

# The Medicinal Functionality of Quinazolines

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## Abstract

Quinazolines are organic compounds that are made up of two fused six-membered rings—benzene ring and pyrimidine ring. Referring to the various positions of N atoms in the cyclic ring, many other isomeric forms play a vital role in biological activities. This review article describes the main functional groups that are present in Quinazolines which are responsible for medicinal, antimicrobial, antiviral, antibacterial and anticancer actions. This review focuses on the properties of these functional groups responsible for various biological activities of Quinazolines. The heterocyclic ring structures are mainly responsible for the pharmacological effects of quinazolines. The presence of benzyl-, halo-, methoxy and amino derivatives has many anticancer, antimicrobial and antimalarial properties. The article aims to review the medicinal functionality of Quinazolines.

**Keywords:** Heterocyclic, Cancerous cells, Microbial, Hypertension, Green Chemistry, Obesity, Inflammation.

## INTRODUCTION

Quinazoline (Figure 1) is an organic compound having an aromatic heterocycle and a bicyclic structure. Two six-membered aromatic rings fused have a benzene ring and a pyrimidine ring.

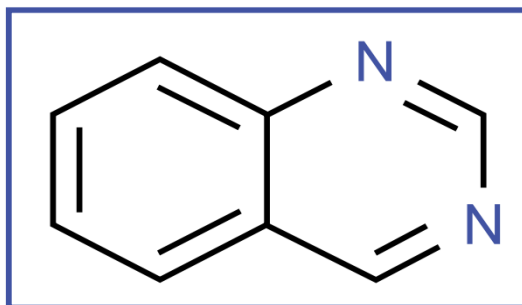


Figure1. Structure of Quinazoline

Benzene is an aromatic compound with a ring of six carbon atoms bonded by alternate single and double bonds. Kekule (Figure 2) proposed two resonance structures, since all the carbon atoms in the benzene ring are  $sp^2$  hybridised. [1]

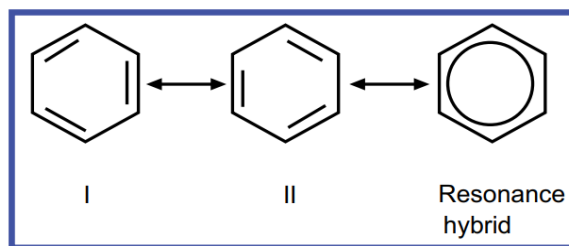


Figure2. Resonance Structure in Benzene

The pyrimidine ring (Figure 3) is also an aromatic heterocycle six-membered ring containing two nitrogen atoms and four carbon atoms. It is a planar structure with nitrogen atoms having lone pair of electrons, which plays an important role in the drug field [2,3], leading to many pharmacological studies on pyrimidine and its derivatives.

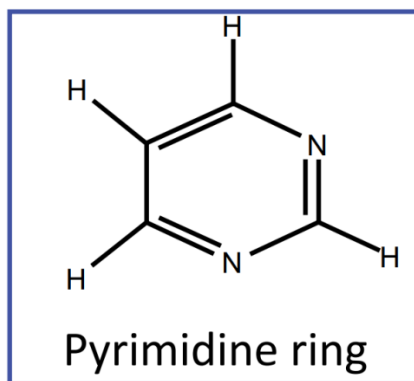


Figure3. Structure of Pyrimidine ring

#### Quinazoline Derivatives as Anticancer agent

A tumour is developed in the human body due to genetic factors or when exposed to harmful chemicals and radiation. Though there are many techniques such as complex surgery and chemotherapy, still the application of anticancer drug agents would help in the removal of the tumour efficiently without damaging the healthy tissues. There are many unique drugs available to inhibit the further growth of cancerous cells but this special class of compounds – Quinazoline derivatives, is of great importance in biological and pharmacological chemistry. [4-6]

