Biological activity of Quinazoline: A Review

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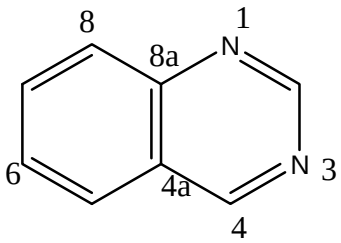
Abstract:

The aim of this review is to provide an overview of diverse pharmacological activities of quinazoline moiety. Quinazoline are well known and important nitrogen containing heterocyclic compound made chemical formula $C_8H_6N_2$ and various methods have been worked out for their synthesis. Quinazoline has become a popular topic up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring having due to its manifold uses. Numerous quinazoline derivatives have been found to possess a broad spectrum of biological activities, which stimulated the research activity in this field. Quinazolines and its derivatives represent one of the most active classes of compounds, which possess wide range of biological activities like anti-bacterial, analgesic, anti-microbial, anti-inflammatory, anticancer, and anti-hypertensive ,antifungal, anti-HIV, antioxidant, analgesic, anticonvulsant, antimalarial, antitumor, anti-tubercular activities. The purpose of this review was to collate literature work reported by researchers on Quinazoline for their various pharmacological activities and also reported recent efforts made on this moiety.

(**Keywords:** Quinazoline, Antibacterial, Anti-inflammatory, Antifungal, Antitumor, Anti-tubercular)

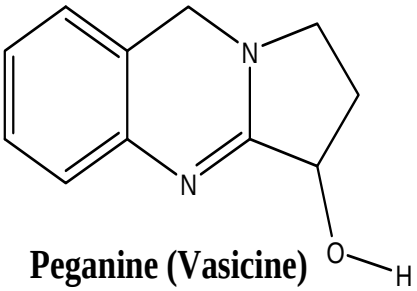
Introduction:

Quinazoline / Benzopyrimidine



$C_8H_6N_2$
CAS registary No. 253-82-7
Molar mass: 130.15 g mol−1

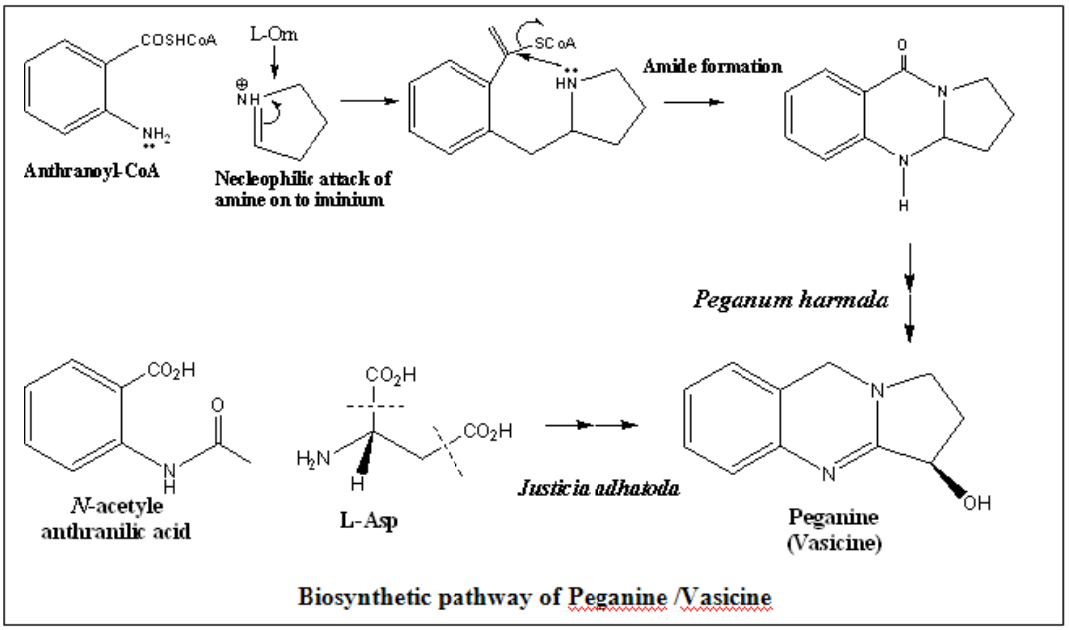
A yellow solid, usually in crystalline form, heterocyclic compound comprise of two fused six membered simple aromatic rings, i.e. a benzene ring and a pyrimidine ring. Medicinally it is used as antimalarial agent.



