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IN-SILICO MOLECULAR DOCKING AND PHARMACOKINETIC PREDICTION STUDIES OF NOVEL PYRAZOLE LINKED FURAN AND THIOPHENE DERIVATIVES FOR ANTIFUNGAL ACTIVITY

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ABSTRACT

In silico studies were conducted on twenty newly designed pyrazole derivatives as 14- α demethylase enzyme inhibitors to select the best possible drug candidates based on drug properties and bioactivity score of the compounds. Molecular properties of designed compounds were studied by using Molinspiration. ADMET studies were performed by using pkCSM software. Molecular docking studies were performed on 14- α demethylase enzyme by using Glide 5.5 extra precision (XP) maestro Schrodinger software. The results of this study give room for designing new antifungal compounds with better inhibitory activity against 14-α demethylase enzyme, a key enzyme in ergosterol biosynthesis. Analogues 8, 18 and 19 were found to have higher docking score and significant binding interaction with the enzyme. Molecular docking explained the possible binding mode of compound 18 in the 14- α demethylase active site. Our studies indicated that the pyrazole–furan hybrid is a new scaffold of 14- α demethylase inhibitors.

KEYWORDS: 14-α demethylase; docking; furan; pyrazole; thiophene.

INTRODUCTION

Drug discovery and development pipeline have more and more depends on in vitro testing and in silico predictions to reduce investments and optimize lead compounds. Computer-aided techniques are employed not just in the discovery of new lead compounds but embedded as part of the entire drug development process where the ADME profiling and big data analysis adds a new layer of complexity to those systems. Fungal infections are devastating. Fungal infections can be contagious. They can spread from one person to another. Our range of antifungal agents is limited, in comparison to the number of agents available for bacterial infections. Also, treatment of fungal infection has several limitations, such as undesirable side effects, narrow activity spectrum, a small number of targets and fungal resistance, which are still of major concern in clinical practice. Hence it is essential to find out new antifungal agents. Major antifungal classes are azoles, echinocandins, polyenes, allylamines and pyrimidine analogues. Cytochrome P450 enzyme lanosterol 14α-demethylase (LDM) is the target of the azole antifungals used in prophylaxis or treatments of infections or diseases caused by fungus. Inhibition of 14α-lanosterol demethylase, a key enzyme in ergosterol biosynthesis, results in depletion of ergosterol and accumulation of toxic 14α-methylated sterols in membranes of susceptible yeast species.[1] Finally it leads to cell death. The compounds are designed in such a way that it will inhibit this enzyme.

Pyrazole derivatives represent an important class of compounds due to their highly pronounced pharmacological and biological activities such as anti-inflammatory[2], antimicrobial[3], antidepressant[4], antiviral[5] and antitumor activities.[6] Among these, 4-functionalized pyrazoles occupy a position in medicinal chemistry because of their antimicrobial[7], anti-inflammatory[8], anti-parasitic[9] and antitumor activities.[10] Thiophene is a five membered heteroaromatic compound containing a sulfur atom at 1 position. In medicinal chemistry, thiophene derivatives are very important heterocycles exhibiting remarkable applications in different disciplines. In medicine, thiophene derivatives show antimicrobial[11], analgesic and anti-inflammatory[12], antihypertensive[13] and antitumor activity.[14] Furan is a five membered aromatic ring with one oxygen atom. Incorporation of furan nuclei is an important synthetic strategy in drug discovery. These moieties are widely employed as antibacterial, antiviral, anti-inflammatory, antifungal, antitumor,

antihyperglycemic, analgesic, anti-convulsant etc.[15] Chalcone is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds Studies revealed that compounds with a chalcone-based structure possess a wide variety of biological activities such as anti-inflammatory[16], anti-bacterial[17], anti-fungal[18] and anticancer activities.[19] Based on the above findings, present study aims to design potentially active novel pyrazole-thiophene and pyrazole- furan derivatives through in-silico drug design and to evaluate their antifungal activity via molecular docking studies.

