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Retraction

Retracted: DFT Based QSAR Study of Enzyme Ribonucleoside Diphosphate Reductase

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Journal of Chemistry has retracted the article titled "DFT Based QSAR Study of Enzyme Ribonucleoside Diphosphate Reductase" [1], as it is essentially identical in technical content with a previously published paper titled "QSAR Study on Inhibitors of Enzyme Ribonucleoside Diphosphate Reductase," by Ved Prakash Singh, Durga Nath Dhar, and Ravi Kumar Srivatsava in *Asian Journal of Chemistry*, Volume 21, Issue 10, pp. 2052–2058, 2009 [2].

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DFT Based QSAR Study of Enzyme Ribonucleoside Diphosphate Reductase

MOHIUDDIN ANSARI, AHMAD KHALID RAZA KHAN and SUHAIL AHMAD KHAN

Department of Chemistry,
Maharani Lal Kunwari Post Graduate College, Balrampur, U.P., India.
ansari.mohiuddin@rediffmail.com

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Abstract: Quantum chemical descriptors such as heat of formation, energy of HOMO, total energy, absolute hardness and chemical potential in different combinations have been used to develop QSAR models of inhibitors of enzyme ribonucleoside diphosphate reductase, RDR. The inhibitors are mainly derivatives of 1-formylisoquinoline thiosemicarbazone and 2-formylpyridine thiosemicarbazone. The values of various descriptors have been evaluated with the help of Win MOPAC 7.21 software using DFT method. Multiple linear regression analysis has been made with the help of above mentioned descriptors using the same software. Regression equations have been found to be successful models as indicated by the regression coefficient r^2 having the value as high as 0.96 and cross validation coefficient r_{CV}^2 having the value approaching 0.95. The value of these two coefficients is indicative of high order of reliability for the proposed prediction. The results obtained are also validated on account of the closeness of observed and predicted inhibitory activities. The best combination of descriptors is heat of formation, total energy and energy of HOMO. Thus the prediction of suitability of inhibitors of the enzyme RDR can be made with the help of the best regression equation.

Keywords: QSAR, DFT, MLR, Inhibitor, Ribonucleoside diphosphate reductase.

Introduction

Quantitative Structure Activity Relationship, QSAR, a quantum chemical technique[1-3] is known to relate the biological activity of compounds with their molecular structure[4] and has been extensively used as predicting tool in rational drug design[5-10]. QSAR is being used in various phenomenon of science and recently it has been used to study the enzyme's inhibition[11,12]. Literature survey reveals that attempts have never been made to explore the inhibition of the enzyme ribonucleoside diphosphate reductase by inhibitors with the help of

QSAR. So we have taken this task into consideration and proceeded accordingly and have presented QSAR study of inhibitors of the enzyme, RDR, in this paper. Enzyme, RDR[13,14], is important to cell growth as it catalyses the conversion of ribonucleotides to deoxyribonucleotides[15,16] which is needed for the synthesis of DNA but when uncontrolled leads to the development of malignant growth. So the right time inhibition of RDR with a suitable inhibitor is important to avoid the development of malignancy. Hence the QSAR is invoked to design useful inhibitor (drug). A number of *α-N*-formyl heteroaromatic thiosemicarbazones are known to inhibit the action of the enzyme ribonucleoside diphosphate reductase[17,18]. QSAR study of inhibitory activity of 30 derivatives of 2-formylpyridine thiosemicarbazone and 21 derivatives of 1-formylisoquinoline thiosemicarbazone with the help of new set of descriptors; heat of formation[19], eigen value of highest occupied molecular orbital[20], eigen value of lowest unoccupied molecular orbital[21], total energy[22], absolute hardness[23,24] and chemical potential[25] against the enzyme, RDR, have been made in this paper. These descriptors have been successfully employed for QSAR study recently[8].

