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Significance of Statistical Methods in Theoretical Chemistry Research

Kishor Arora
Department of Chemistry, Govt. Postgraduate College (Autonomous); Datia; M.P. -475661

Abstract: *It is a demand in the modern era of chemical sciences to develop and design new and useful compounds for the service of mankind without the use of methods which are traditional one. Workers were trying to develop and synthesize series of new compounds since past in the laboratories using traditional synthetic methods and they used to check their properties thereafter. This process is time consuming and this lead to synthesis of a large number of compounds. Some recent trends have emerged and developed in the field of designing of compounds which may include microwave synthesis, computer aided designing etc.. This helps in studies and designing of compounds with required properties. This can be done with the help of software which are developed on the basis of quantum chemical theoretical methods. Results so obtained from these software packages may be checked and validated using some or other statistical method. This presentation includes studies of significance of statistical methods especially of correlation and regression methods in QSAR and 3D- QSAR studies.*

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I. Introduction

Computational Chemistry represents molecular structures as numerical models simulate their behavior with the help of quantum mechanics. Programs available in this field provide geometrical and energy related studies of the molecules. One can compute energy related properties such as electronic properties, spectroscopic properties for the molecules under studies

QSAR studies include establishment of correlation equations, relationships between variations in the values of various molecular properties with their biological activities for the series of compounds.
This is a common technique now-a –days used in designing of a drug

In most general form QSAR equation may be written as a linear equation:-

(Biological activity) = C+ m1p1+m2p2+……

In the above equation 'C' is a constant with m1,m2……. Coefficients for the properties/ parameters p1,p2 …….
It is clear from the equation that biological activity (or log of it) is function of properties/ parameters

QSAR technique
Various types of descriptors used in QSAR technique

- **Constitutional descriptors**
- Molecular weight
- Counts of atoms and bonds
- Counts of rings etc.
- **Topological descriptors**
- **Connectivity indices**

One of the most significant and widely used method is using software computed descriptors in QSAR techniques.
These software/s are in common use by various researchers/ workers now- a-days. These computational Chemistry software/s provide structural properties/ parameters which may be used to generate / establish QSAR equations by correlating biological activity of series of compounds under study.

Application of Statistics

Statistical methods are the backbone of QSAR studies as:-

(i) Equations generated/ established in QSAR studies are linear regression equations.

(ii) A number of equations may be generated / established for one problem/ case under study. Statistics also helps in selecting one suitable best fit equation out of them.

(iii) This may be done by checking standard deviation/ variance and other related statistical parameters for the data set used for QSAR studies for a given series of compounds.

(iv) Correlation coefficient computed for the data set under study also helps in selecting appropriate QSAR equation.

