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Review Article

Quinazolinone Synthetic Strategies and Medicinal Significance: A review

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ABSTRACT

Quinazolinone derivatives represent a vital class of heterocyclic compounds known for their structural diversity and wide-ranging biological activities. Their synthesis has been extensively studied, employing both conventional and advanced techniques. Traditional routes often involve the condensation of anthranilic acid with carbonyl compounds, while newer methods utilize microwave irradiation, multicomponent reactions, and greener alternatives to enhance efficiency and reduce environmental impact. In the field of medicinal chemistry, quinazolinones have attracted considerable attention due to their therapeutic potential against various diseases. They exhibit notable pharmacological properties such as anticancer, antibacterial, antifungal, anti-inflammatory, and central nervous system activities. The core structure allows for flexible chemical modifications, enabling the optimization of biological efficacy and pharmacokinetic profiles through structure-activity relationship (SAR) studies. Overall, quinazolinones continue to be valuable scaffolds in the development of novel therapeutic agents. Looking ahead, future research should focus on designing new derivatives with improved selectivity and bioavailability, exploring their roles in molecular targeting, and integrating them into advanced drug delivery systems. Such efforts are expected to contribute significantly to the development of innovative and effective pharmaceuticals

INTRODUCTION

Quinazolinones are a class of fused bicyclic heterocycles that exhibit a broad range of biological activities, including antibacterial, anticancer, anticonvulsant, and anti-inflammatory properties. Due to their structural diversity, they have been extensively studied in medicinal and pharmaceutical chemistry. Quinazolinones are an essential class of nitrogen-containing heterocyclic compounds that exhibit a broad range of biological and catalytic applications. Their unique fused bicyclic structure allows for extensive modifications, leading to compounds with

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significant pharmacological potential, including antibacterial, anticancer, anticonvulsant, anti-inflammatory, and antiviral properties[1]. Due to their diverse biological activities, quinazolinones have been extensively studied as therapeutic agents in drug discovery. The FDA-approved drugs Erlotinib, Gefitinib, and Lapatinib are prime examples of quinazolinone-based anticancer agents that target epidermal growth factor receptors (EGFRs)[2]. Similarly, quinazolinone derivatives are being explored for their anticonvulsant and antimicrobial properties, making them valuable candidates for treating drug-resistant bacterial infections and neurological disorders. Beyond medicinal applications, quinazolinone derivatives are also widely used in catalysis, particularly in C-C coupling reactions, oxidation-reduction transformations, and organocatalysis. Recent research has focused on green synthesis approaches, including the use of nanocatalysts and recyclable supports, to make quinazolinone-based catalysis more sustainable and eco-friendlier. Quinazolinones are key scaffolds in drug discovery. Medicinal chemistry strategies include Halogenation & Hydroxylation Enhance bioavailability and potency.Heterocyclic Fusion Expands pharmacological applications[3].

Structural Characteristics of Quinazolinone

Quinazolinone is a heterocyclic compound that consists of a benzene ring fused with a quinazoline ring, which itself contains a nitrogen atom. The core structure of quinazolinone is as follows .The molecule features a fused bicyclic system made up of a benzene ring and a quinazoline ring. The quinazoline ring is a six-membered ring containing a nitrogen atom at position 1 and a carbonyl group (lactam) at position 2 [4]. The quinazolinone structure includes a lactam group (a cyclic amide) at position 2 of the quinazoline ring. This functional group is crucial for the compound's reactivity and interactions with biological targets[5].

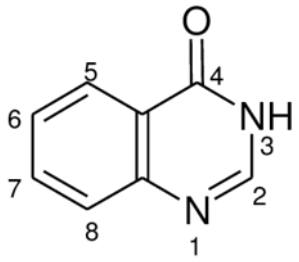


Fig:1

Structural Features and Modifications

The structure of quinazolinone derivatives allows for substitutions at various positions on both the benzene and quinazoline rings, significantly influencing their pharmacological activity. Structural modifications can enhance biological efficacy by targeting specific regions of the molecule. For instance, alkyl, aryl, or heteroaryl substitutions at the 2-position have been shown to improve anticancer and antimicrobial properties[6]. The introduction of hydrophilic groups increases solubility and bioavailability, making the compounds more effective in biological systems. Additionally, incorporating amino, hydroxyl, or carboxyl groups at the 3-position has been associated with enhanced anti-inflammatory and anticancer activities. The presence of benzyl or phenyl groups can improve receptor binding affinity, which is crucial for therapeutic effectiveness. The carbonyl group in quinazolinone derivatives plays a vital role in maintaining biological activity, and bioisosteric replacements of this moiety can lead to variations in pharmacological effects[7]. Furthermore, electron-withdrawing groups such as halogens and nitro groups enhance lipophilicity and membrane permeability, while electron-donating groups like hydroxyl and methoxy contribute to increased antioxidant and anti-inflammatory properties.

These structural modifications collectively influence the biological activity of quinazolinone derivatives, making them valuable in medicinal chemistry[8].

