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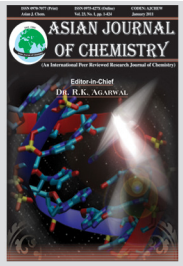

Quantitative Structure-Activity Analysis of 1,3,5-Trisubstituted Pyrazoline Derivatives as Monoamine Oxidase Inhibitors

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Quantitative structure activity relationship (QSAR) study has been performed on twenty four derivatives of 1,3,5-trisubstituted pyrazolines for identifying important physicochemical properties responsible for their binding affinity towards monoamineoxidase enzyme. QSAR study was performed using various physicochemical (hydrophobic, electronic, steric, *etc*.) parameters as independent variables and monoamine oxidase inhibitory activity as dependent parameter. The 2D QSAR studies revealed that the activity is mainly influenced by hydrophobicity parameter, where the hydrophobicity (log P) contributes negatively and polorizability parameter (MR) contributes positively towards the biological activity. All derived models display satisfactory correlation coefficient (> 0.7).

Key Words: QSAR, Pyrazoline derivatives, Monoamine oxidase inhibitors.

INTRODUCTION

Amine oxidases (AOs) are enzymes widely distributed among all organisms, with important oxidatively deaminated biological function[1]. They are divided into two classes amine oxidases (AOs) containing flavin adenine dinucleotide as a cofactor (FAD-AOs) and semicarbazide sensitive AOs (ssAOs) containing copper(II)-2,4,5-trihydroxyphenyl alanine quinone as a cofactor (TPQ-Cu AOs). FAD-AOs are located on outer membrane of the mitochondria and named as monoamine oxidase (MAO). Monoamine oxidase [EC-1.2.3.4] is found in two isoforms, MAO-A and MAO-B, which are encoded by two different genes[2]. They also differ in substrate specificity, sensitivity to inhibitors and amino acid sequence[3]. Physiologically this enzyme is involved in the metabolism and regulation of monoamine neurotransmitters such as serotonin, nor adrenaline and dopamine[4]. Isoforms MAO-A and B are found to possess substrate specificity. MAO-A prefers serotonine and nor-epinephrine as substrate whereas MAO-B prefers dopamine and benzylamine as substrates[5]. Changes in the activity of these enzymes have been observed in numerous neuropsychiatric disorders and the employment of MAO inhibitors often produces a therapeutic effect[6]. The role of monoamine oxidase inhibitors (MAOIs) for patients with depressive disorders is well established[7,8]. Later on 2-pyrazoline structures were shown to have similarity with the isocarboxazide[9] (a well known MAO inhibitor). Apart from these there are several studies revealed the role of 2-pyrazoline as monoamine oxidase inhibitors[10,11]. Therefore with this background it becomes necessary to understand that which physico-chemical properties of 2-pyrazolines are going to affected monoamine oxidase inhibition.

Quantitative structure activity relationship (QSAR) has been a very useful tool in designing libraries of various ligands targeted towards particular receptors and to ensure the increase in probability of synthesizing therapeutically active drug[12,13]. Therefore, to understand the influence of physicochemical and structural properties of 1,3,5-trisubstituted pyrazoline for MAO binding affinity, QSAR studies have been carried out and the results are presented in this paper[14].

EXPERIMENTAL

The monoamine oxidase (MAO) inhibitory activity of 1,3,5-trisubstituted pyrazoline derivatives is listed in Table-2. IC_{50} refers to the micro molar concentration of the compounds required for 50 % inhibition of the MAO enzyme. IC_{50} values were transformed to pIC_{50} (negative logarithm of IC_{50}) to get the linear relationship in the QSAR equations. CAChe software (6.1 version) was employed to generate parameters of the optimized structures. Structures of the compounds were drawn in Work Space module of the CAChe software. Generated structures were subjected to geometry optimization, to get minimum energy conformer of the structure. All the minimum energy conformers of the compounds were then imported into

TABLE-1
QSAR PARAMETERS VALUES OF 1,3,5-TRISUBSTITUTED PYRAZOLINE DERIVATIVES[a]

