Potent Oxadiazoles: Unraveling Electronic and Structural Frontiers

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By

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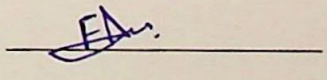
Student/Author Signature: 

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Dedication

In profound gratitude to my steadfast pillars of support—my parents, siblings, my loving husband, and my cherished son, **Muhammad Bin Haris**—whose unwavering encouragement and sacrifices have guided me through every milestone of this journey. This thesis is dedicated to you, with heartfelt appreciation for your enduring belief in my potential.

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List of Abbreviations

DFT	Density Functional Theory
ADME	Absorption, Distribution, Metabolism, Excretion
HER-2	Human Epidermal Growth factor Receptor 2
Erα	Estrogen receptor alpha
Erβ	Estrogen receptor Beta
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
OPLS-4 force field	Optimized Potentials for Liquid Simulations
PDB	Protein Data Bank

ABSTRACT

Oxadiazoles are a versatile class of heterocyclic compounds having a wide range of applications in materials science, pharmaceuticals and other disciplines. They have a variety of functions due to their unique molecular structure, which can be described by a five-membered ring consisting of two nitrogen atoms and oxygen. The molecular structures, electronic characteristics, binding interactions, and pharmacological profiles of different oxadiazoles derivatives with particular biological targets are investigated in this study using a combined computational approach that includes molecular docking simulations, Density Functional Theory (DFT) calculations, in silico ADME (Absorption, Distribution, Metabolism, and Excretion) and Cardiotoxicity predictions. This thorough study intends to clarify the structure-activity correlations and forecast important ADME characteristics and Cardiotoxicity profiles of these reported derivatives of 1,2,4 oxadiazoles , that is opening the door for the creation of new medication formulations and the discovery of innovative materials.

The present research offers an in-depth understanding of the complex interactions that occur between drugs molecules and their biological targets, as well as how they behave inside the body. Molecular docking simulations are crucial for predicting the preferred binding orientations and affinities of ligands inside the active site of receptor. In this study, molecular docking will be employed to screen a series of 1,2,4 oxadiazoles derivatives against selected biological targets related to breast and ovarian cancer. Lead compounds with significant binding affinity and favorable binding poses will be found through this in silico screening, yielding a collection of compounds for preparation of further anti-cancer drugs.

The pharmacokinetic (ADME) properties along with its safety profile is equally important to the development of drugs as its target binding and electrical characteristics. In order to evaluate important factors including the absorption, distribution, metabolism, and excretion of oxadiazoles derivatives, in silico ADME predictions will be carried out. These predictions will be useful in identifying possible risks associated with clearance pathways, drug-drug interactions, and bioavailability. Additionally, in order to evaluate these compounds' ability to influence the heart function—a crucial safety factor in medication development—in silico Cardiotoxicity studies will be carried out. For the purpose of prioritizing

candidates for additional research, these ADME and Cardiotoxicity forecasts will offer vital information.

CHAPTER 1

INTRODUCTION

1.1 Oxadiazoles:

The Oxadiazoles is a pharmacologically potent class of compounds with great potential, and for more than three decades an extensive research has been devoted to the study of these derivatives in various fields including Medicine. Oxadiazoles are popular in therapeutic activity due to their amazing anti-inflammatory, analgesic and antimicrobial effects. These compounds are often hailed as the multitasking powerhouses of modern medicine.(1)

Oxadiazoles are a modified version of furans in which two methane groups (-CH=) are replaced by nitrogen atoms (-N=), similar to those found in pyridine. There are four main types of oxadiazoles: 1, 2, 4-oxadiazoles, 1, 3, 4-oxadiazoles, 1, 2, 3-oxadiazoles, and 1, 2, 5-oxadiazoles. These compounds differ in their atom's structure, resulting in different behaviors. These compounds play different important roles in pharmaceutical products due to their ability to solve various problems and are studied for everything from antimicrobial to anti-inflammatory effects. Their adaptability makes them valuable in drug development.(2, 3)

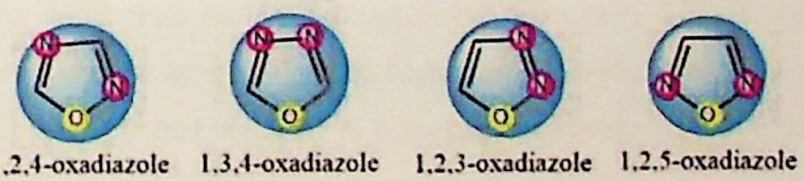


Figure 1.1: Types of oxadiazoles

In recent years, with the development of substantial biochemical progress therapeutics based on heterocyclic compounds are found to be a promising drug discovery areas due to their wide interaction in various biological targets primarily involved in cancer pathways. Among them, oxadiazoles have gained much of attention due to their wide ranging pharmacological activities such as anti-inflammatory, antimicrobial and anticancer effects. Oxadiazole derivatives represent interesting samples for medicinal chemistry because of their effectiveness in

modifying biological pathways associated with cancer. Numerous preclinical studies have already showed that such compounds may promote apoptosis, inhibit the proliferation of cancerous cells, and disrupt important pathways involved in tumor growth and metastasis.(4)

Numerous studies have also highlighted the use of oxadiazole derivatives and their effectiveness against many cancer cell types, including ovarian and breast cancer.(5) As cancer is the second most common disease with more than 63 % of deaths occurring in developing countries. This increasing burden of cancer at international level demands more novel therapeutic interventions to improve care and increase survival. Surgery, chemotherapy and radiotherapy are the conventional treatments that are currently available. It is always said — the early detection of cancer is an important factor to determine the outcome.(6)

Human epidermal growth factor receptor 2, or HER2, is a type of receptor molecule that is part of a larger family familial of proteins, which are membrane proteins with an extracellular region that contains a signal domain (ErbB2).(7) This protein is involved in cellular processes such as growth, cell division and maturation. In case of normal cells, the synthesis and activity of HER2 is highly controlled; however, overproduction or development of HER-2 gene is evident in a number of malignancies, particularly breast and stomach cancer.(8) This deregulation results in the continuous stimulation of downstream pathways, which lead to uncontrolled proliferation of the cells, thus promoting aggressive tumor.(9) The likelihood of developing recurrent tumors is significantly higher in individuals with a positive HER2 status. This implies that there is a correlation between the likelihood of recurrence and metastasis and HER2 overexpression.(10, 11)

In 2024, breast cancer remains a major health problem among men and women with approximately 313,510 estimated new cases in the U.S. Among the female, expected deaths to occur due to breast cancer is approximately 42,250 while in males it is approximately 530. These numbers shows that it is necessary for further progress in scientific understanding of breast cancer and improvements to its prevention, early detection, biological profiling and multimodality treatments.(12)

Moreover, recent studies have highlighted that the antitumor efficacy of various chemotherapeutic agents is closely linked to their ability to induce apoptosis (The

process of controlled cell death known as apoptosis is essential for getting rid of cancer cells) . This connection underscores the importance of identifying and developing new compounds that can trigger apoptosis as a strategy for anticancer drug discovery. Apoptosis inducers hold great promise in overcoming resistance to conventional cancer therapies, which is a significant challenge in cancer treatment. Tumors often develop resistance to standard chemotherapy and radiation due to various genetic and molecular alterations. However, by specifically targeting the apoptotic pathways, these new agents may bypass such resistance mechanisms, leading to more effective treatments. The exploration of apoptosis-inducing compounds could, therefore, result in breakthroughs in cancer therapeutics, offering hope for patients who do not respond well to current treatments. This approach is gaining momentum in the quest for more selective and potent anticancer agents.(13) These reported molecules may also act as apoptotic inducers. One of the gynaecological tumours with the greatest death rate is ovarian cancer, which is extremely dangerous for women's health. (14). The health of women worldwide is seriously threatened by ovarian cancer, which is acknowledged as one of the gynaecological malignancies with the highest death rates. Around 313,000 new cases of ovarian cancer were detected worldwide in 2020. Ovarian cancer is the fifth most common cause of cancer-related deaths among women in the United States. (15)

With improved treatment, one would expect mortality rates to lower. However, there's an indication of the neglect we have given it as the rates remain high. There is increasing evidence indicating an important relationship connecting estrogen signaling and ovarian cancer (16). Estrogens (significant female reproductive hormones) mainly perform function through the two receptors i.e. receptors of estrogen alpha (ERα) and estrogen receptor beta (ERβ) (17) . Remarkably, differential expression patterns of these receptors distinguish between the primary ovarian and the metastatic ovarian tumors. Most of the studies report a decrease of ERβ expression in primary ovarian epithelial tumors compared to normal ovarian tissue. In contrast, however, in metastatic ovarian tumors a remarkable alteration takes place, with the almost total or sole presence of ERα. This differential expression suggests that ERα might be involved in tumor progression and metastasis.(18)

1.2 Density Functional Theory Method:

This research is using a computational method called DFT with the B3LYP method to calculate certain properties of titled compounds. DFT simulations are integral to this study, as they will aid in determining optimal thermodynamic parameters, HOMO-LUMO energy levels, and molecular structural characteristics.(19)

These days, determining the quantum mechanical ground states of condensed matter systems using DFT techniques is a popular and important part of materials research. DFT's increasing significance is a result of the development of functionals that are sufficiently accurate, efficient algorithms, and continual improvements in computational capability. The sets of computations required to look into a particular problem have grown in size and complexity along with the materials challenges to which DFT is used. This development demonstrates DFT's versatility and its vital role in solving today's materials science problems by enabling the more accurate and computationally affordable investigation of innovative materials and their properties.(20)

DFT is a quantum-mechanical approach; it has been a cornerstone in physics and chemistry since the 1970s for analyzing the electronic structure of atoms, molecules, and solids, particularly in computational solid-state physics. DFT techniques primarily use general functionals, which are functions of a function in mathematics, to calculate electron correlation. These functionals rely on the electron density in the context of DFT, offering a strong basis for accurately characterizing complex quantum systems. To improve precision, DFT functionals split down the total electronic energy into several separate parts, each of which is calculated separately. The systematic investigation of the different components to the overall energy, including kinetic energy, exchange-correlation energy, and electrostatic interactions, is made simpler by this decomposition. Traditional functionals and hybrid functionals are the two main categories into which the functionals in DFT can be generally divided.(21)

1. **Traditional functionals:**

Traditional functionals encompass local exchange and correlation functionals as well as gradient-corrected functionals.

i. Local Exchange and Correlation Functionals:

These functionals depend on electron spin density values. The Vosko, Wilk, and Nusair (VWN) functional is a well-known example that efficiently predicts exchange-correlation effects based on localized electron densities.

ii. Gradient-Corrected Functionals:

These functionals, commonly referred to as Generalised Gradient Approximation (GGA) functionals, enhance the local density approximation by include both the electron spin densities and their respective gradient values. One well-known example in this category is the Becke-Lee-Yang-Parr (BLYP) functional, which provides improved accuracy for systems with large variations in electron density.

2. Hybrid functionals:

It involves both the combine elements of both Hartree-Fock theory and density functional theory (DFT) to improve the accuracy of electronic structure calculations compared to standard DFT functionals. It involves B3LYP & B3PW91 keyword in Gaussian.(22) Keywords like B3LYP and B3PW91 are used in computational executions, like Gaussian software, to describe the required hybrid functional for electronic structure calculations.

Despite DFT's proficiency in predicting ground-state properties, it falls short in accurately predicting electronic excitation energies. To address this, the research will employ extensions to standard DFT, such as Time-Dependent DFT (TD-DFT), which has become increasingly popular for excited state computations. This holistic approach enhanced the understanding of molecular interactions and properties, contributing to the fields of photovoltaic, photochemistry, and molecular electronics. DFT is an essential technique for dealing with large systems, particularly in π-systems where double excitations are essential. When researching conjugated molecules and materials with large π-electron networks, DFT is essential due to its ability to effectively handle the electronic correlation in such delocalised systems. This characteristic is especially crucial for comprehending the electronic characteristics of complex nanostructures, such as organic semiconductors and

graphene-like materials, where computing constraints may make traditional approaches ineffective.(23)

The biological activity of oxadiazoles is mainly influenced by their electronic properties with respect to the energy gaps of HOMO and LUMO. Density Functional Theory (DFT) calculations provide important information about the electronic structures and molecular shapes of these molecules aiding in developing novel potential anticancer agents. In addition, molecular docking studies provide the opportunity to predict interactions between oxadiazoles derivatives and different cancer-associated receptors which help in delineating the compounds with superior binding affinity as well as selectivity.

