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ANTICANCER ACTIVITY OF QUINOXALINE: A SYSTAMIC REVIEW

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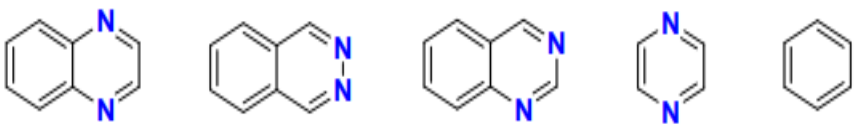
ABSTRACT

There has been a lot of research done on the quinoxalines class of n-heterocyclic chemicals since they are significant biological agents. Their pharmacological effects include anticancer, antifungal, antibacterial, antiviral, and antimicrobial properties. The pharmaceutical industry relies heavily on the medicinal properties of quinoxalines with various substitutions. A possible platform for the search for effective chemotherapeutics is the quinoxaline scaffold. In this review, studies on the therapeutic potential of quinoxaline derivative's anticancer activities are compiled and discussed.

KEYWORDS: Anticancer, Quinoxaline.

INTRODUCTION

The first moiety of quinoxaline is a member of a class of nitrogen-containing benzoheterocycles with a wide range of biological activities, including antitumor, antibacterial, antiviral, anticonvulsant, antifungal, antimicrobial, anti-cancer, anti-tubercular, antimalarial, and anti-inflammatory properties[1]. A benzene ring and a pyrazine ring are fused together to form quinoxaline, also known as benzopyazine. Quinoxaline is isomeric with phenazines 2, quinoazoline 3, and cinnolenes. Diazine 4 and the benzene 5 ring combine to create quinoxaline.[2]



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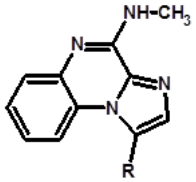
Anywhere in the world, cancer is a major cause of mortality and a substantial public health problem. Several effective anticancer treatments are on the market, including the traditional chemotherapy agents that stop DNA replication and cell division.

However, the majority of drugs on the market right now are not targeted, which creates issues like the common side effects of chemotherapy and well-known multidrug resistance. To reduce the negative effects of chemotherapy, effective tailored medications are being developed thanks to a better understanding of cancer immunology.

Quinoxalines have drawn a lot of interest because of the wide spectrum of biological activity they display. It is regarded as an important beginning point for anticancer drugs. Several quinoxalinone compounds were developed and investigated in the 1980s for their potential as an anticancer scaffold. The quinoxaline scaffold has attracted a lot of attention recently as a component of numerous medicinal entities that may be used alone[12] or in their N-oxide or N,N0 -dioxide forms.[13] Quinoxalines created a promising platform for the discovery of efficacious chemotherapeutic drugs because they are isosteric to purine antimetabolites.[14]

The 2-imidazole carboxylic acid condensation method was used by deleuze *et al*., To create the imidazo[1,2-a]quinoxaline analogues 79 and 80, which were then coupled with orthofluoroaniline. These quinoxaline derivatives effectively combated a human amelanotic melanoma cell line tumour (A 375 cells). These analogues were utilised in vitro or ex vivo cytokine studies, but not in vivo.[3]



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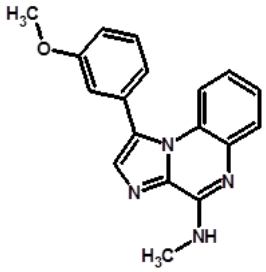

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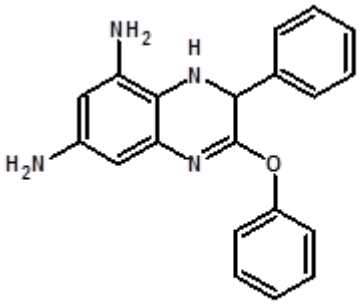
Paola *et al*., Created new quinoxaline compounds with 5,7-diamino-3-phenyl-2-benzylamino, 2-phenoxy 81, and 2-thiophenyl 82 substitutes that showed anticancer activity in nine different human cancer cell lines.[4] such as (z)-5- quinoxaline-6-carbaldehyde (quinoxalin-2-ylmethylene) the compound thiazolidine-2,4-dione 83 (e)-1-(2,5-dimethoxyphenyl)-3-(quinoxalin-2-yl)prop the chalcones from which -2-en-1-one 84 derivatives were generated showed a highly effective impact and activities against glioma cell lines obtained from human and rat brain tumours.[5]



