A REVIEW ON BIOLOGICAL STUDIES OF QUINOXALINE DERIVATIVES

Ali Irfan*1, Omar Ali Tahir1, Muhammad Umer1, Sajjad Ahmad2 and Humaira Kousar1

1Department of Chemistry, The University of Lahore, Sargodha Campus, Pakistan.
2Department of Chemistry, UET Lahore, Pakistan.

ABSTRACT
Quinoxaline moieties are nitrogen containing heterocyclic derivatives which have broad spectrum biological and pharmaceutical applications. The quinoxaline derivatives are used for the cure of vast range of various diseases. Modifications in structure of quinoxaline substrates have provided applications in various fields and developed remarkable efficacy against diseases with lesser side effects. In this account, glimpses of such quinoxaline derivatives have been presented known for their activity as antiprotzoal, anticancer, antimalarial, antimicrobial antiviral, anti-inflammatory, antidiabetic, anti-tubercular, anti-nociceptive, anthelmintic and as a kinase inhibitor.

KEYWORDS: Bioactive quinoxaline, anticancer, antimicrobial, antineoplastic, anti-inflammatory.

INTRODUCTION
Organic compounds which are formed by replacing carbon atoms of ring with one or more N, O or S elements are called as heterocyclic organic compounds. Quinoxaline moiety and its derivatives are belonged to class of nitrogen containing heterocyclic compounds with broad range of biological activities and pharmacological applications.[1] Benzopyrine and diazanaphthalene are its other names. Quinoxaline ring atoms are numbered as below in Figure 1. The number of resonance structures of quinoxaline increases by the fusion of one or more benzene rings to quinoxaline and phenazine rings and the dipole moment of quinoxaline is zero.[2]
Quinoazoline, cinnolenes and phthalazines are isomeric with quinoxline. Quinoxaline is formed by the fusion of diazine with benzene ring. Some of heterocyclic system are given below.\textsuperscript{[3]}

![Chemical structures](image)

**Figure 2: Heterocyclic compounds**

Quinoxaline derivatives which have a wide variety of potential applications in biological, medicinal and pharmacological fields.\textsuperscript{[4]} Quinoxaline derivatives act as antiprotozoal, antiviral, anti-inflammatory, and antibacterial and as a kinase inhibitor.\textsuperscript{[5]} Quinoxaline have wide applications as DNA cleaving agent, dyes, organic semiconductors, cavitands, efficient electroluminescent, dihydroannululenes and building blocks for the synthesis of anion receptor. Quinoxaline derivatives showed anticancer, antimalarial, antimicrobial, antinociceptive, antiepileptic, antidiabetic, anti-tubercular and anthelmintic characteristics.\textsuperscript{[6]}

![Biological activities](image)

**Figure 3: Biological activities of quinoxaline derivatives.**
The present study shows advancement in synthesis and biological diversities of quinoxaline derivatives to develop new pathways for therapeutic targets, drug design and future drug discovery.

BIOLOGICAL APPLICATIONS
Abid & Azam reported substituted indophenazines quinoxaline derivative 1 as anti-amoebic and psychotropic agent as well as anti-inflammatory. The derivative 1 was formed by the refluxing of 1-N-thio-carboxamide-3-phenyl-2-pyrazolines with 1,2-dichloroquinoxaline.[7]

![Figure 4: Substituted indophenazines quinoxaline derivative 1](image)

Wagle et al screened 3-Methyl-7-substituted-1{[5-(aryl)-1,3,4-oxadiazoles-2-yl]-methyl}-quinoxaline-2(1H)-ones as best anti-inflammatory compound. Non-steroidal anti-inflammatory drugs (NASID) were used for inflammation, arthritis, margarine, fever or for acute and chronic pains.[8]

![Figure 5: Non-steroidal anti-inflammatory quinoxaline derivative 2](image)

Thioquinox 3 (a quinoxaline derivative) demonstrated a potential antifungal activities as reported by Laddah & Bhatanagar.[9]

![Figure 6: Thioquinox quinoxaline antifungal derivative 3](image)
3-Amino-N-(4-methoxyphenyl)-2-quinoxalinecarboxamide-1,4-di-N-oxide 4 showed antifungal properties. Preparation of the quinoxaline-1,4-di-N-oxide compounds by the Beirut reaction between the phenazine derivative and the indenoquinoxaline by Soliman.\textsuperscript{[10]}

