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Review Article

Biological Activity of Quinoxaline Derivatives

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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.

Key Words: Quinoxaline, 1, 4-di-N-Oxide, Antibacterial, Anticancerous, Antineoplastic

INTRODUCTION

The heterocycles are those cyclic organic compounds in which N, O or S elements replaced one or more of the ring carbon atoms. The sulphur and nitrogen atoms are important components of functional materials since heteroatoms present in their rings stabilize ion radical species and extended π-conjugation facilitate in decreasing columbic repulsion..Quinoxaline is one of the benzo-fused six-membered heterocycles shown in figure 1.[1]

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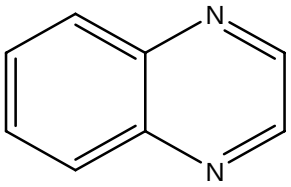


Fig. 1:Quinoxaline

Quinoxaline shown below in figure 1 is a white crystalline powder having a molecular weight of 130.1466400 and its molecular formula is $C_8H_6N_2$.

The 2,3,7,8-tetrakis(2-pyridyl)pyrazino [2,3-*g*] quinoxaline **(a and b)** are monoclinic and both **a and b** are very similar with respect to each other except difference in stacking pattern in crystal lattice. Both form the one dimensional zigzag chain structure shown in figure 2.[2]

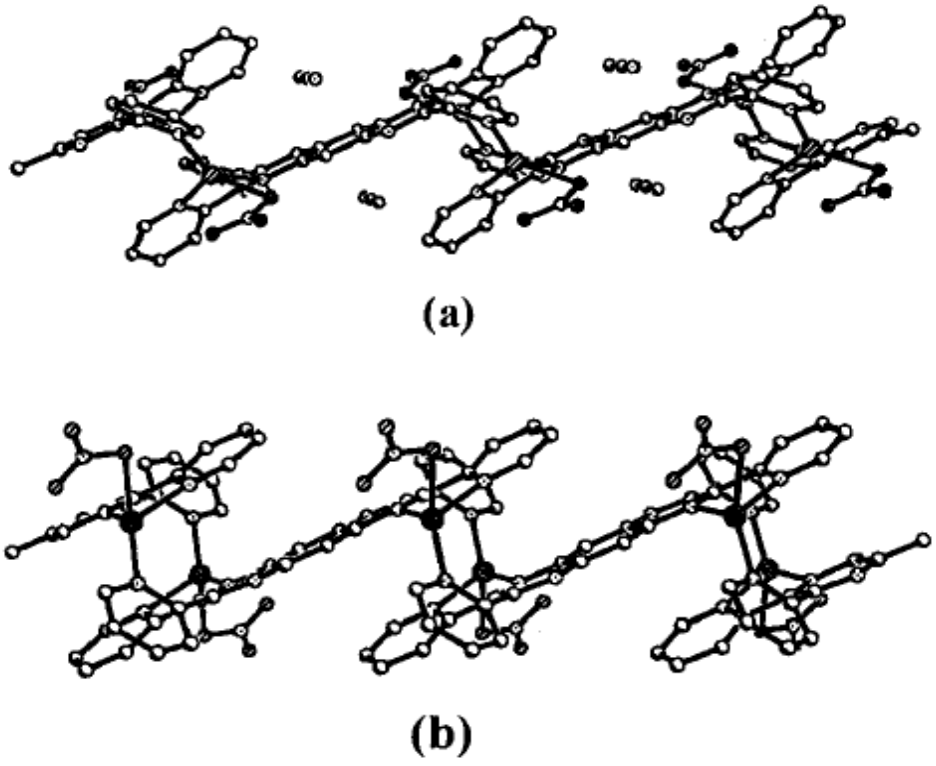


Fig.2: One dimensional zigzag chain structures of 2,3,7,8-tetrakis(pyridyl)pyrazino[2,3-*g*] quinoxaline(a and b) (ORTEP representation)

Quinoxaline is a important part of antibiotic echinomycin.[3] Quinoxaline hold up as a core unit in number of biologically active compounds includes anticancer, antibacterial, antiviral, and anti-inflammatory, anti HIV activity .[4]

