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A Short Review on Quinazoline Heterocycle

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ABSTRACT: Quinazoline is a heterocyclic compound with 2 nitro group present in its structure. Quinazoline gives over 200 biological activity like antimicrobial, antimalarial, analgesic, anti HIV, antitumour, antitussive, anti-inflammatory etc. This review article provides you in short the knowledge about the quinazoline heterocycle. Some of the methods used for synthesis of quinazoline are been incorporated in this article. The marketed drugs containing quinazoline nucleus are been incorporated in this article.

KEYWORDS: Quinazoline, anti tubular, antifungal, antibacterial, antimalarial, antitubercular.

I. INTRODUCTION

Quinazolines are classes of fused heterocycles that are of considerable interest because of their diverse pharmacological profile.⁽¹⁾ Quinazoline attract the scientists since 1888, with the discovery of the first natural representative of them - (+)-peganine (vasicine).⁽²⁻⁴⁾ Quinazoline has become a well-liked topic up of two fused six-membered simple aromatic system, a pyrimidine ring and a benzene ring due to its manifold uses.

Numerous quinazoline moieties have been found to possess a broad spectrum of pharmacological activities, which encouraged the research activity in this area.

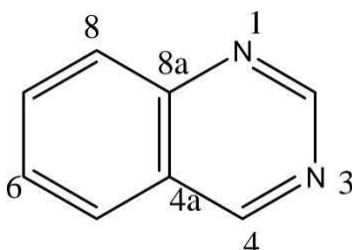


Figure 1. Chemical structure of quinazoline

The development of research on biological activity of quinazoline compounds started when the compound 2-methyl-1,3-aryl-4-quinazoline derivative was synthesized. This compound has soporific & sedative action. In last 10 to 15 years of research for medicinal has been characterized by significant advances. In 1968 only two derivatives were used, soporific & anticonvulsant- methaqualone and diuretic quinathazone. By 1980, about 50 kinds of derivatives of this class includes medicinal with different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, antiallergic, bronchodilating, antidiabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal etc. The search for substance of cardiovascular agents began in quinazoline derivatives after pharmacological screening of hypotensive activity of quinazoline that have a glycine amide or β -alanine amide residue in 3rd position. But unfortunately due to volume & density of general material on quinazoline derivatives, more specific problem of investigation of cardiovascular agents not has been successfully reflected in some reviews.⁽⁵⁻¹⁰⁾

