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Article

Drug-Receptor Interaction of Peptidic HIV-1 Protease: Polar Effect-II

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Abstract: Klopman described the chemical reaction of metal ions and base ions in term of softness, $E^{\ddagger}_{n}$ and $E^{\ddagger}_{m}$, respectively. By simple modification of known methods, Singh et al. made it applicable for neutral Lewis acids (transition metal salts) and bases (organic molecules) and also extended its application to biological systems for site selectivity and to explain reaction mechanism (markovnikov and anti-markovnikov rule), ligand-receptor interaction of testosterones, estrogens and tetrahydroimidazobenzodiazepinone. In this study effective atomic softness $E^{\ddagger}_{n(eff)}$ and $E^{\ddagger}_{m(eff)}$, and their change $\Delta E^{\ddagger}_{nm}$ have been used for site selectivity and polar interaction between 51 peptidic HIV-1 protease inhibitors and receptor amino acids. $\Delta E^{\ddagger}_{nm}$ values derived from drug-receptor interaction show that when one moiety on receptor behaves as nucleophile (O of valine amino acid) at the same time maximum electrophilic site of the drug (C-atom of the maximum $E^{\ddagger}_{n(eff)}$ value) orient itself to come close the respective site and make maximum interaction, while when another moiety on receptor behaves as electrophilic site (C of isoleucine amino acid), at the same time maximum nucleophilic site of the drug (O-atom of the maximum $E^{\ddagger}_{m(eff)}$ value) also orient itself to come close the respective site and make maximum interaction.

Keywords: Effective atomic softness, $\Delta E^{\ddagger}_{nm}$, HIV-1 protease inhibitors, PM3

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1. Introduction

In our successive publications, we have studied pharmacokinetics followed by hydrophobic interaction of peptidic HIV-1 protease inhibitors [1, 2]. The present work describes the polar interaction based on effective atomic softness. Klopman provides a very convenient way to describe the chemical reactivity of a compound with the help of atomic softness values in terms of $E^{\ddagger}_{n}$ and $E^{\ddagger}_{m}$ [3]. This concept was based on the charge and frontier orbital controlled chemical reaction of perturbation theory.

$$E_m^{\ddagger} = IP_m - a^2(IP_m - EA_m) - \left[\frac{\chi_r\left(C_r^m\right)^2}{R_r}\right]\left(1-\frac{1}{\epsilon}\right)\left[q_r + 2b^2\chi_r\left(C_r^m\right)^2\right] \quad (1)$$

$$E_n^{\ddagger} = IP_n - b^2(IP_n - EA_n) - \left[\frac{\chi_s\left(C_s^n\right)^2}{R_s}\right]\left(1-\frac{1}{\epsilon}\right)\left[q_s + 2b^2\chi_s\left(C_s^n\right)^2\right] \quad (2)$$

where, $E^{\ddagger}_{n}$ = softness of an acid, $E^{\ddagger}_{m}$ = softness of a base, IP = ionization potential of atom, EA = electron affinity of atom, a^2 = ¾, b^2 = ¼, C = 1, ϵ = dielectric constant of the medium in which reaction is carried out, R = radius of atom whose softness is to be de-

termined, q = charge on the atom, C = electron density, $\chi = q - (q - 1)\sqrt{k}$, and k = 0.75, a and b are variational parameters. By a simple modification of known methods [4-7], Singh et al. were calculated the values of IP, q and R and made it applicable for a neutral chemical system [8]. The softness values so derived by them are termed as "effective softness" and are designated by symbols $E^{\ddagger}_{n(eff)}$ for Lewis acid and $E^{\ddagger}_{m(eff)}$ for Lewis base [9-11]. In this study semiempirical method has been used to calculate effective atomic softness: $E^{\ddagger}_{n(eff)}$ and $E^{\ddagger}_{m(eff)}$, for 51 peptidic HIV-1 protease inhibitors (HIV-1-PRIs).

2. Materials and Methods

Fifty-one HIV-1-PRIs have been used as study material and are separately listed in Table 1, 2 and 3 with their observed biological activities in term of IC_{50} [12-14]. All the fifty-one inhibitors have been divided in three sets on the basis of their structural similarities (Figure 1, 2and 3). The first, second and third set comprises of eighteen, seventeen and sixteen inhibitors, respectively. The logarithms of the inverse of IC_{50} have been used as biological end point (log1/C) in the study. For solving the modified Klopman equations, the 3D modeling and geometry optimization of all the compounds have been performed with the help of CAChe Pro software of Fujitsu [15, 16]. The study is based on semiempirical PM3 method [17, 18]. The PM3 based calculations have been performed with MOPAC 2002 software associated with CAChe. The values of various parameters to solve modified Klopman softness have been calculated by softness calculator which was developed by Singh research group [4]. Singh et al. made Klopman equations applicable for neutral Lewis acids (transition metal salts) and bases (organic molecules) and also extended its application to biological systems for site selectivity and to explain reaction mechanism (markovnikov and anti-markovnikov rule), ligand-receptor interaction of testosterones, estrogens and tetrahydroimidazobenzodiazepinone [19-23].

