IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Molecular Docking Comparison of flucanazole drug and its derivatives for Candida albicans

Dr.D.Ravi sankara Reddy*[1],T.Srinivasarao*[2]

1.Assistant Professor, Department of Pharmaceutical Chemistry Acharya Nagarjuna University College of Pharmaceutical Sciences,Guntur-522510

2. Department of Pharmaceutical Chemistry Acharya Nagarjuna University College of Pharmaceutical Sciences

ABSTRACT

Candidiasis is a common infection of skin, oral, cavity, esophagus, gastrointestinal tract, vagina and vascular systems of humans. The ability of this highly adaptable fungal species to transition from commensal to pathogen is due to a repertoire of virulence factors. Specifically, the ability to switch morphology and form biofilms are properties central to Candida albicans pathogenesis. In past two decades, it has been observed abnormal overgrowth in the gastrointestinal, urinary and respiratory tracts, not only in immunocompromised patients, but also related to nosocomial infections and even in healthy individuals. There are wide variety of causal factors that contribute to yeast infections which means candidiasis is a good example of multifactorial syndrome. This disease transition in the pathophysiology of the onset and progression of infection is also influenced by Candida's virulence traits that lead to the development of candidiasis the disease candidiasis is treated with the drug Fluconazole. In this project I had taken fluconazole as a drug with 10 different similar analogues and 1ea1A as my target protein. Then docking is done at the active site site of the protein by using autodock 1.5.7 version. Then after docking ligands with different binding energies were found out. At the end of this work . I have been screened out one of the analog is with highest binding energy bases on all other binding energy parameters. Finally ligand with PUBCHEM CID-129829800 has highest binding affinity with 8.1kcal/mol among al other similar analogs of Fluconazole.

Key words: Fluconazole, molecular docking, Candida albicans, Variconazole, Anti-fungal drugs

1. INRODUCTION

1.1. Disease and disease pathway:

Disease: Candida albicans, a commonly encountered fungal pathogen, causes diseases varying from superficial mucosal complaints to life threatening systemic disorders. Candida albicans can, not only infect skin and mucosa, but can also cause life threatening systematic candidiasis. The spectrum ranges from vaginal infections, which affect up to 75% of the woman at least once in their life time, to deep infections in hospitalized patients which leads to high mobility and mortality rates. Candida albicans is a producer of extracellular hydrolytic enzymes. Among them lipases, phospholypases and secreted aspartyl proteinases (Sap) are most significant in virulence. Sap proteins contribute to pathogenisis by digestion of host cell membranes and molecules of the host immune systems to avoid antimicrobial attack by the host.

CANDIDA ALBICANS

The yeast is a common commensal of the gastrointestinal tract. Most *Candida* species are opportunistically occurring in debilitated persons e.g. Diabetes patients, those who are taking anticancer therapy and immunocompromised patients, HIV patients, and so on.

CLASSIFICATION

Scientific classification
Kingdom: Fungi
Division: Ascomycota
Class: Saccharomyces's
Order: Saccharomycetales
Family: Saccharomycetaceae
Genus: *Candida*
Species: *C. albicans*
Other medically important *Candida tropicalis, Candida parapsilosis, Candida glabrata and Candida krusei.*

MORPHOLOGY OF CANDIDA ALBICANS

Yeasts are small, oval, measuring 3-4 µm in diameter. Single, budding of the cells may be seen. The yeast cells can also be seen attached with pseudohyphae.

PATHOGENICITY OF CANDIDA ALBICANS

It causes a disease called candidiasis also called moniliasis. It is an infection causing fungi of the genus formerly Monilia or now *Candida* (especially *Candida albicans*).

The various forms of diseases are –

1. Oral thrush: Also known as Candidiasis of the mouth or oropharyngeal candidiasis which is seen as white patches on the mucosa of the mouth including the tongue. The affected site can become inflamed and may cause difficulty in swallowing causing cracking and inflammation which may occur around the mouth. Such a condition is referred to as oral cheilitis. Oral thrush may spread to the esophagus (esophagitis). Although most people harbor Candida species, oral candidiasis is typically found in immunocompromised hosts like AIDS patients (9 to 31%), people taking immunosuppressive drugs for cancer chemotherapy (20%), and organ transplantation. Other factors associated with oral thrush are diabetes, certain dentures, and the use of corticosteroids. 5 and 7% of neonates develop oral candidiasis (CDC) and untreated oral thrush can lead to serious invasive disease.
2. Vaginal thrush: Also called genital or vulvovaginal candidiasis cause genital itching, a burning sensation, and vaginal discharge in females and while in men, the penis may have an itching rash. This is rare in men but most women will have at least one episode of vulvovaginal candidiasis.
3. Leucorrhoea : It is a flow of a whitish, yellowish, or greenish discharge from the vagina that may be normal or a sign of infection. Discharges may originate from the various female reproductive parts such as the vagina, ovaries, fallopian tubes, or, most commonly, the cervix. Leukorrhea may occur during pregnancy and is considered normal when the discharge is thin, white, and relatively odorless. Physiologic leukorrhea is a normal condition occurring within several months to a year of the onset of the menstrual cycle in adolescent girls and is sometimes present in newborn girls, usually lasting one to two months. However, in many cases, leukorrhea is a sign of infection, especially when the discharge is yellow or green, with an offensive odor, and is accompanied by irritation, itching, pain, or tissue inflammation due to *Candida.*
4. Candidemia: Also called Invasive candidiasis is a serious disease when *Candida*, which is normally on the skin or the gastrointestinal tract (GIT), enters the bloodstream where it can disseminate to other organs. Patient with such condition has symptoms like fever and chills that do not respond to antibacterial agents. These are often nosocomial (hospital-acquired) infections of people who have a central venous catheter are immunosuppressed take broad-spectrum antibiotics show neutropenia are on hemodialysis have diabetes
5. Meningitis and meningoencephalitis: Meningitis due to *Candida* is mucocutaneous and deeply Invasive Candidiasis are uncommon. Infection can be secondary to hematogenous dissemination or direct inoculation. Neurosurgery, recent antibiotics, and corticosteroids are predisposing factors. Fever, meningismus, elevated CSF pressures, and localizing neurologic signs are commonly noted.

LABORATORY:

Diagnosis of Staphylococcus aureus

Sample collection

Samples are collected according to the site of infections. They may be-

- vaginal swab
- Tongue swab
- Blood
- CSF
- Tissue
- Urine
- Exudate
- Swabs from the mucosal surface

Direct microscopic examination

Wet mount preparation

Gram stain

Culture: Culture on Sabouraud Dextrose agar (SDA) at 37° C for 24-48 hours. After incubation observes colonial morphology.

Colony characteristics

Cream-colored pasty and glistening as shown above picture.

IDENTIFICATIONS OF CANDIDA ALBICANS:

Wet mount preparation: Single or budding yeast with or without pseudo hyphae.

Gram stain: single or budding of yeast with or without pseudo hyphae and gram-positive

Germ tube test: Positive

The test is carried out using 0.5 ml rabbit or human serum in which test yeast cells are inoculated and incubated at 37°C for 2-3 hours.

Put a drop of this after 2-3 hours incubation on the slide and cover with the coverslip. Focus at 10X objective and finally observe at high power objective (40X) of a compound microscope.

TREATMENT

Treatment of Candidiasis depends on location and severity.

For oral thrush–Oral nystatin suspension

Similarly, for skin and vulvovaginitis –topical antifungals while in resistant case

azole antifungal medication

In severe infections

- Amphotericin B
- azole antifungals
- Echinocandins like micafungin

KEYPOINTS

1. All fungi are gram-positive.
2. To diagnose Moniliasis, a serological test in patient serum to detect the antibody to *Candida albicans* should perform. Four folds rise in titer of antibody in paired sera of the patient is diagnostic.
3. Chromagar Candida or Hicrome candida differential agar recommendation is for rapid isolation and identification of *Candida* species from mixed cultures in clinical and non-clinical samples.
4. For *Candida* spp. identification other physiological tests like sugar , fermentation and assimilation tests are used.
5. Differences between hyphae and pseudohyphae are in a table.

