Research Article

QSAR MODELING OF BENZOXAZINE-3-ONES DERIVATIVES AGAINST *CANDIDA KRUSEI*Chaturvedi Neha^{1*}, Chaturvedi Dev Sharan², Mishra Ashutosh², Bajpai Pawan² and Neeraj Upmanyu²¹Department of Pharmaceutical Chemistry, R. K. D. F. College of Pharmacy, Bhopal (M.P), India²Daksh Institute of Pharmaceutical Science, Chhatarpur (M.P.), India

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ABSTRACT

QSAR Study on the inhibition of *Candida krusei* by Benzoxazine-3-ones derivative using several physiochemical descriptors was performed. Antifungal activity for 16 Benzoxazine-3-ones derivatives was modeled by using multiple regression procedure. The best model is selected $r^2 = 0.9985$, adjusted $r^2 = 0.9981$. The result obtained from QSAR studies could be used in designing better antifungal agent.

Keywords: Antifungal activity, *Candida krusei*, Benzoxazine -3-ones, QSAR

INTRODUCTION

Benzoxazine and its derivatives are used in organic synthesis for building natural and designed synthetic compounds and they have been frequently utilized as suitable skeletons for the design of biologically active compound¹. The investigation of the QSAR of substance is an important aspect of modern chemistry, biochemistry, medicinal chemistry and drug discovery². The information obtained is composed of mathematical equation relating the chemical structure of the compound to a wide variety of their physical, chemical, biological and technological properties³. Once a correlation between structure and activity is found, any number of compound, including those not synthesized yet, can be readily be screened for selection of structure with desired properties⁴. Hence it is possible to select the most promising compound for synthesis and testing in the laboratory⁵. Mycotic illness in human are divided into three groups: contagious skin and hair infection, non contagious soil borne or air borne systemic infection and non contagious food borne toxemias⁶. The responsible organisms and method of prevention and treatment differ with each group⁷. The prevalence of systemic fungal infection has increased significantly during the past decade⁸. The fungal infection is mainly cause by a *Candida* species⁹. This increase is due to greater use of broad-spectrum antibiotics, immunosuppressive agent, center venous catheters, intensive care low birth weight infants, organ transplantation and the acquired immunodeficiency syndrome (AIDS) epidemic¹⁰. *Candida krusei* is budding yeast involved in the chocolate production, *Candida krusei* is an emerging fungal nosocomial pathogen primarily found in the immune compromised and those with hematological malignancies¹¹. It has natural resistance to fluconazole, a standard antifungal agent¹². Infection generally occurs when a person's immune system is compromised to some degree, causing the *Candida* cell to colonize in various areas within the body¹³. In patient with a deficiency in their immune system, *Candida krusei* can lead to a more systemic illness¹⁴. The uses of antifungal drug is limited and restricted due to rapid development of drugs resistance. They also produce the side effect in the prolonged uses. Therefore the development of new class of drugs as a

potent antifungal is becomes a crucial point. A group of drugs 1, 4-benzoxazine-3-ones was extracted from rye, wheat, maize. 2, 4-dihydroxy-1, 4-benzoxazine-3-one (DIBOA) Figure 1 and its methoxy derivative (DIMBOA) Figure 1 have been shown to inhibited germination of spore of phytopathogenic fungi and play an important role in defense of cereal against deleterious pest such as insect, pathogenic fungi and bacteria .

Figure 1: Biologically active 1, 4 benzoxazines

These molecules are naturally present in plants as plants as glucosidase from which aglycones are released rapidly by enzymatic hydrolysis after physical and biological injury to plant and shows antifungal, antibacterial, insecticide effects. Now-a-days only limited numbers of compounds congaing 1, 4-benzoxazine ring have been studied i.e. ofloxacin (Figure 1)¹⁵. So it is prolific to further investigate the nucleus with different substitutions with expected positive results with different physiological parameters. In the present study, we have performed the QSAR analysis by various regression methods. Regression methods are used to build a QSAR model in the form of a mathematical equation. This equation explains variation of dependent in terms of independent variables.

