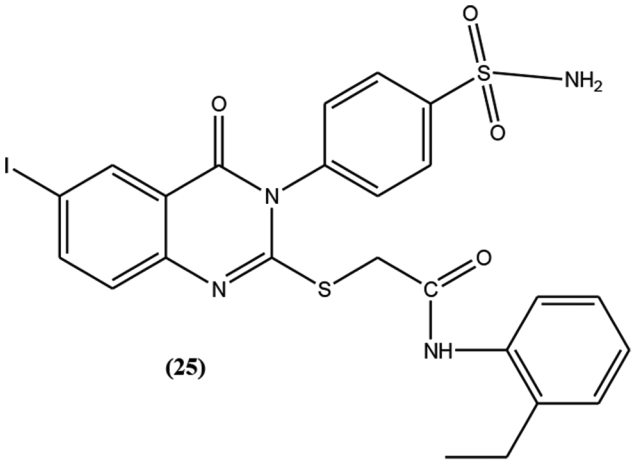

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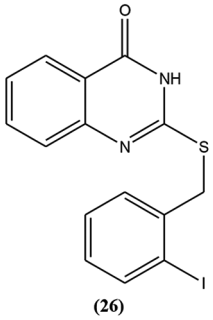
Monoamine oxidases (MAO)inhibitory activity

MAOs are mitochondrial enzymes responsible for the oxidative deamination metabolism of neurotransmitters including dopamine, serotonin, norepinephrine, and epinephrine in humans. Since the MAO-A enzyme isoform in the brain metabolizes serotonin, specific MAO-A inhibitors are used to treat anxiety and depression. MAO-B enzyme, on the other hand, metabolizes dopamine in the brain, so MAO-B inhibitors are used to treat Parkinson's disease.[37]

In the literature studies, seven quinazolinone compounds with IC_{50}<1 μM are mentioned which act as specific and potent MAO-B inhibitor. Among them, 2-[(3-iodobenzyl)thio]quinazolin-4-one found to be most effective **(26)**.[38] Studies were also done on various heterocyclic ring on sulfur like piperazine to determine the MAO inhibitory activity **(27)**.[39]



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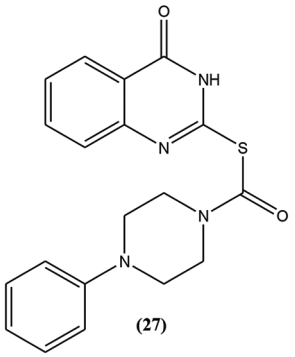

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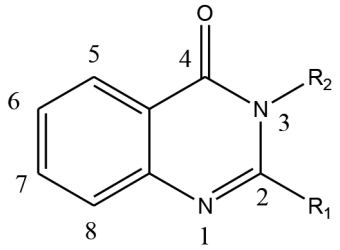
STRUCTURE–ACTIVITY RELATIONSHIP

The substitution position on quinazoline ring can change the activity as well as the potency. The various possible substitutions according to literature are described as follows.



Substitution onN_1

Nitrogen at 1st position is essential for potent activity of quinazoline nucleus. Critical H- bonding is formed with another N-H. Thus, replacement of N with carbon results in loss of activity.[40]

Substitution on N_1 can lead to have anti-inflammatory action.[41]

Substitution on 2nd position -R_1

For anticonvulsant properties, 2nd position is substituted with bulkier or long chain substitutions to increase the lipophilicity of the resultant compound.

For antibacterial properties, cyclopropyl, 2-pyridylthio, and 2-phenylcarbonylthio-substitutions are favorable. Replacement of these groups can result in loss of antibacterial property styryl group increases the antibacterial properties. Double-bond linkers at this position favor the activity.[33]

Linkers like 4-aminopiperidines can be used to extend the substitution length on 2nd position.[17]

2,4-diones and subsequent substituted quinazoline have bacterial gyrase and topoisomerase inhibitory action.[30] Branched alkyl at 2nd position increases the rate of inhibition while polar, unbranched substitutions affect the activity.[42]

Substituted anilines can be further substituted at 2nd position. If the phenyl ring of substituted amine has meta/para substitution with electron withdrawing nature such as -Cl, -F, and -NO_2,[43] the potency increases. Nitrogen of the amine should not be disubstituted. Benzyl substitution at 2nd position has remarkable anti-Leishmanial properties.[44]

Substitution on 3rd position- R_2

N-Phenyl with ortho, para, or meta substitution increases the activity. However, benzyl group is essential for antibacterial activity. Substitution with H-bond donor and acceptor at ortho, meta, or para position on 3-N phenyl will increase the activity. Substituted aromatic ring is essential for anticonvulsant activity.[30] Monosubstituted ortho

compounds increase the activity, while methoxy at para position increases the activity.
Replacement of aromatic ring with 3-acetoxypropyl substitution results in complete loss of activity. The N at 3rd position can be replaced by C-N without affecting the activity.

