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QSAR Models of Triazine Derivatives Developed Using Quantum-Chemical Energy Descriptors and Topological Descriptors : A Comparative Study

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ABSTRACT

QSAR Models of 25 derivatives of triazine have been developed using quantum chemical and energy descriptors and topological descriptors. The quantum chemical and energy descriptors used are a combination of heat of formation, steric energy, total energy and LUMO energy. The topological descriptors have a combination of connectivity index, shape index, molar refractivity and conformation minimum energy. It was observed that quantum chemical and energy descriptors are able to produce more reliable QSAR model as compared to topological descriptors.

Keywords: QSAR, Multilinear regression, connectivity index, PM3, heat of formation.

I. INTRODUCTION

Now a days Triazine derivatives are frequently used as inhibitor of enzyme dihydrofolate reductase. The enzyme forms covalent bond with highly reactive derivatives of triazines. The compounds are highly electrophilic and react through carbonium ion intermediate. These compounds form covalent bonds with amino, hydroxyl and carbonyl group. Baker and his students synthesized 256 variations of compounds and studied their inhibiting effect on dihydrofolate reductase [1]. The activity of these compounds measured by different methods is available in literature. The multilinear regression analysis has been applied for QSAR study of triazine derivatives. A relationship has been worked out between the log 1/C values of a series of compounds and quantum chemical and energy descriptors. Log1/C is the biological activity of the compound and C is molar concentration of inhibitor causing 50% reversible inhibition of enzyme. Quality of QSAR model depends on the value of regression and cross-validation coefficients of its MLR equation [3-4].

II. METHODS AND MATERIAL

Study material is the collection of 25 triazine derivative of compound shown in figure 1 whose activity in terms of log 1/C is known.

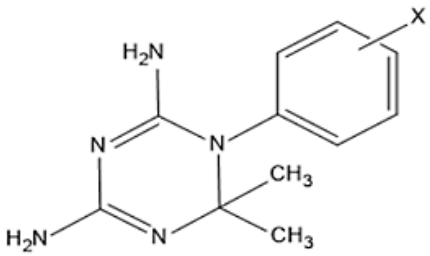

Figure 1 : 4, 6-diamino-1,2,dihydro-2,2,dimethyl-1-1 (x-phenyl)-s-triazines

The derivatives are listed in table 1 along with their biological activity. Biological activity has been taken from the literature.

No.	X	Log1/C (Observed)
1	3-Cl,4-$(CH_2)_4C_6H_3$-2`-Cl,4`- SO_2F	7.77
2	3-Cl,4-$CH_2NHCONH$-C_6H_4-3`-Me,4`-SO_2F	7.80
3	3-Cl,4-$O(CH_2)_2$-NHCONH-C_6H_3-3`-Me,4`-SO_2F	7.82
4	3-$O(CH_2)_2C_6H_4$-4`-SO_2F	7.82
5	3-Cl,4-$(CH_2)_4C_6H_3$-4`-Cl,2`-SO_2F	7.82
6	3-Cl,4-$(CH_2)_2C_6H_4$-4`-SO_2F	7.85
7	3-Cl,4-$(CH_2)_2C_6H_3$-5`-Cl,2`-SO_2F	7.85
8	3-Cl,4-$(CH_2)_2C_6H_3$-3`-Cl,4`-SO_2F	7.85
9	3-Cl,4-$CH_2NHCONH$-C_6H_4-4`-SO_2F	7.92
10	3-Cl,4-$O(CH_2)_2NHCONH$-C_6H_4-3`-SO_2F	7.92
11	3- $(CH_2)_4C_6H_3$-5`-Cl,2`- SO_2F	7.96
12	3-Cl,4-O-$CH_2C_6H_3$-4`-Cl,3`- SO_2F	8.00
13	3-$(CH_2)_4C_6H_3$-2`-Cl,4`- SO_2F	8.00
14	3-Cl,4-$(CH_2)_4C_6H_4$-3`- SO_2F	8.03
15	3-Cl,4-$(CH_2)_2C_6H_3$-4`-Cl,2`- SO_2F	8.05
16	3-Cl,4-$O(CH_2)_3$ NHCONH-C_6H_4-4`-Me,3`-SO_2F	8.06
17	3-$(CH_2)_4$ C_6H_4-4`- SO_2F	8.10
18	3-$(CH_2)_4$ C_6H_4-3`- SO_2F	8.10
19	3-$(CH_2)_2$ C_6H_4-4`- SO_2F	8.10
20	3-Cl,4-$(CH_2)_4C_6H_3$-4`-Cl,3`- SO_2F	8.11
21	3-Cl, 4-$(CH_2)_4$ C_6H_4-4`- SO_2F	8.14
22	3-Br,4-OCH_2CONH-C_6H_4-4`-SO_2F	8.14
23	3-Cl,4-$(CH_2)_4C_6H_3$-3`-Cl,2`- SO_2F	8.20
24	3-Cl,4-$(CH_2)_2C_6H_3$-4`-Cl,3`- SO_2F	8.27
25	3-Cl,4-$(CH_2)_2C_6H_3$-3`-Cl,2`- SO_2F	8.30

