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IDENTIFICATION OF NEW ANTAGONIST AGAINST LUNG CANCER THORUGH MOLECULAR DOCKING AND PHARMACOPHORE MODELLING APPROACH

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ABSTRACT

Lung Cancer is one of the most common Cancers in the world. It is a leading cause of cancer death in men and women in the United States. Cigarette Smoking causes most lung cancer.The more cigarettes you smoke per day and the earlier you started smoking, the greater your risk of lung cancer. High levels of pollution, radiation and asbestos exposure may also increase risk

HDAC2 gene product belongs to the Histone deacetylase family. Histone deacetylases act via the formation of large multiprotein complexes and are responsible for the deacetylation of lysine residues at the N-Terminal regions of core histone (H2A,H2B,H3&H4). This Protein forms transcriptional repressor complexes by associating with many different proteins, a mammalian Zinc-finger transcriptional factor.Thus,it plays an important role in transcriptional regulation,cell cycle progression and development events. Alternative splicing results in multiple transcript variants.

Analysis of docking results reveals that the all predicted molecules binding well in the active site of HDAC2 (PDBID: 5IWG) all ligand active site residues, the molecule ZINC000010120338 showed strong binding energy and pharmacophore generation was performe with six features and by auto search 178 Unique compounds hits were obtained. These Zinc database compounds may act as potential anti-cancer agents to treat lung Cacer.

KEY WORDS: Lung Cancer, Molecular Docking, Pharmacophore Modelling.

INTRODUCTION:

Cancer is caused by changes to the DNA within the cells by accumulated damage to genes. Cancer is caused by certain changes to genes, in which uncontrolled growth and divisions of cells occur. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally human cells grow & divide to form new cells as the body needs them. Cancerous tumors are malignant, which means they can spread into or invade nearby tissues. In addition, as these tumors grow, some cancer cells can break off and travel to distant places in the body through the blood or the lymph system and form new tumors.

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The substance that causes the cancer called Carcinogens. Carcinogens may be chemical substances, such as certain molecules in tobacco smoke.

Lung Cancer:

Lung cancer is a disease in which certain cells in the lungs become abnormal and, multiply uncontrollably to form a tumour. Lung cancer is the most common cancer in the world. Lung cancer begins in the lungs and may spread to lymph nodes (or) other organs in the body, such as the brain. When cancer cells spread from one organ to another, they are called Metastases. Lung cancer is a malignant tumour developed in the lung which is caused due to uncontrollable growth of cells within the lung tissues.

Lung cancer is generally divided into two types such as Small cell lung cancer and Non-small cell lung cancer, based on the size of the affected cells when viewed under a microscope. Non-small cell lung cancer accounts for 85% of lung cancer, while small cell lung cancer accounts for the remaining 15%.

Small cell lung cancer:

This cancer grows quickly and in more than half of cases the cancer has spread beyond the lung by the time the condition is diagnosed. Small cell lung cancer often Metastasize, most commonly to the liver, brain, bones and adrenal glands. After diagnosis, most people with small cell lung cancer survive for about 1year in those less than seven percent survive 5years.

Non-small cell lung cancer is divided into 3main sub types:

- Adeno Carcinoma
- Squamous cell carcinoma
- Large cell lung carcinoma

Adeno carcinoma: This arises from the cells that line the small air sacs (alveoli) located throughout the lungs.

Squamous cell carcinoma: This cancer arises from squamous cells that line the passages leading from the windpipe (trachea) to the lungs (bronchi).

Large cell carcinoma arises from epithelial cells that line the lungs. Large cell carcinoma encompasses Non-small Cell lung cancers that don't appear to be adeno carcinoma or squamous cell carcinomas. The 5-year survival rate for people with NSCLC is usually between 11 & 17 percent; it can be lower or higher depending on the subtype and stage of the cancer.

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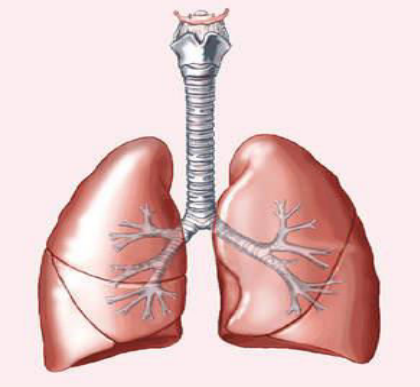
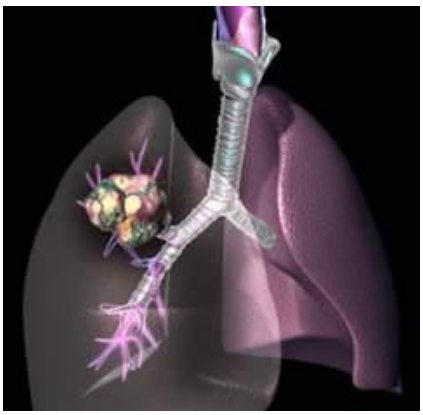


Normal Lung



Cancer lung

Primary versus Secondary lung cancer:

Primary lung cancer starts in the lungs. The Cancer cells are abnormal lung cells. Sometimes people will have Cancer travel from another part of their body or metastases size to their lungs. This is called Secondary lung cancer because the lungs are secondary site compared to the original Primary location of the cancer.

