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G-QSAR studies of novel 1,2,4 triazolo [3,4-b]-1,3,4-thiadiazole derivatives

Mayura A. Kale* and Kirtee G. Baheti

Department of Pharmaceutical Chemistry, Government College of Pharmacy, Osmanpura, Aurangabad, Maharashtra, India

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ABSTRACT

In the present work, we have studied group quantitative structure–activity relationship (G-QSAR) to understand the correlation between the structures of a new emerging family of 1,2,4-triazolo [3,4-b]-1,3,4-thiadiazole derivatives and their antifungal activities. We have developed descriptive validated models, for development of newer antifungal agents containing the thiadiazole linked triazole pharmacophore. These studies have been performed on V-Life molecular design suite (MDS) software. For model validation, the dataset was divided into various training and test sets using sphere exclusion method. The developed G-QSAR models were found to be statistically significant with respect to training (r^2>0.7), cross-validation (q^2>0.5), and external validation (pred_r^2>0.5). The developed G-QSAR model suggests that the nature of substitution on one of the aryl fragment is highly influential in determining biological activity.

Keywords: G-QSAR, Thiadiazole, Triazole, Antifungal, Model generation.

INTRODUCTION

Various computational approaches to search the lead molecules have been widely used to accelerate the drug discovery process. Some of these approaches include Hansch method, Free-Wilson method and conventional 2-D / 3-DQSAR methods. Among these, a new Fragment-based/Group-based QSAR (G-QSAR) methodology has shown promising results in current drug discovery and lead optimization efforts. This method provides models with predictive ability similar or better to conventional methods and in addition provides hints for sites of chemical modifications of the pharmacophore in the parent molecule [1]. G-QSAR provides descriptor evaluation only for the substituent groups or molecular fragments rather than for whole molecule. In addition, cross terms are calculated from product of descriptors at different substituent sites or fragments and used as descriptors to improve the QSAR models. The descriptor range for substituents or fragments are used to search for new groups or fragments; respectively leading to design of novel molecules with improved activity and / or physicochemical properties [2]. Recently, many successful applications of G-QSAR for lead optimization have been reported [3]. G-QSAR developed models provide hints about the impact of each fragment on variation in biological activity. Thus, the interpretation of G-QSAR models to develop new molecules is a more practical and achievable task compared to 2D and 3D QSARs [4, 5].

Among the several diseases occurring worldwide, microbial infections are gaining an upper hand due to the resistance offered to the current traded drugs. This has been attributed to the rapid mutations occurring in the microbial fraternity. One of such microbial infection hitting the third world countries is that caused by fungi. The recognition and importance of fungal infections, the difficulties encountered in their treatment and the increase in resistance to anti-fungal drugs have stimulated the search for various therapeutic alternatives [6,7]. These factors have led to the development and marketing of new drugs, but most of them have similar pharmacologically active groups and mechanisms of action as those that were commercially available previously. Therefore, the search for discovery of new antifungal agents is necessary and this stimulates the search for newer chemotherapeutic agents

[8]. The current antifungal drug therapies suffer from drug-related toxicity, resistance and serious drug-drug interactions. This has triggered the need for new generations of broad spectrum antifungal drugs with selectivity and solution for multi-drug resistance problems [9]. Hence, we thought it worthwhile to attempt G-QSAR modelling studies of the some novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles derivatives which have been reported in literature. The synthesized derivatives have displayed potent and selective antifungal activity. Pursuing these research consequences, we have performed G-QSAR study on these derivatives. The aim of the study was to identify the molecular descriptors that influence the antifungal activity [10].

MATERIALS AND METHODS

Data Set

A total of 24 substituted triazolothiadiazoles derivatives have been reported to exhibit antifungal activities [11]. These were used as the data set in QSAR analysis. The IC50 (μM) values reported in the literature were used for QSAR study as shown in Table 1.

