

REVIEW ARTICLE

An Updated Review on the Mechanism of Action, Therapeutic Effects, and Biological Prospects of Quinazolinone Hybrids

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Abstract: The broad range of medicinal applications of quinazolinone scaffolds has drawn much interest in biological sciences. Almost 200 different organic alkaloids have a family of fused heterocycles that make up their analogues in heterocyclic chemistry. Quinazolines and quinazolinones are a specialized type of heterocyclic compounds having a benzene ring and pyrimidine ring, and due to their manifold uses, heterocyclic scaffolds are well-known for their versatility. The biological prospects of quinazolinone derivatives and their therapeutic applications, such as antimicrobial, anticancer, analgesic, antihypertensive, antiviral, antimalarial, antibacterial, and antifungal activities, are significant for treating the diseases. A number of quinazolinone derivatives have been reviewed here, emphasizing their notable biological and therapeutic applications upon their interactions with enzymes and receptors. The quinazolinone-bearing molecules have shown a number of therapeutic applications, which have been compiled in this updated review.

ARTICLE HISTORY

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1. INTRODUCTION

In medicinal chemistry, quinazolinone and its derivatives have been discovered to be efficient and adaptable pharmacophoric units for designing and developing a wide range of bioactive molecules [1]. Derivatives of quinazolinone are an important class of aromatic chemicals with an effective role in synthetic and semisynthetic drug chemistry [2]. Quinazolinone scaffolds have become well-known medicinal drugs; therefore, compounds based on it have been produced for a variety of pharmacological aspects. In various therapeutic classes, new methods and technological research have discovered a large number of nitrogen-containing heterocyclic compounds with enormous biological potential [3].

Quinazolinones are classified into four isomeric forms: quinazolines, quinoxaline, cinnoline, or palatine. Quinazolines are heterocyclic compounds that include nitrogen and are made up of two fused bicyclic aromatic rings, a pyrimidine ring and a benzene ring [4]. It has become possible to isolate a greater number of naturally occurring alkaloids from different kinds of bacteria, animals, and plants. These alkaloids have been found to be derived from quinazolinones. In the late 1860s, the first quinazolinone, or 2-cyanoquinazolinone, was produced by mixing cyanogens with anthranilic acid [5]. Quinazolinones are the most prominent compounds with a wide spectrum of biological activities [6].

The quinazolinone skeleton is found in copious amounts in a variety of natural chemical constituents, including rutaecarpine, luotonin A, tryptanthrin, evodiamine, and quinazolinones and 2-methyl quinazolinone [7]. Quinazolinone (German: *Chinazoline*) was the name given to this molecule after it was shown to be isomeric with cinnoline, quinoxaline, and several other derivatives of the quinazolinone system, including keto-quinazolines, also known as quinazolinone [8]. The heterocycles play a vital role in drug design; the synthetic and natural molecules act on biological targets that typically contain heterocyclic substances [9]. The new derivatives of quinazolinone are significant for developing methods to enhance the intrinsic chemical diversity of natural substances. Natural quinazolinones are predominantly biosynthesised using tryptophan and anthranilic acid. Indolquinazolinones primarily originate from the plant *Polygonum tentorium* Lour [10]. The remarkable biological activity of quinazolinones makes them an important subclass of fused heterocyclic alkaloids. The natural phytoconstituents and their compounds make these metabolites and their derivatives essential for the current medication development approaches [11].

2. QUINAZOLINONES: STRUCTURAL CHEMISTRY AND BIOLOGICAL PROSPECTS

The use of chemical research methods for the manufacture of medications is known as medicinal chemistry. Quinazolinone and quinazolinone are heterocyclic compounds and the derivatives of quinazolinone have become popular in the field of organic chemistry. Quinazolinone structures, or 4(3H)-quinazolinones, are among the most prevalent natural

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products or intermediates involved in several proposed biosynthetic pathways. Due to the presence of multiple physiologically active pharmacophores within a single molecule, their ability to interact with various biological targets and perform diverse biological functions is enhanced [12].

Based on the ring and substitution system, these pharmacophores are divided into the following classes (Fig. 1) [13]:

- Quinazoline
- 2-substituted 4-3H-quinazolin-ones
- 3-substituted 4-3H-quinazolin-ones
- 2,4-disubstituted 4-3H-quinazolin-ones

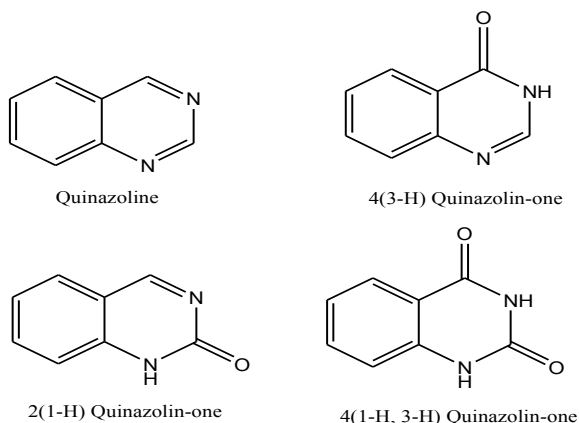
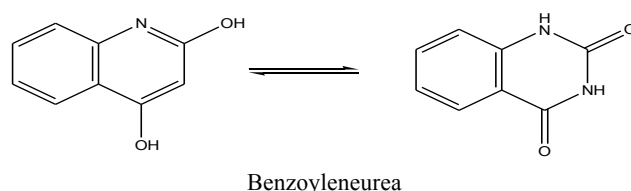


Fig. (1). Structures of quinazoline and quinazolinones.

In terms of chemistry, quinazoline and quinazolinone together form a significant class of six-membered fused heterocyclic rings or aromatic rings [14].

Quinazolinones have garnered a lot of attention due to their many biological prospects, such as anti-carcinogenic [15], anti-tubercular [16], anti-tumor [17], anticonvulsant [18], antiviral [19], anti-inflammatory [20], analgesic [21], antimicrobial, antihypertensive, antioxidant, anthelmintic, anti-diabetic, antihistaminic, and anti-cytotoxic activities (Fig. 2) [22-26].

New approaches and techniques for the synthesis of quinazolinone derivatives have expanded due to the prominence of N-heterocycles as a crucial structural motif in a number of physiologically active drugs [27]. Quinazolinones containing hydroxyl groups at positions 2 or 4 are tautomeric with their equivalent keto dihydroquinazolinones, referred to as benzoyleneurea [28].



The mechanisms of action and therapeutic uses of naturally and semisynthetic quinazolinone-based marketed drugs are provided in Table 1. The synthesized quinazolinones, along with their structures, therapeutic activities, and mechanisms of action, are shown in Table 2.

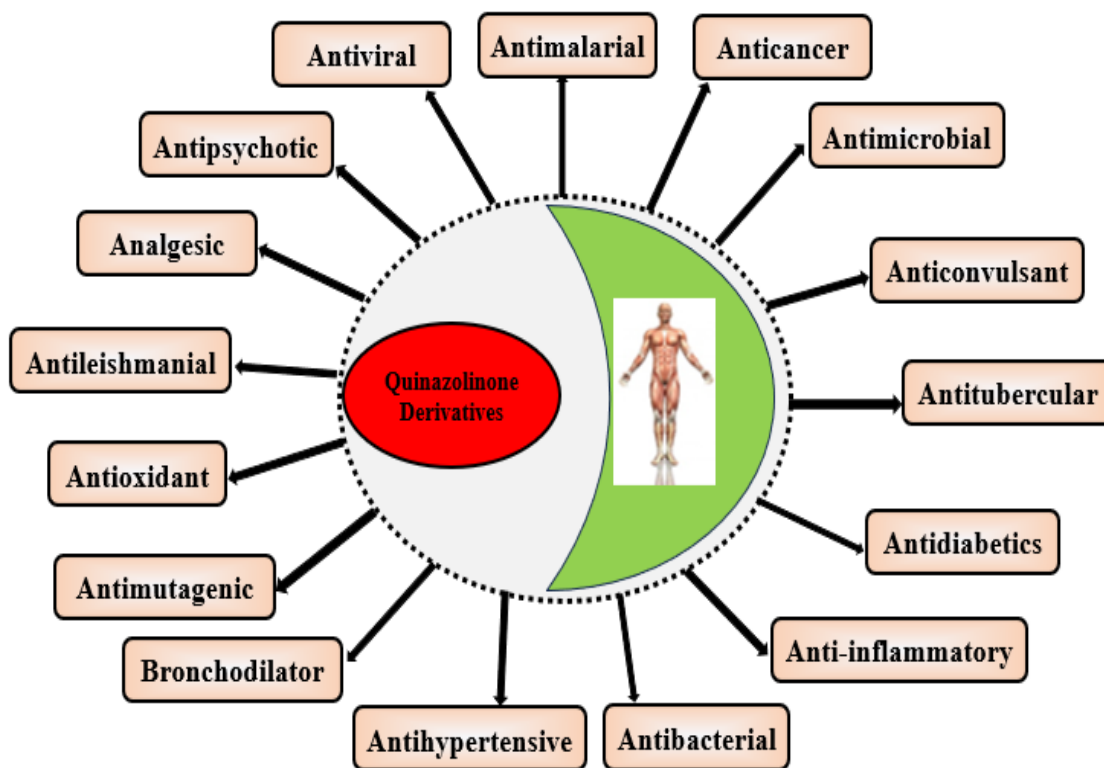
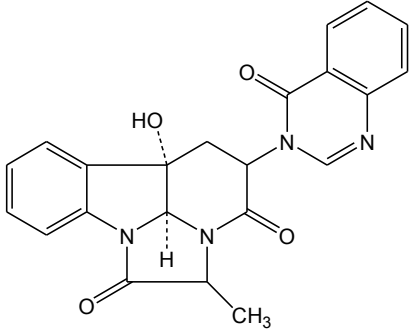
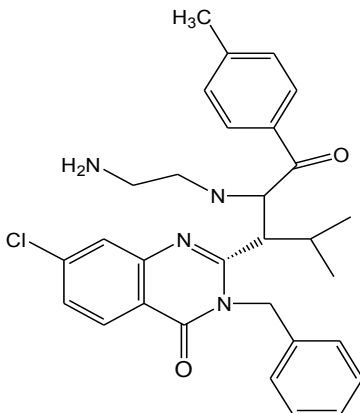
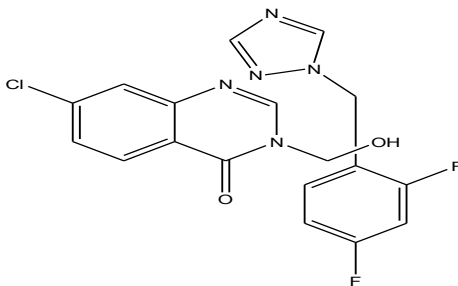
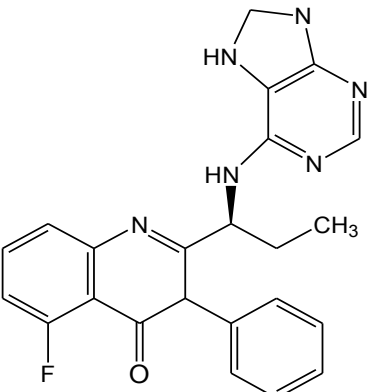
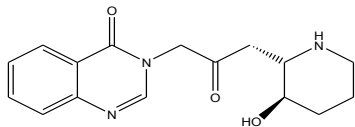
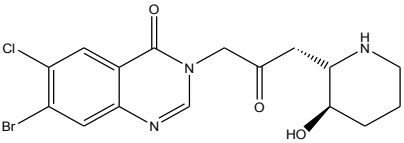
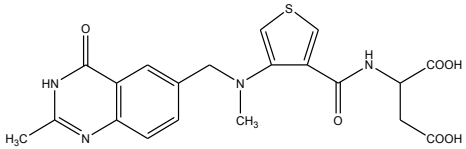
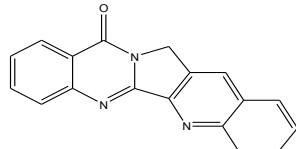
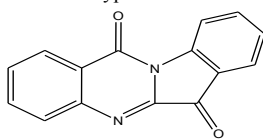
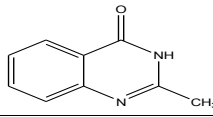
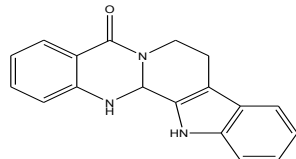
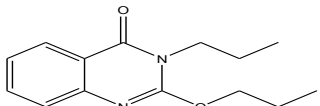
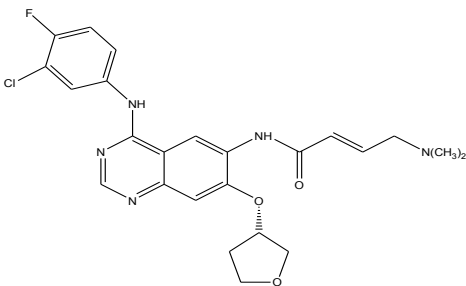


