الجمهورية الجزائرية الديمقراطية الشعبية

République Algérienne Démocratique et Populaire

وزارة التعليم العالي و البحث العلمي

Ministère de l'Enseignement Supérieur et de la Recherche Scientifique

Université Mohamed Khider - Biskra
Faculté des Sciences Exactes et des Sciences de la Nature et de la Vie

جامعة محمد خيضر- بسكرة
كلية العلوم الدقيقة و علوم الطبيعة و الحياة

Thèse présentée en vue de l'obtention

du diplôme de

Doctorat en chimie

Spécialité ou option: **Chimie moléculaire**

Etude par la modélisation moléculaire des relations structures-propriétés de quelques séries hétérocycliques bioactives.

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ACKNOWLEDGEMENTS

The present work was carried out at computational and pharmaceutical chemistry Research Group under guidance of Prof. **BELAIDI salah**, *Department of science of matter, Faculty of pure sciences and natural and life sciences, University of Mohamed khider Biskra, Algeria.*

First of all, I pray to Allah, the almighty for providing me this opportunity and granting me the capability to proceed successfully.

At the outset, I would like to thank my supervisor Prof. **BELAIDI salah** *for providing me an opportunity to do my doctoral research under his tutelage and for his excellent supervision, generous guidance, continuous support, encouragement throughout my research and for their extremely useful comments and discussion to make my thesis complete.*

I want to express my deep thanks to my esteemed co-supervision Dr. **BOUMEDJANE Youcef** *for the trust, the insightful discussion, offering valuable advice, for your support during the whole period of the research.*

I wish to extend my sincere thanks to Prof. **OMARI Mahmoud**, *Professor at the University of Biskra, for accepting to chair the dissertation of my thesis.*

I would also like to thank the committee members, Prof. **LANEZ Touhami** *and Prof.* **OUAHRANI Med Ridha**, *Professors at the University of El-oued, for agreeing to examine and judge the work.*

I would like to thank all the members of group of computational and pharmaceutical chemistry, LMCE Laboratory at Biskra university, with whom I had the opportunity to work. They provided a friendly and cooperative atmosphere at work and also useful feedback and insightful comments on my work.

I would like to express my special thanks to ***Prof. ÇINAR Mehmet*** *from Turkish bayburt university for his help with a smile, for his good hospitality and good reception during my stay in his university.*

Last, but not least, I would like to dedicate this thesis to my beloved parents whom raised me with a love of science and supported me in all my pursuits, my husband, my siblings and my friends for their love and continuous support – both spiritually and materially.

To my beloved parents

To my husband

To my siblings

To my friends

To all the people whom love me

Overview of the Thesis

The thesis consists of five chapters.

General Introduction

Chapter 1 : *Overview of Synthesis, Reactivity and Biological Activity of Oxadiazole*
Chapter 2 : *Molecular Modeling*
Chapter 3 : *Geometric, Electronic Structure and Substituent effects of 1,2,4-oxadiazol-5-Amine*
Chapter 4 : *Computational Study of Structure -Property Relationships (SPR) for 1,2,4-oxadiazole-5-amine Derivatives*
Chapter 5 : *QSAR Modeling of Some 3-(Aryl)-N-(Aryl)-1, 2, 4-Oxadiazol-5-Amine Derivatives*

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LIST of ABBREVIATIONS

DFT	=	Density-functional theory
HOMO	=	Highest Occupied Molecular Orbital
1D, 2D, 3D	=	One-Dimensional, Two-Dimensional, Three-Dimensional
ADMET	=	Absorption, Distribution, Metabolism, And Excretion - Toxicity
ANOVA	=	Analysis of Variance
BLYP	=	Becke's Lee, Yang and Parr
CNS	=	The Central Nervous System
GETAWAY	=	Geometry, Topology And Atom-Weights Assembly
GGA	=	Generalized Gradient Approximation
GROMOS	=	Gronigen Molecular Simulation
HF	=	Hartree-Fock
HSAB	=	Hard and Soft Acids And Bases
IC50	=	The Half Maximal Inhibitory Concentration
LDA	=	Local Density Approximations
LUMO	=	Lowest Unoccupied Molecular Orbital
LOO	=	leave one out
MES model	=	The Maximal Electroshock Seizure
MESP	=	Electrostatic Potential Surface
MLR	=	Multiple Linear Regression
MM	=	Molecular Mechanics
MP	=	Møller-Plesset
MPA	=	Mulliken Population Analysis
MR	=	Molecular Refractivity
MW	=	Molecular Weight
PCA	=	Principal Component Analysis
Pol	=	Polarizability
PRESS	=	Predicted Residual Sum of Squares
PTZ	=	Pentylenetetrazol
QSAR	=	Quantitative Structure-Activity Relationship
SAG	=	Surface Area Grid
SPR	=	Structure-Propriety Relationship
SSY	=	Sum of The Squares of The Response Value
WHIM	=	Weighted Holistic Invariant Molecular
ΔE	=	HOMO-LUMO energy gap
ΔH_f	=	Heat of Formation

General Introduction

General Introduction

The advent of high-speed computers, availability of sophisticated algorithms, and state-of-the-art computer graphics have made plausible the use of computationally intensive methods such as quantum mechanics, molecular mechanics, and molecular dynamics simulations to determine those physical and structural properties most commonly involved in molecular processes. The power of molecular modeling rests solidly on a variety of well-established scientific disciplines including computer science, theoretical chemistry, biochemistry, and biophysics. Molecular modeling has become an indispensable complementary tool for most experimental scientific research. [1]

Molecular modelling is focused on applying the fundamental laws of physics and chemistry to the study of molecules. The ultimate aim is to create models and simulations, which can help by predicting, rationalizing, and estimating the properties of molecules and their interactions. Today, computational techniques performed by powerful computers have revolutionized molecular modelling to the extent that most calculations could not be performed without the use of a computer. [2]

It allows chemists to study chemical phenomena by running calculations on computers rather than by examining reactions and compounds experimentally. Some methods can be used to model not only stable molecules, but also short-lived, unstable intermediates and even transition states. In this way, they can provide information about molecules and reactions, which is impossible to obtain through observations. Molecular modelling and computational chemistry is therefore both an independent research area and a vital adjunct to experimental studies. [2]

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties [3]. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive ab initio/HF electron correlation methods are required [4-6]. Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules. [7-16]

Hetero-aromatic ring system is the pivotal part of any biologically active drug molecule. Hetero-aromatic rings are essential because they provide similarity with respect to the biologically active compounds within our body for e.g. all the nucleic acids, hormones, neurotransmitters etc. which constitutes one or the other hetero-aromatic ring [17].

Among many hetero-aromatic rings present, fused and pendent [1, 2, 4]-oxadiazoles are also ubiquitous feature of many pharmaceutical products. Compounds having five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or furodiazoles in the older literature. [17]

Druglikeness is a qualitative concept used in drug design, which is estimated from the molecular structure before the substance is even synthesized and tested. The calculation of drug-like property can give us better assumption of biological activity of certain molecule. The theoretical calculation and maintain of certain properties of a molecule can fulfill the parameters which are essential to show certain biological activity. Lipinski's rule of five is a rule of thumb to evaluate druglikeness or determine a chemical compound with a certain pharmacological or biological activity that would make it a likely orally active drug in humans. [18]

Drug-likeness appears as a promising paradigm to encode the balance among the molecular properties of a compound that influences its pharmacodynamics and pharmacokinetics and ultimately optimizes their absorption, distribution, metabolism and excretion (ADME) in human body like a drug. [19, 20]

Molecular physicochemical and the drug-likeness are the two most significant properties to be considered for a compound to become a successful drug candidate. It is also important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's rule [21].

The QSAR is a knowledge-based method where a statistical prediction model is made about biological activity and the presence of molecular descriptors. The aim of carrying out a QSAR study is with the help of computational methods the QSAR model can help evaluate biological activity; this is mostly done to reduce failure rate in the drug development process [22]. The historical aim of QSAR studies is to predict the specific biological activity of a series of test compounds.

Nowadays the main objective of these studies is to predict biological activity of In-silico-designed compounds on the basis of already synthesized compounds [23]. The molecular modeling and QSAR calculations are used in many fields specially, physics, chemistry, biology, material science as well as tissue engineering and drug design.[24-31]

Multiple linear regression (MLR), which is one of the most common and simplest method for constructing QSAR models, was used in this study [32 –34]. The advantage of MLR is that it is simple to use and the derived models are easy to interpret.

Our work is placed in the context of fundamental and original research on 1,2,4-oxadiazole and their derivatives, the main objective of this work is the application of different methods of molecular modeling to predict the chemical reactivity and biological activities expected in new bioactive molecules studied.

The structure of the memory, composed by five chapters, has been conceptually divided into two differentiated parts. On one hand, the theoretical background section, which is composed by chapter 1 and chapter 2. On the other hand, chapter 3, chapter 4 and chapter 5 devoted to applications and results, deepens into specific practical applications.

Next, the content of the chapters is briefly described

- **Chapter 1** : *Overview of Synthesis, Reactivity and Biological Activity of Oxadiazole*

We will present general information on the physicochemical properties, the various biological activities, some ways of synthesis and chemical reactivity of oxadiazole.

- **Chapter 2** : *Molecular Modeling*

This chapter contains the main concepts and definitions related to computational methods (quantum mechanics methods, Semi - empirical methods and molecular mechanics methods).

- **Chapter 3** : *Geometric, Electronic Structure and Substituent effects of 1,2,4-oxadiazol-5-Amine*

The third chapter contains a structural, electronic and energetic study of 1,2,4 - Oxadiazol-5-Amine and its derivatives. In this chapter we present the results of a comparative study on two methods used in the calculation of the density functional theory (DFT) and ab initio, as well, the substitution effect on energy and electronic parameters of the basic nucleus of 1,2,4-Oxadiazol-5-Amine.

- **Chapter 4** : *Computational Study of Structure -Property Relationships (SPR) for 1,2,4-oxadiazole-5-amine Derivatives*

This chapter highlights the importance of a qualitative study of structure-property relationships and drug likeness proprieties of a bioactive series of 1,2,4-oxadiazol-5-amine derivatives.

- **Chapter 5** : *QSAR Modeling of Some 3-(Aryl)-N-(Aryl)-1, 2, 4-Oxadiazol-5-Amine Derivatives*

In this chapter, we take a small apercu about QSAR study (QSAR History, Several Purposes and Applications of QSAR Models, molecular descriptors, Statistical Parameters.....), then, we establish a quantitative relationship between physiochemical properties and biological activity of a series of bioactive derivatives of 1,2,4 -Oxadiazol-5-Amine (QSAR Model).

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Overview of Synthesis, Reactivity and Biological Activity of Oxadiazole

CHAPTER 1

Summary

CHAPTER I : Overview of Synthesis, Reactivity and Biological Activity of Oxadiazole

1. Introduction

Heterocyclic compounds are well known for their pharmacological potential that is exploitable in the synthesis of new bioactive molecules. Moreover, nowadays heterocyclic chemistry becomes more and more advanced in the development of new poly-heterocyclic compounds. These compounds are extremely valuable because they possess not only the pharmacological potential owned by the heterocycles themselves, but also a new one due to the reciprocal influence between the contained Heterocycles. [1]

Azolic derivatives such as thiazole, triazole, oxadiazole and thiadiazole are pharmacologically useful compounds and have been intensely investigated for various biological activities, due to their promising application in the medicinal chemistry. [1]

Oxadiazole, a heterocyclic nucleus has attracted a wide attention for the chemist in search for the new therapeutic molecules. Oxadiazoles and their derivatives are considered as simple five membered heterocycles possessing one oxygen and two nitrogen atoms.

Oxadiazole exists in different isomeric forms such as 1,2,4-, 1,2,5-, 1,3,4- and 1,2,3-oxadiazole (Figure I.1).

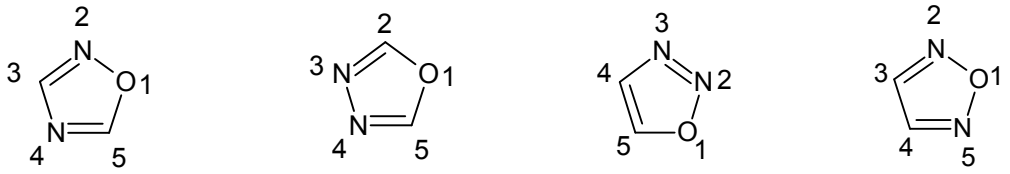


Figure I.1: Different isomeric forms of oxadiazole

Electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of

halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2carbon atom.

Nitrogen-oxygen containing heterocycles are of synthetic interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities [2].

The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) stems from the occurrence of saturated and partially saturated 1,2,4-oxadiazoles in biologically active compounds and natural products [3,4].

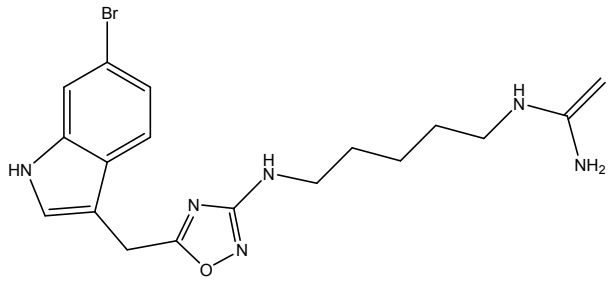
Oxadiazole rings have been introduced into drug discovery programs for several different purposes. In some cases, they have been used as an essential part of the pharmacophore, favorably contributing to ligand binding [5]. In other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker to place substituents in the appropriate orientation [6] as well as modulating molecular properties by positioning them in the periphery of the molecule [4]. It has also recently been shown that significant differences in thermodynamic properties can be achieved by influencing the water architecture within the aldose reductase active site by using two structurally related oxadiazole regioisomers [7]. Also, oxadiazoles have been used as replacements for carbonyl containing compounds such as esters, amides, carbamates, and hydroxamic esters [8].

In drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, including Zibotentan as an anti-cancer agent [9] and Ataluren for the treatment of cystic fibrosis [10]. So far, one oxadiazole containing compound, Raltegravir [11], an anti-retroviral drug for the treatment of HIV infection, has been launched onto the marketplace.

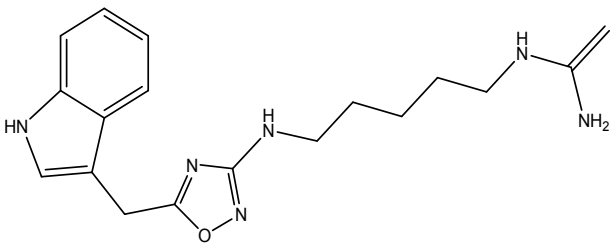
It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes, obesity [12], inflammation [13] cancer [14] and infection [15]. Aside from being biologically active themselves, 1,2,4-oxadiazoles also present an important linking site, for instance, for terminal amino groups of biologically important molecules. There are many drugs containing 1,2,4-oxadiazoles also many molecules are under development stages.

2. Naturally Occurring Oxadiazoles:

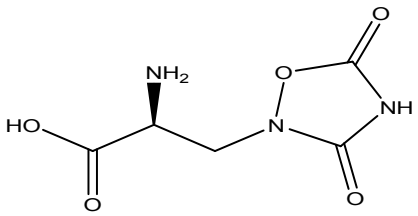
There are only few examples of natural products with oxadiazole core or a structure based on it . One among this is phidianidines A and B (Figure I.2), this is a 3-substituted indole alkaloid. Phidianidines A and B have been isolated by Carbone et al. from the aeolid opisthobranch Phidiana militaris [16]. They selectively inhibits dopamine transporter DAT and also acts as partial agonists of the μ opioid receptor [17]. Phidianidine A and B do not have cytotoxic action and therefore it can be used as CNS targets. Quisqualic acid is another example for naturally occurring oxadiazole (Figure I.2). This is a metabolite which is obtained from the seeds of Quisqualis indica and Q. fructus .Quisqualic acid is a strong agonist for α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors and group I metabotropic glutamate receptors [18].



Phidianidine A



Phidianidine B



Quisqualic Acid

Figure I.2: Example for naturally occurring oxadiazole

3. Physical Properties of Oxadiazoles

Almost all of the oxadiazoles are solid at room temperature. Their color ranges from white to dark brown. They are soluble in polar solvents like chloroform and dimethyl formamide but insoluble in non-polar solvents like ethers, etc. [19]

4. Chemistry of 1, 2, 4-oxadiazoles

Compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. As an example, five-membered ring heterocycles containing two carbon atoms, two nitrogen atoms, and one oxygen atom, known as oxadiazoles (Figure I.3), are of considerable interest in different areas of medicinal and pesticide chemistry and also polymer and material science [20]. The level of interest is clearly shown, over years, the number of patent applications containing oxadiazole rings have increased considerably. Within drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, ataluren for the treatment of cystic fibrosis.

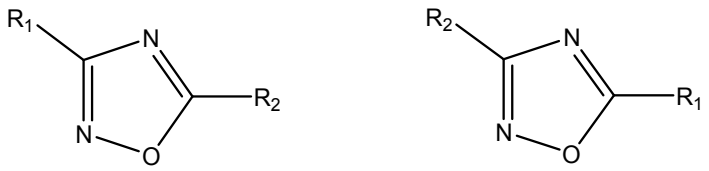


Figure I.3: Isomeric forms of 1, 2, 4-oxadiazole

5. Biological Significance of 1, 2, 4-oxadiazoles

It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes [21], obesity [22], inflammation [23], cancer [24] and infection, in turn leads to the chemists to think about introducing the oxadiazole rings into drug discovery programs for several different purposes, Ataluren (Figure I.4) is one of the 1,2,4-oxadiazole containing compounds in clinical development.

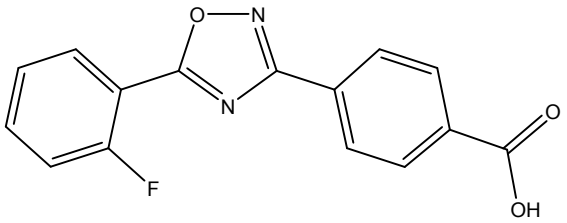


Figure I.4: Structure of Ataluren molecule

ADX-47273 (Figure I.5) is a drug used in scientific research which acts as a positive allosteric modulator selective for the metabotropic glutamate receptor subtype mGluR5 [25]. It has nootropic and anti-psychotic effects in animal studies [26], and has been used as a lead compound to develop improved derivatives [27].

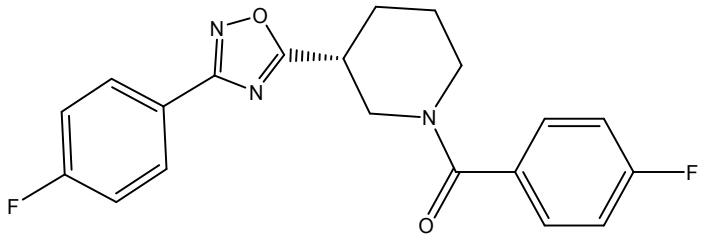


Figure I.5: Structure of ADX-47273

5.1. Anti-cancer Activity

William. K. et al. [28] efforts to discover and develop the 3-aryl-5-aryl-1,2,4-oxadiazole series of apoptosis inducers as potential anti-cancer agents, in which 5-(3-bromo-2-furyl)-3-(4-chloro-2-methyl-phenyl)-1,2,4-oxadiazole (Figure I.6) was found to have good in-vivo efficacy in animal studies via intravenous administration.

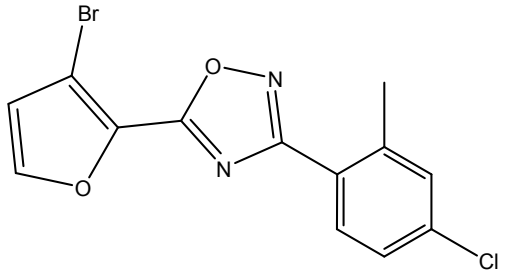


Figure I.6: Structure of 5-(3-bromo-2-furyl)-3-(4-chloro-2-methyl-phenyl)-1,2,4-oxadiazole

Ziedan. N. I. et al. [29] designed and synthesized a series of new indole-based 3,5-disubstituted 1,2,4-oxadiazoles, In which ethyl N-[(1S)-5-amino-1-[5-[[4-(2-phenylethoxy) phenyl]methyl]-1,2,4-oxadiazole-3-carbonyl] pentyl]carbamate (Figure I.7) was possess in-vitro anti-tumour activity.

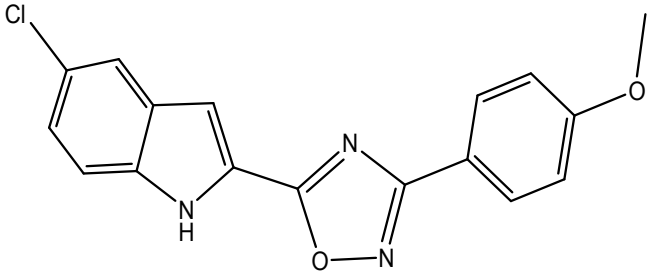
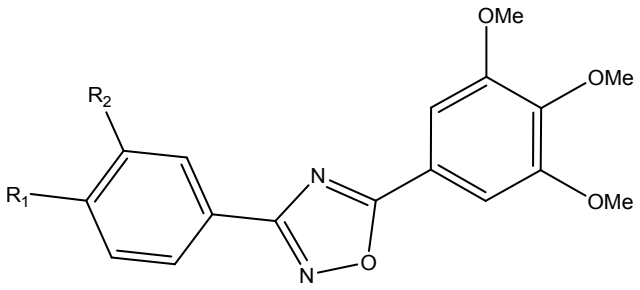


Figure I.7: Structure of EthylN-[(1S)-5-amino-1-[5-[[4-(2-phenylethoxy)phenyl]methyl]-1,2,4-oxadiazole-3-carbonyl]pentyl]carbamate

5.2. Anti-tubulin and Anti-mitotic Activity

Bhaskar. C. D. et al. [30] have designed and synthesized a small library of 3,5-disubstituted-1,2,4-oxadiazole containing combretastatin A-4 (CA-4) analogs (Figure I.8) to increase the efficacy of the CA-4 as an anti-tubulin and anti-mitotic agent by substituting the cis-alkene bond with one of its bio-isosteres, the 1,2,4-oxadiazole ring.



R1: OMe, R2:OH
R1: H, R2:OMe
R1: H, R2:Br

Figure I.8: Structure of (CA-4) analogs

5.3. Anti-bacterial Activity

Piccionello. A. P. et al. [31] developed two series of 1,2,4-oxadiazoles, among the series of molecules N-[[5-(4-morpholinophenyl)-1,2,4-oxadiazol-3-yl]methyl] acetamide (Figure I.9) is found to have considerable anti-bacterial activity.

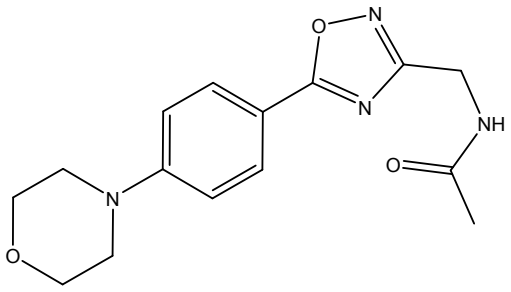


Figure I.9: Structure of N-[[5-(4-morpholinophenyl)-1,2,4-oxadiazol-3-yl]methyl] acetamide

5.4. Anti-fungal Activity

Sangshetti. J. N. et al. [32] discovered 5-[1-(1-methylsulfonyl-4-piperidyl) triazol-4-yl]-3-phenyl-1,2,4-oxadiazole (Figure I.10) as equipotent with Miconazole against Cryptococcus neoformans .

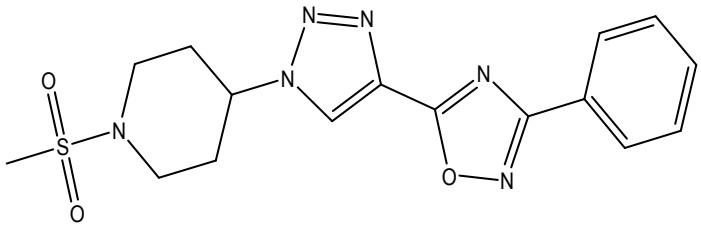


Figure I.10 : Structure of 5-[1-(1-methylsulfonyl-4-piperidyl) triazol-4-yl]-3-phenyl-1,2,4-oxadiazole

5.5. Human Histone Deacetylase Inhibitors

Ester. M. et al. [33] developed 2-trifluoroacetylthiophene oxadiazole derivatives, in which 2,2,2-trifluoro-1-[5-[3-[[4-(1,3,4-oxadiazol-2-yl)phenoxy]methyl]-1,2,4-oxadiazol-5-yl]-2 thienyl] ethanone (Figure I.11) exhibited potent and selective class II human histone deacetylase inhibition activity.

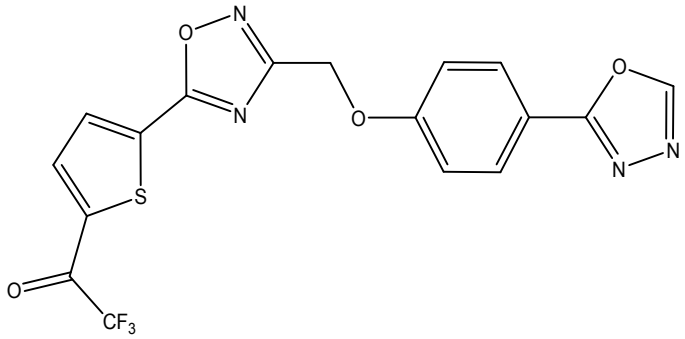
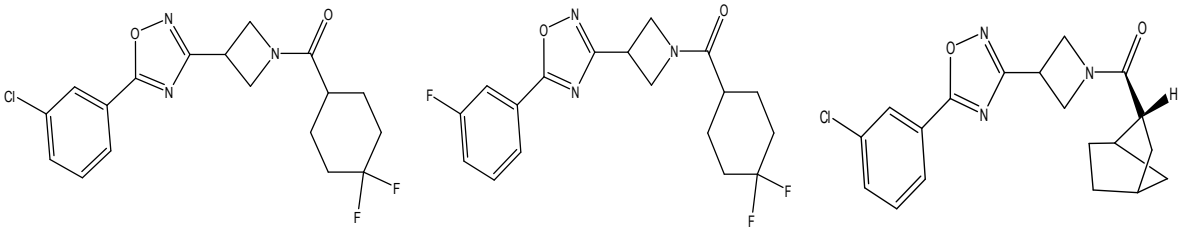


Figure I.11: Structure of 2,2,2-trifluoro-1-[5-[3-[[4-(1,3,4-oxadiazol-2-yl)phenoxy]methyl]-1,2,4-oxadiazol-5-yl]-2 thienyl] ethanone

5.6. Allosteric Modulators

Packiarajan. M. et al. [34] designed and synthesized a series of novel 1,2,4-oxadiazole derivatives, in which [3-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]azetidin-1-yl]-(4,4-difluoro-cyclohexyl) methanone (a), (4,4-difluorocyclohexyl)-[3-[3-(3-fluorophenyl)-1,2,4-oxadiazol-5-yl]azetidin-1-yl]methanone (b), [3-[3-(3-chlorophenyl)-1,2,4-oxadiazol-5-yl]azetidin-1-yl]-norbornan-2-yl-methanone (c) (Figure I.12) had shown considerable activity as a potent mGluR5 positive allosteric modulators.



(a) (b) (c)

Figure I.12: structures of 1,2,4-oxadiazole derivatives (a), (b) and (c)

5.7. Anti- kinetoplastid Parasites

Cottrell. D. M. et al. [15] synthesized 5-thiocyanatomethyl- and 5-alkyl-3-aryl-1,2,4 oxadiazoles, evaluated for their activity against kinetoplastid parasites. 3-(4-Chlorophenyl)-5-(thiocyanatomethyl)-1,2,4-oxadiazole) (Figure I.13) displayed modest selectivity.

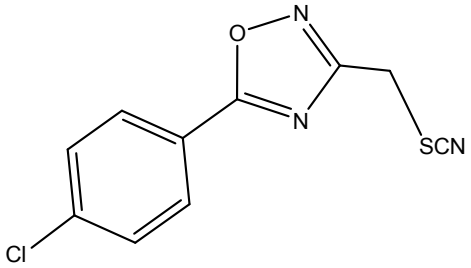


Figure I.13: Structure of 3-(4-Chlorophenyl)-5-(thiocyanatomethyl)-1,2,4-oxadiazole)

5.8. Anti-convulsant Activity

Hans-Joachim. L. et al. [35] developed a series of 3- and 5-aryl-1, 2, 4-oxadiazole derivatives and tested for anti-convulsant activity in a variety of models. 5-Phenyl-3-(1,2,4-triazol-1-ylmethyl)-1,2,4-oxadiazole (Figure I.14) was protective in the PTZ model in rats with an oral ED50 of 25.5 mg/kg and in the MES model in rats with an oral ED50of 14.6 mg/kg.