Experimental

The data set of 16 molecules with their antifungal activity has been taken from the literature¹⁶. The observe log₁/C value is given in Table 1 (Define the Activity in term of log₁/C). All structures of benzoxazine derivative are sketched by using chem. sketch software¹⁷. The multiple regression analysis programs are done by NCSS¹⁸. The descriptors are calculated

like thermodynamic, electronic, steric and topological parameter. Thermodynamic parameter describes free energy change during drug receptor complex formation. Spatial parameters are the quantified steric features of drug molecule required for its complimentary fit with receptor. Electronic parameter describes weak non covalent bonding between drug molecule and receptor. The physico-chemical parameters Molecular weight (MW), Molar refractivity (MR), Molar volume (MV), Parachor (PC), Index of refraction (IR), Density (d), Polarizability (POL) were calculated by chem. sketch software by ACD labs. These calculated parameters and their values are reported in Table 2. The correlation matrix showing inter-correlation among the descriptors are reported in Table 3 a value more than 0.7 will indicate auto-correlation. A perusal of this Table clearly indicates that many indices highly correlated with each other. In sequential multiple regression the program search for all permutation and combination sequentially for the data set. The best model was selected from the various statistically significant equation on the basis of observed squared correlation coefficient (r^2), the standard error of the estimate (Se), Fisher test (F), the bootstrapping standard deviation (Sbs), the cross-validated squared correlation coefficient using leave-one-out procedure (q^2).

Table 1: Benzoxazine -3-one derivative used in this study

Compd. No.	R	R ₁	R ₂	Obs. log 1/C
1.	H	H	H	3.973
2.	H	CH ₃	H	3.998
3.	H	Cl	H	4.032
4.	H	COOC ₂ H ₅	H	4.089
5.	H	H	NO ₂	4.049
6.	H	Cl	NO ₂	4.099
7.	CH ₃	H	H	3.998
8.	CH ₃	CH ₃	H	4.022
9.	CH ₃	Cl	H	4.054
10.	CH ₃	COOC ₂ H ₅	H	4.106
11.	CH ₃	Cl	NO ₂	4.118
12.	CH ₃	H	NO ₂	4.070
13.	C ₂ H ₅	H	H	4.022
14.	C ₂ H ₅	Cl	H	4.075
15.	C ₂ H ₅	H	NO ₂	4.091
16.	C ₂ H ₅	Cl	NO ₂	4.136

Table 2: Values of the calculated physicochemical parameters used in the present study

Compd. No	MW	MR	MV	PC	IR	ST	D	POL
1.	235.236	59.26	193.9	489.9	1.523	40.7	1.213	23.49
2.	249.263	64.09	210.1	528.2	1.521	39.9	1.185	25.4
3.	269.68	64.16	205.8	527.1	1.535	42.9	1.31	25.43
4.	307.299	75.67	248.3	633.9	1.521	42.4	1.237	29.99
5.	280.24	65.81	205.7	547	1.552	49.9	1.362	26.08
6.	314.679	70.7	217.6	584.1	1.563	51.8	1.445	28.03
7.	249.263	64.19	208.9	528.1	1.526	40.8	1.193	25.44
8.	263.29	69.01	225.2	566.3	1.525	40	1.169	27.36
9.	283.7076	69.08	220.8	565.2	1.538	42.8	1.284	27.38
10.	321.326	80.59	263.3	672	1.524	42.4	1.22	31.95
11.	328.7052	75.63	232.7	622.3	1.563	51.1	1.412	29.98
12.	294.26	70.73	220.7	585.1	1.553	49.3	1.332	28.04
13.	263.29	68.81	226.5	568.1	1.519	39.5	1.162	27.27
14.	297.74	73.7	238.4	605.3	1.53	41.5	1.248	29.21
15.	308.287	75.35	238.3	625.2	1.545	47.3	1.293	29.87
16.	342.7317	80.25	250.2	662.3	1.554	49	1.369	31.81

Table 3: Correlation matrix

	Obs.	MW	MR	MV	PC	IR	ST	D	POL
Obs.	1.000								
MW	0.998	1.000							
MR	0.914	0.916	1.000						
MV	0.775	0.777	0.959	1.000					
PC	0.909	0.911	0.998	0.962	1.000				
IR	0.622	0.618	0.298	0.017	0.281	1.000			
ST	0.677	0.674	0.369	0.103	0.369	0.969	1.000		
D	0.655	0.653	0.299	0.032	0.290	0.957	0.948	1.000	
POL	0.914	0.916	1.000	0.959	0.998	0.298	0.370	0.299	1.000

RESULT AND DISCUSSION

All the data presented in Table 2 have been subjected to regression analysis using NCSS software¹⁸. The regression analysis yielded in to 10 statistically significant models which are recorded in Table 4. Cross validation has been done by using leave one out (LOO) procedure. Best three models are obtained.

