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ENTITLE:

Anti-HIV Small Molecules as SARS-CoV-2 Inhibitors : Molecular Docking Study.

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Anti-HIV Small Moleculesas SARS-CoV-2 Inhibitors : Molecular Docking Study.

Abstract (English)

COVID-19 pandemic situation urges researchers to investigate intensively towards finding a drug by several theoretical techniques mainly by the molecular docking approach. It was found that there are similarities between DNAs of HIV and SARS-CoV2, therefore molecules with anti-HIV activity may have an anti-SARS-CoV2 simultaneously.

In this investigation we selected 27 anti-HIV molecules from the scientific literature. These molecules were docked by the DockThor server and ranked by its score function against SARS-CoV2 Main Protease (PDB id: 6LU7). It was found that two molecules A20 and A19 have significant anti-SARS-CoV2 activities i.e. -8.428 and -8.234 respectively. These molecules were bound in the active site of the SARS-CoV2 Main Protease especially with the residues : Lys5, Lys137,Agr4, Glu288.

Acknowledgments

Firstofall,wepraiseALLAHourcreatorforgivingusthestrengthandpatienceto accomplish this work.

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Wewouldalsoliketothankourprofessorsfortheirmightyeffortsoverthepast3years.

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,gavemepatience,andsupportedmeinallaspectsofmylifetoreachwhatIamnow. To my dear family 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.
The loss of my father will always sting. But now, everything that I do is in honor of him. Dad ,your guiding hand on my shoulder will remain with me forever ,and Everything I do in my life I do to make my mum and dad proud. I want to carry on in my dad's footsteps and make sure that his legacy lives on forever. "Dad, your guiding hand on my shoulder will remain with me forever."

to my family who supported and helped me, especially my mother and my dearest brothersfortheirconstantencouragementtomeandfortransformingmomentsofanxiety into moments of laughter and joy

To all my friends for their support and useful advice.

Amine

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Introduction

COVID-19 pandemic situation urges researchers to investigate intensively towards findingadrugbyseveraltheoreticaltechniquesmainlybythemoleculardockingapproach.It was found that there are similarities between DNAs of HIV and SARS-CoV2, therefore molecules with anti-HIV activity may have an anti-SARS-CoV2 simultaneously.

In this investigation we screened and selected 27 anti-HIV molecules from the scientific literature to be tested by the molecular docking approach against SARS-CoV-2 Main Protease protein which is directly related to the replication of the coronavirus.

The molecular docking was adopted as a computational method to find the best leads among a series of anti-HIV compounds. The DockThor algorithm was utilized to rank thedataset.Severaladditionalsoftwarewerealsoemployedforoptimization,conformational search and the visualization.

This dissertation starts with an introduction then followed by four chapters. in the first chapter we exposed the biomolecules chemistry and their related biological activities especially the antiviral one. The second chapter described the main theoretical approaches utilized in Computational chemistry and biology from molecular mechanics to DFT approaches. The third chapter describes the materials i.e. the software and servers which were utilized to perform our calculations. The last chapter the results were shown and the discussions were developed and finally a conclusion.

CHAPTER I:

Biomolecules Chemistry and Antiviral Activity

The animal orplantcellscanperformthelife-sustainingtaskswiththehelpofseveral organic molecules present in them. These organic molecules are referred to as biomolecules also called biological molecules.

The biomolecules have a wide range of sizes and structures,andtheyareinvolvedina vast array of life functions. They are composed of more than 25 naturally occurring elements,withtheprimaryelementsbeingcarbon,hydrogen,oxygen,phosphorus,andsulfur.
Carbon compounds have major involvement in the formation of biomolecules. They covalently bind with other elements to form several other compounds. Biomolecules are theessential buildingblocks of life and perform important functions in living organisms.[1]. Some biomoleculesareconsideredderivativesofhydrocarbons;theyareformedbyreplacing hydrogen atoms from functional groups like alcohols, amines, aldehydes, ketones, and carboxylic groups.[2].

1.1- Phytochemicals

Phytochemicals are chemicals of plant origin. Phytochemicals (from Greek *phyto*, meaning "plant") are chemicals produced by plants through primary or secondary metabolism. They generally have biological activity in the plant hostandplayaroleinplant growth or defense against competitors, pathogens, or predators.

Phytochemicals generally are regarded as research compounds rather than essential nutrients because proof of their possible health effects has not been established yet. Phytochemicals under research can be classified into major categories, such as carotenoids and polyphenols, which include phenolic acids, flavonoids, and stilbenes/lignans.Flavonoids can be further divided into groups based on their similar chemical structure, such as anthocyanins, flavones, flavanones, and isoflavones, and flavonols.Flavanols further are classified as catechins, epicatechins, and proanthocyanidins. In total, there have been over 25,000 phytochemicals discovered and in most cases, thesephytochemicalsareconcentrated in colourful parts of the plants like fruits, vegetables, nuts, legumes, and whole grains, etc.

Phytochemists study phytochemicals by first extracting and isolating compoundsfrom the origin plant, followed by defining their structure or testing in laboratory model systems,such as cell cultures, in vitro experiments, or in vivo studies using laboratoryanimalsChallengesinthatfieldincludeisolatingspecificcompoundsanddeterminingthe ir

structures, whichareoftencomplex,andidentifyingwhatspecificphytochemicalisprimarily responsible for any given biological activity [3].

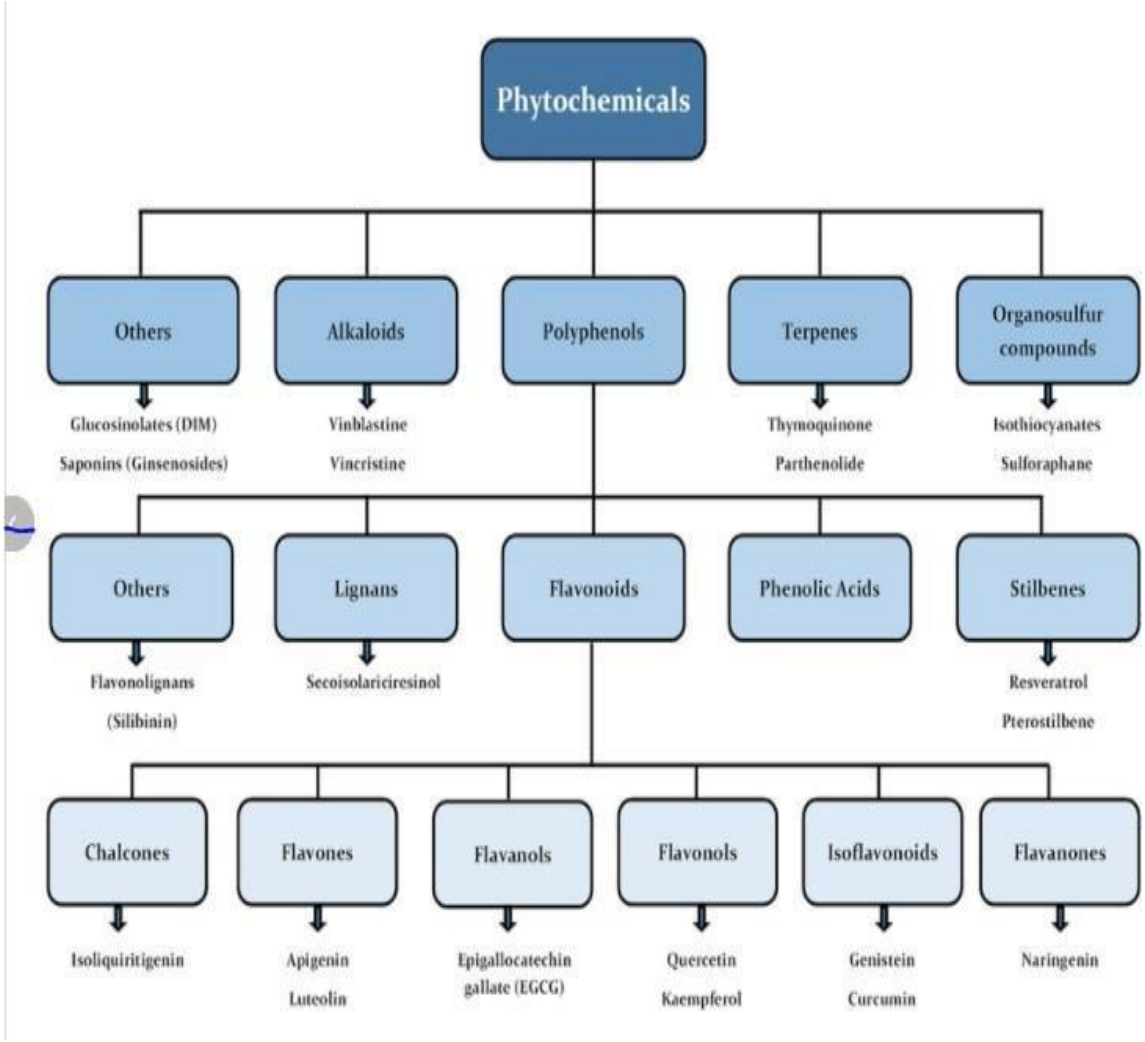


Figure1:Classification of phytochemical sinvolved inbreastcancer chemoprevention

1.2- Zoochemicals

The prefix 'zoo' refers to animals, making this an easy term to recall as well. Zoochemicals are natural chemicals found in animals. Sozoochemicals are the animal equivalent of phytochemicals in plants. A couple of examples are omega-3 fatty acid, obtained from fatty fish, and conjugated linoleic acid, (Paszczyk and Łuczyńska 2020b)

Some compounds can be both phytochemicals and zoochemicals. An example of compounds that can be classified as both are the yellow carotenoids lutein and zeaxanthin. Kale, spinach, and corn contain phytochemicals and are good sources of lutein and zeaxanthin. These compounds have health benefits as shown in **Figure 2**

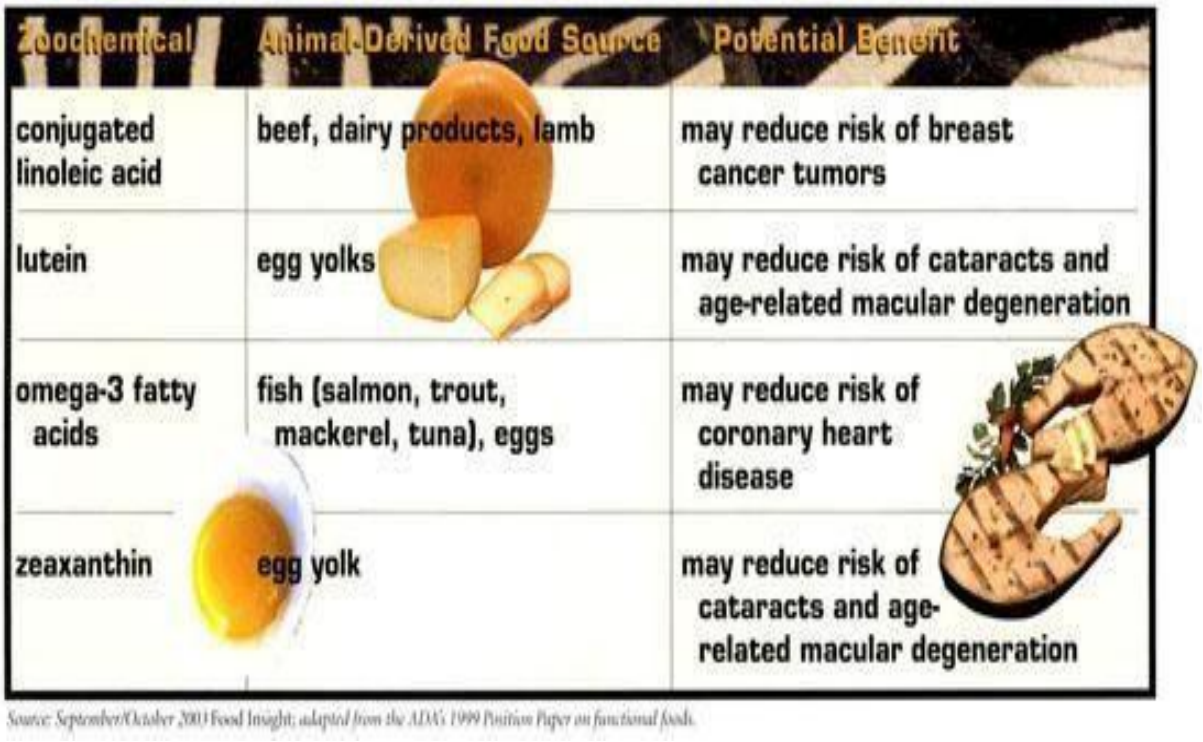


Figure2:Sourceand benefit of some classes of Zoochemicals

1.3- 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[4]. Synthetic biomolecules are the amalgamation of the physical and chemical aspects of biomolecules, which can be used in various biological platforms, which require a broad range of applications. [5]

Ingeneral,thetermsynthesispertainstothecreationofsomething.Itistheprocessof combining two or more components to produce an entity. In biochemistry, it refers to the production of an organic compound in a living thing, especially as aided by enzymes.[6].

Synthetic analogues of biomolecules can be used as antimicrobial agents, as well as possessing pharmacological applications. Synthetic equivalents of naturally occurring biomolecules can be constructed to function in a manner more potent as compared to the naturally occurring biomolecule [5,7]

1.4- Small and Macromolecules:

A biomolecule can be classified as small and macromolecule, it is a molecule that participates in the metabolism and maintenance of a living organism, for example carbohydrates, fats, proteins, water and nucleic acids [8]. Large molecules can be called macromolecules. They can be classified as biopolymers (lignin, cellulose, etc.) or as natural macromolecule (proteins, nucleic acids, etc.). These macromolecules can have a primary, secondary, tertiary or quaternary structure.[9]

1.4.1- Small Molecules

A small molecule is a low molecular weight (< 900 daltons) organic compound that may regulate a biological process, with a size on the order of 1 nm[citation needed]. Many drugs are small molecules. Larger structures such as nucleic acids and proteins, and many polysaccharides are not small molecules but macromolecules, although their constituent monomers (ribo- or deoxyribonucleotides, amino acids, and monosaccharides, respectively) are often considered small molecules. Small molecules may be used as research tools toprobe biological function as well as leads in the development of new therapeutic agents. Some can inhibit a specific function of a protein or disrupt protein–protein interactions.

Pharmacology usually restricts the term "small molecule" to molecules that bind specific biological macromolecules and act as an effector, altering the activity or function of the target. Small moleculescanhaveavarietyofbiologicalfunctionsorapplications,serving ascellsignalingmolecules,drugsinmedicine,pesticidesinfarming,andinmanyotherroles. These compounds can be natural (such as secondary metabolites) or artificial (such as antiviral drugs).

1.4.2- Macromolecules:

Biological macromolecule. A large, organic molecule such as carbohydrates, lipids, proteins, and nucleic acids. Monomer is a molecule that is a building block for larger molecules (polymers).[10]. There are four major classes of biological macromolecules [11]:

- Polycarbohydrates.
- lipids.
- Proteins and peptides.
- DNA

macromoleules are polymere because they are a large molecule made of repeating subunits (monomers). For example, a carbohydrate is a polymer that is made of repeating monosaccharides.[12].

