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IN-SILICO DESIGN AND DOCKING STUDIES OF NOVEL 1,3,4-OXADIAZOLE DERIVATIVES OF 2-(1*H*-BENZOTRIAZOL-1-YL)ACETOHYDRAZIDE

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ABSTRACT

Cancer is the second most common cause of death. Despite prominent progress in the field of anticancer agents, many patients suffer from resistance to currently available anticancer drugs and associated adverse effects. In the present work, different novel 1,3,4-Oxadiazole derivatives of 2-(1*H*-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 3f, 3j and 3g showed excellent activities on Focal adhesion kinase, compounds 3g, 3h and 3f showed good activities on Enoyl-acyl carrier protein reductase and compounds 3f, 3g and 3j showed good 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 1,3,4-Oxadiazole derivatives of 2-(1*H*-benzotriazol-1-yl) acetohydrazide could be considered as promising scaffolds towards the development of novel anticancer, antibacterial and antifungal agents.

KEYWORDS

Benzotriazole, Oxadiazoles, Anticancer activity, Antibacterial activity, Antifungal activity,

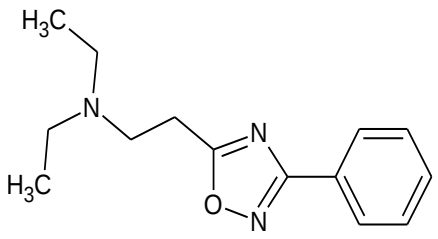
In- silico studies, Biovia Discovery Studio

INTRODUCTION

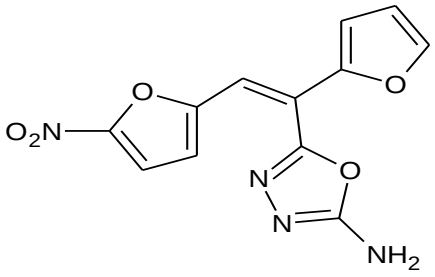
Drug discovery is a process which aims at identifying a compound therapeutically useful in curing and treating disease. This process involves the identification of candidates, synthesis, characterization, validation, optimization, screening and assays for therapeutic efficacy. Once a compound has shown its significance in these investigations, it will initiate the process of drug development earlier to clinical trials. New drug development process must continue through several stages in order to make a medicine that is safe, effective, and has approved all regulatory requirements.[1,2]

Azoles are nitrogen, sulfur and oxygen containing compounds with a five- membered ring system that comprises thiadiazole, oxadiazole, triazole, imidazole, pyrazole and other rings. These compounds exhibit wide range of medicinal applications in the treatment of various types of diseases. Benzo-fused azoles are heterocyclic organic compounds which have a ring system containing three nitrogen atoms and fused benzene ring showing a variety of biological activities. The biological activities of benzotriazole is of immense use in the pharmaceutical field, choleretic, anti bacterial, anti fungal, anti protozoal, anti viral, anti oxidant, analgesic, anti inflammatory, anti hyperglycemia and anti proliferative agents.[3,4]

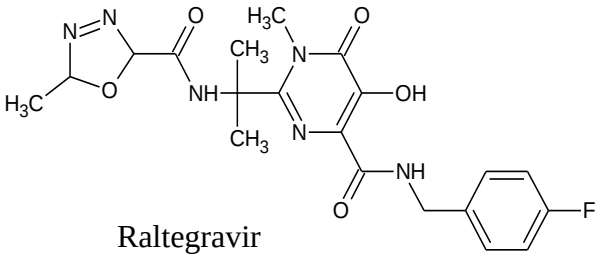
Oxadiazoles are five membered ring heterocyclic compounds containing oxygen and nitrogen atoms. Nucleus exists in four possible isomer forms but 1,3,4-oxadiazole is widely explored for various applications. 1,3,4-oxadiazoles possess wide range of biological activities such as antibacterial, anifungal, anti-inflammatory and anticancer activity[5,6]. Some clinically used oxadiazoles are;



Oxolamine



Furamizole



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Cancer is the second most common cause of death. Despite prominent progress in the field of anticancer agents, many patients suffer from resistance to currently available anticancer drugs and associated adverse effects. Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that plays an important role in cell proliferation, survival, motility, invasion, metastasis, and angiogenesis. Enhanced FAK signaling may result in uncontrolled proliferation, survival or migration of cells, as observed in cancer development and progression process. So FAK may be a promising target for an anticancer drug. The derivatives of benzotriazole and 1,3,4-oxadiazole have been found to exhibit potential anticancer, antibacterial, and antifungal activity. So novel drugs needs to be developed to overcome the treatment failures emerging out of drug resistance.[7,8,9]

In this study, we have designed and evaluated a series of new 1,3,4-Oxadiazole derivatives of 2-(1*H*-benzotriazol-1-yl) acetohydrazide in search of potent anti-cancer and 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 log*P*. 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.[9]

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[10]. 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.[11]

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 pbd format[12,13]. The protein structures were cleaned (water molecules and other hetero atoms removed), prepared and minimized before docking. Steps includes;

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 tautomer's and geometry optimization.

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.

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 LibDock 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. Generally, polar and non-polar drugs in their unionized form are usually more readily

transported through membranes than polar drugs and drugs in their ionized 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 : The size, shape, and bulk of a drug will influence the ease with which it can approach and interact with a target or binding site. A bulky substituent may act like a hinder or shield for the ideal interaction between a drug and its binding site. Alternatively, a bulky substituent may help to orientate a drug properly for maximum binding and better activity. Steric properties are more difficult to quantify than electronic or hydrophobic properties

Lipophilic parameters : Lipophilicity is one of the most studied physicochemical properties. The partition coefficient is the measure of the lipophilicity of a drug and an indication of its ability to cross the cell membrane. It is defined as the ratio between unionized drugs distributed between the organic and aqueous layers at equilibrium. Drugs with high partition-coefficient value can easily permeate through biological membrane. The diffusion of drug molecules across rate-controlling membrane or through the matrix system essentially relies on the partition-coefficient. Drugs having lower partition-coefficient value are not suitable for translating in to oral controlled release formulations and drugs that have higher partition-coefficient are also poor candidates for oral controlled formulations.[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 1,3,4-Oxadiazole 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 1,3,4-Oxadiazole derivatives of 2-(1*H*-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.

