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RESEARCH ARTICLE

PHARMACOPHORE MODELING STUDIES ON XANTHONES AS MONOAMINE OXIDASE-A INHIBITORS

Himangini Bansal, Anuradha Sharma, Vikas Sharma and Vipin Kumar*

Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136 119, Haryana, India

**E-mail*: vipbhardwaj@rediffmail.com, vikumar@kuk.ac.in
Tel.: +91-9416391274, +91-1744-239617

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Pharmacophore mapping studies were undertaken for a set of 42 xanthone as monoamine oxidase-A inhibitors. Five point pharmacophores with three hydrogen bond acceptor, and two aromatic ring as pharmacophoric features were developed. Amongst them the pharmacophore hypothesis AAARR1 yielded a statistically significant 3D-QSAR model with 0.81 as R-square value and was considered to be the best pharmacophore hypothesis. The developed pharmacophore model was externally validated by predicting the activity of test set molecules. The squared predictive correlation coefficient of 0.79 was observed between experimental and predicted activity values of test set molecules. The geometry and features of pharmacophore were expected to be useful for the design of selective MAO-A inhibitors.

Key words: Xanthone, Monoamine oxidase-A, Pharmacophore hypothesis, Regression coefficient.

INTRODUCTION

Monoamine oxidases (MAOs), widely distributed in all living organism, are flavin adenine dinucleotide cofactor covalently linked to a cysteine residue in the active centre (Santana *et al* 2006), containing enzymes present in the outer mitochondrial membranes of neuronal, glial and other cells (Chimenti *et al* 2008). MAO exists in two isoforms: MAO-A and MAO-B, differing in their substrate preferences, inhibitor selectively, tissue distribution, molecular genetics (Gallardo-Godoy *et al* 2005) and amino acid sequence (Chimenti *et al* 2004). MAO-A metabolize the principal biogenic amines, serotonin (Chimenti *et al* 2007), epinephrine and nor-epinephrine and MAO-B mainly acting on dopamine, *β*-phenylethylamine and benzylamine (Mai *et al* 2002). MOA-A is selectively inhibited by clorgyline (Medvedev *et al* 1996) and moclobemide (Medvedev *et al* 1998) and MAO-B is selectively inhibited by selegiline (Silvestri *et al* 2003). MAO-A and MAO-B have essential roles in vital physiological processes and are involved in the pathogenesis of various human disease. The MAO inhibitors are used for the treatment of psychiatric and neurological disorders (Regina *et al* 2007). Selective MAO-A inhibitors are currently used for treating neurological disorders such as anxiety (Pacher *et al* 2001) and depression (Binda *et al* 2008), while selective inhibitors of the B isoform are administered alone or together with Levo-DOPA for the treatment of Parkinson's syndrome (Sant *et al* 2005; Kalgutkar *et al* 1994) and Alzheimer's disease (Hubalek *et al* 2004). In the last decade, remarkable progress in computer technology has allowed us to perform complex computational operations in a feasible and even interactive time frame. Among such operations, pharmacophore modeling is successfully used in drug discovery. A pharmacophore model consists of a 3D arrangement of a collection of features necessary for the biological activity of the ligands (Roy *et al* 2010). These models are hypothesis on the 3D arrangement

of structural properties such as hydrogen bond and acceptor properties, hydrophobic groups and aromatic rings of a compound that bind to a biological target (Langer and Wolber, 2004). Xanthones of natural and synthetic origin are of biological and pharmacological interest, being used in traditional medicines. They are of particular importance in chemotaxonomy as systemic markers (Gnerre *et al* 2001). This paper describes the development of a robust ligand-based 3D-pharmacophore hypothesis using pharmacophore alignment and scoring engine PHASE for xanthones as monoamine oxidase –A (MAO-A) inhibitors. The alignment obtained from the pharmacophoric points is used to derive pharmacophore-based 3D-QSAR model.

MATERIALS AND METHODS

Dataset

A data set comprising 42 analogues (Nunez *et al* 2004) of xanthones having MAO-A inhibitory activity was selected for the present investigations. The basic structure for these analogues is shown in **Figure 1** and various substituents are enlisted in **Table 1**. The dataset was divided randomly into training set and test set by considering the 75% of the total molecules in the training set and 25% in the test set.