These derivatives have a unique property to block the activity of a protein and so they can act as powerful inhibitors of the protein which is responsible for tumour growth(EGFR). EGFR found on the surface of the cancer cells is mainly responsible for its growth and cellular division. For instance, the ultraviolet radiation from the Sun directly falling on the skin can damage the DNA of pigment-producing cells.[3] This leads to a type of skin cancer that eventually grows over time in various parts of the body like the liver and lungs. Naturally, our body's immune system can support destroying these tumour cells to some extent but on the other side, the cancerous cells keep growing and widespread rapidly. Researchers have found that the introduction of the functional group benzyl substitutedquinazoline derivatives are attractive antitumour agents that play the role of broad-spectrum, potentially selectively active growth inhibitorstoward cancerous cells. This review of novel 3-benzyl-4(3H) quinazolinone analogues proves that these are promising compounds for the development of antitumor activities. [7-9]

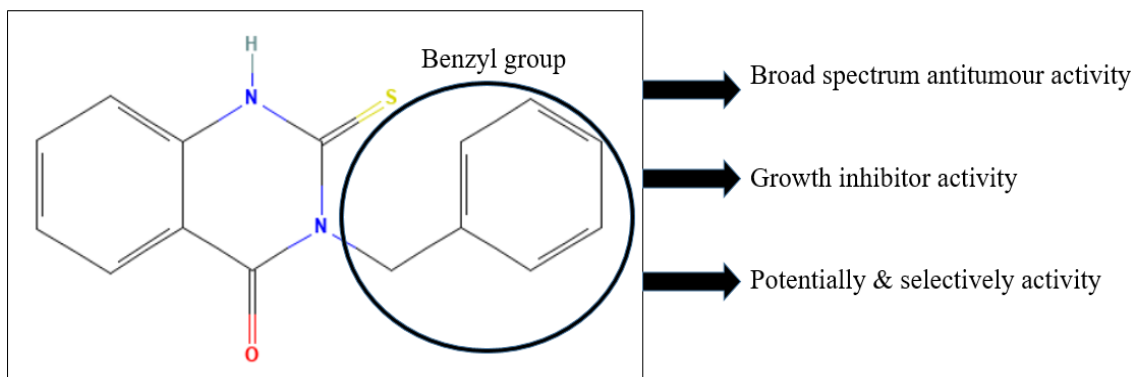


Figure 4. The presence of Benzyl- group in Quinazoline derivatives

#### Quinazoline Derivatives as Antimicrobial agent

When quinazoline isothiocyanate reacts with various nucleophiles containing nitrogen, sulphur or oxygen resulted in a heterocyclic system—quinazoline derivatives, were tested for antimicrobial activity. [9] This review is an attempt to recognize the functional group responsible for the antimicrobial activity of quinazoline derivatives. When gram-positive bacteria and gram-negative bacteria of different concentrations were tested using antimicrobial drugs, the variation in the action of inhibition was measured and analysed. [10] A series of innovative halo- substituted quinazoline derivatives showed remarkable antimicrobial activities. More the halo- groups attached to the quinazolines, the rate of inhibition also increased. Antimicrobial drug absorption occurs swiftly and enters the bloodstream leading to bioavailability which depends on the properties of the drugs, the structural aspects of the human body and the pH levels to treat the microbial infection caused by bacteria, viruses and fungi. The main functions of antimicrobial drugs include inhibition of cell walls, protein, metabolites and nucleic acid synthesis, and damage of plasma membrane. [11-13]

The numerous structural alterations around the fused ring of quinazolines with several halo- substituents are useful in treating different microbial diseases and applied a wide range of beneficial abilities. To conclude, researchers believe that these quinazoline compounds with a much stronger impact will be developed soon towards curing many deadly illnesses.

