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Review Article

A State-Of-The-Art Overview of Quinoxaline, Its Derivatives, and Applications

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ABSTRACT

A significant type of heterocycle molecules are quinoxaline derivatives, in which N substitutes for some of the carbon atoms in the naphthalene ring. It is made up of the fusion of two aromatic rings, pyrazine and benzene, and has the chemical formula C8H6N2. Although it is uncommon in nature, it is simple to synthesize them. The State of the Art will be discussed in this review, along with an overview of the advancements in understanding the structure and mechanism of quinoxaline and its derivatives, as well as their related industrial, medicinal, and biological importance. Numerous biomedical uses, including the treatment of chronic and metabolic illnesses and antibacterial properties, can be obtained by altering the structure of quinoxaline.

INTRODUCTION

Quinoxaline derivatives represent a significant group of heterocyclic compounds, where nitrogen substitutes for one or more carbon atoms in the naphthalene ring(1) . The designated location for the quinoxaline ring system is depicted in Fig. 1, with positions 2 and 3 referred to as a-positions(2) . In the pharmaceutical sector, they have garnered considerable interest because of their broad range of biological activities. For instance, these compounds can be effective against bacteria, fungi, viruses, leishmania, tuberculosis, malaria, cancer, depression, and various neurological disorders, among others. The structural nucleus of quinoxaline facilitates all these biological activities. The quinoxaline structure serves as a basis for the development of numerous new compounds for various applications.(3) Benzene and pyrazine, two aromatic rings, fuse to generate quinoxaline. Because of this, it is also known as benzopyrazine and is defined as a bioisoster of benzothiophene, quinoline, and naphthalene(4). Because they stabilize ion radical species, the

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atoms S and N are crucial to the ring. Under normal circumstances, quinoxaline has a molecular weight of 130.15, a chemical formula of C8H6N2, and a white, crystalline powder(4). Quinoxaline is a low melting solid that can be refined through distillation; a fraction of it with a boiling point of 108–111/12 mm has a melting point of 29–30 C (4) When quinoxalines are treated with quaternizing agents such as dimethyl sulfate and methyl p-toluene sulphonate, they yield monoquaternary salts and are soluble in water(5). The unstable quaternary salts of 2-alkylquinoxalines undergo oxidation to produce complicated colorful compounds. 5-nitroquinoxaline (1.5%) and 5,7-dinitro-quinoxaline (24%) are the two compounds that are formed when nitration takes place under forcing conditions (Conc. HNO3, Oleum, 90 C). It is acidic, with a pKa of 0.60 in water at 20 C Quinoxaline is considerably diprotonated in a strongly acidic media, as indicated by its second pKa of 5.52 (2) .

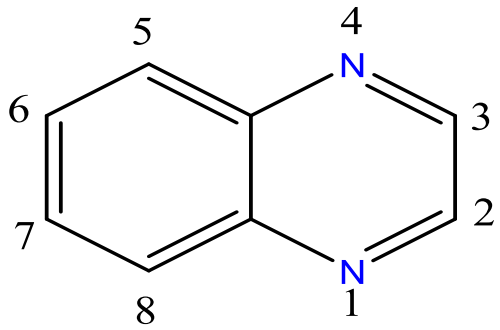


Figure 1

Most of quinoxaline derivatives are synthetic and natural quinoxaline derivatives are rare(4), such as echinomycin and triostin-A.

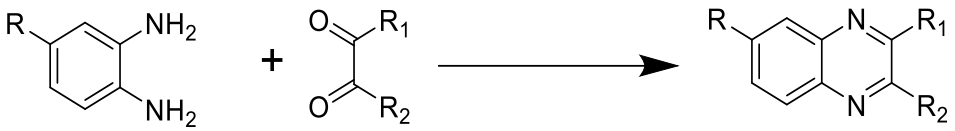
1. Methods of Preparation of Quinoxalines

Numerous researchers have attempted to create a library of quinoxaline derivatives due to its enormous synthetic significance and diverse medicinal applications (1)(7)(8). There are two categories of quinoxaline preparation techniques:

1. The conventional chemical pathway, which relies on the condensation of o-phenylenediamines and dicarbonyl compounds under particular circumstances, including potent catalysts, high temperatures, prolonged periods, or organic solvents. Furthermore, side products could be created and the reaction yield could be low. The ecosystem is negatively impacted by these kinds of reactions.
2. The green chemistry pathway, which produces quinoxalines at a lower cost by employing green chemical techniques. This method is distinguished by its use of a recyclable catalyst that is safe for the environment, cheap cost, low energy usage, one-pot synthesis, lack of side products, quick turnaround time, and high yield. It can be carried out by the microwave reactor or at room temperature in an aqueous media.

2.1 Traditional Chemistry Pathway

Condensation of 1,2-Dicarbonyl Derivatives and o-Phenylenediamine In 1884, Korner and Hinsberg created the first quinoxaline derivative by condensing o-phenylenediamine with a 1,2-dicarbonyl derivative. This reaction produced a variety of derivatives (Scheme 1). (6)

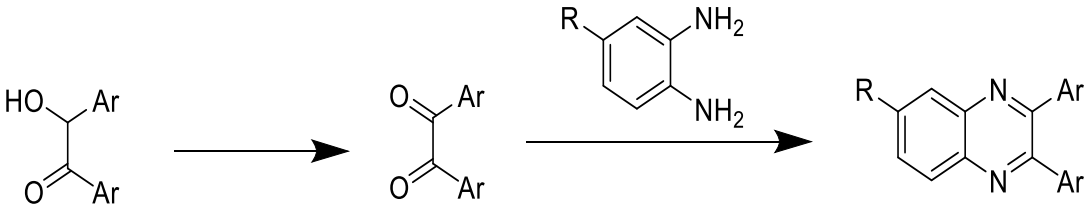


R= H, Me, Cl, NO_2
R_1=R_2= H, Ph,Me, 4-Me-Ph, 2-Furyl

Figure 2 Scheme 1. Synthesis of quinoxaline by the condensation technique: diamine (1 mmol), dicarbonyl (1mmol), Glycerol (5 ml), water (2ml), 90 ^{0}C, yield (85- 91 %)

2.2 o-Phenylenediamine and In Situ Produced 1,2-Dicarbonyls

Quinoxalines were synthesized via catalytic iodine, which was used to accelerate the oxidative cyclization cascade between different 1,2-diamino compounds and hydroxyl ke- tones (Scheme 2)(8)

