

Antimicrobial Activity of Quinoxaline Derivatives

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Abstract: Different types of quinoxaline derivatives show antimicrobial activity. Quinoxalines, also named as Benzopyrazines, having a nitrogen ring, in organic chemistry is a heterocyclic compounds containing a ring complex made up of a benzene ring and a pyrazine ring. To modify in their nucleus, they form different derivatives of quinoxaline which contains antimicrobial activity. To modify in their structure shows a wide variety of new therapeutic agents having better potency and lesser toxicity. This article is shows to review history, chemistry, synthesis and the derivatives of quinoxaline which shows antimicrobial activity.

Keyword: Quinoxaline, Benzopyrazine, Antimicrobial activity

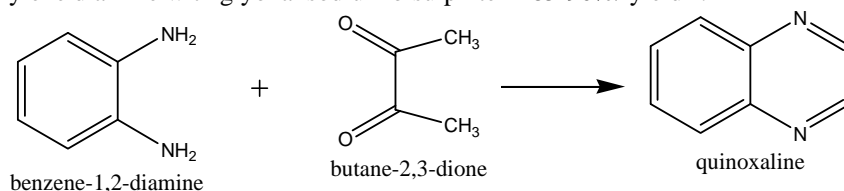
Introduction

Quinoxalines, also called a Benzopyrazines, in organic chemistry, it is a heterocyclic compounds containing a ring complex made up of a benzene ring and a pyrazine ring, isomeric with the cinnolones, phthalazines and quinazolines¹. Quinoxaline derivatives exhibit a broad spectrum of biological activity such as antibacterial²⁻⁴, antifungal^{5,6}, antiviral⁷, anticancer⁸, anti-tubercular⁹, antimalarial¹⁰ and anti-inflammatory¹¹. Quinoxaline is well known for its broad coverage in the field of medicine as well as for its application in the pharmaceuticals. Quinoxalines constitute an important class of compounds, of which some analog has synthesized and evaluated for antimicrobial activity. Many possess different biological activity such as insecticides, fungicides, herbicides, anthelmintic and antiviral. Among the various classes of nitrogen containing heterocyclic compounds, a quinoxaline derivative constitutes synthetic libraries for drug discovery. Synthetic quinoxaline nucleus is the part of a number of antibiotics which are known to inhibit the growth of gram positive bacteria and are also active agents to treat tuberculosis^{12,13}. Recent studies has shown that some quinoxaline derivatives inhibit selectively the platelet-derived growth factor (PDGF) receptor kinase, PDGF- dependent DNA synthesis in cell lines¹⁴ and it inhibit the human cancer cell lines¹⁵. On the other hand, a quinonimine system such as naphthooxazinoquin-oxalinone derivative¹⁶, is of interest because this system constitutes the structure of several antitumor antibiotics such as actinomycin D¹⁷, questiomycinA¹⁸ and glycosyl questiomycin¹⁹. Also, among the wide variety of heterocycles that have been explored for the viral and antifungal activities of developing pharmaceutically important molecules²⁰. Cyanopyridines^{21,22} and isoxazoles²³⁻²⁵ have been similarly investigated.

Chemistry

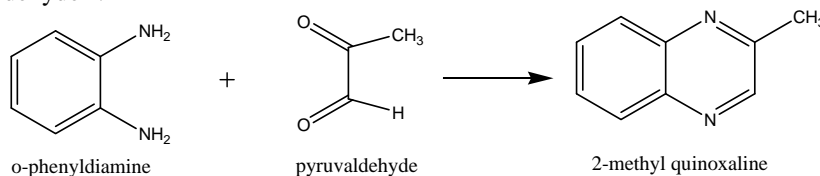
Quinoxaline is a weak, basic, bicyclic compound commonly called 1,4- diazaphthalene or benzopyrazine containing a fused benzene and pyrazine ring.