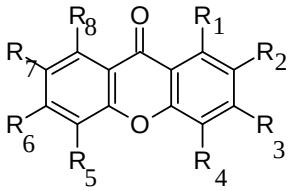

Figure 1. Basic structure of xanthone derivatives.

Thirty two compounds forming the training set were used to generate pharmacophore models and prediction of activity of test set molecules was used as a method to validate the proposed models. The MAO-A inhibitory activity (Gnerre *et al* 2001) was reported quantitatively as IC_{50} (μM) at different concentrations. The analogues possessing IC_{50} values of less than 10 μM are considered as highly active, those with IC_{50} values from 10 μM to 30 μM are considered as moderately active and those with IC_{50} values of more than 30 μM are considered as poorly active for the purpose of present study.

Table 1. Various substitutents attached to basic structure of xanthone

Comp. no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	Comp. no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	H	H	H	H	H	H	H	H	22	OH	H	MeO	H	MeO	H	H	H
2	OH	H	H	H	H	H	H	H	23	MeO	H	MeO	H	MeO	H	H	H
3	MeO	H	H	H	H	H	H	H	24	OH	H	OH	Me	H	H	H	H
4	H	OH	H	H	H	H	H	H	25	OH	Me	OH	H	H	H	H	H
5	H	MeO	H	H	H	H	H	H	26	OH	Me	OH	Cl	H	H	H	H
6	H	H	OH	H	H	H	H	H	27	OH	Me	OH	Br	H	H	H	H
7	H	H	MeO	H	H	H	H	H	28	OH	H	OH	X[a]	OH	H	H	H
8	H	H	H	OH	H	H	H	H	29	OH	Y[b]	H	OH	OH	H	H	H
9	H	H	H	MeO	H	H	H	H	30[c]	OH	H	Z[c]	OH	OH	H	H	H
10	OH	H	H	H	OH	H	H	H	31	OH	MeO	OH	H	OH	H	H	H
11	H	H	OH	H	OH	H	H	H	32	OH	MeO	OH	H	MeO	H	H	H
12	H	H	OH	H	MeO	H	H	H	33	MeO	MeO	MeO	H	MeO	H	H	H
13	OH	H	MeO	H	H	H	H	H	34	OH	H	OH	H	H	H	OH	H
14	MeO	H	MeO	H	H	H	H	H	35	OH	H	OH	H	OH	H	H	OH
15	H	H	MeO	H	MeO	H	H	H	36	OH	H	MeO	H	OH	H	H	OH
16	MeO	H	H	H	OH	H	H	H	37	OH	H	OH	H	H	H	OH	OH
17	H	H	MeO	OH	H	H	H	H	38	OH	H	MeO	H	H	H	OH	OH
18	H	H	OH	MeO	H	H	H	H	39	OH	H	MeO	H	H	H	MeO	MeO
19	H	H	MeO	MeO	H	H	H	H	40	OH	H	OH	H	H	OH	OH	H
20	OH	H	OH	H	OH	H	H	H	41	MeO	H	H	Me	OH	H	MeO	H
21	OH	H	MeO	H	OH	H	H	H	42	OH	MeO	OH	H	MeO	OH	H	H

[a] Me_2C=CH-CH_2-CH_2-C(Me)=CH-CH_2, [b] CH_2=CH-CMe_2, [c] CMe_2=CH-CH_2

Pharmacophore modeling

Ligand preparation

The 2-dimensional chemical structures of all the ligands were drawn in maestro (20) and converted to corresponding low energy 3-dimensional structures using LigPrep. Initially, the ligands were imported in to the Phase module. Then, ionization states (at pH 7 $\pm$ 2) and stereoisomers were generated. After that low energy ring conformations for each ligand were generated using confgen option in macromodel module (Maestro, version 8.5; Macromodel, version 9.6; Glide, version 5.0, 2008) by maintaining the maximum relative energy difference of 10.00 Kcal/mol and geometries were optimized using the OPLS_2005 force field parameters to ensure maximum coverage of conformational space.

