

## Biological Profile of Quinazoline

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### ABSTRACT

This article outlines the medicinal and biological significance of one of the most important heterocycles, the quinazoline. Quinazoline is a highly active scaffold exhibiting wide variety of medicinal and biological activities. An attempt is made in this article to cover the medicinally active compounds, along with the recent discoveries, which were reported to possess various biological activities. This might be helpful in the development of these novel lead molecules to potential drug candidates.

**Keywords:** Heterocycles, Quinazolines, Scaffold, Medicinal significance, biological significance.

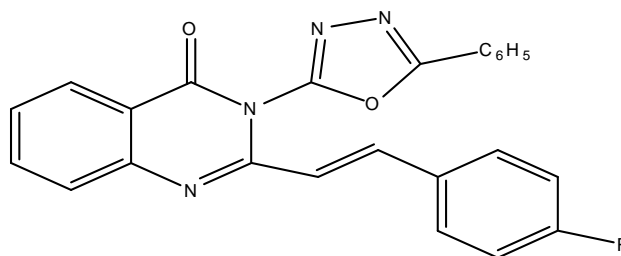
### INTRODUCTION

Quinazoline derivatives are found to show CNS depressant<sup>1</sup>, anticancer<sup>2</sup>, antibacterial<sup>3</sup>, antiinflammatory<sup>4-5</sup>, antifungal<sup>6</sup> properties, etc. 1,3,4-oxadiazoles itself possesses antiinflammatory<sup>7</sup>, insecticidal<sup>8</sup>, antibacterial<sup>9</sup>, antimicrobial<sup>10-11</sup> and anticonvulsant<sup>12</sup> activities.

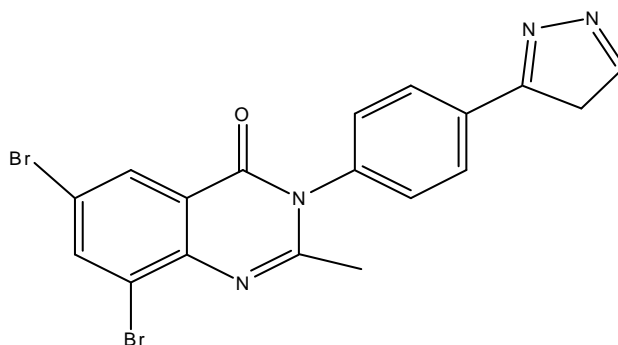
Quinazoline is a compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. It is also called benzopyrimidine. It has the molecular formula C<sub>8</sub>H<sub>6</sub>N<sub>2</sub> and molecular mass 130.15 g/mol. It is isomeric with quinoxaline, phthalazine and Cinnoline. Earlier research in nineteen fifties and sixties revealed effectiveness of quinazolines not only as anti-malarial but also against various diseases caused by bacteria, protozoa and virus. But the research was restricted mostly to anti

microbials. An important stage in the development of research on the biological activity of quinazoline compounds was the discovery of considerable soporific and sedative action of 2-methyl-3-aryl-4-quinazolone derivatives. Synthesis of these compounds with general concepts stimulated an extensive search for various pharmacologically active compounds. In the last 10-15 years the search for quinazoline compounds has been characterized by significant advances. They have been reported to possess wide spectrum of biological activities like analgesic and anti-inflammatory, antimicrobial, anti-tubercular, antihistaminic, anti-tussive and bronchodilator, anti-diabetic, antidiuretic, antihypertensive, sedative-hypnotic activity, antidepressant, antiparkinsonian, Phosphodiesterase inhibition, anticancer.