Fig. (2). Biological prospects of quinazolinones. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Table 1. Mechanisms of action and therapeutic uses of naturally and semisynthetic quinazolinones-based marketed drugs.

S. No.	Marketed Drugs	Mechanism of Action	Therapeutic Uses	References
1.	<p>Chaetominine</p> 	Inhibit cell division and regulate K562 cell cycle-dependent kinase	Cytotoxic activity against colon cancer	[29]
2.	<p>Ispinesib</p> 	Potent inhibitor of the KSP ATPase and inhibit the growth of cell division	Antineoplastic activity	[30]
3.	<p>Albaconazole</p> 	Inhibit cell wall synthesis and DNA and RNA synthesis	Antifungal activity and treatment of onychomycosis	[31]
4.	<p>Idelalisib</p> 	Protein kinase inhibitor and dihydrofolate reductase inhibitor	Haematological activity and regulation of folic acid	[32]

(Table 1) Contd...

S. No.	Marketed Drugs	Mechanism of Action	Therapeutic Uses	References
5.	<p>Febrifugine</p> 	Prevent cell damage and protect proteins, DNA, and RNA	Antimalarial, fibrosis, and coccidiostat activity	[33]
6.	<p>Halofuginone</p> 	Phosphoinositide-3 kinase signaling pathway and inhibit tumor cell proliferation	Activity against restenosis, carcinoma, and scleroderma	[34]
7.	<p>Raltitrexed</p> 	Decreased synthesis of thymidine triphosphate	Treatment of colon and rectum cancer	[35]
8.	<p>Luotonin A</p> 	Inhibition of pathogen (tobacco mosaic virus)	Fungicidal activity	[36]
9.	<p>Tryptanthrin</p> 	Inhibition of tumor proliferation in the cell phase (G ₁ and G ₂)	Antiproliferative and anti-inflammatory activity	[37]
10.	<p>Evodiamine</p> 	Inhibition of the proliferation of cell division and cell activity	Antitumor and neuroprotective activity and regulation of NSAIDs	[38]
11.	<p>2-methylquinazolinone</p> 	Inhibition of polymerization and detoxification of haemoglobin cells and inhibition of replication and transcription of nucleic acid	Antiviral and antimalarial activity	[39]
12.	<p>Proquinazid</p> 	Reduce blood sugar level and inhibit glucagon production	Anti-diabetic activity	[40]
13.	<p>Afatinib</p> 	Tyrosine kinase inhibitor	Treatment of cancer or regulation of epidermal growth factor receptor	[41]

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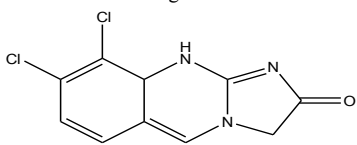
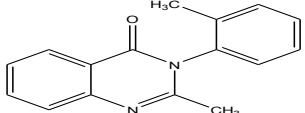
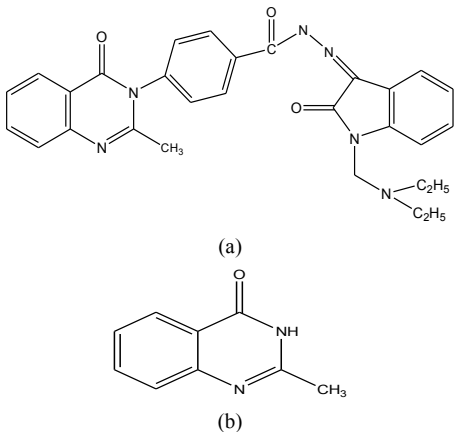
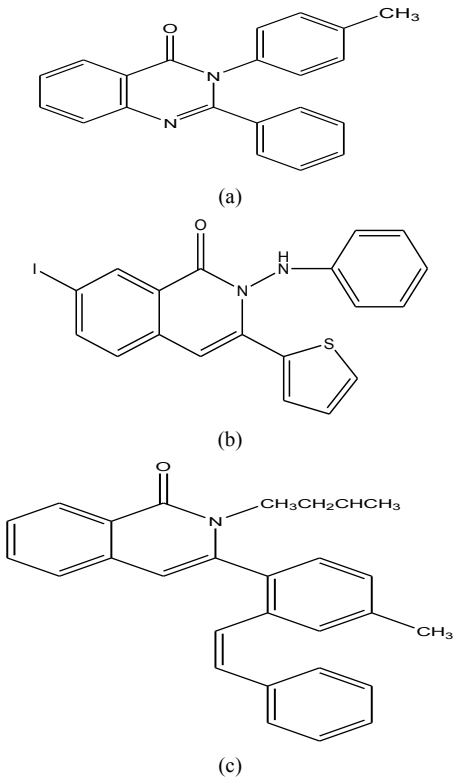
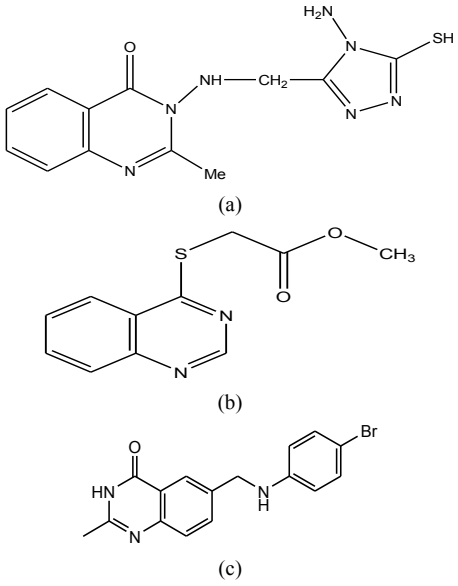
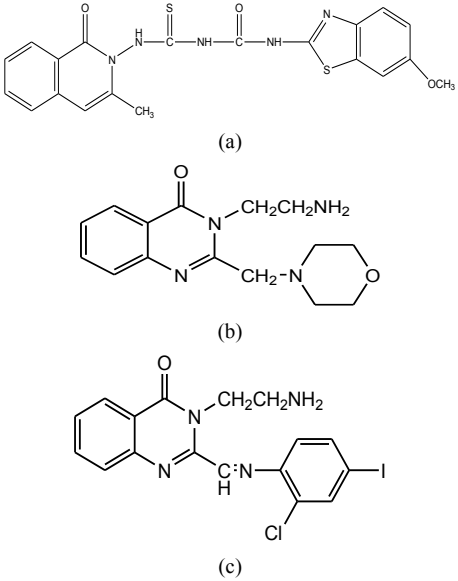
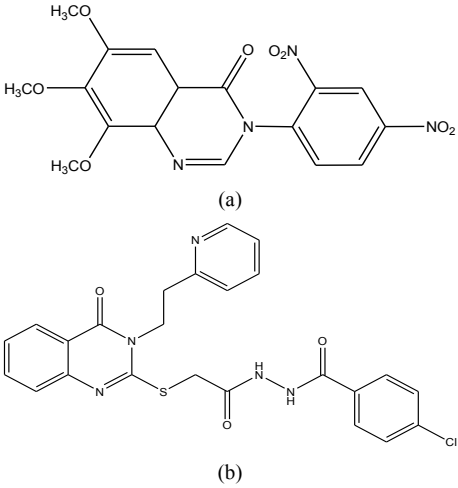
S. No.	Marketed Drugs	Mechanism of Action	Therapeutic Uses	References
14.	<p>Anagrelide</p> 	Reduce platelets and inhibit megakaryocytes	Treatment of blood disorders, <i>i.e.</i> , thrombocythemia	[42]
15.	<p>Methaqualone</p> 	Reduce anxiety and inhibit the γ -amino butyric acid level	Treatment of insomnia and relaxant activity	[43]