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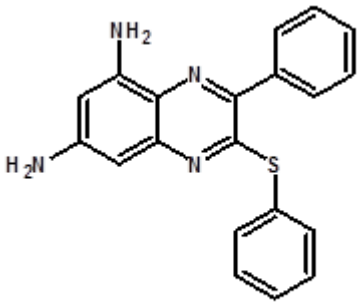

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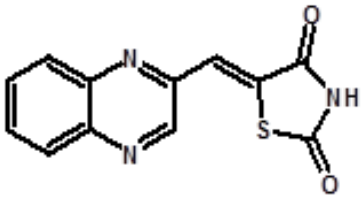

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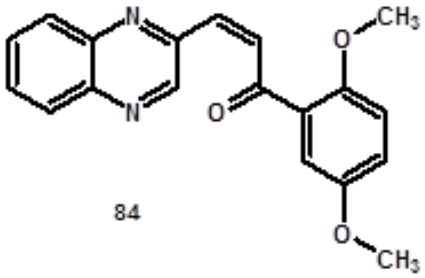

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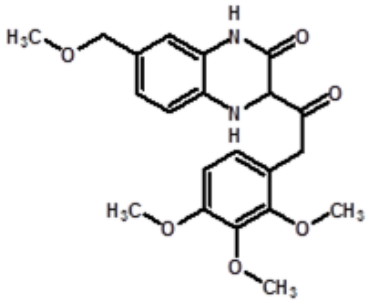
In 2017, Zhang and colleagues published a study on the anti-proliferative effect of n-substituted-3-oxo-1,2,3,4-tetrahydroquinoxaline-6- carboxylic acid derivatives. The highest anti-proliferative effect was demonstrated by the scaffold methyl 3- oxo-1-(2-(3,4,5-trimethoxyphenyl)acetyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylate 85 against Hela, SMMC-7721, and K562 cell lines, with ic_{50} values of 0.126 m, 0.071 m, and 0.164 m, respectively.[6] imidazo[1,5-a]quinoxaline and pyrazolo[1,5-a]quinoxaline derivatives were investigated for their antiproliferative properties. The greatest anti-proliferative drug for the Human Melanoma Cell Line A375 Was The imidazoquinoxaline derivative 1-bromo-n, 8-dimethylimidazo [1,2-a]quinoxalin-4-amine, with a 66% inhibition rate.[7]



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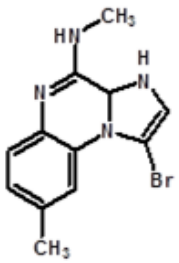

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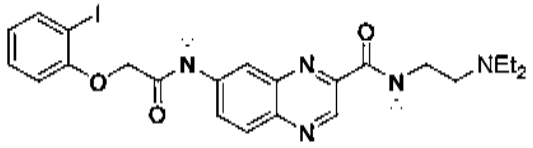
In dry tetrahydrofuran, 4-nitro phenyl(2-((diethylamino)ethyl)carbomoyl)quinoxalin-6-yl)-carbamate and n,n-diisopropyl ethylamine were combined to create novel quinoxaline derivatives. Compound 87 shown strong anticancer activity with 3.30 0.75% id/g when these compounds were tested for antitumor activity against melanoma cell line.[8]



