QSAR STUDIES OF SOME PHENOXY ACETAMIDE DERIVATIVES AS SELECTIVE MAO-B INHIBITORS

Bharti Sahu[1*], Varsha Nadkar[2], Avadhesh Kumar[3], Achal Anand[4], Mahendra Kumar Sahu[5]

Abstract

The project work involves the development and computational investigation of 2-phenoxyacetamide derivatives as MAO -B inhibitors. A series of 28 compounds based on 2-phenoxyacetamide derivatives were selected for the construction of the 2D QSAR model. The QSAR model was constructed using Chem Office 2002 and VALSTAT 6.0. The model was validated based on various statistical parameters and was able to significantly predict the biological activity of the compounds from the "test set" and the "training set". The reported experimental IC50 value was used as the biological data set for the development of the QSAR model. A total of 75 new molecules were designed by varying the different substituents on the 3-phenoxyacetamide scaffold. All designed molecules were subjected to the calculation of the molecular descriptors involved in the construction of the QSAR model (PMI-Y, PMI-Z), followed by the prediction of the biological activity for each of them. Of the total 75 designed molecules, 40 molecules with comparable predicted biological activity were subjected to molecular docking analysis along with a standard ligand using the AutoDock module of PyRx software to determine their binding efficacy and interaction with target protein i.i.e. MAO -B (PDB ID 4CRT), out of all 40 ligands docked, a total of 20 ligands showed good electrostatic and hydrophobic interaction with the active site residues of MAO -B protein(4crt), and they have better docking score compared to the standard ligand (rasagiline) docked. Going forward, a PreADMET study was performed for all 20 ligands that showed promising results in docking analysis using the web-based online application Pre-ADMET. The PreADMET study directly correlated the pharmacokinetic and toxicological properties of the molecules. Of the 20 ligands subjected to the PreADMET study, ligand "9G" showed the best pharmacokinetic profile, including the ability to cross the BBB, and it showed negative results in terms of toxicity in rat and mouse.

Key Words:- QSAR**,** MAO -B inhibitors, Phenoxyacetamide & PreADMET.

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DOI: 10.48047/ecb/2023.12.si10.00424

Introduction

Man has used herbs and potions as medicines for several thousand years. However, it is only since the mid-nineteenth century that serious efforts were made to isolate and purify the active principles of these remedies; medicinal chemistry received a further boost in 1940 as pharmacology, which until then had been dominated by physiology, became increasingly biochemical with a new understanding of the role of enzymes and cell receptors—chance observations of folk medicines or by noting the side effect of other drugs. Medicinal chemistry is the application of chemical research techniques used to identify, synthesize and develop chemicals. Medicinal chemistry as a scientific discipline has introduced several new techniques to speed up drug discovery over the last few years, such as combinatorial chemistry, microwave-assisted organic synthesis, and high-throughput purification to develop a novel drug from natural sources.1

About Mono Amino Oxidase

Monoamine oxidase (MAO) is an enzyme originally discovered by Mary Bergheim in the liver and named tyramine oxidase. They belong to the protein family of FAD (flavin adenine dinucleotide) found in the outer mitochondrial membrane of neuronal, glial, and other mammalian cells. Monoamine oxidases (MAO) play a major role in the metabolism of intracellular Neurotransmitters of the central nervous system (CNS). **2**MAO plays an important role in the metabolism of several neurotransmitters and is useful in treating neurological diseases. MAO-A and MAO-B have been identified based on their amino acid sequences, three-dimensional structures, substrate specificity, and inhibitor selectivity.**3**MAO-A preferentially metabolizes the neurotransmitters serotonin, epinephrine, and norepinephrine, and MAO-B is predominantly involved in the metabolism of benzylamine and beta phenylethylamine.**4**