1.3 Molecular Docking Study:

Molecular docking is a computational modeling technique that predicts preferred orientation of a molecule when it forms a stable interaction with another molecule. Based on the binding characteristics of a ligand and targeted molecules (these targeted molecules may be some proteins), it calculates the three-dimensional structures of complexes. To find the most stable docked conformer, molecular docking techniques produce a number of alternative configurations that are assessed and ranked using scoring algorithms. These simulations help in drug discovery and materials science research by optimizing docking, based on the overall energy of the system and offering insightful information about molecular interactions.(24)

Molecular docking techniques are widely employed in modern drug design to investigate the conformations of ligands embraced by macromolecular targets within their binding sites. This method also evaluates significant events in the intermolecular recognition process to quantify the free energy of ligand-receptor binding. Since many different docking algorithms are available, it is crucial to comprehend the benefits and drawbacks of each technique to create appropriate results and successful techniques.(25)

Molecular docking plays a vital role for understanding complex molecular interactions in diverse chemical contexts. Parallely, molecular docking studies are planned to decode the binding interactions of the most active derivatives with enzyme active sites. Since its inception in the 1980s, the process for discovering

novel medicines involves the use of molecular docking. Its growing importance in both academic and industrial spheres is attributed to methodological advancements, increased availability to small molecule and protein structures and significant improvements in computational power. These developments have made molecular docking more efficient and accurate. Docking studies, especially molecular docking, are instrumental in drug discovery and design. They provide a detailed understanding of the interactions between small molecules (ligands) and targeted biomolecules (typically proteins) at the molecular level. This understanding is crucial for the rational design of new drugs, allowing researchers to predict how different compounds will interact with biological targets, thereby streamlining the drug development process. This dual approach, encompassing both DFT and molecular docking, promises comprehensive insights into molecular behaviors and interactions, paving the way for innovative therapeutic discoveries.

1.4 ADME:

Drug discovery and development is a complex and challenging process. In pharmacokinetics, a subfield of pharmacology that examines how drugs behave and persist in living things is called ADME. ADME stands for "Absorption, Distribution, Metabolism, and Excretion". It describes the phases that a medicinal substance goes through in an organism. These four stages determine how medications are metabolized, absorbed, and retained in the body, which in turn affects how well they work and how pharmacologically active they are.(26)

The extent to which a medication is absorbed into the bloodstream from the place where it is given is known as absorption. The process by which the drug allocates throughout the body is referred to as distribution. The process by which the medicine is broken down by the body is called metabolism. The body eliminates the drugs and their metabolites through excretion. (27)

A drug's safety and effectiveness can be greatly impacted by its ADME characteristics. A medicine may not reach its target in sufficient proportions to be effective, for instance, if it is poorly digested. However, if a medicine is metabolized too quickly, its effectiveness may be short-lived. Likewise, if a medicine is not effectively eliminated from the body, it may accumulate and become hazardous.(28, 29, 30)

For the development of safe and efficient medications, an understanding of ADME is essential. Researchers are able to identify any issues and alter the drug's structure or formulation by looking at ADME features early in the drug discovery process. This may improve the medication's chance of passing clinical trials and, eventually, result in the creation of novel treatment options for patients. (26, 31, 32)

AIMS AND OBJECTIVES

This research aims to investigate the potential of a series of 1, 2, 4 oxadiazoles as anticancer agents.

The characterization of the electronic properties of these compounds takes place by using Density Functional Theory (DFT) calculations. This includes determining HOMO-LUMO energy gaps, electron affinity, ionization energy (I), electrophilic index (E), chemical softness(S), and hardness (H). Density functional theory (DFT) calculations were performed using Gaussian software to provide insights into the electronic properties of the compounds.

Molecular docking simulations will perform to investigate the potential binding interactions of the 1,2,4-oxadiazole derivatives with key protein targets associated with cancer, specifically HER2 and ERα. This will involve:

- Retrieving 3D protein structures of HER2 and ERα from the Protein Data Bank (PDB).
- Preparing protein structures for docking by removing water molecules and adding hydrogen atoms.
- Performing docking simulations using software such as Schrödinger Maestro.
- Analyzing docking poses and calculating binding affinities to identify potential binding modes and key interactions between the 1,2,4-oxadiazole derivatives and HER2/ERα.This indicates the strong potential of these compounds as effective anticancer agents. These findings underscore the therapeutic value of the studied ligands. This makes them interesting for the pharmaceutical industry. The insights gained from this study may have important implications for the development of new anticancer drugs. This leads to progress in treating serious diseases in the future.

To predict the in silico ADME (Absorption, Distribution, Metabolism, Excretion) properties of the compounds using computational tools and databases. This will involve:

- Estimating absorption, including parameters such as lipophilicity (logP), aqueous solubility, and intestinal absorption.
- Predicting distribution properties, such as plasma protein binding and volume of distribution.
- Assessing metabolism by predicting potential sites of metabolic transformation by enzymes such as cytochrome P450.
- Evaluating excretion properties, such as renal clearance and potential for drug-drug interactions.

Additionally, in silico ADME profiling (absorption, distribution, metabolism and excretion) identifies promising candidates for further clinical evaluation. Anticancer screening results show that many of the effective compounds demonstrate their potential efficacy.

CHAPTER 2

LITERATURE REVIEW

The research delves into the unique chemical properties and pharmaceutical applications of oxadiazoles, a group of aromatic heterocyclic compounds exhibiting interesting electronic characteristics due to its additional heteroatoms. As Oxadiazoles are weak base, now, when we compare it to furan, oxadiazoles compound has two nitrogen atoms instead of two –CH= groups. These nitrogen atoms are similar to the ones found in pyridine. This replacement of the –CH= groups with the nitrogen atoms affects how the compound's aromaticity is reduced. Aromaticity is a property that relates to the stability and structure of certain compounds. Because of the nitrogen atom's electron-withdrawing function, this modification results in a low electron density on the carbon atom, which makes electrophilic substitutions on the oxadiazoles ring difficult at the carbon atom. Oxadiazoles undergoes nucleophilic substitution reactions to an aliphatic sp^2 carbon atom.(3)

Cancer, a progressive and aggressive disease affecting various tissues and organs, continues to claim millions of lives annually. The challenge in treating cancer stems from factors such as late diagnosis, tumor cell type and its location, and drug resistance. In response, developed anticancer drugs target key biological processes like angiogenesis, apoptosis, tumor invasion, and metastasis. Notably, heterocyclic compounds, which made up 70% of FDA-approved anticancer drugs between 2010 and 2020, play a critical role in cancer therapy. These compounds exhibit diverse biological activities through their ability to engage in intermolecular interactions, including hydrogen bonding, metal coordination complexes, π-stacking interactions, van der Waals, and hydrophobic forces.(33, 34, 35)

Derivatives of the oxadiazoles are a prominent class of heterocyclic compounds, as is well known. With two carbons, one oxygen atom, two nitrogen atoms, and two double bonds, oxadiazoles are a heterocyclic, five-membered ring. They are created by replacing two methylene groups (= CH) in furan with two nitrogen (-N =) atoms. By replacing these groups, the aromaticity of the furan ring was considerably reduced, leading to a conjugated diene property. 1,2,4-oxadiazole, 1,2,3-oxadiazole,

1,2,5-oxadiazole, and 1,3,4-oxadiazole were the four different oxadiazoles isomers that have been proven to exist at the time. Among these, 1,3,4-oxadiazoles and 1,2,4-oxadiazoles are the most well-known and studied due to their wide range of chemical and biological characteristics. 1,2,4-oxadiazoles are now crucial in the creation of novel medications. Antibacterial, anti-mycobacterial, anticancer, antiviral, and antioxidant properties are among the biological actions of the oxadiazoles derivatives. Among the five membered nitrogen heterocyclic compounds, oxadiazoles core exhibits a variety of pharmacological properties.(36, 37)

Oxadiazoles has been shown to be the physiologically active component of several drugs in recent years. The antibacterial, anti-inflammatory, anti-tuberculosis, anti-fungal, anti-diabetic, and anticancer properties of oxadiazoles derivatives are demonstrated.(38)

The investigation of frontier molecular orbitals (FMOs) of these substances is instrumental. Analysis of the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) provides a qualitative characterization of molecular orbitals. LUMOs and HOMOs, often exhibiting π symmetry, play a significant role in determining optical absorption. A substantial spatial overlap between HOMO and LUMO can lead to enhanced optical absorption, indicative of the transition from HOMO to LUMO. Furthermore, the spatial distribution of LUMOs and HOMOs offers insights into the nature of charge-transfer transitions. It is widely recognized that the strength of electron donor/acceptor capabilities greatly influences the photo physical properties of intramolecular charge transfer. Electronic excitations cause redistribution of electron density, affecting the molecule. Changes in excited state bond lengths compared to ground state geometries reflect alterations in bonding character.(39)

In order to progress the field of materials science, a vast amount of raw data has to be stored and interpreted. Machine learning algorithms have been performing this task of identifying correlations and patterns from large amounts of complex data for decades, and the materials science community has recently begun to invest in these methodologies to extract knowledge and insights from the accumulated data. Recent advances in experimental and computational methods have increased the quantity and enhanced the quality of knowledge. Density functional theory include data mining, screening, and machine learning techniques, employ the data generated.(40)

When creating high-performance electro catalysts, computational techniques based on density functional theory (DFT) have shown to be very important. The purpose of DFT calculations is to verify the catalytic sites on the surface, assess the catalytic activity, identify potential reaction pathways, and create new structures with excellent catalytic efficiency. (41)

By using different databases, novel inhibitors against any target of interest can be found. A computational technique called "molecular docking" is used to predict the shape of a receptor-ligand combination.(42)

Molecular docking has become an essential tool in medicinal chemistry and drug discovery. This technique involves placing ligands within a protein receptor in various conformations, assimilation, and locations, using their computer-generated three-dimensional structures. It provides insights into molecular recognition and is a crucial component of Computer-Aided Drug Design and Discovery (CADDD). Traditional docking methods have limitations, such as the semi-flexible or static treatment of targets and ligands. However, advancements in proteomics, genomics, and computational techniques over the past decade have led to the advancement of various docking methods. These new methods consider the flexibility of proteins and ligands, along with their multiple binding conformations. (43)

Molecular docking is a drug design technique that interprets the molecular interactions and predicts the mechanism of binding and shows the type of attraction between ligands and receptors. In recent years, this method has been widely used in drug design research. It is straightforward for researchers to buy, synthesize, and finish follow-up pharmacological testing when they use the compounds database to screen for prospective pharmacophore. This approach also significantly increases efficiency and lowers research costs.(44)

Table 2.1: Different software used for DFT calculations

Reference	Sr. #	Name of software	Advantages	Disadvantages
(45)	1	Gaussian	i. It contains a large variety of basis sets and DFT functional. ii. It interacts with visualization tools that are easy to use. iii. Ability to do complicated computations, such as geometry optimization.	i. Large systems have high computational requirements. ii. Variation in performance depending on basis set and functional preference.
(46)	2	ORCA	i. DFT with high performance for large molecules. ii. Advanced techniques (like coupled-cluster) that go beyond DFT. iii. Open-source with the ability to customize.	i. It restricted the graphics user interface. ii. It requires a high level of understanding of computational chemistry.
(47)	3	ASP (Vienna Ab initio Simulation Package)	i. Useful for materials science and solid-state physics. ii. Plane-wave basis sets provide precise energy estimations. iii. Facilitates GW computations and hybrid functionals.	i. It has a complicated layout and refinement. Cost and limitations on license. ii. It requires solid-state simulation expertise.
(48)	4	NWChem	i. Modular architecture and open-source software.	i. More difficult to use than commercially available software.

			ii. Accommodates a variety of theoretical models, including Hartree-Fock and DFT. iii. Developed for use in parallel computing.	ii. Lengthy setup. iii. Limited resources and assistance.

