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THE:

Molecular docking studies of small molecules for targeting Estrogen Receptor (ER)

Jury:

Ms.	Harkati Dalal	Pr.	University Mohamed Khider- Biskra	Supervisor
Mr.	Daoud Ismail	Pr.	University Mohamed Khider- Biskra	President
Ms.	Mellaoui Malika	Dr.	University Mohamed Khider- Biskra	Examiner

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Abstract

Selective Estrogen Receptor Degraders (SERDs) represent a promising therapeutic strategy for the treatment of estrogen receptor-positive (ER+) breast cancer. This study focuses on the design and evaluation of coumarin-based small molecules as potential oral SERDs using advanced computational approaches. Molecular docking and ADME (Absorption, Distribution, Metabolism, and Excretion) prediction, were employed to assess the physicochemical properties, pharmacokinetics, and safety profiles of selected compounds.

Two lead candidates, previously reported in the literature, were further optimized based on their structural and pharmacological features. The compounds were evaluated for their ability to bind and degrade ERα, while maintaining properties suitable for oral administration. The results revealed promising drug-like profiles, including favorable absorption and metabolic stability.

This work provides valuable insights into the development of next-generation, orally bioavailable SERDs with improved efficacy and safety, potentially overcoming the limitations of current treatments such as fulvestrant. The findings contribute to the advancement of hormone therapy options for patients with ER+ breast cancer.

Keywords: SERDs; Estrogen receptor alpha; Breast cancer; Molecular docking; Coumarin derivatives; ADME-T Prediction.

Résumé

Les dégradeurs sélectifs du récepteur aux œstrogènes (SERDs) représentent une stratégie thérapeutique prometteuse pour le traitement du cancer du sein exprimant le récepteur aux œstrogènes alphas (ER+). Cette étude porte sur la conception et l'évaluation de petites molécules dérivées de la coumarine comme SERDs oraux potentiels, en utilisant des approches computationnelles avancées. Des techniques de molecular docking et de prédiction ADME (Absorption, Distribution, Métabolisme et Excrétion) ont été utilisées pour analyser les propriétés physico-chimiques, les paramètres pharmacocinétiques et les profils de sécurité des composés sélectionnés.

Deux candidats principaux, déjà rapportés dans la littérature, ont été optimisés sur la base de leurs caractéristiques structurales et pharmacologiques. Leur capacité à se fixer au récepteur ERα et à induire sa dégradation a été analysée, tout en veillant à conserver des propriétés compatibles avec une administration orale. Les résultats ont révélé des profils prometteurs en termes de propriétés médicamenteuses, notamment une bonne absorption et une stabilité métabolique favorable.

Ce travail apporte des éléments précieux pour le développement de SERDs de nouvelle génération, biodisponibles par voie orale, avec une efficacité et une sécurité améliorée. Il contribue à surmonter les limites des traitements actuels, tels que le fulvestrant, et à faire progresser les options de thérapie hormonale pour les patientes atteintes de cancer du sein ER+.

Mots-clés : SERDs ; Récepteur aux œstrogènes alphas ; Cancer du sein ; Molecular docking ; Dérivés de la coumarine ; Prédiction ADME-T.

ملخص

يمثل تطوير مثبطات مستقبلات الإستروجين الانتقائية (SERDs) نهجًا علاجيًا واعدًا لعلاج سرطان الثدي، لا سيما الأنواع الفرعية الإيجابية لمستقبلات الإستروجين (+ER) .

تركّز هذه الأطروحة على تصميم وتقييم مشتقات الكومارين كعوامل محتملة تُتناول عن طريق الفم من مثبطات مستقبلات الإستروجين الانتقائية، وذلك باستخدام منهجيات حسابية متقدمة. تم استخدام تقنيات الإرساء الجزيئي (molecular docking) والتنبؤ بخواص الامتصاص، التوزيع، الأيض، الإخراج (ADME-T) لتحليل الخصائص الفيزيائية الكيميائية، والحركية الدوائية، ومعايير الأمان لمجموعة مختارة من المركبات.

استُند في هذه الدراسة إلى مركبين رئيسيين تم ذكرهما سابقًا في الأدبيات العلمية، حيث خضعا لمزيد من التحسين البنيوي والدوائي. وقد تم تقييم قدرة هذه المركبات على الارتباط بمستقبل Erα وتحفيز عملية تكسيره، مع الحفاظ على الخصائص الضرورية للامتصاص الفموي. أظهرت النتائج أن هذه المركبات تمتلك خصائص دوائية واعدة، بما في ذلك قابلية امتصاص جيدة وثباتًا أيضيًا عاليًا.

تقدم هذه الدراسة رؤى مهمة لتطوير مثبطات مستقبلات الإستروجين الانتقائية القابلة للتناول عن طريق الفم، ذات فعالية وأمان محسّنين، والتي قد تساعد في تجاوز القيود المرتبطة بالعلاجات الحالية مثل الفولفسترانت. كما تسهم النتائج في إثراء جهود تطوير علاجات هرمونية أكثر تقدمًا للمريضات المصابات بسرطان الثدي الإيجابي لمستقبلات الإستروجين.

الكلمات المفتاحية :مستقبل الإستروجين ألفا ; مثبطات مستقبلات الإستروجين الانتقائية ; سرطان الثدي ; الإرساء الجزيئي ; مشتقات الكومارين ; التنبؤ بـADME-T.

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LIST OF ABBREVIATIONS

A

ADMET: Absorption, Distribution, Metabolism, Elimination, and Toxicity

B

BBB: Blood-Brain Barrier

BC: Breast Cancer

C

CADD: Computer Aided Drug Design

Caco-2: Human colorectal adenocarcinoma cells

CL: Clearance

E

ER: Estrogen Receptor

ERα: Estrogen Receptor alpha

EREs: Estrogen Response Elements

H

hERG: human ether-à-go-go-Related Gene

HER2: Human Epidermal growth factor Receptor 2

Hyd: Hydrophobic

L

LBD: ligand-binding domain

P

PPB: Plasma Protein Binding

PR: Progesterone Receptor

PDB: Protein Data Bank

R

RMSD: Root-Mean Square Deviation

S

SERD: Selective Estrogen Receptor Degrader

SERM: Selective Estrogen Receptor Modulator

T

T1/2: Half-Life

V

VD: Volume of Distribution

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Genetal

Introduction

Breast cancer (BC) is the most commonly diagnosed malignancy among women and remains a leading cause of cancer-related mortality worldwide. [1] While many benign tumors can be effectively treated with surgery, a significant proportion of BC cases are biologically aggressive, with the potential for silent progression and rapid metastasis. Recurrence is common and contributes substantially to the high fatality rate of the disease. BC is a heterogeneous condition, classified into molecular subtypes using specific biomarkers that guide diagnosis, prognosis, and treatment strategies.[2] Approximately 70% of BCs are Hormone Peceptor-positive (HR+), meaning they express Estrogen Receptors (ER) and/or Progesterone Receptors (PR), with 65% being PR-positive. These subtypes respond well to endocrine therapy. In contrast, 20% of cases overexpress the Human epidermal growth factor (HER2+) oncogene, and about 10% are Triple-negative, lacking ER, PR, and HER2+ expression both associated with poorer outcomes and fewer treatment options. Endocrine therapy is a cornerstone in the treatment of ER-positive breast cancer. It includes Aromatase Inhibitors (AIs), Selective Estrogen Receptor Modulators (SERMs) and Selective Estrogen Receptor Degraders (SERDs) in Figure 1. [3.4.5]

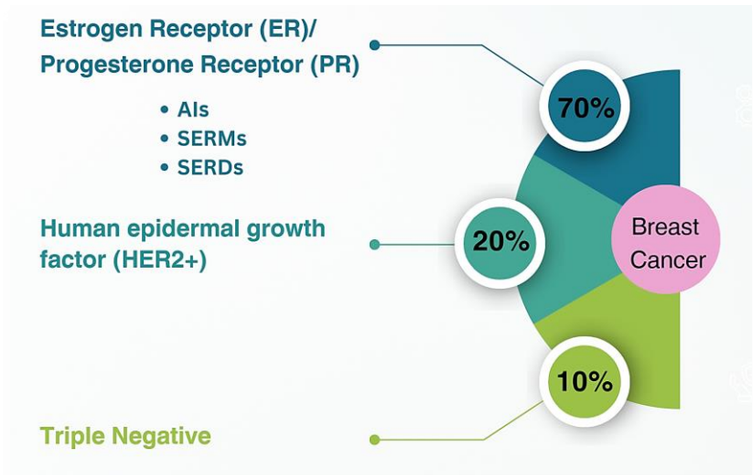

Figure 1. Different forms of Breast Cancer along.

Among these, SERDs such as fulvestrant (Figure 2) have shown effectiveness in degrading ERα and inhibiting its signaling pathway. However, fulvestrant's poor oral bioavailability and intramuscular administration limit its clinical utility.[6. 7. 8]

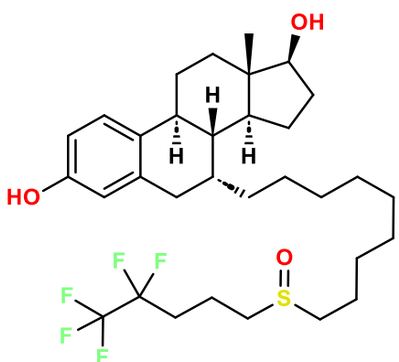

Figure 2. Chemical structure of fulvestrant.

In recent years, there has been significant interest in the development of novel, orally bioavailable SERDs to overcome the limitations of current therapies and improve patient outcomes. This study focuses on the design and evaluation of coumarin-based SERD candidates using computational tools, including molecular docking and ADME-Tox prediction, to identify promising compounds with improved pharmacological and pharmacokinetic profiles for the treatment of ER+ breast cancer. [9. 10. 11. 12. 13]

Research Objective

SERDs are a promising treatment for estrogen receptor-positive (ER+) breast cancer. This study focuses on designing and evaluating coumarin-based small molecules as potential oral SERDs using Molecular Docking and ADME- Tox prediction. The study aims to assess the physicochemical properties, pharmacokinetics, and safety profiles. The results suggest promising drug-like profiles with favorable absorption and metabolic stability, advancing the development of next-generation SERDs that could overcome the limitations of current treatments like fulvestrant.

Thesis structure

- **Chapter 1**: This chapter discusses the role of computational techniques in drug discovery, emphasizing molecular docking for predicting compound-protein interactions. It also highlights the importance of evaluating drug-likeness and ADME-Tox profiles to assess efficacy and safety before laboratory testing. The chapter focuses on estrogen receptor alpha (ERα) as a key target in breast cancer therapy and explores the mechanism of action of SERDs, along with promising candidates for overcoming hormone therapy resistance.
- **Chapter 2**: This chapter details the computational methods used to evaluate SERD candidates, including receptor preparation, active site identification, and docking validation. It also covers ligand preparation and the execution of docking simulations. An ADME-Tox analysis is conducted using specialized software to assess the pharmacokinetics and toxicity profiles of the compounds.
- **Chapter 3**: This chapter presents the results of the computational analysis of 101 coumarin derivatives, with a focus on ADME-Tox properties. The findings identify the most promising molecules as potential therapeutic agents.

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Chapter I:

An overview

Chapter I: An overview

TOPIC 1: Molecular Modeling

TOPIC 2: Estrogen Receptor Alpha In Breast Cancer

TOPIC 1:

Molecular Modeling

Computational chemistry has become a widely used method for developing new drugs in a short and cost-effective manner[1]. It has been employed for modeling molecular interactions, predicting the physical and chemical properties of compounds, and optimizing drug design using chemical databases and data processing algorithms.[2]

Docking and ADMET are important tools in the field of Computer-Aided Drug Design (CADD). Both contribute to understanding how drug compounds interact with their biological targets in the body, which helps in improving the drug's effectiveness and reducing side effects.

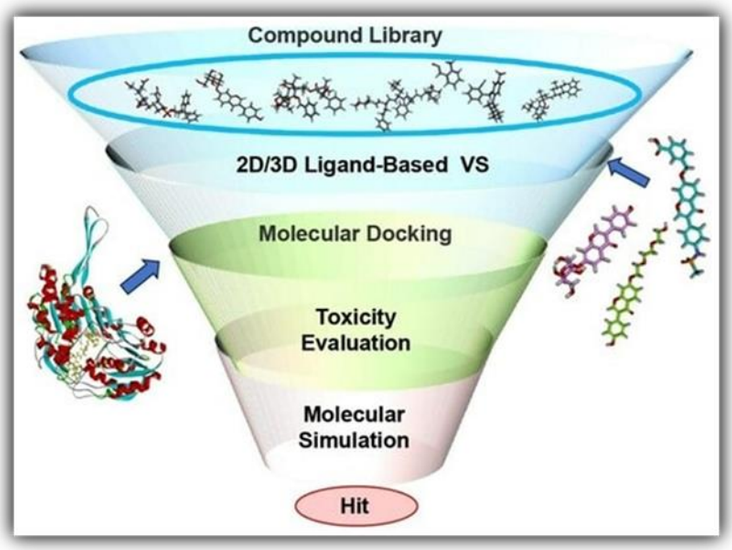


Figure I-1: Overview of virtual screening process[3]

I. Molecular Docking:

Molecular docking has become a key tool in computer-aided drug design to predict the interaction and binding of molecules through various methods for studying the interactions between large molecules (such as proteins) and small molecules. The main objective is to adjust the conformation that defines the appropriate binding site and relative orientation, particularly at the receptor level.[4,5]

This process involves complementary interactions with protected architectural features and forces that may be steric, electronic, or dipole in nature, with contributions from non-covalent interactions and electrostatic bonds. Protein-protein interactions and binding play a crucial role in regulating biological systems, contributing to the regulation of certain biological processes, signal transduction, or activation of biochemical reactions.

Molecular docking is a computational study of the mechanisms and interactions between potential drug compounds and the body’s proteins, aiming to predict and reconstruct the complex structure formed by the binding of receptors and ligands, and to identify the active site for the development of selective and potent drugs.[5,6]

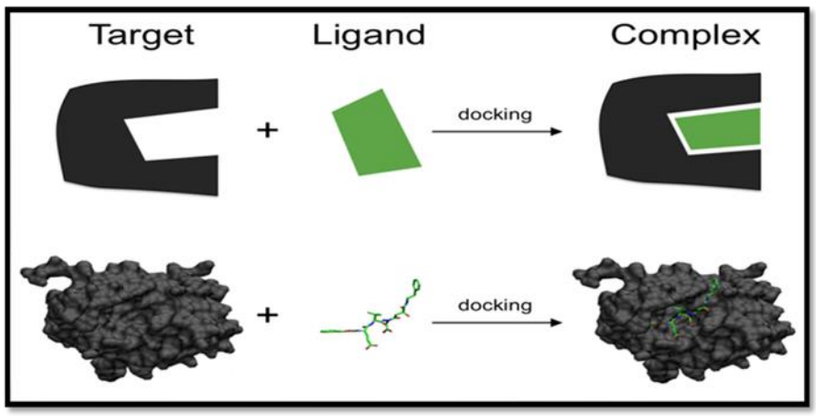


Figure I-2: Schematic representation of docking [7]

I.1.Types of molecular docking:

Molecular docking can be categorized into several types based on the methods and features being focused on. Here are the main types of molecular docking:

1-Rigid docking:

It is more commonly used and simpler for modeling protein-protein docking. The protein and the ligand are considered rigid entities, meaning they retain their internal geometry fixed during the docking process.[8.9]

2-Flexible docking:

Both the ligand and the protein undergo conformational changes during the docking process. Unlike rigid docking, flexible docking allows for the adjustment of the protein and ligand shapes to better fit together, accommodating flexibility in both molecules. This approach is particularly useful when dealing with proteins or ligands that undergo significant conformational changes upon binding.[8]

3- Semi-flexible docking:

This is the middle ground between rigid and fully flexible docking. Typically, the ligand is allowed some flexibility (such as rotating around its bonds), but the receptor (protein) remains rigid. This is often more computationally feasible than fully flexible docking while still allowing some flexibility in the ligand, which is usually important for achieving better accuracy in predicting binding.[9]

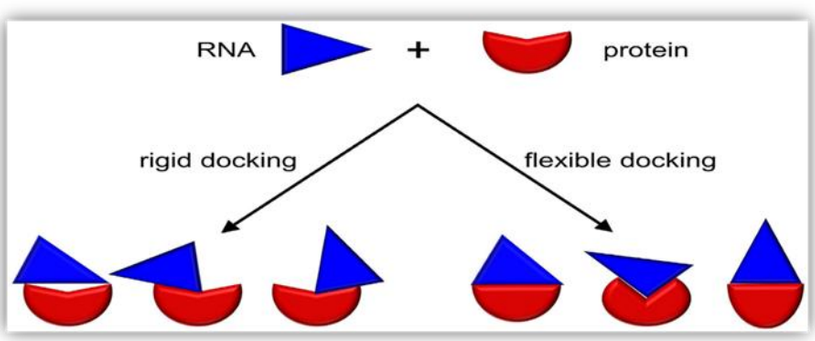


Figure I-3: Comparison of rigid and flexible docking methods [1]

I.2.Typical steps in molecular docking:

The docking protocol can be divided into several stages, as follows:

- Obtaining the future structure using X-ray crystallography or modeling techniques used to determine protein structures[11]. The majority of protein structures are available through the Protein Data Bank.[12]
- The preparation of structures: The docking of future structures can only be performed after the relevant structures have been determined. To do this, it is essential to resolve issues related to steric clashes, as well as protonation state problems. The initial conformation of the docking is usually modified and refined during the docking process, and therefore, in principle, it is not extremely crucial.[13]
- In the field of molecular modeling, docking is a technique that determines the optimal orientation of one molecule relative to another when they bind to form a stable complex.[14]
- Once the molecular docking parameters are established, the docking software suggests one or more potential binding poses, which we use to predict and then evaluate them.[13]

II. *In silico* assessment of ADME-Toxicity profiling prediction:

In the drug development process, the activities of candidate drugs are evaluated based on their properties, drug kinetics, and toxicity[15]. This leads to a small number of drugs, often just one that successfully pass the final stage (good in terms of efficacy and safety). This is usually the result of factors such as absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties.[16]

In recent years, in vitro and in vivo prediction methods for ADMET properties have become common, but the tests were complex, expensive, and challenging to perform on a large number of drugs. As a cost-effective and high-throughput alternative to experimental testing methods, in silico ADMET prediction has become particularly attractive .[17]

We will explore the aspects of ADME-Tox to understand its importance and familiarize ourselves with some of the tools and techniques used to assess it: [18-24]

Figure I-4: An illustration showing the ADME properties

1. Absorption:

Absorption refers to how well and how quickly a drug is absorbed into the bloodstream (for example, from the stomach or intestines for orally administered drugs) after ingestion. It is an important factor that directly affects the drug's bioavailability, which is the portion that reaches the systemic circulation from the given dose.

The criteria for absorption are:

- **Caco-2 permeability:** refers to the ability of a drug to pass through a monolayer of Caco-2 cells, which are human colon cancer cells commonly used in laboratory studies to model the intestinal barrier. Caco-2 cells express conjugating enzymes, efflux proteins, and transport proteins, and their permeability is often used to predict how a drug will be absorbed in the human gastrointestinal system.
- **Intestinal absorption (human):** refers to the process through which drugs or other substances are absorbed into the bloodstream after crossing the walls of the intestines. It is a crucial step for drugs that are taken orally, as it determines how much of the drug will enter the systemic circulation and influences its therapeutic effect.
- **Skin permeability:** refers to the ability of a substance, such as a drug, to pass through the skin and enter the bloodstream. The skin serves as a protective barrier, and its permeability is an important factor in determining the effectiveness of topical or transdermal drug delivery systems.

2. Distribution:

Refers to the process by which a drug or active ingredient is dispersed throughout the body after being absorbed into the bloodstream. Once the drug enters the bloodstream, it is carried to various tissues and organs after binding to plasma proteins. The parameters of Distribution are:

- **VDss (human):** It is a measure used to determine the extent of a drug's distribution throughout the body after it reaches equilibrium between its concentration in the blood and tissues. It reflects how the drug is distributed in the body; the higher the VDss, the more extensively the drug is distributed in tissues, especially those with high fat content.
- **BBB permeability:** refers to the ability of a drug to cross the blood-brain barrier, which is a semi-permeable barrier separating the bloodstream from the brain tissue. This barrier serves to protect the brain from harmful substances and toxins, while preventing many large molecules and compounds that are not lipophilic (fat-soluble) from entering the brain.
- **Fraction unbound (human):** The portion of the drug present that is not bound to proteins is known as the free fraction or fraction unbound.

Assuming a plasma protein binding (PPB) of 90%, the fraction that remains unbound is 10%, or 0.1 of the total. Assuming no active processes, the free concentration will be the same throughout the body at equilibrium. The fraction that is deemed free is thought to be accessible for distribution in order to interact with receptors, metabolize enzymes, and perform renal filtration, among other functions.

3. Metabolism:

Is the process through which a drug is chemically altered in the body this transformation, which is typically carried out by liver enzymes, aims to make the drug more water-soluble to facilitate its elimination. Metabolism can also render the drug either active, inactive, or toxic.

The parameters of Metabolism are:

- **CYP2D6 substrate:**

The second-highest number of drugs metabolized by P450 enzymes are attributed to CYP2D6. Because of its genetic polymorphism, CYP2D6 is an especially difficult enzyme to comprehend and research.

- **CYP1A2 inhibitor.**
- **CYP2C19 inhibitor.**
- **CYP2C9 inhibitor.**
- **CYP2D6 inhibitor.**
- **CYP3A4 inhibitor.**

4. Excretion:

Is the process by which drugs or other substances that have not been used or metabolized are removed from the body. This is primarily done through the kidneys via urine, but it can also occur through feces, sweat, breath, or breast milk.