Creating pharmacophore site

One of the critical steps in developing a pharmacophore model is to use a set of pharmacophore features to create pharmacophore sites for all the ligands. An initial analysis revealed that two chemical feature types, i.e., three hydrogen-bond acceptor (A), and two ring aromatic (R) features could effectively map all critical chemical features of all molecules. The minimum and maximum sites for all the features were kept 4 and 5 respectively. These features were selected and used to build a series of hypothesis with the find pharmacophore option in Phase.

Finding common pharmacophore and scoring hypothesis

In this step, pharmacophores from all conformations of the ligands are examined and those pharmacophores that contain identical sets of features with very similar spatial arrangements are grouped together. If a given group is found to contain at least one pharmacophore from each ligand, then this group gives rise to a common pharmacophore. Any single pharmacophore in the group could ultimately become a common pharmacophore hypothesis. After that, common pharmacophores are examined and a scoring procedure is applied. The scoring procedure provides a ranking of the different hypotheses and allows making rational choices about which hypotheses are most appropriate for further investigation. The statistical parameters are computed by the regression analysis using the fitness score. In the present work, three pharmacophore hypotheses were generated using training set molecules. Their survival score and other statistical parameters are given in **Table 2**.

Validation of pharmacophore model

Validation is a crucial aspect of pharmacophore design, particularly when the model is built for the purpose of predicting activities of molecules in external test series. In the present case, the developed pharmacophore model was validated by predicting the activity of test set molecules. The correlation between the experimental and predicted activities of the test set molecules was determined.

RESULTS AND DISCUSSION

MAO-A regulates both the free intraneuronal concentration and the releasable stores of 5-HT and noradrenaline. MAO-A inhibitors, such as phenelzine, bind to and inhibit MAO-A, preventing monoamine degradation. This results in greater stores of monoamines available for release. MAO inhibitors are used in the treatment of depression. When ingested orally, MAO inhibitors inhibit the catabolism of dietary amines. To either avoid or decrease the adverse effects of current agents and also to provide more candidates of drug choices, it is still necessary to search for new MAO-A inhibitors for further drug development.

Ligand-based drug design may be used to derive a pharmacophore which defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target. These approaches consider 2 or 3 dimensional chemistry, shape, electrostatic and interaction points such as pharmacophore points to assess similarity. Ligand based QSAR approaches require a number of active molecule spanning a wide range of activity against the target receptor.

Thirty two molecules forming the training set were used to develop the pharmacophore models. The pharmacophoric features selected for creating sites were hydrogen bond acceptor (A), hydrogen bond donor (D), aromatic ring (R) and hydrophobic group (H). Pharmacophore models containing three to four features were generated. The three and four featured pharmacophore hypotheses were rejected due to the low value of survival score, as they were unable to define the complete binding space of the selected molecules. Five featured pharmacophore hypotheses were selected and subjected to the stringent scoring function analysis.

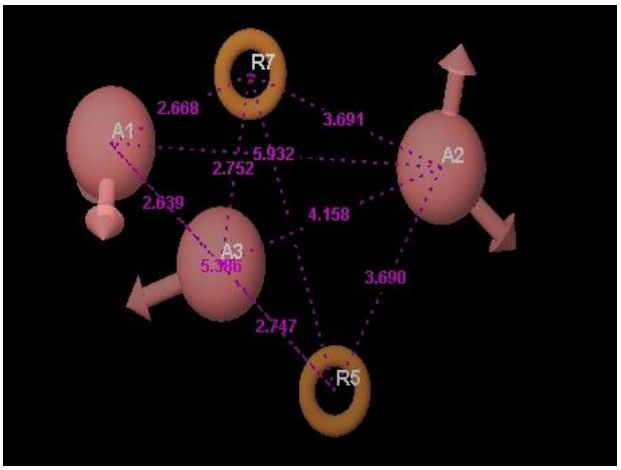

Figure 2. PHASE generated pharmacophore model AAARR1 illustrating hydrogen bond acceptor (A1, A2, A3; pink) and aromatic ring (R6, R7; orange) features with distances (in Å) between sites of AAARR1.

