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3D-QSAR Study on Coumarin Analogues as Potent Inhibitors of MAO-B using a COMFA Approach.

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ABSTRACT

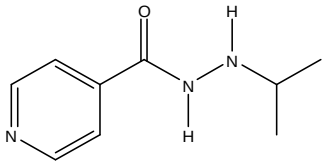
Comparative molecular field analysis (CoMFA) is a promising new approach to structure/activity correlation. With the aim to find out the structural features intended for the MAO inhibitory activity, in the present communication we report COMFA Analysis of Coumarin Analogues. The resulting model exhibited good q^2 and r^2 values up to 0.713 and 0.881 for CoMFA. The contributions from the steric and electrostatic fields were 1.361 and 0.908 respectively. The 3D QSAR analysis provides interesting insights in understanding the Steric and Electronic structural requirements for MAO-B inhibitory activity. Further all molecules were subjected to the toxicity assessment using Molinspiration and Osiris Calculations. Among the various MAO-B inhibitors, compound no-3 is the optimum drug candidate with respect to the activity and toxicity.

Keywords: MAO-B, CoMFA, Steric, Electronic, QSAR, Molinspiration, Osiris.

INTRODUCTION

A major goal in chemical research is to predict the behavior of new molecules, using relationships derived from analysis of the properties of previously tested molecules. Relationships derived primarily by empirical analysis of a data table, whose columns are numerical property values and whose rows are compounds, usually taking the form of a linear equation, are called quantitative structure/activity relationships (QSAR)[1].

Mono amine oxidases (MAOs) are flavoenzymes bound to the outer mitochondrial membrane and are responsible for the oxidative deamination of neurotransmitters and dietary amines.[2,3] Two isoforms, namely MAO-A and MAO-B, have been identified on the basis of their amino acid sequences, three-dimensional structure, substrate preference and inhibitor selectivity.[4,5]. MAO-B preferentially deaminates phenylethylamine and benzylamine. These properties determine the clinical importance of MAO-B inhibitors. Selective and irreversible MAO-B inhibitors such as selegiline and rasagiline are useful in the treatment of Parkinson's [6,7] and Alzheimer's diseases.[8,9]



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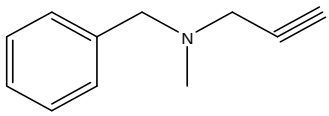

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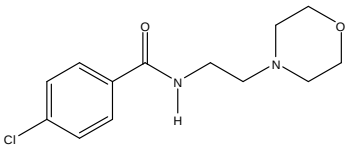

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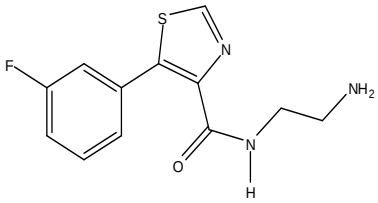

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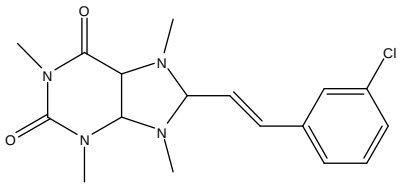

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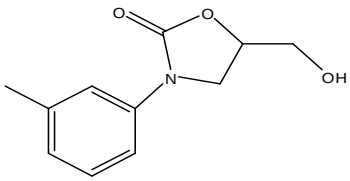

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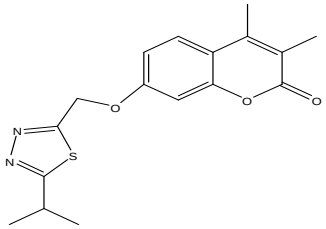
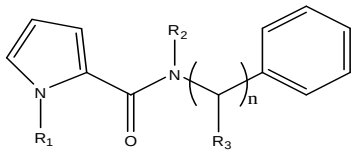
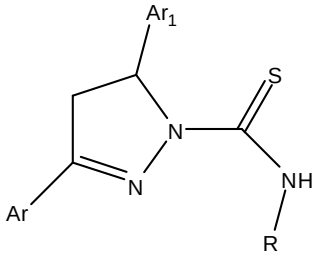
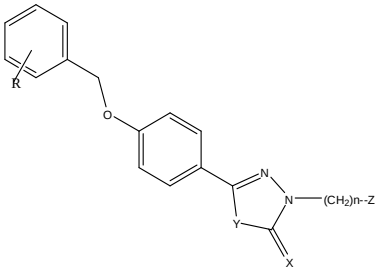


LU 53439 (B)







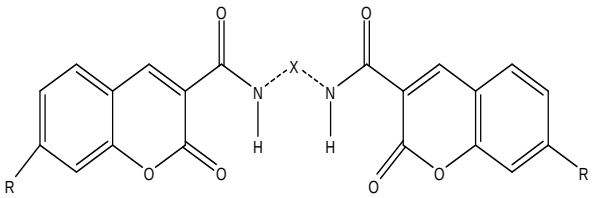


Figure 1 shows the chemical structures of some representative MAO inhibitors used in research or clinical practice.