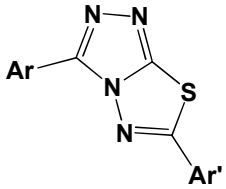
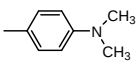
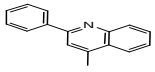
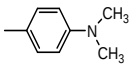
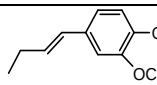
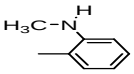
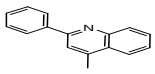
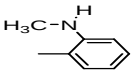
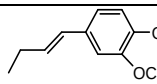
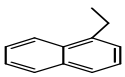
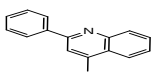
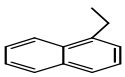
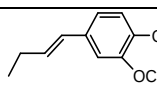
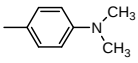
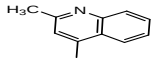
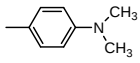
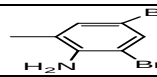
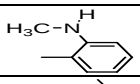
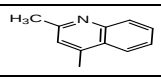
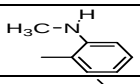
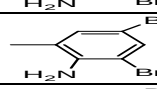
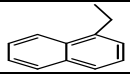
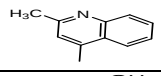
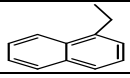
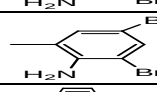
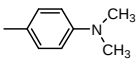
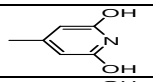
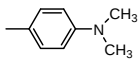
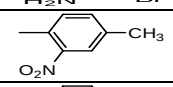
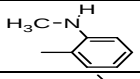
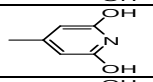
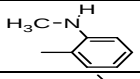
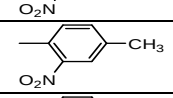
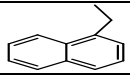
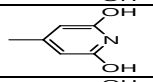
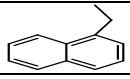
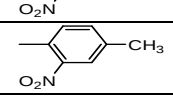
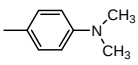
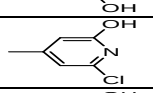
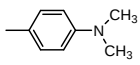


Fig. 1: Basic Moiety

Table 1: Chemical and biological data of 1,2,4-triazolo[3,4-b]-1,3,4thiadiazoles derivatives

Comp. No.	Ar	Ar'	IC_{50} value (OA)	Comp. No.	Ar	Ar'	IC_{50} value (OA)
4a			5.36	8a			2.58
4b			4.71	8b			1.92
4c			4.73	8c			1.88
5a			5.21	9a			1.03
5b			4.56	9b			0.37
5c			4.56	9c			0.41
6a			4.54	10a			2.06
6b			3.88	10b			1.38
6c			3.90	10c			1.43
7a			5.13	11a			6.22
7b			4.47	11b			5.60
7c			4.47	11c			5.58

Molecular Structure Generation

The structures of the reported molecules were drawn in the 2D draw application of Molecular Design Suit (MDS) software. Then these 2D structures were converted in to 3D structures by exporting in to QSAR Plus window. After the conversion, structures were subjected to energy minimization with the help of MMFF force field and optimized

molecules were used to calculate the physicochemical and alignment descriptors.

Fragmentation of molecule

The fragmentation of drug has been used for some time to simplify the computational analysis of ligand binding and to map out different pharmacophoric elements required for high-affinity binding. The concept of this approach is simple in that proper optimization of each unique interaction in the binding site and subsequent incorporation into a single molecular entity should produce a compound with a binding affinity that is the sum of the individual interactions. So, in order to effectively use fragments in drug design, an experimental method was required that could rapidly and reliably screen thousands of low-molecular-mass test compounds for weak (millimolar range) binding to the target protein [12].

Selection of Training and Test Set

The 24 molecules were divided into the training set (18 molecules) and test set (6 molecules) by sphere exclusion (SE) method with a dissimilarity value of 13.8 and pIC50 activity field as dependent variable and various 3D descriptors calculated for the compounds as independent variables. Selection of molecules in the training set and test is a key and important feature of any QSAR model. SE is a rational selection method which takes into consideration both biological and chemical space for division of dataset dissimilarity value used to vary train/test set size. It needs to be adjusted by trial and error for desired division of train and test set. As a rule, increase in dissimilarity value will lead to increase in number of molecules in the test set.

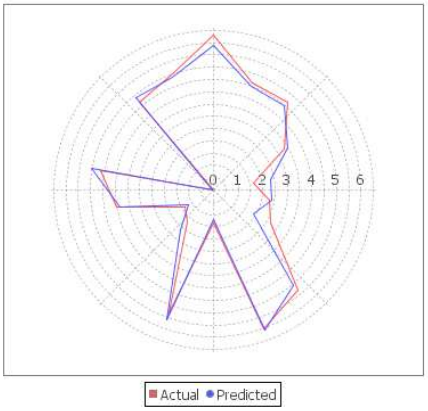
Group-Based QSAR

In G-QSAR analysis, all the methods distributed the compounds in training set of 18 derivatives and test set of 6 derivatives. Different statistical methods like multiple linear regression (MLR)[13], partial least squares regression (PLS) and principal component regression (PCR) [14] were employed for model building. The G-QSAR methodology allows ease of interpretation of specific site where it has to be optimized for design of new molecules [15]. In G-QSAR, fragmentation is done by applying specific chemical rules for breaking the molecules along specific bonds and/or bonds on ring fusion and/or any pharmacophoric feature such as hydrogen bond acceptor, hydrogen bond donor, hydrophobic group, charged group, and so forth. Group-based descriptors were calculated for various groups present at different substitution sites of the molecules (Fragments Ar and Ar') [16]. The various derivatives of 1,2,4-triazolo[3,4-b]-1,3,4thiadiazoles belong to the parent skeleton shown in Fig. 1.

