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## Review Article

### REVIEW ON LITERATURE STUDY OF QUINOXALINE

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### ABSTRACT

Literature study of quinoxaline gives idea about naturally occurring quinoxaline like echinomycin & triostin-A. Literature study reveals that anti-tubercular, antibacterial, antifungal, antimalarial, anti-inflammatory & AMPA-NMDA receptor antagonist spectrum of activity. Quinoxalines are becoming the attractive target of extensive research due to its inherent diverse properties in future. In the recent year, 2, 3-disubstituted quinoxalines reported to possess significant antimicrobial potential against bacteria, fungi, and mycobacterium.

**Keywords:** Quinoxaline, Echinomycin, Triostin-A, Antimicrobial.

### INTRODUCTION

Heterocyclic compounds are those cyclic compounds whose ring contain besides, carbon, one or more atoms of other elements. The non-carbon atoms such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, sulphur and oxygen. The heterocyclic compounds having lesser common atoms such phosphorus, tin, boron, silicon, bromine, etc. have been a subject of much investigation in recent years. The heterocyclic compounds having three to six carbons in the ring are numerous, but only those having five or six atoms in the ring are by far the most important. Heterocyclic compounds are very widely distributed in nature and are particularly important because of the wide variety of physiological activities associated with this class of substances. Several of the important compounds contain heterocyclic rings, e.g. most of the members of vitamin B complex, alkaloids, antibiotics, chlorophyll, other plants pigments, amino acids, dyes, drugs, enzymes, the genetic material, DNA etc. Few of the basic rings of the heterocyclic compounds are listed below.<sup>1</sup>

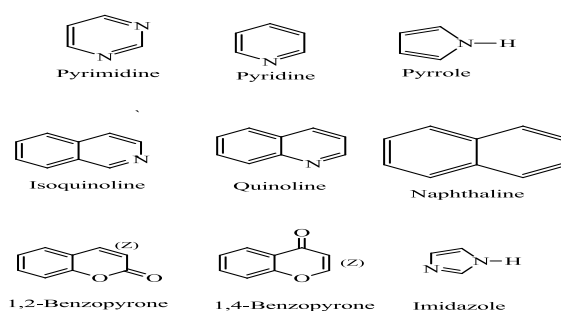
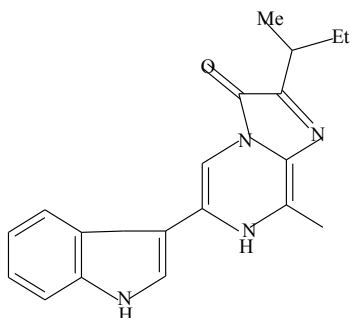


Figure 1: Different Heterocyclic Rings Compounds

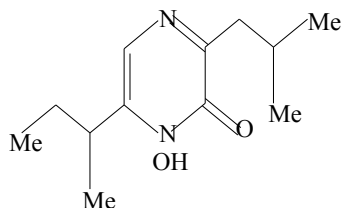
## Quinoxaline

Naturally occurring Pyrazine & Quinoxaline

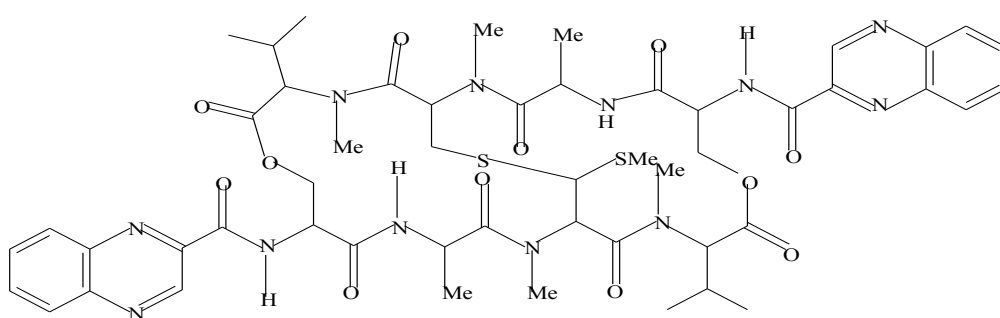
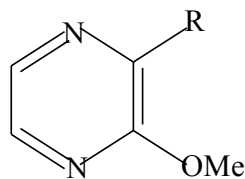
Cypridina luciferin



