PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA

MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH

UNIVERSITY OF THE BROTHERS MENTOURI 1 CONSTANTINE

FACULTY OF NATURAL AND LIFE SCIENCES

FIELD OF BIOLOGICAL SCIENCES

DEPARTEMENT OF APPLIED BIOLOGY

Graduation note Submitted to the Department of Applied Biology in Partial Fulfillment of the Requirements for a Master's Degree in Bioinformatics

ENTITLED:

COMPUTER AIDED ANTIBACTERIAL DRUG DESIGN: DOCKING APPROACHES

Submitted and presented by: **Sustained on:**

DEBIZET Wafa 19-09-2021

SAADOUNE Rahma

Evaluation Jury:

Jury composed of.

Pr. BELKHIRI Lotfi	Freres Mentouri University of Constantine 1	President
Pr. KRID Adel	Freres Mentouri University of Constantine 1	Examiner
Dr. MENACER Rafik	Pharmaceutical Sciences Research Center CRSP	Supervisor
Dr. BOUCHEKOUIA Saad	Pharmaceutical Sciences Research Center CRSP	Co-supervisor

2021/2022

Acknowledgments

First, we praise ALLAH our creator for giving us the strength and patience to accomplish this work.

We would like to extend our gratitude to Mme Bouhalouf Habiba Professor at Department of applied Biology and Head of our Master training of Bioinfomratics, for her help and guidance.

We thank Mr. Menacer Rafik a Doctor at Computational Chemistry CRSP Constantine. To Pr. Belkhiri Lotfi, a professor at the Chemistry Department in University of Mentouri Constantine, Pr.Krid for generously providing us with infinite help and insightful guidance, without it, we would not have been able to finish our work and submit it on time.

We would also to thank our professors for their mighty efforts over the past 3years.

Finally, we thank the jury members who kindly did us the honor of participating in the evaluation of our work.

Dedication

Above all, to ***ALLAH***, the Generous and the Sustainer, who gave me the mind, strength and health, gave me patience, and supported me in all aspects of my life to reach what I am now.

To my ***dear parents*** for all their sacrifices, their love, their tenderness, their support and their prayers throughout my studies. The too person that gave the tool and value necessary to be where I am standing today.

To my dear fiance **"*Chouaib*"** for his support in all my moments of anxiety and tension, as well as his valuable advices to me.

To ***my brothers and sister*** for their constant encouragement to me and for transforming moments of anxiety into moments of laughter and joy

To all my friends **"*Wafa, Amina, Roumaissa.M, Anfel, et Roumaissa*"** for their support and useful advices. Especially to ***Imene and Yasmine***, who stood with me in difficult times .

To all ***my family*** for their support throughout my university career
Thank you for always being there for me.

Rahma.

Dedication

I would like to extend my gratitude to everyone whoever stood by my side in my life especially in my bad ones.

To the memory of my beloved father ***A.Elhamid***, I made it and I hope you are proud.

Also to my family who supported and helped me, especially my ***mother*** and my dearest sister ***Yasmine*** thank you.

To my friends***: Imene.M, Yasmine, Max***. My partner ***Rahma*** and our colleagues: ***Amina, Roumaissa, Anfel, Roumaissa.M*** .I thank you all.

Wafa.

List of Figures

Figure **Page**

List of Tables

Table **Page**

ACRONYMS

SBDD	Structure-based drug design
LBDD	Ligand-based drug design
CADD	Computer-aided drug design
RNA	Ribonucleic acid
SAR	Structure-activity relationship
CLA	Conjugated Linoleic Acid
EPA	Eicosa Pentaenoic Acid
DHA	Docosa Hexenoic Acid
MWs	Molecular Weights
mRNA	messenger RNA
RRNA	Ribosomal RNA
TRNA	Transfer RNA
IUBMB	International Union of Biochemistry and Molecular Biology unites
IUPAC	International Union of Pure and Applied Chemistry Society
CSBDD	Computational Structure-Based Drug Discovery
NDDO	Neglect of Diatomic Differential Overlap
MNDO	Modified Neglect of Diatomic Overlap
PDDG	Pairwize Distance Directed Gaussian
WFT	Wave function theory
QSAR	Quantitative Structure Activity Relationship
GPCRs	Récepteur Couplé aux Protéines Group
PDB	Protein Data Bank
Gyrb	Bacterial DNA gyrase
PMx	Parameter for semiempirical x method
HOMO	Lightest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
S.aureus	Staphylococcus aureus

TABLE OF CONTENTS

Table of contents

INTRODUCTION

Introduction

Antibiotic resistance has been declared a serious threat to public health worldwide in 2001 and is still on the rise. The bacteria resistant to most antibiotics in clinical use are mainly ESKAPE species, i.e., E. *faecium*, S. *aureus*, K. *pneumoniae*, A. *baumannii*, P. *aeruginosa* and Enterobacter. Among them, the Gram-positive bacteria represented by methicillin-resistant S. *aureus* (MRSA) and vancomycin-resistant E. faecium (VRE) have been categorized as serious threats by the US Centers for Disease Control and Prevention in 2013. The situation becomes even worse as the number of new drugs approved for the treatment of drug- resistant bacterial infections is on the decline in recent years. For these reasons, the discovery of novel resistance-breaking antibacterial agents is of utmost importance [1].

Computational approaches are useful tools to interpret and guide experiments to expedite the antibiotic drug design process. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) are the two general types of computer-aided drug design (CADD) approaches in existence. SBDD methods analyze macromolecular target 3-dimensional structural information, typically of proteins or DNA, to identify key sites and interactions that are important for their respective biological functions. Such information can then be utilized to design antibiotic drugs that can compete with essential interactions involving the target and thus interrupt the biological pathways essential for survival of the microorganism(s). LBDD methods focus on known antibiotic ligands for a target to establish a relationship between their physiochemical properties and antibiotic activities, referred to as a structure-activity relationship (SAR), information that can be used for optimization of known drugs or guide the design of new drugs with improved activity [2].

Therefore, we aimed in our work to find the most appropriate compound to inhibit the bacterial activity of S.*aureus* by docking novel class of antibacterial agents: N-thiadiazole4-hydroxy-2-quinolone-3-carboxamides as ligands and a target 4uro.

Chapter I

Chemistry and Antibacterial Activity of Bioactive molecules

1. INTRODUCTION

Biomolecules, also called biological molecules**,** any of numerous substances that are produced by cells and living organisms. Biomolecules have a wide range of sizes and structures and perform a vast area of functions. The four major types of biomolecules are carbohydrates, lipids, nucleic acids, and proteins [3].

Among biomolecules, nucleic acids, namely DNA and RNA, have the unique function of storing an organism's genetic code the sequence of nucleotides that determines the amino acid sequence of proteins, which are of critical importance to life on Earth. There are 20 different amino acids that can occur within a protein; the order in which they occur plays a fundamental role in determining protein structure and function. Proteins themselves are major structural elements of cells. They also serve as transporters, moving nutrients and other molecules in and out of cells, and as enzymes and catalysts for the vast majority of chemical reactions that take place in living organisms. Proteins also form antibodies and hormones, and they influence gene activity. Likewise, carbohydrates, which are made up primarily of molecules containing atoms of carbon, hydrogen, and oxygen, are essential energy sources and structural components of all life, and they are among the most abundant biomolecules on Earth. They are built from four types of sugar units monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Lipids, another key biomolecule of living organisms, fulfill a variety of roles, including serving as a source of stored energy and acting as chemical messengers [4].

Antibacterial as well as antiviral activity of a molecule is completely associated with the compounds that provincially kill bacteria and viruses or slow down their rate of growth, without being extensively toxic to nearby tissues. Most recently discovered antimicrobial agents are modified natural compounds [5].

2. Phytochemicals and Phytochemistry

Phytochemicals (‘phyto-‘from Greek -phyto meaning ‘plant’) or phytoconstituents are responsible for protecting the plant against microbial infections or infestations by pests also against UV radiation [6]. They contribute to the plant’s color, aroma and flavor [7] literally meaning “plant chemicals”. Scientists have identified thousands of different phytochemicals, found in vegetables, fruits, beans, whole grains, nuts and seeds. These active compounds are flavonoids, carotenoids, sterols and stanols, isothiocyanates, phenolic acid, dietary fibers etc. [8]

Phytochemicals are biologically active, naturally occurring chemical compounds found in plants, which provide health benefits for humans as medicinal ingredients and nutrients [7]. The proper understanding of phytochemical is essential for drug discovery and for the development of novel therapeutic agents against major diseases [9]. The major classes of phytochemicals are shown in figure bellow**.**

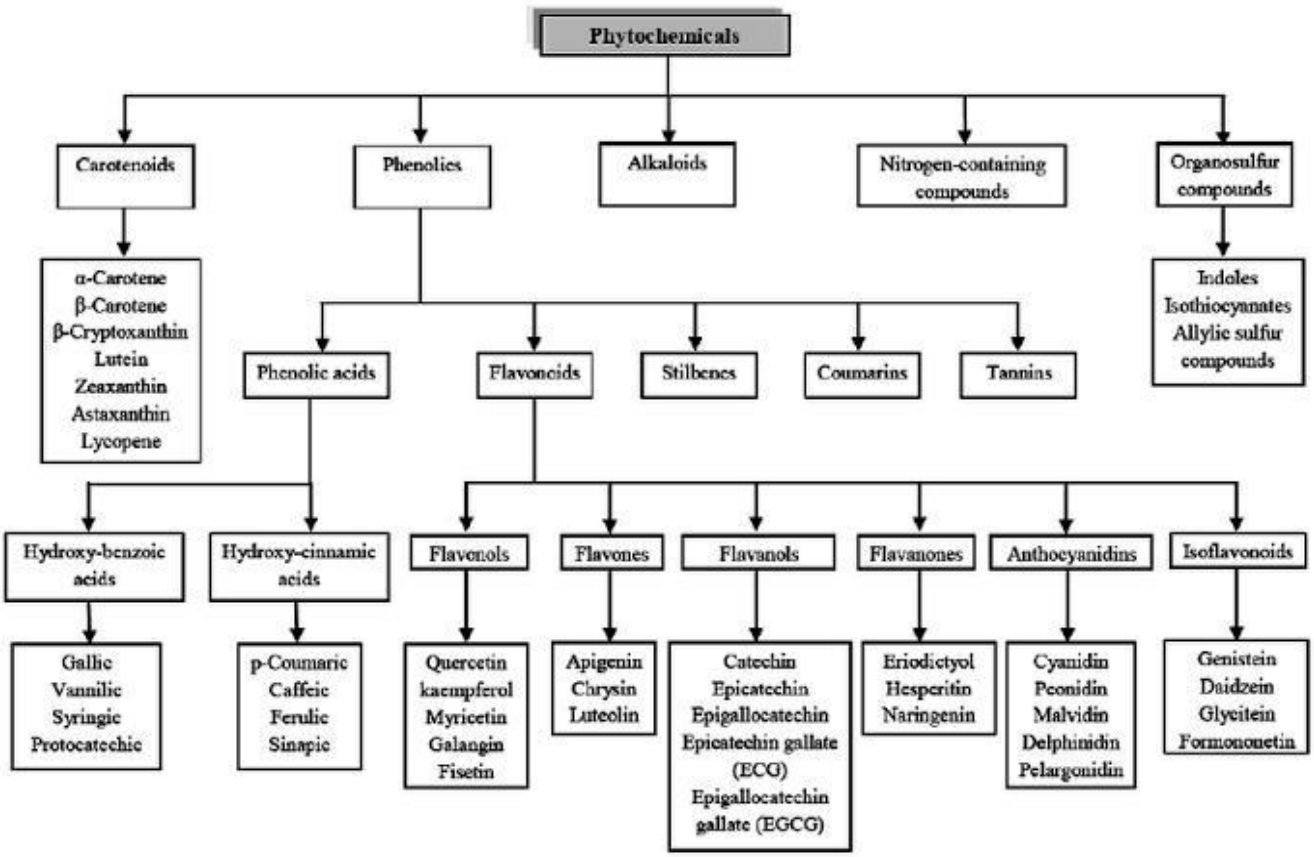


Figure1: Major classes of phytochemicals

3. Zoochemicals and Zoochemistry

Zoochemistry is the branch of biochemistry that is concerned with the constituents of an animal's body [10]. Zoochemicals are natural chemicals found in animal-based foods. These food components are not the traditional nutrients we think of when we study nutrition. They're not vitamins, minerals, carbohydrates, proteins or fats [11] are the ingredients which improve the metabolic activity of the body along with curing of certain diseases. Some important Zoochemicals are: Conjugated Linoleic Acid (CLA), Eicosapentaenoic acid (EPA), Docosahexenoic acid (DHA), Spingolipids, Choline, and Lecithin [8]. The table shows some Zoochemicals and their origin**.**

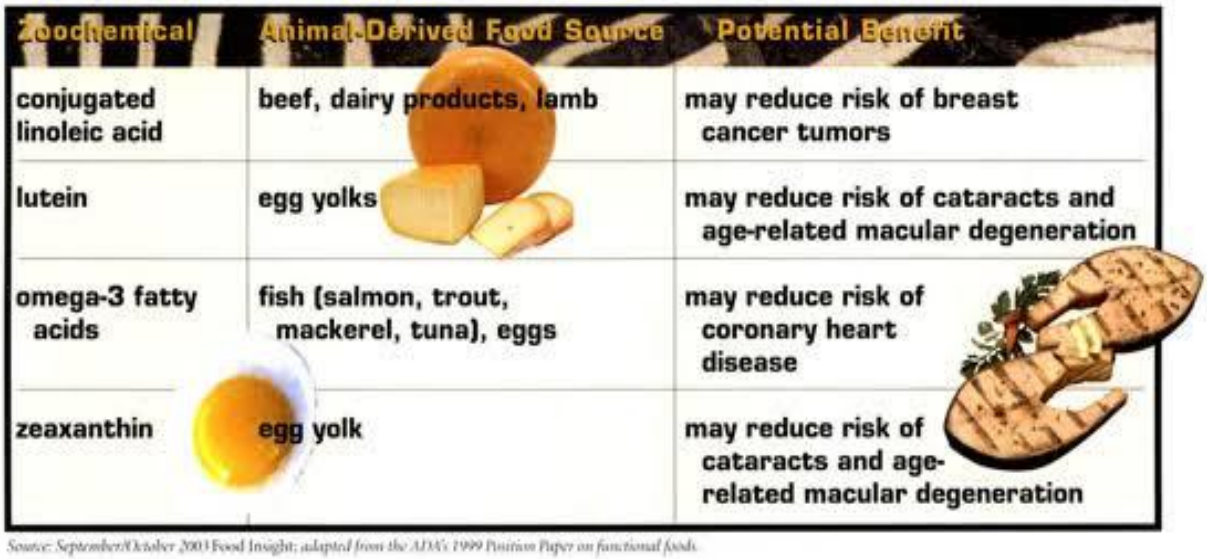


Figure2: Source and benefit of some classes of Zoochemicals

4. Synthetic Biomolecules

Chemical synthetic biology (CSB) is a branch of synthetic biology (SB) oriented toward the synthesis of chemical structures alternative to those present in nature [10].This branch has a great relationship in terms of study in the synthetic molecule and synthetic biomolecules.

Synthetic biomolecules are those moieties which are synthetically produced and mimic the properties and action of naturally-occurring biomolecules. They possess great significance in fields such as vaccines, drug delivery…etc. [14]

5. Biomolecules

A biomolecule is, by definition, any molecule presents in a living being. There are 4 main biomolecules: proteins, nucleic acids, carbohydrates and lipids. All these have their own unique functions and necessities. Proteins, made up of amino acids, are responsible for enzymatic actions and other structural necessities of a cell. Nucleic acids, made up of nucleotides, are responsible for genetic information. Carbohydrates, made up of monosaccharides, are the energy source of cells and have other structural responsibilities. [12]

5.1 Small molecules

Small molecules are molecules with a molecular weight of < 900 g/Mol. Small molecules make up 90% of pharmaceutical drugs (such as insulin, aspirin, and antihistamines). They also include biological molecules such as fatty acids, glucose, amino acids, and cholesterol and secondary metabolites such as lipids, glycosides, alkaloids, and natural phenols. Small molecules do not include larger molecules such as polysaccharides, proteins, and nucleic acids and can be involved in biological reactions as a product or substrate [15,16].

