International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.8, No.9, pp 165-170, 2015

2D-QSAR Studies of Some N-((1H-Benzo[d] Imidazol-1-yl) (Phenyl) Methylene) Benzenamine Analogues as Antifungal Activity

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Abstract: In the present study quantitative structure activity relationship studies were performed on a series of N-{(1H-Benzo[d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamine analogues as antifungal activity using Chem Office ultra 8.0.3. Multiple linear regression analysis was performed to derive quantitative structure activity relationship models which were further evaluated internally as well as externally for the prediction of activity. This study indicates that thermodynamic descriptors Molar refractivity, ovality, log P play important role for the antifungal activity. The information generated from the present study may be useful in the design of more potent substituted compounds N-{(1H-Benzo [d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamine analogues as antifungal activity.
Key words: Benzimidazole, QSAR, Chem draw ultra, Descriptor, Antifungal activity.

1.Introduction

The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Antimicrobial resistance refers to micro-organism that have developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents[1]. Benzimidazole Compounds constitute an important class of heterocyclic aromatic organic compounds for their versatile pharmacological activities such as antibacterial, antifungal, antihelmintic, antiallergic, antineoplastic, local analgesic, antihistaminic, vasodilative, hypotensive, and spasmolytic activities[2-5]. In the present study, QSAR, analysis of some N-{(1H-Benzo [d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamine analogues with antimicrobial activity were performed by using multiple linear regression analysis. No QSAR studies have been carried out on N-{(1H-Benzo [d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamine analogues. It appears to be interesting to perform QSAR analysis employing Chem Office ultra 8.0.3 to correlate various physiochemical parameters to the antifungal activity for the design of some N-{(1H-Benzo [d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamines compounds. QSAR generally takes the form of a linear equation:

Biological Activity = Constant + (C1 * P1) + (C2* P2) + (C3 * P3) + …..... (Cn * Pn)

where the parameters P1 through Pn are computed for each molecule in the series and the coefficients C1 through Cn are calculated by fitting variations in the parameters and the biological activity.

2.Experimental

2.1 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 Concentration (MIC) was determined by means of standard two fold 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. MIC values were manually converted into pMIC (predicted MIC) using the formula given below. The term 'pMIC' is a scale for expressing MIC value exponentially which normalizes the actual activity using negative logarithmic function which is considered as a prediction. Hence, the term 'predicted' is used.

pIC50 = -log IC50

2.2 QSAR analysis

A data set of 16 compounds[19] containing benzimidazole ring as antifungal agent (Table-1) was used for present QSAR study. The molar concentration of MIC was converted to logarithmic values for undertaking the QSAR study. All 16 compounds structure were draw on ChemDraw 8.0.3.[59] then built on workspace of Chem3D 8.0.3.[59] and energy minimization of the molecules was done using MM2 force field followed by semi empirical PM3 method available in MOPAC module until the RMS gradient value becomes smaller than 0.01 kcal/mol. Energy minimize for each compound was generated and used for calculating various physico-chemical descriptors like thermodynamic, steric, lipophylic and electronic.

2.3 Descriptors calculation and selection, QSAR models development and validation:

The 10 descriptors calculated by Chem3D version 8.0.3 were considered as independent variable and biological activity as depended variable.

Descriptors selections were done by correlation matrix and selected descriptor have no mutual correlation and high correlated with biological activity.

To generate QSAR models by multiple linear regression analysis using Microsoft excel. Statistical measures used were n= number of compound in regression, r= correlation coefficient, F= test (Fischer's value) for statistical significance, SEE= standard error of estimation and correlation matrix to show correlation among the parameters.

The squared correlation coefficient r^2 is a relative measure of fit by the regression equation. Corresponding, it represents the part of the variation in the observed data that is explained by the regression. The correlation coefficient values closer to 1.0 represent the better fit of the regression. The F- test reflects the ratio of the variance explained by the model and variance due to error in regression. High value of the F- test indicates that the model is statistically significant. Standard deviation is measured by the error mean square, which expresses the variation of residuals or the variation about the regression line. Thus standard deviation is absolute measurement of quality of fit and should have a low value for the regression to be significant.

The prediction ability of the generated correlation was evaluated by cross validation method employing a 'leave-one-out (LOO)' method. Validation parameters consider were cross validated r^2 or q^2, standard deviation based on predicted residual sum of squares (SPRESS) and standard error of prediction (SDEP).

After multiple linear regression analysis, the best equation received for antibacterial activity against three different strains.

Most effective model for *candida albicans* was described in Equation **[1]**. It was infer that structural (Ovality), lipophillic (PC) and Steric (MR) parameters have important role in activity of the compounds of series.

An ovality term represents the ratio of the Molecular Surface Area to the Minimum Surface Area. The Minimum Surface Area is the surface area of a sphere having a volume equal to the Solvent-Excluded Volume of the molecule. Computed from the Connolly Molecular Surface Area and Solvent-Excluded Volume properties. Its negative value in the equation indicates that biological activity Log (MIC) was decreased by increasing ovality.