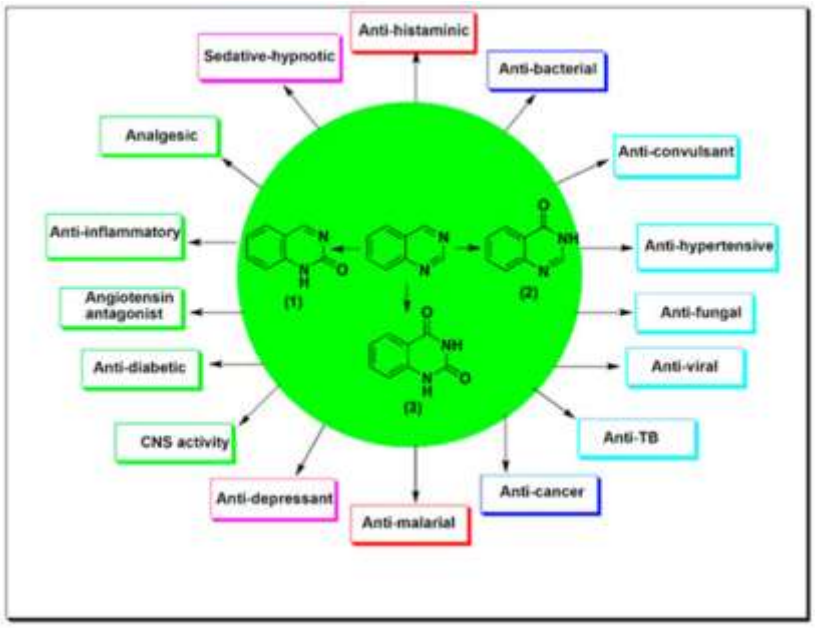
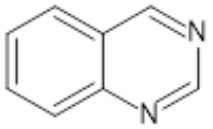
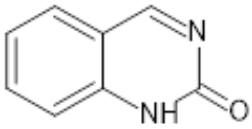


Fig:2

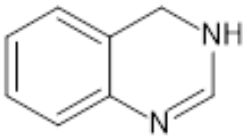
Types of Quinazolinones



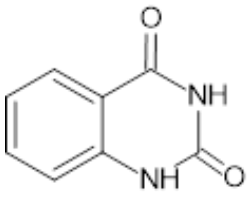
Quinazoline



Quinazoline-2(1*H*)-one



3,4-dihydroquinazoline



Quinazoline-2,4 (1*H*,3*H*)-dione

Fig:3

Quinazolinones are a diverse class of heterocyclic compounds derived from the quinazoline nucleus, characterized by the fusion of a benzene ring with a pyrimidine ring. Substitution at various positions and the degree of saturation at C-3 and C-4 results in structurally distinct subclasses, each with specific chemical and biological properties. The most commonly studied types include Quinazolin-2(1H)-ones, 3,4-Dihydroquinazoline derivatives, and Quinazoline-2,4(1H,3H)-diones[9].

- **Quinazolin-2(1H)-ones**

Quinazolin-2(1H)-one is the most basic and widely explored scaffold within this family. It consists of a carbonyl group at position 2 and a hydrogen atom at the N-1 position. This framework allows for functionalization at positions 3 and 4, making it a versatile platform for drug development. Compounds in this category exhibit a range of biological activities including

anti-inflammatory, anticancer, and antimicrobial effects[10].

- **3,4-Dihydroquinazoline**

3,4-Dihydroquinazoline derivatives are partially saturated analogues where the double bond between positions 3 and 4 is reduced. This saturation often alters the electronic distribution and three-dimensional conformation, influencing interactions with biological targets. These derivatives have been associated with notable anticonvulsant, antihypertensive, and CNS-modulating properties[11].

- **Quinazoline-2,4(1H,3H)-diones**

These are diketone analogues containing carbonyl groups at both the 2 and 4 positions. Quinazoline-2,4-diones are recognized for their strong binding affinities to several enzymatic and receptor targets due to their hydrogen-bonding capabilities. These compounds are particularly significant in the development of anticonvulsant and anticancer agents[12].

