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IN-SILICO DESIGN AND DOCKING STUDIES OF NOVEL 5-FURFURYLIDENE THIAZOLIDIN-4-ONE DERIVATIVES OF 2-(1H-BENZOTRIAZOL-1- YL) ACETOHYDRAZIDE.

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ABSTRACT

One of the primary causes of death worldwide is infection brought on by bacteria. A significant issue is posed by the limited number of antibiotics that are available for the treatment of illnesses and the ongoing emergence of antimicrobial agent resistance. So, the development of novel and effective antimicrobial drugs may be the only means to address the issue of resistance and create a successful treatment for infectious diseases. 4-Thiazolidinones have recently been reported to be novel inhibitors of the bacterial enzyme Mur B and also to block some pathogenic mechanisms of bacteria . In the present work, different novel Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide were designed using ACD Lab Chemsketch12.0 and their properties were predicted using the molinspiration software. The designed leads having required physicochemical properties, drug – likeness and obeying the Lipinski Rule of Five were selected for docking studies via Biovia Discovery Studio.Compounds 3i, 3b and 3h showed excellent activities on UDP-N-acetylenol pyruvyl glucosamine reductase enzyme (Mur B) and compounds 3i, 3b and 3j showed excellent activities on 14 α - Demethylase enzyme. Molecular docking studies were done to assess the binding mode and interactions of designed leads to hits at the binding site of the receptors. Results of in-silico studies showed that most of the compound have excellent drug likeness properties and pharmacokinetic profile. Here in we concluded that Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide could be considered as promising scaffolds towards the development of novel antibacterial and antifungal agents.

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KEYWORDS

Benzotriazole, Thiazolidinone, Furfural, Antibacterial activity, Antifungal activity, In- silico studies, Biovia Discovery Studio.

INTRODUCTION

Patients lives and deaths frequently depend on the discovery, development, and administration of medications for the prevention, management, and treatment of illness, injuries, and other disorders, the drug discovery and development process is one of the most challenging and difficult processes. Finding a molecule that is therapeutically effective in treating and curing disease is the goal of the drug discovery process. Drug discovery and development is an intense, lengthy and an interdisciplinary endeavour. The discovery process includes several steps, including the identification and validation of targets, the identification of hits, the generation and optimization of leads, and the identification of a candidate for further development[1] .More over half of all known chemical compounds belong to the significant class of heterocycles. The majority of vitamins, many natural products, biomolecules, and biologically active compounds-including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents[2]- as well as a wide range of medications also contain heterocycles. Moreover, they are typically discovered as a crucial structural component in synthetic medications and agrochemicals. A chemical is considered heterocyclic if it has at least two different types of heteroatoms in its cyclic structure. The most prevalent hetero atoms are those of nitrogen, oxygen, and sulphur.

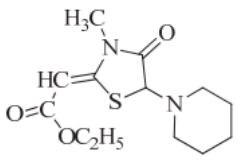
Traditionally, drugs were discovered by synthesizing compounds in a time consuming multi-step processes against a battery of in vivo biological screens and further investigating the promising candidates for their pharmacokinetic properties, metabolism and potential toxicity. Sophisticated *in-silico* approaches has given a tremendous opportunity to pharmaceutical companies to identify new potential drug targets which in turn affect the success and time of performing clinical trials for discovering new drug targets.

In-silico methods[3] can help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for possible binding active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics.

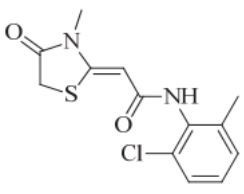
Azole heterocyclic compounds have a wide range of therapeutic uses in the management of different disorders[4]. Triazole derivatives in particular have been playing significant roles as pharmaceuticals in medicinal chemistry, and many triazole analogues, such as imidazole, thiazole, carbazole, oxazole, and benzimidazole have also been discovered to be widely employed in clinic[5]

Benzotriazole is a fused aromatic nitrogen heterocycle of benzene ring with triazole, and its derivatives have been paid increasingly special attention due to their widely potential applications as medicinal drugs[6],corrosion inhibitors[7],man-made materials[8], supramolecular ligands[9]. A wide range of biological activities are produced by benzotriazole derivatives due to their increased ability to interact non-covalently with a wide range of biological enzymes and receptors.

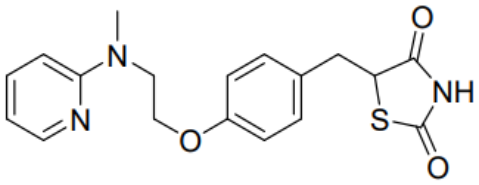
Thiazolidin-4-one is an odourless, yellow crystal substance. It is soluble in ethanol, water, and solvent ether. Thiazolidine is the tetra hydro derivative of the thiazole ring[10]. Due to their availability in both natural products and pharmaceutical substances, 4- thiazolidinone and its derivatives have a high pharmacological relevance. Some clinically used thiazolidinones are ,



Etozoline (anti-hypertensive)



Ralitoline (anti-convulsant)



Rosiglitazone (antidiabetic)

In this study, we have designed and evaluated a series of New 5-Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide in search of potent anti microbial agents through in-silico studies using Biovia Discovery Studio2020.

MATERIALS AND METHODS

ACD/ChemSketch

ACD/ChemSketch is a molecular modelling program used to create and modify images of chemical structures. It also includes features such as calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures (fewer than 50 atoms and 3 rings), and prediction of logP. Chemical structures and SMILES notations of the compounds were obtained by using ACD labs Chemsketch version 12.0. (www.acdlabs.com/resources/freeware/chemsketch/) .

ACD/ChemSketch has the following major capabilities:

- Structure Mode for drawing chemical structures and calculating their properties.
- Draw Mode for text and graphics processing.
- Molecular Properties calculations for automatic estimation of formula weight, percentage composition, molar refractivity, molar volume, parachor, surface tension, density, dielectric constant, polarizability.

Molinspiration

Molinspiration is an independent research organization focused on development and application of modern cheminformatics techniques, especially in connection with the internet. It offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SDfile conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure search or similarity and pharmacophore similarity search. SMILES notations of the selected derivatives were fed in the online Molinspiration software (https://www.molinspiration.com/) to predict the drug likeness properties. Lipinski's rule of five is used in drug design and development to predict oral bioavailability of potential lead or drug molecules.

Lipinski rule is also known as Pfizers rule of five / Lipinski's rule of 5. The rule was formulated by the scientist Christopher A Lipinski[11]. The Lipinski rule of five states that an orally active drug should obey the following criteria:

1. Not more than five hydrogen bond donors .
2. Not more than 10 hydrogen bond acceptors .
3. Molecular weight less than 500 Daltons .
4. An octanol-water partition coefficient log P not greater than 5.
5. Not more than 5 rotatable bonds.

Molecular docking studies

Molecular docking is used to predict the structure of the intermolecular complex formed between two molecules. The small molecule called ligand usually interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of compounds. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. It also predicts the strength of the binding, the energy of the complex; the types of signal produced and calculate the binding affinity between two molecules using scoring functions[12]. Protein–small molecule (ligand) docking represents a simpler end of the complexity spectrum, and there are many available programs that perform particularly well in predicting molecules that may potentially inhibit proteins. Protein–protein docking is typically much more complex. The reason is that proteins are flexible and their conformational space is quite vast.