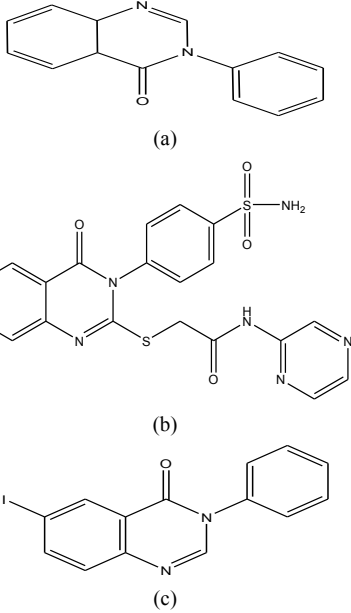
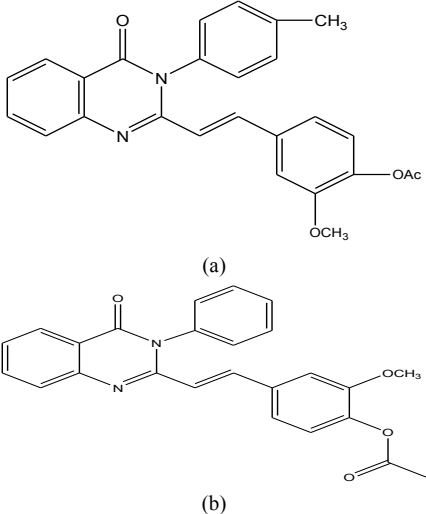
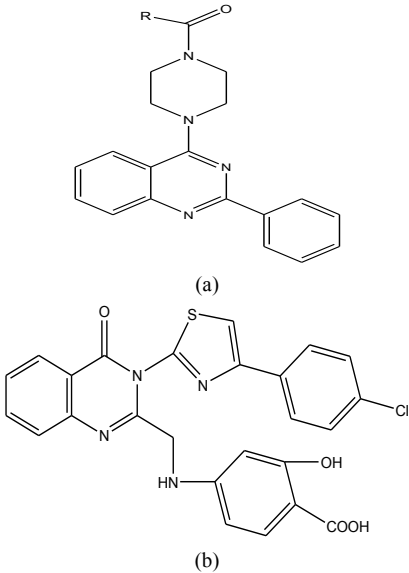
Table 2. Mechanism of action and therapeutic activities of synthesized quinazolinone compounds.

S. No.	Quinazolinone Compounds	Therapeutic Activities	Mechanism of action	References
1.	 <p>(a)</p> <p>(b)</p>	Analgesic activity	The drug molecule binds to the cyclooxygenase enzymes (COX-1 and COX-2), which are responsible for inhibiting the prostaglandin E2 synthesis and pain.	[44-46]
2.	 <p>(a)</p> <p>(b)</p> <p>(c)</p>	Anti-carcinogenic activity	The synthesized carcinogenic agents inhibit the biosynthesis of protein synthesis, nucleic acids, and apoptosis. The potential mechanism includes inhibiting epidermal growth factor receptor and neurofibromatosis signaling pathway, tumour proteasome, and topoisomerase-I and topoisomerase-II.	[47-53]

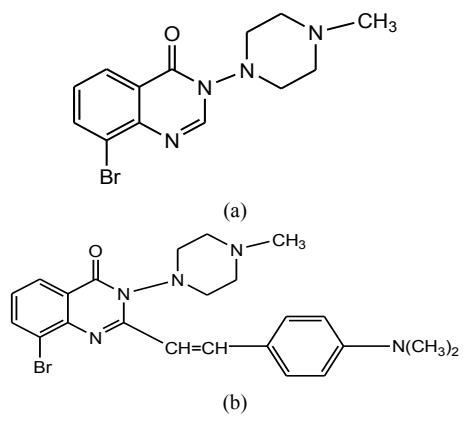
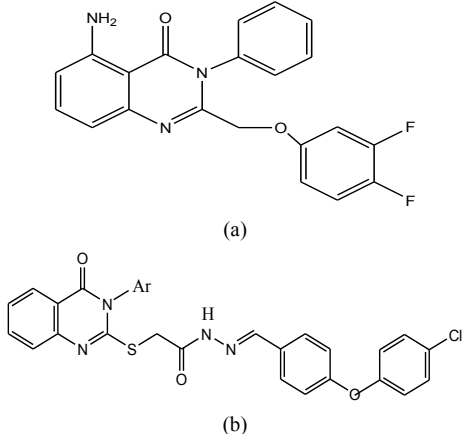
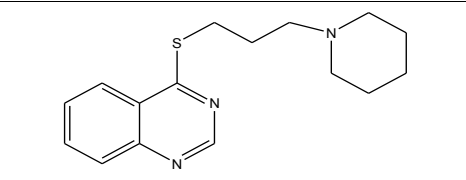
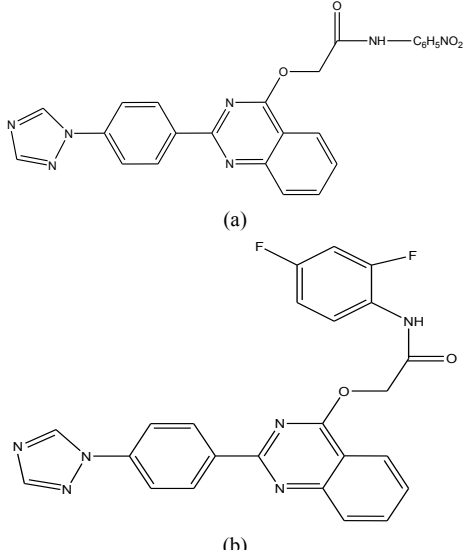
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S. No.	Quinazolinone Compounds	Therapeutic Activities	Mechanism of action	References
3.	 <p>(a)</p> <p>(b)</p> <p>(c)</p>	Antibacterial activity	Bacterial membranes consist of phospholipids that are stabilized by inorganic divalent ions, specifically calcium (Ca^{2+}) and magnesium (Mg^{2+}). The mechanism involves the inhibition of RNA synthesis, protein synthesis, ribosomal function, and structural proteins in cells. The newly synthesized drugs target both gram-negative and gram-positive bacteria.	[54-56]
4.	 <p>(a)</p> <p>(b)</p> <p>(c)</p>	Anticonvulsant activity	The mechanism includes effectively inhibiting seizures and convulsions through the use of synthesized derivatives of quinazolinone. The neuronal membrane potential relies on cellular channels, including sodium, potassium, and calcium. The drugs interact with the GABAergic system, which regulates neuronal activity.	[57-60]
5.	 <p>(a)</p> <p>(b)</p>	Anti-inflammatory activity	The drugs majorly act on the phospholipid cell membrane, including cyclic prostaglandin endoperoxide synthase. The drugs bind to opioid receptors, closed calcium channels, and open potassium channels, resulting in hyperpolarization. The new compounds also inhibit adenylyl cyclase.	[61-63]

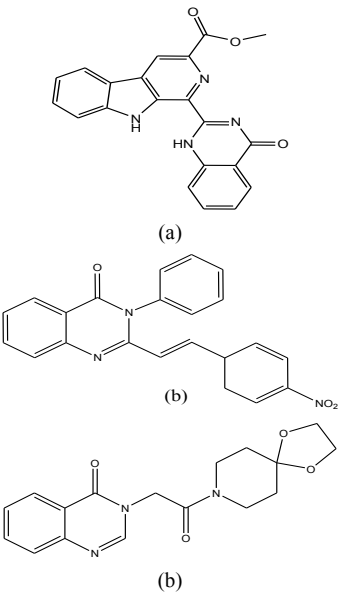
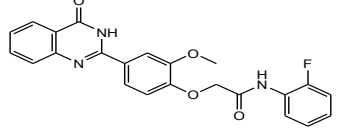
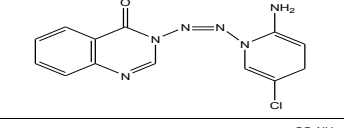
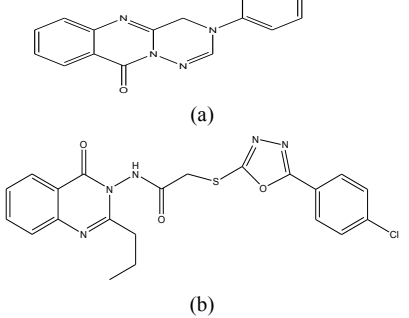
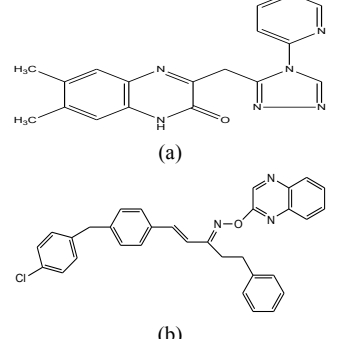
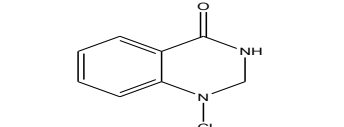
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S. No.	Quinazolinone Compounds	Therapeutic Activities	Mechanism of action	References
6.	 <p>(a)</p> <p>(b)</p> <p>(c)</p>	Antioxidant activity	The drugs minimise <i>in vitro</i> radicals produced during the oxidative process. The mechanism is contingent upon an appropriate number of free radicals and oxidizing agents.	[64, 65]
7.	 <p>(a)</p> <p>(b)</p>	Antimalarial activity	The drugs control the concentration-dependent blockade of Na ⁺ ionisation (Na ⁺ ↑ & K ⁺ ↓), conduction delay, and declining conduction velocity, exerting anti-malarial effects.	[66, 67]
8.	 <p>(a)</p> <p>(b)</p>	Antitubercular activity	The mechanism involves inhibiting mycolic acid synthesis, protein synthesis, and RNA-DNA polymerase activity. The drugs also diminish the development of bacteria in culture.	[68-70]

(Table 2) Contd...

S. No.	Quinazolinone Compounds	Therapeutic Activities	Mechanism of action	References
9.	 <p>(a)</p> <p>(b)</p>	Antihypertensive activity	The drugs reduce aminopeptidase A (APA) and the Na ⁺ /K ⁺ channel exchange mechanism. The primary function involves serving as an agonist at the β ₂ receptor and an antagonist at the β ₁ receptor, thereby regulating cardiovascular activity.	[71]
10.	 <p>(a)</p> <p>(b)</p>	Antitumor activity	ATP synthesis is impeded, and the permeability of membranes to Ca ²⁺ channels is elevated. Adenosine mono-phosphate-17 may induce apoptosis in K562 leukemia cells by impairing their electron transport chain and activating caspase-3.	[72-75]
11.		Bronchodilator activity	The drugs serve as agonist β ₂ receptors and regulate the gastrointestinal tract with the help of cytochrome P450 enzymes.	[76]
12.	 <p>(a)</p> <p>(b)</p>	Antimicrobial activity	The drugs act against growing bacterial strains that inhibit the bacterial ribosome, glycopolypeptide synthesis, physiological cell cycle integrity, and microbial cell wall synthesis.	[55, 2, 77-83]

(Table 2) Contd...

