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ADMET, Pharmacokinetic and Docking properties of the fungal drug 2-(2, 4-difluorophenyl)-1, 3-bis (1, 2, 4-triazol-1-yl) propan-2-ol by using Quantum computational methods

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The current study contributes to a better knowledge of the FCZ's characteristics and bioactivity. The ADMET properties have been calculated and the results have been illustrated; as a result, it has become quite popular for virtual pharmaceutical analysis. This research aims to examine FCZ's optimized structure and properties by analyzing various computational calculations. Bond length, Bond angle, Mulliken charges have been analyzed for the studies. The experimental geometrical parameters and theoretical data were compared with ADME parameters, biomarker properties, pH value, drug like nature, Marvin sketch, Swiss ADME to quantify molecular descriptors just as to survey atomic elements. ADMET properties introduce the influence of the drug levels and its kinetics with the tissues of the body. It also explains about the metabolism, toxicity of the drugs when introduced to the system. The analysis on pharmacokinetic properties has helped a lot in the drug development for further studies. The target prediction of FCZ has been studied along with the docking study. Docking study is an important program in order to study about the binding of the small ligand into a receptor like proteins. This method is very useful in drug discovery which provides insights into various studies. This will help in further development of the drugs which will finally help the society in large scale. FCZ helps pharmaceutical industry in developing the drugs to treat chronic disease when combined with other molecules. Hence the present study is really helpful in drug designing and in the development of new drugs.

Keywords: Bond angle, Bond length, FCZ, Health care drug development, Physico-chemical properties

FCZ is a 306.27 g/mol antifungal medication used to diagnose a variety of fungal illnesses[1]. 2- (2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl) propan-2-ol is the IUPAC name and $C_{13}H_{12}N_6F_2O$ is its molecular formula. It is a member of the azole group (biz triazole), which inhibits the growth of certain forms of fungus. Like other triazoles, it features a 5-membered ring structure with three nitrogen atoms. As previously stated, FCZ is a kind of triazole in which propan-2-ol is replaced at positions 1 and 3 with 1H-1,2,4-triazole-1-yl groups, and at position 2 with a 2,4-difluorophenyl group. Literature survey shows that many concepts have been studied on FCZ[2-7]. Also, different work on various compounds[8-11] made us interesting to work on FCZ. Galgiani *et al* found that usage of FCZ has been increased to treat bone and joint infection, meningitis, pneumonia patients and pneumonia as a primary infection in HIV positive or severely debilitated patients[12]. Sert *et al*[13]has studied the applications of triazole based molecule and has found that these derivatives have a lot of medicinal applications. Merve *et al.*[14] studied the triazole based azo molecules and they proved it as very good antibacterial agents with the help of docking, pharmacokinetic properties *etc*. Docking study places an important role in the study of molecules as drugs and their uses in the daily life to cure many diseases.

The current research focuses on a variety of phrases and concepts. We have placed a strong emphasis on both experimental and computational studies. Swiss ADME is used for the pharmacokinetic properties. As a result, these calculations piqued our curiosity in experimenting with other parameters. Hence, FCZ makes a signature compound in the biological as well as the pharmacy field.

Computational Details

We have analyzed the whole quantum chemical calculations of FCZ by Gaussian09 software. We have also obtained the optimized structure of FCZ (Fig. 1). To visualize the program and the results, Gauss

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viewsoftware is used. The calculations like Mulliken charges have been understood with the help of B3LYP/6-311++G (d, p) basis set. Swiss ADME and Marvin sketch are used to understand the pharmacokinetic properties and drug likeness of the molecule[15,16].

Materials and Methods

Protein preparation

RCSB PDB was used to obtain the protein of 17-β-hydroxysteroid dehydrogenase which included 1I5R (–7.05) and 3BH4 (–7.32). The proteins were downloaded in PDB format from the protein data bank. The proteins underwent energy minimization and removal of ions, ligands, and water molecules in MOE 2018. Further using AutoDock 4.2, polar hydrogens, Kollman, and gasteiger charges were added for the preparation of the target in PDBQT format.

