Kurdistan Regional Government- Iraq

Ministry of Higher Education & Scientific Research

Salahaddin University–Erbil (SUE)

College of Science

Department of Chemistry

Chemistry and biological activity of Quinazoline and its derivatives

A project submitted to the scientific committee in the chemistry department in partial fulfillment of the requirement for the degree of bachelor science in Chemistry

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M.SC. Naween M

April, 2023 **Nowruz, 2723** **Ramadan, 1444**

Acknowledgement

First, I want thanks my God that letting me through all the difficulties .and I would also thanks my family and all of them that helped me .

And I have a special thanks for my supervised (M.SC. Naween M) to guide and advise me step by step to complete my project .

And I am very happy with my first project and I hope that this project will be a useful begin to success in other future project in my life.

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Abstract

Quinazoline is a compound made up of two fused six member simple aromatic rings- benzene & pyrimidine ring. Its chemical formula is C8H6N2. It is yellow colour and found in the crystalline form. Molecular optimization of potentially lead compounds through a chemist is a needy and upcoming approach for the discovery of new pharmaceuticals.

In medicinal chemistry, one of the most significant heterocyclic compounds are quinazolines, possessing broad range of biological properties such as anti-bacterial, anti-fungal, anti-HIV, anti-cancer, anti-inflammatory, and analgesic potencies. Owing to its numerous potential applications, in the past two decades, there is an increase in the importance of designing novel quinazolines,

Keywords: quinazoline, biological activities, quinazoline derivative, Synthesis

1.Introduction

Quinazoline derivatives are among the most significant families of heterocyclic. Quinazoline (1,3-diazanaphthalene; 1) is a moiety made up of two condensed six-membered aromatic rings,a pyrimidine ring, and a benzene ring, . It is yellow and amorphous, and its molar mass is 130.15 g.mol−1, and the chemical formula is C8H6N2. On the basis of various substitution patterns of nitrogen atoms, it is isomeric with quinoxaline 2, cinnoline 3, and pthalazine 4 (Figure 1). These isomeric forms are also called diazanaphthalenes. Analogs of this family, which contain a pyrazine ring and a benzene ring, are called Quinoxaline 2. These are also known as benzopyrazine. Cinnoline 3 also comprises a pyrazine ring and a benzene ring. Phthalazine 4 is also called benzopyridiazine or benzo-orthodiazine, which contains a benzene ring and a pyridiazine ring. Many substituted quinazoline derivatives possess an extensive range of biological activity such as anticancer, antimalarial, anticonvulsant, antiviral, antifungal, anti-protozoan, antimicrobial, anti-inflammatory, diuretic, muscle relaxant, antidepressant, anti-tubercular, acaricidal, weedicide, and many other pharmacological activities. Quinazoline compounds are also used in preparation of a variety of functional materials for synthetic medicinal chemistry and also present in many drugs molecules.

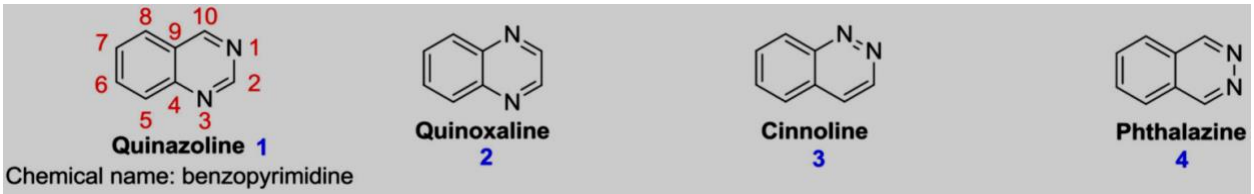
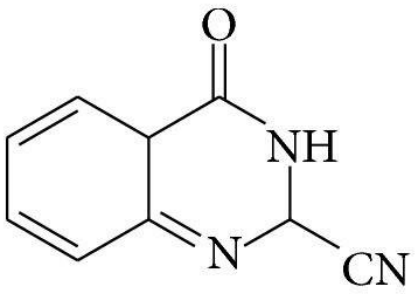


Figure 1 (Structure of quinazoline and its isomers)

1.2.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. 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 (Scheme 1).



Scheme 1 (structure of 2-cyano-3,4dihydro-4-oxoquinazolin)

2.Physical and chemical properties of quinazoline

Properties	
Chemical formula	$C_8H_6N_2$
Molar mass	130.150 g·mol^{-1}
Appearance	light yellow crystals
Density	1.351 g/cm^3, solid
Melting point	48 °C (118 °F; 321 K)
Boiling point	243 °C (469 °F; 516 K)
Solubility in water	Soluble
Acidity (pK_a)	3.51

Table 1 (properites of quinazoline)

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.

