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COMBINED 3D-QSAR, MOLECULAR DOCKING AND ADMET PROPERTIES TO IDENTIFY EFFECTIVE TRIAZOLE COMPOUNDS AGAINST *Candida albicans*

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Abstract

Due to a lack of effective antifungal medicines, treating *candida albicans* infection remains challenging for clinicians. Consequently, searching for new drugs, active constituents of natural or traditional medicines, and methods to beat antifungal resistance is urgently needed. In this study, a series of 21 triazole molecules that were previously synthesized and evaluated for *C. albicans* inhibitory activity was addressed by using the three-dimensional quantitative structure-activity relationship (3D-QSAR) study. The best-established CoMFA model afforded a Q^2 value of 0.601 and R^2 value of 0.985. The generated model was validated and checked for its capacity, which the R^2 test obtained was 0.967, indicating the best-predicted ability of CoMFA model. The CoMFA contour maps reveal the sites affecting *C. albicans* activity. These findings led us to design five new triazole compounds with good predicted activities. The docking findings were consistent with CoMFA contour maps, which provided the information for interactive mode exploration. The newly suggested triazole molecules, along with potential and largely used antifungal molecule, namely Fluconazole was subjected to *in silico* ADMET studies. These outcomes suggest that the new proposed triazole molecules will be of great value in treating *C. albicans* infections.

INTRODUCTION

Candida albicans is a human microbiota and is considered an opportunistic pathogen of the *candida* infections [1]. The *C. albicans* is a commensal organism found in the skin and mucosa, which may also cause candidiasis in immunocompromised people [2]. Antimycotic resistance diminishes the efficacy of anti-infection therapies, making candidiasis a serious concern in hospitals with an ever-increasing death rate and economic expenses [3-4]. The *C. albicans* has unique characteristics that allow it to colonize epithelial cells, develop biofilms, adhere and penetrate deeper layers of the host epithelium, and induce stress response [5]. The antifungal medicines in clinical use have either two or three nitrogens in the azole ring and are divided into two groups: imidazoles (miconazole and ketoconazole) and triazoles (fluconazole and metronidazole), respectively. The imidazoles, with the exception of ketoconazole, are limited to the cure of superficial mycoses, while the triazoles have a wide variety of uses in the treatment of both superficial and systemic fungal infections. Another benefit of triazoles is that they have a higher affinity for fungal cytochrome P-450 enzymes than mammalian, which adds to a better safety profile [6]. Fluconazole is the most usually adopted antifungal drug for *C. albicans* infection [7]. Unfortunately, with the frequent use of fluconazole in the first line of antifungal therapy, fluconazole-resistant *C. albicans* has emerged more frequently [8].

Quantitative structure-activity relationship (QSAR) analyses might be helpful in the search for sites on molecules that could be changed to provide better specific ligands [9]. The comparative molecular field analysis (CoMFA) is an

efficient and useful tool in rational drug design and related applications [10]. The CoMFA technique samples the steric and electrostatic fields around a set of ligands and molding a 3D-QSAR model by associating these fields (steric and electrostatic) with their experimental biological activities [10]. This approach is employed to make predictions of the biological activity value of non-synthesized molecules that are structurally associated with the training sets [11]. The molecular docking simulation is a modern technique that is widespread employed in medicinal chemistry field to guess the types and modes of interactions between a macromolecule called receptor and a small molecule called ligand [12].

The goal of this research was to develop the new anti-*C. albicans* medicines by using a set of triazole molecules as a database and using CoMFA technique, molecular docking, and ADMET properties as computational methods.

MATERIALS AND METHODS

Dataset

In this study, a series of 21 triazole molecules that were previously synthetized and assessed for *C. albicans* activity by Wu et al. [13] were studied by using 3D-QSAR (CoMFA) approach and molecular docking simulation. The concerned molecules were divided into two sets; the seventeen molecules as a training set employed to establish a CoMFA model, and the four remaining molecules were used as a test set to test the CoMFA model's competence. For the calculations, the biological activities of minimum inhibitory concentration (MIC; µM/mL) were transfigured into the corresponding planktonic minimum inhibitory concentration (pMIC) values using the following expression pMIC = $-\log_{10}$ (MIC). The chemical structure of the 21 triazole

