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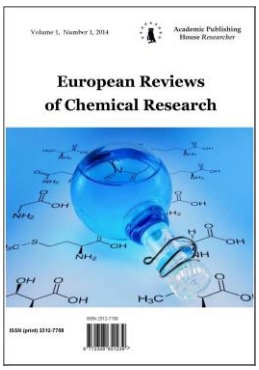

Articles and Statements

UDC 544

Synthetic Methods and Exploring Biological Potential of Various Substituted Quinoxalin-2-one Derivatives

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Abstract

Substituted quinoxaline have considerable interest in chemistry, biology and pharmacology. Quinoxaline derivatives are capable with variety of biological activities and possess different biological activities, of which the most potent are anti-microbial, analgesic and anti-inflammatory activities. It facilitated the researchers to develop various methods for their synthesis and their applications. In this review represented different methods of synthesis, reactivity and various biological activities of quinoxaline derivatives.

Keywords: Quinoxaline, reactivity, biological activities, synthetic methods.

Introduction

Quinoxaline and its derivatives are important nitrogen containing heterocyclic compounds of various biologically properties. Quinoxaline and its derivatives are mostly of synthetic origin. Substituted quinoxalines are an important class of benzoheterocycles, which constitute the building blocks of wide range of pharmacologically active compounds having antibacterial [1-4] antifungal [5], anticancer [6, 7], antitubercular [8], antileishmanial [9], antimalarial [10] and antidepressant activities [11]. Also, some quinoxalin-2-ones and quinoxaline-2,3-diones have been reported to show antimicrobial [12, 13], potent antithrombotic [14], anti-pain and anti-inflammatory [15] activities. The quinoxaline is described as a bioisoster of quinoline, naphthalene, benzothiophene and other aromatic rings such as pyridine and pyrazine. Because of the similarity between some antitubercular drugs and quinoxaline, as well as the presence of the quinoxaline moiety in some broad spectrum antibiotics, it was hoped that quinoxaline analogs would exhibit antitubercular activity [16]. The quinoxaline antibiotics are agents of bicyclic desipeptide antibiotic that have been reported activity against gram-positive bacteria and certain tumors and to inhibit RNA synthesis [17]. Quinoxaline has also been used in reactive dyes and pigments, azo dyes, fluroscein dyes and it also forms a part of certain antibiotics. Quinoxaline m.p. 29-30°C and is miscible with water. It is weakly basic (*p*ka 0.56) and thus considerably weaker base than the isomeric diazonapthalenes namely cinnoline (*p*ka 2.42), pthalizine (*p*ka 3.47) or quinazoline (*p*ka 1.95). 2-Hydroxy-but not 2-amino quinoxaline exist in tautomeric forms.

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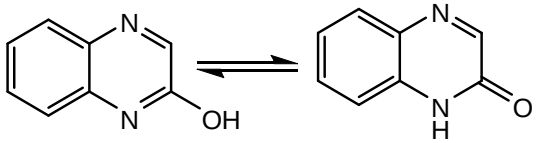
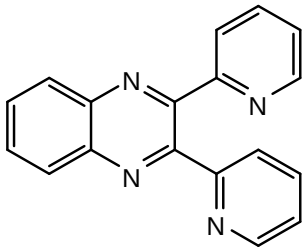
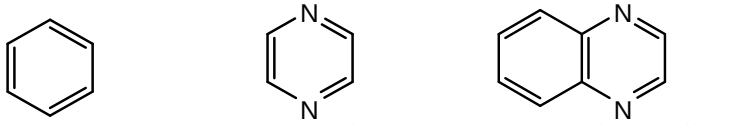


Some of quinoxaline analogues, such as 2,3-bis (2-pyridyl)-quinoxaline (DPQ) complexed with transition metals are of current interest in view of its binding to DNA. This may suggest that conjugation of biologically active peptides with quinoxaline analogs can lead to new therapeutic agents possessing interesting anticancer properties [18].



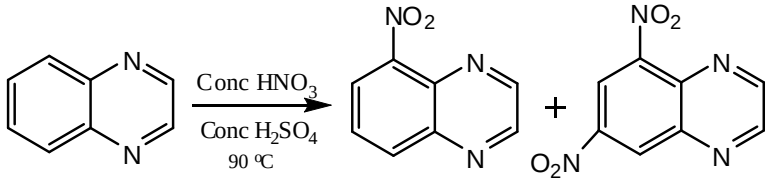
2,3-bis(2-pyridyl)-quinoxaline (DPQ): Quinoxaline derivatives constitute the basis of many insecticides, fungicides, herbicides, as well as being important in human health and as receptor antagonists. Although rarely described in nature, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin, levomycin and actinomycin which are known to inhibit the growth of Grampositive bacteria and also active against various transplantable tumors. In addition, quinoxaline derivatives are reported for their application in dyes, efficient electroluminescent materials, organic semiconductors and DNA cleaving agents [19].

History: Quinoxaline is also called as benzopyrazine. It is heterocyclic compound containing benzene ring and pyrazine ring. Pyrazine are stable, colorless compound which are soluble in water. Unlike pyridine, they are expensive, not readily available and 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 fruits and vegetable such as Peas and Capsicum peppers and also of wines [20].



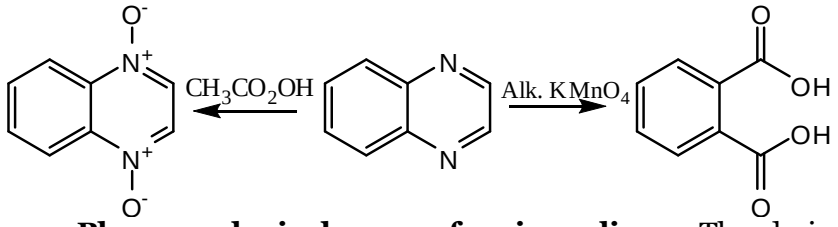
Benzene **Pyrazine** **Quinoxaline**

Quinoxaline is a low melting solid, m.p 29-30˚C and is miscible with water. It is weakly basic pKa 0.56. Quinoxaline forms salts 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 (24%).



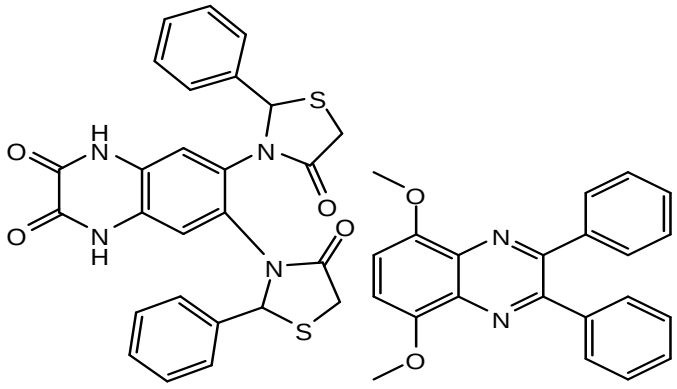
1.5% **24%**

Oxidation of quinoxaline results in the formation of the product depending on the nature of the oxidizing agent employed. With alkaline potassium permanganate pyrazine 2,3-dicarboxylic acid is formed, while with peracid quinoxaline di-N-oxide results [52].



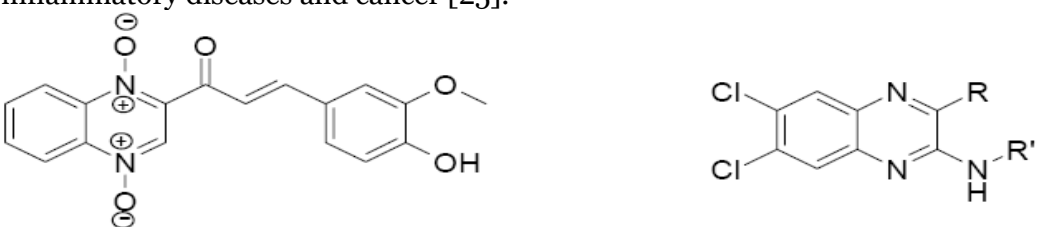
Pharmacological uses of quinoxalines: The derivatives of quinoxalinone occupy a significant place in several areas, particulary in pharmacology. Also, the modifications in the basic structure of the quinoxalinone, have enabled the emergence of new derivatives with a wide spectrum of biological activity. These derivatives have shown that structural modification can improve its pharmacological profile conferring antibacterial, anticancer, anti-HIV, tranquilizers and sedative properties. The anticancer and antidepressant activities are the most encouraging activities for the pharmacists.

Antimicrobial agent shows activity against bacteria, fungi, mycobacterium species, called antibacterial, antifungal, antituberculer activity respectively. There are various quinoxaline derivatives showing antimicrobial activity. Some new condensed bridge head nitrogen heterocycles of quinoxalines were evaluated for antimicrobial activity against the gram positive bacteria *Staphyllococus aureus* and *Bacillus subtilis*, the gram-negative *Psudomonas aeruginosa* and *proteus vulgaris*, the fungi *Aspergillus niger* and the *Mycobacterium tuberculosis* H37Rv species. The pyrrolo[3,4-*b*]quinoxalines were tested for their antibacterial activity against *S. aureus, Escherichia coli* and their antifungal activity against *Candida albicans* at a concentration of 3mg/mL. Steptomycin (25 µg) and Mycostatin (30 µg) were used as reference for the antibacterial and antifungal activities, respectively [1]. A series of 6,7-Bis[2-(substituted Phenyl)-4-oxothiazolidin-3-yl]quinoxaline-2,3-(1*H*,4*H*)-diones (1) were screened for anti-TB activity against H37Rv strains of *M. tuberculosis* at a concentration of 6.250 g/ml. Isoniazid (0.0250 g/ml) and Rifampicin (0.1250 g/ml) were used as standards [21,22]. Antiamoebic activity of 2,3-diaryl-5,8-dimethoxy-quinoxalines (**2**). The *in vitro* activity of the compounds against *Entamoeba histolytica* was determined. Most of the compounds displayed *in vitro* activity at 50-200 µg/ml concentrations. Standard drugs Nitroimidazole and Diloxanide furoate showed *in vitro* activity at 2-5 µg/ml concentrations [23].



