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QSAR study of inhibitors of enzyme dihydropteroate synthetase

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ABSTRACT

QSAR study of 23 compounds of the series of N[l]-phenylsulfonamides and N[l]-3-pyridylsulfonamides whose inhibitory antibacterial activity are reported in terms of I_{50} μM has been made. MLR analysis has been done with the help of descriptors, heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity. Twenty eight QSAR models have been found to have high degree of predictive power with regression coefficient above 0.8 and six models above 0.856. The combination of descriptors providing best models are heat of formation, molecular weight alongwith any of the two descriptors viz. HOMO energy, LUMO energy, absolute hardness and electronegativity.

KEYWORDS

QSAR;
HOMO energy;
LUMO energy;
Absolute hardness;
N[l]-phenylsulfonamides;
N[l]-3-pyridylsulfonamides.

INTRODUCTION

In the sequential pathway of folate synthesis in bacteria, the bacterial growth factor is mediated by the enzyme dihydropteroate synthetase[1]. studies on N'-substituted sulfonamides (Figures 1,2) have established that these drugs exert their antibacterial action by inhibiting this enzyme. The enzyme inhibitory activity was well correlated with pKa. MLR equations also showed perfect regression with pKa[2-4]. Recently, new set of descriptors have been tried for QSAR study of testosterones and estrogen[5-8]. The results have provided very good regression. In this paper we have used these descriptors for QSAR study of series of N[l]-phenylsulfonamides and N[l]-3-pyridylsulfonamides whose inhibitory antibacterial activity in terms of I_{50} μM is reported[1].

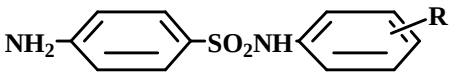


Figure 1: N'-phenylsulfonamides

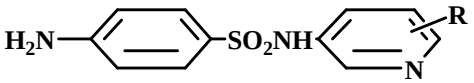


Figure 2: N'-3-pyridylsulfonamides

MATERIAL AND METHOD

The study materials of this paper are derivatives of N[l]-phenylsulfonamides and N[l]-3-pyridylsulfonamides and are presented in TABLE 1 alongwith their inhibitory activity in terms of I_{50}, μM. For QSAR prediction, the 3D modeling and geometry optimization[9,10] of all the compounds have been done with the help of Cache software using MOPAC2000. The values of descrip-

TABLE 1: Inhibitiory antibacterial activities of N'-phenylsulfonamides and N'-3-pyridylsulfonamides against enzyme dihydropteroat synthetase

Compound	R(N'-phenyl)	I_{50} μM
T1C1	4-OCH_3	75
T1C2	H	45
T1C3	4-CI	35
T1C4	4-I	25
T1C5	2-Cl-4-OCH_3	19
T1C6	3-CF_3	15
T1C7	2-Cl	13.5
T1C8	4-$COCH_3$	10.5
T1C9	4-CN	7
T1C10	4-NO_2	7
T1C11	2-OCH_3-4-NO_2	6
T1C12	2-Cl-4NO_2	6
	R(N'-3-pyridylsulfonamides)	
T1C13	2-NO_2-4-CF_3	5
T1C14	2-Br-4-NO_2	4
T1C15	2-Cl-4-SO_2NH_3	6.5
T1C16	6-$(C_2H_5)_2N$	95
T1C17	6-$(CH_3)_2N$	80
T1C18	6-CH_3O	55
T1C19	2-Cl-6-CH_3O	18.5
T1C20	H	14
T1C21	6-CH_3S	12
T1C22	6-Cl	6.5
T1C23	2-Cl	6.5