S. No.	Quinazolinone Compounds	Therapeutic Activities	Mechanism of action	References
13.	 <p>(a)</p> <p>(b)</p>	Antileishmanial activity	The drugs exhibit activity against <i>Leishmania amazonensis</i> and <i>Leishmania infantum</i> promastigotes and amastigotes. The infection is inhibited using pre-treated parasites.	[84-86]
14.		Antidiabetic activity	The drugs exert anti-diabetic effects by stimulating the β -pancreatic insulin cells against α -glucokinase inhibitors and reducing the glycogen levels.	[86-89]
15.		Antipsychotic effects	The drugs regulate dopamine receptor (D2) and inhibit neuronal transmission. Selective serotonin reuptake inhibitors have an inhibitory effect on dopaminergic receptors.	[90]
16.	 <p>(a)</p> <p>(b)</p>	Cytotoxic activity	The drugs inhibit cell division by targeting mitochondrial reductase, hence suppressing the cell cycle and proliferation of microbiological culture.	[90, 91]
17.	 <p>(a)</p> <p>(b)</p>	Antiviral activity	The drugs act on nucleotides to inhibit the RNA polymerase synthesis and act against the viral pathogen of <i>Tobamovirus</i> species.	[92, 93]
18.		Antianthelmintic activity	The drugs inhibit glycerophospholipid metabolism. They also exhibit activity against gastrointestinal parasites, such as <i>Fasciola spp.</i> and earthworms.	[94-97]

3. RECENT THERAPEUTIC APPLICATIONS OF QUINAZOLINONES

3.1. Analgesic Activity

Quinazolinone compounds were evaluated for analgesic activity using the tail-flick and carrageenan-induced paw tests. The tests were performed on Wistar albino mice. The drugs at a dose level of 10 and 20 mg/kg were administered orally for comparison. The test compounds were also orally administered at two dose levels (10 and 20 mg/kg). After that, the results were recorded three times; the percentage analgesic activity (PAA) was calculated by using the below formula: $PAA = [T_2 - T_1/10 - T_1] \times 100$, where T_1 is the reaction time (sec) before treatment, and T_2 is the reaction time (sec) after treatment. The compounds showed analgesic properties. The ulcer index of reference medications, aspirin and diclofenac, also demonstrated anti-inflammatory effectiveness [44, 45]. Quinazolinone ring modifications exhibited greater activity by substituting the butyl group for the methyl group, increasing lipophilicity at the C-2 position [46].

3.2. Anti-carcinogenic Activity

Newly synthesized quinazolinone compounds were evaluated for anticancer activity against the MCF-7 breast cancer cell line. Flow cytometric analysis revealed that the compounds induced cell cycle arrest in a dose-dependent manner, leading to increased accumulation at specific stages of the cell cycle. These effects were likely mediated by the compounds' potent binding affinity for the EGFR target protein, disrupting downstream signaling pathways involved in cell proliferation [47, 48]. The synthesized quinazolinone derivatives also exhibited effective antitumor activity [49]. The quinazolinone derivatives demonstrated the highest potential against human breast adenocarcinoma and human ductal breast epithelial tumor with significant IC_{50} values [50, 51]. Quinazolinones have recently been studied for their activity against EGFR/PI3-K pathways, tubulin-related production, and cancer cells. Designing and synthesizing quinazolinone derivatives have emerged as a promising path for the development of cancer therapeutics by elucidating the complexities of structure-activity interactions [52, 53].

3.3. Anti-bacterial Activity

Quinazolinone derivatives were further subjected to elementary analysis and computational structure evaluation in a study. The antibacterial activity of the compounds was evaluated *in vitro* activity using bacterial strains, such as *Escherichia coli*, *Staphylococcus aureus*, and *Proteus mirabilis* [54]. The antibacterial activity was evaluated by incubation of nutrient agar plates, which were then kept at 37°C for 24 hours and at set times (0, 30, 60, 90, and 120 minutes) during the incubation period; 10 μ L of each bacterial suspension was diluted and spread out on nutrient agar plates. The compounds demonstrated good antibacterial activity against gram-negative bacteria *E. coli* with the maximum inhibition at the drug concentration of 0.31 μ g/ml [55]. New quinazolinone derivatives were also synthesized by using new methods and evaluated for their ability to inhibit the biofilm of *Pseudomonas aeruginosa* [56].

3.4. Anti-convulsant Activity

Quinazolinone derivatives were designed and evaluated as anticonvulsants using a variety of newly developed epileptic models. The anticonvulsant properties of the compounds were investigated in mice using maximal electroshock therapy shock convulsion approaches administered intraperitoneally (i.p.) and subcutaneous pentylenetetrazole. Rats were quantitatively evaluated to determine the most powerful synthetic drug. The ED_{50} values of the compounds were 82.5 mmol/kg and 510.5 mmol/kg, respectively. The compounds proved superior to reference antiepileptic medications, ethosuximide and phenytoin [57, 58]. The anticonvulsant activity of newly synthesized quinazolinone derivatives was investigated *via* the maximal electroshock approach. The synthesized compounds demonstrated moderate anticonvulsant activities; the molecular modeling and pharmacological activity approaches confirmed GABA receptor to be an essential target for anticonvulsant activity [59, 60].

3.5. Anti-inflammatory Activity

The synthesized quinazolinone derivatives were evaluated for their anti-inflammatory activity by using the carrageenan-induced paw inflammatory model. The results showed effective anti-inflammatory activity [61]. The synthesized compounds with substituted 6-nitro quinazolinone-4-amine demonstrated promising anti-inflammatory activity [62]. The synthesized quinazolinone derivatives were evaluated for their inhibitory effects on COX-I and COX-II, and these compounds showed significant activity against COX-I and COX-II [63].

3.6. Antioxidant Activity

A series of quinazolinone-4-(3H)-one scaffolds were synthesized and evaluated for oxidant activity; they were characterized using FT-IR, NMR, and mass spectral analysis. Modern research techniques were utilized to investigate the *in vivo* antioxidant activity of quinazolinones [64]. Antioxidant chemicals exhibit their effects by chelating transition of metal ions, electron migration, or hydrogen atom shift. The synthesized quinazolinones were evaluated for antioxidant properties and compared to ascorbic acid by using the DPPH assay. In the study, the compounds exhibited higher metal scavenging activity than ascorbic acid [65].

3.7. Anti-malarial Activity

The heterocyclic compounds were cyclized containing nitrogen atoms and they showed promising antimalarial activity. The compounds were investigated using mice infected with *Plasmodium berghei* for their *in vivo* antimalarial activity. The therapy against *Plasmodium berghei* using the targeted compounds was carried out for four consecutive days. Then, the blood smear was collected from the mice's tail after 24 hours. The mean parasitaemia level of groups was microscopically determined by counting the number of red blood cells. Enhanced effectiveness against malaria was demonstrated by the test drugs, with a percent inhibition of 70.01 and 74.18, respectively [66]. The newly synthesized quinazolinone compounds were evaluated against the active resistant strains of malaria and they showed maximum ef-

fects than the standard drug *in vivo* against the murine model of malaria [67].

3.8. Anti-tubercular Activity

The piperazine-linked quinazolinone derivatives were synthesized and the drug molecules were evaluated for their inhibition activity against *Mycobacterium tuberculosis*. The nitrate reductase assay method relies on the capacity of *Mycobacterium tuberculosis* to convert nitrate to nitrite, with the reduction identified by particular chemicals that induce a colour shift. The anti-mycobacterial activity was demonstrated by the drugs with MIC values ranging from 2 to 16 mg/ml [68-70].

3.9. Anti-hypertensive Activity

The substituted quinazolinone scaffolds were evaluated for their *in vivo* antihypertensive activity in another research work. The investigation was conducted on cats of both sexes weighing between 2.5 and 4 kg. The animals were anesthetized using α -chloralose (80 mg/kg) suspended in propylene glycol. The femoral vein on one side was cannulated with an implanted polyethylene tube for intravenous administration of chemicals at a dosage of 5 mg/kg body weight. Compared to the reference drug prazosin, which lowers blood pressure by inhibiting α_1 adrenergic molecules, substituted quinazolinone compounds demonstrated more potent hypotensive activity. An approximate lethal dose (ALD) of $50 > 1000$ mg/kg has been demonstrated by the substances, with > 1200 mg/kg being the greatest [71].

3.10. Antitumor Activity

A number of newly synthesized derivatives of 3-methyl quinazolinone were assessed for their potential to inhibit tumor growth of human cancer cell lines *in vitro* and epidermal cells. The most effective compounds were found to require EGFR inhibition for their activity, and their receptor binding mechanisms were elucidated through molecular docking studies [72, 73]. The anticancer activity of the newly developed 6-iodo-3-quinazolinone derivatives was characterized by computational investigations. The computational studies showed that the newer quinazolinone molecules exhibited significant effectiveness against tumor cells [74, 75].

3.11. Bronchodilator Activity

The synthesized quinazolinone and quinazolinone derivatives were evaluated for their *in vitro* bronchodilator activity. The rats were anesthetized using thiopental sodium (80 mg/kg, i.p.). The drugs were injected by the cannula through the intravenous route to induce bronchodilation. Newly synthesized compounds were assessed for *in vitro* bronchodilator activity in anesthetized rats at different doses (5, 10, 20, and 40 mg/kg); they demonstrated greater biological effects than theophylline, which was used as a reference drug [76].

3.12. Antimicrobial Activity

The synthesized quinazolinone derivatives were evaluated for their activity against Gram-positive bacteria, including *Bacillus cereus*, *Bacillus subtilis*, and *Staphylococcus aureus*, using the agar well method. The standard drugs ciprofloxacin and fluconazole were used for the measurement of

the diameters of inhibition zones. The antimicrobial activity was based on the substitution at the C-2 position of quinazolinone compounds [55, 2, 77]. The synthesized 1,2,4-triazolo[1,5-a]quinazolinone derivatives were evaluated for their antibacterial, antifungal, and anticorrosion activities, and their inhibition of bacterial and fungal strains was evaluated by the well diffusion method [78-80]. Also, the synthesized quinazolinone-4-(3H)-one derivatives were evaluated for their antimicrobial activity using the cup plate method by measuring their zone of inhibition in interacting with the targeted bacterial proteins and molecules [81-83].

