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Review Article

HETEROCYCLIC CHEMISTRY OF QUINOXALINE AND POTENTIAL ACTIVITIES OF QUINOXALINE DERIVATIVES – A REVIEW

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ABSTRACT

The present review article is concerned about the heterocyclic chemistry of Quinoxaline, and pyrazines their history, natural occurrence of pyraznes and quinoxalines. Reactions with electrophilic reagents like protonation, oxidation and halogenation , oxidizing agent, nucleophilic reagent, reducing agent, radical reagents, Electrocyclic reaction, its ring synthesis from the self condensation of 2-aminoketone and from 1, 2-dicarbonyl compound and 1, 2-diamino compound. In this review article emphasis is given on the potential biological activities of quinoxaline derivatives .these exhibits many biological activities antimicrobial anti-inflammatory, ant tumor anti hyperglycemic and anti oxidant. Quinoxaline is an important lead owing to its inherent properties and therapeutic actions.

Keywords: Heterocyclic Chemistry, Quinoxaline, Pyrazine, Self-Condensation, Antimicrobial Activity.

INTRODUCTION

To provide an understanding of principles of the medicinal chemistry, it is necessary to consider the physicochemical properties used to develop new pharmacologically active compounds and their mechanism of action, the drug's metabolism including possible biological activities of the metabolites, the importance of stereochemistry in drug design, and the methods used to determine what 'space' a drug occupies. All of the principles are based on the fundamental organic chemistry, physical chemistry and biochemistry. Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur

and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important. Quinoxaline is nitrogen containing six membered heterocyclic, in which two nitrogen atoms are based on pyrazine so called Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings, e.g. as benzopyrazine. α dicarbonyl compounds reacts with aromatic ortho-diamine by consecutive addition-elimination mechanism to give quinoxaline.[1] Quinoxaline have become attractive target of extensive research due to its inherent properties and therapeutic uses. Quinoxaline finds many pharmacological activities like antibacterial, antifungal, antituberculer, anti-inflammatory, antihyperglycemic, antitumor etc.

mostly the members of vitamin B complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, the genetic material, DNA etc. Few of the basics rings of the heterocyclic compounds are listed below.[2]

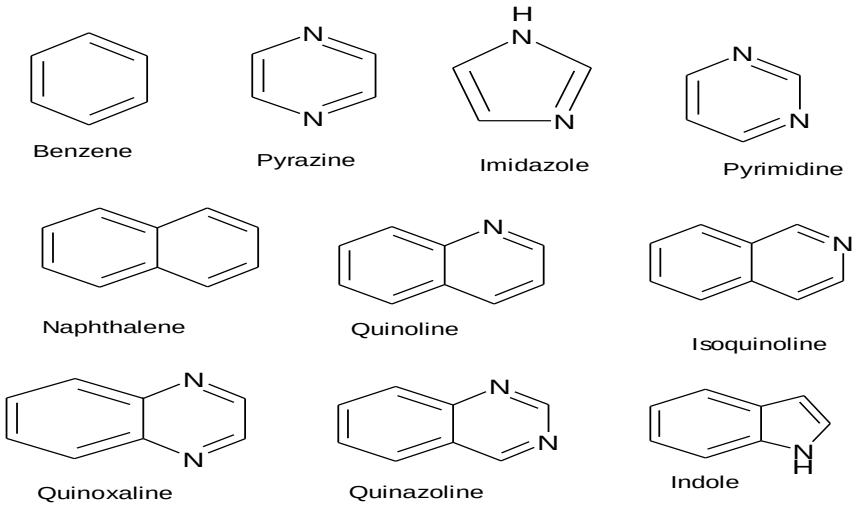
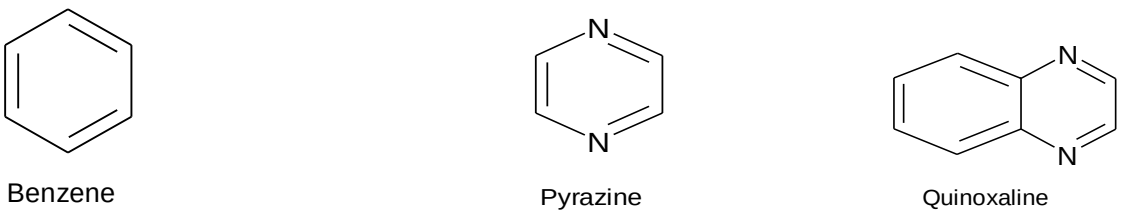


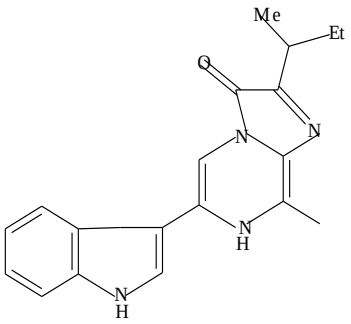
Figure 1: Different heterocyclic ring.

