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PM3 based QSAR analysis of PR inhibition data of cyclic ureas

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ABSTRACT

Cyclic urea is known protease inhibitor and has been used for treatment of HIV. Thirty eight derivatives of cyclic urea whose activity is reported in terms of K_i have been chosen for QSAR study. Seven descriptors, heat of formation, molecular weight, total energy, HOMO energy, LUMO energy, absolute hardness and electronegativity in different combinations have been used for development of QSAR models. Fifty nine models have been recognized to provide good predictive models. The best among them are six which have regression coefficient values above 0.82. The combination of descriptors providing these models are (i) heat of formation, total energy, HOMO energy and electronegativity (ii) heat of formation, total energy, HOMO energy and LUMO energy (iii) heat of formation, total energy, HOMO energy and absolute hardness (iv) heat of formation, total energy, LUMO energy and absolute hardness (v) heat of formation, total energy, LUMO energy and electronegativity (vi) heat of formation, molecular weight, total energy and HOMO energy. It has been noticed that best three descriptors are heat of formation, total energy and molecular weight.

KEYWORDS

Cyclic urea;
PM3;
QSAR models;
Protease inhibitors.

INTRODUCTION

An essential step in the life cycle of the human immunodeficiency virus (HIV)[1] is the proteolytic cleavage of the viral polyprotein gene products of *gag* and *gag-pol* into active structural and replicative proteins[1,2]. The finding that a viral-encoded protease is responsible for processing these precursors, and that its inactivation produces immature, noninfectious viral particles, elicited an intense search for synthetic inhibitors. The first competitive inhibitors of HIV protease (PR) were transition-state analogs (peptidomimetics) in which the scissile bonds were replaced with nonhydrolyzable isosteres such as a reduced amide, phosphinate, hydroxyethylene, dihydroxyethylene, statine, and hydroxyethylamine[3-5]. Recently, the Food and Drug Administration (FDA) has approved the use of four peptidomimetic protease inhibitors (saquinavir, ritonavir, indinavir, and nelfinavir) to treat HIV infection. Although these compounds are potent inhibitors of the wild-type protease, their therapeutic benefit is, in most cases, short-lived because they select for variants of HIV that have a reduced sensitivity toward inhibitors, as a result of mutations within the HIV protease sequence[6-10]. In an attempt to delay the onset of drug resistance, the FDA approved the use of combination therapy, i.e. a mixture of protease and reverse transcriptase antiretroviral agents. Although multidrug therapy has reduced the plasma viral load of some HIV-infected individuals to undetectable levels[11], the daunting ability of the virus to rapidly mutate suggests an ongoing need for new antiretroviral drugs.

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In order to design new and more potent inhibitors of HIV protease, we must improve our understanding of the principles of molecular recognition for the protease. So far researchers have identified two unique features of the viral protease that distinguish it from the human aspartic proteases pepsin and renin:

1. The active form of the viral enzyme is a homodimer, in which each monomer contributes equally to the active site and
2. The presence of a structural water molecular that bridges linear inhibitors to the flap of the protein via hydrogen bonds.

Although hydroxyethylene isosteres and phosphinates were among the first C_2 symmetric molecules reported to bind HIV PR[12,13], C_2 symmetric cyclic urea-based inhibitors were one of the first molecules capable of displacing the structural water[14]. The cyclic urea (CU) scaffold is therefore well suited to interact with the viral protease and to discriminate against human proteases. Since these inhibitors were first reported, the number of CU mimics has rapidly increased, and this class of cyclic compounds may soon become a viable alternative to the currently available antiretroviral agents[15-18]. In this research paper we have performed QSAR analysis of cyclic ureas given in the TABLE 1 which enables us to predict the activity in terms of K_i of any cyclic urea by calculating the values of the descriptors.

MATERIAL AND METHOD

Electronegativity 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 $\nu(\gamma)$[19].