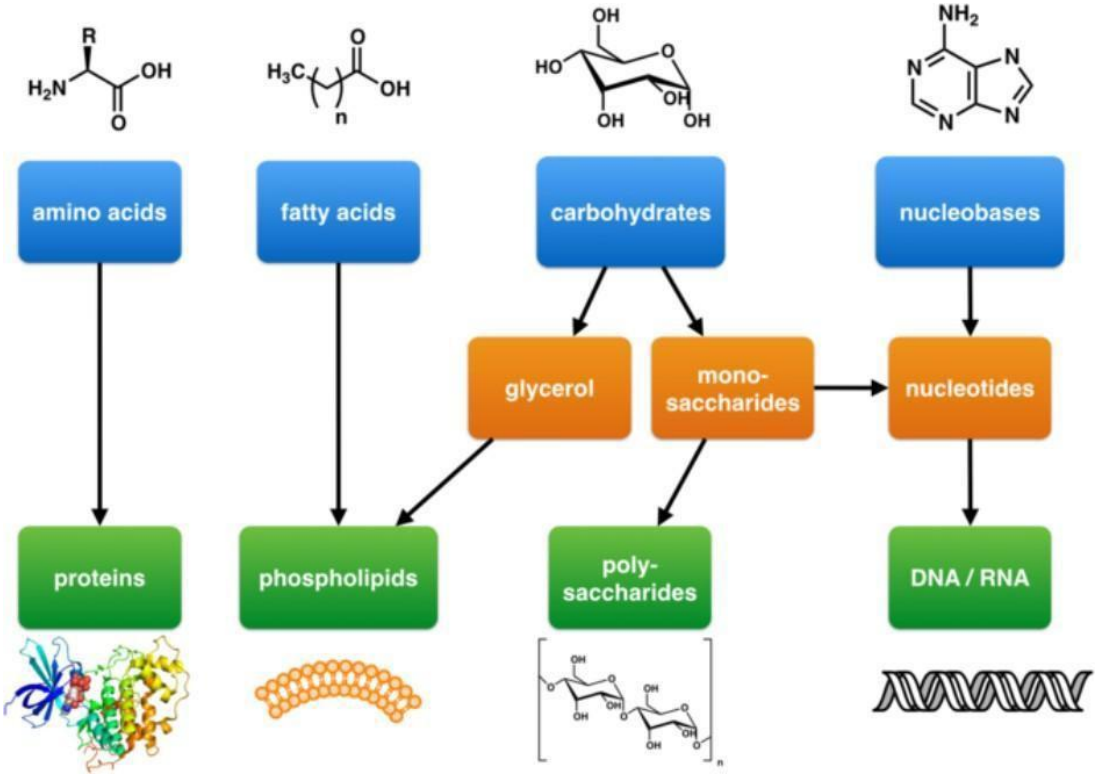


Figure3:Someexamplesofmacromolecules

1.4.2.1-From Amino Acids to Peptides and Proteins

An amino acid is an organic molecule that is mad eupofabasicaminogroup($-NH_2$), an acidic carboxyl group ($-COOH$), and an organic *R* group (or side chain) that is unique to each amino acid. The term *amino acid* is short for α-amino [alpha-amino] carboxylic acid. Each molecule contains a central carbon (C) atom, called the α-carbon, to which both an amino and a carboxyl group are attached. There maining two bonds of the α- carbonatomare generally satisfied by a hydrogen (H) atom and the *R* group. Amino acids function as the building blocks of peptides and proteins. There are 20 amino acids that function as building blocks of proteins. Nine of these amino acids are considered essential—they must be

consumed in the diet—while five are considered non essential in that they can be made byt he human body. The remaining six protein-building amino acids are conditional,beingessential only at certain life stages or in certain disease states. The essential amino acids are histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine.The nonessential amino acids are alanine, asparagine, aspartic acid, glutamic acid, and serine. Conditional amino acids include arginine, cysteine,glutamine,glycine,proline,andtyrosine. Some authorities recognize a 21st amino acid, selenocysteine, which is derived from serine during protein biosynthesis.[13].

Bioactive peptides (BP) are organic substances formed by amino acids joined by covalent bonds known as amideorpeptidebonds. Although some BP sexistfreeinitsnatural source, the vast majority of known BPs are encrypted in the structure of the parent proteins and are released mainly by enzymatic hydrolysisofproteininthegastrointestinaltract. They can also be produced by microorganisms in the fermentation" . Some BP could be prepared by chemical synthesis.[14][15] . BP properties are essentially related to their amino acid sequences having hydrophobic/hydrophilicpropertieshenceadirecteffectonbothfunctional and health effects [16,17]. i.e. digestive, endocrine, cardiovascular, immune, and nervous systems and various diseases and disorders. [14]whereas the design of biologically active peptides is of critical importance for the development of potent, selective, nontoxic bioavailable drugs."[18].Therearedipeptidesandtripeptidesalsocyclicpeptideswhichhave biological activities, such as antiviral, antibacterial activity, immune suppressive activity,and anti-tumor activity, [19]. [20].

Protein, a highly complex substance that is present in all living organisms. Proteins are of great nutritional value andaredirectly involved in the chemical processes essential for life. The importance of proteins was recognized by chemists in the early 19th century, including Swedish chemist JönsJacob Berzelius, who in 1838 coined the term *protein*, a wordderivedfromtheGreek*prōteios*,meaning“holdingfirstplace.”Proteinsare species-specific; thatis,the proteins of one species differ from those of another species.They are also organ-specific; for instance, within a single organism, muscle proteins differ from those of the brain and liver.[21].

1.4.2.2-FromNucleicAcid to DNAand RNA

Nucleic acid, naturally occurring chemical compound that is capable of being broken down to yield phosphoric acid, sugars, and a mixture of organic bases (purines and

pyrimidines). Nucleic acids are the main information-carrying molecules of the cell,and,by directing the process of protein synthesis, they determine the inherited characteristics ofevery living thing. The two [16,17], main classes of nucleic acids are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the master blueprint for life andconstitutesthe genetic material in all free-living organisms and mostviruses.RNA is the genetic material of certain viruses, but it is also found in all living cells, where it plays an important role in certain processes such as the making of proteins.[22].

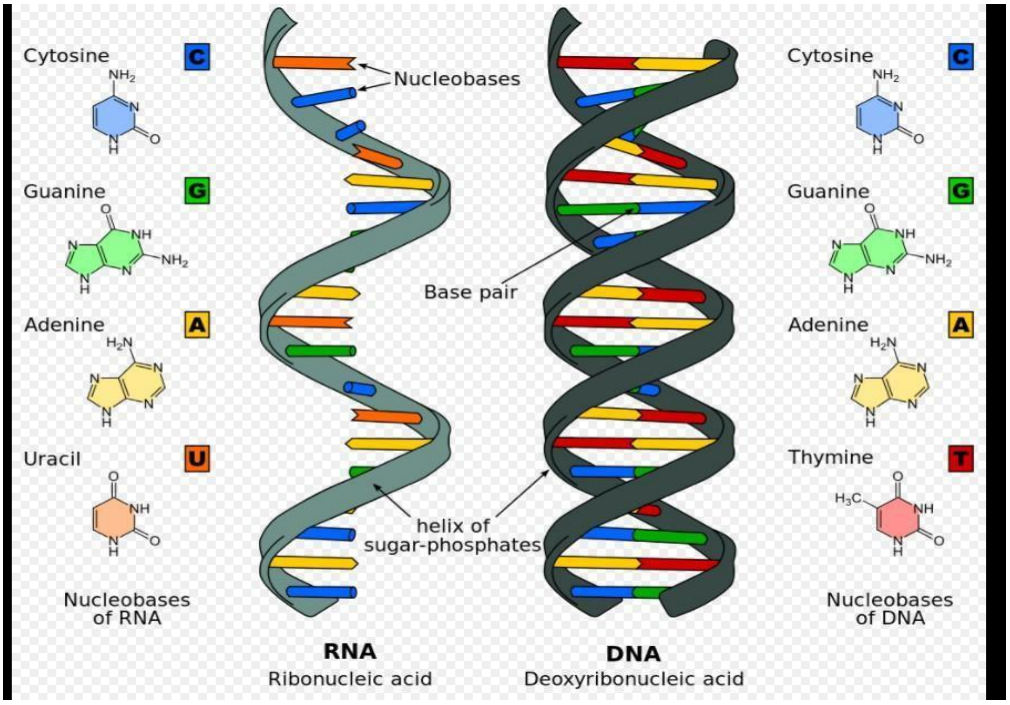


Figure4:deoxyribonucleicandribonucleicacids.

1.4.2.3-FromCarbohydratetoPolycarbohydrates

A carbohydrate is a molecule consisting of carbon (C), hydrogen (H) and oxygen (O) atoms, usually with a hydrogen–oxygen atom ratio of 2:1 (as in water) and thus with the empiricalformula$C_m(H2O)_n$(wheremmayormaynotbedifferentfromn).However,notall carbohydrates conform to this precise stoichiometric definition (e.g., uronic acids, deoxy-sugarssuchasfucose),norare all chemicals thatdoconformtothisdefinition automatically classified as carbohydrates (e.g. formaldehyde and acetic acid).

The term is most common in biochemistry, where it is a synonym of saccharide, a group that includes sugars, starch, and cellulose. The saccharides are divided into four chemical groups: monosaccharides, disaccharides, oligosaccharides, and polysaccharides. Monosaccharidesanddisaccharides,thesmallest(lowermolecularweight)carbohydrates, are commonly referred to as sugars. The word saccharide comes from the Greek word (sákkharon), meaning "sugar". While the scientific nomenclature of carbohydrates is complex,thenamesofthemonosaccharidesanddisaccharidesveryoftenendinthesuffix -ose,whichwasoriginallytakenfromglucose,fromAncientGreek(gleûkos,“wine,must”), and is used for almost all sugars, e.g. fructose (fruit sugar), sucrose (cane or beet sugar), ribose, amylose, lactose (milk sugar), etc.

1.4.2.4-FromFattyAcidstoLipids

A lipid is any of various organiccompoundsthatareinsolubleinwater.Theyincludefats,waxes,oils,hormones,andcertainc omponentsofmembranesandfunctionasenergy-storage molecules and chemical messengers. Together with proteins andcarbohydrates, lipids are one of the principal structural components of living cells.[23].

Lipids are a diverse group of compounds and serve many different functions. At a cellular level, phospholipids and cholesterol are some of the primary components of the membranes that separate a cell from its environment. Lipid-derived hormones, known assteroidhormones,are important chemical messengers and include etestosterone and estrogens.At an organismal level triglycerides stored in adipose cells serve as energy-storage depots and also provide thermal insulation[24].

Although biological lipids are not large macromolecular polymers (e.g., proteins, nucleic acids, and polysaccharides), many are formed by the chemical linking of several small constituent molecules. Many of these molecular building blocks are similar, or homologous, in structure. The homologies allow lipids to be classified into a few major groups: fatty acids, fatty acid derivatives, cholesterol and its derivatives, andlipoproteins.[13].

CHAPTER2:
Computational Methods and Approaches

2.1 – Molecular Modeling and Computational Methods

Computational chemistry simulates chemical structures and reactions numerically, based fully or partially on the elemental laws of physics. It allows chemists to review chemicalphenomenabyrunningcalculationsoncomputersinsteadofbyexaminingreactions and compounds experimentally. Some methods are often wont to model not only stable molecules, but also short-lived,unstableintermediatesandtransitionstates.Duringthisway, they will provide information about molecules and reactions which is impossible to get through observation. There are two broad areas within computational chemistry dedicated to the structure of molecules and their reactivity :molecular mechanics and electronicstructure theory. They perform an equivalent basic sorts of calculations : Computing the energy of a specific molecular structure. Properties associated with the energy can also be predicted by some methods performing geometry optimizations, which are an effort to locate rockbottom energy molecular conformation computing the vibrational frequencies of molecules resulting from interatomic motion within the molecule[25]

Molecular modeling is becoming ever more important within the fields of protein engineeringanddrugdesign[26],alsocalledrationaldrugdesignisaseriesofcomputational methods that represent, and manipulate the structure and reaction of molecules. [27].(Molecules 3D, Molecular Arts Corporation; Chem-X, Chemical Design)[28].

The studies of MM can provide insight into the microscopic structure and therefore the macroscopic properties of molecular systems,which could give a significant contribution to our understanding of the chemical phenomena.

2.1.1- Molecular Mechanics Methods (MM):

Molecular mechanics methods may be a calculation method that uses the potential function in classical physics to calculate the potential energy region of a particular arrangement of atoms[29]. MM methods are simpler, fast, and are able to handle very large systems including enzymes. Molecular mechanics may give extremely accurate energies if the right parameters are available. A disadvantage of molecular mechanics is that parameters

Are derived for ground state systems and are consequently unable to adequately represent geometries involved in bond making and bond breaking processes.

2.1.2- Semi-empirical methods (SE):

These methods use parameters derived from experimental data to simplify the computation. They solve an approximate sort of the Schrödinger equation that depends on having appropriate parameters available for the sort of chemical system in question [30].

Semi empirical Methods are simplified versions of Hartree-Fock theory using empirical corrections so as to enhance performance. These methods are usually mentioned through acronyms encoding a number of the underlying theoretical assumptions. The foremost frequently used methods (MNDO, AM1, PM3). For MNDO, AM1, and PM3 the parameterization is performed such that the calculated energies are expressed as heats of formations rather than total energies [31].

2.1.3- Quantum Chemistry Methods (QC):

Unlike either molecular mechanics or semi-empirical methods, the Quantum Chemistry Methods use no experimental parameters in their computations. Instead, their computations are based solely on the laws of quantumphysics,the first principles mentioned within the name ab initio and on the values of a little number of physical constants: The speed of light the masses and charges of electrons and nuclei Plank's constant[32].

Quantum chemistry may be a very powerful tool to review the properties of molecules and their reactions. The recent years development in quantum chemistry methods, especially that of density functional theory(DFT)methods, has made it possible for quantum chemistry calculations to succeed in accuracies like those obtained in experiments for molecules of moderate sizes. The rapid development of computer technologies has greatly encouraged chemists to use quantum chemistry to know, model, and predict molecular properties and their reactions, properties of nanometer rmaterials,and reactions and processes happening in biological systems [33].

2.1.3.1- Density functional theory (DFT):

Density functional theory (DFT) may be a quantum-mechanical (QM) method utilized in chemistry and physics to calculate the electronic structure of atoms, molecules and solids.

it'sbeenextremelypopularincomputationalphysicssincethe1970s[34].DFTisnowfarand away the foremost widely used electronic structure method(Topolovec-Pintarić2019),There are roughly three types, or categories, of density functional methods. Local density approximation(LDA)methodsassumethatthedensityofthemoleculeisuniformthroughout 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 [35].

2.2- Optimization

Mathematical optimization (alternatively spelled *optimization*) or mathematical programming is the selection of a best element, with regard to some criterion,from someset of available alternatives. Optimization problems of sorts arise in all quantitative disciplines from computer science and engineering to operations research and economics, and the development of solution methods has been of interest in mathematics for centuries.

