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QSAR Study on Inhibitors of Enzyme Ribonucleoside Diphosphate Reductase

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Descriptors heat of formation, energy of HOMO, total energy, absolute hardness and chemical potential in different combination, have been used to develop QSAR models of inhibitors of enzyme ribonucleoside diphosphate reductase. The inhibitors are mainly derivatives of 2-formylpyridine thiosemicarbazone and 1-formylpyridine thiosemicarbazone. The derivatives of 2-formylpyridine thiosemicarbazone have been devided into two sets, on the basis of difference in position of substituents and the derivatives of 1-formylpyridine thiosemicarbazone have also been divided in two sets, on the basis of difference of inhibitory activity. One QSAR model having the best predictive power is presented in each set. The correlation coefficient value is above 0.9 in first, third and fourth set and above 0.79 in second set. The best combinations of descriptors are heat of formation, total energy and energy HOMO.

Key Words: QSAR, PM3, Ribonucleoside diphosphate reductase, Quantum chemical descriptors.

INTRODUCTION

Enzyme ribonucleoside diphosphate reductase[1,2] (RDR) is important to cell growth as it catalyzes the conversion of ribonucleotides to deoxyribonucleotides, but when uncontrolled leads in the development of malignant growth. Hence, the study of RDR inhibition is important to the design of useful drugs. A number of α-N-formyl heteroaromatic thiosemicarbazones are known to inhibit ribonucleoside diphosphate reductase. The paper presents the QSAR study of 30 derivatives of 2-formylpyridine thiosemicarbazone and 21 derivatives of 1-formylisoquinoline thiosemicarbazone, with the help of new set of descriptors *i.e.*, heat of formation[3], eigen value of highest occupied molecular orbital[4], eigen value of lowest unoccupied molecular orbital[5], total energy[6], absolute hardness[7,8] and chemical potential[9]. These descriptors have been successfully employed for QSAR study recently[10].

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EXPERIMENTAL

The study materials of this paper are inhibitors of enzyme ribonucleoside diphosphate reductase and are presented in Tables 1-4. Tables 1 and 2 include derivatives of 2-formylpyridine thiosemicarbazone and derivatives of 1-formylisoquinoline thiosemicarbazone are presented in Tables 3 and 4. The biological activity of these derivatives has been measured in term of inhibitory activity I_{50}. For QSAR prediction, the 3D modeling and geometry optimization of all the compounds have been done with the help of PCMODEL software using the semiemipical PM3 Hamiltonian. All calculations have been performed with Win MOPAC 7.21 software by applying key words PM3 Charge = 0 Gnorm = 0.1, Bonds, Geo-OK, Vectors Density. The values of heat of formation (ΔH_f), eigen value of highest occupied molecular orbital (εHOMO), eigen value of lowest unoccupied molecular orbital (εLUMO), total energy (TE), absolute hardness (η) and chemical potential (μ) have been obtained from this software by solving the equations given below and result are also reported in the Tables 1-4.

Parr *et al.*[11] 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[12]

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

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

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

The operational definition of absolute hardness and electronegativity 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 ionization potential is simply the eigen value of the HOMO with change of sign[11] and the electron affinity 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

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

where P is the density matrix and H is the one-electron matrix. These parameters and the charges on atoms were obtained from PM3 calculations[13].

RESULTS AND DISCUSSION

On the basis of difference in the position of substitutent, 2-formyl pyridine thiosemicarbazone derivatives are divided into two different sets. The first set includes derivatives of 5-substituted-2-formylpyridine thiosemicarbazones[4] and the second set includes derivatives of 4′-substituted-5-hydroxy-2-formyl pyridine thiosemicarbazone[14]. The compounds of both set are included in Tables 1 and 2, respectively.

1-Formyl isoquinoline thiosemicarbazone derivatives[15,16] are also divided into two different sets, on the basis of the measurement of their biological activity and are presented in Table-3 (biological activity has been measured in terms of K_{50}) and Table-4 (biological activity in terms of I_{50}). Thus, the QSAR study of all the four sets has been discussed as below.

First set: In this set 21 derivatives of 5-substituted-2-formyl pyridine thiosemicarbazones (Fig. 1) have been taken for study. The values of various descriptors evaluated by PM3 method and included in Table-1, along with their reported inhibitory activity I_{50}.

