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QSAR study of inhibitors of enzyme dehydrogenases and reductages using topological and quantum chemical descriptors

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Abstract: QSAR models of inhibitors of two enzymes MDH and RDR have been developed using topological descriptors viz. valence connectivity index, shape index, solvent accessibility surface area, molar refractivity, log P**,** molecular weight, conformation minimum energy and quantum chemical descriptors viz. heat of formation, steric energy, total energy, HOMO energy, LUMO energy, absolute hardness, electronegativity in 360 combinations. Best QSAR model with regression coefficient 0.88312 has been obtained using the descriptors shape index, solvent accessibility surface area, molar refractivity and log P for inhibitors of MDH enzyme; and the best QSAR model with regression coefficient 0.871613 has been obtained using the descriptors connectivity index, shape index, solvent accessibility surface area and molecular weight for inhibitors of RDR enzyme**.** In case of inhibitors of MDH enzyme, the molar refractivity is capable to produce good QSAR model with regression coefficient 0.868064 but no single descriptor in the case of inhibitors of RDR enzyme is capable to predict the activity. The combination of best quantum chemical descriptor for inhibitors of MDH enzyme is heat of formation, total energy, HOMO energy, electronegativity with regression coefficient 0.849353; and for inhibitors of RDR enzyme is steric energy, total energy, HOMO and LUMO energies with regression coefficient 0.913457. The quantum chemical descriptor total energy is the best descriptor for inhibitor of MDH enzyme and steric energy for inhibitor of RDR enzyme.

Key Words: QSAR model, Multilinear regression, molar refractivity, topological descriptors, quantum chemical descriptor, inhibitor, enzyme.

Introduction:

QSAR plays an important role in the prediction of activities of the compounds.[1-6] This paper describes the QSAR study of inhibitors of two enzymes, mitochondrial malate dehydrogenase (MDH) and ribonucleoside diphosphate reductase (RDR). The enzyme MDH plays a role in the Krebs cycle by the conversion of malate to oxalacetate.[7-17] Some cancer cells have exhibited abnormal label or activities of MDH[18-20] and some other enzymes. Selective inhibition of the enzyme increases the prospects of chemotherapy. Coates et. al.[21] synthesized a series of 7-substituted-4-hydroxyquinoline-3-carboxylic acids (Fig.-1) and studied their inhibition activities against MDH [22, 23].

The enzyme RDR is important to cell growth. It catalyzes the conversion of ribonucleotides to deoxyribonucleotides. Hence the study of RDR inhibition is very important to the design of useful anticancerous drugs. A number of compounds are known to inhibit RDR. RDR inhibitory activities of 5-substituted-2-formylpyridinethiosemi carbazone[22](Fig-2) and of 4'-substituted-5-hydroxy-2-formylpyridinethiosemicarbazones[23] (Fig.-3) are reported.

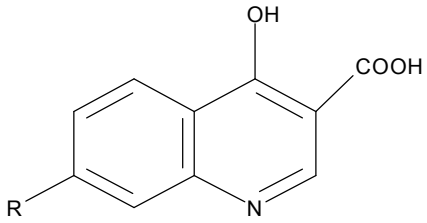


Fig.-1: Structure of 7-substituted-4-hydroxyquinoline-3-carboxylic acid

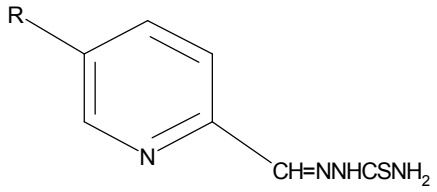


Fig.-2. Structure of 5-substituted-2-formylpyridine thiosemicarbazone

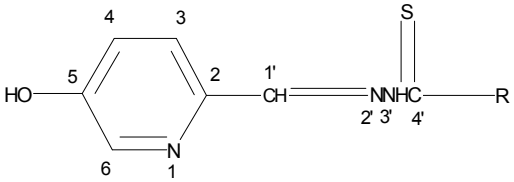


Fig.-3. Structure of 4'-substituted-5-hydroxy-2-formylpyridinethiosemicarbazone

Material and Method:

The QSAR study of derivatives of compounds shown in Fig.-1, 2, 3 has been made with the help of both quantum chemical and topological descriptors. The study materials are the derivatives of parent compounds shown in Fig,-1, 2, 3 and are listed in Tables 1-3. Topological descriptors which we have used are valence connectivity index (β), shape index (Ψ), solvent accessibility surface area (α), molar refractivity (Ω), log P (**λ),** molecular weight (μ) and conformation minimum energy (ε). Quantum chemical descriptors are heat of formation (ΔH_f), steric energy (SE), total energy (TE), HOMO energy (∈HOMO), LUMO energy (∈LUMO), absolute hardness (η) and electronegativity (χ).

The values of topological descriptors have been evaluated with the help of Cache software by solving the equations described below for each descriptor.

A measure of the drug's hydrophobicity is its partition coefficient (p) between two immiscible solvents, octanol and water at equilibrium [24, 25].

$$p = \frac{\text{Concentration of drug in octanol}}{\text{Concentration of drug in water}} \quad (1)$$

Biological activity may be expressed as log l/C, where C is the drug concentration required to achieve a specified level of biological function and can be expressed as:

$$\text{Log } (1/C) = k_1 \log P + k_2 \quad (2)$$

where k_1 and k_2 are constants.