Common Quinazolinone derivatives and their biological activities

<table>
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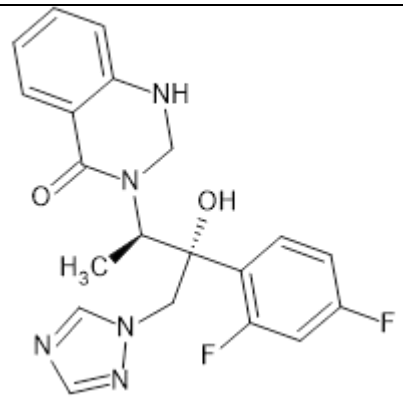
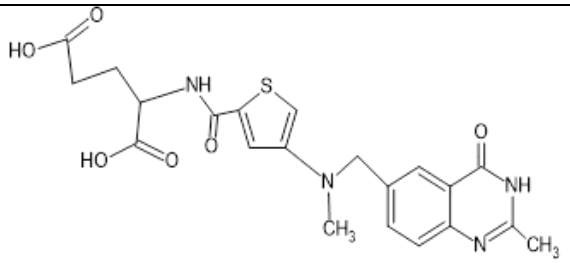
<td> 
Albaconazole
Anti-fungal agent</td>
<td> 
Raititrexed
Anti-Cancer agent</td>
</tr>
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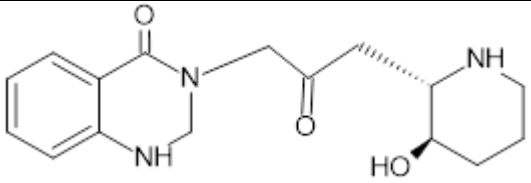
<td> 
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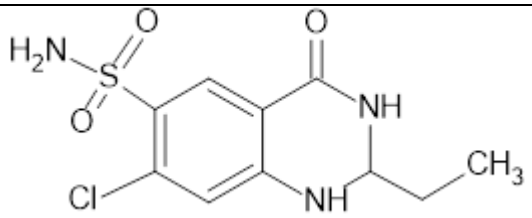
Anti-Malarial agent</td>
<td> 
Quinethazone
Anti-hypertensive agent</td>
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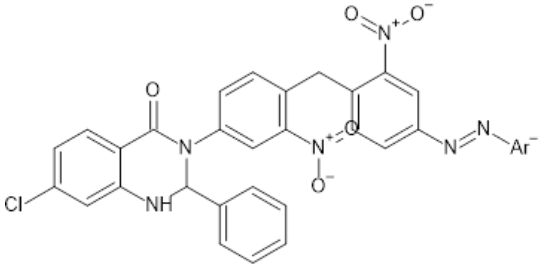
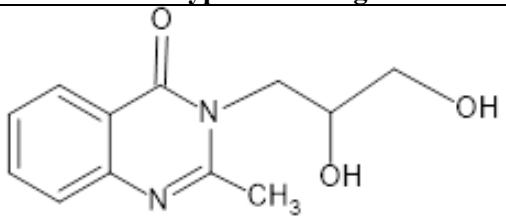
<td> 
Heterocyclic Monoazo Dyes Derived from 4-Oxoquinazolines</td>
<td> 
Diproqualone
GABAergic agent</td>
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</table>

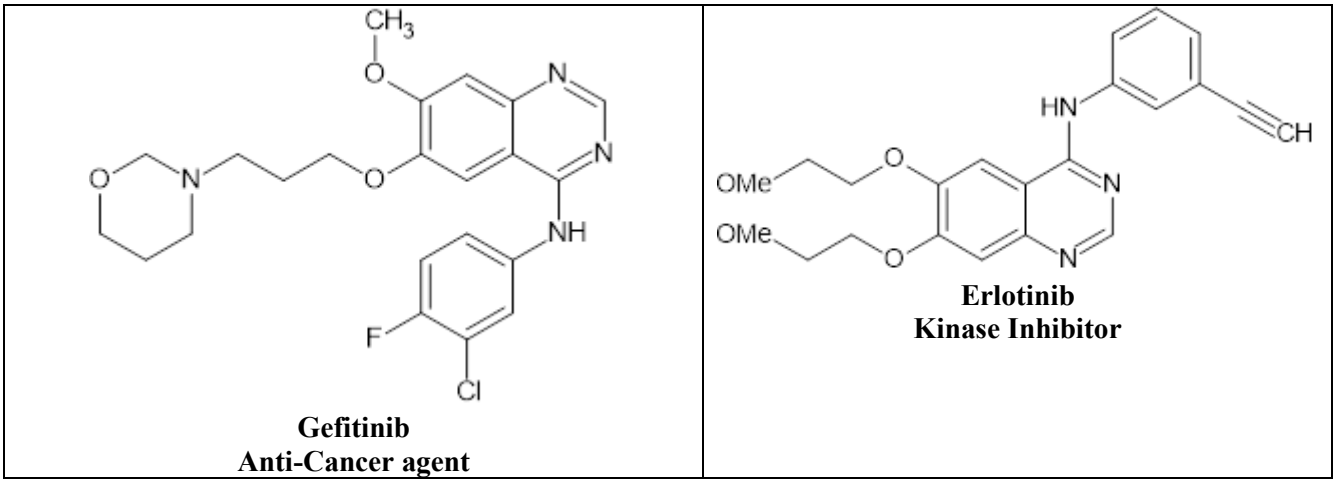

Fig:4

Synthesis Methods of Quinazolinone Derivatives

Green Chemistry Approaches

Nanocatalyst-Assisted Synthesis: Fe_3O_4-based and SBA-15-supported catalysts enable the synthesis of quinazolinone derivatives under mild and solvent-free conditions[13].

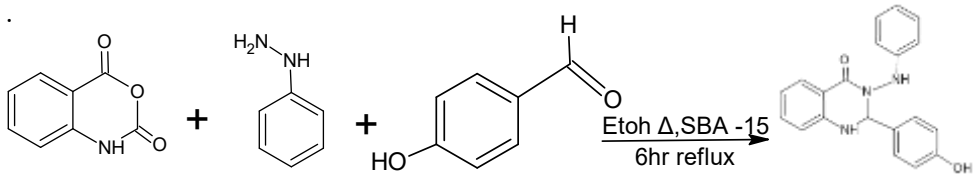

Fig:5

Biocatalysis and Enzyme-Catalyzed Synthesis: Enzymatic catalysis provides a sustainable and highly selective synthesis route[14].

