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QSAR Studies of 2-Phenoxyacetamide Analogues, a Novel Class of Potent and Selective Monoamine Oxidase Inhibitors

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ABSTRACT

The primary objective of this investigation was to develop a QSAR model for novel series of phenoxy acetamide derivatives as Monoamine Oxidase Inhibitors. The data series were taken from the reported work of Wei Shen et al., 2014. The selected series consists of total 20 compounds, divided into two sets training set having 18 compounds and test set with 2 compounds. All the structures of phenoxy acetamide derivatives were sketched using Chem Office 2001. QSAR models were obtained by using VALSTAT software. The best-developed model showed a good correlative and predictive ability having regression coefficient (r2) of 0.9033 and q2 is 0.8376. For MAO B inhibitor activity, MW has positively correlated. The positive correlation of MW indicates that bulky group or higher molecular weight compounds are important for better MAO enzymes inhibition activity. The negative correlation of HOMO indicated that electrophilic group may increase the activity. The BetaPol also negatively correlated indicated less polar group give more activity. Based on the developed QSAR model, it may be concluded that highest occupied molecular orbital (HOMO) energy, molecular weight and Beta Polarizability are to be considered while designing newer compounds, for their potential MAO inhibitory activity.

Key words: Monoamine Oxidise inhibitors, Quantitative Structure Activity Relationship (QSAR), Phenoxyacetamide, MAO-B, Statistical Analysis

1. INTRODUCTION

Monoamine oxidases (MAOs) are flavoenzymes found in the outer mitochondrial membrane and are responsible for the oxidative degradation of neurotransmitters and amines.[1] There are two isoforms are found namely MAO-A and MAO-B.[2] MAO plays an essential role in the regulation of significant role in central nervous system activity and contributes to the pathogenesis of human neurodegenerative and depressive disorders.[3] MAO-A is primary type found in fibroblasts, and metabolise the neurotransmitter like Dopamine, Serotonin, epinephrine and norepinephrine.[4] The MAO-B is found in platelets and in the brain of a human. MAO-B is mainly involved in the metabolism of benzylamine and beta-phenylethylamine, but enzymatic metabolism of Dopamine and tryptamine is carried out by both isoforms.[5] MAO protect the peripheral tissue of the body (liver, lungs, intestine, gastrointestinal lumen and placenta) by reducing the entry of different oxidizing amines in body systemic circulation.[6] Both the enzymes play a vital role in the regulation of intracellular amine contents.[7,8]

Many selective MAO inhibitors have been developed which makes a significant therapeutic effect in the treatment of neurological and neuropsychiatric disorders.[9] It is also responsible for the converting of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine into 1-methyl-1,4-phenylpyridinium(MPP+) parkinsonian producing neurotoxins by degrading dopamine-generating neurons in substantial nigra.[10] During the death of cells action of MAO limit the neuron firing in the within homeostasis condition.[11,12] The study about MAO-A and MAO-B stated that they are involved in the different pathophysiological situation like anxiety, atypical depression, bipolar depression, Alzheimer's and Parkinson diseases.[13]

Quantitative Structure-Activity Relationship (QSAR) modelling related to the building of predictive models of biological activities as a functional and molecular information of compound library.[14] Several approaches were done to perform the rational design of new inhibitors described by theoretical calculation, starting with the crystalline structure of MAO-A.[15,16] Establishment of structure-activity relationship helpful in understanding the interaction of the newly designed molecule with MAO enzyme.[17]

Some acetamide derivatives with potent MAO inhibiting activity were found among them safinamide was found potent MAO inhibitor.[18,19] On the basis of these, a series of 20, 2-phenoxy acetamide compounds were synthesized and examined for MAO inhibitors.[20] The present QSAR study of various phenoxy acetamide derivatives was discussed by their physiochemical properties required for specific MAO-A and MAO-B inhibitory activity, based on Hansch type of analysis.[21,22] These studies helped in designing newer molecules with improving and specific MAO inhibitory activity.

