Journal of Advanced Zoology

ISSN: 0253-7214

*Volume **45** Issue -**01 Year 2024** Page 1166:**1184***

Study of Pharmacologically Active Drugs Containing Quinazoline Pharmacophore: A Brief Overview

Rizwan Ul Hasan[1], Syed Shariq Mian[2], Sadaf Arfi[3], Bushra Begum[4], Soumya Verma[5], Rizwan Ahmad[6], Imran Hussain[7], Mohammad Asif[8*]

[1,2,3,4,5,8]Era College of Pharmacy, Era University, Lucknow, 226003, Uttar Pradesh, India.*
[6]Seth Vishambhar Nath Institute of Pharmacy, Lucknow, Uttar Pradesh, India.
[7]Department of bioengineering, Faculty of Engineering and Information Technology, Integral University, Lucknow, 226026, India

***Corresponding Author:** Dr. Mohammad Asif*
Professor, Department of Pharmaceutical Chemistry, Era College of Pharmacy, Era University, Lucknow, 226003, Uttar Pradesh, India

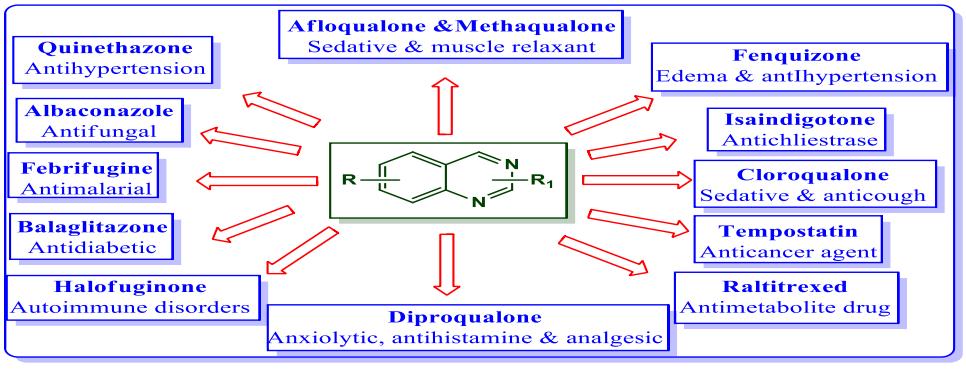
Article History

Received: 02 January 2024
Revised: 18 January 2024
Accepted: 30 January 2024

Abstract

Heterocyclic compounds have been the subject of extensive research due to their diverse pharmacological effects. Among these molecules are quinazolinone analogs, which have demonstrated a range of pharmacological potentials. In search of novel therapeutic pharmaceutical molecules, medicinal chemistry researchers are drawn to the quinazolinone nucleus. This article aims to provide an overview of the many pharmacological activities of the quinazolinone moiety. Based on the quinazolinone moiety, more modern molecules have been developed and synthesized. These compounds show negligible toxicity and outstanding anti-disease capabilities. This paper reviews several different quinazolinone analogs and makes recommendations for future research paths in the quest to create effective quinazolinone drugs for a range of biological objectives.

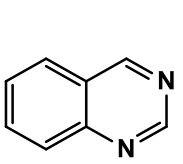
***Keywords:** Heterocyclic, pharmacologically active, quinazolinone analogs, drugs, diseases.*



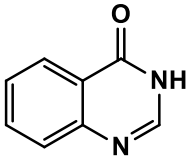
Quinazolinone coantaining drug molecules

1. Introduction

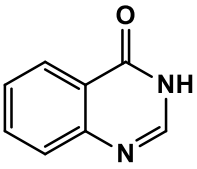
These days, there are many different heterocyclic compounds known that contain oxygen, nitrogen, sulfur, and other heteroatoms. In the fields of agrochemicals and pharmaceuticals, organic molecules with heterocycle nuclei carry out pharmacological functions. Furthermore, nitrogen-containing heterocyclic molecules are extremely important in medical chemistry. Two nitrogen-containing heterocyclic compounds, quinazoline, and quinazolinone, are created when the benzene ring fuses with the pyrimidine and pyrimidinone moiety, respectively. According to where the oxygen and hydrogen atoms are located on the nitrogen (NH) atom, quinazolinones can be divided into the following six subcategories (Chaudhary, et al., 2018; Selvam, and Kumar. 2011). The modern human population suffers from several ailments that are directly related to lifestyle advancements, which highlights the urgent need for new medicine development. Quinazolinone moiety is an essential component of many bioactive synthetic and natural chemicals and is involved in medicinal chemistry. The advancement of these compounds' structural designs for powerful and specific pharmacological actions throughout the past ten years is still very desirable. This section covers the novel quinazolinone-containing biologically active chemicals that have been produced during the past ten years for a variety of disorders. Quinazolinone, or quinazolin-4(3H)-one in chemistry, is also known as quinazolindiones (Asif. 2014; Chen, *et al*., 2006). Quinazolinone is a chemical molecule that is heterocyclic. 2-quinazolinone and 4-quinazolinone are the two structural isomers; the latter is the more prevalent. Another class of medications with a 4-quinazolinone core that is used as a hypnotic or sedative is called quinazolinones. It has also been suggested that they be used to treat cancer. Afloqualone, cloroqualone, and diproqualone are a few examples. The quinzolinone core is present in alkaloids such as halofuginone and febrifugine.



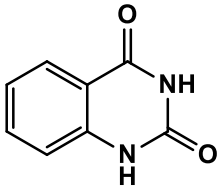
Quinazoline



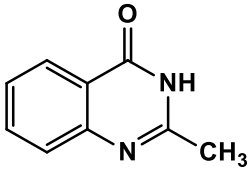
Quinazolinone



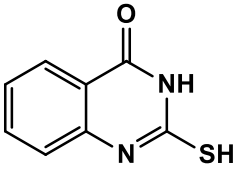
Quinazolin-4(*3H*)-one (**I**)



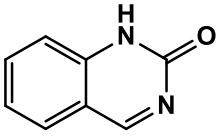
Quinazolin-2,4(*1H,3H*)-dione (**II**)



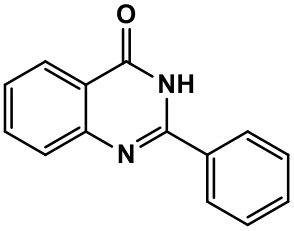
2-Methylquinazolin-4(3H)-one (**III**)



2-Mercatoquinazolin-4(*3H*)-one (**1V**)



Quinazolin-2(*1H*)-one (**V**)



2-phenylquinazolin-4(*3H*)-one (**VI**)

Quinazolines are compounds with various pharmacophores, combining knowledge of a target with an awareness of the types of molecules that may interact with the target family. Quinazoline is a six-membered heterocyclic ring system that has been reported for its biological activities. To do the job, a strong, adaptable, and scalable chemistry must be used. This quinazoline property would be a useful model for a library of lead production materials. The biological actions carried out for different targets, coupled with a brief explanation of the targets, are the main emphasis of the current review paper.

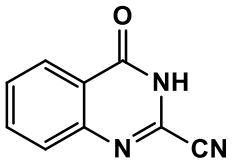
The fields of discovery, development, laboratory synthesis, and identification of physical and chemical processes are all under the purview of medicinal chemistry. New organic molecules, whether manufactured or natural, are the focus of most activity in this area. Inorganic compounds are still crucial for treating nutritional treatment, radiopharmaceuticals, and trace elements in food. New synthetic techniques for the development of organic compounds have emerged recently, including the fascinating discipline of biotechnology which uses a cell's biology to create new compounds. Methods such as site-directed mutagenesis, recombinant DNA, and cell line fusion have expanded the potential for novel disease-treating entities. With the aid of medicinal chemistry, pharmacists are now able to prescribe human insulin that has been modified to provide more convenient dosing schedules, cell-stimulating factors that have altered chemotherapy dosage schedules, humanized monoclonal antibodies that are targeted to specific tissues, and fused receptors that block cytokines produced by immune cells. Understanding the physiochemical characteristics that are employed to create novel pharmacologically active elements and their mechanisms of action is essential for comprehending the fundamentals of medicinal chemistry. Every year, thousands upon thousands of novel organic compounds are created globally, and a large number of these undergo pharmacological screening to ascertain their biological activity (Badolato, et al., 2018; Wdowiak, et al., 2021; Rezaeinasab, et al., 2022; Faisal, and Saeed. 2020; Wang, and Gao. 2013; Grivas, et al., 2013).

