

IDENTIFICATION OF NOVEL INHIBITORS FOR MULTI RESISTANCE PROTEIN-1 BY APPLYING INSILICO TECHNIQUES

Submitted in partial fulfilment of the requirements for the award of
Bachelor of Technology degree in Biotechnology

By

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SATHYABAMA

INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)

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BONAFIDE CERTIFICATE

This is to certify that this project report is the bonafide work of **GURIKANI BHAVYA (37230022)**, **PRANOV SKANDA VISHNU (37230056)** who carried out the project entitled "**IDENTIFICATION OF NOVEL INHIBITORS FOR MULTI RESISTANCE PROTEIN-1 BY APPLYING INSILICO TECHNIQUES**". Under my supervision from November 2020 to March 2021.

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Certification of Project Work

This is to certify that GURIKANI BHAVYA. (Reg: 37230022), B.tech Biotechnology, Sathyabama Institute of Science and Technology, Chennai, has been with us for working on a project work under the title " Identification of novel inhibitors for Multi Resistance Protein-1 by applying insilico techniques." from December 7th 2020 to March 8th 2021. The work embodied in this dissertation is strictly confidential and is the sole property of the institute and should not be published / used in part of full or patented without the prior permission of the supervisor.

Thanks and regards,

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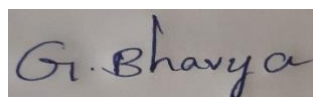
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DECLARATION

We, GURIKANI BHAVYA (37230022), PRANOV SKANDA VISHNU (37230056), hereby declare that project Report entitled “IDENTIFICATION OF NOVEL INHIBITORS FOR MULTI RESISTANCE PROTEIN - 1 BY APPLYING INSILICOTECHNIQUES”. Done by us under the guidance of DR. SABITHA.Y (External guide), Managing director at Ciencia Life Sciences, Hyderabad and DR. BAVANI LATHA.M (INTERNAL GUIDE) Associate professor at department of Biotechnology at SATHYABAMA INSTITUTE OF SCIENCE AND TECHNOLOGY, CHENNAI is submitted in partial fulfilment of the requirements for the award of Bachelor of Technology degree in Biotechnology.

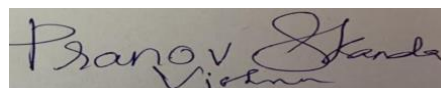
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ABSTRACT

Human multidrug resistance protein 1 (MRP1) is a membrane protein that has a place with the ATP-binding cassette (ABC) superfamily of transport proteins. MRP1 adds to chemotherapy failure by trading a wide scope of hostile to disease drugs when over communicated in the plasma membrane of cells. Cell efflux of xenobiotics is often mediated by means of individuals of the ABC (ATP binding cassette) superfamily of transmembrane proteins which make use of the strength of ATP binding and hydrolysis to perform their capabilities. In the present study, we are performing pharmacophore feature-based virtual screening for identifying potent target specific MRP1 inhibitors by applying Insilco strategies. In Insilco studies virtual screening technique is useful for fast and cost efficient lead discovery and it serves as an efficient de novo drug design. Identification of ligands with pharmacological activity against a biological target (protein) is the initial step in drug discovery

Understanding of MRP1–NBD1 pharmacophore (interactions between receptors and their ligands) is requiring developing novel therapeutic compounds to get better clinical outcomes. Hence in this study, we used computational techniques virtual screening, and molecular docking to target druggable sites of nucleotide binding domains (NBD) of ABC transporters. It was possible to explore important information on the interactions between receptor and their ligand to know favourable combinations of drug-like compounds and ADME/Tox properties from different databases as novel and potential candidate inhibitors.

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CHAPTER 1

INTRODUCTION

Multidrug resistance protein-1 is a human ATP-binding cassette (ABC) carrier in the plasma membrane. Multidrug resistance protein-1 encoded by ABCC1 was initially found as a reason for multidrug obstruction in tumor cells and furthermore it serves a more extensive part than essentially interceding the ATP-subordinate efflux of medications from cells. ABCC1 is an exceptionally saved quality with polymorphisms happening at low frequencies of under five percent. Polymorphisms in this gene are for the most part found as a single nucleotide polymorphism. The multidrug resistance-associated protein 1 (MRP1) quality has been discovered to be reliably overexpressed in most of patients with non-small cell cellular breakdown in the lungs. MRP1 is known for its capacity to effectively diminish intracellular medication fixation, restricting the adequacy of malignancy chemotherapy.

The ATP-binding cassette (ABC) carriers are individuals from a protein superfamily that are known to move different substrates across membranes, including metabolic items, lipids and sterols, and xenobiotic drugs. Multidrug resistance proteins (MRPs) have a place with the subfamily C in the ABC carrier superfamily. MRPs have been involved in intervening multidrug obstruction by effectively expelling chemotherapeutic substrates. Besides, some MRPs are known to be fundamental in physiological excretory or administrative pathways. The significance of MRPs in disease treatment is likewise suggested by their clinical experiences. Regulating the capacity of MRPs to re-sharpen chemotherapeutic specialists in malignant growth treatment shows incredible guarantee in disease treatment; consequently, numerous MRP inhibitors have been grown as of late.

MRP1 was first distinguished and cloned in the anthracycline-chosen human small cell lung carcinoma cell line. MRP1 is an individual from the subfamily C of ATP-binding cassette (ABC) carriers, and is henceforth otherwise called ABCC1. Disseminated all through an assortment of typical human tissues, MRP1 is available in organs like the lungs, spleen, testicles, kidneys, thyroid, bladder and adrenal organs. In ordinary cells, MRP1 intervenes the efflux of endogenous metabolites, including glutathione,

cysteinyl leukotriene C4, nitric oxides, lipid-determined flagging atoms and cancer prevention agents. Overexpression of MRP1 is a common phenomenon in different malignant growth tissues, reducing cytotoxicity and the adequacy of antineoplastic specialists by boosting the efflux of the medications, including cisplatin, vinorelbine and gemcitabine, bringing about more limited sans tumor endurance and by and large endurance (OS) times in patients.

Multidrug resistance is a significant snag to malignant growth treatment and prompts helpless anticipation for the patient. Multidrug resistance associated protein 1 (MRP1) transports a wide scope of remedial specialists just as different physiological substrates and may play a part in the improvement of medication obstruction in a few tumours counting those of the lung, breast and prostate, just as youth neuroblastoma. Most of patients with neuroblastoma present with broadly scattered infection at analysis and notwithstanding escalated treatment, the anticipation for such patients is horrid. There is expanding proof that MRP1 is a MYCN target quality included in the improvement of multidrug opposition in neuroblastoma. Given the significance of MRP1 overexpression in neuroblastoma, MRP1 restraint might be a clinically applicable way to deal with improving patient result in this illness. It ships a wide scope of medications, just as different physiological substrates, and assumes a critical part in the improvement of medication obstruction in a few tumours, particularly lung, bosom, and prostate, intense myeloid leukaemia and ovarian malignant growth, just as in youth neuroblastoma. Most of patients with neuroblastoma present with broadly spread sickness at conclusion and, disregarding comprehensive therapy, the possibility for such patients is upset.

A definitive reason for treatment disappointment for some types of harmful and irresistible infections is the advancement of protection from an expansive scope of cytotoxic medications. Hence, in spite of critical advances malignancy treatment, multidrug resistance(MDR) stays a significant clinical issue and prompts restricted helpful choices and helpless patient result in various malignant growths, including those of prostate, breast, lung and ovary, as well as leukaemia and youth neuroblastoma. Subsequently, acquiring a superior comprehension of the instruments that lead to drug obstruction is of basic significance to improve.

MRP1 is a basolateral carrier whose action brings about the development of mixtures into tissues that lie underneath the cellular membrane. Transport of glutathione and glucuronate forms by MRP1 is of interest since they address stage II digestion and cell detoxification.

Clinically, MRP1 levels are raised in various disease types, for example, non-small cell cellular breakdown in the lungs (NSCLC), breast malignant growth, and prostate cancer, and they are likewise identified with quickened backslide in breast cancer. MRP1 articulation has been accounted for in a few strong and haematological diseases. Negative relationship between's MRP1 articulation and reaction to treatment has additionally been found. Such investigations have been looked into in detail elsewhere. In any case, there is no unmistakable agreement attracted concerning the job of MRP1 in obtained obstruction or in anticipation.

Multidrug resistance related protein 1 (MRP1/ABCC1) and multidrug resistance protein 1 (MDR1/P-glycoprotein/ABCB1) are both layer bound medication carriers. Rather than MDR1, MRP1 likewise ships glutathione (GSH) and medications formed to GSH. Because of its uncommon vehicle properties, MRP1/ABCC1 adds to a few physiological capacities and pathophysiological occurrences. By and large, MRPs can move sedates that vary basically and unthinkingly, including regular anticancer medications, nucleoside analogues, antimetabolites, and tyrosine kinase inhibitors. A significant number of these MRPs transport physiologically significant anions, for example, leukotriene C₄, bilirubin glucuronide, and cyclic nucleotides. This review centres fundamentally around the physiological capacities, cell opposition attributes, and plausible in vivo part of MRP1 to MRP9.

Mediates export of natural anions and medications from the cytoplasm mediates ATP-subordinate transport of glutathione and glutathione forms, leukotriene C₄, estradiol-17-beta-o-glucuronide, methotrexate, antiviral medications and other xenobiotic. Presents protection from anticancer medications by diminishing collection of medication in cells, and by interceding ATP-and GSH-subordinate medication send out. Hydrolyzes ATP with low productivity. Catalyses the export of sphingosine 1-phosphate from pole cells freely of their degranulation. Takes an interest in

provocative reaction by permitting fare of leukotriene C4 from leukotriene C4-synthesizing cells

MRP1 has a chemo protective job in numerous tissues. Identified with the defensive properties of MRP1 are the expanding number of studies that report a relationship between the presence of certain ABCC1 single nucleotide polymorphisms and the event of unfavourable medication responses. A significant model is the cardiotoxicity frequently experienced with anthracycline use in grown-up and paediatric malignancy patient.

As well as adding to sedate affectability and obstruction, MRP1 has been embroiled in the etiology of a wide cluster of human pathologies. Along these lines, MRP1 may have an impact in fiery and other immunological infections, age-related macular degeneration, cardiovascular illness, and certain neurological problems just as tumor movement. This possibly more extensive part of MRP1 in human wellbeing and infection has happened related to a developing enthusiasm for its capacity to intervene the efflux of bioactive OAs and directing oxidative pressure. Subsequently, solutes effluxed by MRP1 likewise incorporate hydrophilic formed xenobiotic and normally happening OA metabolites. Outstanding instances of the last incorporate the cysteinyl LTC4 and the formed estrogen, E217 β G, just as diminished and oxidized glutathione (GSH and GSSG).

Transport by MRP1 (and other ABC carriers) is controlled by the limiting and hydrolysis of ATP, which encourage the fundamental protein compliance changes that empower solute movement to happen.

Chemotherapy is one of the significant therapy modalities accessible for malignancy patients. Sadly, throughout therapy, malignant growth cells create protection from practically and fundamentally unique anticancer medications by either obtained (because of host factors) or natural (because of hereditary or epigenetic) mechanisms. This phenomena of protection from various classes of anticancer medications by malignant growth cells is named multidrug obstruction (MDR). This inescapable and guileful clinical issue in the long run prompts malignancy backslide and demise among patients. The instruments of MDR have been seriously examined, albeit not all systems creating MDR have been clarified. The itemized systems that malignancy cells use or create to sidestep chemotherapy are unpredictable and have been

depicted in detail in a few ongoing reviews. Quite possibly the main instruments fundamental MDR is overexpression of adenosine triphosphate (ATP)- binding cassette. (ABC) carriers, which efflux a wide range of anticancer medications against the focus slope utilizing ATP-driven energy.

Transport by MRP1 (and other ABC carriers) is powered by the limiting and hydrolysis of ATP, which encourage the important protein conformity changes that empower solute translocation to occur. MRP1 generally engaged on its job in malignancy multidrug resistance, the revelation that it could transport both formed and unconjugated OAs greatly broadened its pharmacological and physiological relevance. The obstruction of MRP-transfected cells is related with an energy-subordinate lessening in drug collection and an increment in drug efflux. Hence MRP presents a type of multidrug opposition that imparts a few qualities to that brought about by overexpression of P-glycoprotein (P-gp). The amino corrosive grouping of MRP1 predicts that it contains a centre construction that is normal to numerous ABC proteins, to be specific two hydrophobic layer crossing areas (MSDs) each followed by a nucleotide restricting space.

Transport examines utilizing both MRP1-advanced plasma layer vesicles and purged reconstituted MRP1 have set up that MRP1 can effectively move a basically assorted cluster of formed natural anions, including the cysteinyl leukotriene LTC₄ and oxidized glutathione. Conversely, examines utilizing MRP1-advanced plasma film vesicles under comparative conditions have neglected to show that MRP1 straightforwardly moves unmodified chemotherapeutic specialists. Nonetheless, ongoing examinations recommend that certain unconjugated medications like vincristine and daunorubicin are effectively co-moved by MRP1 with decreased glutathione. These vehicle properties of MRP1 are very not the same as those depicted for P-gp, and the underlying highlights answerable for these contrasts between the two medication obstruction proteins are not yet known.

The main source of chemotherapy disappointment is the multi drug resistance (MDR) showed by disease cells because of which chemotherapeutic medications are removed out of the cells. The overexpressed efflux protein siphons having a place with ATP Binding Cassette (ABC) family¹ are the critical explanation behind MDR in disease cells. The ABC superfamily can be separated into two significant

classifications in particular, ABC carriers which require ATP for substrate movement and non-carrier proteins that are answerable for DNA support and quality regulation². In bacterial framework, ABC carriers go about as merchants just as exporters. They move particles like particles, amino acids, sugar and so forth all-around of the bacterial cells. In spite of this, lone ABC family exporters are surviving in a eukaryotic framework. These medication siphons are a significant piece of a cell's protection instrument and this was first acknowledged by Danø who in 1973 showed that Ehrlich ascites cells bring down the convergence of intracellular daunorubicin by removing it out³. After the disclosure of P-glycoprotein by Ling and Juliano in 1976 as a 170 kDa transmembrane glycoprotein, a second kind of medication transport protein for example multidrug obstruction related protein (MRP) was subsequently found by Chole in 1992⁴. It was cloned from H69R cellular breakdown in the lungs cell line. Both the P-gp and MRP have a place with the group of ABC carriers and both are liable for giving multidrug protection from cells. Regardless of an exceptionally low underlying personality among MRP1 and P-gp, there was an impressive comparability between the aggregate of H69AR cells and cells communicating P-gp⁵.

The advancement of multidrug resistance (MDR) is one of the significant difficulties to the accomplishment of chemotherapy therapy of malignant growth. This phenomenon is regularly connected with the overexpression of the ATP-binding cassette (ABC) carriers P-gp (P-glycoprotein, ABCB1), multidrug obstruction related protein 1, ABCC1 and breast malignancy resistance protein, ABCG2 (BCRP). These carriers are constitutively communicated in numerous tissues assuming applicable defensive parts by the guideline of the porousness of organic films, however they are likewise overexpressed in threatening tissues. P-gp is the principal efflux carrier found to be engaged with malignancy drug obstruction, and throughout the long term, inhibitors of this siphon have been unveiled to direct them in mix with chemotherapeutic specialists. Three ages of inhibitors of P-gp have been inspected in preclinical and clinical investigations; notwithstanding, these preliminaries have generally neglected to exhibit that Coad ministration of siphon inhibitors inspires an improvement in helpful adequacy of antitumor specialists, albeit probably the most recent mixtures show better outcomes. Accordingly, new and inventive procedures, for example, the fall back to common items and the find of double movement ligands arose as new viewpoints. BCRP is the most as of late ABC protein recognized to be associated with

multidrug obstruction. It is overexpressed in a few haematological and strong tumours along with P-gp, undermining the restorative viability of various chemotherapeutic medications.

