In Silico Development of Pyrimidine-Based Antifungal Compounds Using 3D-QSAR, ADMET and Molecular Docking Approaches

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Abstract

Fungal infections, ranging from superficial to life-threatening systemic diseases, pose significant health challenges, especially in immunocompromised individuals. Pathogenic fungi like *Candida* and *Aspergillus* contribute to severe infections, necessitating the development of effective antifungal agents. This research focuses on designing pyrimidine derivatives for antifungal activity using Schrodinger 2023-1 (version 13.4) software. A 3D-QSAR model was developed based on 23 pyrimidine derivatives, leading to the identification of a top pharmacophore hypothesis, ADHRR_1, through virtual screening and ADMET studies. The new chemical entities that adhered to Lipinski's rule of five were further evaluated via molecular docking against lanosterol 14 α-demethylase (PDB ID: 4UYM). Seven of these compounds demonstrated superior docking and glide scores compared to Voriconazole. These findings suggest that the newly identified compounds hold promise as potential antifungal agents.

Keywords: Antifungal, 3DQSAR, Schrodinger, Virtual screening, Molecular Docking, Pyrimidine

1. Introduction

The World Health Organisation (WHO) claims that the world may soon enter a "post-antibiotic era" due to the diminishing effectiveness of antifungal and other antimicrobial medicines. [1-3]. Antifungal resistance is a global health concern due to the overuse of antimicrobial drugs in recent decades. An estimated 1.7 million people die each year from invasive fungal diseases, making them a global issue.[4, 5]. The pathogen *Botrytis Cinerea* is highly contagious, especially in people with weakened immune systems[6]. Numerous nations have reported finding strains of Botrytis Cinerea that are extremely resistant to pyrimidine derivatives.[7-17].

Development of novel antifungal agents is therefore constantly in demand. Heterocyclic compounds are generally widely accessible and are important in the developmet of novel bioactive antifungal drugs. [18-20]. While there are many antifungal medications in the market, Voriconazole (vcz) stands out due to its pyrimidine ring and is very good at preventing the growth of fungi. Antifungal medications work by selectively inhibiting the enzyme lanosterol 14α-demethylase, which stops the synthesis of ergosterol.[21-27]. Pyrimidine is one of the most commonly employed heterocycles in antifungal derivatives. [28-30]. The Pyrrolopyrimidines, Pteridine, Pyridopyrimidines and purines are some examples of merged pyrimidines occurring in nature. Because of its wide range of biological activities, which include antiviral, antibacterial and antifungal properties, pyrimidines have attracted attention. [31-40] Application of computational approaches allows for the combination of 3D-QSAR, pharmacophore hypothesis and virtual screening to develop novel pharmaceutical compounds with the desirable properties. Additionally, to improve the development and discovery of new chemical entities (NCE's), ADMET studies and molecular docking provide favourable findings like the Lipinski rule of five and the binding affinity of a ligand into the protein. [41-48]. In this study, we have carried out extensive Quantitative Structure-Activity Relationship (QSAR) analysis on a diverse group of 23 pyrimidine derivatives, all of which have been shown to have antifungal activity against *Botrytis Cinerea* and to have a variety of chemical structures and biological activities. Additionally pharmacophore hypothesis, virtual screening, ADMET analysis and molecular docking was performed to develop pyrimidine derivatives with antifungal potential.

2. Material and method

2.1 Material

Tasks and software used in the presented work mentioned in (Table 1)

Table 1. Software and modules used in the present work.

