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QSAR Study of Interaction between Estrogen Derivatives and Receptor Amino Acids using Softness Parameters

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Abstract: Four sets of estrogen derivatives have been studied in respect of their interaction with receptor amino acids. The estrogen derivatives are divided into four sets on the basis of the positions of the substituents. The first set is substituted at the position 16, second at 17, third at 11, 16, 17 and fourth at 2, 4, 7, 11, 17. The receptor amino acids are lysine, tyrosine, cysteine and histidine. The softness parameter $E_n^{\ddagger}$ at different sites of estrogen and softness parameter $E_m^{\ddagger}$ at different sites of lysine, tyrosine, cysteine and histidine has been evaluated with the help of PM3 calculation. The highest value of $E_n^{\ddagger}$ of estrogen and highest value of $E_m^{\ddagger}$ of amino acids have been chosen. The difference between the values of $E_n^{\ddagger}$ and $E_m^{\ddagger}$ have been derived and are shown as $\Delta E_{nm}^{\ddagger}$. The reciprocal of $\Delta E_{nm}^{\ddagger}$, $E_n^{\ddagger}$ and $E_m^{\ddagger}$ values have been used as descriptors for development of QSAR models. QSAR models of all the four sets of estrogen derivatives have been developed which show high degree of predictive power as the regression coefficient values are about 0.90. The best descriptor for all the four sets of estrogen derivatives can be supposed to be $1/H\,\Delta E_{nm}^{\ddagger}$, where $H\,\Delta E_{nm}^{\ddagger}$ denotes the difference between acidic softness values $E_n^{\ddagger}$ of derivatives of estrogen and basic softness values $E_m^{\ddagger}$ of histidine. The quality of interaction of estrogen derivatives with different amino acids has also been obtained by $\Delta E_{nm}^{\ddagger}$ values.

Key Words: Estrogen, acidic and basic softnesses, QSAR, histidine, amino acids.

Introduction

Klopman [1] calculated quantitative values of softness of acid $E_n^{\ddagger}$ and base ions $E_m^{\ddagger}$ and derived the reactivity by the difference of the softness values of acid and base ions $\Delta E_{nm}^{\ddagger}$. The $\Delta E_{nm}^{\ddagger}$ values [2, 3] provide a very convenient framework for acid base interaction.

Semiempirical quantum-chemical methods can be used for the calculation of molecular descriptors. Various semiempirical methods like Extended Huckel Theory (EHT), complete neglect of differential overlap (CNDO)[4,5], intermediate neglect of differential overlap (INDO)[6], modified intermediate neglect of differential overlap (MINDO)[7], modified neglect of diatomic overlap (MNDO)[8], Austin model 1[9] and parametric model 3 (PM3)[10] have been developed over the last few decades. MNDO, AM1 and PM3 are the methods based on the correct inclusion of one-centre overlap and provide good descriptions even for anions and hydrogen-bonded systems.

In order to evaluate the donor-acceptor interaction between estrogen derivatives and receptor amino acids, the softness values at different sites in estrogen derivatives have been evaluated. Similarly, softness values of amino acids like lysine, cysteine, tyrosine and histidine have also been evaluated. The difference in softness values of estrogen derivatives and the amino acids has been calculated and represented by $\Delta E_{nm}^{\ddagger}$. Reciprocal values of $E_n^{\ddagger}$ and $\Delta E_{nm}^{\ddagger}$ values have been used as descriptor for the QSAR studies of 33 estrogen derivatives.

Materials and methods

Thirty three estrogen derivatives and four amino acids have been use as study material. The relative binding affinity (RBA) of estrogens has been collected from literature[17-21]. For QSAR prediction, the three-dimensional modeling and geometry optimization of all

the estrogen derivatives and their receptors proteins have been done with the help of CAChe software, using PM3 Hamiltonian. The MOPAC calculations have also been performed with CAChe software.

The softness of an atom in a molecule was described by Klopman [1] and modified by Singh et al.[2]. The Klopman equation is given by

$$E_m^{\ddagger} = IP_m - a^2(IP_m - EA_m) - [\chi_r(C_r^m)^2/R_r]$$
$$(1-1/\in)\,[q_r + 2b^2\chi_r\,(C_r^m)^2] \qquad (1)$$

$$E_n^{\ddagger} = IP_n - b^2(IP_n - EA_n) - [\chi_s(C_s^n)^2/R_s]$$
$$(1-1/\in)[q_s - 2b^2\chi_s\,(C_s^n)^2] \qquad (2)$$

where $E_n^{\ddagger}$ is the softness of a Lewis acid; $E_m^{\ddagger}$ is the softness of a Lewis base; IP is the ionization potential of an atom in a molecule; EA is the electron affinity of an atom in a molecule; $\in$ is the dielectric constant of the medium in which reaction is carried out; R and q are the radius and charge of atom s and r; C is the electron density; $\chi_r = q - (q - I)\sqrt{k}$ and k = 0.75; a and b are the variational parameters defined as $a^2 + b^2 = 1$.

