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RESEARCH ARTICLE

Inhibitor Based Comparative QSAR Study of *O*-phosporylated Oxime Derivatives Against the Enzyme Acetylcholinesterase

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Abstract: Quantum chemical reactivity descriptors such as molecular weight, heat of formation, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity have been used to develop QSAR model of the inhibitors of the enzyme, acetylcholinesterase, AchE. The inhibitors used are *O*-phosphorylated oxime derivatives. The inhibitory activities of various derivatives against the enzyme, acetylcholinesterase has been taken from literature. The values of various descriptors have been evaluated by using Win MOPAC 7.21 software with the help of PM3, PM5 and DFT methods. Thus three different methods have been employed to certify the reliability of QSAR study. Multiple linear regression analysis has been made with the help of above mentioned descriptors using the same software. Three different sets of regression equations are thus obtained corresponding to the three different methods. The first set of models has been drawn up with the help of PM3 calculations and the best model in this set having the correlation coefficient, r^2as 0.78 and the cross-validation coefficient, r^2cv as 0.60 has been chosen as the QSAR model. The second set of models has been drawn up with the help of PM5 calculations and the best model in this set having the correlation coefficient, r^2as 0.78 and the cross-validation coefficient, r^2cv as 0.63 has been chosen as the QSAR model. Finally, the third set of models has been developed with the help of DFT calculations for the same series of derivatives by using B88-PW91 GGA energy functional with the DZVP basis set. The best model by DFT method has correlation coefficient, r^2 as 0.79 and cross-validation coefficient, r^2cv as 0.64 and so this has been chosen as the QSAR model for this method. The DFT models have a higher predictive power than PM3 and PM5 methods as evident from the regression parameters. Present study has also been helpful in developing a relationship between electronegativity and anticholinesterase activity of *O*-phosphorylated oxime derivatives which has never been studied before.

Keywords: *O*-Phosphorylated oxime derivatives, QSAR, DFT, Acetylcholinesterase, Electronegativity

Introduction

Acetylcholinesterase, AchE, an enzyme responsible for various neurological disorders in the human beings works by breaking down the neuromessenger, acetylcholine which assists memory, thought and judgment and thus reducing the level of the same in the brain cells. Various anticholinesterases, the inhibitors of the enzyme, AchE, have been synthesized by different workers at different times and one of them being the *O*-phosphorylated oxime derivatives. Organophosphorous compounds (OPCs) including *O*-phosphorylated oxime derivatives have been widely used as anticholinesterases for treating schistosomiasis, glaucoma and Alzheimer's disease[1-3]. QSAR, a quantum chemical technique[4,5], is known to relate the biological activity of compounds with their molecular structure[6] and has been extensively used as predicting tool in rational drug design[7-11]. QSAR analysis makes it possible to determine the contributions of various chemical structural elements of the molecules to its physiological effect as well as to detect the potential role of particular derivative. QSAR has recently been used to study the enzyme's inhibition[12,13]. Literature survey reveals that attempts have never been made to explore the inhibition of the enzyme acetylcholinesterase, AchE, by inhibitors with the help of QSAR with the parameters we are employing to study. So we have taken this task into consideration and proceeded accordingly and have presented QSAR study of inhibitors of the enzyme AchE in this paper. We have taken 35 derivatives of *O*-phosporylated oxime derivatives and to corroborate the reliability of present work we have conducted a comparative QSAR study with the help of PM3[5], PM5[14] and DFT techniques. This QSAR study of inhibitory activity of 35 derivatives of *O*-phosporylated oximes against the enzyme AchE has been made with the help of new set of descriptors; heat of formation[15], eigen value of highest occupied molecular orbital[16], eigen value of lowest unoccupied molecular orbital[17], total energy[18], absolute hardness[19,20] and chemical potential[21]. These descriptors have been successfully employed for QSAR study recently[10]. Comparison of all the regression models indicate that the DFT models provide better results than other on the basis of correlation coefficient and other regression parameters and similarly on the basis of various statistical parameters.