Quinoxaline displays a wide spectrum of potential pharmacological activities for examples, imidazo quinoxalines ribonucleosides as antiviral.[5]Pyrazoloquinoxaline showed a relatively high antibacterial activity[6] and also quinoxaline-1,4-di-N-oxides are used for the treatment of

bacterial disease.[7] Also some 6(7)-substituted-3-methyl-2-phenylthio-quinoxaline-1,4-di-N-oxides display good antituberculosis activity.[8]

Quinoxaline derivatives such as pyrazoloquinoxaline used as a antifungal agents.[9] The importance of quinoxalines as pharmaceutical agents was recognised by the Brimonidins. The drug acts through reducing the intraocular pressure, thus alleviates the symptoms of glaucoma.[10] Recently, a new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline 1,4-di-N-oxide derivatives have been recognized and evaluated for in vitro antitumor activity against a 3-cell line panel (breast, lung, CNS).[11]

Our aim in this review is to focus on quinoxaline structure and to analyze how slight modification in quinoxaline nucleus can act as a precursor for assembly of large number of quinoxaline derivatives and providing a tremendous number of pharmacologically active molecules having a wide variety of biological activity and also their therapeutic applications and to highlight the importance of quinoxaline moiety as a novel drug template for the discovery of new agents in various areas of medicines.

BIOLOGICAL ACTIVITY OF QUINOXALINE

A) Antibacterial activity

1) Most of the quinoxaline-1,4-di-N-oxide derivatives have been identified as antibacterial agents. Thus, 2- hydroxy methyl 3- methyl quinoxaline 1, 4-di-N-oxide (R=CH_2OH) and a metabolite of 2, 3- dimethyl quinoxaline-1, 4- di-N-oxide **(**R=CH_3**)** are found extremely active against Gram negative bacteria as shown in figure 3.[7]

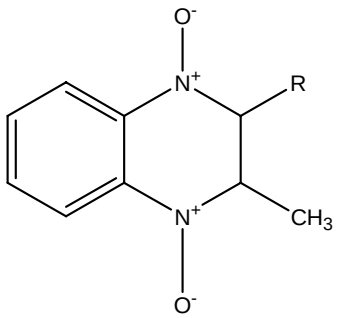


Fig.3: 2- hydroxy methyl 3- methyl quinoxaline 1, 4-di-N-oxide (R=CH_2OH)

Or

2, 3- dimethyl quinoxaline-1, 4- di-N-oxide (R=CH_3)

2) Carbadox, a quinoxaline -1, 4-dioxide, is widely used in research field as an antibacterial agent shown in figure 4. [12]

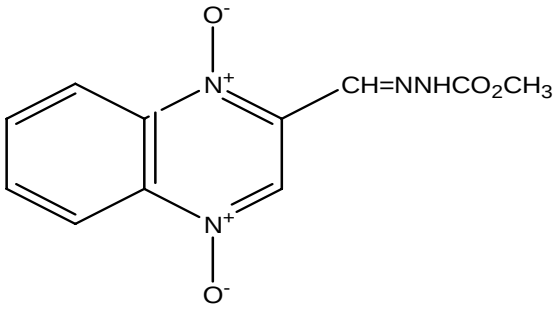
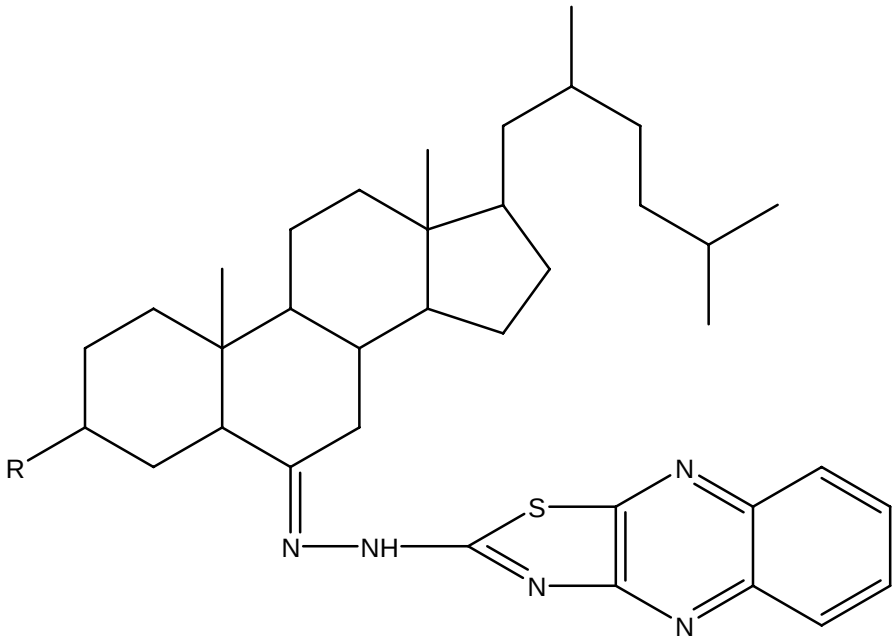


