

**COMPREHENSIVE STUDY OF ANTICANCER
PHYTOCHEMICALS FROM THE PLANTS OF
NILGIRIS HILLS AGAINST
GYNAECOLOGICAL CANCER TARGET
PI3KCA**

Submitted in partial fulfillment of the requirements for the
award of Bachelor of Science Degree in Bioinformatics
and Data Science

By

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DEPARTMENT OF BIOINFORMATICS

SCHOOL OF BIO AND CHEMICAL ENGINEERING

SATHYABAMA

**INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)**

Accredited with Grade "A" by NAAC

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MAY 2023



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BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of **S.DIKSHA (Reg.No: 40738004)** who carried out the project titled "**COMPREHENSIVE STUDY OF ANTICANCER PHYTOCHEMICALS FROM THE PLANTS OF NILGIRIS HILLS AGAINST GYNAECOLOGICAL CANCER TARGET PI3KCA**" under my supervision from January 2023 to May 2023.

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DECLARATION

I, **S.DIKSHA** hereby declare that the project report entitled “**COMPREHENSIVE STUDY OF ANTICANCER PHYTOCHEMICALS FROM THE PLANTS OF NILGIRIS HILLS AGAINST GYNAECOLOGICAL CANCER TARGET PI3KCA**” done by me under the guidance of **Dr. Jemmy Christy H, M.Tech., Ph.D** is submitted in partial fulfillment of the requirements for the award of Bachelor of Science Degree in Bioinformatics and Data science.

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ACKNOWLEDGEMENT

I am pleased to acknowledge my sincere thanks to **Board of Management** of **SATHYABAMA INSTITUTE OF SCIENCE AND TECHNOLOGY** for their kind encouragement in doing this project and for completing it successfully. I am grateful to them.

I convey my thanks to **Dr.V. RAMESH KUMAR**, Dean, School of **BIO AND CHEMICAL ENGINEERING** and **Dr. JEMMY CHRISTY H, M.Tech., Ph.D., Head of the Department, Dept. of BIOINFORMATICS** for providing me necessary support and details at the right time during the progressive reviews.

I would like to express my sincere and deep sense of gratitude to my Project Guide **Dr. Jemmy Christy, M.Tech., Ph.D** for his valuable guidance, suggestions and constant encouragement paved way for the successful completion of my project work.

I wish to express my thanks to all Teaching and Non-teaching staff members of the **Department of Bioinformatics** who were helpful in many ways for the completion of this project

ABSTRACT

The PIK3CA gene is frequently mutated in gynecological cancers, promoting cell survival, proliferation, and metastasis thus making it a promising therapeutic target. The Nilgiris, a mountainous region in South India, is known for its rich biodiversity and is home to many medicinal plants that have been traditionally used for various ailments, including cancer. This thesis presents a Comprehensive study of Anticancer phytochemicals from the plants of Nilgiris hills against gynecological cancer target- PI3KCA. The study involves a systematic analysis of the reported Nilgiris plants compounds, binding affinity towards the PIK3CA. Twenty-six indigenous plant species and their 450 phytochemicals were subjected for anticancer compound screening. Series of structural and functional studies revealed that *Rubia cordifolia*- IMPHY001728- Nordamnacanthal, IMPHY004653- Serotonin. *Schleichera oleosa*- 10836412- Schleicherastatin 6 , *Cytisus scoparius*- IMPHY011933- Caffeic acid, IMPHY004643- Genistein, IMPHY003477- Epinine. *Cestrum aurantiacum*- IMPHY012273- Tigogenin, were having similar binding affinity like ALPELISIB (FDA approved drug for PIK3CA). These proposed bio active compounds can be further investigated for their efficacy and safety through invitro and invivo studies for the development of novel therapeutics for gynecological cancer.

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LIST OF ABBREVIATIONS

PI3KCA - Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

IMPPAT - Indian Medicinal Plants, Phytochemistry And Therapeutics

PDB - Protein Data Bank

DFT - Density-functional theory

EV - Electron volts

EPS - Electronic polarizability

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CHAPTER 1

INTRODUCTION

1.1 GYNECOLOGICAL CANCERS

Gynecological cancers refer to a group of cancers that affect a woman's reproductive system they are among the most common cancers in women and hence an important public health issue. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from this disease.

Gynecologic cancer is any cancer that starts in a woman's reproductive organs. Five main types of cancer affect a woman's reproductive organs are cervical, ovarian, uterine, vaginal and vulvar. As a group, they are referred to as gynecologic cancer. A sixth type of gynecologic cancer is the very rare fallopian tube cancer.

Uterine cancer is the most common gynecological cancer, followed by ovarian cancer. (Bala Bhagavath et al., 2020). Although cervical cancer is on a declining trend due to the widespread use of Pap tests and HPV vaccination. (Suneeta Krishnan et al., 2018). There are various risk factors for gynaecological cancers. It all depends upon the age and the kind of cancer. Some of the risk factors are- Diabetes, Obesity, a weak immune system, Smoking, History of gynaecologic cancer, Use of oral birth control and/or fertility drugs, Estrogen therapy, High-fat diet.

1.2 SYMPTOMS OF GYNAECOLOGICAL CANCER

The symptoms of gynaecological cancer can vary depending on the type and stage of cancer.

cervical cancer : symptoms of cervical cancer can include abnormal vaginal bleeding, such as bleeding between periods or after menopause. Other symptoms may include pelvic pain, and abnormal vaginal discharge. (Sung & Abramovitz, 2022)

The most common symptom of endometrial cancer is abnormal vaginal bleeding, particularly in postmenopausal women (Clarke et al., 2018)

Ovarian cancer can be difficult to detect in its early stages, and symptoms may not appear until the cancer has spread. But it can be noted that some common symptoms of ovarian cancer can include abdominal bloating or swelling, pelvic pain or pressure, difficulty eating or feeling full quickly, and changes in bowel or bladder habits. (Jayson.,et al.,2019)

Vaginal cancer is a rare type of gynaecological cancer, symptoms of vaginal cancer can include abnormal vaginal bleeding and a mass or lump in the vagina. (Kaltenecker et al., 2023)

Vulvar cancer is another rare type of gynaecological cancer. symptoms of vulvar cancer can include itching, burning, or bleeding on the vulva, as well as a lump or sore that does not heal.

1.3 TREATMENTS

Gynaecological cancer treatments have evolved significantly in recent years.

Surgery is the primary treatment for most gynaecological cancers. The goal of surgery is to remove the tumour and surrounding tissues to prevent the cancer from spreading. Surgery can be performed through traditional open surgery or minimally invasive techniques such as laparoscopy and robot-assisted surgery. The type of surgery performed depends on the location and stage of the cancer.

Chemotherapy: Chemotherapy involves the use of drugs to kill cancer cells. It is often used in combination with surgery to kill any remaining cancer cells. Chemotherapy can be given intravenously or orally. The drugs used for chemotherapy depend on the type and stage of the cancer. (Okusaka, T., & Furuse, J. 2020.)

Radiation therapy: Radiation therapy uses high-energy radiation to kill cancer cells. It is often used after surgery to kill any remaining cancer cells or as the primary treatment for certain types of gynaecological cancers. Radiation therapy can be given externally or internally. (Baskar, R ET AL., 2012).

Targeted therapy: Targeted therapy involves the use of drugs that target specific proteins or genes in cancer cells to stop their growth and spread. Targeted therapy is often used in combination with chemotherapy or radiation therapy. The drugs used for targeted therapy depend on the specific type of cancer. (Huang, R et al., 2021).

1.4 FDA APPROVED DRUGS

There are several FDA-approved drugs for treating gynaecological cancers, Some of the commonly used drugs for gynaecological cancer treatment are:

- 1.Carboplatin: It is a chemotherapy drug used for the treatment of ovarian cancer.
- 2.Paclitaxel: It is another chemotherapy drug used for the treatment of ovarian cancer, as well as for cervical and uterine cancers.
- 3.Bevacizumab: It is a targeted therapy drug that blocks the formation of blood vessels that supply nutrients to cancer cells. It is used for the treatment of ovarian and cervical cancers.
- 4.Trastuzumab: It is another targeted therapy drug that blocks the growth of cancer cells that overexpress the HER2 protein. It is used for the treatment of some types of ovarian and uterine cancers.
- 5.Olaparib: It is a PARP inhibitor drug used for the treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer.

One FDA-approved drug that inhibits PI3K for treating gynaecological cancer is alpelisib (brand name: Piqray). It is a targeted therapy drug that specifically targets the PI3K pathway.

1.5 PI3K

There have been several recent studies on gynaecological cancer that have focused specifically on the role of the PI3K pathway in these diseases.

Phosphoinositide 3-kinases (PI3Ks) are a family of enzymes that play a critical role in cell signalling pathways regulating cell growth, proliferation, survival, and metabolism. Mutations or overexpression of PI3K have been identified in many types of cancer, making them a promising target for cancer therapy.

PI3K signalling is frequently dysregulated in cancer cells, leading to increased cell survival and proliferation. This can occur through a variety of mechanisms, including mutations in PI3K itself, as well as in downstream signalling components such as AKT and mTOR. Dysregulated PI3K signalling has been implicated in the development and progression of many types of cancer, including breast, ovarian, colorectal, and prostate cancer, among others. (Fresno Vara et al.,2004)

Inhibition of PI3K has emerged as a potential therapeutic strategy for cancer treatment. Several PI3K inhibitors have been developed and are currently being tested in clinical trials for various types of cancer.

A study has shown the efficacy and safety of the dual PI3K inhibitor gedatolisib in patients with recurrent or persistent endometrial cancer. The study showed that gedatolisib had antitumor activity in patients with PIK3CA-mutant or PTEN-deficient endometrial cancer, and had a manageable safety profile. (Del Campo et al., 2016) .Targeting the PI3K pathway with a PI3K inhibitor could sensitize ovarian cancer stem cells to chemotherapy, and improve the efficacy of chemotherapy in vitro and in vivo. (Rinne et al., 2021)

Alpelisib is approved for the treatment of advanced or metastatic breast cancer that has a PIK3CA mutation, which is a type of genetic alteration that results in overactivation of the PI3K pathway. This drug may also have potential in the treatment of gynaecological cancers, particularly those with PIK3CA mutations, although it is not currently FDA-approved for this indication. (Chang et al., 2021)

1.6 PI3K AND GYNAECOLOGICAL CANCER

Ovarian cancer is one of the most lethal gynecological cancers, with a high rate of recurrence and drug resistance. Several studies have shown that the PI3K pathway is frequently activated in ovarian cancer and plays a critical role in tumor growth and progression (Matulonis et al., 2016)

For example, a study found that inhibition of PI3K activity using a specific inhibitor significantly reduced ovarian cancer cell growth and induced cell death. Similarly, a study by showed that targeting the PI3K pathway using a combination of drugs resulted in significant tumor regression in a mouse model of ovarian cancer

Endometrial cancer is another gynecological cancer in which the PI3K pathway is frequently dysregulated. Studies have shown that mutations in PIK3CA, which encodes the PI3K-alpha catalytic subunit, are common in endometrial cancer and are associated with poor prognosis. (Mjos et al., 2017) Cervical cancer is another gynecological cancer in which dysregulation of the PI3K pathway has been implicated. A study found that inhibition of PI3K activity using a specific inhibitor significantly reduced cervical cancer cell growth and induced cell death (10). In addition, a study by showed that mutations in PIK3CA were associated with poorer survival outcomes in patients with cervical cancer. (Ediriweera et al., 2019)

1.7 PHYTOCHEMICALS

The bioactive substances known as phytochemicals are present in plants and have been demonstrated to have positive impacts on human health, including the potential to lower the risk and progression of gynecological cancer.

Phytochemicals are bioactive compounds found in plants that have been shown to have beneficial effects on human health, including potential roles in reducing the risk and progression of gynecological cancers.

Recent studies shows the anti-cancer effects of various phytochemicals in ovarian cancer. The potential of polyphenols (such as resveratrol and EGCG) and flavonoids (such as quercetin and kaempferol) to inhibit cancer cell growth and induce apoptosis (programmed cell death). The potential of curcumin and I3C to inhibit cancer cell growth and metastasis (spread of cancer cells to other parts of the body) in ovarian cancer. (Woźniak et al., 2021)

Recent study found that women who consumed high amounts of flavonoids (such as apigenin and luteolin) had a lower risk of developing endometrial cancer compared to those who consumed lower amounts of these phytochemicals. (Liu et al., 2022)

CHAPTER 2

LITERATURE SURVEY

The paper titled "Targeting the PI3K/AKT/mTOR pathway in epithelial ovarian cancer, therapeutic treatment options for platinum-resistant ovarian cancer" provides an overview of the current understanding of the PI3K/AKT/mTOR signaling pathway in epithelial ovarian cancer (EOC) and its potential as a therapeutic target. The authors highlight the role of this pathway in EOC progression, chemoresistance, and metastasis. They also discuss the existing inhibitors of this pathway and their clinical trials in EOC, including monotherapy and combination therapies. The authors conclude that targeting the PI3K/AKT/mTOR pathway is a promising therapeutic strategy for EOC, particularly for platinum-resistant cases. They suggest that combination therapies may be more effective in targeting this pathway, and that the development of predictive biomarkers is essential to improve patient selection and treatment outcomes. Overall, the paper provides valuable insights into the potential of PI3K/AKT/mTOR pathway inhibitors as a treatment option for EOC. (Natasha Rinne., et al., 2021)

The paper titled "Survey of Some Ethno Medicine Used by Tribal Population in Nilgiri Hills, South India" presents an investigation on the traditional medicinal practices of the tribal population in the Nilgiri Hills region of South India. The study was conducted to document the use of ethno-medicinal plants for various ailments among these tribal communities. The authors collected data on the plants' local name, parts used, preparation methods, and therapeutic indications. The study identified plant species belonging to 34 families used for medicinal purposes by the tribal communities. The most commonly used families were Asteraceae, Lamiaceae, and Fabaceae. The plants were used for treating various health conditions such as fever, diarrhea, skin diseases, respiratory problems, and gynecological disorders. The authors concluded that the traditional medicinal knowledge of the tribal communities in Nilgiri Hills is vast and holds potential for drug discovery and development. The paper provides valuable information on the use of ethno-medicinal plants by the tribal population of Nilgiri Hills. It highlights the importance

of traditional medicinal knowledge and suggests that further research is necessary to establish the safety and efficacy of these plants. Overall, the study contributes to the growing body of literature on ethno-medicinal practices and emphasizes the need to conserve and document traditional medicinal knowledge for future generations. (Abubacker MN., et al., 2018)

The paper titled "Targeting PI3K in cancer: mechanisms and advances in clinical trials" provides an overview of the PI3K signaling pathway and its role in cancer, as well as current approaches for targeting PI3K in cancer therapy. The authors discuss the various isoforms of PI3K and their downstream effectors, highlighting their role in cell growth, proliferation, and survival. They also review the preclinical and clinical evidence for targeting PI3K in cancer, including the development of PI3K inhibitors and their efficacy in different types of cancer. The paper provides insights into the challenges associated with PI3K inhibitor therapy, including drug resistance and toxicity, and discusses the potential for combination therapy with other targeted agents. Overall, the authors conclude that targeting PI3K signaling holds great promise for cancer therapy and has become an active area of research and clinical development. (Jing yang., et al., 2019)

The article highlights the potential of plants found in the Nilgiris Biosphere Reserve (NBR) in India as sources of anticancer compounds. The authors discuss the rich biodiversity of the region and the traditional knowledge of indigenous communities in using plants for medicinal purposes. They describe several plant species found in the NBR that have been studied for their anticancer properties, including *Andrographis paniculata*, *Phyllanthus amarus*, and *Tinospora cordifolia*. The authors also discuss the challenges in developing these phytochemicals into effective anticancer drugs, such as issues with bioavailability and toxicity. Finally, they emphasize the need for further research and conservation efforts to preserve the biodiversity of the NBR and to fully explore the potential of these neglected anticancer phytoceutical treasures. (M.V.N.L Chaitanya., et al., 2018)

CHAPTER 3

AIM AND SCOPE

3.1 AIM

The aim of this comprehensive study is to evaluate the therapeutic potential of plants from Nilgiris hill for the treatment of gynecological cancers, with a particular focus on targeting the PI3K pathway. Despite advances in cancer treatment, gynecological cancers remain difficult to treat, and there is a need for new therapies that can improve patient outcomes with minimal side effects.

3.2 SCOPE

The PI3K pathway has emerged as an important therapeutic target in gynecological cancers, as it is frequently dysregulated in these cancers. PIK3CA, which encodes the catalytic subunit of PI3K, is one of the most commonly mutated genes in cancer, making it an attractive target for drug development. Natural compounds may contribute to improving the effectiveness of the therapy while lowering the hazardous side effects of chemotherapy. The development of novel drug formulations that can deliver phytochemicals and PI3K inhibitors directly to the site of the tumor could enhance the therapeutic potential of these compounds. Future research could involve developing such formulations and evaluating their efficacy in treating gynecological cancer.

CHAPTER 4

MATERIALS AND METHODS

4.1 MATERIALS

4.1.1 Indian Medicinal Plants, Phytochemistry And Therapeutics (IMPPAT)

A comprehensive database that offers details on the phytochemicals, therapeutic benefits, and therapeutic uses of Indian medicinal plants is known as Indian Medicinal Plants, Phytochemistry And Therapeutics 2.0 (IMPPAT 2.0). The first IMPPAT database was introduced in 2011, and this is an updated version of it.

Information on more than 3,000 Indian medicinal plants, including their phytochemical makeup, can be found in the IMPPAT 2.0 database. Along with information on their pharmacological characteristics and potential therapeutic uses, it also provides information on the conventional uses of these plants in Ayurveda, Unani, and Siddha medicine.

A group of scientists from the Indian Institute of Integrative Medicine, CSIR, Jammu, and the Central Council for Research in Ayurvedic Sciences, New Delhi, created the database. The data in the database was gathered from a variety of sources, including academic research, classic books, and professional opinions.

It is the goal of the IMPPAT 2.0 database to serve as a helpful tool for academics, medical professionals, and the general public. It can be used to locate possible sources of herbal treatments for a variety of illnesses and to direct additional investigation into the pharmacological characteristics of Indian medicinal plants. (Singh VK et al., 2019).

4.1.2 PUBCHEM

The National Centre for Biotechnology Information (NCBI), a division of the United States National Library of Medicine (NLM), is responsible for maintaining PubChem, a database of chemical compounds that is open to the public. It is a thorough resource that offers details on the traits and functions of countless chemical substances.

A variety of data on chemical compounds, including their chemical composition, physical characteristics, bioactivity, and pharmacological characteristics, can be

found in the PubChem database. It can be searched for using several criteria, including chemical name, molecular formula, and chemical structure. PubChem offers a variety of tools and resources for academics in addition to its enormous repository of chemical data, such as chemical screening tests, molecular modelling tools, and data visualization tools. Users can contribute their own data to the database, such as bioassay results and chemical structures, to help it become more accurate and comprehensive. (Cheng T, et al., 2017).

4.1.3 PROTEIN DATA BANK (PDB)

The Protein Data Bank (PDB) is a database that provides 3D structural information of proteins, nucleic acids, and complex assemblies. It contains information on the atomic coordinates of these macromolecules, as well as their experimental data and related information.

The PDB is a vital resource for researchers in various fields, including biochemistry, biophysics, structural biology, and drug discovery. It allows researchers to analyze the structures of biological molecules and understand their functions, interactions, and mechanisms of action.

The PDB has contributed significantly to various fields, including drug discovery and design, structural genomics, and protein engineering. It has led to the development of new drugs, improved our understanding of disease mechanisms, and facilitated the design of novel proteins and enzymes for industrial applications.