Substitution on 4th position

4-Quinazolinone itself has different therapeutic applications. 2,3-disubstituted quinazolinones have anticonvulsant, antibacterial, and analgesic effect.[45] At 4th position, oxygen can be replaced by sulfur. Amino substitution at this position has anticancer and potent antimicrobial activity. Long chain amino quinazoline irreversibly blocks EGFR, induces apoptosis in tumor cell line. Aliphatic branched chain of quinazoline shows modest activity.[46] Phenyl/ benzyl group at 4th position inhibits the growth of *S. aureus*.[47] Disubstituted amine decreases the activity. Favorable substitutions – substituted benzylamines, aminomethyl, substituted benzyl amine, and long chain alkyl substitution.

Substitution on 5th position

Along with 4-amino substitution, 5th position if substituted with heteroaryl ring like morpholine is considered as superior EGFR inhibitors with nanomolar concentration. Replacement of C with C-CH_3 is favorable but replacement with nitrogen at 5th position is not favorable.[48]

Substitution on 6th and 7th position

Substitution at positions is essential for antimicrobial activity. At 6th position, electron-withdrawing group -NO_2 and electron-donating group -CH_3, -OCH_3, aryl, alkynyl, 1,2,3-triazole showed significant antibacterial activity.[49] Bulky and lipophilic substitutions are beneficial. The 6th position is more potent than 7th for bromo/ methyl substitution. Electron-withdrawing group at 6th and 7th is more potent than corresponding methyl and methoxy substitution.[50]
6,7-disubstituted compounds act as a dual inhibitor of EGFR and VEGFR-2.[51,52] Benzenoid ring is essential for activity. Replacement with pyridine was tolerated.[53]

Substitution on 8th position

Replacement of carbon at 8th position with C-CH_3 is favorable but -N is not favorable.

MARKETED PREPARATIONS[54]

The quinazolinone and its various derivatives have diverse application in the field of medicines, agriculture, and in different industries. Initially, in 1968, methaqualone and quinethazone which are

Table 1: Marketed preparations of quinazoline

S. No.	Name of drug	Category	Brand name
1.	Prazosin	Alpha-adrenergic blocker	Minipress, Nu-prazo
2.	Gefitinib	Epidermal growth factor receptor inhibitor	Apo-gefitinib, Iressa
3.	Erlotinib	Epidermal growth factor receptor inhibitor	Tarceva
4.	Tetrodotoxin	Potent neurotoxin	-
5.	Alfuzosin	Alpha-1 blocker	Alcinin, Alfoo, Xatral
6.	Trimetrexate	DHFR inhibitor	Neutrexin
7.	Bunazosin	Alpha-1 adrenergic inhibitor	Andate
8.	Vandetanib	Vascular epidermal growth factor receptor inhibitor	Caprelsa
9.	Anagrelide	Platelet reducing agent	Agrylin
10.	Evodiamine	Fat burning benefits	-
11.	Proquazone	Nonsteroidal anti-inflammatory drugs	-
12.	Nolatrexed	Thymidylate synthase inhibitor	Under investigation
13.	Quinethazone	Thiazide diuretic	Aquamox
14.	Albaconazole	Triazole antifungal	-
15.	Febrifugine	Antimalarial activity	-
16.	Afloqualone	Sedative and muscle relaxant	-
17.	Fenquizone	Sulfonamide diuretic	-
18.	Linagliptin	Antidiabetic	Tradjenta, Glyxambi
19.	Quazodine	Cardiotonic and vasodilator	Dozonone, posicor
20.	Ketanserin	Selective serotonin receptor antagonist	-
21.	Benzouracil	Antiviral	-
22.	NSC127213	Anti-inflammatory	-
23.	NSC137192	Antiproliferative, anticancer	-

anticonvulsant and diuretic, respectively, were marketed.

After 1980, by the advancement in development of synthetic strategies, approximately 50 classes of therapeutic agents with quinazoline were available with variety of mode of action. Soporific, sedative, diuretic, anticonvulsant, analgesic, tranquilizing, antidiabetic, and cardioprotective were reported. As the time passed, several adverse effects arose and some of the drugs are withdrawn from market or banned.

