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Article

Drug-Receptor Interaction of Peptidic HIV-1 Protease: Intermolecular Interaction-III

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Abstract: Recently, we have studied drug-receptor interaction of the peptidic HIV-1 protease inhibitors based on polar and hydrophobic interactions. We have also studied pharmacokinetics of these inhibitors based on Lipinski's rule of five and its extended form. After that there was a need to study intermolecular interactions. From literatures, drug-receptor interaction involves hydrogen bonds between acceptor and donor sites of drug and its receptor. These donor acceptor sites must be more than four to be dominant. As single intermolecular H-bond is relatively weak and unlikely to support this type of interaction. It is also clear from literature that this interaction contribute to the alignment of reacting species in proper three-dimensional space in such a position that strong and effective polar or hydrophobic or both interaction occurs to form drug-receptor adduct or enzyme inhibitor complex as appropriate. The strength of H-bonds formed between drug and receptor was judged by bond lengths, bond angles and bond orders. As well as, its nature (strong, moderate or weak) and its number, too. Along with H-bonding, we have also studied Van der Walls i.e. non-bonding type interaction. These non-bonding interactions were studied using charge transfer from donor to acceptor and this results transfer of electron flux from donor molecule (drug/receptor) towards acceptor (receptor/ drug). Thus, lowering of energy of the system under investigation will occur. For this resulted interaction energy was also studied that very clearly explain feasibility of interactions. As we know that all above phenomena are molecular properties and do not cover involvement of orbitals. To cover this we have also studied drug-receptor interaction involving molecular orbital. It was HOMO of one reacting molecule (B) that donates electron pair, electron cloud or electron density to LUMO of another reacting molecule (A) that accepts or accommodates this electron pair, electron cloud or electron density. The quantity of the electron flux from HOMO to LUMO was judged by the value of ΔE_{LH}. A lower value of this will support strong and effective drug-receptor interaction. Results of orbital based study have also been found to supports the results as abstracted from interaction energy.

Keywords: H-Bonding, Energy of Protonation, Charge Transfer, Lowering of Energy, Interaction Energy and Frontier Orbitals

1. Introduction

In our previous publications we have studied pharmacokinetics followed by drug-receptor interaction based on hydrophobic and polar effect [1-3]. Here, we have studied intermolecular interaction between drug and receptor's amino acids that strengthen the formation of enzyme-inhibitor (EI) complexes [4]. In the mater of describing the stability of EI-complexes formed based on various factors among them one is intermolecular interaction [5]. This interaction also has same importance as the other bindings. This work is selective and covers both hydrogen bonding [6] and Van der Waals i.e. nonbonding type interaction [7, 8]. In H-bonding only intermolecular bonding is studied. From literatures, drug-receptor interaction involves hydrogen bonds between acceptor and donor sites of drug and its receptor. These donor acceptor sites must be more than four to be dominant. As single intermolecular H-bond is relatively weak and unlikely to support this type of interaction. It is also clear from literature that this interaction contribute to the alignment of reacting species in proper three-dimensional space in such a position that strong and effective polar or hydrophobic or both interaction occurs to form drug-receptor adduct or enzyme inhibitor complex as appropriate. The strength of H-bonds formed between drug and receptor was judged by bond lengths, bond angles and bond orders. As well as, its nature (strong, moderate or weak) and its number, too. Further, its nature and number is an important factor for controlling the interaction phenomenon and also affect the ADMET property of the drug [4, 9]. While, Van der Waals type interaction is based on (i) charge transfer (ΔN), (ii) energy lowering (ΔE), (iii) the interaction energy ($\Delta E_{int.}$) [10-12] and followed by (iv) change in energies of frontier orbitals (ΔE_{LH}) [13, 14]. Intermolecular interactions govern the formation of many systems of interest: Lewis acid-base complexes [15], pharmaceuticals-absorbers complexes [16] and protein-drug systems [17]. Our research group also studied 324 intermolecular interactions between metal halides and organic bases [18] and 150 interactions between metal-bicyclam complex and aspartic acid [17]. In these systems metal salts were present. But in this work, both parts of the system under investigation are organic molecules.