4.1.4 SWISS ADME

SwissADME is a free online tool for predicting the physicochemical and pharmacokinetic characteristics of small molecules. It offers users a variety of tools for drug research and discovery and is maintained by the Swiss Institute of Bioinformatics (SIB). Based on a small molecule's molecular structure, SwissADME forecasts a variety of pharmacokinetic characteristics like absorption, distribution, metabolism, and excretion (ADME). It offers details on physical and chemical characteristics such as molecular weight, lipophilicity, solubility, and pKa values. SwissADME also forecasts a compound's probable toxicity based on its structural makeup. To assure the accuracy of its forecasts and to incorporate new prediction algorithms, the tool is frequently updated. As of 2017, researchers in the

pharmaceutical sector and academia frequently employed SwissADME, which had been mentioned in more than 50 papers. (Daina A et al., 2017).

4.1.5 DISCOVERY STUDIO

Dassault Systèmes BIOVIA created and maintains Discovery Studio, a comprehensive software suite for molecular modelling, simulations, and visualisation. It is extensively utilised for drug development and discovery in both the pharmaceutical sector and academia.

Virtual screening, molecular docking, and pharmacophore modelling are just a few of the tools that Discovery Studio offers for ligand-based and structure-based drug creation. It also has an intuitive user interface. It also has resources for forecasting a compound's ADME and toxicity. It offers other research fields in addition to drug creation, such as protein modelling, chemical biology, and materials science. It has sophisticated molecular dynamics simulation techniques as well as tools for simulating protein-ligand interactions. Discovery Studio makes it possible to visualise molecular structures and their interactions with proteins, which aids in understanding how drugs work. It also makes it possible to identify important binding residues and analyse protein-ligand interactions.(Chen, J. et al., 2019).

4.2 METHODOLOGY

4.2.1 TARGET IDENTIFICATION

The process of identifying the biological molecule or pathway that a medicine or chemical substance affects is known as target identification. It is a crucial stage in the discovery and development of new therapeutics since it enables researchers to comprehend how a drug functions and spot any negative effects or interactions with other medications. In order to discover possible targets, this includes employing computational tools to analyse and interpret data from diverse sources.

The first step is to conduct disease biology research to identify potential targets that are involved in the disease's pathology. This can be done through various sources such as scientific literature, databases, and genetic studies. The target will be obtained from the PDB, and heteroatoms will be removed. The Protein Data Bank (PDB) contains three-dimensional (3D) structures of biological substances such as DNA, RNA, and proteins. The identification of the structure of macromolecules aids

in the discovery of illness mechanisms. It aids in the understanding of how structure and biomolecules communicate.

Researchers can start creating medications that selectively interact with a target once it has been discovered to deliver the desired therapeutic effect. As new technologies and insights help us to understand disease mechanisms and potential drug targets, target identification is a continuous process throughout the drug discovery and development pipeline.

4.2.2 LIGAND IDENTIFICATION

Ligand identification is a crucial step in drug discovery and development. It involves the identification of small molecules that can bind to the specific target protein and modulate its activity. Virtual screening is a computational method that involves the screening of large chemical libraries to identify potential ligands that can bind to a target protein. This process is typically performed using various computational methods, including virtual screening, molecular docking, and molecular dynamics simulations.

Identification of plants from Nilgiris hills using various sources, such as literature review, traditional knowledge, ethnobotanical databases.

Identified phytochemicals present in the plants using IMPPAT database and PubChem. And the SDF file for these compounds has been downloaded to visualize the compounds in Discovery studio.

and affinity of a ligand to a target protein. Molecular dynamics simulations are used to study the dynamic behavior of ligand-protein complexes over time.

4.2.3 ADMET PREDICTION

Discovery Studio includes several modules for ADMET prediction .These modules use different algorithms and methods to predict various ADMET properties, such as solubility, permeability, metabolism, and toxicity.

Steps involved in using the ADMET Predictor module in Discovery Studio for ADMET prediction: Import the compounds into Discovery Studio by importing the files in a supported format (such as .mol or .sdf).

Prepare the compounds for ADMET prediction: This involves generating a 3D structure .

ADMET Predictor module: This module uses various algorithms and models to predict ADMET properties based on the structure and physicochemical properties of the compound. In general, the ADMET Predictor can predict properties such as solubility, permeability, metabolism, plasma protein binding, and toxicity.

Interpret the results: The ADMET Predictor provides a detailed report on the predicted ADMET properties of the compound, including numerical values and graphical representations.

4.2.4 PHARMACOKINETICS PROPERTIES

pharmacokinetic analysis can be performed to evaluate the drug-likeness and ADME (absorption, distribution, metabolism, and excretion) properties. This analysis can be done using in silico tools such as SwissADME.

The tool uses a variety of machine learning models to predict properties such as oral bioavailability, blood-brain barrier penetration, and toxicity.

Steps involved in using SwissADME for ADMET prediction:

Import the compounds into SwissADME by uploading the smiles notation for each compound.

Prediction of physicochemical properties: Once the input molecule is uploaded, SWISSADME will predict various physicochemical properties such as molecular weight, logP, polar surface area, and number of hydrogen bond donors and acceptors. These properties are important in determining the drug-likeness of the natural compound.

The molecules will be screened based on Lipinski's rule of five, which is a set of rules utilised in medication discovery and development.

- Lipinski's guidelines : Molecular weight [≤ 500 Daltons]
- LogP (partition coefficient) [≤ 5]
- Number of hydrogen bond donor [≤ 5]
- Number of hydrogen bond acceptors [≤ 10]
- TPSA [<140]

4.2.5 MOLECULAR DOCKING

Molecular docking is a computational method used to predict the binding of a small molecule (ligand) to a target protein. It is a powerful tool in drug discovery and design, as it can help identify potential drug candidates and guide optimization efforts.

Discovery Studio includes a molecular docking module called the CDOCKER module, which uses a combination of molecular dynamics and Monte Carlo simulations to predict the binding of a ligand to a protein target.

Steps involved in using the CDOCKER module in Discovery Studio

Import the ligand and protein into Discovery Studio. we can do this by drawing the ligand using the built-in sketcher, or by importing a file in a supported format (such as .mol or .sdf). The protein should be in a PDB format.

Preparation of the ligand and protein for docking: This involves generating a 3D structure and optimizing the geometry to minimize energy. Discovery Studio includes tools for ligand and protein preparation, such as removing water molecules and adding missing atoms.

Defining the docking parameters: This includes specifying the search space (i.e., the region of the protein where the ligand can bind), the scoring function (i.e., the algorithm used to evaluate the binding affinity), and the number of docking runs to perform.

Running the docking simulation: The CDOCKER module uses a combination of molecular dynamics and Monte Carlo simulations to predict the binding of the ligand to the protein. The output of the simulation includes a set of docked poses (i.e., the predicted binding orientations of the ligand), as well as a score for each pose that reflects its binding affinity.

Analyzing the results: The docked poses and scores can be used to evaluate the potential binding affinity of the ligand to the protein, and guide further experimental studies.

4.2.6 PHARMACOPHORE AND DISTANCE ANALYSIS USING DISCOVERY STUDIO

Ligand-based Pharmacophore Analysis

Ligand-based pharmacophore analysis involves identifying the common features of a set of ligands that are responsible for their biological activity. These features can include hydrogen bond acceptors, hydrogen bond donors, aromatic rings, and hydrophobic regions. A pharmacophore model is then generated based on these common features, which can be used to identify new compounds with similar pharmacophoric properties.

Distance Analysis:

Distance analysis is another important technique used in drug discovery. This technique involves measuring the distances between atoms or functional groups in a ligand or protein, and using this information to guide the design of new compounds with improved binding affinity.

Discovery Studio includes several tools for distance analysis, including the Distance Measurements tool. This tool can be used to measure the distances between atoms or functional groups in a ligand or protein. This information can be used to identify potential binding sites or guide the design of new compounds with improved binding affinity.

4.2.7 Density Functional Theory (DFT)

Density Functional Theory (DFT) is a widely used computational method in chemistry and materials science to study the electronic structure and properties of molecules, materials, and solids. In Discovery Studio, the DMol3 module is used to perform DFT calculations, including the calculation of HOMO, LUMO, and EVS energies.

In Discovery Studio's DMol3 module, these energies can be calculated using various DFT functionals and basis sets can be used to guide the design of new compounds or materials with specific properties.

CHAPTER 5

RESULT AND DISCUSSION

5.1 TARGET IDENTIFICATION

The Co-crystal structure of the target protein was retrieved from the PDB database. The target name is lipid kinase PI3K alpha from *the organism- Homo sapiens* , its PDB ID is 4JPS.

PI3K (phosphoinositide 3-kinase) are enzymes involved in cellular function such as cell growth, proliferation, differentiation, motility, survival, which in turn involved in cancer. They consists of 3 subunits, that is P85 regulatory, P55 regulatory, P110 catalytic subunit.

Aberrant activation of the PI3K/AKT pathway promotes the survival and proliferation of tumor cells in many human cancers. In normal cells, PI3K signaling is tightly regulated, but in cancer cell, genetic mutation can lead to the activation of PI3K pathway, resulting in uncontrolled cell growth and survival.

FDA approved drug- Alpelisib

Alpelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor with potent antitumor activity. It works by selectively inhibiting class I PI3K p110 α , which is the catalytic subunit of PI3K. FDA granted the use of alpelisib in the treatment of PIK3CA-Related Overgrowth Spectrum (PROS) in adults and children who require systemic therapy. Alpelisib is marketed in the name of Piqray for the treatment of breast cancer , it is available as a oral tablet.



Fig 5.1 PI3K 3D STRUCTURE

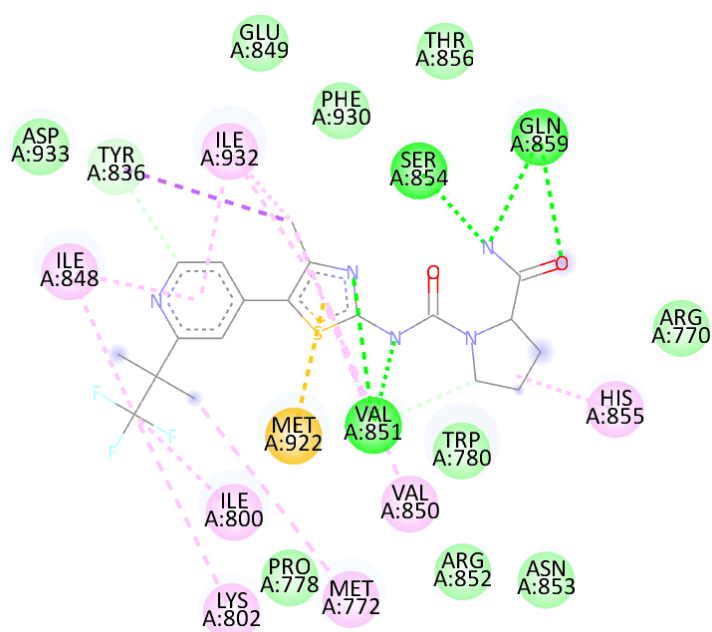


Fig 5.2 INTERACTION BETWEEN ALPELISIB AND PI3K

5.2 LIGAND IDENTIFICATION

Phytochemicals from the plants of nilgiris hill were identified and there SDF file was downloaded from IMPPAT. Total 450 phytochemicals were subjected for anticancer compound screening.

Using discovery studio ADMET prediction was done where the compounds got filtered to 30 compounds, with respect to the drug absorption, distribution, metabolism, excretion and toxicity values.

The 30 compounds were further considered for docking, among which only 20 compounds got docked and showed affinity towards the protein.

Toxicity analysis

The toxicity of the identified compounds was investigated, so that any candidate lead molecule should be physiologically safe.

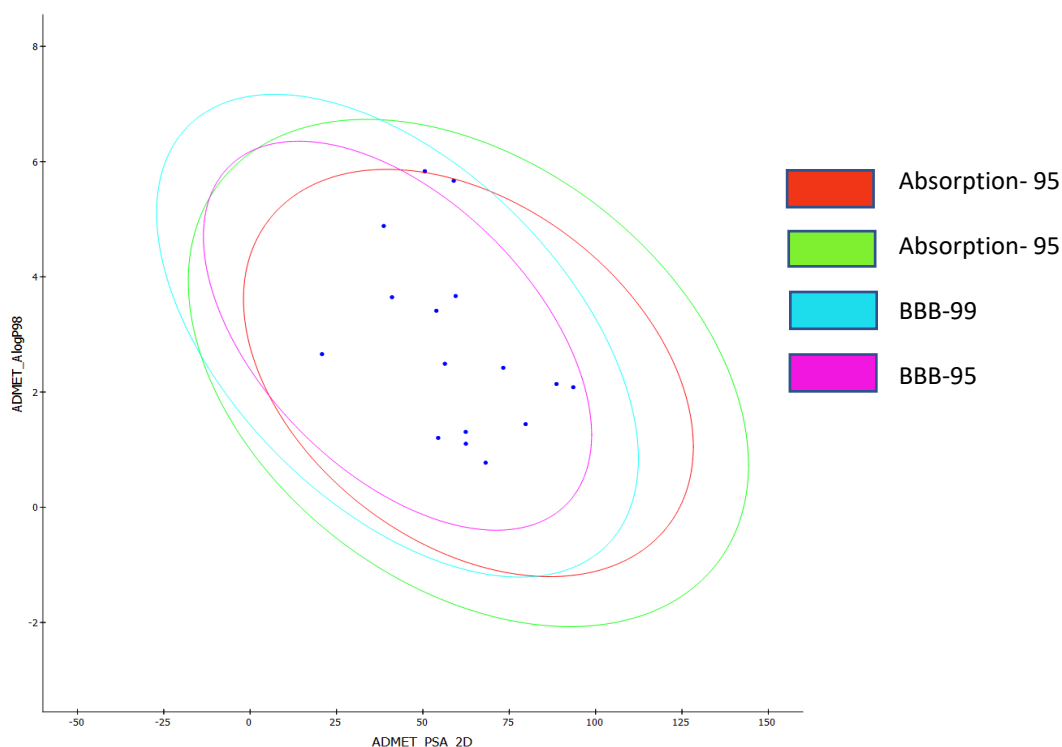
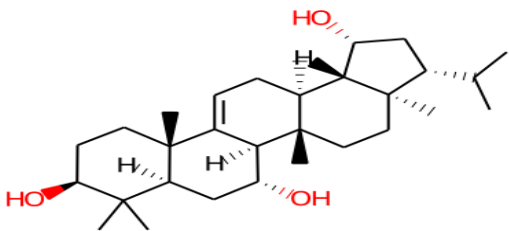
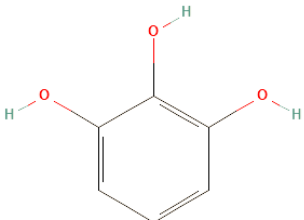
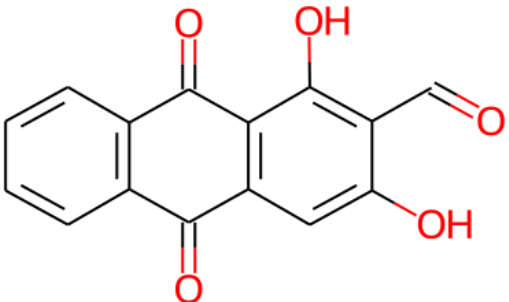
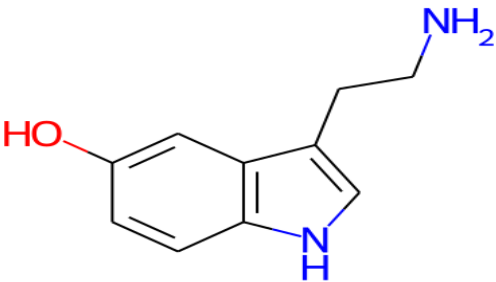
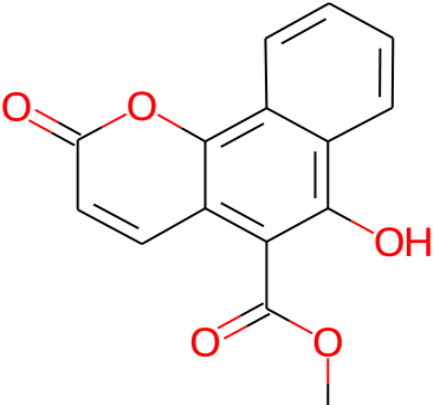
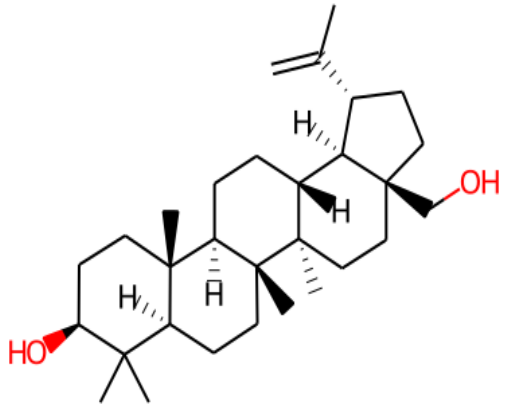
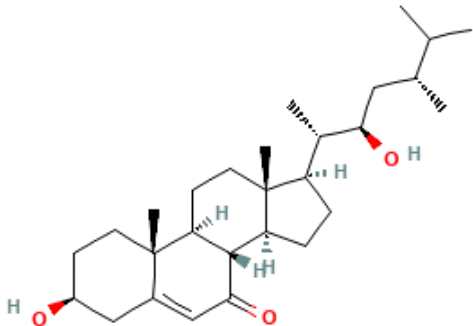
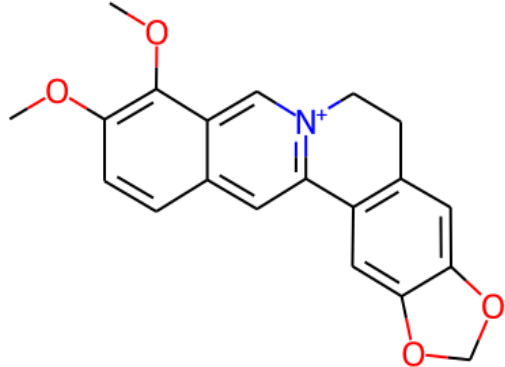
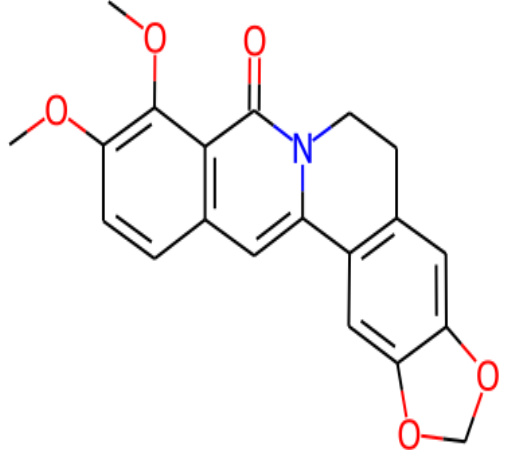


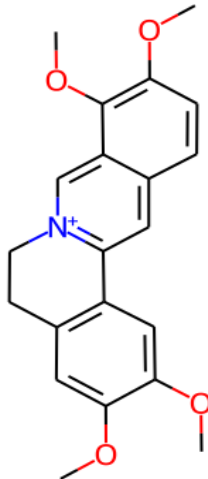
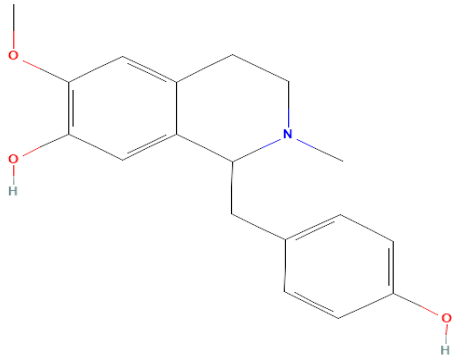
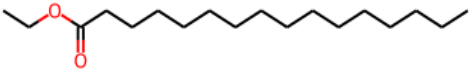
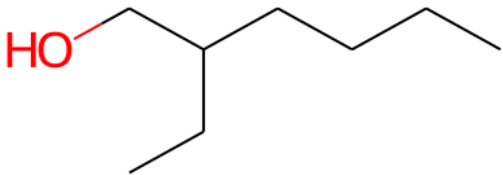
FIG 5.3 ADMET PLOT OF THE PLANTS COMPOUND