The ionization potential of an atom in a molecule (IP), electron affinity of an atom in a molecule (EA), charge on atom in a molecule *(q)* and electron density (C) of an atom in a molecule are essential requirements for the solution of Klopman equations. The method for calculation of ionization potential of an atom in a molecule (IP) has been described by Dewar and Morita[11] by the following equation

$$IP = a + bq + cq^2 \qquad (3)$$

where *a,* band c are constants and *q* is the total electronic charge and partial charge on it that is total number of electrons of the atom and the charge developed on them within a molecule. The charge and electron density of an atom in a molecule are obtained by PM3[10] calculation on CAChe software. Water has been chosen for medium hence the value of dielectric constant is taken as 81.[12]

The method for calculation of electron affinity of an atom in a molecule (EA) has been described by us earlier[13].

$$EA = -(\varepsilon HOMO + \varepsilon LUMO) - IP \qquad (4)$$

Negative value of HOMO energy is equal to the ionization potential, therefore, electron affinity EA is the negative value of LUMO energy.

It is well established that the stability of the compound formed between nucleophile and electrophile depends upon the value of difference between softness values $E_m^{\ddagger}$ of nucleophile, and softness values $E_n^{\ddagger}$ of electrophile. Let $\Delta E_{nm}^{\ddagger}$ represents the difference between $E_n^{\ddagger}$ and $E_m^{\ddagger}$. The higher is the value of $\Delta E_{nm}^{\ddagger}$, the greater is the stability of the compound[14-16].

$$\Delta E_{nm}^{\ddagger} = \Delta E_n^{\ddagger} - \Delta E_m^{\ddagger} \qquad (5)$$

Estrogen-amino acid interaction

Recently[22] we have studied the interaction of estrogen with amino acids in the following manner.

Parent Skeleton of Estrogen is shown in Fig.-1.

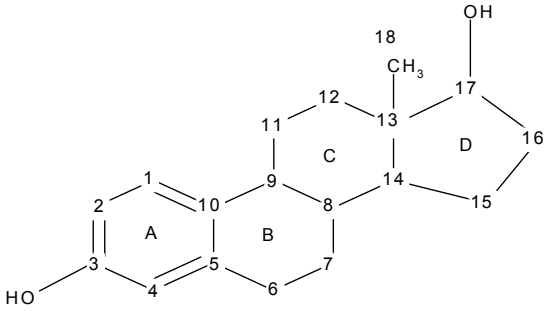


Fig.-1: Parent Skeleton of Estrogen

Human estrogen receptor ER is composed of 595 amino acids. Although ER is found in monomeric, dimeric and oligomeric states[23,24], its primary structure is conserved in all tissues where it is found. Most of the ER within affected cells is located in the nucleus. Estrogens make initial contact with the receptors polar region, encompassing amino acids 518-532. This region contains three residues of lysine, and a residue each of cysteine, tyrosine and histidine.

In contrast to the generally polar composition of residues 518-532, the regions, which flank this sequence, are composed of primarily of nonpolar amino acid residues, consisting of alanine, phenylalanine, isoleucine, leucine and valine [25]. It has been proposed [26] earlier that structure affinity relationship studies be focused on the composition of region 518-532, which may clarify the specific functional group interaction of ER and its estrogen ligands. In the light of earlier findings the following four amino acids viz. lysine, histidine, cysteine and tyrosine (shown in Fig.-2-5) have been considered for ER interaction and for QSAR study.

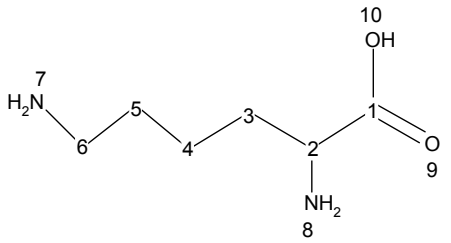


Fig.-2: Lysine

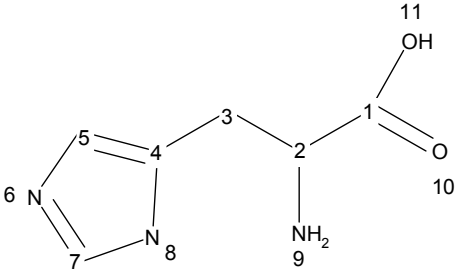


Fig.-3: Histidine

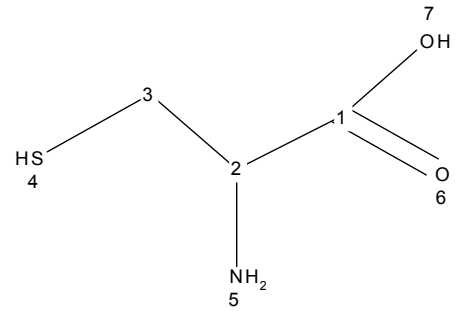


Fig.-4: Cysteine

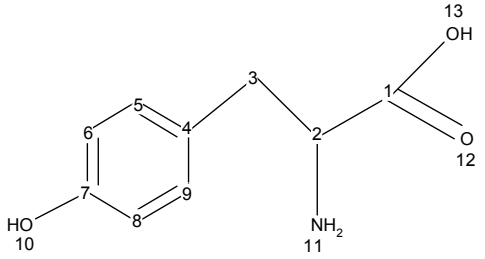


Fig.-5: Tyrosine

Since receptors are protein, and protein has large number of amino acids and amide group, they have been considered as nucleophile and estrogen derivatives as electrophile. The softness values are therefore represented by $E_m^{\ddagger}$ and $E_n^{\ddagger}$ respectively.