MATERIALS AND METHODS

In silico Drug Likeness Study Using Molinspiration Molecule Viewer

Molinspiration Molecule Viewer software permits perception of molecules by employing sophisticated Bayesian statistics, which match the structures and properties of representative compound active on the specific target with the structures of inactive molecules, to recognize substructure features typical for active molecules. The drug likeness of designed compounds was evaluated using the tool Molinspiration Cheminformatics server (http://www.molinspiration .com). In this computational chemistry technique large chemical databases are analyzed in order to identify possible new drug candidates. Only SMILES or SD file structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary.[20]

In silico Pharmacokinetic Properties Study

There is an increasing need for good predictive tools of ADMET properties to serve two key aims — first, at the design stage of new compounds and compound libraries so as to reduce the risk of late-stage attrition, and second, to optimize the screening and testing by looking at only the most promising compounds. It predicts properties that provide information about dose size and dose frequency, such as oral absorption, bioavailability, brain penetration, clearance and volume of distribution. Here in this study we are using the software called pkCSM. It is a novel method for predicting and optimizing small-molecule pharmacokinetic and toxicity properties which relies on distance-based graph signatures. They adapted the Cutoff Scanning concept to represent small-molecule structure and chemistry in order to represent and predict their pharmacokinetic and toxicity properties, building 30 predictors divided into five major classes: absorption (seven predictors), distribution (four predictors), metabolism (seven predictors), excretion (two predictors), and toxicity (10 predictors).[21] It serves as an integrated freely available platform to rapidly screen multiple pharmacokinetic properties and toxicity properties.

Molecular Docking

Molecular docking is a simulation technique that explores ligand's best binding pose with the active site of a target. This technique involves the selection of 3D-coordinate space of the binding site in the target and calculating the binding affinity of the resultant orientation of the molecule within the binding site which forms the complex.[22] The significance and sensitivity of binding affinity values are determined by the largest magnitude negative number (highest binding affinity or lowest binding energy) depicting the most favourable conformation of the complex formed when the ligand involved efficiently binds with the active pockets of the target. Docking studies were performed using Glide, 2020. Steps involved are given below.

Ligand Preparation: It is the initial step for molecular docking studies. LigPrep module, version 2.4, 2017, was used for geometrical refining of chemical structures (drawn in Maestro module) of selected macromolecules. LigPrep is intended to set up premium 3D structures with accurate chiralities. Original states of ionization were retained; tautomers and conformations were generated by the Monte Carlo method as implemented in MacroModel version 9.8, using OPLS-2005 force field. The conformers with an energy difference of 30 kcal/ mol as compared to the global energy minimum conformer were retained.[23]

Protein Preparation: Protein preparation wizard of Maestro software was used for protein preparation. The protein structures, namely, 5TZ1 and 5FRB[24] were taken from Protein Data Bank. The selected chains were edited for missing hydrogens and for assigning proper bond orders. The H-bonds were optimized using sample orientations. All the polar hydrogens were displayed. Finally, the protein structure was minimized to the default Root Mean Square Deviation (RMSD) value of 0.30. 3.3.

Receptor Grid Generation: From the defined receptor, the cocrystallized ligand was separated from the active site of receptor chain. The atoms were of size equal to Van der Waals radii of 1.0> while the partial atomic charge was less than 0.25 defaults. The active site represents an enclosing box at the centroid of the workspace ligand. Following this protocol, a grid centered on the ligand was generated using the default Glide settings. All ligands were docked into this grid structure.

Molecular Docking Analysis: On a defined receptor grid, flexible docking was performed using the extra precision (XP) feature of Glide module. The constraints to defined ligand-receptor interactions were not set. The structure output format was set to pose viewer file so as to view the output of the resulting docking studies from pose viewer.

Selection of the Best-Scored Pose. The best docking poses were selected primarily by considering the docking scores but values of different energies, number of Hbonds, and visual inspection of all docking poses in

Maestro (Schrodinger) were also taken into account. Interaction energy between protein and ligand can be related to binding affinities. Different criteria were laid down to select best docked structure for each ligand. Then, rankings were derived by directly using the *Glide GScore*.

