Review Article

Recent advances on the Synthesis, Reactions and Evaluation of the pharmacological properties of quinoxaline, quinoxaline-2-one and quinoxaline-2,3-dione

Abstract

The review article attempts to give recent advances on quinoxaline and its derivatives. Some pathways to the synthesis of quinoxaline, quinoxaline-2-one and quinoxaline-2,3-dione were reported using simple reactive quinoxaline synthon. In addition, the reactions, biological and technological applications of derivatives of quinoxaline and related compounds were reported.

INTRODUCTION

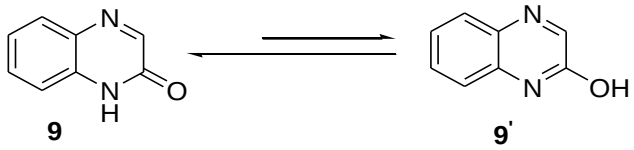
Biologically active molecules derived from heterocyclic compound (Sakata *et al*., 1998). particularly, those that were prepared from quinoxaline derivatives have gained so much attention from researchers in recent years. Quinoxalines are, in general, easy to prepare and numerous derivatives have been reported in the literature due to the fact that the possesses high biological activity, specifically as antimicrobial (Badran *et al*., 2003; Jaso *et al*., 2003; Hearn and Cynamon 2004; Kaurase *et al*., 2011; Aswartha *et al*., 2012; Achutha *et al.*, 2013), antibacterial (Bailly *et al*.,1999; Burguete *et al*., 2007; Beheshtiha *et al*., 2010), anti-cancer (Chen *et al*., 2004), antiaminoceptive (Deepika and Nath, 2012), anti-inflammatory (Wagle *et al*., 2008; Rajitha *et al*., 2011) anti-viral (Michael *et al*., 2002; Lindsley *et al*., 2005; Geefhavani *et al*., 2012), antimalaria (Rangisetty *et al*., 2001) agents. Some of their biological activities includes AMPA receptor antagonist (Nikam *et al.*, 1999), antihistaminic (Sridevi *et al.*, 2010), anti-trypanosomal (Urquiola *et al.*, 2006), anti-herps (Harmenberg and Wahren 1988), trypanocida (Romeiro *et al*., 2009), antiplasmodial(Zarranz *et al.*, 2006), Ca^{2+} uptake or release inhibition (Xia *et al*., 2005), and inhibitor of vascular smooth muscle cell proliferation (Chung and Jung,

2005). Quinoxaline and its derivatives were major components of many insecticides, fungicides, herbicides, synthetic quinoxaline moiety is a part of number of antibiotics such as echinomycin (Dell *et al.,* 1975), levomycin and actinomycin which are known to inhibit the growth of Gram-positive bacteria and also active against various transplantable tumors (Sato *et al.,* 1967; Bailly *et al.,* 1999). In addition, quinoxaline derivatives are reported for their application in dyes, efficient electroluminescent materials, organic semiconductors and DNA cleaving agents (Srinivas *et al*, 2007). Numerous methods are available for the synthesis of quinoxaline derivatives. Extensive researches have generated numerous synthetic approaches for the construction of the skeleton of such heterocycles. Among the methods, the most widely used one relies on the condensation of aryl-1,2- diamines with 1,2-dicarbonyl compounds or their equivalents (Brown and Taylor, 2004). Considering the significant applications in the fields of medicinal, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinoxalines. Recent improvements on the reaction conditions were reported via solid-phase (Jeon *et al.*, 2005), oxidative coupling of epoxides with ene-1,2-diamines (Antoniottia and Duach, 2002). Further improved methods have been reported via condensation processes catalyzed by Cerium (iv) ammonium nitrate (CAN) (More *et al*., 2006), molecular iodine (More *et al*., 2005), manganese octahedral molecular sieves (Sithambaram *et al*., 2008), task-specific ionic liquid (Dong *et al*., 2008), from PEG-400 (Zhang *et al*., 2010), from o-iodoxybenzoic acid (IBX) (Heravi *et al.*, 2006), Lead oxide (PbO) (Kotharkar 2006), mixed metal oxides (Ajaikumar and Pandurangan, 2009), and from galactose (Yan *et al*., 2007).

1,2-Dihydroquinoxaline-2-One

The 1,2-dihydroquinoxaline-2-one **9** and its derivatives are well-known derivatives of quinoxaline. They are readily prepared by condensation of α-ketocarboxylic acids or their

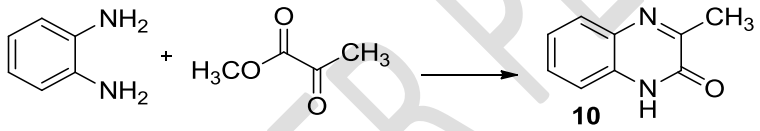
derivatives with o-phenylenediamine. The 1, 2-dihydro-quinoxaline-2-ones are high melting crystalline compounds, slightly soluble both in water and in organic solvents, but soluble in basic solvents. Some authors present its structure as 2-hydroxy-quinoxaline form **9**′, however most of their chemical properties confirm 1,2-dihydro-2-oxo-tautomeric form **9**. Structure **9** is also in agreement with its IR and NMR spectra (Seki *et al*, 1997).



9 **9**′

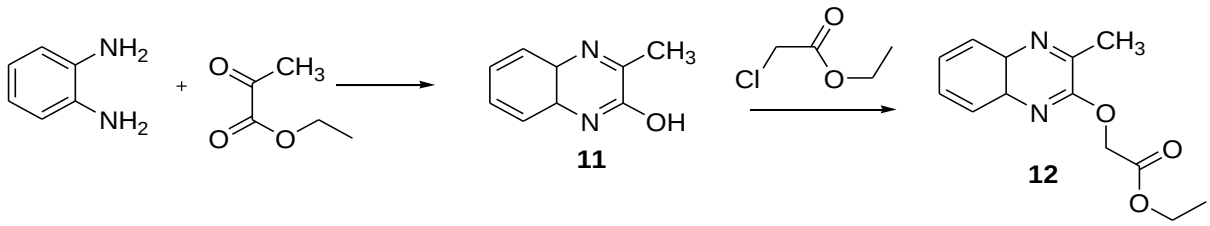
Synthetic Methods of 1,2-dihydroquinoxaline-2-one and Its Derivatives

Reacting 1,2-diaminobenzene with methyl 2-oxopropanoate have been found to be a very good pathway to the synthesis of 1,2-Dihydroquinoxaline-2-one. Some biologically derivatives of 1,2-dihydroquinoxaline-2-one **10** have been prepared by this reaction (Wolf *et al*., 1948).

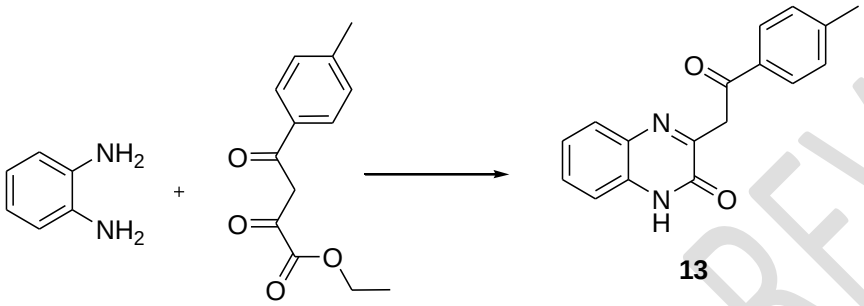


10

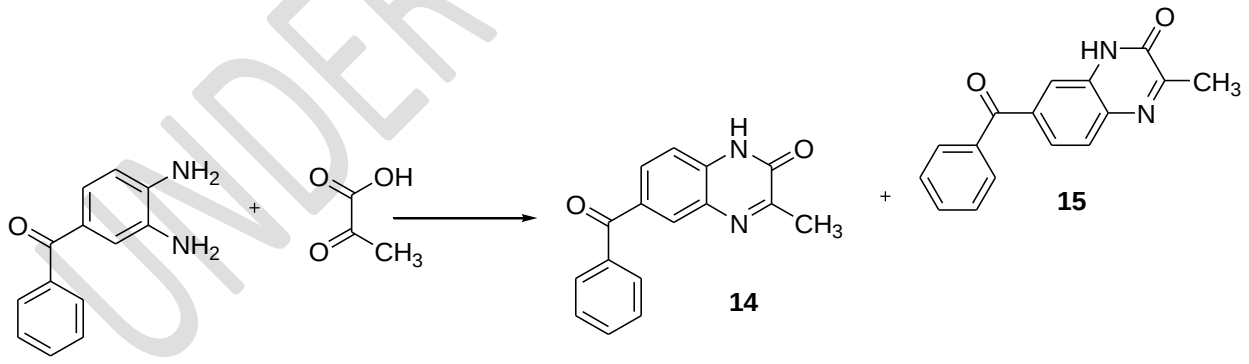
Singh *et al*., 2010 synthesized ethyl [(3-methylquinoxaline-2-yl) oxyl] acetate via condensation of o-phenylenediamine with ethyl pyruvate in toluene under reflux using conventional heating to afforded 3-methylquinoxaline-2-ol **11** which was treatment with ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate afforded ethyl [(3-methylquinoxaline-2-yl) oxyl] acetate **12** (Singh *et al*., 2010).