Table 1. First set of peptidic HIV-1-PRIs with observed biological activities [12]

Compd.No	Substiunts				o(log1/C)
	R	X	Y	Z	
1	Cbz[a]	H	$CHMe_2$	Me	5.82
2	Cbz	H	$CHMe_2$	n-Bu	6.03
3	Qua[b]	H	$CHMe_2$	n-Bu	6.90
4	Cbz	H	$CHMe_2$	n-Pr	6.29
5	Cbz	H	$CHMe_2$	Et	6.48
6	Cbz	H	$CHMe_2$	i-Pr	6.59
7	Cbz	H	$CHMe_2$	t-Bu	7.46
8	Qua	H	$CHMe_2$	t-Bu	8.22
9	Cbz	H	CH_2CHMe_2	t-Bu	7.89
10	Qua	H	CH_2CHMe_2	t-Bu	8.52
11	Cbz	H	C_6H_{11}	t-Bu	7.54
12	Qua	H	C_6H_{11}	t-Bu	8.30
13	Cbz	H	C_6H_5	t-Bu	7.72
14	Qua	H	C_6H_5	t-Bu	8.52
15[c]	Cbz	Me	C_6H_5	t-Bu	5.19
16[d]	Cbz	Me	C_6H_5	t-Bu	5.29
17	Cbz	H	4-Py	t-Bu	6.98
18	Qua	H	4-Py	t-Bu	7.72

[a]Carbobenzyloxy. [b]Quinolinyl-2-carboxamide. [c]CHXY in R-configuration. [d]CHXY in S-configuration.

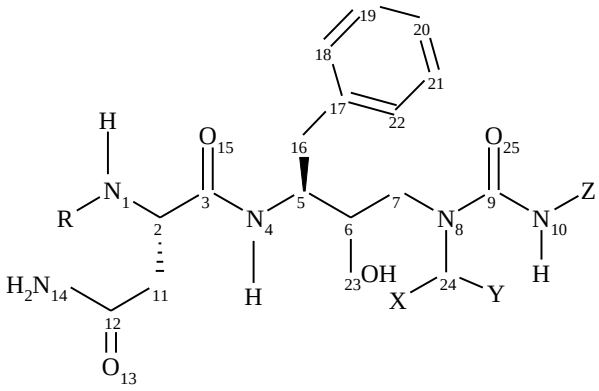


Figure 1. Parent skeleton along with reactive sites (compound no. 1-18)

Table 2. Second set of fifty one peptidic HIV-1-PRIs with observed biological activities [13]

Compd.No.	Substiunts			o(log1/C)
	R_1	**R2**	**R3**	
19	CH_2Ph	H	H	9.6
20	CH_2Ph	Me	H	8.11
21	CH_2CH_2Ph	H	OH	9.72
22	CH_2-4-CF_3Ph	H	H	9.59
23	CH_2CH=$CHPh$	H	H	9.64
24	$CH_2C_6F_5$	H	H	9.22
25	CH_2-4-CH_3Ph	H	H	9.54
26	CH_2-4-NH_2Ph	H	H	9.51
27	CH_2-4-NO_2Ph	H	H	9.57
28	H	H	H	5.53
29	CH_2-4-OHPh	H	H	9.8
30	CH_2CH=CH_2	H	H	7.56
31	CH_2-4-IPh	H	H	9.14
32	CH_2C(O)Ph	H	H	8.27
33	CH_2-4-Pyridyl	H	H	9.28
34	CH_2SPh	H	H	9.60
35	CH_2-4-CMe_3Ph	H	H	9.77