NSCLC is most commonly staged using a system called TNM classification:

T - Tumour size and location.

N - The number of nearby lymph nodes that have become involved.

M - Metastasis, or how far cancer has spread.

The stages in Non-small cell lung cancer are of four kinds.

Stage 1 is when the tumour is in a single lung, and has not spread to any lymph nodes or distant organs.

Stage 2 means that cancer has spread to the lymph nodes inside the lung, but has not spread to any distant organs.

Stage 3 is diagnosed when cancer has spread to lymph nodes at the center of the chest, but has not spread to any distant organs.

In **stage 3a**, cancer has not spread to the opposite side of the body.

In **stage 3b**, it has spread to lymph nodes in the opposite lung, and has progressed above the collar bone to the throat and neck.

Stage 4 is diagnosed when cancer has spread throughout the body.

The stages in Small cell lung cancer are of two kinds: Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer cases. The most common staging system for SCLC breaks the disease down into two categories:

- **Limited stage**, when there is cancer on only one side of the chest.
- **Extensive stage**, when cancer has spread to the opposite side of the body.

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Common symptoms of lung cancer includes Wheezing, Chest pain for an extended period, Swelling in face and neck, Trouble during Swallowing, Repeated respiratory infections such as Pneumonia, Weakness in shoulders and arms, Coughing up blood, Weight loss, Hoarseness, A Severe head ache, Joint pain etc.,

Causes of Lung Cancer: Many factors are responsible for lung cancer and they include.
Smoking: It can be considered as one of the primary patrons for lung cancer. A person who inhales smoke While another persons. Smoking may also be caused to the type of cancer.
Air Pollution: Pollution due to traffic fumes, factories etc., and its contribution is less for rising lung disease in recent times.
Other Causes: Due to a production of rubber Toxic gases, incomplete combustion of coal and due to different kinds of metals.

FDA Approved Drugs for Lung Cancer

1) Abraxane(Paclitaxel Albumin-Stabilized Nanoparticle formulation), Afatinib Dimaleate (Gilotrif), Afinitor (Everolimus), Alecensa (Alectinib), Alimta, Alunbrig (Brigatinib), Carboplatin, Ceritinib, Crizotinib, Dabrafenib, Dacomitinib, Docetoxel, Erlotinib Hydrochloride, Gefitinib (Iressa), Gemzar, Lorbrena (Lorlatinib), Mechlorethamine Hydrochloride, Mekinist, Methotrexate, Navelbine(vinorelbine Tartrate) Etc.,

Disease Pathway

Lung cancer begins with exposure to Carcinogens. The most significant contributor is cigarette smoke, accounting for 85% of lung cancer cases. Additional risks include exposure to pollutants such as asbestos and tar, as well as metals such as arsenic and chromium. Environmental exposure is often compounded by genetic susceptibility in those who develop lung cancer. Small cell and Non-Small cell lung cancers arise from different cell types and have different cell types and have different clinical features. SCLC form central tumours while NSCLC can form both central and peripheral tumours. SCLC metastasizes rapidly, but often responds well to Chemotherapy. NSCLC is less metastatic but is less responsive to Chemotherapy. Both SCLC and NSCLC can cause para neoplastic syndrome.

MATERIALS AND METHODS:

The main Objectives of Current Work includes

- Identification of Target protein.
- Modelling of Pharmacophore using Pharmit server.
- Screening of ZINC database based on the Pharmacophore model.
- Identification of best suitable ligands from screening.
- Characterising protein ligand binding interactions using molecular docking.

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Identification of Target Protein

HDAC2 is highly up-regulated in lung cancer. HDAC2 inactivation resulted in regression of tumour cell growth and activation of cellular apoptosis Via P53 and Wax activation and BCL_2 Suppression.

Functions of Target Protein:

HDAC2 act as a transcriptional repressor through the deacetylation of lysine residues present at the N-terminal tail of histone proteins (H2A, H2B, H3 and H4). HDAC2 regulates gene expression through the de acetylation of specific transcription factors that include STAT3 and SMAD7. HDAC2 containing complexes are also implicated the gene transcription regulation mediated by nuclear receptor. HDAC2 is also a key regulator of nervous system function acting as a repressor of synaptic plasticity genes.