	Hyphae	Pseudohyphae
Growth process	Apical elongation	Budding
Terminal cell	Longer , cylindrical	Shorter, spherical
Cell wall	Parallel	Constricted at septa
Septa	Straight , perpendicular	Curved or pinched
Origin of branches	No constriction, septum is required.	Constriction and septum present

List of Antifungal Drugs:

1. **Fluconazole**
2. **Voriconazole**
3. **Flucytosine**
4. **Nystatin**
5. **Itraconazole**
6. **Posaconazole**

1.2. Traget protein:

Cytochrome P450 14alpha-sterol demethylases (CYP51) are essential enzymes in sterol biosynthesis in eukaryotes. CYP51 removes the 14alpha-methyl group from sterol precursors such as lanosterol, obtusifoliol, dihydrolanosterol, and 24(28)-methylene-24,25-dihydrolanosterol. Inhibitors of CYP51 include triazole antifungal agents fluconazole and itraconazole, drugs used in treatment of topical and systemic mycoses. The 2.1- and 2.2-A crystal structures reported here for 4-phenylimidazole- and fluconazole-bound CYP51 from Mycobacterium tuberculosis (MTCYP51) are the first structures of an authentic P450 drug target. MTCYP51 exhibits the P450 fold with the exception of two striking differences-a bent I helix and an open conformation of BC loop-that define an active site-access channel running along the heme plane perpendicular to the direction observed for the substrate entry in P450BM3. Although a channel analogous to that in P450BM3 is evident also in MTCYP51, it is not open at the surface. The presence of two different channels, with one being open to the surface, suggests the possibility of conformationally regulated substrate-in/product-out openings in CYP51. Mapping mutations identified in Candida albicans azole-resistant isolates indicates that azole resistance in fungi develops in protein regions involved in orchestrating passage of CYP51 through different conformational stages along the catalytic cycle rather than in residues directly contacting fluconazole. These new structures provide a basis for rational design of new, more efficacious antifungal agents as

1.3. Protein Crystal Structure

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 choosed in X-ray diffraction method.

- **Classification: OXIDOREDUCTASE**
- **Organism(s):** Mycobacterium tuberculosis
- **Expression System:** Escherichia coli
- **Mutations**
- **Method** : X-RAY DIFFRACTION
- **Resolution** : 2.21 Å
- **R-Value Free** : 0.249
- **R-Value Work** : 0.204
- **R-Value Observed** : 0.204
- **Space Group** : **P 2_1 2_1 2_1**

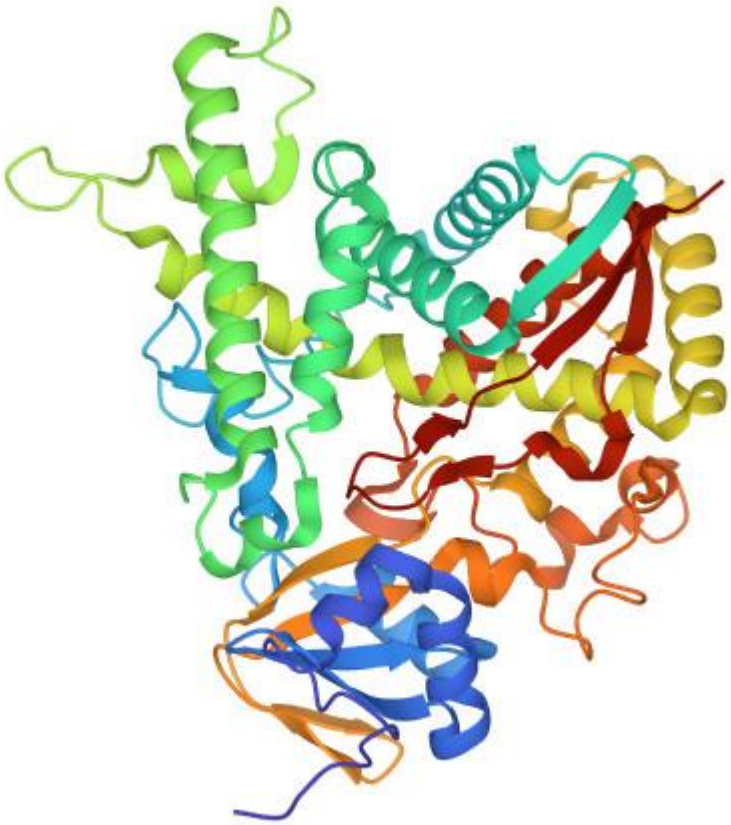

Fig :01, 1EA1 Protein

Molecule	Chains	Sequence length	Organism	Details
CYTOCHROME P450 51-LIKE RV0764C	A	455	mycobacterium tuberculosis	Mutation(s):0 Gene Names: CYP51 OR RV0764C OR MTCY369.09C EC:1.14.14.154

1.4. Mechanism of action

Fluconazole is a very selective inhibitor of fungal cytochrome P450 dependent enzyme lanosterol 14-alpha-demethylase. This enzyme normally works to convert lanosterol to ergosterol, which is necessary for fungal cell wall synthesis. The free nitrogen atom located on the azole ring of fluconazole binds with a single iron atom located in the heme group of lanosterol 14-alpha-demethylase. This prevents oxygen activation and, as a results, inhibits the demethylation of lanosterol, halting the process of ergosterol biosynthesis. Methylated sterols are then found to accumulated in the fungal cellular membrane, leading to

an arrest of fungal growth. These accumulated sterols negatively affect the structure and function of the fungal cell plasma membrane.

1.5. Scope

The amount of resolves X-ray structures of protein-ligand complexes have exploded during the last decade. This has initiated much improvement of docking methods by an advanced knowledge about the key interactions in the complexes. A number of docking methods for predicting binding modes of small molecules have been developed, methods which are also thought to help to quantity energetic of different molecular interactions. Ligand docking is mainly used by the pharma industry for identifying possible compounds for development in the drug discovery process. Scoring functions are especially important since minimization algorithms rely on these functions. Therefore, an accurate scoring function is absolutely crucial to obtain correct results, i.e. correct binding modes but also correct ranking of docked ligands.

1.6. Objectives of current work:

- ❖ Molecular docking of the Fluconazole drug and its analogs with 1EA1 protein involved in candidiasis disease.
- ❖ Fluconazole drug works by blocking the ability of the fungi candida to prevent the candidiasis disease
- ❖ docking techniques is utilized to predict the tentative binding parameters.
- ❖ This technique shows the interactions like hydrogen bond, hydrophobic interactions

