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STUDY ON QUINAZOLINONE DERIVATIVE AND THEIR PHARMACOLOGICAL ACTIONS

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ABSTRACT

The heterocyclic compounds have a great importance in medicinal chemistry. One of the most important heterocycles in medicinal chemistry are quinazolines possessing wide spectrum of biological properties like antibacterial, antifungal, anticonvulsant, anti-inflammatory, anti-HIV, anticancer and analgesic activities.in the synthesis and bioactivities research. This review summarizes the recent advances in the synthesis and biological Owing to the significant biological activities, quinazoline derivatives have drawn more and more attention activities investigations of quinazoline derivatives. The biological activities of the synthesized quinazoline derivatives also are discussed. The first quinazoline derivative (2-cyano-3,4-dihydro-4-oxoquinazoline) was synthesized in 1869 by the reaction of cyanogens with anthranilic acid.[15] Many years later quinazoline was obtained by decarboxylation of the 2-carboxy derivative (quinazolinone) which can be synthesized more easily by a different method. Active heterocyclic compounds are one of the main topics of interest for the medicinal chemists as they display a number of pharmacological activities. Nitrogen, sulfur, and oxygen containing five- and six-membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry. The most important six-membered heterocyclic compounds are quinazoline and quinazolinone derivatives for their biological activities. The current chapter outlined the different methods for synthesis of quinazoline and quinazolinone derivatives that possess broadspectrum of biological activity. Quinazoline and its oxidized analogs, quinazolinones, are privileged motifs due to their frequent occurrence in natural products and bioactive compounds. Therefore, the development of efficient methods for the synthesis of quinazoline derivatives has been a significant research objective in organic and medicinal

chemistry. Although conventional syntheses of quinazoline derivatives generally depend on acid/base-mediated condensation reactions, hetero Diels-Alder reactions, aza-Wittig reactions, etc., modern approaches that utilize transition-metal catalysts have also been developed, enabling streamlined construction of quinazoline frameworks. In this chapter, Cu-mediated methods for the construction of quinazolines and related benzodiazines are surveyed. In addition, Cu-mediated modifications of quinazoline and quinoxaline scaffolds are discussed briefly.

KEYWORD: Quinazolinone Derivative and Their Pharmacological Actions.

INTRODUCION

Quinazoline (1,3-diazanaphthalene or 5,6-benzopyrimidine) and 4(3H)-quinazolinone derivatives have a great interest in organic synthesis and medicinal chemistry fields as they possess a broad range of pharmacological activities. They exhibit antimicrobial antimalarial antioxidant anti-inflammatory anticonvulsant antihypertensiveantidiabetic and antitumor activities.

• Chemistry of Quinazoline

Quinazoline is a compound made up of two fused six-membered simple aromatic rings—benzene and pyrimidine ring. The properties of the pyrimidine ring were affected by the presence of fused benzene ring. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected in the reactions of quinazoline. The properties of quinazoline derivatives depend on the following three factors.

1. The nature of the substituents.
2. The presence of substituent whether they are in the pyrimidine ring or in the benzene ring.
3. The presence of conjugation in the pyrimidine ring.

The first synthesized quinazoline in laboratory was achieved. Quinazoline is an organic compound with the formula $C_8H_6N_2$. It is an aromatic heterocycle with a bicyclic structure consisting of two fused six-membered aromatic rings, a benzene ring and a pyrimidine ring. ... Also known as 1,3-diazanaphthalene, quinazoline received its name from being an aza derivative of quinoline.

Thesynthetically useful quinazoline-2-carbaldehyde was prepared and was employed as a useful precursor for the synthesis of symmetric 2,2′- bis-quinazoline using this cooperative

catalytic system. Applying the strategy for the synthesis of heterocycles using PI/CB-Pt catalysts under aerobic oxidative conditions, bis-heterocyclic compounds were obtained in excellent yields (Scheme 37). These compounds may serve as potentially useful ligands or materials with unique properties. The heterogeneous catalyst was recovered and reused for five times without loss of reactivity and the leaching of the metals.