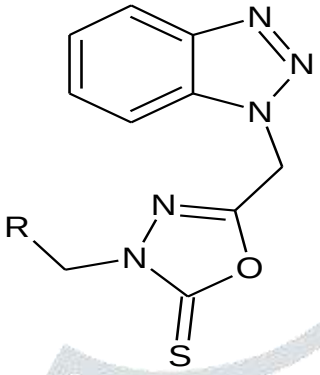


Figure 1: Designed ligand

Compound Code	R	Log P	MW	nON	nOHNH	nrotb	N violation
3a	C_6H_5NH	2.47	338.40	7	1	5	0
3b	4-BrC_6H_4NH	3.28	417.29	7	1	5	0
3c	4-ClC_6H_4NH	3.15	372.84	7	1	5	0
3d	3-ClC_6H_4NH	3.12	372.84	7	1	5	0
3e	2-ClC_6H_4NH	3.10	372.84	7	1	5	0
3f	4-$O_2NC_6H_4NH$	2.43	383.39	10	1	6	0
3g	3-$O_2NC_6H_4NH$	2.40	383.39	10	1	6	0
3h	4-$OCH_3C_6H_4NH$	2.52	368.42	8	1	6	0
3i	2,6-$(CH_3)_2C_6H_3NH$	2.33	366.45	7	1	5	0
3j	2,4-$(CH_3)_2C_6H_3NH$	3.29	366.45	7	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 Focal adhesion kinase(PDB ID:2ETM)[12] enzyme for anticancer activity, 14 α -Demethylase enzyme (PDB ID:6UEZ)[13] for antifungal activity and Enoyl-acyl carrier protein reductase enzyme (PDB ID:4CVI) [15]for antibacterial activity. The docking scores of the first 10 derivatives are shown in Table 2.

Sl.no	Compound code	LibDock Score		
		Focaladhesion kinase	Enoyl-acylcarrier protein reductase	14 α -Demethylase
1	3a	96.358	134.880	107.467
2	3b	100.049	150.218	115.452
3	3c	93.414	149.715	115.234
4	3d	99.149	140.975	111.117
5	3e	94.026	146.100	107.330
6	3f	108.804	154.789	121.668
7	3g	105.668	156.847	118.820
8	3h	101.053	155.126	116.213
9	3i	96.129	147.794	109.013
10	3j	107.601	150.208	117.195
11	Doxorubicin	76.521	-	-
12	Gentamicin	-	164.449	-
13	Fluconazole	-	-	93.429

Table 2: Docking scores of proposed derivatives.

Docking with Focal Adhesion Kinase (PDB ID: 2ETM)

The three-dimensional structure of Adhesion Kinase Domain Complexed with 7H-Pyrrolo [2,3-d] pyrimidine Derivative was downloaded from PDB database with PDB ID: 2ETM with crystallographic resolution 2.30 A^0. The protein chain consists of two polypeptide chain A and B with total 525 amino acids and has a molecular weight of 60241.8Daltons.The active site of protein interacting with the standardised ligand molecules was selected as the binding site. Compounds 3f, 3j and 3g shows excellent activities on Focal adhesion kinase. The docked complex of 2ETM with Compounds 3f(Fig 2), 3j(Fig 3) and 3g and Standard ligand Doxorubicin(Fig 4) (PubChem CID - 51066577)were analysed to study non-bond interactions between the target and the ligand molecule (Fig 2). The results are summarised in the Table 3.

Sl. No.	**Ligands**	**LibDock Score**	**Interacting Residue**	**Bond Distance**	**Nature of Bonding**
1	3f	108.804	A:LYS454:HZ3 -3f:N8	2.52231	Hydrogen Bond
			A:GLY505:HN - 3f:O27	3.0553	Hydrogen Bond
			A:GLY505:HA2 - 3f:O27	3.0415	Hydrogen Bond
			3f:H33 - A:GLU471:OE2	2.94781	Hydrogen Bond
			3f - A:LEU553	4.38572	Hydrophobic
			3f - A:ALA452	4.65318	Hydrophobic
			3f - A:VAL484	5.22239	Hydrophobic
			3f - A:MET499	4.80679	Hydrophobic

			3f - A:LEU553	4.99376	Hydrophobic
			3f - A:ILE428	4.14863	Hydrophobic
			3f - A:LEU501	5.36092	Hydrophobic
			3f - A:LEU553	5.40124	Hydrophobic
2	3g	105.668	A:CYS502:HN - 3g:N7	2.16272	Hydrogen Bond
			A:ASP564:HN - 3g:S24	2.60075	Hydrogen Bond
			A:LYS454:HE2 - 3g:N13	2.42073	Hydrogen Bond
			A:LEU501:HA - 3g:N7	2.73517	Hydrogen Bond
			A:GLU506:HA - 3g:O26	2.99206	Hydrogen Bond
			3g:H34 - A:GLU471:OE2	2.87774	Hydrogen Bond
			3g:H35 - A:GLU471:OE2	3.02696	Hydrogen Bond
			A:MET499:SD - 3g	3.68698	Other
			3g:S24 - 3g	4.74103	Other
			3g - A:ILE428	5.23634	Hydrophobic
			3g - A:ALA452	3.63959	Hydrophobic
			3g - A:ALA452	4.91885	Hydrophobic
			3g - A:LEU501	5.38474	Hydrophobic
			3g - A:CYS502	4.76911	Hydrophobic
			3g - A:LEU553	4.37191	Hydrophobic
			3g - A:LEU553	4.26967	Hydrophobic
			3g - A:VAL484	4.88803	Hydrophobic
			3g - A:LEU553	5.31315	Hydrophobic
			3g - A:LEU553	4.13568	Hydrophobic
3	3 j	107.601	A:CYS502:HN - 3 j:N7	2.532	Hydrogen Bond
			A:ASP564:HN - 3 j:S24	2.53102	Hydrogen Bond
			A:LYS454:HE2 - 3 j:N13	2.45705	Hydrogen Bond
			3 j:H33 - A:GLU471:OE2	2.24869	Hydrogen Bond
			A:MET499:SD - 3 j	5.98831	Other
			3 j:S24 - 3 j	5.21115	Other
			3 j:C26 - A:LEU553	3.85179	Hydrophobic
			3 j - A:ILE428	5.36221	Hydrophobic
			3 j - A:ALA452	4.75425	Hydrophobic
			3 j - A:ALA452	3.70136	Hydrophobic
			3 j - A:CYS502	5.44048	Hydrophobic
			3 j - A:CYS502	4.86019	Hydrophobic
			3 j - A:LEU553	4.24189	Hydrophobic
			3 j - A:LEU553	4.26283	Hydrophobic
			3 j - A:VAL484	4.80025	Hydrophobic
			3 j - A:MET499	4.74751	Hydrophobic
			3 j - A:LEU553	5.37193	Hydrophobic
			3 j - A:LEU553	4.58901	Hydrophobic