Quinoxaline is a low melting solid, having a melting point 20-30 °C. They are miscible with water. It is white crystalline powders containing a molecular formula $C_8H_6N_2$. The molecular weight of quinoxaline contains 130.1466²⁶. Quinoxaline are formed by condensing of orthodiamine with 1,2 diketone²⁷. Quinoxaline itself prepared by the reaction of *o*-phenyldiamine and glyoxal²⁸. Natural products containing quinoxaline ring are rare and can be easily prepared or synthesized. Quinoxaline itself prepared by the condensation of *o*-phenylene diamine with glyoxal sodium bisulphite in 85-90% yield²⁹.



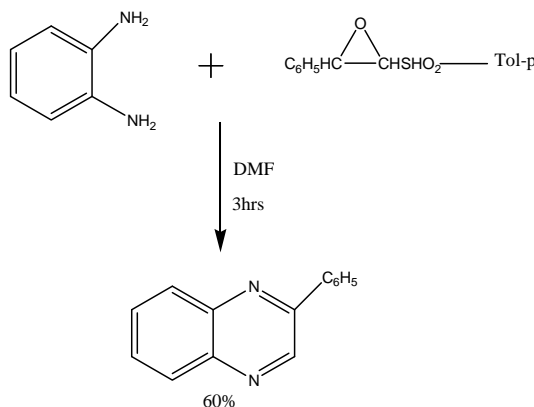
Scheme 1. Synthesis of Quinoxaline

2-Methyl quinoxaline has been prepared by the reaction of *o*-phenyldiamine and pyruvaldehyde³⁰.



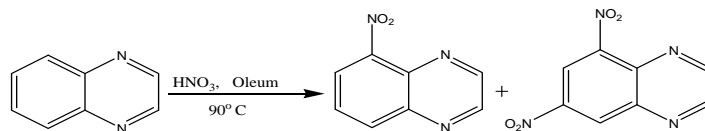
Scheme 2. Synthesis of 2-methyl Quinoxaline

Taylor recently reported that 1-(*p*-tolylsulfonyl)-2-phenloxirane, obtained from the condensation of chloromethyl *p*-tosylsulfone with benzaldehyde, on reaction with *o*-phenylenediamine yields 2-phenylquinoxaline with good yield³¹.



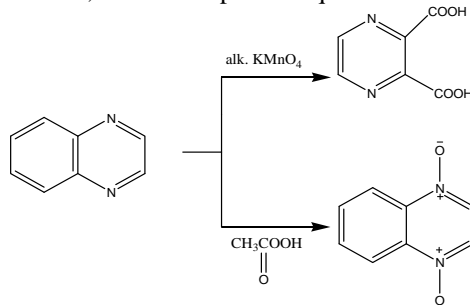
Scheme 3. Synthesis of 1-(*p*-tolylsulfonyl)-2-phenloxirane

Quinoxaline forms salt with acids. Nitration occurs only under forcing conditions (conc. HNO_3 , Oleum, 90 °C) to give 5-nitroquinoxaline (1.5%) and 5,7-dinitro-quinoxaline (95%)³².

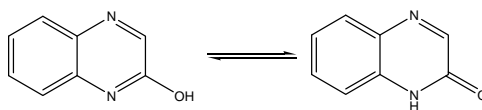


Scheme 4. Synthesis of 5-nitroquinoxaline and 5,7-dinitroquinoxaline

Oxidation of quinoxaline results in the formation of the product and depending on the nature of the oxidizing agent employed with alkaline pot. Permanganate pyrazine. 2,3-Dicarboxylic acid is formed, while with per acid quinoxaline di-*N*-oxide results³³.