1.1 MOLECULAR DOCKING

Molecular docking is the cycle that includes setting particles in suitable setups to associate with a receptor. Molecular docking is a characteristic cycle which happens inside seconds in a cell.

In sub-atomic demonstrating the expression "sub-atomic docking" alludes to the investigation of how at least two atomic designs fit together

1.2 MOLECULAR FLEXIBILITY ON PROTEIN LIGAND DOCKING

The common transformation of a ligand with its receptor is pivotal to understanding ligand restricting and protein work

One of the significant difficulties in Molecular docking is the means by which to represent this variation in docking calculations.

The docking issue can be classified according to the way adaptability is demonstrated. In rising request of complexity:

- **Rigid body docking:** disregards the adaptability of the particles also, deals with them like unbending items.
- **Rigid receptor – Flexible ligand docking:** just the ligand is treated as adaptable, receptor is inflexible.
- **Flexible receptor – Flexible ligand docking:** both protein and ligand are treated as adaptable.

1.3 LIGAND BASED DRUG DESIGN:

- Ligand-put together medication configuration depends with respect to information on different particles that tight spot to the natural objective of interest.
- Used to infer pharmacophore

1.4 DRUG SIMILARITY WITH A BASIC TALLYING STRATEGY "RULE OF FIVE".

Octanol-water partition(logP) ≤ 5

- Octanol-water partition(logP) < 5
- Molecular weight < 500
- No. hydrogen bond acceptors (HBA) < 10
- No. hydrogen bond givers (HBD) < 5
- If at least two of these principles are disregarded, the compound may have issues with oral bioavailability.

1.5 IN SILICO DRUG DESIGNING:

- In silico is an articulation used to signify "performed on PC or through PC recreation."
- In silico drug planning is characterized as the ID of the medication target atom by utilizing bioinformatics instrument.

1.6 TARGET SELECTION:

- Bio substance pathways could get strange and bring about sickness.
- Select an objective at which to disturb the biochemical cycle.

1.7 CATEGORIES OF TARGETS:

Focus for mechanistic medication configuration typically fall into three classifications:

- Enzymes
- Receptors
- Nucleic acids

1.8 LIGAND SELECTION:

- Also called as lead distinguishing proof.

- High throughput screening of normal item and engineered compound libraries is completed to screen lead compound

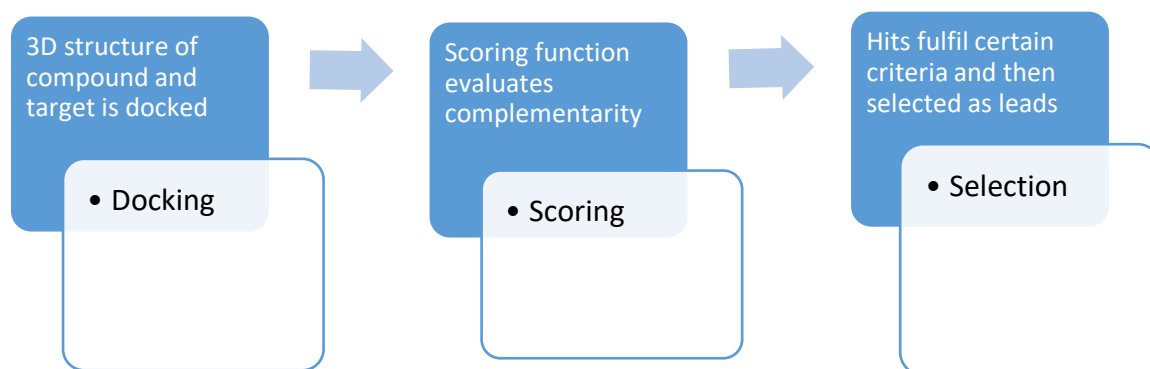


Fig 1.1 ligand selection

1.9 MECHANICS OF DOCKING:

To perform a docking screen, the main essential is a development of the protein of interest. Normally, the design has been settled using a biophysical technique like x-shaft crystallography, NMR spectroscopy or cryo electron microscopy (cryo-EM), anyway can in like manner get from homology showing improvement. This protein structure and an informational index of potential ligands fill in as commitments to a docking program. The accomplishment of a docking program depends upon two portions: the search algorithm and the scoring function.

1.10 APPLICATIONS:

A binding association between a small molecule ligand and a catalyst protein may bring about activation or inhibition of the compound. On the off chance that the protein is a receptor, ligand binding may bring about agonism or antagonism. Docking is most usually utilized in the field of medication configuration most medications are little natural particles, and docking might be applied to:

- Hit identification – docking joined with a scoring capacity can be utilized to immediately separate enormous information bases of potential medications silico to distinguish atoms that are probably going to tie to protein focus of revenue (see virtual screening).

- Lead enhancement – docking can be utilized to anticipate in where and in which relative direction a ligand ties to a protein (likewise alluded to as the limiting mode or posture). This data may thusly be utilized to plan more powerful and specific analogs.
- Bioremediation – Protein ligand docking can likewise be utilized to predict pollutants that can be corrupted by compounds

Molecular docking gives a stage where utilizing the precious stone construction of a protein as a layout novel ligands can be resolved. A library of mixtures and a protein layout is needed to perform docking studies. Docking has been applied fundamentally to compounds and has been demonstrated valuable in tracking down the novel ligands with great substrate affinities. To find a promising ligand for a macromolecule, it is imperative to comprehend the collaborations and standards by which the ligand will perceive and associate with it. This structures the premise of construction based medication planning (SBDD). For SBDD, technique for sub-atomic docking is utilized in light of the fact that it can foresee the compliance and restricting of a ligand into the dynamic site of the macromolecule with exactness. Utilizing atomic docking, the limiting method of ligand and macromolecule, sorts of associations (electrostatic, hydrophobic, pi cation) and the limiting affinities can be analysed. In spite of the fact that docking calculations have created and improved over years, a few issues like inclusion of water particles in the protein structure, conformational changes that happen following ligand restricting actually should be settled.

Sirisha et al. utilized sub-atomic docking to discover the inhibitors of MRP1 among dihydropyridine derivatives. Likewise, expected substrates for other ABCC individuals have been resolved utilizing atomic elements re-enactments. Besides, the inhibitory impact of curcumin on MRP1 has been concentrated by in silico contemplates.

Focusing on ATP-restricting site for drug revelation is certainly not another idea. The methodology has been investigated against numerous proteins including tyrosine kinases. In 1999, Novartis Pharmaceuticals built up a pharmacophore model of the ATP-restricting site present in Epidermal Growth Factor Receptor (EGFR). From that point forward this model has been utilized to discover helpful atoms that can focus on the ATP restricting site. Furthermore, with the assistance of docking and atomic

elements concentrates on intensifies like indirubins, it was anticipated that these mixtures tie at the dynamic site where the adenine ring of the ATP binds. In addition, to focus on the ATP restricting site of topoisomerase II a purine inhibitor framework was planned prompting ID of novel compounds²⁰. In 2012, another examination bunch focused on the ATP-restricting site of type II topoisomerase by integrating 5-aryl-1, 3,4-thiadiazole coupled phthalimide derivatives²¹. These mixtures were docked against the ATP-restricting site of the protein. The mixtures with best in silico results were additionally assessed in vitro.

Multidrug resistance (MDR) is a sort of obtained drug obstruction of malignant growth cells, yet additionally microorganisms, to an assortment of chemotherapeutic medications that are basically and robotically inconsequential even to medications to which they have not been uncovered already. When MDR is procured, the counter disease impacts of chemotherapeutic medications decline. Malignant growth cells that are initially touchy to a solitary enemy of disease drug later become impervious to various enemy of malignancy drugs.

Multidrug Resistance Protein (MRP) presents protection from common item sedates when overexpressed in cultured cells. It has likewise been identified in human tumours and sometimes, articulation has been related with a helpless reaction to chemotherapy. MRP is available in typical tissues where it most likely capacities as a functioning carrier of amphiphilic anions. It is additionally attempted to move the medications to which it presents opposition, yet how and in what structure has not been settled.

The MDR aggregate is frequently connected to the overexpression of transmembrane efflux carriers. Indeed, the most broadly involved and considered system of MDR is that subsequent from modified cell film transport. This sort of MDR is because of a lower intracellular medication fixation, related with sped up efflux of the chemotherapeutic medication as an outcome of the overexpression of various essential layer carriers that go about as expulsion siphons. A few groups of efflux siphons, that can utilize an assortment of fuel sources, are available in warm blooded animals and miniature organisms. Among these, the most significant and best portrayed family in people is the ATP-restricting tape (ABC) superfamily of efflux carriers, that utilization ATP as energy source. Overexpression of ABC carriers, often

recognized in human strong and hematologic malignant growths, is a marker for drug opposition and diminished patient survival in addition, significant degrees of ABC carriers can be discovered likewise in disease stem cells.

The human ABC carriers comprise of 49 individuals that are grouped into seven subfamilies assigned ABC-A to ABC-G as per the likeness of their amino corrosive sequences. These proteins are overexpressed in malignant growth cells, yet they are likewise present in a few significant tissues where they assume a physiological part. Indeed, they have been found in the epithelium cells at blood-mind boundary (BBB), the intestinal epithelium, the biliary canalicular film of hepatocytes and the proximal tubules of kidney, where they catalyse the vehicle of an enormous assortment of primarily different mixtures across cell layers by controlling the discharge of lipophilic atoms and the expulsion of xenobiotic that entered the organism. Some ABC carriers are additionally liable for the homeostasis of endogenous specialists, and individuals conveying abandoned ABC qualities might be more defenceless to explicit illnesses like the Tangier's sickness, Stargardt's infection, cystic fibrosis and adrenoleukodystrophy.

The most significant and most popular carriers having a place with the ATP-Binding Cassette superfamily in people are P-glycoprotein (P-gp/MDR1/ABCB1), multidrug Resistance protein 1 (MRP1/ABCC1) and bosom disease safe protein (BCRP/ABCG2/MXR).

CHAPTER 2

REVIEW OF LITERATURE

Vivek K. Vyas, Manjunath Ghate, Ashutosh Goel (2013) described a level-headed system for the ID of novel PKB inhibitors utilizing joined pharmacophore based virtual screening alongside docking and in silico pharmacokinetic and harmfulness contemplates. The best pharmacophore model was set up utilizing DISCOtech and GASP module and was approved through ROC and GH scoring strategies. The best pharmacophore model was additionally utilized as a 3D hunt inquiry to screen NCI information base. Ten (10) particles were picked dependent on Qfit estimation of more than 95 for sub-atomic docking concentrate alongside three known PKB inhibitors. Atomic docking study was performed to improve the dependability and exactness of virtual screening. At that point, two ideal hits dependent on the best docking score were chosen for in silico pharmacokinetic and poison levels. Aftereffects of in silico pharmacokinetic and poisonousness study showed great pharmacokinetic properties. Thus, it was presumed that mix of the above displaying techniques can distinguish new hits from synthetic information bases which might be a decent lead to create novel PKB inhibitors for the therapy of disease.

Taylor and Francis .2014. Investigation of design based docking and ligand connections of little atoms with MMR protein prompted the ID of new pump inhibitors that can be potential other option, powerful anti- tuberculosis drugs. The M. tuberculosis microorganism utilizes dynamic efflux siphons as a typical medication opposition system Virtual screening is performed utilizing ChemBank information base to recognize new cationic particles which can restrain the cation efflux in the MTB. The ligand particles with fine Glide score and restricting proclivity are recognized as new lead atoms which restrain the action of the MMR protein in MTB. The current investigation of design based docking and ligand cooperations of little particles with MMR protein prompted the recognizable proof of new siphon inhibitors that can be potential other option, powerful anti-tuberculosis drugs.

Divya Dhasmana, Ashutosh Singh, Rohit Shukla, Timir Tripathi & Neha Garg (2018) ..., Described two mixtures, potassium citrate and technetium Tc-99m medronate that showed the arranged of exchanging MDR in disease cells. These blends were screened through intensive nuclear docking methods and presented to diversions study Eight stores (Gly681, Cys682, Lys684, Cys685, Ser686, Gln713, His827) were short-recorded and thereafter the relationship of ligands with the target developments was reviewed using mooring. In view of the docking score and the amount of correspondences of the ligand with the goal developments, the blends for MD entertainments were shortlisted. Reasoned that NBD1-potassium citrate is all the more consistent when stood out from NBD1-technetium Tc-99m medronate and as such can be the lead compound against NBD1 of MRP1. Furthermore, as the NBD space is apportioned among the people from ABC transporter family the ligand could show its assurance against other prescription siphons as well. The preliminary considers subject to our disclosures would provoke a prevalent understanding of working with potassium citrate to deal with MDR in disease cells.

Hee choi, young; yu, Ai-Ming. (2014)., their work based on ABC transporters in multi drug resistance and pharmacokinetics and strategies for drug development. In this survey, they gave an outline of the job of ABC efflux carriers in MDR and pharmacokinetics. Preclinical examines for the evaluation of medication transport and advancement of MDR modulators are additionally talked about.

Dexin zhang and daiming fan (2015)., their work based on multi drug resistance in gastric cancer; recent research advances and ongoing therapeutic challenges. The shortfall of P-gp and MRP1 articulation in some gastric disease cases additionally shows that there may be different instruments answerable for human gastric malignant growth MDR. These particles have a place with various utilitarian families and might cooperate to give MDR aggregates. The new discoveries may give new insights to the instruments of MDR and empower the determination of new possibility for focusing on MDR in human gastric malignant growth.

Xiu-bao Chang (2007) work based on A molecular understanding of ATP-dependent solute transport by multidrug resistance-associated protein MRP1. Overexpression of

MRP1 presents a comparative medication opposition profile as that of P-gp, consequently, they may assume a comparable useful part. however, the finding that MRP1 transports amphiphilic anionic forms across organic film plainly shows that it is unique in relation to the customary medication carrier P-gp. An enormous measure of work, including MRP1 quality association, area, articulation, tissue circulation and physiological capacity, geography, substrate restricting site and ATP-subordinate substrate transport and so forth, has been done since the cloning of MRP1 cDNA. there is motivation to be hopeful in accomplishing the objective of battling the MDR in malignant growth cells brought about by overexpression of MRP1.

ERIC F. PETTERSEN, THOMAS D. GODDARD, CONRAD C. HUANG, GREGORY S. COUCH, DANIEL M. GREENBLATT, ELAINE C. MENG, THOMAS E. FERRIN (2004)., The design, execution, and abilities of an extensible perception framework, UCSF Chimera, are examined. chimera is openly accessible to scholastic and charitable specialists from <http://www.cgl.ucsf.edu/fabrication/>, and can be authorized by business foundations for an expense. Expansions to Chimera created by outside scientists can be rearranged unreservedly. Since Chimera's first open delivery in March 2000, downloads of Chimera have consistently expanded, adding up to roughly 1000 every month at this composition and adding up to more than 12,000. (As expressed before, conveyability has been one of the essential plan objectives of Chimera. Our execution, in view of numerous generally accessible norms, for example, OpenGL,¹⁵ has demonstrated to be very versatile, and there are Chimera conveyances for Microsoft Windows XP/NT/2000/98, Linux, Apple Mac OS X, SGI IRIX, and HP Tru64 Unix. objective of empowering others to broaden Chimera has appreciated expanding accomplishment as the utilization of Chimera has gotten more boundless. As of now, augmentations composed or potentially disseminated by others include: SSD, which broadens Chimera for use with the Structure Superposition Database²² (a Web-open asset); ViewFeature,⁴² which permits Chimera to show results from FEATURE,⁴³ a program for anticipating metal-restricting or dynamic locales in biomolecules; and EMANimator (S. Ludtke, Baylor College of Medicine, unpublished), which makes it simple to make movement successions in Chimera and save them as MPEG documents. Likewise, Chimera is upheld as a showcase

application for arrangement and design data by the Web-open information bases ModBase44 and the Structure Function Linkage Database.