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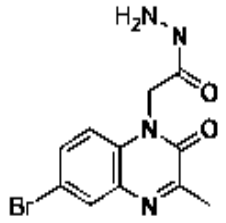
To test its anticancer efficacy against Breast Cancer Cell Line (MCF-7), Non-Small Cell Lung Cancer Cell Line (NCIH460), And CNS Cancer Cell Line, Abbas Sh. And Colleagues Produced Substituted Quinoxaline (Sf-268). Doxorubicin was a Commonly Prescribed Medication. The Most Effective Derivatives Among All The Others Examined Were 2-(6-Bromo-3-Methyl-2-(1h) Quinoxalinon-1-Yl)Acetohydrazide 88 and 4-(6-Bromo-3-Methyl Quinoxalin-2-Yloxy)Cyclohexa-1,5-Dienamine 89. Compound 88 Had IC_{50} Values For MCF-7, NCI-H460, and SF-268 Of 0.01±0.001, 0.02 ± 0.004, And 0.06 ± 0.002, Respectively. The Scaffold 89's IC_{50} Values For the MCF-7, NCI-H460, and SF-268 Cell Lines are 0.02 ± 0.001, 0.03 ± 0.006, and 0.06 ± 0.008 G/L, Respectively.[9] Refluxing N-[3-(Dimethylamino) Propyl] gave rise to Indeno[1,2-B] Quinoxaline Compounds For Tseng and Colleagues. The Hydrochlorides Of 3-(Dimethylamino)Propoxyamine and 11-Oxo11h-Indeno[1,2-B]Quinoxaline-6-Carboxamide in Ethanol. The Substances were Tested Against the Human Foetal Lung Fibroblast Cell Line, MDA-MB231, PC-3, HUH-7, And Other Cancerous Cell Lines (MRC-5). The Substance 11-[3-(Dimethylamino)Propoxy]Imino Stood Out Among the Others Tested. [3-(Dimethylamino) Propyl]-N The Quinoxaline-6-Carboxamide -11h-Indeno[1,2-B] With IC_{50} Values of 0.87 M, 0.82 M, And 0.64 M, Respectively, Shown Greater Potency Against MDA-MB231, PC-3, And HUH-7. With An IC_{50} Value of 31.51 M, it Displayed Little Activity Against the MRC-5 Cell Line. While Substitution of Amino Alkoxyimino Groups Increases The Anti-Cancer Action, Substitution of the Methyl Group has no Effect on the Activity.[10]



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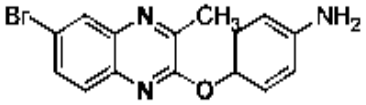

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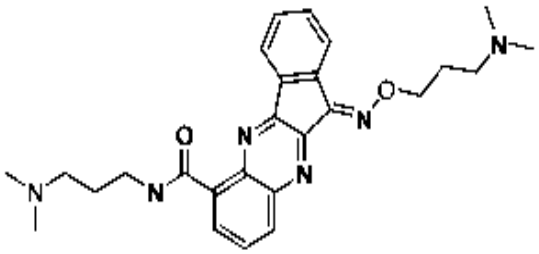

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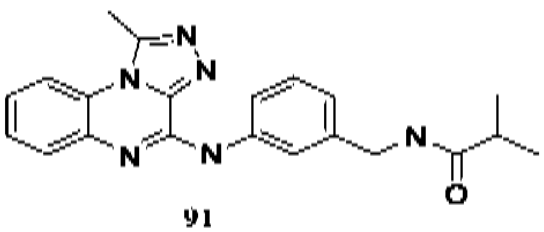
By treating n-(3-(aminomethyl)phenyl)-1-methyl-[1,2,4]triazolo[4,3-a]quinoxalin-4-amine with acetyl chloride in the presence of n,n-diisopropylethylamine, Ali I. and coworkers reported to synthesise quinoxaline derivatives. These substances were tested against luekemia cell lines for their ability to fight cancer. Thp-1 and ty-82. With IC_{50} values of 2.50 m and 1.60 m against ty-82 and THP-1 cell lines, respectively, the derivative 91 was the most effective anticancer agent compared to all other synthetic compounds respectively. Substitution of isobutyl amide group enhance the anti-cancer activity while removal of tertiary butyl carbamate group lessen the activity.[11]