For compounds with a larger range of log P values it is better described by quadratic equation:

$$\text{Log } (1/C) = k_1(\log P)^2 + k_2 \log P + k_3 \quad (3)$$

To calculate the connectivity indices [26], the sigma and valence electron descriptors are given by Equation-4 and -5 respectively.

$$\delta = \sigma - h \quad (4)$$

where σ is the count of sigma electrons

$$\delta^v = Z^v - h \quad (5)$$

where Z^v is the count of valence electrons. A more general expression for which includes atoms in the 2nd, 3rd, 4th rows of periodic chart is

$$\delta^v = (Z^v - h) / (Z - Z^v - 1) \quad (6)$$

where Z is the atomic number. A connectivity index calculation is made by multiplying the δ (or δ^v) values for each atom in a fragment within a molecule. This product is then converted to the reciprocal square root and called the connectivity sub graph term C_j. These terms are then summed over all the sub graphs in the entire molecule, Ns, to calculate the molecular connectivity index of order m and t type.

$$^mC_i = \prod_{k=1}^{m+1} (\delta_k)^{-0.5} \quad (7)$$

$$^m\chi_t = \sum_{i=1}^{Ns} {}^mC_i \quad (8)$$

The valence molecular connectivity indices $^m\chi^v$ t are calculated in the same way using δ^v values

$$^mCi^v = \prod_{k=1}^{m+1} (\delta_k{}^v)^{-0.5}$$

$$^m\chi_t{}^v = \sum_{i=1}^{Ns} {}^mCi^v \quad (9\text{-}10)$$

The values of Kappa indices [27] can be calculated directly form the path count ^mP_i and the number of atoms using the equation:

$$^1k = A(A-1)^2 / (^1P_i)^2 \quad (11)$$

$$^2k = A(A-1)(A-2)^2 / (^2P_i)^2 \quad (12)$$

$$^3k = A(A-3)(A-2)^2 / (^3P_i)^2 \quad (13)$$

(A is even)

$$^3k = A(A-1)(A-3)^2 / (^3P_i)^2 \quad (14)$$

(A is odd)

The presence of atoms other than $C(sp^3)$ is taken in to consideration then in the relation for Kappa indices, A is replaced by the values $(A+\alpha)$ and ${}^mP_i$ is replaced by $({}^mP_i+\alpha)$. The resulting values are designated by ${}^mK_\alpha$, where α is given by

$$\alpha = r(x) / r[C(sp^3)] - 1 \qquad (15)$$

where r(x) is the covalent radius of x and $r[C(sp^3)]$ is the covalent radius of carbon in sp^3 state.

Molar refractivity can be used as a steric parameter [28],

$$MR = [(n^2-1)/(n^2+2)]MW/d \qquad (16)$$

where n is the refractive index for the sodium D line, MW is the molecular weight and d is the density of the compound.

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

The values of quantum chemical descriptors such as HOMO energy[29], LUMO energy[30], absolute hardness[31-34], electronegativity[35], total and steric energy[38-40], heat of formation[41] have been evaluated with the help of CAChe software using PM3 hamiltonian.

Parr et. al.[36] define the electronegativity as the negative of chemical potential

$$\chi = -\mu = -(\partial E/\partial N)_v \qquad (17)$$

The absolute hardness η is defined as[37]

$$\eta = 1/2(\delta\mu/\delta N)v_{(r)} = 1/2\,(\delta^2E/\delta^2N)v_{(r)} \qquad (18)$$

where E is the total Energy, N the number of electrons of the chemical species and $v_{(r)}$ the external potential

The corresponding global softness S, which bears an inverse relationship with the global hardness is defined as

$$S = 1 / 2\eta = (\partial N / \partial \mu)v_{(r)} \qquad (19)$$

The operational definition of absolute hardness, global softness and electronegativity is defined as:

$$\eta = (IP-EA)/2 \qquad (20)$$

$$S = 1 / (IP-EA) \qquad (21)$$

$\chi = -\mu = (IP + EA)/2$ (22),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 HOMO with change of sign and EA is the eigen value of LUMO with change of sign [37]; hence, Eqs. 20-22 can be written as

$$\eta = ½.(\varepsilon\,LUMO - \varepsilon\,HOMO) \qquad (23)$$

$$S = 1 / (\varepsilon\,LUMO - \varepsilon\,HOMO) \qquad (24)$$

$$\chi = ½.(\varepsilon\,LUMO + \varepsilon\,HOMO) \qquad (25)$$

The energy descriptors[38-41] are useful parameters for describing QSAR of a chemical system. A more useful quantity is the heat of formation of the compound from its elements in their standard state. This is equal to the energy required to ionize the valence electrons of the atoms involved. The heat of formation is defined as

$$\Delta H_f = E_{elect} + E_{nuc} - E_{isol} + E_{atom} \qquad (26)$$

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-

$$E = ½.P(H + F) \qquad (27)$$

where P is the density matrix and H is the one electron matrix. These parameters and the charges on atoms has been obtained from PM3[42] calculations. Multilinear regression (MLR) analysis has been performed by using Project Leader program associated with CAChe Pro software of Fujitsu.

Result and discussion

QSAR studies of the inhibitors of MDH and RDR enzymes listed in Table-1-3 have been done with the help of topological descriptors and quantum chemical descriptors described under material and method.

PM3 based calculations of the above descriptors have been made on the compounds listed in Table-1-3 with the help of MOPAC and Cache Software and their relationship with the known activity has been studied. The values of the descriptors have been used to prepare the regression equations using MLR analysis and the predicted activities obtained from the regression equations have been compared with the known activities. The correlation coefficient and cross validation coefficients have been evaluated for the evaluation of the qualities of QSAR models. Values of the topological descriptors used in MLR analysis for inhibitors of MDH and RDR enzymes are shown in the Table-4 and Table-5 respectively. Values of the quantum chemical descriptors used in MLR analysis for inhibitors of MDH and RDR enzymes are shown in the Table-6 and Table-7

respectively. Outlier compounds in the development of QSAR models for the inhibitor of RDR enzyme using topological descriptors are 4, 9, 22 and 31 of Table-1. Other sets of descriptors have no outliers.