Both MAO carries out the enzymatic breakdown of tryptamine and dopamine. Monoamine oxidase B (MAO-B) activity is also increased in association with gliosis, which can result in high levels of H2O2 and oxidative free radicals, which are a possible source of oxidative stress for vulnerable neurons affected by Alzheimer's disease. MAO-A inhibitors act as antidepressants, and MAO-B inhibitors are used alone or in combination to treat Alzheimer's and Parkinson's disease.**5**

Structure of MAOs

Binda and colleagues published an article showing the high-resolution structure of human MAO-B crystals diffracted to 3.0 Å in complex with the irreversible inhibitor pargyline and with a diffraction resolution of 1.65 Å structure has now been published. The structure of rat MAO-A was also determined, and more recently, human MAO-A**.** A detailed comparison of the overall structures of both isoforms and some new insights regarding their active sites are also published.**6**

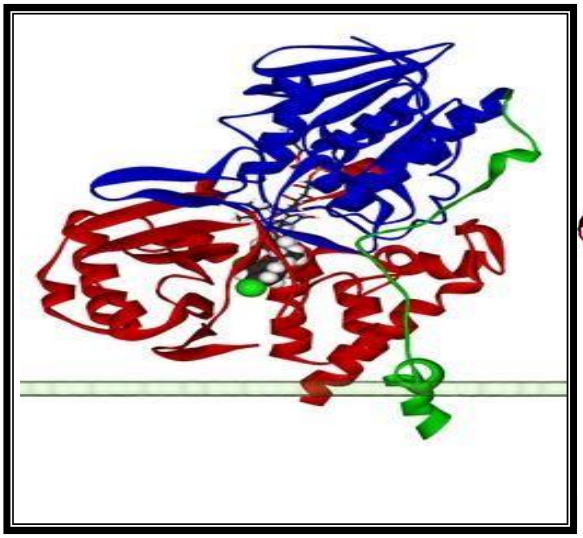


Figure 1 Structure of MAO A

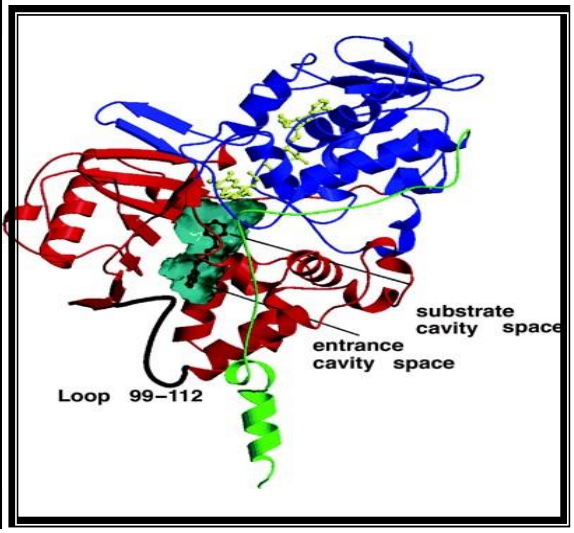


Figure 2 Structure of MAO B

The three-dimensional structure of human MAO-A (**Figure 1**) monomeric unit is a FAD-binding domain (residues 4–79, 211–285, and 391–453) in blue, the substrate-binding domain (residues 80–210, 286–390, and 454–488) is in red, and the C-terminal membrane-binding region (residues 489–500) is in green.

Three-dimensional structure of human MAO-B monomeric unit (**Figure 2**) in complex with 1,4-diphenyl-2-butene has a FAD-binding domain

(residues 4–79, 211–285, and 391–453) is in blue, the substrate-binding domain (residues 80–210, 286–390, and 454–488) is in red, and the C-terminal membrane-binding region (residues 489–500) is in green. The FAD cofactor and the inhibitor are shown as yellow and black ball-and-stick models, respectively.**7**