Although this approach of random screening has been ineffective, it has produced new lead compounds whose structures have been refined to yield effective therapeutic drugs. Understanding the molecular mechanisms of medication action is the primary goal of medicinal chemists. Chemistry containing heterocyclic compounds—compounds with at least two different element atoms in each ring—is known as heterocyclic chemistry. Despite the complex having carbon atoms in the ring, the heterocyclic atoms may be inorganic. "Different from carbon and hydrogen" is what the word hetero signifies. Both plants and animals can biosynthesize a large number of physiologically active heterocyclic molecules. Certain heterocyclic substances, such as the haem derivatives found in blood and the chlorophyll necessary for photosynthesis in plants, are important to life. Homocycles are also present in DNA and RNA. Plant-based dyes include indigo blue, which is used to color pants. The basic structural nucleus of several heterocycles includes nicotine, pyridoxine, cocaine, morphine, and other substances. Benzene and pyrimidine rings, two fused six-member simple aromatic rings, make comprise the compound quinazoline. This chemical has a yellow hue and is typically found in crystallized form. It is used as an antimalarial medication. In 1903, Gabriel made the first preparation of it and isolated it from the Chinese herb aseru. With the synthesis of the molecule 2-methyl-1,3-aryl-4-quinazoline derivative, research on the biological activity of quinazoline compounds began. This substance has sedative and soporific properties. Significant advancements have been made in medical research over the past ten to fifteen years. Methaqualone, a diuretic, and quinathazone, a soporific and anticonvulsant, were the only two compounds used in 1968. Approximately fifty different types of derivatives belonging to this class were known by 1980. These included medications with various biological actions, such as sedative, analgesic, anticonvulsant, antitussive, myorelaxant, antirheumatic, hypotensive, antiallergic, broncho-dilating, antidiabetic, cholagogues, diuretic, antimalarial, spermicidal, and so on (Hricovíniová, et al., 2021; Borah, et al., 2022; Mohammadkhani, and Heravi. 2020; Mohammed, et al., 2022).

Quinazolinone-Based Biologically Active Molecules

Out of the six quinazolinone moieties mentioned above, quinazolin-4(3H)-ones are more common and can be found as natural products or as intermediates in several hypothesized biosynthetic processes. Organic molecules with a quinazolinone core, both synthetic and natural, display a range of biological activities such as antimicrobial (Chavan, et al., 2014), anti-inflammatory (Priya, et al., 2011), antitumor (Srivalli, et al., 2012), anticonvulsant (El-Azab, et al., 2012), anti-tubercular (Devi, and Kachroo. 2014), antidiabetic (Ahmed, et al., 2012), anticancer (Zhang, et al., 2015), diuretic (Bouley, et al., 2016), cellular phosphorylation inhibition (Traxler, et al., 1999), antimalarial

(Ganguli, et al., 2012), antihypertensive (Khan, et al., 2016; Abou-Seri, et al., 2011) and kinase inhibitory activities (Bridges, et al., 1996). The primary sources of the quinazoline-(3H)-one unit include anthranilic acid, different esters, isatoic anhydride, anthranilamide, and anthranilonitrile; on the other hand, anthranilonitrile is the source of quinazolin-2(H)-one. Numerous heterocyclic compounds with the nucleus of quinazolinone have been identified in a range of plants, animals, and microbes. To create 2-cyanoquinazolinone, the first quinazolinone chemical was created in the late 1860s using cyanogen and anthranilic acid. Currently, there are over 200 recognized naturally occurring quinazolinone alkaloids (Selvam, et al., 2011). The remarkable pharmacological activity and simple availability like quinazolinone derivatives have recently piqued the interest of biologists and chemists in their synthesis.



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

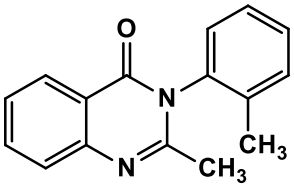
In addition to delving further into the synthesis process for quinazolinone and its derivatives, we attempt to condense the biological importance of quinazolinone and its derivatives here.

Quinazolinone-Based Drug Molecules

Many compounds based on quinazolinone have been produced and tested for a wide range of pharmacological properties since quinazolinone skeleton is a well-known therapeutic agent. The current state of rapid development indicates that several quinazolinone derivatives with a wide range of potential applications for various disorders have been patented and made accessible on the market. This section includes a summary of certain marketed medications.

Methaqualone

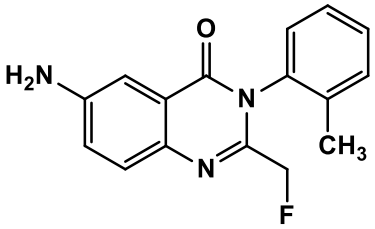
It is chemically 2-methyl-3-(2-methylphenyl) quinazolin-4-(*3H*)-one (**1**) and was first synthesized in 1951. It possesses both central and peripheral muscle relaxant activity and also exhibits sedative–hypnotic effects (Rakesh, et al., 2017).



(1)

Afloqualone

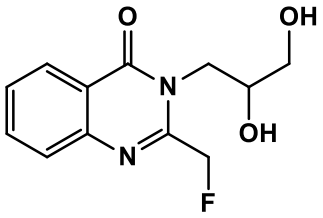
It is an amino and fluoro analog of Methaqualone and chemically known as 6-amino-2-(fluoro methyl)-3-(2-methyl phenyl)quinazolin-4(*3H*)-one (**2**). It has sedative and muscle relaxant actions. It causes skin problems like dermatitis through photosensitization (Ishikawa, et al., 1994; Ochiai, *et al*., 1982, Ishikawa, *et al*., 1994).



(2)

Diproqualone

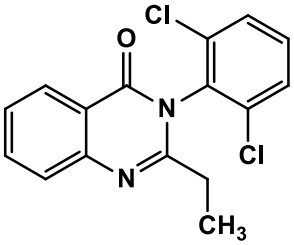
It is a Methaqualone analog and chemically known as 3-(2,3-dihydroxypropyl)-2-methylquinazolin-4(*3H*)-one (**3**). It is used for the treatment of osteoarthritis, rheumatoid arthritis, insomnia, and neuralgia. This drug is also used for anxiolytic, antihistamine, and analgesic properties (Ishikawa, et al., 1994).



(3)

Cloroqualone

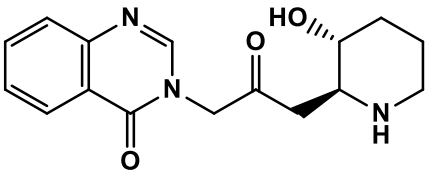
It is a Methaqualone analog, chemically known as 3-(2,6-Dichlorophenyl)-2-ethyl-4-quinazolinone (**4**), and was developed in 1980. It has weaker sedative properties than Methaqualone. It also has cough suppressing effect (Darias, et al., 1992; Ochiai, and Ishida. 1982).



(4)

Febrifugine

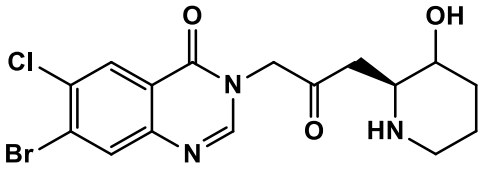
Febrifugine alkaloid was extracted from *Dichroa febrifuga* leaves and also found in the garden plant Hydrangea. Its chemically known as 3-[3-((2S, 3R)-3-Hydroxypiperidin-2-yl)-2-oxo propyl] quinazolin-4(*3H*)-one (**5**). It has diverse effects as an antimalarial agent (McLaughlin, *et al*., 2010; Chen, et al., 2006).



(5)

Halofuginone

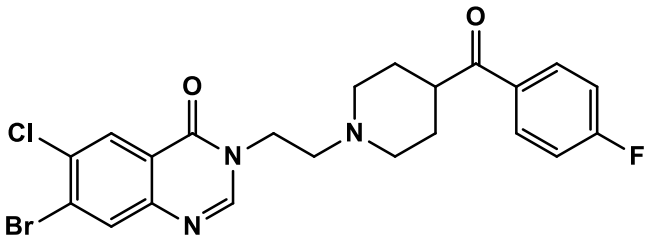
This is a synthetic halogen derivative of Febrifugine alkaloid and isolated from the Chinese herb *Dichroa febrifuga*. Its chemically 7-bromo-6chloro-3-[3-((2S,3R)-3-hydroxy piperidin-2-yl)-2-oxopropyl]quinazolin-4(*3H*)-one (**6**). It is used as a coccidiostat in veterinary medicine and the treatment of scleroderma. It plays a major role in the inhibition of T helper 17 cells, immune cells, and other autoimmune diseases but it does not affect other kinds of T cells which are involved in normal immune function. It exhibits varied effects for the treatment of autoimmune disorders (Mishra, et al., 2015; Gnainsky, et al., 2004).



