POTENTIAL ACTIVITIES OF QUINOXALINE DERIVATIVES – A REVIEW

Gollapalli Naga Raju*, Ramayanam Lakshmi Madhuri, Pattan Shaheena, Nadendla Ramarao

Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur-522 034, Andhra Pradesh, India.

ABSTRACT
Quinoxaline derivatives constitute an important class of heterocycles in drug discovery. They are clinically effective as antibacterial, antifungal, anti-inflammatory, anticancer, anti-tubercular and antineoplastic agents. Interestingly, it also shows hypoglycemic and antiglaucoma activity. Modification in their structure has offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity. Considering the extensive research on quinoxaline in the past, it was essential to review the wide spectrum of biological activity of quinoxalines. To conclude, this review will be beneficial for new drug discovery of quinoxaline moiety.

KEYWORDS: Quinoxaline, Antibacterial, Anticancer, Anti-oxidant, Anti-inflammatory.

INTRODUCTION
Quinoxalines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties. Quinoxaline nucleus are known to exhibit anti-inflammatory activity, differently substituted Quinoxaline moiety has been found to have other interesting activities such as antianxiety, antibacterial, anticonvulsant, antipsychotic, antitumor, antifungal, antispasmodic, antihistamic, antinociceptive, antioxidant, antimicrobial activities. Quinoxaline is one of the most important heterocyclic compound, weak base, having varied biological activities and still of great scientific interest now a days. They are widely found in bioorganic and medicinal chemistry.
with application in drug discovery. This review was focused on the Quinoxalines and its
different derivatives that posses different biological activities.

**BIOLOGICALLY ACTIVE QUINOXALINES AND ITS DERIVATIVES**

**Anticancer activity**

The compound 3-chloro-2-hydrazine quinoxaline was condensed with 2-furaldehyde to
derive a Schiff base 2-furaldehyde-2-(3-chloro-2-quinoxalinyl) hydrazone (FCCQH). The
ligand and also its complexes with VO (IV), Cr (III), Mn (II), Fe (III), Co (II), Ni (II), Zn (II),
and Pd (II) have been synthesized and these complexes have been screened for antibacterial
activity towards *staphylococcus aureus* (gram +ve), *Escherichia coli* (gram -ve) bacteria,
antifungal activity towards *fusarium oxysporum* and anticancer activities of the compounds
were evaluated by MTT assay on HeLa (cervical cancer) cell lines.

A series of forty-seven quinoxaline derivatives, 2-(XYZC6H2CH@N–NH)-quinoxalines, 1,
have been synthesized and evaluated for their activity against four cancer cell lines: The
structure–activity relationship (SAR) analysis indicated that the number, the positions and the
type of substituents attached to the aromatic ring are critical for biological activity. The
activities do not depend on the electronic effects of the substituents nor on the lipophilicities
of the molecules.

A novel isatin incorporated quinoxaline derivatives have been synthesized by V. Harinadha
Babu et al. In anti-proliferative screening, compounds showed promising activity against
MDAMB cell line at IC50 values of 4.10, 4.79 and 5.15 Mm.
Novel thioureido sulfaquinoxaline derivatives were synthesized by MARWA G. EL-GAZZAR et al. All the newly synthesized compounds were evaluated for their in vitro anticancer activity against a human liver cell line (HEPG2) and showed higher activity than the reference drug doxorubicin.\cite{16}

N-Butylpyridoquinoxaline 1,4-Dioxide (NBPQD) derivatives were synthesized by Salem A. Habib et al. All the newly synthesized compounds were evaluated for their in vitro anticancer activity against a human liver cell line (HEPG2) and showed higher activity than the reference drug doxorubicin.\cite{17}

Patrice Vanelle et al investigated the reactivity of carbanion formed via TDAE in quinoxaline series. The new synthesized compounds were tested for their anti-proliferative activity on two neuroblastoma cell lines.\cite{18}

**Anticonvulsant activity**

Ratnadeep V. Ghadage and Pramod J. Shirote synthesized the Schiff’s bases of 3-[[2-((E)-[(substituted) phenyl] methylidene] amino) ethyl] amino] quinoxalin-2(1H)-one and
evaluated for *in-vivo* anticonvulsant activity. This activity was carried out on pentylenetetrazole-induced seizure model.\(^{[19]}\)