1 **2**

Various studied the anti-inflammatory and antioxidant activity of several quinoxalines. Compound **3** presented the most interesting activity [24]. Similarly, in anti-inflammatory activity of the quinoxaline B **(4)** by varying R and R substituents. Compounds B_1 and B_2 were found to be non-peptide antagonists of the interleukin-8 molecule receptor, which is involved in several inflammatory diseases and cancer [25].



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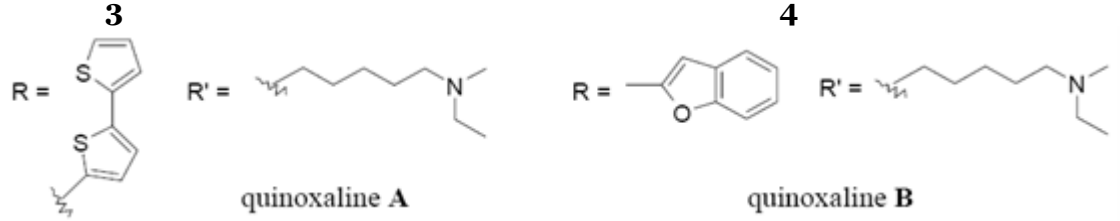
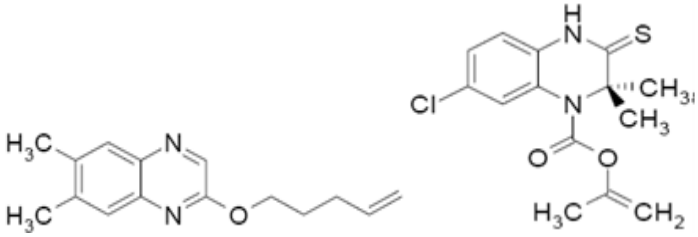


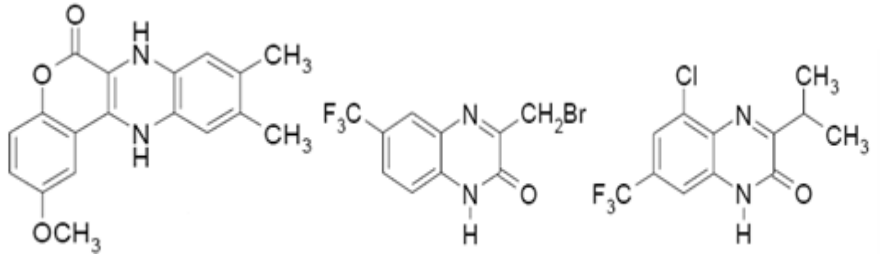
quinoxaline **A** quinoxaline **B**

Similarly, the quinoxalinone derivatives have antiviral properties [26, 27]. Many studies have shown the activity of a few quinoxaline compounds towards the human immunodeficiency virus (HIV-1), including the 6,7-dimethyl-2-(pent-4-enyloxy)quinoxaline **5**, [29] and S-2720 **6**, which not only inhibit HIV-1 RT, but prevent its replication at the cellular membrane [30].

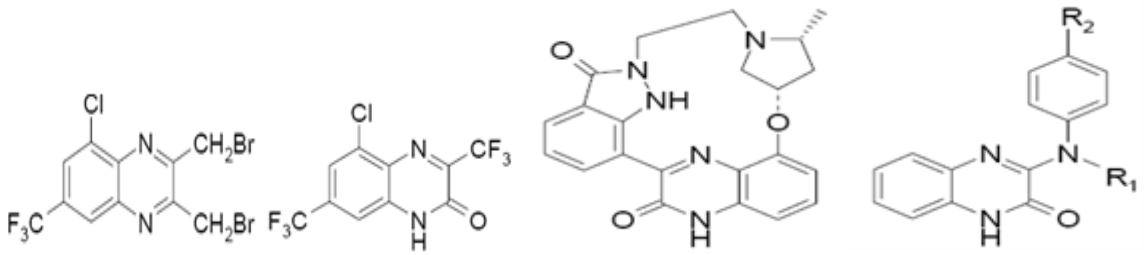


4 **5**

Another activity of quinoxalines is the anti-microbial one. The 9,10-dimethyl-2-methoxy-6-oxo-7,12-dihydro–chromo-[3,4-b]quinoxaline **6** has both, antibacterial and antifungal activities [31]. The quinoxalines **7**, **8**, **9**, and **10** possess the same activities [32]. The compound **11** is a molecular macrocycle derived from the quinoxalin-2-one inhibitor of cyclin-dependent kinases CDK1, 2, 4 and 6 [33]. While the compound **12** [34] inhibiting glycogen phosphorylase is the enzyme responsible for the metabolism of glycogen to glucose since glucose is over produced in patients suffering from diabetes.

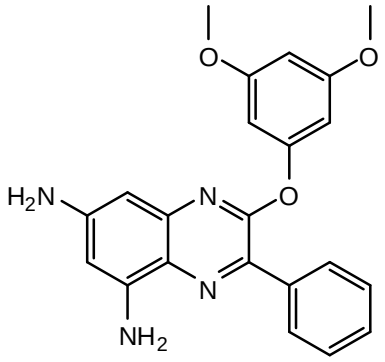


6 **7** **8**



9 **10** **11** **12**

Some quinoxaline derivatives which showed antitumor activity, 5,7-diamino-3-phenyl-2-[(3,5-dimethoxy)phenoxy]quinoxaline **13** has an antitumor activity in vitro, towards several types of tumors [36]. Also the 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline-1,4-dioxide **14**, has an activity against the tumor in the hypoxia stage, which is a phase where the tumor shows a resistance during chemotherapy and radiotherapy [37]. Various results are showing activities of quinoxaline, as an inhibitor of the kinase protein [38], or as antagonists of bradykinin, which is a peptide responsible for the dilatation of blood vessels, thus leading to the lowering of blood pressure [39]. A series of quinoxaline derivatives **15**, which could act as modulators of the AMPA receptor mediators of synaptic responses [40].



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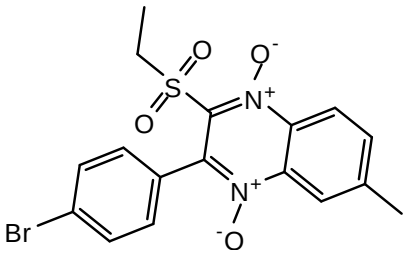

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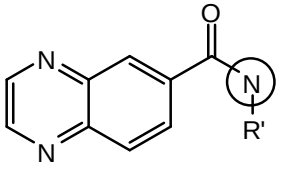
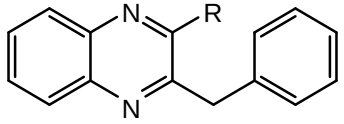


15

The circle containing nitrogen designates a heterocycle of 5 to 8 rings, the group R' may be a group 2- or 3-alkyl, cycloalkyl, hydroxy, alkoxy, alkoxy-alkyl, hydroxy-alkyl, or carbamoyl.

The 3-benzyl-2-substituted quinoxalines as novel monoamine oxidase A (MAO-A) inhibitors. MAO inhibitors is useful for the treatment of several neurological diseases such as Parkinson's disease and depression. MAO-A inhibitors are used as antidepressant and anti-anxiety drugs. The compounds (**16**) were evaluated for their MAO-A inhibitory activity *in vitro* using serotonin as substrate. All these compounds were used at a concentration of 1×10^{-4} M [41]. Methyl [4-(substituted 2-quinoxalinyloxy) phenyl] acetates (**17**) and ethyl N-{[4-(substituted-2-quinoxalinyloxy) phenyl] acetyl} glutamate analogs of Methotrexate were evaluated for *in vitro* anti cancer activity by bioisosteric replacement [42].



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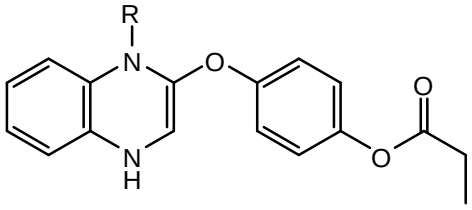
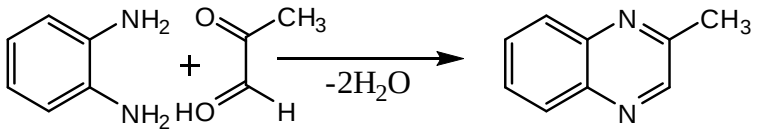


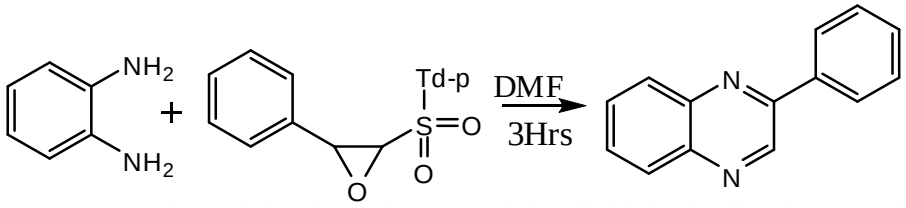
17

The 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 [43].