The parameters of Excretion are:

- **Total clearance:** It is a measure used to determine the body's ability to remove a drug from the bloodstream. It represents the volume of plasma that is completely cleared of the drug per unit of time (typically in milliliters per minute or liters per hour). Total clearance is an important measure to understand how a drug is eliminated from the body, depending on its removal by the liver, kidneys, and all other tissues combined.
- **T1/2 (half-life):** is the time it takes for the systemic concentration of a drug to decrease by 50%. It is also the time it takes to reach 50% of the steady-state concentration of the drug.
- **Renal OCT2 substrate**.

5. Toxicity:

Is the condition in which harmful or poisonous effects occur as a result of the body's exposure to a substance, such as drugs or chemicals .Toxicity can occur when the concentrations of the

substance in the body exceed the safe threshold, which is why it is one of the most important criteria for toxicity assessment in ADME-Tox evaluation. It involves identifying the potential harmful effects of the drug on living organisms. The criteria for toxicity include:

- **AMES toxicity:** The Ames test is a bacterial assay used to assess the potential for mutations in chemical substances. Named after its inventor, Dr. Bruce N. Ames, it is a fast and cost-effective screening tool for identifying mutagens and potential carcinogens. It helps evaluate the genotoxicity of chemicals and supports regulatory decision-making processes.
- **Skin sensitisation.**

TOPIC 2:

Estrogen Receptor Alpha

In Breast Cancer

Breast cancer is one of the most common cancers among women, accounting for approximately 25% of new cases and 16% of cancer-related deaths worldwide. This disease is highly heterogeneous, containing various subtypes that can be identified through molecular biomarkers, which also help predict prognosis and treatment response. Among these subtypes, luminal breast cancer is the most common, characterized by the presence of estrogen receptor-positive (ER+) and/or progesterone receptor-positive (PR+). In contrast, HER2-positive breast cancer is defined by overexpression of the HER2 gene, while triple-negative breast cancer is characterized by the lack of expression of ER/PR and HER2. [25.26.39]

In cases of metastatic breast cancer, the luminal subtype accounts for more than 65% of cases. The recommended treatment for this subtype is endocrine-based therapy, as numerous studies and recommendations have concluded that chemotherapy is not the best option for hormone-sensitive disease, except in cases such as visceral crisis. These biological classifications play a significant role in guiding optimal treatment and achieving the best outcomes for patients.

I. Types of receptors in breast cancer:

There are several types of receptors in breast cancer that play a significant role in the growth of the tumor and its response to treatment. These include:

I.1.Progesterone Receptor (PR):

Are intracellular proteins that undergo a conformational change upon binding with progesterone, becoming transcription factors. This receptor regulates the transcription of specific genes depending on the cellular and hormonal context. PR plays a critical role in several physiological processes, including fertility, regulation of the menstrual cycle, initiation and maintenance of pregnancy, and response to sex steroids. There are two isoforms of the receptor: PR-A and PR-B, which have slightly different roles in transcriptional regulation and in interacting with other transcription factors.

I.2.Human Epidermal Growth Factor Receptor 2 (HER2):

HER2 is a membrane protein. The HER-2/neu oncogene belongs to the erbB-like oncogene family and is associated with the epidermal growth factor receptor, although it differs from it. In some forms of cancer, particularly breast cancer, HER2 overexpression is observed, indicating an excess of HER2 receptors on the surface of cancer cells. This acts as a stimulant and may also lead to abnormal behavior.[27]

I.3.Estrogen Receptor (ER):

The estrogen receptor (ER) is a protein found on the surface of cells in certain types of cancer, including breast cancer. This receptor binds with the hormone estrogen, and the ER plays an important role in the biology of breast cancer. It is an accepted factor that predicts favorable disease outcomes and response to treatment.[28]

- Estrogen receptors (ERs) are primarily classified into two main types: ERα and ERβ [29], with particular reference to membrane receptors that involve rapid (non-genomic) effects. I will focus on ERα for further study.

II. Estrogen Receptor alpha (ERα) :

Is a member of the nuclear receptor superfamily of transcription factors whose activity is primarily regulated by binding of estrogen/estradiol (E2). E2 plays an indispensable role in growth, development, reproduction and maintenance of numerous physiological systems in mammals.[30]

II.1. Targeted mechanisms for activating ERα:

The estrogen receptor alpha (ERα) plays a central role in cell proliferation, survival, and tumor progression in ER-positive (ER+) breast cancers, which represent the majority of breast cancers. Here are the key steps of the mechanism of action of ERα in this context:

- Activation by estrogen: Estrogen, the primary ligand for the ERα receptor, binds to the ligand-binding domain (LBD) of the receptor. This process leads to a conformational change in the receptor, enabling its activation. After binding to estrogen, the estrogen-ERα complex dimerizes and binds to estrogen response elements (EREs) on DNA, allowing the transcriptional activation of target genes[31]
- The three current categories of approaches specifically targeting estrogen receptor alpha (ERα) signaling in breast cancer, chosen based on disease progression, are:

a) Aromatase inhibitors (AIs):

Third-generation aromatase inhibitors have become the cornerstone in the treatment of breast cancer in postmenopausal women with ER+ tumors. Drugs such as anastrozole, letrozole, and exemestane have proven effective in lowering estrogen levels, thereby reducing the growth and spread of estrogen-dependent breast cancer. However, despite offering better outcomes compared to older treatments, their side effects, particularly regarding bone health and joint pain, must be carefully managed.[32.33]

b) Selective Estrogen Receptor Modulators (SERMs):

SERMs are compounds that selectively modulate the activity of ERα. They act as agonists in some tissues and antagonists in others, or modulators depending on their structure and the tissue environment[34]. An example is the drug tamoxifen, which is one of the widely used SERMs in the treatment of estrogen receptor-positive (ER+) breast cancer. It selectively blocks the receptors by preventing estrogen binding and ER signaling. It inhibits the activating function of the AF2 domain but leaves the AF1 domain of ERα open, which may cause agonist activity in some tissues (such as the uterus), potentially leading to tumor growth.[35.36]

c) Selective Estrogen Receptor Degraders (SERDs):

Selective Estrogen Receptor Degraders (SERDs) are nonsteroidal small molecules with an ER binding motif and an amino base terminal or acrylic acid side chain that provides antiestrogenic and ER-degrading activity[37]. Selective Estrogen Receptor Down regulators (SERDs) are a class of targeted therapeutic agents that not only block estrogen receptors (ER) but also promote the degradation of the receptors themselves (thereby inhibiting growth and proliferation). For this reason, our study has focused on them. Given the urgent need for new

and effective treatments for breast cancer, we will focus on discovering a new compound that allows oral drug delivery by utilizing toxic properties and other techniques in the treatment of breast cancer.

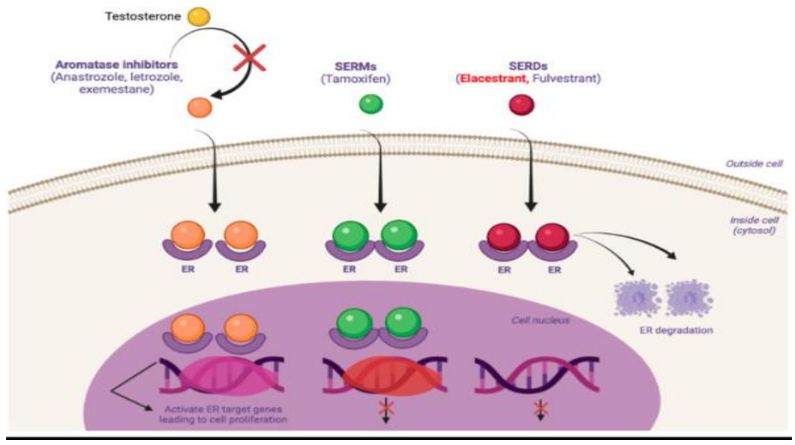


Figure I-5: Mechanism of action of the different ET: aromatase inhibitors, SERMs and SERDs. ER and its activity modulated by AI, SERMs and SERDs: AI block estrogen production by inhibiting the aromatization of androgens to estrogens. SERMs (tamoxifen) competitively inhibit the binding of estrogen to ER. SERDs produce a reduction of SERD-bound ER ability to translocate to the nucleus, inhibiting transcription of ER-regulated genes. SERD-bound ER undergoes degradation as a consequence of impaired mobility.[39]

III. Mechanism of action of SERDs in breast cancer treatment:

Selective Estrogen Receptor Degraders (SERDs) work by binding to the estrogen receptor (ERα) in the cytoplasm of cancer cells, causing a structural change in the receptor. This structural change destabilizes the receptor and triggers its degradation by proteasomes associated with the nuclear matrix, leading to its complete destruction. As a result, the receptor is unable to activate target genes that contribute to cancer cell proliferation, effectively halting tumor growth. This mechanism makes SERDs an effective treatment option for estrogen receptor-positive breast cancer, especially in resistant cases.[38.40]

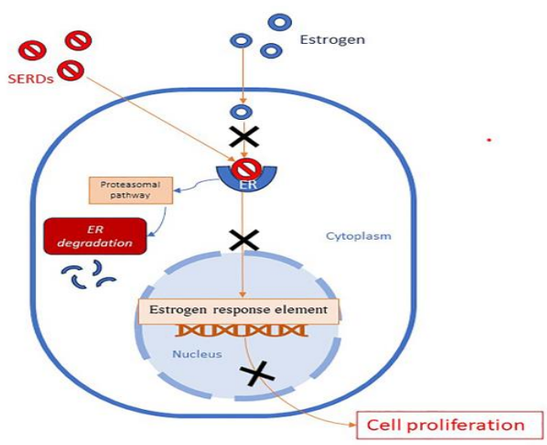


Figure I-6: The impact of Selective Estrogen Receptor Degraders (SERDs) on the estrogen receptor pathway. SERDs degrade ER, blocking ER signaling.[40]

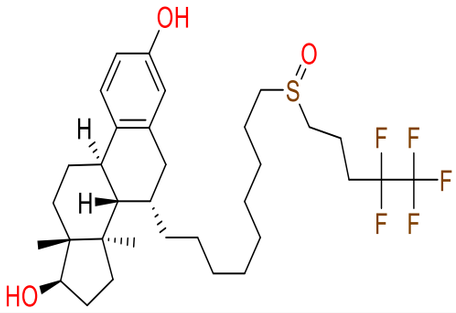
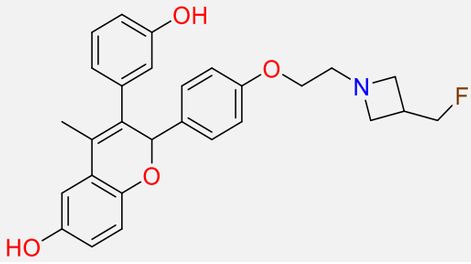
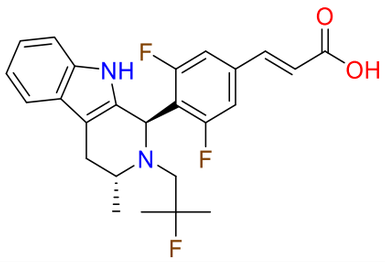
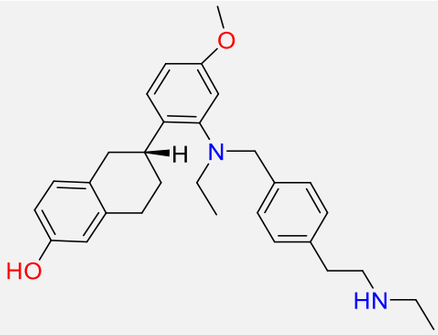
IV. The new treatment for breast cancer:

Selective Estrogen Receptor Down regulators (SERDs) are a new class of therapies for the treatment of estrogen receptor-positive (ER+) breast cancer. These drugs work by destroying

estrogen receptors on cancer cells, preventing estrogen from stimulating the growth of cancer cells. While previous treatments such as tamoxifen and aromatase inhibitors have been effective, oral SERDs represent the new generation that offers additional advantages.[38]

One of the prominent drugs in this field is Fulvestrant, which acts as an estrogen receptor antagonist by binding to it and degrading it using the ubiquitin-proteasome system[41]. There are also new non-steroidal drugs that contain an acrylic acid side chain, which are effective at degrading ER in specific cell lines, but may not be as effective in all ER+ cell lines. Notable examples include GDC-0810 and AZD9496[42.43]. Other drugs contain a basic amino side chain, which have been optimized for more efficient ERα degradation across multiple cell lines, have oral bioavailability, and can reach the brain, making them more effective in overcoming hormonal therapy resistance. An example of such a drug is RAD1901 (Elacestrant) .[44.45].

Table I-1: List of notable selective estrogen receptor degraders.[46]

Compound	Structure	Company	Effects
Fulvestrant		AstraZeneca	-development of resistance -Low bioavailability.
GDC-0927		Seagon pharmaceuticals/genetic Inc.	High Bioavailability. Highly active in Tam-resistant cells.
AZD9496		AstraZeneca	High Bioavailability. Cross-resistant to fulvestrant.
Elacestrant		Radius pharmaceutical	High Bioavailability Dose dependent SERM/SERD hybrid.

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CHAPTER II:

Materials and Methods

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This study investigated the interaction of 101 coumarin-based Selective Estrogen Receptor Down-regulators (SERDs) featuring obtained from the ChEMBL database [1] [2](https://www.ebi.ac.uk/chembl/), with the Estrogen Receptor Alpha (ERα) using the Molecular Operating Environment (MOE) 2019 software [3]. Additionally, Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME-Tox) analysis was conducted using the ADMETlab[4] (https://admetmesh.scbdd.com/) and SwissADME[5] (http://www.swissadme.ch/) web servers, revealing favorable pharmacokinetic and safety profiles for the SERDs, thereby enhancing their potential as drug candidates. However, some compounds exhibited poor oral bioavailability due to extensive first-pass metabolism, high plasma protein binding, or low intestinal permeability, highlighting the need for further structural modifications to optimize their pharmacokinetic properties. [6] [7]

I. Computer system and web servers:

For theoretical quantum chemical calculations, we utilized a performance computing system with the following specifications: Processor: AMD Ryzen 5 5600, 6-Core, Memory (RAM): 32.0 GB and Operating System: Windows 11 Pro (Version 10.0.22631).

To investigate the interaction mechanisms between SERDs and ERα, we employed the following specialized software and web servers: ChemDraw Ultra 12.0 software [8] for molecular structure visualization and modification, MOE 2019 software [3] for molecular docking and interaction analysis. Pharmacokinetic parameters were estimated using ADMETlab [4] and Swiss ADME [5] web servers which revealed favorable pharmacokinetic and safety profiles for the SERDs.

II. Molecular Docking:

II.1. Preparation of receptor:

To conduct the docking study, we selected the Estrogen Receptor Alpha [9] (ERα) (PDB ID: 3ERT) from the Protein Data Bank [10] (PDB) (https://www.rcsb.org) and downloaded. The 3D structure of (PDB ID: 3ERT) was co-crystallized ligand with 4-Hydroxytamoxifen (OHT), as shown in Figure 1.

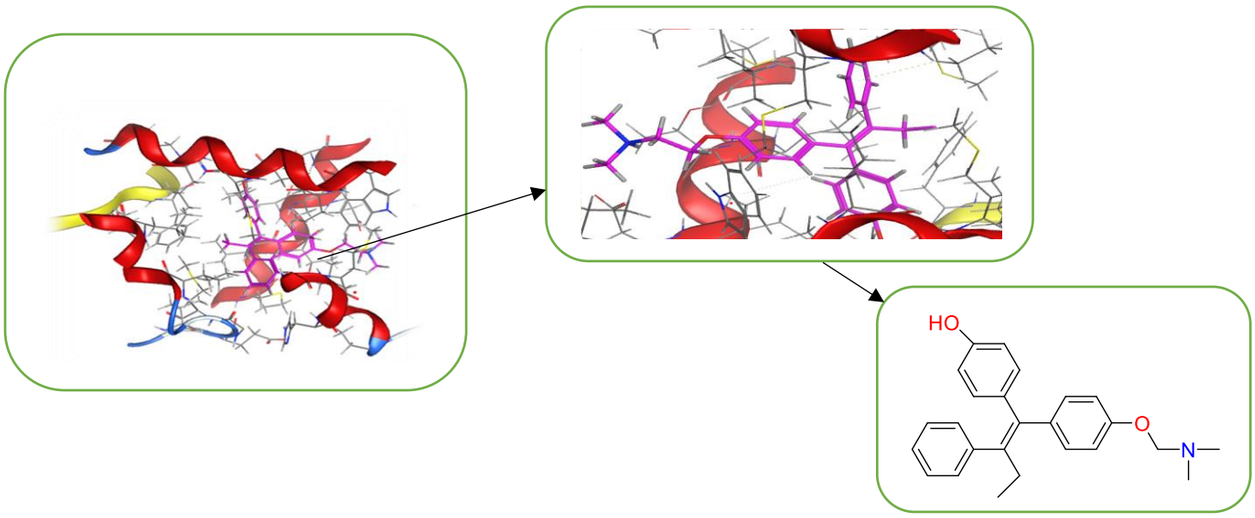
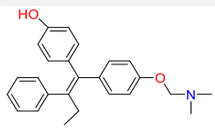


Figure II-1: 3D Structure of ERα complexed with OHT (PDB ID: 3ERT).

- The three-dimensional structure of 3ERT was obtained through X-ray diffraction. The properties of the ERα selected for this study are summarized in Table II.1

Table II.1: Properties of the selected protein (PDB ID: 3ERT).

Receptor	Co-crystallized ligand OHT	Classification	Chain	Resolution (Å)	Molecular mass (KDa)	Polymer (Å)
REα PDB ID: 3ERT		Nuclear receptor	A	1.9	30.24	1

After downloading the enzyme receptors, the structures were simplified by: removing water molecules, ions, and catalysts, performing 3D protonation and assigning partial atomic charges and determining the active site using the site finder tool in MOE software.

II.2 Active site selection:

To identify the most suitable active site for docking, we used the Site Finder tool in MOE software, which detected a total of 23 cavities in the 3ERT protein. For this study, we selected the first cavity based on its co-crystallization with the ligand OHT. Table II.2 and Figure II.2 summarize the active site residues of 3ERT.

Table II.2: Characteristics of the active site in 3ERT

PDB	Size	PLB	Hyd	Side	Residues
3ERT	218	4.45	74	118	1:(GLU323 PRO324 PRO325 ILE326 LEU327 MET343 LEU346 THR347 LEU349 ALA350 ASP351 GLU353 HIS356 MET357 TRP360 GLU380 TRP383 LEU384 ILE386 LEU387 MET388 GLY390 LEU391 TRP393 ARG394 PHE404 ALA405 PRO406 GLU419 GLY420 MET421 ILE424 LEU428 PHE445 LYS449 GLY521 MET522 HIS524 LEU525 TYR526 MET528 LYS529 CYS530 VAL533 VAL534 PRO535 LEU536)

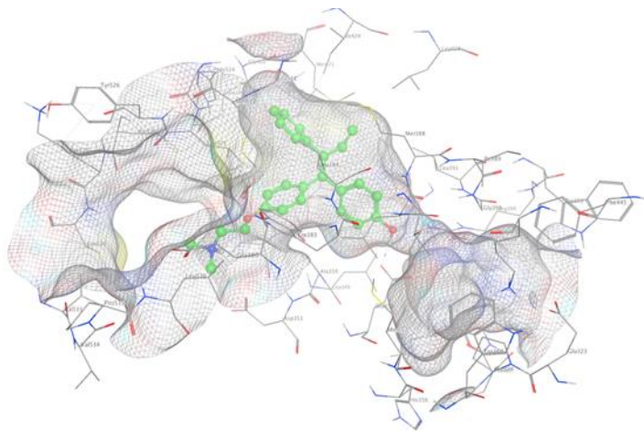


Figure II-2: Active site residues of 3ERT.

II.3. Validation of receptor:

To validate the precision and reliability of our docking protocol, we conducted a re-docking experiment by reintroducing the co-crystallized ligand 4-Hydroxytamoxifen (OHT) into its active site within the 3ERT complex. The resulting Root Mean Square Deviation (RMSD) values were below 2.5 Å, indicating a high degree of consistency between the predicted and experimental binding conformations, thus, confirming the reliability and effectiveness of the docking method.

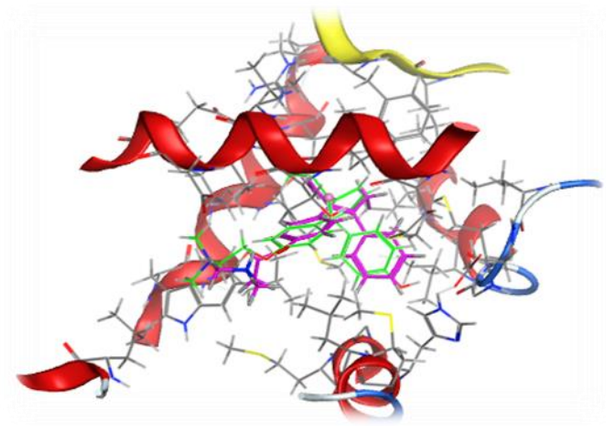


Figure II-3: Validation of the docking by re-docking in 3ERT.

II.4. Ligand preparation:

Based on the findings from scientific literature [11], we selected the two most promising compounds, A and B, for further optimization represented in Figure II.4. Compound A, a potent 7-hydroxycoumarin derivative, demonstrated strong estrogen receptor down-regulation but suffered from poor oral bioavailability. Compound B, where the 7-hydroxy group was removed, resulting in improved pharmacokinetic properties and enhanced bioavailability while retaining SERD potency. These lead compounds serve as valuable candidates for further development in the pursuit of orally active SERDs with enhanced therapeutic potential.