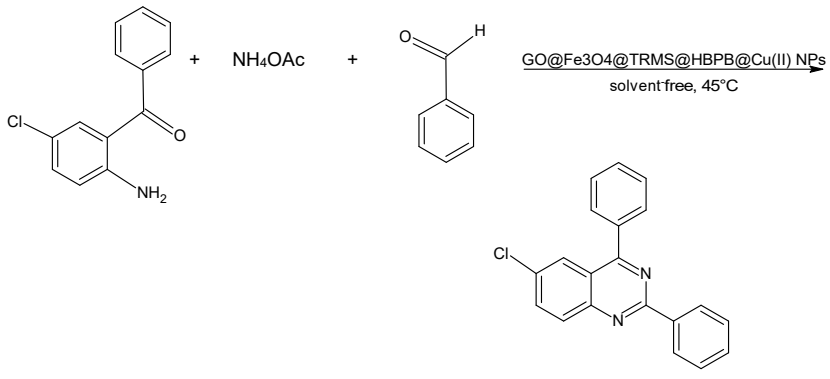

Fig:6

Conventional Synthetic Approaches

Amidation and Cyclization

The most common approach involves amidation of 2-aminobenzonitrile with 3-phenylacryloyl chloride followed by oxidative ring closure under

basic conditions produced 2-aryryl-4(3H)quinazolinone[15].

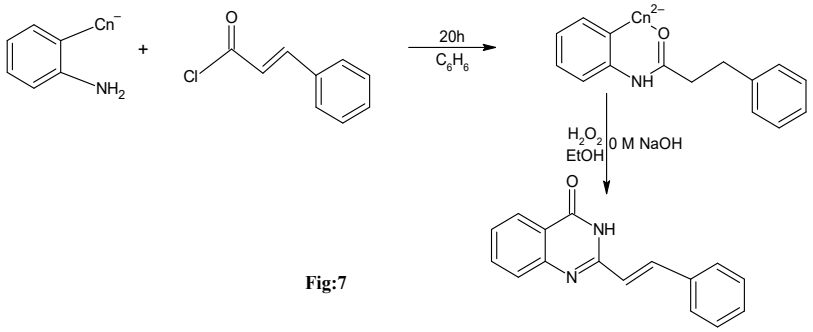

Fig:7

Via condensation reaction of 4-chloroanthranilic acid amide with triethyl orthoformate, the 7-chloro-substituted derivative has been prepared[16].

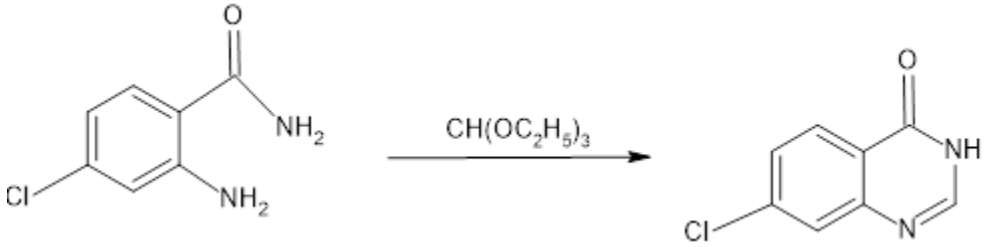

Fig:8

From Anthranilic Acid and Urea. The fusion of anthranilic acid with urea gave 1,2,3,4-tetrahydro-2,4-dioxo quinazoline[17].

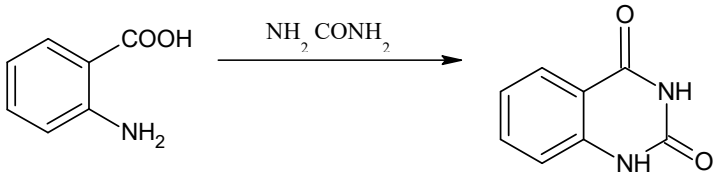

Fig:9

Importance in Medicinal Chemistry

Quinazolinone is a heterocyclic compound featuring a fused benzene and pyrimidine ring structure, and it holds significant importance in medicinal chemistry due to its diverse pharmacological properties. Its structure allows it to interact with various biological targets, making it a valuable scaffold for designing therapeutic agents. Here are several key reasons why quinazolinones are important in medicinal chemistry[18].

Anticancer Activity

Some new 3-substituted quinazolin-4(3H)-one and 3,4-dihydroquinazolin-2(1H)-one derivatives have been reported. Among them, compounds 2-

[2-(4-chlorophenyl)-2-oxo-ethylthio]-3-(4-methoxyphenyl)quinazolin-4(3H)-one and 3-(4-chlorophenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylthio]quinazolin-4(3H)-one exhibit broad-spectrum antitumor activity. These compounds demonstrate effectiveness against numerous cell lines from different tumor subpanels (see fig 13)Additionally, a series of novel quinazoline derivatives containing a thiosemicarbazide moiety have been synthesized and evaluated for their biological activity as antitumor agents. The therapeutically important candidates are illustrated in (Fig 14) Furthermore, a series of phenyl N-mustard-quinazoline derivatives have been assessed for their antitumor activity, showing promising results. A series of 4,6-di-substituted-(diaphenylamino)quinazoline derivatives were evaluated for their antitumor activity and were identified as potent EGFR inhibitors .Additionally, a series of quinazoline derivatives were assessed for their function as EGFR inhibitors through radioiodination. Furthermore, all these compounds were investigated for their potential SPECT (Single Photon Emission Computed Tomography) activity in molecular imaging of breast cancer (fig 15)[19].