Fig.4: Carbadox

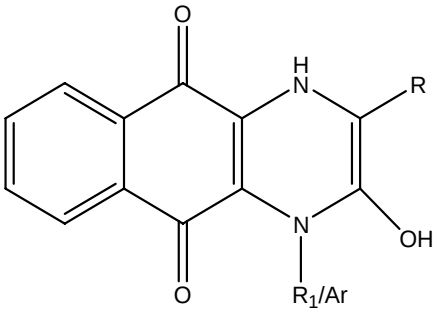
3) The derivatives of different steroidal thaizolo quinoxaline have been synthesized antibacterial agents against E.coli shown in figure 5. By In vitro study it is observed that the compound (b) containing chloro group at 3ß position shows highest activity with respect to compound (a) and (c). [13]



R=(a)CH3COO(b)Cl(c)H

Fig. 5- Thiazolo(4,5-b)quinoxaline-2-yl-hydrazone

4) Vishnu et al synthesized a series of 1, 2, 3-trisubstituted-1, 4-dihydrobenzo quinoxaline-5, 10-diones showed in vitro antibacterial activity against Klebs. Pneumoniae and E. coli as shown in figure. [14]



R=H
R_1=4-OH-C_6H_4.$C(CH_3)_3$

Fig. 6: 1, 2, 3-trisubstituted-1, 4-dihydrobenzo[g] quinoxaline-5, 10-diones

B) Antifungal

Kurasawa et al prepared a series of pyrazoloquinoxalines which were observed to be active against fungal infections shown in figure 7.

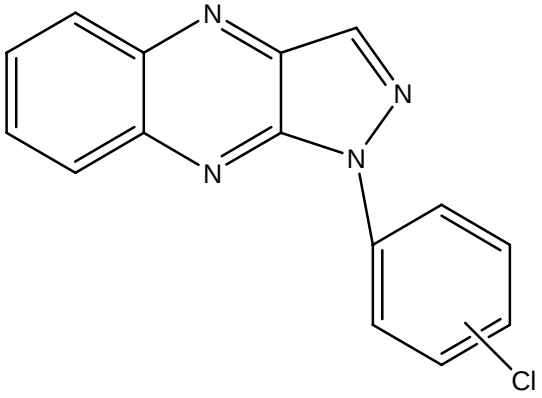
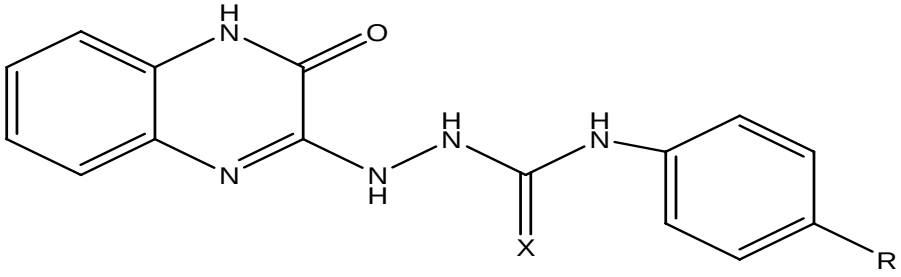


Fig.7: Pyrazoloquinoxaline

C) Hypoglycemic activity

(N-arylcarbamoyl and N- aryl thiocarbamoyl) hydrazinequinoxalin – 2 (1H) have been informed as mild hypoglycaemic agents shown in figure 8. [15]



R=H,F
X=O,S

Fig. 8: (N-arylcarbamoyl and N- aryl thiocarbamoyl) hydrazinequinoxalin – 2 (1H)

D) Antiglaucoma activity

Brimonidin (Alphagan) is a drug used to treat glaucoma.It demonstrating the importance of quinoxaline as Pharmaceutical-agent which reduces the intraocular pressure, thus mitigate the symptoms of glaucoma shown in figure 9. [10]

