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Ovarian Cancer Drug Designing Using PI3 Kinase Catalytic Subunit p110α Through Docking

Vinee Govila

Sam Higginbottom Institute of Agriculture, Technology and Sciences, Rewa Road, Naini, Allahabad 211007, India

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Abstract: For the drug designing for ovarian cancer, finding the inhibitor of PI3 Kinase protein catalytic subunit p110α having interaction with the protein, p110α was docked with a list of inhibitors known to interact with it. After retrieving the sequence and the structure of protein, it was docked with its inhibitors and the inhibitor with best docking results provides best interaction with the PI3 Kinase protein catalytic subunit p110α.

As is evident from AutoDock docking programme in this study, ZSTK474 proves to be the best inhibitor among the others to inhibit PI3 Kinase protein catalytic subunit p110α because it has low docked energy which signifies better interaction of ligand with the protein. The present article provides general information regarding the ovarian cancer and also includes various existing information collected from various databases.

Keywords: Ovarian cancer, PI3 kinase, p110α, Computer aided drug designing

Ovarian cancer is a growth of abnormal malignant cells that begins in the ovaries (women's reproductive glands that produce ova). Cancer that spreads to the ovaries but originates at another site is not considered ovarian cancer. Ovarian tumors can be benign or malignant (Abramowicz and Timmerman, 2017). Cancer has become an important Public Health Problem with over 800,000 new cases occurring every year, and is one of the ten leading causes of death in India (Uma Devi, 2009),. At any point of time, it is estimated that there are nearly 2.5 million cases in the country with nearly 400,000 deaths occurring due to cancer. Cancer incidence in India is estimated to be around 70-90 per 100,000 populations. According to Ramnath Takiar *et al*. (2010), the estimated Number of Gynaecological Related Cancers by Years - India - (2010-2020) are shown below:

Cancer Site	2010	2015	2020
Vulva	1,792	1,920	2,092
Vagina	2,238	2,439	2,657
Crevix	103,821	113,138	123,291
Corpus Uteri	14,848	16,181	17,533
Ovary	30,482	33,218	36,199
Placenta	484	527	574
Breast	90,659	106,124	123,634

Phosphoinositide 3-Kinase (PI3-kinase)

Foster *et al.* (2003) pointed out that Phosphoinositide (PI) 3-kinase was first observed in 1984 as a minor inositol lipid kinase activity associated with immunoprecipitated oncogene products (e.g. Src, Abl and polyoma mT antigen) and present in activated growth factor receptor complexes (e.g. PDGF receptor). In 1988, the enzyme associated with this activity was found to have the novel ability to phosphorylate the 3 position hydroxyl group of the inositol ring of phosphatidylinositol (PtdIns). PI 3- kinase activities have been subsequently found in all eukaryotic cell types. The emerging links between PI 3-kinase activity and many human maladies, including allergy, inflammation, heart disease and cancer, has made them the focus of intense study, and inhibitors of these enzymes are considered potential therapeutic agents Foster *et al.* (2003).

According to Hennessy *et al.* (2005), the PI3K family constitutes a large family of lipid and serine/threonine kinases, which includes a number of phosphatidylinositol kinases, as well as the related DNA-dependent protein, ataxia telangiectasiamutated (ATM) and ataxia telangiectasia and Rad3 related (ATR) kinases1–4. Class 1A PI3Ks are composed of heterodimers of an inhibitory adaptor/regulatory (p85) and a catalytic (p110) subunit. p85 binds and integrates signals from various cellular proteins, including transmembrane tyrosine kinase-linked receptors and intracellular proteins such as protein kinase C (PKC), SHP1, Rac, Rho, hormonal receptors, mutated Ras and Src, providing an integration point for activation of p110 and downstream molecules. The SH2 domain of p85 has two major divergent functional activities: activation of small G-proteins and relief of *trans*-inhibition of p110.