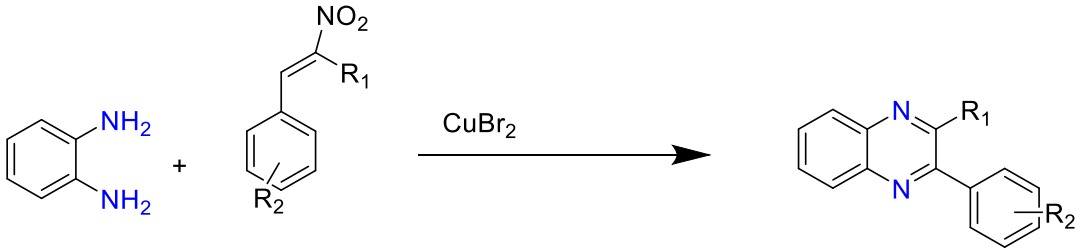


R= H, NO_2, Cl, Me
Ar = 4-OCH_3-Ph

Figure 3 Scheme 2. Synthesis of quinoxaline from o-phenylenediamine and in situ generated 1,2-dicarbony derivatives o-phenylenediamine (1mmol) hydroxyl ketone (1 m moL),I_2 (0.25 mmol) DMSO (2ML) RT, 12 h, yield (80–90%).

2.3 Metal-Catalyzed Cyclization of Imines and Azides

Quinoxalines were made from ketimines and azides. This cyclization reaction, which is catalyzed by metal, yields quinoxaline derivatives (Scheme 3)(9)(10)(11).



R_1= 2-Cl, 2-Br, 2-OMe, 2-NO_2
R_2= H, 4-Cl, 4-Br, 4-Me, 4-OCH_3

Figure 4 Synthesis of quinoxalines from imines and azides: imine (1 mmol), sodium azide (3 mmol), (diacetoxyiodo)benzene (3 mmol), CuO (1 mmol), ethyl acetate, Rt, 16h, yield (35-80%)

2.4 Cyclocondensation of o-Phenylenediamine and Aromatic Alkynes

Quinoxalines were synthesized via cyclocondensation of phenylene diamine and aromatic alkynes in the presence of Cu(OAc)2 as a catalyst (Scheme 4) (12).

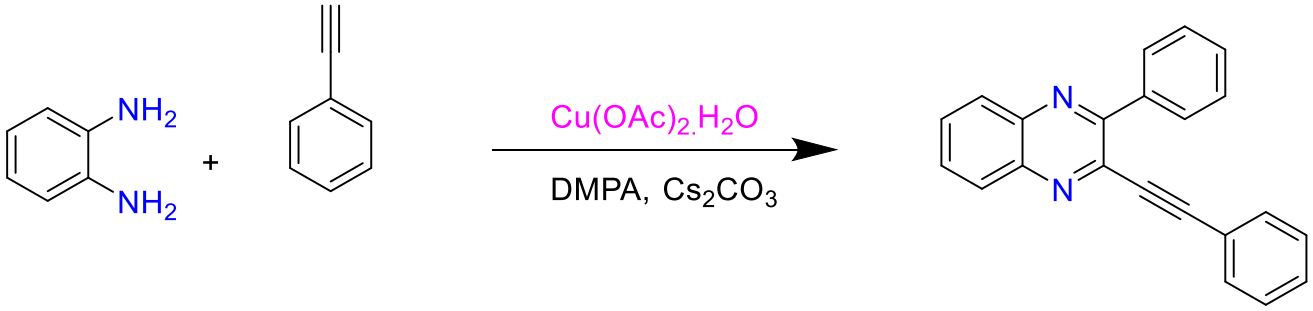
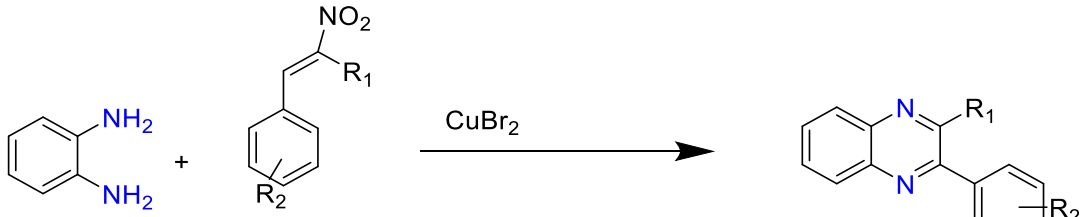


Figure 5 Synthesis of quinoxalines from aromatic alkynes and amines: o-phenylenedia mine (0.25 mmol) in toluene, phenyl acetylene (1 mmol), Cs2CO3 (0.75 mmol), Cu (OAc)2.H2O (10 mol % from the o-phenylenediamine), DMPA (0.75 mmol), 70 ◦C, 8 h, yield (86%).

2.5 Cyclocondensation of o-Phenylenediamine and Nitro-Olefins

Using CuBr2 as a catalyst, phenylenediamine and nitro-olefins reacted to produce quinoxalines (Scheme 5)(13)

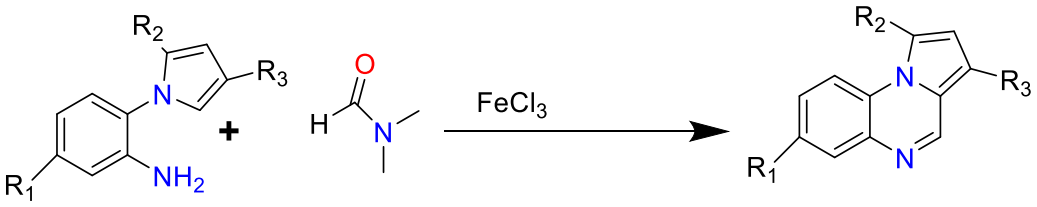


R_1= 2-Cl, 2-Br, 2-OMe, 2-NO_2
R_2= H, 4-Cl, 4-Br, 4-Me, 4-OCH_3

Figure 6 Scheme 5. Synthesis of quinoxalines from nitro-olefins and amines: phenylenediamine (1 mmol), nitro-olefins (1 mmol), CuBr2 (1 mmol), ethanol, 110 °C, 2–4 h, yield (35–90%)

2.6 Cyclocondensation of Aromatic Amines and DMF

By employing ferric chloride as a Lewis acid and an initiator for a simple reaction, a novel method for the synthesis of pyrrol [1,2-a]quinoxaline derivatives was presented. Carbon was obtained from DMF solvent (Scheme 6)(14).