Quinoxalinone derivatives were synthesized and investigated for some neuropharmacological effects (analgesia, sedation, convulsion, anxiety, memory and psychosis) in mice and rats by C. A. Obafemi et al. N,N-dibenzyl-2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-sulfonamide showed significant anticonvulsant action.\(^{[20]}\)

A series of novel indeno[1, 2-b]quinoxalin-11-ylidenamines 2-9 have been synthesized by A. Rajasekaran. Compounds 2-9 were screened for anti-nociceptive, anti-inflammatory and antiepileptic activity by AcOH induced writhing method, carrageenan induced paw edema method and maximal electroshock induced convulsion method respectively.\(^{[21]}\)

1-Ethyl-3-hydrazinylquinoxalin-2-1H-one and many other newly synthesized by Ashraf Bayoumi et al. Docking studies were performed to all the synthesized compounds in order to rationalize the anticonvulsant activity of the proposed compounds in a qualitative way. There
is a strong correlation between the results of molecular modeling and the anticonvulsant activity of the synthesized compounds.\[^{22}\]

![Chemical structure](image)

Various 1-(substituted benzylidene)-5-(3-hydroxyquinoxaline-2-yl) carbonohydrazide were synthesized by Sahu et al. All the newly synthesized compounds were screened for anticonvulsant activity. Some of the compounds showed significant anticonvulsant activity with no neurotoxicity.\[^{23}\]

![Chemical structure](image)

**Antioxidant activity**

*In vitro* antioxidant activity of some novel quinoxaline derivatives was investigated by 1,1-diphenyl-2-picrylhydrazyl (DPPH) method with respect to ascorbic acid by Hossain MM et al. The present findings revealed that some quinoxalines and their precursors exhibited a marked scavenging effect on DPPH radical.\[^{24}\]

![Chemical structure](image)

Indoloquinoxalin was fused with 2,3 diphenyl quinoxaline by a methylene bridge which was then allowed for acetylation. The acetylated product was made to react with different aromatic aldehydes to givechalcones. Chalcones refluxed with substituted acid hydrazides to
afford different indoloquinoxaline pyrazolines. All the synthesized compounds were screened for their antioxidant, anti-inflammatory and antihistamic activities.[25]

![Chemical structure](image)

8-chloro-1,4-substituted-[1,2,4]triazolo[4,3-a]quinoxaline derivatives were synthesized by C. Venkata Rao et al. All the above compounds were screened for anti-microbial activity, anti-oxidant activity and their bioassay showed them to possess significant antimicrobial activity and anti-oxidant activity.[26]

![Chemical structure](image)

1-(4-(3-chloroquinoxalin-2-ylamino) phenyl) ethanone then reacted with corresponding aromaticaldehydes to form quinoxaline derived chalcone by claisen Schmidt reaction by Vijay Kotra et al and the newly synthesized compounds were screened for anti bacterial, anti oxidant activities.[27]

![Chemical structure](image)

**Antibacterial activity**

Keesari Srinivas et al Synthesized the Novel Quinoxaline-6-Carboxamide Derivatives. The newly synthesized quinoxaline carboxamides have been screened against four bacterial strains such *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Streptococcus pyogenes*.[28]
Raju et al. World Journal of Pharmaceutical Research

A series of substituted Hydrazone and Quinoxaline derivatives have been synthesized by Arvind Kumar et al. All the compounds have been screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Some of these compounds have been screened for anti-inflammatory activity against the carageenan induced rat paw edema in albino wistar rats.\(^{29}\)

Smd. Noorulla et al worked on the Antibacterial Activity of Novel Substituted Quinoxaline Heterocycles with Isoniazide. Quinoxaline and isoniazid molecules are responsible for antibacterial activity, but it is interesting to note that isoniazid moiety when fused with other moieties showed a broad spectrum antibacterial activity.\(^{30}\)
Steroidal [oxazolo(4,5-b)quinoxaline-2-yl-hydrazone] derivatives were prepared by Salman Ahmad Khan. The antibacterial activity of these compounds was evaluated by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria and then the minimum inhibitory concentration (MIC) of compounds was determined.\textsuperscript{[31]}

\[
\begin{align*}
\text{R} & = \text{CH}_3\text{COO}^-, \text{Cl}, \text{H}
\end{align*}
\]