In the simplest case, an optimization problem consists of maximizing or minimizing a real function by systematically choosing input values from within an allowed set and computing the value of the function. The generalization of optimization theory and techniques to other formulations constitutes a large area of applied mathematics. More generally, optimization includes finding "best available" values of some objective function given a defined domain (or input), including a variety of different types of objective functions and different types of domains.

2.3- Conformers Search

A conformer search affords the low-energy arrangements of atoms that may be obtained via rotation around bonds. Conformers provide insight about the chemical reactivity and physical properties of a molecule. With increase in gmolecular size, the number of possible conformers increases exponentially [36].

Conformers are important in determining rates of reaction and inter conversion. counting on the temperature, pressure, and solvents used during an experiment, the favoured conformation may change, leading to more or fewer side-products. In computational chemistry, an initial geometry is required to run most calculations. A conformer search can afford good starting structures from which to perform computational simulations of chemical processes[37].

The Conformational Search application contains three methods for generating conformations:

• exhaustive/brute-force - explore all possible conformations by a combinatorial algorithm

• systematic –starting with a given conformation, follow a sequence of steps to produce a "better" geometry. Usually this approach involves sampling the space of conformations consistent with a grid (e.g. of regularly-spaced torsion angles).

• stochastic - randomly generate conformations and choose the simplest one from those generated.

• domain-knowledge - use known template structures (i.e. from a crystal structure database) for a molecules sub-domain or substructures and piece these together (similar to homology modelling in protein structure prediction).

• directed-search - starting with a subset of conformers, use information from the current subset to explore nearby structures[38].

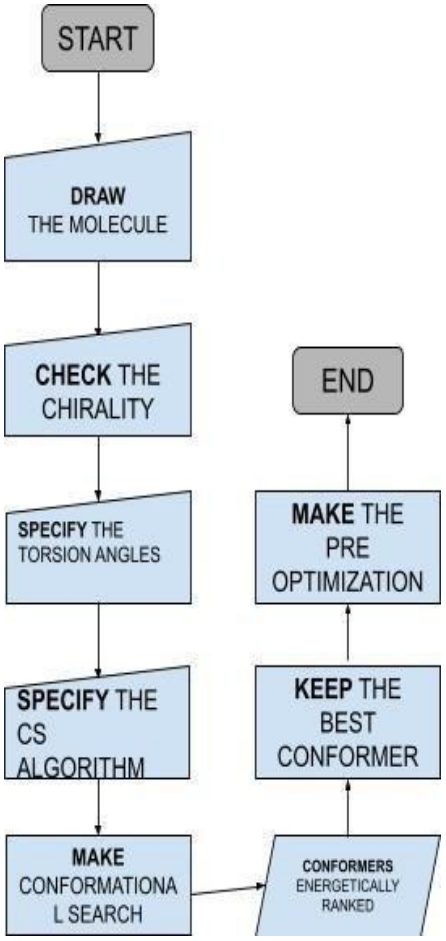


Figure5: FlowChart of conformational search process

2.4-QuantitativeStructure-ActivityRelationship(QSAR)Modeling

Quantitative structure-activity relationship (QSAR) is a computational modeling method for revealing relationships between structural properties of chemical compounds and their biological activities. QSAR modeling is essential for drug discovery, but it has many constraints [39].

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 applicability for correlating

molecular information with not only biological activities but also with other physicochemical properties, which has therefore been termed quantitative structure-activity relationship (QSAR). A given compilation of data sets is then subjected to data pre-processing and data modeling through the use of statistical and/or machine learning techniques to finally generate a QSAR model [40].

2.4.1- Molecular Descriptors

A molecular descriptor is a structural or physicochemical property of a molecule or part of a molecule.[41].Molecular descriptors derived from atomic or molecular properties that translate physicochemical, topological, and surface properties of compounds to establish the foundation for in silico predictive QSAR models.[42]

2.5- Docking

In the field of molecular modeling, 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 a ligand and a protein for example, scoring functions.[43].

The associations between biologically relevant molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonismvs antagonism). Therefore, docking is useful for predicting both the strength and type of signal produced.[44].

Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes[45].

2.5.1- Docking Algorithms

Molecular docking is a computer simulation procedure to predict the conformation of a receptor- ligand complex.Each docking program makes use of one or more specific search algorithms, which are the methods used to predict the possible conformations of a binary complex [46].

Docking algorithms predict a number of orientations(poses)for the ligand inside the binding site. The evaluation and ranking of envisaged ligand conformations are executed by some approximate mathematical functions known as scoring functions.[47]

Each docking application is based on a specific search algorithm, such as Incremental Construction (IC) , Genetic Algorithm (GA), Monte Carlo (MC),etc.Each one has its specific parameters set and search method [48]**Table 1** shows the main docking programs widely used nowadays and their algorithms.

Table1.DockingAlgorithms

Program	Search Method
AutoDock	GA
DOCK	IC
ZDOCK	SM
MS-DOCK	SM
MCDOCK	MC
ICM	MC
GOLD	GA
Surflex	IC
FLEXX	IC
M-ZDOCK	SM
SYSDOC	SM
EUDOC	SM
FLOG	IC

CHAPTER 3:

Materials

3.1- Materials:

In our study the following Software and databases were utilized:

3.1.1- Personal computer

In our study we used a personal computer with a processor of 2.50 GHz Intel(R)Core (™) i5-3210M CPU with installed memory of 6.00 GB, under exploitation system: Windows 10 Professionnel, 64 bits.

3..1.2- Databases

RSCB

PDB:https://www.rcsb.org/structure/4UROPubChem:https://pubche

m.ncbi.nlm.nih.gov/DrugBank:https://go.drugbank.com/

3.1.3- Programs:

3.1.3.1- HyperChem

HyperChem is a commercial sophisticated molecular modeling environment that is known for its quality, flexibility, and easy of use. It allows the 3D visualization and animation with quantum chemical calculations, molecular mechanics and dynamics. It includes all the components of structure, thermodynamics, spectra, and kinetics. **Figure6** shows the 2D optimized structure of molecule A7 in HyperChem Interface. Molecule structures were saved in .mol file format.

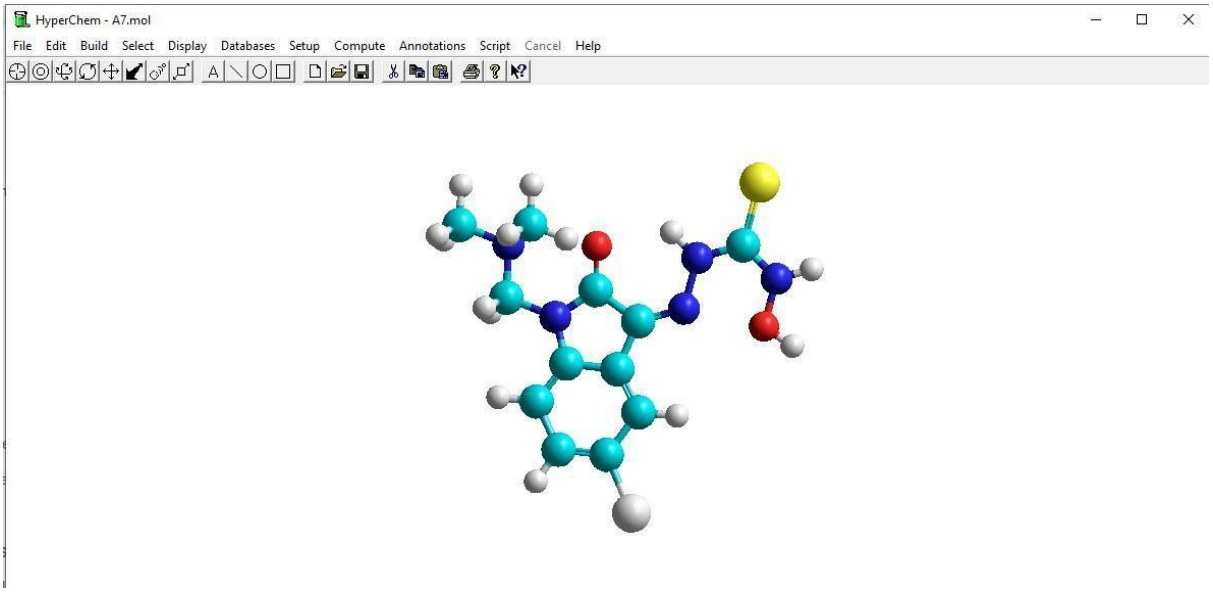


Figure6:2Doptimized structure of moleculeA7inHyperChemInterface.

3.1.3.2-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. **Figure7 shows the** 3D optimized structureA7 in Avogadro Interface.

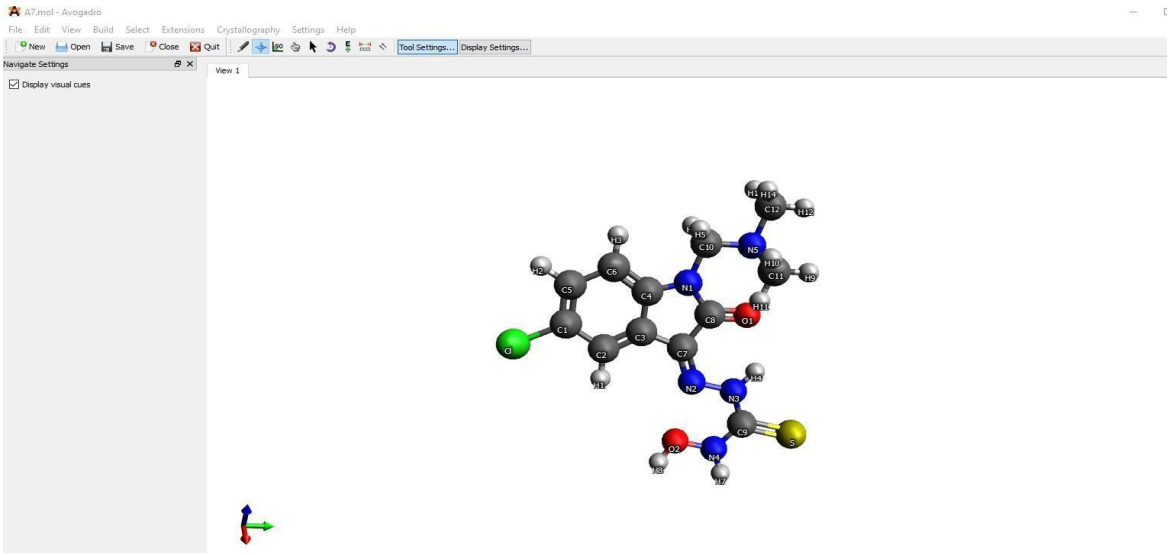


Figure7:3D optimized structure A7 in Avogadro Interface

3.1.3.3- MOPAC

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 substitutingmanyintermediatecalculationswiththeirempiricallydetermined values. As such, it relies on specific parameter sets. MOPAC parameter sets are mostly oriented to biochemistry. Mopac was utilized to perform PM7 optimization of the molecular structures.

3.1.3.4- DockThor

The DockThor server was developed by GMMSB/LNCC group, 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. This 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.In our study 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 poseis found. In **Figure8**, the DockThor access portal is shown.

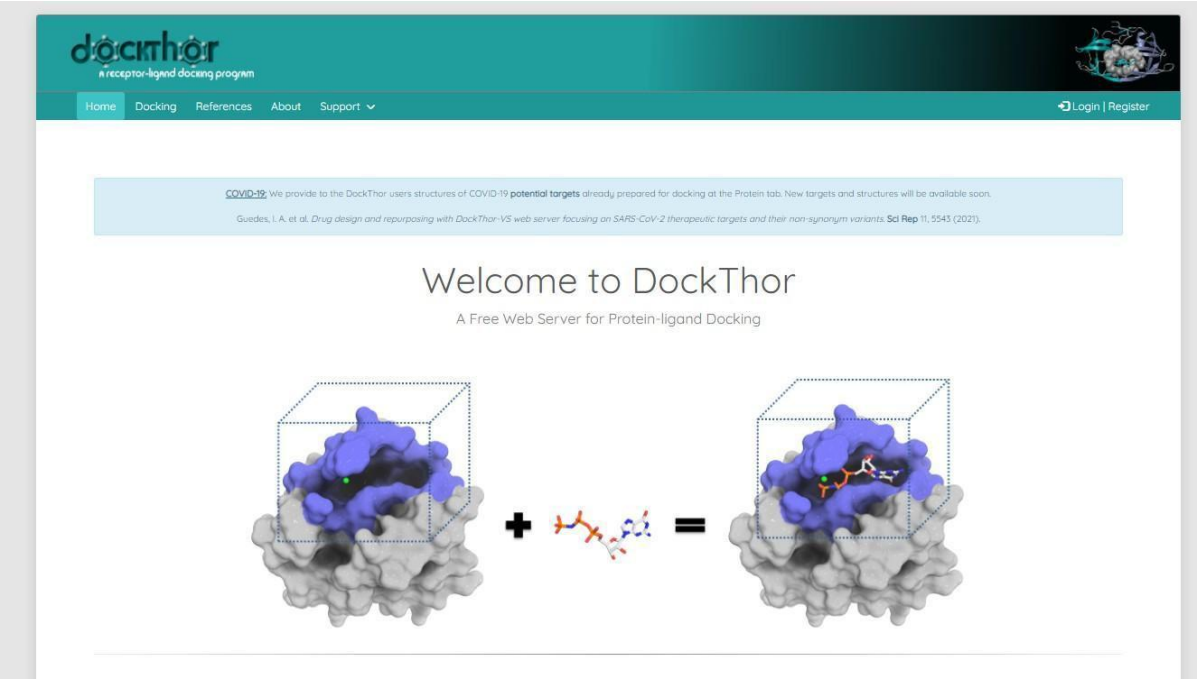


Figure8:DockThor accessportal.

3.1.3.5- Biovia Discovery Studio:

Discovery Studio(**Figure9**)is a suite of software for simulating small molecules and macromolecule systems. It is developed and distributed by Dassault Systemes BIOVIA.

It covers the following areas:

- SimulationsIncludingMolecularMechanics,MolecularDynamics,Quantum Mechanics, it also includes the ability to perform hybrid QM/MM calculations
- Ligand Design including tools for enumerating molecular libraries and library optimization
- Pharmacophore modeling including creation, validation and virtual screening
- Structure-basedDesignincludingtoolsforfragment-basedplacementandrefinement, receptor-ligand docking and pose refinement, de novo design
- Macromolecule design and validation
- Macromolecule engineering it is a specialist tools for protein-protein docking In addition to the antibody design and optimization.