The softness values $E_n^{\ddagger}$ at all 18 sites of all the derivatives of estrogen and the softness values $E_m^{\ddagger}$ at 10 sites of lysine, 11 sites of histidine, 7 sites of cysteine and 13 sites of tyrosine receptor have been evaluated by solving Klopman equations.

The reaction medium has been considered fresh water hence dielectric constant (ε) has been taken for fresh water 81[12]. The highest values of $E_n^{\ddagger}$ of each derivative of estrogen and highest values of $E_m^{\ddagger}$ of each receptor have been used for deriving $\Delta E_{nm}^{\ddagger}$ values. The highest values of softness and the $\Delta E_{nm}^{\ddagger}$ derived from them are given in Tables 5-8.

Results and discussion

On the basis of difference in the position of substituents on the parent skeleton of the estrogen, the 33 derivatives have been divided into four sets. The first set of seven compounds has substitution at 16α position; the second set has four compounds with substitution at 17α sites. The third set has nine compounds with substitution at 11β, 16α and 17α sites, and fourth set has 13 compounds with substitution at 2, 4, 7α, 11β, 17α sites. The four sets of derivatives have been included in Tables 1-4.

The highest values of softness $E_n^{\ddagger}$ of estrogen derivatives and $E_m^{\ddagger}$ of amino acids have been chosen for deriving $\Delta E_{nm}^{\ddagger}$ values by using Equation (5). The highest $E_m^{\ddagger}$ values of amino acids and highest $E_n^{\ddagger}$ values of estrogen derivatives are placed in Tables 5-8. The $\Delta E_{nm}^{\ddagger}$ values derived by the difference in $E_n^{\ddagger}$ and $E_m^{\ddagger}$ values are also placed in the same Table, alongwith the values of biological activity in terms of RBA. [17, 18, 20, 22] The QSAR study[27, 28] is based on the relationship between $\Delta E_{nm}^{\ddagger}$ and RBA values.

First set of compounds contains seven compounds which are shown in the Table-1. We have taken the following descriptors for MLR analysis of these compounds-

1. Reciprocal of $E_n^{\ddagger}$ of the estrogen ($1/E_n^{\ddagger}$)
2. Reciprocal of the difference of $E_n^{\ddagger}$ of estrogen and $E_m^{\ddagger}$ of histidine ($1/H\,\Delta E_{nm}^{\ddagger}$)
3. Reciprocal of the difference of $E_n^{\ddagger}$ of estrogen and $E_m^{\ddagger}$ of cysteine ($1/C\,\Delta E_{nm}^{\ddagger}$)
4. Reciprocal of the difference of $E_n^{\ddagger}$ of estrogen and $E_m^{\ddagger}$ of lysine ($1/L\,\Delta E_{nm}^{\ddagger}$)
5. Reciprocal of the difference of $E_n^{\ddagger}$ of estrogen and $E_m^{\ddagger}$ of tyrosine ($1/T\,\Delta E_{nm}^{\ddagger}$)

In the first set of compounds, the compound 3 is outlier. The values of $E_n^{\ddagger}$, $H\,\Delta E_{nm}^{\ddagger}$, $C\,\Delta E_{nm}^{\ddagger}$, $L\,\Delta E_{nm}^{\ddagger}$ and $T\,\Delta E_{nm}^{\ddagger}$ of the compounds are shown in the Table-5 alongwith their RBA activities. MLR analysis has been done in the 25 combinations of the descriptors. We have ignored cross-validation coefficients and considered the regression coefficients (r^2) only as there are only few compounds in the each set. The regression equation in which the value of regression coefficient (r^2) is greater than 0.5 is said to have good predictive power. As the value of regression coefficient approaches to unity, the predictive power increases. The predicted activities have been calculated by substituting the values of the descriptors in the MLR equations (also called regression equations).

Best descriptors of activity of the first set of compounds are $1/E_n^{\ddagger}$, $1/H\,\Delta E_{nm}^{\ddagger}$ and $1/C\,\Delta E_{nm}^{\ddagger}$. The predicted activity PA1 is given by the following equation in which the value of regression coefficient is 0.903488. Graph between predicted activity PA1 and observed activity A is shown in Graph-1.

PA1=1.01128e+007*($1/E_n^{\ddagger}$)+6.19126e+008*($1/H\,\Delta E_{nm}^{\ddagger}$) -6.29086e+008*($1/C\,\Delta E_{nm}^{\ddagger}$) - 145.595

r^2=0.903488

Second best descriptors of activity of the first set of compounds are $1/E_n^{\ddagger}$, $1/H\,\Delta E_{nm}^{\ddagger}$ and $1/T\,\Delta E_{nm}^{\ddagger}$. The predicted activity is given by the following equation in which the value of regression coefficient is 0.903399.