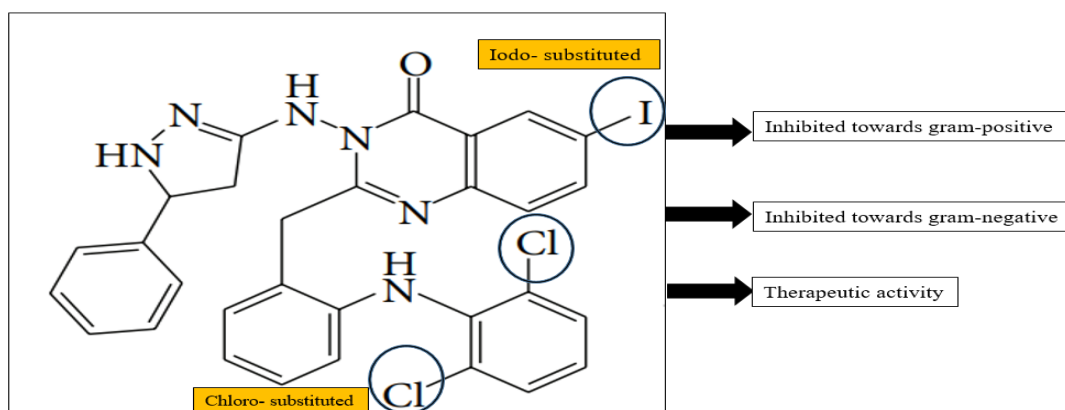


Figure 5. The presence of Halo- substituents in Quinazoline derivatives

#### Quinazoline Derivatives as Antihypertensive agent

Over one billion individuals around us have high blood pressure also called hypertension. This is a very common but serious concern due to the damage to cell linings. Though the problem can be reduced by simple physical procedures like regular exercise, proper lifestyle and diet, the need for antihypertensive medication has become essential in many case studies. Quinazoline derivatives have been very famous for antihypertensive activity. Diverse quinazoline analogues have one functional group in common, the presence of the alkoxy- group, which supports these antihypertensive drugs lower the blood pressure to the optimal ranges.

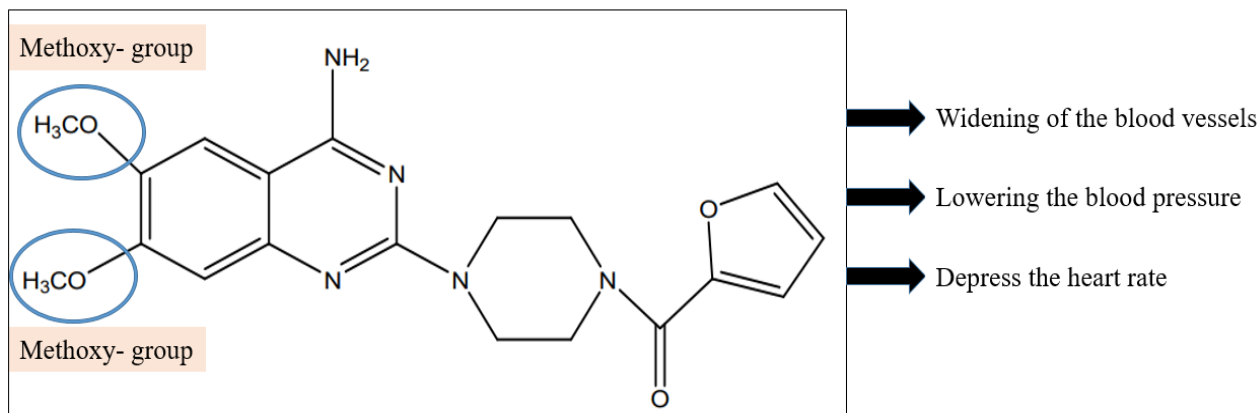


Figure 6. The presence of Methoxy- substituents in Quinazoline derivatives

Generally, antihypertensive drugs are well absorbed from the intestinal tract and eliminated after undergoing extensive metabolism. The bioavailability of these drugs is rather low, and the elimination half-life is quite short. Such substituted quinazoline derivatives did show significant biological activities. The suggested modifications in the new synthetic green chemistry involved methods and the novel compounds developed will definitely show a new original initiative for these biologically active compounds.

#### Green Approach towards Quinazolines synthesis

The scientific challenges that are faced in protecting human and environment-related issues can be solved by applying the concept of Green Chemistry [11]. This concept prevents the wastage of raw materials and the generation of toxic substances during the synthesis of various chemical compounds. Atom economy is one of the most efficient synthetic paths that can be applied to convert most of the reactants into useful desired products.

