Quinoxaline, its derivatives and applications: A State of the Art review

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A B S T R A C T

Quinoxaline derivatives are an important class of heterocycle compounds, where N replaces some carbon atoms in the ring of naphthalene. Its molecular formula is $C_8H_6N_2$, formed by the fusion of two aromatic rings, benzene and pyrazine. It is rare in natural state, but their synthesis is easy to perform.

In this review the State of the Art will be presented, which includes a summary of the progress made over the past years in the knowledge of the structure and mechanism of the quinoxaline and quinoxaline derivatives, associated medical and biomedical value as well as industrial value.

Modifying quinoxaline structure it is possible to obtain a wide variety of biomedical applications, namely antimicrobial activities and chronic and metabolic diseases treatment.

Keywords: Quinoxaline Quinoxaline derivatives Biological activity Therapeutic application Biomedical applications

1. Introduction

Quinoxaline derivatives are an important class of heterocyclic compounds, in which N replaces one or more carbon atoms of the naphthalene ring [1]. The approved location for the quinoxaline ring system is shown in Fig. 1, where 2 and 3 are designated α-positions [2]. They are important in industry due to their ability to inhibit the metal corrosion [3–5], in the preparation of the porphyrins, since their structure is similar to the chromophores in the natural system, and also in the electroluminescent materials [6]. In pharmacological industry, they have absorbed a great deal of attention due to their wide spectrum of biological properties [1,7–10]. For example, they can be used against bacteria, fungi, virus, leishmania, tuberculosis, malaria, cancer, depression, and neurological activities, among others. The quinoxaline structural nucleus renders all these activities possible. Quinoxaline structure acts as a precursor to assembly a large number of new compounds for diverse applications [1].

Quinoxaline is formed by the fusion of two aromatic rings, benzene and pyrazine. For this reason is also called benzopyrazine, and is described as a bioisoster of quinoline, naphthalene and benzothiophene [11]. The atoms S and N play an important role in the ring since they stabilize ion radical species. Molecular weight of the quinoxaline is 130.15, with a molecular formula of $C_8H_6N_2$, and it is a white crystalline powder, at standard conditions [1].

Chemically, quinoxaline is a low melting solid, purified by distillation, and a fraction of boiling point 108°–111°/12 mm has a melting point 29–30 °C [2,11]. Quinoxalines are soluble in water, and produces monoquaternary salts when treated with quaternizing agents, like dimethyl sulfate and methyl *p*-toluene sulphonate. The quaternary salts of 2-alkylquinoxalines are unstable and converted into complex colored products by oxidation [2]. It is acidic with a pKa of 0.60 in water at 20 °C, and nitration occurs only under forcing conditions (Conc. HNO_3, Oleum, 90 °C), resulting in the formation of two compounds: 5-nitroquinoxaline (1.5%) and 5,7-dinitro-quinoxaline (24%) [11]. Its second pKa is −5.52 indicating that quinoxaline is significantly diprotonated in a strongly acidic medium [2].

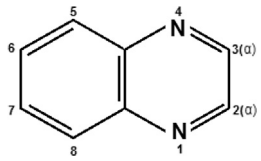


Fig. 1. Quinoxaline.

Quinoxaline has a dipole moment of 0.51 Debye, and their first and second ionization potentials, measured by photon electron spectroscopy, are 8.99 and 10.72 eV, respectively [2]. However, it is not clear that the first electron is lost from which orbital, since highest-occupied π-orbital and non-bonding orbitals are very close in energy. The heat of aromatization was calculated to be 79.739 eV using a self-consistent field molecular orbital treatment [2]. The molecular orbital calculations of the π electron density showed that the higher the electron density on the carbon ring is in positions 5 and 8, followed by the C-6 and C-7 positions, and the lower C-2 and C-3 positions. [2].

Most of quinoxaline derivatives are synthetic and natural quinoxaline derivatives are rare [12], such as echinomycin and triostin-A. The common procedure for their synthesis consists of condensing *o*-disubstituted benzene with a two carbon synthon. Therefore, the condensation of *o*-phenylenediamine with α-dicarbonyl compounds results in quinoxaline formation (Fig. 2) [2].

Numerous methods are available for the synthesis of quinoxaline derivatives which involve condensation of 1,2-diamines with α-diketones [13], 1,4-addition of 1,2-diamines to diazenylbutenes [14], cyclization—oxidation of phenacyl bromides [15] and oxidative coupling of epoxides with ene-1,2-diamines [16]. Recent research groups have presented reports concerning the synthesis of different quinoxaline derivatives involving several green methodologies, including recyclable catalysts, microwave-assisted synthesis and reactions in aqueous medium [17].

Quinoxaline and its derivatives could be converted in both mono and di-*N*-oxides by oxidation with peracids [2].