- QSAR: Coveringmethodssuchasmultiplelinearregression,partialleastsquares, recursive partitioning, Genetic Function approximation and 3D field-based QSAR

- ADME for a predictive toxicity

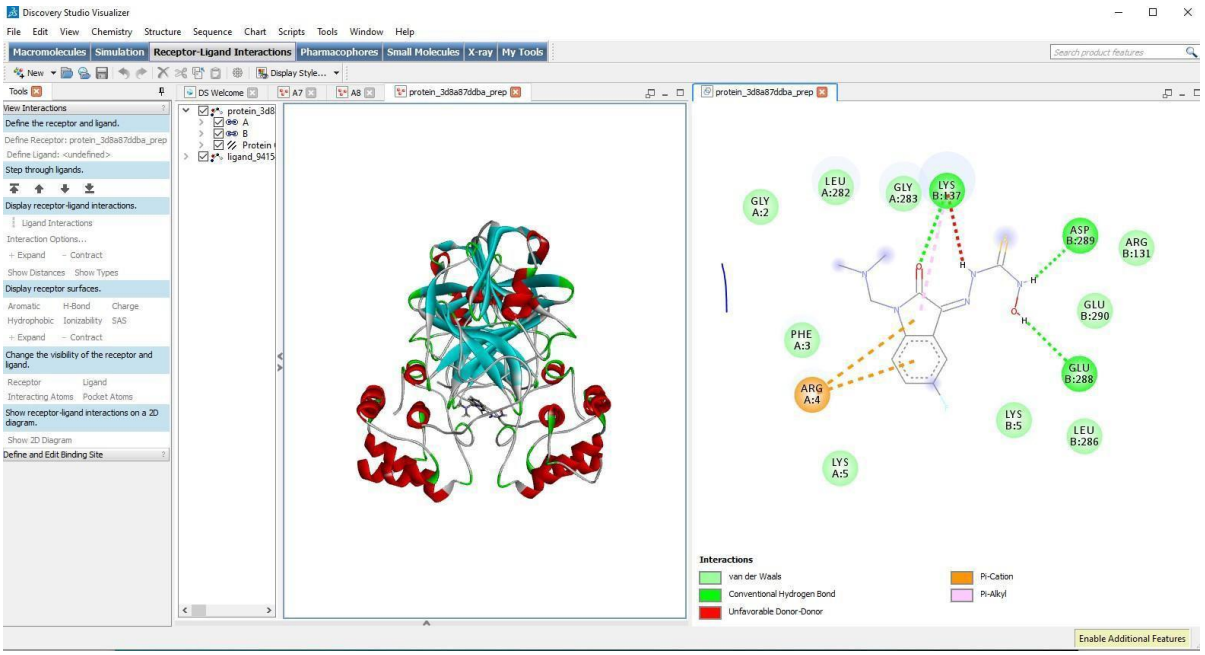
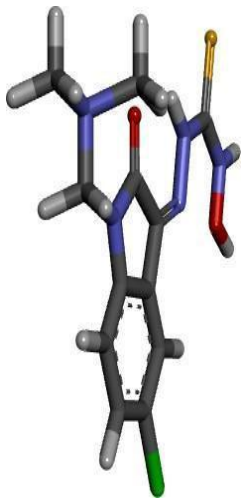
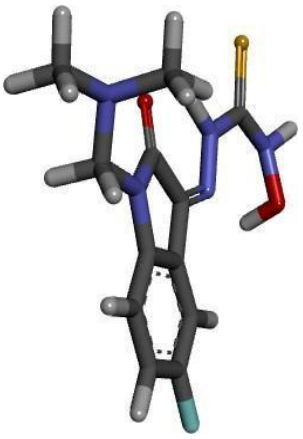
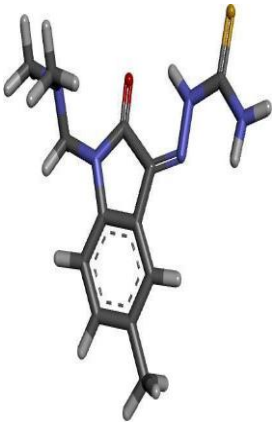
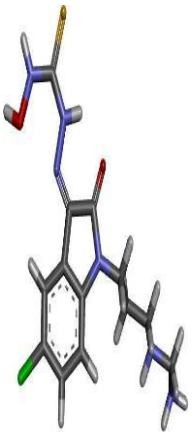
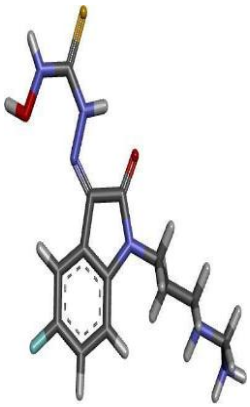
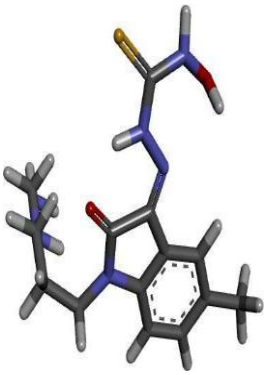
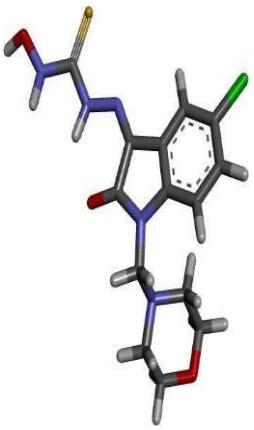
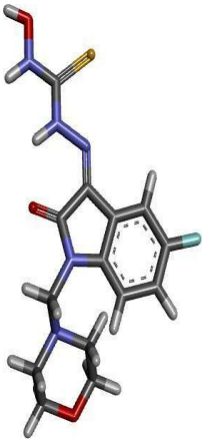


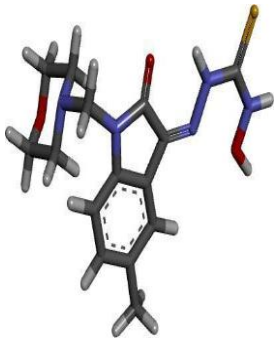
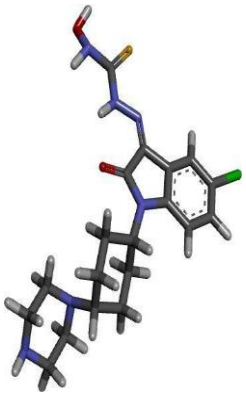
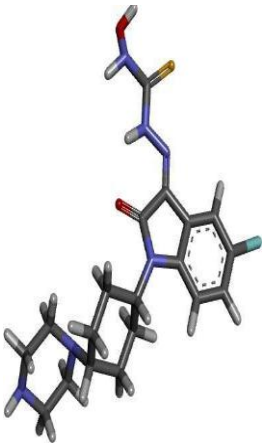
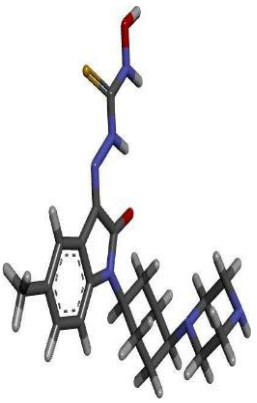
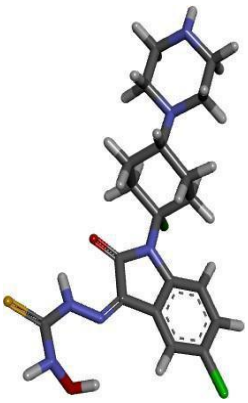
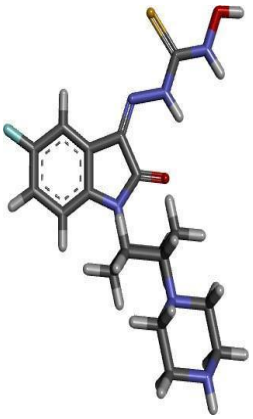
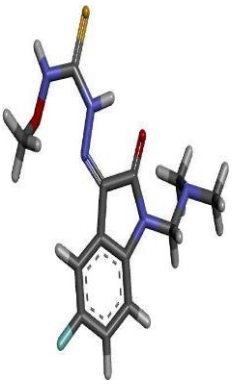
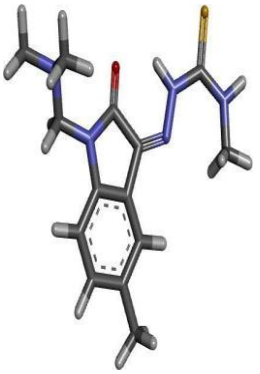
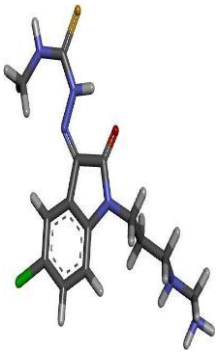
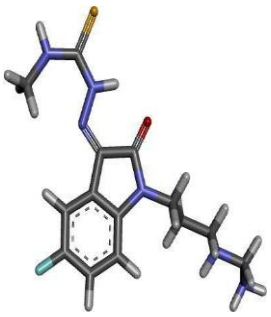
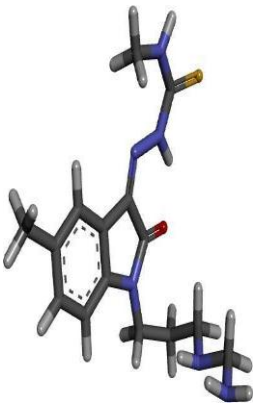
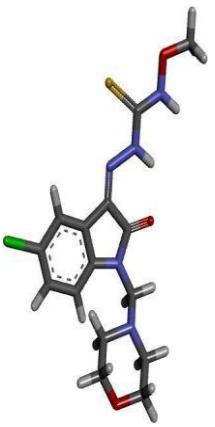
Figure9:3D optimized structure of the A8/6LU7complexin Discovery Studio Interface.

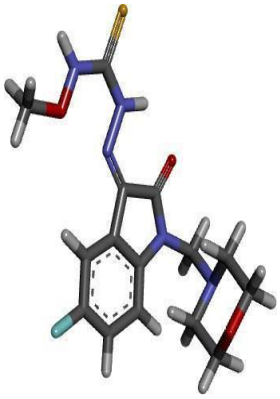
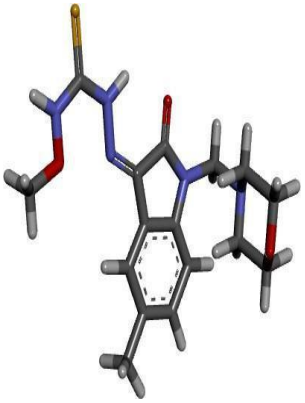
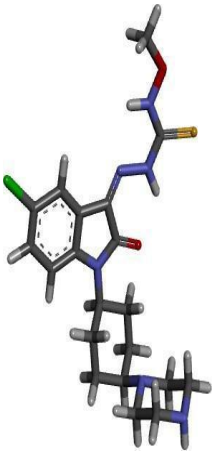
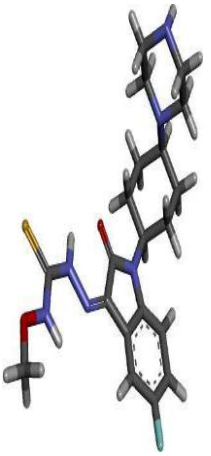
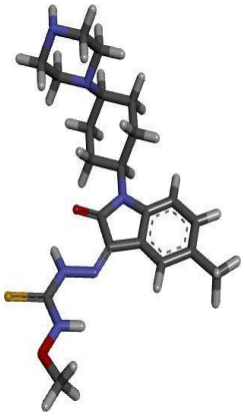
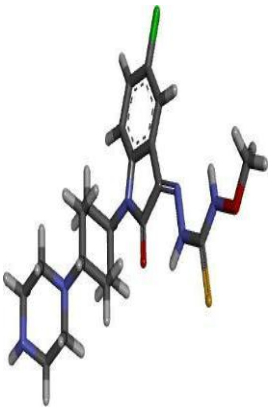
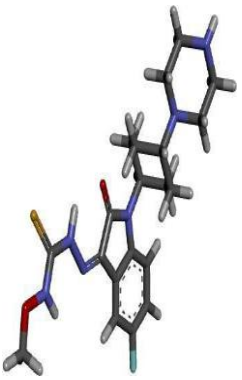
3.1.4 Molecules set

Table2 represents the selected anti-HIVmolecules studied in this investigation.

Table2:Nomenclatures and structures of molecules.

 **A7**	 **A8**	 **A9**	 **A10**
 **A11**	 **A12**	 **A13**	 **A14**

 **A15**	 **A16**	 **A17**	 **A18**
 **A19**	 **A20**	 **B 8**	 **B9**
 **B10**	 **B11**	 **B 12**	 **B13**

 **B14**	 **B 15**	 **B 16**	 **B17**
 **B18**	 **B 19**	 **B 20**	

CHAPITRE4:Results and Discussions

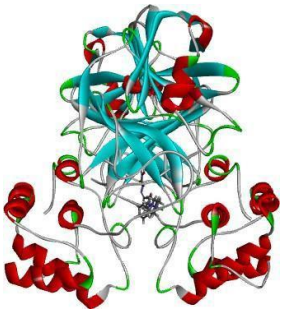
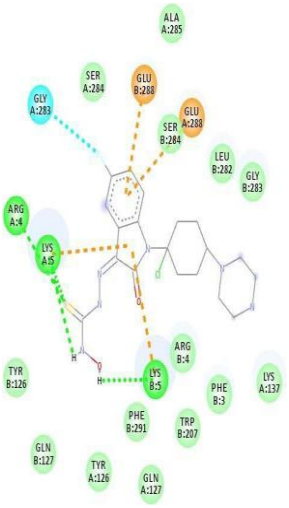
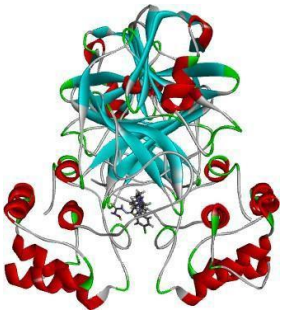
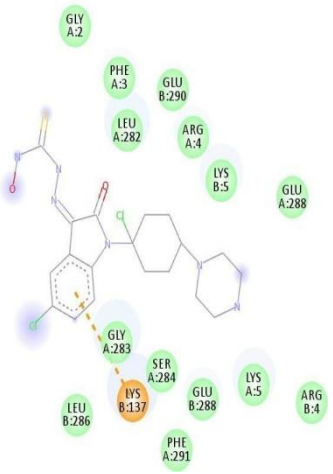
The global pandemic caused by the new SARS-COV-2 corona virus makes it necessary to search for drugsforits control. Within of this research it has been known that the ivermectin drug, a FDA-approved drugs which is formulated as an 80:20 mixture of ivermectin B1a and B1b and used commonly for parasitic infections, has an inhibitory effect on viruses, includes SARS-COV-2. Therefore the two ivermectin B1a and B1b were chosen as standards or references. In addition to SARS-CoV-2 Mpro protein was chosen as target because it is directly associated to the risk of replication and proliferation of corona virus[24].