**Antimicrobial**

Yellajyosula Lakshmi Narasimha Murthy et al synthesized the 2,3-Diphenyl Quinoxaline 1,4-di-N-oxide Derivatives and investigate the antimicrobial activities. The study would be a fruitful matrix for the development of 2, 3-diphenyl quinoxaline 1,4-di-N-Oxide derivatives for further biological evaluation.\textsuperscript{[32]}

The quinoxaline derivatives were synthesized by the M.C. Somasekhar Reddy et al. As the results of antibacterial screening tests done by paper disc method, quinoxaline derivatives revealed significant inhibition zone on Bacillus *spericus* and quinoxaline derivatives on *Escherichia coli* cultures.\textsuperscript{[33]}

4-(2-methylquinoxalin-3-yloxy)-N-substituted benzyldine benzamines derivatives were synthesized by Dharmchand Prasad Singh et al. All the synthesized compounds were tested
in-vitro for their antifungal activity against microorganisms such as Aspergillus niger and Candida albicans.\cite{34}

A new series of quinoxaline 1,4-di-N-oxides were synthesized and evaluated for their antibacterial and antifungal activities by Dalia Hussein Soliman. The best result was demonstrated by 3-amino-N-(4-methoxyphenyl)-2-quinoxalinecarboxamide 1,4-di-N-oxide, MIC (0.24 μg/ml) against Aspergillus fumigatus, and (0.12 μg/ml) against Streptococcus pneumoniae.\cite{35}

A series of N-(4H-imidazo[4,5-b]quinoxalin-2(9H)-ylidene)substituted amine was designed, synthesized by Usha Kiran Garlapati et al and evaluation of potential antibacterial activity screened against gram negative viz Escherichia coli, Klebsella pneumonia and gram positive bacteria viz Staphylococcus aures and Bacillus subtilis. Ciprofloxacin used as standard drug.\cite{36}

Miscellaneous
Quinoxalinone derivatives were synthesized by C. A. Obafemi et al. and investigated for some neuropharmacological effects (analgesia, sedation, convulsion, anxiety, memory and psychosis) in mice and rats.\cite{37}
The *in-vitro* antiplasmodial activity of some 3-trifluoromethyl-2-carbonylquinoxaline di-N-oxide derivatives is reported by B. Zarranz et al. The evaluation was performed on cultures of FcB1 strain (chloroquine-resistant) of *P. falciparum* and the most interesting compounds were then evaluated on MCF7 tumor cells in order to evaluate an index of selectivity.\[^{38}\]

Indoloquinoxalin was fused with 2,3 diphenyl quinoxaline by a methylene bridge which was then allowed for acetylation. The acetylated product was made to react with different aromatic aldehydes to givechalcones. Chalcones refluxed with substituted acid hydrazides to afford different indoloquinoxaline pyrazolines. All the synthesized compounds were screened for their antioxidant, anti-inflammatory and antihistamic activities.\[^{39}\]

**CONCLUSION**

From the above literature review concluded that the Quinoxalines and their derivatives have shown a wide spectrum of biological activities. It is a versatile nucleus in the field of medicinal chemistry. Hence this unique molecule must serve as future therapeutic leads of developing various biological agents. The biological profiles of this new generation of Quinoxalines represent much progress with regard to the older compounds.
ACKNOWLEDGEMENT
The authors are grateful to Department of Pharmaceutical Analysis, Chalapathi Institute of Pharmaceutical Sciences, Guntur for providing facilities to perform the review work.

REFERENCES
2. Abdelhalem Mesfioui et al, Synthesis and Influence of Two Quinoxalinone Derivatives on Anxiety- and Depressive-Like Responses in Wistar Rat, Neuroscience & Medicine, 2012: 3; 330-336.
6. Hanlin Gao et al, DNA Sequence Specificity for Topoisomerase II Poisoning by the Quinoxaline Anticancer Drugs XK469 and CQS, Molecular Pharmacology., 63(6).


22. A. Bayoumi et al, Synthesis and evaluation of some new 1,2,4-triazolo(4,3-a)quinazolin-4-5H-one derivatives as AMPA receptor antagonists, *Bulletin of Faculty of Pharmacy, Cairo University.*, 2012; 50: 141–146.