Table 2.2: Different software used for Molecular docking simulation

Reference	Sr #	Name of softwares	Advantages	Disadvantages
(49)	**1.**	AutoDock Vina	i. Precise and effective docking simulations. ii. Easy to use and compatible with several threads. iii. Accurately predicts ligand-receptor interactions.	i. Restricted to scoring functions derived from actual data. ii. It might ignore the complex flexibility of receptors. iii. Needs to be verified for accuracy.
(50)	**2.**	AutoDock	i. Compatible while optimizing receptor flexibility. ii. Accurately predicts binding affinities and binding modes. iii. Widely employed in both industries and educational institutions.	i. Updates may not be accessible in older versions. ii. Requires knowledge of setting up and verifying parameters. iii. Less support than in more recent applications.
(51)	**3.**	DOCK	i. Designed to facilitate research on ligand-receptor docking. ii. Incorporates rating systems for precise forecasting. iii. Used for virtual	i. It has to be optimised for various systems. ii. Complexity while working with big datasets. iii. Support and updates might

			screening and drug discovery.	differ.
(52, 53)	**4.**	Schrodinger Suite	i. Maestro for managing processes and visualization. ii. With enhanced scoring, glide for precise docking. iii. Comprehensive molecular modeling tools.	i. License fees for business use. ii. To utilize the advanced functions, training is necessary. iii. Demands on computation for extensive research.

A drug's interactions with the human body are governed by a series of dynamic processes known as absorption, distribution, metabolism, and excretion, or ADME.(54) The term "absorption" defines how the medication departs the point of intake and enters the bloodstream. Distribution explains how the medication travels to its designated locations throughout the body. The medicine is converted by the body into metabolites during metabolism, which frequently makes the drug more soluble in water for excretion. Finally, excretion is the mechanism via which the medication and its metabolites are removed from the body, primarily by the liver and kidneys.(27, 30)

For novel drug development to be beneficial, it is essential to comprehend ADME features. A medicine must have the ideal ADME properties in order to be both safe and effective. Adequate absorption guarantees that enough medication enters the bloodstream to have its intended therapeutic impact. While reducing accumulation in non-target organs, favorable distribution enables the medication to reach its target areas. Drug accumulation and toxicity can be avoided with effective metabolism, and rapid drug and metabolite removal is ensured by suitable excretion mechanisms.(55)

The first and most important stage of a drug's effect is absorption. The method of administration (oral, intravenous, etc.), drug solubility (lipid and water solubility), drug ionization, and the presence of efflux transporters in the gastrointestinal tract are some of the factors that affect drug absorption. For example, medications that are lipophilic are typically more easily absorbed through biological membranes. (56)

The medicine enters the bloodstream and travels throughout the body after absorption.

Tissue permeability, protein binding, and blood flow are some of the variables that affect medication distribution. Drugs have the ability to attach to plasma proteins like albumin after they enter the bloodstream, which limits the quantity of free drug that can enter target tissues. The distribution and effectiveness of drugs can be greatly impacted by this protein binding. (57)

Biotransformation, another name for metabolism, is a crucial process in which the body changes the drug molecule chemically. This is mostly caused by the activity of cytochrome P450 enzymes in the liver. The drug may become inactive metabolites, become more water soluble for excretion, or change its activity as a result of

metabolism. On the other hand, hazardous metabolites can occasionally be produced during metabolism.(58)

The negative effects of medications on the heart are referred to as **Cardiotoxicity**. It includes a variety of cardiac problems, such as a myocardial infarction (heart attack), heart failure (weakened heart muscle), and arrhythmias (irregular heartbeats). Numerous methods, including direct toxicity to cardiac cells, disruption of cardiac ion channels, or indirect effects on the circulatory system, can result in cardio toxicity.(59)

Since the risk for serious and even fatal results, Cardiotoxicity presents a significant clinical problem.It may have some major side effects on the health of patients and restrict the therapeutic use of many beneficial medications. Cardio toxicity may complicate treatment plans and even threaten therapeutic efficacy by requiring dose reductions, treatment termination, or the use of cardio protective medications. (60)

Cardiotoxicity must be detected early and prevented in order for new medications to be developed successfully. Cardiotoxicity must be thoroughly evaluated both preclinical and clinically in order to guarantee medication safety and reduce the possibility of adverse cardiac events in patients. During clinical trials, patients are closely monitored, and possible cardiac effects are evaluated using in vitro and in vivo models.(61)

CHAPTER 3

METHODOLOGY

Using Erlotinib as a typical anti-cancer medication, a few reported oxadiazoles derivatives were chosen from the literature for docking experiments against HER2 and Erα. ChemDraw Ultra 12.0 was then used to draw their structures. The following table shows the selected molecules.

Selected Oxadiazoles compounds:(62)



Figure 3.1: Molecular structure of derivatives of oxadiazoles

3.1 DFT Studies:

The structures of all the selected molecules (1-20) were initially drawn from ChemDraw Ultra 12.0, and a corresponding .mol file was generated for each structure. The .mol file was then opened in Gauss View for further processing and the calculations were done by going to energy optimization with a DFT method and chosen basis sets. This brought up two output files that would be generated for any molecule: chk file and gjf file. Molecular modeling of the compounds was performed using Gauss View 6.0 , while all calculations were done on Gaussian 09W.

3.2 Molecular docking studies:

3.2.1. Preparation of Ligands:

For this purpose, Chem Draw Ultra 12.0 was used to draw the molecular structures of 1, 2, 4 oxadiazoles. After saving them as a mol file, these structures were added to Maestro 13.5. LigPrep command was used to prepare ligand structures with the default settings. By creating potential states at the target pH of 7.0, 2.0 using Epik, desalting, generating a tautomer, and saving them in a designated folder, their confirmation was optimized in the OPLS-4 force field.(63)

3.2.2. Preparation of Proteins (PDB code: 7JXH and 1A52):

The selected proteins (i.e. PDB ID: 7JXH and 1A52) was retrieved from Protein Data Bank (RCSB). Protein preparation was carried out by "Protein Preparation" Wizard by using Maestro to add hydrogen and setting protonation's state suitable for pH 7. The protein molecule was then induced to have hydrogen atoms attached to it, and bond orders were assigned. Then protein was processed. The water molecules beyond 5 Å were removed and protein was minimized.(63)

3.2.3. Grid generation:

After that, grid generation was carried out to the prepared protein.(64) The co-crystallized ligands from PDB and protein-related literature were used to determine the active site of the processed protein in order to create a grid box.

3.2.4. Mechanism of docking:

The prepared ligands and grid-defined docking target were imported into the Ligand Docking interface inside the Maestro environment of Schrödinger to perform protein docking studies. All docking simulations were carried out in GLIDE under the Standard Precision (SP) mode without changing the default settings. The evaluation of absolute LOA goes through the following stages - a Glide scoring function to predict the binding affinity, followed by docking scores to determine the extent and type of interactions each ligand has with the protein target.(65) Detailed analysis of the ligand positioning within the HER2 and Erα substrate binding sites was performed using Glide SP docking in Schrödinger Maestro software. Reported 1,2,4-

oxadiazole Precise ligand alignment to the active site was identified that is based on the docking score and visual inspection of the internal structure of protein vesicles to show the most suitable structure. Representative images were taken. Additionally, a table was created to relate the binding energies to the connectivity scores. It provides deeper insights into the anchoring interactions.

3.3 ADME analysis:

After comparable calculations, ADME (absorption, distribution, metabolism, and excretion) analysis was performed to predict the pharmacokinetic properties of the previously reported selected compounds (1-20), and the reference drug Erlotinib. This was included as a standard of comparison to evaluate the therapeutic potential of new drugs was carried out using the compound. It provides detailed insights into the suitability of each compound as a therapeutic agent.

CHAPTER 4

RESULTS

4.1 DFT Studies:

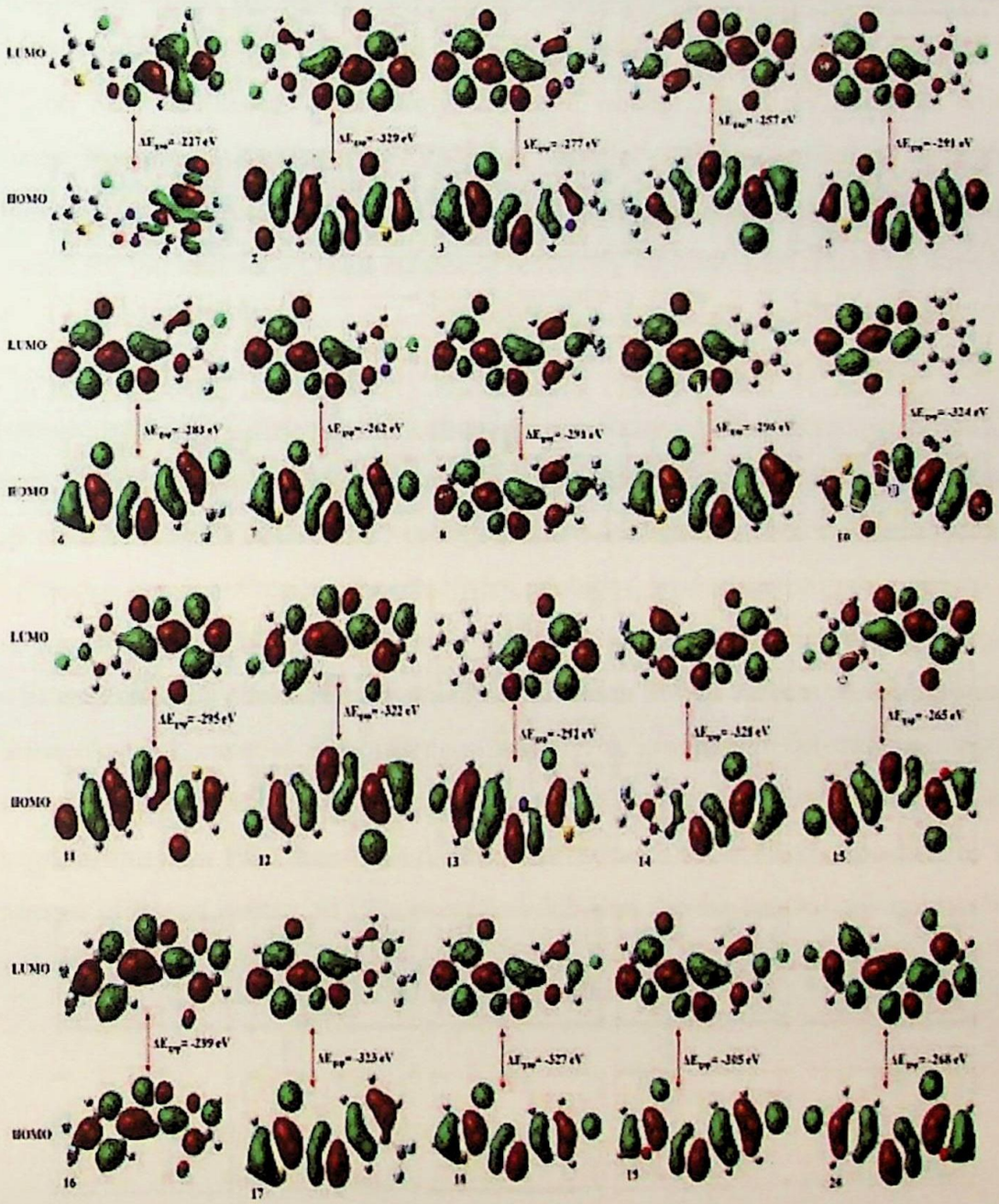


Figure 4.1: HOMO-LUMO energy gap of Oxadiazole's derivatives

Molecular Orbital Analysis:

Crucial data on the electrical characteristics and reactivity of substances interacting with protein targets can be obtained by frontier molecular orbital (FMO) studies(66). Regions of electron donation and acceptance are shown by the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) distributions, which are represented by DFT calculations as seen in the provided molecular orbital diagrams. Red and green lobes, which stand for areas of electron donation and acceptance, respectively, are used to represent these orbitals using Density Functional Theory (DFT)(67). A smaller ΔEgap indicates a higher propensity for electronic transitions, increased chemical reactivity, and a greater potential for bio interaction. This enhanced reactivity facilitates interactions with the protein target, crucial for pharmaceutical applications. According to Fleming (2009), a smaller ΔEgap denotes a stronger potential for biointeraction, a higher tendency for electronic transitions, and increased chemical reactivity. This increased reactivity makes it easier to interact with the protein target, which is essential for therapeutic purposes(68). The HOMO-LUMO energy gap is a fundamental descriptor in rational drug design, as it influences the reactivity, stability, and electronic transitions of bioactive molecules(69). A compound's ability to interact with bimolecular targets can be improved by decreasing the energy gap, which in turn affects the compound's pharmacological potential and binding efficiency. A number of substances may be more effective as ERα-targeted inhibitors based on the trend that shows them to have a larger affinity for ERα than HER2. This conclusion is especially important to the treatment of breast cancer, as ERα specific inhibition can be crucial for controlling the disease.

