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Therapeutic Potential And Pharmacological Profiling Of Quinazoline Derivatives: A Review

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Abstract:

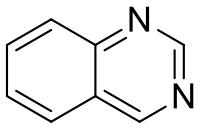
This review presents a comprehensive overview of the diverse pharmacological activities associated with quinazoline derivatives, nitrogen-containing heterocyclic compounds characterized by the chemical formula C8H6N2. Quinazolines have attracted considerable attention due to their versatile applications in medicinal chemistry. Through various synthetic approaches, researchers have explored the extensive pharmacological potential of quinazoline derivatives, which encompass a wide range of biological activities. These include antibacterial, analgesic, antimicrobial, anti-inflammatory, anticancer, antihypertensive, antifungal, anti-HIV, antioxidant, anticonvulsant, antimalarial, antitumor, and antitubercular effects. This review aims to consolidate and synthesize the literature on the pharmacological activities of quinazoline derivatives, while also highlighting recent advancements in this research domain.

Keywords: Quinazoline, pharmacological activities, heterocyclic compounds.

1. Introduction:

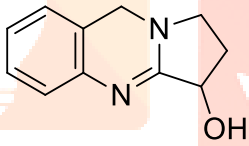
Quinazoline is a heterocyclic compound composed of two fused six-membered aromatic rings: a benzene ring and a pyrimidine ring. This structure grants it significant medicinal value, particularly as an antimalarial agent. Since 1888, when the first natural quinazoline alkaloid, (+)-peganine (also known as vasicine), was discovered, these compounds have captivated scientists. Quinazoline alkaloids exhibit diverse biological activities, leading to extensive research into their therapeutic potential. Peganine, derived from plants such as Peganum harmala, and vasicine, from Justicia adhatoda (also known as Adathoda vasica), are notable for their bronchodilator properties and are used in treating respiratory ailments.[1]

The biosynthesis of vasicine involves the transformation of anthranilic acid into peganine, which serves as a precursor to vasicine. Research on Peganum harmala has elucidated that peganine is synthesized from anthranilic acid, with the pyrrolidine ring component supplied by ornithine. The formation of the peganine skeleton is a complex process involving a nucleophilic attack by the anthranilate nitrogen on the pyrrolinium cation, followed by amide formation. This biosynthetic pathway is distinct in Justicia adhatoda, where a less predictable sequence involving acetylanthranilic acid and aspartic acid is observed. Understanding these biosynthetic pathways not only sheds light on the intricate chemistry of these plants but also opens avenues for synthetic modifications and the development of new therapeutic agents. [2]



Quinazoline

A yellow solid, usually in crystalline form, heterocyclic compound comprise of two fused six membered simple aromatic rings, i.e. a benzene ring and a pyrimidine ring. Medicinally it is used as antimalarial agent.



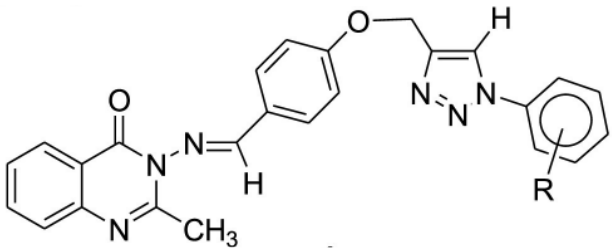
1,2,3,9-Tetrahydropyrrolo[2,1-b]quinazolin-3-ol

Numerous quinazoline derivative compounds have been synthesized and are currently utilized in medical applications. These derivatives, known as quinazolines, have been employed in various therapeutic areas, particularly as anti-malarial agents and in cancer treatment.

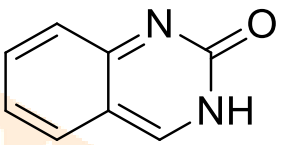
2. Pharmacological activity:

a. Antibacterial activity:

Neha Manhas et.al.[4] developed a novel series of quinazoline-4(3H)-one-tagged triazole conjugates via copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Structural elucidation was performed using 2D-NMR techniques. The synthesized compounds were evaluated for in vitro antibacterial activity against gram-negative strains, showing potent activity and selectivity, with compound 4i exhibiting the most promising efficacy against Klebsiella pneumoniae, a multidrug-resistant strain. Structure-activity relationship (SAR) analysis revealed the influence of triazole ring incorporation and para-substitution on antibacterial activity. Molecular docking studies provided insights into the compounds' binding characteristics in the DNA gyrase binding site of Staphylococcus aureus. This study underscores the potential of these conjugates as effective antibacterial agents against gram-negative bacteria, particularly multidrug-resistant strains.