Table 1: Interactions between target and ligands

Table 3

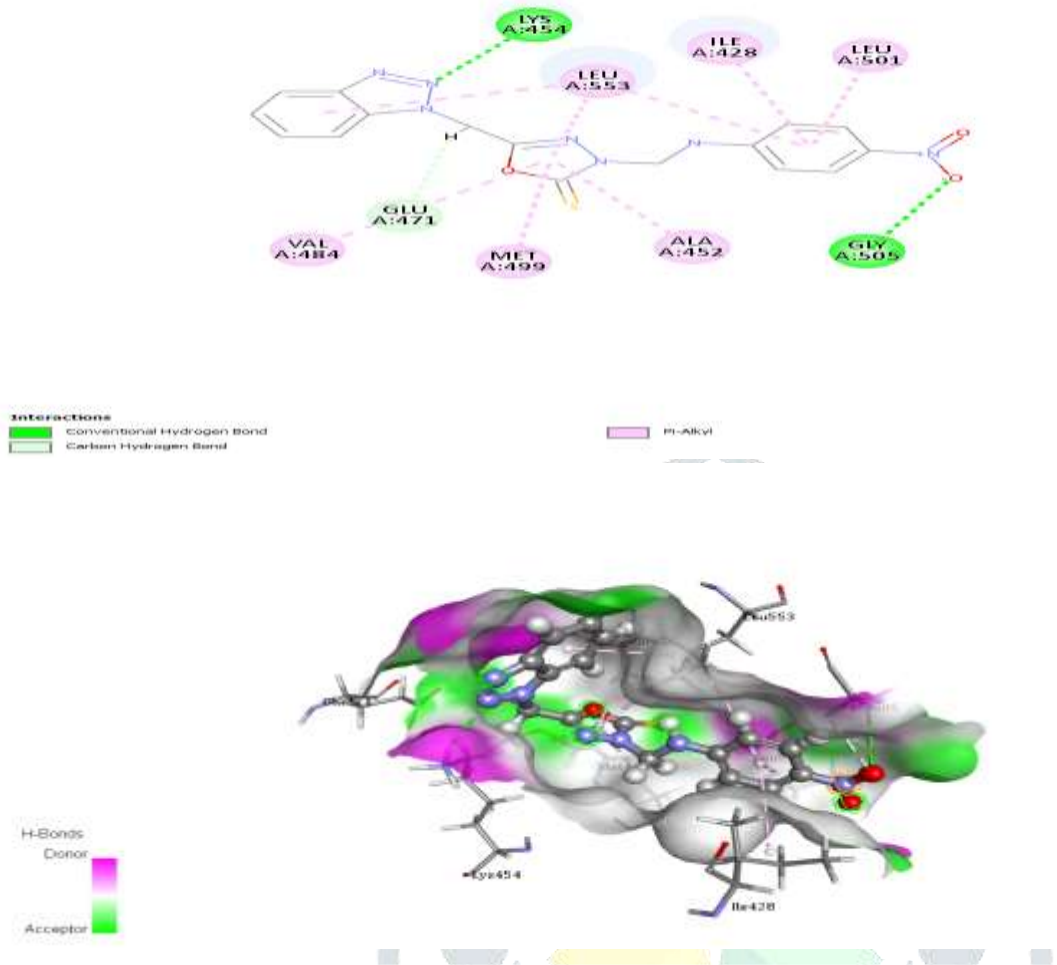
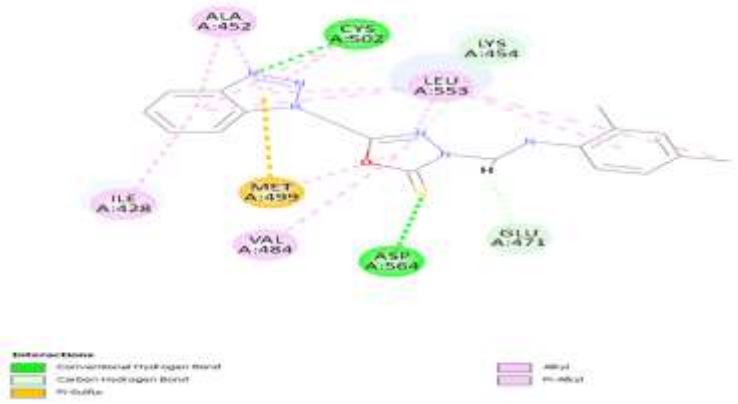


Figure 2: 2D and 3D binding interactions of compound 3f on 2ETM.