Ligand preparation

The ligand in 3D form was obtained from PubChem for the study against Breast cancer. It was retrieved in SDF format and converted to PDB format using Open Babel software. Further using Auto Dock 4.2, torsions are set for the ligand and saved in PDBQT format for docking studies.

Results and Discussion

Mulliken atomic charge analysis

Mulliken atomic charges play a vital role in the molecular system as many properties are explained by the effect of atomic charges. For example, dipole moment, polarizability, electronic structure *etc*. Mulliken's method assigns each contributing orbital half of the overlap population, resulting in the number of inhabitants of each atomic orbital. The mulliken charges of FCZ are as shown in the (Table 1) and the distribution chart is represented in (Fig. 2). The table below shows that all hydrogen atoms have positive charge which implies they are donors. The more negative charge and positive charge on the carbon

Table 1 — Calculated Mulliken charges of FCZ

Sl. No	Atoms	Mulliken Charges B3LYP/6-311++	Sl. No	Atoms	Mulliken Charges B3LYP/6-311++
1	F	–0.13943	18	C	–0.01106
2	F	–0.15966	19	C	–0.06329
3	O	–0.19928	20	C	–0.57563
4	N	0.088776	21	C	–0.12958
5	N	0.103041	22	C	–0.09446
6	N	–0.09444	23	H	0.245483
7	N	–0.15037	24	H	0.218909
8	N	–0.13619	25	H	0.222568
9	N	–0.12774	26	H	0.241761
10	C	0.638514	27	H	0.324631
11	C	–0.54678	28	H	0.213329
12	C	–0.58154	29	H	0.242735
13	C	0.712345	30	H	0.219545
14	C	–0.58753	31	H	0.176678
15	C	–0.34664	32	H	0.166581
16	C	0.142375	33	H	0.166235
17	C	–0.35687	34	H	0.176972