2. Biological activity

The study of quinoxaline and its derivatives has become a subject of interest in recent years due to their wide variety of biological activities as well as therapeutic applications. Since they are rare in nature, synthetic quinoxalines are included in various antibiotics such as echinomycin, levomycin and actinomycin, well-known to inhibit the growth of Gram-positive bacteria and are also active against transplant tumors [11,18].Echinomycin, for example have quinoxalinyl moiety in their structure and also some known drugs, like Brimonidins, alleviates glaucoma symptoms [1].

The vast scope of synthesized quinoxaline and derivatives potential is well referenced and published in a wide range of scientific journals. Scientific data concerning the potential relevance of quinoxaline and derivatives in the literature were analyzed.

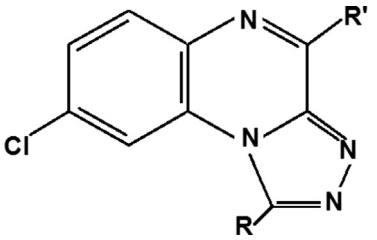


Fig. 3. 8-Chloro-1,4-substituted[1,2,4]triazolo[4,3-*a*] quinoxaline derivatives core.

2.1. 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 [11,20–22]. There are a wide range of quinoxaline derivatives with antimicrobial activity documented [22].

2.1.1. Antibacterial activity

A new series of 8-chloro-1,4-substituted[1,2,4]triazolo[4,3-*a*] quinoxaline derivatives (Fig. 3), being the substituents R and R′ listed in Table 1, was synthesized and screened for antimicrobial and antioxidant activities [23]. The antibacterial activity was screened against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative *Proteus vulgaris* and *Klebsiella pneumoniae*, using chloramphenicol as reference drug [21].

Ammar et al [24], have synthesized thieno[2,3-*d*]pyrimidines and pyrrolo[3,4-*b*]quinoxalines which antibacterial activity was tested against *S. aureus* and *Escherichia coli*.

2.1.2. Antitubercular activity

Mycobacterium is a particular bacteria that is responsible for a contagious disease, an infection called Tuberculosis (TB), caused by *Mycobacterium tuberculosis*. This disease has a high rate of mortality in the world. About 3 million people die every year from TB, and 8 million new cases are estimated each year, which 95% of them occur in developing countries [25].

The therapy used in these days to fight TB consists in the administration of one of three drugs (isoniazid, rifampin or pyrazinamide) for 2 months, followed by 4 months of follow-up therapy with isoniazid and rifampin. However, due to the arising of multidrug resistant (MDR) TB it is required the development of new therapeutic agents, with a unique mechanism of action, able to treat MDR forms of the disease [26].

Several studies have been described, concerning synthesis and biological activity of a large amount of quinoxalines and 1,4-di-*N*-oxide quinoxaline derivatives, where compounds such as 7-chloro-3-(*p*-substituted)-phenylaminoquinoxaline-2-carbonitrile-1,4-di-*N*-oxide, 6,7-dichloro-2-ethoxycarbonyl-3-methylquinoxaline-1,4-di-*N*-oxide and 3-acetamide-6,7-dichloroquinoxaline-2-carbonitrile-1,4-di-*N*-oxide derivatives have been shown to

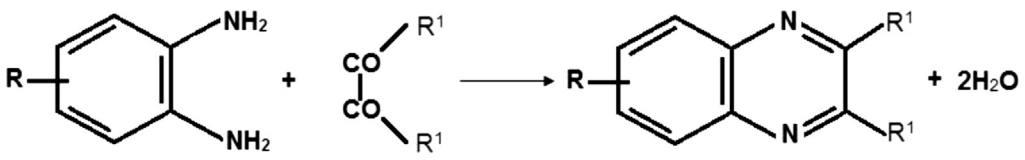


Fig. 2. Quinoxaline synthesis.

possess *M. tuberculosis* growth inhibition values from 99 to 100% [21,27]. However, it is observed that the lack of the two *N*-oxide groups lead to the loss of the *antimycobacterial activity* [27,28].

Some novel condensed bridgehead nitrogen heterocycles of quinoxalines have been synthesized and activity against *M. tuberculosis* $H_{37}Rv$ species was obtained [11,21,29]. The compound 3-methyl-2-phenylthioquinoxaline-1,4-dioxide generally presented a good activity against *M. tuberculosis* in the preliminary *in vitro* evaluation and exhibited *Minimum Inhibitory Concentration* (MIC) between 0.39 and 0.78 μg mL^{-1} (rifampicin MIC = 0.25 μg mL^{-1}) [7]. The MIC is defined as the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation. The range of antibiotic concentrations used for determining MICs is universally accepted to be in doubling dilution steps up and down from 1 mg/L as necessary [30].

A new class of anti-infective agents against MDR *M. tuberculosis*, with no cytotoxicity reported was presented and includes 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-(1,2,3)-triazolo[4,5-*h*] quinolone-carboxylic acids and their esters [31].

2.1.3. Antiviral activity

Viruses are small infectious agents that replicate only inside the living cells of an organism and can infect all types of organisms, from animals and plants to bacteria [32].