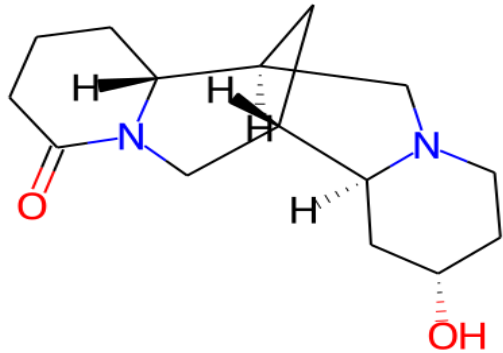
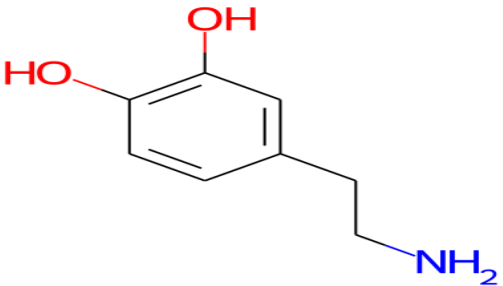
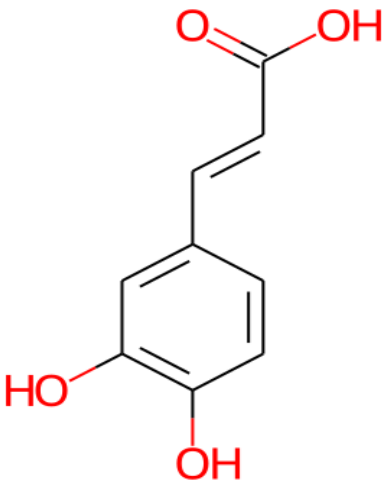
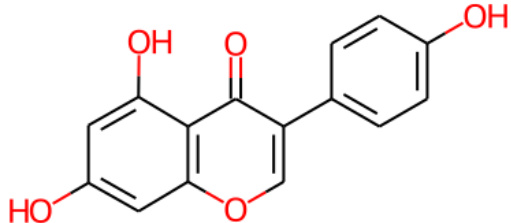
The ellipse represents the optimal range of ADMET properties, and the compounds located within the ellipse are predicted to have properties within this optimal range. Therefore, having compounds centered within the ellipse indicates that they are likely to have favorable pharmacological properties and may be good candidates for further development as drug candidates

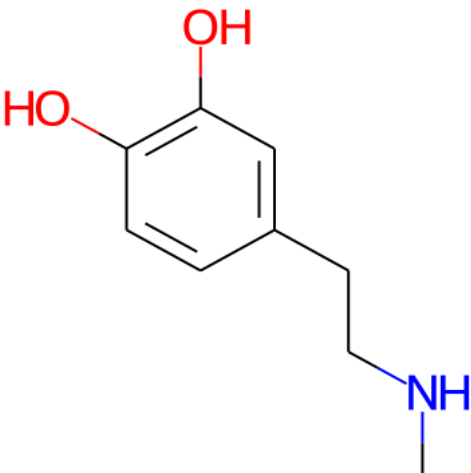
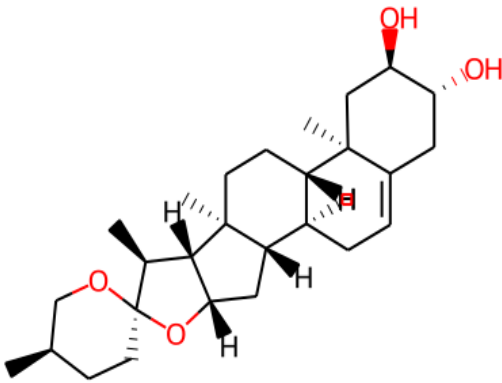
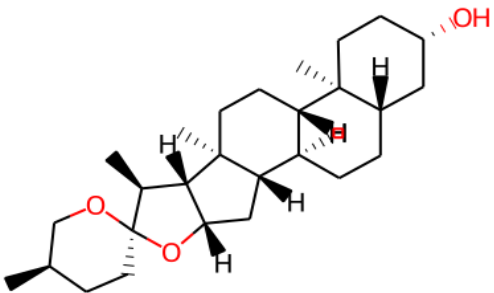
TABLE NO. 5.1 DETAIL ON OF IDENTIFIED COMPOUNDS

SNo.	Plant Name	Molecule Name / Id	Molecule structure
1.	Rubia cordifolia 	Rubiatriol IMPHY009172	
		Pyrogallol 1057 – Pubchem ID	
		Nordamnacanthal IMPHY001728	
		Serotonin IMPHY004653	
		Rubilactone IMPHY009636	

3.	Schleichera oleosa 	Betulin IMPHY004271	
		SCHLEICHERAS TATIN 6 10836412- Pubchem ID	
4.	Berberis Lycium 	Berberine IMPHY005665	
		Oxyberberine IMPHY000342	

		Palmatine IMPHY005330	
		N-Methylcoclaurine 2752274- pubchem	
5.	Phytolacca acinose 	Ethyl palmitate IMPHY009624	
		2-Ethylhexanol IMPHY006032	

6.	Cytisus scoparius 	Hydroxylupanine IMPHY014728	
		Dopamine IMPHY007257	
		Caffeic acid IMPHY011933	
		Genistein IMPHY004643	

		Epinine IMPHY003477	
7.	Cestrum aurantiacum 	Yuccagenin IMPHY010851	
		Tigogenin IMPHY012273	

5.3 PHARMACOKINETICS ANALYSIS

Prediction of physicochemical properties: Once the input molecule is uploaded, SWISSADME will predict various physicochemical properties such as molecular weight, logP, polar surface area, and number of hydrogen bond donors and acceptors. These properties are important in determining the drug-likeness of the natural product candidate.

Prediction of ADME properties: SWISSADME also predicts various ADME properties such as oral bioavailability, blood-brain barrier penetration, and metabolic stability. These properties are important in determining the pharmacokinetics of the natural product.

OPTIMAL VALUES

- Lipophilicity (logP): Generally, a logP value between 0 and 5 is considered optimal for oral bioavailability.
- Solubility: A solubility value greater than 1 mg/mL is usually desirable for drug-like molecules.
- Blood-brain barrier (BBB) permeation: A predicted logBB value of greater than -1 is often indicative of good BBB permeation.
- Human oral absorption: A predicted human oral absorption (HOA) value of greater than 30% is usually desirable for drug-like molecules.
- CYP450 inhibition: A predicted IC₅₀ value of less than 10 μ M is considered a potential inhibitor of CYP450 enzymes.

It is important to note that these are just general guidelines and the optimum values may vary depending on the specific application and intended use of the molecule.

TABLE NO. 5.2 Pharmacokinetics properties of Identified compounds

Compound Properties		Berberine	Oxyberberine
Lipophilicity:	(iLOGP)	0	3.28
	XLOGP3	3.62	2.94
	WLOGP	3.1	2.97
	MLOGP	2.19	2.38
	Silicos-IT Log P	3.74	3.65
	Consensus Log P	2.53	3.04
Water Solubility:	ESOL Log S	-4.55	-4.19
	ESOL Solubility (mol/l)	9.53e-03 mg/ml ; 2.83e-05 mol/l	2.25e-02 mg/ml ; 6.40e-05 mol/l
	ESOL Class	Moderately soluble	Moderately soluble
	Ali Log S	-4.16	-3.84
	Ali Solubility (mol/l)	2.30e-02 mg/ml ; 6.85e-05 mol/l	5.09e-02 mg/ml ; 1.45e-04 mol/l
	Ali Class	Moderately soluble	Soluble
	Silicos-IT LogSw	-5.92	-5.82
	Silicos-IT Solubility (mol/l)	4.00e-04 mg/ml ; 1.19e-06 mol/l	5.33e-04 mg/ml ; 1.52e-06 mol/l
	Silicos-IT class	Moderately soluble	Moderately soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	Yes	Yes
	Pgp substrate	Yes	Yes
	CYP1A2 inhibitor	Yes	Yes
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	Yes
	CYP2D6 inhibitor	Yes	Yes
	CYP3A4 inhibitor	Yes	Yes
	log Kp (cm/s)	-5.78 cm/s	-6.36 cm/s
Druglikeness	Lipinski #violations	Yes; 0 violation	Yes; 0 violation
	Ghose #violations	Yes	Yes
	Veber #violations	Yes	Yes
	Egan #violations	Yes	Yes
	Muegge #violations	Yes	Yes
	Bioavailability Score	0.55	0.55
Medicinal Chemistry	PAINS #alerts	0 alert	0 alert
	Brenk #alerts	1 alert: quaternary_nitrogen_1	0 alert
	Leadlikeness #violations	No; 1 violation: XLOGP3>3.5	No; 1 violation: MW>350

	Synthetic Accessibility	3.14	3.26
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Compound Properties		Palmatine	N-Methylcoclaurine
Lipophilicity:	(iLOGP)	0.1	2.78
	XLOGP3	3.75	3.04
	WLOGP	3.38	2.17
	MLOGP	2.01	2.08
	Silicos-IT Log P	3.97	2.87
	Consensus Log P	2.64	2.59
Water Solubility:	ESOL Log S	-4.58	-3.82
	ESOL Solubility (mol/l)	9.30e-03 mg/ml ; 2.64e-05 mol/l	4.56e-02 mg/ml ; 1.52e-04 mol/l
	ESOL Class	Moderately soluble	Soluble
	Ali Log S	-4.3	-3.82
	Ali Solubility (mol/l)	1.77e-02 mg/ml ; 5.02e-05 mol/l	4.56e-02 mg/ml ; 1.52e-04 mol/l
	Ali Class	Moderately soluble	Soluble
	Silicos-IT LogSw	-6.42	-4.61
	Silicos-IT Solubility (mol/l)	1.35e-04 mg/ml ; 3.83e-07 mol/l	7.35e-03 mg/ml ; 2.45e-05 mol/l
	Silicos-IT class	Poorly soluble	Moderately soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	Yes	Yes
	Pgp substrate	Yes	Yes
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	Yes	Yes
	CYP3A4 inhibitor	Yes	No
	log Kp (cm/s)	-5.79 cm/s	-5.97 cm/s
Druglikeness	Lipinski #violations	Yes; 0 violation	Yes; 0 violation
	Ghose #violations	Yes	Yes
	Veber #violations	Yes	Yes

Medicinal Chemistry	Egan #violations	Yes	Yes
	Muegge #violations	Yes	Yes
	Bioavailability Score	0.55	0.55
	PAINS #alerts	0 alert	0 alert
	Brenk #alerts	1 alert: quaternary_nitrogen_1	0 alert
	Leadlikeness #violations	No; 2 violations: MW>350, XLOGP3>3.5	Yes
	Synthetic Accessibility	3.18	2.92

Compound Properties		Yuccagenin	Tigogenin
Lipophilicity:	(iLOGP)	4.21	4.53
	XLOGP3	4.7	6.49
	WLOGP	4.68	5.79
	MLOGP	4.09	5.08
	Silicos-IT Log P	3.39	4.3
	Consensus Log P	4.21	5.24
Water Solubility:	ESOL Log S	-5.47	-6.51
	ESOL Solubility (mol/l)	1.46e-03 mg/ml ; 3.38e-06 mol/l	1.28e-04 mg/ml ; 3.08e-07 mol/l
	ESOL Class	Moderately soluble	Poorly soluble
	Ali Log S	-5.67	-7.1
	Ali Solubility (mol/l)	9.30e-04 mg/ml ; 2.16e-06 mol/l	3.32e-05 mg/ml ; 7.97e-08 mol/l
	Ali Class	Moderately soluble	Poorly soluble
	Silicos-IT LogSw	-3.67	-4.51
	Silicos-IT Solubility (mol/l)	9.19e-02 mg/ml ; 2.13e-04 mol/l	1.29e-02 mg/ml ; 3.10e-05 mol/l
	Silicos-IT class	Soluble	Moderately soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	Yes	Yes
	Pgp substrate	Yes	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No

Druglikeness	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No
	log Kp (cm/s)	-5.59 cm/s	-4.23 cm/s
	Lipinski #violations	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15
	Ghose #violations	No; 1 violation: #atoms>70	No; 2 violations: WLOGP>5.6, #atoms>70
	Veber #violations	Yes	Yes
	Egan #violations	Yes	Yes
	Muegge #violations	Yes	No; 1 violation: XLOGP3>5
Medicinal Chemistry	Bioavailability Score	0.55	0.55
	PAINS #alerts	0 alert	0 alert
	Brenk #alerts	1 alert: isolated_alkene	0 alert
	Leadlikeness #violations	No; 2 violations: MW>350, XLOGP3>3.5	No; 2 violations: MW>350, XLOGP3>3.5
	Synthetic Accessibility	7.06	6.88

Compound Properties		Hydroxylupanine	Dopamine
Lipophilicity:	(iLOGP)	2.44	1.27
	XLOGP3	0.6	-0.98
	WLOGP	0.08	0.6
	MLOGP	1.42	0.6
	Silicos-IT Log P	0.42	0.8
	Consensus Log P	0.99	0.46
Water Solubility:	ESOL Log S	-1.86	-0.44
	ESOL Solubility (mol/l)	3.67e+00 mg/ml ; 1.39e-02 mol/l	5.51e+01 mg/ml ; 3.60e-01 mol/l
	ESOL Class	Very soluble	Very soluble
	Ali Log S	-1.09	0.07
	Ali Solubility (mol/l)	2.13e+01 mg/ml ; 8.07e-02 mol/l	1.80e+02 mg/ml ; 1.17e+00 mol/l
	Ali Class	Very soluble	Highly soluble
	Silicos-IT LogSw	-0.87	-1.68

	Silicos-IT Solubility (mol/l)	3.54e+01 mg/ml ; 1.34e-01 mol/l	3.19e+00 mg/ml ; 2.08e-02 mol/l
	Silicos-IT class	Soluble	Soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	No	No
	Pgp substrate	Yes	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No
	log Kp (cm/s)	-7.49 cm/s	-7.93 cm/s
Druglikeness	Lipinski #violations	Yes; 0 violation	Yes; 0 violation
	Ghose #violations	Yes	No; 1 violation: MW<160
	Veber #violations	Yes	Yes
	Egan #violations	Yes	Yes
	Muegge #violations	Yes	No; 1 violation: MW<200
	Bioavailability Score	0.55	0.55
Medicinal Chemistry	PAINS #alerts	0 alert	1 alert: catechol_A
	Brenk #alerts	0 alert	1 alert: catechol
	Leadlikeness #violations	Yes	No; 1 violation: MW<250
	Synthetic Accessibility	3.46	1.01

Compound Properties		Caffeic acid	Genistein	Epine
Lipophilicity:	(iLOGP)	0.97	1.91	1.72
	XLOGP3	1.15	2.67	-0.47
	WLOGP	1.09	2.58	0.86
	MLOGP	0.7	0.52	0.92
	Silicos-IT Log P	0.75	2.52	1.21

	Consensus Log P	0.93	2.04	0.85
Water Solubility:	ESOL Log S	-1.89	-3.72	-0.75
	ESOL Solubility (mol/l)	2.32e+00 mg/ml ; 1.29e-02 mol/l	5.11e-02 mg/ml ; 1.89e-04 mol/l	2.96e+01 mg/ml ; 1.77e-01 mol/l
	ESOL Class	Very soluble	Soluble	Very soluble
	Ali Log S	-2.38	-4.23	-0.17
	Ali Solubility (mol/l)	7.55e-01 mg/ml ; 4.19e-03 mol/l	1.59e-02 mg/ml ; 5.88e-05 mol/l	1.14e+02 mg/ml ; 6.83e-01 mol/l
	Ali Class	Soluble	Moderately soluble	Very soluble
	Silicos-IT LogSw	-0.71	-4.4	-2.49
	Silicos-IT Solubility (mol/l)	3.51e+01 mg/ml ; 1.95e-01 mol/l	1.07e-02 mg/ml ; 3.94e-05 mol/l	5.44e-01 mg/ml ; 3.25e-03 mol/l
	Silicos-IT class	Soluble	Moderately soluble	Soluble
Pharmacokinetics	GI absorption	High	High	High
	BBB permeant	No	No	Yes
	Pgp substrate	No	No	No
	CYP1A2 inhibitor	No	Yes	No
	CYP2C19 inhibitor	No	No	No
	CYP2C9 inhibitor	No	No	No
	CYP2D6 inhibitor	No	Yes	No
	CYP3A4 inhibitor	No	Yes	No
	log Kp (cm/s)	-6.58 cm/s	-6.05 cm/s	-7.65 cm/s
Druglikeness	Lipinski #violations	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
	Ghose #violations	Yes	Yes	Yes

	Veber #violations	Yes	Yes	Yes
	Egan #violations	Yes	Yes	Yes
	Muegge #violations	No; 1 violation: MW<200	Yes	No; 1 violation: MW<200
	Bioavailability Score	0.56	0.55	0.55
Medicinal Chemistry	PAINS #alerts	1 alert: catechol_A	0 alert	1 alert: catechol_A
	Brenk #alerts	2 alerts: catechol, michael_acceptor_1	0 alert	1 alert: catechol
	Leadlikeness #violations	No; 1 violation: MW<250	Yes	No; 1 violation: MW<250
	Synthetic Accessibility	1.81	2.87	1.09

Compound Properties		Ethyl palmitate	2-Ethylhexanol
Lipophilicity:	(iLOGP)	4.65	2.5
	XLOGP3	7.88	3.08
	WLOGP	6.03	2.2
	MLOGP	4.67	2.22
	Silicos-IT Log P	6.28	1.97
	Consensus Log P	5.9	2.39
Water Solubility:	ESOL Log S	-5.51	-2.26
	ESOL Solubility (mol/l)	8.75e-04 mg/ml ; 3.07e-06 mol/l	7.19e-01 mg/ml ; 5.52e-03 mol/l
	ESOL Class	Moderately soluble	Soluble
	Ali Log S	-8.28	-3.17
	Ali Solubility (mol/l)	1.49e-06 mg/ml ; 5.24e-09 mol/l	8.76e-02 mg/ml ; 6.73e-04 mol/l
	Ali Class	Poorly soluble	Soluble
	Silicos-IT LogSw	-6.41	-2.12

	Silicos-IT Solubility (mol/l)	1.10e-04 mg/ml ; 3.88e-07 mol/l	9.99e-01 mg/ml ; 7.67e-03 mol/l
	Silicos-IT class	Poorly soluble	Soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	No	Yes
	Pgp substrate	No	No
	CYP1A2 inhibitor	Yes	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No
	log Kp (cm/s)	-2.44 cm/s	-4.91 cm/s
Druglikeness	Lipinski #violations	Yes; 1 violation: MLOGP>4.15	Yes; 0 violation
	Ghose #violations	No; 1 violation: WLOGP>5.6	No; 1 violation: MW<160
	Veber #violations	No; 1 violation: Rotors>10	Yes
	Egan #violations	No; 1 violation: WLOGP>5.88	Yes
	Muegge #violations	No; 2 violations: XLOGP3>5, Rotors>15	No; 2 violations: MW<200, Heteroatoms<2
	Bioavailability Score	0.55	0.55
Medicinal Chemistry	PAINS #alerts	0 alert	0 alert
	Brenk #alerts	0 alert	0 alert
	Leadlikeness #violations	No; 2 violations: Rotors>7, XLOGP3>3.5	No; 1 violation: MW<250
	Synthetic Accessibility	2.8	1.9