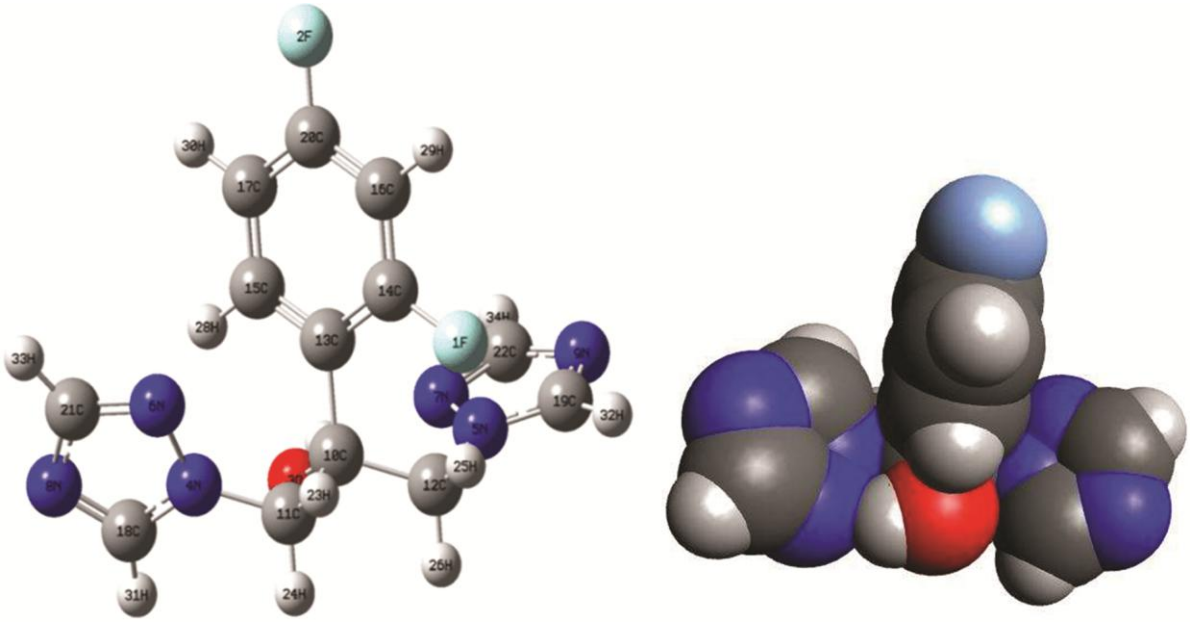


Fig.1 — Optimized geometric structure and Vander Waals structure of FCZ

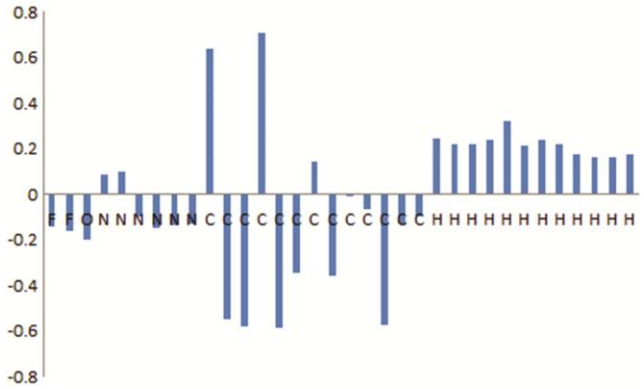


Fig. 2 — Mulliken charge distribution of FCZ

atoms (–0.58753 e and +0.638514 e) suggests large delocalization in the molecule. Also, it is clear from the table that fluorine atom is highly electronegative. Some carbon atoms and nitrogen atoms which are affected by their surroundings show different Mulliken's nature.

Structural Evaluation

The revised molecular structure of FCZ was calculated using the B3LYP/ 6-311++G (d, p) basis set (Fig. 3). In Table 2, the bond length and bond angle properties are listed. Changes in the bond angles of C-C=0 bonds owing to intramolecular hydrogen bonding can be seen in the table. The shortening of N-N bond lengths in the semicarbazone section demonstrates conjugation. Table 6 shows the rest of the numbers. Carbon atoms connected to fluorine have a bond angle greater than 120° (C16-C20-C17=122.17°, C13-C14-C16=123.96°). This is due to the fluorine atom's electron-donor character. The C-C bonds at the substitution group's ends are somewhat longer than the other C-C bonds. This is due to the fluorine atom's electron-donor character. The C-C bonds at the substitution group's ends are somewhat longer than the other C-C bonds. The length of the O3-H27 bond is extremely short. This could be because oxygen has a higher electronegative charge than hydrogen. In addition, when compared to F1-C14 bond length, F1-H25 bond length is extremely long. This could be due to the electron distribution within the molecule. The N-C bonds are almost all in the same range. Similarly, the table displays the various ranges for C-H and C-C bonds.

ADMET Descriptors

The ADMET indicator instrument[17] was used to compute the physico-compound and ADMET property counts. The ADMET Predictor offers a