Docking can be performed by placing the rigid molecules or fragments into the protein's active site using different approaches like clique-searching, geometric hashing, or pose clustering[13] .

Methodology of docking in Biovia discovery studio

1. **Protein preparation**

X-ray crystallographic structure of the target protein were procured from protein data bank in PDB format.

The protein structures were cleaned (water molecules and other hetero atoms removed), prepared and minimized before docking.

Steps include;

Select macromolecule → Prepare protein → Automatic preparation based on protocol Input protein → Run. Then save the resultant protein in DSV format.

2. **Ligand preparation**

Ligands were prepared according to ligand preparation protocol, which include generation of possible tautomers and geometry optimization. Steps include; Click on, Small molecule → Prepare /Alter-ligands → Prepare ligand → Input ligand (select the saved ligand structure) → Run. The resultant prepared structures of ligands are saved in new file in DSV format.

3. **Define binding site**

For defining the binding site;

Click on, Receptor ligand interaction → Define & Edit binding site →Select the residues → Select from current Selection.

4. **Docking**

Docking module **LibDock** using Discovery Studio 2020 was used to study interaction between the Protein and ligand molecules. The binding site of the protein defined and the docking performed. The LibDock scores, nature of bonding and bond length of the docked ligands were estimated.

Steps include;

Click on Receptor ligand interaction → Dock Ligands → LibDock

During this procedure, favourable ligand poses were then generated to determine their spatial fit into the active site of receptor and those who fitted best were then evaluated. The Lib Dock scores, hydrogen bonds and pi-pi interactions formed with the surrounding amino acids were used to predict the binding affinities and proper alignment of these compounds at the active site of the receptors.

Determination of Quantitative Structure Activity Relationship Parameters

Quantitative structure-activity relationship (QSAR) is a computational modeling method for revealing relationships between structural properties of chemical compounds and biological activities.

Electronic parameters : The electrons distribution in a drug molecule will have a considerable influence on the activity and distribution of a drug. A drug normally has to pass through a number of biological membranes in order to reach its target. In general, unionised polar and non-polar drugs are usually more easily transported through membranes than polar and non-polar drugs in their ionised forms. Furthermore, the electronic distribution in drug structure will control the type of bonds it forms with the target, once it reaches the site of action, which in turn affects its biological activity.

Steric factor: A drug's size, shape, and bulk will have an impact on how easily it can interact with a target or binding site. A large substituent could obstruct or obscure a drug's optimum interaction with its binding site. As an alternative, a bulky substituent might aid in properly orienting a medication for maximal binding and improved efficacy. Steric characteristics are more challenging to measure than electrical or hydrophobic characteristics.

Lipophilic parameters: As a physicochemical property, lipophilicity is one of the most researched. The lipophilicity of a drug and an indicator of its capacity to cross cell membranes are determined by the partition coefficient. According to its definition, it is the proportion of unionised medicines that are evenly distributed across the organic and aqueous layers at equilibrium. Medicines with high partition coefficients have an easy time passing across biological membranes. Partition coefficients are essentially what allow medicinal molecules to diffuse through matrix systems or across rate-controlling membranes. Medications with a low partition-coefficient value are not good choices for oral controlled release formulations, whereas pharmaceuticals with a high partition-coefficient are likewise not good candidates [14].

The physicochemical properties like electronic feature(polarisability), steric feature (molar volume) and hydrophobicity (log P) were determined for the newly designed compounds using ACD LabChemSketch (12.0).

RESULTS AND DISCUSSION

Fifty analogues of Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazole-1-yl) acetohydrazide were designed using ACD Lab Chemsketch 12.0. Initially the designed fifty analogues were subjected to Lipinski rule analysis using molinspiration software.

Theoretical determination of drug-likeness properties

We predicted the drug likeliness profile of the compounds through analysis of pharmacokinetic properties of the compounds by using molinspiration online software. Based on the results obtained from molinspiration it was observed that all of the proposed compounds obeyed Lipinski rule of five. According to the Lipinski's rule of five new molecule designed for oral route should have a MW < 500, log P o/w < 5, No more than 5 hydrogen bond donors and No more than 10 hydrogen bond acceptor. From the Lipinski rule analysis, twenty eight compounds were selected for further studies, since the compound did not show any violations from the Lipinski rule of five.

Structure of proposed Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide is shown in Figure 1. The results of Lipinski rule analysis of first 10 compounds are shown in the table 1.

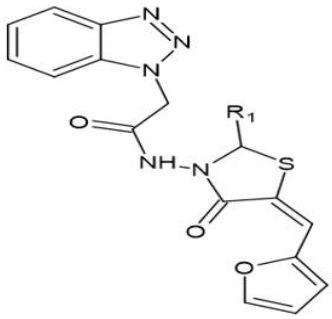


Fig 1 : Designed Ligand

Compound Code	Log P	MW	nON	nOHNH	nrotb	N violation
3a	2.59	431.48	8	1	5	0
3b	3.27	465.92	8	1	5	0
3c	3.22	465.92	8	1	5	0
3d	2.50	472.47	8	1	5	0
3e	2.55	472.47	8	1	5	0
3f	2.52	472.47	8	1	5	0
3g	2.60	461.50	9	1	6	0
3h	1.93	477.50	8	1	5	0
3i	1.93	477.50	8	1	5	0
3j	2.69	474.55	8	1	5	0

Table 1: Lipinski rule analysis of proposed derivatives

Molecular docking studies

Further the selected twenty eight analogues were subjected to docking studies against 14 α -Demethylase enzyme (PDB ID:6UEZ)[15] for antifungal activity and UDP-N-acetylenol pyruvylglucosamine reductase (MurB) enzyme (PDB ID: 1HSK) for antibacterial activity. The docking scores of the first 10 derivatives are shown in Table 2.

Sl.no	Compound code	MurB enzyme	14 α –Demethylase
1	3 a	131.198	119.663
2	3b	139.726	121.932
3	3c	130.515	114.513
4	3d	112.756	110.433
5	3e	126.687	118.963
6	3f	121.242	120.497
7	3g	124.486	109.719
8	3h	134.988	117.12
9	3i	148.576	126.981
10	3j	130.610	120.817
11	Gentamicin	155.231	-
12	Fluconazole	-	92.9395

Table 2: Docking scores of proposed derivatives.