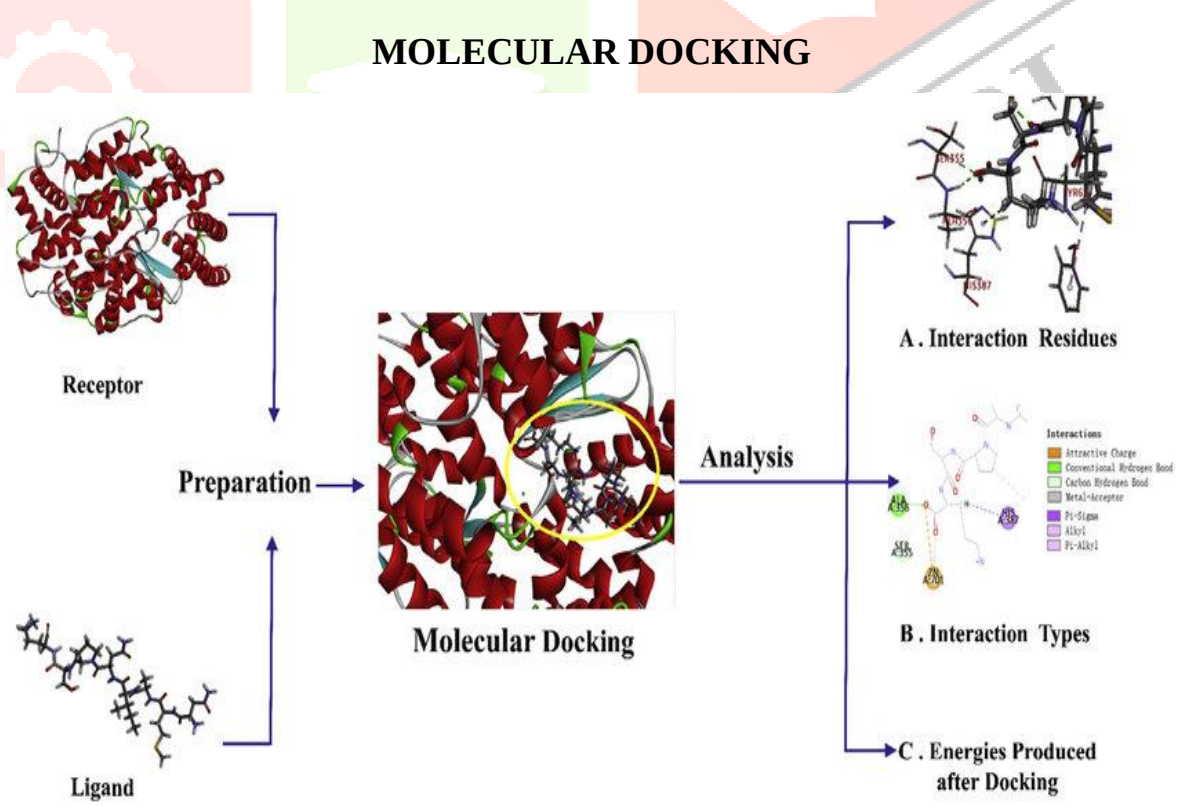

Fig:02, DAIGRAMATIC REPRESATION OF MOLECULAR DOCKING

It predicts the structure of intramolecular complex formed between two or more constituents molecules. Drugs discovery takes years to discovering a new drug and very frequently, efforts to cut down the research timeline and cost by reducing wet-lab experiment by the use of computer modeling.

Molecular docking explains interaction of drugs with protein receptors. It gives distances between binding group in Angstroms and the type of interaction. Docking involves useful ways of representing the molecules and molecular properties. Exploration of the configuration, spaces available for interaction between ligand and receptor. Molecular docking is a key tool in structural biology and computer- assisted drug design. The goal of ligand- protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three- dimensional structure. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypothesis of how the ligands inhibit the target.

Autodock is a molecular modeling simulation software. It is effective for protein- ligand docking. Autogrid for pre- calculating grids around the active site. Autodock is for docking of the ligand into the grids describing the target active site.

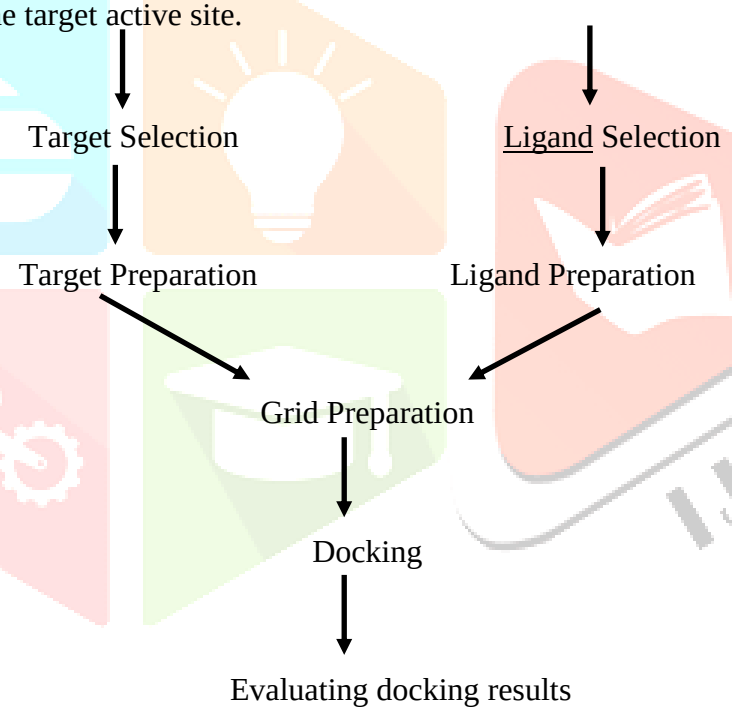

Fig 03, docking procedure chart

3. Results and Discussion:

3.1 Selection of Protein:

The EGFR has a protein 1EA1 with resolution less than two in the X-ray diffraction method. The Protein 1EA1 is choosed due to its resolutioch that if give a clear structure. The Protein 1EA1 is collected from PDB and downloaded in pdb format then saved in the folder.

PDB_ID: 1EA1

Method: X-ray Diffraction

Resolution: 2.86A^0

R-Value count: 0.256

R-Value work: 0.241

3.2 selection of Ligand:

The FLUCONAZOLE is used as ligand . It is a drug approved for the treatment of CANDIDA ALBICANS. It has received "Fast Track" designation by the FDA for the treatment of different kinds of fungus. The ligand is collected from Drug Bank and saved in pdb form.

Fluconazole 200 MG Tablet is an anti-fungal medicine. It is used in the treatment of various fungal infections affecting your skin, lungs, mouth, throat, meninges (protective layer covering the brain and spinal cord), etc. It works by stopping the growth of fungi, thus preventing the spread of infections. Fluconazole 200 MG Tablet can cause side effects like nausea, vomiting, headache, stomach discomfort, etc. Consult with your doctor if these side effects are persistent and/or getting worse. Avoid activities like driving vehicles or operating machines while taking this medicine as it can occasionally cause dizziness. Fluconazole 200 MG Tablet can be taken with or without food. Continue to take this medicine for the prescribed duration even if you feel better after a few doses as it may increase the risk of re-infection. Fluconazole 200 MG Tablet is not recommended for use if you are allergic to it. Inform your doctor if you have liver or kidney problems, or any other medical conditions. Report all your current medicines to your doctor before starting the treatment as they can interact with Fluconazole 200 MG Tablet and cause side effects. Consult your doctor if you are pregnant or are breastfeeding before taking this medicine.

Name: **FLUCONAZOLE**

Accession Number: DB00398(APRDO1304, DBO7438)

Molecular weight: 306.27g/mol

Molecular formula: $C_{13}H_{12}F_2N_6O$

IUPAC,Name: 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol

Properties: White crystalline powder

Melting point: 138-140°C

3.3. Autodock

In recent years there has been a growing interest in computer based screening computational docking and scoring bioinformatics by providing unprecedented insights on key aspects of ligand –receptor interaction. Autodock and Autodock Tools are free of charge techniques that have been cited in the literature as essential tools in structure – based drug design. In this the Autodock-4.2.6 version is used for docking process. Molecular docking process is to perform protein & ligand binding interactions in drug discovery. The driving forces for these specific interactions in biological systems aim toward

complementarities between the shape and electrostatics of the binding site surface and the ligand. The Autodock is a user friendly and easy to understand docking as a computational tool for structure based drug design.