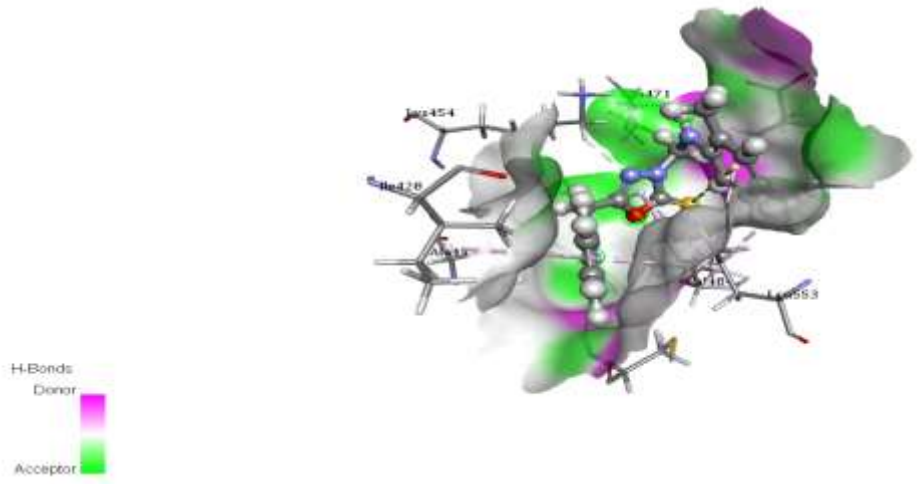


Figure 3: 2D and 3D binding interactions of compound 3j on 2ETM.

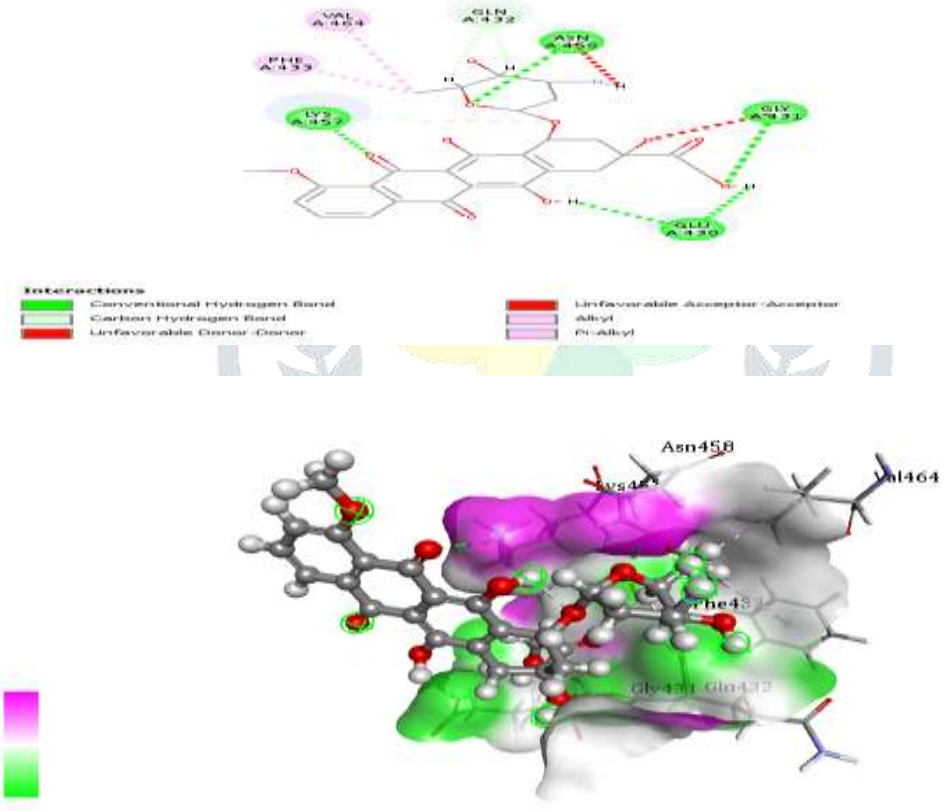


Figure 4: 2D and 3D binding interactions of doxorubicin on 2ETM.

Docking with Enoyl-acylcarrier protein reductase (PDB ID:4CVI)

The three-dimensional structure of Enoyl-acylcarrier protein reductase was downloaded from PDB database with PDB ID: 4CVI with crystallographic resolution 2.10 A^0. The protein chain consists of one polypeptide chain A with total 292 amino acids and has a molecular weight of 33549.4 Daltons. The active site of protein interacting with the standardised ligand molecules was selected as the binding site. Compounds 3g, 3h and 3f

showed good activities on Enoyl-acyl carrier protein reductase. The docked complex of 4CVI with Compound3g(Fig 5), 3h and 3f and Standard ligand Gentamycin (PubChem CID-3467)(Fig 6)were analysed to study non-bond interactions between the target and the ligand molecule. The results are summarised in the Table 4.