MAO is known to regulate central nervous system (CNS) activity and trigger numerous neurodegenerative and depressive illnesses. Anxiety, atypical depression, bipolar depression, Alzheimer's, and Parkinson's diseases involve MAO-A and MOA-B. Serotonin toxicity includes excess CNS serotonin and life-threatening intra-synaptic serotonin levels. Serotonin poisoning is a toxidrome that starts with clonuses, agitation, and hyperreflexia and progresses to autonomic hyperactivity, tachycardia, pyramidal stiffness, confused mental state, and tachypnoea. Much research has recently been done on medicinal plants, and their bioactive constituents are isolated with MAO inhibitory activity. MAO inhibitors are used in treating neurodegenerative diseases such as depression, Parkinson and Alzheimer's disease.**6**

Nucleus introduction

In order to address the need for new MAO inhibitors with fewer side effects, we can aim for compounds previously discovered for their potential as MAOIs. Among them, safinamide was reported to be a potent anti-MAO B agent, and milacemide (**Figure 3**) was found to be a potent MAO inhibitor and a prodrug for glycine.**8**

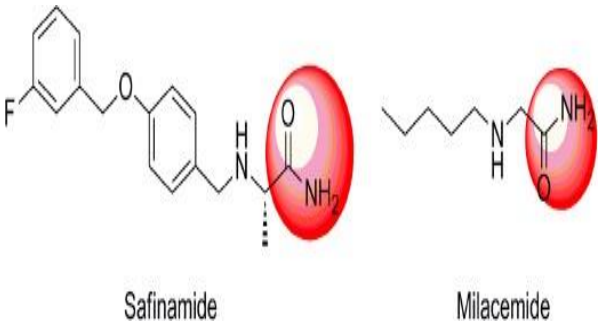


Figure 3 Structure of nucleus

Both compounds possess an acetamide group and acetamide might play an important role in inhibition of MAO activities.

Phenoxy acetamide: According to Wei et al., several substitutions are possible at R1- R5 of phenoxy acetamide (**Figure 4**), which can affect the MAO inhibitory activity of the enzyme and gives a variety of compounds with satisfactory MAO activity.**9**

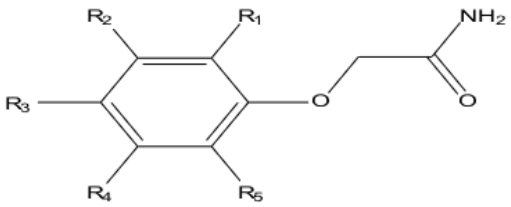


Figure 4 Phenoxy acetamide

The QSAR study to target MAO enzyme selection of series is based on IC50 value. The Maximum and minimum IC50 values ratio should be≥ 1000, and the Phenoxy acetamide derivatives were selected on the same basis.

Drug Design

The discovery of a lead compound is assumed to be the most complicated aspect of the drug scheming process. Once a lead compound for a novel therapeutically vigorous drug has been revealed, it is subjected to effectual toxicological studies to evaluate its worth and protection before its clinical trials.**10**

The development of analogues and prodrugs is measured as the vital process through which a lead compound's chemical structure is altered. Nowadays, the effectiveness of random screening has significantly amplified through automated High Throughput Screening (H.T.P.S.) system utilizes cell culture organization with associated receptor molecule resultant through gene cloning and enzyme assay. The surfacing of new technologies has made it promising to partition many libraries of peptides and nucleic acid resultant from combinatorial chemistry measures. The advance of drug discovery via besieged screening and rational design is more or less arbitrary nature-wise as it rivets a thorough understanding of the therapeutic goal on which testing is regularly done.**8**

QSAR

QSAR uses methodologies to establish a relationship between the structural attributes of chosen compounds and their properties. These structural descriptors are determined experimentally or through computing methods, and they may comprise numerous characteristics that account for a compound's hydrophobic properties, topological properties, electronic properties, and steric effects. In general, the activities utilized in QSAR to compare with its descriptors are chemical dimensions and biological tests. QSAR techniques are now being used in a variety of drug design fields.**11**

QSAR equations technically help shape a functional relationship between a molecule's

elected descriptors and activity. Multiple regression is a method that is presently applied extensively for constructing a QSAR model.