All of these aspects have led to an intensive search for novel MAO inhibitors (MAOIs) and this effort has increased considerably in recent years. However, earlier MAOIs introduced into clinical practice were abandoned due to adverse effects, such as hepatotoxicity, orthostatic hypotension and the so-called "cheese effect", which was characterized by hypertensive crisis. [10,11]

Comparative molecular field analysis (CoMFA) is one of the well known 3D-QSAR descriptors which has been used regularly to produce the three dimensional models to indicate the regions that affect biological activity with a change in the chemical substitution[12]. The advantages of CoMFA are the ability to predict the biological activities of the molecules and to represent the relationships between steric/electrostatic property and biological activity in the form of contour maps gives key features on not only the ligand-receptor interaction but also the topology of the receptor [13].

The coumarin analogs are a family of natural and/or synthetic compounds with different Pharmacological activities, one of which is MAO inhibitory activity.[14, 15] Hence to find out the structural features for the MAO-B inhibitory activity, we have carried out COMFA analysis of Coumarin analogues.

MATERIALS AND METHODS

Molecular Modeling

The structures of the coumarin derivatives and the biological activities data were obtained from the reference[16] . The negative logarithm of IC50 (pIC50) was used as the biological activity in the 3D-QSAR study (Table 1). Three-dimensional structure building and all modeling were performed using the Sybyl–X program package on a personal computer equipped with a Pentium IV processor. Molecular building was done with Chemsketch 10.0 freeware program. Geometry optimization was carried out using MAXIMIN molecular mechanics and Tripos force field, Gasteiger–Hückle charges supplied convergence criterion set at 0.05 kcal / (Å mol).

CoMFA analysis

Dataset

Data sets of 8 compounds, whose structures and associated biological activities are given in Figure 1 and Table 1, respectively. QSAR models were random derived from a training set of 6 molecules. An external test set consisting of two molecules was used to validate the CoMFA models. The most active compound 7 was used as a template molecule for alignment.

Figure no-1 Compounds used in COMFA training set

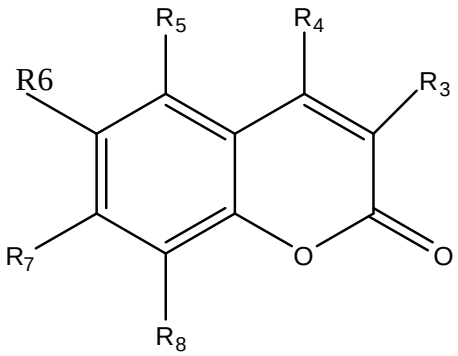


Table 1. Newly designed series of Coumarin derivatives 3-10.

Compound	R3	R4	R5	R7/(CH_2)n	R8
3		$–(CH_2)_3–$	H	$MeCOCH_2O–$	Me
4		$–(CH_2)_4–$	H	$MeCOCH_2O–$	Me
5		$–(CH_2)_4–$	H	$MeCOCH_2O–$	OMe
6		$–(CH_2)_3–$	H	$CH_2C(Br)CH_2–$	Me
7		$–(CH_2)_4–$	H	$CH_2C(Br)CH_2–$	Me
8		Ph	H	$MeCOCH_2O–$	Me
9		Ph	H	$MeCOCH_2O–$	OMe
10		Ph	H	$CH_2C(Br)CH_2–$	Me

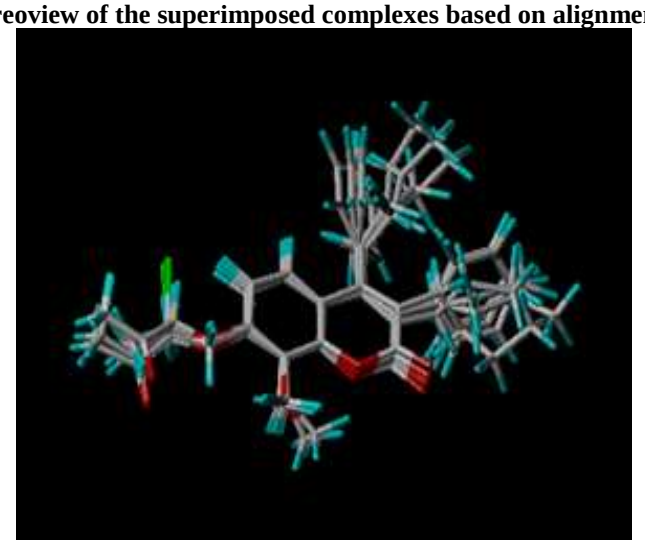
The experimental and calculated activities of all compounds by the best model are given in Table 2.