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

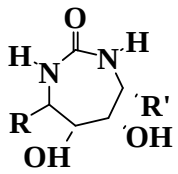
In accordance with the earlier work of Iczkowski and Margrave,[24] it should be stated that when assuming a quadratic relationship between E and N a finite difference approximation Eq. 1 may be rewritten as:

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

Where IE and EA are the vertical ionization energy and electron affinity, respectively, thereby recovering the electronegativity definition of Mullken[21]. Moreover, a theoretical justification was provided for Sanderson's principle of electronegativity equalization, which states that when two are more atoms come together to form a molecule, their electronegativities become adjusted to the same intermediate value[22-24]. The absolute hardness η is defined as[25].

$$\eta = 1/2.\ (\delta\mu / \delta N)_{\nu(\gamma)} = 1/2.\ (\delta 2E/\delta N2)_{\nu(\gamma)} \quad (3)$$

TABLE 1: PR inhibition data of cyclic ureas (Observed activity in terms of K_i)



No.	R/R'	Observed activity
1	$CH_2C_6H_5$(A)[a]	8.47
2	Me(A)	5.30
3	$CH_2C_6H_4$-4$CHMe_2$(A)	8.96
4	$CH_2C_6H_4$-4$CHMe_2$(A)	8.47
5	CH_2CHMe_2(A)	5.77
6	CH(Me)SMe(A)	5.96
7	CH_2-3indolyl(A)[a]	6.24
8	CH_2-Cy-C_6H_{11}(A)[a]	7.55
9	$CH_2CH_2C_6H_5$(A)[a]	6.50
10	CH_2-2-naphthyl(A)	8.01
11	CH_2-3-furanyl(A)	8.08
12	CH_2C6H_4-3-SMe(A)	8.60
13	CH_2C6H4-4-SO_2-Me-(A)	8.60
14	$CH_2C_6H_4$-2-OMe-(A)	7.22
15	$CH_2C_6H_4$-2-OH(A)	7.46
16	$CH_2C_6H_4$-3-OMe(A)	8.33
17	$CH_2C_6H_4$-4-OMe(A)	8.07
18	$CH_2C_6H_4$-4-OH(A)	8.96
19	$CH_2C_6H_4$-3-NH_2(A)	8.55
20	$CH_2C_6H_4$-3-NMe_2(A)	8.37
21	$CH_2C_6H_4$-4-NH_2(A)	8.07
22	C_6H_4-4-NH2-2HCI(A)	8.15
23	$CH_2C_6H_4$-4-NMe_2(A)	7.34
24	CH_2-4-pyridyl(A)	7.66
25	3-2,5-Me-pyrolyl)-$CH_2C_6H_4$ (A)	6.80
26	$CH_2C_6H_4$-3,4-(-OCH_2O-)(A)	8.89
27	$CH_2C_6H_5$(B)[b]	8.72
28	CH_2CHMe_2(B)[c]	7.07
29	$CHMe_2$(B)[c]	6.60
30	CH(Me)SMe(B)	5.60
31	$CH_2C_6H_4$-4-F(B)	8.24
32	$CH_2C_6H_4$-2-OMe(B)	7.19
33	$CH_2C_6H_4$-3-OMe(B)	9.06
34	$CH_2C_6H_4$-3-OH(B)	7.89
35	$CH_2C_6H_4$-4-OMe(B)	8.54
36	CH_2naphthyl(B)	8.37
37	$CH_2C_6H_3$-3,5-OMe(B)	8.57
38	CH_2-2-thienyl(B)	8.04

Where E is the total energy, N is the number of electrons of the chemical species, and $\nu(\Upsilon)$ is the external potential. The operational definition of absolute hardness and electronegativity is given as:

$$\eta = (IP - EA)/2, \quad \chi = (IP + EA)/2 \qquad (4)$$

Where IP and EA are the ionization potential and electron affinity, respectively, of the chemical species. According to Koopman's theorem, the IP is simply the eigenvalue of the HOMO with change of sign and the EA is the Eigen value of the LUMO with change of sign[26]; hence, equation (4) can be written as:

$$h = (\varepsilon LUMO - \varepsilon HOMO)/2 \qquad (5)$$

$$c = -\mu = -(\varepsilon LUMO + \varepsilon HOMO)/2 \qquad (6)$$

With regard to QSAR of a chemical system, the total energy also played an important role. The total energy of a molecular system is the sum of the total electronic energy, E_{ee} and the energy of the internuclear repulsion, E_{nr}. The total electronic energy of the system is given by[27].

$$E = R(H+F)/2 \qquad (7)$$

Where P is the density matrix and H is the one-electron matrix.

Finally, a more general, but important, property of a molecular system, the molecular weight has also been tested as a descriptor.

