Instituto Politécnico do Porto

Escola Superior de Tecnologia da Saúde do Porto

JOANA ALVES PEREIRA

COMPUTATIONAL ANALYSIS OF QUINOXALINE *N,N*-DIOXIDE AND ITS DERIVATIVES

MSc in Biochemical Technologies in Health

Vila Nova de Gaia, May of 2013

Instituto Politécnico do Porto

Escola Superior de Tecnologia da Saúde do Porto

COMPUTATIONAL ANALYSIS OF QUINOXALINES *N,N*-DIOXIDE AND ITS DERIVATIVES

MSc in Biochemical Technologies in Health

JOANA ALVES PEREIRA

Dissertation submitted to the Escola Superior de Tecnologia da Saúde do Porto to meet the requirements for the Master degree in Tecnologia Bioquímica em Saúde under the scientific guidance of Ana de Moura Pessoa MSc, and co-supervision of Rúben Fernandes PhD and Mónica Vieira MSc.

Vila Nova de Gaia, May of 2013

Agradecimentos

À **Escola Superior de Tecnologia da Saúde do Porto**, em especial a Área Científica das Ciências Químicas e das Biomoléculas pelo acolhimento e dedicação a este mestrado.

Ao **Prof. Doutor Rúben Fernandes** e à **Profª. Doutora Cristina Prudêncio,** que me acompanham desde a minha entrada no ensino superior, pela sua enorme dedicação e incentivo, pelos sorrisos e boa disposição que sempre demonstraram e pelo grande exemplo de preserverança.

À minha orientadora, **Mestre Ana de Moura Pessoa**, pelo tempo e paciência de Job, pela simpatia e pela motivação, pelo empenho e dedicação que sempre demonstrou, e pelas conversas científicas e as conversas de café, não menos importantes.

À **Mestre Mónica Vieira**, pela disponibilidade, pelos 500 mil e-mails repondidos, por todo o carinho e simpatia, e por me dar conhecimento daquele programa fantástico que me vai permitir poupar imenso tempo no futuro.

Ao grande **Turno C do CRC Monsanto**, fabuloso grupo de trabalho, que apesar de não ajudar, também não atrapalha, e isso já é uma grande coisa ☺. É um prazer trabalhar convosco!

Aos **amigos**, porque as saídas, os jantares, os lanches, as tardes de esplanada e os mojitos também fazem parte, e sem isto a minha massa encefálica desintegrava-se.

A toda a família (aos Cunhas e aos Pereiras), em particular à **mãe Dora**, ao **pai Carlos**, à **irmã Raquel** e à **irmã Beatriz**, que estão sempre lá quando mais ninguém está, e por serem a família mais espectacular à face da Terra.

Ao meu **Peter**, por tudo!

A todos o meu maior e sincero **obrigado**!

Resumo

A quinoxalina e seus derivativos são uma importante classe de compostos heterocíclicos, onde os elementos N, S e O substituem átomos de carbono no anel. A fórmula molecular da quinoxalina é $C_8H_6N_2$, formada por dois anéis aromáticos, benzeno e pirazina. É rara em estado natural, mas a sua síntese é de fácil execução. Modificações na estrutura da quinoxalina proporcionam uma grande variedade de compostos e actividades, tais como actividades antimicrobiana, antiparasitária, antidiabética, antiproliferativa, anti-inflamatória, anticancerígena, antiglaucoma, antidepressiva apresentando antagonismo do receptor AMPA. Estes compostos também são importantes no campo industrial devido, por exemplo, ao seu poder na inibição da corrosão do metal.

A química computacional, ramo natural da química teórica é um método bem desenvolvido, utilizado para representar estruturas moleculares, simulando o seu comportamento com as equações da física quântica e clássica. Existe no mercado uma grande variedade de ferramentas informaticas utilizadas na química computacional, que permitem o cálculo de energias, geometrias, frequências vibracionais, estados de transição, vias de reação, estados excitados e uma variedade de propriedades baseadas em várias funções de onda não correlacionadas e correlacionadas. Nesta medida, a sua aplicação ao estudo das quinoxalinas é importante para a determinação das suas características químicas, permitindo uma análise mais completa, em menos tempo, e com menos custos.

Palavras-chave: Quinoxalina, derivativos, actividade biológica, indústria, química computacional.

Abstract

Quinoxaline derivatives are an important class of heterocycles compounds, where N, S and O elements replace some carbon atoms in the ring. Quinoxaline molecular formula is $C_8H_6N_2$, formed by two aromatic rings, benzene and pyrazine. It is rare in natural state, but their synthesis is easy to perform. Modifying its structure is possible to obtain a wide variety of compounds and activities such as antimicrobial, antitubercular, antiviral, antifungal, antiamoebic, antimalarial and leishmanial, antidiabetic, antiproliferative, anti-inflamatory, anticancer, antiglaucoma, antidepressant presenting AMPA receptor antagonism. These

compounds are also important in industrial field due to, for example, its power in metal corrosion inhibition.

Computational chemistry, natural branch of theorical chemistry, is a method well developed, used to represent molecular structures, simulating their behavior with quantic and classic physics equations. There are several softwares on the market, that allows the calculation of energies, geometries, vibrational frequencies, transition states, pathways of reaction, excited states properties and a variety of functions based on various uncorrelated and correlated waves. Its application to the study of quinoxalines is important for the determination of their chemical properties, enabling a more complete analysis in less time with lower costs.

Keywords: Quinoxaline, derivatives, biological activity, industry, computational chemistry.

Contents

Figure Contents

Table Contents

Abreviations Contents

5HT – 5-Hydroxytryptamine

AA – Arachidonic Acid

AIDS – Acquired Immunodeficiency Syndrome

AM1 – Austin Method 1

AMPA-R – α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor

AQ – Acenaphtho [1,2-*b*] quinoxaline

b.p. – Boiling Point

BLYP – Beck, Lee, Yang and Parr

CNS – Central Nervous System

DFT – Density Functional Theory

DNA – Desoxiribonucleic Acid

dsRNA – Double strain Ribonucleic Acid

EAA – Excitatory Amino Acid

GI_{50} – Growth Inhibition by 50%

GPCR – G-Protein Coupled Receptor

GTO – Gaussian-type Orbital

HF – Hartree Fock

HIV1 – Human Imunodeficiency Virus type 1

HIV2 – Human Imunodeficiency Virus type 2

HSV-1 – Herpes Simplex Virus type 1

HSV-2 – Herpes Simplex Virus type 2

HSV – Herpes Simplex Virus

IC_{50} – Inhibitory Concentration by 50%

IMA – Indomethacin

INQUI – Indeno-1-one [2,3-*b*] quinoxaline

IR – InfraRed

LED – Light-Emitting Diode

LOX – Lipoxygenase

m.p. – Melting Point

MAO – Monoamine Oxidase

MAO-A – Monoamine Oxidase A

MDR – Multi Drug Resistance

MHPQ – 3-methyl-2(2-hydroxyphenyl) quinoxaline

MIC – Minimum Inhibition Concentration

MMtHPQ – 3-methyl-2(3-methoxy,4-hydroxyphenyl) quinoxaline

MNDO – Modified Neglect of Differential Overlap

MO – Molecular Orbital

MPA – Mycophenolic Acid

MPQ – 3-methyl-2-phenyl quinoxaline

NS1A – Non-structural protein 1 of influenza A

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

OGTT – Oral Glucose Tolerance Test

OLED – Organic Light-Emitting Diode

PHOLED – Phosphorescent Organic Light-Emitting Diode

PHPQ – 3-phenyl-2-(2-hydroxyphenyl)-quinoxaline

PM3 – Parameterization Method 3

PPQ – 2,3-diphenyl quinoxaline

QD – 2,3-quinoxalinedione

RAoSMC – Rat Aortic Smooth Cell

RM1 – Recife Model 1

RT – Reverse Transcriptase

SCF – Self Consistent Field

SMCs – Smooth Cells

STO – Slater-type orbital

TB – Tuberculosis

USA – United States of America

UV-Vis – Ultra Violet-Visible

Chapter I:

Introduction

1.Introduction

The present study emerges in the following of the investigations carried out by the Center for Health and Environmental Research, in the School of Allied Health Sciences. In such studies, the researchers synthezised the quinoxalines derivatives under study, and evaluated their antimicrobial activity. The group also evaluated the toxicity and antitumoral activity in cell lines, such as human gingival fibroblasts, human MG-63 osteoblast-like cells, murine skin melanoma B16-F10, murine brain BC3H1 cells and human colorectal adenocarcinoma HT29. Those studies showed some very promising results. The main aim of this work is to determine the quinoxaline derivatives chemical properties and reactivity. These results will then help to understand if the antimicrobial activity and toxicity are related or not with chemical features of the compounds.

This introduction will provide a review regarding chemical properties of quinoxaline compound and its derivatives.

1.1.Quinoxaline and its derivatives features

Quinoxaline derivatives are an important class of heterocycles compounds, in which N, S and O elements replace one or more carbon atoms of the ring[1], and the approved number for the quinoxaline ring system is shown in **Figure 1**, where 2 and 3 are designated α-positions[2]. They are important in industry due to their power to inhibit the metal corrosion[3-5], in the prepare of the porphyrins since their structure is similar to the chromophores in the natural system, and their utility in the electroluminescent materials[6-8], and are even more significant in pharmacological industry since they show wide biological properties[1, 9-12] such as antibacterial, antifungal, anticancer, antitubercular, antileishmanial, antimalarial, antidepressant, antimycobacterial and anticandida, and neurological activities, among others. All this activities are possible due to the quinoxaline structure once its nucleus, in numerous cases, act as a precursor to assembly a large number of quinoxaline derivatives, which consequently, provide a large number of new compounds with biological and therapeutic applications[1].

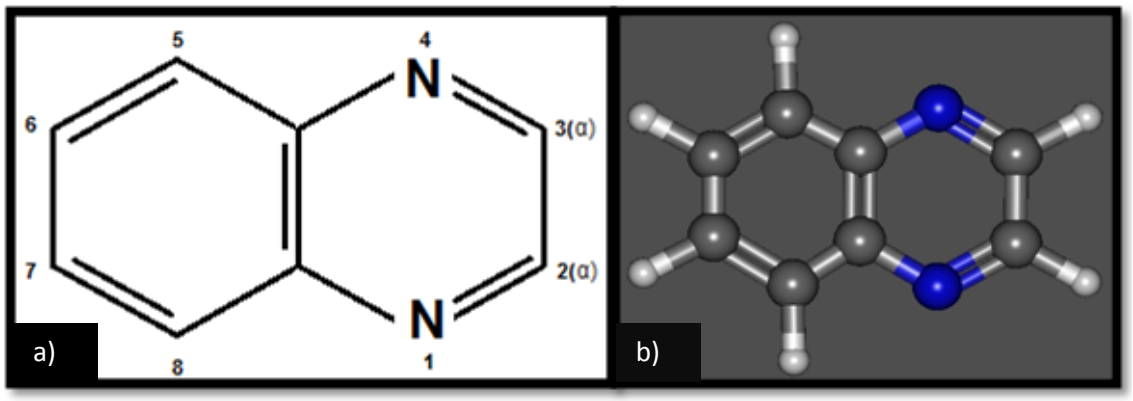


Figure 1: Quinoxaline compound: a) Lewis structure; b) non-optimized 3D structure.

Particularly, quinoxaline is formed by two aromatic rings, benzene and pyrazine, reason why it is also called benzopyrazine, and is described as a bioisoster of quinoline, naphatelene and benzothiophene[13]. The atoms S and N play an important role in the ring since they stabilize ion radical species and extended π-conjugation facilitate in decreasing columbic repulsion. Molecular weight of the quinoxaline is 130.1466400, with a molecular formula of $C_8H_6N_2$, and it is a white crystalline powder[1].

Chemically, quinoxaline is a low melting solid, purified by destilation, and a fraction of boiling point (b.p.) 108º-111º/12mm has a melting point (m.p.) 29-30ºC[2, 13]. Quinoxalines are soluble in water, and produce monoquaternary salts when treated with quaternizing agents, like methyl sulfate and methyl *p*-toluenesulfate. The quaternary salts of 2-alkylquinoxalines are unstable and can be converted into complex colored products when under oxidation[2]. It is weakly basic with a *pKa* of 0,60 in water at 20ºC, and nitration occurs only under forcing conditions (Concentrated Nitric Acid (HNO_3), Oleum, 90ºC), resulting the formation of two compounds: 5-nitroquinoxaline (1,5%) and 5,7-dinitro-quinoxaline (24%)[13]. Its second *pKa* is -5,52, meaning that quinoxaline is significantly diprotonated only in a strongly acidic medium[2].

Quinoxaline has a dipole moment of 0,51 D in benzene ring, and its first and second ionization potentials, measured by photon electron spectroscopy, are 8,99 and 10,72 eV, respectively[2]. However it is not known certainly from which orbital the first electron is lost, since highest-occupied π-orbital and non-bonding orbitals are very close in energy. The heat of atomization was calculated to be 79,739 eV by a self-consistent field molecular orbital treatment[2]. Molecular orbital calculations of the π-electron density were made, and showed that the highest electron density at the ring carbon is at positions 5 and 8, followed by positions 6 and 7, and the lowest at 2 and 3 positions[2].

Table 1: Quinoxaline properties.

Quinoxaline Properties	
Formula	$C_8H_6N_2$
Molecular Weight	130.1466400
Acidity (*pKa*)	0,56
Second *pKa*	-5,52
Melting Temperature	29-30ºC
Natural State	White crystaline powder
Dipole Moment	0,51 D
Ionization ($1^{st}/2^{nd}$)	8,99/10,72 eV
Atomization Heat	70,739eV

Quinoxaline compounds are rare in natural state, being the most of them, of synthetic origin. There are different ways to sinthezised quinoxalines. One of the method used to synthesized quinoxalines is to condense *o*-disubstituted benzene with a two carbon synthon. Therefore, the condensation of *o*-phenylenediamine with *α*-dicarbonyl compounds result in quinoxaline formation **(Figure 2)**[2].

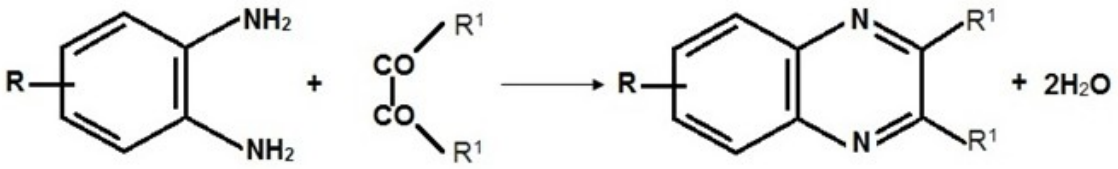


Figure 2: Quinoxaline synthesis.

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

Chapter II:

Quinoxalines Activities

2.Quinoxaline Activities

Quinoxalines are compounds with a vast fiel of applications, including medical field with their biological activities, and in industry, where quinoxalines are used, for example, to reduce maintenance costs, and as host compounds in phosphorescent organic light-emitting diode (PHOLEDs).

2.1.Biological Activity

The study of quinoxaline and its derivatives has become a subject of interest in recent years on account of their wide variety in biological activity and also their therapeutic applications, such as antimicrobial agents, since some antibiotics have quinoxaline compound in their structure (echinomycin), as well as some recognized drugs like Brimonidins which alleviates glaucoma symptoms[1]. Although rare in nature, synthesized quinoxaline and derivatives are included in various antibiotics such as echinomycin, levomycin and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and also active against transplant tumors[13, 14].

The vast scope of synthesized quinoxaline and derivatives potentials is well referenced and published in a wide range of scientific journals. We analyze in detail, transversally and in context the relevant scientific data pertaining great potentials of quinoxaline and derivatives in literature.

2.1.1.Antimicrobial Activity

The antimicrobial resistance is a serious threat to global public health, mainly result of the widely disseminated and careless use of antimicrobials, and demands a continuous effort in order to seek for better antimicrobial agents effective against resistant pathogenic microorganisms[13, 15-17]. There are a wide range of quinoxaline derivatives with antimicrobial activity documented, of which we present a relevant survey in the following paragraphs.

2.1.1.1.Antibacterial Activity

A new series of 8-chloro-1,4-substituted(1,2,4)triazolo(4,3a) quinoxaline derivatives **(Figure 3)** was synthesized and screened for antimicrobial and antioxidant activities[18].

The antibacterial activity was screened against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative *Proteus vulgaris* and *Klebsiella pneumonia*, using chloramphenicol as reference drugs[16].

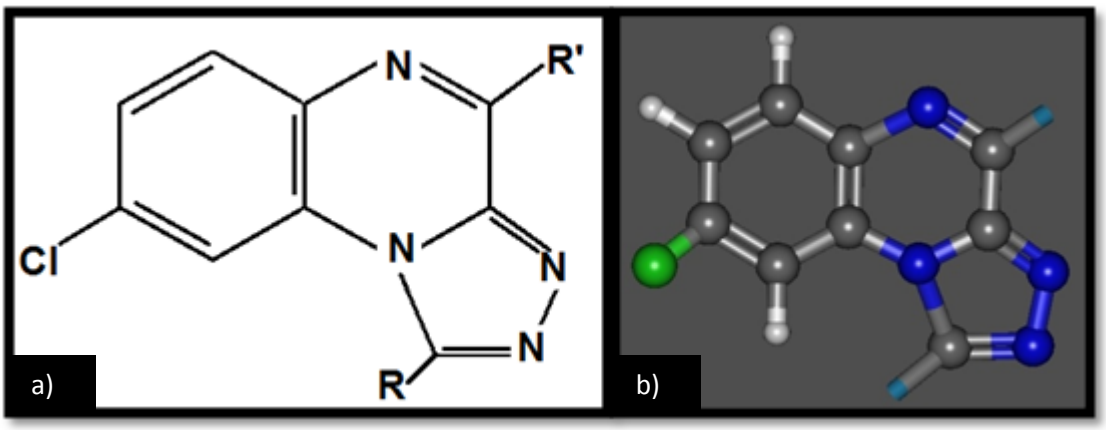


Figure 3: 8-chloro-1,4-disubstituted (1,2,4)triazolo(4,3a) quinoxaline derivatives core : a) Lewis structure; b) non-optimized 3D structure.

Ammar *et al*[19], have synthesized thieno(2,3-*d*)pyrimidines and pyrrolo(3,4-*b*)quinoxalines which antibacterial activity was tested against *S. aureus* and *Escherichia coli*.

2.1.1.2.Antitubercular Activity

Tuberculosis (TB) is a contagious disease, caused by the infection of *Mycobacterium tuberculosis,* which have 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[20-22].

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 TB multidrug resistant (MDR) it is required the development of new therapeutic agents, with a unique mechanism of action, able to treat MDR forms of the disease.

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 possess *M. tuberculosis* growth inhibition values from 99 to 100%[16, 23]. However, it is observed that the lack of the two *N*-oxide groups lead to the loss of the antimycobacterial activity [23-25].

Some novel condensed bridgehead nitrogen heterocycles of quinoxalines has been synthesized and showed activity against *M. tuberculosis* H_{37}Rv species [13, 16, 26]. The compound 3-methyl-2-phenylthioquinoxaline-1,4-dioxide generally showed a good activity against *M. tuberculosis* in the preliminary *in vitro* evaluation and exhibited *Minimum Inhibitory Concentration* (MIC) between 0.39 and 0.78µg mL^{-1}(rifampicin MIC=0.25µg mL^{-1})[9]. The MIC is defined as the lowest concentration of an antimicrobial that will inhibit 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[27].

Antonio Carta *et al*[28], reported the activity of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-(1,2,3)-triazolo(4,5-*h)*quinolone-carboxylic acids and their esters as a new class of anti-infective agents against MDR *M. tuberculosis*, with no cytotoxicity reported.

2.1.1.3.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[29].

Viruses such as Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the *Herpesviridae* family, are double-stranded DNA[30], and share high homology in genome structure and DNA sequence. These viruses can cause various illnesses states from assymptomatic infection to fulminant disseminated diseases, including labials herpes, keratitis (cornea inflammation), genital herpes, and encephalitis[31, 32].

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)[30, 33], being acyclovir the most common drug used. However, there are drug-resistant strains of HSV emerging and increasing[30, 34], 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)5*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 to 5μM, 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 **(Figure 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].

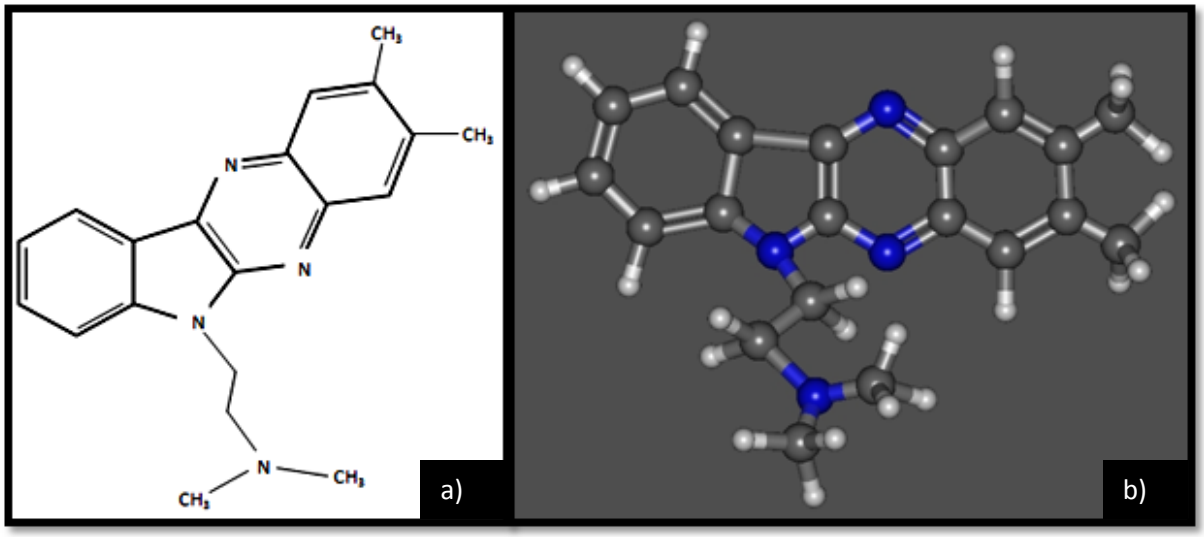


Figure 4: 2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo-(2,3-*b*)quinoxaline compound: a) Lewis structure; b) non-optimized 3D structure.

There is also reference to IndQloquinoxalines with capacity to inactivate virions in high concentrations (around 300μM), and decrease the synthesis of viral DNA and protein at lower concentrations (around 3μM)[16].

Concerning human immunodeficiency virus type 1 (HIV-1), which is the agent causative of acquired immunodeficiency syndrome (AIDS)[35-37], 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[13]. Compound 6-chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-3,4-dihydroquinoxalin-2(1*H*)-thione **(Figure 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)[16].

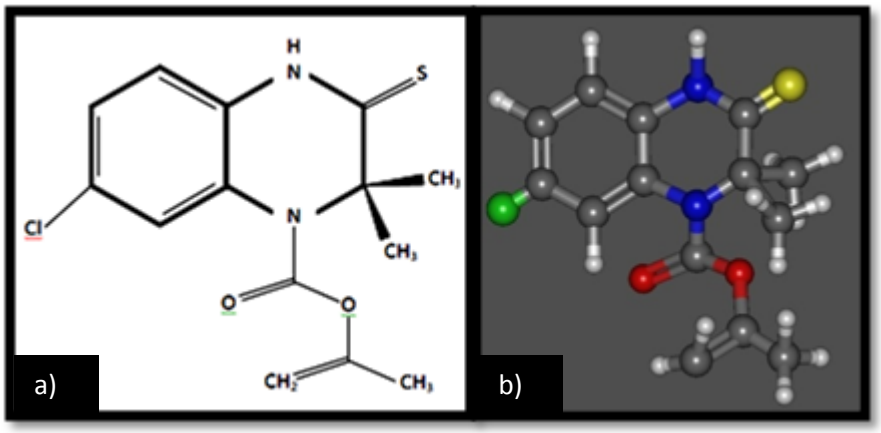


Figure 5: 6-chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-3,4-dihydroquinoxaline-2(1*H*)-thione compound: a) Lewis structure; b) non-optimized 3D structure.

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].

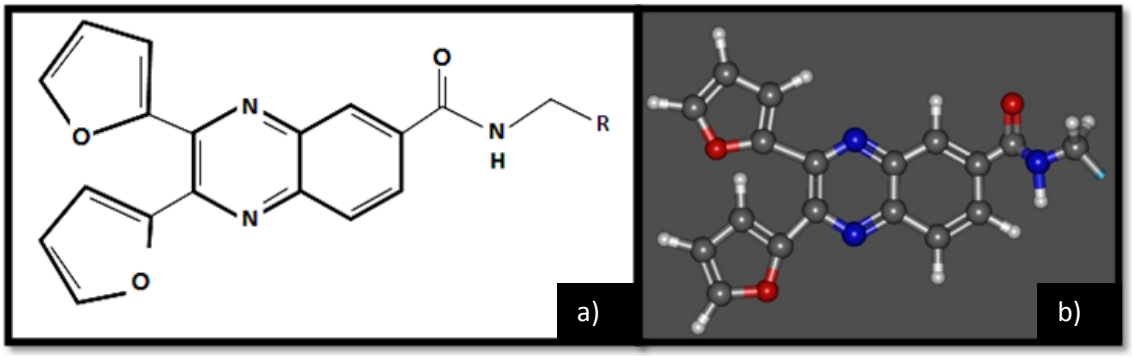


Figure 6: 2,3-difurylquinoxaline-4-(R)methylcarboxamide: a) Lewis structure; b) non-optimized 3D structure.