PA2=1.069e+007*(1/ $E_n^{\ddagger}$) +1.12354e+009 * (1/H $\Delta E_{nm}^{\ddagger}$)-1.13407e+009* (1/T $\Delta E_{nm}^{\ddagger}$) -154.603
r^2=0.903399

Third best descriptors of activity of the first set of compounds are 1/ $E_n^{\ddagger}$, 1/H $\Delta E_{nm}^{\ddagger}$ and 1/L $\Delta E_{nm}^{\ddagger}$. The predicted activity is given by the following equation in which the value of regression coefficient is 0.902889.

PA3=1.05312e+007*(1/ $E_n^{\ddagger}$)-1.31008e+ 009 *(1/H $\Delta E_{nm}^{\ddagger}$) +1.29972e+009 *(1/L $\Delta E_{nm}^{\ddagger}$) -155.616
r^2=0.902889

The interaction of individual amino acids with estrogen derivatives of Table-1, as derived by values of regression coefficients indicate the following order of estrogen-amino acid interaction-
Lysine > Histidine > Cysteine > Tyrosine

Best descriptors of activity of the second set of compounds are 1/ $E_n^{\ddagger}$ and 1/H $\Delta E_{nm}^{\ddagger}$. The predicted activity PB1 is given by the following equation in which the value of regression coefficient is 0.968445. Graph between predicted activity PB1 and observed activity A is shown in Graph-2.

PB1=4.4653e+007*(1/ $E_n^{\ddagger}$)-5.27035e+007 *(1/H $\Delta E_{nm}^{\ddagger}$)+14784.1
r^2=0.968445

Second best descriptors of activity of the second set of compounds are 1/H $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PB2 is given by the following equation in which the value of regression coefficient is 0.968441.

PB2=-4.97094e+009*1/H $\Delta E_{nm}^{\ddagger}$ +4.96181e +009*1/T $\Delta E_{nm}^{\ddagger}$ +16095.3
r^2=0.968441

Third best descriptors of activity of the second set of compounds are 1/C $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PB3 is given by the following equation in which the value of regression coefficient is 0.968438.

PB3=7.08515e+009*1/C $\Delta E_{nm}^{\ddagger}$ -7.09431e+009 * 1/T $\Delta E_{nm}^{\ddagger}$ +16179.2
r^2=0.968438

The interaction of individual amino acids with estrogen derivatives of Table-2, as derived by values of regression coefficients indicate the following order of estrogen-amino acid interaction-
Histidine > Tyrosine > Cysteine > Lysine

Best descriptors of activity of the third set of compounds are 1/H $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PC1 is given by the following equation in which the value of regression coefficient is 0.704139. Graph between predicted activity PC1 and observed activity A is shown in Graph-3.

PC1=1.33571e+010*1/H $\Delta E_{nm}^{\ddagger}$ -1.33324e+010 *1/T $\Delta E_{nm}^{\ddagger}$ -44160.5
r^2=0.704139

Second best descriptors of activity of the third set of compounds are 1/ $E_n^{\ddagger}$ and 1/L $\Delta E_{nm}^{\ddagger}$. The predicted activity PC2 is given by the following equation in which the value of regression coefficient is 0.704119.

PC2=-1.18991e+008*1/ $E_n^{\ddagger}$ + 1.40925e+008*1/ L $\Delta E_{nm}^{\ddagger}$ - 40703.6
r^2=0.704119

Third best descriptors of activity of the third set of compounds are 1/H $\Delta E_{nm}^{\ddagger}$, 1/C $\Delta E_{nm}^{\ddagger}$, 1/L $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PC3 is given by the following equation in which the value of regression coefficient is 0.700391.

PC3=5.20153e+009*1/ H $\Delta E_{nm}^{\ddagger}$ -1.96938e+010 *1/C $\Delta E_{nm}^{\ddagger}$ -3.095e+009 *1/L $\Delta E_{nm}^{\ddagger}$ + 1.7612e+ 010*1/T $\Delta E_{nm}^{\ddagger}$ - 44098
r^2=0.700391

The interaction of individual amino acids with estrogen derivatives of Table-3, as derived by values of regression coefficients indicate the following order of estrogen-amino acid interaction-
Lysine > Histidine > Tyrosine > Cysteine

Best descriptors of activity of the fourth set of compounds are 1/ $E_n^{\ddagger}$, 1/H $\Delta E_{nm}^{\ddagger}$ and 1/C $\Delta E_{nm}^{\ddagger}$. The predicted activity PD1 is given by the following equation in which the value of regression coefficient is 0.824377. Graph between predicted activity PD1 and observed activity A is shown in Graph-4.

PD1=6.60127e+007*1/ $E_n^{\ddagger}$ +4.01252e+009*1/H $\Delta E_{nm}^{\ddagger}$ - 4.07761e+009*1/C $\Delta E_{nm}^{\ddagger}$ - 848.448
r^2=0.824377

Second best descriptors of activity of the fourth set of compounds are 1/ $E_n^{\ddagger}$, 1/H $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PD2 is given by the following equation in which the value of regression coefficient is 0.822339.