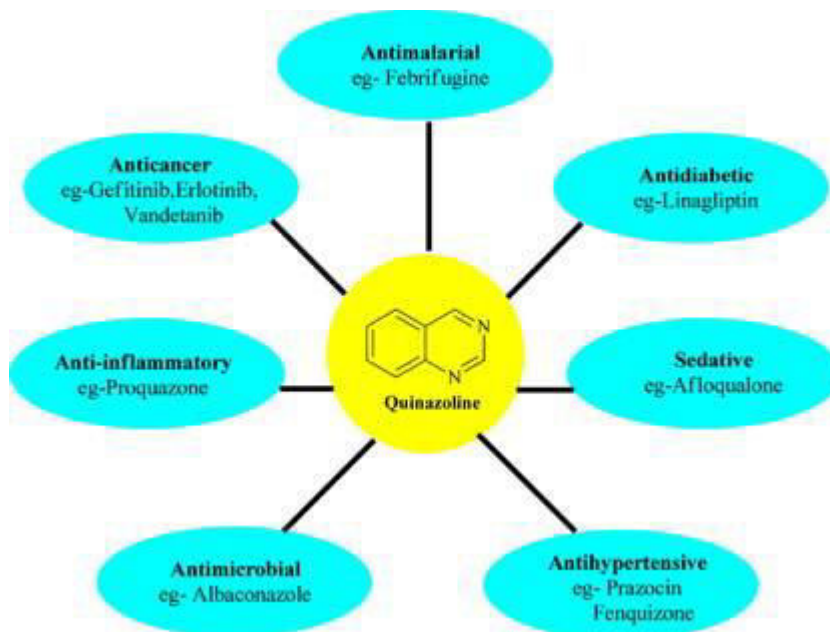


Figure 2. Application of Quinazoline

II. GENERAL STRUCTURE

Quinazoline is an organic heterocyclic compound having molecular formula $C_8H_6N_2$. Quinazoline is a yellow color solid which is crystalline in nature and also has solubility in water. Quinazoline is made from fusion of benzene and pyrimidine ring. The presence of fused benzene ring affects the properties of pyrimidine ring. The presence of two nitrogen atoms in quinazoline are not equivalent. Scientists got attracted by quinazoline alkaloids since 1888 with the discovery of (\pm)peganine (vasicine).⁽¹⁰⁾

Source

Quinazoline is Alkaloid compound. It derived from plant and animal source. Quinazoline is obtained from family Rutaceae. Quinazoline alkaloid contains arberine, vasicune, Febrifugine, glycosmihine, glycorine, hemoglomerine, glomerine etc. Febrifugine acts as antimalarial agent. Vasicine stimulate uterian. Vasicine isolate from *Adhatoda vasica*. They present in various parts of plant like leaf roots, stem, bark and obtained from animal also.

History

The first quinazoline derivative, 2-cyano-3,4-dihydro-4-oxoquinazoline was been prepared Griess in 1869, by reacting cyanogens with anthranilic acid. The bicyclic product was called bicyanoamido benzoyl and used this name until 1885. The preparation of the quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative. In 1903 Gabriel gave a more better method of synthesis. Other names which are used are phenmiazine, benzyleneamidine, benzo-1,3- diazine, 5,6-benzopyrimidine, and 1,3-diazanaphthaline.⁽¹¹⁻¹⁴⁾

Chemical properties

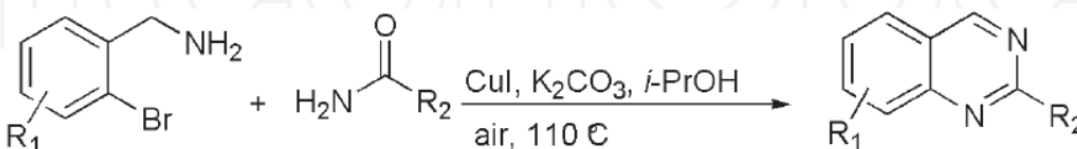
Williamson in 1957 derived the chemistry of quinazoline. In 1956 Lindquist found chemistry of quinazoline. Quinazoline is soluble in water. It stable in cold acid or cold dilute alkaline solution but it destroy when the solution is boiled. Oxidation of quinazoline is stopped after consumption of one molecule of hydrogen to give 3,4 dihydro quinazoline. Reduction of quinazoline is done with sodium amalgum to give 1,2,3,4 tetrahydro quinazoline. Lithium aluminium hydride and sodium hydride to give 3,4 dihydro or 1,2,3,4 tetrahydro quinazoline. It undergoes reaction like oxidation reaction, reduction reaction, nucleophilic reaction and electrophilic substitution reaction, alkylation and addition reaction.

Electrophilic substitution reaction of quinazoline in it migration process depends upon reactivity order of quinazoline is $8 > 6 > 5 > 7 > 4 > 2$

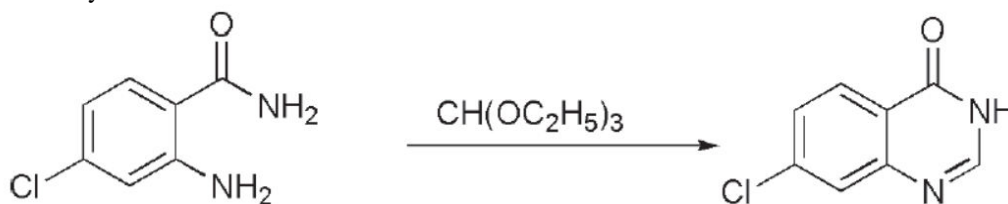
Addition reaction is more reactive about anionic reagent attack on fourth position.⁽¹⁴⁾