Partition coefficient terms represent the drug distribution between an organic phase and aqueous phase. Its positive (+) value indicate that biological activity Log(MIC) was decreased by decreasing PC, and PC were decreased by increasing hydrophilicity of compounds.

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 benzimidazole should be far for the activity to be maximum.

3. Result and Discussion

The computed molecular descriptors, reported and predicted biological activities (pMIC) of the ligand dataset were shown in Table 1. The model was trained with training set using MLR analysis which generated a 2D QSAR equation, Biological activity = (1.7018*Parttion Coefficient)-(0.0902***Molar Refractivity**) + (1.4732***Ovality**) + 7.644 In the above equation, biological activity was taken as dependent variable and all the descriptors were considered as independent variables which influenced the regression line of Fitness (Table-2).

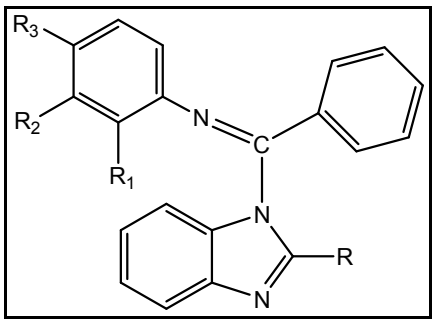

Table 1: Biological activity data and structures of the compound in series

Model No.	Equation	n	r	r^2	$r^{2\ adj}$	F
1	pMIC= (1.7018***logP**)-(0.0902***MR**) + (1.4732***Ovality**) + 7.644	16	0.941	0.8865	0.8581	31.24
2	pMIC= (1.5606***logP**)- (0.0727***MR**) + 8.890	16	0.929	0.8636	0.8426	41.16
3	pMIC= (1.234***logP**) + (0.109***Ovality**) + 3.432071	16	0.881	0.7774	0.74318	22.70

Table 2: Developed QSAR Models of the Compound in Series

Comp. No.	R	R_1	R_2	R_3	Log P	MR (cm^3 /mol)	Ovality	Observed pMIC	Predicted pMIC
2a	H	H	H	H	4.78	90.06	1.50	10.28	9.86
2b	H	H	H	Cl	5.34	94.67	1.39	9.92	10.24
2c	H	H	H	NO_2	5.14	93.76	1.51	10.34	10.16
2d	H	H	H	CH_3	5.26	95.96	1.36	10.09	9.94
2e	H	CH_3	H	H	5.27	95.78	1.44	10.29	10.09
2f	CH_3	H	H	H	5.45	94.44	1.44	11.07	10.52
2g	CH_3	H	H	Cl	6.01	99.04	1.47	11.18	11.09
2h	CH_3	H	H	NO_2	5.41	98.02	1.54	10.43	10.26
2j	H	H	OH	H	4.39	91.88	1.50	9.09	9.03
2k	H	H	H	OCH_3	4.65	97.31	1.54	9.34	9.05
2l	H	H	NO_2	H	5.14	97.58	1.65	10.87	10.01
2m	CH_3	NO_2	H	H	5.41	98.04	1.45	10.90	10.13
2n	CH_3	OCH_3	H	H	5.32	101.69	1.50	10.67	9.73
2o	H	CH_3	H	H	5.26	95.96	1.47	10.06	10.12
2p	CH_3	H	CH_3	H	5.94	100.34	1.50	11.23	10.91
2q	CH_3	H	H	OH	5.06	96.25	1.53	10.98	9.83

Correlation among descriptors was initially analyzed to identify the descriptors producing partial positive impact on the overall model. The following were the high correlating descriptor pairs with correlation coefficient shown in bracket: parttion coefficient with molar refractivity (0.86), ovality with parttion coefficient (0.77), partition coefficient, molar refractivity and ovality (0.88). Hence, it was distinguished that Structural, polarizability and refractivity were good descriptors to generate the model.

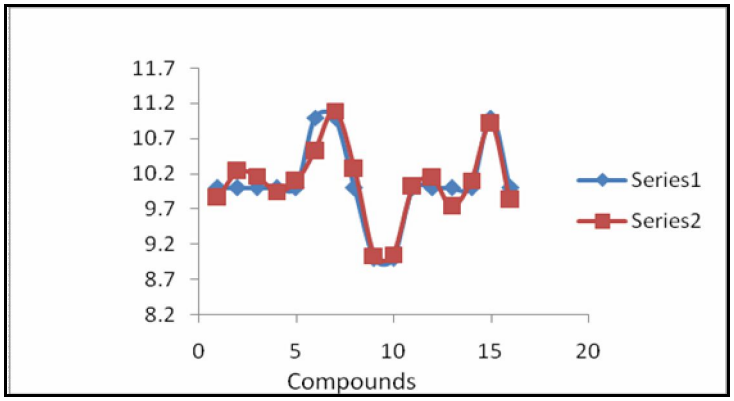

Figure 1: The comparison between experimental and predicted MIC value Series-1: Actual pMIC, Series -2: predicted pMIC

However, ovality descriptor was identified as the worst descriptor due to the non-involvement in correlation with other descriptors. To study the contribution of individual descriptor in biological activity,

correlation was performed with individual descriptor and its respective pMIC values. Descriptors such as LogP and refractivity was found to be negatively correlated.