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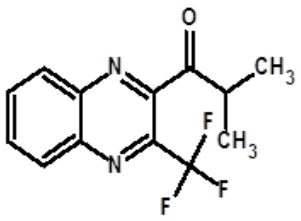
The in vitro antitumor activity of a new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1,4-di-n-oxide derivatives against a panel of three tumour cell lines (MCF7 (breast), NCIH 460 (lung), and SF-268 (CNS), as well as a panel of 60 human tumour cell lines derived from nine cancer cell types, was evaluated. 2- (3-methylbut-1-en-2-yl)-3-(trifluoromethyl)quinoxaline-1,4-din-oxide (compound 1), 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-n-oxide (compound 2), their difluorinatedanalogs(6,7-difluoro-2-isobutyryl-3-trifluoromethylquinoxaline 1,4-di-n-oxide and 2-benzoyl-6,7-difluoro-3-trifluoromethylquinoxaline 1,4-di-n-oxide) (compound 3 and 4), and 2-(2,2-dimethylpropanoyl)-3-trifluoromethyl-quinoxaline 1,4-di-n-oxide (compound5) were the most active, with higher anticancer activity with mean GI_{50} (growth inhibition) values of 1.02, 0.42, 0.52, 0.15, and 0.49 mm, respectively.[15,16]



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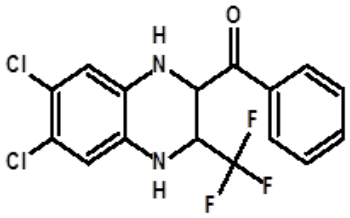

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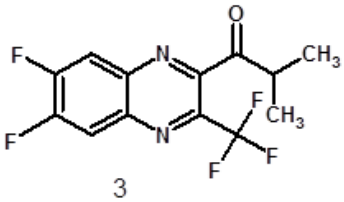

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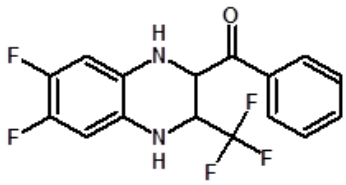

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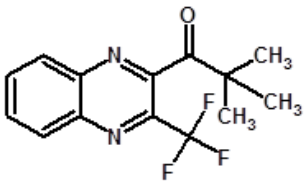

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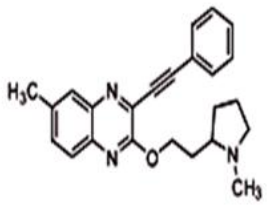
Compound 18 showed potential action as an inhibitor of the wnt/b-catenin signal pathway in lung Cancer cell lines studied by S.B. Lee *et. Al.*, With an IC_{50} Value Of 0.905 nmol L^{-1}.[17] Lung Cancer Cell Hop-92 Used By S.S. Karki *et. Al.* For anticancer activities exhibited no growth in the presence of compound 19 at 1.0 x 10-5 mol L^{-1}.[18] Compound 20 was created By Y.B. Lee *et. al.*, And has also been shown to limit the growth of drug-resistant lung cancer cell lines.[19]



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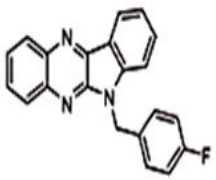

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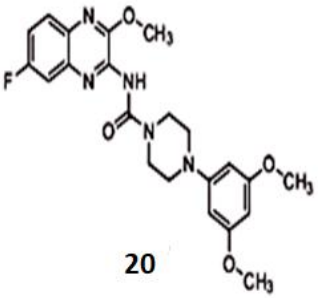
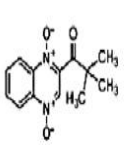


20

With 75% of GI_{50} Values as Low as 0.01 To 0.15 Mol L^{-1}, B.Zarranz *et. al.*, claimed that a series of quinoxalines they had synthesised had growth inhibitory effect against the leukaemia cell lines Hl-60.[20] with an IC_{50} Of Less Than 0.01 Mol L^{-1} against the SR leukaemia cell line, compound 21 was the most effective.[20,21] At nanomolar concentrations, compound 22, which has a 3,4,5-trimethoxyanilino pharmacophore at position 2 of the ring system, inhibited the leukaemia Cell Lines Hl-60 And Molt-4[21,22] Quinoxaline Template 23's Anticancer Activity was enhanced Significantly by The 2-Oxypropionic Acid Framework Against The Leukaemia Cell Line Hl-60.[22]



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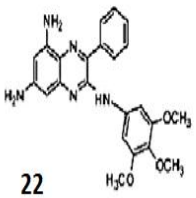

