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POTENTIAL ACTIVITIES OF QUINOXALINE DERIVATIVES – A REVIEW

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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

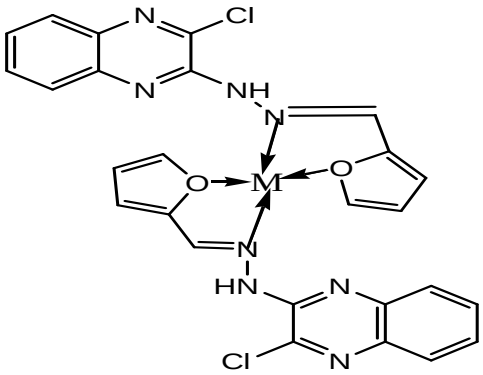
Quinoxalines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties. Quinoxaline nucleus are known to exhibit anti-inflammatory[1] activity, differently substituted Quinoxaline moiety has been found to have other interesting activities such as antianxiety[2], antibacterial[3], anticonvulsant[4], antipsychotic[5], antitumor[6], antifungall[7], antispasmodic[8], anthistamic[9], antinociceptive [10], antioxidant[11], antimicrobial[12] 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.

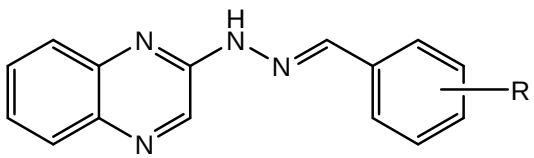
BIOLOGICALLY ACTIVE QUINOXALINES AND ITS DERIVATIVES

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.[13]

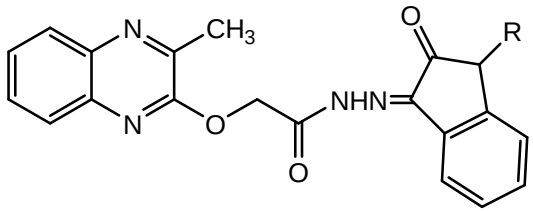


A series of forty-seven quinoxaline derivatives, 2-(XYZC6H2CH@N–NH)-quinoxalines, 1, have been synthesized and evaluated for their activity against four cancer cell lines: The structure–activity relationship (SAR) analysis indicated that the number, the positions and the type of substituents attached to the aromatic ring are critical for biological activity. The activities do not depend on the electronic effects of the substituents nor on the lypophilicities of the molecules.[14]



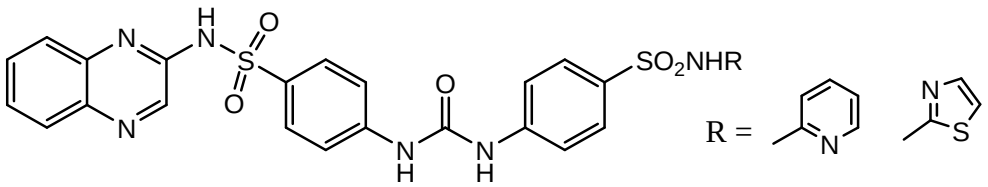
R = 2,3-OH, H; 2,3-Cl, OH,

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.[15]

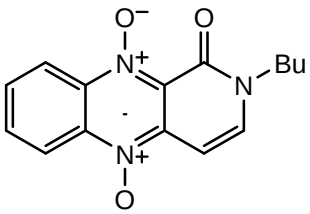


5a -$COCH_3$,
5b -$CH_2C_6H_5$,
5c -$CH_2N(CH_3)_2$,

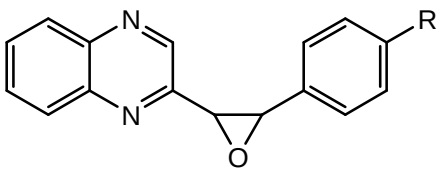
Novel thioureido sulfaquinoxaline derivatives were synthesized by MARWA G. EL-GAZZAR et al. All the newly synthesized compounds were evaluated for their *in vitro* anticancer activity against a human liver cell line (HEPG2) and showed higher activity than the reference drug doxorubicin.[16]



N-Butylpyridoquinoxaline 1,4-Dioxide (NBPQD) derivatives werte 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.[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.[18]