The structures of proteins used in this work were downloaded from the Protein Data Bank. The detailed information of the selected proteins, their PDB IDs, inbuilt inhibitor, X-ray resolution, etc., was given in Table 1.

RESULT AND DISCUSSION

Various derivatives of pyrazole incorporated heterocyclic nucleus were designed through *in-silico* studies. Structure of proposed analogs is given in figure 1 and derivatives are given in Table 2. A novel group of 3-(1, 3-diphenyl-1H-pyrazol-4-yl)-1-(furan-2-yl)prop-2-en-1-one and 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one derivatives were undergone drug likeness, pharmacokinetic prediction and molecular docking studies.

In silico Drug Likeness Study Using Molinspiration Molecule Viewer

Lipinski's rule of five is used in drug design and development to predict oral bioavailability of potential lead or drug molecules. According to Lipinski's ''rule of five'', a candidate molecule will likely to be orally active, if: i) the molecular weight is under 500, ii) the calculated octanol /water partition coefficient (Log P)<5, iii) there were fewer than 5 hydrogen bond donors(OH and NH groups) and, iv) there are less than ten hydrogen bond acceptors (notably N and O). The best possible drug candidates were reported after comprehensive analysis on predicted miLogP, solubility, molecular weight, topological molecular polar surface area (TPSA) and drug- likeness. The molecular properties of designed compounds were calculated by using Molinspiration cheminformatics software and are presented in Table 3. Most of the compounds did not violate any of the Lipinski's rule of five, however one violation was observed for seven compounds (2, 3, 4, 5, 7, 14 and 15).

Molecular hydrophobicity or lipophilicity is indicated by Log P or partition coefficient. Log P values of all the compounds except 2, 3, 4, 5, 7, 14 and 15 were found to be more than 5 and are in clear violation of Lipinski's rule of five, suggesting poor permeability across cell membrane. Molecular weight of fifty five compounds was found to be less than 500 and thus these molecules are anticipated to be easily transported, diffused and absorbed as compared to large molecules. Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in designed compounds were in accordance with the Lipinski's rule of five i.e. less than 10 and 5 respectively.

In silico Pharmacokinetic Properties Study

Absorption, distribution, metabolism, excretion and toxicity known as 'ADMET' are important properties to be considered in the discovery. Pharmacokinetic properties study was done using online-based software pkCSM.

Water solubility of a compound (logS) reflects the solubility of the molecule in water at 25°C. This model is built using experimental water solubility measurements of 1708 molecules. Predicted water solubility of a compound is given as the logarithm of the molar concentration (log mol/L). Caco-2 monolayer of cells is widely used as an *in vitro* model of the human intestinal mucosa to predict the absorption of orally administered drugs. This model is based on 674 drug like molecules with Caco-2 permeability values and predicts the logarithm of the apparent permeability coefficient (log Papp; log cm/s). A compound is considered to have a high Caco-2 permeability if it has a Papp > 8 x 10^{-6} cm/s. The Intestine is normally the primary site for absorption of a drug from an orally administered solution. This method is built to predict the proportion of compounds that were absorbed through the human small intestine. For a given compound it predicts the percentage that will be absorbed through the human intestine. A molecule with an absorbance of less than 30% is considered to be poorly absorbed. All the compounds designed shows good water solubility, Caco-2 permiability and intestinal absorbtion, hence they may exhibit good absorption. The steady state volume of distribution (VDss) is the theoretical volume that the total dose of a drug would ne plasma. The higher the VD is, the more of a drug is distributed in tissue rather than plasma. VDss is considered low if below 0.71 L/kg (log VDss < -0.15) and high if above 2.81 L/kg (log VDss > 0.45). Most drugs in plasma will exist in equilibrium between either an unbound state or bound to serum proteins. For a given compound the predicted fraction that would be unbound in plasma will be calculated. Drug clearance is measured by the proportionality constant CLtot, and occurs primarily as a combination of the clearance (excretion via the kidneys). The predicted total clearance log(CLtot) of a given compound is given in log(ml/min/kg). The maximum recommended tolerated dose (MRTD) provides an estimate of the toxic dose threshold of chemicals in humans. For a given compound, a MRTD of less than or equal to 0.477 log(mg/kg/day) is considered low, and high if greater than 0.477 log(mg/kg/day). The Ames test is a widely employed method to assess a compounds mutageneic potential using bacteria. It predicts whether a given compound is likely to be Ames positive and hence mutagenic. The designed compounds were found to have good pharmacokinetics absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. ADMET properties calculated using pkCSM software were given in Table 4.

