INSILICO IDENTIFICATION OF NATURAL PRODUCTS AGONIST FOR GLP-1 INVOLVED IN OBESITY

Submitted in partial fulfillment of the requirements for the
award of Bachelor of Sciences 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 **HAMSA PRIYAA.M (40738006)** who carried out the project entitled " **INSILICO IDENTIFICATION OF NATURAL PRODUCTS AGONIST FOR GLP-1 INVOLVED IN OBESITY**" under my supervision from January 2023 to May 2023.

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DECLARATION

I, **HAMSA PRIYAA.M** hereby declare that the project report entitled "**INSILICO IDENTIFICATION OF NATURAL PRODUCTS AGONIST FOR GLP-1 INVOLVED IN OBESITY"**done by me under the guidance of **Dr.Swetha sunkar** is submitted in partial fulfillment of the requirements for the award of Bachelor of Science Degree in Bioinformatics and Data science.

DATE:9-5-23 **HAMSA PRIYAA.M**

PLACE: CHENNAI **SIGNATURE OF THE CANDITATE**

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. SWETHA SUNKAR** for her 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

Obesity is an epidemic disease that threatens to inundate health care resources by increasing the incidence of diabetes, heart disease, hypertension, and cancer. These effects of obesity result from two factors: the increased mass of adipose tissue and the increased secretion of pathogenetic products from enlarged fat cells. This concept of the pathogenesis of obesity as a disease allows an easy division of disadvantages of obesity into those produced by the mass of fat and those produced by the metabolic effects of fat cells. In the former category are the social disabilities resulting from the stigma associated with obesity, sleep apnea that results in part from increased parapharyngeal fat deposits, and osteoarthritis resulting from the wear and tear on joints from carrying an increased mass of fat. The second category includes the metabolic factors associated with distant effects of products released from enlarged fat cells. The insulin-resistant state that is so common in obesity probably reflects the effects of increased release of fatty acids from fat cells that are then stored in the liver or muscle. When the secretory capacity of the pancreas is overwhelmed by battling insulin resistance, diabetes develops. The strong association of increased fat, especially visceral fat, with diabetes makes this consequence particularly ominous for health care costs. The release of cytokines, particularly IL-6, from the fat cell may stimulate the proinflammatory state that characterizes obesity. The increased secretion of prothrombin activator inhibitor-1 from fat cells may play a role in the procoagulant state of obesity and, along with changes in endothelial function, may be responsible for the increased risk of cardiovascular disease and hypertension. For cancer, the production of estrogens by the enlarged stromal mass plays a role in the risk for breast cancer. Increased cytokine release may play a role in other forms of proliferative growth. The combined effect of these pathogenetic consequences of increased fat stores is an increased risk of shortened life expectancy. Drug design based on degradation-resistant, long-acting Glucagon- like peptide-1 receptor (GLP-1R) agonists for treating type 2 diabetes is attracting a lot of attention. Here, the authors have examined in detail how in silico drug design is aiding in developing novel GLP-1 receptor agonist drugs. Their pharmacotherapy and adverse effects have also been summarized. After the analysis of currently available information on this topic, the authors feel that in

silico method is a great auxiliary tool in almost all the experimental studies on GLP-1 receptors and is highly efficient in identifying novel drug molecules that can act as GLP-1 receptor agonists.

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CHAPTER-1

INTRODUCTION

Obesity is considered a complicated multifactorial disease. Globally, almost one third of the world population is classified as overweight or obese. Obesity has negative impacts on physiological functions, causing a threat to public health. It increases the risk of developing metabolic syndromes such as diabetes mellitus, cardiovascular disease and several types of cancers. Even though the prevalence of obesity has increased in both sexes at all ages with different geographical locality, ethnicity or socioeconomic background, older people and women seem to have greater obesity rates.(Agha, M., & Agha, R. 2017)

There are various approaches to reduce weight, including decreasing nutrition absorption or suppressing appetite. Glucagon-like peptide-1(GLP-1) is one of the “satiety signals’’ that reduces hunger. It is known as an incretin hormone, secreted by enteroendocrine L cells in the gastrointestinal tract. Obesity has become a major public health concern worldwide, with increasing prevalence and associated health risks. Obesity is a medical condition characterized by excessive body fat that increases the risk of other health problems. It is typically defined as having a body mass index (BMI) of 30 or higher. Obesity is a growing problem worldwide, with an estimated 650 million adults and 124 million children and adolescents affected globally. It is associated with a wide range of health issues, including heart disease, type 2 diabetes, high blood pressure, stroke, sleep apnea, and certain types of cancer. (GLP-1 agonists 2022)

The causes of obesity are complex and can include a combination of genetic, environmental, and behavioral factors. Some common risk factors for obesity include a sedentary lifestyle, unhealthy diet, lack of sleep, stress, and certain medications. Treatment for obesity typically involves a combination of lifestyle changes, such as adopting a healthy diet and increasing physical activity, along with behavior modification and, in some cases, medications or surgery. It's important to work with a healthcare professional to develop a personalized treatment plan that takes into account your individual health status and goals.(Childhood obesity is a complex health issue. 2022)

Natural products, including plant-derived compounds, have been a rich source of biologically active molecules with therapeutic potential. In recent years, computational methods have been increasingly applied to the identification of natural product-based drug candidates, providing a cost-effective and efficient approach for drug discovery.

There are various approaches to reduce weight, including decreasing nutrition absorption or suppressing appetite. Glucagon-like peptide-1(GLP-1) is one of the “satiety signals’’ that reduces hunger. It is known as an incretin hormone, secreted by enteroendocrine L cells in the gastrointestinal tract (GI). The amount of GLP-1 secretion is in response to calory intake. It can be stimulated by both fats and carbohydrates, while protein has only a minor impact [6]. The existing two major molecular forms of GLP-1 include GLP-1 (7-36) and GLP-1 (7-37), while the circulating active GLP-1 is mainly found in the form of GLP-1

Reports showed that native GLP-1 has a very short half-life (less than 2 min) in vivo as a result of degradation by dipeptidyl peptidase-4 (DPP-4) in plasma . Liraglutide, a stable GLP-1 analogue, was approved by FDA for treating obesity in 2014. It can suppress appetite and increase satiety by activating the GLP-1 receptor, which is located in the hypothalamus, gastrointestinal tract and pancreas. However, it is a daily injectable treatment that is also relatively high cost.
Obesity is a complex condition that can be caused by a combination of genetic, environmental, and behavioural factors. Here are some of the most common factors that contribute to obesity:

Genetics: Certain genes can make people more prone to gaining weight and storing fat.

Environmental factors: A person's environment can also play a role in the development of obesity. This can include factors like access to healthy food, level of physical activity, and exposure to stress.
Diet: A diet high in calories, unhealthy fats, and added sugars can contribute to weight gain and obesity.

Physical activity: A sedentary lifestyle with little to no physical activity can contribute to weight gain and obesity.

Sleep: Lack of sleep or poor sleep quality can disrupt hormones that regulate hunger and appetite, leading to overeating and weight gain.

Medications: Certain medications, such as antidepressants and corticosteroids, can cause weight gain as a side effect.

Medical conditions: Certain medical conditions, such as hypothyroidism and Cushing's syndrome, can also cause weight gain and obesity.

1.1 MEDICAL CONSEQUENCES OF OBESITY

The effect of excess weight on morbidity and mortality have been known for more than 2000 yr. Hippocrates recognized that “sudden death is more common in those who are naturally fat than in the lean,” and Malcolm Flemyng in 1760 observed that “corpulency, when in an extraordinary degree, may be reckoned a disease, as it in some measure obstructs the free exercise of the animal functions; and hath a tendency to shorten life, by paving the way to dangerous distempers.”

Obesity is a chronic disease in the same sense as hypertension and atherosclerosis. The ethology or cause of obesity is an imbalance between the energy ingested in food and the energy expended. The excess energy is stored in fat cells that enlarge and/or increase in number. It is this hyperplasia and hypertrophy of fat cells that is the pathological lesion of obesity. Enlarged fat cells produce the clinical problems associated with obesity either because of either the weight or mass of the extra fat or because of the increased secretion of free fatty acids and numerous peptides from enlarged fat cells. The consequence of these two mechanisms is other diseases, such as diabetes mellitus, gallbladder disease, osteoarthritis, heart disease, and some forms of cancer. The spectrum of medical, social, and psychological disabilities includes a range of medical and behavioral problems.(Pillon, N. J., et al ., 2021)

Obesity can have numerous negative consequences on a person's health and well-being, including:

Increased risk of chronic diseases: Obesity is linked to several chronic health conditions, such as heart disease, stroke, diabetes, high blood pressure, and certain types of cancer.(McCafferty, B. J., et al ., 2020)

Reduced life expectancy: Obesity can shorten a person's life expectancy by several years due to the increased risk of developing chronic diseases.
Poor mental health: Obesity can also have a negative impact on a person's mental health, leading to conditions such as depression, anxiety, and low self-esteem.
Joint problems: The excess weight carried by obese individuals can put pressure on joints, leading to joint pain, arthritis, and decreased mobility.

Sleep apnea: Obesity increases the risk of developing sleep apnea, a condition that causes breathing to stop and start repeatedly during sleep, leading to poor quality of sleep and fatigue.

Fertility issues: Obesity can also impact fertility, making it more difficult for women to become pregnant and increasing the risk of complications during pregnancy.
Social stigma: Obese individuals may face social stigma and discrimination, leading to feelings of isolation, low self-esteem, and poor body image.(Puhl, R. M., & Lessard, L. M. 2020)

Increased healthcare costs: Treating obesity and its related conditions can be costly, placing a burden on both individuals and the healthcare system.

1.2 PATHOLOGY OF EXCESS FAT

Each disease whose risk is increased by overweight can be classified into one of two pathophysiological categories. The first category of disabilities arises from the increased mass of fat itself. These include the stigma of obesity and the behavioural responses it produces, osteoarthritis, and sleep apnea. The second category is risks that result from the metabolic changes associated with excess fat.

These include diabetes mellitus, gallbladder disease, hypertension, cardiovascular disease, and some forms of cancer associated with overweight.(Lin, X., & Li, H. 2021)

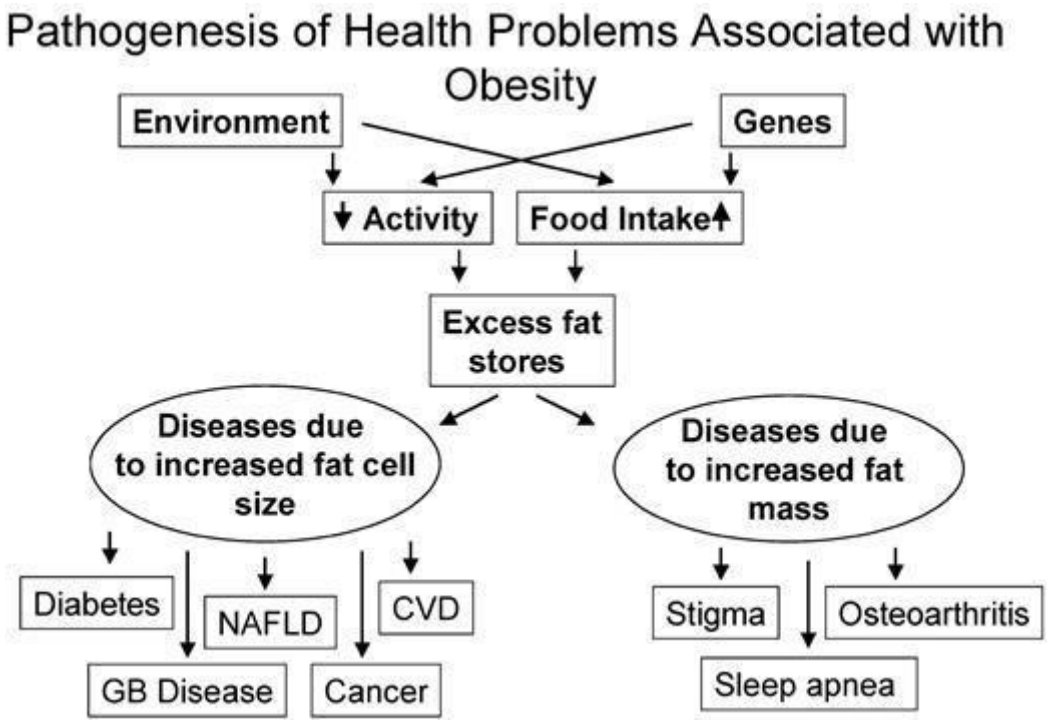


Fig:1.1 Pathogenesis of Health Problems Associated With Obesity

The pathology of obesity produces the myriad of health-related problems. These health-related problems can be attributed to either the increased mass of fat or the increased release of peptides from enlarged fat cells. CVD, Cardiovascular disease; GB, gallbladder.(Turk, B. R., et al ., 2020)

1.3 OBTAINABLE TREATMENTS FOR OBESITY

The treatment for obesity typically involves a combination of lifestyle changes, such as diet and exercise, and medical interventions. Here are some of the common treatment options for obesity:

Diet and exercise: A healthy diet and regular exercise are the cornerstone of obesity treatment. A balanced diet that is low in calories and high in fibre, protein, and nutrients can help individuals lose weight and maintain a healthy weight.

Regular exercise, such as walking, jogging, swimming, or cycling, can help burn calories and improve cardiovascular health.(Paccosi, S., et al ., 2020)

Behavioural therapy: Behavioural therapy may help individuals change their eating habits and lifestyle choices. This may include setting realistic weight loss goals, keeping a food diary, and identifying triggers that lead to overeating.

Medications: Several medications are available to help individuals lose weight, including appetite suppressants and drugs that interfere with the absorption of fat in the intestines.

Bariatric surgery: In severe cases of obesity, bariatric surgery may be recommended. This surgery involves reducing the size of the stomach to limit food intake or rerouting the digestive tract to reduce nutrient absorption.
Other treatments: Other treatments for obesity may include counselling, support groups, and weight loss programs that provide education, guidance, and support for making healthy lifestyle choices.

It's important to note that successful weight loss requires a long-term commitment to lifestyle changes, and treatment plans may vary depending on the individual's needs and medical history. It's essential to consult with a healthcare professional before starting any weight loss program or treatment.

1.4 SIDE EFFECTS OF DRUG

Gastrointestinal side effects: GLP-1 receptor agonists can cause gastrointestinal side effects, such as nausea, vomiting, diarrhoea, and constipation. These side effects usually improve over time and can be managed with adjustments to the medication dose or timing.

Hypoglycemia:GLP-1 receptor agonists can cause low blood sugar (hypoglycaemia) when used in combination with other diabetes medications that lower blood sugar. This is more likely to occur in individuals with kidney disease or those who are elderly.

Pancreatitis: There have been reports of pancreatitis (inflammation of the pancreas) in individuals taking GLP-1 receptor agonists. Symptoms may include abdominal pain, nausea, and vomiting. If pancreatitis is suspected, treatment with the drug should be stopped immediately.

Thyroid tumours: In preclinical studies, GLP-1 receptor agonists have been associated with the development of thyroid tumours in rodents. However, the relevance of these findings to humans is still unclear.

Allergic reactions: Some individuals may experience allergic reactions, such as rash, itching, or difficulty breathing, when taking GLP-1 receptor agonists. If an allergic reaction occurs, treatment with the drug should be stopped immediately.

Gallbladder disease: Liraglutide may increase the risk of developing gallbladder disease, such as cholelithiasis (gallstones).

Injection site reactions: Liraglutide is administered by subcutaneous injection, and some individuals may experience injection site reactions, such as pain, swelling, or redness.

1.5 BENEFITS OF WEIGHT LOSS

If overweight increases the risk of mortality, then we would anticipate that intentional weight loss would reduce it. A definitive demonstration of this prediction is not available, but several studies suggest that intentional weight loss does reduce risk. Weight loss maintained for 2 year reduces blood pressure, improves abnormal lipid levels, and reduces the risk of diabetes. A follow-up of women aged 40–64 yr in the American Cancer Society study who intentionally lost weight found a significant reduction in all-cause mortality of 20–25%. Using the National Health Interview Survey with a 9-yr follow-up, intentional weight loss lowers mortality rate (Hazard Rate Ratio) by 24% (0.76; 95% confidence interval, 0.60–0.97). In contrast, those with unintentional weight loss had a 31% higher mortality rate (1.31; 95% confidence interval, 1.01–1.70) .(Vidal, J. 2002)

Weight loss affects a number of risk factors. The data from participants in the Swedish Obesity Study show the degree of weight loss for individual risk factors. Changes in blood pressure and triglycerides are very responsive to weight loss, decreasing after a 5–10% weight loss. HDL cholesterol increases with a similar weight-related change. Total cholesterol, on the other hand, does not show a sustained effect until weight loss exceeds 20%. For most comorbidities, however, a 10% weight loss is sufficient to see significant improvement in risk factors. However, blood pressure returns to baseline by 4–6 year even when weight loss is maintained. Recent studies buttress the idea that losing about 5% of body weight can significantly reduce the risk of developing type 2 diabetes in high risk individuals. In studies from Finland and the United States, conversion rates from impaired glucose tolerance to diabetes were reduced by 58% (Factors Affecting Weight & Health.2022).

CHAPTER 2

LITERATURE SURVEY

The study used virtual screening to identify natural compounds that could inhibit the GLP-1 receptor, which is a potential therapeutic target for obesity. (Gupta et al 2020)

The study used virtual screening to identify natural compounds that could activate the GLP-1 receptor, and validated their activity using in vitro assays. (JRiyaphan, J., et al. 2021)

Another study used molecular docking and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential therapeutic applications for diabetes and obesity. (Zhao, X., et al. 2021)

One study used molecular docking and pharmacophore-based screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-obesity therapy. (Yaribeygi, H., et al 2021)

The study used machine learning algorithms and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential therapeutic applications in diabetes and obesity. (Sun, L., et al. 2022).