Table 1 : Log1/C data for reversible inhibition of dihydrofolate reductase

Topological descriptors used for QSAR study of these compounds are shown below [5]

1. Connectivity index (order 0, standard) β
2. Shape index (basic Kappa, order 1) ψ
3. Molar refractivity Ω
4. Conformation minimum energy ϵ

For developing QSAR models following quantum chemical and energy descriptors are used [6-7]:

1. Heat of formation (ΔHf)
2. Steric energy (SE)
3. Total energy (TE)
4. LUMO energy (ϵ LUMO)

For QSAR production, the 3-D modelling and geometry optimization of all the derivatives Triazines have been done with the help of CAChe software using semi-empirical PM3 Hamiltonian.

III. RESULTS AND DISCUSSION

Values of descriptors connectivity index, shaped index, molar refractivity and conformation minimum energy have been substituted in MLR equations in order to predict the activity of all 25 derivatives of triazine. The values of quantum chemical and energy descriptors namely heat of formation, steric energy, total energy, LUMO energy have been substituted in MLR equation in order to predict the activity of all 25 derivatives of triazine.

Compound	Connectivity Index	Shape Index (basic kappa, order 1)	Molar Refractivity	Conformation Minimum Energy (kcal/mole)	Activity predicted APA
1	23.445	26.291	129.551	-156134.674	7.784
2	23.374	26.246	127.515	-156969.214	7.763
3	23.312	26.287	133.455	-156192.240	7.798
4	23.347	26.222	113.416	-156492.240	7.822
5	23.323	26.214	129.551	-155492.240	7.851
6	23.307	26.354	124.746	-156226.779	7.804
7	23.307	26.122	129.551	-156226.779	7.828
8	23.331	26.166	129.551	-156226.779	7.818
9	23.001	26.012	122.474	-156107.371	7.918
10	23.213	26.054	127.229	-155107.371	7.918
11	23.159	25.123	124.746	-155153.423	8.065
12	23.106	25.927	117.086	-154199.476	8.023
13	23.106	25.872	124.746	-154199.476	8.016
14	23.065	25.833	124.746	-155134.015	7.980
15	23.011	25.234	120.349	-154157.041	8.136
16	23.025	25.801	133.455	-154168.554	8.027
17	22.972	25.702	119.941	-154114.607	8.078
18	22.912	25.767	119.941	-155014.607	8.032
19	22.923	25.761	110.739	-154914.607	8.053
20	22.934	25.751	129.551	-153126.120	8.112
21	22.911	25.703	124.746	-153660.659	8.104
22	22.918	25.703	123.068	-153660.659	8.106
23	22.837	25.321	129.551	-152929.738	8.202
24	22.743	25.490	120.349	-153110.330	8.202
25	22.711	25.441	120.349	-152144.869	8.266

Table 2 : Values of topological descriptors of triazine derivatives used in the development of QSAR models