PD2=6.34183e+007*1/ $E_n^{\ddagger}$ +6.61586e+009*1/H $\Delta E_{nm}^{\ddagger}$ - 6.67839e+009*1/T $\Delta E_{nm}^{\ddagger}$ - 815.11
r^2=0.822339

Third best descriptors of activity of the fourth set of compounds are 1/ $E_n^{\ddagger}$, 1/H $\Delta E_{nm}^{\ddagger}$, 1/C $\Delta E_{nm}^{\ddagger}$, 1/L $\Delta E_{nm}^{\ddagger}$ and 1/T $\Delta E_{nm}^{\ddagger}$. The predicted activity PD3 is

given by the following equation in which the value of regression coefficient is 0.819201.

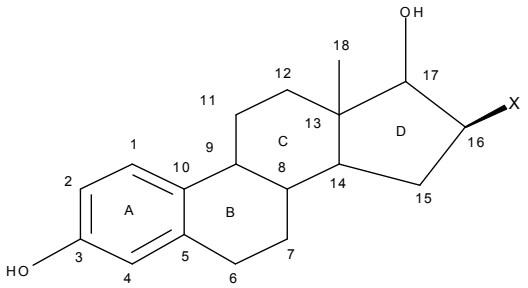
PD3=5.92751e+007*1/ $E_n^{\ddagger}$ +1.02682e+010*1/H $\Delta E_{nm}^{\ddagger}$ -2.13888e+009*1/C $\Delta E_{nm}^{\ddagger}$ - 3.01237e+009*1/L $\Delta E_{nm}^{\ddagger}$ - 5.17544e+009 *1/T $\Delta E_{nm}^{\ddagger}$ - 734.79

r^2=0.819201

The interaction of individual amino acids with estrogen derivatives of Table-4, as derived by values of regression coefficients indicate the following order of estrogen-amino acid interaction-

Tyrosine > Cysteine > Lysine > Histidine

Table-1: The first set of 16α-substituted estradiol derivatives containing seven compounds

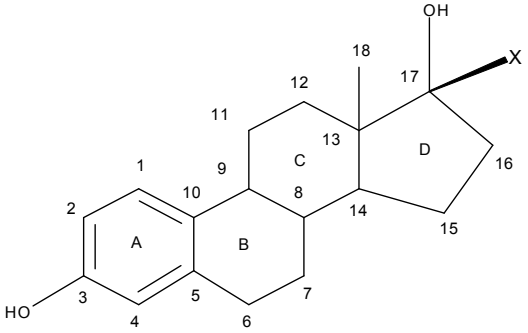


PARENT SKELETON OF FIRST SET OF DERIVATIVES

Compound	Substituents	Activity (A)
1	Cl	2.00
2	H	2.00
3	F	1.91
4	I	1.90
5	CH_2Cl	1.74
6	$CH_2CH{=}CH_2$	1.58
7	$CH_2CH(Me)F$	0.70

A is observed biological activity in terms of RBA.

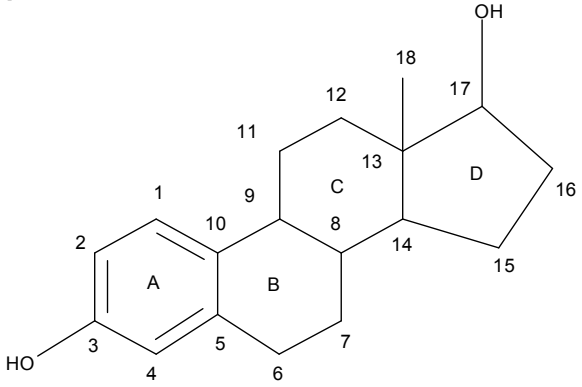
Table-2: The second set of 17α -substituted estradiol derivatives containing four compounds



PARENT SKELETON OF SECOND SET OF DERIVATIVES

Compound	Substituents	A
8	C_3H_7	0.79
9	C_4H_9	0.67
10	$CH_2C_6H_5$	0.63
11	$CH_2CH_2CH_2OH$	0.15

Table-3: The second set or 11β-, 16α- and 17α- substituted estradiol derivatives containing nine compounds

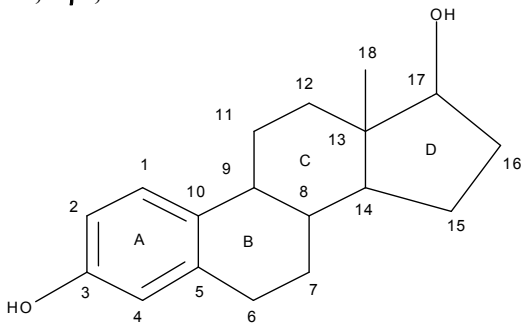


PARENT SKELETON OF THIRD SET OF DERIVATIVES

No.	**11β**	**16α**	**17α**	**A**
12	Et	H	H	2.60
13	H	H	C≡CH	2.05
14	H	H	H	2.00
15	Et	OH	C≡CH	1.90
16	H	H	Me	1.76
17	H	H	C_6H_5	1.48
18	Et	OH	H	1.45
19	OMe	H	C≡CMe	1.26
20	OMe	OH	C_6H_5	0.70

A is observed biological activity in terms of RBA.