History

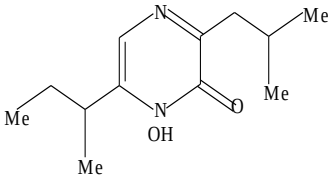


Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring & pyrazine ring. Pyrazine are stable, colorless compound which are soluble in water. Unlike pyridine, they are expensive & not readily available & so are seldom used as starting material for synthesis of their derivative. Diazines are fused to benzene ring to form quinoxaline. The pyrazine ring system is found in the fungal metabolite aspergillic acid and in dihydro form in luciferin of several bettles including the fire fly is responsible for the chemiluminescence of this ostracod. Methoxy pyrazine are very important component of aroma of many fruit's and vegetable such as Peas and Capsicum peppers and also of wines.

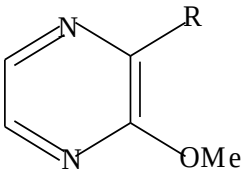
Naturally Occurring Pyrazine & Quinoxaline



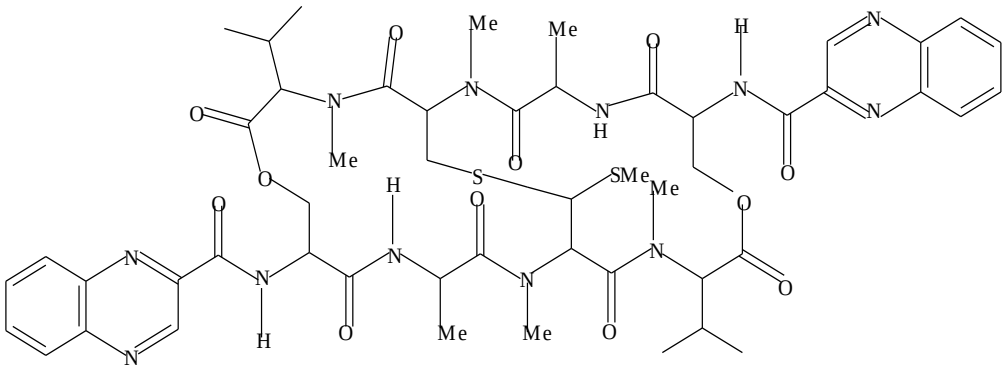
Cyridina Luciferin



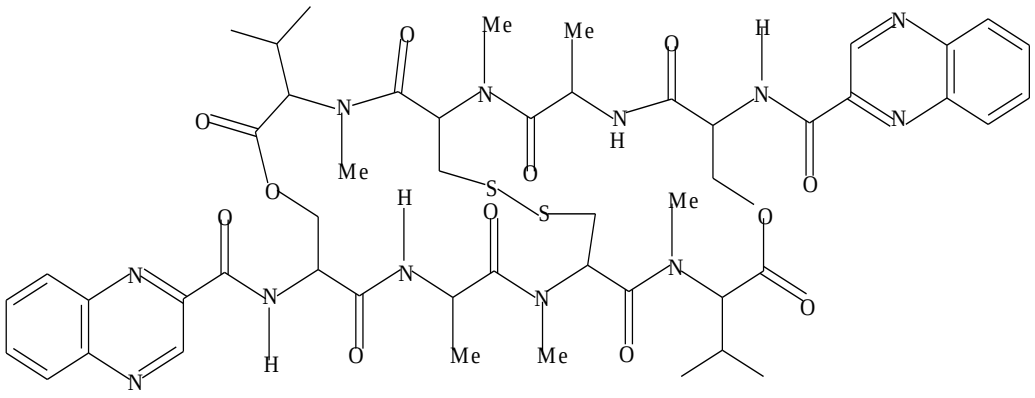
Aspergillic acid



Methoxy Pyrazine (Food Aroma)

