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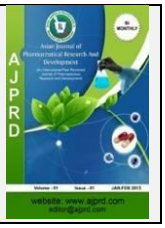

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Review Article

Quinoxaline-2, 3-Dione: Chemical Structure, Synthetic Strategies, Structure–Activity Relationship, Reactivity, and Pharmacological Activities

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A B S T R A C T

Quinoxaline-2,3-dione, a bicyclic heteroaromatic scaffold, has emerged as a versatile pharmacophore with wide-ranging biological activities. Its fused benzene–pyrazine ring system bearing adjacent carbonyl groups at positions 2 and 3 provides a reactive framework for diverse synthetic modifications. Several methodologies, including solvent-free grinding, acid-catalyzed reflux, thermal conditions, and microwave irradiation, have been developed for efficient synthesis of quinoxaline-2,3-dione derivatives, highlighting their accessibility and reproducibility. Structure–activity relationship studies reveal that substitution at positions C-6 and C-7 with nitro groups enhances antibacterial and anti-inflammatory properties, while reduction to amines or incorporation of p-fluorophenyl and dimethylamino groups confers potent analgesic activity. The compound's reactivity encompasses N-alkylation, nitration, chlorination, and nucleophilic substitution, enabling the generation of structurally diverse analogues. Pharmacological investigations demonstrate promising anticancer potential, with derivatives showing cytotoxicity against lung and cervical cancer cell lines, alongside neuroprotective effects in demyelination models. Antibacterial activity against Gram-positive and Gram-negative pathogens further underscores its therapeutic relevance. Additionally, receptor antagonism studies highlight its role in modulating AMPA and GlyN receptors, supporting neuroprotective applications. Collectively, quinoxaline-2,3-dione represents a privileged scaffold for drug discovery, with synthetic versatility, favorable pharmacokinetics, and broad pharmacological potential across oncology, neurology, and infectious disease research.

KEY WORDS: Quinoxaline-2,3-dione, Synthesis, SAR

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INTRODUCTION

Quinoxaline derivatives have different pharmacological activities such as bactericides and insecticides, antibacterial, antifungal, antitubercular, analgesic and anti-inflammatory. The importance of quinoxaline derivatives comes from its nitrogen contents (heterocyclic compounds).

A structure of ring fused with quinoxalines, display diverse pharmacological activities (antibacterial, anticancer and antiviral), antimalarial and anti- depressant activities. Quinoxaline-diones derivatives use on treatment of epilepsy, pain and other neurodegenerative disorders.

Certain condensed quinoxalines exhibit antibacterial, analgesic, tuberculostatic, antileukemic activities. Biologically active polypeptides such as levomycin and echinomycin have been shown to possess one or more quinoxalinyl residues.[1]

CHEMICAL STRUCTURE AND PROPERTIES

Quinoxaline-2,3-dione is a bicyclic heteroaromatic compound with a fused benzene and pyrazine ring system, bearing two adjacent carbonyl groups at positions 2 and 3.

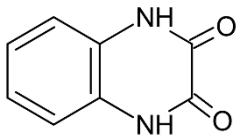


Figure 1: Structure of Quinoxaline-2,3-dione

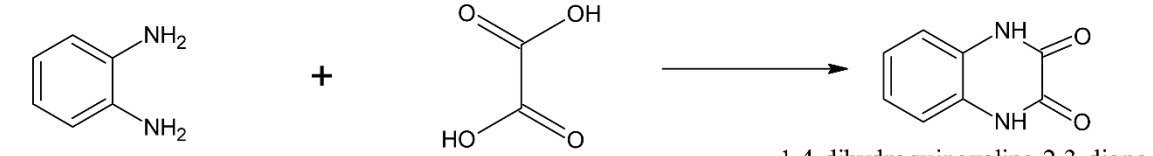
Table 1: Properties of Quinoxaline-2,3-dione

IUPAC Name	1,4-dihydroquinoxaline-2,3-dione
Molecular Formula	$C_8H_6N_2O_2$
SMILES	O=C1Nc2ccccc2NC1=O
Molecular Weight	162.15 g/mol
Physical Description	White or light brown powder