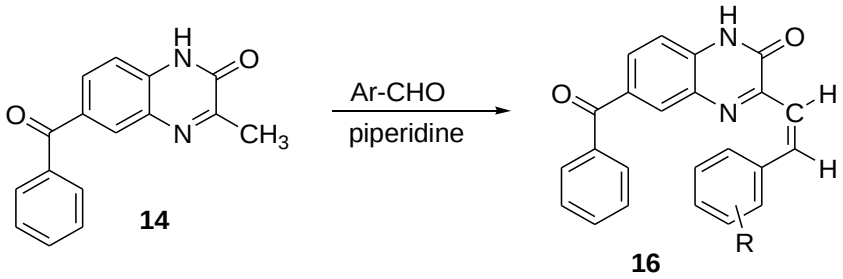
Reaction of o-phenylenediamine and ethyl-2,4-dioxo-4-p-tolylbutanoate gave 3-[2-oxo-2-p-toylethyl] quinoxalin-2(1H)-one **13** in a high yield (Badawy *et al*, 2010).



To synthesize quinoxaline derivatives with a substituent on the benzene ring requires appropriate substituted o-phenylenediamines. For instance, the reaction of 4-benzoyl- 1,2-phenylenediamine and sodium pyruvate in acetic acid afforded two products which are 6-benzoyl-3-methylquinoxaline-2-one **14** and 7-benzoyl-3-methyl-2-(1H)-quinoxaline-2-one **15** (Ali, 2000).

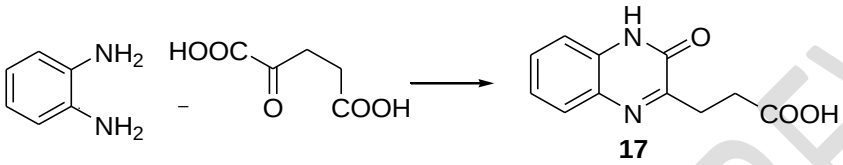


6-benzoyl-3-substituted-styryl-(1H)-quinoxalinones **16** was prepared by the reaction of 6-benzoyl-3-methyl-2-(1H)-quinoxaline-2-one **14** and aromatic aldehydes in the presence of piperidine (Ali, 2000).



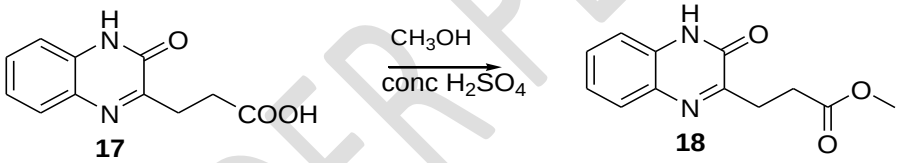
14 **16**

Addition of o-phenylenediamine with α-ketoglutaric acid gave 3-(3-oxo-3,4-dihydroquinoxalin-2-yl) propionic acid **17** in very high yield (Nath and Pandeya, 2012).



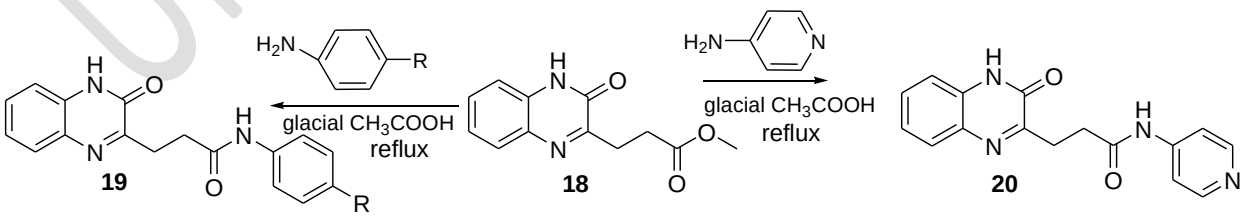
17

Ester derivative of **17** was prepared from its reaction with methanol in the presence of concentrated sulfuric acid as a catalyst under reflux gave methyl-3-(1,2-dihydro-2-oxoquinoxalin-3-yl) propanoate **18** (Nath and Pandeya, 2012).



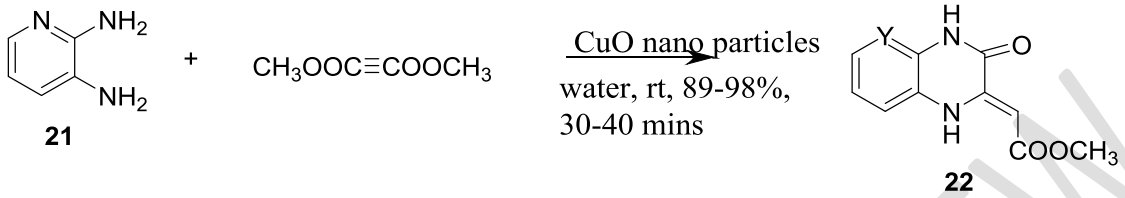
17 **18**

Reaction of **18** with different p-substituted anilines and 2 or 4- amino pyridines in glacial acetic acid under refluxing condition gave the amide derivatives **19** and **20** (Nath and Pandeya, 2012).

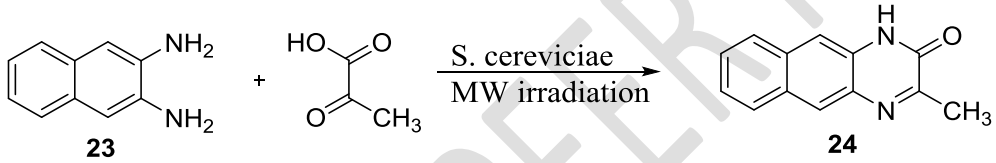


19 **18** **20**

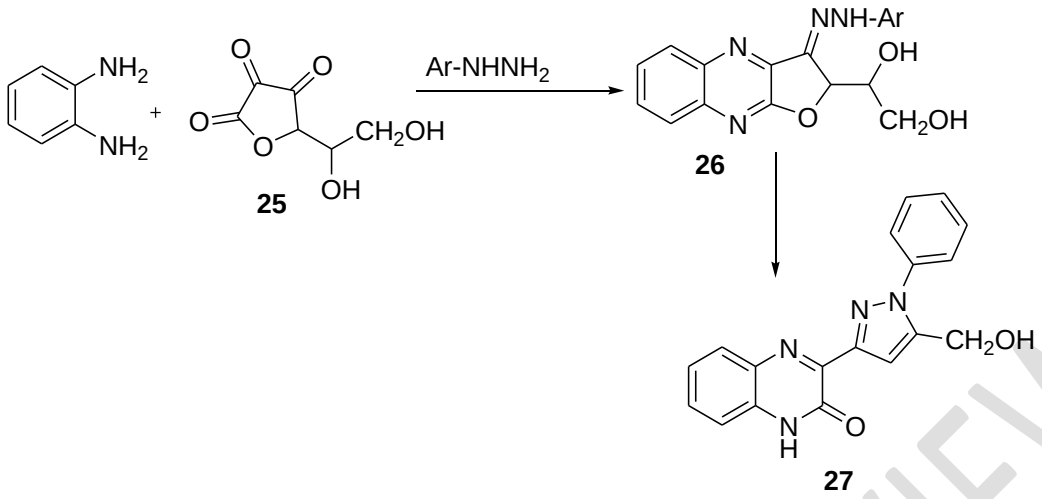
Green synthesis of quinoxaline-2-one derivatives was achieved by the reaction of pyridine-2,3-diamine **21** and 1,2-bis(methylperoxy)ethyne in aqueous medium in the presence of CuO nano particles gave (Z)-methyl-2-(3,4-dihydro-3-oxopyrido[3,2-b]pyrazin-2(1H)ylidene)acetate **22** .