Ogan demir abaan, pelin kaya mutlu, Yusuf baran, can atalay&ufuk gunduz (2009)., their work based on multidrug resistance mediated by MRP1 gene over expression in breast cancer patients. The point of this examination was to research the statement of MRP1 in tumor tissues from bosom malignancy patients. In this investigation, a semi-quantitative RT-PCR approach was used. Our outcomes propose that MRP1 overexpression can intervene MDR in patients. Pre-assessment of the degree of such MDR middle people before chemotherapy can build the adequacy of the treatment.

Amresh et al. discovered five best potential CA IX by using molecular docking and several others in silico methods. Using Auto dock 4.2 docked crystal structure of CA IX (PDB:3IAI) and all the selected inhibitors. from the analysis of docking scores top five scoring compounds were ZINC08828920, ZINC03363328, ZINC03622539, ZINC12941947, and ZINC16650541. Results obtained from this study have confirmed the value of molecular docking in identifying new inhibitors for CA IX that provides a promising hope as an anticancer therapy.

Seetha Lakshmi Srinivasan, sathyabarathi ravichandran, umashankar vetrivel and Subramanian Krishna Kumar. (2012)., their work based on *in vitro* and *in silico* studies on inhibitory effects of curcumin on multi drug resistance associated protein (MRP1) in retinoblastoma cells... In the current examination, docking collaboration investigation of MRP1-curcumin complex showed organization of reinforced and non-fortified communications with Curcumin to the amino corrosive buildups living in the archived substrate restricting locale. Docking concentrates likewise derived that oxygen molecules of phenolic and methoxy useful gatherings crossing terminal phenyl rings of curcumin to assume a vital part for inhibitory activity. in vitro results showed the capability of curcumin in adjusting the capacity and articulation of multi-drug opposition proteins MRP1. Moreover, in silico sub-atomic docking investigations of

these MDR proteins with curcumin gives a knowledge on the dynamic restricting method of curcumin. Hence, curcumin can be utilized as a promising MDR chemo sensitizer in regulating the multidrug obstruction property in different tumors.

Sabine L.A. Plasschaert, Eveline S.J.M. de Bont, Marike Boezen, Dorina M. vander Kolk, Simon M.J.G. Daenen, Klaas Nico Faber, Willem A. Kamps, Elisabeth G.E. de Vries and Edo Vellenga (2005)., The point of this examination was to explore the articulation levels of MRP1 to MRP6 and study their impact on prognosis. Patients with intense lymphoblastic leukaemia all are treated with an assortment of chemotherapeutic medications, which can be shipped by six multidrug obstruction related proteins (MRP). These MRPs have unequivocally covering utilitarian exercises The mRNA articulation levels of MRP1 to MRP6 were broke down by quantitative continuous PCR in leukemic impacts of 105 again ALL patients (grown-ups, n = 49; youngsters, n = 56) including 70% B-heredity and 30% T-ancestry ALL patients. Grown-ups showed a higher articulation of MRP1 ($P = 0.008$), MRP2 ($P = 0.026$), and MRP3 ($P = 0.039$) than kids. Curiously, this distinction vanished when patients were classified dependent on clinical result. Backslid patients showed a higher articulation of all MRP qualities, aside from MRP4. For the all-out gathering, everything being equal, the outflows of MRP1, MRP2, MRP3, MRP5, and MRP6 anticipated backslide. Also, high articulation of all MRP qualities, aside from MRP4, was related with a decreased backslide free endurance in kids and grown-ups (MRP1, $P = 0.005$; MRP2, $P = 0.008$; MRP3, $P = 0.001$; MRP5, $P = 0.016$; MRP6, $P=0.037$). The current examination shows that a subset of ALL patients with high MRP articulation has a troublesome forecast freely old enough.

Yun-Kai Zhang, Yi-Jun Wang, Pranav Gupta, and Zhe-Sheng Chen (2015) work dependent on Multidrug Resistance Proteins (MRPs) and Cancer Therapy. Nine MRPs have various examples in topological design, subcellular confinement, tissue articulation, substrate specificities, just as their capacities. In disease treatment, MRPs have been shown to present protection from a few extensively utilized anticancer medications... Effective preclinical investigations uncover the promising possibilities of

adjuvant chemotherapeutic in clinical disease treatment practice. crystallographic and system learns at the sub-atomic level are as yet required with the end goal of better arrangement and creating viable MRP modulators.

David Kreutzer, Christoph A. Ritter and Andreas Hilgeroth (2020). their work dependent on Novel Nonsymmetrical 1,4-Dihydropyridines as Inhibitors of Nonsymmetrical MRP-Efflux Pumps for Anticancer Therapy. The traditional 1,4-dihydropyridine arrangements form the atomic framework which is created by the response of three parts, specifically a for the most part fragrant aldehyde, a dicarbonyl work, and an amino compound, ideally smelling salts. A hindrance of their action is a technique to battle MDR. Thusly, there was just a little impact in the increment of the anticancer medication harmfulness. Along these lines, we exhibited the verification of-rule for a hindrance of the efflux siphons to switch MDR brought about by efflux siphon movement. The outcomes urge to follow the system to battle MDR-interceded malignancy by such novel inhibitors.

Liliana Manciu^a, Xiu-Bao Chang^b, John R. Riordan^b, Fr  de  ric Buyse^a, Jean Marie Ruyschaert, (2001). work dependent on Nucleotide-actuated conformational changes in the human multidrug opposition protein MRP1 are identified with the limit of chemotherapeutic medications to aggregate or not in safe cells. Liliana Manciu^a, Xiu-Bao Chang^b, John R. Riordan^b, Fr  de  ric Buy sea, Jean Marie Ruyschaert, first distributed this online on 7 March 2001. These perceptions unequivocally propose that, within the sight of medications dismissed external safe cells, the protein goes through subsequent to restricting and hydrolysis of MgATP, conformational changes which are critical advances associated with the reactant pattern of medication transporthe tests detailed here show that ATP restricting is vital for the protein to go through the conformational change prompting the vehicle of DNR and DOX outside the phone. Taking everything into account, we show here that the coupling between the medication restricting site(s) and the synergist destinations is divergently ajected by restricting of anthracycline subordinates which gather or don't amass in safe cells.

CHAPTER 3

AIM AND OBJECTIVES

AIM:

The present study is to identify the novel inhibitors for multi resistance protein-1 by applying Insilico techniques.

OBJECTIVES:

- Identification of inhibitors against MRP-1 by applying Insilico techniques.
- Designing of pharmacophore for multi-resistance protein-1.
- Virtual screening for finding potent target specific multi resistance protein-1 inhibitors using designed pharmacophore.
- Identification of best molecular interacting inhibitors by using molecular docking.

SCOPE:

- MRP1/ABCC1 play an important role in the extrusion of drugs from the cell and their overexpression can be a cause of failure of anticancer and antimicrobial chemotherapy. It was the first to be characterized and was originally identified as being responsible for the multidrug resistance phenotype in a drug selected human small cell lung carcinoma cell line.
- Generally, MRP1 is mainly found to be expressed in physiology barriers such as blood–brain barrier and may limit drug uptake and retention.

CHAPTER 4

MATERIALS AND METHODS

The materials that are used for the process are:

4.1. PDB:

The Protein Data Bank (PDB) is a crystallographic database for the three-dimensional basic information of extensive organic atoms, for example, proteins and nucleic acids. The information, normally acquired by X-ray crystallography, NMR spectroscopy or, progressively, cryo-electron microscopy. The PDB is a key asset in zones of basic science, for example, basic genomics. By using this PDB, we get the code of MRP1 i.e. 2CBZ (Odile Ramaen et al, 2006).

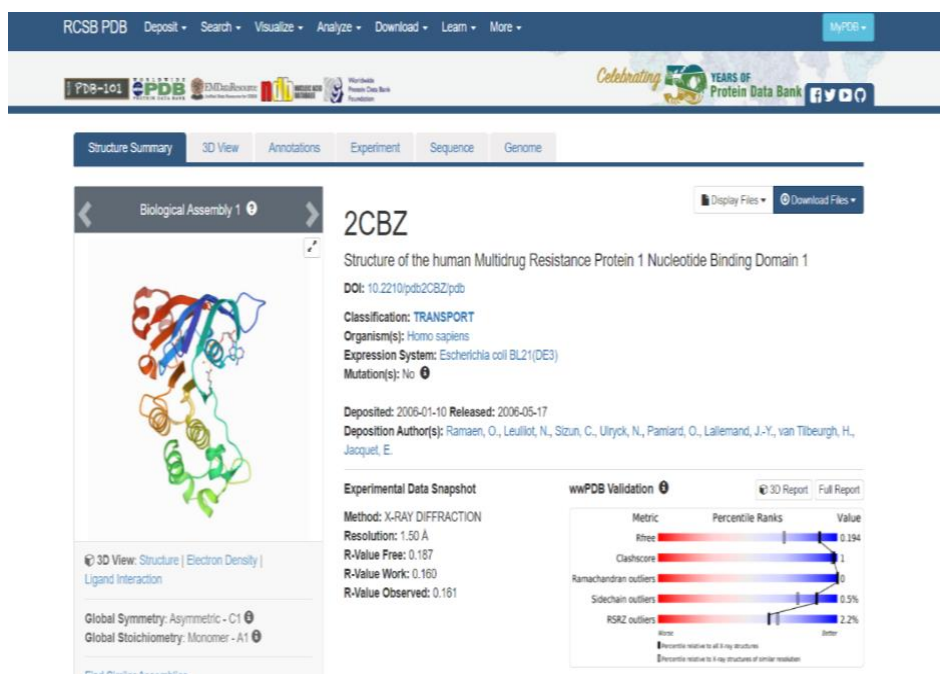


FIG 4.1 2cbz- Protein databank.

4.2. SWISS PROT:

SWISS-PROT is a commented on protein succession database, which was made at the Department of Medical Biochemistry of the University of Geneva and has been a community exertion of the Department and the European Molecular Biology Laboratory (EMBL), since 1987. SWISS-PROT is currently an equivalent organization between the EMBL and the Swiss Institute of Bioinformatics (SIB). The EMBL exercises are completed by its Hinxton Outstation, the European Bioinformatics Institute (EBI). The SWISS-PROT protein grouping database comprises of arrangement passages. Arrangement sections are made out of various line writes, each with their own organization. For institutionalization purposes the configuration of SWISS-PROT takes after as nearly as conceivable that of the EMBL Nucleotide Sequence Database (AmosBairoch and Rolf Apweiler 2000).

4.3. PUB CHEM:

PubChem is a database of compound molecules and their activities against natural examines. The framework is kept up by the National Centre for Biotechnology Information (NCBI), a segment of the National Library of Medicine, which is a piece of the United States National Institutes of Health (NIH). PubChem can be gotten to for nothing through a web user interface. A large number of compound structures and distinct datasets can be openly downloaded by means of FTP. PubChem contains substance depictions and little particles with less than 1000 molecules and 1000 bonds. In excess of 80 database merchants add to the developing PubChem database. From this database we get the three dimensional structure of MRP1 inhibitors for pharmacophore designing.

4.4. UCSF CHIMERA:

The plan, execution, and abilities of an extensible representation framework, UCSF Chimera, are talked about. chimera is fragmented into a center that offers fundamental types of assistance and representation, and expansions that give most more significant level usefulness. This design guarantees that the augmentation system fulfills the requests of outside engineers who wish to consolidate new

highlights. Two irregular expansions are introduced: Multiscale, which adds the capacity to envision huge scope sub-atomic congregations like viral coats, and Collaboratory, which permits specialists to share a Chimera meeting intuitively notwithstanding being at independent regions. Different expansions incorporate Multalign Viewer, for showing numerous succession arrangements and related designs; ViewDock, for screening docked ligand directions; Movie, for replaying atomic elements directions; and Volume Viewer, for show and investigation of volumetric information. A conversation of the utilization of Chimera in true circumstances is given, alongside expected future bearings. Fabrication incorporates full client documentation, is free to scholarly and not-for-profit clients, and is accessible for Microsoft Windows, Linux, Apple Mac OS X, SGI IRIX, and HP Tru64 Unix from <http://www.cgl.ucsf.edu/delusion/>.

4.5. PHARMACOPHORE DESIGNING:

A pharmacophore is an abstract description of molecular features that are necessary for molecular recognition of a ligand by a biological macromolecule. The IUPAC characterizes a pharmacophore to be "a group of steric and electronic highlights that is important to guarantee the ideal supramolecular collaborations with a particular organic objective and to trigger (or obstruct) its natural reaction. A pharmacophore model clarifies how fundamentally assorted ligands can tie to a typical receptor site. Moreover, pharmacophore models can be utilized to recognize through once more plan or virtual screening novel ligands that will tie to a similar receptor. The interaction for building up a pharmacophore model by and large includes the accompanying advances:

4.5.1 A). Select a training set of ligands – Choose a fundamentally different arrangement of particles that will be utilized for building up the pharmacophore model. As a pharmacophore model ought to have the option to segregate between atoms with and without bioactivity, the arrangement of particles ought to incorporate both dynamic and latent mixtures

4.5.2 b). Conformational analysis – Generate a bunch of low energy conformances that is probably going to contain the bioactive conformation for every one of the chosen particles.

4.5.3 c). Molecular superimposition – Superimpose ("fit") all mixes of the low-energy conformations of the particles. Comparative (bioisosteric) practical groupings normal to all particles in the set may be fitted (e.g., phenyl rings or carboxylic acid groupings). The arrangement of conformances (one conformation from every dynamic particle) that outcomes in the best fit is dared to be the dynamic conformation.

4.5.4 d). Abstraction – Transform the superimposed atoms into a theoretical portrayal. For instance, superimposed phenyl rings may be alluded to all the more theoretically as an 'fragrant ring' pharmacophore component. Moreover, hydroxyl groupings could be assigned as a 'hydrogen-bond benefactor/acceptor' pharmacophore component. We get the pharmacophore based highlights by utilizing pharma substance online worker.

4.6. CHEMBI DATABASE:

Chembi is a research tool for investigators seeking chemical matter for their biological targets. It incorporates purchasable compounds from over one hundred vendors and annotated compounds from over twenty databases. Since it originally seemed eight years' prior, chembi has developed more than 10-fold in size, the nature of its 3D atomic portrayals have been improved, and new highlights have been added to its interface. Though it holds its unique spotlight on organically applicable structures for sub-atomic docking, chembi now upholds other chemo-informatics methods. By this data set we get fundamentally comparative mixtures.