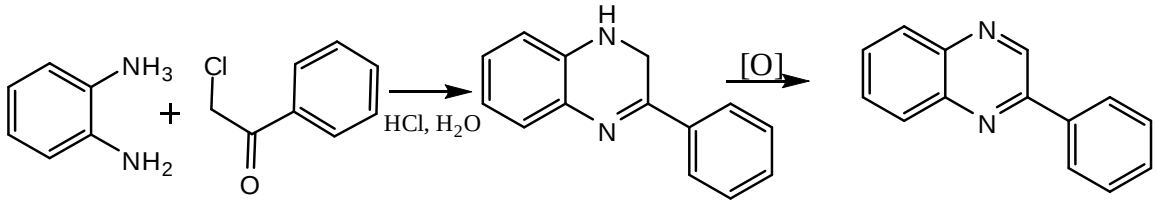
Synthesis of quinoxalines: The synthesis methods proposed can be divided into two categories. The first one involves cyclocondensation reactions between *o*-phenylenediamines and aliphatic electrophile compounds, in conventional terms, or in the presence of metal salts in solution or solid support under microwaves. The pyrazine nucleus may also be formed using derivatives of *o*-substituted aniline. Another class of reactions involves nitrogen heterocycles which has different links likely to opening reactions or rearrangements in different conditions, leading to opened intermediates that, later, cyclize to give the quinoxaline derivatives. The fusion of one or two benzene rings in quinoxaline and phenazine increases the number of resonance structure, which are available to these systems. It posses the dipole moment of zero. Quinoxaline itself is prepared by the reaction of *o*phenyldiamine and glyxol [44]. Simillarly 2-Methyl Quinoxaline has been prepared by the reaction of *o*-phenyldiamine and pyruvaldehyde.



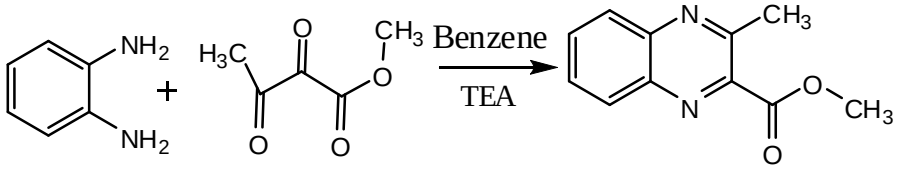
The 1-(*p*-tolysulfonyl)-2- phenyloxirane, obtained from the condensation of chloromethyl *p*-tolysulfone with benzaldehyde, on reaction with *o*-Phenylenediamine yields 2-phenyl quinoxaline in good yield [45].



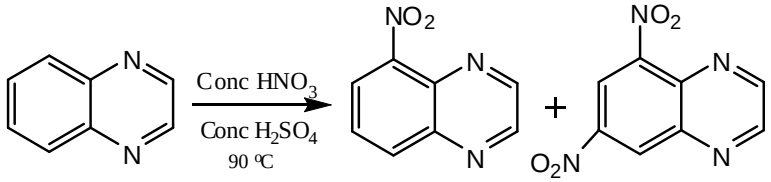
A number of simple variations of the dialdehyde diamine reaction appear to work well. Thus replacement of the dialdehyde with a α-halogenketone results in the formation of 2- substituted quinoxaline.2-phenylquinoxaline has been prepared in this manner from phenacyl chloride and *o*-phenylenediamine [46].



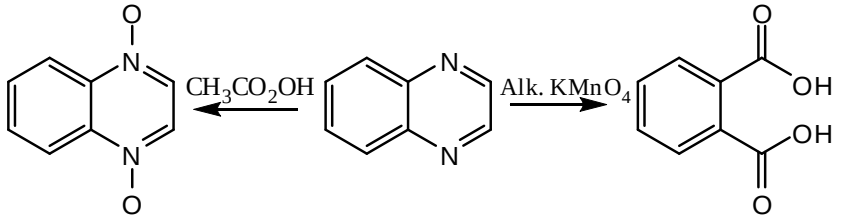
Compounds containing 1,2,3-tricarbonyl functionality have been used in the synthesis of a variety of Heterocyclic derivatives [47]. The tricarbonyl group containing compounds can be prepared by treating 3-keto ester with *p*-nitro sulphonyl peroxide 6, to give 2-(p-nitro phenyl)-sulfonyl) oxy)-3-keto esters.



Treatment of the resulting 2-(nosyloxy)-3-ketoesters with triethyl amine (TEA) in benzene at roosm temperature results in *vic* tricarbonyl compound. The tricarbonyl compound can be trapped *in situ* with *o*-phenylenediamine to give quinoxaline derivatives. Quinoxaline forms salt with acids. Nitration occurs only under forcing conditions (Conc.HNO_3, Oleum) to give 5-nitro-quinoxaline (1.5%) and 5,-7-dinitroquinoxaline (95%) [48].

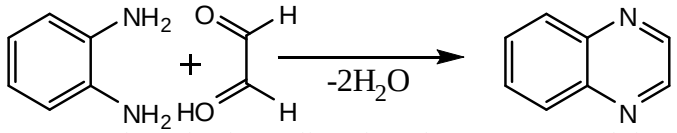


The 2-chloroquinoxaline has been prepared by the action of phosphorous oxychloride on quinoxaline -2-one or quinoxaline-1- oxide [49]. Oxidation of quinoxaline results in the formation of the product depending upon the nature of the oxidizing agent employed. With alkaline potassium permagnate pyrazine 2, 3-dicarboxylic acid is formed, while with peracid quinoxaline *di*-N-oxide results. 2-methylquinoxalineon selenium dioxide oxidation affords quinoxaline 2-carboxaldehyde.

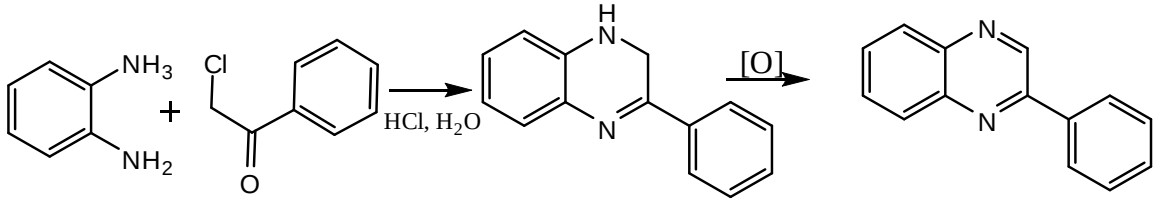


Alkyl radicals produced from acyl peroxide or alkyl hydro peroxide give high yields of 2-substituted alkyl derivatives. Reduction (Na, C_2H_5OH) of quinoxaline gives a 1,2,3,4-tetrahydro Derivatives [50, 51].

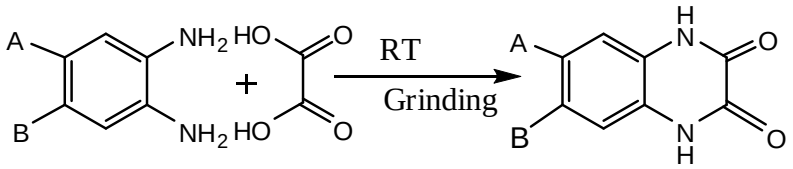
Quinoxaline itself is prepared by the reaction of o-phenylenediamine and glyoxal.



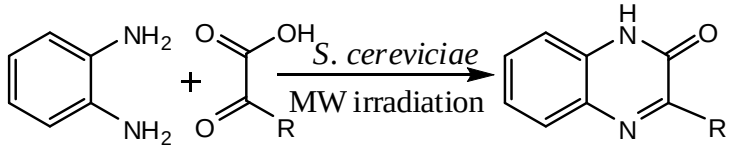
2-Phenylquinoxaline has been prepared in this manner from phenylacylchloride and *o*-phenylenediamine [52].

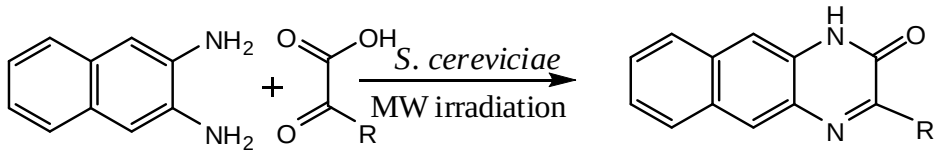


Several methods for synthesis are available in literature which involves conventional one pot, and microwave synthesis methods [53]. One-pot efficient green synthesis of 1,4-dihydro-quinoxaline-2,3-dione derivatives has reported by potential pharmacophore 1,4-dihydro-quinoxaline-2,3-dione has been achieved in a one-pot reaction at room temperature from substituted *o*-phenylene diamine and oxalic acid under solvent free conditions by a simple grinding method. Thermal and powder X-ray diffraction analysis was carried out for some crystals [54].

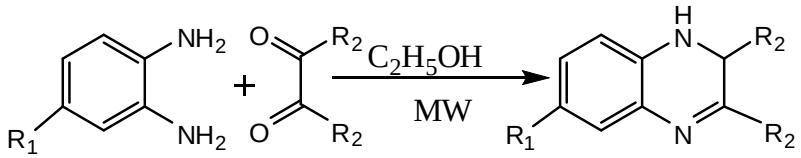


The microwave-assisted Hinsberg reaction of quinoxalinone derivatives by reacting *o*-phenylenediamine or 2,3-diaminenaphthalene with a variety of α-ketoacids through enzymatic catalysis or microwave irradiation [55].

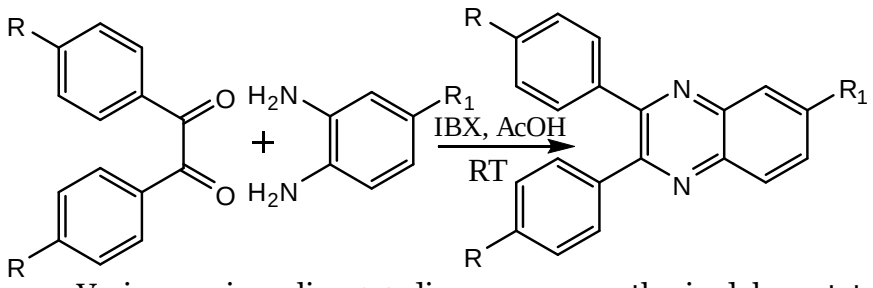




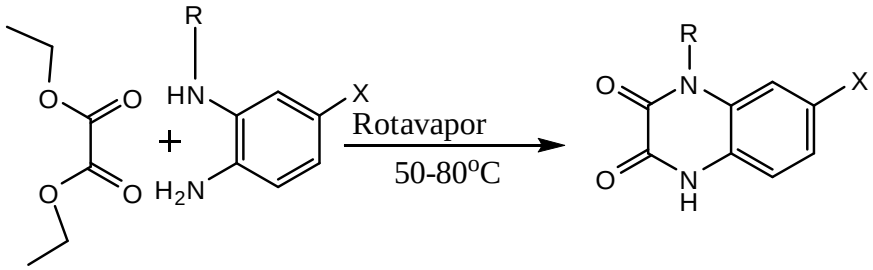
Quinoxalines are effectively synthesized in a few min by the condensation reaction of *o*-phenylenediamine with α-dicarbonyl compounds in ethanol under microwave irradiation [56]. High yield, short reaction time, pure products without purification and using only ethanol instead of toxic and expensive solvents for isolation of the products, are the advantages of this method.



