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SUBSTITUTED QUINOXALINES POTENTIAL TO TARGET CYTOTOXIC ACTIVITY: A STATE OF REVIEW

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ABSTRACT

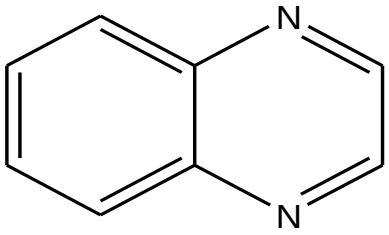
Quinoxalines are becoming the attractive target of deeper research due to its inherent diverse properties. Literature study gives an idea about various synthetically derived Quinoxalines which constitute a rising biomedical class of low-molecular weight heterocyclic compounds with potential functions as antitumour, anti-inflammatory, antibacterial, antiviral, antifungal, antiparasitic and antidiabetic agents. In the present review, we are discussing about the cytotoxic potential of Quinoxaline derivatives discovered to date, thus providing a first reference index for researchers to identify the potential targets of their Quinoxalines derived collections, which could facilitate the development of new Quinoxaline based therapies.

Keywords: Quinoxaline; anticancer; Antibacterial, Antidiabetic agents.

INTRODUCTION

The current review mainly concern with the cytotoxic potential of Quinoxaline derivatives. Quinoxaline is commonly called as benzopyrazine. Quinoxaline and its derivatives are mostly of synthetic origin.The fusion of one or two benzene rings in Quinoxaline and phenazine increases the number of resonance structure. It posses the dipole moment of zero. Considering these properties, various research workers have shown a keen interest in this small heterocyclic moiety as the target structure for evaluation of many pharmacological activities including anticancer activity.[1]
Nitrogen containing heterocyclic compounds is indispensable structural units for both the chemists and biochemists. Among the various classes of benzene fused six-membered nitrogen containing heterocyclic compounds, Quinoxaline derivatives form an important class of pharmacologically active compounds.2 The chemical structure is as shown below

Numerous Quinoxaline derivatives have important biological activity such as antibacterial[3], anticancer [4], anti-inflammatory agents [5], antimycobial and anticandida [6],cytotoxic [7], Antioxidant [8], Anticonvulsant [9], antiviral, SR protein-specific kinase-1 inhibitor activity. [10]



2. Cytotoxic activity

1. D. M. Asif Husain *et al* in 2001 performed studies on Quinoxaline nuclei exhibiting potential anticancer activity. A new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1,4-di-N-oxide derivatives were synthesized and evaluated for in vitro antitumor activity against a 3-cell line panel (MCF7 (breast), NCIH 460 (lung) and SF-268 (CNS) and then evaluated in full panel of 60 human tumor cell lines, derived from nine cancer cell types. Among these compounds 13 c, 14 e, 13g and 14 g were found to be more active.[11]

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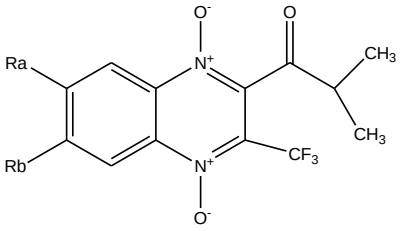
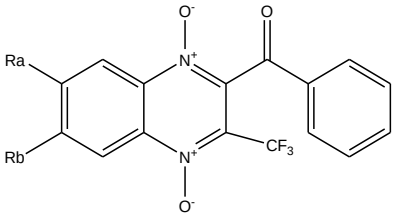
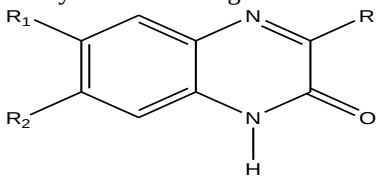


13 (a-g)



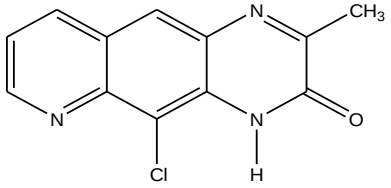
14 (a-g)