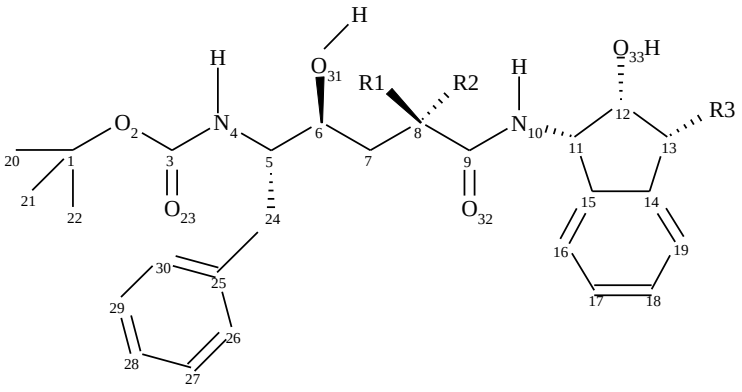
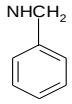
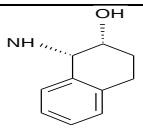
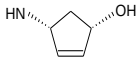
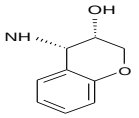
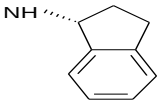
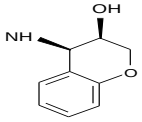
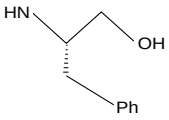
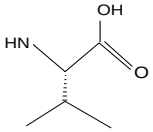
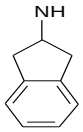
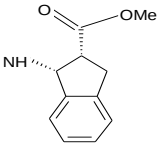
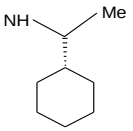
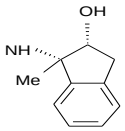
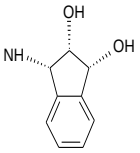
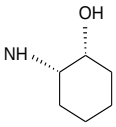
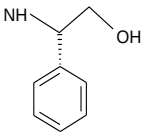


Figure 2. Parent skeleton along with reactive sites (compound no. 19-35)

Table 3. Third set of fifty one peptidic HIV-1-PRIs with observed biological activities [13]

Compd. No.	X	o(log1/C)	Compd. No.	X	o(log1/C)
36		6.94	44		9.16
37		8.02	45		9.75
38		7.47	46		7.39
39		6.16	47		4.52
40		6.79	48		6.89
41		7.18	49		6.84
42		6.67	50		10.00
43		6.91	51		7.41

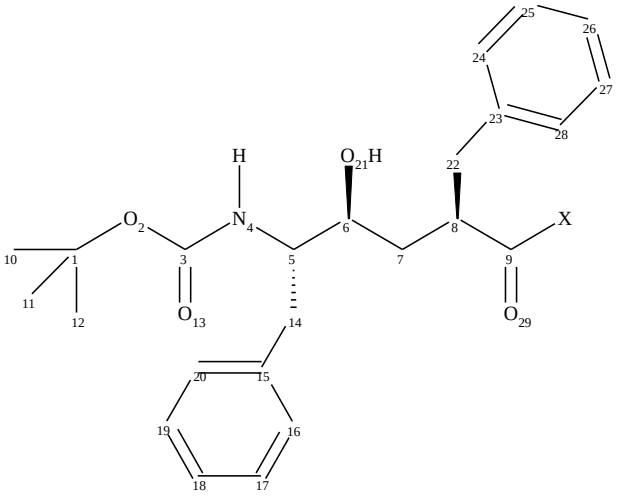


Figure 3. Parent skeleton along with reactive sites (compound no. 36-51)