3.13. Antileishmanial Activity

The synthesized derivatives of quinazolinone showed promising *in vitro* antileishmanial activity. The compounds were subjected to cyclization, condensation, and hydrolysis reactions. The compounds were assessed by TLC, melting point, FT-IR, ¹H-NMR, and elemental microanalyses. Their *in vitro* antileishmanial activity against the bacterial strain *Leishmania donovani* was observed to be promising (IC₅₀ = 0.0212 μ g/mL) [84, 85]. The 4(3H)-quinazolinone skeleton was explored for the design and development of novel molecules, with their activities evaluated against *Leishmania donovani* and other *Leishmania* species [86].

3.14. Antidiabetic Activity

A series of quinazolinone derivatives were synthesized and evaluated for anti-diabetic activity. The activity was induced by intravenous injection of a 120 mg/kg body weight dosage, administered one hour after alloxan administration. The mice were administered a 5% dextrose solution *via* a feeding bottle. The diabetic activity was monitored, and after 72 hours, blood glucose levels were assessed using a glucometer. Diabetic rats (with blood glucose levels ranging from 200-300 mg/dL) were selected for the study, and the effects of glucosidase inhibitors were evaluated [87, 88]. Newly synthesized quinazolinone-4(3H)-one derivatives were assessed in comparison to α -glucosidase with an IC₅₀ value of 14.4 μ m. The compounds exhibited the strongest α -glucosidase inhibition *in vitro*, approximately 50 times stronger than acarbose. The quinazolinone-4(3H)-one derivatives were further examined by molecular docking studies [89].

3.15. Antipsychotic Activity

Moreover, the newly synthesized quinazolinone-4-one derivatives were evaluated for their antipsychotic properties in the treatment of schizophrenia [90]. The derivatives of quinazolinone were evaluated for their antagonistic effects compared to serotonin and dopamine receptors. Atypical antipsychotics function by binding to the D₂ and 5HT_{2A} receptors, which in turn alters serotonin and dopamine levels. According to structure-activity relationship (SAR) studies, the inclusion of electron-withdrawing groups enhanced the antibacterial activity of the compounds. The most potent molecules exhibited therapeutic profiles that compared favorably with the standard drug. Molecular docking studies further supported their potential, with the synthesized compounds showing strong binding affinities. Validation of their antipsychotic activity was conducted using conventional ketanserin as a reference ligand [91].

3.16. Cytotoxic Activity

The newly synthesized quinazolinone derivatives were evaluated using the MTT assay for their cytotoxic effects on human tumour cell lines, HCT-116 (colon) and MCF-7 (breast). The synthesized compounds showed to be the most potent anticancer drugs for a range of tumor cell lines, when compared to doxorubicin [92]. The oxadiazole-quinazolinone derivatives having an amide linker were further examined for their cytotoxicity against HeLa and MCF-7 cell lines. The quinazolinone compounds showed potential cytotoxic activities with an IC₅₀ value of 7.52 μm against the HeLa cell line [93].

3.17. Antiviral Activity

The synthesized quinazolinone analogs were assessed for their antiviral activity. The heterocyclic compounds have a wide range of biological properties and potential uses. The quinazolinone compounds were evaluated for their effectiveness against different RNA and DNA viruses in terms of cytotoxicity and antiviral activity [94]. To optimize viral suppression, the pharmacokinetic characteristics of amprevir and ritonavir were evaluated in individuals infected with human immunodeficiency virus (HIV), assessing the likelihood of achieving effective target exposure. Substantial suppression was observed for both wild-type and reduced-susceptibility HIV isolates, with EC₅₀ values ranging from 0.12 μM to as low as 0.05 μM. These findings indicated that significant exposure to protease inhibitors can maintain effective antiviral activity, supporting their role in achieving sustained viral suppression [95].

3.18. Anthelmintic Activity

Quinazolinone-chalcone derivatives were evaluated for their anthelmintic activity *in vitro*. For the assessment of anthelmintic activity, equal-sized *Pheretima posthuma* (earthworms), each measuring approximately 9 ± 1.5 cm in length, were procured from Guntur agricultural sources. To get rid of the sticking debris, the worms were cleaned with regular saline. To obtain a 10 mg/ml concentration, the synthesized compounds were dissolved in 1% DMF in normal saline and then placed in a 4-inch Petri dish. The movement of the earthworms was monitored until they became paralyzed and eventually died. Paralysis was confirmed when the worms failed to respond to external stimuli. Death was further indicated by a loss of motility and the gradual fading of the worms' external coloration. Under the same circumstances, the activity of the compounds was compared to that of conventional anthelmintic drugs, such as piperazine citrate [96, 97]. Synthesized brominated derivatives of 2, 3-dihydroquinazolin-4(1H)-ones were evaluated for their anthelmintic activity and interaction with newly synthesized bioactive molecules using bovine serum albumin [98].

CONCLUSION

Many biological activities, including analgesic, anti-cancer, antibacterial, anticonvulsant, anti-inflammatory, antioxidant, antimalarial, anti-tubercular, antihypertensive, antitumor, bronchodilator, antimicrobial, antileishmanial, antidiabetic, antipsychotic, cytotoxic, antiviral, antifungal, and anthelmintic, of quinazolinone-based compounds have

been reported by researchers. Therefore, quinazolinones can prove to be important heterocyclic molecules in the treatment of diseases and infections. Recent studies on quinazolinones have shown their therapeutic and biological prospects upon interaction with various receptors. Quinazolinones have been demonstrated to possess significant therapeutic applications and can prove to be useful in drug design and development.

AUTHORS' CONTRIBUTION

A.K. contributed to the writing of the review and preparation of the original draft; S.K. performed supervision, review, and editing.

LIST OF ABBREVIATIONS

PAA	=	Percentage Analgesic Activity
ALD	=	Approximate Lethal Dose
SAR	=	Structure-Activity Relationship

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

- [1] Faraji, A.; Motahari, R.; Hasanvand, Z.; Oghabi Bakhshaiesh, T.; Toolabi, M.; Moghimi, S.; Firoozpour, L.; Boshagh, M.A.; Rahmani, R.; Ketabforoosh, S.H.M.E.; Bijanzadeh, H.R.; Esmaeili, R.; Foroumadi, A. Quinazolin-4(3H)-one based agents bearing thiadiazole-urea: Synthesis and evaluation of anti-proliferative and anti-angiogenic activity. *Bioorg. Chem.*, **2021**, *108*, 104553. <http://dx.doi.org/10.1016/j.bioorg.2020.104553> PMID: 33376012
- [2] Kohli, D.; Hashim, S.R.; Vishal, S.; Sharma, M.; Singh, A.K. Synthesis and antibacterial activity of quinazolinone derivatives. *Int. J. Pharm. Pharm. Sci.*, **2009**, *1*(11), 63-169.
- [3] Hameed, A.; Rashida, M.A.; Uroos, M.; Ali, S.A. Quinazoline and quinazolinone as important medicinal scaffolds: A comparative patent review. *Expert Opin. Ther. Pat.*, **2018**, *28*(4), 281-297. <http://dx.doi.org/10.1080/13543776.2018.1432596> PMID: 29368977
- [4] Kumar, P.; Tomar, V.; Joshi, R.K.; Nemiwal, M. Nanocatalyzed synthetic approach for quinazoline and quinazolinone derivatives: A review (2015–present). *Synth. Commun.*, **2022**, *52*(6), 795-826. <http://dx.doi.org/10.1080/00397911.2022.2041667>
- [5] Jothieshwari, D.; Reddy, K.B. Antioxidant activity of some newer dihydro quinazolin-4-one derivatives. *IJNTPS*, **2015**, *(5)*, 5.
- [6] Sanobar, S.A.; Sreelatha, K.; Sruthi, K. Structure-based virtual screening, design, synthesis and biological evaluation of 3-Sulfonamido substituted quinazolinones as anti-zika viral agents. *J. Pharm. Sci. & Res.*, **2020**, *12*, 1452-1465.
- [7] Peng, J-W.; Yin, X-D.; Li, H.; Ma, K-Y.; Zhang, Z-J.; Zhou, R.; Wang, Y-L.; Hu, G-F.; Liu, Y-Q. Design, synthesis, and structure-