2. Paoloe *et al* in 1999 synthesized a new series of quinoxalinones 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 the different biological activities in vitro. Some of these compounds were found to be active against different strains of Candida & some of them shows interesting anticancer activity as shown in figure.[12]

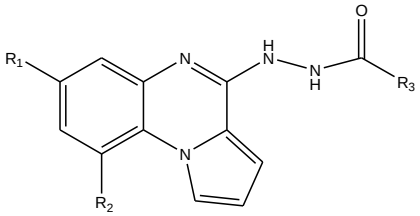


R= $CH_2CH_2CH_3$, CH $(CH3)_2$, CH_2Ph, Ph, CH_2Br, CF_3
R1/R2= F, CF_3, NO_2.

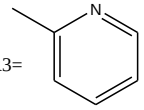
3. Antonio *et al* in 2001 synthesized a series of pyrido [2,3-g] quinoxalines and found that compound has encouraging anticancer activity during in vitro evaluation of anticancer testing shown in figure. [13]



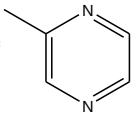
4. Fedora *et al* in 2007 synthesized derivatives of quinoxaline in panel of cancer cell lines, a breast cancer cell and three colon cancer cells and found that compound (a) was moderately active against colon cancer lines, while compound (b) was highly active in all cells show in figure.[14]



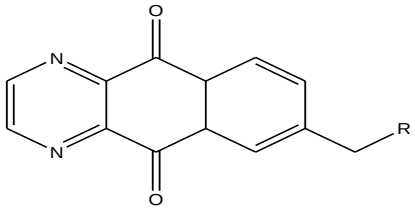
(a) R1=F.R2=H,R3=



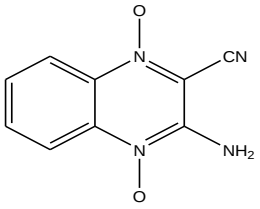
(b) R1=F,R2=H,R3=



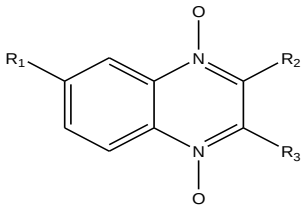
5. Lee Heesoon *et al* in 2004 studied the in vitro cytotoxic activities of the newly synthesized was 7-dialkylaminomethylbenzo[g]quinoxaline - 5,10 – dione derivatives were evaluated against panel of human cancer cell lines. These are ovarian carcinoma, colon cancer, breast cancer.The concentrations of benzo[g]quinoxaline-5, 10-dione derivatives inhibiting cellular growth by 50%, IC50 values shown in figure.[15]



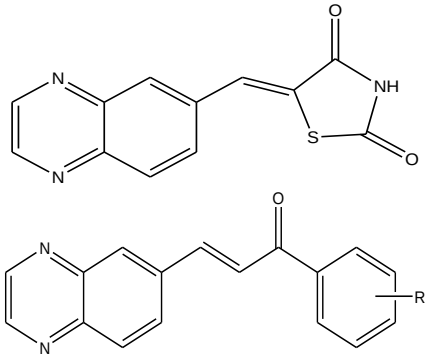
6. Kamelia M. Amin *et al* in 2006 synthesized new series of Quinoxaline 1,4-di-*N*-oxides and fused quinoxaline di-*N*-oxides were synthesized and evaluated for hypoxic–cytotoxic activity on EAC cell line. Compound was the most potent cytotoxin IC50 0.9 µg/ml, potency 75 µg/m, and was approximately 15 times more selective cytotoxin than 3-aminoquinoxaline-2- carbonitrile which has been used as a standard. Compounds and were more selective than the standard. In addition, antitumor activity against Hepg2 (liver) and U251 (brain) human cell lines was evaluated, compounds and were the most active against Hepg2 with IC50values 1.9 and 2.9 µg/ml, respectively, however, all the tested compounds were nontoxic against U251 cell line.[16]



