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Study On Triazines Derivatives Inhibiting Dihydrofolate Reductase

Mithlesh Tiwari*

Department of Chemistry, Dr.Ram Manoher Lohiya Awadh University Ayodhya

Abstract:

In the QSAR study of triazine derivatives based on quantum chemical and energy values, descriptors used are heat of formation, steric energy, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity. Total number of combinations of descriptors tried in QSAR analysis is 10. All QSAR models have been found to have good predictive power.

Keywords: QSAR, Triazine derivatives, HOMO Energy, LUMO Energy

Introduction:

On the frontier of chemical structure-activity relationship, especially in bio- and medicinal chemistry, so little solid theory is at hand on which to build that all kinds of purely empirical ideas need to be of great help in sorting out important structure-activity features which can then be used to form more firmly based theory.[1-3] Techniques such as pattern recognition, discriminate analysis, cluster analysis, and regression analysis, which have been developed and used heavily out side of chemistry are now beginning to be used by those working with structure-activity relationship. In this present paper the regression analysis has been applied for QSAR study[4-10]. The relationship has been worked out between the Log1/C values of a series of compounds and certain quantum chemical and energy descriptors.

Baker[11-14] and few graduate students synthesized variations of 4,6—diamino – 1,2 dihydro- 2,2 dimethyl 1-1-1(phenyl) –s- triazine to achieve dimethyl acetyl benzamide, a drug now in clinical trials against cancer. group synthesized 256 variations of 4,6—diamino – 1,2 dihydro- 2,2 dimethyl 1-1-1(phenyl) –s- triazine and studied their inhibiting effect on dihydrofolate reductase. Out of 256 compounds synthesized by Baker[15-16] the QSAR study of 50 compounds has recently been reported. The remaining compounds leave a wide scope for their QSAR study.

Table-1 Log1/C and □ Log 1/C data for reversible inhibition of dihydrofolate reductase by 2,6-Diamino-1, 2 dihydro-2, 2 dimethyl-1- (X phenyl)-S-triazines			
1	3-Cl, 4 -$OCH_2C_6H_4$ -3'-$CONHC_6H_4$ -4'' -SO_2F	6.92	0.37
2	3-Cl, 4 -$OCH_2C_6H_4$ -4'-$CONHC_6H_4$ -4'' -SO_2F	6.92	0.37
3	3-$OCH_2CONHC_6H_4$-4' -SO_2F	6.92	0.38
4	3-Cl, 4 -$(CH_2)_4C_6H_3$-5'-Cl, 2'-SO_2F	7.06	1.06
5	3-Cl, 4 -O $(CH_2)_3$ OC_6H_4-4'-SO_2F	7.07	0.38
6	3-Cl, 4 -OCH (CH_3)- $CONHC_6H_4$-4'-SO_2F	7.13	0.31
7	3-Cl, 4 -O $(CH_2)_2$ O $(CH_2)_2OC_6H_4$-4'-SO_2F	7.14	0.29
8	3Cl, 4 -O $(CH_2)_3$ CONH-C_6H_4-4'-SO_2F	7.15	0.27
9	3-Cl, 4 -O $(CH_2)_3$ $CONHC_6H_4$-3'- SO_2F	7.17	0.25
10	3 - $(CH_2)_2$ $CONHC_6H_4$-4'-SO_2F	7.19	1.10

This paper covers study of anticancer drugs of triazine series only. Triazines have been tried as anticancer drugs since 196. This class of compound has been developing since that time and is still in practice. The activity of these compounds measured by different method is also available in literature[4]. Attempts were regularly made to correlate the activity of drugs with their structure and physico-chemical properties. Before the general availability of computers, one often spoke of fitting data to an equation. This was a tedious and time-consuming process in which one simply could not consider many possibilities. The situation is now completely turned around and one can readily explore hundreds or thousands of possible equations in studying the inter relationship of sets of data with activity of drugs. Today, one often speaks of fitting equations to data. On the frontiers of chemical structure-activity relationship, especially in bio- and medicinal chemistry, so little solid theory is at hand on which to build that all kinds of purely empirical ideas need to be explored. Computerized statistical techniques promise to be of great help in sorting out important structure-activity features which can then be used to form more firmly based theory. Techniques such as pattern recognition discriminate analysis,[17-19] cluster analysis and regression analysis which have been developed and used heavily outside of chemistry are now beginning to be used by those working with structured-activity relationship.[20-25]