2. MATERIALS AND METHODS

2.1 Data set

QSAR analysis was performed to relate monoamine oxidase inhibition activity of phenoxy acetamide derivatives to its physicochemical properties. The data series were taken from the reported work of Wei Shen et al., 2014[20]. The selected series consists of total 28 numbers of compounds but QSAR software did not able to calculate the descriptors of some compounds. Therefore we have taken 20 compounds and divided into two data sets, one was training set having 18 compounds and other, was the test set with the remaining 2 compounds. The selection of training and test sets was done by VALSTAT software on the basis of automatic mode available in the software and ratio of test and training was 1 to 10 because the structure and activity diversity in both sets should be maintained for QSAR models development. The biological activities were expressed in terms of inhibitory concentration (IC50) in μM concentration. For correlation purposes, reported IC50 values were converted to their molar units and subsequently to free energy related negative logarithmic state, i.e., Log (1/ IC50) or pIC50. These compounds along with their inhibition data are presented in table 1.

2.2 Molecular structure generation

All the structures of phenoxy acetamide derivatives were sketched using Chem Draw Ultra 6.0. The molecular mechanics (MM_2) method was applied to search for lower energy conformations for each molecule. The energy minimized molecules were subjected to re-optimization using molecular orbital property accompany name (MOPAC). To avoid the local stable conformations of the compounds, geometry optimization was run many times with different starting points for each molecule, and conformation with the lowest energy was considered for calculation of the molecular descriptors. The thermodynamic, electronic, steric, and molecular descriptors were calculated by the Chemoffice 2001[23] for the QSAR analysis and reported in table 2.

2.3 Statistical analysis

In the case of each enzyme inhibition activity, the calculated descriptors were collected in a data matrix (D) with the dimension of ($n \times m$), where n and m being the number of molecules in each data set and the number of calculated descriptors for each molecule, respectively. Firstly, the descriptors were checked for constant or near constant values and those detected were removed from the original data matrix. Then, the correlation of descriptors with each other's and with the activity data was determined. In order to select the predominant descriptors affecting the activity, the correlation analysis was performed using the statistical software VALSTAT.[24] The Pearson correlation matrix of selected descriptors is given in table 3.

2.4 Model development and validation

QSAR models were obtained by multiple linear regression (MLR) analysis. The stepwise selection of variables, a combination of forwarding selection and backward elimination procedure, was used to select the most relevant subset of descriptors. Regression analyses were performed by VALSTAT software.

External validation was performed to validate the QSAR model. In this approach, the activity of each compound in the test set is computed. With the help of observed activity and calculated activity cross-validation coefficient, q2 was calculated. Cross-validation coefficient q2 can be considered as an indicator of the predictive performance and stability of a model. For a reliable model, the square of cross-validation coefficient q2 should be$\geq$0.5.

3. RESULT AND DISCUSSION

Multiple linear regressions and other statistical analysis were carried out on all the compounds of the training set. Descriptors were selected for the model based on their correlation coefficient and those descriptors having interred correlation coefficient below 0.6 were considered. Various models were obtained after performing multiple linear regression (MLR) analysis. Model predictive power was judged based on various statistical parameters like correlation coefficient, regression coefficient (r2), Fischer statistical value (F), and standard error. All

these statistical parameters were computed as defined in the VALSTAT.

The initial regression analysis was performed on all the 18 molecules of training which resulted in the regression model. The best QSAR model has the characters of large F, low p-value, r2 and q2 values close to 1, as well as P<0.001. Model 1-5 are obtained with the combination of seven descriptors Beta Pol(Beta Polarizabilities), Mass(ExactMass), MW(molecular weight), HOMO (HOMO Energy), Eb (Bend Energy), E(Total Energy), ElcE(Electronic energy). The best models observed in this QSAR study are as follow:

Model-1
BA= [-4.32191(± 1.22159)] +Eb [-0.119775(± 0.029081)] +HOMO [-0.572675(± 0.101801)] +MW [0.0141506 (± 0.00251478)]
n=18, r=0.86468, r^2=0.747672, r^2adj=0.693602, variance=0.021837, std=0.147773, QF=5.8514, PE=0.0396495, F=13.8278, FIT=1.53642, LOF=0.818615, AIC=0.0343152

Model 1 was developed by using Eb, HOMO and MW descriptors having r^2 0.747672 and std 0.147773. The r^2 was less and std was more. So, we develop Model 2 by changing MW descriptor with Mass descriptor and found r^2 value 0.748107 and std 0.147646.