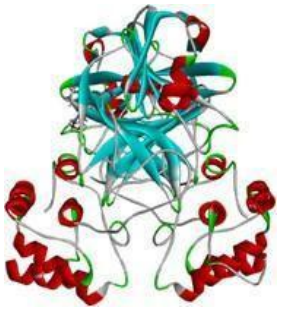
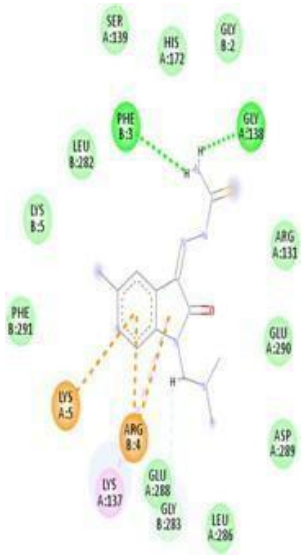
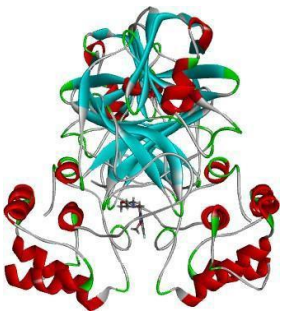
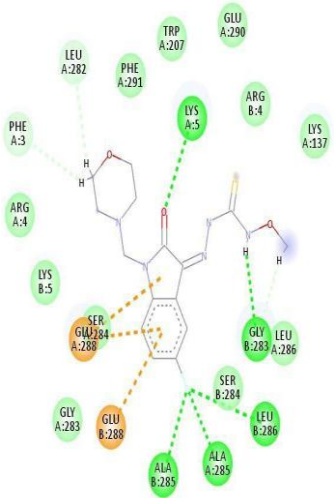
As shownin **Table3** and **table4** Ivermectinasstandardit interacts with SARS-CoV-2Mpro with the following residues:Lys-5HB,Leu-282HB,Glu-288SI, Ser-284SI , Phe-3 SI, Phe-291SI,Arg-4 SI, Lys-137SI, Val125SI, Gln-127SI, Tyr-126SI, Ser-139SI,Gly138SI,Ile-281SI,Trp-207SI,Gly-283SIas our best ranked anti-HIV molecules.

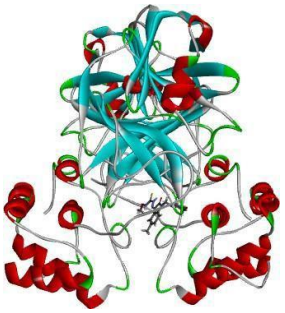
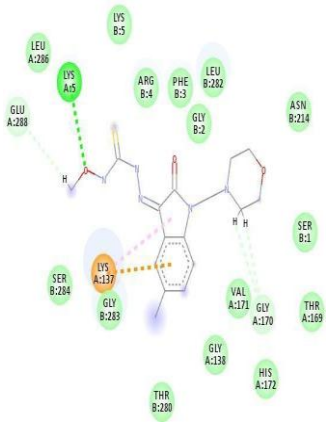
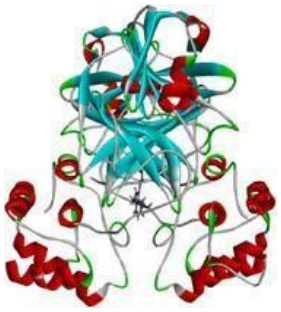
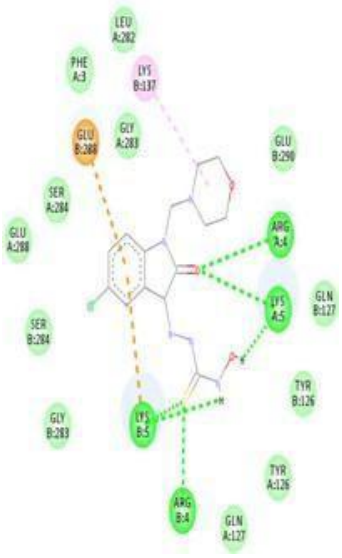
Table3:Sars-Cov2Mpro protein and the studied compounds series interactions: residues, and type of interactions

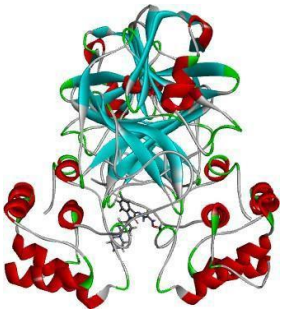
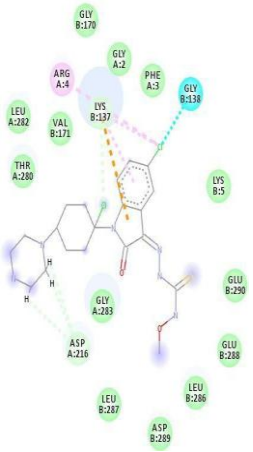
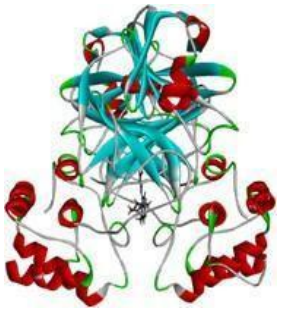
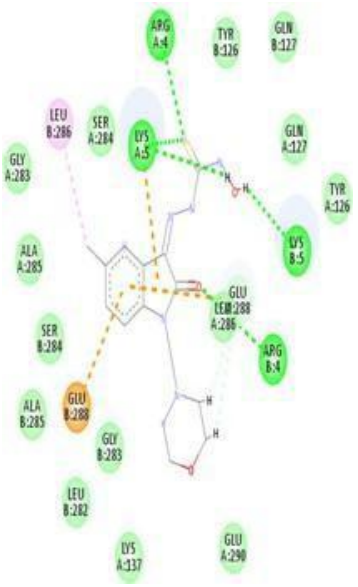
	vanderWaals		ConventionalHydrogen Bond		Pi-Cation		Pi-Alkyl
	CarbonHydrogen Bond		Unfavorable Positive-Positive		Pi-Sulfur		

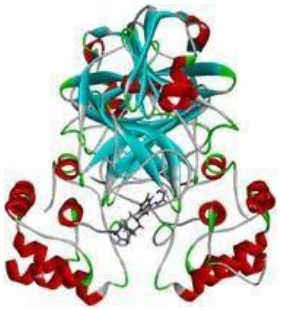
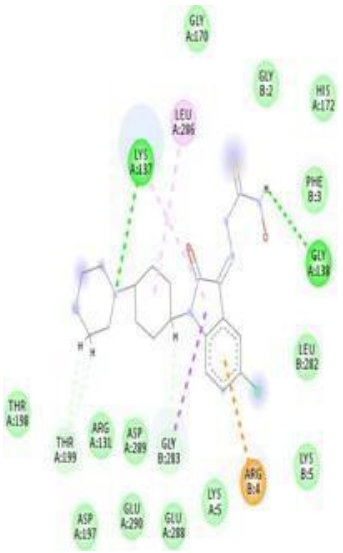
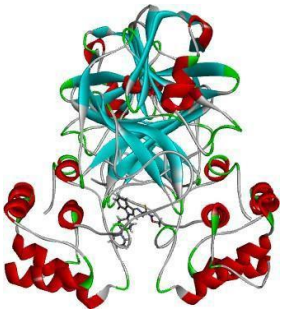
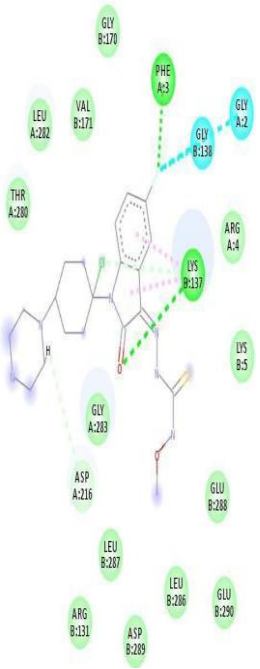
Molecule	H-BondPocket	2D-Interactions	Dockthor Score(kcal/mol)
IvermectinB1a			-8.642

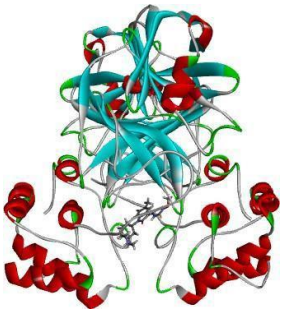
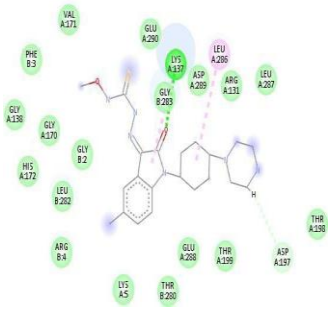
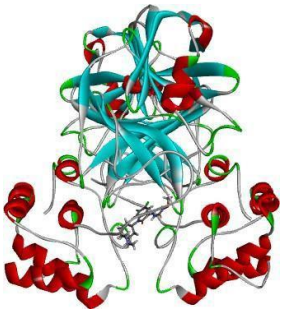
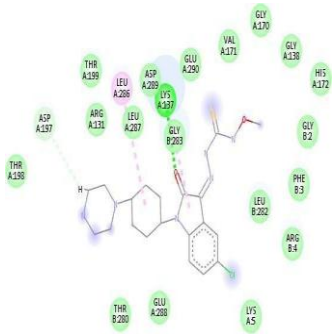
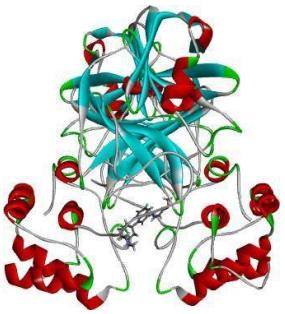
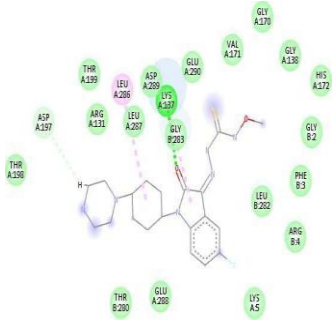
A20			-8.428
IvermectinB1b			-8.287
A19			-8.234

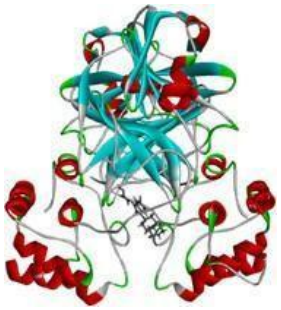
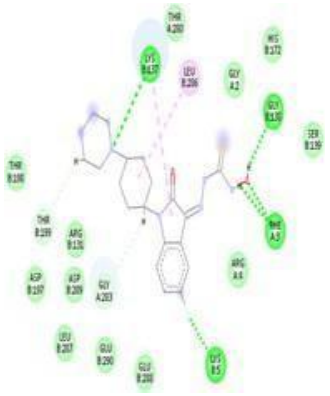
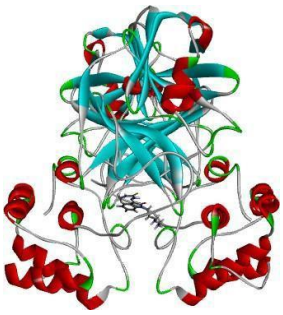
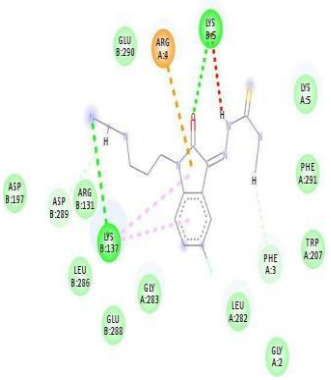
A14			-8.005
B14			-7.852

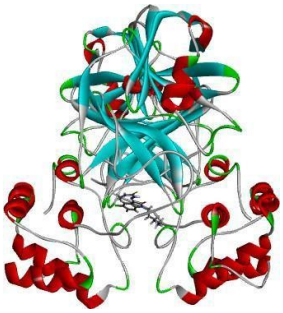
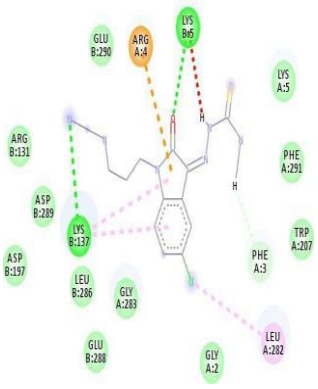
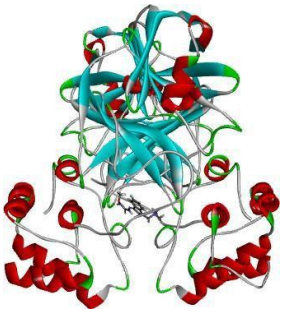
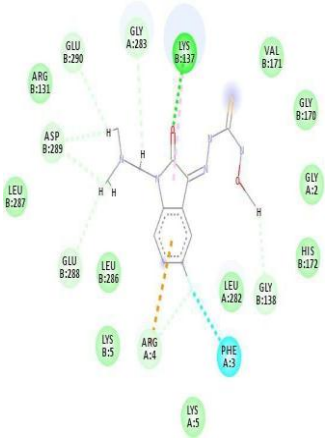
B15			-7.852
A13			-7.784

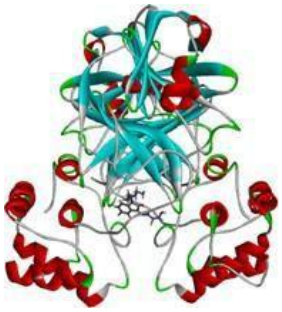
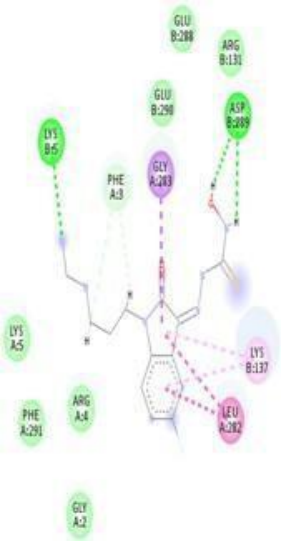
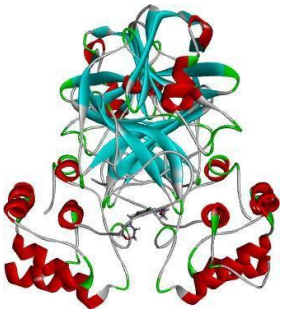
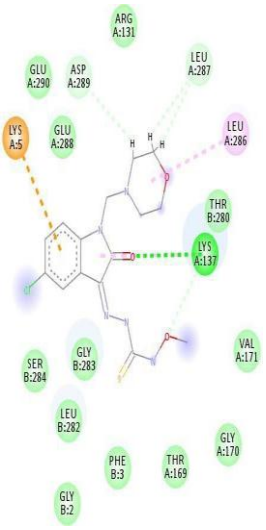
B19			-7.749
A15			-7.724

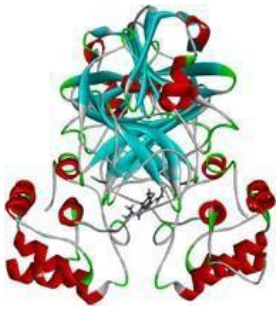
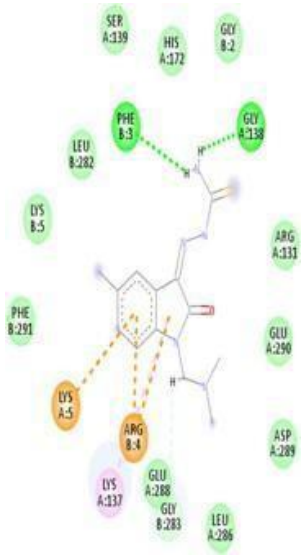
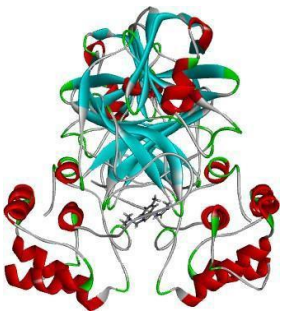
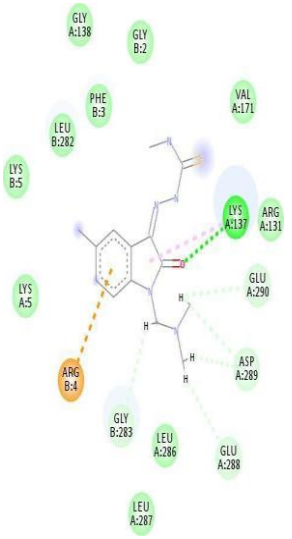
A16			-7.671
B20			-7.591

