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2D-QSAR STUDY ON SOME NOVEL 6-ACETYL-3-[3-CHLORO-2-(SUBSTITUTED)-4-OXOAZETIDIN-1-YL]-2, 5-DIPHENYL-2, 3-DIHYDROPYRIDINE-4-CARBONITRILE ANALOGUES AS AN ANTIFUNGAL ACTIVITY

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Abstract:
A series of 6-Acetyl-3-[3-Chloro-2-(Substituted)-4-Oxoazetidin-1-yl]-2, 5-Diphenyl-2, 3-Dihydropyridine-4-Carbonitrile were screened for their antifungal activity against fungi Candida albicans. These compounds have showed moderate and very good antifungal activity. The Quantitative Structure Activity-Relationships (QSAR) study on the pyridine series was made using lipophilic, electronic and steric parameters. Several statistical expressions were developed and best models were validated. The studies confirm that the antifungal activity is dependent on selected lipophilic and electronic parameters. The study suggests that substitution on R_1 group with increasing lipophilic nature and decreasing electronic factor favorable for antifungal activity. The QSAR study provides important structural insights in designing of potent antimicrobial agents.

Key Words: *QSAR, antifungal agents, pyridine, multiple linear regressions*

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INTRODUCTION:

The development of new antibacterial agents has been a very important step for researchers. Most of the research programme efforts are directed toward the design of new drugs, because of the unsatisfactory status of present drugs side effects and the acquisition of resistance by the infecting organisms to present drugs. The resistance of common pathogens to standard antibiotic therapy is rapidly becoming a major health problem throughout the world [1,2]. There is real perceived need for the discovery of new compounds endowed with antifungal property. The responsible organisms and methods of prevention and treatment differ with each group. The prevalence of systemic fungal infections has increased significantly during the past decade [3].

This increase is due to greater use of broad-spectrum antibiotics, In the past 10 years there has been a major expansion in the development of antifungal drugs, but there are still weaknesses in the range and scope of current antifungal chemotherapy [4,5]. New developments have included the modification of existing drug molecules to eliminate toxicity and improve activity [6]. In short, antifungal therapy has advanced rapidly in the last few years compared to previous years and recommendations for treatment of fungal infections are likely to change in the near future as our understanding of fungal infections improves and new antifungal therapies are discovered [7]. The investigation of the quantitative structure activity/property relationships (QSAR/QSPR) of substances is an important aspect of modern chemistry, biochemistry, medicinal chemistry, and drug discovery.

The information obtained is composed of mathematical equations relating the chemical structure of the compounds to a wide variety of their physical, chemical, biological and technological properties. Once a correlation between structure and activity/property is found, any number of compounds, including those not synthesized yet, can readily be screened in silico for selection of structures with desired properties. Hence, it is possible to select the most promising compounds for synthesis and testing in the laboratory [8,9]. An extra thermodynamic approach in the analysis of quantitative structure activity relationships (QSAR) has been most widely and effectively used for theoretical drug design. This method has also been called the Hansch approach and it assumes that the potency of a certain biological activity exerted by a series of congeneric compounds can be expressed in terms of a function of various physicochemical (electronic, steric and hydrophobic) effects [10-12].

This assumption is summarized in an equation as follows: f (biological activity) =f (electronic) +f (steric) +f(hydrophobic) +[f (structural) +f (theoretical)] If these functions could be formulated in an equation showing ccertain effects favorable for the activity, structural modifications that enhance such properties would be expected to generate potent active compounds.

RESULT AND DISCUSSION:

The synthesized molecules were screened for antifungal activity. The biological activity data MIC (Minimum Inhibitory Concentration) was converted to negative log dose in moles (pMIC) for QSAR analysis. The data set was subjected to stepwise MLR analysis, in order to perform QSAR analysis between antibacterial activity as dependant variable and substituent constants as independent variables, several equations were obtained. The regression analysis of antibacterial data and physicochemical descriptors, statistically significant equation with coefficient of correlation (r^2 =) was obtained as model for antifungal activity in *Candida albicans*.

