Synthesis, pharmacological application of quinoxaline and its derivative

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***Abstract*: Quinoxaline is nitrogen containing heterocyclic ring which has benzene and pyrazine ring (benzopyrazine) Quinoxaline has the best nucleus which gives all types of biological activity and its derivative has wide range of application Quinoxaline and its derivatives has many applications in the pharmaceutical industry so it can be synthesised in various ways which described in this review Quinoxaline and its derivative use as an anti-cancer Anti-protozoal, anti-malarial, anti-viral, anti-inflammatory, anti-tuberculosis, and kinase inhibitor drugs are available. The synthesis of Quinoxaline, as well as its derivatives and applications, are covered in this review.**

***Keywords*: Quinoxaline, derivative, biologically application, use, synthesise, chemistry**

INTRODUCTION:

Synthesis of new drug is majorly done because of heterocyclic compound and their substitution .modification on heterocyclic compound show many biological activity.(1)

Quinoxaline derivatives exhibit a wide variety of application in dyes, fluorescent material, semiconductor in organic photovoltaic (opv) cells, insecticide, fungicides, herbicides, anthelmintic (2)

1),quinoxaline 2) phthalazine, 3) quinazoline, and cinnolenes are isomenes of quinoxaline.

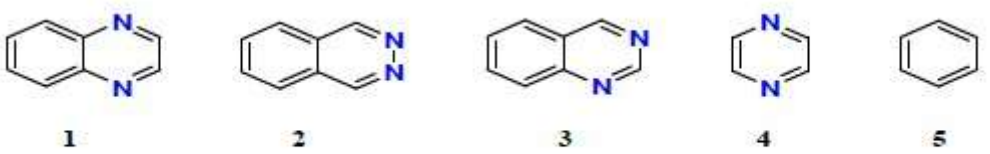


Figure. 1.0: Structures of quinoxaline and related heterocycles.

Quinoxaline is formed by fusion of diazine with benzene of ring

Benzopyrazine &diazanapthaleve are other names of quinoxaline (2)

Chemistry of quinoxaline:

Quinoxaline is a slightly weak, basic in nature, bicyclic compound basically called 1,4- diaza naphthalene or benzopyrazine contains a fused benzene and pyrazine ring.

Quinoxaline has a low melting point because of substitution that is a melting point equivalent to 27c. They are miscible with water. It is a white crystalline powder having the molecular formula C8H6N2. The The molecular weight of quinoxaline contains (3)

PREPARATION OF QUINOXALINE:

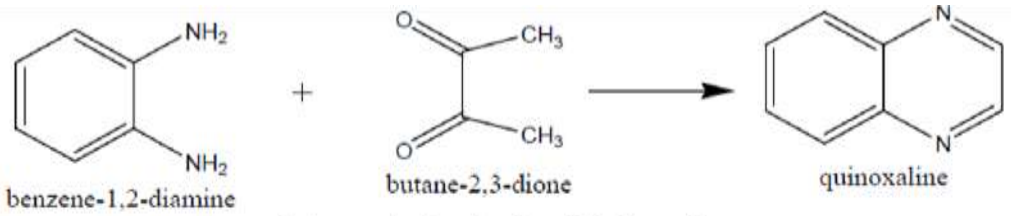
When orthodiamine is combined with 1,2 diketones, quinoxaline is produced.

O-phenylenediamine and glycol 28 are used to make quinoxaline. Natural compounds with a quinoxaline ring are uncommon, but they are simple to make or synthesise.Quinoxaline is made by combining o-phenylenediamine with glyoxal sodium bisulfite in a yield of 85-90 percent (4)

reaction of 1,2-phenylenediamine (1 mmol) with benzil (1 mmol) in

In the presence of varied quantities of the catalyst, various solvents such as ethanol, THF,MeCN, and toluene were used, as well as solvent-free classical heating conditions. The best result was obtained when the reaction was carried out in EtOH with 10 mg TiO2-Pr-SO3H [2 a novel, mild, eco-friendly, and efficient method for the preparation of quinoxaline derivatives in high yields via a one-pot condensation of aromatic diamine and