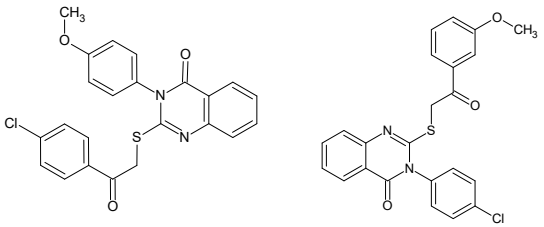

Fig:10

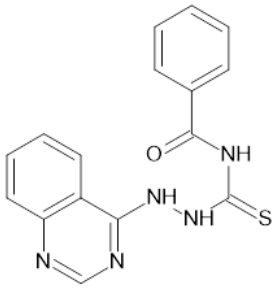

Fig:11

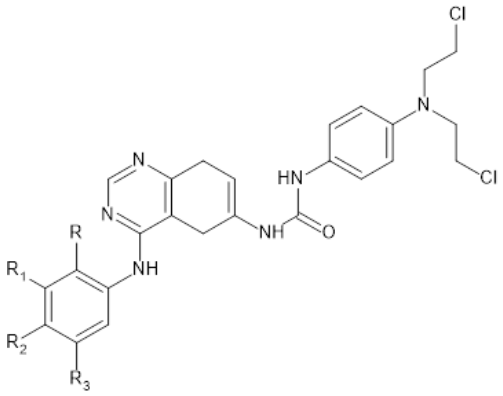

Fig:12

R	R1	R2	R3
-H	-OCH3	-OCH3	-OCH3
F	CL	H	H
H	CL	F	H
H	HC≡≡CH	H	H

Antimicrobial Properties

Quinazolinone derivatives also exhibit significant antimicrobial activity. They have been studied for their effects against bacteria, fungi, and viruses. Some quinazolinones are known to inhibit the growth of both Gram-positive and Gram-negative bacteria, and they show promise as potential candidates for the development of novel antimicrobial agents. The new quinazolinone derivatives demonstrated antimicrobial activity against three Gram-positive bacteria (B. cereus ATCC 6629, B. subtilis ATCC 6633, and S. aureus ATCC 6538), as well as two Gram-negative bacteria (K. pneumoniae ATCC 13883 and P. aeruginosa ATCC 27953). Structure shows the inhibitory zone sizes (in mm) for the reference medications ciprofoxacin and fuconazole. The antibacterial activity of the investigated compounds varied depending on the secondary amine substitution on the quinazolinone ring's C-2 position. Almost all the pyrrolidine derivatives[20].

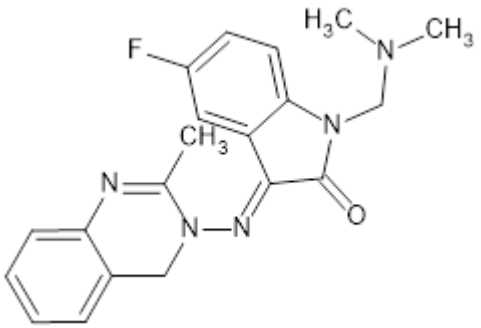

Fig:13

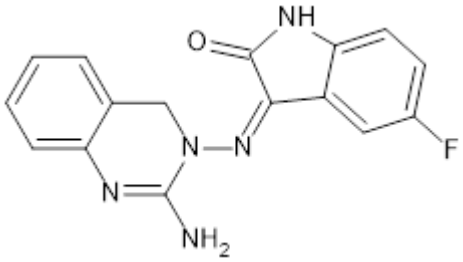

Fig:14

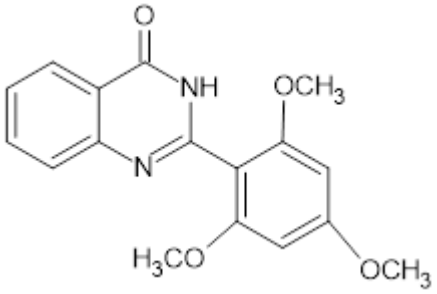

Fig:15

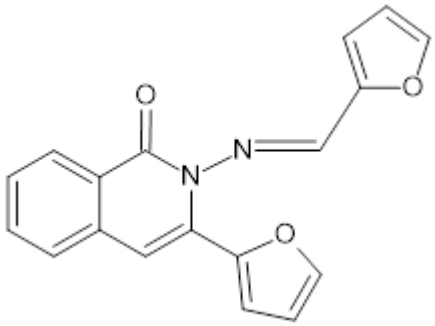

Fig:16

Antimalarial Activity

In this study, the in vivo antimalarial activities of the synthesized compounds were evaluated using a mouse model. This model is ideal for understanding the prodrug effects of the target compounds, which may be activated through metabolic processes, as well as their potential role in infection eradication through immune system involvement.To establish a stable infection, the Plasmodium berghei ANKA strain was used as the test parasite. The antimalarial effects of the target compounds were assessed using the standard four-day suppressive test, a widely accepted method for evaluating early-stage infections. This test measures the percent inhibition of parasitemia, which is considered one of the most reliable indicators in in vivo antimalarial studies[21]. Chloroquine phosphate (CQ), a standard antimalarial drug, was used for comparison. Equimolar doses of the synthesized 3-aryl-2-styry-substituted-4(3H)-quinazolinone derivatives were administered orally to experimental groups. The effects of these compounds were compared to a control group receiving a solution containing 7% Tween 80 and 3% ethanol in distilled water.The analysis revealed that the target compounds significantly reduced parasitemia levels compared to the negative control group, confirming their potential antimalarial activity. These findings align with previous studies on 4(3H)-quinazolinone derivatives, which have demonstrated promising efficacy against the same test strain[22].