Inhibitor of Target Protein:

HDAC2 are a class of inhibitors enzymes that remove acetyl groups from an N-Acetyl lysine amino acid on a histone, allowing to Wrap DNA more tightly.HDAC2 acts as inhibitor which blocks the activity of protein. It acts as tumour suppressor gene under the control of Chromatin modifications is a major underlying cause of unregulated cellular proliferation and transformation. That inactivates the regression of tumour cell growth and activation of cell apoptosis. HDAC2 inhibitors also modify the acetylation state of a large number of cellular proteins involved in oncogenic processes, resulting in antitumor effects. The histone deacetylase in protumorigenic mechanism and developed status prospects for their in cancer therapy. The inhibitor thus acts on the tumour growth cells and arrest the cell cycle.

PROTEIN PDB.ID

The PDB gives information about, experimentally determined structures of proteins. PDB is useful to give clear results in protein. In this we get multiple crystal structures of the same protein from this the protein with less resolution like less than 2 are selected by that the structure is clear and it is choose in X-ray diffraction method. PDB_ID:5IWG HDAC2 with ligand BRD4884

MOLECULAR DOCKING:

Computational methodologies have become a crucial component of many drug discovery programs which range from hit identification to lead optimization and approaches such as ligand or structure based virtual screening techniques. One key methodology-docking of small molecules to protein binding sites was pioneered during the early 1980's, and still remains a highly active area of research. Molecular docking is a method that attempts to find the best orientation or conformation of small molecule/ligand that fits into another biological target/receptor. In other words, molecular docking methodology is: Given the atomic coordinates of Receptor and Ligand, to predict how best the ligand binds in the active site of receptor and predict its activity of binding. Prediction of correct binding modes between protein and ligand is of vital importance in structure based drug design and prediction of activity of binding is important in ranking the potential drugs.

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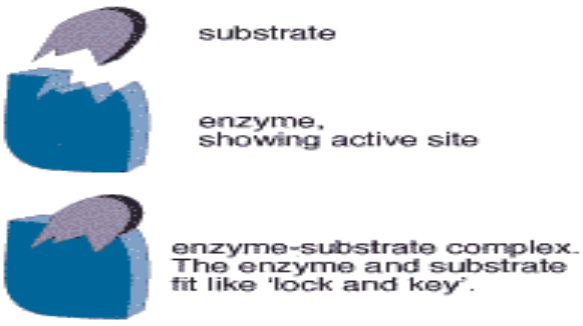
Docking programs can be categorized as:

- Rigid body docking, in which both the receptor and ligand are considered as rigid bodies. The basis for this type of rigid docking is widely known Emil Fischer's lock-and-key hypothesis according to which the key or ligand fits into the lock or protein in only one unique orientation when the pair is active. In other words, ligand binds to the enzyme only if there is a shape complimentarity at the binding surface. Most of the early docking programs relied on the lock-and-key model because both the receptor and ligand were treated as rigid bodies.

- Flexible docking, in which either the ligand is flexible or both receptor and ligand are conformatically flexible. This is Koshland's "induced fit" hypothesis is the basis for flexible docking approaches. It says that since the enzyme is a flexible structure, the active site continuously changes until the substrate is completely bound to it. Due to computational complexity, so far the most successful algorithms include only flexible ligand binding/docking with a fixed rigid receptor.

Based on the above concept of flexibility and rigidity of molecules, there are two broad ways in which docking routines operate: shape complementarity and docking simulation. In the shape complimentarity. approach, the active site of the enzyme is modeled in such a way the ligand docks as a rigid body by matching its shape to that of active site (lock and key). Programs like DOCK use this kind of approach. It is widely used in protein-protein docking. But, mostly in real applications, the active site of the receptor or protein is not known. So, all the dock programs work only where the active site is already known from protein-ligand complex. In simulation approaches, the ligand is kept away from the enzyme by some physical distance, and the ligand finds its position in the active site of the enzyme by moving itself across to the enzyme. The movement of the ligand is caused by translations, rotations and also internal flexibility of ligand which includes torsion. Each move of ligand induces a total energetic cost of the system, and is calculated as total energy of system. These techniques are relatively slow since they have to explore a large space. However techniques which employ grids have tried to solve these problems to some extent.AutoDock is an example of this approach.

Models for a) Lock and Key hypothesis



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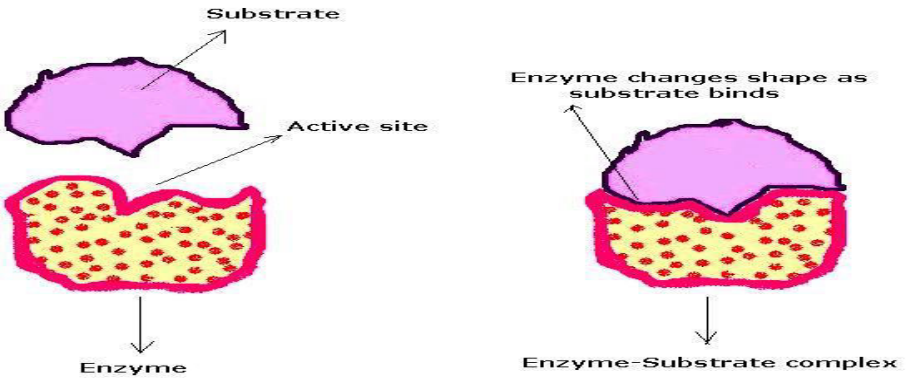
b) induced fit hypothesis:



Components of docking programs: Computationally docking is achieved by these basic steps:

1) Representation of system.
2) Search Algorithm.