Table 4.1: Different parameters calculated in DFT Studies

Ligand	E_{LUMO}	E_{HOMO}	ΔEgap (eV)	Ionization Energy IE (eV)	Electron affinity A (eV)	Chemical Hardness η (eV)	Chemical Softness ζ (/eV)	Electronegativity χ (eV)	Chemical Potential μ (eV)	Electrophilicity Index ω (eV)	overlap integral S (a.u)
1.	-0.10897	-0.33591	-0.227	0.336	0.109	0.113	4.406	0.222	-0.222	0.218	-3807.92
2.	-0.04212	-0.37154	-0.329	0.372	0.042	0.165	3.036	0.207	-0.207	0.130	-3881.95
3.	-0.03789	-0.31599	-0.278	0.316	0.038	0.139	3.596	0.177	-0.177	0.113	-3996.42
4.	-0.03603	-0.29260	-0.257	0.293	0.036	0.128	3.898	0.164	-0.164	0.105	-3996.42
5.	-0.04493	-0.33638	-0.291	0.336	0.045	0.146	3.431	0.191	-0.191	0.125	-3996.42
6.	-0.04567	-0.32862	-0.283	0.329	0.046	0.141	3.534	0.187	-0.187	0.124	-3996.42
7.	-0.04816	-0.30987	-0.262	0.310	0.048	0.131	3.821	0.179	-0.179	0.122	-3996.42
8.	-0.04033	-0.33099	-0.291	0.331	0.040	0.145	3.440	0.186	-0.186	0.119	-3996.42
9.	-0.04858	-0.34478	-0.296	0.345	0.049	0.148	3.376	0.197	-0.197	0.131	-3996.42
10.	-0.04324	-0.36725	-0.324	0.367	0.043	0.162	3.086	0.205	-0.205	0.130	-3996.42

Ligand	E_{LUMO}	E_{HOMO}	ΔEgap (eV)	Ionization Energy IE (eV)	Electron affinity A (eV)	Chemical Hardness η (eV)	Chemical Softness ζ (/eV)	Electronegativity χ (eV)	Chemical Potential μ (eV)	Electrophilicity Index ω (eV)	overlap integral S (a.u)
11.	-0.05133	-0.34625	-0.295	0.346	0.051	0.147	3.391	0.199	-0.199	0.134	-3996.42
12.	-0.04754	-0.36926	-0.322	0.369	0.048	0.161	3.108	0.208	-0.208	0.135	-3996.42
13.	-0.04259	-0.33440	-0.292	0.334	0.043	0.146	3.427	0.188	-0.188	0.122	-3996.42
14.	-0.03511	-0.36269	-0.328	0.363	0.035	0.164	3.053	0.199	-0.199	0.121	-3996.42
15.	-0.03484	-0.29976	-0.265	0.300	0.035	0.132	3.775	0.167	-0.167	0.106	-3996.42
16.	-0.04007	-0.33928	-0.299	0.339	0.040	0.150	3.342	0.190	-0.190	0.120	-3996.42
17.	-0.03985	-0.36332	-0.323	0.363	0.040	0.162	3.091	0.202	-0.202	0.126	-3996.42
18.	-0.03764	-0.36465	-0.327	0.365	0.038	0.164	3.058	0.201	-0.201	0.124	-3995.42
19.	-0.04506	-0.35039	-0.305	0.350	0.045	0.153	3.275	0.198	-0.198	0.128	-3994.42
20.	-0.03739	-0.30510	-0.268	0.305	0.037	0.134	3.735	0.171	-0.171	0.110	-3993.42

The HOMO-LUMO energy gap (ΔEgap) is a crucial indicator of a molecule's reactivity, where a smaller gap signifies higher chemical activity and potential bio interaction. Among the HER2-bound molecules (PDB Code: 7JXH), molecule 3 exhibits the smallest energy gap (-277 eV), indicating the highest reactivity in this group. Other molecules such as 9 (-296 eV), 11 (-295 eV), and 5 (-291 eV) show relatively larger gaps, suggesting slightly lower reactivity. In contrast, ERα-bound molecules (PDB Code: 1A52) display a wider range of energy gaps, with molecule 1 (-227 eV) having the smallest, making it the most reactive overall. Molecule 7 (-262 eV) and 3 (-277 eV) also show significant reactivity, whereas molecule 17 (-323 eV) has the largest gap, making it the least reactive in this set. Comparatively, ERα-bound molecules generally exhibit lower energy gaps than HER2-bound molecules, suggesting that they may have stronger electronic interactions and higher potential bioactivity. Molecule 1, with the smallest gap, stands out as the most promising candidate for ERα-targeted drug design, while molecule 3, appearing in both groups, may have a preferential interaction with ERα due to its lower energy gap in that category. These findings indicate that molecules binding to ERα could be more chemically active, making them potential candidates for selective inhibition in breast cancer therapy.

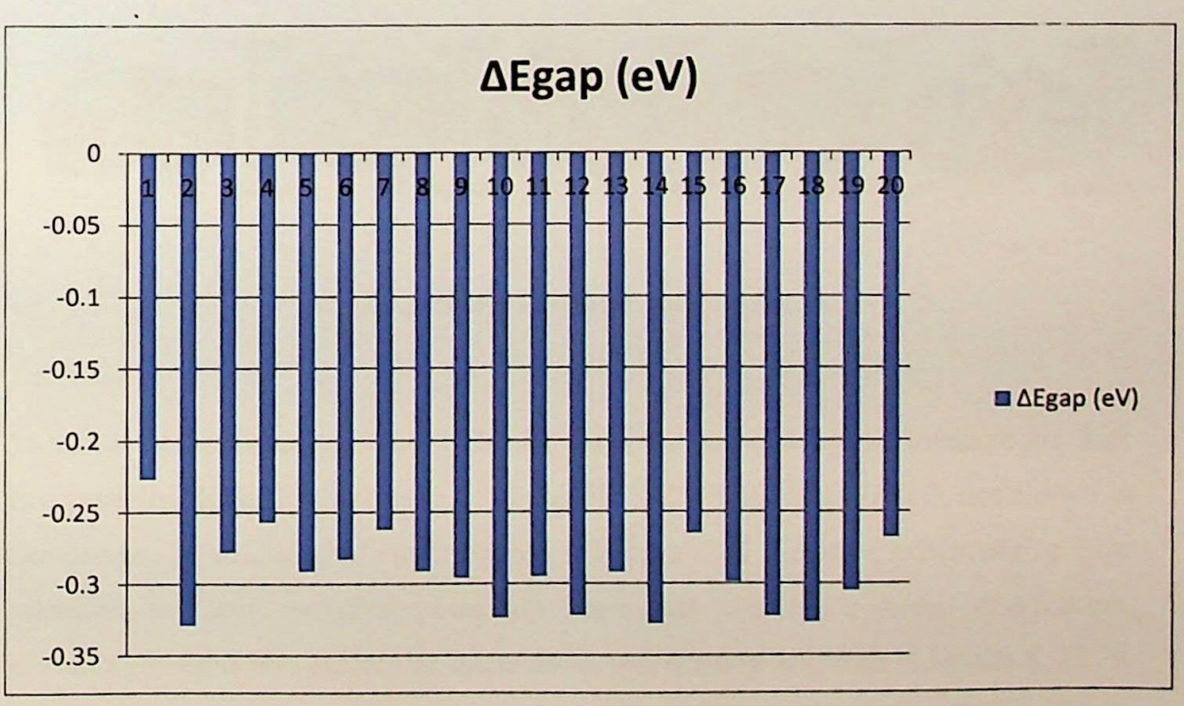


Figure 4.2: ΔEgap (eV) values for 1-20 molecules

EMP:

The highest positive and negative regions on the MEP map are indicated by the colours blue and red, respectively, and are the favored locations for nucleophilic and electrophilic attacks. In terms of colour grading, MEP plays an important role because it simultaneously shows molecular size, shape, and positive, negative, and neutral electrostatic potential regions(70).

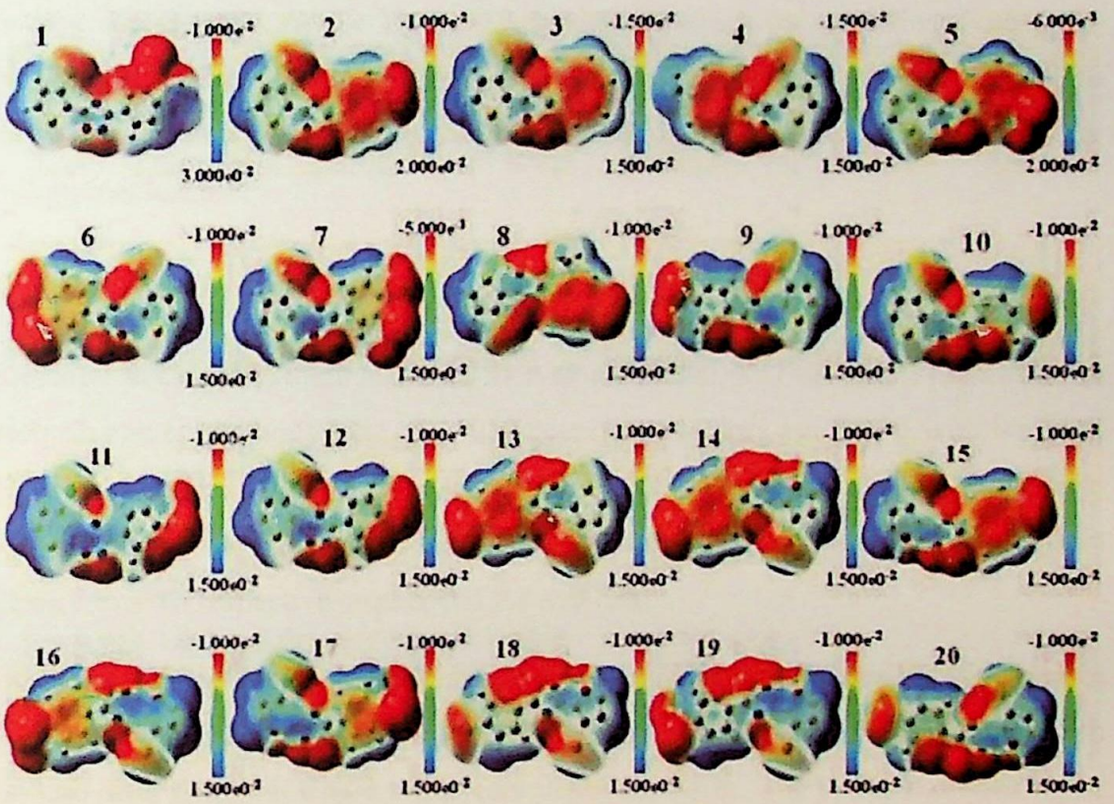


Figure 4.3: MEP of all selected potent oxadiazoles

Molecular electrostatic potential (MEP) maps for various ligand interactions with two proteins, ERα (PDB code: 1A52) and HER-2 (PDB code: 7JXH), are shown in the image. A colour gradient from red (electron-rich, negative potential) to blue (electron-deficient, positive potential) represents the electrostatic distribution, providing insight into molecular interactions and binding affinities. Ligands 5, 11, 9, 3, and 8 show different distributions of electrostatic potential for HER-2. While ligand 11 seems more balanced, with a uniform distribution of electrostatic potential, ligand 5 displays a more noticeable red zone, indicating significant electron-donating

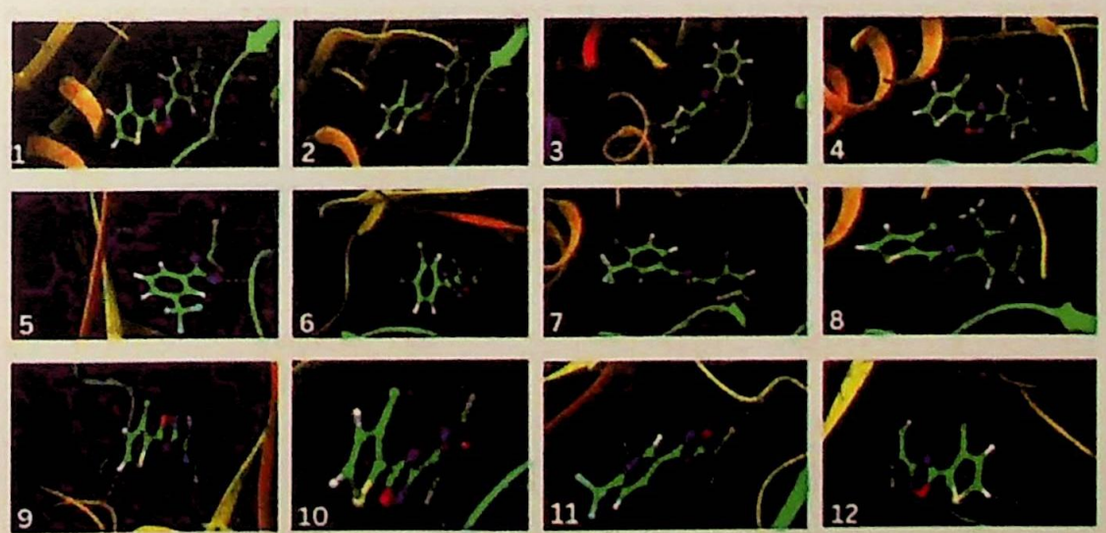
properties. Ligands 3 and 9 have comparable charge distributions, with notable negative potentials surrounding particular molecular areas. In contrast to the other ligands, ligand 8 has a more scattered electrostatic pattern, which could suggest distinct interaction dynamics.