Sr. No.	Task	Material (Software and module)
1.	To draw the structure	ChemDraw Ultra (8.0)
2.	Ligand preparation and Optimization	Schrodinger's Maestro 13.4/LigPrep
3.	3D QSAR, Pharmacophore hypothesis, Virtual Screening	Schrodinger's Maestro 13.4/PHASE
4.	ADMET studies	Schrodinger's Maestro 13.4/QikProp
5.	Molecular Docking	Schrodinger's Maestro 13.4/GLIDE

2.2 Method

2.2.1 Ligand preparation and optimization

The dataset of 23 Pyrimidine derivatives with diverse chemical structure and biological activity was selected and ligand structures were prepared. For the development of QSAR model, IC_{50} values were converted into pIC_{50}. [49, 50] The table of IC_{50}, pIC_{50} values and series of 23 derivatives are given in the supplementary material (Table **S1**)

2.2.2. Atom-based 3D QSAR

To generate the QSAR model, dataset was randomly divided into 70 percent molecules in training set and 30 percent molecules in test set (5, 7, 14, 20, 23) using the PLS factor 3. [49, 51-53]

2.2.3. Development of pharmacophore hypothesis

The pharmacophore hypothesis was generated with the five pharmacophoric features. These features include Hydrogen bond acceptor (A), Hydrogen bond donor (D), Hydrophobic group (H) and the Aromatic ring (R). Pharmacophore hypothesis was generated with all structures were divided into active (11), inactive (8) and moderate (4) structures. [54-58]

2.2.4. Accumulation of compounds and virtual screening

130,000 ChEMBL database was used for virtual screening of the top hypothesis and 88,000 NCEs were screened for ADMET analysis. [59-63]

2.2.5. Lipinski rule, pharmacokinetics and drug-likeness

ADMET analysis determined various important descriptors and properties of organic molecules, such as hydrogen bond donors, acceptors, molecular weight, and LogP (octanol-water coefficient). From 88,000 NCEs, 800 were selected for docking studies. [64-67]

2.2.6. Molecular docking studies

The protein structure was taken from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSBPDB) site (PDB ID 4UYM) for molecular docking studies. This PDB contains vcz as a co-crystal ligand and key amino acids such as Serine, Tyrosine and Phenylalanine. Co-crystal vczhave shown interaction with Heme and Heme showed interaction with key amino acids. The molecular docking consists of protein preparation, energy minimization, protein optimization and elimination of hydrogen bonds. Molecular docking was done with the standard vcz and NCEs. [68 69 70 71]The residue protein was further modified to form a grid associated with the active space that the ligand surrounded. The receptor grid was created by taking the active site area of the protein and placing it right at the centre, resulting in a highly confident and accurate model. The cuboidal shape that forms on the active space of the ligand indicated the active site of the protein. [72-75].

3. Result and discussion

3.1Atom-based 3D QSAR

QSAR model was generated and validated by different statistical parameters such as R^2, correlation coefficient Q^2, stability, F value, P value supported with low value of variance ratio, standard deviation, RMSE and Pearson value. (Table 2)

Table 2. Values of Generated QSAR model

Factors	SD	R^2	R^2CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.0152	0.9140	0.1155	0.6779	0.328	49.6	1.05e-07	0.00	0.8953	0.9541

- Standard Deviation value was obtained as 0.01 which refers to the variability in predicted versus actual biological activity values.
- R^2 value was obtained as 0.91 whichis the statistical measure showing the similarity between predicted and actual activity.
- R^2 Scramble value was obtained as 0.11 which is the measure that shows the correct or consistent value even after randomly scrambling the dataset.
- Stability was observed as 0.3 which refers to the model's robustness and reliability.
- F value was obtained as 49.5 which represents the overall significance of the regression model.
- Pvalue was obtained as 1.05 which represents the probability that the observed results are due to chance.
- Root Mean Square Error value was obtained as 0.00 provides an indication of the model's predictive accuracy, with lower values indicating better predictive performance and less error in the predictions.
- Q^2value was obtained as 0.89. Q^2 in 3D QSAR is often referred to as the cross-validated R^2. It measures the predictive accuracy of the model using cross-validation techniques. A higher Q^2 value indicates that the model has strong predictive power
- Pearson-r value was obtained as 0.95 which is a correlation coefficient that measures the linear relationship between predicted and observed values of biological activity.