Synthetic Methodologies

Method 1

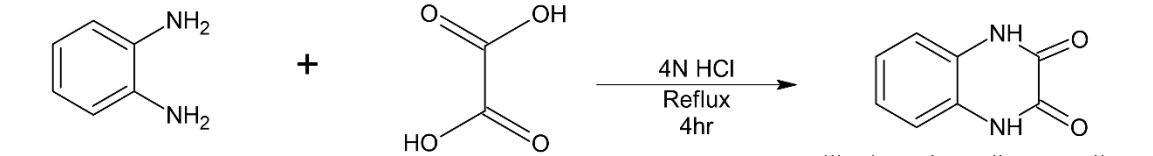
This solvent-free method has an operationally simple procedure. In a typical experiment, a mixture of oxalic acid (1 mmol, 0.126 g) and o-Phenylene di amine (1 mmol, 0.108 g) was thoroughly ground with a pestle in a mortar at room temperature in an open atmosphere until the mixture turned into a melt. Then the melt was crystallized from water to get the pure product.[2]



o-Phenylene diamine oxalic acid 1,4-dihydroquinoxaline-2,3-dione

Method 2

A solution of o-phenylene diamine (0.005 mol) and oxalic acid (0.05 mol) in 4 N HCl (90 ml) was refluxed for 4 h. The mixture was subjected for cooling in the refrigerator overnight to give respective quinoxaline-2, 3-(1H, 4H) – diones. The white solid recovered was filtered and underwent for cold water washing and recrystallized by using ethanol.[3]

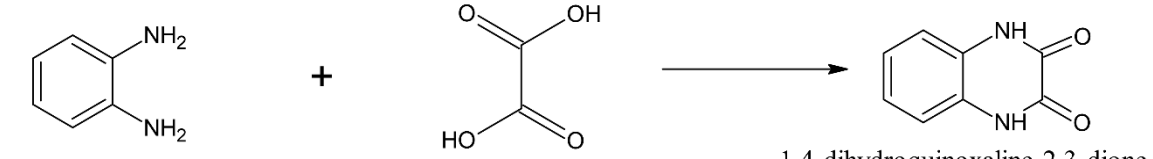


o-Phenylene diamine oxalic acid 1,4-dihydroquinoxaline-2,3-dione

Method 3

Under Thermal Conditions - A powdered mixture of oxalic acid dihydrate (0.01 mole, 1.26 g) and o-phenylene diamine (0.01 mole, 1.0814 g) was refluxed using an oil bath for 1.5 hours and cooled. The product that separated was filtered and washed with water and crystallized with 5% NaOH/dil HCl to give the colour less crystals.

Under Microwave Irradiation - A powdered mixture of oxalic acid dihydrate (0.01 mole, 1.26 g) and o-phenylene diamine (0.01 mole, 1.0814 g) was put in an open beaker and 1 ml of water added and mixed thoroughly. The mixture was irradiated in a catalyst micro wave system at an emitted power of 400 W for 3 min. 100 mL of water was added, followed by further irradiation for 1 min to give a clear solution and then left to stand at room temperature. The product obtained was filtered, washed with water and crystallized with 5% NaOH/ dil HCl to give colourless crystals.[4]



o-Phenylene diamine oxalic acid 1,4-dihydroquinoxaline-2,3-dione

Structure–Activity Relationship (SAR)