Ligands 17, 16, 7, 1, and 3 also exhibit different electrostatic potential distributions for ERα. Strong negative potential is shown by ligand 1's most intense red zone, which could be a sign of a stronger binding affinity via electrostatic or hydrogen bonding interactions. While ligand 17 seems to have a more diffused potential distribution, ligands 16 and 7 exhibit heterogeneous electrostatic patterns. Ligand 3's charge distribution is similar to that of its HER-2, which may indicate a similar binding mechanism.

4.2 Molecular Docking Assay:

Molecular docking research was used to evaluate bindings of the target proteins with Erlotinib and compounds 1-20.(71, 72) The target receptors are HER2 with the PDB 7JXH and estrogen receptor alpha (Erα, PDB 1A52). We evaluated their affinities to these receptors. The comparison showed that all the selected compounds had the best interaction with respective protein (HER2 and Erα).

The results of molecular docking analysis showed that all compounds had greater docking scores (binding energy values) with HER2 (PDB code: 7JXH) compared to standard drug Erlotinib where stable complexes can form. The molecular docking of these compounds with HER2 is represented in few 3D figures 4.4 Table summarizes the docking scores of all the docked molecules.



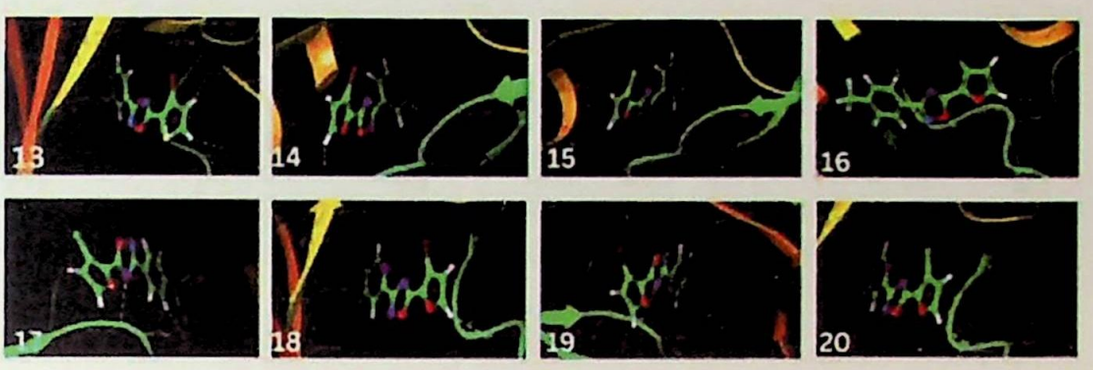
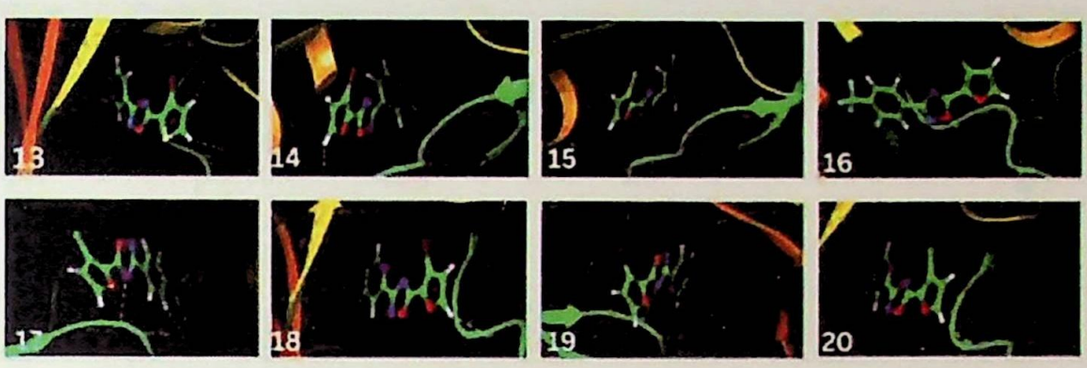


Figure 4.4: Interaction between HER-2 (PDB code: 7JXH) and oxadiazoles

This shows the 3D pictures of interaction between HER-2 (PDB code: 7JXH) and all the 20 derivatives of 1,2,4 Oxadiazoles. Here Hydrogen bonding is represented by Yellow dotted lines, Halogen bond is represented by purple dotted lines, pi-pi stacking is represented by magenta dotted lines, green dotted lines shows pi-cation formation while light blue and navy blue color dotted lines shows the interaction between ligand and protein.

The docking studies with the estrogen receptor alpha (Erα PDB: 1A52) revealed significant binding information for these compounds. Compound 17,16,7,1 and 3 showed extraordinary binding activity on receptor proteins; their docking scores are -6.310, -6.303, -6.292, -6.137 and -5.971respectively. This docking score shows better interaction than that of the reference drug Erlotinib. This implies that these compounds could have considerable therapeutic potential for targeting estrogen receptor alpha. Each of the remaining compounds that studied, also interacted with the receptor, even with greater extent than did Erlotinib, suggesting they could employ particularly effective antitumor effects themselves.



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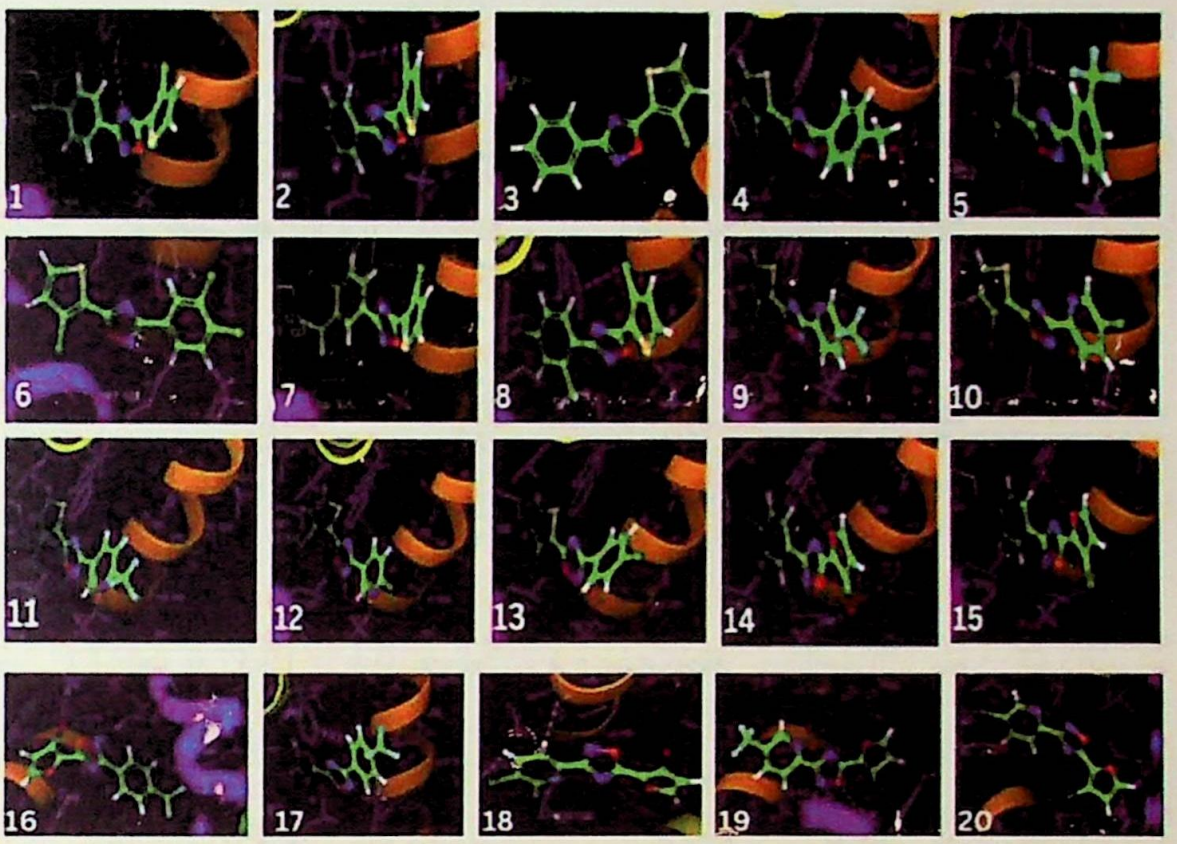

Figure 4.5: interaction between Erα (PDB code: 1A52) and 1, 2, 4 oxadiazoles

This shows the 3D pictures of interaction between Erα (PDB code: 1A52) and all the 20 derivatives of 1,2,4 Oxadiazoles. Here Hydrogen bonding is represented by Yellow dotted lines, Halogen bond is represented by purple dotted lines, pi-pi stacking is represented by magenta dotted lines, green dotted lines shows pi-cation formation while light blue and navy blue color dotted lines shows the interaction between ligand and protein.

Table 4.2: Molecular docking studies of 1,2,4 oxadiazoles derivatives with HER-2 and Erα proteins.

Ligands	EG50 values against different cell lines.		7JXH		1A52	
	T47D	DLD1	Docking score Kcal/mol	ΔG Energy Kcal/mol	Docking score Kcal/mol	ΔG Energy Kcal/mol
1	1.21± 0.10	0.44 ± 0.06	-6.601	-43.13	-6.137	-30.82
2	1.77 ± 0.20	0.79 ± 0.11	-6.112	-54.67	-5.391	-30.96
3	2.82 ± 0.13	0.76 ± 0.09	-6.881	-43.07	-5.971	-40.62
4	3.66 ± 0.39	1.42 ± 0.08	-6.507	-38.68	-4.798	-31.56
5	0.90 ± 0.13	0.28 ± 0.02	-7.349	-47.04	-5.549	-24.75
6	1.41 ± 0.19	0.37 ± 0.05	-6.687	-46.39	-5.353	-29.96
7	0.93 ± 0.18	0.56 ± 0.17	-6.528	-39.27	-6.292	-33.66
8	0.91 ± 0.09	0.38 ± 0.06	-6.825	-50.09	-5.675	-36.15
9	1.44 ± 0.05	0.41 ± 0.11	-6.919	-54.12	-5.349	-29.76
10	1.59 ± 0.09	0.39 ± 0.06	-6.587	-55.46	-5.229	-32.81
11	0.92 ± 0.14	0.24 ± 0.06	-7.290	-46.19	-5.524	-32.10
12	0.75 ± 0.04	0.29 ± 0.05	-6.082	-53.25	-5.845	-32.71
13	3.32 ± 0.56	1.32 ± 0.13	-5.931	-52.85	-4.609	-33.63
14	1.08 ± 0.14	0.83 ± 0.12	-5.922	-39.81	-5.166	-28.00
15	1.74 ± 0.18	1.49 ± 0.20	-6.115	-41.88	-5.343	-30.68
16	2.01 ± 0.14	1.07 ± 0.15	-6.099	-39.14	-6.303	-28.73
17	0.52 ± 0.01	0.48 ± 0.09	-6.643	-34.49	-6.310	-34.22
18	1.61 ± 0.11	0.84 ± 0.10	-6.096	-53.18	-4.822	-29.12
19	0.61 ± 0.15	0.70 ± 0.21	-6.457	-35.32	-5.544	-29.82
20	1.11 ± 0.08	0.58 ± 0.08	-6.327	-54.60	-4.813	-33.79
Erlotinib			-5.686	-42.90	-4.013	-0.23