One study used virtual screening and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in obesity treatment. (Klen, J., et al. 2022).

The study used a combination of docking and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential therapeutic applications in diabetes and obesity (Lee et al. 2020).

Another study used molecular docking and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-diabetic therapy. (Sánchez-Garrido, M. A., et al. 2017).

The study used molecular docking and dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in obesity and diabetes treatment (Liao, H. J., et al. 2022)

One study used virtual screening and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-obesity therapy. (Liao, H. J.,et al. 2022).

The study used insilico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-obesity therapy. (Klen, J., & Dolžan, V. 2022).

Another study used insilico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-obesity therapy. (Klen, J., & Dolžan, V. 2022).

The study used insilico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in diabetes and obesity treatment. (Sun, L., et al. 2022).

One study used insilico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-diabetic therapy. (Ramesh et al. 2020)

Another study used in-silico methods to identify natural compounds that could activate the GLP-1 receptor, with potential applications in diabetes treatment. (Sharma, P., et al. 2020).

The study used molecular dynamics simulations and free energy calculations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in anti-obesity therapy. (Li et al. 2019).

This study used in-silico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in obesity treatment. (Pasternak, B., et al. 2020).

One study used virtual screening and molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in diabetes treatment. (Liao, H. J., & Tzen, J. T. C. 2022).

Another study used insilico screening to identify natural compounds that could activate the GLP-1 receptor, with potential applications in the treatment of obesity and diabetes. (Van Bloemendaal, L., et al. 2014).

The study used molecular dynamics simulations to identify natural compounds that could activate the GLP-1 receptor, with potential applications in the treatment of diabetes and obesity. (Shenoy et al. (2019).

In a study published in the Journal of Ethnopharmacology, Li et al. (2021) used insilico and in vitro functional validation to identify two natural products, Luteolin

and Baicalin, as GLP-1 receptor agonists. They found that these two compounds significantly improved glucose tolerance and insulin sensitivity in high-fat-diet-fed mice. (Li et al. 2021)

In a study Molecular docking to screen natural products from various databases and identified several potential GLP-1 receptor agonists. They found that the compound Quercetin, a flavonoid found in many fruits and vegetables, had high binding affinity to the GLP-1 receptor and increased insulin secretion in pancreatic β-cells. (Alawadhi et al. 2019)

In a study molecular docking to screen a library of 300 natural products and identified 10 compounds that showed promising binding affinity to the GLP-1 receptor. One of the compounds, resveratrol, a polyphenol found in grapes, berries, and peanuts, showed strong GLP-1 receptor activation and improved glucose tolerance in high-fat-diet-fed mice. (Sohretoglu et al. 2017)

In a study published in the Frontiers in Pharmacology, used a virtual screening approach to identify potential GLP-1 receptor agonists from a database of natural products. The authors found that the compound astragaloside IV, a saponin found in the roots of the astragalus plant, had high binding affinity to the GLP-1 receptor and improved glucose tolerance in high-fat-diet-fed mice. (Park et al. (2021)

CHAPTER 3

AIM AND SCOPE

3.1 AIM

The study aims to identify a natural product as agonist for GLP-1 involved in obesity through computational studies.

3.2 SCOPE

Insilico identification of natural products as agonists for GLP-1 (glucagon-like peptide-1) involved in obesity is an interesting and promising area of research. GLP-1 is a hormone that plays a crucial role in regulating glucose metabolism, appetite, and body weight, and its agonists have been shown to be effective in the treatment of type 2 diabetes and obesity. Insilico methods, such as molecular docking, virtual screening, and machine learning, can be used to identify potential natural products that can act as GLP-1 agonists. These methods can help in the identification of compounds with high binding affinity and selectivity for GLP-1 receptors. Once potential GLP-1 agonists have been identified, in vitro and in vivo experiments can be performed to validate their activity and determine their potential for use as therapeutics. The use of Insilico methods in the initial screening process can significantly reduce the time and cost involved in drug discovery, making it an attractive option for identifying new GLP-1 agonists for the treatment of obesity. Overall, there is a significant scope for insilico identification of natural products as GLP-1 agonists involved in obesity, and it is an area of research that has the potential to lead to the development of effective treatments for this complex and challenging health problem.

CHAPTER 4

MATERIALS AND METHODS

4.1 TARGET IDENTIFICATION

Target identification is a critical step in drug discovery, as it helps to identify and validate specific molecular targets that can be modulated to achieve a therapeutic effect. 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. Obtaining info on biological molecules is a valuable resource for researchers and students. The Protein Data Bank (PDB) contains the 3D structures of proteins found in nature. 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. Uniprot is used to obtain knowledge about proteins and their functions. Uniprot annotates protein sequence data in great depth, including localization, post-translational modifications, and interactions. Uniprot is a collaboration between the Swiss Institute of Bioinformatics (SIB), the European Bioinformatics Institute (EBI), and the Protein Information Resource. Uniprot connects to several other protein sequence libraries, including UniprotKB/Swiss- prot, UniProtKB/TrEMBL, and UniRef. The UniProtKB/TrEMBL ratio has yet to be found experimentally. UniProtKB/Swiss-Prot is an experimentally characterised library. To prevent redundancy, protein sequences are grouped. Uniprot offers tools for sequence analysis, including BLAST, which can be used to identify identical sequences, and PROSITE, which can be used to find protein motifs and domains.(Luo, S., et al ., 2020)

4.1 LIGAND IDENTIFICATION/ SCREENING OF COMPOUNDS

Ligand identification and screening of compounds using insilico methods can help to identify natural product. This approach can accelerate the drug discovery process and lead to the development of more effective treatments for obesity and other metabolic disorders. Another approach is to use virtual screening, which involves screening large databases of natural products . Identifying ligands with natural sources can be done by using various resources, such as literature review, traditional knowledge, ethnobotanical databases, or natural product databases like PubChem, ChEMBL, or ZINC. Using the MTI (Medical Text Indexer) open screening tool can also be a useful approach to identify potential ligands for a specific target protein. MTI is a natural language processing tool that can analyze and extract information from scientific literature to identify compounds that are associated with the target protein.(Swedberg, J. E., et al 2015)

The MTI open screen method is used to identify potential therapeutic compounds that bind to specific target molecules. The initial stage in screening is to choose specific target compounds. The target may already be identified as a possible target, or it may have an important role in a specific disease.(Bharadwaj, S., et al., 2021)

Following the identification of the target, the MTi open screen programme will scan a wide library of small molecules for compounds that are more likely to bind to the target protein with high affinity. Small molecule prediction is accomplished through the use of computational approaches such as machine learning and molecular docking. The best resource for drug development is the MTi open screening tool, which may be used to predict novel drug candidates. Complete ligand information can be obtained through databases such as pubchem, zinc database, and so on.

4.2 PHARMACOKINETICS ANALYSIS

SWISSADME is a free web application developed by the Swiss Institute of Bioinformatics (SIB) for predicting the pharmacokinetic features of small compounds. It specifically use computational models to forecast critical ADME (absorption, distribution, metabolism, and excretion) features of substances, such as:
Lipophilicity (LogP); Water solubility; Absorption; Distribution; Metabolism; Excretion

These predictions can help with drug discovery and development by predicting how a molecule will behave in the body and whether it has the potential to be an effective medicine. However, it is important to highlight that these predictions are simply approximations and should be validated by more experimental research. (Patil, S. M., et al ., 2022)

SWISSADME predicts a wide range of ADME-related properties, including permeability, blood-brain barrier penetration, solubility, and others. To anticipate the properties of the molecules, it employs a variety of computer algorithms such as ML and SVM. 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]
- ✓ Rotatable bonds [≤ 9]

4.4 TOXICITY ANALYSIS

OSIRIS (Online Simple Interface for Research on the Toxicity of Chemicals) is a web-based toxicity analysis tool for small compounds. OSIRIS predicts probable toxicity endpoints based on a compound's chemical structure using a combination

of expert rules and quantitative structure-activity relationship (QSAR) models.(Sharma, P., et al ., 2022)

To use OSIRIS, a user enters the chemical structure of the compound of interest, chooses the appropriate organism (human, rat, or mouse), endpoint (acute toxicity, MUTAGENIC, TUMORIGENIC, IRRITANT, REPRODUCTIVE EFFECTIVE), and then submits the compound for analysis. OSIRIS then generates a report that includes a summary of the important chemical properties that contribute to the prediction as well as the projected toxicity endpoints for each substance.

OSIRIS can be a useful tool in early-stage drug discovery for identifying potential toxicities and prioritising compounds for further testing. However, it should be noted that OSIRIS predictions are not a substitute for experimental assays, and experimental validation is required to confirm anticipated toxicity endpoints and assure the safety of proposed drug candidates.

4.5 DOCKING

Docking is a computational method used in drug discovery to predict how a small molecule, typically a drug candidate, will bind to a target protein. The goal of docking is to predict the most energetically favorable binding orientation of the ligand within the binding pocket of the protein.(Das, U., et al ., 2020)

The basic idea behind docking is to predict the best orientation of a tiny molecule within a target protein's binding site. The procedure entails producing small molecule conformations and calculating the energy of interaction between the ligand and the protein. The projected binding pose is then chosen based on the tiny molecule's most energetically favorable conformation.(Weng, L., et al., 2021)

Docking consists of four basic steps: target preparation, which includes downloading the target protein in 3D format and removing unnecessary elements like water. Ligand is currently being downloaded in SDF format. The binding location is then defined and edited. Docking is handled by Lib doc, a module in

Discovery Studio that employs rigid body docking techniques. The results are then analyzed based on the binding site and ligand affinity for the target protein.

Docking is frequently used to identify prospective drug candidates as a first stage in the drug discovery process. It can also be used to improve existing pharmaceuticals or to discover new applications for existing drugs.

CHAPTER 5

RESULTS AND DISCUSSION

5.1 TARGET IDENTIFICATION

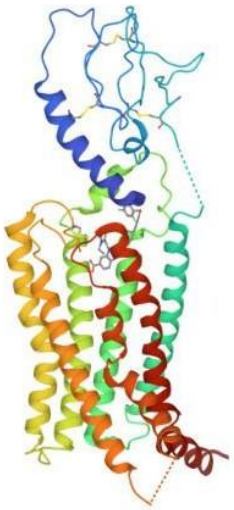
Target is obtained from PDB, Uniport ,Target id – 7S15 ; uniport id- P43220
NAME OF THE DRUG: LIRAGLUTIDE

Liraglutide is a medication that has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity. It is a type of medication called a glucagon-like peptide-1 (GLP-1) receptor agonist, which works by mimicking the effects of a hormone called GLP-1 in the body.

GLP-1 is a hormone that is released in response to food intake and helps regulate blood sugar levels and appetite. Liraglutide works by stimulating the GLP-1 receptors in the body, which can help reduce appetite and food intake, leading to weight loss. It's important to note that Liraglutide is a prescription medication and should only be taken under the guidance of a healthcare provider. Like all medications, it can have potential side effects and should be used with caution in certain populations, such as people with a history of pancreatitis or thyroid cancer.

NAME OF THE TARGET: GLP-1 R (glucagon-like peptide-1)
GLP-1 (glucagon-like peptide-1) is a hormone that plays a key role in regulating blood sugar levels and promoting weight loss. Agonists of GLP-1 are used as a treatment for type 2 diabetes and obesity. Natural products have been shown to be a rich source of new drugs, and many of them have been identified as potential agonists for GLP-1. identify natural products that can act as agonists for GLP-1, insilico methods can be used. One approach is to use molecular docking, which involves predicting the binding affinity of natural products to the GLP-1 receptor. Molecular docking can be performed using software such as discovery studio, which use computational algorithms to predict the binding affinity of small molecules to a target protein. Once potential agonists have been identified using insilico methods, they can be further tested using in vitro and in vivo assays to determine their efficacy and safety as GLP-1 agonists. This approach can lead to

the discovery of new natural product-based drugs for the treatment of obesity and other metabolic disorders.



Molecule	Chains	Sequence Length	Organism	Details
Glucagon-like peptide 1 receptor	A [auth R]	399	Homo sapiens	Mutation(s): 8 Gene Names: GLP1R Membrane Entity: Yes

Ligands 1 Unique

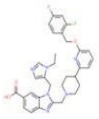
ID	Chains	Name / Formula / InChI Key	2D Diagram	3D Interactions
82L (Subject of Investigation/LOI) Query on 82L Download Ideal Coordinates CCD File Download Instance Coordinates	B [auth R]	2-[(4-{6-[(2,4-difluorophenyl)methoxy]pyridin-2-yl}piperidin-1-yl)methyl]-1-[(1-ethyl-1H-imidazol-5-yl)methyl]-1H-benzimidazole-6-carboxylic acid $C_{32}H_{32}F_2N_6O_3$ IFXPEJAGKQFBER-UHFFFAOYSA-N		Ligand Interaction

Fig:5.1: GLP-1 receptor bound with Pfizer small molecule agonist

PDB ID: 7S15

5.2 LIGAND IDENTIFICATION/ SCREENING OF COMPOUNDS

Ligand identification and screening of compounds using insilico methods can help to identify natural product agonists for GLP-1 involved in obesity. Identifying ligands with natural sources can be done by using various resources, such as literature review, traditional knowledge, ethnobotanical databases, or natural product databases like PubChem, ChEMBL, or ZINC.

Using the MTI (Medical Text Indexer) open screening tool can also be a useful approach to identify potential ligands for a specific target protein. MTI is a natural language processing tool that can analyze and extract information from scientific literature to identify compounds that are associated with the target protein.
Here are some steps to follow:

Select the target protein: Choose the protein target of interest, such as an enzyme or a receptor.

Collect literature: Gather relevant scientific literature that mentions the target protein and its potential ligands.

Use MTI: Submit the collected literature to the MTI tool to identify compounds that are associated with the target protein.

Filter and select compounds: Analyze the output from MTI and filter out irrelevant or unlikely compounds. Select the most promising compounds for further analysis.
Molecular docking and validation: Perform molecular docking simulations and validation studies to confirm the predicted ligand-target protein interactions.

Overall, both approaches can be used in combination to increase the chances of identifying potential ligands for a target protein.

Ligands were retrieved from phytohub where I obtained 44 sources mentioned in the given table .

(https://phytohub.eu/)

299 Compounds were from the MTI open screening of chemicals, with the combination of FOOD-lib and natural products.

(https://bioserv.rpbs.univ-paris-diderot.fr/services/MTiOpenScreen/)

To provide valuable starting points for open virtual screening, we provide five electronic drug-like chemical libraries: a diverse chemical compound collection (Diverse-lib) and a focused chemical compound collection (iPPI-lib) to target protein-protein interactions (PPI), a collection of purchasable approved drugs (Drugs-lib), a food constituent compound collection **(FOOD-lib) and a natural product**

2	Compound	SMILE:	Formula	MW	#Heavy atoms	#Aromatic heavy	Fraction Csp3	#Rotatable bond	#H-bond accept	#H-bond donors	MR	TPSA
3	alpha_Humulene_ZINC000585660568	CC1=CCC(C)(C	C15H24	204.35	15	0	0.6	0	0	0	70.42	
4	Isospirene_ZINC000100779593	CC1=CC[C@H]	C13H20O	192.3	14	0	0.69	0	1	0	60.55	
5	Tetrahydroharmol_ZINC000002508127	C[C@H]1NCCc	C12H14N2O	202.25	15	9	0.33	0	2	3	64.47	
6	4_5_Dihydro_8_9_dehydrotheaspirone_ZINC000096014469	CC1=CC[C@@]	C13H20O2	208.3	15	0	0.77	0	2	0	60.97	
7	Octahydro_2_5_5_8a_tetramethyl_7H_1_benzopyran_7_one_ZIN	C[C@@H]1CC(=	C13H22O2	210.31	15	0	0.92	0	2	0	61.44	
8	Androst_5_ene_3beta_17beta_diol_ZINC000006472629	C[C@]12CC[C@	C19H30O2	290.44	21	0	0.89	0	2	2	86.32	
9	Stanozolol_ZINC000004097376	C[C@]12Cc3cn[	C21H32N2O	328.49	24	5	0.86	0	2	2	97.66	
10	S__2_3_Dihydro_5_hydroxy_2_methyl_1_4_naphthoquinone_ZIN	C[C@H]1CC(=C	C11H10O3	190.2	14	6	0.27	0	3	1	51.55	
11	Baptifoline_ZINC000006095060	O=c1cccc2n1C[	C15H20N2O2	260.33	19	6	0.67	0	3	1	77.02	
12	S_E__Zearalenone_ZINC000100007202	C[C@H]1CCCC	C18H22O5	318.36	23	6	0.44	0	5	2	88.4	
13	Tuberosin_ZINC000014824334	CC1(C)C=Cc2c	C20H18O5	338.35	25	12	0.3	0	5	2	91.84	
14	dehydroascorbate__bicyclic_form__ZINC000197356509	O=C1O[C@@H	C6H8O7	192.12	13	0	0.83	0	7	4	33.82	
15	Echinocystic_acid_ZINC000004097828	CC1(C)CC[C@@	C30H48O4	472.7	34	0	0.9	1	4	3	137.82	
16	Jatamansone_ZINC000005751121	CC(C)[C@@H]1	C15H26O	222.37	16	0	0.93	1	1	0	69.67	
17	2alpha_3alpha_19alpha_Trihydroxyurs_12_en_28_oic_acid_ZINC	C[C@@H]1CC[C	C30H48O5	488.7	35	0	0.9	1	5	4	139.28	
18	3beta_6alpha_19alpha__3_6_19_Trihydroxy_12_ursen_28_oic_a	C[C@@H]1CC[C	C30H48O5	488.7	35	0	0.9	1	5	4	139.28	
19	2_Methoxyestradiol_3_methylether_ZINC000012493591	COc1cc2c(cc1O	C20H28O3	316.43	23	6	0.7	2	3	1	91.99	
20	Dioxindole_3_acetic_acid_ZINC000013462234	O=C(O)C[C@]1(	C10H9NO4	207.18	15	6	0.2	2	4	3	54.17	
21	6_Lactoyltetrahydropterin_ZINC000012495479	C[C@@H](O)C(	C9H13N5O3	239.23	17	6	0.44	2	4	5	67.41	
22	5_7_Dihydroxy_3__4_hydroxybenzyl__4_chromanone_ZINC0000	O=C1c2c(O)cc(	C16H14O5	286.28	21	12	0.19	2	5	3	76.38	
23	Esculentic_acid__Diplazium__ZINC000076945336	C[C@@H]1CC[	C30H48O5	488.7	35	0	0.9	2	5	4	139.24	
24	4a_Carbinolamine_tetrahydrobiopterin_ZINC000004228252	C[C@H](O)[C@	C9H13N5O3	239.23	17	0	0.56	2	6	5	74.72	

Fig:5.2 Zinc compounds got from MTI open screening

5.3 PHARMACOKINETICS ANALYSIS

After identifying potential natural product candidates with GLP-1 agonistic activity, 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 ADMET Predictor, and SwissADME.