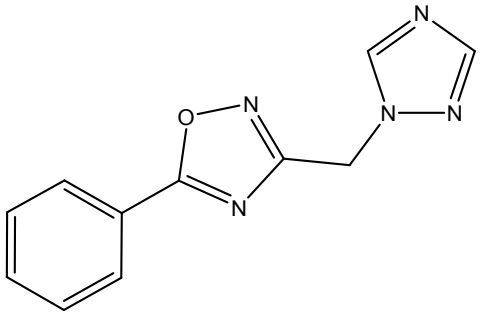


Figure I.14: Structure of 5-Phenyl-3-(1,2,4-triazol-1-ylmethyl)-1,2,4-oxadiazole

6. Synthesis of 1,2,4-oxadiazoles

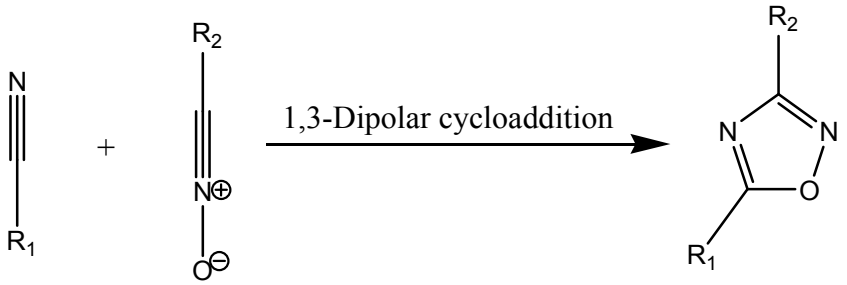
1,2,4-Oxadiazoles are generally prepared by

(i) 1,3-dipolar cycloadditon of nitrile oxides with nitriles and;

(ii) cyclocondensation of amidoximes with carbonyl-containing reactants; such as activated acids, acid chlorides and fluorides, acid anhydrides, esters and β-ketoesters [36].

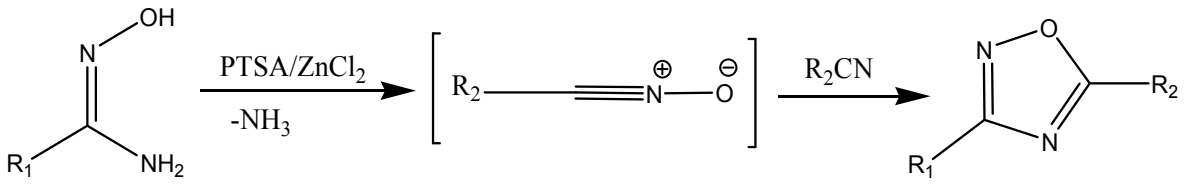
6.1. Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar Cycloaddition of Nitrile Oxides with Nitriles

It was previously mentioned that 1,3-dipolar cycloaddition reactions are one of the most common methods for the synthesis of heterocyclic compounds. 1,2,4-Oxadiazoles were also prepared by the cycloaddition between nitrile oxides and nitriles, and 3,5-disubstituted-1,2,4-oxadiazole derivatives were isolated from these reactions as illustrated in (Schema I.1) [37].



Schema I.1: Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides with nitriles.

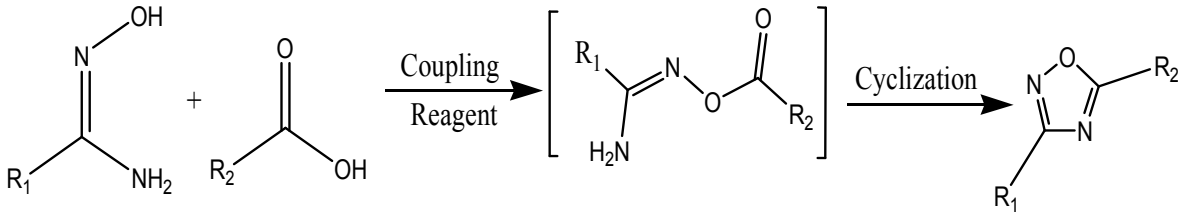
Augustine developed one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and nitriles in the presence of PTSA/ZnCl2catalyst system as depicted in (Schema I.2) [38]. Interestingly, amidoximes were used as a nitrile oxide precursor in this methodology.



Schema I.2: Synthesis of 1,2,4-oxadiazoles from amidoxime and nitriles.

6.2. Synthesis of 1,2,4-oxadiazoles by Cyclocondensation of Amidoximes with Carboxylic Acid Derivatives

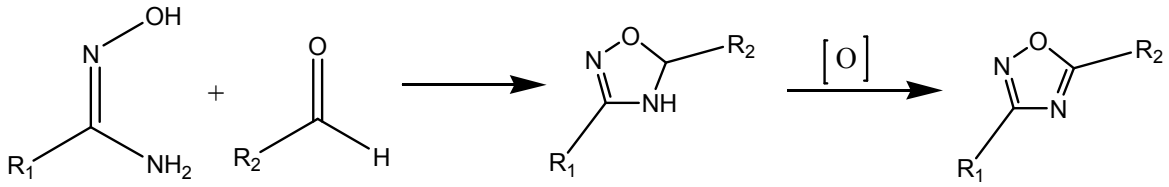
Cyclocondensation of amidoximes with carboxylic acids in the presence of a coupling reagent is most common method for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles (Schema I.3) [39]. The reaction consists of two steps; coupling and cyclization. Amidoximes are often either commercially available or easily prepared by the reaction of nitriles with hydroxylamine [40]. Activated carboxylic acid derivatives, such as acid chlorides and fluorides, esters and anhydrides, are also used for the formation of O-acylated amidoxime intermediates. N,N-Carbonyl-diimidazole (CDI) [41], acyl-palladium complex [42], N,N-dicyclohexyl-carbodiimide (DCC) [43], (N,N-dimethylamino) isopropyl chloride (DIC) [44], 1-[3 (dimethylamino)propyl]-3-ethylcarbodiimide (EDC) [45, 46] and 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) are commonly used as coupling (activating) agents for carboxylic acids [47].



Schema I.3: Synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acids.

6.3. Other Methods for the Synthesis of 1,2,4-oxadiazoles

Reactions of amidoximes with aldehydes gave 4,5-dihydro-1,2,4-oxadiazoles, instead of 1,2,4-oxadiazoles (Schema I.4) [42, 49]. Then, oxidation of dihydrooxadiazoles by using potassium permanganate, MnO2 or sodium hypochlorite furnished 1,2,4-oxadiazoles. Recently, Okimoto electrochemically oxidized dihydrooxadiazoles to 1,2,4-oxadiazoles in good yields [50].



Schema I.4: Synthesis of 1,2,4-oxadiazoles via oxidation of 4,5-dihydro-1,2,4-oxadiazoles.

7. N-substituted 1,2,4-oxadiazoles

1,2,4-Oxadiazoles [50-52] and specifically their N-substituted (on the 3-, or 5-, or 3,5-positions) derivatives is a class of heterocyclic compounds evaluated in numerous therapeutic areas. They were found to be potent anti-viral agents, [53] muscarinic receptor antagonists, [54, 55] histamine H2 receptor antagonists, [56, 57] hypocholsterolemic agents [58] and anti-inflammatories. [59, 60]

The variety of their biological activities was ascribed to the bio-isosteric replacement [61, 62] of an ester or amide functionality and the electronic effects of the main heterocyclic ring. The latter was interpreted in terms of the hydrogen bonding capacity of the pharmacophore.

A number of structure-activity relationship studies revealed that the attachment of an additional amine functional group to the heterocyclic core increased the efficacy of the compound, by increasing the hydrogen bonding capacity of the pharmacophore. [54, 55] Furthermore, changes in hydrophilicity by introduction of side chains on the nitrogen atom also affected the biological activity. [53-55, 59, 60]

7.1 Synthesis of N-substituted 1,2,4-oxadiazole

For the synthesis of N-substituted 1,2,4-oxadiazole derivatives Eloy and Lenaers [63, 64] have reported a two-step procedure:

Initially, formation of the 5-trichloromethyl- or 5-chloro-1,2,4-oxadiazole derivatives from a proper amidoxime and then, nucleophilic substitution of the trichloromethyl or chloro substituent by the desired amine.

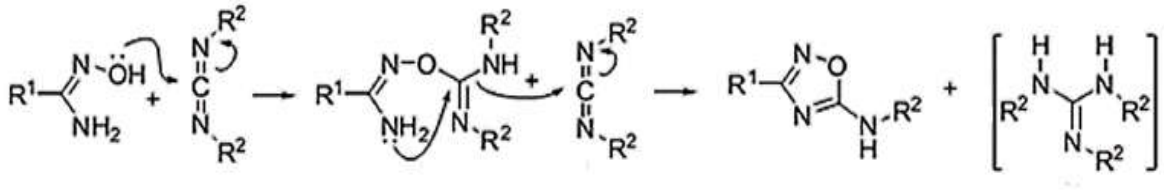
The same team discovered [63, 64] the formation of primary or secondary amine derivatives upon the reaction of hydroximoyl chlorides with guanidine derivatives. These are widely used methodologies for the synthesis of the above mentioned heterocycles in the area of medicinal chemistry, though, in most of the cases, the first step is usually low to moderate yielded.

A straightforward formation of 5-amino-substituted 1,2,4-oxadiazoles from amidoximes, relies on condensation with cyanoguanidine, [65] N,N-dialkylcyanamides, [66] diphenyl cyanocarbonimidate, [60] phosphorous ylides, [67] and N,N´-dicyclohexylcarbodiimide (DCC), [68] methodologies which suffer generality or provide the products in low yields. (Schema I.5)

Interestingly, to the best of our knowledge, the procedure involving the DCC was demonstrated only with the reaction with benzamidoxime, under dry conditions and the yield did not exceeded 54%, even when a bi-equimolar quantity of the carbodiimide was employed. [68]

Our interest in the chemistry and biology of amidoximes [67, 69-72] has prompted us to investigate thoroughly this reaction, taking into account that a relatively large number of carbodiimides, as well as amidoximes (or their precursors, nitriles) are nowadays commercially available. We envisaged that the construction in a single step of the 1,2,4-oxadiazole heterocyclic ring bearing an N-substituent at position 5 and a variety of alkyl

or aryl substituents at position 3, could be a useful synthetic tool in the area of medicinal chemistry.



Schema I.5: Synthesis of 5-amino-substituted 1,2,4-oxadiazoles

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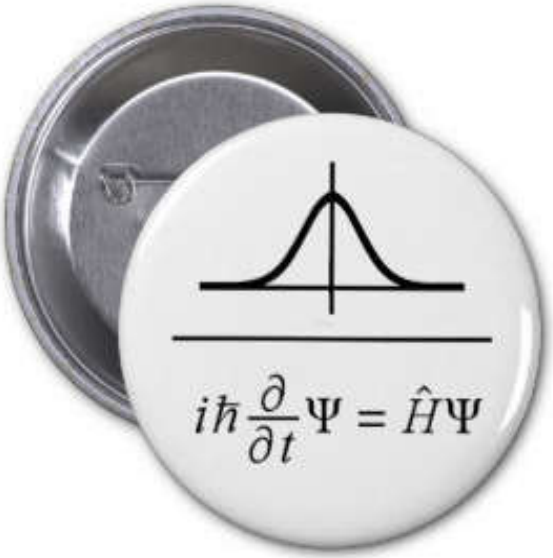
Molecular Modeling

CHAPTER 2



Summary

CHAPTER II: Molecular Modeling

1. Introduction

Computational chemistry may be defined as the application of mathematical and theoretical principles to the solution of chemical problems. Molecular modelling, a subset of computational chemistry, concentrates on predicting the behaviour of individual molecules within a chemical system. The most accurate molecular models use ab initio or ″first principles″ electronic structure methods, based upon the principles of quantum mechanics, and are generally very computer-intensive. However, due to advances in computer storage capacity and processor performance, molecular modelling has been a rapidly evolving and expanding field, to the point that it is now possible to solve relevant problems in an acceptable amount of time. [1]

Molecular modeling can be considered as a range of computerized techniques based on theoretical chemistry methods and experimental data that can be used either to analyze molecules and molecular systems or to predict molecular, chemical, and biochemical properties[2-4]. It serves as a bridge between theory and experiment to:

1. Extract results for a particular model.
2. Compare experimental results of the system.
3. Compare theoretical predictions for the model.
4. Help understanding and interpreting experimental observations.
5. Correlate between microscopic details at atomic and molecular level and macroscopic properties.
6. Provide information not available from real experiments.

All molecular calculation techniques can be classified under three general categories:

- Quantum Mechanical Methods,
- semi-empirical methods, and
- Molecular Mechanics

2. Quantum Mechanical Methods

2.1. Schrödinger Equation

The starting point of the following overview is the Schrödinger equation [5 - 8] in its time dependent and time independent forms (1) and (2) respectively

$$\frac{\partial \Psi}{\partial t} = -\frac{i}{\hbar}\hat{H}\Psi \qquad (1)$$

$$\hat{H}\,\Psi = E\Psi \qquad (2)$$

where the wave functions Ψ and Ψ are functions of all coordinates of the relevant system and Ψ is also a function of time. In our case of a molecular Hamiltonian $\hat{H}$ is given by:

$$\hat{H} = -\frac{\hbar^2}{2}\sum_I \frac{1}{m_I}\nabla_I^2 - \frac{\hbar^2}{2m_e}\nabla_i^2 + \sum_I \sum_{J<I} \frac{Z_I Z_J e^2}{r_{IJ}} - \sum_I \sum_i \frac{Z_I e^2}{r_{iI}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \qquad (3)$$

where I and J refer to the nuclei i and j refer to electrons. The first term in (3) is the operator of the kinetic energy of the nuclei. The second term is the operator of the kinetic energy of the electrons. The third term is the potential energy of repulsions between the nuclei, r_{IJ} is the distance between the nuclei I and J with atomic numbers Z_I and Z_J . The fourth term is the potential energy of the attractions between the electrons and the nuclei and r_{iI} is the distance between electron i and nucleus I. The last term is the potential energy of the repulsions between the electrons, r_{ij} is the distance between electrons i and j .

2.2. The Born-Oppenheimer Approximations: simplifies the general molecular problem by separating nuclear and electronic motions. This approximation is reasonable since the mass of a typical nucleus is thousands of times greater than that of an electron. The nuclei move really slowly with respect to the electrons. Thus, the electronic motion can be described as occurring in a field of fixed nuclei.

We can use the Born-Oppenheimer approximation to construct an electronic Hamiltonian, which neglects the kinetic energy term of the nuclei,

$$\hat{H} = -\frac{\hbar^2}{2m_e}\nabla_i^2 + \sum_I \sum_{J<I} \frac{Z_I Z_J e^2}{r_{IJ}} - \sum_I \sum_i \frac{Z_I e^2}{r_{iI}} + \sum_j \sum_{i>j} \frac{e^2}{r_{ij}} \qquad (4)$$

This Hamiltonian is used in the Schrödinger equation describing the motion of the electrons in the field of the fixed nuclei:

$$\hat{H}^{elec}\,\Psi^{elec} = E^{eff}\,\Psi^{elec} \qquad (5)$$

Solving this equation for the electronic wave function will produce the effective-nuclear potential function E^{eff} that depends on the nuclear coordinates and describes the potential energy surface of the system. For bond electronic problem, Ψ should satisfy two requirements: antisymmetricity and normalization. Ψ should change sign when two electrons of the molecule interchange and the integral of Ψ over all space should be equal to the number of electrons of the molecule.

3. Hartree-Fock Self-Consistent Field Method

Much of the difficulty of solving the Schrödinger equation stems from the need to simultaneously determine the energy of each electron in the presence all other electrons. In the Hartree-Fock (HF) method this is avoided by calculating the energy of each electron in the averaged staticfield of the others. Initially a guess is made of the electron energies.

The energy of each electron is then calculated in the field of the initial electron configuration. This procedure is repeated in an iterative loop until convergence (Self-Consistent referring to this iterative calculation).

The Hartree-Fock method can therefore be thought of as a kind of mean-spherical approximation at the electron level. The difference between the Hartree-Fock energy and the energy for the full Schrödinger equation is called the correlation energy. Hartree-Fock calculations are sufficiently accurate to provide insight into many problems and they are widely used. As Hartree-Fock calculations have been applied to different problems it has however become increasingly clear that the correlation energy is of great significance indetermining the properties of a system. Efforts have therefore been made to improve on the Hartee-Fock energy.

3.1. Post-HF Methods

There a number of different methods that go beyond Hartree-Fock calculations, one of the widely used approaches is perturbation theory. In perturbation theory the Hartree-Fock solution is treated as the first term in a Taylor series. The perturbation terms added involve the electron repulsion. One of the more common forms was developed by Møller and Plesset. The second order perturbation form is referred to as MP2. This form will be utilized in the present work.

It should be noted that the electron-electron repulsion energy is not necessarily a small perturbation. In cases in which this term is large the application of perturbation theory can become more difficult.

There are a number of other techniques to include electron correlation that can potentially provide very accurate results, such calculations can however become very time consuming and at present they tend to be used for small molecules with maybe 3-4 heavy (non-hydrogen)atoms. The molecules studied in the present work are somewhat larger and the decision has been made not to use such time-consuming methods.

3.2. Moller-Plesset perturbation theory (MPn)

The Moller-Plesset (MPn) Perturbation Theory attempts to correct the HF theory, which as mentioned earlier provides an approximation for the repulsion term between electrons and determines the position of an electron solely with respect to the atom's nu-cleus and the average of other electrons. As this model is not quite accurate, the MP theory uses HF as a starting point and then corrects it for the attraction term between the nu-cleus and the electron as well as the position of an electron with respect to another electron.

The number following MP, such as MP2 or MP3, indicates the number of perturbations, or approximation terms, used in the theory. Generally, the higher this number, the greater the accuracy of the method.

3.3. Density-Functional Theory (DFT)

DFT theory models electron correlation as a functional of the electron density, ρ. The functional employed by current DFT methods partitions the electronic energy via the Kohn-Sham equations [9, 10] into several terms :

$$\boldsymbol{E = E^T + E^V + E^J + E^{XC}} \qquad (6)$$

where E^T is the kinetic energy term (arising from the motion of the electrons), E^V is the potential energy term that includes nuclear-electron and nuclear-nuclear interactions, E^J is the electron-electron repulsion term and E^{XC} is the electron correlation term. All terms except nuclear-nuclear repulsions are functions of the electron density. The terms $E^T + E^V + E^J$ represent the classical energy of the electron distribution, while E^{XC} represents both the quantum mechanical exchange energy, which accounts for electron spin, and the dynamic correlation energy due to the concerted motion of individual electrons.

Pure DFT methods calculate E^{XC} by pairing an exchange functional with a correlation functional and so are designated by the choice of combination. For example, BLYP combines Becke's gradient-corrected exchange functional with the gradient-corrected correlation functional of Lee, Yang and Parr [11].

DFT calculations fall into three general categories: local density approximations (LDA), generalised gradient approximations (GGA), and ″hybrid″ combinations of DFT and Hartree-Fock terms. LDA exchange and correlation functionals only contain terms related to electron density- an approach that works for some bulk materials, but fails to accurately predict properties in isolated molecules. GGA (″nonlocal″) functionals contain terms that depend upon both the electron density and the density gradients.

The gradient-corrected density functional method BLYP is capable of predicting intramolecular bond dissociation energies to within a few kJ/mol [12]. However, the generalised gradient approximation severely underestimates activation barriers for some

reactions due to neglect of Coulomb ″self-interaction″ of the electrons [13]. This problem is remedied with hybrid methods that combine Hartree-Fock self-interaction corrections with density functional exchange and correlation. Examples of hybrid methods are B3LYP and B3PW91, where B3 denotes Becke's three-parameter hybrid functional [14,15], while 'PW91' and 'LYP' are gradient-corrected correlation functionals of Perdew and Wang [16] and, as above, Lee, Yang and Parr.

4. Semi-Empirical Method

Most molecular computations done by organic chemists, especially those examining minimum energy geometries, are done using this method because it provides the best compromise between speed and accuracy. This method can be thought of as a hybrid of molecular mechanics-type models based on experimentally measured empirical data and pure theory quantum chemical, thus the name semi-empirical. It uses the Schrödinger equation approximations, but in order to make the calculations less time-consuming, it only calculates the locations of valence electrons, not all electrons. For the inner shell electrons, empirical data from typical organic molecules is used to estimate their locations.
The semiempirical methods are presented by :

- **MNDO method (Modified Neglect of Diatomic Overlap)** [17] which takes in account the repellencies between the electrons pairs and the electron-electron perellence directions;

- **ZDO method(zero differential overlap)** is based on the Huckel method for the π electrons

- **CNDO method (Complete Neglect of Differential Overlap)** which takes in account only the atomic orbital of spherical symmetry and assesses the repellence integrals as the orbital would be sphere. In this case are two methods CNDO/1 and CNDO/2 which are used for the spectrum parameters;

- **INDO method** [18] (Intermediate Neglect of Differential Overlap) which includes the monoelectronic repellence integrals between atomic orbital of the same atom;

❖ **NDDO method (Neglect of Differential diatomic orvelap)** which takes in account the orientation direction of the orbital; MINDO/3 [19] method is an particular case of the NNDO method which assesses the monoelectronic repellence integrals;

❖ **SAM1 (Semi-Ab-Initio Model 1)**

The final 1993 offering in Michael Dewar's name was Semi-Ab-Initio Model 1 [20].

In SAM1, two-electron integrals are calculated using a standard STO-3G basis set (and hence the appearance ofab initioin the title). The resulting integrals were then scaled, and the Gaussian terms in the core–core repulsions were retained in order to fine-tune the calculations.

❖ **AM1 (Austin Model 1)**

Next came Austin model 1 (AM1), due toM. J. S. Dewaret al. [21]. AM1 was designed to eliminate the problems from MNDO caused by a tendency to overestimate repulsions between atoms separated by the sum of their van der Waals radii. The strategy adopted was tomodify the core–core terms bymultiplication of the Coulomb term with sums of Gaussian functions. In the original AM1 paper there are four terms in the Gaussian expansion. Each Gaussian is characterized by its position along the A–B vector and by its width. This significantly increased the number of parameters for each atom.

The performances of the semiempirical method consist in the smaller cost of them and it their speed, but also in the fact they can determine some properties that can not be established experimentally.

❖ **PM3 (parameterized method 3)**

PM3 is the third parameterization of MNDO, and the PM3 model contains essentially all the same terms as AM1. The parameters for PM3 were derived by J. J. P. Stewart [22] in a more systematic way than for AM1, many of which were derived by 'chemical intuition'. As a consequence, some of the parameters are quite different from those of MNDO but the two models seem to predict physical properties to the same degree of accuracy.

5. Molecular Mechanics (MM)

Molecular mechanics describes molecules in terms of "bonded atoms", which have been distorted from some idealized geometry due to non-bonded van der Waals and Coulombic interactions. [23, 24]

Molecular mechanics calculates the energy of a molecule and then adjusts the energy through changes in bond lengths and angles to obtain the minimum energy structure.

Molecular mechanics models are useful in studying structures, conformational energies and other molecular properties, including vibrational frequencies, conformational entropies and dipole moments, etc. [25, 44].

5.1. Steric Energy

A molecule can possess different kinds of energy such as bond and thermal energy. Molecular mechanics calculates the steric energy of a molecule (the energy due to the geometry or conformation of a molecule). Energy is minimized in nature, and the conformation of a molecule that is favored is the lowest energy conformation. Knowledge of the conformation of a molecule is important because the structure of a molecule often has a great effect on its reactivity. The effect of structure on reactivity is important for large molecules like proteins. Studies of the conformation of proteins are difficult and therefore interesting, because their size makes many different conformations possible.

Molecular mechanics assumes the steric energy of a molecule to arise from a few, specific interactions within a molecule. These interactions include the stretching or compressing of bonds beyond their equilibrium lengths and angles, torsional effects of twisting about single bonds, the Van der Waals attractions or repulsions of atoms that come close together, and the electrostatic interactions between partial charges in a molecule due to polar bonds. To quantify the contribution of each, these interactions can be modeled by a potential function that gives the energy of the interaction as a function of distance, angle, or charge [23,29].

The total steric energy of a molecule can be written as a sum of the energies of the interaction:

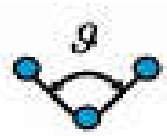
$$E_{steric\ energy} = E_{str} + E_{bend} + E_{tor} + E_{VdW} + E_{qq} \qquad (7)$$

The bond stretching, bending and torsion interactions are called bonded interactions because the atoms involved must be directly bonded or bonded to a common atom. The Van der Waals and electrostatic (qq) interactions are between non-bonded atoms.

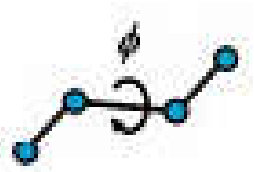
$$E_{steric\ energy} = E_{tot} = \sum_{bonds} k_r(r - r_{eq})^2 + \sum_{bonds} k_\vartheta(\vartheta - \vartheta_{eq})^2 + \sum_{bonds} \frac{V_n}{2}[1 + cos(n\Phi - \gamma)] + \sum_{i<j} \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \sum_{i<j} \frac{q_i q_j}{\varepsilon R_{ij}} \quad (8)$$

$$E_{str} = \sum_{bonds} k_r(r - r_{eq})^2 \quad (9)$$

$$E_{bend} = \sum_{bonds} k_\vartheta(\vartheta - \vartheta_{eq})^2 \quad (10)$$

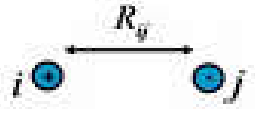


$$E_{tor} = \sum_{bonds} \frac{V_n}{2}[1 + cos(n\Phi - \gamma)] \quad (11)$$



$$E_{VdW} = \sum_{i<j} \frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} \quad (12)$$

$$E_{qq} = \sum_{i<j} \frac{q_i q_j}{\varepsilon R_{ij}} \quad (13)$$



5.2. Examples of MM Force Fields : In Common use are:

- ✓ **AMBER**

(Assisted Model Building with Energy Refinement) - primarily designed for the study of biomolecules such as proteins and nucleotides [45].

- ✓ **CHARMM**

(Chemistry at HARvard Molecular Mechanics) - primarily designed for biological and pharmaceutical study, but has also been applied to micelles and self-assembling macromolecules [46].

- ✓ **MMx** (MM2, MM3, etc)

Optimised for structural and thermodynamic studies of small non-polar molecules [47]. MMx force fields include third- and fourth-order corrections to standard quadratic fits for the potential energy surfaces of bonds and bond angles, thus allowing for non-harmonic effects in molecular vibrations. The various MMx versions differ primarily in their parameterisations. The higher versions tend to be more modern and address deficiencies in their predecessors. However, for the newer versions such as MM4, parameters may not be available for all classes of molecules.

- ✓ **OPLS**

(Optimised Potentials for Liquid Simulations)-optimised for reproducing the physical properties of biomolecules in liquid solutions [47].

The authors are not aware of any published study discussing the use of AMBER, CHARMM, MMx or OPLS with energetic materials. Since these packages are optimised for biochemistry and pharmaceutical applications, it is unlikely that they will accurately reproduce the behaviour of energetic materials without further modification. However, it is likely they can be used for limited applications with only slight modification.

- ✓ **CFF**

The consistent force field (CFF) [48-51] was developed to yield consistent accuracy of results for conformations, vibrational spectra, strain energy, and vibrational enthalpy of proteins. There are several variations on this, such as the Ure-Bradley version (UBCFF), a

valence version (CVFF), and Lynghy CFF. The quantum mechanically parameterized force field (QMFF) was parameterized From ab initio results. CFF93 is a rescaling of QMFF to reproduce experimental results. These force fields use five to six valence terms, one of which is an electrostatic term, and four to six cross terms.

- ✓ **DREIDING**[52]

DREIDING is an all-purpose organic or bio-organic molecule force field. It has been most widely used for large biomolecular systems. It uses five valence terms, one of which is an electrostatic term. The use of DREIDING has been dwindling with the introduction of improved methods.

- ✓ **MMFF**

The Merck molecular force field (MMFF) is one of the more recently published force fields in the literature. It is a general-purpose method, particularly popular for organic molecules. MMFF94[53] was originally intended for molecular dynamics simulations, but has also seen much use for geometry optimization. It uses five valence terms, one of which is an electrostatic term, and one cross term.

- ✓ **MOMEC**

MOMEC[54] is a force field for describing transition metal coordination compounds. It was originally parameterized to use four valence terms, but not an electrostatic term. The metal-ligand interactions consist of a bond-stretch term only. The coordination sphere is maintained by nonbond interactions between ligands. MOMEC generally works reasonably well for octahedrally coordinated compounds.