3. Results and Discussion

Out of fifty-one compounds under study, the eighteen compounds (compound no. 1-18) have the parent skeleton of Figure 1, which has 25 sites. Out of remaining thirty-three, the seventeen compounds (compound no. 19-35) have the parent skeleton of Figure 2, which has 33 sites. While the remaining sixteen compounds (compound no. 36-51) have the parent skeleton of Figure 3, which has 29 sites [10, 11]. The effective softness values represented by $E^{\ddagger}_{n(eff)}$ describe the electrophilic character of compound, whereas $E^{\ddagger}_{m(eff)}$ describe the nucleophilic character of compound [19-23]. $E^{\ddagger}_{n(eff)}$, IP and EA of electron deficient carbon center (electrophilic site) have been evaluated at sixteen sites (C2, C3, C5, C6, C7, C9, C11, C12, C16, C17, C18, C19, C20, C21, C22 and C24) of compound no 1-18, twenty six sites (C1, C3, C5, C6, C7, C8, C9, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C24, C25, C26, C27, C28, C29 and C30) of compound no 19-35 and twenty three sites (C1, C3, C5, C6, C7, C8, C9, C10, C11, C12, C14, C15, C16, C17, C18, C19, C20, C22, C24, C25, C26, C27 and C28) of compound no 36-51. While $E^{\ddagger}_{m(eff)}$, IP and EA of electron rich center (nucleophilic site) have been evaluated at nine sites (N1, N4, N8, N10, O13, N14, O15, O23 and O25) of compound no 1-18, seven sites (O2, N4, N10, O23, O31, O32 and O33) of compound no 19-35 and six sites (O2, N4, O13, O21, O23 and O29) of compound no 36-51. Softness parameter is a very dominating factor when correlated with the mechanism of action of a variety of known therapeutic agents and their pharmacoactivities. Because it included atomic radius (R), electron density (C), charge (q), ionization potential (IP), and electron affinity (EA) of atom. The incorporation of dielectric constant (ε) shows the effect of medium in which reaction is carried out. Correlation of this dominating factor, with mechanism of action of various therapeutic agents and their pharmacoactivities, would be very valuable in search of a new advance drug before its synthesis. This technique when applied saves time and resources with the limited facilities for a medicinal scientist. Effective softness values represented by $E^{\ddagger}_{n(eff)}$ describe the electrophilic character of an atom within a molecule. Higher the value of $E^{\ddagger}_{n(eff)}$ of a site greater will be the electrophilic character of that site within the molecule. Further, the site of highest $E^{\ddagger}_{n(eff)}$ value characterizes the susceptibility of the molecules toward the attack of nucleophile. The highest $E^{\ddagger}_{n(eff)}$ values of compounds are placed in Table 4. A reference to this table shows that, in case of compounds of group-A, the $E^{\ddagger}_{n(eff)}$ value of all the compounds is highest at position C11, except compounds 5, 6, 10 and 12, which has highest $E^{\ddagger}_{n(eff)}$ value at position C7. A close look at parent skeleton of compounds of group-A clearly indicates that the positions C7 and C11 are carbon to which the urea isostere and -$CONH_2$ group is linked to it, respectively. In group-B, the $E^{\ddagger}_{n(eff)}$ value of compounds 19, 22, 23, 27, 31, 33, 34 and 35 is highest at position C21. While of compounds 20, 21, 25, 26, 28, 29 and 30, it is highest at position C22 and in compounds 24 and 32 it is highest at position C7. A close look at parent skeleton of compounds of group-B clearly indicates that the position C7, C21 and C22 is carbon of methylene, methyl and methyl moiety, respectively. In group-C, the $E^{\ddagger}_{n(eff)}$ value of compounds 37, 38, 40-45, 47-49 and 51 is highest at position C11. While of compounds 36 and 39, it is highest at position C12 and in compounds 46 and 50 it is highest at position C7. A close look at parent skeleton of compounds of group-C clearly indicates that the position C7, C11 and C12 is also carbon of methylene, methyl and methyl moiety, respectively. The examination of Table 1 indicates that there must be a relationship between effective softness, $E^{\ddagger}_{n(eff)}$, and observed biological activity. Of course, there exist relationship between $E^{\ddagger}_{n}$ and log 1/C but there no sequential rise or fall. In order to provide sequential relationship, we have divided the compounds into subgroups, group-A: subgroup-a, b, c and d; group-B: subgroup-e, f, g and h; and group-C: subgroup-i, j and k. A close look to these subgroups has shown that (i) In subgroup-a, compound 1, 2 and 16; in subgroup-b, compound 3, 5 and 17; in subgroup-c, compound 6, 7, 8, 9, 11 and 13; and in subgroup-d, compound 10, 14 and 18 show the direct relationship very clearly. Compound 4, 12 and

15 do not follow the sequential trend, (ii) In subgroup-e, compound 20, 24, 30, 31 and 32 and in subgroup-f, compound 22, 25, 26 and 27 show the direct relationship very clearly. While in subgroup-g, compound 21, 23 and 35 and in subgroup-h, compound 19, 33 and 34 shows the inverse relationship very clearly. Compound 28 and 29 do not follow the sequential trend, and (iii) In subgroup-i, compound 36, 38, 42, 43 and 50; and in sub-group-j, compound 40, 47 and 49 show the direct relationship very clearly. While in subgroup-l, compound 39, 41, 45, 46 and 48 shows the inverse relationship very clearly. Compound 28, 29, 37 and 44 do not follow the sequential trend.