Prazosin is a sympatholytic, selective alpha-receptor blocker which is still in use to treat high blood pressure. Prazosin antagonizes the action of neurotransmitter called norepinephrine. Another name of prazosin is Minipress.

Gefitinib and erlotinib both are potent EGFR inhibitors used in different types of cancer treatment such as lung cancer and breast cancer. The mode of action of both the drugs is based on inhibition of EGFR tyrosine kinase.

Linagliptin is another example of quinazoline containing drug which acts as DPP-4 antagonist. It effectively lowers the blood sugar level. Linagliptin is marketed under trade name Ondero.

The list of marketed preparations below shows the brand name of the medicine with active ingredient containing quinazoline moiety with its therapeutic category. It gives the glimpse of diversity of therapeutic applications of quinazoline and its derivatives.

Table 1 gives the glimpse of status of quinazoline in the market. It also shows the examples of preparations which are still present in the market.

CONCLUSION

This review article concludes with the development stages of quinazoline alkaloid, wide application in medicinal chemistry, current status in therapeutics and general structure activity relationship studies which are helpful for further development of newer quinazoline compounds.

REFERENCES

1. Khan I, Zaib S, Batool S, Abbas N, Ashraf Z, Iqbal J, *et al*. Quinazolines and quinazolinones as ubiquitous structural fragments in medicinal chemistry: An update on the development of synthetic methods and pharmacological diversification. Bioorg Med Chem 2016;24:2361-81.
2. Shang XF, Morris-Natschke SL, Liu YQ, Guo X, Xu XS, Goto M, *et al*. Biologically active quinoline and quinazoline alkaloids part I. Med Res Rev 2018;38:775-828.
3. Liljegren DR. Biosynthesis of quinazoline alkaloids of *Peganum harmala*. Phytochemistry 1971;10:2661-9.
4. Shang XF, Morris-Natschke SL, Yang GZ, Liu YQ, Guo X, Xu XS, *et al*. Biologically active quinoline and quinazoline alkaloids part II. Med Res Rev 2018;38:1614-60.
5. Patel TS, Bhatt JD, Vanparia SF, Patel UH, Dixit RB, Chudasama CJ, *et al*. Ionic liquid mediated stereoselective synthesis of alanine linked hybrid quinazoline-4 (3H)-one derivatives perturbing the malarial reductase activity in folate pathway. Bioorg Med Chem 2017;25:6635-46.
6. Tiwari R, Chhabra G. Evaluation of antibacterial activity of novel quinazoline derivatives. Asian J Chem 2010;22:5981-6.
7. Tiwary BK, Pradhan K, Nanda AK, Chakraborty R. Implication of quinazoline-4 (3H)-ones in medicinal chemistry: A brief review. J Chem Biol Ther 2015;1:104.
8. Jatav V, Mishra P, Kashaw S, Stables JP. Synthesis and CNS depressant activity of some novel 3- [5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones. Eur J Med Chem 2008;43:135-41.
9. Ajani OO, Aderohunmu DV, Umeokoro EN. Quinazoline pharmacophore in therapeutic medicine. Bangladesh J Pharmacol 2016;11:716-33.
10. Mai A, Massa S, Rotili D, Cerbara I, Valente S, Pezzi R, *et al*. Histone deacetylation in epigenetics: An attractive target for anticancer therapy. Med Res Rev 2005;25:261-309.
11. Gupta T, Rohilla A, Pathak A, Akhtar J, Haider R, Yar MS. Current perspectives on quinazolines with potent biological activities : A review. Synth Commun 2018;2018:1-29.
12. El-Hashash MA, Darwish KM, Rizk SA, El-Bassiouny FA. The reactivity of 2-ethoxy-4-chloroquinazoline and its use in synthesis of novel quinazoline derivatives. Org Chem Int 2011;2011:1-7.
13. Sabry MA, Ewida HA, Hassan GS, Ghaly MA, El-Subbagh HI. Synthesis, antitumor testing and molecular modeling study of some new 6-substituted amido, azo or thioureido-quinazolin-4(3H)-ones. Bioorg Chem 2019;88:102923.
14. Allam HA, Aly EE, Farouk AK, El Kerdawy AM, Rashwan E, Abbass AE. Design and synthesis of some new 2,4,6-trisubstituted quinazoline EGFR inhibitors as targeted anticancer agents. Bioorg Chem 2020;98:103726.
15. Kassab, Gedawy E, Mahmoud Z, Khattab RA. Design, synthesis, antitumor and antimicrobial activity of some novel 6,7-dimethoxyquinazoline derivatives. Heterocycles 2016;92:272.