- ✓ **GROMOS**

(Groningen Molecular Simulation) developed at the University of Groningen and the ETH (Eidgenössische Technische Hochschule) of Zurich [55] is quite popular for predicting the dynamical motion of molecules and bulk liquids, also being used for modelling biomolecules. It uses five valence terms, one of which is electrostatic [56]. Its parameters are currently being updated [57].

5.3. Energy Minimization and Geometry Optimization

The basic task in the computational portion of MM is to minimize the strain energy of the molecule by altering the atomic positions to optimal geometry. This means minimizing the total nonlinear strain energy represented by the force field equation with respect to the independent variables, which are the Cartesian coordinates of the atoms [58]. The following issues are related to the energy minimization of a molecular structure:

- The most stable configuration of a molecule can be found by minimizing its free energy, G.
- Typically, the energy E is minimized by assuming the entropy effect can be neglected.
- At a minimum of the potential energy surface, the net force on each atom vanishes, there for the stable configuration.

Because the energy zero is arbitrary, the calculated energy is relative. It is meaningful only to compare energies calculated for different configurations of chemically identical systems.

- It is difficult to determine if a particular minimum is the global minimum, which is the lowest energy point where force is zero and second derivative matrix is positive definite. Local minimum results from the net zero forces and positive definite second derivative matrix, and saddle point results from the net zero forces and at least one negative eigenvalue of the second derivative matrix.

6. Research Methods of Global Minimum

The most widely used methods fall into two general categories:

(1) steepest descent and related methods such as conjugate gradient, which use first derivatives,and

(2) Newton Raphson procedures, which additionally use second derivatives.

6.1. Steepest Descent Method: [59] depends on:

1- either calculating or estimating the first derivative of the strain energy with respect to each coordinate of each atom and

2- moving the atoms.

The derivative is estimated for each coordinate of each atom by incrementally moving the atom and storing the resultant strain energy change. The atom is then returned to its original position, and the same calculation is repeated for the next atom. After all the atoms have been tested, their positions are all changed by a distance proportional to the derivative calculated in step 1. The entire cycle is then repeated. The calculation is terminated when the energy is reduced to an acceptable level. The main problem with the steepest descent method is that of determining the appropriate step size for atom movement during the derivative estimation steps and the atom movement steps. The sizes of these increments determine the efficiency of minimization and the quality of the result. An advantage of the first-derivative methods is the relative ease with which the force field can be changed.

6.2. Conjugate Gradient Method:

The conjugate Gradient Method is a first-order minimization technique. It uses both the current gradient and the previous search direction to drive the minimization. Because the conjugated gradient method uses the minimization history to calculate the search direction and contains a scaling factor for determining step size, the method converges faster and makes the step sizes optimal as compared to the steepest descent technique. However, the number of computing cycles required for a conjugated gradient calculation is approximately proportional to the number of atoms(N), and the time per cycle is proportional to N.

The Fletcher-Reeves approach chooses a descent direction to lower energy by considering the current gradient, its conjugate, and the gradient for the previous step. The Polak-Ribiere algorithm improves on the Fletcher-Reeves approach by additional consideration of the previous conjugate and tends to converge more quickly.

6.3. Newton-Raphson Method:

The Newton-Raphson Method of energy minimization [23] utilize the curvature of the strain energy surface to locate minima. The computations are considerably more complex than the first-derivative methods, but they utilize the available information more fully and therefore converge more quickly. These methods involve setting up a system of

simultaneous equations of size (3N-6)(3N-6) and solving for the atomic positions that are the solution of the system. Large matrices must be inverted as part of this approach.

The general strategy is to use steepest descents for the first 10-100 steps (500-1000 steps for proteins or nucleic acids) and then use conjugate gradients or Newton-Raphson to complete minimization for convergence(using RMS gradient or/and energy difference as an indicator). For most calculations, RMS gradient is set to 0.10 (you can use values greater than 0.10 for quick, approximate calculations).

The calculated minimum represents the potential energy closest to the starting structure of a molecule. The energy minimization is often used to generate a structure at a stationary point for a subsequent single-point calculation or to remove excessive strain in a molecule, preparing it for a molecular dynamic simulation.

7. Types of Calculations

Computational chemistry (also called molecular modelling; the two terms mean about the same thing) is a set of techniques for investigating chemical problems on a computer. Questions commonly investigated computationally are:

7.1. Molecular Geometry:

The shapes of molecules – bond lengths, angles and dihedrals.

7.2. Geometry Optimization [60] is a standard computational chemistry calculation to find the lowest energy or most relaxed conformation for a molecule. The approach is the same for all levels of calculation, involving an iterative "jiggling" process like that described for molecular mechanics.

At each step, the molecular geometry is modified slightly and the energy of the molecule is compared with the last cycle. The computer moves the molecule a little, calculates the energy, moves it a little more, and keeps going until it finds the lowest energy. This is the energy minimum of the molecule and is obtained at the optimized geometry. Recall that the energies from molecular mechanics can only be used in a relative sense, while those from quantum electronic structure methods can be compared in an absolute sense, like heats of formation.

7.3. Single Point Calculations [60] are often used in combination with a geometry optimization to investigate steric hindrance. In this case the method only performs one computational cycle to calculate the energy of a particular fixed geometry. In a thermodynamically controlled reaction, the energetic difference between two conformations is often due to steric hindrance. If the product molecule optimizes in one conformation, you can use single point calculations to determine how much more energy is needed to form the non-preferred conformation.

The structure drawing and manipulation part of the software will allow you to move only that part of the molecule that changes in the higher energy form, leaving the rest of the molecule optimized.

The single point calculation performed on this modified molecule will give an energy that you can directly compare with the optimized energy to find the energy difference between the lower and higher energy conformers. For example, the energetic difference between having a constituent in the axial or equitorial position on a cyclohexane ring can be determined.

7.4. Transition State Calculations [60] can be thought of as the reverse of geometry optimizations. In this case, the method searches for a structure of maximum energy, a transient intermediate which cannot be isolated experimentally. For example, this type of calculation allows one to examine transition state energies and geometries of intermediates involved in carbocation rearrangements.

The literature contains standard models that should use as the starting point for these calculations. It takes a far amount of effort and experience to properly analyze transition state structures and energies.

7.5. Electronic Density and Spin Calculations, Graphical Models and Property Maps [60] Allow visualization of electronic properties such as electron densities, electrostatic potentials, spin densities and the shapes and signs of molecular orbitals. The values for a particular property at each point in the 3-dimensional space around a molecule are displayed on the 2-dimensional computer screen as a surface of constant numerical value, often called an isosurface which can be rotated in any direction

to study it. Alternately, numerical variations of a given property (such as electron density) at a defined distance from the molecule can be displayed as property maps using color as a key yielding what is called a property map. Carrying out surface calculations and viewing their graphical representations are major activities in computational chemistry and can provide useful insight into the mechanisms of organic reactions.

7.6. Chemical Reactivity: [61]

For example, knowing where the electrons are concentrated (nucleophilic sites) and where they want to go (electrophilic sites) enables us to predict where various kinds of reagents will attack a molecule.

7.7. IR, UV and NMR spectra: [61] these can be calculated, and if the molecule is unknown, someone trying to make it knows what to look for. allow the calculation of infrared stretching and bending absorption frequencies and it is a lot of fun to view animations of these types of motions in molecules. The vibrational frequency of a two-atom system is proportional to the square root of the force constant (the second derivative of the energy with respect to the interatomic distance) divided by the reduced mass of the system (which depends on the masses of the two atoms).

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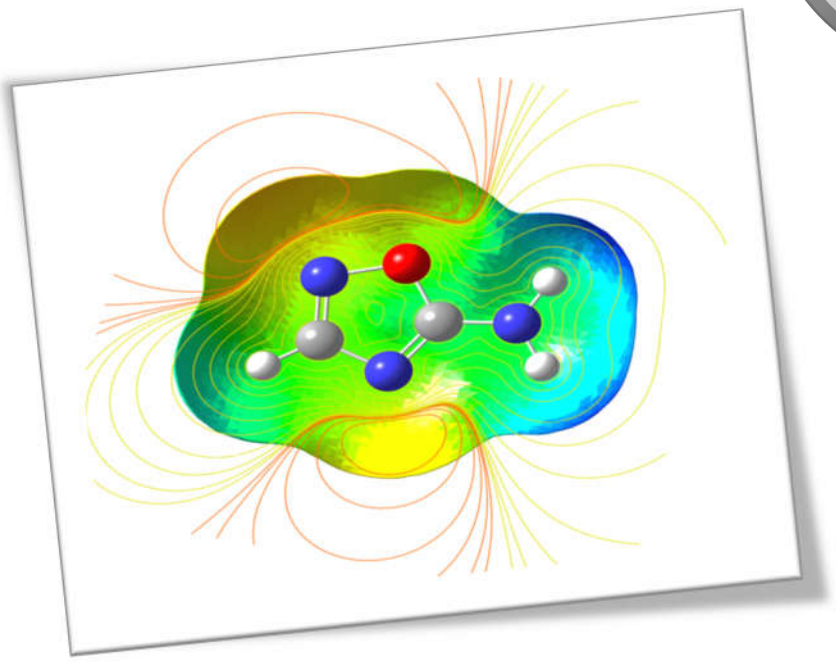
Geometric, Electronic Structure and Substituent effects of 1,2,4-oxadiazol-5-Amine

CHAPTER 3



Kerassa Aicha, Salah Belaidi and Touhami Lanez,

Quantum Matter, Vol. 5, 45–52, 2016 .

Summary

CHAPITER III : Geometric, Electronic Structure and Substituent effects of 1,2,4-oxadiazol-5-Amine

1. Introduction

Molecular modeling can be defined as the generation, manipulation, calculation, and prediction of realistic molecular structures and associated physicochemical as well as biochemical properties by the use of a computer. It is primarily a mean of communication between scientist and computer, the imperative interface between human-comprehensive symbolism, and the mathematical description of the molecule.[1]

The types of predictions possible for molecules and reactions include [2]:

- Heats of formation
- Bond and reaction energies
- Molecular energies and structures (thermochemical stability)
- Energies and structures of transition states (activation energies)
- Reaction pathways, kinetics and mechanisms
- Charge distribution in molecules (reactive sites)
- Substituent effects
- Electron affinities and Ionization potentials
- Vibrational frequencies (IR and Raman spectra)
- Electronic transitions (UV/Visible spectra)
- Magnetic shielding effects (NMR spectra)

Prediction of these properties has many applications in energetic materials research, including studies of synthesis pathways, reaction products and initiation mechanisms.

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties[3]. To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive ab initio/HF electron correlation methods are required [4-6]. Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules [7-16].

2. Mulliken population analysis (MPA)

This population analysis is the oldest and one of the most widely used. MPA divides bond orbital populations equally between the two atoms of a bond. This approach is very simplified and does not take into consideration that one of bonded atoms can attract electrons markedly more than the second one. On the other hand, the simplicity of MPA is sometimes an advantage because the method can be easily used.[17]

3. Electrostatic Potential Surface(MESP)

The molecular electrostatic potential is the potential energy of a proton at a particular location near a molecule.

- Negative electrostatic potential corresponds to an attraction of the proton by the concentrated electron density in the molecules (from lone pairs, pi-bonds, etc.) (colored in shades of red).

- Positive electrostatic potential corresponds to repulsion of the proton by the atomic nuclei in regions where low electron density exists and the nuclear charge is incompletely shielded(colored in shades of blue).

The more red / blue differences, the more polar the molecule. If the surface is largely white or lighter color shades, the molecule is mostly non-polar.

The MESP may be employed to distinguish regions on the surface which are electron rich (subject to electrophilic attack) from those which are electron poor (subject to nucleophilic attack) and has been found to be a very convenient tool in exploration of correlation between molecular structure and the physiochemical property relationship of molecules including bio molecules and drugs [18-23].

The electrostatic potential V(r) at any point in space around a molecule by charge distribution is given by:

$$\boldsymbol{V(r) = \sum \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')}{|r' - r|} dr'} \qquad \textbf{(1)}$$

Where the summation runs over all the nuclei A in the molecule and polarization and reorganization effects are neglected. Z_A is the charge of the nucleus A, located at R_A and ρ(r') is the electron density function of the molecule.

4. Dipole Moment

An electric dipole consists of a pair of charges of equal magnitude and opposite signs (+q and –q), separate by a distance (r). The dipole moment of an electric dipole is a vector directed from the negative to the positive charge. The magnitude of the dipole moment is measured in Coulomb meters (Cm) or in debye (D), where 1D = $3.338*10^{-30}$ Cm. [24]

If the positive and negative charges in a molecule do not overlap, the molecule possesses a permanent dipole moment (μ) (polar molecule). Molecular dipole moment is usually calculated using the following formula:

$$\boldsymbol{\mu} = \sum \boldsymbol{q_i} \times \boldsymbol{r_i} \qquad (\mathbf{2})$$

Where r is the radius-vector of an atom i from the origin of the coordinate system (Centre of charge or Centre of mass)

- q is the partial charge of atom i
- The summation is over all atoms in the molecule.

5. Heat of Formation (ΔH_f)

The heat of Formation is known as the change in enthalpy accompanying the formation of one mole of a compound from its elements in their natural and stable states, under standard conditions of one atmosphere at a given temperature [25].

The quantum chemical and energy descriptors are useful parameters for describing QSAR of a chemical system. A more useful quantity the heat of formation of the compound from its elements in their standard state.

This is equal to the energy required to ionize the valence electrons of the atoms involved. The heat of formation is defined as:

$$\Delta H_f = E_{elec} + E_{nuc} - E_{iso} + E_{atom} \qquad (3)$$

Where E_{elec} is the electronic energy, E_{nuc} is the nuclear-nuclear repulsion energy, E_{iso} is the energy required to strip all the valence electrons of all the atoms in the system and E_{atom} is the total heat of atomization of all the atoms in the system.

6. Energies of the Frontier Molecular Orbitals HOMO and LUMO

The energies of the frontier orbitals HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) are commonly used descriptors in QSAR analysis. They reflect the reactivity of a molecule. A higher HOMO energy suggests higher affinity of a molecule to react as a nucleophile, a lower LUMO energy suggests stronger electrophilic nature of a molecule.

Additionally, electrophilic and nucleophilic attack will most likely occur at atoms where the coefficients of the corresponding atomic orbitals in HOMO and LUMO, respectively, are large. [24]

7. Substituent Effects on the Electronic Structure

The measure of some important electronic properties such as ionization energy, electron affinity, etc., through the introduction of electron donating (ED) or electron withdrawing (EW) substitutions follows a long established method in bio-chemical and molecular electronics engineering. [26-30]

ED substituents (donor Substituents) can increase the energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) relative to that of bare molecule (M), allowing a significant modification of the molecular electronic properties.(FigureIII.1)

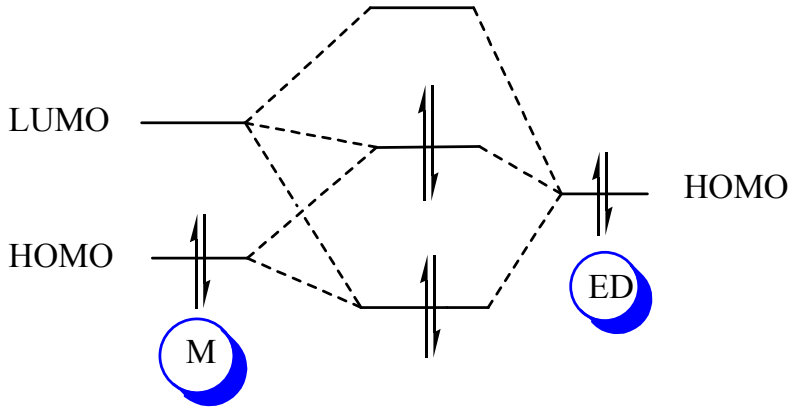


Figure III.1: Influence of energy level of the donor group (ED)

EW substituents (Acceptor Substituents) can decrease the energies of lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) relative to that of bare molecule (M), allowing a significant modification of the molecular electronic properties. (Figure III.2)

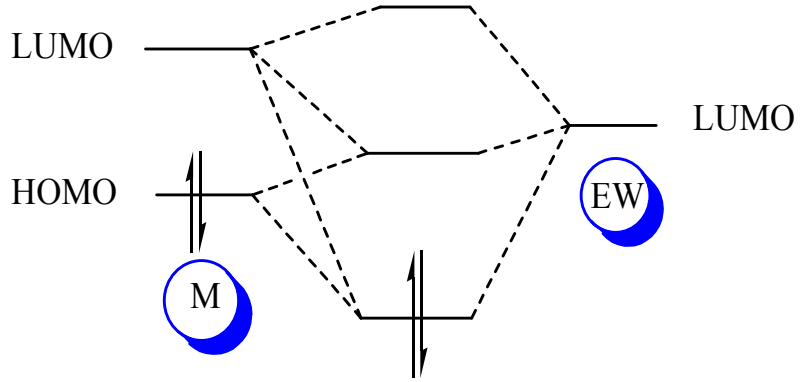


Figure III.2: Influence of energy level of the acceptor group (EW)

8. Material and Methods

Initial calculations were optimized using HyperChem 8.03 software [31]. The geometries of 1,2,4-oxadiazol-5-amine and its derivatives; were first fully optimized by molecular mechanics, with MM+ force-field (rms = 0.001 Kcal/Å). Further, geometries were fully re-optimized by using RM1 method.

In the next step, a parallel study has been made using Gaussian 09 program package[32], at various computational levels, HF/6-31++G(d, p) ,MP_2/6-31++G(d, p) and B3LYP/6-31++G(d, p).

9. Results and Discussion

9.1. Geometric Structure of 1,2,4-oxadiazol-5-amine

The optimized geometrical parameters of 1,2,4-oxadiazol-5-amine by ab initio/HF, ab initio/MP2 and DFT method listed in (Table III.1) are in accordance with numbering scheme given in (Figure III.3).

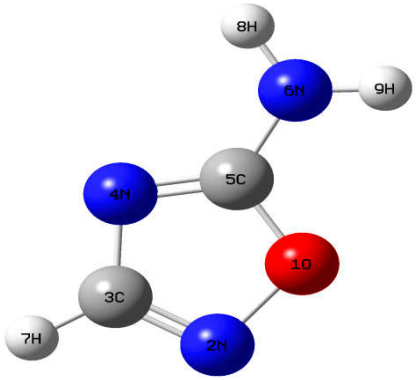


Figure III.3: 3D conformation of 1,2,4-oxadiazol-5-amine (GaussView 05)

Table III.1: Calculated values of bond lengths, valence angles and dihedral angle of 1,2,4-oxadiazol-5-amine

	Parameters	Ab initio/HF 6-31++G(d, p)	Ab initio/MP2 6-31++G(d, p)	DFT/B3LYP 6-31++G(d, p)
Bond length (Angstrom)	O1-N2	1.399	1.421	1.435
	N2-C3	1.278	1.317	1.306
	C3-N4	1.360	1.376	1.370
	N4-C5	1.293	1.312	1.313
	C5-N6	1.335	1.352	1.348
Valence angle	N2-O1-C5	106.511	105.836	105.805
	O1-N2-C3	102.430	102.440	102.050

(degree)	N2-C3-N4	116.060	116.382	116.745
	C3-N4-C5	100.906	100.957	101.138
	O1-C5-N4	114.092	114.384	114.261
	O1-C5-N6	118.268	117.200	117.991
	N4-C5-N6	127.639	128.416	127.748
	O1-N2-C3-N4	0	0	0
	C3-N2-O1-C5	0	0	0
	N2-O1-C5-N4	0	0	0
dihedral	N2-O1-C5-N6	180.000	180.000	180.000
angle(degree)	N2-C3-N4-C5	0	0	0
	C3-N4-C5-O1	0	0	0
	C3-N4-C5-O1	0	0	0
	C3-N4-C5-N6	180.000	180.000	180.000

The efficiency of DFT/B3LYP method may be scrutinized by comparison with the results obtained by more elaborate calculation such as ab initio/HF and initio/MP2.
We can note a good correlation between the ab initio and DFT for bond lengths. The dihedral angles of cycle of this molecule are 0° or 180°, therefore, the geometry of the 1,2,4-oxadiazol-5-amine is planar.

9.2. Mulliken Population Analysis of 1,2,4-Oxadiazol-5 Amine

Mulliken population analysis is a good way to account for differences in electro-negativities of atoms within the molecule and frequently uses for supporting the MEP contour map. MEP and Mulliken population method can be used for interpreting and predicting the reactive behavior of a wide variety of chemical systems in both electrophilic and nucleophilic reactions.

Charge densities calculated by the ab initio/HF are similar than ab initio/MP2 and slightly different with regard to DFT method (Table III. 2).

According to Mulliken population in the Table III. 2, we can see that the atoms O1, N2, N4 and N6 have negative charges which leads to electrophilic substitution, whereas the atom C3 and C5 have positive charge which lead to preferential site to nucleophilic attack.

Table III.2: Mulliken charges of 1,2,4-oxadiazol-5 amine

Atoms	Ab initio/HF 6-31++G(d, p)	Ab initio/mp2 6-31++G(d, p)	DFT/B3LYP 6-31++G(d, p)
O1	-0.263	-0.275	-0.158
N2	-0.296	-0.288	-0.288
C3	0.168	0.172	0.119
N4	-0.531	-0.510	-0.421
C5	0.686	0.659	0.403
N6	-0.676	-0.676	-0.525

9.3. MESP of 1,2,4-oxadiazol-5 amine

MESP is an important factor by which we can confirm the electrostatic potential region distribution of size and shape of molecules as well as the total physiology of the molecules [33].

A portion of the molecule that has a negative electrostatic potential is susceptible to electrophilic attack. The red and blue regions in the MESP map refer to the regions of negative and positive potentials and correspond to the electron rich and electron-deficient regions respectively whereas the green color signifies the neutral electrostatic potential [34].

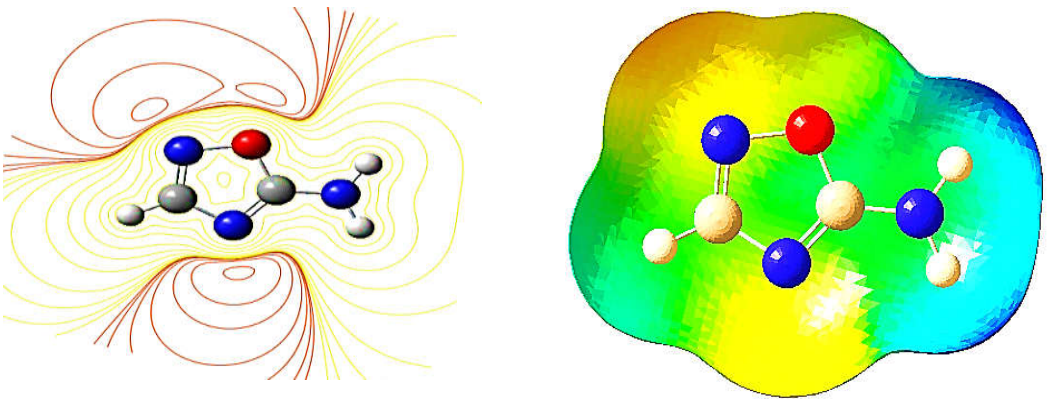


Figure III.4: 2D MESP and 3D MESP contour map for 1,2,4-oxadiazole-5-amine molecule.

The MESP map of 1,2,4-oxadiazole-5-amine (Figure III.4) suggests that there are three electron rich regions (yellow) around oxygen atom and at nitrogen N(2) and N(4) atoms of the heterocyclic ring. The oxygen atom and nitrogen atoms reflect the most electronegative region and have excess negative charge.

The hydrogen atom attached to nitrogen bear the maximum brunt of positive charge (dark blue) as compared to the rest of the H atoms of the molecule.

9.4. Substitution Effect on 1,2,4-oxadiazol-5 amine

The calculated values of (methyl, ethyl) substituted 1,2,4-oxadiazol-5-amine and (cyanide, fluorine) substituted 1,2,4-oxadiazol-5-amine (Figure III.5) are given in (Table III.3), (Table III.4), (Table III.5).

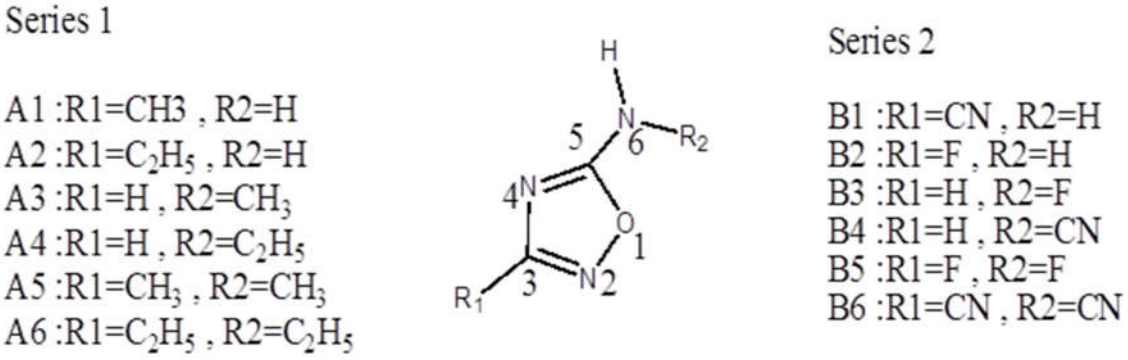


Figure III.5: Scheme of 1,2,4-oxadiazol-5-amine systems

In Table III.3, heat of formation, dipole moment, HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital) and their difference (ΔE) are reported for 1,2,4-oxadiazol-5-amine and its derivatives. In (Table III.4), (Table III.5),net atomic charges are also reported.

The final heat of formation of studied compounds is varying from-85.779 Kcal/mol to224.306Kcal/mol. The compound B6 has the lowest heat of formation and needs small change in enthalpy to form one mole of this compound, while the compound A6 has the highest heat of formation and needs large change in enthalpy to form one mole of this compound.

The values of dipole moment are varying from 1.9405 Debye to 6.7711 Debye. It is stated that if the total dipole moment of certain structure increases, then its molecular

reactivity increases as well, and accordingly the given structure becomes more interacting with other systems strongly in solution [35].

Table III.3: Energies of 1,2,4-oxadiazol-5-amine derivatives

Comp	System	H_f (kcal/mol)	$-E_{HOMO}$ (eV)	$-E_{LUMO}$ (eV)	ΔE (eV)	μ (D)
A	**1,2,4-oxadiazol-5-amine**	36.542	7.029	0.679	6.349	3.2906
A1	**3-methyl-1,2,4-oxadiazol-5-amine**	62.878	6.841	0.603	6.238	2.8683
A2	**3-ethyl-1,2,4-oxadiazol-5-amine**	124.352	6.927	0.613	6.314	2.6675
A3	***N*-methyl-1,2,4-oxadiazol-5-amine**	78.363	6.679	0.581	6.097	3.7056
A4	***N*-ethyl-1,2,4-oxadiazol-5-amine**	136.697	6.664	0.559	6.105	3.7542
A5	***N*,3-dimethyl-1,2,4-oxadiazol-5-amine**	104.744	6.518	0.517	6.001	3.2257
A6	***N*,3-diethyl-1,2,4-oxadiazol-5-amine**	224.306	6.501	0.497	6.004	3.3709
B1	**5-amino-1,2,4-oxadiazole-3-carbonitrile**	88.170	7.713	2.024	5.689	6.7711
B2	**3-fluoro-1,2,4-oxadiazol-5-amine**	-57.049	7.339	0.855	6.484	4.8796
B3	**1,2,4-oxadiazol-5-ylcyanamide**	99.984	7.902	1.493	6.408	4.0530
B4	***N*-fluoro-1,2,4-oxadiazol-5-amine**	6.466	7.310	0.925	6.385	1.9405
B5	**(3-cyano-1,2,4-oxadiazol-5-yl) cyanamide**	153.190	8.456	2.757	5.699	3.4844
B6	***N*,3-difluoro-1,2,4-oxadiazol-5-amine**	-85.779	7.612	1.292	6.319	3.7568

Heat of formation (H_f)by RM1, ΔE and μ by DFT

As has been seen by calculating the effect of a substituent donor increase the energy of the HOMO and that of the LUMO, while we see by calculating the effect of a substituent acceptor decrease the energy of the HOMO and that of the LUMO , Results in a stabilization of the HOMO and LUMO.

9.4.1. Effect of Donor Substituents

The heat of formation is increased at each addition of methyl and ethyl groups.

In the substituted alkyl group category the negative atomic charge on nitrogen atoms is increased considerably for methyl and ethyl derivatives, except atom N_6 is decreased considerably also oxygen O atom.

In the mono-substituted alkyl group category, the N-methyl-1,2,4-oxadiazol-5-amine (compound A3) has smaller ΔE energy gap (6.097) (Table III.3) depicts the chemical reactivity of the compound; higher is the ΔE energy gap, lesser is the transfer of electrons to the higher energy state, making the molecule hard and less reactive.