The heterocyclic fused rings quinazoline and quinazolinone have drawn a huge consideration owing to their expanded applications in the field of pharmaceutical chemistry. Quinazoline and quinazolinone are reported for their diversified biological activities and compounds with different substitutions bring together to knowledge of a target with understanding of the molecule types that might interact with the target receptors. Quinazolines and quinazolinones are considered as an important chemical for the synthesis of various physiological significance and pharmacological utilized molecules. Quinazolines and quinazolinone are a large class of biologically active compounds that exhibited broad spectrum of biological activities such as anti-HIV, anticancer, antifungal, antibacterial, antimutagenic, anticoccidial, anticonvulsant, anti-inflammatory, antidepressant, antimalarial, antioxidant, antileukemic, and antileishmanial activities and other activities. Being considered as advantaged scaffold, the alteration is made with different substituent. Quinazolines and quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties.[1] Many substituted quinazoline and quinazolinone derivatives possess a wide range of bioactivities such as antimalarial, anticancer, antimicrobial, antifungal, antiviral, antiprotozoan, anti-inflammatory, diuretic, muscle relaxant, antitubercular, antidepressant, anticonvulsant, acaricidal, weedicide, and many other biological activities. Quinazoline and quinazolinone compounds are also used in preparation of various functional materials for synthetic chemistry and also present in various drugs molecules.

WHAT IS QUINAZOLINE USED FOR?

- One of the most important heterocycles in medicinal chemistry are quinazolines possessing wide spectrum of biological properties like **antibacterial, antifungal, anticonvulsant, anti-inflammatory, anti-HIV, anticancer and analgesic activities.**
- Severalquinazolinone-based drugs including **idelalisib and fenquizone** have been shown to exhibit a broad spectrum of antimicrobial, antitumor, antifungal, and cytotoxic activities. Lapatinib has been displayed to be effective in combination therapy for breast cancer.

- The pharmacologically important **tryptanthrine**, a quinazoline alkaloid is known for its antimycotic activity and is used against skin infections.
- There are several approved drugs with quinazoline structure in the market such as, **prazosin hydrochloride**, doxazosinemesylate and terazosine hydrochloride.