Molecular Docking

The structure-based drug design promotes in silico method for molecular docking before going to lab screening. In silico methods can site the binding pores and predict the mechanism of protein-ligand interactions as well as target binding. Moreover, the analysis and interpretation of the binding behavior play a crucial role in rational drug designs.

The results of the molecular docking studies (Table 5) revealed that ligands 18 and 19have the highest docking scores on 5TZ1 receptor and the compounds 19, 8 and 18 have highest docking score on 5FRB receptor. In *Candida albicans* all the designed compounds exhibit more dock score than the standard fluconazole. In *Aspergillus fumigates* most of the compounds exhibit high dock score than standard fluconazole. 2D and 3D interaction of the compounds having high docking score with the receptors are given in figure 2, 3, 4, 5 and 6.

Table 1: Receptors under study.

S. No	Protein	Organism	PDB-ID	Inbuilt inhibitor	X-ray resolution	Ligands	Activity
1	14-alpha demethylase	*Candida albicans*	5TZ1	VT1	2.00 Å	HEM, VT1	Antifungal
2	14-alpha demethylase	*Aspergillus fumigators*	5FRB	VT2	2.99 Å	HEM, VT2	Antifungal

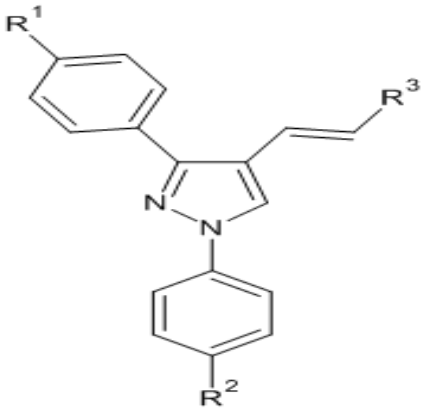

Fig 1: Chemical structure of designed compound.

Table 2: List of proposed analogs.

Compound	R_1	R_2	R_3
1	H	H	Thiophene
2	F	H	Thiophene
3	Cl	H	Thiophene
4	Br	H	Thiophene
5	I	H	Thiophene
6	OCH_3	H	Thiophene
7	CH_3	H	Thiophene
8	OH	H	Thiophene
9	NH_2	H	Thiophene
10	NO_2	H	Thiophene
11	H	H	Furan
12	F	H	Furan
13	Cl	H	Furan
14	Br	H	Furan
15	I	H	Furan
16	OCH_3	H	Furan
17	CH_3	H	Furan
18	OH	H	Furan
19	NH_2	H	Furan
20	NO_2	H	Furan

Table 3: Predicted drug-likeness score of designed compounds.

S. No	milogP	MW	nON	nOHNH	nrotb	nviolations
1	4.86	356.45	3	0	5	0
2	5.02	374.44	3	0	5	1
3	5.53	390.89	3	0	5	1
4	5.66	435.35	3	0	5	1
5	5.94	482.35	3	0	5	1
6	4.91	386.43	4	0	6	0
7	5.3	370.48	3	0	5	1
8	4.38	372.45	4	1	5	0
9	3.93	371.46	4	2	5	0
10	4.81	401.45	6	0	6	0
11	4.21	340.38	4	0	5	0
12	4.38	358.37	4	0	5	0
13	4.89	374.84	4	0	5	0
14	5.02	419.28	4	0	5	1
15	5.3	466.28	4	0	5	1
16	4.27	370.41	5	0	6	0
17	4.66	354.41	4	0	5	0
18	3.73	356.38	5	1	5	0
19	3.29	355.4	5	2	5	0
20	4.17	385.38	7	0	6	0

Logarithm of partition coefficient betweenn-octanol and water (miLogP)
Number of hydrogen bond acceptors (n-ON)
Number of hydrogen bond donors (n-OHNH)
Number of rotatable bonds (nrotb)
Number of violation (n violation)

Table 4: Predicted ADMET properties of designed compounds.