The results of five featured pharmacophore hypotheses, labeled AAARR1, AAARR2 and AAHRR3 are presented in **Table 2**. The first hypothesis AAARR1 is the best hypothesis in this study, characterized by highest survival score (3.65), the good regression coefficient (0.903), lowest RMSE (13.18) and highest F (66.9). The pharmacophore hypothesis AAARR1 is presented in **Figure 2**. The features represented by this hypothesis are three hydrogen bond acceptor (A) and two aromatic ring (R). The distances between different sites of AAARR1 are given in **Table 3**. Validation method to characterize the quality of AAARR1 is represented by its capacity for correct activity prediction of training set molecules. AAARR1 was regressed against the training set compound.

Table 2. Parameters of five featured pharmacophore hypotheses

Sr. no.	Hypothesis	Survival score	Regression coefficient	RMSE	F
1	AAARR1	3.65	0.807	13.18	66.9
2	AAARR2	3.39	0.84	15.2323	50.8
3	AAHRR3	3.20	0.83	17.339	46.5

Table 3: Distances between different sites of model AAARR1

Site1	Site2	Distance (Å)	Site1	Site2	Distance (Å)
A1	A2	5.932	A3	R7	2.752
A1	A3	2.639	A1	R5	5.386
A2	A3	4.158	A3	R5	2.747
A1	R7	2.668	A2	R5	3.690
A2	R7	3.691	R5	R7	5.932

Table 4 shows the actual and estimated inhibitory activities of the 32 molecules from the training set based on the pharmacophore hypothesis AAARR1. The predicted MAO-A inhibitory activity of training set molecule exhibited a correlation of 0.8071 with reported MAO-A inhibitory activity using model AAARR1 (**Figure 3**). The validity and predictive character of AAARR1 were further assessed by using the test set prediction. The test set having ten molecules was analyzed. All the test set molecules were built and minimized as well as used in conformational analysis like all training set molecules. Then, the activities of test set molecules were predicted using AAARR1 and compared with the actual activity. Actual and predicted activity values of test set molecules are given in the **Table 5**.

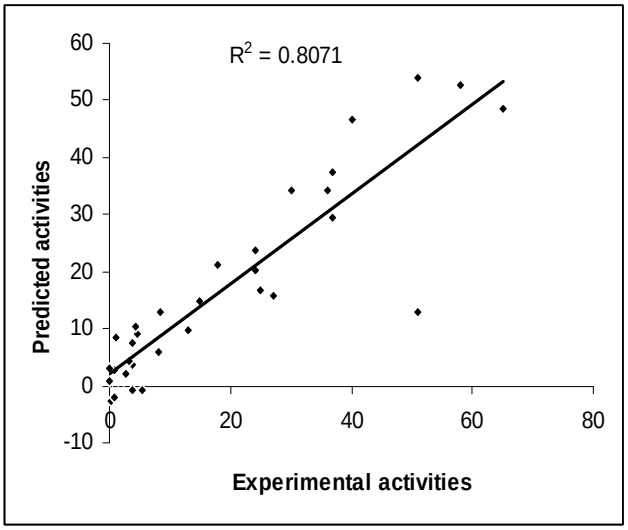

Figure 3. Relation between experimental and predicted MAO-A inhibitory activity values of training set molecules using model AAARR1.

The predicted MAO-A inhibitory activity of test molecule exhibited a correlation of 0.7727 with reported MAO-A inhibitory activity using the model AAARR1 (**Figure 4**). For a reliable model, the squared predictive correlation coefficient should be >0.60 (Dureja *et al* 2007; Wold, 1991). The results of this study reveal that model AAARR1 can be used for the prediction of MAO-A inhibitory activity.