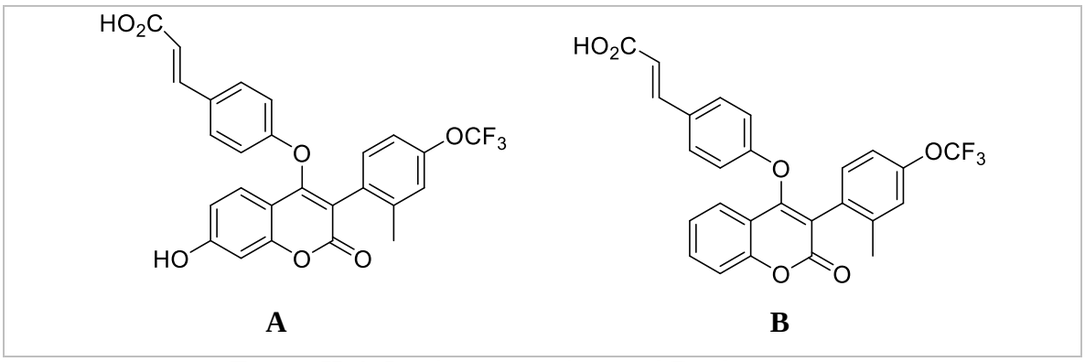


Figure II-4: Lead compounds A and B selected.

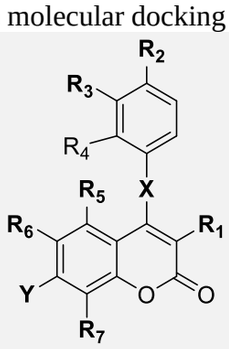
For this study, we used 101 SERDs, specifically coumarin-based derivatives, obtained from the ChEMBL database [1 2] (https://www.ebi.ac.uk/chembl/) represented in Table II.3. These SERDs were selected based on their potential interaction with ERα.

Ligand preparation process:

1. Chemical structures were drawn using ChemDraw and saved in MDL. mol format.

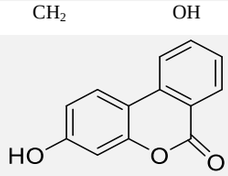
2. Structural optimization was performed using MOE.

Table II.3: Comarine core derivatives used in molecular docking studies.



entry	code	X	Y	R_1	R_2	R_3	R_4	R_5	R_6	R_7
1	CHEMBL3427400	/	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
2	CHEMBL113712	/	OH	Ph	H	$OC_3H_6NC_5H_{10}$	H	H	H	H
3	CHEMBL115000	/	OH	Ph	H	$OC_4H_8NC_5H_{10}$	H	H	H	H
4	CHEMBL325889	/	OH	Ph	$OC_5H_{10}NC_5H_{10}$	H	H	H	H	H
5	CHEMBL115194	/	OH	Ph	$OC_3H_6NC_5H_{10}$	H	H	H	H	H
6	CHEMBL421892	/	OH	Ph	$OC_6H_{12}NC_5H_{10}$	H	H	H	H	H
7	CHEMBL115489	/	OH	Ph	H	$OC_5H_{10}NC_5H_{10}$	H	H	H	H
8	CHEMBL117263	/	OH	Ph	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
9	CHEMBL115060	/	OH	Ph	$OC_4H_8NC_5H_{10}$	H	H	H	H	H
10	CHEMBL262042	/	OH	Ph	H	$OC_2H_4NC_5H_{10}$	H	H	H	H
11	CHEMBL3427389	CH_2	OH	PhF	$C_3H_2O_2H$	H	H	H	H	H
12	CHEMBL3427396	CH_2	OH	1-fluoro-3-methoxybenzene	$C_3H_2O_2H$	H	H	H	H	H
13	CHEMBL3427394	CH_2	OH	1,3-difluorobenzene	$C_3H_2O_2H$	H	H	H	H	H
14	CHEMBL3427408	CH_2	OH	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	CH_3
15	CHEMBL3427398	CH_2	OH	1-chloro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
16	CHEMBL3427387	CH_2	OH	anisole	$C_3H_2O_2H$	H	H	H	H	H
17	CHEMBL3425530	CH_2	OH	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	CH_3	H
18	CHEMBL3427395	CH_2	OH	1-chloro-3-fluorobenzene	$C_3H_2O_2H$	H	H	H	H	H

19	CHEMBL3427407	CH_2	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	F
20	CHEMBL3427399	CH_2	OH	1-methyl-3-(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
21	CHEMBL3427393	CH_2	OH	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
22	CHEMBL3427397	CH_2	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
23	CHEMBL3427385	CH_2	OH	Ph	$C_3H_2O_2H$	H	H	H	H	H
24	CHEMBL3427390	CH_2	OH	PhCl	$C_3H_2O_2H$	H	H	H	H	H
25	CHEMBL3427388	CH_2	OH	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
26	CHEMBL3427386	CH_2	OH	toluene	$C_3H_2O_2H$	H	H	H	H	H
27	CHEMBL3427392	CH_2	OH	anisole	$C_3H_2O_2H$	H	H	H	H	H
28	CHEMBL3427391	CH_2	OH	(trifluoromethyl)benzene	$C_3H_2O_2H$	H	H	H	H	H
29	CHEMBL3427412	CH_2	OCH_3	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
30	CHEMBL3427409	CH_2	H	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
31	CHEMBL3427413	CH_2	F	(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
32	CHEMBL115303	CH_2	OH	Ph	$OC_4H_8NC_5H_{10}$	H	H	H	H	H
33	CHEMBL326146	CH_2	OH	Ph	$OC_3H_6NC_5H_{10}$	H	H	H	H	H
34	CHEMBL439967	CH_2	OH	Ph	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
35	CHEMBL3427403	NH	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
36	CHEMBL3427404	NCH_3	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
37	CHEMBL4063544	NH	OH	anisole	NHC_2H_3	H	H	H	H	H
38	CHEMBL3427500	O	HCF_2	1,2-dimethyl-4-(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
39	CHEMBL3427501	O	OC_2H_5	1-methyl-3-(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
40	CHEMBL3427414	O	H	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
41**	CHEMBL3427415	O	H	1-methyl-3-(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
42	CHEMBL3427406	O	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	F	H
43	CHEMBL3427401	O	OH	1-fluoro-3-methylbenzene	$C_3H_2O_2H$	H	H	H	H	H
44*	CHEMBL3427402	O	OH	1-methyl-3-(trifluoromethoxy)benzene	$C_3H_2O_2H$	H	H	H	H	H
45	CHEMBL4166688	O	OH	PhOH	$OC_2H_4N(CH_3)_2$	H	H	H	H	H
46	CHEMBL4170100	O	OH	PhOH	$OC_2H_4NC_4H_8$	H	H	H	H	H
47	CHEMBL4162191	O	OH	PhOH	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
48	CHEMBL4173553	O	OH	fluorobenzene	$OC_2H_4N\ (CH_3)_2$	H	H	H	H	H
49	CHEMBL4177322	O	OH	phOH	$OC_2H_4N(C_2H_5)_2$	H	H	H	H	H
50	CHEMBL4176917	O	OH	fluorobenzene	$OC_2H_4NC_4H_8$	H	H	H	H	H
51	CHEMBL4169053	O	OH	fluorobenzene	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
52	CHEMBL4165622	O	OH	fluorobenzene	$OC_2H_4N(C_2H_5)_2$	H	H	H	H	H
53	CHEMBL4177323	O	OCH_3	anisole	$OC_2H_4N(C_2H_5)_2$	H	H	H	H	H
54	CHEMBL4169469	O	OCH_3	anisole	$OC_2H_4N\ (CH_3)_2$	H	H	H	H	H
55	CHEMBL1504784	CH_3	OH	Ph	/	/	/	H	H	H
56	CHEMBL3114441	/	OH	PhOH	H	H	H	H	H	H

57	CHEMBL1255978	CH_3	OH	PhOH	/	/	/	H	H	H
58	CHEMBL5284565	OH	OH	PhOH	/	/	/	H	H	H
59	CHEMBL1548614	CH_3	OH	$PhOCH_3$	/	/	/	H	H	H
60	CHEMBL1988509	/	H	OPhCl	OH	H	H	H	H	H
61	CHEMBL2333797	C_2H_2	OH	Ph	OCH_3	H	H	H	H	H
62	CHEMBL2413913	/	OH	Ph	OH	H	H	H	H	H
63	CHEMBL4081061	NH	OH	$PhOCH_3$	OCH_3	H	H	H	H	H
64	CHEMBL2413896	/	OH	PhOH	OH	H	H	H	H	H
65	CHEMBL2413901	/	$OC_2H_4NC_4H_8O$	Ph	OH	H	H	H	H	H
66	CHEMBL2333799	C_2H_2	OH	Ph	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
67	CHEMBL2333806	C_2H_2	OCH_3	Ph	$OCOCH_3$	H	H	H	H	H
68	CHEMBL4282511	OH	H	COC_2H_2PhOH	/	/	/	H	H	H
69	CHEMBL4102487	NH	OH	$PhOCH_3$	OCH_3	OCH_3	OCH_3	H	H	H
70	CHEMBL1980963	/	OCH_3	OPh	OH	H	H	H	H	H
71	CHEMBL1258302	CH_3	OH	C_2H_2PhOH	/	/	/	H	H	H
72	CHEMBL4285469	OH	OH	$COC_2H_2Ph_2$	/	/	/	H	H	H
73	CHEMBL1969472	/	OH	CONHPhBr	H	H	H	H	H	H
74	CHEMBL1968491	/	H	OPh	OH	H	H	H	H	H
75	CHEMBL1974086	C_2H_5	OH	$PhOCH_3$	/	./	/	H	H	H
76	CHEMBL2413903	/	$OC_2H_4NC_5H_{10}$	Ph	OH	H	H	H	H	H
77	CHEMBL2413895	/	OCH_3	Ph	OH	H	H	H	H	H
78	CHEMBL79777	CH_3	$OCON(CH_3)_2$	H	H	H	H	H	H	H
79	CHEMBL1596578	CH_3	OCH_2COCH_3	Ph	/	/	/	H	H	H
80	CHEMBL1588517	CH_3	H	Ph	/	/	/	H	OH	H
81	CHEMBL1258415	C_2H_2COPh	OH	H	H	H	H	H	H	H
82	CHEMBL1972786	/	OCH_3	OPhCl	OH	H	H	H	H	H
83	CHEMBL3114453	/	$OC_2H_4N(CH_3)_2$	$PhOC_2H_4N(CH_3)_2$	H	H	H	H	H	H
84	CHEMBL3612755	/	H	$PhOCOCH_3$						
85	CHEMBL2070342	OCH_2	H	Ph	H	H	H	H	H	H
86	CHEMBL2333798	C_2H_2	OCH_3	Ph	$OCH(CH_3)CH_2N(CH_3)_2$	H	H	H	H	H
87	CHEMBL1996594	/	$OCOCH_3$	OPhCl	H	H	H	H	H	H
88	CHEMBL2413902	/	$OC_2H_4NC_4H_8$	Ph	OH	H	H	H	H	H
89	CHEMBL12580	$C_2H_2CO_2H$	OCH_3	H	/	/	/	H	H	
90	CHEMBL4878531	OH	OH	NHCOPhOPh	/	/	/	H	H	H
91	CHEMBL2112018	OCH_3	OH	$CHPhC_2H_2OCH_3$	/	/	/	H	H	H
92	CHEMBL1526978	/	H	H	H	H	H	H	H	H
93	CHEMBL2413904	/	$OC_2H_4N(C_2H_5)_2$	Ph	OH	H	H	H	H	H
94	CHEMBL2333800	C_2H_2	OCH_3	Ph	$OC_2H_4NC_5H_{10}$	H	H	H	H	H
95	CHEMBL145263	CH_3	OCH_2Ph	Ph	/	/	/	H	H	H
96	CHEMBL2112874	OCH_3	OH	$CHPhCH_2COCH_3$	/	/	/	H	H	H
97	CHEMBL5287553	OH	OH	(Z)-4,7-dihydroxy-3-(4-styrylbenzyl)-2H-chromen-2-one	/	/	/	H	H	H
98	CHEMBL5277698	OH	OCH_3	Ph	/	/	/	H	H	H
99	CHEMBL2333807	C_2H_2	OCH_3	Ph	OH	H	H	H	H	H
100	CHEMBL193518	CH_2	OH	PhCl	H	H	H	H	H	H
101	CHEMBL1526978									

Note: *: Compound A, **: Compound B in figure II.4

II.2.5. Docking execution (Protocol):

All molecular docking calculations and scoring were performed using the MOE software. A total of 30 docking poses were generated to explore the most suitable binding conformation at the active site of the 3ERT, justifying the formation of various types of interactions between the SERDs and ERα.

The potential degradation was evaluated using key molecular features such as binding site interactions, receptor backbone (amino acid residues), interaction types, bond lengths, internal energies, and docking scores. The docking procedure was carried out using the following parameters: Triangle Matcher for pose generation and London dG for rescoring.

III. *In silico* study of ADME-Tox properties:

ADME-Tox analysis is a crucial step in drug development, as it helps optimize compound efficacy and minimize adverse effects, ultimately contributing to the production of safer and more stable drugs. For this analysis, the chemical structures of SEDRs were submitted in Canonical Simplified Molecular Input Line Entry System (SMILES) format to estimate pharmacokinetic parameters using the SwissADME (SwissADME). ADME-Tox properties were further predicted using ADMETlab (ADMETlab 3.0).

The following pharmacokinetic parameters were analyzed:

- **Absorption :**
  - Caco-2 permeability (> -5.15)
  - P-glycoprotein (Pgp) inhibition and substrate classification
  - Human intestinal absorption (HIA)
- **Distribution :**
  - Plasma protein binding (PPB)
  - Volume of distribution (Vd)
  - Blood-brain barrier (BBB) penetration
- **Metabolism:**
  - Interaction with **CYP450 enzymes** (1A2, 3A4, 2C9, 2C19, and 2D6) as inhibitors or substrates
- **Excretion:**
  - Half-life (T1/2)
  - Clearance (CL)
- **Toxicity:**
  - hERG inhibition (cardiotoxicity)
  - Human hepatotoxicity (H-HT)
  - Ames mutagenicity test
  - LD50 (lethal dose 50)

III.1.ADME-Toxicity evaluation of coumarin derivatives using ADMETlab 3.0:

Using the online platform **ADMETlab 3.0**. These derivatives were selected based on their favorable results obtained during molecular docking with the target protein, which indicated promising biological activity. The goal of this step was to predict the pharmacokinetic and toxicity profiles of the selected compounds, focusing on the following key properties:

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

➢ Methodology:

1. Preparation of the chemical structures of the selected derivatives in SMILES format.
2. Individual submission of each structure into the ADMETlab 3.0 web platform.
3. Running the predictive analysis for each compound to retrieve ADMET-related data.
4. Compilation and comparison of the results in order to identify the most promising compounds in terms of drug-likeness and safety.

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CHAPTER III:

Results and Discussion

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I. Molecular docking studies:

A molecular docking study was conducted on 101 coumarin derivatives within the active site of the estrogen receptor alpha (ERα) (PDB ID: 3ERT) to evaluate their potential as Selective Estrogen Receptor Degraders (SERDs) for breast cancer treatment. The docking simulations were carried out using the Molecular Operating Environment (MOE) software, and the results were analyzed based on binding affinity scores, interaction types, and Root Mean Square Deviation (RMSD) values. Table III. 1 presents the docking results, highlighting the most promising compounds based on their binding interactions and stability within the active site. The molecular docking results are shown in the following table (the supplement contains the results of the remaining comarins A) :

Table III.1: Molecular docking results most promising coumarin derivatives at the active site of the 3ERT protein

Ligands	S score (kcal/mol)	RMSD (Å)	Bonding between atoms and active site residues					
			Atom of compounds	Atom of receptor	Evolved receptor residue	Type of interaction bond	Distance (Å)	E (kcal/mol)
Ref.	-6.4041	1.0328	N 47	NH_2	ARG 394	H-acceptor	2.27	-0.8
			6-ring	CD1	ILE 424	pi-H	4.11	-0.6
2	-8.8868	1.7101	O 15	OE2	GLU 353	H-donor	2.77	-4.9
			C 55	6-ring	TRP 383	H-pi	3.76	-0.5
			6-ring	CD1	LEU 346	pi-H	3.90	-0.8
			6-ring	CD2	LEU 346	pi-H	4.11	-0.5
			6-ring	CD1	ILE 424	pi-H	4.01	-0.5
19	-9.1465	1.7454	C 17	SD	MET 343	H-donor	3.52	-0.6
			O 32	OD1	ASP 351	H-donor	2.85	-6.5
			O 43	OE2	GLU 353	H-donor	2.76	-6.5
			6-ring	CD1	ILE 424	pi-H	3.98	-0.5
23	-8.1748	1 .4934	O 39	OE2	GLU 353	H-donor	2.77	-5.7
			O 47	OD1	ASP 351	H-donor	2.90	-3.1
			6-ring	CB	LEU 387	pi-H	4.61	-0.5
			6-ring	CD1	ILE 424	pi-H	4.03	-0.6
27	-7.8816	1.4600	O 38	O	GLY 521	H-donor	3.21	-1.8
			O 46	OD1	ASP 351	H-donor	3.00	-6.1
			C 49	OE1	GLU 353	H-donor	3.13	-0.6
			6-ring	CD1	LEU 346	pi-H	4.31	-0.5
			6-ring	CA	THR 347	pi-H	4.42	-0.7
31	-7.0948	1.3088	C 22	SD	MET 343	H-donor	3.67	-0.5
			C 41	SD	MET 343	H-donor	3.73	-0.5
			O 47	N	CYS 530	H-acceptor	2.99	-0.6
			6-ring	6-ring	TRP 383	pi-pi	3.82	-0.0
35	-8.8539	2.5992	O 19	OE2	GLU 353	H-donor	2.77	-5.8
			C 28	SD	MET 343	H-donor	3.58	-0.5
			O 36	OD1	ASP 351	H-donor	2.86	-5.8
			6-ring	CB	LEU 387	pi-H	4.75	-0.5
			6-ring	CD1	ILE 424	pi-H	3.93	-0.6
40	-8.3162	1.5238	O 26	SD	MET 343	H-donor	3.51	-0.6
			O 34	OD1	ASP 351	H-donor	2.85	-6.6
			6-ring	CB	LEU 387	pi-H	4.56	-0.7
			6-ring	CDA	ILE 424	pi-H	3.97	-0.5
42	-8.6161	1.5399	O 15	O	LEU 387	H-donor	3.31	-0.7
			C 26	SD	MET 343	H-donor	3.45	-0.5
			O 34	OD1	ASP 351	H-donor	2.86	-6.5
			6-ring	CA	THR 347	pi-H	4.22	-0.5
			6-ring	CD1	ILE 424	pi-H	3.89	-0.6
51	-9.5932	2.1670	O 36	O	LEU 387	H-donor	3.10	-1.3

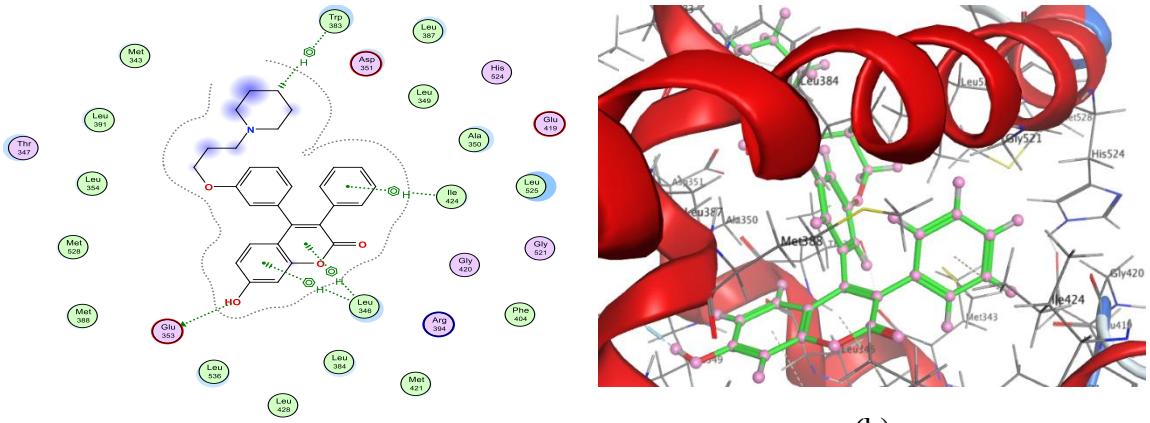
			C 25	6-ring	TRP 383	H-pi	3.78	-0.5
			6-ring	CD1	ILE 424	pi-H	3.77	-0.5
41 **	-7.1140	2.2182	F 48	NH_2	ARG 394	H-donor	2.80	-0.9
			6-ring	CE	MET 343	pi-H	4.30	-0.6
			6-ring	CA	THR 347	pi-H	4.67	-0.5
44*	-7.8225	1.5178	O 36	OE1	GLU 353	H-donor	2.84	-29
			O 36	OE2	GLU 353	H-donor	2.74	-4.0
56	-7.9100	0.8470	O 36	OE2	GLU 353	H-donor	2.70	-4.6
			O 38	O	GLY 420	H-donor	3.06	-0.5
			6-ring	CB	LEU 346	pi-H	4.75	-0.5
			6-ring	CA	THR 347	pi-H	4.55	-0.5
62	-7.9780	1.0456	O16	OE2	GLU353	H-donor	2.85	-5.5
			C23	SD	MET343	H-donor	3.57	-0.5
			O27	OG1	THR 347	H-donor	3.29	-0.5
			6-ring	CD1	LEU 387	pi-H	4.38	-0.5
			6-ring	CD1	ILE 424	pi-H	3.92	-0.5

Note: *: Compound A, **: Compound B in figure II.4

The molecular docking analysis revealed that the binding energy of the tested compounds ranged from -6.9013 to -9.9030 kcal/mol. The most promising compounds forming stable complexes with the 3ERT protein were identified as ligands 2, 19, 23, 27, 31, 35, 40, 41 **, 42, 44*, 51, 56 and 62. Their corresponding Root Mean Square Deviation (RMSD) values were 1.7101, 1.7454, 1.4934, 1.4600 , 1.3088, 2.5992, 1.5238 ,1.5399,2.1670, 2.2182, 1.5178, 0.8470and 1.0456 Å, respectively, while their binding energy values were -8.8868, -9.1465, -8.1748, -7.8816 , -7.0948, -8.8539,-8.3162, -8.6116, -9.5932, -7.1140, -7.8225, -7.9100 and -7.9780 kcal/mol.