Compound Properties		Rubiatriol	Pyrogallol
Lipophilicity:	(iLOGP)	4.29	0.97
	XLOGP3	6.32	0.52
	WLOGP	5.97	0.8
	MLOGP	5.12	0.18
	Silicos-IT Log P	5.01	0.43
	Consensus Log P	5.34	0.58
Water Solubility:	ESOL Log S	-6.6	-1.44

	ESOL Solubility (mol/l)	1.15e-04 mg/ml ; 2.51e-07 mol/l	4.55e+00 mg/ml ; 3.61e-02 mol/l
	ESOL Class	Poorly soluble	Very soluble
	Ali Log S	-7.38	-1.37
	Ali Solubility (mol/l)	1.89e-05 mg/ml ; 4.13e-08 mol/l	5.44e+00 mg/ml ; 4.31e-02 mol/l
	Ali Class	Poorly soluble	Very soluble
	Silicos-IT LogSw	-5.07	-0.63
	Silicos-IT Solubility (mol/l)	3.89e-03 mg/ml ; 8.47e-06 mol/l	2.96e+01 mg/ml ; 2.34e-01 mol/l
	Silicos-IT class	Moderately soluble	Soluble
Pharmacokinetics	GI absorption	High	High
	BBB permeant	No	Yes
	Pgp substrate	Yes	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	Yes
	log Kp (cm/s)	-4.61 cm/s	-6.70 cm/s
Druglikeness	Lipinski #violations	Yes; 1 violation: MLOGP>4.15	Yes; 0 violation
	Ghose #violations	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 3 violations: MW<160, MR<40, #atoms<20
	Veber #violations	Yes	Yes
	Egan #violations	No; 1 violation: WLOGP>5.88	Yes
	Muegge #violations	No; 1 violation: XLOGP3>5	No; 1 violation: MW<200
	Bioavailability Score	0.55	0.55

Medicinal Chemistry	PAINS #alerts	0 alert	1 alert: catechol_A
	Brenk #alerts	1 alert: isolated_alkene	1 alert: catechol
	Leadlikeness #violations	No; 2 violations: MW>350, XLOGP3>3.5	No; 1 violation: MW<250
	Synthetic Accessibility	6.61	1

Compound Properties		<u>Nordamnacanthal</u>	<u>Serotonin</u>	<u>Rubilactone</u>
Lipophilicity:	(iLOGP)	1.08	1.18	2.1
	XLOGP3	2.72	1.49	3.21
	WLOGP	1.69	1.37	2.44
	MLOGP	0.02	0.65	1.84
	Silicos-IT Log P	2.73	1.95	2.87
	Consensus Log P	1.65	1.33	2.49
Water Solubility:	ESOL Log S	-3.59	-2.25	-3.92
	ESOL Solubility (mol/l)	6.82e-02 mg/ml ; 2.54e-04 mol/l	9.87e-01 mg/ml ; 5.60e-03 mol/l	3.22e-02 mg/ml ; 1.19e-04 mol/l
	ESOL Class	Soluble	Soluble	Soluble
	Ali Log S	-4.3	-2.4	-4.49
	Ali Solubility (mol/l)	1.35e-02 mg/ml ; 5.03e-05 mol/l	7.01e-01 mg/ml ; 3.98e-03 mol/l	8.67e-03 mg/ml ; 3.21e-05 mol/l
	Ali Class	Moderately soluble	Soluble	Moderately soluble
	Silicos-IT LogSw	-4.04	-3.16	-4.79
	Silicos-IT Solubility (mol/l)	2.43e-02 mg/ml ; 9.06e-05 mol/l	1.23e-01 mg/ml ; 6.98e-04 mol/l	4.39e-03 mg/ml ; 1.63e-05 mol/l
	Silicos-IT class	Moderately soluble	Soluble	Moderately soluble

Pharmacokinetics	GI absorption	High	High	High
	BBB permeant	No	Yes	Yes
	Pgp substrate	No	No	No
	CYP1A2 inhibitor	No	No	Yes
	CYP2C19 inhibitor	No	No	No
	CYP2C9 inhibitor	No	No	No
	CYP2D6 inhibitor	No	No	No
	CYP3A4 inhibitor	Yes	No	No
	log Kp (cm/s)	-6.00 cm/s	-6.32 cm/s	-5.67 cm/s
Druglikeness	Lipinski #violations	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
	Ghose #violations	Yes	Yes	Yes
	Veber #violations	Yes	Yes	Yes
	Egan #violations	Yes	Yes	Yes
	Muegge #violations	Yes	No; 1 violation: MW<200	Yes
	Bioavailability Score	0.55	0.55	0.55
Medicinal Chemistry	PAINS #alerts	<u>1 alert: quinone A</u>	0 alert	0 alert
	Brenk #alerts	<u>1 alert: aldehyde</u>	0 alert	<u>2 alerts: cumarine, polycyclic aromatic hydrocarbon 3</u>
	Leadlikeness #violations	Yes	No; 1 violation: MW<250	Yes

	Synthetic Accessibi lity	2.52	1.42	2.77
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Compound Properties		Betulin	<u>SCHLEICHERASTATIN</u> <u>6</u>
Lipophilicity:	(iLOGP)	4.47	4.15
	XLOGP3	8.28	6.39
	WLOGP	7	5.78
	MLOGP	6	4.62
	Silicos-IT Log P	6.21	5.56
	Consensus Log P	6.39	5.3
Water Solubility:	ESOL Log S	-7.67	-6.21
	ESOL Solubility (mol/l)	9.48e-06 mg/ml ; 2.14e-08 mol/l	2.68e-04 mg/ml ; 6.23e-07 mol/l
	ESOL Class	Poorly soluble	Poorly soluble
	Ali Log S	-8.99	-7.39
	Ali Solubility (mol/l)	4.50e-07 mg/ml ; 1.02e-09 mol/l	1.75e-05 mg/ml ; 4.07e-08 mol/l
	Ali Class	Poorly soluble	Poorly soluble
	Silicos-IT LogSw	-6.17	-4.73
	Silicos-IT Solubility (mol/l)	2.99e-04 mg/ml ; 6.75e-07 mol/l	8.09e-03 mg/ml ; 1.88e-05 mol/l
	Silicos-IT class	Poorly soluble	Moderately soluble
Pharmacokinetics	GI absorption	Low	High
	BBB permeant	No	No
	Pgp substrate	No	No
	CYP1A2 inhibitor	No	No
	CYP2C19 inhibitor	No	No
	CYP2C9 inhibitor	No	No
	CYP2D6 inhibitor	No	No
	CYP3A4 inhibitor	No	No
	log Kp (cm/s)	-3.12 cm/s	-4.39 cm/s

Druglikeness	Lipinski #violations	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15
	Ghose #violations	No; 3 violations: WLOGP>5.6, MR>130, #atoms>70	No; 2 violations: WLOGP>5.6, #atoms>70
	Veber #violations	Yes	Yes
	Egan #violations	No; 1 violation: WLOGP>5.88	Yes
	Muegge #violations	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
	Bioavailability Score	0.55	0.55
Medicinal Chemistry	PAINS #alerts	0 alert	0 alert
	Brenk #alerts	1 alert: isolated_alkene	0 alert
	Leadlikeness #violations	No; 2 violations: MW>350, XLOGP3>3.5	No; 2 violations: MW>350, XLOGP3>3.5
	Synthetic Accessibility	5.68	6.21

5.4 PHARMACOPHORE ANALYSIS

The pharmacophore analysis of compounds has been done.

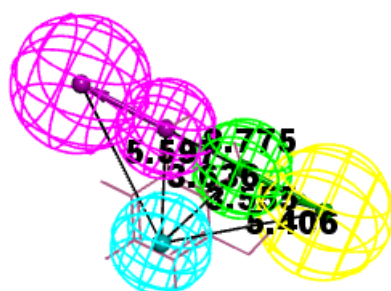
The output of pharmacophore analysis includes a 3D model of the pharmacophore, which displays the key features such as hydrogen bond acceptors and donors, aromatic rings, and hydrophobic regions. The analysis also provides information on the quality of the pharmacophore model, such as the degree of fit to the active compounds, and the statistical significance of the pharmacophore features.

Pharmacophore features include:

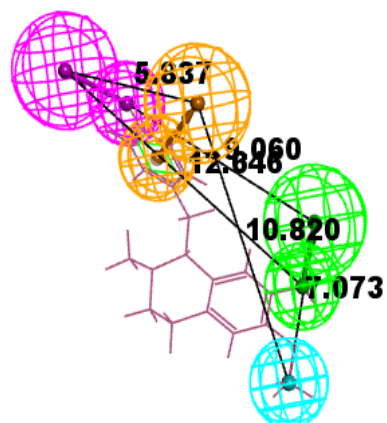
1. Hydrogen bond acceptor: A chemical group that can accept hydrogen bonds.
2. Hydrogen bond donor: A chemical group that can donate hydrogen bonds.
3. Aromatic ring: A flat, cyclic arrangement of atoms with alternating double bonds that can interact with aromatic amino acids in a protein.
4. Aliphatic group: A linear or branched hydrocarbon chain that can interact with hydrophobic regions in a protein.
5. Positive ionizable group: A chemical group that can be protonated to form a positive charge, which can interact with negatively charged amino acids in a protein.
6. Negative ionizable group: A chemical group that can be deprotonated to form a negative charge, which can interact with positively charged amino acids in a protein.

Fig 5.4 PHARMACOPHORE OF IDENTIFIED COMPOUNDS

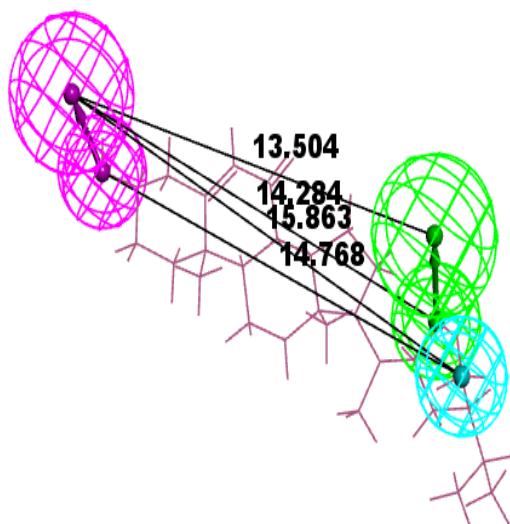
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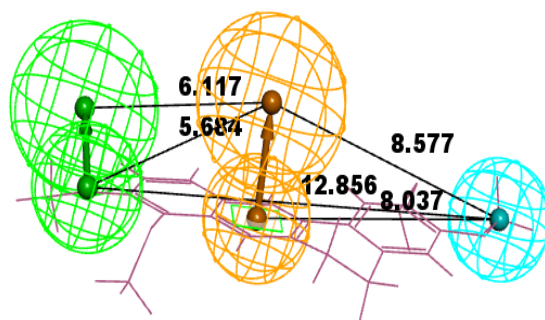
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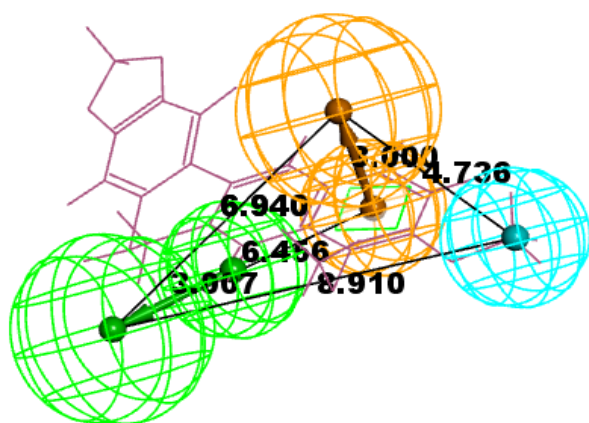
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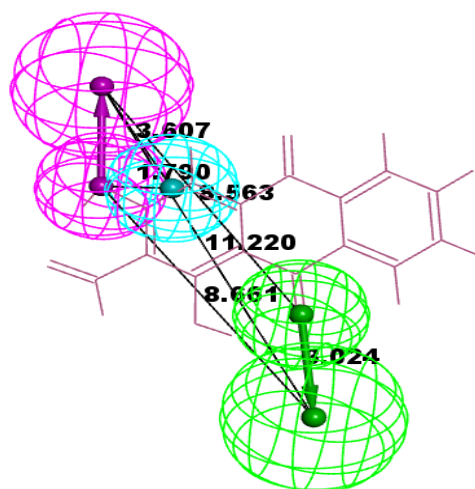
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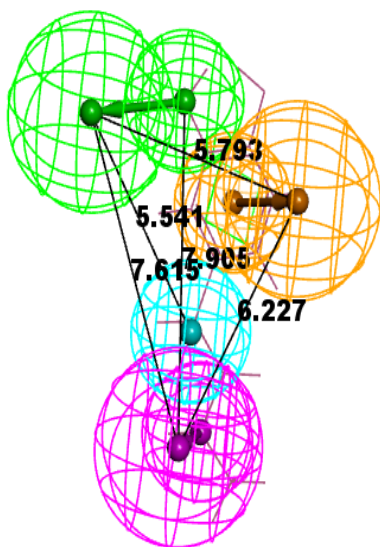
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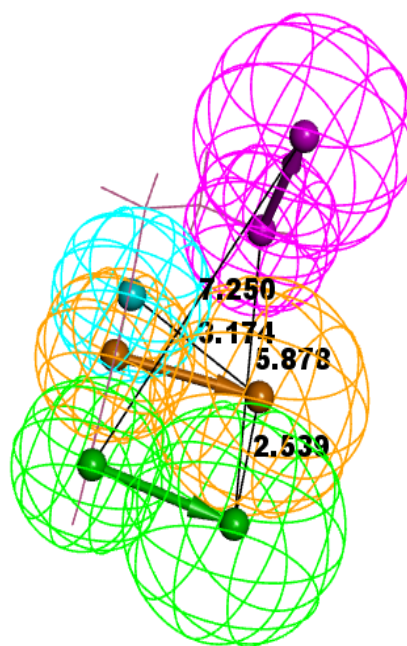
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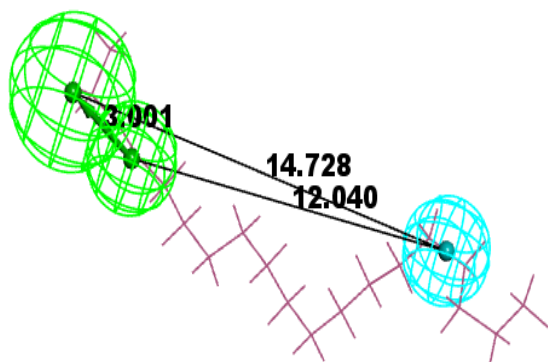
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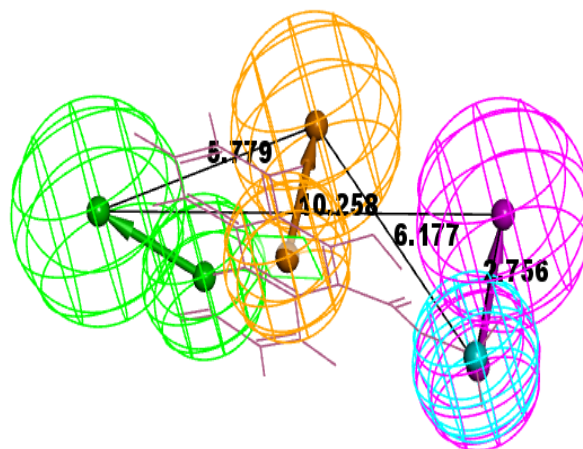
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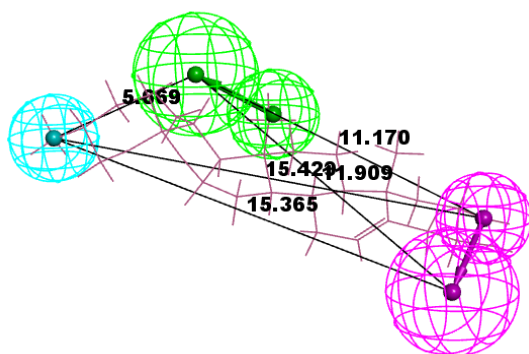
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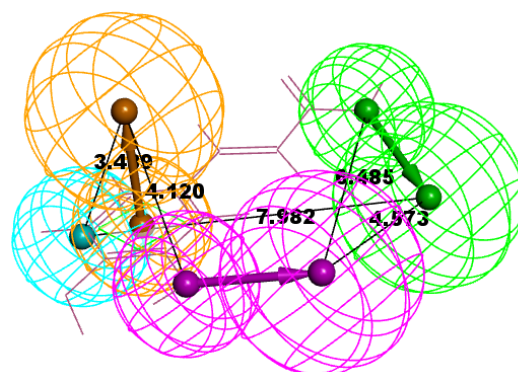
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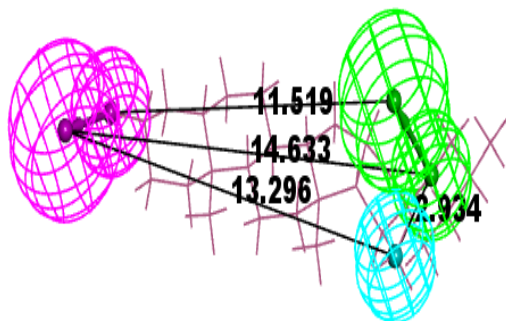
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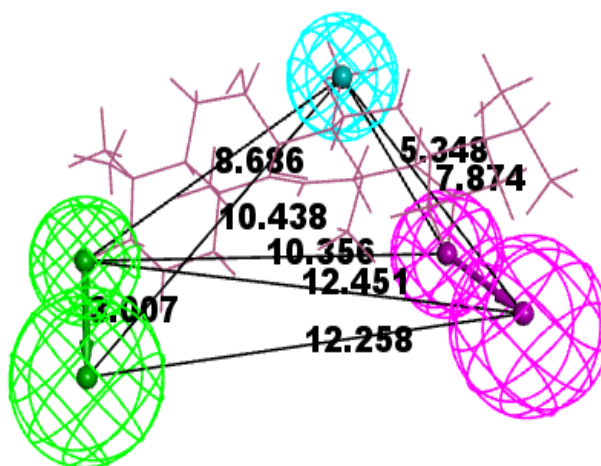
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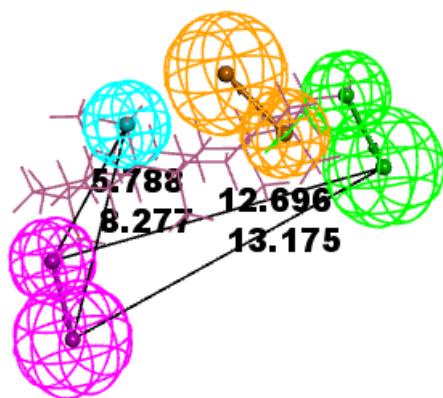
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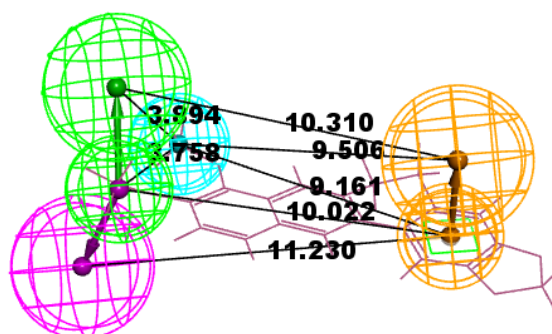
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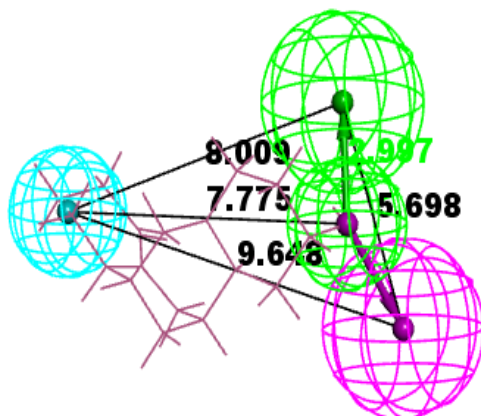
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16.