In this study, investigators have prepared a library based on 2,3-difuryl-4-quinoxaline(R)metilcarboxamide derivatives **(Figure 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 2*** have shown the highest potency. 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].

Table 2: Activities of amide derivatives of 2,3-difurylquinoxaline-4-(R)methylcarboxamide compound[38].

Compound	R	% Binding at 50μM	% Intercalation at 50 μM	IC_{50} μM
1	3-OMe-Ph-	74,0	4,5	6,2
2	2-Furyl-	79,5	5,9	3,5

2.1.1.4.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, 41]. This fungus can also develop resistance to antimycotic drugs that already exist in the market[42], 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 [13, 19].

Researchers also reported some 2-sulphonylquinoxalines and 3-[(alkylthio)methyl]quinoxaline-1-oxide derivatives as compounds with high antifungal activity[9], and also pyrazoloquinoxalines which were observed to be active against fungal infections[1].

2.1.1.5.Antiamoebic Activity

Entamoeba histolytica is a protozoan responsible for the amoebiasis infection[43, 44], causing amoebic colitis, brain and liver abscess, being the second 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[45].

Some 1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazolines derivatives produced **(Figure 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[45].

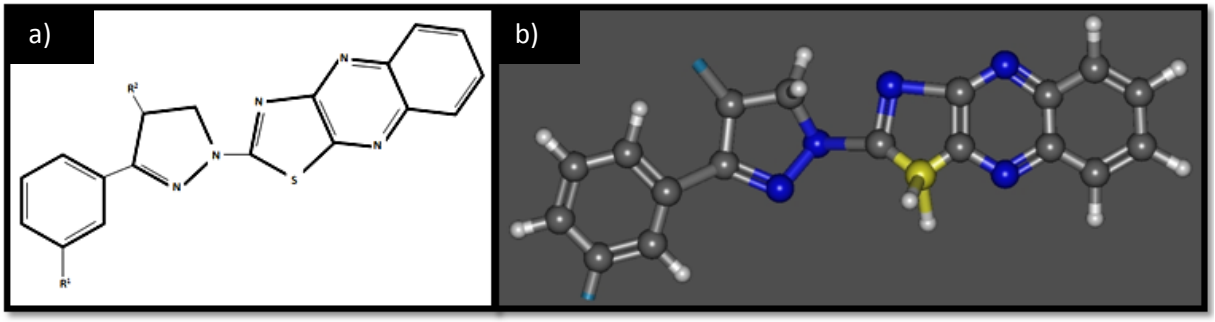


Figure 7: 1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazolines core: a) Lewis structure; b) non-optimized 3D structure.

In this study metronidazole was used as the reference drug and had a 50% inhibitory concentration (IC_{50}) ranging from 1.69 to 1.82 μM, and compound 6 showed great effectiveness, being the most active **(Table4)**[45].

Table 3: In vitro antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2 pyrazolines derivatives against HM1:IMSS strain of Entamoeba histolytica ([a]Standard Deviation) [45].

Compound	R^1	R^2	IC_{50} μM	SD[a]
1	H	H	6,76	0,20
2	Br	H	4,98	0,11
3	Cl	H	1,09	0,08
4	H	CH3	2,34	0,23
5	Br	CH3	1,45	0,14
6	Cl	CH3	0,72	0,10
Metronidazole			1,69	0,24

2.1.1.6.Antileishmanial and Antimalarial 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[16, 46]. Most of the drugs available against leishmaniasis are expensive and require a long treatment and are becoming more and more ineffective[11].

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[11, 47-49].

Carlos Barea, *et al*[11], synthesized 14 new 3-amino-1,4-di-*N*-oxide quinoxaline-2-carbonitrile derivatives. These compounds were evaluated for their in vitro antimalarial and antileishmanial activity 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.

2.1.2.Antidiabetic Activity

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, biguanides, etc. However these treatments have limited efficacy and tolerability, and could cause severe side effects[50]. In this regard, new transition metal complexes of quinoxaline-thiosemicarbazone ligands L^1H_2 and L^2H_2 were prepared **(Figure 8)**. 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 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[12].

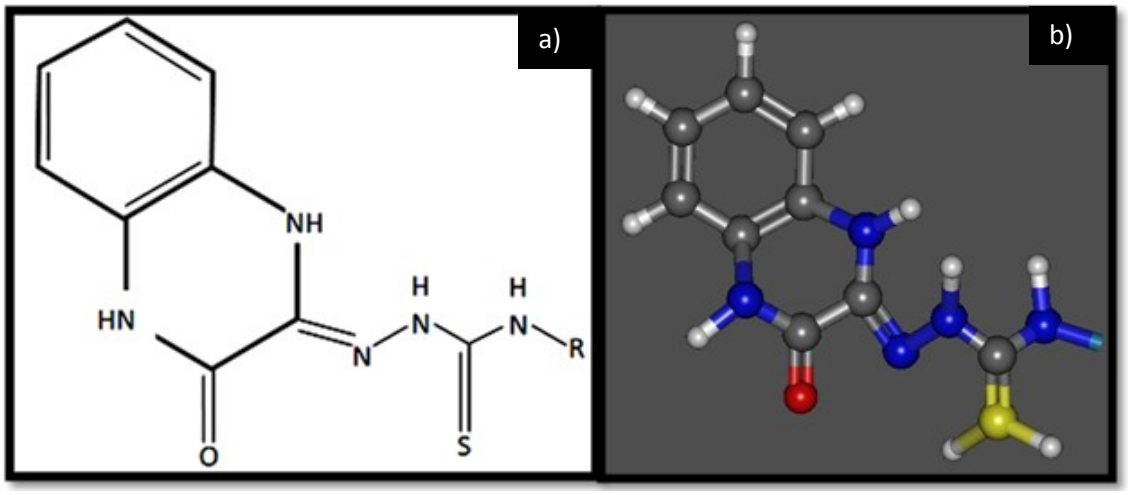


Figure 8: Ligands L^1H_2 and L^2H_2. For L^1H_2, R=CH_3 and for L^2H_2, R=C_6H_5: a) Lewis structure; b) non-optimized 3D structure.

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

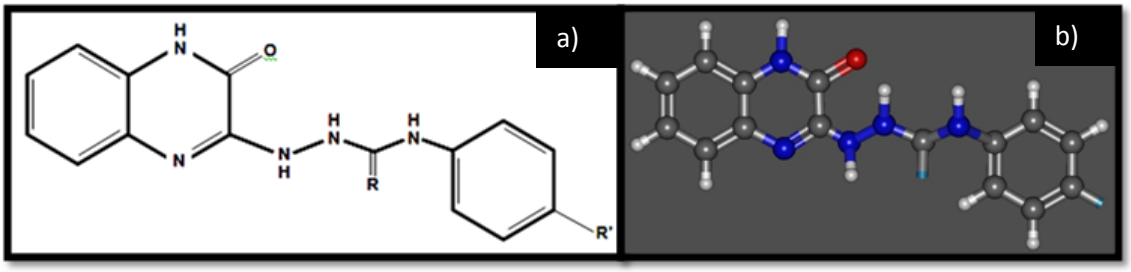


Figure 9: (*N*-arylcarbamoyl and *N*-aryl thiocarbamoyl) hydrazinequinoxalin-2(1*H*) compounds: a) Lewis structure; b) non-optimized 3D structure.

2.1.3.Anti-inflammatory Activity

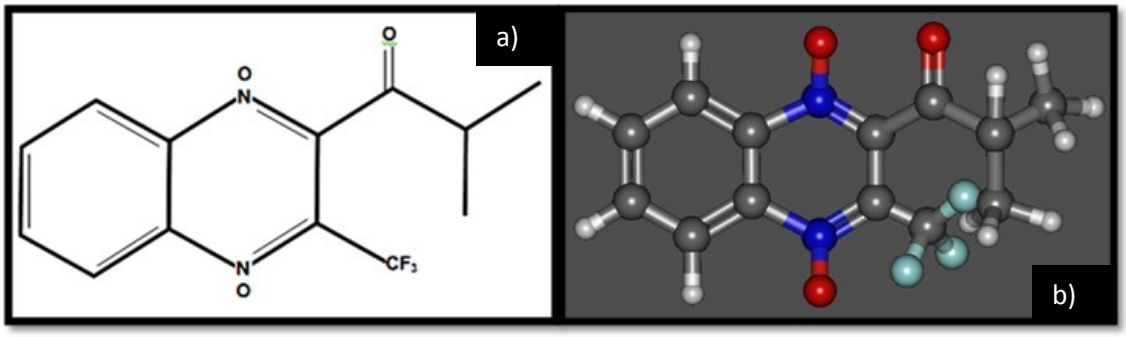
Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in therapeutics, generally for the treatment of pain and inflammation, but its long-term usage can lead to significant side effects like gastrointestinal lesions, bleeding, and nephrotoxicity. Due to those reasons mentioned it is important the discovery of new safer anti-inflammatory drugs [51-53].

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[54, 55]. 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 activity[51].

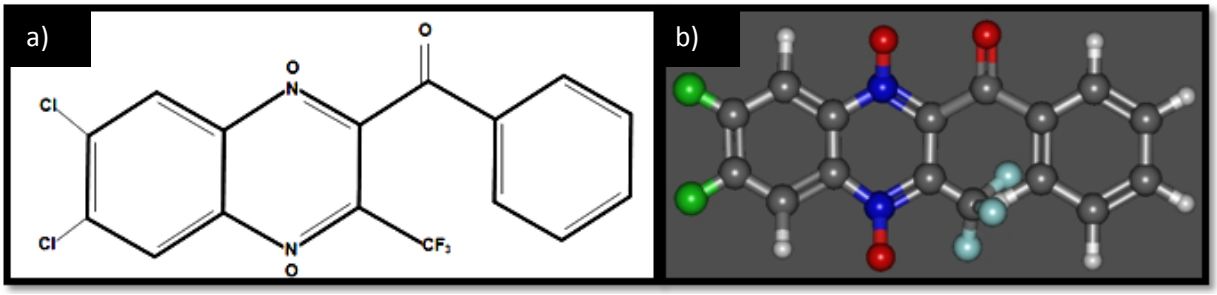
2.1.4. Anticancer Activity

Cancer is the main cause of death in developed countries nowadays, and the second cause of death in developing countries, result of population aging and growth, and the adoption of lifestyle choices, included in risk factors to cancer development, such as smoking, physical inactivity and diet[56, 57].

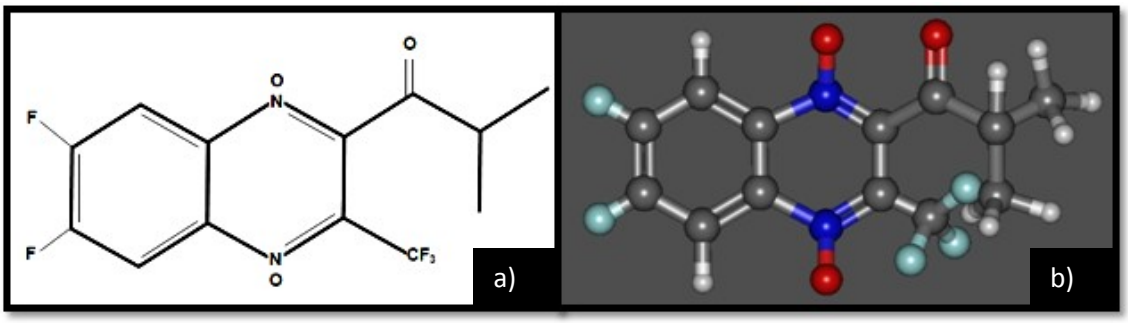
It is known that quinoxaline nucleuses exhibit potential anticancer activity, which makes them an important basis for the anticancer drugs[16]. A new series of 2-alkylcarbonyl and 2-benzoyl-3-triflurомethylquinoxaline-1,4-di-*N*-oxide derivatives was synthesized and evaluated for *in vitro* antitumor activity against a 3-cell line panel (MCF7 (breast), NCIH 460 (lung) and SF-268 (CNS)), and then evaluated in a full panel of 60 human tumor cell lines, derived from nine cancer cell types (Leukemia, Non-small cell lung cancer, Colon cancer, CNS cancer, Melanoma, Ovarian cancer, Renal cancer, Prostate cancer and Breast cancer). 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 **(Figure 10)** 2-isobutyryl-3-trifluoromethylquinoxaline-1,4-di-*N*-oxide **(Compound 1)**, 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline-1,4-di-*N*-oxide **(Compound 2)**, their difluorinated analogs (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-trifluoromethylquinoxaline-1,4-di-*N*-oxide **(Compound 5)** were the most active, with higher anticancer activity with mean GI_{50} values of 1.02, 0.42, 0.52, 0.15, and 0.49 μM, respectively **(Table 5)**[10, 16].



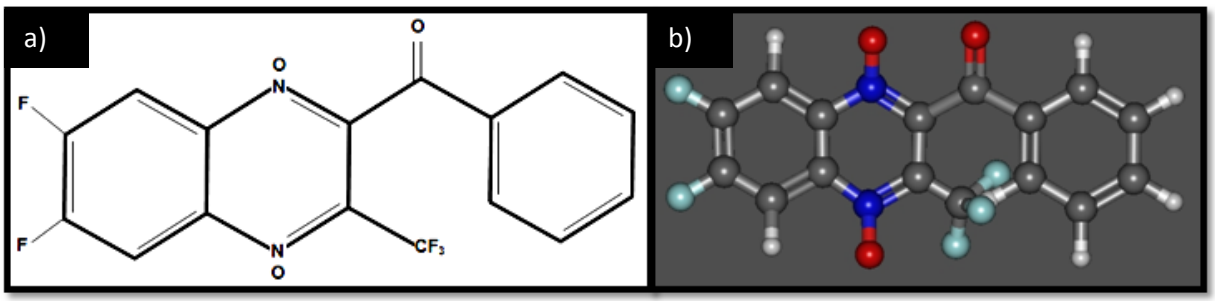
Compound 1: 2-Isobutyryl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



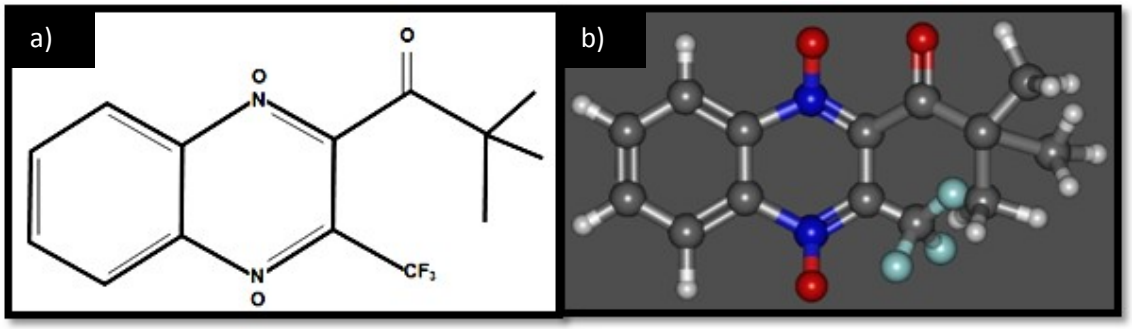
Compound 2: 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



Compound 3: 6,7-difluoro-2-isobutyryl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



Compound 4: 2-benzoyl-6,7-difluoro-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



Compound 5: 2-(2,2-dimethylpropanoyl)-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.
Figure 10: Compounds 1 to 5: a) Lewis structure; b) non-optimized 3D structure.

Table 4: In vitro inhibitory activity test for compounds against 60 human tumor cells lines**[10]**.

Compound	IG_{50} µM
1	1,02
2	0,42
3	0,52
4	0,15
5	0,49

2.1.5.Antiglaucoma Activity

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[58-60]. Almost 67 million people worldwide are

affected by glaucoma, remaining the leading cause of irreversible blindness, responsible for 14% of blindness after cataract and trachoma[61, 62].

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 **(Figure 11)**. This drug works as an antiglaucoma agent, due to its power to reduce the intraocular pressure, alleviating the symptoms of glaucoma[1, 16].

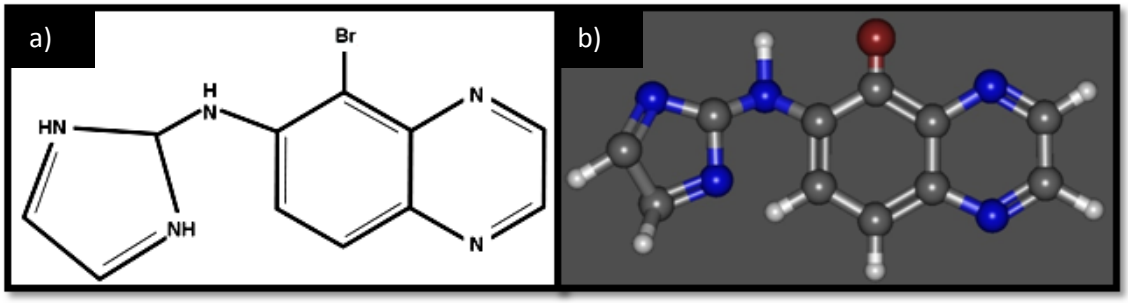


Figure 11: Alphagan chemical structure: a) Lewis structure; b) non-optimized 3D structure.

2.1.6.Antiproliferative Activity

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[63]. 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[64, 65].

A series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8-diones **(Figure 12)** were synthesized and screened for their inhibitory activity on rat aortic smooth muscle cell (RAoSMC) proliferation. IC_{50} values were determined and compared to the positive control mycophenolic acid (MPA) **(Table 6)**, and most of the compounds showed good activity, and the quinoxaline-5,8-diones was found as an potent antiproliferative agent[1, 16, 66].

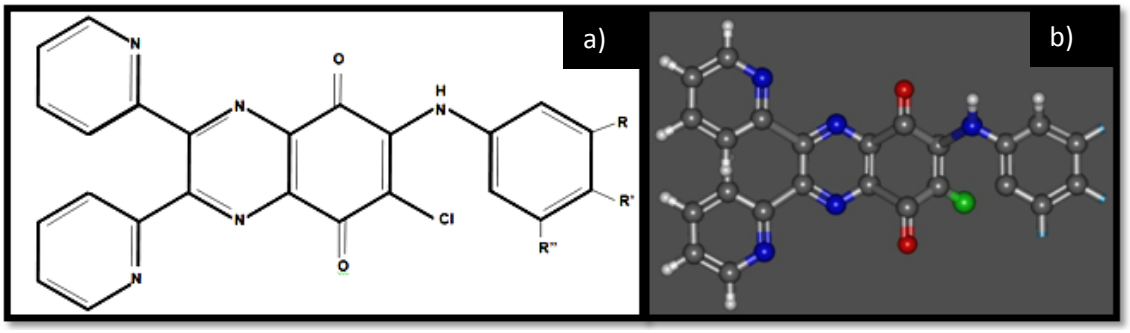


Figure 12: 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8-diones compounds: a) Lewis structure; b) non-optimized 3D structure.

Table 5: Structures and IC_{50} values of 6-arylamino-2,3-bis(pyridin-2-yl)-7-chloro-quinoxaline-5,8-diones for inhibition of SMC proliferation**[66]**.

Compound	R^1	R^2	R^3	SMC IC_{50} (μM)
2a	H	Cl	H	1.5
2b	H	OH	H	5.5
2c	H	F	H	1.0
2d	H	CF_3	H	1.1
2e	H	OCF_3	H	1.0
2f	H	OCH_3	H	3.5
2g	H	H	H	3.1
2h	Cl	Cl	H	1.0
2i	F	F	F	1.2
4				>100
MPA				1.0

2.1.7.Antidepressant Activity

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, which are 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[67, 68]. 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-phsycotic and anti-inflammator. 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[67, 68].

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*-indole-3-yl)ethyl)-3-ethoxyquinoxaline-2-carboxamide[68]. The compound *N*-{3-[(4-methylpiperazin-1-yl)methyl]-4-hydroxyphenyl}-3-methoxyquinoxalin-2-carboxamide showed most favorable 5-HT_3 receptor antagonism[16].

Also 3-benzyl-2-substituted quinoxalines were synthesized as novel monoamine oxidase (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[13].

2.1.8.Anti-exocitotoxicity activity of glutamate

A major excitatory neurotransmitter in the central nervous system in mammalian species is the glutamic acid, an excitatory amino acid (EAA). 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[69-73]. 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[74].

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 characterеristics, meets the criteria, in an injectable formulation, for use in the treatment of acute cerebral ischemia[74].

2.2.Industrial applications

In industry, the quinoxalines and derivatives have also various applications. They can be used to prevent metal corrosion, leading to a decrease in maintenance of some materials and equipment, and can be used as host materials in some light-emitting diode (LED) lights, for example.

2.2.1.Corrosion Inhibition

The use of acid solution is very common in industry, and has important fields of application like acid pickling, industrial acid cleaning, acid descaling and oil well acidizing. However, the continuous use of acid solutions can lead to the metal corrosion, leading to enormous economic losses, thence the importance of having inhibitors to minimize the metal dissolution and acid consumption, instruments malfunction and contamination[5, 75].

The most effective inhibitors used in industry to minimize these losses are organic compounds. Their inhibitory effect is reinforced by the presence of heteroatoms such as sulphur, nitrogen and oxygen, which will facilitate its adsorption on the mild steel surface following the sequence S>N>O[3, 75].

Other studies revels that the adsorption in mild steel surface also depends on the physicochemical properties of the inhibitor group, planarity of the system, presence of multiple adsorption active centers with lone pair and/or π orbitals, molecular size and electronic density at the donor atom. On this basis, the choice of effective inhibitors is done taking in consideration their structure, their mechanism of action and their electron donating ability[3]. Many *N*-heterocyclic organic compounds are good corrosion inhibitors, but some of them are highly toxic to both human beings and environment, leading to a continue search for an eco-friendly and harmless *N*-heterocyclic compounds as inhibitors[76].

Quinoxaline derivatives are *N*-heterocyclic aromatic compounds that have been proved to be excellent corrosion inhibitors for mild steel in acidic media, easy to synthesized and ready available[77].

Compound 2,3-quinoxalinedione (QD) **(Figure 13)** was used to study its corrosion inhibition properties for mild steel in 1M HCl, due to the presence of heteroatoms N and O, and π-electrons. It was shown that QD can act as a good corrosion inhibitor for mild steel

in 1M HCl, with an inhibition efficiency of 88% at 10^{-3}M (measured through weight loss)[75].

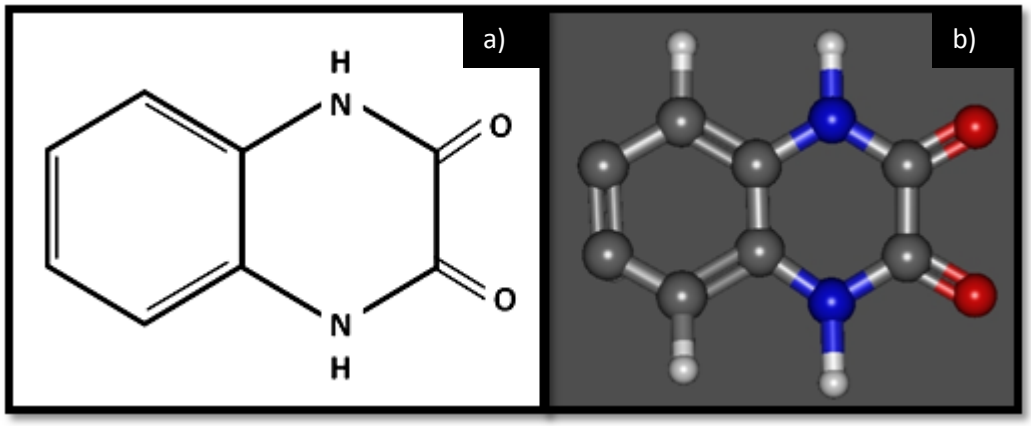


Figure 13: 2,3-quinoxalinedione compound: a) Lewis structure; b) non-optimized 3D structure.

Indeno-1-one [2,3-*b*] quinoxaline (INQUI) **(Figure 14)**, was synthesized and tested for inhibition corrosion of mild steel in 0,5M H_2SO_4, and showed about 81% of inhibition efficiency at 10^{-6}M. This efficiency increases with INQUI concentration but decreases with immersion time[76].

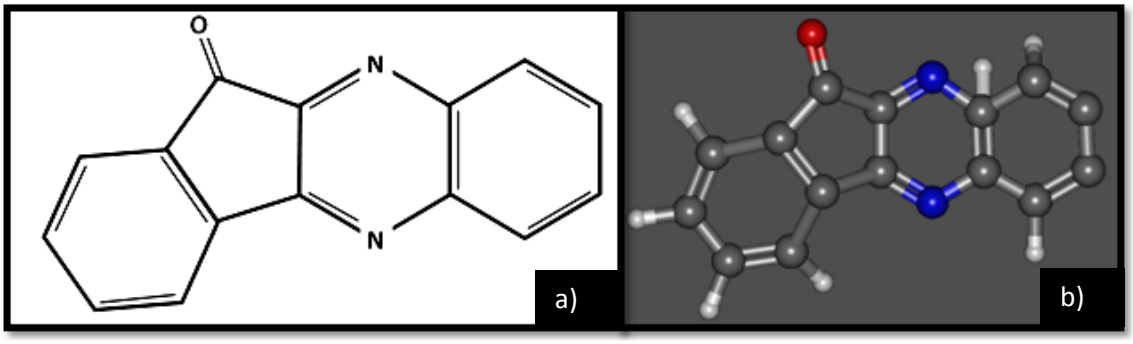


Figure 14: Indeno-1-one [2,3-*b*] quinoxaline (INQUI) compound: a) Lewis structure; b) non-optimized 3D structure.