Small molecules are drugs developed with a specific target, usually to a cellular pathway or molecule within that pathway. [17, 16] They can regulate the function of proteins as they bind to proteins to form protein–ligand complexes and induce conformational changes of the proteins at the same time. Small molecules that are the inhibitors of clinically important proteases, kinases, and bromodomains proteins are thus frequently used in drug design .Nowadays, computer-aided drug discovery has been widely used to explore small molecules as potential lead compounds [18, 16].

5.2 Macromolecules

Biological macromolecules are very large molecules created by the polymerization of small units called monomers. These macromolecules are a great source of energy and building materials for our body, which we gain through our food [19].

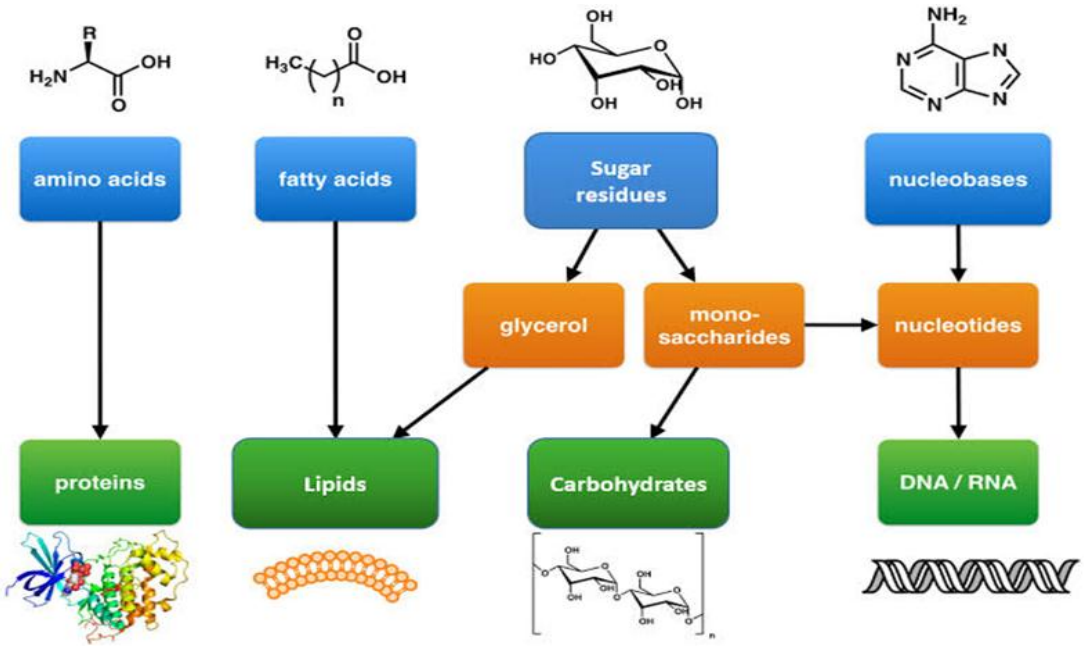


Figure3: Some examples of macromolecules

Macromolecule	Elements	Subcomponents/ monomers	Function
Carbohydrates (aka polysaccharides)	C, H, O	Monosaccharides, disaccharides (aka sugars)	Energy source, short-term energy storage
Lipids	C, H, O	Usually glycerol combined with fatty acids	Long-term energy storage, cell membranes, hormones
Proteins (aka polypeptides)	C, H, O, N	Amino Acids	Regulate reactions, transport molecules, membrane channels and pumps, chemical messengers, fight disease
Nucleic Acids	C, H, O, N, P	Nucleotides	Store and transmit genetic information, code for and help build proteins

Figure 4: Function of macromolecules

There are four classes of macromolecules (polysaccharides or carbohydrates, triglycerides or lipids, polypeptides or proteins, and nucleic acids such as DNA & RNA). Car bohydrates,

lipids are made of only carbon, hydrogen, and oxygen (CHO). Proteins are made of carbon, h ydrogen, oxygen,

and nitrogen (CHON). Nucleic acids such as DNA and RNA contain carbon, hydrogen, oxyge

n, nitrogen, and phosphorus (CHONP) [20]. Sometimes consist of long chains of repetitive units of atoms and are known as polymers, but not all macromolecules are polymers. These large molecules play a number of vital roles in living organisms [21].

5.2.1 Peptides

The word peptide, derived from the Greek word “peptós/digested,” refers to a chain of amino acids (AAs) linked together via amide or peptide bonds. The formation of the covalent peptide bond is an example of a condensation reaction, which generates water from the combination of the α-carboxyl group of one AA and the α-amino group of another. An AA unit within a peptide chain is called a "residue”. A peptide can be as short as two residues with only one peptide bond (named “dipeptide”) or as long as several residues forming a continuous and unbranched peptide chain (named “oligopeptide” if containing 20 AAs). Proteins are composed of many peptide chains and sometimes the terms “polypeptide” and “protein” are used interchangeably. There are several different conventions for making a distinction between the two, but in general, molecules referred to as polypeptides have molecular weights (MWs) below 10,000 Daltons or less than 50 AAs, and molecules above these limits are considered as proteins

Each peptide has its own unique structural and biochemical characteristics, such as an isoelectric pH (pI) and ionization behavior. These features are derived from the peptide’s AA components. Therefore, the overall characteristics of a peptide can change depending on the quantity, type and combination of AA within the chain [22].

5.2.2. Amino acid

Amino acids are the building block of proteins. They are important organic compounds that contain amine (-NH2) and Carboxyl (-COOH) functional groups, along with a side-chain (R group) that is specific for each amino acid .Twenty different amino acids are commonly found in proteins. All of these 20 common amino acids are α-amino acids except proline and their general structure is shown below. They have a carboxyl group and amino group which are covalently bonded to an α-carbon atom. They differ from each other in their side chain R groups. Since, the remaining structures are the same therefore properties of these amino acids are primarily determined by the side chain groups. The nature of these side chains may be polar, nonpolar (aliphatic), hydrophilic, hydrophobic, acidic, basic and aromatic as shown in **Figure5;**

they are linked together by peptide bond to make a protein molecule. These amino acids have been abbreviated using either three letter word or one letter word [23]. Additionally, AA are key precursors for syntheses of hormones and low-molecular weight nitrogenous [24]. Furthermore, dietary supplementation with one or a mixture of these AA may be beneficial for ameliorating health problems such diabetes, cardiovascular disease. [25]

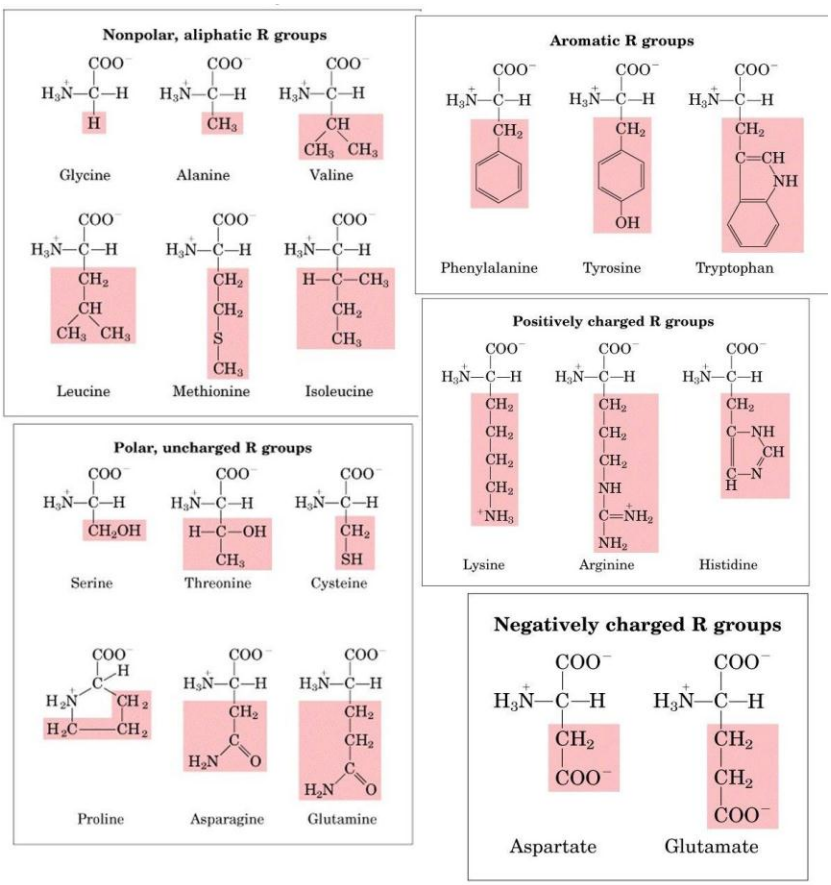


Figure5: Classification of amino acids

5.2.3 Nucleic acid

Nucleic acids are high molecular mass com-pounds found in all living cells and viruses. Their name originates from their discovery in the nucleic of eucaryotic cells. They can be chemically degraded to yield phosphoric acid, pentoses, and nitrogen-containing heterocycles (bases). [24]

As constituents of living organisms, are comparable in importance to the proteins. There is evidence that they are involved in the processes of cell division and growth, that they

participate in the transmission of hereditary characters, and that they are important constituents of viruses. An understanding of the molecular structure of the nucleic acids should be of value in the effort to understand the fundamental phe-nomena of life [26] . The functions of nucleic acids have to do with the storage and expression of genetic information. Deoxyribonucleic acid (DNA) encodes the information the cell needs to make proteins. A related type of nucleic acid, called ribonucleic acid (RNA), comes in different molecular forms that participate in protein synthesis. [27]

Nucleic acids can be divided into two main classes depending on the sugar they contain: de-oxyribonucleic acids (DNA) contain 2-deoxy-d-ribose and ribonucleic acids (RNA) contain d-ribose. [26]

5.2.3.1 Deoxyribonucleic acid (DNA)

DNA is a nucleic acid (biomolecule) that contains the genetic instructions specifying the biological development of all cellular forms of life (and many viruses). DNA is often referred to as the molecule of heredity, as it is responsible for the genetic propagation of all traits. [28]

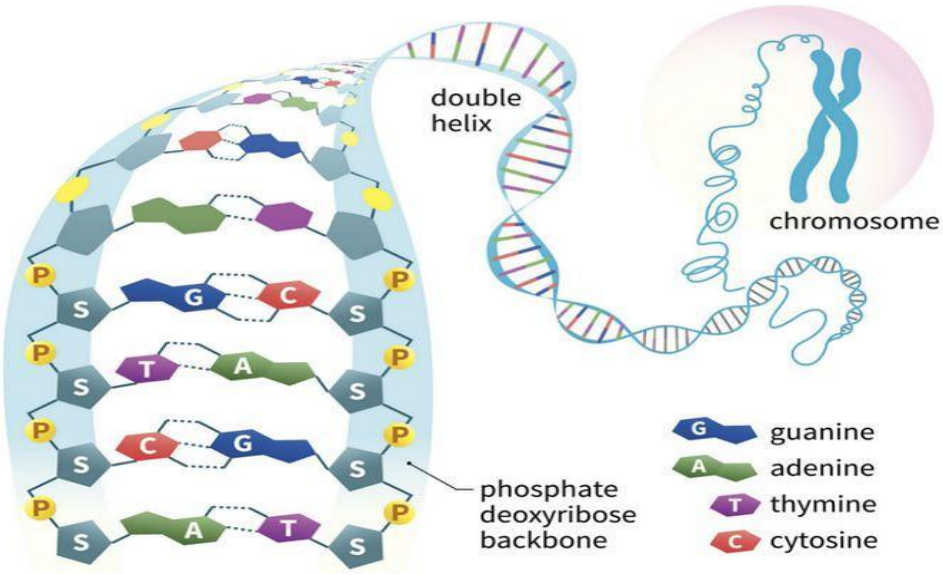


Figure6: DNA Double helix by hydrogen bonding interaction

During reproduction, DNA is replicated and transmitted to the offspring. Its sequence defines many features ranging from organism type through physical traits to disease susceptibility. As it is nowadays well-established, the DNA sequence is copied (transcription)

onto RNA biomolecules, which are then used in protein synthesis to encode a specific protein sequence (translation). [28]

5.2.3.2 Ribonucleic acid (RNA)

Ribonucleic acid (RNA) is a molecule similar to DNA. Unlike DNA, RNA is single-stranded. An RNA strand has a backbone made of alternating sugar (ribose) and phosphate groups. Attached to each sugar is one of four bases--adenine (A), uracil (U), cytosine (C), or guanine (G). Different types of RNA exist in the cell: messenger RNA (mRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). More recently, some small RNAs have been found to be involved in regulating gene expression. [29]

RNA converts the instructional genetic information stored in deoxyribonucleic acid (DNA) into proteins. However, some viruses use RNA (rather than DNA) to carry the genetic information. [30]

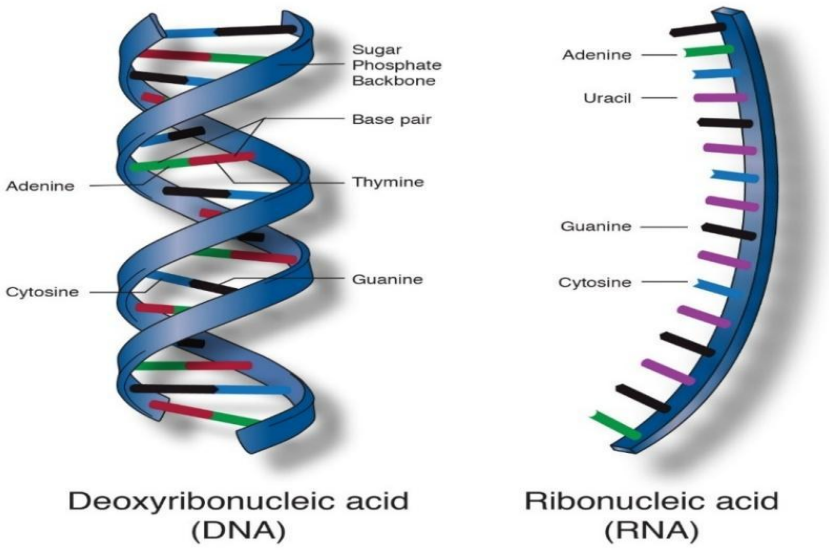


Figure7: deoxyribonucleic and ribonucleic acids

5.2.4 Proteins

Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs. The Swedish chemists J. J. Berzelius in 1938 coined the name

’protein’ from the Greek word proteios which means “of the first rank”.Proteins (Greek proteios, “primary” or “of first importance”) are biochemical molecules consisting of polypeptides joined by peptide bonds between the amino and carboxyl groups of amino acid residues.[31]

Proteins are made up of hundreds or thousands of smaller units known as amino acids. There are 20 different kinds of amino acids that are linked together by peptide bond to make a protein molecule. The sequence of amino acids determines each protein’s unique 3-dimensional structure and its specific function such as catalysis of biochemical reactions, mechanical support and immune protection, movement, transport of ligand, transmits nerve impulses, and control growth and differentiation, they play an important role in various biological processes.[31]

5.2.5 Carbohydrates

Carbohydrates are the most abundant biomolecules belonging to class of organic compounds found in living organisms on earth, are polyhydroxylated aldehydes or ketones and their derivatives. which are made up of carbon, hydrogen, and oxygen, are organic compounds that serve as a source of energy for animals and humans .[38] and serve as the main source of energy in diets fed to pigs [33].The word "carbohydrate" includes polymers and other compounds synthesized from polyhydroxylated aldehydes and ketones. They can be synthesized in the laboratory or in living cells. Simple carbohydrates or the entire carbohydrate family may also be called saccharides. In general carbohydrates have the empirical formula (CH2O) n. The term generated from carbon and hydrate; though some also contain nitrogen, phosphorus, or sulfur. Chemically, carbohydrates are molecules that are composed of carbon, along with hydrogen and oxygen - usually in the same ratio as that found in water (H2O) [34].