(6)

Ketanserin

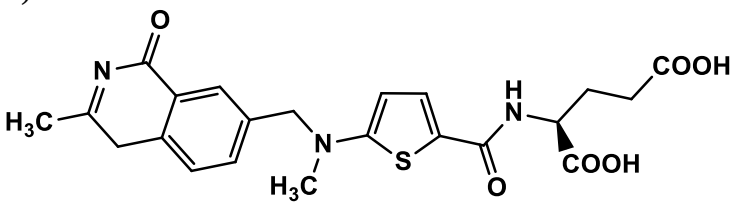
Ketanserin is chemically 3-[2-(4-(4-fluorobenzoyl) piperidin-1-yl) ethyl]-*1H*-quinazoline-2,4-dione (**7**) and used in the treatment of chronic vascular hypertension and have considerable role in blocking of actions of serotonin. It is a selective serotonin receptor antagonist with weak adrenergic receptor-blocking properties. It is also responsible for inhibition of platelet accumulation (Sundrud, et al., 2009). It inhibits platelet aggregation. It is well tolerated and is particularly effective in older patients. The drug binds to but does not activate serotonin receptors, thereby blocking the actions of serotonin, thus known as serotonin receptor antagonists.



(7)

Raltitrexed

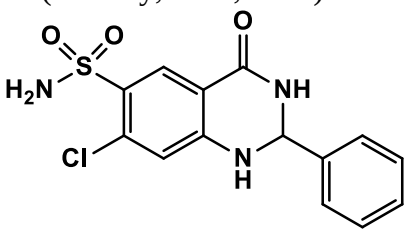
It is chemically known as *N*-[(5-(methyl [(2-methyl-4-oxo-1, 4-dihydroquinazolin-6-yl) methyl]amino)-2-thienyl)carbonyl]-L-glutamic acid (**8**), is an antimetabolite drug used in cancer chemotherapy. It is structurally similar to folic acid and acts as an inhibitor of thymidylate synthase; hence it is a folate antimetabolite. It is used in the treatment of colorectal cancer. It is used in the inhibition of thymidylate synthase and dihydrofolate reductase enzyme synthesis. It prevents the formation of DNA and RNA by preventing the formation of pyrimidine nucleotides which are required for the growth and survival of both normal and cancer cells (Zabludowski, et al., 1984; Widemann, et al., 1999).



(8)

Fenquizone

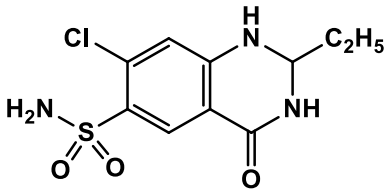
It is known as Idrolone and chemically 7-chloro-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (**9**). Its structurally similar to thiazides like diuretics sulphonamides. It is used in the treatment of edema and hypertension (Mackay, et al., 2001).



(9)

Quinethazone

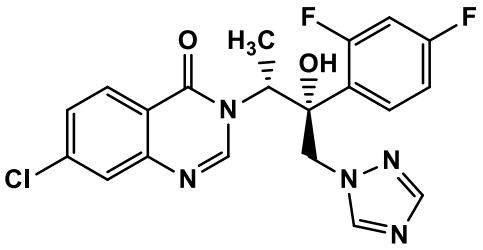
Quinethazone is an introduced oral diuretic agent in which a cyclic carbamyl group has replaced the cyclic sulphamyl group present in the thiazides. It's chemically known as 7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide (**10**). It is used in the treatment of hypertension and its adverse effects include dizziness, dry mouth, nausea, and low potassium levels (Katague. 2006; Cohen, *et al*., 1960). It is a thiazide diuretic used to treat hypertension. Common side effects include dizziness, dry mouth, nausea, and low potassium levels.



(10)

Albaconazole

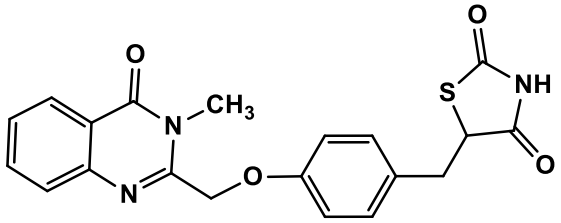
Albaconazole (UR-9825) is chemically 7-chloro-3-[(2R,3R)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1H,1,2,4-triazol-1-yl)butan-2-yl]quinazolin-4(*3H*)-one (**11**) is a triazole antifungal drug. The triazole moiety has diverse effects on fungal disease and the whole molecule has greater potential for broad-spectrum antibacterial activity (Cohen, et al., 1960; Sorbera, et al., 2003).



(11)

Balaglitazone

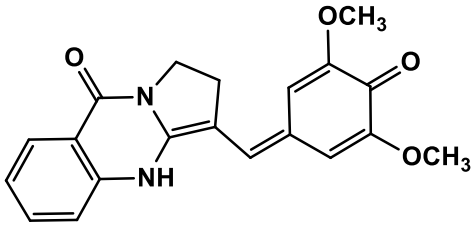
It is chemically 5-[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinyl) methoxy] phenyl]methyl]-2,4-thiazolidinedione **(12)**. It is type 2 diabetes, antagonists for peroxisome Proliferator–Activator Receptor γ(PPARγ) and plays a significant role in the maintenance of glucose levels in the blood by insulin sensitization activity. It has adverse effects such as oedemas, infarctions, and increased fracture rates, limiting its applicability (Garau, et al., 2003).



(12)

Isaindigotone

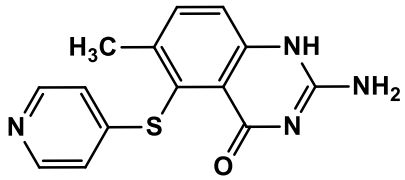
Isaindigotone is a natural alkaloid, commonly used in traditional Chinese medicine. It is chemically 3-[(3,5-dimethoxy-4-oxocyclohexa-2,5-dien-1-ylidene)methyl]-2,4-dihydro-*1H*-pyrrolo[2,1b]quinazolin-9-one (**13**). It is used as an inhibitor of cholinesterase (ChEs) and self induced b-amyloid (Ab) aggregation (Yousefi, et al., 2017; Molina, et al., 2001).



(**13**)

Nolatrexed

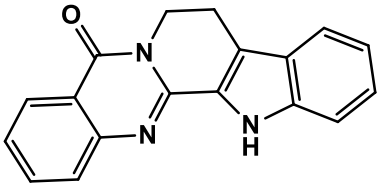
Nolatrexed is chemically 2-Amino-6-methyl-5-(4-pyridylthio)-*1H*-quinazolin-4-one (**14**). It is a lipophilic inhibitor of thymidylate synthase enzyme (Yan, et al., 2012; Estlin, et al., 2001; Hughes, *et al*., 1999).



(14)

Rutaecarpine

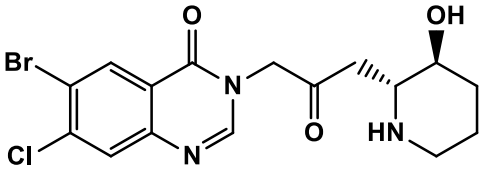
Rutaecarpine is an indolopyridoquinazolinone alkaloid isolated from the fruit of various plants and trees of the Rutaceae family, such as Evodia ruraecarpa. It is chemically known as 8,13-Dihydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5(*7H*)-one (**15**). This drug is used for the treatment of gastrointestinal disorders, headache, dysentery, and inflammation-related disorders. It also has cytotoxic, anti-platelet, vasorelaxation, and anti-anoxic activities (Jodrell, et al., 1999; Bubenyák, et al., 2010).



(15)

Tempostatin

Tempostatin is chemically 7-bromo-6-chloro-3-[3-[(2R,3S)-3-hydroxy-2-piperidyl]-2-oxopropyl]quinazolin-4-one (**16**). Tempostatin plays an essential role in the inhibition of cancer cell growth by inhibiting the production of new blood vessels (Lee, et al., 2008).