Table-1: m-MDH Cell Respiration Inhibition Activities of 7-substituted-4-hydroxyquinoline-3-carboxylic acids

Comp.	R	pI_{50}
C1	H	2.98
C2	SO_2CH_3	3.18
C3	OCH_3	3.28
C4	OH	3.31
C5	CI	2.44
C6	F	1.98
C7	$CONH_2$	3.13
C8	COOH	2.97
C9	SO_3^-	2.67
C10	SO_2NH_2	3.02
C11	$COCH_3$	3.04
C12	NO_2	2.92
C13	$N(CH_3)_2$	3.32
C14	$OCH_2C_6H_5$	4.49
C15	$OCH_2C_6H_3$-3,4-Cl_2	5.32
C16	$OCH_2C_6Cl_5$	5.32
C17	OCH_2-□-$C_{10}H_7$	4.48
C18	$OCH_2C_6H_4$-4-F	4.4
C19	$OCH_2C_6H_4$-4-Br	5.17
C20	OCH_2-□-$C_{10}H_7$	5.39
C21	$OCH_2C_6H_4$-4-C_6H_5	4.51
C22	$O(CH_2)_2C_6H_5$	3.81
C23	$O(CH_2)_2C_6H_4$-4-F	4.83
C24	$O(CH_2)_2C_6H_4$-4-Br	4.04
C25	$O(CH_2)_2$-□-$C_{10}H_7$	5.66
C26	$O(CH_2)_2C_6H_4$-4-OC_6H_5	5.74
C27	$O(CH_2)_2OC_6H_5$	4.22
C28	$O(CH_2)_2OC_6H_4$-4-F	4.74
C29	$O(CH_2)_2OC_6H_4$-4-Br	5.29
C30	$O(CH_2)_2O$-□-$C_{10}H_7$	5.8
C31	$O(CH_2)_2OC_6H_4$-4-OC_6H_5	5.61

m-MDH-mitochondrial malate dehydrogenase

With the help of MLR analysis, we have developed 90 QSAR models for each inhibitor using topological descriptors in which three best regression equations are PA1-PA3 for the inhibition of MDH enzyme and APA1-APA3 for the inhibition of RDR enzyme, arranged in decreasing order of predictive power, are given below: -

1. PA1=-0.264428* Ψ +0.0391952* α +0.048759* Ω -0.0533384* λ -0.362642
   rCV^2=0.828857
   r^2=0.88312
2. PA2=-0.148535* Ψ +0.0407398* α +0.0357435* Ω +1.37899e-005* ε -0.240514
   rCV^2=0.808283
   r^2=0.883039
3. PA3=0.0236084* α +0.0347292*Ω +0.00346217*μ+2.7735e-005* ε +0.0413952
   rCV^2=0.776189
   r^2=0.882918
4. APA1=-2.25479*β +1.67901*Ψ -0.044379*α +0.00869196*μ +12.4171
   rCV^2=0.718013
   r^2=0.871613
5. APA2=-2.32805*β +1.71699*Ψ -0.0355538*α +0.0170825*Ω +12.6636
   rCV^2=0.659373
   r^2=0.847838
6. APA3=-2.23959*β +1.6449*Ψ -0.0257724*α +0.0453767*λ +12.3997
   rCV^2=0.73365
   r^2=0.847019

All the above regression equations give reliable predictive power as the cross-validation coefficient rCV^2 is above 0.7 and the regression coefficient r^2 above 0.84. Three best predicted activities of enzyme inhibitors obtained with the help of MLR equations are shown in the Tables 8-9.

The regression equation for PA1 forms the best QSAR model i.e. with the help of this regression equation the activity of any unknown compound can be best predicted by substituting the values of the descriptors used in this equation. Descriptors used in the QSAR model PA1 are Shape Index, Solvent Accessibility Surface Area, Molar Refractivity and Log P.

Thus above four descriptors form the best QSAR model and with the help of these values of descriptors the activity of any inhibitor of MDH enzyme (whose activity is unknown) can be obtained by substituting the values of the descriptors in the above equation. The graph between the actual activities obtained experimentally and the predicted activities PA1 of the compounds under study is shown in the Graph-1.

Graph-1: Graph between the actual activities and the predicted activities obtained by QSAR model PA1

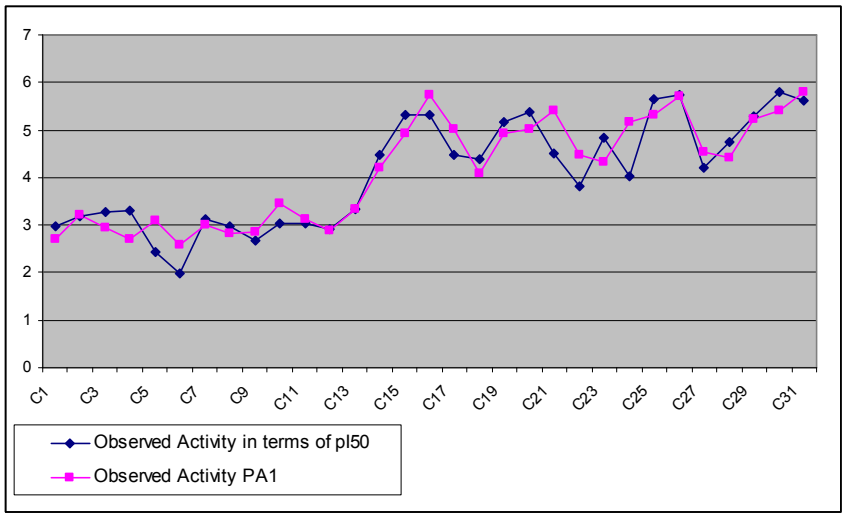


TABLE-2: RDR Inhibitory Activities of 5-substituted-2-formylpyridine thiosemicarbazones