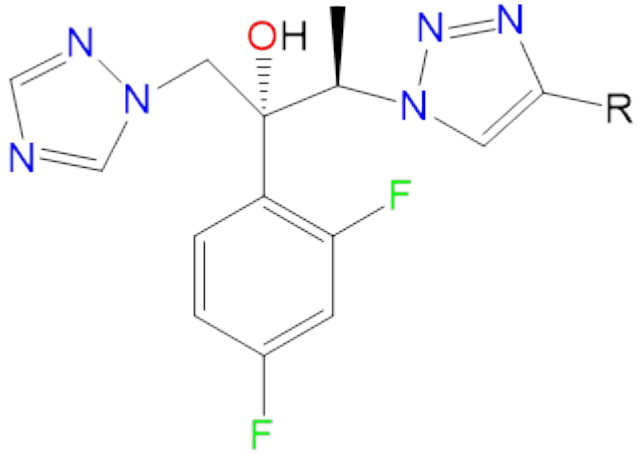

Figure 1. The general structure of the 21 triazole molecules

Table 1. The structures of the 21 triazole compounds and their activities against *C. albicans*

N°	R	MIC*	pMIC	N°	R	MIC	pMIC
1	Phenyl	0.125	6.903	12	4-Br- phenyl	0.250	6.602
2	4-CH_3-phenyl	0.125	6.903	13	3-Br- phenyl	0.500	6.301
3	4-CH_3CH_2-phenyl	0.500	6.301	14	4-NH_2- phenyl	0.500	6.301
4	4-$CH_3(CH_2)_3$phenyl	4.000	5.398	15	3-NH_2- phenyl	0.500	6.301
5	4-CH_3-O-phenyl	0.125	6.903	16	2-thienyl	0.0625	7.204
6	4-F- phenyl	0.0625	7.204	17	3-thienyl	0.0625	7.204
7	3-F- phenyl	0.250	6.602	18*	2-pyridyl	1.000	6.000
8*	2-F- phenyl	0.125	6.903	19	3-pyridyl	0.500	6.301
9	4-Cl- phenyl	0.125	6.903	20	Cyclopropyl	0.0625	7.204
10*	3-Cl- phenyl	0.0625	7.204	21*	NH_2-CH_2-	0.250	6.602
11	2-Cl- phenyl	0.0156	7.807		*Test set molecules		

*Source of MIC values were adapted from [13]

molecules and their values of pMIC (biological activities) are shown in Figure 1 and Table 1.

CoMFA Analysis

CoMFA is the most representative technique employed in 3D-QSAR analysis. It is executed in this analysis by using Sybyl X-2.0 software. The CoMFA methodology [10] was accomplished on the basis of electrostatic and steric and fields, and using Lennard Jones and Coulomb potential. A sp^3 hybridized carbon atom with a Van Der Waals radius of 1.52 Å and a net +1.0 charge were adopted for the calculations of the steric and electrostatic energies along with the default value of 30kcal/mol was set for energy cutoff calculations [14]. The partial least square approach [15] was executed to set up a linear correlation between CoMFA descriptor, and *C. albicans* activity. As a matter of fact, leave-one-out (LOO) cross-validation technique existing in PLS analysis was put into effect in order to generate the optimum number of components (N) value and the value of cross-validation correlation coefficient (Q^2). The value of N parameter was taken into consideration to determine the correlation coefficient (R^2), F-test value (F) as well as the standard error of estimate (SEE) using the non-cross validation technique. The good values of R^2, Q^2, and SEE were employed in order to develop a robust and effective CoMFA model.

Molecular Docking Analysis

Surflex-dock program was applied to execute molecular docking in order to validate the outcomes of the contour maps generated from CoMFA model [12]. The crystal structure of *C. albicans* was extracted from Protein Data Bank (PDB code: 4UYM). Before undertaking the molecular docking, the 4UYM receptor was readied by eliminating water molecules, the principal ligand founded in it and all non-protein elements. Afterwards, the polar hydrogen atomswere introduced to the 4UYM receptor. The database's more active molecule (molecule 11), the suggested triazole molecules, and fluconazole were sketched and optimized, then they were docked to the 4UYM receptor. Finally, yet importantly, the outcomes generated from surflex-dock were examined using the PyMol [16] and Discovery Studio 2016 [17] programs.

ADMET Prediction Analysis

Finding possible medicinal compounds is a major issue for many researchers but there are many drugs fail to arrive in clinical trials owing to their poor ADMET (absorption, distribution, metabolism, elimination, and toxicity) parameters [18]. For this great importance and to avoid any further problems associated to the suggested molecules, we determined the ADMET parameters of these inhibitors along with the fluconazole by using the pkCSM [19] and SwissADME [20] online servers.