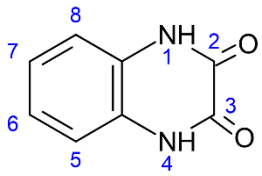


Figure 1: Quinoxaline-2,3-dione

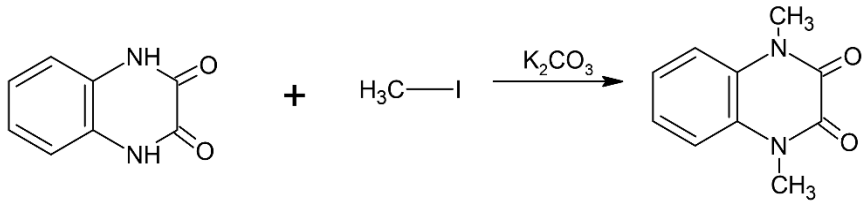
- Moderate antibacterial, analgesic and anti inflammatory activity was observed at substitution of C-6 and C-7 with two nitro groups in quinoxaline-2,3 (1H,4H)-dione.
- Potent analgesic activity was observed reduction of nitro groups at C- 2 and C-3 of quinoxaline-2,3(1H,4H)-dione into amine group using nickel and hydrazine.
- Poor analgesic activity observed when no substitution of quinoxaline-2,3 (1H,4H)-dione
- Most potent anti inflammatory activity when substitution of p- dimethyl amino group by Claisen-schmidt condensation at 6th position of '6-acetylquinoxaline-2, 3 (1H, 4H) -dione.
- Decrease in anti inflammatory activity observed when substitution of 2, 4, 6-trimethoxyphenyl group at position 6th of 6-acetyl quinoxaline-2, 3 (1H, 4H) -dione.
- p-fluro phenyl group substitution results with potent analgesic activity.[3]

REACTIONS OF QUINOXALINE-2, 3-DIONES

1. Reactivity of the Nitrogen Atom of Quinoxaline-2, 3-dione –

N-alkylation reaction

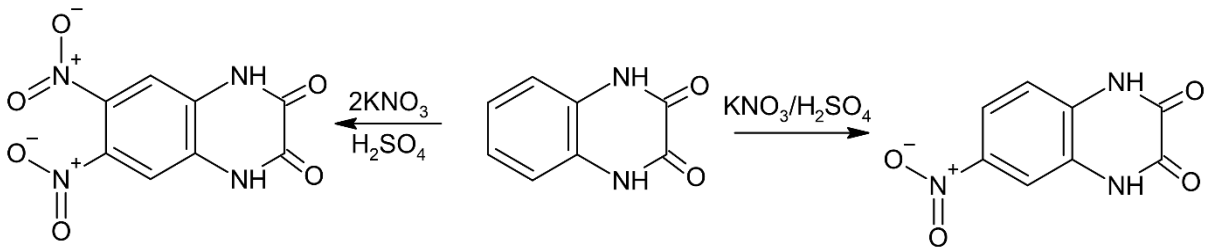
Quinoxaline-2,3-diones reacts with iodomethane in the presence of K2CO3 to afford 1,4 dimethylqunoxaline-2,3-diones.



