A QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP STUDY OF AZOLE DERIVATIVES WITH ANTIFUNGAL ACTIVITY

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ABSTRACT

It was reported that some 3-amino 2-aryl-1-azolyl-2-butanol have antifungal effects. To understand the structural basis for antifungal activity and guide in the design of more potent agents, we performed quantitative structure activity. The Minimum Inhibitory Concentration (MIC) values of 3-amino-2-aryl-1-azolyl-2-butanol on yeast exhibited a strong correlation with the prediction made by the model developed in the present study. The statistical results of the Training Set, Regression coefficient r (0.841648) and r² (0.708371) values gave reliability to the prediction of inhibitory activity of a series of Azole derivatives.

Key words: *Anti-fungal, Azole, Quantitative Structure Activity Relationship.*
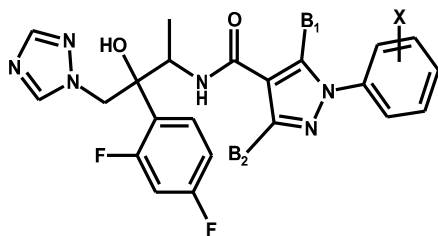
INTRODUCTION

Azole antifungal agents are widely used for the treatment of topical or internal mycoses[1-4]. Llife-threatening fungal infections frequency and different types have been increasing in immunocompromised patients such as people affected with AIDS, bone marrow and organ transplant and cancer patients[5,6]. Azole antifungal agents prevent the synthesis of ergosterol, a major component of fungal membranes by inhibiting the Cytochrome P-450 dependent enzyme 14 α-lanoesterol demethylase (CYPS)[7-8]. This enzyme contains an iron protoporphyrin unit located in its active site, which catalyzes the oxidative removal of the 14 α-methyl group of lanosterol by typical mono oxygenase activity[9]. Due to an increase mycotic infections and frequent accounts of resistance there has been an interest in developing new effective antifungal agents with novel mode of action. To understand the structural basis for the antifungal activity and to guide in the design of more potent compounds, we performed quantitative structure-activity relationship studies.

MATERIAL AND METHODS

The molecular structures of all Azole derivatives were constructed in WORKSPACE system in CAChe software (6.1version). The Molecular structures were subjected to Geometry Optimization by choosing "Standard procedure" from the menu option to get corresponding minimum energy structure. In this experimental aspect of QSAR study we searched the most stable conformation and its corresponding energy values of the drawn compounds. After Geometry Optimization the energy minimized structures were brought in PROJECT LEDER and different physicochemical parameters were evaluated. Regression analysis and Calculations were run on a PC by using SYSTAT software package.

Series: 3- amino-2-aryl-1-azolyl-2-butanol
Template selected for QSAR Studies

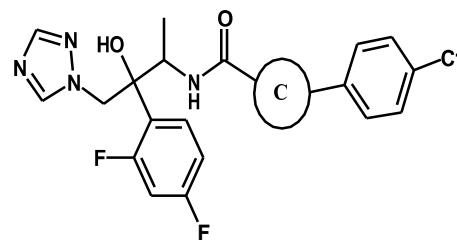**Pyrazole**

(Fig. 1)

The C Ring: Pentaheterocycles

(Fig. 2)

Training set and Test set data were randomly divided into a Training set 22 and Test set of 4. QSAR model development and validation is done by Multiple Linear Regression Stepwise (MLR) analysis is performed with Leave-one-out (LOO) cross validation technique was applied to Training set. F-to-enter and F-to-leave values were both 4. Model with the number of descriptor greater than 5, F-ratio higher than 20, and cross validation r^2cv greater than 6, F-ratio higher than 20 and correlation coefficient R higher than 0.8 between the predicted and the experimental antifungal activities was validated using Compounds of test set. Molecular Descriptors included in the model are Molecular Volume, Ellipsoidal Volume, Total Dipole moment, Log P, Total Lipole and Molecular refractivity.

QSAR équation

**MIC : Y = 0.66623396*X1 +
0.0082175275*X2 + 1.173947*X3
+ 1.2633812*X4 - 5.414907*X5 -
2.1313353*X6 + 119.03123**

Where,

X1: Molecular Volume.
X2: Ellipsoidal Volume.
X3: Total Dipole Moment.
X4: Log P.
X5: Total Lipole.
X6: Molecular refractivity.

RESULTS

Regression coefficient, r : 0.841648, r^2 : 0.708371, n:22.The MIC values (μg/ml) and structures of compounds of series are shown in Table: 1. The plot of the predicted versus the actual activity values of the MIC of compounds against yeast using the best QSAR equation is shown in Fig 3. The comparison between the experimental (Actual) and predicted activities of compounds for training set is shown in Table (2). The model has good predictive power according to the statistical result (r: 0.841648, r^2: 0.708371, n=22). The goodness of the structure activity correlation was estimated by r^2 (r^2: 0.708371).