1.2.6 Lipids

The study of lipids has developed into a research field of increasing importance as their multiple biological roles in cell biology, physiology and pathology are becoming better understood [36].

The nomenclature of lipids falls into two main categories: systematic names and common or trivial names. The latter includes abbreviations which are a convenient way to define

acyl/alkyl chains in glycerolipids, sphingolipids and glycerophospholipids. The generally accepted guide-lines for lipid systematic names were initially defined by the International Union of Pure and Applied Chemists and the International Union of Biochemistry and Molecular Biology (IUPAC-IUBMB) Commission on Biochemical Nomenclature in 1976 [36]

Lipids are a diverse and ubiquitous group of compounds which have many key biological functions, such as acting as structural components of cell membranes, serving as energy storage sources and participating in signaling pathways. A comprehensive analysis of lipid molecules, "lipidomics," in the context of genomics and proteomics is crucial to understanding cellular physiology and pathology; consequently, lipid biology, has become a major research target of the post-genomic revolution and systems biology. [36]

''Lipids'' refers to compounds that are relatively insoluble in water but are soluble in organic solvents such as chlo-roform, ether, hexane, and benzene. There are many types of lipids, and their classification has been undertaken in several ways. For instance, they have been differenti-ated either by the presence or absence of fatty acids orof the alcohol glycerol in their basic structure or according to their polarity. [37]

6. Antibacterial activity

One of the greatest medical achievements of the 20th century was the discovery of

Antibiotics. Unfortunately, their extensive, disproportionate, and unacceptable use has resulted in the selection and proliferation of resistant bacterial strains and a significantly increased ratio of treatment failure. Bacteria have developed several different resistance mechanisms, such as modification of the antibiotic binding site. Development of enzymes that can kill or modify the antibiotic structure. Mutations in genes that encode transportation proteins that cause disruption of the permeability of the cell wall and vigorous pumping out of antibiotic molecules. Because the production and introduction of a new antimicrobial drug is a complex, time-consuming, and very costly process and the production of resistance mechanisms by bacteria is swift and virtually boundless. Thus, the quest for and introduction of natural substances that can enhance the antibacterial efficacy of traditional antibiotics is the promising alternative in the ongoing fight against multi-drug resistant bacterial strains. [38]

Antibiotics with novel mechanisms of action are becoming increasingly important in the battle against bacterial resistance to all currently used classes of antibiotics. Bacterial DNA gyrase and topoisomerase IV (topoIV) are the familiar targets of fluoroquinolone and coumarin

antibiotics. DNA gyrase is uniquely responsible for introducing negative supercoils into DNA, while the primary function of topoIV appears to be decatenation of replicated chromosomes and relaxation of DNA. The catalytic functions of both enzymes involve the breakage and rejoining of double-stranded DNA, with the intermediate passage of a second double strand of DNA through the break. Consistent with their high degree of structural and functional relatedness, both DNA gyrase and topoIV have been identified as the primary and secondary targets of the fluoroquinolone class of antibiotics which stabilize the enzyme-DNA complex in the double-strand break stage formed by gyrase and topoIV in bacteria. DNA gyrase and topoIV are also inhibited by members of the coumarin class of antibiotics, which target the ATP-binding sites of the corresponding B subunits, thereby inhibiting the energy source necessary for strand passage. [39]

7. Conclusion

Bacterial cells develop their internal strategies to inhibit the effects of antibiotics and their resistance mechanisms may help in the discovery and design of new targets computational predictions of bioactive molecule targets are helpful to narrow down the set of potential targets to be tested and to predict off-target effects of known molecules or drugs. Novel antibiotics are urgently needed, N-thiadiazole4-hydroxy-2-quinolone-3-carboxamides are a potential new class of antibacterial agents, as one of its derivatives was identified as an antibacterial agent against *Staphylococcus aureus* (ATCC29213).

CHAPTER II

Part A: Computational Methods and Docking tools

1. Introduction

The definition currently accepted of what molecular modeling is, can be stated as this: `Molecular modeling is anything that requires the use of a computer to paint, describe or evaluate any aspect of the properties of the structure of a molecule` (Pensak, 1989). Methods used in the molecular modeling arena regard automatic structure generation, analysis of three-dimensional (3D) databases, docking of ligands or continuum methods. Thus, today molecular modeling is regarded as a field-concerned with the use of all sort of different strategies to model and to deduce information of a system at the atomic level. On the other hand, this discipline includes all methodologies used in computational chemistry, like computation of the energy of a molecular system, energy minimization, Monte Carlo methods or molecular dynamics. In other words, it is possible to conclude that computational chemistry is the nucleus of molecular modeling. Identification of biomolecular moieties involved in the interaction with the specific receptor permits to understand the molecular mechanism responsible of its specific biological activity. In turn, this knowledge is aimed at designing new active molecules that can be successfully used as drugs. Because simulation accuracy is limited to the precision of the constructed models, when it is possible, computational simulations have to be compared with the experimental results to confirm model accuracy and to modify them, if necessary, in order to obtain better representations of the system. [44]

APPLICATIONS OF MM

- Reaction studies / enzymatic mechanisms
- Protein structure and function
- Homology modelling
- Docking/Drug design
- MD simulations
- Simulations of large systems (membranes, colloids, fibers)

2. Molecular modeling MM

Theoretical methods and computational techniques for simulating the behavior of molecules and molecular systems. Molecular modeling (also known as rational drug design) is a series of computational methods used to obtain, represent, and manipulate the structure and reaction of molecules and the properties of dependent production. On these three-dimensional structures, it helps us visualize molecules and discover new drug compounds. A common feature of the MM method is the atomic description of the molecular system. [45]

Molecular modeling (MM) is one of the fastest growing fields in science. It may vary from building and visualizing simple molecules in three dimensions (3D) to performing complex computer simulations on large proteins and nanostructures. MM is a collection of computer-based techniques for driving, representing and manipulating the structures and reactions of molecules, and those properties that are dependent on these 3D structures. The techniques in MM cover several issues among them computational chemistry, drug design, computational biology, nanostructures, and material science. [46]

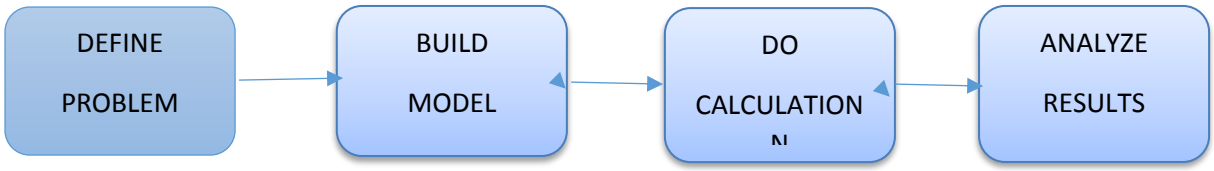
Molecular modeling covers a wide variety of theoretical and computational methods used to represent the structure of molecules, ions and/or particles. They can be classified according to the length and time scale of the modeling matter from electronic to continuous levels. Considering solute/solvent systems, there are three main categories for molecular modeling: implicit methods, integral equations and classical density functional theory, and explicit methods. Thus, in order to present the main idea of each class of methods available in chemical engineering field, this work comprehends three methods: Poisson Boltzmann equation, classical density functional theory, and molecular dynamics simulation. Finally, scale integration is presented as a strategy for efficient modeling and simulation. [47]

Molecular modeling provides scientist with five major types of information:

- The 3D structure of molecules
- The chemical and physical characteristics of the molecules
- Comparison of structure of a molecule with other different molecules
- Visualization of complexes formed between different molecules/macromolecules
- Prediction about how new related molecules might look. [48]

Its main goal is to develop a sufficient accurate model of the system so that physical experiment is not necessary.

MM is a multi-step Progress…



2.1 Computational methods

2.1.1 Molecular mechanics methods MM

MM is a calculation method that uses the potential function in classical physics to calculate the potential energy region of a certain arrangement of atoms. MM is a form of mathematical formalism, which attempts to reproduce molecular geometry, energy and other characteristics by adjusting the bond length and angelic bondage. The twist angle to the equilibrium value depends on the hybridization of the atoms and their bonding scheme. MM ignores the electronic movement and calculates the potential energy of the system based only on the position of the core. The MM method is the basis of other methods, such as homology modeling, molecular dynamics, crystal structure refinement and combination.

Molecular mechanics methods are widely used to give accurate structures and energies for molecules. The method employs fundamental principles of vibrational spectroscopy as well as the idea that bonds have natural lengths and angles and molecules will adopt geometries that can best reach these natural values. [49]

Molecular Mechanics (MM) force fields are the methods of choice for protein simulations, which are essential in the study of conformational flexibility. Given the importance of protein flexibility in drug binding, MM is involved in most if not all Computational Structure-Based Drug Discovery (CSBDD) projects. This section introduces the reader to the fundamentals of MM, with a special emphasis on how the target data used in the parameterization of force fields determine their strengths and weaknesses. Variations and recent developments such as polarizable force fields are discussed. The section ends with a brief overview of common force fields in CSBDD. [50]

MM strategies:

Direct drug design: In the direct method, X-ray crystallography used to determine the three-dimensional properties of known receptor sites to create lead molecules. In direct design, the geometry of the acceptor site is known; the challenge is to find a molecule that satisfies certain geometric constraints and a good chemical combination. Once a good candidate found according to these criteria, the energy minimization-binding step can be used to predict the binding strength. Drug development methods involve comparative analysis of the structural features of known active and inactive molecules complementary to hypothetical receptor sites. If the geometry of the site is unknown, usually, the designer must design another ligand molecule that can bind to the site well.

Indirect drug design: The indirect drug design approach involves a comparative analysis of the structural properties of known active and inactive molecules that are complementary to a hypothetical receptor site; the design must be based on other ligand molecules that bind well to the site. [51]

2.1.2 Semiempirical methods SE

Semi-empirical (SE) methods are derived from Hartree-Fock (HF) or Density Functional Theory (DFT) by neglect and approximation of electronic integrals. Thereby, parameters are introduced which have to be determined from reference calculations and/or by fitting to available experimental data. This leads to computational methods that are about 2-3 orders of magnitude faster than the standard HF/DFT methods using medium sized basis sets while being about 3 orders of magnitude slower than empirical force field methods (Molecular Mechanics: MM). Therefore, SE methods are most appropriate for a specific range of applications. These include the study of systems that contain a large number of atoms and therefore being too large for ab initio or DFT methods and problems where dynamic or entropic effects are particularly important. In the latter case, the errors made by considering a very limited number of molecular structures or neglecting entropic contributions can be much larger than the accuracy lost due to the use of SE methods. Another area where SE methods are attractive concerns the analysis of systems for which reliable MM models are not readily available. Therefore, even in an era when rapid progress is being made in ab initio methods, there is considerable interest in further developing SE methods. We illustrate this point by focusing on the discussion of recent development and application of the Density Functional Tight Binding method. [52].

Semiempirical quantum chemistry attempts to address two limitations, namely slow speed and low accuracy, of the Hartree-Fock calculation by omitting or parameterizing certain integrals based on experimental data, such as ionization energies of atoms, or dipole moments of molecules. As a result, semiempirical methods are very fast, applicable to large molecules, and may give accurate results when applied to molecules that are similar to the molecules used for parameterization. On the downside, accuracy of semiempirical methods is erratic on many systems. Modern semiempirical models are based on the Neglect of Diatomic Differential Overlap (NDDO) method in which the overlap matrix S is replaced by the unit matrix. This allows one to replace the Hartree-Fock secular equation $|H-ES| = 0$ with a simpler equation $|H-E|=0$. Existing semiempirical models differ by the further approximations that are made when evaluating one-and two-electron integrals and by the parameterization philosophy [53].

2.1.2.1 Semiempirical NDDO Models: MNDO, AM1, PM3, and PDDG/PM3

A modified Neglect of Diatomic Overlap, MNDO (by Michael Dewar and Walter Thiel, 1977)**:**

Is the oldest NDDO-based model that parameterizes one-center two-electron integrals based on spectroscopic data for isolated atoms, and evaluates other two-electron integrals using the idea of multipole-multipole interactions from classical electrostatics. A classical MNDO model uses only s and p orbital basis sets while more recent MNDO/d adds d-orbitals that are especially important for the description of hypervalent sulphur species and transition metals. MNDO has a number of known deficiencies, such as inability to describe the hydrogen bond due to a strong intermolecular repulsion. The MNDO method is characterized by a generally poor reliability in predicting heats of formation. For example, highly substituted stereoisomers are predicted to be too unstable compared to linear isomers due to overestimation of repulsion is sterically crowded systems [54].

B.Austin Model 1, AM1 (by Dewar and co-workers)

Takes a similar approach to MNDO in approximating two-electron integrals but uses a modified expression for nuclear-nuclear core repulsion. The modified expression results in non-physical attractive forces that mimic van der Waals interactions. The modification also necessitated reparameterization of the model, which was carried out with a particular emphasis on dipole moments, ionization potentials, and geometries of molecules. While this allows for some description of the hydrogen bond, other deficiencies, such as systematic over-estimates of basicities, remained. In addition, the lowest energy geometry for the water dimer is predicted

incorrectly by the AM1 model. On the other hand, AM1 improves nicely some properties, such as heats of formation, over MNDO [55].

C.Parametric Method 3, PM3 (by James Stewart)

Uses a Hamiltonian that is very similar to the AM1 Hamiltonian but the parameterization strategy is different. While AM1 was parameterized largely based on a small number of atomic data, PM3 is parameterized to reproduce a large number of molecular properties. In some sense, chemistry gave way to statistics with the PM3 model. Different parameterization, and slightly different treatment of nuclear repulsion allow PM3 to treat hydrogen bonds rather well but it amplifies non-physical hydrogen-hydrogen attractions in other cases. This results in serious problems when analyzing intermolecular interactions (methane is predicted to be a strongly-bound dimer) or conformations of flexible molecules (OH is strongly attracted to CH3 in 1-pentanol). The accuracy of thermochemical predictions with PM3 is slightly better than that of AM1. The PM3 model has been widely used for rapid estimation of molecular properties and has been recently extended to include many elements, including some transition metals [56].

D.PDDG/PM3 (by William Jorgensen and co-workers)

Overcomes some of the deficiencies of the earlier NDDO based methods by using a functional group-specific modification of the core repulsion function. The Pairwize Distance Directed Gaussian (PDDG) modification provides good description of the van der Waals attraction between atoms, and the PDDG/PM3 model appears to be suitable for calculations of intermolecular complexes. Furthermore, careful reparameterization has made the PDDG/PM3 model very accurate for estimation of heats of formation. However, some limitations common to NDDO methods remain in the PDDG/PM3 model: the conformational energies are unreliable, most activation barriers are significantly overestimated, and description of radicals is erratic. So far, only C, N, O, H, S, P, Si, and halogens have been parameterized for PDDG/PM3 [57].

2.1.3 Quantum chemistry methods QC

Computational quantum chemistry combines the power of computation and the foundations of physics to understand chemical problems. The dawn of quantum chemistry coincided with the advent of computing technology as solving many-electron problems could take years if done by hand. Modern day computation comes from the use of nodes and processors to handle large amounts of data typically run through a quantum chemical

software package. These quantum chemical methods are the foundation of most theoretical studies of medium to small molecules. Two theories have driven this approach, wave function theory (WFT) and density functional theory (DFT). Wave function techniques look at each individual electron while density functional theory view the total electron density to explain chemical properties. Each give reasonable solutions that agree with experimental results, but theory did not always match experiment. New and better methods had to be obtained over the years in order to accurately describe the motion of the electrons so that reliability and confidence was reached. This is still the goal of method development today as the many-body problem becomes much more complicated for increasingly challenging cases [58].