We have used the following descriptors for the prediction of activity of cyclic ureas given in TABLE 1.

Heat of Formation (kcal/mole)	ΔHf
Molecular Weight	MW
Total Energy (Hartree)	TE
HOMO Energy (eV)	εHOMO
LUMO Energy (eV)	εLUMO
Absolute Hardness	η
Electronegativity	χ

Values of above descriptors of the cyclic ureas given in TABLE 1 have been calculated using Computer Aided Chemistry software (CAChe) by PM3 method and shown in the TABLE 2. Outliers are the compounds 1, 5, 7, 9, 13, 14, 18, 23, 25, 27, 33 and 38. These compounds have been excluded from the QSAR study. QSAR models APA1 to PA59 have been developed using the combinations of above descriptors which provide good quality of prediction of activities of cyclic ureas.

TABLE 2: Values of descriptors used in QSAR analysis of cyclic ureas

Comp.	Heat of formation (kcal /mole)ΔHf	Molecular weight MW	Total energy (Hartree) TE	HOMO energy (eV) εHOMO	LUMO energy (eV) εLUMO	Absolute hardness η	Electron-egativity χ	Activity in terms of K_i
2	-81.065	324.419	-171.436	-9.509	0.091	4.800	-4.709	5.300
3	-60.967	560.775	-286.826	-9.232	-0.004	4.614	-4.618	8.960
4	-59.934	560.775	-286.816	-9.176	0.042	4.609	-4.567	8.470
6	-73.245	444.646	-218.388	-8.869	-0.135	4.367	-4.502	5.960
8	-25.262	476.614	-243.797	-9.437	0.087	4.762	-4.675	7.550
10	75.592	576.734	-291.650	-8.563	-0.636	3.963	-4.600	8.010
11	-80.572	456.537	-243.058	-9.123	0.113	4.618	-4.505	8.080
12	47.825	568.788	-277.032	-8.380	-0.232	4.074	-4.306	8.600
15	-36.126	508.613	-268.720	-8.369	-0.021	4.174	-4.195	7.460
16	-26.914	536.666	-283.011	-8.487	-0.050	4.219	-4.268	8.330
17	146.747	536.666	-282.863	-8.769	-0.022	4.374	-4.396	8.070
19	2762.641	506.643	-263.456	-8.452	0.055	4.253	-4.198	8.550
20	2749.742	562.750	-291.953	-8.418	0.068	4.243	-4.175	8.370
21	7.958	506.643	-263.227	-8.382	-0.029	4.176	-4.205	8.070
22	-79.492	547.480	-271.909	-8.553	-0.193	4.180	-4.373	8.150
24	109.801	478.590	-248.096	-8.496	-2.079	3.209	-5.288	7.660
26	-148.360	564.634	-303.990	-8.700	-0.039	4.331	-4.370	8.890
28	-139.519	364.567	-196.204	-10.385	0.719	5.552	-4.833	7.070
29	-122.456	336.514	-181.848	-10.406	0.716	5.561	-4.845	6.600
30	-36.539	400.634	-200.175	-7.977	-1.921	3.028	-4.949	5.600
31	-136.175	468.583	-257.435	-9.340	-0.323	4.509	-4.831	8.240
32	-124.421	492.654	-264.331	-8.915	-0.027	4.444	-4.471	7.190
34	-144.907	464.600	-250.052	-8.894	-0.099	4.397	-4.496	7.890
35	-130.571	492.654	-264.351	-8.723	0.043	4.383	-4.340	8.540
36	-13.488	532.721	-272.933	-8.521	-0.690	3.915	-4.606	8.370
37	-200.923	552.706	-303.111	-8.667	0.037	4.352	-4.315	8.570

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RESULT AND DISCUSSION

MLR equations have been developed with the help of Project Leader of CAChe software in all the combinations of the descriptors. Fifty nine MLR equations have been found to provide good QSAR models. These equations are given below-

APA1=0.000139954*ΔHf-0.0278183* TE -0.525574*εHOMO-0.11325*χ-4.56318
rCV^2=0.735679
r^2=0.820245

APA2=0.000139954*ΔHf-0.0278183* TE-0.582199*εHOMO-0.056625* εLUMO -4.56318
rCV^2=0.735679
r^2=0.820245