Synthesis

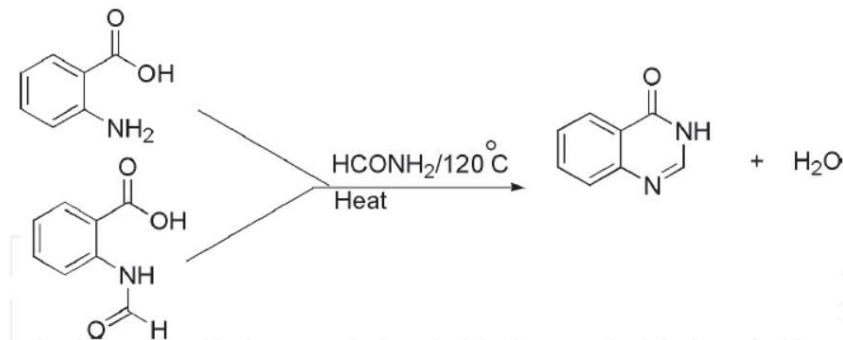
1. Anthranilic acid or formyl anthranilamide were used to synthesis 4(3H)-quinazolinone. ⁽¹⁵⁾



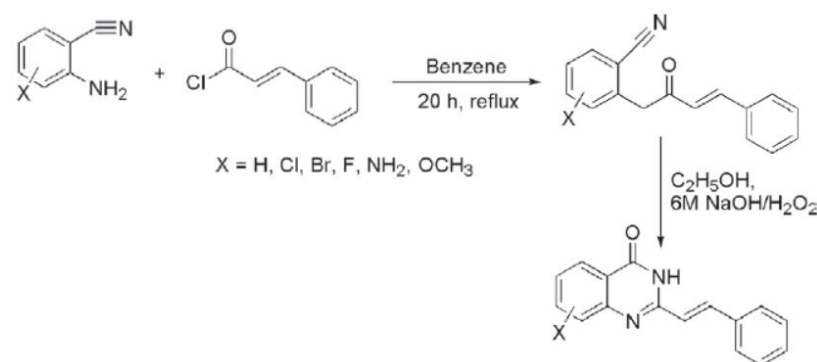
2. The 7-chloro-substituted derivative has been prepared via condensation reaction of 4-chloroanthranilic acid amide with triethyl orthoformate. ⁽¹⁶⁾



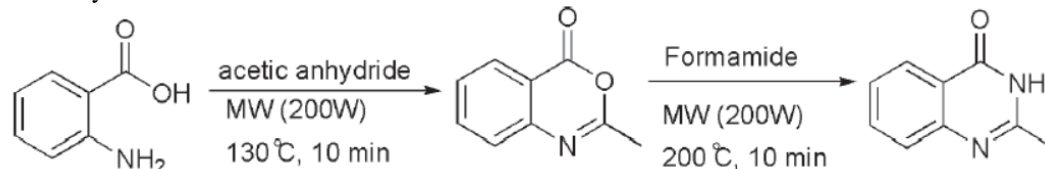
3. The reaction of anthranilic acid with excess formamide at 120°C in an open air gave Quinazolin-4(3H)-one. This is also known as Niementowski reaction. ⁽¹⁷⁾



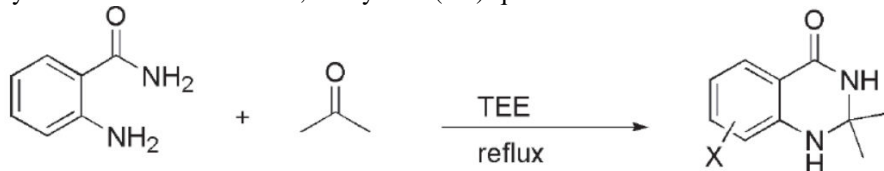
4. 2-styryl-4(3H)-quinazolinone derivatives were prepared using starting substrate 2-aminobenzonitrile with 3-phenyl cinnamoyl chloride. Under alkaline conditions, intramolecular cyclization of cinnamamide derivative was carried out to afford 2-styryl-4(3H)-quinazolinone. This procedure was tolerated to a wide range of different substituted benzene rings. ⁽¹⁸⁾