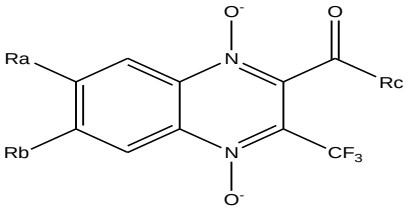
(a).3-Amino,2-quinoxalinecarbonitrile,1-4-Di-N-Oxide



7. Tania R. Mielcke *et al* in 2012 synthesized Chalcones derived from quinoxaline-6-carbaldehyde, structurally based on the selective PI3Kγ inhibitor AS605240, were assayed in glioma cell lines from human and rat origin, and compound presented the best activity.[17]

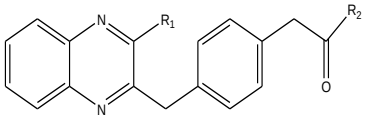


8. Belen Zarranz *et al* 2004 synthesis new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide derivatives have been synthesized and evaluated for in vitro antitumor activity against a 3-cell line panel, consisting of MCF7 (breast), NCIH460 (lung), and SF-268 (CNS). These active compounds were then evaluated in the full panel of 60 human tumor cell lines derived from nine cancer cell types. The results have shown that, in general, anticancer activity depends on the substituent's in the carbonyl group, improving in the order: ethyl - isopropyl -tert-butyl - phenyl-ones show in figure.[18]

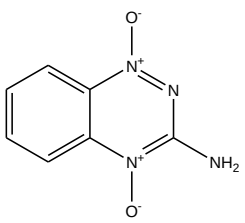


Ra=Rb,c=H,e=Ct,g=F
Rc,4-ipropyl,5=I butyl,6=ph

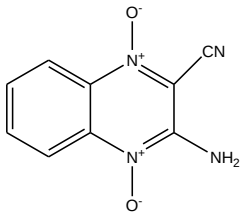
9. Sandra Piras *et al* in 2002 synthesized a new series of 4-(3-substituted-2-quinoxalylamino) phenylacetates and 4-(3-substituted-2-quinoxalylamino) phenylacetyl-L-glutamates, eightwere selected at NCI for evaluation of their in vitro anticancer activity. The results obtained in comparison with the corresponding nor-compounds series seem to indicate that this type of homologation is shown in figure.[19]



10. Magda M.F. Ismail *et al* in 2010 synthesized, A new series of quinoxaline 1,4-di-*N*-oxides were synthesized and evaluated for antitumor and hypoxic-selective cytotoxic activities. Antitumor activity against liver carcinoma and brain tumor human cell lines were evaluated, among the tested compounds, and exhibited potential cytotoxic effect against Hepg with IC50 values of 0.77 and 0.50 µg/ml, respectively, whereas, all the tested compounds lack antitumor activity against U251 human cell line. Moreover, the compound was the most potent hypoxia selective cytotoxin on EAC cell line; IC50 2.5 µg/ml, potency 22 µg/ml, and was approximately 5.4-times more selective cytotoxin than 3-amino-2-quinoxalinecarbonitrile1, 4-dioxide Compounds and were more selective than the standard show in figure .[20]