R_1= H, F, Cl, Br, Me,CF_3, OMe, OCF_3 T-But
R_2=R_3= H, Me

Figure 7 .Scheme6. Synthesis of quinoxalines from amines and DMF in Fe-mediated catalyst: aniline derivative ive (0.3 mmol), DMF (2 mL), FeCl3 (0.3 mmol), TBPB (0.9 mmol), 120 °C, 5–12 h, yield (40-97%)

2.7 Clay-10 Based Method

This method of quinoxaline production is environmentally friendly. With no conventional drawbacks like high temperatures, costly reagents, low yields, or contamination, it is ecologically benign. Clay is an inexpensive, environmentally friendly substance that is always available. This reaction is carried out by combining the two reagents with room-temperature bentonite K-10, followed by ethanol and a celite pad. After diluting the mixture with 10 mL of water, it is concentrated to 5 mL. For one hour, the reaction is left to stand. After the product forms, the clay can be retrieved as pure crystals and used five more times. In order to circumvent the issues with the conventional pathway, this approach is advised for the synthesis of various quinoxaline derivatives and is consistent with the green chemistry procedure. Scheme 7 illustrates the response (15).

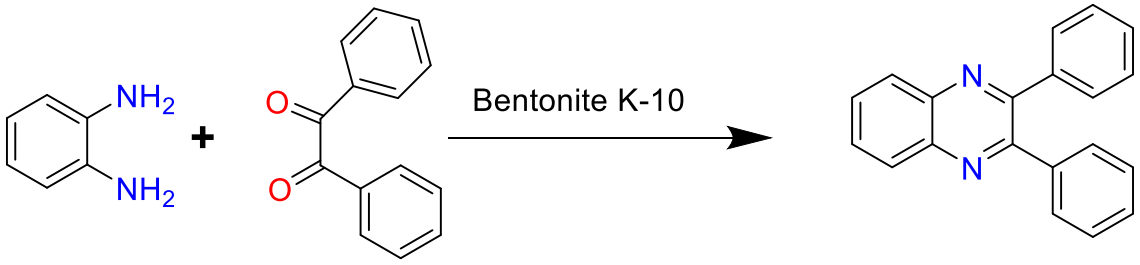
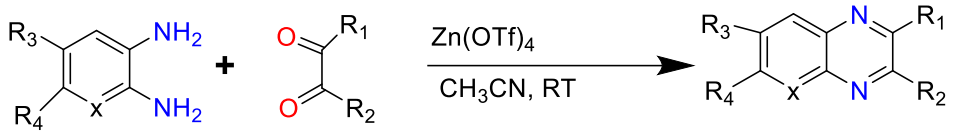


Figure 8 Scheme7. Synthesis of quinoxalines by one-pot cascade method: o-phenylene-diamine (1 mmol) benzil (1 mmol), bentonite K-10 (3 gm), ethanol 50 mL, RT, 20 min, yield (95%)

2.8 Zinc Triflate Catalyst

Trifluoromethanesulfonic acid's zinc salt is called zinc triflate. It is a very efficient and environmentally friendly catalyst. It is a catalyst for green chemistry. Acetonitrile solvent or a microwave-assisted reactor can be used to finish the reactions carried out by the zinc triflate catalyst without the need for a solvent. Using a zinc triflate catalyst, o-phenylenediamine and alpha diketones were reacted at room temperature in acetonitrile to produce quinoxaline derivatives. The yield from this reaction was 90% (scheme8) (16).

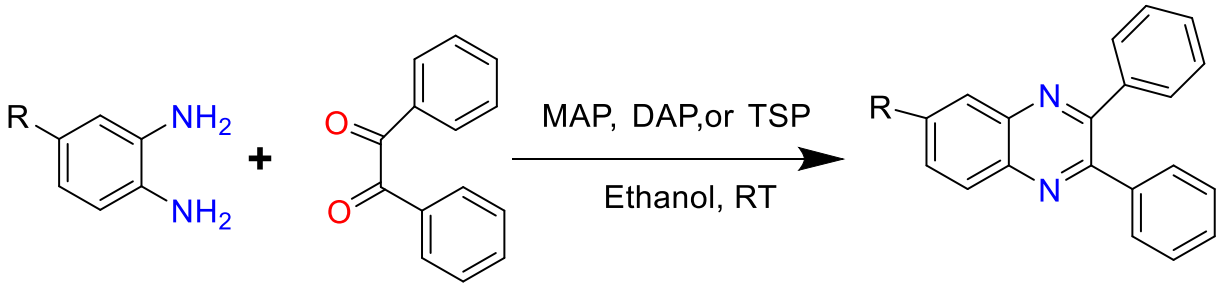


R_1=R_2= Me,Ph, Naphthylene-1,2-dione
R_3=R_4= H, Me
X= CH, N

Figure 9 Scheme 8. Synthesis of quinoxaline by using zinc triflate catalyst: diamine (1.1 mmol), dicarbonyl 1 mmol), Zn(OTf)4 (0.2 mmol), CH3CN (5 mL), RT, yield (85–91%).

2.6 Phosphate-Based Catalyst

Monoammonium phosphate (MAP), diammonium phosphate (DAP), and triple super phosphate (TSP), a fertilizer component mostly composed of monocalcium phosphate Ca(H2PO4)2, are examples of phosphate catalysts. A tiny quantity (0.006 gm) of this kind of catalyst is required to carry out the one molar equivalent reaction. While the catalyst is recovered from the reaction by straightforward filtration, washing with hot ethanol, and drying for six hours, the resultant product crystallizes from the ethanol (Scheme 9) (17).



R= H, Me, NO_2

Figure 10 Scheme 9. Synthesis of quinoxaline by using phosphate-based catalyst: amine (1 mmol), benzyl (1 mmol), MAP, DAP, or TSP (0.0006 gm), ethanol, RT, yield (85–91%).

2.10 Green Chemistry Pathway

2.10.1 Lanthanide-Based Catalyst

CAN, or cerium (IV) ammonium nitrate, is a lanthanide reagent. Its low cost, availability, high reactivity, safety, and miscibility in water have garnered attention in organic chemistry synthesis processes. Because of its distinct qualities, it is utilized in green chemistry. At room temperature, the reaction between o-phenylenediamine and benzil derivatives in the presence of cerium (IV) ammonium nitrate (CAN) easily occurs in 20 minutes with no byproducts, yielding a good yield of up to 98%. It is also carried out in an aqueous media. Acetonitrile or any other aprotic solvent is combined with the CAN catalyst. The production of quinoxaline derivatives is carried out using one of the green chemistry techniques (Scheme 10) (18)