3.Source of Quinazoline

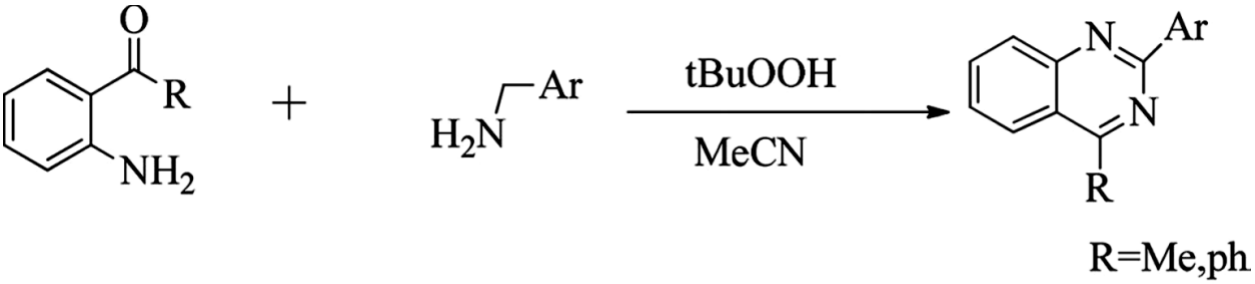
Quinazoline alkaloids can be found mainly in plants, such as acanthaceae (Adhatoda vasica), rutaceae, saxifragaceae (Dichroa febrifuga) and in linaria species (Scrophulariaceae) and peganum harmala (Zygophyllaceae); also in animals (e. g. tetrodotoxin).

Figure 2 (quinazoline in peganum harmala)

4.Synthesis of quinazoline and quinazoline derivatives

4.1.Synthesis of 2-phenyl quinazolines

hydroperoxide in acetonitrile 2-aminobenzophenones and benzylic amines yields quinazoline derivatives (Scheme 2).

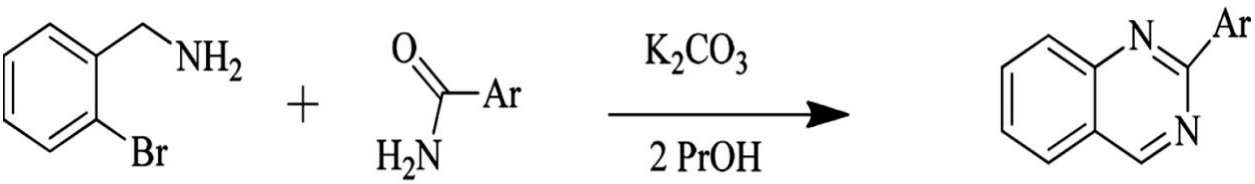


Synthesis of 2-phenyl quinazolines

Scheme 2(Synthesis of 2-phenyl quinazoline)

4.2.Synthesis of 2-aryl quinazoline

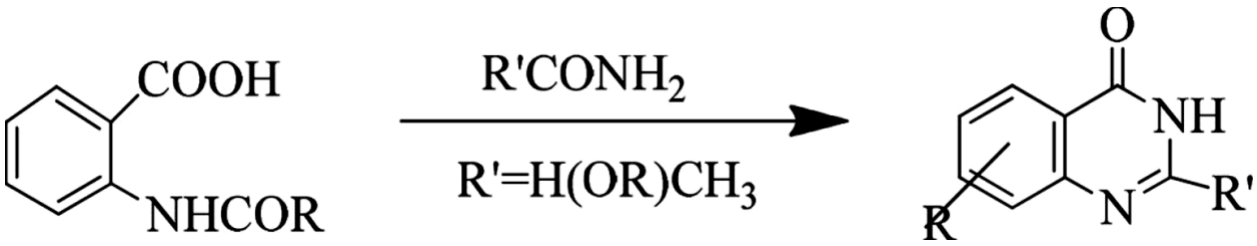
Quinazoline derivatives are prepared by reaction of 2-bromophenyl methyl amines and amindes catalyzed by ligand free copper (Scheme 3).



Scheme 3(Synthesis of 2-aryl quinazoline)

4.3.**Synthesis of 2,3-disubstituted 3,4-dihydro-4-oxo quinazoline**

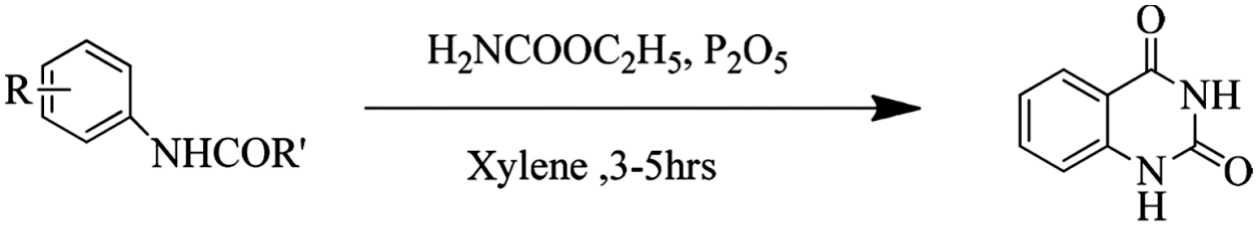
When 4-substituted anthranilic acid reacted with formamide at 125–130 °C gave 2,3-disubstituted 3,4-dihydro-4-oxo quinazoline [Niementowski's synthesis] (Scheme4).