Table 4. Experimental and predicted IC_{50} values of training set molecules based on hypothesis AAARR1

Comp. no.	Exptl. value	Pred. value	Exptl. score	Pred. score	Comp. no.	Exptl. value	Pred. value	Exptl. score	Pred. score
1	0.84	2.82	+++	+++	24	4.3	10.41	+++	++
2	0.31	-2.78	+++	+++	25	3.7	7.35	+++	+++
4	3.8	-0.77	+++	+++	26	27	15.75	++	++
5	5.3	-0.77	+++	+++	27	14.9	14.71	++	++
6	1.1	8.46	+++	+++	28	37	29.37	+	++
9	30	34.13	+	+	29	3.3	4.41	+++	+++
10	0.73	-2.10	+++	+++	30	40	46.74	+	+
11	4.5	8.96	+++	+++	31	2.7	2.11	+++	+++
13	0.11	3.15	+++	+++	32	51	53.91	+	+
15	36	34.38	+	+	33	37	37.54	+	+
16	51	12.87	+	++	34	8	5.76	+++	+++
17	18	21.32	++	++	35	13	9.74	++	+
18	65	48.67	+	+	37	24	20.09	++	++
20	3.8	3.63	+++	+++	38	8.5	12.78	+++	++
21	0.04	0.95	+++	+++	40	25	16.68	++	++
23	58	52.56	+	+	41	24	23.86	++	++

Table 5. Experimental and predicted IC_{50} values of test set molecules based on hypothesis AAARR1

Comp. no.	Exptl. value	Pred. value	Exptl. score	Pred. score
3	0.9	15.14	+++	++
7	0.18	7.45	+++	+++
8	1.3	12.97	+++	++
12	23	25.77	++	++
14	20.2	17.60	++	++
19	31	44.56	+	+
22	29	26.47	++	++
36	0.66	13.71	+++	+++
39	19	22.03	++	++
42	32	35.48	+	+

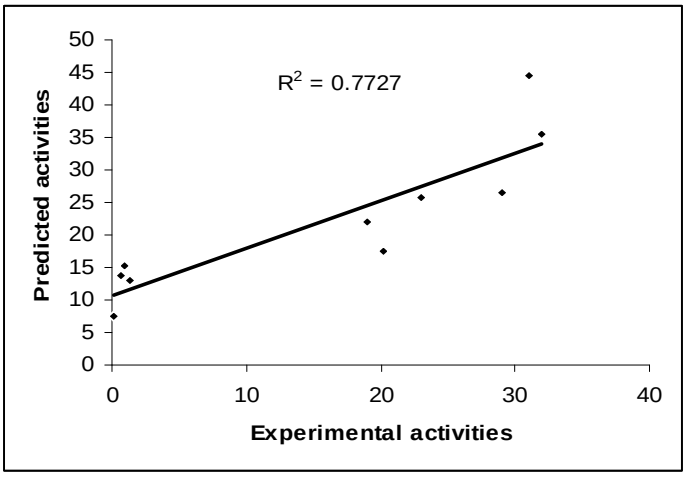

Figure 4. Relation between the experimental and predicted MAO-A inhibitory activity value of test set molecules using model AAARR1.

The purpose of the hypotheses is not just to predict the activity of the training set molecules accurately but also to predict the activity of the test set molecules and classify them correctly as highly active, moderately active or poorly active so that the model AAARR1 can be used as virtual screening tool to find new MAO-A inhibitors. Retrofit analysis of the data in **Table 4** and **Table 5** reveals following information with regard to predictive character of AAARR1.

Based on training set:

- MAO-A inhibitory activity was predicted for a total of 32 analogs in highly active, moderately active and poorly active ranges. Out of which activity of 27 analogs was correctly predicted, resulting in approximately 84% accuracy with regard to MAO-A inhibitory activity of training set molecules.
- Fourteen out of sixteen analogs in the highly active range were predicted correctly resulting in 87.5% accuracy with regard highly active range. Similarly, six out of seven analogs in the moderately active range were predicted correctly resulting in 85.7% accuracy with regard to moderately active range.
- Seven out of nine analogs in the poorly active range were predicted correctly resulting in 77.7% accuracy with regard to poorly active range of training set molecules.

Based on test set:

- MAO-A inhibitory activity was predicted for a total of 10 analogs in highly active, moderately active and poorly active ranges. Out of which activity of 08 analogs was correctly predicted, resulting in 80% accuracy with regard to MAO-A inhibitory activity of test set molecules.
- All the analogs in the moderately active range and poorly active range were predicted correctly resulting in 100% accuracy with regard to moderately active and poorly active range of test set molecules.

