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Research Article

Molecular Docking and QSAR studies for Modeling Antifungal Activity of Triazine Analogues against Therapeutic Target NMT of *Candida albicans*

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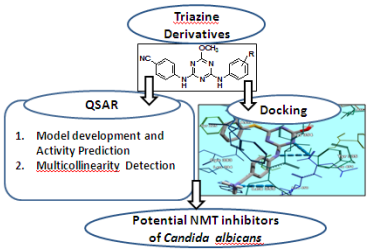
ABSTRACT

The s-triazine derivatives have been attracting the attention of researchers due to a broad range of biological applications. Present research deals with a combination of genetic algorithm-multiple linear regression (GA-MLR) based quantitative structure–activity relationships (QSAR) modeling and molecular docking as relevant to triazine analogs in an attempt to investigate their role as novel NMT inhibitors of *Candida albicans*. A penta-varient model which assure all validation criteria up to considerable echelon (R^2 = 0.792, Q^2 = 0.679 and = 0.603) supplemented by multicollinearity diagnosis by VIF and tolerance data analysis, signaling the robustness of the QSAR model**.** The descriptors RDF040v, Ds, Mor04m, X4v, and MATS2p in the projected QSAR model have quantified the role of atomic properties such as topology; atomic van der Waals volume, mass, and polarizability execute vital part to modify the antifungal activity of compounds under investigation. Further, a molecular docking simulation study revealed that three compounds, in particular, showed a superior binding affinity with a re-rank score of -142.594, -138.972, -137.540 kcal/mol. Consequently, this study may turn out to be helpful towards the development and optimization of existing antifungal activity of compounds under investigation.

GRAPHICAL ABSTRACT



Introduction

The s-triazine derivatives have been attracting the interest of researchers on account of wide biological activity *viz.* anti-bacterial, anti-cancer, anti-inflammatory, anti-viral, anti-malarial fungicidal, anthelmintic, and anti-tubercular.[1-7]

Life-threatening, invasive fungal infections especially caused by *Candida* species, are the main cause of morbidity

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mortality and, thus, causing universal health problems and economic burden.[8-10] Large arsenals of available antifungal drugs are not effective due to the issues like drug resistance, narrow antifungal spectrum, poor efficacy, and toxicity. In this framework, the scientific community has been functioning hard to search for novel drug candidate(s) and target.[11-17]

It has been evidence from biochemical and genetic studies that enzyme myristoyl CoA: protein N-myristoyl transferase (NMT) plays key responsibility to preserve the viability of *Candida albicans*;[18] the principal cause of systematic fungal infections in immune-compromised persons. In this context, NMT has been recognized as a promising target for current investigation.[19-21]

Computer-aided drug design (CADD); especially QSAR and molecular docking, has been gaining researchers' attraction to combat the problems associated with traditional methods of drug design and discovery.[22-23]

A combination of QSAR and molecular docking studies have been pursued linking chemical structure and pharmacological activities (physical, chemical, and biological properties) quantitatively, along with forecasting the preferred binding orientation of a ligand within the active site of the target protein NMT.[24-30] Present research investigation deals with the combination of GA- MLR based QSAR modeling and molecular docking as relevant to triazine analogs in an effort to investigate their role as novel NMT inhibitors of *Candida albicans*. Consequently, this study may be useful for the development and optimization of prevailing antifungal activity of compounds under investigation.

Materials and Methods

The activity data minimum inhibitory concentration (MIC) of the antifungal compounds were taken from the published work[3] and converted to-log MIC in a micromolar level. The 2D structures of all the analogues under investigation were first sketched in Chemdraw Ultra version 8.0 software[31] then transformed into 3D structures using Chem3D Ultra version 8.0.[32] Energy minimization of stated structures was carried out through molecular mechanics (MM2) force field followed by geometry optimized *via* semi-empirical Austin model (AM1) method workable through MOPAC module. Initially, A vast pool of 2D and 3D descriptors (autocorrelation, topological, gateway, RDF, MoRSE, geometrical, constitutional, edge adjacency descriptors subsets) were calculated for the optimized compounds using Parameter Client software.[33,34] The descriptors possessing constant numerical values along with those showing high correlation with others were eliminated by using the V-WSP algorithm proposed by Davide and Todeschini[35] using NanoBRIDGES" software based on cut-off values of variance (0.0001) and correlation coefficient (0.99).[35-37] The hybrid GA-MLR approach linked with error-based fitness function has been used as the feature selection and model generation tool.[38-39]