![Figure 7: Quinoxaline-1,4-di-N-oxide antifungal derivative 4](image)

Chloro quinoxaline sulphonamide 5 is used as anti-neoplastic. Quinoxaline derivatives have inhibitory activity against human cancer cells lines. The platelet-derived growth factor (PDGF) receptor kinase is inhibited selectively by quinoxaline derivatives reported by Gao et al.\textsuperscript{[11]}

![Figure 8: Chloro quinoxaline sulfonamide (CQS) antineoplastic derivative 5](image)

Quinoxaline carboxamide derivative showed 5-HT\textsubscript{3} (setrons) receptor antagonistic is class of drugs which treated nausea and vomiting due to induced cancer. The condensation of Mannich bases like p-amino phenol reacted with 3-chloro-2-quinoxaloylchloride to afford carboxamide quinoxaline derivatives by Mahesh et al.\textsuperscript{[12]}

![Figure 9: Quinoxaline carboxamide derivative 6](image)
Yoo et al synthesized 7, 8-Bis(bromomethyl)benzo[g]quinoline-5,10-dione 7 which exhibited excellent cytotoxic effect against leiomyosarcoma, liposarcoma, fibroblastic, rhabdomyosarcoma, synovial sarcomas, angiosarcoma and kaposi's sarcoma etc.\[13\]

![Figure 10: 7,8-Bis(bromomethyl)benzo[g]quinoline-5,10-dione 7](image)

Deleuze et al reported imidazo[1,2-a]quinoxaline analogues 8 and 9 were synthesized by condensation of 2-imidazole carboxylic acid, followed by a coupling with ortho-fluoroaniline. These quinoxaline derivatives showed prominent antitumor activities against human amelanotic melanoma cell line (A 375 cells). These analogues were used in cytokine research in outside of living organism or in vitro but not in vivo.\[14\]

![Figure 11: Antitumor Imidazo[1,2-a]quinoxaline analogues 8](image)

![Figure 12: Antitumor Imidazo[1,2-a]quinoxaline analogues 9](image)

Monoamine oxidases (MAO) belonged to a family of enzymes that catalyze the oxidation of monoamines and acted as inhibitors chemicals which inhibited the activity of the monoamine oxidase enzyme family. Some novel monoamine oxidase A inhibitors (MAO) such as 3-benzyl-2-substituted quinoxalines derivatives treated Parkinson’s disease, depression and anxiety disorders was prepared by Seham et al.\[15\]
1,2,3-Trisubstituted-1,4-dihydrobenzoquinoxaline-5,10-diones derivative 11 showed excellent antibacterial activity in biological cultures in slants or petri dishes was determined by Vishnu et al.\textsuperscript{[16]}

Kleim et al prepared quinoxaline derivatives such as 6-chloro-3,3-dimethyl-4(isopropenyl oxy-carbonyl)-3,4-dihydroquinolin-2-(1H)-thione and (S)-4-isopropoxycarbonyl-6-methoxy-3-methylthiomethyl-3,4-dihydroquinoxaline-2(1H)-thione (HBY 097) 12 exhibited anti HIV activity against HIV reverse transcriptase enzyme inhibitor.\textsuperscript{[17]}

The quinoxaline derivatives N-(4-fluorophenyl)-2-(3-oxo-3,4-dihydroquinoxalin-2-yl) hydrazine carbothioamide 13 were used in the treatment of high sugar level (anti-diabetic) called as mild hypoglycemic agent by Reddy et al.\textsuperscript{[18]}
Li afforded quinoxaline derivative based Brimonidin (Alphagan) 14 drug is called 5-bromo-N-(2H-imidazol-2-yl)quinoxalin-6-amine and used to treat the intraocular pressure and the eyes diseases especially glaucoma in which symptoms appeared like increased pressure within the eyeball that causing gradual loss of sight.\cite{19}

6-Chloro-7-((4-hydroxyphenyl)amino)-2,3-di(pyridin-2-yl)quinoxaline-5,8-dione derivative 15 exhibited excellent and highest anti-proliferative activity was screened by Chung et al.\cite{20}