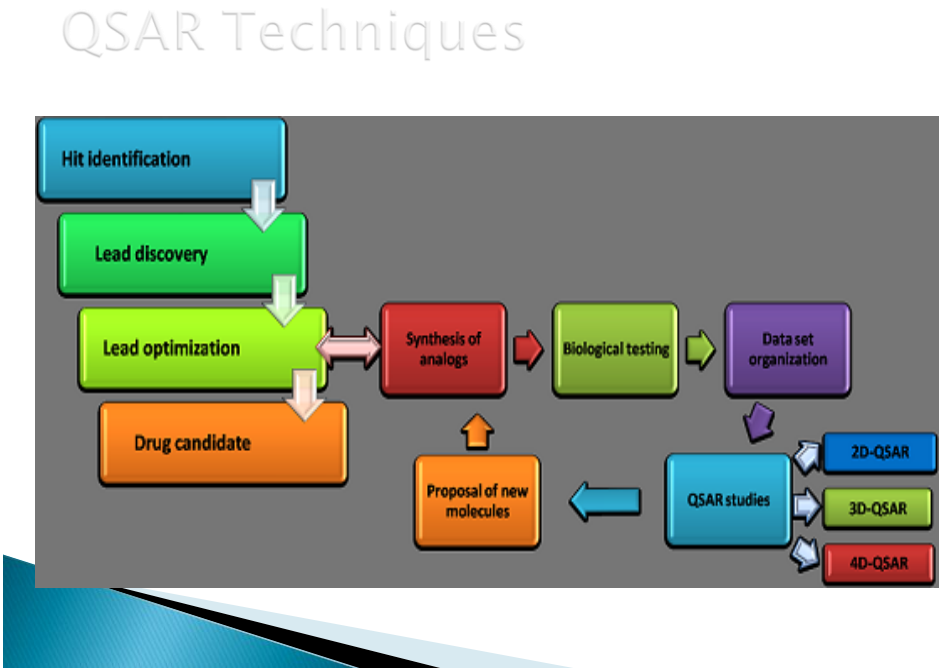


Fig.1: QSAR Techniques

Molecular modeling is rapidly becoming one of the important tools, along with basic lab skills and the use of specialized chemistry tools such as infrared spectrophotometers and spectroscopy instruments. Keeping this in mind, this paper has been presented which includes the QSAR studies of simple organic compounds which are carried out by our research group (1,2).

Computational details:-

Intel based Pentium core-2 Duo machine with configuration Intel (R) core TM 2 Duo CPU, T5450 @ 1.66 GHZ, 2 GB RAM , 250 GB HDD was used to run all the calculations.

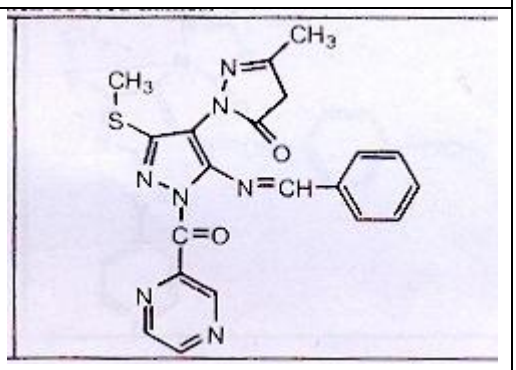
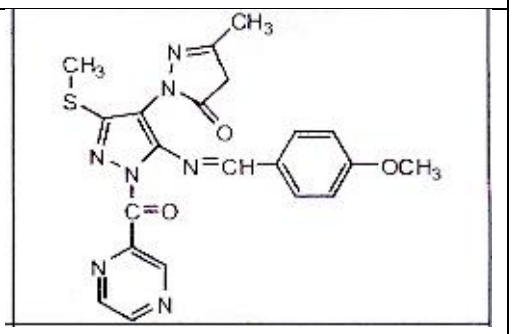
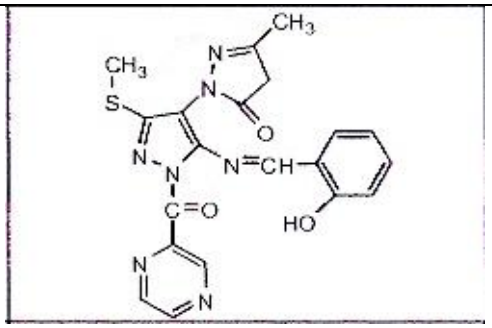
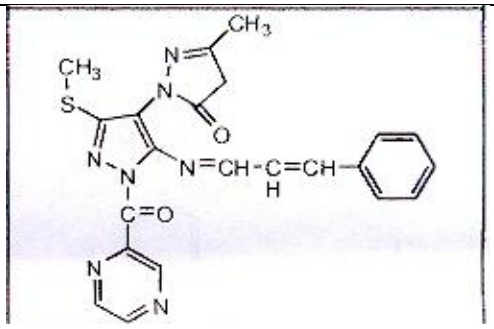
Semi-empirical **AM1 (Austin modulated 1), and PM3 (Parameterized3)** quantum chemical calculations were carried out by the computer software HYPERCHEM 8.0 version and calculated parameters such as normal modes frequencies of vibration (1-6)