RESULTS AND DISCUSSION

Molecular Alignment

The 21 triazole molecules were aligned using a distil-rigid alignment technique existing in SYBYL software and using the database's more active molecule (molecule 11). The suggested alignment is shown in Figure 2.

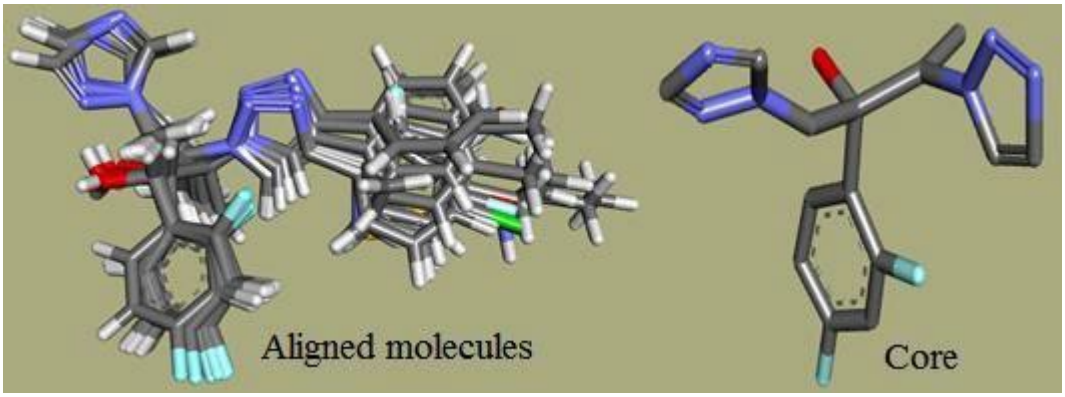

Figure 2. The 3D-QSAR structure superposition and alignment of 21 triazole molecules using molecule 11 as a template

COMFA Analysis

The CoMFA model was molded on the basis of descriptor available on SYBYL to quantitatively describe and predict the effects of steric and electrostatic fields of substituents on the antifungal activity of a set of twenty-one triazole molecules. The obtained statistical keys for the CoMFA model, as Q^2, R^2, Scv, and F values were determined by PLS analysis as described in Table 2.

As elucidated in Table 2, the Q^2 and R^2 values of CoMFA model are 0.601 and 0.985, respectively. The optimal number of principal components used to mold the CoMFA model is 4. The F value and standard error are 199.9 and 0.061, respectively. The molded CoMFA model was subjected to an external validation in order to see how accurate it might predict, the generated R^2test was 0.967. Moreover, the fractions of the steric and electrostatic fields were 82.8 %, and 17.2%, respectively. So, the steric fields will be very influenced in proposing of new *C. albicans* inhibitors. Those statistics findings pointed out the established CoMFA model's good stability and the powerful predictive capacity.

The predicted and experimental anti-*C. albicans* activity values and their residual value for both the training and test sets by using CoMFA model are revealed in Table 3. The residual value of the 21 triazole molecules is very small (less than 1), exhibiting the CoMFA model's high robustness.

Table 2. The statistical indicators of CoMFA model

Model	Q^2	R^2	Scv	F	N	R^2test	Fractions	
							Steric	Electrostatic
CoMFA	0.601	0.985	0.061	199.9	4	0.967	0.828	0.172

R^2: Non-cross-validated correlation coefficient, Q^2: Cross-validated correlation coefficient, Scv: Standard error of the estimate, N: Optimum number of components, R^2test: External validation correlation coefficient, F: F-test value

Table 3. The observed and predicted anti-*C. albicans* activities of the 21 triazole molecules

Nº	pMIC (Observed)	CoMFA		Nº	pMIC (Observed)	CoMFA	
		pMIC (Predicted)	Residuals			pMIC (Predicted)	Residuals
1	6.903	6.928	-0.025	12	6.602	6.842	-0.240
2	6.903	6.726	0.177	13	6.301	6.838	-0.537
3	6.301	6.201	0.100	14	6.301	6.809	-0.508
4	5.398	5.522	-0.124	15	6.301	6.823	-0.522
5	6.903	6.363	0.540	16	7.204	7.095	0.109
6	7.204	6.836	0.368	17	7.204	7.123	0.081
7	6.602	6.885	-0.283	18*	6.000	6.153	-0.153
8*	6.903	6.989	-0.086	19	6.301	6.969	-0.668
9	6.903	6.761	0.142	20	7.204	7.300	-0.096
10*	7.204	7.338	-0.134	21*	6.602	6.466	0.136
11	7.807	7.106	0.701	*Test set molecules			