The robustness of generated models was ensured by applying various validation techniques.[40-43] A research report by Roy *et al*. has come out to be worth mentioning in the aforementioned context.[44] Therefore, the metrics proposed by Roy *et al*. were also evaluated to check the stability of the QSAR models. Additionally, VIF index, tolerance and Y scrambling analysis were performed to make sure non-existence of the multicollinearity issue in the proposed QSAR model.[45-46] Furthermore, to gain insight into ligand-protein interaction, QSAR analysis has been amalgamated with docking studied data under investigation. Molegro virtual docker (MVD) software[47] with default parameters were used to perform molecular docking simulation. Proceeding to docking simulation, validation of the software protocol has been performed by RMSD value calculation. The 3D Crystal structure of the target; NMT (1IYL) was retrieved in the MVD from RCSB protein data bank (https://www.rcsb.org/). The hydrogen bonds interactions, scoring functions, steric data were investigated for a better understanding of NMT- triazine binding interaction.[47-48]

Result and Discussion

In the current research, a combination of QSAR analysis followed by docking simulation has been carried out with a view to work out the important structural attributes of s-triazine analogs needed for antifungal activity against *Candida albicans*. The structures of 35 triazine derivatives are listed in Fig. 1. Initially, approximately

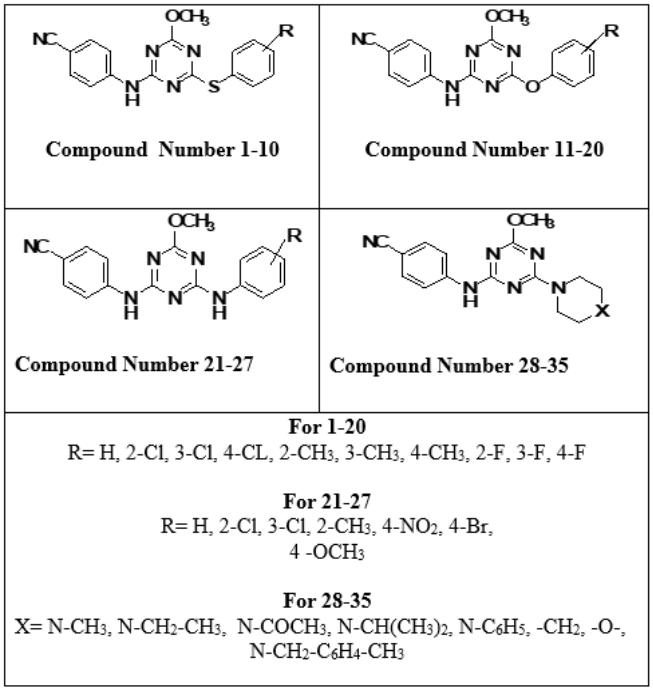

Fig. 1: Structure of thirty five triazine derivatives under investigation

3000 descriptors were calculated using Parameter Client software.[33] The descriptors holding constant numeric values, more than 90% zero values and highly mutually correlated were eliminated as described in the aforesaid section "Materials and Methods". Subsequently, various mono, bi, tri, tetra, and penta-metric QSAR models were generated using genetic algorithm as descriptor screening approach followed by MLR analysis MLR from a large pool of descriptors.[36-37] Few best QSAR models among various generated models are presented below, and the statistical parameters to check the quality of these QSAR models are compiled in Table 1.