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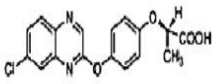
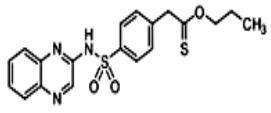


23

Compound 24 Was Created By F. Grande *et. al.*, And Was Extremely Effective Against The HCT116 P53, HCT P53, And HT 29 Colon Cancer Cell Lines, With Respective IC_{50} Values Of 0.40± 0.01, 0.30± 0.07, And 0.30± 0.06 Mol L-1[23] Tricyclic Quinoxaline 25 was created By G. Moarbess *et. al.*, And was Well Tolerated With No Obvious Adverse Effects. It Was Found To Suppress The Development Of LS174T Colon Cancer Cells With An IC_{50} Of 4.12± 0.67 Mol L^{-1}.[24] The

Synthesis Of Quinoxaline Derivatives Was Carried Out By S. Tanimori *et. al*., The Most Effective Quinoxaline Derivative, Substituted Dihydroquinozalin-2-One[25], With an IC_{50} of 4.96 mol l^{-1} against the Hela3 cancer cell line[25], was produced from a library of quinoxaline derivatives

M.M.Ghorab created substances that were tested on a human liver cell line (HEPG2). At an IC_{50} of 4.29 mol l^{-1}, compound 30 emerged as this serie's most powerful compound.[26] According to a preliminary mechanistic research, Y.Hu *et.al.*, Synthesized quinoxaline motif 31 was revealed to be effective against HEPG2 at an IC_{50} of 1.76 mol l^{-1}[27]



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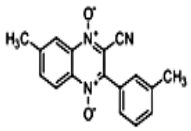
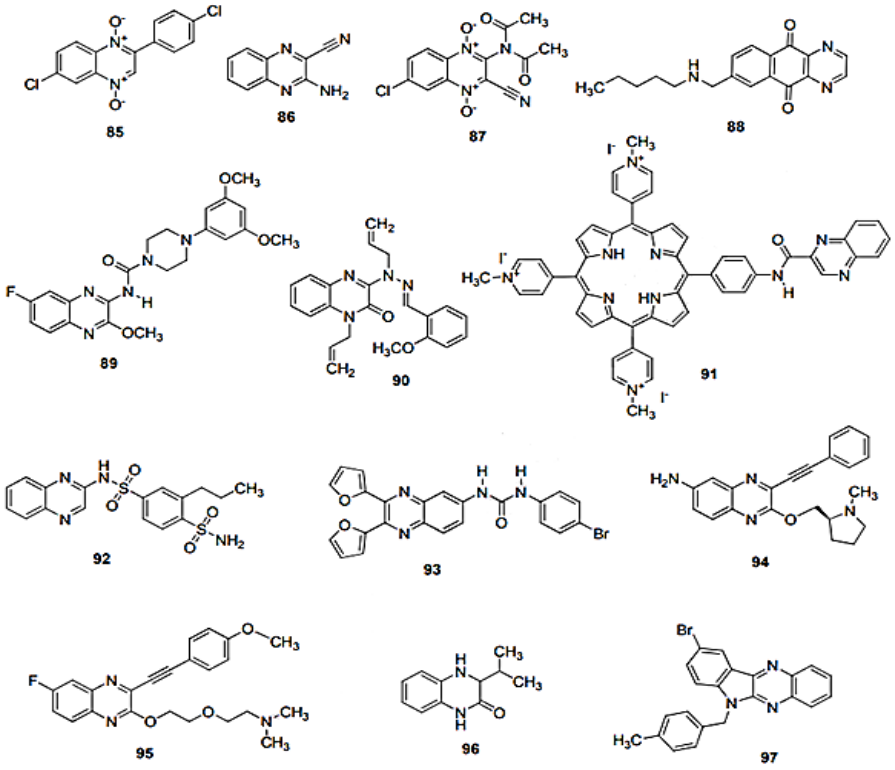


31

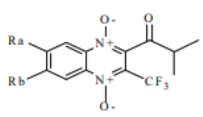
6-chloro-2-(4-chlorophenyl)quinoxaline 1,4-diol, a powerful cytotoxin with an IC_{50} of 0.9 G/Ml and a Potency of 75 G/Ml, was Synthesised By K.M. Amin *et al*.,[28] It had an HCR > 111 Rating And was around 15 Times More Selective Than 3-Aminoquinoxaline-2-Carbonitrile 86.[28]