Compound	Heat of Formation (kcal/mole)	Steric Energy (kcal/mole)	Total Energy (Hartree)	LUMO Energy (eV)	Activity predicted PA
1	-87.544	-45.475	-255.231	-1.008	7.713
2	-86.982	-45.021	-249.669	-1.012	7.814
3	-87.735	-44.718	-246.812	-1.011	7.843
4	-86.731	-44.718	-249.387	-1.012	7.831
5	-86.996	-45.211	-247.131	-1.061	7.780
6	-86.259	-44.263	-248.964	-1.004	7.870
7	-86.952	-44.263	-246.713	-1.004	7.884
8	-86.250	-44.263	-245.123	-1.091	7.805
9	-86.897	-45.234	-247.977	-1.002	7.854
10	-85.992	-43.203	-247.977	-1.002	7.914
11	-84.475	-42.597	-247.413	-1.000	7.978
12	-84.835	-43.671	-246.848	-0.998	7.961
13	-83.839	-41.991	-247.123	-0.998	8.013
14	-83.349	-41.537	-246.425	-0.997	8.047
15	-83.993	-41.234	-248.333	-0.996	8.006
16	-84.868	-41.082	-247.985	-0.991	7.997
17	-82.923	-41.912	-241.234	-0.994	8.136
18	-83.456	-40.476	-241.345	-0.994	8.144
19	-82.215	-42.772	-245.438	-0.991	8.082
20	-82.054	-40.325	-248.112	-0.994	8.084
21	-81.579	-39.871	-244.874	-0.999	8.147
22	-81.570	-39.871	-244.874	-0.993	8.156
23	-81.762	-38.962	-244.028	-0.990	8.182
24	-79.471	-35.354	-243.041	-0.981	8.337
25	-78.980	-37.447	-248.114	-0.986	8.230

Table 3 : Values of quantum chemical and energy descriptors used in development QSAR models along with predicted activity

MLR equation which best describes the QSAR model of all 25 derivatives developed by the use of topological descriptors is given by-

APA= -0.177223* β -0.14493* ψ – 0.00182899* Ω +5.2918e-005* ϵ +24.2484
rCV^2= 0.953201
r^2=0.966117

The MLR equation for the best QSAR model developed by using heat of formation, steric energy, total energy and LUMO energy is-
PA=0.0282435* ΔHf +0.0171513* SE +0.0151976* TE +1.41916* ϵ LUMO+ 16.2793
rCV^2=0.788624
r^2=0.971913

Compound	Observed Activity (OA)	Predicted Activity (PA)	Predicted Activity (APA)	Difference Between OA and PA	Difference Between OA and APA
1	7.770	7.713	7.784	0.057	0.014
2	7.800	7.814	7.763	0.014	0.037
3	7.820	7.843	7.798	0.023	0.022
4	7.820	7.831	7.822	0.011	0.002
5	7.820	7.780	7.851	0.040	0.031
6	7.850	7.870	7.804	0.20	0.046
7	7.850	7.884	7.828	0.034	0.022
8	7.850	7.805	7.818	0.045	0.032
9	7.920	7.854	7.918	0.066	0.002
10	7.920	7.914	7.918	0.006	0.002
11	7.960	7.978	8.065	0.018	0.105
12	8.000	7.961	8.023	0.039	0.023
13	8.000	8.013	8.016	0.013	0.016
14	8.030	8.047	7.980	0.017	0.050
15	8.050	8.006	8.136	0.044	0.086
16	8.060	7.997	8.027	0.063	0.033
17	8.100	8.136	8.078	0.036	0.022
18	8.100	8.144	8.032	0.044	0.068
19	8.100	8.082	8.053	0.018	0.047
20	8.110	8.084	8.112	0.026	0.002
21	8.140	8.147	8.104	0.007	0.036
22	8.140	8.156	8.106	0.016	0.034
23	8.200	8.182	8.202	0.018	0.002
24	8.270	8.337	8.202	0.067	0.068
25	8.300	8.230	8.266	0.070	0.034
Sum of errors				0.812	0.856
Percentage error				3.248	3.424

Table 4 : Difference of best predicted actvities with observed activities

IV. CONCLUSION

Value of regression coefficient in the best QSAR model developed by using quantum chemical and energy descriptors is greater than that in the best QSAR model developed by using topological descriptors. This shows that the activity of triazine derivatives is best predicted using quantum chemical and energy descriptors. The table 4 shows the difference of best predicted activities PA and APA with observed activities (OA). Average percentage error in the best QSAR model developed by using quantum chemical and energy descriptor is 3.248 and average percentage error in the best QSAR model developed by using topological descriptors is 3.424. This shows that quantum chemical and energy descriptor are able to produce more reliable QSAR model as compared to topological descriptor.

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