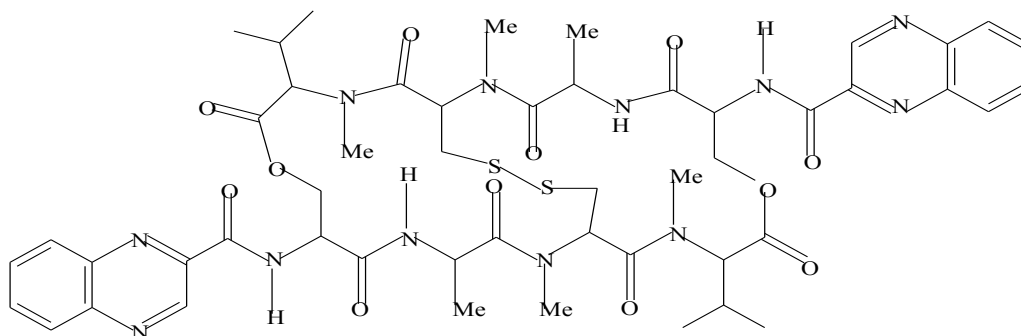
Aspergillilic acid



Methoxy Pyrazine (food aroma)

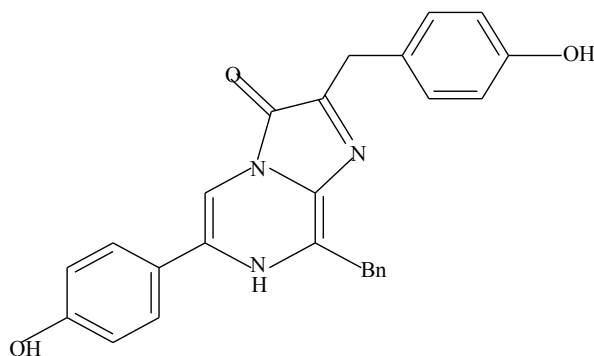


Echinomycin

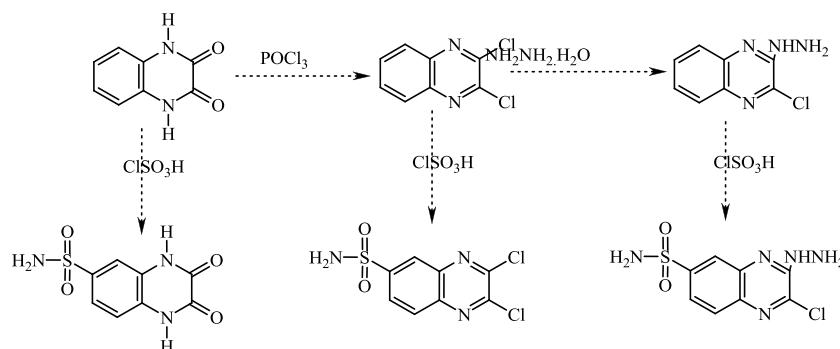


Triostin A

Coelenterazine: It is synthesized from chloropyrazine. It is bioluminescent compound from a jellyfish, which potential for use in bioassays.