Input molecule: The first step is to input the chemical structure of the natural product candidate into the SWISSADME tool. This can be done by drawing the chemical structure using the built-in chemical editor or by uploading a file in various formats such as SDF, MOL, and PDB.

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 candidate.

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]
- ✓ Rotatable bonds [≤ 9]
- ✓

On analysing of pharmacokinetics with ADME properties retrieved 143 compounds with the set of Lipinski's rule . retrieved compounds are mentioned in the given table.

	Compound	SMILE:	Formula	MW	#Heavy atoms	#Aromatic heavy	Fraction Csp3	#Rotatable bond	#H-bond accept	#H-bond donors	MR	TPSA	iLOGP	XLOGP3	WLOGP
2	Isospirene_ZINC	CC1=CC[C@H](	C13H20O	192.3	14	0	0.69	0	0	0	60.55	9.23	2.99	2.93	
3	Tetrahydroharm	C[C@H]1NCCc2	C12H14N2O	202.25	15	9	0.33	0	0	3	64.47	48.05	1.6	1.53	
4	4_5_Dihydro_8_	CC1=CC[C@@]	C13H20O2	208.3	15	0	0.77	0	0	0	60.97	26.3	2.62	2.49	
5	Octahydro_2_5_	C[C@@H]1CC[(	C13H22O2	210.31	15	0	0.92	0	0	0	61.44	26.3	2.52	2.15	
6	Androst_5_ene_	C[C@]12CC[C@	C19H30O2	290.44	21	0	0.89	0	0	2	86.32	40.46	3.11	3.55	
7	Stanozolol_ZINC	C[C@]12Cc3cn[	C21H32N2O	328.49	24	5	0.86	0	0	2	97.66	48.91	2.7	4.46	
8	S__2_3_Dihydro	C[C@H]1CC(=C	C11H10O3	190.2	14	6	0.27	0	0	1	51.55	54.37	1.75	1.88	
9	Baptifoline_ZINC	O=c1cccc2n1C[(	C15H20N2O2	260.33	19	6	0.67	0	0	1	77.02	45.47	2.21	0.59	
10	S_E__Zearalenol	C[C@H]1CCCC(	C18H22O5	318.36	23	6	0.44	0	0	2	88.4	83.83	2.62	3.62	
11	Tuberosin_ZINC	CC1(C)C=Cc2cc	C20H18O5	338.35	25	12	0.3	0	0	2	91.84	68.15	2.99	3.36	
12	Echinocystic_aci	CC1(C)CC[C@@(	C30H48O4	472.7	34	0	0.9	1	1	3	137.82	77.76	3.41	6.88	
13	Jatamansone_ZI	CC(C)[C@@H]1	C15H26O	222.37	16	0	0.93	1	1	0	69.67	17.07	2.96	4.43	
14	2alpha_3alpha_	C[C@@H]1CC[(	C30H48O5	488.7	35	0	0.9	1	1	4	139.28	97.99	3.52	4.96	
15	3beta_6alpha_1	C[C@@H]1CC[(	C30H48O5	488.7	35	0	0.9	1	1	4	139.28	97.99	3.46	4.59	
16	2_Methoxyestra	COc1cc2c(cc1O	C20H28O3	316.43	23	6	0.7	2	2	1	91.99	38.69	3.42	4.31	
17	Dioxindole_3_ac	O=C(O)C[C@]1(	C10H9NO4	207.18	15	6	0.2	2	2	3	54.17	86.63	0.57	0.09	
18	6_Lactoyltetrahy	C[C@@H](O)C(	C9H13N5O3	239.23	17	6	0.44	2	2	5	67.41	133.13	-0.24	-1.6	
19	5_7_Dihydroxy_	O=C1c2c(O)cc((	C16H14O5	286.28	21	12	0.19	2	2	3	76.38	86.99	1.95	2.85	
20	Esculentic_acid_	C[C@@H]1CC[(	C30H48O5	488.7	35	0	0.9	2	2	4	139.24	97.99	3.05	5.7	
21	Rhapontigenin_	COc1ccc(/C=C/(	C15H14O4	258.27	19	12	0.07	3	3	3	74.37	69.92	2.21	3.59	
22	1_3_Diphenyl_1	O=C(CCc1ccccc	C15H14O	210.27	16	12	0.13	4	4	0	65.93	17.07	2.58	3.5	
23	2_Methyl_1_phe	CC(=O)OC(C)(C	C12H16O2	192.25	14	6	0.42	4	4	0	56.77	26.3	2.64	2.69	

Fig:5.3:Pharmacokinetics analysis with Lipinski'srule

On analysing of pharmacokinetics with ADME properties retrieved 143 compounds with the set of Lipinski's rule . retrieved compounds are mentioned in the given table.

5.4 TOXICITY ANALYSIS

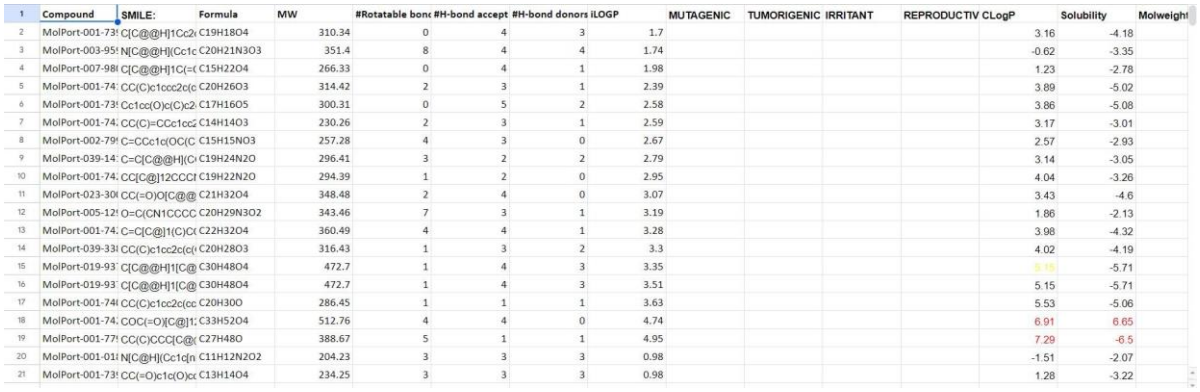
OSIRIS (Online Simplified Interfacial Representation of Input Structures) is an online tool that predicts the potential toxicity of small molecules based on their chemical structures. It uses a set of over 80 different rules to identify potentially toxic functional groups and structural features.

A web-based application that allows for the prediction of various toxicity

predict a range of toxicity endpoints – Mutagenicity, tumorigenicity, reproductive toxicity, or irritant.

	#Rotatable bond	#H-bond accept	#H-bond donors	iLOGP	MUTAGENIC	TUMORIGENIC	IRRITANT	REPRODUCTIV	CLogP	Solubility	Molweight	TPSA	Druglikeness	Drug score
2	0	4	3	1.7					3.16	-4.18	310	77.76	0.44	0.6
3	8	4	4	1.74					-0.62	-3.35	351	108.2	-13.8	0.43
4	0	4	1	1.98					1.23	-2.78	266	63.6	2.4	0.88
5	2	3	1	2.39					3.89	-5.02	314	54.37	-3.18	0.32
6	0	2	1	2.46					4.02	-4.07	270	37.3	-0.14	0.3
7	0	5	2	2.58					3.86	-5.08	300	75.99	-1.59	0.36
8	2	3	1	2.59					3.17	-3.01	230	46.53	-4.45	0.48
9	4	3	0	2.67					2.57	-2.93	257	46.61	1.53	0.8
10	3	2	2	2.79					3.14	-3.05	290	39.26	1.29	0.75
11	3	5	2	2.84					3.14	-2.93	302	68.15	-0.62	0.34
12	1	2	0	2.95					4.04	-3.26	294	25.24	4	0.76
13	0	5	2	2.95					3.25	-3.77	338	68.15	-1.97	0.21
14	2	5	0	2.97					2.49	-3.74	276	53.99	-0.77	0.33
15	6	4	3	3.04					4.1	-3.24	316	69.92	0.06	0.34
16	2	4	0	3.07					3.43	-4.6	348	52.6	-4.33	0.34
17	7	3	1	3.19					1.86	-2.13	343	52.65	2.01	0.8
18	1	3	2	3.22					3.32	-4.2	346	57.53	2.41	0.42
19	4	1	1	3.25					3.88	-3.22	210	20.23	-3.08	0.25
20	4	4	1	3.28					3.98	-4.32	360	63.6	-5.76	0.33
21	1	3	2	3.3					4.02	-4.19	316	49.69	-4.46	0.35

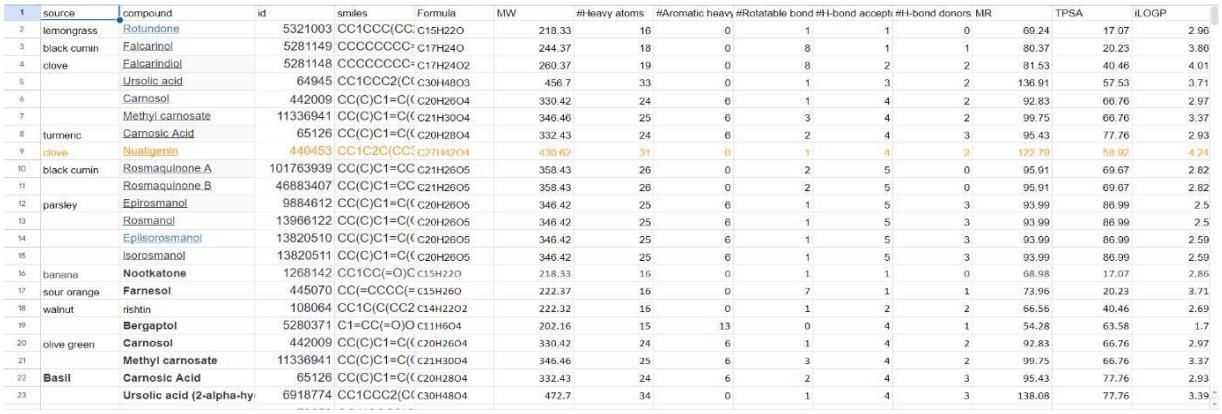
Fig 5.4: Filtering of toxicity



	Compound	SMILE:	Formula	MW	#Rotatable bonc	#H-bond accept	#H-bond donors	iLOGP	MUTAGENIC	TUMORIGENIC	IRRITANT	REPRODUCTIV	CLogP	Solubility	Molweight
2	MolPort-001-73!	C[C@@H]1Cc2(	C19H18O4	310.34	0	4	3	1.7					3.16	-4.18	
3	MolPort-003-95!	N[C@@H](Cc1c	C20H21N3O3	351.4	8	4	4	1.74					-0.62	-3.35	
4	MolPort-007-98(	C[C@@H]1C(=(	C15H22O4	266.33	0	4	1	1.98					1.23	-2.78	
5	MolPort-001-74:	CC(C)c1ccc2c(c	C20H26O3	314.42	2	3	1	2.39					3.89	-5.02	
6	MolPort-001-73!	Cc1cc(O)c(C)c2	C17H16O5	300.31	0	5	2	2.58					3.86	-5.08	
7	MolPort-001-74:	CC(C)=CCc1cc2	C14H14O3	230.26	2	3	1	2.59					3.17	-3.01	
8	MolPort-002-79(	C=CCc1c(OC(C	C15H15NO3	257.28	4	3	0	2.67					2.57	-2.93	
9	MolPort-039-14:	C=C[C@@H](C(	C19H24N2O	296.41	3	2	2	2.79					3.14	-3.05	
10	MolPort-001-74:	CC[C@]12CCC(	C19H22N2O	294.39	1	2	0	2.95					4.04	-3.26	
11	MolPort-023-30(	CC(=O)O[C@@	C21H32O4	348.48	2	4	0	3.07					3.43	-4.6	
12	MolPort-005-12!	O=C(CN1CCCC	C20H29N3O2	343.46	7	3	1	3.19					1.86	-2.13	
13	MolPort-001-74:	C=C[C@]1(C)C(	C22H32O4	360.49	4	4	1	3.28					3.98	-4.32	
14	MolPort-039-33!	CC(C)c1cc2c(c(	C20H28O3	316.43	1	3	2	3.3					4.02	-4.19	
15	MolPort-019-93	C[C@@H]1[C@	C30H48O4	472.7	1	4	3	3.35					5.15	-5.71	
16	MolPort-019-93	C[C@@H]1[C@	C30H48O4	472.7	1	4	3	3.51					5.15	-5.71	
17	MolPort-001-74(	CC(C)c1cc2c(cc	C20H30O	286.45	1	1	1	3.63					5.53	-5.06	
18	MolPort-001-74:	COC(=O)[C@]1(	C33H52O4	512.76	4	4	0	4.74					6.91	6.65	
19	MolPort-001-77!	CC(C)CC[C@(	C27H48O	388.67	5	1	1	4.95					7.29	-6.5	
20	MolPort-001-01!	N[C@H](Cc1c[n	C11H12N2O2	204.23	3	3	3	0.98					-1.51	-2.07	
21	MolPort-001-73!	CC(=O)c1c(O)cc	C13H14O4	234.25	3	3	3	0.98					1.28	-3.22	

Fig 5.5: Filtered compounds

On analysing of toxicity with Osiris properties retrieved 90 compounds , retrieved compounds are mentioned in the given figure.



	source	compound	id	smiles	Formula	MW	#Heavy atoms	#Aromatic heavy	#Rotatable bond	#H-bond accepti	#H-bond donors	MR	TPSA	iLOGP
2	lemongrass	Rotundone	5321003	CC1CCC(CC	C15H22O	218.33	16	0	1	1	0	69.24	17.07	2.96
3	black cumin	Falcarinol	5281149	CCCCCCCC	C17H24O	244.37	18	0	8	1	1	80.37	20.23	3.86
4	clove	Falcarindiol	5281148	CCCCCCCC	C17H24O2	260.37	19	0	8	2	2	81.53	40.46	4.01
5		Ursolic acid	64945	CC1CCC2(C(	C30H48O3	456.7	33	0	1	3	2	136.91	57.53	3.71
6		Carnosol	442009	CC(C)C1=C((	C20H26O4	330.42	24	6	1	4	2	92.83	66.76	2.97
7		Methyl carnosate	11336941	CC(C)C1=C((	C21H30O4	346.46	25	6	3	4	2	99.75	66.76	3.37
8	turmeric	Carnosic Acid	65126	CC(C)C1=C((	C20H28O4	332.43	24	6	2	4	3	95.43	77.76	2.93
9	clove	Nuatigenin	440453	CC1C2C(CC	C27H42O4	430.62	31	0	1	4	2	122.79	58.92	4.24
10	black cumin	Rosmaquinone A	101763939	CC(C)C1=CC	C21H26O5	358.43	26	0	2	5	0	95.91	69.67	2.82
11		Rosmaquinone B	46883407	CC(C)C1=CC	C21H26O5	358.43	26	0	2	5	0	95.91	69.67	2.82
12	parsley	Epirosmanol	9884612	CC(C)C1=C((	C20H26O5	346.42	25	6	1	5	3	93.99	86.99	2.5
13		Rosmanol	13966122	CC(C)C1=C((	C20H26O5	346.42	25	6	1	5	3	93.99	86.99	2.5
14		Epiisorosmanol	13820510	CC(C)C1=C((	C20H26O5	346.42	25	6	1	5	3	93.99	86.99	2.59
15		isorosmanol	13820511	CC(C)C1=C((	C20H26O5	346.42	25	6	1	5	3	93.99	86.99	2.59
16	banana	**Nootkatone**	1268142	CC1CC(=O)C	C15H22O	218.33	16	0	1	1	0	68.98	17.07	2.86
17	sour orange	**Farnesol**	445070	CC(=CCCC(=	C15H26O	222.37	16	0	7	1	1	73.96	20.23	3.71
18	walnut	rishtin	108064	CC1C(C(CC2	C14H22O2	222.32	16	0	1	2	2	66.56	40.46	2.69
19		**Bergaptol**	5280371	C1=CC(=O)O	C11H6O4	202.16	15	13	0	4	1	54.28	63.58	1.7
20	olive green	**Carnosol**	442009	CC(C)C1=C((	C20H26O4	330.42	24	6	1	4	2	92.83	66.76	2.97
21		**Methyl carnosate**	11336941	CC(C)C1=C((	C21H30O4	346.46	25	6	3	4	2	99.75	66.76	3.37
22	**Basil**	**Carnosic Acid**	65126	CC(C)C1=C((	C20H28O4	332.43	24	6	2	4	3	95.43	77.76	2.93
23		**Ursolic acid (2-alpha-hy**	6918774	CC1CCC2(C(	C30H48O4	472.7	34	0	1	4	3	138.08	77.76	3.39

Fig 5.6: Filtered compounds of small molecules

5.5.DOCKING (Identification of binding sites and its analysis of interactions between ligands and target)

Drug designing docking is a powerful tool in drug discovery, as it allows researchers to screen large libraries of compounds quickly and efficiently, and to prioritize the most promising candidates for further development. However, it is important to note that drug designing docking is just one step in the drug discovery process, and experimental validation is still required to confirm the efficacy and safety of potential drug candidates.