Table-4: The fourth set of 2-, 4-, 7α-,11β-, 17α- substituted estradiol derivatives containing thirteen compounds



PARENT SKELETON OF FOURTH SET OF DERIVATIVES

No.	**2**	**4**	**7α**	**11β**	**17α**	**A**
21	H	F	H	H	C≡CH	2.08
22	H	H	H	H	C≡CH	2.00
23	H	H	H	H	H	2.00
24	H	H	H	Et	H	1.89
25	F	H	H	H	C≡CH	1.81
26	H	H	H	Me	H	1.81
27	H	H	H	H	CH=CHI (Z)	1.70
28	H	H	Me	H	CH=CHI (Z)	1.65
29	H	H	H	Me	CH=CHI (E)	1.64
30	H	H	Et	H	CH=CHI (E)	1.57
31	H	H	H	OMe	CH=C(I)Cl	1.54
32	H	H	H	OEt	H	1.00
33	H	Br	H	H	H	0.70

Table-5: The higher acidic softness ($E_n^{\ddagger}$) of estrogen derivatives and the higher basic softness ($E_m^{\ddagger}$) of four main amino acids followed by calculation of $\Delta E_{nm}^{\ddagger}$ for first set of derivatives containing seven compounds

Comp.	Site	$E_n^{\ddagger}$	Difference between $E_n^{\ddagger}$ and $E_m^{\ddagger}$				A
			Histidine H $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.5523	Cysteine C $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.109	Lysine L $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.777	Tyrosine T $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.292	
1	2	318.404	340.9563	340.513	341.181	340.696	2.00
2	2	258.712	281.2643	280.821	281.489	281.004	2.00
3	4	446.998	469.5503	469.107	469.775	469.290	1.91
4	4	256.982	279.5343	279.091	279.759	279.274	1.90
5	4	319.141	341.6933	341.25	341.918	341.433	1.74
6	4	259.052	281.6043	281.161	281.829	281.344	1.58
7	2	448.306	470.8583	470.415	471.083	470.598	0.70

Table-6: The higher acidic softness ($E_n^{\ddagger}$) of estrogen derivatives and the higher basic softness ($E_m^{\ddagger}$) of four main amino acids followed by calculation of $\Delta E_{nm}^{\ddagger}$ for second set of derivatives containing four compounds

Comp.	Site	$E_n^{\ddagger}$	Difference between $E_n^{\ddagger}$ and $E_m^{\ddagger}$				A
			Histidine H $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.5523	Cysteine C $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.109	Lysine L $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.777	Tyrosine T $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.292	
8	2	258.936	281.4883	281.045	281.713	281.228	0.79
9	2	258.933	281.4853	281.042	281.710	281.225	0.67
10	2	259.054	281.6063	281.163	281.831	281.346	0.63
11	2	259.817	282.3693	281.926	282.594	282.109	0.15

Table-7: The higher acidic softness ($E_n^{\ddagger}$) of estrogen derivatives and the higher basic softness ($E_m^{\ddagger}$) of four main amino acids followed by calculation of $\Delta E_{nm}^{\ddagger}$ for third set of derivatives containing nine compounds

Comp.	Site	$E_n^{\ddagger}$	Difference between $E_n^{\ddagger}$ and $E_m^{\ddagger}$				A
			Histidine H $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.5523	Cysteine C $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.109	Lysine L $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.777	Tyrosine T $\Delta E_{nm}^{\ddagger}$ $E_m^{\ddagger}$ = -22.292	
12	4	258.725	281.2773	280.834	281.502	281.017	2.60
13	4	257.964	280.5163	280.073	280.741	280.256	2.05
14	4	258.714	281.2663	280.823	281.491	281.006	2.00
15	4	259.123	281.6753	281.232	281.900	281.415	1.90
16	4	258.368	280.9203	280.477	281.145	280.66	1.76
17	4	259.207	281.7593	281.316	281.984	281.499	1.48
18	4	258.595	281.1473	280.704	281.372	280.887	1.45
19	4	258.418	280.9703	280.527	281.195	280.710	1.26
20	18	259.393	281.9453	281.502	282.170	281.685	0.70

Table-8: The higher acidic softness ($E_n^{\ddagger}$) of estrogen derivatives and the higher basic softness ($E_m^{\ddagger}$) of four main amino acids followed by calculation of $\Delta E_{nm}^{\ddagger}$ for fourth set of derivatives containing thirteen compounds