16. Ji Q, Yang D, Wang X, Chen C, Deng Q, Ge Z, *et al*. Synthesis and evaluation of novel quinazoline-2, 4-dione derivatives as chitin synthase inhibitors and antifungal agents. Bioorg Med Chem 2014;2-10.
17. Kung PP, Casper MD, Cook KL, Wilson-Lingardo L, Risen LM, Vickers TA, *et al*. Structure-activity relationships of novel 2-substituted quinazoline antibacterial agents.J Med Chem 1999;4705-4713.
18. Harris CS, Hennequin L, Morgentin R. Synthesis and functionalization of 4-substituted quinazolines as kinase templates. Targets Heterocycl Syst 2010;19;15546-7.
19. Amin KM, Kamel MM, Anwar MM, Khedr M, Syam YM. Synthesis, biological evaluation and molecular docking of novel series of spiro [(2H,3H) quinazoline-2,1'- cyclohexan]-4(1H)- one derivatives as anti-inflammatory and analgesic agents. Eur J Med Chem 2010;45:2117-31.
20. Chandrika PM, Rao AR, Narsaiah B, Raju MB. Quinazoline derivatives with potent anti-inflammatory and anti-allergic activities. Int J Chem Sci 2008;6:1119-46.
21. Manford M. Recent advances in epilepsy.J Neurol 2017;264:1811-24.
22. Chapman AG. Glutamate and epilepsy.J Nutr 2000;130:1043-5.
23. Arora D, Kumar H, Malhotra D, Malhotra M. Current trends in anticonvulsant 4(3H)-quinazolinone :A review. Pharmacologyonline 2011;668:659-68.
24. Kang D, Zhang H, Zhou Z, Huang B, Naesens L, Zhan P, *et al*. Bioorganic and medicinal chemistry letters first discovery of novel 3-hydroxy-quinazoline-2, 4(1H, 3H)-diones as specific anti-vaccinia and adenovirus agents via "privileged scaffold" refining approach. Bioorg Med Chem Lett 2016;26:5182-6.
25. Piotrowska DG, Andrei G, Schols D, Snoeck R, Łysakowska M. Anti-varicella-zoster virus and anti-cytomegalovirus activity of quinazoline-2, 4-diones containing isoxazolidine and phosphonate substructures. Eur J Med Chem 2017;126:84-100.
26. Hampel F, Kahnt A, Hutterer C, Steingruber M, Bahsi H, *et al*. Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions. Nat Commun 2017;8:2-10.
27. Wellems TE, Plowe CV. Chloroquine-resistant malaria.J Infect Dis 200115;184:770-6.
28. Birhan YS, Bekhit AA, Hymete A. *In vivo* antimalarial evaluation of some 2,3disubstituted-4(3H)-quinazolinone derivatives. BMC Res Notes 2015.
29. Guan J, Zhang Q, O'Neil M, Obaldia N, Ager S, Gerena L, *et al*. Antimalarial activities of new pyrrolo[3,2-f] quinazoline-1,3-diamine derivatives. Antimicrob Agents Chemother 2005;50:1649-55.
30. Cheng D. Prevalence, predisposition and prevention of Type II diabetes. Nutr Metab 2005;2:29-39.
31. Javaid K, Saad SM, Rasheed S, Moin ST, Syed N, Fatima I, *et al*. 2-Arylquinazolin-4(3H)-ones:A new class of α-glucosidase inhibitors. Bioorg Med Chem 2015;23:7417-21.
32. Saeedi M, Mohammadi-Khanaposhtani M, Pourrabia P, Razzaghi N, Ghadimi R, Imanparast S, *et al*. Design and synthesis of novel quinazolinone-1,2,3-triazole hybrids as new anti-diabetic agents: *In vitro*α-glucosidase inhibition, kinetic, and docking study. Bioorg Chem 2019;83:161-9.
33. National High Blood Pressure Education Program. The sixth report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997;157:2413-46.
34. Rahman MU, Rathore A, Siddiqui AA, Parveen G, Yar MS. Synthesis and characterization of quinazoline derivatives : Search for hybrid molecule as diuretic and antihypertensive agents.J Enzyme Inhib Med Chem 2014;29:733-43.
35. Supuran CT. Structure and function of carbonic anhydrases. Biochem J 2016;473:2023-32.
36. Soliman AM, Ghorab MM, Bua S, Supuran CT. Iodoquinazolinones bearing benzenesulfonamide as human carbonic anhydrase I, II, IX and XII inhibitors : Synthesis, biological evaluation and radiosensitizing activity. Eur J Med Chem 2020;200:112449.
37. Lum CT, Stahl SM. Opportunities for reversible inhibitors of monoamine oxidase-a (RIMAs) in the treatment of depression. CNS Spectrums 2012;17:107-20.
38. Radwan AA, Alanazi FK. Biological Activity of Quinazolinones. In: Quinazolinone and Quinazoline Derivatives; 2020. Available from: https://www.intechopen.com/books/quinazolinone-and-quinazoline-derivatives/biological-activity-of-quinazolinones. [Last accessed on 2021 Feb 23].
39. Fernandez HH, Chen JJ. Monoamine oxidase-B inhibition in the treatment of Parkinson's disease. Pharmacotherapy 2007;27:174S-85.
40. Khattab SN, Haiba NS, Asal AM, Bekhit AA, Amer A, Abdel-Rahman HM, *et al*. Synthesis and evaluation of quinazoline amino acid derivatives as mono amine oxidase (MAO) inhibitors. Bioorg Med Chem 2015;23:3574-85.
41. Qhobosheane MA, Petzer A, Petzer JP, Legoabe LJ. Synthesis and evaluation of 2-substituted 4(3H)-quinazolinone thioether derivatives as monoamine oxidase inhibitors. Bioorg Med Chem 2018;26:5531-7.
42. Mostert S, Petzer A, Petzer JP. Indanones as high-potency reversible inhibitors of monoamine oxidase. ChemMedChem 2015;10:862-73.
43. Nasab R, Hassanzadeh F, Khodarahmi GA, Rostami M, Mirzaei M, Jahanian-Najafabadi A, *et al*. Docking study, synthesis and antimicrobial evaluation of some novel 4-anilinoquinazoline derivatives. Res Pharm Sci 2017;12:425.
44. Poojari S, Naik PP, Krishnamurthy G, Kumara KS, Kumar NS, Naik S. Anti-inflammatory, antibacterial and molecular docking studies of novel spiro-piperidine quinazolinone derivatives. Integr Med Res 2017;11:497-511.
45. Gatadi S, Gour J, Shukla M, Kaul G, Das S, Dasgupta A,