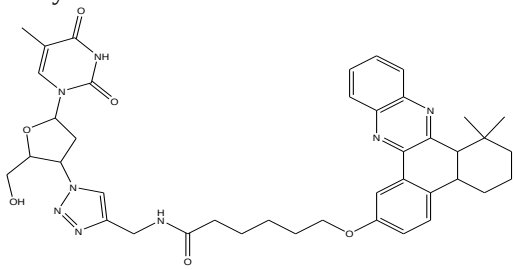
Tirapazamine-A



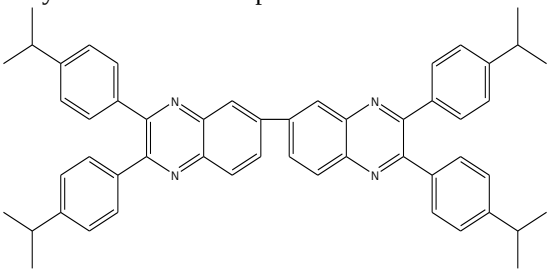
B

11. Paola Corona, *et al* in 2000 synthesized a new series of twentyeight 3-carboxy or carbethoxy quinoxalines bearing a substituted benzylamino or *N*-[4-(aminomethyl) benzoyl]glutamate group on position 2 of the ring and various substituents at C-6, 7 positions, were selected by the National Cancer Institute for evaluation of their in vitro anticancer activity. The results obtained seem to confirm that the carboxy or carbethoxy group at position 3 is not helpful, with a few exceptions, for the anticancer activity. [21]
12. Qiong Wei *et al* in 2015 performed a study of Anticancer activity of a thymidine quinoxaline conjugate is modulated by cytosolic thymidine pathways. We found that the thymidine conjugate had varied activities in liver cancer cells with different levels of TK1 and TYMP. TK1 was responsible for

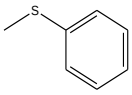
the anticancer activity of dT-QX while levels of TYMP counteracted such an activity. The counteraction by TYMP could be overcome with RNA silencing to significantly enhance the dT-QX selectivity in cancer cells.[22]



13. Ilhan Islkdag *et al* in 2011 conducted a study on the synthesis and anticancer activity of some bisquinoxaline derivatives. 2', 3'-tetrasubstituted-[6,6']-bisquinoxaline derivatives (3a-l) were synthesized by reacting appropriately 1,2-dione derivatives (2a-21) with 3,3'-diaminobenzidine. Anticancer activity screening of the compounds 3a-31 against HT-29 and MCF-7 cell lines was performed. The compound 3e showed poor DNA synthesis inhibition on HT-29 cell line. However, the inhibitory effect of this compound on DNA synthesis of MCF-7 cells is very remarkable. Besides, the DNA synthesis inhibitory effect of the compound 3l was very attractive against MCF-7 cell line.The DNA synthesis inhibition activity of the compounds 3e and 3f were very close to that of cisplatin.[23]



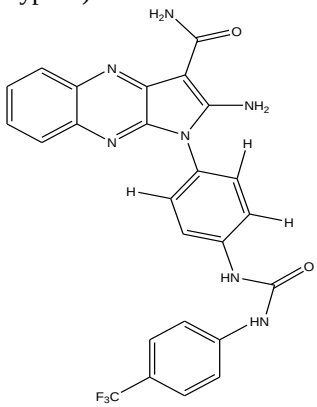
3e



3l

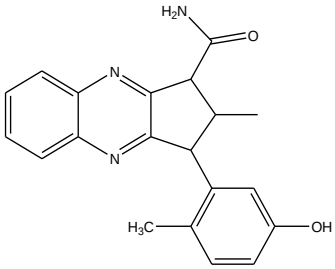
3f

14. Andrea unzue *et al* in 2014 carried out a study on pyrrolo[3,2-*b*]quinoxaline derivatives as types $i_{1/2}$ and ii eph tyrosine kinase inhibitors: structure-based design, synthesis, and *in vivo* validation. The X-ray crystal structures of the EphA3 kinase in complex with two high-nanomolar inhibitors based on the 2-amino-1- phenyl-pyrrolo[3,2-b]quinoxaline-3 carboxamide scaffold confirmed the type I binding mode obtained previously by automatic docking (Figure 1). This structural information was used to design type I1/2 and type II derivatives by taking advantage of the existing knowledge on privileged chemical motifs, i.e., hydroxyl group in meta position of the phenyl ring (for type I1/2) and hydrophobic moieties connected to the phenyl ring by amide or urea linkers (on type II).[24]