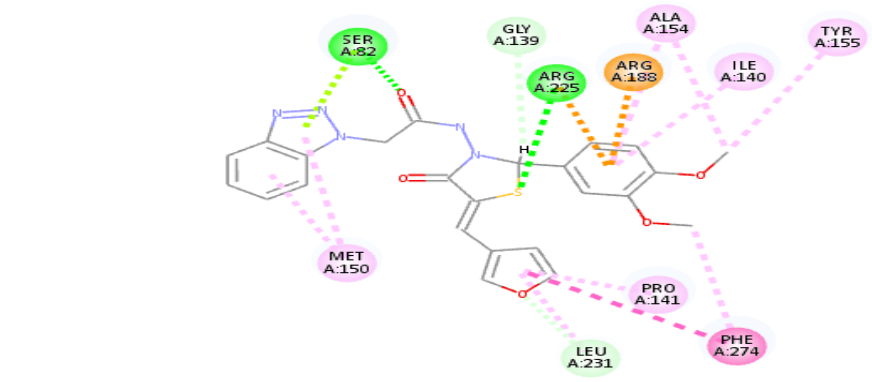
Docking with UDP-N-acetylenolpyruvylglucosamine reductase (MurB) (PDB ID: 1HSK):

The three-dimensional structure of Staphylococcus aureus UDP-N-acetylenolpyruvylglucosamine reductase (MurB) was downloaded from PDB database with PDB ID: 1HSK with crystallographic resolution 2.30 A^0. The protein consists of one polypeptide chain A with 326 amino acids. The receptor cavity was selected as the binding site. 1690 poses of selected ligands in the docked complexes were generated. The interacting molecular complexes among these having high Lib Dock score and maximum number of hydrogen bonds and active residues were selected. Compound 3i,3b,3h showed good activities on **UDP-N-acetylenolpyruvylglucosamine reductase (MurB)**. The docked complex of 1HSK with Compound 3i (Fig 2), 3b and 3h and Standard ligand Gentamycin (PubChem CID-3467)(Fig 3)were analysed to study non-bond interactions between the target and the ligand molecule. The results are summarised in the Table 3.

Sl. No.	Compounds	LibDock Score	Interacting Residues	Bond Distance (Å)	Nature of Bonding
1.	3i	148.576	A:SER82:HG - 3i:O12	2.76385	Hydrogen Bond
			A:ARG225:HH22 - 3i:S17	2.86764	Hydrogen Bond
			A:LEU231:HA - 3i:O25	2.76959	Hydrogen Bond
			3i:H43 - A:GLY139:O	2.95794	Hydrogen Bond
			3i:S17 - A:ARG225:NH2	3.11784	Other
			A:ARG188:NH1 - 3i	4.65486	Electrostatic
			A:ARG225:NH1 - 3i	4.31018	Electrostatic
			A:ARG225:HH22 - 3i	3.07321	Hydrogen Bond
			A:SER82:OG - 3i	2.9712	Other
			3i - A:PHE274	5.43736	Hydrophobic
			A:ALA154 - 3i:C35	3.54278	Hydrophobic
			A:TYR155 - 3i:C35	3.81569	Hydrophobic
			A:PHE274 - 3i:C33	4.41057	Hydrophobic
			3i - A:MET150	5.33281	Hydrophobic
			3i - A:MET150	4.4939	Hydrophobic
			3i - A:PRO141	4.87667	Hydrophobic
			3i - A:LEU231	5.03754	Hydrophobic
			3i - A:ILE140	5.39455	Hydrophobic
			3i - A:ALA154	4.46695	Hydrophobic
2.	3b	139.726	A:ARG188:HH12 - 3b:O12	2.95004	Hydrogen Bond
			A:SER235:HG - 3b:O25	2.35009	Hydrogen Bond
			3b:H40 - A:GLY139:O	2.43845	Hydrogen Bond
			3b:H43 - A:SER235:OG	2.98702	Hydrogen Bond
			3b:S17 - A:ARG225:NH2	3.07205	Other
			A:ARG188:NH1 - 3b	4.74348	Electrostatic
			A:TYR42:HH - 3b	2.48081	Hydrogen Bond
			A:ARG225:HH22 - 3b	3.20401	Hydrogen Bond
			3b - A:PHE274	4.66626	Hydrophobic
			A:TYR155 - 3b:Cl32	3.95374	Hydrophobic
			3b - A:MET150	4.91554	Hydrophobic
			3b - A:MET150	3.70181	Hydrophobic
			3b - A:ALA152	5.29234	Hydrophobic
			3b - A:ALA152	4.876	Hydrophobic
			3b - A:PRO141	4.46582	Hydrophobic
			3b - A:ALA154	4.33541	Hydrophobic
3.	3h	134.988	A:ARG188:NH1 - 3h:O34	3.83029	Electrostatic
			A:ARG225:NH1 - 3h:O34	5.33237	Electrostatic
			A:ARG188:HE - 3h:N8	3.01153	Hydrogen Bond
			A:ARG188:HH11 - 3h:O32	2.29088	Hydrogen Bond
			A:ARG188:HH12 - 3h:N8	2.75812	Hydrogen Bond
			3h:H41 - A:SER82:O	2.85286	Hydrogen Bond
			A:LEU231:HA - 3h:O25	2.66663	Hydrogen Bond
			3h:H45 - A:PRO230:O	2.76387	Hydrogen Bond
			A:ARG225:NH1 - 3h	4.7357	Electrostatic
			3h:O34 - A:TYR155	4.78591	Electrostatic
			3h:H50 - 3h	2.80399	Hydrophobic
			3h - 3h	5.86906	Hydrophobic
			3h - 3h	5.0308	Hydrophobic
			A:ALA152 - 3h:C33	2.78404	Hydrophobic

			A:ALA154 - 3h:C33	3.67311	Hydrophobic
			3h:C33 - A:ILE140	3.52425	Hydrophobic
			3h - A:ILE140	5.32624	Hydrophobic
			3h - A:MET150	4.39934	Hydrophobic
			3h - A:MET150	4.59345	Hydrophobic
			3h - A:ALA152	4.32578	Hydrophobic
			3h - A:ALA152	4.68745	Hydrophobic
			3h - A:PRO141	4.88611	Hydrophobic
			3h - A:LEU231	4.54345	Hydrophobic
			3h - A:ILE140	5.20816	Hydrophobic
			3h - A:ALA154	4.91209	Hydrophobic