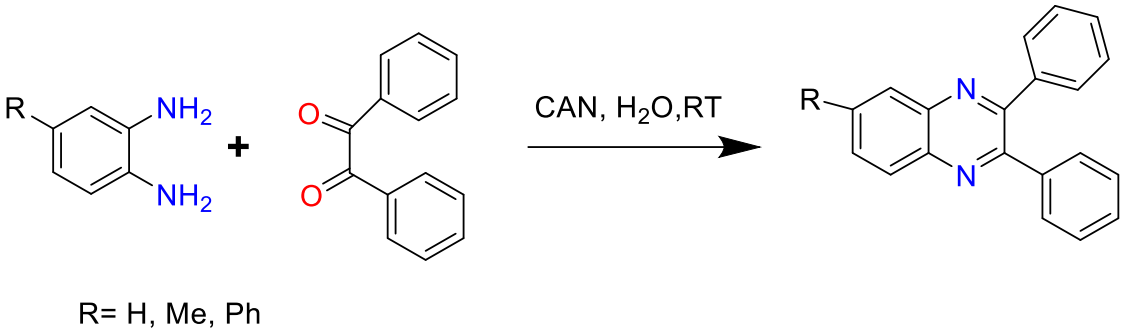


Figure 11 Scheme 10. Synthesis of quinoxaline by using lanthanide-based catalyst. Amine (1 mmol), benzyl (1 mmol), CAN (5 mol), acetonitrile, RT, 20 min, yield (80–98%)

3.0 Biological activity

Because quinoxaline and its derivatives have a wide range of biological functions and therapeutic uses, research on them has gained attention recently. Synthetic quinoxalines are found in several antibiotics, including echinomycin, levomycin, and actinomycin, which are known to suppress the growth of Gram-positive bacteria and to be effective against transplant malignancies, despite their rarity in nature(19)(20). For instance, echinomycin contains a quinoxalinyl moiety, and certain medications, such as Brimonidins, are known to reduce the symptoms of glaucoma.

3.1 Antimicrobial activity

The antimicrobial resistance is a serious threat to global public health, as a result of the widely disseminated and careless use of antimicrobials [19], and demands a continuous effort in order to seek for better antimicrobial agents, effective against resistant pathogenic microorganisms(21). There are a wide range of quinoxaline derivatives with antimicrobial activity documented(22).

3.1.1 Antibacterial activity

The substituents R and R1 in Table 1 were used to create a new series of 8-chloro-1,4-substituted[1,2,4]triazolo[4,3-a] quinoxaline derivatives (Fig. 12), which were then evaluated for antioxidant and antibacterial properties (20). Using chloramphenicol as a reference medication, the antibacterial activity was tested against Gram-negative Proteus vulgaris and Klebsiella pneumoniae, as well as Gram-positive Staphylococcus aureus and Bacillus subtilis.(22)(4). Ammar et al(23), have synthesized thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines which antibacterial activity was tested against S. aureus and Escherichia coli.

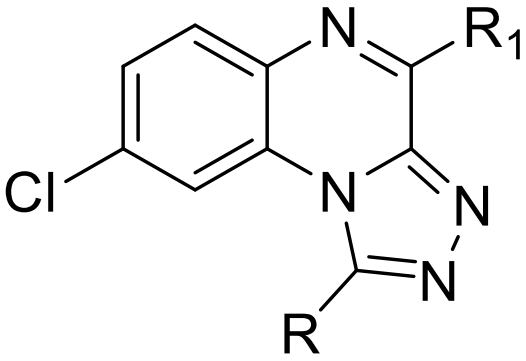


Figure 12 8-Chloro-1,4 substituted[1,2,4]triazolo[4,3-a] quinoxaline derivatives core

3.1.2 Antitubercular activity

One specific type of bacteria called Mycobacterium tuberculosis is the cause of the infectious disease known as tuberculosis (TB). The global death rate for this illness is significant. According to estimates, TB kills over 3 million

people year and causes 8 million new cases, 95% of which take place in underdeveloped nations. Nowadays, the treatment for tuberculosis involves giving one of three medications (isoniazid, rifampin, or pyrazinamide) for two months, then following up with isoniazid and rifampin for four months. However, the emergence of multidrug-resistant (MDR) tuberculosis necessitates the creation of novel treatment drugs capable of treating MDR forms, each with its own mode of action. However, the emergence of multidrug-resistant (MDR) tuberculosis necessitates the creation of novel treatment drugs capable of treating MDR strains of the illness, each with its own distinct mode of action.(24) . The synthesis and biological activity of a large number of quinoxalines and 1,4-di-Noxide quinoxaline derivatives have been examined in a number of studies. It has been demonstrated that compounds like 7-chloro3-(p-substituted)-phenylaminoquinoxaline-2-carbonitrile-1,4-diN-oxide, 6,7-dichloro-2-ethoxycarbonyl-3-methylquinoxaline-1,4-diN-oxide, and 3-acetamide-6,7-dichloroquinoxaline-2-carbonitrile-1,4-diN-oxide derivatives have growth inhibition values ranging from 99 to 100% (25). However, it has been shown that the antimycobacterial activity is lost when the two N-oxide groups are absent (26). Activity against M. tuberculosis H37Rv species was found from the synthesis of several unique condensed bridgehead nitrogen heterocycles of quinoxalines (27). In the preliminary in vitro evaluation, 3-methyl-2-phenylthioquinoxaline-1,4-dioxide showed good efficacy against M. tuberculosis and showed a Minimum Inhibitory Concentration (MIC) of 0.39 to 0.78 mg mL1 (rifampicin MIC ¼ 0.25 mg mL1)(28) . The minimum inhibitory concentration (MIC) is the antibiotic concentration that, following an overnight incubation period, prevents a microbe from growing visibly. It is generally acknowledged that the range of antibiotic concentrations used to calculate MICs is in doubling dilution steps up and down from 1 mg/L as needed (29). They introduced a new class of anti-infective drugs against MDR M. tuberculosis, which comprises 3-methyl-9-substituted-6-oxo-6,9-dihydro-3H-(1,2,3)-triazolo[4,5-h] and has no documented cytotoxicity. Esters of quinolone-carboxylic acids (30).