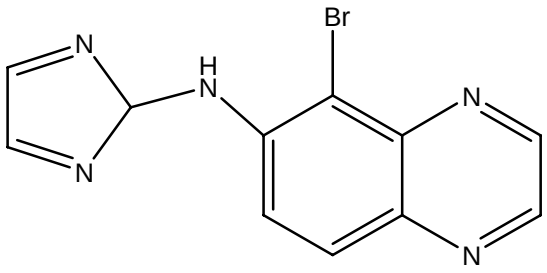
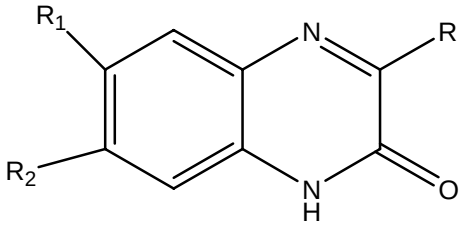


Fig. 9: Brimonidin[5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxalinamine]

E) Anticancerous activity

1) Paoloe et al. (1999) synthesized a new series ofquinoxalinones 6/7-trifluoromethyl or nitro & 6,7-difluoro substitutent having different side-chains (alkyl,halogenoalkyl, benzyl and phenyl groups) at C-3 of the ring system and screened for different biological activities in-vitro.Some of these compound was found to be active against different strains of candida & some of them shows interesting anticancer activity as shown in figure 10. [16]



R=$CH_2CH_2CH_3$,$CH(CH_3)_2$,CH_2Ph,Ph,CH_2Br,CF_3

R_1/R_2=F,CF_3,NO_2

Fig. 10: Quinoxalinones 6:7-trifluoromethyl or nitro- and 6,7-difluoro substituted

2) Antonio et al. (2001) synthesized a series of pyrido [2,3-g] quinoxalines and found that compound has encouraging anticancer activity during in vitro evaluation for anticancer testing shown in figure 11. [17]

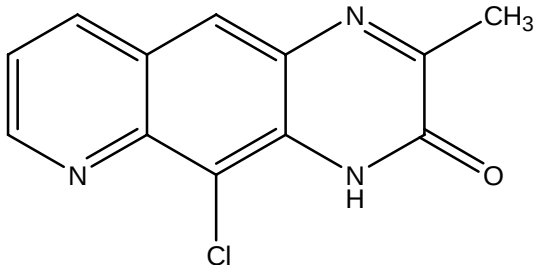


Fig.11: Pyrido [2,3-g] quinoxalines

3) Fedora et al. (2007) synthesized derivatives of quinoxaline in panel of cancer cell lines, a breast cancer cell and three colon cancer cells and found that compound **(a)** was moderately active against colon cancer lines, while compound **(b)** was highly active in all cells shown in figure 12. [18]

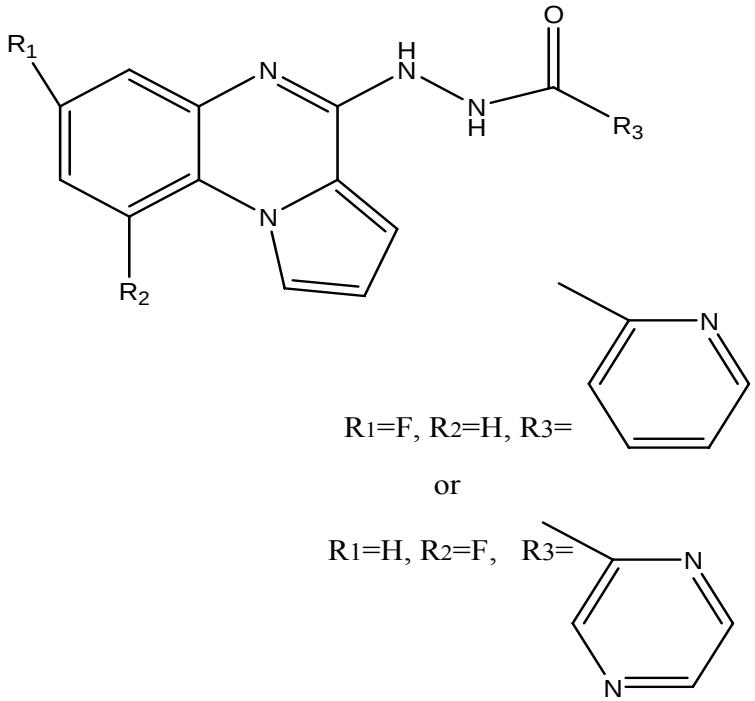
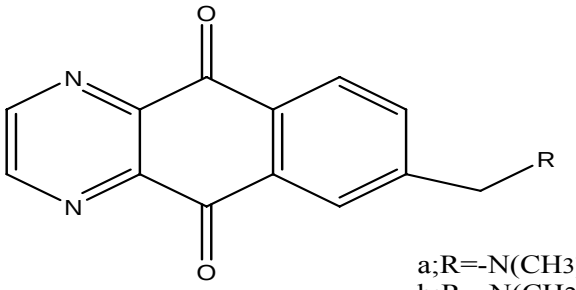


