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Quantitative structure activity relationship of aroyl-pyrrolyl-hydroxy-amide derivatives

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ABSTRACT

In this article we have done QSAR study of ten derivative of Aroyl-Pyrrolyl-Hydroxy-Amide with the help of Quantum chemical parameters. For QSAR prediction, the 3D modeling and geometery optimization of all the compounds have been done with the help of PCModel software using PM3 hamiltonian. The MOPAC calculations have been performed with WINMOPAC 7.21 software, by applying keywords PM3 Charge=0 Gnorm=0.1, Bonds, Geo-OK, Vectors density. Various QSAR model have been obtained with the help of MLR analysis. Only ten models are reported on the basis of correlation coefficient. Model no. ten has been recognized is the best model on the basis of statistical parameters. This model has been evaluated by molecular weight, total energy, HOMO energy and absolute hardness.

INTRODUCTION

QSAR study of phenols with the help of quantum mechanical parameter has recently been made by Singh et al[1]. They developed QSAR models having high degree of predicted power with correlation coefficient value above 0.88. QSAR[2-5] has become increasingly helpful in understanding many aspect of chemical biological activity in drug research and pharmacological sciences[6]. In this present work we have done quantitative structure activity relationship study of some novel heterocyclic compound i.e. Aroyl- Pyrrolyl-, Hydroxy-Amide derivatives with the help of quantum chemical descriptors. Various QSAR model are obtained by multi linear regression analysis. Only ten QSAR model have been selected on the basis of correlation coefficient.

EXPERIMENTAL

The study material for this paper are ten Aroyl-Pyrrolyl-, Hydroxy-Amide derivatives which have been arranged on the basis of 50% inhibitory concentration (IC_{50}). For QSAR study we have been used following descriptors:

1- Molecular weight (M_W)
2- Heat of formation (H_f^0)
3- Total energy (E_T)
4- HOMO value (εHOMO)
5- LUMO value (εLUMO)
6- Electronegativity (χ)
7- Absolute hardness (η)

For QSAR prediction, the 3D modeling and geometery optimization of all the compounds have been done with the help of PCModel software using PM3 hamiltonian[7]. The MOPAC calculations have been performed with WINMOPAC 7.21 software, by applying keywords PM3 Charge=0 Gnorm=0.1, Bonds, Geo-OK, Vectors density. The values of the above descriptors are calculated by solving the equations given below:

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In DFT, the electronegativity, commonly known to a chemist, is define as the negative of a partial derivative of energy E of an atomic or molecular system with respect to the number of electrons N with a constant external potential $_{v(r)}$[8]

$$\mu = -\chi = -(\delta E / \delta N)_{v(r)} \quad (1)$$

In accordance with the earlier work of Iczkowski and Margrave[9], it should be stated that when assuming a quadratic relationship between E and N and in a finite difference approximation, Eq. 1 may be rewritten as

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

where IE and EA are the vertical ionization energy and electron affinity, respectively, thereby recovering the electronegativity definition of Mulliken[10]. Moreover, a theoretical justification was provided for Sandersons principle of electronegativity equalization, which states that when two or more atoms come together to form a molecule, their electronegativities become adjusted to the same intermediate value[11-13]

The absolute hardness η is define as[14]

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

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 and the EA is the eigen value of the LUMO with change of sign hence the equations 2 and 3 can be written as

$$\chi = (\varepsilon LUMO+\varepsilon HOMO)/2 \quad (4)$$

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

The heat of formation is defined as:

$$\Delta H_f^0 = E_{elect.}+E_{nuc.}-E_{isol.}+E_{atom} \quad (6)$$

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. The total electronic energy of the system is given by[15]

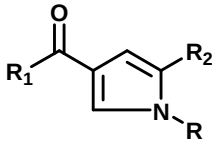
$$E_T = 1/2\, R(H+F) \quad (7)$$

where P is the density matrix and H is the one-electron matrix. F is fock matrix.

For regression analysis, we used project leader programme associated with CAChe pro software of Fujitsu. Various regression equation were developed for the prediction of activity. The values of descriptors have been calculated by the above equation.