4.7 MOLECULAR DOCKING:

Molecular docking is a key device in structural molecular biology and computer based drug design. The objective of ligand-protein docking is to anticipate the overwhelming binding mode of a ligand with a protein of known three-dimensional structure. Fruitful docking strategies seek high-dimensional spaces viably and utilize a scoring capacity that effectively positions competitor dockings. Docking can be utilized to perform virtual screening on expansive libraries of mixes, rank the outcomes, and propose auxiliary theories of how the ligands restrain the objective, which is precious in lead enhancement. (Morris G.M. and Lim Wilby .M, 2008)

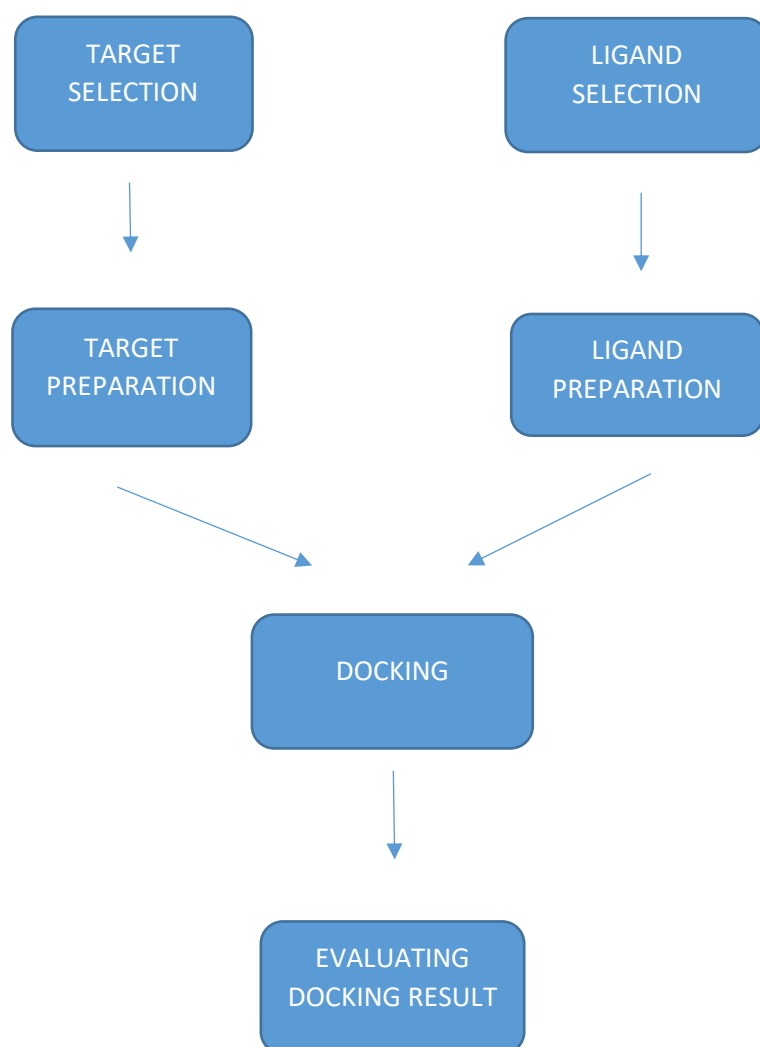


FIG 4.7 molecular docking process

4.7.1. I gem dock:

Structure-based virtual screening and post-screening examination are new assignments in computer based drug delivery. Joining these two strategies to successfully diminish the false positives from an extensive compound database is considered as a key advance to finding the lead mixes. In this consider, we have built up a graphical-programmed medicate disclosure framework, called Igem dock, for coordinating docking.

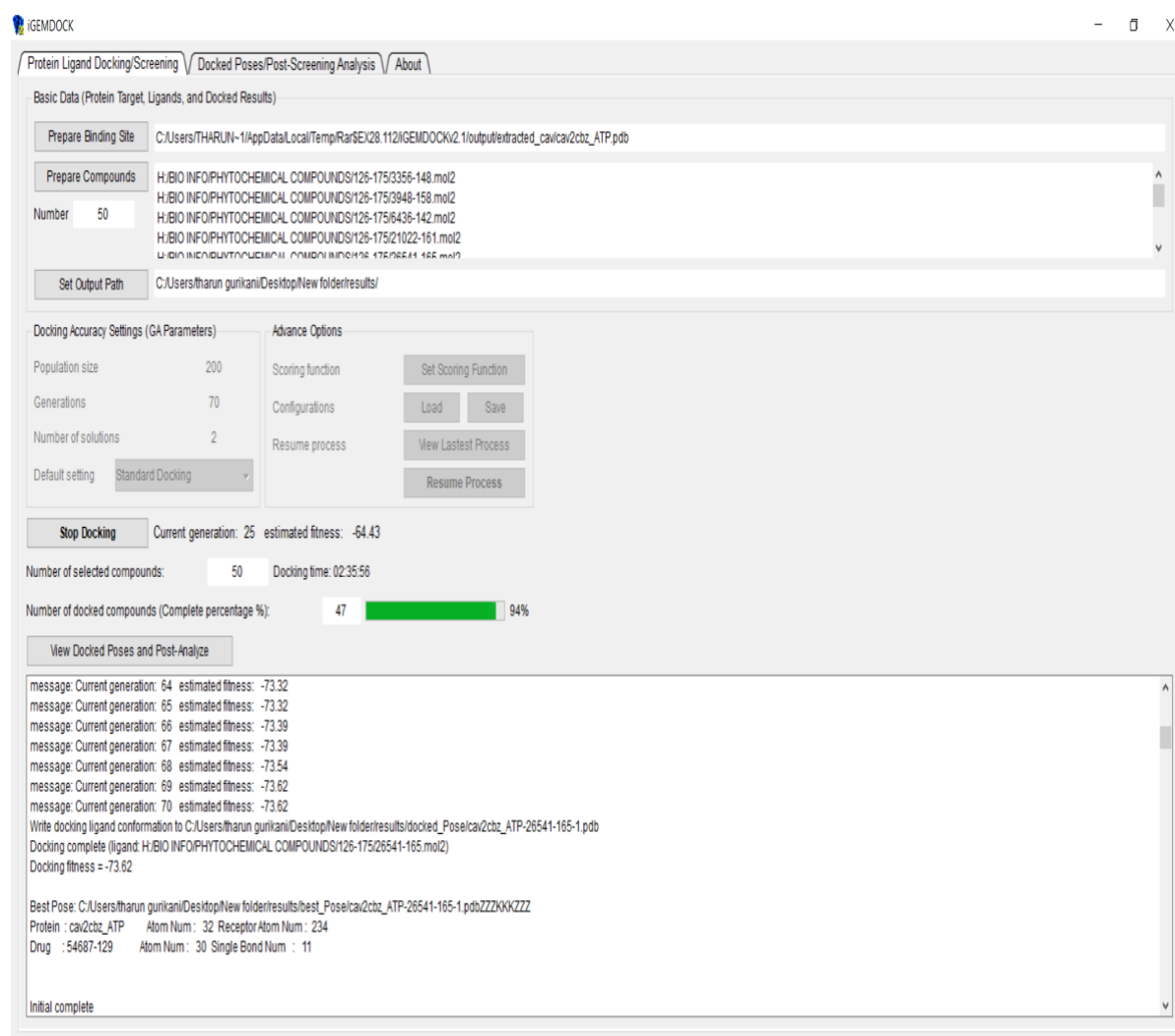


Fig 4.7.1 I gem dock

4.8 METHODOLOGY

UCSF chimera was utilized to picture the receptor, ligand structures, hydrogen-holding organization, and bond lengths and to deliver pictures. The Chembi information base online worker was utilized to recognize fundamentally comparative mixtures utilizing the pharmacophore highlights of mk571, doxorubicin, pronecid, etoposide. I gem dock programming was the essential docking program utilized in this investigation for virtual screening with brisk docking. A MRP1 receptor (PDB ID: 2CBZ) and ligands were ready for virtual screening by adding the hydrogen atoms and by eliminating all water particles that were co-solidified with this objective protein. The expansion of hydrogen molecules guarantees a precise assurance of the ionization conditions of amino corrosive buildups. The energy of the protein structure was then limited utilizing the USCF Chimera, and the got structure was saved in a .pdb document design for additional investigations. Also, ligands were set up by first eliminating the hybridization mistakes in quite a while and afterward adding the missing hydrogen bonds to check the constancy of all bonds in the mixtures. All readied compounds were saved in the mol design for additional docking concentrates after a calculation streamlining stage with the energy-scoring framework box was focused at the dynamic ligand restricting site area and its measurements were set to 60 Å along every pivot (x, y, and z). The network dividing was 0.40 Å, and the default nuclear salvation boundaries were utilized. The matrix was doled out with the end goal that the dynamic site of MRP1 was encased by the three-dimensional lattice box. "A score" scoring capacity with all docking boundaries set to the default esteems was chosen as the docking motor in I gem dock.

Chembi or Chembi data set is a physically curated compound data set of bioactive particles with drug-like properties which is kept up by the European Bioinformatics Institute (EBI), of the European Molecular Biology Laboratory (EMBL), based out of Wellcome Trust Genome Campus, Hinxton, UK. The entire information base is sifted

concerning the clinically tried mixtures. The sifted compound's properties were then found through utilizing Swiss ADME.

Swiss ADME This site permits you to register physicochemical descriptors just as to anticipate ADME boundaries, pharmacokinetic properties, drug like nature and restorative science cordiality of one or different little particles to help drug disclosure. We got ADME properties of each of the 36 medications like mixtures from this worker. The mixtures with most noteworthy docking energies were screened utilizing SWISSADME from this best compound was chosen out of these dependent on their ADME properties.

Lipinski's Rule of Five is a general guideline to assess drug likeness, or decide whether a synthetic compound with a specific pharmacological or organic action has properties that would make it a presumable orally dynamic medication in people. This standard was found by Christopher A. Lipinski in 1997, in view of the perception that most medicine drugs are nearly little and lipophilic atoms.

The standard portrays atomic properties significant for a medication's pharmacokinetics in the human body, including their assimilation, dispersion, digestion, and discharge ("ADME"). Be that as it may, the standard couldn't foresee if a compound is pharmacologically dynamic.

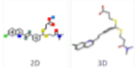
The standard is significant for drug improvement where a pharmacologically dynamic lead structure is enhanced advance insightful for expanded action and selectivity, just as medication like properties as portrayed by Lipinski's standard. The change of the atomic design regularly prompts drugs with higher sub-atomic weight, more rings, more rotatable bonds, and a higher lipophilicity. In this manner, these mixtures were separated utilizing Lipinski's standard of five to discover the medication similarity of the current mixtures.

These ligands were then acquainted with sub-atomic docking to additionally discover their medication similarity. They were docked 2cbz protein utilizing the 'I gem dock' programming. I gem dock is a Graphical Environment for Recognizing Pharmacological Interactions and Virtual Screening. Pharmacological collaborations are valuable for recognizing lead mixtures and understanding ligand restricting components for a remedial objective. Right now, these associations are regularly induced from a bunch of dynamic mixtures that were gained tentatively. Also, most docking programs approximately coupled the phases of design based virtual screening (VS) from arrangements through to post-screening examination. An incorporated VS climate, which gives the agreeable interface to consistently consolidate diverse stage programs for VS and recognizing the pharmacological communications from screening compounds, is important for drug revelation.

The information gathered from sub-atomic docking were then contrasted with the properties of the compound 'MK571' which as well, is docked with similar protein to discover viable ligands which fill in as inhibitors for mrp-1 protein.

MK-571 (5-(3-(2-(7-chloroquinolin-2-yl) ethenyl) phenyl)-8-dimethylcarbamyl-4,6-dithiaoctanoic acid), an LTD₄ receptor antagonist, has been reported to act as competitive **inhibitor** for MRP1-mediated transport, both for GS-conjugate transport (such as thiodione) as well as for the transport of unconjugated GSH-mediated

MK-571 sodium

PubChem CID	16760569
Structure	 Find Similar Structures
Molecular Formula	$C_{23}H_{29}ClN_2NaO_4S_2$
Synonyms	115103-85-0 MK-571 sodium MK-571 sodium salt MK571 MK-571 More...
Molecular Weight	537.1 g/mol
Parent Compound	 CID 5281888 (Verlukast)
Component Compounds	 CID 5281888 (Verlukast) •  CID 5360545 (Sodium)

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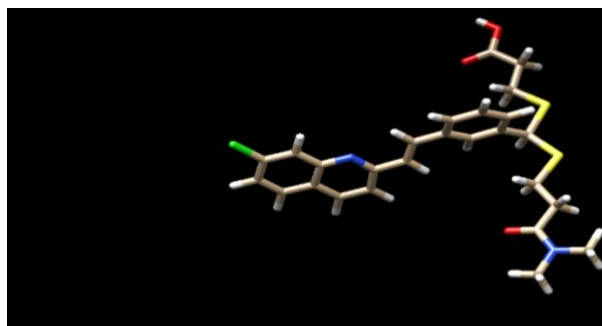


FIG 4.8 3D Structure of MK517

CHAPTER-5

RESULTS

5.1 IDENTIFYING AND STUDYING THE STRUCTURE.

- The ideal protein for interaction was found and its structure was viewed and studied by using USCF Chimera.

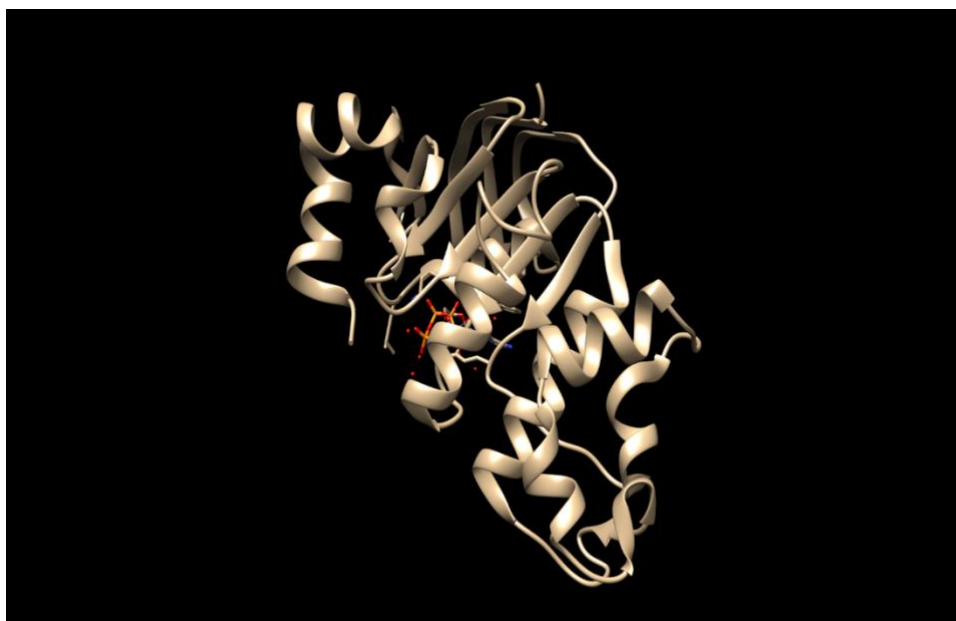


Fig 5.1 3-d structure of 2cbz

5.2 REVIEW AND COLLECTION OF CLINICALLY TRAILED COMPOUNDS.

- Review of literature for already proven drugs resulted in these collection of compounds which are helpful to set guideline for the project.

TABLE 5.2 Clinically trailed compounds

Table 1

S.NO	Compound	M.W (g/mol)				
1	MK571	537.1				
2	ETOPOSIDE	588.6				
3	VINCISTINE	825				
4	TEMOZOLOMIDE	194.15				
5	PROBENECID	285.36				
6	1,4 DIHYDROPYRIDINE	81.12				
7	LEVOFLOXACIN	361.4				
8	LAMOTRIGINE	256.089				
9	POSACONAZOLE	700.8				
10	RANITIDINE	314.41				
11	EZOMEPRAZOLE	345.4				
12	INDOMETHACIN	357.8				
	AVERAGE	403.93575				

5.2.1 PHARMACOPHORE MODELLING

- And later pharmacophore modelling for the above compounds were done to find out their properties.