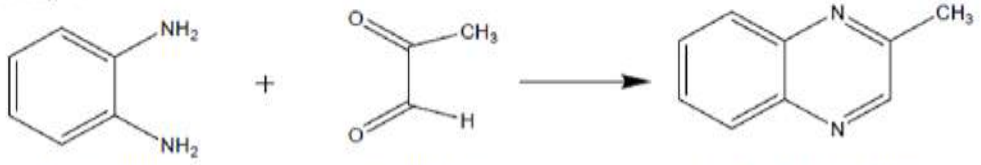
1,2-dicarbonyl compounds in the presence of [2-(sulfoxy)ethyl]sulfamic acid (SESA) (5)



benzene-1,2-diamine butane-2,3-dione quinoxaline

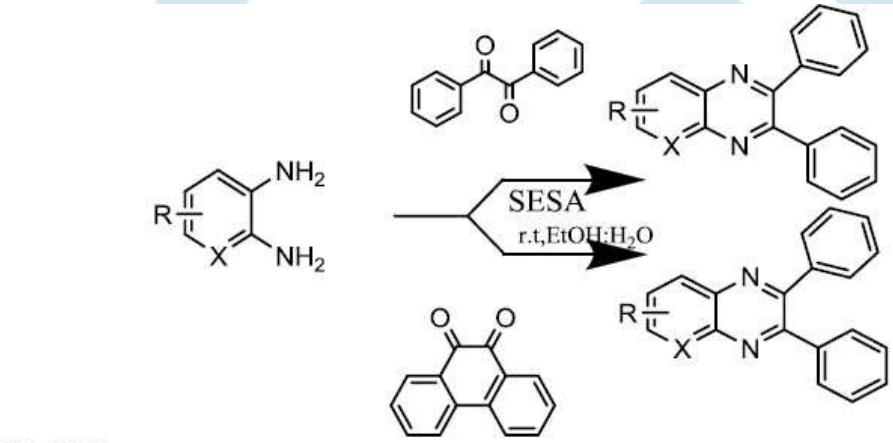
Scheme 1. Synthesis of Quinoxaline

2-Methyl quinoxaline has been prepared by the reaction of *o*-phenyldiamine and pyruvaldehyde[30].



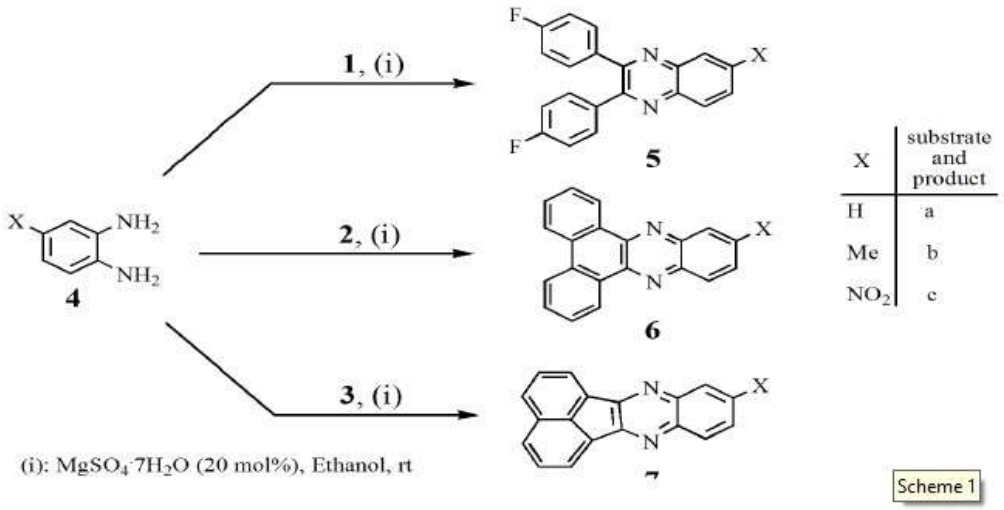
o-phenyldiamine pyruvaldehyde 2-methyl quinoxaline

