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Overview of the Biological Activities of Quinazolines

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Keywords

Quinazoline, anti-bacterial, anti-inflammatory, anti-fungal, anti-tubercular, anti-Tumor

Abstract

Quinazoline is a renowned and significant heterocyclic molecule containing nitrogen atom with the chemical formula C8H6N2, and numerous techniques for their synthesis have been developed. Due to its numerous applications, quinazoline, which is composed of two six-membered hetero aromatic rings one is benzene and second one is pyrimidine. Quinazoline derivatives were found to be a versatile molecules and exhibit a broad range of pharmacological activities which made interest to this area of study. Quinazolines and their derivatives are among the most pharmacologically potent compounds, with variety of biological activities and proved an activity against to an infectious diseases such as malaria and tuberculsois, inflammation, cancer, and hypertension. They also act as anti convulsant. Quinazoline posses mild to moderate anti bacterial and ani fungal activity.When quinazoline fused with pyrazoline leads to the formation of potent analgesics.Some phenyl quinazoline derivatives have showed greater anti inflammatory activity even than indomethacin. Benzimidazo quinazolines proved an effective anti cancer agents.If smaller alkoxy groups such as methoxy groups attached to quinazoline nucleus led to the development of new leads for an antihypertensive activity. Development of novel dihydro benzo(h)quinazolines were proved as an effective anti retro viral molecules.The derivatives of dichloro quinazolines showed an excellent anti convulsant activiy.Development of 2,3- di substitited quinazolinones have prepared and studied their antiplasmodiall activity. Study of anti tubercular activity of 2-trichloro methyl quinazolines reveals that this moiety may also serve as potent leads for anti tubercular activity.The overall intention of this review is to seeks the attention of researchers to explore medicinal and biological importance of quinazoline nucleus.

Introduction

Benzene and pyrimidine rings are fused together to form a heterocyclic molecule (figure 1), which is often a yellow solid in crystalline form. It serves as an antimalarial agent in medicine.

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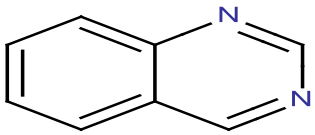

Figure 1. Quinazoline / benzopyrimidine

Since the discovery of (+)-peganine or vasicine (figure 2), the first naturally occurring representative of the quinazoline alkaloids, in 1888, they have drawn the attention of scientists[1]. Vasicine's production pathway: Peganine (from *Peganoin hamala*) and Vasicine (from *Justicia adhatoda*, sometimes known as *Adathoda vasica*), the first naturally occurring quinazoline alkaloids, are used as bronchodilators and to treat pulmonary problems. Studies on Peganum harmata have unequivocally shown that peganine is generated from anthranilic acid, with ornithie providing the final component of the structure, a pyrolidine ring. Here anthranilate nitrogen acts as a nucleophile and attack the pyrrolinium cation, sequentially amide production, is easily explained as the cause of the peganine skeleton.a considerably less predictable sequence between acetyl anthranillic acid and aspartic acid is observed in *justicia adhatoda*, which is remarkable because this pathway is not active in this organism [2].

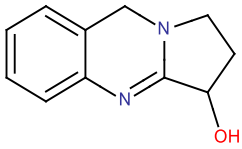

Figure 2. Peganine (vasicine)

Numerous quinazoline derivative compounds have been created and are used in medicine Quinazolines are the name for quinazoline derivatives. It has been utilized medically in a number of contexts, most notably as a cancer therapy and antimalarial drug.[3]

A) Anti-microbial activity:

For a medical chemist, heterocyclic rings with nitrogen atoms constitute an important class of molecules. Due to the vast range of pharmacological activity that the quinazoline nucleus exhibits, it has caught the interest of medicinal chemists. Anthranilic acid, formaldehyde, and primary amines have been used in the procedure to create certain 3-substituted-4-(2H)-quinazolinones. IR and NMR spectroscopy are used to characterise the molecule. Staphylococcus aureus is the target of its antibacterial action on Nutrient Agar Medium. A total of four substances had their antibacterial properties examined. The most potent antibacterial properties are found in nitro group-containing compounds

