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Original Article

QSAR Study of Coumarin Derivatives as Monoamine Oxidase A and B Inhibitors

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ABSTRACT

A set of 33 compounds of coumarin derivatives were used in the model development, where 12 of compounds were used in the training set and 12 compounds were used as cross-validation (external set). The QSAR models involve the use of the multiple linear regression analysis method. Based on the method the eight models were chosen for the prediction purposes of coumarin derivatives with R^2 value (0.903, 0.855, 0.842, 0.841, 0.828, 0.855, 0.774and o.814) This work aim to develop a QSAR models that could correlate the structural features of coumarin derivatives with physicochemical, steric properties.

Keywords: coumarins derivative, QSAR, MLR method,MAO inhibitor

1. INTRODUCTION

Quantitative structure-activity relationship (QSAR) is a tool to rationalize the interaction of chemical compounds with living subject. QSAR is used to connect the information from molecules with known experimental activity to molecules for which newer experiments are yet to be carried out in drug discovery project[1]. In the past, the descriptors used for QSAR interrelated the chemical environment and steric properties of groups. These were considered to be independent of each other and their interactions were completely ignored. After introduction of several molecular descriptors such as topological, electro-topological and others; the current generated QSAR models using these descriptors represent properties of whole molecule rather than contributions by individual groups. These models do

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not clearly specify the site at which modification is required.[2]

Mono amine oxidizes (MAOs) are flavoenzymes bound to the outer mitochondrial membrane and are responsible for the oxidative deamination of neurotransmitters and dietary amines.[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-A has a higher affinity forSerotonin and noradrenalin whereas MAO-B preferentially delaminates phenyl ethylamine and benzyl amine.[6] These properties determine the clinical importance of MAO inhibitors. Selective MAO-A inhibitors such as clorgyline (irreversible) and moclobemide (reversible) are used in the treatment of neurological disorders such as depression.[7] Whereas the selective and irreversible MAO-B inhibitors such as selegiline and rasagiline are useful in the treatment of Parkinson's.[8]

Coumarins and their derivatives are a well- known class of heterocycles, that are very attractive due to their extended spectral range, high emission quantum yields, versatility in a large number of applications and mainly investigated due to their important biological activities anti-coagulant, anti-HIV, ant hyper pro- liferative, cytotoxic properties as well chemo preventive activity against cancer and due to their role as anti-histamic, anti-microbial, anti-inflammatory rodenticides and photodynamic activity.[9]The coumarins analogs are a family of natural and/or synthetic compounds with different pharmacological activities, one of which is MAO inhibitory activity. In many cases, it is known that activity and selectivity are determined by the nature of the substituents at the 7- and the 4/3-positions.[10]

2. MATERIALS AND METHODS

MAO inhibition data of total of 33 compound of coumarins derivatives was cited from the work that authored by (Carmela et al, 2000). These were used as data set in QSAR analysis. The pic50 (µM) value reported in literature were used for QSAR study.

The structures were drawn in 2D draw application by ACD/lab version 15. Also the physiochemical properties were calculated.[11]

2.1Data Selection

For the evaluation of QSAR model externally, the data set was divided into

training set and test set by using sphere exclusion method and manual selection method. Training set is used to develop the QSAR model for which biological activity data are known. Test set is used to challenge the QSAR model developed based on the training set to assess the predictive effectiveness of the model which is not included in model generation.[12]

2.2Model Building

Models were generated by using multiple linear regression (MLR), partial least square regression(PLS) and principle component regression(PCR), in conjunction with stepwise (SW) forward-backward variable selection method with pic50 activity field as dependent variable and descriptors as independent variable.[13, 14]

2.3 Validation of Models

Models were validated internally and externally. In internal validation(cross validation), a compound is eliminated in the training set and its biological activity is predicted. This step is repeated until every compound in the training set has been eliminated and its activity is predicted once. External validation [(pred_r^2)] is done by calculating predicted correlation coefficient (pred_r^2) value using following equation:

$Pic50 = \beta o + \beta 1X + \beta 2Y$

3 RESULTS AND DISCCUSSION

3.1 QSAR Study

The structures of the set of coumarins derivatives were optimized using the molecular mechanics option in Chemo Sketch version 2016. The resulting optimized structures were then processed to calculate five sets of physiochemical parameters representing surface tension (ST), molar refractivity (MR), density (D), polarizability and partition coefficient (log P) as shown in the tables bellow

Regression analysis was performed using SPSS software version 16. As follows; start, regression and then the biological activity (pic50 or – logpic50) is put in a response space and the two of the calculated physiochemical properties (molar refractivity, log P, density, surface tension and polarizability) were put in the predictions space. In general, a QSAR model is acceptable when it has an $\boldsymbol{r^2}$value greater than 0.6 and r^2 (*CV*)greater than 0.5. The regression equations with high $\boldsymbol{r^2}$values (> 0.6).