APA3=0.000139954*ΔHf-0.0278183* TE- 0.638824*εHOMO-0.11325*η-4.56318
rCV^2=0.735679
r^2=0.820245

APA4=0.000139954*ΔHf-0.0278183* TE -0.638824* εLUMO +1.1644*η-4.56318
rCV^2=0.735679
r^2=0.820245

APA5=0.000139954*ΔHf-0.0278183* TE+0.525574*∑LUMO-1.1644*χ4.56318
rCV^2=0.735679
r^2=0.820245

APA6=0.000130667*ΔHf-0.00104636 * MW-0.0293102*TE-0.516619* εHOMO -3.83743
rCV^2=0.739129
r^2=0.819897

APA7=0.000130193*ΔHf-0.0274241* TE-0.530248*εHOMO-3.98933
rCV^2=0.746226
r^2=0.819638

APA8=-0.000884559*MW-0.0291132 * TE-0.471436*εHOMO +0.00843069*εLUMO-3.44308
rCV^2=0.749665
r^2=0.810105

APA9=-0.000884559*MW-0.0291132 *TE-0.463005*εHOMO +0.0168614*η-3.44308
rCV^2=0.749665
r^2=0.810105

APA10=-0.000884559*MW-0.0291132 * TE-0.479866*εHOMO + 0.0168614*χ-3.44308
rCV^2=0.749665
r^2=0.810105

APA11=-0.000884559*MW-0.0291132 *TE-0.463005*εLUMO +0.942871*η-3.44308
rCV^2=0.749665
r^2=0.810105

APA12=-0.000884559*MW-0.0291132 *TE+0.479866*εLUMO-0.942871 *χ-3.44308
rCV^2=0.749665
r^2=0.810105

APA13=-0.000884559*MW-0.0291132 *TE+0.479866*η-0.463005 *χ-3.44308
rCV^2=0.749665
r^2=0.810105

APA14=-0.000902676*MW-0.0292062 *TE-0.478487*εHOMO-3.52213
rCV^2=0.774152
r^2=0.81009

APA15=-0.0275026*TE-0.481194 *εHOMO+0.0106117* εLUMO -3.55139
rCV^2=0.749716
r^2=0.809921

APA16=-0.0275026*TE-0.470582*εHOMO+0.0212235*η-3.55139
rCV^2=0.749716
r^2=0.809921

APA17=-0.0275026*TE-0.491806* εHOMO+0.0212235*χ-3.55139
rCV^2=0.749716
r^2=0.809921

APA18=-0.0275026*TE-0.470582* εLUMO+0.962388*-3.55139
rCV^2=0.749716
r^2=0.809921

APA19=-0.0275026*TE+0.491806* εLUMO-0.962388*-3.55139
rCV^2=0.749716
r^2=0.809921

APA20=-0.0275026*TE+0.491806*η-0.470582*χ-3.55139
rCV^2=0.749716
r^2=0.809921

APA21=-0.0275786*TE-0.490369* εHOMO -3.65422
rCV^2=0.77687
r^2=0.809897

APA22=-0.0275026*TE-1.09375* εHOMO +0.65625*LUMO-1.25*η-3.43735
rCV^2=0.766381
r^2=0.809811

APA23=8.15696e-005*ΔHf-0.00202203 *MW-0.0287341*TE+0.411197 *η-0.404072
rCV^2=0.704548
r^2=0.803913

APA24=-0.0275026*TE-0.5* εHOMO +0.125*εLUMO+0*χ-3.69835
rCV^2=0.721723
r^2=0.803684

APA25=7.81846e-005*ΔHf-0.024981 *TE+0.435918*η-0.543305
rCV^2=0.708372
r^2=0.802943

APA26=-0.00168109*MW-0.0283839 *TE +0.408714*η-0.458255
rCV^2=0.741546
r^2=0.799972

APA27=-0.0252543*TE+0.429498*η-0.572944

rCV^2=0.744301
r^2=0.799297

APA28=5.75446e-005*ΔHf-0.0039588 *MW-0.0307578*TE +0.237179*εLUMO +1.86473
rCV^2=0.665684
r^2=0.784697

APA29=-0.00360377*MW-0.0303022 *TE+0.244974*εLUMO +1.81741
rCV^2=0.694151
r^2=0.782757

APA30=4.72362e-005*ΔHf-0.023217 *TE+0.271859*εLUMO +1.85899
rCV^2=0.657442
r^2=0.780821