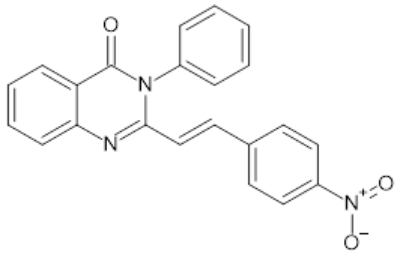

Fig:17

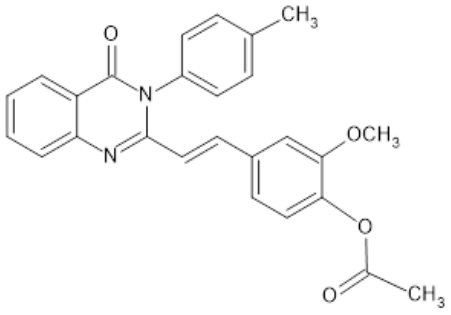

Fig:18

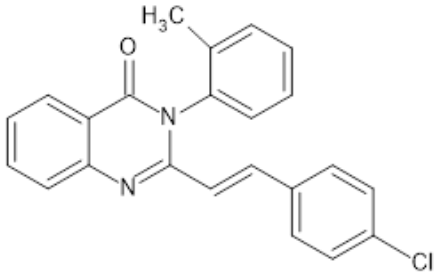

Fig:19

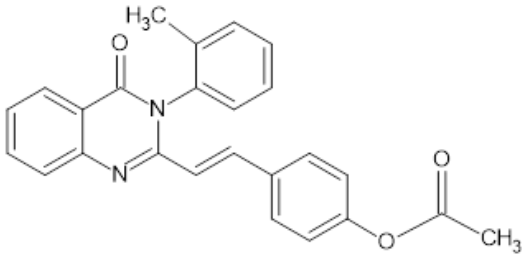

Fig:20

Anti-inflammatory and Analgesic Effects

Schiff base compounds developed from quinazolinone were also employed as new anti-inflammatory and antioxidant medicines. Ascorbic acid (AA), gallic acid (GA), butylated hydroxytoluene (BHT), DPPH assay, and other commercial antioxidants were used to assess and compare these compounds' in vitro antioxidant properties[23]. Data shows that compounds with an electron withdrawing moiety (Cl, NO2) were found to be effective anti-inflammatory drugs, while quinazolinone-derived Schiff bases with an electron donating moiety (OH, OCH3) were found to be great antioxidants[24].

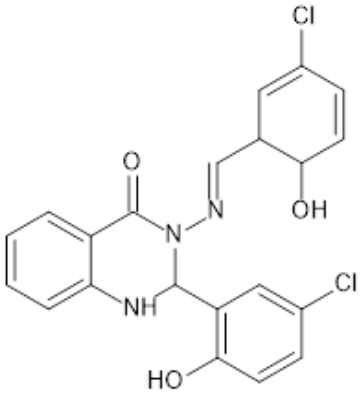

Fig:21

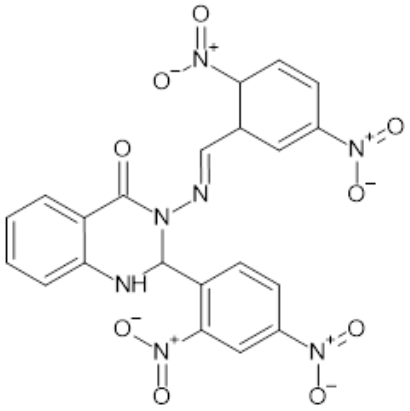

Fig:22

Neuroprotective Properties

The neuroprotection assay was conducted using human neuroblastoma SH-SY5Y cells treated with rotenone, a mitochondrial toxin that disrupts the electron transport chain, leading to oxidative stress and cell death. Rotenone exposure is known to mimic key pathological features of neurodegenerative diseases, such as Parkinson's disease, in both in vitro and in vivo models.To assess neuroprotective effects, the MTT assay was used to measure cell viability after exposure to rotenone[25]. Various synthesized compounds were tested at multiple concentrations to determine their potential protective effects against rotenone-induced toxicity[26]. A compound was considered neuroprotective if it exhibited significant protection in a dose-dependent manner, with at least one concentration providing over 25% protection.At higher concentrations, most tested compounds showed increased toxicity, ensuring they were assessed at their maximal tolerated dose (MTD). Some compounds demonstrated neuroprotective activity, while others did not display significant protection.[27]