Viruses such as Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the *Herpesviridae* family, are double-stranded DNA [33], and share high homology in genome structure and DNA sequence. These viruses can cause various illnesses states from asymptomatic infection to fulminant disseminated diseases, including labials herpes, keratitis (cornea inflammation), genital herpes, and encephalitis [34].

There are a wide number of drugs for treatment of HSV infections like acyclovir, ganciclovir, penciclovir, valaciclovir (converted to acyclovir) and famciclovir (converted to penciclovir) [33,35], being acyclovir the most common drug used. However, there are drug-resistant strains of HSV emerging and increasing [33,36], leading to the search of new antiviral drugs.

Quinoxalines have a variable antiviral activity, suggesting that their activity depends on specific substitution patterns. Novel series of al 6*H*-indolo-[2,3-*b*]quinoxalines were synthesized and evaluated for antiherpes virus activity and the compound 2,3-dimethyl(dimethylaminoethyl)-6*H*-indolo-[2,3-*b*]quinoxaline had the major antiviral activity. This specific compound was tested for its antiviral effect and action mechanism, showing the capacity to inhibit replication of HSV-1, cytomegalovirus, and varicella–zoster virus in tissue culture, in concentrations of 1–5 μM, depending on the virus amount and cell type used in the assay. Also the compound 2,3-dimethyl-6-(dimethylaminoethyl)-6*H*-indolo-(2,3-*b*) quinoxaline (Fig. 4) presented high activity against HSV, and derivatives with 6-(2-dimethylaminoethyl) side chain, due to their DNA binding properties, showed an improved biological activity [1].

There is also reference to IndQloquinoxalines(2,3-dimethyl-6-(dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline) with capacity to inactivate virions in high concentrations (around 300 μM), and decrease the synthesis of viral DNA and protein at lower concentrations (around 3 μM) [21].

Concerning human immunodeficiency virus type 1 (HIV-1), which is the agent causative of acquired immunodeficiency syndrome (AIDS) [37], there are a wide number of clinical drugs used to fight the disease, such as non-nucleoside reverse transcriptase (RT) inhibitors, which interact with a specific allosteric non-substrate binding site on HIV-1 RT [11]. Compound 6-chloro-3,3-dimethyl-4-isopropenyloxycarbonyl-3,4-dihydroquinoxalin-2-[1*H*]-thione (Fig. 5) was synthesized and evaluated for enzyme activity, and was found to be a very potent inhibitor for both HIV-1 RT activity and HIV-1 replication in tissue cultures. Although, like some other non-nucleoside RT inhibitors, this compound was not effective against human immunodeficiency virus type 2 (HIV-2 RT) [21].

Also, an *in vitro* fluorescence polarization assay demonstrated that a library of quinoxaline derivatives, prepared to target non-structural protein 1 of influenza A (NS1A), disrupted the dsRNA–NS1A interaction to varying extents, which lead to the development of anti-influenza drugs [38].

In this study, investigators have prepared a library based on 2,3-difuryl-4-quinoxaline-**R-**metilcarboxamide derivatives (Fig. 6), with 2-furyl groups at position 2 and 3 and phenyl group in position 6 through an amide linker. Among all the compounds in the library, compounds listed in Table 1 have shown the highest effectiveness, being the R the possible substituents. These compounds do not inhibit NS1A–dsRNA interactions by interfering with dsRNA but by the binding to NS1A dsRNA-binding domain itself. Also, the compound 2 was able to inhibit influenza A virus growth [38].

2.1.4. Antifungal activity

Prevalence of fungal diseases has increased significantly in the past 50 years. Fungal diseases manifest themselves differently, including mycoses in the skin, hair, nails, but also as systemic mycoses, being the last one an issue of great medical concern due to the increase in the immunocompromised patient population [39].

One of the most common fungal infections is candidiasis, caused by *Candida albicans*, a diploid fungus that grows both as yeast and filamentous cells [40]. This fungus can also develop resistance to antimycotic drugs that already exist in the market [41], being important a constant search for new drugs and treatments.

Thieno[2,3-*d*]pyrimidines and pyrrolo[3,4-*b*]quinoxalines were synthesized and tested against *C. albicans*, and presented antifungal activity [11,24].

Researchers also reported some 2-sulphonylquinoxalines and 3-[(alkylthio)methyl]quinoxaline-1-oxide derivatives as compounds with high antifungal activity [7], and also pyrazoloquinoxalines which were observed to be active against fungal infections [1].

2.1.5. Antiprotozoan activity

2.1.5.1. Antiamoebic activity. Entamoeba histolytica is a protozoan responsible for the amoebiasis infection [42], causing amoebic colitis, brain and liver abscess, being an important leading cause of death worldwide. The traditional treatment used is based in antiamoebic compounds such as nitroimidazoles, but not always effective, raising the possibility of drug resistance, leading to the search of new compounds able to fight the infection successfully [43].