APA31=-0.0234019*TE+0.275767* εLUMO+1.81995
rCV^2=0.689165
r^2=0.779492

APA32=9.93633e-005*ΔHf-0.007025 *MW-0.0374062*TE-0.244574*χ +0.51267
rCV^2=0.669786
r^2=0.767881

APA33=7.67099e-005*ΔHf-0.006895 *MW-0.0362243*TE+ 1.86291
rCV^2=0.703563
r^2=0.765033

APA34=-0.00656259*MW-0.0364708 *TE-0.141106*χ+1.00917
rCV^2=0.735566
r^2=0.762596

APA35=0.00011835*ΔHf+0.0138896*MW-0.593866*εHOMO+ 0.0554938*εLUMO -4.33998
rCV^2=0.629665
r^2=0.762335

APA36=0.00011835*ΔHf+0.0138896*MW-0.538372*εHOMO+0.110988*η-4.33998
rCV^2=0.629665
r^2=0.762335

APA37=0.00011835*ΔHf+0.0138896*MW-0.64936*εHOMO +0.110988*χ-4.33998
rCV^2=0.629665
r^2=0.762335

APA38=0.00011835*ΔHf+0.0138896*MW-0.538372*εLUMO +1.18773*η-4.33998
rCV^2=0.629665
r^2=0.762335

APA39=0.00011835*ΔHf+0.0138896*MW+0.64936*εLUMO-1.18773*χ-4.33998
rCV^2=0.629665
r^2=0.762335

APA40=0.00011835*ΔHf+0.0138896*MW+0.64936*η-0.538372*χ-4.33998
rCV^2=0.629665
r^2=0.762335

APA41=0.000127917*ΔHf+0.0140798*MW-0.645822*εHOMO-4.90614
rCV^2=0.671966
r^2=0.761731

APA42=-0.00654716*MW-0.0358523 *TE+1.79906
rCV^2=0.741246
r^2=0.761547

APA43=0.0137763*MW-0.510279* εHOMO +0.110424*LUMO -3.51367
rCV^2=0.635569
r^2=0.754933

APA44=0.0137763*MW-0.399855* εHOMO+0.220848*-3.51367
rCV^2=0.635569
r^2=0.754933

APA45=0.0137763*MW-0.620702* εHOMO+0.220848*-3.51367
rCV^2=0.635569
r^2=0.754933

APA46=0.0137763*MW-0.399855* εLUMO+1.02056*η-3.51367
rCV^2=0.635569
r^2=0.754933

APA47=0.0137763*MW+0.620702*εLUMO-1.02056*χ-3.51367
rCV^2=0.635569
r^2=0.754933

APA48=0.0137763*MW+0.620702*η-0.399855*χ-3.51367
rCV^2=0.635569
r^2=0.754933

APA49=8.2441e-005*ΔHf-0.0239064 *TE-0.222918*χ+0.620297
rCV^2=0.687086
r^2=0.754213

APA50=0.014168*MW-0.60804 *εHOMO-4.59373
rCV^2=0.692944
r^2=0.752331

APA51=6.20448e-005*ΔHf-0.0230548 *TE+1.85118
rCV^2=0.696883
r^2=0.751843

APA52=-0.0238675*TE-0.137294 *χ+1.03096
rCV^2=0.72218
r^2=0.750534

APA53=6.79917e-005*ΔHf +0.012632 *MW+0.559571*η-0.885223
rCV^2=0.648058
r^2=0.750094

APA54=0.0127678*MW+0.555987*η-0.92558
rCV^2=0.676896
r^2=0.74735

APA55=3.05861e-005*ΔHf+0.011405 *MW+0.368716* εLUMO+2.22453
rCV^2=0.565871
r^2=0.723337

APA56=0.0114734*MW+0.371845* εLUMO+2.19635
rCV^2=0.591043
r^2=0.722785

APA57=5.36456e-005*ΔHf+0.011013 *MW+0.0192655*

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χ+2.43683
rCV^2=0.583073
r^2=0.670636

APA58=5.53752e-005*ΔHf+0.011049 *MW+2.33167
rCV^2=0.605156
r^2=0.670617

APA59=0.01102*MW+0.0721741*χ+2.68173
rCV^2=0.606628
r^2=0.669077

In MLR equations, the regression coefficients are denoted by r^2 and cross-validation coefficients are denoted by rCV^2. The MLR equation is said to have good predictive power if regression coefficient is greater than 0.5 and the cross-validation coefficient is greater than 0.2. As the value of regression coefficient increases, the predictive power of MLR equation increases. The maximum value of regression coefficient may be unity and in that case the predictive power is 100%.