The process of drug designing docking typically involves the following steps:

Preparation of the protein structure: The target protein structure is obtained from experimental techniques or from computational methods, and is prepared by removing any unwanted water molecules, ions, and other ligands that may interfere with docking.

Preparation of ligand structures: The small molecule drug candidates are prepared by optimizing their geometry and assigning partial charges, to allow them to interact with the protein in a meaningful way.

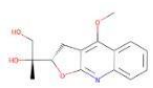
Docking: The ligands are docked onto the protein structure using computational algorithms that predict the most favorable orientation and conformation of the ligand in the protein binding site.

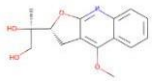
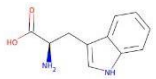
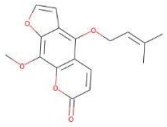
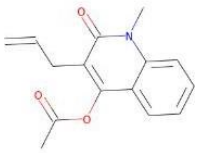
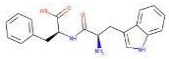
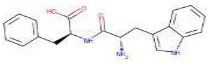
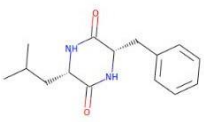
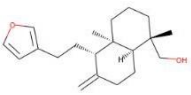
Scoring: The predicted ligand-protein complexes are scored based on their predicted binding energy or other parameters that are indicative of the strength of the interaction.

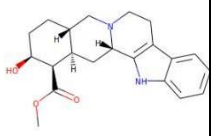
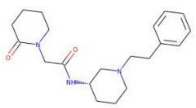
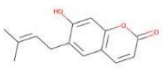
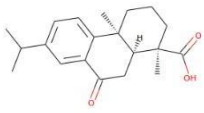
Analysis and selection:
The ligand-protein complexes are analysed to identify the most promising drug candidates, which can be further optimized and tested in vitro and in vivo for their efficacy and safety.

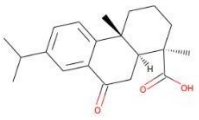
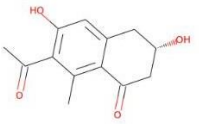
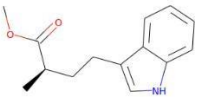
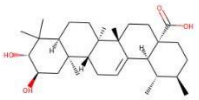
5.6 DOCKING RESULT

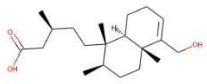
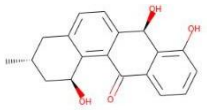
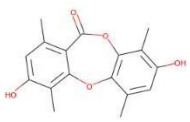
Table 5.1: ZINC COMPOUNDS

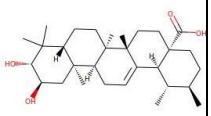
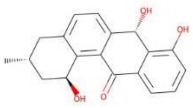
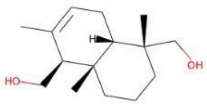
S.No	NAME	STRUCTURE	MW	CDOCKER ENERGY	No.of H-BONDS and Amino acids	NON H-BONDS	UNFAVOURABLE BONDS
1.	Dubinidine		275.30	-15.656	2 (GLN234) (ARG380)	7	0

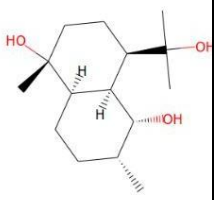
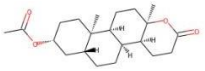
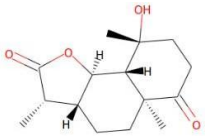
2.	Dubinidine		275.30	-17.443	1(LYS197)	8	0
3.	D-Tryptophan		204.22	21.9485	1(LYS197)	2	0
4.	Kinidilin		300.30	-2.26552	2(ARG380) (LYS197)	13	0
5.	3-Allyl-1-methyl-2-oxo-1,2-dihydro-4-quinolinyl acetate		257.28	1.06139	1(ARG380)	5	0
6.	Trp-Phe		351.4	39.5474	2(GLN234) (ARG380)	5	0
7.	Trp-Phe		351.4	39.7841	1(ARG380)	5	0
8.	Cyclo leucyl-L- (L-phenylalanyl)		260	20.3451	2(ARG380) (LYS197)	9	0
9.	[(1S,4aR,5S,8aS)-5-[2-(furan-3-yl)ethyl]-1,4a-dimethyl-6-		302.5	-21.4131	2(CYS296) (THR298)	14	0

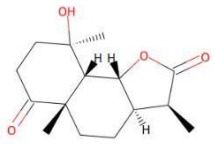
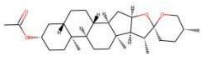
	methylidene-3,4,5,7,8,8a-hexahydro-2H-naphthalen-1-yl]methanol						
10.	methyl (1S,15S,18S,19R,20R)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate		354.4	-1.97035	2(ARG380) (ARG299)	7	0
11.	2-(2-oxopiperidin-1-yl)-N-[(3S)-1-(2-phenylethyl)piperidin-3-yl]acetamide		343.471	24.8573	2(ARG380) (GLN234)	7	0
12.	Demethylsuberosin		230.263	2.39676	2(LYS197) (GLN221)	6	0
13.	(1R,4aS,10aS)-1,4a-dimethyl-9-oxo-7-propan-2-yl-3,4,10,10a-tetrahydro-2H-		314.425	5.1622	2(GLU364) (ARG190)	9	1(TYR241)

	phenanthrene-1-carboxylic acid						
14.	(1R,4aR,10aS)-1,4a-dimethyl-9-oxo-7-propan-2-yl-3,4,10,10a-tetrahydro-2H-phenanthrene-1-carboxylic acid		314.4	6.9926	2(ARG310) (TYR241)	6	0
15.	(3S)-7-acetyl-3,6-dihydroxy-8-methyl-3,4-dihydro-2H-naphthalen-1-one		234.251	14.694	2(ARG380) (LYS197)	5	0
16.	Methyl (2r)-4-(1h-indol-3-yl)-2-methylbutanoate		231.295	25.8309	2(ARG380) (ARG299)	5	0
17.	1S,2R,4aS,6aR,6aS,6bR,8aS,10R,11R,12aR,14bS)-10,11-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7		472.71	-189.523	1(ARG380)	17	0

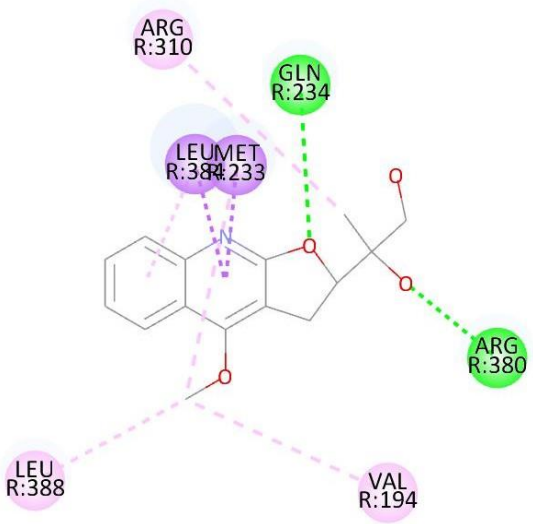
	,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid						
18.	3S)-5-[(1S,2R,4aR,8aR)-5-(hydroxymethyl)-1,2,4a-trimethyl-2,3,4,7,8,8a-hexahydronaphthalen-1-yl]-3-methylpentanoic acid		322.489	-30.5743	2(ARG380) (GLN221)	10	0
19.	(1S,3R,7R)-1,7,8-trihydroxy-3-methyl-2,3,4,7-tetrahydro-1H-benzo[a]anthracen-12-one		310.349	17.7913	3(LYS197) (GLN234) (ARG380)	8	0
20.	3,9-Dihydroxy-1,4,7,10-tetramethylbenzo[b][1,4]benzodioxepin-6-one		300.30	10.9024	2(LYS197) (THR298)	12	0

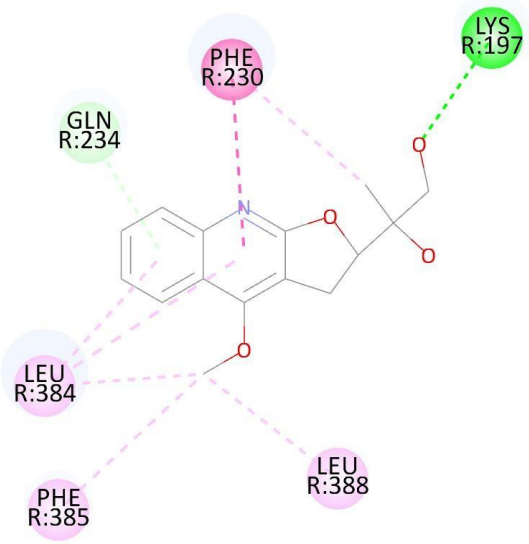
21.	(1S,2R,4aS,6aS,6aS,6bR,8aR,10R,11R,12aR,14bS)-10,11-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid		472.71	-457.689	2(GLN234) (THR298)	14	0
22.	(1S,3R,7S)-1,7,8-trihydroxy-3-methyl-2,3,4,7-tetrahydro-1H-benzo[a]anthracen-12-one		310.349	17.445	3(ARG380) (GLN234) (LYS197)	7	0
23.	[(1S,4aS,5R,8aS)-5-(hydroxymethyl)-2,5,8a-trimethyl-1,4,4a,6,7,8-hexahydronaphthalen-1-yl]methanol		238.371	-21.4184	2(GLN234) (GLU387)	8	0

24.	(1R,2R,4aR,5R,8R,8aR)-8-(2-hydroxypropan-2-yl)-2,5-dimethyl-2,3,4,4a,6,7,8,8a-octahydro-1H-naphthalene-1,5-diol		256.386	-5.20356	2(ARG190) (ARG380)	8	0
25.	[(4aS,4bS,6aR,8R,10aR,10bS,12aR)-10a,12a-dimethyl-2-oxo-3,4,4a,4b,5,6,6a,7,8,9,10,10b,11,12-tetradecahydronaphtho[2,1-f]chromen-8-yl] acetate		348.5	-15.606	3(ARG380) (GLM234) (THR298)	9	0
26.	(3S,3aR,5aS,9R,9aR,9bR)-9-hydroxy-3,5a,9-trimethyl-3,3a,4,5,7,8,9a,9b-octahydrobenzo[g][1]benzofuran-2,6-dione		266.337	-5.04458	2(LYS197) (ARG360)	5	0

27.	(3S,3aR,5aS,9R,9aS,9bR)-9-hydroxy-3,5a,9-trimethyl-3,3a,4,5,7,8,9a,9b-octahydrobenzo[g][1]benzofuran-2,6-dione		266.33	-13.9327	2(ARG380) (ARG190)	6	0
28.	[(1S,2R,4R,5'R,6R,7R,8S,9S,12R,13S,16S,18S)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icosane-6,2'-oxane]-16-yl] acetate		458.683	-583.074	0	16	1(MET233)

2D IMAGES





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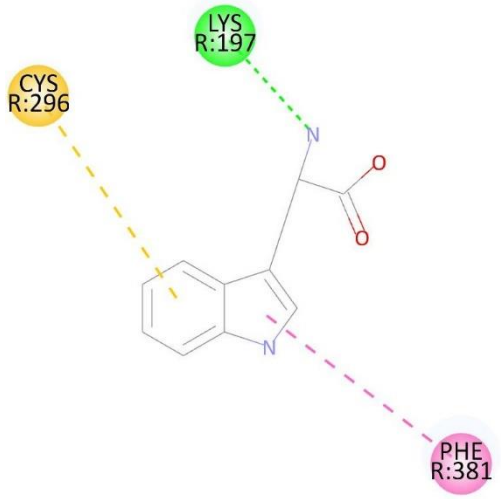

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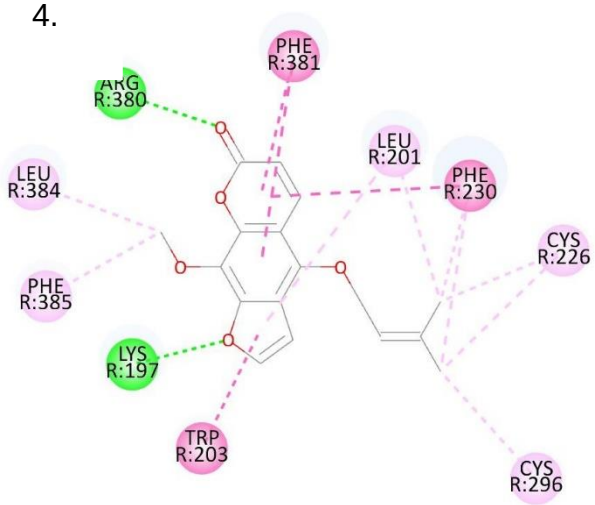

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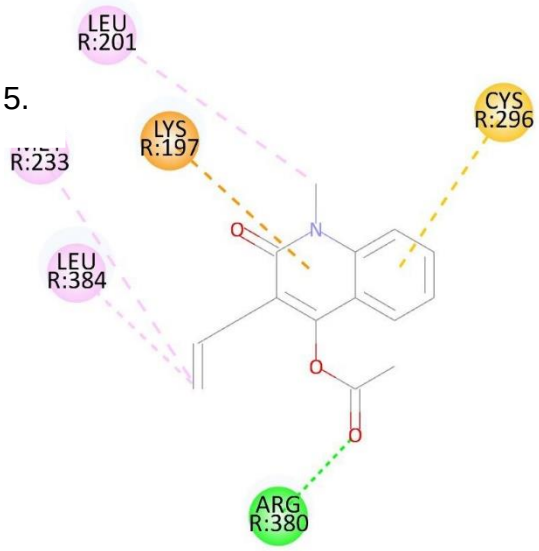

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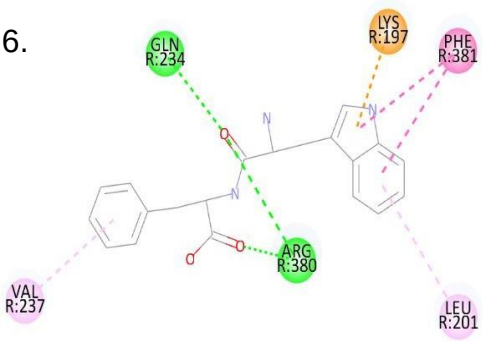

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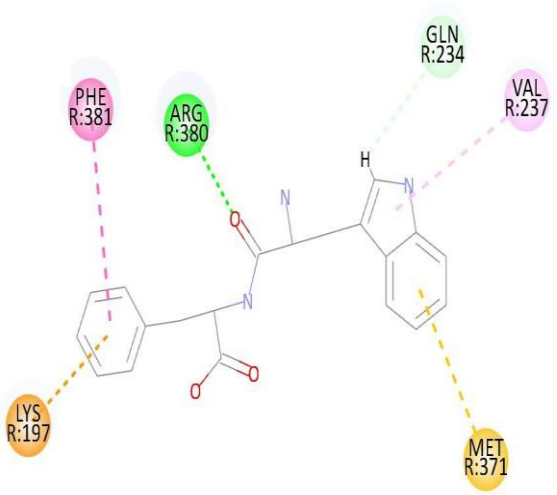
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ARG
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VAL
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LYS
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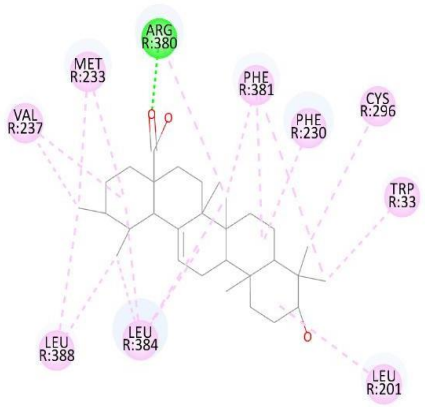
MET
R:371

8.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PHE
R:381
CYS
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VAL
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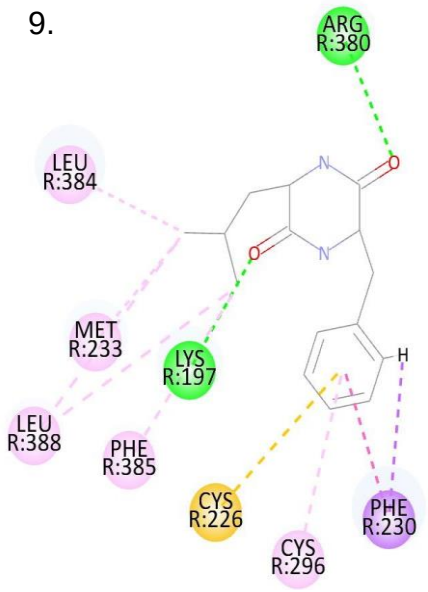
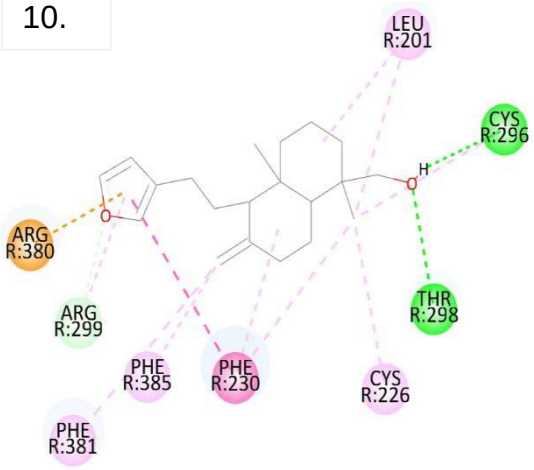
PHE
R:230
TRP
R:33
LEU
R:388
LEU
R:384
LEU
R:201

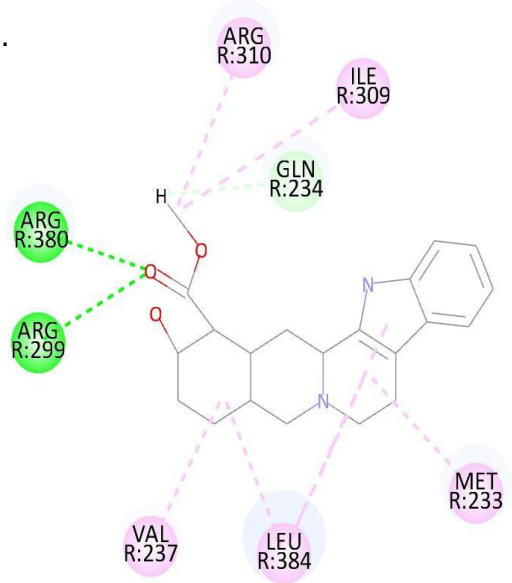
9.