Mao-B Inhibitor Design And Benefits

MAO has an affinity for several substrates and is implicated in Alzheimer's and Parkinson's disease (MAOB). As a result, the discovery of selective MAO inhibitors has made major contributions to treating various neuropsychiatric and neurological illnesses. In experimental models, selective MAO-B inhibitors display antioxidant and antiapoptotic effects, which may translate into long-term therapeutic neuroprotective benefits. MAOIs are still being studied utilizing CADD to decrease effort and time and get a better outcome. Ligand-based models are useful in developing novel drugs with enhanced MAO inhibitory action. It will be critical to produce new, more effective, reversible, and selective MAO-B inhibitors using Ligand-based drug design and molecules structurally related to chemical components that have previously shown MAO inhibitory action.**12**

Materials and Procedures

The Data Set

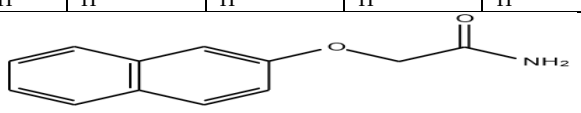
Developing a QSAR/QSPR model requires accurate and precise biological data and normally consists of two primary steps: (i) molecular structure description and (ii) multivariate analysis for matching molecular descriptors with observed activities/properties. Selecting an acceptable series is the most critical challenge for QSAR analysis and developing an effective model. A series chosen for a QSAR investigation must have an acceptable level of molecular diversity. Previously, different substituted 2-phenoxy acetamide derivatives were evaluated for MAO inhibitory activity, with the majority of the molecules demonstrating good MAO inhibitory activity, and this series of compounds were chosen for QSAR analysis based on a wide range of reported biological activities. To eliminate the skewness of the data set and provide a linear connection in the QSAR equation, the MAO inhibitory activity of the compounds was represented as the negative logarithm (pIC50).**13**

Molecular structure generation:

Chemoffice version 7.0, provided by Cambridge Software Company, USA, was used to investigate 2-phenoxy acetamide derivatives. ChemDraw Ultra was used to create all of the molecules. The Chem3D Ultra module converted two-dimensional (2D) structures into three-dimensional (3D) structures. The resultant 3D structures were energy-minimized using the molecular mechanics (MM2) approach, and the energy-minimized molecules were then re-optimized using the Austin model molecular orbital package (MOPAC). The most stable structure for each molecule was created and utilized to calculate several physicochemical characteristics. The numerical descriptors encode significant elements of the molecule's structure and are classified as electronic, steric, and thermodynamic properties. The program's "compute properties" module generated the descriptor values for all compounds. We computed spatial, thermodynamic, and steric descriptors. Spatial characteristics for steric features of drug molecules required for interaction with the enzyme or receptor were measured. The thermodynamic parameters describe the change in free energy during the creation of drug-receptor complexes. Electronic characteristics show medication molecules have weak non-covalent bonds with the target enzyme or receptor.**14**

Types of QSAR are based on the dimensionality of molecular descriptors used: 2D-A molecular graph contains topological or two-dimensional (2D) information, and 3D is calculated starting from a geometrical or three-dimensional representation of a molecule **(Table1)**. 15

Table. 1 In-vitro MAO B inhibitory activities of compounds 1-9 on the different substituents of Phenoxy acetamide (*Figure 4)*.

COMP NO.	R_1	R_2	R_3	R_4	R_5	X	IC50 (MM)
1*	H	H	H	H	H	O	778
2*	 (2-napthalenyl)					O	542
3**	H	H	F	H	H	O	255
4**	H	H	Cl	H	H	O	202
5*	Cl	H	H	H	H	O	697
6*	H	H	CHO	H	H	O	457
7*	CHO	H	H	H	H	O	559
8*	H	CH_3	CH_3	H	H	O	534
9**	CH_3	H	CH_3	H	H	O	663

*Compounds selected into training set

**Compounds selected into test set

Calculate descriptors:

Molecular descriptors can be defined as the essential information of a molecule in terms of its physicochemical properties such as constitutional, electronic, geometrical, hydrophobic, lipophilicity, solubility, steric, quantum chemical, and topological descriptors. Molecular descriptors are chemical information that is encoded within the molecular structures for which numerous sets of algorithms are available for such transformation **(Table 2).13**

Table 2 Descriptor values for each compound (Continued…)

COMP NO.	TE	VDWE**	TC*	CAA*	CMA*	CSEV*	SE**	PMI-X*
1.	2.68373	3.90729	0.556	330.215	155.035	118.119	0.439704	144.06
2.	-6.02768	6.76152	1.73	397.727	196.094	156.19	0.590204	227.25
3.	2.47585	3.93953	0.839	336.888	159.184	121.692	0.423407	147.705
4.	2.83679	4.3494	1.409	354.951	170.477	132.868	0.434043	150.969
5.	3.02771	4.47687	1.179	349.285	168.448	133.257	0.523003	354.07
6.	5.3904	4.82934	0.2738	361.075	174.442	135.126	0.447868	162.038
7.	2.95984	5.25458	0.2738	342.851	168.045	135.962	0.540093	305.699
8.	1.23503	4.96193	1.504	383.117	189.453	151.252	0.657679	216.298
9.	0.389425	4.9725	1.554	385.481	191.498	152.306	0.68304	254.713

TE= Total energy, **VDWE**= Van-der Waals 1,4 Energy, TC= Total Connectivity, **CAA**= Connolly Accessible Area, CMA= Connolly Molecular Area, **CSEV**= Connolly Solvent-Excluded Volume, **SE** = Stretch Energy, **PMI-X** = Principal Moment of Inertia-X, *= Steric Properties, **=Thermodynamic Properties

Table 2 Descriptor values for each compound (Continued…)

COMP NO.	PMI-Y*	PMI-Z*	MTI*	SVD*	SA*	Sc*	Eb**	DDE**
1.	1034.17	1105.94	1302	40	9.09091	0.75	1.3315	-0.546242
2.	2086.63	2310.27	2950	54	13.0667	0.8	2.76507	-0.556329
3.	1435.15	1487.28	1518	48	10.0833	1	1.21915	-0.452003
4.	1833.32	1881.14	1518	41.7778	10.0833	1	1.275	-0.458946
5.	1070.93	1326.38	1478	41.7778	10.0833	0.75	1.32505	-0.179004
6.	1776.21	1827.8	2001	50	11.0769	0.8	1.59457	-0.464912
7.	999.737	1256.81	1881	50	11.0769	0.75	1.68858	-3.61209
8.	1566.28	1772.45	2023	44	11.0769	1	3.06969	-0.492882
9.	1387.42	1632.1	1996	14	11.0769	1	2.95128	-0.736797

PMI-Y = Principal Moment of Inertia-Y **PMI-Z**= Principal Moment of Inertia-Z, **MTI**= Molecular topological index, **SVD**= Sum of Valence Degree, **SA**=Shape Attitude, **Sc**=Shape Constant, **Eb**= Bend Energy, **DDE**=Dipole-Dipole Energy, *= Steric Properties, **=Thermodynamic Properties

Table 2 Descriptor values for each compound

COMP NO.	Ev**	TVC*	TC*	SBE**	SA*	Log
1.	-1.5532	1.O9121e-003	2.94628e 002	3.2929e- 002	0.000778	3.10902
2.	-1.22444	9.09345e -005	4.91046e-003	7.6875e- 002	0.000542	3.266001
3.	-1.82008	3.57184e -004	2.40563e-002	1.60983e- 002	0.000255	3.59346
4.	-1.93436	1.07155e- 003	2.40563e-002	2.46499e- 002	0.000202	3.694649
5.	-1.97533	1.07155e- 003	2.40563e 002	2.58946e- 002	0.000697	3.156767
6.	-1.74285	2.22743e- 004	1.70103e-002	3.91241e -002	0.000457	3.340084
7.	-7.84187	2.22743e- 004	1.70103e 002	5.12398e- 002	0.000559	3.252588
8.	0.859571	8.18411e- 004	1.96419e-002	7.20378e- 002	0.000534	3.272459
9.	-1.04302	8.18411e- 004	1.96419e 002	4.63722e -002	0.000663	3.178486