Also acenaphtho [1,2-*b*] quinoxaline (AQ) **(Figure 15)** was tested as a corrosion inhibitor for mild steel in 0,5 M H_2SO_4. AQ acts as an effective inhibitor for mild steel in acidic medium, with 80% of inhibition efficiency at 10^{-6}M (measured through weight loss)[77].

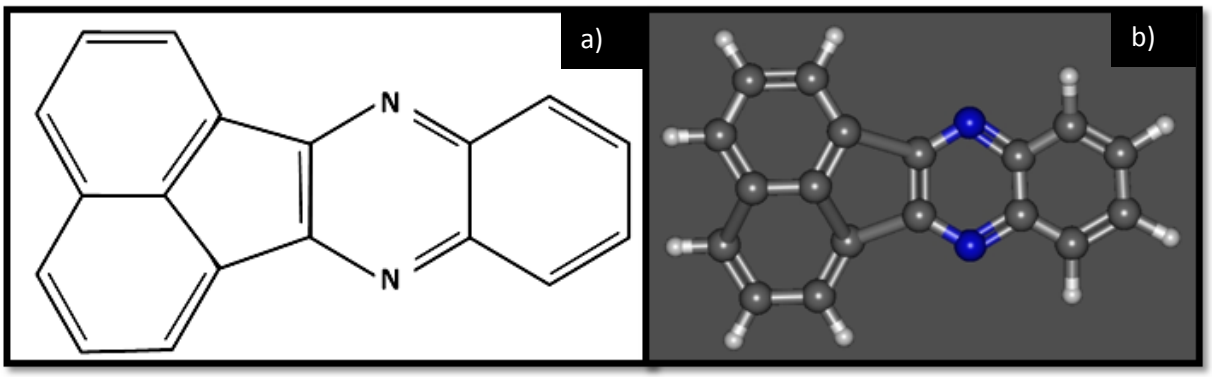


Figure 15: Acenaphtho [1,2-*b*] quinoxaline (AQ) compound: a) Lewis structure; b) non-optimized 3D structure.

Quinoxaline derivatives, namely 3-methyl-2-phenyl quinoxaline (MPQ), 2,3-diphenyl quinoxaline (PPQ), 3-methyl-2(2-hydroxyphenyl)quinoxaline (MHPQ), 3-phenyl-2(2-hydroxyphenyl)quinoxaline (PHPQ) and 3-methyl-2(3-methoxy,4-hydroxyphenyl)quinoxaline (MMtHPQ), have been shown through experimental studies to have high corrosion inhibition efficiencies for copper in nitric acid, with the order of inhibition efficiency being MMtHPQ > PPQ > MPQ > PHPQ > MHPQ[5].

2.2.2.Cu^{2+} detection

Cu^{2+} is a transition-metal ion, crucial in the life processes, since it has an important role as a catalytic cofactor for a variety of metallo-enzymes such as superoxide dismutase, cytochrome c oxidase, lysyl oxidase and tyrosinase, etc. However when overloading, exhibit toxicity and could cause a variety of neurological diseases. Besides, it is also important in pollution matters, since the formulation of copper-containing pesticides uses various forms of copper, which in the end dissociates into Cu^{2+}[78, 79].

There are technologies well developed to detect Cu^{2+} such as inductively coupled plasma detectors, surface-plasmon resonance detectors, fluorescence anisotropy assays, quantum-dot-based assays, electrochemical sensors and fluorescence sensors. These are technologies with high sensitivity and specificity for Cu^{2+} detection, but also very expensive, due to the need of sophisticated instruments and highly trained operators. On the other hand, it is possible to use a naked-eye detection method, which gives a more fast response without involving any costly instrument, although it is a method with lower sensitivity and only give a qualitative response[79].

A colorimetric receptor ninhydrin–quinoxaline based was designed, synthesized

and characterized, and exhibited high sensitivity and selectivity for Cu^{2+} in aqueous medium over a wide variation of cations such as Na^{+}, Mg^{2+}, Al^{3+}, Co^{2+}, Fe^{3+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+}. In this study Cu^{2+} was added to the receptor solution giving a clear colour change from olive green to pink. The detection limit was found to be $3{,}43 \times 10^{-7}$ M which is one of the lowest for the Cu^{2+} in an aqueous solution by any naked-eye receptor[79].

2.2.3.OLED - organic light-emitting diode

Phosphorescent OLEDs (PHOLEDs) are well known due to its high efficiency (possibility of 100% internal quantum efficiency)[80], leading to the research and synthesis of new compounds and materials as hosts, charge transporting materials and emitters. The high efficiency is due to PHOLED capacity to harvest both singlet and triplet excitons for light emission[81, 82]. However, triplet emitters tend to decrease the efficiency because of the triplet-triplet annihilation concentration during device operation despite of owing long emissive lifetimes. The solution is to develop new bipolar host materials, which will contribute to the balanced transport of carriers and help to increase the probability of carrier recombination, and will grant better device stability due to its amorphous nature[82].

New series of carbazole/quinoxaline hybrids with 1,3,5-benzene core have been synthesized, and showed excellent thermal and morphological stabilities, due to their twisted geometry. These compounds, bipolar along with high thermal stability and favorable electrochemical properties, are promising for their use as host materials in red and green phosphorescent based OLEDs[82].

Chapter III:

Computational Chemistry

3.Computational Chemistry

In this chapter is made an introduction to the computational chemistry and an overview to the most important topics to this study.

3.1.An introduction to Computational Chemistry

Computational chemistry is the science, or art, that is a natural branch of theoretical chemistry[83], and is used to represent molecular structures, simulating their behavior with classic and quantum physics equations. Computational chemistry programs allow scientists to generate and present molecular data, such as geometries (bond length, bond angles, and torsion angles), energy (activation energy, etc) electronic properties (ionization potential, charges, electronic affinity, etc) spectroscopic properties (vibration, *shifts*), and mass properties (volumes, viscosity, diffusion, etc). However, it is necessary, from the investigator, intuition and training to understand the results more properly, being these results measure up with experimental data, when available, which is a very important tool to guide both laboratorial and computational work[84].

Computational chemistry is a well developed method and can be automated. However, few chemical aspects can be precisely processed at computational level, whereas results are described in a qualitative and approximately quantitative computational scheme[85]. The Schrödinger equation is the basis for most of the computational chemistry because it models the atoms and molecules with mathematics[86].

Currently, to determine molecular properties, there are three quantum approaches: *ab initio* methods, semi-empiric methods and methods based on Density Funcional Theory (DFT)[87, 88].

3.1.1.Quantum Chemical Models

The quantum models refer electrons not as particles, but as waves and its features[86]. Models such as Shrödinger equation and Hartree-Fock Approximation, which will be explained next, are examples of quantum chemical models used to describe a wavefunction of a physical system.

3.1.1.1. Shrödinger equation

Shrödinger equation, also called the Schrödinger wave equation, is a partial differential equation that describes how the wavefunction of a physical system evolves over time[89].

Quantum mechanics describes molecules and molecular geometry in terms of interactions between nuclei and electrons, and in terms of minimum energy arrangements of the nuclei, respectively. All quantum mechanical methods ultimately trace back to the Shrödinger equation, which is represented next.

$$\hat{H}\Psi = E\Psi$$

This Shrödinger equation is for multinuclear and multielectron systems. The Ψ represents a many-electron wavefunction and $\hat{H}$ represents the Hamiltonian operator, which in atomic units is given by.

$$\hat{H} = -\frac{1}{2}\sum_{i}^{electrons}\nabla_i^2 - \frac{1}{2}\sum_{A}^{nuclei}\frac{1}{M_A}\nabla_A^2 - \sum_{i}^{electrons}\sum_{A}^{nuclei}\frac{Z_A}{r_{iA}} + \sum_{i<j}^{electrons}\sum\frac{1}{r_{ij}} + \sum_{A<B}^{nuclei}\sum\frac{Z_A Z_B}{R_{AB}}$$

In here, Z is the nuclear charge, M_A is the ratio of mass of nucleus A to the mass of an electron, R_{AB} is the distance between nuclei A and B, r_{ij} is the distance between electrons i and j and r_{iA} is the distance between electron i and nucleus A.

However, the many-electron Shrödinger equation cannot be solved exactly, even for a two-electron system, and approximations to the equation are needed to provide practical methods[90].

3.1.1.2. Hartree-Fock Approximation

The Hartree Fock (HF) method expresses the total wavefunction of the system as a product of one-electron orbitals, and in this method, the wavefunction is an antisymmetrized determinantal product of one-electron orbitals (Slater determinant). Due to the impossibility (so far) to solve the Shrödinger equation, this one is transformed into a set of HF equations. The HF equation is also known as the self-consistent field (SCF) method[86, 90].

This method begins with a set of approximate orbitals for all the electrons in the system. After that, one electron is selected, and the potential in which it moves is calculated by freezing the distribution of all the other electrons and treating their averaged distribution as the centrosymmetric source of potential. The Schrödinger equation is solved for this potential, which gives a new orbital for it, and the procedure is repeated for all the other electrons in the system, using the electrons in the frozen orbitals as the source of the potential. At the end of one cycle, there are new orbitals from the original set, and the process is repeated until there is little or no change in the orbitals.[86]

3.1.2.Quantum Approches

Before start any investigation, we have to take into account the compound, and the results we expect in order to choose the better method. The most important methods, and the most used, are the *ab initio*, semi-empirical and DFT methods.

3.1.2.1. ab initio methods

ab initio methods are the methods obtained directly from classic physic theoretical principles, without any inclusion of experimental data[85, 87] and provides a systematic pathway toward the exact solution of the Schrödinger equation[91]. The more common *ab initio* type of calculation *ab initio* more common is called Hartree-Fock, where elctron-electron repulsion is not taking in account, being an approximation method for the wave determination, in the fundamental state of energy. These methods provide, generally, good qualitative results and are able to provide quantitative results each time more precise, as the molecules in question decrease in size[85].

For molecular systems of larger dimensions it was necessary the introduction of simplification in the *ab initio* methods, leading to the semi-empiric methods group[87].

3.1.2.2. Semi-empirical methods

Semi-empirical methods are simplified versions of HF theory using empirical corrections (derived from experimental data) in order to improve the performance. This method only takes into account the valence electrons and their respective orbitals[87], and is faster than *ab initio* methods [85].

Modeling tools have been widely applied for theoretical studies of various organic molecules with π-conjugated electron systems, in semi-empirical methods[92-94]. The

most popular semi-empirical methods are Austin Method 1 (AM1), Parameterization Method 3 (PM3) and Modified Neglect of Differential Overlap (MNDO). Recently, a new semi-empirical method named Recife Model 1 (RM1), being essentially an extensive re-parameterization of AM1, has come to use[92, 95].

3.1.2.3. DFT methods

DFT methods came up as the solution for molecular systems of large dimensions, treating the electronic correlation in a faster way [87]. These methods are a valuable research tool since they allow to validate conclusions achieved by experimental methods or to distinguished between probabilities left open. The calculation of a wide range of molecular properties with DFT methods allows a straight conection between the theory and experimental work, and conduct to important clues about geometry, electronic and spectroscopic properties[96].

The DFT principle is based on the idea that the energy of an electronic system can be described in terms of the electronic density probability ρ. The electronic energy E, is a functional of electronic density, designated by E[ρ]. In this case one function $\rho(r)$ corresponds to a single energy[87, 97]. This method is similar to the Schrödinger equation resolution, from which it follows that also has a detailed theory in the electronic structure and matter properties descriptions.

The pure DFT methods are defined through the combinations of exchange functional with a correlation functional. For example, the BLYP functional combine the exchange functional from Becke (B) gradient-corrected with the correlation functional Lee, Yang and Parr gradient-corrected (LYP).

The hybrid DFT methods are defined through the combination of the HF exchange term, which reflects the exchange interaction between electrons with equal spins and exchange-correlation functional of DFT. Currently the most widely used functional hybrids are functionals developed by Becke.

The Becke functionals hybrids have the general form:

$$E_{xc}^{\text{hib}} = C_{HF} E_x^{HF} + C_{DFT} E_x^{DFT}$$

In this equation, C_{HF} and C_{DFT} are constants. For example, the Becke hybrid functional with three parameters (B3LYP), E_{xc}^{B3LYP}, can be defined by the equation:

$$E_x^{LDA} + C_0(E_x^{HF} - E_x^{LDA}) + C_x E_x^{B88} + E_c^{VWN3} + C_c(E_c^{LYP} - E_c^{VWN3})$$

In here, $C_0 = 0.20$, $C_x = 0.72$ e $C_c = 0.81$. As this equation shows, the B3LYP hybrid method includes a misture of HF exchange terms and DFT, associated with the gradient-corrected correlation functional. From all recent functionals, the B3LYP remains the most popular due to its extremely high global performance[87].

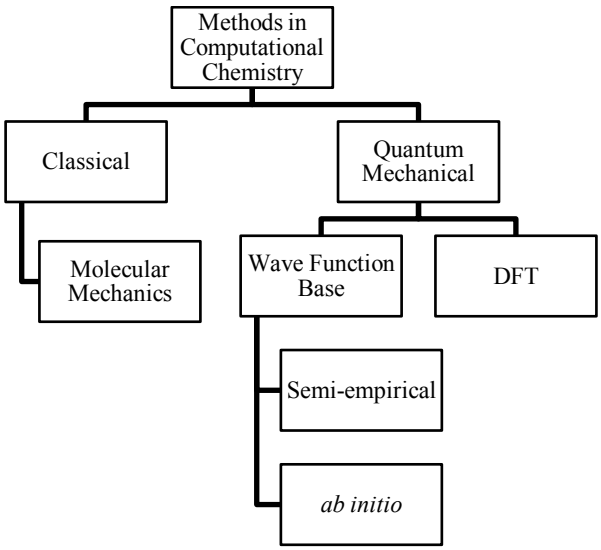


Figure 16: Classification of computational chemistry methods[98].

Table 6: Specifics of *ab initio*, semi-empirical and DFT methods.

Method	Advantages	Disadvantages	Best for
***ab initio*[99]**	- Uses quantum physics - Mathematically rigorous, no empirical parameters - Uses approximation extensively - Useful for a broad range of systems	- Computationally expensive	- Small systems (tens of atoms) - Systems involving electronic transitions - Molecules or systems without available experimental data ("new" chemistry) - Systems requiring rigorous accuracy

Semi-Empirical[99]	- Uses quantum physics - Uses experimentally derived empirical parameters - Uses approximation extensively - Less demanding computationally than *ab initio* methods - Capable of calculating transition states and excited states	- Requires experimental data (or data from *ab initio*) for parameters - Less rigorous than *ab initio*) methods	- Medium-sized systems (hundreds of atoms) - Systems involving electronic transitions
DFT	- Increase in computational accuracy without additional increase in computing time - Does not depend on experimental data - Capable of calculating transition states and excited states[99]	- Hard to determine the most appropriate method for a particular application[99]	- Molecular systems of large dimensions[87]

3.2.Software

There are some softwares in the market used in computational chemistry. The softwares that will be used to analyze quinoxalines are the Gabedit and Gaussian.

3.2.1.Gabedit

Gabedit is a free graphic interface which offers an adapted pre and pos-processing to new computational chemical software packages, such as Gamess-US, Molcas, Gaussian, Molpro and MPQC. This software includes edition, visualization, analysis and conversion tools, and animated molecular systems. Computational chemistry software files can be generated through Gabedit. It is possible to present molecular orbitals, electronic density, electrostatic potential, nuclear magnetic resonance density, among other volumetric data properties, as Ultraviolet-Visible (UV-Vis), InfraRed (IR) and Raman computed spectra. Gabedit also allows to creat Povray files to geometries, surfaces, contour and colour coded planes, and animated picture.

Gabedit includes an advanced Molecule Builder which can be used to draw molecules and examine them in three dimensions[100].

This interface also will be used to draw and to determine the Z-matrix (nonredundant internal coordinates)[101] of all the quinoxaline compounds. Gabedit will generate a input file for a computational chemistry software, which will be Gaussian.

3.2.1.1. Z-matrix

Z-matrix is a simple, although rough, geometrical approximation, good for large molecules once they can be converted to Cartesian coordinates. Z-matrix works by identifying each atom in a molecule by a bond distance and angle, and dihegral angle (angle between two planes) in relation to other atoms in the compound[86, 102]. The Z-matrix reading will be explained in the Chapter VI.

```
C
C       1       1.387106
N       2       1.332415        1       120.970461
C       3       1.332409        2       118.059032      1       0.000000
C       4       1.316025        3       118.837252      2       -0.631900
N       5       1.330426        4       126.840180      3       1.403764
O       6       1.251683        5       125.811668      4       165.250690
O       7       5.127817        6       6.228936        5       -92.670321
C       8       4.446039        7       31.076583       6       84.288111
C       9       1.296330        8       90.527948       7       -171.168698
C       10      2.320148        9       91.367475       8       0.501411
C       11      1.358653        10      31.626427       9       -176.934461
H       12      5.955234        11      48.922021       10      -3.186188
H       13      2.548770        12      70.952158       11      6.298723
H       14      5.786219        13      50.482378       12      9.951872
H       15      2.483421        14      110.369655      13      -157.421804
H       16      4.378584        15      89.878202       14      -5.112137
H       17      2.567778        16      30.969139       15      -168.678885
```

Figure 17: Z-matrix example of quinoxaline-1,4-dioxide compound, made on Gabedit software.

3.2.1.2. Basis Set

For the calculation of the Molecular Orbitals (MOs) the chemist must tell the computer some information first, such as geometry (bond lengths and angles, and dihedrals), kind of calculations (single point energy, frequency, transition state, electronic density, electrostatic potential) and the starting set of mathematics and approximations (calculation method (*ab initio*, semi-empirical or DFT), type of approximation (HF, Moller-Plesset,etc.) and basis set approximation).

In quantum chemistry, the "basis set" usually refers to the set of (nonorthogonal) one-particle functions used to build MOs. A MO theory calculation is a mathematical expression of an electron in a molecule. There are many types of MO functions, being the Slater Type Orbitals (STOs) and the Gaussian Type Orbitals (GTOs) two well known functions. There is no significant difference between these two functions when calculating

small molecules, but in larger molecules, with 30 or more atoms, the discrepencies come up[86].

STOs requires more time than GTOs due to the great number of calculations that are made. However their calculations were found to be more accurate. Nevertheless, GTOs are much faster, and scientists realized that by adding several GTOs, they were able to mimic STOs accuracy.

When using GTOs to model STOs, the new equations are given a new name, and identified as STO-xG equations, being the x a constant that represents the number of GTOs used. Two common equations are the STO-3G and the STO-6G in which 3 and 6 GTOs are used respectively[86].

3.2.2.Gaussian

Gaussian, a computational chemistry software, allows the calculation of energies, geometries, vibrational frequencies, transition states, reaction pathways, excited states and a number of properties based in wave functions correlated and non-correlated. This software is widely used by chemists, chemical engineers, biochemists, and physics, among others.

Based on quantum mechanic basic laws, Gaussian can predict energies, molecular structures, and vibration frequencies of molecular systems, along with several molecular properties derived therefrom. This software can be used to study molecules and reactions under a wide range of different conditions, including stable species and compounds, which are from difficult or impossible observation experimentally, as like as short life intermediates and transition structures. Several research groups use Gaussian to perform advanced theorical calculations, which are used to predict numerous properties of atoms, molecules, radicals, ions, strongly and weakly ligand complexes, among others. Though, Gaussian is also widely used to determine structures in equilibrium, IR and Raman intensities and frequencies, and to determine the enthalpie calculations of formation from several chemical species. It is specially usefull when there are no experimental data available, or when is difficult to determine their properties by experimental methods[102, 103].

The Gaussian will be used to optimize geometries of all quinoxalines models constructed in Gabedit, using DFT at the B3LYP level with 6-31G** basis set. In this basis

set, the interior orbital layer *s* is represented by three functions, with interior and exterior character. The first asterisk means the addition of a complete set of *d* type Gaussian polarization functions for each atom from second period present in the system under study, and the second asterisk, the addition of a set of Gaussian functions of *p* type to each hydrogen atoms[87].

Chapter IV:
Objectives

4.Objectives

This study pretends to determine the molecular properties of the quinoxaline *N*,*N*-dioxide and some of its derivatives, through computational chemistry methods. Being such a wide scope, the main objective was refined in the following specific objectives, which were the basis for the work timeline:

1) State of the art review of quinoxalines and its derivatives.
    - This objective allowed a specialization in the quinoxalines features and activities, and resulted in an article already submitted in a peer reviewed journal, the European Journal of Medicinal Chemistry.
2) Design the quinoxaline *N*,*N*-dioxide and its derivatives in Gabedit and extract the Z-matrix, as the first step of the computational calculations.
    - This objective was fully reached, and all the Z-matrices were extracted and are presented in the results chapter.
3) Using the Gaussian program, determine the single-point energy of each compound, and therefore obtain the numeric value of the potential energy surface.
    - The data files were written and prepared for all the compounds. The specific single-points calculations followed and already two reached a successful final. The remaining compounds are running at the present time.
4) Using the Gabedit, analyze various properties of the compounds, to understand their different reactivity and compare with biological activity already observed by the investigation group.
    - Due to computational logistic, it was not possible to accomplish this specific objective in this present work, though the analysis is on course.

Chapter V:

Methods and Materials

5.Materials and Methods

In this section are presented the compounds, materials and methods used in the present study.

5.1.Compounds

The compounds which will be analysed in this study have been studied previously by the research group members, in order to determine their energetic properties as well as biological activity.

Table 7: Compounds under study.

Compounds
Quinoxaline 1,4-dioxide (QNX)
2-methylquinoxaline-1,4-dioxide (2MQNX)
2-methyl-3-benzoylquinoxaline-1,4-dioxide (2M3BenzoilQNX)
2-methyl-3-benzylquinoxaline-1,4-dioxide (2M3BQNX)
2-amino-3-cyanoquinoxaline-1,4-dioxide (2A3CQNX)
3-methyl-2-quinoxalinecarboxamide-1,4-dioxide (3M2QNXC)
2-hydroxyphenazine-*N*-dioxide (2HF)
3-amino-2-quinoxalinecarbonitrile-1,4-dioxide (3A2QNXCN)
3-methyl-*N*-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide (3MN(2MF)QNXC)

5.2.Methods

The analysis of the quinoxalines and its derivatives will be performed using computational chemistry programs. For this were used computers (Hardware: HP Portable Computer and Cluster Matheor from Faculty of Science from Porto University) in which the necessary softwares are installed to procced to the compounds analysis (Software: Gabedit 2.1.0 in HP Portable Computer, and Gaussian on Cluster Matheor from Faculty of Science from Porto University).

Gabedit can be used to draw the compounds and extract the Z-matrices, as the first step of the computational calculations. The file extracted from Gabedit can be processed in

Gaussian to determine the single-point energy of each compound, and therefore obtain the numeric value of the potential energy surface.

Table 8: Hardware and software used in the study.

Hardware	Software
Portable Computer HP	Gabedit 2.1.0
Super Computer Cluster Matheor: 216 processors dispersed in 27 nodes with the following features: - vendor_id : GenuineIntel - cpu family : 6 - model : 30 - model name : Intel(R) Xeon(R) CPU X3430 @ 2.40GHz - cpu MHz : 2394.187 - cache size : 8192 KB	Gaussian

Chapter VI:

Results

6.Results

In this chapter it will be presented the design and the respective Z-matrix of each compound in study. For the first compound, quinoxaline 1,4-dioxide, is presented also a *dat.* file generated by Gaussian software.

6.1. *Quinoxaline-1,4-dioxide* (QNX)

Results from quinoxaline-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 18)**; Z-matrix obtained in Gabedit **(Figure 19)**; and *dat.* file generated by Gaussian, after analysis **(Figure 20)**.

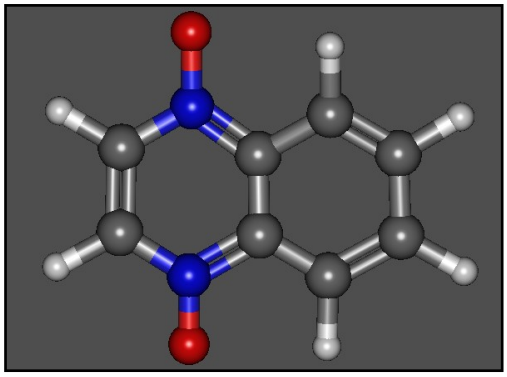


Figure 18: Quinoxaline-1,4-dioxide 3D structure (non-optimized), designed in Gabedit software**.**

```
C
C       1       1.387106
N       2       1.332415        1       120.970461
C       3       1.332409        2       118.059032      1       0.000000
C       4       1.316025        3       118.837252      2       -0.631900
N       5       1.330426        4       126.840180      3       1.403764
O       6       1.251683        5       125.811668      4       165.250690
O       7       5.127817        6       6.228936        5       -92.670321
C       8       4.446039        7       31.076583       6       84.288111
C       9       1.296330        8       90.527948       7       -171.168698
C       10      2.320148        9       91.367475       8       0.501411
C       11      1.358653        10      31.626427       9       -176.934461
H       12      5.955234        11      48.922021       10      -3.186188
H       13      2.548770        12      70.952158       11      6.298723
H       14      5.786219        13      50.482378       12      9.951872
H       15      2.483421        14      110.369655      13      -157.421804
H       16      4.378584        15      89.878202       14      -5.112137
H       17      2.567778        16      30.969139       15      -168.678885
```

Figure 19: Z-matrix of Quinoxaline-1,4-dioxide compound, generated by Gabedit.