			Difference between $E_n^{\ddagger}$ and $E_m^{\ddagger}$				
			Histidine	Cysteine	Lysine	Tyrosine	
			H $\Delta E_{nm}^{\ddagger}$	C $\Delta E_{nm}^{\ddagger}$	L $\Delta E_{nm}^{\ddagger}$	T $\Delta E_{nm}^{\ddagger}$	
Comp.	Site	$E_n^{\ddagger}$	$E_m^{\ddagger}$ = -22.5523	$E_m^{\ddagger}$ = -22.109	$E_m^{\ddagger}$ = -22.777	$E_m^{\ddagger}$ = -22.292	A
21	2	438.808	461.3603	460.917	461.585	461.1	2.08
22	2	258.164	280.7163	280.273	280.941	280.456	2.00
23	2	258.676	281.2283	280.785	281.453	280.968	2.00
24	2	258.679	281.2313	280.788	281.456	280.971	1.89
25	4	440.293	462.8453	462.402	463.07	462.585	1.81
26	4	258.659	281.2113	280.768	281.436	280.951	1.81
27	4	258.222	280.7743	280.331	280.999	280.514	1.70
28	4	258.603	281.1553	280.712	281.38	280.895	1.65
29	4	258.219	280.7713	280.328	280.996	280.511	1.64
30	4	258.23	280.7823	280.339	281.007	280.522	1.57
31	4	258.295	280.8473	280.404	281.072	280.587	1.54
32	4	259.337	281.8893	281.446	282.114	281.629	1.00
33	4	258.646	281.1983	280.755	281.423	280.938	0.70

Table-9: Values of predicted activities PA1 to PA3

Comp	PA1	PA2	PA3
1	1.859	1.859	1.856
2	1.797	1.795	1.801
4	1.918	1.925	1.932
5	1.877	1.878	1.875
6	1.775	1.771	1.777
7	0.695	0.693	0.680

Table-10: Values of predicted activities PB1 to PB3

Comp	PB1	PB2	PB3
8	0.728	0.728	0.728
9	0.73	0.73	0.731
10	0.632	0.632	0.632
11	0.15	0.151	0.149

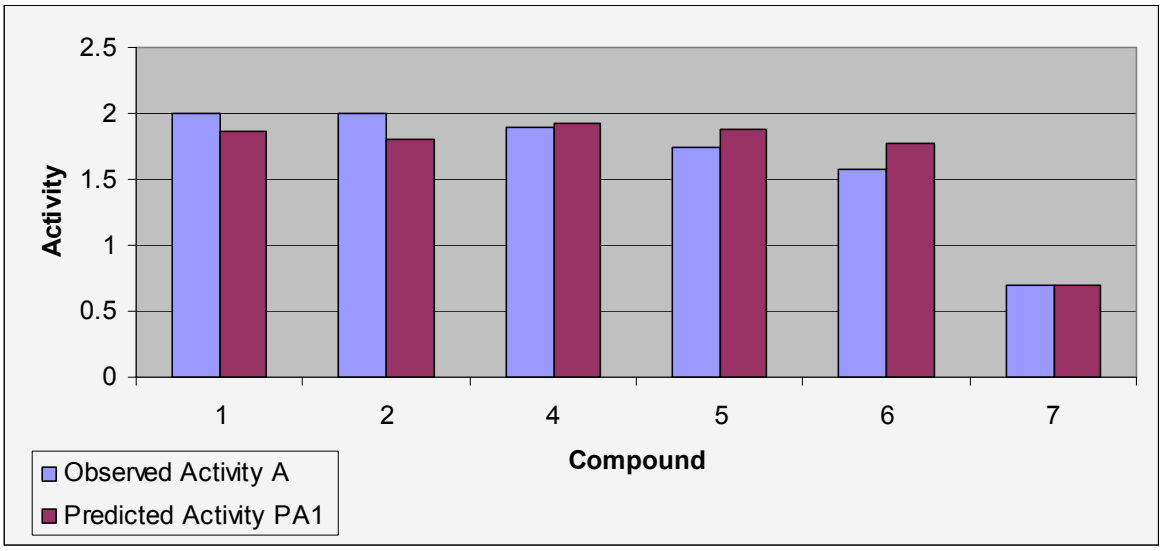
Table-11: Values of predicted activities PC1 to PC3

Comp	PC1	PC2	PC3
13	1.952	1.952	1.995
14	1.697	1.697	1.697
16	1.893	1.893	1.912
17	1.190	1.189	1.161
18	1.779	1.779	1.786
20	0.929	0.929	0.889

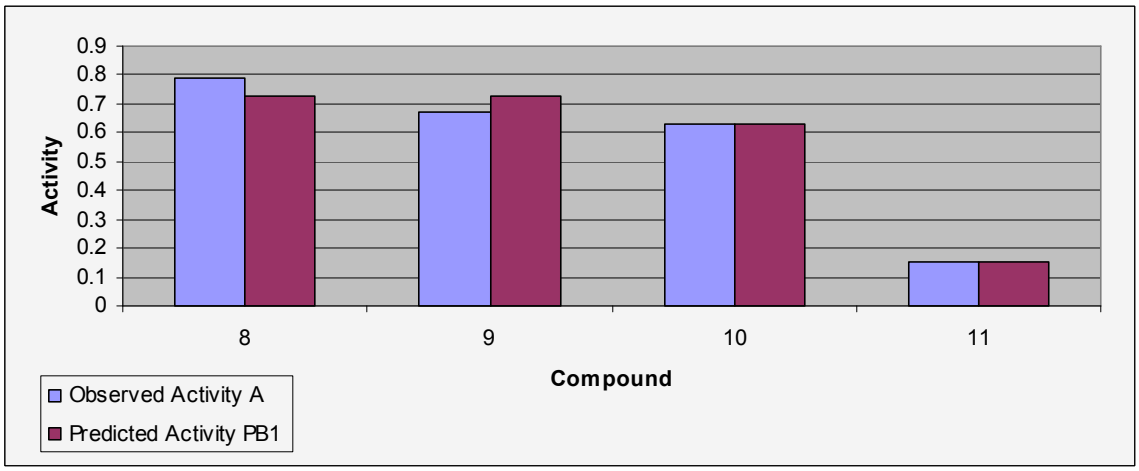
Table-12: Values of predicted activities PD1 to PD3