Upon activation, PI3Ks phosphorylate phosphatidylinositol-4,5-bisphosphate (PtdIns (4,5)P_2) to produce PtdIns(3,4,5)P3, a second messenger that binds a subset of pleckstrin-homology (PH), FYVE, Phox (PX), C1, C2 and other lipid-binding domains in downstream targets to recruit them to the activation nidus at the membrane. The PH domain is the predominant domain involved in this interaction although only a subset of PH domains bind to PtdIns(3,4,5)P3, providing one level of specificity to the interaction. Genetic screens in model organisms have identified AKT as the primary downstream mediator of the effects of PI3K; however, the presence of a large number of proteins with FYVE, PH and other lipid binding domains that interact with PtdIns(3,4,5)P3 suggest additional crucial targets. PtdIns(3,4,5) P3 is subsequently metabolized by SHIP-1 and -2 to generate PtdIns(3,4)P2, which regulates a separate subset of PH domains and thus downstream signaling molecules. PTEN dephosphorylates the 3′OH group phosphorylated by PI3K, acting as the 'yin' tumour suppressor to the 'yang' oncogene, PI3K.

There are three known isoforms of Class IA p110 (p110α/p110β/p110δ), which contain an amino-terminal p85/p55-interacting region, a domain that binds to Ras, a 'PIK domain' homologous to other phosphoinositide kinases, and a carboxy-terminal catalytic domain. Class 1B PI3Ks consist of p110γ and a regulatory subunit, p101, and are activated directly by G-protein-

coupled receptors and indirectly by other receptors.

Class II PI3Ks are monomeric, lack adapter subunits and preferentially use PtdIns and PtdIns(4)P as substrates. Three mammalian class II isoforms have been identified: the ubiquitously expressed PI3K-C2α and PI3K-C2β, and liver-specific PI3K-C2γ. Class III PI3Ks are heterodimeric enzymes consisting of adaptor (p150) and catalytic (Vps34, 100 kDa) subunits (Hennesey *et al.*, 2005). Kang *et al.* **(**2005) idnentified that mutations in genes that encode components of the phosphatidyl-inositol 3-kinase (PI3-kinase) signaling pathway are common in human cancer. *PIK3CA*, which encodes for the catalytic subunit p110α of class IA PI3-kinase, is amplified and overexpressed in some cases of ovarian cancer. Mutations in the regulatory subunit p85 of PI3-Kinase, that in PTEN a lipid phosphate counteracting the activity of PI3-Kinase, or overexpression of Akt, a downstream effector of PI3-Kinase have been identified in ovarian, breast, colon and other type of cancers. They determined the growth-regulatory and signaling properties of the three most frequently observed PI3-kinase mutations: E542K, E545K, and H1047R. Expressed in chicken embryo fibroblasts, all three mutants induce oncogenic transformation with high efficiency. This transforming ability is correlated with elevated catalytic activity in *in vitro* kinase assays. The mutant-transformed cells show constitutive phosphorylation of Akt, of p70 S6 kinase, and of the 4E-binding protein 1. Phosphorylation of S6 kinase and of 4E-binding protein 1 is regulated by the target of rapamycin (TOR) kinase and affects rates of protein synthesis. The inhibitor of TOR, rapamycin, strongly interferes with cellular transformation induced by the PI3-kinase mutants, suggesting that the TOR and its downstream targets are essential components of the transformation process. The oncogenic transforming activity makes the mutated PI3-kinase proteins promising targets for small molecule inhibitors that could be developed into effective and highly specific anticancer drugs (Kang *et al.***,** 2005).

Kingsbury and Gout (2003) explained that cellular functions are controlled by a network of signaling pathways, which allow cells to interact with and respond to their external environment. These pathways are mediated by proteins that activate signaling cascades in response to external stimuli. One such protein is phosphoinositide 3-kinase (PI3K), a lipid kinase which exits in a number of different isoforms and participates in the modification of phospholipids. These secondary messengers are involved in signaling pathways which regulate cell growth, proliferation, differentiation, cytoskeletal re-arrangements, metabolic control, vesicular transport, membrane trafficking and apoptosis. Dysregulation of these signaling cascades can lead to abnormal cell cycle progression, altered cell mobility and adhesion properties, induction of angiogenesis and inhibition of apoptosis. The involvement of PI3K and the products of its activities in these processes points to a role of PI3K in a number of pathological disorders, including cancer Kingsbury and Gout (2003).