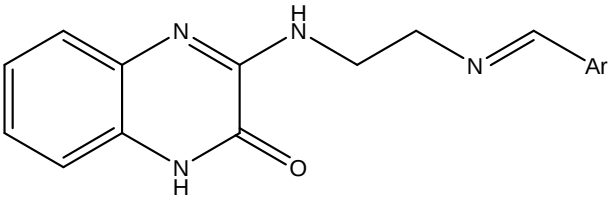


R = CN, NO_2

Anticonvulsant activity

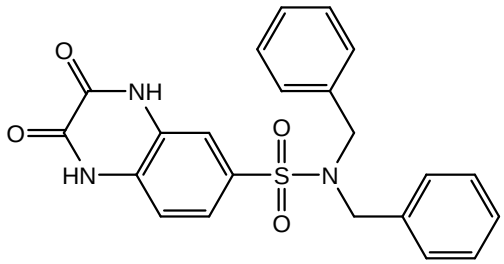
Ratnadeep V. Ghadage and Pramod J. Shirote synthesized the Schiff's bases of 3-{[2-({(E)-[(substituted) phenyl] methylidene} amino) ethyl] amino} quinoxalin-2(1H)-one and

evaluated for *in-vivo* anticonvulsant activity. This activity was carried out on pentylenetetrazole-induced seizure model.[19]

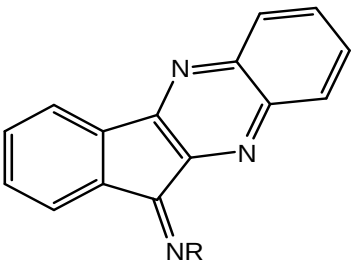


III a C_6H_5.CHO
III b 3 NO_2-C_6H_4.CHO
III c 2 NO_2-C_6H_4.CHO
III d 2 OH-C_6H_4 CHO
III e CH_3O-C_6H_4 CHO
III f C_6H_5-CH_2CH=CH CHO
III g 3 Cl - C_6H_4CHO
III h $(CH_3)_2N$-C_6H_4CHO
III i 3, 4 Cl- C_6H_3 CHO
III j 1 OH $C_{12}H_8CHO$

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]



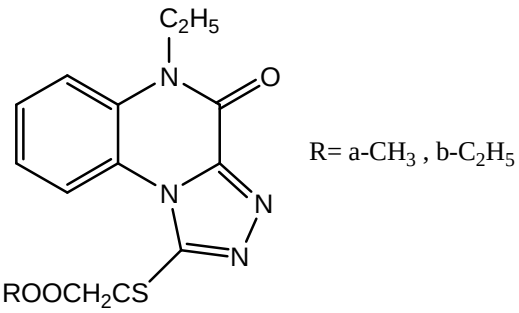
A series of novel indeno[1, 2-b]quinoxalin-11-ylidenamines 2-9 have been synthesized by A.Rajasekaran. Compounds 2-9 were screened for anti-nociceptive, anti-inflammatory and antiepileptic activity by AcOH induced writhing method, carrageenan induced paw edema method and maximal electroshock induced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



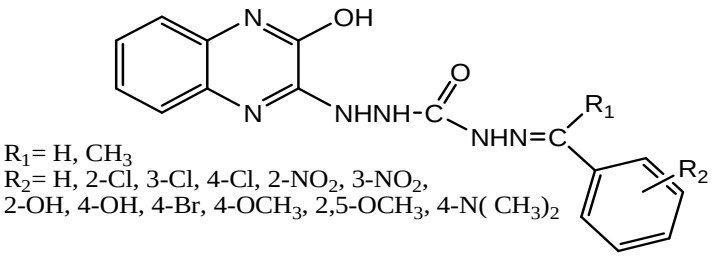
R = p-Benzene sulphonamine, phenyl, p-nitrophenyl, 4-hydroxyphenyl, N-Aniline, 2,4-Dinitroaniline,

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]

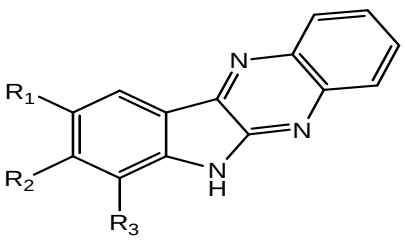


Various 1-(substituted benzylidene)-5-(3-hydroxyquinoxaline-2-yl) carbonohydrazide were synthesized by Sahu *et al*. All the newly synthesized compounds were screened for anticonvulsant activity. Some of the compounds showed significant anticonvulsant activity with no neurotoxicity.[23]