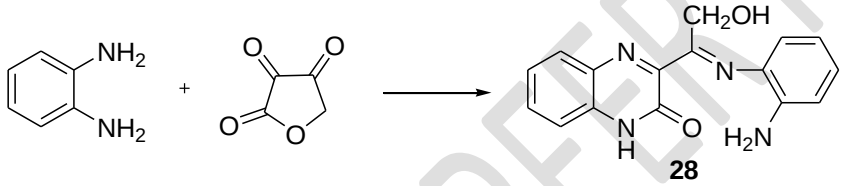
Similarly, 3-methylbenzo(g)quinoxaline-2(1H)-one **24** was synthesized by using microwave-assisted Hinsberg reaction (Hinsberg, 1887) which was achieved by reacting 2,3-diaminenaphthalene **23** and pyruvic acid through enzymatic catalysis or microwave irradiation (Gris *et al.,* 2008).



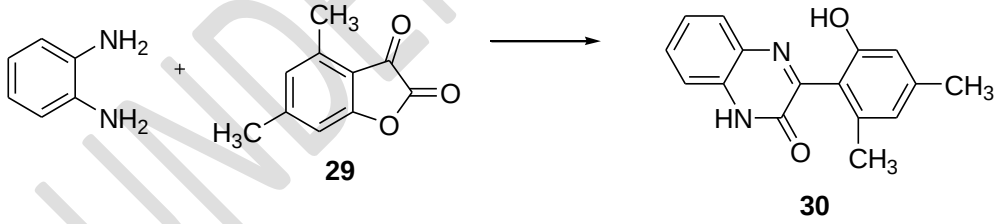
Some Lactones of α-ketocarboxylic acids were found to be a suitable precursor for the synthesis of 3-substituted-1, 2-dihydroquinoxaline-2-ones. The condensation reactions of ascorbic acid **25** with o-phenylenediamine and phenyl hydrazine gave **26** which when cyclized gave pyrazolyl quinoxaline **27**.



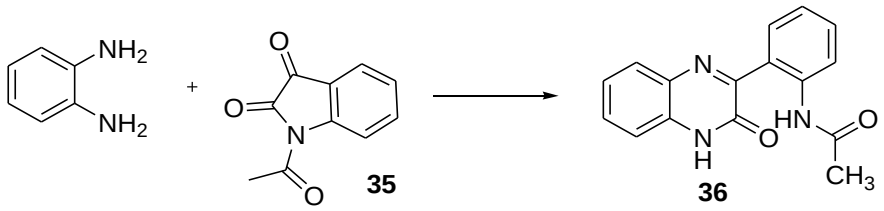
Similarly, the condensation reaction of furan-2,3,4-trione with o-phenylenediamine followed by cyclization reaction gave 3-((z)-1-(2-aminophenylimino)-2-hydroxyethyl)quinoxaline-2(1H)-one **28**.



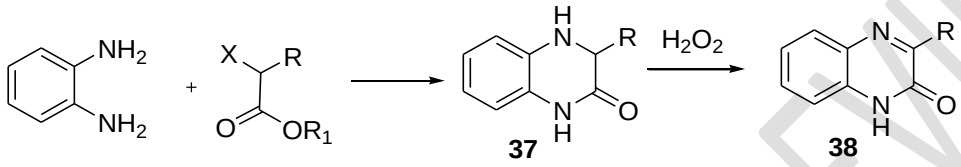
The reacting 4,6-dimethylbenzofuran-2,3-dione **29** with o-phenylenediamine gave 3-(2-hydroxy-4,6-dimethylphenyl)quinoxalin-2(1H)-one **30**.



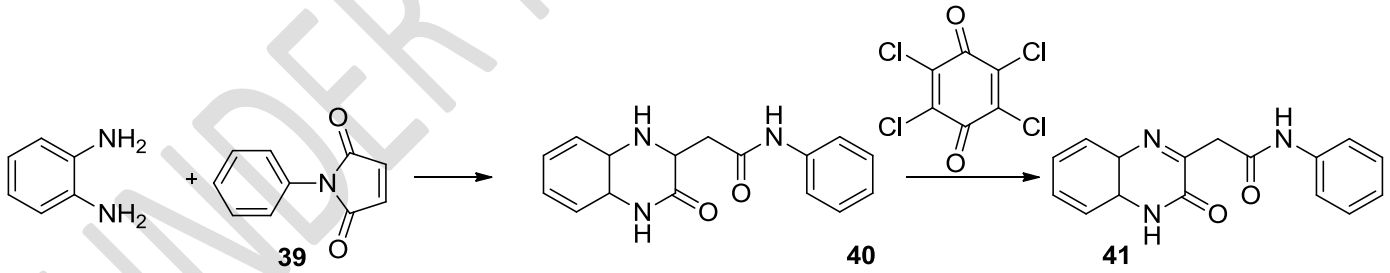
The reaction of o-phenylenediamines with N- acetylisatin **35** has been reported by Olayiwola *et al*., (2007).



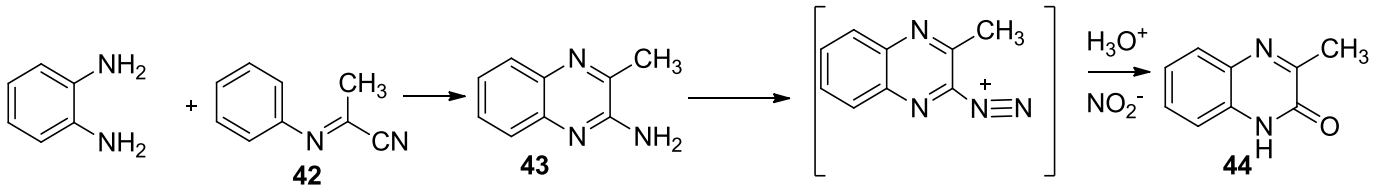
The condensation reaction of α-halogen esters with o-phenylenediamine afforded the 1,2,3,4-tetrahydro derivative **37**. The dehydrogenation of the saturated ring under mild conditions with hydrogen peroxide gave the quinoxaline-2-one derivative **38**.



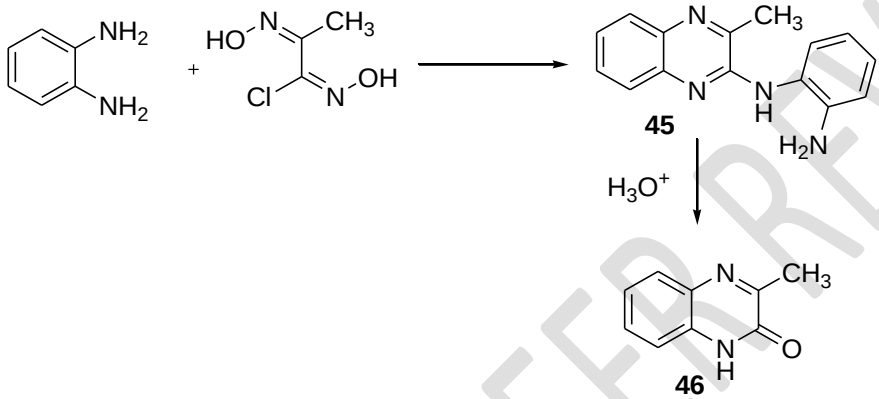
The 1,2,3,4-tetrahydroquinoxaline-2-one derivatives **40** can be prepared by the reactions of o-phenylenediamine with 1-phenyl-1H-pyrrole-2,5-dione **39**. The dehydrogenation could be achieved by the reaction of 1,2,3,4-tetrahydroquinoxaline-2-one derivatives with chloranil to afford the corresponding substituted 1,2-dihydroquinoxaline-2-ones **41**.