Key interactions of selected ligands (interaction of remaining coumrins are in the supplement B).

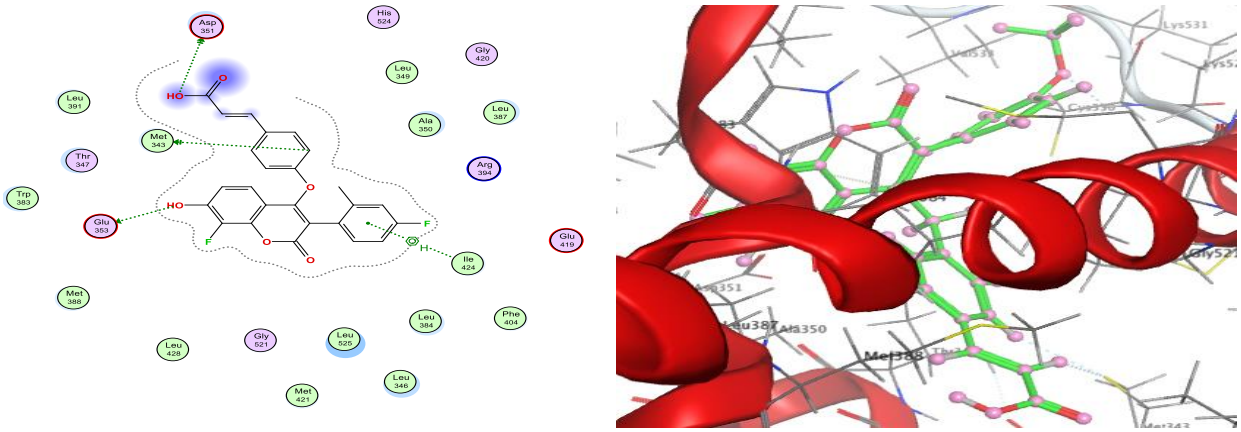
- **Ligand 2:** Forms hydrogen bonds with **GLU 353** (H-donor, 2.77 Å) and **TRP 383** (H-Pi, 3.76 Å). Additionally, it interacts via Pi-H bonds with **LEU 346** and **ILE 424** (3.90, 4.11, and 4.01 Å). *(Figure III.1)*



(a) (b)

Figure.1: Molecular interactions of **ligand 2** with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

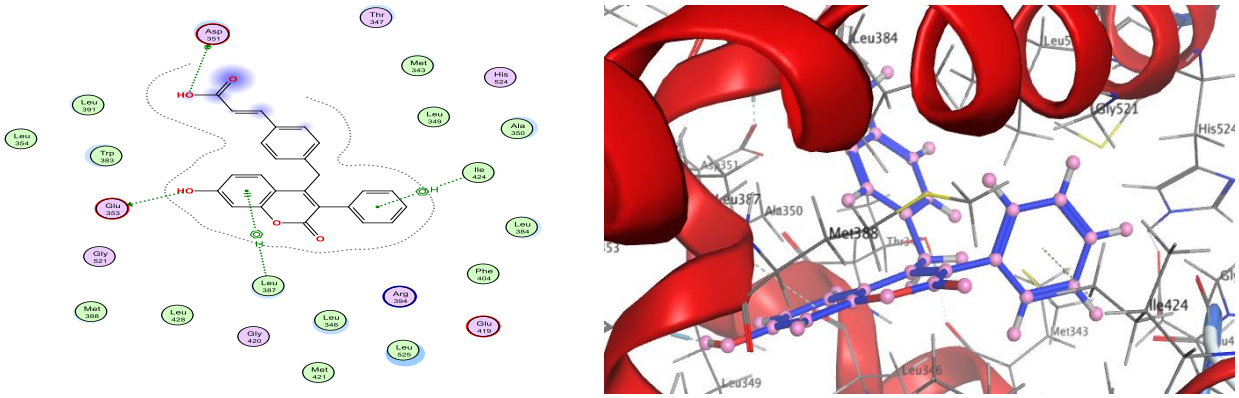
- **Ligand 19:** Engages in hydrogen bonding with **MET 343** (3.52 Å), **ASP 351** (2.85 Å), and **GLU 353** (2.76 Å). A Pi-H interaction is observed with **ILE 424** (3.98 Å). (*Figure III.2)*



(a) (b)

Figure. III-2: Molecular interactions of **ligand 19** with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

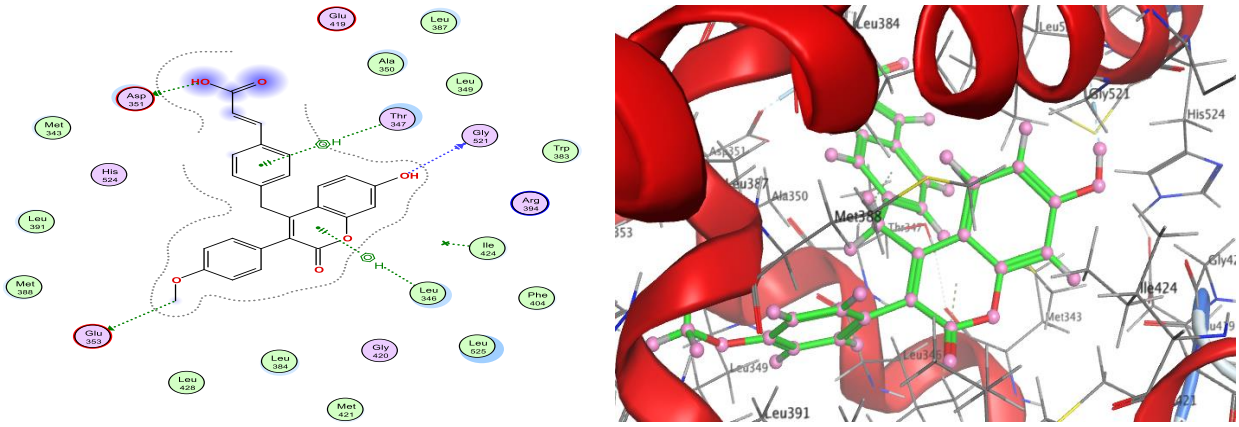
- **Ligand 23:** Interacts via hydrogen bonding with **GLU 353** (2.77 Å) and **ASP 351** (2.90 Å), while Pi-H interactions occur with **LEU 387** and **ILE 424** (4.61 and 4.03 Å). (*Figure III.3*)



(a) (b)

Figure -3: Molecular interactions of **ligand 23**with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

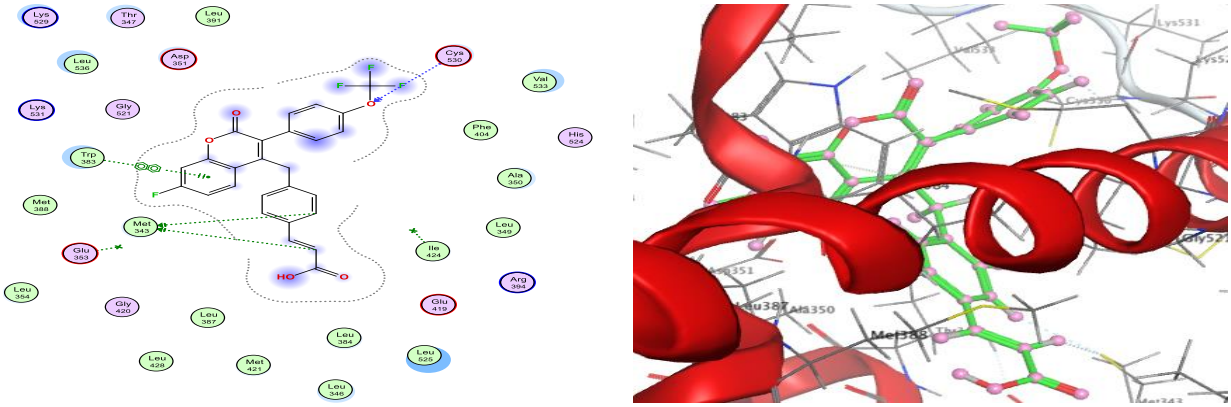
- **Ligand 27:** Exhibits hydrogen bonding with **GLY 521** (3.21 Å), **ASP 351** (3.00 Å), and **GLU 353** (3.13 Å). Additional Pi-H interactions occur with **LEU 346** and **THR 347** (4.31 and 4.42 Å). (*Figure III.4)*



(a) (b)

Figure.III-4:Molecular interactions of **ligand 27** with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

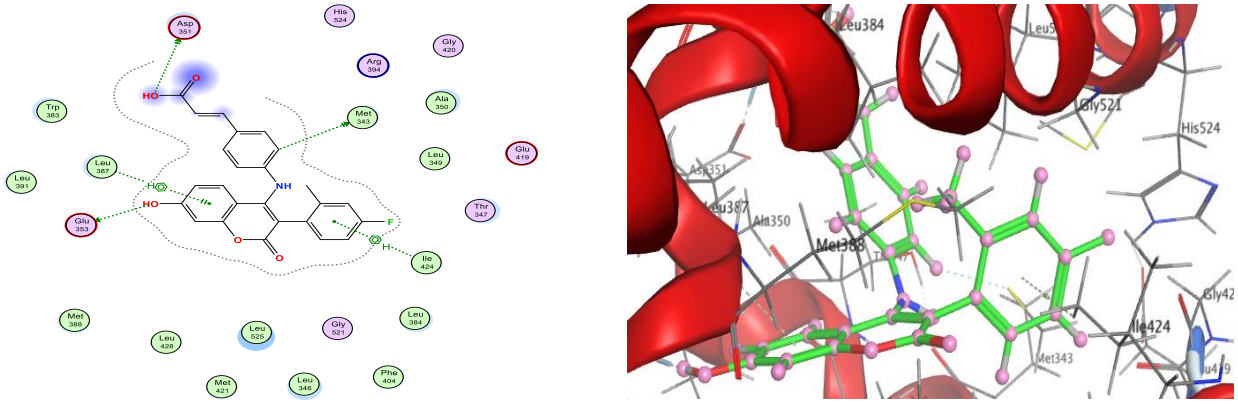
- **Ligand 31:** Forms hydrogen bonds with **MET 343** (3.67 and 3.73 Å) and **CYS 530** (2.99 Å). It also exhibits pi-pi interactions with **TRP 383** (3.82 Å). (*Figure III.5*)



(a) (b)

Figure III-5: Molecular interactions of **ligand 31** with the estrogen receptor alpha (ERα) (PDB:3ERT) 2D (a) ;3D (b)

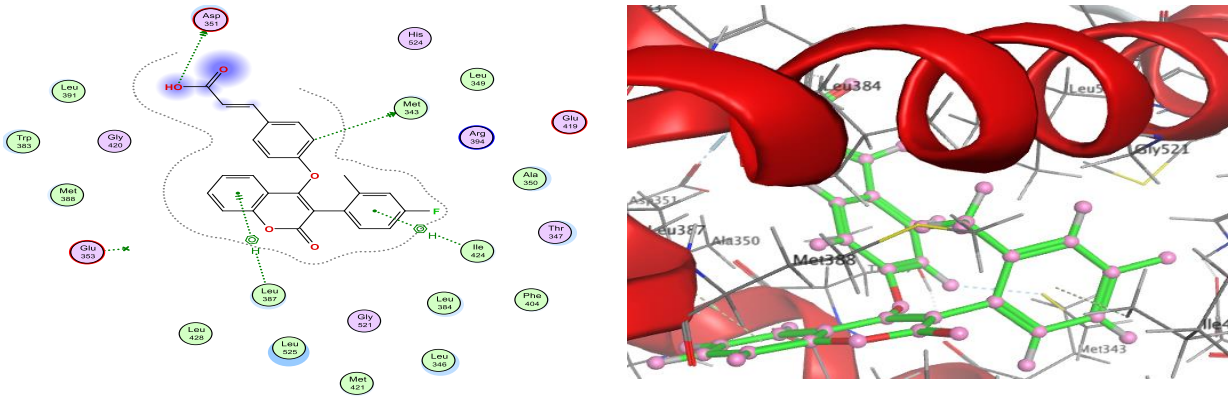
- **Ligand 35**: Interacts via hydrogen bonds with **GLU 353** (2.77 Å), **MET 343** (3.58 Å), and **ASP** 351 (2.86 Å). It also forms Pi-H interactions with **LEU 387** and **ILE 424** (4.75 and 3.93 Å). (*Figure III.6*)



(a) (b)

Figure.III-6: Molecular interactions of **ligand 35** with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

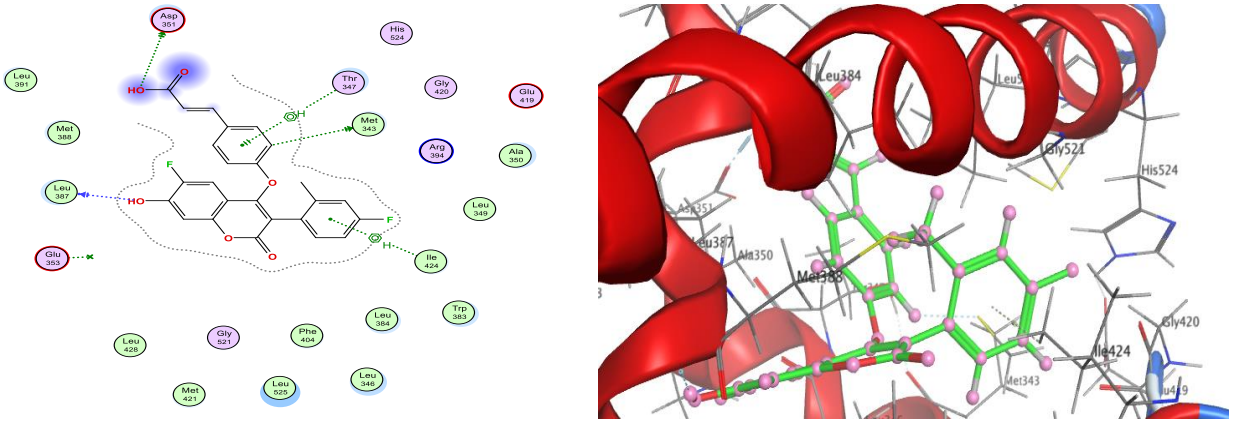
- **Ligand 40:** Forms hydrogen bonds with **MET 343** (3.51 Å) and **ASP 351** (2.85 Å), alongside Pi-H interactions with **LEU 387** and **ILE 424** (4.56 and 3.97 Å). (*Figure III.7*)



(a) (b)

Figure -7: Molecular interactions of **ligand 40** with the oestrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

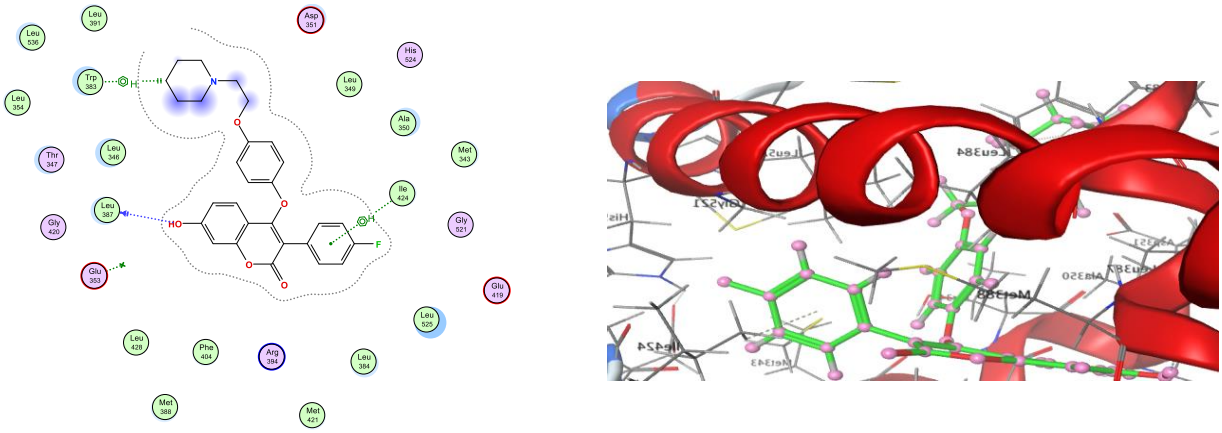
- **Ligand 42**: Exhibits hydrogen bonding with **LEU 387** (3.31 Å), **MET 343** (3.45 Å), and **ASP 351** (2.86 Å). Pi-H interactions are observed with **THR 347** and **ILE 424** (4.22 and 3.89 Å). *(Figure III. 8)*



(a) (b)

Figure. III-8: Molecular interactions of **ligand 42** with the estrogen receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

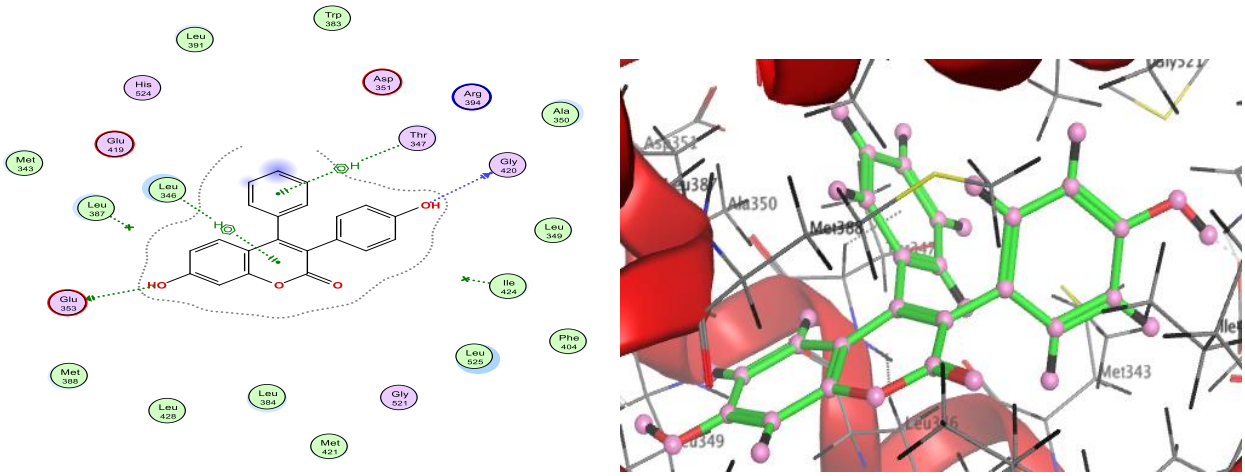
- **Ligand 51**: Forms hydrogen bonds with **LEU 387** (3.10 Å), **TRP 383** (H-Pi, 3.78 Å), and **ILE 424** (Pi-H, 3.77 Å). *(Figure III. 9)*



(a) (b)

Figure.III-9: Molecular interactions of **ligand 51** with the estragon receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

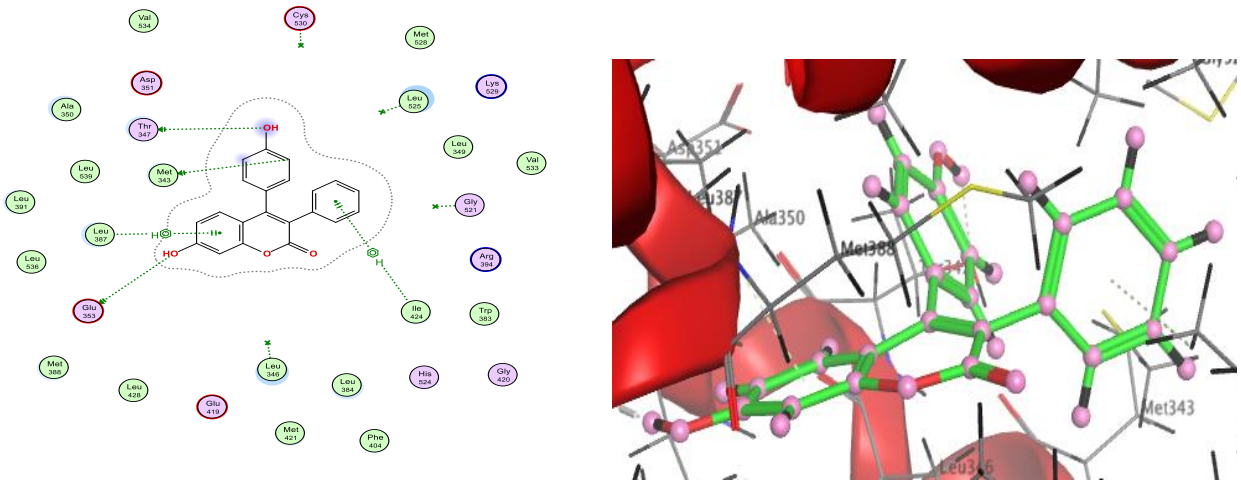
- **Ligand 56:** Forms hydrogen bonds with **GLU 353** and **GLY** 420 (2.70 and 3.06 Å), alongside Pi-H interactions with **LEU 346** and **THR 347** (4.75 and 4.55 Å). (*Figure III.12)*



(a) (b)

Figure.III-10: Molecular interactions of **ligand 56** with the estragon receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

- **Ligand 62:** Forms hydrogen bonds with **GLU 353** and **MET 343** and **THR 347**(2.85 and 3.57 and 3.29 Å), alongside Pi-H interactions with **LEU 387** and **ILE 424** (4.38 and 3.92 Å). (*Figure III.13*)



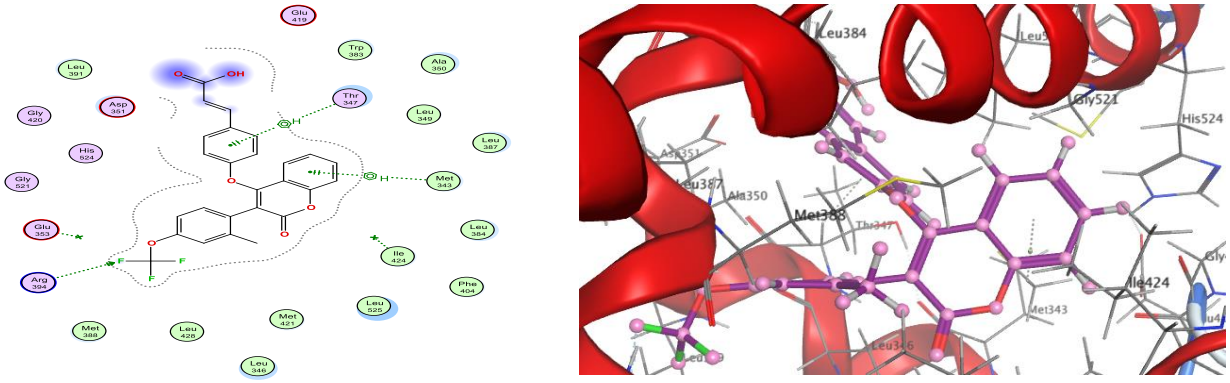
(a) (b)

Figure .III- 11: Molecular interactions of **ligand 62** with the estragon receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

- These findings suggest that the selected ligands exhibit strong binding affinity and stability within the active site of 3ERT, highlighting their potential as effective degraders targeting ERα.

