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Research Article

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QSAR Study of rat liver angiotensin II antagonists compounds

B. N. Singh[1], Kalpana Singh[1] and Kaleem Ahmad[2*]

[1]Department of Chemistry, Kisan (P.G.) College, Bahraich (U.P.), INDIA
[2]Department of Chemistry, Mahila (P.G.) College, Bahraich (U.P.), INDIA

ABSTRACT

The various QSAR models have been developed to predict the activities in terms of log 1/C for 11 Rat Liver Angiotensin II Antagonists compounds with the help of quantum chemical and energy descriptors viz. heat of formation, Gibbs free energy, Molar Refractivity, HOMO energy, LUMO energy, absolute hardness, Softness, Chemical Potential and electronegativity. The parameter adopted in this calculation is the semi-empirical PM3 based. The QSAR model sixth provides a good arrangement between obs log 1/c & predicted activity.

Key words: Absolute hardness; Chemical potential; electronegativity; Global Softness; Gibbs free energy (ΔS), Heat of formation(ΔH), HOMO; LUMO, Molar Refractivity (MR). PM3.

INTRODUCTION

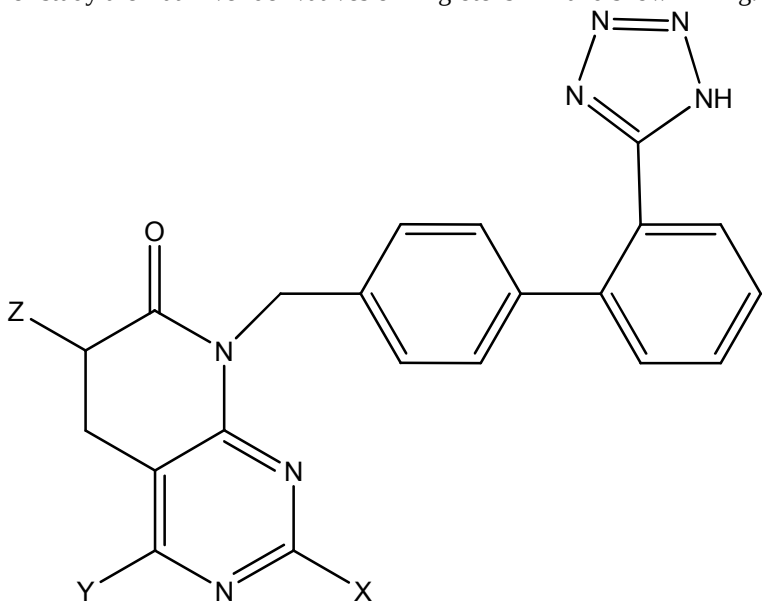
The rennin-angiotensin system (RAS) plays a major role in the regulation of blood pressure, blood volume and electrolyte homeostasis [1]. RAS is a cascade of proteolytic enzymes (rennin and angiotensin converting enzyme (ACE)) that result in the production of the systemic hormone angiotensin II (AII).The blockade of RAS with inhibitors of ACE has demonstrated the effectiveness of the reduction of levels of AII on cardiovascular and kidney heamodynamics, aldosterone production and release, and the absorption of sodium. Antagonists of AII constitute an alternative method blocking the RAS. Several peptidic and nonpeptidic AII receptor antagonists are known. The therapeutic availability is less for the peptidic AII antagonist due to their poor bioavailability, short plasma half-life and partial agonist activity but the nonpeptidic AII receptors antagonist lack the defect of peptidic antagonist [2].The therapeutic profile of AII receptor antagonist is thought to be similar to that of angiotensin converting enzyme (ACE) inhibitors such as captopril, enalapril, and lisinopril. In addition, since AII receptor antagonist does not affect the metabolism of bradykinin so they may not have the side effect of ACE inhibitors, such as dry cough and angiodema. Recently, the QSAR analysis is a highly interested area for designing the compound before synthesis [3–5].

A derivatives of 2, 4-Disubstituted -8-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5, 8-dihydro-6H-pyrido [2, 3-d] pyrimidin-7-one dual-acting AII antagonists has been taken from literature. [6].

In the present study we have taken structures of a set of above derivatives of Angiotensin II and then compared to the numerical values of a biological activity. The challenge here has been to find some numerical information for a molecule. This structure information and the measured property or activities are then converted into a mathematical model of relationship. From a quality model it is possible to predict and to design compounds for synthesis and testing that have a good possibility for activity. In this paper, the multi linear regression analysis has been applied for QSAR study. The relationship has been worked out between the Log1/C values of a series of compounds and certain quantum chemical descriptors.