2. Reactivity of the Aromatic Nucleus –

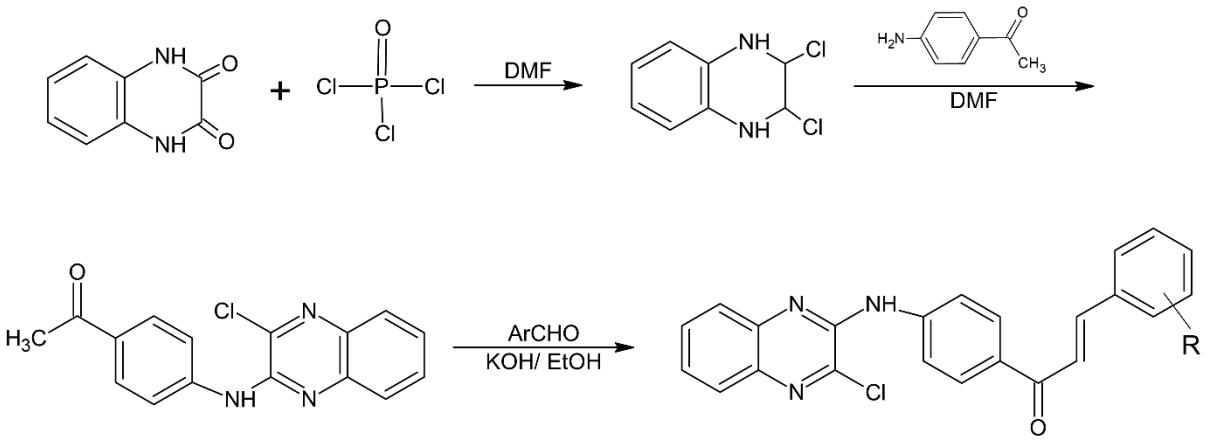
Nitration reaction

Treatment of quinoxaline-2,3-dione with one mole equivalent of potassium nitrate in sulphuric acid results in nitration at position-6, reaction of quinoxaline-2,3-dione with 2 moles equivalents of potassium nitrate 6,7-dinitro compoundis formed.



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 dichloroquinoxalinewhich upon reaction with 4-aminoacetophenone in DMF afforded 1-(4-(3 Chloroquinoxalin-2-ylamino)phenyl)ethenone which when reacted with substituted benzaldehydes in ethanol in the presence of potassium hydroxide afforded the corresponding chalcones derivatives.



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.[5]

PHARMACOLOGICAL ACTIVITIES

Seqqat Y, Hafez B, Lahyaoui M, Toscano F, et al, 2024.This study reports the synthesis and characterization of a novel series of quinoxaline-2,3-dione derivatives, prepared through condensation and alkylation reactions followed by hydrazine modification, and confirmed by NMR, LC-MS, and melting point analysis. The compounds were evaluated for cytotoxicity against A549 lung cancer, HeLa cervical cancer, and HFF fibroblast cell lines using the MTT assay, where compound 3b exhibited the most promising activity with an IC50 of 29.4 µM. ADME properties were predicted using SwissADME, showing favorable pharmacokinetic profiles, while molecular docking against proteins 6G77, 1M17, and 1Z68 revealed strong binding interactions consistent with the biological results. Overall, the findings highlight quinoxaline-2,3-dione derivatives, particularly 3b, as potential anticancer candidates with promising pharmacological and computational support.[6]

Jubie S, Gayathri R, Kalirajan R, 2012. This article describes the synthesis and neuropharmacological evaluation of novel quinoxaline-2,3-dione derivatives prepared via cyclocondensation of o-phenylenediamine with oxalic acid followed by Mannich reactions with ketones and formaldehyde. The compounds were structurally confirmed using IR, ^{1}H NMR, and mass spectrometry. Their pharmacological activity was assessed in rats against ethidium-bromide-induced demyelination, a model for neurodegenerative disorders. Behavioral and motor coordination tests—including open-field exploratory behavior, grip strength, rota rod, beam walk, and photoactometer—demonstrated that the synthesized compounds significantly reversed muscle weakness, locomotor deficits, and neuromuscular discoordination caused by ethidium bromide. Histopathological studies further confirmed remyelination in treated groups. Overall, the results suggest that these quinoxaline-2,3-dione derivatives possess promising neuroprotective potential against demyelinating conditions such as multiple sclerosis and related disorders.[7]

El Janati A, Ouzidan Y, Kandri Rodi Y, et al, 2021. This study reports the synthesis of new quinoxaline-2,3-dione derivatives starting from 6-chloro and 6-nitroquinoxaline-2,3-dione as core nuclei, prepared via condensation of substituted o-phenylenediamines with oxalic acid. Subsequent N-alkylation reactions under phase transfer catalysis conditions yielded a series of dialkylated products, which were characterized by ^{1}H and ^{13}C NMR spectroscopy. The antibacterial activity of these compounds was evaluated against Staphylococcus aureus (Gram-positive) and Salmonella typhi (Gram-negative) using MIC assays. Results showed that compound 2a was the most effective against S. aureus (MIC = 1.25 mg/ml), while compounds 2a, 3b, and 6b exhibited the strongest inhibition against S. typhi (MIC = 2.5 mg/ml). Overall, the findings highlight the potential of quinoxaline derivatives as promising antibacterial agents, with activity influenced by the nature of the substituents and electronic effects on the quinoxaline nucleus.[8]