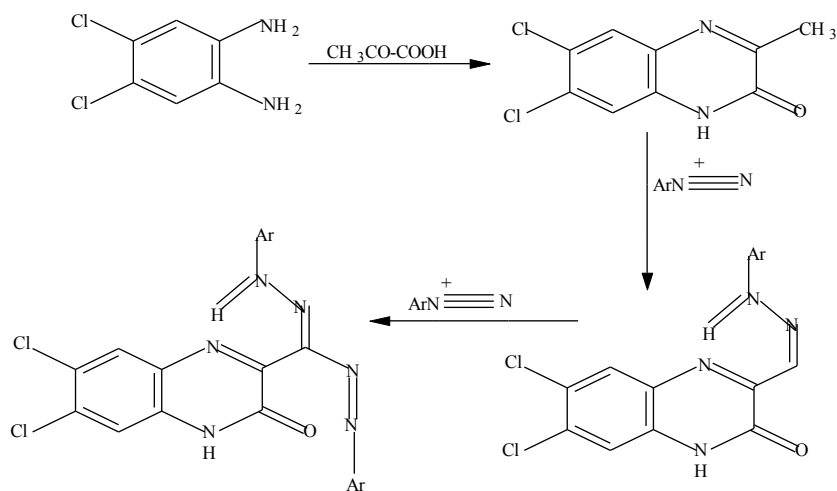


S. Ganapaty, Ramalingam and Ch. Babu Rao *et al.* synthesized some new 2-substituted hydrazine/benzylidino/methyl hydrazones and 7-Sulfonamides of 1H, 4H-3-oxo-quinoxaline from 1H, 4H-quinoxaline-2, 3-diones and characterized by IR,  $H^1$ -NMR, LC MS and CHN analytical data. All the synthons of work were evaluated for their in vitro antimicrobial activity against the bacteria *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, the fungi *C. albicans*, *A. niger* and the *Mycobacterium tuberculosis* H<sub>37</sub>HRV. The result were interpreted and concluded that 2-Hydrazino, 7-Sulfonamido and 2, 3- Dichloro substitution on quinoxaline showed potent antitubercular, antibacterial, and antifungal spectrum respectively.<sup>1</sup>



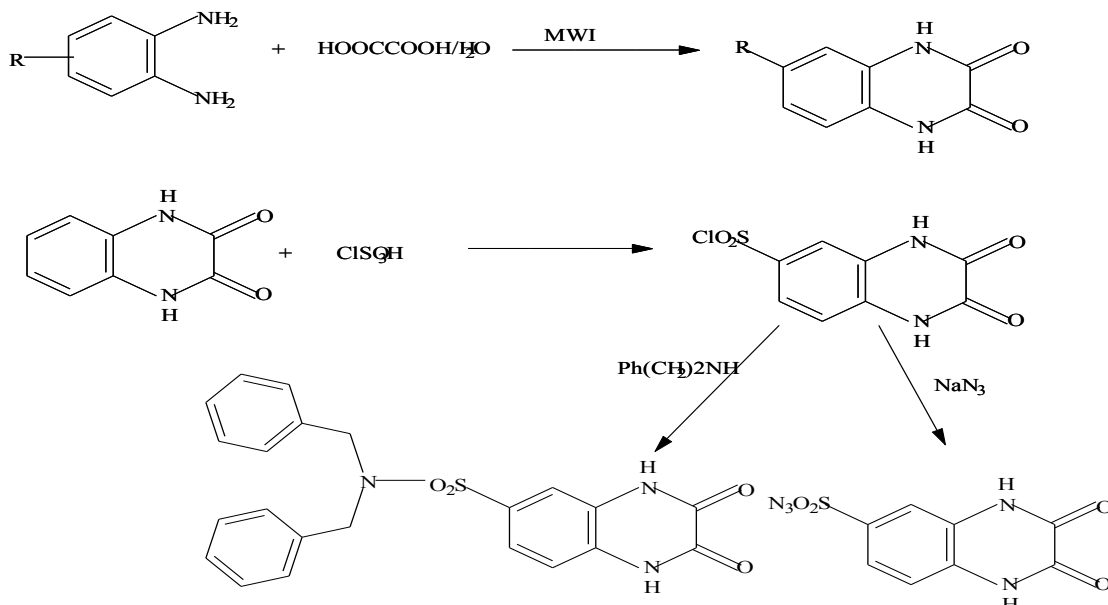
**Figure 2:** Scheme for synthesis of 7- Sulfonamide of 1H, 4H- 3oxo- quinoxaline

Iveta Wiedermannova *et al* gave scheme for synthesis of some Arylhydrazones of 2-Oxo-6, 7-dichloro-1, 2-dihydro quinoxaline-3-carbaldehyde showing tuberculostatic activity. By diazotization of aniline, 4-Toluidine, 4-Anisidine, 4-Chloroaniline, 4-Bromoaniline, 2-Iodoaniline, 2-Toluidine, 2-Chloroaniline, 3-Toluidine and by azo coupling of formed diazonium salt with 3-Methyl-6, 7-dichloro-1, 2-dihydro quinoxaline-3-one were prepared corresponding hydrazones.<sup>2</sup>