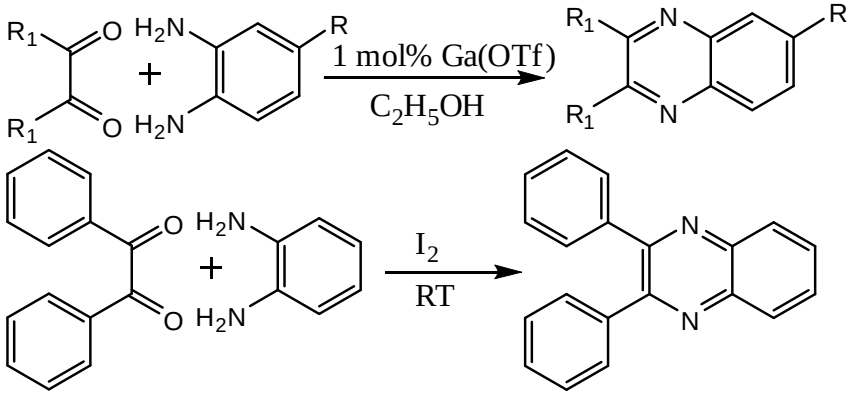
A facile synthesis of quinoxaline derivatives and quinoxaline-2, 3-diones as NMDA receptor antagonists 32 were also reported. *o*-Iodoxybenzoic acid (IBX), a readily available hypervalent iodine reagent, was found to be highly effective in synthesis of quinoxaline derivatives, from 1,2-diketones and *o*phenylenediamines at room temperature in very high yield [57].



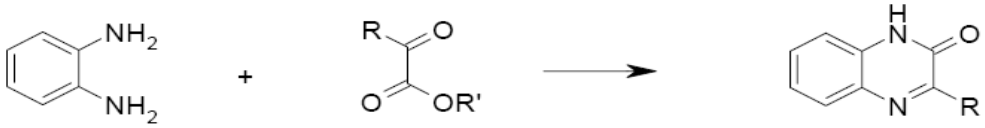
Various quinoxaline-2,3-diones were synthesized by rotatory evaporation of 1,2-diamino aromatic compounds in diethyl oxalate at 50-800C [58].



Gallium (IIII) triflate-catalyzed reactions of phenylene-1,2-diamines and 1,2-diketones produce quinoxalines in excellent to quantitative yields. The reactions proceed with 1 mol% catalyst in ethanol at room temperature. The catalyst can be recycled for at least 10 times. Attempt to synthesize quinoxaline derivatives at room temperature using molecular iodine as the catalyst are present in the literature as reported by several aromatic as well as aliphatic 1,2-diketones and aromatic 1,2-diamines, such as substituted phenylene diamines, tetra amines were further subjected to condensation using catalytic amounts of iodine to afford the products in excellent yield [59].

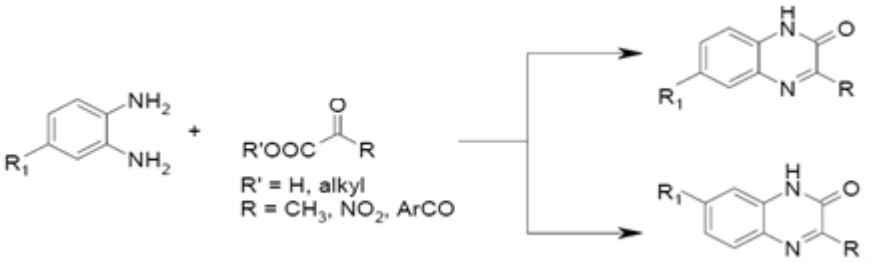


Condensation of *o*-phenylenediamine with α-ketocarboxylic acid and ketoesters: The 1,2-dihydroquinoxalin-2-ones and their derivatives substituted in position 3 were obtained by condensation of *o*-phenylenediamine with α-ketocarboxylic acid and ketoesters or their correspondents in accordance with the method of Hinsberg [60-62].

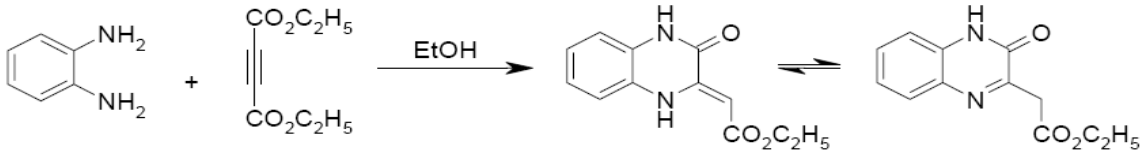


R' = H, alkyl

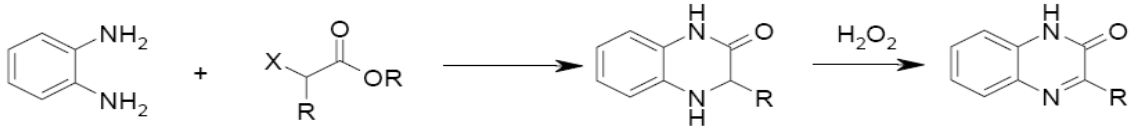
It should be noted that when the reaction involves the monosubstitued *o*-phenylendiamines, it was possible to obtain a mixture of two isomers [63-65].



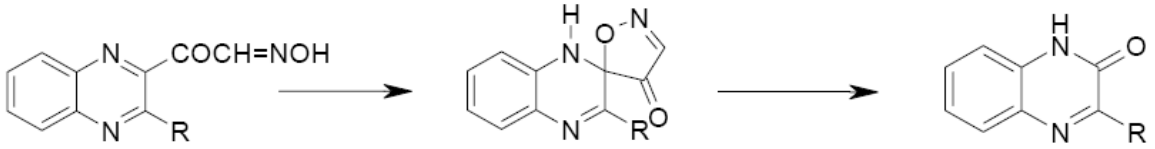
The condensation of *o*-phenylenediamine with diethyl acetylenedicarboxylate in ethanol, used to prepare a compound with quinoxaline structure which exist in two tautomeric forms [66].



From quinoxaline intermediates: The quinoxaline by condensing the α-halogenoesters with *o*-phenylenediamine and creating an oxidation by means of hydrogen peroxide [67].

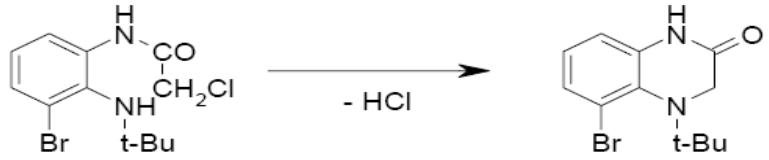


Several examples have been described in the literature on the hydrolysis of 2-aminoquinoxalines leading to quinoxalinones. Thus, the 2,3-diaminoquinoxaline is hydrolyzed by hydrochloric acid (2.5M) at 100 °C, for 5 minutes to give 3-aminoquinoxalin-2-one [68]. In the same way, the treatment of 2-amino-3-phenylquinoxaline by nitric acid, give 3-phenylquinoxalin-2-one with an excellent performance [69]. By leading the oxime quinoxalinylglyoxal to reflux of dimethylaniline, it was possible to prepare the quinoxalinone from a spiro intermediate [70].

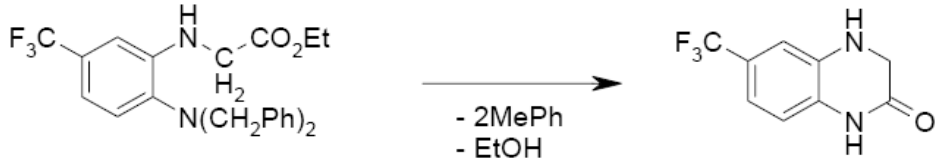


R = Me ou Ph

From derivatives of aniline: The 2-bromo-*N*-tert-butyl-6-(2-chloroacetamido) aniline leads in reflux of acetonitrile for 24 hours to 5-bromo-4-tertbutyl-3,4-dihydro-2(1*H*)-quinoxalinone with a yield of 79% [71].

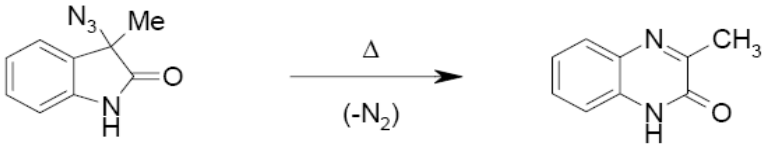


By subjecting the *N*,*N*-dibenzyl-2-(ethoxycarbonylmethyl)amino-4-(trifluoromethyl) aniline to a reduction under a pressure of 3 atmospheres, which induces a spontaneous cyclization, giving the 6-trifluoromethyl-3,4-dihydro-2(1*H*)-quinoxalinone with good yield [72].