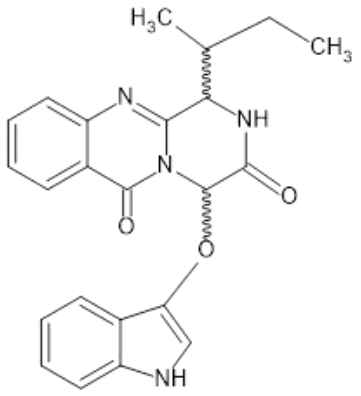

Fig:23

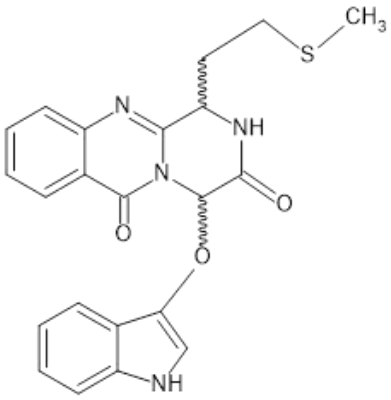

Fig:24

Targeting Protein Kinases

The quinazolinone scaffold is particularly attractive for the development of protein kinase inhibitors. Protein kinases are enzymes that regulate key cellular functions such as growth, differentiation, and apoptosis. Abnormal activity of certain kinases is associated with diseases like cancer, and quinazolinone derivatives have been developed to selectively inhibit these kinases[28].

Anti-convulsant Properties

Quinazolinone derivatives are promising anticonvulsant agents due to their structural flexibility and pharmacological potential. Seizure models, particularly MES and scPTZ, are widely used to assess their efficacy, targeting tonic-clonic and absence seizures, respectively[29]. Structural modifications play a crucial role in enhancing activity, with lipophilic, electron-withdrawing, and electron-donating groups influencing pharmacokinetics and receptor interactions. Benzyl substitution and heteroalkyl incorporation have been found to improve seizure protection, with some derivatives exhibiting 100% efficacy in preclinical studies[30]. The presence of benzodiazoxazole and morpholinoethyl moieties enhances anticonvulsant activity, preventing seizure propagation. Additionally, bioisosteric modifications and cyclization strategies have been explored to optimize pharmacological properties. Neurotoxicity assessments using rotarod assays confirm that select quinazolinone derivatives provide effective seizure control without motor impairment. Their structural versatility allows for further fine-tuning of therapeutic effects. Future studies will focus on optimizing molecular interactions, receptor binding affinities, and in vivo efficacy to establish their role in epilepsy management[31].

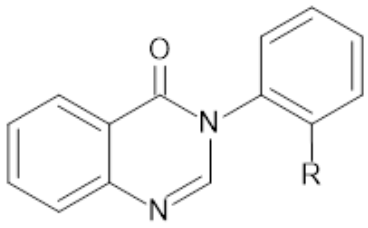

Fig:25

I : R =CH_3

II : R =CL

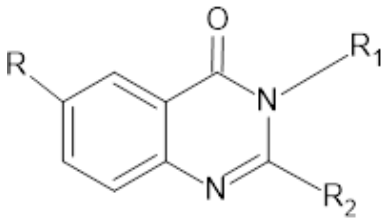

Fig.26

III : R =I, R_1 =benzyl, R_2 = S-acetic acid

IV : R =CL, R_1 = phenyl, R_2 = S-acetylpropionohydrazide

V : R =NH2, benzamide, isoindoline-1,3-dione

Versatility in Structure-Activity Relationships (SAR)

The quinazolinone structure is versatile, which makes it a valuable core for designing new drug molecules. Modifying different positions on the quinazolinone ring system can lead to compounds with a variety of biological activities. This flexibility enables medicinal chemists to tailor quinazolinone derivatives to meet specific therapeutic needs[32].

Angiogenesis Inhibitor

Angiogenesis plays a crucial role in cancer progression by supplying tumor cells with oxygen and nutrients, thereby facilitating metastasis[33]. This process is regulated by a balance between pro-angiogenic factors, such as Angiopoietin-2 (Ang-2), Vascular Endothelial Growth Factor (VEGF), and Basic Fibroblast Growth Factor (BFGF), and anti-angiogenic factors. Disruptions in this balance can contribute to tumor growth and dissemination. A quinazolinone-based compound containing sulfon chloropyrazine has been investigated for its potential to inhibit VEGFR-2, a key receptor in angiogenesis. Studies have shown that such compounds can modulate apoptotic pathways by influencing the expression of Bax and Bcl-2 proteins, increasing caspase-3 activity, and inducing cell cycle arrest. Additionally, these inhibitors have demonstrated the ability to suppress cell migration and interfere with cancer cell proliferation[34].

