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QSAR STUDIES ON BENZOXAZOLES AND OXAZOLO PYRIDINES AS ANTIFUNGAL AGENTS

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ABSTRACT

Quantitative Structure Activity relationship is a computational statistical method which gives a data set to predict the biological activity. A QSAR study has been carried out on 30 molecules of benzoxzoles and oxazol pyridines in order to determine the structural properties required for antifungal activity. Topological and connectivity descriptors are used for best model with r^2=0.8616, r^2adj=0.8394. Cross validation is also carried out. The model thus obtained from this study can be useful for the designing and development of new potential antimicrobial agents.

KEYWORDS: Antimicrobial, Benzoxazoles, Indicator descriptor, QSAR.

INTRODUCTION

Azole compounds have a broad spectrum antimicrobial activity[1] mainly antifungal activity. In this paper we have worked on Benzoxazoles and Oxazolo-(4, 5-b) pyridines as antifungal agents and inhibitory activity as pIC_{50} value, which is used as a dependent variable is directly taken from work of Shaheen Begum et.al.[2]

Quantitative structure activity relationship is computational statistical method, which gives data set to predict the biological/structural activity. The analysis of QSAR/QSPR of compounds is an important aspect of drug chemistry. The information obtained is composed of mathematical equation relating the chemical structure of the compounds to a wide variety of their physical, chemical, biological and technological properties.[3-13] Once a correlation between structure and property is found can readily be screened in silico for selection of

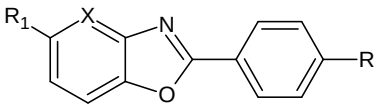
structure with desired properties. Hence, it is possible to select the most potent compounds set for synthesis and testing in laboratory.

The present QSAR studies have been widely utilized and have become increasingly helpful in understanding many aspects of chemical-biological interaction in drug as well as many other areas.. This analysis represents an attempt to relate structural descriptors of compounds with their topological properties and biological activities. This method included development of models, molecular descriptor selection, correlation model development and finally developed model evaluation. It provide mechanism of drug receptor interactions.[14]

Presentation of Data

In this study, Table 1 represents the structure of selected Benzoxazoles and Oxazolo pyridines compounds with their inhibitory activity[15] while Table 2 indicates the calculated topological index: ZM1Mad, ZM1Per, ZM2V, MSD, connectivity index: XMOD, X1with indicator index: IX. Table 3 has cross validation statistical parameters. Table 4 represents the calculated and observed inhibitory activity with residual of Benzoxazoles and Oxazolo pyridines compounds.

Table 1: Structure and in vitro anti-fungal activity of training set compounds.



Compound No.	X	R	R1	pIC50
1	CH	-H	-H	3.892
2	CH	-C(CH3)3	-H	4.001
3	CH	-NH2	-H	3.924
4	CH	NHCH3	-H	3.952
5	CH	-CH2CH3	-Cl	4.013
6	CH	-NHCOCH3	-Cl	4.059
7	CH	-NHCH3	-Cl	4.015
8	CH	-Cl	-Cl	4.024
9	CH	-NO2	-Cl	4.040
10	CH	-H	-Cl	4.282
11	CH	-CH3	-NO2	4.308
12	CH	-C(CH3)3	-NO2	4.375
13	CH	-NH2	-NO2	4.310
14	CH	-Cl	-NO2	4.342
15	CH	-Br	-NO2	4.406
16	CH	-CH2CH3	-NH2	3.976
17	CH	-F	-NH2	3.960
18	CH	-N(CH3)2	-NH2	4.005

19	CH	-CH3	-CH3	3.950
20	CH	-CH2CH3	-CH3	3.977
21	CH	-F	-CH3	3.958
22	CH	-NHCOCH3	-CH3	4.027
23	CH	-NHCH3	-CH3	3.979
24	CH	-N(CH3)2	-CH3	4.004
25	N	-CH3	-H	4.225
26	N	-CH2CH3	-H	4.253
27	N	OCH3	-H	4.257
28	N	-OCH2CH3	-H	4.283
29	N	-NH2	-H	4.227
30	N	-NO2	-H	4.285

RESULT AND DISCUSSIONS

In order to determine the correlation between the observed antimicrobial/antifungal activity (in terms of pIC_{50}) of the reported compounds with their structural parameters, QSAR investigation has been carried out by model proposed by Hansch et. al.[16] It is observed that any single descriptor is not strongly correlated with this biological activity. So then multiple regression analysis is used for modelling of these Benzoxazoles and Oxazolo pyridines compounds. Various models are obtained, some significant are discussed here.

P^{Ic}_{50}=3.1501+0.0018*ZM1Per+0.2430*IX ……..1

n=30 R^2=0.5826 R^2Adj=0.5517 F-Ratio=18.841

For antifungal activity the developed QSAR model eq.1 indicates the importance of topological descriptor ZM1Per which has positive coefficient with the antifungal activity. Similarly presence of indicator parameter IX represents the positive effect of presents of -N in place of group X in these Benzoxazoles and Oxazolo pyridines compounds. The value of IX is taken 1 if -N is present in place of X otherwise it is zero. Variance of this equation is only 58.26% indicates that the model is not significant that's why we need the development of triparametric model.