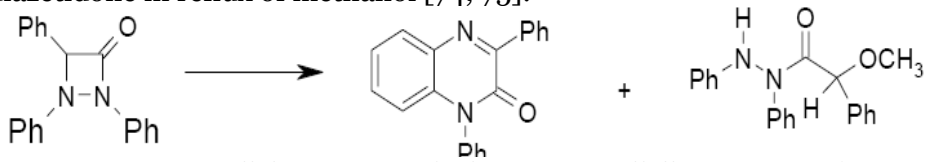


From heterocyclic systems-by cycle extension

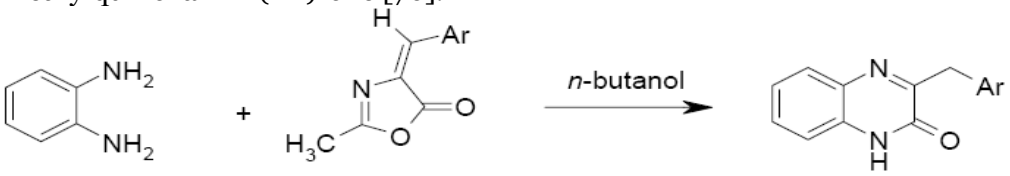
From indolinone: The 3-methylquinoxalinone may also be prepared by an extension of cycle [73]. Thus the 3-azido-3-methyl-2-indolinone is transformed into quinoxalinone in xylene at reflux.



From diazetidone: The quinoxaline was obtained with a yield of 34% by heating diazetidone in reflux of methanol [74, 75].

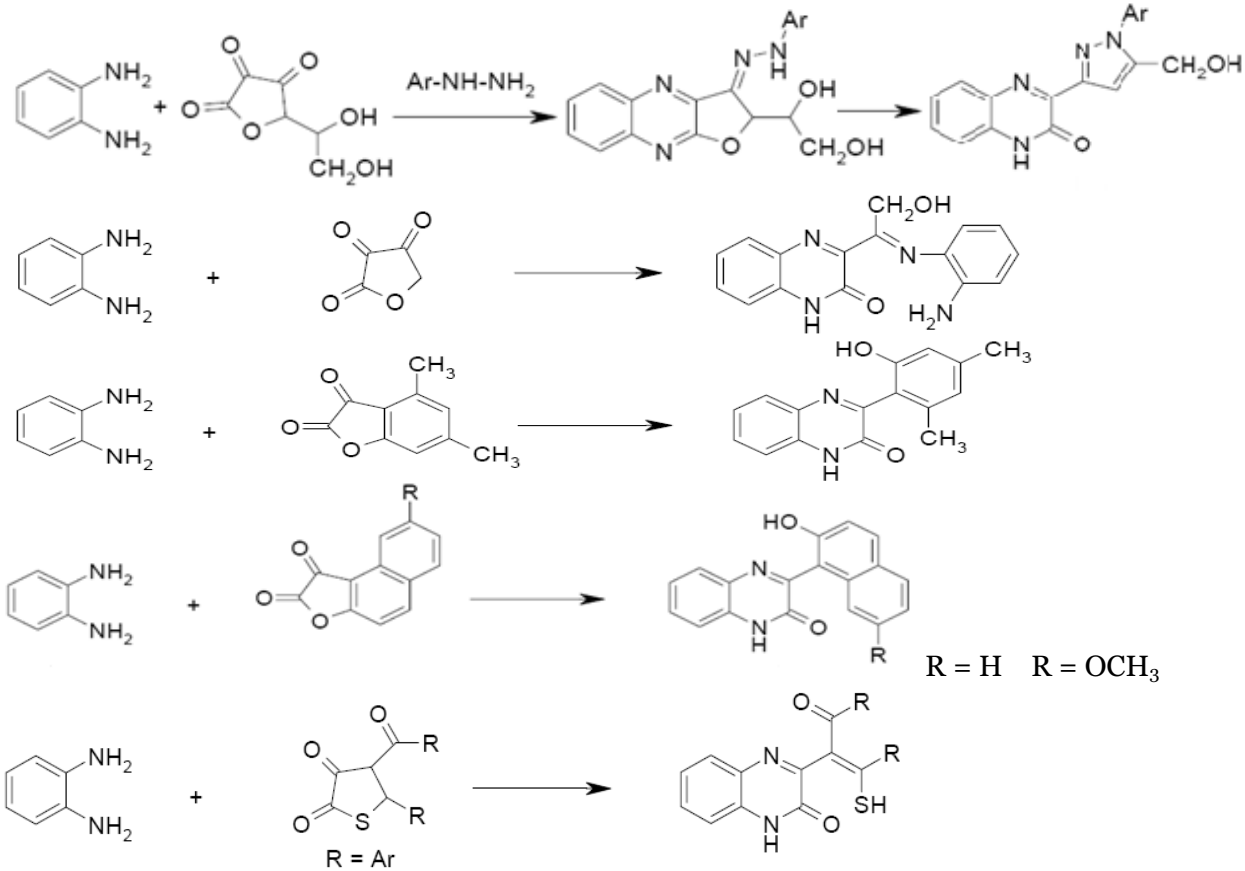


From 4-arylidene-2-methyl-1,3-oxazolidin-5-one: The condensation in *n*-butanol at reflux, *o*-phenylenediamine and 2-arylidene-methyloxazolin-5-one, for accessing the 3-aryl-methylquinoxalin-2(1*H*)-one [76].



From dehydroascorbic acid: Similarly, the condensation of dehydroascorbic acid with *o*-phenylenediamine, led to compound which turns into pyrazolylquinoxalinone in the presence of arylhydrazines [77].

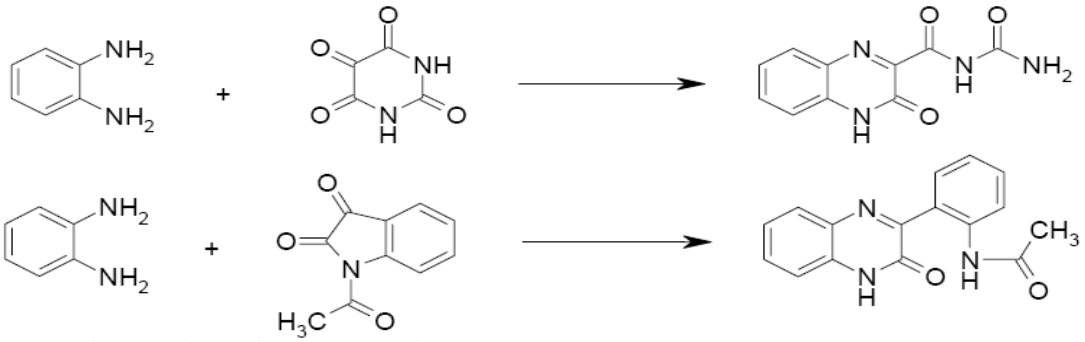
From dicarbonylated five-membered ring compounds: In a similar way, the quinoxalines by condensing *o*-phenylenediamine with heterocyclic dicarbonyl compounds [78].



R = H R = OCH_3

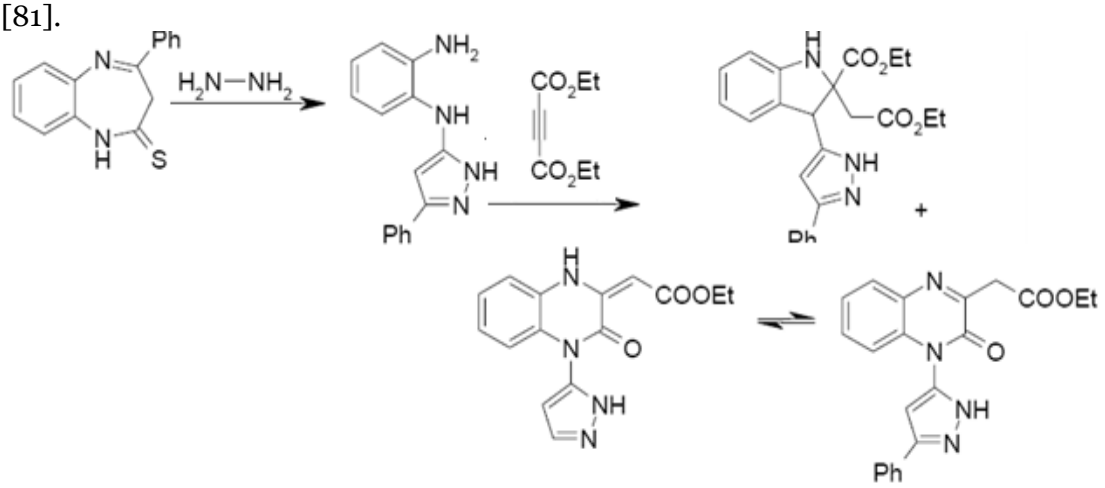
R = Ar

From nitrogenous polycarbonylated heterocycles: Other compounds containing function lactams and were also used as agents of cyclization for the preparation of quinoxalinones and [79-80].

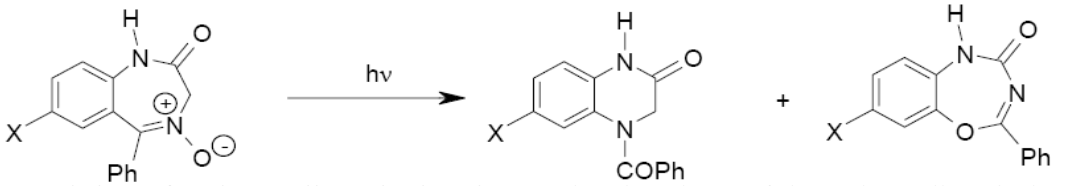


Through cycle contraction

From 1,5-benzodiazepin-2-one: The quinoxaline from benzodiazepine-2-thione in two steps. First, they made an opening round of the seven membered ring, by reacting hydrazine on benzodiazepine-2-thione, obtained by sulfuration of 1,5-benzodiazepin-2-one. The *o*-amino-phenylaminopyrazole obtained undergoes condensation with diethyl acetylene dicarboxylate, gave benzimidazoline, beside of a new quinoxaline derivative which takes form in two tautomeric forms [81].

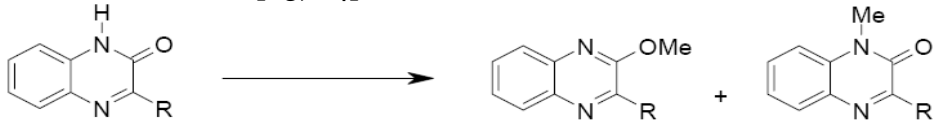


From 1,4-benzodiazepin-2-one N-oxide: Irradiation of 1,4-benzodiazepine gives quinoxaline when (X=Cl). Conversely, we note the formation of oxadiazocine, when (X = SMe) [82].