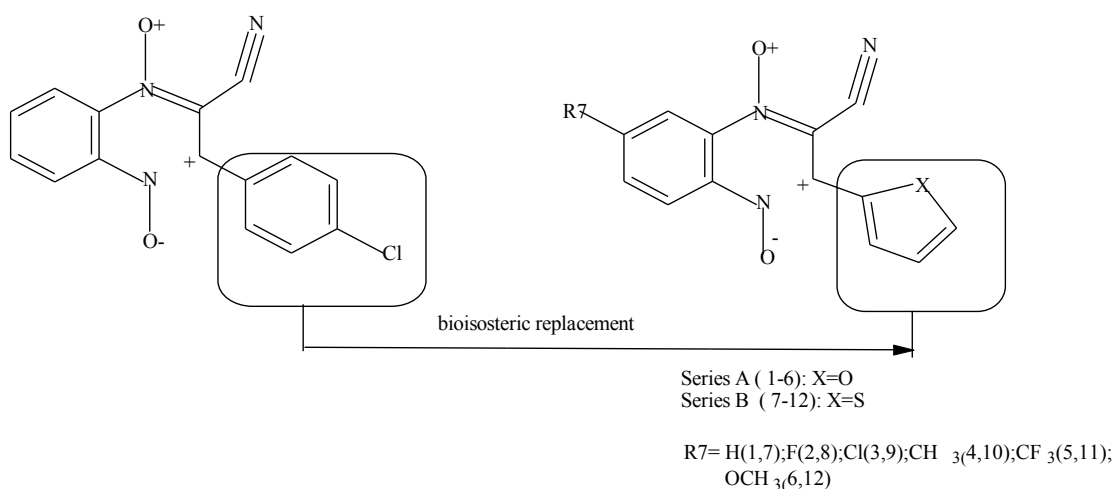
**Figure 3:** Scheme for synthesis of Arylhydrazone of 2-oxo-6, 7-dichloro-1, 2-dihydro quinoxaline- 3-carbaldehyde

G. Olayiwala *et al* synthesized quinoxalinone derivatives and investigated for some neuropharmacological effect (analgesia, sedation, convulsion, anxiety, memory and psychosis) in mice and rat. In the CNS depressant activity, N, N- Dibenzyl- 2, 3 – dioxo- 1, 2, 3, 4- tetrahydroquinoxaline-6-sulfonamide is most active. While other compound appears variously dose dependent. N, N-Dibenzyl -2, 3-dioxo-1, 2, 3, 4-tetrahydroquinoxaline-6-sulfonamide showing the highest activity at 2.5 mg/kg. The LD<sub>50</sub> (24 h) calculated for the compound were between 74 and 760 mg/kg i.p.<sup>3</sup>



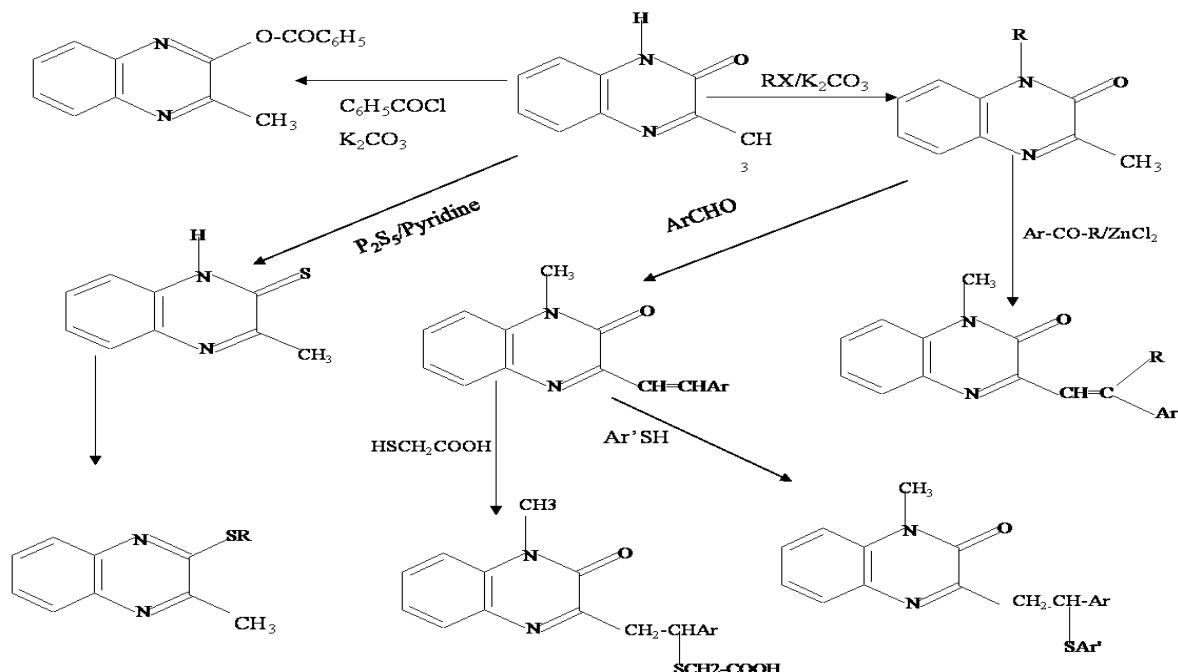
**Figure 4:** Scheme for synthesis of Quinoxalinone-6-sulfonamide derivative