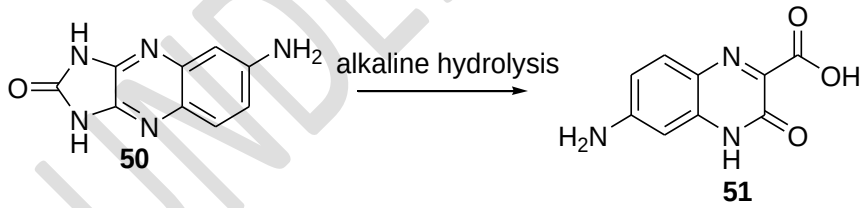
The reaction of (E)-2-(phenylimino)propanenitrile **42** with o-phenylendiamine gave 3-methylquinoxalin-2-amine **43**. The amino derivative can be transformed to 3-methl-1,2-dihydro-quinoxaline-2-one **44** by the diazotization and subsequent splitting of the diazonium salt.



The reaction of o-phenylenediamine with α-oximinohydroxam chlorides afford N-(2-methylquinoxalin-3-yl)benzene-1,2-diamine **45,** which upon hydrolysis in acidic medium gave 3-methylquinoxaline-2-(1H)-one **46**.



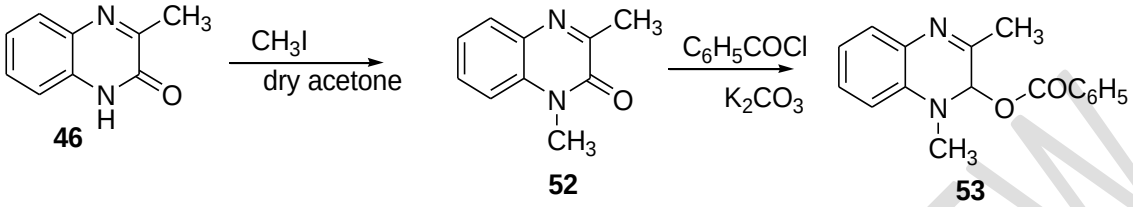
Quinoxaline-2-ones have been reported to be synthesized by degradative reaction of larger ring systems such as alloxazine. For example, alkaline hydrolysis of 8-amino-3,4-dihydrobenzo [pteridin]-2(1H)-one **50** gave 1,2-dihydro-2-oxoquinoxaline-3-carboxylic acid **51** in good yield**.**



Reactivity of the Nitrogen Atom of 1,2-dihydroquinoxaline-2-one

(i) N-alkylation

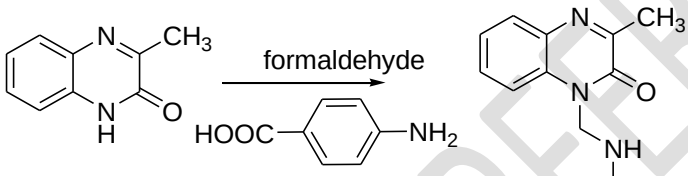
3-methylquinoxaline-2(1H)-one **46** reacts with iodomethane in the presence of potassium carbonate in dry acetone to give the 1,3-dimethylquinoxalin-2-(1H)-one **52**. The reaction of **52** with benzoyl chloride gave 1,2-dihydro-1,3-dimethylquinoxalin-2-yl benzoate **53**.



46 **52** **53**

(ii) Mannich reaction

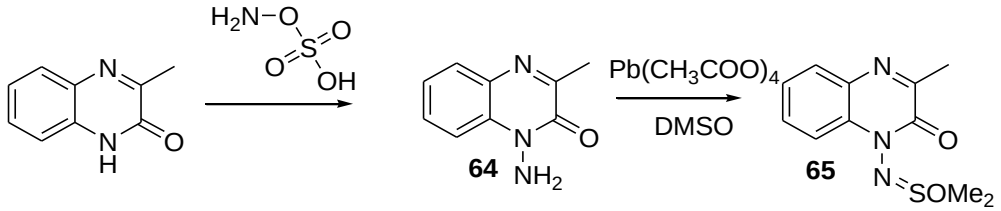
Reaction of 3-methylquinoxaline-2(1H)-one with formaldehyde and 2-aminobenzoic acid via mannich reaction to give 4-{[-3methyl-2-oxoquinoxalin-1-(2H)methyl]amino}benzoic acid **63**(Mahmoud and Youssef, 2012).



63

(iii) N-sulfonation reaction

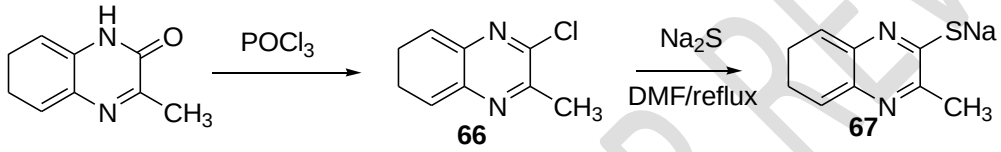
Direct amination of quinoxalinones with hydroxylamine-o-sulfonic acid produces the 1-amino derivatives **64**. Oxidations of **64** with lead tetra acetate gave the l,2,4-benzotriazines. The nitrene intermediate was trapped as the sulfoxide **65** when the oxidation was carried out in the presence of dimethyl sulfoxide.



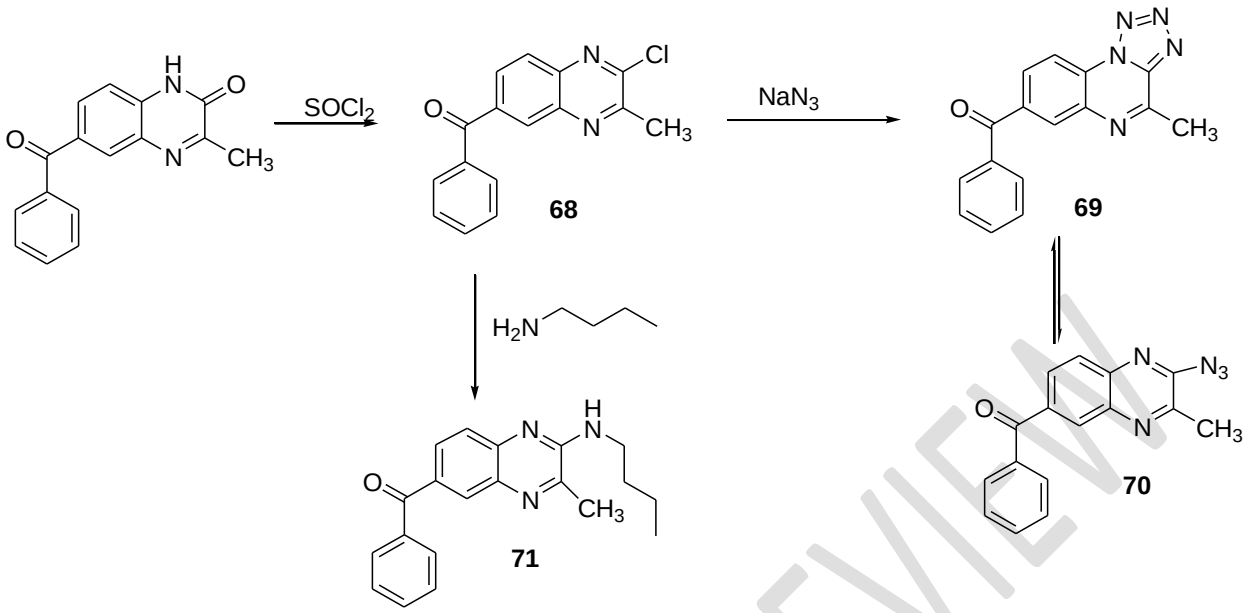
Reactivity of the Aromatic Nucleus of 1,2-dihydroquinoxaline-2-one

(i) Reaction with nucleophiles

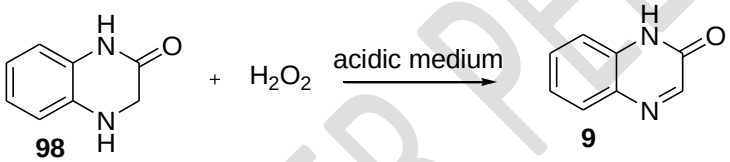
Reaction of 3-methylquinoxaline-2(1H)-one with $POCl_3$ afford 2-chloro-3-methylquinoxaline **66**, which upon reaction with sodium sulphide in DMF under reflux gave 3-methylquinoxalin-2-thiosodium **67**.