The Model was generated by pic50 as dependent variables and physicochemical properties as independent variables. We fit the model to fit the best compounds that have higher (r square) value to predict unknown activity compounds.

We select randomly 12 compounds as training set from 33 compounds to derive the model bellow:

3.1.1Model 1

This model relates the biological activity to log p and molar refractivity withR^2 = 0.903 for the training set is a very good indication of the fitness of the model to the data.

Pic50 MAO-A = 83.283-4.897(±0.815) log p- 0.679(±0.09) Mr cm^3

3.1.2 Model 2

This model relates the biological activity to log p and Polarizability with R^2 = 0.774 for the training set is a good indication of the fitness of the model to the data.

Pic50 MAO-A = 74.346(±12.580)-4.897(±1.236) log p- 1.479E24(±3.374E23) Pola

Table 1: Chemical structure, MAO inhibition data and physiochemical properties of coumarins derivative

Comp n	R1	R2	R3	R4	MOA-A	MOA-B	Log p	MR cm3	ST	Density	Pola

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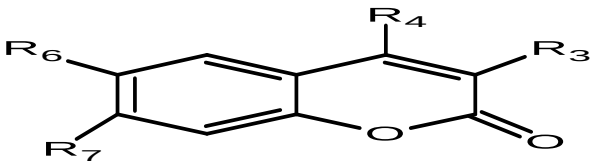
1	H	H	H	H	4.39	4.92	1.39	39.76	1.248	1.248	-1.57E-23
2	H	H	H	$OCH_2C_6H_5$	5.17	7.26	3.43	79.93	1.25	1.25	-2.81E-23
3	H	H	H	$CH_2OC_6H_5$	6.41	7.07	2.96	70.93	1.25	1.25	-2.81E-23
4	H	H	H	$CH_2NHC_6H_5$	4.38	5.67	2.3	73.86	1.273	1.273	-2.93E-23
5	H	H	O CH_3	$OCH_2C_6H_5$	18	5.17	3.25	77.61	1.25	1.25	-3.08E-23
6	H	H	$OCH_2C_6H_5$	OH	4.63	5.69	2.94	72.81	1.339	1.339	-2.89E-23
7	H	H	glucosyl	OH	9	7	-1.52	77.35	1.679	1.679	-3.07E-23
8	H	H	glycosyl	$OCH_2C_6H_5$	15	11	0.26	100.06	1.485	1.485	-3.97E-23
9	H	CH_3	H	$OCH_2C_6H_5$	5.71	7.74	4.02	75.63	1.211	1.211	-3.00E-23
10	H	CH_3	H	$OCH_2C_6H_4$-3'- NO_2	6.9	7.88	3.75	82.18	1.343	1.343	-3.26E-23
11	H	C_6H_5	H	$OCH_2C_6H_5$	4	4	5.63	95.37	1.243	1.243	-3.78E-23
12	H	CF_3	H	$OCH_2C_6H_5$	5	5.86	4.47	75.91	1.361	1.361	-3.01E-23
13	H	OH	H	$OCH_2C_6H_5$	26	5.8	3.2	72.51	1.363	1.363	-2.87E-23
14	H	CH_3	H	$OCH_2C_6H_5$	6.16	8.36	4.61	80.34	1.178	1.178	-3.18E-23
15	CH_3	CH_3	H	$NHCH_2C_6H_5$	5.8	6.79	4.27	83.27	1.197	1.197	-3.30E-23
16	CH_3	CH_3	H	$O(CH_2)_2C_6H_5$	6	8.25	4.84	84.97	1.157	1.157	-3.37E-23
17	CH_3	CH_3	H	$OCH(CH_3)C_6H_5$	5.45	6.49	4.96	84.97	1.154	1.154	-3.37E-23
18	$(CH_2)3$	$(CH_2)3$	H	$OCH_2C_6H_5$	5.8	8.46	4.49	82.83	1.27	1.27	-3.28E-23
19	$(CH_2)_4$	$(CH_2)_4$	H	$OCH_2C_6H_5$	5.8	8.46	5.05	87.47	1.25	1.25	-3.47E-23
20	$(-CH=CH-)_2$	$(-CH=CH-)_2$	H	$OCH2C_6H_5$	7	7.3	5.47	86.69	1.268	1.268	-3.44E-23
21	C_6H_5	CH_3	H	$OCH_2C_6H_5$	4	8	6.22	100.07	1.124	1.124	-3.97E-23
22	CH_3	CH_3	H	$NHCOC_6H_5$	5.86	6.72	2.22	63.44	1.242	1.242	-2.52E-23
23	CH_3	CH_3	H	$OSO_2C_6H_5$	7.12	5.28	3.86	84.43	1.338	1.338	-3.35E-23
24	CH_3	CH_3	H	$OSO_2C_6H_4$-4-CH_3	7.33	17	4.32	89.05	1.309	1.309	-3.53E-23
25	CH_3	CH_3	H	$OSO_2C_6H_4$-4-OCH_3	7.15	4.77	3.76	83.75	1.264	1.264	-3.32E-23
26	CH_3	CH_3	H	$OSO_2C_6H_4$-4-NO_2	7.9	20	4.06	90.46	1.451	1.451	-3.59E-23
27	CH_3	CH_3	H	$NHSO_2C_6H_4$-4-CH_3	4.17	29	4.18	90.96	1.328	1.328	-3.61E-23
28	CH_3	CH_3	H	*trans*-$CH=CHC_6H_5$	6.39	7.55	5.63	86.56	1.169	1.169	-3.43E-23
29	CH_3	CH_3	OH	$OCH_2C_6H_5$	5.03	7.55	3.98	82.22	1.254	1.254	-3.26E-23
30	CH_3	CH_3	$OCH_2C_6H_5$	OH	3.95	5.51	4.46	82.22	1.254	1.254	-3.26E-23
31	CH_3	CH_3	$OCH_2C_6H_5$	$OCH_2C_6H_5$	0.4	0.4	6.24	111.5	1.198	1.198	-4.42E-23
32	CH_3	CH_3	H	$OCH_2C_6H_5$	6.25	5.48	4.61	80.34	1.178	1.178	-3.18E-23
33	CH_3	CH_3	H	OH	35	18	2.96	51.05	1.255	1.255	-2.02E-23