1) Representation of systems:

The structures of Receptor-Ligand are obtained from the PDB and care has to be taken to choose high resolution structures to obtain meaningful results. Once the co-ordinates of the structure are available the molecular surfaces has to be defined. The surface of the molecule is often represented by its geometric features. There are three kinds of representations for a receptor:

- Atomic representation
- Surface representation
- GRID representation

In atomic representation, the protein surface is represented as atoms of the exposed residues and pair wise atomic interactions between these exposed residues and the other molecule to be docked is evaluated using potential energy function. This function is used to rank the structures based on energy. Surface-based docking programs are typically used in protein-protein docking where the surface complementarity between receptor and ligand protein molecules is considered. In GRID representation, the active site of the receptor is captured by placing a grid over it. The basic idea is to store information about the receptor's energetic contributions on grid points so that the ligand need not search the whole 3D space for binding and scoring.

2) Search Algorithm:

Each molecule used in docking has six degrees of translational and rotational freedom. Apart from this, the molecules can also possess internal degrees of freedom (torsion).It implies that ligand and the receptor can bind each other in many modes. The space containing all these binding modes is called search space. A Search Algorithm is required to explore this complex 3D search space containing all the degrees of freedom.

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Search algorithms are designed in order to locate the position of the best fit. There are three search methods used so far base on ligand flexibility:

a) Systematic search: These searches are made by incremental construction, conformational search databases. FlexX and DOCK programs work by incremental construction. Computationally it is not possible to explore the search space with all the degrees of freedom because of large size. Therefore, ligands are incrementally docked into the active site of receptor. An incremental search is performed by detecting the rotatable bonds first in molecular rings and then non-ring bonds followed by division of molecule into overlapping rigid segments based on the location of rotatable bonds and then organizing the atoms of molecule into non-overlapping segments arranged concentrically around the rigid portion of the ligand. Then a conformation search starts from the rigid positions generated in the previous step. After completion of this step, each conformation is locally optimized to relieve any strain incorporated during the construction process. If additional portions of ligand are suitable as anchors, the process can be repeated.
b) Random or stochastic methods: These searches include Monte Carlo, genetic algorithms and tabu searches. These generate random moves to the system and then accept or reject the move. A newly obtained ligand is evaluated on the basis of Boltzmann probability in the Monte Carlo approach. Examples of this method are AutoDock and ICM. Early implementations of AutoDock used Metropolis MC simulated annealing with a grid based evaluation of free energy, based on AMBER force field, to dock flexible ligands into binding pocket of rigid receptor.
c) Simulation methods: These searches include molecular dynamics and energy minimization.

AUTODOCK:

The software package used for docking in this study is AUTODOCK 4.0.This software is developed by the Scripps Research Institute and is available from http://AutoDock.scripps.edu/ for free and version 4 is distributed under the GPU General Public License. AutoDock works on many platforms: Windows, Linux and Mac OS. The program was developed in order to provide an automated procedure for predicting the bound conformations of ligands with macromolecular targets. AutoDock has successful applications in the prediction of bound conformations of enzyme-inhibitor complexes, peptide –antibody complexes, peptide-nucleic acid and even protein-protein interactions.

Initial versions of AutoDock combined a rapid grid-based method for energy evaluation, recalculating ligand-protein pair wise interaction energies so that they may be used as a lock up table during simulation, with a Monte Carlo simulated annealing search for optimal conformations of ligand.Then current version ,AutoDock 4.0 has two advancements: The first is the addition of three new search methods: a genetic algorithm, a local search method, and a novel, adaptive global-local search based on Lamarckian genetics, the Lamarckian genetic algorithm LGA..The second advancement is the inclusion of an empirical binding free energy

force field that predicts the binding free energies, and hence binding constants, for docked ligands.