Table 2: Calculated Topological Descriptors.

S. No.	pIc50	X1	ZM1Mad	ZM1Per	ZM2V	MSD	XMOD	IX
1	3.892	7.433	86.372	401.78	296	3.917	45.821	0
2	4.001	9.038	110.372	495.22	360	4.993	55.452	0
3	3.924	7.826	93.399	435.99	316	4.222	48.472	0
4	3.952	8.365	97.76	460.72	336	4.572	51.969	0
5	4.013	8.758	117.891	510.15	356	4.794	56.95	0
6	4.059	9.614	132.159	593.01	404	5.445	63.071	0
7	4.015	8.758	119.279	522.69	364	4.794	57.508	0
8	4.024	8.22	129.411	525.72	352	4.448	56.898	0
9	4.04	9.131	130.068	596.86	404	5.041	61.085	0
10	4.282	7.826	107.891	463.75	324	4.146	51.359	0
11	4.308	9.131	114.549	558.25	392	4.938	57.91	0
12	4.375	10.342	132.549	628.33	440	5.706	65.178	0
13	4.31	9.131	115.575	569.1	396	4.938	58.198	0
14	4.342	9.131	130.068	596.86	404	4.938	61.085	0
15	4.406	9.131	180.419	596.86	404	4.938	66.281	0
16	3.976	8.758	103.399	482.39	348	4.794	54.064	0
17	3.96	8.22	103.23	497.96	344	4.448	51.702	0
18	4.005	9.131	111.147	519.98	376	5.041	57.044	0
19	3.95	8.22	98.372	448.5	328	4.448	50.547	0
20	3.977	8.758	102.372	471.54	344	4.794	53.775	0
21	3.958	8.22	102.203	487.11	340	4.448	51.413	0
22	4.027	9.614	116.64	554.4	392	5.445	59.896	0
23	3.979	8.758	103.76	484.08	352	4.794	54.333	0
24	4.004	9.131	110.12	509.13	372	5.041	56.755	0
25	4.225	7.826	94.148	437.78	320	4.222	48.638	1
26	4.253	8.365	98.148	460.82	336	4.572	51.866	1
27	4.257	8.365	101.027	487.94	352	4.572	52.981	1
28	4.283	8.865	105.691	511.14	368	4.955	55.774	1
29	4.227	7.826	95.175	448.63	324	4.222	48.927	1
30	4.285	8.737	110.325	547.53	384	4.818	56.001	1

P^{Ic}_{50}=1.4005+1.4167*X1-2.0355*MSD+0.3347*IX 2

n=30 R^2=0.8027 R^2Adj=0.7799 F-Ratio=35.261

The developed QSAR model eq.2 describes the importance of connectivity and indicator descriptors with antimicrobial activity. According to the developed model MSD show the negative coefficient while IX and X1 show positive coefficient. The correlation coefficient between the descriptors and the antifungal activity r=0.89 with the variance 80.27% which is not better.

P^{Ic}_{50}=1.6799+1.1310*X1-1.7884*MSD+0.0186*XMOD+0.3351*IX ……..3

n=30 R^2=0.8616 R^2Adj=0.8394 F-Ratio=38.904

Our regression analysis is performed by using eight combinations of topological, connectivity and indicator descriptors. X1 plays a leading role to predict antimicrobial activity. The positive coefficient of X1 indicates that the activity increases with increasing the value of X1 (eq.3) similarly XMOD and IX also increases the activity whether MSD decreases value of Ic50, because its coefficient is negative. The correlation coefficient r=0.93. The PRESS/SSY is also less than eq.1 and 23 indicate that this model is the best model. For the validation of developed model cross validation is applied with their descriptors is given below in table 4.

Table 3: Cross Validation Statistical parameters.

Model	n	PRESS	SSY	PRESS/SSY	R^2CV	Spress
1	30	0.3834	0.7554	0.5075	0.4925	0.1130
2	30	0.2168	0.7554	0.2870	0.7130	0.0850
3	30	0.1554	0.7554	0.2057	0.7942	0.0720

The developed QSAR model is validated with high correlation coefficient between the topological descriptors and antimicrobial activity. With the using of four high parametric model in multiple regression analysis and by cross-validation procedure, modelling of the best antifungal as well as antimicrobial benzoxazole derivatives performed. Fewer parameters: PRESS, SSY, R^2cv, Spress are important cross validation parameters. According to table 4. PRESS values are less than SSY. Model no. 4 has high R^2cv and low PRESS/SSY indicate of its reliability in predicting the inhibitory activity.

Table 4: Antibacterial Screening Summary of Benzoxazole derivatives.