Peganine (Vasicine)

Quinazoline alkaloids attract the scientist since 1888, with the discovery of the first natural representative of them - (+)-peganine (vasicine)[1].

The biosynthesis pathway of vasicine: The first natural quinazoline alkaloid Peganine (from *Peganoin hamala*) / Vasicine (from *Justicia adhatoda syn. Adathoda vasica*) are in use for bronchodilator activity and in the treatment of respiratory alignments. Studies in Peganum harmata have clearly demonstrated peganine to be derived from anthranilic acid, the remaining part of the structure being a pyrolidine ring supplied by ornithie. The peganine skeleton is readily rationalized as a result of neucleophilic attack from the anthranilate nitrogen on to the pyrrolinium cation, followed by amide formation. Remarkably this pathway is not operative in *Justicia adhatoda* and a much less predictable sequence from acetylanthranilic acid and aspartic acid is observed [2].



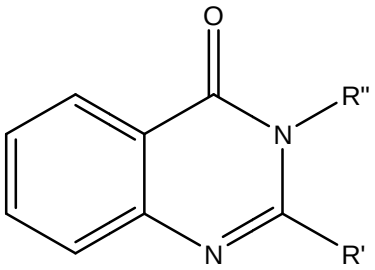
A number of quinazoline derivative compound are synthesized and is in medically use [3].

Derivatives of quinazoline are called quinazolines. Medicinally it has been used in various areas especially as an anti-malarial agent and in cancer treatment

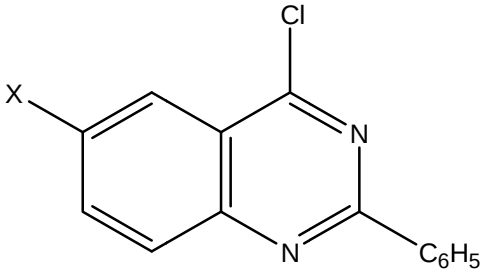
Pharmacological activity:

[a] Antibacterial activity:

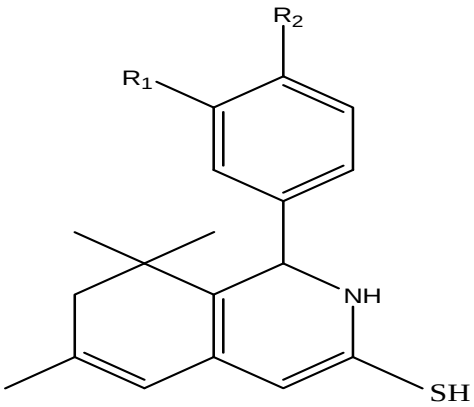
Nagar *et al* [4] synthesized and found antibacterial activity of quinazolin-(3H)one The activity of some derivatives were comparable with that of fluconazole.



Gautam *et al* [5]synthesized some novel 4, 6-disubstituted derivatives and evaluated their antimicrobial activity starting from anthranilic acid derivatives through conventional methods. Initially acylation followed by cyclisation to obtain benz-oxazinones which on further treatment with ammonia yielded the crucial intermediate, 2-substituted benzamide. The products were subsequently cyclised to obtain quinazolones, chlorinated, then hooked to have various 4, 6-disubstituted quinazoline derivatives .