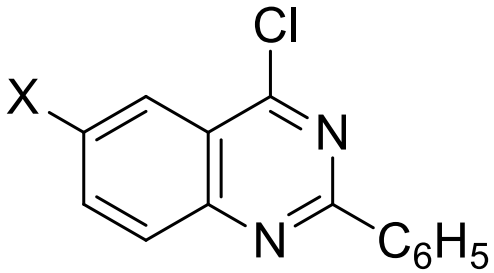


Nagar et.al.[5] conducted a synthesis of quinazolin-(3H)one and discovered its antibacterial properties. Remarkably, several derivatives exhibited antibacterial efficacy on par with fluconazole. This finding underscores the potential significance of quinazolin-(3H)one derivatives as a novel class of antibacterial agents.

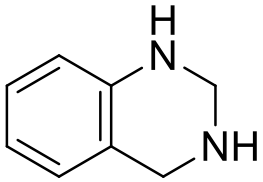


quinazolin-(3H)one

Gautam et.al. [6] undertook the synthesis of innovative 4,6-disubstituted derivatives and evaluated their antimicrobial potential employing traditional methodologies. Their synthetic approach commenced with anthranilic acid derivatives, subjected to acylation and cyclization processes to generate benzoxazinones. The subsequent treatment involving ammonia led to the formation of a pivotal intermediate, 2-substituted benzamide. These intermediates underwent further cyclization to yield quinazolones, which were subsequently chlorinated and subjected to additional modifications to yield a diverse array of 4,6-disubstituted quinazoline derivatives. This multi-step synthesis pathway highlights the intricate and systematic approach adopted to access these novel compounds with potential antimicrobial activity.



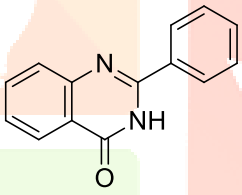
Doshi et.al. [7] synthesized a diverse array of tetrahydro-quinazoline analogues and meticulously screened them to gauge their antibacterial efficacy. Their study targeted both gram-positive bacteria, typified by Bacillus subtilis, and gram-negative bacteria, exemplified by Pseudomonas aeruginosa and Escherichia coli. By conducting this thorough screening process, the researchers aimed to ascertain the potential of the synthesized analogues as robust antibacterial agents, capable of addressing a wide range of bacterial strains, thus contributing to the development of novel therapeutic options in combating bacterial infections.



Tetrahydro-quinazoline

b. Anti-inflamatory activity:

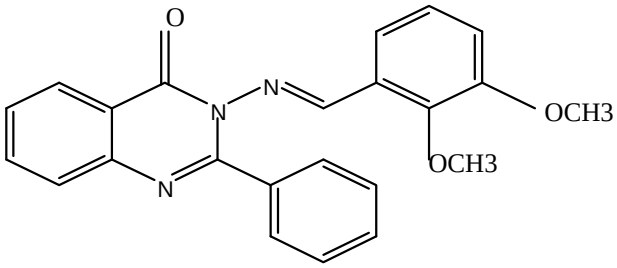
Mohamed et.al. [8] synthesized two distinct series of 2-phenyl-4(3H) quinazolinone derivatives. Through their experimentation, they observed that a significant proportion of these synthesized quinazolinone derivatives exhibited notable anti-inflammatory and analgesic properties, demonstrating a superior gastrointestinal safety profile compared to indomethacin, a commonly used reference drug. Additionally, certain compounds within these series displayed exceptional potency as anti-inflammatory agents in experimental rat models, surpassing even the efficacy of indomethacin. These findings highlight the promising therapeutic potential of these quinazolinone derivatives as effective and safe alternatives for the treatment of inflammatory conditions and pain management



2-phenyl-4(3H) quinazolinone

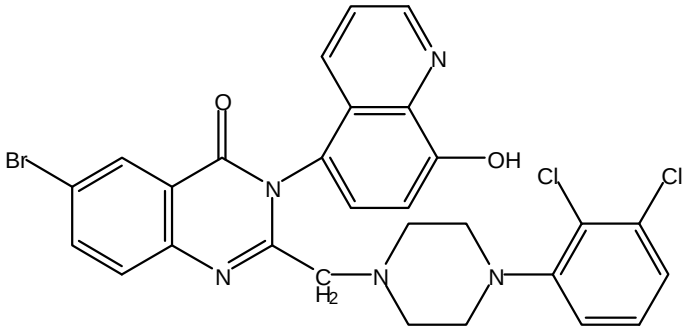
c. Cytotoxic activity:

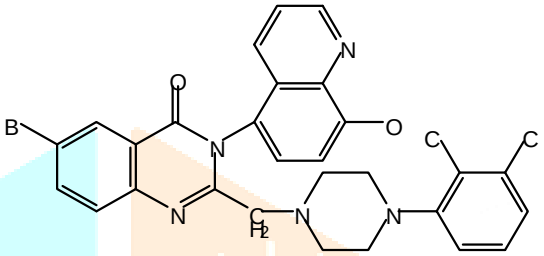
Krishnan et al.[9] synthesized a series of 3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones by reacting 3-amino-2-phenyl-3H-quinazoline-4-one with various carbonyl compounds. They subsequently investigated the cytotoxic activity of these synthesized compounds. This research aimed to explore the potential cytotoxic effects of the newly synthesized quinazoline derivatives, shedding light on their possible applications in cancer treatment or related fields.



Vashi et al.[10] synthesized a compound and examined its antifungal activity. The compound under investigation was a ligand named 6-bromo-2[(4-(2,3-dichlorophenyl)) piperazine-1yl)methyl]-3-[8-hydroxyquinoline -5-yl]-3-quinazolin-4-one, along with its transition metal chelates. This study aimed to

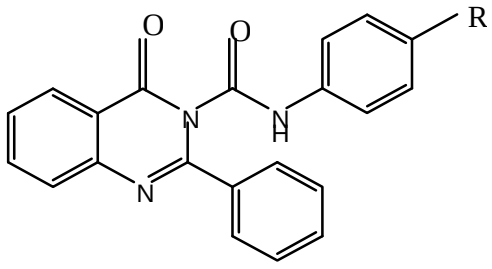
evaluate the antifungal properties of both the ligand and its metal chelates, potentially contributing to the development of novel antifungal agents.





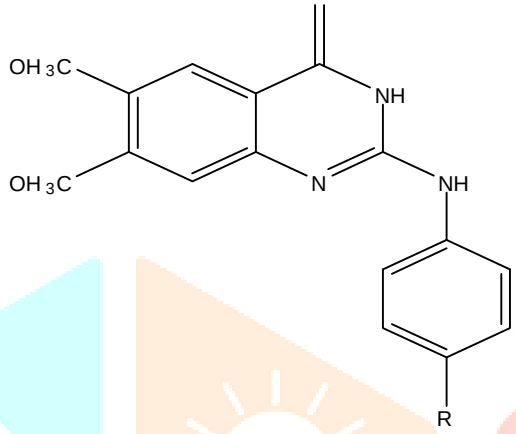
Vijai Anand et.al.[11] embarked on the synthesis of a series of novel 4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid derivatives, specifically 4-substituted phenyl amides. This synthesis involved condensing 2-phenyl-3,1-benzoxazine-4-one with various 4-substituted phenyl ureas. The process began with the condensation of N-benzoyl anthranilic acid and acetic anhydride to yield 2-phenyl-3,1-benzoxazine-4-one, while various 4-substituted anilines were condensed with sodium cyanide to produce the 4-substituted phenyl ureas.

Subsequently, all synthesized compounds were subjected to evaluation for their in vitro antifungal activity against four pathogenic fungi, utilizing the standard agar dilution method to determine the zone of inhibition. Clotrimazole was employed as the reference standard for comparison. Notably, the study revealed that all the synthesized compounds lacked activity against Aspergillus fumigatus.



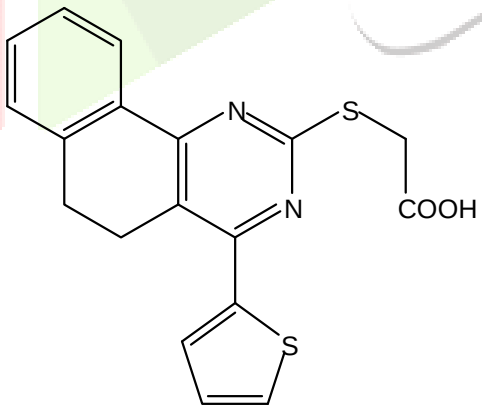
d. Antihypertensive activity:

Vashi et al. [12] synthesized a compound and examined its antifungal activity. The compound under investigation was a ligand named 6-bromo-2[(4-(2,3-dichlorophenyl)) piperazine-1yl)methyl]-3-[8-hydroxyquinoline -5-yl]-3-quinazolin-4-one, along with its transition metal chelates. This study aimed to evaluate the antifungal properties of both the ligand and its metal chelates, potentially contributing to the development of novel antifungal agents.