The antifungal activity against *Candida albicans* according to QSAR equation 1 is dependent on logP, molar refractivity and index of refraction. Among the three descriptors studied; molar refractivity has more potency, index of refraction has moderate potency and log P has minimum potency. The logP value is a property of lipophilicity. The property indicates the lipid solubility and affinity of compounds toward lipid. The lopP value has positive correlation with the activity; this indicates that the substituents which decrease solubility in water will lead to increased activity. The decrease in solubility in water or increase in the lipophillic nature of compounds will lead to increased penetration of the compounds across the cell wall.

The molar refractivity is a steric parameter that is dependent on the spatial array of the aromatic ring in the synthesized compounds. The spatial arrangement also is necessary to study the interaction of the ligand with the receptor. The molar refractivity is positively correlated with the activity against *Candida albicans*. This indicates that the arrangement of the aromatic rings present on the pyridine ring should be far for the activity to be maximum.

The index of refraction of compounds is negatively correlated with the activity and decreases in the index of refraction of molecules might be responsible for the kinetics or dynamics of the compounds inside the fungal cell. Thus, molecule having less index of

refraction will require less energy of activation for interaction with the receptor target. Increase in activity may be achieved by substitutions favoring high lipophilic values and high molar refraction.

CALCULATED PHYSICO-CHEMICAL PROPERTIES

Table1: Showing calculation of physicochemical properties done for training set compounds

Sr No	Compounds	Log P	index of refraction	parachor	Zone of inhibition
1	**PYN1**	4.43	140.82	184.81	8.55
2	**PYN2**	4.55	133.57	349.14	8.67
3	**PYN4**	4.16	135.39	171.83	8.20
4	**PYN5**	5.16	152.56	268.87	9.33
5	**PYN7**	5.38	141.27	364	10.24
6	**PYN8**	4.04	142.64	145	7.50
7	**PYN9**	4.17	155.32	143.85	8.22
8	**PYN10**	5.04	139.47	317	9.33
9	**PYNI**	6.02	165.97	427.85	10.50
10	**PYNII**	6.15	158.72	592.18	11.22
11	**PYNIII**	6.71	163.32	564.97	11.85
12	**PYNIV**	5.76	160.53	414.87	10.28
13	**PYNV**	6.75	177.7	511.91	14.33
14	**PYNVII**	6.98	166.41	607.04	13.32
15	**PYNVIII**	5.63	167.78	250.54	10.70
16	**PYNX**	6.63	164.62	560.07	10.50

Table2: Showing calculation of physicochemical properties done for test set compounds

Sr No	COMPOUND	Log P	index of refraction	parachor	Zone of inhibition
1	**PYN3**	5.11	138.18	321.93	10.33
2	**PYN6**	4.84	148.75	363.92	8.33
3	**PYNVI**	6.43	173.9	606.96	14.83
4	**PYNIX**	5.77	180.47	405.6	12.44

DEVELOPMENT OF 2D-QSAR MODELS

Table 3: Developed 2D-QSAR Models.

Model No.	Equation	Observations	R^2	Standard Error	F
1	ZOI= -1.06+(1.77*log p)+(0.013*MR)-(0.0014*Heat of formation)	16	0.924	0.799	23.55
2	ZOI= -1.06+(1.48*log p)+(0.02*MR)	16	0.913	0.771	37.87
3	ZOI= -2.06+ (0.064*MR)-(0.006*Heat of formation)	16	0.901	0.870	28.32
4	ZOI= -0.324+(2.08*log p)-(0.0025*Heat of formation)	16	0.900	0.772	37.71

TRAINING SET

Table 4: Comparison of predicted value and observed value for training set.