Some 1-[thiazole[4,5-*b*]quinoxaline-2-yl]-3-phenyl-2-pyrazolines derivatives produced (Fig. 7), were found to be a potent inhibitor of HM1:IMSS strain of *E. histolytica*, where the presence of 3-bromo or 3-chloro substituents on the phenyl ring and 4-methyl group on the pyrazoline ring affected antiamoebic activity to a great extent [43].

2-Cyano-3-(4-phenylpiperazine-1-carboxamido)quinoxaline 1,4-dioxide derivatives have also presented activity against Leishmania, but were not effective against *Plasmodium* [44].

In such study metronidazole was used as the reference drug and had a 50% inhibitory concentration of IC_{50} 1.69–1.82 μM, and compound 5 with 3-bromo and 4-methyl substitution, and compound 6 with 3-chloro and 4-methyl substitution on pyrazoline ring (Table 1), showed great effectiveness, being the most actives, presenting IC_{50} 1.45 μM and IC_{50} 0.72 μM, respectively [43]. In Table 1, the positions 3 and 4 are represented by R and R′.

Table 1
Published experimental data (percentage of binding, intercalation, IC_{50} and IG_{50}) of quinoxaline derivatives and their substituents.

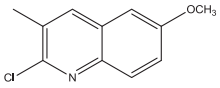
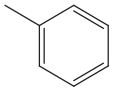
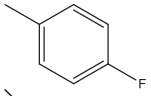
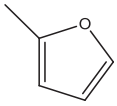
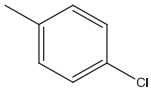
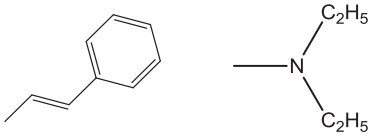
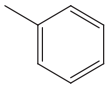
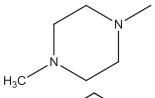
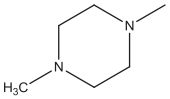
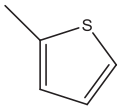
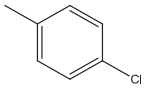
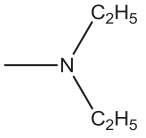
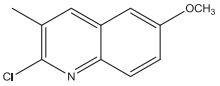
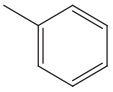
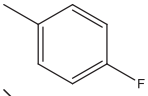
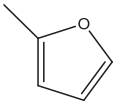
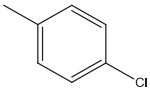
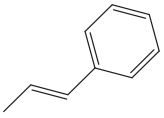
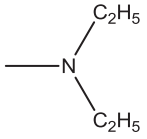
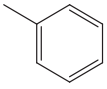
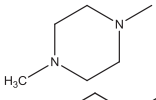
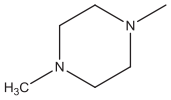
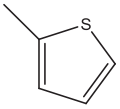
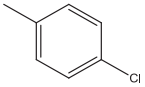
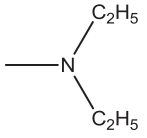
Main compound	Compound	R	R′	R″	% binding at 50 μM	% intercalation at 50 μM	IC_{50} μM	IG_{50} μM	Reference
8-Chloro-1,4-substituted (1,2,4)triazolo[4,3-*a*] quinoxaline derivatives	1		–Cl	–	–	–	–	–	21
	2		$-SCH_2COOH$	–	–	–	–	–	
	3		–OMe	–	–	–	–	–	
	4		$-SCH_2COOH$	–	–	–	–	–	
	5		–Cl	–	–	–	–	–	
	6			–	–	–	–	–	
	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-	–	–	79.5	5.9	3.5	–	
1-[Thiazolo[4,5-*b*]cquinoxaline-2-yl]-3-phenyl-2-pyrazolines derivatives	1	H–	H–	–	–	–	6.76	–	43
	2	Br–	H–	–	–	–	4.98	–	
	3	Cl–	H–	–	–	–	1.09	–	
	4	H–	H_3C–	–	–	–	2.34	–	
	5	Br–	H_3C–	–	–	–	1.45	–	
	6	Cl–	H_3C–	–	–	–	0.72	–	
	Metronidazole	–	–	–	–	–	1.69	–	
2-Alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1, 4-di-*N*-oxide derivatives	1	H–	H–	–	–	–	–	1.02	8
	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(pyridin-2-yl)-7-chloro-quinoxaline 5,8-diones	**1**	H–	Cl–	H–	–	–	1.5	–	58
	2	H–	HO–	H–	–	–	5.5	–	
	3	H–	F–	H–	–	–	1.0	–	
	4	H–	F_3C–	H–	–	–	1.1	–	
	5	H–	F_3CO–	H–	–	–	1.0	–	
	6	H–	H_3CO–	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	–	

Table 1 (*continued*)