Comp.	R	pI_{50}
1	H	6.55
2	CH_3	6.51
3	C_2H_5	6.66
4	F	5.22
5	Cl	6.25
6	Br	6.3
7	I	6.39
8	CF_3	5.62
9	OH	5.17
10	OCH_3	5.92
11	OCF_3	5.6
12	OC_2H_5	6.07
13	$OC_2H_4N(CH_3)_2$	4.62
14	$O(C_2H_4O)_2C_2H_5$	5.69
15	$OOCCH_3$	5.44
16	$OOCC_2H_5$	5.28
17	n-$OOCC_3H_7$	5.17
18	n-$OOCC_{15}H_{31}$	3.96
19	$OOCCH_2OCH_3$	5.3
20	$OOCCH_2OC_2H_5$	5.25
21	$OOCCH_2N(CH_3)_2$	5.24
22	$OOCCH_2OC_6H_5$	4.89
23	$NHCOCH_3$	5.92
24	$N(CH_3)_2$	6.4

TABLE-3: RDR Inhibitory Activities of 4'-Substituted 5-Hydroxy-2-formylpyridine Thiosemicarbazones

Comp.	R	pI_{50}
25	NH_2	5.52
26	c-$N(CH_2CH_2)O$	4.16
27	c-NC_5H_{10}	4.38
28	c-$N(CH_2CH_2)_2NCH_3$	4.14
29	c-$N(CH_2CH_2)S$	4.09
30	c-NC_4H_8	4.18
31	SCH_3	4.94
32	NCH_2CH_2	4.1
33	C_6H_5	4.14

QSAR models developed using single descriptor also give very good predictive activities of the compounds.

PA4=0.0520228* Ω +0.111231

rCV^2=0.841382

r^2=0.868064

QSAR model PA4 is the best which has molar refractivity as the single descriptor. Although every single descriptor provides good QSAR model because regression coefficient is greater than 0.7 in every regression equation having single descriptor. The highest regression coefficient is 0.868064 in the QSAR model developed using the predicted activity PA4 among all the QSAR models developed using single descriptor. Therefore, we can say that the descriptor molar refractivity is the best descriptor for QSAR analysis and any QSAR model developed using molar refractivity as one descriptor provide reliable predictive power of the activity of any inhibitor of MDH enzyme.

Table-4: Values of topological descriptors used in the development of QSAR models for inhibitors of MDH enzyme

Compound	Connectivity Index (order 0, standard)	Shape Index (basic kappa, order 1)	Solvent Accessibility Surface Area	Molar Refractivity	Log P	Molecular Weight	Conformation Minimum Energy (kcal/mole)	Activity
C1	10.129	10.516	91.033	48.432	1.550	189.170	-66133.859	2.980
C2	13.284	14.410	116.683	57.938	0.294	269.272	-92439.190	3.180
C3	11.707	12.457	102.249	54.895	1.297	219.196	-78295.371	3.280
C4	11.000	11.484	94.997	50.126	1.266	205.170	-73808.731	3.310
C5	11.000	11.484	102.032	53.237	2.068	223.615	-73518.562	2.440
C6	11.000	11.484	94.151	48.648	1.689	207.161	-76119.779	1.980
C7	12.577	13.432	105.922	57.012	0.384	232.195	-83032.936	3.130
C8	12.577	13.432	104.767	55.190	1.248	233.180	-84784.215	2.970
C9	13.284	14.410	115.569	52.084	0.674	268.221	-94082.244	2.670
C10	13.284	14.410	117.363	62.464	0.150	268.244	-92867.202	3.020
C11	12.577	13.432	107.350	58.835	0.858	231.207	-81606.084	3.040
C12	12.414	13.432	106.494	55.355	1.597	234.168	-86013.354	2.720
C13	12.577	13.432	108.852	62.860	1.814	232.238	-81004.557	3.320
C14	15.527	16.844	135.846	79.508	3.074	295.294	-100987.432	4.490
C15	17.267	18.781	156.502	89.117	4.110	364.184	-115756.925	5.320
C16	19.878	21.703	180.797	103.532	5.664	467.519	-137905.289	5.320
C17	18.096	19.322	154.047	95.958	4.076	345.354	-115843.768	4.480
C18	16.397	17.811	139.072	79.724	3.213	313.285	-110972.897	4.400
C19	16.397	17.811	152.275	87.130	3.866	374.190	-107192.185	5.170
C20	18.096	19.322	153.708	95.958	4.076	345.354	-115845.664	5.390
C21	19.510	21.240	166.794	104.644	4.758	371.392	-123707.675	4.510
C22	16.234	17.811	143.094	84.262	3.326	309.321	-105482.576	3.810
C23	17.104	18.781	146.241	84.479	3.465	327.311	-115466.776	4.830
C24	17.104	18.781	158.987	91.885	4.117	388.217	-111685.754	5.600
C25	18.803	20.280	162.426	100.712	4.328	359.381	-120343.202	5.660
C26	20.924	23.168	180.087	110.503	4.755	401.418	-135848.139	5.740
C27	16.941	18.781	149.459	85.447	2.913	325.320	-113120.392	4.220
C28	17.811	19.753	152.585	85.664	3.053	343.311	-123103.755	4.740
C29	17.811	19.753	165.413	93.070	3.705	404.216	-119325.806	5.290
C30	19.510	21.240	169.106	101.897	3.916	375.380	-127977.012	5.800
C31	21.631	24.135	186.773	111.688	4.342	417.417	-143482.033	5.610