E. Vicente *et al.*, synthesized 3-Phenylquinoxaline-2-carbonitrile 1, 4-Di-N-oxide derivative. Antimalarial activity was evaluated in vitro against *Plasmodium falciparum* (3D7 and K1 strains) by the incorporation of [<sup>3</sup>H] hypoxanthine. Cytotoxicity was tested in KB cell by Alamar Blue assay. Twelve compounds were synthesized and evaluated for antimalarial activity. Eight of them showed an IC<sub>50</sub> < 1 μM against 3D7 strain. Derivative demonstrated high potency (IC<sub>50</sub> = 0.63 μM) and good selectivity (SI = 10.35), thereby becoming a new lead-compound.<sup>4</sup>



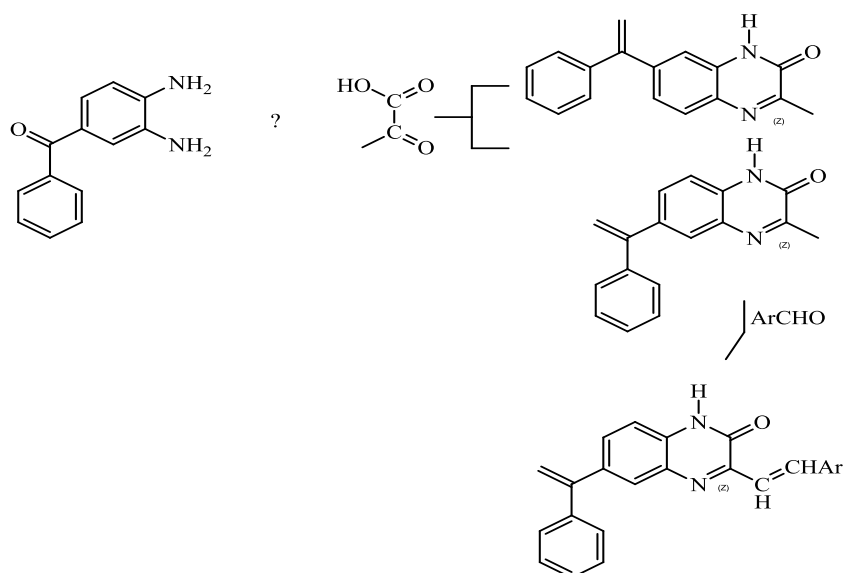
**Figure 5:** Scheme for synthesis of 3-Phenylquinoxaline-2-carbonitrile-1, 4-di-N-oxide derivative

Mahmoud Zarif Amin BADR *et al.*, gave scheme for synthesis and reaction of 3-Methyl-2-(1H)-quinoxalinone with alkyl, benzyl, and arenesulfonyl halides in the presence of K<sub>2</sub>CO<sub>3</sub> in dry acetone gave 1-substituted 3-Methyl-2-(1H)-quinoxalinone. 3-Methyl-2-(1H)-quinoxalinone (1) react with benzoyl chloride under the same condition to give 3-Methyl-2-quinoxalinyl benzoate, while it react with P<sub>2</sub>S<sub>5</sub> in dry pyridine to give 3-Methyl-2-(1H)-quinoxaline thione. Treatment of this with methyl iodide in the presence of K<sub>2</sub>CO<sub>3</sub> in dry acetone gave 2-Methyl-3-(methylthio)-Quinoxaline, but not 1,3-Dimethyl-2-(1H)-Quinoxaline thione with benzyl bromide and/ or p-nitro benzyl bromide in the presence of K<sub>2</sub>CO<sub>3</sub> in dry acetone gave 2-Benzylthio and 2-(P-Nitro benzylthio)-3-Methylquinoxaline.<sup>5</sup>