CoMFA Contour Maps

CoMFA contour maps were built in this study to determine the effects of substituents with steric and electrostatics nature, and their results are depicted in Figure 3(a,b). The steric contour map is represented by the yellow and green colors while the electrostatic contour map is represented by blue and red colors.

The green contours around *ortho*, *meta*, and *para* positions of phenyl group and the third position of 1,2,4-triazole moiety hint that steric hindrance moieties will have a high influence on increasing the *C. albicans* activity (Figure 3a). On the other hand, the blue contours around *ortho* and *meta* positions of the two phenyl groups make clear that electro-donating moieties are useful for antifungal activity (Figure 3b). These results will lead us to determine the favorable groups to propose new triazole molecules.

New *C. albicans* Inhibitors

CoMFA contour maps findings were invested to determine the favourable and unfavourable substituents for *C. albicans* activity. Based on these results, we designed five new triazole molecules with excellent *C. albicans* activity compared to the compound 11, which is the dataset's more active molecule (Table 4). The five new triazole molecules were sketched, minimized, and aligned using SYBYL software, and their chemical structures are shown in Figure 4. Compound S1 was designed by substituting the hydrogen atom that is located in the *meta* position of the phenyl group with the nitrile group (-CN) according to the CoMFA contour plot results. Similarly, the compound S2 was designed by replacing the chlorine atom with the nitrile group, as this position should be occupied by a bulky substituent. The methoxy group ($-OCH_3$) was useful in

enhancing the activity of *C. albicans* and replaced the hydrogen atom to design compound S3. The hydrogen atom of the 1,2,4-triazole group must be occupied by a bulky group to improve steric hindrance, thus, the introduction of the methyl group at this position was beneficial for activity (Compound S4). By the same way, compound S5 was designed by substituting the hydrogen atom of the 1,2,4-triazole group with the ethyl group according to the CoMFA contour maps results.

The new suggested molecules were used for further analysis in order to confirm their viability and good pharmacokinetics properties. For that, pkCSM [19] and SwissADME [20] online servers were adopted to determine Lipinski's properties of the new triazole molecules. The generated findings are exhibited in Table 5.

Results of Table 5 hinted that the new proposed triazole molecules have MW less than 500 Da, HBD not more than 5, HBA not over than 10, and LogP less than 5. Thus, they can be easily absorbed and diffused [21]. The new compounds S1, S2, S3, S4 and S5 have a TPSA values less than 140 Å and nrotb not more than 10; demonstrating that the new scaffolds present good bioavailability [22]. Moreover, the synthetic accessibility values of the new triazole molecules were near to 1 and away from 10, thus, these molecules can be easily synthesized, from 1 (easy to synthesize) to 10 (very difficult to synthesize) [23]. Table 5 indicates that all proposed molecules follow Lipinski, Veber, and Egan rules, which turn out that these molecules have good pharmacokinetics properties.