1. pMIC (C. albicans) = -1.032(±0.868)E1s +5.282(± 1.473) -0.246(± 0.1734) EEig03x +1.066(± 0.365) EEig08d... Equation 1
2. pMIC (C. albicans) = 0.849(± 0.641) -11.946(± 5.584) HATS7v +0.396(± 0.105) RDF155m +14.513(± 2.249) Ds... Equation 2
3. pMIC (C. albicans) = -0.203(± 1.222) + 0.408(± 0.0999) RDF155m +11.987(± 2.014) Ds -0.003(± 0.499) J3D +0.897(± 0.306) GATS8p... Equation 3
4. pMIC (C. albicans) = -0.721(± 0.836) +0.911(± 0.302) GATS8p +11.017(± 2.268) Ds +0.074(± 0.087) RTp +0.417(± 0.099) RDF155m... Equation 4
5. pMIC (C. albicans) = -1.845(± 0.820) +0.342(± 0.064) RDF040v +14.471(± 2.238) Ds -0.373(± 0.123) Mor04m -0.831(± 0.261) X4v +0.993(± 0.424) MATS2p... Equation 5
6. pMIC (C. albicans) = -2.557(± 0.592) +15.655(± 2.151) Ds +2.941(± 0.498) RDF155v -0.353(± 0.220)Mor05v -0.795(± 0.222) RDF145v +1.1823(± 0.541) MATS2v... Equation 6

The regression results (Table 1) show that the tri-parametric (Model I) does not meet the statistical parameters' threshold value. Similarly, Models II-IV seem to be sound as per statistical validation parameters (R^2 and R^2adj > 0.5 along with Y-randomization parameter ^{c} >0.6) but not considered as good one due to a lower Q^2 value than 0.5. It is worthy of mentioning that a report published in 2009 by Kunal Roy and co-workers [49] has evidently highlighted the task of validation as a vital aspect of the QSAR model building approach. They have advocated the need to integrate two new parameters r^2_m and $^cR^2_p$ for a stricter parameter of QSAR model validation (particularly when a regulatory discussion is concerned) rather than considering just the conventional validation parameters,. Accordingly, conventionally used statistic validation parameters have been add-on with various metrics r^2_m and $^cR^2_p$ validation parameters in the present investigation.

Additionally, Models I-IV are not convincing as per the acceptable QSAR model criteria of Roy *et al*. as the Average $r^2_{m(LOO)}$ is less than 0.5.

Penta-variant Models V and VI represented in Equations 5 and 6 respectively satisfied all the aforesaid validation criteria along with various r^2_m metrics and $^cR^2_p$ generated by Roy and Mitra[44] (Table 1).

Thus, these two models appear to be statically robust subjected to the green signal from multicollinearity criteria pointed out by Bolboac and Lorentz.[46] In this context, to check the multicollinearity among the modeled descriptors, the corresponding statistical finding of VIF and tolerance data are listed in Table 2. High VIF values 7.119 (VIF > 5, and low tolerance value

Table 1: Statistical parameters to check the quality of these QSAR models

Model No.	*R^2*	*R^2adj*	*SEE*	*Q^2*	*SDEP*	*Average*	*delta*	*$^cR^2_p$*
Threshold value	>0.6	>0.6	Low	>0.5	High	>0.5	< 0.2	^{c} >0.6
Model I	0.548	0.504	0.399	0.382	0.439	0.273	0.158	508
Model II	0.648	0.614	0.352	0.459	0.411	0.394	0.068	610
Model III	0.686	0.644	0.337	0.469	0.407	0.412	0.045	638
Model IV	0.694	0.652	0.334	0.483	0.402	0.426	0.040	626
Model V	0.754	0.712	0.304	0.671	0.321	0.576	0.122	0.689
Model VI	0.792	0.756	0.280	0.679	0.317	0.603	0.052	0.708

R^2: coefficient of determination, R^2 adj: Square of adjusted regression coefficient: SEE: Standard error of estimate, Q^2:Leave-one-out cross-validated coefficient of determination, SDEP: standard deviation error of prediction, Average delta and ^{c}are various metrics for validation developed by Roy and Mitra (2012)

Table 2: Collinearity statistical output to check multicollinearity among descriptors (as per models V and VI)

Collinearity statistics (Model V)			*Collinearity statistics (Model VI)*		
Descriptor	*Tolerance*	*VIF*	*Descriptor*	*Tolerance*	*VIF*
RDF040v	0.221	4.523	Ds	0.579	1.727
Ds	0.630	1.586	RDF155v	0.189	5.299
Mor04m	0.571	1.751	Mor05v	0.510	1.959
X4v	0.237	4.225	RDF145v	0.140	7.119
MATS2p	0.453	2.206	MATS2v	0.569	1.758

Table 3: Observed activity, predicted biological activity, and residual error data of triazine derivatives as per the proposed QSAR model.