ARG
R:380
LEU
R:384
MET
R:233
LYS
R:197
LEU
R:388
PHE
R:385
CYS
R:226
PHE
R:230
CYS
R:296

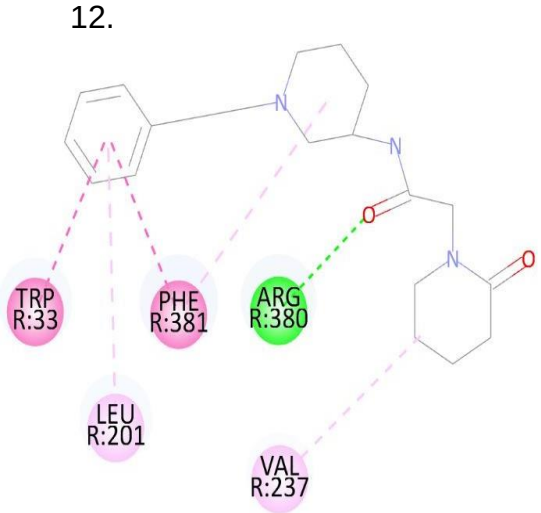
10.


LEU
R:201
CYS
R:296
ARG
R:380
THR
R:298
ARG
R:299
PHE
R:385
PHE
R:230
CYS
R:226
PHE
R:381

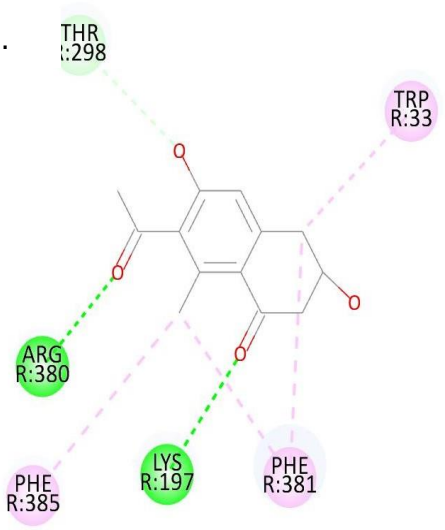
11.


ARG
R:310
ILE
R:309
GLN
R:234
ARG
R:380
ARG
R:299
MET
R:233
VAL
R:237
LEU
R:384

12.


TRP
R:33
PHE
R:381
ARG
R:380
LEU
R:201
VAL
R:237

13.



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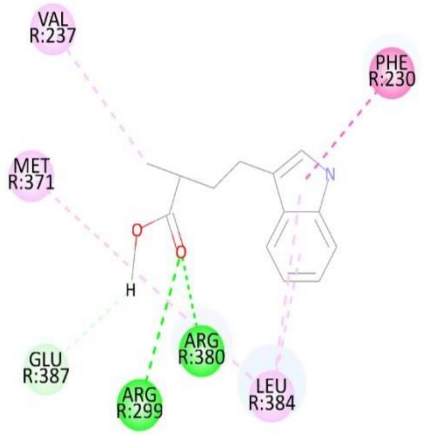

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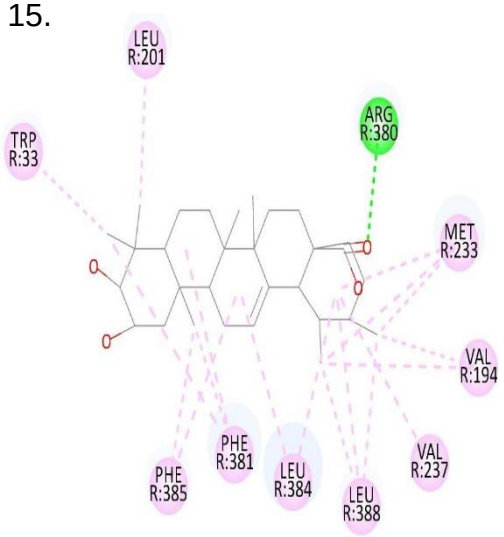

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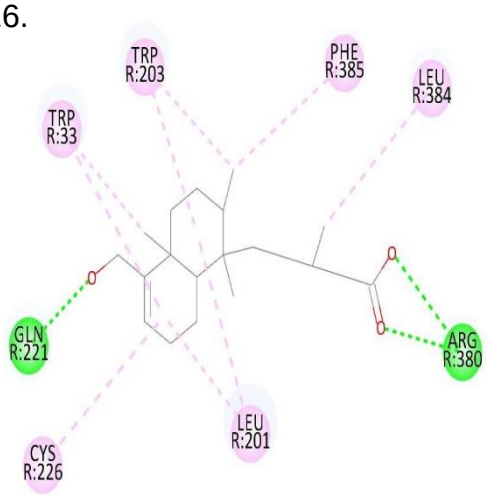

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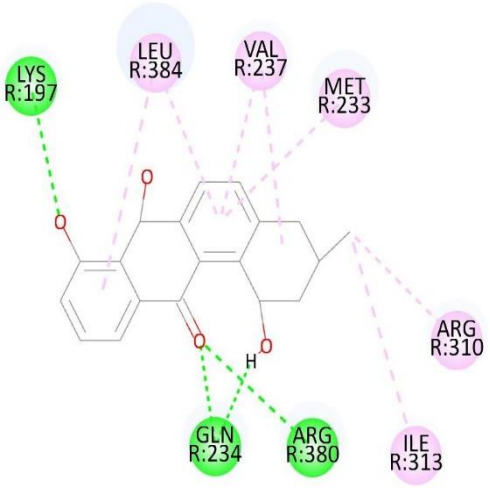

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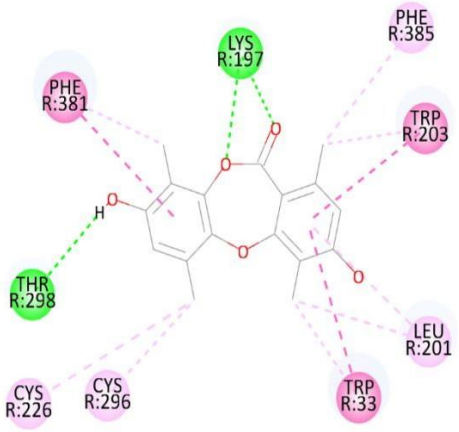

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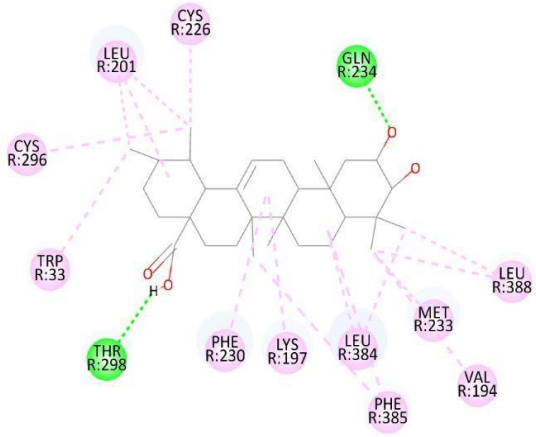

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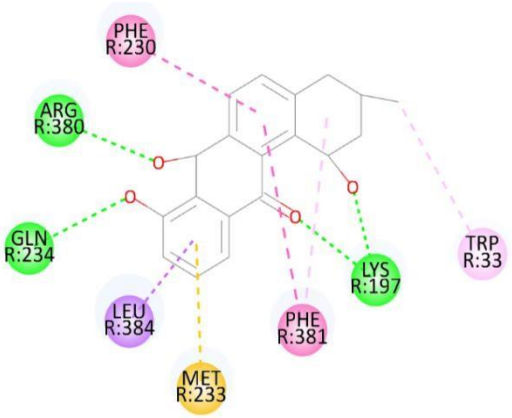

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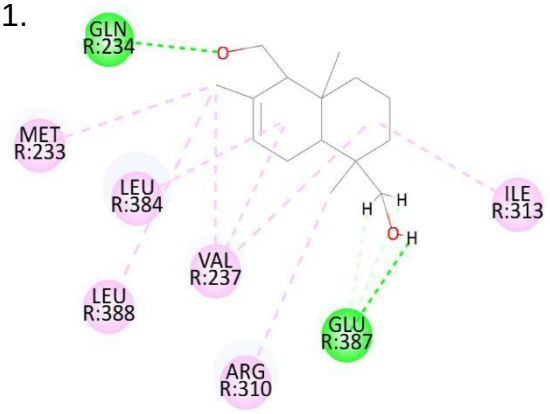

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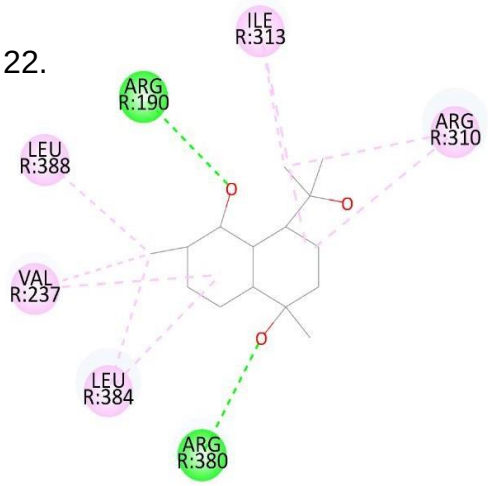

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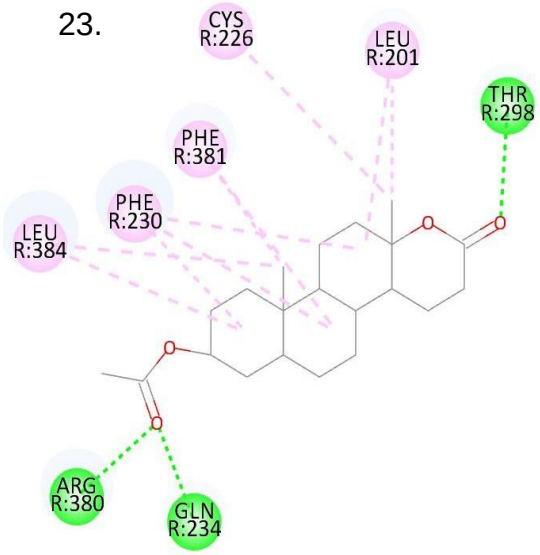

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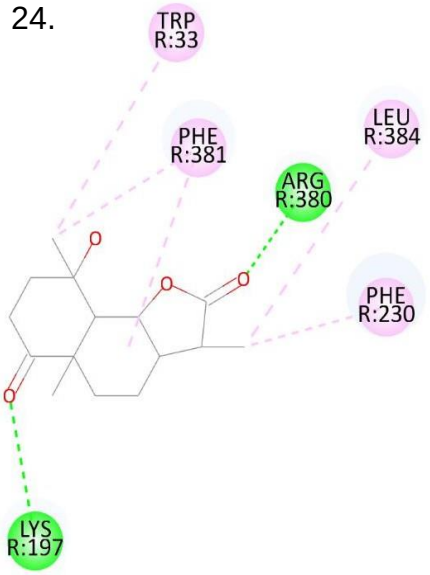

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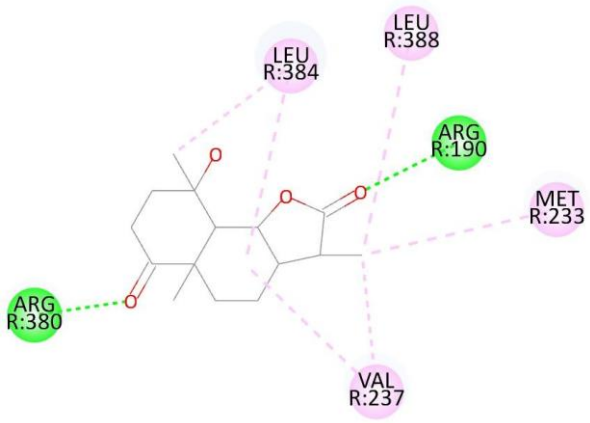

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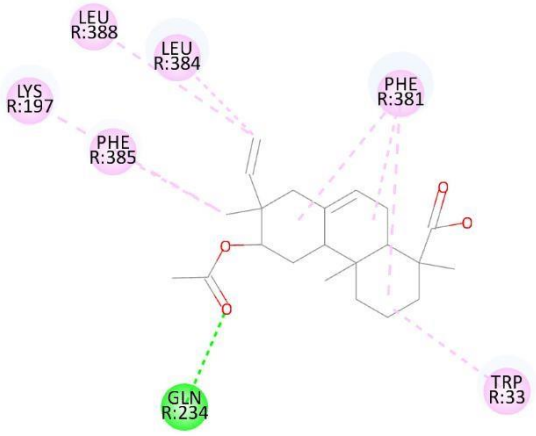

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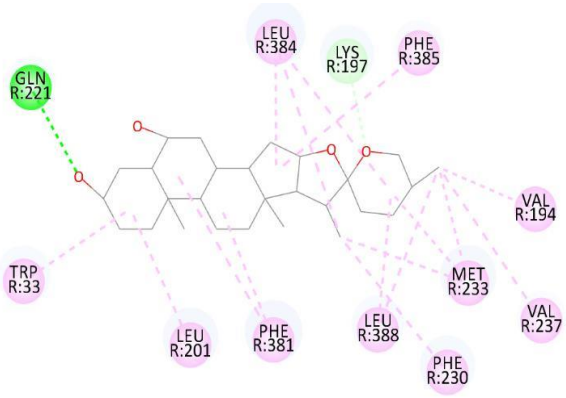

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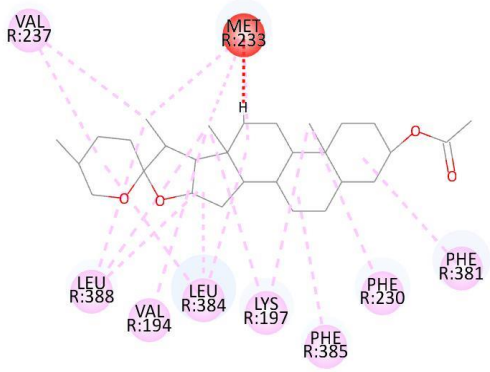
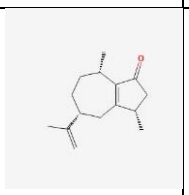
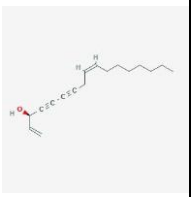
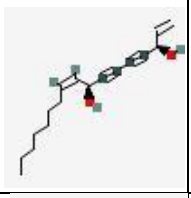
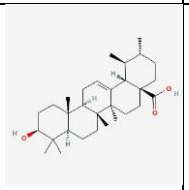
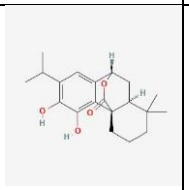
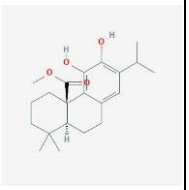


