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# VIRTUAL SCREENING OF SMALL MOLECULES AGAINST DEOXYCYTIDINE TRIPHOSPHATE DEAMINASE OF MYCOBACTERIUM *TUBERCULOSIS*

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## ABSTRACT

Bifunctional dCTP deaminase – Deoxyuridine triphosphatase (dUTPase) from Mycobacterium tuberculosis was selected as drug target from database DDTRP (Database of Drug Targets for Resistant Pathogens) that provides a list of potential drug target for different drug resistant infectious diseases including Tuberculosis (TB).The Deoxycytidine triphosphate deaminase ( dCTP) was docked with 131 molecules screened from four different databases, Pubchem, Drugbank, Zinc, and Chembank. Ninety three molecules were successfully docked with dCTP. Eight molecules, two from each database screened were suggested as better molecules over others to bind with dCTP. These eight molecules taken further studies to check their efficiency *in vitro*.

**KEYWORDS:** Tuberculosis, *Mycobacterium tuberculoisis*, Deoxycytidine triphosphate deaminase, Database for Drug Targets of Resistant Pathogens, Deoxyuridine triphosphatase.

## INTRODUCTION

Tuberculosis is a worldwide pandemic. Every second someone in this planet is newly infected with *Mycobacterium tuberculosis*, the etiologic agent of tuberculosis (TB), of which 5-10% become sick infectious at some point time during their life. Overall, one-third of the human race is currently infected with the TB bacillus.[1] Globally, 9.2 million new cases and 1.7 million deaths from TB occurred in 2006.[2] There were 9.27 million new TB cases identified in 2007 and a total of 1.77 million people died from TB in 2007 (including

456 000 people with HIV), equal to about 4800 deaths a day. 80% of the new TB cases identified in 2007 were in just 22 countries. Per capita, the global TB incidence rate is falling, but the rate of decline is very slow - less than 1%. TB is a disease of poverty, affecting mostly young adults in their most productive years. The vast majority of TB deaths are in the developing world, with more than half occurring in Asia. Among the 15 countries with the highest estimated TB incidence rates, 13 are in Africa, while half of all new cases are in six Asian countries (Bangladesh, China, India, Indonesia, Pakistan and the Philippines).[3] The integration of principles from different disciplines like genomics, proteomics and bioinformatics will help us in enhancing our knowledge about the TB bacilli and enable us to develop new therapies against the TB. In 1998, Cole *et al.*, published the complete genome sequence of *Mycobacterium tuberculosis*[14] that is freely available in the NCBI GenBank, the accession number is NC_000962. The information from this paper was incorporated into the public database Tuberculist.[15]

Complete genome sequences are important source for any organism to understand the basic principles necessary to make an organism. Such understanding would provide us to have clear insight into the pathogenesis of infectious diseases too. However comprehensive analysis of entire genomes is required to understand what the genomecodes for and how the genes interact and carry out complex and coordinated cellular function In *Mycobacterium tuberculosis*, as well as in *E.coli* dCTP deaminase in the form of bifunctional. It does mean the enzyme doing two steps at the same time at a reaction. Bifuntional dCTP deaminase:dUTPase represents the enzyme containing two distinct catalytic capacities in the same polypeptide chain.

**Bifunctional dCTP deaminase: dUTPase enzyme**

dUMP is the origin of thymidine precursors for DNA in all organisms. It is the substrate of thymidylate synthase that catalyzes the formation of dTMP.

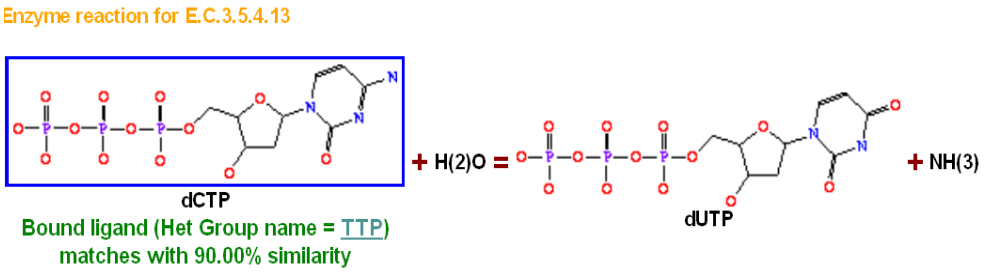
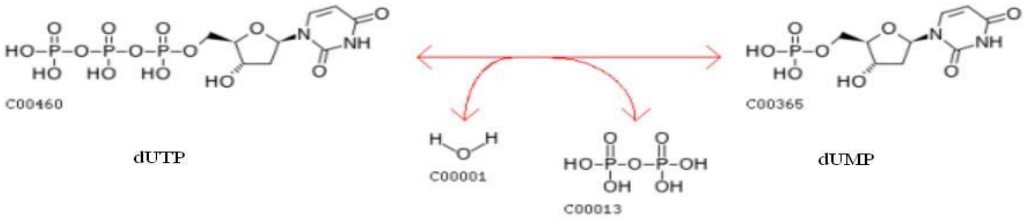



**Fig (1) shows the reaction between the dCTP deamination and dephosphorylation.**

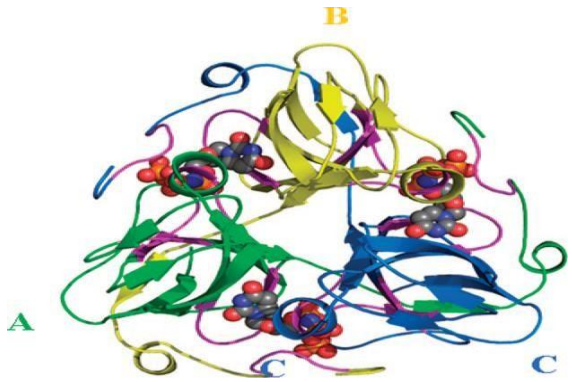
The main pathway for dUMP generation differs markedly between different organisms.. dUMP is produced on the monophosphate level by the action of dCMP deaminase in eukaryotes and Gram-positive bacteria, whereas in Gram-negative bacteria such as Escherichia coli and some Archaea, dCTP is deaminated and dephosphorylated. dCTP deaminase (EC 3.5.4.13) and dUTPase (EC3.6.1.23) catalyze the two consecutive steps where dUMP is formed .




**Fig(2): shows the enzyme reaction (EC3.6.1.23) conversion of dUTP to dUMP formation and removal of water molecule and pyrophosphate.**

**The structure of *M. tuberculosis* dCTP deaminase:dUTPase(Rv0321)**

dCTP deaminase:dUTPase is a homotrimeric enzyme. The structure of *M. tuberculosis* dCTP deaminase: dUTPase–dTTP complex(PDB ID:2QXX)was already solved with two subunits (A and B) in the asymmetric unit.




**Fig(3): This shows the each subunit of *M.tuberculosis* dCTP deaminase:dUTPase is composed of 13 β-strands (β1–β13), two α-helices (α1–α2) and one $3^{10}$-helix (γ1) . here the green colour shows the A chain, yellow colour shows the B chain, and blue colour shows the C chain. Each active site was predicted between the two chains.**

The pyrimidine moiety forms hydrogen bonds with Arg*106, Gln174, Thr127 and water molecules 51 and 66. Ser*102 is on one side of the pyrimidine plane and on the otherside the pyrimidine is stacking with Ile126. The thymidine moiety rests on a hydrophobic surface

generated by residues Ile118, Phe122, Ile126, Tyr162 and Tyr171. The deoxyribosyl makes a single hydrogen bond with Asp119. The triphosphate moiety of the nucleotide chelates the magnesium ion that also coordinates to water molecules 60, 65and 166, generating an octahedral coordination sphere. The triphosphoryl is furthermore hydrogen-bonded to Lys*101, Ser*102, Ser*103, and Gln*148 and the active site lid via Tyr162 and Lys170 as well as water molecules 53, 60, 65 and116. (Signe Smedegaard Helt,*et.al*,(2008)

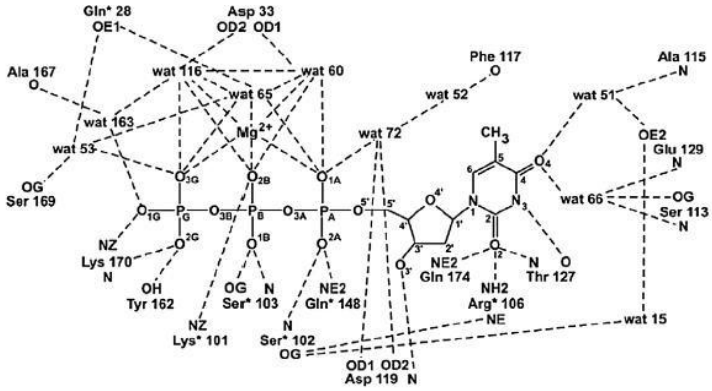
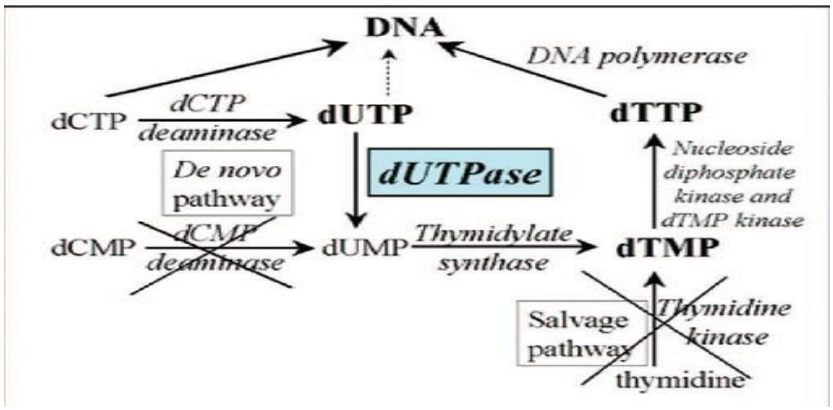



**Fig. (4) Shows the extensive hydrogen bonding present in the hydrophobic surface.**

**The dCTP Deaminase/dUTPase Bifunctional Enzymes**




**Fig(5):*De novo* and salvage pathways for dTTP biosynthesis. Enzymes not present in *Mycobacteria* and *Plasmodia* are crossed out.**

*M. tuberculosis* also encodes *a bonafide* dUTPase, the catalytic power of which exceeds that of the bifunctional dCTP deaminase/dUTPase by several orders of magnitude. The bifunctional enzyme represents a direct channeling pathway from dCTP into dUMP for thymidylate synthase.. The relative significance of these two enzymes was assessed in knockout studies where dUTPase was shown to be the bifunctional enzyme was dispensable for viability of *M. tuberculosis*. (Be´ata g ve´rtessy* and Judit to´ th,. 2008).