Ev = Non-1,4 VDW Energy, TVC= Total Valence connectivity, TC=Total Connectivity, SBE= Stretch-Bend Energy, SA= Shape Attitude, *= Steric Properties, **=Thermodynamic Properties

Test And Training Set Division

For the estimation of the true predictive power of a model, it should be tested on a satisfactorily large collection of compounds from an external test set. There should be at least three compounds in a test set whose activities and structure should cover the range of activities and structures of compounds from the training set. This application is needed to

get appropriate statistics for comparing these compounds observed and predictive activities from this series of nine compounds, and three compounds were selected as a test set. This set was used to validate the developed models and select one with the highest predictive power.**16**

Statistical Analysis

In constructing a QSAR model, it is essential to validate the model and apply statistical parameters to evaluate its predictive performance. Statistical methods facilitate building models, estimating a model's predictive power, and finding relationships and correlations between activities and variables.

The inter-correlation between the parameter was less than 0.5, which show that inter-pair correlations among the selected descriptors are very low. Acceptability of the regression model can be judged by examining the different statistical parameters, i.e number of samples in regression (n), regression coefficient (r), squared regression coefficient (r2), adjusted squared regression coefficient (r2adj), F-test (Fischer's value) for statistical significances, standard error of estimate (std), cross-validated squared correlation coefficient (q2), bootstrapped squared correlation coefficient (bsr2), Friedman lack of fit measure (LOF), quality factor (QF), Probable error of correlation (PE), Kubinyi function (FIT), Akaike's information Criterion (AIC), AND correlation matrix to show a mutual correlation among the parameters.

Statistical parameters

Pearson's correlation coefficient (r) is a commonly used parameter to describe the degree of association between two variables of interest. The calculated r-value of two variables of interest can take a value ranging from –1 to +1, where the former indicates an indirect (negative) correlation. At the same time, the latter suggests a direct (positive) correlation. The relative predictive performance of a QSAR model, r, is used to measure the correlation between experimental (x) and predicted (y) values of interest to observe the variability between the variables.

Model Development & Validation:

A data set's prediction performance may be evaluated by separating it into training and testing sets. The training set is used to build a predictive model, the predictive performance of which is tested on the testing set. Internal performance is often measured using the training set's predicted performance.

On the other hand, external performance may be examined using the prediction performance of an independent testing set that is unknown to the training model. The N-fold cross-validation method is a popular strategy for internal validation in which a data set is partitioned into N folds. In 10-fold cross-validation, for example, one fold is excluded as the testing set. In contrast, the other nine folds are utilized as the training set for model creation and verified with the fold excluded. Leave-one-out cross-validation is preferable when the number of samples in the data set is restricted.

Similarly, the number of folds matches the number of samples in the data set; hence, one sample is excluded as the testing set, while the remainder is utilized as the training set for model creation. Finally, the data sample that was earlier excluded is validated. It is repeated repeatedly until all data samples can be excluded from the testing set.