Main compound	Compound	R	R′	R″	% binding at 50 μM	% intercalation at 50 μM	IC_{50} μM	IG_{50} μM	Reference
8-Chloro-1,4-substituted(1,2,4) triazolo[4,3-*a*] quinoxaline derivatives	1		−Cl	–	–	–	–	–	20
	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	–	35
	2	2-Furyl-	–	–	79.5	5.9	3.5	–	
1-[Thiazolo[4,5-*b*]cquinoxaline-2-yl]-3-phenyl-2-pyrazolines derivatives	1	H–	H–	–	–	–	6.76	–	40
	2	Br–	H–	–	–	–	4.98	–	
	3	Cl–	H–	–	–	–	1.09	–	
	4	H–	H_3C–	–	–	–	2.34	–	
	5	Br–	H_3C–	–	–	–	1.45	–	
	6	Cl–	H_3C–	–	–	–	0.72	–	
	Metronidazole	–	–	–	–	–	1.69	–	
2-Alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1, 4-di-*N*-oxide derivatives	1	H–	H–	–	–	–	–	1.02	8
	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(pyridin-2-yl)-7-chloro-quinoxaline 5,8-diones	**1**	H–	Cl–	H–	–	–	1.5	–	54
	2	H–	HO–	H–	–	–	5.5	–	
	3	H–	F–	H–	–	–	1.0	–	
	4	H–	F_3C–	H–	–	–	1.1	–	
	5	H–	F_3CO–	H–	–	–	1.0	–	
	6	–	H_3CO–	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	–	

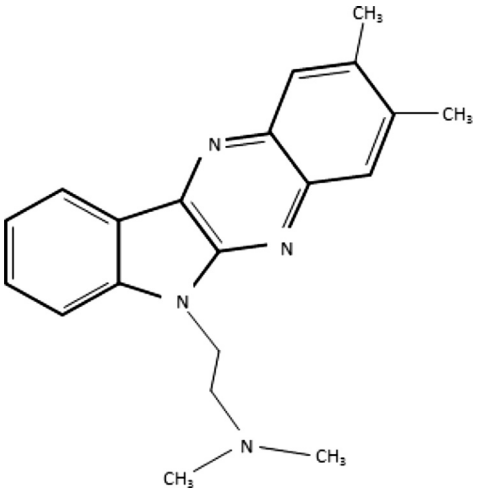


Fig. 4. 2,3-Dimethyl-6-(dimethylaminoethyl)-6*H*-indolo-[2,3-*b*]quinoxaline.

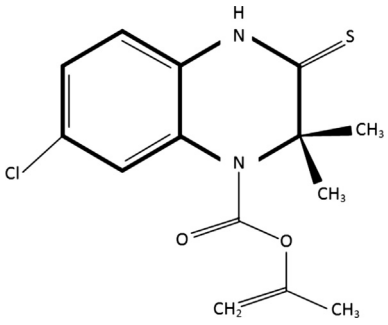


Fig. 5. 6-Chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-3,4-dihydroquinoxalin-2(*1H*)-thione.

2.1.5.2. Antiparasitic activity. Leishmaniasis is a parasitic disease cause by protozoan of the genus *Leishmania* in tropical and subtropical areas of the World, and despite all efforts to fight this disease about 1–2 million new cases are registered every year [21,45]. Most of the drugs available against leishmaniasis are expensive and require a long treatment and are becoming more and more ineffective [9].

Malaria is also a tropical parasitic disease, cause by *Plasmodium falciparum*, leading to over a million deaths annually, and rising, probably due to a resistance increasing, requiring the development of cheaper and more effective drugs [46,9,47].

Recently, 14 new 3-amino-1,4-di-*N*-oxide quinoxaline-2-carbonitrile derivatives were synthesized. These compounds were evaluated for their *in vitro* antimalarial and antileishmanial activity

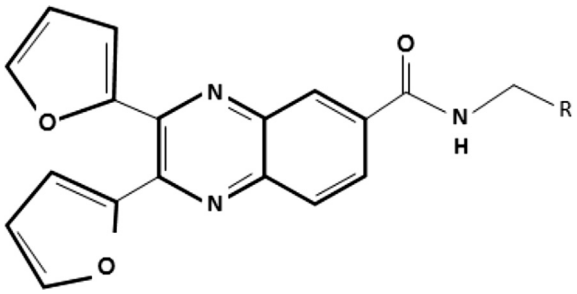


Fig. 6. 2,3-Difuryl-4-quinoxaline(R)metilcarboxamide derivatives.