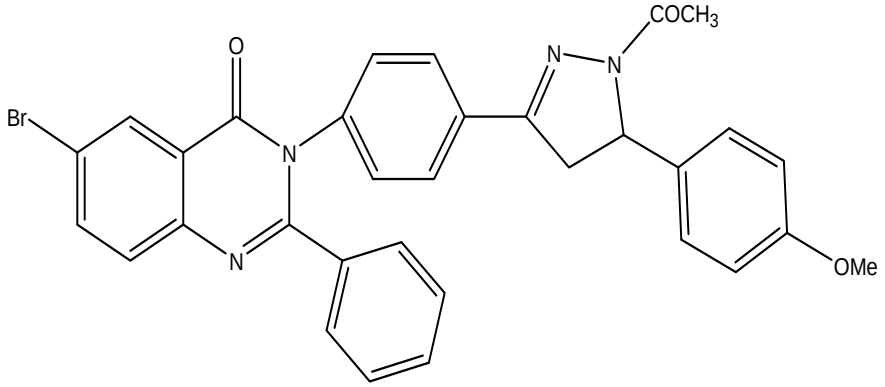


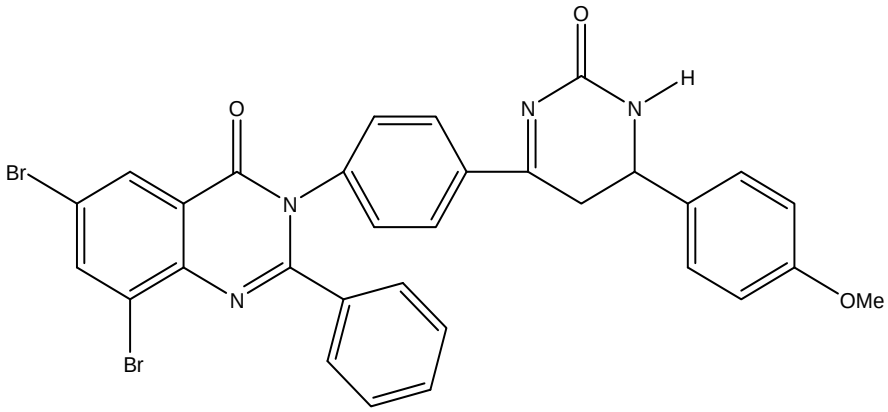
Doshi *et al* [6]synthesized a new Tetrahydro-quinazoline analogues and screened for their antibacterial (*Pseudomonas aurigenosa Bacillus subtilis* and *Escherichia coli*) against gram positive and gram negative bacteria .



[b] Anti-inflamatory activity:

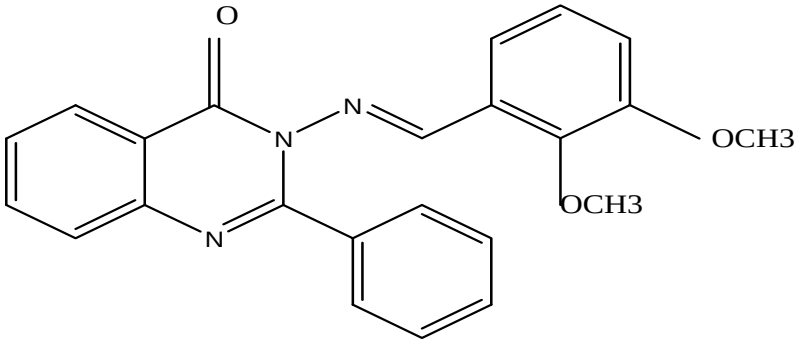
Two series of 2-phenyl-4(3H) quinazolinone derivatives have been synthesized by Mohamed *et al* [7].Most of the tested quinazolinone derivatives showed considerable potent anti-inflammatory and analgesic activity of superior GIT safety profile in experimental rats in comparing to indomethacin as reference drug. Some compounds were the most potent anti-inflammatory in experimental rats in comparing to indomethacin as reference drug.





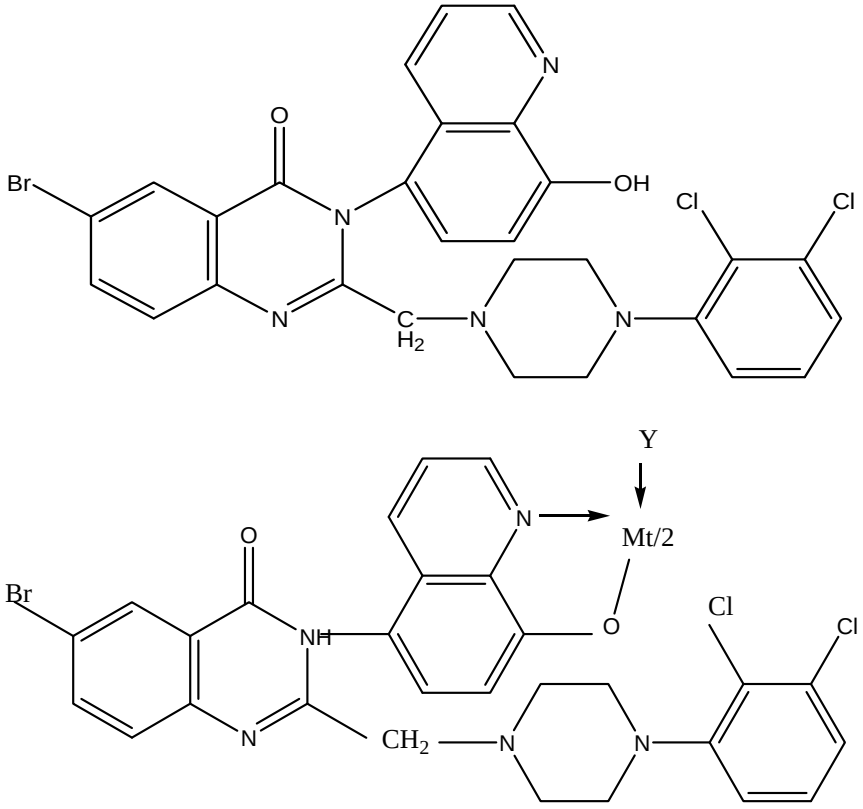
[c]Cytotoxic activity:

Krishnan *et al* [8] synthesized series of 3-(benzylideneamino)-2-phenyl quinazoline-4(3H)-ones was synthesized by reaction of 3-amino-2-phenyl-3H-quinazoline-4- one with various carbonyl compounds and investgated cytotoxic activity.

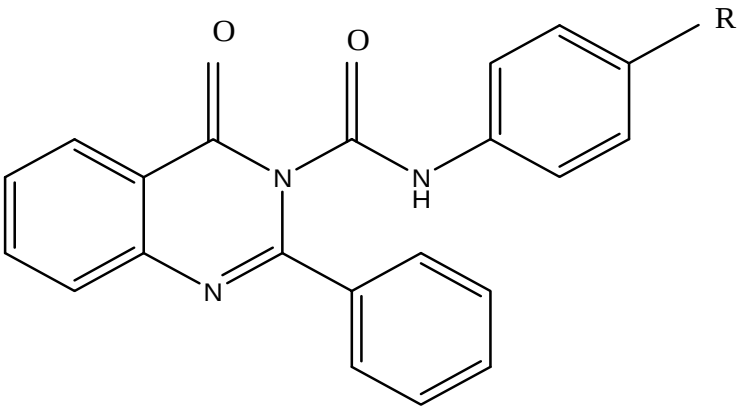


[d] Antifungal activity:

Vashi *et al* [9]synthesized and observed antifungal activity of 6-bromo-2[(4-(2,3-dichlorophenyl)) piperazine-1-yl)methyl]-3-[8-hydroxyquinoline -5-yl]-3-quinazolin -4-one ligand and its transition metal chelates .

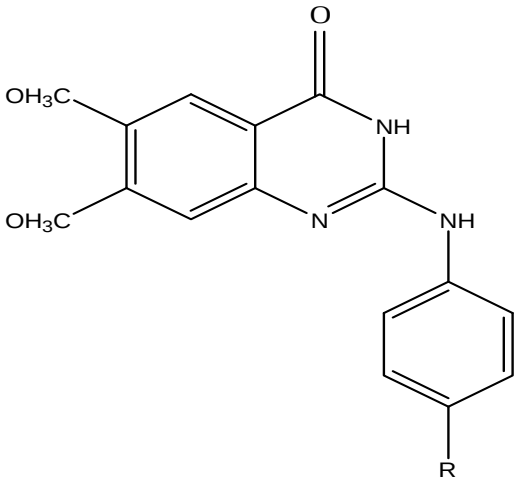


Vijai Anand *et al* [10]synthesized a series of novel 4-oxo-2-phenyl-4*H*-quinazoline-3-carboxylic acid(4-substituted phenyl amides) by condensing 2-phenyl-3,1-benzoxazine-4-one and 4-substiuted phenyl ureas. A mixture of N-benzoyl anthranilic acid and acetic anhydride was condensed to form 2-phenyl-3,1-benzoxazine-4-one and various 4-substituted anilines were condensed with sodium cyanide to form 4-substituted phenyl ureas. All the synthesized compounds were evaluated for their *in vitro* antifungal activity against four pathogenic fungi by standard agar dilution method and the zone of inhibition was determined. Clotrimazole was taken as reference standard. All the compounds were not active against *Aspergillus fumigates*.



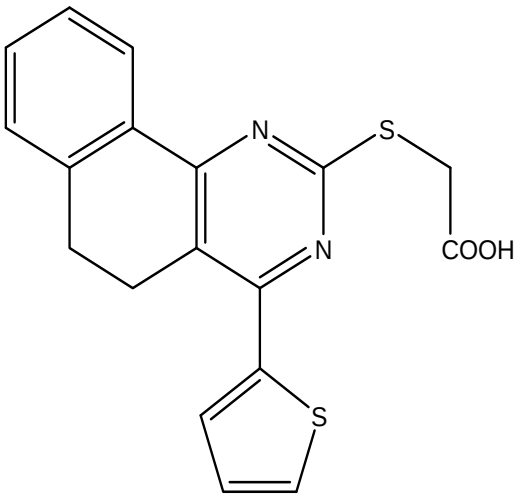
[e] Antihypertensive activity:

Patel *et al* [11]synthesized Seven new Quinazoline derivatives by three steps.and screened for α1-adrenergic receptor blocking activity.