Masahiro *et al.* (2009) studied the requirements for the oncogenic effects of PI3K.They explained that the coding of retroviral oncogene p3k (v-p3k) of avian sarcoma virus 16 (ASV16) for the catalytic

subunit of phosphoinositide (PI) 3-Kinase, p110α, established an active role of PI 3-Kinase in oncogenic transformation. v-p3k was cloned from the genome of ASV16, an agent causing hemangiosarcomas in chickens. The v-P3k protein differs from its cellular counterpart c-P3k, in two major points – (i) The first 13 amino acids of c-P3k deleted are in v-P3k and replaced by retroviral Gag sequences, and (ii) v-P3k carries several amino acid substitutions; they are located outside the kinase domain. Expression of v-p3k induces oncogenic transformation in cultures of chicken embryo fibroblasts (CEF) and hemangiosarcomas in young chickens, suggesting that a constitutively active PI 3-kinase is sufficient for the transformation of chicken cells.

Findings of Masahiro *et al.* (2009) further support the involvement of PI 3-kinase in development of cancer. These include amplification of PIK3CA, the human counterpart of the human counterpart of c-*p3k*, in human ovarian cancer cell lines. Mutations that inactivate lipid kinase activity abolish oncogenicity. The transforming activity of P3k is correlated with the ability to induce activating phosphorylation in Akt. Point mutations and amino-terminal deletions recorded in v-P3k were shown to be irrelevant to the activation of oncogenic potential. Interactions of P3k with the regulatory subunit of PI 3-kinase, p85, or with Ras are not required for transformation. These results support the conclusion that the oncogenicity of P3k depends on constitutive lipid kinase activity. Akt is an important and probably essential downstream component of the oncogenic signal from P3k.

Kong and Yamori (2008) pointed out that Phosphatidylinositol 3-kinases (PI3K) are a group of lipid kinases that phosphorylate phosphoinositides at the 3-hydroxyl group of the inositol ring to generate phosphatidylinositol 3,4,5-trisphosphate, a second messenger with key roles in fundamental cellular responses such as cell proliferation and metabolism. Frequent mutations found in or amplification of the *PIK3CA* gene and loss of phosphatase and tensin homolog deleted on chromosome 10 function in human tumors suggest that PI3K is a potential target for cancer therapy. During the last 5 years, several specific PI3K inhibitors were developed that were directed against various diseases. Some of them revealed potent anticancer efficacy and are now undergoing clinical trials. Some PI3K inhibitors showed antiangiogenic effects. Combined use of PI3K inhibitors with other chemotherapeutic agents or with radiotherapy produced synergistic therapeutic efficacies in treating cancer and showed reduced side effects. The rapid progress made in developing novel PI3K inhibitors in recent years promises bright prospects for finding a PI3K-targeted anticancer drug in the near future. Foremost inhibitors of PI3K in cancer were recognized as LY294002, Wortmannin, PX-866, PI-103, NVP-BEZ235, SF1126 and ZSTK 474 (Kong and Yamori, 2008).

In yet another effort to study the oncogenic effects of p110α subunit of PI3K, Minghao *et al.* (2010) studied that Cancer-specific mutations in the iSH2 (inter-SH2) and nSH2 (N-terminal SH2) domains of p85α, the regulatory subunit of phosphatidylinositide 3- kinase (PI3K), show gain of function. They

induce oncogenic cellular transformation, stimulate cellular proliferation, and enhance PI3K signaling. Quantitative determinations of oncogenic activity reveal large differences between individual mutants of p85α. The mutant proteins are still able to bind to the catalytic subunits p110α and p110β. Studies with isoform-specific inhibitors of p110 suggest that expression of p85 mutants in fibroblasts leads exclusively to an activation of p110α, which is the sole mediator of p85 mutant-induced oncogenic transformation. The characteristics of the p85 mutants are in agreement with the hypothesis that the mutations weaken an inhibitory interaction between p85α and p110α while preserving the stabilizing interaction between p85α iSH2 and the adapter-binding domain of p110α.

PI 3-Kinase catalytic subunit, p110α as a drug target

Chuan-Hsiang *et al.* (2008) reported that sequencing of PI3K genes in a variety of human cancers revealed a high frequency of mutations in the *PIK3CA* gene, which codes for p110α. In cancers such as colorectal, breast, and hepatocellular carcinomas these mutations occur in 30% of all tumors examined, making *PIK3CA* one of the two most frequently mutated oncogenes together with K-Ras. *In vitro* and *in vivo* studies show that most cancer-associated *PIK3CA* mutations lead to enhanced enzymatic activity, upregulation of the signaling cascade, and oncogenic transformation of cells. Due to the importance of the PI3K-AKT pathway in tumorigenesis and the high frequency of p110α mutations in human cancers, small molecule inhibition of PI3Kα is regarded as a promising strategy for cancer treatment (Chuan-Hsiang *et al.*, 2008).