Reactivity of quinoxaline derivatives: The chemistry of the quinoxaline derivatives with great opportunities due to the presence of different reactive sites: the lactam function involving the nitrogen atom and the carbonyl group; and is involved in alkylation reactions, amination, chlorination, and the sulfuration and in 1,3-dipolar cycloaddition.

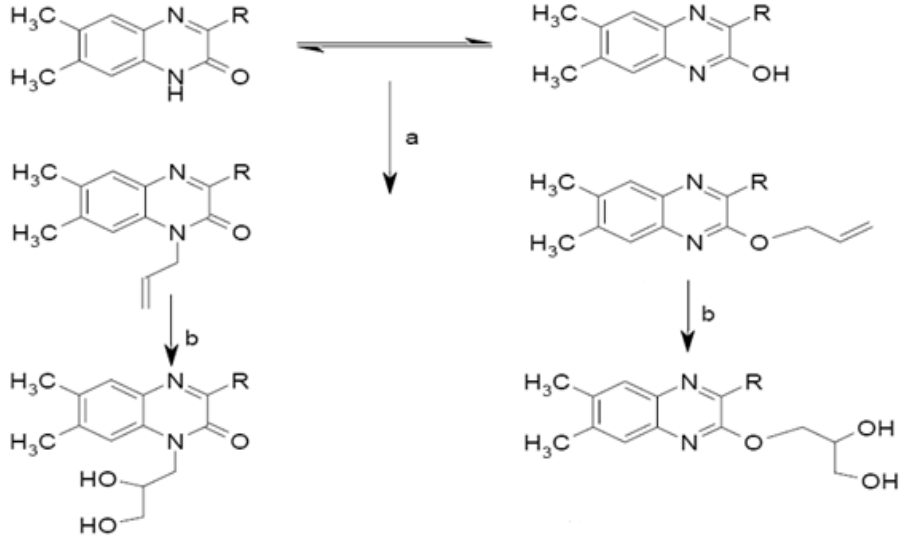
Alkylation: The alkylation reaction of quinoxalin-2-one gives a mixture of *O*-alkyl and *N*-alkyl derivatives. Thus the methylation of quinoxaline by diazomethane involved the two centers of the lactam function [83, 84].



This reaction has been generalized to other alkylating agents, using phase transfer catalysis conditions, to lead to the *N* and *O* alkyl compounds [85].

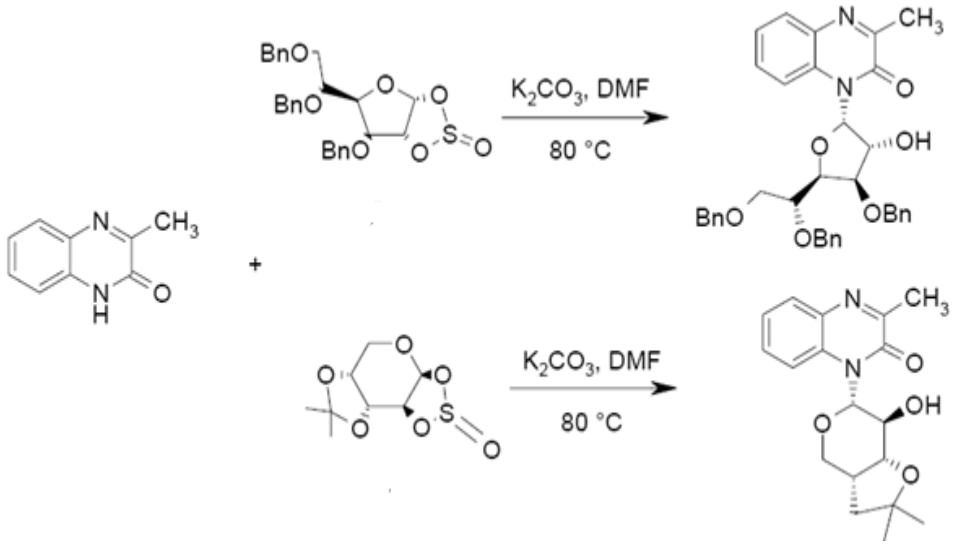
The alkylation reactions have been exploited to prepare quinoxalines differently functionalized in position 1 and 2. Thus, a protocol of using allyl bromide as an alkylating agent

and sodium hydride in dimethylformamide at 100 °C. The dihydroxylation of *N* and *O* alkyl derivatives and compound, was performed with AD-mix β in a mixture *t*-butanol-water [86].

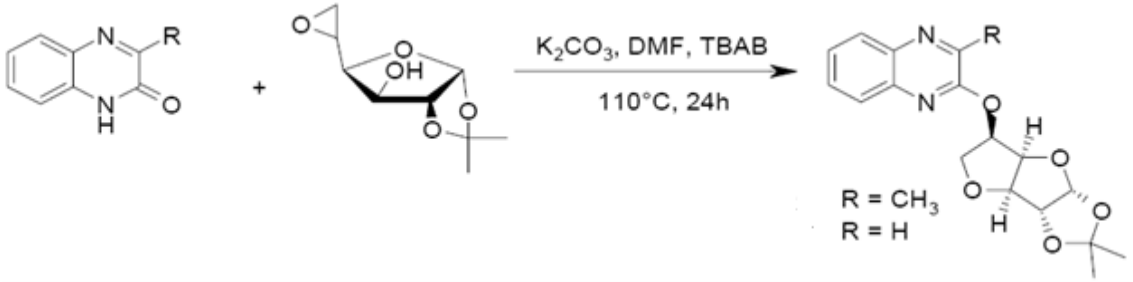


a) Allyl bromide, NaH, DMF, 100 °C b) AD-mixβ. *t*BuOH, H_2O, 0 °C

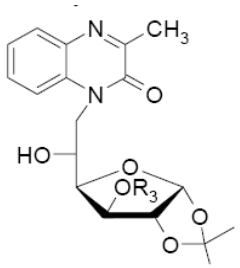
An efficient synthesis method for obtaining nucleoside analogues and, from the quinoxalinone by reacting derivatives1,2-*O*sulfonyl of gluco- and arabino- structure with 3-methylquinoxalin-2(1*H*)-one in the presence of a weak base K_2CO_3 in DMF at 80 °C [87].



The condensation of quinoxalinone with 5,6-anhydro-1,2-*O*-isopropylidene-α-Dglucofuranose, leads to *O*-glucoquinoxalines. In a reaction involving the rearrangement of the 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose to the corresponding 3,6-anhydro, which preferentially reacts with the oxygen atom of the lactam function of quinoxaline. The *O*-glucoquinoxalines obtained were identified [88].

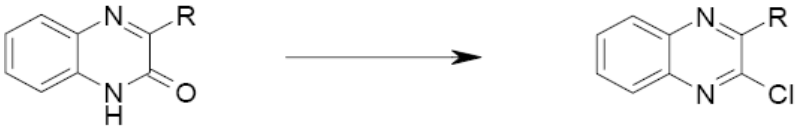


It should be noted that when the hydroxyl group of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose, is protected by an alkyl group, the same reaction is used to isolate the compound of *N*-alkylation beside the compound of *O*-alkylation.

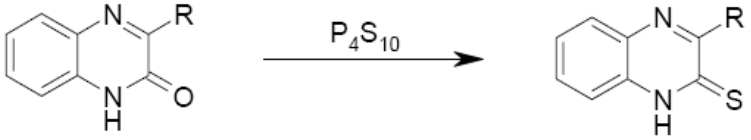


$R_3 = CH_3C_{19}H_{24}N_2O_6$
$R_3 = C_3H_5C_{21}H_{26}N_2O_6$
$R_3 = C_4H_9C_{22}H_{30}N_2O_6$
$R_3 = C_8H_{17}C_{26}H_{38}N_2O_6$
$R_3 = C_{10}H_{21}C_{28}H_{42}N_2O_6$
$R_3 = C_{12}H_{25}C_{30}H_{46}N_2O_6$

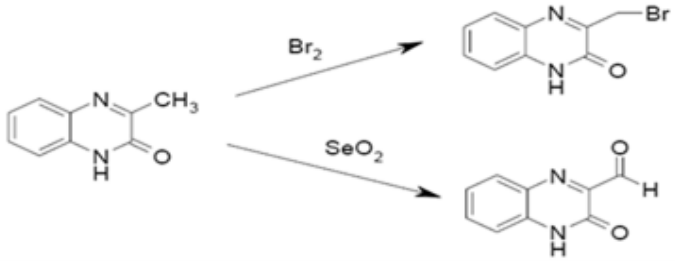
Nucleophilic substitution in position 2: Nucleophilic substitution in position 2 of the 1,2-dihydroquinoxalin-2-one has enabled to isolate the chlorinated products by action of $POCl_3$ or PCl_5 [89].



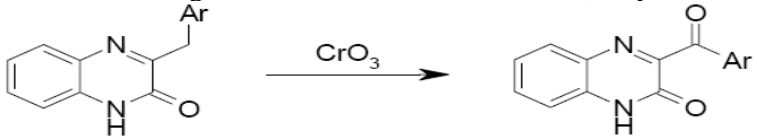
In the case where R = H [90], the chlorination reaction gives the 2,3-dichloroquinoxaline. The reaction of thionation was achieved by the action of phosphorus pentasulfide in pyridine [91, 92].



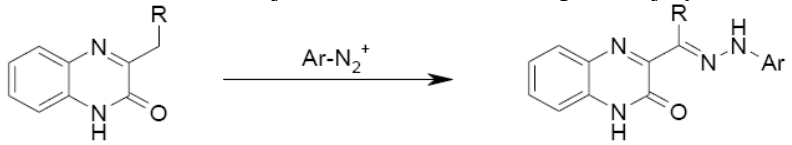
Reactivity of alkyl group in position 3: The alkyl group in position 3 of the quinoxalin-2-one is very reactive to some electrophil agents. Thus, it is easily made the bromination of 3-methylquinoxalin-2-one. The oxidation of quinoxaline 3 by selenium oxide to obtain 3-formyl-quinoxaline [93].