## 2. METHODOLOGY: Selection of The Drug Target

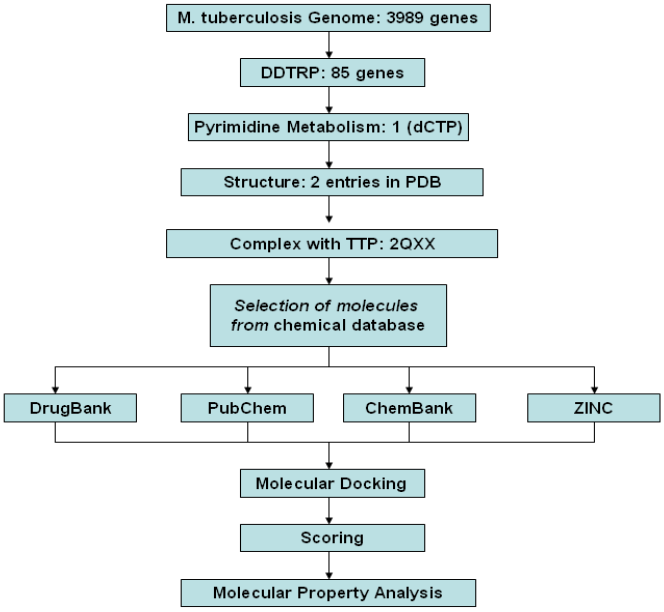
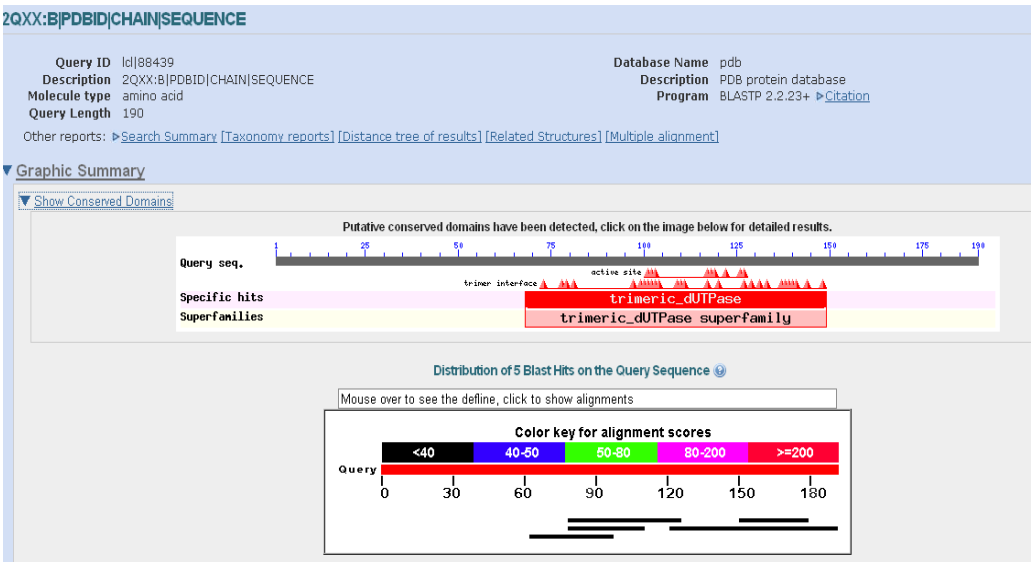



**Fig: (6) The flowchart describes the method followed in the current study from the drug target selection to molecular docking to scoring and property analysis.**

### Protein-Protein Blast (Blastp)

This program, given a protein query, returns the most similar protein sequences from the protein database that the user specifies. By using this tool, we can search the similarity homologs for this protein. In order to get the alignment score based on the E Value and z score. But unfortunately we get low percentage levels for this protein. Therefore it doesn't affect the *Homo sapiens*, to design the drug, and this protein was chosen as potential drug target.



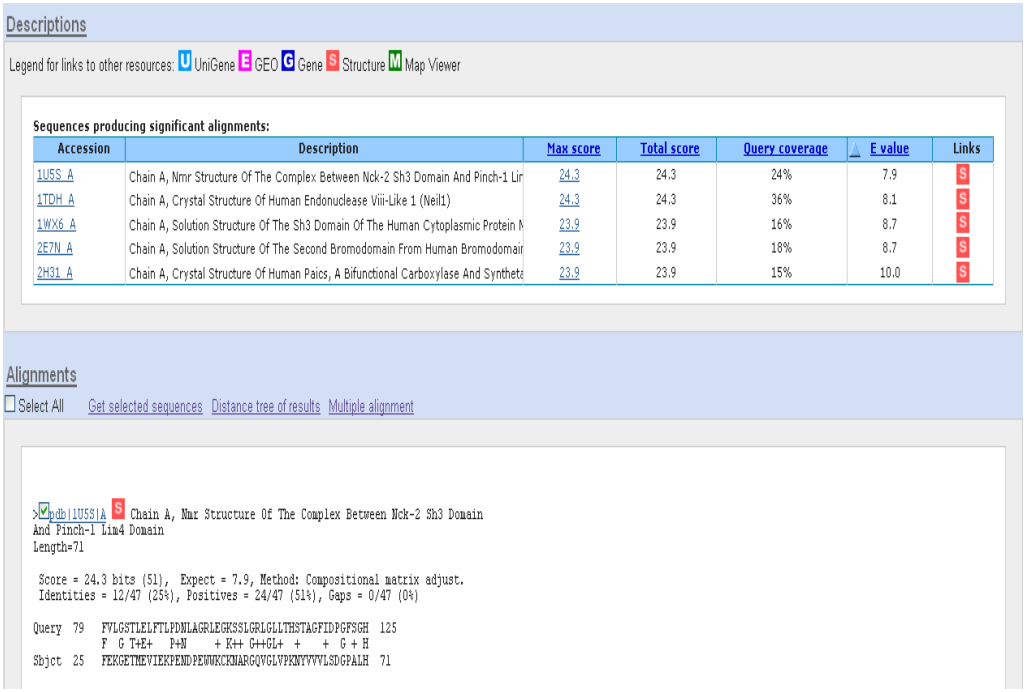
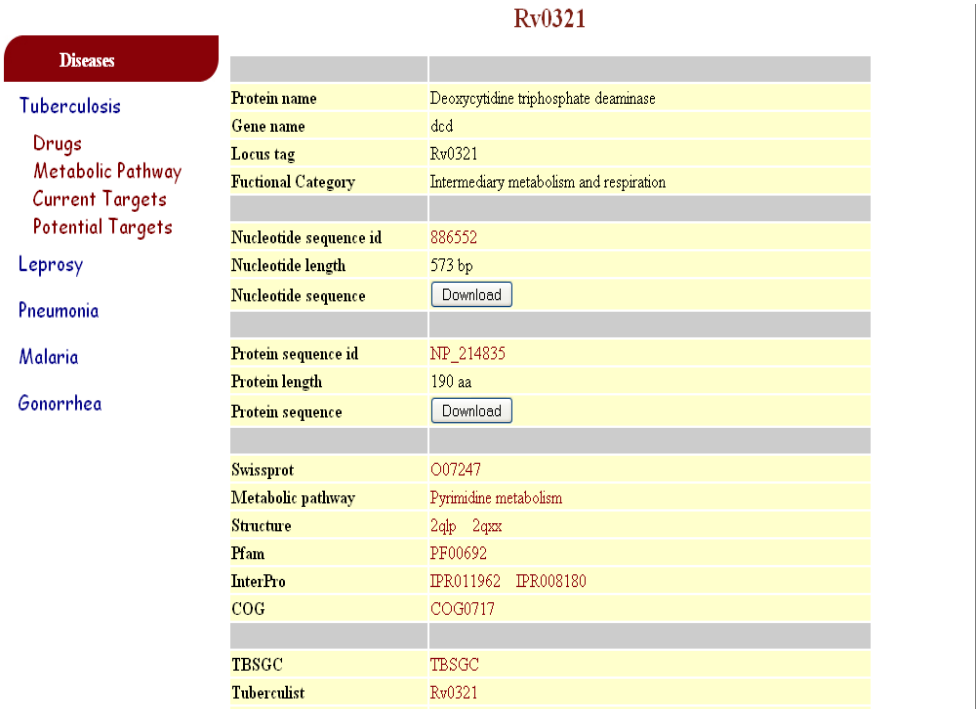



**Fig (7): This snap shot shows the blast alignment scores with 2qxx :DCD. This alignment black codes for poor similarity less than 40%. The specific hits shows the trimeric _dUTPase family.**

**DDTRP(Database for Drug Targets of Resistant Pathogens)**

This database is very useful for researchers for the process of drug target identification of potential drug targets against pathogens which have become resisitant to existing drugs .This database having drug targets ,metabolic pathway ,and a list of current targets and a list of potential targets of the resistant pathogens. Now this database was having a list of organisms which is resistant to present drugs as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Plasmodium falciparum*, *Plasmodium vivax* and *Neisseria gonorroheae.*

Under the each disease having a list of presently using the first line drugs ,genes involved in the metabolic pathway ,current targets and a list of proposed targets . In potential targets for every genes having information about the nucleotide sequence, protein sequence, pathway details, swissprot ID,PDB ID, Pfam ID, Interpro ID,COG ID, TBSGC,TubercuList ID and details of the functional category.




**Fig(8): This snapshot shows the target [Rv0321 with 2qxx: PDB ID] with all details present in the DDTRP database.**

**PDB: (Protein Data Bank)**

The Protein Data Bank is a computer-based archival file for macromolecular structures. The Bank stores in a uniform format atomic co-ordinates and partial bond connectivities, as derived from crystallographic studies. Over the history of the Protein Data Bank this archive of three dimensional structural data has grown from 7 files in 1971 to a database containing over 18 800 structures as of October 2002. The archive's growth has been accompanied by increases in both data content and the structural complexity of individual entries. http://www.rcsb.org/pdb/.

The PDB database was the main tool that was used to download the protein structure(2QXX) and to find their ligand (TTP)using the ligand explorer available as an additional option in the PDB database. The protein's detail was obtained from the PDB database when the PDB ID was entered. By using this helpful to download the structure details and their ligand information using the ligand explorer available with the protein information in the same page. The PDB structure that was downloaded from the database was helpful to know the information regarding the Hetatom, Binding Site and the number of available chains in that particular protein.

**KEGG (Kyoto Encyclopedia of Genes and Genomes)**

This Kyoto Encyclopedia of Genes and Genomes (KEGG:http://www.genome.ad.jp/kegg) is one of the best known database for metabolic and regulatory pathway .this number shows the enzyme classification number or E.C.number.metabolic pathway assumes great importance in th context fo genome anotation .The pathway represents as schematic diagrams showing enzymes,their substrates,cofactors,and products and each diagrams contains appropriate hyperlinks and information .

In our protein (Rv0321- deoxycytidine triphosphate deaminase) involved in the pyrimidine metabolism which was retrieved by the ID :KEGG: mtu00240 .the enzyme classification number is (EC:3.5.4.13). dCTP deaminase (EC 3.5.4.13) and dUTPase (EC3.6.1.23) catalyze the two consecutive steps where dUMP is formed. . The bifunctional enzyme represents a direct channeling pathway from dCTP into dUMP. Deamination of cytosine compounds also takes place in the pyrimidine salvage pathways, where in preformed cytosine and (deoxy)cytidine is converted into uracil and (deoxy)uridine, respectively.

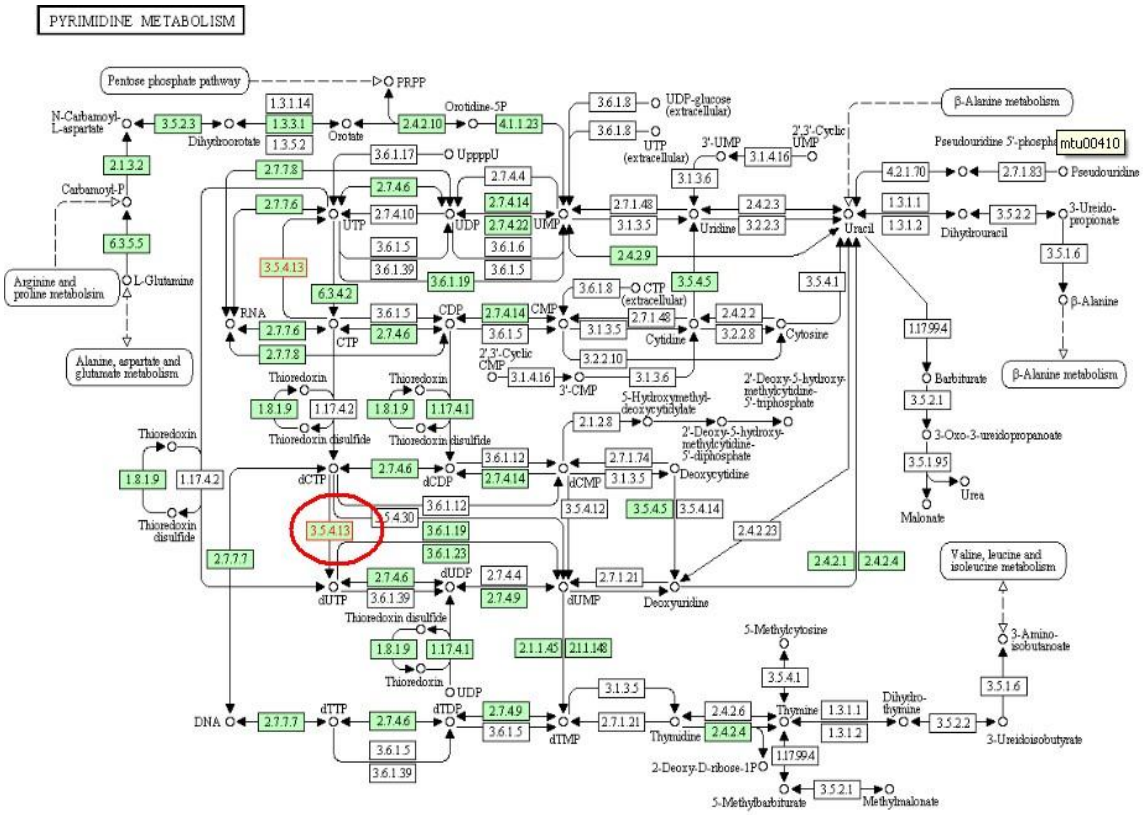



**Fig (9): this figure shows the KEGG pathway number mtu00240:pyrimidine metabolism.The red ring shows the enzyme number EC:3.5.4.13 .**

**Reconstruction of Metabolic Pathway**

The gene that encodes this enzyme was first annotated as coding for a dCTP deaminase , but enzymatic studies revealed the bifunctionality, which implies that dUTP is never released from the enzyme. UTP is also formed upon spontaneous deamination of dCTP, and the reaction catalyzed by dUTPase is there for essential in keeping the cellular concentration of dUTP low to suppress misincorporation of uracil into DNA.