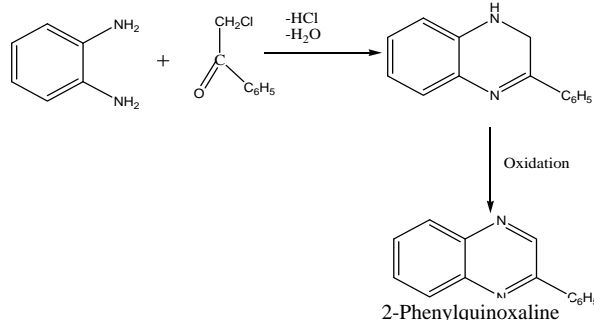
2-Hydroxy quinoxaline exists in tautomeric form as



Scheme 5. Tautomeric form of Quinoxaline

The parent substance of the group, quinoxaline, resulting when glyoxal is condensed, when substitution derivatives arise when a ketonic acids, a chlor ketones, an aldehyde alcohols and a ketone alcohols are used in place of diketones³⁴.

The fusion of one or two benzene rings in quinoxaline and phenazine increases the number of resonance structure which are available to these systems. Quinoxaline possess a dipole moment of zero³⁵. A number of simple variations in the diamine appear to well work. Thus replacement of the dialdehyde with an - halogenoketone results in the formation of 2- substituted quinoxaline has been prepared in this manner from phenachloride and *o*-phenylenediamine.

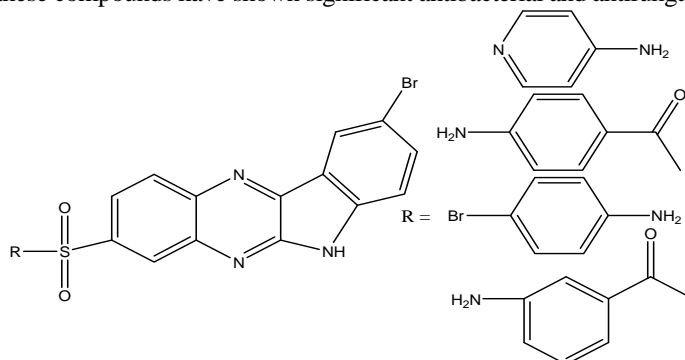


Scheme 6. Synthesis of 2-phenylquinoxaline

Antimicrobial activity

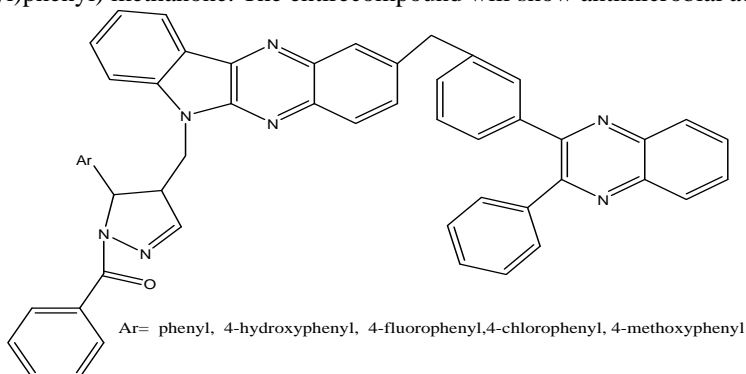
1) *o*-phenylenediamine is reacted with 5-bromo Isatin and the resultant compound is reacted with various aromatic and aliphatic amines to form the 9-bromo-*N*-substituted- 6*H*- indolo [2,3-*b*] quinoxaline-3-sulfonamide derivatives of quinoxaline were evaluated with anti-microbial

activity against a variety of bacterial strains (both Gram +ve and Gram -ve) and fungal strains and some of these compounds have shown significant antibacterial and antifungal activities³⁶.