Pharmacophore modelling:

The structure and ligand based pharmacophore modeling and screening of databases can be performed by using the Pharmit server (http://pharmit.csb.pitt.edu/). Protein-ligand complex structure based pharmacophore modeling will utilise the 3D-structural features of a protein active site residues interacting with its crystal bound or docked ligand molecules. Hence, the generated pharmacophore is more proficient with comprehensive information about the protein active site regions that help in designing or searching for new ligand with specific features. Pharmit web server is free, user-friendly and more interactive for generating the pharmacophore and screening of multiple inbuilt databases and user-created databases. The results could be the pharmacophore based molecular shapes and energy minimization conformations. In this objective, we have uploaded a HDAC2 with ligand BRD4884 PDBID:5IWG to the Pharmit server to generate pharmacophore and molecule library search. ZINC database molecule library was selected for the screening of the generated pharmacophore model results in the most similar molecules with pharmacophore mapping. The best mapped 10 molecules were docked into the HDAC2 active site using AutoDock software.

RESULTS & DISCUSSION

The results generated from Autodock shows the binding affinity of selected compounds against HDAC2 target protein. Amoung 10 selected ligands, highest binding energy shown by ZINC000010120338 compound with -9.1 Kcl/mol respectively and taken for Pharmacophore modelling.

Table 1: Protein ligand binding energy (in kcal/mol) of selected 10 molecules and HDAC2 active site

Compounds	Binding score (in Kcal/mol)
ZINC000040400529	-8.0
ZINC000100811322	-4.8
ZINC000010120338	**-9.1**
ZINC000408627623	-7.9
ZINC000100628008	-6.5
ZINC000105356420	-8.7
ZINC000101762753	-3.7
ZINC000020166498	-6.0
ZINC000002773953	-4.7
ZINC000016383861	-6.9

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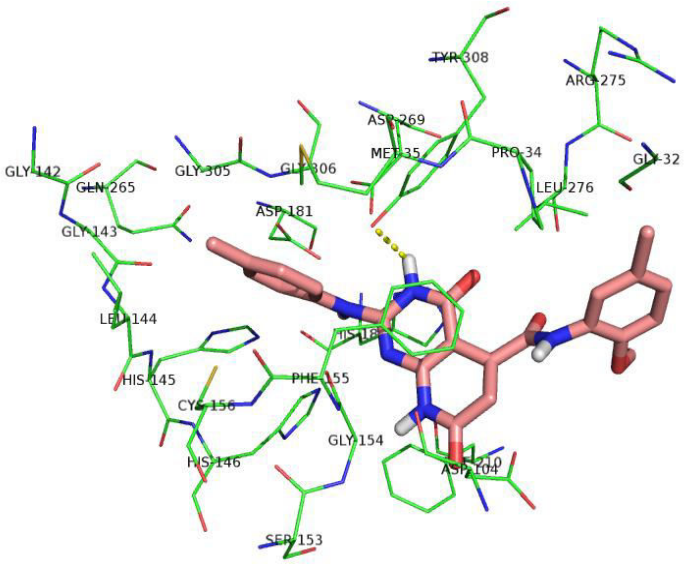

Figure 1: Molecular docking of ZINC000040400529 in the active site of HDAC2 active site

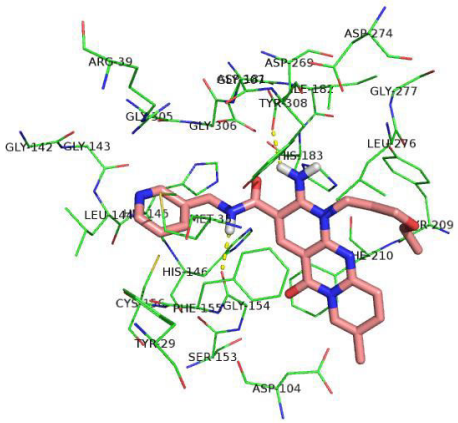

Figure 2: Molecular docking of ZINC000100811322 in the active site of HDAC2 active site

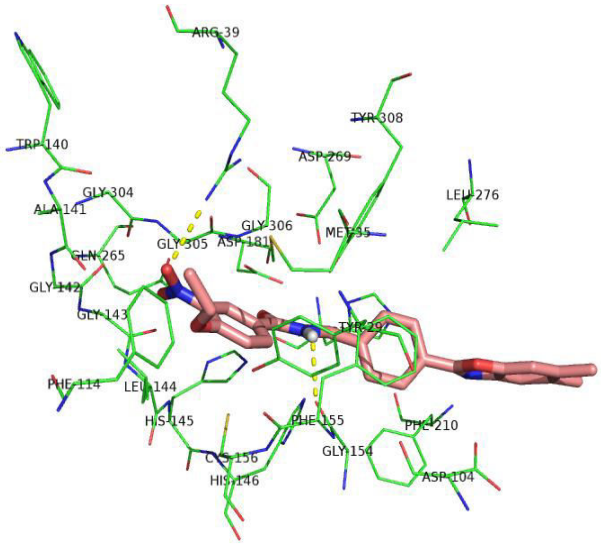

Figure 3: Molecular docking of ZINC000010120338 in the active site of HDAC2 active site