3.4 Ligand binding energies:

Total grid points per map:

No. of X- dimensions: 40

No. of Y- dimensions: 40

No. of Z- dimensions: 40

Spacing (Angstrom): 0.375

Centre grid box:

X- Centre: -18.47

Y- Centre: -1.581

Z- Centre: 66.58

Docking of Ligand-1: CID: 3365

Molecular formula: $C_{13}H_{12}F_2N_6O$

Molecular Weight: 306,27 g/mol

IUPAC Name: 2-[2,4-difluorophenyl]-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol

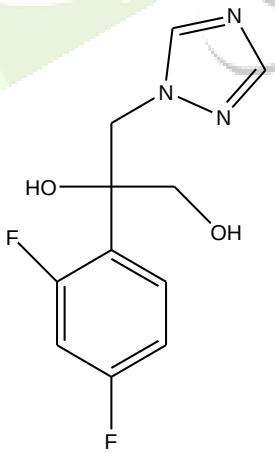

Fig 04,The above picture is one of the analog of fluconazole

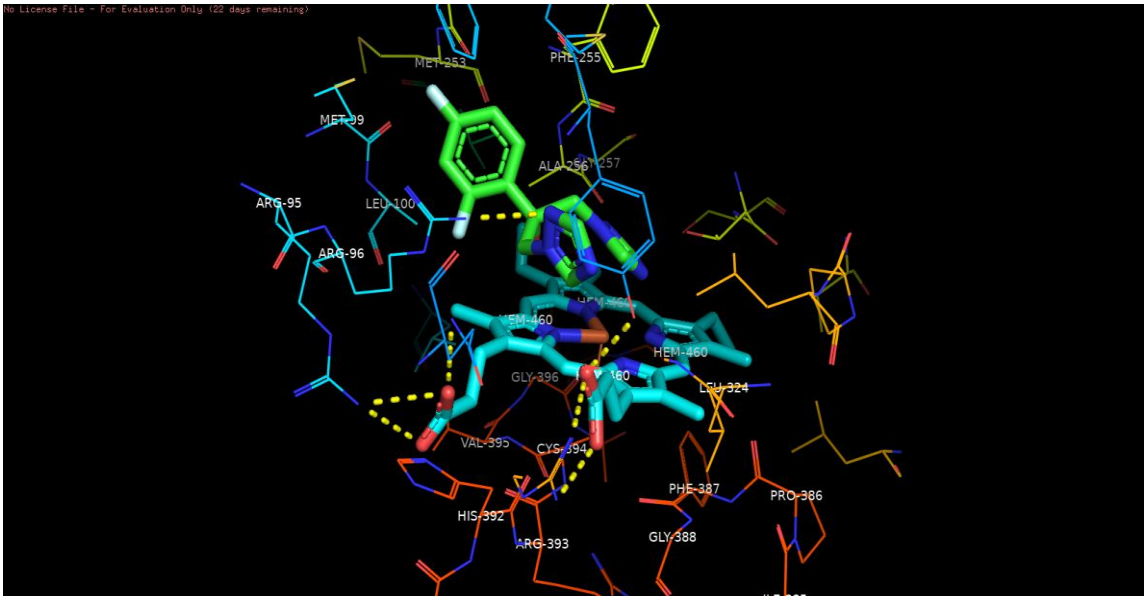

Fig-5 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -7.27 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 7 hydrogen bonding acceptors and has 5 rotatable bonds. In this7 hydrogen bonding are found which are linked with the different amino acids residues ARG-96, ARG-95 has two hydrogen bondings, GLN-72, TYR-76 and ARG-326 has two hydrogen bonding . in this 6 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76, PHE-83. This ligand complex is showing hydrophobic interactions with ALA-256 and LUE-321 it also has hydrophic interactions with other side chains.

Docking of Ligand-2: CID: 11624578

Molecular formula: $C_{15}H_{14}FN_9O$

Molecular weight: 355.33 g/mol

IUPAC Name: 4-[4-[3-[4-chloro-3-(trifluoromethyl)phenyl]-5-(2-methoxyethyl)-2-oxo-1,3,5-triazinan-1-yl]-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide

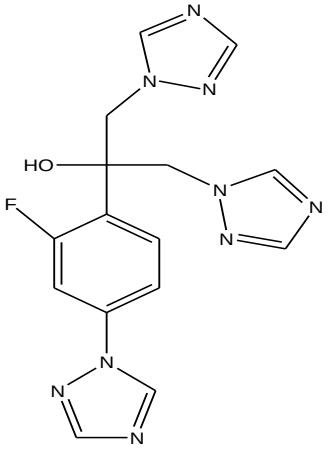

Fig 06,The above picture is one of the analog of fluconazole

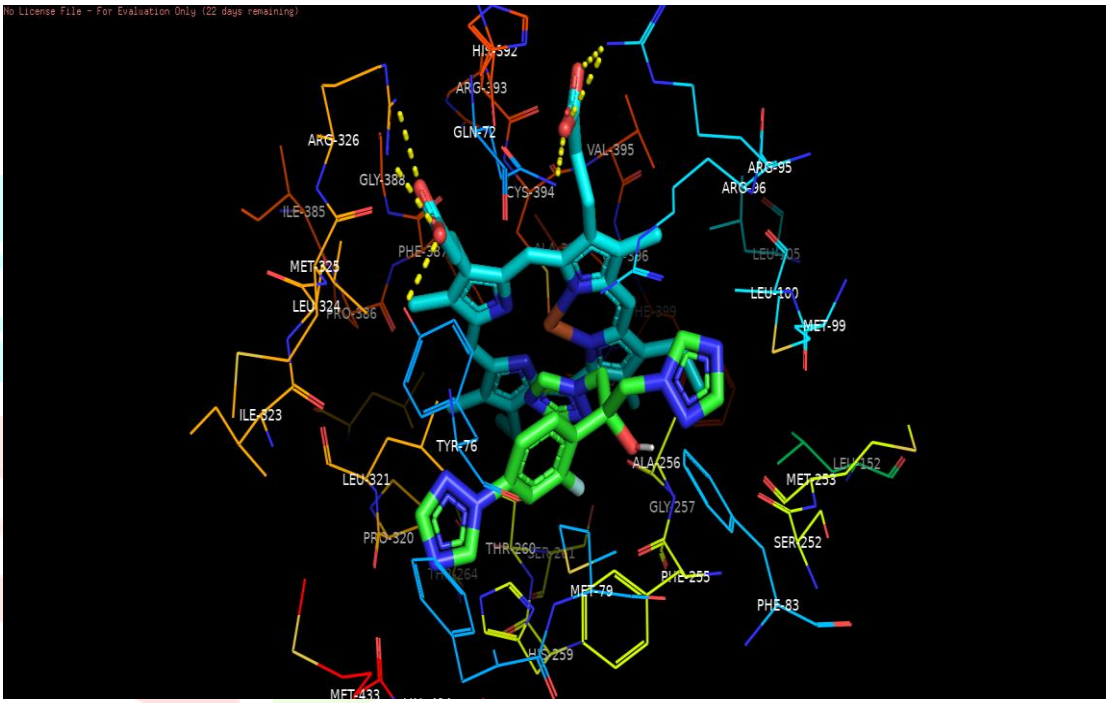

Fig-7 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -8.07 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 8 hydrogen bonding acceptors and has 6 rotatable bonds. In this 5 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-96 has two hydrogen bondings, GLN-72, TYR-76 and ARG-326. in this 6 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 and PHE-83. This ligand complex is showing hydrophobic interactions with THR-260 and LUE-321 it also has hydrophic interactions with other side chains.