CONCLUSION

The present study shows the generation of a pharmacophore model AAARR1 for xanthone-7-one acting as MAO-A inhibitors. Pharmacophore modeling correlates activities with the spatial arrangement of various chemical features. Hypothesis AAARR1 represents the best pharmacophore model for determining MAO- A inhibitory activity. AAARR1 consists of three hydrogen bond acceptor and two aromatic ring features. This pharmacophore model was able to accurately predict MAO-A inhibitory activity and the validation results also provide additional confidence in the proposed pharmacophore model. Results suggested that the proposed pharmacophore model AAARR1 can be useful to rationally design new xanthone-7-one molecules as MAO-A inhibitors and also to identify new promising molecules as MAO-A inhibitors in large 3-D database of molecules. High predictability of the proposed pharmacophore model AAARR1 offers vast potential for providing lead structures for the development of potent MAO-A inhibitors.

REFERENCES

Binda C, Wang J, Li M, Hubalek F, Mattevi A, Edmondson DE. Structural and mechanistic studies of arylalkyl hydrazine inhibition of human monoamine oxidases A and B. *Biochemistry* 2008;47(20):5616-25. [DOI: 10.1021/bi8002814]

Chimenti F, Bolasco A, Manna F, Secci D, Chimenti P, Befani O, Turini P, Giovannini V, Mondovi B, Cirilli R, Torre FL. Synthesis and selective inhibitory activity of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives against monoamine oxidase. *J. Med. Chem.* 2004;47(8): 2071-4. [DOI: 10.1021/jm031042b]

Chimenti F, Maccioni E, Secci D, Bolasco A, Chimenti P, Granese A, Befani O, Turini P, Alcaro S, Ortuso F, Cardia MC, Distinto S. Selective inhibitory activity against MAO and molecular modeling studies of 2-thiazolyl hydrazone derivatives. *J. Med. Chem.* 2007;50(4):707-12. [DOI: 10.1021/jm060869d]

Chimenti F, Maccioni E, Secci D, Bolasco A, Chimenti P, Granese A, Carradori S, Alcaro S, Ortuso F, Yanez M, Orallo F, Cirilli R, Ferretti R, Torre FL. Synthesis, stereochemical identification, and selective inhibitory activity against human monoamine oxidase-B of 2-methylcyclohexylidene-(4-arylthiazol-2-yl)hydrazones. *J. Med. Chem.* 2008;51(16):4874-80. [DOI: 10.1021/jm800132g]

Dureja H, Kumar V, Gupta S, Madan AK. Topochemical models for the prediction of lipophilicity of 1,3-disubstituted propan-2-one analogs. *J. Theor. Comput. Chem.* 2007;6(3):435-48. [DOI: 10.1142/S021963360700309X]

Gallardo-Godoy A, Fierro A, McLean TH, Castillo M, Cassels BK, Reyes-Parada M, Nichols DE. Sulfur-substituted α-alkyl phenethylamines as selective and reversible MAO-A inhibitors: Biological activities, CoMFA analysis, and active site modeling. *J. Med. Chem.* 2005;48(7):2407-19. [DOI: 10.1021/jm0493109]

Gnerre C, Thull U, Gaillard P, Carrupt P-A, Testa B, Fernandes E, Silva F, Pinto M, Pinto MMM, Wolfender J-L, Hostettmann K, Cruciani G. Natural and synthetic xanthones as monoamine oxidase inhibitors: Biological assay and 3D-QSAR. *Helv. Chim. Acta* 2001;84(3):552-70.

Hubalek F, Binda C, Li M, Herzig Y, Sterling J, Youdim MBH, Mattevi A, Edmondson DE. Inactivation of purified human recombinant monoamine oxidases A and B by rasagiline and its analogues. *J. Med. Chem.* 2004;47(7): 1760-6. [DOI: 10.1021/jm0310885]

Kalgutkar AS, Castagnoli K, Hall A, Castagnoli Jr. N. Novel 4-(aryloxy)tetrahydropyridine analogs of MPTP as monoamine oxidase A and B substrates. *J. Med. Chem.* 1994;37(7):944-9. [DOI: 10.1021/jm00033a012]

Langer T, Wolber G. Lead optimization. Pharmacophore definition and 3D searches. *Drug Discov. Today: Technol.* 2004;1(3):203-7. [DOI:10.1016/j.ddtec.2004.11.015]

Maestro, version 8.5; Macromodel, version 9.6; Glide, version 5.0; Schrodinger, New York, NY, 2008; LigPrep, version 2.2; Schrodinger, New York, NY, 2005; Phase, version 3.0, Schrodinger, LLC, New York, NY, 2008.

