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Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(5):682-689

ISSN No: 0975-7384
CODEN(USA): JCPRC5

QSAR analysis of indanone and aurone derivatives as acetylcholine esterase inhibitors

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ABSTRACT

QSAR analysis of indanone and aurone derivatives as AChE inhibitor has been performed using various physicochemical parameters on Chem- Office software. Energy minimization was carried out using molecular mechanics (MM2) force field and MOPAC. The biological activity data were taken as negative logarithmic dose in moles (pIC_{50}) for QSAR analysis. Sequential multiple linear regression method was used to develop relationship between inhibitory activity and physicochemical parameters, employing VALSTAT. The series was divided into a training set of 23 compounds and test set of 9 compounds. Several equations were obtained, the statistically significant equation was considered as best model. LUMO (Lowest Unoccupied Molecular Orbital) energy, Diameter and Gibbs Free Energy (G) contributes the equation. The model has correlation coefficient (r) of 0.873. The equation shows significance level more than 95% against tabulated value F=8.53, with a low standard deviation of estimation demonstrate accuracy of the model.

Keywords: QSAR analysis, Indanone and Aurone derivatives, Acetylcholine esterase inhibitors.

INTRODUCTION

Alzheimer's disease, the most common form of dementia among the elderly, is a progressive, degenerative disorder of the brain with a loss of memory and cognition. AChE inhibitors are still the major and most developed class of drugs approved for Alzheimer's disease therapy, such as donezepil, rivastigmine and galanthamine have been approved by FDA and EMEA for the symptomatic treatment of Alzheimer's disease.[1]

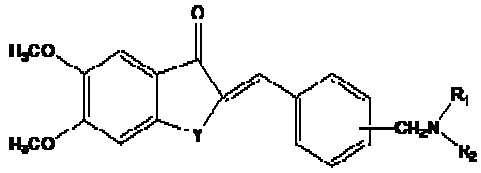
Aurones (aurone, sulfuretol, maritimetol, leptosidol, etc.) are natural yellow pigments of plants related to flavonoids [2]. Aurones have a limited occurrence. The first aurone was discovered in 1943 and, because of the limited methods of synthesis [1,3], aurones have received very limited attention. Analogy with flavonoids suggests that aurones could have interesting biological properties [3].

A defining characteristic of Alzheimer's disease is the deposition of amyloid fibrils and neurofibrillary tangles in the brain of afflicted individuals. Biochemically, they are mainly composed of amyloid protein and phosphorylated tau proteins, respectively. There is also a loss of the presynaptic markers of the cholinergic system, such as acetylcholine, in the brain areas related to memory and learning. The biochemical pathways leading to Alzheimer's disease are presently unknown and are a subject of intensive study with current theories favouring a hypothesis where amyloid protein aggregates to toxic forms that induce tau phosphorylation and aggregation. It is believed that this ultimately leads to dysfunction and death of cholinergic neurons, and compensation for this loss had been the primary focus of first generation therapeutic agents.[4,5]
The aim of this analysis is to derive quantitative structure activity relationship from sequential multiple linear regression analysis in order to investigate the quantitative effect of structural properties of the previously synthesized Indanone and aurone derivatives as AChE inhibitor used for treatment for Alzheimer's disease. The QSAR analysis investigates the relationship between the various physicochemical parameter and biological activity of various synthesized derivatives. Thus the objective of present work is development of potent AChE inhibitor for Alzheimer's disease.[6,7]

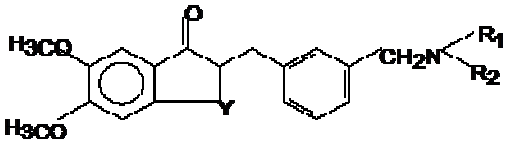
EXPERIMENTAL SECTION

The table 1 shows the structural features of indanone and aurone derivatives along with their biological activities (pIC_{50} in µg/ml) reported by Sheng *et al*.[1]