Deamination of cytosine compounds also takes place in the pyrimidine salvage pathways, where in preformed cytosine and (deoxy)cytidine is converted into uracil and (deoxy)uridine, respectively. The first of these reactions is catalyzed by cytosine deaminase, an enzyme that only is present in bacteria and fungi. Cytidine deaminase that catalyzes the second reaction is, on the other hand, present in almost all organisms, including higher eukaryotes. (Eva Johansson.*et.al, 2003*)

Enzyme function deficiency results in an elevated dUTP/dTTP ratio, and a highly uracil-substituted DNA, due to the low substrate specificity of DNA polymerases, and the relatively increased level of deoxyuridine triphosphate. Since uracil also appears in the DNA by the spontaneous oxidative deamination of cytosine and this base replacement introduces a point mutation into the DNA, base excision repair enzymes remove uracil generating an abasic site and a single strand nick. (Eva Johansson.*et.al, 2003*)

Although the replacement of thymine by uracil in the DNA, which becomes excessive in dUTPase deficiency, would not be mutagenic by itself, base excision repair enzymes usually cannot distinguish between uracil bases by their origin, and consequently remove all uracils from the DNA. High dUTP concentration results in the repeated misincorporation of uracil instead of thymine, and thus a high number of nicks in the DNA strands as a result of the hyperactivated base excision repair enzymes, leading to DNA fragmentation and a subsequent cell death. This process is known as thymine-less cell death. (Joy L. Huffman.,et.al(2003)

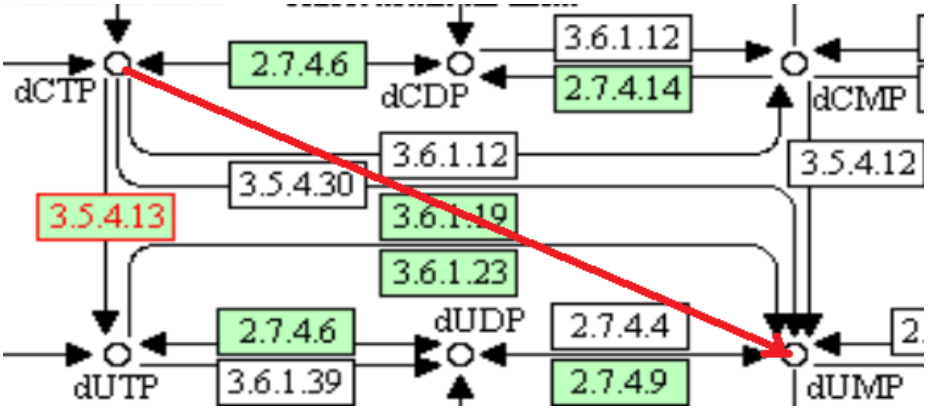
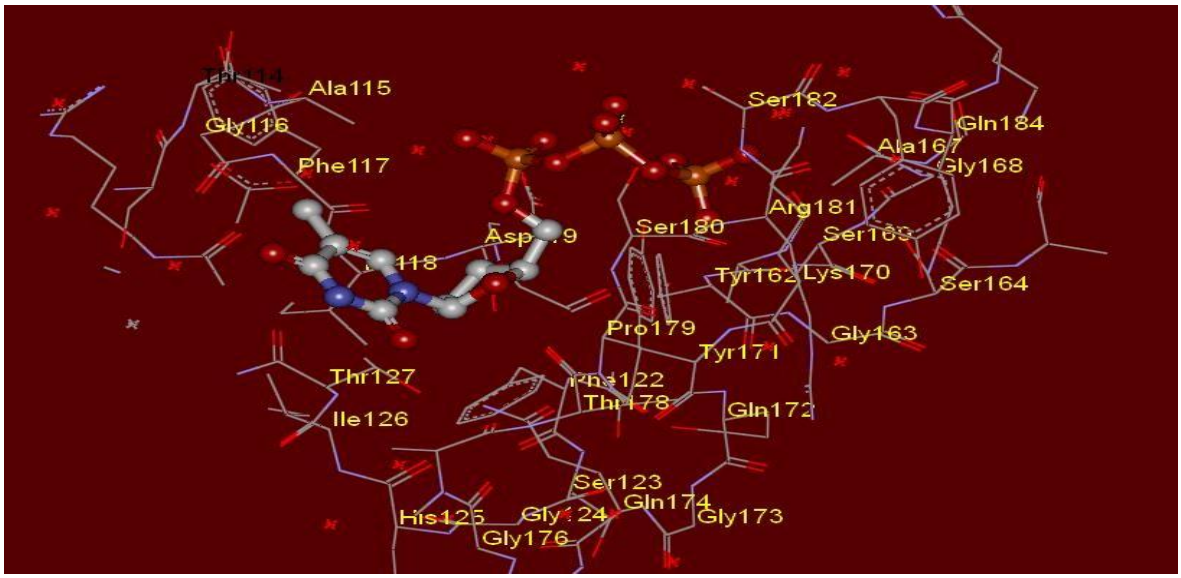



**Fig (10): this red line shows the enzyme as having dual role as bifuntional dCTPdeaminase: dUTPase enzyme.(KEGG mtu00240: pyrimidine metabolim**

**Active Site Analysis**

The active site is usually a big pocket or cleft surrounded by amino acid- and other side chains at the surface of the enzyme that contains residues responsible for the substrate specificity (charge, hydrophobicity, steric hindrance) and catalytic residues which often act as proton donors or acceptors or are responsible for binding a cofactor such as PLP, TPP or NAD. In 2QXX: DCD protein, having 8 cavities(active sites), are present in the protein,by determine the best binding site by using Accerlys discovery studio,and the thymindine -5'-triphosphate, found in the active site 4. Here the snapshots show the residues around the active site which we used. In the figure lines those the amino acids and ball&stick model shows the original ligand TTP(thymindine -5'-triphosphate).




**Fig(11): This snapshots shows the active site present in the (Chain:B) with Thymidine-5'- triphosphate ligand and hydrophobic residues around the ligand .**

In this protein, Rv0321-dcd gene -deoxycytidine triphosphate deaminase , assembling the trimer generates three active sites, which is common to the enzyme family. Each active site is located ina pocket between two subunits. In the dTTP complex structure, the C-terminal folds back upon the active site like a lid, rendering the bound nucleotide almost completely shielded from the solvent. Since the active site is composed of residues from neighbouring subunits.

## SCREENING OF SMALL MOLECULES

### Pubchem

It is new and comprehensive database of chemical structures and their biological activities was felt as a need for drug discovery research by NIH. Therefore, a database called PubChem was developed by NCBI at NIH and available ate http://pubchem.ncbi.nlm.nih.gov/. PubChem provides information on the biological activities of small chemical molecules. It can be accessed for free through a web user interface.. PubChem is organized as three linked databases as PubChem Substance, PubChem Compound, and PubChem BioAssay. PubChem also provides a fast chemical structure similarity search tool. PubChem contains substance descriptions and small molecules with fewer than 1000 atoms and 1000 bonds. More than 80 database vendors contribute to the growing PubChem database.

This database was used to search for similarity molecules based on the thymidine triphosphate. In first we choosen the molecule ID: 119623. By using this molecule, searching for 95% similarity by structure search tool, in the this database. Totally we get 130 molecules, we selected based on the lipinski's rule of five, finally we get 39 molecules. among these molecules first 30 molecules be selected for docking studies.

### Chembank

Chembank is a public, web based bioinformatic environment developed through collaboration between the chemical biology program and the broad institute of Havard and MIT. ChemBank stores an increasingly varied set of measurements derived from cells and other biological assay systems treated with small molecules. http://chembank.broadinstitute.org/

The ChemBank database was mainly used to search for the similar structure of the small molecule which was used for docking with the protein. The similar structures were found

using the SMILES notation that was noted from the PubChem database. The similarity threshold parameter was set to 0.9 and the similarity metric was set to tanimoto in order to obtain the most similar structures. Incase of unavailability of the similar structures then the similarity threshold was set to 0.8.

**Zinc**

The ZINC database is a collection of commercially available chemical compounds prepared especially for virtual screening. ZINC is used by investigators generally people with training as biologists or chemists in pharmaceutical companies, biotech companies, and research universities. It is available in http://zinc.docking.org/.

The molecules have been assigned biologically relevant protonation states and are annotated with properties such as molecular weight, calculated LogP, and number of rotatable bonds. Each molecule in the library contains vendor and purchasing information and is ready for docking using a number of popular docking programs. This database is available for free download (http://zinc.docking.org) in several common file formats including SMILES, mol2, 3D SDF, and DOCK flexibase format.

In this database by using the TTP Molecule as target molecule, based on the molecular properties, we can get similarity about 31 molecules and then move on to docking studies.

**Drug Bank**

Drug Bank is a dual purpose bioinformatics–cheminformatics database with a strong focus on quantitative, analytic or molecular-scale information about both drugs and drug targets. There four different ways in which an user can search the Drug Bank for details. They are Chem Query, Text Query, Sequence Query & Data Extractor. Chem Query.

Four different options are available to search using the chemquery. They are:

- Structure
- Molecular weight
- SMILES and
- Chemical formula

The structure of the chemical molecule can be drawn to find similar drugs available in the DrugBank. Options are made available to restrict the search to that of the type / category

of drugs (FDA approved or so on, listed somewhere), molecular weight, and substructure. By using this chemquery , we can get the similarity about 112 molecules, finally we selected as 40 molecules based on the molecular properties for docking studies.

**TOOLS: CDOCKER—A CHARMM-BASED MOLECULAR DYNAMICS DOCKING ALGORITHM**

In this era of computer-aided structure-based drug design, molecular docking is frequently used to predict the putative geometry of a protein-ligand complex. The success of this computational methodology can be rapidly verified by parallel crystallography efforts. In addition, docking is often used in conjunction with scoring functions to predict binding affinities of ligands in virtual screening experiments and in studying structure activity relationships to prioritize synthesis of new compounds. Molecular dynamics (MD) is a general simulation technique.that is included in many molecular modeling packages such as CHARMm19 and AMBER.20 Despite its popularity for the simulationof biomolecules. It is interesting that MD is rarely used for protein-ligand docking and has not currently been includedas an available docking methodology in commercial docking packages.