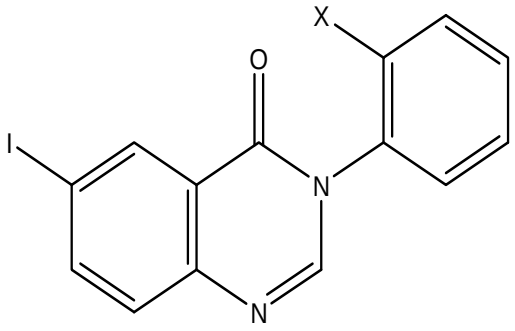
[f] Anti-HIV activity:

Yahia et al [12] synthesized a series of dihydrobenzo[h]quinazoline derivatives using arylmethylene thiopyrimidine and 2-(4-(thiophen-2-yl)-5,6-dihydrobenzo[h]quinazolin-2-ylthio) acetic acid **(4)** as a starting materials. The biological screening showed that many of these compounds have good anticancer and antiviral activities .



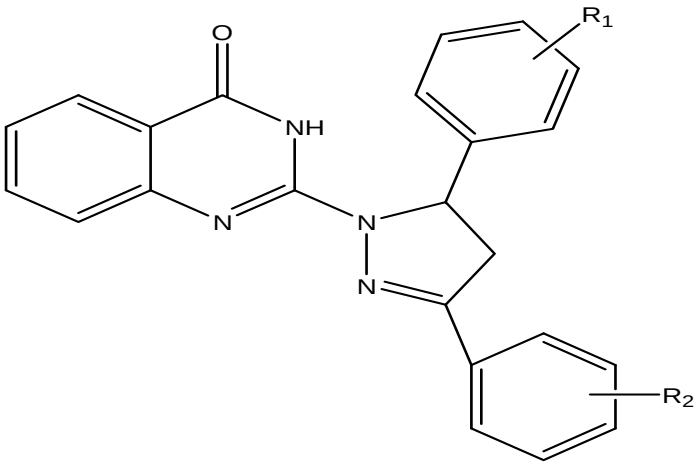
[g] Antioxidant activity:

Al-Omar *et al*[13] 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% .



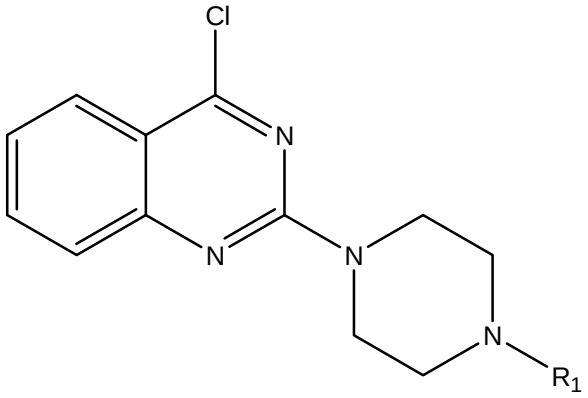
(i)Analgesic activity:

Sinha *et al* [14] synthesized and evaluated the analgesic and anti-inflammatory activities of pyrazoline bearing 4(3H)-quinazolinone derivatives. : The synthesized compound 6b, 6d, 6e, 6i and 6j showed good analgesic and anti-inflammatory activities whereas others showed significant activities.



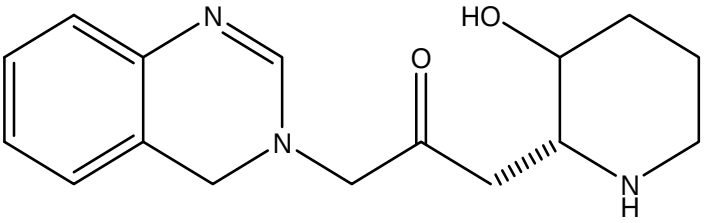
(j)Anticonvalsant activity:

Mukhergee *et al*,[15] synthesized 2, 4-dichloroquinazoline (5) and the compound was reacted with different N-substituted piperazines to obtain a series of title compounds [6(A-G)]. All the new title compounds were characterized by spectral data and were screened for anticonvulsant activity.

