**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, $E_n$ and $E_m$, 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 $E^{|\text{eff}|}$ and $E^{|\text{eff}|}_m$ and their change $\Delta E^{|\text{eff}|}$ have been used for site selectivity and polar interaction between 51 peptidic HIV-1 protease inhibitors and receptor amino acids. $\Delta E^{|\text{eff}|}$ 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 of the maximum $E^{|\text{eff}|}$ 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 of the maximum $E^{|\text{eff}|}_m$ value) also orient itself to come close the respective site and make maximum interaction.

**Keywords:** Effective atomic softness, $\Delta E^{|\text{eff}|}$, HIV-1 protease inhibitors, PM3

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 $E_n$ and $E_m$ [3]. This concept was based on the charge and frontier orbital controlled chemical reaction of perturbation theory.

$$E^{|\text{eff}|}_n = IP_n - a^2(IP_n - EA_n) - \left[ \frac{X_r}{R_f} \left( \frac{C^{|\text{eff}|}_r}{q_s + 2b^2 X_s} \right)^2 \right] \left[ 1 - \frac{1}{\epsilon} \right]$$ (1)

$$E^{|\text{eff}|}_m = IP_m - b^2(IP_m - EA_m) - \left[ \frac{X_s}{R_s} \left( \frac{C^{|\text{eff}|}_s}{q_s + 2b^2 X_s} \right)^2 \right] \left[ 1 - \frac{1}{\epsilon} \right]$$ (2)

where, $E_n$ = softness of an acid, $E_m$ = softness of a base, $IP$ = ionization potential of atom, $EA$ = electron affinity of atom, $a^2 = \frac{3}{4}$, $b^2 = \frac{1}{4}$, $C = 1$, $\epsilon$ = dielectric constant of the medium in which reaction is carried out, $R$ = radius of atom whose softness is to be de-
terminated, \( q \) = 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 \( E_{n(eff)} \) for Lewis acid and \( E_{m(eff)} \) for Lewis base [9-11]. In this study semiempirical method has been used to calculate effective atomic softness: \( E_{n(eff)} \) and \( E_{m(eff)} \), 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 | R          | Substiunts          | o(log1/C) |
|----------|------------|---------------------|-----------|
| 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\(_2\) | t-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\(_2\)CHMe\(_2\) | t-Bu | 7.89     |
| 10       | Qua        | H                   | CH\(_2\)CHMe\(_2\) | t-Bu | 8.52     |
| 11       | Cbz        | H                   | C\(_6\)H\(_11\) | t-Bu | 7.54     |
| 12       | Qua        | H                   | C\(_6\)H\(_11\) | t-Bu | 8.30     |
| 13       | Cbz        | H                   | C\(_6\)H\(_5\) | t-Bu | 7.72     |
| 14       | Qua        | H                   | C\(_6\)H\(_5\) | t-Bu | 8.52     |
| 15\(^c\) | Cbz        | Me                  | C\(_6\)H\(_5\) | t-Bu | 5.19     |
| 16\(^d\) | Cbz        | Me                  | C\(_6\)H\(_5\) | 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.
Table 2. Second set of fifty one peptidic HIV-1-PRIs with observed biological activities [13]

| Compd.No. | Substituents | \( \log_1 (C) \) |
|-----------|--------------|------------------|
| 19        | CH\(_2\)Ph   | H                | H                | 9.6 |
| 20        | CH\(_2\)Ph   | Me               | H                | 8.11 |
| 21        | CH\(_2\)CH\(_2\)Ph | H      | OH               | 9.72 |
| 22        | CH\(_2\)-4-CF\(_3\)Ph | H | H                | 9.59 |
| 23        | CH\(_2\)=CHPh | H                | H                | 9.64 |
| 24        | CH\(_2\)C\(_6\)F\(_5\) | H | H                | 9.22 |
| 25        | CH\(_2\)-4-CH\(_2\)Ph | H | H                | 9.54 |
| 26        | CH\(_2\)-4-NH\(_2\)Ph | H | H                | 9.51 |
| 27        | CH\(_2\)-4-NO\(_2\)Ph | H | H                | 9.57 |
| 28        | H            | H                | H                | 5.53 |
| 29        | CH\(_2\)-4-0HPh | H | H                | 9.8  |
| 30        | CH\(_2\)CH=CH\(_2\) | H | H                | 7.56 |
| 31        | CH\(_2\)-4-IPh | H                | H                | 9.14 |
| 32        | CH\(_2\)C(O)Ph | H | H                | 8.27 |
| 33        | CH\(_2\)-4-Pyridyl | H | H                | 9.28 |
| 34        | CH\(_2\)SPh   | H                | H                | 9.60 |
| 35        | CH\(_2\)-4-CMe\(_3\)Ph | H | H                | 9.77 |