3.1.3. Antiviral activity

All kinds of species, including bacteria, plants, and animals, can become infected by viruses, which are tiny infectious agents that can only reproduce inside an organism's live cells(31). Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are double-stranded viruses that have a significant degree of commonality in their genome structure and DNA sequence. They are members of the Herpesviridae family (32), and share high homology in genome structure and DNA sequence. These viruses can cause labial herpes, vaginal herpes, keratitis (inflammation of the cornea), encephalitis, and other illnesses ranging from asymptomatic infection to fulminant disseminated infections. Acyclovir is the most often used medication for treating HSV infections, although there are several others, including ganciclovir, penciclovir, valaciclovir (which can be turned to acyclovir), and famciclovir (which can be converted to penciclovir)(33)(34). However, novel antiviral medications are being sought for because to the emergence and growth of drug-resistant strains of HSV (35).The varied antiviral activity of quinoxalines implies that particular substitution sequences determine its effectiveness. The compound 2,3-dimethyl(dimethylaminoethyl)-6H-indolo-[2,3-b]quinoxaline exhibited the strongest antiviral activity among the novel series of al 6H-indolo-[2,3-b]quinoxalines that were produced and tested for antiherpes virus activity. Depending on the

amount of virus, this particular compound's antiviral activity and method of action shown the ability to block the reproduction of HSV-1, CMV, and varicellaezoster virus in tissue culture at concentrations ranging from 1 to 5 mM. This specific compound was tested for its antiviral effect and action mechanism, showing the capacity to inhibit replication of HSV-1, cytomegalovirus, and varicellaezoster virus in tissue culture, in concentrations of 1-5 mM, depending on the virus amount and cell type used in the assay. Also the compound 2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo-(2,3-b) quinoxaline (Fig 13) presented high activity against HSV, and derivatives with 6-(2-dimethylaminoethyl) side chain, due to their DNA binding properties, showed an improved biological activity (36). There is also reference to IndQloquinoxalines(2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo[2,3-b]-quinoxaline) with capacity to inactivate virions in high concentrations (around 300 mM), and decrease the synthesis of viral DNA and protein at lower concentrations (around 3 mM)(4). Many clinical medications are used to combat HIV-1, the agent that causes AIDS(37), One such medication is non-nucleoside reverse transcriptase (RT) inhibitor, which interacts with a particular allosteric non-substrate binding site on HIV-1 RT. After being produced and tested for enzyme activity, compound 6-chloro-3,3-dimethyl4-isopropenyloxycarbonyl-3,4-dihydroquinoxalin-2-[1H]-thione (Fig. 14) was discovered to be a very strong inhibitor of HIV-1 replication in tissue cultures as well as HIV-1 RT activity. However, this substance did not work against HIV-2 RT, as several other nonnucleoside RT inhibitors did.

Additionally, a library of quinoxaline derivatives developed to target nonstructural protein 1 of influenza A (NS1A) was shown to disrupt the dsRNAeNS1A association to variable degrees by an in vitro fluorescence polarization experiment. This led to the development of anti-influenza medicines(38). Additionally, a library of quinoxaline derivatives developed to target nonstructural protein 1 of influenza A (NS1A) was shown to disrupt the dsRNAeNS1A association to variable degrees by an in vitro fluorescence polarization experiment. This led to the development of anti-influenza medicines. By attaching to the NS1A dsRNA-binding domain itself, these substances block NS1AedsRNA interactions rather than interfering with dsRNA. Additionally, compound 2 inhibited the development of the influenza A virus(38).

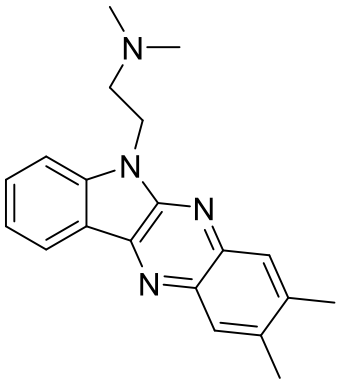


Figure 13 6-Chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-

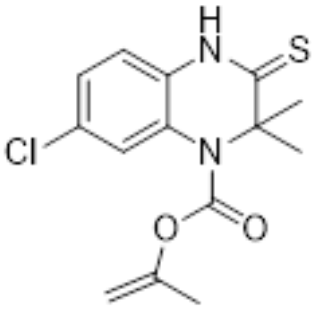


Figure 14 2,3-Dimethyl-6-(dimethylaminoethyl)-3,4-dihydroquinoxalin-2(1H)-6H-indolo-[2,3-b]quinoxaline.

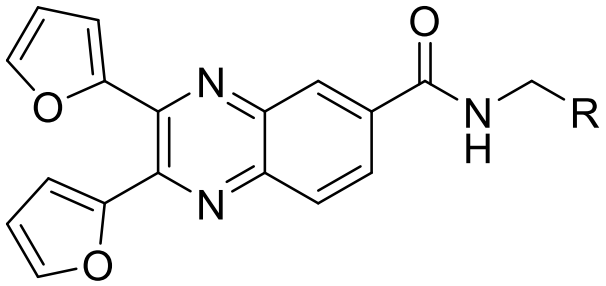


Figure 15 2,3-Difuryl-4-quinoxaline(R)metilcarboxamide derivatives.

3.1.4 Antifungal activity

Over the past 50 years, the prevalence of fungal diseases has dramatically increased. In addition to mycoses in the skin, hair, and nails, fungal illnesses can also cause systemic mycoses, the latter of which is a major medical concern because of the rise in the number of patients with weakened immune systems(39). Candida albicans, a diploid fungus that grows as both filamentous cells and yeast, is the cause of candidiasis, one of the most prevalent fungal infections. It's crucial to continuously look for novel medications and therapies because this fungus can also become resistant to antimycotic medications that are now on the market(40). After being produced and tested against Candida albicans, thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines shown antifungal efficacy(19)(41). Additionally, several 2-sulphonylquinoxalines and 3-[(alkylthio)methyl]quinoxaline-1-oxide derivatives were identified by researchers as having strong antifungal activity. Pyrazoquinoxalines were also found to be effective against fungal infections.

3.1.5 Antiprotozoan activity

3.1.5.1 Antiamoebic activity.

The protozoan Entamoeba histolytica is the cause of amoebiasis infection, which results in amoebic colitis, liver and brain abscesses, and is a major cause of death globally. Since the conventional treatment, which is based on antiamoebic substances like nitroimidazoles, is not always successful and increases the risk of drug resistance, novel compounds that can effectively combat the infection are being sought after(42). 1-[thiazole[4,5-b]quinoxaline-2-yl] comes in some The HM1:IMSS strain of E. histolytica was shown to be strongly inhibited by the derivatives of 3-phenyl-2-pyrazolines (Fig. 16), where the presence of 3-bromo or 3-chloro substituents on the phenyl ring and a 4-methyl group on the pyrazoline ring significantly impacted antiamoebic action. Although 2-cyano-3-(4-phenylpiperazine-1-carboxamido)quinoxaline 1,4-dioxide derivatives did not work against Plasmodium, they did show action against Leishmania. Compound 5 with 3-bromo and 4-methyl substitution on the pyrazoline ring and compound 6 with 3-chloro and 4-methyl substitution on the pyrazoline ring (Table 1) demonstrated great effectiveness and were the most active, presenting IC50 1.45 mM and IC50 0.72 mM, respectively. Metronidazole was used as the reference drug in this study and had a 50% inhibitory concentration of IC50 1.69e1.82 mM(4). R and R0 stand in for locations 3 and 4 in Table 1.