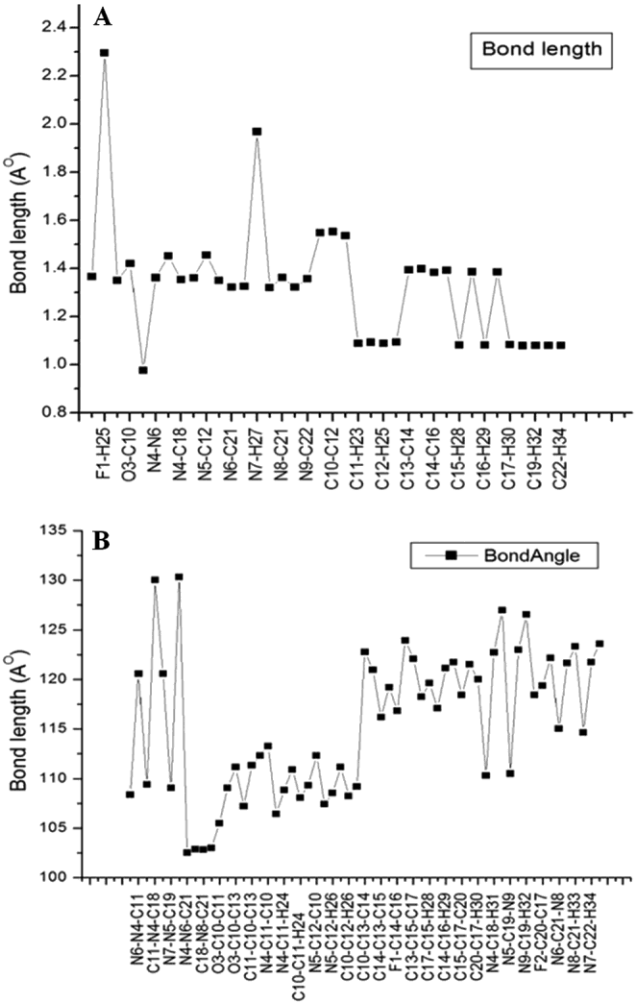


Fig. 3 — (A) The bond length graph; and (B) The graph for bond angles by B3LYP method on FCZ

simple user interface that makes it easy to track and calculate data for a variety of chemicals. The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) findings are valuable descriptors, especially for biological boundary-crossing such as brain access and absorption[18] as shown in (Table 3). This has proven to be a valuable descriptor in models to determine specific ADMET features, particularly those related to biological barrier crossing such as brain access and absorption. In terms of pharmacokinetics, the current compound has been shown to have a high GI absorption. Hence, FCZ can be very well used in pharmaceutical industries.

ABS: Absorption, WS: Water Solubility, PERM: permeability, Int.ABS: Intestinal Absorption, Skin Perm.: Skin Permability, P-gp subs.: P-glycoprotein substrate, P-gp I inhib.: P-glycoprotein I Inhibitor, P-gp II inhib.: P-glycoprotein II Inhibitor, VDss

Table 2 — Optimized geometric parameters of FCZ

Bond Length		B3LYP/6-311++ (A°)		Bond Length	B3LYP/6-311++ (A°)
F1-C14		1.3653		C10-C12	1.5526
F1-H25		2.2946		C10-C13	1.5359
F2-C20		1.3505		C11-H23	1.0885
O3-C10		1.42		C11-H24	1.0923
O3-H27		0.9754		C12-H25	1.0881
N4-N6		1.3611		C12-H26	1.0928
N4-C11		1.4513		C13-C14	1.3942
N4-C18		1.3531		C13-C15	1.3981
N5-N7		1.3605		C14-C16	1.3834
N5-C12		1.4558		C15-C17	1.3922
N5-C19		1.3494		C15-H28	1.0813
N6-C21		1.3214		C16-C20	1.3857
N7-C22		1.3248		C16-H29	1.0815
N7-H27		1.969		C17-C20	1.3844
N8-C18		1.3199		C17-H30	1.0822
N8-C21		1.3617		C18-H31	1.0781
N9-C19		1.3214		C19-H32	1.0793
N9-C22		1.3565		C22-H33	1.0792
C10-C11		1.549		C22-H34	1.0791
Bond Angle	B3LYP/6-311++ (°)	Bond Angle	B3LYP/6-311++(°)	Bond Angle	B3LYP/6-311++ (°)
C10-O3-H27	108.3717	C14-C16-H29	121.1423	C10-C11-H23	110.9073
N6-N4-C11	120.5942	C20-C16-H29	121.7413	C10-C11-H24	108.0545
N6-N4-C18	109.3799	C15-C17-C20	118.4538	H23-C11-H24	109.3179
C11-N4-C18	130.0171	C15-C17-H30	121.5206	N5-C12-C10	112.3143
N7-N5-C12	120.6028	C20-C17-H30	120.0243	N5-C12-H25	107.3935
N7-N5-C19	109.0634	N4-C18-N8	110.3076	N5-C12-H26	108.5115
C12-N5-C19	130.331	N4-C18-H31	122.7366	C10-C12-H25	111.1488
N4-N6-C21	102.4929	N8-C18-H31	126.951	C10-C12-H26	108.2435
N5-N7-C22	102.8278	N5-C19-N9	110.4918	H25-C12-H26	109.1631
C18-N8-C21	102.8021	N5-C19-H32	122.9915	C10-C13-C14	122.7991
C19-N9-C22	102.9723	N9-C19-H32	126.5164	C10-C13-C15	120.9782
O3-C10-C11	105.4777	F2-C20-C16	118.4289	C14-C13-C15	116.1881
O3-C10-C12	109.067	F2-C20-C17	119.3947	F1-C14-C13	119.2104
O3-C10-C13	111.1397	C16-C20-C17	122.1762	F1-C14-C16	116.8232
C11-C10-C12	107.1969	N6-C21-N8	115.0172	C13-C14-C16	123.9664
C11-C10-C13	111.321	N6-C21-H33	121.649	C13-C15-C17	122.0992
C12-C10-C13	112.3305	N8-C21-H33	123.3327	C13-C15-H28	118.2637
N4-C11-C10	113.2587	N7-C22-N9	114.6432	C17-C15-H28	119.6308
N4-C11-H23	106.4091	N7-C22-H34	121.7752	C14-C16-C20	117.1144
N4-C11-H24	108.8301	N9-C22-H34	123.5814	C10-C11-H23	110.9073