Table-5: Values of topological descriptors used in the development of QSAR models for inhibitors of RDR enzyme

Compound	Connectivity Index (order 0, standard)	Shape Index (basic kappa, order 1)	Solvent Accessibility Surface Area	Molar Refractivity	Log P	Molecular Weight	Conformation Minimum Energy (kcal/mole)	Activity
1	8.812	10.083	101.411	51.672	2.044	180.224	-55543.813	6.550
2	9.682	11.077	107.061	56.263	1.759	194.251	-60037.812	6.510
3	10.389	12.071	112.376	60.890	2.387	208.278	-64529.750	6.660
5	9.682	11.077	111.441	56.976	2.827	214.669	-62892.691	6.250
6	9.682	11.077	115.904	59.575	3.127	259.120	-61735.897	6.300
7	9.682	11.077	123.371	64.181	3.126	306.120	-61079.444	6.390
8	12.182	14.063	115.484	57.273	2.870	248.222	-89966.030	5.620
10	10.389	12.071	111.023	57.887	2.384	210.250	-67696.999	5.920
11	12.889	15.059	119.389	57.966	4.129	264.222	-97669.127	5.600
12	11.096	13.067	119.110	62.635	2.727	224.277	-72178.996	6.070
13	13.380	16.056	139.179	75.906	2.363	267.345	-87010.415	4.620
14	15.339	19.048	161.882	84.722	2.397	312.383	-105395.876	5.690
15	11.966	14.063	122.172	62.556	2.136	238.261	-78660.194	5.440
16	12.673	15.059	130.635	67.183	2.764	252.287	-83153.276	5.280
17	13.380	16.056	136.948	71.784	3.160	266.314	-87646.486	5.170
18	21.866	28.033	225.685	126.996	7.916	434.636	-141556.844	3.960
19	13.380	16.056	135.782	69.010	1.858	268.287	-90788.959	5.300
20	14.088	17.053	143.736	73.757	2.201	282.314	-95270.947	5.250
21	14.251	17.053	142.405	75.985	2.002	281.329	-93492.728	5.240
23	11.966	14.063	123.055	64.506	1.486	237.276	-76911.269	5.920
24	11.259	13.067	117.515	65.852	2.901	223.292	-70384.949	6.400
25	9.682	11.077	105.820	56.124	1.854	195.239	-61451.833	5.520
26	11.380	12.457	120.479	64.546	3.294	237.276	-77065.220	4.160
27	12.795	14.410	130.861	77.993	3.623	263.357	-82950.809	4.380
28	13.665	15.390	137.300	81.902	2.702	278.371	-88804.936	4.140
29	11.380	12.457	127.173	70.720	3.736	253.336	-75201.644	4.090
30	12.088	13.432	126.731	73.392	3.227	249.330	-78462.657	4.180
32	10.673	11.484	119.237	63.883	2.723	221.276	-69391.285	4.100
33	12.795	14.410	130.181	76.436	3.672	256.322	-78252.014	4.310

Clearly, best QSAR model with regression coefficient 0.871613 has been obtained using the descriptors connectivity index, shape index, solvent accessibility surface area and molecular weight for inhibitors of RDR enzyme. In the case of inhibitors of RDR enzyme, single descriptor is not capable to produce good QSAR model. Graph between predicted and observed activities of inhibitors of RDR enzyme is given in Graph-2 for QSAR models APA1.

Three best QSAR models developed by using quantum chemical descriptors for the inhibitors of MDH and RDR enzymes are BPA1-BPA3 and CPA1-CPA3 respectively. These are shown below-

1. BPA1=0.00472946*ΔHf-0.0281333*TE-1.79317*∈HOMO-2.23677*χ-4.86566
   rCV^2=0.689769
   r^2=0.849353
2. BPA2=0.00472946*ΔHf-0.0281333*TE-0.674784*∈HOMO+1.11839*∈LUMO-4.86566
   rCV^2=0.689769 r^2=0.849353
3. BPA3=0.00472946*ΔHf-0.0281333*TE+0.443602*∈LUMO+1.34957*η-4.86566 rCV^2=0.689769 r^2=0.849353
4. CPA1=-0.0185399*SE+0.0506553 *TE +0.662867*∈HOMO-0.294238 *∈LUMO + 17.3749
   rCV^2=0.871961

r^2=0.913457

5. CPA2=-0.000109075*ΔHf-0.0221376*SE+0.0468205*TE+0.325088*∈HOMO+14.2969 rCV^2=0.86312 r^2=0.912051
6. CPA3=-0.0217637*SE+0.04722*TE+0.309956*∈HOMO+14.2093 rCV^2=0.875981 r^2=0.912024

Best QSAR model developed by using quantum chemical descriptors for the inhibitors of MDH enzyme is given by BPA1 with the descriptors heat of formation, total energy, HOMO energy, electronegativity whose regression coefficient is 0.849353. Total energy alone provides QSAR model with 0.799600 regression coefficient. Values of predicted activity from QSAR models BPA1-BPA3 are given in Table-10. Graph for observed activity and predicted activity by BPA1 is shown in Graph-3.