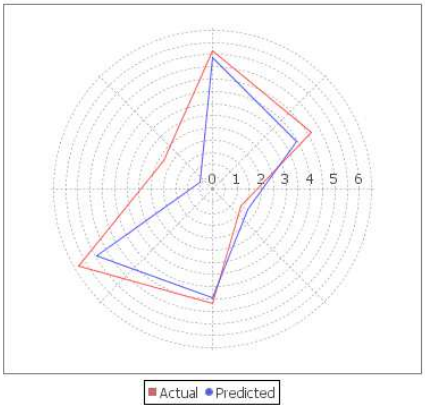
RESULTS AND DISCUSSION

Thus, G- QSAR model was developed according to MLR, PLS and PCR using genetic algorithm method and simulating annealing method. As the former method resulted in better predictability, the contribution of descriptors in all these methods have been considered [17].

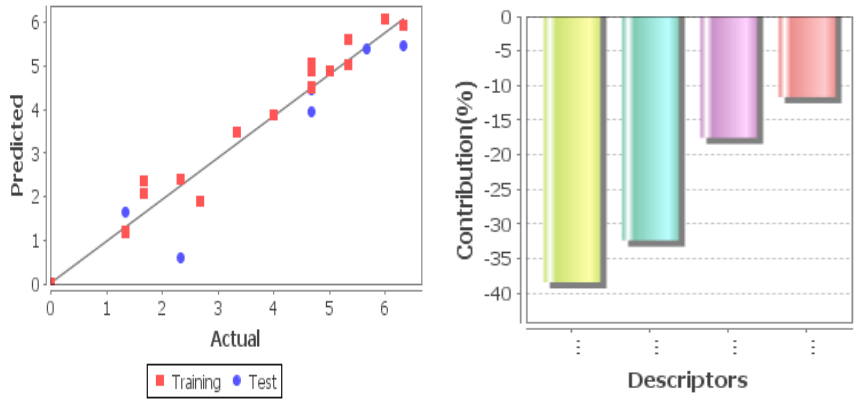
Model 1



Training Set



Test Set



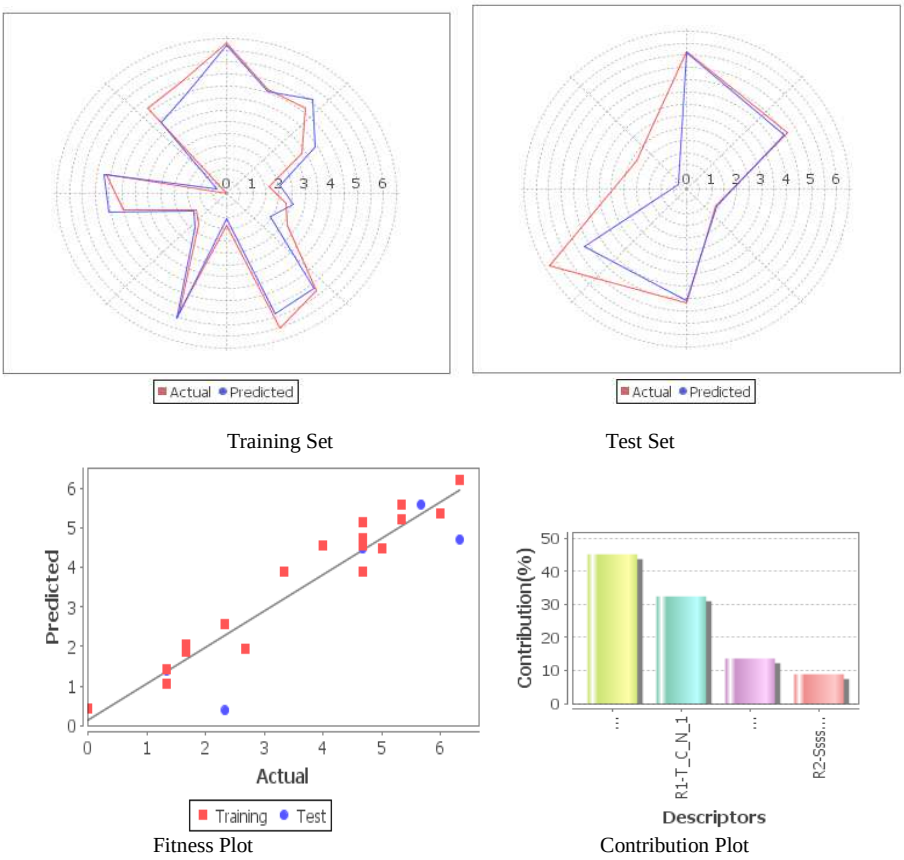
Fitness Plot Contribution Plot

Fig. 2: Model 1 (MLR method)

Equation

PIc50 = -5.2289 R1-XKMostHydrophobic +-2.0152 R1-BalabanIndexJ +-62.4656+ R2-DeltaEpsilonB +-89.0742 R1-AveragePotential +13.1321 (constant) .The equation explains ~96% (r2 = 0.9671) of the total variance in the training set and has an internal (q2) and external (pred_r2) predictive ability of ~93% and ~78%; respectively with the Fcal value 13 shows the statistical significance of 99.99% of the model. It means that probability of failure of the model is 1 in 10000. In addition, the randomization test shows confidence of >99.99% (Alpha R and R2=0.05000) and that the generated model is not random and hence is chosen as the QSAR model as shown in Fig. 2.

Model 2



Training Set Test Set

Fitness Plot Contribution Plot

Fig. 3: Model 2 (PCA method)

Equation

PIc50 = 47.6479 R1XAHydrophillic area+ 1.3918R1 R1-T_C_N_1+ 13.8289R1SAAverage +0.3142R2-SsssNE-index +-0.0178(constant). The equation explains ~94 % (r2 = 0.9439) of the total variance in the training set and has an internal (q2) and external (pred_r2) predictive ability of ~91% and ~68%; respectively. The Fcal value of 54 shows the statistical significance of 99.99% of the model. It means that probability of failure of the model is 1 in 10000. The summary of models with statistical parameters is depicted in Table 2. In addition, the randomization test

shows (Alpha R and R2=0.0000) and that the generated model is not random and hence is chosen as the QSAR model as shown in Fig. 3.

Table 2: Summary of best two models developed along with statistical parameters

Method	r2	q2	F test	Pred r2	Variable selection &Coefficient