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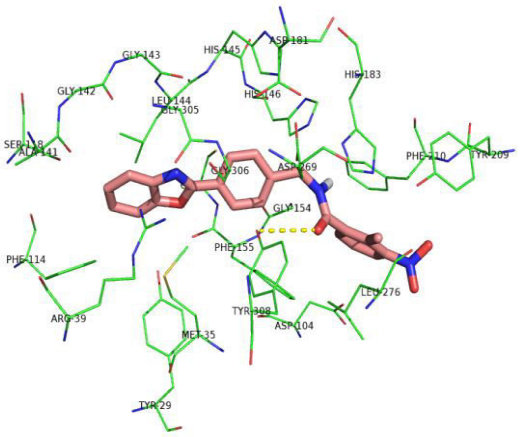

Figure 4: Molecular docking of ZINC000408627623 in the active site of HDAC2 active site

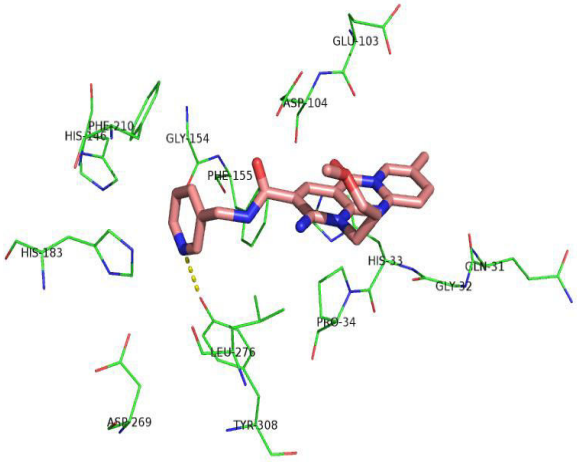

Figure 5: Molecular docking of ZINC000100628008 in the active site of HDAC2 active site

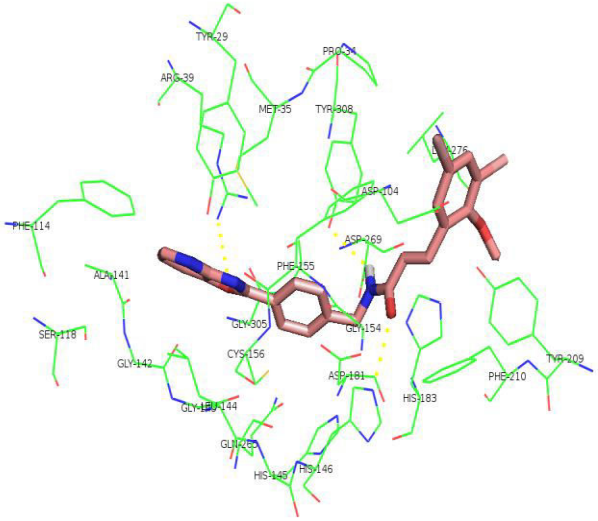

Figure 6: Molecular docking of ZINC000105356420 in the active site of HDAC2 active site

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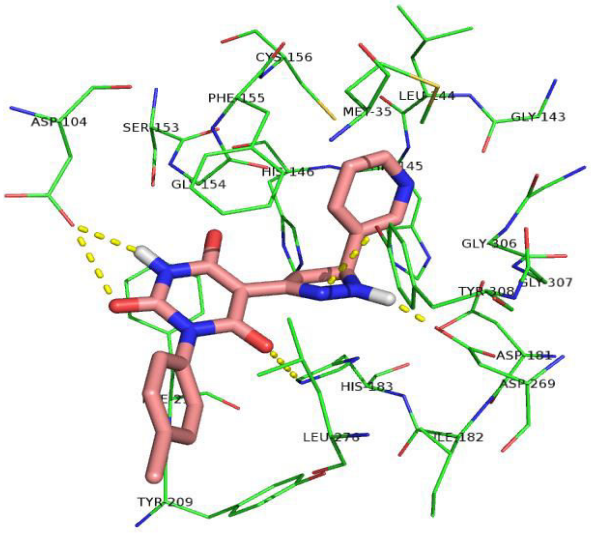

Figure 7: Molecular docking of ZINC000101762753 in the active site of HDAC2 active site

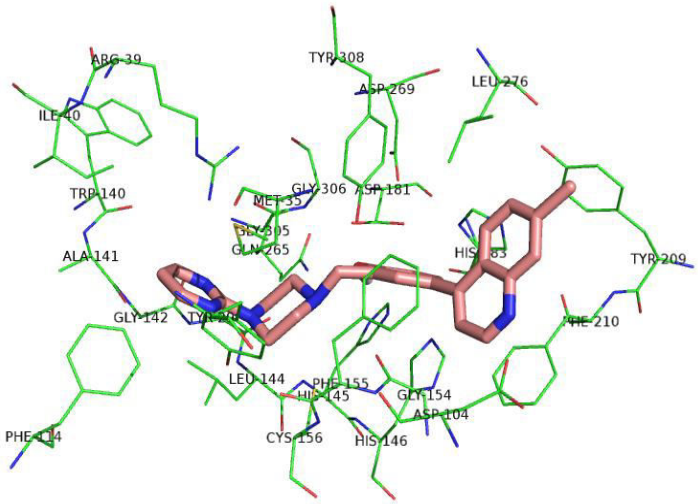

Figure 8: Molecular docking of ZINC000020166498 in the active site of HDAC2 active site