His maximum positive charge on 5rd position carbon (0.265) which leads to nucleophilic substitution (Table III.4). On the other hand in smaller ΔE gap, there is easy transfer of electrons to the higher energy state making it softer and more reactive (HSAB principle: hard and soft acids and bases).

Hard bases have highest-occupied molecular orbitals (HOMO) of low energy, and hard acids have lowest-unoccupied molecular orbitals (LUMO) of high energy [36].
According to HSAB principle: compound A6 has the highest energy of HOMO therefore, this compound is soft base. And compound B5 has the lowest energy of LUMO therefore, this compound is soft acid compared to other compounds.

Table III.4: Mulliken charges of 1,2,4-oxadiazol-5-amine and derivatives (series 1)

Compound	A	A1	A2	A3	A4	A5	A6
O1	-0.158	-0.114	-0.102	-0.154	-0.127	-0.097	-0.046
N2	-0.288	-0.390	-0.371	-0.313	-0.312	-0.441	-0.463
C3	0.119	0.619	0.384	0.204	0.217	0.762	0.613
N4	-0.421	-0.437	-0.411	-0.368	-0.349	-0.400	-0.365
C5	0.403	0.313	0.288	0.265	0.193	0.100	-0.073
N6	-0.525	-0.525	-0.482	-0.389	-0.361	-0.377	-0.347
C-methyl 3	-----	-0.698	-----	-----	-----	-0.662	-----
C-methyl N_6	-----	-----	-----	-0.308	-----	-0.304	-----
C-1'ethyl 3	-----	-----	-0.308	-----	-----	-----	-0.201

C-2'ethyl 3	-----	-----	-0.504	-----	-----	-----	-0.504
C-1'ethyl N_6	-----	-----	-----	-----	-0.176	-----	-0.162
C-2'ethyl N_6	-----	-----	-----	-----	-0.439	-----	-0.458

In the case of dimethyl and diethyl substituted of 1,2,4-oxadiazol-5-amine the C-3 position (compound A5) shows maximum charge (0.762), smaller E_{HOMO}-E_{LUMO} energy gap (6.001) (TableIII.3), (Table III.4) which leads to preferential site of nucleophilic attack.

9.4.2. Effect of Acceptor Substituents

The heat of formation is increased at each addition of (fluorine substituted) while, cyanide-substituted is changing according to position of substitution.

In the substituted acceptor group category, the negative atomic charge on nitrogen and oxygen atoms is decreased considerably for cyanide and fluorine derivatives, except atom N2 is increased considerably except for compound (A3 and A4) (Table III.5).

In the present work, we study cyanide and fluorine substituted 1,2,4-oxadiazol-5-amine along the same line of methyl and ethyl substituted 1,2,4-oxadiazol-5-amine for a comparative study.

Table III.5: Mulliken charges of 1,2,4-oxadiazol-5-amine and derivatives (series 2)

Compound	A	B1	B2	B3	B4	B5	B6
O1	-0.158	-0.073	-0.165	-0.131	-0.138	-0.031	-0.144
N2	-0.288	-0.345	-0.319	-0.273	-0.268	-0.363	-0.301
C3	0.119	0.784	0.558	0.225	0.163	0.866	0.622
N4	-0.421	-0.402	-0.488	-0.325	-0.386	-0.325	-0.461
C5	0.403	0.554	0.556	0.226	0.449	0.283	0.592
N6	-0.525	-0.549	-0.535	-0.495	-0.235	-0.508	-0.245
C-cyano 3	-----	-0.116	-----	-----	-----	0.052	-----
N-cyano 3	-----	-0.562	-----	-----	-----	-0.549	-----
C-cyano N_6	-----	-----	-----	0.600	-----	0.570	-----
N-cyano N_6	-----	-----	-----	-0.399	-----	-0.385	-----
Fluro 3	-----	-----	-0.318	-----	-----	-----	-0.313
Fluro N_6	-----	-----	-----	-----	-0.131	-----	-0.124

In mono-substituted cyanide and fluorine derivatives,5-amino-1,2,4-oxadiazole-3carbonitrile (compound B1) shows maximum charge on 3th position carbon (0.78) which leads to nucleophilic substitution (Table III.5) This is further supported by the least ΔE energy gap (5.69) (Table III.3) which depicts the chemical reactivity of the compound; the higher is the ΔE energy gap, the lesser is the transfer of electrons to the higher energy state, making the molecular hard and less reactive.

In di-substituted cyanide and fluorine derivatives, (3-cyano-1,2,4-oxadiazol-5-yl) cyanamide (compound B5) shows maximum charge on 3th position carbon (0.87) which leads to nucleophilic substitution (Table III.5) is more reactive than *N*,3-difluoro-1,2,4-oxadiazol-5-amine (compound B6), this is due to smaller ΔE energy gap (5.69) (Table III.3).

The compound B1 is predicted to be the most reactive with least ΔE energy gap of all 1,2,4-oxadiazol-5-amine systems and is predicted to be the most soluble in the in polar solvents because it has maximum dipole moment value μ (6.77 D) (Table III.3).

We note also that the cyanide substituent (acceptor effect) lowers the energies of HOMO and LUMO. His influence on the energy of the LUMO is more important (Table III.5).

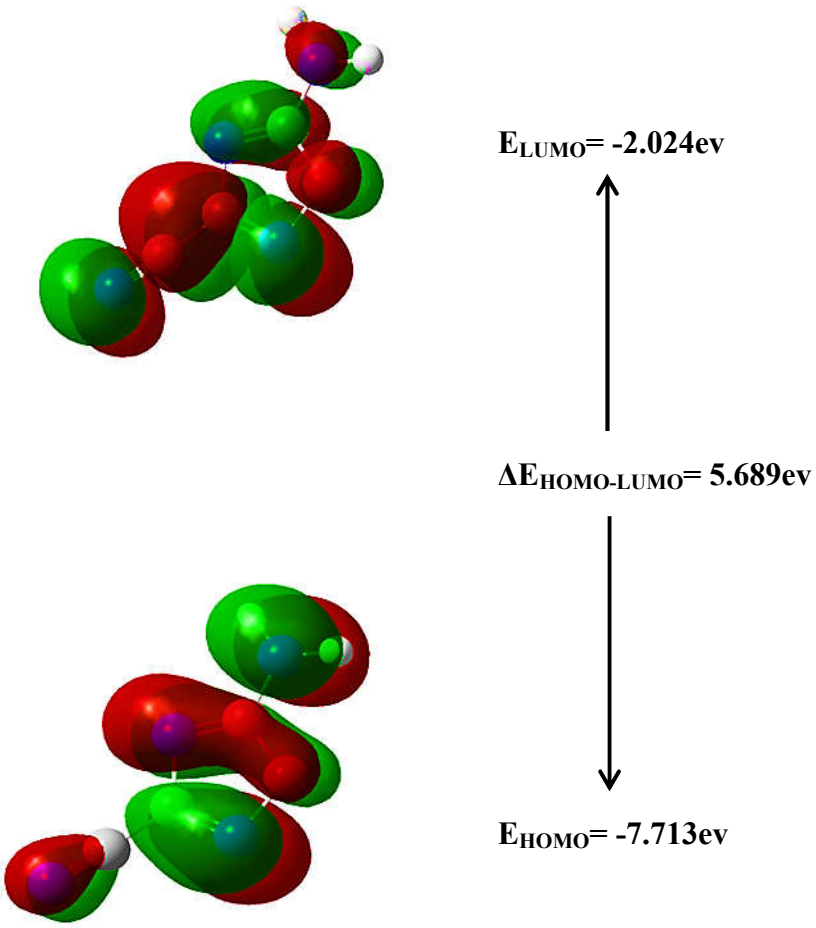


Figure III.6: Schematic drawings of the HOMO and LUMO of compound B1

The contour plots of the π-like frontier orbital's for the ground state of compound B1 are shown in (Figure III.6), The positive phase is red and the negative one is green. from the plots, one can find that the HOMO mainly concentrates on N2 and the oxadiazole ring with some delocalization along N2-C3 and N1-C5-N4, whereas, the LUMO distributes over the whole molecule with some delocalization along C3- C-cyano and N4-C5 These further demonstrate that there exists the delocalization of the conjugated π-electron system in the molecule of compound B1.

10. Conclusion

The present work studied the molecular proprieties of 1,2,4- oxadiazol-5-amine. The RM1, DFT and ab initio method can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron.

The donor substituents (methyl and ethyl) increases the energy of HOMO and slight augmentation of energy of LUMO, and for acceptor substituents (cyanide and fluorine) had caused decreasing in HOMO and LUMO energy levels.

The 5-amino-1,2,4-oxadiazole-3-carbonitrile (B1) is predicted to be the most reactive with least ΔE energy gap of all 1,2,4-oxadiazol-5-amine systems and this latter has the highest dipole moment thus, compound B1 more interacting with other systems strongly in solution

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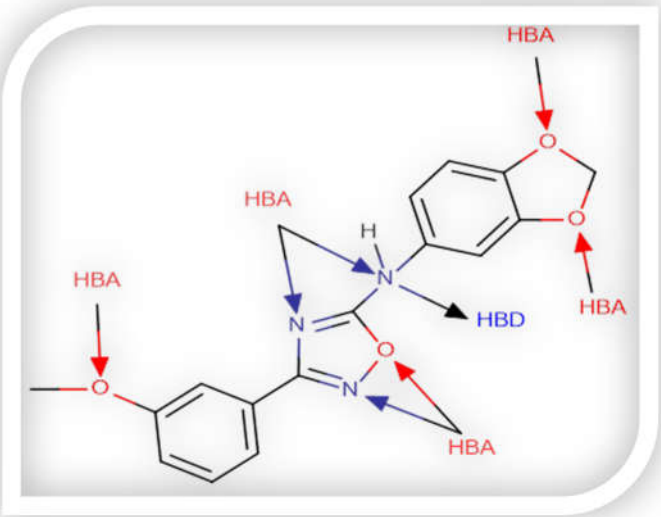
Computational Study of Structure -Property Relationships (SPR) for 1,2,4-oxadiazole-5-amine Derivatives

CHAPTER 4



Kerassa Aicha, Salah Belaidi and Touhami Lanez,

Quantum Matter, Vol. 5, 45–52, 2016 .

Summary

CHAPTER IV : Computational Study of Structure -Property Relationships (SPR) for 1,2,4-oxadiazole-5-amine Derivatives

1. Introduction

The process of drug development is time-consuming and cost-intensive. Several years are required for lead identification, optimization, in vitro and in vivo testing before starting the first clinical trials [1, 2]. A new strategy introduced into drug discovery is structure–property relationships (SPRs). This is complementary to SAR. The structures of compounds are correlated to their property performance. SPR allows medicinal chemists to understand how structural modifications improve properties for their scaffold. Thus, the established strategy of structure-based design is supplemented with the new strategy of "property-based design" by van de Waterbeemd et al., [3] the study and modification of structure to achieve property improvement.

There are many reasons for a drug discovery project team to strive toward selecting leads with good drug-like properties and optimizing properties for their compound series during drug discovery.

The process of drug discovery balances a relentless search for molecules that have structural features that produce:

(1) Strong target binding using structure-based design and the structure–activity relationship (SAR)

(2) High performance at in vivo barriers, using property-based design [3] and the structure–property relationship (SPR)

In the same way that design of structural features using SAR is known as structure-based design, the design of structural features using SPR has become known as property-based design [3]. How a medicinal chemist goes about balancing these often disparate processes is a matter of experience and strategy. [4]

Here we carry out the Structure Activity/Property Relationship (SAR/SPR) studies which are attempting to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design [5-8] and to give us the correlation between molecular structures and properties [9-11] such as lipophilicity, polarizability, electronic and steric parameters. The molecular properties, used in the correlations, relate as directly as possible to the key physicochemical processes taking place in the target activity.

2. Structure-Property Relationships (SPR) Properties

2.1. Molecular Volume And Surface Area

Molecular volumes are often calculated by a numerical integration grid technique [12] that I can illustrate by considering the trivial problem of finding the volume of an atom whose van der Waals radius is R (the volume is of course $\frac{4}{3}\pi R^3$)

Figure IV.1 shows a two-dimensional representation of the atom whose van der Waals radius is R, surrounded by a three-dimensional grid of equally spaced points.

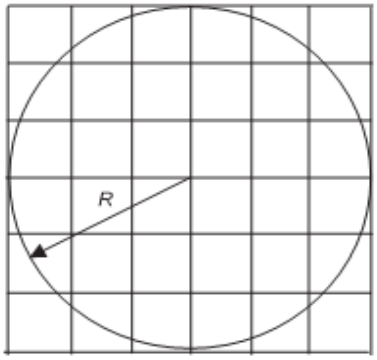


Figure IV.1: Grid around atom

The grid has its centre at the atom centre, and the edges of the grid correspond to the van der Waals radius.

For each grid point in turn we calculate its distance from the centre and determine whether the grid point lies inside or outside the atom. If n is the total number of grid points and n_a the number that lie within the atom whose volume is V, then we have

$$\frac{\mathbf{V}}{\mathbf{8R^3}} = \frac{\mathbf{n_a}}{\mathbf{n}} \qquad (1)$$

For a polyatomic, we have to give special consideration to grid points that lie in the overlap region. Figure IV.2 shows two atoms, A and B, with radii R_A and R_B. The overlap region is labelled X.

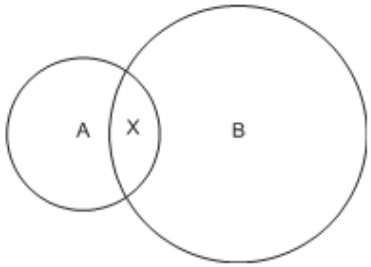


Figure IV.2: Atoms A, B and overlap region X

For atom A, we know that the volume is $\frac{4}{3}\pi R^3$. We now surround atom B with a grid, as described above, and test each grid point in turn. If the grid point lies within sphere B, then we test to see if it lies in region X and so has already been counted as part of the volume of atom A. The algorithm proceeds until all atoms have been considered in turn.

The molecular volume is found by adding all atomic contributions. There are similar methods for the estimation of molecular surface area.

2.2. Molecular Refractivity (MR)

The molar refractivity is a steric parameter that is dependent on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interaction of the ligand with the receptor. [13]

This parameter is a measure of the volume occupied by an atom or group of atoms. The molar refractivity is a constitutive-additive property that is calculated by Lorenz-Lorentz formula:

$$\boldsymbol{MR = \frac{n^2-1}{n^2+2} \times \frac{Mw}{\rho}} \qquad (2)$$

where n is the refraction index, Mw is the molecular weight, and ρ is the density. The $(n^2 - 1)/(n^2 + 2)$ term provides a correction factor by defining how easily the substituent can be poralized, whereas the Mw/ρ term defines a volume. Molar refractivity is related to the lipophilicity, volume, and steric of the molecules. Moreover, it has been correlated with the London dispersive force that acts in the drug-receptor interaction.

2.3. Molecular Polarizability (Pol)

Molecular Polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities. [14]

It is widely used to describe the inductive and dispersive interaction of a molecule or molecular system. In addition, polarizability values have been shown to be related to hydrophobicity and thus to other biological activities. It is one of the descriptors that are extensively used in QSAR study.

Highly polarizable molecules can be expected to have strong attractions with other molecules. The molecular polarizabity (α) is also related to molecular refractivity (MR) by the Lorentz-Lorenz equation (3) where N_0 is the Avogadro constant.

$$MR = \frac{4}{3}\pi N_0 \alpha \qquad (3)$$

2.4. Molecular Weight (MW)

Molecular weight descriptor has been used as a descriptor in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross resistance of various drugs in multi-drug resistant cell lines. [15] Molecular weight is correlated with the size of the molecule. [4]

High molecular weight compounds are likely to show high toxicity as promiscuity of compounds is also likely to increase [16]. Additionally, the systemic clearance of a compound is inversely proportional to the molecular weight [17].

2.5. Hydration Energy (HE)

Hydration energy is very important in the selectivity filter of ion channels where the drug is almost entirely strip from the hydration water. [18]

Indeed, in the biological environments the polar molecules are surrounded by water molecules. They are established hydrogen bonds between a water molecule and these molecules. The donor sites of the proton interact with the oxygen atom of water and the

acceptor sites of the proton interact with the hydrogen atom. The first corresponds to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction. These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible [19].

2.6. Partition Coefficient (Log P)

One of the most important physicochemical properties much interest in QSAR studies is lipophilicity (or hydrophobicity). Because it directly relates to solubility in aqueous phase, to membrane permeation (an important factor contributing to the toxicity of chemicals), and to its contribution to ligand binding at the receptor site.

The ability of a molecule to cross the biological membranes (permeability) is a very important bio-pharmaceutic parameter that governs the absorption, distribution, metabolism and excretion (pharmacokinetics) of a drug.

Enroute to its bio-phase, the drug has to partition between the lipid bio-membranes and the aqueous biological fluids. Although constituents vary from one membrane to the other, major constituents of bio-membranes are phospholipids, cholesterol, sphingolipids, and glycolipids. (Figure IV.3)

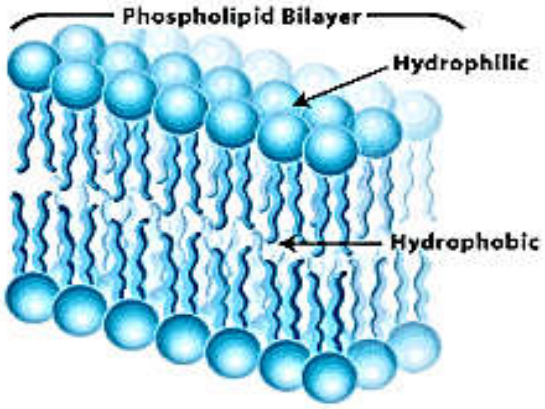


Figure IV.3: Polarity of different cellular milieus

All of these lipids are amphipathic in nature. Therefore, to successfully cross the various bio-membranes and to reach its site of action, any drug molecule should have a balance between hydrophilic and lipophilic properties.

The partition coefficient P, defined as the ratio of molar concentration of a chemical dissolved at equilibrium in octanol phase C_{oct} to its molar concentration in aqueous phase C_{aq} [20-22], (Figure IV.4), and is given by the equation:

$$\mathbf{P} = \left(\frac{C_{oct}}{C_{aq}}\right)_{equilibrium} \qquad (4)$$

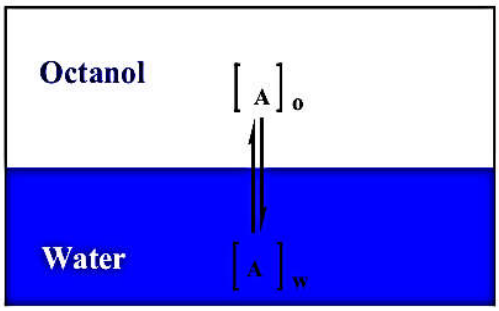


Figure IV.4: Schematic depictions of the partition of species between octanol and water

Which $[A]o$ and $[A]w$ are the concentrations of the compound A in organic and aqueous phases, respectively.

The best choice out of various non-polar and slightly polar solvents available is n-octanol [23] because, it mimics the biological membranes in several aspects:

- n-octanol has a saturated alkyl chain,
- it has a hydroxyl group that can act as both hydrogen bond donor as well as acceptor, it dissolves water to the extent of 1.7 M,
- and its solubility parameter ($\delta_{octanol}$=10) is close to that of biological membranes, for example skin (δ_{skin}=10).

This combination of lipophilic chains, hydrophilic groups, ability to take up water molecules and similar solubility parameter gives n-octanol properties very close to those of natural membranes.

LogP values between 0 and 3 constitutes an optimal window for passive drug absorption. A logP value below 0 means that the compound is hydrophilic, and hence it will have a good solubility but it may have poor permeability. Whereas, a logP value far higher than 3 means that the compound is highly lipophilic, hence, tends to favour absorption, and

renders the compounds more susceptible to metabolism and / or biliary clearance [24, 25]. The influence of lipophilicity on the metabolic clearance of drugs is attributed mainly to the increased affinity of drugs for the enzymes [26]

2.7. Number of Hydrogen Bond Donors and Bond Acceptors

Hydrogen bonding is now seen as an important property related to membrane permeation. Various scales have been developed [27]. Some of these scales describe total hydrogen bonding capability of a compound, while others discriminate between donors and acceptors [28].

Hydrogen bonds increase solubility in water and must be broken in order for the compound to permeate into and through the lipid bilayer membrane. Thus, an increasing number of hydrogen bonds reduces partitioning from the aqueous phase into the lipid bilayer membrane for permeation by passive diffusion. [4] Thus, the number of hydrogen bond donors and acceptors should be limited in order to minimize the stability of compound in aqueous media.

In this work, hydrogen donor (HBD) is either N or O with an attached hydrogen H, and hydrogen acceptor (HBA) is either N or O in functional groups except nitro and cyano.

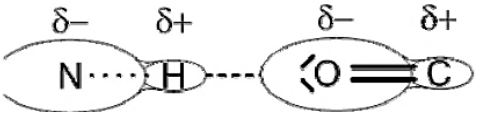


Figure IV.5: Hydrogen bonding

2.8. Druglikeness

The term drug-like captures the concept that certain properties of compounds are most advantageous in their becoming successful drug products. The term became commonly used following the pivotal work of Lipinski and his colleagues at Pfizer [29]. Their work examined the structural properties that affect the physicochemical properties of solubility and permeability and their effect on drug absorption. The term drug-like property has expanded and has been linked to all properties that affect ADME/Tox. Although medicinal chemists and pharmaceutical scientists had used structural properties in various ways for

many years, rules became more prominent and defined in the field with the report by Lipinski et al [29] of the "rule of 5," or what has become known as the "Lipinski rules." These rules are a set of property values that were derived from classifying key physicochemical properties of drug-like compounds. The rule of five is based on four properties of molecules; namely, molecular weight (MW), logP, number of hydrogen-bond donors (HBD) taken as equivalent to the number of –OH and –NH groups, and the number of hydrogen-bond acceptors (HBA) taken as equivalent to the number of oxygen and nitrogen atoms. A 'flag' is set if a molecule's MW is greater than 500, its logP is greater than 5, the number of its HBDs exceeds 5 and the number of its HBAs exceeds 10. Because the values of the decision points for all of the property values are multiples of five, the above set of rules has been called the 'Rule of Five'[29].

2.9. Lipinski Rules

Although medicinal chemists and pharmaceutical scientists had used structural properties in various ways for many years, rules became more prominent and defined in the field with the report by Lipinski et al. [30] of the "rule of 5," or what has become known as the "Lipinski rules."

These rules are a set of property values that were derived from classifying the key physicochemical properties of drug-like compounds. The rules were used at Pfizer for a few years prior to their publication and since then have become widely used. The impact of these rules in the field has been very high. This acceptance can be attributed to many factors:

- ✓ The rules are easy, fast, and have no cost to use.
- ✓ The "5" mnemonic makes the rules easy to remember.
- ✓ The rules are intuitively evident to medicinal chemists.
- ✓ The rules are a widely used standard benchmark.
- ✓ The rules are based on solid research, documentation, and rationale.
- ✓ The rules work effectively.

The rule states that the compounds are more likely to be orally bioavailable if they obey the following criteria :

- hydrogen bond donors ≤5 (expressed as the sum of all OHs and NHs)
- MW ≤ 500
- logP ≤ 5
- hydrogen bond acceptors ≤10 (expressed as the sum of all Ns and Os)

Molecules that violate more than one of these rules may have problems with bioavailability. Therefore, this rule establishes some structural parameters relevant to the theoretical prediction of the oral bioavailability profile, and is widely used in designing new drugs. However, classes of compounds that are substrates for biological transporters such as antibiotics, antifungals, vitamins, and cardiac glycosides, are exceptions to the rule [30].

3. Results and Discussion

3.1. Structural Comparison of the 1,2,4-oxadiazol-5-amine Derivatives

Based on our conclusions on the effect of substitution on the 1,2,4-oxadiazol-5-amine molecules. We chose a series of 1,2,4-oxadiazol-5-amine derivatives, these molecules have a biological activity , This series of 1,2,4-oxadiazol-5-amine derivatives are given in (Table IV.1). Initially, we performed a structural comparison of this series. We used molecular mechanics, with MM+ force-field to calculate the stable conformations of this series. These molecules have a weak conformational flexibility, with regard to the other macrocycles of macrolide type [31-37].

3.2. Study of Structure-Property Relationships for 1,2,4-oxadiazol-5-amine Derivatives

We have studied six physical and chemical proprieties of a series of fifteen 1,2,4-oxadiazol-5-amine derivatives (3-(Aryl)-N-(Aryl)-1,2,4-Oxadiazol-5-amines) [38] (Table IV.1) using HyperChem 8.03 software [39].

For example, (Figure IV.6) shows the favored conformation in 3D of the compound1 (Appendix B). We will continue this work in the future by a quantitative calculation.