Fig.12: Pyridine-2-carboxylic acid N-(7-fluoro-pyrrolo[1,2-a]quinoxalin-4-yl)hydrazide

4) The in vitro cytotoxic activities of the newly synthesized 7-dialkylaminomethylbenzo[g]quinoxaline - 5,10 – dione derivatives was evaluated against panel of human cancer cell lines. These are ovarian carcinoma, colon cancer, breast cancer. The concentrations of benzo[g]quinoxaline-5, 10-dione derivatives inhibiting cellular growth by 50%, IC_{50} values shown in figure 13. [19]



a;R=-N(CH_3)2
b;R=-N(CH_2CH_2OH)2
c;R=-N(CH_2CH_2)2
d;R=-N(CH_2CH_2)2CH_2
e;R=-N(CH_2CH_2)2O

Fig. 13: 7-Dialkylaminomethylbenzo[g]quinoxaline - 5, 10 – dione derivatives

F) Antiviral activity

2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo-[2,3-b]quinoxaline shows highest activity against the herpes virus shown in figure 14. Those derivatives having 6-(2-dimethylaminoethyl) side chain shows improved biological activity due to DNA binding properties of these compounds.[20]

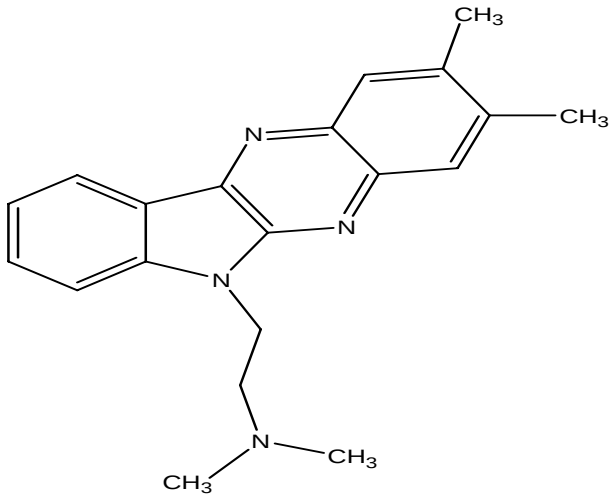


Fig.14: 2,3-dimethyl-6(2-dimethylaminoethyl)6*H*-indolo[2,3-*b*]quinoxaline

G) Cytotoxic with antitumor activity

Antonio et al synthesized some substituted quinoxaline 1, 4-di-N-oxides and tested for tumour inhibiting activity and the compound 15 was found highly active as a cytotoxic agent with highest Hypoxic cytotoxicity ratio of 340 as in comparison with other derivatives shown in figure 15. [21]

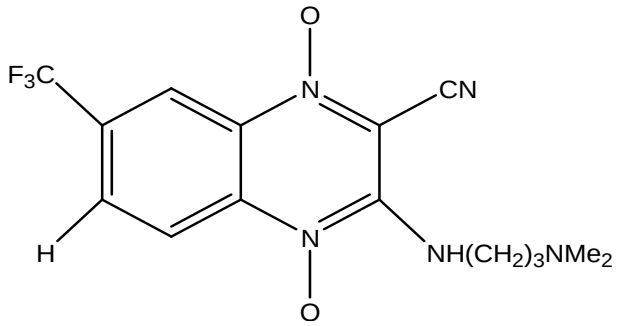


Fig. 15: 3-[[(N-Dialkylamino)alkyl]amino]-2-quinoxalinecarbonitrile Quinoxaline 1, 4-di-N-oxides