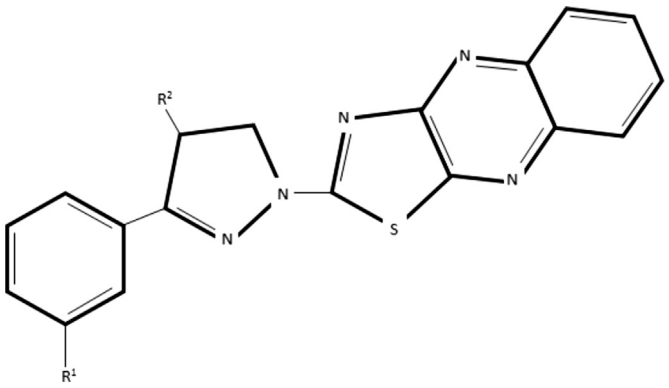


Fig. 7. 1-[Thiazolo[4,5-*b*]quinoxaline-2-yl]-3-phenyl-2-pyrazolines core.

against *P. falciparum* (Colombian FCR-3 strain) and *Leishmania amazonensis* (strain MHOM/BR/76/LTB-012A). The study showed that compounds with one halogenous group in position 6 and 7 provide an efficient approach for further development of antimalarial and antileishmanial agent.

Growth inhibition of some quinoxaline *N,N*-dioxide derivatives and related compounds against *Trypanosoma cruzi* was reported. Results evidence a structure-activity relationship, expressing important cross-correlation between the descriptors used (physicochemical properties, biological activity and liposolubility) [48].

2.2. Chronic and metabolic disease bioactivity

Besides antimicrobial activity, quinoxaline derivatives have shown innumerous applications regarding the treatment of several chronic and metabolic diseases, such as cancer, diabetes, neurological disorders, atherosclerosis and inflammation. These conditions will be explored in the next sections.

2.2.1. Diabetes

Diabetes Mellitus is a disease caused by the dysfunction of glucose homeostasis, in which glucose levels appear abnormal with tendency to hyperglycemia. Diabetes type 1 is insulin-dependent and requires a daily subcutaneous injection of insulin, while diabetes type 2 is non-insulin-dependent and can be treated with several drugs such as sulfonylureas, nateglinide, and biguanides, among others [10,49]. However these treatments have limited efficacy and tolerability, and could cause severe side effects [49]. In this regard, new transition metal complexes of quinoxaline–thiosemicarbazone ligands L^1H_2 and L^2H_2 (Fig. 8) were prepared. The ligands were explored with copper and zinc complexes in diabetes induced Wister rats. The compounds $[ZnL^1(H_2O)]$ and L^2H_2 have showed prominent reduction in blood glucose level and

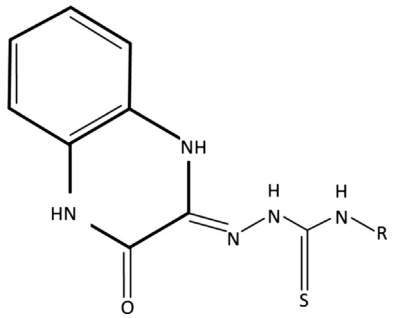


Fig. 8. Ligands L^1H_2 and L^2H_2. For L^1H_2, R = CH_3 and for L^2H_2, R = C_6H_5.

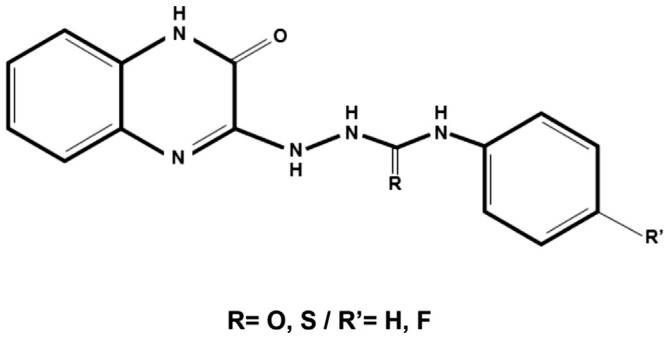


Fig. 9. (N-arylcarbamoyl and N-arylthiocarbamoyl) hydrazinequinoxalin-2(1*H*).

the complexes $[CuL^1(H_2O)]$, $[ZnL^1(H_2O)]$ and $[CuL^2(H_2O)]$ have exhibited good activity in oral glucose tolerance test (OGTT) and showed low toxicity [10].

Also (*N*-arylcarbamoyl and *N*-aryl thiocarbamoyl)hydrazinequinoxalin-2-(1*H*) (Fig. 9) have been reported as mild hypoglycaemic agents [1].

2.2.2. Chronic inflammation

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in therapeutics, generally for the treatment of the pain and inflammation. Nevertheless its long-term usage can lead to significant side effects like gastrointestinal lesions, bleeding, and nephrotoxicity. Due to the reasons mentioned it is important the discovery of new safer anti-inflammatory drugs [50,51].

Quinoxaline 1,4-di-*N*-oxide derivatives such as 4-(7-fluoro-3-methyl-quinoxalin-2-yl)-6-(3,4,5-trimethoxy-phenyl)-pyrimidin-2-ylamine and 2,6,7-trimethyl-3-[5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-quinoxaline, showed an *in vivo* anti-inflammatory effect, higher than one reference drug, IMA (indomethacin), and *in vitro* decreasing values of LOX (lipoxygenase). LOX is an enzyme essential to arachidonic acid (AA) metabolism, which leads to the formation of leukotrienes, a type of pro-inflammatory mediator involved in processes like fever, asthma and cardiovascular disease [52]. It was demonstrated that the incorporation of pyrimidine, thiazolopyrimidine, pyrazolopyridine, pyridopyridine, *p*-chlorophenyl, *p*-methoxyphenyl or pyridine nucleus to quinoxaline moiety cause significant anti-inflammatory activity, and also analgesic [50].