The role of MD in the drug design process is likely to grow as computer power increases and as these MD methodologies are incorporated into practical docking packages. This article studies our implementation of a grid-based MD docking algorithm, CDOCKER (CHARMm-based DOCKER), which offers all the advantages of full ligand flexibility (including bonds, angles, dihedrals), the CHARMm19 family of force fields,the flexibility of the CHARMm engine, and reasonable computation times. CDOCKER is based on previous work demonstratingthe improved efficiency and accuracy of automated MD dockingwith a soft-core potential over MC and GA in searching a large configuration space when using a detailed atomic force field.*(Wu et al. )*

**Procedure**

The Dock Ligands (CDOCKER) protocol docks ligands into the active site of a receptor. It may also be used to refine existing docked poses. In both cases the protocol uses CHARMm to perform a simulation on the protein ligand complex, keeping the protein rigid. If the ligands are not pre-docked, the *Input Site Sphere* parameter should be specified. In this case, the input ligand is translated to the center of the sphere (the radius is not used) prior to running the refinement protocol.

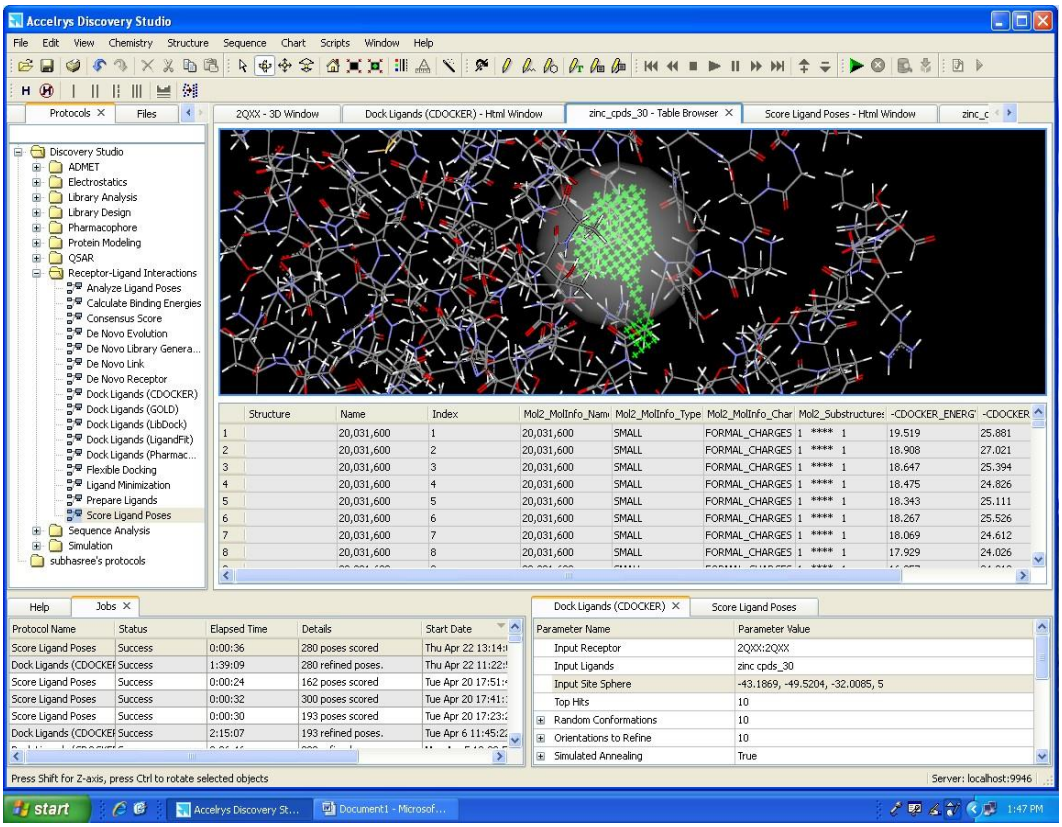



**Fig (12): This snapshot shows the accerlys discovery studio with protocols explorer in the left side and in the bottom jobs explorer, cdocker tool, score ligand poses tool, and table browser. To set up a Dock Ligands (CDOCKER) protocol.**

- The DCD structure (receptor) was loaded into the graphics view.
- Hydrogen atoms were added to the receptor
- The force field *Charm* was applied
- Once Charm was applied, the receptor was typed as receptor for docking.
- All sites from cavities present in the receptor were predicted.
- Based on the Signe Smedegaard Helt,*et.al*,(2008), characterization of DCD structure, the active site was chosen in the predicted sites.
- Sphere was created in the selected active site residues.
- small molecules were loaded
- CDOCKER was run with default parameters.
- Hydrogen bond interactions were analysed using the script menu.

**Chemsketch**

ACD/ChemSketch is the powerful all-purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and easily draw molecular structures,

reactions, and schematic diagrams, calculate chemical properties, and design professional reports and presentations.

**ACD/ChemSketch includes**

- Structure mode for drawing chemical structures and calculating their properties.
- Draw mode or text and graphics processing.
- Additional modules that extend the ChemSketch possibilities.
- Save or load structures to or from a file on the disk, export or import structures to or from MDL molfiles, cut and paste structures to other Windows applications, by using the File menu commands.
- For format conversion , IUPAC NAME generate we use this software and similarity search tool.

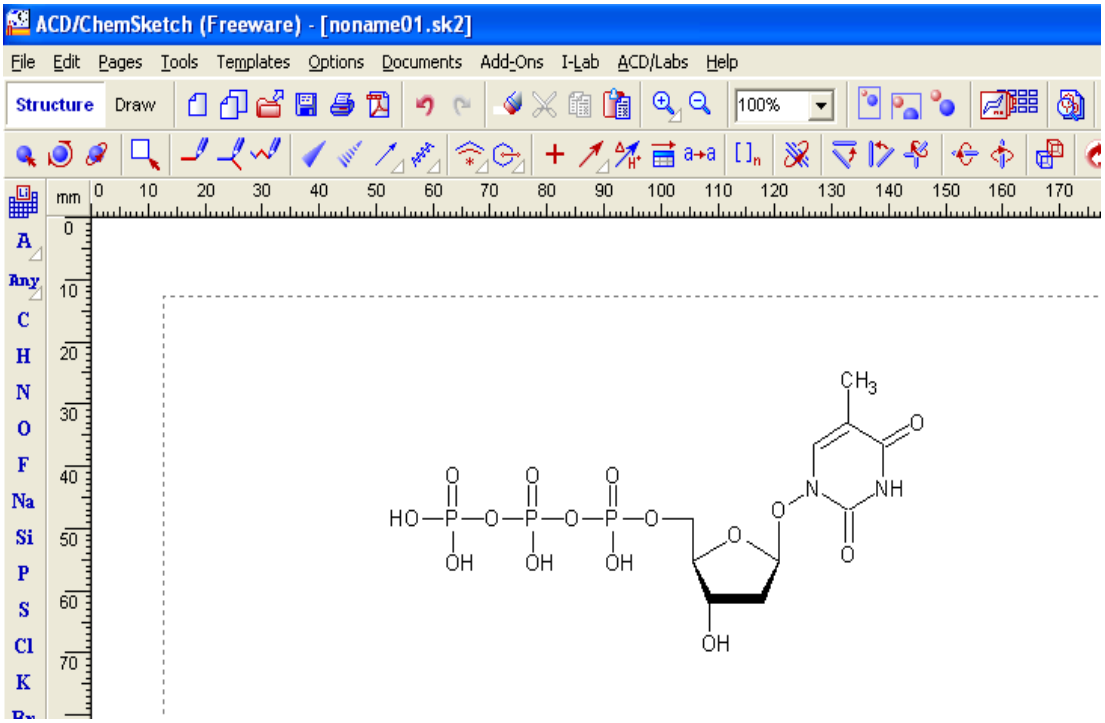
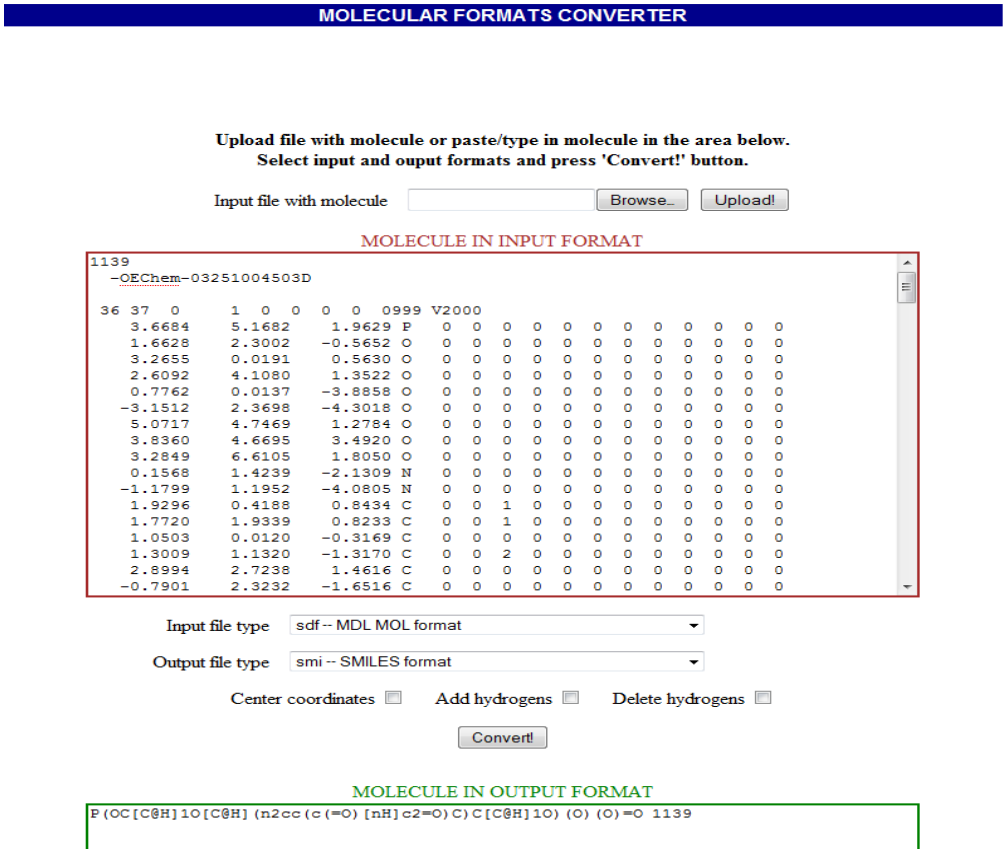



**Fig (13): This snapshots shows the thymidine triphosphate structure for similarity search and snapshot with the chemsketch tool.**

**Chemical Portal**

The Chemical Portal is an online tool that was used for the conversion of the small molecule from one format to the other format. This tool can take the input as Alchemy format, MSI BGF format, Dock 3.5 box format, Ball & Stick format, Chem 3D Cartesian format, MDL Mol format, Sybyl Mol2 Format, Protein data bank format, Smiles

format & many more formats. The output can be converted into the format that is available for the input format. *http://www.webqc.org/*




**Fig(14):this snapshot shows the molecular format converter with the uploaded molecule in the SDF format (input format)conversion to smiles format(output format).**

The conversions that were carried out in that tool were from sdf format to the pdb format. The sdf file format was obtained from the PubChem database for the similar structures of the small molecule and this file format was given as the input then the conversion was carried out for the smiles file format. This format conversion was done to apply the smiles format to the accerlys Discovery Studio in order to carry out the docking in the CDOCKER.

**Molecular Property Analysis**

**Lipinski's Rule Of Five**

In 1997 Christopher A. Lipinski published a seminal paper identifying a series of features commonly found in orally active drugs. These features are referred to as Lipinski's rule of five and can be used as a rule of thumb to indicate whether a molecule is likely to be orally bioavailable (bioactive). The "rule of five" is so called because most of the features start with

the number five. In general, an orally active drug has:

- Not more than 5 hydrogen bond donors (OH and NH groups)
- Not more than 10 hydrogen bond acceptors (notably Nand O)
- Molecular weight under 500.
- x LogP under 5

## RESULTS AND DISCUSSION

The atomic coordinates of DCD (2QXX) was downloaded from PDB. The DCD has three identical chains each of them has the length of 190 amino acids. The subcellular location of the dcd in the *M. tuberculosis* is cytoplasm. 2qxx contains three ligands, thymidine -5'-triphosphate, magnesium and penta ethylene glycol with the DCD. The active site of the DCD is made of 17 amino acid residues.