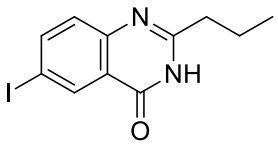
a. Anti-HIV activity:

Yahia et.al. [13] undertook the synthesis of a series of dihydrobenzo[h]quinazoline derivatives utilizing arylmethylene thiopyrimidine and 2-(4-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinazolin-2-ylthio) acetic acid (4) as starting materials. Following synthesis, biological screening assays were conducted, revealing that several of these compounds exhibited promising anticancer and antiviral activities. This research sheds light on the potential therapeutic significance of these derivatives in the treatment of cancer and viral infections.



b. Antioxidant activity:

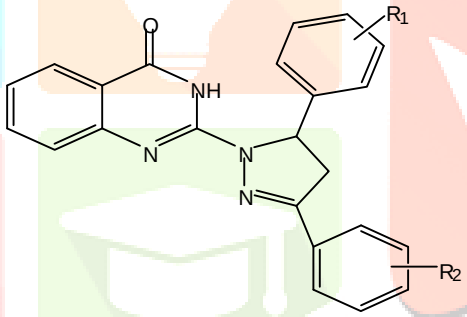
Al-Omar et al.[14] synthesized a new series of 6-iodo-2-propyl-4(3H)-quinazolinone and its fused heterocyclic and screened for their antioxidant activity.It was found that some compounds inhibited aldehyde oxidase exclusively by more than 98%.



6-iodo-2-propyl-4(3H)-quinazolinone

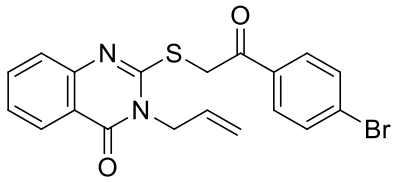
c. Analgesic activity:

Sinha et.al. [15] synthesized a series of pyrazoline-bearing 4(3H)-quinazolinone derivatives and subsequently assessed their analgesic and anti-inflammatory activities. Among the synthesized compounds, 6b, 6d, 6e, 6i, and 6j demonstrated notable analgesic and anti-inflammatory activities, while others also exhibited significant efficacy in these activities. This research underscores the potential of these derivatives as promising candidates for the development of analgesic and anti-inflammatory agents.



d. Anticonvalsant activity:

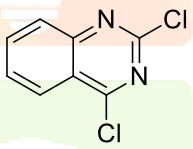
Pele et al.[16] developed two series of chemical compounds, "a" and "b", each comprising nine derivatives with a 2,3-disubstituted quinazolin-4(3H)-one scaffold. These compounds were assessed for their anticonvulsant activity and investigated as potential positive allosteric modulators of the GABAA receptor at the benzodiazepine binding site, as well as inhibitors of carbonic anhydrase II. In vivo evaluation using the pentylenetetrazole (PTZ)-induced seizure model in mice (administered intraperitoneally at doses of 50, 100, 150 mg/kg) compared their efficacy with phenobarbital and diazepam. In silico studies suggested that the compounds act as anticonvulsants by binding to the allosteric site of the GABAA receptor rather than inhibiting carbonic anhydrase II, as ligands-carbonic anhydrase II predicted complexes were unstable in molecular dynamics simulations. This mechanism was confirmed through in vivo flumazenil antagonism assay. The evaluation revealed promising anticonvulsant activity for both series, with the "b" series, particularly compound 8b, showing more favorable results based on parameters such as percentage of protection against PTZ, latency until onset of the first seizure, and reduction in the number of seizures.



3-allyl-2-((2-(4-bromophenyl)-2-oxoethyl)thio)quinazolin-4(3H)-one

Mukherjee et.al.[17] embarked on a synthetic endeavor wherein they first synthesized 2,4-dichloroquinazoline (5). This key intermediate was then subjected to a series of reactions with diverse N-substituted piperazines, resulting in the generation of a set of novel compounds labeled as [6(A-G)]. The synthesis process was meticulously characterized using spectral analysis techniques to ensure the structural integrity and purity of the synthesized compounds.

Following synthesis, the newly derived compounds underwent thorough screening assays to evaluate their potential anticonvulsant properties. Anticonvulsant activity screening serves as a crucial step in identifying compounds that could potentially serve as therapeutic agents for the management of seizure disorders. By conducting this screening, Mukherjee and colleagues aimed to elucidate the efficacy of the synthesized compounds in modulating epileptic activity, thus contributing to the advancement of antiepileptic drug discovery efforts.