3.2Development of pharmacophore hypothesis

Pharmacophore hypothesis was obtained with 11 active, 8 inactive and the remaining moderate compounds after giving ligands an activity threshold of 4.044-4.034. After defining all the structures into active inactive and running the hypothesis 11 possible hypothesis were generated. The top score hypothesis ADHRR_1 with 5 features was generated by using the ChEMBL database. Based on survival and vector score, top most hypothesis ADHRR_1 was selected for further studies. This hypothesis shows the involvement of hydrogen bond acceptor, hydrogen bond donor, hydrophobic group and two aromatic rings. (Table 3)

Table 3. Predicted top hypothesis

Hypothesis ID	Survival score	Vector score	Site Score	Number matched	Inactive score
ADHRR_1	5.43	1	0.82	11	2.27

3.3 Accumulation of compounds and virtual screening

From the results of the pharmacophore hypothesis, top hypothesis ADHRR_1 was screened with 1,30,000 compounds. Out of 1,30,000 compounds88000 NCEs were screened. All these 88,000 NCESs show a good match with the required features of the top hypothesis. Out of these 88,000 NCEs top 800 NCEs were selected for ADMET studies

3.4 Lipinski rule, pharmacokinetics, and drug-likeness

After the ADMET analysis, out of the 800 compounds, 156 compounds violated the Lipinski rule of five and the remaining 667 compounds resulted in zero violation, which were selected for further docking studies. In the analysis of ADMET results, all compounds have shown molecular weight between the ranges of 384-463. Hydrogen bond donor and acceptor are less than 5 and 10 respectively. All compounds have shown partition coefficient index below 5. QPlog HERG values were found less thus making it safe and less toxic. Percent human oral absorption was found almost above 85% as well as it has been confirmed that the presence of Thiazine, Isoxazole, and Benzoxazole rings, as well as Trifluoromethyl group and higher molecular weight in the structure, leads to violations.

3.5 Molecular docking studies

All the 667 NCEs were docked with the PDB ID: 4UYM. Topmost seven NCE's (Figure1) showed comparable results as compared to the standard drug vcz. (Table 4)

Table 4 Docking interactions of NCEs with PDB ID: 4UYM

Comp no.	Docking score kcal/mol	Glide energy kcal/mol	Type of interaction	Interactions atom of ligand	Amino acid	Distance (Å)
01	-10.129	-10.325	H bond	NH_2	**HEM580**	1.62
			Pi cation	NH of Morpholine ring	**HEM580**	3.51
			Salt Bridge	NH of Morpholine ring	**HEM580**	3.25
02	-10.030	-10.030	H bond	Oxygen of Acetyl group	TYR122	2.42
			Pi-Pi stacking	Benzopyrrole	PHE234	4.38
03	-9.948	-10.015	H bond	NH_2	**HEM580**	2.37
			H bond	NH_2	**HEM580**	1.62
			Pi cation	NH of Morpholine ring	**HEM580**	3.49
			Salt Bridge	NH of Morpholine ring	**HEM580**	3.24
			Halogen bond	Br	GLN146	3.06
04	-9.819	-9.886	H bond	NH_2	**HEM58**	2.33

					0	
			H bond	NH_2	**HEM580**	1.62
			Pi cation	NH of Morpholine ring	**HEM580**	3.61
			Salt Bridge	NH of Morpholine ring	**HEM580**	3.33
05	-9.697	-9.697	H bond	OH	HIE374	2.33
			H bond	OH	SER375	1.74
			Pi-Pi stacking	Benzene	**PHE204**	4.98
06	-9.634	-10.040	H bond	NH_2	**HEM580**	2.01
			H bond	NH_2	**HEM580**	2.09
			H bond	Oxygen of Amide Moiety	HIE374	2.35
			H bond	Oxygen of Amide Moiety	SER375	2.18
07	-9.619	-9.619	H bond	Oxygen of Acetyl group	TYR122	2.39
vcz	-9.305	-9.305	H bond	NH of Triazole	**HEM580**	2.10
			Salt Bridge	NH of Triazole	**HEM580**	3.04
			Pi cation	NH of Pyrazole	**PHE504**	4.70

*NCEs that exhibit similar interactions as standard drug are shown in bold letters.