QSAR (Quantitative Structure Activity Relationship)

QSAR is a process whereby the structures of a set of compounds are quantified and then compared to the numerical values of a biological activity or a physical property. The challenge here has been to find some numerical code for a molecule or a fragment that is information-rich. This structure information and the measured property or activity are then processed 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.[19]

Among the various toxicity endpoints, chemical carcinogenicity is of primary interest because it drives much of the current regulatory actions on new and exiting chemical and its experimental determination involves time-consuming and expensive animal testing. However, only a relatively small percentage of the chemical in commerce have currently undergone testing, so the support of structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) approaches (as tools

for both predictive toxicology and mechanism elucidation) in this field are of particular interest. The present level of SAR knowledge permits the identification of many potentially carcinogenic chemical functionalities. Thus, application of the SAR knowledge is already reliable for an efficient use in priority setting.

Table-2: Log 1/C data for reversible inhibition of dihydrofolate reductase by 2,6-Diamino-1, 2 dihydro-2, 2 dimethyl-1- (X phenyl)-S-triazines

Comp	X	Log 1/C (Observed)
C1	3-Cl, 4 -$OCH_2C_6H_4$ -3'-$CONHC_6H_4$ -4" -SO_2F	6.92
C2	3-Cl, 4 -$OCH_2C_6H_4$ -4'-$CONHC_6H_4$ -4" -SO_2F	6.92
C3	3-$OCH_2CONHC_6H_4$-4' -SO_2F	6.92
C4	3-Cl, 4 -$(CH_2)_4C_6H_3$-5'-Cl, 2'-SO_2F	7.06
C5	3-Cl, 4 -O $(CH_2)_3$ OC_6H_4-4'-SO_2F	7.07
C6	3-Cl, 4 -OCH (CH_3)- $CONHC_6H_4$-4'-SO_2F	7.13
C7	3-Cl, 4 -O $(CH_2)_2$ O $(CH_2)_2OC_6H_4$-4'-SO_2F	7.14
C8	3Cl, 4 -O $(CH_2)_3$ CONH-C_6H_4-4'-SO_2F	7.15
C9	3-Cl, 4 -O $(CH_2)_3$ $CONHC_6H_4$-3'- SO_2F	7.17
C10	3 - $(CH_2)_2$ $CONHC_6H_4$-4'-SO_2F	7.19

COMPUTATIONAL CHEMISTRY

DFT is concerned with a quantum mechanical description of atomic and molecular systems in terms of electron density. DFT has extraordinary potential for qualifying chemical concepts and providing then with a theoretical basis. We have based our QSAR study of aziridines and triazines derivatives on the following reactivity indices

1- Effective Softness Values (given by Klopman[57] in terms of $E_n^{\ddagger}$ and $E_m^{\ddagger}$)

2- Chemical Potential (μ)

3- Absolute Hardness (η)

4- Global Softness (S)

5- Electronegativity (χ

Result and Discussion

The values of the descriptors Heat of Formation (ΔHf), Steric Energy (SE), Total Energy (TE), HOMO Energy (∈HOMO), LUMO Energy (∈LUMO), Absolute Hardness (η) and Electronegativity (χ) of all the derivatives

of triazine have been evaluated and given in the Table-1 and 2. Outlier Compounds are C3, C4, C15, C76, C77 and C78. Outlier compounds are those compounds which are excluded in multilinear regression (MLR) analysis. Values of regression coefficients (r^2) and cross-validation coefficients (rCV^2) have been calculated for each MLR equation. QSAR model is characterized by the values of regression coefficients (r^2) and cross-validation coefficients (rCV^2). If the value of regression coefficient is greater than 0.5 then the QSAR model is said to have good predictive power besides the value of

cross-validation coefficient is greater than 0.2. As the value of regression coefficient increases, the predictive power increases. The maximum value of regression coefficient may be unity. Combination of quantum chemical and energy descriptors in the predicted activities PA1 to PA90 are shown in the Table-3.