H) Antineoplastic activity

Yoo et al synthesized 2, 3-bis (bromomethyl)-5, 10-benzo[g]quinoxalinedione(tricyclic quinone) derivative showing remarkable cytotoxic effect against different Sarcoma type shown in figure 16. [22]

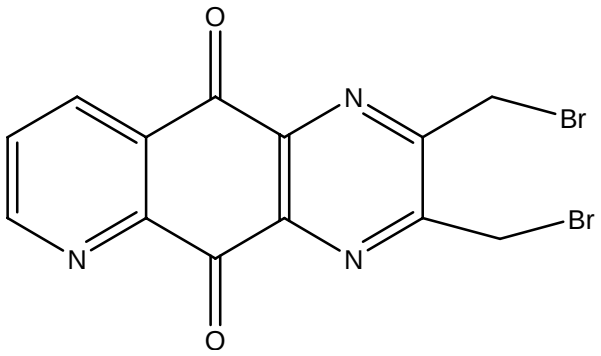


Fig.16:2,3-bis(bromomethyl)-5,10-benzo[g]quinoxalinedione

I) Antimicrobial activity

Hanan et al synthesized a 2-[4-Arylidene hydrazinocarbonyl)aniline]-3-methyl quinoxalines and screened for their biological activity *in vitro.*These compound exhibiting a broad spectrum of antimicrobial activity, having a moderate activity against C. Albicans and little activity against Gram positive and Gram negative bacteria as shown in figure 17. [23]

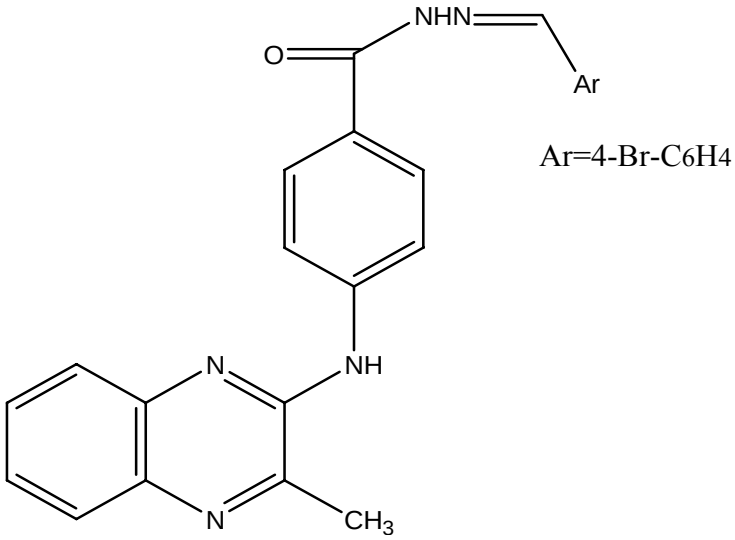


Fig.17: 2-[4-Arylidene hydrazinocarbonyl)aniline]-3-methyl quinoxaline

J) Antiproliferative activity

Chung et al synthesized a series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8 diones and screened for their inhibitory activity on aortic smooth muscle cell of rat and the quinoxaline-5,8-diones was found as an potent antiproliferative agent. The compound 18 showing

a highest IC_{50} values of 5.5 among the all 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8 diones shown in figure 18. [24]

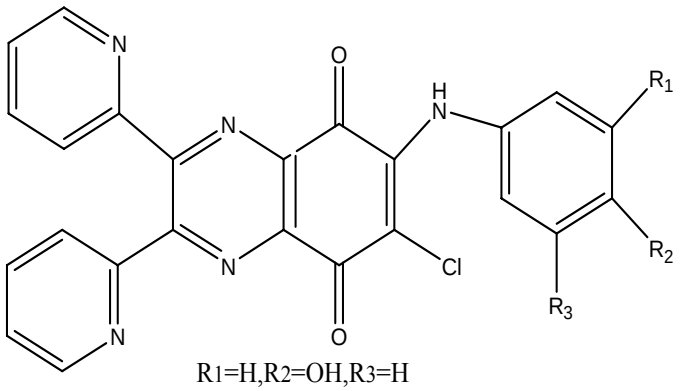


Fig.18: 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8 diones

K) Antiameobic activity

In an effort to develop potent antiamoebic agents, synthesis of 2-(5-substituted-3-phenyl-2-pyrazolinyl)-1, 3-thiazolino[5,4-b] quinoxaline derivatives and tested for their in vitro antiamoebic activity against strain of E. histolytica. Encouraging antiamoebic was observed in case of quinoxaline derivatives as shown in figure 19. [25]