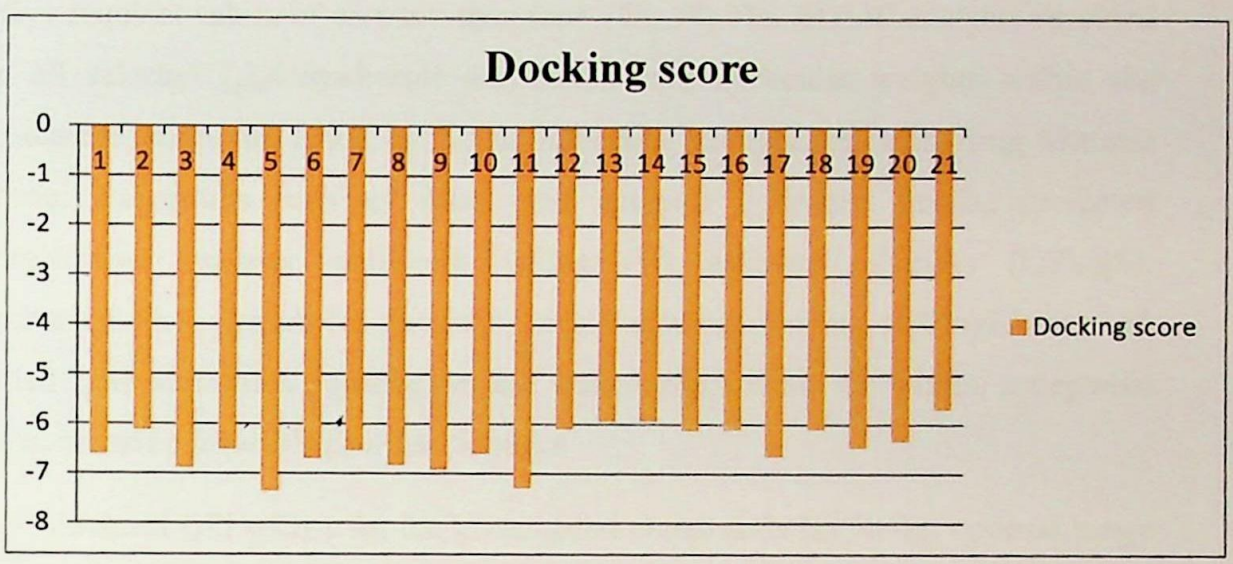

Figure 4.6: Graphical representation of Docking score (1-20 molecules and Erlotinib) with 7JXH protein



Figure 4.7: Graphical representation of Docking score (1-20 molecules and Erlotinib) with 1A52 protein

4.3 Results of ADME:

Twenty selected molecules were studied to calculate important physicochemical parameters. Including molecular weight, brain/blood partition coefficient (QPlogBB)) Human Oral absorption (HOA), human oral bioavailability percentage (HOA %), MDCK cell permeability (QPPMDCK), as well as compliance with the fifth rule and third rule. These calculations were performed using Maestro software and the results are summarized in table 3.The rule of three and the rule of five are critical in evaluating drug similarity across all evaluated criteria. For optimum treatment efficiency the rule of three requires values between 0 and 3, while the rule

of five requires values of no more than four. (73, 74) The ADME analysis revealed that all selected 1,2,4-oxadiazole derivatives have molecular weights within the permissible range of 130.0 to 725.0, indicating compliance with drug-likeness criteria. Parameters such as donor and acceptor hydrogen bonds, predicted octanol/water partition coefficient (QPlogPo/w), aqueous solubility (QPlogS), number of likely metabolic reactions, serum albumin binding (QPlogKhsa), and human oral absorption (qualitative and quantitative) were all within acceptable limits, ensuring favorable pharmacokinetics

The calculated QPlogKhsa for the investigated compounds lay in the optimal range of -1.5 to 1.5 which shows adherence to plasma proteins and therefore acceptable binding to human serum albumin. This means that the majority of the substances will most probably stay unbind in the plasma, and thus ensure better circulation in the blood and larger opportunities for them to get to their targets. A decrease in the plasma binding leads to the new substances showing good distribution and Trans membrane diffusion, which acts as key to drug therapy. Apart from this, the acceptable QPlogKhsa values of the oxadiazoles derivatives indicate that most of those compounds contain all necessary pharmacophore elements that allow effective drug delivery and have significant potential for further development.

Table 4.3: ADME analysis for derivatives of 1,2,4 oxadiazoles

Ligand	Mol-MW	Donor HB	Accept HB	QP logPo/w	QP logS	QPP Caco	Metab	Qplog Khsa	QPlog BB	QPPMDCK	HOA	HOA%	Rule of Five	Rule of Three
1	330.711	0.000	3.000	4.302	-5.028	3171.517	2	0.383	0.557	10000.000	3	100.000	0	0
2	297.158	0.000	3.000	3.918	-5.038	3135.957	1	0.262	0.507	10000.000	3	100.000	0	0
3	262.713	0.000	3.000	3.501	-4.249	3135.884	1	0.129	0.342	6240.691	3	100.000	0	0
4	276.740	0.000	3.000	3.763	-4.856	3135.911	2	0.303	0.327	6240.748	3	100.000	0	0
5	330.711	0.000	3.000	4.224	-4.724	3135.903	2	0.365	0.536	10000.000	3	100.000	0	0
6	331.603	0.000	3.000	4.414	-5.689	3135.904	1	0.382	0.643	10000.000	3	100.000	0	0
7	365.157	0.000	3.000	4.607	-5.202	3135.953	2	0.468	0.648	10000.000	3	100.000	0	0
8	311.185	0.000	3.000	4.240	-4.849	4168.518	2	0.364	0.631	10000.000	3	100.000	0	0
9	331.699	0.000	4.000	3.464	-4.716	1950.934	2	0.064	0.331	10000.000	3	100.000	0	0
10	298.146	0.000	4.000	3.220	-4.424	1950.815	2	-0.038	0.308	9339.177	3	100.000	0	0
11	331.699	0.000	4.000	3.555	-4.733	2228.963	2	0.069	0.402	10000.000	3	100.000	0	0

12	298.146	0.000	4.000	3.200	-4.415	1860.652	2	-0.042	0.295	9138.953	3	100.000	0	0
13	341.609	0.000	3.000	4.022	-5.107	3154.742	1	0.280	0.520	10000.000	3	100.000	0	0
14	325.549	0.000	3.500	3.339	-4.069	2954.000	1	0.016	0.405	8646.258	3	100.000	0	0
15	281.098	0.000	3.500	3.347	-3.980	2965.920	1	-0.001	0.398	8312.767	3	100.000	0	0
16	359.102	0.000	3.500	3.652	-4.573	2955.103	1	0.142	0.454	10000.000	3	100.000	0	0
17	314.651	0.000	3.500	3.495	-4.470	2937.450	1	0.123	0.441	10000.000	3	100.000	0	0
18	326.536	0.000	4.500	2.473	-3.456	1837.707	2	-0.284	0.215	5188.843	3	100.000	0	0
19	360.090	0.000	4.500	2.824	-3.828	1838.361	2	-0.181	0.241	6143.832	3	100.000	0	0
20	282.085	0.000	4.500	2.472	-3.388	1827.446	2	-0.302	0.203	4891.893	3	100.000	0	0
Erlotinib	393.441	1.5	8	3.054	-4.452	2762.225	2	0.047	-0.177	1483.539	3	100	0	0

4.4 Cardio toxicity of compounds:

The potassium ion channel of the human ether-a-go-go-related gene, or hERG, which causes LQTS (Long QT syndrome), a serious and potentially lethal cardiac condition, has been known to be compromised by the medication options. As a result, by filtering out toxicities early in the drug development process, virtual screening techniques that can predict hERG-related Cardiotoxicity will play a crucial role in drug discovery.(75)

Table 6 shows the main features of the Cardiotoxicity profile of ligands 1–20. It shows the confidence percentage, the distribution of probability and validity, as well as the relative confidence. Understanding these indicators is important because Cardiotoxicity remains a major challenge in drug development and the potential damage to the heart may limit the therapeutic potential of the drug. Accurate assessment of these factors can help to predict the risk of Cardiotoxicity and enable safer drug candidates to reach the market.

Compound 1 is considered as "non-blocker" with 60.01 % reliability. Its strength is labeled as "moderate blocker" with a confidence level of 39%. Its potency for human's heart are 5.293.Compound 2 is considered as "non-blocker" with 91.37% reliability. Its strength is labeled as "moderate blocker "with a confidence level of 39% .its potency for human's heart is 5.203.

Compound 3 is considered as "Non-blocker" with 89.02% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 38.1%. Its potency for human's heart is 5.055.

Compound 4 is considered as "Non-blocker" with 92.92% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 39.57%. Its potency for human's heart is 5.117.

Compound 5 is considered as "Non-blocker" with 74.21% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 39.5. Its potency for human's heart is 5.262.

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Compound 6 is considered as "Non-blocker" with 92.83% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 38.67%. Its potency for human's heart is 5.26.

Compound 7 is considered as "Non-blocker" with 73.73% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 37.37%. Its potency for human's heart is 5.235.

Compound 8 is considered as "Non-blocker" with 82.69% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 41.6%. Its potency for human's heart is 5.284.

Compound 9 is considered as "Non-blocker" with 78.0% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 38.2%. Its potency for human's heart is 5.265.

Compound 10 is considered as "Non-blocker" with 89.75% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 38.23%. Its potency for human's heart is 5.208.

Compound 11 is considered as "Non-blocker" with 76.38% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 37.57%. Its potency for human's heart is 5.15.

Compound 12 is considered as "Non-blocker" with 66.27% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 36.47%.Its potency for human's heart is 5.153.

Compound 13 is considered as "Non-blocker" with 79.88% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 36.1%. Its potency for human's heart is 5.271.

Compound 14 is considered as "Non-blocker" with 87.95% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 36.8%. Its potency for human's heart is 5.364.

Compound 15 is considered as "Non-blocker" with 79.8% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 40.0%. Its potency for human's heart is 5.442.

Compound 16 is considered as "Blocker" with 62.38% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 41.2%. Its potency for human's heart is 5.353.

Compound 17 is considered as "Blocker" with 56.72% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 42.9%. Its potency for human's heart is 5.482.

Compound 18 is considered as "Non-blocker" with 76.09% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 37.3%. Its potency for human's heart is 5.263.

Compound 19 is considered as "Blocker" with 58.77% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 37.67%. Its potency for human's heart is 5.286.

Compound 20 is considered as "Non-blocker" with 57.79% reliability. Its strength is labeled as "Moderate blocker" with a confidence level of 39.6%. Its potency for human's heart is 5.374.