Scheme 4(Synthesis of 2,3-disubstituted-3,4-dihydro-4 oxo quinazoli)

4.4.Synthesis of 2-propyl and 2-isopropyl-3,4-dihydro-4-oxo-quinazolines

If a solution of normal or isobutrylanilides is boiled with urethane and phosphorous pentoxide in xylene 2-propyl and 2-isopropyl-3,4-dihydro-4-oxo-quinazolines is obtained [Sen and Ray's synthesis] (Scheme 5).

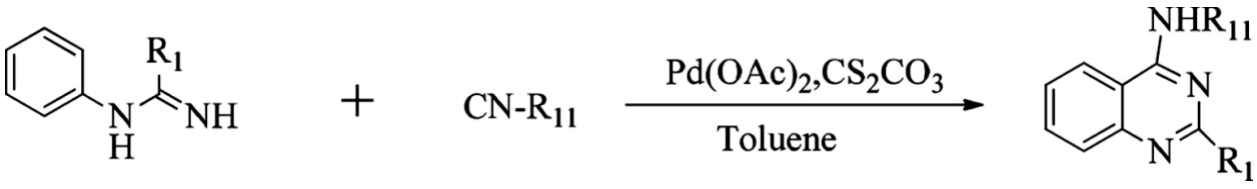


(R=Me,OMe,OEt;
R'=Me,Et,Pr,Iso-Pro,Ph)

Scheme 5(Synthesis of 2-isopropyl-3,4-dihydro-4-oxo-quinazoline)

4.5.Synthesis of 4-amino-2-aryl quinazolines

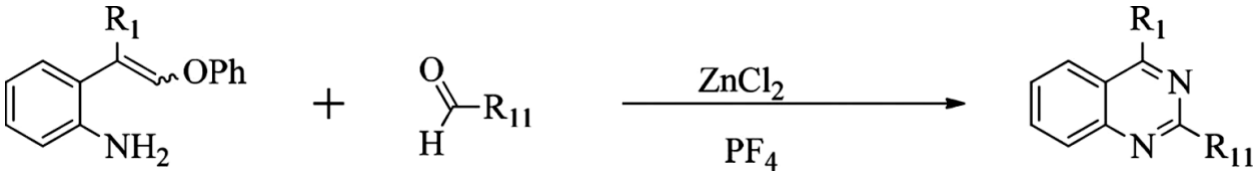
4-Amino-2-aryl quinazolines can be synthesized from isonitriles and N-aryl amidines by palladium-catalyzed intramolecular aryl C–H amidination by insertion of acetonitrile (Scheme 6).



Scheme 6(Synthesis of 4-amino-2-aryl quinazolines.)

4.6.Synthesis of functionalized Quinazoline

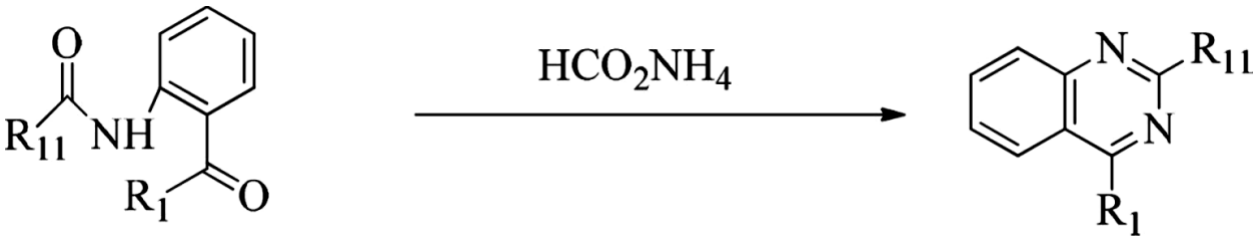
One efficient method of synthesis of functionalized quinazolines having no radicals is by microwave promoted reactions of *o*-phenyl oximes and aldehydes in presence of ZnCl2 (Scheme 7).



Scheme 7(Synthesis of functionalized Quinazoline having no radicals)