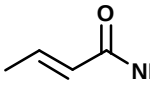
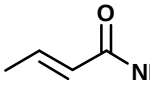
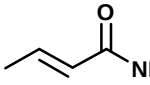
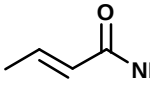
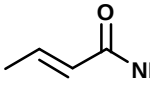
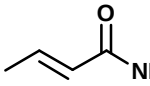
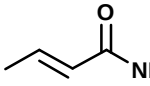
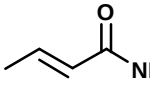
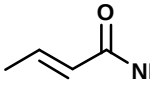
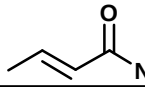
RESULT AND DISCUSSION

The parent skeleton of Aroyl-Pyrroyl-Hydroxy-Amide[16] is given below:



The 10 derivatives of Aroyl-Pyrroyl-Hydroxy-Amide and their observed biological activity in terms of inhibitory growth concentration (PIC^{50}). The values of various quantum chemical descriptors of Aroyl-Pyrroyl-Hydroxy-Amide derivatives, along their observed biological activity are placed in TABLE 1. The quantities of descriptors in a number of combinations have been used for MLR analysis and QSAR models. Out of them only

TABLE 1 : Aroyl-pyrroyl-hydroxy-amide derivatives with their observed activity

Comp.No.	R	R1	R2	IC_{50}
1	CH_3	Ph		3.8
2	CH_3	4-Cl-Ph		2.4
3	CH_3	4-F-Ph		3.8
4	CH_3	4-O_2N-Ph		3.9
5	CH_3	4CH_3-Ph		1.9
6	CH_3	4-CH_3OPh		2.9
7	CH_3	4Me_2-N-Ph		2.4
8	CH_3	Ph-CH_3		0.1
9	CH_3	Ph.CH═CH		1.0
10	H	Ph		5.0

10 QSAR models presented below, have been found to have very high-predicted power. The predicted activities of these QSAR models are placed in TABLE 3.

QSAR model

The predicted activity PA_1 is calculated by solving regression equation 1

PA_1=-0.000783155* H_f +0.00515297* MW -1.89565

rCV^2=0.796811

r^2=0.813363

Equation 1 involves heat of formation as first descriptor and molecular weight as second descriptor. The values of quantum chemical descriptos are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.813363 and cross validation coefficient 0.796811. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_1 are listed in the TABLE 3.

TABLE 2 : Values of various quantum chemical descriptors with observed activity (IC_{50})

N0.	MW	H_f	E_T	εHOMO	ε LUMO	χ	η	IC_{50}
1	270.287	-42.788	-146.753	-9.101	-0.774	-4.937	4.163	3.8
2	256.26	-44.933	-139.63	-9.173	-0.793	-4.983	4.19	2.4
3	304.732	-49.462	-143.74	-9.156	-0.818	-4.987	4.169	3.8
4	288.278	-87.011	-158.23	-9.187	-0.841	-5.014	4.173	3.9
5	315.285	-70.266	-178.569	-9.405	-1.349	-5.377	4.028	1.9
6	284.314	-52.425	-153.941	-9.081	-0.76	-4.921	4.16	2.9
7	300.313	-83.312	-166.13	-9.081	-0.763	-4.922	4.159	2.4
8	313.355	-49.261	-170.447	-8.649	-0.725	-4.687	3.962	0.1
9	284.314	-52.186	-153.941	-9.086	-0.764	-4.925	4.161	1
10	372.423	-7.688	-195.47	-8.828	-0.806	-4.817	4.011	5

TABLE 3 : Values of predicted activities from PA1 to PA10

Compd.No.	PA_1	PA_2	PA_3	PA_4	PA_5	PA_6	PA_7	PA_8	PA_9	PA_{10}
1	2.639	2.338	2.546	2.711	2.628	2.693	2.498	2.502	2.557	2.633
2	2.492	2.163	2.403	2.72	2.468	2.63	2.356	2.547	2.584	2.564
3	2.831	2.971	2.641	3.227	2.837	2.919	3.993	3.328	2.737	2.616
4	2.165	2.561	2.737	2.076	2.193	2.053	2.756	3.689	2.616	3.328
5	2.625	1.299	1.608	3.731	2.493	3.345	1.505	2.114	2.055	1.974
6	2.62	2.501	2.36	2.576	2.633	2.565	2.903	2.739	2.527	2.616
7	2.317	1.975	1.4	1.957	2.374	2.04	3.075	1.652	0.947	1.996
8	2.906	2.549	2.533	1.473	2.946	2.388	0.537	0.363	1.762	0.133
9	2.623	2.501	2.367	2.601	2.635	2.579	2.92	2.769	2.546	2.647
10	3.982	4.173	4.283	4.128	3.993	3.988	4.658	4.814	4.522	4.936