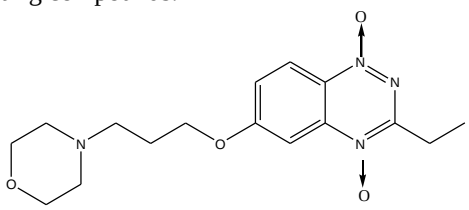


7m

15. Andrea Unzue *et al* in 2016 performed a review on Three stories on Eph kinase inhibitors: From in silico discovery to in vivo validation, in which compound qui B4 was found to be having strong cytotoxic activity.[25]

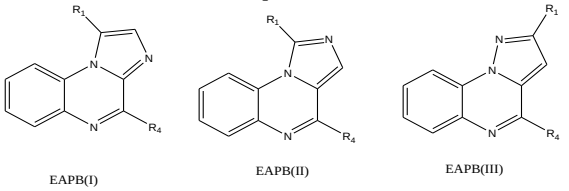


16. Guyue Cheng *et al* in 2016 performed study on Quinoxaline 1,4-di-*N*-Oxides: Biological Activities and Mechanisms of Actions Quinoxaline 1,4-di-*N*-oxides (QdNOs) h arouse widespread interest, the evaluation of their medicinal chemistry is still in progress. The structure-activity relationship and the mode of actions of each type of activity of QdNOs are summarized, and the toxicity and the underlying mechanisms are also discussed, providing insight for the future research and development of these fascinating compounds.[26]



17. Moarbess G *et al* were assessed In vitro cytotoxicity studies against melanoma (A375, M4Be, and RPMI-7591), colon (LS174T), breast (MCF7), and lymphoma (Raji) human cancer cell lines. In vivo studies were carried out in M4Be xenografted athymic

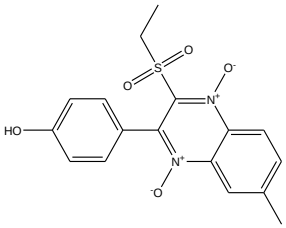
mice. EAPB (I), EAPB (II), EAPB (III), showed significant in vitro activities against A375 compared to fotemustine and imiquimod used as references.[27]



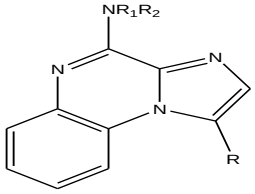
EAPB(I) EAPB(II) EAPB(III)

Where, R1= (CH3)2–CH–CH2–,C6H5–(CH2)2– andR4=CH3– NH–, NH2–

18. Weng Q *et al* Synthesized compounds and showed that 3-(4-bromophenyl)-2-(ethylsulfonyl)-6-methylquinoxaline 1,4-dioxide (Q39), derived from Quinoxaline 1,4-Di-N-oxide, possessed high anti-cancer activity in hypoxia. Cytotoxicity assay demonstrated that Q39 is a potential and highly efficient anti-cancer compound in all tested cell. In their work showing the mechanism of Q39 in hypoxia.

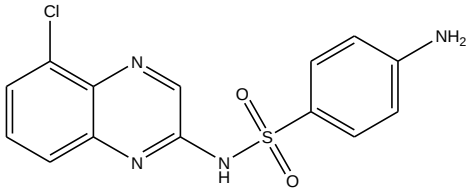


19. Masquefa C *et al* synthesized New series of imidazo[1,2-a]quinoxaline analogues have been in good yields via a bimolecular condensation of 2-imidazole carboxylic acid, followed by a coupling with ortho-fluoroaniline and subsequent substitution on the imidazole ring by Suzuki Cross-coupling reaction using microwave assistance. Antitumor activities of these derivatives were evaluated by growth inhibition of A375 cells in vitro. It was proposed that all compounds exhibited high activities compared to imiquimod and fotemustine used as reference.