TABLE 2: Values of the descriptors of compounds T1C1-T1C23

Compound	Heat of formation	Molecular weight	Total energy	HOMO energy	LUMO energy	Absolute hardness	Electroneg ativity	Observed activity
T1C1	189.211	258.276	-0.045	-8.720	-0.322	4.199	-4.521	75.000
T1C2	117.660	228.250	0.015	-8.937	-0.346	4.296	-4.641	45.000
T1C3	92.213	262.695	0.004	-8.954	-0.431	4.262	-4.693	35.000
T1C4	43.530	354.146	0.069	-8.135	-0.410	3.862	-4.273	25.000
T1C5	133.971	292.721	-0.054	-8.815	-0.388	4.214	-4.602	19.000
T1C6	36.114	296.248	-0.217	-8.521	-0.510	4.006	-4.515	15.000
T1C7	3.745	262.695	0.006	-8.965	-0.370	4.297	-4.668	13.500
T1C8	19.837	270.287	-0.032	-8.365	-0.482	3.942	-4.424	10.500
T1C9	28.756	253.260	0.071	-9.067	-0.767	4.150	-4.917	7.000
T1C10	33.292	273.248	0.158	-8.513	-1.519	3.497	-5.016	7.000
T1C11	64.194	303.274	0.102	-8.322	-1.550	3.386	-4.936	6.000
T1C12	93.805	307.693	0.149	-8.570	-1.629	3.471	-5.100	6.000
T1C13	58.485	341.246	-0.093	-8.831	-1.880	3.476	-5.356	5.000
T1C14	51.914	352.144	0.172	-8.626	-1.643	3.491	-5.134	4.000
T1C15	39.319	386.220	0.063	-8.966	-1.154	3.906	-5.060	6.500
T1C16	456.636	395.460	0.121	-8.575	-0.358	4.109	-4.466	95.000
T1C17	157.976	271.318	0.013	-8.857	-0.209	4.324	-4.533	80.000
T1C18	146.887	258.276	-0.043	-8.912	-0.303	4.304	-4.607	55.000
T1C19	31.739	292.721	-0.051	-8.887	-0.411	4.238	-4.649	18.500
T1C20	0.265	242.277	0.000	-8.870	-0.339	4.266	-4.605	14.000
T1C21	15.770	274.337	0.025	-8.852	-0.530	4.161	-4.691	12.000
T1C22	4.596	262.695	0.007	-8.887	-0.413	4.237	-4.650	6.500
T1C23	3.695	262.695	0.006	-8.971	-0.385	4.293	-4.678	6.500

tors that have been used for QSAR models have been evaluated using the same software by PM3[11,12] methods. The descriptors that have been used are-

1. Heat of Formation ΔHf
2. Molecular Weight MW
3. Total Energy TE
4. HOMO Energy εHOMO
5. LUMO Energy εLUMO
6. Absolute Hardness η
7. Electronegativity χ

The values of descriptors have been derived by solving the relevant equation given below:-

Parr et al.[13] defined electronegativity as the negative of chemical potential:

$$\chi = -\mu = -(\partial E/\partial N)\, v_{(r)} \quad (1)$$

The absolute hardness,η,is defined as[14]

$$\eta = 1/2.\ (\delta\mu/\delta N)_{v(r)}$$

$$= 1/2.\ (\delta^2 E/\delta N^2)_{v(r)} \quad (2)$$

where E is the total energy, N the number of electrons of the chemical species, and v(r) the external potential.

The operational definition of absolute hardness and electronegativity[15] is defined as:

$$\eta = (IP-EA)/2 \quad (3)$$

$$\chi = -\mu = (IP+EA)/2 \quad (4)$$

where IP and EA are the ionization potential and electron affinity respectively, of the chemical species.

According to the Koopman's theorem, the IP is simply the eigen value of the HOMO with change of sign[16] and the EA is the eigen value of the LUMO with change of sign hence the equations 5 and 6 can be written as

$$\eta = (\varepsilon LUMO - \varepsilon HOMO)/2 \quad (5)$$

$$\chi = (\varepsilon LUMO + \varepsilon HOMO)/2 \quad (6)$$

The heat of formation is defined as:

$$\Delta H_f = E_{elect.} + E_{nuc.} - E_{isol.} + E_{atom} \quad (7)$$

where $E_{elect.}$ is the electronic energy, $E_{nuc.}$ is the nuclear-nuclear repulsion energy, E_{isol} is the energy required to strip all the valence electrons of all the atoms in the system, and E_{atom} is the total heat of atomization of all the atoms in the system.

Total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of internuclear repulsion, E_{nr}.

The total electronic energy of the system is given by[17]

$$E = P(H + F)/2 \quad (8)$$

where P is the density matrix and H is the one-electron matrix

Finally a more general but important property of a chemical system is the molecular weight (Mw) which has been tested as descriptor.

RESULT AND DISCUSSION

Compounds T1C5 and T1C17 are treated as outliers. The values of the descriptors obtained by PM3 calculation are included in TABLE 2. With the help of these values 90 QSAR models using different combination of descriptors have been tried, out of which 28 models provide regression coefficient above 0.8 and six models above 0.8566. The six models are presented below along with two more models which are next best. The predicted activities (PA1 to PA8) of these models are included in TABLE 3.