Eg., **prazosin hydrochloride**

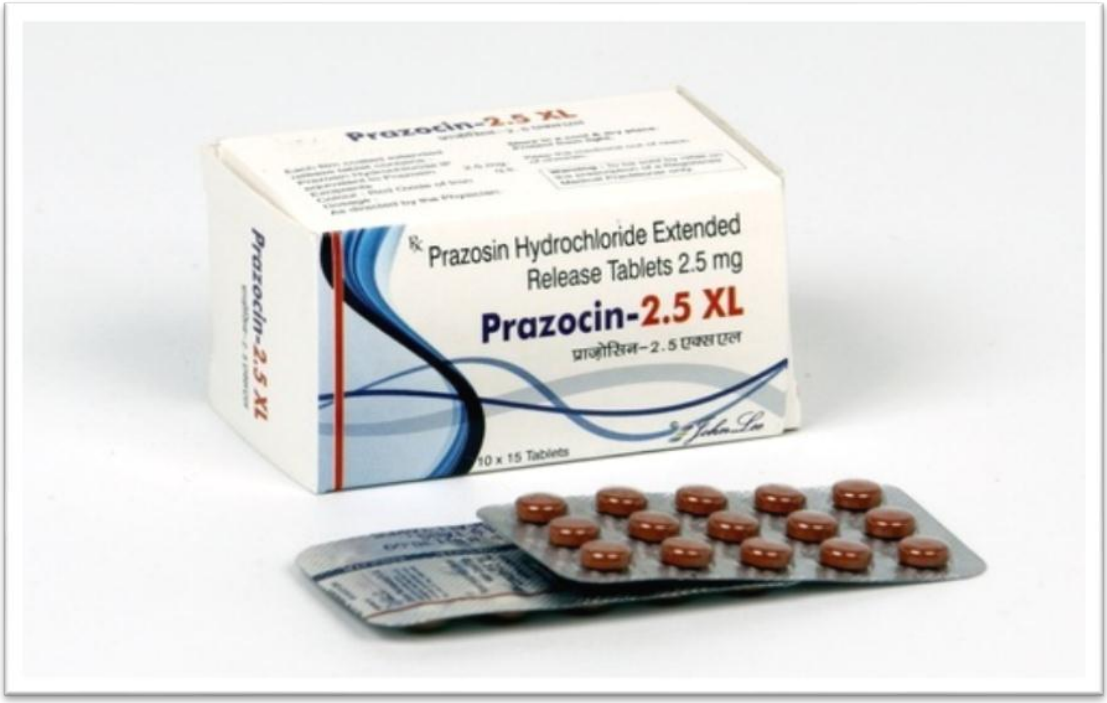


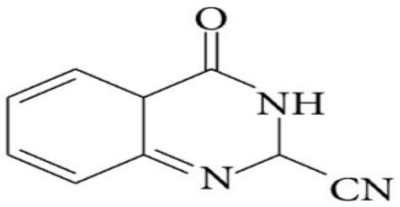
Figure prazosin hydrochloride.

LITERATURE SURVEY

- Martine Demeunynckthe present review focuses on the synthesis and biological evaluation of polycyclic 4(3H)-quinazolinones containing fused aromatic or heteroaromaticRings.
- Imtiaz Khan, AliyaIbrar, Naeem Abbas, AamerSaeed-Drug development has been a Principal driving force in the rapid maturation of the field of medicinal chemistry during the Past several decades. During this period, the intriguing and challenging molecular architectures of nitrogen-containing heterocycles with potential bioactive properties have received significant attention from researchers engaged in the areas of natural product. Synthesis and heterocyclic methodology, and constituted a continuous stimulus for development in bio(organic) chemistry.

History

In 1869 Griess prepared the first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline, by the reaction of cyanogens with anthranilic acid. The bicyclic product was called bicyanoamido benzoyl and used this name until 1885.[5] The preparation of the quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel in 1903. The name was proposed by Widdege. Other names such as phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5,6-benzopyrimidine, and 1,3-diazanapthaline have occasionally been used. The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3,4-double bond is reflected in the reactions of quinazoline. The properties of substitute's quinazolines depend largely on (a) the nature of the substituents, (b) whether they are in the pyrimidine ring or in the benzene ring, and (c) whether or not complete conjugation is present in the pyrimidine ring.



2-Cyano-3,4-dihydro-4-oxoquinazoline

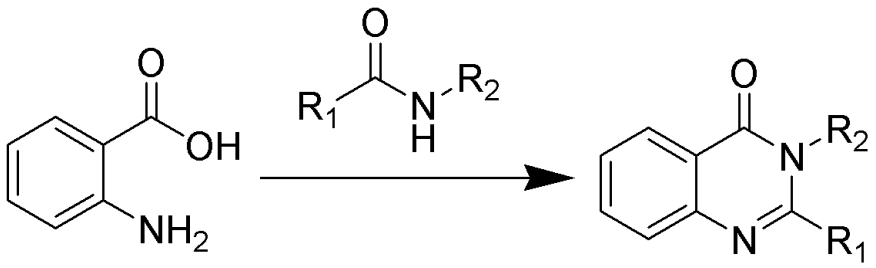
Chemical Properties of Quinazolines

- The chemistry of quinazoline was reviewed by Williamson in 1957 and then by Lindquist in 1959 and brought up to date by Armarego in 1963.
- Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. O-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.
- Synthesis of Quinazoline Compounds.
- Various methods were reported for the synthesis of oxoquinazolinesaci. Niementowski's Synthesis.
- Compound 3 or 4-substituted anthranilic acid when reacted with formamide at 125–130°C gave 3,4-dihydro-4-oxoquinazoline.

SYNTHESIS OF QUINAZOLINE COMPOUNDS

Various methods were reported for the synthesis of oxoquinazolines.

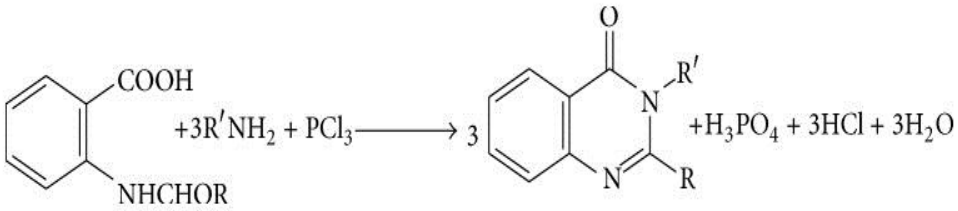
1. Niementowski'sSynthesis



Compound 3 or 4-substituted anthranilic acid when reacted with formamide at 125–130°C gave 3,4-dihydro-4-oxoquinazoline.