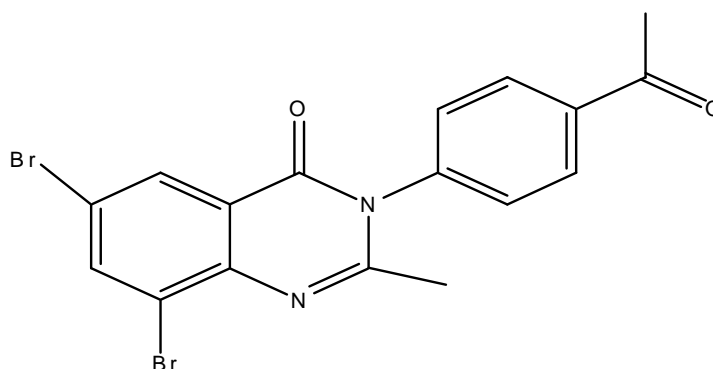
### Antibacterial agent



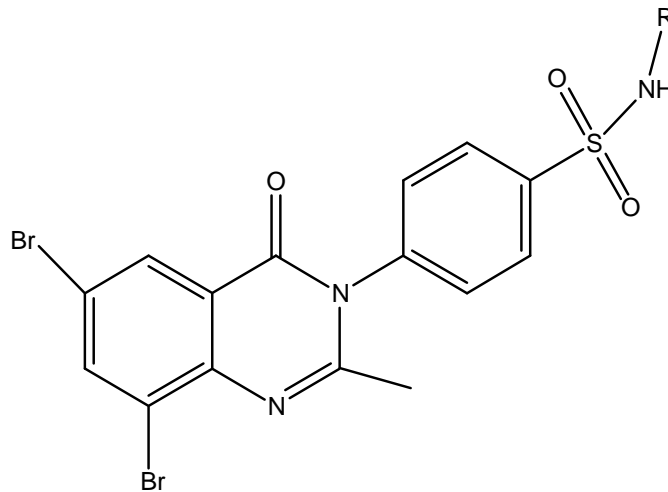
3-[5-phenyl -1,3,4-oxadiazole-2-yl]-2-(substituted styryl) quinazoline-4(3H)-ones  
(a)



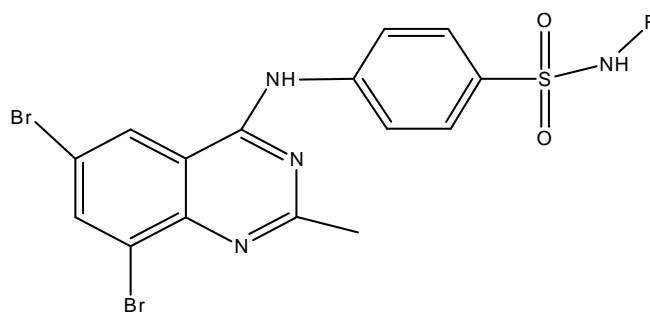
6,8-dibromo-2-methyl-3-[4-(4*H*-pyrazol-3-yl)phenyl]quinazolin-4(3*H*)-one  
(b)



4-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzaldehyde  
(c)



(d)



(e)

### Antibacterial activity

The new derivatives obtained from the reaction sequence were screened by four test organisms such as *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus* (gram-positive) and *Proteus vulgaris* (gram-negative) by using Streptomycin and penicillin as standard drug.

### Cup Plate Method

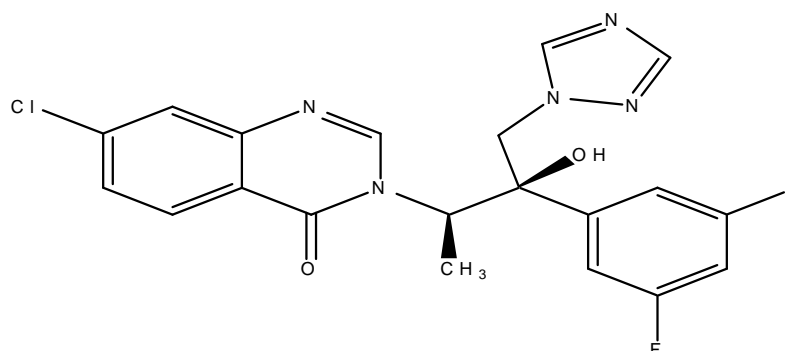
Antibacterial activity was performed by cup plate method by measuring zone of inhibition. All the test compounds were screened for antibacterial activity against bacterial strains *Bacillus subtilis*, *Staphylococcus aureus* (gram-positive), *Escherichia coli* and *Proteus vulgaris* (gram-negative) at a concentration of 100 µg/ml. Streptomycin and penicillin were used as standard drugs at a concentration of 100 µg/ml. Nutrient agar was used as culture medium & dimethylsulfoxide (DMSO) was used as solvent control. Laminar airflow bench was swapped with 70 % alcohol and UV lamp was switched on. After 30 min, the UV lamp was switched off.

All the reagents, media, inoculums and glassware were placed in laminar airflow bench observing all aseptic conditions. The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums had dried, cups of diameter 6mm were made in the

agar plate with a sterile cork borer. The drugs solutions were added to these cups with a micropipette and the plates were then incubated at 37 °C for 24 hours. The zone of inhibition was measured using mm scale.