Scheme 2. Synthesis of 2-methylQuinoxaline

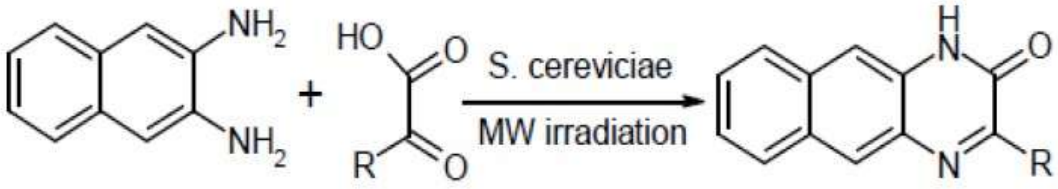


X=CH.N

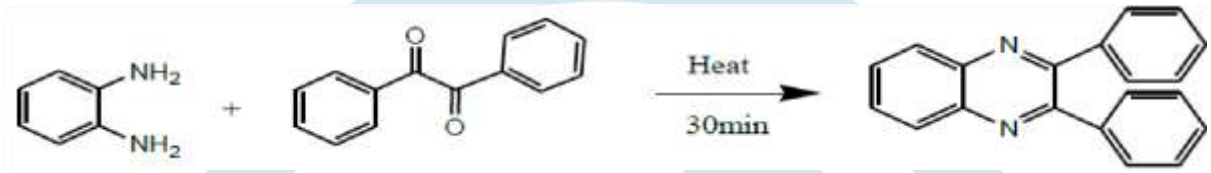
Reaction between o-phenylenediamine with 1,2dicarbonyl compound gives phenazine and quinoxaline derivative.
At room temperature condensation occurs between o-phenylenediamine and 1,2dicarbonyl compound because of catalytic activity of magnesium sulphate heptahydrate(5)



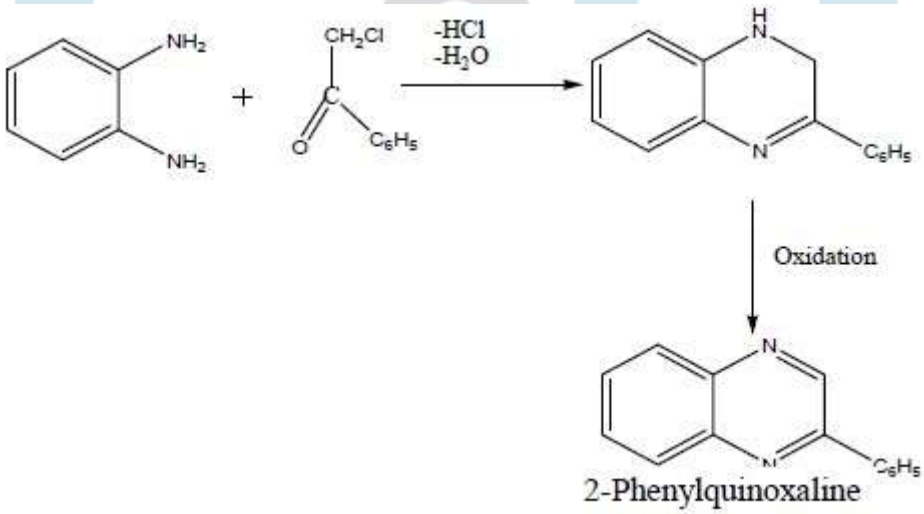
SYNTHESIS OF QUINOXALINE DERIVATIVE:
Many methods of quinoxaline synthesis are available in literature which compile has carried out the microwave-procedeHinsberg type of mechanism of quinoxaline derivatives by reacting o'phenylenediamine or 2,3-diaminonaphthalene with a variety of α-keto acids through enzymatic catalysis or microwave irradiation"[5]



Add 1.1 gm of O-Phenylenediamine diamine to a heated Benzil solution of 2.1 gm in 8 ml of rectified spirit. Warm for 30 minutes in a water bath, then add water until a tiny cloudiness remains and chill. In a 100ml round bottomed flask, filter and recrystallize aqueous absolute ethanol (95%) with 2-3 drops of glacial acetic acid. At the refluxing temperature, the reaction mixture was cooked for half an hour. The products were then recrystallized from ethanol after being chilled in an ice bath.(4)



In quinoxaline and phenazine, the fusion of one or two benzene rings increases the number of resonance configurations possible. The dipole moment of quinoxaline is 0 degrees. Several simple diamine modifications appear to be effective. Pentachloride and o-phenylenediamine were used to make 2- substituted quinoxaline by substituting an aldehyde with a – halogen ketone(6)



Scheme 6. Synthesis of 2-phenylquinoxaline

PHARMACOLOGICAL APPLICATION OF QUINOXALINE AND ITS DERIVATIVE:

1] as antifungal: The derivatives listed below have antifungal properties.