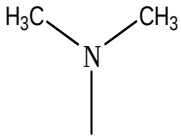
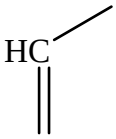
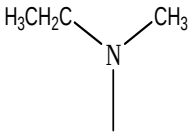
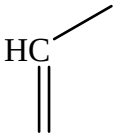
Table 1: Structure and ACHE inhibitory Activities of Compounds used in QSAR model:

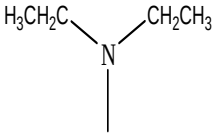
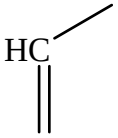
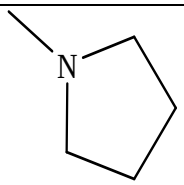
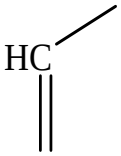
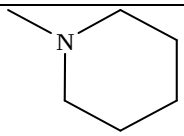
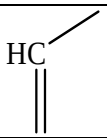
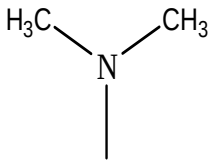
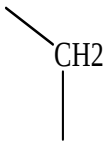
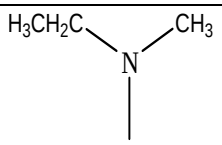
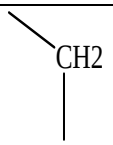
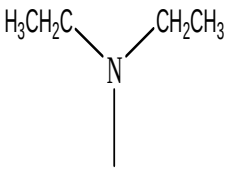
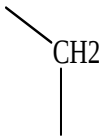
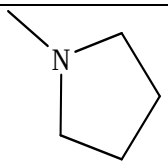
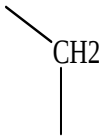
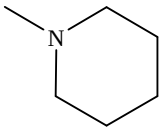
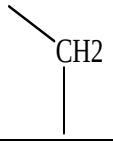


a. Indanone Derivative



b. Aurone Derivative

Compounds No.	**NR_1R_2**	**X**	**Y**	**Substituted Position**	**PIC_{50}**
1a **1b**			CH_2	Meta Para	8.1977 8.9049
1c **1d** **1e**			CH_2 O	Meta Para Para	8.8556 9.1144 8.7031

1f **1g** **1h** **1i**			CH_2 O	Meta Para Meta Para	8.9194 10.018 8.4933 9.4190
1j **1k** **1l** **1m**			CH_2 O	Meta Para Meta Para	9.1802 9.9072 9.1004 9.3586
1n **1o** **1p**			CH_2 O	Meta Para Para	9.3727 9.5769 9.6653
2a **2b**			CH_2	Meta Para	7.9578 8.3908
2c **2d** **2e**			CH_2 O	Meta Para Para	8.7094 8.9685 8.3632
2f **2g** **2h** **2i**			CH_2 O	Meta Para Meta Para	8.3949 9.1028 8.5381 8.9241
2j **2k** **2l** **2m**			CH_2 O	Meta Para Meta Para	8.1512 9.3867 7.7188 8.7728
2n **2o** **2p**			CH_2 O	Meta Para Meta	8.7596 9.5000 9.2012

The QSAR analysis on Indanone and aurone derivatives has been carried out using CS Chem-Office software 2001 version 6.0 (Cambridge soft). Energy minimization was performed, using MM2 and molecular orbital package (MOPAC) respectively. Biological activity data were taken from Sheng et.al,[1]. IC_{50} (concentration in μM) were converted to negative logarithmic dose in moles (pIC_{50}) for QSAR analysis. The series was divided into a training set of 23 compounds and test set of 9 compounds. The series was subjected to sequential multiple linear regression analysis in order to establish correlation between physicochemical parameters and inhibitory activity using VALSTAT program [8,9,10].