Presently, the most popular techniques in quantum chemical calculations are the Hartree–Fock (HF) method and the Kohn–Sham (KS) method in the Density Functional Theory (DFT) framework [59].

2.1.4 Density functional theory DFT

Density functional theory (DFT) is a quantum-mechanical (QM) method used in chemistry and physics to calculate the electronic structure of atoms, molecules and solids. It has been very popular in computational solid-state physics since the 1970s. However, it was not until the 1990s that improvements to the method made it acceptably accurate for quantum-chemical applications, resulting in a surge of applications. The real forte of DFT is its favorable price/performance ratio compared with electron-correlated wave function-based methods such as Moller–Plesset perturbation theory or coupled cluster. Thus, larger (and often more relevant) molecular systems can be studied with sufficient accuracy, thereby expanding the predictive power inherent in electronic structure theory. As a result, DFT is now by far the most widely used electronic structure method. The 1998 award of the Nobel Prize to Walter Kohn ‘for his development of the density-functional theory’ evidences the huge importance of DFT in physics and chemistry [60].

There are roughly three types, or categories, of density functional methods. Local density approximation (LDA) methods assume that the density of the molecule is uniform throughout the molecule, and is typically not a very popular or useful method. Gradient corrected (GC) methods look to account for the non-uniformity of the electron density. Hybrid methods, as the name suggests, attempt to incorporate some of the more useful features from ab initio methods (specifically Hartree-Fock methods) with some of the improvements of DFT mathematics.

Hybrid methods, such as B3LYP, tend to be the most commonly used methods for computational chemistry practitioners [61].

The most significant advantage to DFT methods is a significant increase in computational accuracy without the additional increase in computing time. DFT methods such as B3LYP/6-31G (d) are oftentimes considered to be a standard model chemistry for many applications [62].

2.2 Optimization

Optimization in Computational Chemistry and Molecular Biology: Local and Global Approaches covers recent developments in optimization techniques for addressing several computational chemistry and biology problems. A tantalizing problem that cuts across the fields of computational chemistry, biology, medicine, engineering and applied mathematics is how proteins fold. Global and local optimization provide a systematic framework of conformational searches for the prediction of three-dimensional protein structures that represent the global minimum free energy, as well as low-energy biomolecular conformations. Each contribution in the book is essentially expository in nature, but of scholarly treatment. The topics covered include advances in local and global optimization approaches for molecular dynamics and modeling, distance geometry, protein folding, molecular structure refinement, protein and drug design, and molecular and peptide docking. Audience: The book is addressed not only to researchers in mathematical programming, but to all scientists in various disciplines who use optimization methods in solving problems in computational chemistry and biology [63].

2.3. Conformer's search

Conformational search algorithm should identify the largest possible number of low-energy structures covering the widest possible range of molecular shapes (geometric criterion). Geometric analysis consisted in comparing the distribution of conformations within the generated ensembles by multidimensional scaling and by analyzing the eigenvalue structure of the pairwise coordinate covariance matrices. The energetic comparison was carried out by assessing the energy distribution of conformers after minimizing them all using the same semi-empirical quantum mechanics optimization protocol [64].

The purpose of the Conformational Search application is to generate energetically reasonable 3D atomic configurations of molecular systems comprising small molecules, multiple molecules, macrocycles, and protein loops, with or without geometric constraints or fixed atoms [65].

The Conformational Search application contains three methods for generating conformations, the output of each of which is subjected to energy minimization:

- Systematic Search. Systematic generation of rotatable bond dihedral angle combinations.
- Stochastic Search. Random assignment of dihedral angle combinations, even for rings, and stereochemistry inversions, where permitted.
- LowModeMD Search. A short molecular dynamics simulation using velocities with little kinetic energy on the high-frequency vibrational modes. [66].

Table1: Properties of methods of conformational search application.

Property	Systematic	Stochastic	LowModeMD
Systematic Sampling	**Y**	**N**	**N**
Single Bond Rotation	**Y**	**Y**	**Y**
Amide Bond Rotation	**Y**	**Y**	**N**
Amide Bond Rotation	**Y**	**Y**	**N**
Chiral Center Inversion	**N**	**Y**	**N**
Small Ring Conformations	**N**	**Y**	**Y**
Macrocycle Conformations	**N**	**N**	**Y**
Protein Loop Conformations	**N**	**N**	**Y**
Disconnected Systems	**N**	**N**	**Y**
Restraints and Tethers	**N**	**N**	**Y**
Complex Nonbonded Networks	**N**	**N**	**Y**

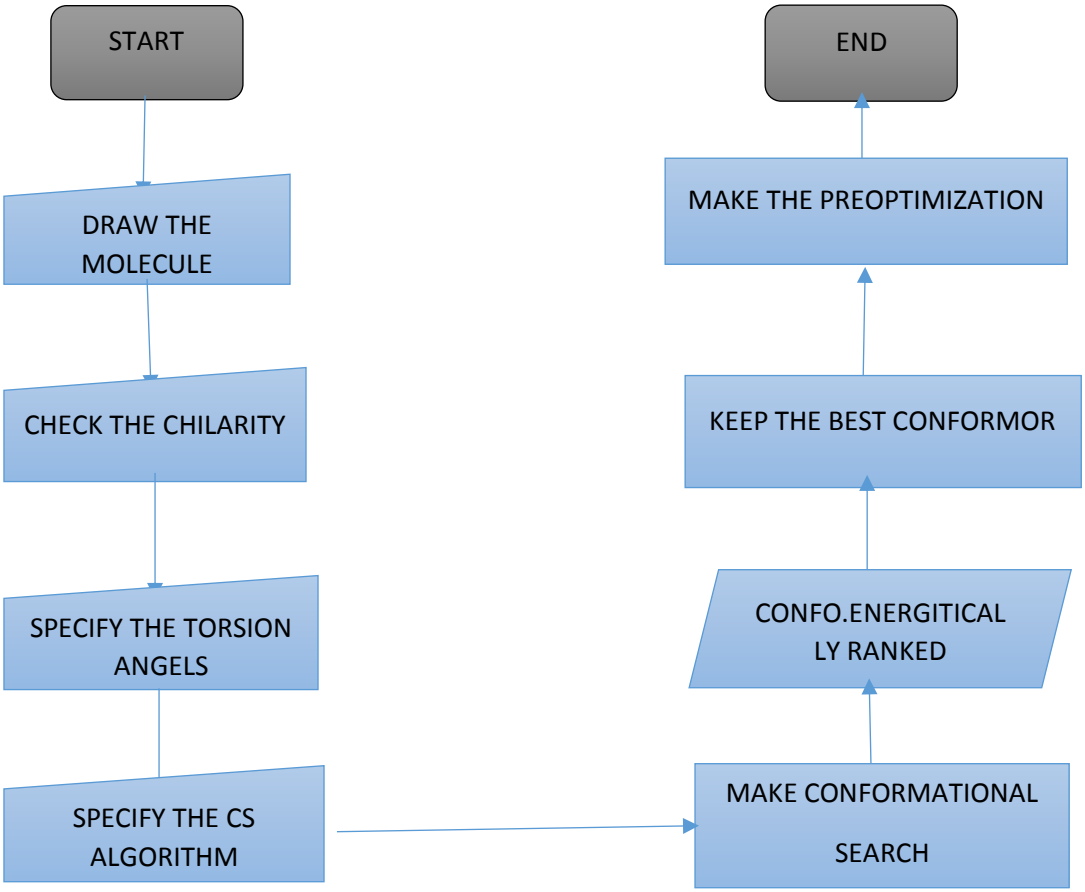


Figure8: Flowchart of conformational search process

2.4 Software

Instructions that tell a computer what to do. Software comprises the entire set of programs, procedures, and routines associated with the operation of a computer system. The term was coined to differentiate these instructions from hardware, the physical components of a computer system. As defined by Britannica.

2.4.1 Avogadro

Avogadro is a free, open source molecular editor and visualization tool, designed for use on Mac, Windows, and Linux in computational chemistry, molecular modeling, bioinformatics, materials science, and related areas. It offers flexible high-quality rendering and a powerful plugin architecture; it is designed to be easy to use to construct and view molecules and materials in 3D. It runs on Windows, Linux, and Mac [67].

2.4.2 HyperChem

HyperChem is a sophisticated molecular modeling environment that is known for its quality, flexibility, and ease of use. Uniting 3D visualization and animation with quantum chemical calculations, molecular mechanics and dynamics, HyperChem puts more molecular modeling tools at your fingertips than any other Windows program. It includes all the components of structure, thermodynamics, spectra, and kinetics [68].

2.4.3 ArgusLab

A molecular modeling, graphics, and drug design program. ArgusLab is a very useful, highly featured and easy-to-use molecular modeling, graphics, and drug design program. The program contains two docking engines and a simple scoring function, based on an enhancement of the X-Score method. The docking engine is less accurate comparing to the specialized docking suites (such as AutoDock, Glide, etc.) but still biologically meaningful. This program is specially recommend as an effective teaching tool to demonstrate molecular docking to beginners in this area [69].

3. Quantitative structure-activity relationship

QSAR (quantitative structure activity relationship) are mathematical models that seek to predict complicated physicochemical / biological properties of chemicals from their simpler experimental or calculated properties QSAR enables the investigator to establishes a reliable quantitative relationship between structure and activity which will be used to derive an in silico model to predict the activity of novel molecules prior to their synthesis. The past few decades have witnessed much advances in the development of computational models for the prediction of a wide span of biological and chemical activities that are beneficial for screening promising compounds with robust properties. This review covers the concept, history of QSAR and the components involved in the development of QSAR models [70].

Quantitative structure – activity relationship (QSAR) modeling pertains to the construction of predictive models of biological activities as a function of structural and molecular information of a compound library. The concept of QSAR has typically been used for drug discovery and development and has gained wide application for correlating molecular information with not only biological activities but also with other physicochemical properties, which has therefore been termed quantitative structure – property relationship (QSPR). QSAR is widely accepted predictive and diagnostic process used for finding associations between

chemical structures and biological activity. QSAR has emerged and has evolved trying to fulfill the medicinal chemist' s need and desire to predict biological response (Hansch C., 1979). It first found its way into the practice of agro chemistry, pharmaceutical chemistry, and eventually most facets of chemistry. QSAR is the final result of computational processes that start with a suitable description of molecular structure and ends with some inference, hypothesis, and predictions on the behavior of molecules in environmental, physicochemical and biological system under analysis (Eriksson et al., 2003).The final outputs of QSAR computations are set of mathematical equations relating chemical structure to biological activity (Golbraikh et al., 2003; Hansch, Sinclair, & Sinclair, 1990; Wedebye, Dybdahl, Nikolov, Jónsdóttir, & Niemelä, 2015). Multivariate QSAR analysis employs all the molecular descriptors from various representations of a molecule (1D, 2D and 3D representation) to compute a model, in a search for the best descriptors valid for the property in analysis [71]. QSAR methodologies have the potential of decreasing substantially the time and effort required for the discovery of new medicines (Gramatica, Giani, & Papa, 2007). A major step in constructing the QSAR models is to find a set of molecular descriptors that represents variations of the structural properties of the molecule (Gramatica, 2007). The QSAR analysis employs statiscal methods to derive quantitative mathematical relationship between chemical structure and biological activity (Ghafourian & Cronin, 2005). The process of QSAR modelling can be divided into three stages: development, model validation and application [72].

The success of any quantitative structure–activity relationship model depends on the accuracy of the input data, selection of appropriate descriptors and statistical tools and, most importantly, the validation of the developed model. Validation is the process by which the reliability and relevance of a procedure are established for a specific purpose. This review focuses on the importance of validation of quantitative structure–activity relationship models and different methods of validation. Some important issues, such as internal versus external validation, method of selection of training set compounds and training set size, applicability domain, variable selection and suitable parameters to indicate external predictively, are also discussed [73].

3.1 Molecular descriptors

Molecular descriptors are powerful tools in QSAR studies, and, according to definition, are the results of the logical and mathematical procedure transforming chemical information encoded within a symbolic representation of a molecule into useful numbers used in some standardized experiments. Molecular descriptors play an increasing role in scientific calculations. Due to their large number within diversified sources of chemical information, they are useful in understanding relationships between molecular structure and experimental evidence [74].

Molecular descriptors encode a wide variety of molecular information and have become the support of many contemporary chemoinformatic and bioinformatics applications. They grasp specific molecular features (e.g., geometry, shape, Pharmacophore, or atomic properties) and directly affect computational models, in terms of outcome, performance, and applicability. This chapter aims to illustrate the impact of different molecular descriptors on the structural information captured and on the perceived chemical similarity among molecules. After introducing the fundamental concepts of molecular descriptor theory and application, a step-by-step retrospective virtual screening procedure guides users through the fundamental processing steps and discusses the impact of different types of molecular descriptors [75].

A molecular descriptor must:

- ✓ Be invariant to atom labeling and numbering.
- ✓ Be invariant to the molecule roto-translation.
- ✓ Be defined by an unambiguous algorithm.
- ✓ Have a well-defined applicability on molecular structures.
- ✓ Additionally, in order to be potentially useful, a molecular descriptor should meet the following requirements:
- ✓ Should have structural interpretation.
- ✓ Should have a good correlation with at least one experimental property.
- ✓ Should not have trivial relation with other molecular descriptors.
- ✓ Should not be based on experimental properties.
- ✓ Should preferably be continuous.
- ✓ Should preferably show minimal degeneracy.
- ✓ Should preferably be simple.

- ✓ Should preferably be applicable to a broad class of molecules.
- ✓ Should preferably be able to discriminate among isomers.
- ✓ Should preferably have calculated values in a suitable numerical range for the set of molecules where it is applicable. [76].

4. DOCKING

Molecular Docking is a method, which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. Given the biological and pharmaceutical significance of molecular docking, considerable efforts have been directed towards improving the methods used to predict docking.

Molecular docking may be defined as an optimization process, which would describe the "best-fit" orientation of a ligand that binds to a particular protein of interest. However since both the ligand and the protein are flexible, a "hand-in-glove" analogy is more appropriate than "lock-and-key". During the course of the process, the ligand and the protein adjust their conformation to achieve an overall "best-fit" and this kind of conformational adjustments resulting in the overall binding is referred to as "induced-fit". The focus of molecular docking is to computationally stimulate the molecular recognition process. The aim of molecular docking is to achieve an optimized conformation for both the protein and ligand and relative orientation between protein and ligand such that the free energy of the overall system is minimized [77].

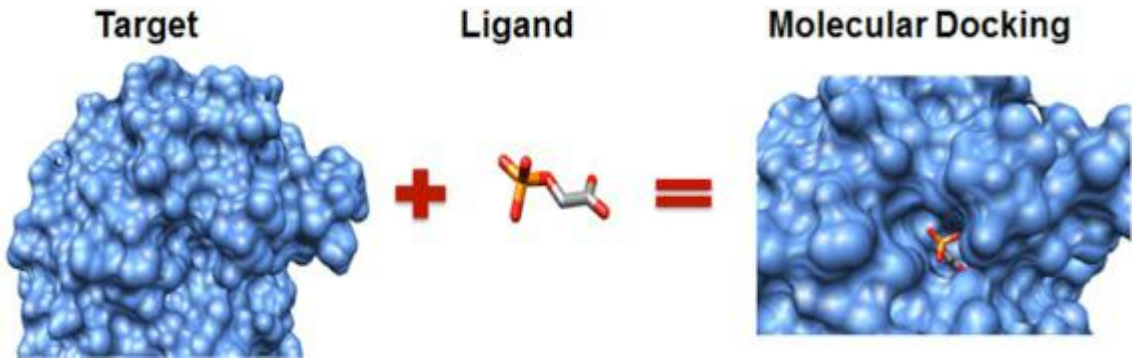


Figure9: Molecular docking

4.1 Software and server

4.1.1 Mopac

Is a semi-empirical quantum mechanics (SQM) package, it has become the QM package of choice in biological calculations. SQM speeds up quantum mechanics calculations by substituting many intermediate calculations with their empirically determined values. As such, it relies on specific parameter sets. MOPAC parameter sets are mostly oriented to biochemistry [78].