In **Figure 19**, the first line specifies an atom, in this case a carbon. The next line lists another carbon atom and specifies the internuclear distance between it and the first carbon as 1,387106 Ångstroms (Å). The third line defines the nitrogen with an N-C distance of 1,332415

Å (i.e., from atom 2, which is the second carbon atom) and having an N-C-C angle (with atoms 1 and 2) of 120,970461 degrees. After the fourth line all three internal coordinates need to be given. It defines the other carbon as bonded to the nitrogen with an C-N distance of 1,332409 Å, an C-N-C angle of 118,06 degrees (atom 4 - N - atom 2) and a C-N-C-C (i.e., atom 4 - N - atom 2 – atom 1) dihedral angle of 0 degrees. This explanation applies to the following Z-matrices.

After the determination of the Z-matrix, we have calculated the optimized structure. We used a *dat.*file, showed in ***Figure 20***, generated in Gaussian. This *dat.*file will allow the computation of the optimized structure, in order to use it in a single point energy calculation, on a subsequent phase, and therefore obtain the energetic parameters pretended.

In the *dat.*files, the first line represents the number of processors used in the analysis (seven processors in this case); the second line represents the memory extension (500MB); the third line the name of the single point; in the fourth and fifth lines are represented the specific instructions for the calculation; the sixth line is the file name given by the user; the seventh line represents the charge and multiplicity (in this case the charge is 0 and multiplicity 1); the remaining lines refers to the optimized Z-matrix of the Quinoxaline-1-4-dioxide compound.

The instructions for the remaining coumpounds will as follows:

```
%nproc=8
%mem=500MB
%chk=opt_quinoxalina_2A3CQNX
#B3LYP/6-31G** opt=(maxcyc=500) scf=(maxcyc=500) TEST.
```

The name of the third line, change in accordance with the compound in analysis.

```
%nproc=7
%mem=500MB
%chk=sp_ quinoxaline-1,4-dioxide
#B3LYP gen pseudo=read sp
scf=(maxcyc=500,Conver=6)
#P Gfinput IOP(6/7=3) Pop=full

Quinoxaline-1,4-dioxide (QNX)

0 1
C
C     1    dist1
N     2    dist2  1    ang1
C     3    dist3  2    ang2   1    died1
C     4    dist4  3    ang3   2    died2
N     5    dist5  4    ang4   3    died3
O     6    dist6  5    ang5   4    died4
O     7    dist7  6    ang6   5    died5
C     8    dist8  7    ang7   6    died6
C     9    dist9  8    ang8   7    died7
C     10   dist10 9    ang9   8    died8
C     11   dist11 10   ang10  9    died9
H     12   dist12 11   ang11  10   died10
H     13   dist13 12   ang12  11   died11
H     14   dist14 13   ang13  12   died12
H     15   dist15 14   ang14  13   died13
H     16   dist16 15   ang15  14   died14
H     17   dist17 16   ang16  15   died15

dist1    1.387106      dist11   1.358653
dist2    1.332415      ang10    31.626427
ang1     120.970461    died9    -176.934461
dist3    1.332409      dist12   5.955234
ang2     118.059032    ang11    48.922021
died1    0.000000      died10   -3.186188
dist4    1.316025      dist13   2.548770
ang3     118.837252    ang12    70.952158
died2    -0.631900     died11   6.298723
dist5    1.330426      dist14   5.786219
ang4     126.840180    ang13    50.482378
died3    1.403764      died12   9.951872
dist6    1.251683      dist15   2.483421
ang5     125.811668    ang14    110.369655
died4    165.250690    died13   -157.421804
dist7    5.127817      dist16   4.378584
ang6     6.228936      ang15    89.878202
died5    -92.670321    died14   -5.112137
dist8    4.446039      dist17   2.567778
ang7     31.076583     ang16    30.969139
died6    84.288111     died15   -168.678885
dist9    1.296330
ang8     90.527948
died7    -171.168698
dist10   2.320148
ang9     91.367475
died8    0.501411
```

Figure 20: *dat.* file of Quinoxaline-1,4-dioxide generated by Gaussian.

6.2. *2-methylquinoxaline-1,4-dioxide* (2MQNX)

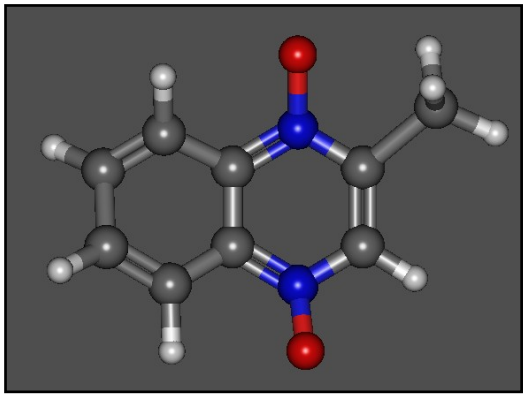


Figure 21: 2-methylquinoxaline-1,4-dioxide 3D structure (non-optimized), designed in Gabedit software.

C						
C	1	1.387106				
N	2	1.332415	1	120.970461		
C	3	1.332409	2	118.059032	1	0.000000
C	4	1.387112	3	120.970497	2	0.000048
N	5	1.332410	4	120.970461	3	0.000100
H	6	3.339772	5	21.124656	4	0.000085
O	7	4.465069	6	11.948781	5	29.967508
O	8	5.217537	7	26.673945	6	41.676448
C	9	4.870843	8	29.610485	7	14.425791
H	10	1.179000	9	93.805947	8	-163.960271
H	11	1.978546	10	32.957118	9	-106.368623
H	12	1.841415	11	59.777856	10	-40.288324
C	13	6.182113	12	72.140881	11	93.493556
C	14	2.656163	13	50.086027	12	104.579221
C	15	2.268791	14	30.471912	13	-167.569297
C	16	1.528882	15	32.413664	14	-127.781228
H	17	3.439625	16	26.551946	15	72.178904
H	18	4.861391	17	22.801749	16	-94.537488
H	19	3.892649	18	32.662951	17	58.687292
H	20	3.043393	19	45.622334	18	-96.858255

Figure 22: Z-matrix of 2-methylquinoxaline-1,4-dioxide compound, generated by Gabedit.

Results from 2-methylquinoxaline-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 21)**; and Z-matrix obtained in Gabedit **(Figure 22)**.

6.3. *2-methyl-3-benzoylquinoxaline-1,4-dioxide* (2M3BenzoilQNX)

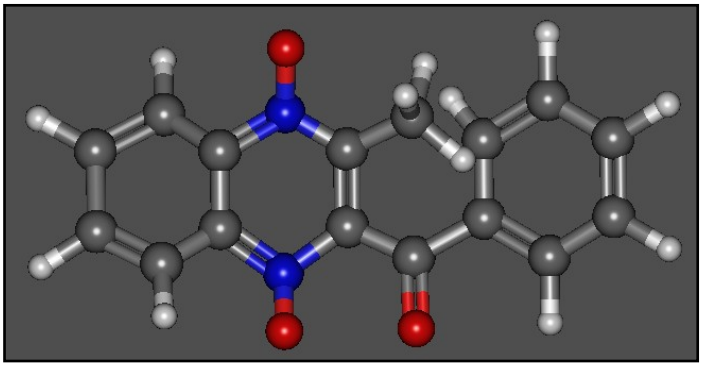


Figure 23: 2-methyl-3-benzoylquinoxaline-1,4-dioxide 3D structure (non-optimized), designed in Gabedit software.

C						
C	1	1.397342				
C	2	2.502601	1	32.678595		
C	3	4.712780	2	43.623921	1	-173.951387
C	4	1.387106	3	72.371052	2	-152.262554
N	5	1.418591	4	125.239360	3	-3.383236
C	6	1.392365	5	108.748544	4	0.900748
C	7	1.387112	6	126.005310	5	-0.909443
C	8	2.286966	7	30.835651	6	-159.638725
C	9	5.191122	8	32.746833	7	34.242702
C	10	2.510670	9	60.754215	8	-160.500486
O	11	1.318773	10	159.801381	9	-88.335504
C	12	4.716158	11	35.462947	10	-61.702951
C	13	1.399946	12	89.846118	11	-166.702371
C	14	1.399961	13	119.995045	12	7.045526
C	15	1.400059	14	120.002956	13	0.000014
C	16	1.399691	15	119.996122	14	-0.045174
C	17	1.399961	16	120.000897	15	0.045173
N	18	3.586372	17	98.330540	16	-166.784104
O	19	3.916974	18	82.139632	17	5.303269
O	20	5.045140	19	6.431751	18	85.687606
H	21	4.706214	20	74.069998	19	76.355166
H	22	2.726071	21	28.703937	20	-105.240557
H	23	4.562105	22	33.210138	21	68.745821
H	24	2.645759	23	88.034660	22	-149.468909
H	25	5.840747	24	113.920887	23	10.653697
H	26	2.911862	25	152.709053	24	-103.722931
H	27	2.579028	26	117.342313	25	-73.659974
H	28	2.578979	27	119.996028	26	38.436530
H	29	2.579067	28	120.001274	27	0.000012

Figure 24: Z-matrix of 2-methyl-3-benzoylquinoxaline-1,4-dioxide compound, generated by Gabedit.

Results from 2-methyl-3-benzoylquinoxaline-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 23)**; and Z-matrix obtained in Gabedit **(Figure 24)**.

6.4. *2-methyl-3-benzylquinoxaline-1,4-dioxide* (2M3BQNX)

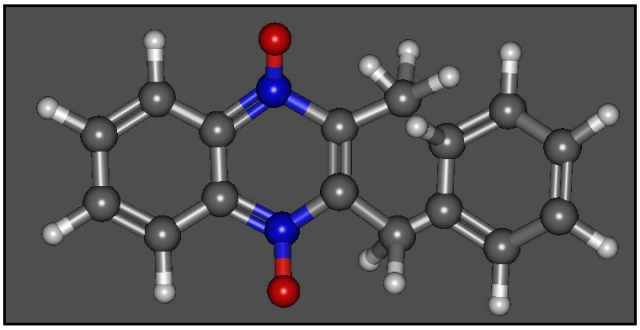


Figure 25: 2-methyl-3-benzylquinoxaline-1,4-dioxide 3D structure (non-optimized), design in Gabedit software.

C						
C	1	2.784681				
C	2	2.496665	1	30.533081		
C	3	2.494339	2	116.799215	1	-177.841546
C	4	1.399304	3	89.094531	2	-0.908111
C	5	1.398938	4	119.608146	3	176.125706
C	6	1.397066	5	120.560122	4	-0.116445
C	7	1.397281	6	119.796593	5	0.065554
C	8	1.397594	7	119.772474	6	0.086075
C	9	6.298642	8	126.517828	7	-4.675892
C	10	1.399946	9	168.434936	8	-7.455862
C	11	1.399961	10	119.995084	9	-166.743919
C	12	1.400059	11	120.002957	10	0.000049
C	13	1.399691	12	119.996091	11	-0.045123
C	14	1.399961	13	120.000890	12	0.045123
N	15	3.825145	14	178.110349	13	71.455982
N	16	2.874435	15	65.279196	14	104.080910
C	17	2.532616	16	32.279711	15	-10.023588
O	18	3.654295	17	16.008981	16	-151.677904
O	19	5.562298	18	19.876237	17	44.928207
H	20	5.675555	19	31.578238	18	-17.305353
H	21	1.841415	20	45.855672	19	156.889764
H	22	3.353625	21	140.784021	20	-16.883385
H	23	1.863759	22	52.551310	21	97.030560
H	24	4.835683	23	76.191323	22	-116.882409
H	25	2.572882	24	141.441673	23	122.414435
H	26	2.580119	25	119.881028	24	-16.060472
H	27	2.574458	26	119.854370	25	0.180930
H	28	8.871665	27	110.271763	26	-3.859333
H	29	2.578978	28	115.070825	27	-173.325355
H	30	2.579067	29	120.001268	28	-2.025745
H	31	2.578717	30	119.997445	29	-0.086495

Figure 26: Z-matrix of 2-methyl-3-benzylquinoxaline-1,4-dioxide compound, generated by Gabedit.

Results from 2-methyl-3-benzylquinoxaline-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 25)**; and Z-matrix obtained in Gabedit **(Figure 26)**.

6.5. *2-amino-3-cyanoquinoxaline-1,4-dioxide* (2A3CQNX)

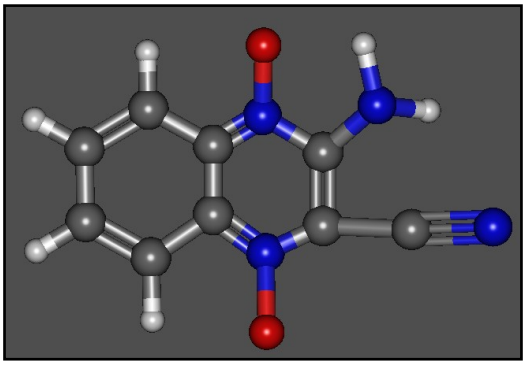


Figure 27: 2-amino-3-cyanoquinoxaline-1,4-dioxide 3D structure (non-optimized), design in Gabedit software.

C						
N	1	1.332415				
C	2	1.332409	1	118.059032		
C	3	1.387112	2	120.970497	1	0.000048
N	4	1.332410	3	120.970461	2	0.000100
C	5	3.403273	4	138.936479	3	0.003747
C	6	1.399947	5	99.132934	4	-0.036755
C	7	1.399962	6	119.995069	5	0.026933
C	8	2.424607	7	90.005370	6	-0.022610
C	9	1.399961	8	89.994589	7	0.000000
H	10	2.153433	9	145.741496	8	0.003909
H	11	2.479917	10	94.267896	9	0.000562
H	12	4.295819	11	29.996951	10	0.010220
H	13	4.485071	12	32.860863	11	-153.641811
O	14	5.188134	13	25.535909	12	-146.043295
O	15	6.109915	14	30.359150	13	151.772019
N	16	5.426848	15	23.201063	14	142.815618
H	17	1.179000	16	143.128576	15	15.305966
H	18	1.939842	17	34.647600	16	-159.693201
C	19	2.376386	18	112.837845	17	-11.506882
N	20	1.605680	19	86.410818	18	-120.896490

Figure 28: Z-matrix of 2-amino-3-cyanoquinoxaline-1,4-dioxide compound, generated by Gabedit.

Results from 2-amino-3-cyanoquinoxaline-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 27)**; and Z-matrix obtained in Gabedit **(Figure 28)**.

6.6. *3-methyl-2-quinoxalinecarboxamide-1,4-dioxide* (3M2QNXC)

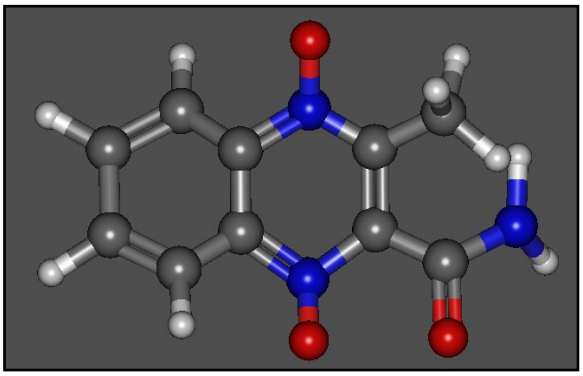


Figure 29: 3-methyl-2-quinoxalinecarboxamide-1,4-dioxide 3D structure (non-optimized), design in Gabedit software.

C						
C	1	1.397342				
C	2	2.502601	1	32.678595		
C	3	4.712780	2	43.623921	1	-173.951387
C	4	1.387106	3	72.371052	2	-152.262554
N	5	1.418591	4	125.239360	3	-3.383236
C	6	1.392365	5	108.748544	4	0.900748
C	7	1.387112	6	126.005310	5	-0.909443
C	8	2.286966	7	30.835651	6	-159.638725
C	9	5.191122	8	32.746833	7	34.242702
C	10	2.510670	9	60.754215	8	-160.500486
O	11	1.318773	10	159.801381	9	-88.335504
N	12	4.535262	11	30.092074	10	80.285786
O	13	3.916974	12	31.343004	11	161.483226
O	14	5.045140	13	6.431751	12	86.148385
H	15	4.706214	14	74.069998	13	76.355166
H	16	2.726071	15	28.703937	14	-105.240557
H	17	4.562105	16	33.210138	15	68.745821
H	18	2.645759	17	88.034660	16	-149.468909
H	19	6.660655	18	104.567837	17	-2.949632
H	20	1.978545	19	64.554000	18	-166.583416
H	21	1.841415	20	59.777842	19	-65.725998
N	22	3.168809	21	9.509961	20	110.518958
H	23	1.179000	22	53.020394	21	-43.365951
H	24	1.939842	23	34.647572	22	-173.349567

Figure 30: Z-matrix of 3-methyl-2-quinoxalinecarboxamide-1,4-dioxide compound, generated by Gabedit.

Results from 3-methyl-2-quinoxalinecarboxamide-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 29)**; and Z-matrix obtained in Gabedit **(Figure 30)**.

6.7. *2-hydroxyphenazine-N-dioxide* (2HF)

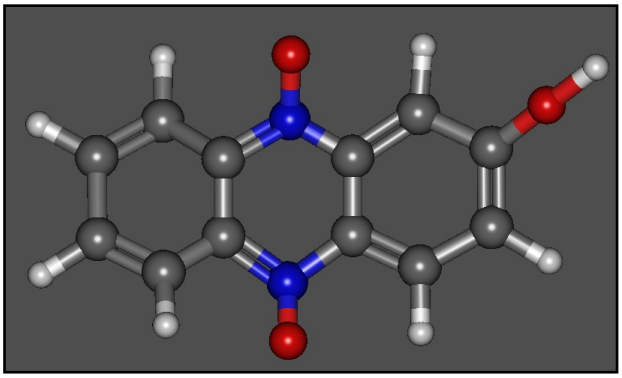


Figure 31: 2-hydroxyphenazine-*N*-dioxide 3D structure (non-optimized), design in Gabedit software.

C						
C	1	1.397342				
C	2	2.502601	1	32.678595		
C	3	4.712780	2	43.623921	1	-173.951387
C	4	1.387106	3	72.371052	2	-152.262554
N	5	1.418591	4	125.239360	3	-3.383236
C	6	1.392365	5	108.748544	4	0.900748
C	7	1.387112	6	126.005310	5	-0.909443
C	8	2.286966	7	30.835651	6	-159.638725
C	9	5.191122	8	32.746833	7	34.242702
C	10	2.510670	9	60.754215	8	-160.500486
C	11	1.444228	10	61.441341	9	-172.776141
C	12	1.399961	11	118.242641	10	-6.440197
N	13	3.586372	12	98.330540	11	0.946438
O	14	3.916974	13	82.139632	12	5.303269
O	15	5.045140	14	6.431751	13	85.687606
H	16	4.706214	15	74.069998	14	76.355166
H	17	2.726071	16	28.703937	15	-105.240557
H	18	4.562105	17	33.210138	16	68.745821
H	19	2.645759	18	88.034660	17	-149.468909
H	20	4.588523	19	136.583926	18	-39.468090
H	21	4.469483	20	90.918179	19	51.813423
H	22	3.948887	21	35.112605	20	161.052434
O	23	2.779891	22	40.687397	21	-148.839026
H	24	1.179000	23	127.016883	22	-170.080233

Figure 32: Z-matrix of 2-hydroxyphenazine-*N*-dioxide compound, generated by Gabedit.

Results from 2-hydroxyphenazine-*N*-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 31)**; and Z-matrix obtained in Gabedit **(Figure 32)**.

6.8. *3-amino-2-quinoxalinecarbonitrile-1,4-dioxide* (3A2QNXCN)

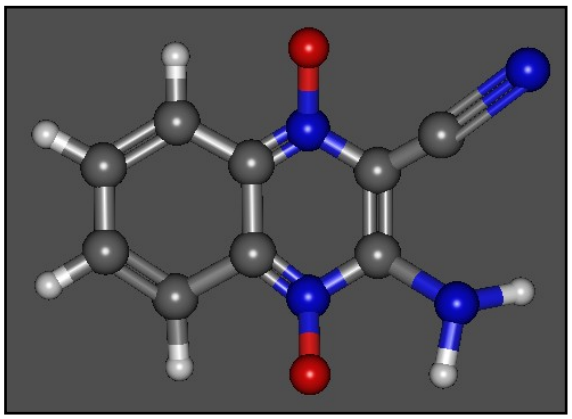


Figure 33: 3-amino-2-quinoxalinecarbonitrile-1,4-dioxide 3D structure (non-optimized), designed in Gabedit software.

C						
N	1	1.332415				
C	2	1.332409	1	118.059032		
C	3	1.387112	2	120.970497	1	0.000048
N	4	1.332410	3	120.970461	2	0.000100
C	5	3.403273	4	138.936479	3	0.003747
C	6	1.399947	5	99.132934	4	-0.036755
C	7	1.399962	6	119.995069	5	0.026933
C	8	2.424607	7	90.005370	6	-0.022610
C	9	1.399961	8	89.994589	7	0.000000
H	10	2.153433	9	145.741496	8	0.003909
H	11	2.479917	10	94.267896	9	0.000562
H	12	4.295819	11	29.996951	10	0.010220
H	13	4.485071	12	32.860863	11	-153.641811
O	14	5.188134	13	25.535909	12	-146.043295
O	15	6.109915	14	30.359150	13	151.772019
N	16	3.076839	15	51.767231	14	144.335314
H	17	1.179000	16	142.847108	15	-133.496578
H	18	1.939843	17	34.647553	16	-32.981169
C	19	3.972819	18	45.898252	17	5.386614
N	20	1.836666	19	121.067208	18	-40.162643

Figure 34: Z-matrix of 3-amino-2-quinoxalinecarbonitrile-1,4-dioxide compound, generated by Gabedit.

Results from 3-amino-2-quinoxalinecarbonitrile-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 33)**; and Z-matrix obtained in Gabedit **(Figure 34)**.

6.9. *3-methyl-N-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide* (3MN(2MF)QNXC)

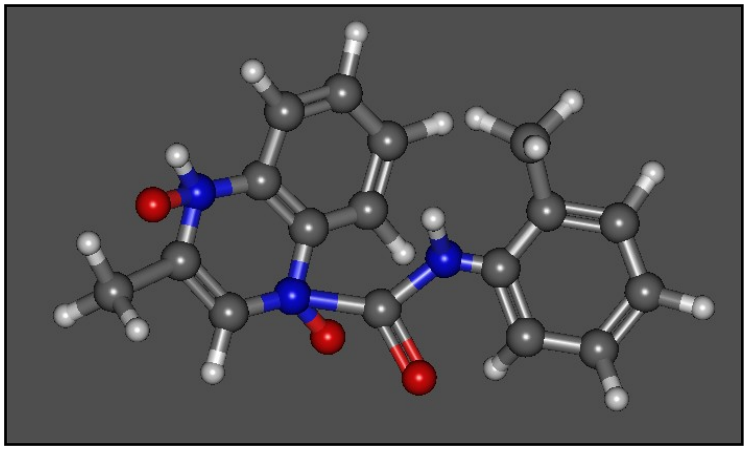


Figure 35: 3-methyl-*N*-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide 3D structure (non-optimized), designed in Gabedit software.

```
C
C     1     1.387106
N     2     1.332415   1     120.970461
C     3     1.332409   2     118.059032  1     0.000000
C     4     1.316025   3     118.837252  2     -0.631900
N     5     1.330426   4     126.840180  3     1.403764
O     6     3.885897   5     54.992413   4     -4.693075
C     7     4.446039   6     30.935075   5     6.120323
C     8     1.296330   7     90.527948   6     -167.289768
C     9     2.320148   8     91.367475   7     0.501411
C     10    1.358653   9     31.626427   8     -176.934461
H     11    5.661607   10    24.011571   9     3.401917
H     12    5.786219   11    34.564252   10    178.135248
H     13    2.483421   12    110.369655  11    4.947779
H     14    4.378584   13    89.878202   12    -5.112137
H     15    2.567778   14    30.969139   13    -168.678885
H     16    5.678610   15    69.230947   14    3.747338
O     17    1.053068   16    123.392389  15    4.237250
C     18    1.843407   17    178.334255  16    53.603691
H     19    1.179000   18    120.752376  17    17.857133
H     20    1.978545   19    32.957162   18    -177.914392
H     21    1.841415   20    59.777859   19    -40.288354
C     22    6.274670   21    79.052749   20    58.054825
O     23    1.505114   22    123.009432  21    -65.095132
N     24    2.314888   23    40.975178   22    -141.024470
H     25    1.179000   24    123.012646  23    75.897949
C     26    1.812553   25    34.800383   24    104.660134
C     27    1.399946   26    91.532249   25    140.248741
C     28    1.399962   27    119.995081  26    152.581431
C     29    1.400059   28    120.002927  27    0.000017
C     30    1.399691   29    119.996159  28    -0.045276
C     31    1.399961   30    120.000856  29    0.045289
C     32    3.760932   31    98.013196   30    -8.566157
H     33    1.179000   32    97.294387   31    -83.115159
H     34    1.978546   33    32.957127   32    -113.555786
H     35    1.841415   34    59.777837   33    -40.288323
H     36    4.648482   35    112.524446  34    64.079089
H     37    2.773453   36    16.156186   35    138.703552
H     38    4.821054   37    62.012332   36    -56.078805
H     39    2.785147   38    64.389609   37    14.069855
```

Figure 36: Z-matrix of 3-methyl-*N*-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide compound, generated by Gabedit.

Results from 3-methyl-*N*-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide compound: 3D structure (non-optimized) designed in Gabedit **(Figure 35)**; and Z-matrix obtained in Gabedit **(Figure 35)**.