Sr No	Compounds	pMIC	predicted value
1	**PYN1**	8.55	8.40
2	**PYN2**	8.67	8.29
3	**PYN4**	8.2	7.87
4	**PYN5**	9.33	9.73
5	**PYN7**	10.24	9.84
6	**PYN8**	7.5	7.79
7	**PYN9**	8.22	8.19
8	**PYN10**	9.33	9.28
9	**PYNI**	10.5	11.21
10	**PYNII**	11.22	11.12
11	**PYNIII**	11.85	12.21
12	**PYNIV**	10.28	10.70
13	**PYNV**	14.33	12.55
14	**PYNVII**	13.32	12.67
15	**PYNVIII**	10.7	10.80
16	**PYNX**	10.5	12.09

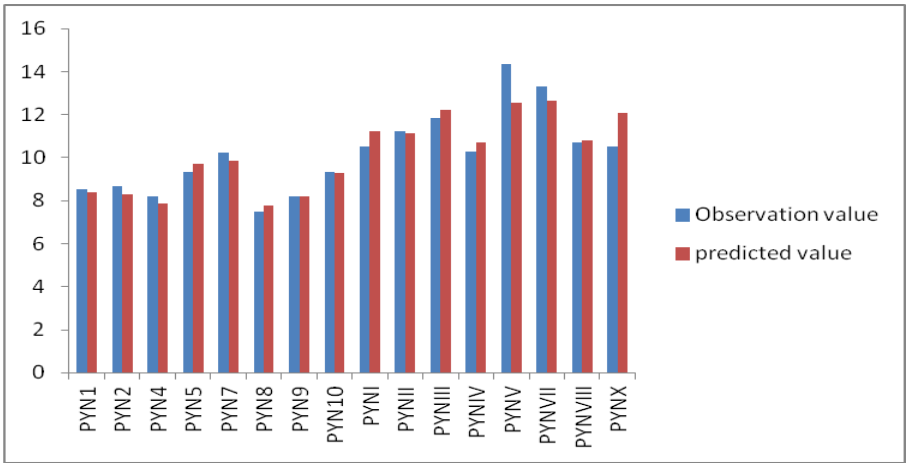

Fig.1: Chart of comparison between observed and predicted zone of inhibition for training set.

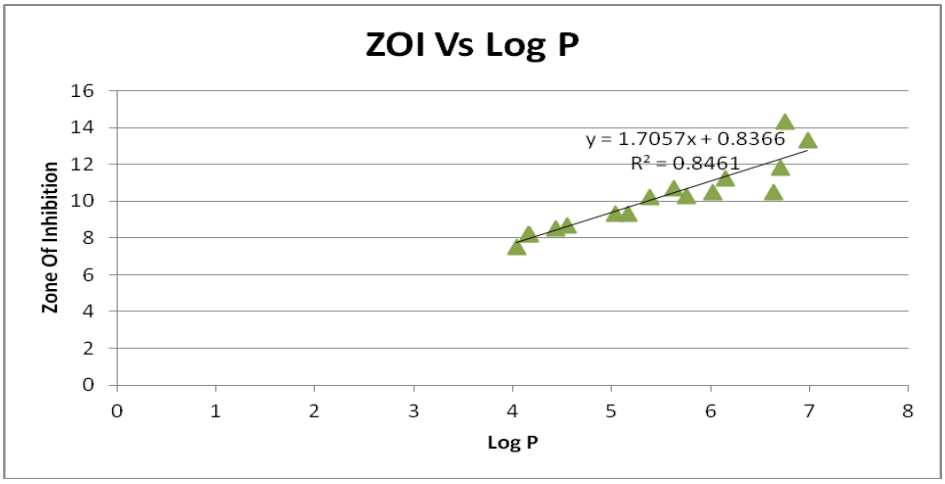

Fig.2: Chart of comparison between parameter(Log P) and zone of inhibition values for training set