PharmaGist

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Input Molecules [view details: visualization of the detected features](#)

#	Molecule	Atoms	Features	Spatial Features	Aromatic	Hydrophobic	Donors	Acceptors	Negatives	Positives
1	Temozolomide.mol2	20	10	10	2	1	1	5	0	1
2	Etoposide.mol2	74	24	21	3	5	3	13	0	0
3	esomeprazole.mol2	43	16	15	3	6	1	5	0	1
4	posaconazole.mol2	23	7	7	2	0	2	3	0	0
5	ranitidine.mol2	43	11	11	1	3	2	5	0	0
6	indomethacin.mol2	40	11	11	3	2	0	4	1	1
7	Probenecid.mol2	37	11	11	1	4	0	5	1	0
8	vincristine.mol2	98	24	23	5	9	1	8	0	1
9	levofloxacin.mol2	45	10	10	2	2	0	5	1	0
10	mk571.mol2	60	14	14	3	4	0	6	1	0
11	1,4Dihydropyridines.mol2	12	3	3	0	2	0	1	0	0

[Sort by score](#)

Fig 5.2.1 PHARMACOPHORE MODELLING

5.2.2. CHEMBI DATABASE

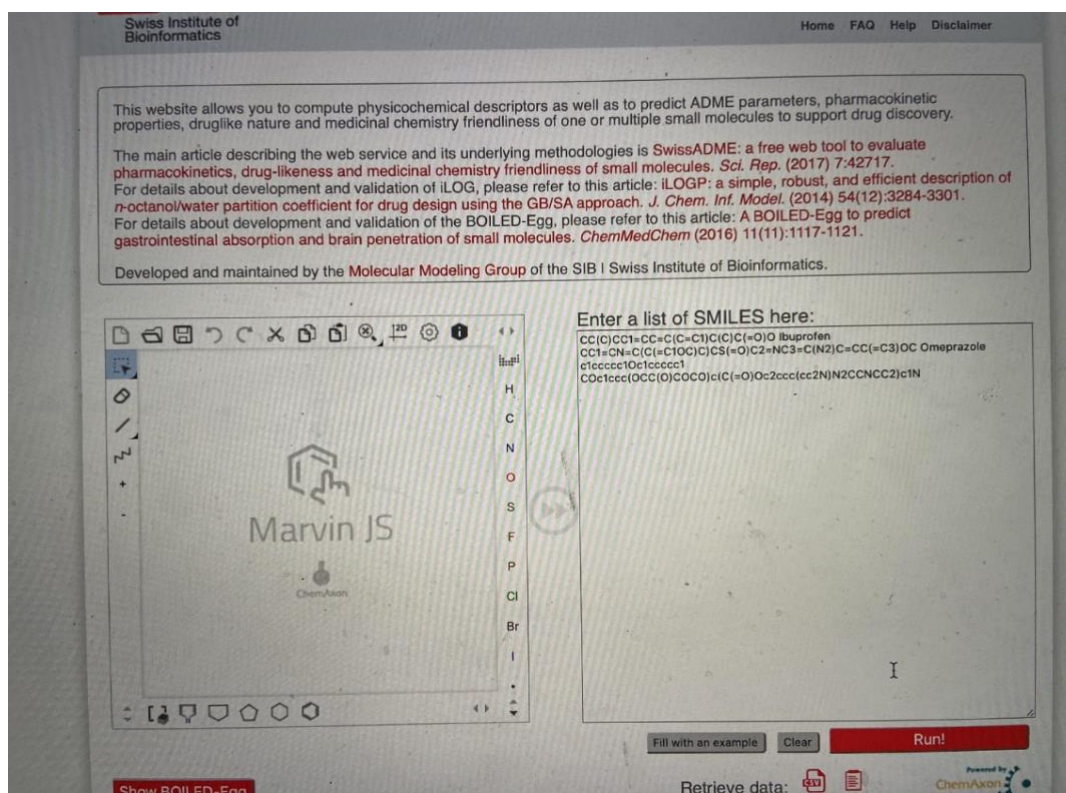
- The chembi database (12k) was downloaded and was filtered using the pharmacophore modelling results.

Table 5.2.2 CHEMBI DATABASE

[illegible]

5.3 SWISS ADME

- Swiss-ADME was used to find out all the ADME properties of all the compounds available.
- It is a tool to evaluate pharmacokinetics, drug like nature and medicinal chemistry of one or multiple small molecules to support drug discovery.
- ADME properties include absorption, distribution, metabolism, excretion and toxicity of a drug molecule.
- ADMET properties play an important role as they account for failure of 60% of drug molecules during drug development process



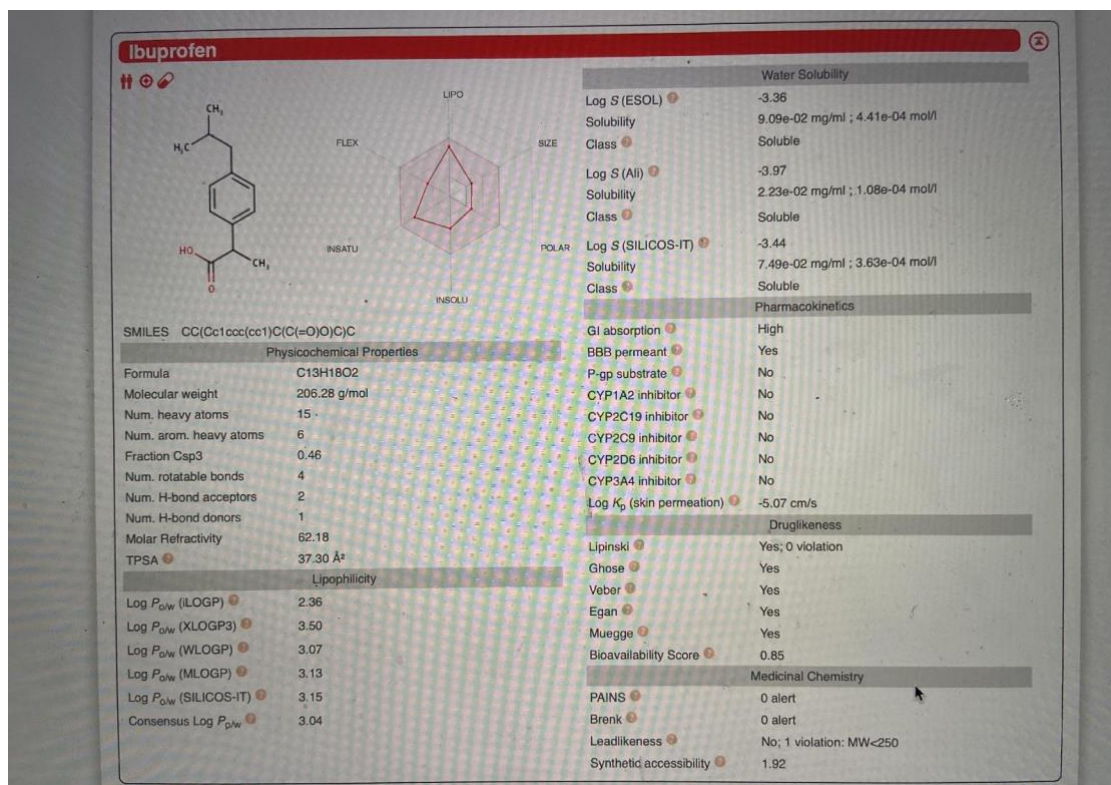


Fig 5.3 Filtering chembi database using ligand based pharmacophore through Swiss-ADME

5.4 FILTERING COMPOUNDS ACCORDING TO 'LIPINSKI RULE OF FIVE'.

- The compounds with the help of their ADME properties were filtered using the lipinski rule of five to work with compounds that have higher chance of drug-likeness.