Theory

The quantum chemical descriptors such as 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) are defined as follows: Parr *et al.* [26] defined electronegativity as the negative of chemical potential,

$$\chi = -\mu = -\ (\partial E/\partial N)\ v(r) \tag{1}$$

The absolute hardness, η, is defined as[27],

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

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

Where, E is the total energy, N the number of electrons of the chemical species, and v(r) the external potential. The operational definitions of absolute hardness and electronegativity is as,

$$\eta = (IP-EA)\ /\ 2 \tag{3}$$

$$\chi = -\mu = (IP+EA)\ /\ 2 \tag{4}$$

Where, IP and EA are the ionization potential and electron affinity of the chemical species respectively. According to the Koopman's theorem, the IP is simply the eigen value of the HOMO with change of sign[27] and the EA is the eigen value of the LUMO with change of sign hence the equations 5 and 6 can be rewritten as:

$$\eta = (\varepsilon LUMO - \varepsilon HOMO)/2 \tag{5}$$

$$\chi = (\varepsilon LUMO + \varepsilon HOMO)/2 \tag{6}$$

The heat of formation is defined as:

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

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

$$E = P\ (H + F)\ /2 \tag{8}$$

Where, P is the density matrix and H is the one-electron matrix. These parameters and the charges on atoms were obtained from PM3[3] calculations.

Experimental

The study materials of this paper are inhibitors of enzyme ribonucleoside diphosphate reductase and are presented in Tables 1-4. The biological activities of these derivatives have been measured in term of inhibitory activity I_{50} and have been taken from literature. For QSAR prediction, the 3D modeling[3] and geometry optimization[28,29] of all the derivatives have been done with the help of PCMODEL software using the DFT method. All the calculations have been performed with Win MOPAC 7.21 software with the help of DFT method[30-32] by applying key words Charge = 0 Gnorm = 0.1, Bonds, Geo-OK, Vectors Density.

Results and Discussion

2-Formylpyridine thiosemicarbazone derivatives have been divided into two different sets on the basis of difference in the position of substituents. The first set includes derivatives of 5-substituted-2-formylpyridine thiosemicarbazones and the second set includes derivatives of 4'-substituted-5-hydroxy-2-formylpyridine thiosemicarbazone[33]. The derivatives of both the sets are included in Table 1 and 2 respectively.1-Formylisoquinoline thiosemicarbazone derivatives[34,35] have also been 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.

Table 1. RDR inhibitory activities of 5-substituted 2-formylpyridine thiosemicarbazones.

Derivatives No.	Substitutents 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/mole, η-Absolute hardness, μ-Chemical potential and TE-Total energy.*

Table 2. RDR Inhibitory Activities of 4'-substituted 5-hydroxy-2-formylpyridine thiosemicarbazones.

Derivative No.	Substitutents R	Observed	Descriptors						Predicted
		I_{50}	ΔH_f	TE	εHOMO	εLUMO	η	μ	I_{50}
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/mole, η-Absolute hardness, μ-Chemical potential and TE-Total energy.*

Table 3. RDR Inhibitory Activities of 5-substituted 1- formylisoquinoline thiosemi- carbazones.

Derivative No.	Substitutents 5-R	Observed	Descriptors						Predicted
		K_{50}	ΔH_f	TE	εHOMO	εLUMO	η	μ	K_{50}
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

*K_{50} -Inhibitory activity, *ΔH_f -Heat of formation in k.cal/mole, η-Absolute hardness, μ-Chemical potential and TE-Total energy.*

First set

In this set, twenty one derivatives of 5-substituted-2-formylpyridine thiosemicarbazones (Figure 1) have been taken for study. The values of various descriptors evaluated by DFT method are included in Table 1 along with their reported inhibitory activity I_{50}.

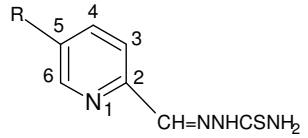

Figure 1. 5-Substituted-2-formylpyridine thiosemicarbazones.

Table 4. RDR Inhibitory Activities of 5-substituted 1-formylisoquinoline thiosemicarbazones.