Compound	*Observed pMIC*	*Predicted pMIC*	*Residuals*	*Standard residuals*
1	3.526	3.308	0.217	0.774
2	3.869	4.123	-0.254	-0.905
3	5.074	4.751	0.323	1.150
4	4.471	4.431	0.041	0.144
5	4.145	4.349	-0.204	-0.725
6	3.543	3.532	0.011	0.041
7	3.242	3.479	-0.237	-0.844
8	3.849	3.757	0.093	0.330
9	4.150	4.329	-0.179	-0.637
10	4.451	4.448	0.003	0.010
11	3.203	3.511	-0.308	-1.097
12	3.824	3.584	0.240	0.854
13	3.523	3.800	-0.277	-0.985
14	4.125	3.604	0.521	1.856
15	3.528	3.395	0.133	0.473
16	4.431	4.316	0.115	0.409
17	3.829	4.234	-0.404	-1.440
18	3.248	3.889	-0.642	-2.285
19	4.452	4.762	-0.310	-1.104
20	4.753	4.566	0.187	0.665
21	3.202	3.486	-0.284	-1.012
22	3.849	3.765	0.084	0.299
23	4.752	4.507	0.245	0.871
24	3.522	3.485	0.036	0.129
25	4.165	4.127	0.038	0.136
26	3.298	3.042	0.256	0.912
27	4.445	4.037	0.408	1.454
28	3.512	3.506	0.007	0.024
29	3.531	3.845	-0.314	-1.118
30	5.054	4.315	0.739	2.633
31	4.150	4.144	0.007	0.024
32	4.792	4.853	-0.061	-0.217
33	3.191	3.109	0.082	0.291
34	3.194	3.354	-0.161	-0.573
35	3.922	4.073	-0.151	-0.538

0.140 (Tolerance < 0.3) indicate collinearity amongst modeled descriptors (Ds, RDF155v, Mor05v, RDF145v, and MATS2v) in Model VI, whereas the non-existence of multicollinearity in generated model V as revealed from statistical parameters of Table 2, i.e., VIF has been found to be less than five and tolerance is greater than 0.3 for all the modeled descriptors. It is apparent from a comparison of various statistical parameters that model V is more robust than other models achieved and discussed above in the present QSAR studies.

Further, In order to ascertain the predictive ability of the developed Model V, pMIC values of all the training set compounds under investigation were calculated through equation 5 and have been compared with the experimental values. As shown in Table 3 the experimental pMIC values are in good agreement with predicted pMIC values as indicated by the low value of standard residual. Further, the plot between predicted and observed pMIC values (Fig. 2) and correlation matrix (Table 4) confirms that the proposed QSAR Model V has fantastic prediction ability.

A combined examination of statistic validation parameters, r^2_m and $^cR^2_p$ metrics validation parameters as per Roy and Mitra,[44,49] ($R^2 = 0.792$, $Q^2 = 0.679$ and = 0.603.

VIF and tolerance data analysis enable us to conclude a reasonable agreement of the wide range of validation criteria. Thereby signaling the robustness of the proposed penta-variant QSAR Model V. Therefore, penta-variant

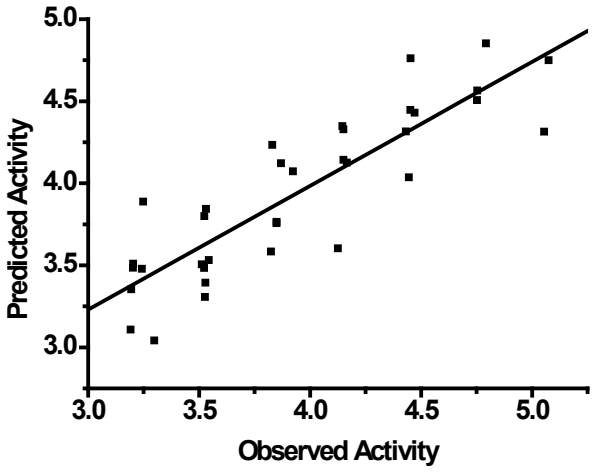

Fig. 2: Plot of experimental versus predicted pMIC values of triazine derivates as generated by the QSAR model V

Table 4: Correlation matrix showing mutual correlations among the variables used in model V

Descriptor	*RDF040v*	*Ds*	*Mor04m*	*X4v*	*MATS2p*	*C. albicans pMIC*
RDF040v	1					
Ds	0.422	1				
Mor04m	0.583	0.285	1			
X4v	0.870	0.426	0.539	1		
MATS2p	0.576	-0.587	-0.564	-0.560	1	
C. albicans pMIC	0.440	0.642	-0.051	0.249	-0.177	1

expression (Equation V) which assures all validation criteria up to considerable echelon, was considered as the best QSAR model for further study.