Chapter VII:

Discussion

7.Discussion

The aim of the present study was to analyze, by means of theoretical and computational chemistry, quinoxaline *N-N*-dioxide and the derivatives presented, and to determine some of their chemical properties. This work required an extensive analysis about quinoxalines, its properties and potentials, resulting in an article (present in the *Adendum* of this work) submitted and render review in a peer reviewed journal, the European Journal of Medicinal Chemistry, allowing a tranverse and deep insight about the theme.

There were used nine quinoxalines: quinoxaline 1,4-dioxide (QNX), 2-methylquinoxaline-1,4-dioxide (2MQNX), 2-methyl-3-benzoylquinoxaline-1,4-dioxide (2M3BenzoilQNX), 2-methyl-3-benzylquinoxaline-1,4-dioxide (2M3BQNX), 2-amino-3-cyanoquinoxaline-1,4-dioxide (2A3CQNX), 3-methyl-2-quinoxalinecarboxamide-1,4-dioxide (3M2QNXC), 2-hydroxyphenazine-*N*-dioxide (2HF), 3-amino-2-quinoxalinecarbonitrile-1,4-dioxide (3A2QNXCN) and 3-methyl-*N*-(2-methylphenyl)quinoxalinecarboxamide-1,4-dioxide (3MN(2MF)QNXC).

The first step was to design all the molecules in the Gabedit software. Gabedit allows drawing molecules by atom or by fragment, owning a database with more than 100 fragments available (linear molecules, ring molecules, polypeptides, polynucleic acids, among others). It is important to double check all the structures, to examine if all the bonds and atoms are in the right positions, since this step will constrain all the further results.

After all compounds have been correctly drawn, the next step was to obtain the Z-matrix and consequently the input file for Gaussian software. Still in Gabedit software, we selected the Gaussian icon, to introduce all the desirable parameters. In here we had to choose the method, basis set and type of calculation. The method used was HF, the basis set was 6-31G** (as explained in Chapter III), and the type of calculation was the geometry optimization. For the calculation was choosed the geometry optimization and selected the Z-matrix box (can also be selected XYZ coordinates), to obtain the Z-matrix of each quinoxaline. After all paramethers selected we click in the NEXT button, obtaining a new window with Z-matrix of the molecule. In page 32 of this work is explained how to read the Z-matrix file. The geometry can be optimized by defining variables, but in this study the Z-matrix don't have any variable defined. Then, clicking on the FINISH button, Gabedit software generates the input file, necessary for Gaussian.

The files are then introduced in Gaussian, and after processed, it will prepared a *dat.* file, which will allow us to calculate the single point energy. The single point energy will be introduced in Gabedit, to analyze various properties of the compounds and to understand their different reactivity. At this moment only two compounds reached the final stage of the Gaussian process, and the remaining quinoxaline files are running. In this work we present the single point energy of the quinoxaline-1,4-dioxide, present in the Chapter VI. The first line of the file indicates the number of processors used in the analysis; the second line indicates the memory extention necessary for the process; the third line indicates the name of the single point *chk.* file; the fourth and fifth line indicates all the specific instruction for the calculation (B3LYP and SCF); the sixth line is the name the user give to the file; the seventh give us the charge (in this case is 0, i.e., do not have positive or negative charge) and multiplicity (for this compound is 1, which means that there are no unpaired electrons); the next lines correspond to the Z-matrix, optimized with variables.

The computational processes are cumbersome and require a certain amount of time. By restrainments imposed by the article 20th of the 74/2006 law from Education and Science Ministry of the Portuguese government, which dictates the duration for the dissertation required time, it is not possible, at the present time, to describe all the results proposed in the objectives.

Chapter VIII:

Conclusions

8.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, that include antimicrobial, antitubercular, antiviral, antifungal, antiamoebic, antimalarial and leishmanial, antidiabetic, antiproliferative, anti-inflamatory, 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 benefict humanity. Regarding quinoxaline derivatives potential in industry, they have shown great outcomes in metal corrosion inhibition, led to an increase in both sensitivity and selectivity in Cu^{2+} detection in colorimetric sensors, and showed to be excellent as host materials for use in phosphorescent OLEDs. These findings are very important for the industry field, decreasing costs (inhibition metal corrosion) and increasing efficiency (OLED).

The experimental studies of the quinoxalines and its derivatives provide a valious information about their features, but it is crucial a deep understanding of the molecules. Thus, theoretical chemistry methods have been introduced as novel, effective and inexpensive ways to perform the primary characterization of the compounds. Computational chemistry is the natural sequence of the theoretical chemistry, which is used to represent molecular structures, simulating its behavior with classic and quantum physics equations. It is a well developed method to determine molecular properties, using one of the three quantum approaches: *ab initio* methods, semi-empiric methods and methods based on DFT.

The softwares that were used to analyze quinoxalines are the Gabedit and Gaussian, computational chemistry softwares which allow determining a large number of compounds features such as the calculation of energies, geometries, vibrational frequencies, transition states, reaction pathways, excited states and a number of properties based in wave functions correlated and non-correlated.

In the present work, the Gabedit proved indeed to be a useful method to design the compounds and extract the Z-Matrix, as well as the preliminary stage of writing the Gaussian *dat.* files. The computational data is being obtained, as the computer cluster runs the single-point calculations and future perspectives of a insightful analysis are positive.

There is some enthusiastic hope that the present work will allow us to understand the particular microscopic features that may explain the differences in the quinoxalines reactivity and biological activity, as the computational calculations reach successful end and are then analyzed.

References:

1. Deepika Y., N.P., Sachin K., Shewta S., *Biological activity of quinoxaline derivatives.* International Journal of Current Pharmaceutical Review and Research, 2011. **1**(3): p. 33-46.
2. G. W. H. Chesseman, R.F.C., *The Chemistry of Heterocyclic Compounds, Condensed Pyrazines*, 1979, John Wiley & Sons, Inc.
3. Z. El Adnani, M.M., M. Sfaira, M. Benzakour, A. Benjelloun, M. Ebn Touhami, B. Hammouti, M. Taleb, *DFT Study of 7-R-3methylquinoxalin-2(1H)-ones (R=H; CH_3; Cl) as Corrosion Inhibitors in Hydrochloric Acid.* International Journal of Electrochemical Science, 2012. **7**: p. 13.
4. I.B. Obot, N.O.O.-E., *2,3-Diphenylbenzoquinoxaline: A new corrosion inhibitor for mild steel in sulphuric acid.* Corrosion Science, 2010. **52**(1): p. 3.
5. Mwadham M. Kabanda, E.E.E., *Density Functional Theory and Quantitative Structure-Activity Relationship Studies of some Quinoxaline derivatives as potential Corrosion Inhibitors for Copper in Acidic Medium.* International Journal of Electrochemical Science, 2012. **7**: p. 20.
6. Gitanjali Sharma, P.R., Ignatious Abraham, R T Pardasani, Tulsi Mukherjee, *Synthesis of quinoxaline quinones and regioselectivity in their Diels-Alder Cycloadditions.* Indian Journal of Chemistry, 2009. **48B**: p. 6.
7. K. R. Justin Thomas, M.V., Jiann T. Lin, Chang-Hao Chuen, Yu-Tai Tao, *Chromophore-Labeled Quinoxaline Derivatives as Efficient Electroluminescent Materials.* Chem. Mater., 2005. **17**: p. 6.
8. Dong Wook Chang, S.-J.K., Jin Young Kim, Liming Dai, Jong-Beom Baek, *Multifunctional quinoxaline xontaining small molecules with multiple electron-donating moieties: Solvatochromic and optoelectronic properties.* Synthetic Metals, 2012. **162**(13-14): p. 7.
9. Carta A., P.G., Nikookar M., Sanna P., Sechi L., Zanetti S., *Novel substituted quinoxaline 1,4-dioxides with in vitro antimycobacterial and anticandida activity.* European Journal of Medical Chemistry, 2002. **37**: p. 355-366.
10. Belén Zarranz, A.J., Ignacio Aldana, Antonio Monge, *Synthesis and anticancer activity evaluationnof new 2-alkylcarbonyl and 2-benxoyl-3-trifluoromethyl-quinoxaline 1,4-do-N-oxide derivatives.* Bioorganic & Medicinal Chemistry, 2004. **12**: p. 10.
11. Carlos Barea, a.p., Denis Castillo, Mirko Zimic, Miguel Quiloano, Silvia Galiano, Silvia Pérez-Silanes, Antonio Monge, Eric Deharo, Ignacio Aldana, *New salicylamide and sulfonamide derivatives of quinoxaline 1,4-di-N-oxide with antileishmanial and antimalarial activities.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
12. Naveen Kulkarni, V.K.R., B. N. Kirasur, Mallinath H. Hugar, *Transition metal complexes of thiosemicarbazones with quinoxaline hub. an emphasis on antidiabetic property.* Medical Chemistry Research, 2012. **21**: p. 8.
13. Patidar A., J.M., Mobiya A., Selvam G., *Exploring potential of quinoxaline moiety.* International Journal of PharmTech Research, 2011. **3**: p. 386-392.
14. Salman Ahmad Khan, K.S., Zaheer Khan, *Synthesis, characterization an in vitro antibacterial activity of new steroidal thiazolo quinoxalines.* European Journal of Medicinal Chemistry, 2007. **42**: p. 5.
15. Kimberly Ann Nollette, M., RN, *Antimicrobial Resistance.* Journal of the American Academy of Nurse Practitioners, 2000. **12**(7).
16. Asif Husain, D.M., *Recent advances in pharmacological activities of quinoxaline derivates.* Journal of pharmacy research, 2011. **4**(3): p. 924-929.
17. Alice N Neely, I.A.H., *Antimicrobial resistance.* Burns, 1999. **25**(1): p. 7.
18. Suresh, M.L., P.; Suchakar, D.; Vashu, K.; Rao, C. V., *Synthesis and biological activity of 8-chloro-[1, 2,4]triazolo[4,3-a]quinoxalines.* J. Chem. Pharm. Res., 2010. **2**(1): p. 8.
19. Ammar Y.A., I.M.M.F., El-Gaby M.S.A., Zahran M.A., *Some reactions with quinoxaline-2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines as antimicrobial agents.* Indian Journal of Chemistry, 2002. **41B**: p. 5.
20. Lei You, E.J.C., John Leavitt, Li-Chung Ma, Gaetano Montelione, Eric Anslyn, Robert Krug, Andrew Ellington, Jon D. Robertus, *Synthesis and evaluation of quinoxaline derivatives as potential influenza NS1A protein inhibitors.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
21. A. D. Harries, C.D., *Tuberculosis.* Annals of Tropical Medicine and Parasitology, 2006. **100**: p. 16.
22. Parvathi Tiruviluamala, L.B.R., *Tuberculosis.* Annual Review of Public Health, 2002. **23**: p. 23.
23. Onyebujoh P., R.G., *Tuberculosis.* Nature Reviews Microbiology, 2004. **2**(12): p. 2.
24. Jaso A., Z.B., Aldana I., Monge A., *Synthesis of new 2-acetyl and 2-benzoyl quinoxaline 1,4-di-N-oxide derivaties as anti-Mycobacterium tuberculosis agents.* European Journal of Medical Chemistry, 2003. **38**: p. 791-800.

25. Badawy M., M.G., Omar M., Nassar M., Kamel A., *Synthesis, spetroscopic and thermal characterization of quinoxaline metal complexes* European Journal of Chemistry, 2010. **1**(4): p. 282-288.
26. M. Elena Montoya, Y.S., M. Angel Ortega, Adela Lopez De Cerain, Antonio Monge, *Synthesis and antituberculosis activity of some new 2-quinoxalinecarbonitriles.* Il Farmaco, 1998. **53**(8-9): p. 3.
27. Enrique Torres, E.M., Saioa Ancizu, Carlos Barea, Silvia Galiano, Igancio Aldana, Antonio Monge, Silvia Pérez-Silanes, *New 1,4-di-N-oxide-quinoxaline-2-ylmethylene isonicotinic acid hydrazide derivatives as anti-Mycobacterium tuberculosis agents.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
28. Andrews, J.M., *Determination of minimun inhibitory concentrations.* Journal of Antimicrobial Chemotherapy, 2001. **48**(1): p. 12.
29. Antonio Carta, M.P., Giuseppe Paglietti, paola Molicotti, Bianca Paglietti, Sara Cannas and Stefania Zanetti, *[1,2,3]Triazolo[4,5-h]quinolones. A new class of potent antitubercular agents against multidrug resistant Mycobacterium tuberculosis strains.* Bioorg. Med. Chem. Lett., 2007. **17**: p. 3.
30. Koonin EV, S.T., Dolja W., *The ancient Virus World and evolution of cells.* Biology Direct, 2006. **1**(29): p. 27.
31. Iou-Jiun Kang, L.-W.W., Tsu-An Hsu, Andrew Yueh, Chung-Chi Lee, Yen-Chun Lee, Chin-Yin Lee, Yu-Sheng Chao, Shin-Ru Shih, Jyh-Haur Chern, *Isatin-b-thiosemicarbazones as potent herpes simplex virus inhibitors.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
32. Yang-Fei Xiang, C.-W.Q., Guo-Wen Xing, Jing Hao, Min Xia, Yi.Fei Wang, *Anti-herpes simplex virus efficacies of 2-aminobenzamide derivatives as novel HSP90 inhibitors.* Bioorg. Med. Chem. Lett., 2012. **22**(14): p. 3.
33. Kolokotronis A, D.S., *Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis.* Clin. Microbiol. Infect., 2006. **12**(3): p. 9.
34. Balfour Jr., H.H., *Antiviral Drugs.* New England Journal of Medicine, 1999. **340**(16): p. 10.
35. A. K. Field, K.K.B., *'The end of innocence' revisited: Resistance of herpes viruses to antiviral drugs.* Clinical Microbiology Reviews, 1994. **7**(1): p. 13.
36. Judie B. Alimonti, T.B.B., Keith R. Fowke, *Mechanisms of CD_4^+ T lymphocyte cell death in human immunodeficiency virus infection and AIDS.* Journal of General Virology, 2003. **84**: p. 12.
37. Organization, W.-W.H., *AIDS epidemic update.* UNAIDS, 2002.
38. Amy L. Fairchild, R.B., *HIV Surveillance, Public Health, and Clinical Medicine - Will the Walls Come Tumbling Down?* New England Journal of Medicine, 2011. **365**: p. 2.
39. Dorr, P., *7.14 - Fungi and Fungal Disease.* Comprehensive Medicinal Chemistry II, 2007. **7**: p. 24.
40. Ryan KJ, R.C., *Sherris Medical Microbiology*, ed. M. Hill2004.
41. Thomas J. Walsh, D.M.D., *Spectrum of Mycoses*, in *Medical Microbiology. 4th edition*, e. Baron S, Editor 1996.
42. Leah E. Cowen, A.N., Malcolm S. Whiteway, David Y. Thomas, Daniel C. Tessier, Linda M. Kohn, James B. Anderson, *Population genomics of drug resistance in Candida albicans.* Proc Natl Acad Sci USA, 2002. **99**(14): p. 4.
43. Shadab Miyan Siddiqui, A.S., *Thiosemicarbazone fragment embedded within 1,2,4-triazole ring as inhibitors of Entamoeba histolytica.* Bioorg. Med. Chem. Lett., 2012. **22**(8): p. 3.
44. C.C. Hung, P.J.C., S.M. Hsieh, J.M. Wong, C.T. Fang, S.C. Chang, M.Y. Chen, *Invasive amoebiasis: An emerging parasitic disease in patients infected with HIV in an area endemic for amoebic infection.* AIDS, 1999. **13**(17): p. 7.
45. Mohammad Abid, A.A., *Synthesis, characterization and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives.* Bioorg. Med. Chem. Lett., 2006. **16**: p. 4.
46. S. L. Croft, G.H.C., *Leishmaniasis - current chemotherapy and recent advances in the search for novel drugs.* Trends Parasitol, 2003. **19**(11): p. 11.
47. Esther Vicente, S.C., Emily Bongard, Raquel Villar, Asunción Burguete, Beatriz Solano, Saioa Ancizu, Silvia Pérez-Silanes, Ignacio Aldana, Livia Vivas, Antonio Monge, *Synthesis and Antiplamodial Activity of 3-Furyl and 3-Thienylquinoxaline-2-carbonitrile 1,4-Di-N-oxide Derivatives.* Molecules, 2008. **13**: p. 8.
48. WHO, *Guidelines for the treatment of Malaria.* World Health Organization: Second Edition, 2010.
49. Kathryn N. Suh, K.C.K., Jay S. Keystone, *Malaria.* Canadian Medical Association Journal, 2004. **170**(11): p. 9.
50. Moller, D.E., *New drug targets for type 2 diabetes and the metabolic syndrome.* Nature, 2001. **414**: p. 6.
51. A.A. Abu-Hashem, M.A.G., F.A. Badria, *Synthesis of some new pyrimido[2',1':2,3]thiazolo[4,5-b]quinoxaline derivatives as anti-inflammatory and analgesic agents.* European Journal of Medical Chemistry, 2010. **45**: p. 5.
52. Kim Peterson, M.M., Sujata Thakurta, Tracy Dana, Carol Roberts, Roger Chou, Mark Helfand, *Drug Class Review: Nonsteroidal Antiinflamatory Drugs (NSAIDs)*, in *Oregon Health & Science University*2010.

53. R. Micklewright, S.L., W. Linley, C. McQuade, F. Thompson, N. Maskrey, *NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors.* Alimentary Pharmacology & Therapeutics, 2003. **17**(3): p. 11.
54. Asunción Burguete, E.P., Dimitra Hadjipavlou-Litina, Saioa Ancizu, Raquel Villar, Beatriz solano, Elsa Moreno, Enrique Torres, Silvia Pérez, Ignacio Aldana, Antonio Monge, *Synthesis and Biological evaluation of New Quinoxaline Derivatives as Antioxidant and Anti-Inflammatory Agents.* Chem Biol Drug Des, 2011. **77**: p. 11.
55. Claus Schneider, W.E.B., Huiyong Yin, Donald F. Stec, Markus Voehler, *Convergent oxygenation of arachidonic acid by 5-lypoxygenase and cyclooxygenase-2.* Journal of the American Chemical Society, 2006. **128**(3): p. 2.
56. Ahmedin Jemal, F.B., Melissa M., Jacques Ferlay, Elizabeth Ward, David Forman, *Global cancer statistics.* CA: A Cancer Journal for Clinicians, 2011. **61**(2): p. 21.
57. Organization, W.H., *The Global Burden of Disease: 2004 Update.* Geneva: World Health Organization, 2008.
58. Anahory, B.B., *Factores de neuroprotecção do nervo óptico no glaucoma.*, in *Departamento de Ciências Médicas*2009, Universidade da Beira Interior.
59. Quigley, H.A., *Glaucoma.* The Lancet, 2011. **377**(9774): p. 10.
60. Toris, C., *Glaucoma.* xPharm: The Comprehensive Pharmacology Reference, 2007: p. 7.
61. Wasim Rashid, S.R., Tejit Singh, *Profile of Patients of Glaucoma In Kashmir Valley (A Hospital Based Study).* JK Science, 2010. **12**: p. 4.
62. Lahren William J., S.s.T.W., *Pseudo Exfoliative Glaucoma.* Yanoff M, Duker Jay S.Ophthalmology. Vol. 2. 2004: Mosby. 1499.
63. Ross, R., *The pathogenesis of atherosclerosis: a perspective for the 1990s.* Nature, 1993. **362**: p. 9.
64. Sung-Yu Hongb, K.-H.C., Hea-Jung Youa, Ik Hwa Choia, Mi Jin Chaea, Ja-Young Hana, Ok-Jai Junga, Soo-Jung Kang, Chung-Kyu Ryu, *Synthesis and biological evaluation of benzimidazole-4,7-diones that inhibit vascular smooth muscle cell proliferation.* Bioorg. Med. Chem. Lett., 2004. **14**(13): p. 4.
65. Newby A. C., G.S.J., *Proposed roles for growth factors in mediating smooth muscle proliferation in vascular pathologies.* Cardiovascular Research, 1993. **27**(7): p. 11.
66. H Chung, O.J., M J Chae, S Hong, K Chung, S K Lee, C Ryu, *Synthesis and biological evaluation of quinoxaline-5,8-diones that inhibit vascular smooth cell proliferation.* Bioorg. Med. Chem. Lett., 2005. **15**: p. 5.
67. Peroutka, S.J., *5-Hydroxytryptamine receptor subtypes.* Pharmacochemistry Library, 1997. **27**: p. 11.
68. Radhakrishnan Mahesh, T.D., Dilip Kumar pandey, Shvetank Bhatt, *Discovery of new anti-depressants from structurally novel 5-HT_3 receptor antagonists: Design, synthesis and pharmacological evaluation of 3-ethoxyquinoxalin-2-carboxamides.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 3.
69. Rudolf Mueller, S.R., Martina E. Tedder, Yong-Xin Li, Sheng Zhong, Aidan Hampson, Jolanta Ulas, Mark Varney, Lena Nielsson,Gary Rogers, *Substituted benzoxazinones as potent positive allosteric AMPA receptor modulators: Part II.* Bioorg. Med. Chem. Lett., 2011. **21**(13): p. 4.
70. Stefano Marenco, D.R.W., *Therapeutic Potential of Positive AMPA Receptor Modulators in the Treatment of Neuropsychiatric Disorders.* CNS Drugs, 2006. **20**(3): p. 14.
71. Andrew Alt, E.S.N., David Bleakman, Jeffrey M. Witkin, *A role for AMPA receptors in mood disorders.* Biochemical Pharmacology, 2006. **71**: p. 16.
72. Patrick M. Kanju, K.P., Catrina Sims, Ben A. Bahr, Brian C. Shonesy, Vishnu Suppiramaniam, *Ampakine CX516 ameliorates functional deficits in AMPA receptors in a hippocampal slice model of protein accumulation.* Experimental Neurology, 2008. **214**: p. 7.
73. Michael J. O'Neill, D.B., Dennis M. Zimmerman and Eric S. Nisenbaum, *AMPA Receptor Potentiators for the Treatment of CNS Disorders.* Current Drug Target -CNS & Neurological Disorders, 2004. **3**(3): p. 14.
74. Yasuo Takano, F.S., Jun Asano, Naoki Ando, Hideharu Uchiki, Tsuyosi Anraku, *Synthesis and AMPA Receptor Antagonistic Activity of a Novel Class of Quinoxalinecarboxylic Acid with a Substituted Phenyl Group at C-7 Position.* Bioorg. Med. Chem. Lett., 2003. **13**: p. 4.
75. Y. Abboud, A.A., T. Saffaj, M. Berrada, M. Charrouf, A. Bennamara, N. Al Himidi, H. Hannache, *2,3-Quinoxalinedione as a novel corrosion inhibitor for mild steel in 1 M HCl.* Materials Chemistry and Physics, 2007. **105**: p. 5.
76. I.B. Obot, N.O.O.-E., *Indeno-1-one [2,3-b] quinoxaline as an effective inhibitor for the corrosion of the mild steel in 0.5 M H_2SO_4 solution.* Materials Chemistry and Physics, 2012. **122**: p. 3.
77. I.B. Obot, N.O.O.-E., N.W. Odozi, *Acenaphtho [1,2-b] quinoxaline as a novel corrosion inhibitor for mild steel in 0.5 M H_2SO_4.* Corrosion Science, 2012. **52**: p. 3.
78. Barceloux, D.G., *Copper.* Clinical Toxicology, 1999. **37**(2): p. 4.