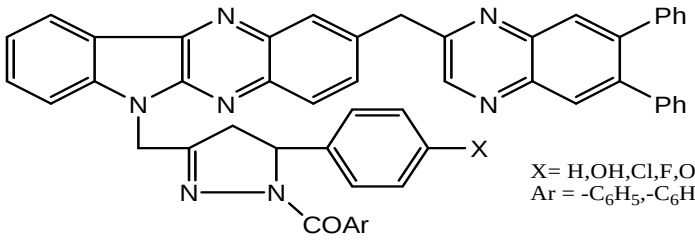
Antioxidant activity

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]



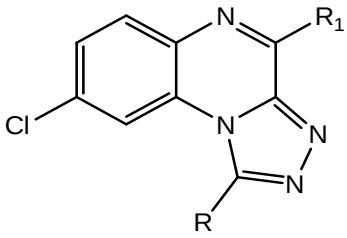
Indoloquinoxalin was fused with 2,3 diphenyl quinoxaline by a methylene bridge which was then allowed for acetylation. The acetylated product was made to react with different aromatic aldehydes to givechalcones. Chalcones refluxed with substituted acid hydrazides to

afford different indoloquinoxaline pyrazolines**.** All the synthesized compounds were screened for their antioxidant, anti-inflammatory and antihistamic activities.[25]



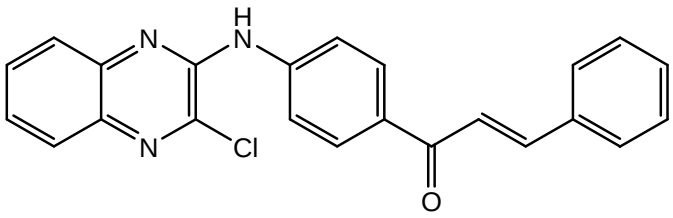
X= H,OH,Cl,F,OCH_3
Ar = -C_6H_5,-C_6H_4OH,-C_6H_4Cl

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]



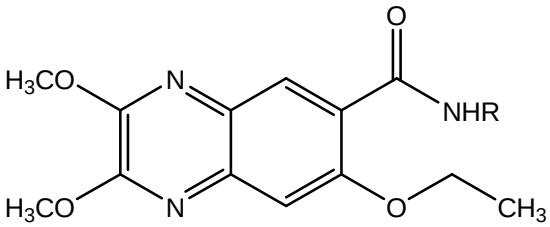
R = Phenyl, 4-flurophenyl, 2-furyl, 4-chlorophenyl, 2-thionyl
R_1 = Cl, SCH_2COOH, OCH_3, SCH_2COOH, OCH_3

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]



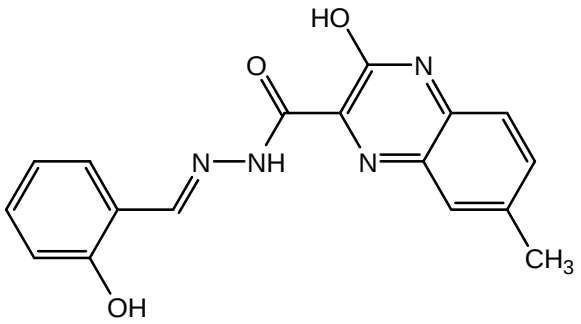
Antibacterial activity

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]