Table 2: Results of Regression Summary

Model NO	N	R^2	MSE	F	P-Value	
1	12	0.903	10.35	37.078	0.000	significant
2	12	0.774	24.036	13.681	0.003	significant
3	12	0.855	0.012	23.499	0.001	significant
4	12	0.855	24.036	13.681	0.003	significant
5	12	0.828	0.0014	19.215	0.001	significant
6	12	0.814	19.712	17.560	0.001	significant
7	12	0.842	2.362	19.215	0.000	significant
8	12	0.841	2.375	23.858	0.000	significant



3.1.3 Model 3

This model relates the reciprocal of inhibitory concentration (1/pic50) to log p and PolarizabilitywithR^2= 0.855 for the training set is a very good indication of the fitness of the model to the data.

1/Pic50 MAO -A = 0.193(±0.276) - 0.129(±0.027) log p – 2.796E22(±7.414E21) Pola

3.1.4 Model 4

This model relates the reciprocal of inhibitory concentration (1/pic50) to log p and molar refractivity with R^2 = 0.855 for the training set is a very good indication of the fitness of the model to the data.

1/Pic50 MOA-A = 0.248(±0.289)-0.127(±0.27) log p + 0.012(±0.003) Mr cm^3

3.1.5 Model 5

This model relates the reciprocal of inhibitory concentration (1/pic50) to log p and surface tension with R^2 = 0.828 for the training set is a very good indication of the fitness of the model to the data.

1/Pic50 MAO-A = -1.625(±0.740) + 0.041(±0.065) log p + 0.034(±0.010) ST

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3.1.6 Model 6

This model relates the biological activity to log p and surface tension with R^2 = 0.814 for the training set is a very good indication of the fitness of the model to the data.

3.1.7 Model 7

This model relates the biological activity to log p and molar refractivity with R^2 = 0.842 for the training set is a very good indication of the fitness of the model to the data.

Pic50 MAO-B = 30.833(±3.448) + 4.433(±0.904) log p - 0.529(±0.080) MR cm^3

3.1.8 Model 8

This model relates the biological activity to log p and Polarizability with R^2 = 0.841 for the training set is a very good indication of the fitness of the model to the data.

