ISSN : 2350-0743

International Journal of Recent Advances in Multidisciplinary Research

Vol. 12, Issue 02 pp.10827-10830, February, 2025

RESEARCH ARTICLE

QUINAZOLINONES AS NOVEL ANTITUMOR AGENTS

Sergio Resta[1,*] and Giacomo Resta[2]

[1]Surgeon, specialist in General Surgery and Oncologic Surgery - freelancer, 53043 Chiusi (SI), Via Montegrappa, 1- Italy;
[2]Student at the Faculty of Pharmacy of the University of Perugia

ARTICLE INFO

Article History

Received 19th November, 2024
Received in revised form
17th December, 2024
Accepted 26th January, 2025
Published online 28th February, 2025

Keywords:

Quinazolinones, Anti-inflammatory properties, Antitumor Efficacy, Angiogenic activity, Antiapoptosis, Antimetastatic Activity.

Corresponding author:
Sergio Resta

ABSTRACT

The long struggle to combat and definitively eradicate the various forms of cancer that affect millions of patients worldwide is constantly being enriched with new therapeutic tools. In this challenge, many substances extracted from plants are gaining much attention, which, compared to traditional synthetic chemotherapeutics, have the advantage of a lower incidence of side effects, with the same antitumor efficacy. Among the substances of plant origin there are the Quinazolinones, from which many chemical derivatives have been synthesized, which have demonstrated a broad spectrum of therapeutic efficacy. In this work, we will review the therapeutic properties of the main Quinazolinone derivatives, and their supposed mechanism of action. They are very promising substances with positive developments in the fight against neoplastic pathology.

Citation: Sergio Resta and Giacomo Resta. 2025. *"*Quinazolinones as Novel Antitumor Agents*", International Journal of Recent Advances in Multidisciplinary Research,* 12, (02), 10827-10830.

INTRODUCTION

Quinazolinones are a class of nitrogen - containing heterocyclic compounds characterized by the presence of the quinazoline nucleus, a structure well known for its pharmacological properties, including anti-inflammatory, analgesic, antitumor, and antiviral effects. Quinazolinones are a group of synthetic compounds, and do not occur naturally as such in nature. However, the quinazoline nucleus, which is the basis of many of the molecules belonging to this class, can be derived from natural structures present in some plants, fungi or other organisms, although the quinazolinones themselves are generally obtained through chemical synthesis processes in the laboratory. Although quinazolinones are not natural compounds, the chemical structure of some derivatives may be inspired by biologically active compounds found in nature. Some alkaloids and secondary metabolites, produced by plants and marine organisms, contain chemical structures similar to that of the quinazoline nucleus and could serve as models for the development of these compounds. In particular, some natural alkaloids and metabolites can present nitrogenous ring patterns (as in the case of quinazole, the basic structure), which are then modified in the laboratory to obtain quinazolinones. An example of compounds that inspire studies on quinazolinones are those belonging to the family of indole alkaloids or molecules of plant origin that interact with biological receptors. The quinazoline nucleus is a fundamental chemical structure that forms the basis of a wide range of bioactive compounds, known as quinazolinones. This nucleus belongs to the class of nitrogenous heterocycles, which are organic compounds characterized by a ring containing nitrogen atoms, in addition to carbon and hydrogen Fig.1. Quinazoline derivatives of Quinazolinone have a wide range of pharmacological activities. They are used as an anticancer, antiviral, antibacterial, antitubercular, analgesic, antihypertensive, anti-inflammatory, antidiabetic, sedative-hypnotic, antihistaminic, anticonvulsant and antidiabetic, sedative-hypnotic, antihistaminic, anticonvulsant and many other uses Fig. 2. quinazoline nucleus is composed of a bicyclic system that includes a benzene ring (with six atoms) and a five-atom ring containing a nitrogen atom. The basic structure of a quinazolinone consists of a sequence of bonds and substitutions that give the molecules that contain it a variety of biological properties. The characteristics of the quinazoline nucleus are represented in the structural formula Fig.1:

- Cyclic structure: The quinazoline nucleus is composed of two six-membered benzyl rings, one of which contains two nitrogen atoms called the pyrimidine ring and this ring is fused to the second aromatic ring of benzene, therefore, quinazoline is a phenylpyrimidine compound Fig.1.
- Position of nitrogen: Nitrogen in the nucleus is generally placed in a position that confers a certain stability to the structure and chemical reactivity of the compound.