Docking of Ligand-3: CID : 15788287

Molecular formula: $C_{13}H_{12}F_2N_6O$

Molecular weight: 306.27 g/mol

IUPAC,Name:; -(2,4-difluorophenyl)-1-(1,2,4-triazol-1-yl)-3-(1,2,4-triazol-4-yl)propan-

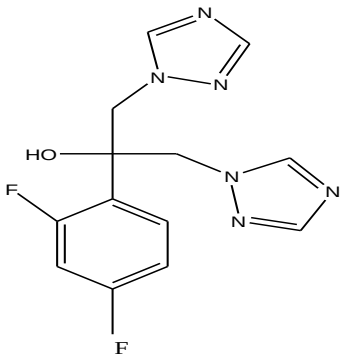

Fig 08,The above picture is one of the analog of fluconazole

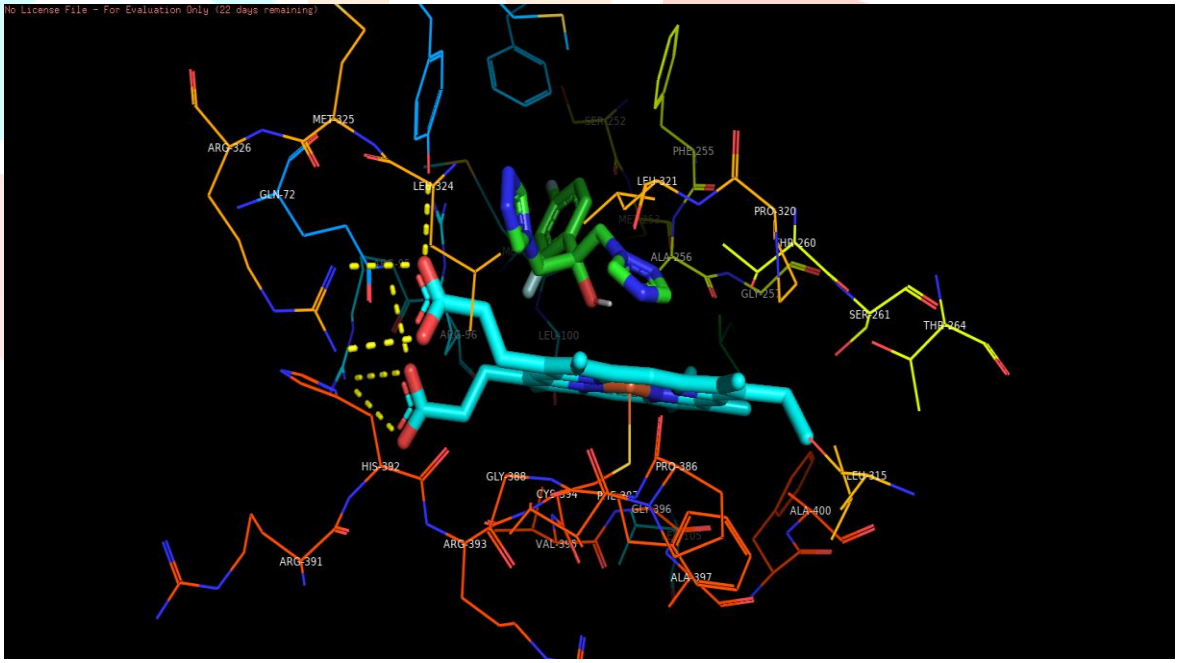

Fig-9 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -7.21 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 7 hydrogen bonding acceptors and has 5 rotatable bonds. In this 6 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 has two hydrogen bondings, GLN-72, TYR-76 . In this 6 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 and PHE-83. This ligand complex is showing hydrophobic interactions with THR-260,ALA 256 and LUE-321 it also has hydrophic interactions with other side chains.

Docking of Ligand-4: CID: 129829800

Molecular formula: $C_{13}H_{13}F_2N_7O_3S$

Molecular weight: 385.35 g/mol

IUPAC Name : 2-(2,4-difluorophenyl)-2-hydroxy-1,3-bis(1,2,4-triazol-1-yl)propane-1-sulfonamide

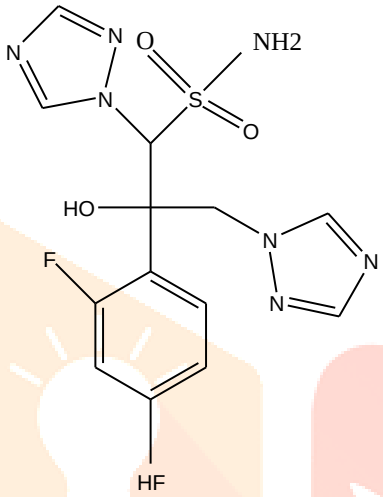

Fig-10,The above picture is one of the analog of fluconazole

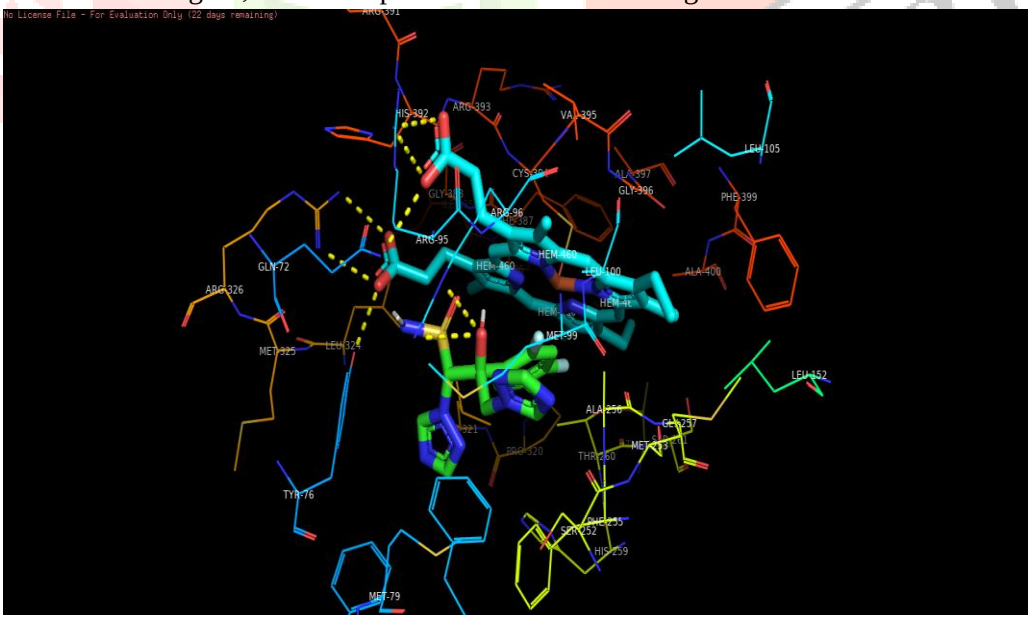

Fig-11 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -8.10 kcal/mol added gasteiger charges. It has 0 hydrogen bond donor and 10 hydrogen bonding acceptors and has 6 rotatable bonds. In this 8 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bonding, ARG-96 with two hydrogen bonding, ARG-95 has two hydrogen bonding, GLN-72, TYR-72. In this 6 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 and PHE-83. This ligand complex is showing hydrophobic interactions with MET-79 and LUE-321 it also has hydrophobic interactions with other side chains.