4.1.2 DockThor

The program DockThor, developed by the group GMMSB/LNCC, has obtained promising results in comparative studies with other well-established docking programs for predicting experimental binding modes, considering several molecular targets and chemical classes of ligands. The DockThor program has implemented a grid-based method that employs a steady-state genetic algorithm for multiple solutions as the search engine and the MMFF94S force field as the scoring function for pose evaluation. The web server provides the major steps of ligand and protein preparation, being possible to change the residues protonation states and to define the degree of flexibility of the ligand.

There are two types of entries of docking in DockThor: the user defined entry and the Blind docking. Here we used the second entry Blind docking; that refers to docking a ligand to the whole surface of protein without any prior knowledge of the target pocket. Blind docking involves several trials/runs and several energy calculations before a favorable protein-ligand complex pose is found [79].

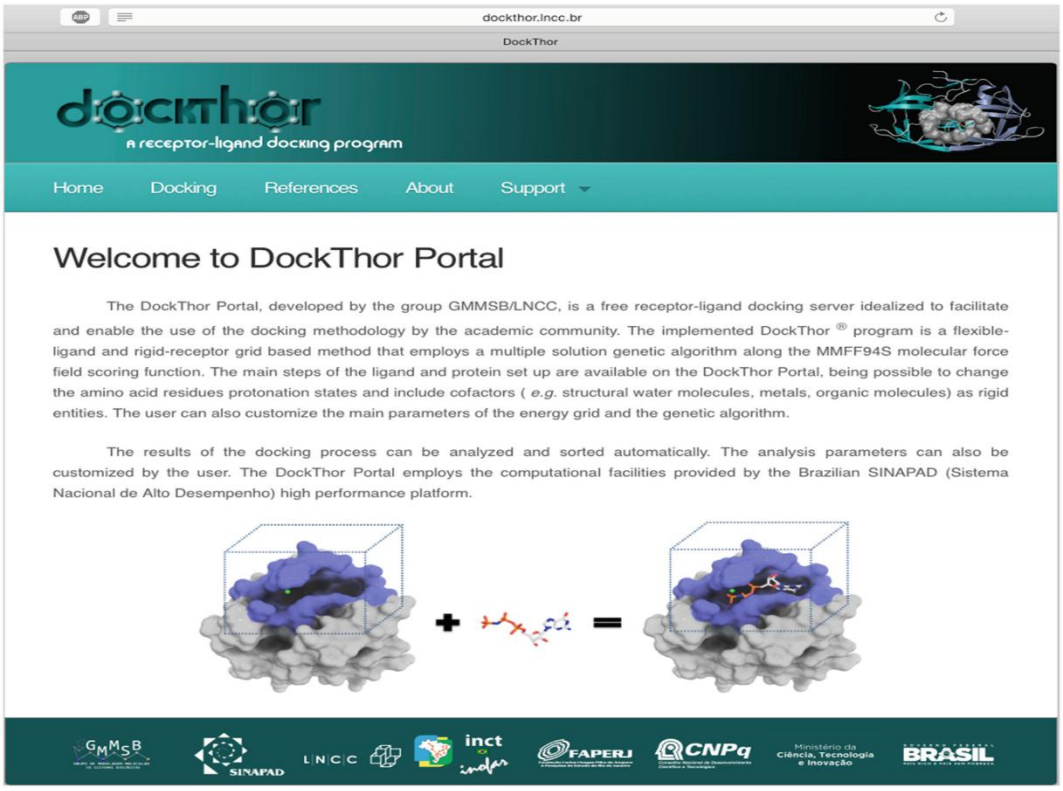


Figure10: DockThor access portal.

4.1.2 Biovia Discovery Studio

Discovery Studio is a suite of software for simulating small molecules and macromolecule systems. It is developed and distributed by Dassault Systemes BIOVIA. Discovery Studio provides software applications covering the following areas:

- Simulations.
- Ligand Design.
- Pharmacophore modeling.
- Structure-based Design.
- Macromolecule design and validation.
- Macromolecule engineering.
- QSAR.
- ADME [80].

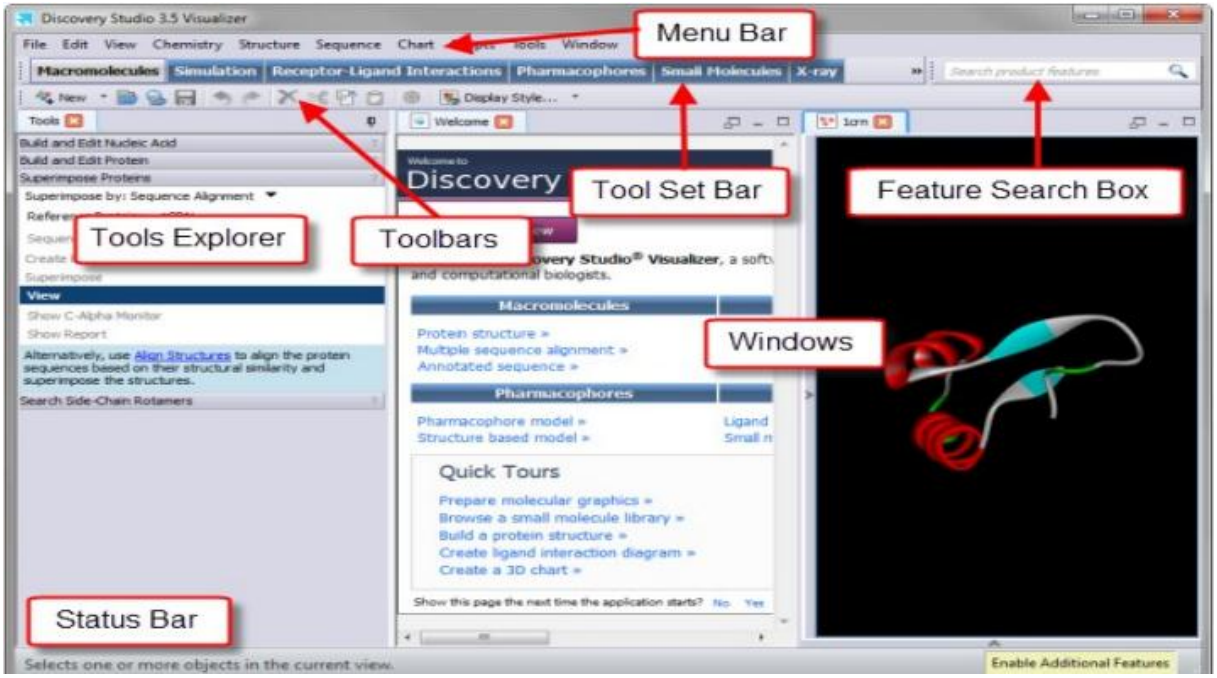


Figure11: DISCOVERY STUDIO VISUALISER

5. Conclusion

In this chapter we have mentioned the different methods used in molecular docking, especially the ones we used in our work in order to reach the desired results and the ability to extract the information to be disclosed. From different molecules structures and binding interactions to docking results and interpretations.

Part B:

Materials and Methods

1. Materials

Molecular docking require the use of the following utilities:

1.1 Personal computer

In our study we used personal computer with a processor of 2.40 GHz Intel Core I5 with installed memory of 4.00 GB, under exploitation system: Windows 2010, 64 bits.

1.2 Data Bases

RSCB PDB: https://www.rcsb.org/structure/4URO

PubChem: https://pubchem.ncbi.nlm.nih.gov/

DrugBank: https://go.drugbank.com/

1.3 Programs

- HyperChem: Molecules structure are saved as .mol file.
- Avogadro: *Molecules structure saved as .mol file in first.

*For the Biovia Discovery Studio the files were converted to .mol2 format.

- Mopac: Atomic coordinates file saved as .mop and dragged to mop.exe to run the calculation and obtain the .aux file with all the optimized information of the molecule.

DockThor: two files' formats: The protein file in (.pdb).

The ligand file in (.mol2).

Resulting a ZIP file containing docking results

- Biovia Discovery Studio: Visualizing docking results with the use of the two previous formats in the resulting of DockThor.

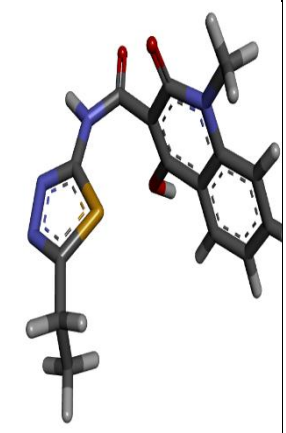
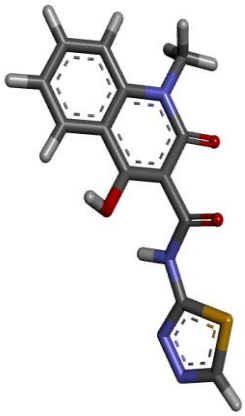
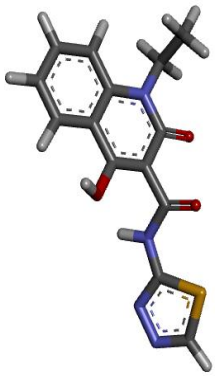
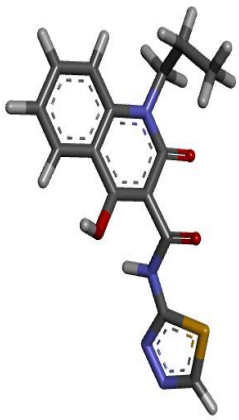
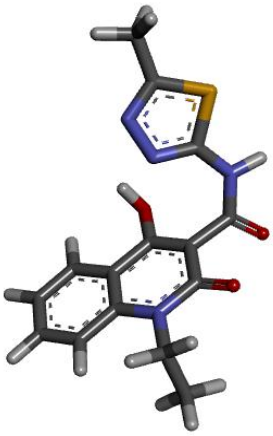
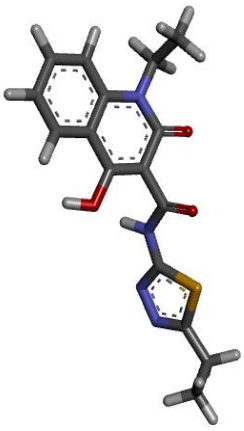
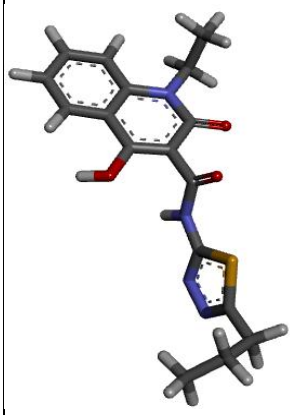
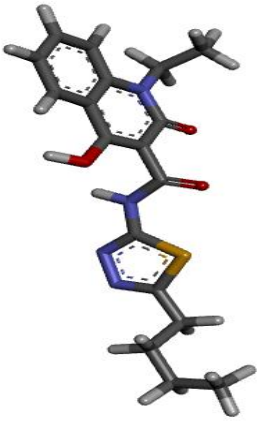
1.4 Molecules set

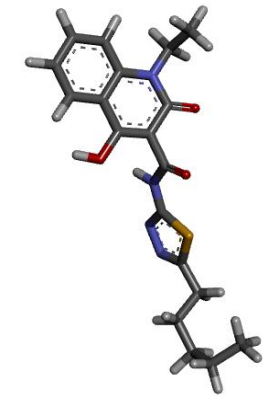
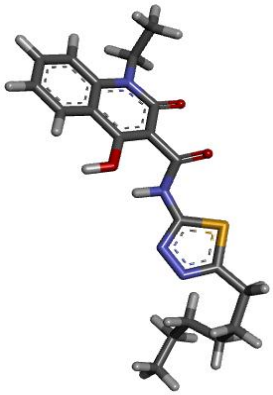
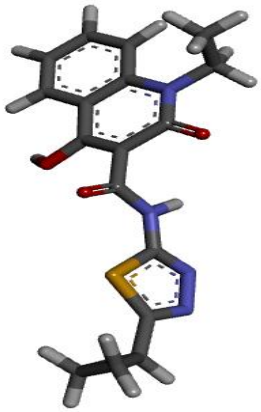
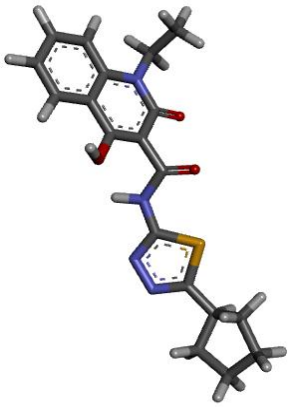
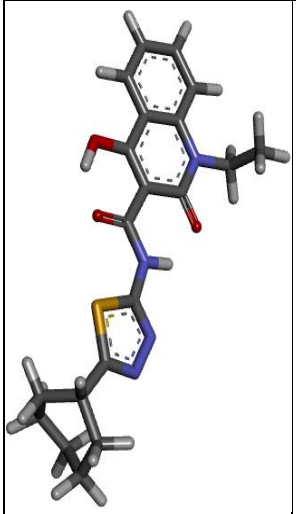
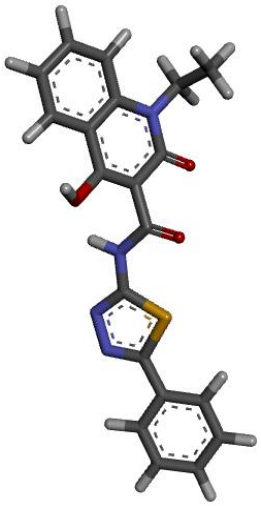
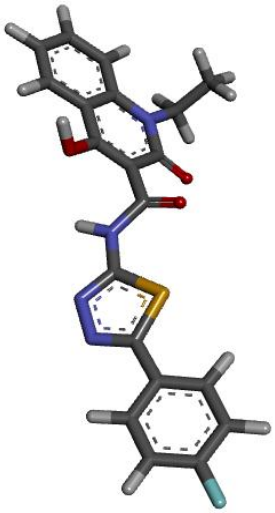
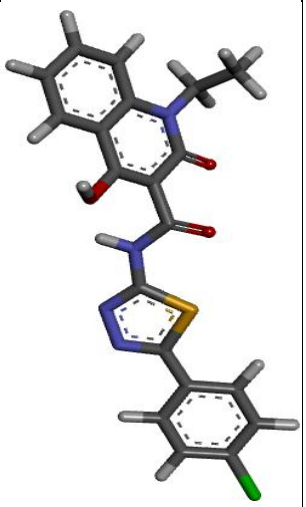
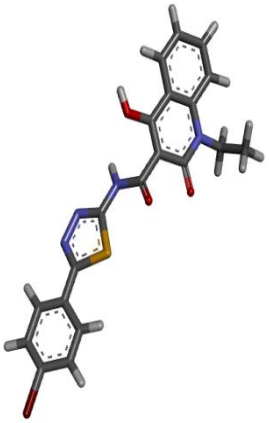
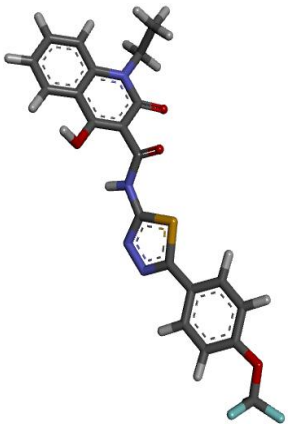
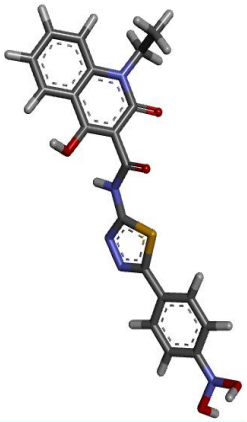
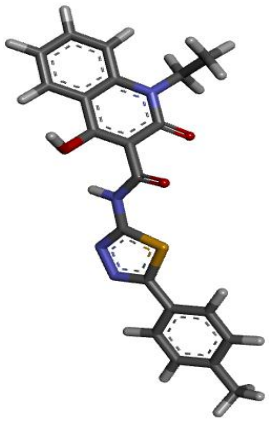
Docked molecules