Chlorination of 7-benzoy-3-methyl-2-(1H)quinoxaline-2-one **14** with thionyl chloride furnished the 2-chloro derivative **68** which upon treatment with sodium azide in ethanol afforded 7-benzoyl-4-methyltetrazolo[1,5-a]quinoxaline **69** which was found to be in tautomeric equilibrium with the 2-azido derivative **70**. Similarly, the 2-chloro derivative **68** undergoes amination reaction with n-butylamine to furnished 7-benzoyl-2-butylamino-3-methylquinoxaline **71** (Ali, 2000). The reaction of 3-methyl-2-oxo-l,2-dihydroquinoxaline with aryldiazonium chlorides gave the arylhydrazones **72**, which upon chlorination with $POC1_3$ afforded the 2-chloro derivative **73**.



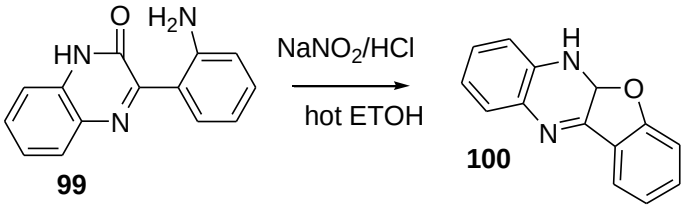
The oxidation of 3,4-dihydro-1H-quinoxalin-2-one **98** in acidic medium using H_2O_2 afforded 1,2-dihydro-quinoxalin-2-ones **9** (Perkin and Riley, 1923).



(iii) Cyclocondensation reactions.

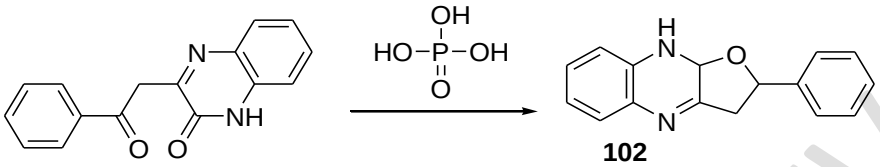
(a) The cyclization with closure of oxygen or sulfur heterocycles

Cyclization where new oxygenous or sulphurous heterocyclic compound is formed is known as Marchlewski and Sosnowski reaction. The reaction is carried out by mixing hot ethanolic solution of 3-(2-aminophenyl)-1,2-dihydroquinoxaline-2-one **99** and alkaline nitrite with hydrochloric acid to afford 5a,6-dihydrobenzofuro[3,2-b]quinoxaline **100** (Wiedermannová *et al.*, 2000; Wiedermannová *et al*., 2001; Wiedermannová, 2002).



99 **100**

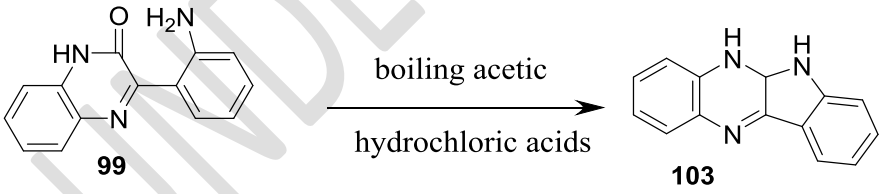
Heating 3-Acylmethyl-1,2-dihydroquinoxaline-2-ones **101** in polyphosphoric acid undergoes cyclization to afford 2,3,9,9a-tetrahydro-2-phenylfuro[3,2-b]quinoxaline **102**.



101 **102**

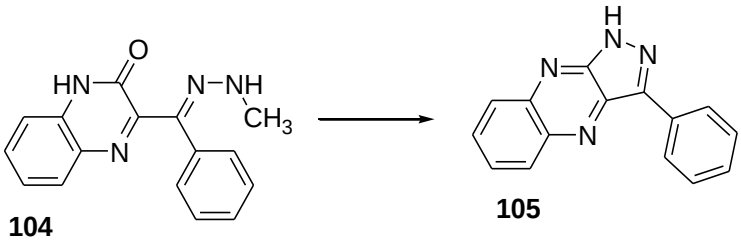
(b) The cyclization with closure of nitrogen heterocycles

The cyclization of 3-(o-aminophenyl)-1,2-dihydroquinoxaline-2-one **99** in boiling acetic or hydrochloric acids gave 5a,6-dihydro-5H-indolo[3,2-b]quinoxaline **103** (Wiedermannová *et al.*, 2001).



99 **103**

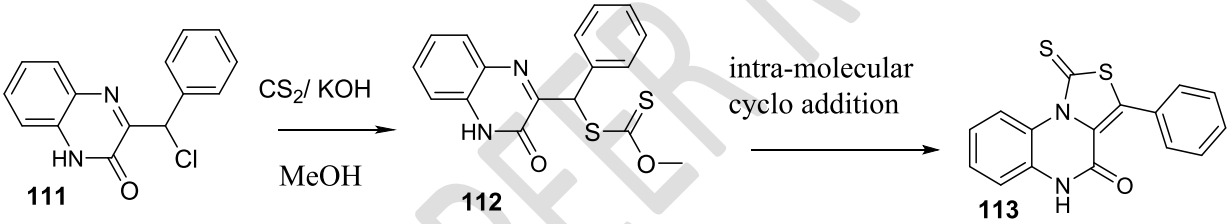
The cyclization of quinoxaline hydrazones **104** in alkaline medium or by boiling in acetic acid gave derivatives of pyrazolo[3,4-b]-quinoxaline (flavazole) **105**.



104 **105**

(iv) Reduction reactions

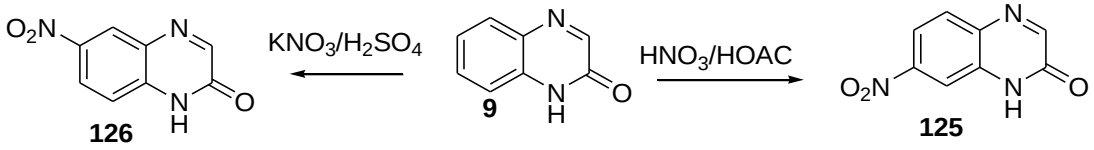
The 3-(α-chlorobenzyl)quinoxalin-2-(1H)-ones **110**, which function as a triatomic synthon when reacted with carbon disulfide yield, S-(1,2-dihydro-2-oxoquinoxalin-3-yl)(phenyl)methyl-O-methylcarbonodithioate **112**, which then undergo intra-molecular cyclocondenzation with ring closure to form 3-phenyl-1-thioxo-1H-thiazolo[3,4-a]quinoxalin-4(5H)-one **113** (Kalinin *et al*., 2004).



111 **112** **113**

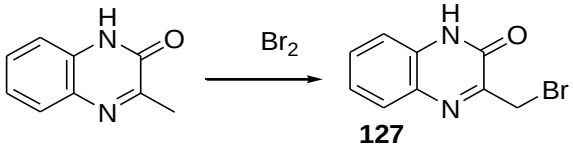
(v) Nitration reaction

Quinoxaline-2-one is a weak base and so the different orientation of substitution in acetic acid and sulphuric acid may mean that in acetic acid, the principal species undergoing nitration is the neutral molecule and in sulphuric acid, the monocation. For example, nitration of quinoxaline-2-one **9** in acetic acid gives mainly the 7-nitro derivative **125** while in sulphuric acid, the 6-nitro derivative **126** is formed.