Docking of Ligand-5: CID: 134034

Molecular formula: $C_{13}H_{13}FN_6O$

Molecular weight: 288.28 g/mol

IUPAC Name 2-(4-fluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propan-2-ol

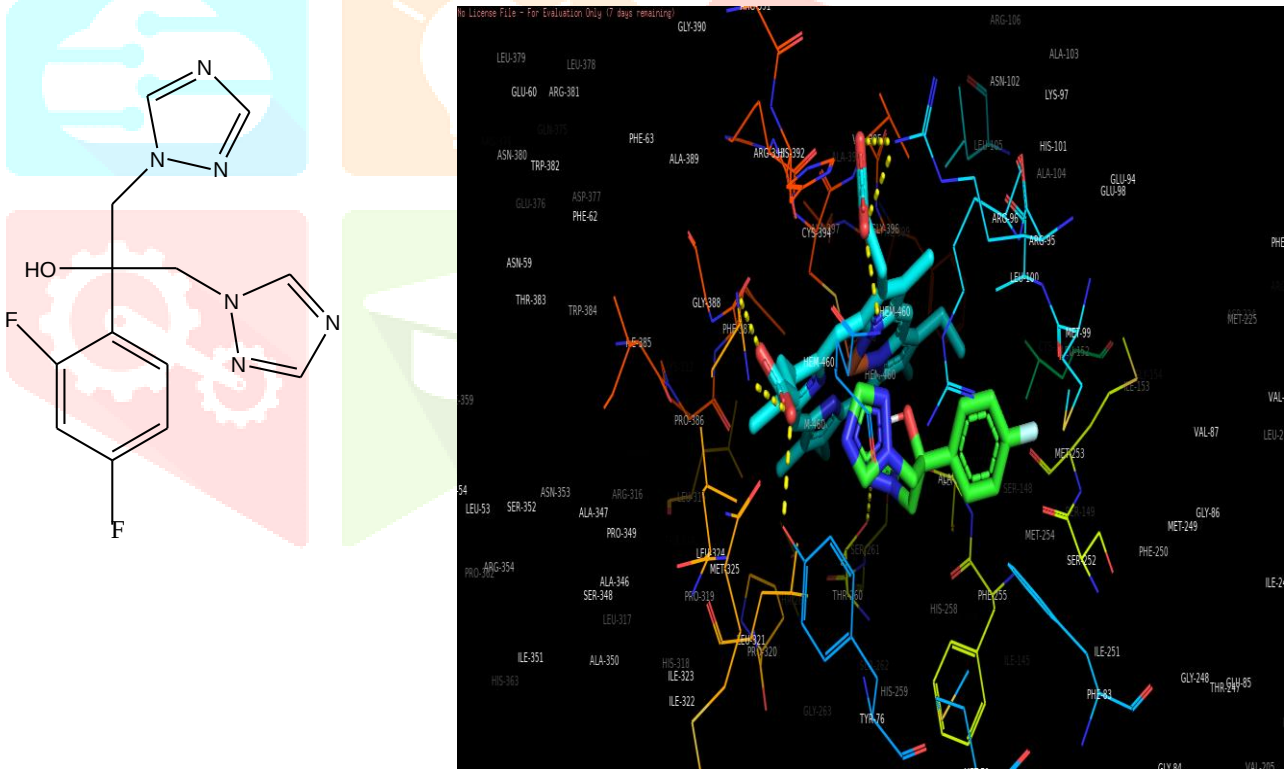

Fig 12,The above picture is one of the analog of fluconazole

Fig-13 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -7.03 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 6 hydrogen bonding acceptors and has 5 rotatable bonds. In this 6 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 has two hydrogen bondings, GLN-72, TYR-76 and THR260 . In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 and ARG-96 it also has hydrophobic interactions with other side chains.

Docking of Ligand-6: CID NO 10988840

Molecular formula: $C_{11}H_{11}F_2N_3O_2$

Molecular weight: 255.22g/mol

IUPAC Name:; 2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)propane-1,2-diol

Fig 13,The above picture is one of the analog of fluconazole

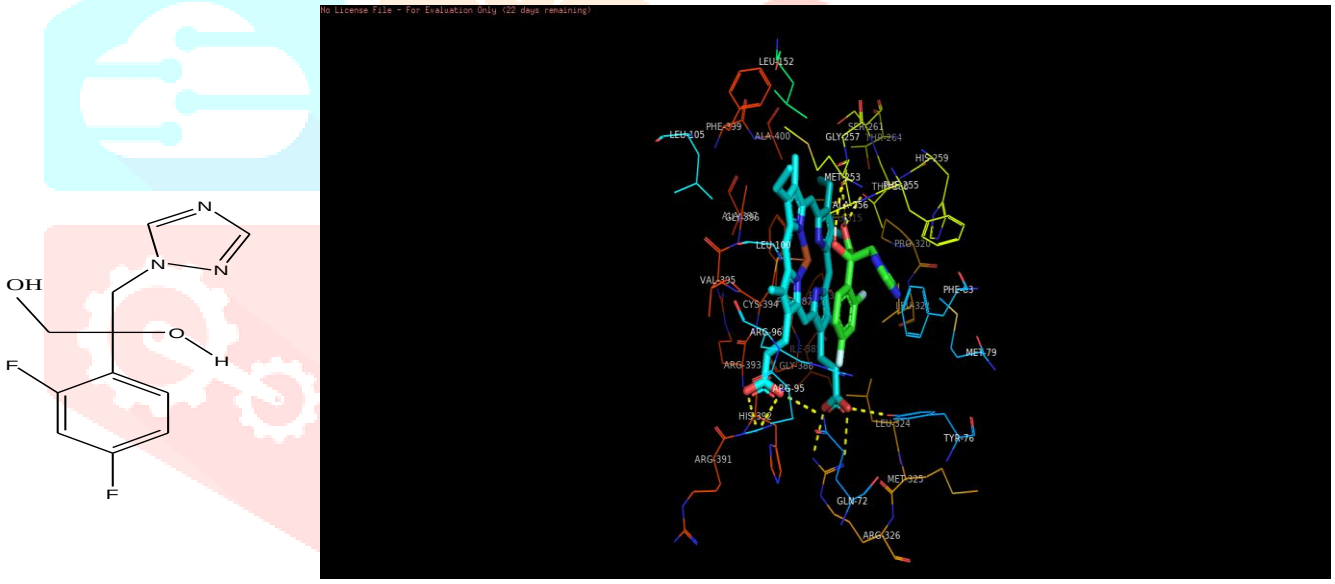

Fig-14 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -6.09 kcal/mol added gasteiger charges. It has 2 hydrogen bond donor and 6 hydrogen bonding acceptors and has 4 rotatable bonds. In this 9 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 has two hydrogen bondings, GLN-72, TYR-260, TYR-72 and ALA-256 with two hydrogen bonds . In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chains.