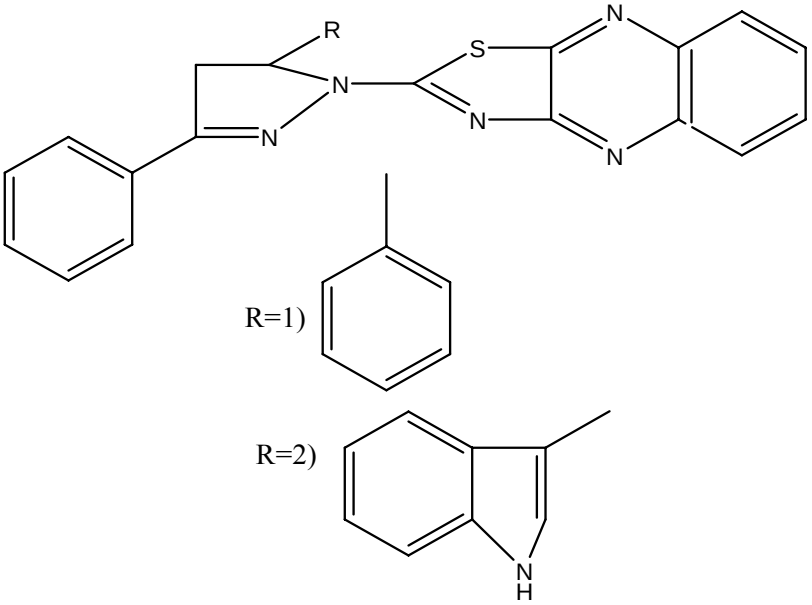
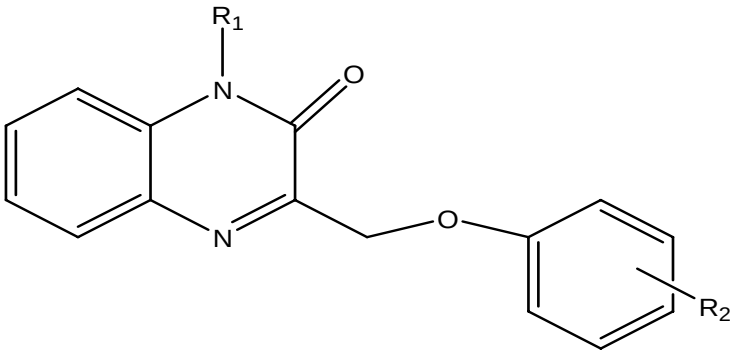


Fig.19: 2-(5-substitued-3-phenyl-2-pyrazolinyl)-1,3-thiazolino[5,4-b]quinoxaline derivatives

L) Antitumor activity

The new series of Phenoxymethylquinoxalines have been synthesized and they all show moderate antitumour activity where the compound (b) in a) and b) shows most encouraging antitumour activity against MCF-7 cells.The Phenoxymethyl –quinoxalines chosen because of availability of substitution at several sites are possible as shown in figure 20.



a)R1=CH3 and R2=H
or
b) R1=Benzyl and R2=2-C(O)NH-Phenyl

Fig.20:Phenoxymethylquinoxalinones

CONCLUSION

In conclusion a wide variety of biological activity of quinoxaline has been described. Quinoxaline moiety containing 1,4-di-N oxide shows broad spectrum of activity against wide number of bacterial species and also exhibited cytotoxic activity. Those drugs containing quinoxaline moiety are carbadox and Brimonidin. Carbadox**,** a well known synthetic antibacterial agent used for treatment of various bacterial diseases & Brimonidins showed the importance of quinoxalines as a pharmaceutical agent as it palliates the symptoms of glaucoma through reducing intraocular pressure. Quinoxalines act as a core unit in number of biologically active compounds and used as a pharmaceutically important moiety in treatment of wide variety of diseases.

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