- activity relationship of quinazolinone derivatives as potential fungicides. *J. Agric. Food Chem.*, **2021**, *69*(16), 4604-4614. <http://dx.doi.org/10.1021/acs.jafc.0c05475>
- [8] Mahato, A.K.; Srivastava, B. Chemistry, structure-activity relationship and biological activity of quinazoline-4(3H)-one derivatives. *Med. Chem.*, **2011**, *2*, 1-6.
- [9] Balakumar, C.; Lamba, P.; Pran Kishore, D.; Lakshmi Narayana, B.; Venkat Rao, K.; Rajwinder, K.; Raghuram Rao, A.; Shireesha, B.; Narsaiah, B. Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines. *Eur. J. Med. Chem.*, **2010**, *45*(11), 4904-4913. <http://dx.doi.org/10.1016/j.ejmech.2010.07.063> PMID: 20800934
- [10] Vijayakumar, B.; Prasanthi, P.; Teja, K.M. Quinazolinone derivatives and pharmacological activities: A review. *IJPCA*, **2013**, *3*(1), 10-21.
- [11] He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. Pharmaceutical prospects of naturally occurring quinazolinone and its derivatives. *Fitoterapia*, **2017**, *119*, 136-149. <http://dx.doi.org/10.1016/j.fitote.2017.05.001> PMID: 28495308
- [12] Kerru, N.; Singh, P.; Koorbanally, N.; Raj, R.; Kumar, V. Recent advances (2015–2016) in anticancer hybrids. *Eur. J. Med. Chem.*, **2017**, *142*, 179-212. <http://dx.doi.org/10.1016/j.ejmech.2017.07.033> PMID: 28760313
- [13] Mhaske, S.B.; Argade, N.P. The chemistry of recently isolated naturally occurring quinazolinone alkaloids. *Tetrahedron*, **2006**, *62*(42), 9787-9826. <http://dx.doi.org/10.1016/j.tet.2006.07.098>
- [14] Bisht, A.S.; Negi, J.S.; Sharma, D.K. Chemistry and activity of quinazolinone moiety: A systematic review study. *IJPCA*, **2020**, *7*(2), 61-65. <http://dx.doi.org/10.18231/j.ijpca.2020.009>
- [15] Abuelizz, H.A.; Marzouk, M.; Ghabbour, H.; Al-Salahi, R. Synthesis and anticancer activity of new quinazolinone derivatives. *Saudi Pharm. J.*, **2017**, *25*(7), 1047-1054. <http://dx.doi.org/10.1016/j.jsps.2017.04.022> PMID: 29158714
- [16] Al-deeb, O.; Alafeefy, A.M. Synthesis of some new 3H-quinazolinone derivatives as potential antitubercular agents. *World Appl. Sci. J.*, **2008**, *5*, 94-99.
- [17] Auti, P.S.; George, G.; Paul, A.T. Recent advances in the pharmacological diversification of quinazolinone/quinazolinone hybrids. *RSC Advances*, **2020**, *10*(68), 41353-41392. <http://dx.doi.org/10.1039/D0RA06642G> PMID: 35516563
- [18] Bhandari, S.V.; Deshmane, B.J.; Dangare, S. Anticonvulsant activities of some novel 3-[5-Substituted-1, 3, 4-thiadiazole-yl]-2-styryl quinazolinone-4(3H)-ones. *Pharmacologyonline*, **2008**, *2*, 604-613.
- [19] Wang, Z.; Wang, M.; Yao, X.; Li, Y.; Tan, J.; Wang, L.; Qiao, W.; Geng, Y.; Liu, Y.; Wang, Q. Design, synthesis and antiviral activity of novel quinazolinones. *Eur. J. Med. Chem.*, **2012**, *53*, 275-282. <http://dx.doi.org/10.1016/j.ejmech.2012.04.010> PMID: 22546200
- [20] Chandrika, M.P.; Yakaiah, T.; Raghu Ram Rao, A.; Narsaiah, B.; Chakra Reddy, N.; Sridhar, V.; Rao, V.J. Synthesis of novel 4, 6-disubstituted quinazolinone derivatives, their anti-inflammatory and anti-cancer activity (cytotoxic) against U937 leukemia cell lines. *Eur. J. Med. Chem.*, **2008**, *43*(4), 846-852. PMID: 17689837
- [21] Alagarsamy, V.; Muthukumar, V.; Pavalarani, N.; Vasanthanathan, P.; Revathi, R. Synthesis, analgesic and anti-inflammatory activities of some novel 2,3-disubstituted quinazolinone-4(3H)-ones. *Biol. Pharm. Bull.*, **2003**, *26*(4), 557-559. <http://dx.doi.org/10.1248/bpb.26.557> PMID: 12673044
- [22] Dinakaran, M.; Selvam, P.; DeClercq, E.; Sridhar, S.K. Synthesis, antiviral and cytotoxic activity of 6-bromo-2,3-disubstituted-4(3H)-quinazolinones. *Biol. Pharm. Bull.*, **2003**, *26*(9), 1278-1282. <http://dx.doi.org/10.1248/bpb.26.1278> PMID: 12951471
- [23] Nanda, A.K.; Ganguli, S.; Chakraborty, R. Antibacterial activity of some 3-(arylideneamino)-2-phenylquinazolinone-4(3H)-ones: synthesis and preliminary QSAR studies. *Molecules*, **2007**, *12*(10), 2413-2426. <http://dx.doi.org/10.3390/12102413> PMID: 17978766
- [24] Ghabrial, S.S.; Gaber, H.M. Dipolar cycloaddition reactions with quinazolinones: A new route for the synthesis of several annelated pyrrolo and pyridazine quinazolinone derivatives. *Molecules*, **2003**, *8*(5), 401-410. <http://dx.doi.org/10.3390/80500401>
- [25] Refaie, F.M.; Esmat, A.Y.; Gawad, S.M.A.; Ibrahim, A.M.; Mohamed, M.A. The antihyperlipidemic activities of 4(3H) quinazolinone and two halogenated derivatives in rats. *Lipids Health Dis.*, **2005**, *4*(1), 22. <http://dx.doi.org/10.1186/1476-511X-4-22> PMID: 16202158
- [26] Mourad, A.F.E.; Aly, A.A.; Farag, H.H.; Beshr, E.A. Microwave assisted synthesis of triazoloquinazolinones and benzimidazoquinazolinones. *Beilstein J. Org. Chem.*, **2007**, *3*, 11. <http://dx.doi.org/10.1186/1860-5397-3-11> PMID: 17338816
- [27] Rakesh, K.P.; Darshini, N.; Shubhavathi, T.; Mallesha, N. Biological application of quinazolinone analogues; A review. *Int. J. Org. Med. Chem.*, **2017**, *2*(2), 555-585.
- [28] Asif, M. Chemical characteristics, synthetic methods, and biological potential of quinazolinone and quinazolinone derivatives. *Int. J. Med. Chem.*, **2014**, *2014*, 1-27. <http://dx.doi.org/10.1155/2014/395637> PMID: 25692041
- [29] Yao, J.; Xiao, J.; Wei, X.; Lu, Y. Chaetominine induces cell cycle arrest in human leukemia K562 and colon cancer SW1116 cells. *Oncol. Lett.*, **2018**, *16*(4), 4671-4678. <http://dx.doi.org/10.3892/ol.2018.9161> PMID: 30214601
- [30] Lad, L.; Luo, L.; Carson, J.D.; Wood, K.W.; Hartman, J.J.; Copeland, R.A.; Sakowicz, R. Mechanism of inhibition of human KSP by ispinesib. *Biochemistry*, **2008**, *47*(11), 3576-3585. <http://dx.doi.org/10.1021/bi702061g> PMID: 18290633
- [31] Bharti, S.K.; Nath, G.; Tilak, R.; Singh, S.K. Synthesis, antibacterial and anti-fungal activities of some novel Schiff bases containing 2,4-disubstituted thiazole ring. *Eur. J. Med. Chem.*, **2010**, *45*(2), 651-660. <http://dx.doi.org/10.1016/j.ejmech.2009.11.008> PMID: 19932927
- [32] Niculescu-Duvaz, I. Thymitaq (Zarix). *Curr. Opin. Investig. Drugs*, **2001**, *2*(5), 693-705. PMID: 11569949
- [33] Zhu, S.; Wang, J.; Chandrashekar, G.; Smith, E.; Liu, X.; Zhang, Y. Synthesis and evaluation of 4-quinazolinone compounds as potential antimalarial agents. *Eur. J. Med. Chem.*, **2010**, *45*(9), 3864-3869. <http://dx.doi.org/10.1016/j.ejmech.2010.05.040> PMID: 20538379
- [34] Keller, T.L.; Zocco, D.; Sundrud, M.S.; Hendrick, M.; Edenius, M.; Yum, J.; Kim, Y.J.; Lee, H.K.; Cortese, J.F.; Wirth, D.F.; Dignam, J.D.; Rao, A.; Yeo, C.Y.; Mazitschek, R.; Whitman, M. Halofuginone and other febrifugine derivatives inhibit prolyl-tRNA synthetase. *Nat. Chem. Biol.*, **2012**, *8*(3), 311-317. <http://dx.doi.org/10.1038/nchembio.790> PMID: 22327401
- [35] Van Cutsem, E.; Cunningham, D.; Maroun, J.; Cervantes, A.; Glimelius, B. Raltitrexed: Current clinical status and future directions. *Ann. Oncol.*, **2002**, *13*(4), 513-522. <http://dx.doi.org/10.1093/annonc/mdf054> PMID: 12056700
- [36] Hao, Y.; Wang, K.; Wang, Z.; Liu, Y.; Ma, D.; Wang, Q. Luotonin A and its derivatives as novel antiviral and antipathogenic fungus agents. *J. Agric. Food Chem.*, **2020**, *68*(33), 8764-8773. <http://dx.doi.org/10.1021/acs.jafc.0c04278> PMID: 32806124
- [37] Popov, A.M.; Degenkova, L.G.; Moskovkina, T.V.; Grammatikova, N.E.; Kuzmich, A.S.; Chernikov, O.V.; Schekotichin, A.E.; Stonik, V.A. Biological activity and probable mechanisms of action of derivatives of tryptanthrin and mostotrin alkaloids. *Dokl. Biochem. Biophys.*, **2022**, *507*(1), 363-366. <http://dx.doi.org/10.1134/S1607672922340105> PMID: 36787003
- [38] Luning, Li. Research advances in antitumor mechanism of evodiamine. *J. Chem.*, **2022**, 2784257.
- [39] Zhou, W.; Wang, H.; Yang, Y.; Chen, Z.S.; Zou, C.; Zhang, J. Chloroquine against malaria, cancers and viral diseases. *Drug Discov. Today*, **2020**, *25*(11), 2012-2022. <http://dx.doi.org/10.1016/j.drudis.2020.09.010> PMID: 32947043
- [40] Peter, R.; Rehani, H. Safety and mode of action of diabetes Medications in comparison with 5-Aminolevulinic acid (5-ALA). *J. Diabetes Res.*, **2019**, 4267357.
- [41] Keating, G.M. Afatinib: A review in advanced non-small cell lung cancer. *Target. Oncol.*, **2016**, *11*(6), 825-835. <http://dx.doi.org/10.1007/s11523-016-0465-2> PMID: 27873136
- [42] Birgegård, G. The use of anagrelide in myeloproliferative neoplasms, with focus on essential Thrombocythemia. *Curr. Hematol. Malig. Rep.*, **2016**, *11*(5), 348-355. <http://dx.doi.org/10.1007/s11899-016-0335-0> PMID: 27497846