Docking of Ligand-7: CID: 68169234

Molecular formula: $C_{10}H_8N_6$

Molecular weight: 212.21 g/mol

IUPAC, Name 1-[3-(1,2,4-triazol-1-yl)phenyl]-1,2,4-triazole

Fig 15 ,The above picture is one of the analog of fluconazole

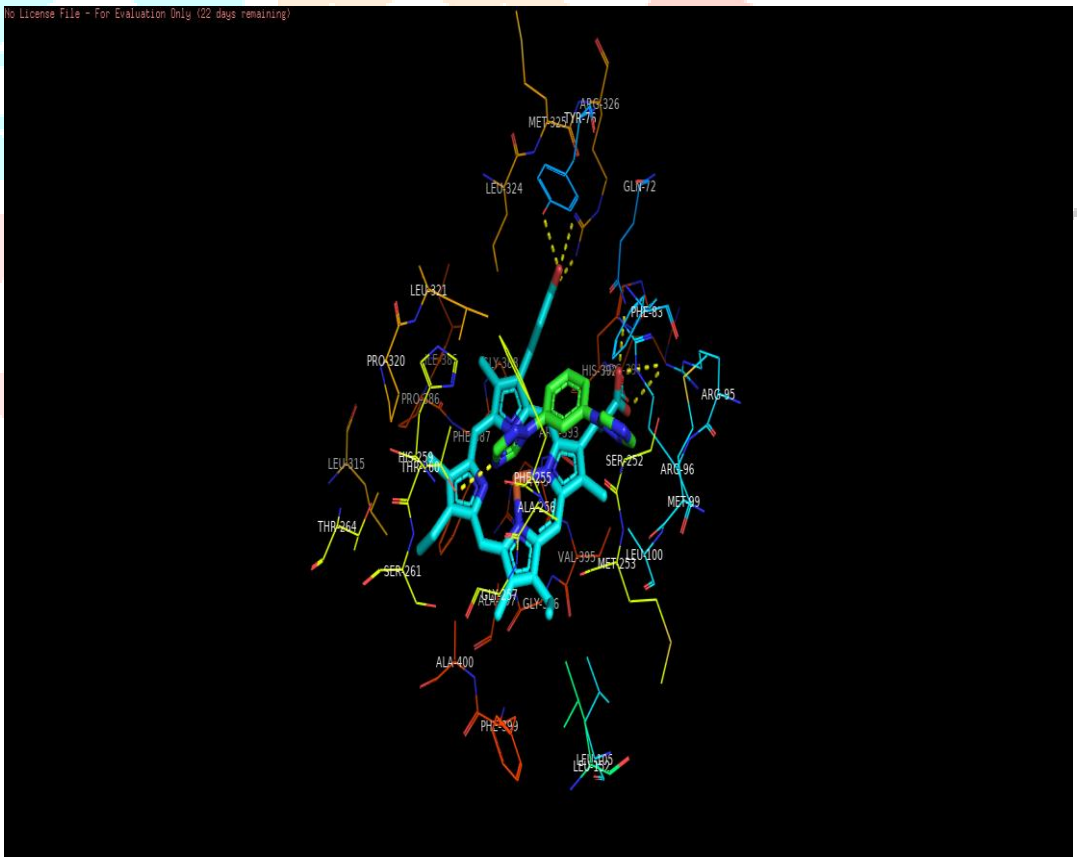

Fig-16 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -6.87 kcal/mol added gasteiger charges. It has 0 hydrogen bond donor and 4 hydrogen bonding acceptors and has 2 rotatable bonds. In this 7 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95, GLN-72, TYR-260, TYR-76 and THR-260. In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chains.

Docking of Ligand-8: CID: 10130921

Molecular formula: $C_{11}H_9F_2N_3O$

Molecular weight: 237.21 g/mol

IUPACName: 1-[[2-(2,4-difluorophenyl)oxiran-2-yl]methyl]-1,2,4-triazole

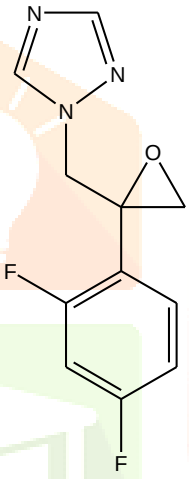

Fig 17,The above picture is one of the analog of fluconazole

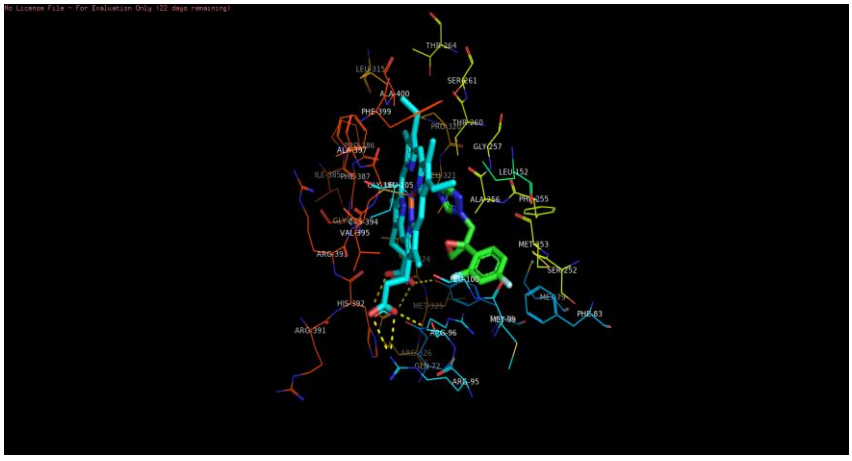

Fig-18 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -6.64 kcal/mol added gasteiger charges. It has 0 hydrogen bond donor and 5 hydrogen bonding acceptors and has 3 rotatable bonds. In this 7 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 with two hydrogen bondings, GLN-72, TYR-76 . In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chains.

Docking of Ligand-9: CID: 15390420

Molecular formula: $C_{11}H_{10}BrF_2N_3O$

Molecular weight: 318.12 g/mol

IUPAC, Name 1-bromo-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)propan-2-ol

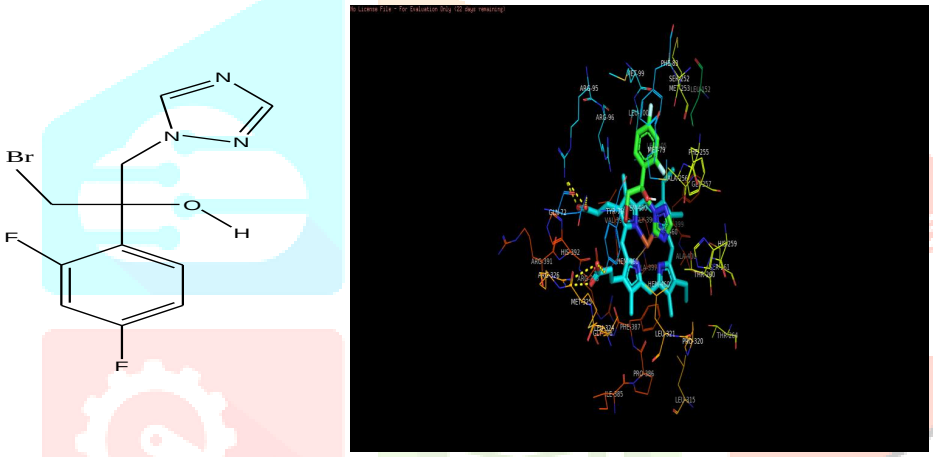

Fig-20 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -6.65 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 5 hydrogen bonding acceptors and has 4 rotatable bonds. In this 6 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 with two hydrogen bondings, GLN-72, TYR-76 . In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chains.