The electronegativity, in DFT, is defined 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 $\nu(r)$[22]

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

According to the earlier work of Iczkowski and Margrave[23], eq. (1) may be rewritten as given below (assuming a quadratic relationship between E and N and in a finite difference approximation),

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

Where IE and EA are the vertical ionization energy and electron affinity respectively, which leads to the recovery of the electronegativity definition of Mullikan[24]. Moreover, a theoretical justification was provided for Sanderson's principle of electronegativity equalization, which states that when two or more atoms come together to form a molecule, their electronegativity become adjusted to the same intermediate value[25-27]. The absolute hardness[28], η, is defined as

$$\eta = 1/2\,(\delta\mu / \delta N)_{\nu(r)} = 1/2\,(\delta^2 E / \delta N^2)_{\nu(r)} \quad (3)$$

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

$$\eta = 1/2(IE - EA) \quad (4)$$

$$\chi = -\mu = -(IE + EA)/2 \quad (5)$$

Where IE and EA are the ionization energy and electron affinity of the chemical species respectively. According to Koopman's theorem, IE is simply the eigen value of HOMO with change of sign and EA is eigen value of LUMO with change of sign[29]; hence Eqs. 4 and 5 may be rewritten as

$$\eta = 1/2(\varepsilon\,LUMO - \varepsilon\,HOMO) \quad (6)$$

$$\chi = -\mu = 1/2(\varepsilon\,LUMO + \varepsilon\,HOMO) \quad (7)$$

The total energy has also been used as quantum chemical descriptor and is sum of the total electronic energy (E_{ee}) and the energy of the internuclear repulsion (E_{nr}).The total energy[19] of the system is given by

$$T_E = 1/2\ P(H+F) \quad (8)$$

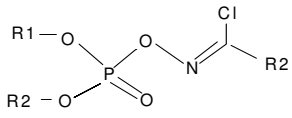
Where, P is the density matrix and H is the one-electron matrix[5].

Experimental

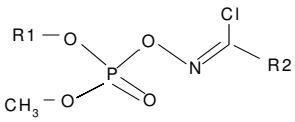
The study materials of this paper are thirty five O-phosphorylated oxime derivatives which are presented in Table 1. For QSAR prediction, the 3D modeling[5] and geometry optimization[30] of all the derivatives have been done with the help of PCMODEL software using PM3 and PM5 Hamiltonian. The MOPAC calculations have been performed by Win MOPAC 7.21 software with the help of PM3, PM5 and DFT methods by applying keywords Charge=0 Gnorm=0.1, Bonds, Geo-OK, Vectors density. The results are presented in the Tables 2-4. The statistical parameters have been calculated with the help of STATISTICA 8.0 software and the values are tabled in Table 5.

Results and Discussion

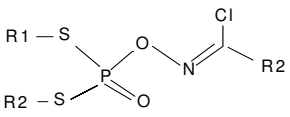
The various derivatives of O-phosphorylated oximes belong to the following three parent skeletons A, B and C.



A



B



C

Derivatives 1-19, 23 and 30-35 belong to the parent skeleton A and derivatives 20-22 and 24-25 are based on the parent skeleton B. Similarly derivatives 26-29 represent the parent skeleton C. The anticholinesterase activity values have been taken from literature[33] and are given in Table 1.

The values of all the 7 chosen descriptors for all the thirty five derivatives of *O*-phosphorylated oxime derivatives have been calculated with the help of PM3, PM5 and DFT methods.

For the development of first set of QSAR models based on PM3 Hamiltonian, we have generated various regression equations by employing all variables and the best fitted equation of this set is Eq. (9). The predicted activity (PA_{PM3}) from Eq. (9) is given in Table 2.

Table 1. The anticholinesterase activity values of *O*-phosphorylated oxime derivatives