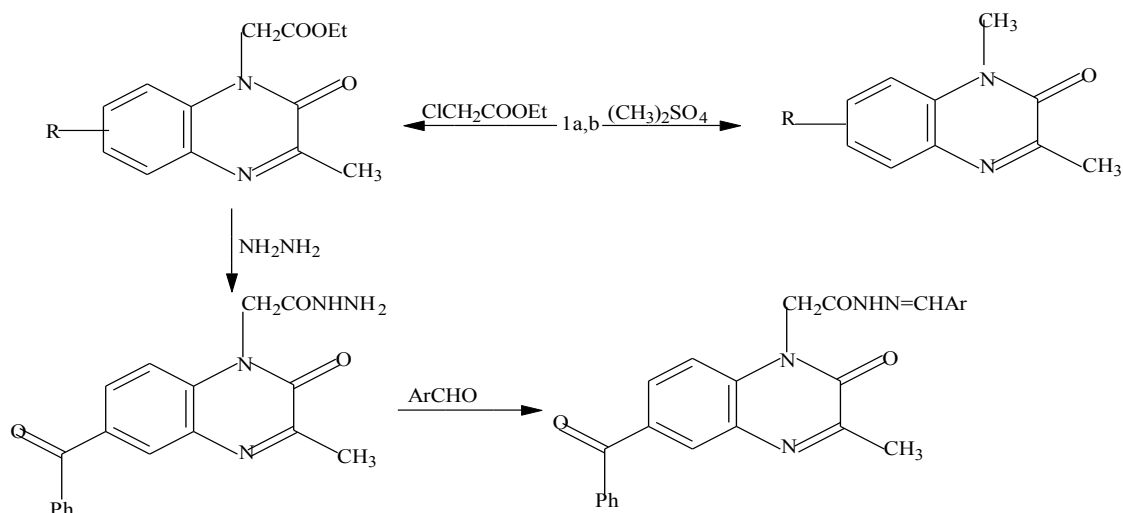


**Figure 6:** Scheme for synthesis and reaction of 3-Methyl-2-(1H)-quinoxalinone

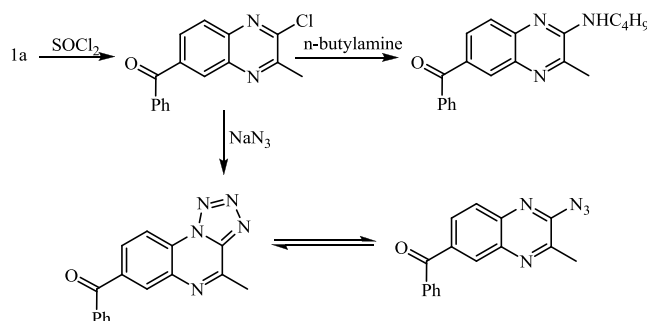
M.M.Ali *et al.* synthesized some novel quinoxalinone derivative and evaluated for antimicrobial activity. Condensation of 4-Benzoyl-1, 2-phenylenediamine with sodium pyruvate in acetic acid furnished two product which were identified as 6-Benzoyl and 7-Benzoyl-3-methyl-2-(1H)-Quinoxalinone. Fusion of 1a with aromatic aldehydes furnished the styryl derivatives. Alkylation of 1a, b with dimethyl sulphate or ethyl chloroacetate produced the N-Alkyl derivative. Hydrazinolysis of the ester derivative with hydrazine hydrate afforded the hydrazide derivative which underwent condensation with aldehyde to give hydrazone derivative.<sup>6</sup>