Above QSAR models are arranged in decreasing order of quality of prediction which depends on the value of regression coefficient (r^2).

We have calculated the predicted activities by substituting the values of descriptors in MLR equations 1 to 10 and shown in TABLE 3.

Best QSAR models

Above TABLE indicates that there are five best QSAR models APA1, APA2, APA3, APA4 and APA5. In all these QSAR models, the value of cross-validation coefficient is 0.735679 and regression coefficient is 0.820245. These values indicate that these QSAR models have very good predictive power. These QSAR models are discussed below-

QSAR model APA1

In this QSAR model, the descriptors are heat of formation, total energy, HOMO energy and electronegativity. Multilinear regression equation of this model is given by

APA1=0.000139954*ΔHf-0.0278183* TE-0.525574*εHOMO-0.11325* χ-4.56318
rCV^2=0.735679
r^2=0.820245

Line graph between observed activity and predicted activity APA1 of cyclic ureas is shown in Graph-1 which shows that this QSAR model has very good predictive

TABLE 3: Predicted activities of cyclic ureas from APA1 to APA10

Comp	APA1	APA2	APA3	APA4	APA5	APA6	APA7	APA8	APA9	APA10
2	5.726	5.726	5.726	5.726	5.726	5.750	5.744	5.745	5.745	5.745
3	8.782	8.782	8.782	8.782	8.782	8.744	8.764	8.764	8.764	8.764
4	8.747	8.747	8.747	8.747	8.747	8.715	8.734	8.737	8.737	8.737
6	6.673	6.673	6.673	6.673	6.673	6.671	6.693	6.702	6.702	6.702
8	7.704	7.704	7.704	7.704	7.704	7.681	7.697	7.682	7.682	7.682
10	8.582	8.582	8.582	8.582	8.582	8.541	8.559	8.569	8.569	8.569
11	7.492	7.492	7.492	7.492	7.492	7.512	7.504	7.531	7.531	7.531
12	8.042	8.042	8.042	8.042	8.042	8.023	8.058	8.068	8.068	8.068
15	7.781	7.781	7.781	7.781	7.781	7.826	7.813	7.876	7.876	7.876
16	8.250	8.250	8.250	8.250	8.250	8.277	8.269	8.322	8.322	8.322
17	8.433	8.433	8.433	8.433	8.433	8.441	8.437	8.451	8.451	8.451
19	8.070	8.070	8.070	8.070	8.070	8.082	8.077	7.764	7.764	7.764
20	8.841	8.841	8.841	8.841	8.841	8.839	8.839	8.528	8.528	8.528
21	7.642	7.642	7.642	7.642	7.642	7.679	7.675	7.723	7.723	7.723
22	7.980	7.980	7.980	7.980	7.980	7.968	7.992	8.019	8.019	8.019
24	7.418	7.418	7.418	7.418	7.418	7.337	7.334	7.344	7.344	7.344
26	8.940	8.940	8.940	8.940	8.940	8.957	8.941	9.009	9.009	9.009
28	6.881	6.881	6.881	6.881	6.881	6.879	6.880	6.848	6.848	6.848
29	6.496	6.496	6.496	6.496	6.496	6.501	6.500	6.465	6.465	6.465
30	5.753	5.753	5.753	5.753	5.753	5.727	5.726	5.775	5.775	5.775
31	8.035	8.035	8.035	8.035	8.035	8.025	8.006	8.038	8.038	8.038
32	7.965	7.965	7.965	7.965	7.965	7.984	7.971	8.019	8.019	8.019
34	7.556	7.556	7.556	7.556	7.556	7.581	7.565	7.618	7.618	7.618
35	7.848	7.848	7.848	7.848	7.848	7.885	7.869	7.930	7.930	7.930
36	8.028	8.028	8.028	8.028	8.028	8.005	8.012	8.043	8.043	8.043
37	8.884	8.884	8.884	8.884	8.884	8.920	8.893	8.979	8.979	8.979

power.