(vi) Bromination reaction

The alkyl group in position-3 is reactive to some electrophilic agents. Bromination of 3-methylquinoxalin-2(1H)-one with bromine gave 3-(bromomethyl)quinoxalin-2(1H)-one **127** proceed easily.



1,4-DIHYDROQUINOXALINE-2,3-DIONES

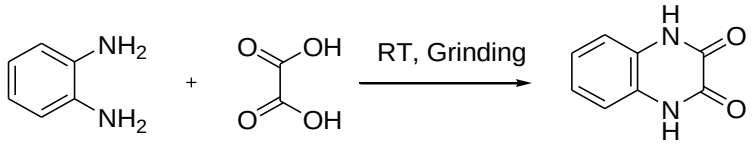
The 1,4-dihydroquinoxaline-2,3-dione and their derivatives are important members of heterocyclic compounds that are widely applied in many fields, as curatorial intermediates, bactericides and insecticides. It is one of the main classes of known antagonists of amino propionic acid (AMPA). Due to their wide range of applications, these compounds have received a great deal of attention in connection with their synthesis. One-pot efficient synthesis of1,4-dihydroquinoxaline-2,3-dione derivatives may permit the development of novel therapies for the treatment of epilepsy, pain and other neurodegenerative disorders (Cheon *et al*., 2004).

Synthetic Methods for 1,4-dihydroquinoxaline-2,3-dione and Its Derivatives

Many synthetic methods for 1,4-dihydroquinoxaline-2,3-diones have been reported which include the use of catalysts and/or some special techniques (Cheon *et al*., 2004).

(i) Synthesis of 1,4-dihydroquinoxaline-2,3-dione

An efficient and simple method of preparing 1,4-dihydroquinoxaline-2,3-dione **135** was reported by Thakuria and Das (2006). In this method o-phenylenediamine was allowed to react with oxalic acid dihydrate at room temperature by simple grinding in pestle mortar. This involves solvent free method which has advantage to prevent use of expensive and toxic solvent.



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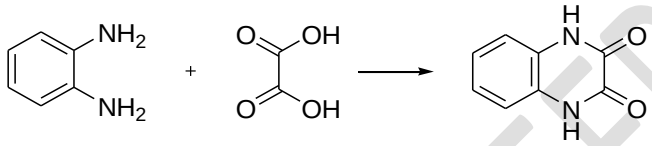
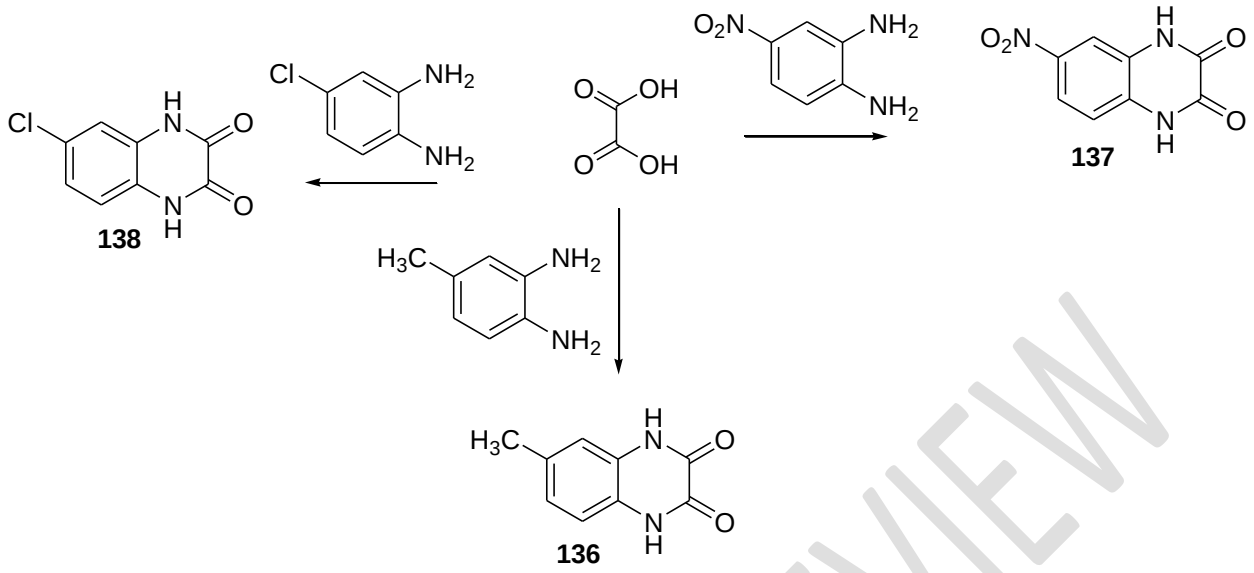
Similarly, condensation of o-phenylenediamine with oxalic acid in hot aqueous hydrochloric acid using conventional heating gave quinoxaline-2,3-diones **135** (Obafemi and Pfleiderer, 1994).



135

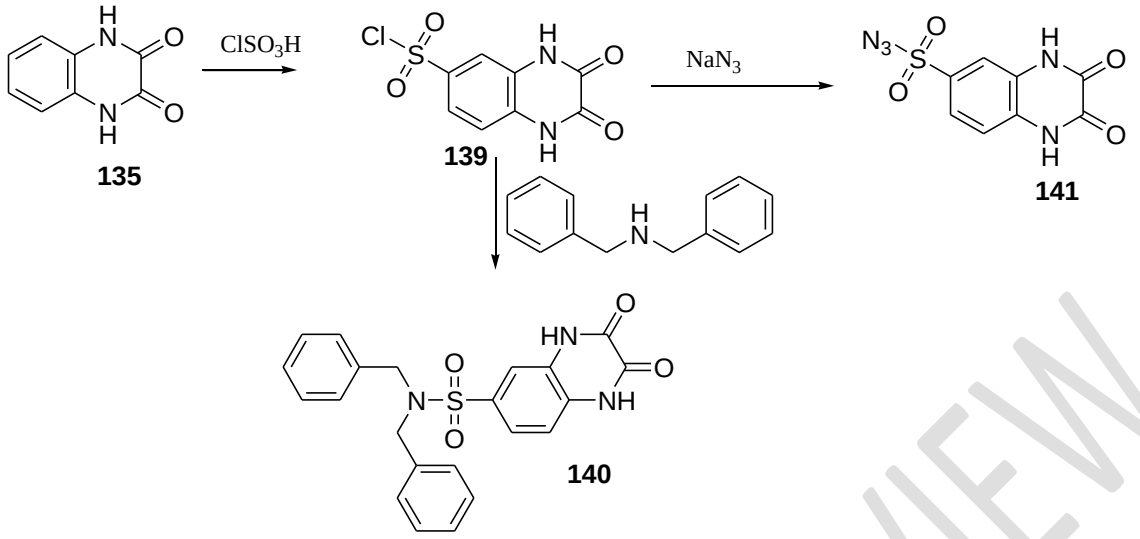
The condensation reaction of oxalic acid with 4-methyl-1,2-diaminobenzene, 4-nitro-1,2-diaminobenzene and 4-chloro-1,2-diaminobenzene in hot hydrochloric acid using conventional heating method afforded the expected 6-methyl-1,4-dihydroquinoxaline-2,3,-dione **136**, 6-nitro-1,4-dihydroquinoxaline-2,3-dione **137** and 6-chloro-1,4–dihydroquinoxaline-2,3-dione **138** respectively (Obafemi and Pfleiderer 1994, Olayiwola *et al*., 2007).