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

Figure 2. Parent skeleton along with reactive sites (compound no. 19-35)
| Compd. No. | X          | o(\log 1/C) | Compd. No. | X          | o(\log 1/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 \( E^{n(eff)} \) describe the electrophilic character of compound, whereas \( E^{m(eff)} \) describe the nucleophilic character of compound [19-23]. \( E^{n(eff)} \), 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, C24, C25, C26, C27, C28, C29 and C30) 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 \( E^{m(eff)} \) IP and EA of electron rich center (nucleophilic site) have been evaluated at nine sites (N1, N4, N8, N10, O13, O14, 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 (\( \epsilon \)) 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 \( E^{n(eff)} \) describe the electrophilic character of an atom within a molecule. Higher the value of \( E^{n(eff)} \) of a site greater will be the electrophilic character of that site within the molecule. Further, the site of highest \( E^{n(eff)} \) Value characterizes the susceptibility of the molecules toward the attack of nucleophile. The highest \( E^{m(eff)} \) values of compounds are placed in Table 4. A reference to this table shows that, in case of compounds of group-A, the \( E^{n(eff)} \) value of all the compounds is highest at position C11, except compounds 5, 6, 10 and 12, which has highest \( E^{n(eff)} \) 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; group is linked to it, respectively. In group-B, the \( E^{n(eff)} \) 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 \( E^{n(eff)} \) 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 4 indicates that there must be a relationship between effective softness, \( E^{n(eff)} \) and observed biological activity. Of course, there exist relationship between \( E^{n} \) 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 subgroup-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-PPIs