Derivative	Skeleton	R1	R2	OA
1	A	CH_3	CH_3	4.041
2	A	$C3H_7$	CH_2Cl	5.248
3	A	C_4H_9	CH_2Cl	6.064
4	A	i-C_4H_9	CH_2Cl	5.896
5	A	C_5H_{11}	CH_2Cl	5.908
6	A	CH_3	$CHCl_2$	5.715
7	A	C_2H_5	$CHCl_2$	5.104
8	A	C_3H_7	$CHCl_2$	5.848
9	A	C_4H_9	$CHCl_2$	6.689
10	A	C_5H_{11}	$CHCl_2$	6.479
11	A	CH_3	F	4.463
12	A	C_2H_5	CH_3	3.642
13	A	C_2H_5	F	5.27
14	A	C_3H_7	F	5.179
15	A	C_4H_9	F	5.294
16	A	C_5H_{11}	F	5.994
17	A	C_2H_5	C_2H_5	3.467
18	A	C_2H_5	C_3H_7	3.632
19	A	C_2H_5	C_4H_9	3.777
20	B	C_2H_5	CH_3	3.316
21	B	C_3H_7	CH_3	3.493
22	B	C_4H_9	CH_3	3.929
23	A	C_3H_7	CH_3	4.462
24	B	C_4H_9	CH_3	3.663
25	B	C_4H_9	C_2H_5	5.911
26	C	C_2H_5	F	6.068
27	C	C_3H_7	F	6.23
28	C	C_4H_9	F	6.102
29	C	C_5H_{11}	F	6.086
30	A	C_4H_9	CH_3	3.468
31	A	i-C_4H_9	CH_3	3.435
32	A	C_5H_{11}	CH_3	4.094
33	A	CH_3	CH_2Cl	4.964
34	A	CH_3,C_2H_5	CH_2Cl	5.081
35	A	C_2H_5	CH_2Cl	4.833

A, B &C are skeletons of O-phosphorylated Oxime derivatives; R1&R2 are substituents on derivatives. OA is the observed activity

Table 2. Calculated values of quantum chemical descriptors and predicted activity of *O*-phosphorylated oximes by PM3 method

Deriva.	Skelet.	MW	H_f^0	E_T	εHOMO	εLUMO	χ	η	PA_{PM3}	OA
1	A	201.546	-219.43	-105.656	-10.629	0.31	-5.16	5.469	3.525	4.041
2	A	292.099	-252.06	-145.993	-10.795	-0.163	-5.479	5.316	5.13	5.248
3	A	320.152	-265.639	-160.289	-10.793	-0.161	-5.477	5.316	5.429	6.064

Contd…

4	A	306.125	-247.69	-153.119	-10.695	-0.073	-5.384	5.311	5.237	5.896
5	A	348.206	-279.352	-174.593	-10.793	-0.161	-5.477	5.316	5.732	5.908
6	A	270.436	-227.384	-129.145	-10.977	-0.404	-5.69	5.287	5.683	5.715
7	A	298.49	-240.716	-143.437	-10.918	-0.353	-5.635	5.282	5.684	5.104
8	A	326.544	-254.381	-157.737	-10.914	-0.35	-5.632	5.282	5.967	5.848
9	A	354.597	-267.957	-172.033	-10.911	-0.347	-5.629	5.282	6.261	6.689
10	A	382.651	-281.668	-186.329	-10.91	-0.347	-5.628	5.282	6.561	6.479
11	A	233.564	-261.947	-128.672	-10.851	-0.129	-5.49	5.361	4.86	4.463
12	A	229.6	-233.158	-119.951	-10.589	0.335	-5.127	5.462	3.612	3.642
13	A	233.564	-261.984	-128.681	-10.841	-0.116	-5.479	5.362	4.808	5.27
14	A	261.617	-275.653	-142.98	-10.837	-0.112	-5.474	5.362	5.089	5.179
15	A	289.671	-289.23	-157.277	-10.834	-0.109	-5.472	5.362	5.382	5.294
16	A	317.724	-302.941	-171.573	-10.833	-0.108	-5.471	5.362	5.68	5.994
17	A	243.627	-239.144	-127.097	-10.568	0.377	-5.095	5.473	3.686	3.467
18	A	257.653	-245.972	-134.245	-10.565	0.38	-5.092	5.472	3.822	3.632
19	A	271.68	-252.796	-141.394	-10.563	0.381	-5.091	5.472	3.967	3.777
20	B	199.574	-175.143	-100.57	-10.421	0.456	-4.982	5.439	3.736	3.316
21	B	213.6	-181.965	-107.719	-10.422	0.456	-4.983	5.439	3.894	3.493
22	B	227.627	-188.757	-114.867	-10.421	0.456	-4.983	5.439	4.047	3.929
23	A	257.653	-246.125	-134.257	-10.581	0.348	-5.116	5.465	3.906	4.462
24	B	241.654	-195.609	-122.015	-10.422	0.456	-4.983	5.439	4.2	3.663
25	B	241.654	-194.729	-122.014	-10.403	0.497	-4.953	5.45	4.136	5.911
26	C	265.685	-102.27	-122.334	-9.992	-2.575	-6.283	3.708	5.559	6.068
27	C	293.738	-116.309	-136.627	-10.032	-2.62	-6.326	3.706	6.067	6.23
28	C	321.792	-129.96	-150.923	-10.022	-2.617	-6.32	3.703	6.318	6.102
29	C	349.846	-143.691	-165.219	-10.022	-2.617	-6.32	3.703	6.622	6.086
30	A	285.707	-260.314	-148.548	-10.577	0.346	-5.116	5.461	4.168	3.468
31	A	285.707	-259.703	-148.553	-10.578	0.351	-5.113	5.465	4.2	3.435
32	A	313.761	-273.413	-162.849	-10.578	0.351	-5.113	5.465	4.502	4.094
33	A	235.991	-220.765	-117.413	-10.989	-0.32	-5.655	5.334	5.741	4.964
34	A	250.018	-231.864	-124.548	-10.822	-0.18	-5.501	5.321	4.803	5.081
35	A	264.045	-238.394	-131.694	-10.796	-0.164	-5.48	5.316	4.83	4.833