Sl. No.	Ligands	LibDock Score	Interacting Residue	Bond Distance	Nature of Bonding
1	3f	154.789	A:ARG48:NH1 - 3f:O27	5.17755	Electrostatic
			3f:N25 - A:ASP37:OD2	5.31139	Electrostatic
			A:TYR36:HH - 3f:O27	2.51282	Hydrogen Bond
			A:ARG48:HH11 - 3f:O26	2.42859	Hydrogen Bond
			3f:H36 - A:LEU177:O	2.53991	Hydrogen Bond
			3f:H34 - A:LEU177:O	2.63007	Hydrogen Bond
			A:HIS175:NE2 - 3f	3.79166	Electrostatic
			A:MET172:SD - 3f	4.74149	Other
			3f:S24 - A:TRP51	5.98996	Other
			3f:S24 - A:HIS175	4.64563	Other
			3f:S24 - 3f	5.09586	Other
			A:TRP51 - 3f	4.08614	Hydrophobic
			A:TRP51 - 3f	4.36271	Hydrophobic
			A:TRP51 - 3f	5.08554	Hydrophobic
			3f - A:TRP51	5.34097	Hydrophobic
			A:HIS175 - 3f	4.47824	Hydrophobic
			A:VAL47:C,O;ARG48:N - 3f	5.37883	Hydrophobic
			3f - A:ALA174	3.62286	Hydrophobic
			3f - A:ALA174	4.16224	Hydrophobic
			3f - A:ARG48	4.27031	Hydrophobic
			3f - A:ALA174	5.0484	Hydrophobic
			3f - A:VAL45	5.114	Hydrophobic
			3f - A:ARG48	4.7939	Hydrophobic
2	3g	156.847	A:ARG48:NH1 - 3g:O27	5.45347	Electrostatic
			A:HIS175:NE2 - 3g:O27	4.81662	Electrostatic
			3g:H36 - A:PRO44:O	2.97679	Hydrogen Bond
			A:ARG48:HA - 3g:O12	2.72859	Hydrogen Bond
			A:TRP51:HD1 - 3g:O12	2.43935	Hydrogen Bond
			3g:H34 - A:ALA174:O	2.41214	Hydrogen Bond
			3g:H34 - A:LEU177:O	2.95312	Hydrogen Bond
			A:HIS175:NE2 - 3g	4.50385	Electrostatic
			A:MET172:SD - 3g	4.70413	Other
			3g:S24 - A:TRP51	5.09064	Other
			3g:S24 - A:HIS175	4.84155	Other
			A:TRP51 - 3g	4.23589	Hydrophobic
			A:TRP51 - 3g	4.12025	Hydrophobic
			A:TRP51 - 3g	4.63959	Hydrophobic
			3g - A:TRP51	4.79905	Hydrophobic
			A:HIS175 - 3g	5.52866	Hydrophobic
			3g - A:LEU171	5.04852	Hydrophobic
			3g - A:LEU171	4.68644	Hydrophobic
			3g - A:ALA174	4.6164	Hydrophobic
			3g - A:ALA174	4.32197	Hydrophobic
			3g - A:VAL47	5.05446	Hydrophobic
			3g - A:ARG48	4.50804	Hydrophobic
			3g - A:ALA174	4.04812	Hydrophobic
			3g - A:ARG48	4.4737	Hydrophobic
3	3h	155.126	A:ARG48:HH11 - 3h:N8	2.61298	Hydrogen Bond
			A:ARG48:HD1 - 3h:N8	2.34295	Hydrogen Bond
			3h:H32 - A:LYS179:O	2.12833	Hydrogen Bond
			3h:H33 - A:ALA174:O	2.42444	Hydrogen Bond
			A:ASP37:OD2 - 3h	4.01997	Electrostatic
			A:PRO44:HB2 - 3h	2.79519	Hydrophobic

			3h:S24 - 3h	5.78818	Other
			A:TRP51 - 3h	4.15488	Hydrophobic
			A:TRP51 - 3h	5.48356	Hydrophobic
			A:HIS181 - 3h	4.76684	Hydrophobic
			A:HIS181 - 3h	4.8193	Hydrophobic
			A:LEU177:C,O;GLY178:N - 3h	4.23378	Hydrophobic
			3h:C26 - A:LEU171	3.53689	Hydrophobic
			3h:C26 - A:LEU269	4.24883	Hydrophobic
			A:TRP51 - 3h:C26	4.63802	Hydrophobic
			A:TRP51 - 3h:C26	4.64813	Hydrophobic
			A:PHE266 - 3h:C26	5.32139	Hydrophobic
			3h - A:VAL45	4.6094	Hydrophobic
			3h - A:VAL45	4.51619	Hydrophobic
			3h - A:ARG48	5.01865	Hydrophobic
			3h - A:ARG48	4.52951	Hydrophobic
			3h - A:ALA174	3.50551	Hydrophobic