One-variable model

Out of 8 one-variable model MW has been found to be the best in model.

$$\log 1/C = 0.0015 (\pm 0.0000) MW + 3.6229$$

$$n=16, R^2 = 0.9970, R^2A = 0.9968, Se = 0.0007, F = 4614.032, Q = 1426.427$$

Here and here after the n is the total number of compounds; Se is the standard error of estimation; R^2 is the correlation coefficient; R^2_{adj} is the adjusted R^2 ; F is the Fisher's ratio and Q is the pogliani's quality factor which is the ratio of R/Se

The 99.7 % data has been found to be explained by the above model. MW is positive and the means that compounds with increase of MW value have increase activity.

Two variable model

$\log 1/C = 0.3403 (\pm 0.0063) MV + 0.0019 (\pm 0.0000) D + 3.1949$
 $n = 16, R^2 = 0.9982, R^2A = 0.9979, Se = 0.0005, F = 3608.325, Q = 1998.199$
 $PRESS/SSY = 0.0018, S_{PRESS} = 0.0027, PSE = 0.0025$
 MV and D as correlating parameters has been found to be the best in two-variable models

The model showing 99.8 % variance in the data; both the descriptor show positively results.

Three variable model

$\log 1/C = 0.0015 (\pm 0.0003) MV + 0.3135 (\pm 0.0185) D + 0.0036 (\pm 0.0024) POL + 3.2278$
 $n = 16, R^2 = 0.9985, R^2A = 0.9981, Se = 0.0005, F = 2655.061, Q = 1998.499$
 $PRESS/SSY = 0.0015, S_{PRESS} = 0.0021, PSE = 0.0018$
 MV, D and POL as correlating parameter have been found to be the best Out of three-variable models.

This model has $R^2 = 0.9985$. Suggesting that addition of POL in the two-parametric model is justified. This tri-parametric model has highest Q value suggesting this model to be the best among all the tried Three-variable models

Table 4: Regression parameters and quality of correlation when physicochemical parameters are used

Model No.	Parameters used	$A_i = (1---3)$	B	Se	R^2	R^2A	F	Q
1.	IR	1.8813 (± 0.6335)	1.1667	0.0095	0.3864	0.3426	8.818	65.433
2.	D	0.3534 (± 0.1088)	3.6069	0.0092	0.4296	0.3889	10.544	71.243
3.	ST	0.0073 (± 0.0021)	3.7353	0.0089	0.4585	0.4198	11.855	76.082
4.	MV	0.0020 (± 0.0004)	3.6180	0.0077	0.6002	0.5716	21.015	100.614
5.	PC	0.0008 (± 0.0001)	3.5741	0.0051	0.8266	0.8142	66.736	178.270
6.	MR	0.0071 (± 0.0008)	3.5573	0.0049	0.8349	0.8231	70.78	186.475
7.	POL	0.0179 (± 0.0021)	3.5576	0.0049	0.8350	0.8232	70.845	186.486
8.	MW	0.0015 (± 0.0000)	3.6229	0.0007	0.9970	0.9968	4614.032	1426.427
9.	MV D	0.3403 (± 0.0063) 0.0019 (± 0.0000)	3.1949	0.0005	0.9982	0.9979	3608.325	1998.199
10.	MV D POL	0.0015 (± 0.0003) 0.3135 (± 0.0185) 0.0036 (± 0.0024)	3.2278	0.0005	0.9985	0.9981	2655.061	1998.499

Table 5: Observed and Estimated

Compd. No.	Obs. log 1/C	Est. log 1/C	Residual
1.	3.973	3.976	-0.003
2.	3.998	3.998	0.000
3.	4.032	4.031	0.001
4.	4.089	4.087	0.002
5.	4.049	4.049	0.000
6.	4.099	4.100	-0.001
7.	3.998	3.999	-0.001
8.	4.022	4.022	0.000
9.	4.054	4.052	0.002
10.	4.106	4.110	-0.004
11.	4.118	4.119	-0.001
12.	4.070	4.069	0.001
13.	4.022	4.021	0.001
14.	4.075	4.073	0.002
15.	4.091	4.089	0.002
16.	4.136	4.137	-0.001

Figure 2: Observed vs estimated Log 1/c values using model no.10

The graph between experimental and predicted biological activity by using model 4 is shown in Figure 2

CONCLUSION

In the summary, from the derived QSAR model it can be concluded that antifungal activity of benzoxazine derivative against *Candida krusei* is strongly influenced by steric, electrostatic interaction and hydro phobic interaction nature

of substituent. The model obtained by this study will used for designing of new compound.

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