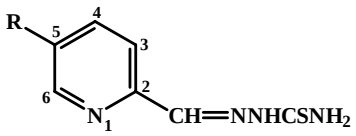

Fig. 1. 5-Substituted-2-formylpyridine thiosemicarbazones

The best fitted regression equation given below is chosen as QSAR model to predict the activity of the compounds of this set.

$$pI_{50} = -0.00133044*\Delta H_f+0.0187545*TE+1.62882*\varepsilon HOMO+ 0.958398*\mu+17.7454$$
$$rCV^2 = 0.70259$$
$$r^2 = 0.901714 \quad (9)$$

This model includes the heat of formation (ΔH_f) as first, total energy (TE) as second, εHOMO as third and chemical potential (μ) as fourth descriptor. The predicted biological activity (pI_{50}) from eqn. 9 is also reported in Table-1. MLR analysis of this set using regression eqn. 9 provides best result and the predicted activity is close to observed activity. On the basis of statistical quality of result, it is clear that one can use this equation to predict the inhibitory activity of any hypothetical compound of this series.

TABLE-1
RDR INHIBITORY ACTIVITIES OF 5-SUBSTITUTED
2-FORMYLPYRIDINE THIOSEMICARBAZONES [Ref. 4]

Compd. No.	Substituents 5-R	Observed I_{50}	Descriptors						Predicted I_{50}
			ΔH_f	TE	εHOMO	εLUMO	η	μ	
1	H	6.55	50.26	-88.51	-8.86	-1.29	3.78	5.07	6.450
2	CH_3	6.51	48.04	-95.68	-8.57	-1.14	3.71	4.86	6.574
3	C_2H_5	6.66	45.88	-102.83	-8.55	-1.12	3.71	4.84	6.454
4	Cl	6.25	50.05	-100.23	-8.90	-1.39	3.75	5.15	6.226
5	Br	6.30	58.11	-98.38	-9.06	-1.45	3.80	5.26	6.095
6	I	6.39	70.54	-97.33	-8.81	-1.41	3.70	5.11	6.366
7	CF_3	5.62	-93.89	-143.38	-9.06	-1.82	3.61	5.44	5.636
8	OCH_3	5.92	13.18	-107.88	-8.73	-1.00	3.86	4.87	6.142
9	OCF_3	5.60	-146.13	-155.64	-9.13	-1.41	3.85	5.27	5.200
10	OC_2H_5	6.07	8.22	-115.02	-8.71	-0.97	3.87	4.84	6.021
11	$O(C_2H_4O)_2C_2H_5$	5.69	-40.16	-155.81	-8.73	-1.00	3.86	4.87	5.310
12	$OOCCH_3$	5.44	-28.91	-125.35	-8.95	-1.28	3.83	5.11	5.758
13	$OOCC_2H_5$	5.28	-26.16	-132.51	-8.93	-1.25	3.84	5.09	5.621
14	*n*-$OOCC_3H_7$	5.17	-31.63	-139.67	-8.93	-1.26	3.83	5.10	5.498
15	*n*-$OOCC_{15}H_{31}$	3.96	-103.88	-225.59	-8.94	-1.26	3.83	5.10	3.982
16	$OOCCH_2OCH_3$	5.30	-60.45	-144.68	-8.92	-1.27	3.82	5.10	5.464
17	$OOCCH_2OC_2H_5$	5.25	-64.73	-151.82	-8.97	-1.29	3.83	5.13	5.290
18	$OOCCH_2N(CH_3)_2$	5.24	-25.94	-149.00	-8.88	-1.22	3.83	5.05	5.358
19	$OOCCH_2OC_6H_5$	4.89	-28.03	-173.70	-9.02	-1.37	3.82	5.19	4.808
20	$NHCOCH_3$	5.92	19.83	-122.55	-8.52	-1.02	3.75	4.77	6.113
21	$N(CH_3)_2$	6.40	47.59	-112.16	-8.59	-0.94	3.82	4.76	6.154

I_{50} = Inhibitory activity, *ΔH_f = Heat of formation in k cal/mol, η = Absolute hardness, μ = Chemical potential, TE = Total energy.

Second set: This set comprises of only 9 derivatives of 4′-substituted-5-hydroxy-2-formylpyridinethiosemicarbazone[14] (Fig. 2) and are reported in Table-2.

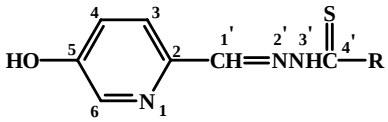

Fig. 2. 4'-Substituted-5-hydroxy-2-formylpyridinethiosemicarbazone

The values of various descriptors of compounds of this set are included in Table-2 alongwith the observed inhibitory activity. The best fitted regression equation given below is chosen as QSAR model to predict the activity of the compounds of this set.

$$pI_{50} = 0.0267616*TE-1.65195*\mu+15.7705$$
$$rCV^2 = 0.611361$$
$$r^2 = 0.796285 \quad (10)$$

This model includes TE as first and μ as second descriptor. The predicted biological activity (pI_{50}) from eqn. 10 is also reported in Table-2. MLR analysis of this set using regression eqn. 10 indicates good prediction result. The observed activity and predicted activity are also very close.