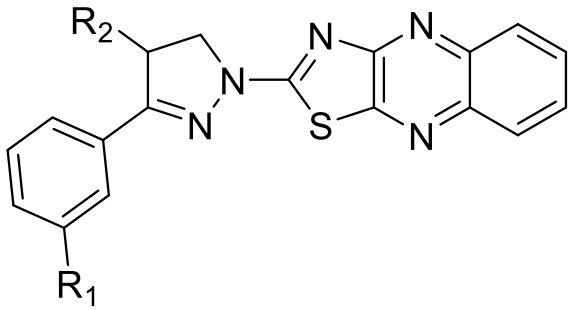


Figure 16 1-[Thiazolo[4,5-b]quinoxaline-2-yl]-3-phenyl-2-pyrazolines core

3.1.5.2 Antiparasitic activity.

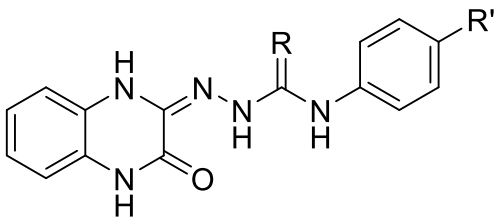
Approximately 1 to 2 million new cases of leishmaniasis are reported each year, despite all attempts to combat the parasitic disease, which is caused by the protozoan of the genus Leishmania in tropical and subtropical regions of the world(43). The majority of the medications used to treat leishmaniasis are costly, time-consuming, and increasingly ineffective. Plasmodium falciparum is the parasite that causes malaria, a tropical disease that kills over a million people a year and is likely becoming more resistant, necessitating the creation of more affordable and potent medications (44)(45). Fourteen novel compounds of 3-amino-1,4-di-N-oxide quinoxaline-2-carbonitrile were recently synthesized. The antimalarial and antileishmanial properties of these compounds were assessed in vitro against Leishmania amazonensis (strain MHOM/BR/76/LTB-012A) and P. falciparum (Colombian FCR-3 strain). As demonstrated by the study, compounds containing a single halogenous group at positions 6 and 7 offer an effective way to produce antimalarial and antileishmanial agents. It has been reported that certain quinoxaline N,N-dioxide derivatives and related chemicals limit the growth of Trypanosoma cruzi. Significant cross-correlation between the descriptors utilized (physicochemical characteristics, biological activity, and liposolubility) is demonstrated by the results, which show a structure-activity relationship(46).

3.1.6 Chronic and metabolic disease bioactivity

In addition to their antibacterial properties, quinoxaline derivatives have demonstrated a wide range of uses in the management of various chronic and metabolic illnesses, including diabetes, cancer, neurological conditions, atherosclerosis, and inflammation. The following sections will examine these circumstances.

Diabetes Diabetes

The disorder known as mellitus is brought on by a breakdown in glucose homeostasis, which results in abnormal glucose levels and a propensity for hyperglycemia. Diabetes type 2 is not insulin-dependent and can be managed with a variety of medications, including biguanides, nateglinide, and sulfonylureas. In contrast, diabetes type 1 is insulin-dependent and necessitates a daily subcutaneous injection of insulin. Nevertheless, these therapies are not very effective or tolerable, and they may have serious adverse effects. (47)(48). To this end, quinoxaline ethiosemicarbazone ligands L1H2 and L2H2 were synthesized as novel transition metal complexes (Fig. 17). In Wister rats with diabetes, the ligands were investigated using copper and zinc complexes. The complexes [CuL1 (H2O)], [ZnL1 (H2O)], and [CuL2 (H2O)] shown low toxicity and good efficacy in the oral glucose tolerance test (OGTT), while the compounds [ZnL1 (H2O)] and L 2H2 demonstrated a significant drop in blood glucose levels(48). Additionally, it has been found that N-arylcarbamoyl and N-aryl thiocarbamoyl)hydrazinequinoxalin-2-(1H) (Fig. 18) are mild hypoglycemic agents.



R= O,S
R'= H,F

Figure 17 Ligands L1H2 and L2H2. For L1H2, R ¼ CH3

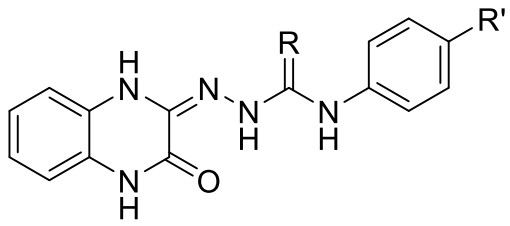
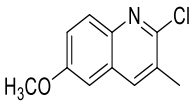
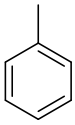


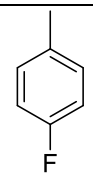
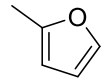
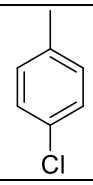
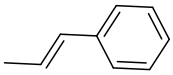
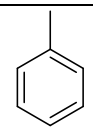
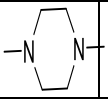
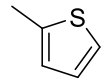
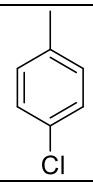
Figure 18 . (N-arylcarbamoyl and N- and for L2H2, R ¼ C6H5 arylthiocarbamoyl) hydrazinequinoxalin-2(1H).

3.1.7 Chronic inflammation

In medicine, non-steroidal anti-inflammatory medications, or NSAIDs, are frequently used to relieve pain and inflammation. However, prolonged use may result in serious adverse effects such as nephrotoxicity, hemorrhage, and gastrointestinal ulcers. The aforementioned factors make the development of new, safer anti-inflammatory medications crucial.(49). Derivatives of quinoxaline 1,4-di-N-oxide, including 4-(7-fluoro-3-methyl-quinoxalin-2-yl) -6-trimethoxy-phenyl (3,4,5-) 2,6,7-trimethyl-3-[5-(3,4,5-trimethoxy-phenyl) and pyrimidin2-ylamine The compound 4,5-dihydro-1H-pyrazol-3-yl -quinoxaline demonstrated a greater anti-inflammatory impact in vivo than one reference medication, indomethacin, and a decrease in LOX (lipoxygenase) levels in vitro. An enzyme called LOX is necessary for the metabolism of arachidonic acid (AA), which produces leukotrienes, a proinflammatory mediator implicated in conditions like fever, asthma, and cardiovascular disease.(50). Significant anti-inflammatory and analgesic effects were shown when pyrimidine, thiazolopyrimidine, pyrazolopyridine, pyridopyridine, p-chlorophenyl, p-methoxyphenyl, or pyridine nucleus were added to the quinoxaline moiety. (51). 4-Triazolo[4,3-a] and 4-Alkoxy-6,9-dichloro[1,2,4] Inhibitors of the pro-inflammatory cytokines TNF-a and IL-6, quinoxalines were also produced and their anti-inflammatory properties evaluated. The findings showed that both cytokines were efficient.