Comp.	R	R'	R''	log P	MR[b]	HOMO[c]	HOF[d]	DM[e]	LUMO[f]
1	4-OH	$-COCH_3$	2-Cl	3.107	86.709	-8.842	-8.316	3.411	-0.607
2	4-OH	$-COCH_3$	3-Cl	3.107	86.709	-8.877	-9.723	3.895	-0.633
3	4-OH	$-COCH_3$	4-Cl	3.107	86.709	-8.875	-9.877	3.683	-0.64
4	4-OH	$-COCH_3$	3-CH_3	3.057	86.945	-8.803	-12.47	3.103	-0.576
5	4-OH	$-COCH_3$	4-CH_3	3.057	86.945	-8.792	-12.55	3.185	-0.568
6	4-OH	$-COCH_3$	2-OCH_3	2.337	88.367	-8.751	-38.46	2.817	-0.524
7	4-OH	$-COCH_3$	4-OCH_3	2.337	88.367	-8.799	-41.23	3.608	-0.576
8	4-OH	$-COCH_3$	2,4-OCH_3	2.084	94.830	-8.728	-76.8	2.84	-0.512
9	2,4-OH	$-COCH_3$	4-Cl	2.823	88.403	-8.987	-52.68	2.301	-0.422
10	2,4-OH	$-COCH_3$	4-CH_3	2.772	88.639	-8.918	-55.55	1.525	-0.343
11	2,4-OH	$-COCH_3$	2-OCH_3	2.052	90.061	-8.930	-82.92	1.353	-0.342
12	2,4-OH	$-COCH_3$	4-OCH_3	2.052	90.061	-8.921	-84.2	2.217	-0.349
13	2-OH	$-C_6H_5Cl$	3-Br	5.882	106.94	-8.577	74.028	2.745	-0.448
14	2-OH	$-C_6H_5Cl$	4-Br	5.882	106.94	-8.576	74.162	2.147	-0.474
15	2-OH	$-C_6H_5Cl$	4-CH_3	5.558	104.36	-8.468	56.57	3.33	-0.328
16	2-OH	$-C_6H_5Cl$	2-OCH_3	4.838	105.78	-8.427	30.549	4.157	-0.263
17	2-OH	$-C_6H_5Cl$	3-OCH_3	4.838	105.78	-8.490	28.331	3.175	-0.344
18	2-OH	$-C_6H_5Cl$	4-OCH_3	4.838	105.78	-8.485	27.856	3.658	-0.322
19	2-OH	$-C_6H_5Cl$	2-NO_2	5.044	106.64	-8.664	61.495	4.854	-1.377
20	2-OH	$-C_6H_5Cl$	3-NO_2	5.044	106.64	-8.774	56.639	4.852	-1.394
21	2-OH	$-C_6H_5Cl$	4-NO_2	5.044	106.64	-8.612	59.917	7.469	-1.329
22	2-OH	$-C_6H_5Cl$	4-$N(CH_3)_2$	5.355	113.75	-8.449	62.166	4.775	-0.282
23	2-OH	$-C_6H_5Cl$	4-Cl	6.126	108.93	-8.587	54.147	2.111	-0.654
24	2-OH	$-C_6H_5Cl$	3-OCH_3	4.585	112.24	-8.217	-1.92	4.626	-0.464

[a]Fig. 1 for structures, [b]Molecular refactivity, [c]Highest occupied molecular orbital, [d]Heat of formation, [e]Dipole moment, [f]Lowest unoccupied molecular orbital.

TABLE-3
CORRELATION MATRIX OF THE PARAMETERS USED IN QSAR STUDY

	BA	log P	DM	MR	HOMO	LUMO	HOF
BA	1	–	–	–	–	–	–
log P	-0.743	1	–	–	–	–	–
DM	-0.743	1	1	–	–	–	–
MR	0.128	-0.201	-0.201	1	–	–	–
HOMO	-0.688	0.952	0.952	-0.348	1	–	–
LUMO	-0.619	0.737	0.737	0.119	0.644	1	–
HOF	-0.085	0.180	0.180	0.12	0.328	-0.141	1

the project leader module for the calculations of various physico-chemical parameters.

Multiparameters regression analysis was carried out on Compaq Pentium-IV using SYSTAT software (Version 10.2) for statistical studies to obtain sensitive and significant results. In the present study out of several parameters only log P, dipole moment and molecular refractivity along with some other electronic parameters on which most of the drug-receptor interactions depend were chosen. All these explaining descriptors (independent variables) values for the compound under study are listed in Table-2. Intercorrelations between various parameters are reported in Table-3. In order to obtain QSARs the multiple regression analysis (MRA) following a method of least square was considered. To obtain quantitative models, the numbers of statistical parameters were obtained in conjunction with such calculation to access the significance of the derived results. These are the correlation coefficient (r), standard error of estimation (s), coefficient of determination (r^2) and F-value representing the ratio of the variance of calculated to observed activities. The ± data within parentheses represents standard error of coefficient.

RESULTS AND DISCUSSION

From the listed compounds of Table-1, related with the structure (Fig. 1) the data set produced highly significant QSAR equations (eqns. 1 and 2).

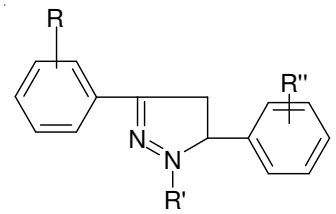

Fig. 1

$$\log IC_{50} = -0.492(0.095) \log P + 0.151 \quad (1)$$

N = 24, r = 0.743, F = 27.07, s = 0.637

$$\log IC_{50} = -0.0451(0.093)\ DM + 8.877(4.079)MR + 10.324(4.690)\ HOF - 0.765 \quad (2)$$

N = 24, r = 0.800, F = 11.825, s = 0.599

Though the data contains 24 compounds, still the correlation coefficients obtained were highly significant (r = 0.743

for eqn. 1 and r = 0.800 for eqn. 2). The standard deviation were also very less (s = 0.637 for eqn. 1 and s = 0.599 for eqn. 2). If we look at statistical significance, F-values, obtained were outstanding (27.07 for eqn. 1 and 11.825 for eqn. 2) indicating the robustness of the QSAR equations. The data within the parentheses, associated with coefficients value of the descriptors in the regression equation was very less indicating the high sensitivity of the equations. From the above-derived models (from eqn. 1) it is clear that improved hydrophobic nature of the pyrazoline derivatives will not be in favour of the enzyme inhibitory activity.