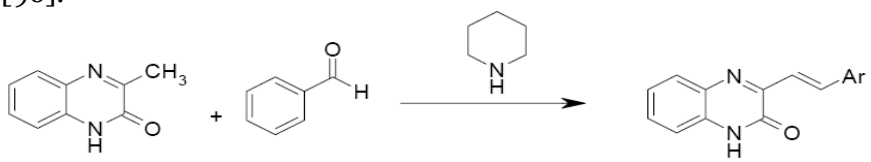
According to an oxidation reaction, the 3-acyl-1,2-dihydroquinoxalin-2-one [94].



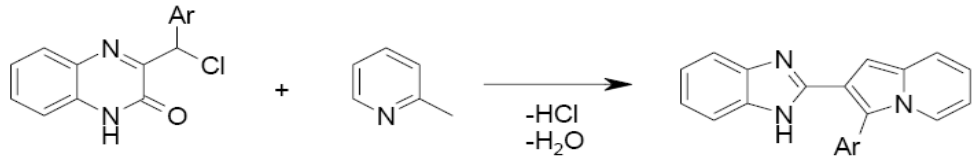
The action of aryldiazonium salt with 3-methylquinoxalin-2-one [95].



The condensation of 3-methylquinoxalin-2-one with aromatic aldehydes gives the compound [96].

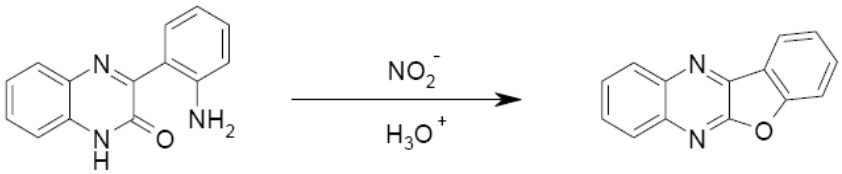


The 2-(indolizin-2-yl) bezimidazole, by condensing 3-(arylchloromethyl-quinoxalin-2-one, with α-picoline [97].

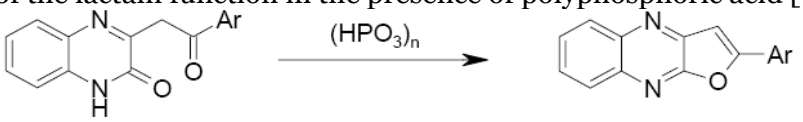


Ar = 4-$NO_2C_6H_4$, Ph, 2,4-$Cl_2C_6H_3$, 3,5-$Cl_2C_6H_3$, CH_2Ph

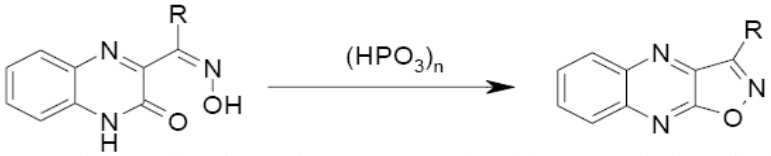
Cyclization reactions involving positions 2 and 3 of the quinoxaline: The cyclization reactions leading to oxygenated heterocyclic systems have been known for a long time and they can give an oxygen and sulfur heterocycles joined to quinoxaline. The Marchlewski and Sosnowski reaction, conducted in the presence of hydrochloric acid, constitutes an oldest example [98].



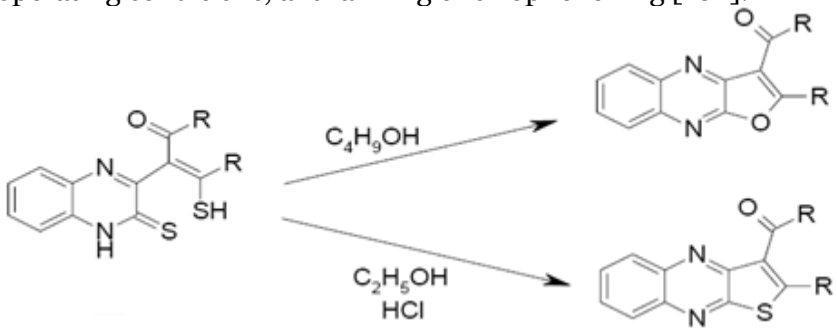
The cyclization of 3-aroylmethyl-1,2-dihydroquinoxalin-2-one, involving the carbonyl group of the lactam function in the presence of polyphosphoric acid [99].



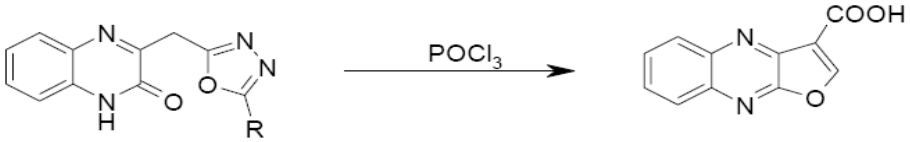
In the same conditions as before, the cyclization of oximes [100,101].



The cyclization of unsaturated sulfur-containing derivatives can provide, according to the operating conditions, a furan ring or thiophene ring [102].

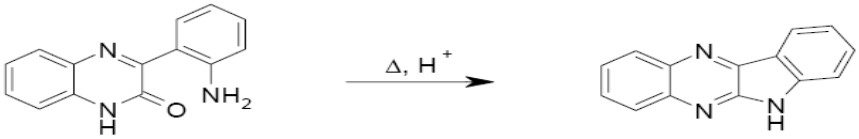


The heating of 3-(1,3,4-oxadiazol-2-yl)-methyl-1,2-dihydroquinoxalin-2-one, in the presence of phosphorus oxychloride allows the preparation of the furoquinoxaline [103].



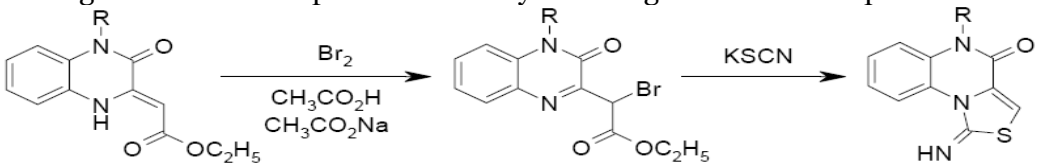
The synthesis of 2-(3-thienyl)-2,3-dihydrofurano[2,3-b] quinoxaline by condensing the 3-methylquinoxaline-2-one with 3-formylthiophene, at 150 °C [104].

The contiguous quinoxaline nitrogen heterocycles such as indole and pyrazole. To cyclize the 3-(*o*-aminophenyl)-1,2-dihydroquinoxalin-2-one **93** (Scheme 34), with the reflux of acetic acid or hydrochloride acid [105, 106].

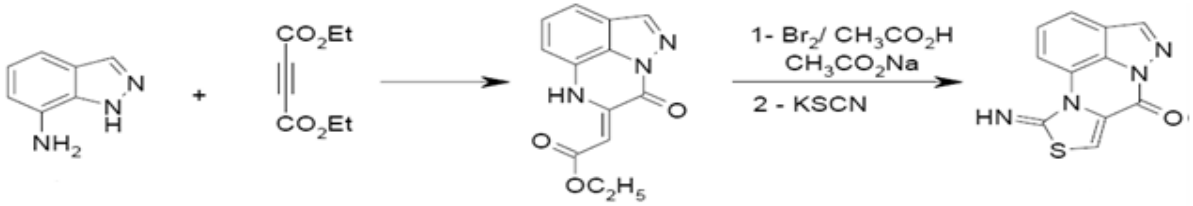


he cyclization of hydrazone to obtain the derivatives of pyrazolo[3,4-b]quinoxalines called « Flavazoles » [107, 108].

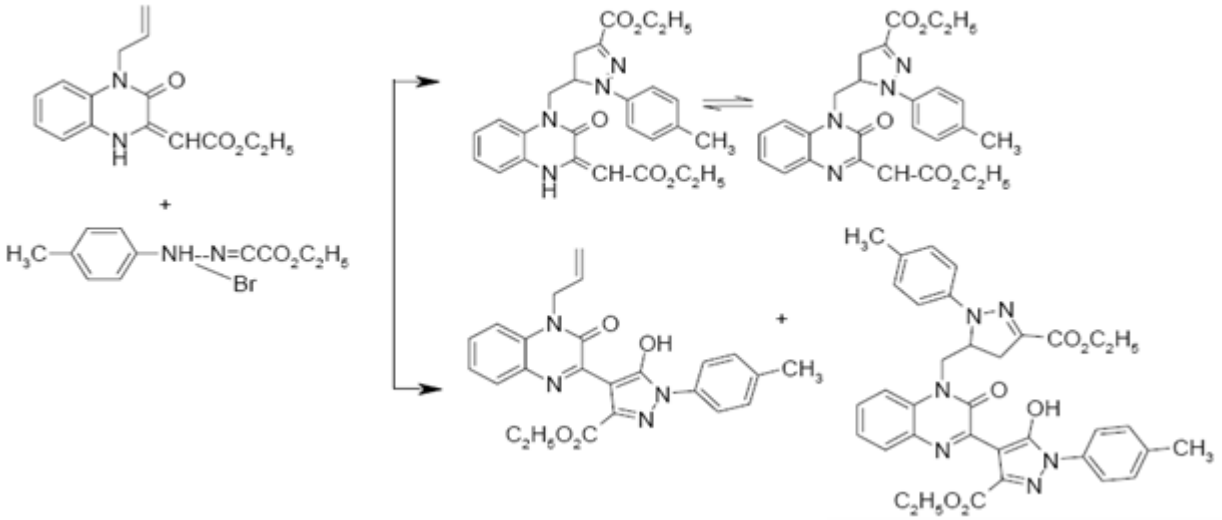
The cyclization occurs in an alkaline solution [109] or at reflux of acetic acid [110]. Several flavazoles were well prepared, when R=aryl or sugar. When R=H, the cyclization could not take place, neither in alkaline, or by heating in acid. A tricyclic system containing the quinoxaline contiguous to the thiazole was obtained by exploiting the presence of β-enaminoester synthon. Thus, the bromination of 3-ethoxycarbonylmethylidene-quinoxalin-2-one by the bromine in acetic acid in the presence of sodium acetate leads to the bromo compound which subsequently undergoes the action of potassium thiocyanate to give the thiazoloquinoxalin-2-one [111].