Table 1 Published experimental data (percentage of binding, intercalation, IC50 and IG50) of quinoxaline derivatives and their substituents.

Main compound	Compound	R	R'	R "	% binding at 50 mM	% intercalation at 50 mM	IC50 mM	IG50 mM	Reference
8-Chloro-1,4-substituted (1,2,4)triazolo[4,3-a] quinoxaline derivatives	1		-Cl	_	_	_	_	_	(52)
	2		-SCH_2COOH	_	_	_	_	_	

	3		-OMe	_	_	_	_	_	
	4		-SCH_2COOH	_	_	_	_	_	
	5		-Cl	_	_	_	_	_	
	6			_	_	_	_	_	
	7			_	_	_	_	_	
	8	-C_3H_7		_	_	_	_	_	
	9		-SCH_2COOH	_	_	_	_	_	
	10			_	_	_	_	_	
2,3-Difuryl-4-quinoxaline (R) metilcarboxamidederivatives	1	3-O-Me-Ph-	_	_	74.0	4.5	6.2	_	(38)
	2	2-Furyl-	-H	-	79.5	5.9	3.5	-	
1-[Thiazolo[4,5-b]cquinoxaline2-yl]-3-phenyl-2-pyrazolines derivatives	1	-H	-H	-	-	-	6.76	-	(42)
	2	-Br	-H	-	-	-	4.98	-	
	3	-Cl	-H	-	-	-	1.09	-	
	4	-H	-CH_3	-	-	-	2.34	-	
	5	-Br	-CH_3	-	-	-	1.45	-	
	6	-Cl	-CH_3	-	-	-	0.72	-	
	Metronidazole	_	_	_	_	_	1.69	_	
2-Alkylcarbonyl and 2-benzoyl3-trifluromethylquinoxal	1	-H	-H	-	-	-	-	1.02	(53)

ine-1, 4-di-N-oxide derivatives									
	2	-Cl	-Cl	-	-	-	-	0.42	
	3	-F	-F	-	-	-	-	0.52	
	4	-F	-F	-	-	-	-	0.15	
	5	-H	-H	-	-	-	-	0.49	
6-Arylamino-2,3-bis(pyridin2-yl)-7-chloro-quinoxaline 5,8-dione	1	-H	-Cl	-H	-	-	1.5	-	(54)
	2	-H	-OH	-H	-	-	5.5	-	
	3	-H	-F	-H	-	-	1.0	-	
	4	-H	$-CF_3$	-H	-	-	1.1	-	
	5	-H	$-C0F_3$	-H	-	-	1.0	-	
	6	-H	$-COH_3$	-H	-	-	3.5	-	
	7	-H	-H	-H	-	-	3.1	-	
	8	-Cl	-Cl	-H	-	-	1.0	-	
	9	-F	-F	-F	-	-	1.2	-	
	10	-	-	-	-	-	>100	-	
	MPA	-	-	-	-	-	1.0	-	

3.1.8 Cancer

Quinoxaline nucleuses are a key building block for anticancer medications because they may have anticancer properties. The in vitro antitumor activity of a novel series of 2-alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1,4-di-N-oxide derivatives was assessed against a panel of three cell lines (MCF7 (breast), NCIH 460 (lung), and SF-268 (CNS)), and subsequently assessed in a full panel of sixty human tumor cell lines, which were derived from nine cancer cell types. It was demonstrated that the substituents in the carbonyl group generally determine the anticancer action, with ethyl < isopropyl < tertbutyl < phenyl-ones having the highest activity. These chemicals include (Fig. 19). Secondly, 3-methylbut-1-en-2-yl Compound 1, Compound 2, 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-N-oxide, 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), and 2-(2,2-dimethylpropanoyl)-3-trifluoromethylquinoxaline 1,4-di-N-oxide (Compound 5) were the most active and had the strongest anticancer activity (Table 1).(4)(46). The possible substituents of these compounds are presented in Table 1, represented by R and R'.

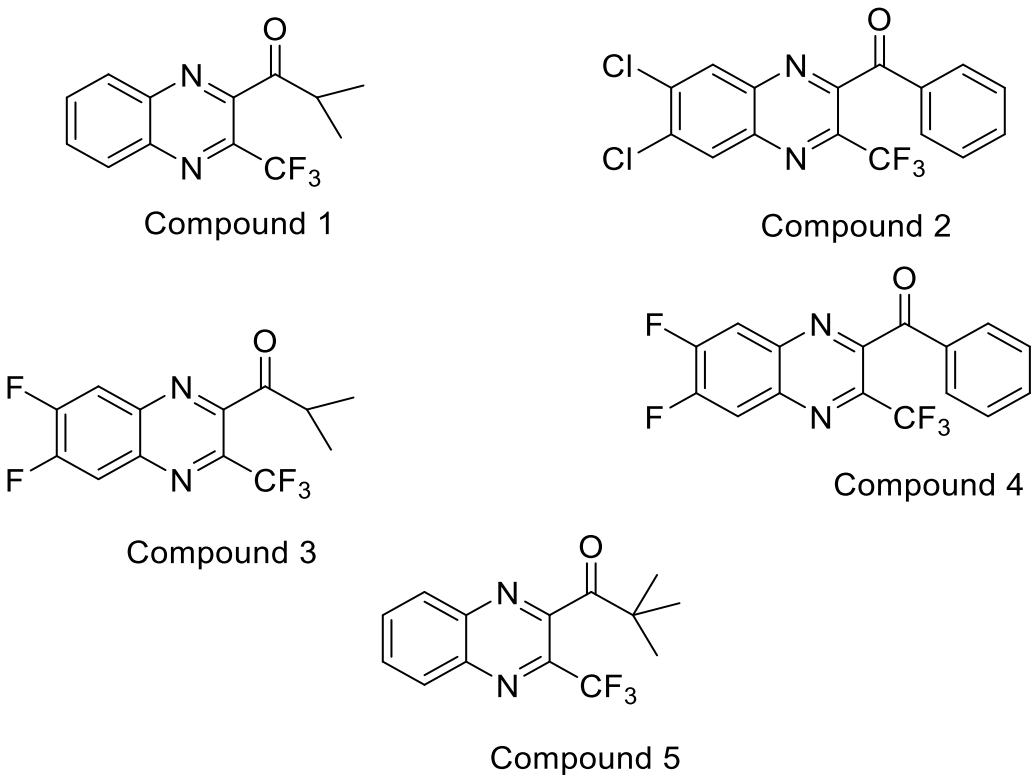


Figure 19 Compounds 1-5

3.1.9 Glaucoma

Glaucoma is the term used to describe conditions that impact the optic nerve, including nerve head excavations and the loss of retinal ganglion cells in a pattern typical of optic neuropathy (51). Glaucoma, which accounts for 8% of blindness after cataracts, affects almost 67 million people globally and is still one of the causes of permanent blindness. An alpha-2 adrenergic receptor agonist that is moderately selective, Alphagan® (Brimonidin) is made up of 5-bromo-N- (4,5-dihydro-1H-imidazol-2-yl)-6-quinoxaline (Fig. 20). Because it can lower intraocular pressure, this medication acts as an antiglaucoma agent, reducing glaucoma symptoms(4).