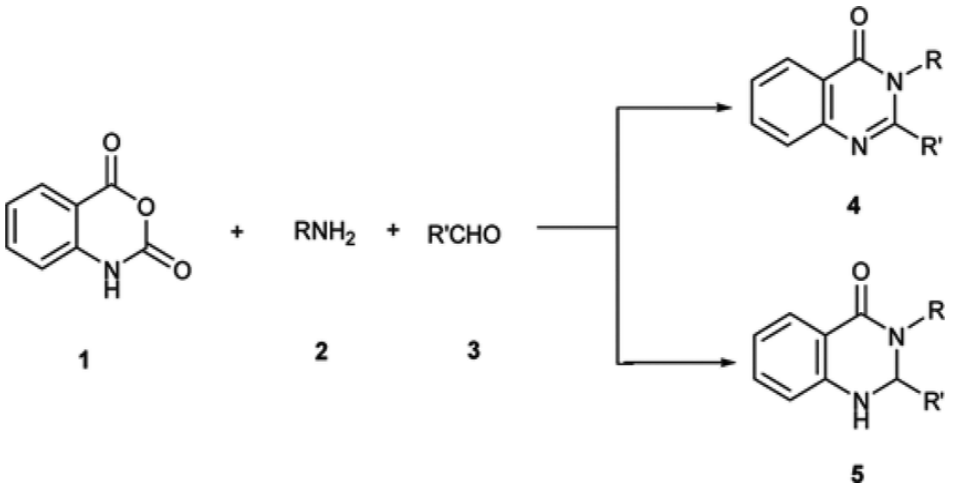
2. Grimmel, Guinther, and Morgan's Synthesis

The o-amino benzoic acids, when heated with an amine together with phosphorous trichloride in toluene for two hours, gave 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines.

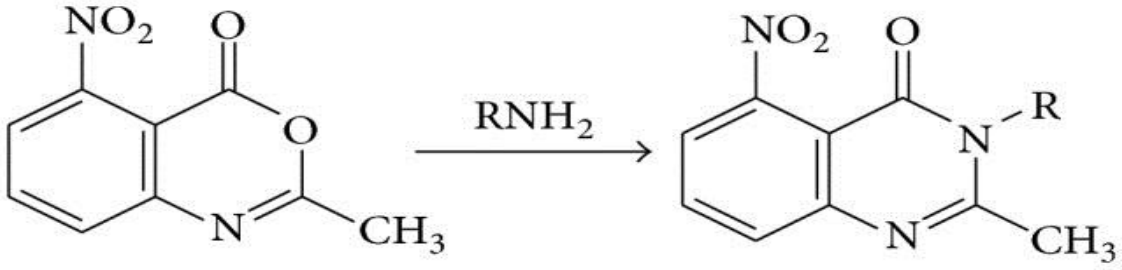


3. From Isatoic Anhydride

Isatoic anhydride was readily reacted with amines to dihydro-4-oxoquinazolines by refluxing ethyl orthoformate for 1–6 hrs without isolating the intermediate amides

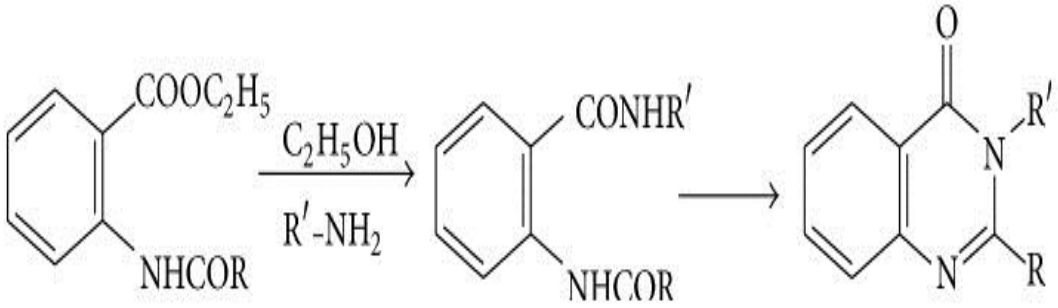


4. From 3,1,4-Benoxazones (Acylanthranils) and Amines



Benoxazones react with amines to give 3,4-dihydro-4-oxoquinazolines. Primary aliphatic amines and anilines react with 2-methyl-5-nitro-4-oxoquinazolines (see.