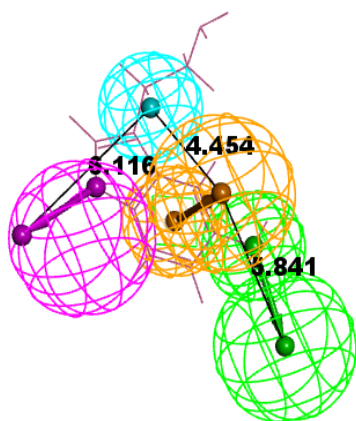
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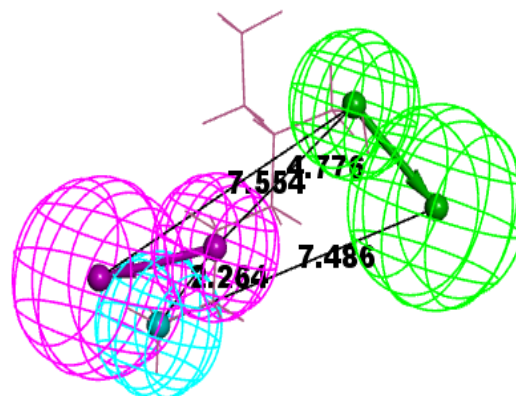
18.



19.



20.



H bond ACCEPTOR



HYDROPHOBIC



H bond DONOR



RING_AROMATIC

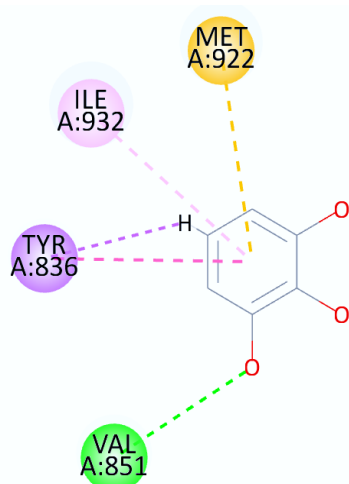
1.Pyrogallol 2. N- Methylcoclaurine 3. SCHLEICHERASTATIN (6) 4. Palmatine
5.Oxyberberine 6.Nordamnacanthal 7.Epinine 8.Dopamine 9.Ethyl Palmitate
10.Rubilactone 11.Yuccagenin 12.Caffeic acid 13.Tigogenin 14.Rubiatriol
15.Betulin 16.Berberine 17.Hydroxylupanine 18.Genistein 19.Serotonin 20.
2-Ethylhexanol

5.5 INTERACTION STUDIES OF DOCKED COMPOUNDS

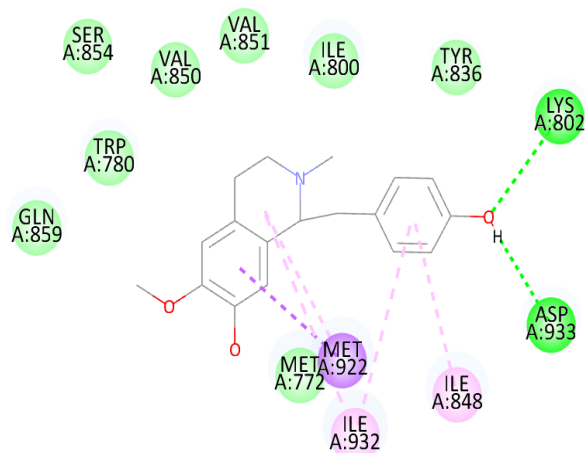
The 2D AND 3D image shows the various types of interactions that occur between the ligand and protein, such as hydrogen bonds, van der Waals interactions, and electrostatic interactions. The image also display information about the binding affinity between the ligand and protein, as well as the specific amino acids or residues involved in the interaction.

Fig 5.5 2D IMAGES OF RECEPTOR-LIGAND INTERACTION

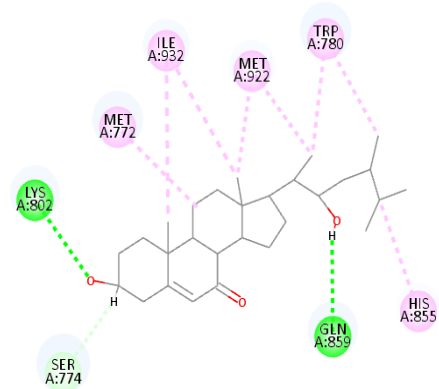
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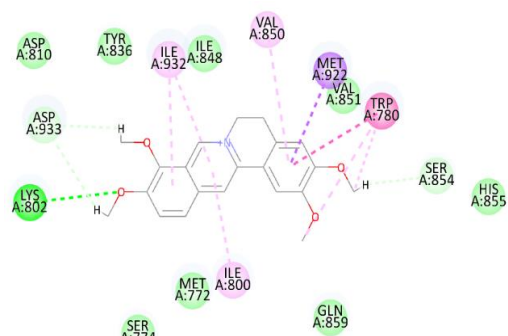
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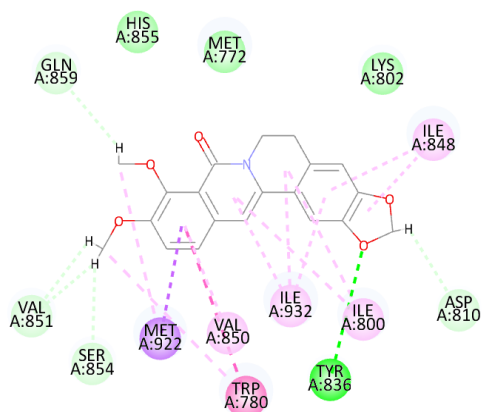
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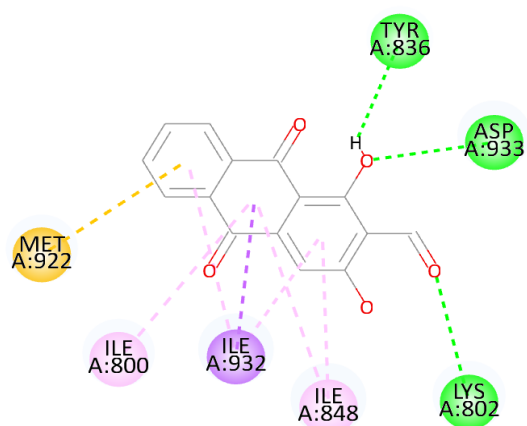
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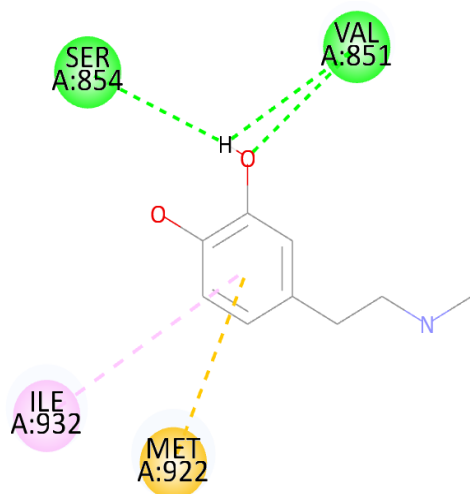
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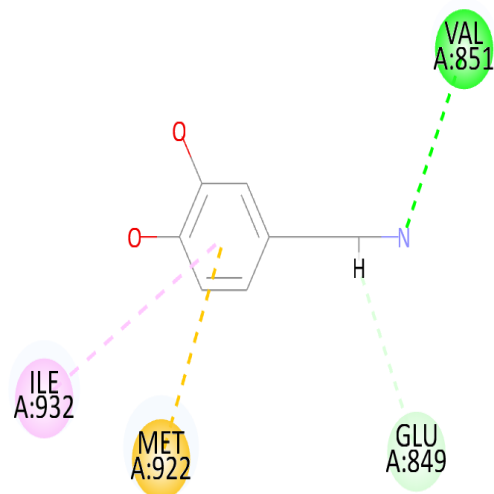
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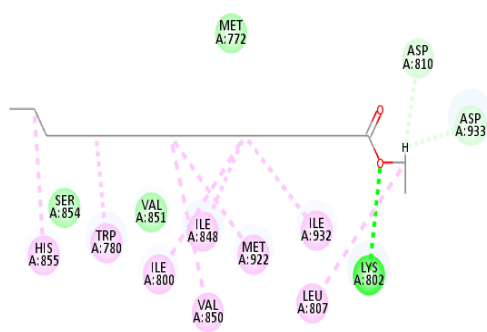
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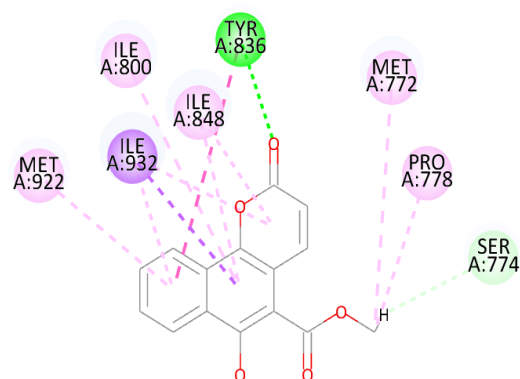
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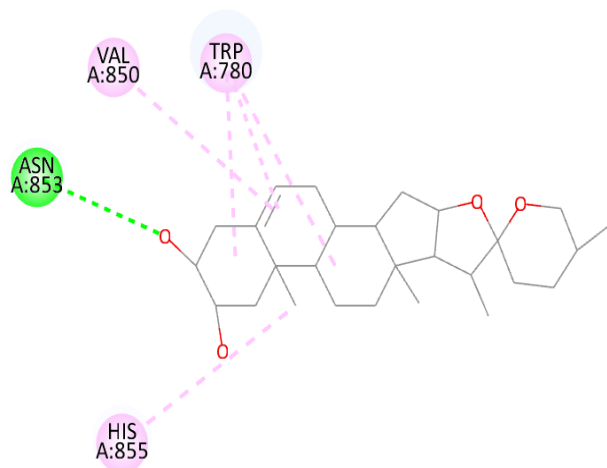
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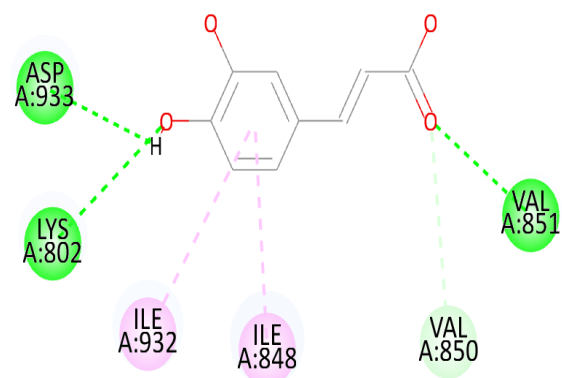
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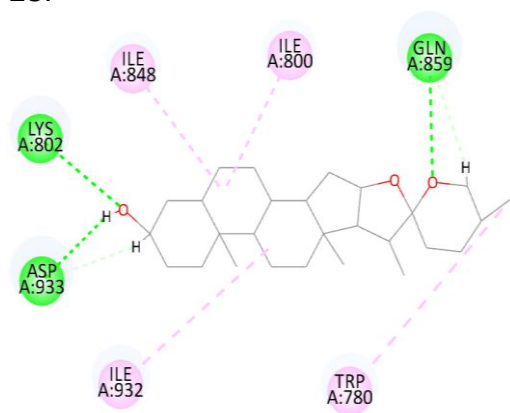
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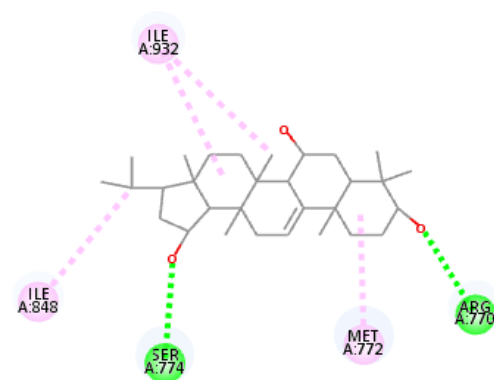
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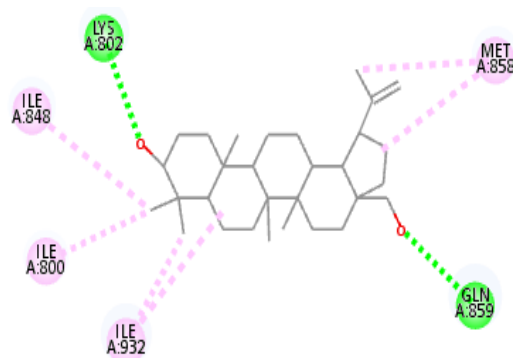
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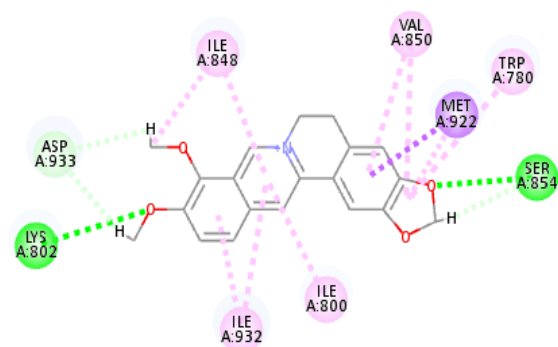
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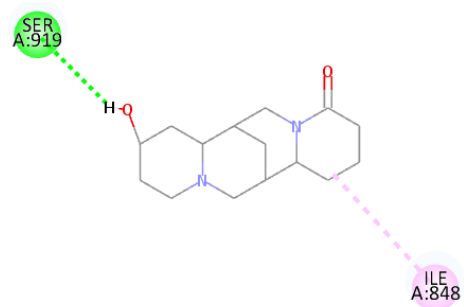
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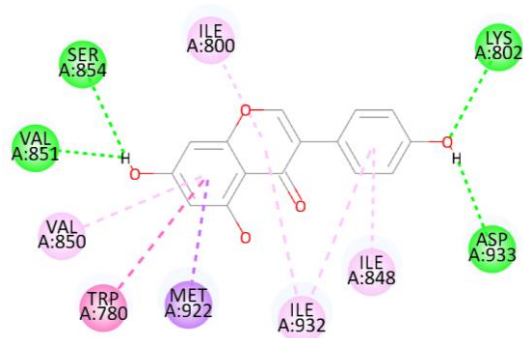
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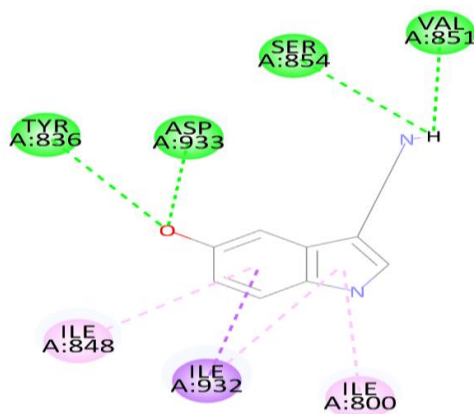
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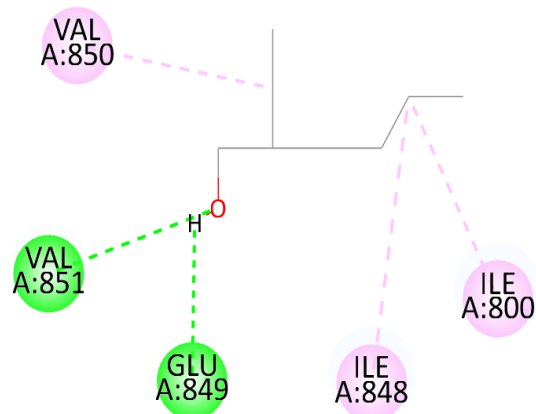
18.



19.



20.



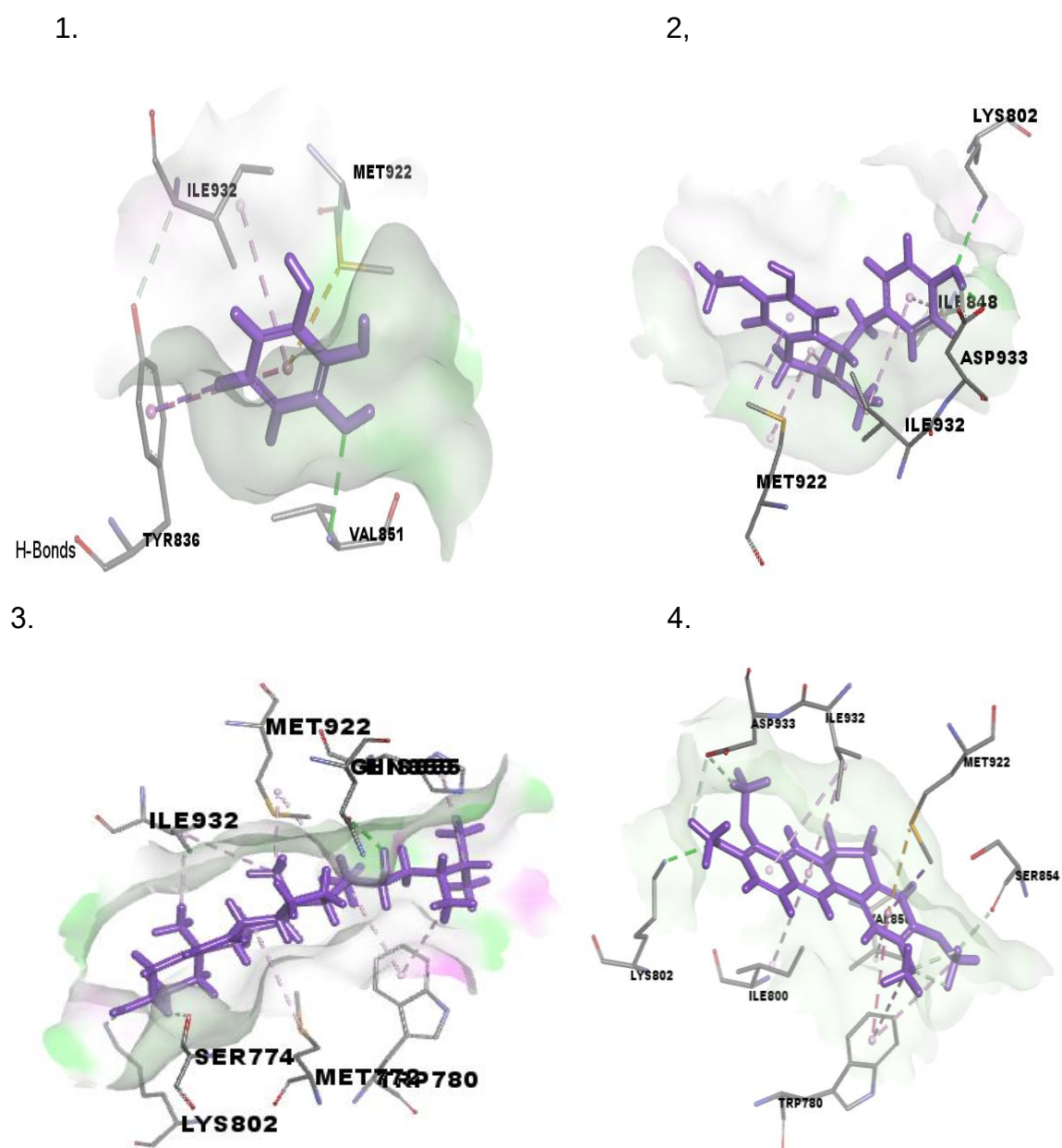
Interactions

	Conventional Hydrogen Bond
	Carbon Hydrogen Bond
	Pi-Sigma

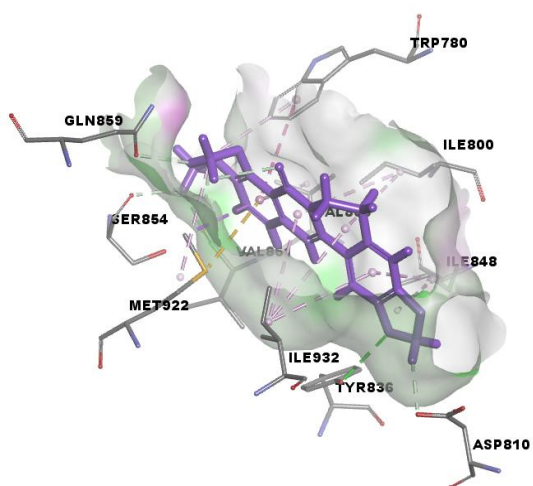
	Pi-Sulfur
	Alkyl
	Pi-Alkyl

1.Pyrogallol 2. N- Methylcoclaurine 3. SCHLEICHERASTATIN (6) 4. Palmatine
 5.Oxyberberine 6.Nordamnacanthal 7.Epinine 8.Dopamine 9.Ethyl Palmitate
 10.Rubilactone 11.Yuccagenin 12.Caffeic acid 13.Tigogenin 14.Rubiatriol
 15.Betulin 16.Berberine 17.Hydroxylupanine 18.Genistein 19.Serotonin 20.
 2-Ethylhexanol