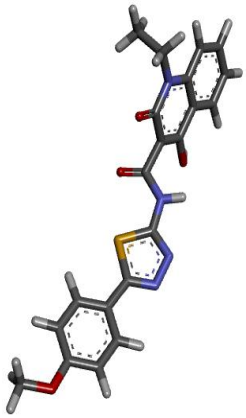
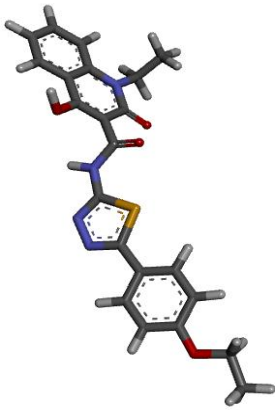
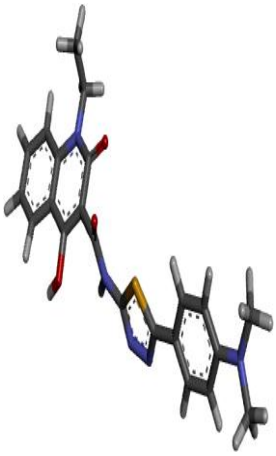
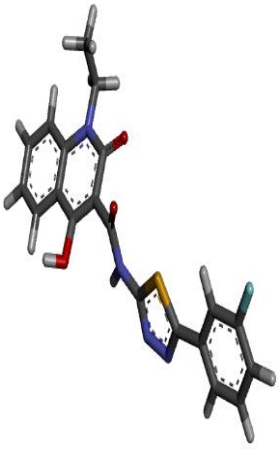
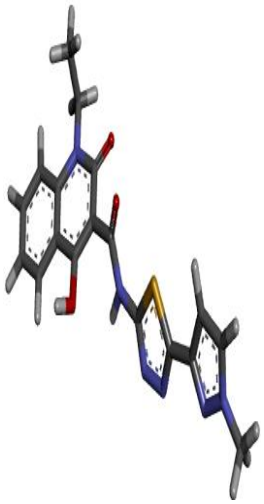
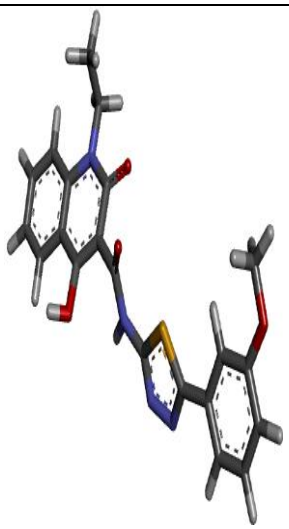
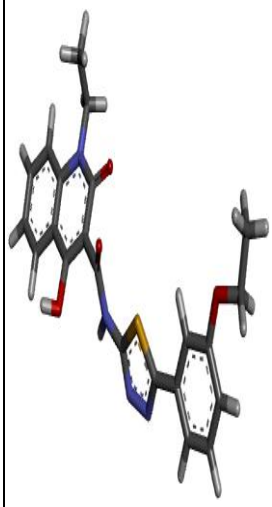
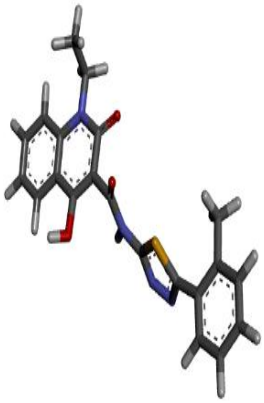
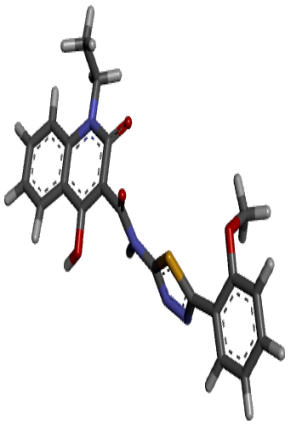
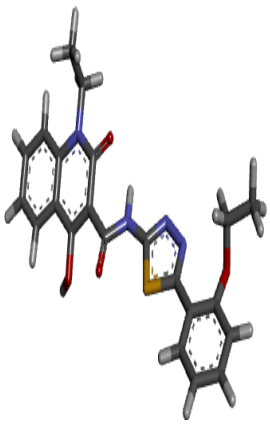
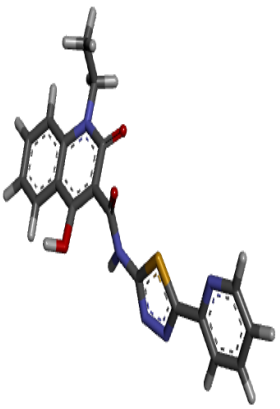
The molecule set selected for this study is composed of 38 molecules extracted from experimental work titled: "N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides bearing heteroaromatic rings as novel antibacterial agents: Design, synthesis, biological evaluation andtargetidentification"(https://www.sciencedirect.com/science/article/abs/pii/S0223523419311808).

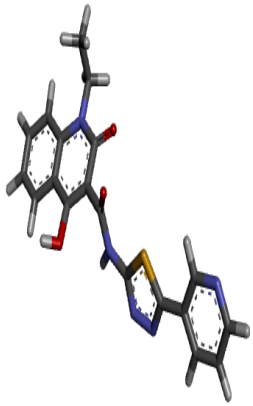
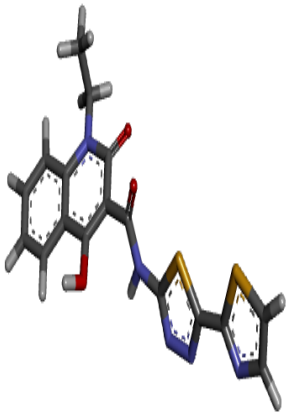
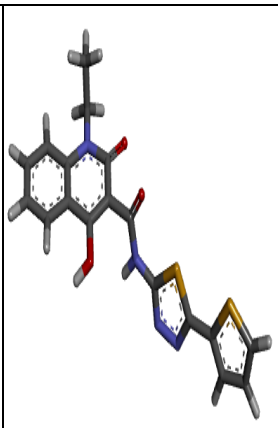
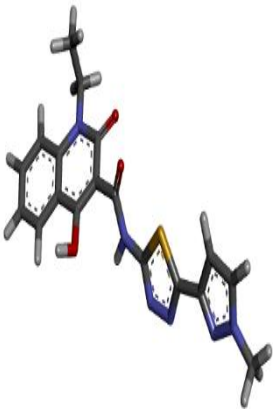
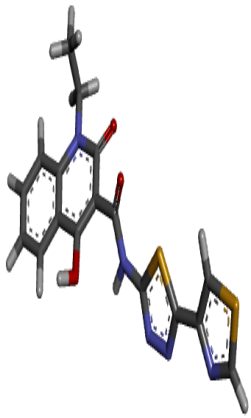
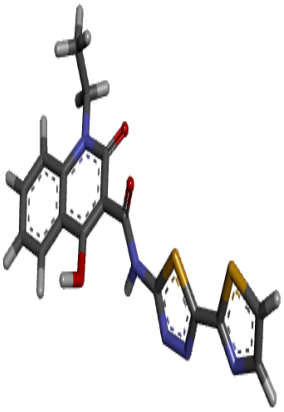
Their nomenclatures and structures are shown in the table below.

Table2: Nomenclatures and structures of molecules.

 11	 g1	 g2	 g3
 g4	 g5	 g6	 g7

 g8	 g9	 g10	 g11
 g12	 g13	 g14	 g15
 g16	 g17	 g18	 g19

 g20-	 g21	 g22	 g23
 g24	 g25	 g26	 g27
 g28	 g29	 g30	 g31

 g32	 g33	 g34	 g35
 g36	 g37		

2. Methods

2.1 Ligand preparation

We draw the molecules (***N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides and it's and derivatives*** from **11** to **g37**) structures 2D using HyperChem,where we performed both optimzation and conformational search.We take as example molecule 11 bellow.

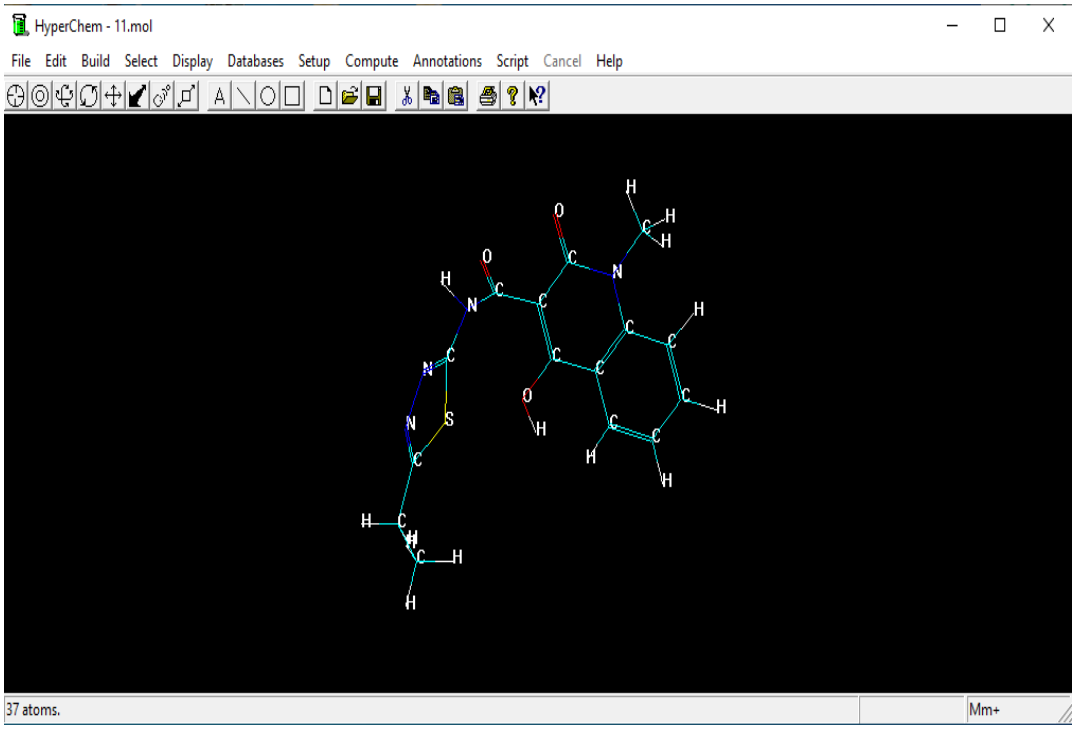


Figure12: 3D optimized structure of molecule 11 in HyperChem

Than we moved them to Avogadro where we performed the same operations to obtain the most stable structure, its visualization and Cartesian editor to extract the atomic coordinates of each atom.

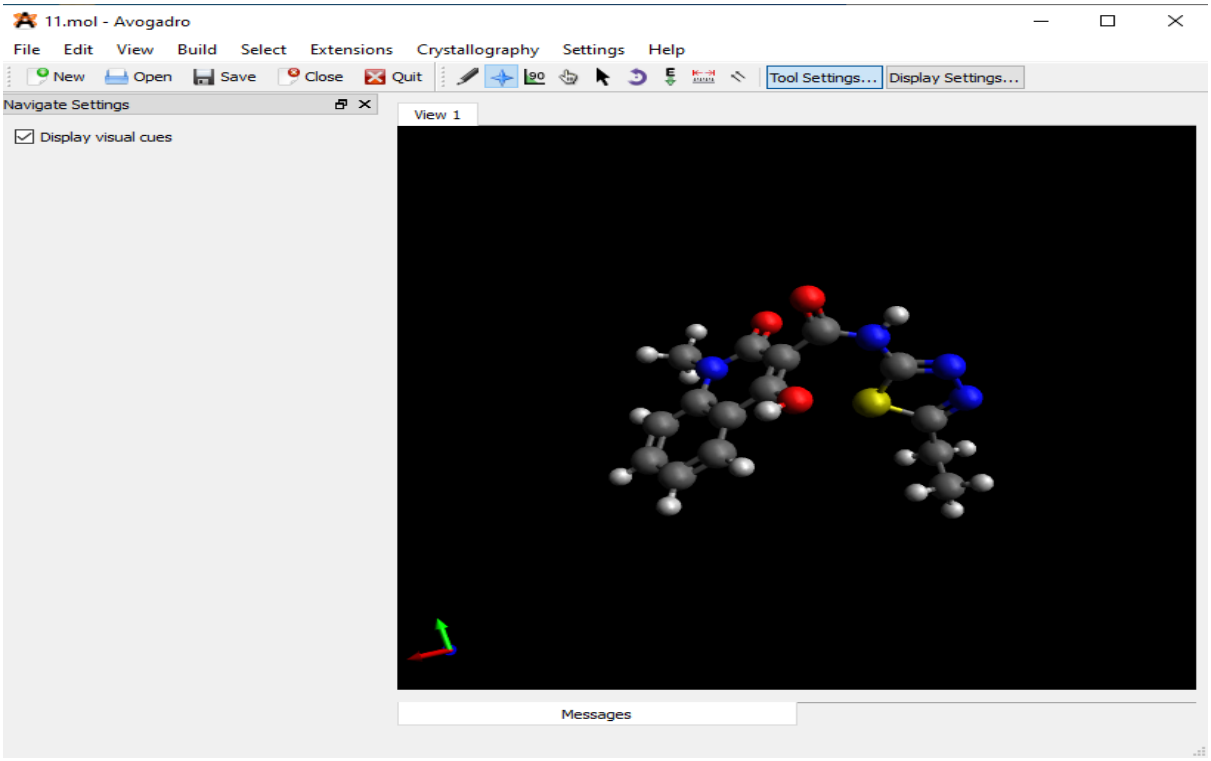


Figure13: 3D optimized structure of molecule 11 in Avogadro.

The coordinates were used as input file MOP format for MOPAC using PM7 method and started the calculations by dragging into mopac.exe .We obtained an AUX file, to extract the atomic values needed of each molecule: the heat of formation, the dipole moment, the total energy, and lastly the values of HOMO and LUMO of each molecule in table below.

Table3: MOPAC calculations results.