The various descriptors used in QSAR model using CS Chem-Office software 2001 version 6.0 (Cambridge soft) are described in following table 2-

Table 2: Various Descriptors used in QSAR Analysis

S. No.	Descriptor	S. No.	Descriptor
1	Henry's Law Constant	22	D2
2	LogP	23	D3
3	Molar Refractivity	24	D4
4	Standard Gibbs Free Energy	25	DipoleLength
5	Connolly Accessible Area	26	ElectronicEnergy
6	Connolly Molecular Area	27	HOMOEnergy
7	Connolly Solvent-Excluded Volume	28	LUMOEnergy
8	Ovality	29	RepulsionEnergy
9	Principal Moment of Inertia - X	30	TotalEnergy
10	Principal Moment of Inertia - Y	31	Balaban Index
11	Principal Moment of Inertia - Z	32	Cluster Count
12	Molar Refractivity	33	Diameter
13	Partition Coefficient (Octanol/Water)	34	Molecular Topological Index
14	Bend Energy	35	Radius
15	Non-1,4 VDW Energy	36	Shape Attribute
16	Stretch Energy	37	Shape Coefficient
17	Stretch-Bend Energy	38	Sum Of Degrees
18	Torsion Energy	39	Sum Of Valence Degrees
19	Total Energy	40	Total Connectivity
20	VDW 1,4 Energy	41	Total Valence Connectivity
21	D1	42	Wiener Index

RESULT AND DISCUSSION

Data set was subjected to sequential multiple linear regression analysis, in order to develop QSAR between biological activity as dependent variables and substituent constants as independent variables. The series was run on auto mode for sequential multiple linear regression analysis it generate test set as 9 compounds (1e, 1f, 1g, 1i, 1k, 2a, 2b, 2k and 2l) and remaining 23 compound as training set. Several equations were obtained, the statistically significant equation was considered as best model.

pIC_{50} = G [0.0022 (± 0.001)] + Diam. [0.397 (± 0.131)] – LUMO [0.6388 (± 0.323)] + [2.312 (± 1.946)]

n=23, r=0.873, r^2=0.762, Std =0.226, F=20.30, r^2_{bs}=0.788, q^2=0.647, S_{press}=0.275, S_{dep} =0.250, r^2_{pred} =0.583

Table 3: CORRELATION MATRIX

	G	Lumo	Diam
G	1.000000		
Lumo	0.108072	1.000000	
Diam	0.066313	0.006943	1.000000

The values of the descriptors for the significant equation can be shown by following table-

Table 4: Values of Descriptors used in the QSAR model

Sr. No.	Compound Name	G	LUMO	Diameter
1	1a	204.35	-0.6873	13
2	1b	204.35	-0.7226	14
3	1c	212.77	-0.6831	14

4	1d	212.77	-0.7202	15
5	1e	118.23	-1.0685	15
6	1f	221.19	-0.6049	14
7	1g	221.19	-0.6397	15
8	1h	126.65	-0.9039	14
9	1i	126.65	-0.9548	15
10	1j	277.55	-0.6531	14
11	1k	277.55	-0.6499	15
12	1l	183.01	-0.9394	14
13	1m	183.01	-1.0057	15
14	1n	273.87	-0.6321	15
15	1o	273.87	-0.7204	16
16	1p	179.33	-0.9947	16
17	2a	151.18	-0.4246	13
18	2b	151.18	-0.4257	14
19	2c	159.6	-0.3714	14
20	2d	159.6	-0.3282	15
21	2e	65.06	-0.5435	15
22	2f	168.02	-0.3079	14
23	2g	168.02	-0.4094	15
24	2h	73.48	-0.5094	14
25	2i	73.48	-0.5168	15
26	2j	224.38	-0.3948	14
27	2k	224.38	-0.3098	15
28	2l	129.84	-0.5128	14
29	2m	129.84	-0.5028	15
30	2n	220.7	-0.3079	15
31	2o	220.7	-0.3299	16
32	2p	126.16	-0.5839	15