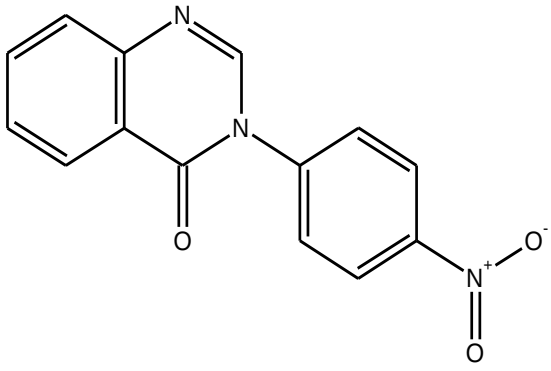

Figure 3a. 3(4-nitrophenyl)-4-(3H)-quinazolinone

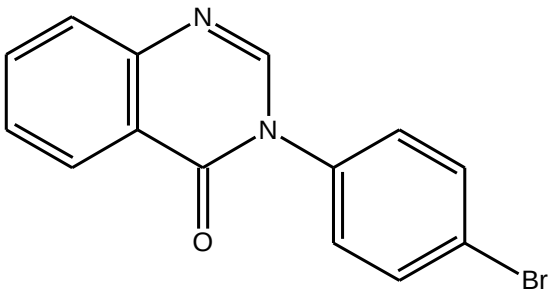

Figure 3b. 3(4-bromophenyl)-4-(3H)-quinazolinone

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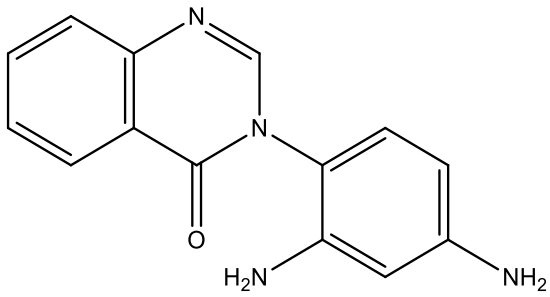

Figure 3c. 3(2,6-di amino phenyl)-4-(3H)-quinazolinone

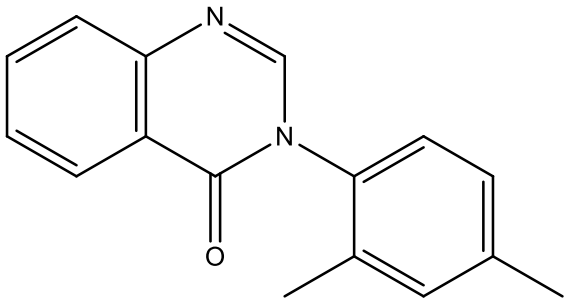

Figure 3d. 3(2,6-di methyl phenyl)-4-(3H)-quinazolinone

Quinazoline and its analogues are found to have a significant inhibitory potential against the gram positive bacteria and tumors.

Quinazolin-4-(3H)-one's new Schiff bases were created in good yields, and their potential antimicrobial and antifungal properties were tested. The spectral analysis of the freshly synthesized chemicals provided evidence of their structures. By using the plate hole diffusion method, their antibacterial and antifungal properties were assessed against *Aspergillus niger*, *Candida albicans*, and gram positive and gram negative bacteria. When compared to traditional drugs, the synthesized compounds had mild to considerable bactericidal and fungicidal properties. The findings indicated that the most effective compounds might serve as a lead molecule for the development of more potent pharmacophores in future.

By combining 2-methyl benzoxazine with different amino acids, leads to the formation of new 2, 3-disubstituted quinazolinone derivatives . These compounds were then reacted with aromatic aldehydes to produce the title compounds. By using the melting point, chromatographic , spectroscopic, and Elemental Analysis, the structures of the produced compounds were verified. Using molinspiration software, the Lipinski's rule of five and Drug likeness qualities were assessed. Using Dihydrofolate Reductase Inhibitor as a target enzyme, Auto Dock software conducted a docking analysis of the produced chemical. Derivatives that were synthesized were tested for their anti-fungal and anti-bacterial properties.[4]