The pyrimidine moiety forms hydrogen bonds with Arg*106, Gln174, Thr127 and water molecules 51 and 66. Ser*102 is on one side of the pyrimidine plane and on the otherside the pyrimidine is stacking with Ile126. The thymidine moiety rests on a hydrophobic surface generated by residues Ile118, Phe122, Ile126, Tyr162 and Tyr171. The deoxyribosyl makes a single hydrogen bond with Asp119. The triphosphate moiety of the nucleotide chelates the magnesium ion that also coordinates to water molecules 60, 65and 166, generating an octahedral coordination sphere. The triphosphoryl is furthermore hydrogen-bonded to Lys*101, Ser*102, Ser*103, and Gln*148 and the active site lid via Tyr162 andLys170 as well as water molecules 53, 60, 65 and116. (Signe Smedegaard Helt,*et.al*,(2008).

### Selection of Small Molecules

The ligand thymidine -5'- triphosphate that were reported as potential inhibitors of of *M.tuberculosis*. Hence these two molecules were used to screen two databases *PubChem* and *ChemBank*. 95% similarity in *PubChem* and 0.8 Tanimoto coefficient (similarity threshold) in ChemBank were set as threshold for the selection of small molecules. 30 molecules were found from *PubChem*, 31 molecules from ChemBank, 30 molecules from zinc, and 40 molecules from drug bank as related to dTTP. Based on manual inspection of the structure of these molecules, totally 93 out of 131 molecules were selected for molecular docking with DCD. The structures of all these molecules are displayed.

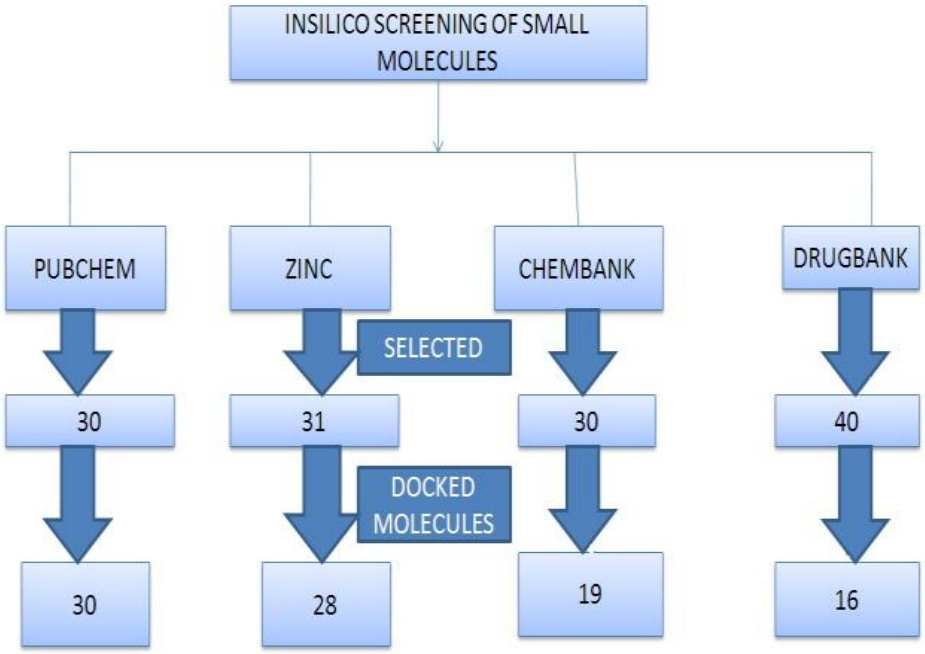
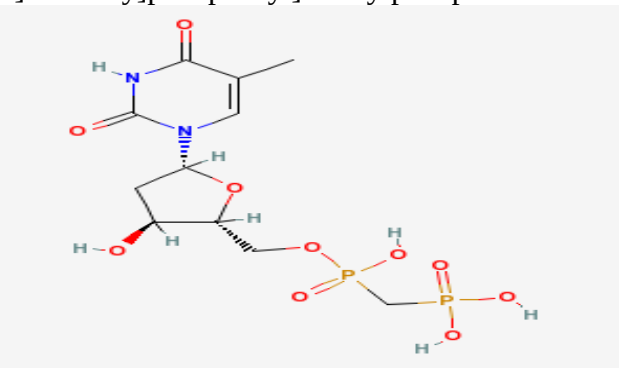
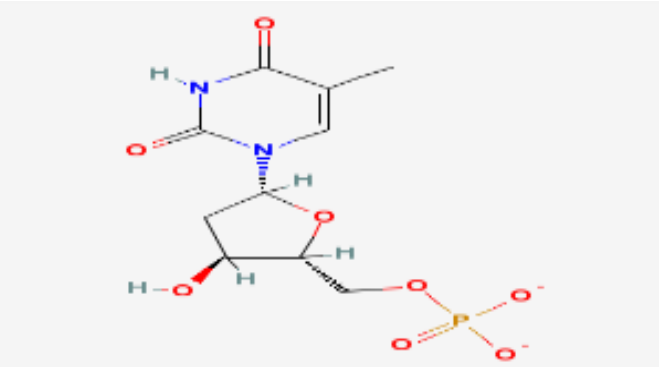
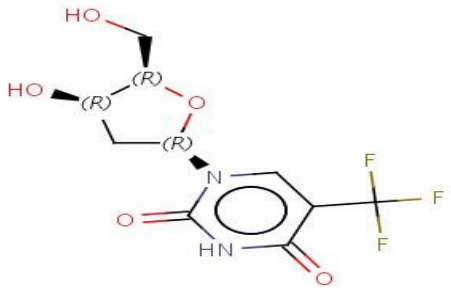
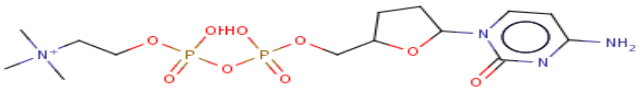
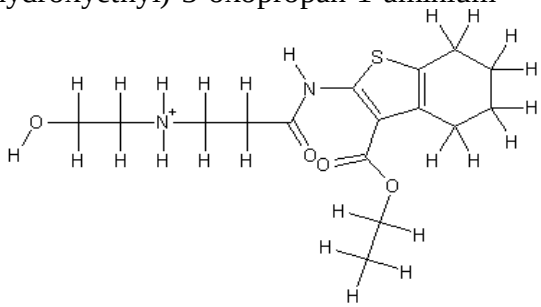
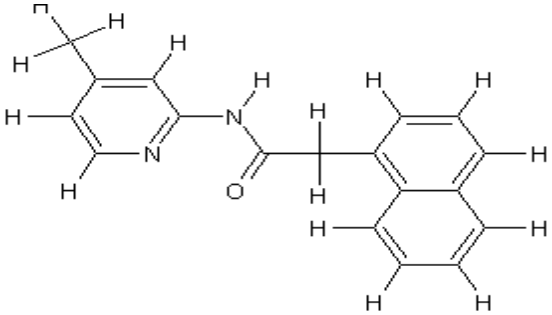
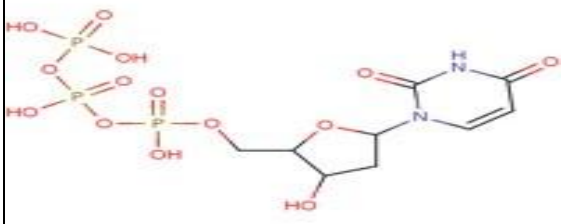



**Fig (15): This Flow chart describes the small molecules selection and screening on the basis of lipinski's rule of five from cheminformatics databases.**

**Molecular docking of bifunctional dCTP deaminase: dUTPase of *Mycobacterium tuberculosis***

This dcd protein as docked with 131 small molecules using cdocker .For each of the docking ,10 different poses were generated and best pose for each complex has been displayedin fig(15).those molecules related to dTTP were targets to dock with binding site residues Arg*106, Gln174, Thr127, Ile118, Phe122, Ile126, Tyr162, Tyr 170 and Tyr171.

Out of 131 molecules 93 were shortlisted as successive fully docked to the DCD protein. The complex of the receptor, dcd and the ligand were analyzed using Cdocker's interaction energy, PLP2 Values with scoring ligand poses, and Cdocker's energy was takes part in determining the and hydrogen bond energy interaction between the residues from active site with that of the atoms of the small molecules.

| BASED ON PLP 2VALUES | BASED ON CDOCKER ENERGY |
|---|---|
| 1.[hydroxy-[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphoryl]methylphosphonic acid  | 1.[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate  |
| 2. 1- (2- deoxy- beta- D- threo- pentofuranosyl) - 5- (trifluoromethyl) pyrimidine- 2,4(1H,3H) – dione(trifluridine)  | 2. 2- {[(R) - {[(S) - {[(2S,5S) - 5- (4- amino- 2- oxopyrimidin- 1(2H) - yl) tetrahydrofuran- 2- yl]methoxy}(hydroxy) phosphoryl]oxy}(hydroxy) phosphoryl]oxy}- N,N,N- trimethylethanaminium  |
| 3.3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro- 1-benzothiophen-2-yl]amino}-N-(2-hydroxyethyl)-3-oxopropan-1-aminium  | 3.N-(4-methylpyridin-2-yl)-2-(naphthalen-1-yl)acetamide  |
| 4.1-[(2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione  | 4. Deoxyuridine-5'-Triphosphate  |

**Table(1): This tabulation shows the best top ranking molecules from the pubchem database based on the PLP2 values**

| ID NUMBER | Molecule name | Mol.formula | Mol.weight | xlogp | h-bond donor | h-bond acceptor | Rotatable bonds | = -PLP2 |
|---|---|---|---|---|---|---|---|---|
| 11795248 | [hydroxy-[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphoryl]methylphosphonic acid | C11H18N2O10P2 | 400.215542 | -4.1 | 5 | 10 | 6 | 96.23 |
| 10382350 | hydroxymethyl-[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphinic acid | C11H17N2O8P | 336.235041 | -2.9 | 4 | 8 | 5 | 79.98 |
| 16755648 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl hydrogen phosphate | C10H14N2O8P- | 321.200521 | -2.9 | 3 | 8 | 4 | 78.28 |
| 10916266 | [(2R)-2,3-dihydroxypropyl] [(2R,3S,5R)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] hydrogen phosphate | C13H21N2O10P | 396.287001 | -3.2 | 10 | 5 | 8 | 77.93 |
| 18531120 | (5R)-3-hydroxy-5-(5-methyl-2,4 dioxopyrimidin-1-yl)oxolan-2-yl]methyl dihydrogen phosphate | C10H15N2O8P | 322.208461 | -2.8 | 4 | 8 | 4 | 76.25 |
| 16755631 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate | C10H13N2O8P-2 | 320.192581 | -3 | 2 | 8 | 3 | 74.56 |
| 452554 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl dipropyl phosphate | C16H27N2O8P | 406.367941 | -3.2 | 5 | 10 | 8 | 74.33 |
| 452555 | dibutyl[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate | C18H31N2O8P | 434.421101 | 0.8 | 2 | 8 | 12 | 74.18 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5274147 | carbamoyl-[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphinic acid | C11H16N3O8P | 349.233801 | -3.1 | 4 | 8 | 5 | 73.64 |
| 10916266 | (2R)-2,3-dihydroxypropyl(2R,3S,5R)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] hydrogen phosphate | C13H21N2O10P | 396.287001 | -3.2 | 5 | 10 | 8 | 73.22 |