Comparison with Literature-Reported Compounds

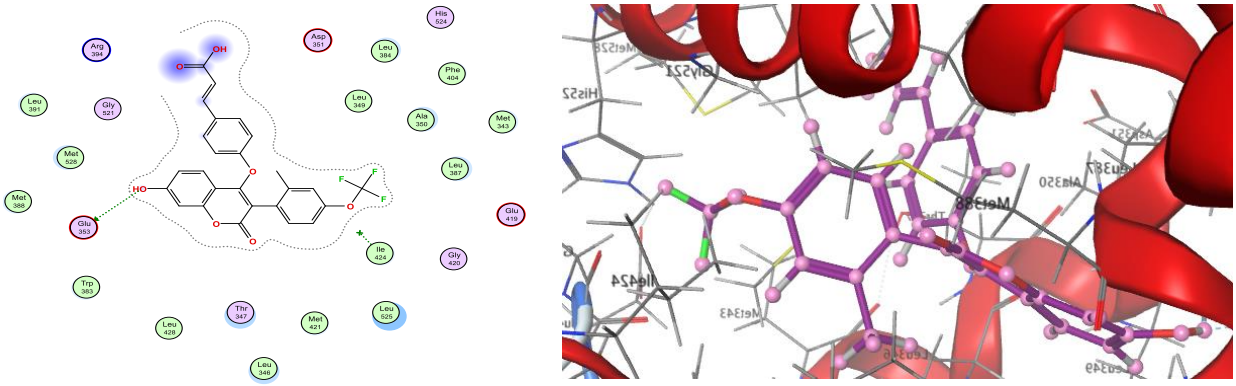
- **Ligand B (41**):** Forms hydrogen bonds with **ARG 394** (2.80 Å), alongside Pi-H interactions with **MET 343** and **THR 347** (4.30 and 4.67 Å). (*Figure III.10*)



(a) (b)

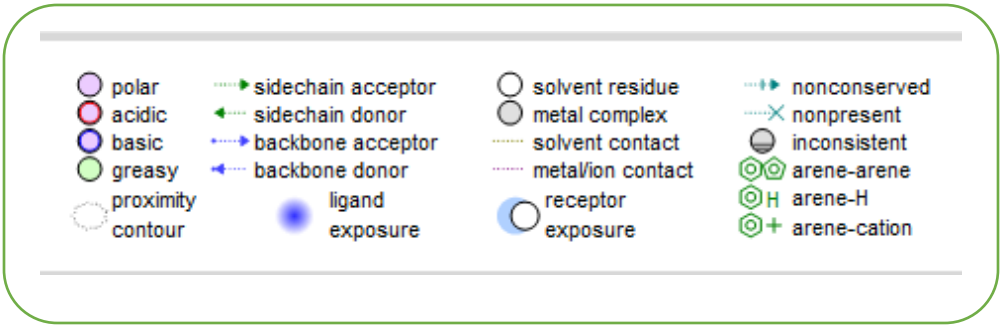
Figure.III-12: Molecular interactions of **ligand 41**** with the estragon receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)

- **Ligand A (44*)** : Forms hydrogen bonding with **GLU 353**(H-donor, 2.84 and 2.74 Å). (*Figure III.11*)



(a) (b)

Figure.III-13: Molecular interactions of **ligand 44*** with the estragon receptor alpha (ERα) (PDB: 3ERT) 2D (a) ;3D (b)



II. Evaluation of ADME-Toxicity prediction:

The ADMET properties of the top nine comarine derivatives based on docking results are summarized in Table III.2.

- **Absorption:**

Ligand **51,** had a **Caco-2** permeability value close to the desired threshold (**Caco-2 > -5.15**). None of the compounds were classified as **P-gp substrates** or **P-gp inhibitors**. Additionally, none of the compounds achieved **human intestinal absorption (HIA)**. Regarding **oral bioavailability**, compounds **23, 27, and 31** exhibited **F < 20%**, while compounds **19, 23, and 27** achieved **F < 30%**.

- **Distribution:**

All ligands had **plasma protein binding (PPB) values > 90%**, indicating strong binding to plasma proteins, which can reduce the free active drug fraction but may also prolong drug action. Only **ligand 1** met the **blood-brain barrier (BBB) permeability criteria** [1], while the rest did not. Regarding the **volume of distribution (VD)**:

- **VD < 0.07 L/kg**: High hydrophilicity
- **0.07–0.7 L/kg**: Even distribution
- **VD > 0.7 L/kg**: High lipophilicity

Ligands **2 and 51** were evenly distributed, while the remaining ligands were highly hydrophilic.

- **Metabolism:**

None of the ligands inhibited the enzymes **CYP1A2, CYP2C9 (substrate), or CYP3A4 (inhibitor)**. However:

- **CYP3A4 substrate**: Ligands **2, 31, and 51** were substrates, while the others were not.
- **CYP2C9 inhibitors**: All ligands except **2 and 51** were inhibitors.
- **CYP2C19 inhibitors:** Ligands **40** inhibitor, while ligand **2** was **not a substrate** for CYP2C19.

- **Excretion:**

All ligands had **half-life (T1/2) > 0.5h** and **clearance (CL) < 5 mL/min/kg**, comparable to **canertinib**.

- **Toxicity:**
    - All ligands were classified as **hepatotoxic (H-HT)**.
    - Ligands**19, 23, 27, 35, 40, 42, 56and 62** were **not HERG hormone blockers**, while the rest were.
    - Ligands **23 and 31** did not exhibit **Ames mutagenicity**.
    - **Acute lethal dose 50 (LD50) classification**:
        - **>500 mg/kg**: Low toxicity (**ligands 23,27, 35, and 40**)
        - **50–500 mg/kg**: Moderate toxicity
        - **<50 mg/kg**: High toxicity

Table III.2: ADME properties and drug-likeness of the 9 best degraders.

N°	Absorption						Distribution			MetabolismCYP450								Excretion		Toxicity			
	Caco-2 permeability	P-gp inhibitor	P-gp substrate	HIA	f-20%	f-30%	PPB%	BBB	VD(L/kg)	1A2-inhibitor	1A2-substrat	3A4-inhibitor	CYP3A4substrate	CYP2C9inhibior	CYP2C9substrate	CYP2C19inhibitor	CYP2C19substrate	T1/2(h)	CL(ml/min/kg)	hERG	HHT	AMES	LD50 (gk/gu005<)
2	-4.992	yes	yes	yes	yes	yes	97.3	-	0.323	---	---	---	+++	---	---	---	+++	0.557	4.682	0.958	0.715	0.306	0.618
19	-4.629	yes	yes	yes	NO	NO	99.0	---	-0.539	---	---	---	---	+++	---	-	---	1.139	2.722	0.093	0.932	0.378	0.347
23	-4.88	yes	yes	yes	NO	NO	97.8	---	-0.632	---	---	---	---	+++	---	---	---	1.249	1.869	0.067	0.8	0.221	0.109
27	-4.893	yes	yes	yes	NO	NO	98.2	---	-0.667	---	---	---	---	+++	---	---	---	1.305	1.922	0.103	0.782	0.317	0.093
31	-4.64	yes	yes	yes	NO	yes	99.5	---	-0.409	---	---	---	+	+++	---	---	---	1.111	1.933	0.429	0.957	0.076	0.434
35	-4.758	yes	yes	yes	NO	NO	98.5	---	-0.656	---	---	---	--	+++	---	--	---	1.357	0.952	0.087	0.879	0.406	0.292
40	-4.288	yes	yes	yes	NO	NO	99.1	---	-0.625	---	---	---	---	+++	--	+	---	1.186	1.372	0.137	0.886	0.343	0.219
42	-4.505	NO	yes	yes	yes	yes	99.1	---	-0.556	---	---	---	---	+++	---	--	---	1.296	1.367	0.128	0.916	0.4	0.373
51	-5.127	yes	yes	yes	yes	yes	98.0	---	0.253	---	---	---	+++	---	---	---	---	0.92	3.735	0.918	0.756	0.601	0.621
56	-4.925	yes	yes	yes	yes	yes	98.2	---	-0.5	+++	--	---	--	+++	---	-	---	1.024	3.818	0.2	0.54	0.41	0.389
62	-4.925	yes	yes	yes	yes	yes	98.1	---	0.583	+++	---	---	+	++	++	--	--	0.978	3.847	0.193	0.532	0.406	0.381

Tips:

- For the classification endpoints, the prediction probability values are transformed into six symbols: 0-0.1 (---), 0.1-0.3 (--), 0.3-0.5 (-), 0.5-0.7 (+), 0.7-0.9 (++), and 0.9-1.0 (+++).
- Additionally, the corresponding relationships of the three labels are as follows: excellent ; medium ; poor ;

CONCLUSION

CONCLUSION

The objective of this work was to search for a compound with properties that could achieve oral bioavailability in breast cancer and understand the interaction between comarine derivatives and the 3ERT receptors (**Pdb ID: 3ERT)** using docking. The docking results suggest that some of the compound's bonds may have the potential to inhibit ERα receptors.

Molecular docking results revealed that among all the comarine-derived compounds studied, **compounds 2, 19, 23, 27, 31, 35, 40, 42,51,56 and 62** showed a high affinity for the ERα target (Pdb ID: 3ERT), which was confirmed through the formation of strong hydrogen bonds and hydrophobic interactions with residues of the active site of the target. ADMET predictions for the selected compounds, composed of 9 comarine, based on docking results, indicated that compounds 1 and 90 have the most favorable pharmaceutical properties.

Molecular docking results revealed that among all the Coumarine-derived compounds studied, **compounds 2, 19, 23, 27, 31, 35, 40, 42,51,56 and 62** showed a high affinity for the ERα target **(Pdb ID: 3ERT)**, which was confirmed through the formation of strong hydrogen bonds and hydrophobic interactions with residues of the active site of the target. ADMET predictions for the selected compounds, consisting of 11 coumarin compounds based on docking results, indicated that compounds **2** and **51**have the most favorable pharmaceutical properties, promising oral bioavailability.

Finally, the integrated computational approach, which includes molecular docking, ADMET characterization, and drug-likeness prediction, provided a good and validated drug candidate, where our study showed that compounds**2** and **51** inhibit breast cancer.

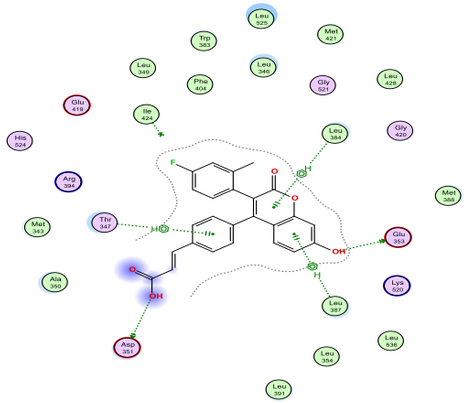
APPENDIX

Table A: Molecular docking results of all coumarin derivatives at the active site of the 3ERT protein.

Ligands	S score (kcal/mol)	RMSD (Å)	Bonding between atoms and active site residues					
			Atom of compounds	**Atom of receptor**	**Evolved receptor residue**	**Type of interaction bond**	**Distance (Å)**	**E (kcal/mol)**
Ref.	-6.4041	1.0328	N 47	NH_2	ARG 394	H-acceptor	2.27	-0.8
			6-ring	CD1	ILE 424	pi-H	4.11	-0.6
1	-8.7255	1.2168	O 17	OE2	GLU 353	H-donor	2.73	-5.9
			O 47	OD1	ASP 351	H-donor	2.92	-5.9
			6-ring	CA	THR 347	pi-H	4.67	-0.5
			6-ring	CD1	LEU 384	pi-H	4.06	-0.5
			6-ring	CD1	LEU 387	pi-H	4.23	-0.6
3	-9.5561	2.0755	O 17	OE2	GLU 353	H-donor	2.85	-5.5
			6-ring	CD1	LEU 387	pi-H	4.32	-0.5
			6-ring	CD1	ILE 424	pi-H	3.91	-0.5
4	-9.7177	1.7945	O 17	OE2	GLU 353	H-donor	2.86	-5.5
			6-ring	CD1	LEU 387	pi-H	4.41	-0.5
			6-ring	CD1	ILE 424	pi-H	3.94	-0.5
5	-9.3565	1.2481	O 17	OE2	GLU 353	H-donor	2.85	-5.5
			C 24	SD	MET 343	H-donor	3.66	-0.5
			6-ring	CD1	LEU 387	pi-H	4.44	-0.5
			6-ring	CD1	ILE 424	pi-H	3.87	-0.5
6	-9.7466	1.4924	O 17	OE2	GLU 353	H-donor	2.81	-5.7
			C24	SD	MET 343	H-donor	3.61	-0.5
			6-ring	CB	LEU 387	pi-H	4.34	-0.5
			6-ring	CD1	LEU 387	pi-H	4.42	-0.5
			6-ring	CD1	ILE 424	pi-H	3.97	-0.5
7	-9.7799	1.9845	O 17	OE2	GLU 353	H-donor	2.84	-5.6
			6-ring	CD1	LEU 387	pi-H	4.32	-0.5
			6-ring	CD1	ILE 424	pi-H	3.95	-0.5
8	-9.1543	1.5606	O 17	OE2	GLU 353	H-donor	2.84	-5.5
			6-ring	CD1	LEU 387	pi-H	4.33	-0.5
			6-ring	CD1	ILE 424	pi-H	3.92	-0.5
9	-9.5768	1.6517	O 17	OE2	GLU 353	H-donor	2.86	-5.4
			C 24	SD	MET 343	H-donor	3.62	-0.5
			6-ring	CD1	LEU 387	pi-H	4.41	-0.5
			6-ring	CD1	ILE 424	pi-H	3.91	-0.5
10	-9.0155	2.1324	O 17	OE2	GLU 353	H-donor	2.84	-5.5
			6-ring	CD1	LEU 387	pi-H	4.25	-0.5
			6-ring	CD1	ILE 424	pi-H	3.94	-0.5
11	-8.3396	1.7308	O 14	OE2	GLU 353	H-donor	2.77	-5.8
			O 37	OD1	ASP 351	H-donor	2.87	-5.4
			6-ring	CD1	LEU 384	pi-H	4.14	-0.5
			6-ring	CD1	LEU 387	pi-H	4.23	-0.5
12	-8.2937	2.5100	O 14	OE2	GLU 353	H-donor	2.71	-5.1
			C 43	O	GLU 419	H-donor	3.41	-0.5
			6-ring	CD1	LEU 346	pi-H	4.16	-0.5
			6-ring	CD1	ILE 424	pi-H	3.60	-0.5
13	-8.4455	1.7574	O 14	OE2	GLU 353	H-donor	2.77	-5.8
			O 37	OD1	ASP 351	H-donor	2.85	-5.6
			6-ring	CD1	LEU 384	pi-H	4.14	-0.5
			6-ring	CD1	LEU 387	pi-H	4.23	-0.5
14	-6.9315	1.5150	6-ring	6-ring	TRP 383	pi-pi	3.98	-0.0
15	-7.8018	1.4604	O 19	O	GLY 521	H-donor	3.01	-2.9
			CL 47	OE1	GLU 353	H-donor	3.52	-0.7
16	-8.0786	2.1230	O 18	OE2	GLU 353	H-donor	2.77	-5.7
			O 37	OD1	ASP 351	H-donor	2.87	-6.2
17	-6.9013	2.1033	/	/	/	/	/	/
18	-8.3480	1.3720	O 35	OD1	ASP 351	H-donor	2.85	-6.0
			O 46	OE2	GLU 353	H-donor	2.71	-5.9
			6-ring	CD1	GLU 353	pi-H	4.04	-0.5
20	-7.0943	2.2700	O 46	OD1	ASP 351	H-donor	3.02	-4.0
			6-ring	CA	THR 347	pi-H	4.28	-0.5
21	-7.1600	2.0160	O 39	O	ASP 351	H-donor	3.30	-0.5
22	-8.1894	1.9158	O 38	OE2	GLU 353	H-donor	2.70	-5.9
24	-8.0397	0.8230	O 38	O	GLY 521	H-donor	3.27	-1.5
			CL 48	OE1	GLU 353	H-donor	3.44	-0.9
			6-ring	CD1	LEU 346	pi-H	4.18	-0.5
			6-ring	CA	THR 347	pi-H	2.32	-0.5
25	-7.4177	2.2190	O 38	OE2	GLU 353	H-donor	2.61	-2.4
			O 46	OD1	ASP 351	H-donor	3.81	-6.0
			6-ring	CA	THR 347	pi-H	4.35	-0.5
			6-ring	CB	LEU 387	pi-H	4.54	-0.5
26	-8.0633	1.8120	O 38	OE2	GLU 353	H-donor	2.70	-4.0
			O 46	OD1	ASP 351	H-donor	2.98	-4.4
			6-ring	CA	THR 347	pi-H	4.20	-0.5
			6-ring	CD1	LEU 384	pi-H	4.32	-0.5

28	-8.3790	1.4597	O 38	OE2	GLU 353	H-donor	2.62	-5.2
			O 46	OD1	ASP 351	H-donor	2.82	-5.9
			6-ring	CA	THR 347	pi-H	4.32	-0.5
29	-7.0950	2.1263	C 32	SD	MET 343	H-donor	3.67	-0.5
			6-ring	6-ring	TRP 383	pi-pi	3.91	-0.0
30	-6.8543	1.9017	C 32	SD	MET 522	H-donor	3.77	-0.9
			C 40	SD	MET 343	H-donor	3.81	-0.6
			6-ring	CB	LEU 525	pi-H	3.76	-0.6
32	-8.8304	1.7612	O 49	OE2	GLU 353	H-donor	2.86	-5.4
			6-ring	CD1	LEU 387	pi-H	4.24	-0.5
			6-ring	CD1	ILE 424	pi-H	3.96	-0.5
33	-9.0620	1.4664	O 40	OE2	GLU 353	H-donor	2.78	-5.2
			6-ring	CD1	ILE 424	pi-H	3.67	-0.5
34	-8.7686	2.1263	O 39	O	GLY 521	H-donor	3.28	-1.3
36	-8.5879	1.3076	C 25	SD	MET 343	H-donor	3.79	-0.5
			O 36	OE2	GLU 353	H-donor	2.72	-5.9
			6-ring	CD1	ILE 424	pi-H	3.87	-0.6
37	-8.4141	1.5460	O 39	OE2	GLU 353	H-donor	2.68	-5.8
			6-ring	CD1	ILE 424	pi-H	3.83	-0.5
38	-7.2509	1.2288	O 35	OG1	THR 347	H-donor	3.26	-0.6
39	-7.1713	1.7568	C 1	SD	MET 343	H-donor	3.65	-0.5
			6-ring	CB	LEU 525	pi-H	4.77	-0.5
43	-8.9242	1.3929	O 14	OE2	GLU 353	H-donor	2.71	-5.1
			C 43	O	GLU 419	H-donor	3.41	-0.5
			6-ring	CD1	LEU 346	pi-H	4.16	-0.5
			6-ring	CD1	ILE 424	pi-H	3.60	-0.5
45	-8.6718	1.9878	O 14	OE2	GLU 353	H-donor	2.66	-5.3
46	-8.9885	1.0563	O 14	OE2	GLU 353	H-donor	2.75	-5.8
			6-ring	CB	LEU 387	pi-H	4.09	-0.5
47	-8.9989	1.3577	O 14	O	GLY 521	H-donor	3.40	-0.9
			O 46	OE2	GLU 353	H-donor	2.81	-5.2
			6-ring	CD1	LEU 346	pi-H	4.27	-0.5
			6-ring	CA	THR 347	pi-H	4.39	-0.5
48	-9.5768	1.6517	O 37	OE2	GLU 353	H-donor	2.76	-5.8
			6-ring	CB	LEU 387	pi-H	4.53	-0.5
			6-ring	CD1	ILE 424	pi-H	3.73	-0.5
49	-8.9894	1.8144	O 44	O	GLY 521	H-donor	3.32	-1.3
			O 60	O	LEU 387	H-donor	3.07	-1.3
			6-ring	CD1	LEU 346	pi-H	4.24	-0.5
50	-9.7834	1.4191	O 37	OE2	GLU 353	H-donor	2.77	-5.8
			C 53	6-ring	TRP 383	pi-H	3.73	-0.7
52	-9.9030	1.0128	O 45	OE2	GLU 353	H-donor	2.78	-5.8
			6-ring	CB	LEU 387	pi-H	4.50	-0.5
53	-8.1065	1.7739	6-ring	CB	LEU 387	pi-H	4.52	-0.5
54	-7.7910	1.2917	C 27	SD	MET 343	H-donor	3.77	-0.5
			6-ring	CD1	LEU 384	pi-H	4.16	-0.6
55	**-6.75011**	**0.7182**	**O29**	**OE2**	**GLU 353**	**H-donor**	**2.80**	**-5.7**
			6-ring	**CB**	**LEU 387**	**pi-H**	**4.44**	**-0.5**
			6-ring	**CD1**	**ILE 424**	**pi-H**	**3.88**	**-0.6**
57	-6.8553	0.6456	O19	O	GLY 420	H-donor	3.26	-0.7
			O31	OE2	GLU 353	H-donor	2.76	-5.5
			6-ring	CE	MET343	pi-H	4.49	-0.7
			6-ring	CD1	LEU 387	pi-H	4.26	-0.5
58	-6.6522	0.9064	C8	SD	MET421	H-donor	3.76	-0.5
			O 18	O	GLY 42	H-donor	2.27	-0.6
			O29	OE2	GLU 353	H-donor	2.75	-5.4
			6-ring	CE	MET343	pi-H	4.46	-0.7
			6-ring	CD1	LEU 387	pi-H	4.29	-0.5
59	-6.3465	1.0541	O18	O	GLY 420	H-donor	3.07	-1.3
			C23	OE1	GLU 353	H-donor	3.15	-0.5
			6-ring	CE	MET343	pi-H	4.45	-0.7
60	-7.0560	2.1394	O37	OE2	GLU 353	H-donor	3.10	-3.3
			6-ring	CG2	THR 347	pi-H	4.47	-0.5
			6-ring	CD1	LEU 387	pi-H	4.11	-0.5
			6-ring	CD2	LEU 525	pi-H	4.29	-1.0
61	-7.1971	1.3659	6-ring	CA	THR 347	pi-H	4/37	-0.5
			6-ring	CB	ALA 350	pi-H	4.71	-0.5
			6-ring	CD1	LEU 384	pi-H	3.86	-0.5
63	-7.3536	0.9682	O38	O	GLY 521	H-donor	3.38	-1.0
			C44	OE1	GLU 353	H-donor	3.11	-0.6
			6-ring	CD1	LEU 346	pi-H	4.28	-0.5
			6-ring	CA	THR 347	pi-H	4.40	-0.5
64	-8.1410	1.1477	O16	OE2	GLU353	H-donor	2.79	-5.7
			C20	SD	MET343	H-donor	3.62	-0.5
			O39	OG1	THR 347	H-donor	3.29	-0.5
			6-ring	CD1	LEU 387	pi-H	4.35	-0.5