4-Alkoxy-6,9-dichloro[1,2,4]triazolo[4,3-*a*]quinoxalines were also synthesized and anti-inflammatory activity was tested as inhibitors of the pro-inflammatory cytokines TNF-α and IL-6 [53]. Results revealed efficiency in both cytokines was demonstrated.

2.2.3. Cancer

Quinoxaline nucleuses exhibit potential anticancer activity, which makes them an important basis for the anticancer drugs [21]. A new series of 2-alkylcarbonyl and 2-benzoyl-3-trifluromethylquinoxaline-1,4-di-*N*-oxide derivatives was 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. It was showed that, in general, anticancer activity depends on the substituents in the carbonyl group, increasing the activity in the order: ethyl < isopropyl < *tert*-butyl < phenyl-ones. Among these the compounds (Fig. 10) 2-(3-methylbut-1-en-2-yl)-3-(trifluoromethyl)quinoxaline-1,4-di-*N*-oxide (Compound 1), 2-benzoyl-6,7-dichloro-3-trifluoromethyl-quinoxaline 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-trifluoromethyl-quinoxaline 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 μM, respectively (Table 1) [8,21]. The possible substituents of these compounds are presented in Table 1, represented by R and R′.

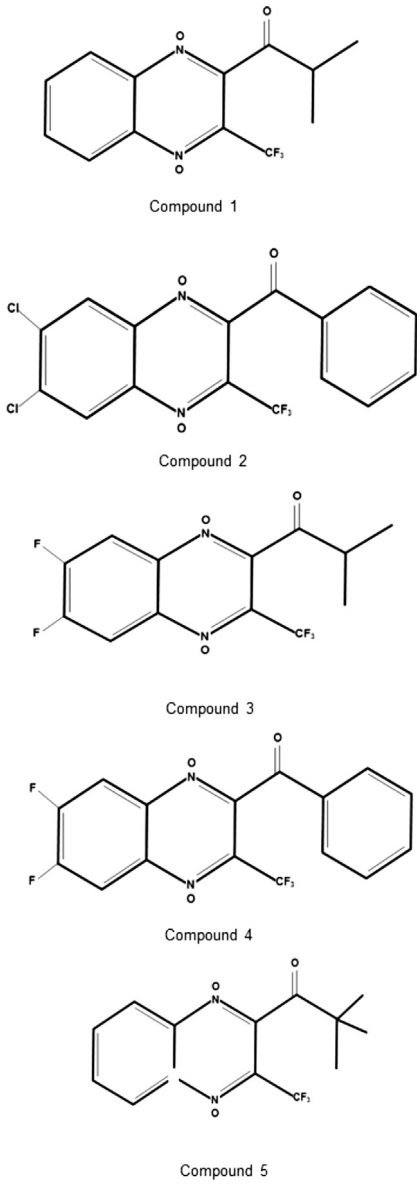


Fig. 10. Compounds 1–5.

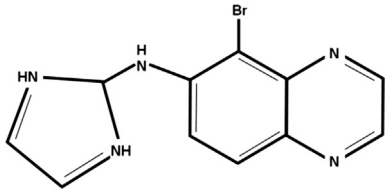


Fig. 11. Alphagan chemical structure.

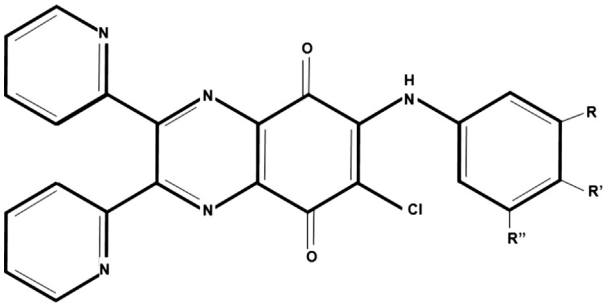


Fig. 12. 6-Arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8-diones.

2.2.4. Glaucoma

Glaucoma is the designation to refer the diseases that affect the optic nerve, involving the loss of retinal ganglion cells in a characteristic pattern of optic neuropathy, and excavations of the nerve head [54]. Almost 67 million people worldwide are affected by glaucoma, remaining one of the causes of irreversible blindness, responsible for 8% of blindness after cataract [55].

Alphagan® (Brimonidin) is a relatively selective alpha-2 adrenergic receptor agonist, and its composition consists in (5-bromo-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)-6-quinoxaline (Fig. 11). This drug works as an antiglaucoma agent, due to its power to reduce the intraocular pressure, alleviating the symptoms of glaucoma [1,21].