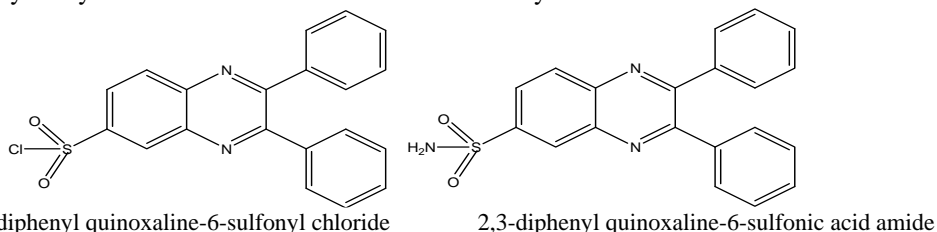
Scheme 7. 9-Bromo-*N*-substitute-6*H*-indolo [2,3-*b*] quinoxaline-3-sulfonamide

2) 1-(2-((2,3-Diphenylquinoxalin-6-yl)methyl)-6*H*-indolo[2,3-*b*]quinoxalin-6-yl)propan-2-one is reacted with aromatic aldehyde in the presence of sodium hydroxide it gives 4-aryl-1-(2-((2,3-diphenylquinoxalin-6-yl)methyl)-6*H*-indolo[2,3-*b*]quinoxalin-6-yl)but-3-en-2-one then it reacted with benzoic acid hydrazide in glacial acetic acid it gives (4,5-dihydro-5-aryl-3-((2-((2,3-diphenylquinoxalin-6-yl)methyl)-6*H*-indolo[2,3-*b*]quinoxalin-6-yl)methyl)pyrazol-1-yl)phenyl) methanone. The entire compound will show antimicrobial activity³⁷.



Scheme 8. 4,5-Dihydro-5-aryl-3-((2-((2,3-diphenylquinoxalin-6-yl)-6*H*-indolo[2,3-*b*] quinoxalin-6-yl) methyl) pyrazol-1-yl)phenyl)methanone

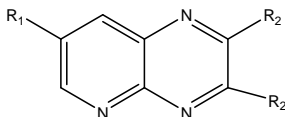
3) *o*-Phenylenediamine was the starting material for the synthesis of 2,3-diphenyl quinoxaline. Different derivatives were prepared by replacing hydrogen at 6th position of 2, 3-diphenyl quinoxaline by using different groups such as nitro, sulfonyl chloride, sulfonic acid amide according to the literature. All compounds were synthesized in good yields and high purity. They were evaluated with anti-bacterial activity³⁸.



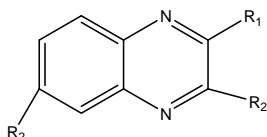
2,3-diphenyl quinoxaline-6-sulfonyl chloride

2,3-diphenyl quinoxaline-6-sulfonic acid amide

4) 6-Substituted quinoxalines and 7-substituted pyrido[2,3b]pyrazines were evaluated for their anti microbial activity³⁹.



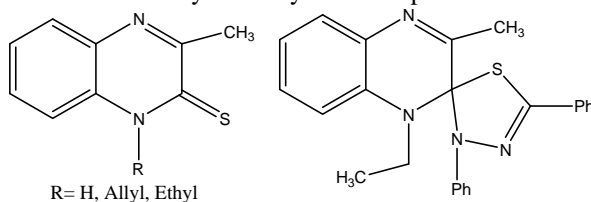
R1=H; R2=Ph, R1=H; R2=Me, R1=H; R2=Pyr, R1=Br; R2=Ph, R1=Br; R2=Me, R1=Br; R2=Pyr,