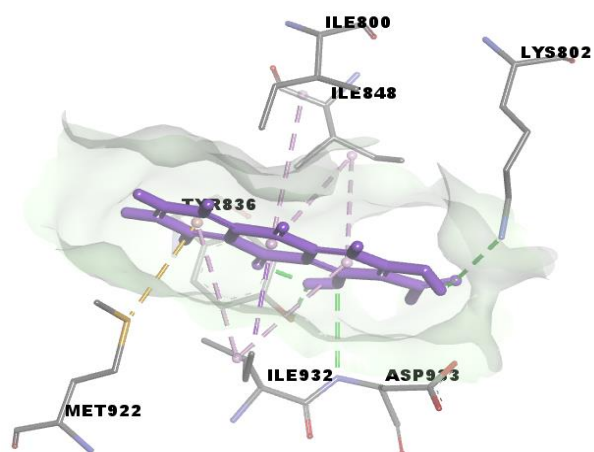
Fig 5.6 3D IMAGE OF RECEPTOR-LIGAND INTERACTION



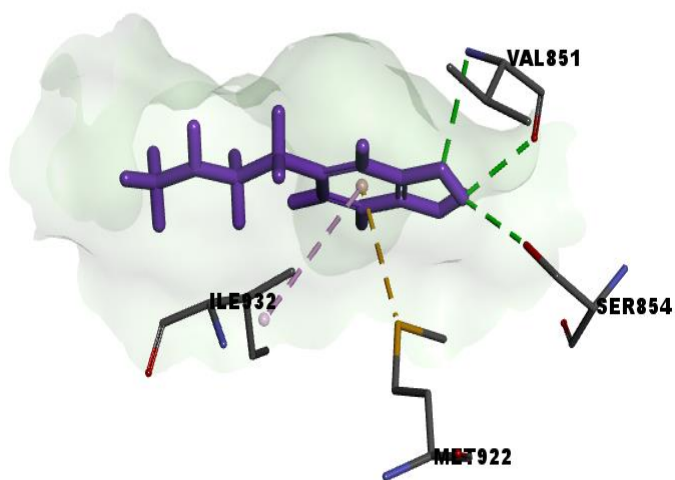
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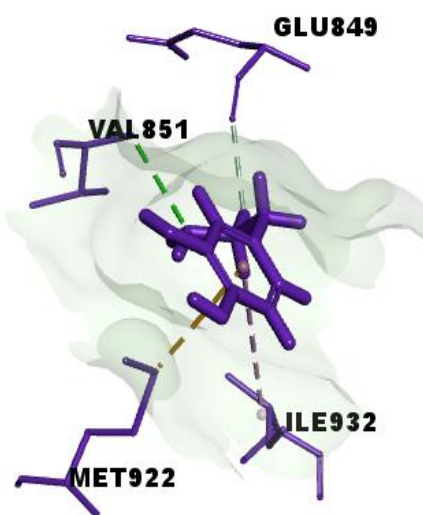
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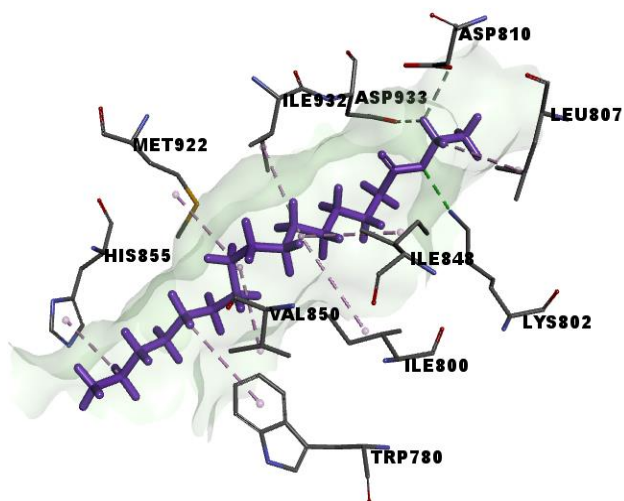
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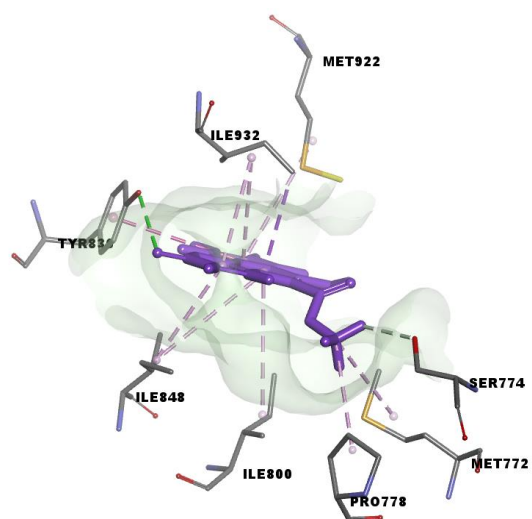
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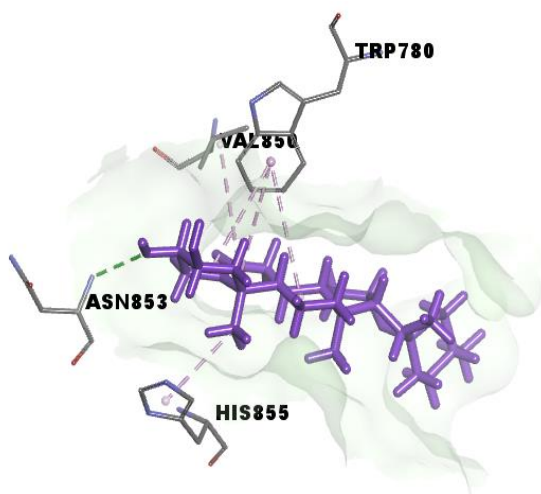


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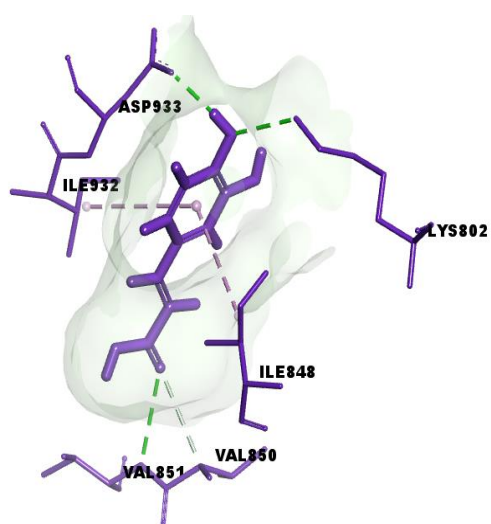


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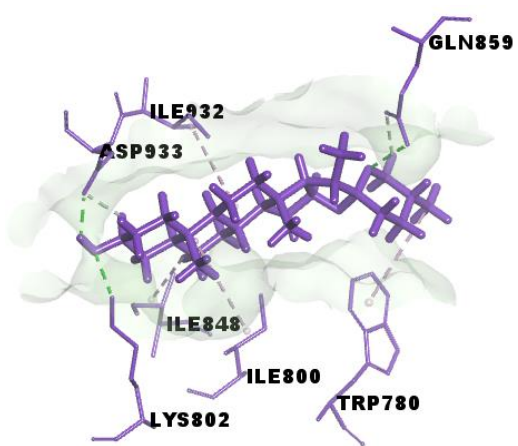
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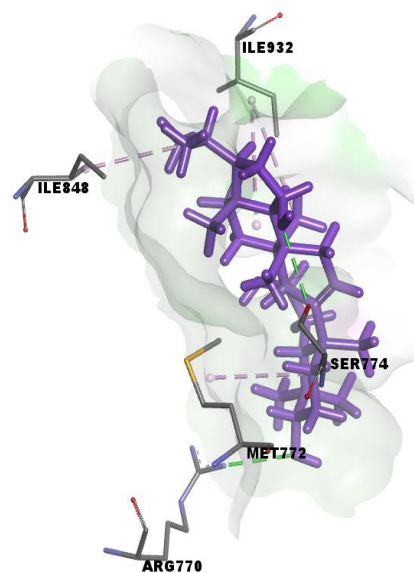
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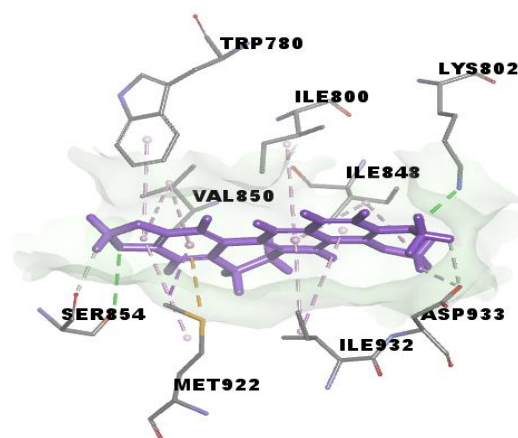
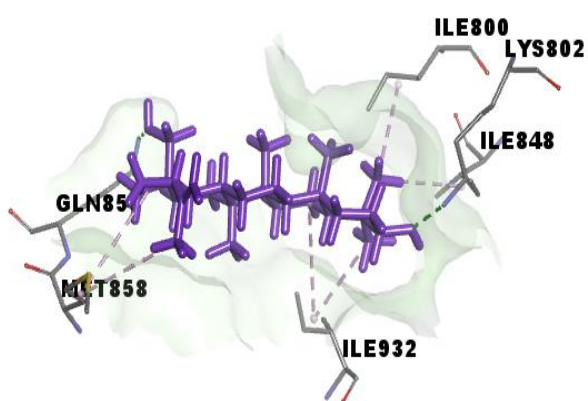
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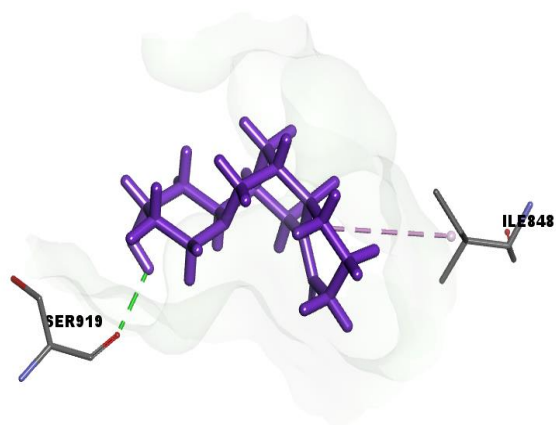
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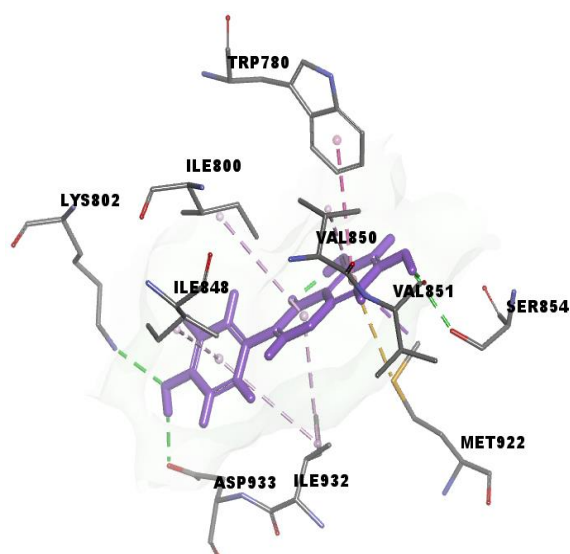
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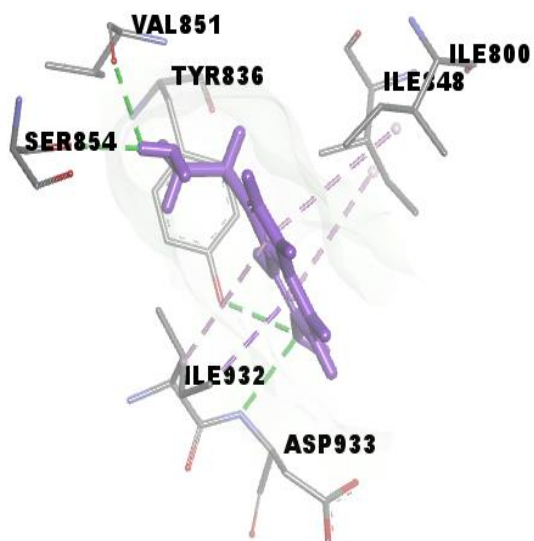
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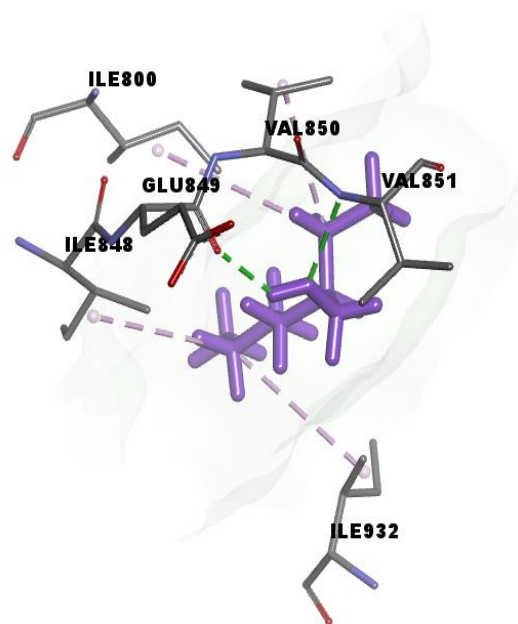
18.



19.



20.



1. Pyrogallol 2. N- Methylcoclaurine 3. SCHLEICHERASTATIN (6) 4. Palmatine
5. Oxyberberine 6. Nordamnacanthal 7. Epinine 8. Dopamine 9. Ethyl Palmitate
10. Rubilactone 11. Yuccagenin 12. Caffeic acid 13. Tigogenin 14. Rubiatriol
15. Betulin 16. Berberine 17. Hydroxylupanine 18. Genistein 19. Serotonin 20.
2-Ethylhexanol

TABLE 5.3 DOCKED COMPOUNDS INTERACTION TABLE

Name	ID	Hydrogen Bond (Interaction)	Carbon Hydrogen interaction	Alkyl	Pi- Sigma	Pi-alkyl interaction	Pi-sulphur	Pi-Pi T-shaped	Dock score
Rubiatriol	IMPHY009172	ARG770		MET772					-102.014
		SER774		ILE932					
				ILE932					
				ILE848					
Betulin	IMPHY004271								-70.7089
		LYS802		ILE932					
		GLN859		MET858					
				ILE932					
				ILE800					
				ILE848					
Yuccagenin	IMPHY010851			MET858					-56.6635
		ASN853		VAL850		TRP780			
						TRP780			
						TRP780			
Tigogenin	IMPHY012273					HIS855			-39.3754
		LYS802	ASP933	ILE800		TRP780			
		GLN859	GLN859	ILE848					
		ASP933		ILE932					
SCHLEICHERASTATIN 6	10836412	LYS802	SER774	MET772		TRP780			-30.6703
		GLN859		MET922		TRP780			
				ILE932		HIS855			
				ILE932					
				MET922					

Name	ID	Hydrogen Bond (Interaction)	Carbon Hydrogen interaction	Alkyl	Pi- Sigma	Pi-alkyl interaction	Pi-sulphur	Pi-Pi T-shaped	Dock score
Berberine	IMPHY005665	LYS802	SER854	VAL850	MET922	TRP780	MET922		
		SER854	ASP933	MET922		ILE800			
			ASP933	ILE848		ILE848			
						ILE932			
						VAL850			
Hydroxylupanine	IMPHY014728	SER919		ILE848		ILE932			-9.30917
Palmatine	IMPHY005330	LYS802	ASP933		MET922	TRP780	MET922	TRP780	0.305772
			SER854			TRP780			
			ASP933			ILE800			
						ILE932			
						VAL850			
Oxyberberine	IMPHY000342	TYR836	ASP810	ILE800	MET922	TRP780	MET922	TRP780	4.36952
			GLN859	ILE932		ILE800			
			VAL851	ILE848		ILE932			
			SER854	MET922		ILE848			
			VAL851			ILE932			
Rubiactone	IMPHY009636	TYR836	SER774	MET772	ILE932	ILE848		TYR836	12.2707
				PRO778		ILE932			
						ILE800			
2-Ethylhexanol	IMPHY006032	VAL851		ILE800					19.3445
		GLU849		VAL850					
				ILE848					
				ILE932					
Pyrogallol	1057	VAL851			TYR836	ILE932	MET922	TYR836	20.1171
Dopamine	IMPHY007257	VAL851	GLU849			ILE932	MET922		23.3297

Name	ID	Hydrogen Bond (Interaction)	Carbon Hydrogen interaction	Alkyl	Pi- Sigma	Pi-alkyl interaction	Pi-sulphur	Pi-Pi T-shaped	Dock score
Serotonin	IMPHY004653	TYR836			ILE932	ILE800			23.3737
		ASP933				ILE932			
		VAL851				ILE848			
		SER854							
Epinine	IMPHY003477	VAL851				ILE932	MET922		25.9441
		VAL851							
		SER854							
N- Methylcoclaurine	2752274	LYS802		MET922	MET922	ILE848			27.2261
		ASP93		ILE932		ILE932			
		LYS802			MET922	ILE800	MET922	TRP780	
		VAL851				ILE932			
Genistein	IMPHY004643	SER854				VAL850			27.7645
		ASP933				ILE848			
						ILE932			
						ILE848			
Caffeic acid	IMPHY011933	LYS802	VAL850			ILE848			29.2261
		VAL851				ILE932			
		ASP933							
Nordamnacanthal	IMPHY001728	LYS802			ILE932	ILE800	MET922		32.669
		ASP933				ILE848			
		TYR836				ILE848			
						ILE932			
Ethyl Palmitate	IMPHY009624	LYS802	ASP810	VAL850		LEU807			45.682
			ASP933	MET922		HIS855			
				ILE800					
				ILE848					
				ILE932					
				LEU807					

5.6 DFT ANALYSIS

DFT for the 20 compounds has been done and calculated.