1. PA1=0.230722*ΔHf -0.0962101*
   MW +2.24851*εHOMO + 14.2204 * εLUMO +64.1642
   rCV^2=0.74232
   r^2=0.856631
2. PA2=0.230722*ΔHf -0.0962101*
   MW+16.4689* εHOMO + 28.4408 * η+ 64.1642
   rCV^2=0.74232
   r^2=0.856631
3. PA3=0.230722*ΔHf -0.0962101 *
   MW-11.9719* εHOMO + 28.4408* χ +64.1642
   rCV^2=0.74232
   r^2=0.856631
4. PA4=0.230722*ΔHf -0.0962101*
   MW +16.4689* εLUMO – 4.49701*η + 64.1642
   rCV^2=0.74232
   r^2=0.856631
5. PA5=0.230722*ΔHf -0.0962101*
   MW +11.9719*εLUMO + 4.49701*χ+64.1642
   rCV^2=0.74232
   r^2=0.856631
6. PA6=0.230722*ΔHf -0.0962101 *
   MW+11.9719*η+ 16.4689*χ + 64.1642
   rCV^2=0.74232
   r^2=0.856631
7. PA7=0.230761*ΔHf -0.0920922*
   MW + 14.09* ∈LUMO + 43.2067
   rCV^2=0.745684
   r^2=0.85628
8. PA8=0.236341*ΔHf -0.13235*MW + 24.2764*χ+159.249
   rCV^2=0.736517
   r^2=0.847898

With the help of above MLR equations the activity of any sulfonamide inhibitor can be best predicted using descriptors in following combinations.

TABLE 3: Predicted activities PA1 to PA8 of compounds

S.no.	Compd	PA1 to PA6	PA7	PA8
1	T1C1	58.785	58.547	60.033
2	T1C2	44.342	44.470	44.174
3	T1C3	33.901	34.219	32.354
4	T1C4	16.008	14.856	18.939
5	T1C6	17.587	17.076	18.958
6	T1C7	14.332	14.662	12.053
7	T1C8	17.071	16.100	20.773
8	T1C9	15.132	15.706	13.151
9	T1C10	4.812	4.321	9.178
10	T1C11	9.038	8.246	14.448
11	T1C12	13.770	13.565	16.897
12	T1C13	-1.769	-1.217	-2.114
13	T1C14	-0.500	-0.396	0.266
14	T1C15	-0.492	0.453	-5.411
15	T1C16	107.105	107.121	106.405
16	T1C18	48.860	49.050	47.932
17	T1C19	17.493	17.780	15.139
18	T1C20	16.154	16.184	15.463
19	T1C21	13.970	14.116	12.790
20	T1C22	14.096	14.257	12.686
21	T1C23	14.101	14.447	11.791

1. HOMO energy, LUMO energy; 2. HOMO energy, Absolute hardness; 3. HOMO energy, electronegativity; 4. LUMO energy, Absolute hardness; 5. LUMO energy, Electronegativity; 6. Absolute hardness, Electronegativity

On the basis of the values of regression coefficients, the QSAR models have been arranged in decreasing order of quality of prediction and are included in TABLE 4.

The predicted activities PA1 to PA6 give best QSAR models with regression coefficient 0.8566 and cross-validation coefficient 0.74232. With the help of these MLR equations, the activity of any sulfonamide inhibitor can be best predicted. Graph for the predicted activities PA1 to PA6 is shown in the Graph 1.

In all the above QSAR models, the first descriptor is heat of formation. Even the single descriptor heat of formation provides good predictive power. The descriptor heat of formation is supposed to be the prime descriptor for QSAR models. The predicted activities and the observed activities are included in TABLE 5.

A reference to TABLE 5 indicates that the predicted activities are very close to observed activities. The highest difference in the observed and predicted activity is 16.215. The values of observed activities,

TABLE 4: Good QSAR models with regression coefficient (r^2), cross-validation coefficient (rCV^2) and descriptors used

S. no.	Predicted activity	rCV^2	r^2	Descriptors used
1	PA1	0.7423	0.8566	Heat of formation, Molecular weight, HOMO energy, LUMO energy
2	PA2	0.7423	0.8566	Heat of formation, Molecular weight, HOMO energy, Absolute hardness
3	PA3	0.7423	0.8566	Heat of hormation, Molecular weight, HOMO energy, Electronegativity
4	PA4	0.7423	0.8566	Heat of formation, Molecular weight, LUMO energy, Absolute hardness
5	PA5	0.7423	0.8566	Heat of formation, Molecular weight, LUMO energy, Electronegativity
6	PA6	0.7423	0.8566	Heat of formation, Molecular weight, Absolute hardness, Electronegativity
7	PA7	0.745684	0.85628	Heat of formation, Molecular weight, LUMO energy
8	PA8	0.736517	0.847898	Heat of formation, Molecular weight, Electronegativity

predicted activities and the difference between these two activities, when two compounds T1C5 and T1C17 are treated as outliers, are shown in the TABLE 5. A graph between predicted activity PA1-PA6 and observed activity is shown in Graph 1, in order to demonstrate the quality of prediction.

