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3D-Quantitative Structure Activity Relationship: A Strategic Approach for *In Silico* Prediction of Anti-Candididal Action of 1,2,4-Triazole Derivatives

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ABSTRACT: The three dimensional quantitative structure activity relationships(3D-QSAR) of a series of previously synthesized 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanol analogs(TDFPP) as antifungal against *candida albicans*, were studied using kNN(K nearest neighbour) protocol. This was in order to explore the selectivity requirements for fungicidal activity against C. albicans among these congeners. Theoretical active conformers for these TDFPP were generated. The best kNN model(N=44, q2= 0.8650, r2= 0.86504) showed contribution of the steric and electrostatic fields. The models were also external validated using 6 compounds(test set) not included in the model generation process. The statistical parameters from model indicate that the data are well fitted and have predictive ability. Moreover, the resulting contours and isosurface maps provide useful guidance for designing highly active ligands. The model is not only able to predict the activity of new compounds but also explains the important region in the molecules in the quantitative manner.

KEYWORDS: 3D QSAR; *Candida Albicans*; Triazole; *In Silico* Studies; Anti-Candididal Activity.

INTRODUCTION

Candida is the leading cause of oesophagitis (Throat inflammation) in the people with AIDS. Such a causative agent requires an equally effective focus of research [1]. The synthesis and biological activities of 1,2,4-triazole derivatives have always been an interesting topic in the fields of medicinal and agricultural chemistry for many years. 1,2,4-triazoles have already proved themselves as potent antifungal agents as in the form of fluconazole, itraconazole etc. But its structure activity relationship is not well established. As QSAR studies are undoubtedly of great importance in modern chemistry. This methodology is mostly used to correlate structural descriptors with biological properties, but it can also be applied to predict the activity value of non synthesized compounds structurally related to training sets [2]. Previously we have studied the 2D-QSAR model for 1,2,4-triazoles and calculated important descriptors responsible for activity. Topographical descriptors played important role in those QSAR model [1]. These trends have emphasized the pressing need for new, more effective and safe antimicrobial agents[3]. Keeping this observation in view and in continuation of our work on QSAR studies and its interpretation, this paper presents the kNN based 3D-QSAR study[4] on these

analogues(**Table 1**) along with their generalized structure (**Figure 1-2**) which has been conducted to provide the rationale for drug design using VLife Molecular Design Suite 3.5(Manipal, India). kNN methodology is used to obtain insights into the structural requirements of anticandididal agents which can be useful in the improvement of anticandididal selectivity. Alignment based on atom overlapping was adopted for aligning all molecules in the series. The derived 3D-QSAR kNN model for different chemical series reported as anticandididal agents give insight into the influence of various interactive fields on the activity and thus aid in designing and forecasting the anticandididal activity of novel compounds.[5-6]

MATERIALS & METHODS

Data set

The compound derived from1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanol moiety(**Table** 1, Refer **Figure 1 & 2**) was selected from the literature[7,8] along with their in-vitro antifungal activity(MIC80) against *Candida albicans* . Three dimensional quantitative structure-activity relationship studies of these 1,2,4-triazole derivatives were carried out by using Molecular Design Suite software version 3.5. The structures of the compounds under study have been drawn in the 2D Draw app of MDS 3.5 using standard procedure. These structures were converted into 3D objects by using the default conversion procedure implemented in the MDS 3.5 software. The generated 3D- structures of the compounds were subjected to batch energy minimization in the Force field module using Merck Molecular Force Field (MMFF) and MMFF charge followed by considering distance dependent dielectric constant of 1.0 and convergence criteria of 0.01 kcal/mol . This will ensure a well defined conformer relationship across the compounds of the study[Singla & bhat, 2010]. All these energy minimized structures of respective compounds have been ported to the 3D-QSAR of QSARPLUS module (MDS 3.5) for computing the parameters corresponding to electrostatic and steric descriptor classes. As the total number of the descriptors involved in this study is very large{3762(1836 steric & 1836 electrostatic)}, only the name of the descriptor classes and the actual descriptor involved in the model have been listed. The K-nearest neighbour model with stepwise forward-backward variable selection(kNN-SFB) procedure used in developing 3D QSAR model is briefly described below.