At the same time (from eqn. 2) molar refractivity, which accounts for the size and polarity of the substituents is contributing positively to the biological activity of the molecules. But when we go for the contribution provided by the dipole moment (DM) parameter in the same model, it is contributing negatively to the biological activity. Therefore when these two considered simultaneously, it is clear that bulky substituents still with low polarity can be placed on the pyrazoline nucleus and this combination should provide favourable molecular structures for the enzyme inhibitory activity. The observed biological activity *versus* calculated activity plot of eqns. 1 and 2 is given in Figs. 2 and 3, respectively.

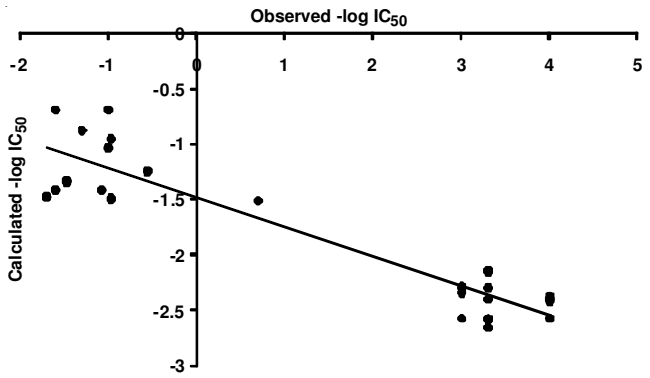

Fig. 2. Graph between observed and calculated biological activity (-log IC_{50}) calculated through eqn. 1

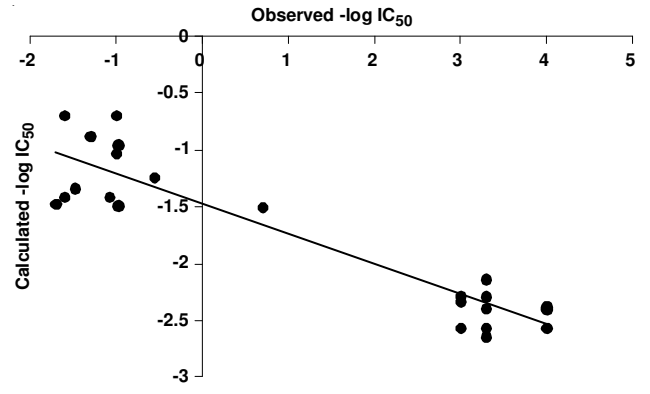

Fig. 3. Graph between observed biological activity and calculated biological activity (-log IC_{50}) calculated through eqn. 2

Thus the present study explores the physico-chemical properties necessary for the drug to interact with active site of monoamine oxidase enzyme. This study also provides the basis for the selection of substituents in analogue drug design strategy.

TABLE-2
OBSERVED AND CALCULATED BIOLOGICAL ACTIVITY (-log IC_{50}) of 1,3,5-TRISUBSTITUTED PYRAZOLINE DERIVATIVES[a]

Comp	Observed -log IC_{50}	Calculated -log IC_{50}		
		by eqn. 1	by eqn. 2	by eqn. 3
1	-1.699	-1.3773	-1.4717	-1.2247
2	-1.079	-1.3773	-1.4104	-1.1457
3	-1.602	-1.3773	-1.4118	-1.2079
4	-0.978	-1.3521	-1.4898	-1.2677
5	0.699	-1.3527	-1.5044	-1.2586
6	-1.477	-0.9985	-1.3342	-1.0081
7	-0.556	-0.9985	-1.2427	-0.9122
8	-1	-0.8741	-1.0293	-0.9011
9	-1.301	-1.2376	-0.8789	-1.1683
10	-0.978	-1.2125	-0.9502	-1.2700
11	-1.602	-0.8584	-0.6929	-1.3805
12	-1	-0.8584	-0.6942	-0.7819
13	-2	-2.7421	-2.5662	-2.7263
14	-2.699	-2.7421	-2.5688	-2.6886
15	-3	-2.5828	-2.5653	-2.7849
16	-2.699	-2.2286	-2.3940	-2.4616
17	-3	-2.2286	-2.2864	-2.5198
18	-2.699	-2.2286	-2.2892	-2.0458
19	-3	-2.3299	-2.3344	-3.1925
20	-2.699	-2.3299	-2.1378	-1.8877
21	-2	-2.3299	-2.3932	-2.1160
22	-2.699	-2.4829	-2.6411	-2.6051
23	-2	-2.8621	-2.3775	-2.5587
24	-2	-2.1042	-2.4025	-1.9533

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