(hum.): VDss human, FUb: Fraction Unbound, BBB perm.: BBB permeability, CNS perm.: CNS permeability, subs.: substrate, inhib.: inhibitor, TL CL: Total Clearance, RL subs.: Renal Substrate, TXCTY: Toxicity, MTD(hum.): Maximum Tolerated Dose (human), inhib.: Inhibitor, HPTXT: Hepatotoxicity, ORA: Oral Rat Acute, ORC: Oral Rat Chronic

Biological Activity, Physicochemical Parameters and Molecular Docking

To compute physicochemical descriptors, Swiss ADME was used. It is a model to calculate and express ADME (absorption, distribution, metabolism and excretion) parameters, a study of an organism affecting a drug (pharmacokinetic properties), drug nature and therapeutic chemical reliability of FCZ, which were analyzed in (Table 4). The remarkable biological activity of this compound may be arising from phenyl and triazole, which play a very remarkable role in the antimicrobial activity. Bioavailability Radar is displayed for a quick evaluation of the molecule's drug-likeness. Six physico-chemical properties are studied under FCZ. Adapted descriptors have established a physico-chemical range on each axis. The pink site outlines the best possible area for each location. Figure 4 shows the optimized structure, Molecular lipophilicityability, and Bioactivity radar on each

Table 3 — ADMET of extracted compounds

ABS	FCZ	Metabolism	FCZ
WS (log mol/L)	–3.293	CYP2D6 subs.	No
$CaCo_2$ PERM (log Papp in 10-6 cm/s)	0.905	CYP3A4 subs.	No
Int.ABS(human) (% Absorbed)	94.964	CYP1A2 inhib.	Yes
Skin Perm. (log Kp)	–2.8	CYP2C19 inhib.	No
P-gp subs.	No	CYP2C9 inhib.	No
P-gp I inhib.	No	CYP2D6 inhib.	No
P-gp II inhib.	No	CYP3A4 inhib.	No
TXCTY	FCZ	Excretion	FCZ
AMES TXCTY	No	TL CL(log ml/min/kg)	0.29
MTD (hum.) (log mg/kg/day)	0.114	RL OCT2 subs.	No
hERG I inhib.	No	Distribution	FCZ
hERG II inhib.	No	VDss (hum.)(log L/kg)	–0.441
ORA TXCTY (LD50) (mol/kg)	2.328	FUb (human)(Fu)	0.381
ORC TXCTY (LOAEL) (log mg/kg_bw/day)	1.033	BBB perm. (log BB)	–1.067
HPTXT	Yes	CNS perm.(logPs)	–3.185
Skin Sensitisation	No		
T. Pyriformis TXCTY (log ug/L)	0.312		
Minnow TXCTY (log mM)	3.872		