Pic50 MOA-B = 30.689(±3.440) + 4.428(±0.906) log p + 1328.932(±202.425) Pola

Model 1 shows a considerably very high R^2values (0.903),small standard error, significant coefficients, significant model and the p-value of this model = 0.000 that makes this model so far considerablygood enough for prediction purposes so that gives a higher number of predicted compounds

According to the rest R^2value we observed that model (2,3,4,5,6,7 and 8) were closely value of R^2 this implies that those models have strongly contribution of independent variables (Log P, Pola, Mr, D,ST) with biological activity.

4. CONCLUSION

QSAR has been observed in the drug discovery area to enable the design of safe and potent drug candidates. During drug discovery and development phases, pharmacodynamics and pharmokinetic profiles of molecules can be derived using QSAR models from the above discussion it was concluded that all the eight models can be used to predict the biological activity of coumarins derivatives.

5. REFERENCES

1. Maria M. J; Lourdes S; Patricia J; Eiias, Q; Eugenio U; Humberto Diza-G; Dolores Viana; Francisco O. Design, Synthesis and Pharmacological Evaluation Of New Coumarin Derivatives As Monoamine Oxidase A and B Inhibitors. International Electronic Conference on Synthetic Organic Chemistry. 2008. http//www.Usc.es/congresos/ecsoc/12/Ecsoc12.htm & http://www.mdpi. org/ ecsoc-12.
2. T. P. Singer. Monoamine oxidases. In Chemistry and Biochemistry of Flavoenzymes (II). Fifth Edition, CRC Press, London,1991; 437-470.
3. Binda, C; Li, M.; Hubálek, F; Restelli, N; Edmondson, D. E; Mattevi, A. Insights into the mode of inhibition of humanmitochondrial monoamine oxidase B from high-resolution crystal structures. Proc. Natl. Acad. Sci. U. S. A. 2003; 100: 9750-9755.
4. Grimsby, J; Lan, N. C; Neve, R; Chen, K; Shih, J. C. Tissue distribution of human monoamine oxidase A and B mRNA. J.Neurochem. 1990;55: 1166-1169.
5. Yamada, M; Yasuhara, H. Clinical pharmacology of MAO inhibitors: safety and future. Neurotoxic ology 2004;25: 11-20.
6. Rudorfer, M. V; Potter, V. Z; Antidepressants. A comparative review of the clinical pharmacology and therapeutic use of the “newer” versus the “older” drugs. Drugs 1989;37: 713-738.
7. Borges, F; Roleira, F; Mihazes, N; Santana, L; Uriarte, E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. Curr. Med. Chem, 2005; 12: 887-916.
8. Chimenti, F; Secci, D; Bolasco, A; Chimenti, P; Granese, A; Befani, O; Turini, P; Alcaro, S; Ortuso, F. Inhibition ofmonoamine oxidases by coumarin-3-acyl derivatives: biological activity and computational study. Bioorg. Med. Chem. Lett. 2004; 14: 3697-3703.
9. Catto, M; Nicolotti, O; Leonetti, F; Carotti, A; Soto-Otero, R; Mendez-Alvarez, E; Carotti, A. Structural Insights intoMonoamine Oxidase Inhibitory Potency and Selectivity of 7-Substituted Coumarins from Ligand- and Target-Based Approaches.J. Med. Chem. 2006;49: 4912-4925.
10. Carotti, A; Altomare, C; Catto, M; Gnerre, C; Summo, L; De Marco, A; Rose, S; Jenner, P; Testa, B. Lipophilicity Plays aMajor Role in Modulating the Inhibition of Monoamine Oxidase B by 7-Substituted Coumarins. Chem. Biodiversity 2006;3: 134-149.
11. Zheng W, Topsha A. Novel variable selection quantitative structure--property relationship approach based on the k-nearestneighbor principle. J Chem Inf Comput Sci. 2000; 40: 185-194.
12. Ajmani S, Kamaiakar J, Kulkarni SA. Three-Dimensional QSAR Using the k-Nearest Neighbor Method and Its Interpretation. J Chem Inf Model 2006; 46: 24-31.
13. Rogers D, Hopfinger AJ. Application of Genetic Function Approximation to Quantitative Structure-Activity Relationships and Quantitative Structure-Property Relationships. J Chem Inf Comp Sci. 1994; 34: 854-866.

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