Jubie S, Gayathri R, Srividya AR, et al, 2011. This article describes the synthesis and characterization of novel quinoxaline-2,3-dione derivatives incorporating benzimidazole moieties via electrophilic substitution at the 6-position of the quinoxaline ring. The synthetic pathway involved cyclocondensation of o-phenylenediamine with oxalic acid to yield quinoxaline-2,3-dione, followed by reaction with chlorosulphonic acid to form the sulphonyl chloride intermediate, which was subsequently coupled with various substituted benzimidazoles to afford compounds 4a–4e. Structural confirmation was achieved using IR, ^{1}H NMR, and mass spectrometry. The cytotoxicity of these derivatives was evaluated against HEp-2 human epithelial carcinoma cells using the sulforhodamine B assay, with results indicating moderate activity and CTC_{50} values ranging between 25–60 µg/ml. These findings suggest that quinoxaline-2,3-dione sulphonyl benzimidazole derivatives may serve as promising scaffolds for anticancer drug development.[4]

Nikam SS, Cordon JJ, Ortwine DF, et al, 1999. This article reports the design and synthesis of novel quinoxaline-2,3-dione derivatives as antagonists of AMPA and GlyN receptors, aimed at improving the poor aqueous solubility of the lead compound PNQX. By opening the pyridine ring of PNQX to generate nonplanar analogues, several derivatives were obtained with enhanced solubility while retaining receptor affinity. Among them, the sarcosine analogue (compound 9) demonstrated strong binding to both AMPA (IC_{50} = 0.14 µM) and GlyN (IC_{50} = 0.47 µM) receptors, comparable to PNQX, but with markedly improved solubility (420 µg/mL vs. 8.6 µg/mL for PNQX). Structure–activity relationship studies confirmed the importance of the nitro group at C-7 and the amide carbonyls at C-2 and C-3 for receptor interactions. Overall, the strategy of introducing nonplanar amino acid side chains successfully produced analogues with better physicochemical properties, supporting their potential as neuroprotective agents.[9]

Baashen M, 2018. This review article discusses the synthesis and chemical reactivity of quinoxaline-2,3(1H,4H)-dithione, a versatile heterocyclic compound derived mainly from thionation of quinoxaline-2,3-dione using reagents such as phosphorus pentasulfide, thiourea, or sodium hydrogen sulfide. The compound exists in tautomeric equilibrium with quinoxaline-2,3-dithiol and serves as a key precursor for numerous transformations. Its reactions typically involve deprotonation and electrophilic substitution at sulfur atoms, enabling the formation of a wide variety of substituted derivatives and poly-fused heterocyclic systems. Reported methodologies include reactions with halo compounds, bromoacetylenes, nitriles, cyanoacetamides, and sulfonyl reagents, producing diverse structures with yields ranging from moderate to excellent. The review highlights the compound's synthetic utility and its role in generating heterocycles with potential pharmacological and industrial applications.[10]

CONCLUSION

Quinoxaline-2,3-dione and its derivatives constitute an important class of heterocyclic compounds with significant medicinal relevance due to their nitrogen-rich bicyclic framework and versatile chemical reactivity. These compounds exhibit a broad range of pharmacological activities, including antibacterial, antifungal, antitubercular, analgesic, anti-inflammatory, anticancer, and neuroprotective effects, making them attractive scaffolds in drug discovery. Various efficient and economical synthetic methodologies—such as solvent-free grinding, conventional reflux, and microwave-assisted techniques—enable easy preparation and structural modification of quinoxaline-2,3-dione derivatives. Structure–activity relationship studies highlight the critical influence of substituents at different ring positions on biological activity, particularly electron-withdrawing and amino groups. Additionally, the rich chemistry of quinoxaline-2,3-dione allows diverse functionalization through N-alkylation, nitration, halogenation, and nucleophilic substitution reactions. Recent studies combining biological evaluation with computational and ADME analyses further support the therapeutic potential of these compounds. Overall, quinoxaline-2,3-dione remains a promising and versatile scaffold for the development of new agents targeting infectious, inflammatory, neurological, and cancer-related diseases.

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