Table 4 — Biological activity and physicochemical parameters of FCZ

Physicochemical Properties		Water Solubility	
Form.	$C_{13}H_{12}F_2N_6O$	Log *S* (ESOL)	–2.17
MW	306.27 g/mol	Solub.	2.08e+00 mg/mL; 6.80e-03 mol/l
Num. heavy atoms	22	Class	Soluble
Num. arom. heavy atoms	16	Log *S* (Ali)	–1.63
Frac. Csp3	0.23	Solub.	7.20e+00 mg/mL; 2.35e-02 mol/l
Num. rot. bonds	5	Class	Very soluble
Num. H-bond accpt.	7	Log *S* (SILICOS-IT)	–3.54
Num. H-bond donors	1	Solub.	8.83e-02 mg/mL; 2.88e-04 mol/l
TPSA	70.71	Class	Soluble
Num. rot. bonds	81.65 Å²		
Lipophilicity		Pharmacokinetics	
Log $P_{o/w}$ (iLOGP)	0.41	GI absorption	High
Log $P_{o/w}$ (XLOGP3)	0.35	BBB permeant	No
Log $P_{o/w}$ (WLOGP)	1.47	P-gp substrate	No
Log $P_{o/w}$ (MLOGP)	1.47	Log K_p (skin permeation)	–7.92 cm/s
Log $P_{o/w}$ (SILICOS-IT)	0.71		
Consensus Log $P_{o/w}$	0.88		
Druglikeness		Medicinal Chemistry	
Lipinski	Yes; 0 violation	PAINS	0 alert
Ghose	Yes	Brenk	0 alert
Veber	Yes	Leadlikeness	Yes
Egan	Yes	Synthetic accessibility	2.91
Muegge	Yes		
Bio.av. Score	0.55		

axis, with adapted descriptors specifying a physico-chemical range of the extracted compounds.

Most of the bioactive molecules show their importance by interacting with the proteins or other macromolecules. Figure 5 gives the target prediction of the FCZ molecule. Target prediction of FCZ with different ligands and proteins explains very well about the pharmacological properties of FCZ. It gives us clear idea that the FCZ can bind highest with Kinase protein as mentioned in the target prediction graph.