A multistep synthesis was constructed to create many new quinazolinones from anthranilic acid. By using the spectroscopic studies and elemental analysis, the structures of the produced compounds were confirmed. By using an agar streak method against different harmful species of bacteria and fungus, whole test substances were studied their bactericidal and fungicidal activities. The synthesized compounds showed moderate and good anti fungal and antibacterial activity respectively, according to antimicrobial investigations. Discussion was had regarding the connection between the pharmacological activity of the molecules found during the screening and the functional group variation. Out of the thirteen tested analogues, 3 -(2-(1(4-chlorophenyl)-3-methyl-5-oxo-1H-pyrazol-4(5H)-ylidene)hydrazinyl)-2-methylquinazolin-4(3H)-one VIIg was shown to be the most effective substance .[5]

Imines (Schiff bases) and the products of their reactions are a fascinating class of organic compounds that have attracted a lot of attention over the years. It has been reported that they have a variety of biological activities, including antimicrobial, antioxidant, cytotoxic, and anticonvulsant properties. The Schiff bases produced in an alcoholic medium by straightforward condensation of amine and aldehydes to generate an azomethine linkage12. By using thin layer chromatography plates covered with silica gel G. benzene: chloroform as the mobile phase, iodine vapour used as detecting agent, and recrystallizing the pure compounds from ethanol, the purity of the compounds was established. The NMR spectrum research was carried out using DMSO as the solvent on JOEL, and the IR spectra of the compounds were acquired in the range, 4000-400 cm-1 using KBr discs on JASCO 4100 FT. [6]

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B)Anti-hyper glycemic activity:

The antihyperglycemic effect of 5H-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo (2, 3-b) quinazoline 6a-o derivatives have investigated through the use of the streptozotocin (STZ) and sucrose-loaded (SLM) models, their antihyperglycemic activity was assessed. IR, 1H-NMR, mass spectroscopy, and elemental studies all served to corroborate the chemical structures of the newly synthesised compounds. In streptozotocin and sucrose-loaded rat models, the research findings show that the chemicals 6a, b, d, j, and o significantly reduced blood glucose levels.[7]

C)Antibacterial activity:

Quinazolin-(3H) one was synthesised and was found to have antibacterial properties. Some compounds have action that was comparable to fluconazole's.[8]

Novel 4,6-disubstituted compounds were created and used traditional techniques to assess their antibacterial efficacy beginning with anthranillic acid derivatives. A critical step, 2-substituted benzamide, was produced after initial acylation was followed by cyclization to produce benz-oxazinones. Following cyclization to produce quinazolones, the products were chlorinated and hooked to produce a variety of 4,6-disubstituted quinazoline derivatives.9

Novel tetra hydro - quinazoline analogues and tested them for their ability to combat both gram positive and gram negative bacteria, including *pseudomonas aeruginosa*, *bacillus subtilis*, and *escherichia coli.*[10]

D) Anti-inflammatory activity:

Two analogues of 2-phenyl-4(3H) quinazoline were produced, and the majority of the evaluated quinazolinone compounds significantly outperformed indomethacin as the reference medicine in terms of anti-inflammatory and pain releiving activities in experimental rats. In comparison to the reference medicine indomethacin, several molecules were the most effective molecules as NSAID'S in rat models.[11]

E) Cyto toxic activity:

By reacting 3-amino-2-phenyl-3H-quinazoline-4-one with various carbonyl compounds created a variety of 3-(benzylidene amino)-2-phenyl quinazoline - 4(3H)-ones (figure 4) and examined their cytotoxic activities. [12]

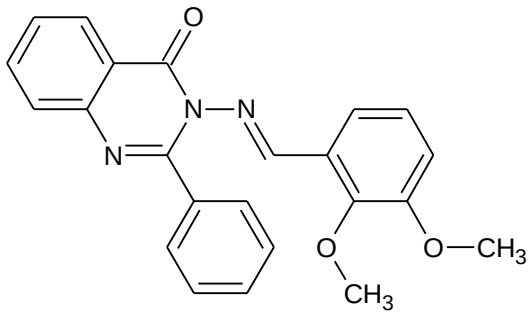

Figure4. 3-(benzylidene amino)-2-phenyl quinazoline - 4(3H)-one

EGFR plays a crucial role in controlling cell proliferation, is one of the most carefully researched targets for tyrosine kinase (TK) inhibitors. Numerous TKs play a part in cell proliferation, differentiation, and metastasis as well as in survival and tolerable activation via processes including point mutation, which may be the cause of a significant fraction of clinical malignancies. Numerous cancers, including those of the ovary, breast, bladder, head, brain, prostate, and lung, express excessive amounts of the EGFR protein. Based on a literature review, it was discovered that quinazolin 4(3H) is one of the structurally modified derivatives with the potential to have cytotoxic effects. by EGFR-TKs enzyme inhibition. In this, we carefully investigated binding affinity and mechanism of action of newly synthesized quinazolinones molecules.[13]