TABLE 5: Observed, Calculated and Predicted value for training set compounds

Sr. No.	Compound No.	Predicted	Calculated	Observed
1	1a	8.44291	8.37695	8.19776
2	1b	8.78584	8.79746	8.90492
3	1c	8.78387	8.79084	8.85566
4	1d	9.22061	9.21248	9.1145
5	1h	8.80532	8.74142	8.49331
6	1j	8.84691	8.91498	9.18024
7	1l	8.84109	8.88877	9.10041
8	1m	9.32117	9.32904	9.35869
9	1n	9.2759	9.29136	9.37278
10	1o	9.81262	9.74569	9.5769
11	1p	9.73516	9.71182	9.66535
12	2c	8.44029	8.47413	8.7095
13	2d	8.82699	9.74569	8.96856
14	2e	8.88787	8.77288	8.36324
15	2f	8.46269	8.45215	8.39498
16	2g	8.89708	8.91491	9.10285
17	2h	8.32812	8.37176	8.53819
18	2i	8.73762	8.7744	892412
19	2j	8.71905	8.63235	8.15124
20	2m	8.90184	8.89018	8.7728
21	2n	9.00631	8.96663	8.75967
22	2o	9.33363	9.37856	9.50003
23	2p	8.90737	8.93379	9.20125

Finally the predicted activity of the compounds were calculated using LOO method and a comparison of these with the corresponding observed activities were made, which is shown in Tables and Graphs.

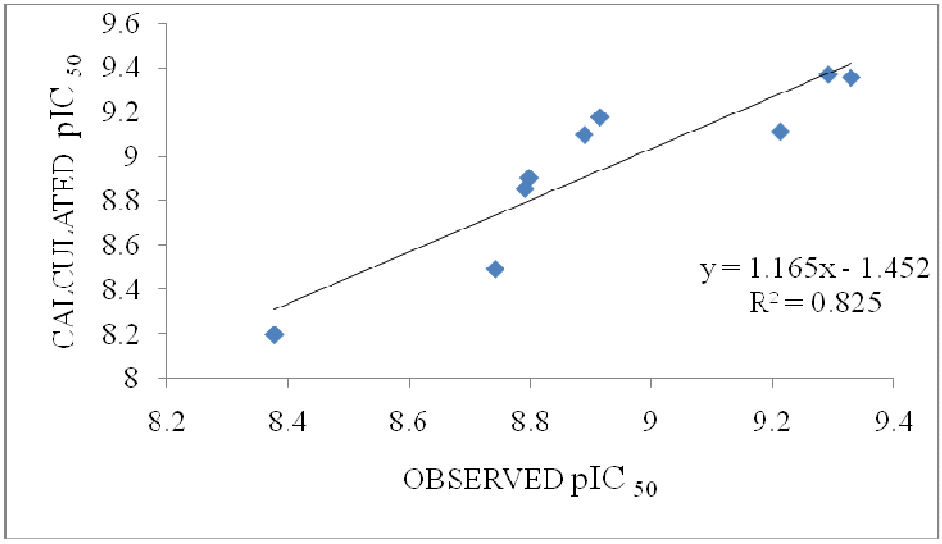


Figure 1: Scatter plot between the Observed and Calculated values of Training set compounds

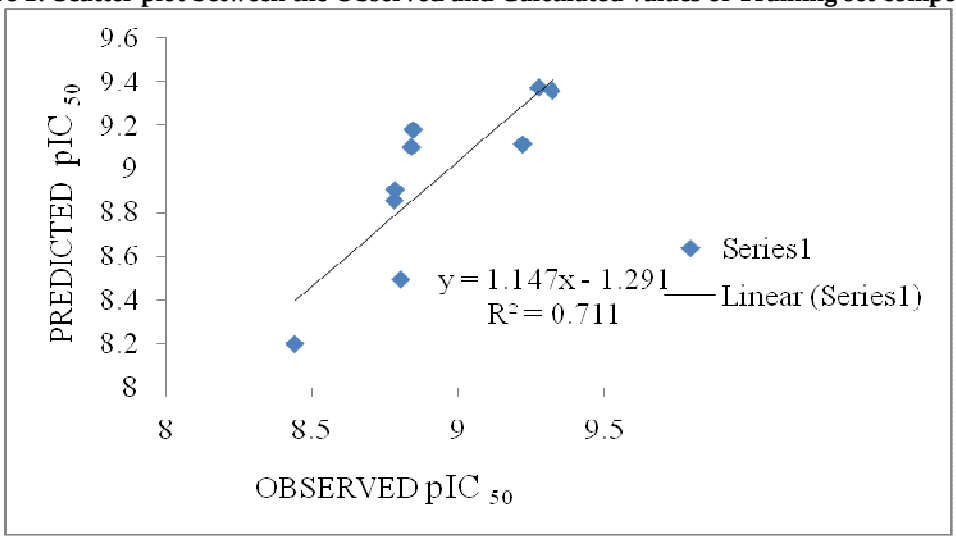


Figure 2: Scatter plot between the Observed and Predicted values of Training set compounds