Table 4

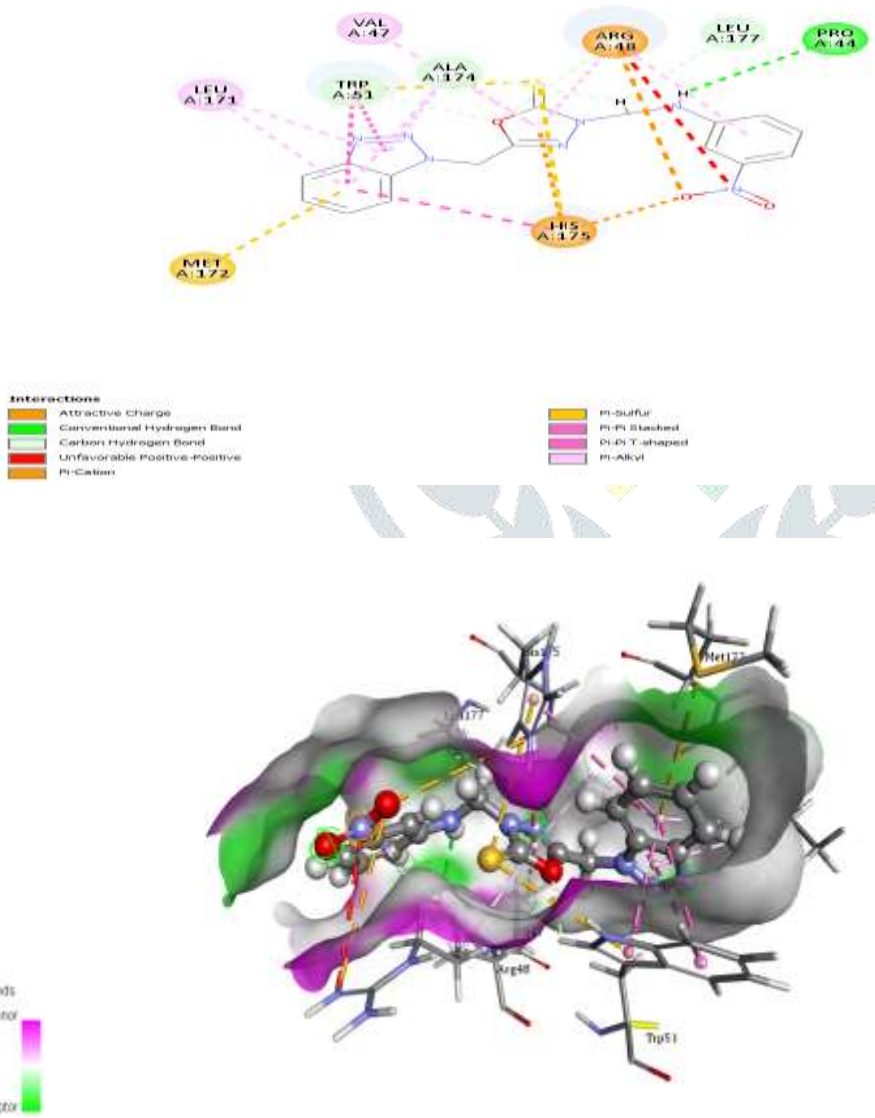


Figure 5: 2D and 3D binding interactions of compound 3g on 4CVI

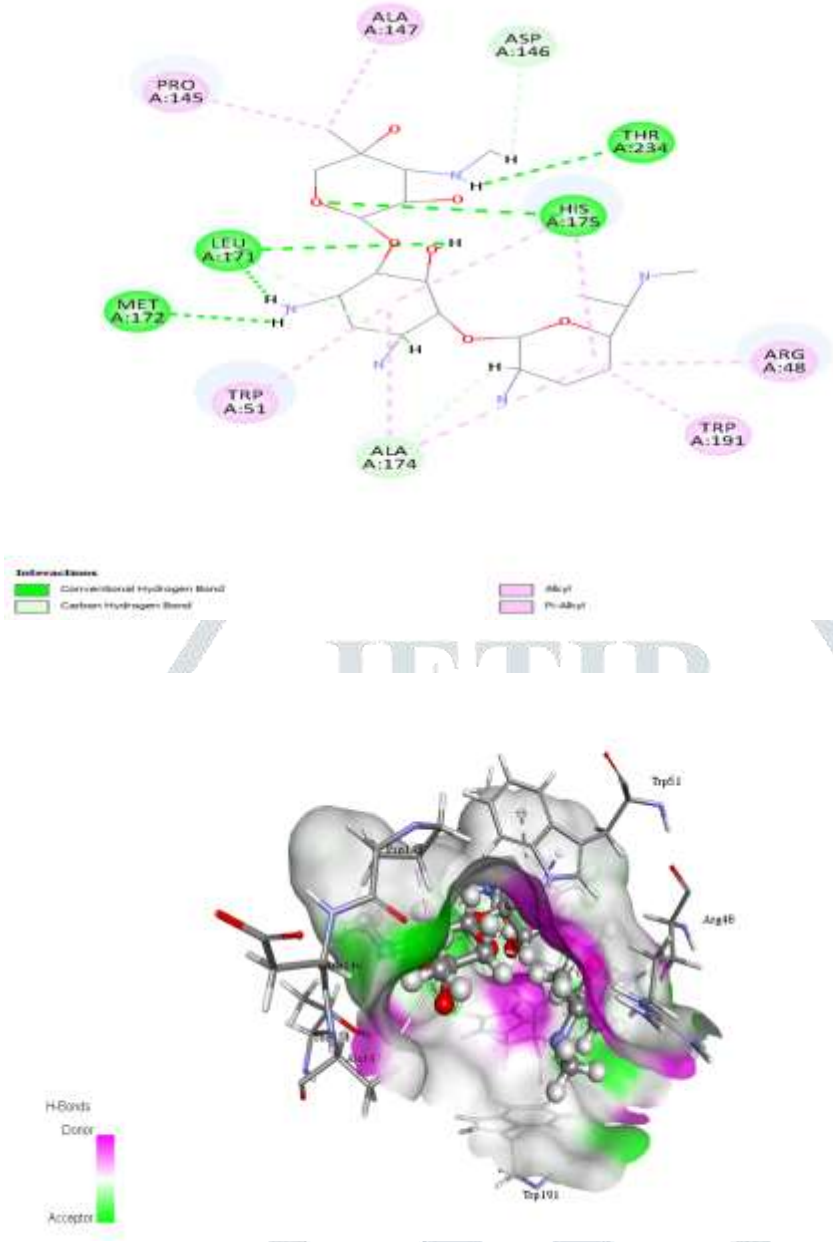


Figure 6: 2D and 3D binding interactions of Gentamicin on 4CVI

Docking with Sterol 14a-demethylase (CYP51) (PDB ID:6UEZ)

The three-dimensional structure of Human sterol 14a-demethylase (CYP51) in complex with the substrate lanosterol was downloaded from PDB database with PDB ID: 6UEZ with crystallographic resolution 1.98 A^0. The protein chain consists of two polypeptide chain A and B with total 891 amino acids and has a molecular weight of 101002 Daltons. The active site of protein interacting with the standardised ligand molecules was selected as the binding site. Compounds 3f, 3g and 3j showed good activities on 14 α -Demethylase enzyme. The docked complex of 6UEZ with Compounds 3f(Fig 6), 3g and 3j and Standard ligand Fluconazole (PubChem CID-3365)(Fig 8)were analysed to study non-bond interactions between the target and the ligand molecule. The results are summarised in the Table 5.