### Antifungal Agent

The antifungal activity of quinazoline compounds were tested against the pathogenic fungi *Aspergillus niger*, *Candida albicans*, *Trichoderma viridae* by cup-plate method. Nutrient agar medium was prepared by the same method as explained under evaluation of antibacterial activity. One and half day prior to the experiment, the fungal cultures of *Aspergillus niger*, *Candida albicans* and *Trichoderma viridae* prepared in the inoculation medium were incubated at 37 °C for 36 h. The fungal medium was prepared by dissolving peptone (0.5%), sodium chloride (0.36%), monopotassium phosphate (0.13%), and glucose (2%) in distilled water (100 mL). The pH of the solution was adjusted to 7.2 by adding sodium hydroxide solution (4%) and the resulting solution was autoclaved for 20 min at 15 psi. This was cooled to 45-50 °C with gentle shaking. One and half day, grown cultures were added aseptically to this medium and mixed thoroughly to get uniform distribution. The solutions of the test samples and standard were evaluated for antifungal activity by cup-plate method at a concentration of 1000 µg. The zone of inhibition was measured in millimeter for the particular test sample with each organism at 48 hours interval. Ketoconazole was used as the standard.

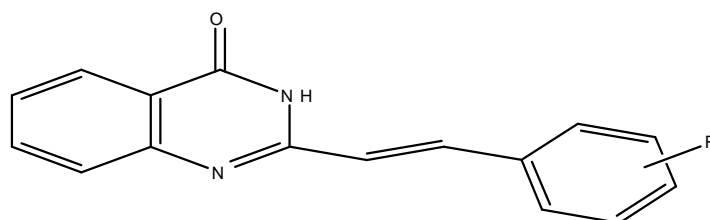


(f)

**Anti-tubercular agents**

There are no promising quinazolines marketed presently in the category of tuberculosis. But several novel molecules have been synthesized in the past which showed promising results but unfortunately could not make it up to the marketing stage. Josef et al. Synthesized novel 2-styrylquinazolin-4(3*H*)-one and 4-

chloro-2-styrylquinazoline derivatives. It was found that the electronic withdrawing properties of the R substituent, and not the total lipophilicity of the compound, were decisive for the compounds to exhibit potent antitubercular activity when compared with isoniazid by invitro method<sup>22</sup>.

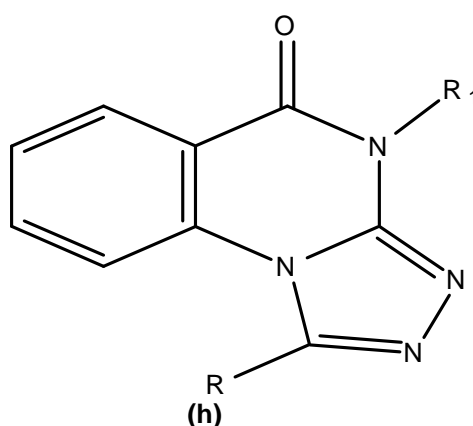


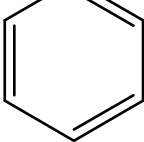
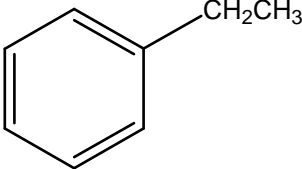
**2-styrylquinazolin-4(3*H*)-one  
(g)**

**Anti-Histaminic agents**

In the recent days lot of research is being done in the category of histaminic antagonists with relatively less sedation effect than existing drugs. Though few drugs possessing this activity are presently in the market novel drugs are still being synthesized. Diproqualone (4) - Diproqualone was found to pose potent anti-histaminic activity though it was never marketed under this category. Alagaraswamy et al. synthesized several 4-(3-ethylphenyl)-1-substituted-4*H* [1,2,4] triazolo [4,3-*a*]quinazolin-5-ones<sup>35,4</sup>-(4-

ethylphenyl)-1-substituted-substituted-4*H* [1,2,4] triazolo [4,3-*a*]quinazolin-5-ones<sup>36</sup> and 1-substituted-4-cyclohexyl-4*H*-[1,2,4] triazolo [4,3-*a*] quinazolin-5-ones. It was found that by varying substitution over the first position of the triazoloquinazoline ring there was variation in the biological activity. The anti-histaminic potential was tested in vivo by comparing with chlorpheniramine maleate in which the following compound showed promising anti-histaminic activity with less sedation<sup>25,26,27</sup>.