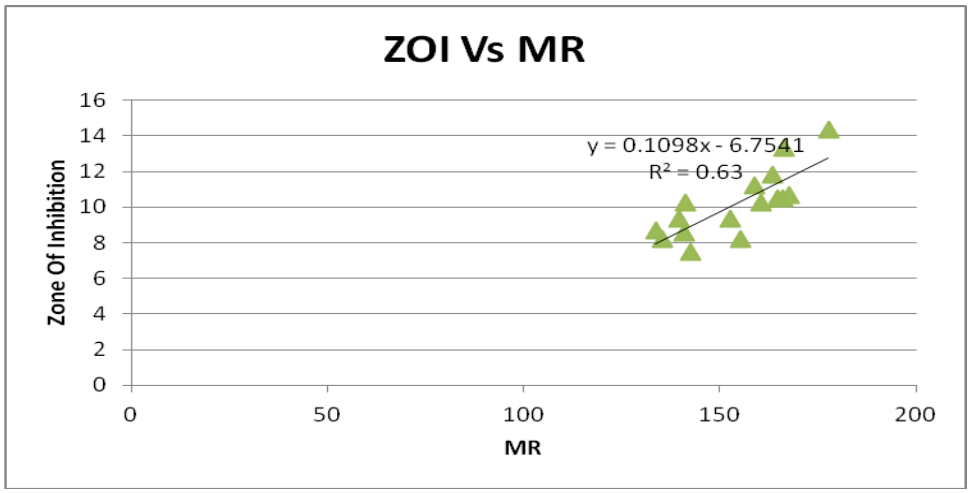

Fig.3: Chart of comparison between parameter (Molar refraction) and zone of inhibition values for training set

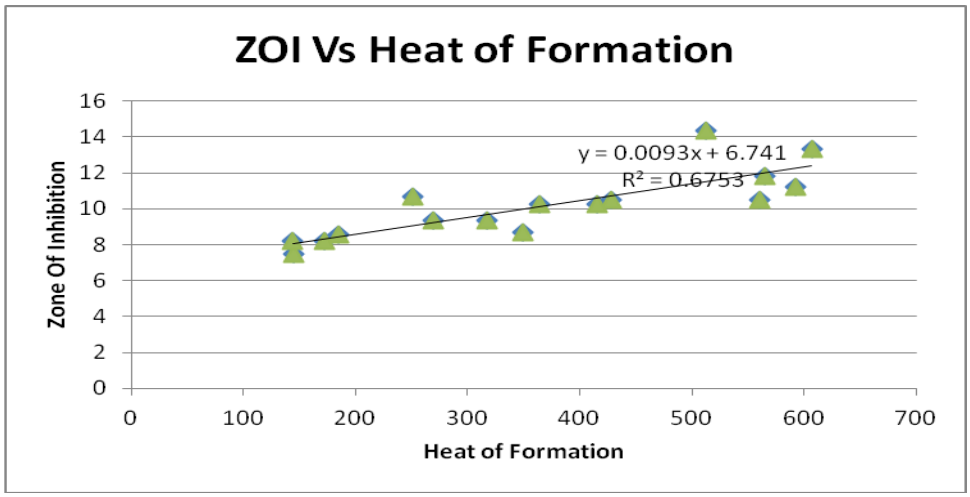

Fig.4: Chart of comparison between parameter (heat of formation) and zone of inhibition values for training set

TEST SET

Table 5: Comparison of predicted value and observed value for test set.

Sr No	Compounds	Observed Value	Predicted Value
1	**PYN3**	10.33	10.23
2	**PYN6**	8.33	9.95
3	**PYNVI**	14.83	13.43
4	**PYNIX**	12.44	12.07

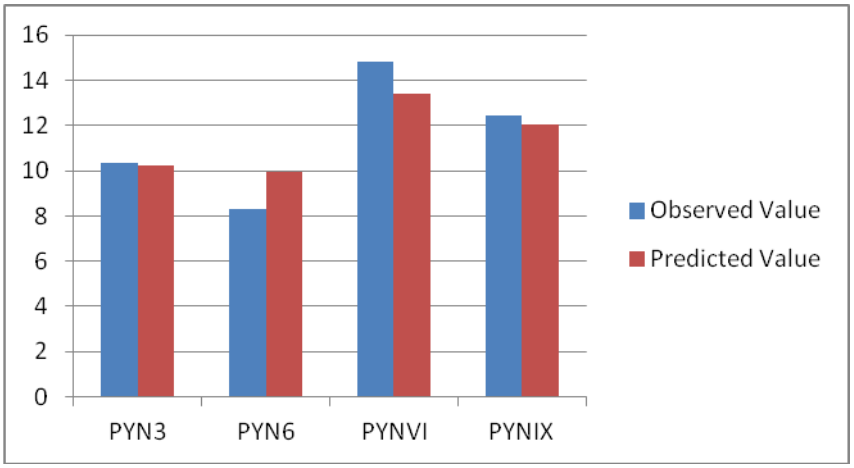

Fig. 5: Chart of comparison between observed and predicted zone of inhibition value for test set.