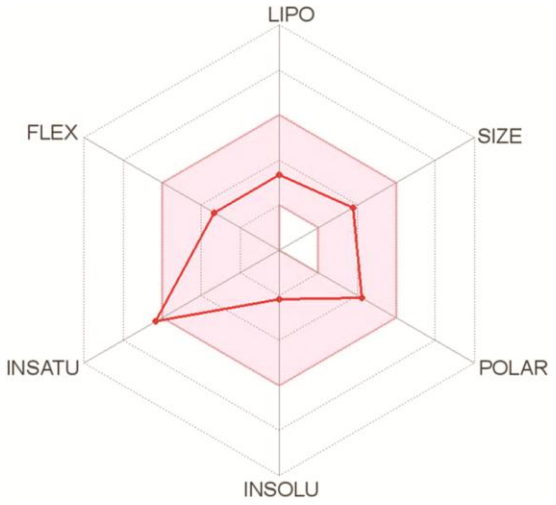


Fig. 4 — Physicochemical Bio radar representation of FCZ

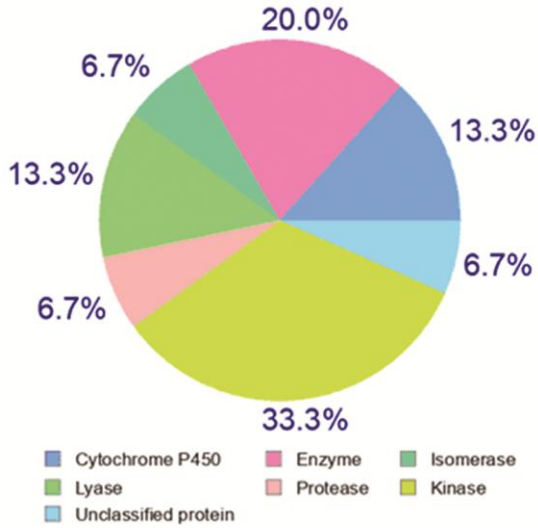
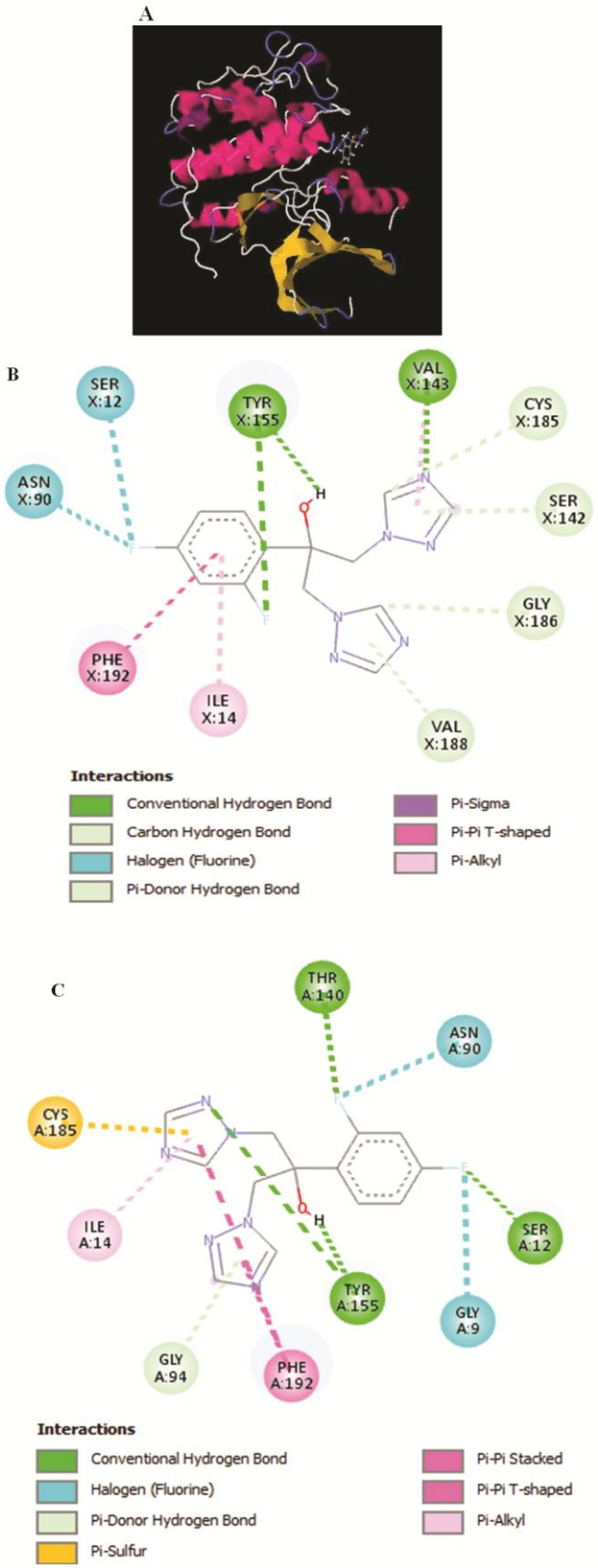


Fig. 5 — Target Prediction of FCZ

We have also studied the molecular docking of FCZ with different ligands, enzymes, proteins *etc*[19]. Docking study is the computational procedure to study how two or more ligands or protein fit together both energetically and geometrically. It is very essential to know about the biologically active molecules in giving the insights for the development of new drugs[20]. Figure 6A-C are the docking studies of FCZ with the kinase protein. It was carried out by Autodock. The regions of binding are highlighted with different colours. The ligand in 3D form was obtained from PubChem for the study against Breast cancer. It was retrieved in SDF format and converted to PDB format using Open Babel software. Further, torsions are set for the ligand and saved in PDBQT format for docking studies.



Figs 6 — (A-C) Docking study of FCZ with Kinase protein

Conclusion

Using the DFT method and the basis set B3LYP/6-311++G (d, p), the geometry of FCZ was optimized. The mulliken charges show that the changes in the charges on some atoms are due to the presence of the surrounding substituents. The structural evaluation has got a greater importance on the study of bond length and bond angles. Some distortion in the lengths and angles are studied extensively with the help of the graphs. The effective descriptors and methodologies can be used to predict important ADMET behavior in the context of pharmacokinetics optimization and evaluation of the current chemical. By the docking study, we can reveal that FCZ combines well with 1I5R and 3BH4 proteins as target. FCZ's extensive investigation especially in the pharmacokinetic properties and docking fields will benefit future medical research and the development of new materials and thus help the pharmaceutical field in drug discovery.

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Conflict of interest

All authors declare no conflict of interest.

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