Table 5: Observed and Predicted Values for Test Set Compounds

Sr. No.	Compound name	Predicted	Observed
1	1e	9.22584	8.70319
2	1f	8.75954	8.9194
3	1g	9.17963	10.0188
4	1i	9.17185	9.41907
5	1k	9.31084	9.90724
6	2a	8.09158	7.95789
7	2b	8.49016	8.39088
8	2k	8.97599	9.38677
9	2l	8.4986	7.71886

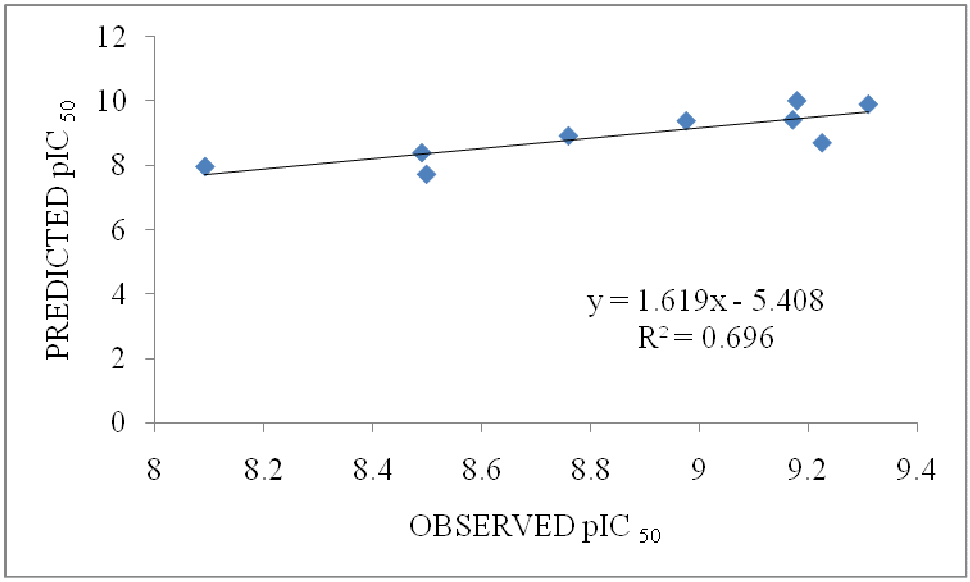


Figure 3: Scatter plot between the Observed and Calculated values of Test set compounds

The Eqn. indicate that thermodynamic parameter (Standard Gibbs Free Energy) and steric parameters (diameter) shows positive contribution while Electronic parameter (LUMO Energy) shows negative contribution towards the activity. The model has correlation coefficient (r) of 0.873. It shows significance level more than 95% against tabulated value F=8.53, with a low standard deviation of estimation 0.226, demonstrate accuracy of the model. The robustness of model was shown by magnitude of the bootstrapping r^2, which was near to conventional r^2. The internal predictivity of model (q^2=0.647) was also good. The model once again favored by the least S_{press} and S_{dep} values. The value of cross-validated squared correlation coefficient (q^2=0.647), predictive residual sum of square (S_{press}=0.275) and standard error of predictivity (S_{dep}=0.250) suggested good predictive ability of the activity. Randomized biological activity data test (chance<0.001) revealed that result was not based on chance correlation

CONCLUSION

LUMO (Lowest Unoccupied Molecular Orbital) energy indicate the n-bonding interaction of species, is crucial for electrophilicity of the molecules. Negative contribution suggest that electronegative group is unfavourable for activity. Diameter is related to the largest dimension of molecule which contributes positively. The Gibbs Free Energy (G) contributes positive to the equation.

ACKNOWLEDGEMENT

Authors thank the Director, Jodhpur National University, Jodhpur, for providing facilities to complete this work.

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