Table 3 - Interactions between target and ligands



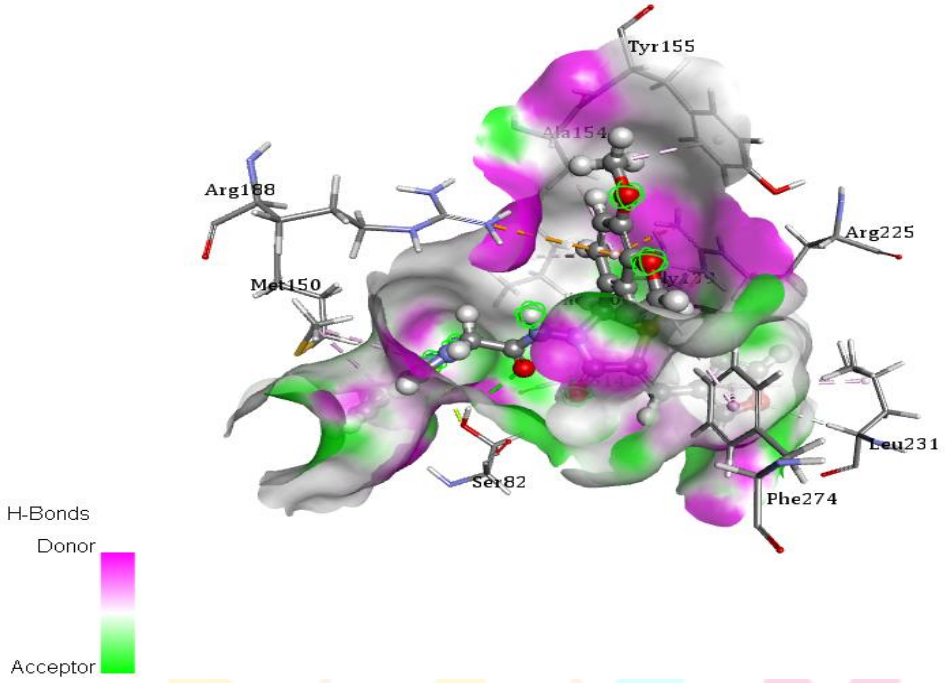
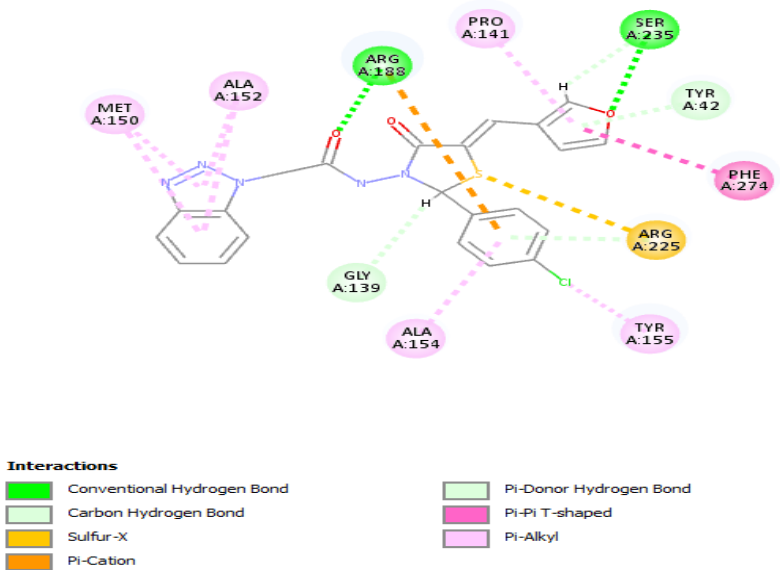


Figure 2: 2D and 3D binding interactions of compound 3i on 1HSK



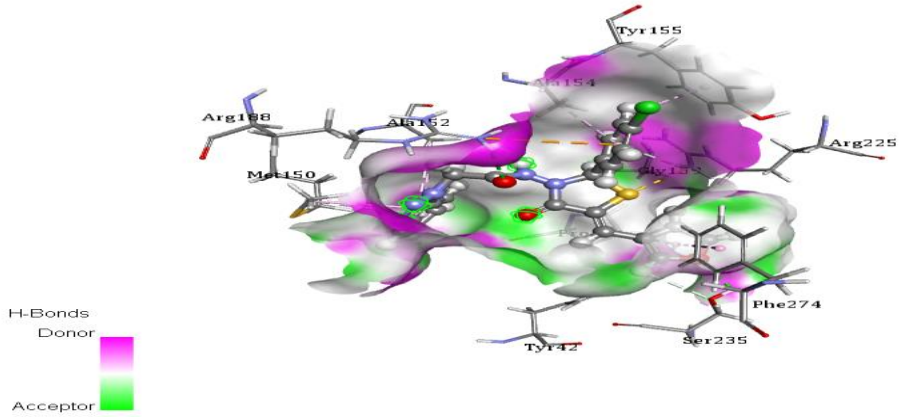


Figure 3: 2D and 3D binding interactions of compound 3b on 1HSK

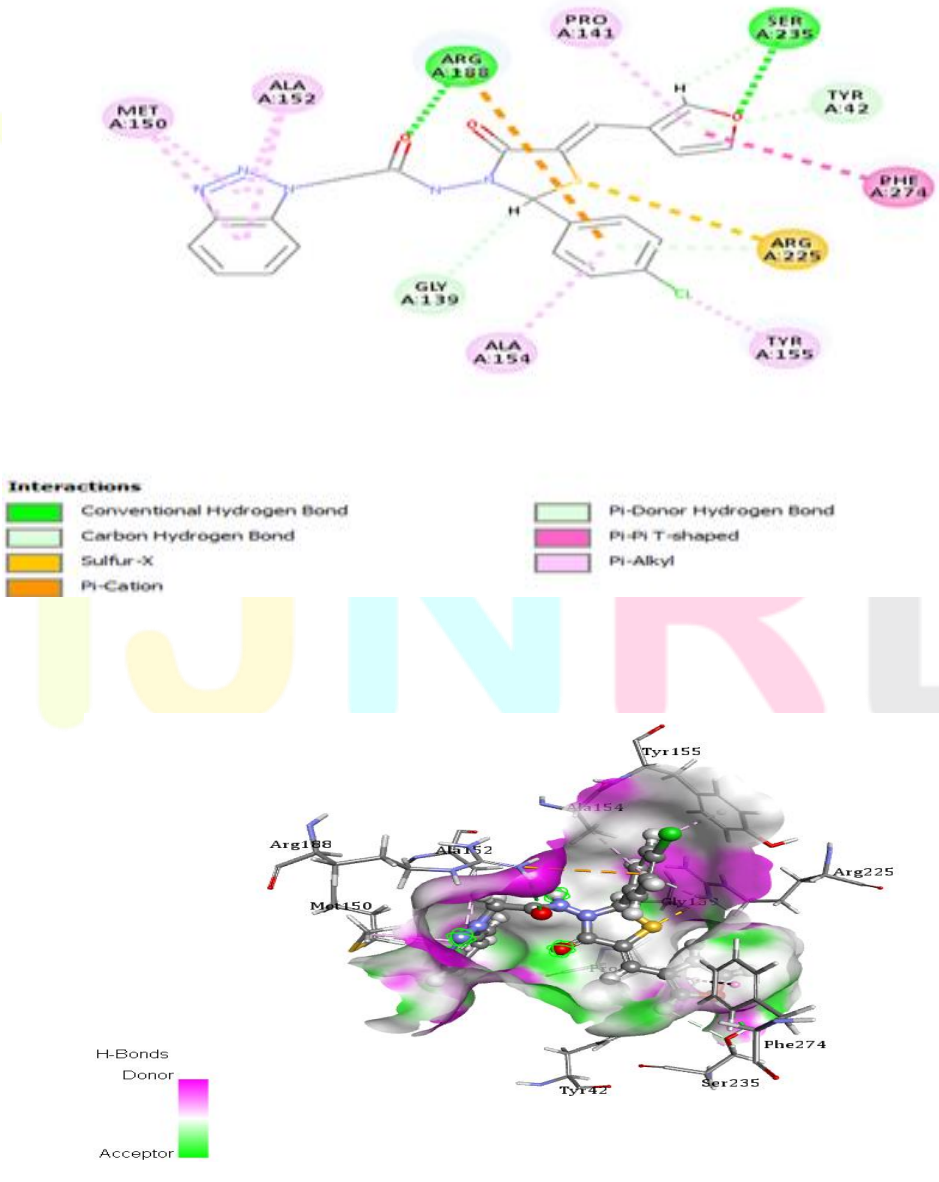
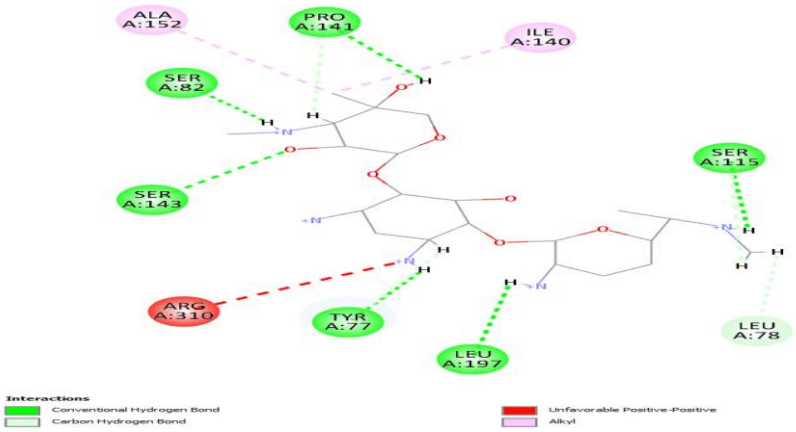