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A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	
ChemBI1296	Molecule 1	CCCCC1C2C3C4C5C6C7C8C9C10C11C12C13C14C15C16C17C18C19C20C21C22C23C24C25C26C27C28C29C30C31C32C33C34C35C36C37C38C39C40C41C42C43C44C45C46C47C48C49C50C51C52C53C54C55C56C57C58C59C60C61C62C63C64C65C66C67C68C69C70C71C72C73C74C75C76C77C78C79C80C81C82C83C84C85C86C87C88C89C90C91C92C93C94C95C96C97C98C99C100C101C102C103C104C105C106C107C108C109C110C111C112C113C114C115C116C117C118C119C120C121C122C123C124C125C126C127C128C129C130C131C132C133C134C135C136C137C138C139C140C141C142C143C144C145C146C147C148C149C150C151C152C153C154C155C156C157C158C159C160C161C162C163C164C165C166C167C168C169C170C171C172C173C174C175C176C177C178C179C180C181C182C183C184C185C186C187C188C189C190C191C192C193C194C195C196C197C198C199C200C201C202C203C204C205C206C207C208C209C210C211C212C213C214C215C216C217C218C219C220C221C222C223C224C225C226C227C228C229C230C231C232C233C234C235C236C237C238C239C240C241C242C243C244C245C246C247C248C249C250C251C252C253C254C255C256C257C258C259C260C261C262C263C264C265C266C267C268C269C270C271C272C273C274C275C276C277C278C279C280C281C282C283C284C285C286C287C288C289C290C291C292C293C294C295C296C297C298C299C300C301C302C303C304C305C306C307C308C309C310C311C312C313C314C315C316C317C318C319C320C321C322C323C324C325C326C327C328C329C330C331C332C333C334C335C336C337C338C339C340C341C342C343C344C345C346C347C348C349C350C351C352C353C354C355C356C357C358C359C360C361C362C363C364C365C366C367C368C369C370C371C372C373C374C375C376C377C378C379C380C381C382C383C384C385C386C387C388C389C390C391C392C393C394C395C396C397C398C399C400C401C402C403C404C405C406C407C408C409C410C411C412C413C414C415C416C417C418C419C420C421C422C423C424C425C426C427C428C429C430C431C432C433C434C435C436C437C438C439C440C441C442C443C444C445C446C447C448C449C450C451C452C453C454C455C456C457C458C459C460C461C462C463C464C465C466C467C468C469C470C471C472C473C474C475C476C477C478C479C480C481C482C483C484C485C486C487C488C489C490C491C492C493C494C495C496C497C498C499C500C501C502C503C504C505C506C507C508C509C510C511C512C513C514C515C516C517C518C519C520C521C522C523C524C525C526C527C528C529C530C531C532C533C534C535C536C537C538C539C540C541C542C543C544C545C546C547C548C549C550C551C552C553C554C555C556C557C558C559C560C561C562C563C564C565C566C567C568C569C570C571C572C573C574C575C576C577C578C579C580C581C582C583C584C585C586C587C588C589C590C591C592C593C594C595C596C597C598C599C600C601C602C603C604C605C606C607C608C609C610C611C612C613C614C615C616C617C618C619C620C621C622C623C624C625C626C627C628C629C630C631C632C633C634C635C636C637C638C639C640C641C642C643C644C645C646C647C648C649C650C651C652C653C654C655C656C657C658C659C660C661C662C663C664C665C666C667C668C669C670C671C672C673C674C675C676C677C678C679C680C681C682C683C684C685C686C687C688C689C690C691C692C693C694C695C696C697C698C699C700C701C702C703C704C705C706C707C708C709C710C711C712C713C714C715C716C717C718C719C720C721C722C723C724C725C726C727C728C729C730C731C732C733C734C735C736C737C738C739C740C741C742C743C744C745C746C747C748C749C750C751C752C753C754C755C756C757C758C759C760C761C762C763C764C765C766C767C768C769C770C771C772C773C774C775C776C777C778C779C780C781C782C783C784C785C786C787C788C789C790C791C792C793C794C795C796C797C798C799C800C801C802C803C804C805C806C807C808C809C810C811C812C813C814C815C816C817C818C819C820C821C822C823C824C825C826C827C828C829C830C831C832C833C834C835C836C837C838C839C840C841C842C843C844C845C846C847C848C849C850C851C852C853C854C855C856C857C858C859C860C861C862C863C864C865C866C867C868C869C870C871C872C873C874C875C876C877C878C879C880C881C882C883C884C885C886C887C888C889C890C891C892C893C894C895C896C897C898C899C900C901C902C903C904C905C906C907C908C909C910C911C912C913C914C915C916C917C918C919C920C921C922C923C924C925C926C927C928C929C930C931C932C933C934C935C936C937C938C939C940C941C942C943C944C945C946C947C948C949C950C951C952C953C954C955C956C957C958C959C960C961C962C963C964C965C966C967C968C969C970C971C972C973C974C975C976C977C978C979C980C981C982C983C984C985C986C987C988C989C990C991C992C993C994C995C996C997C998C999C1000C1001C1002C1003C1004C1005C1006C1007C1008C1009C1010C1011C1012C1013C1014C1015C1016C1017C1018C1019C1020C1021C1022C1023C1024C1025C1026C1027C1028C1029C1030C1031C1032C1033C1034C1035C1036C1037C1038C1039C1040C1041C1042C1043C1044C1045C1046C1047C1048C1049C1050C1051C1052C1053C1054C1055C1056C1057C1058C1059C1060C1061C1062C1063C1064C1065C1066C1067C1068C1069C1070C1071C1072C1073C1074C1075C1076C1077C1078C1079C1080C1081C1082C1083C1084C1085C1086C1087C1088C1089C1090C1091C1092C1093C1094C1095C1096C1097C1098C1099C1100C1101C1102C1103C1104C1105C1106C1107C1108C1109C1110C1111C1112C1113C1114C1115C1116C1117C1118C1119C1120C1121C1122C1123C1124C1125C1126C1127C1128C1129C1130C1131C1132C1133C1134C1135C1136C1137C1138C1139C1140C1141C1142C1143C1144C1145C1146C1147C1148C1149C1150C1151C1152C1153C1154C1155C1156C1157C1158C1159C1160C1161C1162C1163C1164C1165C1166C1167C1168C1169C1170C1171C1172C1173C1174C1175C1176C1177C1178C1179C1180C1181C1182C1183C1184C1185C1186C1187C1188C1189C1190C1191C1192C1193C1194C1195C1196C1197C1198C1199C1200C1201C1202C1203C1204C1205C1206C1207C1208C1209C1210C1211C1212C1213C1214C1215C1216C1217C1218C1219C1220C1221C1222C1223C1224C1225C1226C1227C1228C1229C1230C1231C1232C1233C1234C1235C1236C1237C1238C1239C1240C1241C1242C1243C1244C1245C1246C1247C1248C1249C1250C1251C1252C1253C1254C1255C1256C1257C1258C1259C1260C1261C1262C1263C1264C1265C1266C1267C1268C1269C1270C1271C1272C1273C1274C1275C1276C1277C1278C1279C1280C1281C1282C1283C1284C1285C1286C1287C1288C1289C1290C1291C1292C1293C1294C1295C1296C1297C1298C1299C1300C1301C1302C1303C1304C1305C1306C1307C1308C1309C1310C1311C1312C1313C1314C1315C1316C1317C1318C1319C1320C1321C1322C1323C1324C1325C1326C1327C1328C1329C1330C1331C1332C1333C1334C1335C1336C1337C1338C1339C1340C1341C1342C1343C1344C1345C1346C1347C1348C1349C1350C1351C1352C1353C1354C1355C1356C1357C1358C1359C1360C1361C1362C1363C1364C1365C1366C1367C1368C1369C1370C1371C1372C1373C1374C1375C1376C1377C1378C1379C1380C1381C1382C1383C1384C1385C1386C1387C1388C1389C1390C1391C1392C1393C1394C1395C1396C1397C1398C1399C1400C1401C1402C1403C1404C1405C1406C1407C1408C1409C1410C1411C1412C1413C1414C1415C1416C1417C1418C1419C1420C1421C1422C1423C1424C1425C1426C1427C1428C1429C1430C1431C1432C1433C1434C1435C1436C1437C1438C1439C1440C1441C1442C1443C1444C1445C1446C1447C1448C1449C1450C1451C1452C1453C1454C1455C1456C1457C1458C1459C1460C1461C1462C1463C1464C1465C1466C1467C1468C1469C1470C1471C1472C1473C1474C1475C1476C1477C1478C1479C1480C1481C1482C1483C1484C1485C1486C1487C1488C1489C1490C1491C1492C1493C1494C1495C1496C1497C1498C1499C1500C1501C1502C1503C1504C1505C1506C1507C1508C1509C1510C1511C1512C1513C1514C1515C1516C1517C1518C1519C1520C1521C1522C1523C1524C1525C1526C1527C1528C1529C1530C1531C1532C1533C1534C1535C1536C1537C1538C1539C1540C1541C1542C1543C1544C1545C1546C1547C1548C1549C1550C1551C1552C1553C1554C1555C1556C1557C1558C1559C1560C1561C1562C1563C1564C1565C1566C1567C1568C1569C1570C1571C1572C1573C1574C1575C1576C1577C1578C1579C1580C1581C1582C1583C1584C1585C1586C1587C1588C1589C1590C1591C1592C1593C1594C1595C1596C1597C1598C1599C1600C1601C1602C1603C1604C1605C1606C1607C1608C1609C1610C1611C1612C1613C1614C1615C1616C1617C1618C1619C1620C1621C1622C1623C1624C1625C1626C1627C1628C1629C1630C1631C1632C1633C1634C1635C1636C1637C1638C1639C1640C1641C1642C1643C1644C1645C1646C1647C1648C1649C1650C1651C1652C1653C1654C1655C1656C1657C1658C1659C1660C1661C1662C1663C1664C1665C1666C1667C1668C1669C1670C1671C1672C1673C1674C1675C1676C1677C1678C1679C1680C1681C1682C1683C1684C1685C1686C1687C1688C1689C1690C1691C1692C1693C1694C1695C1696C1697C1698C1699C1700C1701C1702C1703C1704C1705C1706C1707C1708C1709C1710C1711C1712C1713C1714C1715C1716C1717C1718C1719C1720C1721C1722C1723C1724C1725C1726C1727C1728C1729C1730C1731C1732C1733C1734C1735C1736C1737C1738C1739C1740C1741C1742C1743C1744C1745C1746C1747C1748C1749C1750C1751C1752C1753C1754C1755C1756C1757C1758C1759C1760C1761C1762C1763C1764C1765C1766C1767C1768C1769C1770C1771C1772C1773C1774C1775C1776C1777C1778C1779C1780C1781C1782C1783C1784C1785C1786C1787C1788C1789C1790C1791C1792C1793C1794C1795C1796C1797C1798C1799C1800C1801C1802C1803C1804C1805C1806C1807C1808C1809C1810C1811C1812C1813C1814C1815C1816C1817C1818C1819C1820C1821C1822C1823C1824C1825C1826C1827C1828C1829C1830C1831C1832C1833C1834C1835C1836C1837C1838C1839C1840C1841C1842C1843C1844C1845C1846C1847C1848C1849C1850C1851C1852C1853C1854C1855C1856C1857C1858C1859C1860C1861C1862C1863C1864C1865C1866C1867C1868C1869C1870C1871C1872C1873C1874C1875C1876C1877C1878C1879C1880C1881C1882C1883C1884C1885C1886C1887C1888C1889C1890C1891C1892C1893C1894C1895C1896C1897C1898C1899C1900C1901C1902C1903C1904C1905C1906C1907C1908C1909C1910C1911C1912C1913C1914C1915C1916C1917C1918C1919C1920C1921C1922C1923C1924C1925C1926C1927C1928C1929C1930C1931C1932C1933C1934C1935C1936C1937C1938C1939C1940C1941C1942C1943C1944C1945C1946C1947C1948C1949C1950C1951C1952C1953C1954C1955C1956C1957C1958C1959C1960C1961C1962C1963C1964C1965C1966C1967C1968C1969C1970C1971C1972C1973C1974C1975C1976C1977C1978C1979C1980C1981C1982C1983C1984C1985C1986C1987C1988C1989C1990C1991C1992C1993C1994C1995C1996C1997C1998C1999C2000C2001C2002C2003C2004C2005C2006C2007C2008C2009C2010C2011C2012C2013C2014C2015C2016C2017C2018C2019C2020C2021C2022C2023C2024C2025C2026C2027C2028C2029C2030C2031C2032C2033C2034C2035C2036C2037C2038C2039C2040C2041C2042C2043C2044C2045C2046C2047C2048C2049C2050C2051C2052C2053C2054C2055C2056C2057C2058C2059C2060C2061C2062C2063C2064C2065C2066C2067C2068C2069C2070C2071C2072C2073C2074C2075C2076C2077C2078C2079C2080C2081C2082C2083C2084C2085C2086C2087C2088C2089C2090C2091C2092C2093C2094C2095C2096C2097C2098C2099C2100C2101C2102C2103C2104C2105C2106C2107C2108C2109C2110C2111C2112C2113C2114C2115C2116C2117C2118C2119C2120C2121C2122C2123C2124C2125C2126C2127C2128C2129C2130C2131C2132C2133C2134C2135C2136C2137C2138C2139C2140C2141C2142C2143C2144C2145C2146C2147C2148C2149C2150C2151C2152C2153C2154C2155C2156C2157C2158C2159C2160C2161C2162C2163C2164C2165C2166C2167C2168C2169C2170C2171C2172C2173C2174C2175C2176C2177C2178C2179C2180C2181C2182C2183C2184C2185C2186C2187C2188C2189C2190C2191C2192C2193C2194C2195C2196C2197C2198C2199C2200C2201C2202C2203C2204C2205C2206C2207C2208C2209C2210C2211C2212C2213C2214C2215C2216C2217C2218C2219C2220C2221C2222C2223C2224C2225C2226C2227C2228C2229C2230C2231C2232C2233C2234C2235C2236C2237C2238C2239C2240C2241C2242C2243C2244C2245C2246C2247C2248C2249C2250C2251C2252C2253C2254C2255C2256C2257C2258C2259C2260C2261C2262C2263C2264C2265C2266C2267C2268C2269C2270C2271C2272C2273C2274C2275C2276C2277C2278C2279C2280C2281C2282C2283C2284C2285C2286C2287C2288C2289C2290C2291C2292C2293C2294C2295C2296C2297C2298C2299C2300C2301C2302C2303C2304C2305C2306C2307C2308C2309C2310C2311C2312C2313C2314C2315C2316C2317C2318C2319C2320C2321C2322C2323C2324C2325C2326C2327C2328C2329C2330C2331C2332C2333C2334C2335C2336C2337C2338C2339C2340C2341C2342C2343C2344C2345C2346C2347C2348C2349C2350C2351C2352C2353C2354C2355C2356C2357C2358C2359C2360C2361C2362C2363C2364C2365C2366C2367C2368C2369C2370C2371C2372C2373C2374C2375C2376C2377C2378C2379C2380C2381C2382C2383C2384C2385C2386C2387C2388C2389C2390C2391C2392C2393C2394C2395C2396C2397C2398C2399C2400C2401C2402C2403C2404C2405C2406C2407C2408C2409C2410C2411C2412C2413C2414C2415C2416C2417C2418C2419C2420C2421C2422C2423C2424C2425C2426C2427C2428C2429C2430C2431C2432C2433C2434C2435C2436C2437C2438C2439C2440C2441C2442C2443C2444C2445C2446C2447C2448C2449C2450C2451C2452C2453C2454C2455C2456C2457C2458C2459C2460C2461C2462C2463C2464C2465C2466C2467C2468C2469C2470C2471C2472C2473C2474C2475C2476C2477C2478C2479C2480C2481C2482C2483C2484C2485C2486C2487C2488C2489C2490C2491C2492C2493C2494C2495C2496C2497C2498C2499C2500C2501C2502C2503C2504C2505C2506C2507C2508C2509C2510C2511C2512C2513C2514C2515C2516C2517C2518C2519C2520C2521C2522C2523C2524C2525C2526C2527C2528C2529C2530C2531C2532C2533C2534C2535C2536C2537C2538C2539C2540C2541C2542C2543C2544C2545C2546C2547C2548C2549C2550C2551C2552C2553C2554C2555C2556C2557C2558C2559C2560C2561C2562C2563C2564C2565C2566C2567C2568C2569C2570C2571C2572C2573C2574C2575C2576C2577C2578C2579C2580C2581C2582C2583C2584C2585C2586C2587C2588C2589C259																									

5.5 MOLECULAR DOCKING

- By using molecular docking, an interaction between a molecule and a protein could be modelled. Therefore, here using 'I gem dock' molecular docking between the remaining ligands which we have filtered already according to "Lipinski rule of 5" and the 2cbz was carried out.

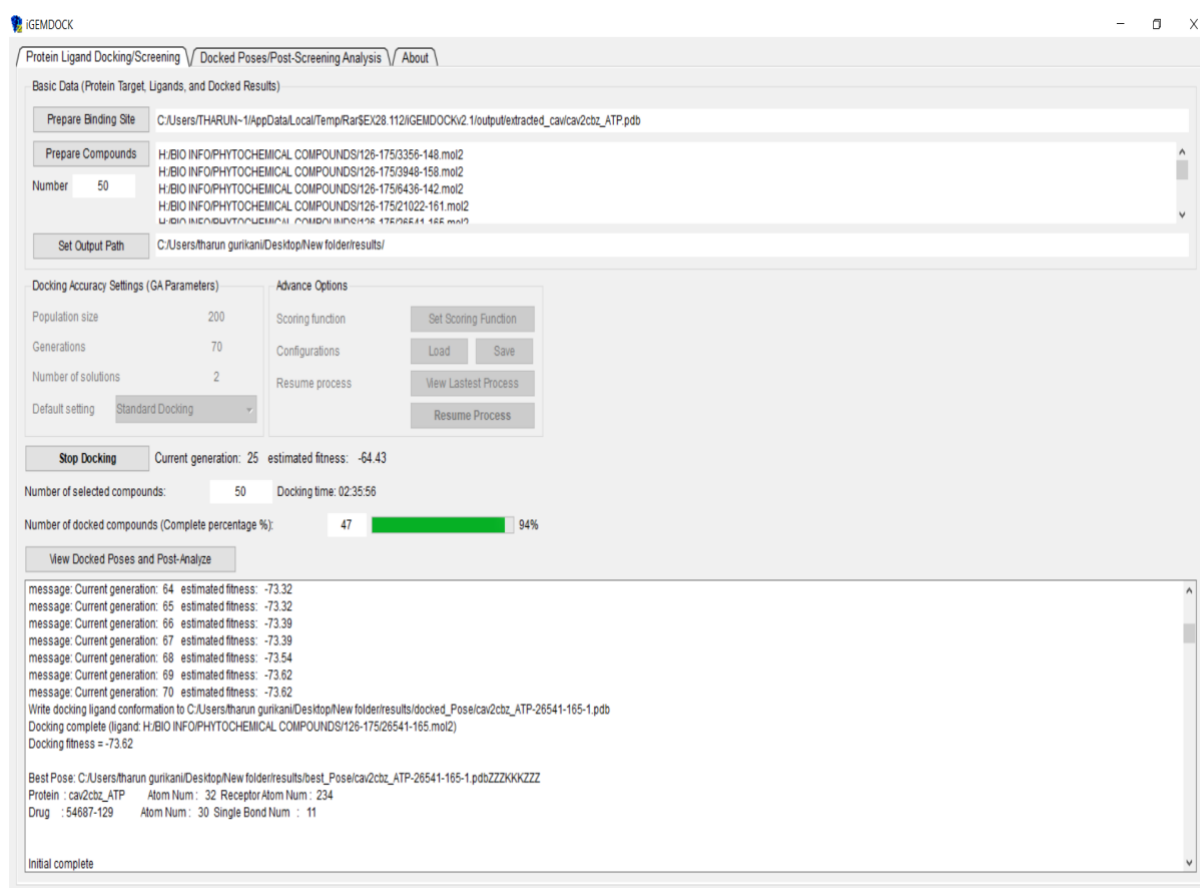


Table 5.5 docking results

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1	#C:/Users/THARUN*1/AppData/Local/Temp/Rar\$EX47.192/GEMDOCKv2.1/output/extracted_cav/cav2cbz_ATP.pdb with C:/Users/tharun gurikani/Desktop/New folder/results/gemdock_out/docking.lst																		
2	#Ligand	TotalEn	VDW	HBond	Elec	AverCo	air												
3	cav2cbz_A	-110.884	-72.5739	-33.8718	-4.43838	20.12													
4	cav2cbz_A	-64.6342	-59.2671	-5.36715	0	16.9048													
5	cav2cbz_A	-99.2168	-67.2383	-26.8936	-5.08493	19.5833													
6	cav2cbz_A	-99.8444	-67.0742	-32.7702	0	19.9706													
7	cav2cbz_A	-93.2403	-83.4457	-9.79457	0	13.3023													
8	cav2cbz_A	-101.334	-64.0368	-37.2975	0	20.0741													
9	cav2cbz_A	-94.8175	-60.0151	-34.8023	0	18.1481													
10	cav2cbz_A	-114.043	-73.149	-36.1839	-4.71053	17.5													
11	cav2cbz_A	-87.0716	-62.3136	-24.758	0	18.4333													
12	cav2cbz_A	-97.8175	-71.2797	-26.5378	0	19.6923													
13	cav2cbz_A	-83.8738	-56.9436	-26.9301	0	16.037													
14	cav2cbz_A	-93.9992	-47.9532	-46.046	0	17.8276													
15	cav2cbz_A	-98.8274	-70.8708	-27.9566	0	20.6154													
16	cav2cbz_A	-107.792	-70.0145	-33.3765	-4.40106	17.7143													
17	cav2cbz_A	-127.342	-80.6734	-41.3747	-5.29416	17.5484													
18	cav2cbz_A	-94.4258	-58.8502	-31.0112	-4.56442	18.32													
19	cav2cbz_A	-92.9942	-67.9634	-25.0307	0	14.2703													
20	cav2cbz_A	-115.208	-84.0069	-25.9712	-5.23028	14.3243													
21	cav2cbz_A	-113.169	-69.4542	-38.9144	-4.80014	19.3704													
22	cav2cbz_A	-87.23	-68.4987	-18.7314	0	13.3947													
23	cav2cbz_A	-89.8818	-75.9627	-13.9191	0	18.7													
24	cav2cbz_A	-100.112	-74.3166	-25.7957	0	15.8571													
25	cav2cbz_A	-90.0815	-64.2272	-25.8543	0	17.7308													
26	cav2cbz_A	-99.8278	-74.6801	-25.1477	0	16.7059													
27	cav2cbz_A	-131.794	-86.7991	-44.9949	0	19.6364													
28	cav2cbz_A	-80.7642	-62.1684	-18.5958	0	17.6538													
29	cav2cbz_A	-92.5074	-60.462	-32.0455	0	17.4483													
30	cav2cbz_A	-112.036	-62.1227	-44.522	-5.39156	16.2727													

5.6 BEST MOLECULAR INTERACTING INHIBITORS

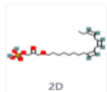
Through the results obtained from molecular docking we were able to find out nine compounds which could act as inhibitors for mrp-1 protein. This conclusion was achieved by understanding and comparing the properties of mk571 compound to the molecular docking results and finding out ligands which possesses similar properties.