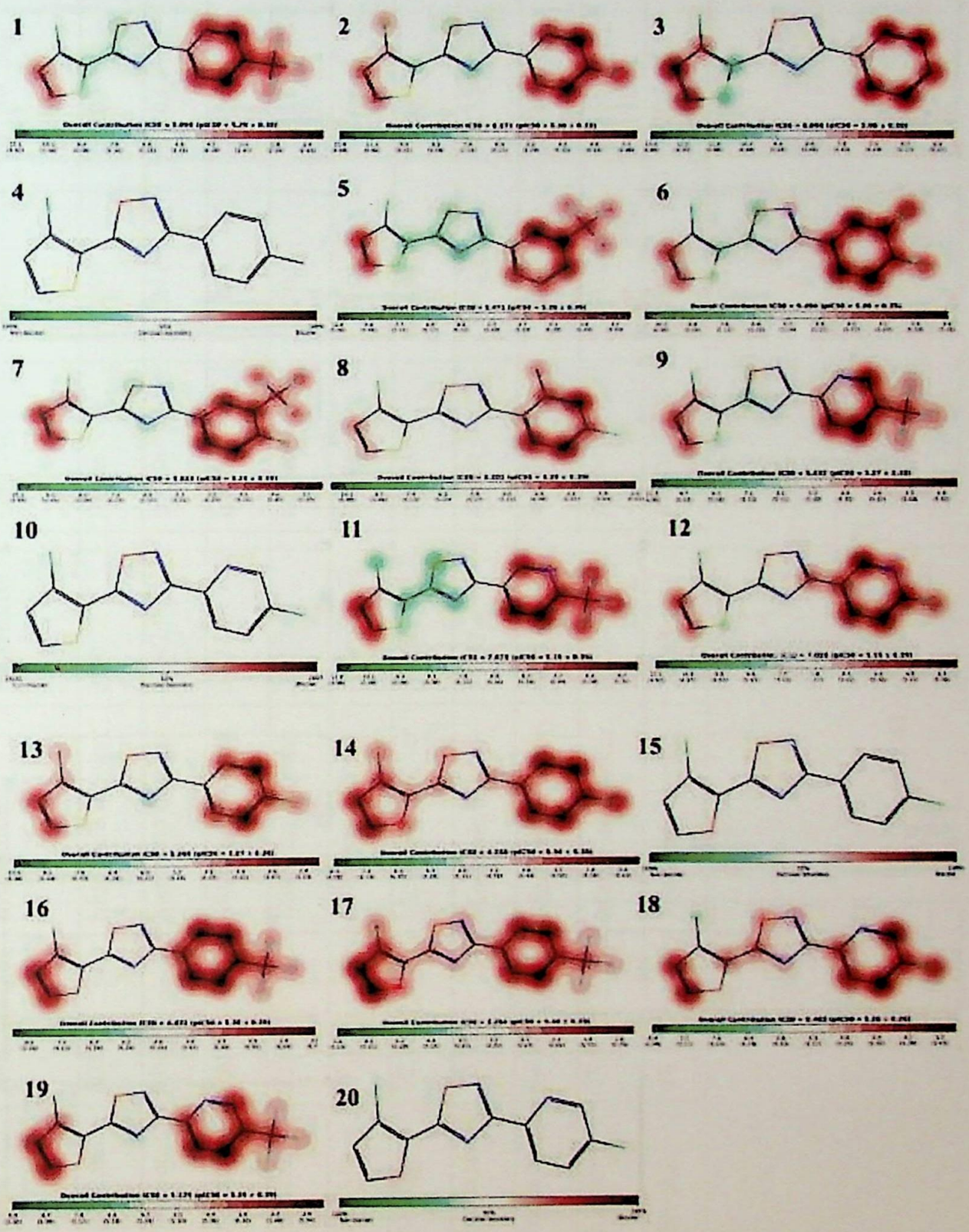


Figure 4.8: Cardio toxicity analysis of 1,2,4 Oxadiazoles

Table 4.4 Cardiotoxicity analysis of 1,2,4 oxadiazoles

Compound	Binary prediction	Binary Reliability%	Multiclass Prediction	Multiclass Reliability%	Applicability Domain	IC50 Values µm	Reg.Prediction (pIC50) Potency
1	Non-blocker	60.01	Moderate blocker	39.0	Inside	5.090	5.293
2	Non-blocker	91.37	Moderate blocker	37.47	Inside	6.271	5.203
3	Non-blocker	89.02	Moderate blocker	38.1	Inside	8.806	5.055
4	Non-blocker	92.92	Moderate blocker	39.57	Inside	5.561	5.117
5	Non-blocker	74.21	Moderate blocker	39.5	Inside	5.471	5.262
6	Non-blocker	92.83	Moderate blocker	38.67	inside	5.494	5.26
7	Non-blocker	73.73	Moderate blocker	37.37	inside	5.823	5.235
8	Non-blocker	82.69	Moderate blocker	41.6	Inside	5.201	5.284
9	Non-blocker	78.0	Moderate blocker	38.2	Inside	5.432	5.265
10	Non-blocker	89.75	Moderate blocker	38.23	Inside	5.160	5.208

Compound	Binary prediction	Binary Reliability%	Multiclass Prediction	Multiclass Reliability%	Applicability Domain	IC50 Values µm	Reg.Prediction (pIC50) Potency
11	Non-blocker	76.38	Moderate blocker	37.57	Inside	7.073	5.15
12	Non-blocker	66.27	Moderate blocker	36.47	Inside	7.026	5.153
13	Non-blocker	79.88	Moderate blocker	36.1	inside	5.360	5.271
14	Non-blocker	87.95	Moderate blocker	36.8	Inside	4.330	5.364
15	Non-blocker	79.8	Moderate blocker	40.0	Inside	6.106	5.442
16	Blocker	62.38	Moderate blocker	41.2	Inside	4.431	5.353
17	Blocker	56.72	Moderate blocker	42.9	Inside	3.294	5.482
18	Non-blocker	76.09	Moderate blocker	37.3	Inside	5.463	5.263
19	Blocker	58.77	Moderate blocker	37.67	Inside	5.175	5.286
20	Non-blocker	57.79	Moderate blocker	39.6	Inside	4.141	5.374

CHAPTER 5

DISCUSSION

In this study, we used a variety of computational techniques to examine the potential of 1,2,4-Oxadiazole derivatives as anticancer drugs. In particular, we used molecular docking, ADME predictions, DFT computations, and Cardiotoxicity evaluations. Our results open the door for more experimental validation and medication development by offering fascinating knowledge about the structural, electrical, and pharmacokinetic characteristics of these molecules.

5.1 DFT Calculations:

Significant electrical and structural features of 1,2,4-Oxadiazole derivatives were discovered by DFT simulations. An important metric for forecasting chemical reactivity, the HOMO-LUMO energy gap, has been investigated. Higher reactivity is typically indicated by a smaller HOMO-LUMO gap, which enhances the possibility that these substances will interact with biological targets more easily. Additionally, the electron-rich and electron-deficient portions of the molecules were visualized by the molecular electrostatic potential (MEP) maps, which offered important insights into ligand-receptor interactions.

ΔEgap (eV) : 2<14<18<10<17<12<19<16<9<11<13<5<8<6<3<20<15<7<4<1

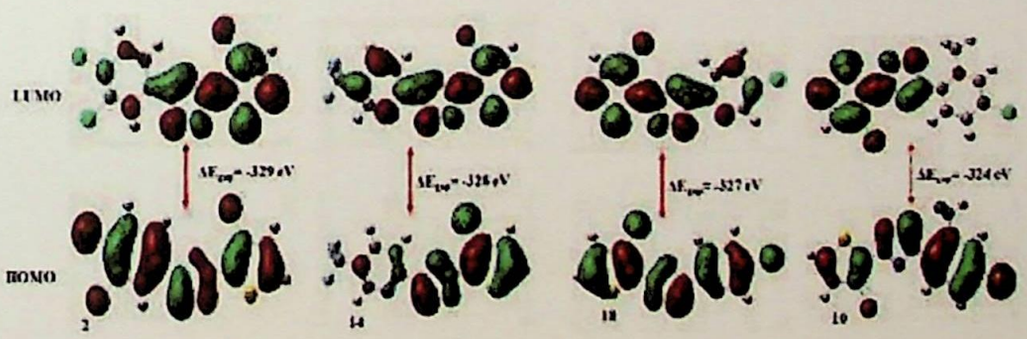
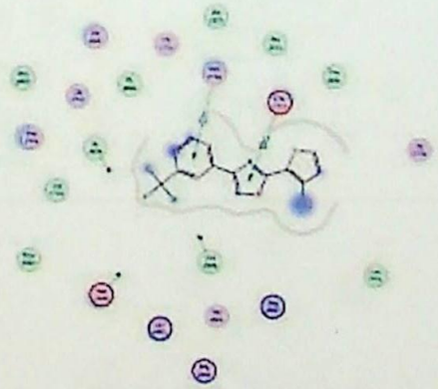
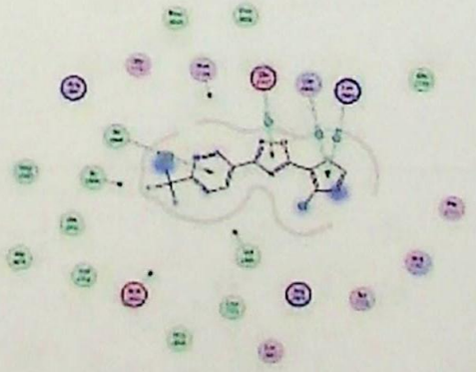


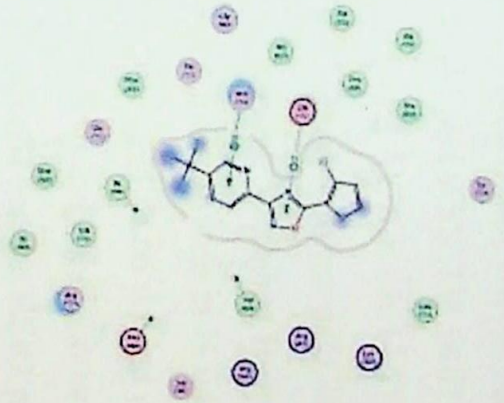
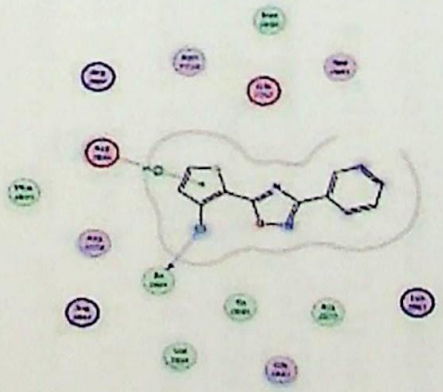
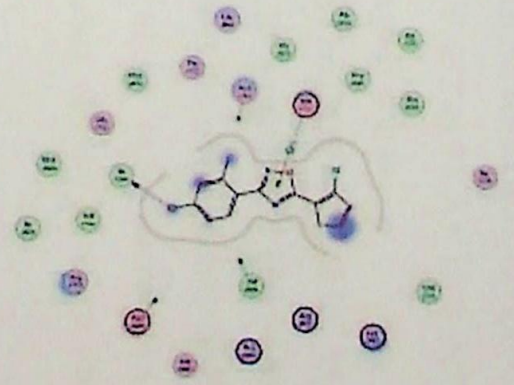
Figure 5.1: Top 4 molecules with lowest energy gap

5.2 Molecular Docking studies:

The purpose of the molecular docking research was to assess the 1,2,4-Oxadiazole derivatives' binding affinities and mechanisms of interaction with particular protein targets. We picked HER2 and Erα with the PDB codes 7JXH and 1A52 respectively, as our targets based on their relevance in breast cancer and ovarian cancer. According to the docking results, molecule 5 exhibits the highest docking score with the 7JXH, whereas molecule 17 exhibits the highest docking score with the 1A52. These results imply that these substances may be able to suppress the target proteins' activity, which would have anticancer effects.