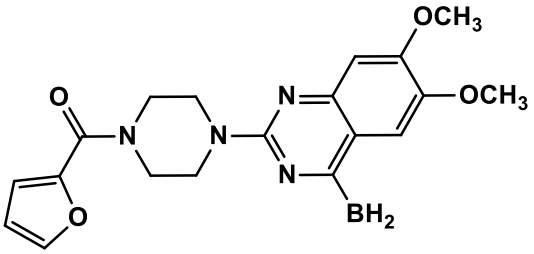


(16)

Prazosin

Prazosin is chemically 2-[4-(2-furoyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4- amine (**17**). It is a sympatholytic drug, an alpha-adrenergic blocker used to treat high hypertension by relaxing blood vessels. Specifically, prazosin is selective for the alpha-1 receptors on vascular smooth muscle.

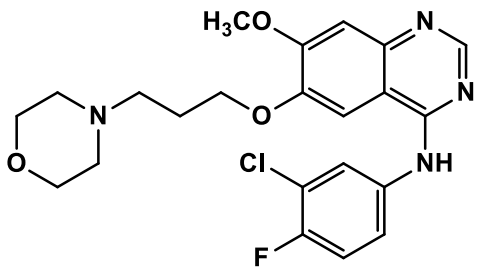
These receptors are responsible for the vasoconstrictive action of norepinephrine, which normally raises blood pressure. By blocking these receptors, prazosin reduces blood pressure (Shen, 2008).



(**17**)

Gefitinib

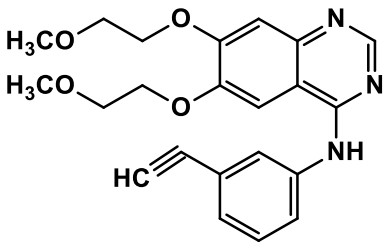
Gefitinib (**18**) is Chemically N-(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine and also known as Iressa and used in the treatment of certain types of cancer. Gefitinib is an epidermal growth factor receptor (EGFR) inhibitor that interrupts signaling through the epidermal growth factor receptor in target cells. Gefitinib is proven to be effective in other cancers, there is potential for its use in the treatment of other cancers where EGFR over-expression is involved. It is a first-line treatment in patients harboring EGFR mutations (Pao *et al*., 2004)



(18)

Erlotinib

Erlotinib (**19**) is chemically N-(3-ethynylphenyl)- 6,7-bis(2-methoxyethoxy)quinazolin-4-amine (Raymond *et.al*., 2000). It is used to treat non-small cell lung cancer, pancreatic cancer, and several other types of cancer. It is a tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). The drug follows Iressa gefitinib, which was the first drug of this type. Erlotinib especially targets the EGFR tyrosine kinase, which is highly expressed and occasionally mutated in various forms of cancer. It binds reversibly to the adenosine triphosphate (ATP) binding site of the receptor.

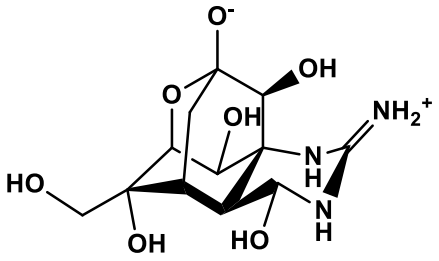


(19)

Tetrodotoxin

Tetrodotoxin is also known as tetrodox (TTX), or "zombie powder" chemically (4R,4aR, 5R,6S,7S,8S,8aR,10S,12S)-2-azaniumylidene-4,6,8,12-tetrahydroxy-6-(hydroxy methyl)-2,3,4, 4a,5,6,7,8-octahydro-1H-8a,10-methano-5,7-epoxy methanoxy) quinazolin-10-olate (**20**). It is a potent neurotoxin, it blocks action potentials in nerves by binding to the voltage-gated, fast sodium

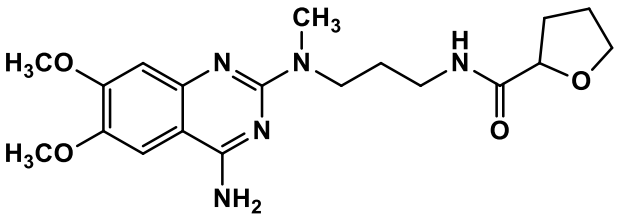
(Na+) channels in nerve cell membranes, essentially preventing any affected nerve cells from firing by blocking the channels used in the process (Rivera *et al*., 1995).



(20)

Alfuzosin

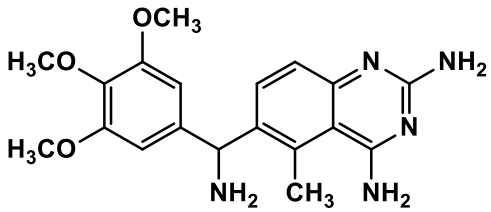
It is chemically *N*-[3-[(4-amino-6,7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl]tetra-hydrofuran-2-carboxamide (**21**). It is an α1 receptor antagonist used to treat benign prostatic hyperplasia (BPH). It works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate. It is used with caution in patients with severe renal insufficiency, and should not be prescribed to patients with a known history of QT prolongation who are taking medications known to prolong the QT interval (Hwang *et al*., 2007).



(21)

Trimetrexate

Trimetrexate is chemically 5-methyl-6-[(3,4,5-trimethoxyphenyl) aminomethyl] quinazoline-2,4-diamine (**22**), is a nonclassical folic acid inhibitor through its inhibition of dihydrofolate reductase. It is being tested for efficacy as an antineoplastic agent and as an antiparasitic agent against pneumocystis pneumonia in AIDS patients. Myelosuppression is its dose-limiting toxic effect. It is used with leucovorin in treating pneumocystis pneumonia. It is investigated for use in treating leiomyosarcoma. It is a methotrexate (MTX) analog that is active against transport-deficient MTX-resistant tumor cells that overcome the acquired and natural resistance to methotrexate. Other uses include skin lymphoma (Wong *et al*., 1990, Smith *et al*., 2002).

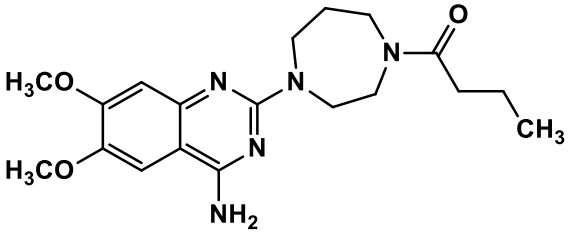


(22)

Bunazosin

Bunazosin is chemically 1-(4-(4-amino-6,7-dimethoxyquinazolin-2-yl)-1,4-diazepan-1-yl)butan-1-one (**23**), is an alpha-1 antagonist. Bunazosin was initially developed to treat benign prostatic hyperplasia (BPH). It is approved in Japan in a topical form to treat glaucoma. The mechanism of action is a reduction of aqueous outflow through the uveoscleral pathway resulting in lowering the intraocular pressure. It also may act to improve blood flow to the ocular nerve. Systemic Alpha-1

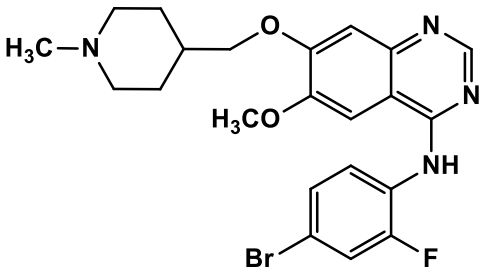
adrenergic receptor antagonists have been implicated in Intraoperative Floppy Iris Syndrome (IFIS). Bunazosin potentially could have the same effect but there has been no research to substantiate this as a risk for cataract surgery.



(23)

Vandetanib

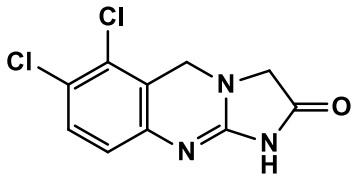
Vandetanib is also known as ZD6474, chemically N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine (**24**), it is an antagonist of the vascular endothelial growth factor receptor (VEGFR) and the epidermal growth factor receptor (EGFR). It is a tyrosine kinase inhibitor. The drug has a third target: inhibits RET-tyrosine kinase activity, an important growth driver in certain types of thyroid cancer.