2. Materials and Methods

Here, fifty-one peptidic HIV-1-PRIs [1] and receptor proteins (scheme 1) are the study materials [1-3]. The sites of interaction on receptor proteins are amino acids. These are valine and isoleucine amino acids of binding site, and aspartic acid, threonine and glycine amino acids of catalytic site [20, 22]. For measurement of enzyme-inhibitor interaction, the molecular modelling and geometry optimization of all the compounds and concerned amino acids of receptor protein were computed with CAChe Pro software by applying semiempirical and opting parametric model 3 [23]. After optimizing all the chemical species and insuring that this represented a minimum energy structure. The energy of protonation is used to determine the correct locations of most favorable hydrogen bonds acceptor sites and results are tabulated in four tables respectively, Table 1(A to C) and 2. After that, we have calculated bond lengths, bond angles and bond orders of H-bonds formed between drug (inhibitor) and receptor (on protease enzyme). These calculated parameters are tabulated in twelve tables, Table 4A1 to 4A4 for first set; Table 4B1 to 4B4 for second set; and Table 4C1 to 4C4 for third set. The values of “ΔN and ΔE”, “ΔE_v, ΔE_μ and ΔE_{int}”, and “ΔE_{LH}” were obtained by solving the respective equation as described in section 3.2 using energy calculator developed by our research group. And the results are presented in Tables 6 to 8, respectively. For this, using absolute electronegativity (χ) [15], firstly each compound has been classified as acid or base with respect to each receptor amino acid and is presented in Table 5 and then respective equations were solved to get the required data.

3. Results and Discussion

For sake of simplicity this section has been divided into two different sections, one based on H-bonds and other on non-bonding.

3.1. H-Boding based study

It has been discussed already that HIV-1-PR is capable of forming multiple hydrogen bonds with the inhibitors. All protease inhibitors bind to the protease binding site pocket that has a considerable number of hydrophobic residues. The residues that make up these pockets are Val-32, Ile-47, Ile-50, and Ile-84 in each monomeric polypeptidic unit of the protease enzyme [19-21]. Out of fifty-one compounds listed in Table 1, the eighteen compounds (compound no. 1-18) have the parent skeleton of Figure 1 (first set that is A group), which has 25 sites. Out of remaining thirty-three, the seventeen compounds (compound no. 19-35) have the parent skeleton of Figure 2 (second set that is B group), which has 33 sites. While the remaining sixteen compounds (compound no. 36-51) have the parent skeleton of Figure 3 (third set that is C group), which has 29 sites. The number of hydrogen bond donors in each set of peptidic HIV-1-PRI was counted by counting the sum of NH and OH groups, while the number of hydrogen bond acceptors was counted by counting the sum of N and O atoms from their parent skeleton structure (Figure 1-3) [24-26]. A close look at the parent skeleton (Figure 1) of first set of peptidic HIV-1-PRI shows that it has five nitrogen and four oxygen atoms. Out of five N-atoms, one (site-8) acts as donor, while the rest (site-1, 4 and 8 to 14) act as both donor and acceptor. In case of oxygen atoms, the one at site-23 acts as both acceptor and donor, while the rest at site-13, 15 and 25 can only accept the hydrogen. Further, from ground-state properties of the individual compounds, we have predicted the hydrogen bond acceptor strength of acceptor site.

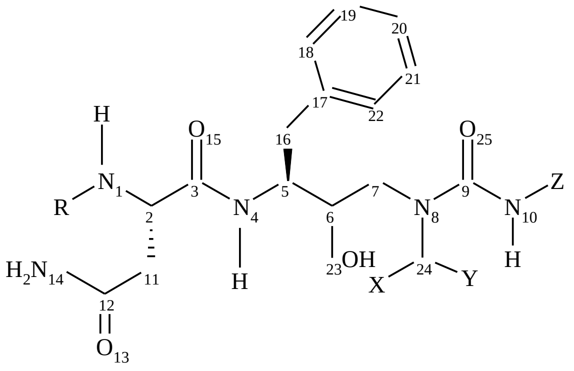


Figure 1. Parent skeleton along with reactive sites (compound no. 1-18, first set = group A)