TABLE-2
RDR INHIBITORY ACTIVITIES OF 4'-SUBSTITUTED 5-HYDROXY-2-FORMYLPYRIDINE THIOSEMICARBAZONES [Ref. 14]

Compd. No.	Substituents R	Observed I_{50}	Descriptors						Predicted I_{50}
			ΔH_f	TE	εHOMO	εLUMO	η	μ	
22	NH_2	5.52	54.00	-97.96	-8.53	-0.80	3.86	4.67	5.43
23	c-$N(CH_2CH_2)_2O$	4.16	33.55	-122.80	-8.88	-1.25	3.81	5.06	4.11
24	c-NC_5H_{10}	4.38	29.51	-124.31	-8.56	-1.12	3.71	4.84	4.43
25	c-$N(CH_2CH_2)_2NCH_3$	4.14	49.34	-141.52	-8.61	-1.01	3.79	4.81	4.03
26	c-$N(CH_2CH_2)_2S$	4.09	80.41	-119.84	-8.92	-1.33	3.79	5.12	4.09
27	c-NC_4H_8	4.18	54.94	-124.65	-8.62	-1.39	3.61	5.00	4.15
28	SCH_3	4.94	55.17	-104.86	-8.76	-1.34	3.71	5.05	4.61
29	c-NCH_2CH_2	4.10	88.64	-110.58	-8.75	-1.18	3.78	4.96	4.60
30	C_6H_5	4.31	81.59	-124.70	-8.61	-1.19	3.70	4.90	4.33

I_{50} = Inhibitory activity, *ΔH_f = Heat of formation in k cal/mol, η = Absolute hardness, μ = Chemical potential, TE = Total energy.

Third set: This set comprises of 11 derivatives of 5-substituted 1-formylisoquinoline-thiosemicarbazone[15] (Fig. 3). The values of various descriptors as calculated by PM3 method are included in Table-3 alongwith their inhibitory activity in term of K_{50}.

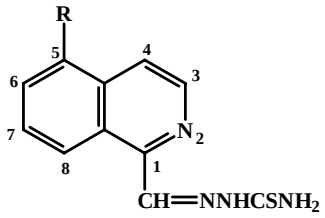

Fig. 3. 5-Substituted 1-formyl-isoquinolinethiosemicarbazone

The best fitted regression equation given below is chosen as QSAR model to predict the activity of the compounds of this set.

$$pK_{50} = -0.0422135*\Delta H_f + 0.121301*TE-0.707807*\varepsilon HOMO+21.6612$$

$$r\text{^}2 = 0.944643 \quad (11)$$

This model includes ΔH_f as first, TE as second and εHOMO as third descriptor. The predicted biological activity (pK_{50}) from eqn. 11 is close to reported activity in Table-3. MLR analysis of this set using regression eqn. 11 indicates good prediction result.

Fourth set: This set comprises of only ten derivatives of 5-subsituted-1-formyl-isoquinoline thiosemicarbazone[16] (Fig. 3). The calculated values of various descriptors alongwith their observed biological activity in terms of I_{50} are presented in Table-4. The best fitted regression equation given below is chosen as QSAR model to predict the activity of the compounds of this set.

TABLE-3
RDR INHIBITORY ACTIVITIES OF 5-SUBSTITUTED
1-FORMYLISOQUINOLINETHIOSEMICARBAZONES [Ref. 15]

Compd. No.	Substituents 5-R	Observed K_{50}	Descriptors						Predicted K_{50}
			ΔH_f	TE	εHOMO	εLUMO	η	μ	
1	$NHCOCH_3$	6.96	41.69	-157.82	-8.64	-1.06	3.78	4.85	6.875
2	NH_2	7.52	85.89	-133.20	-8.50	-1.08	3.70	4.79	7.897
3	$N(CH_3)(C_2H_5)$	6.03	66.35	-154.59	-8.33	-1.14	3.59	4.74	6.006
4	$N(C_2H_5)_2$	5.07	62.66	-161.74	-8.30	-1.15	3.57	4.72	5.271
5	$N(CH_3)COCH_3$	5.75	44.24	-164.93	-8.44	-1.15	3.64	4.79	5.761
6	$N(C_2H_5)COCH_3$	5.70	26.63	-172.08	-8.47	-1.14	3.66	4.80	5.658
7	$NHCH_3$	7.52	85.04	-140.31	-8.39	-1.16	3.61	4.77	6.992
8	NHC_2H_5	6.89	66.14	-147.48	-8.39	-1.17	3.60	4.78	6.917
9	$N(CH_3)_2$	6.64	71.39	-147.45	-8.35	-1.15	3.59	4.75	6.672
10	N-Succinimido	5.30	8.72	-181.04	-8.41	-1.03	3.69	4.72	5.292
11	N-Pyrrolidinyl	5.07	43.01	-170.67	-8.42	-1.17	3.62	4.80	5.109

I_{50} = Inhibitory activity, *ΔH_f = Heat of formation in k cal/mol, η = Absolute hardness, μ = Chemical potential, TE = Total energy.