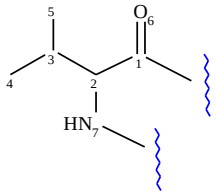
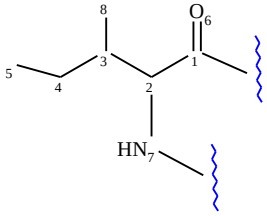
Table 4. Values of quantum chemical descriptors with observed biological activities of fifty one peptidic HIV-1-PRIs

No.	Descriptors								o(log1/C)
	Electrophilic Site				Nucleophilic Site				
	Site	IP_n	EA_n	$E^{\ddagger}_{n(eff)}$	Site	IP_m	EA_m	$E^{\ddagger}_{m(eff)}$	
Group A 1	C11	12.758	-2.827	56.480	O13	26.544	-16.613	-28.032	5.82
2	C11	12.842	-2.823	56.859	O13	26.346	-16.327	-27.693	6.03
3	C11	12.557	-1.846	55.809	O13	27.529	-16.818	-28.872	6.90
4	C11	12.641	-2.618	55.999	O13	26.871	-16.848	-28.427	6.29
5	C7	12.536	-2.585	55.529	O13	28.494	-18.543	-30.771	6.48
6	C7	12.493	-2.456	55.362	O13	28.132	-18.095	-30.198	6.59
7	C11	12.539	-2.423	55.582	O13	27.236	-17.120	-28.876	7.46
8	C11	12.706	-2.027	56.444	O13	25.809	-15.129	-26.478	8.22
9	C11	-3.313	4.170	56.372	O13	-12.725	6.3890	-22.298	7.89
10	C7	12.506	-1.854	55.573	O13	28.020	-17.369	-29.608	8.52
11	C11	12.642	-2.788	55.961	O13	27.661	-17.807	-29.661	7.54
12	C7	12.579	-1.843	55.910	O13	27.892	-17.156	-29.367	8.30
13	C11	12.720	-2.650	56.349	O13	27.208	-17.138	-28.869	7.72
14	C11	12.637	-1.970	56.139	O13	26.921	-16.327	-28.097	8.52
15	C11	12.767	-2.832	56.518	O13	26.840	-16.904	-28.445	5.19
16	C11	12.542	-2.527	55.569	O13	26.490	-16.475	-27.897	5.29
17	C11	12.626	-2.342	56.003	O13	27.517	-17.232	-29.154	6.98
18	C11	12.536	-1.891	55.698	O13	27.185	-16.540	-28.434	7.72
Group B 19	C21	12.773	-2.970	56.510	O23	25.036	-15.233	-26.012	9.60
20	C22	12.743	-2.884	56.396	O23	25.675	-15.816	-26.864	8.11
21	C22	12.713	-2.680	56.311	O23	25.187	-15.154	-26.062	9.72
22	C21	12.789	-2.459	56.712	O23	25.006	-14.676	-25.602	9.59
23	C21	12.779	-3.012	56.526	O23	25.022	-15.255	-26.017	9.64
24	C7	12.877	-2.074	57.200	O23	25.258	-14.455	-25.624	9.22
25	C22	12.729	-3.058	56.291	O32	25.241	-15.570	-26.390	9.54
26	C22	12.738	-3.683	56.170	O32	24.953	-15.898	-26.417	9.51
27	C21	12.725	-1.775	56.590	O32	25.235	-14.286	-25.490	9.57
28	C22	12.804	-2.868	56.676	O23	24.825	-14.889	-25.626	5.53
29	C22	12.725	-3.252	56.225	O32	25.207	-15.734	-26.480	9.80
30	C22	12.721	-2.874	56.297	O32	25.194	-15.348	-26.202	7.56
31	C21	12.786	-2.921	56.579	O23	25.038	-15.174	-25.972	9.14
32	C7	12.726	-2.404	56.437	O32	24.422	-14.099	-24.795	8.27
33	C21	12.777	-2.583	56.624	O23	25.046	-14.852	-25.752	9.28
34	C21	12.767	-2.432	56.618	O23	25.093	-14.759	-25.721	9.60
35	C21	12.706	-2.949	56.213	O32	25.243	-15.486	-26.332	9.77

Group C 36	C12	12.723	-2.807	56.327	O21	25.809	-15.892	-27.011	6.94
37	C11	12.746	-2.961	56.389	O21	25.506	-15.721	-26.680	8.02
38	C11	12.781	-2.996	56.539	O29	25.517	-15.733	-26.696	7.47
39	C12	12.815	-3.118	56.662	O13	25.309	-15.612	-26.466	6.16
40	C11	12.789	-2.996	56.578	O13	24.530	-14.737	-25.314	6.79
41	C11	12.759	-2.720	56.507	O13	25.631	-15.593	-26.678	7.18
42	C11	12.652	-2.770	56.009	O13	25.166	-15.284	-26.137	6.67
43	C11	12.684	-2.939	56.111	O13	25.166	-15.422	-26.234	6.91
44	C11	12.762	-2.869	56.483	O13	25.349	-15.456	-26.385	9.16
45	C11	12.652	-3.120	55.926	O13	25.895	-16.363	-27.401	9.75
46	C7	12.660	-3.025	55.980	O13	25.664	-16.029	-27.006	7.39
47	C11	12.786	-3.000	56.564	O29	25.649	-15.862	-26.879	4.52
48	C11	12.786	-3.180	56.515	O29	25.453	-15.847	-26.731	6.89
49	C11	12.810	-3.014	56.666	O29	25.224	-15.244	-26.150	6.84
50	C7	12.776	-2.796	56.567	O29	25.224	-15.244	-26.150	10.00
51	C11	12.738	-2.794	56.396	O29	25.115	-15.171	-26.023	7.41