The developed QSAR model V shows the association between experimental activities considered as a dependent variable and five descriptors, namely RDF040v, Ds, Mor04m, X4v and MATS2p as independent variables in pursuance to modulate antifungal activities of triazine analogs under study. Descriptors inculcated in the best-projected QSAR model encoded the important properties of the molecules pertinent to the antifungal activity. Density descriptor weighted by atomic electro-topological charges (Ds) is a Whim descriptor and provides information regarding the electronic and topological state of the atom in a molecule. A low value of Ds is required in order to increase antifungal activity as it is negatively correlated with activity.[50] X4V (connectivity descriptor) is a valence connectivity index chi-4. Tetra-valence Connectivity Index of Electronic Density gives a sign of the nature of bond connectivity between atoms. Connectivity is directly linked with the flexibility of molecules. The higher the connectivity, the more rigid the molecule is, leading to low activity.[51] Moran autocorrelation lag 1/weighted by atomic polarizability (MATS2P) is a 2D-autocorrelation descriptor. The positive sign of the regression coefficient of this descriptor indicates elevated activity with a higher value of MATS2P descriptor, and the polarizability plays a vital role in enhancing the activity. The Mor04m (3D-MoRSE-signal04/weighted by atomic masses) belongs to the 3D-MoRSE descriptors family. 3D-MoRSE descriptors provide information regarding the association of activity with mass. The negative sign of Mor04m descriptor illustrates that antifungal activity decreases with increasing molecular mass.[52-53]

As shown in equation 5 the descriptor Ds was the most significant descriptor, as indicated by the highest regression coefficient of +14.471. The positive regression coefficient point towards the high value of Ds is vital for elevated antifungal activity. Likewise, negative regression coefficients of another descriptor, i.e., Mor04m, and X4v indicate a lowering in activity with increased numerical values of these descriptors. Correspondingly, the elevated value of the descriptors with a positive regression coefficient, i.e., RDF040v and MATS2p favor the antifungal activity.

The descriptor Ds was found to be the most influential descriptor, as indicated by the highest regression coefficient of +14.471. Accordingly, topology, atomic van der Waals volume, mass, and polarizability execute a significant role in modulating the antifungal activity of compounds under investigation. Therefore, the substituents that impart the above-mentioned changes in physico-chemical properties included in the proposed model should be attached or removed to the molecules to increase the biological activity.[50-53]

With a view to search for better ligand-protein interaction, QSAR analysis has been followed by molecular docking studies using MVD tool. Validation of software protocol has been ensuring by calculating root mean square deviation (RMSD) value. An RMSD value of 1.04 of all the atoms between co-crystallized and docked poses of R64A confirms software reproducibility.

Consequently, all the 35 triazine derivatives were docked into the binding pocket of NMT. The docked energies, hydrogen bond values of the three most active compounds from the thirty-five dataset are provided in Table 5. It was observed (Ref. Table 5) that compound number 5, 32, and 35, in particular, showed a superior binding affinity with a re-rank score of -142.594, -138.972, -137.540 kcal/mol, respectively in comparison to the co-crystallized ligand R64 with a re-rank score of -135.887 kcal/mol. Hydrogen bond interactions of the most active triazole analogs with NMT are illustrated in Figs. 3-5 It was concluded from the docking simulation that three triazine derivatives were strongly bonded through electrostatic, hydrophobic, and hydrogen bond