Table 1: The MIC values (μg/ml) and structures of compounds 3-amnio-2-aryl-1-azolyl-2-butanol of Javier Bartrdi et al.[10], were used for QSAR studies
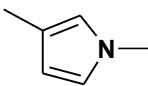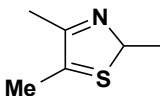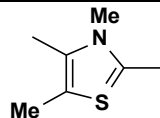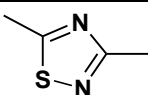
Compound No.	B_1	B_2	X	C	MIC (μg/ml) yeast
1	Me	H	4-Cl		1.8
2	H	H	4-Cl		1.9
3	n-pr	H	4-Cl		1.9
4	i-por	H	4-Cl		3.3
5	C-pr	H	4-Cl		1.8
6	t-But	H	4-Cl		4.6
7	CF_2	H	4-Cl		1.2
8	CF_2	H	$4\text{-}CF_3$		1.8
9	NH_2	H	$4\text{-}CF_3$		2.7
10	Me	H	4-Br		2.0
11	NH_2	H	$4\text{-}CF_3$		3.3
12					6.2
13	Me	H	4-OMe		6.1
14					8.0
15					1.8
16					2.6
17	Me	H	$4\text{-}OCF_3$		1.7
18	Me	H	$4\text{-}CF_3$		4.6
19	Me	H	$3\text{-}CF_3$		5.3
20	Me	H	2, 4-diF		2.1
21	Me	H	2, 6-diCl		1.9
22	Me	H	3,5-diCl		1.0

Table 2: The comparison between the Experimental and Predicted activities of compounds for Training set

Compound No.	Experimental MIC µg/ml	Predicted MIC µg/ml
1	1.8	-3.64717
2	1.9	9.71139
3	1.9	6.69682
4	3.3	7.06014
5	1.8	14.2395
6	4.6	4.08313
7	1.2	5.37705
8	1.8	8.64402
9	2.7	1.55897
10	2	18.6701
11	3.3	13.281
12	1.2	2.95749
13	6.1	2.33017
14	80	59.2266
15	2.6	5.96344
16	11	13.7902
17	2.6	1.63015
18	1.7	1.62639
19	4.6	7.41469
20	5.3	5.66
21	21	8.52749
22	19	27.9899

The plots of the Predicted versus the Actual activity values for the series
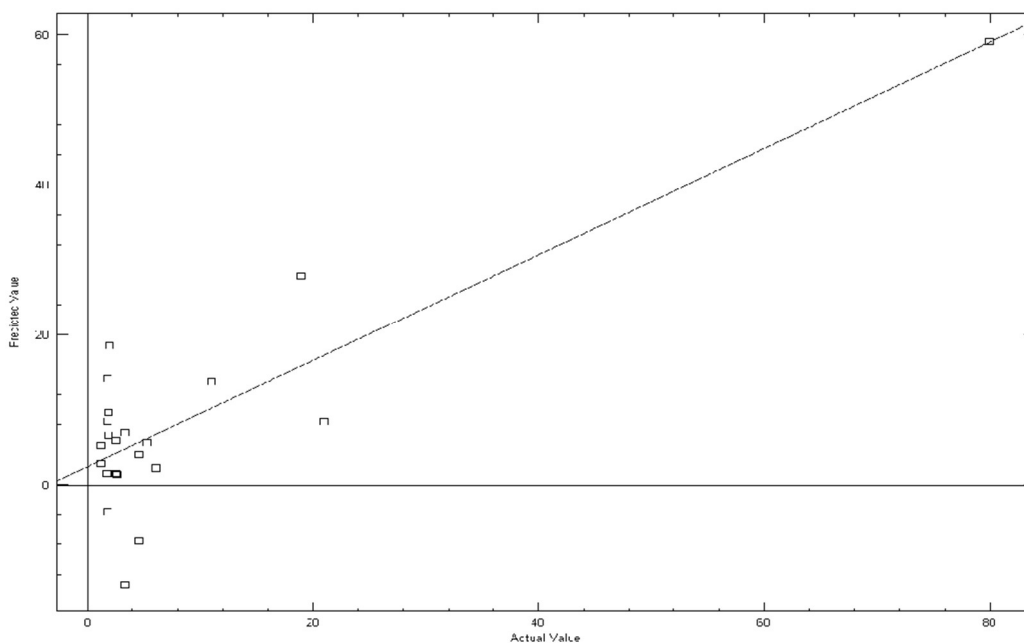
(Fig. 3)

CONCLUSION

Ellipsoidal Volume is related to shape of molecule and is positively correlated to the activity. Total Dipole Moment and Log P, which are electronic and physiochemical descriptor has also got positive correlation with respect to activity. Total Lipole and Molecular Refractivity are negatively correlated. Molecular Refractivity is combination of Molecular Volume and Polarizibility which again related to molecular weight, while Lipole is Atomic Lipophilicity. So this equation clearly says that there is a subtle balance between Log P and molecular volume and which must be properly controlled in order to get superior MIC values.

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