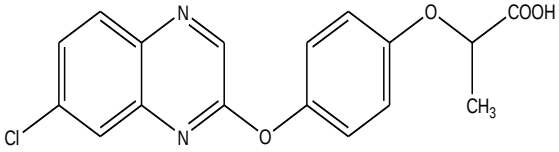


Where, R= $(CH_3)_2CHCH$, R= $C_6H_5(CH_2)_2$

20. Hanlin G *et al* in 2003 performed a study on DNA Sequence Specificity for Topoisomerase II Poisoning by the Quinoxaline Anticancer Drugs XK469 and CQS, The two known antineoplastic Quinoxaline topoisomerase II poisons, XK469 (NSC 697887) and CQS (chloroquinoxaline sulfonamide, NSC 339004), were compared for DNA cleavage site specificity, using purified human topoisomerase II and human topoisomerase II. This indicates that topoisomerase II isozymes can play a major role in DNA cleavage site selection for some classes of topoisomerase II poisons.

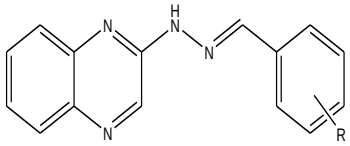


Chloroquinoxaline sulfonamide

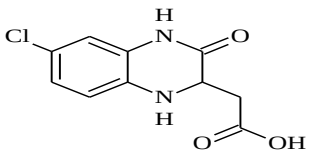


XK469 (NSC 697887)

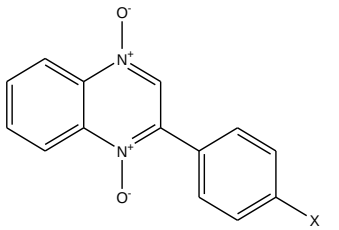
21. Felipe A. R. Rodrigue *et al* in 2014 Designed synthesized and carried out biological evaluation of (E) -2-(2-arylhydrazinyl)quinoxalines, a promising and potent new class of anticancer. A series of forty-seven quinoxaline derivatives, 2-(XYZC6H2CH@N–NH)-quinoxalines, 1, have been synthesized and evaluated for their activity against four cancer cell lines: potent cytotoxicities were found (IC50 ranging from 0.316 to 15.749 lM). 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. A common feature of active compounds is an ortho-hydroxy group in the phenyl ring. A potential role of these ortho-hydroxy derivatives is as N, N, O-tridentate ligands complexing with a vital metal, such as iron, and thereby preventing proliferation of cells. The most active compound was (1: X, Y = 2,3-(OH) 2, Z = H), which displayed a potent cytotoxicity comparable to that of the reference drug doxorubicin.[28]



22. Paola *et al* performed Quinoxalin-3-ones bearing an ethoxy carbonyl or carboxy group in the C-2 position **(4)** has been prepared and evaluated for anticancer activity. The compound bearing chloro group exhibited the maximum activity.

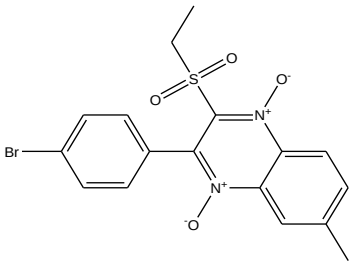


23. Amin K M *et al* 2006 performed A new series of quninoxaline-1,4-di-*N*-oxides and fused quninoxaline-di-*N*-oxides were synthesized and evaluated for hypoxic-cytotoxic activity on EAC cell line, compound 16 a was the most potent cytotoxine with IC_{50} 0.9 µg/ml, potency 75 µg/ml and was approximately 15 times more selective cytotoxine (HCR>111) than 3-aminoquinoxaline-2-cabonitrile which had been used as a standard (HCR>7.5).