| No. | Electrophilic Site | Nucleophilic Site | o(log1/C) |
|-----|-------------------|-------------------|-----------|
|     | Site              | IP<sub>n</sub>   | EA<sub>n</sub> | E<sub>n(eff)</sub> | Site              | IP<sub>m</sub> | EA<sub>n</sub> | E<sub>m(eff)</sub> |
| Group A 1 | C11 | 12.758 | -2.827 | 56.480 | O13 | 26.544 | -16.613 | -28.032 | 5.82 |
|     | C2   | 12.842 | -2.823 | 56.859 | O13 | 26.346 | -16.327 | -27.693 | 6.03 |
|     | C3   | 12.557 | -1.846 | 55.809 | O13 | 27.529 | -16.818 | -28.872 | 6.90 |
|     | C4   | 12.641 | -2.618 | 55.999 | O13 | 26.871 | -16.848 | -28.427 | 6.29 |
|     | C5   | 12.536 | -2.585 | 55.529 | O13 | 28.494 | -18.543 | -30.771 | 6.48 |
|     | C6   | 12.493 | -2.456 | 55.362 | O13 | 28.132 | -18.095 | -30.198 | 6.59 |
|     | C7   | 12.539 | -2.423 | 55.582 | O13 | 27.236 | -17.120 | -28.876 | 7.46 |
|     | C8   | 12.706 | -2.027 | 56.444 | O13 | 25.809 | -15.129 | -26.478 | 8.22 |
|     | C9   | -3.313 | 4.170  | 56.372 | O13 | -12.725 | 6.3890  | -22.298 | 7.89 |
|     | C10  | 12.506 | -1.854 | 55.573 | O13 | 28.020 | -17.369 | -29.608 | 8.52 |
|     | C11  | 12.642 | -2.788 | 55.961 | O13 | 27.661 | -17.807 | -29.661 | 7.54 |
|     | C12  | 12.579 | -1.843 | 55.910 | O13 | 27.892 | -17.156 | -29.367 | 8.30 |
|     | C13  | 12.720 | -2.650 | 56.349 | O13 | 27.208 | -17.138 | -28.869 | 7.72 |
|     | C14  | 12.637 | -1.970 | 56.139 | O13 | 26.921 | -16.327 | -28.097 | 8.52 |
|     | C15  | 12.767 | -2.832 | 56.518 | O13 | 26.840 | -16.904 | -28.445 | 5.19 |
|     | C16  | 12.542 | -2.527 | 55.569 | O13 | 26.490 | -16.475 | -27.897 | 5.29 |
|     | C17  | 12.626 | -2.342 | 56.003 | O13 | 27.517 | -17.232 | -29.154 | 6.98 |
|     | C18  | 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 |
|     | C20  | 12.743 | -2.884 | 56.396 | O23 | 25.675 | -15.816 | -26.864 | 8.11 |
|     | C21  | 12.713 | -2.680 | 56.311 | O23 | 25.187 | -15.154 | -26.062 | 9.72 |
|     | C22  | 12.789 | -2.459 | 56.712 | O23 | 25.006 | -14.676 | -25.602 | 9.59 |
|     | C23  | 12.779 | -3.012 | 56.526 | O23 | 25.022 | -15.255 | -26.017 | 9.64 |
|     | C24  | 12.877 | -2.074 | 57.200 | O23 | 25.258 | -14.455 | -25.624 | 9.22 |
|     | C25  | 12.729 | -3.058 | 56.291 | O32 | 25.241 | -15.570 | -26.390 | 9.54 |
|     | C26  | 12.738 | -3.663 | 56.170 | O32 | 24.953 | -15.898 | -26.417 | 9.51 |
|     | C27  | 12.725 | -1.775 | 56.590 | O32 | 25.235 | -14.286 | -25.490 | 9.57 |
|     | C28  | 12.804 | -2.868 | 56.676 | O23 | 24.825 | -14.889 | -25.626 | 5.53 |
|     | C29  | 12.725 | -3.252 | 56.225 | O23 | 25.207 | -15.734 | -26.480 | 9.80 |
|     | C30  | 12.721 | -2.874 | 56.297 | O32 | 25.194 | -15.348 | -26.202 | 7.56 |
|     | C31  | 12.786 | -2.921 | 56.579 | O23 | 25.038 | -15.174 | -25.972 | 9.14 |
|     | C32  | 12.726 | -2.404 | 56.437 | O32 | 24.422 | -14.099 | -24.795 | 8.27 |
|     | C33  | 12.777 | -2.583 | 56.624 | O23 | 25.046 | -14.852 | -25.752 | 9.28 |
|     | C34  | 12.767 | -2.432 | 56.618 | O23 | 25.093 | -14.759 | -25.721 | 9.60 |
|     | C35  | 12.706 | -2.949 | 56.213 | O32 | 25.243 | -15.486 | -26.332 | 9.77 |
Effective softness values represented by $E_{\text{m(eff)}}$ describe the nucleophilic character of an atom within a molecule. Higher the value of $E_{\text{m(eff)}}$ with negative sign of a site greater will be the nucleophilic character of that site within the molecule. Further, the site of highest $E_{\text{m(eff)}}$ value characterizes the susceptibility of the molecules toward the attack of electrophile. The highest $E_{\text{m(eff)}}$ values of compounds are also placed in Table 4. A reference to this table also shows that, in group-A, the highest $E_{\text{m(eff)}}$ 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, $E_{\text{m(eff)}}$ value of compounds 19-24, 28, 31, 33 and 34, 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 $E_{\text{m(eff)}}$ 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, $E_{\text{m(eff)}}$, and observed biological activity. Of course, there also exist relationship between $E_{\text{m(eff)}}$ 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 sub-divided 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_{n(eff)} | E_{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 |            |

HIV-1 protease enzyme (HIV-1-PR) is a viral encoded homodimeric aspartyl protease with C₂ 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 $E_{n(eff)}$ value of compounds characterize the susceptibility of the molecules toward the attack of nucleophile, while the highest $E_{m(eff)}$ value of compounds characterize the susceptibility of the molecules toward the attack of electrophile. The softness values $E_{n(eff)}$ of at 5 sites of valine and 6 sites of isoleucine, while the softness values $E_{m(eff)}$ 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 $E_{n(eff)}$ of inhibitors and highest values of $E_{m(eff)}$ of amino acids have been used for deriving $\Delta E_{nm}$ values. While, when inhibitors are treated as bases and receptor proteins as acids, the highest values of softness $E_{m(eff)}$ of inhibitors and highest values of $E_{n(eff)}$ of amino acids have been used for deriving $\Delta E_{nm}$ values. The highest values of softness and the $\Delta E_{nm}$ derived from them are given in Table 6. A reference to this Table 1 shows that in the former case the $\Delta E_{nm}$ values in case of Val amino acid is higher than the Ile amino acid, while in later case the $\Delta E_{nm}$ values in case of Ile amino acid is higher than the Val amino acid.