MOLECULE	PM7 HEAT_OF_F	TOTAL_E	HOMO	LUMO	DM
11	KCAL/MOL=+0.128707D+02	EV=-0.383620D+04	-9.392	-1.520	0.156754D+02
g1	KCAL/MOL=-0.406220D+02	EV=-0.353895D+04	-9.444	-1.443	0.116910D+02
g2	KCAL/MOL=-0.467720D+02	EV=-0.368894D+04	-9.500	-1.443	0.115663D+02
g3	KCAL/MOL=-0.510058D+02	EV=-0.383884D+04	-9.347	-1.441	0.115596D+02
g4	KCAL/MOL=-0.508410D+02	EV=-0.383876D+04	-9.386	-1.679	0.757601D+01
g5	KCAL/MOL=-0.626033D+02	EV=-0.398910D+04	-9.395	-1.497	0.757601D+01
g6	KCAL/MOL=-0.671997D+02	EV=-0.413903D+04	-9.397	-1.495	0.110504D+02
g7	KCAL/MOL=-0.713710D+02	EV=-0.428896D+04	-9.396	-1.493	0.110431D+02
g8	KCAL/MOL=-0.748367D+02	EV=-0.443884D+04	-9.395	-1.501	0.108486D+02
g9	KCAL/MOL=-0.755574D+02	EV=-0.458859D+04	-9.393	-1.493	0.968396D+01
g10	KCAL/MOL=-0.293892D+02	EV=-0.411075D+04	-9.403	-1.547	0.117378D+02
g11	KCAL/MOL=-0.625340D+02	EV=-0.441166D+04	-9.392	-1.494	0.104982D+02
g12	KCAL/MOL=-0.716901D+02	EV=-0.456158D+04	-9.444	-1.476	0.891698D+01
g13	KCAL/MOL=-0.119069D+01	EV=-0.447879D+04	-9.500	-1.523	0.107640D+02
g14	KCAL/MOL=-0.687581D+02	EV=-0.493189D+04	-9.410	-1.579	0.126243D+02
g15	KCAL/MOL=-0.307940D+02	EV=-0.473321D+04	-9.401	-1.606	0.131329D+02
g16	KCAL/MOL=+0.296318D+01	EV=-0.468772D+04	-9.499	-1.526	0.131775D+02
g17	KCAL/MOL=-0.114196D+03	EV=-0.582729D+04	-9.512	-1.552	0.137371D+02
g18	KCAL/MOL=+0.683679D+01	EV=-0.526533D+04	-7.949	-1.555	0.512750D+01
g19	KCAL/MOL=-0.961589D+01	EV=-0.462891D+04	-9.499	-9.499	0.104003D+02
g20	KCAL/MOL=-0.387337D+02	EV=-0.492367D+04	-9.404	-1.540	0.103918D+02
g21	KCAL/MOL=-0.457596D+02	EV=-0.507372D+04	-9.400	-1.544	0.102310D+02
g22	KCAL/MOL=+0.660072D+01	EV=-0.497783D+04	-8.282	-1.527	0.899562D+01
g23	KCAL/MOL=-0.357383D+02	EV=-0.493049D+04	-9.508	-1.590	0.127108D+02
g24	KCAL/MOL=-0.897400D+01	EV=-0.462888D+04	-9.499	-1.550	0.110389D+02
g25	KCAL/MOL=-0.366623D+02	EV=-0.492358D+04	-9.501	-1.554	0.127472D+02
g26	KCAL/MOL=-0.430293D+02	EV=-0.507361D+04	-9.500	-1.545	0.972595D+01
g27	KCAL/MOL=-0.331818D+02	EV=-0.493039D+04	-9.490	-1.502	0.105205D+02
g28	KCAL/MOL=-0.108366D+02	EV=-0.462893D+04	-9.499	-1.489	0.112669D+02
g29	KCAL/MOL=-0.369643D+02	EV=-0.492355D+04	-9.495	-1.413	0.114132D+02
g30	KCAL/MOL=-0.407999D+02	EV=-0.507346D+04	-9.502	-1.521	0.119062D+02
g31	KCAL/MOL=+0.876339D+01	EV=-0.452854D+04	-9.520	-1.574	0.101410D+02
g32	KCAL/MOL=+0.895002D+01	EV=-0.452854D+04	-9.504	-1.592	0.132719D+02
g33	KCAL/MOL=+0.958303D+01	EV=-0.452851D+04	-9.494	-1.605	0.151066D+02
g34	KCAL/MOL=+0.280605D+01	EV=-0.438287D+04	-9.460	-1.635	0.119000D+02
g35	KCAL/MOL=+0.172851D+02	EV=-0.460496D+04	-9.497	-1.527	0.815264D+01
g36	KCAL/MOL=+0.125240D+02	EV=-0.443256D+04	-9.487	-1.589	0.106480D+02
g37	KCAL/MOL=+0.133762D+02	EV=-0.443252D+04	-9.515	-1.853	0.118654D+02

For the Target protein. Its 3D structure was downloaded from RCSB PDB as a pdb file, only one chain was selected to work with (chain A). Accession Codes: 4url, 4urm, 4urn and 4uro.

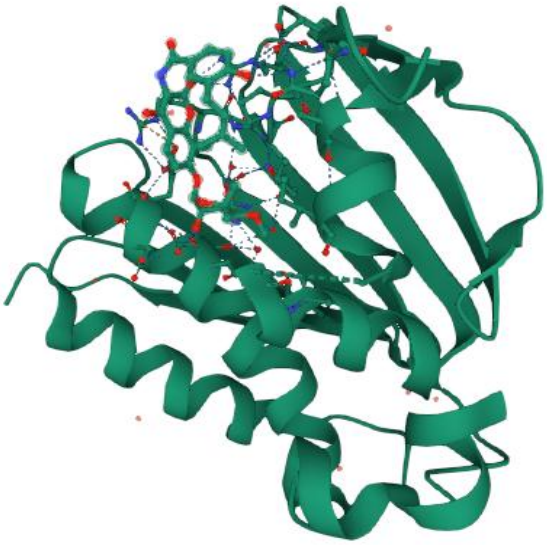


Figure14: 3D structure of 4uro .

A Blind docking was than performed using the online server DockThor, for one of each molecule (*N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides* and its derivatives from 11 to g37) as target ligands with the target protein 4uro results **Table4** in next chapter**.**

We used Biovia Discovery Studio to open data resulted from docking generated by DockThor **Figure** in next chapter.

2.2 Reference Ligand Preparation:

We chose NOVOBIOCINE as a reference ligand to compare it with the other ligands according to their docking scores, in order to select the most suitable ligand with the protein of interest.

Novobiocin; is an antibiotic designed to target DNA gyrase, a bacterial type IIA topoisomerase. Novobiocin acts by competitive inhibition of DNA gyrase. Novobiocin has activity against gram-positive and gram-negative bacteria with higher efficacy against the gram-positive bacteria (most gram-negative bacteria are resistant), especially *S. aureus.*

Firstly, we downloaded the 3D structure from PubChem as a PDB file, then we applied a blind docking of the Novobiocin and 4uro using the DockThor online server.

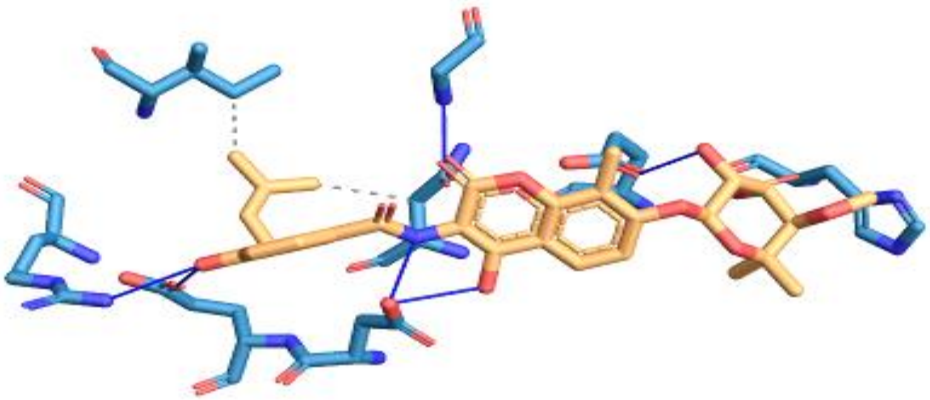


Figure15: NOVOBIOCIN 3D structure

The next step was to collect the results. The obtained results and interactions were displayed in Biovia Discovery Studio.

CHAPTER III

Results and discussion

1. Antibacterial activity

After the in vitro evaluation of the antibacterial activities of *N-thiadiazole-4-hydroxy-2-quinolone-3-carboxamides* are a potential new class of antibacterial agents. The study concluded that the extract has strong antibacterial activity, and based on this study, our work came as an in-silico evaluation to study the antibacterial activity of each of the 38 molecules in this extract and the determination of the molecule responsible for this activity in the case of gram-positive bacteria *Staphylococcus aureus*, with the use of the antibiotic NOVOBIOCIN as a reference.

With the *Staphylococcus aureus* bacteria, we also used DockThor Server to dock the 38 ligands (NOVOBIOCIN is the reference) with the 4URO receptor to determine the molecule responsible for the antibacterial activity in the case of Gram-positive bacteria.

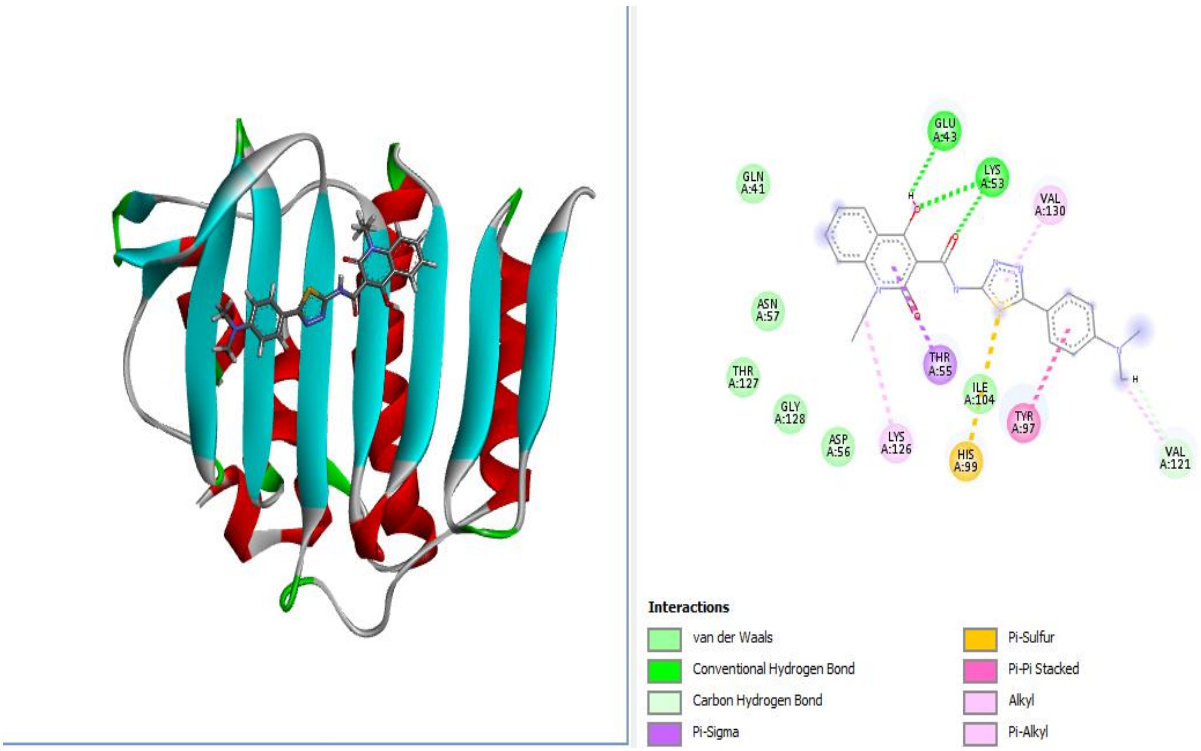


Figure16: Ligand g22-4uro interactions visualization

Out of the top first six results, the ligand with the best docking score with 4uro target protein ranking out of 38 ligands is g22 with score of -8,491kcl/mol, which make it the most active ligand with the protein. There are 8 types of residus in binding site and ligand g22:LYS A:53, GLU A:43, LYS A:126, VAL A:130, THR A:55, HIS A:99, ILE A:104, TYR A:97.

The rest of ligands-protein reaction in the table below:

Table4 : Residus interactions Ligand-Protein.

Complex	**scores(Kcal/mol**	ARGA:132	ARGA:154	ASPA:28	TRPA:51	ASPA:49	GLUA:25	HISA:21	ASPA:32	GLUA:21	GLUA:175	LYSA:53	TRPA:24	GLUA:43	HISA:99	TYRA:97	GLUA:172	VALA:121	THRA:55	ASPA:93	VALA:130	GLUA:33	GLUA:95	ILEA:104	LYSA:126	VALA:54	ILEA:11	ILEA:26	ILEA:61	VALA:96	VALA:82	GLYA:81
g22+4uro	-8,491											++		+	+	+		+ +	+		+										
g25+4uro	-8,479											++		+	+	+			+						+	+						
g17+4uro	-8,414											++		+																		
g24+4uro	-8,396													+	+	+		+	+		+				+							
g20+4uro	-8,386											++		+	+	+		+	+		+					+						
g12+4uro	-8,225		++					++					+																			
g15+4uro	-7,507	++			+ +	+					+																					

g9+4uro	-7,505		+ +	+ + +				+	+																							
g27+4uro	-7,496	+ +				+					+		+				+															
g19+4uro	-7,463	+ +			+						+								+			+										
g28+4uro	-7,440	+ +				+							+ +																			
g11+4uro	-7,416																									+ +		+		+			
g21+4uro	-7,404	+ +			+	+																											
g23+4uro	-7,401	+ +			+ +	+					+																					
g13+4uro	-7,397	+ +			+ +	+					+																					
g26+4uro	-7,370	+ + +			+	+													+			+										
g32+4uro	-7,355	+ +			+ +	+					+																					
g33+4uro	-7,341	+ +			+ + +	+					+																					
g8+4uro	-7,337	+ +			+ +	+																											
g30+	-7,								+ +													+ +							+	+	+	

4uro	328																													
g16+4uro	-7,302		++				+	+	++																					
g29+4uro	-7,295	++			+	+											+													
g31+4uro	-7,292	++			++	+											+													
g34+4uro	-7,275	++			++	+					+																			
g10+4uro	-7,187	++			++	+																								
g14+4uro	-7,029		++	++					+																					
g35+4uro	-6,963		++	++			+	+																						
g37+4uro	-6,901		++	++			+		+																					
g7+4uro	-6,896		++	++			+																							
g36+4uro	-6,871		++	++			+		+																					
g6+4uro	-6,820		++	++			+																							
g18+4uro	-6,791	++			+						+										+									

g3+4uro	-6,730		+	+ +			+	+					+																	
g5+4uro	-6,681		+ +	+ +			+	+																						
g4+4uro	-6,663		+ +	+				+ + +																						
g2+4uro	-6,596		+	+ +			+	+					+																	
11+4uro	-6,582		+ +	+			+																				+			
g1+4uro	-6,524		+ +	+ +			+ +		+																					

+	Conventional Hydrogen Bond	+	Pi-Doner Hydrogen Bond	+	Pi-Alkyl
+	Pi-sulfure	+	Pi-Pi Stacked	+	Pi-Sigma

2. Reference ligand (Novobiocin) docking results

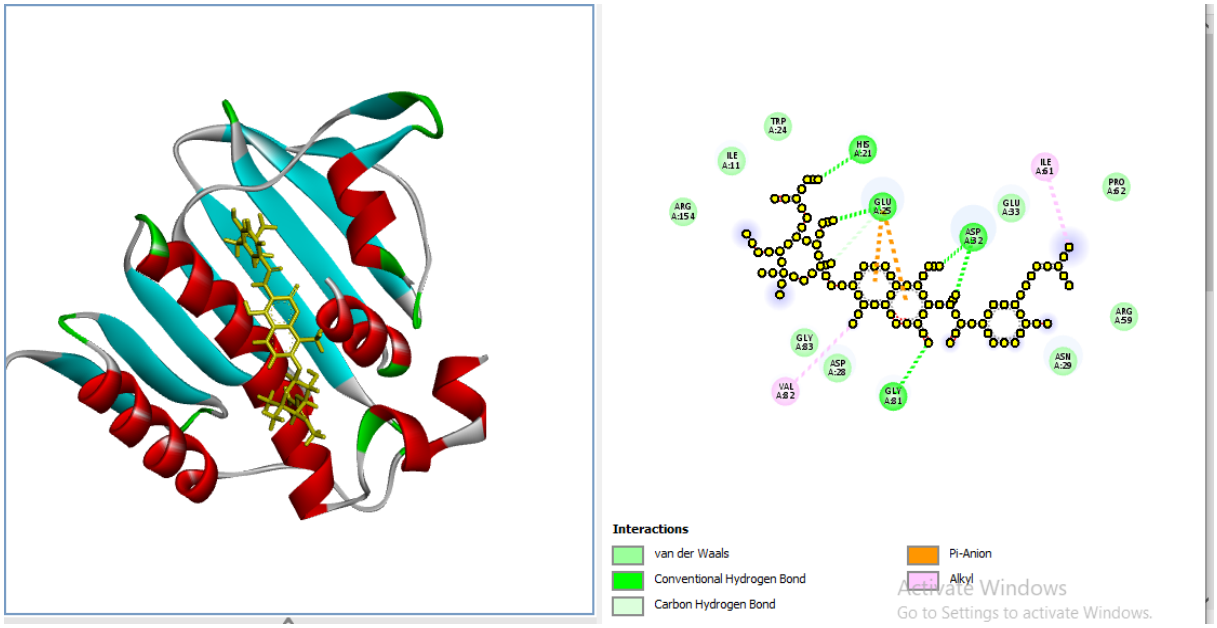


Figure17: Ligand Novobiocin-4uro interactions visualization

The score obtained by docking of Novobiocin and 4uro was of -7,436.And a total of 3 hydrogen bonds interactions: LEU A:202 with two bonds and ILE A:209 with one bond.