Sl. No.	Ligands	LibDock Score	Interacting Residue	Bond Distance	Nature of Bonding
1	3f	121.668	A:ARG382:HH22 - 3f:O26	2.01903	Hydrogen Bond
			A:ALA444:HN - 3f:O27	2.19449	Hydrogen Bond
			A:GLY443:HA1 - 3f:O27	1.78199	Hydrogen Bond
			A:ARG448:HA - 3f:O27	2.3964	Hydrogen Bond
			3f 6:H34 - A:TYR145:OH	2.60113	Hydrogen Bond
			A:ILE377:HG12 - 3f	2.88998	Hydrophobic
			3f:S24 - A:TYR145	5.09933	Other
			3f - A:PHE234	5.18032	Hydrophobic
			3f - A:ILE377	4.93832	Hydrophobic
			3f - A:ILE379	5.27705	Hydrophobic
			3f - A:MET487	4.03371	Hydrophobic
			3f - A:MET487	5.40281	Hydrophobic
			3f - A:ILE488	5.0802	Hydrophobic
			3f - A:MET380	4.23621	Hydrophobic
2	3g	118.82	A:GLY443:HA1 - 3g:O26	1.77465	Hydrogen Bond
			3g:H34 - A:TYR145:OH	2.45933	Hydrogen Bond
			3g:H35 - A:TYR131	2.82103	Hydrophobic
			3g:S24 - A:PHE139	5.22781	Other
			3g:S24 - A:TYR145	4.95954	Other
			3g - A:PHE234	4.99	Hydrophobic
			3g - A:PHE234	5.16604	Hydrophobic
			3g - A:ILE377	4.50369	Hydrophobic
			3g - A:ILE377	4.82889	Hydrophobic
			3g - A:ILE379	5.3966	Hydrophobic
			3g - A:MET487	5.43652	Hydrophobic
			3g - A:MET487	4.08476	Hydrophobic
			3g - A:ILE488	5.06498	Hydrophobic
			3g - A:MET380	4.728	Hydrophobic
3	3j	117.195	3j:H33 - A:TYR145:OH	2.5515	Hydrogen Bond
			A:ILE377:HG12 - 3j	2.86142	Hydrophobic
			A:MET381:SD - 3j	5.19425	Other
			3j:S24 - A:TYR145	4.73022	Other
			3j - A:PHE234	5.08405	Hydrophobic
			3j:C25 - A:ILE377	3.37911	Hydrophobic
			3j:C25 - A:MET380	4.44129	Hydrophobic
			3j:C26 - A:MET380	4.48215	Hydrophobic
			A:PHE118 - 3j:C26	5.40789	Hydrophobic
			3j - A:ILE377	4.64449	Hydrophobic
			3j - A:ILE379	5.39219	Hydrophobic
			3j - A:MET487	4.28385	Hydrophobic
			3j - A:ILE488	5.1959	Hydrophobic
			3j - A:MET380	3.95623	Hydrophobic

Table 5

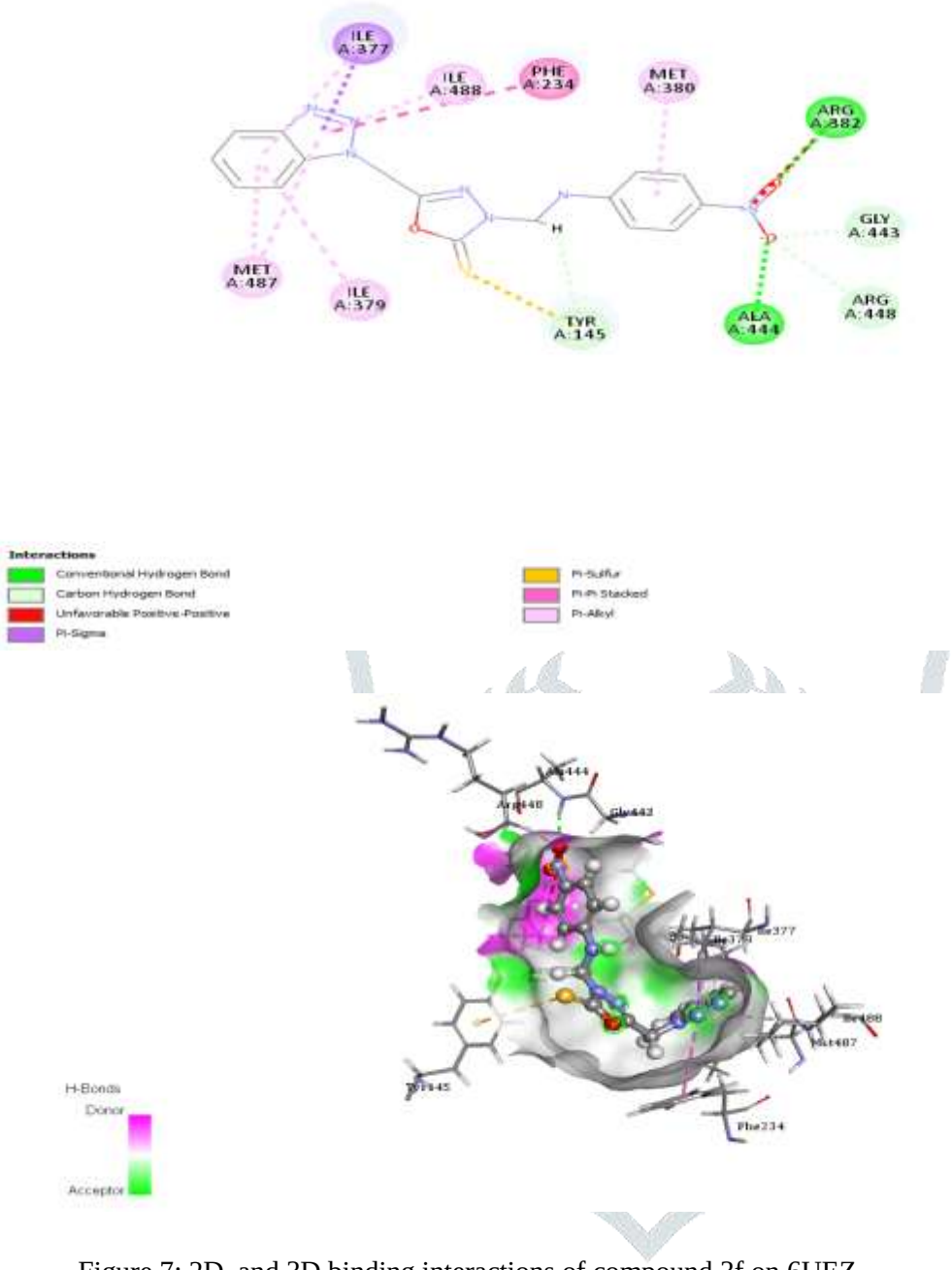
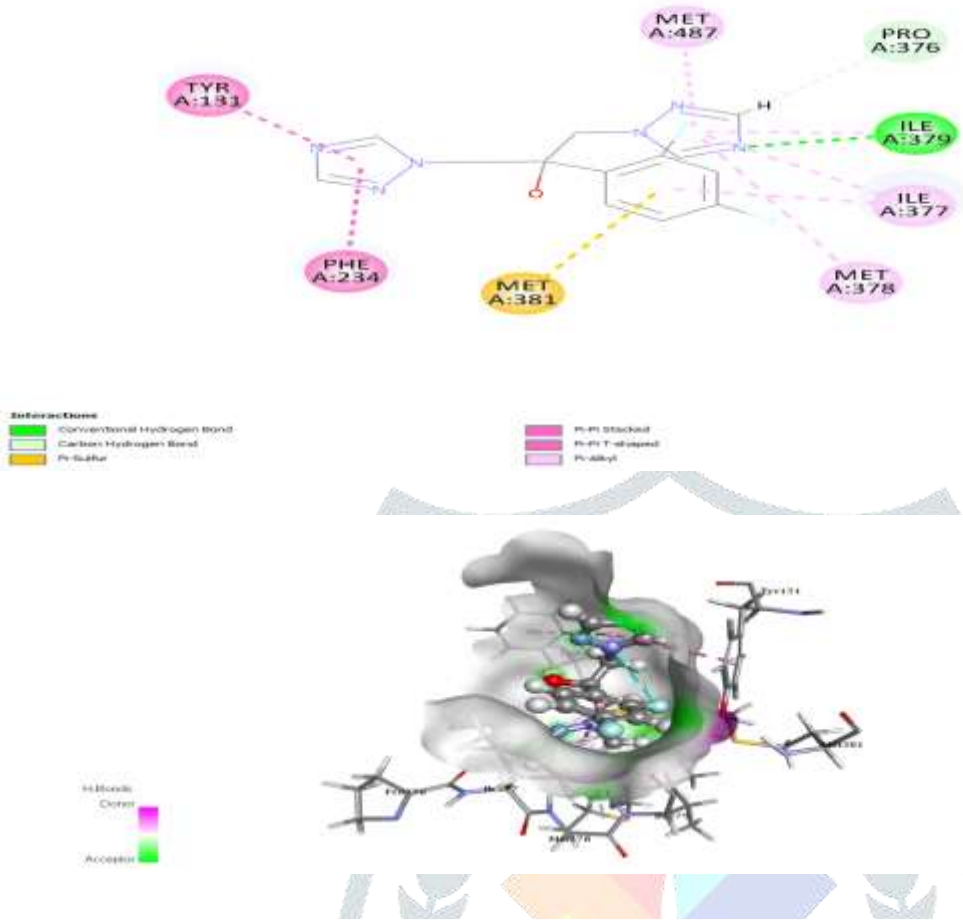