Drugs available against the selected target

Several drugs like BEZ-235, PI-103, PX866, Wortmannin, etc. are available against the selected target.

Computer Aided Drug Designing (CADD)

It is generally recognized that drug discovery and development are very time consuming processes (Kapetanovic, 2008). There is an ever growing effort to apply computational power to the combined chemical and biological space in order to streamline drug discovery, design, development and optimization. In biomedical arena, computer-aided or in silico design is being utilized to expedite and facilitate hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion and toxicity profile and avoid safety issues. Regulatory agencies as well as pharmaceutical industry are actively involved in development of computational tools that will improve effectiveness and efficiency of drug discovery and development process, decrease use of animals, and increase predictability. It is expected that the power of CADDD will grow as the technology continues to evolve.

Retrieval of Protein Sequence of Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform

Sequence of Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform is retrieved through Swiss-Prot (*http://www.expasy.ch*).

Retrieval of data, structure and Inhibitors of PI 3-Kinase catalytic subunit, p110α

PubMed

PubMed is a free digital archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health (NIH), developed

and managed by NIH's National Center for Biotechnology Information (NCBI) in the National Library of Medicine (NLM). PubMed is a free search engine for accessing the MEDLINE database of citations and abstracts of biomedical research articles.

Representation of Pubmed

Protein Data Bank

The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc.

Representation Of PDB

NCBI Pubchem Compound

PubChem Structure Search allows PubChem Compound Database to be queried using a chemical structure. Chemical structure queries may be sketched using the PubChem Sketcher. Anyone can specify the structural query input by PubChem Compound Identifier (CID), SMILES, SMARTS, InChI, Molecular Formula, or by upload of a supported structure file format. This standardizing allows NCBI to compute chemical parameters and similarity relationships between compounds.

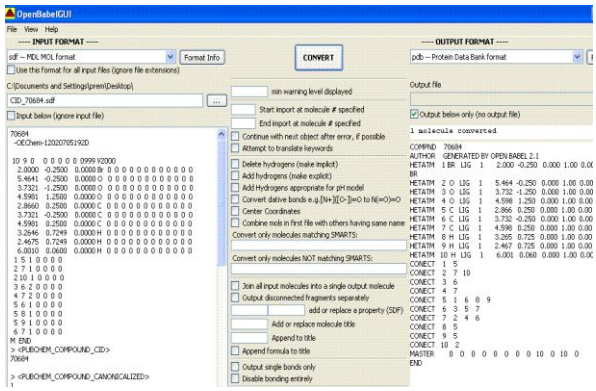
Representation of NCBI PubChem Compound

Building of 3D structure (PDB file) of Inhibitors

Structure of potent inhibitors are obtained by submitting the name of inhibitor to NCBI's Pubchem compound and save it in SDF format then later it is converted into PDB format through Babel Molecule Format Convertor software, which is freely available.

Babel Molecule Format Converter

Babel is a cross-platform program designed to interconvert between many file formats and is used in molecular modeling and computational chemistry and related areas. Babel is a chemical toolbox designed to allow anyone to convert, analyze, or store data from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas Interface of Babel Molecular format converter for converting SDF format to PDB format is shown below:



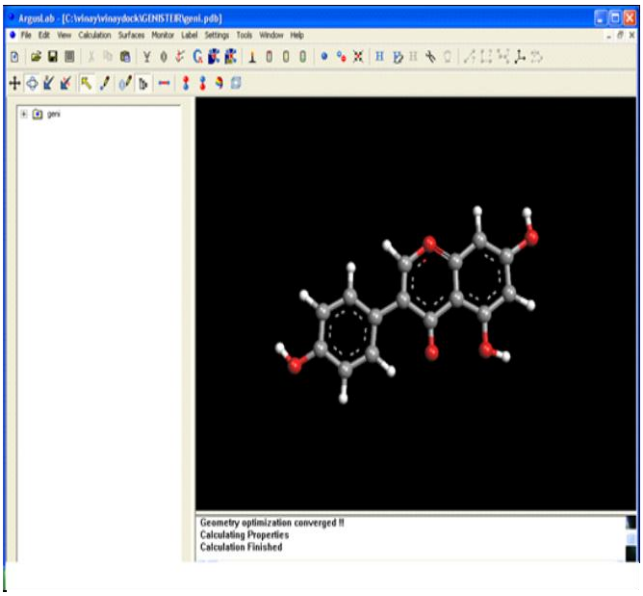
Input format of Babel Molecule Format Converter