All compounds showed interaction with the PDB ID 4UYM

1) Compound 01 showed three interactions
a) The amino group showed hydrogen bond with the HEM580 with a distance of 1.62 Å
b) NH of Morpholine ring showed Pi-cation with the HEM580 with a distance of 3.51 Å
c) NH of Morpholine ring showed salt bridge with the HEM580 with a distance of 3.25 Å
2) Compound 02 showed two interactions
a) Oxygen of acetyl group showed hydrogen bond with the amino acid TYR122 with a distance of 2.42 Å
b) Benzopyrrole showed Pi-Pi stacking with the amino acid PHE234 with a distance of 4.38 Å
3) Compound 03 showed five interactions
a) The amino group showed hydrogen bond with the HEM580 with a distance of 2.37 Å
b) The amino group showed hydrogen bond with the HEM580 with a distance of 1.62 Å
c) NH of Morpholine ring showed Pi-cation with the HEM580 with a distance of 3.49 Å
d) NH of Morpholine ring showed salt bridge with the HEM580 with a distance of 3.24 Å
e) Bromine showed halogen bond with the amino acid GLN146 with a distance of 3.06 Å
4) Compound 04 showed four interaction

a) The amino group showed hydrogen bond with the HEM580 with a distance of 2.33 Å
b) The amino group showed hydrogen bond with the HEM580 with a distance of 1.62 Å
c) NH of Morpholine ring showed Pi-cation with the HEM580 with a distance of 3.61 Å
d) NH of Morpholine ring showed salt bridge with the HEM580 with a distance of 3.33 Å
5) Compound 05 showed three interactions
a) Hydroxyl group showed hydrogen bond with the amino acid HIE374 with a distance of 2.33 Å
b) Hydroxyl group showed hydrogen bond with the amino acid SER375 with a distance of 1.74 Å
c) Benzene ring showed Pi-Pi stacking with the amino acid PHE204 with a distance of 4.98 Å
6) Compound 06 showed two interactions
a) The amino group showed hydrogen bond with the HEM580 with a distance of 2.01 Å
b) The amino group showed hydrogen bond with the HEM580 with a distance of 2.09 Å
c) The Oxygen of amide moiety showed hydrogen bond with the amino acid HIE374 with a distance of 2.35 Å
d) The Oxygen of amide moiety showed hydrogen bond with the amino acid SER375 with a distance of 2.18 Å
7) Compound 07 showed two interactions
a) Oxygen of acetyl group showed hydrogen bond with the amino acid TYR122 with a distance of 2.39 Å
8) Standard drug Showed three interactions
a) NH of triazole showed hydrogen bond with the HEM580 with a distance of 2.10 Å
b) NH of triazole showed salt bridge with the HEM580 with a distance of 2.10 Å
c) NH of Pyrazole showed pi-cation with the amino acid PHE504 with a distance of 4.70 Å

In the molecular docking, amino acid interaction analysis revealed that presence of key amino acids (PHE204, SER375 and TYR122) and Heme in the protein. Vcz have shown interaction with the heme (HEM580) and Phenylalanine (PHE204) amino acid. Almost all NCEs have shown similar interactions with heme (HEM580) and key amino acids. Amino group and NH of morpholine ring have showed more number of interaction with heme (HEM580). Oxygen of acetyl group have showed interaction with key amino acid tyrosine (TYR122). Hydroxyl group and oxygen of amide moiety have showed interaction with key amino acid Serine (SER375). As well as the presence of amide moiety in the structures given higher dock score and glide score than vcz.

