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QSAR Study of α, β unsaturated ketone as potent antifungal agents

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Abstract

To explore physicochemical properties of α, β Unsaturated Ketone derivative for their anti-fungal activity, a quantitative structure activity relationship, Hansch approach was applied on twenty compounds of above mentioned derivative . Various physicochemical and topological descriptor and reported minimum inhibitory concentration value of C. albicans were used as independent variables and dependent variable respectively. It was revealed that mixed descriptor were found to have overall significant correlation ship with antifungal activity and these studies provide an insight to design new molecule

Key-Words: Antifungal activity, QSAR

Introduction

During the past two decades an increasing number of quantitative structure- activity/property relationship (QSAR/ QSPR) models have been using theoretical molecular descriptors for predicting biomedical, toxicological, and technological properties of chemicals.[1-7] QSARs/QSPRs are mathematical models that seek to predict complicated physicochemical/ biological properties of chemicals from their simpler experimental or calculated properties.[8] The main problem with the use of experimental data as independent variables in QSARs is that they are not available for the majority of chemical structures, real or hypothetical.

Major increase in the incidence of systemic fungal infection caused by the yeast *C. albicans* and other fungi has been observed in the past two decades, particularly in immune-compromised patient.[9] The number of agent available to treat fungal infection has increased by 30% since the year 2000, yet still only 15 agents are currently approved for clinical use. The greater number of medication now available allows for therapeutic choices; however differences in antifungal spectrum of activity, bio-availability , formulation , drug interactions and side effects necessitates a detailed knowledge of each drug class.[10]

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α, β Unsaturated Ketone are reported to have an array of important therapeutic activities such as antihypertensive, and cardiovascular activity, anti-protozoal, anti-inflammatory, anti-diabetic, anti-cancer, as well as anti-fungal.[11-18]

The quantitative structure activity relationship (QSAR) study is a useful tool for rational research of bioactive compounds. QSAR study describes a definite role in a quantitative term of a structural feature in molecule with a definite contribution to the activity of a particular physicochemical property of the structural feature. Thus QSAR studies have predictive ability and deeper insight into the mechanism of drug receptor interaction. We therefore, report here a QSAR study on α, β Unsaturated Ketone for their antifungal activity against human fungal pathogen such as *C. albicans.*

Methodology

A set of twenty compounds of α, β Unsaturated Ketone with unsubstituted thiophene ring and thiomethyl substitution at the para position of benzaldehyde has been selected from the reported work of Seem Bag et.al.[19] and is given in Fig. 1.1 and Fig. 1.2 exhibited good antifungal activity and biological activity data MIC is given with calculated descriptor shown in table 1.1 and table 1.2 for QSAR analysis.

Molecular modeling studies were performed using ChemSketch and E-dragon software running in dual core processor. All molecules were constructed and it was saved as the templet structure. The regression analysis were carried out using a computer programme

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NCSS 2007. The auto-correlated parameters were eliminated depending on their individual correlation with biological activity in order to avoid simple collinearly problem.

Multivariate Regression Analysis

Stepwise multiple regression analysis method was used to perform QSAR analysis employing NCSS software. The statistical parameter viz. correlation coefficient (r), explained variance (R^2), standard error of estimate (S), F-Test were considered to compare the generate QSAR model. A cross validated R^2 obtained as a result of this analysis served as a quantitative measure of predictive ability of final QSAR model. Based on the contributing parameter to the selective inhibition data, the selective parameters were correlated to the appropriate to gain an insight into the selectivity. The calculated descriptor for thiomethyl and thiophene are given below with correlation matrix.

Fig. 1.1: Structure of α, β unsaturated ketone molecules of thiophene with antifungal activity

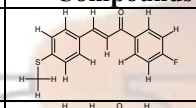
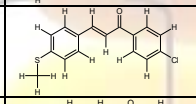
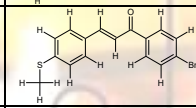
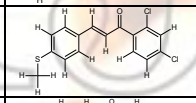
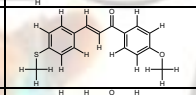
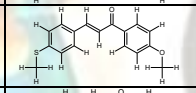
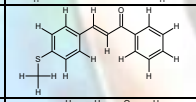
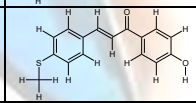
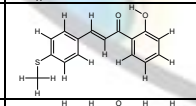
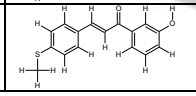
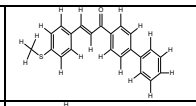
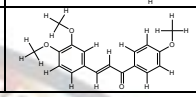
Comp. No.	Structure of Compounds	MIC
1		8
2.		20
3.		100
4.		200
5.		100
6.		20
7.		40
8.		40
9.		20
10		40
11		250
12.		10

Fig. 1.1: Structure of α, β unsaturated ketone molecules of thiomethyl with antifungal activity