- [43] Vankadari, N. Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein. *Int. J. Antimicrob. Agents*, **2020**, *56*(2), 105998. <http://dx.doi.org/10.1016/j.ijantimicag.2020.105998> PMID: 32360231
- [44] Saravanan, G.; Alagarsamy, V.; Prakash, C.R. Synthesis, analgesic, anti-inflammatory and ulcerogenic properties of some novel N'-((1-(substituted amino)methyl)-2-oxoindolin-3-ylidene)-4-(2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl)benzohydrazide derivatives. *Drug Discov. Ther.*, **2012**, *6*(2), 78-87. <http://dx.doi.org/10.5582/ddt.2012.v6.2.78> PMID: 22622017
- [45] Osarumwense, P.O.; Edema, M.O.; Usifoh, C.O. Synthesis and anaginic activities of Quinazolin-4(3H)-One, 2-Methyl-4(3H)-Quinazolinone and 2-Phenyl-4(3H)-quinazolin-4(3H)-one. *J. Drug Deliv. Ther.*, **2020**, *10*(4-s), 87-91. <http://dx.doi.org/10.22270/jddt.v10i4-s.4209>
- [46] Zayed, M.F. Medicinal chemistry of quinazolines as analgesic and anti-inflammatory agents. *ChemEngineering*, **2022**, *6*(6), 94. <http://dx.doi.org/10.3390/chemengineering6060094>
- [47] Gatadi, S.; Pulivendala, G.; Gour, J.; Malasala, S.; Bujji, S.; Parupalli, R.; Shaikh, M.; Godugu, C.; Nanduri, S. Synthesis and evaluation of new 4(3H)-Quinazolinone derivatives as potential anticancer agents. *J. Mol. Struct.*, **2020**, *1200*, 127097. <http://dx.doi.org/10.1016/j.molstruc.2019.127097>
- [48] Manasa, K.; Sidhaye, R.V.; Radhika, G.; Nalini, C.N. Synthesis, antioxidant and anticancer activity of quinazolinone derivatives. *Current Pharma Research.*, **2011**, *1*(2), 101-105. <http://dx.doi.org/10.33786/JCPR.2011.v01i02.002>
- [49] Kanuma, K.; Omodera, K.; Nishiguchi, M.; Funakoshi, T.; Chaki, S.; Semple, G.; Tran, T.A.; Kramer, B.; Hsu, D.; Casper, M.; Thomsen, B.; Sekiguchi, Y. Lead optimization of 4-(dimethylamino)quinazolines, potent and selective antagonists for the melanin-concentrating hormone receptor 1. *Bioorg. Med. Chem. Lett.*, **2005**, *15*(17), 3853-3856. <http://dx.doi.org/10.1016/j.bmcl.2005.05.121> PMID: 16002290
- [50] Mahdavi, M.; Pedroo, K.; Safavi, M.; Saeedi, M.; Pordeli, M.; Ardestani, S.K.; Emami, S.; Adib, M.; Foroumadi, A.; Shafiee, A. Synthesis and anticancer activity of N-substituted 2-arylquinazolinones bearing trans-stilbene scaffold. *Eur. J. Med. Chem.*, **2015**, *95*, 492-499. <http://dx.doi.org/10.1016/j.ejmech.2015.03.057> PMID: 25847767
- [51] Sonousi, A.; Hassan, R.A.; Osman, E.O.; Abdou, A.M.; Emam, S.H. Design and synthesis of novel quinazolinone-based derivatives as EGFR inhibitors with antitumor activity. *J. Enzyme Inhib. Med. Chem.*, **2022**, *37*(1), 2644-2659. <http://dx.doi.org/10.1080/14756366.2022.2118735> PMID: 36146940
- [52] Kaur, J.; Kaur, S. Unveiling the therapeutic potential of quinazolinone derivatives in cancer treatment: A comprehensive exploration. *Chemistry Europe*, **2024**, *9*(45), 2365-6549.
- [53] Dhokale Sandhya, ; Thakar Snehal, ; Bansode Deepali, Design and synthesis of novel 1-substituted -3-(4-oxo-2-phenylquinazolin-3(4H)-yl) urea and thiourea analogues targeting on TACE, as potent anticancer agents. *GSC Biol Pharm Sci.*, **2020**, *12*(2), 194-205. <http://dx.doi.org/10.30574/gscbps.2020.12.2.0255>
- [54] Atia, A.J.K.; Ai-Mufgeiy, S.S. Synthesis and antibacterial activities of new-3-Amino-2-Methyl-Quinazolin-4 (3h)-One derivatives. *Am J Chem.*, **2012**, *2*(3), 150-156. <http://dx.doi.org/10.5923/j.chemistry.20120203.09>
- [55] Hassan, R.M.; Yehia, H.; El-Behairy, M.F.; El-Azzouny, A.A.S.; Aboul-Enein, M.N. Design and synthesis of new quinazolinone derivatives: Investigation of antimicrobial and biofilm inhibition effects. *Mol. Divers.*, **2024**. <http://dx.doi.org/10.1007/s11030-024-10830-y> PMID: 38656598
- [56] Zhan, X.; Xu, Y.; Qi, Q.; Wang, Y.; Shi, H.; Mao, Z. Synthesis, cytotoxic, and antibacterial evaluation of quinazolinone derivatives with substituted amino moiety. *Chem. Biodivers.*, **2018**, *15*(3), e1700513. <http://dx.doi.org/10.1002/cbdv.201700513> PMID: 29333734
- [57] Malik, S.; Bahare, R.S.; Khan, S.A. Design, synthesis and anticonvulsant evaluation of N-(benzo[d]thiazol-2-ylcarbonyl)-2-methyl-4-oxoquinazolinone-3(4H)-carbothioamide derivatives: A hybrid pharmacophore approach. *Eur. J. Med. Chem.*, **2013**, *67*, 1-13. <http://dx.doi.org/10.1016/j.ejmech.2013.06.026> PMID: 23831504
- [58] Magesh, M.; Keerthika, B.; Bharathi, D.; Premavathi, K.; Vijayalakshmi, M.; Lavanya, M. Overview of biological activities of quinazolines. *J. Coast. Life Med.*, **2023**, *11*, 1879-1887.
- [59] Gupta, P.K.; Gupta, S.; Singh, S.D.; Tiwari, S.B. Synthesis, molecular docking and evaluation studies of novel 2-(N-Phenyl Substituted)-3-Alkyl Amino-Quinazolin-4(3H)-One derivatives for anti-inflammatory & anticonvulsant activities. *Eur. Chem. Bull.*, **2023**, *12*(5), 2367-2380.
- [60] Al-Kaf, G.A.; Al-Robaidi, A.R. *Biological activities of recent advances in quinazolinone*; Intech Open, **2024**. <http://dx.doi.org/10.5772/intechopen.111107>
- [61] Krishnarth, N.; Verma, S.K.; Chaudhary, A. Synthesis and anti-inflammatory activity of some novel quinazolinone derivatives. *J. Pharm.*, **2020**, *45*(3), 205-210.
- [62] Priya, M.G.R.; Giriya, K.; Ravichandran, N. *In vitro* study of anti-inflammatory and antioxidant activity of 4-(3h) quinazolinone derivatives. *Rasayan J. Chem.*, **2011**, *4*(2), 418-424.
- [63] Dvorakova, M.; Langhansova, L.; Temml, V.; Pavicic, A.; Vanek, T.; Landa, P. Synthesis, inhibitory activity, and *in silico* modeling of selective COX-1 inhibitors with a quinazolinone core. *ACS Med. Chem. Lett.*, **2021**, *12*(4), 610-616. <http://dx.doi.org/10.1021/acsmmedchemlett.1c00004> PMID: 33854702
- [64] Soliman, A.M.; Karam, H.M.; Mekkawy, M.H.; Ghorab, M.M. Antioxidant activity of novel quinazolinones bearing sulfonamide: Potential radiomodulatory effects on liver tissues via NF- κ B/ PONI pathway. *Eur. J. Med. Chem.*, **2020**, *197*, 112333. <http://dx.doi.org/10.1016/j.ejmech.2020.112333> PMID: 32361176
- [65] Santos, J.S.; Alvarenga Brizola, V.R.; Granato, D. High-throughput assay comparison and standardization for metal chelating capacity screening: A proposal and application. *Food Chem.*, **2017**, *214*, 515-522. <http://dx.doi.org/10.1016/j.foodchem.2016.07.091> PMID: 27507505
- [66] Bule, M.H.; Haymete, A.; Kefale, B. Synthesis and *in-vivo* pharmacological evaluation of some novel 4(3H)-Quinazolinone derivatives as potential anti-malarial agents. *Drug Des.*, **2015**, *4*, 121.
- [67] Laleu, B. Discovery and structure-activity relationships of Quinazolinone-2-carboxamide derivatives as novel orally efficacious antimalarials. *J Med Chem*, **2021**, *64*(17), 12582-12602.
- [68] Malasala, S.; Gour, J. Copper mediated one-pot synthesis of quinazolinones and exploration of piperazine linked quinazolinone derivatives as antimycobacterial agents. *RSC Adv.*, **2020**, *10*, 43533. PMID: 35519697
- [69] Pattan, S.R. Synthesis of N-3[4-(4-Chlorophenyl) thiazole-2-yl]-2-(aminomethyl)quinazolin-4(3H)-one and their derivatives for antitubercular activity. *ChemInform*, **2006**, *37*.
- [70] Sahu, V.; Kushwaha, V.; Sahu, V.; Shukla, S.; Khan, I. Review on synthesis schemes of first line drugs of antitubercular drugs. *Indian J. Sci. Res.*, **2022**, *2*(2), 53-59.
- [71] Pathak, S.; Malhotra, V.; Nath, R.; Shanker, K. Synthesis and anti-hypertensive activity of novel quinazolin-4(3H)-one derivatives. *Cent. Nerv. Syst. Agents Med. Chem.*, **2014**, *14*(1), 34-38. <http://dx.doi.org/10.2174/1871524914666140825144729> PMID: 25174978
- [72] Pérez-Fehrmann, M.; Kesternich, V.; Puelles, A.; Quezada, V.; Salazar, F.; Christen, P.; Castillo, J.; Cárcamo, J.G.; Castro-Alvarez, A.; Nelson, R. Synthesis, antitumor activity, 3D-QSAR and molecular docking studies of new iodinated 4-(3 H)-quinazolinones 3 N -substituted. *RSC Advances*, **2022**, *12*(33), 21340-21352. <http://dx.doi.org/10.1039/D2RA03684C> PMID: 35975048
- [73] Al-Obaid, A.M.; Abdel-Hamide, S.G.; El-Kashef, H.A.; Abdel-Aziz, A.A.M.; El-Azab, A.S.; Al-Khamees, H.A.; El-Subbagh, H.I. Substituted quinazolines, part 3. Synthesis, *in vitro* antitumor activity and molecular modeling study of certain 2-thieno-4(3H)-quinazolinone analogs. *Eur. J. Med. Chem.*, **2009**, *44*(6), 2379-2391. <http://dx.doi.org/10.1016/j.ejmech.2008.09.015> PMID: 18950904
- [74] Le, Y.; Gan, Y.; Fu, Y.; Liu, J.; Li, W.; Zou, X.; Zhou, Z.; Wang, Z.; Ouyang, G.; Yan, L. Design, synthesis and *in vitro* biological evaluation of quinazolinone derivatives as EGFR inhibitors for an-