2.2.5. Atherosclerosis

Atherosclerosis is responsible for 50% of all mortality in the USA, Europe and Japan, is the principal cause of heart attack, stroke and gangrene of the extremities [56]. After artery injury, abnormal proliferation and migration of vascular smooth cells (SMCs) into the intimal layer of the arterial wall occurs, proliferating and synthesizing extracellular matrix components, playing an important role in coronary artery atherosclerosis and restenosis after an angioplasty [57].

A series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8-diones (Fig. 12) were synthesized and screened for their inhibitory activity on rat aortic smooth muscle cell (RAoSMC) proliferation. Possible substituents of this compound are represented in Table 1 by R, R′ and R″. IC_{50} (Inhibition Concentration) values were determined and compared to the positive control mycophenolic acid (MPA) (Table 1), and most of the compounds showed good activity, and the quinoxaline-5,8-diones were found as potent antiproliferative agents [1,21,58].

Quinoxaline derivatives were also tested as specific inhibitors for cancer cells survival, by inhibition of transglutaminase 2 (TGase 2). This enzyme as an important role both in pro-survival and anti-apoptosis during oncogenesis [59].

2.2.6. Neurological disorders

5-Hydroxytryptamine (5HT), commonly known as serotonin, is a neurotransmitter involved in a great number of physiological and patho-physiological processes, acting through the receptor subtypes, from 5-$HT_1$to 5-HT_7. Almost all of the receptors subtypes belong to the family of G-protein coupled receptor (GPCR), but the specific receptor subtype $5HT_3$ is a ligand gated ion channel [60,61]. The antagonists to this receptor lead to various responses, such as anti-emetic action in cancer chemo-/radio-therapy induced nausea and vomiting, anti-depressant, anxiolytic, anti-psychotic and anti-inflammatory. However, the drugs available to depression conditions have a delayed onset of action, which emphasizes the demand of new antidepressant drugs, with a safer and faster action [60,61].

New series of structurally novel 3-substituted-2-carboxamides quinoxaline were designed as 5-HT_3 receptor antagonists using ligand-based approach. All the compounds synthesized exhibited 5-HT_3 receptor antagonism, and some of them showed antagonism greater than the standard drug, ondansetron, like [3-ethoxyquinoxalin-2-yl][4-methylpiperazin-1-yl]-methanone and *N*-[2-(1*H*-indol-3-yl)ethyl]-3-ethoxyquinoxaline-2-carboxamide [61]. The compound *N*-3-methoxyquinoxalin-2-carboxamide showed the most favorable 5-HT_3 receptor antagonism [21].

Also 3-benzyl-2-substituted quinoxalines were synthesized as novel monoamine oxidase A (MAO-A) inhibitors. The MAO inhibitors are very useful for the treatment of several neurological diseases, like Parkinson and depression. MAO-A inhibitors are used as antidepressant and antianxiety drugs. In this study, the final compounds were evaluated for their MAO-A inhibitory activity *in vitro*, using serotonin as substrate [11].

2.2.7. Anti glutameric activity

Glutamate, an excitatory amino acid (EAA), is a major excitatory neurotransmitter in the central nervous system in mammalian species. Although, if a overstimulation of the postsynaptic glutamate receptors occurs due to a high release of EAA, could result in neuronal death, and consequently induce neurodegenerative disorders such as Alzheimer and Huntington's disease [62]. AMPA-R (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor) antagonists have showed to have no side effects such as schizophrenia and protective activity in neural death, and many quinoxalinedione derivatives with competitive AMPA-R antagonistic activity have been synthesized and tested against the EAA receptor [63].

The compound 7-[[4-[*N*-[4-carboxyphenyl]carbamoyloxy] methyl]imidazolyl]-3,4-dihydro-6-nitro-3-oxo-quinoxaline-2-carboxylic acid (GRA-293) was identified as a novel AMPA-R antagonist due to its high potency and good selectivity *in vitro*, and its potent neuroprotective effects in an animal model *in vivo*, higher than the known quinoxalinedione compounds used. These effects are due to a novel substituent, namely substituted benzene ring with urethane linkage to imidazole, in C-7 position, which leads to a potent AMPA-R affinity and contributes to therapeutic efficacy in animal models. This compound, with such characteristics, meets the criteria, in an injectable formulation, for use in the treatment of acute cerebral ischemia [63].

3. Conclusions

The literature survey reveals that quinoxaline and their derivatives have a vast application, with a great potential, being an important class of biological active compounds. Quinoxaline and its derivatives showed a wide field of application in medicine due to its biological activities, which include antimicrobial, antidiabetic, antiproliferative, anti-inflammatory, anticancer, antiglaucoma, antidepressant activities and also with AMPA-R antagonist activity. The biological activities referred are very encouraging for the investigators and pharmacists, leading to new treatments and therapeutic agents that will benefit humanity.

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