Second best QSAR model is that in which the descriptors are Heat of Formation, Molecular Weight and LUMO Energy. In this case the predicted activity is PA7 and is given by-

PA7=0.230761*ΔHf-0.0920922* MW+14.09*∈LUMO +43.2067

rCV^2=0.745684

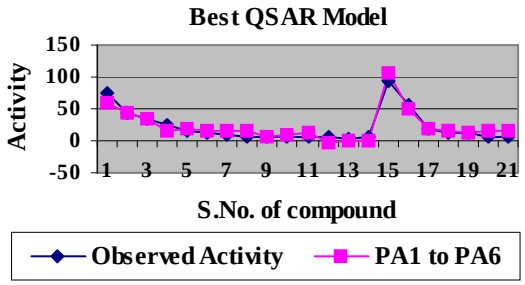
r^2=0.85628

Graph between predicted activity and observed activity PA7 of the compounds of sulfonamide series is shown in the Graph 2.

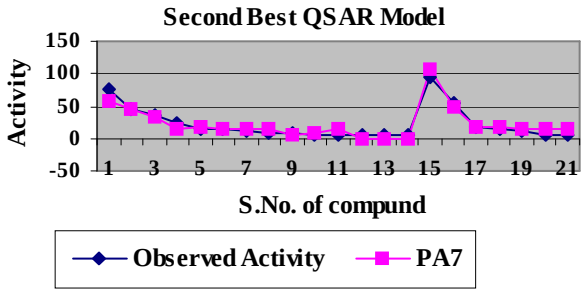
Third best QSAR model is that in which the descriptors are Heat of Formation, Molecular Weight and Electronegativity. In this case the predicted activity is PA8 and is given by-

TABLE 5: Values of observed activity, predicted activity and the difference between these two activities

S. no.	Comp.	Predicted activity PA1	Observed activity	Difference
1	T1C1	58.785	75.000	16.215
2	T1C2	44.342	45.000	0.658
3	T1C3	33.901	35.000	1.099
4	T1C4	16.008	25.000	8.992
5	T1C6	17.587	15.000	2.587
6	T1C7	14.332	13.500	0.832
7	T1C8	17.071	10.500	6.571
8	T1C9	15.132	7.000	8.132
9	T1C10	4.812	7.000	2.188
10	T1C11	9.038	6.000	3.038
11	T1C12	13.770	6.000	7.770
12	T1C13	-1.769	5.000	6.769
13	T1C14	-0.500	4.000	4.500
14	T1C15	-0.492	6.500	6.992
15	T1C16	107.105	95.000	12.105
16	T1C18	48.860	55.000	6.140
17	T1C19	17.493	18.500	1.007
18	T1C20	16.154	14.000	2.154
19	T1C21	13.970	12.000	1.970
20	T1C22	14.096	6.500	7.596
21	T1C23	14.101	6.500	7.601



Graph 1: Graph between predicted activity PA1 to PA6 and observed activity



Graph 2: Graph between predicted activity PA7 and observed activity

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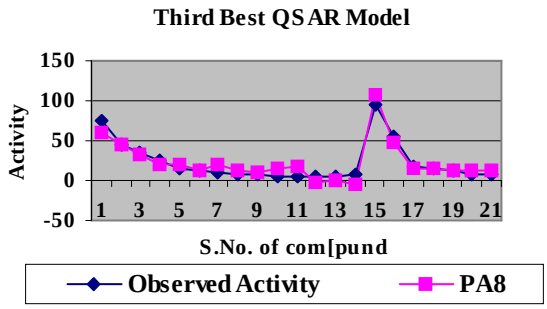

Graph 3: Graph between predicted activity PA8 and observed activity

PA8=0.236341*ΔHf-0.13235*MW+ 24.2764 *χ+159.249
rCV^2=0.736517
r^2=0.847898

Graph between predicted activity and observed activity PA8 is shown in the Graph 3.

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