- titumor treatment. *J. Enzyme Inhib. Med. Chem.*, **2020**, *35*(1), 555-564.
<http://dx.doi.org/10.1080/14756366.2020.1715389> PMID: 31967481
- [75] Tian, Z.; Yang, L.; Huang, M.; Sun, C.; Chen, M.; Zhao, W.; Peng, J.; Guo, G. Antitumor activity and mechanism of action of the antimicrobial peptide AMP-17 on human Leukemia K562 cells. *Molecules*, **2022**, *27*(22), 8109.
<http://dx.doi.org/10.3390/molecules27228109> PMID: 36432210
- [76] Sharma, S.; Hashmi, M.F.; Chakraborty, R.K. Asthma Medications. In: *StatPearls*; StatPearls Publishing: Treasure Island, FL, **2023**; p. 20.
- [77] Singh, S.P.; Qureshi, A.; Hassan, W. Mechanisms of action by antimicrobial agents. *Narr Rev.*, **2021**, *19*, 4.
- [78] Letscher-Bru, V.; Herbrecht, R. Caspofungin: The first representative of a new antifungal class. *J. Antimicrob. Chemother.*, **2003**, *51*(3), 513-521.
<http://dx.doi.org/10.1093/jac/dkg117> PMID: 12615851
- [79] Hassanzadeh, F.; Jafari, E.; Hakimelahi, G.H.; Khajouei, M.R.; Jalali, M.; Khodarahmi, G.A. Antibacterial, antifungal and cytotoxic evaluation of some new quinazolinone derivatives. *Res. Pharm. Sci.*, **2012**, *7*(2), 87-94.
 PMID: 23181085
- [80] Fan, Z.; Shi, J.; Luo, N.; Bao, X. Synthesis, crystal structure and antimicrobial activity of 2-((2-(4-(1H-1,2,4-triazol-1-yl)phenyl)quinazolin-4-yl)oxy)-N-phenylacetamide derivatives against phytopathogens. *Mol. Divers.*, **2019**, *23*(3), 615-624.
<http://dx.doi.org/10.1007/s11030-018-9896-2> PMID: 30511268
- [81] Ettahiri, W.; Salim, R.; Adardour, M.; Ech-chihbi, E.; Yunusa, I.; Alanazi, M.M.; Lahmidi, S.; Barnossi, A.E.; Merzouki, O.; Iraqi Housseini, A.; Rais, Z.; Baouid, A.; Taleb, M. Synthesis, characterization, antibacterial, antifungal and anticorrosion activities of 1,2,4-Triazolo[1,5-a]quinazolinone. *Molecules*, **2023**, *28*(14), 5340.
<http://dx.doi.org/10.3390/molecules28145340> PMID: 37513216
- [82] Juliana Martins, F.; Savacini Sagrillo, F.; Josianne Vinturelle Medeiros, R.; Gonçalves de Souza, A.; Rodrigues Pinto Costa, A.; Silva Novais, J.; Alves Miceli, L.; Campos, V.; Marie Sá Figueiredo, A.; Claudia Cunha, A.; Lidmar von Ranke, N.; Lamim Bello, M.; Abraham-Vieira, B.; De Souza, A.; Ratcliffe, N.; da Costa Santos Boechat, F.; Cecilia Bastos Vieira de Souza, M.; Rangel Rodrigues, C.; Carla Castro, H. evaluation of biological activities of quinone-4-oxoquinoline derivatives against pathogens of clinical importance. *Curr. Top. Med. Chem.*, **2022**, *22*(12), 973-991.
<http://dx.doi.org/10.2174/1568026622666220504124710> PMID: 35524665
- [83] Chaudhary, C.; Kumar, S.; Kumar, S.; Hashim, S.R. Synthesis and antimicrobial evaluation of Quinazolinone-4[3H]-one derivatives. *Lett. Org. Chem.*, **2021**, *18*(7), 547-554.
<http://dx.doi.org/10.2174/1570178617999200818205800>
- [84] Seifu, G.W.; Birhan, Y.S.; Beshay, B.Y.; Hymete, A.; Bekhit, A.A. Synthesis, antimalarial, antileishmanial evaluation, and molecular docking study of some 3-aryl-2-styryl substituted-4(3H)-quinazolinone derivatives. *BMC Chem.*, **2022**, *16*(1), 107-115.
<http://dx.doi.org/10.1186/s13065-022-00903-0> PMID: 36461074
- [85] Amrutkar, R.D.; Amrutkar, S.V.; Ranawat, M.S. Quinazolin-4-One: A versatile molecule. *Curr. Bioact. Compd.*, **2020**, *16*(4), 370-382.
<http://dx.doi.org/10.2174/1573407215666181120115313>
- [86] Prinsloo, I.F.; Zuma, N.H.; Aucamp, J.; N'Da, D.D. Synthesis and *in vitro* antileishmanial efficacy of novel quinazolinone derivatives. *Chem. Biol. Drug Des.*, **2021**, *97*(2), 383-398.
<http://dx.doi.org/10.1111/cbdd.13790> PMID: 32914553
- [87] Moheb, M.; Iraj, A.; Dastyafteh, N.; Khalili Ghomi, M.; Noori, M.; Mojtavavi, S.; Faramarzi, M.A.; Rasekh, F.; Larijani, B.; Zomorodian, K.; Sadat-Ebrahimi, S.E.; Mahdavi, M. Synthesis and bioactivities evaluation of quinazolin-4(3H)-one derivatives as α -glucosidase inhibitors. *BMC Chem.*, **2022**, *16*(1), 97.
<http://dx.doi.org/10.1186/s13065-022-00885-z> PMID: 36380337
- [88] Saeedi, M.; Mohammadi-Khanaposhtani, M.; Pourrabia, P.; Razzaghi, N.; Ghadimi, R.; Imanparast, S.; Faramarzi, M.A.; Bandarian, F.; Esfahani, E.N.; Safavi, M.; Rastegar, H.; Larijani, B.; Mahdavi, M.; Akbarzadeh, T. 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*, 161-169.
<http://dx.doi.org/10.1016/j.bioorg.2018.10.023> PMID: 30366316
- [89] Raju, S.; Hemamalini, K. *In vivo* animal model for screening of anti-diabetic activity. *Biosci. Biotechnol. Res. Asia*, **2012**, *9*(2), 765-772.
<http://dx.doi.org/10.13005/bbra/1062>
- [90] Kaczorowska, K.; Stankiewicz, A.; Bugno, R.; Paluchowska, M.H.; Burnat, G.; Brański, P.; Cieślak, P.; Wierońska, J.M.; Milik, M.; Nowak, M.; Przybyłowicz, A.; Koziol, A.; Hogendorf, A.; Hogendorf, A.S.; Kalinowska-Tłuścik, J.; Duszyńska, B.; Pilc, A.; Bojarski, A.J. Design and synthesis of new Quinazolin-4-one derivatives with negative mGlu₁ receptor modulation activity and antipsychotic-like properties. *Int. J. Mol. Sci.*, **2023**, *24*(3), 1981.
<http://dx.doi.org/10.3390/ijms24031981> PMID: 36768302
- [91] Kumar, P.; Mahendra, V.K.; Bhushan, D.; Alpna, J.A.; Priya, D.D.; Tarwani, R. Synthesis, biological evaluation, and insilico studies of novel 4(3H)-Quinazolinone derivatives as atypical antipsychotics. *Eur. Chem. Bull.*, **2023**, *12*(5), 2064-2080.
- [92] Jafari, E.; Hassanzadeh, F.; Sadeghi-Aliabadi, H.; Sharifzadeh, A.; Dana, N. Synthesis and cytotoxic evaluation of some quinazolinone-5-(4-chlorophenyl) 1, 3, 4-oxadiazole conjugates. *Res. Pharm. Sci.*, **2019**, *14*(5), 408-413.
<http://dx.doi.org/10.4103/1735-5362.268201> PMID: 31798657
- [93] Nowar, R.M.; A Osman, E.E.; Abou-Seri, S.M.; El Moghazy, S.M.; Abou El Ella, D.A. Design, synthesis and biological evaluation of some novel quinazolinone derivatives as potent apoptotic inducers. *Future Med. Chem.*, **2018**, *10*(10), 1191-1205.
<http://dx.doi.org/10.4155/fmc-2017-0284> PMID: 29749767
- [94] De, A.; Sarkar, S.; Majee, A. Recent advances on heterocyclic compounds with antiviral properties. *Chem. Heterocycl. Compd.*, **2021**, *57*(4), 410-416.
<http://dx.doi.org/10.1007/s10593-021-02917-3> PMID: 33994556
- [95] Preston, S.L.; Piliero, P.J.; Bilello, J.A.; Stein, D.S.; Symonds, W.T.; Drusano, G.L. *In vitro-in vivo* model for evaluating the antiviral activity of amprevir in combination with ritonavir administered at 600 and 100 milligrams, respectively, every 12 hours. *Antimicrob. Agents Chemother.*, **2003**, *47*(11), 3393-3399.
<http://dx.doi.org/10.1128/AAC.47.11.3393-3399.2003> PMID: 14576093
- [96] Debnath, S.; Manjunath, S.Y. Conventional and microwave assisted synthesis of 3-(Substituted)-2-phenyl quinazolin-4(3H)-one and their antibacterial and anthelmintic activity. *Int J Pharm Sci Nanotechnol.*, **2011**, *4*(2), 1408-1411. [IJPSN].
<http://dx.doi.org/10.37285/ijpsn.2011.4.2.6>
- [97] Lakshmi, K.; Rao, N.R.; Basaveswararao, M.V. Synthesis, antimicrobial and anthelmintic evaluation of novel quinazolinonyl chalcones. *Rasayan J. Chem.*, **2014**, *7*(1), 44-54.
- [98] Hemalatha, K.; Madhumitha, G. Study of binding interaction between anthelmintic 2, 3-dihydroquinazolin-4-ones with bovine serum albumin by spectroscopic methods. *J. Lumin.*, **2016**, *178*, 163-171.
<http://dx.doi.org/10.1016/j.jlumin.2016.05.041>

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