Molecular weight, MW; Heat of formation, H_f^0; Total energy, E_T ; Eigen value of HOMO, εHOMO; Eigen value of HUMO, εLUMO; Electronegativity, χ; Absolute hardness, η & Predicted activity by PM3, PA_{PM3} have been calculated by respective Eqs. given in the introduction. PA_{PM3} is the predicted activity by PM3 method. OA is the observed activity

The statistical quality of the equation is good as is evident form its cross validation and correlation coefficients 0.600025 and 0.769495 respectively.

$$PA_{PM3} = 0.0404575\ MW + 0.0446805\ H_f^0 - 0.143443\ E_T + 5.15823\chi - 10.5726\eta - 49.8201 \quad (9)$$

rCV^2=0.600025, r^2=0.769495

The second set of QSAR models have been formed with the help of PM5-based results. Various regression equations have been generated by employing all the variables and the best fitted equation of this set is Eq. 10. The predicted activity from equation 10 is reported in Table 3. The statistical quality of the equation is in a better range. The cross validation and correlation coefficients are 0.639776 and 0.786031 respectively.

Table 3. Calculated values of quantum chemical descriptors and predicted activity of *O*-phosphorylated oximes by PM5 method

Deriva	Skelet	MW	H_f^0	E_T	εHOMO	εLUMO	χ	η	PA_{PM5}	OA
1	A	201.546	-222.277	-105.85	-10.236	-1.451	-5.844	4.392	3.914	4.041
2	A	292.099	-252.587	-146.192	-10.289	-1.573	-5.931	4.358	5.088	5.248
3	A	320.152	-263.641	-160.501	-10.284	-1.57	-5.927	4.357	5.412	6.064
4	A	306.125	-261.007	-153.352	-10.267	-1.53	-5.898	4.368	5.062	5.896
5	A	348.206	-274.827	-174.809	-10.285	-1.57	-5.928	4.357	5.756	5.908
6	A	270.436	-227.691	-129.316	-10.5	-1.765	-6.133	4.367	6.043	5.715
7	A	298.49	-244.301	-143.632	-10.381	-1.665	-6.023	4.358	5.616	5.104
8	A	326.544	-254.883	-157.928	-10.382	-1.681	-6.032	4.351	5.983	5.848
9	A	354.597	-265.919	-172.236	-10.377	-1.677	-6.027	4.35	6.303	6.689
10	A	382.651	-277.116	-186.545	-10.379	-1.68	-6.03	4.35	6.659	6.479
11	A	233.564	-269.553	-128.922	-10.54	-1.783	-6.161	4.378	5.026	4.463
12	A	229.6	-237.837	-120.15	-10.118	-1.411	-5.765	4.354	3.504	3.642
13	A	233.564	-270.049	-128.912	-10.487	-1.813	-6.15	4.337	4.721	5.27
14	A	261.617	-280.613	-143.222	-10.488	-1.828	-6.158	4.33	5.089	5.179
15	A	289.671	-291.64	-157.531	-10.48	-1.823	-6.152	4.329	5.398	5.294
16	A	317.724	-302.829	-171.839	-10.482	-1.825	-6.154	4.329	5.75	5.994