Figure 7: 2D and 3D binding interactions of compound 3f on 6UEZ



Determinatic Figure 8: 2D and 3D binding interactions of Fluconazole on 6UEZ

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 6.

Compound code	R	Molar volume	Polarisability	Log P
3a	C_6H_5NH	231.7 ± 7.0cm^3	37.63 ± 0.5 10^{-24} cm^3	2.47
3b	4-BrC_6H_4NH	244.2 ± 7.0cm^3	40.62 ± 0.5 10^{-24} cm^3	3.28
3c	4-ClC_6H_4NH	241.0 ± 7.0cm^3	39.45 ± 0.5 10^{-24} cm^3	3.15
3d	3-ClC_6H_4NH	241.7 ± 7.0cm^3	39.45 ± 0.5 10^{-24} cm^3	3.12
3e	2-ClC_6H_4NH	241.7 ± 7.0cm^3	39.45 ± 0.5 10^{-24} cm^3	3.10
3f	4-$O_2NC_6H_4NH$	236.9 ± 7.0cm^3	39.87 ± 0.5 10^{-24} cm^3	2.43
3g	3-$O_2NC_6H_4NH$	236.9 ± 7.0cm^3	39.87 ± 0.5 10^{-24} cm^3	2.40
3h	4-$OCH_3C_6H_4NH$	253.0 ± 7.0cm^3	39.93 ± 0.5 10^{-24} cm^3	2.52
3i	2,6-$(CH_3)_2C_6H_3NH$	262.7 ± 7.0cm^3	41.14 ± 0.5 10^{-24} cm^3	2.33
3j	2,4-$(CH_3)_2C_6H_3NH$	262.7 ± 7.0cm^3	41.14 ± 0.5 10^{-24} cm^3	3.29

Table 6 : Physicochemical properties of first 10 derivatives

CONCLUSION

In present work, we have designed and evaluated twenty eight derivatives of novel 1,3,4-Oxadiazole derivatives of 2-(1*H*-benzotriazol-1-yl) acetohydrazide against Focal adhesion kinase(PDB ID:2ETM) enzyme for anticancer activity, 14 α -Demethylase enzyme (PDB ID:6UEZ) for antifungal activity and Enoyl-acyl carrier protein reductase enzyme (PDB ID:4CVI) 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 3f, 3j and 3g shows excellent activities on Focal adhesion kinase enzyme with a docking score of 108.804, 107.601 and 105.668 respectively,comparable with standard doxorubicin. Compounds 3g, 3h and 3f shows excellent activities on Enoyl-acyl carrier protein reductase with a docking score of 156.847, 155.126 and 154.789 respectively, comparable with standard gentamicin and compounds 3f, 3g and 3j shows excellent activities on 14 α -Demethylase enzyme with a docking score of 121.668, 118.82 and 117.195 respectively, comparable with standard fluconazole. Based on the *in silico* drug likeness, and molecular docking study, it can be suggested that novel 1,3,4-Oxad : explored with a view to obtain potential anticancer and antimicrobial agents with minimal side effects.

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