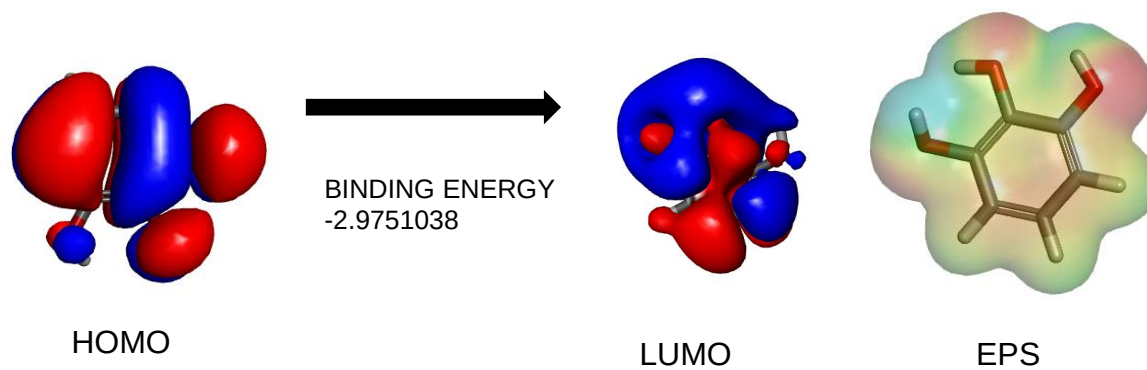
Density Functional Theory (DFT) calculations is performed to predict electronic properties of molecules, such as the Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO), and electronic polarizability (EPS).

The HOMO and LUMO are important properties in understanding the chemical reactivity of a molecule. HOMO is the highest energy molecular orbital that is occupied by electrons, while LUMO is the lowest energy molecular orbital that is unoccupied. The energy difference between HOMO and LUMO is called the HOMO-LUMO gap, and it is a measure of the molecule's ability to donate or accept electrons.

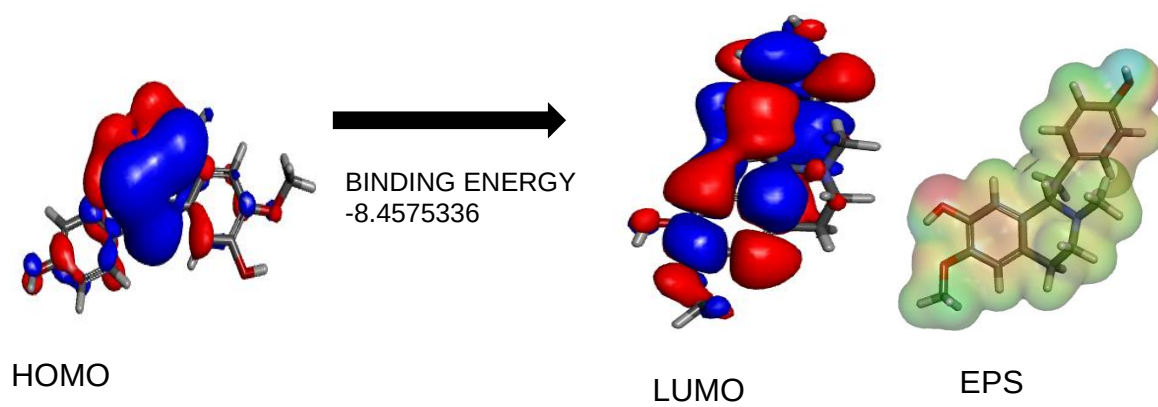
The EPS is a measure of how easily a molecule's electrons can be polarized by an external electric field. It is related to the molecule's susceptibility to interact with electromagnetic radiation.

Fig 5.7 DFT OF DOCKED COMPOUNDS

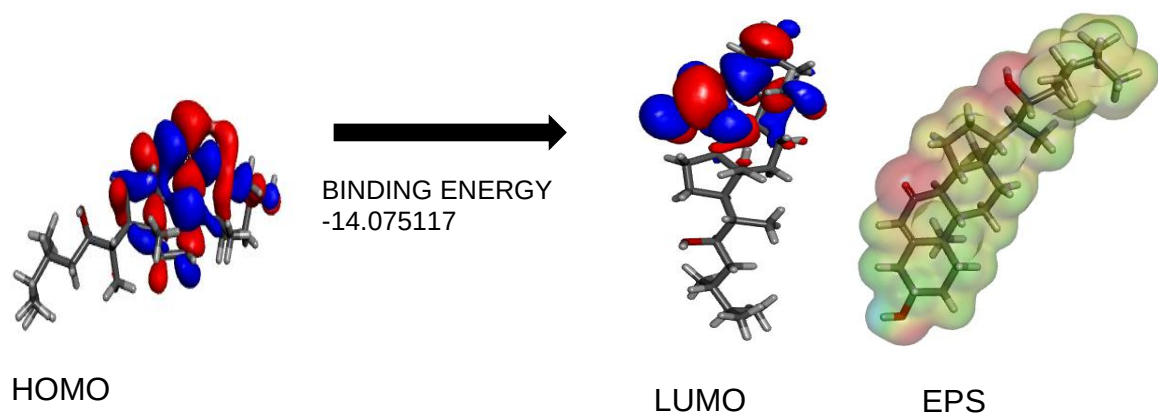
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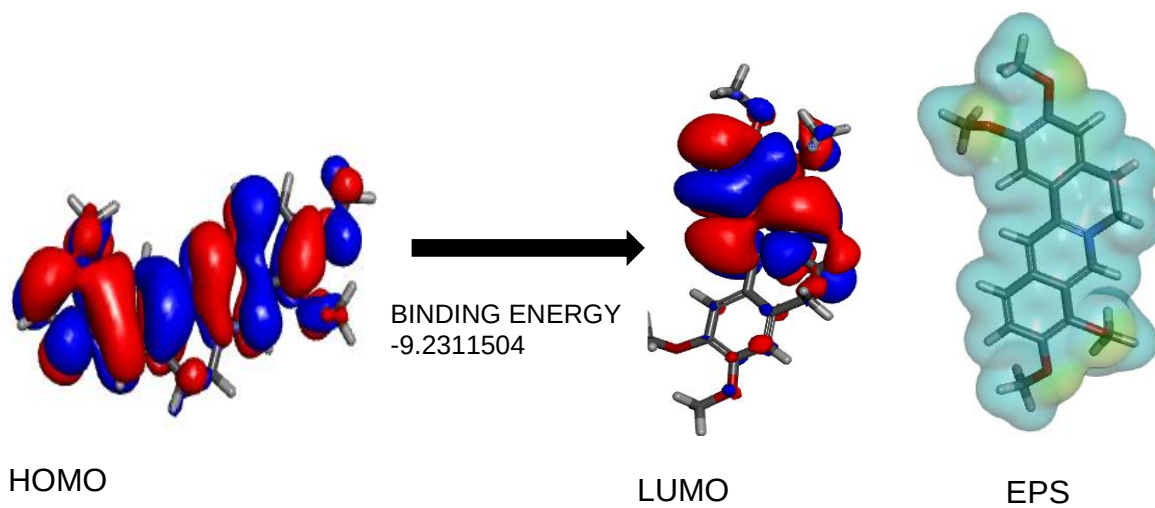
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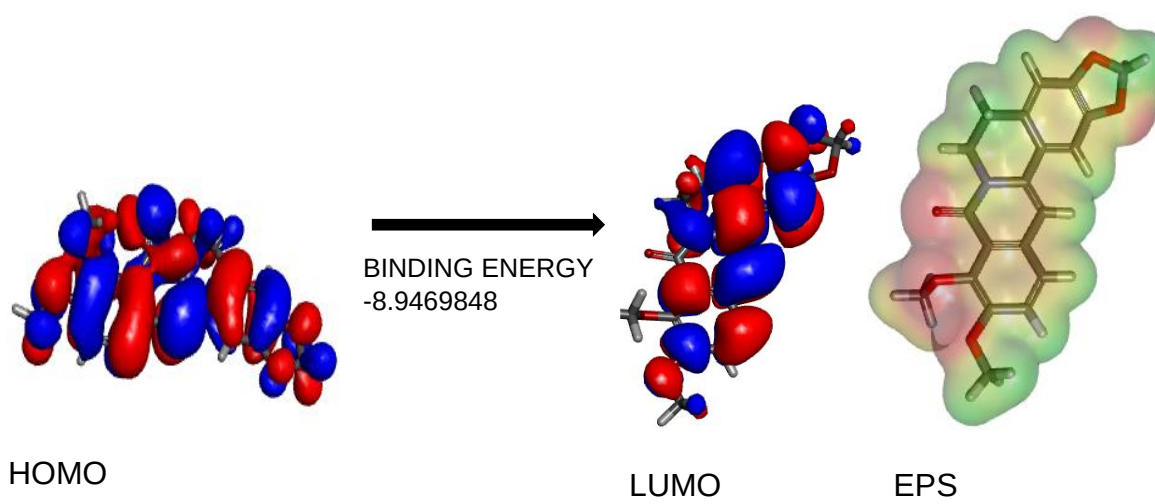
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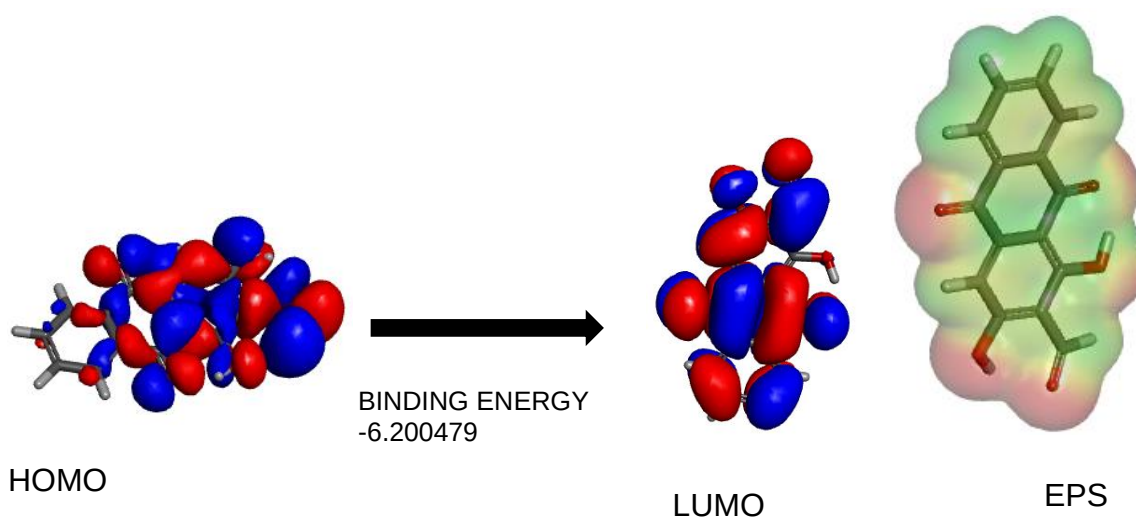
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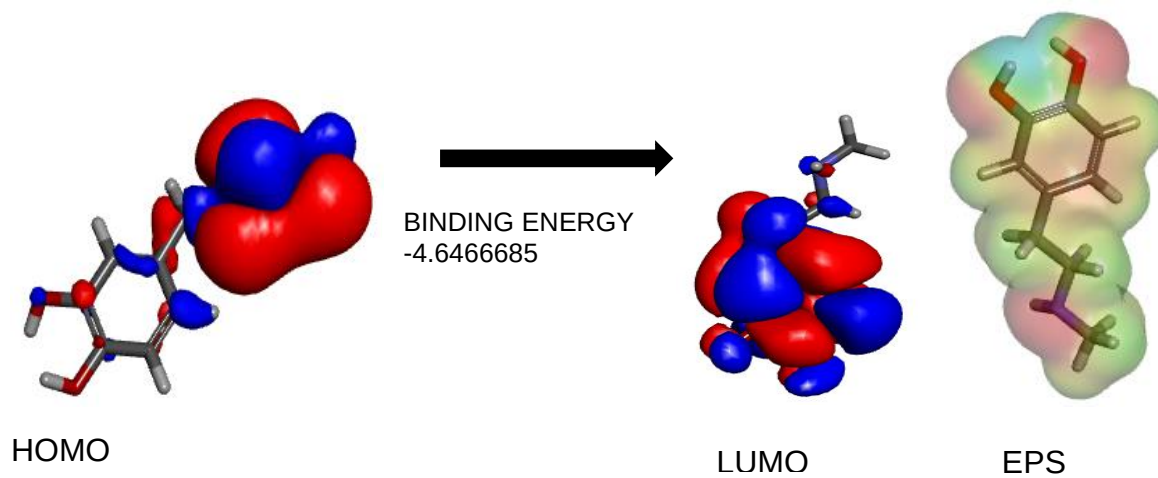
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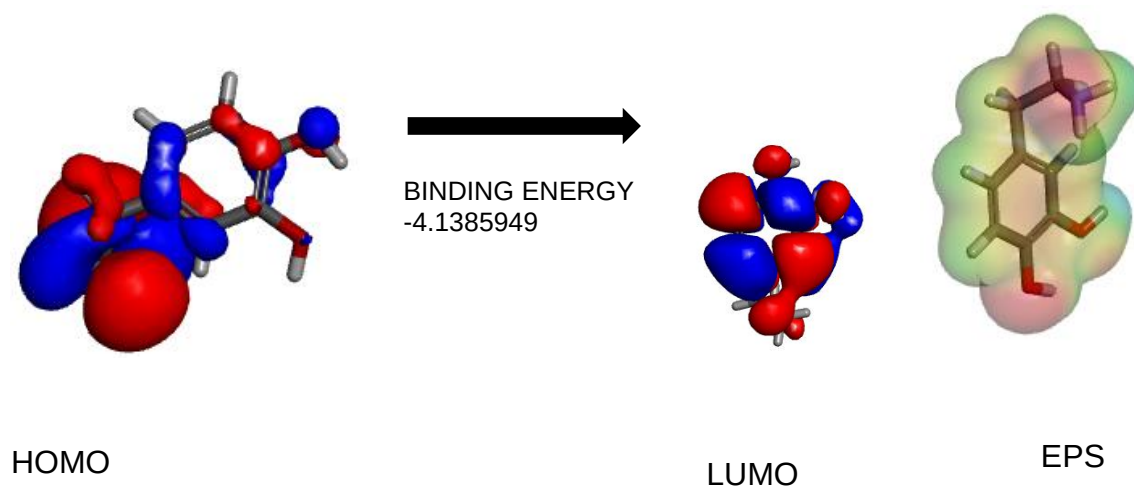
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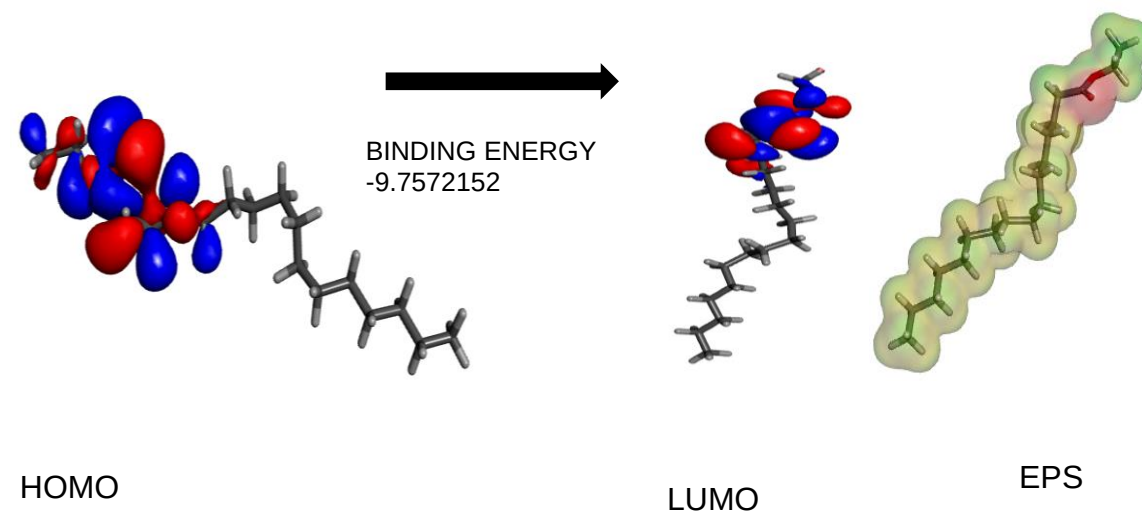
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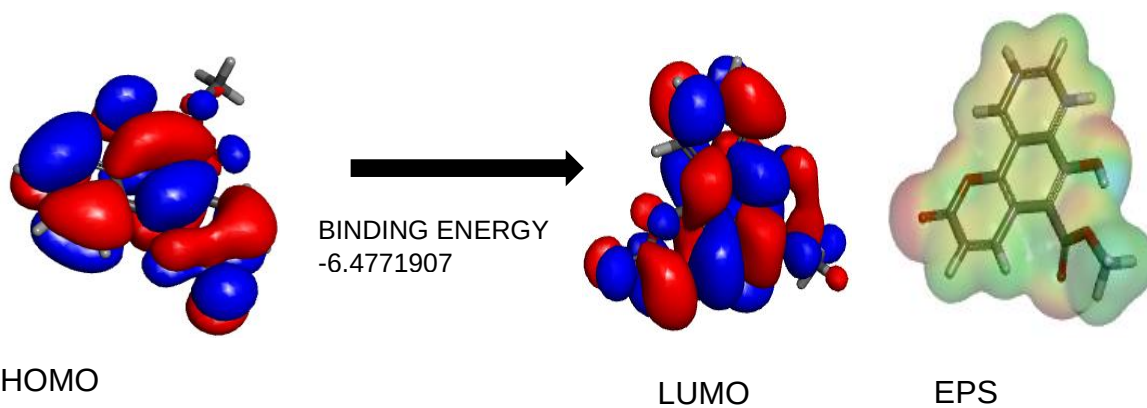
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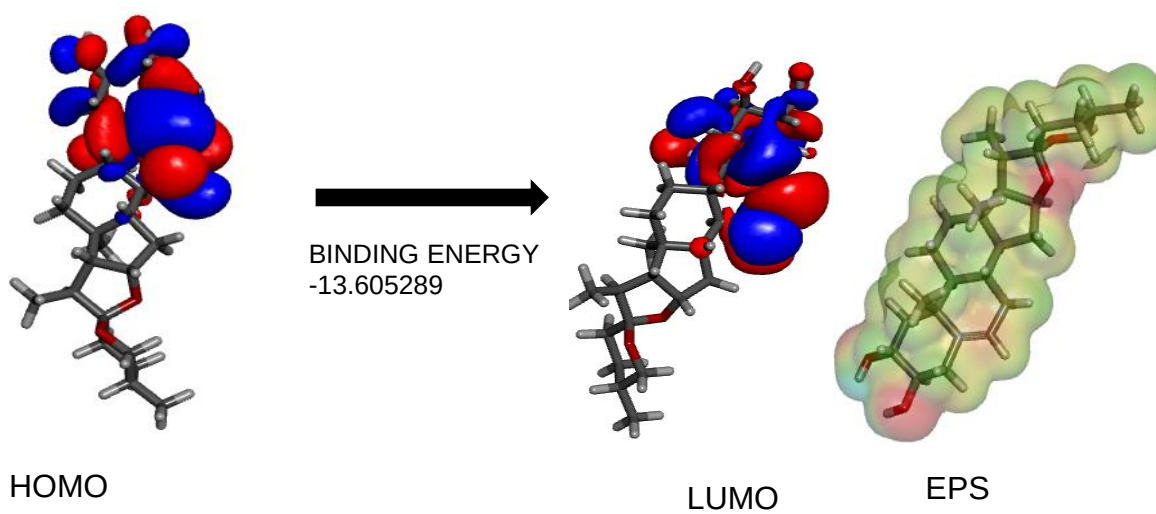
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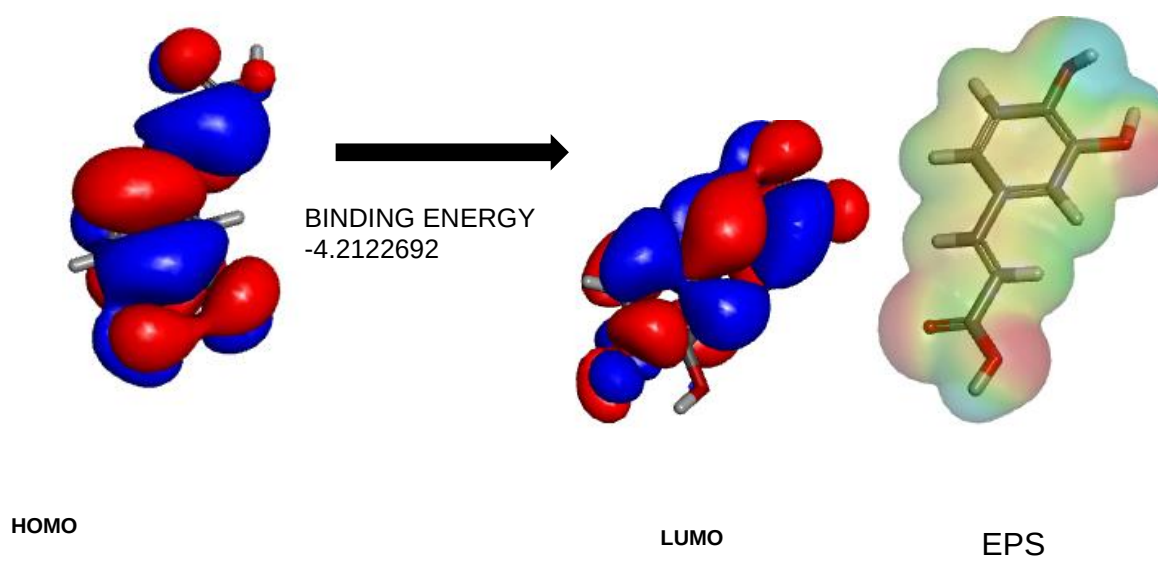
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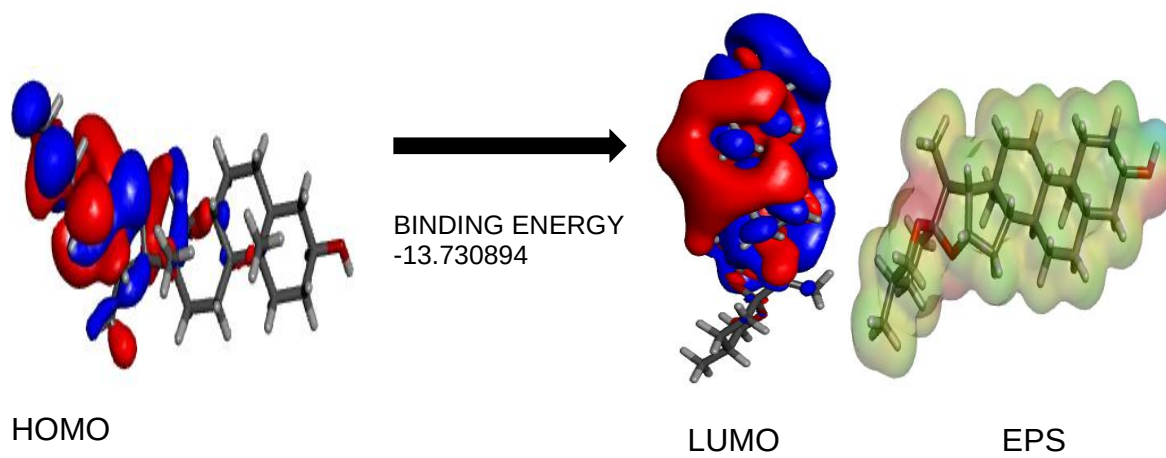
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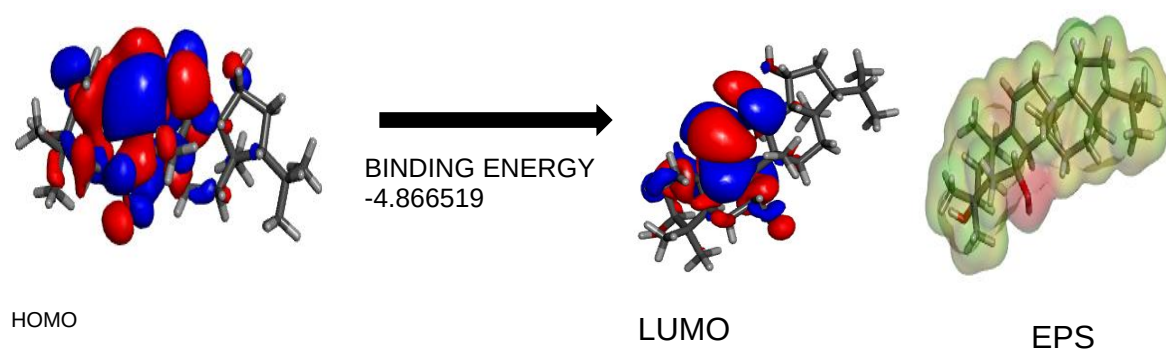
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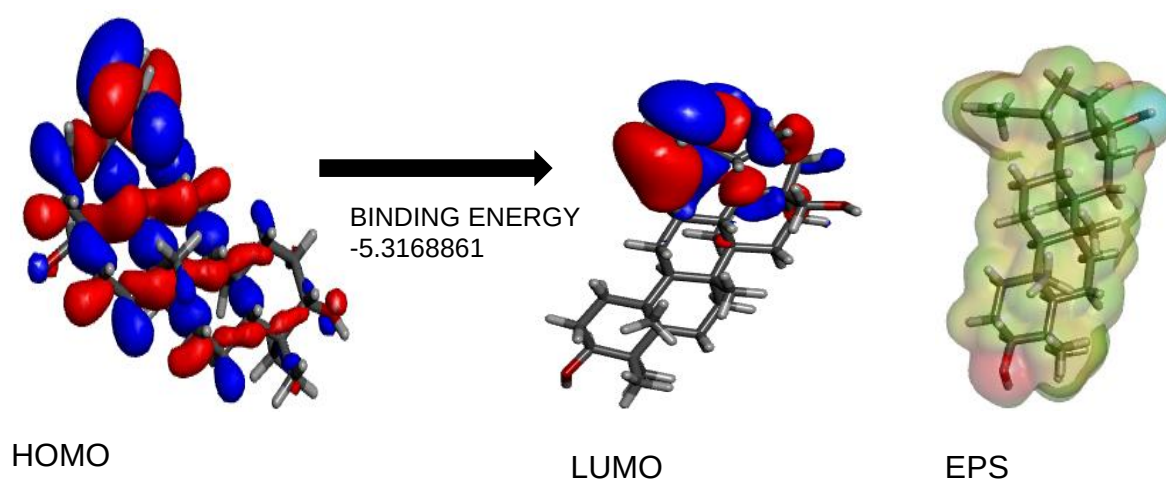
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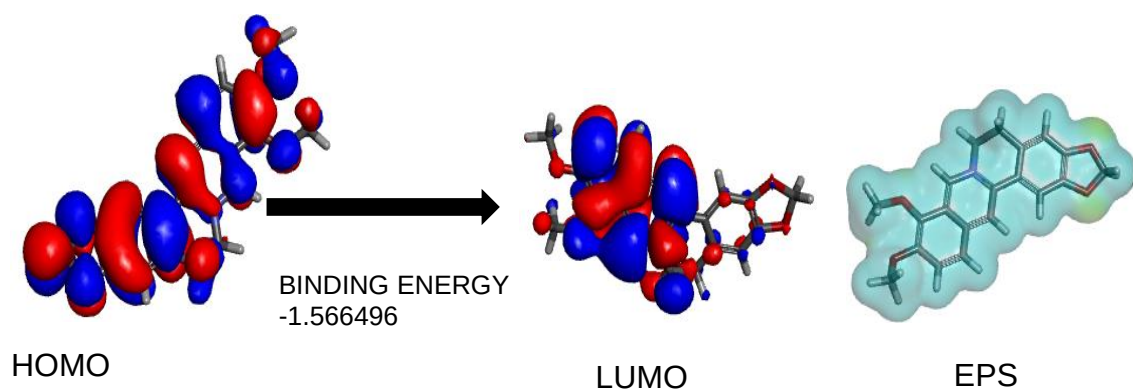
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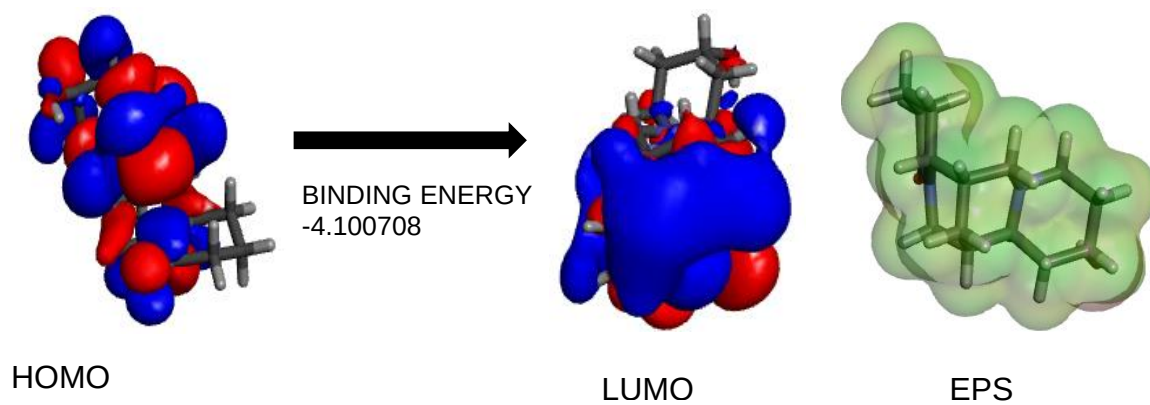
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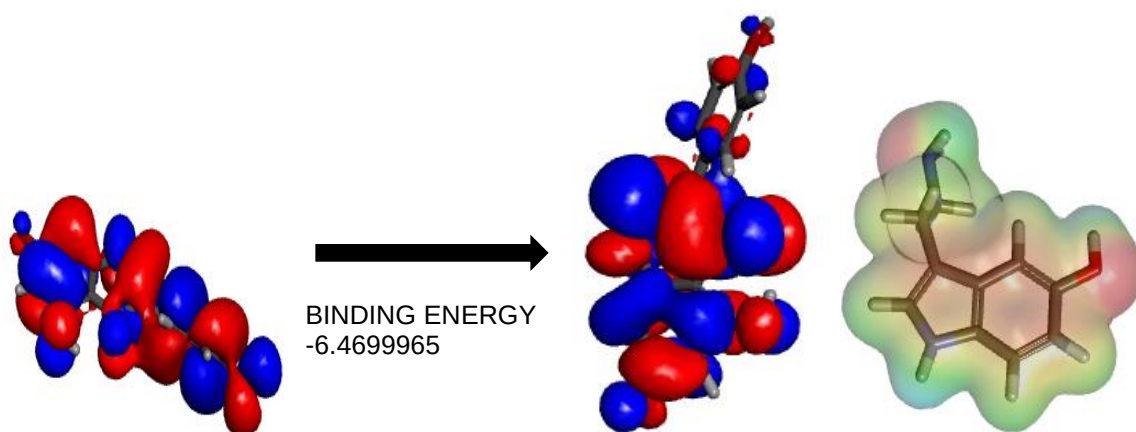
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17.