79. Ajit Kumar, V.K., Uzra Diwan, K. K. Upadhyay, *Highly sensitive and selective naked-eye detection of Cu^{2+} in aqueous medium by a ninhydrin-quinoxaline derivative.* Sensors and Actuators B: Chemical, 2013. **176**: p. 7.
80. Baldo, M.A., O'Brien, D.F., You, Y., Shoustikov, A., Sibley, S., Thompson, M.E., Forrest, S.R., *Highly efficient phosphorescent emission from organic electroluminescent devices.* Nature, 1998. **395**(6698): p. 4.
81. Hsin-Hua Changa, W.-S.T., Chien-Ping Changa, Nien-Po Chenc, Ken-Tsung Wongb, Wen-Yi Hungd, Shou-Wei Chend, *A new tricarbazole phosphine oxide bipolar host for efficient single-layer blue PhOLED.* Organic Electronics, 2011. **12**(12): p. 8.
82. M. Ananth Reddy, A.T., G. Mallesham, B. Sridhar, V. Jayathirtha Rao, K. Bhanuprakash, *Synthesis of novel twisted carbazole-quinoxaline derivatives with 1,3,5-benzene core: bipolar molecules as hosts for phosphorescent OLEDs.* Tetrahedron Letters, 2011. **52**: p. 5.
83. Committee on Mathematical Challenges from Computational Chemistry, N.R.C., *Mathematical Challenges from Theoretical/Computational Chemistry* 1995.
84. Richon, A.B., *An introdution to molecular modeling.* Mathematech, 1994. **1**: p. 83.
85. Young, D., *Introdution to computational chemistry.* Chem. Aust., 1998. **11**: p. 5.
86. The Shodor Education Foundation, I. *ChemViz*. 2000 [cited 2013.
87. Pessoa, A.M., *Estudo teórico de adsorção de OH em suerfícies de Ouro*, in *Departamento de Química* 2005, Universidade do Porto: Faculdade de Ciências. p. 66.
88. Ciarlet, P.G., *Handbook of numerical analyses - computational chemistry*. Vol. 10. 2003: North-Holland.
89. Weilsstein, E.W. *Shrödinger Equation*. Eric Weisstein's World of Physics 2007 [cited 2013.
90. Hehre, W.J., *A Guide to Molecular Mechanics and Quantum Chemical Calculations*2003.
91. Jia Deng, A.T.B.G., Peter M.W. Gill, *Hartree-Fock perturbative corections for total and reaction energies.* Journal of Chemical Physics, 2010. **133**(4): p. 6.
92. Corneliu Cojocaru, A.R., Valeria Harabagiu, Liviu Sacarescu, *Molecular structure and electronic properties of pyridylindolizine derivative containing phenyl and phenacyl groups: Comparison between semi-empirical calculations and experimental studies.* Journal of Molecular Structure, 2013. **1034**: p. 11.
93. Georgiana G. Surpateanu, M.B., Neculai Catalin Lungu, Paul Ionut Dron, Sophie Fourmentin, David Landy, Gheorghe Surpateanu, *Photochemical behaviour upon the inclusion for some volatile organic compounds in new fluorescent indolizine b-cyclodextrin sensors.* Journal of Photochemistry and Photobiology A: Chemistry, 2007. **185**: p. 9.
94. Hameed, A.J., *Study of the structural and electronic properties of the 1-phenyl-3,3-pentamethylenetriazenes.* Journal of Molecular Structure: THEOCHEM, 2005. **725**: p. 5.
95. Gerd B. Rocha, R.O.F., Alfredo M. Simas, James J.P. Stewart, *RM1: A Reparameterization of AM1 for H, C, N, O, P, S, F, Cl, Br and I.* Journal of Computational Chemistry, 2005. **27**(10): p. 11.
96. Maylis Orio, D.P., Frank Neese, *Density functional theory.* Springer, 2009. **102**: p. 443-453.
97. P.W. Atkins, R.S.F., *Molecular Quantum Mechanics, 3rd edition.* Oxford University Press, New York, 1997.
98. Physics, I.f.C., *Chapter 9: Density Functional Theory (DFT) Methods*, 2013: Institute for Computational Physics, Germany. p. 6.
99. Mathias Hofman, H.F.S., *Computational Chemistry.* Encyclopedia of Physical Science and Technology, 2003: p. 20.
100. Allouche, A.-R., *Gabedit - A Graphical User interface for computational chemistry softwares.* Journal of Computational Chemistry, 2011. **32**: p. 174-182.
101. Chunyang Peng, P.Y.A., H. Bernhard Schlegel, *Using Redundant Internal Coordinates to Optimize Equilibrium Geometries and Transition States.* Journal of Computational Chemistry, 1996. **17**(1): p. 8.
102. M.J. Frisch, G.W.T., H.B. Schlegel, G.E. Scuseria, M.A. Rob, J.R. Cheeseman,, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G. Zakrzewski, S. Dapprich, A. D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J. A. Pople. *Gaussian09, Revision A.1*. 2009 [cited 2012 17JUL].
103. SERC. *Gaussian Software*. [cited 2012 17JUL].

***Adendum*: Submitted Review Article (European Journal of Medicinal Chemistry EJMECH-D-13-01270)**

Quinoxaline, its derivatives and biological applications: A state of the art review.

Joana A. Pereira[a)], Rúben Fernandes [a) b)], M. Natália D.S. Cordeiro[c)], Ana M. Pessoa[c) d)], Mónica Vieira[a) e)]

a) Center for Health and Environmental Research, School of Allied Health Sciences, Polytechnic Institute of Porto, Rua Valente Perfeito, 322, 4400-330, Vila Nova de Gaia, Portugal
b) Center of Pharmacology and Chemical Biopathology (U38-FCT), Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
c) REQUIMTE, Rua do Campo Alegre, 4150-180 Porto, Portugal
d) School of Industrial Studies and Management, Polytechnic Institute of Porto, 4480-876 Vila do Conde, Portugal
e) REQUIMTE/CQFB, Chemistry Department, FCT, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

Abstract:

Quinoxaline derivatives are an important class of heterocycles compounds, where N, S and O elements replace the carbon atoms in the ring. Quinoxaline molecular formula is $C_8H_6N_2$, formed by two aromatic rings, benzene and pyrazine with a molecular weight of 130.1466400, and it appears as a white crystalline powder. It is rare in natural state, but their synthesis is easy to perform. Modifying its structure provides a wide variety of activities. They present a large number of biological activities such as antimicrobial, antitubercular, antiviral, antifungal, antiamoebic, antimalarial and leishmanial, antidiabetic, antiproliferative, anti-inflamatory, anticancer, antiglaucoma, antidepressant and presenting AMPA antagonism. They are also important in industrial field due to its power in metal corrosion inhibition, its use in Cu^{2+} detection in colorimetric sensors, and phosphorescent organic light-emiting diodes (OLEDs). The present review attempt to review quinoxaline derivatives characteristics, and its importance in both biological and industrial field.

Keywords: Quinoxaline, biological activity, industry.

Contents:

Introduction:

Quinoxaline derivatives are an important class of heterocycles compounds, in which N, S and O elements replace one or more carbons atoms of the ring[1], and the approved number for the quinoxaline ring system is shown in **Figure 1**, where 2 and 3 are designated α-positions[2]. They are important in industry due to their power 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 are also usefull in the electroluminescent materials[6-8]. In pharmacological industry they are considered promising molecules since they show wide biological properties[1, 9-12] such as antibacterial, antifungal, anticancer, antitubercular, antileishmanial, antimalarial, antidepressant, antimycobacterial and anticandida, and neurological activities, among others. All this activities are possible due to the quinoxaline structure since its nucleus, in numerous cases, acts as a precursor to assembly a large number of quinoxaline derivatives, which consequently, provide a large number of new compounds for diverse applications[1].

Figure 1 should come about here

Quinoxaline is formed by two aromatic rings, benzene and pyrazine. For this reason is also called benzopyrazine, and is described as a bioisoster of quinoline, naphatelene and benzothiophene[13]. The atoms S and N play an important role in the ring since they stabilize ion radical species and extended π-conjugation facilitate in decreasing columbic repulsion. Molecular weight of the quinoxaline is 130.1466400, with a molecular formula of C8H6N2, and it is a white crystalline powder[1].

Chemically, quinoxaline is a low melting solid, purified by destilation, and a fraction of b.p. 108º-111º/12mm has a m.p. 29-30ºC[2, 13]. Quinoxalines are soluble in water, and produces monoquaternary salts when treated with quaternizing agents, like methyl sulfate and methyl *p*-toluenesulfate. The quaternary salts of 2-alkylquinoxalines are unstable and can be converted into complex colored products when under oxidation[2]. It is weakly basic with a pKa of 0,60 in water at 20ºC, and nitration occurs only under forcing conditions (Conc. HNO_3, Oleum, 90ºC), resulting the formation of two compounds: 5-nitroquinoxaline (1,5%) and 5,7-dinitro-quinoxaline (24%) [13]. Its second pKa is -5,52, meaning that quinoxaline is significantly diprotonated only in a strongly acidic medium[2].

Quinoxaline has a dipole moment of 0,51 D in benzene ring, 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 known certainly from which orbital the first electron is lost, since highest-occupied π-orbital and non-bonding orbitals are very close in energy. The heat of atomization was calculated to be 79,739 eV by a self-consistent field molecular orbital treatment[2]. Molecular orbital calculations of the π-electron density were made, and shown that the highest electron density at the ring carbon is at positions 5 and 8, followed by positions 6 and 7, and the lowest at 2 and 3 positions[2].

Table 1 should come about here

Most of quinoxaline compounds are rare in natural state, being of synthetic origin. The

method used to synthesized quinoxalines is to condense o-disubstituted benzene with a two carbon synthon. Therefore, the condensation of o-phenylenediamine with α-dicarbonyl compounds result in quinoxaline formation **(Figure 2)**[2].

Figure 2 should come about here

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

Biological Activity

The study of quinoxaline, and its derivatives, has become a subject of interest in recent years, due to their wide variety in biological activity and also their therapeutic applications, such as antimicrobial agents since some antibiotics have quinoxaline compound in their structure (echinomycin), and some recognized drugs like Brimonidins which alleviates glaucoma symptoms[1]. Although rare in nature, synthesized quinoxaline and derivatives are included in various antibiotics such as echinomycin, levomycin and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and also active against transplant tumors[13, 14].

The vast scope of synthesized quinoxaline and derivatives potentials is well referenced and published in a wide range of scientific journals. We analyze in detail, transversally and in context the relevant scientific data pertaining great quinoxaline and potentials derivatives in literature.

Antimicrobial Activity

The antimicrobial-resistance is a serious threat to global public health, result of the widely disseminated and careless use of antimicrobials, and demands a continuous effort in order to seek for better antimicrobial agents effective against resistant pathogenic microorganisms[13, 15-17]. There are a wide range of quinoxaline derivatives with antimicrobial activity documented.

A new series of 8-chloro-1,4-substituted(1,2,4)triazolo(4,3a) quinoxaline derivatives

(Figure 3) (Table 2) was synthesized and screened for antimicrobial and antioxidant activities[18]. 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 drugs[16]

Figure 3 should come about here

Ammar *et al*[19], have synthesized thieno(2,3-*d*)pyrimidines and pyrrolo(3,4-*b*)quinoxalines which antibacterial activity were tested against *Staphyllococcus aureus* and *Escherichia coli*.

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].

Figure 4 should come about here

In such study, researchers have prepared a library based on 2,3-difuryl-4-quinoxaline(R)metilcarboxamide derivatives **(Figure 4)**, 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, those listed in ***Table 2*** have shown the highest effectiveness. 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].

Antitubercular Activity

Tuberculosis (TB) is a contagious disease, caused by the infection of *Mycobacterium tuberculosis,* which have a high rate of mortality in the world. About 3 million people die every year from TB, and 8 million new cases estimated each year, which 95% of them occur in developing countries[20-22].

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, 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.

Several studies has 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 inhibit *M. tuberculosis* to a rate of 99 to 100%[16, 23]. However, it is observed that the lack of the two *N*-oxide groups lead to the loss of the antimycobacterial activity [23-25].

Some novel condensed bridgehead nitrogen heterocycles of quinoxalines has been synthesized and showed activity against *M. tuberculosis* H_{37}Rv species [13, 16, 26]. The compounds 3-methyl-2-phenylthioquinoxaline 1,4-dioxides generally showed a good activity against *M. tuberculosis* in the preliminary in vitro evaluation and exhibited MIC between 0.39 and 0.78μg mL^{-1}(rifampicin MIC=0.25μg mL^{-1})[9].

It was also reported the activity of 3-methyl-9-substituted-6-oxo-6,9-dihydro-3*H*-(1,2,3)-triazolo(4,5-*h)*quinolone-carboxylic acids and their esters of as a new class of anti-infective agents against MDR *M. tuberculosis*, with no cytotoxicity reported[28].

Antiviral Activity

Viruses such as Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) belong to the *Herpesviridae* family, are double-stranded DNA[30], and share high homology in genome structure and DNA sequence. These viruses can cause various illness states from asymptomatic infection to fulminant disseminated diseases, including labials herpes, keratitis, genital herpes, and encephalitis[31, 32].

There are a wide number of drugs for treatment of Herpes simplex virus (HSV) infections like acyclovir, ganciclovir, penciclovir, valaciclovir (converted to acyclovir) and famciclovir (converted to penciclovir)[30, 33], being acyclovir the most common drug used. However, there are drug-resistant strains of HSV emerging and increasing[30, 34], 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 6H-indol-(2,3-b)quinoxalines were synthesized and evaluated for antiherpes virus activity and the compound 2,3-dimethyl(dimethylaminoethyl)5H-indolo-(2,3-b)quinoxaline had the major antiviral activity. This specific compound was tested for its antiviral affect and action mechanism, showing the capacity to inhibit replication of herpes simplex virus type 1, cytomegalovirus, and varicella-zoster virus in tissue culture, in concentrations of 1 to 5μM, 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 **(Figure 5)** have showed high activity against herpes virus, and derivatives with 6-(2-dimethylaminoethyl) side chain, due to their DNA binding properties, showed an improved biological activity[1].

Figure 5 should come about here

There is also reference to IndQloquinoxalines with capacity to inactivate virions in high concentrations (around 300μM), and decrease the synthesis of viral DNA and protein at lower concentrations (around 3μM)[16].

Concerning human immunodeficiency virus type 1 (HIV-1), which is the agent causative of acquired immunodeficiency syndrome (AIDS)[35-37], 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[13]. Compound 6-chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-3,4-dihydroquinoxalin-2(1H)-thione **(Figure 6)** 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 HIV-2 RT[16].

Figure 6 should come about here

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, 41]. This fungus can also develop resistance to antimycotic drugs that already exist in the market[42], being important a constant search for new drugs and treatments.

Thieno(2,3-*d*)pyrimidines and pyrrolo(3,4-*b*)quinoxalines were synthesized, have antifungal activity, and were tested against *C. albicans*[13, 19].

Researchers also reported some 2-sulphonylquinoxalines and 3-[(alkylthio)methyl]quinoxaline 1-oxide derivatives as compounds with high antifungal activity[9], and also pyrazoloquinoxalines which were observed to be active against fungal infections[1].

Antiamoebic Activity

Entamoeba histolytica is a protozoan responsible for the amoebiasis infection[43, 44], causing amoebic colitis, brain and liver abscess, being the second 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[45].

Some 1-(thiazole[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazolines derivatives produced **(Figure 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[45].

Figure 7 should come about here

In such study metronidazole was used as the reference drug and had a 50% inhibitory

concentration (IC_{50} 1.69–1.82 μM), and compound 6 (Table2) showed great effectiveness, being the most active [45].

Antileishmanial and Antimalarial 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[16, 46]. Most of the drugs available against leishmaniasis are expensive and require a long treatment and are becoming more and more ineffective[11].

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[11, 47-49].

Carlos Barea, *et al*[11], synthesized 14 new 3-amino-1,4-di-*N*-oxide quinoxaline-2-carbonitrile derivatives. These compounds were evaluated for their in vitro antimalarial and antileishmanial activity 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.

Antidiabetic Activity

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, biguanides, etc. However these treatments have limited efficacy and tolerability, and could cause severe side effects[50]. In this regard, were prepared new transition metal complexes of quinoxaline-thiosemicarbazone ligands L^1H_2 and L^2H_2 **(Figure 8)**. 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 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[12].

Figure 8 should come about here

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

Figure 9 should come about here

Anti-inflammatory Activity

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 those reasons mentioned it is important the discovery of new safer anti-inflammatory drugs [51-53].

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-1H-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[54, 55]. 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[51].

Anticancer Activity

Quinoxaline nucleuses exhibit potential anticancer activity, which makes them an important basis for the anticancer drugs[16]. 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 **(Figure 10)** 2-Isobutyryl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide **(Compound 1)**, 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide **(Compound 2)**, their difluorinated analogs (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-trifluoromethylquinoxaline 1,4-di-*N*-oxide **(Compound 5)** 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 (Table2)[10, 16].

Figure 10 should come about here

Antiglaucoma Activity

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[58-60]. Almost 67 million people worldwide are affected by glaucoma, remaining the leading cause of irreversible blindness, responsible for 14% of blindness after cataract and trachoma[61, 62].

Alphagan® (Brimonidin) is a relatively selective alpha-2 adrenergic receptor agonist, and its composition consists in (5-bromo-*N*-(4,5-dihydro-1H-imidazol-2-yl)-6-quinoxaline **(Figure 11)**. This drug works as an antiglaucoma agent, due to its power to reduce the intraocular pressure, alleviating the symptoms of glaucoma[1, 16].

Figure 11 should come about here

Antiproliferative Activity

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[64, 65].

A series of 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8 diones **(Figure 12)** were synthesized and screened for their inhibitory activity on rat aortic smooth muscle cell (RAoSMC) proliferation. IC_{50} (Inhibition Concentration) values were determined and compared to the positive control mycophenolic acid (MPA) (Table 2), and most of the compounds showed good activity, and the quinoxaline-5,8-diones was found as an potent antiproliferative agent[1, 16, 66].

Figure 12 should come about here

Antidepressant Activity

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, which are 5-HT_{1-7}. 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[67, 68]. The antagonists to this receptor lead to a various responses, such an anti-emetic action in cancer chemo-/radio-therapy induced nausea and vomiting, anti-depressant, anxiolytic, anti-phsycotic and anti-inflammator. Although, 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[67, 68].

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-(1H-indol-3-yl)ethyl)-3-ethoxyquinoxaline-2-carboxamide[68]. The compound N-{3-[(4-methylpiperazin-1-yl)methyl]-4-hydroxyphenyl}-3-methoxyquinoxalin -2-carboxamide showed most favorable 5-HT_3 receptor antagonism[16].

Also 3-benzyl-2-substituted quinoxalines were synthesized as novel monoamine oxidase A (MAO-A) inhibitors. These 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[13].

Anti excitotoxicity activity of glutamate

A major excitatory neurotransmitter in the central nervous system in mammalian species is the glutamic acid, an excitatory amino acid (EAA). 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[69-73]. 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[74].

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*, 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 charactereristics, meets the criteria, in an injectable formulation, for use in the treatment of acute cerebral ischemia[74].

Industrial applications

Corrosion Inhibition

The use of acid solution is very common in industry, and has important fields of application like acid pickling, industrial acid cleaning, acid descaling and oil well acidizing. However, the continuous use of acid solutions can lead to the metal corrosion, leading to enormous economic losses. Thence the importance of having inhibitors to minimize the metal dissolution and acid consumption, instruments malfunction and contamination[5, 75].

The most effective inhibitors used in industry to minimize these losses are organic compounds. Their inhibitory effect is reinforced by the presence of heteroatoms such as sulphur, nitrogen and oxygen, which will facilitate its adsorption on the mild steel surface following the sequence S>N>O[3, 75].

Other studies revels that the adsorption in mild steel surface also depends on the physicochemical properties of the inhibitor group, planarity of the system, presence of multiple adsorption active centers with lone pair and/or π orbitals, molecular size and electronic density at the donor atom. On this basis, the choice of effective inhibitors is done taking in consideration their structure, their mechanism of action and their electron donating ability[3]. Many *N*-heterocyclic organic compounds are good corrosion inhibitors, but some of them are highly toxic to both human beings and environment, leading to a continue search for an eco-friendly and harmless N-heterocyclic compounds as inhibitors[76].

Quinoxaline derivatives are *N*-heterocyclic aromatic compounds that have been proved to be excellent corrosion inhibitors for mild steel in acidic media, easy to synthesized and ready available[77].

2,3-quinoxalinedione (QD) **(Figure 13)** was used to study their corrosion inhibition properties for mild steel in 1M HCl, due to the presence of heteroatoms N and O, and π-electrons. It was shown that QD can act as a good corrosion inhibitor for mild steel in 1M HCl, with an inhibition efficiency of 88% at 10^{-3}M (measured through weight loss)[75].

Figure 13 should come about here

Indeno-1-one [2,3-b] quinoxaline (INQUI) **(Figure 14)**, was synthesized and tested for inhibition corrosion of mild steel in 0,5M H_2SO_4, and showed about 81% of inhibition efficiency at 10^{-6}M. This efficiency increases with INQUI concentration but decreases with immersion time[76].

Figure 14 should come about here

Also acenaphtho [1,2-b] quinoxaline (AQ) **(Figure 15)** was tested as a corrosion inhibitor for mild steel in 0,5 MH_2SO_4. AQ acts as an effective inhibitor for mild steel in acidic, with 80% of inhibition efficiency at 10^{-6}M (measured through weight loss)[77].

Figure 15 should come about here

Quinoxaline derivatives namely 3-methyl-2-phenyl quinoxaline (MPQ), 2,3-diphenyl quinoxaline (PPQ), 3-methyl-2(2-hydroxyphenyl)quinoxaline (MHPQ), 3-phenyl-2(2-hydroxyphenyl)quinoxaline (PHPQ) and 3-methyl-2(3-methoxy,4-hydroxyphenyl)quinoxaline (MMtHPQ) have been shown through experimental studies to have high corrosion inhibition efficiencies for copper in nitric acid, with the order of inhibition efficiency being MMtHPQ > PPQ > MPQ > PHPQ > MHPQ[5].

Cu^{2+} detection - Colorimetric Sensor

Cu^{2+} is a transition-metal ion, crucial in the life processes, since it has an important role as a catalytic cofactor for a variety of metallo-enzymes such as superoxide dismutase, cytochrome c oxidase, lysyl oxidase and tyrosinase, etc. However when overloading, exhibit toxicity and could cause a variety of neurological diseases. Besides, it is also important in pollution matters, since the formulation of copper-containing pesticides uses various forms of copper, which in the end dissociates into Cu^{2+}[78, 79].

There are well developed technologies to detect Cu^{2+} such as inductively coupled plasma detectors, surface-plasmon resonance detectors, fluorescence anisotropy assays, quantum-dot-based assays, electrochemical sensors and fluorescence sensors. These are technologies with high sensitive and specificity in the Cu^{2+} detection, but also very expensive, due to the need of sophisticated instruments and highly trained operators. On the other hand, it is possible to use a naked-eye detection method, which gives a more fast response without involving any costly instrument. Although this method allows a good qualitative approach it presents a low sensitivity[79].

A colorimetric receptor ninhydrin–quinoxaline based was designed, synthesized and characterized, and exhibited high sensitivity and selectivity for Cu^{2+} in aqueous medium over a wide variation of cations such as Na^{+}, Mg^{2+}, Al^{3+}, Co^{2+}, Fe^{3+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+} and Pb^{2+}. In this study Cu^{2+} was added to the receptor solution giving a clear colour change from olive green to pink. The detection limit was found to be $3{,}43 \times 10^{-7}$ M which is one of the lowest for the Cu^{2+} in an aqueous solution by any naked-eye receptor[79].

OLED - organic light-emitting diode

Phosphorescent OLEDs are well known due to its high efficiency (possibility of 100% internal quantum efficiency)[80]. This property is driving the investment on research, leading to the synthesis of new compounds and materials as hosts, charge transporting materials and emitters. The high efficiency is due to PHOLED capacity to harvest both singlet and triplet excitons for light emission[81, 82]. However, triplet emitters tend to decrease the efficiency because of the concentration triplet-triplet annihilation during device operation despite of owing long emissive lifetimes. The solution is to develop new bipolar host materials, which will contribute to the balanced transport of carriers and help to increase the probability of carrier recombination, and will grant better device stability due to its amorphous nature[82].

New series of carbazole/quinoxaline hybrids with 1,3,5-benzene core have been synthesized, and showed excellent thermal and morphological stabilities, due to their twisted geometry. These compounds, bipolar along with high thermal stability and favorable electrochemical properties, are promising for their use as host materials in red and green phosphorescent based OLEDs[82].

Conclusions

The literature survey reveals that quinoxaline and their derivatives have a wide application, with a great potential, being an important class of biological active compounds. This review tries to embrace quinoxalines features such its biological activities and industrial value. Quinoxaline and its derivatives showed a wide field of application in medicine due to its biological activities, that include antimicrobial, antitubercular, antiviral, antifungal, antiamoebic, antimalarial and leishmanial, antidiabetic, antiproliferative, anti-inflamatory, anticancer, antiglaucoma, antidepressant activities and also with AMPA receptor antagonist activity. The biological activities referred are very encouraging for the investigators and pharmacists, leading to new treatments and therapeutic agents that will benefict humanity. Regarding quinoxaline derivatives potential in industry, they have shown great outcomes in metal corrosion inhibition, led to an increase in both sensitivity and selectivity in Cu^{2+} detection in colorimetric sensors, and showed to be excellent as host materials for use in phosphorescent OLEDs. These findings are very important for the industry field, decreasing costs (inhibition metal corrosion) and increasing efficiency (OLED). We hope, with this

review along with the easy process of quinoxaline derivatives synthesis, to lead to further development of the quinoxaline nucleus, allowing the research for new compounds, its features and potentials.