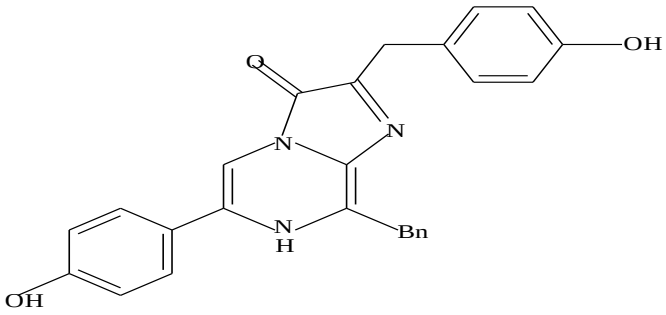


Echinomycin



Triostin A

Cholenterazine: It is synthesized from chloro pyrazine. It is bioluminescent compound from a jellyfish, which potential for use in bioassays.



Cholenterazine

REACTIONS OF QUINOXALINE

Reaction with Electrophilic Reagent

Addition at nitrogen

Protonation

The diazines are essentially monobasic substances and considerably weaker as bases than pyridine. In pyrazine mesomeric interaction between the protonated & neutral nitrogen atoms probably destabilizes the cation. N, N-diprotonation is very easier for pyrazine.[4]

Oxidation

Pyrazine react with peroxide, giving N-Oxides, It can also form N, N- dioxides very easily.

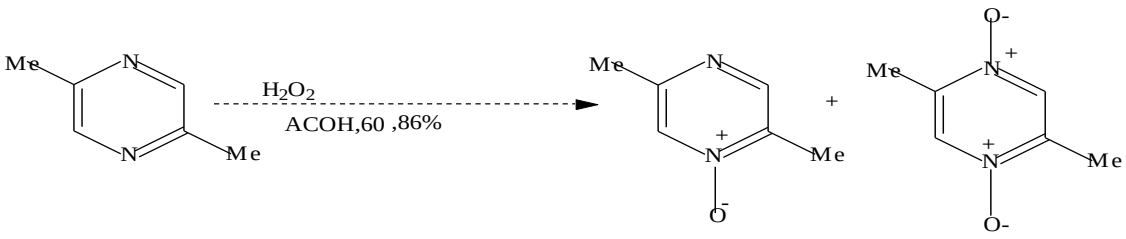


Figure 2: Oxidation of Dimethyl pyrazine with hydrogen peroxide.

Substitution at carbon

Halogenation:

Chlorination of 2-methyl pyrazine occurs under such mild condition that it is almost certain that an addition / elimination sequence is involved, rather than a classical aromatic electrophilic substitution.

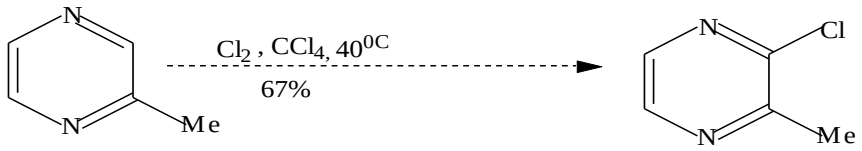


Figure 3: Chlorination of methyl pyrazine in presence of carbon tetrachloride.

Reaction with oxidizing agent

The diazines are generally resistant to oxidative attack at ring carbons through alkaline oxidizing agent can bring about degradation via intermediate produced by initial nucleophilic addition. Alkyl substituents fused aromatic rings can be oxidized to carboxylic acid residue leaving the heterocyclic ring untouched.

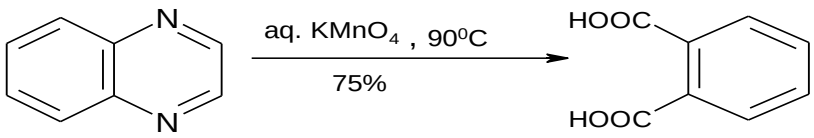


Figure 4: Reaction of quinoxaline with oxidizing agent with potassium permanganate.

Reaction with nucleophilic reagent

Replacement of hydrogen

Alkylation and arylation

The diazine readily add alkyl and aryl lithium, and Grignard reagents to give dihydro-adduct which can be aromatized by oxidation with reagent such as potassium permanganate or 2, 3-dichloro-5,6 dicyano-1,4- benzoquinone.

Replacement of good leaving group

Pyrazine react with soft nucleophiles such as amines, thiolate, and malonate anions, with substitution of halide.

Figure 5: Arylation of Chloropyrazine.