Figure 4 : 2D and 3D binding interactions of compound 3h on 1HSK



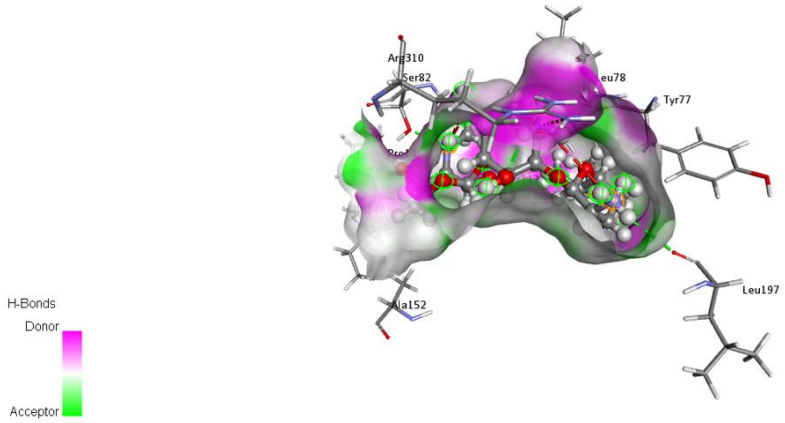


Figure 5: 2D and 3D binding interactions of Gentamicin on 1HSK

Docking with Human sterol 14∞ -demethylase (CYP51) (PDB ID: 6UEZ):

The three-dimensional structure of Human sterol 14a-demethylase (CYP51) was downloaded from PDB database with PDB ID: 6UEZ with crystallographic resolution 1.98 A^0. The protein consists of two polypeptide chain A and B with 458 amino acids. The active site of protein interacting with the standardised ligand molecules was selected as the binding site. 1690 poses of selected ligands in the docked complexes were generated. The interacting molecular complexes among these having high LibDock score and maximum number of hydrogen bonds and active residues were selected. Compounds 3i, 3b and 3j showed good activities on 14 α -Demethylase enzyme. The docked complex of 6UEZ with Compounds 3i (Fig 6), 3b and 3j and Standard ligand Fluconazole (PubChem CID-3365)(Fig 10)were analysed to study non-bond interactions between the target and the ligand molecule. The results are summarised in the Table 4.

Sl. No.	Compounds	LibDock Score	Interacting Residues	Bond Distance (Å)	Nature of Bonding
1.	3i	126.981	A:ILE450:HN - 3i:O19	3.00598	Hydrogen Bond
			A:CYS449:HA - 3i:O19	2.26691	Hydrogen Bond
			3i:H43 - 3i:O12	2.14815	Hydrogen Bond
			3i:S17 - A:PHE152	4.61747	Other
			A:PHE234 - 3i	5.72784	Hydrophobic
			A:ALA314:C,O;THR315:N - 3i	4.14642	Hydrophobic
			A:HIS447:C,O;ARG448:N - 3i	4.62626	Hydrophobic
			A:ALA144 - 3i:C35	3.6699	Hydrophobic
			A:ALA311 - 3i:C33	3.90672	Hydrophobic
			3i:C33 - A:LEU159	4.28022	Hydrophobic
			3i:C33 - A:LEU308	5.05602	Hydrophobic
			3i:C33 - A:ILE450	5.27982	Hydrophobic
			3i:C35 - A:VAL143	4.68707	Hydrophobic
			3i:C35 - A:MET304	4.61454	Hydrophobic
			A:PHE139 - 3i:C35	4.12583	Hydrophobic
			3i - A:ALA314	4.12203	Hydrophobic
			3i - A:PRO376	5.2672	Hydrophobic
			3i - A:PRO376	5.36833	Hydrophobic
			3i - A:ILE377	5.47817	Hydrophobic
			3i - A:ILE377	4.7461	Hydrophobic
			3i - A:ILE488	5.08703	Hydrophobic
			3i - A:LYS156	4.76269	Hydrophobic
			3i - A:ALA144	4.40483	Hydrophobic
2	3b	121.932	A:GLY443:HA1 - 3b:O25	2.53829	Hydrogen Bond
			3b:H40 - A:TYR145:OH	2.96775	Hydrogen Bond
			A:HIS447:HA - 3b	2.86407	Hydrophobic
			A:HIS447:C,O;ARG448:N - 3b	4.51411	Hydrophobic
			3b:Cl32 - A:LEU153	5.38708	Hydrophobic
			3b - A:ALA144	4.2646	Hydrophobic
			3b - A:LEU159	4.42177	Hydrophobic
			3b - A:LEU159	4.73635	Hydrophobic
			3b - A:MET304	5.39159	Hydrophobic
			3b - A:ALA311	5.20409	Hydrophobic
			3b - A:ILE377	5.02338	Hydrophobic
			3b - A:MET380	4.46208	Hydrophobic
			3b - A:LYS156	4.81737	Hydrophobic
3.	3j	120.817	A:THR315:HA - 3j:N8	2.81191	Hydrogen Bond
			A:TYR131 - 3j	5.0504	Hydrophobic
			3j - 3j	4.85497	Hydrophobic
			3j - 3j	5.64157	Hydrophobic
			3j - A:PHE152	5.66743	Hydrophobic
			3j:C33 - A:LEU134	4.15134	Hydrophobic
			3j:C34 - A:LEU134	4.5066	Hydrophobic
			A:TYR131 - 3j:C33	4.03379	Hydrophobic
			A:TYR131 - 3j:C34	4.02578	Hydrophobic
			A:TYR145 - 3j:C34	4.94201	Hydrophobic
			A:PHE234 - 3j:C34	5.38601	Hydrophobic
			3j - A:PRO376	4.68574	Hydrophobic
			3j - A:ILE377	5.31503	Hydrophobic