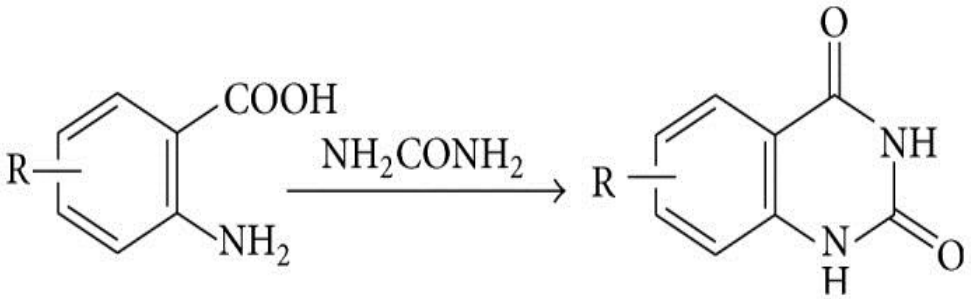
5.From Ethyl 2-Acetamido-5-nitrobenzoate



Ethyl 2-acetamido-5-nitrobenzene and alcoholic ammonia when heated gave 3,4-dihydro-methyl-6-nitro-4-oxoquinazoline (see Scheme 12).

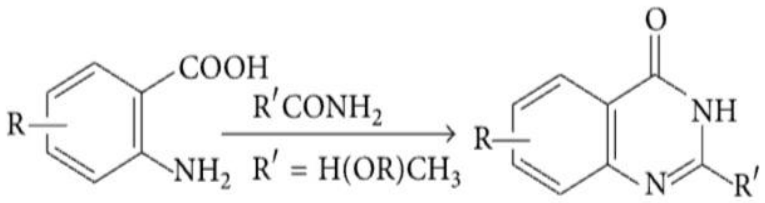
6. Sen and Ray's Synthesis

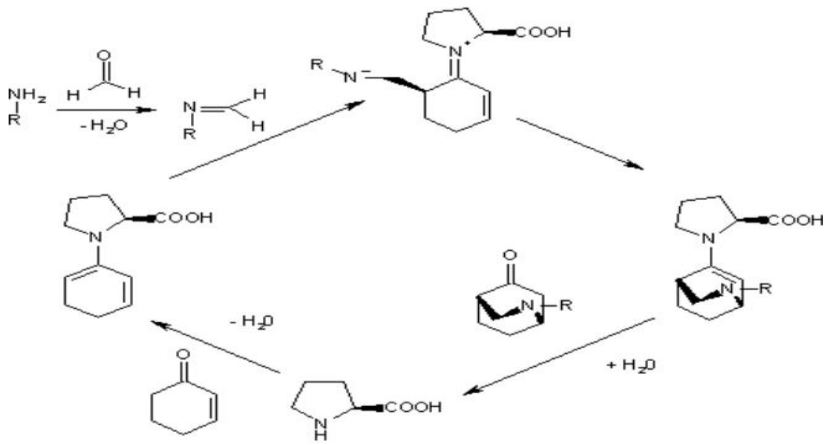
Boiling a solution of normal or isobutyrylanilides with urethane and phosphorous pentoxide in xylene gave 2-propyl and 2-isopropyl-3,4-dihydro-4-oxoquinazolines.



Synthetic methods

Aza-Diels-Alder reaction





The aza-Diels–Alder reaction converts imines and dienes to tetrahydropyridines. This organic reaction is a modification of the Diels–Alder reaction. The nitrogen atom can be part of the diene or the dienophile.