Reaction with reducing agent

Due to their lower aromaticity, the diazines are more easily reduced than pyridines. Pyrazine and pyridazine can be reduced to hexahydro derivatives with sodium in hot ethanol; under this condition pyridazine has a tendency for subsequent reductive cleavage of the N-N bond. Partial reduction of quaternary salt to dihydro compounds can be achieved with borohydride. 1, 4-Dihydropyrazines have been produced with either silicon 62 or amide substitution at the nitrogen atoms and all the diazines can be reduced to tetrahydro-derivatives with carbamate protection on nitrogen, which aid in stabilization and thus allows isolation.[4]

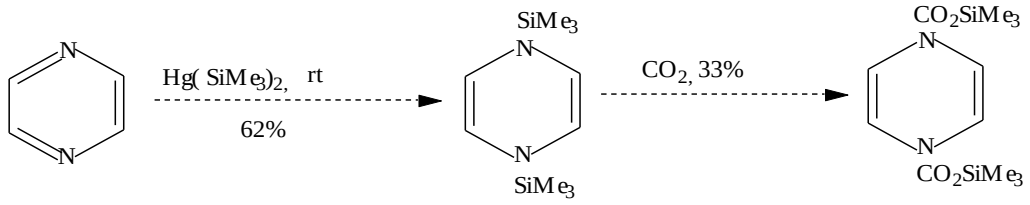


Figure 6: Reaction of pyrazine with reducing agent to give dihydro pyrazine.

Reaction with radical reagents

Radicals add readily to diazines under Minisci condition. Addition to pyrimidine often shows little selectivity, C-2 versus C-4, however a selective Minisci reaction on pyrazines can of course substitute in only one type of position.

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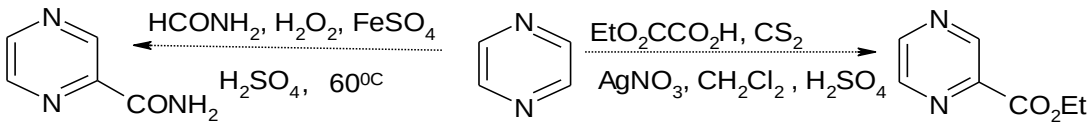


Figure 7: Reaction of pyrazine with radical reagent.

Electrocyclic reaction

Pyrazine having electron withdrawing substituents, undergo Diels-Alder addition with dienophiles. Intermolecular reaction occurs the most readily, these do not even require the presence of activating substituent, immediate product of such process usually loses hydrogen cyanide to generate pyridine product. Singlet oxygen has been added across the 2, 5-position of pyrazine.

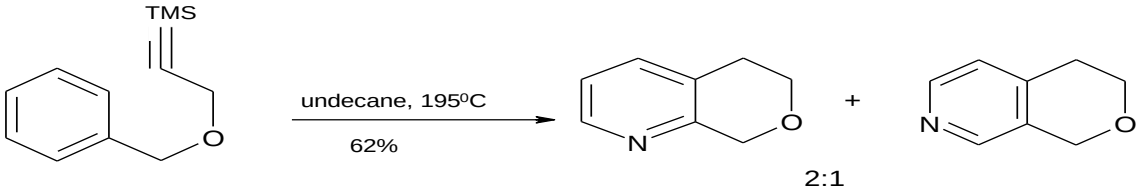


Figure 8: Pyrazine showing Electrocyclic reaction.

Diazine N-Oxides

Pyrazine N-oxide can be readily prepared by oxidation of parent heterocycle. Pyrazine N-oxide behaves like their pyridine counterparts in electrophilic substitution & nucleophilic displacement reaction involving loss of the oxygen. It is interesting that displacement of nitro beta to the N-oxide function occurs about as readily as that of Gama nitro group. Nucleophilic substitution by halides, cyanides, carbon nucleophiles such as enamines, and acetate, with concomitant loss of the oxide fraction occurs smoothly.