M.M.F Ismail *et.al.*, synthesised 3-diacetylamino derivative 87 was reported to act both as An Antitumor and as a hypoxia-selective agent[29] while H.Lee *et.al.*, synthesised compound 88 which showed high activity upon four human cancer cell lines H-15, T-47d, MD-MB-468 And Sk-Ov-3 At IC_{50} Of 0.05, 0.08, 0.20 And 0.40 µm Respectively.[30] Moreover, N-Alkylated Quinoxalinone 90, Synthesised By S.A. Galal, was proposed to function as a potent cancer chemopreventive drug[32], while fluoroquinoxaline 89, produced by Y.B. Lee *et. al.*, Was Shown To Have Outstanding Anticancer Activity.[31a,B] When Compared to Tmpyp, D. Kumar *et. al.*, synthesized Porphyrin Containing Quinoxaline 91 showed improved photocytotoxicity (IC_{50} = 0.06 M) For A549 Cancer Cells.[33] Various authors have also reported the potential utilization of quinoxaline pharmacophores 92[34], 93[35], 94[36], 95[37], 96[38] And 97[39] as anticancer agents of choice.

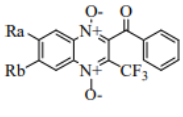


85 86 87 88 89 90 91 92 93 94 95 96 97

A new class of 2-alkylcarbonyl and 2-benzoyl-3-trifluoromethylquinoxaline-1,4-di-n-oxide derivatives was created and tested for in vitro anticancer activity against the breast cancer Cell Line MCF7, The Lung Cancer Cell Line NCI H 460, and the central nervous system cancer cell line SF-268.[12] The active substances were subsequently examined in a comprehensive panel of 60 human tumour cell lines. The findings demonstrated that, in general, anticancer activity was dependent on the substituents at the carbonyl group, and improved in the following order: ethyl isopropyl ter-butyl phenyl. Among these, compound 13c, 14e, Their Difluorinated Analogues (13g&14g), And Compound 15c Were The Most Active, With Mean GI_{50} Values Of .02, 0.42, 0.52, 0.15 & 0.49µm respectively.

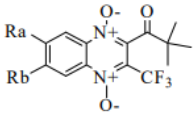


13 (a-g)



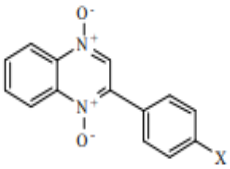
14 (a-g)

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



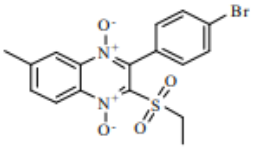
15 (a-g)

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[13], Compound 16a 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>111) Than 3-Aminoquinoxaline-2-Cabonitrile which had been used as a Standard (HCR>7.5).



compound 16
a: X = Cl
b: X = CH_3

3-(4-bromophenyl)-2-(ethyl sulfonyl) (ethyl sulfonyl) quinoxaline-1,4-di-n-oxide was converted into -6-methyl Quinoxaline-1,4-di-N-Oxide[17], also known as Q39, and it's in vitro anticancer activity in hypoxia was assessed.[14] With IC_{50} values of 0.180.03±8.881.12m In Hypoxia and 0.330.04±8.741.28m in Normoxia, Cytotoxic Assays Proved That Q39 is a Potentially Strong and Highly Effective Anti-Cancer Drug in all of the examined cell lines. The Mechanism of Q39 in Hypoxia Proved that this substance might, in time-dependent manner, produce the opposite of K562 Cell.



(17)

CONCLUSION

A crucial group of heterocycles containing nitrogen, quinoxalines have a wide range of physiological effects. This investigation uncovered various biological uses for scaffolds based on quinoxaline that provide great paths to novel biomolecular targets, making them excellent starting points for developing new drugs and potential future prospects for therapeutic research. For researchers and pharmacists, the biological activities mentioned are very encouraging, leading to the development of new therapeutics and treatments that will benefit humanity.

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