S. No	Water solubility (log mol/ lit)	$Caco_2$ permeability (log Papp)	Intestinal absorption (% absorbed)	VDss (human) (loglit/ kg)	Fraction unbound (Fu)	Total clearence (log ml/ min/kg)	Max. tolerated dose (human)	Mutagen icity
1	-6.57	1.057	93.787	-0.178	0.226	0.262	0.713	No
2	-5.533	1.096	93.805	-0.259	0.267	0.002	0.739	No
3	-6.662	1.049	92.71	-0.084	0.229	0.132	0.675	No
4	-6.687	1.046	92.643	-0.069	0.229	0.111	0.675	No
5	-5.561	1.056	93.452	-0.266	0.222	0.228	0.689	No
6	-5.579	1.059	95.218	-0.194	0.249	0.183	0.692	No
7	-6.623	1.051	94.168	-0.092	0.233	0.206	0.677	No
8	-4.753	1.051	91.984	-0.509	0.201	0.034	0.651	No
9	-5.477	1.006	92.019	-0.427	0.169	0.032	0.609	No
10	-6.452	1.007	91.942	-0.572	0.223	0.17	0.568	No
11	-5.661	1.083	96.452	0.315	0.246	0.484	0.633	No
12	-4.952	1.121	96.471	0.35	0.285	0.674	0.614	No
13	-5.788	1.074	95.375	0.427	0.253	0.139	0.541	No
14	-5.831	1.071	95.308	0.446	0.251	0.118	0.544	No
15	-5.17	1.058	96.541	0.456	0.231	0.121	0.508	No
16	-4.942	1.084	97.883	0.442	0.264	0.517	0.582	No
17	-5.7	1.076	96.834	0.42	0.259	0.487	0.537	No
18	-4.12	1.013	94.649	0.173	0.217	0.475	0.647	No
19	-4.62	1.058	94.684	0.143	0.2	0.484	0.602	No
20	-6.05	1.044	94.603	-0.064	0.21	0.507	0.519	No

Table 5: Docking score of designed compounds.

COMPOUND	DOCK SCORE kcal/mol	
	5TZ1	5FRB
1	-9.2	-6.4
2	-9.4	-5.7
3	-9.2	-5.5
4	-7.2	-5.5
5	-9.3	-5.5
6	-8.6	-5.2
7	-9.0	-5.3
8	-9.9	-8.3
9	-9.1	-8.9
10	-9.0	-5.0
11	-9.2	-6.7
12	-9.4	-5.8
13	-9.5	-5.7
14	-9.3	-7.7
15	-9.4	-7.7
16	-8.7	-5.6
17	-9.5	-5.3
18	-10.4	-8.8
19	-10.3	-9.3
20	-9.4	-5.0
Fluconazole	-7.0	-4.9