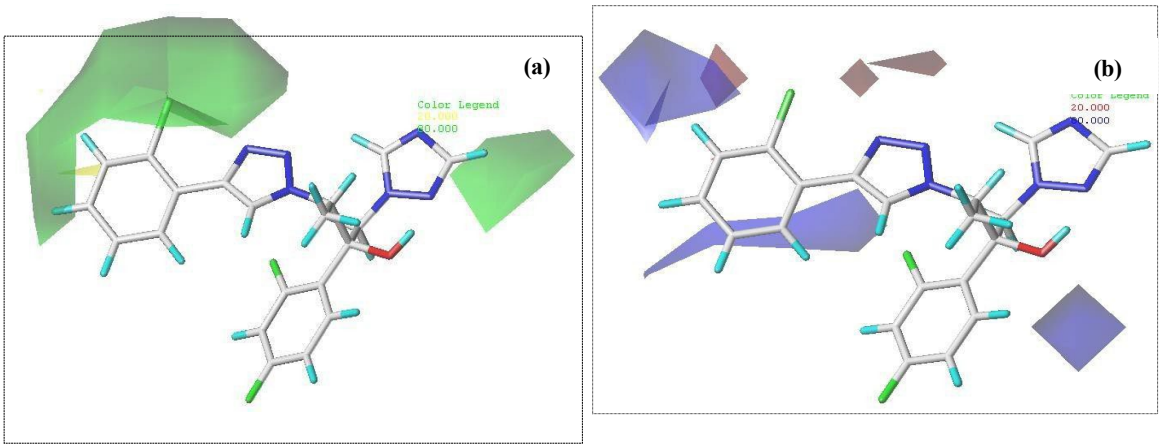

Figure 3. (a) Steric and (b) Electrostatic Contour maps of CoMFA analysis with 2 Å grid spacing using compound 11 as a template

Table 4. Predicted *C. albicans* activity value of the newly designed molecules

Compound	Predicted pMIC
	CoMFA
S1	8.304
S2	8.270
S3	8.152
S4	8.060
S5	7.901
11[a]	7.807