(24)

Anagrelide

It is chemically 6,7-dichloro-1,5-dihydroimidazo(2,1-b)quinazolin-2(3H)-one (**25**), is a drug used for the treatment of essential thrombocytosis (ET), or overproduction of blood platelets. It is also used in the treatment of chronic myeloid leukemia. Anagrelide works by inhibiting the maturation of platelets from megakaryocytes. The exact mechanism of action is unclear, although it is known to be a phosphodiesterase (PDE) inhibitor. It is a potent (IC_{50}=36nM) inhibitor of PDE-II. It inhibits PDE-3 and phospholipase A2. The combination of hydroxyurea with aspirin is superior to the combination of anagrelide and aspirin for the initial management of ET. The hydroxyurea arm had a lower likelihood of myelofibrosis, arterial thrombosis, and bleeding, but it had a slightly higher rate of venous thrombosis (Voglová *et al*., 2006, Petrides, 2006).

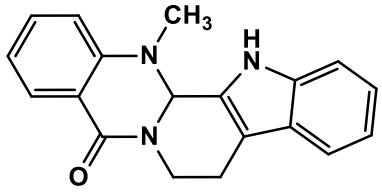


(25)

Evodiamine

Evodiamine is chemically 21-methyl-3,13,21-triazapentacyclo[11.8.0.02,10.04,9.015,20] henicosa-2(10),4,6,8,15,17,19-heptaen-14-one (**26**). It is extracted from the Evodia spp family of plants which has been shown to reduce fat uptake in mouse studies (Kobayashi, 2001, Wang, 2008). Its method is believed to be similar to capsaicin, but retains none of the "hot" taste. This chemical is known to

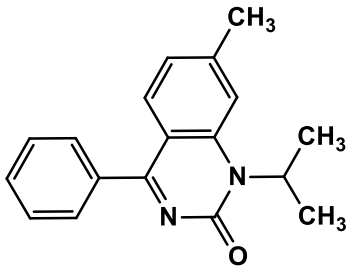
appear in some bodybuilding over-the-counter supplements, while neither its fat-burning benefits, nor its potential risks and side effects. Evodiamine raises your body's temperature and can inhibit the growth of certain cancer cells.



(**26**)

Proquazone

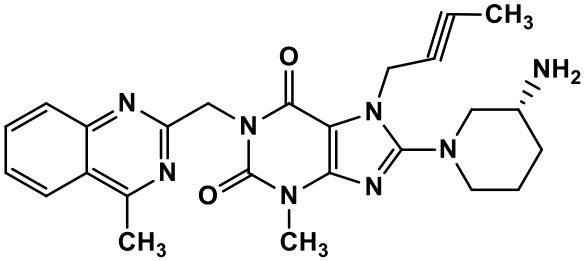
It is chemically 1-isopropyl-7-methyl-4-phenyl quinazolin-2(1H)-one (**27**) is a non-steroidal anti-inflammatory drug.



(**27**)

Linagliptin

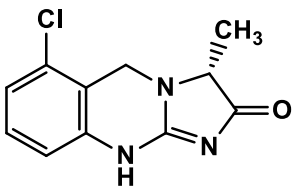
It is chemically 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methyl quinazolin-2-yl) methyl]-3,7-dihydro-1H-purine-2,6-dione (**28**). It is a DPP-4 inhibitor developed by Boehringer Ingelheim undergoing research for type II diabetes. Linagliptin showed that the drug can effectively reduce blood sugar (Wang, *et al*., 2008).



(29)

Quazinone

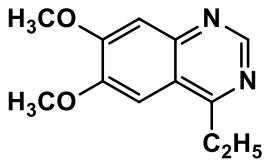
It is chemically (3R)-6-chloro-3-methyl-5,10-dihydroimidazo[2,1-b]quinazolin-2(3H)-one (**30**), it is a cardiotonic and vasodilator drug and used for the treatment of heart disease. It acts as a selective PDE3 inhibitor (Eigenmann, *et al*., 1984, Holck , *et al*., 1984, Belz, *et al*., 1985, Daly, *et al*., 1985, Osinski, *et al*., 2000, Denis *et al*., 1999).



(30)

Quazodine

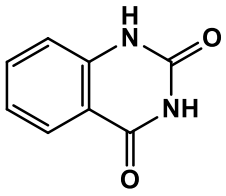
It is also known as quazodinum, and quazodina, chemically 4-ethyl-6,7-dimethoxyquinazoline (**31**). Theophylline and quazodine enhanced maximal twitches and contractural responses to acetylcholine and carbachol. These actions on contractility were exerted directly upon the muscle fibers and were dependent upon the concentration of calcium ions in the bathing solution. In addition, quazodine enhanced the neuromuscular blocking activity of tubocurarine, probably by a prejunctional action (Amer, *et al*., 1971).



(31)

Benzouracil

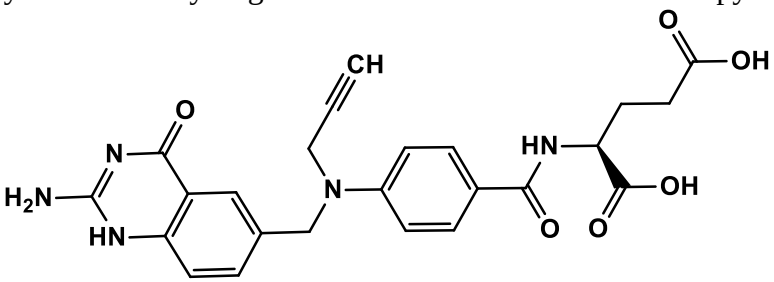
Benzouracil chemically 2,4(1H,3H)-quinazolinedione (**32**). The substituted Benzouracil is used in treating or preventing infection due to a virus from the Flaviridae family by administering it to a patient in need of an effective amount of a quinazoline derivative.



(32)

CB 3717

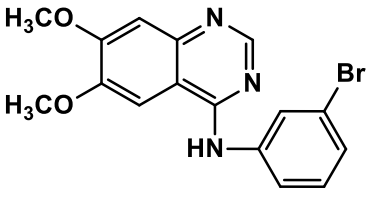
CB 3717 chemically (2S)-2-[[4-[(2-amino-4-oxo-1H-quinazolin-6-yl)methylprop-2-ynylamino] benzoyl]amino]pentanedioic acid (**33**). It is used as an antineoplastic agent, the folic acid antagonist of the enzyme tetrahydrofolate dehydrogenase & used in cancer chemotherapy.



(33)

EBE-A22

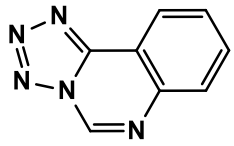
It is also known as PD 153035; PD-153035; PD153035; chemically *N*-(3-bromophenyl)-6,7-dimethoxyquinazolin-4-amine (**34**). It is used as an antineoplastic agent & intercalating agent (capable of inserting themselves between bases of DNA). They are used in the study of DNA (Cheng, *et al*., 2011).



(34)

NSC127213

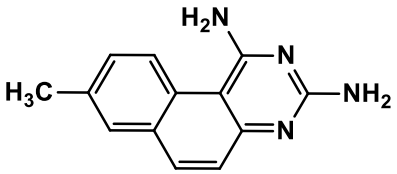
NSC127213 is chemically tetrazolo [1,5-c]quinazoline (**35**). NSC127213 is useful as an inhibitors of H1R and/or H4R for the treatment or prevention of inflammatory, autoimmune, allergic, and ocular diseases.



(35)

NSC137192

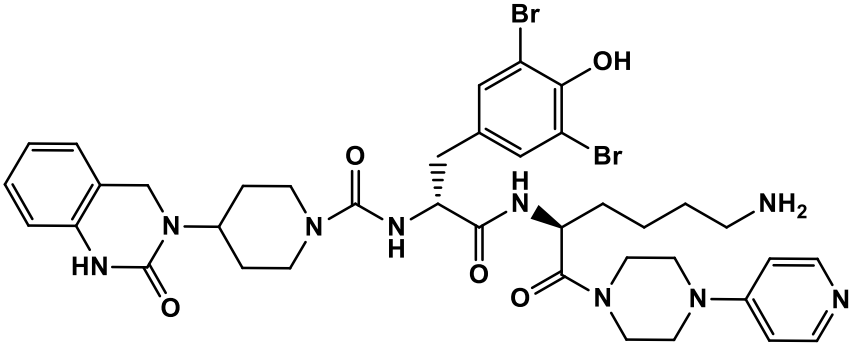
NSC137192 is chemically 8-methylbenzo[f]quinazoline-1,3-diamine (**36**). The drug invention provides compositions and methods for the treatment of B-cell proliferative disorders that employ an A2A receptor agonist or one or more PDE inhibitors.