			3j - A:ILE377	4.69235	Hydrophobic
			3j - A:ILE488	4.39705	Hydrophobic
			3j - A:ILE488	4.59781	Hydrophobic

Table 4 - Interactions between target and ligands

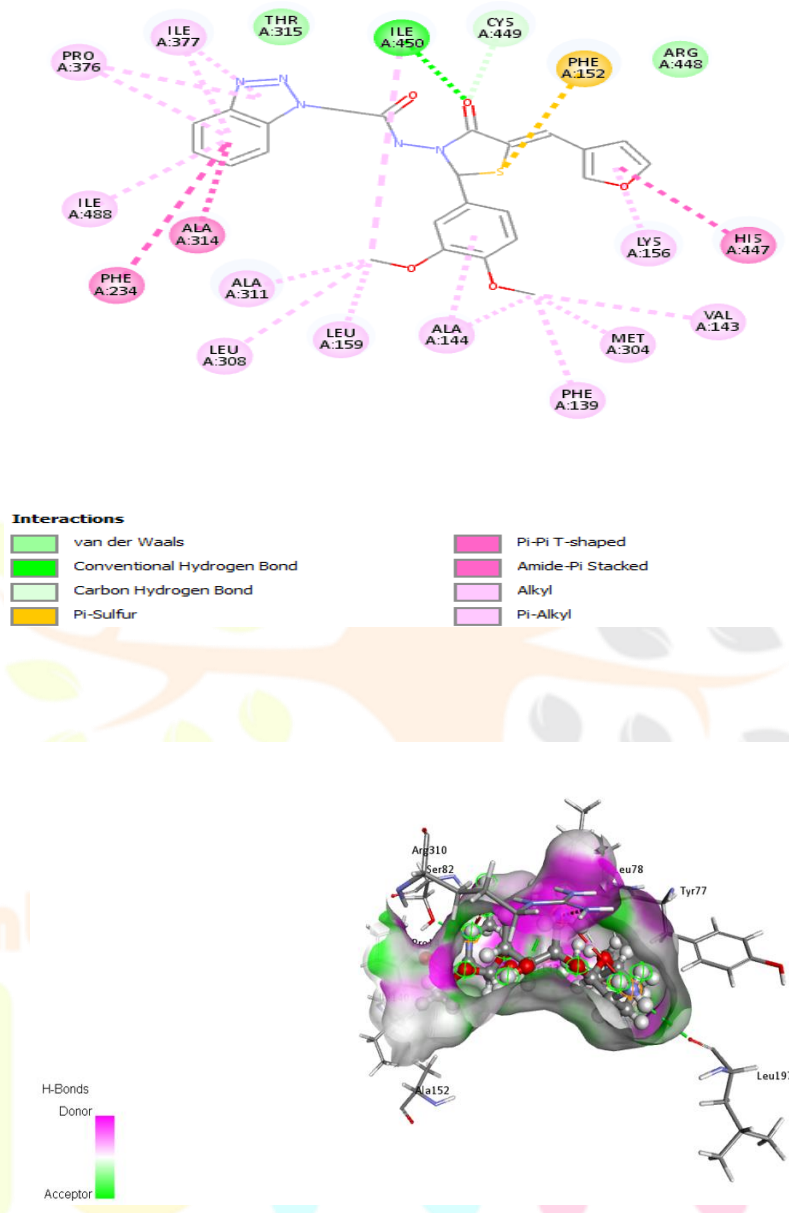


Figure 6: 2D and 3D binding interactions of compound 3i on 6UEZ

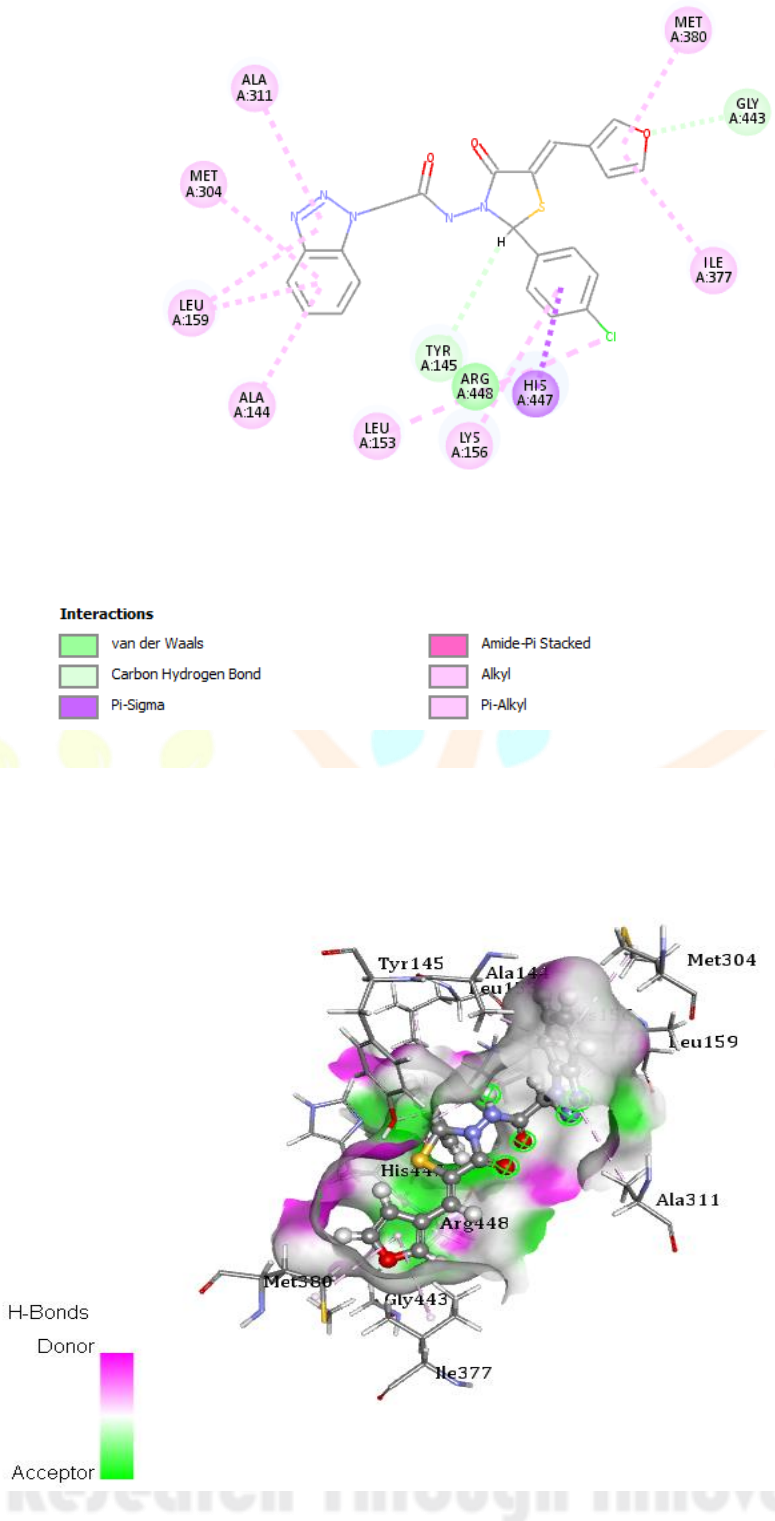
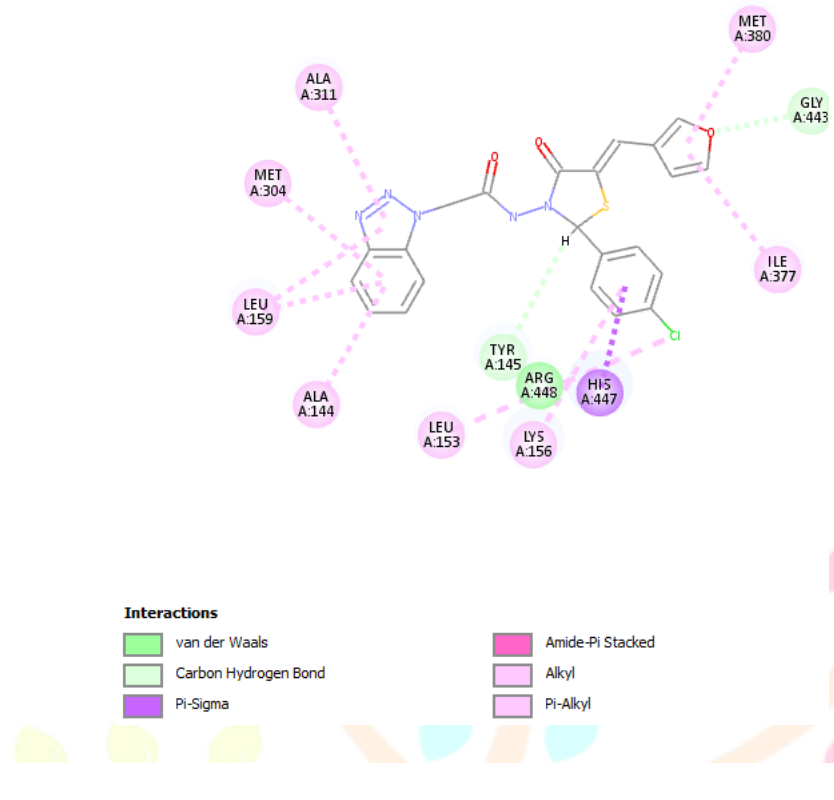