Fig 19 The above picture is one of the analog of fluconazole

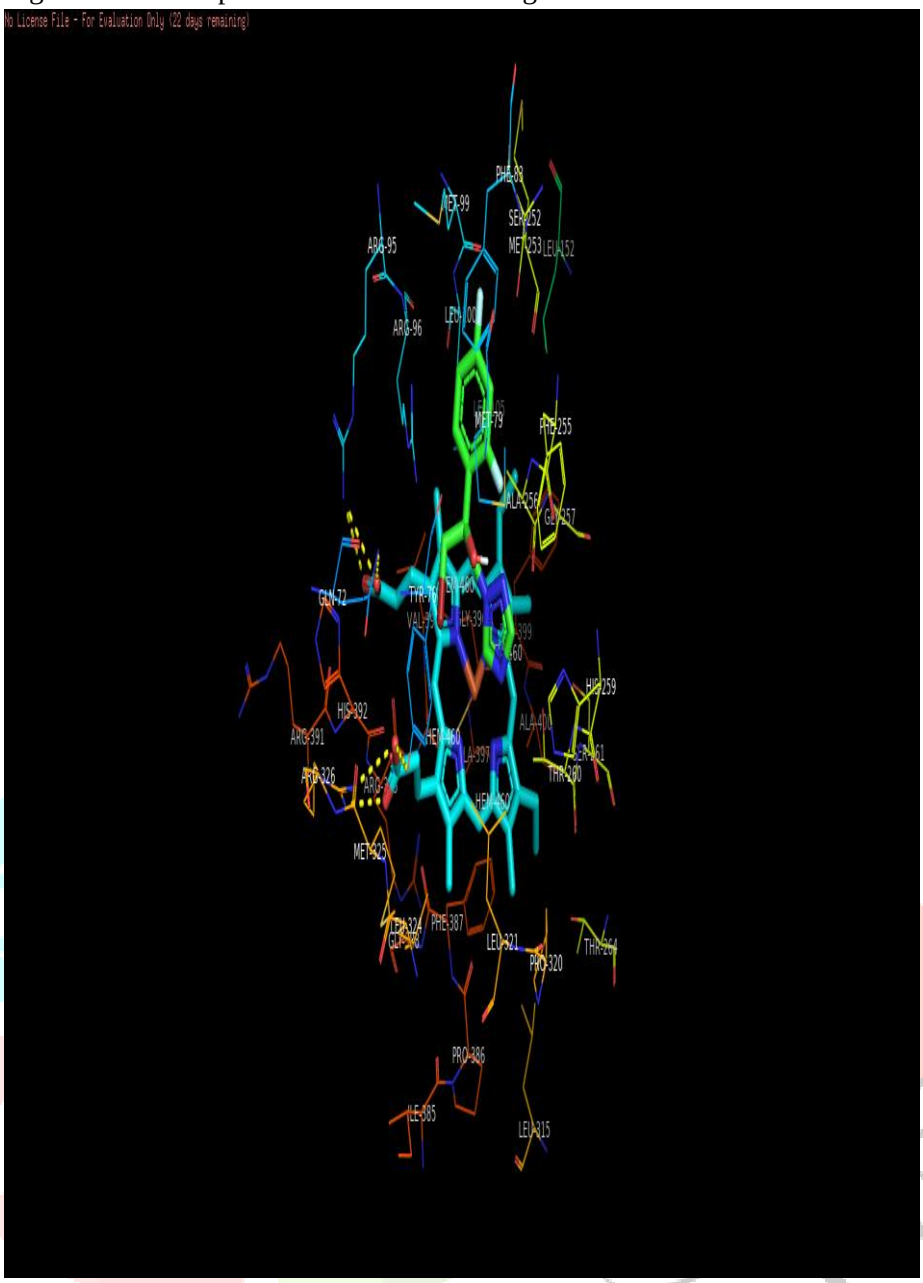

Fig-20 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -6.65 kcal/mol added gasteiger charges. It has 1 hydrogen bond donor and 5 hydrogen bonding acceptors and has 4 rotatable bonds. In this 6 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 with two hydrogen bondings, GLN-72, TYR-76 . In this 5 aromatic interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chains.

Docking of Ligand-10: CID: 11217952

Molecular formula: $C_9H_{10}F_2O_3$

Molecular weight:204.17 g/mol

IUPAC Name 2-(2,4-difluorophenyl)propane-1,2,3-triol

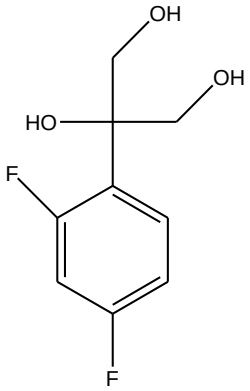

Fig 21,The above picture is one of the analog of fluconazole

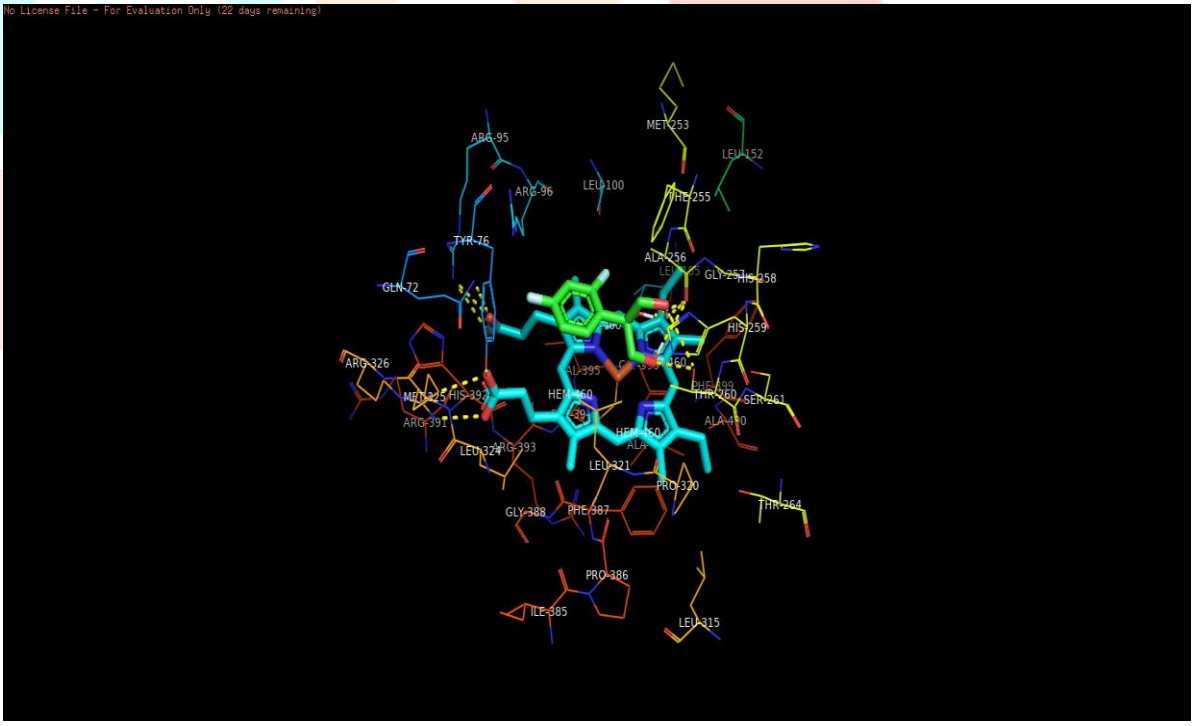

Fig-22 ligand molecule docked into the active site 1EA1 protein. Inhibitor molecules shows in the ball and stick representation and active site residues are shown in sticks model. Hydrogen bonding between protein and inhibitor is shown in broken yellow lines

In this fluconazole binds to 1EA1 protein which cross links with the active site. The binding affinity of this molecule is -5.20 kcal/mol added gasteiger charges. It has 3 hydrogen bond donor and 5 hydrogen bonding acceptors and has 3 rotatable bonds. In this 9 hydrogen bonding are found which are linked with the different amino acids residues ARG-326 with two hydrogen bondings, ARG-95 with two hydrogen bondings, GLN-72, TYR-76, THR-260 with two hydrogen bonding, ALA-256 eith three hydrogen bonding. In this 5 aromatic

interactions are found. Those are TYR-76, PHE-255, PHE-399, PHE-387, TYR-76 . This ligand complex is showing hydrophobic interactions with ALA 256 it also has hydrophobic interactions with other side chain

Comparison:

By comparing the binding affinities, the CID: 129829800 has more binding energy with -8.1 kcal/mol is highest. So this binding affinity is more preferred than compared to others because it shows strong hydrogen bonding interaction with Aspirin residue along with hydrophobic interaction. Such that it acts as potent inhibitor against enzyme.

S.NO	LIGAND CID NO	BINDING ENERGY (kcal/mole)
1	3365	**-7.27**
2	11624578	**-8.07**
3	15788287	**-7.21**
4	129829800	**-8.1**
5	134034	**-7.03**
6	10988840	**-6.09**
7	68169234	**-6.87**
8	10130921	**-6.64**
9	15390420	**-6.65**
10	11217952	**-5.2**

4. Conclusion:

The yeast is a common commensal of the gastrointestinal tract. Most *Candida* species are opportunistically occurring in debilitated persons e.g. Diabetes patients, those who are taking anticancer therapy and immunocompromised patients, HIV patients, and so on. . This disease transition in the pathophysiology of the onset and progression of infection is also influenced by Candida's virulence traits that lead to the development of candidiasis the disease candidiasis is treated with the drug Fluconazole. In this project I had taken fluconazole as a drug with 10 different similar analogues and 1ea1A as my target protein. Then docking is done at the active site site of the protein by using autodock 1.5.7 version. Then after docking ligands with different binding energies were found out. At the end of this work . I have been screened out one of the analog is with highest binding energy bases on all other binding energy parameters. Finally ligand with PUBCHEM CID-129829800 has highest binding affinity with 8.1kcal/mol among al other similar analogs of Fluconazole.

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