**Table(2): This tabulation shows the best top ranking molecules from the pubchem database based on the cdocker energy**

| ID NUMBER | Molecule name | Mol.formula | Mol.weight | Xlogp | h-bond donor | h-bond acceptor | Rotatable bonds | =-cdocker energy |
|---|---|---|---|---|---|---|---|---|
| 16755631 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate | C10H13N2O8P-2 | 320.192581 | -3 | 2 | 8 | 3 | 50.708 |
| 452555 | dibutyl[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate | C18H31N2O8P | 434.421101 | 0.8 | 2 | 8 | 12 | 47.431 |
| 452554 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl dipropyl phosphate | C16H27N2O8P | 406.367941 | -3.2 | 5 | 10 | 8 | 42.503 |
| 16755648 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl hydrogen phosphate | C10H14N2O8P- | 321.200521 | -2.9 | 3 | 8 | 4 | 37.251 |
| 11795248 | hydroxy-[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1yl)oxolan-2yl]methoxy]phosphoryl]methylphosphonic acid | C11H18N2O10P2 | 400.215542 | -4.1 | 5 | 10 | 6 | 36.172 |
| 21595762 | hydroxy-[[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy-oxidophosphoryl]methyl]phosphinate | C11H16N2O10P2-2 | 398.199662 | -4.2 | 5 | 10 | 6 | 32.728 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10472169 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl methyl hydrogen phosphate | C11H17N2O8P | 336.235041 | -2.3 | 3 | 8 | 5 | 31.767 |
| 21796618 | [(2R,3S,5R)-2-(hydroxymethyl)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] hydrogen phosphate | C10H14N2O8P | 321.200521 | -2.5 | 3 | 8 | 4 | 31.519 |
| 21344781 | [2-(hydroxymethyl)-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] methyl hydrogen phosphate | C11H17N2O8P | 336.235041 | -1.9 | 3 | 8 | 5 | 29.002 |
| 21595762 | hydroxy-[[[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy-oxidophosphoryl]methyl]phosphinate | C11H16N2O10P2-2 | 398.199662 | -4.2 | 3 | 10 | 6 | 28.256 |

**Table(3): this tabulation shows the best top ranking molecules from the chembank database based on the PLP 2 values**

| ID NUMBER | Molecule name | Mol.formula | Mol.weight | xlogp | h-bond donor | h-bond acceptor | Rotatable bonds | =-PLP2 |
|---|---|---|---|---|---|---|---|---|
| 3069815 | 1- (2- deoxy- beta- D- threo- pentofuranosyl) - 5- (trifluoromethyl) pyrimidine- 2,4(1H,3H) – dione(trifluridine) | NA | 296.19994 | -0.782 | 3 | 5 | 3 | 82.08 |
| 3061444 | 1- {5- O- [(R) - hydroxy(phosphonooxy) phosphoryl]- beta- D- arabinofuranosyl}pyrimidine- 2,4(1H,3H) - dione | NA | 404.16118 | -2.885 | 6 | 12 | 6 | 71.78 |
| 1047071 | 5- fluoro- 1- {5- O- [(R) - hydroxy(phosphonooxy) phosphoryl]- alpha- L- arabinofuranosyl}pyrimidine- 2,4(1H,3H) - dione | NA | 422.15164 | -2.976 | 6 | 12 | 6 | 70.62 |
| 831828 | 1- alpha- L- arabinofuranosyl- 5- methylpyrimidine- 2,4(1H,3H) - dione (IUPAC), 1- beta- D- | | NA | | NA | NA | NA | 68.95 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | arabinofuranosylthymine (chemical), 2,4(1H,3H) - pyrimidinedione,1- beta- D- arabinofuranosyl- 5- methyl- | NA | | NA | | | | |
| 1000059 | 1- (2- deoxy- alpha- L- threo- pentofuranosyl) - 5- methylpyrimidine- 2,4(1H,3H) - dione | | 242.22856 | | 3 | 5 | 2 | 67.67 |
| 913 | NA | NA | 484.14108 | NA | 7 | 15 | 8 | 66.45 |
| 907315 | 1- (2'- deoxy- beta- D- ribofuranosyl) - 5- ethyluracil (chemical), 1- (2- deoxy- alpha- L- erythro- pentofuranosyl) - 5- ethylpyrimidine- 2,4(1H,3H) – dione | NA | NA | NA | NA | NA | NA | 66.41 |
| 2094560 | NA | NA | 272.25453 | -1.8 | 4 | 6 | 2 | 63.52 |
| 432506 | NA | NA | NA | NA | NA | NA | NA | 59.96 |
| 1041881 | 1- alpha- L- arabinofuranosyl- 5- methylpyrimidine- 2,4(1H,3H) – dione | NA | NA | NA | NA | NA | NA | 59.76 |

**Table(4): This tabulation shows the best top ranking molecules from the chembank database based on the cdocker energy**

| ID NUMBER | Molecule name | Mol.formula | Mol.weight | Xlogp | h-bond donor | h-bond acceptor | Rotatable bonds | = -cdocker energy |
|---|---|---|---|---|---|---|---|---|
| 2082067 | 2- {[(R) - {[(S) - {[(2S,5S) - 5- (4- amino- 2- oxopyrimidin- 1(2H) - yl) tetrahydrofuran- 2- yl] methoxy} (hydroxy)phosphoryl]oxy}(hydroxy)phosphoryl]oxy}-N,N,N- trimethylethanaminium | NA | 457.3331 | NA | 11 | 3 | 10 | 38.251 |
| 3061444 | 1- {5- O- [(R) - hydroxy(phosphonooxy) phosphoryl]- beta- D- arabinofuranosyl}pyrimidine- 2,4(1H,3H) - dione | NA | 404.16118 | -2.885 | 6 | 12 | 6 | 33.628 |
| 913 | NA | NA | 484.14108 | NA | 7 | 15 | 8 | 32.624 |
| 831876 | 1- (2- deoxy- 3,5- di- O- | NA | NA | NA | NA | NA | NA | 28.418 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | phosphonopentofuranosyl) - 5-methylpyrimidine- 2,4(1H,3H) - dione | | | | | | | |
| 1000059 | NA | NA | 242.22856 | NA | 3 | 5 | 2 | 21.48 |
| 1047071 | 5- fluoro- 1- {5- O- [(R) - hydroxy(phosphonooxy) phosphoryl]- alpha- L- arabinofuranosyl}pyrimidine- 2,4(1H,3H) - dione | NA | 422.15164 | -2.976 | 6 | 12 | 6 | 21.268 |
| 831828 | NA | NA | NA | NA | NA | NA | NA | 20.987 |
| 3069815 | 1- (2- deoxy- beta- D- threo- pentofuranosyl) - 5- (trifluoromethyl) pyrimidine- 2,4(1H,3H) - dione | NA | 296.19994 | -0.782 | 3 | 5 | 3 | 18.719 |
| 2098981 | 1- (2- deoxy- 3- O- methyl- alpha- L- erythro- pentofuranosyl) - 5- methylpyrimidine- 2,4(1H,3H) – dione | NA | 256.25514 | -0.83 | 2 | 5 | 3 | 18.529 |
| 2117600 | 1- (2- deoxy- beta- L- erythro- pentofuranosyl) - 5- methylpyrimidine- 2,4(1H,3H) – dione | NA | 242.22856 | -1.238 | 3 | 5 | 2 | 17.203 |

**Table (5): This tabulation shows the best top ranking molecules from the zinc database based on the PLP values**

| ID NUMBER | Molecule name | Molecular formula | Molecular weight | Xlop | h-bond donor | h-bond acceptor | Rotatable bonds | = -PLP2 |
|---|---|---|---|---|---|---|---|---|
| 2258599 | 3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]amino}-N-(2-hydroxyethyl)-3-oxopropan-1-aminium | C16 H25 N2 O4 S | 341.456 | 0.46 | 4 | 5 | 7 | 73.13 |
| 19990070 | (5Z)-5-[(2-carbamoylhydrazinyl) methylidene]-6-oxo-2-thioxo-1-[3-(trifluoromethylphenyl]-1,2,5,6-tetrahydropyrimidin-4-olate | C13H10F3N5O3S | 373.31041 | 1.8 | 4 | 7 | 3 | 41.38 |
| 3901268 | 2-{[2-(2-methoxyphenoxy)ethyl]sulfanyl}-6-methylpyrimidin-4(3H)-one | C14 H16 N2 O3 S | 292.362 | 2.584 | 1 | 5 | 6 | 56.91 |
| 19989886 | diethyl-[2-[[1-(2-methoxyphenyl)-4,6- | C18 H25 N4 O3 | 377.492 | 0.292 | 4 | 3 | 8 | 45.88 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | dioxo-2-sulfanylidene-1,3-diazi nan- 5-ylidene]methylamino]ethyl]azanium | S | | | | | | |
| 8575396 | N-(3,5-dimethylphenyl)-2-[(2E)-4-hydroxy-2-(propan-2-ylidenehydra zinylidene)-2,5-dihydro-1,3-thiazol-5-yl]acetamide | NA | NA | NA | NA | NA | NA | 57.85 |
| 982962 | N-benzyl-2-{[(4-fluorophenyl)sulfonyl]amino}-N-methylacetamide | C16 H17 N2 O3 F S | 336.39 | 1.796 | 1 | 5 | 6 | 73.27 |
| 20030231 | [(4-ethoxyphenyl)amino](oxo)acetate | C10 H10 N O4 | 208.197 | -0.415 | 1 | 4 | 4 | 49.54 |
| 6219168 | 6-(benzylsulfanyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione | C13 H14 N2 O2 S | 262.335 | 2.731 | 3 | 0 | 3 | 63.63 |
| 12378847 | 2-{(2E,5S)-2-[(2E)-(3,3-dimethylbutan-2-ylidene)hydrazinylidene]-4-hydroxy-2,5-dihydro-1,3-thiazol-5-yl}-N-(2-methoxyphenyl)acetamide | C18 H24 N4 O3 S | 376.484 | 3.12 | 2 | 7 | 6 | 63.61 |
| 18153302 | 1,7-dihydro-6H-purin-6-one | C5 H4 N4 O | 136.115 | -0.532 | 2 | 3 | 0 | 48.43 |

**Table(6): This tabulation shows the best top ranking molecules from the zinc database based on the cdocker energy**

| ID NUMBER | Molecule name | Molecular formula | Molecular weight | Xlogp | H bond donor | h-bond acceptor | Rotatable bonds | -Cdocker energy |
|---|---|---|---|---|---|---|---|---|
| 9365179 | N-(4-methylpyridin-2-yl)-2-(naphthalen-1-yl) acetamide | C18 H16 N2 O | 276.34 | 3.433 | 1 | 2 | 3 | 10.558 |
| 982962 | N-benzyl-2-{[(4-fluorophenyl)sulfonyl]amino}-N-methylacetamide | C16 H17 N2 O3 F S | 336.39 | 1.796 | 1 | 5 | 6 | 23.344 |
| 19990034 | 2-{[(4-tert-butylphenyl)carbonyl]amino}benzenethiolate | C17 H18 N O S | 284.404 | 3.864 | 1 | 2 | 3 | 16.908 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5286115 | 2,3-bis[(1-methyl-1H-imidazol-2-yl)sulfanyl]quinoxaline | C16 H14 N6 S2 | 354.462 | 3.879 | 0 | 6 | 4 | 0.506 |
| 2258599 | 3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]amino}-N-(2-hydroxyethyl)-3-oxopropan-1-aminium | C16 H25 N2 O4 S | 341.456 | 0.46 | 4 | 5 | 7 | 36.718 |
| 19794473 | (2E,5E)-5-{3-[(2-chloro benzyl)oxy]-4-methoxy benzylidene}-2-imino-1,3-thiazolidin-4-one | NA | NA | NA | NA | NA | NA | 6.607 |
| 5519407 | [(3R)-1-(3-chloroquinoxalin-2-yl)piperidin-3-yl]methanol | C14 H16 N3 O Cl | 277.756 | 2.885 | 1 | 4 | 2 | 7.468 |
| 3901268 | 2-{[2-(2-methoxyphenoxy)ethyl]sulfanyl}-6-methylpyrimidin-4(3H)-one | C14 H16 N2 O3 S | 292.362 | 2.584 | 1 | 5 | 6 | 26.913 |
| 30345 | 3-(dimethylamino)-N-(4-sulfamoylbenzyl)benzamide | C16 H19 N3 O3 S | 333.415 | 1.489 | 2 | 4 | 5 | 15.596 |
| 1700294 | (2R)-3-cyano-N,N,2-trimethyl-3,3-diphenylpropan-1-aminium | C19 H23 N2 | 279.407 | 2.323 | 1 | 1 | 6 | 18.065 |