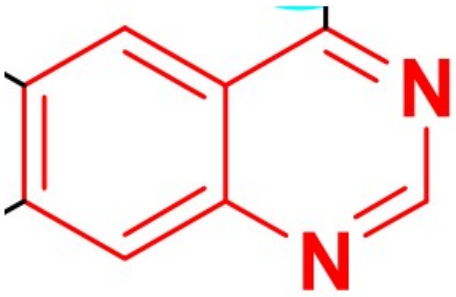

Fig.1. Structural formula of quinazoline

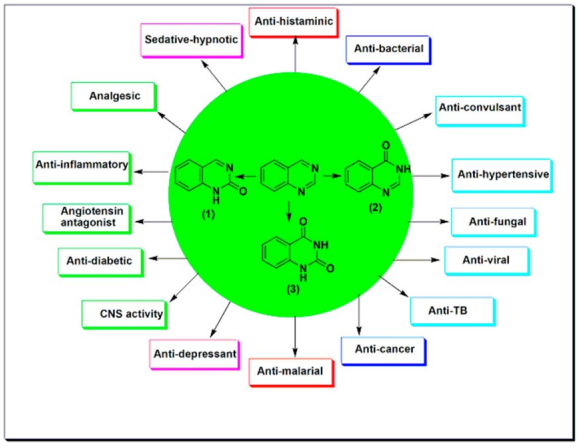

Figure 2. Quinazoline nuclei and therapeutic properties

- Chemical variability: The nucleus can be further modified by the addition of functional groups (such as methyl, alkyne, alkyl or amino groups) which improve its biological and pharmacological activity Fig.3

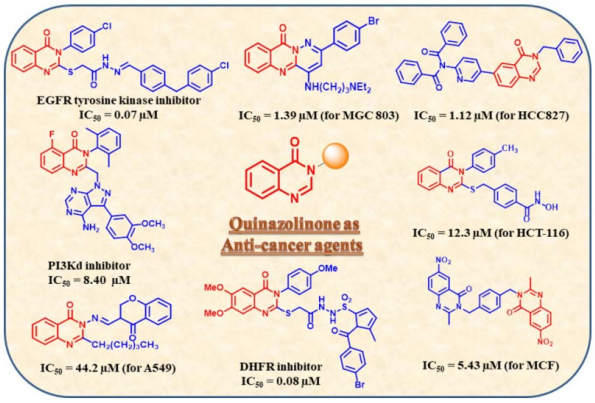

Figure 3. Quinazoline nucleus and derived structures

Interest in quinazolinones as potential therapeutic agents in oncology has increased in recent decades, due to their ability to inhibit various crucial biological mechanisms involved in cancer development and progression. In this article, we will explore the antitumor potential of Quinazolinones, their mechanisms of action, target biochemical pathways, and the progress of research on the synthesis of these compounds.

Chemical Structure and Synthesis: Quinazolinones have a two-ring structure, with a benzene ring and a six-membered nitrogen ring, Fig.1. The synthesis of Quinazolinones occurs through several chemical routes, including the condensation of compounds such as quinazolines with other reagents that have an active carbonyl group (e.g. aldehydes or ketones). Several variations of the basic Quinazolinone structure have been developed to improve pharmacological efficacy and reduce possible side effects Fig.3. Many studies focus on the introduction of functional groups such as alkylations and aromatic substitutions to improve selectivity and biological activity.

Quinazolines represent the core of new compounds that have promising biological activity. They show diverse activities that act on different metabolic targets. These activities are antitumor, antihypertensive, antimicrobial, antifungal, antibacterial, analgesic, anti-inflammatory, antitubercular and antimalarial.

There is a vast literature on the different mechanism of action of the numerous Quinazoline derivatives, tested for multiple antitumor activities; therefore, an exhaustive analysis of the multiple tested derivatives is very difficult. In the following paragraphs we highlight the most relevant proposed mechanisms of action and recent progress on the different biological targets.

Antitumor mechanisms of action: Quinazolinones act on multiple molecular pathways involved in the regulation of the cell cycle, apoptosis, and the response to cellular stress, fundamental factors in the growth and spread of tumor cells. Among the main mechanisms of action of Quinazolinones as antitumor agents, we can mention the following Fig. 4 :

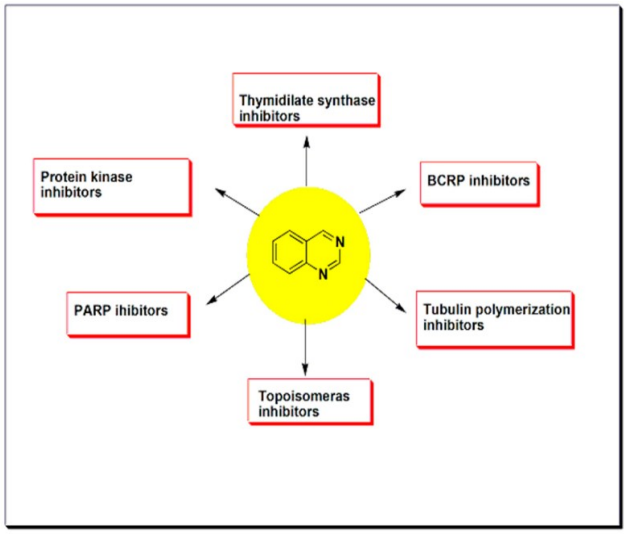

Figure 4 - Modes of action of anticancer quinazolines.