(36)

BIBN4096BS

BIBN4096BS chemically (R-(R*,S*))-N-(2-((5-amino-1-((4-(4-pyridinyl)-1-piperazinyl) carbonyl) pentyl)amino)-1-((3,5-dibromo-4-hydroxyphenyl)methyl)-2-oxoethyl)-4- (1,4-dihydro-2-oxo-3(2H)quinazolinyl)-1-piperidinecarboxamide (Mallee, *et al*., 2002, Doods, *et al*., 2000). It is a potent competitive antagonist of the relaxant effects of alpha-CGRP on the human temporal artery. Calcitonin gene-related peptide (CGRP) is one of the most potent endogenous vasodilators known. This peptide is increased during migraine attacks and has been implicated in the pathogenesis of migraine headaches. *In vitro*, this compound is extremely potent at primate CGRP receptors exhibiting an affinity (*K*i) for human CGRP receptors of 14.4±6.3 (*n*=4) pM. In an *in vivo* model, BIBN4096BS in doses between 1 and 30μgkg−1 (*i.v.*) inhibited the effects of CGRP, released by stimulation of the trigeminal ganglion, on facial blood flow in marmoset monkeys. It is concluded that BIBN4096BS is a potent and selective CGRP antagonist.

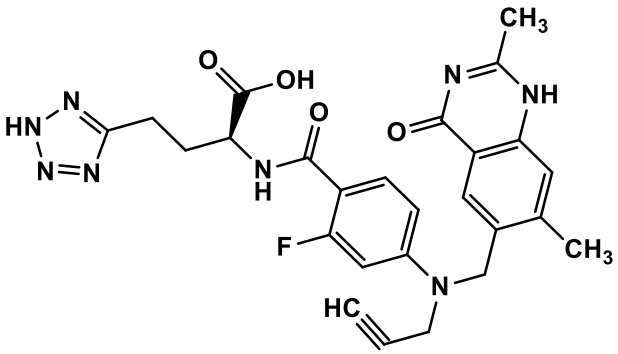


(37)

ZD 9331

It is also known as BGC9331, chemically (2S)-2-[[4-[(2,7-dimethyl-4-oxo-1Hquinazolin-6-yl)methyl-prop-2-ynylamino]-2-fluorobenzoyl]amino]-4-(2H-tetrazol-5-yl)butanoic acid (**38**) (Doods, *et al*., 2000). ZD-9331 is a non-polyglutamate thymidylate synthase inhibitor as a potential treatment for solid tumors and other neoplasia, including colorectal tumors. ZD-9331 resulted in a

period of intracellular 2'-deoxyuridine (dUrd) elevation, a surrogate marker of thymidylate synthase inhibition, with observed myelosuppression being no greater than that seen with raltitrexed and less than with bolus 5-FU. As in previous studies, myelosuppression was the dose-limiting toxicity, occurring at 4.8 and 7.5 mg/m2/day, with one patient at each of these two doses experiencing a DLT. The MTD was not achieved until 12 to 16 mg/m2/day, based on which a fixed dose of 25 mg/day was being evaluated.



ZD 9331

2. Conclusions

The quinazoline scaffold's pharmacological actions have been described in the article. The ease of use, adaptability, and simplicity of the synthesis methods provide medicinal chemists with a wide variety of new quinazoline analogs. This will guarantee that this is an active and significant area of research in heterocyclic chemistry, especially in light of the advancements in synthetic tactics and technology for the development of effective and dependable methods for the production of novel molecules and demonstrated the ongoing interest in the quinazoline pharmacophore in medicinal chemistry and drug development. The significant level of protection against different illnesses may indicate that quinazoline analogs are promising candidates for additional research as bioactive drug delivery systems. Quinazoline analogs show promise as anti-infective medications against microorganisms that are resistant to many treatments due to their strong action. These analogs' wide-ranging antibacterial properties may result in the development of a novel class of antimicrobial drugs. Because of their biological significance, quinazoline analogs have demonstrated a wide range of pharmacological activities, including agonist and antagonist actions on receptors and considerable effects on enzymes. As a result, the quinazoline scaffold has numerous potential pharmacological actions in addition to being significant from a synthetic standpoint. More hopeful results may emerge from quinazoline scaffold research in the future.

Acknowledgements
The authors would like to thank Era College of Pharmacy, Era University, Lucknow, India, for providing technical support and facilities to carry out this work.

Conflict Of Interest
The authors have no conflicts of interest, financial or otherwise.

3. References

1. Abou-Seri, S. M.; Abouzid, K.; Abou El Ella, D. A. A. Molecular Modeling Study and Synthesis of Quinazolinone-Arylpiperazine Derivatives as α1-Adrenoreceptor Antagonists. Eur. J. Med. Chem.**2011**, 46 (2), 647–658.

2. Ahmed, O. M.; Hussein, A. M.; Ahmed, R. R. Antidiabetic and Antioxidant Effects of Newly Synthesized Pyrimido[1,6-A]Pyrimidine Derivatives in Neonatal Streptozotocin-Induced Diabetic Rats. Med. Chem. **2012**, 2, 020–028.
3. Amer, M.S., Browder, H.P. Effect of quazodine on phosphodiesterase. Proc Soc Exp Biol Med. **1971**, 136(3), 750-752.
4. Asif, M. Chemical Characteristics, Synthetic Methods, and Biological Potential of Quinazoline and Quinazolinone Derivatives. Int. J. Med. Chem. **2014**, 2014, 395637.
5. Badolato, M., Aiello, F., Neamati, N. 2,3-Dihydroquinazolin-4(1H)-one as a privileged scaffold in drug design. RSC Adv. **2018**, 8(37), 20894–20921.
6. Belz, G.G., Stern, H.C., Butzer, R. Dose-response following single administrations of a new cardiac performance enhancer RO 13-6438 in normal volunteers. J. Cardiovas. Pharmacol. **1985**, 7 (1), 86-90.
7. Borah, B., Swain, S., Patat, M., Chowhan, L.R. Recent advances and prospects in the organocatalytic synthesis of quinazolinones. Front Chem. **2022**, 10, 991026.
8. Bouley, R.; Ding, D.; Peng, Z.; Bastian, M.; Lastochkin, E.; Song, W.; Suckow, M. A.; Schroeder, V. A.; Wolter, W. R.; Mobashery, S.; Chang, M. Structure-Activity Relationship for the 4(3H)-Quinazolinone Antibacterials. J. Med. Chem. **2016**, 59 (10), 5011–5021.
9. Bridges, A. J.; Zhou, H.; Cody, D. R.; Rewcastle, G. W.; McMichael, A. Mc.; Showalter, H. D. H.; Fry, D. W.; Kraker, A. J.; Denny, W. A. Tyrosine Kinase Inhibitors. 8. an Unusually Steep Structure-Activity Relationship for Analogues of 4-(3-Bromoanilino)-6,7-Dimethoxyquinazoline (PD 153035), a Potent Inhibitor of the Epidermal Growth Factor Receptor. J. Med. Chem.**1996**, 39 (1), 267–276.
10. Bubenyák, M.; Takács, M.; Blazics, B.; Rácz, A.; Noszál, B.; Püski, L.; Kökösi, J.; Hermecz, I. Synthesis of bioisosteric 5-sulfa-rutaecarpine derivatives. Arkivoc, **2010**, 11, 291–302.
11. Chaudhary, A.P., Shukla, A.K., Pandey, J., Kant, P. Study of developments of biologically active Quinazolinones derivatives: A review. *Chem & Biol Interface*, **2018**, 8, 2, 62-83.
12. Chavan, B. B.; Bhalawane, P. P.; Kolsure, A. K.; Chabukswar, A.R. Synthesis and Evaluation of Some New 4, 6- Disubstituted Quinazoline Derivatives for Antimicrobial and Antifungal Activities. Asian J. Biomed. Pharm. Sci.**2014**, 33, 43–46.
13. Chen, K., Wang, K., Kirichian, A.M. 2006. In silico design, synthesis, and biological evaluation of radioiodinated quinazolinone derivatives for alkaline phosphatasemediated cancer diagnosis and therapy. Mol. Cancer Ther. **2006**, 5 (12), 3001-13.
14. Chen, K.; Wang, K.; Kirichian, A. M.; Al Aowad, A. F.; Iyer, L. K.; Adelstein, S. J.; Kassis, A. I. In Silico Design, Synthesis, and Biological Evaluation of Radioiodinated Quinazolinone Derivatives for Alkaline Phosphatase-Mediated Cancer Diagnosis and Therapy. Mol. Cancer Ther. **2006**, 5 (12), 3001–3013.
15. Cheng, C.M., Lee, Y.J., Wang, W.T., Hsu, C.T., Tsai, J.S., Wu, C.M., Ou, K.L., Yang, T.S. Determining the binding mode and binding affinity constant of tyrosine kinase inhibitor PD153035 to DNA using optical tweezers. Biochem Biophys Res Commun. **2011**, 404(1), 297-301.
16. Cohen, E., Klarberg, B., Vaughan, J.R. Quinazolinone Sulfonamides. A New Class of Diuretic Agents. J. Am. Chem. Soci. **1960**, 82, 2731-2735.
17. Cohen, E.; Klarberg, B.; Vaughan, J.R. Quinazolinone Sulfonamides. A New Class of Diuretic Agents 1. J. Am. Chem. Soc. **1960**, 82 (11), 2731–2735.
18. Daly, P.A., Chatterjee, K., Viquerat, C.E. RO13-6438, a new inotrope-vasodilator: systemic and coronary hemodynamic effects in congestive heart failure. Am. J. Cardio. **1985**, 55, 1539-44.
19. Darias, V.; Bravo, L.; Abdallah, S. S.; Sánchez Mateo, C. C. S.; Expósito-Orta, M. A.; Lissavetsky, J.; Manzanares, J.Synthesis and Preliminary Pharmacological Study of Thiophene Analogues of the Antipyretic and Analgesic Agent Ethenzamide. Arch. Pharmazie**1992**, 325 (2), 83–87.