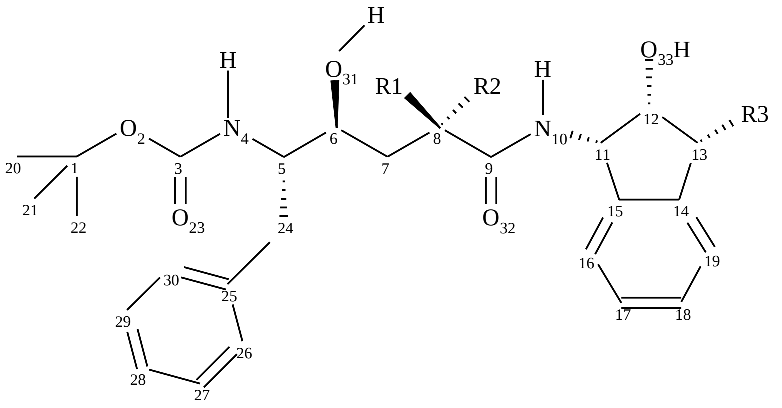


Figure 2. Parent skeleton along with reactive sites of compound no. 19-35 (second set = group b)

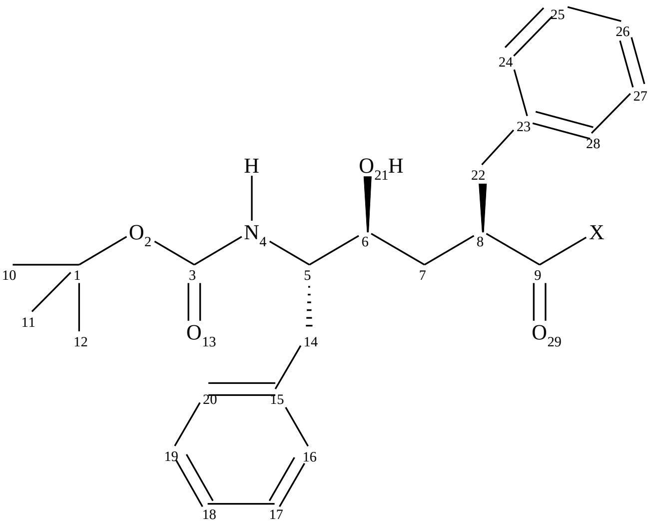
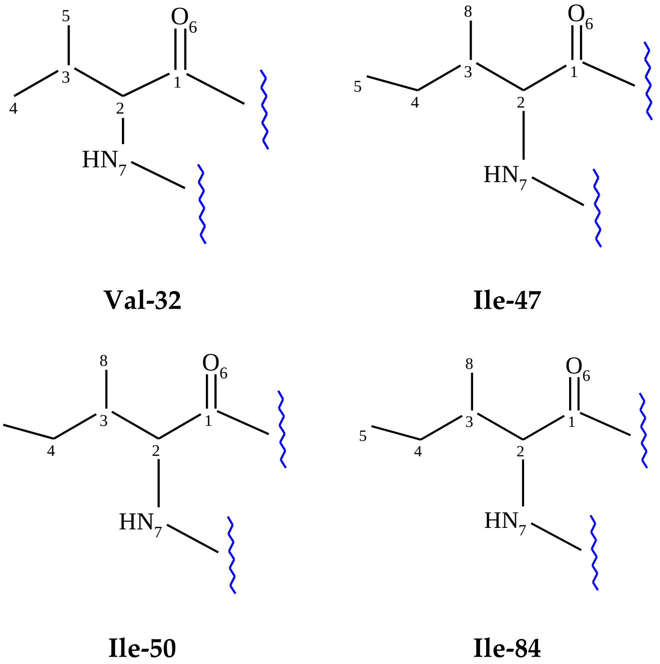


Figure 3. Parent skeleton along with reactive sites of compound no. 36-51 (third set = group C)



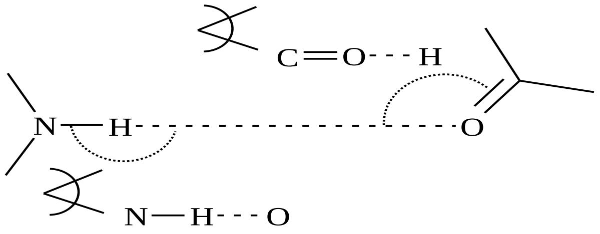
Val-32

Ile-47

Ile-50

Ile-84

Scheme 1. Hydrogen bonds acceptors and donors sites of amino acids of receptor protein (Reference 22).