E) Antifungal activity

6-bromo-2(2,3-dichloro phenyl)) piperazine-1-yl) methyl)-3-(8-hydroquinoline-5-yl)-3-quinazolin-4-0ne

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ligand and its metal chelates were produced and their antifungal activity was observed.[14]

By condensing benzoxazinones and 4-substituted phenyl ureas were.created a number of novel quinazoline-carboxylic acids (also known as 4-substituted phenyl amides). In order to create 2-phenyl-3,1-benzoxazine-4-one, N-benzoyl anthranilic acid and acetic anhydride were combined. Several (Un)substituted anilines were then combined with sodium cyanide. to create phenyl ureas with a 4th substitution. By using the conventional agar dilution method, all the synthesised molecules were studied their invitro activity against four pathogenic species of fungi, and the zone of inhibition was identified. Clotrimazole was used as the benchmark. None of the substances worked against *Aspergillus fumigates*.[15]

G) Anti-hypertensive activity:

The derivativesof 6,7 - di methoxy - 2-(phenylamino)quinazolin - 4(3H)-one (figure 5) in three phases and tested them for their ability to inhibit alpha-1 adrenergic receptors.[16,17]

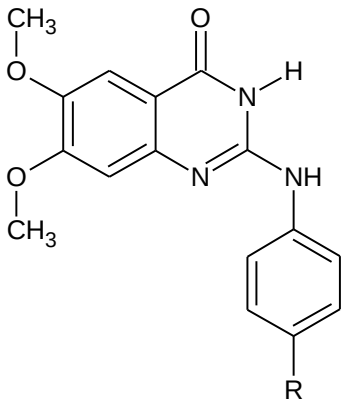

Figure 5. 6,7 - di methoxy - 2-(phenylamino)quinazoline - 4(3H)-one

H) Anti-HIV activity:

Aryl methylene thiopyrimidine and quinazloline derivatives were used as starting materials to manufacture a number of dihydrobenzo(h)quinazoline derivatives. Many of these compounds showed the considerable action against to cancer and viral infection, according to the biological screening.[18]

I) Antioxidant activity

New analogues of quinazolines and its combined heterocyclics have produced and it was discovered some molecules solely inhibited an aldehyde oxidase by greater than 98%.[19]

J) Analgesic activity:

The pain-relieving and anti-inflammatory properties of pyrazolino quinazolines were made and evaluated. The compounds demonstrated good activities like conventional NSAID'S.[20]

K) Anticonvulsant activity:

A series of compounds were created by reacting 2,4-dichloroquinazoline(5), which was created with various piperazines containg substitution at N atom. Synthesized compounds were characterized and studied their anti convulsant activity.[21]

L)Antimalarial activity:

Substituted quinazolinoes were made which are structurally similar to febrifugine (figure 6a)and ketofebrifugine (figure 6b). Synthesized compounds (at dose 5 mg/kg body weight) proved their anti plasmodial activity against to P. *berghei* in mice, at a dose of 5 mg/kg. These compounds have an advantage of feasible synthetic scheme of making when compared with chloroquin and artimisinin.[22]

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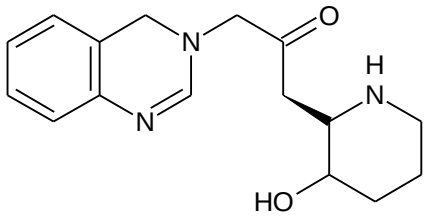