**Figure 7:** Condensation of 4-Benzoyl-1, 2-phenylene diamine with sodium pyruvate

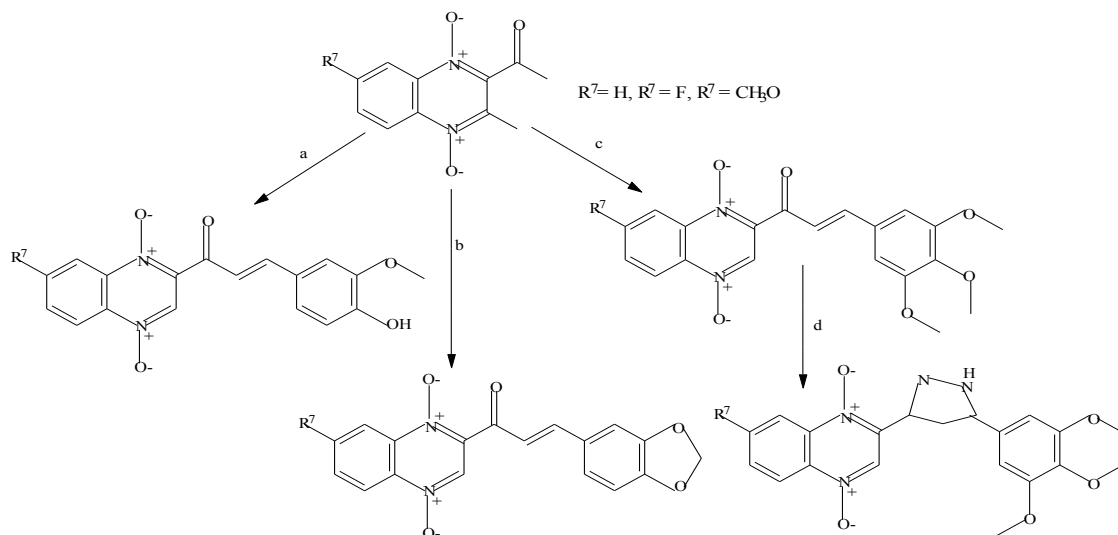


**Figure 8:** Alkylation of 6-Benzoyl and 7-benzoyl-3-methyl-2-(1H)-quinoxalinone



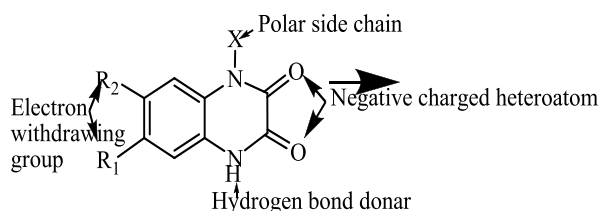
**Figure 9:** Reaction of 7-Benzoyl-3-methyl-2-(1H)-quinoxalinone with sodium azide & thionyl chloride

Asuncion Burguete *et al*, synthesized some new ring substituted 3-Phenyl-1-(1,4-Di-N-oxide quinoxaline-2-yl)-2-Propen-1-one derivatives and their 4,5-Dihydro-(1H)-pyrazole analogues and evaluated for anti-inflammatory/antioxidant activities. The tested compounds inhibit the carrageenan-induced rat paw edema (4.5-56.1%) and present important scavenging activities. Synthesis of all derivatives was carried out by a base-catalyzed Claisen-Schmidt condensation, establishing a required temperature of  $-10^{\circ}\text{C}$ . All the synthesized compounds were characterized by infrared, proton nuclear magnetic resonance, elemental analysis of C, H, and N, and melting point.<sup>7</sup>