17	A	243.627	-242.772	-127.307	-10.093	-1.435	-5.764	4.329	3.559	3.467
18	A	257.653	-248.421	-134.461	-10.09	-1.434	-5.762	4.328	3.712	3.632
19	A	271.68	-253.945	-141.615	-10.089	-1.432	-5.76	4.328	3.88	3.777
20	B	199.574	-175.03	-100.636	-9.915	-0.896	-5.405	4.509	3.714	3.316
21	B	213.6	-180.294	-107.791	-9.917	-0.907	-5.412	4.505	3.908	3.493
22	B	227.627	-185.8	-114.946	-9.915	-0.906	-5.411	4.505	4.072	3.929
23	A	257.653	-248.462	-134.462	-10.143	-1.39	-5.767	4.377	4.005	4.462
24	B	241.654	-191.401	-122.1	-9.917	-0.908	-5.412	4.504	4.25	3.663
25	B	241.654	-190.508	-122.1	-9.903	-0.894	-5.398	4.504	4.211	5.911
26	C	265.685	-143.482	-122.563	-9.982	-2.887	-6.434	3.547	5.38	6.068
27	C	293.738	-154.358	-136.873	-10.046	-2.901	-6.474	3.573	6.07	6.23
28	C	321.792	-165.407	-151.181	-10.029	-2.895	-6.462	3.567	6.33	6.102
29	C	349.846	-176.606	-165.489	-10.032	-2.896	-6.464	3.568	6.686	6.086
30	A	285.707	-259.184	-148.772	-10.106	-1.477	-5.792	4.315	4.141	3.468
31	A	285.707	-260.155	-148.768	-10.097	-1.371	-5.734	4.363	4.095	3.435
32	A	313.761	-271.348	-163.077	-10.099	-1.374	-5.737	4.363	4.45	4.094
33	A	235.991	-226.063	-117.579	-10.426	-1.625	-6.026	4.401	5.24	4.964
34	A	250.018	-233.845	-124.732	-10.37	-1.584	-5.977	4.393	5.059	5.081
35	A	264.045	-241.799	-131.882	-10.294	-1.565	-5.929	4.364	4.758	4.833

Molecular weight, MW; Heat of formation, H_f^0; Total energy, E_T ; Eigen value of HOMO, εHOMO; Eigen value of HUMO, εLUMO; Electronegativity, χ; Absolute hardness, η & Predicted activity by PM5, PA_{PM5} have been calculated by respective Eqs. given in the introduction. PA_{PM5} is the predicted activity by PM5 method. OA is the observed activity

$$PA_{PM5} = -0.00595495\ MW - 0.0621036\ H_f^0 + 0.033805\ E_T - 4.87527\chi + 5.59754\eta - 47.0234$$

rCV^2=0.639776, r^2=0.786031 (10)

The third set of QSAR models have been developed with the help of DFT based results and various regression equation for activity prediction have been generated by employing the variable descriptors. The best fitted equation of this set is Eq. 11. The predicted activity from equation 11 is given in Table 4. The results are reliable as is evident from the cross validation and correlation coefficients 0.647096 and 0.790293 respectively. The predicted values of activity are closer to observed values and hence are more reliable.