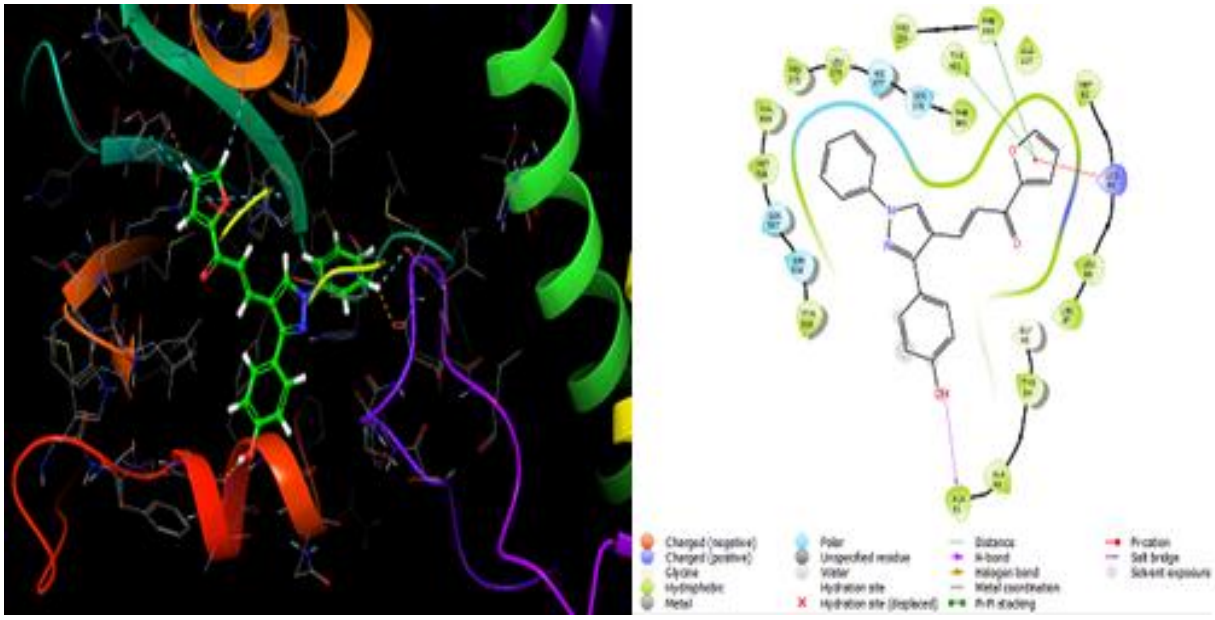

Fig 2: 3D and 2D interaction diagrams of compound 18 on 5TZ1.

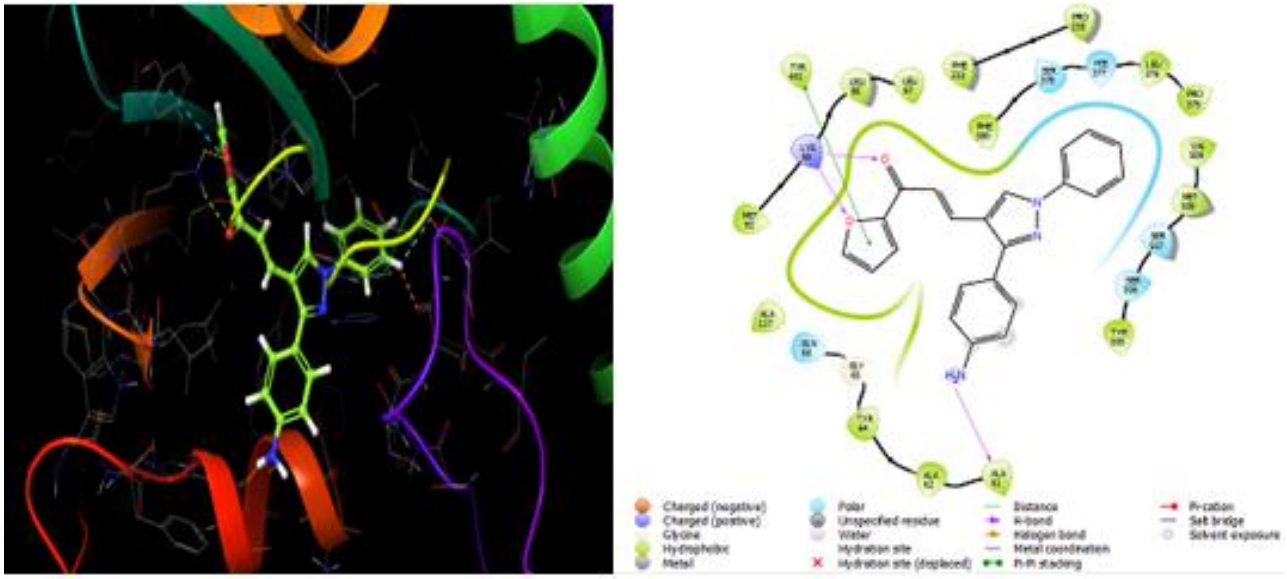

Fig 3: 3D and 2D interaction diagrams of compound 19 on 5TZ1.