QSAR model

The predicted activity PA_2 is calculated by solving regression equation 2

PA_2=0.00515297* MW -0.491437* E_T

-1.89565

rCV^2=0.796811

r^2=0.813363

Equation 2 involves molecular weight as first descriptor and total energy as second descriptor. The values of quantum chemical descriptos are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.813363 and cross validation coefficient 0.796811. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_2 are listed in the TABLE 3.

QSAR model

The predicted activity PA_3 is calculated by solving regression equation 3

PA_3=-0.000488281* H_f+0.00515297* MW -0.0625* E_T

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-1.91301

rCV^2=0.790595

r^2=0.811212

Equation 3 involves heat of formation as first descriptor and molecular weight is second descriptor. The third descriptor is total energy. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.811212 and cross validation coefficient 0.790595. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_3 are listed in the TABLE 3.

QSAR model

The predicted activity PA_4 is calculated by solving regression equation 4

PA_4=-0.00071984* H_f+0.00521657* MW -0.0480385* εHOMO -2.33504

rCV^2=0.764644

r^2=0.815118

Equation 4 involves heat of formation as first descriptor and the second and third descriptors is molecular weight and HOMO energy respectively. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.815118 and cross validation coefficient 0.764644. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_4 are listed in the TABLE 3.

QSAR model

The predicted activity PA_5 is calculated by solving regression equation 5

PA_5=-0.000842964* H_f+0.00534636* MW +0.0670735* ε LUMO -1.9109

rCV^2=0.744483

r^2=0.822225

Equation 5 involves heat of formation as first descriptor and molecular weight as second descriptor. The third descriptor is LUMO energy. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.822225 and cross validation coefficient 0.744483. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA1 are listed in the TABLE 4. Graph between the observed activity and the predicted activities PA_5 are listed in the TABLE 3.

QSAR model

The predicted activity PA_6 is calculated by solving regression equation 6

PA_6=-0.000765366* H_f+0.00532853* MW +0.0834568* χ-2.28681

rCV^2=0.743636

r^2=0.8204

Equation 6 involves heat of formation as first descriptor and molecular weight as second descriptor. The third descriptor is electronegativity. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.8204 and cross validation coefficient 0.743636. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_6 are listed in the TABLE 4

TABLE 4 : Correlation summary of best QSAR models

PA	rcv^2	r^2	VU	SE	SEE	t-Value	p-Value	DOF
1	0.796811	0.813363	H_f, MW	0.996	1.477	1.0029	0.1726	0.0007
2	0.796811	0.813363	MW, E_T	0.594	1.313	1.843	0.0512	0.2105
3	0.790595	0.811212	H_f, MW, E_T	0.561	1.292	1.940	0.0442	0.2350
4	0.764644	0.815118	H_f, MW, εHOMO	0.543	1.313	1.841	0.0514	0.2098
5	0.744483	0.822225	H_f, MW, ε LUMO	0.990	1.476	1.010	0.1709	0.0024
6	0.743636	0.8204	H_f, MW, χ	0.815	1.438	1.225	0.1276	0.0329
7	0.778457	0.819805	H_f, MW, η	0.282	0.977	3.543	0.0038	0.5629
8	0.764744	0.815118	MW, E_T, εHOMO	0.237	0.849	4.388	0.0012	0.6698
9	0.744483	0.822225	MW, E_T, η	0.441	1.195	2.398	0.0217	0.3455
10	0.730729	0.822328	MW, E_T, εHOMO, η	0.237	0.848	4.3966	0.0011	0.6707

QSAR model

The predicted activity PA_7 is calculated by solving regression equation 7

PA_7=-0.000932053* H_f+0.00525805* MW +0.134769*η-1.29462

rCV^2=0.778457

r^2=0.819805

Equation 7 involves heat of formation as first descriptor and molecular weight as second descriptor. The third descriptor is absolute hardness. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.819805 and cross validation coefficient 0.778457. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_7 are listed in the TABLE 3

QSAR model

PA_8=0.00521657* MW -0.451707* E_T -0.0480385* εHOMO -2.33504

rCV^2=0.764644

r^2=0.815118

Equation 8 involves molecular weight as first descriptor and total energy as second descriptor. The third descriptor is HOMO energy. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.815118 and cross validation coefficient 0.764644. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_8 are listed in the TABLE 4.