4.7.Synthesis of 2,4-disubstituted Quinazoline by microwave assisted cyclization

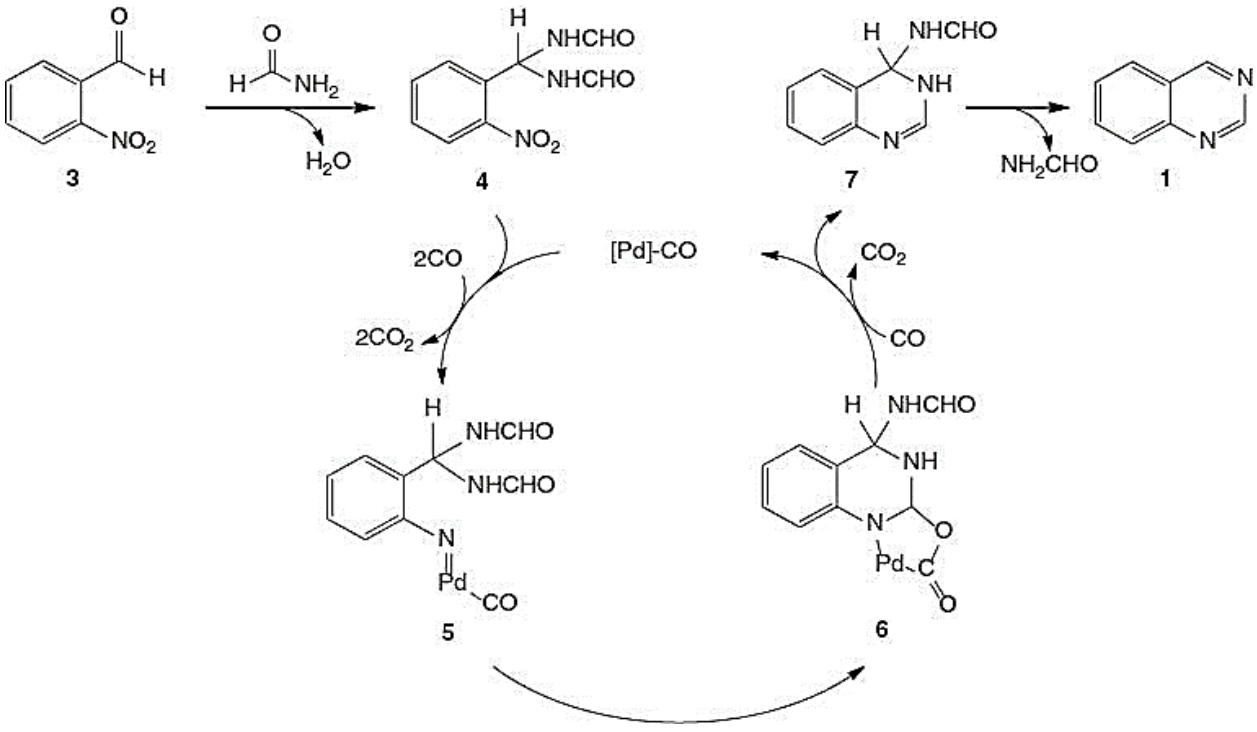
Synthesis of 2,4-disubstituted quinazolines can be done by fries rearrangement reactions of anilides that form derivatives of *o*-aminoacyl benzene which then acylated to form acylamides. Microwave assisted cyclization of acylamides in presence of ammonium formate gave 2,4-disubstituted quinazolines (Scheme 8).



Scheme 8(Synthesis of 2,4-disubstituted Quinazoline by microwave assisted cyclization)

4.8.Catalytic reductive N-heterocyclization of bis-amide using $PdCl_2(PPh_3)_2/MoCl_5$

The reductive *N*-heterocyclization mechanism for 1 is believed to start with the reaction between a carbonyl group of the 2-nitrobenzaldehyde 3 (R = H) and formamide to give the corresponding bis-amide 4 (Scheme 9). Then a nitrene intermediate 5 is generated by the deoxygenation of the nitro group by the reaction with carbon monoxide. Lewis acid $MoCl_5$ is coordinated with the oxygen atoms of the nitro group, which weaken the N-O bond and thereby assist the deoxygenation process. An intramolecular nucleophilic addition of the nitrene to the carbonyl group of the bis-amide followed by the generation of metallacyclic intermediate **6** and then the decarboxylation of **6** results in the formation of another intermediate product 7 and regeneration of the active catalyst.

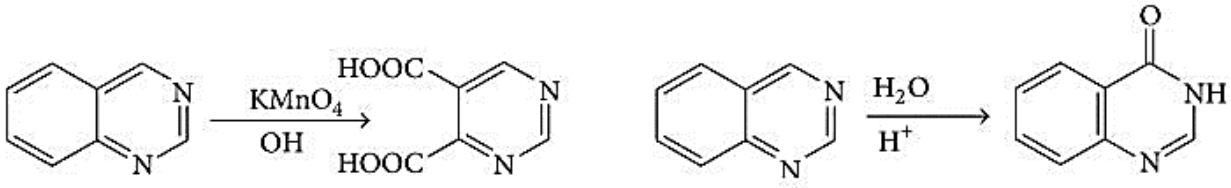


Scheme 9(Proposed mechanism for palladium-catalyzed synthesis of quinazoline)

5.Reactions of quinazoline

5.1.Oxidation

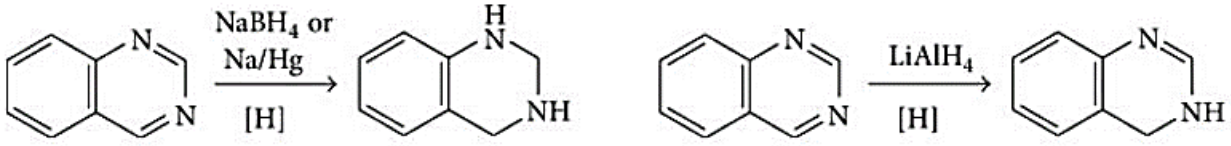
Catalytic hydrogenation of quinazoline stopped after the absorption of one molecule of hydrogen and gave 3,4-dihydro quinazoline (Scheme 10).