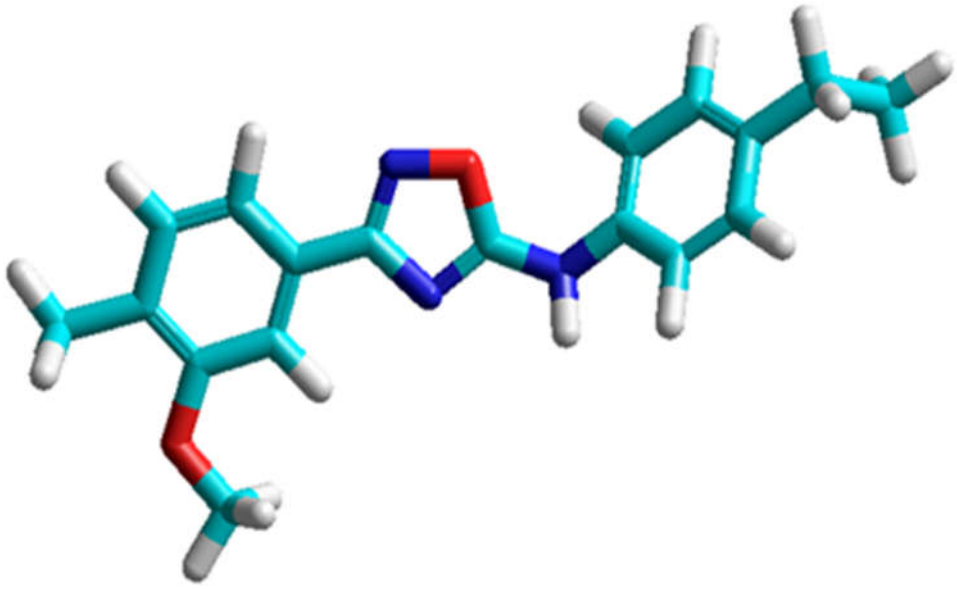
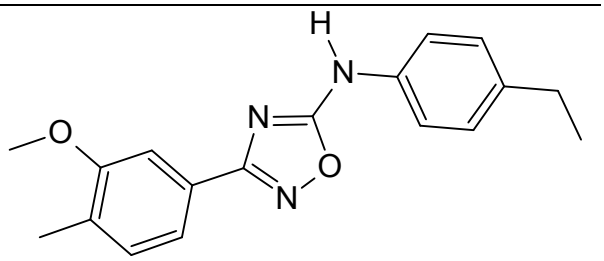
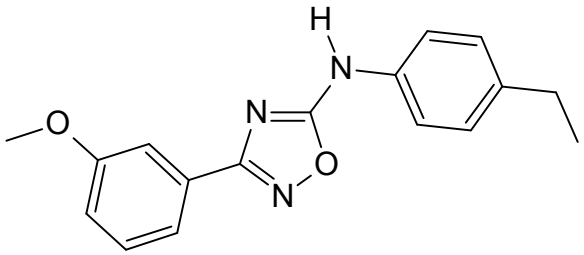
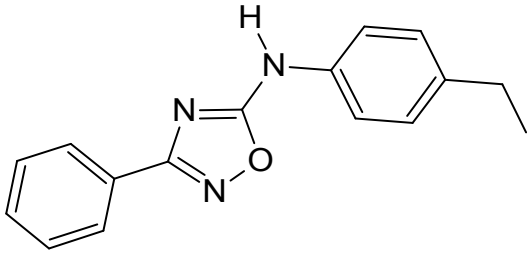
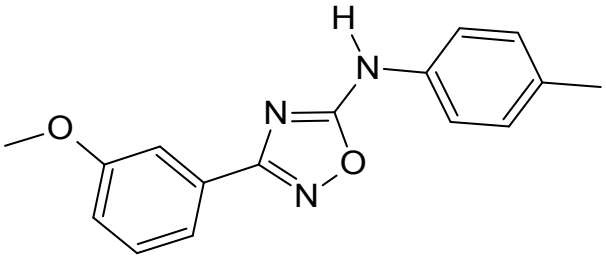
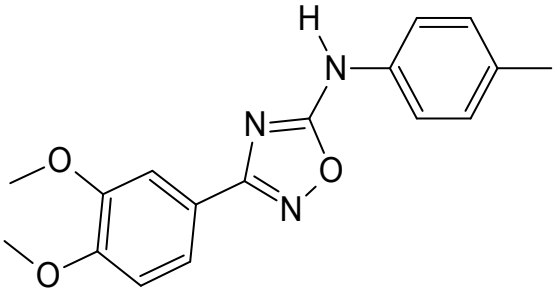
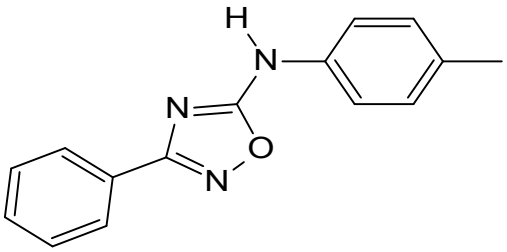
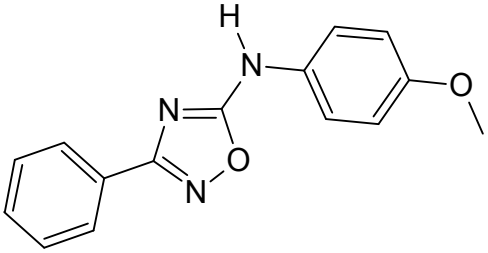


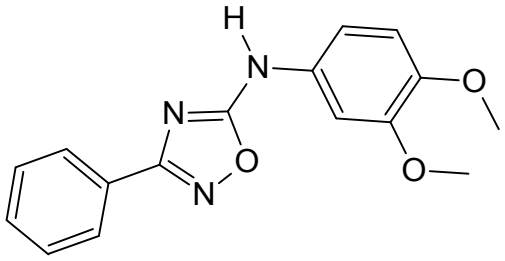
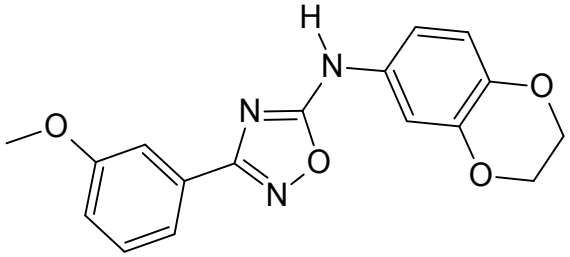
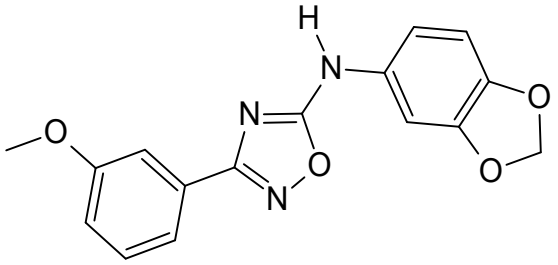
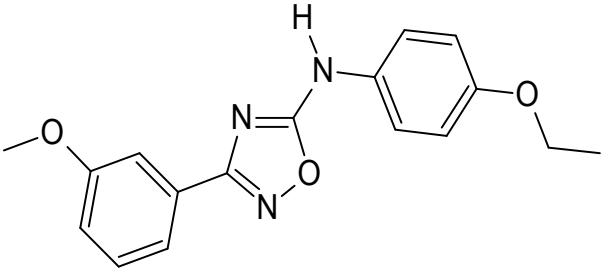
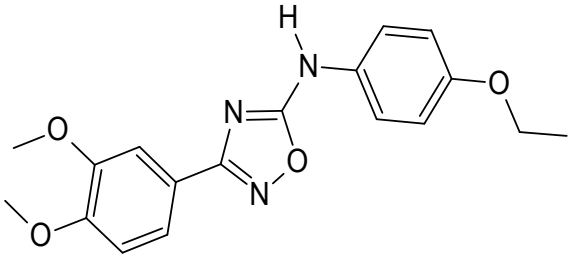
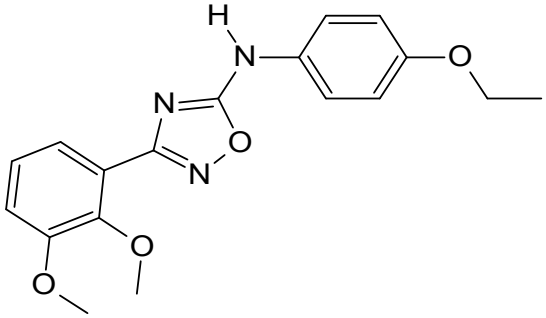
Figure IV.6: 3D Conformation of compound 1 (HyperChem 8.03)

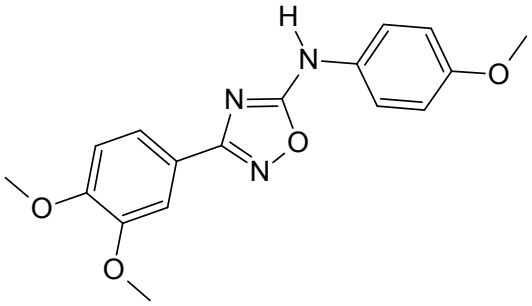
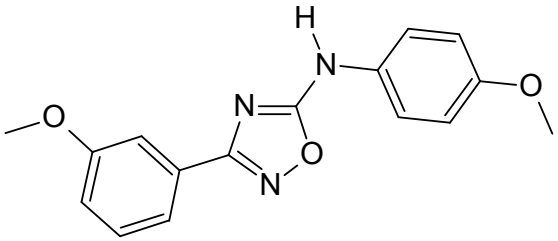
QSAR proprieties are, The properties involved are: Surface area grid (SAG), molar volume (V), hydration energy (HE), partition coefficient octanol/water (logP), molar refractivity (MR), polarizability (Pol) and molecular weight (MW).

Table IV.1: Structural comparison of the 1,2,4-oxadiazol-5-amine derivatives

S. No	The name according to IUPAC	Structure
1	N-(4-ethylphenyl)-3-(3-methoxy-4-methylphenyl)-1,2,4-oxadiazol-5-amine	

2	N-(4-ethylphenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-amine	
3	N-(4-ethylphenyl)-3-phenyl-1,2,4-oxadiazol-5-amine	
4	3-(3-methoxyphenyl)-N-(4-methylphenyl)-1,2,4-oxadiazol-5-amine	
5	3-(3,4-dimethoxyphenyl)-N-(4-methylphenyl)-1,2,4-oxadiazol-5-amine	
6	N-(4-methylphenyl)-3-phenyl-1,2,4-oxadiazol-5-amine	
7	N-(4-methoxyphenyl)-3-phenyl-1,2,4-oxadiazol-5-amine	

8	N-(3,4-dimethoxyphenyl)-3-phenyl-1,2,4-oxadiazol-5-amine	
9	N-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-amine	
10	N-(1,3-benzodioxol-5-yl)-3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-amine	
11	N-(4-ethoxyphenyl)-3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-amine	
12	3-(3,4-dimethoxyphenyl)-N-(4-ethoxyphenyl)-1,2,4-oxadiazol-5-amine	
13	3-(2,3-dimethoxyphenyl)-*N*-(4-ethoxyphenyl)-1,2,4-oxadiazol-5-amine	

14	3-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine	
15	3-(3-methoxyphenyl)-*N*-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine	

3.3. Structure Property Relationships

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity. Lipophilicity has been studied and applied as an important drug property for decades. It can be quickly measured or calculated. Lipophilicity has been correlated to many other properties, such as bioavailability, storage in tissues, permeability, and volume of distribution, toxicity, plasma protein binding and enzyme receptor binding [4, 40]

Polarizability values are generally proportional to the values of surfaces and of volumes, the decreasing order of polarizability for these studied 1,2,4-oxadiazol-5-amine is:

Compound 12 = Compound 13 > Compound 1 > Compound 14 > Compound 5= Compound 11 > Compound 9 > Compound 2 > Compound 15 = Compound 8> Compound 10 > Compound 4 > Compound 3 > Compound 7 > Compound 6 (Table IV.2).

The order of polarizability is approximately the same one for volume and surface. This also is explained by the relation between polarizability and volume, for the relativity non polar molecules. They are directly linked, for the centers of gravity of negative and positive charges in the absence of external fields to coincide, and the dipole moment of the molecule is zero.

Surface and distribution volume of these molecules are definitely higher than those of more polar molecules like the lipopeptides or beta-lactams. For example, Deleu et al. used Tammo software on the surfactins C13, C14 and C15 having cores similar to the macrolides [41].

They found that their surfaces vary from 129 to 157 $Å^2$ [42], contrarily for these 1,2,4-oxadiazol-5-amine derivatives, surfaces vary from 387.21 to 529.21 $Å^2$. These 1,2,4-oxadiazol-5-amine Derivatives has a great variation of distribution volume, in particular compound 12 and compound 13 which have respective volumes: 1006.01 and 1005.22$Å^3$ (Table IV.2).

Table IV.2: QSAR proprieties for 1,2,4-oxadiazol-5-amine derivatives

Molecule	Surface Area $A°^2$	Volume $A°^3$	Polazability $A°^3$	Hydratation Kcal/mol	Refractivity $A°^3$	logP	Mass uma
1	491.533	946.716	34.823	-7.912	96.903	2.410	309.368
2	464.729	898.125	32.988	-9.527	92.621	2.256	295.341
3	409.042	819.945	30.516	-8.128	86.246	3.249	265.315
4	442.884	844.235	31.153	-10.109	88.020	1.860	281.314
5	478.464	922.536	33.625	-10.427	94.394	0.867	311.340
6	387.206	767.588	28.681	-8.713	81.645	2.853	251.288
7	401.884	792.283	29.318	-11.532	83.738	1.706	267.287
8	433.072	870.408	31.790	-11.669	90.112	0.713	297.313
9	432.354	906.639	33.488	-13.878	94.518	-0.458	325.324
10	414.982	861.669	31.653	-14.897	89.328	-0.090	311.297
11	489.687	928.250	33.625	-11.841	94.860	1.056	311.340
12	527.225	1006.009	36.097	-12.288	101.235	0.062	341.366
13	529.205	1005.222	36.097	-12.218	101.235	0.062	341.366
14	495.082	947.696	34.262	-13.163	96.487	-0.280	327.340
15	455.565	871.702	31.790	-12.787	90.112	0.713	297.313

The most important hydration energy in the absolute value, is that of the compound 10 (14.89 kcal/mol) and the weakest is that of compound 1 (7.91kcal/mol) (Table IV.2). Indeed, in the biological environments the polar molecules are surrounded by water molecules. They are established hydrogen bonds between them.

Compound 10 has a site donor of the proton (NH) and six acceptor sites of the proton (O in Aryl group R1 and 2O in Aryl group R2) and 2N in the principal cycle and N_6 of amine, but, in the oxygen O atoms, the acceptor effect is greatly reduced, because of the mesomeric effect. (Figure IV.7)

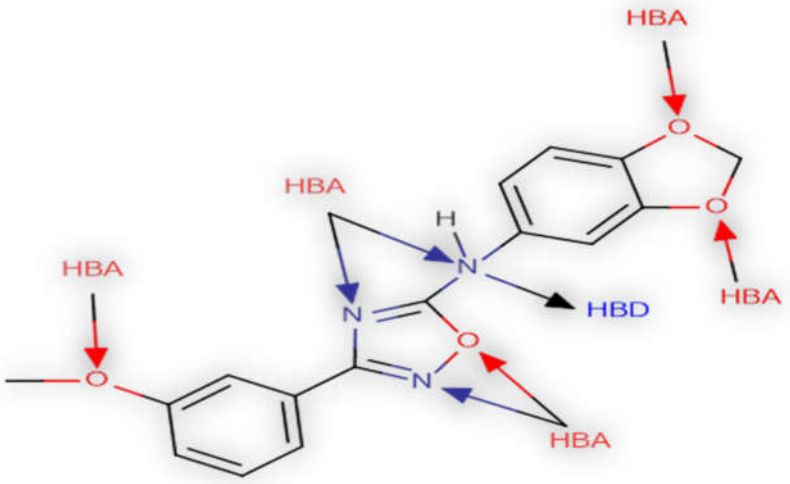


Figure IV.7: Donor and acceptor sites of compound 10

On the other hand, the compound 1 has a site donor of the proton (NH) and four acceptor sites of the proton (O in Aryl group R1) and 2N in the principal cycle and N_6 of amine, but, in the oxygen O atoms, the acceptor effect is greatly reduced, because of the mesomeric effect (Figure IV.8).

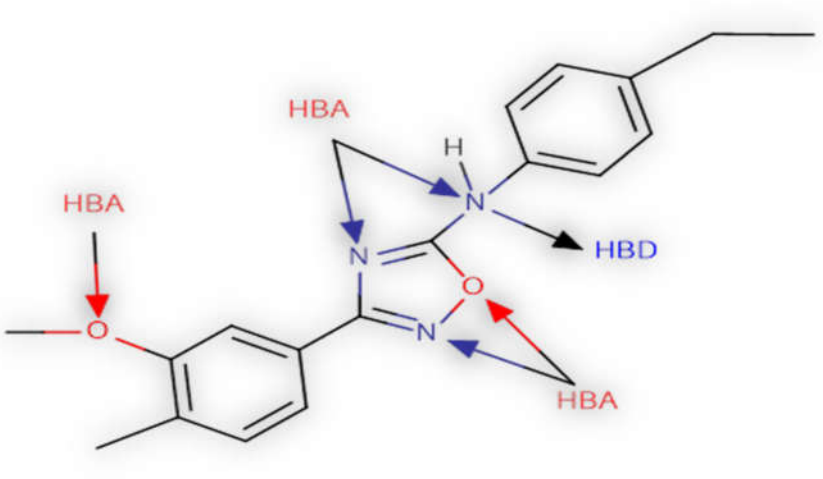


Figure IV.8: Donor and acceptor sites of compound 1

This property supports the first compound, not only by fixing the receiver, but also activates it. It is thus about an agonist. It has as a consequence a better distribution in fabrics.

The decreasing order of log P for these studied 1,2,4-oxadiazol-5-amine is:
Compound 3 > Compound 6 > Compound 1 > Compound 2 > Compound 4 > Compound 7 > Compound 11 > Compound 5 > Compound 8 = Compound 15 > Compound 12= Compound 13 > Compound 10 > Compound 14 > Compound 9 (Table IV.2).

Compound 9 presents the low coefficient of division (-0.458) and comes after compound 14 (-0.280). These molecules possess a good solubility. When the coefficient of division is rather low, it has as a consequence a better gastric tolerance.

Compound 3, 6 and 1 which have, respectively, higher values 3.25, 2.85 and 2.41; these molecules are the most absorbent products and have important capacities to be dependent on plasmatic proteins.

3.4. Drug likeness Calculations on the Basis of Lipinski Rule of Five

Druglikeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding

characteristics, molecular size and flexibility and presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others [43].

The druglikeness was calculated by considering log P (partition coefficient), number of hydrogen donor (HBD), number of hydrogen acceptor (HBD), molecular weight (MW) and number of violation. The druglikeness of various parameters of the isolated compounds (1-15) are in Table IV.3

Table IV.3: Lipinski's rule of five for drug likeliness of 1,2,4-oxadiazol-5-amine derivatives**.**

Compound	MW (Da)	logP	HBD	HBA	No. of violations of Lipinski rule
1	309.368	2.410	1	5	0
2	295.341	2.256	1	5	0
3	265.315	3.249	1	4	0
4	281.314	1.860	1	5	0
5	311.340	0.867	1	6	0
6	251.288	2.853	1	4	0
7	267.287	1.706	1	5	0
8	297.313	0.713	1	6	0
9	325.324	-0.458	1	7	0
10	311.297	-0.090	1	7	0
11	311.340	1.056	1	6	0
12	341.366	0.062	1	7	0
13	341.366	0.062	1	7	0
14	327.340	-0.280	1	7	0
15	297.313	0.713	1	6	0

We can see through the Table IV.3 that all compound have zero violation of Lipinski rule and all compounds have scores of less than 5 for lipophilicity, ranging from -0.458 to 3.249. and its molecular weight less than 500 Da, the maximum value of MW is 341.366 Da for compounds 12 and 13.

We can see also from Table IV.3 that each compound has one hydrogen bond donor (NH) and all these compound have hydrogen bond acceptors under 10 (Ns and Os) (Appendix C).

Thus, all compounds meet the Lipinski rules of the five, suggesting that these compounds theoretically would not have problems with oral bioavailability.

4. Conclusion

The present study, offers the ability to guide design and selection to quickly identify compounds from the 1,2,4-oxadiazol-5-amine derivatives series that are likely to achieve outcome in the clinic and occupy a strong market position. Also it provides a discussion of several qualitative approximations of the structure activity/property relationship.

The compounds 3, 6 and 1 which have higher values of coefficient of division. These lipophilic compounds penetrate in various membranes, including cellular membranes as well as tissues with high lipoid content, to arrive at the receptor site.

Compound 10 has important hydration energy leading to a better distribution in fabrics.

Molecular properties such as membrane permeability and oral bioavailability are usually associated with some basic molecular descriptors, such as log P (partition coefficient), molecular weight (MW), and the acceptors and donor for hydrogen bonding in a molecule. Using these molecular properties, Lipinski established a controversial rule for drug design.

The application of Lipinski rules on the studied 1,2,4-oxadiazol-5-amine derivatives shows that all these compounds, theoretically, will not have problems with oral bioavailability.

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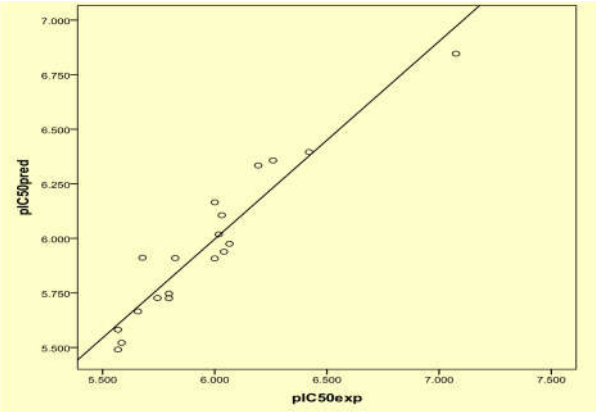
QSAR Modeling of Some 3-(aryl)-N-(aryl)-1, 2, 4-oxadiazol-5-amine Derivatives

CHAPTER



Salah Belaidi, Aicha Kerassa, Touhami Lanez, and Mehmet Cinar, Journal of Computational and Theoretical Nanoscience Vol. 12, 2127–2133, 2015.

Summary

1. Introduction

Quantitative structure-activity relationship (QSAR) analysis is based on the general principle of medicinal chemistry that the biological activity of a ligand or compound is related to its molecular structure or properties, and structurally similar molecules may have similar biological activities [1]. Such molecular structural information is encoded in molecular descriptors and a QSAR model defines mathematical relationships between descriptors and biological activities of known ligands to predict unknown ligands' activities. QSAR methods have been applied in several scientific studies including chemistry, biology, toxicology and drug discovery to predict and classify biological activities of virtual or newly-synthesized compounds [2-5].

QSAR describes the mathematical relationships between the structural attributes and target properties of a set of chemicals [6, 7]. QSARs are applied to predict the biological activities or ADMET properties of database molecules with similar chemical structures. This method is only fruitful if the dataset contains compounds that are structurally related to the molecules used to construct the model.

Therefore, in contrast to lead discovery techniques, such as similarity analysis and pharmacophore modeling, QSARs are frequently used in the optimization phases of drug design [8]. Many different 1D, 2D, 3D and multidimensional QSAR approaches have been developed during the past several decades [7, 9]. The major differences in these methods include the chemical descriptors and mathematical approaches that are used to establish the correlation between the target properties and the descriptors.

QSAR analyses are often used to derive relationships between the molecular properties of compounds and their biological activities by statistical methods [10].

Many statistical methods have been employed to generate QSAR models from descriptive variables. Simple and multiple linear regressions is one of the more successful techniques use by many researcher in construct of QSAR models [11-13].

2. QSAR History

QSAR dates back to the 19th century. In 1863, A.F.A. Cros at the University of Strasbourg observed that toxicity of alcohols to mammals increased as the water solubility of the alcohols decreased.[14] In the 1890's, Hans Horst Meyer of the University of Marburg and Charles Ernest Overton of the University of Zurich, working independently, noted that the toxicity of organic compounds were dependent on the lipophilicity. [14,15] Little additional development of QSAR occurred until the work of Louis Hammett,[16] Who correlated electronic properties of organic acids and bases with their equilibrium constants and reactivity. Hammett observed that adding substituents to the aromatic ring of benzoic acid had an orderly and quantitative effect on the dissociation constant. Hammett also observed that substituents have a similar effect on the dissociation of other organic acids and bases. QSARs based on Hammett's relationship utilize electronic properties as descriptors. Difficulties were encountered when investigators attempted to apply Hammett-type relationships to biological systems, indicating that other structural descriptors were necessary.

Robert Muir, a botanist at Pomona College, was studying the biological activity of com-pounds that resembled indole acetic acid and phenoxyacetic acid, [17] which function as plant growth regulators. In an attempt to correlate the structures of the compounds with their activities, he consulted Corwin Hansch. Using Hammett sigma parameters to account for the electronic effect of substituents did not lead to a meaningful QSAR. However, Hansch recognized the importance of lipophilicity, expressed as the octanol-water partition coefficient, on biological activity. [18]

This parameter is recognized to provide a measure of membrane permeability, since a compound needs to have lipophilic properties to enter a membrane and hydrophilic properties to pass through. The octanol-water partition coefficient is also a driving force when drugs bind into targets.

QSAR models are now developed using a variety of parameters such as descriptors of the structural properties of molecules, descriptors to account for the shape, size, lipophilicity, polarizability, and other properties [19]

3. Several Purposes and Applications of QSAR Models : [20]

- QSAR models are used to predict the activity of new (hypothetical) chemical compounds, even before their synthesis. Thus, QSARs can save time and experimental resources for synthesizing and biological testing of large numbers of compounds. QSARs offer possibilities for reduction or replacement of animal use in research and toxicity testing.
- (Q)SARs can lead to better understanding of the mechanisms of interaction between compounds and biological systems. They may reveal important structural features for the biological effect.
- QSAR models provide useful information about a dose range for a biological effect of a compound, thus helping the experimental design (selection of doses and tests) in drug research and toxicity testing.

4. Main Steps in QSAR Analysis

To develop QSARs, a series of compounds, called a training set, is used. The compounds in the training set ideally ; the same or similar mechanism of biological action to ensure that the same factors influence the activity of all compounds under investigation. For all compounds in the series, biological activities are evaluated and compound structural descriptors are calculated. Statistical tools are then used to derive QSARs.

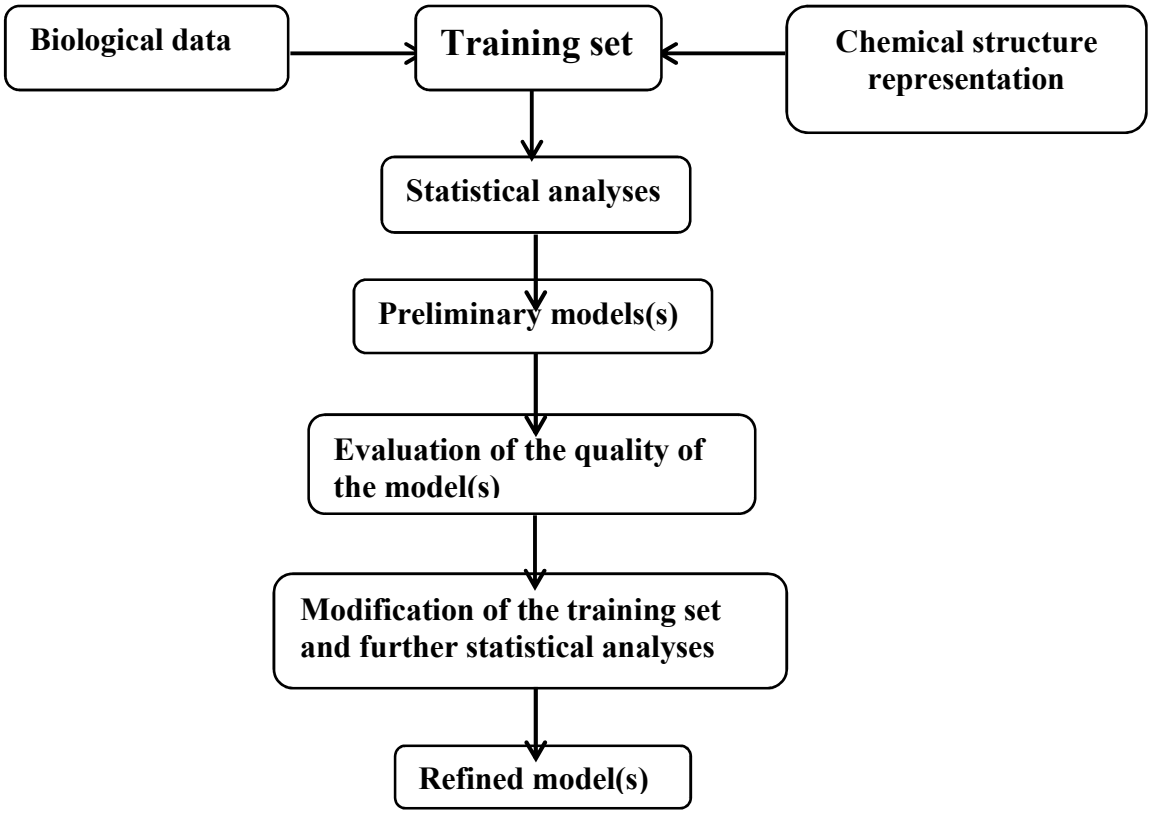


Figure V.1: The main steps in QSAR analysis

5. Tools and Techniques of QSAR

5.1. Molecular Descriptors [21]

The crucial point in the QSPR approach is an appropriate description of the molecular structures. The chemical descriptors take account of the different aspects of the chemical information. The molecular descriptor expresses chemical information transformed and encoded from a molecule and effectively solves chemical, pharmaceutical, and toxicological problems. The advantage of theoretical molecular descriptors is in developing compounds that have never been synthesized or explored experimentally. Molecular descriptors are well known for their ability to establish linear regression relationships with physicochemical and biological properties.

5.1.1. Constitutional Descriptors

Constitutional descriptors can simply obtain the information from the chemical composition of the compounds. Typical constitutional descriptors include molecular weight, total numbers of atoms, bonds, and rings in the molecule. These are one-dimensional (1D) descriptors that can easily be obtained with knowledge of the molecular formula. Unfortunately, the linear relationship between constitutional descriptors and physicochemical properties cannot sufficiently prove that a physical mechanism reflects molecular interactions.

5.1.2. Topological Descriptors

Topological descriptors are two-dimensional (2D) descriptors obtained from information on the molecular topology; they express the atomic connectivity in the molecule and can be calculated from 2D graph representation of molecules [22].

5.1.3. Geometrical Descriptors

Geometrical descriptors are derived from three-dimensional (3D) structures of molecules defined by the coordinates of atomic nuclei and the size of the molecules represented [21]. Weighted holistic invariant molecular (WHIM) descriptors contain another prospective class of molecular geometric parameters, WHIM descriptors are obtained from the molecular (x, y, z) coordinates of the molecules with 3D structure, in which the descriptors capture detailed information on molecular size, shape, symmetry and atomic distribution. The derivation of WHIM descriptors can be obtained from centered molecular coordinates using the PCA approach from the weighted covariance matrix of atomic coordinates [23, 24].

5.1.4. Molecular Descriptors

Geometry, topology and atom-weights assembly (GETAWAY), encode the geometrical information obtained from the molecular matrix together with the topological information obtained from the molecular graph, as well as information from atomic weights [25].

5.1.5. Electronic Descriptors

Electronic descriptors reflect the electronic structure of the molecule, based on 3D structure and the charge distribution in the molecule. The descriptors can be obtained from the calculation with ab initio or semi-empirical approaches.

5.2. Biological Parameters [26]

In QSAR analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model. It must be realized that any resulting QSAR model that is developed is only as valid statistically as the data that led to its development. The equilibrium constants and rate constants that are used extensively in physical organic chemistry and medicinal chemistry are related to free energy values ΔG. Thus for use in QSAR, standard biological equilibrium constants such as K_i or K_m should be used in QSAR studies.

Likewise only standard rate constants should be deemed appropriate for a QSAR analysis. Percentage activities (e.g., % inhibition of growth at certain concentrations) are not appropriate biological endpoints because of the nonlinear characteristic of dose-response relationships. These types of endpoints may be transformed to equi-effective molar doses.

Only equilibrium and rate constants pass muster in terms of the free-energy relationships or influence on QSAR studies. Biological data are usually expressed on a logarithmic scale because of the linear relationship between response and log dose in the mid-region of the log dose-response curve. Inverse logarithms for activity (log 1/C) are used so that higher values are obtained for more effective analogs. Various types of biological data have been used in QSAR analysis. A few common endpoints are outlined in Table V.1.