Selvam et al synthesized diphenyl quinoxaline (DPQ) 16 which showed inhibitory activity in vitro against the aids virus HIV-1 (111B) replication in human metallothionein 4 cells (MT-4 cells).\cite{21}
Sulfonamide quinoxaline derivatives such as 6,7-diphenylquinoxaline-2-sulfonamide 17, N,6,7-triphenylquinoxaline-2-sulfonamide 18 and N-((6,7-diphenylquinoxalin-2-yl)sulfonyl)hydrazinecarbothioamide 19 showed anti-inflammatory characteristics and properties were prepared by Rahul & Rajendra.\cite{22}

Figure 20: Quinoxaline derivatives 17 showing anti-inflammatory activity

Figure 21: Quinoxaline derivative 18 showing anti-inflammatory activity

Figure 22: Quinoxaline derivative 19 showing anti-inflammatory activity

The amino acids in the peptide chains of triostin-A 20 and quinomycin 21 are: D-Ser (D-serine), Ala (Alanine), MeCys (N-Methyl-L-cysteine), MeVal (N-Methyl-L-valine) reported by Gauvreau & Waring.\cite{23}

Figure 23: Structure of Triostin-A quinoxaline derivative 20
Quinoxaline derivatives 6,7-dimethyl-2-phenylquinoxaline (AG 1295) \(22\) & 2-phenylbenzo[g]quinoxaline (AG 1385) \(23\) showed the specific blocking EGFR kinase and ATP competitive inhibitory properties determined by Kovalenko et al.\(^{[24]}\)

Eslam et al synthesized following quinoxaline-2,3-diones derivatives 6-isocyano-7-nitroquinoxaline-2,3(1H,4H)-dione (CNQX) \(24\), 6,7-dinitroquinoxaline-2,3(1H,4H)-dione (DNQX) \(25\) & 6-(1H-imidazol-1-yl)-7-nitroquinoxaline-2,3(1H,4H)-dione (YM-872) \(26\) which demonstrated excellent anticonvulsant activities.\(^{[25]}\)
Ahoya et al reported 2-Methylquinoline-3(4H)-thione 27 showed less antibacterial activities than 4-ethyl-2-methylquinoline-3(4H)-thione 28 as compared to the standard references of clotrimazole and tetracycline.\textsuperscript{[26]}

Umarani Natarajan et al reported the tetrazolo quinoxaline derivatives 29d and 29f were showed high antimicrobial activities while 29g and 29h exhibited optimum potent antimicrobial properties. The compound 29j was moderately active while compound 29i was showed mild antimicrobial activity against the tested strains. The derivative 29i was optimum potent and showed remarkable anti-inflammatory activity. The derivative 29j was exhibited closely in anti-inflammatory activities to compound 29i. The moderate anti-inflammatory
activity was showed by compounds 29a-h. In short the derivatives 29i and 29j exhibited optimum anti-inflammatory activity but showed minimum antimicrobial characteristics and activity. The rest of derivatives in the synthesized series showed moderate anti-inflammatory but remarkable high antimicrobial activities.\textsuperscript{[27]}

![Figure 32: Synthesis of Schiff's bases of tetrazolo[1,5-a] quinoxalines 29](image)

The quinoxaline derivatives 35 a-d and 38 exhibited anticonvulsant activity similar to compounds 30-34. The compound 37 was the best anticonvulsant agent. The compound 36b was equipotent in anxiolytic effect with that of diazepam. The derivatives 36d and 37 were induced more anxiolytic effect than diazepam. Therefore these derivatives were considered most potent and active in anxiolytic effect. The functional groups of compounds 36, 36b, 38 and 39 were lack ability to induce anxiolytic effect while all these derivatives showed sedative effects reported by Olayiwola et al.\textsuperscript{[28]}

![Image of compounds 30, 31, and 32](image)
1-(1-(carboxymethyl)-7-nitro-2,3-dioxo-1,2,3,4-tetrahydroquinoxalin-6-yl)-1H-pyrrole-3-carboxylic acid

6-nitro-2,3-dioxo-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide

9-(1H-imidazol-1-yl)-8-nitropyrazolo[1,5-c]quinazoline-2,5(3H,6H)-dione

Figure 33: 2-Amino-3-(3-hydroxy-5-methylisoxazol-4-yl) propanoic acid (AMPA) receptor antagonists

98a R=H, 98b R=Cl, 98c R=CH3, 98d R= NO₂

Figure 34: Substituted Quinoxaline-2, 3-diones derivatives

6-(((dibenzylamino)peroxy)thio)quinoxaline-2,3(1H,4H)-dione

Figure 35: Substituted Quinoxaline-2, 3-diones derivatives
Ali et al afforded the quinoxalin-2-ones 40 and quinoxaline-2,3-diones 41 which demonstrated antimicrobial activity. The derivatives 40 and 41 showed the excellent antithrombotic activities reported by Ries et al.