Table5: docking scores of all the Ligands-Protein of study

Complex	Docking scores(kcl/mol)
g22+4uro	-8,491
g25+4uro	-8,479
g17+4uro	-8,414
g24+4uro	-8,396
g20+4uro	-8,386
g12+4uro	-8,225
g15+4uro	-7,507
g9+4uro	-7,505
g27+4uro	-7,496
g19+4uro	-7,463
g28+4uro	-7,440
Novobiocin+4uro	-7,436
g11+4uro	-7,416
g21+4uro	-7,404
g23+4uro	-7,401
g13+4uro	-7,397
g26+4uro	-7,370
g32+4uro	-7,355
g33+4uro	-7,341
g8+4uro	-7,337
g30+4uro	-7,328
g16+4uro	-7,302
g29+4uro	-7,295
g31+4uro	-7,292
g34+4uro	-7,275
g10+4uro	-7,187
g14+4uro	-7,029
g35+4uro	-6,963
g37+4uro	-6,901
g7+4uro	-6,896
g36+4uro	-6,871
g6+4uro	-6,820
g18+4uro	-6,791
g3+4uro	-6,730
g5+4uro	-6,681
g4+4uro	-6,663
g2+4uro	-6,596
11+4uro	-6,582
g1+4uro	-6,524

Based on the docking scores obtained and the interactions found we noticed that:

g22-4uro score is inferior than the Novobiocin-4uro score (-8,491kcl/mol<-7,436 kcl/mol)

And number of interactions between binding site of 4uro and g22 are superior to the number of interactions between binding site of 4uro and Novobiocin. For that, we conclude, g22 is more interactive with 4uro which makes it an active ligand.

Conclusion

The main aim of this work was to introduce us to the different tools of biological simulation in particular molecular docking using DockThor in order to search for new bacterial activity inhibitors of the gram positive bacteria *S.aureus*.

Starting from molecule 11 to molecule 37 with target protein 4uro, and taking as reference the antibiotic Novobiocin, we identified six compounds with better antibacterial activity than Novobiocin. Based on docking scores obtained, we identified compound g22 as the most promising compound.

As a future perspective, In *vitro* and/or in *vivo* tests of the biological activity of the g22 inhibitor are recommended to supplement the theoretical results and verify the effectiveness of the in *silico* approach.

References

[1].Https://pubmed.ncbi.nlm.nih.gov/27873247/

[9].https://www.researchgate.net/publication/319406552_INTRODUCTION_TO_PHYTOCHEMISTRY

[10].https://www.collinsdictionary.com/word-lists/chemistry-branches-of chemistry#chemistry-branches-of-chemistry1.

[11].https://study.com/academy/lesson/what-are-phytochemicals-zoochemicals.html

[12]. https://www.sisd.net

[16].https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/small-molecule.

[19].https://link.springer.com/chapter/10.1007/978-3-662-58499-6_2

[20] . https://www.polk.k12.ga.us

[24].https://www.genome.gov/genetics-glossary/Nucleic-Acid

[29].https://www.genome.gov/genetics-glossary/RNA-Ribonucleic-Acid.

[42].https://courses.lumenlearning.com/boundless-biology/chapter/lipids

[44].https://www.tesisenred.net/bitstream/handle/10803/6435/Chapter1.pdf?sequence=2&isAllowed=y/15/06/2021.

[69]. http://www.arguslab.com/arguslab.com/ArgusLab.html

[80].(https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/)

[2]. Argyris S Michalopoulos, Ioannis G Livaditis, Vassilios Gougoutas , The revival of fosfomycin , 2011.

[3]. TAOUTAOU Rania Malek,BENFADEL Yasmine, Computer Aided Drug Design of Novel Active Polyphenols: QSAR,September 16, 2020.

[4].Biomolecule, kara rogers , Aug 09, 2016,https://www.britannica.com/science/biomolecule

[5]. Kushagri Singh, Kavita Singh, Antiviral and Antimicrobial Potentiality of Nano Drugs, 2019.

[6] .James Hamuel Doughari,Phytochemicals: Extraction Methods, Basic Structures and Mode of Action as Potential Chemotherapeutic Agents ,March 2012.
[7]. Deepack Koche, Rupali Shirsat& Mahesh Kawale, an overerview of major classes of phytochemicals: their types and role in disease prevention , August 2018
[8] . Nilesh R. Vaghela, Subrota Hati and H. G. Patel ,Applications of Functional Plant based Food Ingredients.

[13]. Cristiano Chiarabelli, Pasquale Stano and Pier Luigi Luisi, Chemical synthetic biology: a mini-review Front. Microbiol., 23 September 2013.
[14]. Divya narayan ,Significance of synthetic Biomolecules , 2016-06-03.
[15]. Sneha Govardhanagiri , Ganji Purnachandra Nagaraju , Small Molecules and Pancreatic Cancer Trials and Troubles , 2019.

[17]. HM Hatcher , Principles of systemic therapy , 2011.

[18]. Xiaowen Wang , Wenjin Li , Molecular Dynamics Simulation of Biomolecular Interactions , 2021.
[21]. John London ,Updated April 26, 2018 , The Function of Macromolecules.

[22]. Lehninger, AL. et al. Lehninger principles of biochemistry. 2000; Worth Publishers, New York.

[23]. Rizwan Hasan Khan, Mohammad Khursheed Siddiqi and Parveen Salahuddin, Protein Structure and Function , March27,2017.

[24] . Helmut Burtscher, Sibylle Berner,Rudolf Seibl,Klaus Muhlegger , Nucleic Acids , 2007.

[25] . Guoyao Wu , Amino acids: metabolism, functions, and nutrition , Published20 March 2009.
[26] . Linus Pauling And Robert B. Corey, A Proposed Str Ucture For The Nucleic Acids, Communicated, December 31, 1952.

[28] . Brenno A. D. Neto and Alexandre A. M. Lapis , Recent Developments in the Chemistry of Deoxyribonucleic Acid (DNA) Intercalators: Principles, Design, Synthesis, Applications and Trends ,7 May 2009.

[30] . Gray, Michael W ,Beyer, Ann L , Ribonucleic acid (RNA) , Last reviewed:August 2020.

[31] . Damodaran vasudevan , kannan vaidyanathan , Chapter-04 Proteins: Structure and ,Function , January 2017.

[32] . Mr. Kevin A. Boudreaux , Proteins , www.angelo.edu/faculty/kboudrea

[33] . Diego . Navarro, Jerubella J. Abelilla and Hans H. Stein, Structures and characteristics of carbohydrates in diets fed to pigs.2019.

[34] . Suman Khowala, Deepak Verma, Samudra P. Banik , Carbohydrates ,2008.

[35] . Mr. Kevin A. Boudreaux , Carbohydrates , www.angelo.edu/faculty/kboudrea.

[36] . Eoin Fahy, Dawn Cotter, and Shankar Subramaniam , Lipid classification, structures and tools,November2011.

[37] . Dave A. Higgs , Lipids and fatty acids , 17 February 2017 .

[38] . Dr. BEKARA A , Synthèse Des Biomolécules ,(2020/2021)

[39] . Lehninger, Albert L, Nelson, David L.Cox, Michael M ,Lehninger Principles Of Biochemistry. 2000

[40] . Lampe, M. A.et al. "Human Stratum Corneum Lipids: Characterization And Regional Variations**.**

[41] . Ketsia Raynal-Ljutovac,et al , Organisation structurale et moléculaire des lipides dans les aliments : impacts possibles sur leur digestion et leur assimilation par l'Homme (Novembre-Décembre 2011)

[43]. D. Adhya, E. Annuario, and D. P. Srivastava , Understanding the role of steroids in typical and atypical brain development, 3 October 2017, Journal of Neuroendocrinology.

[38]. TAOUTAOU Rania Malek,BENFADEL Yasmine, Computer Aided Drug Design of Novel Active Polyphenols: QSAR,September 16, 2020.

[39]. Nagraj Mani, et al , In Vitro Characterization of the Antibacterial Spectrum of Novel Bacterial Type II Topoisomerase Inhibitors of the Aminobenzimidazole Class, Antimicrob Agents Chemother. Apr2006.

[45].Barbara Calabrese, Cloud-Based Molecular Modeling Systems,in Encyclopedia of Bioinformatics and Computational Biology, 2019

[46]. Cristiano R. W. Guimarães,and Yifat Miller3, Molecular Modeling: Advancements and Applications , 12 Sep 2013.

[47]. Nathalia Salles Vernin Barbosa, ... Frederico Wanderley Tavares, Molecular Modeling inChemical Engineering,2017.

[48]. J. Bentley ,Computers and modelling in paint and resin formulating , 1999,

[49].TAMARA GUND, Molecular Modeling of Small Molecules, in Guidebook on Molecular Modeling in Drug Design, 1996.

[50]. Kenno Vanommeslaeghe et al, Molecular Mechanics, Author manuscript; available in PMC 2015 Jan 1.

[51]. Rama Rao Nadendla, Molecular Modeling: A Powerful Tool for Drug Design and Molecular Docking, RESONANCE, May 2004.

[52]. Qiang Cui and Marcus Elstner, Density Functional Tight Binding: values of

semi-empirical methods in an ab initio era, Physical Chemistry Chemical Physics(Page 1- 29).

[53], [54], [55] Dr. Kalju Kahn, Department of Chemistry and Biochemistry, UC Santa Barbara. 2006-2007.

[56]. Michael Dewar and Walter Thiel in J. Am. Chel. Soc. 99, 4899-4907 (1977)

[57]. Dewar, Zoebisch, Healy, and Stewart, "AM1: A New General Purpose Quantum Mechanical Molecular Model." J. Am. Chem. Soc. 1985, 107, 3902 – 3909.

[58]. Erica Mitchell , Quantum Chemical Methods: Its history and future , Taylor University, December 12, 2019.

[59]. Álvaro Vázquez–Mayagoitia, Robert J. Harrison, , Chapter One - Quantum Chemistry Methods with Multiwavelet Bases on Massive Parallel Computers, Annual Reports in Computational Chemistry ,Volume 10, Pages3-24, 2014.

[60]. Tanja van Mourik, Michael Bühl, and Marie-Pierre Gaigeot , Density functional theory across chemistry, physics and biology , 2014 Mar 13.

[61,62]. Chapter 9: Density Functional Theory (DFT) Methods, Key notes, Institute for Computational Physics Universität Stuttgart Allmandring 3, Germany

[63]. C. A. Floudas , P. M. Pardalos, Optimization in Computational Chemistry and Molecular Biology: Local and Global Approaches, January 2000.

[64]. Markus J. Loferer a, Istvan Kolossvary , Andras Aszodi,Analyzing the performance of conformational search programs on compound databases, (2007).

[65, 66]. Generating and Analyzing Conformations , Chemical Computing Group, https://rcweb.dartmouth.edu/doc/MOE/Documentation/apps/confsrch.htm

[67].Learning Avogadro the molecular editor, https://dasher.wustl.edu/chem430/software/avogadro/learning-avogadro.pdf

[68]. HyperChem, The First Choice for PC-Based Molecular Modeling, F E A T U R E S U MMARY,https://www.chemits.com/en/assets/templates/chemits/download/hypercube/HyperChem.pdf.

[70-72]. Umma Muhammad , et al,Quantitative Structure Activity Relationship (Qsar) Modeling, International Journal of Advanced Academic Research (May 2018).

[73]. Kunal Roy, On some aspects of validation of predictive quantitative structure–activity relationship models, Pages 1567-1577 ,26 Nov 2007.

[74]. Leszek Bober et al Pharmacological Classification of Drugs by Principal Component Analysis Applying Molecular Modeling Descriptors and HPLC Retention Data, Journal of Chromatographic Science, Vol. 49, November/December 20.

[75]. Francesca Grisoni, Viviana Consonni, Roberto Todeschini, Impact of Molecular Descriptors on Computational Models, Computational Chemogenomics pp 171-209

[76]. A.Mauri ,V. Consonni ,R. Todeschini , Molecular Descriptors , pages 2065-2093, 2017.

[77]. Laxmi Tripathi, Praveen Kumar, Jamshed Haneef, Ranjit Singh, Molecular Docking Softwares.

[78]. MOPAC2012, James J. P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA,15/05/2021

[79]. DockThor 2 .0: a Free Web Server for Protein-Ligand Virtual Screening, I. A. Guedes, Eduardo Krempser, E. Dardenne,Published 2017

Abstract

Bacterial infectious diseases have become a serious threat to public health. Novel class: N-thiadiazole4-hydroxy-2-quinolone-3-carboxamides are a potential new class of antibacterial agents. Molecular docking analysis has been one of the most basic and important strategy for drug discovery. It allows prediction of molecular interactions that hold together a protein and a ligand in the bound state

Considering the significance of computer aided approaches in drug design. Multiple approaches and calculations were executed in order to better analyze the compounds used in our work (11-g37). Besides to that, the comparative analysis of the DockThor results of the different complexes of the protein 4uro and the compounds in order to determine the most favorable compound as the inhibitor of the toxic aspect of S. *aureus.*

Keywords: Molecular docking, drug design, S.aureus, inhibiter

Résumé

Les maladies infectieuses bactériennes sont devenues une menace sérieuse pour la santé publique. Nouvelle classe : les N-thiadiazole4-hydroxy-2-quinolone-3-carboxamides sont une nouvelle classe potentielle d'agents antibactériens. L'analyse d'amarrage moléculaire a été l'une des stratégies les plus fondamentales et les plus importantes pour la découverte de médicaments. Il permet de prédire les interactions moléculaires qui maintiennent ensemble une protéine et un ligand à l'état lié.

Tenir compte de l'importance des approches assistées par ordinateur dans la conception de médicaments. Plusieurs approches et calculs ont été effectués afin de mieux analyser les composés utilisés dans notre travail (11-g37).En plus , l'analyse comparative des résultats de DockThor des différents complexes de la protéine 4uro et des composés afin de déterminer le composé le plus favorable comme inhibiteur de l'aspect toxique de S.aureus .

Mots clés : Docking moléculaire, conception de médicaments, S.aureus, inhibiteur

ملخص

أصبحت الأمراض المعدية البكتيرية تهديدا خطيرا للصحة العامة.

N-thiadiazole4-hydroxy-2-quinolone-3-carboxamides هي فئة جديدة محتملة من العوامل المضادة للبكتيريا. يعد تحليل الالتحام الجزيئي أحد أهم الاستراتيجيات الأساسية لاكتشاف الأدوية. يتنبأ بالتفاعلات الجزيئية التي تربط البروتين والجزيء معًا في الحالة المرتبطة.

بالنظر إلى أهمية المقاربات الحاسوبية في تصميم الأدوية. تم تنفيذ العديد من هذه المقاربات والحسابات من أجل تحليل أفضل للمركبات المستخدمة في عملنا (g37-11). إضافة إلى ذلك، نتائج التحليل المقارن المتحصل عليها عن طريق للمركبات المختلفة من البروتين 4uro و الجزيئات من اجل تحديد المركب الأنسب للعمل كمثبط للجانب السام للبكتيريا المدروسة *S.aureus*.

الكلمات المفتاحية :تحليل الإلتحام الجزيئي، تصميم الأدوية،*S.aureus* ، مثبط.