[a] The more active molecule in the dataset

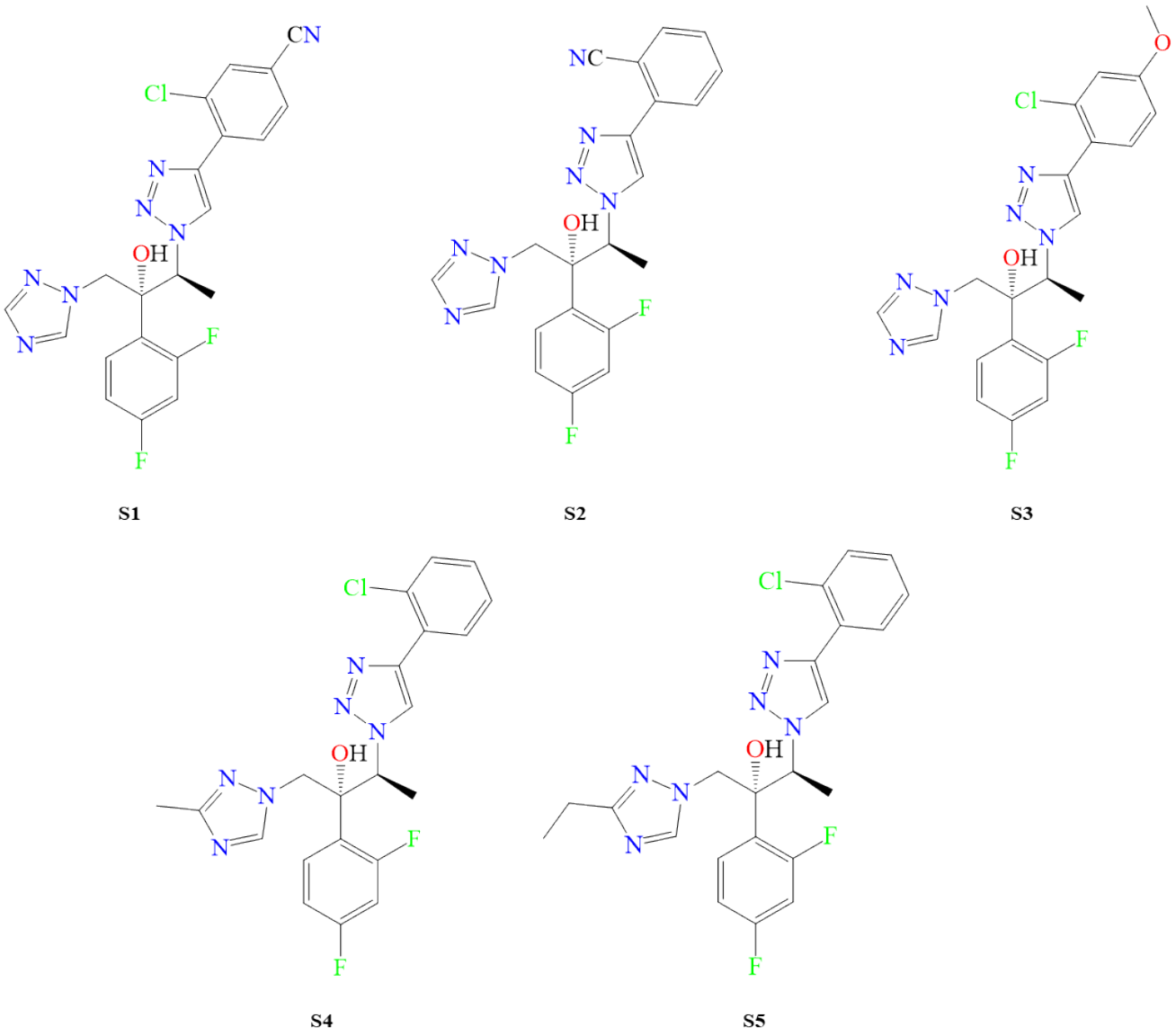

Figure 4. Structures of newly triazole molecules

Table 5. Pharmacokinetics properties of the new triazole molecules

Inhibitor	Property									
	LogP	**HBD**	**HBA**	**TPSA**	**nrotb**	**MW**	**Lipinski's violations**	**Veber violations**	**Egan violations**	**SA**
Rule	**<=5**	**<5**	**<10**	**<140**	**<10**	**<500**	**<=1**	**<=1**	**<=1**	**0<S.A<10**
S1	3.48	1	8	105.44	6	455.85	Yes	Yes	Yes	4.28
S2	2.83	1	8	105.44	6	421.41	Yes	Yes	Yes	4.23
S3	3.32	2	8	101.88	6	446.84	Yes	Yes	Yes	4.21
S4	3.92	1	7	81.65	6	444.86	Yes	Yes	Yes	4.34
S5	4.17	1	7	81.65	7	458.9	Yes	Yes	Yes	4.49
Abbreviations	LogP: logarithm of partition coefficient of compound between n-octanol and water, HBD: number of hydrogen bonds donors, HBA: number of hydrogen bonds acceptors, TPSA: Topological Polar Surface Area, nrotb: number of rotatable bonds, MW: Molecular Weight, SA: Synthetic accessibility									

Molecular Docking Analysis

The goal of molecular docking was to discover the types of interactions and the binding affinity of the triazole molecules in the target. The five proposed triazole molecules, the molecule 11, which is the dataset's more active molecule and fluconazole have been docked into the active site of the concerned receptor and evaluated for their affinity against *C. albicans* receptor (PDB code: 4UYM). Table 6 displays the energy affinity of the studied molecules, Figure 5 (a, b, c, d, e, and f) presents the docking results of compounds 11, S1, S2, S3, S4 and S5, and Figure 6 shows the docking results of fluconazole and the receptor.

Table 6. The energy affinity of the triazole compounds and reference drug

Compound	11	S1	S2	S3	S4	S5	Fluconazole
Energy affinity	2.58	2.61	1.71	3.29	3.25	3.02	0.42

Results of Table 6 reveal that the new triazole molecules, the S1, S3, S4 and S5 that present best energies of interaction compared to the compound 11 and fluconazole. Thus, these molecules could have more inhibitory potential of the studied enzyme than fluconazole.

The results of the interactions of compound 11 and the 4UYM receptor show numerous interactions such as alkyl, pi-alkyl, and hydrogen carbon with different residues (Figure 5a). The docking study of the molecules S1, S2, S3, S4, and S5 in 4UYM receptor shows more type and number of interactions in comparison with compound 11 and the most clinically used drug, which is fluconazole (Pi-pi stacked, pi-pi-T-shaped, pi-sigma, carbon hydrogen bond, Van der Waals, alkyl, pi-alkyl, and conventional hydrogen bond interaction). The presence of hydrogen bonding and Van Der Walls interactions could provide to the new *C. albicans* inhibitors a pharmacological importance compared to the fluconazole (Figure 5 and 6) because ligands' pharmacological action is heavily influenced by hydrogen bonds. As a conclusion, the new triazole molecules, particularly molecules S3, S4, and S5 present high stability in 4UYM receptor, thus, they impose themself to be promising *C. albicans* drugs.

ADMET Predictions Analysis

During the drug discovery effort, many medicines are aborted due to the blood brain permeation failure, poor efficiency, and toxicity. The goal of the preclinical ADMET is to eliminate unsuitable candidates and empower others to be candidate drugs. For this great importance, we determined the ADMET parameters of the new *C. albicans* inhibitors and the reference drug (Fluconazole) using the pkCSM [19] and SwissADME [20] online servers as shown in Table 7.