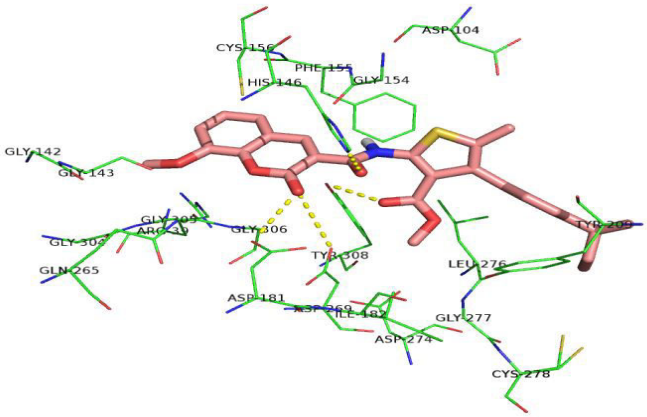

Figure 9: Molecular docking of ZINC000002773953 in the active site of HDAC2 active site

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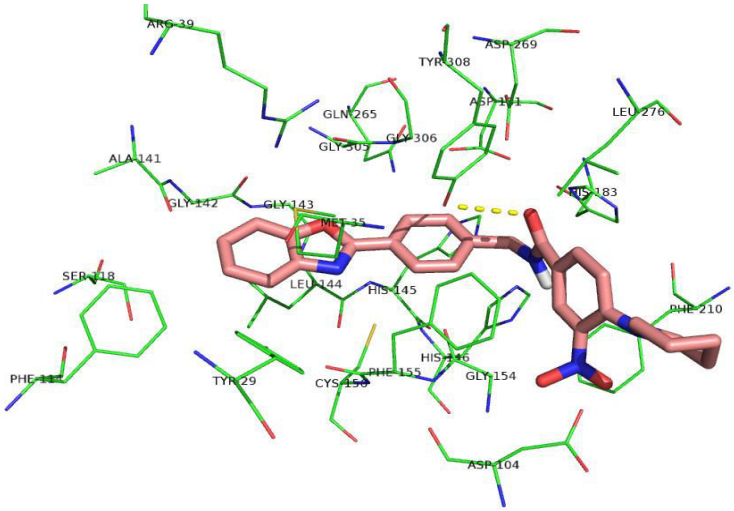

Figure 10: Molecular docking of ZINC000016383861 in the active site of HDAC2 active site

Pharmacophore modelling and molecular docking:

In this study we have used HDAC2 with ligand BRD4884 based pharmacophore generation was performed. Pharmacophore model were generated with six features including hydrogen bond acceptors (orange, radius: 0.5 Å), hydrophobic (green, radius: 1 Å) and aromatic features (purple, radius: 1 Å) (Figure.4A). The constructed pharmacophore models were used to search the ZINC database containing 13,190,317 compounds. The molecules mapping with pharmacophore were adjusted to fit into the active site of the acetyl cholinesterase active site during the searching of the database. A total of 178 unique hits obtained from pharmacophore screening of ZINC database. Autodock molecular docking algorithm was used to screen all the unique molecules identified from three pharmacophores screening into the acetyl cholinesterase active site. Top 10 unique molecules were predicted from pharmacophore search based on the RMSD and binding values. The predicted 10 molecules were further considered for docking analysis using Autodock 4.2.

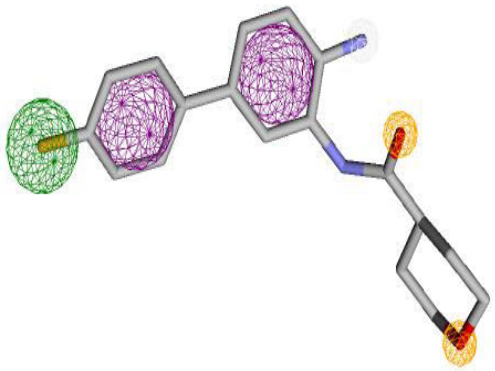

Figure 11: The pharmacophore model generated from the Pharmit.

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Tabel-2: The constructed pharmacophore model were used to search the ZINC database 178 unique hits obtained from 1,31,90,317 lead compounds on pharmacophore screening.