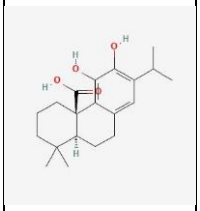
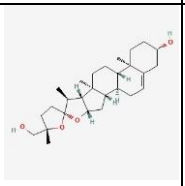
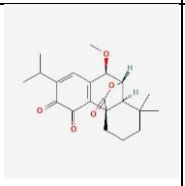
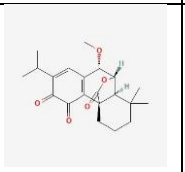
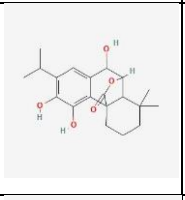
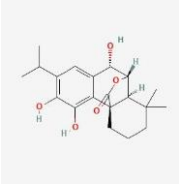
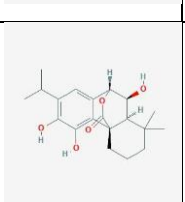
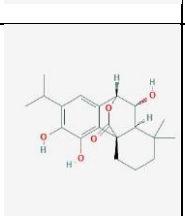
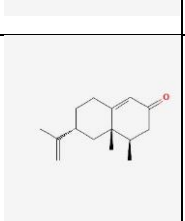
Fig 5.7: 2D IMAGES OF Dubinidine, D-Tryptophan, Kinidilin, 3-Allyl-1-methyl-2-oxo-1,2-dihydro-4-quinolinyl acetate, Trp-Phe, Trp-Phe, Cyclo leucyl-L- (L-phenylalanyl),[(1S,4aR,5S,8aS)-5-[2-(furan-3-yl)ethyl]-1,4a-dimethyl-6-methylidene-3,4,5,7,8,8a-hexahydro-2H-naphthalen-1-yl]methanol,methyl (1S,15S,18S,19R,20R)-18-hydroxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate,2-(2-oxopiperidin-1-yl)-N-[(3S)-1-(2-phenylethyl)piperidin-3-yl]acetamide,Demethylsuberosin,(1R,4aS,10aS)-1,4a-dimethyl-9-oxo-7-propan-2-yl-3,4,10,10a-tetrahydro-2H-phenanthrene-1-carboxylic acid , (1R,4aR,10aS)-1,4a-dimethyl-9-oxo-7-propan-2-yl-3,4,10,10a-

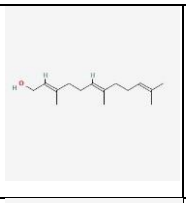
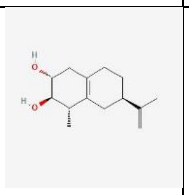
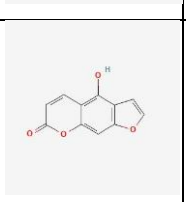
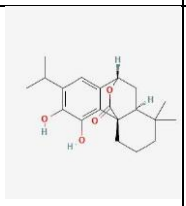
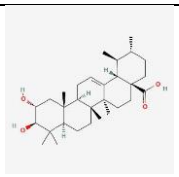
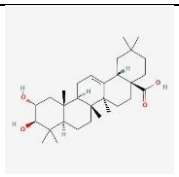
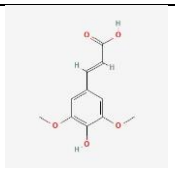
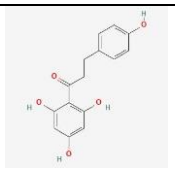
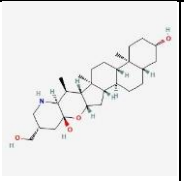
tetrahydro-2H-phenanthrene-1-carboxylic acid,(3S)-7-acetyl-3,6-dihydroxy-8-methyl-3,4-dihydro-2H-naphthalen-1-one,Methyl(2r)-4-(1h-indol-3-yl)-2-methylbutanoate,1S,2R,4aS,6aR,6aS,6bR,8aS,10R,11R,12aR,14bS)-10,11-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid , 3S)-5-[(1S,2R,4aR,8aR)-5-(hydroxymethyl)-1,2,4a-trimethyl-2,3,4,7,8,8a-hexahydronaphthalen-1-yl]-3-methylpentanoicacid,(1S,3R,7R)-1,7,8-trihydroxy-3-methyl-2,3,4,7-tetrahydro-1H-benzo[a]anthracen-12-one,3,9-Dihydroxy-1,4,7,10-tetramethylbenzo[b][1,4]benzodioxepin-6 one,(1S,2R,4aS,6aS,6aS,6bR,8aR,10R,11R,12aR,14bS)-10,11-dihydroxy-1,2,6a,6b,9,9,12a-heptamethyl-2,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydro-1H-picene-4a-carboxylic acid ,(1S,3R,7S)-1,7,8-trihydroxy-3-methyl-2,3,4,7-tetrahydro-1H-benzo[a]anthracen-12-one,[(1S,4aS,5R,8aS)-5-(hydroxymethyl)-2,5,8a-trimethyl-1,4,4a,6,7,8-hexahydronaphthalen-1-yl]methanol , (1R,2R,4aR,5R,8R,8aR)-8-(2-hydroxypropan-2-yl)-2,5-dimethyl-2,3,4,4a,6,7,8,8a-octahydro-1H-naphthalene-1,5-diol,[(4aS,4bS,6aR,8R,10aR,10bS,12aR)-10a,12a-dimethyl-2-oxo-3,4,4a,4b,5,6,6a,7,8,9,10,10b,11,12-tetradecahydronaphtho[2,1-f]chromen-8-yl] acetate,,(3S,3aR,5aS,9R,9aR,9bR)-9-hydroxy-3,5a,9-trimethyl-3,3a,4,5,7,8,9a,9b-octahydrobenzo[g][1]benzofuran-2,6-dione, (3S,3aR,5aS,9R,9aS,9bR)-9-hydroxy-3,5a,9-trimethyl-3,3a,4,5,7,8,9a,9b-octahydrobenzo[g][1]benzofuran-2,6-dione, [(1S,2R,4R,5'R,6R,7R,8S,9S,12R,13S,16S,18S)-5',7,9,13-tetramethylspiro[5-oxapentacyclo[10.8.0.02,9.04,8.013,18]icosane-6,2'-oxane]-16-yl] acetate

5.7 SMALL MOLECULES

Table 5.2: Small Molecules

S. NO	SOURCE	COMPOUND	STRUCTURE	MW	CDOCKER ENERGY	HBONDS AMINO ACID	NON H-BONDS	UNFAVOUABLE BONDS
1.	Pepper	5321003 Rotundone		218.33	-55.4512	1(ARG380)	7	0
2.	Fennel, parsley	5281149 Falcarinol		244.37	6.32068	1(ARG380)	5	0
3.	Fennel, parsley	5281148 Falcarindiol		260.4	12.3581	2(LYS197)(ARG299)	6	0
4.	Apple, Mustard, Olive	64945 Ursolic acid		456.7	-183.004	1(ARG380)	20	0
5.	Basil, Rosemary	442009 Carnosol		330.4	0.966047	3(LYS197)(THR298)(ARG380)	9	0
6.	Basil, Rosemary	11336941Methyl carnosate		346.5	10.7879	3(LYS197)(THR298)(ARG380)	9	0

7.	thyme, Basil, Rosemary	65126 Carnosic Acid		332.4	9.46323	2(ARG299)(ARG380)	13	0
8.	oat	440453 Nuatigenin		430.6	-111.859	3(GLN221)(GLN234)(ARG299)	10	0
9	Rosemary	101763939Rosmaquinone A		358.4	-24.9196	2(ARG380)(ARG299)	10	0
10.	Rosemary	46883407 Rosmaquinone B		358.43	-33.1971	1(ARG380)	8	0
11.	Basil, Rosemary	9884612 Epirosmanol		346.42	-6.4904	2(LYS197)(THR298)	6	0
12.	Rosemary	13966122 Rosmanol		346.42	0.539628	2(ARG380)(THR298)	6	0
13.	Rosemary	13820510 Epiisorosmanol		346.42	-3.69488	1(LYS197)	6	1(GLN221)
14.	Rosemary	13820511 isorosmanol		346.42	-0.325945	1(LYS197)	6	0
15.	Grape Fruit	1268142 Nootkatone		218.33	-11.1008	1(ARG380)	9	0

16.	fennel, parsley, carrot	445070 Farnesol		222.37	-39.4323	1(ARG380)	12	0
17.	tomato	108064 rishitin		222.32	-39.694	0	7	1(GLN221)
18.	Grape Fruit	5280371 Bergaptol		202.16	20.0269	2(ARG380)(LYS197)	5	0
19.	Basil, Rosemary	442009 Carnosol		330.42	0.966047	3(LYS197)(THR298)(ARG380)	8	0
20.	Apple, Mustard, Olive	6918774 Ursolic acid (2-alpha-hydroxy-)		472.7	-216.193	1(ARG380)	16	1(GLN234)
21.	apple olive	73659 Maslinic acid		472.7	-192.068	1(ARG380)	17	1(GLN234)
22.	olive, orange juice	637775 Sinapic acid		224.21	23.4264	2(ARG380)(LYS197)	5	0
23.	Apple	4788 Phloretin		274.27	23.5898	2(ARG380)(LYS197)	4	0
24.	Tomato	11430786 Esculeogenin B		447.65	-88.0534	3(GLN221)(ARG190)(TYR241)	14	1(GLN234)

2D IMAGES

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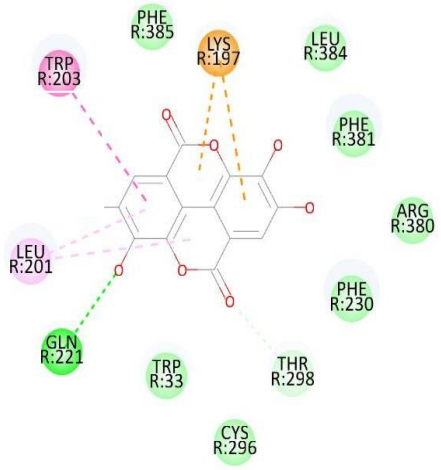

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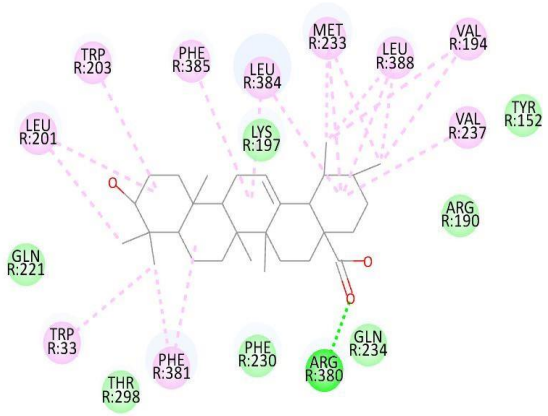

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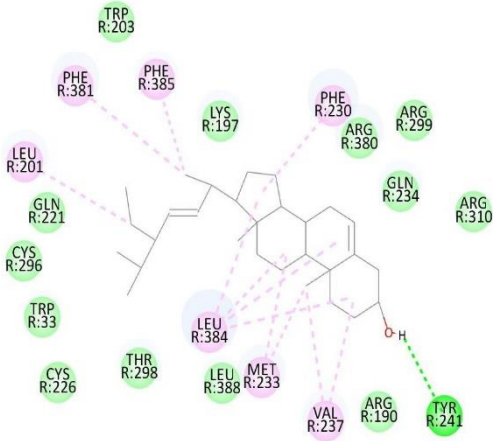

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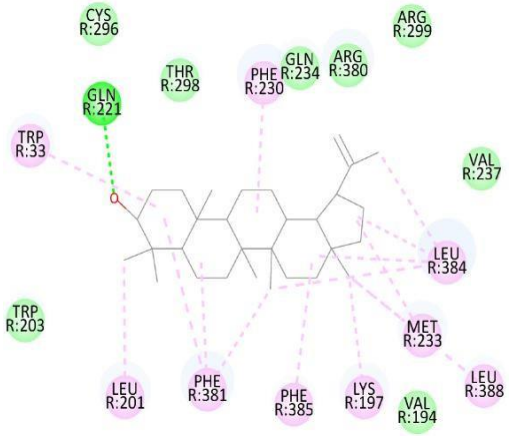

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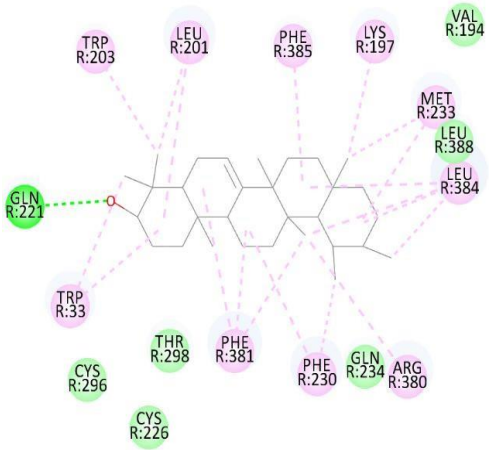

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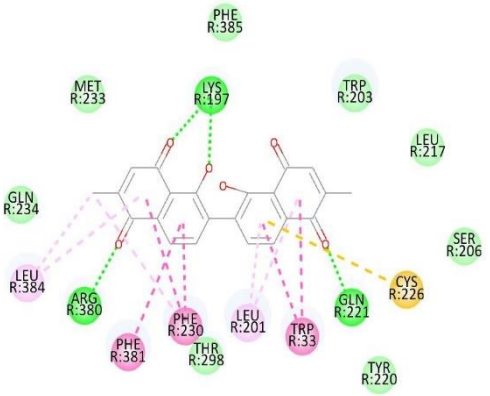

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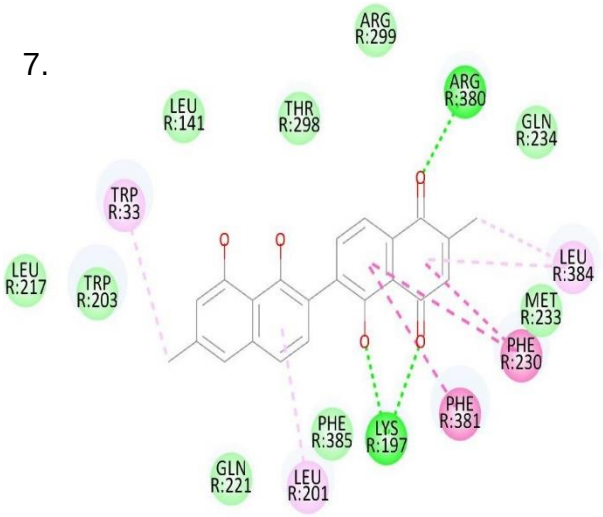
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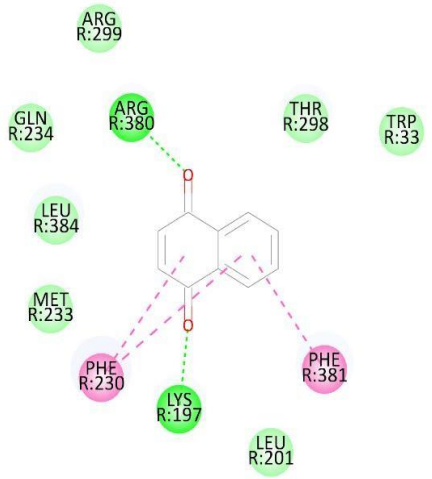
THR R:298
GLN R:234
TRP R:33
LEU R:217
TRP R:203
LEU R:384
MET R:233
PHE R:230
PHE R:381
PHE R:385
LYS R:197
GLN R:221
LEU R:201

8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LEU R:201

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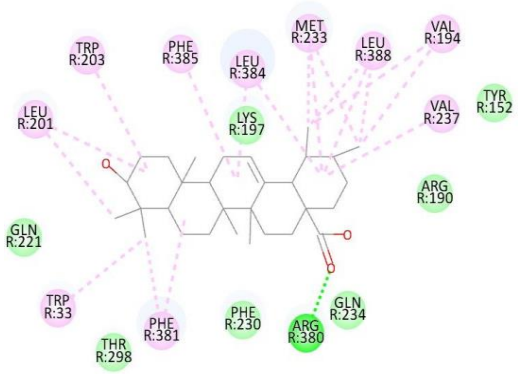
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THR R:298

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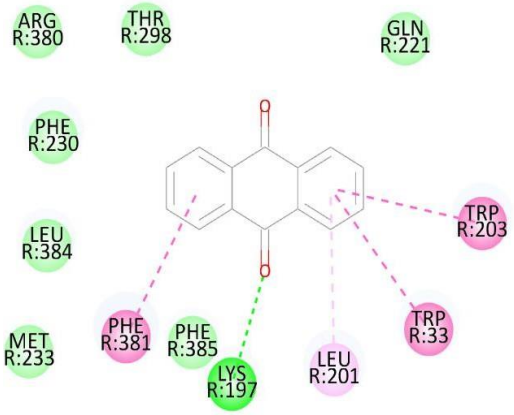
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LEU R:201
LYS R:197

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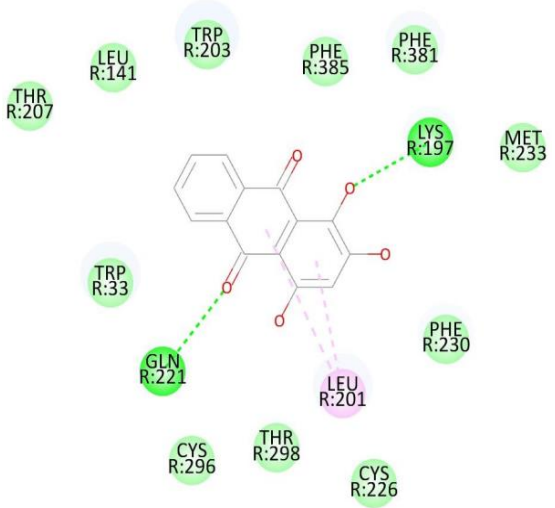
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CYS R:226