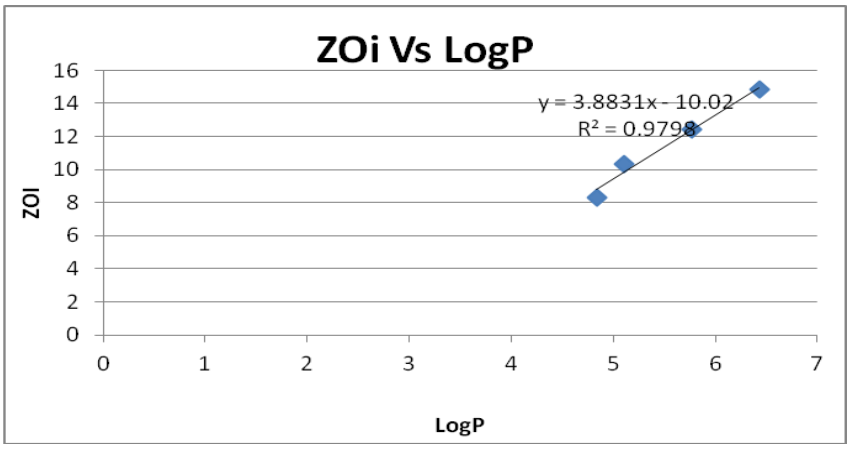

Fig. 6: Chart of comparison between parameter (Log P) andzone of inhibition values for test set

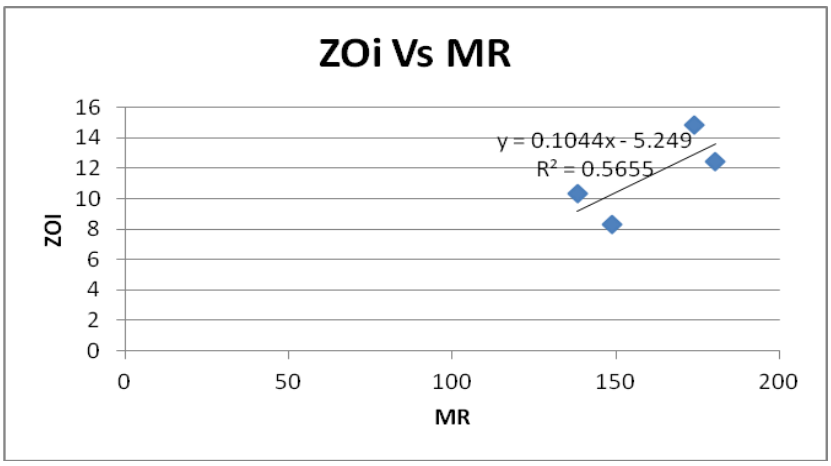

Fig.7: Chart of comparison between parameter (MR) andzone of inhibition values for test set