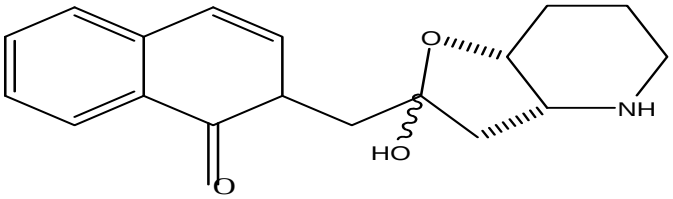


(k)Antimalarial activity:

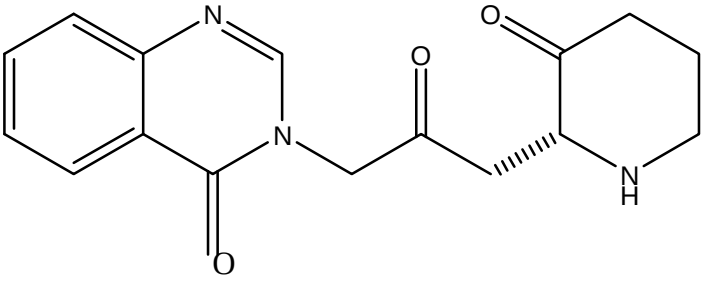
Sen *et al* [16]synthesized a series of 2-substituted and 2,3-substituted quinazolin -4(3H)-one derivatives based on the structure of febrifugine.. The *in vivo* biological activity test results indicated that those compounds exhibited antimalarial activities against *Plasmodium berghei* in mice, at a dose of 5 mg/kg. Compared to Chloroquine and Artemisinin, these compounds have the advantages of shorter synthetic routes and consequently are highly cost effective in nature.



Febrifugine



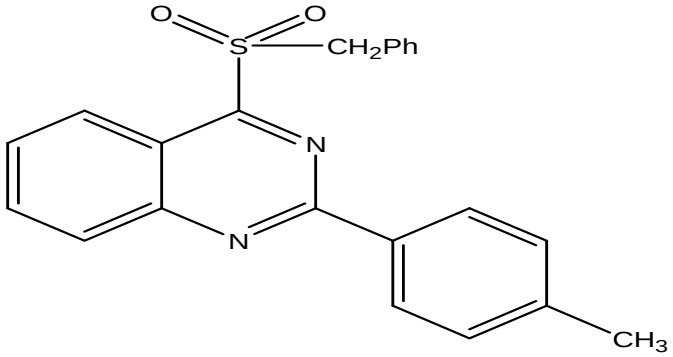
Isofebrifuge



Ketofebrifugine

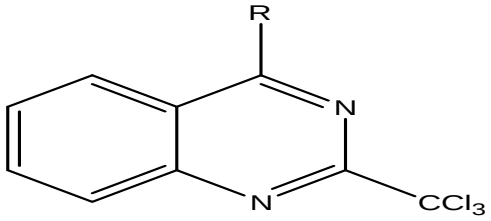
(l)Antitumor activity:

El-Azab *et al*[17] developed novel antitumor molecules containing 4-substituted quinazoline pharmacophore.Three cell lines including human liver cell line (HEPG2), human breast cell line (MCF-7) and human cervix cell line (HELA) were used to measure cytotoxic activity of the proposed quinazoline derivatives. Compounds 5, 9, 15, 18 and 20 exploited broad-spectrum and potent antitumor activity with IC50 range of 3.35e5.59 mg/ml. All tested compounds showed potent and selective activity against breast cancer (MCF-7) with IC50 range of 3.35e6.81 mg/ml. [17].



(m)Anti-tubercular activity:

Maneesh et al [18] synthesized a series of novel 2-trichloromethyl quinazoline derivatives bearing substituted secondary amine group at the 4th position and evaluated for their *in vitro* anti-tubercular activity against bacterial strain of *M. tuberculosis* H37Rv ATCC (American Type Culture Collection) by Alamar Blue assay method(MABA).



Conclusion:

Quinazoline moiety have been most frequently studied, many of its analogs are active against various pathological conditions, which are discussed in brief in this article. On the basis of various literature survey quinazoline derivatives show various activity like antibacterial, anti-inflammatory, analgesic, cytotoxic, antifungal, antihypertensive, analgesic, anticonvalsant, antimalarial, antitumor, antitubercular etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic quinazoline nucleus. Various recent new drugs developments in quinazoline derivatives show better effect and less toxicity.

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