Substituted 3-benzyl quinoxalines were made from substituted phenyl pyruvic acid and o-phenylenediamine. All of the substances were antifungal. (2)

(Z)-3-{2-[1-(6-Chloro-2-oxo-2H-chromen-3-yl)ethylidene]hydrazinyl}quinoxaline-2(1H)-one, and(Z)-3-[2-(propan-2-ylidene)hydrazinyl]quinoxaline-2(1H)-one mainly proved be potent antifungal agents.(7)

2] As antimicrobial:quinoxaline derivative use as antimicrobial

By combining O-phenylenediamine with 5-bromo Isatin and then reacting it with various aromatic and aliphatic amines, 9-bromo-N-substituted O-phenylenediamine is produced. - 6H- indolo [2,3- b] - 2-Phenyl Quinoxaline-3-sulfonamide derivatives of quinoxaline were tested using quinoxaline.(8)Ramalingam and his coworker synthesized 1-substituted quinoxaline-2,3(1H,4H)-diones as the antimicrobial activity. The derivatives 1-((3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-4-yl) methyl)quinoxaline-2,3(1H,4H)-dione(2) It has antimicrobial efficacy against a wide spectrum of bacteria (both Gram +ve and Gram –ve).

3] AS ANTIMALARIAL:

Quinoline methanol shows the antimalarial activity which used as a derivative of quinoxaline ,they show little activity on malarial parasite because of similarity of quinolone and quinoxaline also show quinoxaline moiety as broad spectrum antibiotics (9)

4] AS ANTI LEISHMANIA

To start a new line of study against leishmaniasis, the quinoxaline di-N-oxide moiety was introduced into a chalcone system. Chalcones are ketones found throughout the plant kingdom that have a wide range of biological actions, including antimalarial and leishmanicidal effects. (10)

When given orally, Licochalcone A was isolated from Chinese Liquorice and showed promising effectiveness against visceral and cutaneous leishmaniasis .

3-phenyl-1-(1,4-di-N-oxide quinoxalin-2-yl)-2-propen-1-one substituted derivatives were synthesised and examine for in vitro leishmanicidal activity against L. amazonensis amastigotes in axenic cultures and murine-infected macrophages in this fashion(10)

5] AS ANTIPLASMODIAL:

Many Quinoxaline derivative is pharmacologically active against plasmodium species.

Whether 3-trifluoromethyl-2-aryl carbonyl 1,4-di-N-oxide quinoxaline derivatives might help prevent the spread of chloroquine-resistant Plasmodium falciparum. The researchers came to the conclusion that structural factors including the presence of a trifluoromethyl group, monosubstitution, or one-group replacement on the quinoxaline ring by an amino group were important. An electron-withdrawing group or complete lack of substitution, as well as a short aromatic ring connected to the ketone moiety, affect the antiplasmodial profile of 3-trifluoromethyl-2-carbonyl 1,4-di-N-oxide quinoxaline derivatives. The chemical quinoxaline was the most active and least dangerous of the group. 6-Chloro-3-Phenoxybenzene-6-Chloro-3- (2-furyl carbonyl) 6-Chloro-3-trifluoromethyl-1,4-di-N Oxide and -2-trifluoromethyl-1,4-di-N Oxide are two types of -2-trifluoromethyl-1,4-d (2-furyl carbonyl) There are two forms of chloro-3-methyl-1,4-di-N oxide:

-2-trifluoromethyl-1,4-di-N Oxide and -2-trifluoromethyl-1,4-di-N Oxide (2-furyl carbonyl) 6-Chloro-2-Chloro-2- Chloro-2- Chloro-2- Chloro-2 (2-furyl carbonyl) -2-trifluoromethyl-1,4-difluoromethyl-2-trifluoromethyl-2-trifluoromethyl-2-trifluoromethyl-2-trifluoromethyl-2 -trifluoromethyl-2-trifluoromethyl-2-trifluoromethyl-2-triflu(11)

6] ANTIVIRAL AND HIV ACTIVITY:

Harmenberg et al created a variety of 6H-indolo-(2,3-b)-quinoxaline derivatives and tested them for antiherpes action. In tissue culture, the most potent chemical in this series suppressed herpes simplex virus type 1, cytomegalovirus, and varicella zoster virus reproduction at doses of 01 to 05 g. Another series of 6-chloro-3,3-dimethyl-4(isopropenyl oxycarbonyl)-3,4-dihydroquinolin-2-(1H)-thiones was made and tested for anti-HIV efficacy against an HIV reverse transcriptase enzyme inhibitor.(12)