Scheme10 (oxidation of quinazoline)

5.2.Reduction

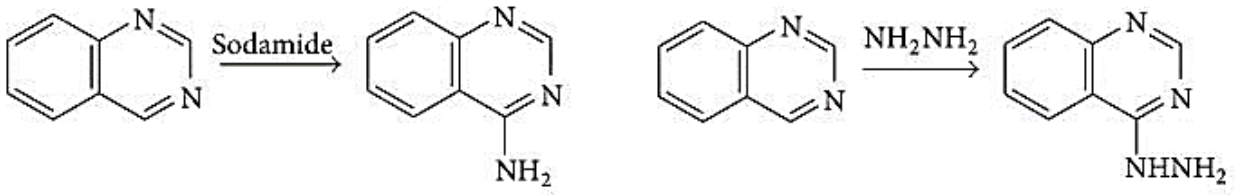
Reduction with sodium amalgam gave 1,2,3,4-tetrahydroquinazoline. Lithium aluminum hydride and sodium borohydride gave 3,4-dihydro and 1,2,3,4-tetrahydroquinazoline (Scheme 11).



Scheme 11 (reduction of quinazoline)

5.3.Nucleophilic and Electrophilic Substitution Reactions

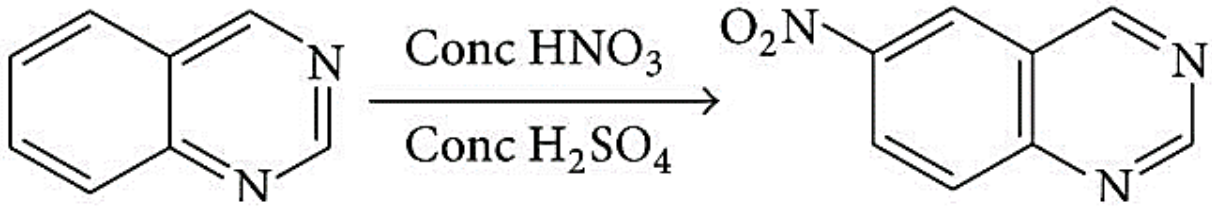
The two known nucleophilic substitution reactions of quinazoline are sodamide and hydrazine most probably proceed via the intermediate addition products, and gave 4-amino and 4- hydrazine quinazoline (Scheme 12).



Scheme 12(Nucleophilic and Electrophilic Substitution Reactions)

5.4.Electrophilic Substitution Reaction of Quinazolin

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 H2SO4.No oxidation of the heterocyclic ring can occur under these conditions because the hydrated cation is not present (Scheme 13).



Scheme 13(Electrophilic Substitution Reaction of Quinazolin)

6.biological activities of quinazoline

Quinazolines are classes of fused heterocycles that are of considerable interest because of their diverse pharmacological profile. Quinazoline has become a well-liked topic up of two fused six-membered simple aromatic systems, 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. Many substituted quinazoline derivatives possess an extensive range of biological activity such as anticancer, antimalarial, anticonvulsant, antiviral, antifungal, anti-protozoan, antimicrobial, anti-inflammatory, diuretic, muscle relaxant, antidepressant, anti-tubercular, acaricidal, weedicide, and many other pharmacological activities. Quinazoline compounds are also used in preparation of a variety of functional materials for synthetic medicinal chemistry and also present in many drugs molecules.

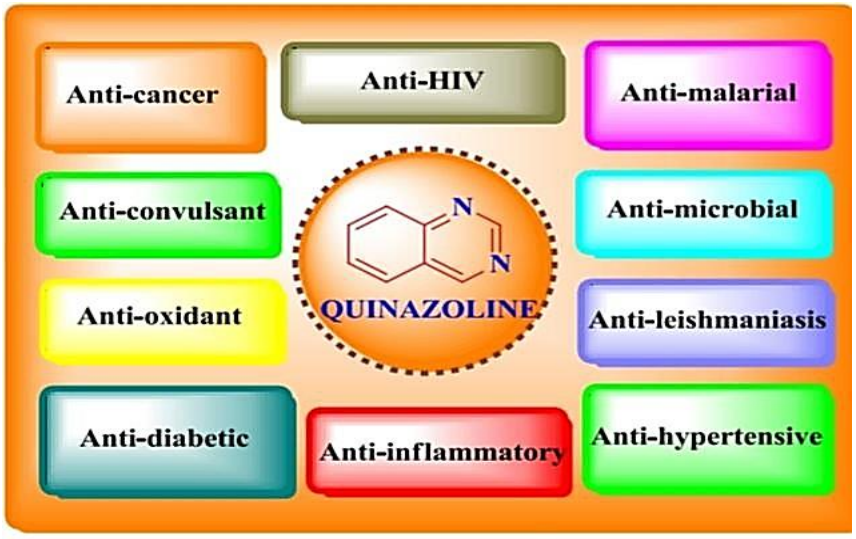
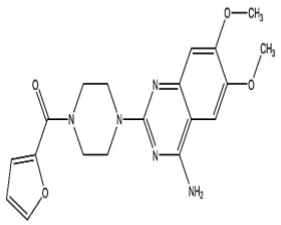


Figure3 (Biological profile of quinazoline scaffold)

7.Quinazoline Marketed drugs

7.1.Prazosin

Prazosin is chemically 2-[4-(2-furoyl) piperazin-1-yl]-6,7-dimethoxyquinazolin-4- amine Fig 4. It is a sympatholytic drug used to treat high blood pressure. It belongs to the class of alpha-adrenergic blockers, which lower blood pressure by relaxing blood vessels. It is also known as Minipress, Vasoflex , Pressin and Hypovase.