Scheme 2. Geometry of a hydrogen bond. The distance H···O is typically between 2.8 and 3.2Ǻ and the angle N–H···O is most often larger than 150°. The angle C=O···H has a much broader range; typical values are between 100 and 180°. (Reference 25)

For this, we have evaluated energy of protonation of all these sites and are presented in Table 1 [27]. A reference to this table shows that the top four favorable hydrogen bond acceptor sites are O25, O15, O13 and N10, as these sites have higher energy of protonation. Parent skeleton (Figure 2) of second set shows that it has five oxygen and two nitrogen atoms. Out of five O-atoms, three (site-2, 23 and 32) act as acceptor, while the rest (site-31and 33) act as both donor and acceptor. In case of nitrogen atoms, both (site-4 and 10) act as both acceptor and donor. We have also evaluated energy of protonation of all these sites and are presented in Table 2. A reference to this table shows that the top four favorable hydrogen bond acceptors are O32, O23, O33 and N10, as these sites have higher energy of protonation. Parent skeleton (Figure 3) of third set shows that it has four oxygen and single nitrogen atoms. Out of four O-atoms, three (site-2, 13 and 29) act as acceptor, while the rest one (site-21) act as both donor and acceptor. The nitrogen atom of site-4 acts as both acceptor and donor. We have also evaluated energy of protonation of all these sites which are presented in Table 3. A reference to this table shows that the top four favorable hydrogen bond acceptor sites are O29, O13, N4 and O21, as these sites have higher energy of protonation. The –NH– and –CO– groups of amino acids Val-32, Ile-47, Ile-50, and Ile-84 (i.e., receptor protein) are responsible for hydrogen bonding (Scheme 1). The nitrogen atom of the group acts as both hydrogen bond acceptor and donor, while the oxygen atom acts as acceptor only. We have also evaluated energy of protonation of all these sites which are presented in Table 4. A reference to table shows that oxygen atom (—CO—) of both Val and Ile have higher hydrogen bond acceptor (HA) potency than nitrogen atom (—NH—), in other word nitrogen atom (—NH—) of both Val and Ile have higher hydrogen bond donor (HD) potency than oxygen atom (—CO—). Thus, it is the hydrogen of the –NH- group that participates in the H-bond formation with the nitrogen and oxygen atoms of the inhibitor [24]. Ligands that interact by hydrogen bonds can only bind in a certain orientation with its counter parts on receptor protein. Cambridge Structural Database (Scheme 2) provides some parameters to classify the existence, nature and strength of H-bond formed between reacting species. The H-bond properties of very strong, moderate and weak hydrogen bonds are given in Table 4 [25]. Bond length, bond order and bond angle have been used to explain the type, nature and strength of these H-bonds [25]. Bond length, bond order and bond angle have been used to explain the type, nature and strength of these H-bonds [25]. Table 4A1 to 4C4 show the H-bonds properties of the bond formed between the top four HA sites (O25, O15, O13 and N10 of first set, O32, O23, O33 and N10 of second set and O29, O13, N4 and O21 of third set compounds) and HD (H-atom of —NH— group of Val-32, Ile-47, Ile-50, and Ile-84) site of receptor protein moieties.[20] A close look at the tables (Table 4A1 to 4A4 for first set; Tables 4B1 to 4B4 for second set; and Tables 4C1 to 4C4 for third set) concluded that site-O25, O15 and O13 of all the compounds of first set form moderate H-bonds ranging from 1.833 to 1.883Ǻ with H-atom (—NH—) of Ile moieties of receptor protein, except compound no.-8 which form strong H-bond (1.017Ǻ) with site-O13. All these moderate H-bonds have well defined bond order. The site-N10 form weak H-bond ranging from 3.635 to 5.826Ǻ with H-atom (—NH—) of Val moiety of receptor protein. Compounds no.-7, 12 and 17 forms only three H-bonds and it is the nitrogen atom of site-10, which fails to form H-bond because of low electron density and have small positive charge 0.016, 0.030 and 0.063, respectively. All the weak H-bonds have zero bond order, except compound no.-4, 10 and 13, which have bond order 0.002, 0.002 and 0.003, respectively. Table 4B1 to 4B4 concluded that site-O32, O23 and O33 of all the compounds of the second set also form moderate H-bonds ranging from 1.842 to 1.887Ǻ with H-atom (—NH—) of Ile moieties of receptor protein, except compound no.-23 (site-O23), 26 (site-O32), 29 (site-O23) and 32 (site-O32) which form weak H-bond. All these moderate H-bonds have well defined bond order, except the weak bonds which have zero bond order.