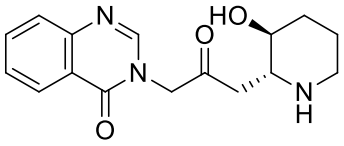
2,4-dichloroquinazoline

(k)Antimalarial activity:

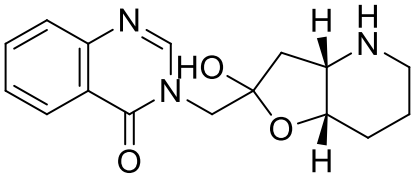
Sen et.al.[18] embarked on synthesizing a series of 2-substituted and 2,3-substituted quinazolin-4(3H)-one derivatives, inspired by the molecular structure of febrifugine, a natural antimalarial compound. Their objective was to explore the antimalarial potential of these derivatives.

Through rigorous in vivo biological activity tests conducted on mice infected with Plasmodium berghei, the researchers found compelling evidence of significant antimalarial activity exhibited by these compounds, particularly at a dosage of 5 mg/kg. What's notable is that compared to established antimalarial drugs like Chloroquine and Artemisinin, the synthesized derivatives displayed distinct advantages. They offered shorter synthetic routes, rendering them highly cost-effective.

This study underscores not only the successful synthesis of novel quinazolinone derivatives but also their promising prospects as cost-effective antimalarial agents. Such findings hold great significance in the ongoing global efforts to combat malaria effectively.



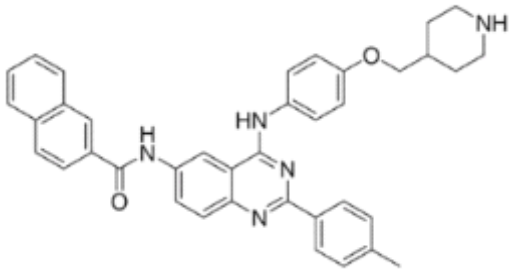
3-(3-((2*R*,3*S*)-3-hydroxypiperidin-2-yl)-2-oxopropyl)quinazolin-4(3*H*)-one



3-[[(3aS,7aS)-2-hydroxy-3a,4,5,6,7,7a-hexahydro-3H-furo[3,2-b]pyridin-2-yl]methyl]quinazolin-4-one

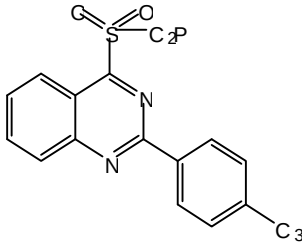
e. Antitumor activity:

Wang et al. (2023)[19] designed, synthesized, and evaluated a series of novel 2,4,6-trisubstituted quinazoline derivatives for their antitumor activity against four human cancer cell lines (Eca-109, A549, PC-3, and MGC-803). Most of the designed compounds exhibited significant antiproliferative activity across all tested cell lines. Compound 28g demonstrated the highest potency, with IC50 values of 1.95 μM and 2.46 μM against MGC-803 and Eca-109 cells, respectively. Mechanism studies revealed that 28g effectively inhibited cell migration and colony formation of MGC-803 cells and induced cellular apoptosis and cell cycle arrest at S phase in a dose-dependent manner. These findings suggest that compound 28g holds promise as a valuable lead compound for the development of antitumor agents.



El-Azab et.al [20] developed a series of novel antitumor molecules incorporating a 4-substituted quinazoline pharmacophore. Their investigation involved evaluating the cytotoxic activity of these quinazoline derivatives using three different cell lines: the human liver cell line (HEPG2), the human breast cell line (MCF-7), and the human cervix cell line (HELA).

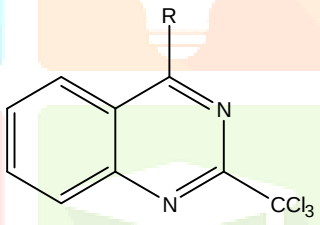
These findings highlight the promising potential of the synthesized quinazoline derivatives as effective antitumor agents, particularly in the context of breast cancer treatment. The study contributes valuable insights into the development of novel therapeutic strategies targeting cancer.