Effective softness values represented by $E^{\ddagger}_{m(eff)}$ describe the nucleophilic character of an atom within a molecule. Higher the value of $E^{\ddagger}_{m(eff)}$ with negative sign of a site greater will be the nucleophilic character of that site within the molecule. Further, the site of highest $E^{\ddagger}_{m(eff)}$ value characterizes the susceptibility of the molecules toward the attack of electrophile. The highest $E^{\ddagger}_{m(eff)}$ values of compounds are also placed in Table 4. A reference to this table also shows that, in group-A, the highest $E^{\ddagger}_{m(eff)}$ value in all the eighteen compounds is associated with position O13. A close look at parent skeleton of compounds of group-A clearly indicates that the position O13 is oxygen of amidic moiety. In group-B, $E^{\ddagger}_{m(eff)}$ value of compounds 19-24, 28, 31, 33 and 34, it is highest at position O23. While of compounds 25-27, 29, 30, 32 and 35 is highest at position O32. A close look at parent skeleton of compounds of group-B clearly indicates that the positions O23 and O32 are oxygen of carboxylic and amidic moiety, respectively. In group-C, the $E^{\ddagger}_{m(eff)}$ value of compounds 36 and 37 it is highest at position O21. While of compounds 39-46, it is highest at position O13 and in compounds 38 and 47-51 it is highest at position C29. A close look at parent skeleton of compounds of group-C clearly indicates that the positions O13, O21 and O29 are oxygen of carboxylic, hydroxyl and carbonyl moiety, respectively. The examination of Table 1 also indicates that there must be a relationship between effective softness, $E^{\ddagger}_{m(eff)}$, and observed biological activity. Of course, there also exist relationship between $E^{\ddagger}_{m(eff)}$ and log 1/C, but there is also no sequential rise or fall. In order to provide sequential relationship, we have divided the compounds into same three groups, group-A: compound no. 1-18; group-B: compound no. 19-35 and group-C: compound no. 36-51, on the basis of their parent skeleton. But, each group has subdivided into different subgroups, group-A: subgroup-a, b, c and d; group-B: subgroup-e, f and g; and group-C: subgroup-h, i and j. A close look to these subgroups has shown that (i) In subgroup-a, compound 2, 8, 15 and 16; in subgroup-b, compound 5, 6, 13, 14, 17 and 18 show the direct relationship very clearly. In subgroup-c, compound 1, 3, 4, 7 and 11; and in subgroup-d, compound 9, 10 and 12 show the inverse relationship very clearly, (ii) In subgroup-e, compound 20, 28 and 30; in subgroup-f, compound 22, 27 and 34 and in subgroup-g, compound 19, 21, 23, 24, 29, 32, 33 and 35 show the *inverse* relationship very clearly. Compound 25, 26 and 31 do not follow the sequential trend, and (iii) In subgroup-h, compound 39, 40, 42 and 47; and in subgroup-j, compound 37, 38, 44, 48 and 50 show the direct relationship very clearly. While in subgroup-i, compound 41, 43, 45, 46 and 49 show the inverse relationship Compound 36 and 51 do not follow the sequential trend.

Table 5. Softness values of receptor amino acids of binding sites

Receptor Protein	Atom	IP	EA	$E^{\ddagger}_{n(eff)}$	$E^{\ddagger}_{m(eff)}$
	C1	8.645	0.780	33.011	
	C2	11.919	-2.494	52.651	
	C3	11.890	-2.465	52.519	
	C4*	12.327	-2.902	54.482	
	C5	12.292	-2.867	54.327	
	O6*	25.448	-16.023		-26.850
	N7	15.745	-6.320		-13.089
	C1	8.688	1.071	33.522	
	C2	11.964	-2.206	52.938	
	C3	11.974	-2.216	52.986	
	C4	12.186	-2.427	53.936	
	C5	12.315	-2.556	54.512	
	C8*	12.490	-2.732	55.280	
	O6*	25.318	-15.559		-26.435
	N7	15.925	-6.166		-13.105