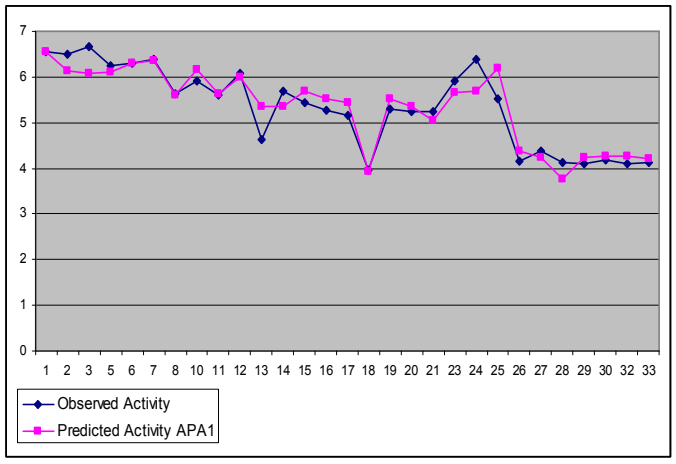
Table-6: Values of quantum chemical descriptors used in the development of QSAR models for inhibitors of MDH enzyme

Compound	Heat of Formation (kcal/mole)	Steric Energy (kcal/mole)	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness	Electronegativity	Activity
C1	-88.703	-24.097	-105.391	-9.263	-1.097	4.083	5.180	2.980
C2	-21.270	-26.180	-147.311	-8.131	-1.315	3.408	4.723	3.180
C3	-127.734	-22.666	-124.772	-9.195	-1.030	4.082	5.112	3.280
C4	-134.728	-26.381	-117.622	-9.236	-1.070	4.083	5.153	3.310
C5	-95.083	-25.272	-117.159	-9.343	-1.260	4.041	5.301	2.440
C6	-131.876	-25.999	-121.305	-9.483	-1.303	4.090	5.393	1.980
C7	-127.319	-43.772	-132.328	-9.502	-1.479	4.012	5.491	3.130
C8	-176.974	-29.977	-135.112	-9.518	-1.539	3.989	5.528	2.970
C9	-157.025	-25.513	-149.930	-4.088	1.300	2.694	1.394	2.670
C10	-66.153	-24.187	-147.993	-9.166	-1.638	3.764	5.402	3.020
C11	-129.776	-18.335	-130.048	-9.439	-1.336	4.052	5.387	3.040
C12	-7.848	-0.622	-137.071	-9.710	-2.310	3.700	6.010	2.920
C13	-93.089	-10.964	-129.089	-8.662	-0.974	3.844	4.818	3.320
C14	-99.625	-31.640	-160.937	-9.166	-1.018	4.074	5.092	4.490
C15	-110.009	-26.862	-184.470	-9.252	-1.078	4.087	5.165	5.320
C16	-124.741	-22.839	-219.766	-9.239	-1.075	4.082	5.157	5.320
C17	-82.023	-39.100	-184.611	-8.928	-1.005	3.962	4.966	4.480
C18	-141.547	-31.553	-176.847	-9.246	-1.075	4.086	5.161	4.400
C19	-91.769	-31.375	-170.822	-9.234	-1.074	4.080	5.154	5.170
C20	-82.392	-41.183	-184.612	-8.947	-1.018	3.964	4.983	5.390
C21	-75.587	-40.740	-197.152	-9.013	-1.019	3.997	5.016	4.510
C22	-103.999	-30.514	-168.101	-9.194	-1.031	4.082	5.112	3.810
C23	-147.481	-30.746	-184.012	-9.249	-1.077	4.086	5.163	4.830
C24	-97.746	-30.117	-177.988	-9.252	-1.097	4.077	5.175	4.040
C25	-88.982	-40.894	-191.779	-8.895	-1.051	3.922	4.973	5.660
C26	-109.205	-38.220	-216.488	-9.072	-1.062	4.005	5.067	5.740
C27	-131.824	-28.518	-180.269	-9.238	-1.070	4.084	5.154	4.220
C28	-175.081	-28.685	-196.178	-9.290	-1.111	4.089	5.200	4.740
C29	-124.166	-28.155	-190.158	-9.286	-1.107	4.089	5.196	5.290
C30	-114.220	-39.075	-203.945	-8.738	-1.068	3.835	4.903	5.800
C31	-134.684	-35.898	-228.653	-9.170	-1.101	4.034	5.135	5.610

Table-7: Values of quantum chemical descriptors used in the development of QSAR models for inhibitors of RDR enzyme