OBJECTIVES

activities of quinazolinone and quinazoline derivatives

Subsequently the innovation of quinazoline ring numeral of structural modifications have been made in order to raise the biological activities such as antitubercular, antihistaminic, analgesic, anticonvulsant, antibacterial, antifungal, and anti-inflammatory activity which attracted the interest of medicinal chemists.

CHEMICAL PROPERTIES OF QUINAZOLINES

The chemistry of quinazoline was reviewed by Williamson in 1957 and then by Lindquist in 1959 and brought up to date by Armarego in 1963.

Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. O-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.

Hydrolysis, Oxidation, and Reduction

Oxidation of quinazoline in dilute aqueous acid with two equivalents of hydrogen peroxide at room temperature gave 3,4-dihydro-4-oxo quinazoline. In alkaline medium, the anhydrous neutral species of quinazoline were predominantly undergo oxidation with $KMnO_4$ and yielded 3,4-dihydro-6 4-oxo quinazoline.

Oxidation

Catalytic hydrogenation of quinazoline stopped after the absorption of one molecule of hydrogen and gave 3,4-dihydro quinazoline.

Reduction;

Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4-tetrahydroquinazoline.

Nucleophilic and Electrophilic Substitution Reactions; The two known nucleophilic substitution reactions of quinazoline are sodamide and hydrazine most probably proceed via the intermediate addition products, and gave 4-amino and 4-hydrazine quinazoline.

Electrophilic Substitution Reaction of Quinazoline

Nitration is the only known electrophilic substitution reaction of quinazoline. The expected order of reactivity is at positions 8 > 6 > 5 > 7 > 4 > 2. Quinazoline gives 6-nitroquinazoline with fuming nitric acid in concentrated H_2SO_4. No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present.

Alkylation Reactions

Alkylation of quinazoline takes place on N atom, 3-methyl, 3-ethyl-3-alkyl, and 3-benzylquinazolinium salts that readily take up a molecule of alcohol to form the corresponding 4-alkoxy-3-alkyl-3,4-dihydro quinazolinium salts. These salts gave the pseudo bases, 3-alkyl-3,4-dihydro-4-hydroxy quinazolines on treatment with strong alkali.

Addition Reactions

Quinazoline is highly reactive towards anionic reagents which attack on position 4. Sodium bisulphate, hydrogen cyanide, acetone, 2-butanone, acetophenone, and cyclohexanone add across the 3,4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl, and phenyl magnesium halides and phenyl lithium also add across the 3,4-double bond to give the corresponding 4-substituted 3,4-dihydroquinazolines.

CONCLUSIONS

Over the past few decades, more effort has been established into searching of better drugs with minimal side effects. Herein number versatile synthetic procedures are discussed for the synthesis of quinazolinone and quinazoline derivatives. In general, quinazolinone and quinazoline derivatives are known to possess wide range of activities .There is possibility for further development as new research into study of medicinal chemistry related field. The various structural modifications around the fused ring of quinazoline and quinazolinone subsequently evaluate are for their usefulness in treating various disease conditions. Quinazoline and quinazolinone, being the central body of the pharmacophore, hold different types of substituent. Based on their various physicochemical properties, they exerted a diversified range of therapeutic efficacy. Thus we can conclude that this review will definitely provide the researchers with a thorough understanding of the structure activity relationship study, which further helps in designing good large number of quinazoline and quinazolinone compounds with a strong impact in curing many fatal disorders.

BIOLOGICAL IMPORTANCE OF QUINAZOLINE DERIVATIVES

The quinazoline and quinazolinone skeleton is frequently encountered in medicinal chemistry. The various substituted quinazolines and quinazolinones are having significant antihypertensive, antineoplastic, antidepressant, and antipsychotic activities whereas some derivatives of quinazoline and quinazolinones are found to be effective agents such as analgesic, antipsychotic, antiarrhythmic, sedative hypnotics, antibacterial, anti-inflammatory, antifungal, antimalarial, anticonvulsant, anticoccidial, anti-Parkinsonism, cancer and other activities.

- **WORK ACTIVITIES COMPLETED;** Anti-bacterial, analgesic, anti-microbial, anti-inflammatory, anticancer, and anti-hypertensive ,antifungal, anti-HIV, antioxidant, analgesic, anticonvulsant, antimalaria.

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