It is well established that the stability of the compound formed between nucleophile and electrophile depends upon the value of difference between softness values of $E^{\ddagger}_{m(eff)}$ of nucleophile, and softness values of $E^{\ddagger}_{n(eff)}$ of electrophile, $\Delta E^{\ddagger}_{nm}$ represent the difference. The higher is the $\Delta E^{\ddagger}_{nm}$ greater is the stability of the compound [24].

$$\Delta E^{\ddagger}_{nm} = \left| E^{\ddagger}_{n(eff)} - E^{\ddagger}_{m(eff)} \right| \tag{3}$$

HIV-1 protease enzyme (HIV-1-PR) is a viral encoded homodimeric aspartyl protease with C_2 symmetry [25, 26]. A catalytic triad of Asp-Thr-Gly contributed by each monomer comprises the active site of the enzyme. The amino acids constituting the binding site (S2/S2′ pocket) are Val-32, Ile-47, Ile-50, and Ile-84 in each monomeric polypeptidic unit of the protease enzyme [27, 28]. HIV inhibitors make initial contact with the receptor amino acids Val and Ile of binding site rather than Asp, Thr and Gly of catalytic site. The study has been made on interaction with Val and Ile of binding site. The nitrogen of amino and oxygen atom of carboxylic group of receptor protein have the nucleophilic character and can interact with the electrophilic center on the inhibitor, while the electron deficient carbon atoms can interact with the nucleophilic site on the inhibitor and vice versa. Thus, the highest $E^{\ddagger}_{n(eff)}$ value of compounds characterize the susceptibility of the molecules toward the attack of nucleophile, while the highest $E^{\ddagger}_{m(eff)}$ value of compounds characterize the susceptibility of the molecules toward the attack of electrophile. The softness values $E^{\ddagger}_{n(eff)}$ of at 5 sites of valine and 6 sites of isoleucine, while the softness values $E^{\ddagger}_{m(eff)}$ of 2 sites of both Val and isoleucine have also been evaluated and are presented in Table 5. When inhibitors are treated as acids and receptor proteins as base, the highest values of softness $E^{\ddagger}_{n(eff)}$ of inhibitors and highest values of $E^{\ddagger}_{m(eff)}$ of amino acids have been used for deriving $\Delta E^{\ddagger}_{nm}$ values. While, when inhibitors are treated as bases and receptor proteins as acids, the highest values of softness $E^{\ddagger}_{m(eff)}$ of inhibitors and highest values of $E^{\ddagger}_{n(eff)}$ of amino acids have been used for deriving $\Delta E^{\ddagger}_{nm}$ values. The highest values of softness and the $\Delta E^{\ddagger}_{nm}$ derived from them are given in Table 6. A reference to this Table 1 shows that in the former case the $\Delta E^{\ddagger}_{nm}$ values in case of Val amino acid is higher than the Ile amino acid, while in later case the $\Delta E^{\ddagger}_{nm}$ values in case of Ile amino acid is higher than the Val amino acid.

Table 6. $\Delta E^{\ddagger}_{nm}$ value derived from interaction between receptor protein of enzyme and inhibitors