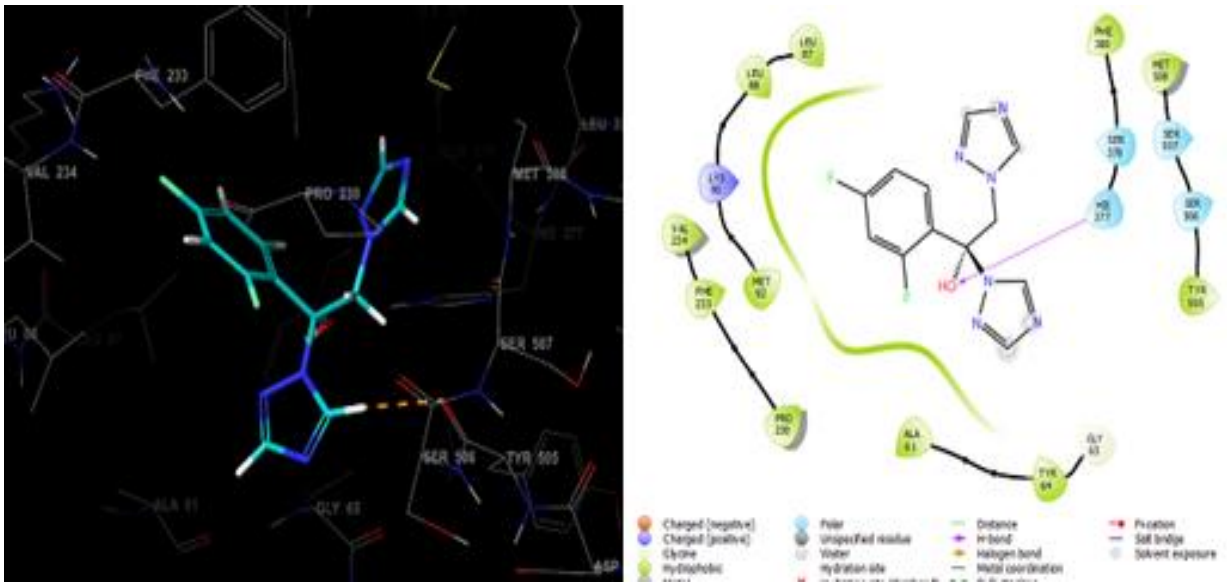

Fig 4: 3D and 2D interaction diagram of standard fluconazole with 5TZ.