R₁= Ph; R₂= H
R₁=Ph; R₂=Cl
R₁=Ph; R₂=Br
R₁=Me; R₂=H

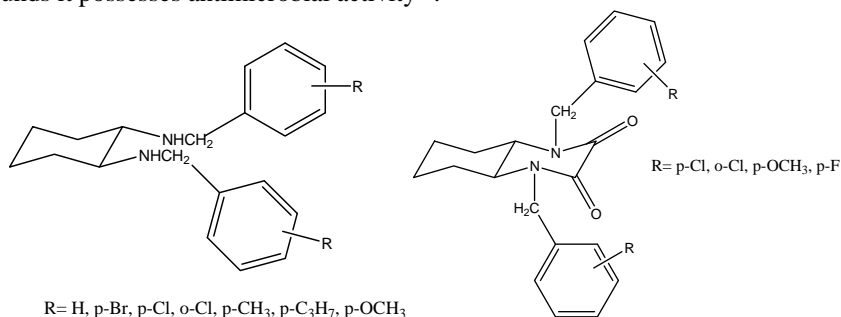
6-Substituted quinoxalines

5) The 1,3-dipolar cyclo addition of 3-methylquinoxaline-2-thione and their *N*-alkylated derivatives to diphenylnitrile imine is presented. Using this method, spiro[thiadiazoline-quinoxaline] derivatives as biologically interesting compounds were produced in high to excellent yields. Antibacterial activity of the synthesized products has been studied⁴⁰.



R= H, Allyl, Ethyl

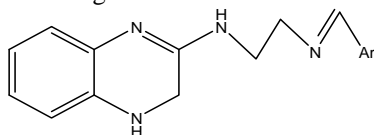
6) The formation of *N,N*-disubstituted cyclohexane-1,2-diamine derivatives through reductive alkylation of 1,2-cyclohexanediamine with different aldehydes in presence of sodium cyanoborohydride. Fusion of compounds with diethyl oxalate affording the target compounds it possesses antimicrobial activity⁴¹.



R= H, p-Br, p-Cl, o-Cl, p-CH₃, p-C₃H₇, p-OCH₃

R= p-Cl, o-Cl, p-OCH₃, p-F

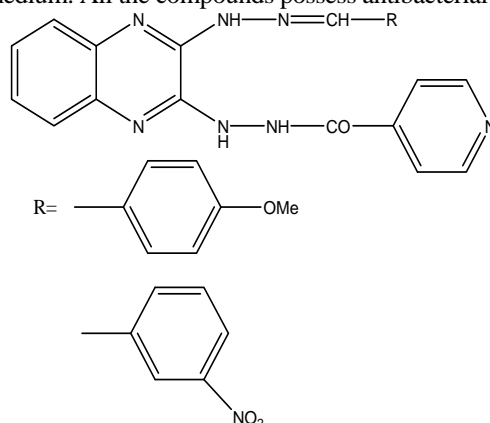
7) In an effort to develop potent anti-microbial agents, we have synthesized some substituted quinoxalin-2(1*H*)-one derivatives by Phillip's condensation mechanism. Final derivatives were screened for their *in vitro* anti-bacterial activity against range of Gram positive and Gram negative and also for their anti-fungal activity against a strain of *Candida albicans* species⁴².



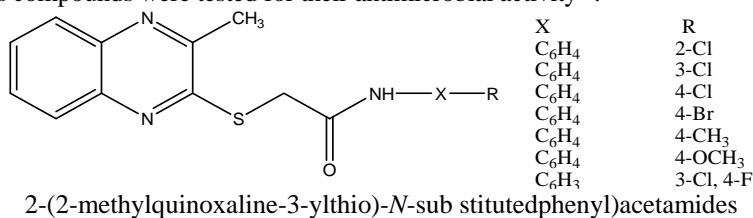
C₆H₅-CH₂CH=CH CHO
III b 3Cl-C₆H₄ CHO
Ar= III c (CH₃)₂N C₆H₄ CHO
III d 3,4 Cl-C₆H₃ CHO
III e OH Cl-H₃ CHO

3-[(2-((*E*)-(substituted phenyl) methyliden)amino)ethyl]amino]quinoxalin-2(1*H*)-one

8) Starting compound quinoxaline-1,2-diol was prepared from *o*-phenylenediamine and diethyloxalate upon refluxing for 1 h in single step. The quinoxaline-1,2-diol was refluxed for 90 min with phosphorous oxy chloride, to furnish 2,3-dichloroquinoxaline. Further 3-chloro-2-hydrzinoquinoxaline was prepared by reaction of 2,3-dichloroquinoxaline and hydrazine hydrate in methanolic medium upon refluxing for 20 min. The different Schiff's bases of 3-chloro-2-hydrzinoquinoxaline were obtained by refluxing the appropriate substituted benzaldehydes and 3-chloro-2-hydrzinoquinoxaline in acetic acid medium for 2 h. The obtained quinoxaline Schiff's bases were further converted into their derivatives by reacting the Schiff's bases with isoniazide in pyridine medium. All the compounds possess antibacterial activity⁴³.