MRM	0.9671	0.9355	95.6800	0.7815	R1-XKMostHydrophobic (-5.2289) R1-BalabanIndexJ(-2.0152) R2-DeltaEpsilonB(-62.4656) R1-AveragePotential(-89.0742) **Constant:** 13.1321
PCA	0.9439	0.9104	54.6789	0.6871	R1-XAMostHydrophilic (47.6479) R1-T_C_N_1(1.3918) R1-SAAverage(13.8289) R2-SsssNE-index(0.3142) **Constant:** -0.0178

From the above mentioned data, it can be seen that the multiple regression (coupled with forward variable selection) has led to a statistically significant G-QSAR model. This model state that the descriptor R1-XK Most Hydrophobic at Ar' position plays most important role (~38%). Another descriptor affecting biological activity is the R1-Balaban IndexJ(~34%) at Ar' position. The R2-DeltaEpsilonB (~17%) is also related to the biological activity at Ar position. Also, the presence of descriptor R1-AveragePotential (~14%) confirms the role of -ve electrostatic potential on Van der Waals surface area of the molecule at Ar' substitution site in determining activity. All these descriptor are inversely proportional to the biological activity.

From the above observations, the model 2 reveals that it is a statistically significant G-QSAR model by using principal component regression (coupled with forward variable selection). The developed G-QSAR model states that the descriptors such as R1-XAHydrophilicArea (~45%) and R1-T_C_N_1(~33%) are directly proportional to the antifungal activity. All the above mentioned descriptors influence activity at Ar' substitution site. Finally, R2-Ssss NE-index (9%) reveals the activity at Ar position.

CONCLUSION

In this paper, we have successfully constructed a predictive G-QSAR model on thiadiazole linked triazole nucleus. All the generated models exhibit excellent predictive ability which is established by the theoretical and test set validation. The analysis of the model suggests that the increase in number of electron withdrawing groups at Ar' position as per model1 and by increasing hydrophilic area at Ar' position as per model 2 increases antifungal activity. Hence, the generated models can be considered to be important tools for designing of newer antifungal drugs.

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