Optimization of Inhibitors

Optimization means, trying to find maxima and minima of a function after a number of inhibitor compounds have been found, SBDD techniques are especially effective in refining their 3D structures to improve binding to protein active sites, a process known as lead optimization. In lead optimization researchers systematically modify the structure of the lead compound, by some software docking each specific configuration of a drug compound in a protein's active site, and then testing how well each configuration binds to the site. In a common lead optimization method known as bioisosteric replacement, specific functional groups in a ligand are substituted for other groups to improve the binding characteristics of the ligand. With SBDD researchers can examine the various bioisosteres and their docking configurations, choosing only those that bind well in the active site we have optimize inhibitors with help of Argus Lab.

Argus Lab

Argus Lab is a molecular modeling program that runs on Windows 98, NT, and 2000. Argus Lab consists of a user interface that supports OpenGL graphics display of molecule structures and runs quantum mechanical calculations using the Argus compute server.



Window showing optimization of protein by Argus Lab

The Argus compute server is constructed using the Microsoft Component Object Model (COM).

Retrieval of Active Site Residues in PI 3-Kinase catalytic subunit, p110α (through literature)

According to Zunder *et al.* (2008), p110a (PIK3CA) is the most frequently mutated kinase in human cancer, and numerous drugs targeting this kinase are currently in preclinical development or early-stage clinical trials. Clinical resistance to protein kinase inhibitors frequently results from point mutations that block drug binding. Similar

mutations in p110a are likely, but currently none has been reported. Using a *Saccharomyces cerevisiae* screen against a structurally diverse panel of PI3K inhibitors like PIK-90, PI-103, PIK-75 etc. and identifie\cation of a potential hotspot for resistance mutations (I800), a drug-sensitizing mutation (L814C), and a surprising lack of resistance mutations at the ‘‘gatekeeper’’ residue which was found to be I848 by sequence alignment. I848 appeared relatively intolerant to mutation, so in the screening seven additional residues surrounding the p110α affinity pocket were included. These residues were chosen because the affinity pocket is occupied by most potent PI3K inhibitors, but not by ATP, making it a likely site for drug-resistant mutations. I800, L807, L814, Y836, G837, C838, and I848 were chosen based on proximity to the affinity pocket and lack of interaction with the catalytic K802, DFG motif (responsible for Mg^{2+} coordination) or ATP. One additional residue outside the affinity pocket, S854, was chosen due to possible inhibitor-specific H bonds. These eight residues are highly conserved in the PI3K family and almost 100% identical among the p110 isoforms. The chosen residues were mutagenized and screened against PI3K inhibitors. The analysis further reveals that clinical resistance to these drugs may be attenuated by using multitargeted inhibitors that simultaneously inhibit additional PI3K pathway members.

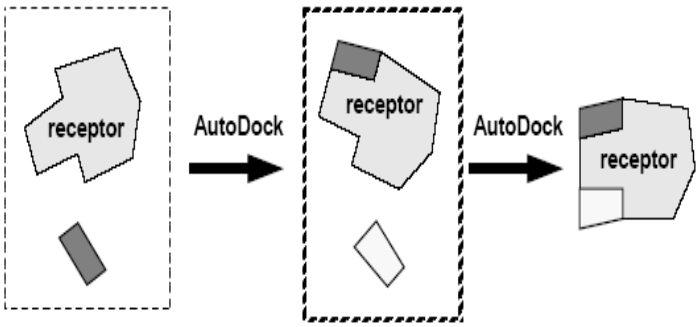
Docking of Flexible Ligands to the Receptors

Theory of Docking

Three-dimensional molecular structure is one of the foundations of structure-based drug design. Often, data are available for the shape of a protein and a drug separately, but not for the two together. Docking is the process by which two molecules fit together in 3D space.

There are an estimated 15,700 known protein-protein interactions in humans only, therefore, understanding such interactions is important for insights into molecular recognition and networks such as signal transduction pathways in cells. To assist in studying protein interactions, we can use DOCK programs for protein-protein docking as well as complementary tools, Evolutionary trace, Profiles-3D etc. Overall, we find protein-protein docking and complementary tools are useful to study protein-protein interactions of unknown complex assemblies.