20. Denis, D., Riendeau, D. Phosphodiesterase 4-dependent regulation of cyclic AMP levels and leukotriene B4 biosynthesis in human polymorphonuclear leukocytes. Euro. J. Pharmacol. **1999**, 367, 343-50.
21. Devi, K.; Kachroo, M. Synthesis and antitubercular activity of some new 2, 3-disubstituted quinazolinones. Pharm.Chem.**2014**, 6, 353–359.
22. Doods, H., Hallermayer, G., Wu, D., Entzeroth, M., Rudolf, K., Engel, W., Eberlein, W. Pharmacological profile of BIBN4096BS, the first selective small molecule CGRP antagonist. Br J Pharmacol. **2000**, 129, 420-423.
23. Eigenmann, R., Gerold, M., Holck, M. Cardiovascular profile of Ro 13-6438, a novel positive inotropic agent with vasodilating properties. J. Cardiovas. Pharmacol. **1984**, 6 (3), 511-9.
24. El-Azab, A. S.; Eltahir, K. E. H. Design and Synthesis of Novel 7-Aminoquinazoline Derivatives: Antitumor and Anticonvulsant Activities. Bioorg. Med. Chem. Lett. **2012**, 22 (5), 1879–1885.
25. Estlin, E. J.; Pinkerton, C.R.; Lewis, I. J.; Lashford, L.; McDowell, H. Mc.; Morland, B.; Kohler, J.; Newell, D. R.; Boddy, A. V.; Taylor, G. A.; Price, L.; Ablett, S.; Hobson, R.; Pitsiladis, M.; Brampton, M.; Clendeninn, N.; Johnston, A.; Pearson, A. D. J.. A Phase I Study of Nolatrexed Dihydrochloride in Children with Advanced Cancer. A United Kingdom Children's Cancer Study Group Investigation. Br. J. Cancer, **2001**, 84 (1), 11–18.
26. Faisal, M., Saeed, A. Chemical insights into the synthetic chemistry of quinazolines: recent advances. Front Chem. **2020**, 8, 594717.
27. Ganguli, S.; Panigrahi, M. K.; Singh, P.; Shukla, P. K. One-pot synthesis of novel quinazoline derivatives and their antimicrobial activity. Int. J. Pharm. Pharm. Sci. **2012**, 4, 434–440.
28. Garau, M.; Pereiro, M.; del Palacio, A.. In Vitro Susceptibilities of Malassezia Species to a New Triazole, Albaconazole (UR-9825), and Other Antifungal CompoundsAntimicrob. Agents Chemother. **2003**, 47 (7), 2342–2344.
29. Gnainsky, Y.; Spira, G.; Paizi, M.; Bruck, R.; Nagler, A.; Abu-Amara, S. N.; Geiger, B.; Genina, O.; Monsonego-Ornan, E.; Pines, M.. Halofuginone, an Inhibitor of Collagen Synthesis by Rat Stellate Cells, Stimulates Insulin-Like Growth Factor Binding Protein-1 Synthesis by Hepatocytes.J.Hepatol.**2004**, 40 (2), 269–277.
30. Grivas, P.D., Day, K.C., Karatsinides, A., Paul, A., Shakir, N., Owainati, I., Liebert, M., Kunju, L.P., Thomas, D., Hussain, M., Day, M.L. Evaluation of the Antitumor Activity of Dacomitinib in Models of Human Bladder Cancer. Mol Med. **2013**, 19(1), 367–376.
31. Holck, M., Thorens, S., Muggli, R., Eigenmann, R. Studies on the mechanism of positive inotropic activity of Ro 13-6438, a structurally novel cardiotonic agent with vasodilating properties. J. Cardiovas. Pharmacol. **1984**, 6 (3), 520-30.
32. Hricovíniová, J., Hricovíniová, Z., Kozics, K. Antioxidant, Cytotoxic, Genotoxic, and DNA-Protective Potential of 2,3-Substituted Quinazolinones: Structure-Activity Relationship Study. Int J Mol Sci. **2021**, 22(2), 610.
33. Hughes, A.N., Rafi, I., Griffin, M.J. Phase I studies with the nonclassical antifolate nolatrexed dihydrochloride (AG337, THYMITAQ) administered orally for 5 days. Clin. Cancer Res. **1999**, 5(1), 111-8.
34. Hwang, D.F., Noguchi T. Tetrodotoxin poisoning. *Adv. Food Nutr Res.* **2007**, 52, 141-236. Ishikawa, T., Kamide, R., Niimura, M. Photoleukomelanodermatitis (Kobori) induced by afloqualone. J. Dermatol. **1994**, 21(6), 430-3.
35. Ishikawa, K.; Ihara, M.; Noguchi, K.; Mase, T.; Mino, N.; Saeki, T.; Fukuroda, T.; Fukami, T.; Ozaki, S.; Nagase, T. Biochemical and Pharmacological Profile of a Potent and Selective Endothelin B-Receptor Antagonist, BQ-788. Proc. Natl. Acad. Sci. U.S.A. **1994**, 91 (11), 4892-4896.
36. Ishikawa, T.; Kamide, R.; Niimura, M. Photoleukomelanodermatitis (Kobori) Induced by Afloqualone. J. Dermatol. **1994**, 21 (6), 430–433.
37. Jodrell, D. I.; Bowman, A.; Rye, R.; Byrne, B.; Boddy, A.; Rafi, I.; Taylor, G. A.; Johnston, A.; Clendeninn, N. J.. A Phase I Study of the Lipophilic Thymidylate Synthase Inhibitor