Comp.	Heat of Formation (kcal/mole)	Steric Energy (kcal/mole)	Total Energy (Hartree)	HOMO Energy (eV)	LUMO Energy (eV)	Absolute Hardness	Electronegativity	Activity
1	50.269	-15.621	-106.804	-8.863	-1.294	3.784	5.079	6.550
2	43.080	-13.045	-117.436	-8.697	-1.246	3.725	4.972	6.510
3	38.595	-15.203	-115.067	-8.680	-1.235	3.722	4.957	6.660
4	14.491	10.512	-127.803	-8.976	-1.427	3.774	5.202	5.220
5	49.738	-15.305	-111.541	-8.949	-1.414	3.768	5.182	6.250
6	58.357	-11.024	-110.751	-9.064	-1.446	3.809	5.255	6.300
7	70.543	-12.319	-109.330	-8.818	-1.413	3.703	5.116	6.390
8	-94.143	10.758	-121.488	-9.172	-1.852	3.660	5.512	5.620
9	5.069	9.931	-128.593	-8.896	-1.060	3.918	4.978	5.170
10	12.801	11.558	-116.751	-8.841	-0.969	3.936	4.905	5.920
11	-146.136	9.045	-111.804	-9.135	-1.418	3.858	5.276	5.600
12	8.220	12.716	-114.383	-8.719	-0.977	3.871	4.848	6.070
13	9.509	15.143	-127.277	-8.843	-0.997	3.923	4.920	4.620
14	-69.507	14.751	-120.383	-8.870	-1.010	3.930	4.940	5.690
15	-32.788	12.347	-124.330	-8.981	-1.376	3.802	5.179	5.440
16	-33.317	16.649	-126.856	-8.939	-1.255	3.842	5.097	5.280
17	-38.723	15.231	-128.593	-8.937	-1.251	3.843	5.094	5.170
18	-103.885	22.637	-137.698	-8.941	-1.256	3.843	5.098	3.960
19	-60.212	16.361	-126.540	-8.976	-1.301	3.837	5.138	5.300
20	-64.659	15.080	-127.330	-8.954	-1.288	3.833	5.121	5.250
21	-20.779	15.224	-127.488	-8.807	-1.234	3.786	5.020	5.240
22	-27.883	13.259	-133.014	-9.029	-1.371	3.829	5.200	4.890
23	6.425	-9.558	-116.751	-8.715	-1.159	3.778	4.937	5.920
24	47.592	-14.463	-119.172	-8.591	-0.943	3.824	4.767	6.400
25	47.178	9.196	-123.067	-8.792	-1.071	3.860	4.931	5.520
26	33.500	20.760	-134.540	-8.878	-1.259	3.809	5.068	4.160
27	37.671	21.595	-141.066	-8.529	-0.906	3.812	4.718	4.380
28	49.138	21.048	-139.856	-8.610	-1.013	3.799	4.811	4.140
29	80.413	26.767	-145.645	-8.922	-1.332	3.795	5.127	4.090
30	41.768	25.472	-144.224	-8.586	-0.883	3.852	4.735	4.180
31	54.261	14.540	-142.224	-8.859	-1.382	3.738	5.120	4.940
32	84.034	22.623	-145.487	-8.782	-1.295	3.743	5.038	4.100
33	81.592	23.048	-144.856	-8.610	-1.194	3.708	4.902	4.140

Graph-2: Graph between the actual activities and the predicted activities obtained by QSAR model APA1



Graph-3: Graph between the actual activities and the predicted activities obtained by QSAR model BPA1

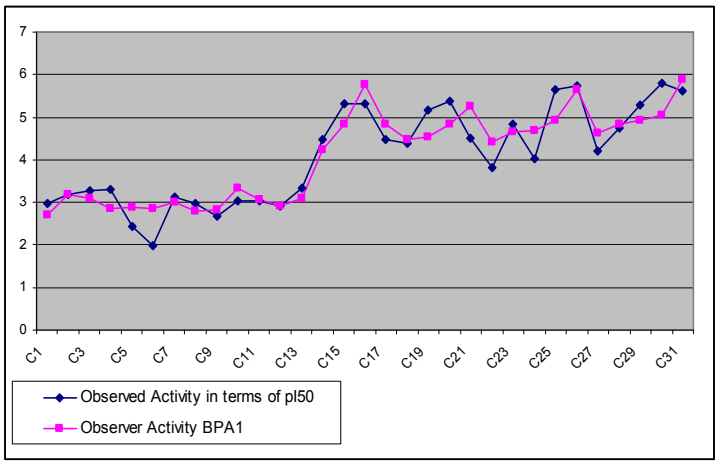


Table-8: Values of three best predicted activities by QSAR models of inhibitors of MDH enzymes using topological descriptors

Comp.	PA1	PA2	PA3
C1	2.704	2.725	2.693
C2	3.210	3.169	3.177
C3	2.959	2.957	2.949
C4	2.701	2.698	2.688
C5	3.085	3.099	3.034
C6	2.573	2.579	2.560
C7	2.997	2.972	3.023
C8	2.816	2.836	2.887
C9	2.860	2.892	2.898
C10	3.465	3.352	3.334
C11	3.116	3.115	3.156
C12	2.873	2.895	2.903
C13	3.320	3.329	3.352
C14	4.221	4.241	4.231
C15	4.931	4.935	4.881
C16	5.731	5.700	5.699
C17	5.027	4.998	4.993
C18	4.094	4.099	4.100
C19	4.938	4.954	4.985
C20	5.014	4.984	4.985
C21	5.407	5.434	5.468
C22	4.467	4.501	4.491
C23	4.337	4.355	4.359
C24	5.163	5.191	5.232
C25	5.321	5.305	5.280
C26	5.704	5.731	5.753
C27	4.540	4.553	4.526
C28	4.409	4.406	4.393
C29	5.238	5.246	5.269
C30	5.409	5.371	5.323
C31	5.790	5.797	5.795

Table-9: Values of three best predicted activities by QSAR models of inhibitors of RDR enzymes using topological descriptors

Comp.	APA1	APA2	APA3
1	6.545	6.740	6.731
2	6.122	6.298	6.257
3	6.084	6.249	6.201
5	6.105	6.154	6.193
6	6.294	6.040	6.092
7	6.371	5.853	5.899
8	5.593	5.322	5.403
10	6.161	6.246	6.236
11	5.638	5.259	5.414
12	6.000	6.102	6.096
13	5.352	5.429	5.363
14	5.344	5.351	5.315
15	5.696	5.676	5.680
16	5.521	5.518	5.545
17	5.442	5.438	5.457
18	3.945	4.038	4.084
19	5.510	5.432	5.428
20	5.359	5.296	5.295
21	5.042	5.002	4.955
23	5.648	5.678	5.628
24	5.695	5.834	5.780
25	6.186	6.339	6.294
26	4.387	4.377	4.447
27	4.244	4.299	4.240
28	3.772	3.793	3.695
29	4.230	4.244	4.294
30	4.258	4.334	4.303
32	4.265	4.386	4.437
33	4.213	4.296	4.259