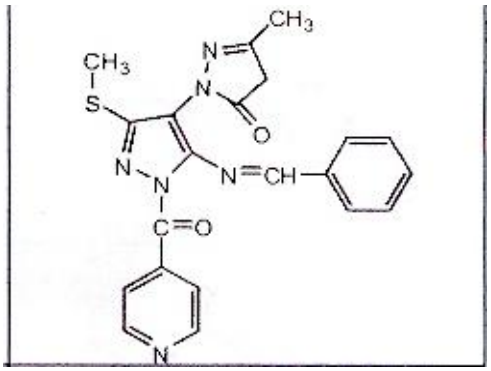
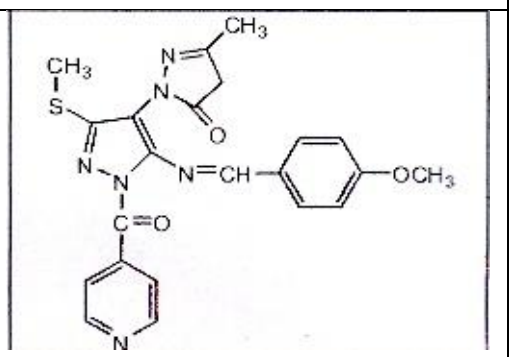
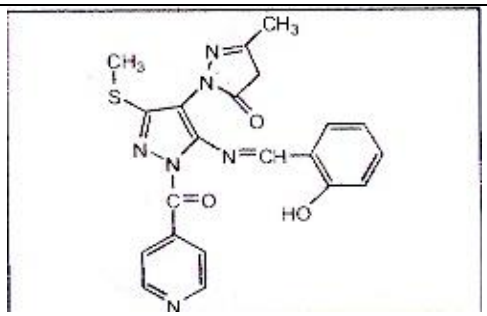
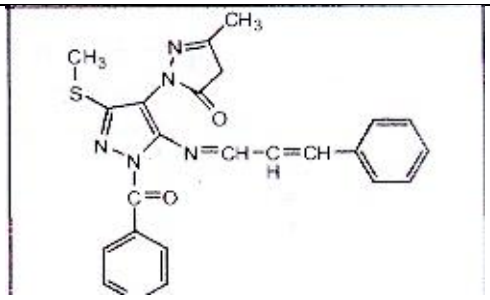
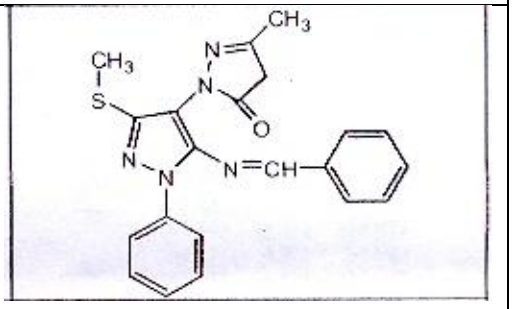
Results and Discussion

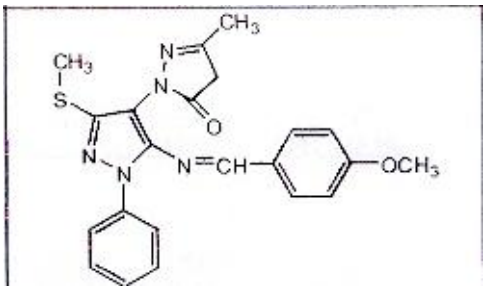
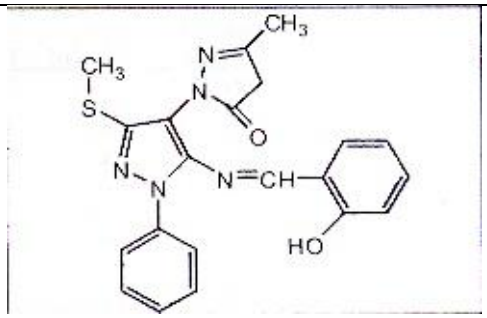
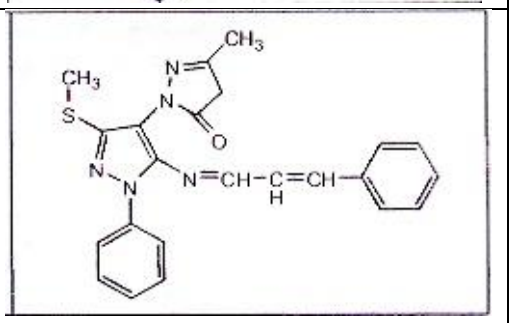
Studies of Twelve pyrazole derivatives have been carried out for their antibacterial activity against *S. aureus.* All the compounds were screened for antibacterial activity at 200µg/ml concentration. (7-13). Structures of the compounds under study are mentioned in table 1.

Structures of the compounds under study are mentioned in Table 1.

