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QSAR study of aroyl-pyrrolyl-hydroxy-amide (APHA) derivatives with the help of PM3 based descriptors

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ABSTRACT

In this present work, we have taken a ten Aroyl-Pyrrolyl-Hydroxy-Amide derivatives and developed QSAR models with the help of Quantum chemical descriptors.The values of quantum chemical descriptors are directly obtained by CAChe software. The first set containsPyrrole derivatives & the correlation coefficient of this set is above 0.81.

KEYWORDS

APHA;
Activity;
Pyrrole QSAR;
Quantum chemical;
Pharmacological.

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] We in this paper present the QSAR study of 10 derivatives of Aroyl-Pyrrolyl-Hydroxy-Amide, with the help of new set of descriptors: heat of formation, total energy, eigen value of highest occupied molecular orbital, eigen value of lowest unoccupied molecular orbital, electronegativity and absolute hardness. These descriptors have been successfully employed for QSAR study recently.

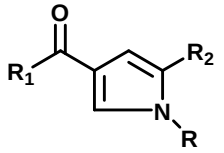


Figure 1 : The parent skeleton of aroyl - pyrrolyl - hydroxy-amide

EXPERIMENTAL

The study materials 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 (T_E)
4. HOMO value (εHOMO)
5. LUMO value (εLUMO)
6. Electronegativity (c)
7. Absolute hardness (h)

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:

In DFT, the electro negativity, 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 signand 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 B.W.Clare[15].

$$TE = 1/2\, P(H+F) \quad (7)$$

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-Pyrrolyl-Hydroxy-Amide are given in figure 1.

The 10 derivatives of Aroyl-Pyrrolyl-Hydroxy-Amide and their observed biological activity in terms of inhibitory growth concentration (PIC50). The values of various quantum chemical descriptors of Aroyl-Pyrrolyl-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 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 eq. 1

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

rCV^2=0.796811

r^2=0.813363

Eq. 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 r^2=0.813363 and cross validation coefficient rCV^2=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.

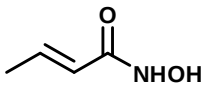
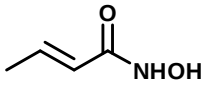
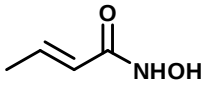
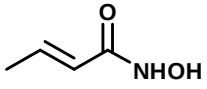
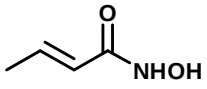
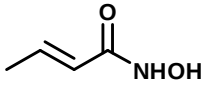
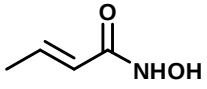
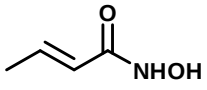
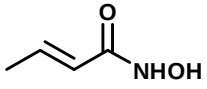
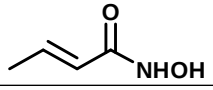
QSAR model

The predicted activity PA_2 is calculated by solving regression eq. 2

PA_2=0.00515297* MW -0.491437* E_T-1.89565

rCV^2=0.796811

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

Comp.no.	R	R_1	R_2	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

r^2=0.813363

Eq. 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 r^2=0.813363 and cross validation coefficient rCV^2=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 eq. 3

PA_3=-0.000488281* H_f+0.00515297* MW-0.0625* E_T-1.91301

rCV^2=0.790595

r^2=0.811212

Eq. 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 r^2=0.811212 and cross validation coefficient rCV^2=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.

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

No.	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

QSAR model

The predicted activity PA_4 is calculated by solving regression eq. 4

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

rCV^2=0.764644

r^2=0.815118

Eq. 4 involves heat of formation as first descriptor and the second and third descriptors are 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 r^2=0.815118 and cross validation coefficient rCV^2=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 eq. 5

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

rCV^2=0.744483

TABLE 3 : Values of predicted activities of aroyl-pyrrolyl-hydroxy-amide derivatives

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

TABLE 4 : Combinations of descriptors providing the QSAR models

PA	rCV^2	r^2	Variables	VC
1	0.796811	0.813363	Heat of formation, Molecular weight	2
2	0.796811	0.813363	Molecular weight, Total energy	2
3	0.790595	0.811212	Heat of formation, Molecular weight, Total energy	3
4	0.764644	0.815118	Heat of formation, Molecular weight, HOMO energy	3
5	0.744483	0.822225	Heat of formation, Molecular weight,LUMO energy	3
6	0.743636	0.8204	Heat of formation, Molecular weight,Electronegativity	3
7	0.778457	0.819805	Heat of formation, Molecular weight,Absolute hardness	3
8	0.764644	0.815118	Total energy, Molecular weight, HOMO energy	3
9	0.744483	0.822225	Molecular weight,Total energy,Absolute hardness	3
10	0.730729	0.822328	Molecular weight,Total energy,HOMO energy	3

r^2=0.822225

Eq. 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 r^2=0.822225 and cross validation coefficient rCV^2=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 eq. 6

$PA_6 = -0.000765366 * H_f + 0.00532853 * MW + 0.0834568 * \chi - 2.28681$

rCV^2=0.743636

r^2=0.8204

Eq. 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 r^2=0.8204 and cross validation coefficient rCV^2=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

QSAR model

The predicted activity PA_7 is calculated by solving regression eq. 7

$PA_7 = -0.000932053 * H_f + 0.00525805 * MW + 0.134769 * \eta - 1.29462$

rCV^2=0.778457

r^2=0.819805

Eq. 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. T he reliability of this regression model can be tested from correlation coefficient r^2=0.819805 and cross validation coefficient rCV^2=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

The predicted activity PA_8 is calculated by solving regression eq. 8

$PA_8 = 0.00521657 * MW - 0.451707 * E_T - 0.0480385 * \varepsilon HOMO - 2.33504$

rCV^2=0.764644

r^2=0.815118

Eq. 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 r^2=0.815118 and cross validation coefficient rCV^2=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 eq. 9

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

rCV^2=0.744483

r^2=0.822225

Eq. 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 r^2=0.813363 and cross validation coefficient rCV^2=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 eq. 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

Eq. 10 involves molecular weight as first descriptor and total energy as second descriptor. The third and fourth descriptor is 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 r^2=0.822328 and cross validation coefficient rCV^2=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

The quality of prediction of QSAR model is adjudged by the values of cross validation and correlation coefficients. The values of various predicted activities of ten *APHA* derivatives are collectively shown in TABLE 3. The combinations of descriptors providing the various models are included in TABLE 4. It is clearly indicated that the entire QSAR model from each sets provide high degree of dependability as they have correlation value is above 0.81.

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.Mulliken; J.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)**.