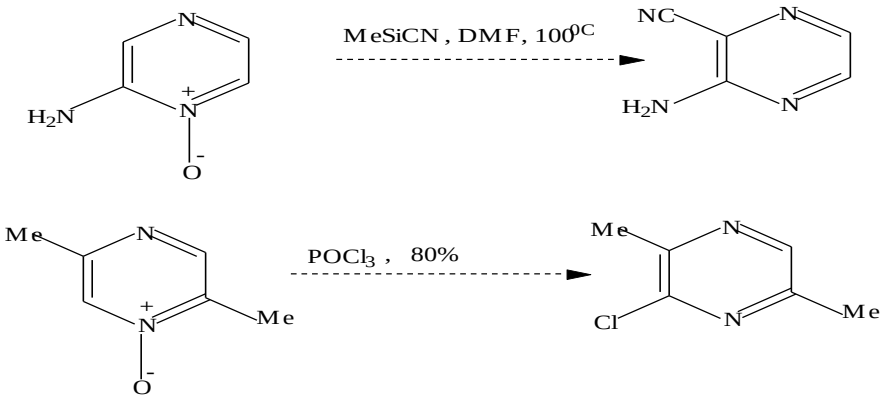
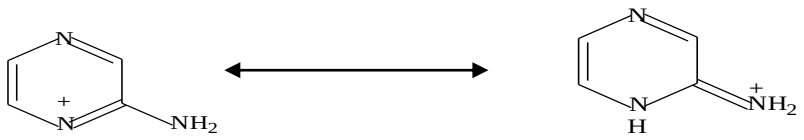


Figure 9: Reaction of pyrazine N-oxide to loss of oxides.

Aminodiazines

Aminodiazine exist in the amino form. They are stronger bases than the corresponding unsubstituted system and always protonated on one of the ring nitrogen atoms: where two isomeric cations are possible, the order of preference for protonation is of ring nitrogen which is γ>α>β to the amino group. e.g.



Aminopyrazines react with nitrous acid to give the corresponding pyrazinone.

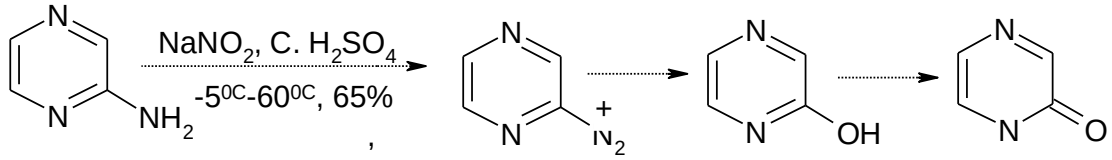


Figure 10: Reaction of aminopyrazine with nitrous acid to give pyrazinone.

Ring synthesis of pyrazine

Pyrazine is not easily made in the laboratory. Commercially, the high temperature cyclodehydrogenation of precursors such as N-hydroxyethyl ethane- 1, 2- diamine is used.

From the self condensation of 2-aminoketone

Symmetrical pyrazines result from the spontaneous self condensation of two mol equivalents of a 2-amionketone, or 2-aminoaldehyde followed by oxidation.[3]

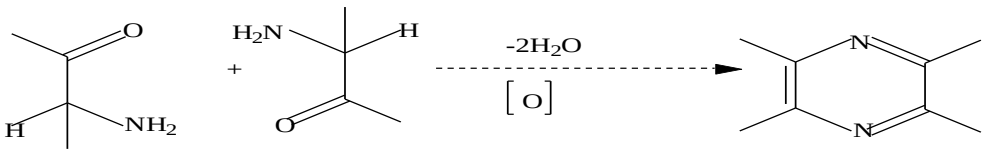


Figure 11: Synthesis of pyrazine ring from 2-aminoketone.

2-Amino-carbonyl compound, which are stable only as their salts, are usually prepared in situ by the reduction of 2-diazo-,-oximino- or –azido-ketones. The dihydropyrazines produced by this strategy are very easily aromatized.

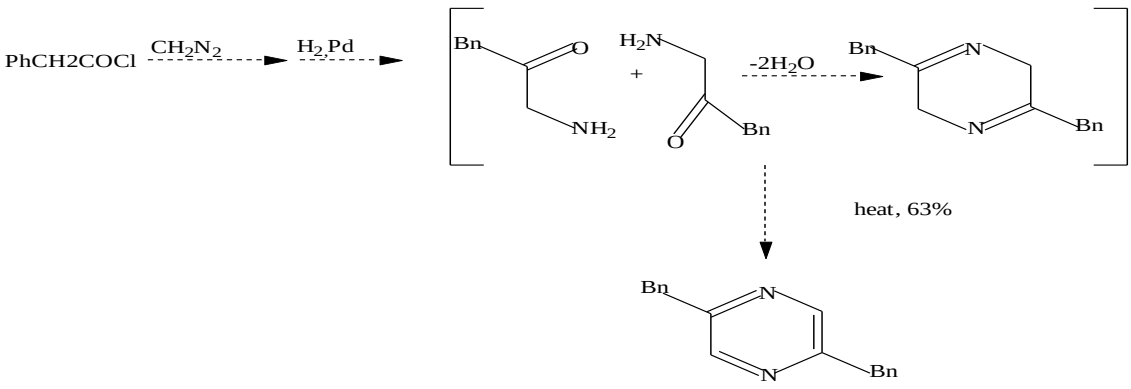


Figure 12: Synthesis of pyrazine ring from 2-amino-carbonyl compound.