18.

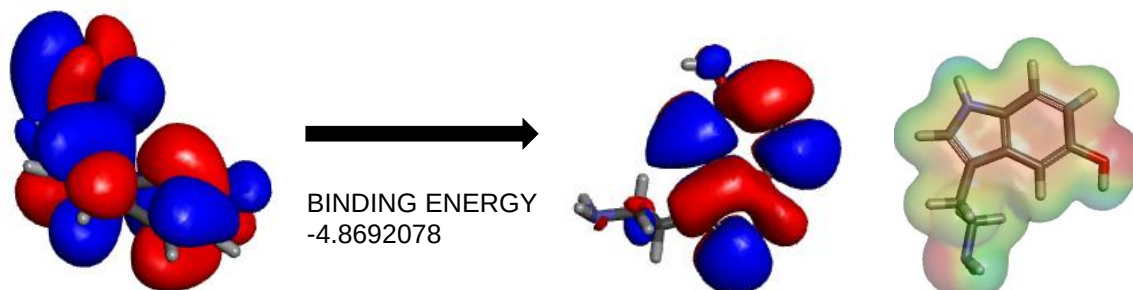


HOMO

LUMO

EPS

19.

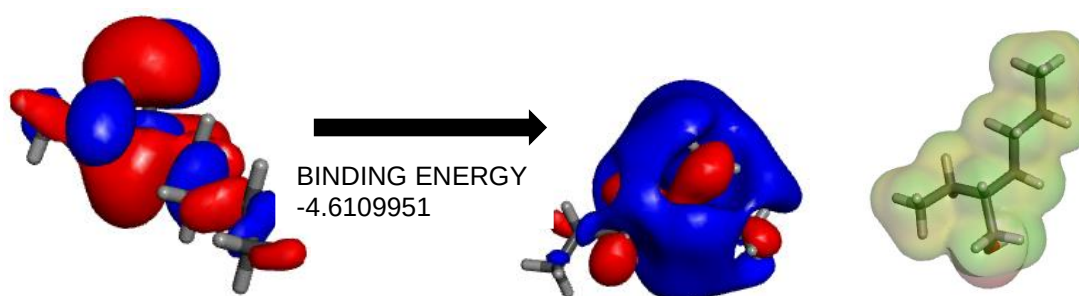


HOMO

LUMO

EPS

20.



HOMO

LUMO

EPS

1. Pyrogallol 2. N- Methylcoclaurine 3. SCHLEICHERASTATIN (6) 4. Palmatine
5. Oxyberberine 6. Nordamnacanthal 7. Epinine 8. Dopamine 9. Ethyl Palmitate
10. Rubilactone 11. Yuccagenin 12. Caffeic acid 13. Tigogenin 14. Rubiatriol
15. Betulin 16. Berberine 17. Hydroxylupanine 18. Genistein 19. Serotonin 20.
2-Ethylhexanol

5.7 Binding Energy EV

In computational chemistry, the energy of molecular orbitals, including HOMO and LUMO, is typically measured in electron volts (eV). The HOMO and LUMO energies are important electronic properties of a molecule that determine its reactivity and ability to donate or accept electrons. The HOMO is the highest occupied molecular orbital, which means that it is the molecular orbital containing the highest energy electrons.

The HOMO energy is often used to determine the ionization potential of a molecule, which is the energy required to remove an electron from the molecule. The LUMO, on the other hand, is the lowest unoccupied molecular orbital, which means that it is the molecular orbital with the lowest energy that does not contain any electrons.

The LUMO energy is often used to determine the electron affinity of a molecule, which is the energy released when an electron is added to the molecule. The energy of HOMO and LUMO can be calculated using various computational methods, including Density Functional Theory (DFT) calculations. In DFT calculations, the energy levels of the HOMO and LUMO are typically reported in electron volts (eV) relative to the vacuum level.

Binding energy is the energy required to break a bond between two atoms or molecules. The binding energy of HOMO and LUMO orbitals can be calculated by subtracting the energy of the orbital from the energy of a free electron. The result is the energy required to remove an electron from the orbital or add an electron to the orbital.

TABLE 5.4 BINDING ENERGY EV

COMPOUND ID	Binding Energy (Ha)	HOMO Energy (Ha)	HOMO Energy (EV)	LUMO Energy (Ha)	LUMO Energy (EV)	BINDING Energy (EV)
1057	-3.00339361	-0.19617203	-5.33812	-0.0282898	-0.76981	-2.9751038
IMPHY001728	-6.35269384	-0.22250925	-6.05479	-0.15221487	-4.14198	-6.200479
IMPHY009636	-6.57922374	-0.20026814	-5.44958	-0.10203306	-2.77646	-6.4771907
10836412	-14.1497039	-0.1834315	-4.99143	-0.07458676	-2.02961	-14.075117
IMPHY000342	-9.0205517	-0.1738225	-4.72995	-0.07356691	-2.00186	-8.9469848
IMPHY005330	-9.46854469	-0.29713701	-8.08551	-0.23739429	-6.45983	-9.2311504
2752274	-8.48853078	-0.15106657	-4.11073	-0.03099719	-0.84348	-8.4575336
IMPHY009624	-9.7933975	-0.23045766	-6.27108	-0.0361823	-0.98457	-9.7572152
IMPHY006032	-4.56657626	-0.21431517	-5.83182	0.04441883	1.208699	-4.6109951
IMPHY007257	-4.16973371	-0.16920269	-4.60424	-0.03113879	-0.84733	-4.1385949
IMPHY011933	-4.30979158	-0.20989198	-5.71145	-0.09752243	-2.65372	-4.2122692
IMPHY004643	-6.56111289	-0.19847647	-5.40082	-0.09111639	-2.4794	-6.4699965
IMPHY003477	-4.67518058	-0.16027876	-4.36141	-0.02851211	-0.77585	-4.6466685
IMPHY010851	-13.6105045	-0.20033789	-5.45147	-0.00521594	-0.14193	-13.605289
IMPHY012273	-13.6806292	-0.20132928	-5.47845	0.05026477	1.367775	-13.730894
IMPHY004653	-4.90007364	-0.16267749	-4.42668	-0.03086581	-0.8399	-4.8692078
IMPHY004271	-15.0383208	-0.19954511	-5.4299	-0.00415324	-0.11302	-5.3168861
IMPHY009172	-15.1981643	-0.18675129	-5.08176	-0.0079101	-0.21524	-4.866519

IMPHY014728	-7.98561568	- 0.15035304	-4.09132	0.00034513	0.009391	-4.100708
IMPHY005665	-8.73530068	- 0.29155084	-7.93351	-0.2339832	-6.36701	-1.566496

CHAPTER 6

SUMMARY AND CONCLUSION

6.1 SUMMARY

The study aimed to identify anticancer phytochemicals from the plants of nilgiris hill against the target- PI3KCA involved in cell signaling pathways that regulate cell growth, survival, and metabolism. PI3KCA mutations have been identified in a variety of cancer types, including breast, colorectal, ovarian, endometrial, and lung cancer. These mutations result in increased PI3K activity and dysregulation of downstream signaling pathways, leading to uncontrolled cell growth and tumor progression. PI3K inhibitors, which target this pathway, are being developed as potential cancer treatments. This study we used in-silico methods, including molecular docking and molecular dynamics simulations using Discovery studio, to screen a library of phytochemicals and evaluate their binding affinity to the PI3K receptor. Here we identified several promising compounds that showed strong binding affinity to the receptor and could potentially inhibit PI3K. The results of this study suggest that phytochemicals from the plant of nilgiris hill could serve as a valuable source of new drugs for the treatment of gynecological cancer.

6.2 CONCLUSION

Alpelisib a FDA approved drug for breast cancer ,inhibits PI3KCA . In this study we found that some phytochemicals such as Oxyberberine , Genistein, Serotonin efficiently attach to the target in the same precise area as the medicine Alpelisib and may have a comparable inhibiting action. This study provides a hint to experimental research that reveal that natural compounds may show anticancer property and in future can be developed as drug , which will have minimum or no side effects

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