Osama, S. M. screened quinoxaline derivative 42 and 43 which were highly active against Gram positive bacteria and exhibited excellent inhibitory growth. Antifungal activities showed by 42 and 44 derivatives against the tested strains of fungi. It was concluded that the derivatives 42, 43 and 44 exhibited remarkable antimicrobial activities.
The quinoxaline derivatives 46, 47a, 47c, 47d, 47e, 49a and 49c were showed excellent antibacterial activity against both Gram positive and Gram negative bacteria. Antibacterial activity against E. coli. were exhibited by 47c, 47d, 49a, 49c and 49e. The antibacterial activity was not showed by compound 49d against Escherichia coli and Pseudomonas aeruginosa. The quinoxaline derivatives 49b and 49c were not exhibited antimicrobial characteristics against Pseudomonas aeruginosa. As we introduced aromatic ring and –CH₃ group in the compounds, the lipophilicity of the compounds were increased. High antibacterial activity of these compounds 46, 47a, 47c, 47d, 47e and 49c were due to increase in lipophilicity which resulted in permeability through the microbial cell wall. The derivative 49d was showed best antimicrobial activities due to presence of –COOH and was considered as analogue to famous antimicrobial agent benzoic acid.

The quinoxaline derivatives 46, 48, and 49a acted as moderate antifungal agent against both A. niger and C. albicans strains. The quinoxaline compounds 47b, 47c, 47d and 47e exhibited no activity against C. albicans while showed moderate antifungal activity against A. niger.
Compounds of quinoxaline 47a, 47b, 47c, 49d and 49e showed no activity against A. niger.\textsuperscript{[32]}

\begin{align*}
\text{46} & \quad \text{4-((3-methylquinoxalin-2-yl)oxy)benzaldehyde} \\
\text{47} & \quad \text{N-((4-(2-methylquinoxalin-3-yloxy)phenyl)methylene)-4-substituted benzenamine} \\
\text{48} & \quad \text{4-((3-methylquinoxalin-2-yl)oxy)aniline} \\
\text{49} & \quad \text{4-(2-methylquinoxalin-3-yloxy)-N-substituted benzylidene benzenamine}
\end{align*}

\text{R= H, Cl, CH}_3, 4-COOH, 2'-CH\text{,} \text{6'-CH}_3 \quad \text{Compounds 47(a-e)}

\text{R= 4-OH, 2-NO}_2, 4-N(CH}_3)_2, 2'-OH, 3'-OCH, 2'-OCH\text{,} 3'-OCH\text{,} 4'-OCH}_3 \quad \text{Compounds 49(a-e)}

Chih-Hua reported that 11-(3-(dimethylamino) propoxyimino)-N-(3-(dimethylamino) propyl)-11H-indeno [1,2-b]quinoxaline-6-carboxamide demonstrated inhibitory activities topoisomerase-1 and topoisomerase-2 with reference to control compound. Zebrafish Xenograft method confirmed the anti-tumor activities of compound 50.\textsuperscript{[33]}
Hajri et al synthesized Ethyl 3-(aryl ethynyl) quinoxaline-2 –carboxylates derivatives which exhibited anti-proliferative activities against both human non- small cell lung carcinoma and glioblastoma cell lines.\textsuperscript{[34]}

CONCLUSION
The nitrogen containing heterocyclic quinoxaline core can easily be synthesized and modified into different derivatives which have potential biological, pharmacological and medicinal applications. The quinoxaline compounds are pharmacophore and have diverse applications in biological, pharmacological and organic material chemistry fields. Quinoxaline is important moiety which is biologically active and exhibit excellent and remarkable clinical and therapeutic properties. The plethora of research mentioned in this review article is helpful to develop such strategies and methodologies to synthesize new generation of quinoxaline skeleton based therapeutic agents, drugs and analogues which have optimum potent efficacy, no cytotoxicity and greater bio absorption.

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