Derivative No.	Substitutents 5-R	Observed	Descriptors						Predicted
		I_{50}	ΔH_f	TE	εHOMO	εLUMO	η	μ	I_{50}
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/mole, η-Absolute hardness, μ–Chemical potential and TE-Total energy.*

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

$$pI_{50} = 0.00133044*\Delta H_f + 0.0187545*TE + 1.62882*\varepsilon HOMO + 0.958398*\mu + 17.7454 \quad (9)$$

$r_{CV}^2 = 0.70259$

$r^2 = 0.901714$

This model includes the ΔH_f as first, TE as second, εHOMO as third and μ as fourth descriptor. The predicted biological activity (pI_{50}) from equation (9) is also reported in Table 1. MLR analysis of this set using regression equation (9) provides best result and the predicted activity is very close to observed activity. This is also clear from the Figure 2, which shows the graphical correlation between the observed and predicted activities. 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.

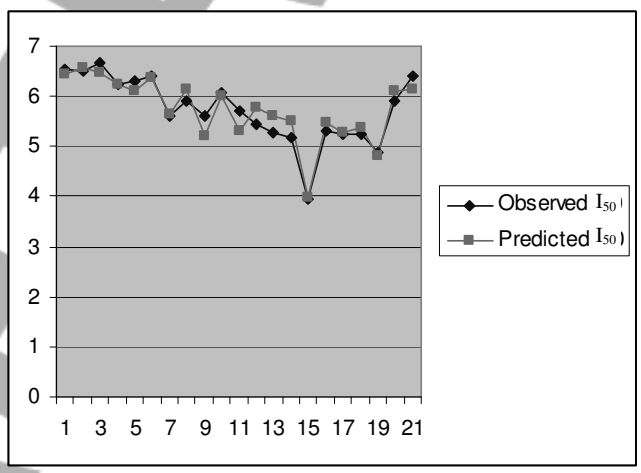

Figure 2. Graphical representation of observed activity and predicted activity of first set.

Second Set

This set comprises of only nine derivatives of 4'-substituted-5-hydroxy-2-formylpyridine thiosemicarbazone (Figure 3) and are reported in Table 2.

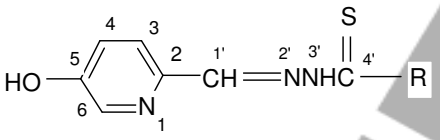

Figure 3. 4'-Substituted-5-hydroxy-2-formylpyridine thiosemicarbazone

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

$$pI_{50}=0.0267616*TE-1.65195*\mu+15.7705 \quad (10)$$

$$r_{CV}^2=0.611361$$

$$r^2=0.796285$$

This model includes TE as first and μ as second descriptor. The predicted biological activity (pI_{50}) from equation (10) is also reported in Table 2. MLR analysis of this set using regression equation (10) provides good prediction result. The observed activity and predicted activity are very close as seen from the Figure 4, which shows the graphical correlation between the observed and predicted activities.

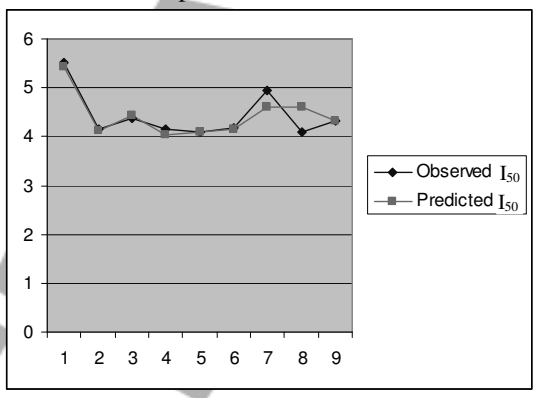

Figure 4. Graphical representation of observed activity and predicted activity of second set.

Third set

This set comprises of eleven derivatives of 5-substituted-1-formylisoquinoline thiosemicarbazone (Figure 5). The values of various descriptors calculated by PM3 method are included in Table 3 along with their inhibitory activities in term of K_{50}.

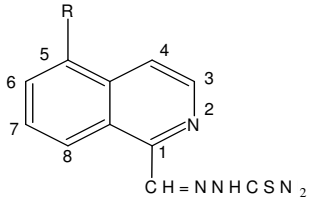

Figure 5. 5-Substituted 1-formylisoquinoline thiosemicarbazone.

