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QSAR Based Study of Derivatives of Triazine Against The Enzyme Dihydrofolate Reductase

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Enzyme level inhibition, a technique being used for the rational development of drug has been used for dihydrofolate reductase, an enzyme found in the tumor cells has been the target of anticancer drugs. Quantum chemical reactivity descriptors such as heat of formation, total energy, steric energy, HOMO energy, LUMO energy, absolute hardness and electronegativity have been used to develop QSAR model of the inhibitors of the enzyme, dihydrofolate reductase. The inhibitors used are 25 triazine derivatives. The inhibitory activities in the terms of log 1/C of various derivatives against the enzyme, dihydrofolate reductase has been taken from literature. The values of various descriptors have been evaluated by using Win MOPAC 7.21 software with the help of PM3 method. Multiple linear regression analysis has been made with the help of above mentioned descriptors using the same software. The best model out of the various models developed with the help of PM3 calculations has the correlation coefficient, r^2as 0.73825 and the cross-validation coefficient, r^2cv as 0.688095 and has been chosen as the QSAR model. Thus prediction of inhibitory activity of this series of derivatives can easily be done with the help of the QSAR model developed.

Key Words: Dihydrofolate reductase, Quantum chemical reactivity descriptors, Heat of formation, QSAR and MLR.

INTRODUCTION

QSAR, a quantum chemical technique[1,2], is known to relate the biological activity of compounds with their molecular structure[3] and has been extensively used as predicting tool in rational drug design[4-9]. QSAR analysis makes it possible to determine the contributions of various chemical structural elements of the molecules to its physiological effect as well as to detect the potential role of particular derivative. QSAR has recently been used to study the enzyme's inhibition[10-13]. Baker *et al.*[14] synthesized various derivatives of triazine, which they found to have anticancer properties. These derivatives have inhibitory activity against the enzyme dihydrofolate reductase. Literature survey reveals that attempts have never been made to explore the inhibition of the enzyme, dihydrofolate reductase with these inhibitors with the help of QSAR with the parameters employing to this study. So we have taken this task into consideration and proceeded accordingly and have presented QSAR study of inhibitors of this enzyme in this paper. We have taken 25 derivatives of triazine derivatives for QSAR study with the help of PM3[15] technique. This QSAR study of inhibitory activity of 25 derivatives of triazine against the enzyme dihydrofolate rductase has been made with the help of new set of descriptors; heat of formation[16], steric energy, HOMO energy[17], LUMO energy[18], total energy[19], absolute hardness[20,21] and electronegativity. These descriptors have been successfully employed for QSAR study recently[7].

The electronegativity, in DFT, is defined as the negative of a partial derivative of energy E of an atomic or molecular system with respect to the number of electrons N with a constant external potential $\nu(r)$[22]

$$\mu = -\chi = -\left(\frac{\delta E}{\delta N}\right)_{\nu(r)} \quad (1)$$

According to the earlier work of Iczkowski and Margrave[23], eqn. 1 may be rewritten as given below (assuming a quadratic relationship between E and N and in a finite difference approximation),

$$\chi = -\mu = -\frac{(IE + EA)}{2} \quad (2)$$

where IE and EA are the vertical ionization energy and electron affinity, respectively, which leads to the recovery of the electronegativity definition of Mullikan[24]. Moreover, a theoretical justification was provided for Sanderson's principle of electronegativity equalization, which states that when two or more atoms come together to form a molecule, their electronegativity become adjusted to the same intermediate value[25-27].

The absolute hardness[28], η, is defined as

$$\eta = \frac{1}{2}\left(\frac{\delta \mu}{\delta N}\right)_{\nu(r)} = \frac{1}{2}\left(\frac{\delta^2 E}{\delta N^2}\right)_{\nu(r)} \quad (3)$$

where E = total energy, N = number of electrons of the chemical species and ν(r) = external potential. Thus the operational definitions of absolute hardness and electronegativity are given as:

$$\eta = \frac{1}{2}(IE - EA) \quad (4)$$

$$\chi = -\mu = -\frac{(IE + EA)}{2} \quad (5)$$

where IE and EA are the ionization energy and electron affinity of the chemical species, respectively. According to Koopman's theorem, ionization energy is simply the eigen value of HOMO with change of sign and electron affinity is eigen value of LUMO with change of sign[29]; hence eqns. 4 and 5 may be rewritten as

$$\eta = \frac{1}{2}(\varepsilon LUMO - \varepsilon HOMO) \quad (6)$$

$$\chi = -\mu = \frac{1}{2}(\varepsilon LUMO + \varepsilon HOMO) \quad (7)$$

The total energy has also been used as quantum chemical descriptor and is sum of the total electronic energy (E_{ee}) and the energy of the internuclear repulsion (E_{nr}). The total energy[20] of the system is given by

$$T_E = \frac{1}{2}P(H + F) \quad (8)$$

where P = density matrix and H = one-electron matrix[5].