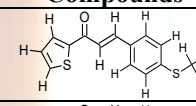
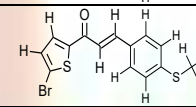
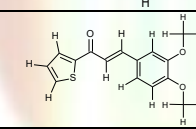
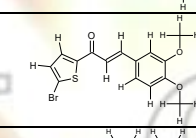
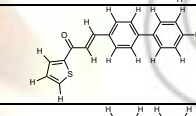
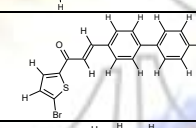
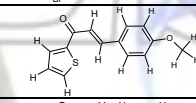
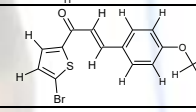
Comp. No.	Structure of Compounds	MIC
1		5
2.		50
3.		20
4.		100
5.		250
6.		250
7.		20
8.		5

Table 1.1: Calculated Descriptors for α,β unsaturated ketone molecule of thiophene

CN	MIC	MR	DEN	POL	X2	X3v
1	8	78.12	1.21	30.97	7.87	3.415
2	20	82.84	1.25	32.84	7.87	3.667
3	100	85.73	1.43	33.98	7.87	3.944
4	200	87.67	1.33	34.75	8.409	4.031
5	100	84.05	1.29	33.32	8.769	3.649

6	20	84.38	1.17	33.45	8.039	3.661
7	40	78	1.15	30.92	7.248	3.345
8	40	79.54	1.24	31.53	7.87	3.438
9	20	79.54	1.24	31.53	7.775	3.456
10	40	79.54	1.24	31.53	7.881	3.417
11	250	102.72	1.18	40.72	9.923	4.455
12	10	87.14	1.139	34.54	8.759	3.209

Table 1.2: Calculated Descriptors for α, β unsaturated ketone molecule of thiomethyl

Comp. No.	MIC	NM	JhetZ	Jhetm	Jhete
1	5	603	2.071	2.102	12.088
2.	50	708	2.068	2.09	12.958
3	20	791	1.931	2.273	13.665
4	100	917	1.944	2.246	14.535
5	250	1097	1.813	1.833	14.493
6	250	1254	1.792	1.806	15.364
7	20	603	1.927	2.131	12.088
8.	100	708	1.939	2.115	12.958

Results and discussion

Among several model one best model was chosen for each micro-organism based on statistical parameter viz. correlation coefficient, cross validated, standard deviation, and F- ratio. Calculated for α, β unsaturated ketone inhibiting activities for candida albicans are summarized in table 3 which is given below. From regression table 3.1 for candida albicans indicated better correlation (r^2 = 0.93) between parameter and fungal inhibitory activity of the thiphene series and it become (r^2 = 0.98) for thiomethyl series.

It is very important for further analysis to develop a correlation matrix (Table 2.1 and 2.2) for the descriptors utilized and their correlation with the biological activities. The best correlation is observed between $^3X^v$ and MIC (r = 0.90) and in thiomethyl series the best correlation is found to be between NM and MIC which is about (r = 0.92) which show positive indication towards the antifungal activity.

The descriptors are mutually correlated, thus if a combination of them is present in the regression expression, then the model may suffer from a defect due to co-linearity. A perusal of table 2.1 and 2.2 show that all chosen are not well correlated with antifungal activities; meaning that in mono-parametric regression, those properties are not appropriate to obtain statistically significant results.

Table 2.1: Correlation Matrix for α, β unsaturated ketone molecule of thiophene

	MIC	MR	DEN	POL	X2	X3v
MIC	1.0000	0.8094	0.3036	0.8093	0.7047	**0.9003**
MR		1.0000	-0.0161	0.9999	0.9058	0.8238
DEN			1.0000	-0.0165	-0.1143	0.3776
POL				1.0000	0.9059	0.8238
X2					1.0000	0.6369
X3v						1.0000

Table 2.2: Correlation Matrix α, β unsaturated ketone molecule of thiomethyl

	MIC	NM	JhetZ	Jhetm	Jhete
MIC	1.0000	0.9249	-0.8277	-0.8411	0.8229
NM		1.0000	-0.8227	-0.6943	0.9582
JhetZ			1.0000	0.6113	-0.7440
Jhetm				1.0000	-0.4710
Jhete					1.0000

All physicochemical and topological descriptor (Table 1.1 and Table1.2) were selected as independent variable and minimum inhibitory concentration were taken as dependent variable and the step wise multiple regression method was used resulting in the following equation (Table 3.1 and Table 3.2).