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

$$pK_{50}=-0.0422135*\Delta H_f +0.121301*TE-0.707807*\varepsilon HOMO+21.6612 \quad (11)$$

$$r_{CV}^2=0.899642$$

$$r^2=0.944643$$

This model includes ΔH_f as first, TE as second, and εHOMO as third descriptors. The predicted biological activity (pK_{50}) from equation (11) is very close to reported activity and is reported in Table 3. MLR analysis of this set using regression equation (11) provides best prediction results. This is also clear from the Figure 6, which shows the graphical correlation between the observed and predicted activities.

Fourth set

This set comprises of only ten derivatives of 5-subsituted-1-formylisoquinoline thiosemicarbazone (Figure 5). The calculated values of various descriptors along with their observed biological activity in terms of I_{50} are presented in Table 4. The best fitted regression equation given below has been chosen as QSAR model to predict the activity of the compounds of this set.

$$pK_{50}=0.00643485*\Delta H_f-0.0146568*TE+0.421728*\varepsilon LUMO-1.06071 \quad (12)$$

$$r_{CV}^2=0.95416$$

$$r^2=0.969369$$

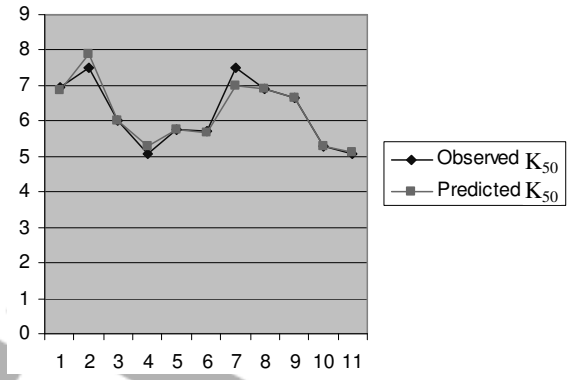

Figure 6. Graphical representation of observed activity and predicted activity of third set

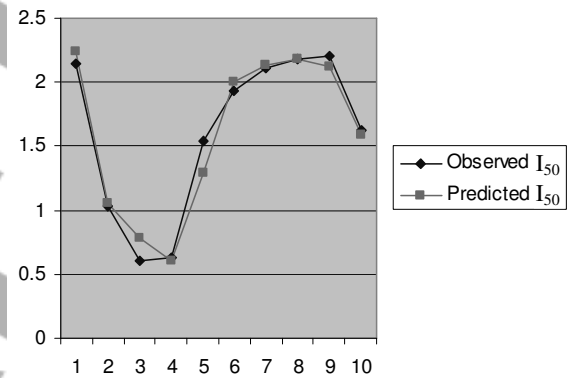

Figure 7. Graphical representation of observed activity and predicted activity of fourth set.

This model is developed by combination of ΔH_f as first, TE as second, and εHOMO as third descriptors. The predicted biological activity (pK_{50}) from equation (12) is also reported in Table 3. MLR analysis of this set using regression equation (12) provides excellent prediction results. The quality of prediction and closeness between observed and predicted activities are well demonstrated by Figure 7, which shows the graphical correlation between the observed and predicted activities.

Conclusion

1. The QSAR model of four sets of derivatives of thiosemicabazone has been developed with reliable predictive power.
2. The first set has twenty one derivatives of 5-substituted-2-formylpyridine 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.
3. The second set comprises of nine derivatives of 4'-substituted-5-hydroxy-2-formylpyridine thiosemicarbazone and the best QSAR model is obtained by the combination of two descriptors, TE and μ. The correlation coefficient value is 0.796.
4. The third set consists of eleven derivatives of 5-substituted-1-formyl isoquinoline thiosemicarbazone and the best QSAR model has been developed by combination of three descriptors, $*\Delta H_f$, *TE and *εHOMO. The correlation coefficient is 0.944.
5. The fourth set comprises of ten derivatives of 5-subsituted-1-formyl isoquinoline thiosemicarbazone and the best QSAR model is obtained by the combination of three descriptors, $*\Delta H_f$, TE and *εLUMO. The correlation coefficient is 0.969.
6. No single descriptor has been noticed to provide any direct relationship with the activity of thiosemicarbazone 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.
7. Quantum chemical descriptors such as absolute hardness, electronegativity and chemical potential have provided little contribution in preparing QSAR model.

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