	A	B	C	D	E	F	G
1	#Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair	
7	cav2cbz_ATP-86289256-1268-1.pdb	-150.784	-98.8009	-44.3343	-7.64921	23.1071	
8	cav2cbz_ATP-86289254-1267-0.pdb	-150.483	-101.491	-40.9258	-8.06658	23.1786	
10	cav2cbz_ATP-86289251-1262-0.pdb	-149.575	-103.035	-38.3291	-8.21136	24.7778	
47	cav2cbz_ATP-86289246-1225-1.pdb	-136.458	-86.5165	-42.2571	-7.68403	25.2083	
48	cav2cbz_ATP-86289249-1261-1.pdb	-135.874	-83.0322	-45.1416	-7.70014	23.12	
53	cav2cbz_ATP-9547165-1561-1.pdb	-134.39	-87.1609	-40.2912	-6.93808	24.625	
57	cav2cbz_ATP-132282462-1812-0.pdb	-133.916	-93.1083	-35.0389	-5.76881	21.963	
72	cav2cbz_ATP-132472339-1834-1.pdb	-131.006	-98.1659	-27.0822	-5.75812	22.25	
87	cav2cbz_ATP-122164877-1646-1.pdb	-127.068	-93.3744	-27.6225	-6.07105	23.5926	

Table 5.6 best molecular interacting inhibitors

[1]

1-(9Z,12Z,15Z)-Octadecatrienylglycerone 3-phosphate

PubChem CID	86289256
Structure	 2D Find Similar Structures
Molecular Formula	$C_{21}H_{37}O_6P$
Synonyms	1-(9Z,12Z,15Z)-octadecatrienylglycerone 3-phosphate ChEBI:78165 Q27147666 3-[(9Z,12Z,15Z)-octadeca-9,12,15-trien-1-yloxy]-2-oxopropyl dihydrogen phosphate
Molecular Weight	416.5 g/mol
Dates	Modify: 2021-03-17 Create: 2014-12-18
1-(9Z,12Z,15Z)-octadecatrienylglycerone 3-phosphate is a 1-alkylglycerone 3-phosphate in which the alkyl group is specified as (9Z,12Z,15Z)-octadecatrienyl. It is a conjugate acid of a 1-(9Z,12Z,15Z)-octadecatrienylglycerone 3-phosphate(2-). ► ChEBI	

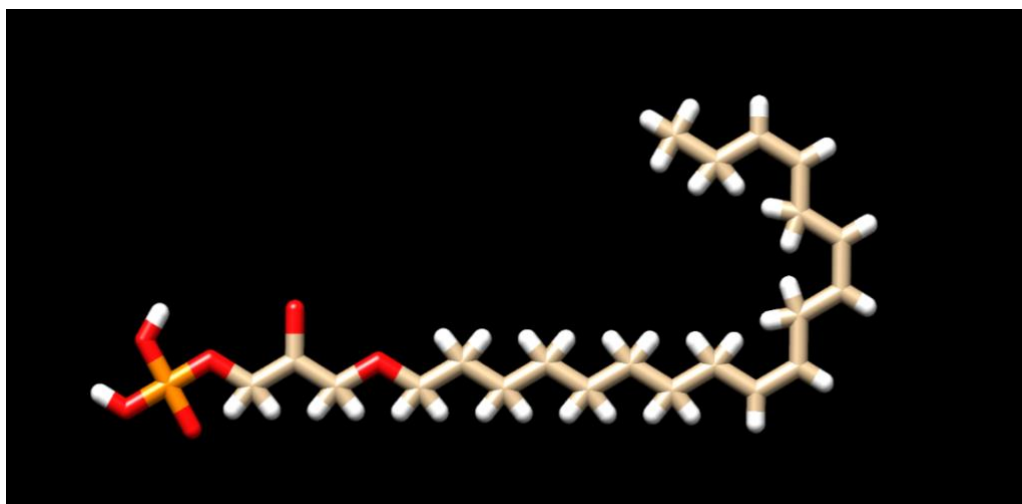


Fig 5.6.1. 2D docking diagram of 1-(9Z,12Z,15Z)-Octadecatrienylglycerone 3-phosphate

[2]

1-(9Z,12Z)-Octadecadienylglycerone 3-phosphate

PubChem CID	86289254
Structure	 2D Find Similar Structures
Molecular Formula	$C_{21}H_{39}O_6P$
Synonyms	1-(9Z,12Z)-octadecadienylglycerone 3-phosphate ChEBI:78164 Q27147665 3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-oxopropyl dihydrogen phosphate
Molecular Weight	418.5 g/mol
Dates	Modify: 2021-03-17 Create: 2014-12-18
1-(9Z,12Z)-octadecadienylglycerone 3-phosphate is a 1-alkylglycerone 3-phosphate in which the alkyl group is specified as (9Z,12Z)-octadecadienyl. It is a conjugate acid of a 1-(9Z,12Z)-octadecadienylglycerone 3-phosphate(2-). ChEBI	

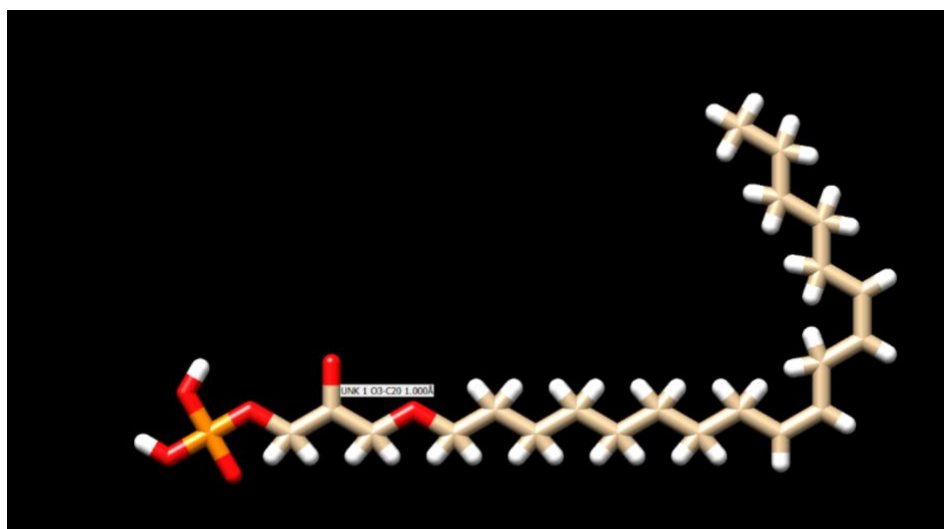
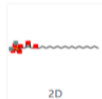


Fig 5.6.2.1-(9Z,12Z)-Octadecadienylglycerone 3 -phosphate

[3]

1-Heptadecylglycerone 3-phosphate

PubChem CID	86289251
Structure	 2D Find Similar Structures
Molecular Formula	C ₂₀ H ₄₁ O ₆ P
Synonyms	1-heptadecylglycerone 3-phosphate CHEBI:78141 3-(heptadecyloxy)-2-oxopropyl dihydrogen phosphate Q27147652
Molecular Weight	408.5 g/mol
Dates	Modify Create 2021-03-17 2014-12-18
1-heptadecylglycerone 3-phosphate is a 1-alkylglycerone 3-phosphate in which the alkyl group is specified as heptadecyl. It is a conjugate acid of a 1-heptadecylglycerone 3-phosphate(2-). ChEBI	

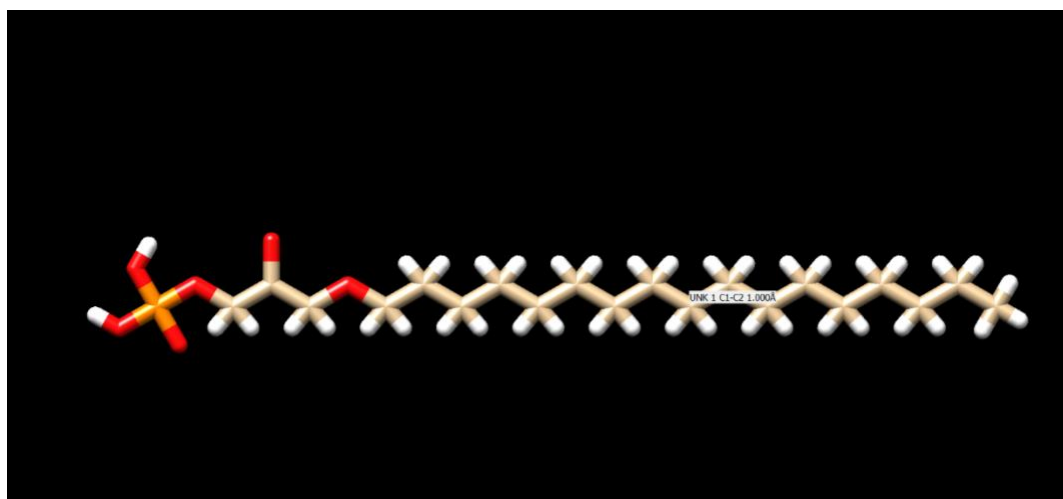


Fig 5.6.3 1-Heptadecylglycerone 3- phosphate

[4]

1-Tetradecylglycerone 3-phosphate(2-)

PubChem CID	86289246
Structure	 2D Find Similar Structures
Molecular Formula	$C_{17}H_{33}O_6P^{2-}$
Synonyms	1-tetradecylglycerone 3-phosphate(2-) 1-O-tetradecyl-DHAP(2-) CHEBI:77467 1-O-tetradecylglycerone 3-phosphate 2-oxo-3-(tetradecyloxy)propyl phosphate More...
Molecular Weight	364.4 g/mol
Parent Compound	 CID 86289247 (1-Tetradecylglycerone 3-phosphate)
Dates	Modify: 2021-03-17 Create: 2014-12-18

1-tetradecylglycerone 3-phosphate(2-) is a 1-alkylglycerone 3-phosphate(2-) obtained by deprotonation of the phosphate OH groups of 1-tetradecylglycerone 3-phosphate; major species at pH 7.3. It is a conjugate base of a 1-tetradecylglycerone 3-

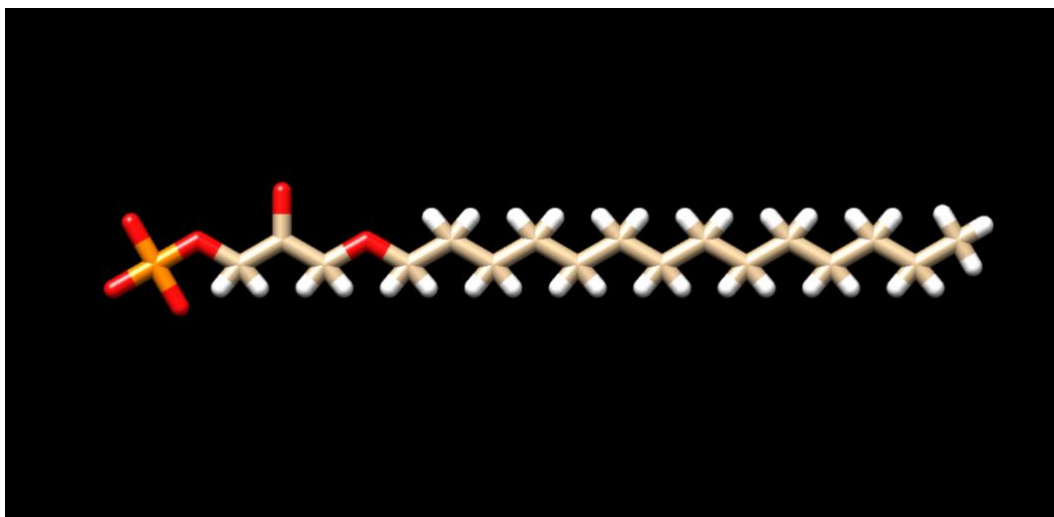


Fig 5.6.4.1-Tetradecylglycerone 3- phosphate (2-)

[5]

1-Pentadecylglycerone 3-phosphate

PubChem CID	86289249
Structure	 20 Find Similar Structures
Molecular Formula	$C_{18}H_{37}O_6P$
Synonyms	1-pentadecylglycerone 3-phosphate ChEBI:78135 2-oxo-3-(pentadecyloxy)propyl dihydrogen phosphate Q27147651
Molecular Weight	380.5 g/mol
Dates	Modify Create 2021-03-17 2014-12-18
1-pentadecylglycerone 3-phosphate is a 1-alkylglycerone 3-phosphate in which the alkyl group is specified as pentadecyl. It is a conjugate acid of a 1-pentadecylglycerone 3-phosphate(2-). ChEBI	

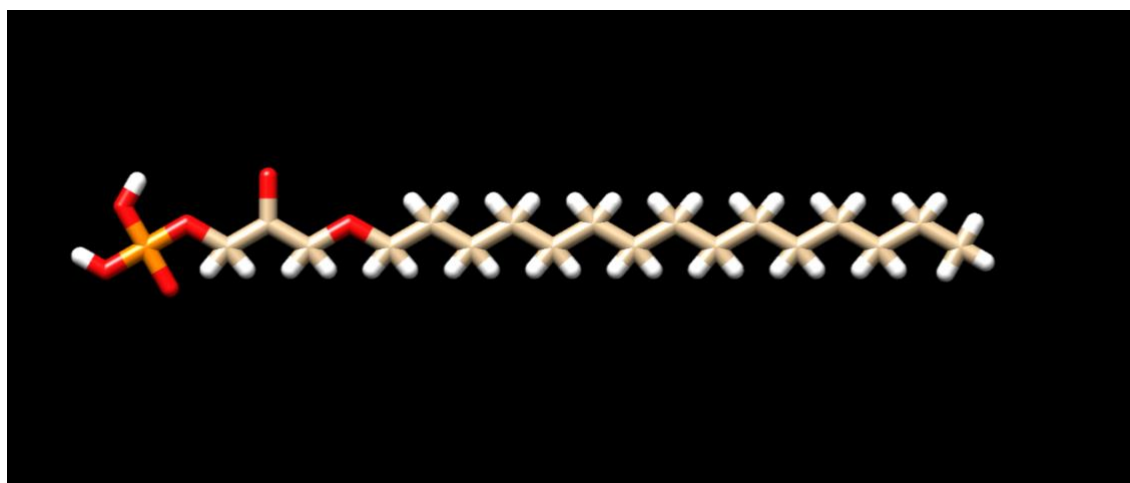


Fig 5.6.5 1-pentadecylglycerone 3- phosphat

[6]

(2r)-3-(Phosphonoxy)propane-1,2-Diyl Dihexanoate

PubChem CID	9547165
Structure	 2D Find Similar Structures
Molecular Formula	C ₁₅ H ₂₉ O ₈ P
Synonyms	1,2-dihexanoyl-sn-glycero-3-phosphate PA(6.0)/6.0) 1,2-Dihexanoyl-sn-glycero-3-phosphatidic acid (2r)-3-(Phosphonoxy)propane-1,2-Diyl Dihexanoate Hexanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, (R)- More...
Molecular Weight	368.36 g/mol
Dates	Modify Create 2021-03-17 2006-08-30
1,2-dihexanoyl-sn-glycero-3-phosphate is a 1,2-diacyl-sn-glycero-3-phosphate in which the acyl groups at positions 1 and 2 are specified as hexanoyl. It is a 1,2-diacyl-sn-glycerol 3-phosphate and a hexanoate ester.	