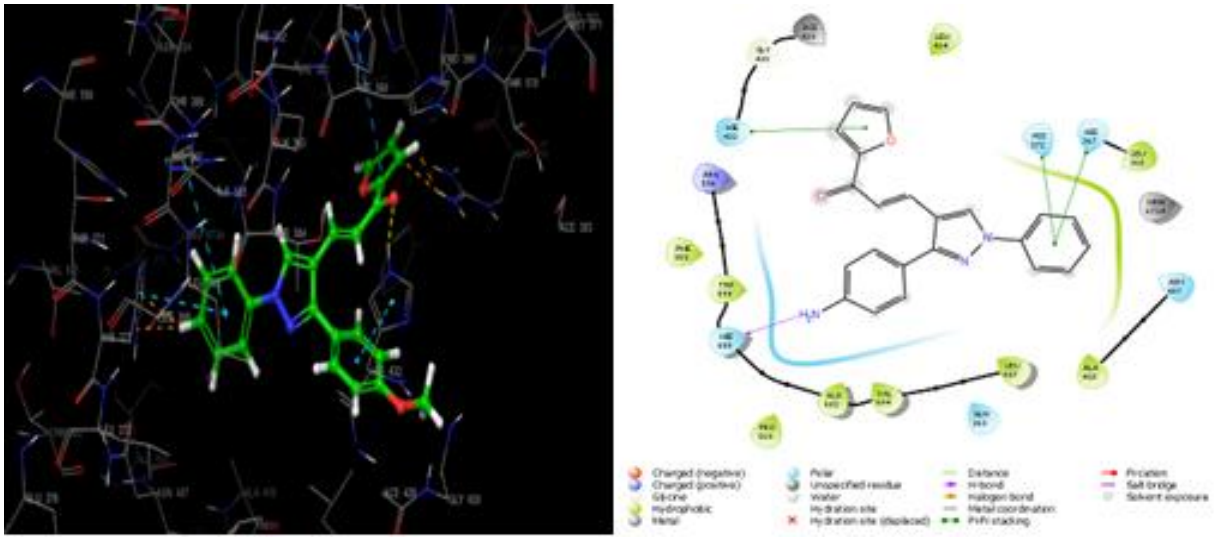

Fig 5: 3D and 2D interaction diagrams of compound 19 on 5FRB.

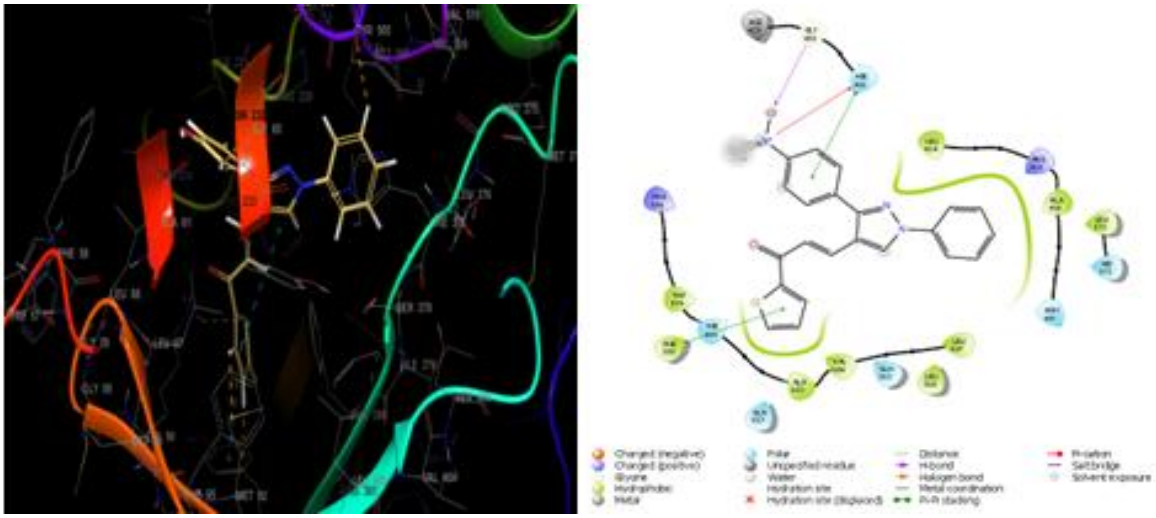

Fig 6: 3D and 2D interaction diagrams of compound 9 on 5FRB.

CONCLUSION

This study identified designed compounds as the best hits against 14-alpha demethylase enzyme with enhanced pharmacological properties and recommends their synthesis, in vivo and ex vivo evaluation to validate our hypothesis. The designed compounds were found to have good pharmacokinetics absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Docking studies were carried out on the proposed analogue to determine the affinity with the enzyme 14- α demethylase enzyme by using Glide 5.5 extra precision (XP) maestro Schrodinger software. The analogue 8, 18 and 19 were found to have higher docking score and significant binding interaction. From the present study it can be concluded that the proposed pyrazole derivatives were found to possess good 14- α demethylase inhibition.

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