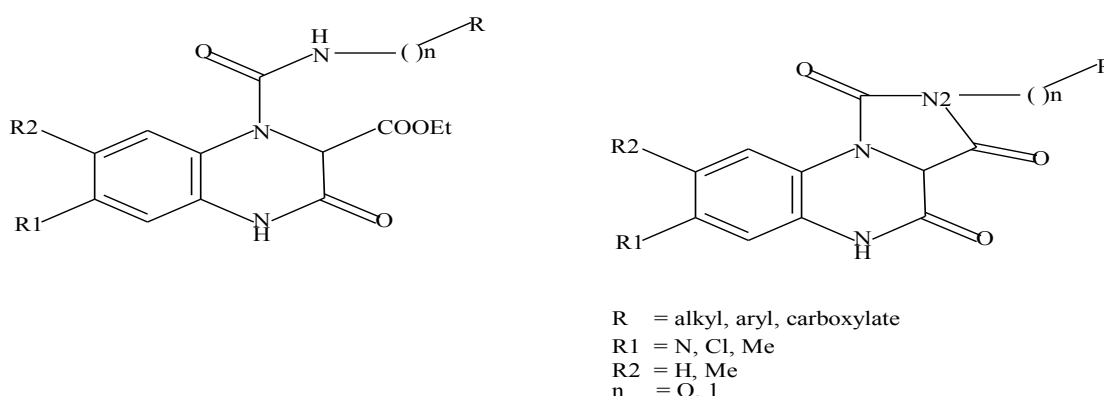


**Figure 10:** Synthesis of 3-Phenyl-1-(1, 4-di-N-oxidequinoxaline-2-yl)-2-propen-1-One derivatives

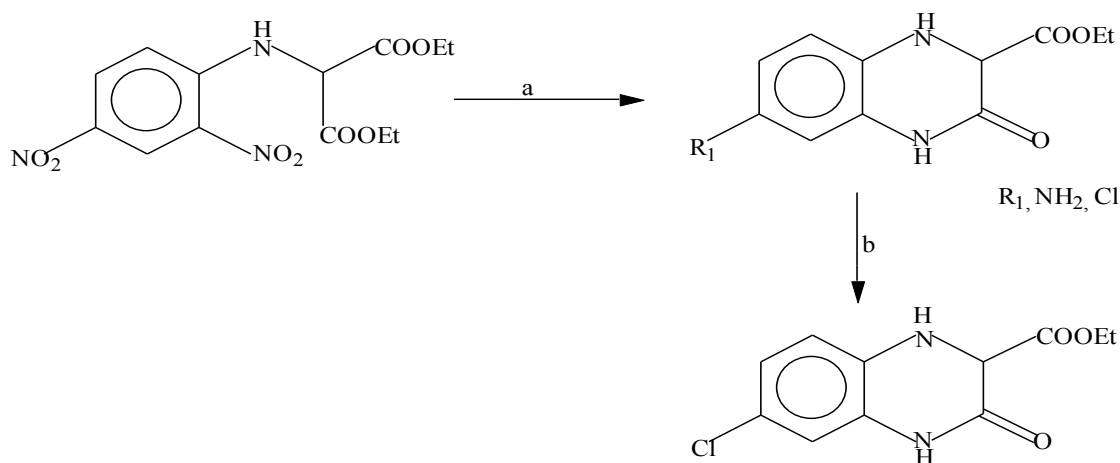
Flavia Varano, *et al*, synthesized set of Ethyl-1-carbamoyl-3-oxoquinoxaline-2-carboxylates and of their constrained analogue Imidazole-[1, 5-a]-quinoxaline-1, 3, 4-triones as Glycine/ NMDA receptor antagonists. Ionotropic glutamate receptors (iGluRs) namely N-Methyl-D-aspartate(NMDA), (RS)-2-Amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-Propanoic acid (AMPA) and kainic acid (KA), play key role in neuronal transmission in the mammalian central nervous system, but are also likely to be involved in numerous pathological and excitotoxic processes. Structure activity relationship studies on quinoxaline-2, 3-diones, which have been reported to have Glycine/NMDA and AMPA receptor antagonist activities. Both Glycine/NMDA and AMPA receptor antagonist possess a N-H proton donor which binds to a proton acceptor of the receptors, as well as negatively-charged heteroatom's able to formed a Columbic interaction with a positive site of the receptors. Both Glycine/NMDA and AMPA receptors can tolerate a polar side-chain Called X and both prefer to accommodate electron-withdrawing group at R1 and R2 although some quinoxaline-2, 3-diones with R1=R2=me have been reported to bind at both receptors with low micro molar affinity.<sup>8</sup>



**Figure 11:** Common structural requirement for Glycine/NMDA and AMPA receptor antagonist



**Figure 12:** Newly synthesized compounds



**Figure 13:** Synthesis of Ethyl (+,-)-6-chloro-1, 2, 3, 4-tetrahydro-3-oxoquinoxaline-2-carboxylate

a) H<sub>2</sub>/Pd/C (b) CuCl<sub>2</sub>, +BuONO

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