QSAR model APA2

In this QSAR model, the descriptors are heat of formation, total energy, HOMO energy and LUMO energy. Multilinear regression equation of this model is given by

APA2=0.000139954*ΔHf-0.0278183*TE-0.582199*εHOMO-0.056625*εLUMO-4.56318

rCV^2=0.735679

r^2=0.820245

Stacked line graph between observed activity and predicted activity APA2 of cyclic ureas is shown in Graph-2 which shows that this QSAR model also has very good predictive power.

QSAR model APA3

In this QSAR model, the descriptors are heat of formation, total energy, HOMO energy and absolute hardness. Multilinear regression equation of this model is given by

APA3=0.000139954*ΔHf-0.0278183*TE-0.638824*εHOMO-0.11325*η-4.56318

rCV^2=0.735679

r^2=0.820245

Trend of observed activity and predicted activity APA3 of cyclic ureas in shape of bars is shown in Graph-3 which shows that this QSAR model also has very good predictive power.

QSAR model APA4

In this QSAR model, the descriptors are heat of formation, total energy, LUMO energy and absolute hardness. Multilinear regression equation of this model is given by

APA4=0.000139954*ΔHf-0.0278183*TE-0.638824*εLUMO+1.1644*η-4.56318

rCV^2=0.735679

r^2=0.820245

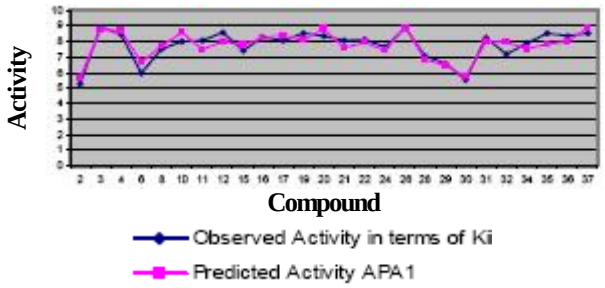
QSAR model APA5

In this QSAR model, the descriptors are heat of formation, total energy, LUMO energy and electro negativity. Multilinear regression equation of this model is given by

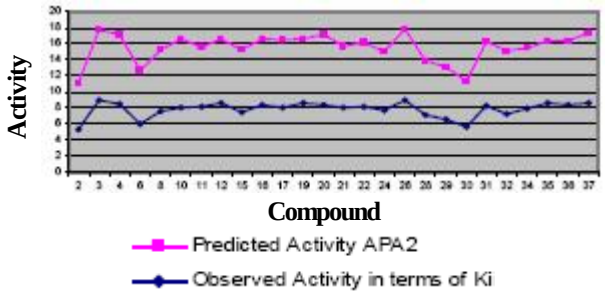
APA5=0.000139954*ΔHf-0.0278183*TE+0.525574*εLUMO-1.1644*χ-4.56318

rCV^2=0.735679

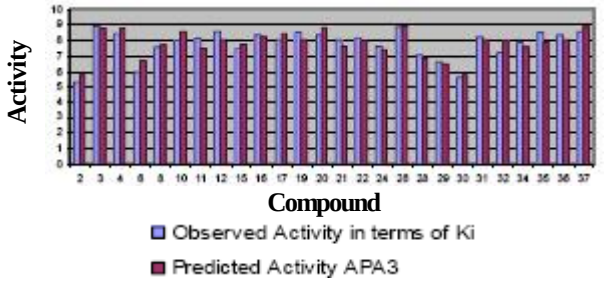
r^2=0.820245



Graph 1: Line graph between observed activity and predicted activity APA1 of cyclic ureas in terms of K_i



Graph 2: Stacked line graph between observed activity and predicted activity APA2 of cyclic ureas in terms of K_i



Graph 3: Bar graph between observed activity and predicted activity APA3 of cyclic ureas in terms of K_i

Next 5 QSAR Models having good quality of prediction

Next 5 QSAR Models having good quality of prediction APA6, APA7, APA8, APA9, and APA10 in which regression coefficient is greater than 0.8. The QSAR models APA8, APA9, APA10, APA11, APA12 and APA13 are at the same level of predictive power because the values of regression and cross-validation coefficients in all these models are same. QSAR models APA6 to APA10 are discussed below-