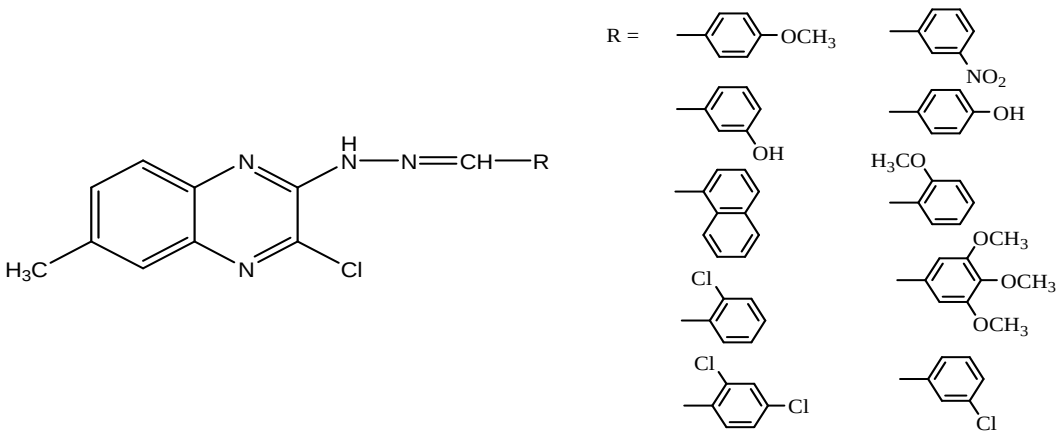


R= 5a. 3F-phenyl, 5b. 3Cl, 4-F-phenyl, 5c. 2,4,6-trimethylphenyl
5d. 3-F, 5-Me-phenyl, 5e. 3,4,6-trimethoxyphenyl, 5f. 4F-benzyl,
5g. 2-Iodo-3CF3-phenyl, 5h. 4-methoxybenzyl, 5i. 4-F, 3-Me-phenyl,
5j. 2-methoxyphenethyl, 5k. 2-Hydroxyethyl, 5l. cyclomethyl hexyl,
5m. morpholine, 5n. N-methyl piperazine, 5o. Ethynyl aniline, 5p. Pyrrolidine

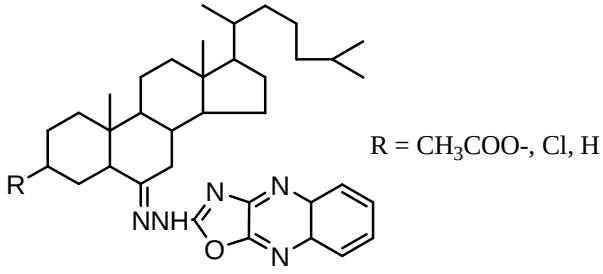
A series of substituted Hydrazone and Quinoxaline derivatives have been synthesized by Arvind Kumar et al. All the compounds have been screened for their antibacterial activity against *staphylococcus aureus* and *Escherichia coli*. Some of these compounds have been screened for anti-inflammatory activity 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]

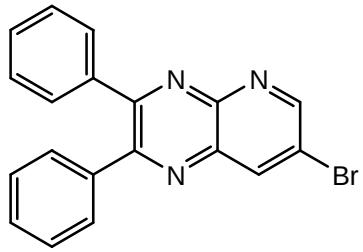


Steroidal [oxazolo(4,5-b)quinoxaline-2-yl-hydrazone] derivatives were prepared by Salman Ahmad Khan. The antibacterial activity of these compounds was evaluated by the disk diffusion assay against two Gram-positive and two Gram-negative bacteria and then the minimum inhibitory concentration (MIC) of compounds was determined.[31]

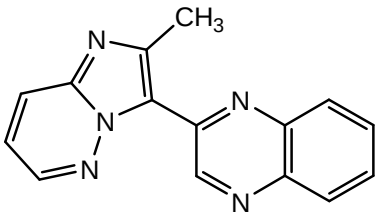


Antimicrobial

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.[32]

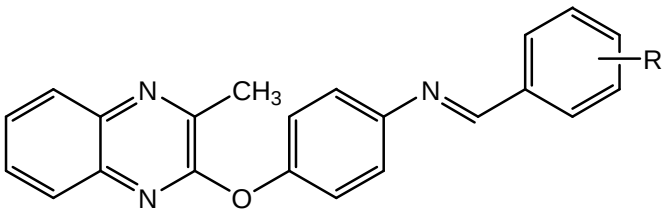


The quinoxaline derivatives were synthesized by the M.C. Somasekhara Reddy et al. As the results of antibacterial screening tests done by paper disc method, quinoxaline derivatives revealed significant inhibition zone on Bacillus *spericus* and quinoxaline derivatives on Escherichia *coli* cultures.[33]



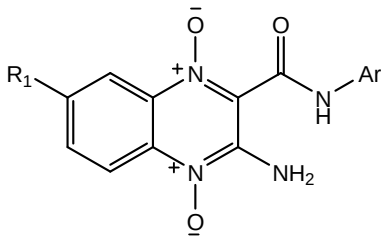
4-(2-methylquinoxalin-3-yloxy)-*N*-substituted benzylidine benzamines derivatives were synthesized by Dharmchand Prasad Singh et al. All the synthesized compounds were tested

in-vitro for their antifungal activity against microorganisms such as *Aspergillus niger* and *Candida albicans.*[34]