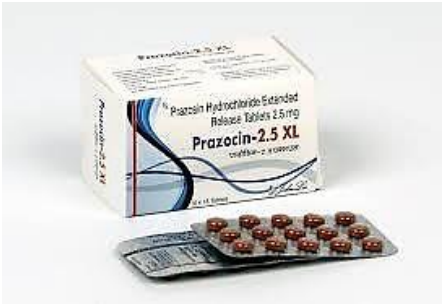


Fig 4 (Prazosin)

7.2.Febrifugine

Febrifugine (Fig 5) chemically known as 3-{3-[(2S,3R)-3-Hydroxypiperidin-2-yl]-2-oxo propyl} quinazolin-4(3H)-one is a quinazolinone alkaloid first isolated from Chinese herb Dichroa febrifuga, but also found in the garden plant Hydrangea. Febrifugine has antimalarial properties and the halogenated derivative halofuginone is used in veterinary medicine as a coccidiostat.

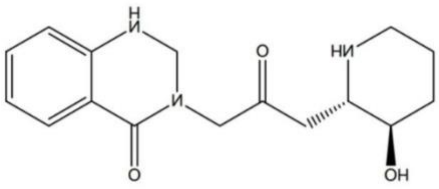


Figure5 (Febrifugine)

7.3.Gefitinib

Gefitinib Fig 6 also known as Iressa marketed by AstraZeneca and Teva. It is a drug used in the treatment of certain types of cancer. Gefitinib is an EGFR inhibitor (epidermal growth factor receptor) which interrupts signaling through the epidermal growth factor receptor in target cells. Gefitinib has yet to be proven to be effective in other cancers, there is potential for its use in the treatment of other cancers where EGFR over expression is involved. Chemically it is N-(3-chloro-4-fluoro-phenyl)-7- methoxy-6-(3-morpholin-4-ylpropoxy) quinazolin-4-amine.

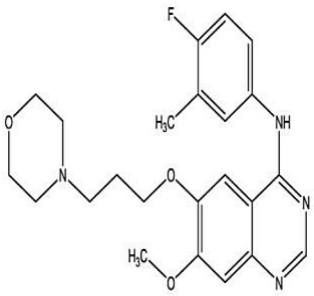
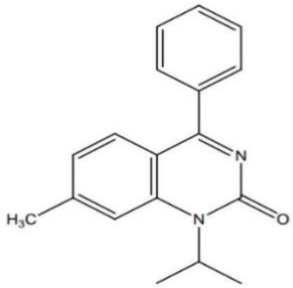


Figure 6(Gefitinib)

7.4.Proquazone

Its trade name is Biarison Fig 7 is chemically known as 1-isopropyl-7-methyl-4- phenylquinazolin-2(1H)-one. Proquazone is a non-steroidal anti-inflammatory drug.



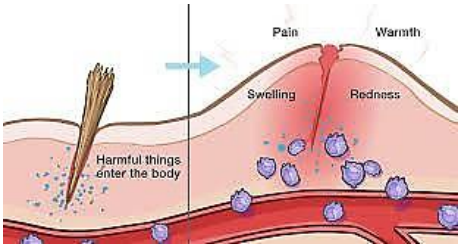
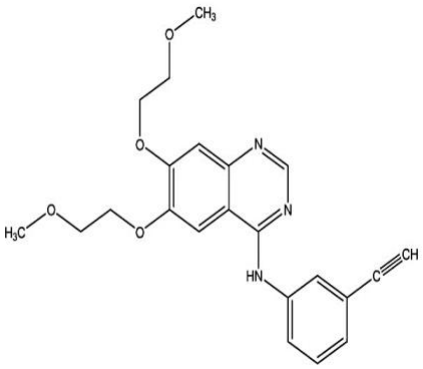


Figure7 (Proquazone)

7.5.Erlotinib

The trade name of Erlotinib Fig 8 is Tarceva and its chemically known as N-(3-ethynylphenyl)- 6,7-bis(2-methoxyethoxy) quinazolin-4-amine. It is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer.