ZINCID	ZINCID	ZINCID	ZINCID	ZINCID
ZINC000016383861	ZINC000009591228	ZINC000034786087	ZINC000008438359	ZINC000023158555
ZINC000100811322	ZINC000010120378	ZINC000080474545	ZINC000016348643	ZINC000253392252
ZINC000040400529	ZINC000020605036	ZINC000080474545	ZINC000057313596	ZINC000253392252
ZINC000101762753	ZINC000095424334	ZINC000408628243	ZINC000096592430	ZINC000253392252
ZINC000002773953	ZINC000003984030	ZINC000224241580	ZINC000096456887	ZINC000008914257
ZINC000010120338	ZINC000170605373	ZINC000102744560	ZINC000096456887	ZINC000100627262
ZINC000100628008	ZINC000170605373	ZINC000101722983	ZINC000000902337	ZINC000034881105
ZINC000105356420	ZINC000101723302	ZINC000222659588	ZINC000003476779	ZINC000046915016
ZINC000105356420	ZINC000100744573	ZINC000408628618	ZINC000006939204	ZINC000033123885
ZINC000408627623	ZINC000022283707	ZINC000408628618	ZINC000002773952	ZINC000002889148
ZINC000020166498	ZINC000102356450	ZINC000016805163	ZINC000001021586	ZINC000225646693
ZINC000010120392	ZINC000102356450	ZINC000015277186	ZINC000585262920	ZINC000223899394
ZINC000010120392	ZINC000035684473	ZINC000034785998	ZINC000006088812	ZINC000575620118
ZINC000010120392	ZINC000032937381	ZINC000006238080	ZINC000010105340	ZINC000034786027
ZINC000023983529	ZINC000150451632	ZINC000032704535	ZINC000024760505	ZINC000119059858
ZINC000006078565	ZINC000057333733	ZINC000013946290	ZINC000078752227	ZINC000069350677
ZINC000077100101	ZINC000006058934	ZINC000016606985	ZINC000002889146	ZINC000223705253
ZINC000077100101	ZINC000096436022	ZINC000009426118	ZINC000033257381	ZINC000007389640
ZINC000015952821	ZINC000012788124	ZINC000040400501	ZINC000033288163	
ZINC000224461038	ZINC000223343540	ZINC000010120366	ZINC000033288163	
ZINC000224133286	ZINC000034786015	ZINC000007989925	ZINC000028296036	
ZINC000224133286	ZINC000016348640	ZINC000007989925	ZINC000020320022	
ZINC000046914415	ZINC000080441415	ZINC000002962464	ZINC000952982532	
ZINC000096141652	ZINC000011664385	ZINC000002962464	ZINC000101666124	
ZINC000010120365	ZINC000046915206	ZINC000010120394	ZINC000040399563	
ZINC000010120365	ZINC000013856275	ZINC000010120394	ZINC000007389209	
ZINC000008719840	ZINC000150439311	ZINC000010120394	ZINC000007389209	
ZINC000012918818	ZINC000004867538	ZINC000010120394	ZINC000408689281	
ZINC000014272266	ZINC000023125446	ZINC000057313285	ZINC000034785939	
ZINC000007389652	ZINC000224709400	ZINC000225388691	ZINC000019370164	
ZINC000007389652	ZINC000049027246	ZINC000102028662	ZINC000095953709	
ZINC000007389652	ZINC000023104547	ZINC000101765290	ZINC000014252144	
ZINC000004807933	ZINC000084304007	ZINC000098212029	ZINC000225397288	
ZINC000225187288	ZINC000084304007	ZINC000101036955	ZINC000225606937	
ZINC000009190357	ZINC000084304007	ZINC000010120422	ZINC000048310901	
ZINC000010120363	ZINC000022067009	ZINC000010120393	ZINC000040400497	
ZINC000010120363	ZINC000020320017	ZINC000010120393	ZINC000040400497	
ZINC000081675758	ZINC000225584022	ZINC000083820441	ZINC000409373186	

ZINC000081675758	ZINC000010120364	ZINC000040399740	ZINC000225872935	
ZINC000225769264	ZINC000040104358	ZINC000040399329	ZINC000225208662	

CONCLUSION:

Analysis of docking results reveals that the all predicted molecules binding well in the active site of HDAC2 (PDBID: 5IWG) all ligand active site residues are represented in Figure 1 to 10. In these, the molecule ZINC000010120338 showed strong binding energy (-9.1 kcal/mol) and molecule ZINC000101762753 have lower binding energy (-3.7 kcal/mol) out of the 10 molecules considered in this study. Protein ligand binding energies are shown in the table 1. These results reveal that the ZINC000010120338 molecule showed two hydrogen bonds with Arg-39 and Gly-154 residues and hydrophobic interactions with His-145, Phe-114 and Tyr-29 residues in the active site. The ZINC000101762753 molecule showed two hydrogen bonding interactions with Asp-104 More hydrophobic interactions played an important role in the stability of ZINC000010120338 molecule.

Conflict of interest: NIL

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