Figure 6. (A) Febrifugine

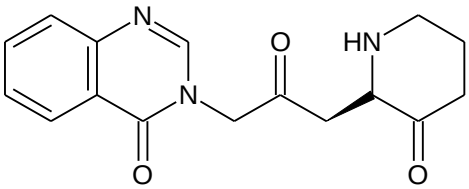

Figure 6. (B) Ketofebrifugine

M) Anti-tumor activity

Novel anticancer compounds with a 4-substituted quinazoline pharmcophore were created . Human liver cell line (HEPG2), human breast cell line (MCF-7) and human cervix cell line (HELA) were the three cell lines used to measure the cytotoxic activity of the proposed quinazoline derivative compounds 5, 9, 15, 18, and 20, which were found to have potent and broad-spectrum anti-tumor activity with an IC50 range of 3.35 to 5.59 Mg/ML. With an IC50 range of 3.35e6.81Mg/Ml, all examined drugs demonstrated strong and selective action against breast cancer (MCF-7).[23]

By utilising anthranilic acid, amine, and orthoester in ethanol under mild circumstances, a series of 3-substituted guinazolinone derivatives have been produced in one pot with good to exceptional yields and great selectivity. Bi(OTf)3 effectively accelerated the reaction, and the catalyst was easily recovered and repurposed after the reactions without clearly losing its reactivity. The studied compounds demonstrate an affinity for anticancer targets, according to docking studies. The information gathered can be used to plan experimental antitumor activity screening[24].

N) Anti-tubercular activity

In order to test a series of novel 2-trichloromethyl quinazoline derivatives for their in vitro anti-tubercular activity against the bacterial strain inserted a secondary amine group at position 4 on each of the compounds. Alamar Blue assay for TB H37Rv ATCC 9 (American type culture collection) (MABA).[25]

O) Anti-cancer activity:

Following our interest in bioactive heterocyclic compounds, two benzoimidazoquinazoline derivatives were produced utilising both conventional heating techniques and microwave assistance. Standard spectroscopic techniques and elemental analyses were used to confirm the compounds' structural details. Inadvertently, the target scaffolds were when subjected to ultraviolet radiation, was discovered to emanate blue light. In light of this, a photoluminescence characterisation was done in accordance with the characterisation protocol. The benzimidazoquinazoline's antitumor properties chemicals were examined using both the high content screen and methylthiazol tetrazolium (MTT) (HCS)tests against the hepatocellular cells in the liver. The outcomes demonstrated a considerable decrease in the inhibitory. The outcomes demonstrated a considerable decrease in the inhibitory when exposed to synthesized compounds, the concentration of the cancer cells increased by 1 and 2.6 times, respectively. For compound (3b), a high content screen (HCS) was performed.[26]

Discussion

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According to the obtained informations quinazolines can possess a wide range of biological activities.Based on the above facts the name of the derivatives and their biological activities listed (Table 1). to provide an information regarding an influence of various functional groups on their pharmacological activities to the medicinal chemists and researchers.

Table 1. Pharmacological activities evaluated in quinazoline derivatives

Sl.No	Name of the derivative synthesized	Biological activity evaluated
1	3-Substituted - 4(2H)- quinazolinone	Anti bacterial against *S.aureus*
2	Quinazolin - 4- (3H)ones	Anti microbial against *A.niger*, *C.albicans*
3	2,3-disubstituted quinazolines	DHFR inhibitor
4	5H-5-phenyl-2-benzylidine-3-substituted hydrazino thiazolo(2,3-b) quinazolines	Anti hyperglycemic activity
5	2-phenyl-4(3H)quinazolines	Anti inflammatory activity
6	3-(benzylidine amino)-2-phenyl quinazoline-4(3H)-one	Cytotoxic activity
7	6-bromo-2(2,3-dichloro phenyl)) piperazine-1yl) methyl)-3-(8-hydroquinoline-5-yl)-3-qunazolin-4-one	Anti fungal activity

Conclusion

Quinazoline analogues are acts against a variety of disease conditions which are briefly explained in this article.Quinazoline moiety has been most frequently studied .Quinazoline derivative exhibts a wide range of biological activities. According to various literature survey by making minor changes to the substituents attached to the Quinazoline nucleus,it would be feasible to further increase the activity.Different novel medications that have recently been developed from Quinazoline derivative have superior effects and less toxicity.

Conflict of Interest:

The authors have no conflicts of interest regarding this investigation.

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