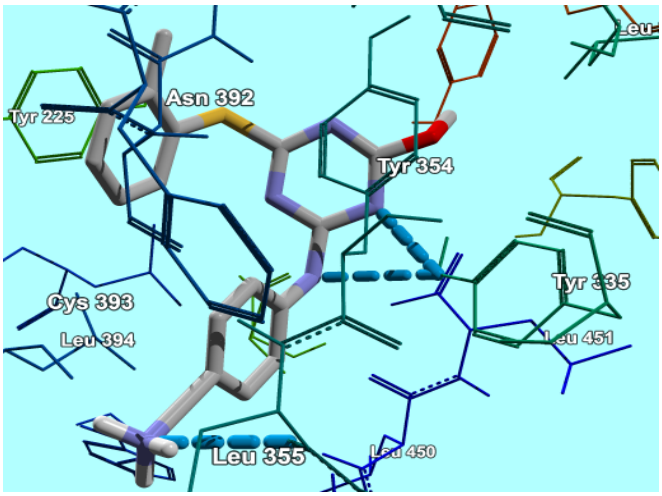

Fig. 3: Hydrogen bond interactions (as shown by blue dotted line) of compound 5 with active amino acids Leu355, and Leu451 of NMT [PDB: 1IYL]

Table 5: Molecular docking interactions of triazine derivatives inside the binding pocket of NMT generated by MVD[47].

Compound No.	*Rank score kcal/mol*	*No of Hydrogen bonds*	*Amino Acid involved in Hydrogen Bonding*	*Hydrogen bond Interaction (Å)*
5	-137.540	03	Leu355, and Leu451	-2.081
32	-138.972	04	Asn110, Asp112 and Asn392	-3.746
35	-142.594	05	Thr211, Cys393, and Tyr107	-1.225
R64A	135.887	03	Asn392, Tyr354,	-4.641

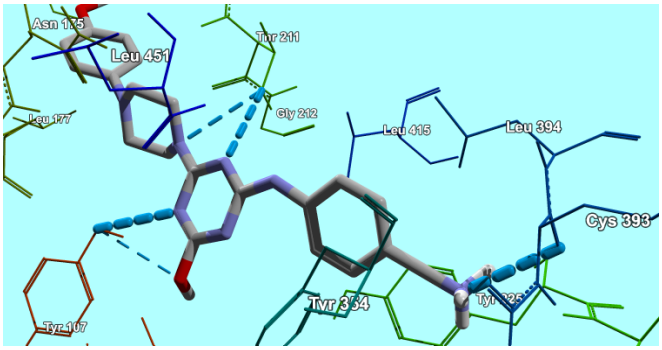

Fig. 4: Hydrogen bond interactions (as shown by blue dotted line) of compound 35 with active amino acids Thr211, Cys393, and Tyr107 of NMT [PDB: 1IYL]

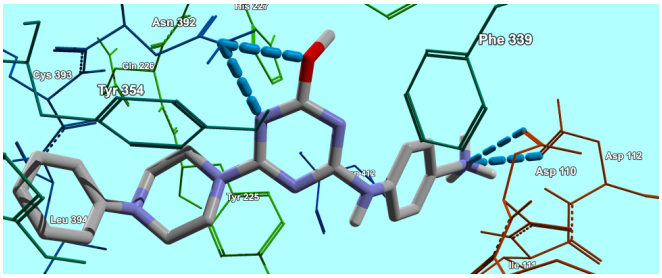

Fig. 5: Hydrogen bond interactions (as shown by blue dotted line) of compound 32 with active amino acids Asn110, Asp112 and Asn392 of NMT [PDB: 1IYL].

interactions and stabilized into the active site of target protein NMT.

Conclusion

Present research findings are associated with a combination of the GA-MLR based QSAR analysis and docking studies, which may help understand the structural necessities for finding novel and selective antifungal drug candidate(s). Consequently, this study may turn out to be useful towards the development and optimization of prevailing antifungal activity of compounds under investigation.

The descriptors RDF040v, Ds, Mor04m, X4v, and MATS2p in the projected QSAR model have quantified the task of atomic properties such as topology, atomic van der Waals volume, mass and polarizability execute vital part to altered the antifungal activity of compounds under investigation. VIF and Tolerance data indicate the non-existence of multicollinearity among the modeled descriptor, and the model is not by chance correlation. Furthermore, molecular docking analysis signifies that compound numbers 5, 32, and 35, in particular, showed a superior binding affinity with a re-rank score of -142.594, -138.972, -137.540 kcal/mol. Combining the GA-MLR based QSAR analysis in association with molecular docking simulation is valuable in understanding the structural requirements for designing novel antifungal drug candidates (s). Accordingly, this research finding may become valuable towards the development of potent antifungals of these congeners.

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