Inhibition of DNA synthesis and cell proliferation: Quinazolinones are able to interfere with DNA synthesis, preventing cell replication and inducing cell cycle arrest. These compounds were studied for their ability to inhibit key enzymes involved in nucleic metabolism, such as topoisomerase I and II, which are essential for the correct separation and recombination of DNA during mitosis. Inhibition of topoisomerase leads to the accumulation of tension in DNA, which can result in double-strand breaks, thus preventing the correct replication of genetic material and promoting the activation of DNA repair mechanisms or apoptosis (programmed cell death) in damaged cells Fig.5.

Interference with DNA polymerases: Another mechanism by which quinazolinones may affect DNA synthesis is the inhibition of DNA polymerases. Inhibition of DNA polymerases is a crucial mechanism by which quinazolinones exert their antitumor activity. DNA polymerases, particularly DNA polymerase α, δ, and ε, are enzymes essential for DNA replication and the repair of damaged DNA. These enzymes catalyze the addition of new nucleotides to the DNA strand during cell replication, ensuring that the genetic material is correctly and faithfully duplicated.

When quinazolinones inhibit the activity of DNA polymerases, they prevent the progression of DNA replication, blocking the cell cycle and preventing the correct duplication of tumor cells. This leads to an accumulation of genetic errors and damages the genomic stability of cells, promoting cell death (apoptosis). In particular, the inhibition of polymerase δ, which is involved in DNA replication at the replication fork, can have devastating effects for tumor cells, which require rapid and incessant replication to grow and proliferate. These enzymes are essential for DNA replication and DNA damage repair. By inhibiting DNA polymerases, quinazolinones can block the progression of cell replication and trigger stress signals that lead to tumor cell death.

Induction of apoptosis: Numerous studies have shown that Quinazolinones can induce programmed cell death (apoptosis) in tumor cells, a process that involves the activation of caspases, key proteins that regulate the self- destruction of damaged cells. Apoptosis can be induced directly, as a response to DNA damage, or through the activation of pro-apoptotic pathways, such as the p53 pathway, a tumor suppressor protein that is critical for the control of cell growth and the response to DNA damage Fig. 5.

Modulation of the response to oxidative stress: Quinazolinones are also known for their ability to modulate the oxidative stress response in tumor cells. Oxidative stress, which results from an accumulation of reactive oxygen species (ROS), is often a factor that stimulates oncogenic transformation. Some Quinazolinones possess antioxidant activity, which could reduce ROS-induced damage, effectively balancing cell proliferation and inducing cell death in tumor cells.

Inhibition of metastasis: Some Quinazolinones are able to inhibit tumor metastasis, the process by which tumor cells migrate and colonize distant tissues. These compounds have been studied for their ability to inhibit cell motility, a property critical for the movement of tumor cells in the blood and lymph nodes. Evidence suggests that Quinazolinones may act as inhibitors of proteases, such as extracellular matrix metalloproteinases, which are involved in the remodeling of the tumor microenvironment. Quinazolinones interfere with cell motility processes, preventing tumor cells from migrating from the primary site and spreading to other organs. Inhibition of migration is mediated by a reduction in cytoskeletal dynamics, which is crucial for tumor cell motility. Studies suggest that quinazolinones can modulate cytoskeletal proteins, such as actins and intermediate filaments, which are involved in cell deformation and its ability to invade surrounding tissues Fig.6.