Model development

Vlife Molecular design suite is very user friendly software[9]. A kNN-SFB is a 'filter' based variable selection procedure for model development in 3D QSAR studies. It is a procedure to examine the impact of each variable step by step. An important task in building a 3D-QSAR model is to evaluate the required descriptors for the molecules under consideration and the Vlife MDS worksheet was provided for this purpose. LogMIC80 was selected as a dependent variable whereas electrostatic and steric descriptors were selected as independent variables. Electrostatic & steric field were computed with dielectric contant 1.0, Gasteiger marsili charge, energy cut off(electrostatic 10.0 Kcal/mol; Steric 30 Kcal/mol) on an existing grid. A total of 3672 descritors were generated via this procedure. MIC 80 of all molecules opted as dependent variable and all descriptors were selected as independent variable. Manual method was adopted as training data set selection method. 44 molecules manually put under training set and 6 molecules under test set(TCA5n, TCA5o, TCA5p, TCA6a, TCA6b, TCA6c). For generation of 3D-QSAR model, advanced method kNN method with forward backward stepwise variable selection strategy to result in selected subset regressions for the extraction of diverse structure- activity models. The 'filters' set in kNN-SFB are intended at (i) cross- correlation limit as 1.0, (ii) F test in[4.0] and out[3.00], (iii) No. of variables in the final equation[9], (iv) r^2 as term selection criteria, (v) 0.5 as variance cut off with autoscaling, (vi) No. of maximum neighbours as 5.0, (vii) No. of minimum neighbours 2.0, (viii) Most active +ve ,(ix) distance based weighted average as prediction method. All

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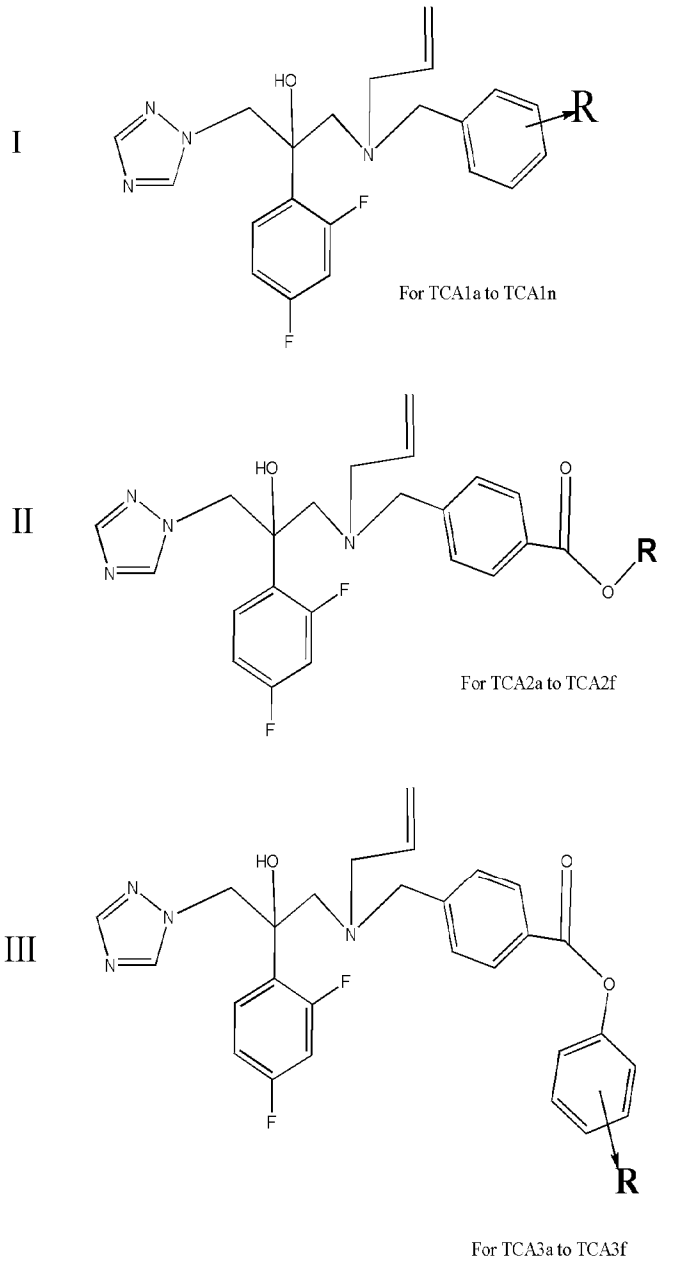