The original procedure developed for AutoDock used a Monte Carlo (MC) simulated annealing (SA) technique for configurational exploration with a rapid energy evaluation using grid-based molecular affinity potentials. It thus combined the advantages of exploring a large search space and a robust energy evaluation. This has proven to be a powerful approach to the problem of docking a flexible substrate into the binding site of a static protein.



Binding of Receptor to Ligand through AutoDock

Receptor: It is a protein on the cell membrane or within the cytoplasm or cell nucleus that binds to a specific molecule (a ligand), such as a neurotransmitter, hormone, or other

substance, and initiates the cellular response to the ligand.

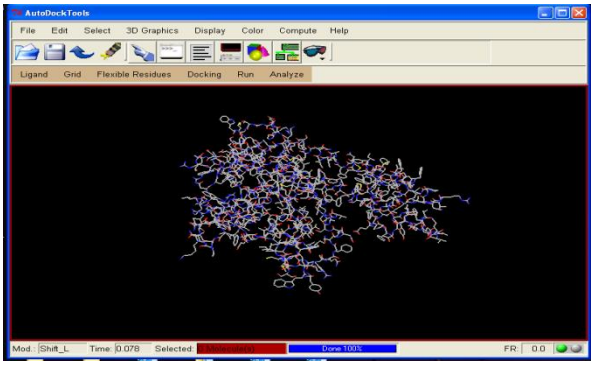
Ligand: Ligand is a molecule that binds specifically to a receptor site of another cell, which allows for cell-to-cell recognition.

AutoDock 3.0.5

AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. AutoDock actually consists of two main programs: AutoDock performs the docking of the ligand to a set of grids describing the target protein; Auto Grid pre-calculates these grids. In additions to using them for docking, the atomic affinity grids can be visualized. This can help, for example, to guide organic synthetic chemists design better binders.

AutoDock Tools

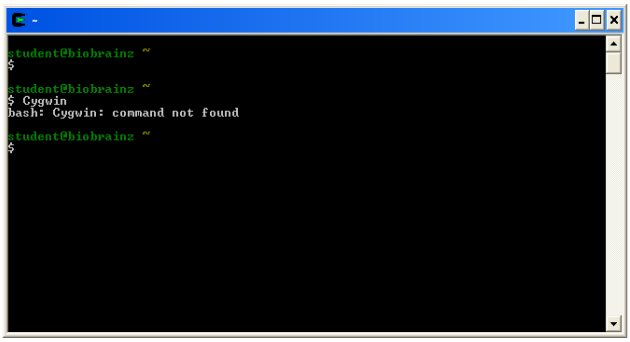
AutoDock Tools, or ADT, is the free GUI for AutoDock developed by the same laboratory that develops AutoDock. We can use it to set up, run and analyze AutoDock dockings and isocontour AutoGrid affinity maps, as well as compute molecular surfaces, display secondary structure ribbons, compute hydrogen-bonds, and do many more useful things.



Interface of AutoDock Tool

Cygwin

Cygwin is a collection of free software tools originally developed by Cygnus Solutions to allow various versions of Microsoft Windows to act similar to a Unix system. It aims mainly at porting software that runs on POSIX systems (such as Linux, BSD, and Unix systems) to run on Windows with little more than a recompilation.