**Table(7): This tabulation shows the best top ranking molecules from the drug bank database based on the PLP 2 values**

| ID NUMBER | Molecule name | Molecular formula | Molecular weight | Xlogp | H bon donor | h-bond acceptor | Rotatable bonds | PLP2 |
|---|---|---|---|---|---|---|---|---|
| 432 | 1-[(2R,4S,5R) -4-hydroxy-5 -(hydroxymethyl) oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione | C10 H11 N2 O5 F3 | 296.206 | -0.587 | 3 | 8 | 2 | 85.87 |
| 2549 | [(2R,3S,5R)-2-[(hydroxy-phosphonooxyphosphoryl)oxymethyl]-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] acetate | C12 H18 N2 O12 P2 | 444.238 | -0.803 | 4 | 12 | 7 | 74.14 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2324 | [(2R,3S,5R)-3-hydroxy-5-(5-iodo-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl dihydrogen phosphate | C9 H12 N2 O8 P I | 434.088 | -1.092 | 4 | 9 | 3 | 72.89 |
| 2023 | 1S,2R,8R,8aR)-1,2,3,5,6,7,8,8a-octahydroindolizine-1,2,8-triol | C10 H14 N5 O8 P | 363.231 | -2.266 | 6 | 9 | 3 | 71.89 |
| 249 | 1-[(2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-iodopyrimidine-2,4-dione | C10 H12 N4 08P | 354.45 | -1.45 | 7 | 7 | 3 | 68.51 |
| 2189 | (2S,5R)-5-(6-aminopurin-9-yl)oxolan-2-yl]methyl (hydroxy-phosphonooxyphosphoryl) hydrogen phosphate | C10 H16 N5 O11 P3 | 475.195 | -1.009 | 11 | 14 | 7 | 68.34 |
| 2623 | [(2R,3S,4R,5R)-5-(2-amino-6-oxo-3H-purin-9-yl)-3,4-dihydroxyoxolan-2-yl]methoxy-hydroxyphosphoryl]oxyphosphonamidic acid | C10 H16 N6 O10 P2 | 442.228 | -3.146 | 7 | 13 | 5 | 64.61 |
| 2380 | [(2R,3S,5R)-3-hydroxy-5-(6-oxo-3H-purin-9-yl)oxolan-2-yl]methyl phosphono hydrogen phosphate | C10 H14 N4 O10 P2 | 412.198 | -1.621 | 5 | 12 | 5 | 61.29 |
| 2309 | (2R,3S,4R,5R)-5-(2,6-dioxo-3,7-dihydropurin-9-ium-9-yl)-3,4-dihydroxyoxolan-2-yl]methyl dihydrogen phosphate | C10H14N4O9 P | 365.2133 | -1.22 | 7 | 9 | 3 | 60.66 |
| 1903 | [(2R,3S,5R)-5-(5-bromo-2,4-dioxopyrimidin-1-yl)-3-hydroxyoxolan-2-yl]methyl dihydrogen phosphate | C9 H12 N2 O8 P Br | 387.087 | -0.922 | 4 | 9 | 3 | 60.4 |

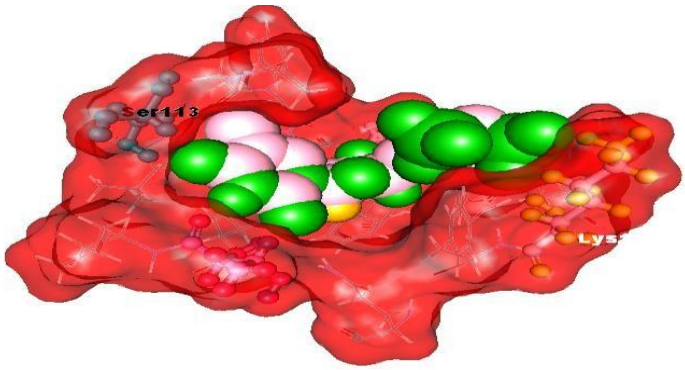
**Table(8): This tabulation shows the best top ranking molecules from the drug bank database based on the cdocker energy**

| ID NUMBER | Molecule name | Molecular formula | Molecular weight | xlogP | H bond donor | h-bond acceptor | Rotatable bonds | Cdocker energy |
|---|---|---|---|---|---|---|---|---|
| 2333 | Deoxyuridine-5'-Triphosphate | C9 H15 N2 O14 P3 | 468.155 | -1.883 | 6 | 14 | 7 | 41.43 |
| 2452 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl (hydroxy-phosphonooxyphosphoryl) hydrogen phosphate | C9 H14 N2 O14 P3 | 428.155 | -1.873 | 7 | 12 | 6 | 41.32 |
| 2189 | (2S,5R)-5-(6-aminopurin-9-yl)oxolan-2-yl]methyl (hydroxy-phosphonooxyphosphoryl) hydrogen phosphate | C10 H16 N5 O11 P3 | 475.195 | -1.009 | 5 | 14 | 7 | 37.256 |
| 2649 | [(2R,3S,5R)-2-[(hydroxy-phosphonooxyphosphoryl)oxymethyl]-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-3-yl] acetate | C12 H18 N2 O12 P2 | 444.238 | -1.009 | 5 | 14 | 7 | 36.292 |
| 2552 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl (hydroxy-phosphonooxyphosphoryl) hydrogen phosphate | C12 H14 N2 O12 P2 | 432.238 | -1.056 | 4 | 12 | 6 | 35.018 |
| 1965 | [(2R,3S,5R)-5-(2,4-dioxopyrimidin-1-yl)-3-hydroxyoxolan-2-yl]methoxy-N-(hydroxy-phosphonoox yphosphoryl)phosphonamidic acid | C9 H16 N3 O13 P3 | 467.177 | -2.019 | 7 | 14 | 7 | 29.792 |
| 1903 | [(2R,3S,5R)-5-(5-bromo-2,4-dioxopyrimidin-1-yl)-3-hydroxyoxolan-2-yl]methyl dihydrogen phosphate | C9 H12 N2 O8 P Br | 387.087 | -0.922 | 4 | 9 | 3 | 25.765 |
| 1965 | [(2R,3S,5R)-5-(2,4-dioxopyrimidin-1-yl)-3-hydroxyoxolan-2-yl]methoxy-N- | C10 H12 N2 O8 P | 372.2 | -0.928 | 4 | 8 | 3 | 24.647 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | (hydroxy-phosphonoox yphosphoryl)phosphonamidic aci | | | | | | | |
| 1643 | [(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl dihydrogen phosphate | C10 H15 N2 O8 P | 322.217 | -0.827 | 7 | 7 | 3 | 24.647 |
| 249 | 1-[(2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-5-iodopyrimidine-2,4-dione | C10 H12 N2 O8 P | 352.218 | -0.728 | 6 | 8 | 3 | 24.647 |

**Successive Docking Results**

1. Among these best molecules were selected based on the PLP2 VALUES and CDOCKER ENERGY. The best molecule was identified as , hydroxy-[[(2R, 3S,5R)-3-hydroxy-5-(5-methyl- 2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphoryl]methyl phosphonic acid – this molecule having the greatest stability molecules with active site and 7 hydrogen bonds. The active site residues are LYS170, TYR171, SER113, and ASP119 with H-BOND distance between the LYS 170:2.22764,2.0554,2.21248; TYR 171:2.17674; SER 113:2.108; and ASP 119:2.1367,1.94393.

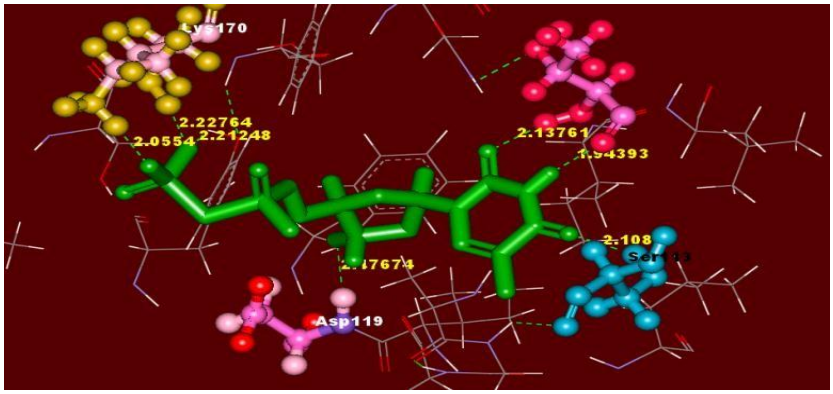



**Fig(16):This shows the surface around the molecule and cavity shows the induced fit model of receptor –ligand interactions. The red colour shows the hydrophobic residues and H-BOND interaction between them.**

**Table (9): This tabulation shows the eight best top ranking molecules**

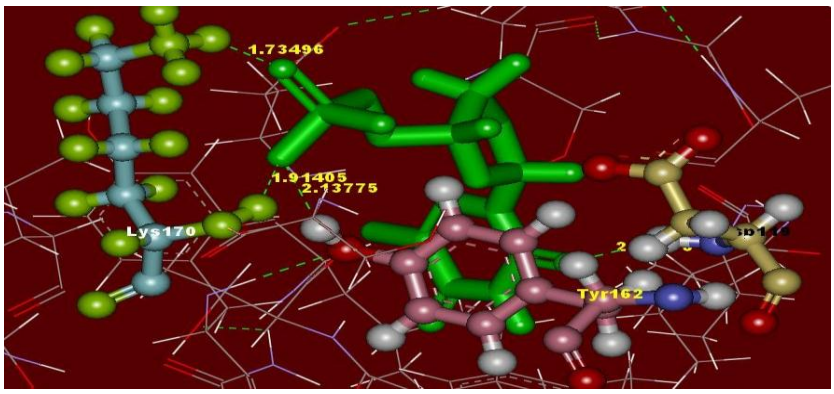
| S.NO | MOLECULE NAME | PLP2 VALUE | CDOCKER ENERGY SCORE | BINDING RESIDUE | Number of H-bonding |
|---|---|---|---|---|---|
| 1 | hydroxy-[[(2R, 3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methoxy]phosphoryl]methyl phosphonic acid | -96.23 | -36.172 | LYS170,TYR171,SER 113, and ASP 119 | 7 |
| 2 | -.[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate | -67.42 | -50.708 | LYS170, TYR 162, and ASP 119 | 5 |
| 3 | 1- (2- deoxy- beta- D- threo- pentofuranosyl) - 5- (trifluoromethyl) pyrimidine- 2,4(1H,3H) – dione(trifluridine) | -82.08 | -16.967 | LYS170, TYR 162, THR127, GLY116, SER113 and ASP 119. | 7 |
| 4 | 2- {[(R) - {[(S) - {[(2S,5S) - 5- (4- amino- 2- oxopyrimidin- 1(2H) - yl) tetrahydrofuran- 2- yl]methoxy}(hydroxy) phosphoryl]oxy}(hydroxy) phosphoryl]oxy}- N,N,N- trimethylethanaminium | -51.94 | -38.251 | THR127, GLY116, and ALA115. | 3 |
| 5 | 3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]amino}-N-(2-hydroxyethyl)-3-oxopropan-1-aminium | -73.13 | -36.718 | THR127, GLY116, and ALA115. | 5 |
| 6 | N-(4-methylpyridin-2-yl)-2-(naphthalen-1-yl) acetamide | -78.72 | -10.558 | TYR162 | 1 |
| 7 | 1-[(2R,4S,5R) -4-hydroxy-5 -(hydroxymethyl) oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione | -85.87 | -21.147 | 0 | 0 |
| 8 | Deoxyuridine-5'-Triphosphate | -55.6 | -41.43 | PHE117,& ASP119. | 4 |

1. Among these eight best molecules , this ligand having the more stablity having with the7 hydrogen bonds between the amino acids LYS170, TYR 171,SER 113, and ASP 119.This figure shows the ligand in the green colour,and The h- bond distance showed as in yellow colour. This molecule picked up based on the PLP2 value (-96.23). This molecule taken from the pubchem database ID: 11795248, based on the Lipinski's rule of five.