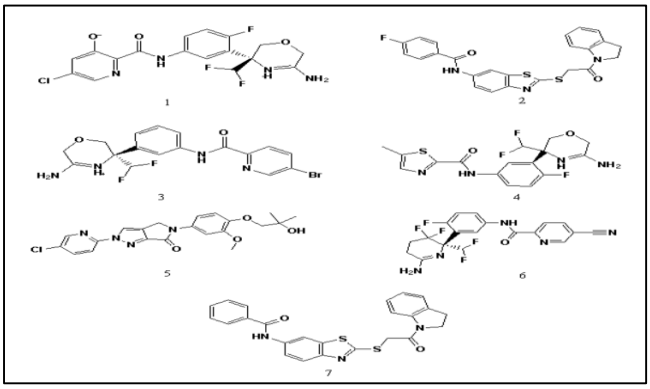

Figure 1. Designed NCEs

9. Conclusion

- QSAR results have been evaluated with good R^2, Q^2 and Stability.
- The pharmacophore hypothesis ADHRR_1 has a good survival score and vector score.
- In the virtual screening top pharmacophore hypothesis was screened against the ChEMBL database, resulting in promising results of survival and vector score.
- Lipinski rule, pharmacokinetics, and drug-likeness evaluation were performed and molecules with zero violations were docked with PDB ID 4UYM.
- Designed NCEs were evaluated using ADMET analysis and Lipinski rule of five to analyse their drug likeness. It has been established that structures containing Thiazine, Isoxazole, and Benzoxazole rings, along with trifluoromethyl groups and higher molecular weight, tend to result in violations.
- In the molecular docking analysis, key amino acids PHE204, SER375, and TYR122, along with the heme group, were identified as crucial interaction sites. Vcz showed interactions with heme (HEM580) and Phenylalanine PHE204. Most NCEs exhibited similar interactions with HEM580 and key amino acids. Notably, the amino group and NH of the morpholine ring displayed numerous interactions with HEM580, while the oxygen of the acetyl group interacted with TYR122, and the hydroxyl group and oxygen of the amide moiety interacted with SER375. The presence of the amide moiety in the structures resulted in higher dock and glide scores compared to vcz.
- Based on the above results it is concluded that compound no 03 showed the similar and promising interactions as per vcz with better docking score and glide score. Therefore, compound no 03 is the best NCE among all the NCEs.
- Techniques like 3D QSAR, pharmacophore hypothesis, ADMET profiling, and molecular docking proved to be invaluable in drug design and discovery studies. They offer the advantage of being less time-consuming while providing accurate insights, thus enhancing the efficiency of the drug development process.

Abbreviations

- Vcz: Voriconazole
- QSAR: Quantitative structural activity relationship
- ADMET studies: Absorption, Distribution, Metabolism, Excretion and Toxicity studies
- RCSBPDB: Research Collaboratory for Structural Bioinformatics Protein Data Bank

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Conflict of interest

Authors declared no conflict of interest.

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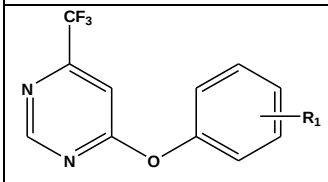
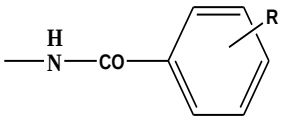
Table **1 – Data set for QSAR**

Pharmacophore		R_1-	
			
Compound. no.	R-	IC50	pIC50
1	H	92.43	4.03
2	Cl	96.76	4.01
3	OCH_3	89.88	4.04
4	4-$(CH_3)_3C$	71.35	4.14
5	CF_3	87.68	4.05
6	2-OCH_3-3CF_3	89.04	4.05
7	3-Br-4-Cl	88.17	4.05
8	2-F-5-Br	89.51	4.04
9	3,4,5-tri-OCH_3	87.97	4.05
10	H	96.84	4.01
11	3-CH_3	81.54	4.08
12	3-F	100.0	4.00
13	2-Cl	90.4	4.04
14	4-Cl	94.63	4.02
15	4-OCH_3	92.84	4.03
16	4-$(CH_3)_3C$	65.87	4.18
17	4-NH_2	76.48	4.11
18	3-CF_3	90.56	4.04
19	4-CF_3	93.47	4.02
20	2,6-di-OCH_3	93.67	4.02
21	3,4-di-OCH_3	89.88	4.04
22	3-Br-5-CF_3	92.64	4.03
23	3,4,5-tri-OCH_3	92.31	4.03