QSAR Modes APA6

Descriptors used in this QSAR model are heat of formation, molecular weight, total energy and HOMO energy. The value of cross-validation coefficient is

0.739129 and the value of regression coefficient is 0.819897. As the value of regression coefficient is very high, therefore, the quality of prediction of the QSAR model is very high. With the help of this QSAR model, the activity of any member of cyclic urea can easily be predicted by substituting the values of descriptors in the following equation-

APA6=0.000130667*ΔHf-0.00104636* MW-0.0293102*TE-0.516619*εHOMO-3.83743
rCV^2=0.739129
r^2=0.819897

QSAR modes APA7

Descriptors used in this QSAR model are heat of formation, total energy and HOMO energy. The value of cross-validation coefficient is 0.746226 and the value of regression coefficient is 0.819638. As the value of regression coefficient is very high, therefore, the quality of prediction of the QSAR model is very high. With the help of this QSAR model, the activity of any member of cyclic urea can easily be predicted by substituting the values of descriptors in the following equation-

APA7=0.000130193*ΔHf-0.0274241*TE-0.530248*εHOMO-3.98933
rCV^2=0.746226
r^2=0.819638

QSAR modes APA8

Descriptors used in this QSAR model are Molecular Weight, Total Energy, HOMO Energy and LUMO Energy. The value of cross-validation coefficient is 0.749665 and the value of regression coefficient is 0.810105. As the value of regression coefficient is very high, therefore, the quality of prediction of the QSAR model is very high. With the help of this QSAR model, the activity of any member of cyclic urea can easily be predicted by substituting the values of descriptors in the following equation-

APA8=-0.000884559*MW-0.0291132*TE-0.471436*HOMO+0.00843069*εLUMO-3.44308
rCV^2=0.749665
r^2=0.810105

QSAR modes APA9

Descriptors used in this QSAR model are Molecular Weight, Total Energy, HOMO Energy and Absolute Hardness. The value of cross-validation coefficient is 0.749665 and the value of regression coefficient is 0.810105. As the value of regression coefficient is very high, therefore, the quality of prediction of the QSAR model is very high. With the help of this QSAR model, the activity of any member of cyclic urea can easily be predicted by substituting the values of descriptors in the following equation-

APA9=-0.000884559*MW-0.0291132 *TE-0.463005*εHOMO+0.0168614*η-3.44308
rCV^2=0.749665
r^2=0.810105

QSAR modes APA10

Descriptors used in this QSAR model are Molecular Weight, Total Energy, HOMO Energy and Electrone gativity. The value of cross-validation coefficient is 0.749665 and the value of regression coefficient is 0.810105. As the value of regression coefficient is very high, therefore, the quality of prediction of the QSAR model is very high. With the help of this QSAR model, the activity of any member of cyclic urea can easily be predicted by substituting the values of descriptors in the following equation-

APA10=-0.000884559*MW-0.0291132 *TE-0.479866*εHOMO+0.0168614*χ-3.44308
rCV^2=0.749665
r^2=0.810105

CONCLUSION

In all the five best QSAR models APA1, APA2, APA3, APA4 and APA5, the descriptors heat of formation and total energy is common. In all these QSAR models, the values of cross-validation and regression coefficients are 0.73569 and 0.820245 respectively. These values indicate that the QSAR models provide very good quality of prediction of activities of cyclic urea. Heat of formation can be treated as best descriptor of activities of cyclic ureas as it provides very good QSAR models combining with the descriptors total energy, HOMO energy, electrone gativity, LUMO energy, molecular weight and absolute hardness. Next best descriptor of activity is total energy as it gives the lowest regression coefficient 0.750534 in combination with electronegativity in QSAR model APA52 and highest regression coefficient 0.820245 in APA1 alongwith electronegativity, HOMO energy and heat of formation. In any other combinations, the regression coefficient is greater than 0.750534. Molecular weight, which is introduced as new

descriptor, also provide very good QSAR models as it gives the lowest regression coefficient 0.669077 in APA59 alongwith the electronegativity and highest regression coefficient 0.819897 in APA6 alongwith total energy, HOMO energy and heat of formation. Thus, we can conclude that the best three descriptors of cyclic ureas are heat of formation, total energy and molecular weight. Most important fact in the cyclic ureas is that the heavier compounds possess more activity.

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