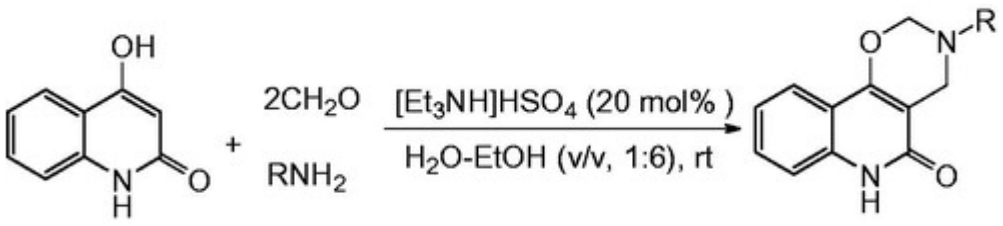
f. Anti-tubercular activity:

Maneesh et.al.[21] undertook the synthesis of a novel series of 2-trichloromethyl quinazoline derivatives featuring substituted secondary amine groups at the 4th position. Following synthesis, these derivatives were subjected to evaluation for their in vitro anti-tubercular activity against the bacterial strain of Mycobacterium tuberculosis H37Rv ATCC (American Type Culture Collection) utilizing the Alamar Blue assay method (MABA).

This study represents a significant endeavor in the search for novel anti-tubercular agents, aiming to address the urgent need for effective treatments against tuberculosis. The utilization of the Alamar Blue assay method provides a reliable means of assessing the inhibitory effects of these derivatives on M. tuberculosis, offering valuable insights into their potential as candidates for further development as anti-tubercular drugs.

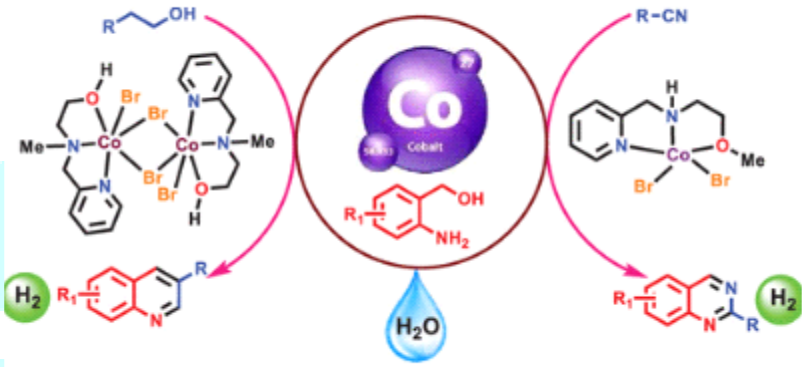


Han and Zhou (2019) [22] developed a simple, efficient, and eco-friendly procedure for synthesizing novel [1,3]oxazino[5,6-c]quinolin-5-one derivatives. This synthesis utilized an acidic ionic liquid, [Et3NH]HSO4, as a catalyst in a one-pot, three-component condensation reaction involving 4-hydroxyquinolin-2(1H)-one, an amine, and formaldehyde in aqueous ethanol at room temperature. The key features of this method include mild and environmentally benign reaction conditions, short reaction times, good to excellent yields, a nontoxic and inexpensive catalyst, reusability of both the catalyst and reaction media, and an easy work-up process.[19]



g. Catalytic activity:

Debjyoti Pal (2024) [23] synthesized three Co(II) complexes with sterically influenced geometries, using the metal-ligand cooperation of the alkoxy arm to explore their catalytic activities. These complexes effectively catalyzed the dehydrogenation of substrates, enabling the high-yield synthesis of C-3-substituted quinoline and quinazoline derivatives. The protocol also facilitated the chemoselective transformation of fatty alcohols into heterocycles with distal unsaturation. Extensive kinetic, mechanistic, and control studies provided insights into the reaction pathways, highlighting the complexes' potential in organic synthesis.[20]



Conclusion:

The extensive exploration of quinazoline derivatives has unveiled a rich tapestry of pharmacological activities, showcasing their versatility as potential therapeutic agents. These compounds have demonstrated efficacy across a wide range of medical conditions, including bacterial infections, inflammatory disorders, pain management, cancer, and neurological diseases. What makes quinazoline derivatives particularly appealing is their structural flexibility, allowing for precise modifications to fine-tune their pharmacological properties. By strategically altering substituents on the quinazoline nucleus, researchers can enhance drug efficacy while minimizing adverse effects, thus paving the way for safer and more effective treatments. Recent advancements in drug development have yielded promising candidates with improved potency and reduced toxicity profiles, signaling a bright future for quinazoline-based therapies. Continued research efforts in this field promise to unlock further potential, driving innovation and breakthroughs in drug discovery and development for the benefit of patients worldwide.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation.

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