EXPERIMENTAL

The study materials of this paper are 25 triazine derivatives which are presented in Table-1 along with the observed activity. For QSAR prediction, the 3D modeling[15] and geometry optimization[30,31] of all the derivatives have been done with the help of PCMODEL software using PM3 Hamiltonian. The MOPAC calculations have been performed by Win MOPAC 7.21 software with the help of PM3 method by applying keywords Charge = 0, Gnorm = 0.1, Bonds, Geo-OK, Vectors density. The results are presented in the Table-2.

TABLE-1
log 1/C DATA FOR REVERSIBLE INHIBITION OF DIHYDROFOLATE REDUCTASE BY 2,6-DIAMINO-1,2-DIHYDRO-2,2-DIMETHYL-1-(X-PHENYL)-S-TRIAZINE

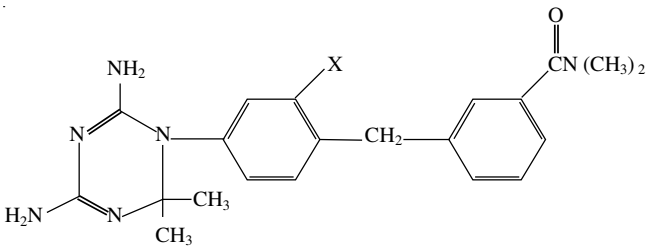
Deriv.	X	log 1/C (Observed)
1	3-Cl, 4 -$OCH_2C_6H_4$-3'-$CONHC_6H_4$-4" -SO_2F	6.92
2	3-Cl, 4-$OCH_2C_6H_4$-4'-$CONHC_6H_4$-4"-SO_2F	6.92
3	3-$OCH_2CONHC_6H_4$-4'-SO_2F	6.92
4	3-Cl, 4-$(CH_2)_4C_6H_3$-5'-Cl, 2'-SO_2F	7.06
5	3-Cl, 4-$O(CH_2)_3OC_6H_4$-4'-SO_2F	7.07
6	3-Cl, 4-$OCH(CH_3)$-$CONHC_6H_4$-4'-SO_2F	7.13
7	3-Cl, 4-$O(CH_2)_2O(CH_2)_2OC_6H_4$-4'-$SO_2F$	7.14
8	3Cl, 4-$O(CH_2)_3CONH$-C_6H_4-4'-SO_2F	7.15
9	3-Cl, 4-$O(CH_2)_3CONHC_6H_4$-3'-SO_2F	7.17
10	3-$(CH_2)_2CONHC_6H_4$-4'-SO_2F	7.19
11	3-Cl, 4-$OCH_2C_6H_4$-3"-SO_2F	7.24
12	3-Cl, 4-$OCH_2C_6H_4$-2'-$CONHC_6H_4$-4"-SO_2F	7.24
13	3-Cl, 4-$O(CH_2)_4$-$CONHC_6H_4$-4"-SO_2F	7.24
14	3-Cl, 4-$OCH_2C_6H_3$-5'-Cl, 2'-SO_2F	7.27
15	3-SO_2F	7.27
16	3-Cl, 4-$O(CH_2)_3NH$-$CONHC_6H_4$-3'-SO_2F	7.28
17	3-Cl, 4-$O(CH_2)_3$-C_6H_4-4'-SO_2F	7.34
18	3-$CH_2CONHC_6H_4$-4'-SO_2F	7.34
19	3-Cl, 4-$OCH_2C_6H_4$-6-Cl, 3'-SO_2F	7.38
20	3-Cl, 4-$OCH_2C_6H_3$-2'-CH_3,4'-SO_2F	7.38
21	3-Cl, 4-$S(CH_2)_2$-$CONHC_6H_4$-4'-SO_2F	7.39
22	3-Cl, 4-$O(CH_2)C_6H_4$-4'-$CONHC_6H_4$-3"-SO_2F	7.41
23	3-Cl, 4-$SCH_2CONHC_6H_4$-4'-SO_2F	7.42
24	3-Cl, 4-$OCH_2C_6H_3$-3'-Cl, 2'SO_2F	7.42
25	3-Cl, 4-OCH_2CONH-C_6H_4-4'-SO_2F	7.43