Compd. No.	Carbon Atom	$E^{\ddagger}_{n(eff)}$	Val ($E^{\ddagger}_{m(eff)}$ =-26.850)	Ile ($E^{\ddagger}_{m(eff)}$ =-26.435)	Compd. No.	Oxygen Atom	$E^{\ddagger}_{m(eff)}$	Val ($E^{\ddagger}_{n(eff)}$ =54.482)	Ile ($E^{\ddagger}_{n(eff)}$ =55.280)
			$\Delta E^{\ddagger}_{nm}$	$\Delta E^{\ddagger}_{nm}$				$\Delta E^{\ddagger}_{nm}$	$\Delta E^{\ddagger}_{nm}$
Group A 1	C11	56.480	82.915	83.330	1	O13	-28.032	82.514	83.312
2	C11	56.859	83.709	83.294	2	O13	-27.693	82.175	82.973
3	C11	55.809	82.659	82.244	3	O13	-28.872	83.354	84.152
4	C11	55.999	82.849	82.434	4	O13	-28.427	82.909	83.707
5	C7	55.529	82.379	81.964	5	O13	-30.771	85.253	86.051
6	C7	55.362	82.212	81.797	6	O13	-30.198	84.680	85.478
7	C11	55.582	82.432	82.017	7	O13	-28.876	83.358	84.156
8	C11	56.444	83.294	82.879	8	O13	-26.478	80.960	81.758
9	C11	56.372	83.222	82.807	9	O13	-22.298	76.780	77.578
10	C7	55.573	82.423	82.008	10	O13	-29.608	84.090	84.888
11	C11	55.961	82.811	82.396	11	O13	-29.661	84.143	84.941
12	C7	55.910	82.760	82.345	12	O13	-29.367	83.849	84.647
13	C11	56.349	83.199	82.784	13	O13	-28.869	83.351	84.149
14	C11	56.139	82.989	82.574	14	O13	-28.097	82.579	83.377
15	C11	56.518	83.368	82.953	15	O13	-28.445	82.927	83.725
16	C11	55.569	82.419	82.004	16	O13	-27.897	82.379	83.177
17	C11	56.003	82.853	82.438	17	O13	-29.154	83.636	84.434
18	C11	55.698	82.548	82.133	18	O13	-28.434	82.916	83.714
Group B 19	C21	56.510	83.360	82.945	19	O23	-26.012	80.494	81.292
20	C22	56.396	83.246	82.831	20	O23	-26.864	81.346	82.144
21	C22	56.311	83.161	82.746	21	O23	-26.062	80.544	81.342
22	C21	56.712	83.562	83.147	22	O23	-25.602	80.084	80.882
23	C21	56.526	83.376	82.961	23	O23	-26.017	80.499	81.297
24	C7	57.200	84.050	83.635	24	O23	-25.624	80.106	80.904
25	C22	56.291	83.141	82.726	25	O32	-26.390	80.872	81.670
26	C22	56.170	83.020	82.605	26	O32	-26.417	80.899	81.697
27	C21	56.590	83.440	83.025	27	O32	-25.490	79.972	80.770
28	C22	56.676	83.526	83.111	28	O23	-25.626	80.108	80.906
29	C22	56.225	83.075	82.660	29	O32	-26.480	80.962	81.760
30	C22	56.297	83.147	82.732	30	O32	-26.202	80.684	81.482
31	C21	56.579	83.429	83.014	31	O23	-25.972	80.454	81.252
32	C7	56.437	83.287	82.872	32	O32	-24.795	79.277	80.075
33	C21	56.624	83.474	83.059	33	O23	-25.752	80.234	81.032
34	C21	56.618	83.468	83.053	34	O23	-25.721	80.203	81.001
35	C21	56.213	83.063	82.648	35	O32	-26.332	80.814	81.612
Group C 36	C12	56.327	83.177	82.762	36	O21	-27.011	81.493	82.291
37	C11	56.389	83.239	82.824	37	O21	-26.680	81.162	81.960
38	C11	56.539	83.389	82.974	38	O29	-26.696	81.178	81.976
39	C12	56.662	83.512	83.097	39	O13	-26.466	80.948	81.746
40	C11	56.578	83.428	83.013	40	O13	-25.314	79.796	80.594
41	C11	56.507	83.357	82.942	41	O13	-26.678	81.160	81.958
42	C11	56.009	82.859	82.444	42	O13	-26.137	80.619	81.417
43	C11	56.111	82.961	82.546	43	O13	-26.234	80.716	81.514
44	C11	56.483	83.333	82.918	44	O13	-26.385	80.867	81.665
45	C11	55.926	82.776	82.361	45	O13	-27.401	81.883	82.681

46	C7	55.980	82.830	82.415	46	O13	-27.006	81.488	82.286
47	C11	56.564	83.414	82.999	47	O29	-26.879	81.361	82.159
48	C11	56.515	83.365	82.950	48	O29	-26.731	81.213	82.011
49	C11	56.666	83.516	83.101	49	O29	-26.150	80.632	81.430
50	C7	56.567	83.417	83.002	50	O29	-26.150	80.632	81.430
51	C11	56.396	83.246	82.831	51	O29	-26.023	80.505	81.303

4. Conclusion

Softness parameter is a very dominating factor when correlated with the mechanism of action of a variety of known therapeutic agents and their pharmacoactivities. Because it included atomic radius (R), electron density (C), charge (q), ionization potential (IP), and electron affinity (EA) of atom. $\Delta E^{\ddagger}_{nm}$ values derived from drug-receptor interaction show that when one moiety on receptor behaves as nucleophile (O of valine amino acid) at the same time maximum electrophilic site of the drug (C-atom of the maximum $E^{\ddagger}_{n(eff)}$ value) orient itself to come close the respective site and make maximum interaction, while when another moiety on receptor behaves as electrophilic site (C of isoleucine amino acid), at the same time maximum nucleophilic site of the drug (O-atom of the maximum $E^{\ddagger}_{m(eff)}$ value) also orient itself to come close the respective site and make maximum interaction.

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