The best QSAR model obtained was:

BA = [3.31786(± 0.0494962)] +PMI-Y [8.31113e-006(± 2.77236e-007)] +PMI-Z [-7.37081e-005(± 4.11189e-005)]

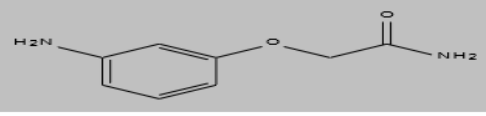
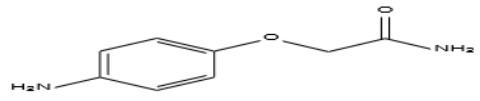
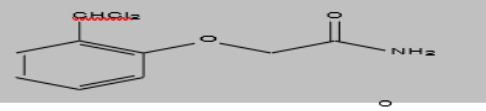
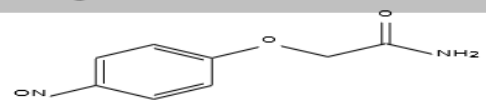
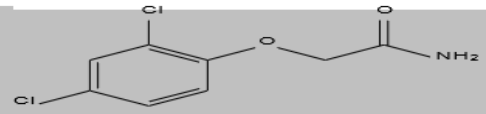
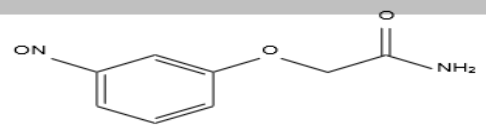
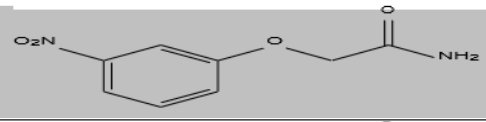
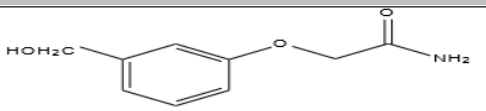
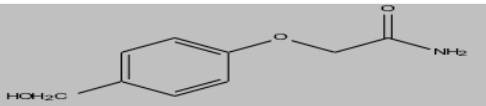
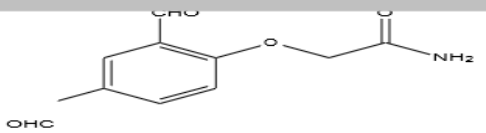
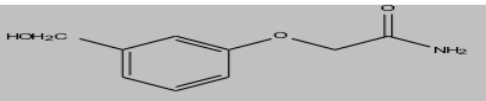
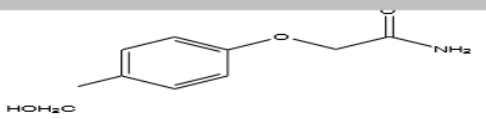
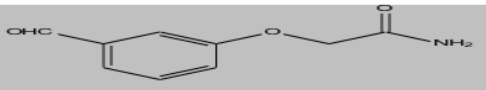
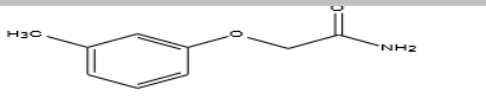
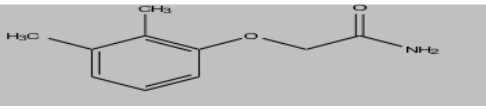
Fraction contribution of PMI-Y is 0.943579, Fraction contribution of PMI-Z is -0.0564212, n=9, r=0.990918, r^2=0.981919, r^2adj=0.979792, variance=0.0126886, std=0.112644, QF=8.7 9692, PE=0.00269539, F=461.6, FIT=40.2266, LOF=0.3 83478, AIC=0.0140209 Standard Fmax value at 95% confidence=10.7908, Q^2 is 0.89796, Spress is 0.267595, SDEP is 0.24671, r^2 is 0.981919, r^2pred is 0.7689.

Model predicted power was judged based on various statistical parameter like: - r2 = Explained variance (squared multiple r), Q2 = Cross validation regression coefficients, Pred_r2 = regression coefficient for external test set.