Thymitaq™ (Nolatrexed Dihydrochloride) Given by 10-Day Oral Administration. Br. J. Cancer**1999**, 79 (5–6), 915–920.
38. Katague, B. D. Chemistry Reviewer Still in Lab. News Along Pike(newsletter of the Food and Drug Administration's Center for Drug Evaluation and Research. **2006**, 2.
39. Khan, I.; Zaib, S.; Batool, S.; Abbas, N.; Ashraf, Z.; Iqbal, J.; Saeed, A. 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 (11), 2361–2381.
40. Kobayashi, Y. Capsaicin-like anti-obese activities of evodiamine from fruits of Evodia rutaecarpa, a vanilloid receptor agonist. In: Planta Med. **2001**, 67(7), 628-33.
41. Lee, S. H.; Son, J. K.; Jeong, B. S.; Jeong, T. C.; Chang, H. W.; Lee, E. S.; Jahng, Y. D.. Progress in the Studies on Rutaecarpine.Molecules. **2008**, 13(2), 272–300.
42. Mackay, H. J.; McInnes, A.; Paul, J.; Raby, N.; Lofts, F. J.; McDonald, A. C.; Soukop, M.; Fullarton, G. M.; Harris, A. L.; Garcia-Vargas, J.; Evans, T. R.. A Phase II Study of Epirubicin, Cisplatin and Raltitrexed Combination Chemotherapy (ECT) in Patients with Advanced Oesophageal and Gastric Adenocarcinoma. Ann.Oncol. **2001**, 12 (10), 1407–1410.
43. Mallee, J.J., Salvatore, C.A., LeBourdelles, B., Oliver, K. R., Longmore, J., Koblan, K.S., Kane, S.A. Receptor activity-modifying protein 1 determines the species selectivity of non-peptide CGRP receptor antagonists. J. Biol. Chem. **2002**, 277, 14294-14298.
44. McLaughlin, Noel, P., Evans, P. Dihydroxylation of vinyl sulfones: stereoselective synthesis of (+)- and (−)-febrifugine and halofuginone. J. Org. Chem. **2010**, 75(2), 518.
45. Mishra, V. K.; Mishra, M.; Mishra, S.; Sahu, P.; Kashaw, S. K. Febrifugine analogues: Promising antimalarial agents. Asian J. Pharm. Pharmacol. **2015**, 1, 10–15.
46. Mohammadkhani, L., Heravi, M.M. Microwave-Assisted Synthesis of Quinazolines and Quinazolinones: An Overview. Front Chem. **2020**, 8, 580086.
47. Mohammed, E.R., Elmasry, G.F. Development of newly synthesised quinazolinone-based CDK2 inhibitors with potent efficacy against melanoma. J Enzyme Inhib Med Chem. **2022**, 37(1), 686–700.
48. Molina, P.; Tárraga, A.; Gonzalez-Tejero, A.; Rioja, I.; Ubeda, A.; Terencio, M. C.; Alcaraz, M. J.. Inhibition of Leukocyte Functions by the Alkaloid Isaindigotone from Isatis Indigotica and Some New Synthetic Derivatives. J. Nat. Prod.**2001**, 64 (10), 1297–1300.
49. Ochiai, T., Ishida, R. Pharmacological studies on 6-amino- 2-fluoromethyl- 3-(o-tolyl)-4(3H)-quinazolinone (afloqualone), a new centrally acting muscle relaxant. (II) Effects on the spinal reflex potential and the rigidity. Japanese J. Pharmacol. **1982**, 32(3), 427-38.
50. Ochiai, T.; Ishida, R. Pharmacological studies on 6-amin0-2-fluoromethyl-3-(o-tolyl)-4(3H)-quinazolinone (afloqualone), a new centrally acting muscle relaxant. (ii) effects on the spinal reflex potential and the rigidity. J. Pharmacol.1982, 32, 427–438.
51. Osinski, M.T., Schrör, K. Inhibition of platelet-derived growth factor-induced mitogenesis by phosphodiesterase 3 inhibitors: role of protein kinase A in vascular smooth muscle cell mitogenesis. Bio.chem. Pharmacol. **2000**, 60(3), 381-7.
52. Pao. W., Miller V., Zakowski, M. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proceed Nat Acad Sci USA. **2004**, 101(36), 13306-11.
53. Petrides, P.E. Anagrelide: what was new in 2004 and 2005?. Semin. Thromb. Hemost. **2006**, 32, 399-408.
54. Priya, M. G. R.; Girija, K.; Ravichandran, N. Priya MGR, Girija K, Ravichandran N. Invitro study of anti-inflammatory and antioxidant activity of 4-(3H)-quinazolinone derivatives. Rasayan J. Chem. **2011**, 4, 418–424.
55. Rakesh, K. P.; Darshini, N.; Shubhavathi, T.; Mallesha, N. Biological Applications of Quinazolinone Analogues: A Review. Org. Med. Chem. **2017**, 2, 555–585.
56. Raymond, E., Faivre, S., Armand, J. Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. Drugs, **2000**, 60 Suppl 1, 15-23.

57. Rezaeinasab, R., Jafari, E., Khodarahmi, G. Quinazolinone-based hybrids with diverse biological activities: A mini-review. J Res Med Sci. **2022**, 27, 68.
58. Rivera, V.R., Poli, M.A., Bignami G.S. Prophylaxis and treatment with a monoclonal antibody of tetrodotoxin poisoning in mice. Toxicon. **1995**, 33(9), 1231-7.
59. Selvam, T.P., Kumar, P.V. Quinazoline Marketed drugs-A Review. Res Pharm. **2011**, 1(1), 1-21.
60. Shen, H. Illustrated Pharmacology Memory Cards*:* Pharmnemonics*, 1st ed.*, Minireview, North Miami Beach, FL, USA, **2008**, 13.
61. Smith, H.O., Blessing, J.A., Vaccarello, L. Trimetrexate in the treatment of recurrent or advanced leiomyosarcoma of the uterus: a phase II study of the Gynecologic Oncology Group. Gynecol. Oncol. **2002**, 84(1),140-4.
62. Sorbera, L. A.; Bartroli, J.; Castaner, J. Albaconazole. Drugs Future, **2003**, 28, 529–537.
63. Srivalli, K.; Satish, K. Synthesis, in Vitro Evaluation of Some Novel Quinazolin-4(3H)-One Derivatives as Anti-Tumor Agents. Chem.Sci. Trans. **2012**, 1(3), 624–631.
64. Sundrud, M. S.; Koralov, S. B.; Feuerer, M.; Calado, D. P.; Kozhaya, A. E. Rhule-Smith, A.; Lefebvre, R.E.; Unutmaz, D.; Mazitschek, R.; Waldner, H.; Whitman, M.; Keller, T.; Rao, A. Halofuginone inhibits TH17 cell differentiation by activating the amino acid starvation response. Science. 324, 2009, 1334–1338.
65. Traxler, P.; Green, J.; Mett, H.; Séquin, U.; Furet, P. Use of a Pharmacophore Model for the Design of EGFR Tyrosine Kinase Inhibitors: Isoflavones and 3-Phenyl-4(1H)-Quinolones.J. Med. Chem.**1999**, 42 (6), 1018–1026.
66. Wang, D., Gao, F. Quinazoline derivatives: synthesis and bioactivities. Chem Cent J. **2013**, 7, 95.
67. Wdowiak, P., Matysiak, J., Kuszta, P., Czarnek, K., Niezabitowska, E., Baj, T. Quinazoline derivatives as potential therapeutic agents in urinary bladder cancer therapy. Front Chem. **2021**, 9, 765552.
68. Widemann, B. C.; Balis, F. M.; Godwin, K. S.; McCully, C. Mc.; Adamson, P.C. The Plasma Pharmacokinetics and Cerebrospinal Fluid Penetration of the Thymidylate Synthase Inhibitor Raltitrexed (Tomudex) in a Nonhuman Primate Model.Cancer Chemother. Pharmacol. **1999**, 44(6), 439–443.
69. Yan, J. W.; Li, Y. P.; Ye, W. J.; Chen, S. B.; Hou, J. Q.; Tan, J. H.; Ou, T. M.; Li, D.; Gu, L. Q.; Huang, Z. S.. Design, Synthesis and Evaluation of Isaindigotone Derivatives as Dual Inhibitors for Acetylcholinesterase and Amyloid Beta Aggregation. Bioorg. Med. Chem. **2012**, 20 (8), 2527–2534.
70. Yousefi, B.; Azimi, A.; Majidinia, M.; Shafiei-Irannejad, V.; Badalzadeh, R.; Baradaran, B.; Zarghami, N.; Samadi, N. Balaglitazone Reverses P-Glycoprotein-Mediated Multidrug Resistance via Upregulation of PTEN in a PPARγ-Dependent Manner in Leukemia Cells. Tumour. Biol. **2017**, 39 (10). DOI: 10.1177/1010428317716501
71. Zabludowski, J. R.; Zoccali, C.; Isles, C.G.; Murray, G.D. Inglis, R. Fraser, S.G. Ball. Effect of the 5-hydroxytryptamine type 2 receptor antagonist, ketanserin, on blood pressure, the renin-angiotensin system and sympatho-adrenal function in patients with essential hypertension. British J. Clin. Pharmacol. 1984, 17 (3), 309–316.
72. Zhang, G. H.; Xue, W. B.; An, Y. F.; Yuan, J. M.; Qin, J. K.; Pan, C. X.; Su, G. F.. Distinct Novel Quinazolinone Exhibits Selective Inhibition in MGC-803 Cancer Cells by Dictating Mutant p53 Function. Eur. J. Med. Chem. **2015**, 95, 377–387.