Model-2
BA= [-4.33079(± 1.22145)] +Eb [-0.120342(± 0.0291313)] +Mass [0.0141928(± 0.00251914)] +HOMO [-0.573232(± 0.101755)]
n=18, r=0.864932, r^2=0.748107, r^2adj=0.694129, variance=0.0217993, std=0.147646, QF=5.85815, PE=0.0395812, F=13.8597, FIT=1.53997, LOF=0.817205, AIC=0.0342561

Model-3
BA= [2.31489(± 0.246381)] +ElcE [4.60811e-005(± 1.02425e-005)] +Mass [0.00783638(± 0.00162759)] +E [0.0108036(± 0.00213916)]
n=17, r=0.880039, r^2=0.774469, r^2adj=0.722423, variance=0.0175312, std=0.132405, QF=6.64655, PE=0.0364663, F=14.8806, FIT=1.78058, LOF=0.658646, AIC=0.0255812

Model 3 was developed by using ElcE descriptor with E descriptor having r^2 0.774469 and std 0.132405. So, we can conclude that when we can use BetaPol, HOMO in combination with MW in place of Mass, Eb, and ElcE and found good r^2 value and less std value.

Model-4
BA= [-4.235 (±0.991054)] +BetaPol [-0.00382211(± 0.000851842)] +HOMO [-0.644916(± 0.091212)] +MW [0.00799622(± 0.00126776)]
n=17, r=0.914423, r^2=0.836169, r^2adj=0.798362, variance=0.0151475, std=0.123075, QF=7.42979, PE=0.0264899, F=22.1167, FIT=2.64644, LOF=0.569091, AIC=0.022103

Model-5
BA= [-4.49085(± 0.775768)] +BetaPol [-0.00354622(± 0.000668992)] +HOMO [-0.678097(± 0.0718013)] +MW [0.00785342(± 0.000987736)]
n=16, r=0.950454, r^2=0.903363, r^2adj=0.879204, variance=0.00917463, q^2=0.8376 std=0.0957843, QF=9.92286, PE=0.0161062, F=37.392, FIT=4.84711, LOF=0.347956, AIC=0.0123577

We tried to develop more models by using different descriptors then we found Model 4 and Model 5 having descriptors BetaPol in combination with HOMO and MW. We found model 5 is the better model among all 5 models having r2 value 0.903363 and q2 0.8376 having two outliers. For MAO-B inhibitor activity, MW has positively correlated. The positive correlation of MW indicates that bulky group or higher molecular weight compounds are important for better MAO enzymes inhibition activity. The negative correlation of HOMO indicated that electrophilic group may increase the activity. The BetaPol also negatively correlated indicated less polar group give more activity. The predicted biological activities values of training set & test set of series by using model-5 is given in table 4 & 5 and shown in figure 1.

4. CONCLUSION

We developed QSAR model of phenoxy acetamide derivatives for their monoamine oxidase inhibitory activity. In summary, it may be concluded that monoamine oxidase inhibitory activity of phenoxy acetamide derivatives is strongly influenced by the thermodynamic and electronic nature of the substituents. Based on the developed QSAR model, it may be concluded that highest occupied molecular orbital (HOMO) energy, molecular weight and Beta Polarizability are to be considered while designing newer compounds, for their potential MAO inhibitory activity. This QSAR model can be utilized for the further development of new molecules to exhibit good enzyme inhibitory activity.