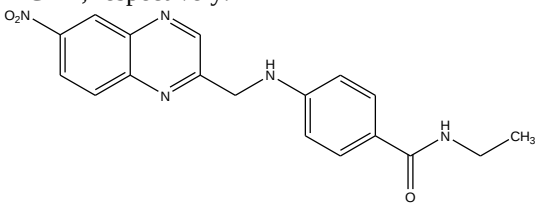


compound 16
a: X = Cl
b: X = CH3

24. Qinjie W *et al* 2008 performed a study on novel synthetic Quinoxaline 1,4-Di-N-oxide compound with anti-cancer activity in hypoxia 3-(4-Bromophenyl) -2-(ethyl sulfonyl)-6-methyl quinoxaline-1,4-di-*N*-oxide (17) or Q39, was synthesized from quinoxaline-1,4-di-*N*-oxide and evaluated for in vitro anticancer activity in hypoxia [14]. Cytotoxic assay demonstrated that Q39 is a potential and highly efficient anti- cancer compound in all the tested cell line with IC_{50} values of 0.18±0.03-8.88□1.12µM in hypoxia and 0.33□0.04-8.74□1.28 µM in normoxia. The mechanism of Q39 in hypoxia confirmed that this compound could cause the opposite of K562 cell in a time dependent manner.

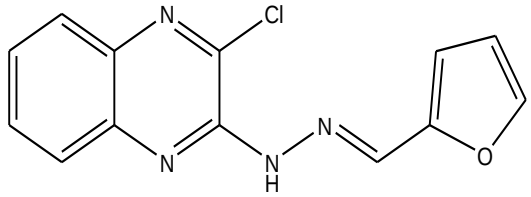


25. E. R. Kotb *et al* conducted Synthesis and Reactions of Some Novel Quinoxalines for Anticancer Evaluation 2006 1,2-Dihydro-3-(2 ′-naphthyl) quinoxaline-2-one was prepared from the reaction of methyl (2 ′-naphthyl)glyoxylate. Also, 2-chloro-and 2-hydrazinoquinoxaline derivatives 5 and 6 were prepared, which, upon reacting with different reagents, afforded the triazolo, tetrazolo, and amino quinoxaline derivatives. Compounds 5 , 8b , 9 , 10b , and 11bwere evaluated for their anticancer activity. The synthesis of some 2-furano-4 (3H)-quinazolinones, diamides (open ring quinazolines), quinoxalines and their biological evaluation as antitumor agents using National Cancer Institute (NCI) disease oriented antitumor screen protocol are investigated. Among the synthesize compounds, seventeen compounds were granted NSC code and screened at National Cancer Institute (NCI), USA for anticancer activity at a single high dose (10 (-5) M) in full NCI 60 cell panel. Among the selected compounds, 3-(2-chloro benzylideneamine)-2-(furan-2-yl) quinazoline-4 (3h) -one 21 was found to be the most active candidate against ovarian and lung cancer.
26. Shlomo G *et al* 1969 performed a study on Quinoxalines. XIV. Potential anticancer agents. Quinoxaline amino acid and dipeptide derivatives related to quinoxaline antibiotics. 2 quinoxaloyl chloride was utilized to preapare 13 N-(2-quinoxaloyl) derivatives of aminoacids and peptides related to quinoxaline antibiotics.N-(2-quinoxaloyl)-L-valyl –L-alanine possessed the most antitumour activity.[29]
27. Elshihawy H *et al* 2013 performed Molecular modeling studies and synthesis of novel Quinoxaline derivatives with potential anti-cancer activity as inhibitors of methionine synthase. The main aim was to develop inhibitors that could inhibit the enzyme reaction by blocking the binding of MTHF. These inhibitors were docked into the MTHF binding domain in such the same way as MTHF in its binding domain. Compound 4-({(6-nitro-quinoxalin-2-yl)methylamino}methyl) benzoic acid showed the lowestfree energy of the binding (-152.62 kJ/mol) and showed the lowest IC50 values of 45 ± 9 and 53 ± 9 lM against two types of cancer cell lines PC-3 and MCF-7, respectively.



28. Michael J W *et al* performed 2,3-Bifunctionalized Quinoxalines: Synthesis, DNA Interactions and Evaluation of Anticancer, Anti-tuberculosis and Antifungal Activity.A variety of 2,3-bifunctionalized quinoxaline have been prepared by the condensation of 1,6-disubstituted-hexan-1,3,4,6-tetraones with o-phenylenediamine, (R,R)-1,2-diaminocyclohexane and p-nitro-o-phenylenediamine. It is concluded that strong intramolecular N-H----O bonds in the favoured keto-enamine form may be responsible for the minimal biological activities observed in DNA footprinting, anti-tubercular, anti-fungal and anticancer tests with these hyper π-conjugated quinoxaline derivatives. However, subtle alteration by the addition of a nitro group affecting the charge distribution confers significant improvements in biological effects and binding to DNA.