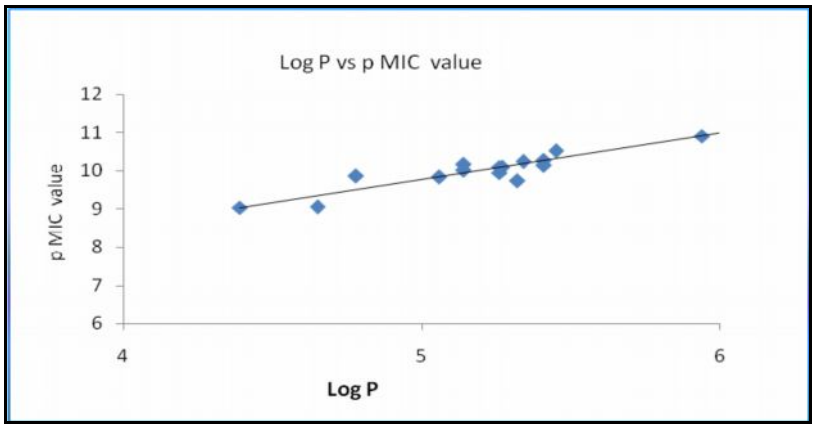

Figure 2: Relationship between Log P and pMIC

The scatter plot of actual versus predicted MIC value was shown in Fig. 1. It showed that 3 molecules were occupied the regression line and 4 molecules were found Overlapping regions indicate the best molecule fitted over the regression equation.

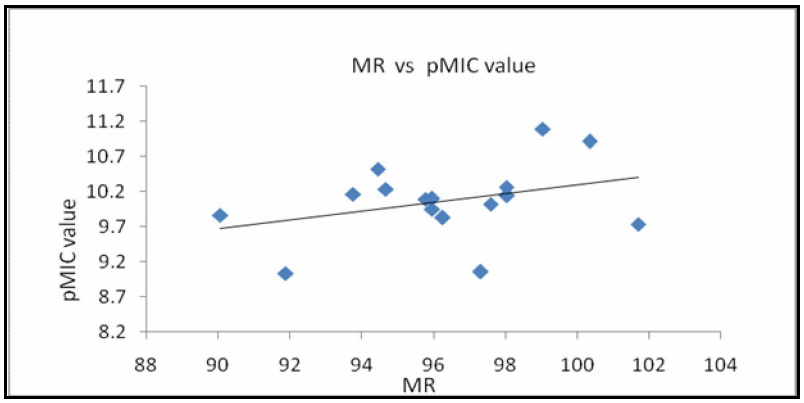

Figure 3: Relationship between MR and pMIC

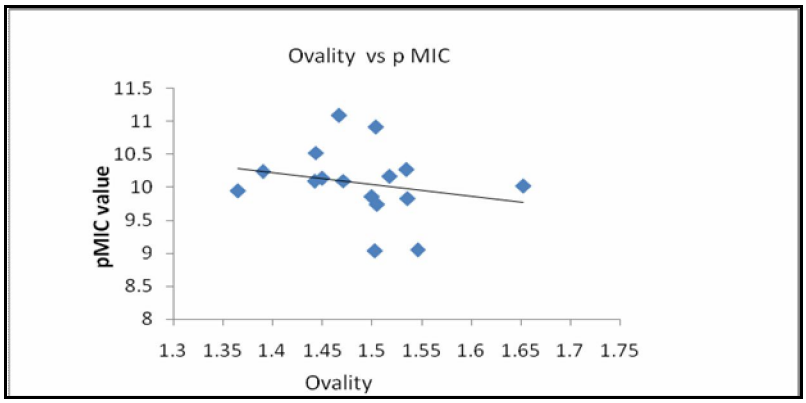

Figure 4: Relationship between Ovality and pMIC

It is evident from the QSAR studies that in model-1, lipophilic, structural and sreric descriptors are responsible for the activity. Out of the three models, model-1 was selected on the basis of statistical criteria; r^2=0.88, r=0.94 and standard deviation = 0.2161. Model-1 shows high statistical significance >99.9% with F-values F= 31.24. Negative contribution of ovality to the biological activity indicates that minimizing the total energy of the molecule increases the activity. Based on the QSAR model obtained from series, for the design of the new molecules.

4.Conclusion

Classical QSAR approach was applied successfully to a 16 compounds from series of some N-{(1H-Benzo [d] Imidazol-1-yl) (Phenyl) Methylene} Benzenamine analogues 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 log P value, the polarizability and the molar refractivity, a steric parameter. Thus a proper substitution of the group with high polarizability at 4 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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