Table 2. Experimental and CoMFA calculated pIC50 values for MAO-A inhibitors

Compound	pIC50 Value (Observed)	pIC50 Value (calculated)	COMFA Value
3	-2.2175	-2.420	152
4	-1.2380	-1.100	157
5	-1.0835	-0.975	138
6	-0.0719	-0.243	148
7	-2.3729	-2.057	164
8	-1.4492	-1.688	163
9	-0.9713	-0.547	150
10	-0.1732	-0.547	150

A common substructure-based alignment was adopted in the present study, which attempted to align molecules to the template molecule on a common backbone.

Figure 2. Stereoview of the superimposed complexes based on alignment (aggregate)



Partial least squares (PLS) analysis

The relationship between the structural parameters (CoMFA interaction energies) and the biological activities has been quantified by the PLS algorithm. PLS regression technique is especially useful in quite common case where the number of descriptors (independent variables) is comparable to or greater than the number of compounds (data points) and/or there exist other factors leading to correlations between variables[17]. The cross-validation analysis was carried out using Leave-One-Out (LOO) method where one compound is removed from the dataset and its activity is predicted using the model derived from the rest of the dataset. The cross-validated q^2 and the optimum number of components were obtained. To speed up the analysis and reduce noise, a minimum column filtering value (σ) of 2.00 kcal/mol was used for the cross-validation. Finally, non-cross-validated analysis was performed to calculate non-cross-validated r^2 using the optimal number of previously identified components was employed to analyze the result of the CoMFA.

Osiris calculations[18]

Structure based design is now fairly routine but many potential drugs fail to reach the clinic because of ADME-Tox liabilities. One very important class of enzymes, responsible for many ADMET problems, is the cytochromes P450. Inhibition of these or production of unwanted metabolites can result in many adverse drug reactions. Of the most important program, Osiris is already available online.

Table 3. Osiris calculations of compounds 3-10

Compd.	Toxicity Risks				Osiris calculations				
	MUT	TUMO	IRRI	REP	MW	CLP	S	DL	D-S
3					316	4.27	-3.89	-0.8	0.46
4					344	5.2	-4.43	-4.47	0.17
5					360	473	-4.1	-4.32	0.19
6					264	5.57	-4.89	-10.9	0.14
7					392	6.5	-6.48	-14.9	0.07
8					384	4.1	-5.12	2.76	0.33
9					400	3.68	-4.79	3.06	0.36
10					432	5.4	-6.12	-7.35	0.07

CLP: cLogP, S: Solubility, DL: Druglikness, DS: Drug-Scor.

Molinspiration calculations [19]

CLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragmentbased contributions and correction factors (Table 5). The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment contributions. O– and N– centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood–brain barrier penetration. Prediction results of compounds 3**–10** molecular properties (TPSA, GPCR ligand and ICM) are valued (Tables 4 and 5).

Table 4. Molinspiration calculations of compounds 3-10

Compd.	Molinspiration calculations					
	MW (g/mol)	cLogP	TPSA	OH--NH Interract.	N violation	Volume
3	344	5.55	57	0	1	340
4	316	4.43	57	0	0	307
5	360	4.96	66	0	0	349
6	365	6.11	30	0	1	314
7	393	7.23	30	0	1	347
8	384	5.41	57	0	1	349
9	400	4.83	66	0	0	358
10	433	7.09	30	0	1	356

Table 5. Drug-likeness calculations of compounds 3-10

Compd.	Drug-likeness			
	GPCR ligand	ICM	KI	NRL
3	-0.78	-0.72	-0.85	-0.45
4	-0.84	-0.78	-0.87	-0.43
5	-0.83	-0.46	-0.78	-0.46
6	-0.86	-1.03	-0.95	-0.75
7	-0.80	-0.96	-0.92	-0.73
8	-0.49	-0.57	-0.39	-0.27
9	-0.55	-0.35	-0.34	-0.29
10	-0.48	-0.76	-0.43	-0.50

RESULTS AND DISCUSSION

Eight molecules were randomly partitioned into a training set of six and a test set of two compounds with bias given to both chemical and biological diversity in both the training set and the test set molecules. Despite the ambiguity of drug-receptor interactions in general, a statistically significant model was obtained from the CoMFA study. A "cross-validated q^2" may then be defined, completely analogously to the definition of the conventional q^2, as

$$\text{cross-validated } q^2 = (SD - press)/SD$$

where press is the standard errors of the cross-validated predictions and SD is the sum of squared deviations of each biological property value from their mean and press, or predictive sum of squares, is the sum, over all compounds, of the squared differences between the actual and "predicted" biological property values [19].