α Amino-ester are more stable than α amino-ketones, easily self condense to give heterocycles known as 2,5-diketopiperazines. These compounds are resistant to oxidation but can be used to prepare aromatic pyrazines after first converting them into dichloro or dialkoxy- dihydro pyrazine.

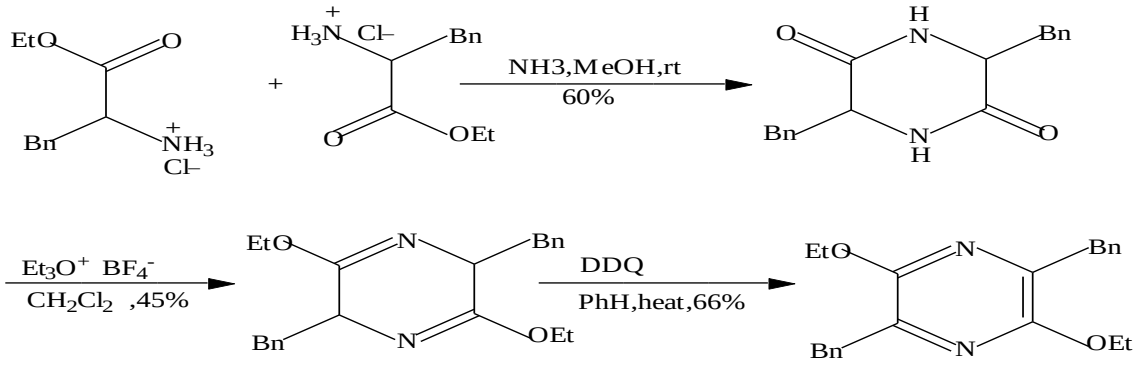


Figure 13: Synthesis of pyrazine ring from α amino ester.

From 1, 2-dicarbonyl compound and 1, 2-diamino compounds

1, 2-Dicarbonyl compounds undergo double condensation with 1, 2-diamines; an oxidation is then required.

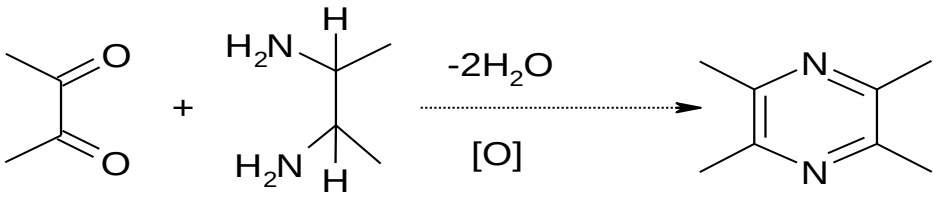


Figure 14: Synthesis of pyrazine ring from 1, 2-dicarbonyl & 1, 2-diamino compound.

This method is well suited to the formation of symmetrical pyrazines. If both diketone and diamine are unsymmetrical, two isomeric pyrazines are formed.

BIOLOGICAL ACTIVITIES OF QUINOXALINE

Antimicrobial activity

Antimicrobial agent shows activity against bacteria, fungi, mycobacterium species, called antibacterial, antifungal, antituberculer activity respectively. There are various quinoxaline derivatives showing antimicrobial activity.