Table 1:

Code	Compound	Structure
A-1	1-(5-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-2	1-(5-(4-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-3	1-(5-(2-benzylideneamino)-3-(methylthio)-1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-4	3-methyl-1-(3-(methylthio)-5-(3-phenylallylideneamino)--1-(pyrazine-2-carbonyl)-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	

A-5	1-(5-(benzylideneamino)-1-isonicotinoyl-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-6	1-(1-isonicotinoyl-5-(4-methoxybenzylideneamino)-3-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-7	1-(5-(2-hydroxybenzylideneamino)-1-isoncotinoyl-3-(methylthio)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-8	1-(1-isonicotinoyl-3-(methylthio)-5-(3-phenylallylideneamino)-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-9	1-(5-(benzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	

A-10	1-(5-(4-methoxybenzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-11	1-(5-(2-hydroxybenzylideneamino)-3-(methylthio)-1-phenyl-1H-pyrazole-4-yl)-3-methyl-1H-pyrazole-5(4H)-one	
A-12	3-methyl-1-(3-(methylthio)-5-(3-phenylallylideneamino)--1-phenyl-1H-pyrazole-4-yl)-1H-pyrazole-5(4H)-one	

The analytical studies related to these compounds are reported in table 2.

Table 2:

Compound	Mol. formula	Mol. wt.	m. p. (^{o}c)	Yield (%)
A-1	$C_{20}H_{17}N_7O_2S$	419.46	140-142	71
A-2	$C_{21}H_{19}N_7O_3S$	449.49	143-145	67
A-3	$C_{20}H_{17}N_7O_3S$	435.46	152-154	63
A-4	$C_{22}H_{19}N_7O_2S$	445.5	194-196	79
A-5	$C_{21}H_{17}N_6O_2S$	418.47	178-180	58
A-6	$C_{22}H_{20}N_6O_3S$	448.5	145-147	56
A-7	$C_{21}H_{18}N_6O_3S$	434.47	146-148	65
A-8	$C_{23}H_{20}N_6O_2S$	444.51	186-188	70
A-9	$C_{21}H_{19}N_5OS$	389.47	126-128	63
A-10	$C_{22}H_{21}N_5O_2S$	419.5	139-141	64
A-11	$C_{21}H_{19}N_5O_2S$	405.47	146-148	68
A-12	$C_{23}H_{21}N_5OS$	415.51	165-167	72

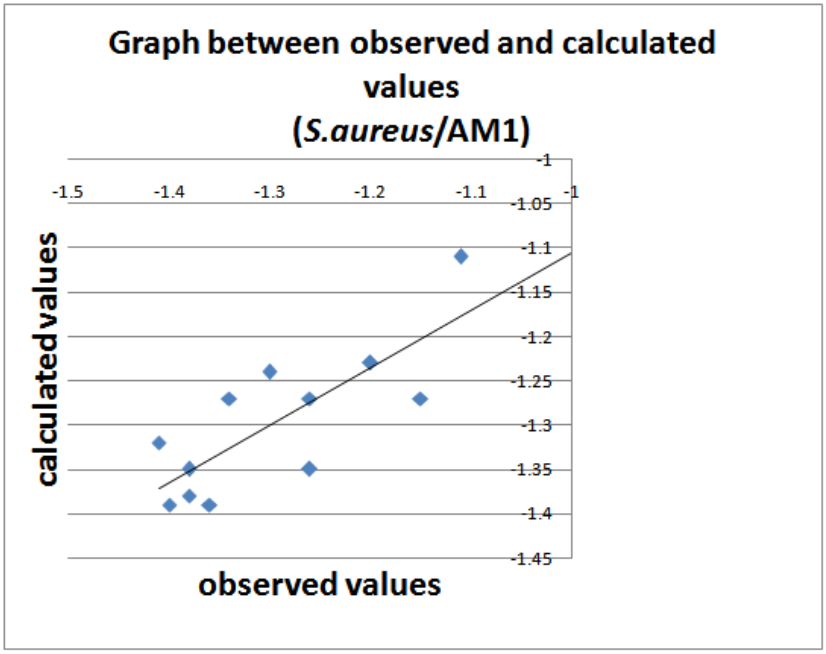
The generated QSAR model was selected on the basis of various statistical parameters such as correlation coefficient which is relative measure of quality of fit, Fischer's value (F-test) which represent F-ratio between the variance of calculated and observed activity, standard error, representing absolute measure of quality of fit respectively(12-13).