5. ACKNOWLEDGEMENT

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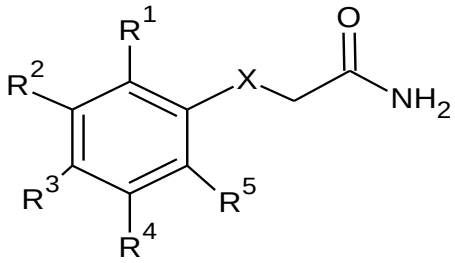
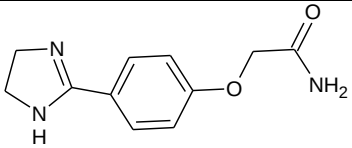
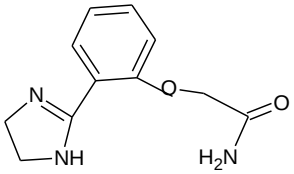
Table 1. Structure and biological activity of phenoxyacetamide analogues



Compd.	Substitution	IC50 (µM)	BA
1	R_1=R_2=R_3=R_4=R_5=H, X=O	778	3.109
2*	2-Naphthalenyl,X=O	542	3.266
3	R_1=R_2=R_4=R_5=H , R_3= F, X=O	255	3.5934
4	R_1=R_2=R_4=R_5=H, R_3=Cl, X=O	202	3.6946
5	R_2=R_4=R_5=H, R_1=Cl, X=O	694	3.1586
6*	R_1=R_2=R_4=R_5=H, R_3=-CHO, X=O	457	3.34
7	R_2=R_4=R_5=H,R_1=-CHO, X=O	559	3.2525
8	R_1=R_4=R_5=H, R_2=R_3=-CH_3, X=O	534	3.2724
9	R_2=R_4=R_5=H, R_1=CH_3,X=O	663	3.1784
10	R_1=R_2=R_4=R_5=H,R_3=CH_3,X=O	541	3.2668
11	R_2=R_3=R_4=R_5=H,R_1=-OCH_3,X=O	775	3.1106
12	R_1=R_2=R_4=R_5=H, R_3=-OCH_3, X=O	980	3.008
13	R_2=R_3=R_4=R_5=H, R_1=-COOH,X=O	177	3.752
14	R_2=R_3=R_4=R_5=H, R_1=-$COOCH_3$,X=O	98	4.0087
15	R_1=R_2=R_4=R_5=H,R_3=NHCOOC$(CH_3)_3$,X=O	296	3.5287
16	R_1=R_2=R_4=R_5=H,R_3=NHCOCH_3,X=O	553	3.2572
17	R_1=R_2=R_3=R_4=R_5=H, X=S	642	3.1924
18	R_1=R_4=R_5=H,R_2=R_3=CH_3, X=S	366	3.4365
19		661	3.2958
20		186	3.1463

* test set compounds

Table 2. Descriptors for training and test set compounds of series

Compd	Beta Pol	ElcE	HOMO	MW	Eb	Mass	E
1	43.5316	-9145.51	-9.62749	151.166	1.23612	151.063	2.44511
2*	-0.6586	-13595.4	-8.57678	201.226	2.69566	201.079	-6.02889
3	-40.5534	-10804.3	-9.54727	169.156	1.2208	169.054	2.45739
4	-43.9173	-10550.2	-9.60669	185.611	1.28212	185.024	-2.87019
5	-0.7716	-10736.1	-9.20432	185.611	2.62751	185.024	2.13779
6*	-49.5931	-11601.5	-9.67171	179.176	5.8707	179.058	17.4804
7	-29.7804	-12075.9	-10.0876	179.176	5.8706	179.058	1.29424
8	-43.5542	-11986.3	-9.2776	179.22	1.58196	179.095	2.47659
9	-30.8477	-10711.3	-9.45944	165.193	1.40969	165.079	1.21837
10	-44.8872	-10468.6	-9.37054	165.193	1.34662	165.079	2.18173
11	-1.3621	-12563.8	-9.56571	181.192	2.30864	181.074	6.58625
12	-4.498	-12091	-9.07342	181.192	3.48957	181.074	7.77319
13	-11.2106	-13.957	-9.69134	195.176	3.89567	195.053	-5.79965
14	-27.0898	-15714.9	-10.0426	209.203	3.62181	209.069	63.15363
15	6.5089	-22049.7	-8.85692	266.298	7.45867	266.127	4.12102
16	-62.3406	-14672.8	-8.79359	208.218	2.94113	208.085	1.57646
17	-68.3613	-8744.85	-8.94161	167.233	0.529503	167.04	-8.25975
18	-85.403	-11560.4	-8.84059	195.287	0.861357	195.072	-8.24208
19	-6.2223	-15752.9	-8.81982	219.244	6.20351	219.101	0.278233
20	62.0398	-18691.8	-8.79785	233.271	6.85759	233.116	4.6202