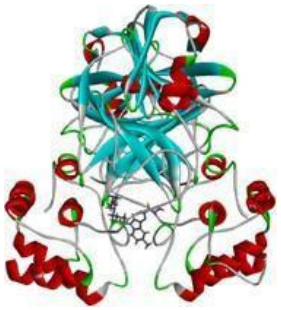
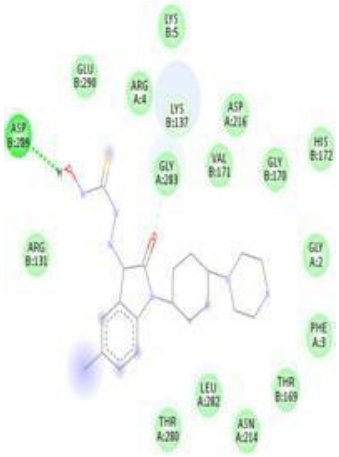
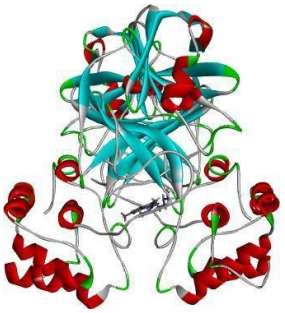
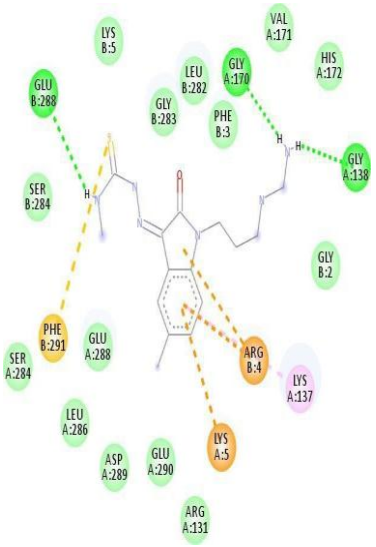
B18			-7.453
B16			-7.444
B17			-7.366

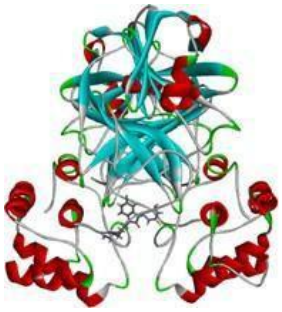
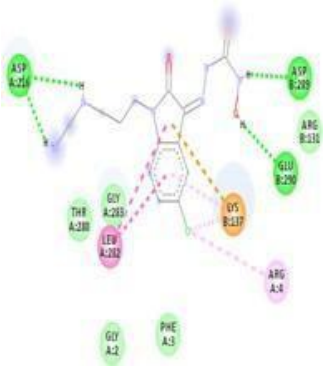
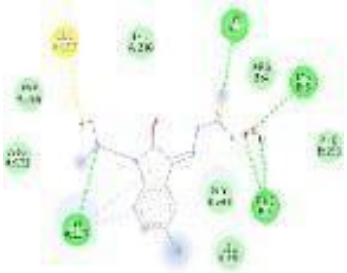
A17			-7.308
B11			-7.234

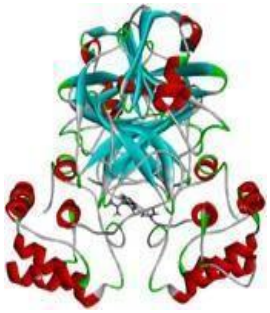
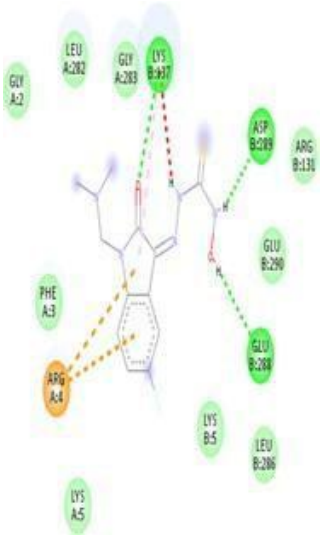
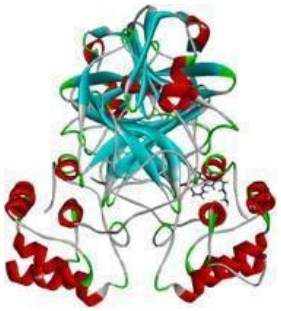
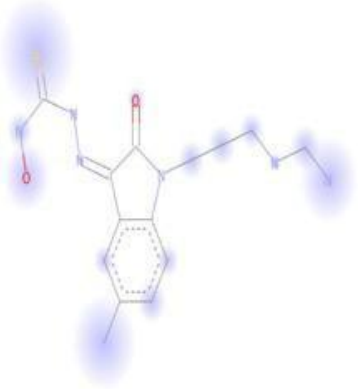
B10			-7.207
B8			-7.159

A11			-7.157
B13			-7.130

A9			-7.101
B9			-7.087

A18			-7.039
B12			-7.031

A10			-6.960
A7			-6.898

A8			-6.607
A12			-5.181

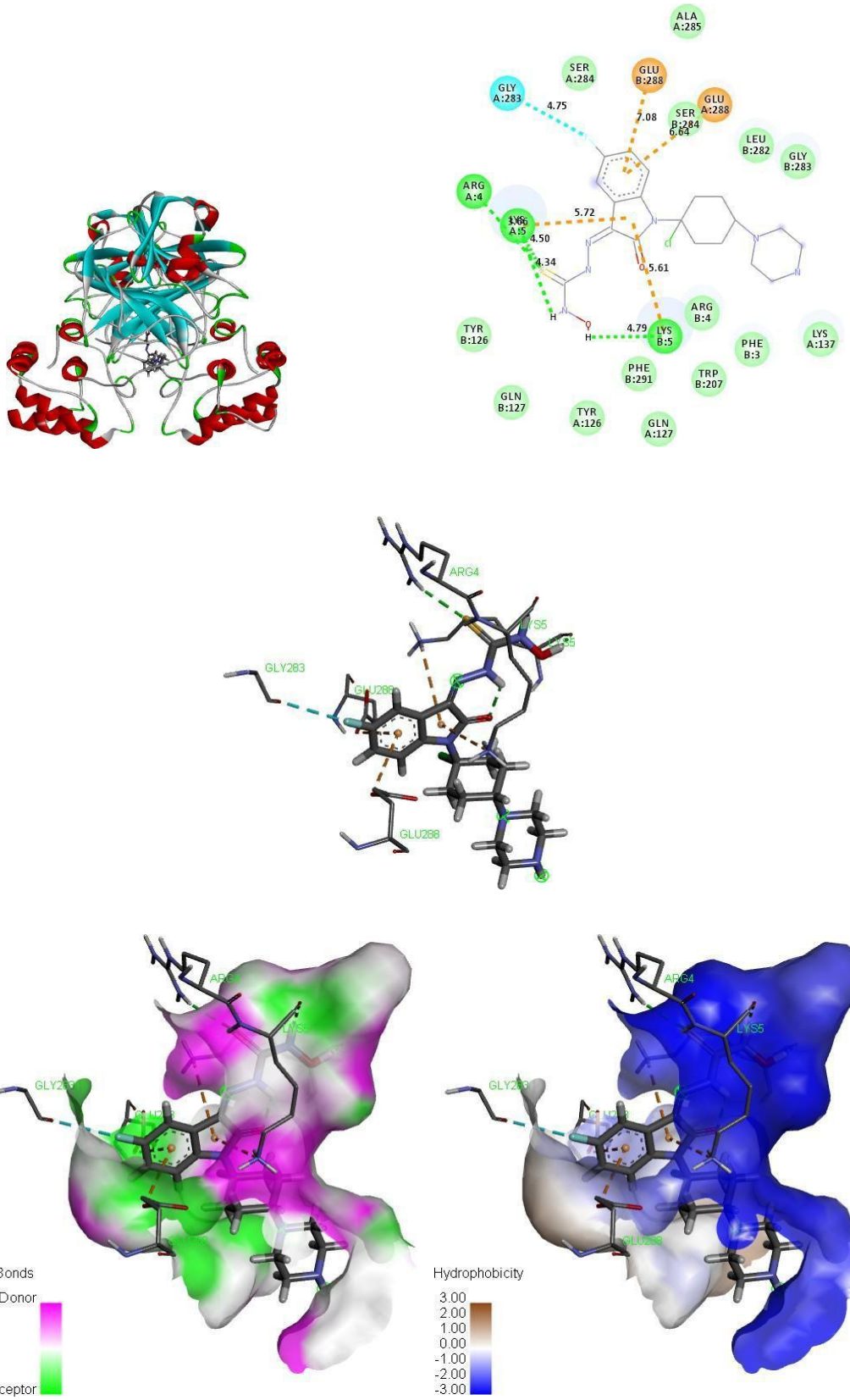


Figure10:A20/SARS-CoV-2Mpro complex, residues in interaction, Hydrogen and hydrophobic pockets.

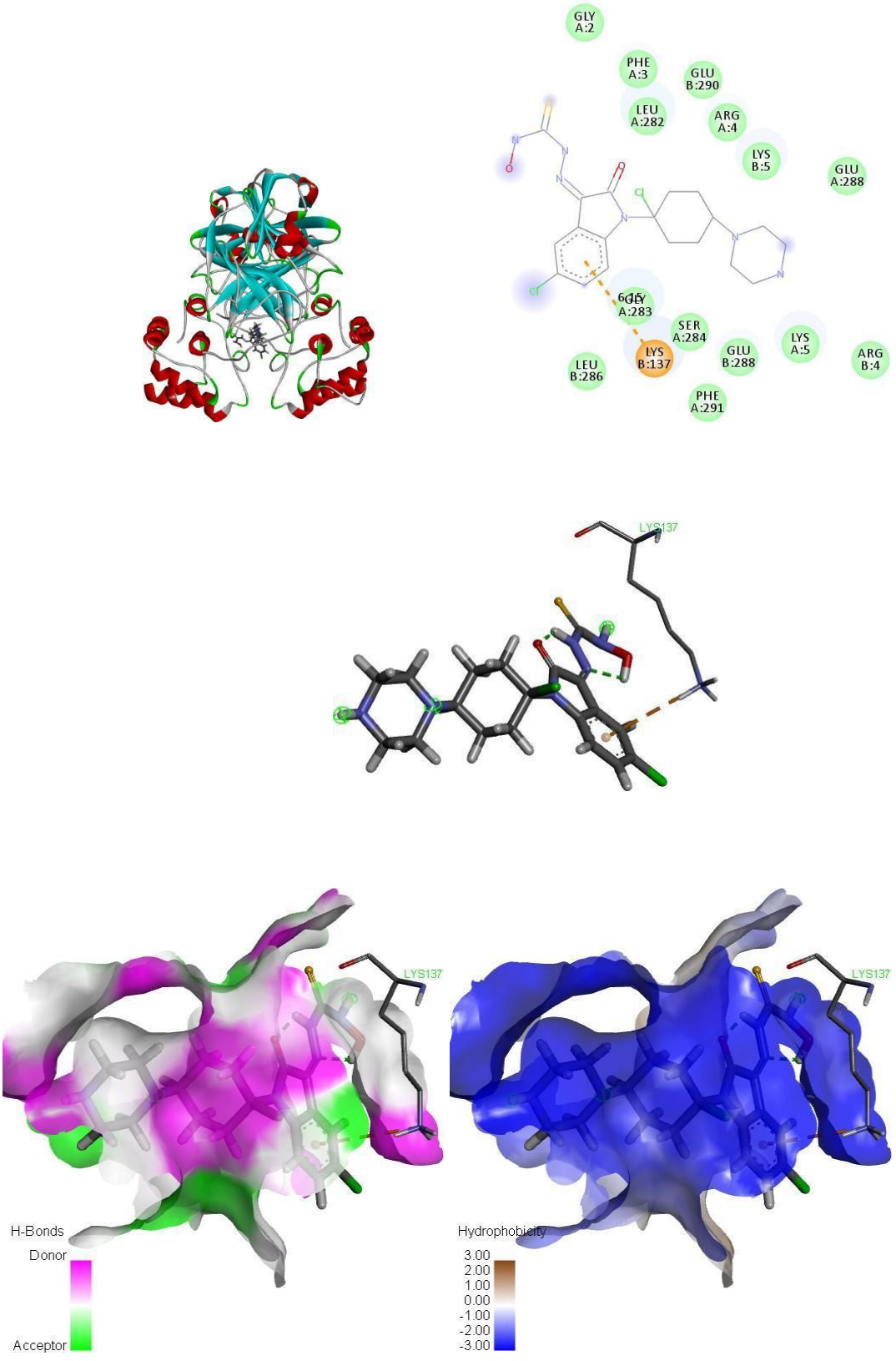


Figure11:A19/SARS-CoV-2Mpro complex,residuesininteraction,Hydrogenand hydrophobic pockets.

	vanderWaals		ConventionalHydrogen Bond		Pi-Cation		Pi-Alkyl
	CarbonHydrogen Bond		Unfavorable Positive-Positive		Pi-Sulfur		

Table4: Sars-Cov2 Mpro protein and the studied compounds series docking interactions: ranked scores, residues and of interactions type compared with the findings in the scientific literature.

PDB (6LU7)	DockthorScore (kcal/mol)	Interactions
IvermectinB1a[49]	-8.642	Lys-5HB,Leu-282HB,Glu-288SI, Ser-284SI,Phe-3SI,Phe-291SI,Arg-4SI, Lys-137SI, Val125SI, Gln-127SI, Tyr-126SI,Ser-139SI,Gly138SI,Ile-281SI, Trp-207SI, Gly-283SI
A20	-8.428	Lys5,Arg4,Gly283,Leu282,Ser284,Ser284, Ala285,Lys137,Phe3,Arg4,Trp207,Phe291, Gln127,Tyr126,Gln127,Tyr126,Glu288,Glu 288,Gly283
Remidesivir[51]	-8.300	-
IvermectinB1b[49]	-8.287	Lys5HB,Arg-4HB-SI,Lys-137SI, Tyr-126SI, Gln127SI, Gly-138SI, Ser-139SI,Phe-3SI,Gly283SI,Phe-291SI, Leu-282SI, Ser-284SI, Glu288S
A19	-8.234	Lys137,Glu288,Lys5,Arg4,Glu290,Leu282,P he3,Gly2
A14	-8.005	Phe3,Gly138,Gly2,Ser139,Leu282,His172,Ar g 131,Glu290,Asp289,leu286,Gly283,Glu 288,Arg4,Lys5,Lys137
B14	-7.852	Lys5,Gly283,Leu286,Ala285,Ala285,Phe29 1,Trp207,Glu290,Arg4,Lys137,Leu282,Phe3 ,Arg4,Lys5,Gly283,Ser284,Ser284,Leu286
B15	-7.852	Lys5,Leu286,Lys5,Arg4,Phe3,Gly2,Leu282, Asn214,Glu288,Ser284,Gly283,Thr281,Gly1 38,Val171,Gly170,Thr169,Ser1
A13	-7.784	Arg4,Lys5,Lys5,Arg4,Leu282,Phe3,Gly283, Glu290,Ser284,Glu288,Ser284,Gly283,Gln12 7,Tyr125,Tyr125,Gln127

Piperine[50]	-	Arg4(HB,SI)

Conclusions

27 anti-HIV molecules from the scientific literature. These molecules were docked by the Dock Thor server and ranked by its score function against SARS-CoV2 Main Protease (PDB id: 6LU7). It was found that two molecules A20 and A19 have significant anti-SARS-CoV2 activities i.e. -8.428 and -8.234 respectively compared to ivermectin and remdesivir. These molecules were bound intheactivesiteoftheSARS-CoV2MainProtease especially with the residues : Lys5, Lys137,Agr4, Glu288.