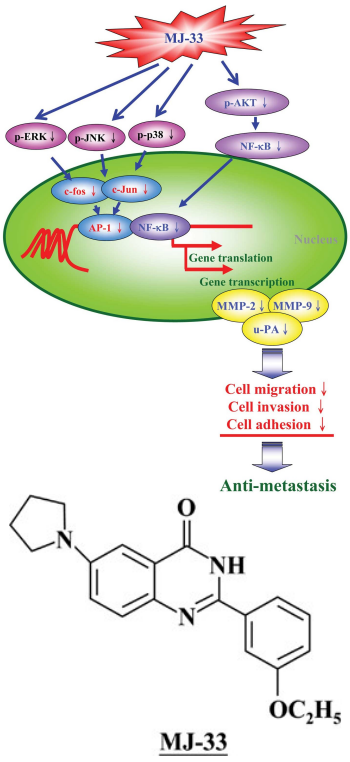

Figure 6. Antimetastatic activity of Quinazoline

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and spread. Some quinazolinones have been shown to reduce the formation of new blood vessels in the tumor microenvironment, thereby limiting the supply of nutrients and oxygen essential for tumor proliferation. By inhibiting angiogenesis, quinazolinones block the supply of resources vital for tumor cell growth and spread. Quinazolinones can alter cell adhesion molecules (CAMs), such as E- cadherin and integrins, which are involved in binding tumor cells to surrounding cells and extracellular matrices. Reduced adhesion allows tumor cells to more easily detach from the primary tumor and migrate to other organs. Some quinazolinones, by modulating the expression of these proteins, reduce the ability of tumor cells to invade blood vessels and distant tissues. The tumor microenvironment, which includes stromal cells, fibroblasts, and endothelial cells, plays a fundamental role in metastasis. Quinazolinones are able to modify the interaction between tumor cells and the microenvironment, reducing the secretion of growth factors that promote tumor cell proliferation and invasiveness. For example, inhibition of matrix metalloproteinases (MMPs), enzymes that allow the degradation of the extracellular matrix, can reduce the ability of tumor cells to invade surrounding tissues.

Preclinical and clinical studies: Preclinical studies of Quinazolinones as anticancer agents have shown promising results, both in vitro and in animal models. The ability of these compounds to reduce tumor growth, block cancer progression, and improve overall survival in animal models has attracted considerable interest. However, clinical studies of Quinazolinones as anticancer drugs are still in their early stages, with few compounds in clinical trials. Difficulties related to the bioavailability, selectivity, and toxicity of Quinazolinones are some of the obstacles that must be

overcome to translate these preclinical results into effective treatments for cancer patients.

Quinazolinones have emerged as potential anticancer agents with mechanisms of action involving modulation of DNA synthesis, induction of apoptosis, modulation of oxidative response, and inhibition of metastasis. Despite the challenges in synthesis and optimization of bioavailability, preclinical results suggest that Quinazolinones could represent a new class of anticancer drugs. Future developments should focus on optimizing their structure to improve efficacy and reduce side effects, thus bringing these compounds to potential clinical application.

REFERENCES

He, X., *et al*. (2020). "Quinazolinone derivatives: A comprehensive review of their biological activities and synthesis." European Journal of Medicinal Chemistry, 207, 112698.

Zhang, L., *et al*. (2019). "Quinazolinone as a promising scaffold for drug discovery in oncology." Medicinal Chemistry Communications, 10(10), 1650-1659.

Mikhailov, D., *et al*. (2018). "Quinazolinone -based compounds as potential anticancer agents." Pharmacology & Therapeutics, 185, 97-104.

Dong, Y., *et al*. (2017). "Anticancer potential of quinazolinone derivatives: A review." Pharmacological Research, 116, 1-10.

Liu, Y., *et al*. (2021). "Quinazolinone derivatives as potent inhibitors of cancer cell migration and metastasis." Journal of Cancer Research and Clinical Oncology, 147(6), 1535-1548.

CHI-CHENG LU *et al*; Inhibition of Invasion and Migration by Newly Synthesized Quinazolinone MJ-29 in Human Oral Cancer CAL 27 Cells through Suppression of MMP-2/9 Expression and Combined Down- regulation of MAPK and AKT Signaling, ANTICANCER RESEARCH *32* : 2895-2904 (2012)

David Preciado *et al*; A potent therapeutic scaffold fusing quinazolinone/melatonin for future colorectal cancer interventions: design, one-pot synthesis, biological and ADME-tox modeling studies, Medicinal Chemistry Research (2024) 33:1698–1713

Marwa F. Ahmed and Naja Magdy; Design, Synthesis and anticancer activity evaluation of new quinazoline derivatives linked to thiazolidinone, azetidinone or oxadiazol moieties, Acta Poloniae Pharmaceutica ñ Drug Research, Vol. 75 No. 6 pp. 1321ñ1328, 2018

Mohamed F. Zayed ; Medicinal Chemistry of Quinazolines as Anticancer Agents Targeting Tyrosine Kinases *Sci. Pharm.* 2023**,** *91,* 18

Zhenxi Niu *et al*; Discovery of Novel Quinazoline Derivatives as Potent Antitumor Agents, *Molecules* 2022**,** *27,* 3906

Ali Gamal Al-Kaf and Rana Abdullah Al- Robaid ; Biological Activities of Recent Advances in Quinazoline, Intech Open *http://dx.doi.org/10.5772/intechopen.1004051*

****