5. 2-substituted-4(3H)-quinazolinones products was synthesized by reacting anthranilic acid with ammonium acetate, followed by formamide under microwave at 200 W. ⁽¹⁹⁾

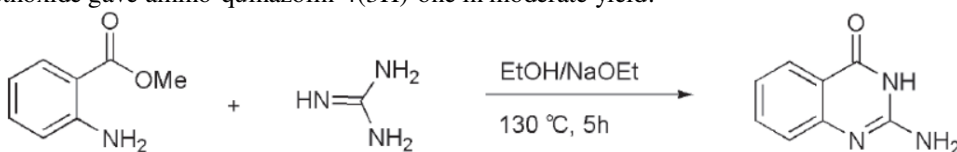


6. Under reflux condition Reaction of anthranilamide with substituted aldehydes or ketones in 2,2,2-trifluoroethanol synthesized 2-substituted- 2,3-dihydro-4(1H)-quinazolinone. ⁽²⁰⁾

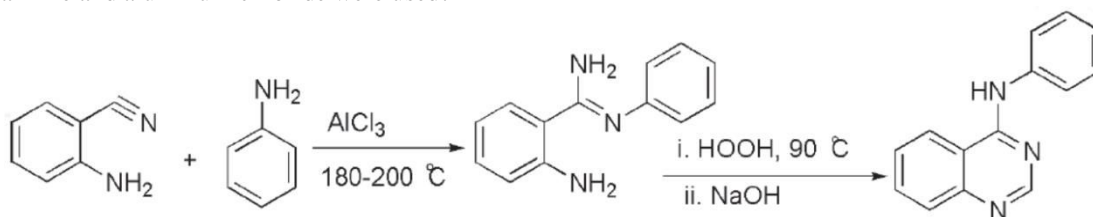


2,2,2-Trifluoroethanol = TEE

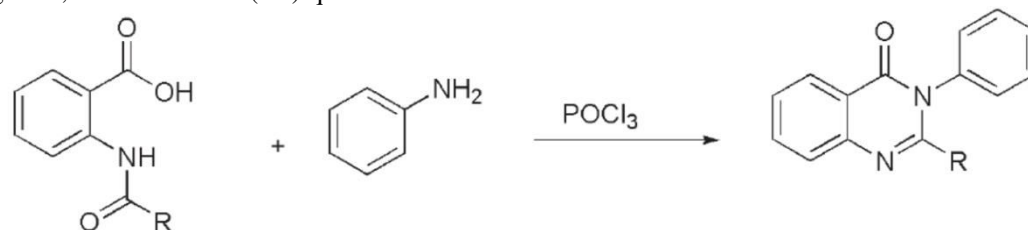
7. The reaction of the methyl anthranilate with an excess amount of guanidine in ethyl alcohol containing sodium ethoxide gave amino-quinazolin-4(3H)-one in moderate yield. ⁽²¹⁾



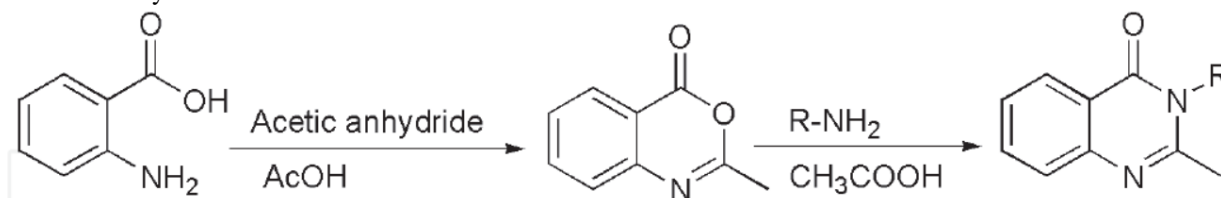
8. The reaction of 2-aminobenzonitrile with different substituted anilines and anhydrous aluminum chloride, amidines were readily produced. Highest yield of the amidine intermediates was obtained, when excess amounts of suitable aniline and aluminum chloride were used. ⁽²²⁾