QSAR model

The predicted activity PA_9 is calculated by solving regression equation 9

PA_9=0.00534636* MW -0.528968* E_T +0.0670735*η-1.9109

rCV=0.744483

r^2=0.822225

Equation 9 involves molecular weight as first descriptor and total energy as second descriptor. The third descriptor is absolute hardness. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.813363 and cross validation coefficient 0.796811. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_9 are listed in the TABLE 3.

QSAR model

The predicted activity PA_{10} is calculated by solving regression equation 10

PA_{10}=0.00534135MW-0.542908* E_T-0.0578958* εHOMO +0.143306*η-1.78611

rCV^2=0.730729

r^2=0.822328

Equation 10 involves molecular weight as first descriptor and total energy as second descriptor. The third and fourth descriptor are HOMO energy and absolute hardness. The values of quantum chemical descriptors are presented in TABLE 2. The reliability of this regression model can be tested from correlation coefficient 0.822328 and cross validation coefficient 0.730729. These coefficients indicate that this regression gives good regression result. The values of the predicted activities PA_{10} are listed in the TABLE 3.

CONCLUSION

In this present study QSAR analysis of Aroyl-Pyrroyl-Hydroxy-Amide derivatives with the help of quantum chemical parameter. The best ten model have been selected. Out of ten QSAR model, model no. 10 is the best model on the basis of correlation coefficient which is greater than 0.822. The predicted activity is close to observed activity. This model is evaluated by with the help of molecular weight, total energy, HOMO energy and absolute hardness, which is presented in TABLE 4.

REFERENCES

[1] F.A.Pasha, H.K.Srivastava, P.P.Singh; Bioorg.Med. Chem., **13**, 6823 **(2005)**.

[2] P.P.Singh, H.K.Srivastava, F.A.Pasha; Bioorg.Med. Chem., **12**, 171 **(2004)**.

[3] P.P.Singh, F.A.Pasha, H.K.Srivastava; QSAR & Comb.Sci., **22**, 843 **(2003)**.

[4] H.K.Srivastava, F.A.Pasha, P.P.Singh; Int.J. Quantum.Chem., **103**, 237 **(2005)**.

[5] F.A.Pasha, H.K.Srivastava, P.P.Singh; Mol.Div., **9**, 215 **(2005)**.
[6] Y.G.Smeyers, L.Bounian, N.J.Smeyers, A.Ezzamarty, Hernandez-Laguna, C.I.Sainz-Diaz; Eur.J.Med.Chem., **33**, 103 **(1998)**.
[7] J.J.P.Stewart; MOPAC 2002, Fujitsu Limited, Tokyo, Japan, **(2002)**.
[8] R.G.Parr, R.A.Donnelly, M.Levy, W.E.Palke; J.Chem.Phys., **68**, 3801 **(1978)**.
[9] R.P.Iczkowski, J.L.Margrave; J.Am.Chem.Soc., **83**, 3547 **(1961)**.
[10] R.S.J.Mulliken; Chem.Phys., **2**, 782 **(1934)**.
[11] R.T.Sanderson; Science, **121**, 207 **(1995)**.
[12] R.T.Sanderson; Chemical Bonds and Bond Energy, Academic Press: New York, **(1976)**.
[13] R.T.Sanderson; Polar Covalence, Academic Press: New York, **(1983)**.
[14] R.G.Parr, R.G.Pearson; J.Am.Chem.Soc., **105**, 7512 **(1983)**.
[15] B.W.Clare; Aust.J.Chem., **48**, 1385 **(1995)**.
[16] Rino Rango, Silvia Simioni, Sergeo Valente, Silvio Massa, Antonello Mai; J.Chem.Inf.Model., **46**, 1420-1430 **(2006)**.