29. Ravinder M *et al* 2015 synthesized and tested metal complexes of quinoxaline based schiff bases for antimicrobial and anticancer activities



30. Gildardo R et al Ester of Quinoxaline-7-carboxylate 1,4-di-N-oxide as Apoptosis Inductors in K-562 Cell Line: An in vitro, QSAR and DFT Study.Sixteen esters of quinoxaline-7-carboxylate 1,4-di-N-oxide were evaluated for antitumor activity on K562 chronic myelogenous leukemia cells and their IC50 values were determined. The mechanism of induced cell death by the most active molecule was assessed by flow cytometry and an in silico study was conducted to optimize and calculate theoretical descriptors of all quinoxaline 1,4-di-N-oxide derivatives. Our results show that compounds C5, C7, C10, C12 and C15 had the lowest IC50 of the series. C15 was the most active compound (IC50= 3.02 μg/mL), inducing caspase-dependent apoptotic cell death via the intrinsic pathway.
31. Loriga *et al* performed Quinoxaline analogues of trimetrexate (TMQ) and 10-propargyl-5,8-dideazafolic acid (CB 3717) and its precursors: synthesis and evaluation of in vitro anticancer activity 18 quinoxalines bearing a methyleneanilino or methyleneaminobenzoylglutamate group on position 6 of the ring and various lipophilic substituents on positions 2 and 3 were prepared in order to discover if their structural analogy with both trimetrexate (TMQ) and 10-propargyl-5,8-dideazafolic acid (CB 3717) might display in vitro anticancer activity. Among these, 12 compounds were selected at the National Cancer Institute, Bethesda, MD, USA; they exhibited moderate to strong cell-growth inhibition at a concentration of 10−4 M. Interesting selectivities were also recorded between 10−8 and 10−6 M. These analogues proved to be less potent inihibitors of tumor cells than other classical and non-classical antifolate analogues previously described by us.
32. Subhas K *et al* 2009 synthesized evaluated anticancer and cytostatic activity of some 6H-indolo[2,3-b]quinoxalines .Various 6-aralkyl-9-substituted-6*H*-indolo[2,3-*b*]quinoxalines were synthesized by reaction of 1,5-disubstituted 2,3-dioxo-2,3-dihydroindole with orthophenylene diamine. Appreciable anticancer activity of compounds **5b**, **5d**, **5g** and **5l** at various cell lines among 59 human tumor cell panels was observed. All the synthesized compounds were evaluated for cytostatic activity against human Molt 4/C8 and CEM T-lymphocytes as well as for murine L1210 leukemia cells. Compound **5h** exhibited an IC_{50} of 71 μmol mL^{-1} against Molt 4/C8 and 117 μmol mL^{-1} against CEM compared to melphalan 3.2 μmol mL^{-1} and 2.5 μmol mL^{-1}, respectively. The $IC_{50}$for compound **7i** against L1210 was 7.2 μmol mL^{-1} compared to melphalan 2.1 μmol mL^{-1}.
33. Mohammad P *et al* conducted one-pot catalyst-free synthesis of functionalized pyrrolo[1,2-a]quinoxaline derivatives of benzene-1,2-diamine, acetylenedicarboxylates and ethyl bromopyruvate.The catalyst-free multicomponent reaction of 1,2-diaminobenzene, dialkyl acetylenedicarboxylates, and ethyl bromopyruvate forms pyrrolo[1,2-a]quinoxaline derivatives in good yields. Ethylenediamine also reacts under similar conditions to produce new pyrrolo[1,2-a] pyrazine derivatives.
34. Debasish B *et al* conducted A green approach toward quinoxalines and bis-quinoxalines and their biological evaluation against A431, human skin cancer cell lines.

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