Structures of newly designed Ligand from 1A-18F for MAO B Inhibitory Activity;

After performing the QSAR study, a good statistical QSAR model was generated which can be used to predict the activity of new molecule of 3-phenoxy acetamide derivatives for MAO- B inhibition. Here we were design 15 novel molecules of phenoxy acetamide derivatives as MAO-B inhibitors. All the structure of designed molecules are shown in Table.3

Table 3 Structure of designed molecules

1	1A		2-(3-Amino-phenoxy)-acetamide
2.	1C		2-(4-Amino-phenoxy)-acetamide
3.	1D		2-(2-Dichloromethyl-phenoxy)-acetamide
4.	3B		2-(4-Nitroso-phenoxy)-acetamide
5.	3C		2-(2,4-Dichloro-phenoxy)-acetamide
6.	4A		2-(3-Nitroso-phenoxy)-acetamide
7.	5A		2-(3-Nitro-phenoxy)-acetamide
8.	6A		2-(3-Hydroxymethyl-phenoxy)-acetamide
9.	6B		2-(4-Hydroxymethyl-phenoxy)-acetamide
10.	6C		2-(2,4-Diformyl-phenoxy)-acetamide
11.	6E		2-(3-Hydroxymethyl-phenoxy)-acetamide
12.	6F		2-(4-Hydroxymethyl-phenoxy)-acetamide
13.	6G		2-(3-Formyl-phenoxy)-acetamide
14.	8A		2-*m*-Tolyloxy-acetamide
15.	8B		2-(2,3-Dimethyl-phenoxy)-acetamide

After designing these novel molecules, they were subjected to descriptor calculations. Before that, all the molecules were converted into 3D form, and optimization and energy minimization were done using MM2 and MOPAC methods.

Table 4 Descriptor calculation of designed molecules and prediction of BA:

Compounds	PMI-Y	PMI-Z	Compounds	PMI-Y	PMI-Z
1	1232.72	1363.96	2	1223.02	1857.95
3	1396.72	1452.38	4	1272.23	1781.85
5	1377.85	1815.56	6	1743.92	1990.45
7	1297.22	1484.02	8	1260.8	1900.52
9	1492.06	1689.09	10	1500.06	1810.85
11	1822.19	2231.28	12	1643.68	2019.83
13	1763.69	1973.21	14	1229.94	1957.54
15	1341.11	1621.12	16	1637.94	1875.67

All the designed molecules were subjected to properties /descriptors calculation which is involved and modulate the MAO-B inhibitory activity of compounds (obtained from the QSAR model) using Chemoffice 7.0. The calculated properties are given above, i.e., PMI-Y, PMI-Z are shown in Table 4.

After calculating desired physio-chemical properties (PMI-Y, PMI-Z) of newly designed molecules, the biological activity was predicted using the QSAR model developed (Selected series). These are selected after comparing the biological activity of newly designed molecules with the predicted QSAR model.

Result And Discussion

Several QSAR models were obtained using the data set of 28 compounds with stepwise multiple linear regression analysis. Compounds were randomly divided into a training set and a test set of 05 and 03 compounds, respectively. Among the various models generated, the best model for each activity was selected based on various statistical parameters like Standard deviation (s<0.3), F value (>99.9%), r2 (>0.8), chance, Spress (Standard deviation of cross-validation prediction) and variance.

For the validation of QSAR models, statistical external validation was used, and the molecules were rationally divided into training and test set. The test set should represent a balanced number of active and inactive compounds for uniform data sampling. Therefore, both sets' structure and activity diversity is maintained for the QSAR model's development. The test set molecules captured the structural features of training set molecules; thus, their activities could be well predicted. The size of the training set was aimed to be about two-thirds of the whole set. In these results, the plot of experimental and predicted activity from the training set and test set compound was found, and good R2 activity is also found to be 0.973(training set) & 0.781 (test set). The coefficient of determination (r2) is a measure that allows us to determine how certain one can be in making predictions from a certain model/graph should be closer to 1 (> 0.7). Cross-validated r2 (Q2) value close to 1 means the model explained well the activity variations in the compounds. Experimental biological activity and predicted biological activity of both the training and test set were compared and are presented. Model 3 was developed based on five compounds selected in the training set. Comparative data for experimental BA and predicted BA are presented. One can see that predicted BA correlates very well with an experimental BA (R2 = 0.973).

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