EXPERIMENTAL SECTION

The compounds taken for study are Rat Liver derivatives of Angiotensin II and shown in Fig.-1.



2, 4-Disubstituted -8-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5, 8-dihydro-6H-pyrido [2, 3-d] pyrimidin-7-one

Fig.-1

The Quantum Mechanical QSAR

The Quantum Chemical parameter based QSAR study was performed by the following important descriptors like Eigen value of Highest occupied molecular orbital (EHOMO), Eigen value of lowest unoccupied molecular orbital (ELUMO) [7] , Absolute Hardness (η) [8] , Chemical Potential (μ) [9] , Global Softness (S) [10], Electronegativity (χ) [11], Heat of formation(ΔH), Gibbs free energy (ΔS), Molar Refractivity (MR). The molecules were drawn by spartan06v110, software and the geometries were optimized at PM3 level in conjunction with molecular mechanics. The global hardness and electronegativities were calculated using frontier orbital energies obtained from PM3 results and reported in table 2. Multiple linear regression analysis (MLR) is performed to establish the QSAR. A data set of Rat Liver of Angiotensin II Antagonists compounds were taken with their observed activity is shown in table 1.

RESULTS AND DISCUSSION

Multiple Linear Regression (MLR) analysis

MLR analyses were performed using Minitab 16 software. The quantum mechanical descriptors were used as independent variables and the Obsd log1/C50 values as the dependent variables. In the statistical analyses, the systematic search was performed to determine the significant descriptors. The correlation matrix was developed to minimize the effect of co-linearity and to avoid dependencies between subsets of the variables and multi-co-linearity (high multiple correlations between subsets of the variables). The MLR equations of different QSAR models are as follows-

First QSAR model

MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 9.00 + 0.73 E LUMO
S = 0.584613
PRESS = 4.81292
r^2= 4.9%

Second QSAR model

MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 69.1 - 4.71 E LUMO + 6.87 E HOMO
S = 0.417843
PRESS = 2.80529
r^2= 56.8%

Third QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 70.4 - 4.2 E LUMO + 7.5 E HOMO + 0.6 S
S = 0.446639
PRESS = 3.39136
r^2= 56.8%

Fourth QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 50.0 - 8.8 E LUMO + 1.0 E HOMO - 4.9 S + 0.00140 ΔH
S = 0.434139
PRESS = 14.6043
r^2= 65.0%

Fifth QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 49.9 + 5.8 E LUMO + 14.1 E HOMO + 10.6 S - 0.0130 ΔH + 0.0139 ΔG
S = 0.312867
PRESS = 12.1049
r^2= 84.9%

Sixth QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 58.0 + 6.1 E LUMO + 15.2 E HOMO + 11.2 S - 0.0158 ΔH + 0.0168 ΔG- 0.0420 MR
S = 0.302352
PRESS = 9.68047
r^2= 88.7%

CONCLUSION

Values of the descriptors of the Angiotensin II Antagonist derivatives have been calculated using PM3 method and are given in table-2. With the help of these values of descriptors, six QSAR models have been developed using MLR analysis in different combinations of descriptors. The Chemical Potential (μ) and Absolute Hardness (η) descriptors have no predicting power and hence not included in the models. Best QSAR models is the model sixth listed below-

Sixth QSAR model
MLR equation of this QSAR model P log 1/C is given by-
Obsd log 1/C = 58.0 + 6.1 E LUMO + 15.2 E HOMO + 11.2 S - 0.0158 ΔH + 0.0168 ΔG- 0.0420 MR
S = 0.302352
PRESS = 9.68047
r^2= 88.7%

This is one of the best QSAR model in all the six models and has been developed using E LUMO, E HOMO, Global Softness (S), Molar Refractivity (MR), Heat of reaction (ΔH) and Gibbs free energy (ΔG). This MLR equation is given by Value of regression coefficient is **88.7%** Prediction sum of squares coefficient (PRESS) is **9.68047** and Standard error of the regression (S) is **0.302352** which indicate the ability of predictive power of this QSAR model. QSAR model sixth can efficiently be used for the prediction of activity of any derivative of compound. The normal probability plot of responses is obsd log 1/C is shown in fig-2, which is clearly illustrates the high predictive power of the QSAR model six.

