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Development of QSAR Models of Triazine Derivatives Using Topological Descriptors

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ABSTRACT

QSAR Models of 25 derivatives of triazine have been developed using topological descriptors. The topological descriptors have a combination of connectivity index, shape index, molar refractivity, molecular weight, log P and conformation minimum energy. Best QSAR has been developed using connectivity index, shape index, molar refractivity, and conformation minimum energy with the regression coefficient 0.966117 and cross-validation 0.953201. Multilinear regression (MLR) equation is said to describe a good QSAR model if the value of correlation or regression coefficient and cross validation coefficient is greater than 0.2. These values indicate very good prediction ability of QSAR model. Topological descriptors which alone can produce good QSAR models are conformation minimum energy, shape index and molar refractivity.

Keywords: QSAR, Multilinear regression, connectivity index, PM3, conformation minimum energy.

1. INTRODUCTION

The QSAR approach attempts to identify and quantify the physiochemical properties of a drug and to see whether any of these properties influences drug's biological activity[1]. To obtain a significant correlation, it is essential that appropriate descriptors are employed, whether they are theoretical, empirical, or derived from readily available experimental characteristics of structures. Many descriptors reflect simple molecular properties and thus can provide insight into the physiochemical nature of the activity/property under consideration[2-6]. Now a days, Triazine derivatives are frequently used as inhibitor of enzyme dihydrofolate

reductase. The specificity of an enzyme for its substrate is known as molecular recognition. The specificity of an enzyme is due to H-bonds, Vanderwaal's forces and dipole-dipole interactions that binds the substrate to the active site. 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[7]. 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 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.

2. 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.

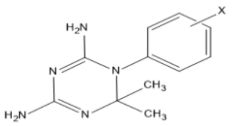

Figure 1 : 4,6-diamino-1,2,dihydro-2,2,dimethyl-1-1 (x-phenyl)-s-triazines

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

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

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-$O(CH_2)_2$NHCONH-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

Topological descriptors used for QSAR study of these compounds are shown below[8-12]

1. Connectivity index (order 0, standard) β
2. Shape index (basic Kappa, order 1) ψ
3. Solvent accessibility surface area α
4. Molar refractivity Ω
5. Log P λ
6. Molecular weight μ
7. Conformation minimum energy ϵ

For QSAR production, the 3-D modelling and geometry optimization of all the derivative Triazines have been done with the help of CAChe software using semi-empirical PM3 Hamiltonian[13].

3. RESULTS AND DISCUSSION

Values of topological descriptors of triazine derivatives have been calculated with the help of CAChe software using PM3 method given in table 2. We have developed QSAR models to predict the activities in terms of log 1/C of triazine derivative given in table 1 by using the combinations of descriptors. Predictive power of QSAR model increases with the increase of the value of regression coefficient. Ninety QSAR models have been developed with the help of multilinear regression of CAChe software. In this paper we have discussed six best QSAR models of triazines.

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

Compound	β	ψ	Ω	ϵ (kcal/mole)	α (angstrom squ)	λ	μ
1	23.445	26.291	129.551	-156134.674	204.830	6.832	500.417
2	23.374	26.246	127.515	-156969.214	201.576	4.112	495.958
3	23.312	26.287	133.455	-156192.240	216.201	3.952	525.984
4	23.347	26.222	113.416	-156492.240	182.265	3.890	435.472
5	23.323	26.214	129.551	-155492.240	203.303	6.832	500.417
6	23.307	26.354	124.746	-156226.779	195.810	6.314	465.972
7	23.307	26.122	129.551	-156226.779	204.201	6.832	500.417
8	23.331	26.166	129.551	-156226.779	204.744	6.832	500.417
9	23.001	26.012	122.474	-156107.371	197.827	3.645	481.931
10	23.213	26.054	127.229	-155107.371	205.155	3.897	495.958
11	23.159	25.123	124.746	-155153.423	195.888	6.314	465.972
12	23.106	25.927	117.086	-154199.476	189.374	5.086	474.336
13	23.106	25.872	124.746	-154199.476	194.807	6.314	465.972
14	23.065	25.833	124.746	-155134.015	195.898	6.314	465.972
15	23.011	25.234	120.349	-154157.041	186.802	6.039	472.365
16	23.025	25.801	133.455	-154168.554	211.847	3.952	525.998
17	22.972	25.702	119.941	-154114.607	187.142	5.796	431.527
18	22.912	25.767	119.941	-155014.607	187.380	5.796	431.527
19	22.923	25.761	110.739	-154914.607	172.013	5.003	403.474
20	22.934	25.751	129.551	-153126.120	203.185	6.832	500.417
21	22.911	25.703	124.746	-153660.659	196.118	6.314	465.972
22	22.918	25.703	123.068	-153660.659	197.698	3.670	527.367
23	22.837	25.321	129.551	-152929.738	200.102	6,832	500.417
24	22.743	25.490	120.349	-153110.330	187.831	6.039	472.364
25	22.711	25.441	120.349	-152144.869	186.082	6.039	472.364