The statistical parameters of CoMFA analysis is summarized in Table 3. The leave-one-out crossvalidated PLS analysis of the best model gave rise to a cross-validated value (q^2) of 0.713 suggesting that the model is a useful tool for predicting MAO-B inhibitory activity. The correlation coefficient between the calculated and experimental activities, non-cross-validated value (r^2) of 0.881 with standard error of estimate 0.380. The respective relative contributions of steric and electrostatic field were 1.361 and 0.908, indicating that steric field is more predominant.

Table 6. PLS statistics of CoMFA 3D-QSAR model

PLS statistics CoMFA	
q^2 (leave-one out cross-validated predicted power of model) =	0.713
r^2 (correlation coefficient squared of PLS analysis) =	0.881
N (optimum number of components obtained from cross-validated PLS analysis and the same used in final non cross-validated analysis) =	2
Standard error of estimate (SEE) =	0.380
F-test value (F-value) =	99.910
Steric field contribution from CoMFA =	1.361
Electrostatic field contribution from CoMFA =	0.908

The contour plot representations of the CoMFA results for MAO-B inhibitors are presented in Figures 3 and 4 using compound **7** as reference structure.

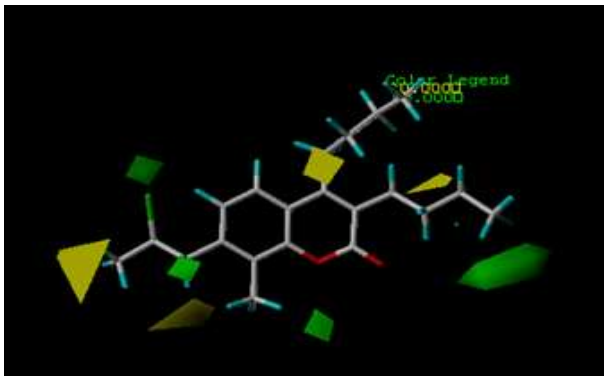


Figure 3. CoMFA contour map of the Steric field with compound 7

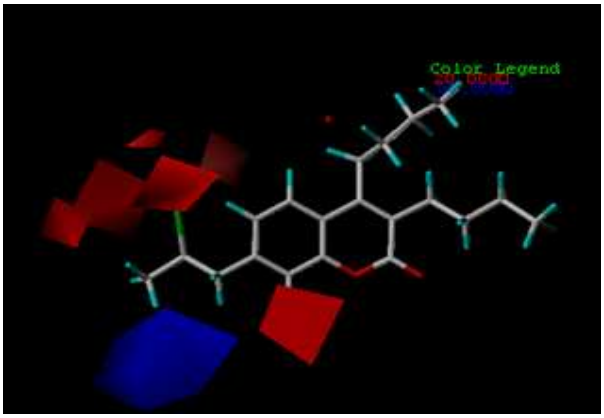


Figure 4. CoMFA contour map of the electrostatic field with compound 7

Graphical representations of CoMFA results for MAO-B inhibitors are shown in Figures 3 and 4, using compound 7 as reference structure. The steric contour map shows a green region at C-3 position of the Coumarin ring, indicating more bulky substituent is preferred at C-3 position to produce higher inhibition activity which is consistent with the fact that molecules 2 3,4,5,6 have higher inhibition activities as shown by pIc50 data. The observation of yellow regions around the C-4 Position in the steric contour map (shown in Fig. 3) suggests that the substitution of less bulky group is favoured at C-4 position increases the activity. Further observation of both yellow and green regions around the C-7 Position in the steric contour map suggests that the substitution effect of the bromoallyloxy group is complex whereas methyl group at C-8 position increases the bulk of coumarin nucleus.

To add further , all the compound were subjected to toxicity assessment studies by using Osiris online programme which reveals that all the compound showed very good ADME pofile which minimizes the toxicity riskof coumarin analogues in human being. Among the all coumarin derivatives subjected for toxicity assessment, compound 3 was found to be free from high risks of undesired effects like mutagenicity or a poor intestinal absorption (as are shown in red Whereas a green color indicates drug conform behavior). In Molinspiration programme, all the coumarin analogues showed very good profile for drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood–brain barrier penetration.

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Note: The OSIRIS Property Explorer shown in this page is an integral part of Actelion's inhouse substance registration system. It lets you draw chemical Structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug conform behavior.
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