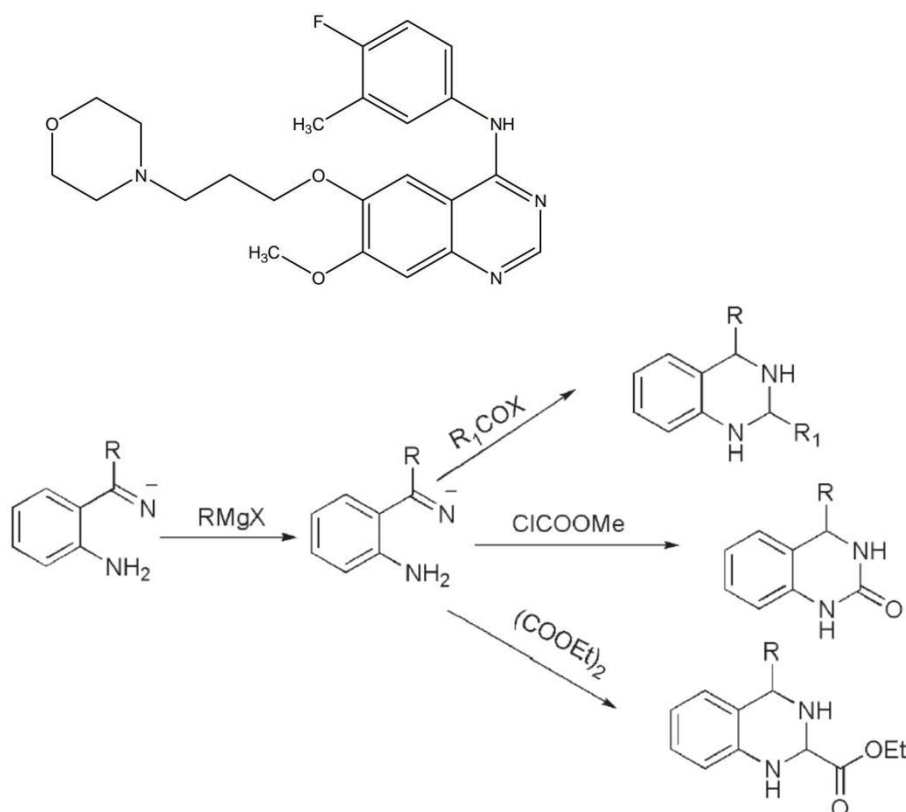
9. The reaction of N-acylanthranilic acid with the appropriate aryl amines in the presence of phosphorous oxychloride gave 2,3-disubstituted-4(3H)-quinazolinone derivatives. ⁽²³⁾



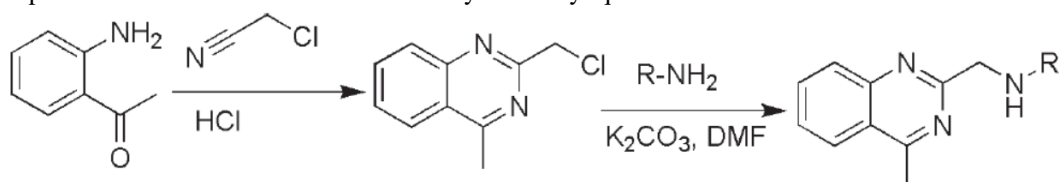
10. Benzoxazinone derivatives are the most widespread intermediates in the formation of 2,3-disubstituted quinazolinone derivatives. 2-methyl-4Hbenzo[d][1,3]oxazin-4-one was prepared by refluxing mixture of anthranilic acid with acetic anhydride in acetic acid. ⁽²⁴⁾