For the inhibitors of RDR enzyme, the best quantum chemical descriptors are steric energy, total energy, HOMO and LUMO energies with regression coefficient 0.913457 as evident by QSAR model CPA1. Steric energy alone provides QSAR model with 0.85 regression coefficient. Electronegativity alone provides QSAR model with 0.799 regression coefficient. Values of predicted activity from QSAR models CPA1-CPA3 are given in Table-11. Graph for observed activity and predicted activity by CPA1 is shown in Graph-4.

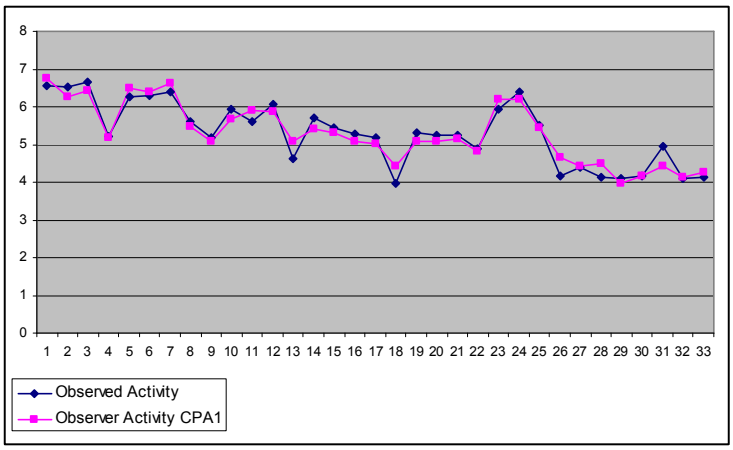
Table-10: Values of three best predicted activities by QSAR models of inhibitors of MDH enzymes using quantum chemical descriptors

Comp.	BPA1	BPA2	BPA3
C1	2.703	2.703	2.703
C2	3.194	3.194	3.194
C3	3.093	3.093	3.093
C4	2.842	2.842	2.842
C5	2.876	2.876	2.876
C6	2.864	2.864	2.864
C7	3.013	3.013	3.013
C8	2.800	2.800	2.800
C9	2.822	2.822	2.822
C10	3.338	3.338	3.338
C11	3.055	3.055	3.055
C12	2.922	2.922	2.922
C13	3.081	3.081	3.081
C14	4.238	4.238	4.238
C15	4.841	4.841	4.841
C16	5.760	5.760	5.760
C17	4.841	4.841	4.841
C18	4.478	4.478	4.478
C19	4.536	4.536	4.536
C20	4.837	4.837	4.837
C21	5.265	5.265	5.265
C22	4.423	4.423	4.423
C23	4.650	4.650	4.650
C24	4.695	4.695	4.695
C25	4.935	4.935	4.935
C26	5.643	5.643	5.643
C27	4.619	4.619	4.619
C28	4.851	4.851	4.851
C29	4.925	4.925	4.925
C30	5.034	5.034	5.034
C31	5.887	5.887	5.887

Table-11: Values of three best predicted activities by QSAR models of inhibitors of RDR enzymes using quantum chemical descriptors

Comp.	CPA1	CPA2	CPA3
1	6.760	6.755	6.759
2	6.270	6.255	6.252
3	6.438	6.420	6.416
4	5.176	5.161	5.163
5	6.492	6.499	6.502
6	6.386	6.403	6.410
7	6.636	6.576	6.582
8	5.486	5.399	5.395
9	5.092	5.164	5.164
10	5.671	5.699	5.704
11	5.906	5.908	5.902
12	5.853	5.824	5.829
13	5.079	5.127	5.129
14	5.421	5.458	5.455
15	5.300	5.286	5.286
16	5.084	5.087	5.086
17	5.023	5.038	5.036
18	4.423	4.453	4.443
19	5.095	5.099	5.096
20	5.089	5.098	5.093
21	5.160	5.130	5.128
22	4.810	4.844	4.841
23	6.202	6.208	6.203
24	6.189	6.239	6.234
25	5.458	5.468	5.473
26	4.661	4.648	4.653
27	4.442	4.437	4.434
28	4.491	4.478	4.479
29	3.978	3.976	3.984
30	4.165	4.185	4.183
31	4.435	4.430	4.431
32	4.146	4.120	4.125
33	4.254	4.197	4.199

Graph-4: Graph between the actual activities and the predicted activities obtained by QSAR model CPA1



Conclusion

Best QSAR model developed with the help of topological descriptors is PA1 for inhibitors of MDH enzyme with regression coefficient 0.88312 in which the descriptors are shape index, solvent accessibility surface area, molar refractivity and log P. No single descriptor is capable to produce good QSAR model but the QSAR model developed using molar refractivity possesses very good predictive power. For inhibitors of RDR enzyme, good QSAR model can not be produced with the help of single descriptor; but the best QSAR model APA1 with regression coefficient 0.871613 has been obtained using the topological descriptors valence connectivity index, shape index, solvent accessibility surface area and molecular weight.

QSAR models developed with the help of quantum chemical descriptors indicate that the best descriptor of activities for inhibitors of MDH and RDR enzymes are total energy and steric energy respectively.

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