TABLE-4
RDR INHIBITORY ACTIVITIES OF 5-SUBSTITUTED
1-FORMYLISOQUINOLINE THIOSEMICARBAZONES [Ref. 16]

Compd. No.	Substituents 5-R	Observed I_{50}	Descriptors						Predicted I_{50}
			ΔH_f	TE	εHOMO	εLUMO	η	μ	
12	$NHCOC_6H_4(p\text{-}SO_2F)$	2.15	77.79	-235.70	-8.64	-1.56	3.54	5.10	2.237
13	OSO_2CH_3	1.03	15.42	-176.28	-8.77	-1.35	3.70	5.06	1.050
14	$OCO_2C_2H_5$	0.61	-39.57	-179.99	-8.75	-1.28	3.73	5.02	0.780
15	OH	0.63	36.61	-136.00	-8.66	-1.32	3.67	4.99	0.609
16	$OCO_2C_6H_5$	1.54	-8.56	-201.86	-8.76	-1.29	3.73	5.03	1.295
17	$OCOC_6H_4(p\text{-}SO_2F)$	1.93	33.82	-238.50	-8.75	-1.53	3.60	5.14	2.003
18	$OSO_2C_6H_4(o\text{-}SO_2F)$	2.11	53.88	-254.11	-8.83	-2.07	3.37	5.45	2.135
19	$OSO_2C_6H_4(m\text{-}SO_2F)$	2.18	50.09	-254.12	-8.83	-1.91	3.46	5.37	2.179
20	$OSO_2C_6H_4(p\text{-}SO_2F)$	2.20	49.92	-254.12	-8.81	-2.05	3.37	5.43	2.118
21	$N(CH_2CH_2Cl)_2$	1.62	49.51	-192.35	-8.37	-1.15	3.61	4.76	1.592

I_{50} = Inhibitory activity, *ΔH_f = Heat of formation in k cal/mol, η = Absolute hardness, μ = Chemical potential, TE = Total energy.

$$pK_{50} = 0.00643485*\Delta H_f-0.0146568*TE+0.421728*\varepsilon LUMO-1.06071$$
$$rCV^2 = 0.95416$$
$$r^2 = 0.969369 \quad (12)$$

This model is developed by combination of ΔH_f as first, TE as second and εHOMO as third descriptor. The predicted biological activity (pK_{50}) from eqn. 12 is also reported in Table-4. MLR analysis of this set using regression eqn. 12 indicates good prediction result.

Conclusion

(**i**) The QSAR model of four set of derivatives of thiosemicabazone have been developed with reliable predictive power. (**ii**) The first set has twenty one derivatives of 5-substituted-2-formyl pyridine thiosemicarbazones and the QSAR model has

been developed by the combination of four descriptors, $*\Delta H_f$, TE, εHOMO and μ. The correlation coefficient value is 0.901. (**iii**) Second set comprises of 9 derivatives of 4′-substituted-5-hydroxy-2-formylpyridinethiosemicarbazone, the best QSAR model is obtained by the combination of two descriptors, TE and μ. The correlation coefficient value is 0.796. (**iv**) The third set consist of 11 derivatives of 5-substituted-1-formyl- isoquinoline thiosemicarbazone, the best model has been developed by combination of three descriptors, $*\Delta H_f$, *TE and *εHOMO. The correlation coefficient is 0.944. (**v**) The fourth set comprises of 10 derivatives of 5-subsituted-1-formyl-isoquinoline thiosemicarbazone. The best model is obtained by the combination of three descriptors, $*\Delta H_f$, TE and *εLUMO. The correlation coefficient is 0.969. (**vi**). No single descriptor has been noticed to provide any direct relationship with the activity of semicarbazone derivatives. The descriptor $*\Delta H_f$, has been the best descriptor in preparing QSAR model. The second best is TE and the third best is *εHOMO. (**vii**) Quantum chemical descriptors, such as absolute hardness, electronegativity and chemical potential have provided little contribution in preparing QSAR model.

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