RESULTS AND DISCUSSION

The various derivatives of triazine belong to the following parent skeleton:

TABLE-2
VALUES OF THE QUANTUM CHEMICAL AND ENERGY DESCRIPTORS OF THE DERIVATIVES OF TRIAZINE

Derivatives	Heat of formation	Steric energy	Total energy	HOMO energy	LUMO energy	Absolute hardness	Electro negativity	Activity
1	104.651	-53.108	-295.559	-8.649	-1.100	3.774	4.874	6.920
2	104.651	-49.867	-295.538	-8.804	-1.170	3.817	4.987	6.920
5	106.920	-26.048	-258.959	-8.872	-0.853	4.009	4.863	7.070
6	117.827	-42.847	-266.491	-8.973	-1.085	3.944	5.029	7.130
7	107.978	-21.483	-278.272	-8.869	-0.842	4.014	4.856	7.140
8	108.129	-42.078	-273.663	-8.836	-0.954	3.941	4.895	7.150
9	110.432	-43.999	-273.667	-8.822	-0.865	3.978	4.843	7.170
10	111.734	-46.895	-242.574	-8.851	-0.912	3.969	4.881	7.190
11	109.491	-31.693	-232.471	-8.776	-1.032	3.872	4.904	7.240
12	112.491	-51.374	-295.569	-8.713	-1.097	3.808	4.905	7.240
13	119.491	-44.016	-280.834	-8.753	-0.971	3.891	4.862	7.240
14	109.944	-31.410	-244.220	-8.779	-1.225	3.777	5.002	7.270
16	114.095	-78.672	-283.059	-8.850	-0.833	4.009	4.841	7.280
17	116.003	-27.797	-246.788	-8.861	-0.947	3.957	4.904	7.340
18	115.003	-47.702	-235.418	-8.883	-1.055	3.914	4.969	7.340
19	121.608	-31.713	-244.238	-8.755	-1.267	3.744	5.011	7.380
20	119.608	-30.705	-239.656	-8.852	-1.043	3.905	4.947	7.380
21	118.759	-47.005	-263.536	-8.855	-1.063	3.896	4.959	7.390
22	117.061	-52.844	-295.558	-8.774	-0.869	3.952	4.822	7.410
23	102.213	-33.088	-256.365	-8.992	-1.251	3.870	5.121	7.420
24	119.213	-27.095	-244.212	-8.729	-1.156	3.787	4.942	7.420
25	112.364	-46.087	-259.342	-8.883	-1.042	3.920	4.962	7.430



[Dimethyl acetyl benzamide derivative of 2,6-diamino-1,2-dihydro-2,2-dimethyl-1-(X-phenyl)-S-triazine]

The inhibitory activity values have been taken from literature and are given in Table-1. The values of all the 7 chosen descriptors for all the 25 derivatives of triazine have been calculated with the help of PM3 method and are presented in the Table-2.

For the development of QSAR models based on PM3 Hamiltonian, we have generated various regression equations by employing all variables and the best fitted equation is given below. The predicted activity (PA) from this equation is given in Table-2. The statistical quality of the equation is good as is evident form its cross validation and correlation coefficients 0.688095 and 0.73825, respectively.

PA=0.0538542*DHf-0.0015478*SE+0.00309132*TE+ 0.0716091*∈HOMO+2.72259
rCV^2=0.688095, r^2=0.73825

Conclusion

Best QSAR model contains the descriptors heat of formation, steric energy, total energy and HOMO energy. Value of regression coefficient is 0.73825, which is too greater than 0.5 and hence indicates that the predictive power of QSAR model is very good.

It has been found that all the best QSAR models have heat of formation as common descriptor. It means the best descriptor to predict the activity is the heat of formation. Also, the predicted activity obtained by taking heat of formation as single descriptor possesses the good value of regression coefficient which is 0.721429. Predicted activity using heat of formation as descriptor is given by:

PA84=0.0579701*ΔHf+0.890529
rCV^2=0.703715, r^2=0.721429

Thus, the inhibitory activity of various other known derivatives of triazine and derivatives to be synthesized in future can easily be predicted with the help of the QSAR model developed in this paper.

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