11. The reaction of 2-aminobenzonitrile with Grignard reagents yields the intermediates. The produced intermediate derivatives were very significant for getting many types of quinazoline derivatives. Upon their cyclization with acid chlorides, anhydrides, and formates, they formed the corresponding quinazoline derivatives in moderate to good yields. This general method for the preparation of various 2,4-disubstituted quinazoline derivatives is highly flexible and useful. ⁽²⁵⁾



12. As shown in the scheme 2-chloromethyl-4-methyl-quinazoline derivatives were synthesized by the reaction 1-(2-amino-phenyl)-ethanone with HCl gas in anhydrous condition in presence of chloro acetonitrile to get 2-chloromethyl-4-methyl-quinazoline. Subsequently treatment of 2-chloromethyl-4-methyl-quinazoline with different amine derivative in presence of base furnished 2-chloromethyl-4-methyl-quinazoline derivatives. ⁽²⁵⁾



Some marketed drugs containing Quinazoline ⁽²⁶⁾

a) Prazosin

Is also called as 2-(4-(2-furoxyl piperazine-1-yl)-6,7-dimethoxyquinazolin-4-amine). This drug used in treatment of high blood pressure.

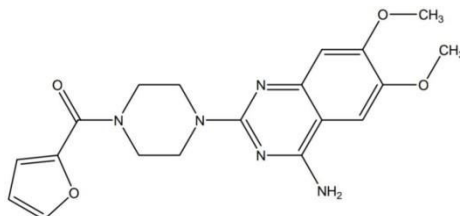


Figure 3. Prazosin

b) Erlotinib

N-(3-ethylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine is chemical name of erlotinib. This drug use to cure non small cell lung, pancreatic cancer and many cancers.

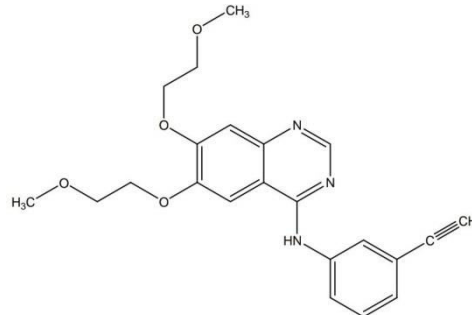


Figure 4. Erlotinib

c) Tetrodotoxin

Zombie powered or tetrode is name of tetrodox. It's chemical name is (4R,4a,5R,6s,7s,8s,R,10s,12s)2azanumylidenes 4,6,8,1,tetrahydroxy 6 (hydroxymethyl 2,3,4,4a,5,6,7,8 octahydroquinazoline.

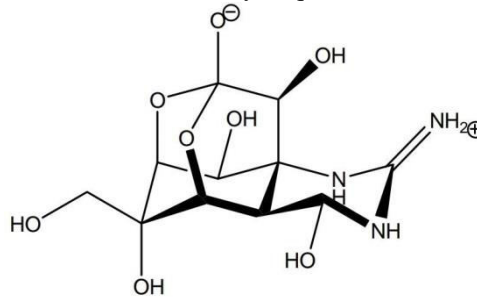


Figure 5. Tetrodotoxin

d) Alfuzosine

N-3(4amino 6,7 dimethoxy quinazoline-2yl-methyl amino propyl is chemical name of alfuzosine. This is alfa - antagonist. It is use in treatment of prostatic hyperplasia.

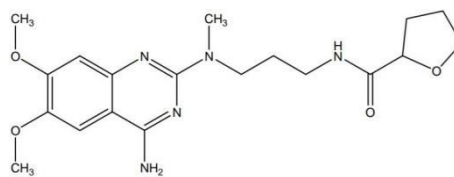


Figure. 6 Alfuzosin

e) Trimetrexate

They are non classical folic acid inhibitor enzyme and chemical name is 6(3,4,5 trimethyle)amino methyl quinozoline2,4diamine.