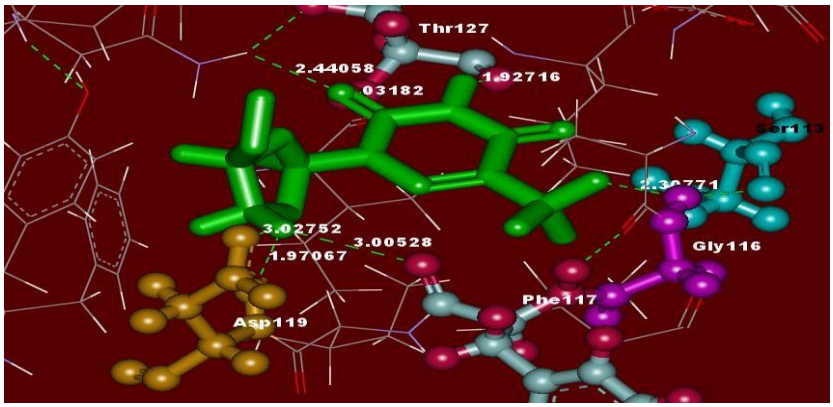

**Fig(17): this snapshot shows the molecule with 7 h-bonding with hydrophobic residue LYS170, TYR 171,SER 113, and ASP 119.**

2. This molcule-.[(2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2-yl]methyl phosphate , having the 5 hydrogen bonds between the amino acids LYS170, TYR 162, and ASP 119. This figure shows the ligand in the green colour. The H- bond distance showed as in yellow colour. This molecule needs required lowest minimum cdocker energy(-50.708) to dock on the site, (PUBCHEM database: 16755631.).



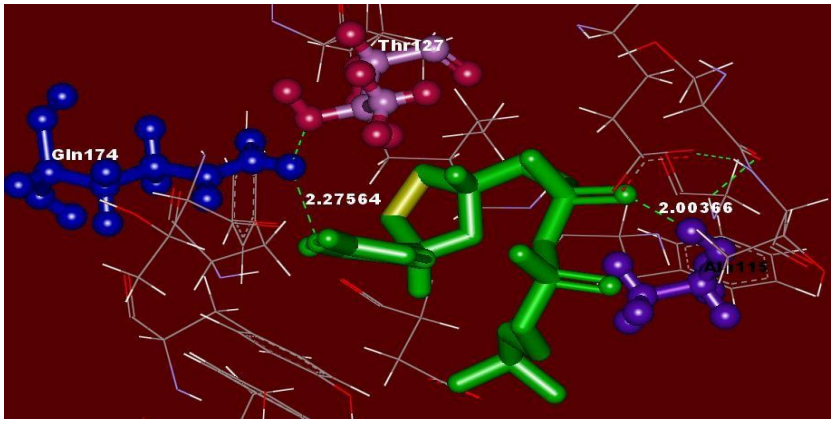

**Fig(18): this snapshot shows the molecule with 5 h-bonding with hydrophobic residue LYS170, TYR 162, and ASP 119.**

3. .This molcule 1- (2- deoxy- beta- D- threo- pentofuranosyl) - 5- (trifluoromethyl) pyrimidine- 2,4(1H,3H) – dione(trifluridine) , having the 7 hydrogen bonds between the amino acids LYS170, TYR 162, THR127, GLY116, SER113 and ASP 119. This figure shows the ligand in the green colour. The H- bond distance showed as in yellow colour. This molecule needs required lowest PLP2 (-82.08)to dock on the site, (CHEMBANK ID: 3069815.)



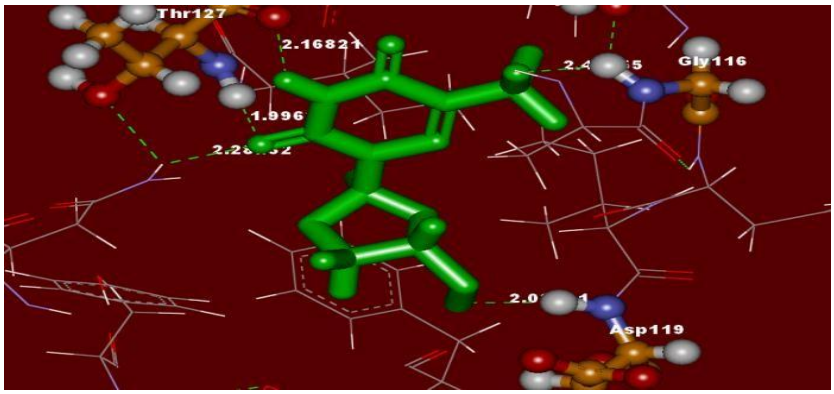

**Fig(19): this snapshot shows the molecule with 7 h-bonding with hydrophobic residue LYS170, TYR 162, THR127, GLY116, SER113 and ASP 119.**

4. This molcule 2- {[(R) - {[(S) - {[(2S,5S) - 5- (4- amino- 2- oxopyrimidin- 1(2H) - yl) tetrahydrofuran- 2- yl]methoxy}(hydroxy) phosphoryl]oxy}(hydroxy) phosphoryl]oxy}- N,N,N- trimethylethanaminium having the 3 hydrogen bonds between the amino acids GLN 174,THR127,and SER113. This figure shows the ligand in the green colour. The H- bond distance showed as in yellow colour. This molecule required only lowest CDOCKER energy (-38.251) to dock on the site, (CHEMBANK ID: 2082067).




**Fig(20): this snapshot shows the molecule with 3 H-bonding with hydrophobic residue THR127, GLY116, and ALA115.**

5. .This molcule 3-{[3-(ethoxycarbonyl)-4,5,6,7-tetrahydro-1-benzothiophen-2-yl]amino}-N- (2-hydroxyethyl)-3-oxopropan-1-aminium, having the 5 hydrogen bonds between the amino acids THR127, GLY116, SER113 and ASP 119. This figure shows the ligand in the green colour. The H- bond distance showed as in yellow colour. This molecule needs required lowest PLP2 (-73.13)to dock on the site, (ZINC ID: 2258599.)




**FIG(21): this snapshot shows the molecule with 5 H-bonding with hydrophobic residue THR127, GLY116, and ALA115.**

6. This molcule N-(4-methylpyridin-2-yl)-2-(naphthalen-1-yl) acetamide, having the 1 hydrogen bonds between the amino acid TYR162. This figure shows the ligand in the green colour. The H- bond distance showed as in yellow colour. This molecule required only lowest CDOCKER energy (-10.558) to dock on the site, (ZINC ID: 9365179).

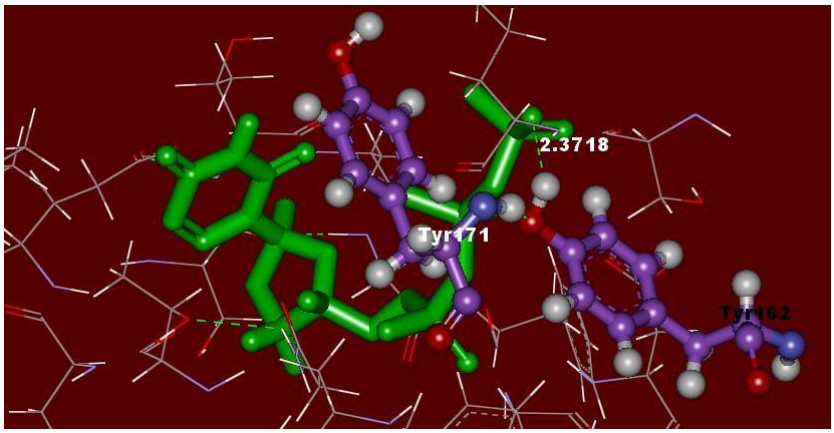
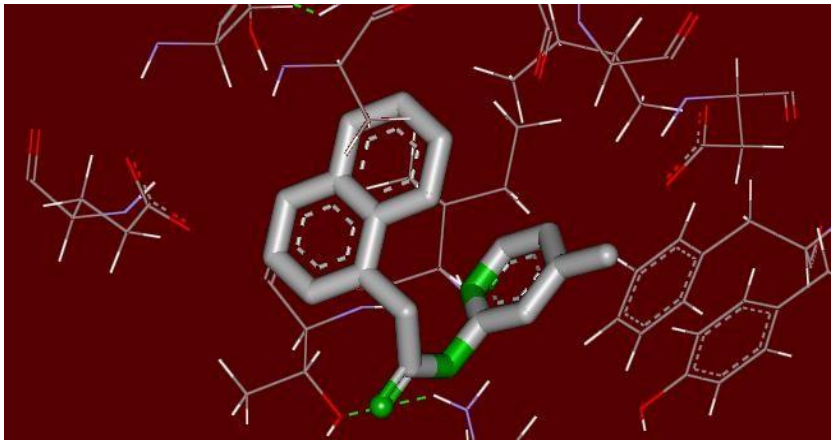



**Fig (22): this snapshot shows the molecule with 1H-bonding with hydrophobic residue**

7. This molecule 1-[(2R,4S,5R) -4-hydroxy-5 -(hydroxymethyl) oxolan-2-yl]-5-(trifluoromethyl)pyrimidine-2,4-dione having no hydrogen bonds between the amino acids.This figure shows the ligand in the green with white colour. This molecule required only lowest PLP2 Value (-85.87) to dock on the site, (DRUG BANK ID: DB00432).



**Fig(23): this snapshots that having NO H –bonding between the molecules and hydrophobic residues.**

8. This molecule Deoxyuridine-5'-Triphosphate having the 4 hydrogen bonds between the amino acid PHE117,& ASP119. This figure shows the ligand in the green colour. The H-bond distance showed as in yellow colour. This molecule required only lowest CDOCKER energy (-41.43) to dock on the site, (DRUG BANK ID:DB02333)

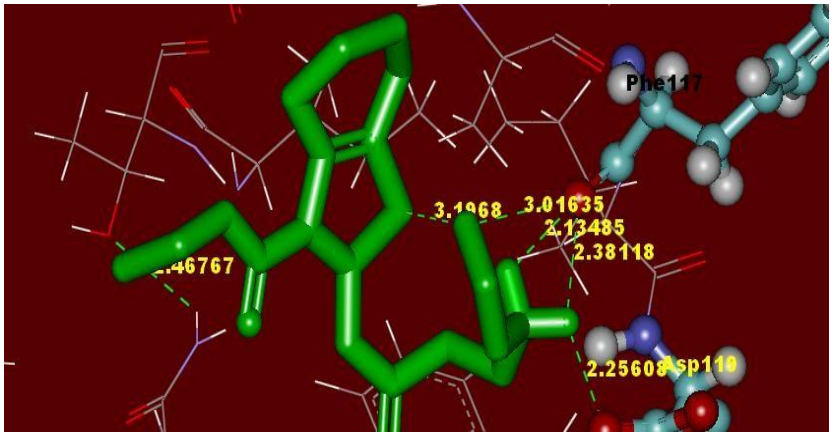



**Fig (24): this snapshot shows the molecule with 4 H-bonding with hydrophobic residue PHE117,& ASP119.**

**SUMMARY**

Bifunctional dCTP deaminase –dUTPase enzyme was chosen as a targetprotein for molecular docking .since it is already reported to be involved in the survival,growth,virulence and persistance of *Mycobacterium tuberculosis.*To get the atomic coordinates from PDB Id:2qxx.Small molecules where selected from different cheminformatics databases such as pubchem,chembank,drug bank,and zinc related to the TTP(thymidine -5'-triphosphate) structure. Molecular docking of DCD gene with 131 molecules was carried out with using

CDOCKER.Out of 131 molecules 93 molecules were found to be bind to the protein.The results are based on the scoring ligand poses of docked molecules and best molecules were examined based on the PLP2 values and CDOCKER'S energy.

## CONCULSION

Among these 93 molecules 2R,3S,5R)-3-hydroxy-5-(5-methyl-2,4-dioxopyrimidin-1-yl)oxolan-2yl]methylphosphate which is related to TTP were better than the rest of the molecules based on the PLP2 values , CDOCKER'S energy and CDOCKER'S interaction energy. The molecular properties of these molecule can be used to design the novel drug for this protein.

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