Table 3.1: Regression parameters and quality of proposed models of α, β unsaturated ketone molecule of thiophene

Parameters Used	Ai(1----5)	Se	R^2	R^2A	F-Ratio
Mono-parametric	-666.5920+202.5111 $^3X^v$	113.1952	0.8105	0.7916	42.784
Bi-parametric	-757.5206+25.1781$^3X^v$ +170.8441^2X	130.8803	0.8396	0.8039	23.552

Tri-parametric	-748.9646-6.3437$^3X^v$ +40.9791^2X +191.0408Pol	138.7087	0.8432	0.7844	14.337
Tetra-parametric	-733.5132+3114.5378$^3X^v$ -7873.0084^2X +68.4803 Pol +213.8706Den	130.9983	0.8784	0.8090	12.647
Penta-Parametric	-49.9716+8594.6997$^3X^v$ -535.1285^2X -21736.0410 Pol +132.0375Den+416.8318 MR	347.3166	0.9291	0.8700	15.728

Table 3.2: Regression parameters and quality of the proposed models α, β unsaturated ketone molecule of thiomethyl

Parameters Used	Ai(1----5)	Se	R^2	R^2A	F-Ratio
Mono-Parametric	-225.1330+0.3886NM	56.3322	0.8555	0.8314	35.521
Bi-Parametric	331.7830+0.2765NM-223.3502Jhetm	238.8526	0.9319	0.9047	34.222
Tri-Parametric	28.7274-0.3749NM-500.8145Jhetm+105.2353Jhete	378.3775	0.9462	0.9058	23.434
Tetra-Parametric	542.5205-1.1867Nm-393.0695Jhetm-773.6347Jhete+215.5259Jhetz	332.5634	0.9816	0.9572	40.113

Among the several model generated the equation 05 from table 3.1 and equation 04 from table 3.2 are the best model which were selected for discussion. The selection was based on the previously mentioned significant result for growth inhibition activity of α, β unsaturated ketone molecule against *C. albicans* using four and five descriptor respectively.

Initial regression analysis indicated of thiophene that the five molecular descriptor used, in combination with other physicochemical and topological descriptors play a dominant role in shaping antifungal activity. The positive coefficients of X^2 , Den, MR indicates that the activity increases as the magnitude of descriptor increases, simultaneously in thiomethyl series the positive coefficients are shown by Jhetz.

Table 4.1: Estimated inhibitory activity of α, β unsaturated ketone molecule of thiomethyl

Comp. No.	Actual MIC	Predicted MIC	Residual
1	8	17.892	-9.892
2	20	22.114	-2.114
3	100	100.849	-0.849
4	200	198.76	1.24
5	100	78.195	21.805
6	20	61.59	-41.59
7	40	-5.868	45.868
8	40	43.716	-3.716
9	20	38.675	-18.675
10	40	36.415	3.585
11	250	241.737	8.263
12	10	13.925	-3.925

The correlation co-efficient were found to be good (0.80-0.98) in all the cases and the f-ratio become between (15-40). In view of the results and discussion above, we have accounted for as much of the variance in the data set as is possible within the limits set by the experimental error, by assuming that there is no systematic global preference for either of the two possible orientation of the fused ring system.

Table: 4.2:-Estimated inhibitory activity of α, β unsaturated ketone molecule of thiomethyl

Comp. No.	Actual MIC	Predicted MIC	Residual
1	5	-7.992	12.992
2	50	65.378	-15.378
3	20	31.536	-11.536
4	100	85.301	14.699
5	250	233.651	16.349
6	250	264.209	-14.209
7	20	26.174	-6.174
8	100	96.743	3.257

In a molecule, all atoms may not be responsible for the biological activity. A part of the structure or some specific atoms, called pharmacophore, are required for the desired activity. The QSAR approach used to derive the MLR based models provided reliable and highly predictive models, as compared to state-of-the-art 3D QSARs. Slight advantage of using PLS regression was observed when compared to N-PLS, though the multilinear regression method led to a more parsimonious model. Furthermore, it has been found that MIA-QSAR may serve as an alternative or

complementary tool when equally simple methods fail in predicting bioactivities.

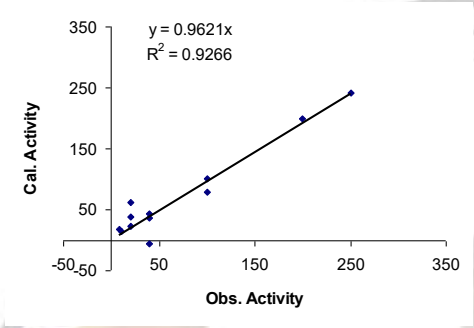


Fig. 2.1: Graph between observed and calculated MIC of thiophene group

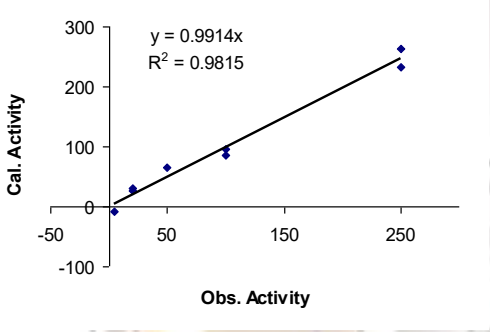


Fig. 2.2: Graph between observed and calculated MIC of thiomethyl group

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