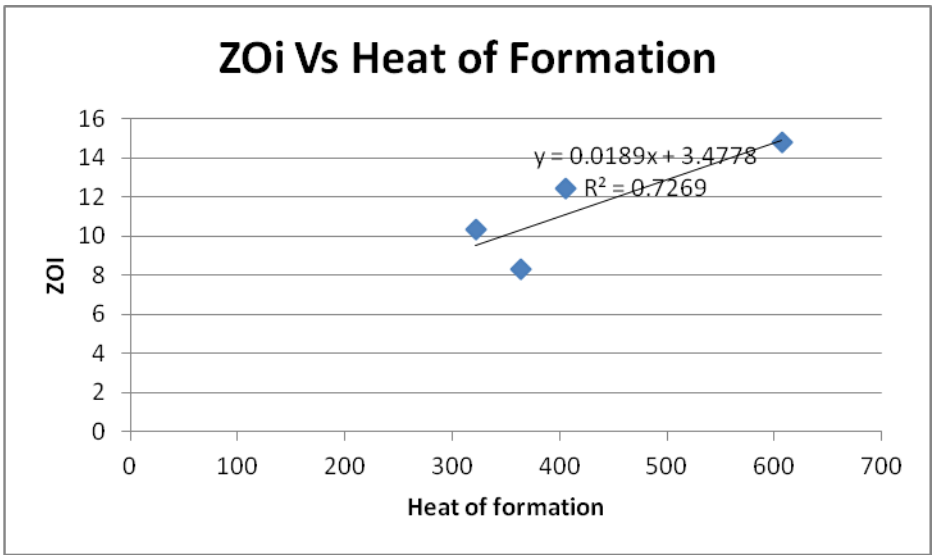

Fig. 8: Chart of comparison between parameter (heat of Formation) and zone of inhibition values for r test set

EXPERIMENTAL SECTION

Antifungal Activity The newly obtained derivatives were evaluated for in vitro antifungal activity against *Candida albicans ATCC 10231*. Nutrient agar and Seaboard dextrose agar were employed for fungal growth. Minimal Inhibitory Concentrations (MIC) were determined by means of standard twofold serial dilution method using agar media. Stock solutions of tested compounds were prepared in DMSO at a concentration of 1 mg/mL. Suspension containing approximately 106 CFUs/mL of fungi was prepared from broth cultures. Fungal plates were made in triplicate and incubated at 37˚C within 48–72 h for fungi. Clotrimazole were also screened under similar conditions as antifungal drug. MIC is defined as the lowest concentration of compound that inhibited visible growth [13].

QSAR ANALYSIS

Data Set:

A congener set of 6-Acetyl-3-[3-Chloro-2-(Substituted)-4-Oxoazetidin-1-yl]-2, 5-Diphenyl-2, 3-Dihydropyridine-4-Carbonitrile were considered in this study. The candidate set of variables used in this analysis includes lipophilic, electronic, steric and structural parameters. The screened physicochemical parameters in this QSAR study were logP for lipophilicity, molar refractivity for steric and index of reflection for electronic parameter. The data set was randomly divided into two subsets: the training set containing 16 compounds and the test set containing 4 compounds. The training set was used to build a regression model, and the test set was used to evaluate the predictive ability of the model obtained. The properties data for the complete set of compounds are presented in Table 2. To derive QSAR models, an appropriate representation of the chemical structure is necessary. For this purpose, descriptors of the structure are commonly used. The physicochemical parameters used in this study were calculated using chem. Draw ultra and ACD Labs software.

Multiple Linear Regression Method

A relationship between independent and dependent variables (physicochemical descriptors and biological activities, respectively) were determined statistically using regression analysis [14]. Linear regression is achieved by fitting a best-fit straight line to the data using the least squares method. Descriptors that are included in a reasonable QSAR equation should exhibit low inter-correlation and thus, behave as independent variables. The inter-correlation between descriptors was used for selecting descriptors for equation and the quality of fit for a regression equation was assessed relative to its correlation coefficient and standard deviation. The F value represents the level of statistical significance of the regression. For a regression model, $r^2$was used to describe the fitness of data.

CONCLUSION:

Classical QSAR approach was applied successfully to a 20 compounds from series of 6-Acetyl-3-[3-Chloro-2-(Substituted)-4-Oxoazetidin-1-yl]-2, 5-Diphenyl-2, 3-Dihydropyridine-4-Carbonitrile with well-expressed antifungal activity, quantitative structure–activity relationship studies revealed that the antifungal activities of these synthesized derivatives against the test microorganisms are mainly governed by the molar refractivity, a polarizability parameter. Thus a proper substitution of the group with high polarizability at 3 position of aromatic ring probably improves the potency of these derivatives as antifungal agents. The effect of modification at this site will be the subject of further optimization and investigation.

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