#### (i). Green Synthetic Preparation of quinazoline-2,4(1H,3H)-diones using the powerful universal solvent

The water, which is a powerful universal solvent, could be used for the preparation of quinazoline derivatives along with the greenhouse gas, carbon dioxide, without any catalyst, resulting in excellent yields, while the reactions were not supportive with organic solvents.

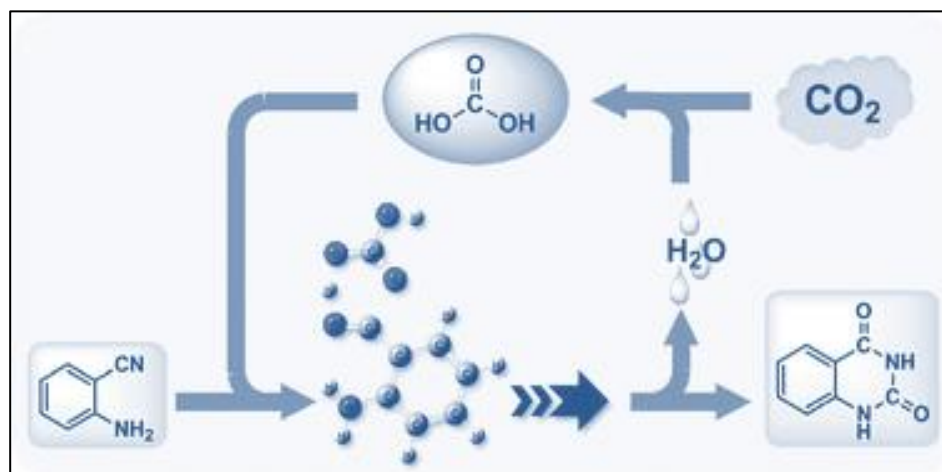


Figure 7. Synthesis of quinazoline-2,4(1H,3H)-diones from CO<sub>2</sub> and 2-aminobenzonitriles

(ii). Synthesis of quinazoline-2,4(1H,3H)-diones using Carbon dioxide in superbase

Superbases are effective catalysts that could be used to perform the quinazoline derivatives in the absence of any solvent whether inorganic or organic, by the conversion of carbon dioxide and 2-aminobenzonitrile to quinazoline-2,4(1H, 3H)-diones.

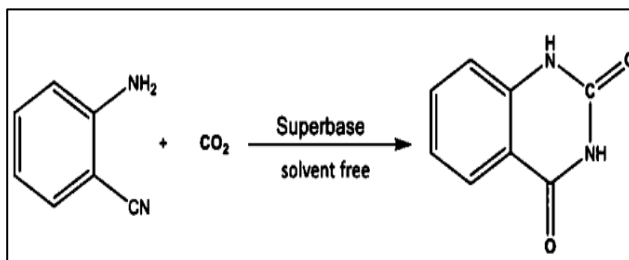


Figure 8. Synthesis of quinazoline-2,4(1H,3H)-diones using carbon dioxide in superbase

Quinazoline Derivatives as Anti-obesity agent

Melanin-concentrating hormone receptor 1 antagonist, popularly known as MCHR1 possesses exclusive anti-obesity activity.[2] Obesity, which means an excessive accumulation of body fat is caused due to the consumption of high calories of food that the body requires, developing adipose tissue. Further increase in obesity may be due to poor diet, lack of physical activity, genetic conditions, and thyroid gland issues.

The related compounds were tested and showed powerful anti-obesity activity. These drugs on oral administration resulted in noticeable weight reduction with a half-maximal inhibitory concentration value proving its high drug efficacy containing key functional groups such as alkoxy-, halo- and amino- groups.