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 $E_{n(eff)}$ of nucleophile, and softness values of $E_{m(eff)}$ of electrophile, $\Delta E_{nm}$ represent the difference. The higher is the $\Delta E_{nm}$ greater is the stability of the compound [24].

$$\Delta E_{nm}^+ = \left| E_{n(eff)}^+ - E_{m(eff)}^- \right|$$

(3)
| Compd. No. | Carbon Atom | $\Delta E_{\text{hm}}$ | $\Delta E_{\text{hm}}$ | $\Delta E_{\text{hm}}$ | $\Delta E_{\text{hm}}$ |
|-----------|-------------|-----------------|-----------------|-----------------|-----------------|
| Group A 1  | C11         | 56.480          | 82.915          | 83.330          | 1 O13           |
|           | C11         | 56.859          | 83.709          | 83.294          | 2 O13           |
|           | C11         | 55.809          | 82.659          | 82.244          | 3 O13           |
|           | C11         | 55.999          | 82.849          | 82.434          | 4 O13           |
|           | C7          | 55.529          | 82.379          | 81.964          | 5 O13           |
|           | C7          | 55.362          | 82.212          | 81.797          | 6 O13           |
|           | C11         | 55.882          | 82.432          | 82.017          | 7 O13           |
|           | C11         | 56.444          | 83.294          | 82.879          | 8 O13           |
|           | C11         | 56.372          | 83.222          | 82.807          | 9 O13           |
|           | C7          | 55.573          | 82.423          | 82.008          | 10 O13          |
|           | C11         | 55.961          | 82.811          | 82.396          | 11 O13          |
|           | C7          | 55.910          | 82.760          | 82.345          | 12 O13          |
|           | C11         | 56.349          | 83.199          | 82.784          | 13 O13          |
|           | C11         | 56.139          | 82.989          | 82.574          | 14 O13          |
|           | C11         | 56.518          | 83.368          | 82.953          | 15 O13          |
|           | C11         | 55.569          | 82.419          | 82.004          | 16 O13          |
|           | C11         | 56.003          | 82.853          | 82.438          | 17 O13          |
|           | C11         | 56.698          | 82.548          | 82.133          | 18 O13          |
| Group B 19| C21         | 56.510          | 83.360          | 82.945          | 19 O23          |
|           | C22         | 56.396          | 83.246          | 82.831          | 20 O23          |
|           | C22         | 56.311          | 83.161          | 82.746          | 21 O23          |
|           | C21         | 56.712          | 83.562          | 83.147          | 22 O23          |
|           | C21         | 56.526          | 83.376          | 82.961          | 23 O23          |
|           | C7          | 57.200          | 84.050          | 83.635          | 24 O23          |
|           | C22         | 56.291          | 83.141          | 82.726          | 25 O32          |
|           | C22         | 56.170          | 83.020          | 82.605          | 26 O32          |
|           | C21         | 56.590          | 83.440          | 83.025          | 27 O32          |
|           | C22         | 56.676          | 83.526          | 83.111          | 28 O32          |
|           | C22         | 56.225          | 83.075          | 82.660          | 29 O32          |
|           | C22         | 56.297          | 83.147          | 82.732          | 30 O32          |
|           | C21         | 56.579          | 83.429          | 83.014          | 31 O23          |
|           | C7          | 56.437          | 83.287          | 82.872          | 32 O32          |
|           | C21         | 56.624          | 83.474          | 83.059          | 33 O23          |
|           | C21         | 56.618          | 83.468          | 83.053          | 34 O23          |
|           | C21         | 56.213          | 83.063          | 82.648          | 35 O32          |
| Group C 36| C12         | 56.327          | 83.177          | 82.762          | 36 O21          |
|           | C11         | 56.389          | 83.239          | 82.824          | 37 O21          |
|           | C11         | 56.539          | 83.389          | 82.974          | 38 O29          |
|           | C12         | 56.662          | 83.512          | 83.097          | 39 O13          |
|           | C11         | 56.578          | 83.428          | 83.013          | 40 O13          |
|           | C11         | 56.507          | 83.357          | 82.942          | 41 O13          |
|           | C11         | 56.009          | 82.859          | 82.444          | 42 O13          |
|           | C11         | 56.111          | 82.961          | 82.546          | 43 O13          |
|           | C11         | 56.483          | 83.333          | 82.918          | 44 O13          |
|           | C11         | 55.926          | 82.776          | 82.361          | 45 O13          |
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 pharmacological activities. Because it included atomic radius (R), electron density (C), charge (q), ionization potential (IP), and electron affinity (EA) of atom. $\Delta E_{int}$ 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-atoms of the maximum E_{nuc} 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-atoms of the maximum E_{nuc} value) also orient itself to come close the respective site and make maximum interaction.

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