- **Best QSAR model PA1**

Descriptors used in the development of this QSAR model are connectivity index, shape index, molar refractivity, and conformation minimum energy. MLR equation which describes the QSAR model is given by

PA1= -0.177223* β -0.14493* ψ – 0.00182899* Ω +5.2918e-005* ϵ +24.2484

rCV^2= 0.953201

r^2=0.966117

Values of regression and cross -validation coefficients are 0.966117 and 0.953201 respectively. These values indicate very good prediction ability of QSAR model. With the help of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

- **Second best QSAR model PA2**

Descriptors used in the development of this QSAR model are connectivity index, shape index, solvent accessibility surface area and conformation minimum energy. MLR equation which describes the QSAR model is given by

PA2= -0.17804* β -0.141135* ψ – 0.00130339* α+5.38568e-005* ϵ +24.3427

rCV^2= 0.953566

r^2=0.965746

Values of regression and cross -validation coefficients are 0.965746 and 0.953566 respectively. These values indicate very good prediction ability of QSAR model. With the help of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

- **Third best QSAR model PA3**

Descriptors used in the development of this QSAR model are connectivity index, shape index, log p and conformation minimum energy. MLR equation which describes the QSAR model is given by

PA3= -0.168406* β -0.158142* ψ – 0.0087629*λ +5.40426e-005* ϵ +24.381

rCV^2= 0.951959

r^2=0.965632

Values of regression and cross -validation coefficients are 0.965632 and 0.951959 respectively. These values indicate very good prediction ability of QSAR model. With the help of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

- **Fourth best QSAR model PA4**

Descriptors used in the development of this QSAR model are connectivity index, shape index, molecular weight, and conformation minimum energy. MLR equation which describes the QSAR model is given by

PA4 = -0.172557* β -0.146267* ψ – 0.000342558* μ +5.39547e-005* ϵ +24.2723

rCV^2= 0.953574

r^2=0.965404

Values of regression and cross -validation coefficients are 0.965404 and 0.953574 respectively. These values indicate very good prediction ability of QSAR model. With the help

of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

- **Fifth best QSAR model PA5**

Descriptors used in the development of this QSAR model are connectivity index, shape index and conformation minimum energy. MLR equation which describes the QSAR model is given by

PA5 = -0.177891* β -0.151537* ψ +5.19941e-005* ϵ +24.0677

rCV^2= 0.953186

r^2=0.964344

Values of regression and cross-validation coefficients are 0.964344 and 0.953186 respectively. These values indicate very good prediction ability of QSAR model. With the help of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

- **Sixth best QSAR model PA6**

MLR equation of QSAR model using conformation minimum energy as descriptor is given below

PA6 = 0.000113457* ϵ +25.561

rCV^2= 0.913733

r^2=0.91972

Values of regression and cross-validation coefficients are 0.91972 and 0.913733 respectively. These values indicate good prediction ability of QSAR model. With the help of this QSAR model, one can easily obtain the activity of any triazine derivative of compound -1 by substituting the values of descriptors in MLR equation.