References:

1. Deepika Y., N.P., Sachin K., Shewta S., *Biological activity of quinoxaline derivatives.* International Journal of Current Pharmaceutical Review and Research, 2011. **1**(3): p. 33-46.
2. G. W. H. Chesseman, R.F.C., *The Chemistry of Heterocyclic Compounds, Condensed Pyrazines*, 1979, John Wiley & Sons, Inc.
3. Z. El Adnani, M.M., M. Sfaira, M. Benzakour, A. Benjelloun, M. Ebn Touhami, B. Hammouti, M. Taleb, *DFT Study of 7-R-3methylquinoxalin-2(1H)-ones (R=H; CH_3; Cl) as Corrosion Inhibitors in Hydrochloric Acid.* International Journal of Electrochemical Science, 2012. **7**: p. 13.
4. I.B. Obot, N.O.O.-E., *2,3-Diphenylbenzoquinoxaline: A new corrosion inhibitor for mild steel in sulphuric acid.* Corrosion Science, 2010. **52**(1): p. 3.
5. Mwadham M. Kabanda, E.E.E., *Density Functional Theory and Quantitative Structure-Activity Relationship Studies of some Quinoxaline derivatives as potential Corrosion Inhibitors for Copper in Acidic Medium.* International Journal of Electrochemical Science, 2012. **7**: p. 20.
6. Gitanjali Sharma, P.R., Ignatious Abraham, R T Pardasani, Tulsi Mukherjee, *Synthesis of quinoxaline quinones and regioselectivity in their Diels-Alder Cycloadditions.* Indian Journal of Chemistry, 2009. **48B**: p. 6.
7. K. R. Justin Thomas, M.V., Jiann T. Lin, Chang-Hao Chuen, Yu-Tai Tao, *Chromophore-Labeled Quinoxaline Derivatives as Efficient Electroluminescent Materials.* Chem. Mater., 2005. **17**: p. 6.
8. Dong Wook Chang, S.-J.K., Jin Young Kim, Liming Dai, Jong-Beom Baek, *Multifunctional quinoxaline xontaining small molecules with multiple electron-donating moieties: Solvatochromic and optoelectronic properties.* Synthetic Metals, 2012. **162**(13-14): p. 7.
9. Carta A., P.G., Nikookar M., Sanna P., Sechi L., Zanetti S., *Novel substituted quinoxaline 1,4-dioxides with in vitro antimycobacterial and anticandida activity.* European Journal of Medical Chemistry, 2002. **37**: p. 355-366.
10. Belén Zarranz, A.J., Ignacio Aldana, Antonio Monge, *Synthesis and anticancer activity evaluationnof new 2-alkylcarbonyl and 2-benxoyl-3-trifluoromethyl-quinoxaline 1,4-do-N-oxide derivatives.* Bioorganic & Medicinal Chemistry, 2004. **12**: p. 10.
11. Carlos Barea, a.p., Denis Castillo, Mirko Zimic, Miguel Quiloano, Silvia Galiano, Silvia Pérez-Silanes, Antonio Monge, Eric Deharo, Ignacio Aldana, *New salicylamide and sulfonamide derivatives of quinoxaline 1,4-di-N-oxide with antileishmanial and antimalarial activities.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
12. Naveen Kulkarni, V.K.R., B. N. Kirasur, Mallinath H. Hugar, *Transition metal complexes of thiosemicarbazones with quinoxaline hub. an emphasis on antidiabetic property.* Medical Chemistry Research, 2012. **21**: p. 8.
13. Patidar A., J.M., Mobiya A., Selvam G., *Exploring potential of quinoxaline moiety.* International Journal of PharmTech Research, 2011. **3**: p. 386-392.
14. Salman Ahmad Khan, K.S., Zaheer Khan, *Synthesis, characterization an in vitro antibacterial activity of new steroidal thiazolo quinoxalines.* European Journal of Medicinal Chemistry, 2007. **42**: p. 5.
15. Kimberly Ann Nollette, M., RN, *Antimicrobial Resistance.* Journal of the American Academy of Nurse Practitioners, 2000. **12**(7).
16. Asif Husain, D.M., *Recent advances in pharmacological activities of quinoxaline derivates.* Journal of pharmacy research, 2011. **4**(3): p. 924-929.
17. Alice N Neely, I.A.H., *Antimicrobial resistance.* Burns, 1999. **25**(1): p. 7.
18. Suresh, M.L., P.; Suchakar, D.; Vashu, K.; Rao, C. V., *Synthesis and biological activity of 8-chloro-[1, 2,4]triazolo[4,3-a]quinoxalines.* J. Chem. Pharm. Res., 2010. **2**(1): p. 8.
19. Ammar Y.A., I.M.M.F., El-Gaby M.S.A., Zahran M.A., *Some reactions with quinoxaline-2,3-dicarboxylic acid anhydride: Novel synthesis of thieno[2,3-d]pyrimidines and pyrrolo[3,4-b]quinoxalines as antimicrobial agents.* Indian Journal of Chemistry, 2002. **41B**: p. 5.
20. A. D. Harries, C.D., *Tuberculosis.* Annals of Tropical Medicine and Parasitology, 2006. **100**: p. 16.
21. Parvathi Tiruviluamala, L.B.R., *Tuberculosis.* Annual Review of Public Health, 2002. **23**: p. 23.

22. Onyebujoh P., R.G., *Tuberculosis.* Nature Reviews Microbiology, 2004. **2**(12): p. 2.
23. Jaso A., Z.B., Aldana I., Monge A., *Synthesis of new 2-acetyl and 2-benzoyl quinoxaline 1,4-di-N-oxide derivaties as anti-Mycobacterium tuberculosis agents.* European Journal of Medical Chemistry, 2003. **38**: p. 791-800.
24. Badawy M., M.G., Omar M., Nassar M., Kamel A., *Synthesis, spetroscopic and thermal characterization of quinoxaline metal complexes* European Journal of Chemistry, 2010. **1**(4): p. 282-288.
25. M. Elena Montoya, Y.S., M. Angel Ortega, Adela Lopez De Cerain, Antonio Monge, *Synthesis and antituberculosis activity of some new 2-quinoxalinecarbonitriles.* Il Farmaco, 1998. **53**(8-9): p. 3.
26. Enrique Torres, E.M., Saioa Ancizu, Carlos Barea, Silvia Galiano, Igancio Aldana, Antonio Monge, Silvia Pérez-Silanes, *New 1,4-di-N-oxide-quinoxaline-2-ylmethylene isonicotinic acid hydrazide derivatives as anti-Mycobacterium tuberculosis agents.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
27. Andrews, J.M., *Determination of minimun inhibitory concentrations.* Journal of Antimicrobial Chemotherapy, 2001. **48**(1): p. 12.
28. Antonio Carta, M.P., Giuseppe Paglietti, paola Molicotti, Bianca Paglietti, Sara Cannas and Stefania Zanetti, *[1,2,3]Triazolo[4,5-h]quinolones. A new class of potent antitubercular agents against multidrug resistant Mycobacterium tuberculosis strains.* Bioorg. Med. Chem. Lett., 2007. **17**: p. 3.
29. Koonin EV, S.T., Dolja W., *The ancient Virus World and evolution of cells.* Biology Direct, 2006. **1**(29): p. 27.
30. Iou-Jiun Kang, L.-W.W., Tsu-An Hsu, Andrew Yueh, Chung-Chi Lee, Yen-Chun Lee, Chin-Yin Lee, Yu-Sheng Chao, Shin-Ru Shih, Jyh-Haur Chern, *Isatin-b-thiosemicarbazones as potent herpes simplex virus inhibitors.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
31. Yang-Fei Xiang, C.-W.Q., Guo-Wen Xing, Jing Hao, Min Xia, Yi.Fei Wang, *Anti-herpes simplex virus efficacies of 2-aminobenzamide derivatives as novel HSP90 inhibitors.* Bioorg. Med. Chem. Lett., 2012. **22**(14): p. 3.
32. Kolokotronis A, D.S., *Herpes simplex virus infection, with particular reference to the progression and complications of primary herpetic gingivostomatitis.* Clin. Microbiol. Infect., 2006. **12**(3): p. 9.
33. Balfour Jr., H.H., *Antiviral Drugs.* New England Journal of Medicine, 1999. **340**(16): p. 10.
34. A. K. Field, K.K.B., *'The end of innocence' revisited: Resistance of herpes viruses to antiviral drugs.* Clinical Microbiology Reviews, 1994. **7**(1): p. 13.
35. Judie B. Alimonti, T.B.B., Keith R. Fowke, *Mechanisms of CD_4^+ T lymphocyte cell death in human immunodeficiency virus infection and AIDS.* Journal of General Virology, 2003. **84**: p. 12.
36. Organization, W.-W.H., *AIDS epidemic update.* UNAIDS, 2002.
37. Amy L. Fairchild, R.B., *HIV Surveillance, Public Health, and Clinical Medicine - Will the Walls Come Tumbling Down?* New England Journal of Medicine, 2011. **365**: p. 2.
38. Lei You, E.J.C., John Leavitt, Li-Chung Ma, Gaetano Montelione, Eric Anslyn, Robert Krug, Andrew Ellington, Jon D. Robertus, *Synthesis and evaluation of quinoxaline derivatives as potential influenza NS1A protein inhibitors.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
39. Dorr, P., *7.14 - Fungi and Fungal Disease.* Comprehensive Medicinal Chemistry II, 2007. **7**: p. 24.
40. Ryan KJ, R.C., *Sherris Medical Microbiology*, ed. M. Hill2004.
41. Thomas J. Walsh, D.M.D., *Spectrum of Mycoses*, in *Medical Microbiology. 4th edition*, e. Baron S, Editor 1996.
42. Leah E. Cowen, A.N., Malcolm S. Whiteway, David Y. Thomas, Daniel C. Tessier, Linda M. Kohn, James B. Anderson, *Population genomics of drug resistance in Candida albicans.* Proc Natl Acad Sci USA, 2002. **99**(14): p. 4.
43. Shadab Miyan Siddiqui, A.S., *Thiosemicarbazone fragment embedded within 1,2,4-triazole ring as inhibitors of Entamoeba histolytica.* Bioorg. Med. Chem. Lett., 2012. **22**(8): p. 3.
44. C.C. Hung, P.J.C., S.M. Hsieh, J.M. Wong, C.T. Fang, S.C. Chang, M.Y. Chen, *Invasive amoebiasis: An emerging parasitic disease in patients infected with HIV in an area endemic for amoebic infection.* AIDS, 1999. **13**(17): p. 7.
45. Mohammad Abid, A.A., *Synthesis, characterization and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives.* Bioorg. Med. Chem. Lett., 2006. **16**: p. 4.
46. S. L. Croft, G.H.C., *Leishmaniasis - current chemotherapy and recent advances in the search for novel drugs.* Trends Parasitol, 2003. **19**(11): p. 11.
47. Esther Vicente, S.C., Emily Bongard, Raquel Villar, Asunción Burguete, Beatriz Solano, Saioa Ancizu, Silvia Pérez-Silanes, Ignacio Aldana, Livia Vivas, Antonio Monge, *Synthesis and Antiplamodial Activity of 3-Furyl and 3-Thienylquinoxaline-2-carbonitrile 1,4-Di-N-oxide Derivatives.* Molecules, 2008. **13**: p. 8.
48. WHO, *Guidelines for the treatment of Malaria.* World Health Organization: Second Edition, 2010.

49. Kathryn N. Suh, K.C.K., Jay S. Keystone, *Malaria.* Canadian Medical Association Journal, 2004. **170**(11): p. 9.
50. Moller, D.E., *New drug targets for type 2 diabetes and the metabolic syndrome.* Nature, 2001. **414**: p. 6.
51. A.A. Abu-Hashem, M.A.G., F.A. Badria, *Synthesis of some new pyrimido[2',1':2,3]thiazolo[4,5-b]quinoxaline derivatives as anti-inflammatory and analgesic agents.* European Journal of Medical Chemistry, 2010. **45**: p. 5.
52. Kim Peterson, M.M., Sujata Thakurta, Tracy Dana, Carol Roberts, Roger Chou, Mark Helfand, *Drug Class Review: Nonsteroidal Antiinflamatory Drugs (NSAIDs)*, in *Oregon Health & Science University*2010.
53. R. Micklewright, S.L., W. Linley, C. McQuade, F. Thompson, N. Maskrey, *NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors.* Alimentary Pharmacology & Therapeutics, 2003. **17**(3): p. 11.
54. Asunción Burguete, E.P., Dimitra Hadjipavlou-Litina, Saioa Ancizu, Raquel Villar, Beatriz solano, Elsa Moreno, Enrique Torres, Silvia Pérez, Ignacio Aldana, Antonio Monge, *Synthesis and Biological evaluation of New Quinoxaline Derivatives as Antioxidant and Anti-Inflammatory Agents.* Chem Biol Drug Des, 2011. **77**: p. 11.
55. Claus Schneider, W.E.B., Huiyong Yin, Donald F. Stec, Markus Voehler, *Convergent oxygenation of arachidonic acid by 5-lypoxygenase and cyclooxygenase-2.* Journal of the American Chemical Society, 2006. **128**(3): p. 2.
56. Ahmedin Jemal, F.B., Melissa M., Jacques Ferlay, Elizabeth Ward, David Forman, *Global cancer statistics.* CA: A Cancer Journal for Clinicians, 2011. **61**(2): p. 21.
57. Organization, W.H., *The Global Burden of Disease: 2004 Update.* Geneva: World Health Organization, 2008.
58. Anahory, B.B., *Factores de neuroprotecção do nervo óptico no glaucoma.*, in *Departamento de Ciências Médicas*2009, Universidade da Beira Interior.
59. Quigley, H.A., *Glaucoma.* The Lancet, 2011. **377**(9774): p. 10.
60. Toris, C., *Glaucoma.* xPharm: The Comprehensive Pharmacology Reference, 2007: p. 7.
61. Wasim Rashid, S.R., Tejit Singh, *Profile of Patients of Glaucoma In Kashmir Valley (A Hospital Based Study).* JK Science, 2010. **12**: p. 4.
62. Lahren William J., S.s.T.W., *Pseudo Exfoliative Glaucoma.* Yanoff M, Duker Jay S.Ophthalmology. Vol. 2. 2004: Mosby. 1499.
63. Ross, R., *The pathogenesis of atherosclerosis: a perspective for the 1990s.* Nature, 1993. **362**: p. 9.
64. Sung-Yu Hongb, K.-H.C., Hea-Jung Youa, Ik Hwa Choia, Mi Jin Chaea, Ja-Young Hana, Ok-Jai Junga, Soo-Jung Kang, Chung-Kyu Ryu, *Synthesis and biological evaluation of benzimidazole-4,7-diones that inhibit vascular smooth muscle cell proliferation.* Bioorg. Med. Chem. Lett., 2004. **14**(13): p. 4.
65. Newby A. C., G.S.J., *Proposed roles for growth factors in mediating smooth muscle proliferation in vascular pathologies.* Cardiovascular Research, 1993. **27**(7): p. 11.
66. H Chung, O.J., M J Chae, S Hong, K Chung, S K Lee, C Ryu, *Synthesis and biological evaluation of quinoxaline-5,8-diones that inhibit vascular smooth cell proliferation.* Bioorg. Med. Chem. Lett., 2005. **15**: p. 5.
67. Peroutka, S.J., *5-Hydroxytryptamine receptor subtypes.* Pharmacochemistry Library, 1997. **27**: p. 11.
68. Radhakrishnan Mahesh, T.D., Dilip Kumar pandey, Shvetank Bhatt, *Discovery of new anti-depressants from structurally novel 5-HT$_3$ receptor antagonists: Design, synthesis and pharmacological evaluation of 3-ethoxyquinoxalin-2-carboxamides.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 3.
69. Rudolf Mueller, S.R., Martina E. Tedder, Yong-Xin Li, Sheng Zhong, Aidan Hampson, Jolanta Ulas, Mark Varney, Lena Nielsson,Gary Rogers, *Substituted benzoxazinones as potent positive allosteric AMPA receptor modulators: Part II.* Bioorg. Med. Chem. Lett., 2011. **21**(13): p. 4.
70. Stefano Marenco, D.R.W., *Therapeutic Potential of Positive AMPA Receptor Modulators in the Treatment of Neuropsychiatric Disorders.* CNS Drugs, 2006. **20**(3): p. 14.
71. Andrew Alt, E.S.N., David Bleakman, Jeffrey M. Witkin, *A role for AMPA receptors in mood disorders.* Biochemical Pharmacology, 2006. **71**: p. 16.
72. Patrick M. Kanju, K.P., Catrina Sims, Ben A. Bahr, Brian C. Shonesy, Vishnu Suppiramaniam, *Ampakine CX516 ameliorates functional deficits in AMPA receptors in a hippocampal slice model of protein accumulation.* Experimental Neurology, 2008. **214**: p. 7.
73. Michael J. O'Neill, D.B., Dennis M. Zimmerman and Eric S. Nisenbaum, *AMPA Receptor Potentiators for the Treatment of CNS Disorders.* Current Drug Target -CNS & Neurological Disorders, 2004. **3**(3): p. 14.
74. Yasuo Takano, F.S., Jun Asano, Naoki Ando, Hideharu Uchiki, Tsuyosi Anraku, *Synthesis and AMPA Receptor Antagonistic Activity of a Novel Class of Quinoxalinecarboxylic Acid with a Substituted Phenyl Group at C-7 Position.* Bioorg. Med. Chem. Lett., 2003. **13**: p. 4.

75. Y. Abboud, A.A., T. Saffaj, M. Berrada, M. Charrouf, A. Bennamara, N. Al Himidi, H. Hannache, *2,3-Quinoxalinedione as a novel corrosion inhibitor for mild steel in 1 M HCl.* Materials Chemistry and Physics, 2007. **105**: p. 5.
76. I.B. Obot, N.O.O.-E., *Indeno-1-one [2,3-b] quinoxaline as an effective inhibitor for the corrosion of the mild steel in 0.5 M H_2SO_4 solution.* Materials Chemistry and Physics, 2012. **122**: p. 3.
77. I.B. Obot, N.O.O.-E., N.W. Odozi, *Acenaphtho [1,2-b] quinoxaline as a novel corrosion inhibitor for mild steel in 0.5 M H_2SO_4.* Corrosion Science, 2012. **52**: p. 3.
78. Barceloux, D.G., *Copper.* Clinical Toxicology, 1999. **37**(2): p. 4.
79. Ajit Kumar, V.K., Uzra Diwan, K. K. Upadhyay, *Highly sensitive and selective naked-eye detection of Cu^{2+} in aqueous medium by a ninhydrin-quinoxaline derivative.* Sensors and Actuators B: Chemical, 2013. **176**: p. 7.
80. Baldo, M.A., O'Brien, D.F., You, Y., Shoustikov, A., Sibley, S., Thompson, M.E., Forrest, S.R., *Highly efficient phosphorescent emission from organic electroluminescent devices.* Nature, 1998. **395**(6698): p. 4.
81. Hsin-Hua Changa, W.-S.T., Chien-Ping Changa, Nien-Po Chenc, Ken-Tsung Wongb, Wen-Yi Hungd, Shou-Wei Chend, *A new tricarbazole phosphine oxide bipolar host for efficient single-layer blue PhOLED.* Organic Electronics, 2011. **12**(12): p. 8.
82. M. Ananth Reddy, A.T., G. Mallesham, B. Sridhar, V. Jayathirtha Rao, K. Bhanuprakash, *Synthesis of novel twisted carbazole-quinoxaline derivatives with 1,3,5-benzene core: bipolar molecules as hosts for phosphorescent OLEDs.* Tetrahedron Letters, 2011. **52**: p. 5.
83. Committee on Mathematical Challenges from Computational Chemistry, N.R.C., *Mathematical Challenges from Theoretical/Computational Chemistry* 1995.
84. Richon, A.B., *An introdution to molecular modeling.* Mathematech, 1994. **1**: p. 83.
85. Young, D., *Introdution to computational chemistry.* Chem. Aust., 1998. **11**: p. 5.
86. The Shodor Education Foundation, I. *ChemViz*. 2000 [cited 2013.
87. Pessoa, A.M., *Estudo teórico de adsorção de OH em suerfícies de Ouro*, in *Departamento de Química* 2005, Universidade do Porto: Faculdade de Ciências. p. 66.
88. Ciarlet, P.G., *Handbook of numerical analyses - computational chemistry*. Vol. 10. 2003: North-Holland.
89. Weilsstein, E.W. *Shrödinger Equation*. Eric Weisstein's World of Physics 2007 [cited 2013.
90. Hehre, W.J., *A Guide to Molecular Mechanics and Quantum Chemical Calculations*2003.
91. Jia Deng, A.T.B.G., Peter M.W. Gill, *Hartree-Fock perturbative corections for total and reaction energies.* Journal of Chemical Physics, 2010. **133**(4): p. 6.
92. Corneliu Cojocaru, A.R., Valeria Harabagiu, Liviu Sacarescu, *Molecular structure and electronic properties of pyridylindolizine derivative containing phenyl and phenacyl groups: Comparison between semi-empirical calculations and experimental studies.* Journal of Molecular Structure, 2013. **1034**: p. 11.
93. Georgiana G. Surpateanu, M.B., Neculai Catalin Lungu, Paul Ionut Dron, Sophie Fourmentin, David Landy, Gheorghe Surpateanu, *Photochemical behaviour upon the inclusion for some volatile organic compounds in new fluorescent indolizine b-cyclodextrin sensors.* Journal of Photochemistry and Photobiology A: Chemistry, 2007. **185**: p. 9.
94. Hameed, A.J., *Study of the structural and electronic properties of the 1-phenyl-3,3-pentamethylenetriazenes.* Journal of Molecular Structure: THEOCHEM, 2005. **725**: p. 5.
95. Gerd B. Rocha, R.O.F., Alfredo M. Simas, James J.P. Stewart, *RM1: A Reparameterization of AM1 for H, C, N, O, P, S, F, Cl, Br and I.* Journal of Computational Chemistry, 2005. **27**(10): p. 11.
96. Maylis Orio, D.P., Frank Neese, *Density functional theory.* Springer, 2009. **102**: p. 443-453.
97. P.W. Atkins, R.S.F., *Molecular Quantum Mechanics, 3rd edition.* Oxford University Press, New York, 1997.
98. Mathias Hofman, H.F.S., *Computational Chemistry.* Encyclopedia of Physical Science and Technology, 2003: p. 20.
99. Physics, I.f.C., *Chapter 9: Density Functional Theory (DFT) Methods*, 2013: Institute for Computational Physics, Germany. p. 6.
100. Allouche, A.-R., *Gabedit - A Graphical User interface for computational chemistry softwares.* Journal of Computational Chemistry, 2011. **32**: p. 174-182.
101. Chunyang Peng, P.Y.A., H. Bernhard Schlegel, *Using Redundant Internal Coordinates to Optimize Equilibrium Geometries and Transition States.* Journal of Computational Chemistry, 1996. **17**(1): p. 8.
102. M.J. Frisch, G.W.T., H.B. Schlegel, G.E. Scuseria, M.A. Rob, J.R. Cheeseman,, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant, J.M. Millam, S.S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G.A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J.E. Knox, H.P. Hratchian, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, P.Y. Ayala, K. Morokuma, G.A. Voth, P. Salvador, J.J. Dannenberg, V.G.

Zakrzewski, S. Dapprich, A. D. Daniels, M.C. Strain, O. Farkas, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. V. Ortiz, Q. Cui, A.G. Baboul, S. Clifford, J. Cioslowski, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, C. Gonzalez, J. A. Pople. *Gaussian09, Revision A.1*. 2009 [cited 2012 17JUL].

103. SERC. *Gaussian Software*. [cited 2012 17JUL].

Anexes:

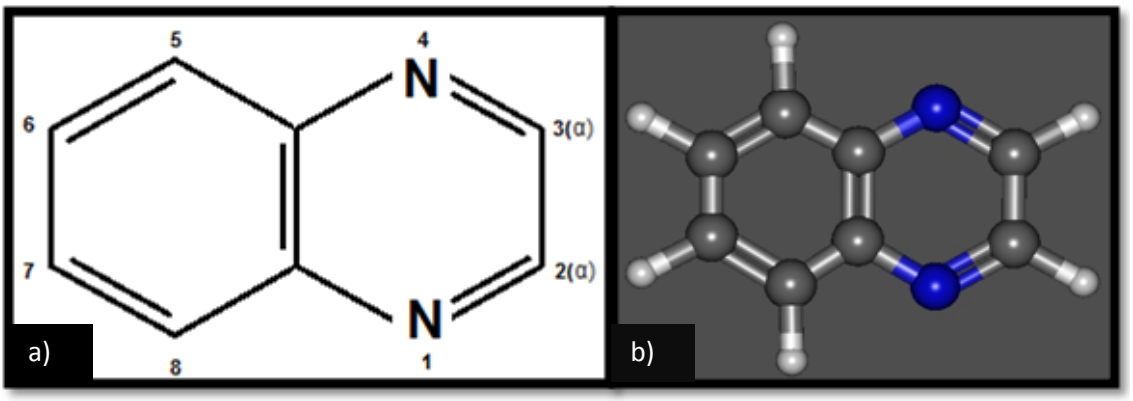


Figure 1: Quinoxaline compound: a) Lewis structure; b) 3D structure.

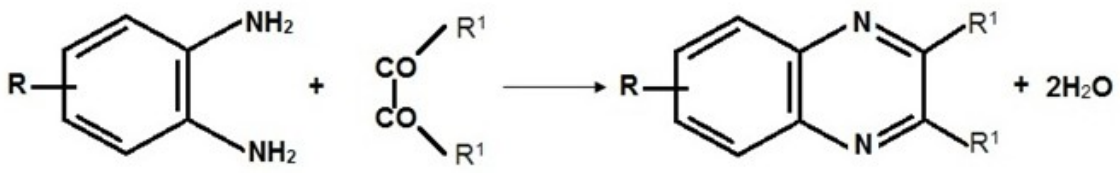


Figure 2: Quinoxaline synthesis.

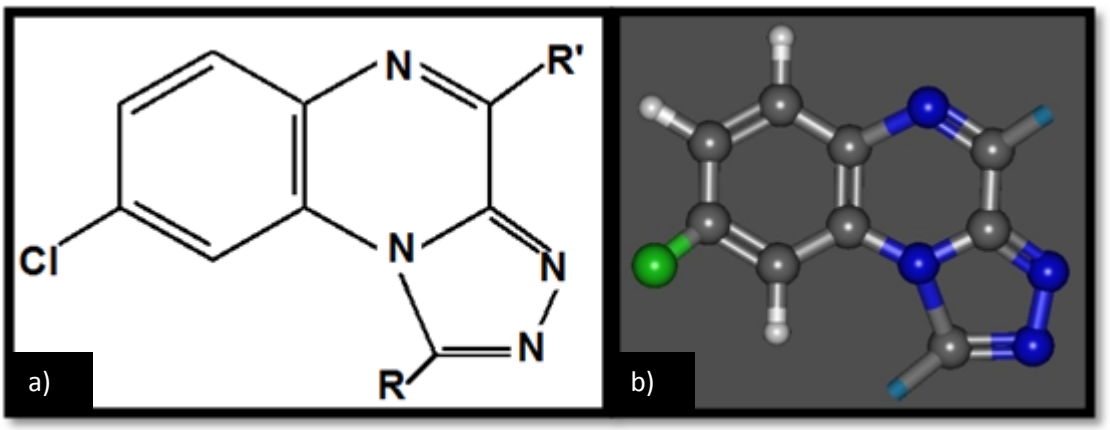


Figure 3: 8-chloro-1,4-substituted(1,2,4)triazolo(4,3a) quinoxaline derivatives core: a) Lewis structure; b) 3D structure.