Table V.1: Types of biological data utilized in QSAR analysis

Source of Activity	Biological Parameters
1. Isolated receptors	
Rate constants	Log *k*
Michaelis-Menten Constants	Log *1/Km*
Inhibition constants	Log *1/Ki*
2. Cellular systems	
Inhibition constants	Log *1/IC50*
Cross resistance	Log *CR*
in vitro biological data	Log *1/C*
Mutagenicity states	Log *TA98*
3. In vivo systems	
Biocencentration factor	Log *BCF*
In vivo reaction rates	Log *I* (Induction)
Pharmacodynamic rates	Log *T* ((total clearance)

5.3. Statistical Methods Used in QSAR Analysis [27]

Statistical methods are an essential component of QSAR work. They help to build models, estimate a model's predictive abilities, and find relationships and correlations among variables and activities. A suitable statistical method coupled with a variable selection method allows analysis of this data in order to establish a QSAR model with the subset of descriptors that are most statistically significant in determining the biological activity. The statistical method can be broadly divided in to two: linear and non-linear method.

In statistics a correlation is established between dependent variables (biological activity) and independent variables (physiochemical properties or molecular descriptor). The liner method fits a line between the selected descriptor and activity as compared to non-linear method which fit a curved between the selected descriptor and activity.

Following are commonly used statistical methods

1. Principal component analysis (PCA)
2. Cluster analysis
3. Simple liner regression
4. Multiple liner regression
5. Stepwise multiple liner regression
6. Principle component regression (PCR)
7. Continuum Regression
8. Partial least squares (PLS)
9. Genetic function approximation (GFA)
10. Genetic partial least squares (GPLS)
11. Logistic regression
12. K-Nearest Neighbor classification (KNN)
13. Neural Network
14. Discriminant analysis
15. Decision Trees
16. SIMCA
17. Canonical Correlation

6. Multiple Linear Regressions

The Multiple Linear Regression (MLR) [28] is an extension of the classical regression method to more than one dimension. MLR calculates QSAR equations by performing standard

Multivariable regression calculations using multiple variables in a single equation.

MLR expresses a single dependent variable (y) as a linear combination of multiple independent variables (x):

$$\boldsymbol{y = ax_1 + bx_2 \ldots + k} \qquad (1)$$

Where a, b are the coefficients of the regression, and k is a constant, the regression model can be built in a stepwise manner.

7. Statistical Parameters

7.1. Coefficient of Determination (R^2)

The coefficient of determination is found by squaring the correlation coefficient and is used as a m ore precise way to interpret the correlation coefficient. It is useful because it gives the proportion of the variance in one variable that is "explained" by the other variable. It represents the percent of the data that is the closest to the line of best fit. [29]
The correlation coefficient can be determined by the mathematical formula:

$$\mathbf{R^2} = \frac{\sum_{\mathbf{i=1}}^{\mathbf{n}} \left(\boldsymbol{y_{i,obs} - y_{i,cal}}\right)^{\mathbf{2}}}{\sum_{\mathbf{i=1}}^{\mathbf{n}} \left(\mathbf{y_{i,obs}} - \bar{\boldsymbol{y}}\right)^{\mathbf{2}}} = \frac{\boldsymbol{ESS}}{\boldsymbol{TSS}} \qquad (\mathbf{2})$$

The coefficient of determination is such that $0 < R^2 < 1$, and the stronger the correlation (R is closer to 1).

7.2. Correlation Coefficient (R)

Correlation coefficient is a simple statistical measure of relationship between one dependent and one or more than one independent variables and it is use as a measure of the statistical fit of a regression based model in QSAR [30].

The value of r is such that $-1 < R < +1$. The + and – signs are used for positive linear correlations and negative linear correlations, respectively. If the predicted and observed values have a strong linear correlation r is close to 1, however if there is no linear correlation or a weak linear correlation r is close to 0.
The value of the correlation coefficient can be strongly influenced by one outlying point.

7.3. Fischer Statistic (F)

The F-statistic is used to test the statistical significance of the regression.[31] Hence, the larger the F value is above the critical value (Appendix D), the better the regression. As can be seen from the equation below the F-statistic increases as the number of data points increase and the coefficient of determination increases.

$$\mathbf{F} = \frac{(\mathbf{n}-\boldsymbol{\nu}-\mathbf{1})\mathbf{R^2}}{(\mathbf{1}-\mathbf{R^2})\boldsymbol{\nu}} = \frac{\boldsymbol{ESS}}{\boldsymbol{P}} \frac{\boldsymbol{n}-\boldsymbol{p}-\mathbf{1}}{\boldsymbol{RSS}} \quad (3)$$

In the above equation R^2 is the coefficient of determination, n is the number of data points, and ν represents the degrees of freedom. The degrees of freedom can be determined by subtracting one from the number of variables in the regression equation.[32]

The formula compares the amount of variability between datasets to the amount of variability within datasets.

7.4. Standard Deviation (S)

Standard deviation (S) is a statistical measure of the spread or uncertainty around the mean. It is defined by the equation:

$$\mathbf{S} = \sqrt{\frac{\sum_{i=1}^{n}(y_{i,cal}-\bar{y})^2}{n-p-1}} = s = \sqrt{\frac{RSS}{n-p-1}} \quad (4)$$

Where, $y_{i,cal}$ is each individual data point, $\bar{y}$ is the mean of the data set, *n* is the number of data points, and *p* is the number of independent variables.

If many data points are clustered tightly around the mean, then the standard deviation is small. However, if data points are scattered widely around the mean, then the standard deviation is large. A useful property of standard deviation is that, unlike variance, it is expressed in the same units as the data.

We can define some parameters used in the regression:

- Total sum of squares: $TSS = \sum(Y_{i,obs} - \bar{Y})^2$ (5)
- Regression sum of squares: $RSS = \sum(Y_{i,obs} - Y_{i,cal})^2$ (6)
- Error sum of squares: $ESS = \sum(Y_{i,cal} - \bar{Y})^2$ (7)
- Regression identity: $TSS = ESS + RSS$ (8)

7.5. Variance (R)

The variance is the average of the squared standard deviation from the mean. Sums of

squares are directly related to variances.

$$\mathbf{r} = \sqrt{\frac{\sum_{\mathbf{i=1}}^{\mathbf{n}} \left(\mathbf{y_{i,obs}} - \bar{y}\right)^2}{\boldsymbol{n-1}}} \qquad (9)$$

7.6. Quality Factor (Q)

Quality factor is calculated by equation:

$$\boldsymbol{Q} = \frac{\boldsymbol{r}}{\boldsymbol{s}} \qquad (10)$$

Where r is variance and S is standard deviation. Over fitting and chance correlation, due to excess number of descriptors, can be detected by Q value. Positive value for this QSAR model suggests its high predictive power and lack of over fitting.[33]

8. Analysis of Variance (ANOVA)

Analysis of variance is generally used with linear regression to assess model selection. When selecting the best model, we seek to strike a balance between goodness of fit and parsimony.

Analysis of variance (ANOVA) is a method for decomposing variance in a measured out-come in to variance that can be explained, such as by a regression model or an experimental treatment assignment, and variance which cannot be explained, which is often attributable to random error. Using this decomposition into component sums of squares, certain test statistics can be calculated that can be used to describe the data or even justify model selection.

Table V.2: Table of Analysis of variance (ANOVA).

Source	Degrees of freedom (df)	Sum of Squares (SS)	Mean Squared Error (MS)	F
Regression	*p*	$RSS = \sum(Y_{i,obs} - Y_{i,cal})^2$	$RMS = \frac{RSS}{P}$	$F = \frac{ESS}{P}\frac{n-p-1}{RSS}$
Error	*n - p - 1*	$ESS = \sum(Y_{i,cal} - \bar{Y})^2$	$EMS = \frac{ESS}{n-P-1}$	
Total	*n - 1*	$TSS = \sum(Y_{i,obs} - \bar{Y})^2$		

The degrees of freedom for the regression is the number of parameters in the regression equation. The degrees of freedom for error is $n-p-1$. Finally, the total number of degrees of freedom is defined as $df_{regression} + df_{error}$. The column MS refers to the mean squared error, which is defined as SS/df for each row in the table V.2.

9. Validation of QSAR Models

The predictive powers of the equations were validated by leave–one–out (LOO) cross–validation method [34–47, 48], cross-validation is a practical and reliable method for testing the significance of a model. Hence, to validate the final models generated individually for different activities / properties, leave one-out method is used to do cross-validation. The leave-one-out method consists of developing a number of models with one compound omitted at the time after developing each model. The omitted sample data are predicted and the difference between observed and predicted values (activities) is calculated. The predictive ability of the model is quantified in terms of the corresponding leave-one-out cross-validated parameters. The cross-validated parameters often used being PRESS (predicted residual sum of squares), SSY (sum of the squares of the response value), R^2_{CV} (overall predictive ability), S_{PRESS} or S_{CV} (uncertainty of prediction), and PSE or S_{pred} (predictive square error). These parameters are defined as below:

$$\boldsymbol{PRESS = \sum_y (y_{i,pred} - y_{i,obs})^2} \qquad \textbf{(11)}$$

$$\boldsymbol{SSY = \sum_y (y_{i,obs} - \bar{y})^2} \qquad \textbf{(12)}$$

$$R^2_{CV} = Q^2 = 1.0 - \frac{\sum_{i=1}^{n}(y_{i,obs} - y_{i,pred})^2}{\sum_{i=1}^{n}(y_{i,obs} - \bar{y})^2} = 1 - \frac{PRESS}{SSY} \quad (13)$$

$$S_{PRESS} = S_{CV} = \sqrt{\frac{\sum_{i=1}^{n}(y_{i,obs} - y_{i,pred})^2}{n-p-1}} = \sqrt{\frac{\text{PRESS}}{n-p-1}} \quad (14)$$

$$PSE = S_{pred} = \sqrt{\frac{\sum_{i=1}^{n}(y_{i,obs} - y_{i,pred})^2}{n}} = \sqrt{\frac{\text{PRESS}}{\text{n}}} \quad (15)$$

$$R^2_{adj} = (1 - r^2)\left(\frac{n-1}{n-p-1}\right) \quad (16)$$

$$PE = 0.6745\,(1 - r^2)/\sqrt{n} \quad (17)$$

Here, $y_{i,obs}$ and $y_{i,cal}$ are the experimental (observed) and predictive (calculated) values of the activity respectively. $\bar{y}$ is the mean value of $y_{i,obs}$. n is the number of compounds used, p is the number of parameters (descriptors) used in the model. For a reliable model, the R^2_{CV} (or q^2) values should be >0.6. The model is considered to be excellent, if R^2_{CV} (or q^2) is >0.9. The performance of the model (its predictive ability or predictive power) can be given by PSE (or S_{pred}).

The S_{PRESS} as well as PSE are good parameters to be used for discussing the uncertainty in prediction. The lower the value of these parameters, the better will be the predictive ability of the model.

It is argued that PRESS is a good estimate of the real predictive error of the model. If PRESS is smaller than SSY, the model predicts better than chance and can be considered statistically significant. The ratio PRESS/SSY can be used to calculate approximate confidence intervals of prediction of new observations (compounds).

10. Observations With Large Influence on The Regression Model, Outliers

Outliers are observations that are not well described by the regression model (have large residuals). The presence of outliers can seriously bias the regression results by greatly influencing the values of the regression coefficients. However, defining an observation as an outlier is subjective, taking into account specific

experimental considerations. [20]

However, generally observations with high residuals (usually higher than ±2 times standard error) are considered as outliers.

Studentised residuals (residuals divided by their standard errors) can also be used to identify outliers. According to a method developed by Tenekedjiev and Radojnowa (2001) each observation is excluded once from the data set and its studentised residual is calculated from a regression model of the remaining observations. After testing the whole sample, all the observations whose studentised residuals do not lie within the calculated confidence interval corresponding to a chosen significance level are rejected. This procedure (representing a single loop) is repeated until either a predetermined number of loops over all the observations are executed, or some loop does not reject any outliers (which is often the second one) [49].

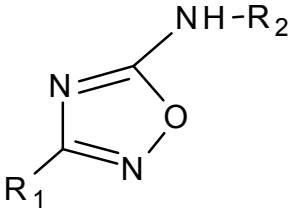
Outliers can be present for different reasons: errors in the measured variable values, extreme values for one or more of the variables, different causality for the value of the dependent variable for the given observation. In some cases, transformations of the data can be applied, or additional independent variables can be included into the model to correctly describe the outliers. Also, separate models excluding outliers can be developed.[20]

11. Limitation in the Fundamental Principle of the QSAR

Any QSAR model will produce some degree of error. This is partially due to the inherent limitation to predict a biological activity solely based on the chemical structure. One can argue from the principles of chemistry that the molecular structure of a chemical is key to understanding its physicochemical properties and ultimately its biological activity and the influence on organisms. Since both molecular structure and physico-chemical properties are associated with the chemical itself, the relationship between structure and physicochemical properties should be apparent and, therefore, more accessible using the QSARs.

In contrast, the biological activity of a chemical is an induced response that is influenced by numerous factors dictated by the levels of biological complexity of the system under investigation. [50]

Table V.3: Chemical structures of the molecules under study.



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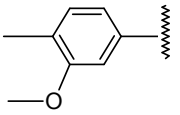
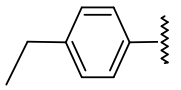
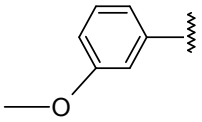
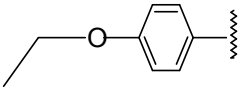
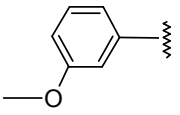
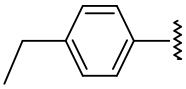
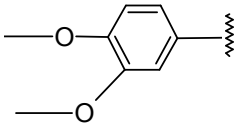
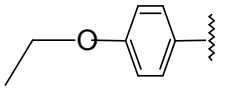
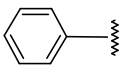
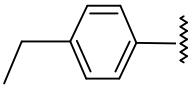
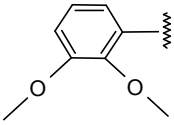
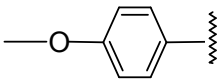
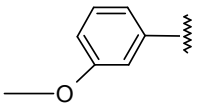
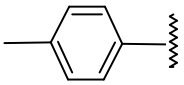
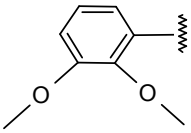
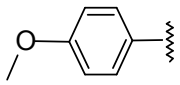
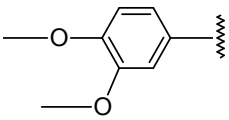
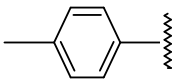
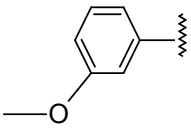
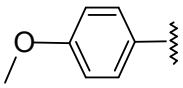
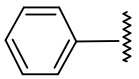
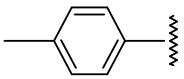
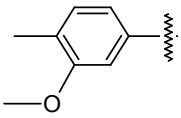
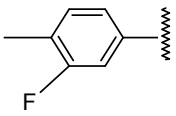
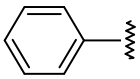
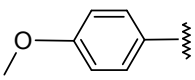
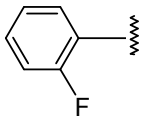
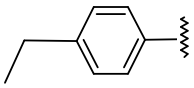
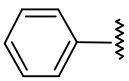
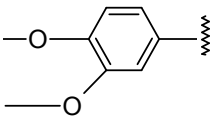
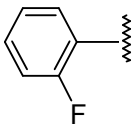
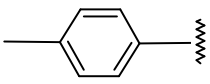
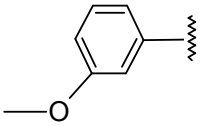
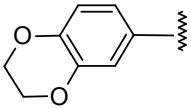
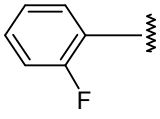
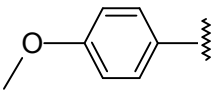
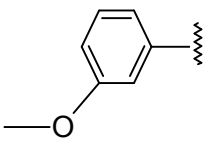
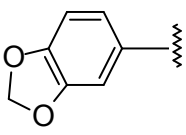
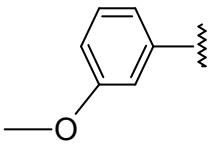
1			**11**		
2			**12**		
3			**13**		
4			**14**		
5			**15**		
6			**16**		
7			**17**		
8			**18**		
9			**19**		
10			**20**		

12. Results and Discussion

12.1. Data Set

In the present study a data set of 3-(aryl)-N-(aryl)-1, 2, 4-oxadiazol-5-amines as anti-proliferative agents as potential treatments for prostate cancer (20 molecules) presented in Table V.3, has been taken from literature [51].

The reported IC_{50} values (μM) have been converted to the logarithmic scale [pIC_{50}], for QSAR study.

12.2. Descriptors Generation

Firstly, the twenty investigated molecules were pre-optimized by means of the Molecular Mechanics, with Force Field (MM+) included in HyperChem version 8.03 package. [52] After that, the resulted minimized structures were further refined using the semi-empirical RM1 Hamiltonian implemented also in HyperChem. We chose a gradient norm limit of 0.01kcal/Å for the geometry optimization.

The QSAR properties module from HyperChem (8.03) was used to calculate: molar polarizability (Pol), the molar refractivity (MR), partition coefficient octanol/water (log P), molar volume (MV), Surface area grid (SAG) and molar weight (MW). RM1 optimized geometry was used to calculate heat of formation $\left(\Delta H^{\circ}_{\mathrm{form}}\right)$. (Table V.4)

The Quantum Chemical descriptors: dipole moment (DM), Energy of frontier orbital's E_{HOMO} and E_{LUMO} and atomic net charges (qO1, qN2, qC3, qN4, qC5 and qN6) were computed using Gaussian 09W software [53] by using DFT/B3LYP with 6-31G basis set (Table V.4).

Table V.4: Values of molecular descriptors used in the regression analysis

Comp. Number	IC_{50}	Chemical descriptors							
		MW	**ΔH°_{form}**	**E_{HOMO}**	**E_{LUMO}**	**MD**	**Pol**	**MR**	**MV**
1	6.066	309.368	859.433	-0.213	-0.044	3.985	34.823	96.903	946.716
2	5.796	295.341	833.390	-0.214	-0.045	2.055	32.988	92.621	898.125
3	6.000	265.315	745.592	-0.216	-0.047	2.701	30.516	86.246	819.945
4	6.000	281.314	803.329	-0.214	-0.045	2.101	31.153	88.020	844.235
5	5.569	311.340	890.633	-0.210	-0.043	5.213	33.625	94.394	922.536
6	6.194	251.288	715.528	-0.216	-0.047	2.769	28.681	81.645	767.588
7	7.076	267.287	777.173	-0.207	-0.046	1.514	29.318	83.738	792.283
8	5.569	297.313	864.871	-0.204	-0.045	5.079	31.790	90.112	870.408
9	6.032	325.324	973.291	-0.205	-0.044	1.225	33.488	94.518	906.639
10	5.745	311.297	945.743	-0.206	-0.047	2.187	31.653	89.328	861.669
11	5.678	311.340	894.236	-0.204	-0.044	0.653	33.625	94.860	928.250
12	6.041	341.366	983.068	-0.202	-0.040	1.606	36.097	101.235	1006.009
13	5.824	341.366	982.574	-0.203	-0.039	3.324	36.097	101.235	1005.222
14	6.420	327.340	951.490	-0.203	-0.038	3.072	34.262	96.487	947.696
15	7.538	297.313	863.149	-0.205	-0.044	0.673	31.790	90.112	871.702
16	5.658	313.331	729.633	-0.218	-0.048	5.246	32.897	92.430	902.520
17	5.585	283.305	648.857	-0.216	-0.055	1.094	30.425	86.374	830.992
18	5.796	269.278	619.418	-0.216	-0.055	1.133	28.690	81.773	775.091
19	6.260	285.278	681.074	-0.206	-0.054	0.929	29.227	83.866	799.950
20	6.018	331.758	640.078	-0.213	-0.048	2.690	33.718	94.829	901.338

Table V.4. Continued

Comp. Number	LogP	SAG	qO1	qN2	qC3	qN4	qC5	qN6
1	2.410	576.813	-0.446	-0.155	0.168	-0.426	0.731	-0.792
2	2.256	551.188	-0.445	-0.154	0.168	-0.416	0.729	-0.442
3	3.249	507.531	-0.445	-0.154	0.173	-0.421	0.729	-0.792
4	1.860	523.172	-0.445	-0.154	0.168	-0.416	0.729	-0.792
5	0.867	565.367	-0.446	-0.156	0.167	-0.428	0.732	-0.792
6	2.853	475.826	-0.445	-0.154	0.173	-0.421	0.729	-0.792

7	1.706	493.789	-0.448	-0.155	0.173	-0.421	0.729	-0.792
8	0.713	533.353	-0.444	-0.152	0.173	-0.422	0.730	-0.797
9	-0.458	557.520	-0.446	-0.152	0.168	-0.417	0.730	-0.797
10	-0.090	527.502	-0.449	-0.150	0.168	-0.416	0.732	-0.798
11	1.056	575.730	-0.448	-0.155	0.168	-0.417	0.728	-0.793
12	0.062	616.681	-0.449	-0.161	0.165	-0.418	0.729	-0.793
13	0.062	611.168	-0.450	-0.154	0.165	-0.425	0.730	-0.793
14	-0.280	575.640	-0.450	-0.153	0.162	-0.424	0.730	-0.793
15	0.713	537.934	-0.448	-0.155	0.168	-0.417	0.728	-0.793
16	1.412	551.571	-0.447	-0.150	0.168	-0.424	0.734	-0.796
17	2.648	513.490	-0.442	-0.149	0.184	-0.386	0.718	-0.792
18	2.252	483.241	-0.442	-0.150	0.185	-0.386	0.719	-0.792
19	1.105	496.360	-0.445	-0.152	0.185	-0.386	0.718	-0.793
20	0.491	550.417	-0.448	-0.149	0.168	-0.414	0.730	-0.794

12.3. Regression Analysis

A relationship between independent and dependent variables (physicochemical descriptors and biological activities, respectively) were determined statistically using regression analysis. In the present work, Multiple Linear Regression MLR analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows. [54]

12.4. Quantitative Structure-Activity Relationships Studies

In the present study we tried to develop best QSAR model to explain the correlations between the physicochemical parameters and the biological activities IC_{50} values of 1,2,4-oxadiazol-5-amine derivatives. Among several QSAR equations the best QSAR models were selected on the basis of various statistical parameters such as :

correlation coefficient R which measures the degree of line association between two variables.

- We have strong relationship if $R \in [0.8, 1]$ or $R \in [-1, -0.8]$;

- moderate relationship if R ∈[0.5, 0.8] or R∈[-0.8, -0.5]; and
- weak relationship if R ∈[-0.5, 0.5] ,

squared correlation coefficient (R^2 > 0.6) which is relative measure of quality of fit. Standard error of estimate (SEE < 0.3) representing absolute measure of quality of fit, Fischer's value (F), F is the Fisher ratio, reflects the ratio of the variance explained by the model and the variance due to the error in the regression. High values of the F–test indicate that the model is statistically significant. [55]

After multiple regression analysis on the software SPSS the best statistically significant correlations generated along with pertinent statistical parameters are given below (model 1):

Log ($1/IC_{50}$) = 51,72 - 1,185 logP + 2,694 POL - 0,046 MV - 0.024 SAG - 0,119 MW - 289,923 qO1 - 232,918 qC5. (model 1)

n = 20 ; R = 0,847 ; R^2 = 0,717 ; SEE = 0,333 ; S = 0,498 ; F = 4,349 ; Q = 2,543

Table V.5. Observed vs. calculated activity (by model 1)of 1, 2, 4-oxadiazol-5-amine derivatives

Number	pIC_{50} Obs.	pIC_{50} pred.	Residue
1	6.066	5.802	0.263
2	5.796	5.864	-0.068
3	6.000	6.142	-0.142
4	6.000	6.173	-0.173
5	5.569	5.427	0.142
6	6.194	6.453	-0.259
7	7.076	6.959	0.116
8	5.569	5.524	0.045
9	6.032	6.183	-0.152
10	5.745	5.762	-0.017
11	5.678	6.009	-0.332
12	6.041	6.004	0.037

13	5.824	5.945	-0.122
14	6.420	6.724	-0.304
15	7.538	6.629	0.908
16	5.658	5.661	-0.004
17	5.585	5.485	0.100
18	5.796	5.741	0.055
19	6.260	6.413	-0.153
20	6.018	5.956	0.0611

We can see from Table V.5 that compound 15 has residual value (0.908) is higher than twice the standard error of estimate (0,666), therefore , The previous model has one outlier's (compound 15).

This outlier has been removed from the data set (number of molecules became (n = 19)), and the multiple regression analysis has been repeated by the software SPSS, thus, We got another model highly significant (model 2)

Log ($1/IC_{50}$) = -10,926 - 1,070 logP + 2,608 POL - 0,045 MV - 0.02 SAG - 0,109 MW - 284,398 qO1 + 54,884 qC3 -162,999 qC5. (model 2)

n = 19 ; R = 0,952 ; R^2 = 0,906 ; SEE = 0,149 ; S = 0,362; F = 12,066 ; Q = 2,629

Table V.6: Observed vs. calculated activity of 1, 2, 4-oxadiazol-5-amine derivatives

Number	pIC_{50} Obs.	pIC_{50} pred.	Residue
1	6.066	5.975	0.090
2	5.796	5.747	0.049
3	6.000	6.165	-0.165
4	6.000	5.908	0.092
5	5.569	5.490	0.078
6	6.194	6.334	-0.140
7	7.076	6.846	0.229
8	5.569	5.581	-0.013
9	6.032	6.106	-0.075

10	5.745	5.727	0.018
11	5.678	5.911	-0.233
12	6.041	5.939	0.102
13	5.824	5.909	-0.086
14	6.420	6.395	0.025
15	5.658	5.665	-0.008
16	5.585	5.521	0.063
17	5.796	5.726	0.069
18	6.260	6.356	-0.097
19	6.018	6.018	0.000

We can see from the Table V.6 that all residual values less than twice of standard error of estimate (0,666) therefore, there aren't any an outlier.

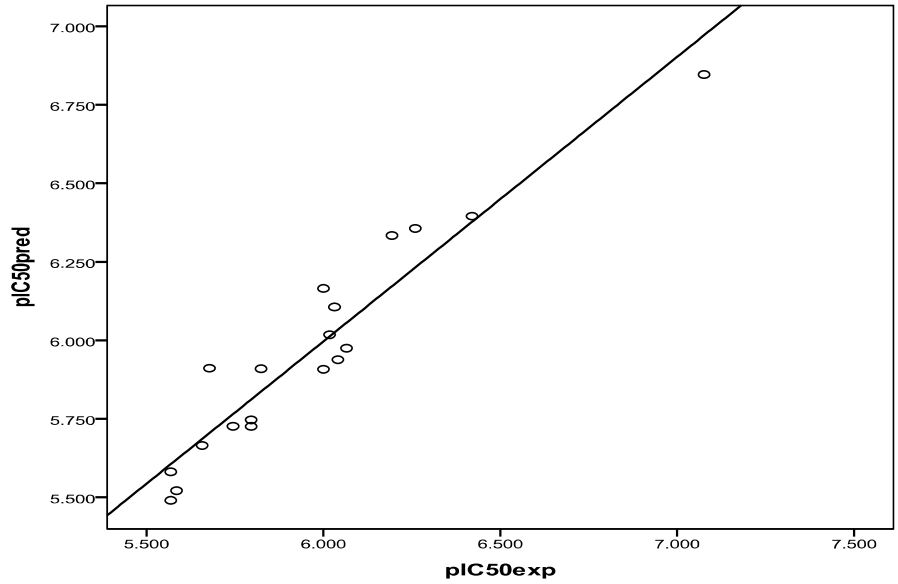


Figure V.2: Scatter Plot between the Observed and Predicted Activities of Model 2

Figure V.2 shows the plot of linear regression predicted versus experimental values of biological activity of 1, 2, 4-oxadiazol-5-amine derivatives outlined above, including also the 19 compounds of the evaluation set. The plot for model 2 shows to be more convenient with $R^2 = 0.906$. The evaluation set has a good distribution along the range of values of the training set, and none of the 19 compounds was detected as an outlier.

12.4.1. Interpretation of the Model 2 (Most Significant)

Model 2 shows a good correlation coefficient (R) of 0.952 between descriptors (Log P, POL, MV, SAG, MW, qO1, qC3 and qC5) and the anti-proliferative activity. Squared correlation coefficient (R^2) of 0.906 explains 90.6% variance in biological activity. The R^2 value is above 0.8, which suggest that a good percentage of the total variance in biological activity is accounted by the model. Low value of standard error of estimate (< 0.3) indicates the accuracy of the statistical fit. All the values of the t-statistic are significant which confirms the significance of each descriptor.