Table 4. Calculated values of quantum chemical descriptors and predicted activity of *O*-phosphorylated oximes by DFT method

Deriva	Skelet.	MW	H_f^0	E_T	εHOMO	εLUMO	χ	η	PA_{DFT}	OA
1	A	201.546	-197.538	-105.435	-9.938	0.065	-4.937	5.002	3.417	4.041
2	A	292.099	-217.779	-145.77	-10.011	-0.113	-5.062	4.949	5.068	5.248
3	A	320.152	-228.499	-160.09	-10.012	-0.117	-5.065	4.948	5.276	6.064
4	A	306.125	-221.786	-152.917	-10.029	-0.124	-5.077	4.953	5.386	5.896
5	A	348.206	-239.342	-174.41	-10.014	-0.12	-5.067	4.947	5.481	5.908
6	A	270.436	-200.985	-128.887	-10.105	-0.215	-5.16	4.945	5.859	5.715
7	A	298.49	-209.569	-143.177	-10.085	-0.198	-5.142	4.943	5.972	5.104
8	A	326.544	-220.031	-157.497	-10.09	-0.206	-5.148	4.942	6.222	5.848
9	A	354.597	-230.753	-171.817	-10.092	-0.21	-5.151	4.941	6.436	6.689
10	A	382.651	-241.594	-186.137	-10.093	-0.212	-5.153	4.941	6.637	6.479
11	A	233.564	-240.977	-128.459	-10.211	-0.132	-5.171	5.04	4.995	4.463
12	A	229.6	-206.087	-119.725	-9.921	0.068	-4.926	4.995	3.557	3.642
13	A	233.564	-240.977	-128.459	-10.211	-0.132	-5.171	5.039	4.995	5.27
14	A	261.617	-251.441	-142.779	-10.216	-0.146	-5.181	5.035	5.251	5.179
15	A	289.671	-262.162	-157.099	-10.219	-0.152	-5.185	5.033	5.469	5.294
16	A	317.724	-273.003	-171.419	-10.22	-0.155	-5.187	5.033	5.67	5.994
17	A	243.627	-209.862	-126.881	-9.933	0.071	-4.931	5.002	3.828	3.467
18	A	257.653	-215.253	-134.041	-9.936	0.067	-4.934	5.002	3.946	3.632
19	A	271.68	-220.635	-141.201	-9.936	0.067	-4.934	5.001	4.043	3.777
20	B	199.574	-152.094	-100.332	-9.792	0.405	-4.693	5.098	3.825	3.316
21	B	213.6	-157.334	-107.492	-9.796	0.397	-4.699	5.096	3.962	3.493
22	B	227.627	-162.709	-114.652	-9.798	0.393	-4.702	5.095	4.078	3.929
23	A	257.653	-216.566	-134.045	-9.928	0.053	-4.937	4.991	3.822	4.462
24	B	241.654	-168.131	-121.812	-9.798	0.391	-4.704	5.095	4.18	3.663
25	B	241.654	-166.267	-121.809	-9.807	0.396	-4.705	5.102	4.334	5.911
26	C	265.685	-109.609	-122.219	-9.645	-2.355	-6	3.645	5.828	6.068
27	C	293.738	-120.165	-136.541	-9.645	-2.365	-6.005	3.64	6.032	6.23
28	C	321.792	-130.947	-150.861	-9.646	-2.367	-6.006	3.639	6.229	6.102
29	C	349.846	-141.804	-165.181	-9.648	-2.368	-6.008	3.64	6.436	6.086
30	A	285.707	-227.327	-148.366	-9.934	0.062	-4.936	4.998	4.069	3.468
31	A	285.707	-227.291	-148.365	-9.931	0.047	-4.942	4.989	4.043	3.435
32	A	313.761	-238.135	-162.684	-9.932	0.044	-4.944	4.988	4.246	4.094
33	A	235.991	-198.733	-117.16	-10.024	-0.107	-5.066	4.958	4.69	4.964
34	A	250.018	-203.024	-124.305	-10.015	-0.103	-5.059	4.956	4.753	5.081
35	A	264.045	-207.308	-131.45	-10.005	-0.1	-5.052	4.953	4.809	4.833

Molecular weight, MW; Heat of formation, H_f^0; Total energy, E_T ; Eigen value of HOMO, εHOMO; Eigen value of HUMO, εLUMO; Electronegativity, χ; Absolute hardness, η & Predicted activity by DFT, PA_{DFT} have been calculated by respective Eqs. given in the introduction. PA_{DFT} is the predicted activity by DFT method. OA is the observed activity