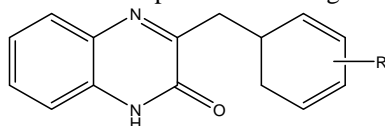


9) 2-Chloro-3-methylquinoxaline was selected as nucleus around which the molecular manipulations were carried out to get new compounds expected to possess better antimicrobial activity. Various quinoxaline derivatives have been synthesized by replacing the chlorine at C-2 with a thioether linkage, which in turn attached to 2-(*N*-(substituted phenyl) acetamides). The synthesized compounds were tested for their antimicrobial activity⁴⁴.



2-(2-methylquinoxaline-3-ylthio)-*N*-substituted phenylacetamides

10) Substituted 3-benzylquinoxalines were synthesized from substituted phenyl pyruvic acid and *o*-phenylenediamine. All the compounds showed good antifungal activity⁴⁵.

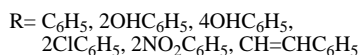
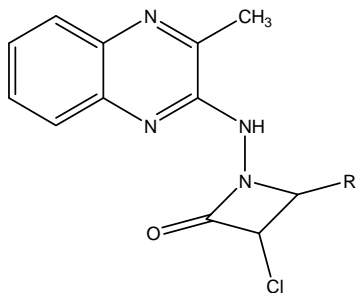


Substituted 3-benzylquinoxaline derivatives

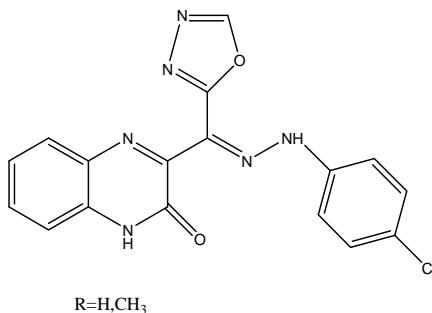
11) Condensation of 4-benzoyl-1,2-phenylenediamine with sodium pyruvate in acetic acid furnished two products which were identified as 6-benzoyl and 7-benzoyl-3-methyl-2(1*H*)quinoxalinones. Fusion of 6-benzoyl compound with aromatic aldehydes furnished the styryl derivatives. Alkylation of 6-benzoyl and 7-benzoyl-3-methyl-2(1*H*)quinoxalinones with dimethyl sulphate or ethyl chloroacetate produced the *N*-alkyl derivatives. Hydrazinolysis of the

ester derivative with hydrazinehydrate afforded the hydrazone derivative which underwent condensation with aldehydes to give the corresponding hydrazone derivatives. In addition, chlorination of 6-benzoyl compound with thionyl chloride afforded the 2-chloro derivative which was subjected to reaction with sodiumazide and *n*-butylamine to yield the corresponding tetrazolo and *n*-butylamino derivatives, the synthesized compounds were screened for antimicrobial activity⁴⁶.

12) 1-*N*-(3-Methyl quinoxaline-2-yl-amino)4-aryl-3-chloro-2-azetines has been synthesized for their antimicrobial activity⁴⁷.



13) Quinoxaline derivatives containing an oxadiazole moiety demonstrated marked antibacterial activity⁴⁸.



Conclusion

The different type of quinoxaline derivatives are shows antimicrobial activity. The plethora of research described in this review indicates an antimicrobial activities exhibited by quinoxalines derivatives. The biological profiles of these new generations of quinoxalines would represent a fruitful matrix for further development of quinoxaline nucleus, which can be a lead nucleus for future developments to get safer and effective therapeutic agents.

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