As a perspective, new anti-HIV molecules will be screened and tested against SARS-CoV2 Main Protease and against the other proteins associated with SARS-CoV2.

References

[1] Y.Fukai,DrasticChangesofLivingOrganismsintheOxygenAge,MolecularHydrogenfor Medicine. (2020) 153–158. https://doi.org/10.1007/978-981-15-7157-2_10.

[2] A. Nouailhat, Introduction aux nanosciences et aux nanotechnologies, 2006.https://books.google.com/books/about/Introduction_aux_nanosciences_et_aux_nan.html?hl =&id =R7fHAAAACAAJ.

[3] B.Paszczyk,J.Łuczyńska,Fattyacidsprofile,conjugatedlinoleicacidcontentsandfatqualityin selected dairy products available on the Polish market, Czech Journal of Food Sciences. 38(2020) 109–114. https://doi.org/10.17221/341/2019-cjfs.

[4] K. Eric Drexler, Engins de création: l'avènement des nanotechnologies, 2005.https://books.google.com/books/about/Engins_de_cr%C3%A9ation.html?hl=&id=_TKO BAAACAAJ.

[5] M.Angell, LaVerite Sur Les Compagnies Parmaceutiques: Comment Elles NousTrompent EtComment Les Contrecarrier, Les Éditions le mieux-être, 2005.https://books.google.com/books/about/La_Verite_Sur_Les_Compagnies_Parmaceutiq.html ?hl=& id=LWnReqj9Ct8C.

[6] Bulletin of the Atomic Scientists, 1972.https://books.google.com/books/about/Bulletin_of_the_Atomic_Scientists.html?hl=&id=4 gsAAAAAMBAJ.

[7] J.T. Kloprogge, J. TheoKloprogge,InfraredandRamanSpectroscopyofNaturallyOccurringHydrotalcitesandtheirS yntheticEquivalents,TheApplicationofVibrationalSpectroscopytoClay Minerals and Layered Double Hydroxides. (2005).https://doi.org/10.1346/cms-wls-13.8.

[8] G.W.Hinsch,HistochemistryofthechickesophagusandtracheaII.Enzymes,nucleicacids, proteins, carbohydrates, and fats, Journal of Morphology. 119 (1966) 327–339.https://doi.org/10.1002/jmor.1051190305.

[9] M.D.Mikkelsen,H.T.T.Cao,T.Roret,N.Rhein-Knudsen,J.Holck,V.T.T.Tran,T.T.Nguyen, V.H.N.Tran, M.J. Lezyk, J. Muschiol,T.D. Pham, M. Czjzek,A.S. Meyer,Anovelthermostable prokaryotic fucoidan active sulfatase PsFucS1 with an unusual quaternaryhexamericstructure,Sci.Rep.11(2021)19523.https://doi.org/10.1038/s41598-021-98588-3.

[10] M.Jones,R.Fosbery,J.Gregory,D.Taylor,CambridgeInternationalASandALevelBiologyCourse book with CD-ROM, Cambridge University Press, 2014.https://books.google.com/books/about/Cambridge_International_AS_and_A_Level_B.ht ml?hl =&id=gYn2AwAAQBAJ.

[11] R.Giegé,A.Ducruix,AnIntroductiontotheCrystallogenesisofBiologicalMacr omolecules, Crystallization of NucleicAcids and Proteins. (1999).https://doi.org/10.1093/oso/9780199636792.003.0005.

[12] W.Wang, F. Kong, Facile Synthesis of a BranchedTrisaccharide–The Repeating Unit ofAntigen O2 Polymer using Orthoester Formation - Rearrangement Strategy, Journal ofCarbohydrateChemistry.18(1999)263–273.https://doi.org/10.1080/07328309908543994.

[13] C. Branden, J. Tooze, Introduction à la structure des protéines, De Boeck, 1996.https://books.google.com/books/about/Introduction_%C3%A0_la_structure_des_prot%C3 %A9i .html?hl=&id=BI53swEACAAJ.

[14] Hippocrates,HippocratesonAirs,Waters,andPlaces..,WentworthPress,2018.

https://books.google.com/books/about/Hippocrates_on_Airs_Waters_and_Places.html?hl=&id=9

[15] A.Jakubczyk,M.Karaś,K.Rybczyńska-Tkaczyk,E.Zielińska,D.Zieliński,CurrentTrendsof Bioactive Peptides-New Sources and Therapeutic Effect, Foods. 9 (2020).https://doi.org/10.3390/foods9070846.
[16] Food andAgriculture Organization of the United Nations, Qu'est-ce que le Code de conduitepour une pêche responsable ?, Food &Agriculture Org., 2005.https://books.google.com/books/about/Qu_est_ce_que_le_Code_de_conduite_pour_u.html ?hl=& id=OtEsQDwtNNsC.
[17] A.Görgüç,E.Gençdağ,F.M.Yılmaz,Bioactivepeptidesderivedfromplantorigin by-products:Biologicalactivitiesandtechno-functionalutilizationsinfooddevelopments-Areview, Food Res. Int. 136 (2020) 109504. https://doi.org/10.1016/j.foodres.2020.109504.
[18] V.J. Hruby, Design of cyclic peptides with biological activities from biologically activepeptides:thecaseofpeptidemodulatorsofmelanocortinreceptors,Biopolymers.106(2016) 884–888. https://doi.org/10.1002/bip.22929.
[19] OECD, Food andAgriculture Organization of the United Nations, Perspectives agricoles del'OCDE et de la FAO 2011, OECD Publishing, 2011.https://books.google.com/books/about/Perspectives_agricoles_de_l_OCDE_et_de_l.html?hl =&id =rx1Lu2F_1J4C.
[20] A.H.Salem,Z.-F.Tao,O.F.Bueno,J.Chen,S.Chen,R.Edalji,S.W.Elmore,K.M.Fournier, K.C.Harper,R.Hong,G.J.Jenkins,J.Ji,R.A.Judge,J.C.Kalvass,R.C.Klix,Y.-Y.Ku,J.D. Leverson, R.A. Marks, K.C. Marsh, R.M. Menon, C.H. Park, D.C. Phillips,Y.-M. Pu, S.H.Rosenberg,Y.D.Sanzgiri,A.Y.Sheikh,Y.Shi,D.Stolarik,A.A.Suleiman,X.Wang,G.G.Z.Zhan g,N.D.Catron,A.J.Souers,Expandingtherepertoirefor"largesmallmolecules":ProdrugABBV-167 efficiently converts to venetoclax with reduced food effect in healthy volunteers,Mol. Cancer Ther. (2021). https://doi.org/10.1158/1535-7163.MCT-21-0077.
[21] A. Karshikoff, R. Ladenstein, Proteins from thermophilic and mesophilic organismsessentiallydonotdifferinpacking,ProteinEngineeringDesignandSelection.11(19 98)867–872. https://doi.org/10.1093/protein/11.10.867.
[22] H.B.Bosmann,H.BruceBosmann,Inhibitionofprotein,glycoprotein,ribonucleicacidanddeoxy ribonucleicacidsynthesisbyd-glucosamineandothersugarsinmouseleukemiccellsL5178Yand selective inhibition in SV-3T3 compared with 3T3 cells, Biochimica etBiophysicaActa (BBA) - NucleicAcids and Protein Synthesis. 240 (1971) 74–93.https://doi.org/10.1016/0005-2787(71)90515-6.
[23] Commission internationale de nomenclature zoologique, International Commission onZoological Nomenclature, Union internationale des sciences biologiques, W.D.L. Ride, C.G.Maggs, International Trust for Zoological Nomenclature, International Union of BiologicalSciences, Code International de Nomenclature Zoologique, International Trust for ZoologicalNomenclatu History Museum, 1999.https://books.google.com/books/about/Code_International_de_Nomenclature_Zoolo.html?h l=&i d=R1gWAQAAIAAJ.
[24] X.Xu,P.Björntorp,Effectsofsexsteroidhormonesondifferentiationofadiposeprecursorcells in primary culture, Experimental Cell Research. 173 (1987) 311–321.https://doi.org/10.1016/0014-4827(87)90273-4.
[25] J.D.Watson,Ladoublehélice:Compterendupersonneldeladécouvertedelastructuredel'ADN, 1999. https://books.google.com/books/about/La_double_h%C3%A9lice.html?hl=&id=zoNlPQAAC AAJ.
[26] P.G. Suárez, L. Fernández, Bacteriophages: Alternatives to Antibiotics and Beyond, MDPI,2020.https://books.google.com/books/about/Bacteriophages.html?hl=&id=V_4KEAAA QBAJ.
[27] A.Pan,G.Pranavathiyani,S.S.Chakraborty,ComputationalModelingofProtein Three-DimensionalStructure:MethodsandResources,MolecularDockingforComputer-AidedDrug Design. (2021) 155–178. https://doi.org/10.1016/b978-0-12-822312-3.00023-0.

[28] R.Lambourne,T.A.Strivens,PaintandSurfaceCoatings:TheoryandPractice,Elsevier,1999.https://books.google.com/books/about/Paint_and_Surface_Coatings.html?hl=&id=cRKkAgAAQ BAJ.

[29] A.Jakubczyk,M.Karaś,K.Rybczyńska-Tkaczyk,E.Zielińska,D.Zieliński,CurrentTrendsof Bioactive Peptides-New Sources and Therapeutic Effect, Foods. 9 (2020).https://doi.org/10.3390/foods9070846.

[30] Food andAgriculture Organization of the United Nations, Qu'est-ce que le Code de conduitepour une pêche responsable ?, Food &Agriculture Org., 2005.https://books.google.com/books/about/Qu_est_ce_que_le_Code_de_conduite_pour_u.html ?hl=& id=OtEsQDwtNNsC.

[31] A.Görgüç,E.Gençdağ,F.M.Yılmaz,Bioactivepeptidesderivedfromplantorigin by-products:Biologicalactivitiesandtechno-functionalutilizationsinfooddevelopments-Areview, Food Res. Int. 136 (2020) 109504. https://doi.org/10.1016/j.foodres.2020.109504.

[32] V.J. Hruby, Design of cyclic peptides with biological activities from biologically activepeptides:thecaseofpeptidemodulatorsofmelanocortinreceptors,Biopolymers.106(2016) 884–888. https://doi.org/10.1002/bip.22929.

[33] OECD, Food andAgriculture Organization of the United Nations, Perspectives agricoles del'OCDE et de la FAO 2011, OECD Publishing, 2011.https://books.google.com/books/about/Perspectives_agricoles_de_l_OCDE_et_de_l.html?hl =&id =rx1Lu2F_1J4C.

[34] A.H.Salem,Z.-F.Tao,O.F.Bueno,J.Chen,S.Chen,R.Edalji,S.W.Elmore,K.M.Fournier, K.C.Harper,R.Hong,G.J.Jenkins,J.Ji,R.A.Judge,J.C.Kalvass,R.C.Klix,Y.-Y.Ku,J.D. Leverson, R.A. Marks, K.C. Marsh, R.M. Menon, C.H. Park, D.C. Phillips,Y.-M. Pu, S.H.Rosenberg,Y.D.Sanzgiri,A.Y.Sheikh,Y.Shi,D.Stolarik,A.A.Suleiman,X.Wang,G.G.Z.Zhan g,N.D.Catron,A.J.Souers,Expandingtherepertoirefor"largesmallmolecules":ProdrugABBV-167 efficiently converts to venetoclax with reduced food effect in healthy volunteers,Mol. Cancer Ther. (2021). https://doi.org/10.1158/1535-7163.MCT-21-0077.

[35] A. Karshikoff, R. Ladenstein, Proteins from thermophilic and mesophilic organismsessentiallydonotdifferinpacking,ProteinEngineeringDesignandSelection.11(19 98)867–872. https://doi.org/10.1093/protein/11.10.867.

[36] H.B.Bosmann,H.BruceBosmann,Inhibitionofprotein,glycoprotein,ribonucleicacidanddeoxy ribonucleicacidsynthesisbyd-glucosamineandothersugarsinmouseleukemiccellsL5178Yand selective inhibition in SV-3T3 compared with 3T3 cells, Biochimica etBiophysicaActa (BBA) - NucleicAcids and Protein Synthesis. 240 (1971) 74–93.https://doi.org/10.1016/0005-2787(71)90515-6.

[37] Commission internationale de nomenclature zoologique, International Commission onZoological Nomenclature, Union internationale des sciences biologiques, W.D.L. Ride, C.G.Maggs, International Trust for Zoological Nomenclature, International Union of BiologicalSciences, Code International de Nomenclature Zoologique, International Trust for ZoologicalNomenclatu History Museum, 1999.https://books.google.com/books/about/Code_International_de_Nomenclature_Zoolo.html?h l=&i d=R1gWAQAAIAAJ.

[38] X.Xu,P.Björntorp,Effectsofsexsteroidhormonesondifferentiationofadiposeprecursorcells in primary culture, Experimental Cell Research. 173 (1987) 311–321.https://doi.org/10.1016/0014-4827(87)90273-4.

[39] J.D.Watson,Ladoublehélice:Compterendupersonneldeladécouvertedelastructuredel'ADN, 1999. https://books.google.com/books/about/La_double_h%C3%A9lice.html?hl=&id=zoNlPQAAC AAJ.

[40] P.G. Suárez, L. Fernández, Bacteriophages: Alternatives to Antibiotics and Beyond, MDPI,2020.https://books.google.com/books/about/Bacteriophages.html?hl=&id=V_4KEAAA QBAJ.

[41] A.Pan,G.Pranavathiyani,S.S.Chakraborty,ComputationalModelingofProtein Three-DimensionalStructure:MethodsandResources,MolecularDockingforComputer-AidedDrug Design. (2021) 155–178. https://doi.org/10.1016/b978-0-12-822312-3.00023-0.