It can be seen from Table 7, the studied compounds have an intestinal absorption value better than fluconazole (the best intestinal absorption value is over than 30%), which prove these molecules are highly absorbed [24]. The blood-brain barrier (BBB) permeation is an important property for medicinal chemistry because it dictates, in which the drugs can or cannot pass the BBB and thereby exert its influence on the brain [25]. A value of logBB<-1 of a given molecule indicates that it is poorly dispersed throughout the brain. Thus, BBB permeability findings in Table 7 clearly elucidate penetrating (BBB) for all proposed molecules and fluconazole. The main enzyme system for drug metabolism in the liver is cytochrome P450s [24]. Regardless, one or more of the suggested molecules might be inhibited some of the cytochrome P450 isoforms. The CYP3A4 and CYP2D6 are the two principal subtypes of cytochrome P450. The five suggested compounds are CYP3A4 substrate and inhibitor, but they are not CYP2D6 substrate and inhibitor (**Table 7**). On the other hand, fluconazole compound is not CYP3A4 inhibitor and CYP2D6 substrate and inhibitor, but it is CYP3A4 substrate. Moreover, lower value of the clearance index points out that the higher the persistence of medications in the body [26]. Results exposed in Table 7 hint that the new compound S3 has a lower value of clearance index, indicating the high persistence of compound S3 in the body. Concerning the toxicity of the new triazole compounds, Table 7 illustrates any toxicity for all proposed molecules and fluconazole, respecting Ames test data. The findings of ADMET prediction supported the new triazole molecules to be candidate drugs for *C. albicans* infection in the future.