R= 4-OH; 2-NO_2 ;4-$N(CH_3)_2$; 2-OH,3-OCH_3 ; 2-OCH_3 , 3-OCH_3 ,4OCH_3

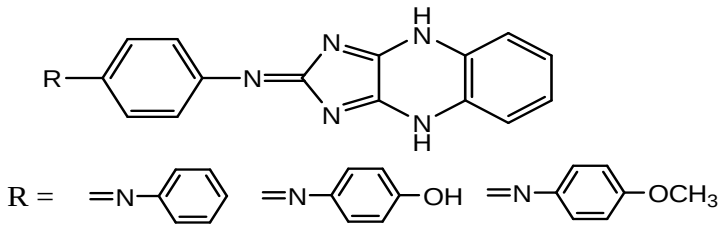
A new series of quinoxaline 1,4-di-N-oxides were synthesized and evaluated for their antibacterial and antifungal activities by Dalia Hussein Soliman. The best result was demonstrated by 3-amino-N-(4-methoxyphenyl)-2-quinoxalinecarboxamide 1,4-di-N-oxide, MIC (0.24 µg/ml) against *Aspergillus fumigatus*,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



a; R_1 = H, Ar = Ph
b, R_1 = H, Ar = Benzyl
c, R_1 = H, Ar = 4-Cl-Ph
d, R_1 = H, Ar = 4-F-Ph
e, R_1 = H, Ar = 4-OCH_3-Ph
f, R_1 = H, Ar = 4-OC_2H_5-Ph
g, R_1 = H, Ar = 4-Pyridine

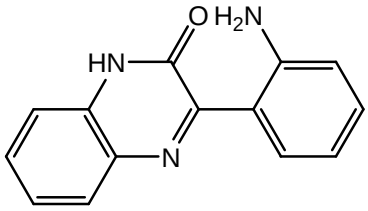
h, R_1 = Cl, Ar = Ph
i; R_1 = Cl, Ar =Benzyl
j, R_1 = Cl, Ar = 4-Cl-Ph
k, R_1 =Cl, Ar = 4-F-Ph
l, R_1 = Cl, Ar = 4-OCH_3-Ph
m, R_1 =Cl, Ar = 4-OC_2H_5-Ph
n, R_1 =Cl, Ar = 4-Pyridine

A series of *N*-(4*H*-imidazo[4,5-b]quinoxalin-2(9*H*)-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.[36]

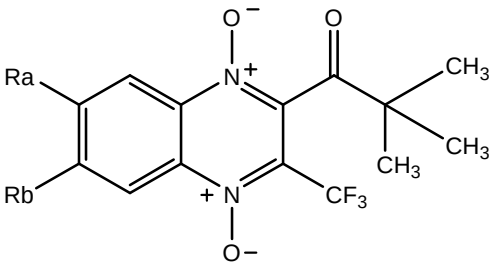


Miscellaneous

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.[37]

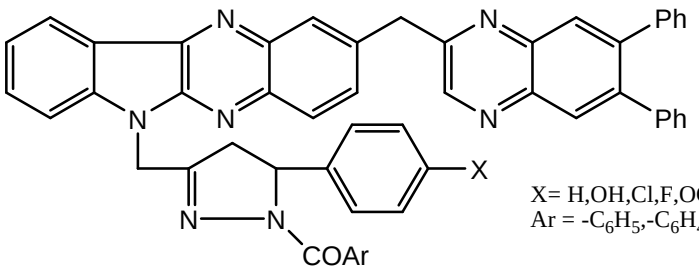


The *in-vitro* antiplasmodial activity of some 3-trifluoromethyl-2-carbonylquinoxaline di-N-oxide derivatives is reported by B. Zarranz et al. The evaluation was performed on cultures of FcB1 strain (chloroquine-resistant) of *P. falciparum* and the most interesting compounds were then evaluated on MCF7 tumor cells in order to evaluate an index of selectivity.[38]



a: Ra = CH_3 Rb = CH_3
b: Ra =H; Rb = CH_3
c: Ra =H; Rb = H
d: Ra =H; Rb = OCH_3
e: Ra =Cl; Rb = Cl
f: Ra =H; Rb = Cl
g: Ra =F; Rb = F

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]



X= H,OH,Cl,F,OCH_3
Ar = -C_6H_5,-C_6H_4OH,-C_6H_4Cl

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

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