Table 5.1 : Top 5 molecules exhibit greater Docking score with the protein HER2

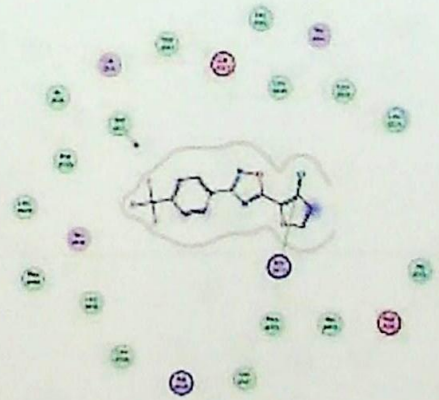
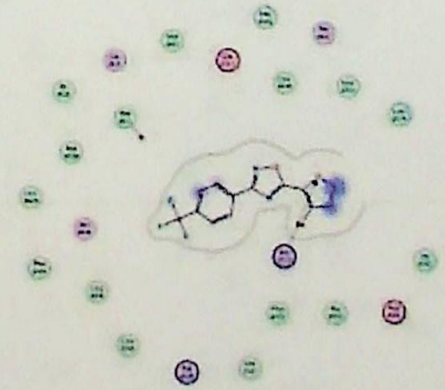
Target	Ligand	Interacting residue	Distance (Å)	Type of Interaction	2D Diagram of interaction
HER2 (7JXH)	5	GLU 757 ASN 758	3.91 4.01	pi-H pi-H	
	11	GLY 882 LYS 883 ILE 886 GLU 757	4.71 4.23 4.57 3.72	pi-H pi-H pi-H pi-H	

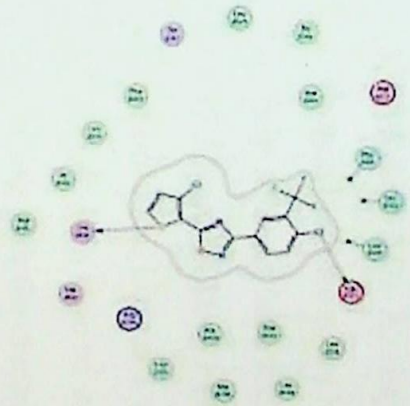
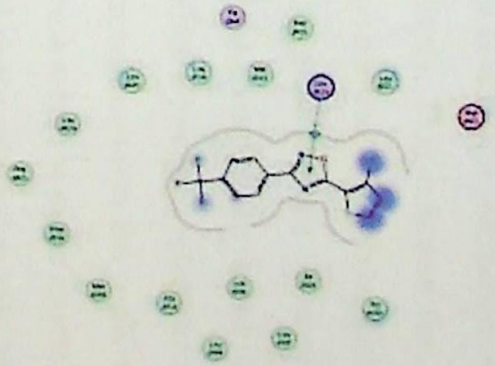
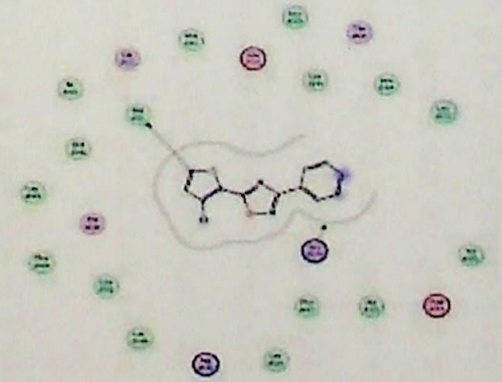
9	GLU 757 ASN 758	3.91 4.01	pi-H pi-H	
3	ILE 894 ASP 880	3.20 4.40	H-donor pi-H	
8	ILE 894 GLU 757	3.66 3.81	H-donor pi-H	

This molecular docking data reveals key interactions between a target protein (HER2 - 7JXH) and various ligands. Ligand 5 shows pi-H interactions with GLU 757 (3.91 Å) and ASN 758 (4.01 Å). Ligand 11 interacts with GLY 882 (4.71 Å), LYS 883 (4.23 Å), ILE 886 (4.57 Å), and GLU 757 (3.72 Å), all via pi-H bonds.

Ligand 9 forms pi-H interactions with GLU 757 (3.91 Å) and ASN 758 (4.01 Å). Ligand 3 exhibits H-donor interactions with ILE 894 (3.20 Å) and ASP 880 (4.40 Å), along with pi-H interactions. Finally, Ligand 8 shows H-donor interaction with ILE 894 (3.66 Å) and pi-H interaction with GLU 757 (3.81 Å). These interactions, particularly the shorter distances, suggest potential binding affinity between the ligands and the HER2 protein.

Table 5.2 : Top 5 molecules exhibit greater Docking score with the protein(Erα)

Target	Ligand	Interacting residue	Distance (Å))	Type of Interaction	2D Diagram of interaction
ERα (1A52)	17	LYS 529	3.09	H-acceptor	
	16	LYS 529	2.99	H-acceptor	

7	GLY 521 GLU 353	3.65 3.27	H-donor H-donor	
1	LYS 529	4.55	pi-cation	
3	MET 421	3.84	H-donor	

This molecular docking data illustrates the interactions between the ERα (1A52) protein and top 5 ligands (17, 16, 7, 1, and 3).

Ligands 17 and 16 both show H-acceptor interactions with LYS 529 at distances of 3.09 Å and 2.99 Å, respectively. This indicates that the ligands are accepting a hydrogen bond from the lysine residue. The shorter distance for ligand 16 suggests a slightly stronger interaction. Ligand 7 forms H-donor interactions with GLY 521 (3.65 Å) and GLU 353 (3.27 Å), meaning the ligand is donating hydrogen bonds to these residues. Ligand 1 exhibits a pi-cation interaction with LYS 529 at a distance of 4.55 Å. This type of interaction involves the positively charged lysine side chain interacting with the electron-rich π system of the ligand.

Finally, Ligand 3 shows an H-donor interaction with MET 421 at a distance of 3.84 Å. These varied interaction types and distances suggest different binding modes and potential affinities of these ligands for the ERα protein. The presence of hydrogen bonds and pi-cation interactions are important for molecular recognition and binding stability.

5.3 ADME Predictions:

The 1,2,4-Oxadiazole derivatives' pharmacokinetic characteristics were better understood due to the ADME predictions. We evaluated important factors like absorption, distribution, metabolism and excretion:

5.3.1 Absorption

5.3.1Absorption:5.3.1.1: Human Oral Absorption (HOA):

All of the substances have high Human Oral Absorption (HOA) values, indicating good oral absorption.

5.3.1.2: Caco-2 Permeability:

This parameter estimates the permeability of the compound across a monolayer of Caco-2 cells, which is a model for intestinal absorption. Higher values generally indicate better intestinal absorption.

5.3.1.3: Solubility:

Different levels with regard to water solubility are suggested by the logS values. Oral bioavailability may be a concern since some substances appear to have decreased solubility while others exhibit moderate solubility.

5.3.2 Distribution:

5.3.2.1: Brain/Blood Partition Coefficient (QPlogBB) :

Normal Range is -3.0 to 1.2.

Analysis: The QPlogBB values for all substances in the table are far greater than the 1.2 upper limits. It suggests that these substances are potentially most likely to enter the brain. As these compounds have considerable potential for brain penetration, as indicated by the high QPlogBB values. This may be helpful in treating disorders of the brain, but it may also raise the possibility of adverse consequences on the central nervous system.

5.3.2.2: Lipophilicity (QPlogPo/w):

A variety of lipophilicities are shown by the logP values. Certain substances have moderate to high lipophilicity, which may improve permeability of membranes.

5.3.3 Metabolism:

5.3.3.1: Metab:

Metab values of 1 or 2 can be observed in the majority of compounds: This implies that these substances would have relatively fewer metabolic pathways predicted, which could result in slower metabolism and possibly longer half-lives for drugs.

5.3.4 Excretion:

5.3.4.1: Predicted Passive Membrane Diffusion Clearance QPPMDCK Interpretation:

Standard values are <25 (poor), >500 (outstanding).

The QPPMDCK values of all the substances are higher than 500. This suggests favorable renal excretion and shows that these chemicals have great potential for passive diffusion across kidney membranes. These substances are probably effectively eliminated by the kidneys, based on the high QPPMDCK levels. In general, this is advantageous for medication clearance.

5.3.5 Drug-likeness:

5.3.5.1: Lipinski's Rule of Five: Every compound satisfies this rule, suggesting that it has favorable drug-like qualities.

5.3.5.2: The Rule of Three by Veber: A "Rule of Three" value of 0 indicates that the compound satisfies all of Veber's Rule of Three's criteria.

5.3.5.3: Cardiotoxicity: None of the compounds mentioned in the table's "Khsa" column had QPlogKhsa values that fall outside of the acceptable range of -1.5 to 1.5. Therefore, the substances listed in the table do not seem to pose a high risk of Cardiotoxicity due to hERG inhibition based only on the QPlogKhsa values.

CHAPTER 6

CONCLUSIONS

Through an in depth computational approach that integrated Density Functional Theory (DFT) calculations, molecular docking studies targeting HER2 (PDB: 7JXH) and ERα (PDB: 1A52), and in silico ADME (Absorption, Distribution, Metabolism, Excretion) predictions, this study investigated the potential of 1,2,4-oxadiazole derivatives as anticancer agents. In order to build the foundation for future therapeutic design and development, this multimodal approach focused on clarifying the structure-activity connections, binding processes with important tumor-causing proteins, and pharmacokinetic profiles of these compounds.

The electrical structure and characteristics of the 1,2,4-oxadiazole derivatives were better understood because of DFT studies. Information regarding the substances' kinetic stability, reactivity, and potential for charge transfer interactions with biological targets was obtained through analysis of the Lowest Unoccupied Molecular Orbital (LUMO) and Highest Occupied Molecular Orbital (HOMO) energies and their energy gaps. Greater reactivity is frequently indicated by a narrower HOMO-LUMO gap, and this can be essential for successful interaction with a target protein. The distribution of electron density within the molecules was shown by the molecular electrostatic potential (MEP) maps, which were produced from the DFT calculations and highlighted areas of positive and negative potential.

Molecular docking studies were essential for evaluating the 1,2,4-oxadiazole derivatives' binding affinity and modes of interaction with two significant proteins associated with cancer: ERα (PDB: 1A52), an estrogen receptor essential in hormone-responsive breast cancers, and HER2 (PDB: 7JXH), a receptor tyrosine kinase overexpressed in a variety of cancers. By analyzing the ligands' conformational landscape within these proteins' interaction pockets and the docking simulations produced a comprehensive image of the essential interactions for complex formation. The docking results revealed a range of binding affinities, indicating that these derivatives interact with both HER2 and ERα with varying strengths. The binding energies for HER2 ranged from -5.922 to -7.349 kcal/mol, while those for ERα spanned from -4.609 to -6.310 kcal/mol. Notably, Ligand 5 exhibited the highest binding affinity for HER2 (-7.349 kcal/mol), suggesting a

strong interaction with this receptor tyrosine kinase. Ligand 11 also demonstrated a substantial binding affinity for HER2 (-7.290 kcal/mol). In the case of ERα, Ligand 17 displayed the strongest binding (-6.310 kcal/mol), followed by Ligand 7 (-6.292 kcal/mol).

Ligand 5 formed a critical hydrogen bond with the HER2 active site, a residue known to be essential for ATP binding. The docking studies provided a molecular rationale for the observed binding affinities, suggesting potential mechanisms of action for these derivatives as inhibitors of HER2 and ERα.

In silico ADME predictions were performed to assess the drug-likeness and pharmacokinetic profiles of the 1,2,4-oxadiazole derivatives. These predictions provide crucial information about the absorption, distribution, metabolism, and excretion of the compounds, guiding the selection of promising candidates for further development. Analysis of the ADME properties revealed key trends across the investigated ligands. Most compounds exhibited favorable predicted human oral absorption (HOA) with high values, suggesting good potential for oral bioavailability. However, ligands 15 and 20 showed slightly lower HOA (83.12% and 78.28%, respectively), which might require further investigation. The Caco-2 permeability values were generally high, indicating good potential for intestinal absorption. Brain penetration, as predicted by QPlogBB, was generally low for most ligands, which is desirable for many therapeutic applications to minimize potential central nervous system side effects. Ligands 1 and 20 showed slightly higher QPlogBB values, suggesting a slightly higher tendency to cross the blood-brain barrier. The majority of ligands had a low number of predicted metabolic pathways (Metab), suggesting potentially slower metabolism and potentially longer half-lives. However, Ligand 20 exhibited a significantly higher number of predicted metabolic pathways , indicating potentially faster metabolism. High QPPMDCK values indicated efficient renal clearance for most ligands. The majority of ligands complied with Lipinski's Rule of Five and Veber's Rule of Three, supporting their drug-like characteristics. Comparing these findings to reference drugs like Erlotinib, which showed moderate HOA and low Caco-2 permeability, and Neratinib, which exhibited low HOA and high brain penetration, highlights the favorable predicted ADME profile of many of the investigated ligands.

This study provides a comprehensive *in silico* characterization of the 1,2,4-oxadiazole derivatives as potential anticancer agents. The integration of DFT calculations, molecular docking studies, and ADME predictions offers a holistic view of their properties, guiding the selection of promising candidates for further development. The favorable binding affinities observed in the docking studies, coupled with promising predicted ADME profiles, suggest that these derivatives warrant further investigation as potential inhibitors of HER2 and ERα.

It is crucial to acknowledge the inherent limitations of computational studies. While these *in silico* methods provide valuable insights and direction for future research, they do not fully replicate the complex interplay of factors governing biological processes *in vivo*. The accuracy of ADME predictions, in particular, depends on the quality of the predictive models and the similarity of the studied compounds to those used to train the models. Therefore, the findings presented here should be considered as preliminary indicators of potential activity and ADME behavior.

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