PA_{DFT}=0.000829381 MW +0.0432 H_f^0-0.0443499 E_T -8.86813χ+8.56448η-79.5063

rCV^2=0.647096, r^2=0.790293 (11)

Finally, on the basis of values of cross validation and correlation coefficients calculated by all the three methods *viz.* PM3, PM5 and DFT, it can be stated that DFT methods have more reliable predictive power in comparison to PM3 and PM5 methods. Furthermore the statistical parameters such as standard error (SE), standard error of estimation (SEE)**,** *F*- Statistics and *p*-Value also direct us to state the same. The values of the various validating parameters of best QSAR models of each method *viz.* PM3, PM5 and DFT methods are collectively presented along with cross validation and correlation coefficients in Table 5.

Table 5. Summary of best models developed by each method along with the statistical parameters

Method	rCV^2	r^2	Standard error	Standard error of estimation	*F*-Statistics	*P*-Value	Variable used	VC
PM3	0.600	0.769	13.76	0.5553	19.34	0.0012	MW, $H_f^{0,}$ $E_{T,}$ εLUMO, χ	5
PM5	0.639	0.786	12.39	0.5346	21.33	0.0000	MW, $H_f^{0,}$ $E_{T,}$ χ, η	5
DFT	0.647	0.790	9.67	0.5308	26.90	0.0000	MW, $H_f^{0,}$ $E_{T,}$ χ, , η	5

VC is the variables counts

Also we have found a direct relationship between the electronegativity of the derivatives and the anticholinesterase activity of the derivatives, as the derivatives R_2=F, CH_2Cl and $CHCl_2$ have higher anticholinesterase activity as compared to the alkyl derivatives which is in accordance to the electronegativity principle. Thus as the electronegativity increases, anticholinesterase activity decreases, but there is no sequential rise or fall. In order to provide sequential relationship the derivatives are divided into four subgroups A, B, C and D. Derivatives 3, 5, 13, 25, 29, 30 and 31 do not follow sequential relationship. Therefore descriptor, electronegativity, provides us additional information for correlating the anticholinesterase activity for *O*-phosphorylated oxime derivatives. These results are presented in Table 6.

Table 6. Relationship between electronegativity and observed activity of *O*-phosphorylated oxime derivatives

Derivatives	Electronegativity	Anticholinesterase Activity(OA)
Subgroup-A		
17	-4.931	3.467
30	-4.936	3.468
1	-4.937	4.041
32	-4.944	4.094
35	-5.052	4.833
33	-5.066	4.964
7	-5.142	5.104
14	-5.181	5.179
15	-5.185	5.294
16	-5.033	5.994

Contd…

26	-6.00	6.068
29	-6.008	6.086
Subgroup-B		
20	-4.693	3.316
21	-4.699	3.493
18	-4.934	3.632
23	-4.937	4.462
11	-5.171	4.463
28	-6.006	6.102
Subgroup-C		
12	-4.926	3.642
19	-4.934	3.777
34	-5.059	5.081
2	-5.062	5.248
6	-5.16	5.715
27	-6.005	6.23
Subgroup-D		
31	-4.942	3.435
8	-5.148	5.848
10	-5.153	6.479

Electronegativity calculated by Eq. 7 and observed activity taken from literature

Conclusion

The study has shown that the best QSAR model (PA_{DFT} =0.000829381 MW +0.0432 H_f^0-0.0443499 E_T -8.86813χ+8.56448η-79.5063) is developed by DFT method. This model has been selected on the basis of the value of correlation coefficient (r^2 =0.790) followed by other regression parameter such as cross validation coefficient (rCV^2 = 0.647) and also on the basis of various validating statistical parameters like standard error (SE), standard error of estimation (SEE), *F*-statistics and *p*-value. This study thus concludes by saying; DFT method with quantum chemical descriptors like MW, $H_f^{0,}$ $E_{T,}$ χ and η has a better predicting power for the anticholinesterase activity of *O*-phosphorylated oxime derivatives. It is also concluded that there is a direct relationship between reported anticholinesterase activity of the *O*-phosphorylated oxime derivatives and electronegativity of the same. Thus, the electronegativity is considered to be the best quantum chemical descriptor to describe the activity of *O*-phosphorylated oxime derivatives against anticholinesterase.

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