Figure 1: General Structure of 1,2,4-Triazole Analogs

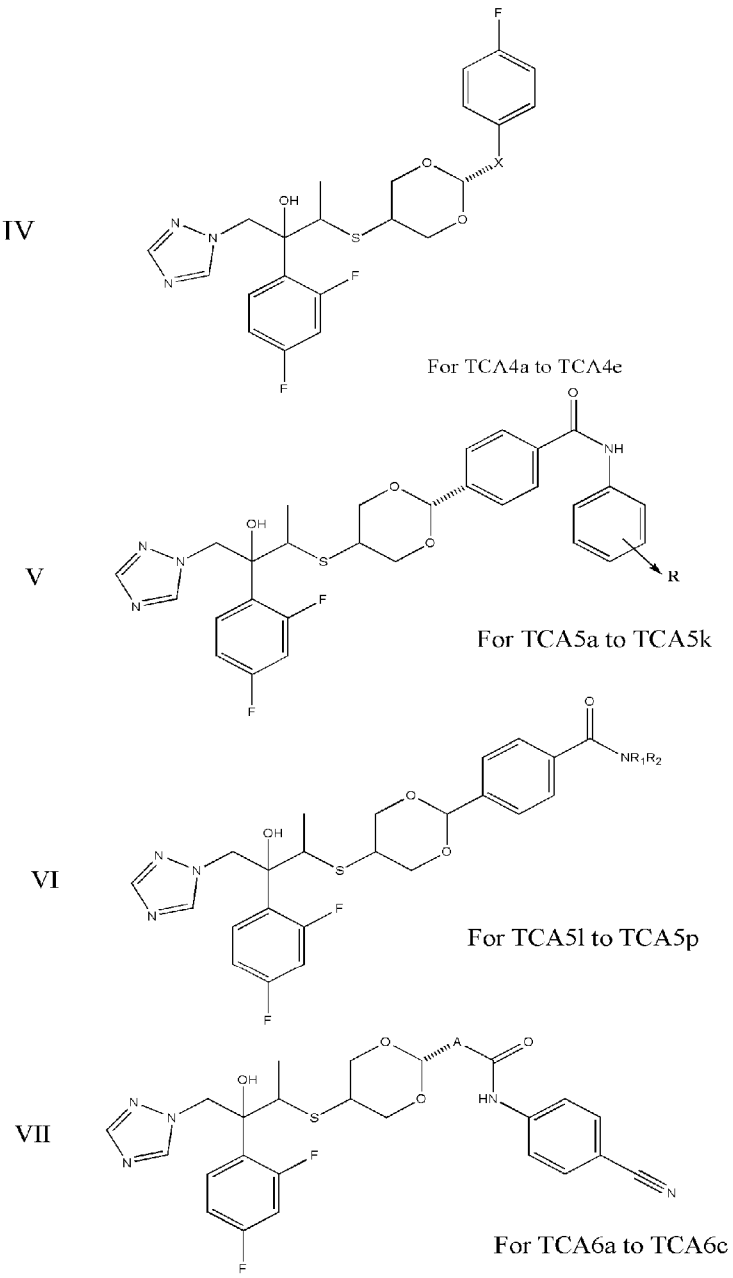

Figure 2: General Structure of 1,2,4-Triazole Analogs

these filters make the variable selection process efficient and lead to unique solution. After the completion of this process, the fitness plot for training and test set were viewed and model summary was evaluated. The kNN-SFB protocol has been applied with default filter thresholds to identify all possible models that could emerge from the descriptors of the compounds and the best out of all was explained here. In addition to this, Isosurface and contours were designed using electrostatic potential. As hydrophobicity was always an important parameter in every studies, isosurface and plane(X-axis & Z-axis) were also plotted.

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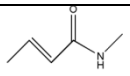
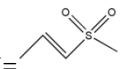
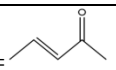
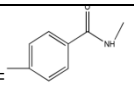
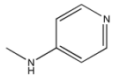
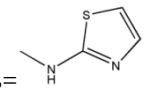
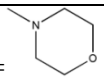
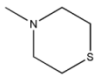
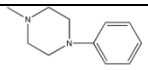
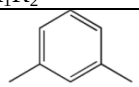
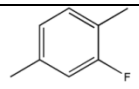
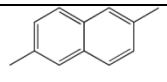
Data Code	R^1	Data Code	X^2
TCA1a	H	TCA4a	X= 
TCA1b	2-F	TCA4b	X= 
TCA1c	3-F	TCA4c	X= 
TCA1d	4-F	TCA4d	X= 
TCA1e	2-Cl	TCA4e	X= 
TCA1f	3-Cl	TCA5a	R= 4- Cl
TCA1g	4-Cl	TCA5b	R= 4- Br
TCA1h	2-Br	TCA5c	R= 4-Me
TCA1i	4-Br	TCA5d	R= 4-CN
TCA1j	2-CH_3	TCA5e	R= 4-Ac
TCA1k	4-CH_3	TCA5f	R= 4-OH
TCA1l	4-NO_2	TCA5g	R= 4-$OCH_2CF_2CHF_2$
TCA1m	4-CH_2CH_3	TCA5h	R= 4-SCF_3
TCA1n	2-Cl, 4-Cl	TCA5i	R= 3,4-$(CN)_2$
TCA2a	CH_3	TCA5j	R= 3-Cl, 4-CN
TCA2b	CH_2CH_3	TCA5k	R= 2-F, 4-CN
TCA2c	$CH(CH_3)_2$	TCA5l	NR_1R_2= 
TCA2d	$(CH_2)_3CH_3$	TCA5m	NR_1R_2= 
TCA2e	$CH_2CH(CH_3)_2$	TCA5n	NR_1R_2= 
TCA2f	$(CH_2)_4CH_3$	TCA5o	NR_1R_2= 
TCA3a	H	TCA5p	NR_1R_2= 
TCA3b	3- NO_2	TCA6a	A= 
TCA3c	4-NO_2	TCA6b	A= 
TCA3d	4-Cl	TCA6c	A= 
TCA3e	2-$COOCH_3$		
TCA3f	4-$COO(CH_2)_3CH_3$		