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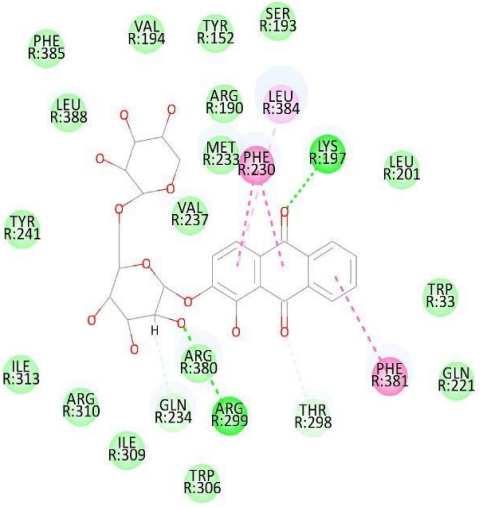
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LYS R:197
LEU R:201
VAL R:237
TYR R:241
TRP R:33
ARG R:380
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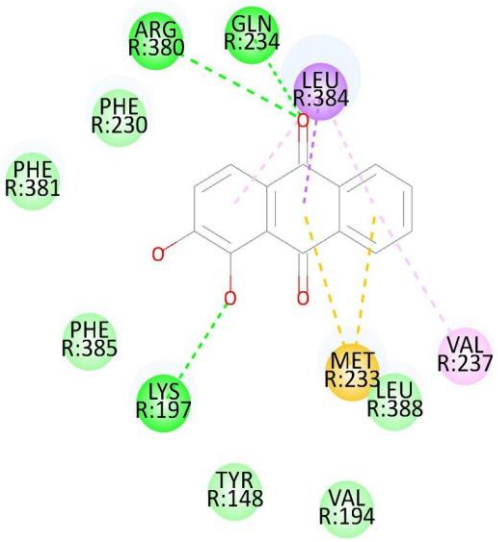

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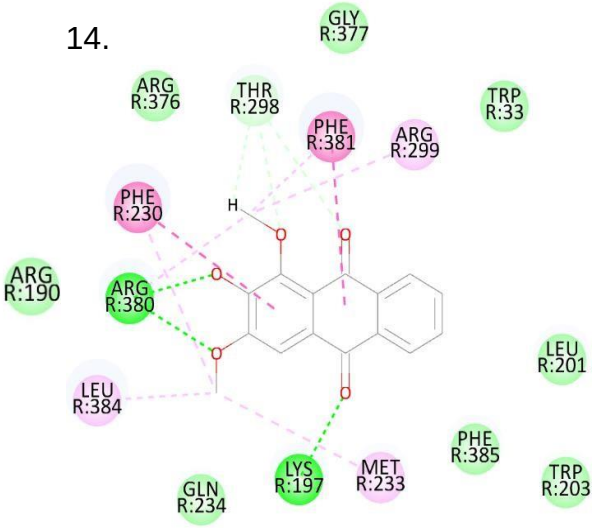

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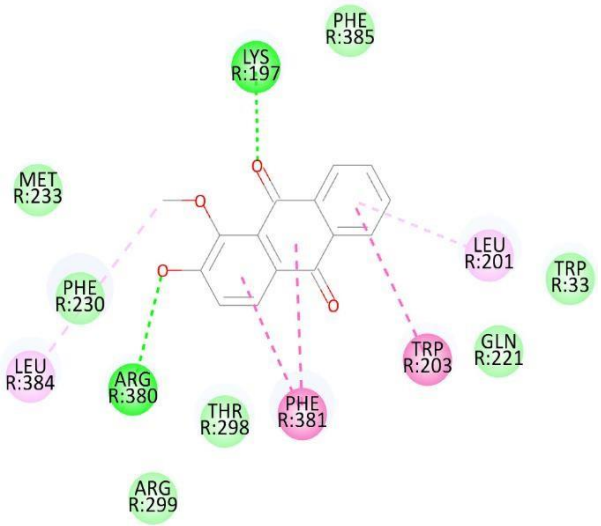

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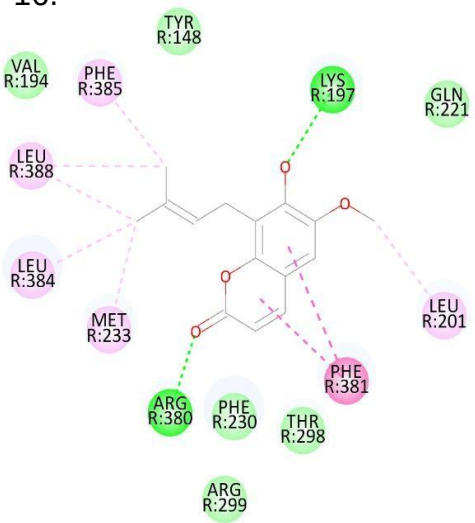

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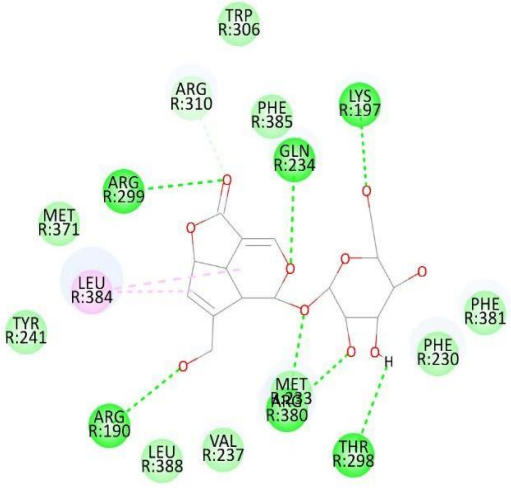

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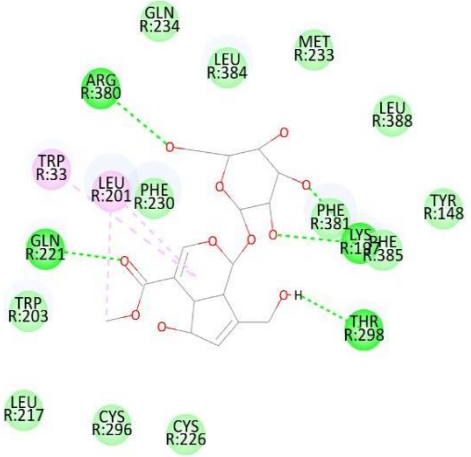

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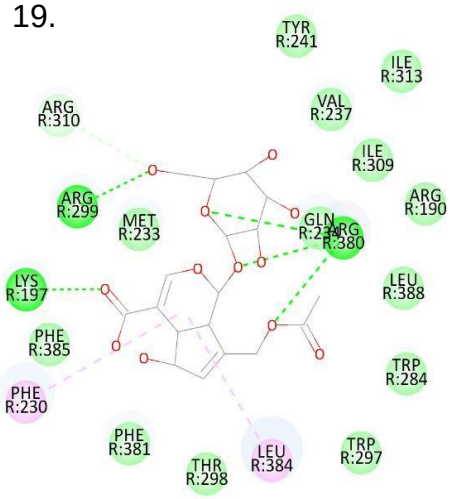

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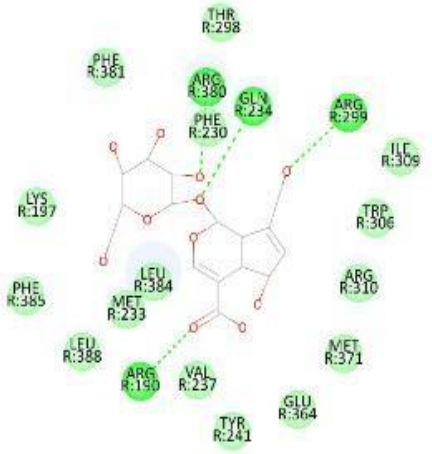

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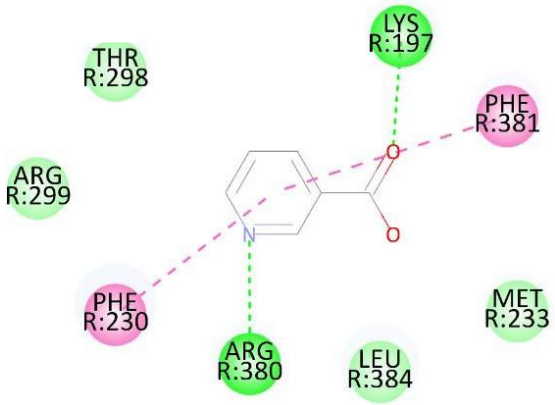
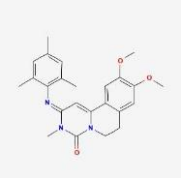
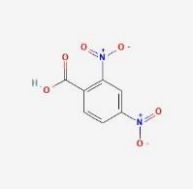
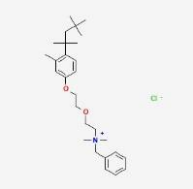
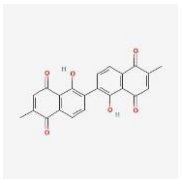
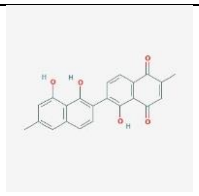
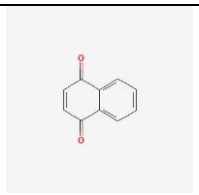
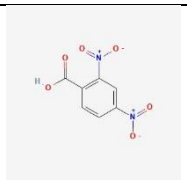
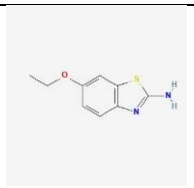
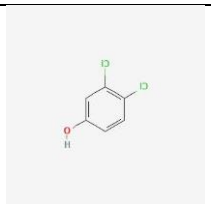
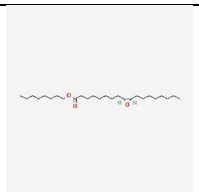
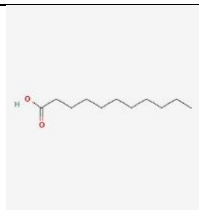


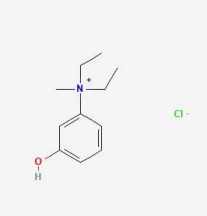
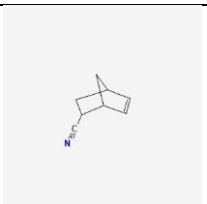
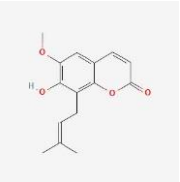
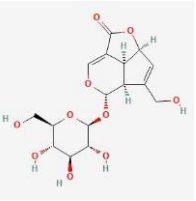
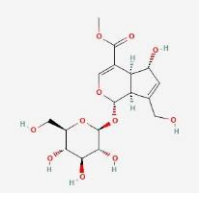
FIG 5.8: IMPHY005537 , Ellagic acid , IMPHY011880 Ursolic acid ,IMPHY014842 Stigmasterol , IMPHY012473 Lupeol, IMPHY012314 Bauerenol ,146680 Elliptinone ,86103922 Ebenone , 8530 1,4-Naphthoquinon , IMPHY011880-Ursolic acid , IMPHY007192 Anthraquinone , IMPHY007258 Purpurin , IMPHY007831 Ruberythric acid , IMPHY008180 Alizarin , IMPHY014325 1,3-Dimethoxy-2-hydroxy-9,10-anthraquinone , IMPHY007218 Alizarin 1-methyl ether , 12302592 cedrelopsin , 44593378 Deacetylasperuloside , 442433 scandoside methyl ester , 11968867 asperulosidic acid , 21602023 scan-doside 938 nicotinic acid

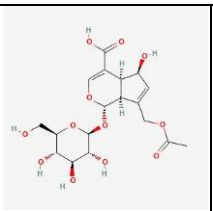
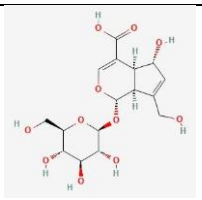
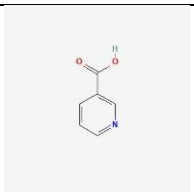
5.8 PLANT COMPOUNDS

Table 5.2: Small Molecules

S. NO	SOURCE (Plant Compounds)	COMPOUND	STRUCTURE	MW	CDOCKER ENERGY	HBONDS AMINO ACID	NON H-BONDS	UNFAVOUABLE BONDS
1.	Diospyros	IMPHY005537 Ellagic acid		405.5	16.8403	GLN 221	11	0
2.	Diospyros	IMPHY011880 Ursolic acid		212.12	-185.2	ARG 380	18	0
3.	Diospyros	IMPHY014842 Stigmasterol		462.1	-108.716	TYR 241	12	0
4.	Diospyros	IMPHY012473 Lupeol		111.10	-606.18	GLN 221	13	0
5.	Diospyros	IMPHY012314 Baueerenol		295.89	-166.703	GLN221	17	0

6.	Diospyros	146680 Elliptinone		374.3	15.2851	ARG380 ,LYS197 , GLN221	11	0
7.	Diospyros	86103922 Ebenone		360.4	8.88714	ARG380 LYS197	7	0
8.	Diospyros	8530 1,4-Naphthoquinone		158.15	19.8404	ARG380 , LYS197	3	0
9.	Diospyros	IMPHY011880-Ursolic acid		212.12	-185.2	ARG380	17	0
10.	Oldenlandia	IMPHY007192 Anthraquinone		194.26	15.5969	LYS197	4	0
11.	Oldenlandia	IMPHY007258 Purpurin		163.00	25.3984	LYS197 GLN221	2	0
12.	Oldenlandia	IMPHY007831 Rubervthric acid		410.7	-29.9747	LYS197 ARG299		
13.	Oldenlandia	IMPHY008180 Alizarin		186.29	19.1367	ARG380 , GLN234 ,		

						LYS197		
14.	Oldenlandia	IMPHY014325 1,3-Dimethoxy-2-hydroxy-9,10-anthraquinone		215.72	15.3801	ARG380, LYS197	10	0
15.	Oldenlandia	IMPHY007218 Alizarin 1-methyl ether		119.16	18.9884	LYS197, ARG380	5	0
16.	Oldenlandia	12302592 cedrelopsin		260.28	5.09562	LYS197, ARG380	8	0
17.	Oldenlandia	44593378 Deacetylasperuloside		372.32	-52.773	ARG380 GLN234 LYS197 ARG190 ARG380 THR298	3	0
18.	Oldenlandia	442433 scandoside methyl ester		404.4	-31.5662	ARG380 GLN221 LYS197 THR298	3	0

19.	Oldenlandia	11968867 asperulosidic acid		432.4	-23.4005	ARG380 GLN221 LYS197 THR298	3	0
20.	Oldenlandia	21602023 scan-doside		390.34	-23.1945	ARG380,GLN234,ARG299,arg190	2	0
21.	Oldenlandia sp	938 nicotinic acid		123.11	19.3308	LYS197 ARG380	2	0

2D IMAGES

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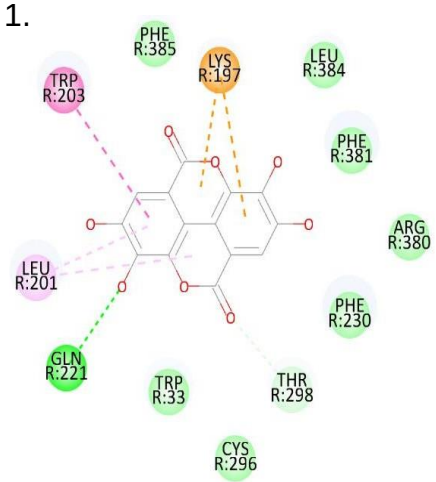

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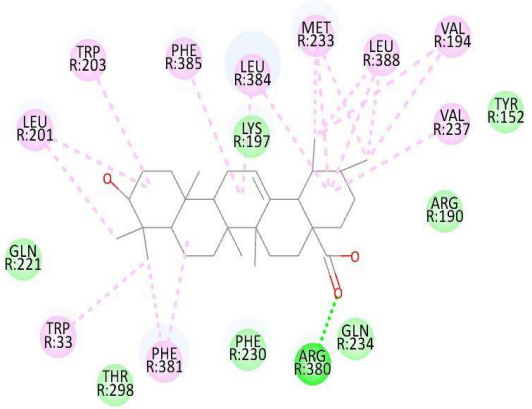

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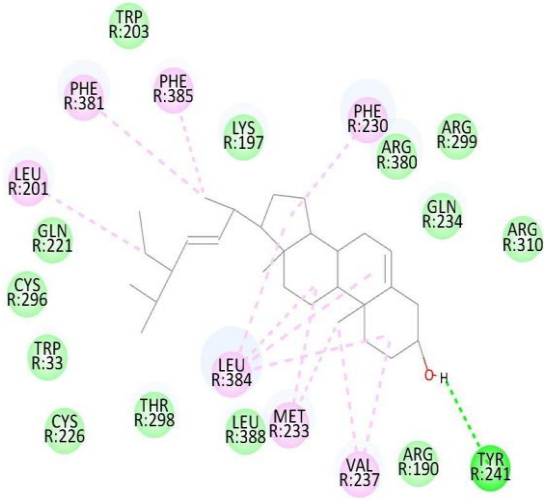

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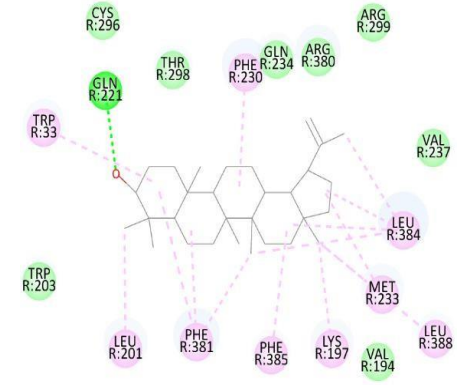