Fig- 2

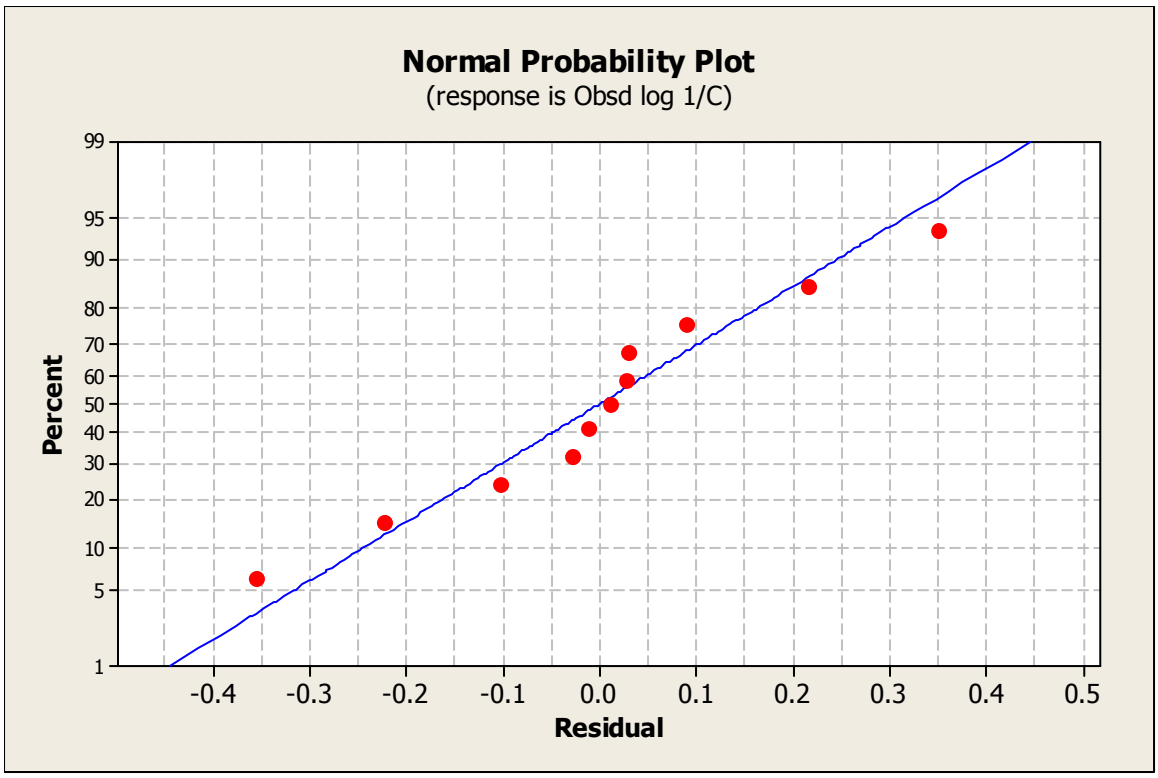


Table 1

Comp. No.	X	Y	Z	Obsd log 1/C
1	-Me	-Me	H	8.28
2	-Me	$-CF_3$	Me	7.61
3	-Me	-Me	H	8.5
4	-Me	$-C_2H_5$	H	8.64
5	-Me	$CHMe_2$	H	7.89
6	-Me	$-C_3H_7$	H	8.75
7	$-C_2H_5$	-Me	H	8.89
8	$-CHMe_2$	-Me	H	8.66
9	$-C_3H_7$	-Me	H	8.87
10	-Me	$-CH_2OH$	H	7.64
11	-Me	-CHO	H	7.3

Table 2

Compound	E LUMO (e.v)	E HOMO (e.v)	μ	η	S	χ	ΔH (kJ/mol)	ΔG (kJ/mol)	MR (cm3/mol)
1	-0.908	-9.459	-5.183	4.275	8.358	5.183	575.480	1131.630	115.010
2	-1.355	-9.831	-5.593	4.238	9.093	5.593	-21.600	550.040	115.160
3	-1.329	-9.796	-5.563	4.233	9.044	5.563	534.500	1132.340	119.720
4	-0.897	-9.431	-5.164	4.267	8.317	5.164	534.500	1132.340	119.730
5	-0.900	-9.415	-5.157	4.258	8.304	5.157	554.840	1140.050	124.370
6	-0.906	-9.436	-5.171	4.265	8.333	5.171	528.920	1146.030	124.370
7	-0.996	-9.460	-5.228	4.232	8.456	5.228	554.840	1140.050	119.730
8	-0.898	-9.462	-5.180	4.282	8.349	5.180	528.920	1146.030	116.640
9	-0.901	-9.467	-5.184	4.283	8.357	5.184	534.200	1148.470	124.370
10	-0.924	-9.578	-5.251	4.327	8.495	5.251	423.250	994.810	116.640
11	-0.959	-9.635	-5.297	4.338	8.593	5.297	489.900	1032.110	116.940

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