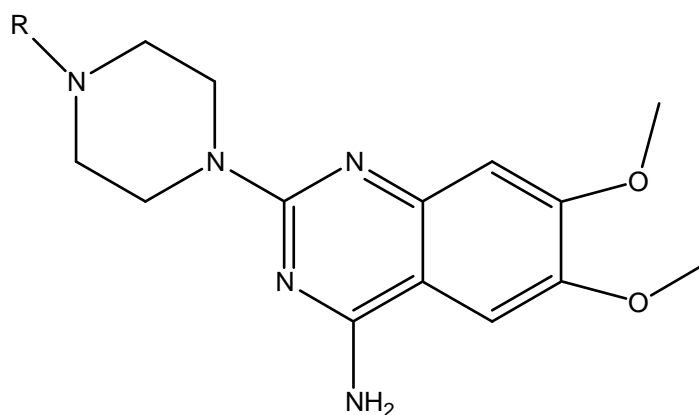


S.no	Substituent ( R)	Substituent ( R1)
1	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub> 
2	CH <sub>3</sub>	

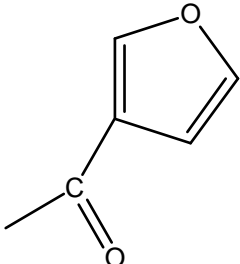
### Anti-hypertensive activity

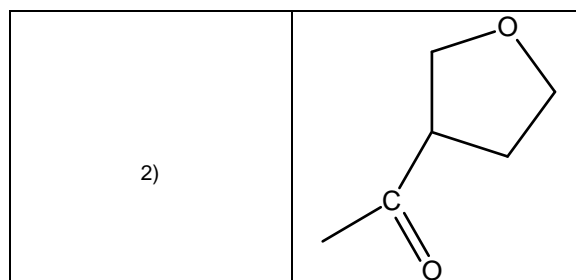
Quinazolines enjoy a promising position in the anti-hypertensive's market. They are also the drugs of choice for renal impaired patients and effectively the drugs of second line choice for newly diagnosed

patients. Prazosin It is a selective alpha-1 receptor blocking agent used for the management of severe hypertension, benign prostrate hyperplasia and post traumatic stress disorders.



(i)

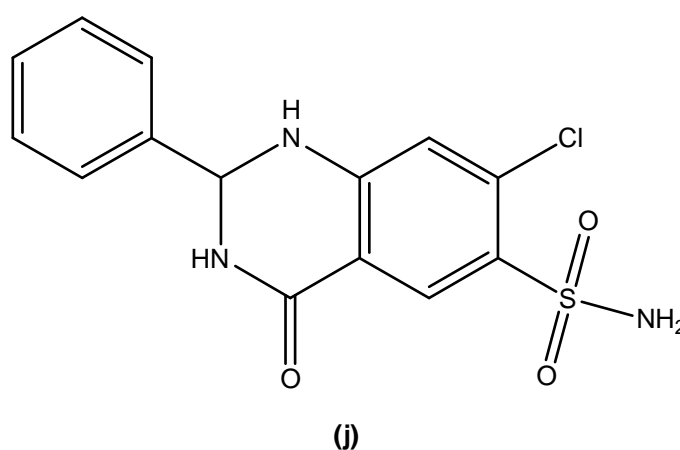
S.No	Substituent( R)
1)	



### Anti-diuretic agents

There are very few promising anti diuretic drugs of quinazoline category, which are presently marketed. They are mostly used for the management of hypertension. To

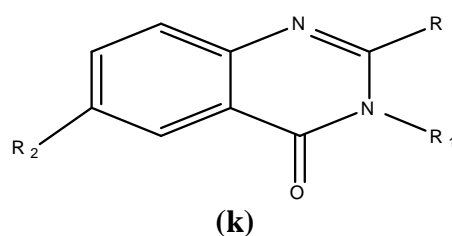
overcome its side effects novel drugs are still being synthesized. Fenquizone . It is a low ceiling sulfonamide diuretic used primarily in the treatment of oedema and hypertension<sup>28</sup>.

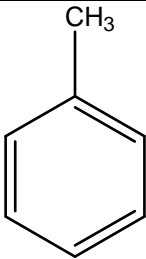
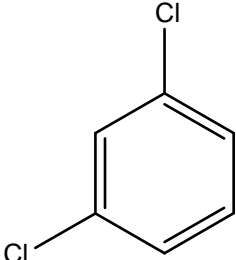
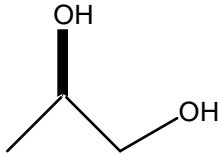


### Sedative –Hypnotic agents

Quinazolines have a greater share in the sedatives and hypnotics market.

Quinazolinones were primarily used in surgical anaesthesia.