Figure 7: 2D and 3D binding interactions of compound 3i on 6UEZ



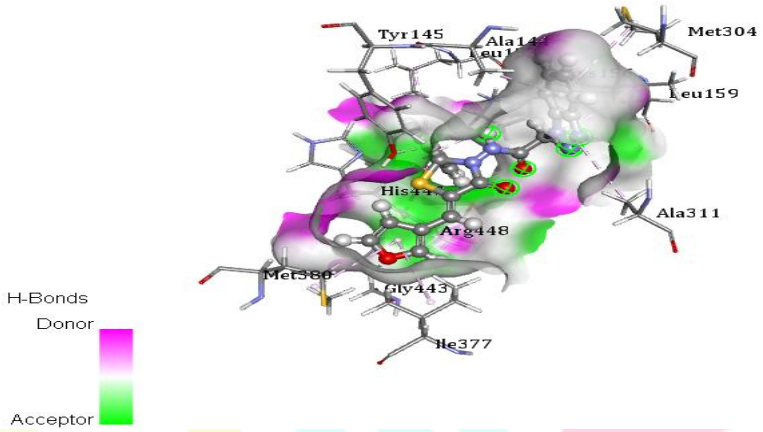


Figure 8: 2D and 3D binding interactions of compound 3b on 6UEZ

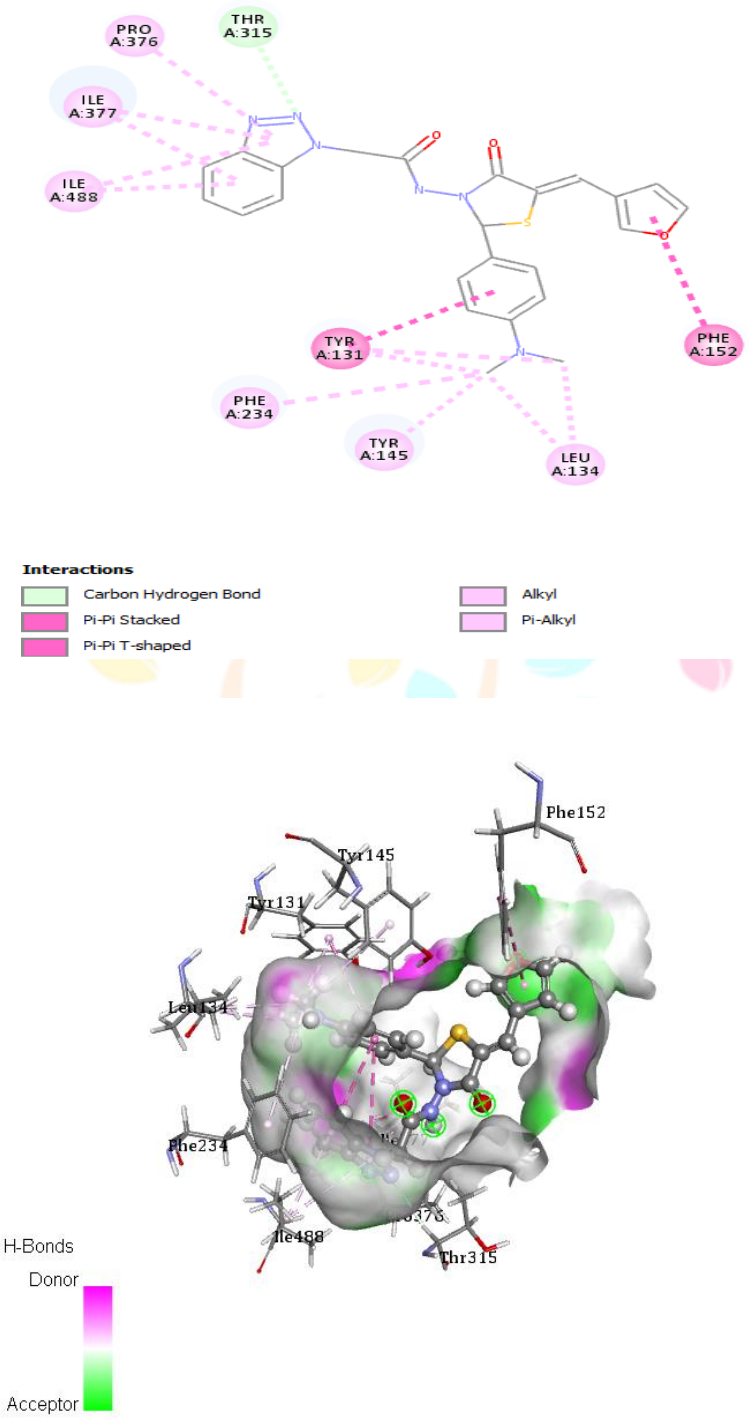


Figure 9: 2D and 3D binding interactions of compound 3j on 6UEZ

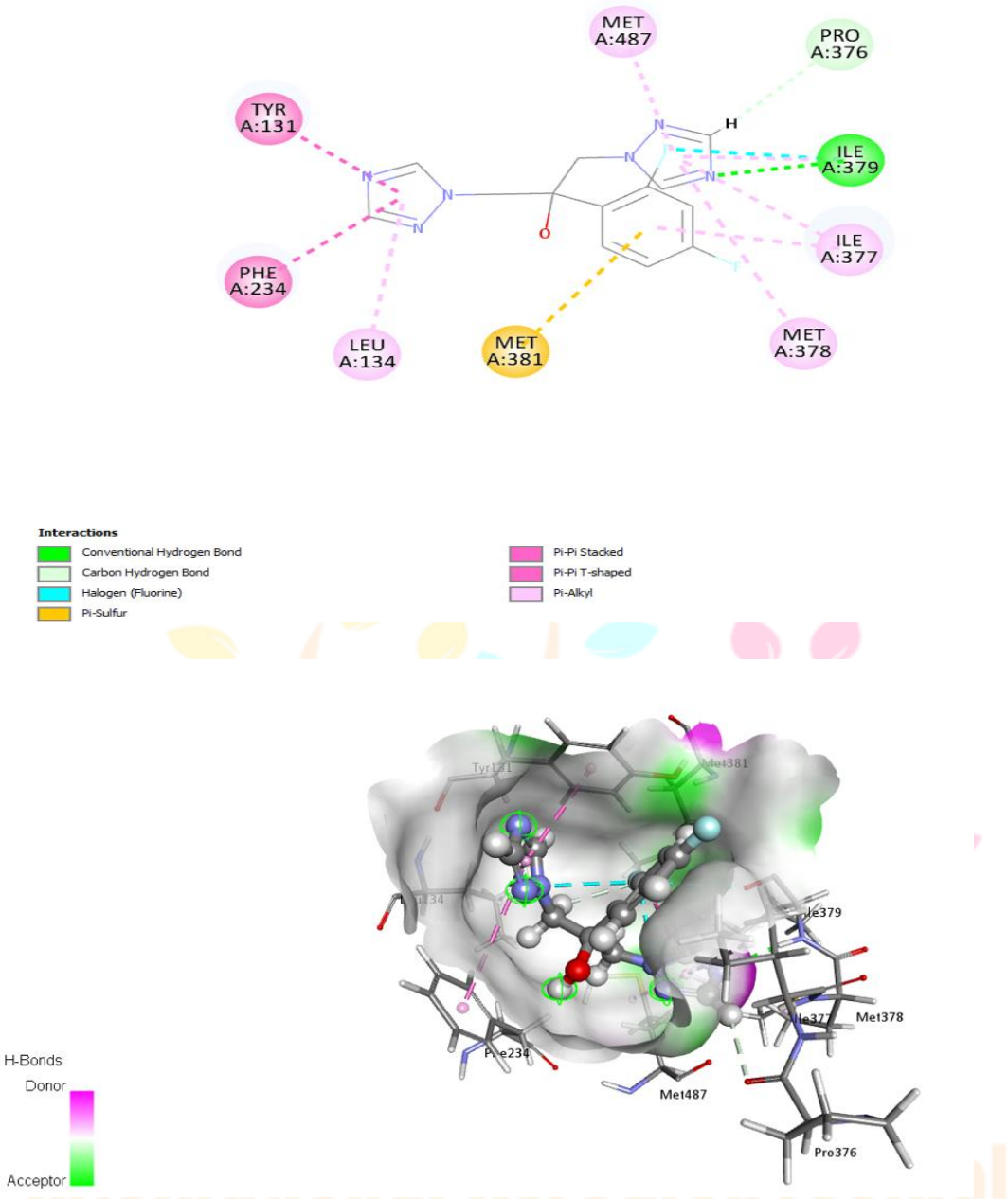


Figure 10: 2D and 3D binding interactions of Fluconazole on 6UEZ

Determination of Physicochemical Properties

The physicochemical properties like electronic (polarisability), steric feature (molar volume) and hydrophobicity (log P) were determined for the newly designed compounds using ACD LabChemSketch (12.0). The results of the first 10 derivatives are summarised in the Table 5.

Compound code	R	Molar volume	Polarisability	log P
3a	C_7H_6O	295.1 ± 7.0 cm^3	47.24 ± 0.5 $10^{-24}cm^3$	2.59
3b	4-C_7H_5ClO	304.4 ± 7.0 cm^3	49.06 ± 0.5 10-$^{24}cm^3$	3.27
3c	2-C_7H_5ClO	304.4 ± 7.0 cm^3	49.06 ± 0.5 $10^{-24}cm^3$	3.22
3d	2-$C_7H_5NO_3$	300.4 ± 7.0 cm^3	49.48 ± 0.5 $10^{-24}cm^3$	2.50
3e	2-$C_7H_5NO_3$	300.4 ± 7.0 cm^3	49.48 ± 0.5 $10^{-24}cm^3$	2.55
3f	3-$C_7H_5NO_3$	300.4 ± 7.0 cm^3	49.48 ± 0.5 $10^{-24}cm^3$	2.52

3g	2-$C_8H_8O_2$	316.8 ± 7.0 cm^3	49.54 ± 0.5 $10^{-24}cm^3$	2.60
3h	4-$C_8H_8O_2$	314.0 ± 7.0 cm^3	49.88 ± 0.5 $10^{-24}cm^3$	1.93
3i	$C_8H_8O_3$	314.0 ± 7.0 cm^3	49.88 ± 0.5 $10^{-24}cm^3$	1.93
3j	$C_9H_{11}NO$	336.2 ± 7.0 cm^3	52.31 ± 0.5 10-$^{24}cm^3$	2.69

Table 5 - Physicochemical Properties of newly synthesised compounds

CONCLUSION

In present work, we have designed and evaluated twenty eight derivatives of novel Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide against 14 α -Demethylase enzyme (PDB ID:6UEZ) for antifungal activity and UDP-N-acetylenol pyruvylglucosamine reductase (MurB) enzyme (PDB ID: 1HSK) for antibacterial activity through docking studies. Compounds obeyed Lipinski rule of five which suggest that these compound have excellent drug likeness properties and are preferable as an orally acting drug. Molecular docking study reveals that Compounds 3i, 3b and 3h shows excellent activities on UDP-N-acetylenol pyruvyl glucosamine reductase enzyme (Mur B) with a docking score of 148.576,139.726 and 134.988 respectively, comparable with standard Gentamicin and compounds 3i, 3b and 3j shows excellent activities on 14 α -Demethylase enzyme with a docking score of 126.981, 121.932 and 120.817 respectively, comparable with standard Fluconazole. Based on the *In-silico* drug likeness, and molecular docking study, it can be suggested that novel Furfurylidene Thiazolidin-4-One derivatives of 2-(1H-benzotriazol-1-yl) acetohydrazide can further be explored with a view to obtain potential antimicrobial agents with minimal side effects.

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