65	-7.6429	1.2554	C8	SD	MET 343	H-donor	3.86	-0.5
			C49	SG	CYS 530	H-donor	3.85	-1.0
			6-ring	CA	THR 347	pi-H	4.32	-0.5
			6-ring	CD2	LEU 525	pi-H	3.92	-0.5
66	-9.0683	1.9115	C1	OE2	GLU353	H-donor	3.18	-5.3
			O18	OE2	GLU353	H-donor	2.89	-0.5
			C40	SD	MET343	H-donor	3.75	-0.5
			6-ring	CD1	LEU 387	pi-H	4.39	-0.5
			6-ring	CD1	ILE 424	pi-H	4.03	-0.5
67	-7.2321	1.4406	6-ring	CE	MET 343	pi-H	4.53	-0.7
			6-ring	CD1	LEU346	pi-H	4.13	-0.5
			6-ring	CA	THR 347	pi-H	4.27	-0.5
68	-6.1131	1.6671	O32	SD	MET343	H-donor	3.01	-1.0
			O34	EO2	GLU353	H-donor	3.07	-3.8
			6-ring	CB	LEU 387	pi-H	4.54	-0.5
69	-7.1357	1.8976	N14	OD1	ASP 351	H-donor	3.38	-1.4
			6-ring	CG	LEU 536	pi-H	3.99	-0.5
70	-7.5418	1.0890	C18	OE1	GLU353	H-donor	3.11	-0.5
			C35	SD	MET343	H-donor	3.47	-0.5
			6-ring	CB	LEU 387	pi-H	4.34	-0.6
71	-6.0339	1.5862	O19	OE1	GLU 353	H-donor	2.90	-3.4
			O19	OE2	GLU 353	H-donor	2.88	-3.2
			O35	O	GLY 420	H-donor	2.57	-1.9
72	-6.5382	0.9559	O17	OE2	GLU353	H-donor	3.49	-0.6
			C20	SD	MET343	H-donor	4.04	-0.5
73	-6.4718	1.7836	6-ring	6-ring	TRP 383	pi-pi	3.68	-0.0
74	-7.1412	1.2231	6-ring	CD1	ILE 424	pi-H	4.30	-0.6
			6-ring	CD1	LEU 525	pi-H	3.84	-0.5
75	-6.7484	1.0158	C12	OE2	GLU 353	H-donor	3.28	-0.5
			O36	O	LEU 387	H-donor	3.22	-1.0
			6-ring	CB	LEU 346	pi-H	4.23	-0.6
76	-7.8648	0.7528	C29	SG	CYS 530	H-donor	4.90	-0.6
			O36	SG	CYS 530	H-donor	3.24	-7.7
			6-ring	CA	THR 347	pi-H	4.45	-0.5
77	-6.7364	0.8968	C7	SD	MET 343	H-donor	3.90	-0.5
			6-ring	CA	THR 347	pi-H	4.33	-0.6
			6-ring	CD2	LEU 525	pi-H	3.92	-0.5
78	-6.1648	1.3891	C38	SG	CYS 530	H-donor	4.20	-0.8
			6-ring	CD1	LEU 346	pi-H	4.33	-0.6
79	-6.2790	1.0844	C7	SD	MET 343	H-donor	3.39	-0.6
			6-ring	CD1	LEU 346	pi-H	4.40	-0.5
80	-6.4762	1.4500	O30	O	LEU 346	H-donor	3.23	-1.5
			6-ring	CD1	ILE 424	pi-H	3.80	-0.7
81	-6.8071	1.2572	O16	OE2	GLU 353	H-donor	2.81	-5.5
			6-ring	CD1	LEU 387	pi-H	4.45	-0.5
82	-7.5450	2.9769	C7	SD	MET 343	H-donor	3.67	-0.6
			CL43	OE1	GLU 353	H-donor	3.35	-0.6
			6-ring	CA	THR 347	pi-H	4.23	-0.5
83	-7.6727	1.4400	C12	SD	MET 343	H-donor	3.76	-0.8
			N42	N	LEU 536	H-acceptor	3.39	-1.8
			6-ring	6-ring	TRP 383	pi-H	3.86	-0.0
84	-6.9005	1.2432	O 34	NH2	ARG 394	H-acceptor	2.77	-5.0
			6-ring	CE	MET 343	pi-H	4.25	-0.7
85	-7.6196	1.0222	6-ring	CB	LEU 387	pi-H	4.53	-0.8
			6-ring	CD1	ILE 424	pi-H	3.38	-0.5
86	-8.1435	1.3891	6-ring	CA	THR 347	pi-H	4.02	-0.5
			6-ring	CD1	ILE 424	pi-H	3.92	-0.6
87	-6.6369	2.0626	C12	SD	MET 343	H-donor	3.67	-1.0
			6-ring	6-ring	TRP 383	pi-pi	3.81	-0.0
88	-7.5505	2.0310	C1	SD	MET 343	H-donor	3.93	-0.5
			O56	SG	CYS 530	H-donor	3.44	-6.9
89	-6.0763	0.6462	O27	OE2	GLU 353	H-donor	2.82	-1.4
90	-6.9930	1.0198	O17	O	GLY 521	H-donor	3.26	-1.5
			CL41	OE1	GLU 353	H-donor	3.36	-1.0
			6-ring	CD1	LEU346	pi-H	4.32	-0.5
91	-6.9962	1.5454	C8	SD	MET 343	H-donor	3.88	-0.7
			C29	SD	MET 343	H-donor	3.49	-0.5
			6-ring	CD1	PHE 404	pi-H	4.45	-0.5
92	-6.1454	0.4962	O17	OE2	GLU 353	H-donor	2.87	-5.4
			6-ring	CD1	LEU 387	pi-H	4.34	-0.5
93	-7.6239	1.3208	C4	SD	MET 343	H-donor	3.65	-0.5
			O47	OE2	GLU 353	H-donor	2.82	-4.6
			6-ring	CB	LEU 346	pi-H	3.79	-0.6
94	-8.8068	1.6027	C5	OE2	GLU 353	H-donor	3.31	-0.6
			C28	SD	MET 343	H-donor	3.74	-1.5
			O31	O	LEU 387	H-donor	2.89	-0.5
			6-ring	CD1	LEU 387	pi-H	4.43	-0.5
			6-ring	CD1	ILE 424	pi-H	4.02	
95	-6.8070	1.5361	C37	SG	CYS 530	H-donor	4.02	-0.7
			6-ring	CD1	LEU 346	pi-H	4.48	-0.6
96	-7.4090	1.5904	C14	SD	MET 343	H-donor	3.65	-0.5
			O30	O	LEU 387	H-donor	2.88	-0.9
97	-6.5661	2.3501	6-ring	CA	THR 347	pi-H	4.17	-0.6
			6-ring	N	CYS 530	pi-H	4.37	-0.6
98	-6.1470	0.9214	C16	OE1	GLU 353	H-donor	3.25	-0.6
			6-ring	CD1	ILE 424	pi-H	4.05	-0.5
99	-7.7704	1.0262	6-ring	CA	THR 347	pi-H	4.09	-0.5
			6-ring	CD1	ILE 424	pi-H	3.93	-0.7
100	/	/	/	/	/	/	/	/
101	-7.0763	2.0310	O 17	O	GLY 521	H-donor	3.26	-1.5
			CL 41	OE1	GLU 353	H-donor	3.36	-1.0
			6-ring	CD1	LEU 346	pi-H	4.32	-0.5



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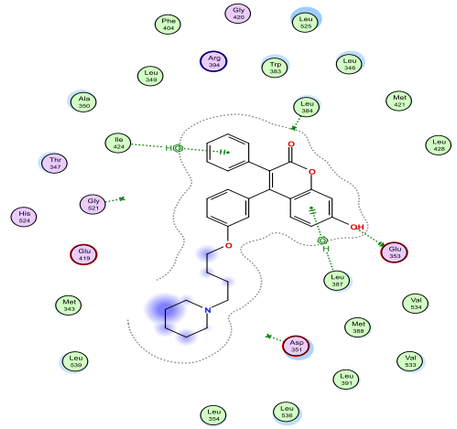

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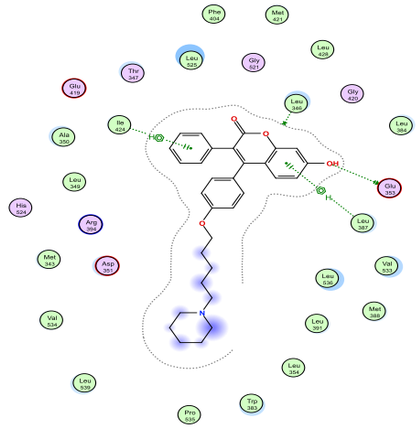

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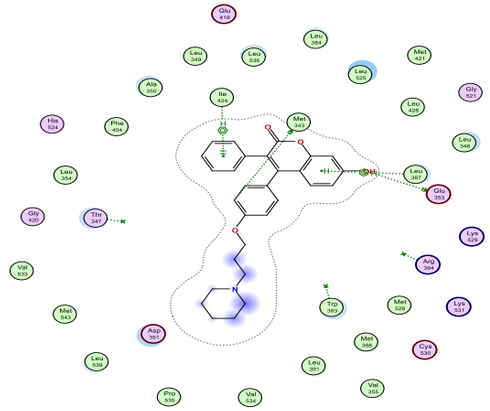

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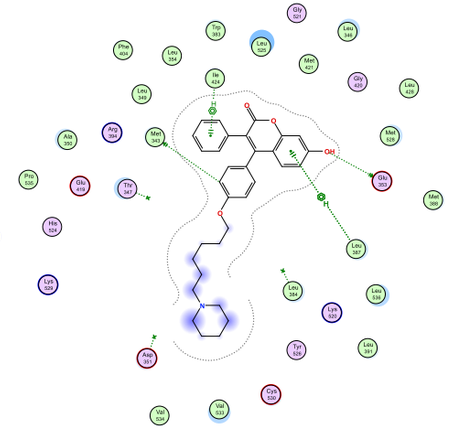

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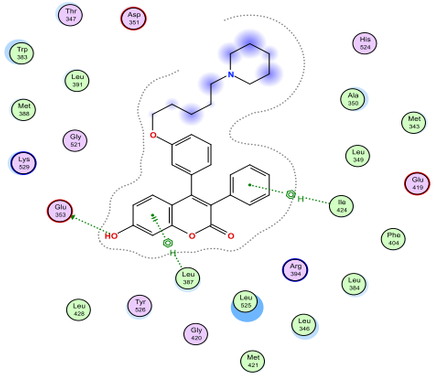

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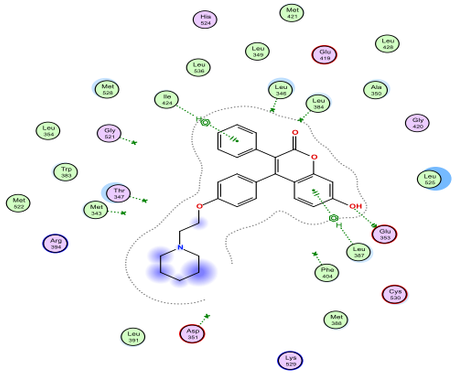

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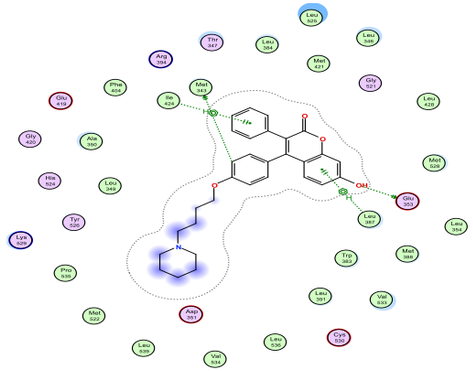

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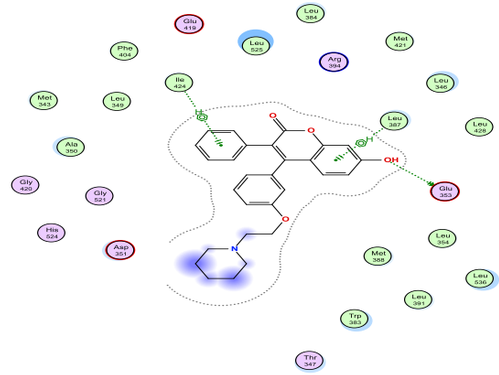

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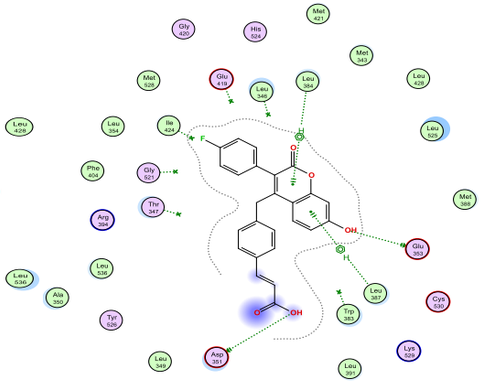

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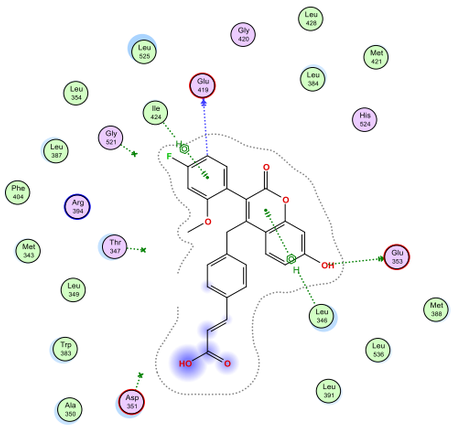

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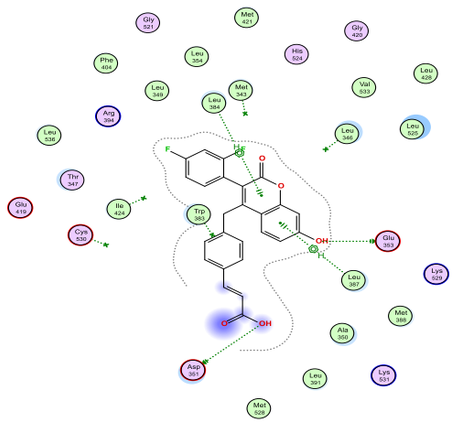

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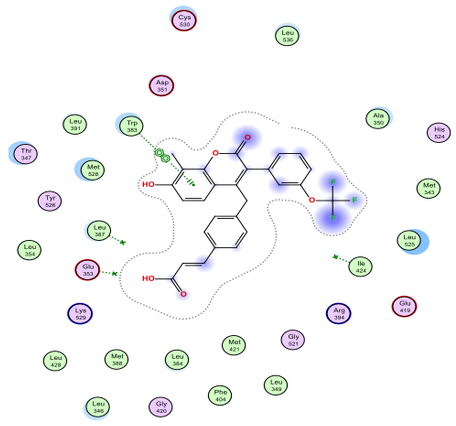

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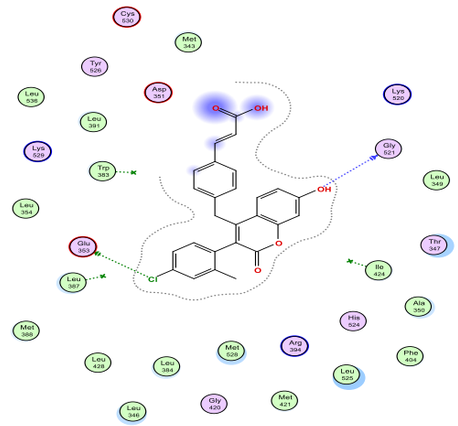

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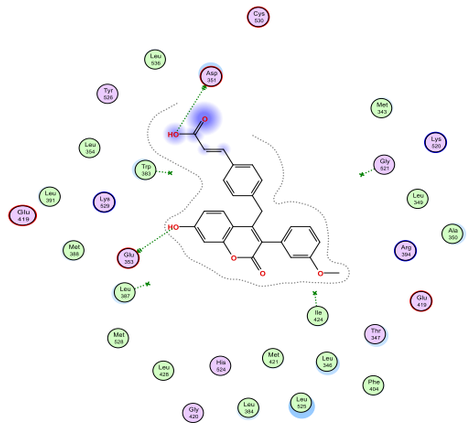

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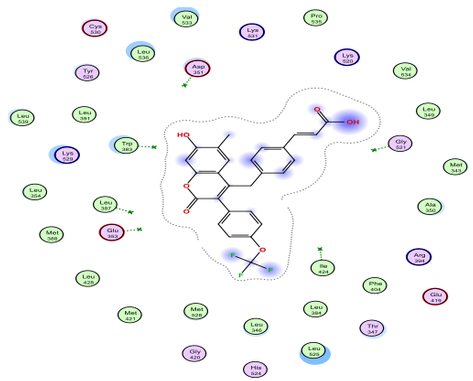

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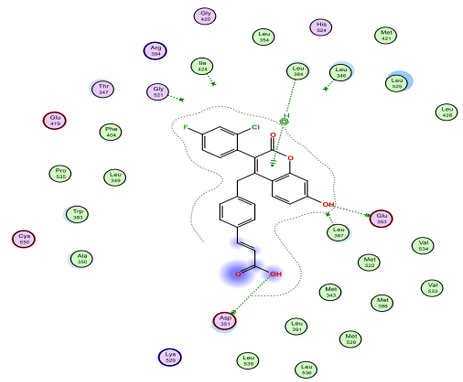

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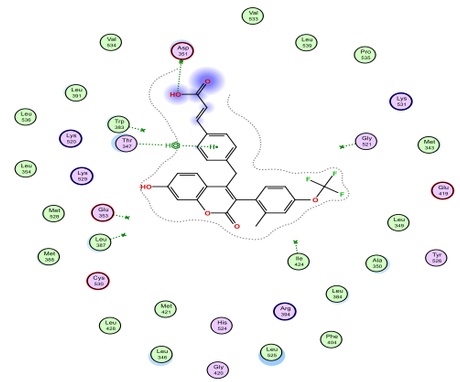

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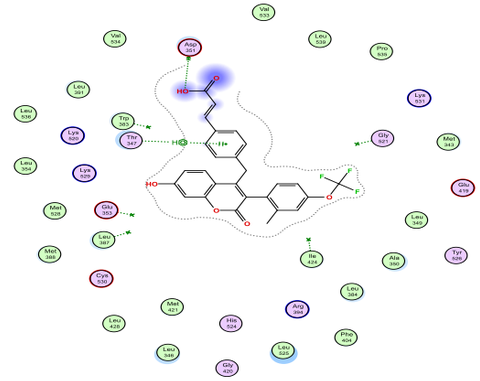

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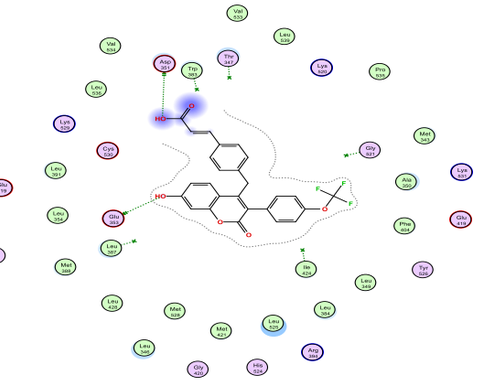