Compound No.	Actual	Predicted	Residual	Compound No.	Actual	Predicted	Residual
1	3.892	3.933	-0.041	16	3.976	4.017	-0.041
2	4.001	4.003	-0.002	17	3.96	3.983	-0.023
3	3.924	3.882	0.042	18	4.005	4.052	-0.047
4	3.952	3.93	0.022	19	3.95	3.962	-0.012
5	4.013	4.07	-0.057	20	3.977	4.011	-0.034
6	4.059	3.988	0.071	21	3.958	3.978	-0.02
7	4.015	4.081	-0.066	22	4.027	3.929	0.098
8	4.024	4.08	-0.056	23	3.979	4.022	-0.043
9	4.04	4.127	-0.087	24	4.004	4.047	-0.043
10	4.282	4.071	0.211	25	4.225	4.22	0.005
11	4.308	4.252	0.056	26	4.253	4.263	-0.01
12	4.375	4.384	-0.009	27	4.257	4.284	-0.027
13	4.31	4.258	0.052	28	4.283	4.217	0.066
14	4.342	4.312	0.03	29	4.227	4.225	0.002
15	4.406	4.408	-0.022	30	4.285	4.321	-0.036

To realize the effect of multicolinearity between the descriptors which affects the activity of model we proceed the ridge trace the graph which show that there is mild multicolinearity problem does not affect the variance of developed model.

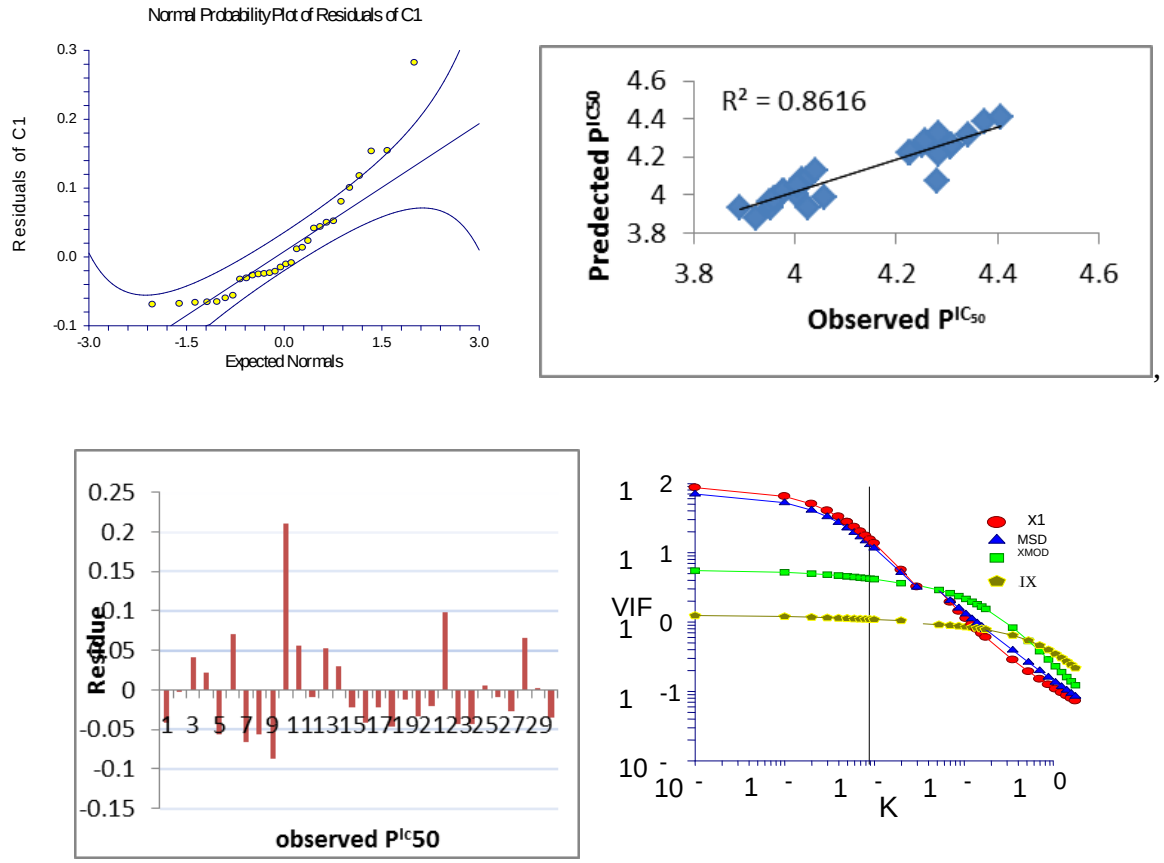


Fig 1: Graph showing Relation between Experimental and Predicted Antibacterial activity.

CONCLUSION

In view of result and discussions, we conclude that topological descriptor X1, MSD, XMOD and indicator descriptor IX can be successfully used for modeling benzoxazoles and oxazolo derivatives as antimicrobial drugs. These results will help medical as well as agriculture scientists in the designing and prediction of new benzoxazoles and oxazolo drugs exhibiting better activities than these reported in this result.

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