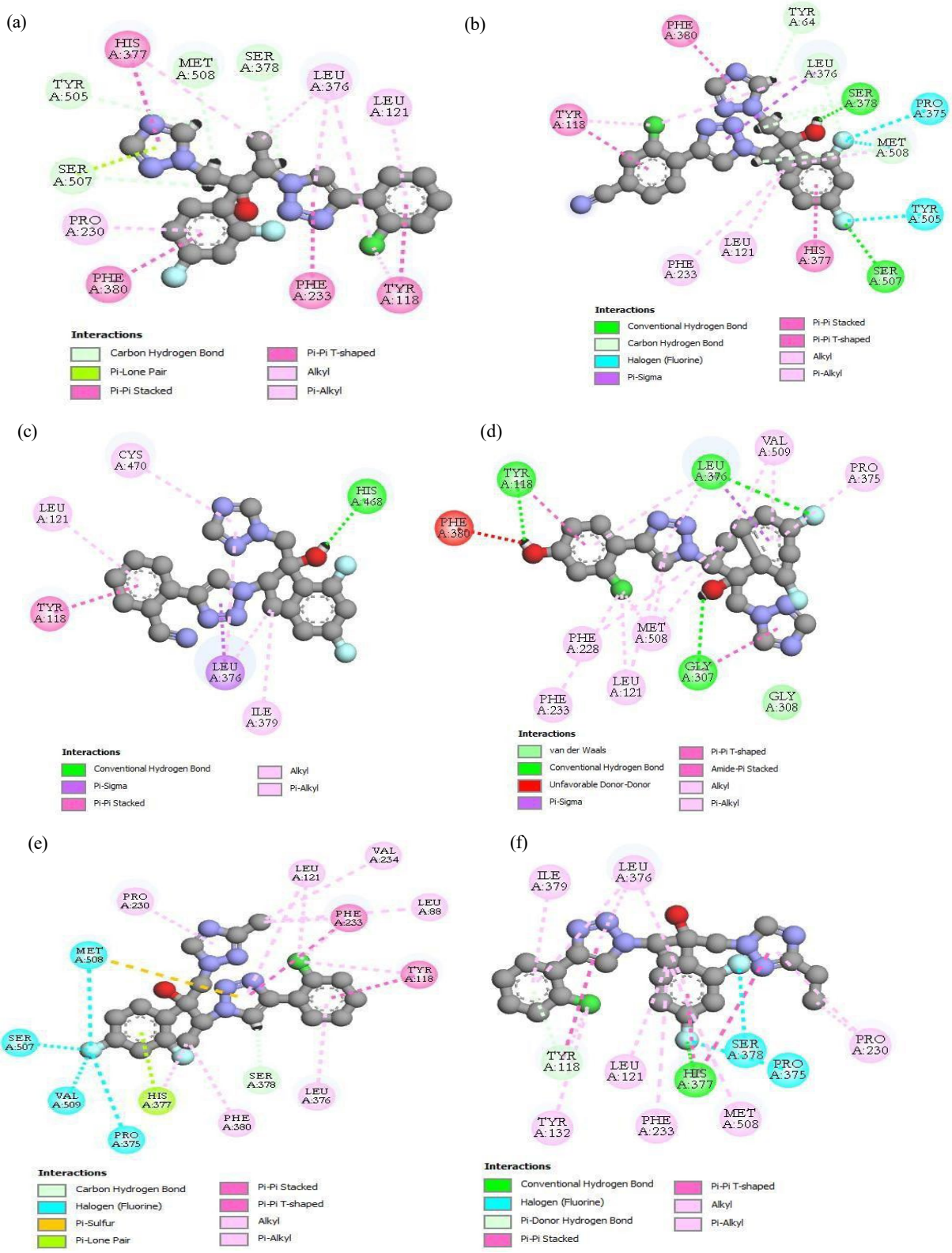

Figure 5. The docking interactions of the triazole molecules and 4UYM receptor; a) compound 11, b) compound S1, c) compound S2, d) compound S3, e) compound S4, f) compound S5

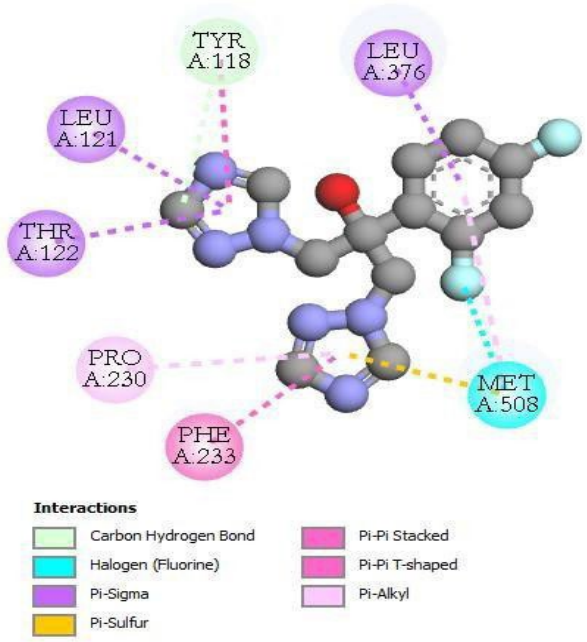

Figure 6. The docking interactions between fluconazole and 4UYM receptor

Table 7. ADMET outcomes of *C. albicans* inhibitors and fluconazole

Models	Compound					
	S1	**S2**	**S3**	**S4**	**S5**	**Fluconazole**
Absorption (A)						
Intestinal absorption(human)	99.877	98.798	83.902	95.498	95.456	78.384
Distribution (D)						
Blood-brain barrier(logBB)	-1.733	-1.55	-1.247	-1.547	-1.568	-1.313
Metabolism (M)						
CYP1A2 inhibitor	Yes	Yes	No	Yes	Yes	Yes
CYP2C9 inhibitor	No	No	No	No	Yes	No
CYP2D6 inhibitor	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	No	No	No	No
CYP3A4 inhibitor	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**
CYP2D6 substrate	No	No	No	No	No	No
CYP3A4 substrate	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Excretion (E)						
Clearance	0.365	0.445	0.294	0.345	0.426	0.343
Toxicity (T)						
AMES toxicity	**No**	**No**	**No**	**No**	**No**	**No**

CONCLUSION

The present analysis was addressed a series of 21 triazole molecules that were already synthetized and evaluated for *C. albicans* activity using 3D-QSAR (CoMFA) approach to establish a strong model that can be adopted to predict the activity of new suggested molecules. The best values of Q^2 (0.601), R^2 (0.985) and R^2test (0.967) illustrate the CoMFA model's high competence. The CoMFA steric and electrostatic contour maps directed us to explore the moieties that have a high influence on the *C. albicans* activity. As a result, five new triazoles were suggested with excellent *C. albicans* activity. Molecular docking findings that designed compounds combined with 4UYM receptor were more stable than the most active molecule with the same targeted protein. The in silico ADMET results illustrate the good pharmacokinetics properties of the newly designed molecules compared to reference drug (fluconazole). Therefore, the high stability and good ADMET parameters of the newly designed molecules confirm their ability to be candidate inhibitors in the treatment of *C. albicans* infections in the future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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