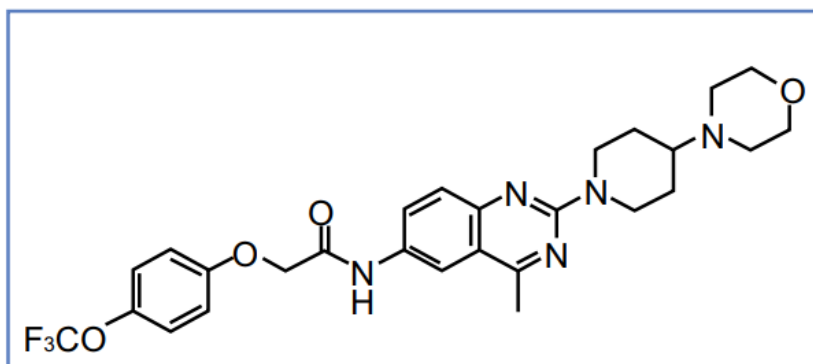


Figure9. Chemical Structure of anti-obesity quinazolines

Further, this compound, due to its good affinity for human Melanin-concentrating hormone receptor 1 (MCHR1) antagonists– is still a practical approach for obesity treatment and enhances the cardiometabolic, central nervous [14] and biological activities. [15]

Nowadays, AOMs promote weight loss and shrink fat because when the fat cells grow larger, and the metabolism of the body slows down. These medications block this metabolic brake from operating in obese white fat cells and in turn the metabolic activities increase.

Quinazoline Derivatives as Anti-inflammatory agent

Inflammation is a condition of any part of the body, where jamming of the blood vessels occurs, with a hindrance in the blood flow and development of dark tissue around it. The consequence is suffering from intense heat and pain.[16-19] It is indeed a

biochemical reaction response related to many disorders such as joint pain, skin diseases and other factors. Anti-inflammatory drugs, generally, inhibit certain specific enzymes responsible for inflammation and mostly consist of sulphur and nitrogen linkages in their chemical structures as the main functional groups. [20]

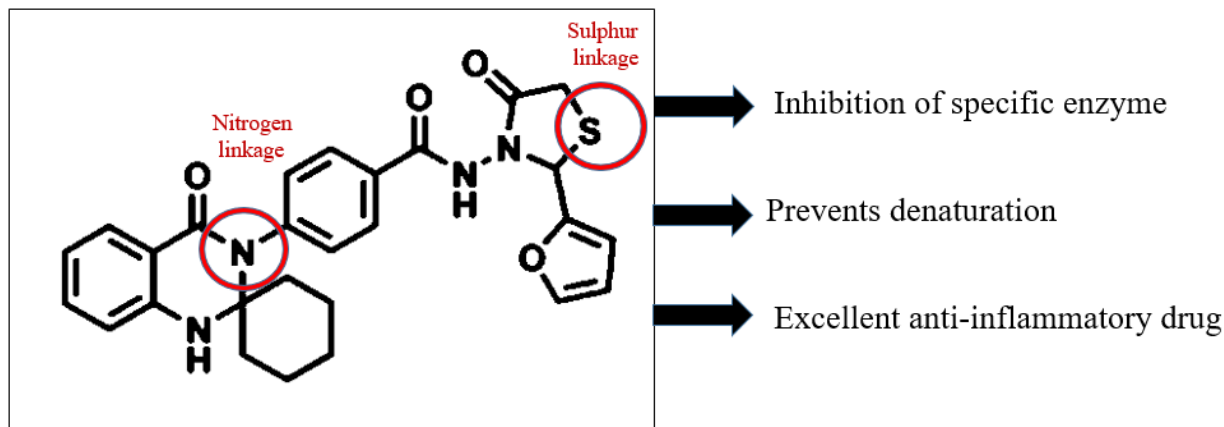


Figure 10. Chemical structure of anti-inflammatory Quinazoline derivatives

## Conclusions

In the near future, quinazoline derivatives that would be attached with several new structural modifications using Green Synthesis would increase the demand for these compounds in both biological and pharmacological solutions. The molecular structures are generally the central part of the pharmacophore and so these various substituents would be the best way to research and characterise these novel compounds by green chemists. These novel compounds will exhibit a diversified range of therapeutic efficacy due to various new substituents attached to the fused heterocyclic rings of quinazolines. [21, 22]

Thus we can conclude that this review will provide the researchers with a thorough understanding of the structure-activity relationship study, which further helps in designing a good large number of quinazoline and quinazolinone compounds with a strong impact in curing many fatal disorders.

Declarations

Acknowledgments

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Funding

Not applicable.

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