The best QSAR equations are given below:-

A. *S. aureus*/**AM1**

p(MIC) = -0.00013(SAA) - 0.00131(VOL) + 0.017406(HE) + 0.461515

N=12, SD = 0.071211, R = 0.79799, F = 4.675247

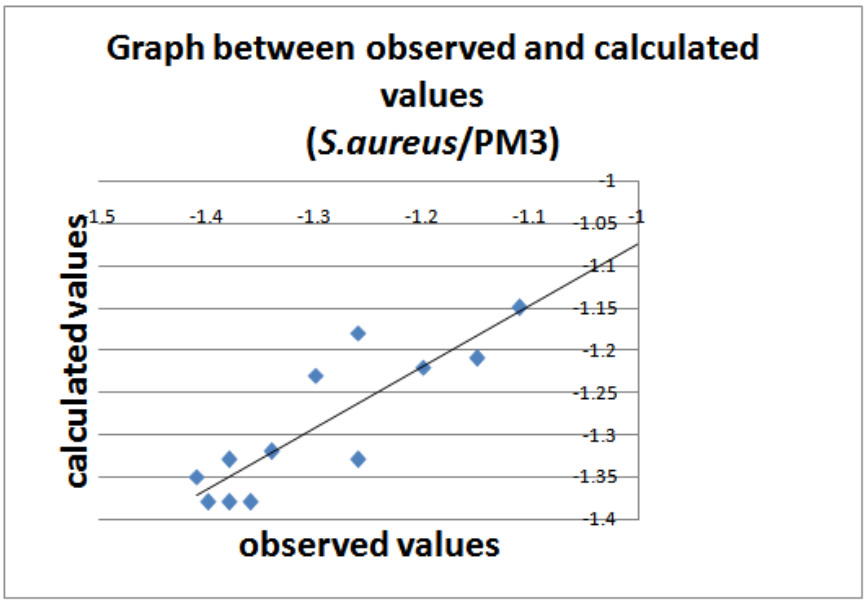


pMIC (observed)	**PMIC(Calculated)**
-1.2	-1.23
-1.36	-1.39
-1.26	-1.27
-1.26	-1.35
-1.15	-1.27
-1.4	-1.39
-1.38	-1.35
-1.34	-1.27
-1.3	-1.24
-1.38	-1.38
-1.41	-1.32
-1.11	-1.11

A. *S.aureus*/**PM3**

p(MIC) = -0.00716(HE) + 1.16E-05(TE) + 0.001534(HF) - 0.22079

N=12, SD = 0.058623, R = 0.868243, F = 8.166643



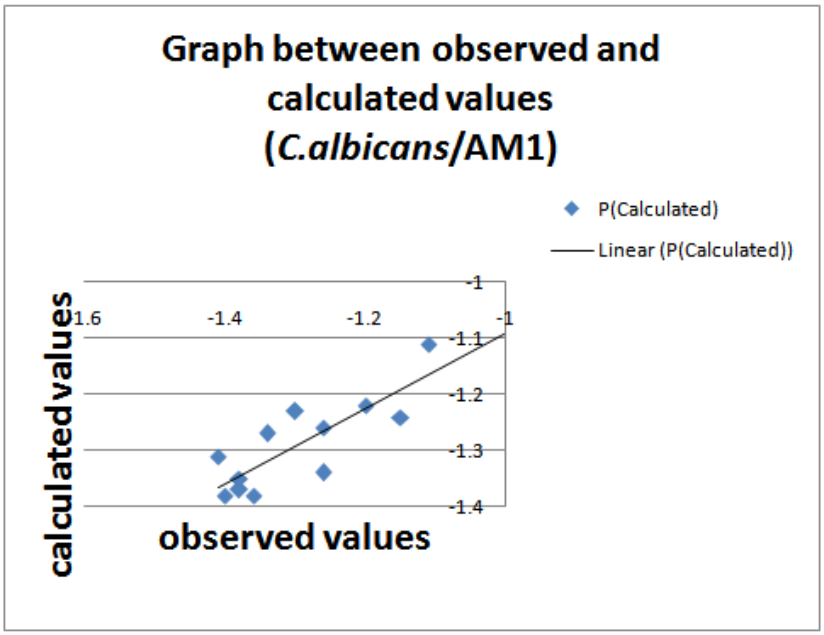
pMIC(observed)	**PMIC(Calculated)**
-1.2	-1.22
-1.36	-1.38
-1.26	-1.33
-1.26	-1.18
-1.15	-1.21
-1.4	-1.38
-1.38	-1.33
-1.34	-1.32
-1.3	-1.23
-1.38	-1.38
-1.41	-1.28
-1.11	-1.09