Table 3 Values of the quantum chemical and energy descriptors of the derivatives of triazine

Comp	Heat of Formation	Steric Energy	Total Energy	HOMO Energy	LUMO Energy	Absolute Hardness	Electronegativity	Activity
C1	104.651	-53.108	-295.559	-8.649	-1.100	3.774	4.874	6.920
C2	104.651	-49.867	-295.538	-8.804	-1.170	3.817	4.987	6.920
C5	106.920	-26.048	-258.959	-8.872	-0.853	4.009	4.863	7.070
C6	117.827	-42.847	-266.491	-8.973	-1.085	3.944	5.029	7.130
C7	107.978	-21.483	-278.272	-8.869	-0.842	4.014	4.856	7.140
C8	108.129	-42.078	-273.663	-8.836	-0.954	3.941	4.895	7.150
C9	110.432	-43.999	-273.667	-8.822	-0.865	3.978	4.843	7.170
C10	111.734	-46.895	-242.574	-8.851	-0.912	3.969	4.881	7.190

Table-4: Combination of quantum chemical and energy descriptors in the predicted

Predicted Activity	First descriptor	Second descriptor
PA1	Heat of Formation	Steric Energy
PA2	Heat of Formation	Total Energy
PA3	Heat of Formation	HOMO Energy
PA4	Heat of Formation	LUMO Energy
PA5	Heat of Formation	Absolute Hardness
PA6	Heat of Formation	Electronegativity
PA7	Steric Energy	Total Energy
PA8	Steric Energy	HOMO Energy
PA9	Steric Energy	LUMO Energy
PA10	Steric Energy	Absolute Hardness

QSAR models PA1 to PA10 are developed and given by the following MLR equations-

1. PA1=0.0579916*ΔHf+0.000449905*SE+0.905356
   rCV^2=0.70403
   r^2=0.722347
2. PA2=0.0550563*ΔHf+0.00217873*TE+1.78497
   rCV^2=0.713752
   r^2=0.733793
3. PA3=0.0579875*ΔHf+0.0134586*∈HOMO+1.00593
   rCV^2=0.690059
   r^2=0.721887
4. PA4=0.0579688*ΔHf-0.00089436*∈LUMO+0.889769
   rCV^2=0.653403
   r^2=0.72143
5. PA5=0.0579665*ΔHf-0.0811096*η+1.20378 rCV^2=0.686067
   r^2=0.722833
6. PA6=0.057986*ΔHf-0.0118822*χ+0.94652
   rCV^2=0.584938
   r^2=0.721628
7. PA7=-0.00168238*SE+0.0080979*TE+9.64485
   rCV^2=0.102934

Table-5: Predicted activities PA1 to PA9 calculated by MLR equations

Comp	PA1	PA2	PA3	PA4	PA5	PA6	PA7	PA8	PA9
C1	6.950	6.903	6.958	6.957	6.964	6.957	7.341	7.641	7.642
C2	6.952	6.903	6.956	6.957	6.960	6.956	7.336	7.643	7.649
C5	7.094	7.107	7.087	7.089	7.076	7.089	7.592	7.654	7.648
C6	7.719	7.691	7.718	7.721	7.714	7.719	7.559	7.647	7.649
C7	7.158	7.124	7.148	7.150	7.137	7.150	7.428	7.655	7.650
C8	7.157	7.142	7.157	7.159	7.152	7.158	7.500	7.647	7.642
C9	7.290	7.269	7.291	7.292	7.282	7.292	7.503	7.646	7.636
C10	7.364	7.408	7.366	7.368	7.359	7.368	7.759	7.645	7.636

r^2=0.178305

8. PA8=0.000414605*SE-0.00563828*∈HOMO+7.61439
   rCV^2=-1.36326
   r^2=0.000496905
9. PA9=0.000696873*SE-0.0555125*∈LUMO+7.61834
   rCV^2=-0.0764998
   r^2=0.00199318
10. PA10=-0.000254574*SE-0.111437*η+8.06759
    rCV^2=-0.0671299
    r^2=0.00162192

Predicted activities PA1 to PA10 have been evaluated by substituting the values of the descriptors in above MLR equations and given in the Tables 4 to 13.

Among all the 10 QSAR models PA1 to PA10, the number of good QSAR mode are those whose regression coefficient is greater than 0.7.

Result and Discussion:

The values of eight descriptors of compounds listed in Table-3 have been calculated with the help of PM3 Hamiltonian and are presented in the Table-2 along with their observed activity in terms of Log 1/C. We have examined QSAR models using combination of maximum four descriptors. MLR equations of these QSAR models are given above. Following five QSAR models have been found to have good regression coefficient. The predicted activities, values of regression coefficients and combination of descriptors of these QSAR models are given in Table 5.

Conclusion:

It is clear that the atomic properties especially Klopman softness values play an important role in QSAR study. The values of r^2 indicates that, on the basis of atomic properties we can construct good QSAR models.

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