Comp	PD1	PD2	PD3
21	2.080	2.033	2.017
22	1.750	1.760	1.756
25	1.840	1.809	1.831
27	1.713	1.724	1.721
28	1.478	1.490	1.490
29	1.715	1.725	1.722
30	1.708	1.719	1.716
31	1.668	1.678	1.676
32	1.039	1.053	1.060

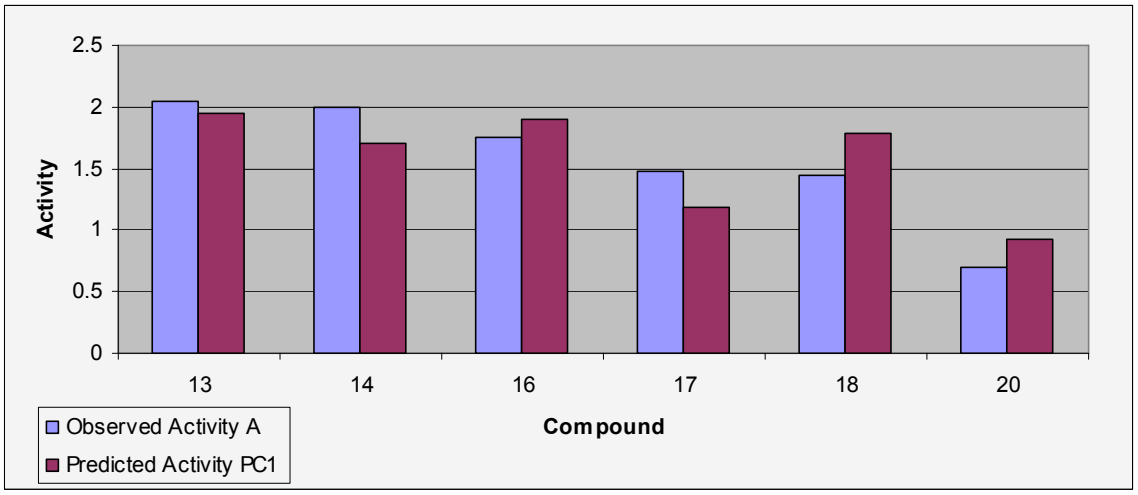
Graph-1: Graph between predicted activity PA1 and observed activity A in terms of RBA



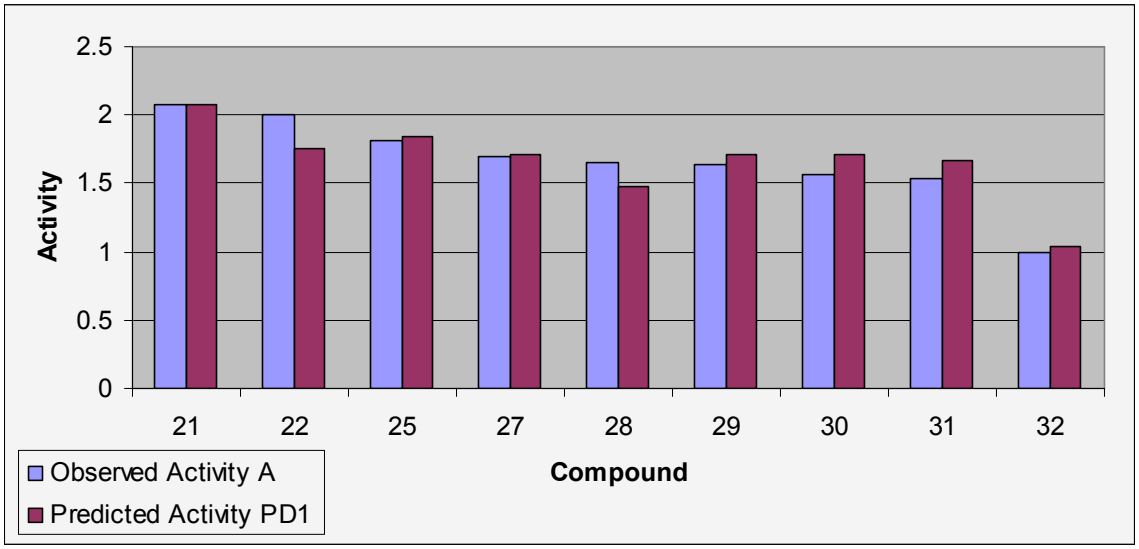
Graph-2: Graph between predicted activity PB1 and observed activity A in terms of RBA



Graph-3: Graph between predicted activity PC1 and observed activity A in terms of RBA



Graph-4: Graph between predicted activity PD1 and observed activity A in terms of RBA



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