Mai A, Artico M, Esposito M, Sbardella G, Massa S, Befani O, Turini P, Giovannini V, Mondovi B. 3-(1*H*-Pyrrol-1-yl)-2-oxazolidinones as reversible, highly potent, and selective inhibitors of monoamine oxidase type A. *J. Med. Chem.* 2002;45(6):1180-3. [DOI: 10.1021/jm015578d]

Medvedev AE, Ivanov AS, Veselovsky AV, Skvortsov VS, Archakov AI. QSAR analysis of indole analogues as monoamine oxidase inhibitors. *J. Chem. Inf. Comput. Sci.* 1996;36(4):664-71. [DOI: 10.1021/ci950126t]

Medvedev AE, Veselovsky AV, Shvedov VI, Tikhonova OV, Moskvitina TA, Fedotova OA, Axenova LN, Kamyshanskaya NS, Kirkel AZ, Ivanov AS. Inhibition of monoamine oxidase by pirlindole analogues: 3D-QSAR and CoMFA analysis. *J. Chem. Inf. Comput. Sci.* 1998;38(6):1137-44. [DOI: 10.1021/ci9802068]

Nunez MB, Maguna FP, Okulik NB, Castro EA. QSAR modeling of the MAO inhibitory activity of xanthones derivatives. *Bioorg. Med. Chem. Lett.* 2004;14(22):5611-7. [DOI: 10.1016/j.bmcl.2004.08.066]

Pacher P, Kohegyi E, Kecskemeti V, Furst S. Current trends in the development of new antidepressants. *Curr. Med. Chem.* 2001;8(2):89-100.

Regina GL, Silvestri R, Artico M, Lavecchia A, Novellino E, Befani O, Turini P, Agostinelli E. New pyrrole inhibitors of monoamine oxidase: Synthesis, biological evaluation, and structural determinants of MAO-A and MAO-B selectivity. *J. Med. Chem.* 2007;50(5):922-31. [DOI: 10.1021/jm060882y]

Roy J, Kumar UC, Machiraju, PK, Muttineni, RK, Suneel Kumar BVS, Gundla R, Dayam R, Sarma JARP. Insilico studies on anthrax lethal factor inhibitors: Pharmacophore modeling and virtual screening approaches towards designing of novel inhibitors for a killer. *J. Mol. Graph. Model.* 2010;29(2):256-65. [DOI: 10.1016/j.jmgm.2010.07.002]

Santana L, Uriarte E, Gonzalez-Diaz H, Zagotto G, Soto-Otero R, Mendez-Alvarez E. A QSAR model for in silico screening of MAO-A inhibitors. Prediction, synthesis, and biological assay of novel coumarins. *J. Med. Chem.* 2006;49(3):1149-56. [DOI: 10.1021/jm0509849]

Santo RD, Costi R, Roux A, Artico M, Befani O, Meninno T, Agostinelli E, Palmegiani P, Turini P, Cirilli R, Ferretti R, Gallinella B, Torre FL. Design, synthesis, and biological activities of pyrrolylethanoneamine derivatives, a novel class of monoamine oxidases inhibitors. *J. Med. Chem.* 2005;48(13):4220-3. [DOI: 10.1021/jm050172c]

Silvestri R, Regina GL, Martino GD, Artico M, Befani O, Palumbo M, Agostinelli E, Turini P. Simple, potent, and selective pyrrole inhibitors of monoamine oxidase types A and B. *J. Med. Chem.* 2003;46(6):917-20. [DOI: 10.1021/jm0256124]

Wold S. Validation of QSAR's. *Quant. Struct. Act. Relat.* 1991;10(3):191-3. [DOI: 10.1002/qsar.19910100302]

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