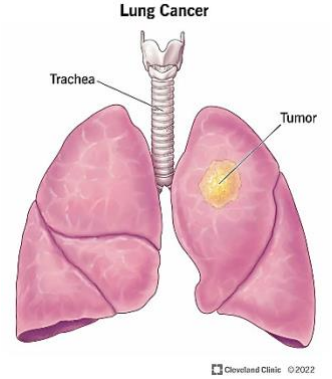
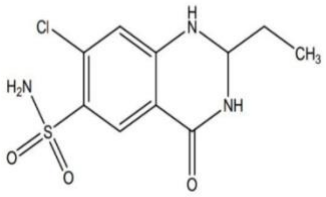


Figure 8(Erlotinib)

7.6.Quinethazone

Its brand name is Hydromox Fig 9 chemically known as 7-chloro-2-ethyl-4-oxo-1,2,3,4- tetrahydroquinazoline-6-sulfonamide. Quinethazone is a thiazide diuretic used to treat hypertension. Common side effects include dizziness, dry mouth, nausea, and low potassium levels.



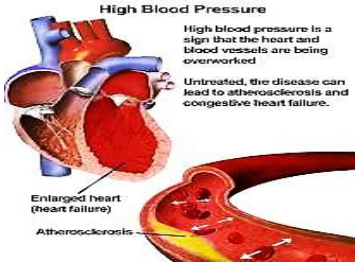


Figure9 (Quinethazone)

7.7.Alfuzosin

The trade name of alfuzosin Fig 10 are UroXatral; Urion; Xatral; Alfetim, chemically known as N- [3-[(4-amino-6,7-dimethoxy-quinazolin-2-yl)-methyl-amino]propyl] tetra- hydrofuran -2- carboxamide . It is a α1 receptor antagonist used to treat benign prostatic hyperplasia (BPH).

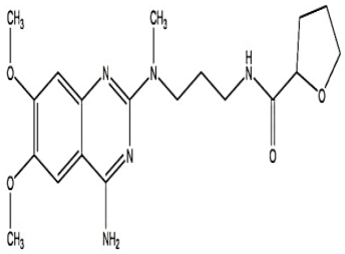
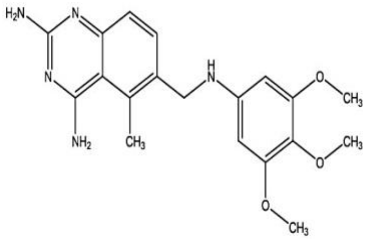


Fig 10(Alfuzosin)

7.8.Trimetrexate

Trimetrexate Fig 11 chemically known as 5-methyl-6-[(3,4,5-trimethoxyphenyl) aminomethyl] quinazoline-2,4-diamine, is a nonclassical folic acid inhibitor through its inhibition of the enzyme dihydrofolate reductase. It is being tested for efficacy as an antineoplastic agent and as an antiparasitic agent against pneumocystis pneumonia in AIDS patients.



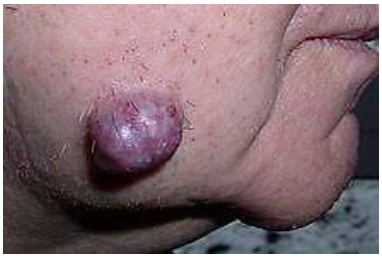


Fig 11(Trimetrexate)