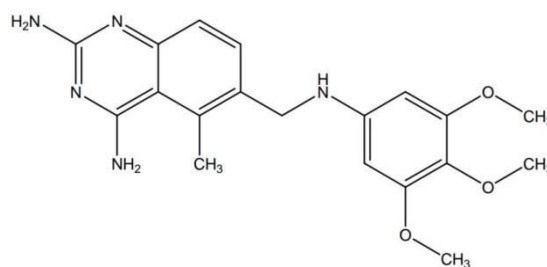
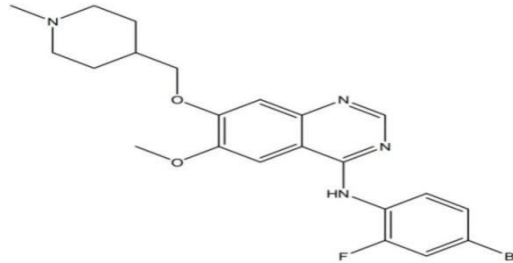


Figure 7 Trimetrexate



f) Vandetanib

Zactima is name of Vandetanib. Its chemical name is N(4 bromo -2 fluorophenyl 6 methoxy-7(1 methyl piperidine-4yl) methoxy quinazoline-4- amine .

Figure 8 Vandetanib

g) Bunazosin

Andante is tread name of 1-4(4amino6,7dimethoxy quinazoline-2yl-methyl - 2yl)1,4 diazepan -1 yl is chemical name of bunazosin. It is used to treat glucoma and prostatic hyperplasia.

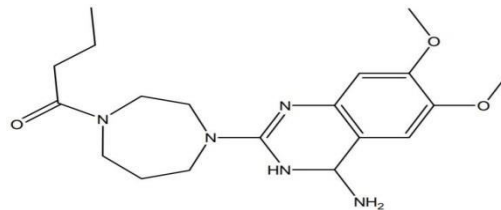


Figure 9. Bunazosin

h) Anagrelide

Agryline is brand name of anagrelide or xagrid , anagride. Chronic myeloid leukemia is treated by anagrilide. It's chemical name 6,7dichlori1,5dihydro imidazole (2,1,b)phenyl -3hydroxyl 4)1,2,4triazole-1ylbutan-2ylquinazoline-4 one. It's imgives antibacterialactivity.

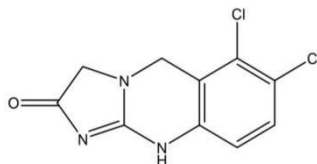


Figure 10. Anagrelide

j) Afloqualone

Chemical name is name isarofuto,6 amino-2fluoronethyl3,2methyl phenyl quinazoline 4-one. It gives not only sedative effect but also give relaxant effect.

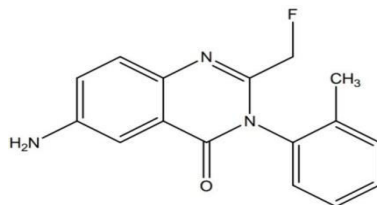


Figure 11. Afloqualone

k) Fenquizone

It's not only used to treat oedema but also treat to hypertension. It's chemical name 7- chloro-4oxo-2phenyl 1,2,3,4 tetrahydroquinazoline 6-sulfonamide.

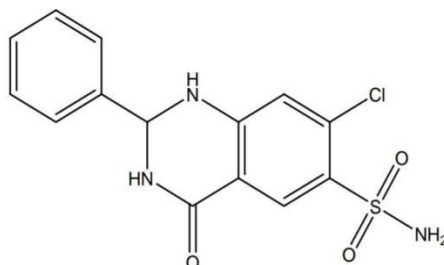


Figure 12. Fenquizone

III. CONCLUSION

Heterocyclic derivatives containing quinazoline ring have a more important role in medicinal chemistry. There are some marketed containing Quinazoline nucleus shows different pharmacological activities. These are very important class of drug. The next generation for quinazoline derivative drug shows better result.

IV. ACKNOWLEDGEMENT

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