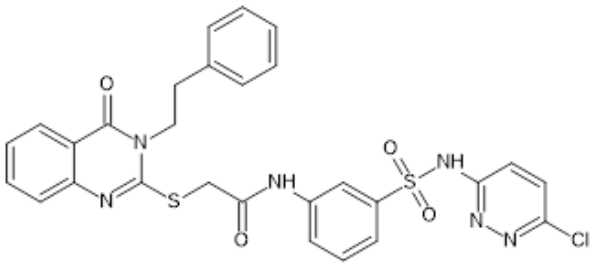

Fig.27

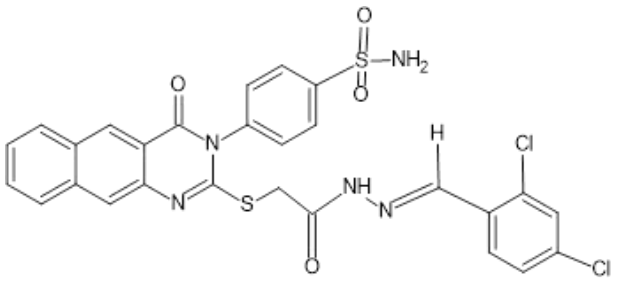

Fig.28

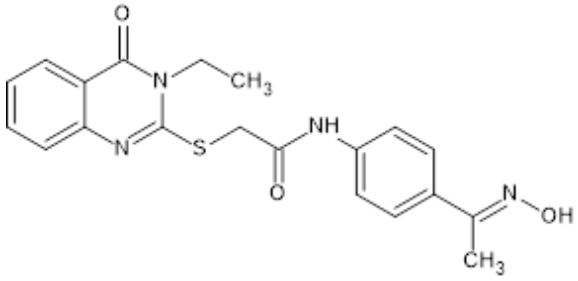

Fig.29

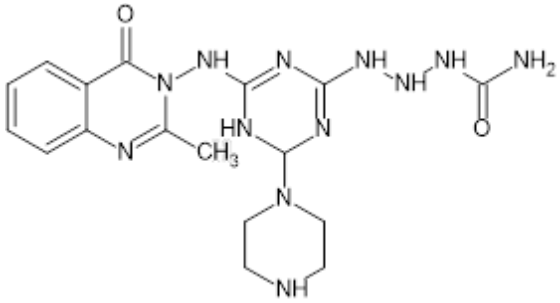

Fig.30

Anti-Tubercular activity

The investigation into the anti-tubercular potential of quinazolinone derivatives identified compound 1 as a particularly promising candidate. Initial screening at 10 µM concentration allowed for the selection of compounds that inhibited more than 50% of bacterial growth. These compounds were further evaluated to determine their minimum inhibitory concentrations (MICs), and those with MIC values below 20 µM were tested against the Mycobacterium tuberculosis H37Rv strain[35]. They stood out with a potent MIC of 38 nM against H37Rv and maintained significant activity in infected mouse macrophages, where it showed an MIC of 163 nM. Notably, compound 1 demonstrated no cross-resistance with strains of

M. tuberculosis resistant to conventional TB drugs, indicating a potential novel mechanism of action. The compound was found to exert a bacteriostatic effect rather than bactericidal activity. In terms of selectivity, compound 1 exhibited moderate cytotoxicity in human liver cells (HepG2) with a TC50 of 13.4 μM, resulting in a selectivity index greater than 10, which is considered acceptable for further development[36]. However, despite its strong potency, the compound faced several limitations. A significant drop in activity was observed in the presence of serum, suggesting high protein binding, likely due to its high lipophilicity (experimental logP of 4.08). Additionally, the compound showed poor aqueous solubility at both neutral and acidic pH levels, further complicating its drug-like profile[37]. Metabolic stability was another major concern, as compound 1 underwent rapid degradation in both mouse and human liver microsomes. The primary metabolic pathways involved O-demethylation and hydroxylation reactions. Moreover, the compound was a potent inhibitor of cytochrome P450 3A4 (CYP3A4), with an IC50 below 1 μM, raising the potential for drug-drug interactions. Although it had favorable absorption characteristics, such as good permeability through Caco-2 cells and no mutagenic activity in the Ames test, its overall pharmacokinetic properties were unsuitable for effective in vivo application.To address these challenges, structure-activity relationship (SAR) studies were undertaken. Modifications to the quinazolinone scaffold, including changes to linker length and ring substituents, aimed to improve metabolic stability, reduce serum binding, and enhance solubility without compromising anti-Mtb activity. Among the new analogues, biaryl derivatives showed improved profiles, with some maintaining or enhancing potency while slightly improving ADMET properties. Nonetheless, the introduction of polar or heteroaromatic groups generally led to reduced activity unless balanced by hydrophobic elements. Despite the improvements seen in vitro, most analogues, including compound 1, did not demonstrate adequate efficacy in mouse infection models, primarily due to poor metabolic stability and unfavorable pharmacokinetics[38].

CONCLUSION AND FUTURE PROSPECTS

Quinazolinone derivatives represent an essential class of heterocyclic compounds with diverse applications in medicinal chemistry, catalysis, and green chemistry. Their structural versatility allows for significant modifications, enabling the development of novel antibacterial, anticancer, anticonvulsant, and anti-inflammatory agents. The FDA-approved drugs Gefitinib, Erlotinib, and Lapatinib highlight the pharmacological potential of quinazolinone-based compounds, particularly in targeted cancer therapies. The synthesis of quinazolinone derivatives has undergone considerable advancements, transitioning from traditional harsh conditions to efficient, eco-friendly methodologies. Green chemistry approaches, such as biocatalysis, nanocatalysts, and solvent-free reactions, are gaining attention due to their sustainability and cost-effectivenessIn addition to their medicinal properties, quinazolinone-based catalysts have shown great promise in organic synthesis, acting as metal ligands, Lewis acid catalysts, and organocatalysts. Their ability to facilitate C–C bond formation, oxidation, and reduction reactions further expands their applicability in pharmaceutical and industrial chemistry Despite these significant developments, challenges remain in optimizing the selectivity, stability, and large-scale production of quinazolinone-based compounds. More research is required to refine synthetic methodologies, improve pharmacokinetics, and explore new biological targets

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