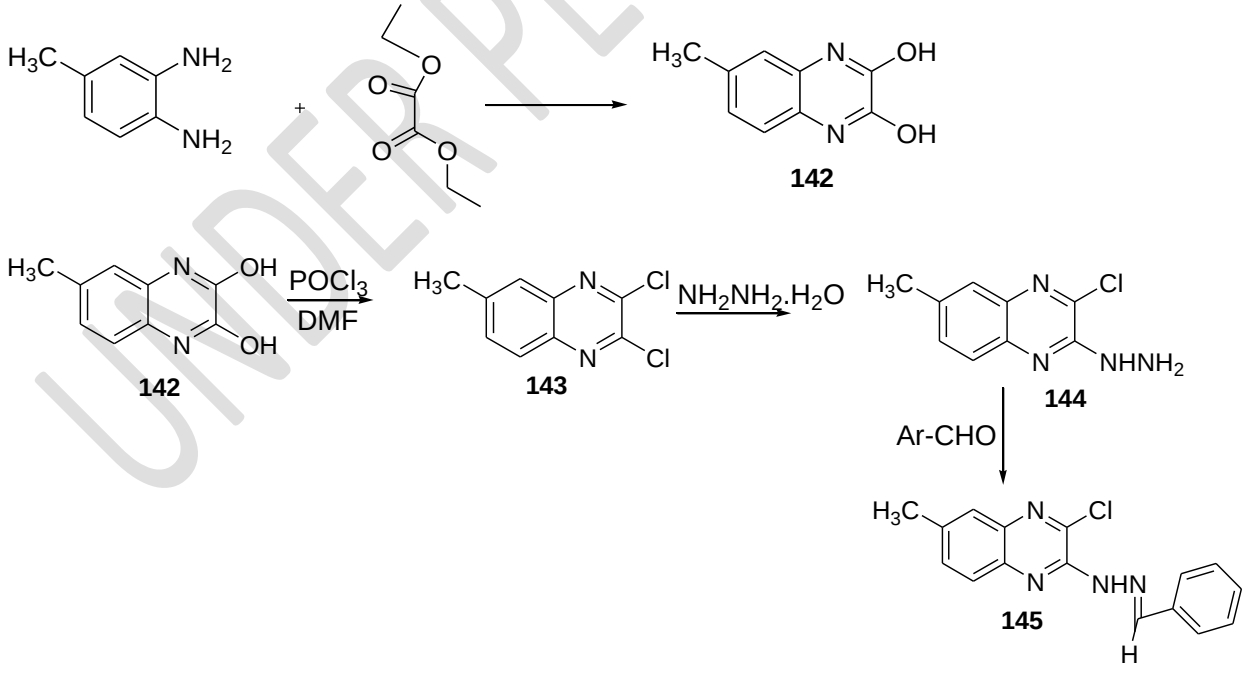
Quinoxaline-2,3-dione can be converted into 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl chloride **139** in good yield, by treatment of **135** with excess chlorosulfonic acid under reflux. The reaction of **139** with dibenzylamine in dimethyl formamide gave N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide **140**, while treatment of **139** with sodium azide was reported to give 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonyl azide **141** (Olayiwola *et al.*, 2007).

6-methyl-2,3-dihydroxylquinoxaline **142** was prepared from condensation of o-phenylenediamine with diethyl oxalate under reflux with conventional heating in good yield.

Further, chlorination of 6-methyl-2,3-dihydroxylquinoxaline **142** with phosphorous oxychloride in the presence of catalytic amount of dimethyl formamide afforded 6-methyl-2,3-dichloroquinoxaline **143**,



which on treatment with hydrazine hydrate furnished 6-methyl-3-chloro-2-hydrazinoquinoxaline **144,** while the reaction of 6-methyl-3-chloro-2-hydrazinoquinoxaline **144** with substituted benzaldehydes was reported to give the expected quinoxaline Schiff bases **145** (Noorulla and Sreenivasulu, 2011).

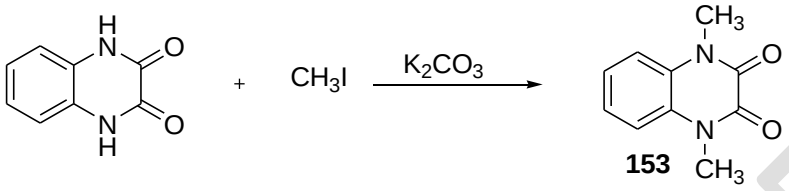


Reactions of Quinoxaline-2, 3-Diones

Reactivity of the Nitrogen Atom of Quinoxaline-2, 3-dione

(i) N-alkylation reaction

Quinoxaline-2,3-diones reacts with iodomethane in the presence of K_2CO_3 to afford 1,4-dimethylqunoxaline-2,3-diones **153** (Dongsheng *et al*,. 2014).



153

Reactivity of the Aromatic Nucleus

(i) Nitration reaction

Treatment of quinoxaline-2,3-dione with one mole equivalent of potassium nitrate in sulphuric acid results in nitration at position-6 **164,** reaction of quinoxaline-2,3-dione with 2 moles equivalents of potassium nitrate 6,7-dinitro compound **165** is formed (Dongsheng *et al.*, 2014).

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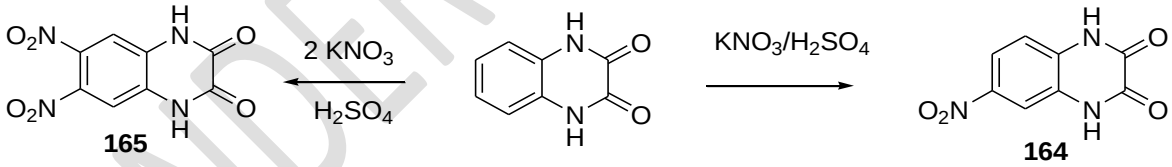


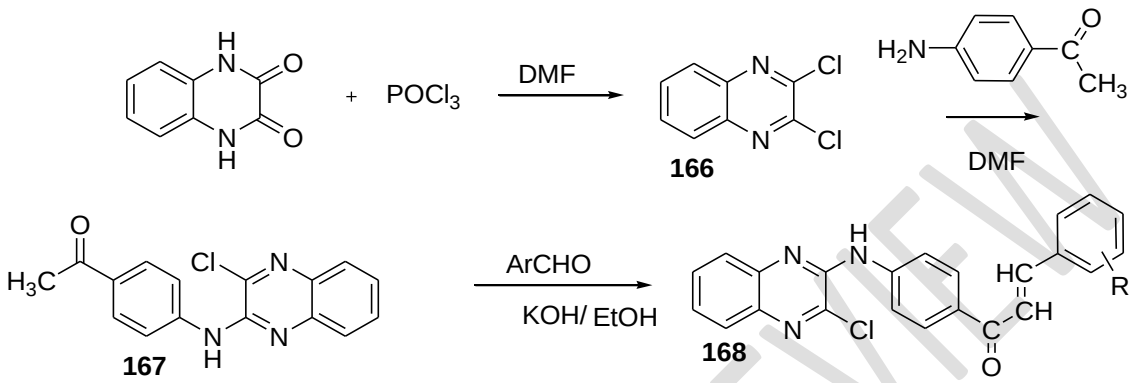
165 **164**

(ii) Chlorination of quinoxaline-2,3-dione

Reaction of quinoxaline-2,3-dione with freshly distilled phosphorous oxychloride in DMF under refluxing condition afforded 2,3-dichloroquinoxaline **166** which upon reaction with 4-aminoacetophenone in DMF afforded 1-(4-(3-Chloroquinoxalin-2-ylamino)phenyl)ethanone **167** which when reacted with substituted benzaldehydes in ethanol in the presence of potassium hydroxide afforded the corresponding chalcones derivatives **168** (Vijay *et al.*, 2013).

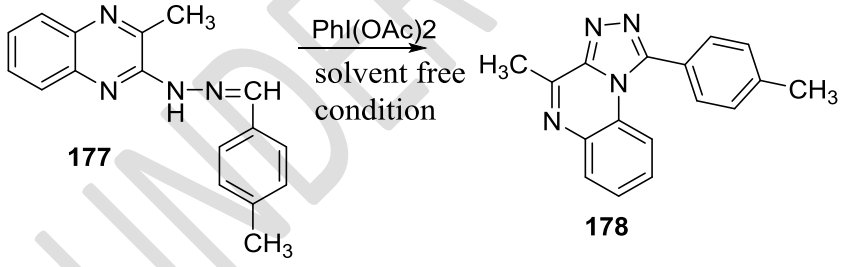
(iii) Reaction with nucleophiles

Quinoxaline-2,3-dione reacts with ethylenediamine in water under refluxing condition to afford 3-[(2-aminoethyl)amino]quinoxalin-2(1H)-one in good yield **169**.



(iv) Cyclocondensation reaction.