8.Infrared spectroscopy of quinazoline

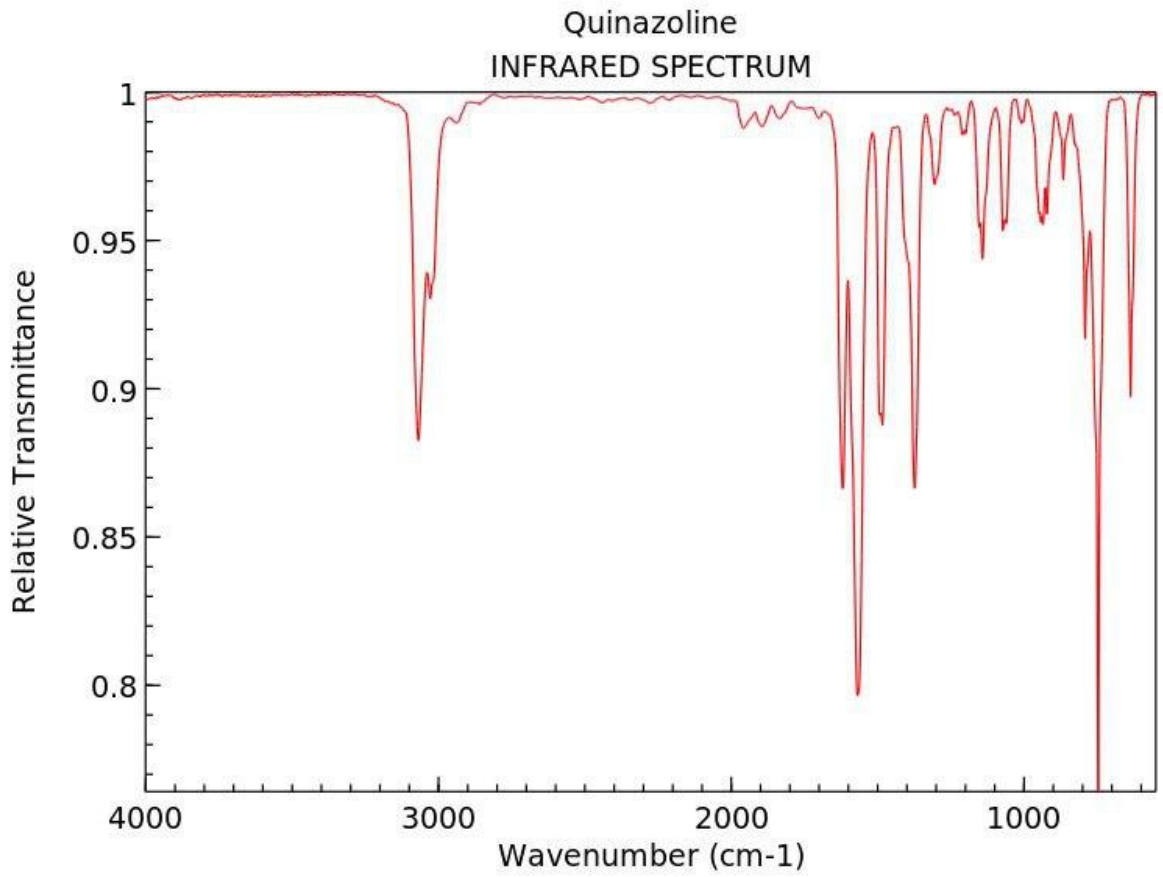


Figure 12 (Infrared spectroscopy of quinazoline)

9.Quinazoline H- NMR

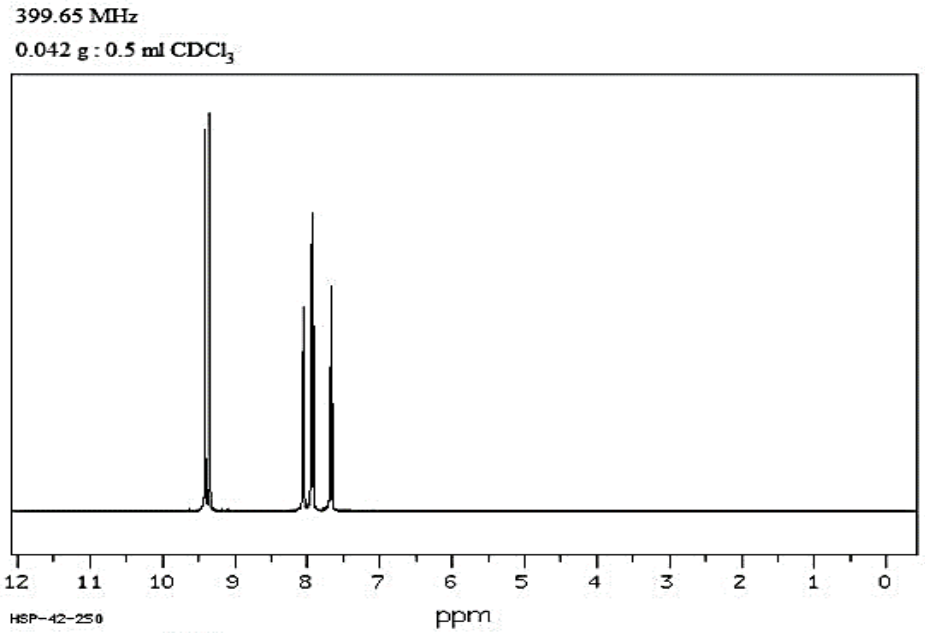


Figure 13 (Quinazoline H- NMR)

10.Conclusion

I can say one of the most hetrocyclic compound that have wide range application in different .quinazoline derivatives useful in pharmacological and biological activity. Many substituted quinazoline derivatives possess an extensive range of biological activity such as anticancer, antimalarial, anticonvulsant, antiviral, antifungal, anti-protozoan, antimicrobial, anti-inflammatory, diuretic, muscle relaxant, antidepressant, anti-tubercular, acaricidal, weedicide, and many other pharmacological activities,and are used to form a very important drug .quinazoline can be prepared in a laboratory by a different way and can be found in many palnt such as acanthaceae (Adhatoda vasica), rutaceae, saxifragaceae (Dichroa febrifuga) and in linaria species (Scrophulariaceae) and peganum harmala (Zygophyllaceae).I can say one of the most hetrocyclic compound that have wide range application in different field .

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زانکۆی سەلاحەدین –هەولێر

Salahaddin university - Erbil

کیمیا و چالاکیە بایۆلۆجیەکانی کوینازۆلین و لێوەرگیراوەکانی

پرۆژەی دەرچون :

پێشکەش بە بەشی کیمیایی کۆلێژی زانسی زانکۆی سەلاحەدین -هەولێر وەک بەشێک لە پێداویستیەکانی بەدەستهێنانی بڕوانامەی بەکالۆریۆس لە زانستی کیمیا

ئامادەکراوە لە لایەن

بێستون یوسف محمد حسین

بەسەرپەرشتی

م.نەوین مشیر یونس

نیسان ، ٢٠٢٣ **نەورۆز، ٢٧٢٣** **ڕەمەزان ،١٤٤٤**