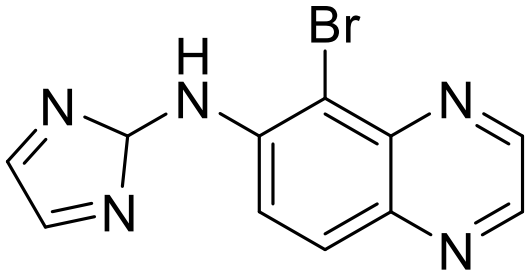


Figure 20 Alphagan chemical structure

3.1.10 Atherosclerosis

In the United States, Europe, and Japan, atherosclerosis is the leading cause of heart attacks, strokes, and gangrene of the extremities, accounting for half of all deaths (55). Following artery damage, vascular smooth cells (SMCs) migrate and proliferate abnormally into the arterial wall's intimal layer, producing extracellular matrix components and contributing significantly to coronary artery atherosclerosis and restenosis following an angioplasty. (56). We produced and tested a variety of 6-arylamino-2,3-bis(pyridin-2-

yl)-7-choloroquinoxaline-5,8-diones (Fig. 21) for their ability to suppress the proliferation of rat aortic smooth muscle cells (RAoSMCs). In Table 1, the letters R, R0, and R00 stand for potential substituents of this molecule. The majority of the compounds shown good action, and the quinoxaline-5,8-diones were discovered to be strong antiproliferative agents when IC50 (Inhibition Concentration) values were calculated and compared to the positive control mycophenolic acid (MPA) (Table 1)(57) .

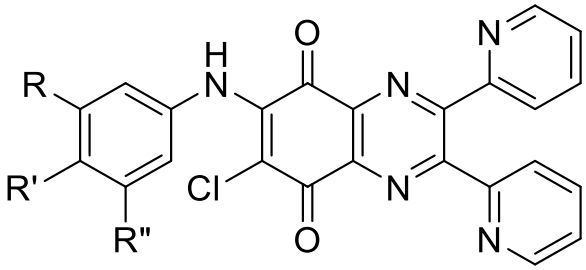


Figure 21 6-Arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8-diones.

3.1.11 Anti glutameric activity

One of the main excitatory neurotransmitters in the central nervous system of mammals is glutamate, an excitatory amino acid (EAA). However, excessive EAA release may cause postsynaptic glutamate receptors to become overstimulated, which could lead to neuronal death and, in turn, neurodegenerative diseases like Alzheimer's and Huntington's.(58)(59) . Numerous quinoxalinedione derivatives with competitive AMPA-R antagonistic activity have been synthesized and tested against the EAA receptor. AMPA-R (a-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor) antagonists have demonstrated protective activity against neural death and no adverse effects, including schizophrenia(60). 7-[[4-[N-[4-carboxyphenyl]carbamoyloxy] methyl]imidazolyl] is the chemical Because of its strong neuroprotective effects in an animal model in vivo and its high potency and good selectivity in vitro, -3,4-dihydro-6-nitro-3-oxo-quinoxaline-2-carboxylic acid (GRA-293) was recognized as a novel AMPA-R antagonist. Its potency was greater than that of the known quinoxalinedione compounds. These effects are caused by a new substituent at the C-7 position of imidazole, namely a substituted benzene ring with urethane linkage, which has a strong AMPA-R affinity and aids in the effectiveness of treatment in animal models. Because of these qualities, this substance satisfies the requirements for usage in an injectable formulation to treat acute cerebral ischemia.(60).

3.1.12 Neurological

The neurotransmitter 5-hydroxytryptamine (5HT), also referred to as serotonin, acts through the receptor subtypes 5-HT1 through 5-HT7 and is involved in a wide range of physiological and pathophysiological activities. The G-protein coupled receptor (GPCR) family includes nearly all of the receptor subtypes, although the particular receptor subtype 5HT3 is a ligand-gated ion channel.(61). Antibodies to this receptor cause a variety of reactions, including anti-inflammatory, anti-depressant, anxiolytic, anti-psychotic, and anti-emetic effects in cancer patients who experience nausea and vomiting from chemotherapy or radiation therapy. However, the delayed beginning of effect of the medications currently available to treat depression problems highlights the need for novel antidepressant medications with a quicker and safer onset of action.(62). A new class of 3-substituted-2-carboxamides with unique structures Quinoxaline was created utilizing a ligand-based strategy to function as a 5-HT3 receptor antagonist. Every synthetic molecule demonstrated 5-HT3 receptor antagonism, and several, such as [3-ethoxyquinoxalin-2-yl], demonstrated antagonism stronger than that of the common medication,

ondansetron. [1-yl 4-methylpiperazin] N-[2-(1H-indol-3-yl)ethyl] and -methanone 2-carboxamide-3-ethoxyquinoxaline(62). Additionally, 3-benzyl-2-substituted quinoxalines were created as brand-new inhibitors of monoamine oxidase A (MAO-A). A number of neurological conditions, including depression and Parkinson's disease, can be effectively treated with MAO inhibitors. MAO-A inhibitors are used to treat anxiety and depression. Using serotonin as a substrate, the resulting compounds' MAO-A inhibitory activity was assessed in vitro (63).

2. CONCLUSIONS

According to the literature review, quinoxaline and its derivatives are a significant class of biologically active chemicals with a wide range of potential uses. The biological effects of quinoxaline and its derivatives, which include antibacterial, antidiabetic, antiproliferative, anti-inflammatory, anticancer, antiglaucoma, antidepressant, and AMPA-R antagonist action, have demonstrated a broad range of applications in medicine. For the researchers and chemists, the biological activities mentioned are highly encouraging since they will result in novel medicinal agents and therapies that will advance humankind.

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