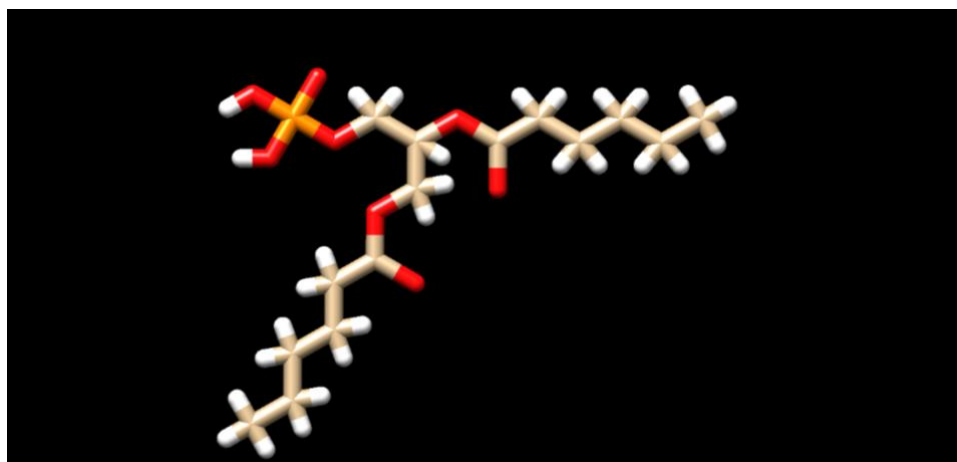
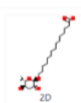


Fig 5.6.6 (2r)-3-(phosphonoxy) propane-1,2-diyl Dihexanoate

[7]

15-[(3,6-Dideoxy- α -L-arabino-hexopyranosyl)oxy]pentadecanoate

PubChem CID	132282462
Structure	 Find Similar Structures
Molecular Formula	C ₂₁ H ₃₉ O ₆
Synonyms	oscr#26(1-) CHEBI:140013 15-[(3,6-dideoxy-α-L-arabino-hexopyranosyl)oxy]pentadecanoate
Molecular Weight	387.5 g/mol
Parent Compound	 CID 86289786 (15-(3'R,5'R-Dihydroxy-6'S-methyl-(2H)-tetrahydropyran-2'-yloxy)-pentadecanoic acid)
Dates	Modify Create 2021-03-17 2018-03-02

Oscr#26(1-) is a hydroxy fatty acid ascaroside anion that is the conjugate base of oscr#26, obtained by deprotonation of the carboxy group; major species at pH 7.3. It is a conjugate base of an oscr#26.

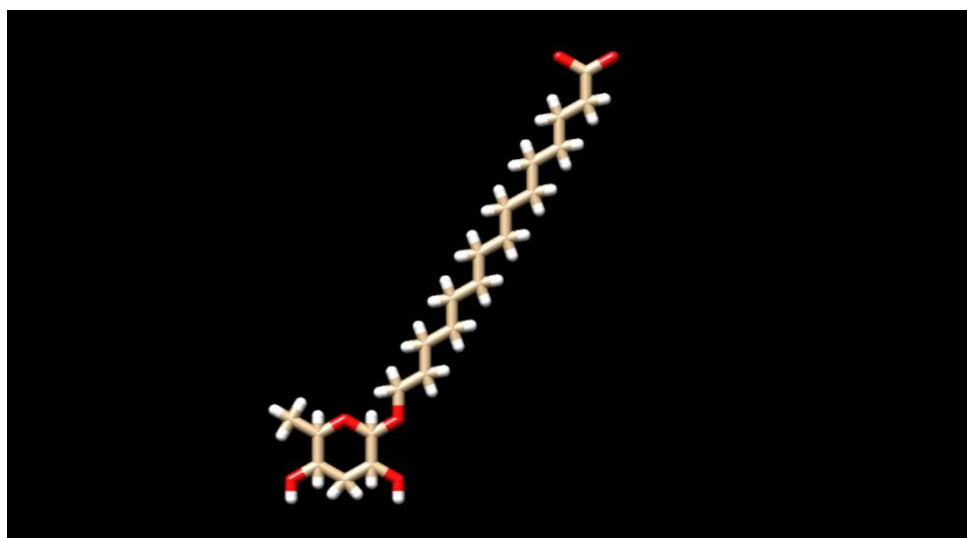


Fig 5.6.7 15-[(3,6-Dideoxy- α -L-arabino-hexopyranosyl) oxy] pentadecanoate

[8]

(8E,10Z,13Z,15E,19Z)-7,17-Bis(hydroperoxy)docosa-8,10,13,15,19-pentaenoate

PubChem CID	132472339
Structure	 2D Find Similar Structures
Molecular Formula	C ₂₂ H ₃₃ O ₆
Synonyms	CHEBI:140381 7,17-diHpDPA(n-3)(1-) 7,17-DHpDPE(n-3)(1-) 7,17-dihydroperoxy-omega3-docosapentaenoate (8E,10Z,13Z,15E,19Z)-7,17-bis(hydroperoxy)docosapentaenoate More...
Molecular Weight	393.5 g/mol
Parent Compound	 CID 132472310 ((8E,10Z,13Z,15E,19Z)-7,17-Bis(hydroperoxy)docosa-8,10,13,15,19-pentaenoic acid)
Dates	Modify 2021-03-17 Create 2018-04-02

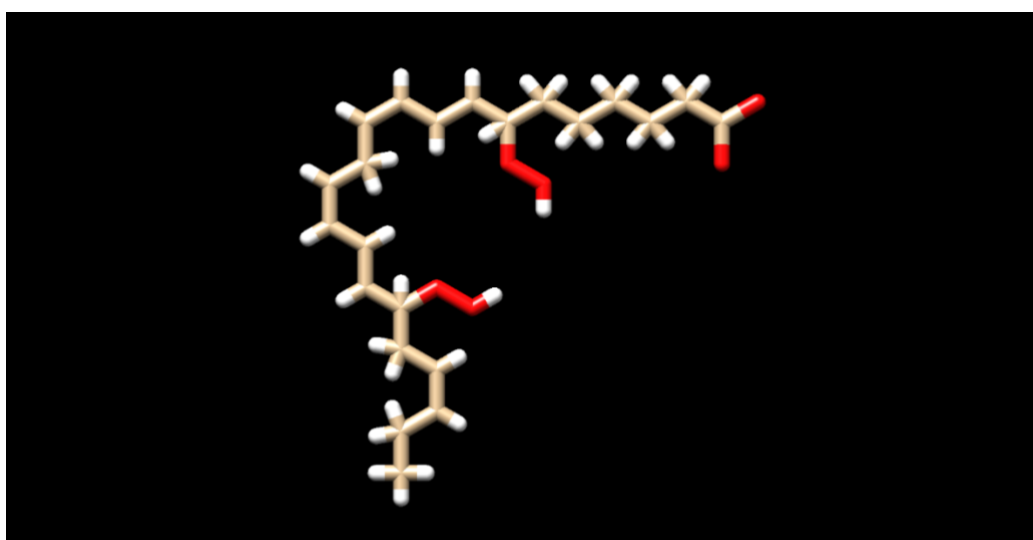


Fig 5.6.8. (8E,10Z,13Z,15E,19Z)-7,17-Bis(hydroperoxy)docosa- 8,10,13,15,19-pentaenoate

[9]

(5S,6Z,8E,12S,14Z)-5,12,20,20,20-Pentahydroxyicosa-6,8,14-trienoate

PubChem CID	122164877
Structure	 2D Find Similar Structures
Molecular Formula	$C_{20}H_{33}O_7^-$
Synonyms	CHEBI:133323 10,11-dihydro-20-trihydroxy-leukotriene B4(1-) 10,11-dihydro-20,20,20-trihydroxyleukotriene B4(1-) (5S,12S,20,20,20)-pentahydroxy-(6Z,8E,14Z)-icosatrienoate (5S,6Z,8E,12S,14Z)-5,12,20,20,20-pentahydroxyicosa-6,8,14-trienoate
Molecular Weight	385.5 g/mol
Parent Compound	 CID 122164878 ((5S,6Z,8E,12S,14Z)-5,12,20,20,20-Pentahydroxyicosa-6,8,14-trienoic acid)
Dates	Modify: 2021-03-17 Create: 2016-10-03

10,11-dihydro-20,20,20-trihydroxyleukotriene B4(1-) is a leukotriene anion that is the conjugate base of 10,11-dihydro-20,20,20-

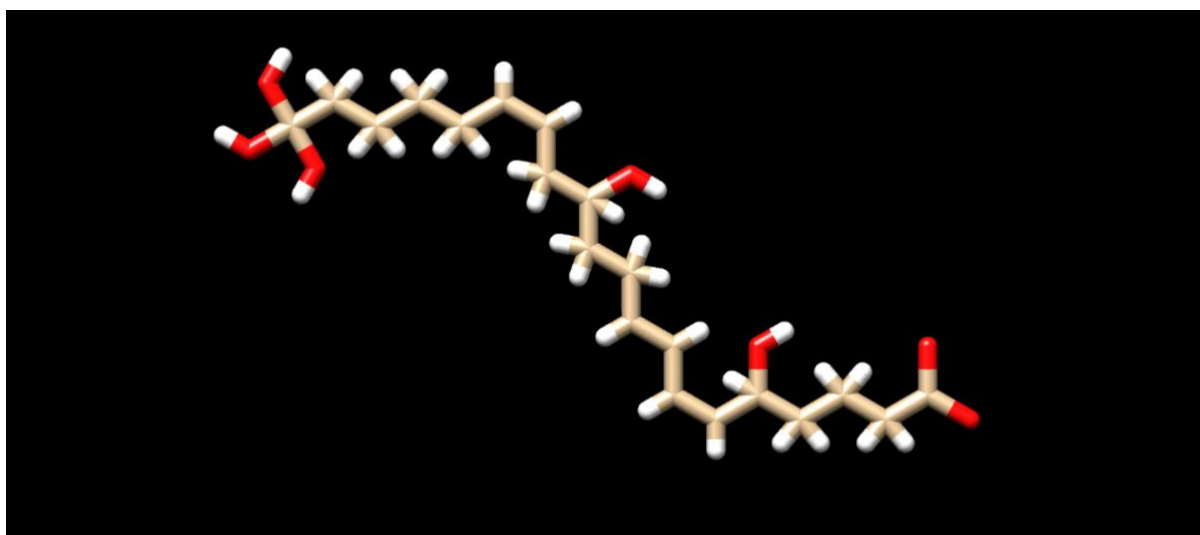


Fig 5.6.9. (5S,6Z,8E,12S,14Z)-5,12,20,20,20-Pentahydroxyicosa-6,8,14-trienoate

ChEMBL	Molecule	Canonical SM	Formula	MW	#Heavy at	#Aromatic	Fraction C	#Rotatable	#H-bond a
CHEBI:78165		<chem>CC/C=C\C/C=C</chem>	C21H37O6P	416.49	28	0	0.67	19	6
CHEBI:78164		<chem>CCCCC/C=C\C</chem>	C21H39O6P	418.5	28	0	0.76	20	6
CHEBI:78141		<chem>CCCCCCCCC</chem>	C20H41O6P	408.51	27	0	0.95	21	6
CHEBI:77467		<chem>CCCCCCCCC</chem>	C17H33O6P	364.41	24	0	0.94	18	6
CHEBI:78135		<chem>CCCCCCCCC</chem>	C18H37O6P	380.46	25	0	0.94	19	6
CHEBI:131508		<chem>CCCCC(=O)C</chem>	C15H29O8P	368.36	24	0	0.87	16	8
CHEBI:140013		<chem>[O-]C(=O)CCC</chem>	C21H39O6	387.53	27	0	0.95	16	6
CHEBI:140381		<chem>CC/C=C\CC/C</chem>	C22H33O6	393.49	28	0	0.5	17	6
CHEBI:133323		<chem>O[C@H](C/C=C</chem>	C20H33O7	385.47	27	0	0.65	16	7

Table 5.7 SWISS-ADME PROPERTIES FOR SELECTED COMPOUNDS

CHAPTER-6

SUMMARY AND DISCUSSION

Multidrug resistance presents quite possibly the main sources of malignant growth treatment disappointment. Various in vitro and in vivo information have clarified that multidrug obstruction is much of the time brought about by upgraded articulation of ATP-restricting tape (ABC) carriers. ABC carriers are film bound proteins associated with cell guard systems, specifically, in outward transport of xenobiotics and physiological substrates. Their capacity accordingly forestalls poisonousness as carcinogenesis on one hand yet may add to the opposition of tumor cells to various medications including chemotherapeutics on the other. Inside 48 individuals from the human ABC superfamily there are a few multidrug resistances related carriers. Because of the very much archived powerlessness of various medications to efflux by means of ABC carriers it is exceptionally attractive to evaluate the situation with ABC carriers for individualization of treatment by their substrates. The multidrug opposition related protein 1 (MRP1) encoded by ABCC1 quality is quite possibly the most considered ABC carriers. there are huge holes in information which block clinical applications. Tissue-explicit examples of articulation and wide hereditary inconstancy make ABCC1/MRP1 an ideal contender for use as a marker or individual from multi-marker board for forecast of chemotherapy opposition. The motivation behind this survey was to sum up examinations about relationship of quality and protein articulation and hereditary inconstancy with anticipation and treatment result of significant malignant growths. Significant advances in the information have been recognized and future exploration headings are featured.

MRP1 predominantly restricts at the basolateral layers of epithelial cells and assumes a significant part in directing the retention and dissemination of different xenobiotics, including numerous restorative specialists and poisons. For tissues with epithelial basolateral layers going up against the blood flow, MRP1 limits the passage of blood-

borne xenobiotics and hence bring down their bioavailability or likely harmful impacts. For example, Mrp1 knockout mice show more noteworthy affectability towards harms of the oropharyngeal mucosal layer and the testicular tubules incited by etoposide, an enemy of malignant growth specialist. In this way, profiling the associations between restorative specialists and MRP1 addresses a significant angle in anticipating and deciding medication bioavailability and Drug–drug collaborations interceded by MRP1. Also, MRP1 is related with clinical MDR of a few sorts of tumors. Resensitization of safe malignancies utilizing MRP1 inhibitors stays a potential road in conquering MDR in chemotherapy, particularly in diseases where MRP1 articulation is unmistakably related with a poor clinical result.

6.1 CONCLUSION

Anticancer treatments experience the ill effects of the continuous multidrug resistance against different drugs. In instance of such a multi drug resistance the quantity of options is low, on the grounds that lone primarily extraordinary enemy of disease medications may not be influenced by the multi drug resistance phenomenon. Primarily epic medications have been uncommon somewhat recently and are generally utilized distinctly if there should be an occurrence of a unique sort of malignancy in the alleged targeted. therapies. An option would be a broader way to deal with switch multi drug resistance. For the most part, multi drug opposition is interceded by transmembrane efflux siphons. A restraint of their movement is a system to battle multi drug obstruction. Inhibitors of such efflux pumps have been looked for, however explored compounds have other pharmacological exercises so their utilization is preposterous in anticancer medication treatments.

- When compared with mk517 total energy value- -120.496, + binding energy -- 5.04481 (MRP-1 inhibitor in market) total 9 molecules showing more binding values.
- Top 3 compounds with more binding energies and hydrogen bonds.

#Ligand	TotalEnergy	VDW	HBond	Elec	AverConPair
• cav2cbz_ATP- 86289256-1268-1.pdb	-150.784	-98.8009	-44.3343	-7.64921	23.1071
• cav2cbz_ATP- 86289254-1267-0.pdb	-150.483	-101.491	-40.9258	-8.06658	23.1786
• cav2cbz_ATP- 86289251-1262-0.pdb	-149.575	-103.035	-38.3291	-8.21136	24.7778

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