Table 3 : Values of predicted activities of triazine derivatives

Compound	PA1	PA2	PA3	PA4	PA5	PA6
1	7.784	7.782	7.777	7.786	7.795	7.846
2	7.763	7.760	7.775	7.761	7.771	7.752
3	7.798	7.788	7.822	7.797	7.816	7.840
4	7.822	7.819	7.811	7.815	7.804	7.806
5	7.851	7.851	7.845	7.853	7.862	7.919
6	7.804	7.804	7.790	7.807	7.805	7.836
7	7.828	7.826	7.822	7.829	7.840	7.836
8	7.818	7.815	7.811	7.819	7.829	7.836
9	7.918	7.911	7.925	7.911	7.918	7.850
10	7.918	7.912	7.935	7.917	7.925	7.963
11	8.065	8.062	8.068	8.070	8.074	7.958
12	8.023	8.018	8.012	8.011	8.011	8.066
13	8.016	8.019	8.010	8.022	8.019	8.066
14	7.980	7.980	7.972	7.984	7.984	7.960
15	8.136	8.138	8.131	8.131	8.135	8.071
16	8.027	8.023	8.057	8.027	8.046	8.070
17	8.078	8.081	8.068	8.086	8.073	8.076
18	8.032	8.034	8.019	8.038	8.027	7.974
19	8.035	8.058	8.031	8.052	8.032	7.985
20	8.112	8.113	8.111	8.115	8.124	8.188
21	8.104	8.105	8.098	8.109	8.108	8.127
22	8.106	8.101	8.120	8.087	8.106	8.127
23	8.202	8.206	8.206	8.205	8.217	8.210
24	8.202	8.205	8.192	8.197	8.198	8.190
25	8.266	8.272	8.258	8.261	8.262	8.299

4. CONCLUSION

Best descriptor of activity of triazine derivatives are a combination of connectivity index, shape index, molar refractivity, and conformation minimum energy. Values of regression and cross -validation coefficients are 0.966117 and 0.953201 respectively. Each descriptor connectivity index, shape index, and conformation minimum energy can predict the activities of triazine derivatives separately in the order

conformation minimum energy > shape index > connectivity index

Any combination of descriptor in which either connectivity index or shape index or conformation minimum energy is present can form QSAR model with reliable predictive power.

5. REFERENCES

1. BW Clare. *Aust. J. Chem*, 48, 1385 (1995).
2. Randic, M. *ChemometricsIntel. Lab. Systems*,10,213 (1991).
3. Randic`, M. *J. Chem. Inf. Comput. Sci*., 37, 672 (1997).
4. Balaban, A.T.; Motoc, I., Bonchev, D.; Mekenyan, O.; Charton, M.; Motoc, I. Eds; *Topics Curr. Chem.*, 114, 21 (1983).
5. Balaban, A. T. Historical developments of topological indices. *Topological Indices and Related Descriptor in QSAR and QSPR;* Devillers, J., Balaban, A. T. Eds; Gordon and Breach: Amsterdam, The Netherlands; p 403 (1999).
6. Balaban, A. T. *J. Mol. Struct. (THEOCHEM)*, 165, 243 (1988).
7. B. R Baker; GL Lowens. *J. Med. Chem*., 10, 1113 (1967).
8. LB Kier. *Acta Pharm. Jugsol.,* 36 ,171 (1986).
9. Gupta, S.P. *Chem. Rev*., 87, 1183 (1987).
10. Hall, L. H.; Kier, L. B.; *Reviews of Computational Chemistry,* Vol 2 (1991).
11. Hall, L. H.; Kier, L. B.; *Eur.J. Med. Chem. – Chimica Therapeutica*., 4, 307 (1997).
12. Balaban, A. T.; *Theoretica Chimica Acta.*, 53, 355 (1979).
13. JJP Stewart. *J. Comp. Chem*., 10, 209 (1989).
14. LB Kier.; LH Hall., Molecular connectivity in structure - Activity, John Wiley and Sons, New York (1986).
15. P P Singh, SB Sharma, KSingh, *J, Chem. Pharm. Res*., 2 (5): 193-205 (2010).
16. Pearson, R.G.; *Acc.Chem. Res*., 26,25-255 (1993).
17. Pearson, R.G.; *Acc.Chem. Res*., 26,25-255 (1993).
18. Pulay, P.; *Modern Theoretical Chemistry*, Vol-3, Applications of Electronic Structure Theory, Plenum Press, New York, p153 (1977).