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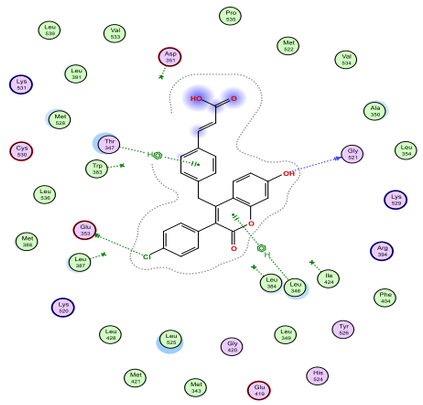

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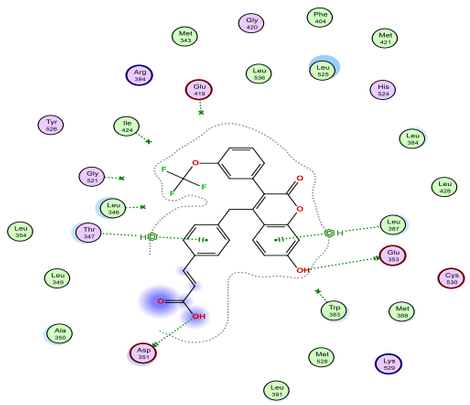

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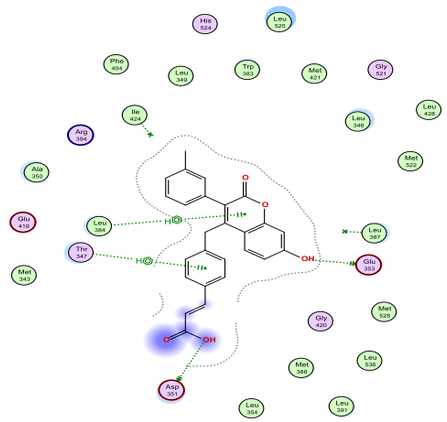

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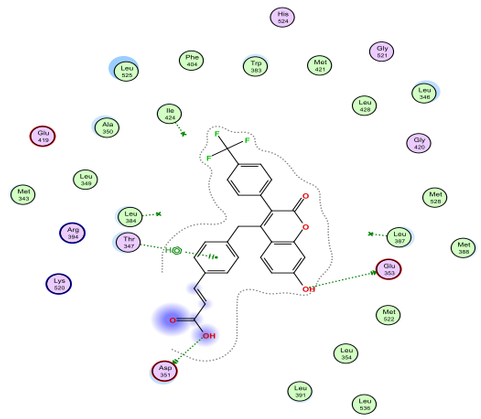

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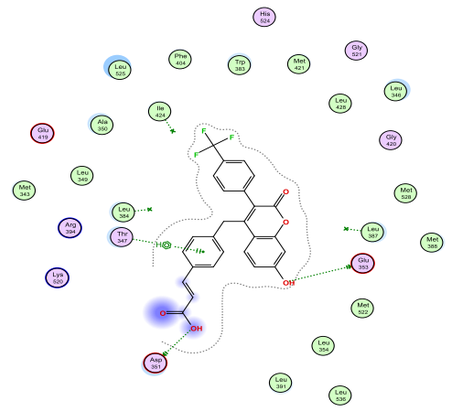

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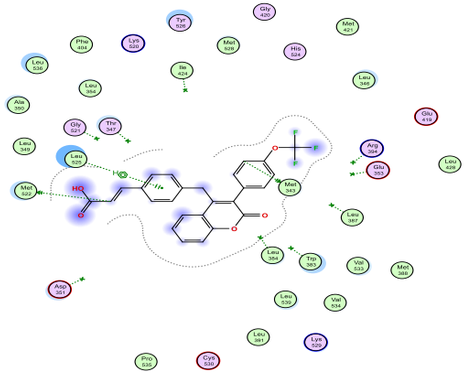

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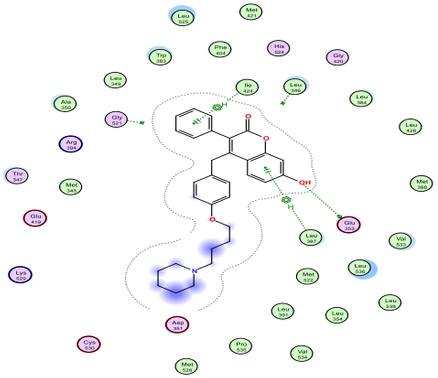

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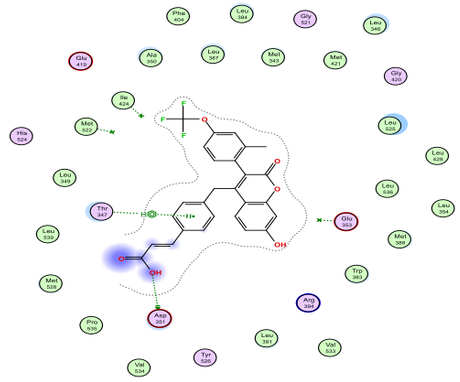

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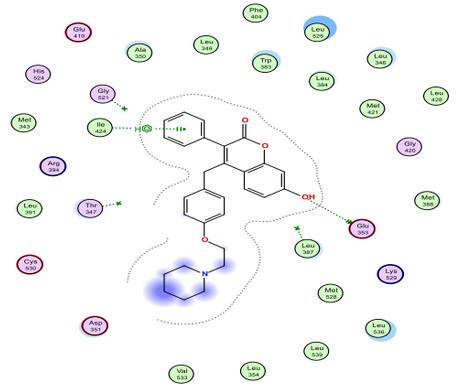

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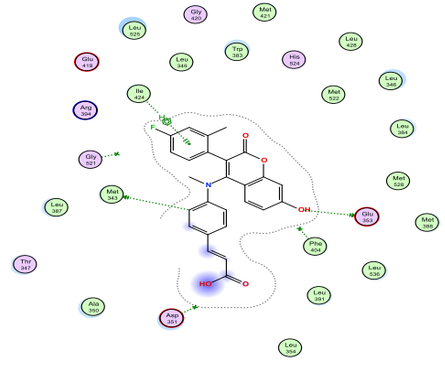

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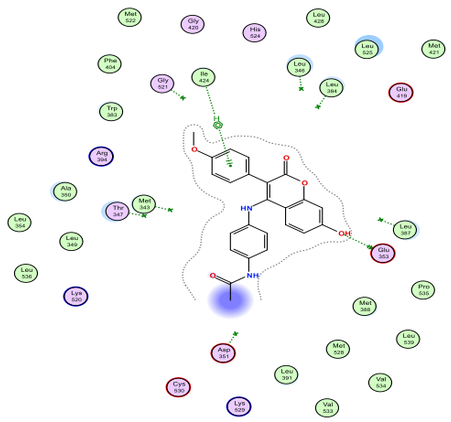

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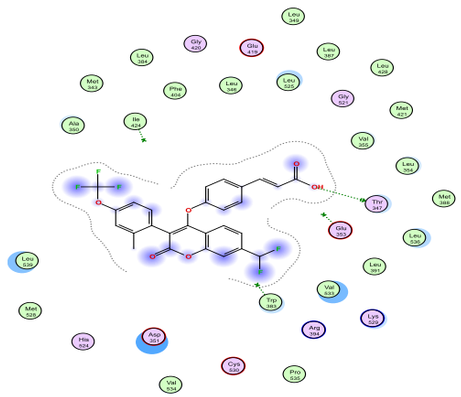

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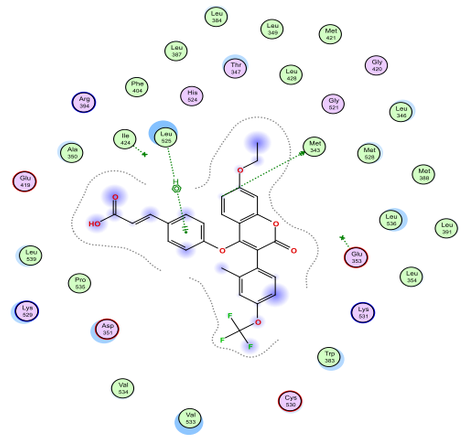

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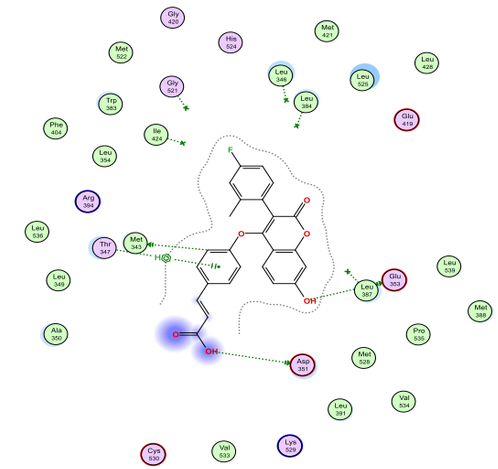

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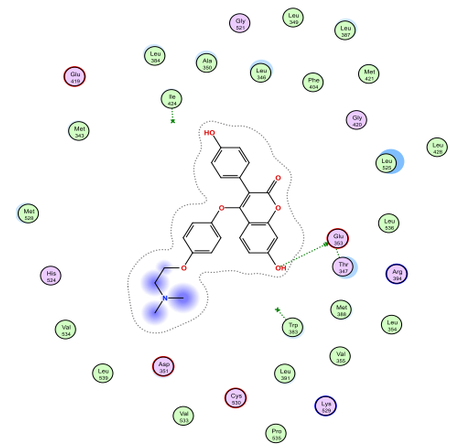

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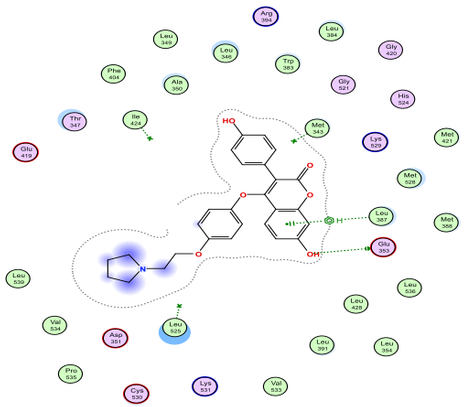

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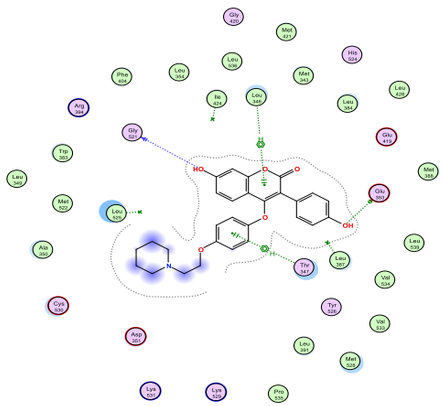

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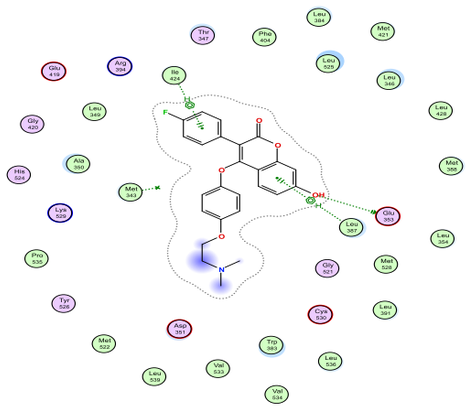

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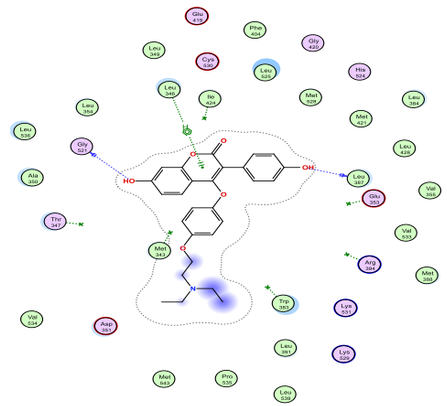

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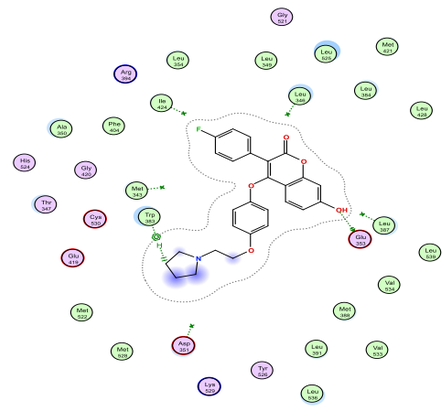

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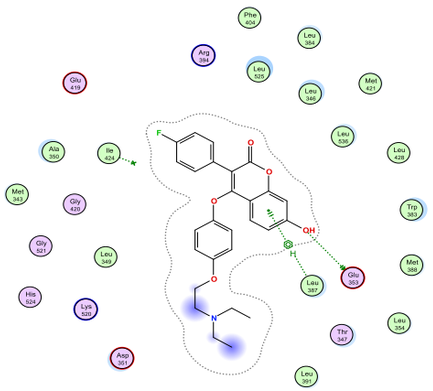

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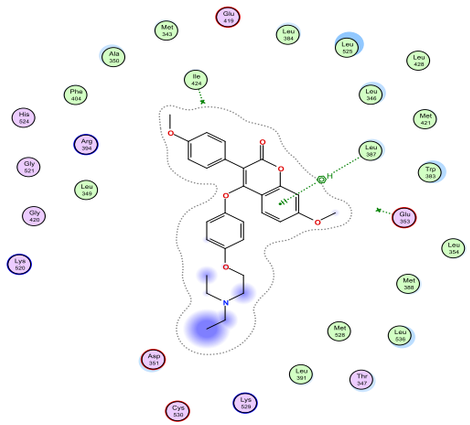

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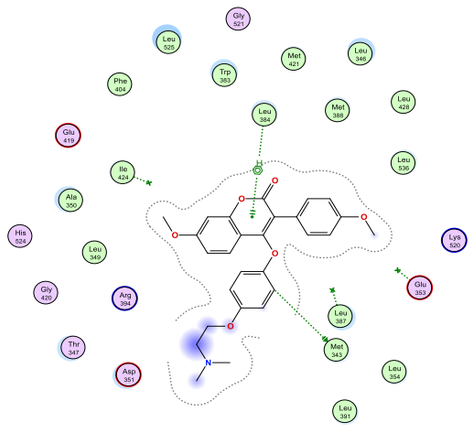

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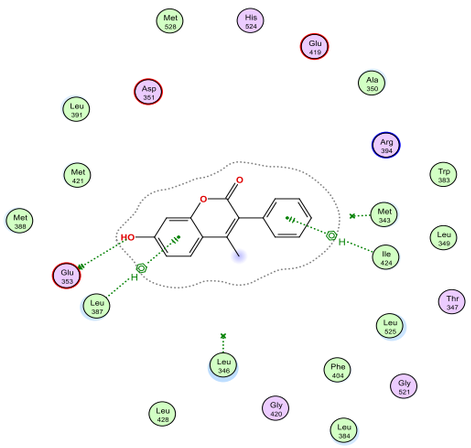

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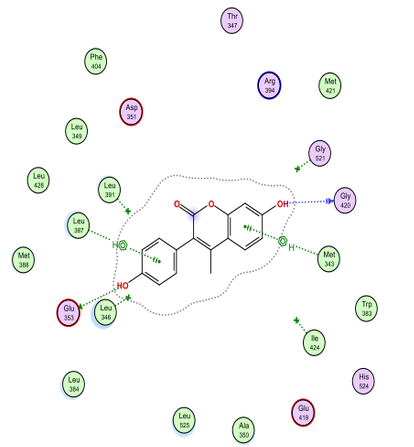

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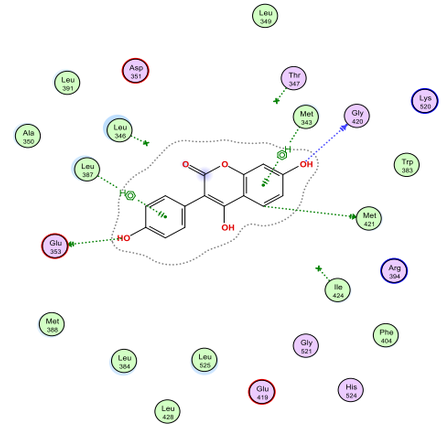

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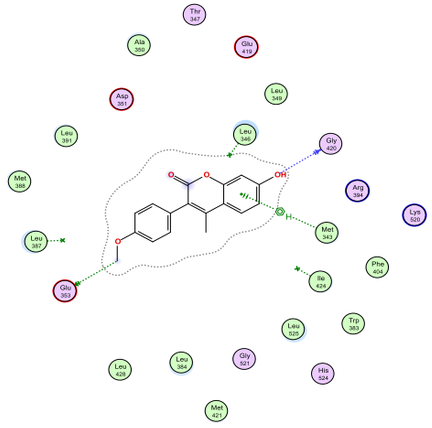

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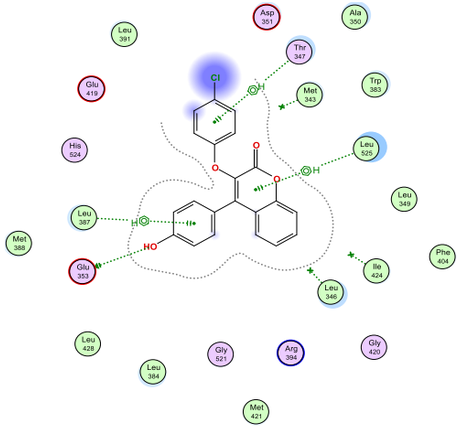

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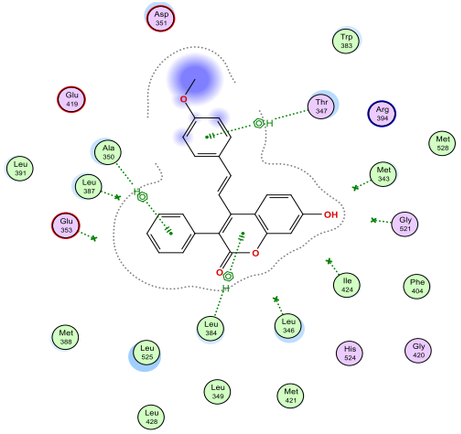

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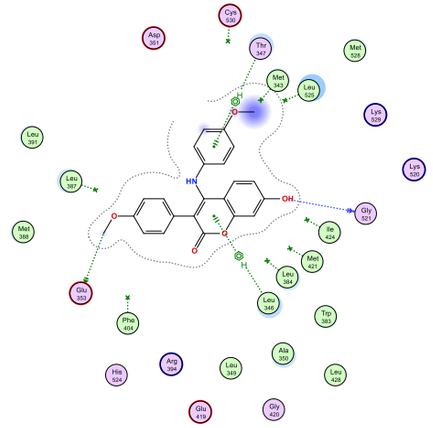

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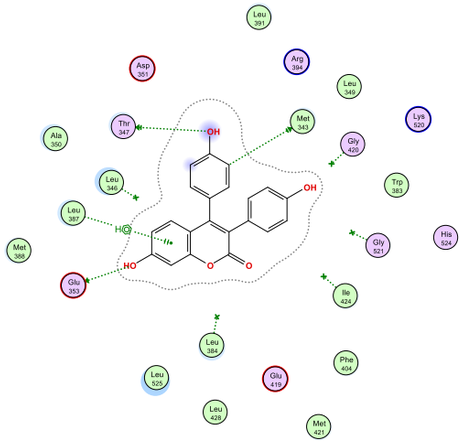

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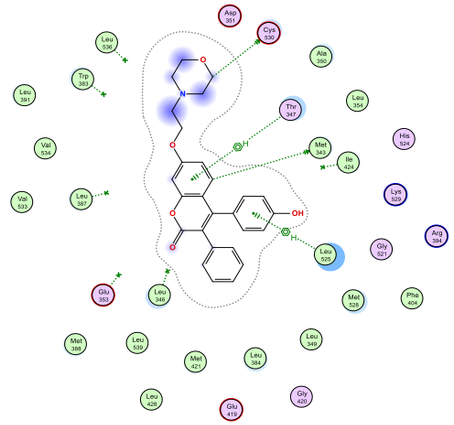

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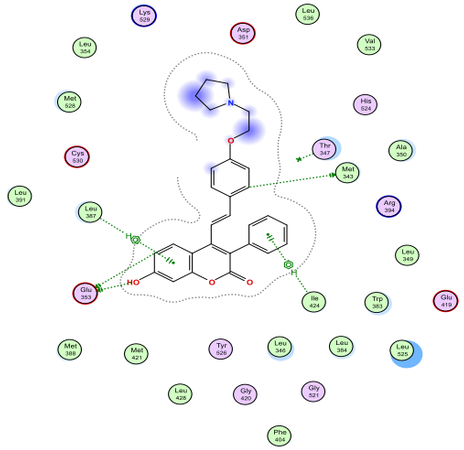

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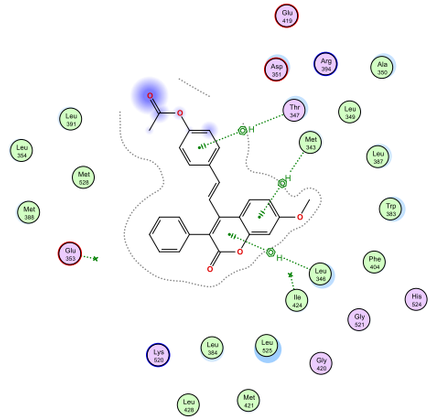

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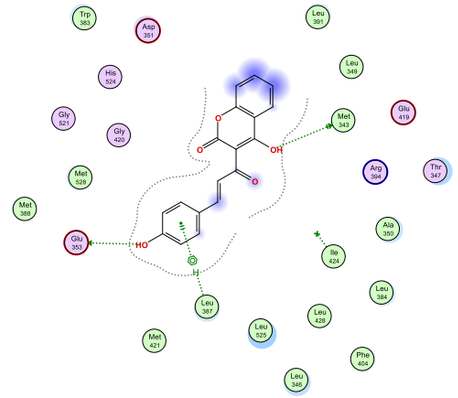