Quinoxaline core antibiotics like Echinomycin, Triostin A showing antimicrobial activity by having DNA cleaving property. Design of quinoxaline antibiotics have undertaken by several workers, but they posses limited application due to their toxic effect. It is believed that the antimicrobial potency of the quinoxaline due to the facilitate approach of the structure to prevent DNA directed RNA synthesis by virtue binding to CPG site on DNA (Ali et.al, 2003).Ganapaty et.al, 2007 has synthesized some new 2-substituted hydrazine /benzylidino / methyl hydrazones and 7-sulfonamides of 1H, 4H 3-oxo-quinoxalines from 1H, 4H-quinoxalin-2,3diones. All the compounds were evaluated for their in vitro antimicrobial activity against the gram-positive bacteria *Staphyllococus aureus*, the gram-negative *Psudomonas aeruginosa*, *Proteus vulgaris* and *Escherichia coli*, the fungi *Aspergillus niger, Candida albicans* and the *Mycobacterium tuberculosis* $H_{37}Rv$ species. Antibacterial and antifungal screening was carried out by agar plate disc diffusion method at 100µg/disc concentration in triplicate and its results were reported as zone of inhibition in millimeter. The antituberculer screening was performed by Micro plate Alamar Blue Assay method. M. M. Ali synthesized some novel quinoxalinone derivatives.[4] The antimicrobial activities of the synthesized compounds were determined by the agar diffusion technique. The organisms tested were *Staphyloccus aureus* (NCTC 7447), *Bacillus cereus* (ATCC-14579), *Serratia marcescens* (IMRU 70), *Proteus merabitis* (NCTC-289), *Aspergillus ochraceus,* Wilhelm (AUCC-230) and *Penicillium chrysogenum*, Thom (AUCC-530).

Other activities of quinoxaline

Antimalarial against Plasmodium falciparum

Malaria is by far the world's most important tropical parasitic disease. Mortality, currently estimated at over a million people per year has risen in recent years, probably due to increasing resistance to antimalarial medicines.E. Vicente *et al*, synthesized new active compound from lead compound 3- (4'-chlorophenyl) quinoxaline -2- carbonitrile 1, 4- di-N-oxide, which was subjected to a structural change in order to obtain new active compounds : replacement of benzene in position 3 of the quinoxaline subunit by a heteroaromatic 5-member ring, 2-furane or 2-thiene. All the synthesized compounds were evaluated for antimalarial activity against Plasmodium falciparum. The 3-(2'-furyl) quinoxaline -2- carbonitrile 1, 4-di-N-oxide derivatives appear to be a novel and promising antimalarial candidates.[5]

Anti-inflammatory and antioxidant activity

Many non-steroidal anti-inflammatory drugs have been reported to act as inhibitors of free radical production or as radical scavenger's compounds with antioxidant properties could be expected to offer protection in rheumatoid arthritis and inflammation and to lead to potentially effective drugs. Thus, Asuncion Burguete *et al.*, synthesized novel ring substituted 3-phenyl -1- (1, 4-di-N-oxide quinoxaline-2-yl) -2-propen-1-one derivatives and of their 4, 5-dihydro-(1H)-pyrazole analogues. Synthesized compounds were evaluated for anti-inflammatory and antioxidant activity. The tested compounds inhibit the carrageenan-induced rat paw edema (4.5-56.1%) and present important scavenging activities.[6]

Anti- HIV activity

Since the human immunodeficiency 1 (HIV-1) was first confirmed as the causative agent of

acquired immunodeficiency syndrome (AIDS). These are many clinical drugs, non-nucleoside reverse transcriptase inhibitors, which interact with a specific allosteric non-substrate binding site on HIV-1 reverse transcriptase, have proved to be effective anti-HIV drugs because of their high potency, low toxicities, and improved pharmacokinetics. Thus, Bailing Xu *et al* synthesized N^4 – (hetero) aryl sulfonyl quinoxalinones and their analogs and tested for anti viral activity as HIV-1 reverse transcriptase inhibitors.

The anti-HIV-1 activities of all target compounds were evaluated by a cell-based HIV-1 replication pharmacological model which was set up by HIV-1 (pNL4-3) core packed with vesicular stomatitis virus glycoprotein. The level of HIV-1 replication was presented by a reporter gene expression (i.e., luciferase activity) in infected cells.

Anti cancer activity

Sandra piras, *et al*, synthesized Methyl [4-(substituted 2-quinoxalinyloxy) phenyl] acetates and ethyl N-{[4-(substituted 2-quinoxalinyloxy) phenyl] acetyl} glutamate analogs of methotrexate and evaluated for in vitro anti cancer activity bioisosteric replacement of pteridine ring with 6 (7) – trifluoromethyl quinoxaline affords a good substrate for the classical antifolate analogs, and bioisosteric replacement of 2- NH group with an oxygen that in some cases was of relevance in anticancer activity. Quinoxalinebearing a 2 - (4 – substituted phenoxy) substituent were endowed with potent antitumor activity.[7]

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