Kumar *et al.* (2004) carried out the reactions of arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazones **177** with iodobenzene diacetate under solvent-free conditions to afforded 3-methyl-1-p-tolyl-[1,2,4]triazolo[4,3-a]quinoxaline **178**.



Antimicrobial Activity of Quinoxalines, 2-quinoxalinones and 1,4–dihydro-2,3-quinoxalinediones

Design and synthesis of quinoxaline-based antibiotics have been undertaken by many synthetic chemists, but these compounds possess limited applications due to their toxic effect. It is believed that the antimicrobial potency of this compound is due to its ability to prevent DNA synthesis (Ali, 2000; Chakraborty *et al.*, 2009). Sanna *et al.* (1999) synthesized some 3,6,7-substituted quinoxaline-2-ones which showed potent antimicrobial activity against Gram-positive and Gram-negative bacteria and hospital isolated fungi. Ali, (2000) synthesized some novel quinoxalinone derivatives and investigated them for their antibacterial activity using agar-well diffusion method. The compounds were found to possess significant antibacterial activity against the tested organisms. Obafemi and Akinpelu, (2005) synthesized some derivatives of quinoxaline and investigated there *in vitro* antimicrobial activity using agar well diffusion method. Their results showed that the compounds possess significant activity when compared with the reference antibiotics used for the study. Ganapaty *et al.* (2007) synthesized some novel 2-substituted quinoxaline hydrazones and 7-sulfonamides of quinoxalinone. All the compounds were screened for their *in vitro* antimicrobial activity against some Gram-positive bacterial strains and fungal strains, using agar disc diffusion method. Singh and co-workers synthesized some new Schiff bases containing quinoxaline moieties. The Schiff bases (N-substituted benzylidine benzamines) were tested for their antimicrobial activity against panel of bacterial strains which comprised of Gram- negative bacteria. The activity of the test compounds was compared with ciprofloxacin as standard antibiotic. The results showed that some of the Schiff bases were active against the test organisms. Taiwo *et al.* (2008) synthesized some quinoxalinone derivatives which were screened *in vitro* for their growth inhibitory activity

against nine strains of Gram-positive bacteria and four Gram-negative bacterial strains. Some of the compounds exhibited broad spectrum activity against the tested organisms. Pawar *et al.* (2009) synthesized some substituted sulpha-quinoxalinones and subjected to preliminary in vitro evaluation of their anti-tubercular activity. The *in vitro* anti-tubercular screening against $H_{37}R_v$ strains of *Mycobacterium tuberculosis* revealed that some of the compounds possess moderate activity. Ajani *et al,* (2010) carried out the synthesis of a series 2-quinoxalinone-3-hydrazone derivatives using microwave irradiation technique and evaluated their anti-microbial activities. The result showed that the skeletal framework of quinoxalinone hydrazones exhibited potency as anti-microbial agents. Ramalingam and Ganapaty, (2010) synthesized 1-((Substituted) methyl)quinoxaline-2,3(1H,4H)-dione and 1-((substituted)acryloyl) quinoxaline-2,3(1H,4H)-dione from quinoxaline-2,3(1H,4H)-dione and screen them for their antimicrobial activities. Results of the anti-tubercular screening against *Mycobacterium tuberculosis* H37 Rv showed that the compounds, exhibited significant anti-tubercular activity. Seckhar *et al.* (2011) synthesized some triazoloquinoxalines which showed anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}R_v$. Kaurase *et.al.* (2011) synthesized some derivatives of quinoxaline hydrazones through microwave assisted reaction between substituted aromatic diamines and α-ketoglutaric acid. The product obtained was allowed to react with hydrazine hydrate to yield the corresponding hydrazones. The antimicrobial activity of the compounds against some bacterial and fungal strains was investigated and found to exhibit some antimicrobial activity. In a similar manner, Wiedermannova *et al.* (2002) synthesized some aryl hydrazones of 2-oxo-6,7-dichloro-1,2-dihydroquinoxaline-3-carbaldehyde. The hydrazones were investigated for their anti-tubercular activity. The results revealed that the synthesized hydrazones possess moderate tuberculostatic activity.

Antimalarial Activity.

Malaria is number one cause of death in the world especially in Africa. Mortality, currently estimated at over a million people per year has surged in recent years, this is probably due to resistance of *Plasmodium falciparum* to existing anti-malarial drugs available. Vincente *et al.* (2009) synthesized active quinoxaline derivatives and investigated *in vitro* effects for their antimalarial activity against *Plasmodium falciparum* by incorporation of [^{3}H] hypoxanthine. All the compounds tested appeared to be promising antimalarial candidates by demonstrating high potency and good selectivity.

Anti-inflammatory Activity and Antioxidant.

Many non-steroidal anti-inflammatory drugs have been reported to acts as inhibitors of free radical production or as radical scavenger's compounds with antioxidant properties, expected to offer protection in rheumatoid arthritis and inflammation and this could lead to potentially effective drugs. Burguete *et al.* (2007) synthesized some novel ring substituted quinoxaline-1,4-dioxides using based-catalyzed Claisen-Schmidt condensation reaction. The compounds were investigated for their anti-inflammatory and antioxidant activity. The tested compounds inhibited carrageenan-induced rat paw edema and contains significant radical scavenging activity. In addition, Noorulla and Sreenivasulu (2011) synthesized some substituted quinoxaline derivatives by incorporating the isoniazide structure into the quinoxaline moiety and evaluated them for anti-inflammatory activity. The compounds were found to possess significant activity. It was suggested that the presence of methoxy group on the phenyl nucleus attached to quinoxaline nucleus may be responsible for the observed anti-inflammatory activity.

Anti-HIV Activity

Since the human immunodeficiency virus-1 (HIV-1) was first confirmed as the causative agent of acquired immunodeficiency syndrome (AIDS), there are many clinical drugs, non-nucleotide reverse transcriptase inhibitors, which interacts with a specific allosteric non-binding substrate site on HIV-1 reverse transcriptase. The compounds have proved to be effective Anti HIV drugs because of their high potency, low toxicities and improved pharmacokinetics. Quinoxalines happens to possess some significant activities as HIV-1 reverse transcriptase inhibitors. Lindsley *et al.* (2005) synthesized N-hetero-aryl sulfonyl quinoxalines and their derivatives which were investigated for antiviral activity, as HIV-1 reverse transcriptase inhibitors. The anti HIV-1 activities of the compounds were evaluated by a cell-based HIV-1 replication pharmacological model. The results indicated that the synthesized compounds possess significant HIV-1 reverse transcriptase inhibition property.

Anti-cancer Activity

Patel *et al.* (1991) synthesized new series of phenoxy methyl quinoxalines and were screened for their anti-cancer activity. The compounds gave encouraging anti-cancer activity against MCF-7 cells. Paola *et al.* (2000) synthesized a new series of 6,7-difluoromethylquinoxalinones or nitro-quinoxalinones derivatives having different side-chains (alkyl, halogeno-alkyl, benzyl and phenyl groups) at C-3 of the ring system and were screened for anti-cancer activity in vitro. Some of the compounds were found to show interesting anticancer activity. Also, Carolina *et al.* (2008) synthesized a series of pyrido[2,3-g] quinoxalines derivatives which were screened *in vitro* for their anti-cancer activities. The compounds were found to possess encouraging anticancer activity. Masquefa *et al.* (2009) synthesized new imidazo [1, 2-a] quinoxaline analogues in good yields via a bimolecular condensation of 2-imidazole carboxylic acid, followed by a coupling with ortho-fluoroaniline and subsequent substitution on the imidazole

ring by Suzuki Cross-coupling reaction using microwave irradiation. Anti-cancer activity of these derivatives was evaluated by growth inhibition of A375 cells in vitro. All the tested compounds exhibited potent anti-cancer activity.

Conclusion

The synthesis of quinoxaline and its various derivatives have been generally easy via condensation reactions of I,2-dicarbonyl compounds with 1,2-diaminobenzene. It was also reported that quinoxaline and its derivative possess potent diverse biological properties. Quinoxaline and its various derivative will always attract the attention of researchers in order to find solutions to adverse problem caused by disease to mankind.

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