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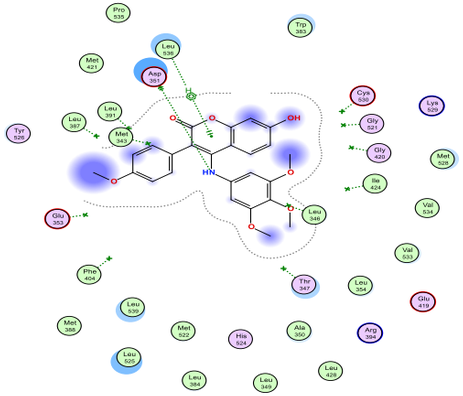

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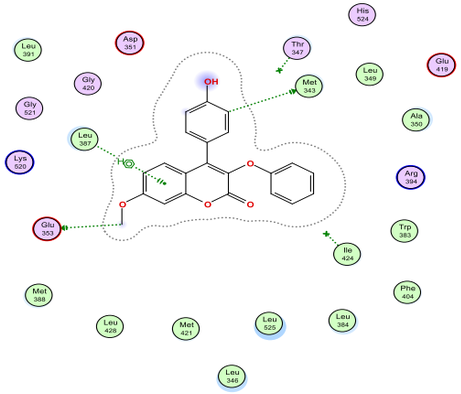

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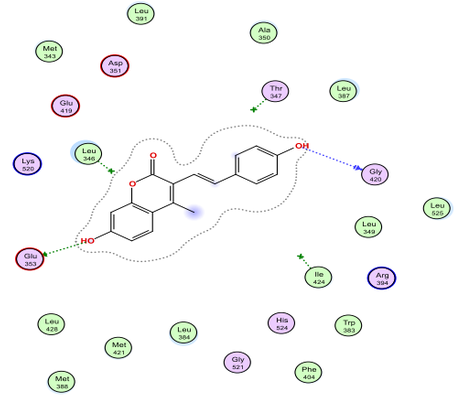

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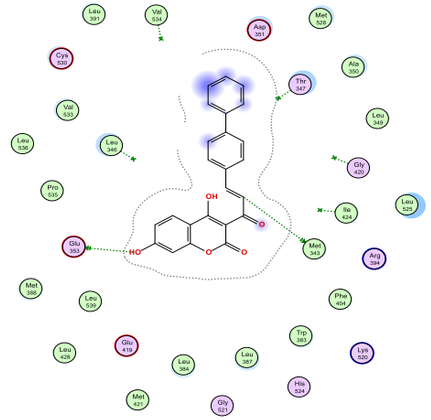

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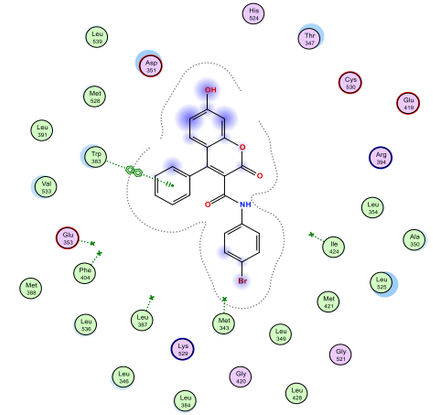

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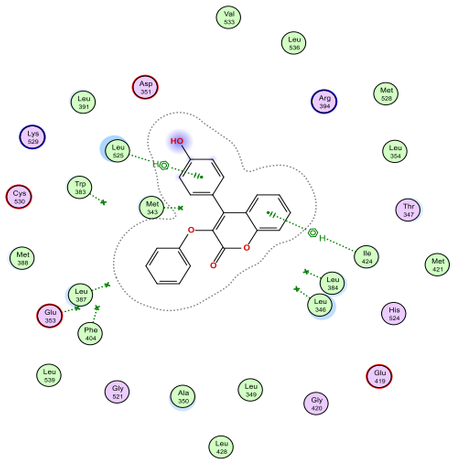

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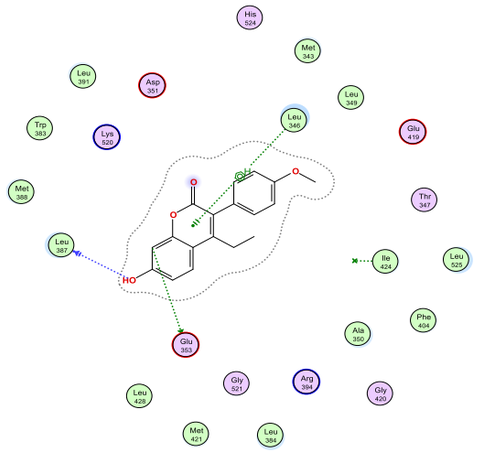

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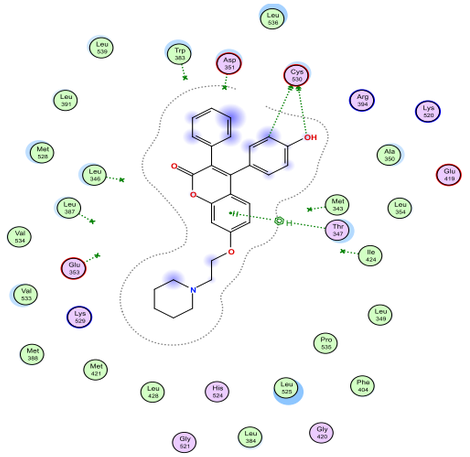

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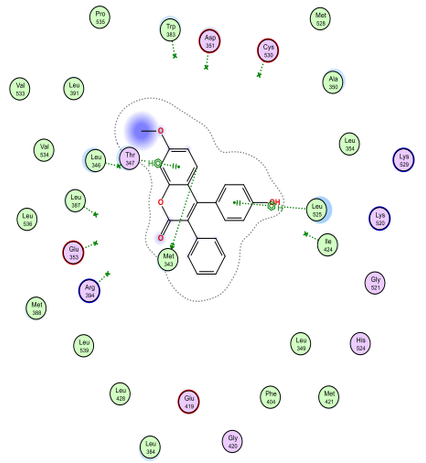

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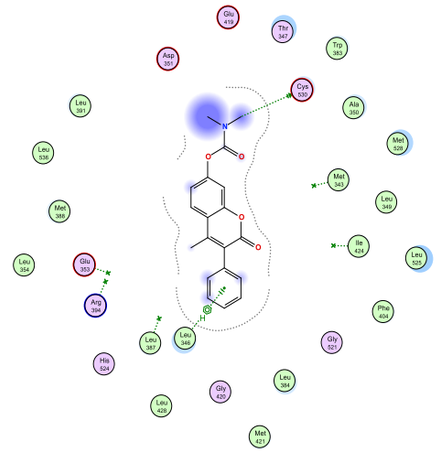

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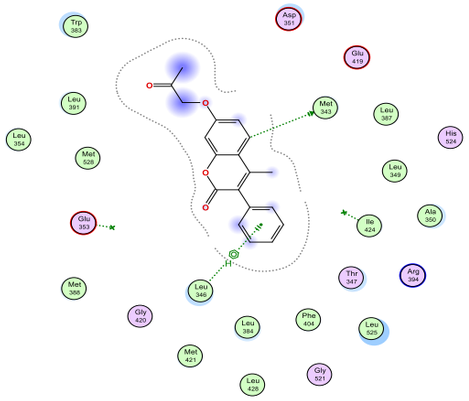

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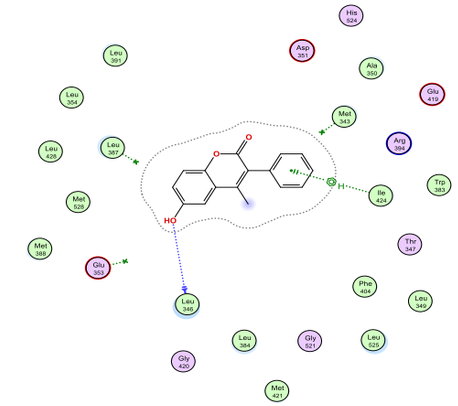

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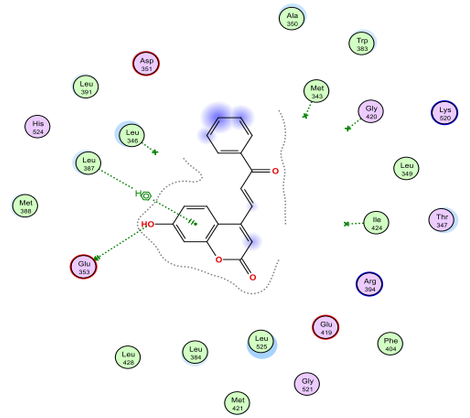

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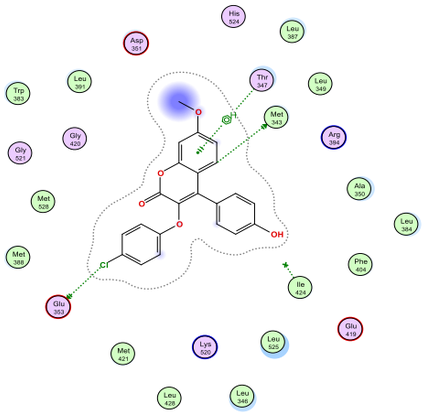

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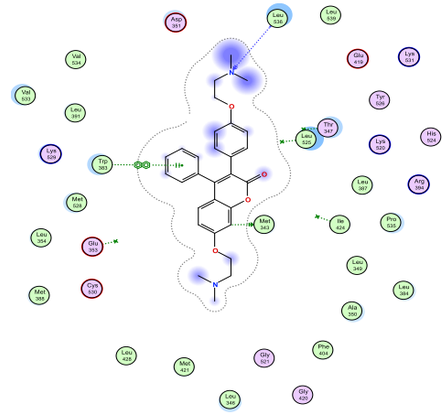

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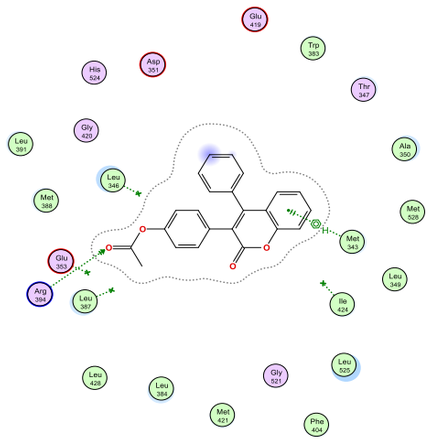

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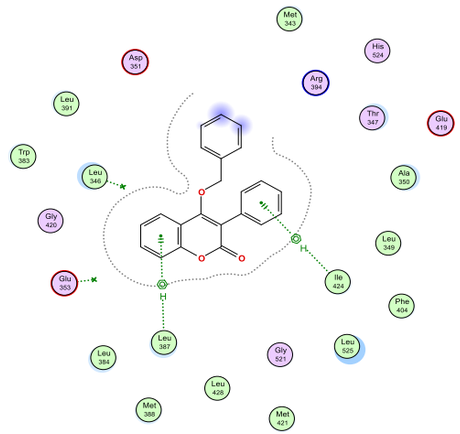

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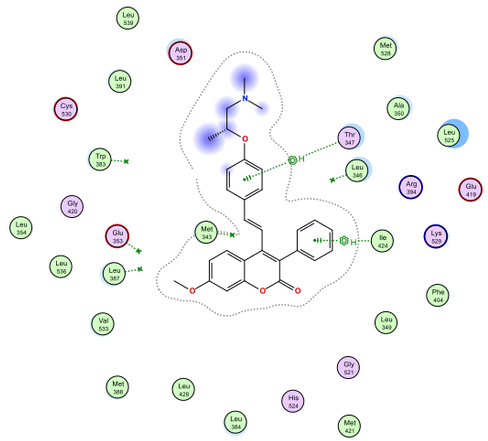

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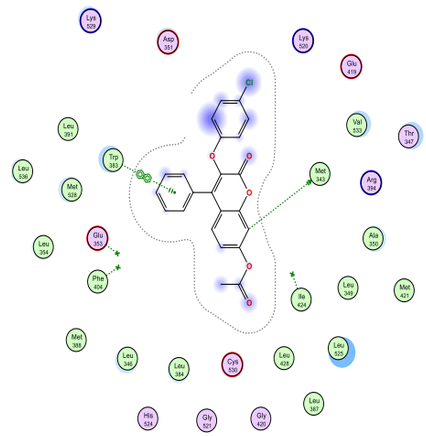

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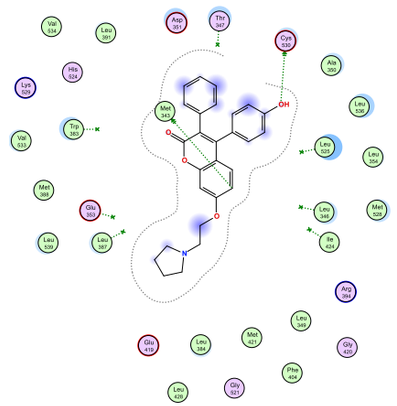

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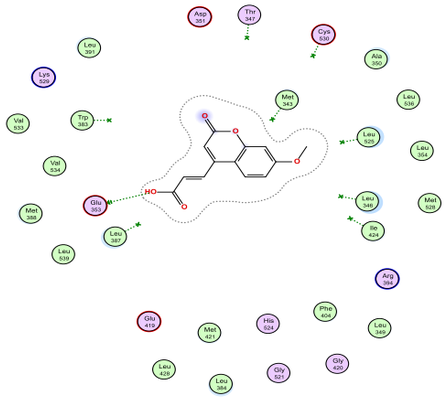

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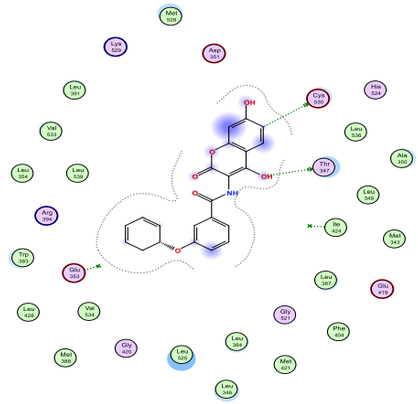

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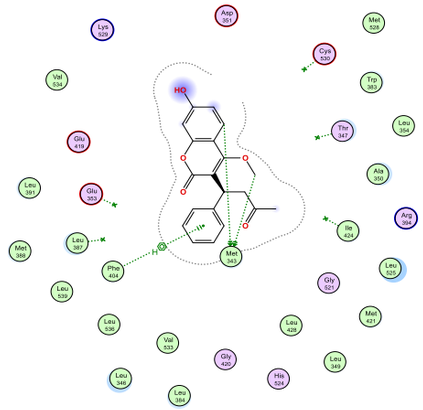

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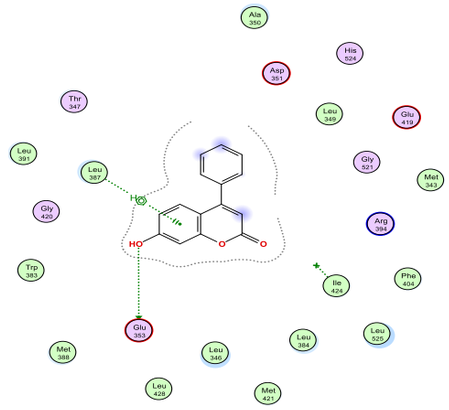

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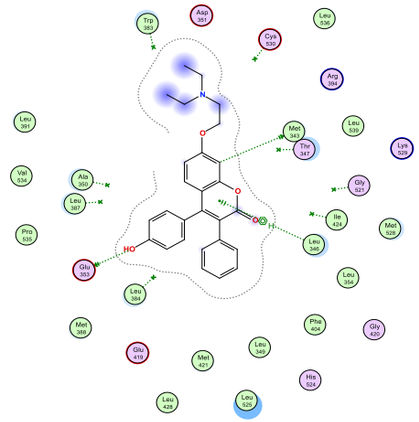

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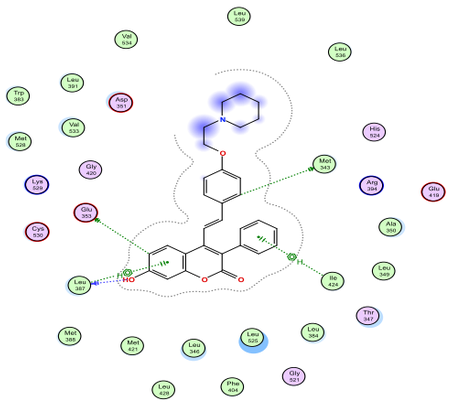

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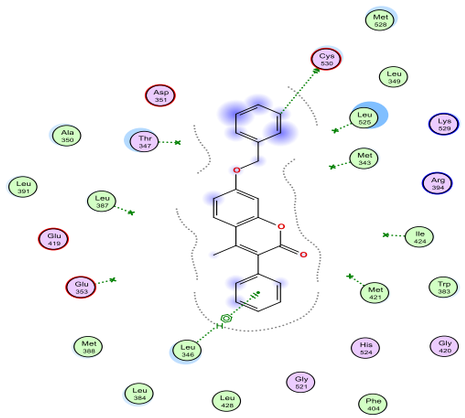

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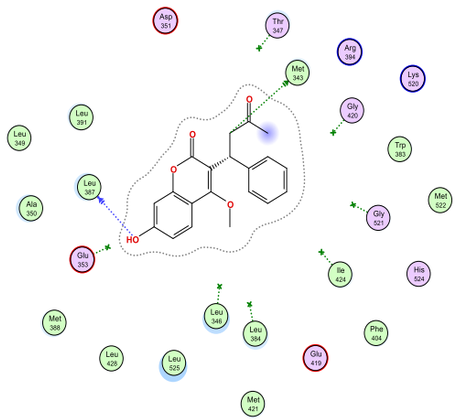

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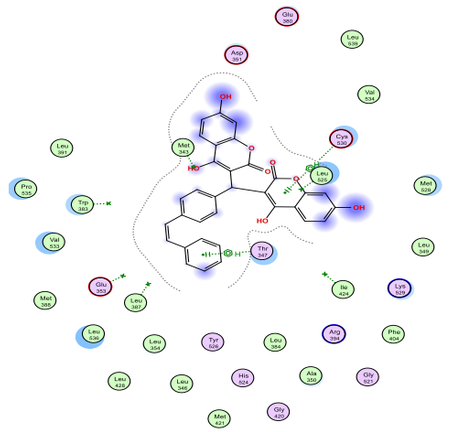

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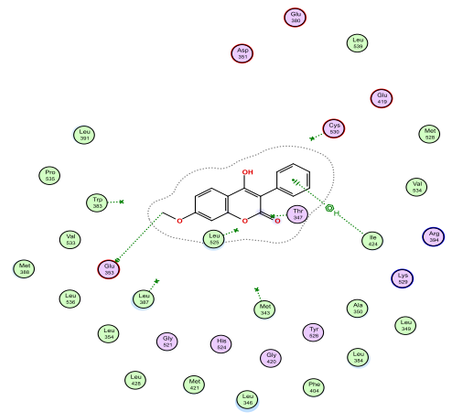

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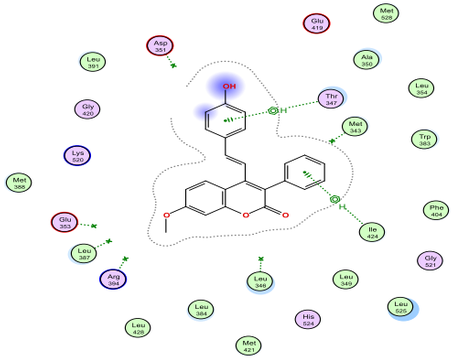

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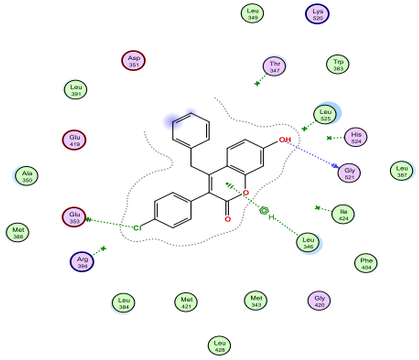

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Figure B:Molecular interactions of ligands with estrogen receptors alpha (ERα) (PDB: 3ERT) in 2D

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الجمهورية الجزائرية الديموقراطية الشعبية
وزارة التعليم العالي و البحث العلمي
جامعة محمد خيضر بسكرة

كلية العلوم الدقيقة
قسم علوم المادة
شعبة الكيمياء

تصريح شرفي

خاص بالالتزام بقواعد النزاهة العلمية لإنجاز بحث

(ملحق القرار 1082 المؤرخ في 2021/12/27)

انا الممضي أسفله،

السيد(ة): اسباع رتيبة

الصفة: طالب سنة ثانية ماستر كيمياء تخصص: كيمياء دوائية

الحامل(ة) لبطاقة التعريف الوطنية رقم: 20879568 الصادرة بتاريخ: 2023/01/29

المسجل بكلية: علوم الدقيقة قسم: علوم المادة والمكلف

بانجاز أعمال بحث : مذكرة ماستر في الكيمياء

عنوانها: Molecular Docking studies of small molecules for targeting Estrogen Receptor (ER)

أصرح بشرفي أني ألتزم بمراعات المعايير العلمية والمنهجية ومعايير الأخلاقيات المهنية والنزاهة الاكاديمية المطلوبة في انجاز البحث المذكور أعلاه وفق ما ينص عليه القرار رقم 1082 المؤرخ في 2021/12/27 المحدد للقواعد المتعلقة بالوقاية من السرقة العلمية ومكافحتها.

التاريخ: 2025/05/26

إمضاء المعني بالمر