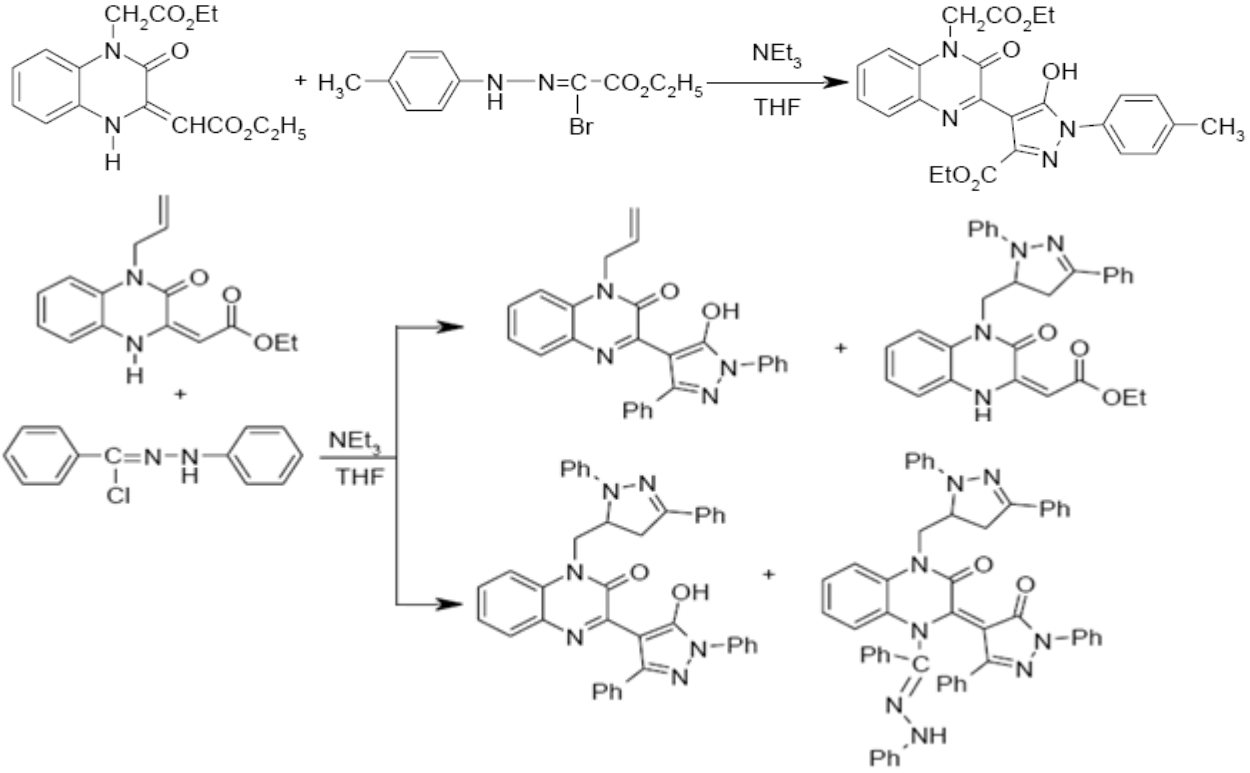
Similar results were observed by condensing the 7-amino-indazole with diethyl acetylenedicarboxylate. The pyrazolo quinoxaline obtained after reaction of bromination followed by action of potassium thiocyanate led to pyrazolothiazolo quinoxaline [112].

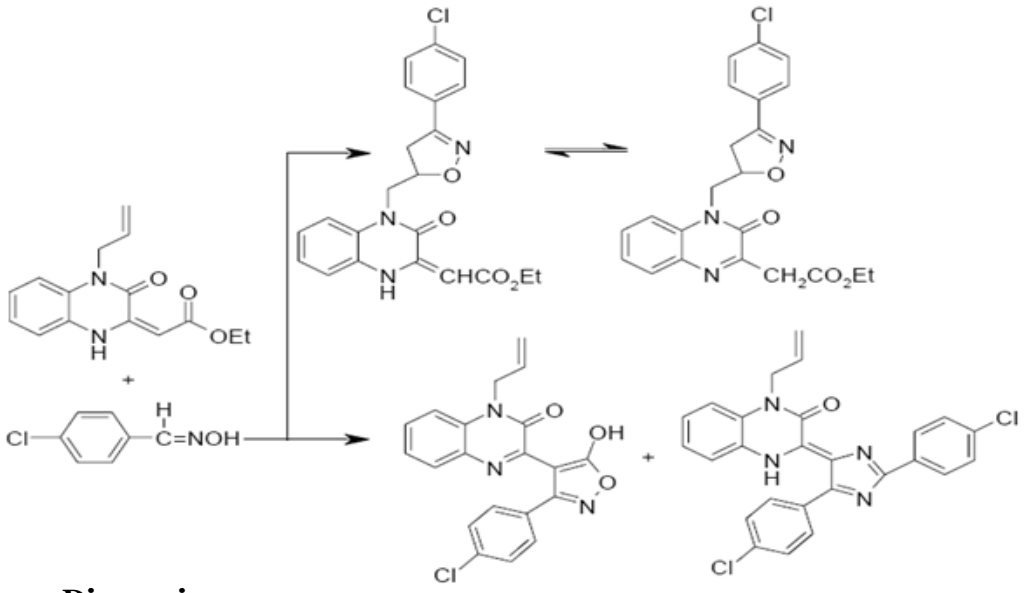


Reaction of 1,3 dipolar cycloaddition on quinoxalinone: The synthesis of heterocyclic systems containing the quinoxaline nucleus linked to various types of pentagonal pyrazole, isoxazole, imidazole and 1,2,3-triazole. The action of diethyl hydrazono-α-bromoglyoxylate on quinoxaline in the presence of triethylamine; the reaction of the 1,3-dipolar cycloaddition leading to a mixture of three products from two competitive reactions, a reaction of 1,3-dipolar cycloaddition involving the double bond of allyl group, leading to the pyrazoline; and a reaction of cyclocondensation involving the enaminoester synthon giving the pyrazole [113-116]. In the same operating conditions as before, the condensation of hydrazonoyle bromide on the 1-ethoxycarbonylmethyl-3-(ethoxycarbonymethylene)-2-oxoquinoxaline, leads exclusively to the 1-(ethoxycarboxymethyl)-5-hydroxypyrazolin-4'-yl)-2-oxoquinoxaline. In the same series of reactions, the treatment of quinoxaline by the α-chloro-phenyl phenylhydrazone for 48 hours leads to a mixture of four products from the reaction of 1,3-dipolar cycloaddition and cyclocondensation, as well as from a reaction of alkylation of the nitrogen atom in position 4 of the quinoxaline ring.



The action of chlorobenzaldoxime of compound, showing a similar behavior towards the dipolarophile sites, leading to a mixture of three products.





Discussion

The quinoxalines are a class of heterocyclic compounds with different applications in various fields, whether pharmacology, agricultural chemistry or chemical industry where various patents were field. Thus, several new synthetic methods have been described in literature. We will show, in this development, the synthesis, reactivity and the biological properties of heterocyclic systems derived from quinoxaline. Quinoxaline also called benzopyrazine is a heterocyclic compound containing a ring complex made up of benzene ring and a pyrazine ring has been considered as a wonder nucleus which posses almost all types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities [17-125]. Quinoxaline showed considerable interest from both academic and industrial Perceptive. Among the various classes of the nitrogen containing heterocyclic compounds quinoxaline is a vital component of various pharmacologically active compounds. Although rarely described in nature synthetic quinoxaline ring is a part of some antibiotics which are known to inhibit the growth of Gram Positive bacteria and are also active against various transplantable tumors. Quinoxaline is commonly called as *1,4-diazanaphthalene* or *benzopyrine*. Most of the present diseases are due to the invasion by the pathogenic organisms like bacteria, fungal, virus, ricketsia. To treat these diseases many potent nd broad spectrum antibiotics were discovered such as ampicillin, amoxicillin, carbenicillin, oflaxacin, tetracyclines, and ciproflaxcine etc. Even though antibiotics are life saving drugs in therapeutics but they are potentially harmful [126-130]. These effects include allergic and anaphylactic reaction, superinfection, development of resistance, destruction of normal non-pathogenic bacterial flora and selective toxicity like aplastic anemia, kidney damage etc. A considerable amount of research activity is directed towards a potent, more specific and less toxic antibiotics. Substituted quinoxaline have received considerable attention during last two decades as they are endowed with variety of biological activities and have wide range of therapeutic properties. The quinoxaline derivative possesses different pharmacological activities. We thought to synthesize novel substituted quinoxaline moiety. Quinoxaline derivatives are widely distributed in nature and they have been shown to have very interesting biological activities like, anti-bacterial, anti-fungal, anti-inflammatory and analgesic activity. Hence in present study we plan to synthesize novel substituted quinoxaline derivatives.

Conclusion

The quinoxaline has diverse biological potential, and the easy synthetic routes for synthesis have been attention of the researchers. Also the research on antitubercular activity has given positive results. By the present scenario and due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis and it can be concluded that quinoxaline have a great potential. Quinoxaline molecules are responsible for

diverse biological activity, but it is interesting to note that this moiety when substituted with other moieties showed a broad spectrum activities. The quinoxaline can be a rich source for exploitation. Therefore in search of new molecules it may be worthwhile to explore the possibility in this area by fusing different moieties and increase the potency.

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