[42] R.Lambourne,T.A.Strivens,PaintandSurfaceCoatings:TheoryandPractice,Elsevier,1999.https://books.google.com/books/about/Paint_and_Surface_Coatings.html?hl=&id=cRKkAgAAQ BAJ.

ojawgEACAAJ.
[43] A.Jakubczyk,M.Karaś,K.Rybczyńska-Tkaczyk,E.Zielińska,D.Zieliński,CurrentTrendsof Bioactive Peptides-New Sources and Therapeutic Effect, Foods. 9 (2020).https://doi.org/10.3390/foods9070846.
[44] Food andAgriculture Organization of the United Nations, Qu'est-ce que le Code de conduitepour une pêche responsable ?, Food &Agriculture Org., 2005.https://books.google.com/books/about/Qu_est_ce_que_le_Code_de_conduite_pour_u.html ?hl=& id=OtEsQDwtNNsC.
[45] A.Görgüç,E.Gençdağ,F.M.Yılmaz,Bioactivepeptidesderivedfromplantorigin by-products:Biologicalactivitiesandtechno-functionalutilizationsinfooddevelopments-Areview, Food Res. Int. 136 (2020) 109504. https://doi.org/10.1016/j.foodres.2020.109504.
[46] V.J. Hruby, Design of cyclic peptides with biological activities from biologically activepeptides:thecaseofpeptidemodulatorsofmelanocortinreceptors,Biopolymers.106(2016) 884–888. https://doi.org/10.1002/bip.22929.
[47] OECD, Food andAgriculture Organization of the United Nations, Perspectives agricoles del'OCDE et de la FAO 2011, OECD Publishing, 2011.https://books.google.com/books/about/Perspectives_agricoles_de_l_OCDE_et_de_l.html?hl =&id =rx1Lu2F_1J4C.
[48] A.H.Salem,Z.-F.Tao,O.F.Bueno,J.Chen,S.Chen,R.Edalji,S.W.Elmore,K.M.Fournier, K.C.Harper,R.Hong,G.J.Jenkins,J.Ji,R.A.Judge,J.C.Kalvass,R.C.Klix,Y.-Y.Ku,J.D. Leverson, R.A. Marks, K.C. Marsh, R.M. Menon, C.H. Park, D.C. Phillips,Y.-M. Pu, S.H.Rosenberg,Y.D.Sanzgiri,A.Y.Sheikh,Y.Shi,D.Stolarik,A.A.Suleiman,X.Wang,G.G.Z.Zhan g,N.D.Catron,A.J.Souers,Expandingtherepertoirefor"largesmallmolecules":ProdrugABBV-167 efficiently converts to venetoclax with reduced food effect in healthy volunteers,Mol. Cancer Ther. (2021). https://doi.org/10.1158/1535-7163.MCT-21-0077.
[49] A. Karshikoff, R. Ladenstein, Proteins from thermophilic and mesophilic organismsessentiallydonotdifferinpacking,ProteinEngineeringDesignandSelection.11(19 98)867–872. https://doi.org/10.1093/protein/11.10.867.
[50] H.B.Bosmann,H.BruceBosmann,Inhibitionofprotein,glycoprotein,ribonucleicacidanddeoxy ribonucleicacidsynthesisbyd-glucosamineandothersugarsinmouseleukemiccellsL5178Yand selective inhibition in SV-3T3 compared with 3T3 cells, Biochimica etBiophysicaActa (BBA) - NucleicAcids and Protein Synthesis. 240 (1971) 74–93.https://doi.org/10.1016/0005-2787(71)90515-6.
[51] Commission internationale de nomenclature zoologique, International Commission onZoological Nomenclature, Union internationale des sciences biologiques, W.D.L. Ride, C.G.Maggs, International Trust for Zoological Nomenclature, International Union of BiologicalSciences, Code International de Nomenclature Zoologique, International Trust for ZoologicalNomenclatu History Museum, 1999.https://books.google.com/books/about/Code_International_de_Nomenclature_Zoolo.html?h l=&i d=R1gWAQAAIAAJ.
[52] X.Xu,P.Björntorp,Effectsofsexsteroidhormonesondifferentiationofadiposeprecursorcells in primary culture, Experimental Cell Research. 173 (1987) 311–321.https://doi.org/10.1016/0014-4827(87)90273-4.
[53] J.D.Watson,Ladoublehélice:Compterendupersonneldeladécouvertedelastructuredel'ADN, 1999. https://books.google.com/books/about/La_double_h%C3%A9lice.html?hl=&id=zoNlPQAAC AAJ.
[54] P.G. Suárez, L. Fernández, Bacteriophages: Alternatives to Antibiotics and Beyond, MDPI,2020.https://books.google.com/books/about/Bacteriophages.html?hl=&id=V_4KEAAA QBAJ.
[55] A.Pan,G.Pranavathiyani,S.S.Chakraborty,ComputationalModelingofProtein Three-DimensionalStructure:MethodsandResources,MolecularDockingforComputer-AidedDrug Design. (2021) 155–178. https://doi.org/10.1016/b978-0-12-822312-3.00023-0.
[56] R.Lambourne,T.A.Strivens,PaintandSurfaceCoatings:TheoryandPractice,Elsevier,1999.https:// books.google.com/books/about/Paint_and_Surface_Coatings.html?hl=&id=cRKkAgAAQ BAJ.

[57] E.Saretta,P.Bonomo,F.Frontini,AcalculationmethodfortheBIPVpotentialofSwissfaçades at LOD2.5 in urban areas:Acase fromTicino region, Solar Energy. 195 (2020)150–165. https://doi.org/10.1016/j.solener.2019.11.062.
[58] R.S.Farr,S.M.Goh,F.Y.S.Yong,UseoftheWeibullequationtoapproximatediffusivereleasefr omparticlesinaclosedsystem,Computers&ChemicalEngineering.39(2012)33–40. https://doi.org/10.1016/j.compchemeng.2011.09.012.
[59] A. Messiah, Mécanique quantique, 1995.https://books.google.com/books/about/M%C3%A9canique_quantique.html?hl=&id=k_bc AQAACAAJ.
[60] J.Dreyer,G.Brancato,E.Ippoliti,V.Genna,M.DeVivo,P.Carloni,U.Rothlisberger,Chapter 9.FirstPrinciplesMethodsinBiology:FromContinuumModelstoHybridAbinitioQuantumMechani cs/Molecular Mechanics, Theoretical and Computational Chemistry Series. (2016)294–339. https://doi.org/10.1039/9781782626831-00294.
[61] S.Tanaka,ABINITIOAPPROACHTOVIBRATIONALPROPERTIESANDQUANTUM DYNAMICSOFMOLECULES,RecentAdvancesinQuantumMonteCarloMethods—Part II.(2002)95–107.https://doi.org/10.1142/9789812775696_0007.
[62] A.Gonis,T.C.Schulthess,P.E.A.Turchi,J.vanEk,Then-particlePictureandtheCalculationoftheElectronicStructureofAtoms,Molecules,andSolids,Adva ncesinQuantumChemistry.(1998) 85–104. https://doi.org/10.1016/s0065-3276(08)60431-1.
[63] B.S. Jursic, The potential energy surface for the oxywater radical cation transformation tohydrogenperoxideradicalcationstudiedbydensityfunctionaltheoryandabinitiomethods.Are hybrid density functional methods as accurate as coupled-cluster ab initio methods?,Journal of Molecular Structure: THEOCHEM. 401 (1997) 45–54.https://doi.org/10.1016/s0166-1280(96)04980-9.
[64] D.Majumdar,S.Roszak,J.Leszczynski,Dothelow-energyconformersofnerveagents(NAs)really have cholinesterase inhibition properties? Investigations of the low-energy conformersofacetylcholineandthetwoNAssarinandsoman,MolecularPhysics.105(2007)2551–2564.https://doi.org/10.1080/00268970701570161.
[65] T.Otomo,H.Suzuki,R.Iida,T.Takayanagi,SN1reactionmechanismsoftert-butylchlorideinaqueous solution: What can be learned from reaction path search calculations and trajectorycalculations for small hydrated clusters?, Computational and Theoretical Chemistry. 1201(2021) 113278. https://doi.org/10.1016/j.comptc.2021.113278.
[66] E.M. Ricketts, J. Bradshaw, M. Hann, F. Hayes, N.Tanna, D.M. Ricketts, Comparison ofconformationsofsmallmoleculestructuresfromtheProteinDataBankwiththosegeneratedby Concord, Cobra, ChemDBS-3D, and Converter and those extracted from the CambridgeStructural Database, Journal of Chemical Information and Modeling. 33 (1993) 905–925.https://doi.org/10.1021/ci00016a013.
[67] J.Liu,L.Zhou,Z.Zuo,AntibacterialActivitiesofCarbapenemDerivativesandQuantitativeStructu re-Activity Relationship for Drug Design, QSAR & Combinatorial Science. 27(2008) 1216–1226. https://doi.org/10.1002/qsar.200710104.
[68] K.Cao,K.Verspoor,E.Chan,M.Daniell,S.Sahebjada,P.N.Baird,Machinelearningwithareduced dimensionality representation of comprehensive Pentacam tomography parametersto identify subclinical keratoconus, Comput. Biol. Med. 138 (2021) 104884.https://doi.org/10.1016/j.compbiomed.2021.104884.
[69] T.Rezić,A.VrsalovićPresečki,Ž.Kurtanjek,Newapproachtotheevaluationoflignocellulosederived by-products impact on lytic-polysaccharide monooxygenase activity by usingmolecular descriptor structural causality model, Bioresour. Technol. (2021) 125990.https://doi.org/10.1016/j.biortech.2021.125990.
[70] M.S.J.Warne, M. St. J.Warne, D.W. Connell, D.W. Hawker, G. Schüürmann, Prediction ofaqueoussolubilityandtheoctanol-waterpartitioncoefficientforlipophilicorganiccompoundsusing molecular descriptors and physicochemical properties, Chemosphere. 21 (1990) 877–888.https://doi.org/10.1016/0045-6535(90)90168-s.
[71] J.Teissié,A.Baudras,Afluorescencestudyofthebindingofcytochrome C to mixed-phospholipidmicrovesicles:Evidenceforapreferredorientationoftheboundprotein,Biochimie. 59

(1977) 693–703. https://doi.org/10.1016/s0300-9084(77)80248-4.

[72] A.H.D. Boer, A.H. De Boer, H.A.A. Korthout, 14–3–3 Protein homologues play a central rolein the fusicoccin signal transduction pathway, Plant Hormone Signal Perception andTransduction. (1996) 147–153. https://doi.org/10.1007/978-94-009-0131-5_20.
[73] D.W. Thompson, J.T. Bonner, Forme et croissance, Seuil, 1994.https://books.google.com/books/about/Forme_et_croissance.html?hl=&id=BIUnAAAACAAJ
.
[74] R.Dias,W.F.deAzevedoJr,Moleculardockingalgorithms,Curr.DrugTargets.9(2008) 1040–1047. https://doi.org/10.2174/138945008786949432.
[75] H.M.Ashtawy,N.R.Mahapatra,Boostedneuralnetworksscoringfunctionsforaccurateliganddocking and ranking, Journal of Bioinformatics and Computational Biology. 16 (2018)1850004. https://doi.org/10.1142/s021972001850004x.
[76] A. ’aAbu-Srhan, E.Al Daoud,AHybridAlgorithm Using a GeneticAlgorithm andCuckooSearchAlgorithmtoSolvetheTravelingSalesmanProblemanditsApplicationtoMultipleSequenceAlignment,InternationalJournalofAdvancedScienceandTechnology.61 (2013) 29–38. https://doi.org/10.14257/ijast.2013.61.04.
[77] L.A.GonzalezPaz,C.A.Lossada,L.S.Moncayo,F.Romero,J.L.Paz,J.Vera-Villalobos,A.E.Perez, E. San-Blas,Y.J.Alvarado, Molecular docking and molecular dynamic study of twoviral proteins associated with SARS-CoV-2 with ivermectin, Preprints. (2020).https://doi.org/10.20944/preprints202004.0334.v1.
[78] L.A.Gonzalez-Paz,C.A.Lossada,L.S.Moncayo,F.Romero,J.L.Paz,J.Vera-Villalobos,A.E.Pérez, E. San-Blas,Y.J.Alvarado, Theoretical molecular docking study of the structuraldisruption of the viral 3CL-protease of COVID19 induced by binding of capsaicin, piperineand curcumin part 1:Acomparative study with chloroquine and hydrochloroquine twoantimalaric drugs, Research Square. (2020). https://doi.org/10.21203/rs.3.rs-21206/v1.
[79] R.Singh,A.Gautam,S.Chandel,A.Ghosh,D.Dey,S.Roy,V.Ravichandiran,D.Ghosh,Protease Inhibitory Effect of Natural Polyphenolic Compounds on SARS-CoV-2:An InSilico Study, Molecules. 25 (2020). https://doi.org/10.3390/molecules25204604.

[80] A.H.D. Boer, A.H. De Boer, H.A.A. Korthout, 14–3–3 Protein homologues play a central rolein the fusicoccin signal transduction pathway, Plant Hormone Signal Perception andTransduction. (1996) 147–153. https://doi.org/10.1007/978-94-009-0131-5_20.
[81] D.W. Thompson, J.T. Bonner, Forme et croissance, Seuil, 1994.https://books.google.com/books/about/Forme_et_croissance.html?hl=&id=BIUnAAAACAAJ
.
[82] R.Dias,W.F.deAzevedoJr,Moleculardockingalgorithms,Curr.DrugTargets.9(2008) 1040–1047. https://doi.org/10.2174/138945008786949432.
[83] H.M.Ashtawy,N.R.Mahapatra,Boostedneuralnetworksscoringfunctionsforaccurateliganddocking and ranking, Journal of Bioinformatics and Computational Biology. 16 (2018)1850004. https://doi.org/10.1142/s021972001850004x.
[84] A. ’aAbu-Srhan, E.Al Daoud,AHybridAlgorithm Using a GeneticAlgorithm andCuckooSearchAlgorithmtoSolvetheTravelingSalesmanProblemanditsApplicationtoMultipleSequenceAlignment,InternationalJournalofAdvancedScienceandTechnology.61 (2013) 29–38. https://doi.org/10.14257/ijast.2013.61.04.
[85] L.A.GonzalezPaz,C.A.Lossada,L.S.Moncayo,F.Romero,J.L.Paz,J.Vera-Villalobos,A.E.Perez, E. San-Blas,Y.J.Alvarado, Molecular docking and molecular dynamic study of twoviral proteins associated with SARS-CoV-2 with ivermectin, Preprints. (2020).https://doi.org/10.20944/preprints202004.0334.v1.
[86] L.A.Gonzalez-Paz,C.A.Lossada,L.S.Moncayo,F.Romero,J.L.Paz,J.Vera-Villalobos,A.E.Pérez, E. San-Blas,Y.J.Alvarado, Theoretical molecular docking study of the structuraldisruption of the viral 3CL-protease of COVID19 induced by binding of capsaicin, piperineand curcumin part 1:Acomparative study with chloroquine and hydrochloroquine twoantimalaric drugs, Research Square. (2020). https://doi.org/10.21203/rs.3.rs-21206/v1.
[87] R.Singh,A.Gautam,S.Chandel,A.Ghosh,D.Dey,S.Roy,V.Ravichandiran,D.Ghosh,Protease Inhibitory Effect of Natural Polyphenolic Compounds on SARS-CoV-2:An InSilico Study, Molecules. 25 (2020). https://doi.org/10.3390/molecules25204604.