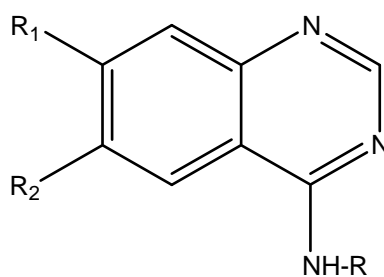


S.No	Substitution (R)	Substitution (R1)	Substitution (R2)
1)	CH <sub>3</sub> F		NH <sub>2</sub>
2)	CH <sub>2</sub> CH <sub>3</sub>		-
3)	CH <sub>3</sub>		-

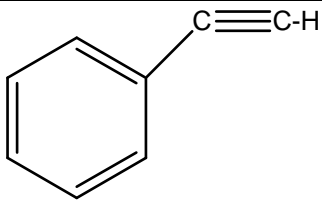
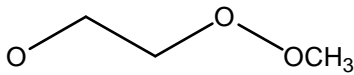
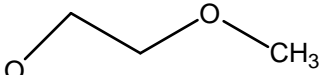
### Anti-cancer agents

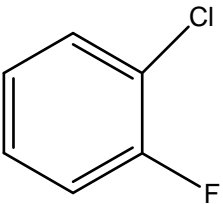
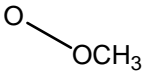
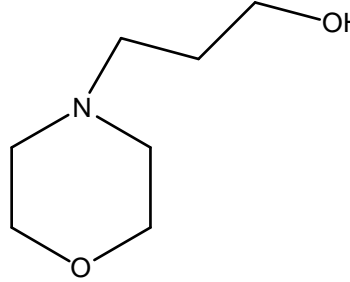
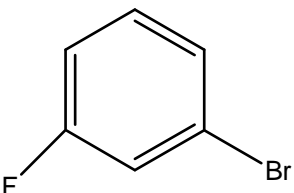
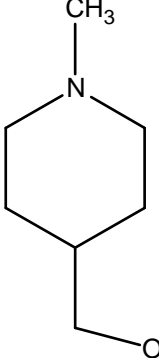
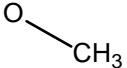
Quinazolines occupy a promising section in the anti-cancer market because of their specificity. Most of the quinazolines are targeting protein tyrosine kinase. Even

more selective compounds targeting EGFR, VEGFR and ERBB-2 are in the market. Receptors are being discovered and still in the developmental stages.



(I)

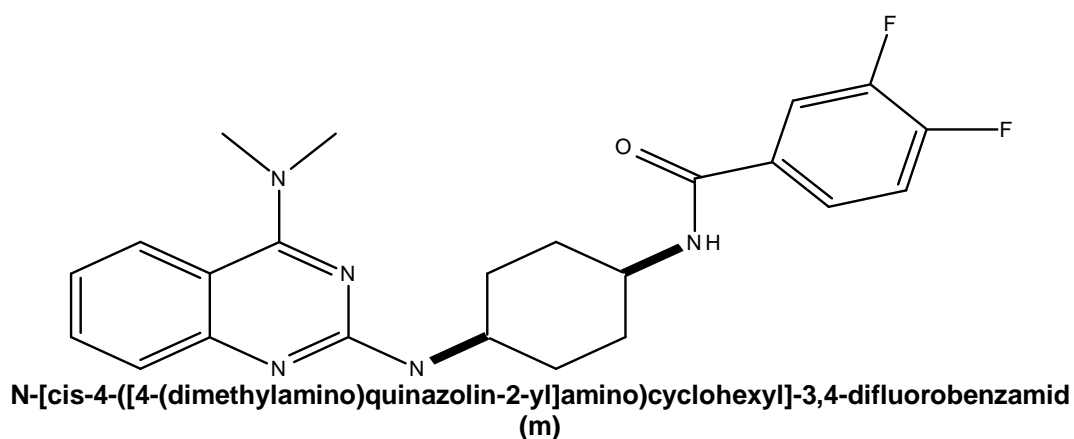
S.NO	Substitution(R)	Substitution(R <sub>1</sub> )	Substitution(R <sub>2</sub> )
1)			

2)			
3)			

### Anti-depressant agents

In the anti-depressant criteria still a promising molecule has yet to be launched. Except some drug candidates like ATC-0175 none of the other derivatives of quinazoline had come to the development phase. ATC-0175: It is the

drug in scientific research, which is a selective, non-peptide antagonist at the melanin concentrating hormone receptor MCH1. In animal studies it produced significant anti-depressant action without sedative and ataxic side effects



Wang et al. synthesized several 5-alkoxy-tetrazolo [1, 5-a] quinazoline derivatives. They stated that length of the alkyl chain appears to have a direct impact on the antidepressant activity of the 5-alkoxy derivatives. Among all the derivatives following were found to be potent when compared with reference standard fluoxetine.

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