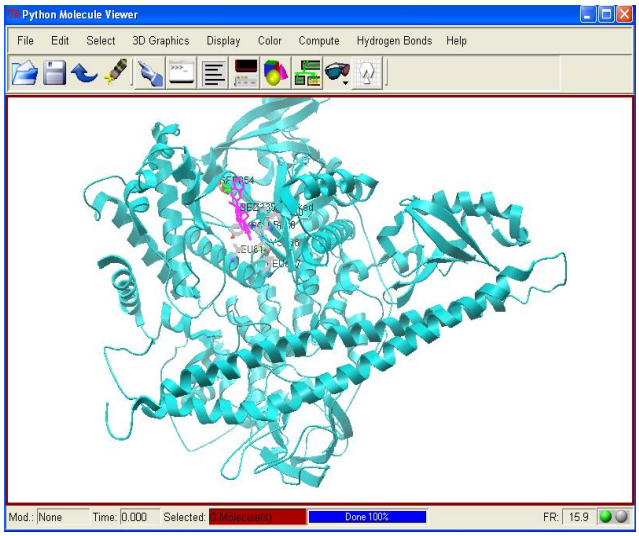


Interface of Cygwin

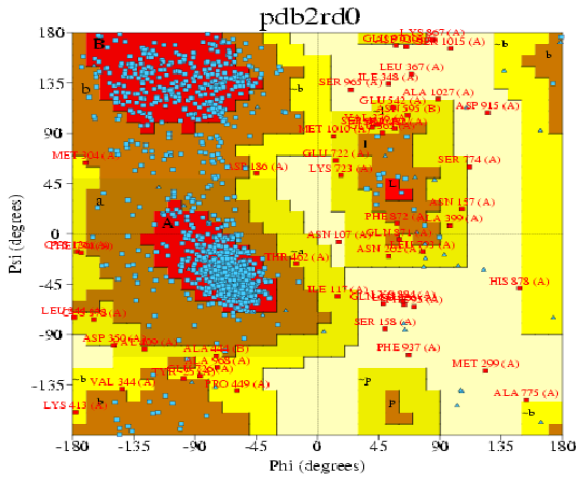
Visualization of Autodock Result

PMV (Python Molecular Viewer)

Python Molecular Viewer is a tool to view the binding of hydrogen bonds in the target molecule. It helps to visualize and analyze the hydrogen bonds. The process of operation of PMV is enlisted below:

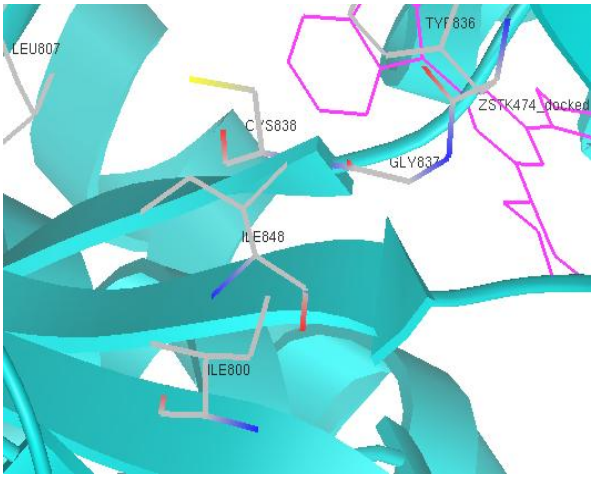


Interface of PMV



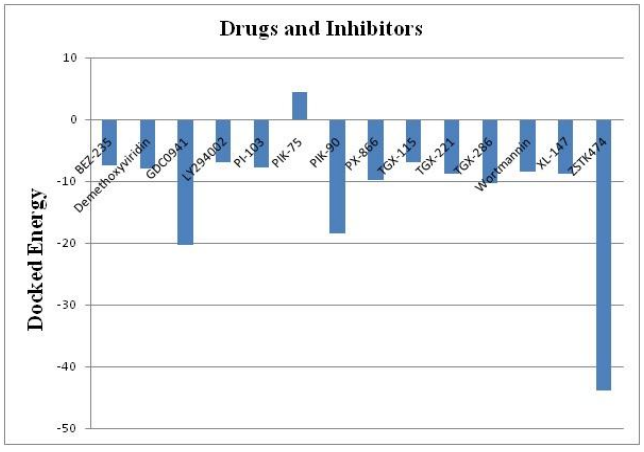
PROCHECK summary 2rd0 for (Ramachandran plot)

Python Molecular Viewer (PMV) Result



Docking Model of inhibitor ZSTK474 into the PI3-kinase Protein catalytic subunit P110α active site

Graphical Representation Of AutoDock Results



Graphical representation of AutoDock results

PI3 Kinase protein catalytic subunit p110α subunit plays a very important role in Ovarian Cancer, therefore it can be widely used as a drug target. Many inhibitors have been recognized to have this protein as their target. According to the docking studies ZSTK474 was found to be the best inhibitor due to low docking energy.

Pharmaceutical companies prefer to use best docking softwares so as to design new drugs with excellent efficacy and with low prices. Rational drug designing strategies help to find out the best inhibitor for any disease and also reduces the cost of the drugs for the disease; therefore this area provides vast opportunities in research and designing of drugs.

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