Table 1 1-(1H-1,2,4-triazole-1-yl)-2-(2,4-difluorophenyl)-3-substituted-2-propanols against Candida albicans. R1-Substitutions in the structure given in figure 1; X2- Substitutions in the structure given in figure 2. Taken for reference 7 & 8.

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RESULTS & DISCUSSION

In the current study, a 3D-QSAR model is presented for $logMIC_{80}$ of fifty 1,2,4-triazole anticandididal agents involving theoretical decsriptors, which have been calculated from the molecular structure. For the selection of the most important descriptors, the aforementioned stepwise forward backward kNN technique was used.

Selected descriptors after model building were E_948, S_818, S_799, S_1236, S_1031. The model summary was as follows:-

K nearest neighbor : 2

N = 44

Degree of freedom = 38

Q^2 = 0.8650

Q2_se = 0.2944

Predr2 = -0.0059

Pred_r2s = 2.0878

The descriptors range in 3D-QSAR model was summarized below.

E_948 (-0.0469 to 0.0884)

S_818 (-0.3564 to -0.3420)

S_799 (-0.4382 to -0.4215)

S_1236 (-0.2453 to -0.0854)

S_1031 (30.0000 to 30.0000)

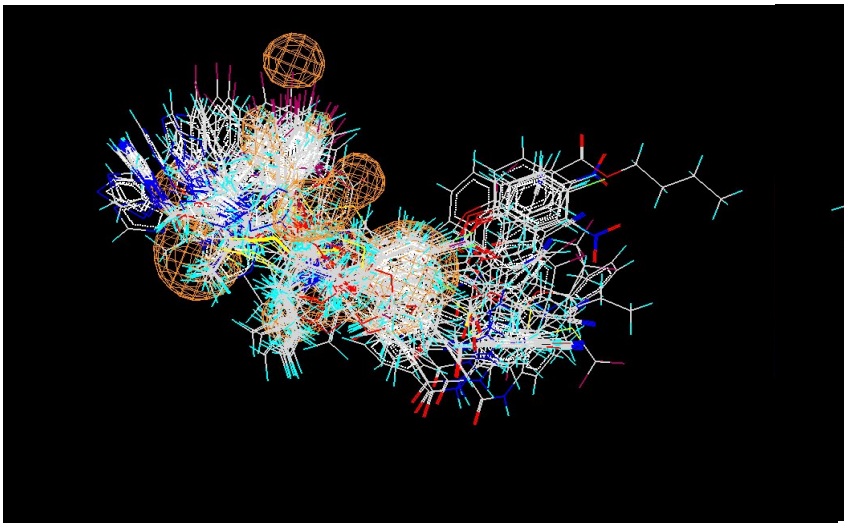

Figure 3 Electrostatic Potential of 1,2,4-Triazole Molecules

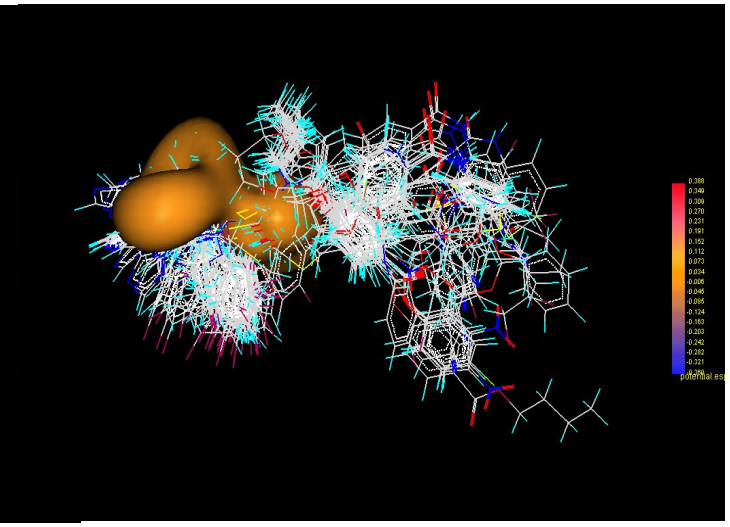

Figure 4 Hydrophobic Surface of 1,2,4-Triazole Molecules

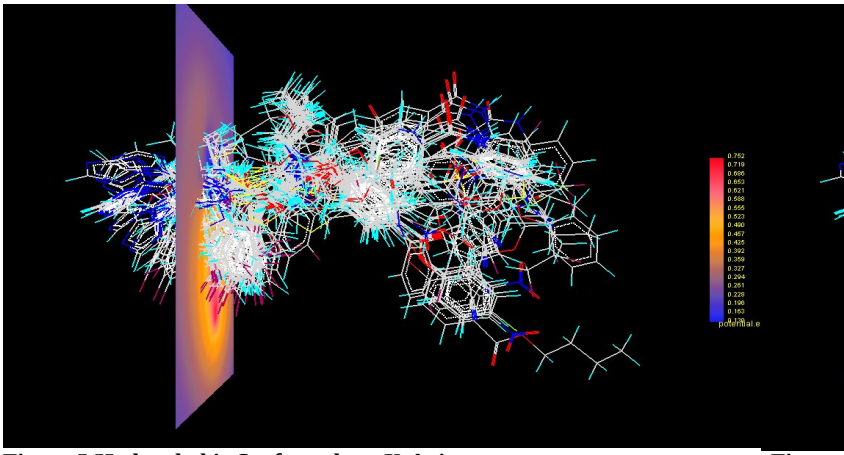

Figure 5 Hydrophobic Surface along X-Axis

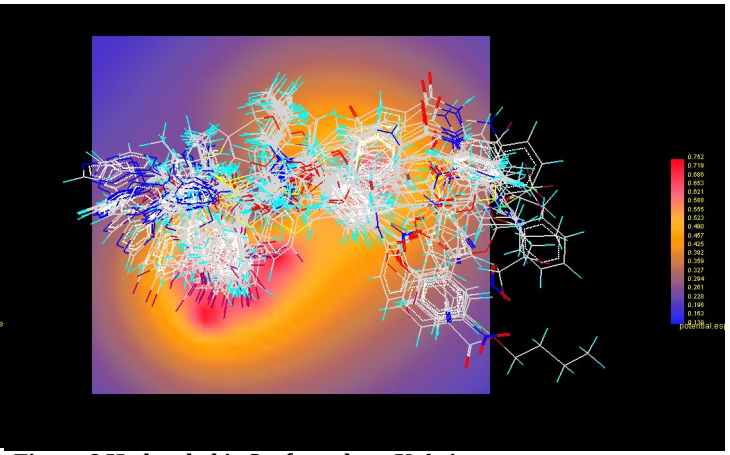

Figure 6 Hydrophobic Surface along Y-Axis

As can be observed by this model, steric parameters were more effective in building 3D-QSAR model than that of electrostatic parameters. From statistical point of view, this is a robust model. Cross validation (q2) was performed on the

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training group (44) and showed that 86.50 % of 44 compounds i.e. 38 were correctly classified. Electrostatic potential of various molecules were well displayed using contour maps(**Figure 3**) and resembling the various regions having high positive and negative electrostatic potential.

Hydrophobicity though not involved in the 3D-QSAR, always having hidden role in the activity. Hydrophobic area were elucidated using isosurface(**Figure 4**) and along X-axis & Y-axis(**Figure 5 & 6**). Finally the 3D-QSAR equation was designed and all the statistical parameters generated after model development were shown above.

The main objective of this study was to build a 3D-QSAR model which enables us to identify antifungal compounds from molecular databases using stepwise forward-backward KNN method. All these results confirm the effectiveness of the steric and electrostatic model proposed here for the search and selection of new potential antifungal drugs against *Candida albicans*. In this work we presented a valid model for the prediction of the antifungal activity of potential molecules against *candida albicans*.

CONCLUSION

Our results lead to the conclusion that triazoles can be successfully modeled with the steric & electrostatic descriptors. The separation of the data into two independent sets(Training & Test Set) shows that our KNN model can predict external data with great accuracy. The proposed methods can be used to screen existing databases or virtual libraries in order to identify novel potent compounds.

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