For the same series of Compounds the best QSAR equations for the *C. albicans* using AM1 and PM3 semi-empirical methods are given below with their correlation graphs between computed and observed activities:-

B. *C. albicans* /**AM1**

p(MIC) = -0.0001261(SAA) - 0.0013068(VOL) + 0.01740588(HE) + 0.46151539

N=12, SD = 0.07121068, R = 0.79799037, F = 4.675247

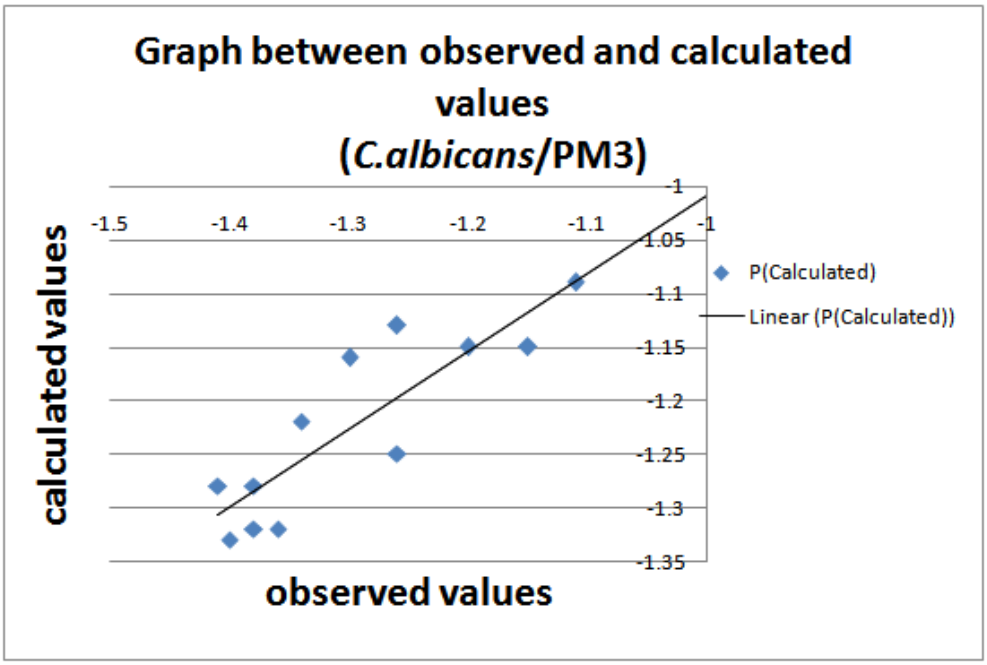


pMIC (observed)	**PMIC(Calculated)**
-1.2	-1.22
-1.36	-1.38
-1.26	-1.26
-1.26	-1.34
-1.15	-1.24
-1.4	-1.38
-1.38	-1.35
-1.34	-1.27
-1.3	-1.23
-1.38	-1.37
-1.41	-1.31
-1.11	-1.11

B. *C. albicans* /**PM3**

p(MIC) = -0.00056(SAA) + 9.7E-06(TE) + 0.001248(HF) - 0.03723

N=12, SD = 0.057574, R = 0.873258, F = 8.565155



pMIC(observed)	**PMIC(Calculated)**
-1.2	-1.15
-1.36	-1.32
-1.26	-1.25
-1.26	-1.13
-1.15	-1.15
-1.4	-1.33
-1.38	-1.28
-1.34	-1.22
-1.3	-1.16
-1.38	-1.32
-1.41	-1.28
-1.11	-1.09

Where symbols used in the above equations are SAA (surface area approx.); VOL (volume); HE (hydration energy); TE (total energy) and HF 9heat of formation) as computed using semi-empirical quantum chemical software.

It is clear from the above discussion that statistical tests and computed parameters viz. SD,(standard deviation), R (correlation coefficient) , F-test along with regression analysis helps in selection of suitable QSAR equation and prediction of appropriate mathematical model

II. Conclusion

The present study involves some pyrazoles compounds (A-1 to A-12) to check their QSAR studies pertaining to their antifungal activity against pathogens. This may be concluded form the studies that some of the compounds showed significant antifungal activity against a pathogen and other against other pathogen with related computed properties. The present paper also discusses Quantitative Structure Activity Relationship equation in the light of statistical calculations or interpretations. In conclusion this may be concluded that statistics has a vital and significant role in QSAR studies and in predicting correct mathematical model.

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