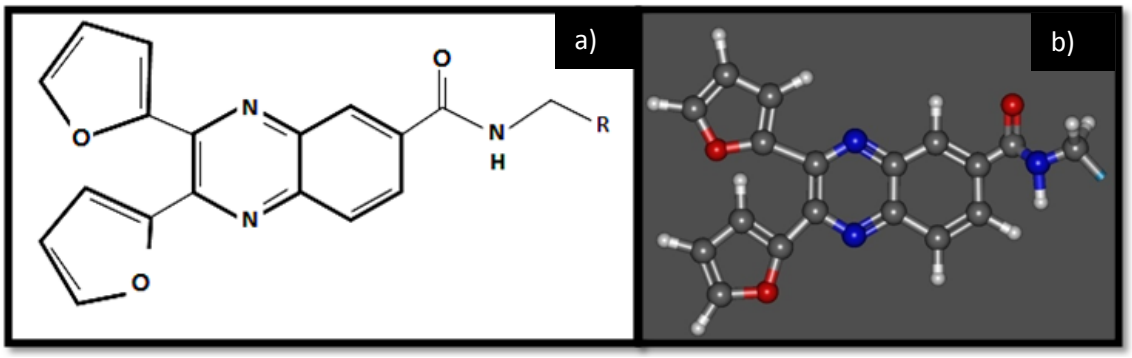


Figure 4: 2,3-difuryl-4-quinoxaline (R) metilcarboxamide derivatives compound: a) Lewis structure; b) 3D structure.

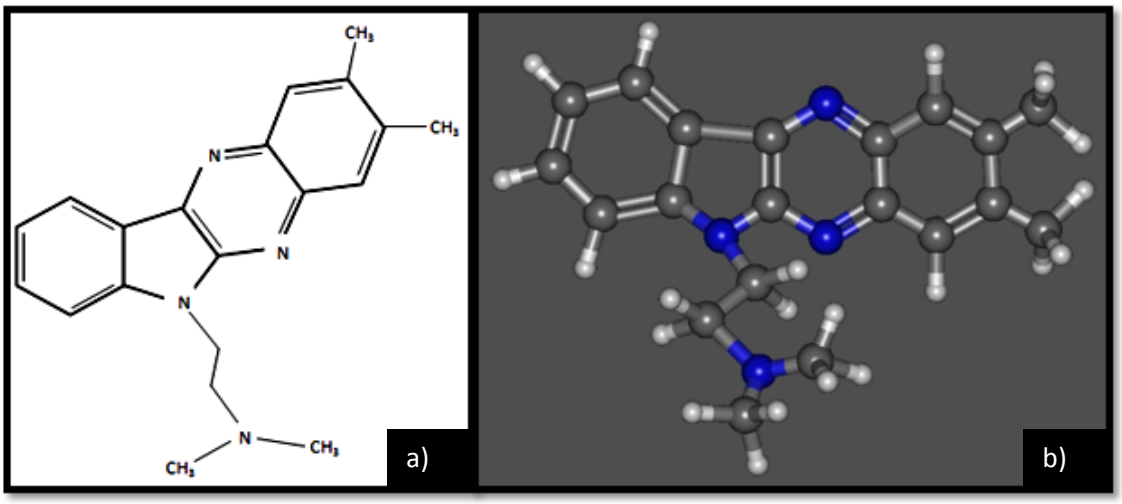


Figure 5: 2,3-dimethyl-6-(dimethylaminoethyl)-6H-indolo-[2,3-*b*]quinoxaline compound: a) Lewis structure; b) 3D structure.

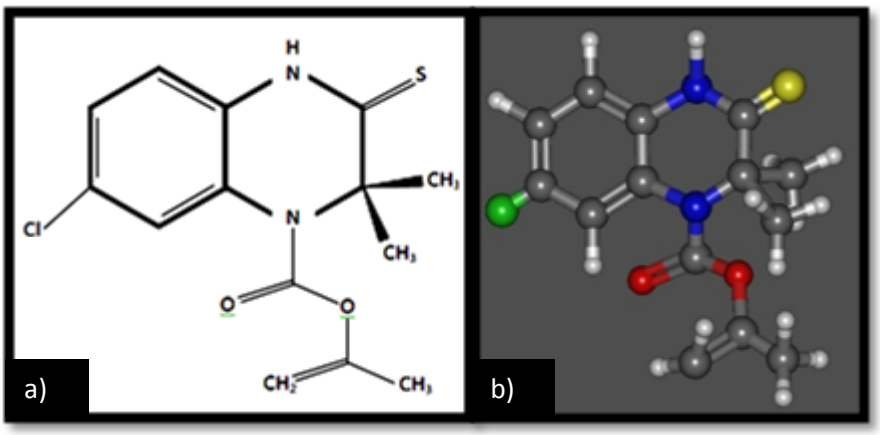


Figure 6: 6-chloro-3,3-dimethyl-4(isopropenyloxycarbonyl)-3,4-dihydroquinoxalin-2(1H)-thione compound: a) Lewis structure; b) 3D structure.

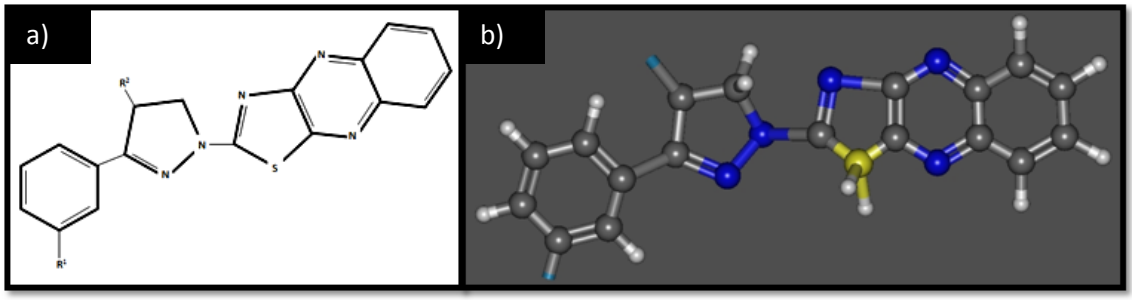


Figure 7: 1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazolines core: a) Lewis structure; b) 3D structure.

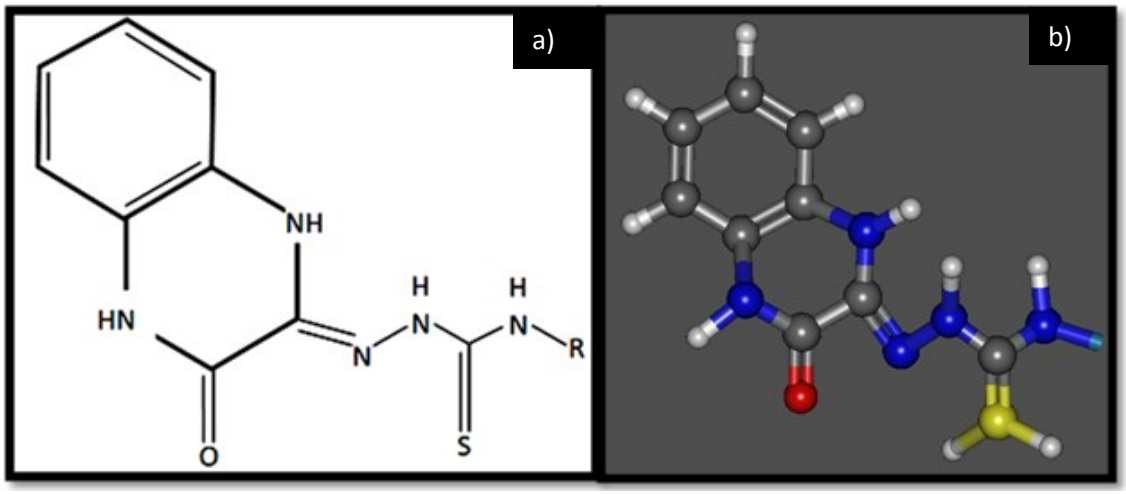


Figure 8: Ligands L^1H_2 and L^2H_2. For L^1H_2, R=CH_3 and for L^2H_2, R=C_6H_5: a) Lewis structure; b) 3D structure.

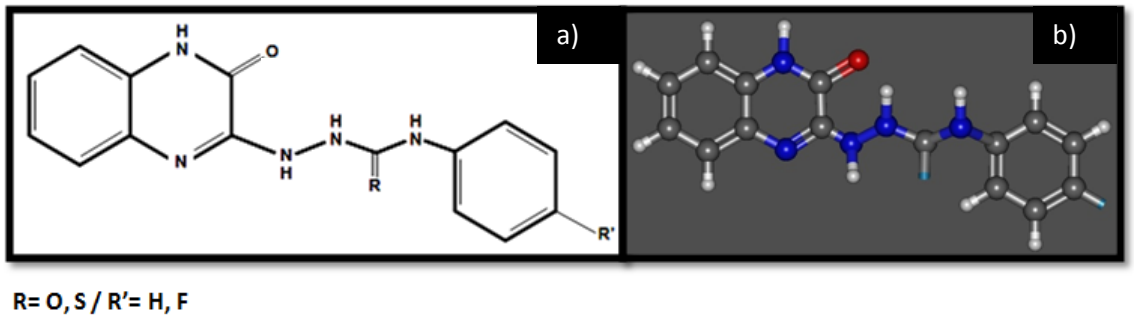
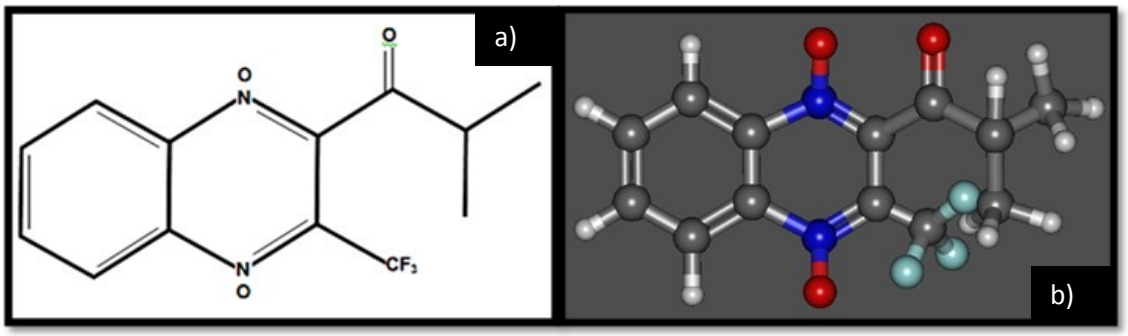
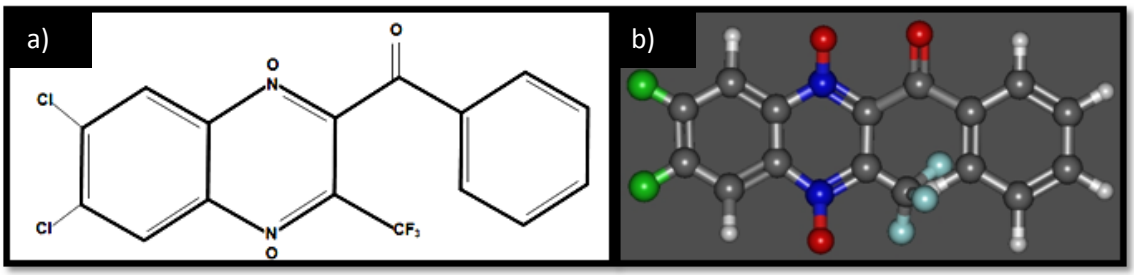


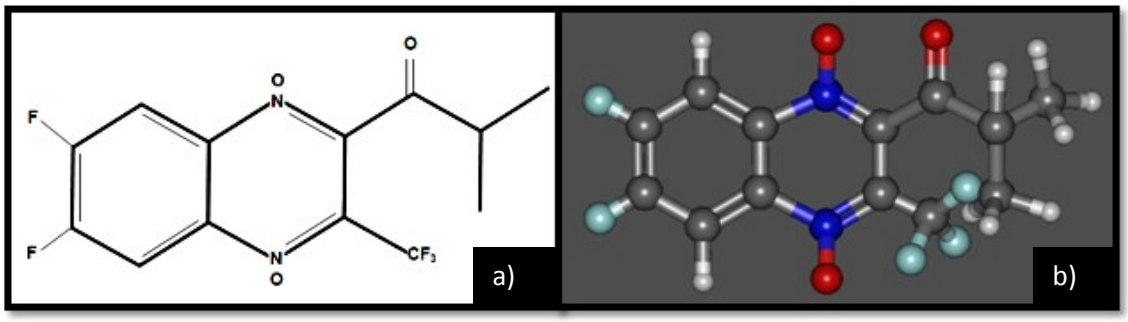
Figure 9: (N-arylcarbamoyl and N- aryl thiocarbamoyl) hydrazinequinoxalin – 2 (1H) compounds: a) Lewis structure; b) 3D structure.



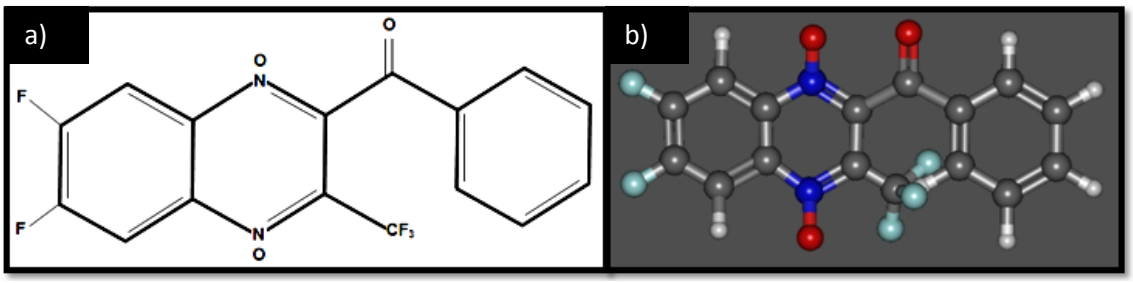
Compound 1: 2-Isobutyryl-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



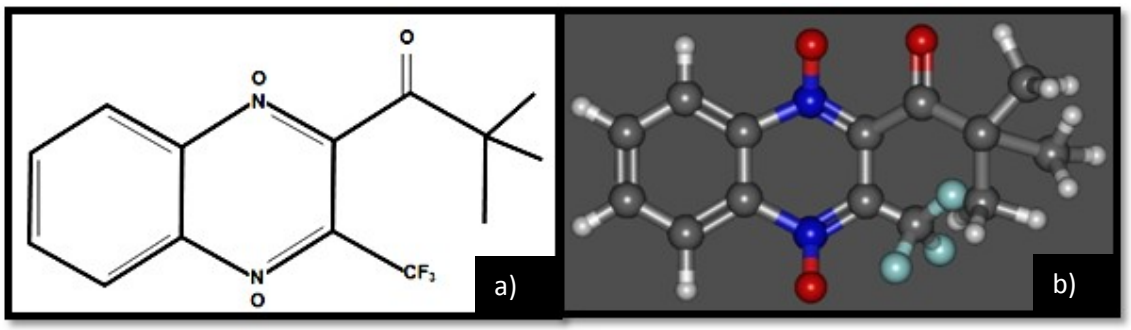
Compound 2: 2-benzoyl-6,7-dichloro-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.



Compound 3: 6,7-difluoro-2-isobutyryl-3-trifluoromethylquinoxaline 1,4-di-N-oxide.



Compound 4: 2-benzoyl-6,7-difluoro-3-trifluoromethylquinoxaline 1,4-di-N-oxide.



Compound 5: 2-(2,2-dimethylpropanoyl)-3-trifluoromethylquinoxaline 1,4-di-*N*-oxide.

Figure 10: Compounds 1 to 5: a) Lewis structure; b) 3D structure.

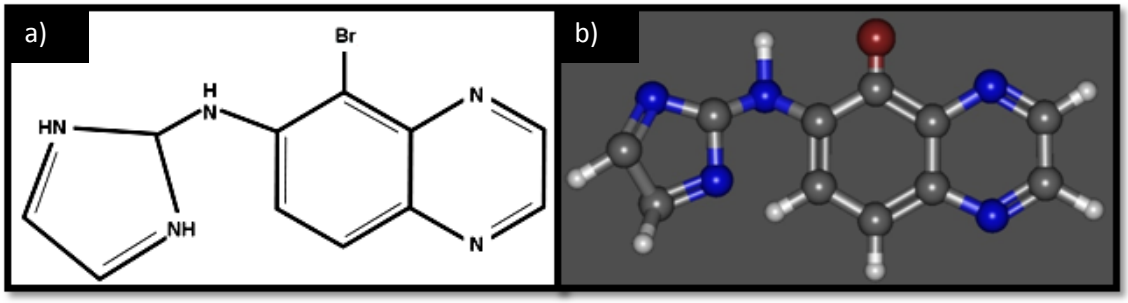


Figure 11: Alphagan chemical structure: a) Lewis structure; b) 3D structure.

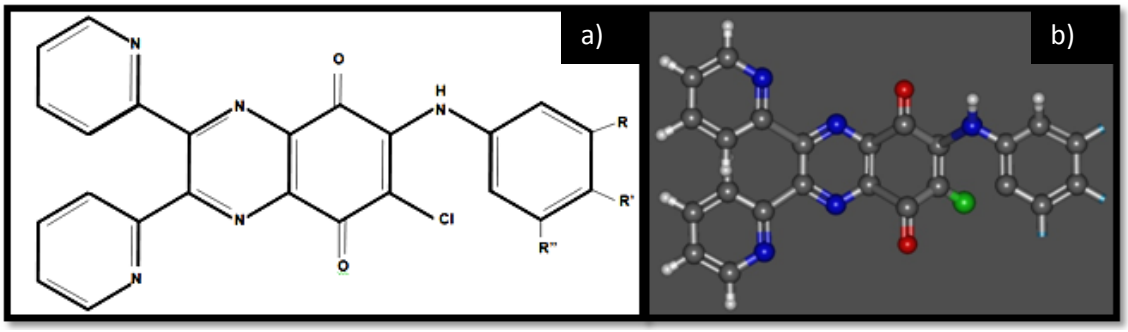


Figure 12: 6-arylamino-2,3-bis(pyridin-2-yl)-7-choloroquinoxaline-5,8 diones compounds: a) Lewis structure; b) 3D structure.

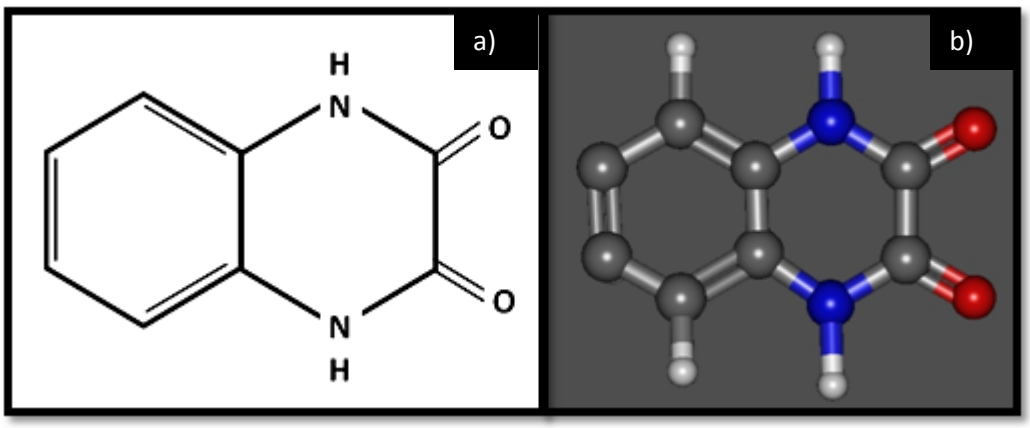


Figure 13: 2,3-quinoxalinedione (QD): a) Lewis structure; b) 3D structure.

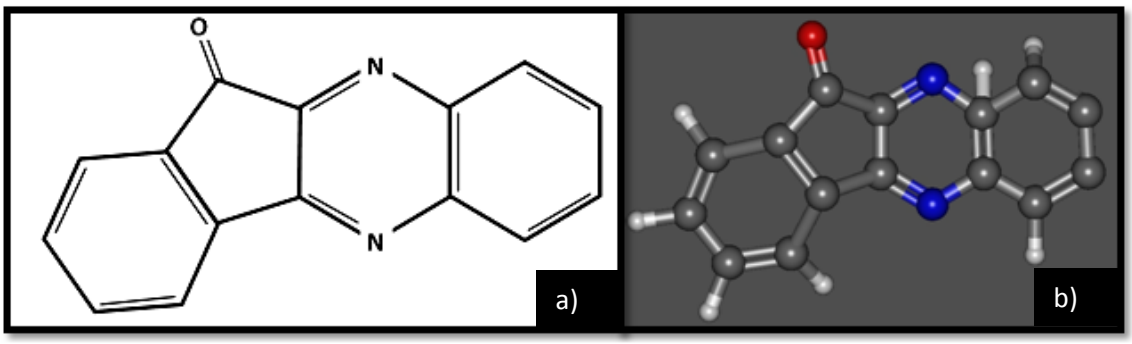


Figure 14: Indeno-1-one [2,3-b] quinoxaline (INQUI) compound: a) Lewis structure; b) 3D structure.

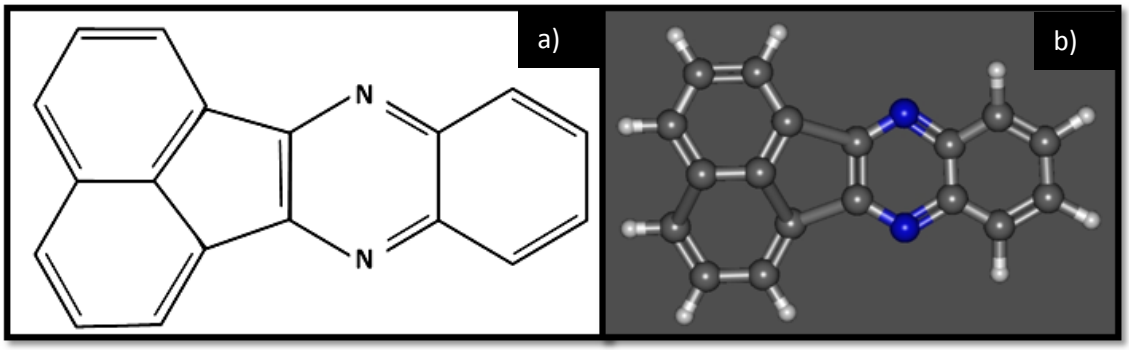
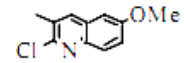
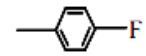
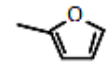
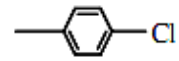
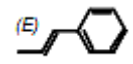
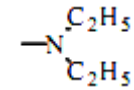
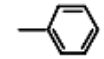
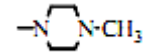
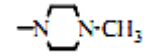
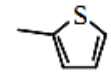
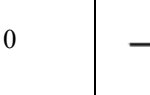


Figure 15: Acenaphtho [1,2-b] quinoxaline (AQ) compound: a) Lewis structure; b) 3D structure.

Quinoxaline Properties	
Formula	$C_8H_6N_2$
Molecular Weight	130.1466400
Acidity (*pKa*)	0,56
Second *pKa*	-5,52
Melting Temperature	29-30ºC
Natural State	White crystaline powder
Dipole Moment	0,51 D
Ionization ($1^{st}/2^{nd}$)	8,99/10,72 eV
Heat of atomization	70,739eV

Table 1: Quinoxaline properties

Main Compound	Compound	R	R'	R''	% Binding at 50μM	% Intercalation at 50 μM	IC_{50}μM	IG_{50}μM	Reference
8-chloro-1,4-substituted(1,2,4)triazolo(4,3a) quinoxaline derivatives	1		-Cl	-	-	-	-	-	[16]
	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) metilcarboxamide derivatives	1	3-OMe-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	-	[45]
	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-benzoyl-3-trifluromethylquinoxaline-1,4-di-N-oxide derivatives	1	H	H	-	-	-	-	1,02	[10]
	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	-	[66]
	2	H	OH	H	-	-	5,5	-	
	3	H	F	H	-	-	1,0	-	
	4	H	CF_3	H	-	-	1,1	-	
	5	H	OCF_3	H	-	-	1,0	-	
	6	H	OCH_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	-	

Table 2: Published experimental data (percentage of Binding, Intercalation, IC_{50} and IG_{50}) of quinoxaline derivatives and their substituents.

1. Asif Husain, D.M., *Recent advances in pharmacological activities of quinoxaline derivates.* Journal of pharmacy research, 2011. **4**(3): p. 924-929.
2. Lei You, E.J.C., John Leavitt, Li-Chung Ma, Gaetano Montelione, Eric Anslyn, Robert Krug, Andrew Ellington, Jon D. Robertus, *Synthesis and evaluation of quinoxaline derivatives as potential influenza NS1A protein inhibitors.* Bioorg. Med. Chem. Lett., 2011. **21**: p. 4.
3. Mohammad Abid, A.A., *Synthesis, characterization and antiamoebic activity of 1-(thiazolo[4,5-b]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives.* Bioorg. Med. Chem. Lett., 2006. **16**: p. 4.
4. Belén Zarranz, A.J., Ignacio Aldana, Antonio Monge, *Synthesis and anticancer activity evaluationnof new 2-alkylcarbonyl and 2-benxoyl-3-trifluoromethyl-quinoxaline 1,4-do-N-oxide derivatives.* Bioorganic & Medicinal Chemistry, 2004. **12**: p. 10.
5. H Chung, O.J., M J Chae, S Hong, K Chung, S K Lee, C Ryu, *Synthesis and biological evaluation of quinoxaline-5,8-diones that inhibit vascular smooth cell proliferation.* Bioorg. Med. Chem. Lett., 2005. **15**: p. 5.