The calculated F value for the generated QSAR model exceed the tabulated F value by large margin as desired for a meaningful regression. Furthermore, the calculated F value also determines a confidence limit superior to 95% for this model. The positive value of quality factor (Q) for QSAR model 2 suggests its high predictive power and lack of over fitting, low standard deviation of the model demonstrates accuracy of the model.

The correlation matrix for pIC50 and selected descriptors to build the 2D-QSAR model is shown in Table V.7. The parameters used in the Model 2 are almost Independent which can be seen from the correlation matrix.

In model 2, the negative coefficient of logP indicates that the substituents which increase solubility in water will lead to increased activity. Which relates to the hydrophobicity of the molecule, suggested that a decrease in the lipophilicity might increase the activity, This corresponds to the absence of hydrophobic binding sites in the 1, 2, 4-oxadiazole-5-amine derivatives.

It can be observed that high coefficients of atomic charges on atoms O1, C3 and C5 (qO1, qC3 and qC5 respectively), thus, high negative and high positive charges for O1 and C3 respectively and low positive charge for C5 lead to increasing anti-proliferative activity.

The charges allowed a physical explanation and electronic molecular properties contributing to anti-proliferative potency as the electronic character related directly to the electron distribution of interacting molecule at the site active.

Table V.7: Correlation Matrix for Model 2

	log(1/IC50)	LogP	Pol	MV	SAG	MW	qO1	qC3	qC5
log(1/IC50)	**1.000**								
LogP	**0.008**	**1.000**							
Pol	**-0.234**	**-0.584**	**1.000**						
MV	**-0.245**	**-0.602**	**0.993**	**1.000**					
SAG	**-0.140**	**-0.568**	**0.897**	**0.902**	**1.000**				
MW	**-0.232**	**-0.810**	**0.915**	**0.916**	**0.802**	**1.000**			
qO1	**-0.299**	**0.660**	**-0.660**	**-0.664**	**-0.575**	**-0.678**	**1.000**		
qC3	**-0.019**	**0.515**	**-0.779**	**-0.749**	**-0.650**	**-0.654**	**0.796**	**1.000**	
qC5	**-0.010**	**-0.327**	**0.573**	**0.525**	**0.355**	**0.436**	**-0.646**	**-0.897**	**1.000**

12.4.2. Model Validation

The last step in QSAR model development is model validation. In order to test the validity of the predictive power of selected MLR model 2, as opposed to traditional regression methods, the method of cross-validation estimates the trustworthiness of a model by predicting data. This method uses cross-validated fewer parameters: PRESS (predicted residual sum squares), SSY (sum of the squares of response value), R^2cv (overall predictive ability), adjusted R^2 and Q^2 .

The high Q^2 value observed for derived QSAR model is indicative of its reliability in prediction of inhibitory activity, PSE (predictive square of error), the lowest value of PSE, the better is the predictive power which indicates that the model has excellent correlation ability and S_{PRESS} (uncertainty of prediction) which is used in deciding uncertainty of prediction.

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the models. Its value being less than SSY points out that the model predicts better than chance and can be considered statistically important. To have a dependable QSAR model, PRESS/SSY should be smaller than 0.4. [56] The indication of the performance of the model is obtained from R^2cv (the overall predictive ability).

Data presented in Table V.8 indicate that for the developed model the ratio is 0.093. Our findings of R^2cv for this QSAR model have been to be 0.906 for the second model. The high value of R^2cv and R^2adj are essential criteria for the best qualification of the QSAR models 2.

Table V.8: Cross-validation parameters.

Model	Q^2	r^2_{adj}	r^2_{cv}	PSE	S_{PRESS}	PRESS/SSY	SSY	PRESS
2	0.907	0.831	0.906	0.012	0.108	0.093	2,367	0.222

To investigate the presence of a systematic error in developing the QSAR models, the residuals of predicted values of the biological activity (log ($1/IC_{50}$) was plotted against the experimental values Table V.6, as shown in Figure V.3.

The propagation of the residuals on both sides of zero indicates that no systemic error exists, as suggested by Jalali-Heravi and Kyani. [57] It indicates that this model can be successfully applied to predict the anti-proliferative activity of this class of molecules.

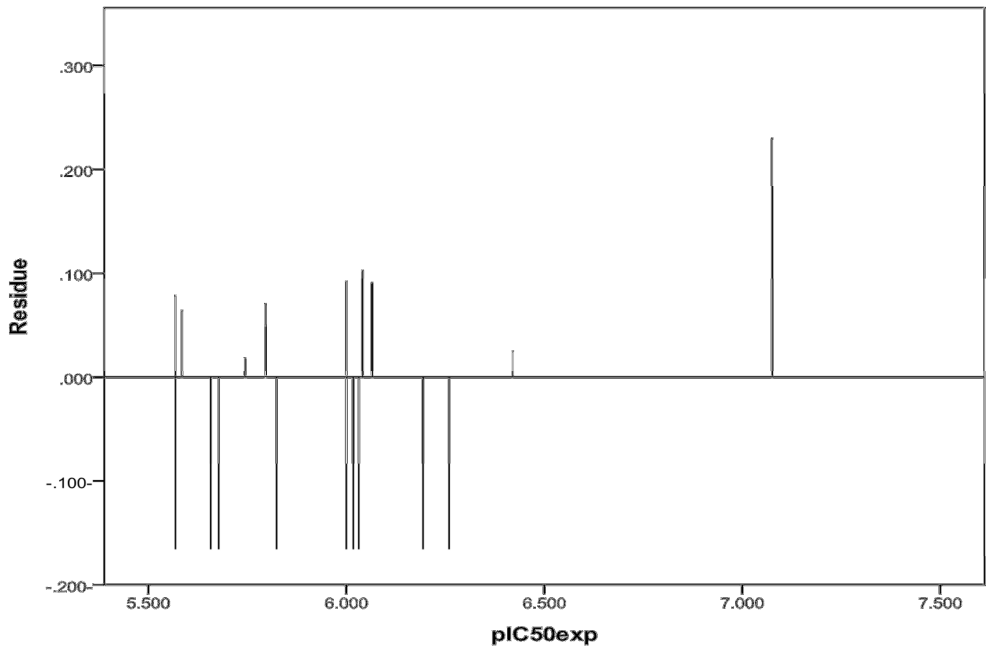


Figure V.3: Plots of the residual values against the experimentally observed

13. Conclusion

QSAR analysis was performed to find the quantitative effects of molecular structure of the compounds on their anti-proliferative activity. Various physicochemical parameters, especially partition coefficient (Log P), POL, MV, SAG, MW, qO1, qC3 and qC5 can be used successfully for modeling anti-proliferative activity of 1, 2, 4-oxadiazole-5-amine derivatives.

The Model 2 (Most significant) is used to predict inhibitory activity of the 1, 2, 4-oxadiazole-5-amine derivatives investigated and close agreement between experimental and predicted values was obtained. The low residual activity and high cross validated R^2 values (R^2_{CV}) observed indicated the predictive ability of the developed QSAR model. It indicates that this model can be successfully applied to predict the anti-proliferative activity of these classes of molecules.

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General Conclusion

General Conclusion

In this work, we applied the methods of computational chemistry on 1,2,4-oxadiazol-5-amine molecule, This study include:

- ✓ Geometric, electronic structure and substituent effects.
- ✓ Computational study of structure -property relationships (SPR) for 1,2,4-oxadiazole-5-amine derivatives
- ✓ QSAR modeling of some 3-(Aryl)-N-(Aryl)-1,2,4-Oxadiazol-5-Amine derivatives

Firstly, the results demonstrate that the structural and electronic comparison of nucleus of 1,2,4 -oxadiazole-5-amine present similar results using different calculation methods: semi-empirical method (RM1) and Ab initio and DFT quantum methods.

Next, we studied the effect of substitution on the electronic and energy parameters of basic nucleus of 1,2,4-oxadiazole-5-amine. Indeed, this study allows us to predict the chemical reactivity of 1,2,4-oxadiazole-5-amine system, for example, compound A6 has nucleophilic character (soft base). And compound B5 has electrophilic character (soft acid) compared to other compounds.

The donor substituents (methyl and ethyl) increases the energy of HOMO and slight augmentation of energy of LUMO, and for acceptor substituents (cyanide and fluorine) had caused decreasing in HOMO and LUMO energy levels.

The 5-amino-1,2,4-oxadiazole-3-carbonitrile (B1) is predicted to be the most reactive with lowest ΔE energy gap of all 1,2,4-oxadiazol-5-amine systems and this latter has the highest dipole moment thus, compound B1 more interacting with other systems strongly in solution.

Then, the results of research on the structure-property relationship (SPR) of the 1,2,4-oxadiazol-5-amine derivatives series have shown that structural units involved in the biological activity.

The compounds 3, 6 and 1 which have higher values of partition coefficient.

These lipophilic compounds penetrate in various membranes, including cellular membranes as well as tissues with high lipoid content, to arrive at the receptor site.

Compound 10 has important hydration energy leading to a better distribution in fabrics.

Molecular properties such as membrane permeability and oral bioavailability are usually associated with some basic molecular descriptors, such as log P (partition coefficient), molecular weight (MW), and the acceptors and donor for hydrogen bonding in a molecule. Using these molecular properties, Lipinski established a controversial rule for drug design.

The application of Lipinski rules on the studied 1,2,4-oxadiazol-5-amine derivatives shows that all these compounds, theoretically, will not have problems with oral bioavailability.

Finally, Quantitative structure activity relationship (QSAR) studies were performed on a series of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines as anti-proliferative agents, multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally for the prediction of activity. The developed models were cross-validated by the 'leave one out' technique as well as by the calculation of statistical parameters.

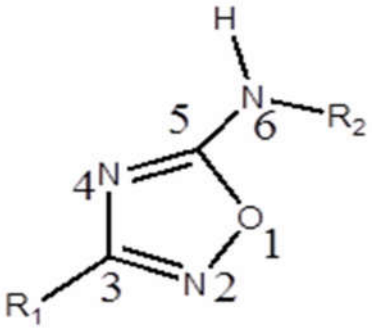
The best QSAR model i.e., model-2 (R^2=0.906, Fischer's test value F=12.066) has acceptable statistical quality and predictive potential as indicated by the value of cross validated squared correlation coefficient (q^2=0.907).

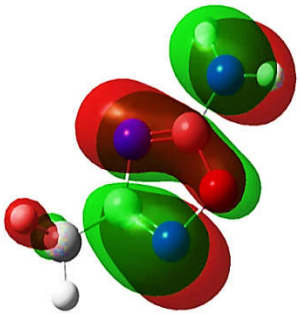
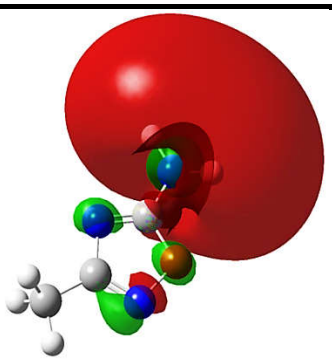
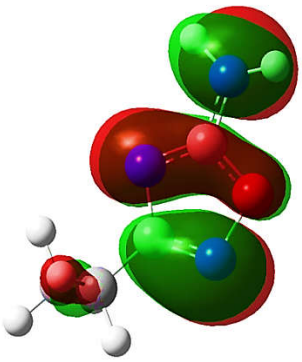
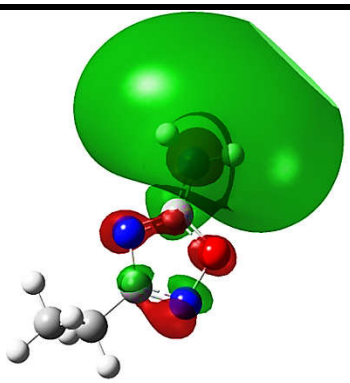
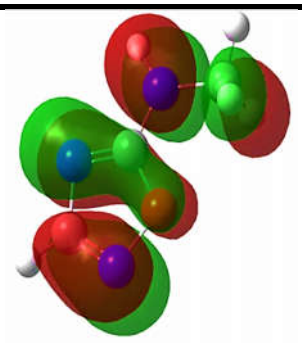
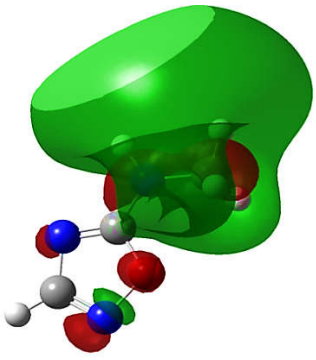
The present investigation indicates the importance of the quantum chemical descriptors, constitutional descriptors and hydrophobicity to study the anti-proliferative activity.

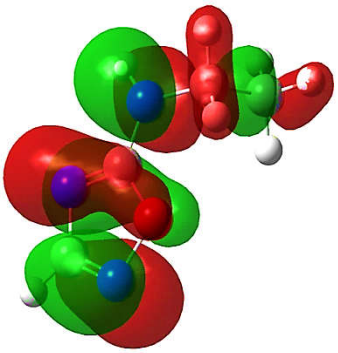
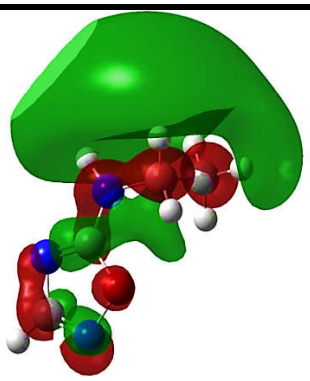
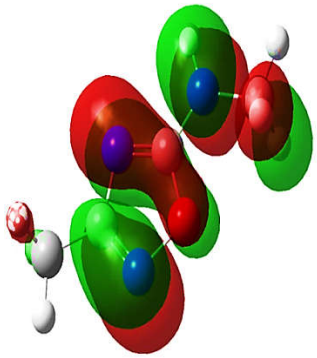
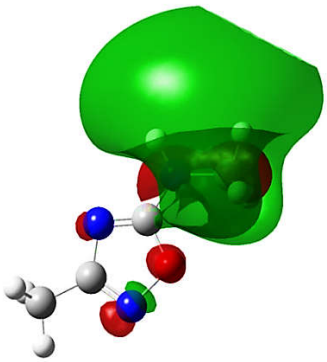
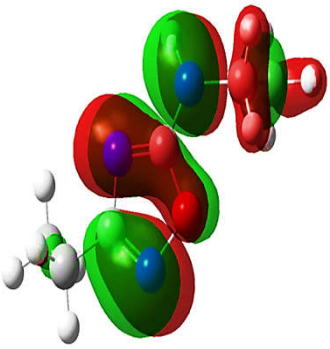
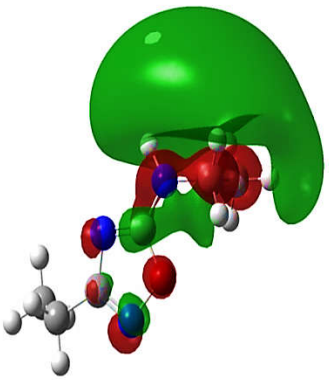
Appendix (A)

The frontier molecular orbitals HOMO and LUMO of 1,2,4-oxadiazol-5-amine derivatives

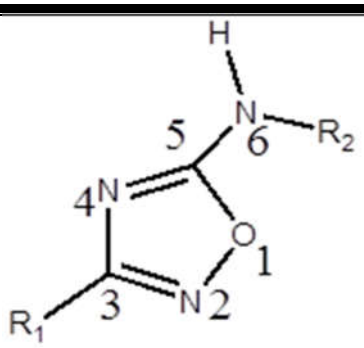
The frontier molecular orbitals HOMO and LUMO of 1,2,4-oxadiazol-5-amine derivatives (series A)

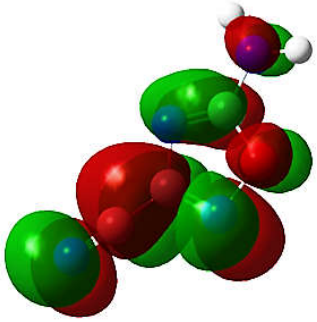
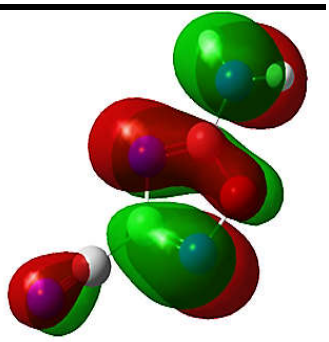
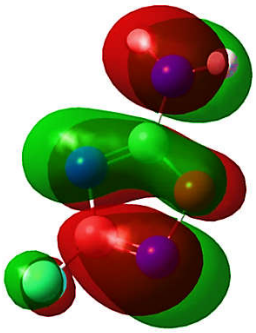
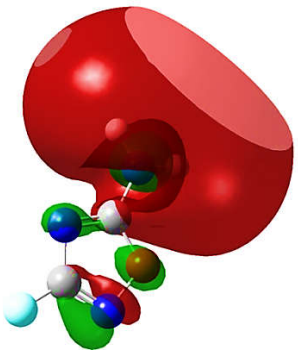
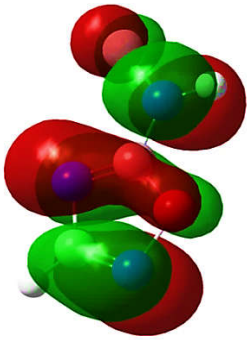
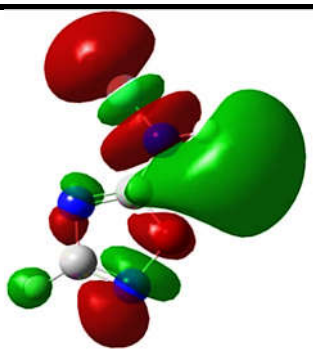


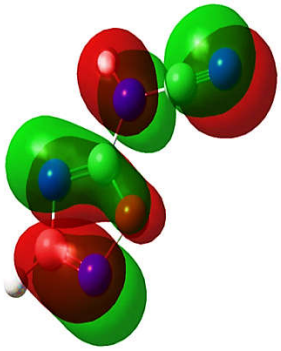
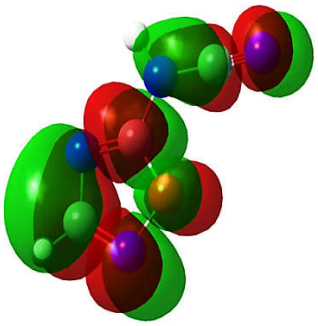
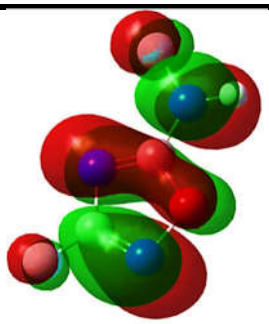
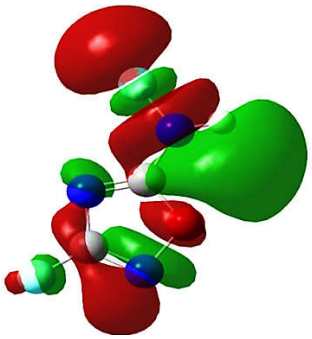
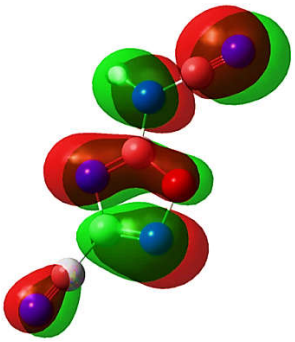
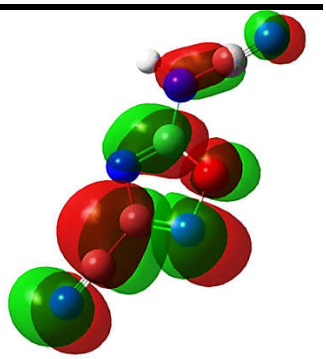
Comp.	R1	R2	HOMO	LUMO
A_1	CH_3	H		
A_2	C_2H_5	H		
A_3	H	CH_3		

A_4	H	C_2H_5		
A_5	CH_3	CH_3		
A_6	C_2H_5	C_2H_5		

The frontier molecular orbitals HOMO and LUMO of 1,2,4-oxadiazol-5-amine derivatives (series B)



Comp.	R1	R2	HOMO	LUMO
B_1	CN	H		
B_2	H	F		
B_3	H	F		

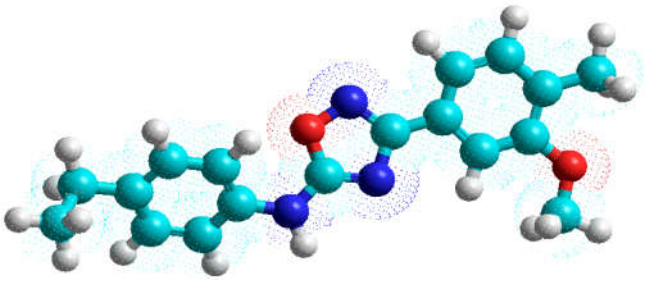
B_4	H	CN		
B_5	F	F		
B_6	CN	CN		

Appendix (B)

3D Structure and SMILE notation of 1,2,4-oxadiazole-5-amine derivatives

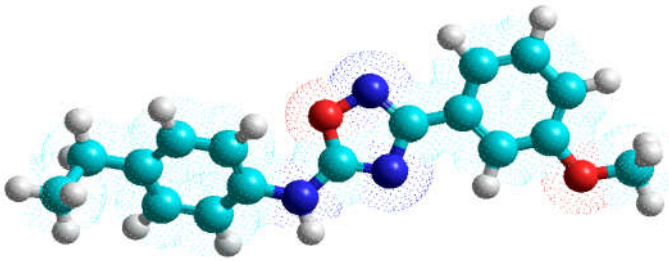
(HyperChem 8.03)