7] ANTIBACTERIAL:

2-Substituted(1,4-dioxo-3,4,4e,5,10,10a,hexahydro-1H-5,10-benzenobenzo[g]phthalazine derivatives prepared as novel antibacterial agent.(13)

Mainly scientist and his worker synthesized (E)-3-(4-or3-Amino Imino)quinoxaline- 2(3H)-one oxime Schiff base derivatives and determined their anti-leptospiral activity(1)

E)-3-(3-(3-nitrobenzylidene amino)phenylimino)quinoxaline-2(3H)-one oxime show more potency as compared to penicillin g and other group of penicillin.(14)

A number of quinoxaline compounds have been shown to be antibacterial. Quinoxaline-2-carboxylic acid derivatives have antibacterial action because of substitution. They have a poor solubility at neutral pH condition due to which parenteral administration is difficult. Quinoxaline-2-carboxylic acid for example bidentate ligands show antibacterial activity . Antibacterial properties of quinoxaline and its derivatives have been demonstrated due to Staphylococcus aureus, Bacillus influenza, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumonia was tested using the cup plate technique on nutritional agar media with ciprofloxacin as the control medication. at doses of 50 g/ml and 100 g/ml against all of the above-mentioned organisms bacillus show body conformation due to antibacterial activity The N-[3-chloro-2-oxo-4-(substituted)phenyl azetidine-1-yl] is another member of the N-[3-chloro-2-oxo-4-(substituted)phenyl azetidine-1-yl] class of molecules which show antibacterial activity.(15)

8] AS ANTICANCER:

Multidrug resistance (MDR) is a major drawback in cancer . MDR is most commonly caused by excessive P-gpextension . P-gp is a transmembrane glycoprotein that plays an important role in ATP-dependent drug transporter ,that transfers intracellular medicines out of cells unilaterally, allowing cells to develop drug resistance. A number of medicines have been discovered to reverse the MDR phenotype and restore drug sensitivity in cancer cells. However, the majority of these medications have proven to be intrinsically toxic and have unfavourable impacts on the pharmacokinetics of anticancer treatments. Efforts to produce MDR modulators, for example, first concentrated on verapamil and cyclosporin. The 2-oxoquinoline of quinoxaline scaffold, in particular, has shown promise as a flexible scaffold for studying P-gp antagonists (16)

9] As anti-inflammatory:

Basically quinoxaline derivative such as 2(1H)quinoxaline and hexahydro derivative show anti inflammatory activity.2(1H)quinoxaline derivative posses 4-chlorophenyl-2,dihydrothiazole moiety show high frequency of anti inflammatory activity also show side effect as ulcer like (17)

10] Enzyme inhibitory activity:
Main pharmacological action of quinoxaline is to inhibit kinase protein
Many derivative uses as enzyme inhibitor are as follows, imidazol[1,5]quinoxaline, chloroquinoxaline ,dihydroquinazoline
Combination of Quinoxaline and imidazole ring shows biologically activity against pathogenic enzyme they are as follows
Imidazo[1,5-a]quinoxalines were synthesized that function as irreversible Bruton's tyrosine kinase (BTK) inhibitors(18)
Quinoxaline derivatives, which act as inhibitors of platelet derived growth factor receptor kinase (PDGF). The Most active compound was a tricyclic benzo[g]quinoxaline(19)

11] Anti-inflammatory activity: many Quinoxaline and their derivative use as anti inflammatory agent
.following two moiety show anti-inflammatory activity
2(1H)quinoxaline
Hexahydro derivative of Quinoxaline
2(1H)quinoxonone derivative posses 4-chlorophenyl 2,3dihydro thiazole moiety which show maximum anti inflammatory activity (17)

12] As metal complexes : Quinoxaline derivative use as a metal complexes.
New series of Cu(II) ternary complex with N-(benzoyl) leucinate and n-(acetyl)phenyl glycinate and some Heterocyclic compound mainly forms complexes.
The metal complexes were categorized by elemental analysis, IR and EPR spectra and thermogravimetric analysis.(20)

Conclusion:
This study give brief idea about quinoxaline nucleus. This review concluded that various method of preparation of quinoxaline, synthesis of quinoxaline along with pharmacological activity.it was observed that quinoxaline moiety may possess substitution which show the different pharmacological activity .basic chemistry of quinoxaline is enlight in this review.

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