et al. Synthesis of 1,2,3-triazole linked 4(3H)-quinazolinones as potent antibacterial agents against *Multidrug-resistant Staphylococcus aureus*. Eur J Med Chem 2018;157:1056-67.
46. Rohini R, Muralidhar Reddy P, Shanker K. Antimicrobial study of newly synthesized 6-substituted indolo[1,2-c] quinazolines. Eur J Med Chem 2010;45:1200-5.
47. Gatadi S, Lakshmi TV, Nanduri S. 4(3H)-quinazolinone derivatives : Promising antibacterial drug leads. Eur J Med Chem 2019;170:157-72.
48. Gilson PR, Tan C, Jarman KE, Lowes KN, Curtis JM, Nguyen W, *et al*. Optimization of 2-anilino 4-amino substituted quinazolines into potent antimalarial agents with oral *in vivo* activity.J Med Chem 2017;60:1171-88.
49. Zhu X, Van Horn KS, Barber MM, Yang S, Wang MZ, Manetsch R, *et al*. SAR refinement of antileishmanial N2,N4-disubstituted quinazoline-2,4-diamines. Bioorg Med Chem 2015;23:5182-9.
50. Alagarsamy V, Chitra K, Saravanan G, Raja Solomon V, Sulthana MT, Narendhar B. An overview of quinazolines: Pharmacological significance and recent developments. Eur J Med Chem 2018;151;628-85.
51. Jyothi S, Chandrika M, Perka H, Deepak G. Novel 2, 4-disubstituted quinazolines as cytotoxic agents and JAK2 inhibitors : Synthesis, *in vitro* evaluation and molecular dynamics studies. Comput Biol Chem 2019;79:110-8.
52. Tsou HR, Mamuya N, Johnson BD, Reich MF, Gruber BC, Ye F, *et al*. 6-Substituted-4-(3-bromophenylamino) quinazolines as putative irreversible inhibitors of the epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor (HER-2) tyrosine kinases with enhanced antitumor activity.J Med Chem 2001;44:2719-34.
53. Ismail RS, Abuserii S, El Ella DA. Recent advances in 4-aminoquinazoline based scaffold derivatives targeting EGFR kinases as anticancer agents. Futur J Pharm Sci 2016;2:9-19.
54. Selvam TP, Kumar PV. Quinazoline marketed drugs-a review. Res Pharm 2011;1:1-21.