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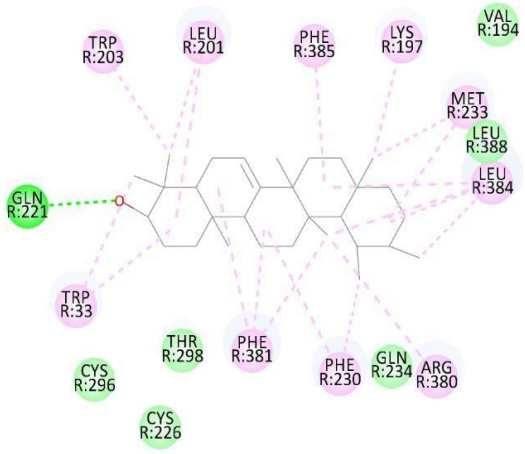

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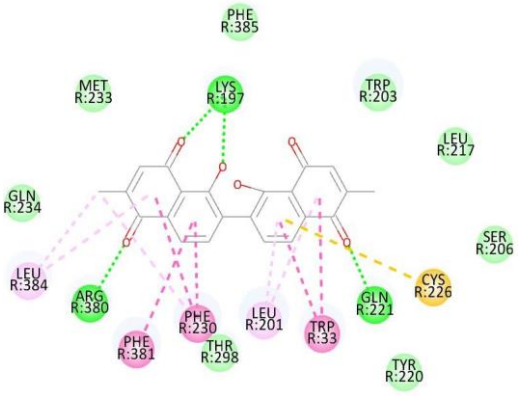

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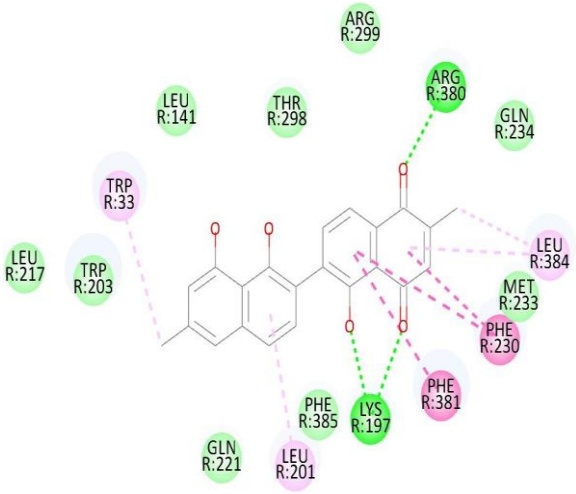
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LEU R:201

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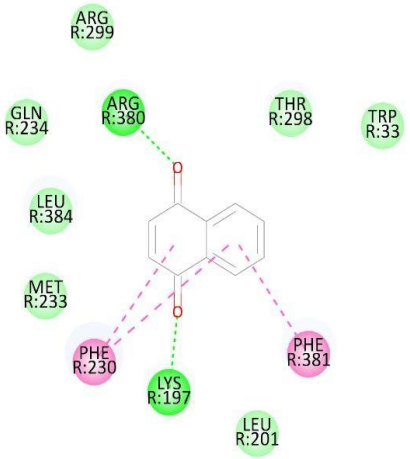
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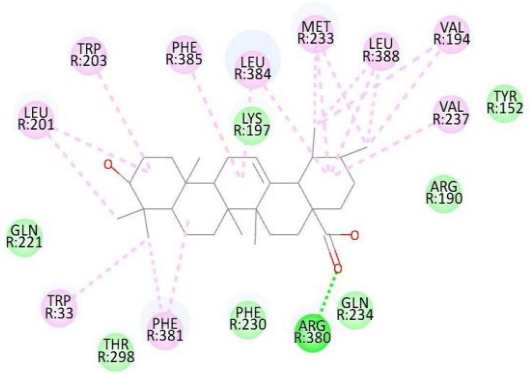
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THR R:298

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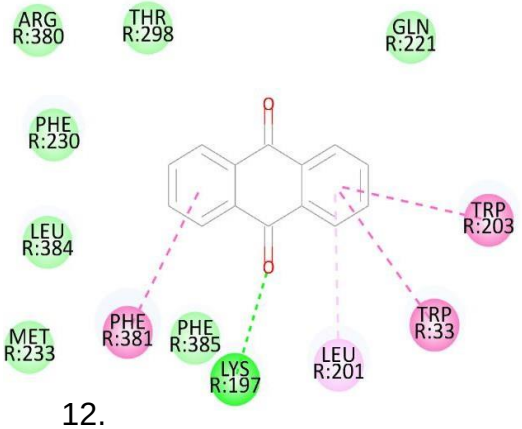
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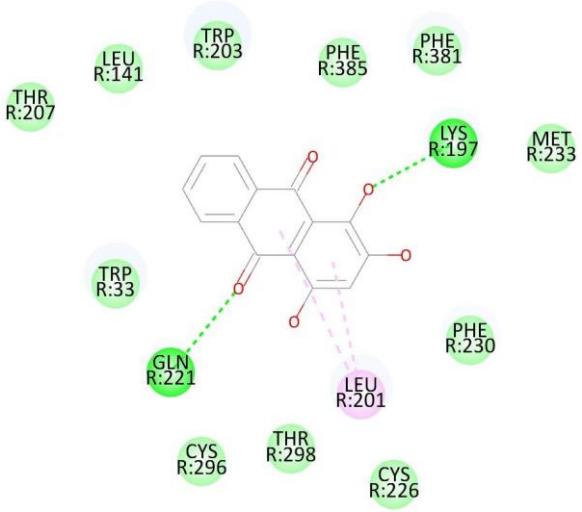
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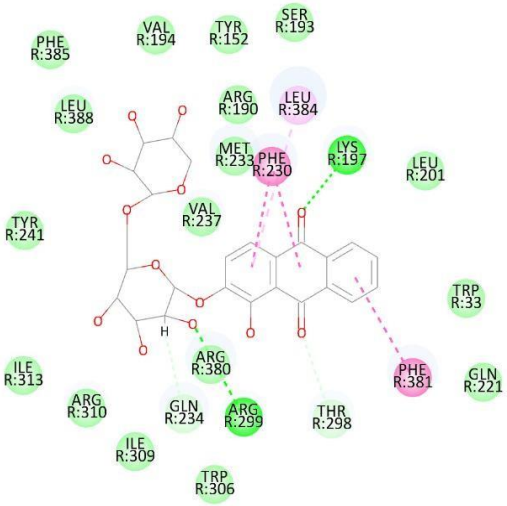
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TYR R:241
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H
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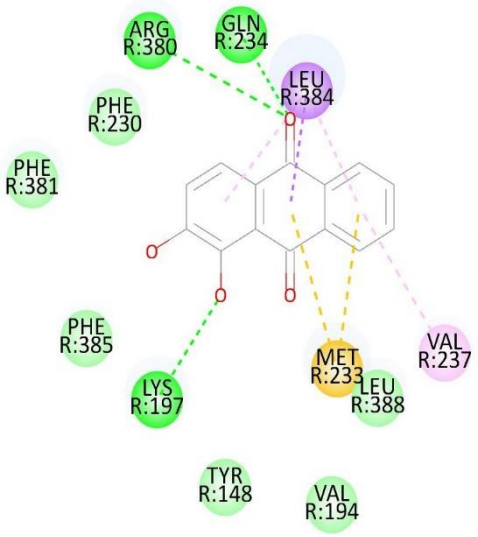

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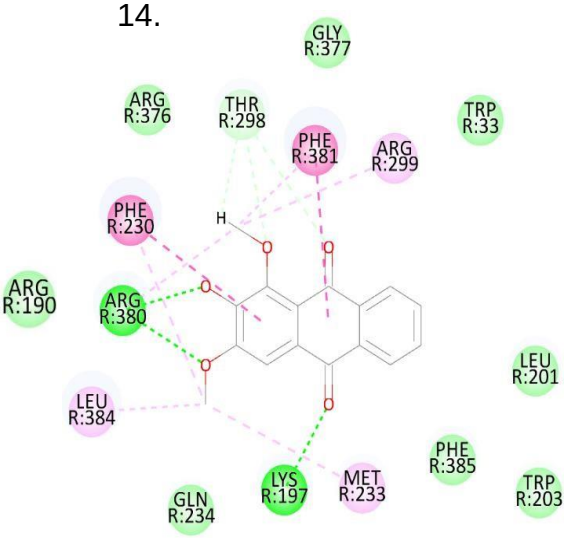

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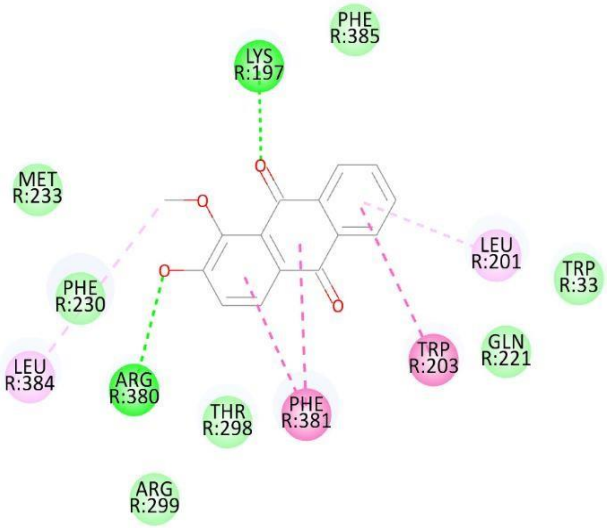

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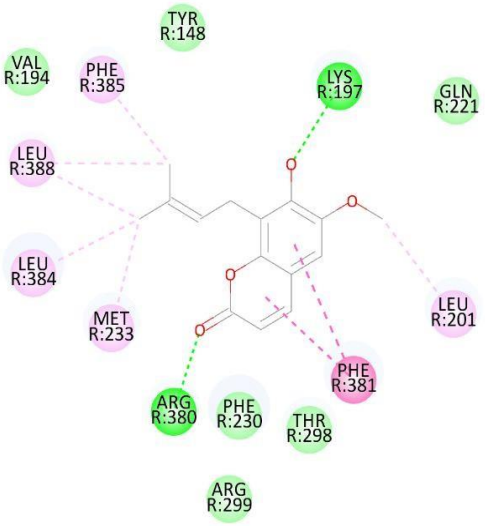

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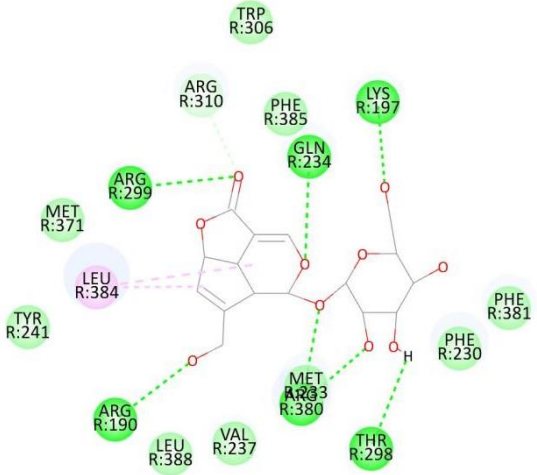

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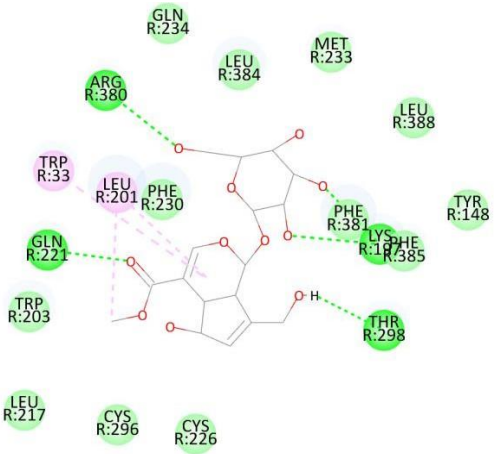

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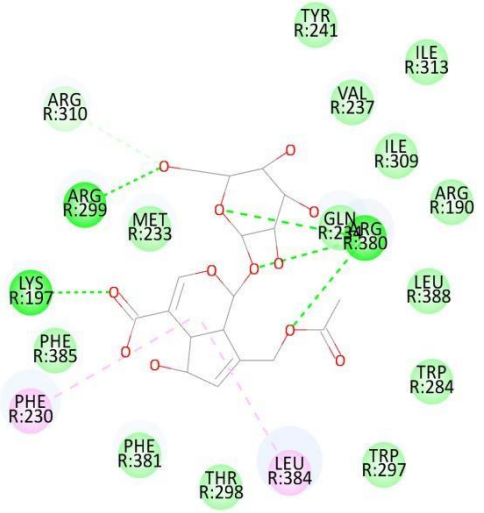

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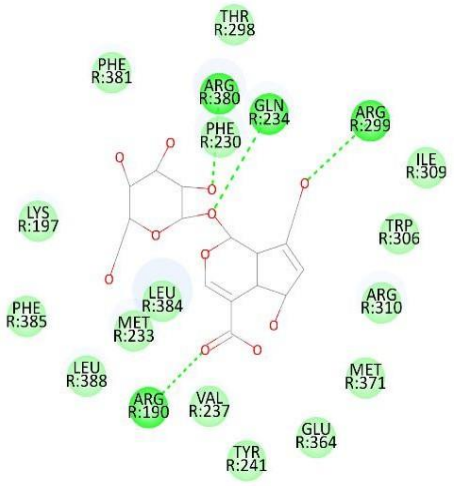

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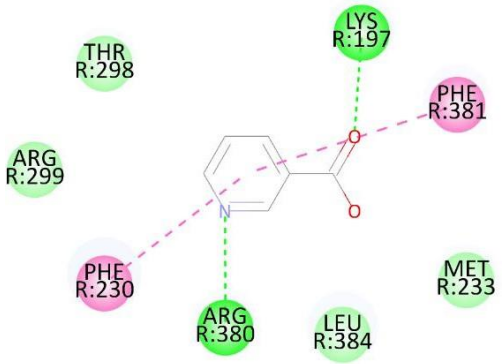

FIG 5.10: IMPHY005537, Ellagic acid, IMPHY011880 ,Ursolic acid , IMPHY014842 Stigmasterol ,IMPHY012473 Lupeol ,IMPHY012314 Bauerenol ,146680 Elliptinone ,86103922 Ebenone ,8530 1,4- Naphthoquinone ,IMPHY011880-Ursolic acid ,IMPHY007192 Anthraquinone ,IMPHY007258 Purpurin ,IMPHY007831 Ruberythric acid ,IMPHY008180 Alizarin ,IMPHY014325 1,3-Dimethoxy-2-hydroxy- 9,10 ,anthraquinone ,IMPHY007218 Alizarin 1-methyl ether ,12302592 cedrelopsin ,44593378 Deacetylasperuloside ,442433 scandoside methyl ester ,11968867 asperulosidic acid ,21602023 scan-doside ,938 nicotinic acid

5.9 Interactions and analysis of ligands

Molecular docking is powerful tools used to investigate protein-ligand interactions. Molecular docking programs predict the binding pose and affinity of a protein- ligand complex, while MD can be used to incorporate flexibility into docking calculations and gain further information on the kinetics and stability of the protein- ligand bond. Molecular docking is a computational technique used to predict the binding mode and strength of a ligand molecule with a receptor or target protein. Ligands are small molecules that can bind to specific binding sites on proteins, and their interactions with the protein determine the effectiveness of the drug in treating a disease.

During molecular docking, the ligand is positioned within the binding site of the protein and its conformation is optimized to achieve the best fit with the protein. The interactions between the ligand and protein are analyzed using various scoring functions to determine the binding affinity of the ligand to the protein.
The interactions between the ligand and protein can be categorized into various types, such as hydrogen bonding, van der Waals interactions, electrostatic interactions, and hydrophobic interactions. These interactions are important for the stability of the ligand-protein complex and its ability to inhibit or activate the protein's function.

In molecular docking, the analysis of ligand-protein interactions involves studying the orientation and conformation of the ligand within the binding site, the amino acid residues in the protein that are involved in the interactions, and the strength and nature of the interactions. This analysis can provide insights into the mechanism of ligand binding, the design of more potent ligands, and the optimization of drug candidates for clinical use.
The compounds were bindind to specific binding pockets like GLN 234, ARG 380, LYS197, CYS 296, TYR241, ARG 310, GLU387, THR 298 with more than 3 hydrogen bonds.

Chapter 6

SUMMARY AND CONCLUSION

6.1 SUMMARY

The study aimed to identify natural compounds that can activate GLP-1, a hormone involved in regulating appetite and glucose metabolism, as a potential strategy for treating obesity. The researchers used in-silico methods, including molecular docking and molecular dynamics simulations, to screen a library of natural compounds and evaluate their binding affinity to the GLP-1 receptor. They identified several promising compounds that showed strong binding affinity to the receptor and could potentially activate GLP-1. The results of this study suggest that natural compounds could serve as a valuable source of new drugs for the treatment of obesity and related metabolic disorders.

6.2 CONCLUSION

Liraglutide, an agonist of glp1, is the first-line therapy for obesity. However, due to the abundance of molecules present in our edible meals, an attempt has been undertaken through computational research to identify natural compounds that can efficiently bind to GLP-1. This study found that several natural substances efficiently attach to the target in the same precise area as the medicine liraglutide and may have a comparable agonist action. This study provides a hint to experimental research that reveal current deliberate by us there by recommending food available in the house as promising home treatments.

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