Compound 1



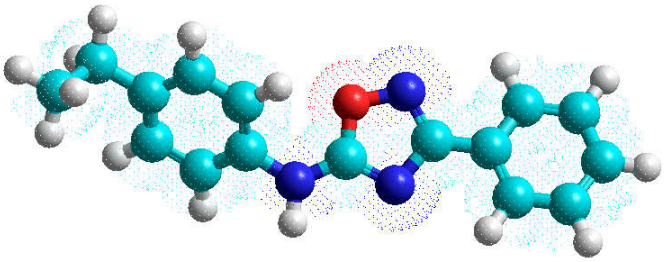
CCc1ccc(cc1)Nc2nc(no2)c3cc(OC)c(C)cc3

Compound 2



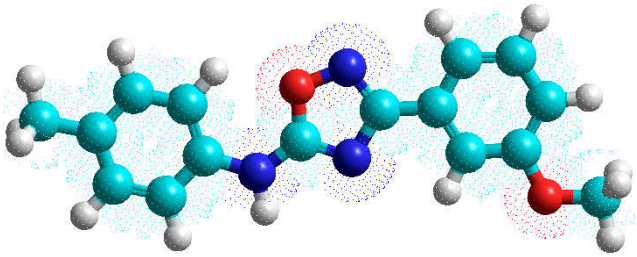
CCc1ccc(cc1)Nc2nc(no2)c3cc(ccc3)OC

Compound 3



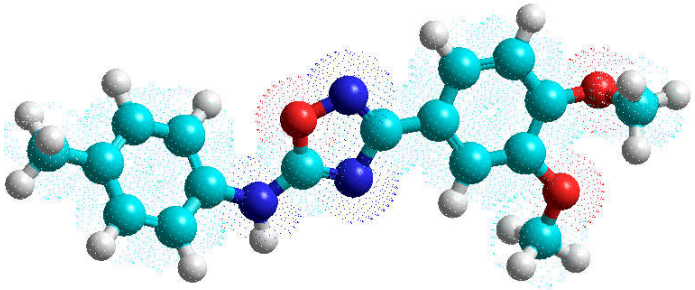
CCc1ccc(cc1)Nc2nc(no2)c3ccccc3

Compound 4



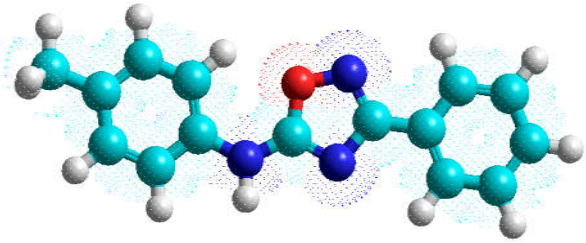
Cc1ccc(cc1)Nc2nc(no2)c3cc(ccc3)OC

Compound 5



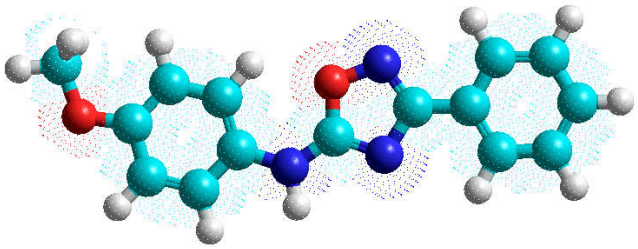
Cc1ccc(cc1)Nc2nc(no2)c3cc(OC)c(OC)cc3

Compound 6



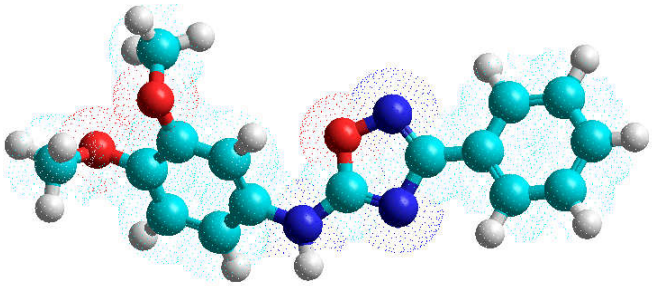
Cc1ccc(cc1)Nc2nc(no2)c3ccccc3

Compound 7



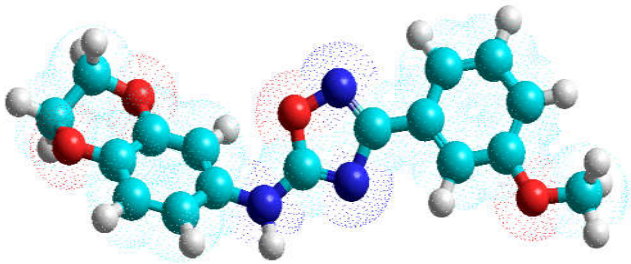
COc1ccc(cc1)Nc2nc(no2)c3ccccc3

Compound 8



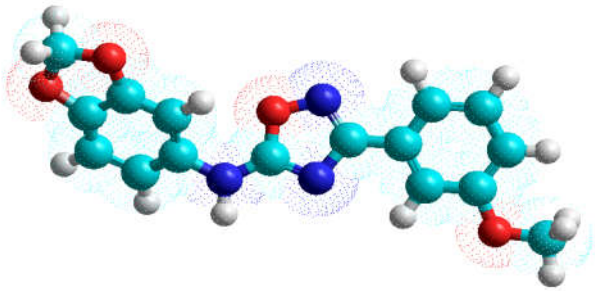
COc1ccc(cc1OC)Nc2nc(no2)c3ccccc3

Compound 9



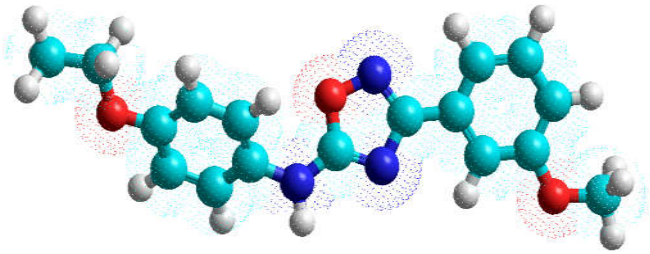
COc1cccc(c1)c2nc(on2)Nc3ccc4OCCOc4c3

Compound 10



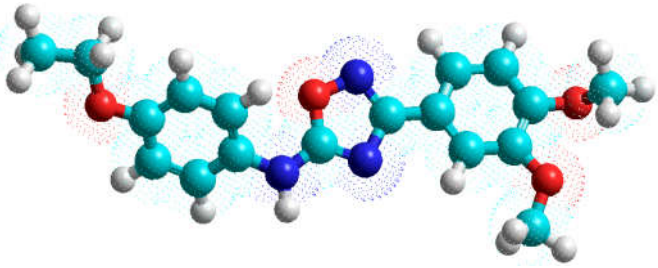
COc1cccc(c1)c2nc(on2)Nc3ccc4OCOc4c3

Compound 11



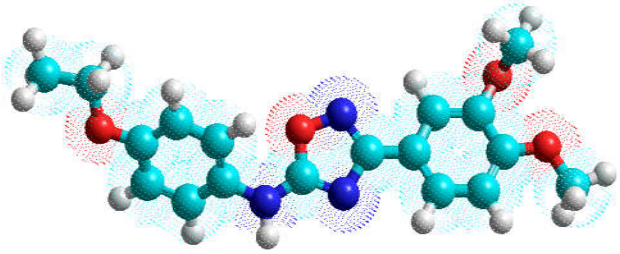
CCOc1ccc(cc1)Nc2nc(no2)c3cc(ccc3)OC

Compound 12



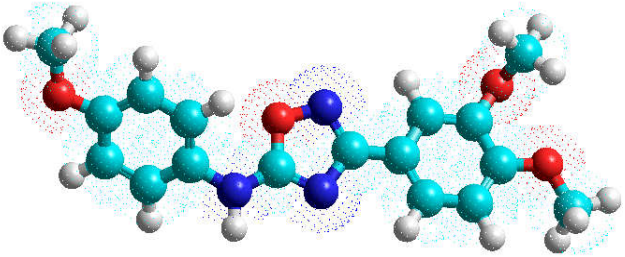
CCOc1ccc(cc1)Nc2nc(no2)c3cc(OC)c(OC)cc3

Compound 13



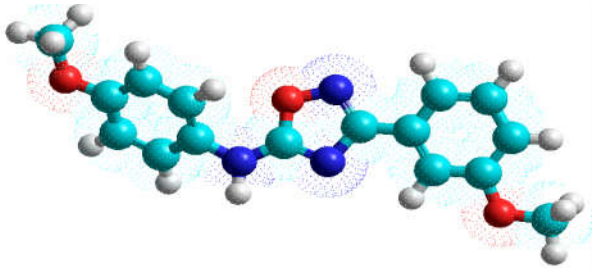
CCOc1ccc(cc1)Nc2nc(no2)c3cc(OC)c(OC)cc3

Compound 14



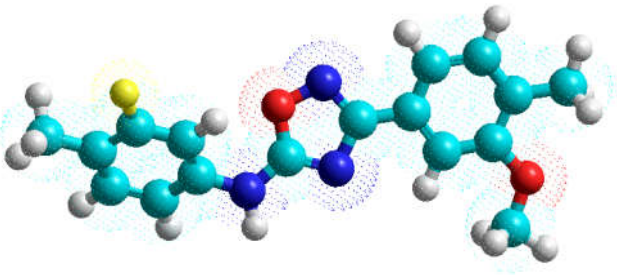
COc1ccc(cc1)Nc2nc(no2)c3cc(OC)c(OC)cc3

Compound 15



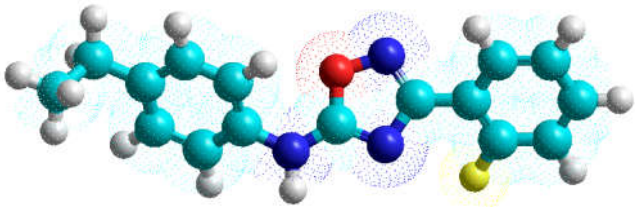
COc1ccc(cc1)Nc2nc(no2)c3cc(ccc3)OC

Compound 16



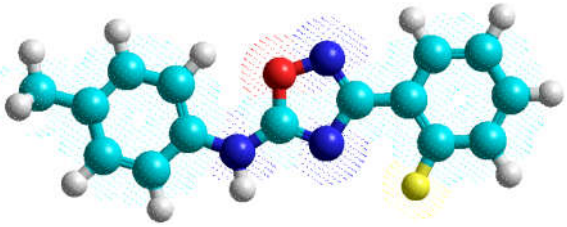
Cc1ccc(cc1F)Nc2nc(no2)c3cc(C)c(OC)cc3

Compound 17



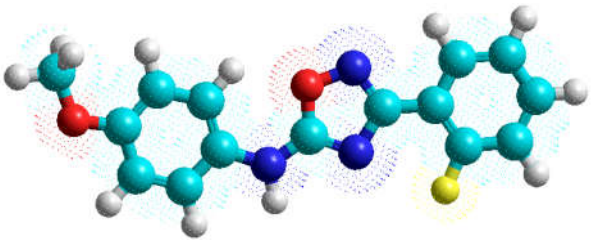
CCc1ccc(cc1)Nc2nc(no2)c3ccccc3F

Compound 18



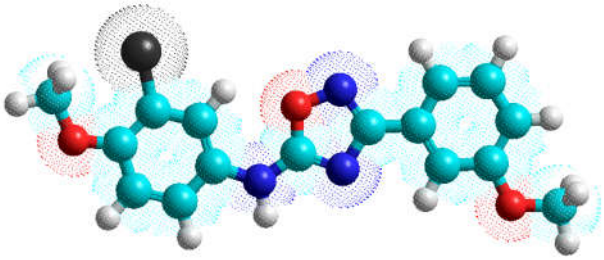
Cc1ccc(cc1)Nc2nc(no2)c3ccccc3F

Compound 19



COc1ccc(cc1)Nc2nc(no2)c3ccccc3F

Compound 20



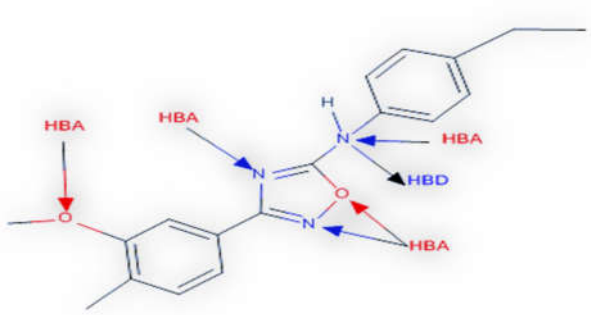
COc1ccc(cc1Cl)Nc2nc(no2)c3ccc(OC)cc3

Appendix(C)

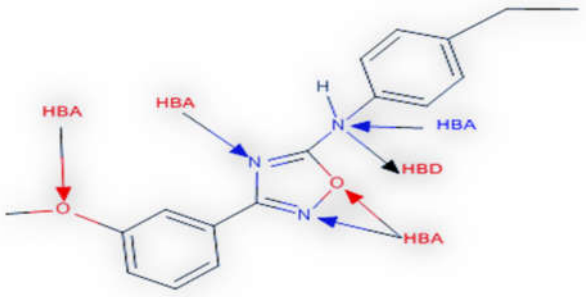
Donor and acceptor sites of

1,2,4-oxadiazole-5-amine derivatives

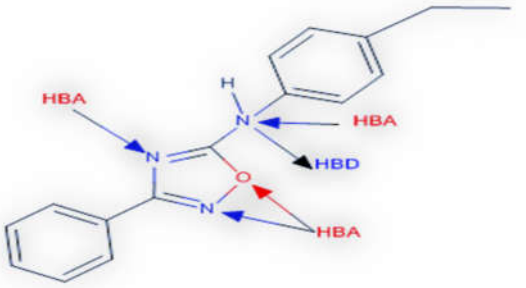
Compound 1



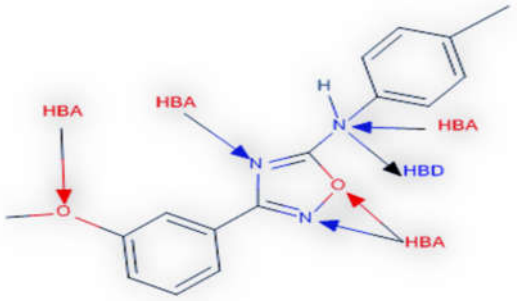
Compound 2



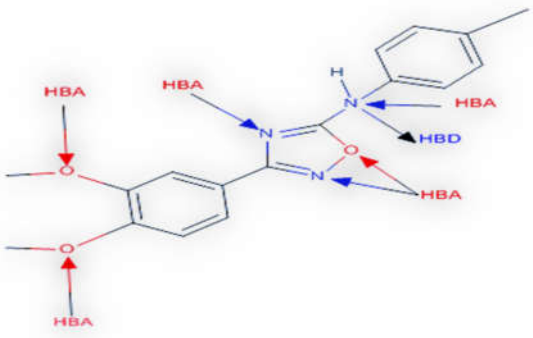
Compound 3



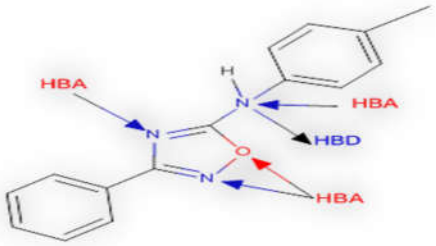
Compound 4



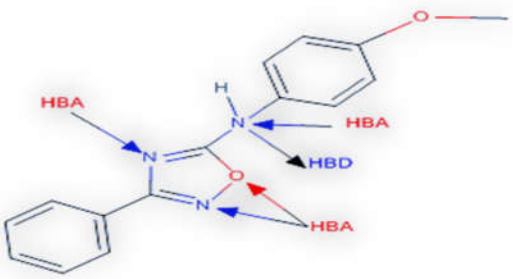
Compound 5



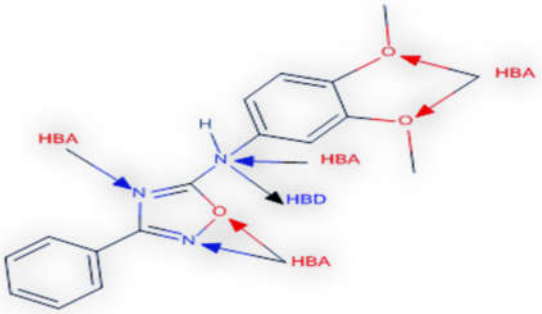
Compound 6



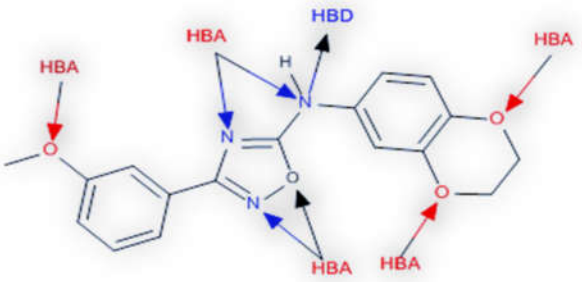
Compound 7



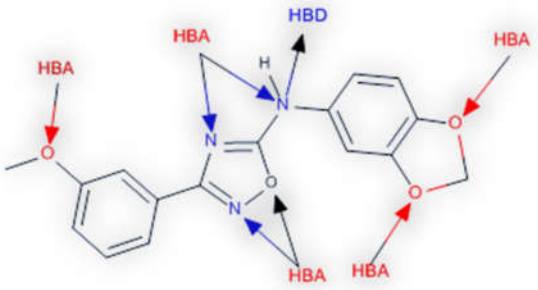
Compound 8



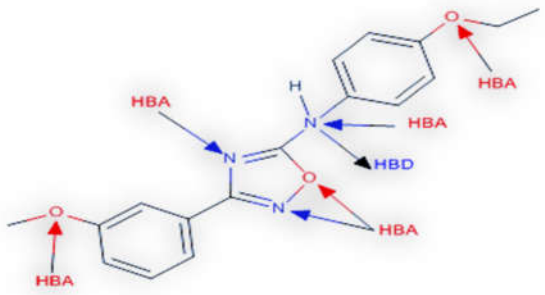
Compound 9



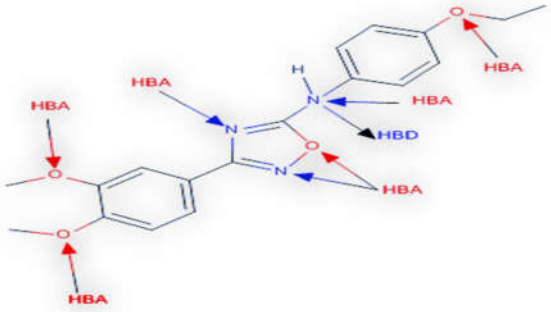
Compound 10



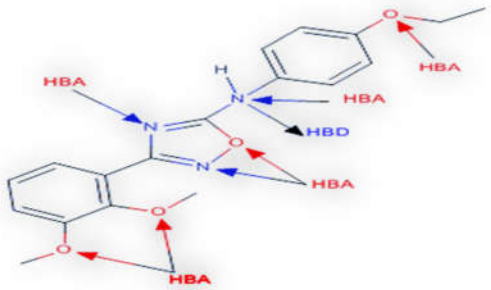
Compound 11



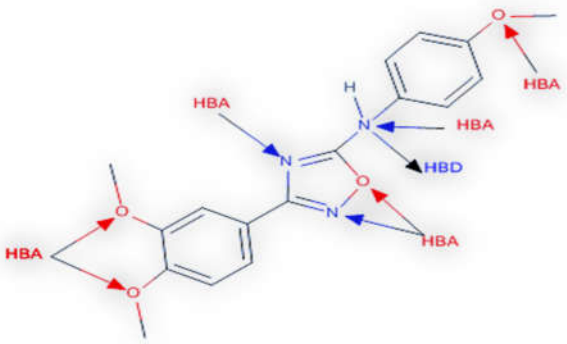
Compound 12



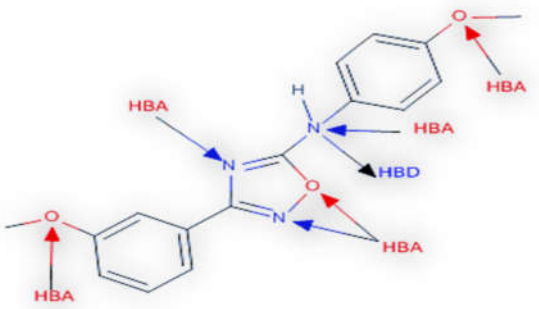
Compound 13



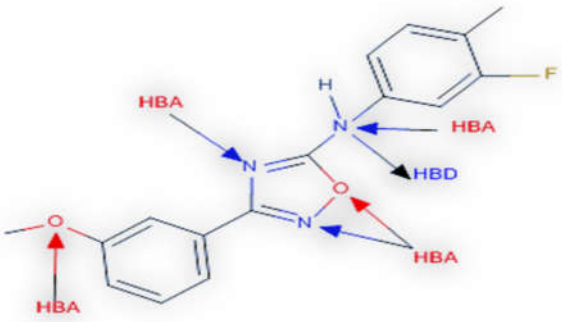
Compound 14



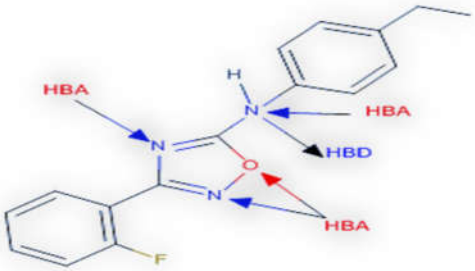
Compound 15



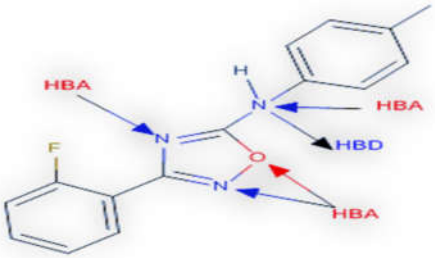
Compound 16



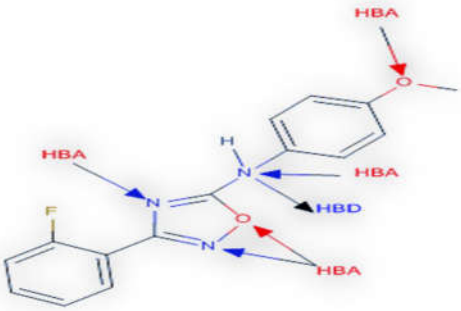
Compound 17



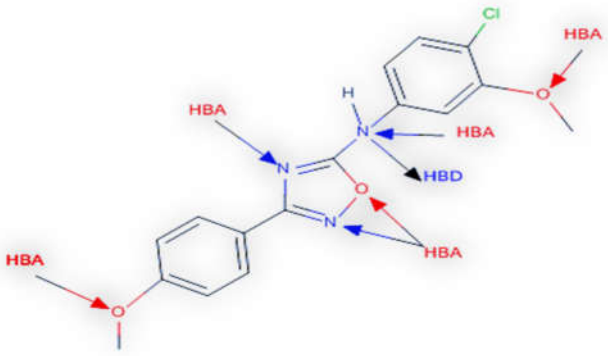
Compound 18



Compound 19



Compound 20



Appendix(D)

Table of F (Fisher-Snedecor)

ν_1= degrees of freedom for numerator

ν_1= degrees of freedom for denominator

$F_{95}(\nu_1, \nu_2)$ α=0.05

ν_2/ν_1	1	2	3	4	5	6	7	8	9	10	12	15	20	24	30	40	60	120	∞
1	161.44	199.50	215.70	224.58	230.16	233.98	236.76	238.88	240.54	241.88	243.90	245.94	248.01	249.05	250.09	251.14	252.19	253.25	254.31
2	18.512	19.000	19.164	19.246	19.296	19.329	19.353	19.371	19.384	19.395	19.412	19.429	19.445	19.454	19.462	19.470	19.479	19.487	19.495
3	10.128	9.5521	9.2766	9.1172	9.0135	8.9406	8.8867	8.8452	8.8123	8.7855	8.7446	8.7029	8.6602	8.6385	8.6166	8.5944	8.5720	8.5494	8.5264
4	7.7086	6.9443	6.5914	6.3882	6.2561	6.1631	6.0942	6.0410	5.9988	5.9644	5.9117	5.8578	5.8025	5.7744	5.7459	5.7170	5.6877	5.6581	5.6281
5	6.6079	5.7861	5.4095	5.1922	5.0503	4.9503	4.8759	4.8183	4.7725	4.7351	4.6777	4.6188	4.5581	4.5272	4.4957	4.4638	4.4314	4.3985	4.3650
6	5.9874	5.1433	4.7571	4.5337	4.3874	4.2839	4.2067	4.1468	4.0990	4.0600	3.9999	3.9381	3.8742	3.8415	3.8082	3.7743	3.7398	3.7047	3.6689
7	5.5914	4.7374	4.3468	4.1203	3.9715	3.8660	3.7870	3.7257	3.6767	3.6365	3.5747	3.5107	3.4445	3.4105	3.3758	3.3404	3.3043	3.2674	3.2298
8	5.3177	4.4590	4.0662	3.8379	3.6875	3.5806	3.5005	3.4381	3.3881	3.3472	3.2839	3.2184	3.1503	3.1152	3.0794	3.0428	3.0053	2.9669	2.9276
9	5.1174	4.2565	3.8625	3.6331	3.4817	3.3738	3.2927	3.2296	3.1789	3.1373	3.0729	3.0061	2.9365	2.9005	2.8637	2.8259	2.7872	2.7475	2.7067
10	4.9646	4.1028	3.7083	3.4780	3.3258	3.2172	3.1355	3.0717	3.0204	2.9782	2.9130	2.8450	2.7740	2.7372	2.6996	2.6609	2.6211	2.5801	2.5379
11	4.8443	3.9823	3.5874	3.3567	3.2039	3.0946	3.0123	2.9480	2.8962	2.8536	2.7876	2.7186	2.6464	2.6090	2.5705	2.5309	2.4901	2.4480	2.4045
12	4.7472	3.8853	3.4903	3.2592	3.1059	2.9961	2.9134	2.8486	2.7964	2.7534	2.6866	2.6169	2.5436	2.5055	2.4663	2.4259	2.3842	2.3410	2.2962
13	4.6672	3.8056	3.4105	3.1791	3.0254	2.9153	2.8321	2.7669	2.7144	2.6710	2.6037	2.5331	2.4589	2.4202	2.3803	2.3392	2.2966	2.2524	2.2064
14	4.6001	3.7389	3.3439	3.1122	2.9582	2.8477	2.7642	2.6987	2.6458	2.6022	2.5342	2.4630	2.3879	2.3487	2.3082	2.2664	2.2229	2.1778	2.1307
15	4.5431	3.6823	3.2874	3.0556	2.9013	2.7905	2.7066	2.6408	2.5876	2.5437	2.4753	2.4034	2.3275	2.2878	2.2468	2.2043	2.1601	2.1141	2.0658
16	4.4940	3.6337	3.2389	3.0069	2.8524	2.7413	2.6572	2.5911	2.5377	2.4935	2.4247	2.3522	2.2756	2.2354	2.1938	2.1507	2.1058	2.0589	2.0096
17	4.4513	3.5915	3.1968	2.9647	2.8100	2.6987	2.6143	2.5480	2.4943	2.4499	2.3807	2.3077	2.2304	2.1898	2.1477	2.1040	2.0584	2.0107	1.9604
18	4.4139	3.5546	3.1599	2.9277	2.7729	2.6613	2.5767	2.5102	2.4563	2.4117	2.3421	2.2686	2.1906	2.1497	2.1071	2.0629	2.0166	1.9681	1.9168
19	4.3807	3.5219	3.1274	2.8951	2.7401	2.6283	2.5435	2.4768	2.4227	2.3779	2.3080	2.2341	2.1555	2.1141	2.0712	2.0264	1.9795	1.9302	1.8780
20	4.3512	3.4928	3.0984	2.8661	2.7109	2.5990	2.5140	2.4471	2.3928	2.3479	2.2776	2.2033	2.1242	2.0825	2.0391	1.9938	1.9464	1.8963	1.8432

21	4.3248	3.4668	3.0725	2.8401	2.6848	2.5727	2.4876	2.4205	2.3660	2.3210	2.2504	2.1757	2.0960	2.0540	2.0102	1.9645	1.9165	1.8657	1.8117
22	4.3009	3.4434	3.0491	2.8167	2.6613	2.5491	2.4638	2.3965	2.3419	2.2967	2.2258	2.1508	2.0707	2.0283	1.9842	1.9380	1.8894	1.8380	1.7831
23	4.2793	3.4221	3.0280	2.7955	2.6400	2.5277	2.4422	2.3748	2.3201	2.2747	2.2036	2.1282	2.0476	2.0050	1.9605	1.9139	1.8648	1.8128	1.7570
24	4.2597	3.4028	3.0088	2.7763	2.6207	2.5082	2.4226	2.3551	2.3002	2.2547	2.1834	2.1077	2.0267	1.9838	1.9390	1.8920	1.8424	1.7896	1.7330
25	4.2417	3.3852	2.9912	2.7587	2.6030	2.4904	2.4047	2.3371	2.2821	2.2365	2.1649	2.0889	2.0075	1.9643	1.9192	1.8718	1.8217	1.7684	1.7110
26	4.2252	3.3690	2.9752	2.7426	2.5868	2.4741	2.3883	2.3205	2.2655	2.2197	2.1479	2.0716	1.9898	1.9464	1.9010	1.8533	1.8027	1.7488	1.6906
27	4.2100	3.3541	2.9604	2.7278	2.5719	2.4591	2.3732	2.3053	2.2501	2.2043	2.1323	2.0558	1.9736	1.9299	1.8842	1.8361	1.7851	1.7306	1.6717
28	4.1960	3.3404	2.9467	2.7141	2.5581	2.4453	2.3593	2.2913	2.2360	2.1900	2.1179	2.0411	1.9586	1.9147	1.8687	1.8203	1.7689	1.7138	1.6541
29	4.1830	3.3277	2.9340	2.7014	2.5454	2.4324	2.3463	2.2783	2.2229	2.1768	2.1045	2.0275	1.9446	1.9005	1.8543	1.8055	1.7537	1.6981	1.6376
30	4.1709	3.3158	2.9223	2.6896	2.5336	2.4205	2.3343	2.2662	2.2107	2.1646	2.0921	2.0148	1.9317	1.8874	1.8409	1.7918	1.7396	1.6835	1.6223
40	4.0847	3.2317	2.8387	2.6060	2.4495	2.3359	2.2490	2.1802	2.1240	2.0772	2.0035	1.9245	1.8389	1.7929	1.7444	1.6928	1.6373	1.5766	1.5089
60	4.0012	3.1504	2.7581	2.5252	2.3683	2.2541	2.1665	2.0970	2.0401	1.9926	1.9174	1.8364	1.7480	1.7001	1.6491	1.5943	1.5343	1.4673	1.3893
120	3.9201	3.0718	2.6802	2.4472	2.2899	2.1750	2.0868	2.0164	1.9588	1.9105	1.8337	1.7505	1.6587	1.6084	1.5543	1.4952	1.4290	1.3519	1.2539
∞	3.8415	2.9957	2.6049	2.3719	2.2141	2.0986	2.0096	1.9384	1.8799	1.8307	1.7522	1.6664	1.5705	1.5173	1.4591	1.3940	1.3180	1.2214	1.0000

الملخص:

في هذا العمل بحث أساسي و أصلي حول حلقة 1,2,4-oxadiazol-5-amine الغير متجانسة و الهدف من ذلك هو توقع الفعالية والنشاط البيولوجي للمركب المدروس و مشتقاته.

المعايير الهيكلية و الالكترونية للنواة 1,2,4-oxadiazol-5-amine في حالتها الأساسية تم حسابها باستخدام الطرق التالية: HF/6-31++G(d, p) , MP2/6-31++G(d, p), RM1 و B3LYP/6-31++G(d, p). طبيعة المستبدل تؤثر على المعايير الالكترونية و الطاقوية للنواة الأساسية ل 1,2,4-oxadiazol-5-amine , في الواقع فان هذه الدراسة الأخيرة تسمح لنا بتوقع الفعالية الكيميائية لمشتقات 1,2,4-oxadiazol-5-amine.

وقد تم أيضا القيام بدراسة نوعية بنية – خصائص(SPR) لسلسلة من مشتقات 1,2,4-oxadiazol-5-amine النشطة بيولوجيا.

وأخيرا قمنا بدراسة العلاقة الكمية بنية – فعالية البيولوجية (QSAR) لعشرين مركب من مشتقات 1,2,4-oxadiazol-5-amine لهم فعالية بيولوجية (عوامل مضادة للتكاثر) وقد استخدمنا الطريقة الإحصائية MLR وذلك لتصميم نموذج رياضي QSAR لغرض التنبؤ بالقيم النظرية للفعالية البيولوجية عن طريق هذا النموذج.

ولتأكد من صحة و فعالية هذا النموذج استخدمنا طريقة LOO وكذلك بعض المعايير الاحصائية. ولقد لاحظنا شدة التقارب بين القيم النظرية و التجريبية للفعالية البيولوجية مما يؤكد فعالية و جودة النموذج QSAR المتحصل عليه.

Résumé :

Dans ce travail, une recherche fondamentale et originale sur l'hétérocycle 1,2,4-oxadiazol-5-amine est réalisée dans le but est de prédire de la réactivité et de l'activité biologique du composé étudié et ses dérivés.

Les méthodes de modélisation moléculaire utilisées dans notre travail sont : RM1, HF/6-31++G(d, p) ,MP2/6-31++G(d, p) et B3LYP/6-31++G(d, p). Ces méthodes ont été utilisées pour déterminer les paramètres structuraux, électroniques et énergétiques associés aux molécules étudiées. La nature de type de substituant influe sur les paramètres électroniques et énergétiques de noyau de base 1,2,4-oxadiazol-5-amine. En effet, cette étude nous permet de prédire la réactivité chimique des dérivés de 1,2,4-oxadiazol-5-amine.

Une étude qualitative de la relation structure-propriétés (SPR) a été effectuée également pour une série bioactive de dérivés de 1,2,4-oxadiazol-5-amine.

Une étude QSAR a été effectuée sur vingt molécules analogues de of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines. Les composés utilisés sont caractérisés par son effet des agents antiprolifératifs. La régression linéaire multiple (MLR) a été utilisée pour quantifier les relations entre les descripteurs moléculaires et la propriété de l'activité antiprolifératif des dérivés du 1,2,4-oxadiazol-5-amine. La prédiction des modèles obtenus a été confirmé par la méthode de validation croisée LOO. Une forte corrélation a été observée entre les valeurs expérimentales et les valeurs prédites de l'activité antiproliférative, ce qui indique la validité et la qualité des modèles QSAR obtenus.

Abstract:

In this work a fundamental and original research on the 1,2,4-oxadiazol-5-amine heterocyclic, the aim is to predict the reactivity and biological activity of the compound studied and its derivatives.

The molecular modeling methods used in our work are: RM1, HF/6-31++G(d, p), MP2/6-31++G(d, p) and B3LYP/6-31++G(d, p). These methods were used to determine the structural parameters, electronics and energy associated with molecules studied. The nature of such substituent (donor, acceptor) affects the electronic and energy parameters of basic core of 1,2,4-oxadiazol-5-amine. Indeed, this qualitative study allows us to predict the chemical reactivity of derivatives of 1,2,4-oxadiazol-5-amine.

A study of structure - property relationships (SPR) for 1,2,4-oxadiazole-5-amine derivatives has been carried out for a series of bioactive derivatives of 1,2,4-oxadiazol-5-amine.

QSAR studies have been performed on twenty molecules of 3-(aryl)-N-(aryl)-1,2,4-oxadiazol-5-amines as anti-proliferative agents, multiple linear regression analysis was performed to derive QSAR models which were further evaluated internally for the prediction of activity. The developed models were cross-validated by the 'leave one out' technique as well as by the calculation of statistical parameters. High correlation between experimental and predicted activity values was observed, indicating the validation and the good quality of the derived QSAR models.