* test set compounds

Table 3. Pearson correlation matrix between selected descriptors

	BetaPol	**HOMO**	**MW**
BetaPol	1.000000		
HOMO	0.024071	1.000000	
MW	0.284043	0.444679	1.000000

Table 4. The Actual and predicted pIC50 values of training set of series by using model-5

Compound	**Actual BA**	**Predicted BA**
1	3.109	3.07031
3	3.5934	3.45538
4	3.6946	3.63683
5	3.1586	3.21098
8	3.2724	3.3622
9	3.1784	3.33028
10	3.1784	3.31979
12	3.008	3.10073
13	3.752	3.65337
14	4.0087	4.05803
15	3.528	3.58326
16	3.2572	3.32853
17	3.1924	3.1282
18	3.4365	3.34045
19	3.2958	3.23372
20	3.1463	3.08691

Note: Compound 7 & 11 was outlier

Table 5. Actual and Predicted pIC_{50} values for test set of series by using model-5

Compound	**Actual BA**	**Predicted BA**
2	3.266	2.90768
6	3.34	3.65051

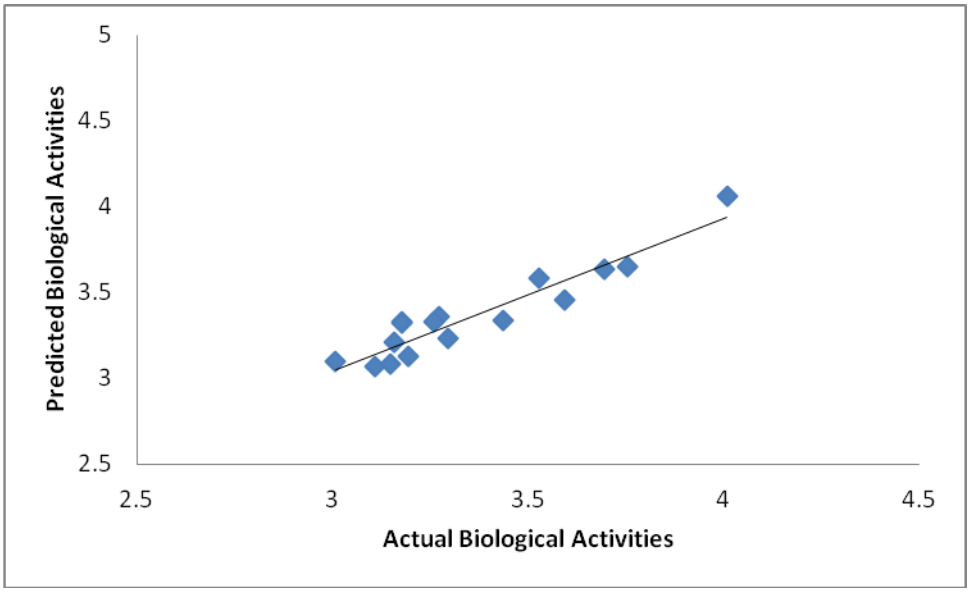


Fig 1. The graph between actual and predicted activities of training set of series by using model-5

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