Table 1A. Evaluation of energy of protonation of first set inhibitors

S. N.	Total energy of neutral compd.	Total energy at respective acceptor sites of protonated derivatives									Energy of protonation at respective acceptor sites								
		N1	N4	N8	N10	N14	O13	O15	O23	O25	N1	N4	N8	N10	N14	O13	O15	O23	O25
1	-300.94	-301.62	-301.60	-301.63	-301.66	-301.61	-301.73	-301.71	-301.59	-301.78	0.68	0.66	0.69	0.72	0.67	0.79	0.77	0.65	0.84
2	-322.41	-323.10	-323.11	-323.09	-323.08	-323.12	-323.21	-323.24	-323.15	-323.26	0.69	0.70	0.68	0.67	0.71	0.80	0.83	0.74	0.85
3	-328.84	-329.54	-329.51	-329.58	-329.61	-329.56	-329.69	-329.68	-329.45	-329.70	0.70	0.67	0.74	0.77	0.72	0.85	0.84	0.61	0.86
4	-315.24	-315.94	-315.94	-315.93	-315.98	-315.93	-316.06	-316.09	-315.98	-316.08	0.70	0.70	0.69	0.74	0.69	0.82	0.85	0.74	0.84
5	-308.08	-308.79	-308.76	-308.77	-308.78	-308.87	-308.96	-308.93	-308.89	-308.99	0.71	0.68	0.69	0.70	0.79	0.88	0.85	0.81	0.91
6	-315.23	-315.92	-315.91	-315.95	-315.96	-315.94	-316.05	-316.02	-315.90	-316.10	0.69	0.68	0.72	0.73	0.71	0.82	0.79	0.67	0.87
7	-322.39	-323.11	-323.09	-323.08	-323.09	-323.10	-323.20	-323.19	-323.11	-323.21	0.72	0.70	0.69	0.70	0.71	0.81	0.80	0.72	0.82
8	-328.84	-329.50	-329.56	-329.57	-329.59	-329.52	-329.70	-329.71	-329.59	-329.70	0.66	0.72	0.73	0.75	0.68	0.86	0.87	0.75	0.86
9	-329.56	-330.26	-330.23	-330.24	-330.30	-330.25	-330.35	-330.36	-330.26	-330.42	0.70	0.67	0.68	0.74	0.69	0.79	0.80	0.70	0.86
10	-336.00	-336.71	-336.69	-336.71	-336.76	-336.67	-336.82	-336.83	-336.67	-336.87	0.71	0.69	0.71	0.76	0.67	0.82	0.83	0.67	0.87
11	-342.45	-343.14	-343.17	-343.11	-343.16	-343.12	-343.24	-343.32	-343.22	-343.30	0.69	0.72	0.66	0.71	0.67	0.79	0.87	0.77	0.85
12	-348.87	-349.61	-349.57	-349.57	-349.60	-349.55	-349.69	-349.71	-349.62	-349.70	0.74	0.70	0.70	0.73	0.68	0.82	0.84	0.75	0.83
13	-337.11	-337.82	-337.81	-337.82	-337.83	-337.81	-337.93	-337.89	-337.80	-337.96	0.71	0.70	0.71	0.72	0.70	0.82	0.78	0.69	0.85
14	-343.53	-344.26	-344.23	-344.26	-344.29	-344.25	-344.39	-344.37	-344.23	-344.41	0.73	0.70	0.73	0.76	0.72	0.86	0.84	0.70	0.88
15	-344.26	-344.98	-344.98	-344.94	-344.94	-344.93	-345.08	-345.03	-344.88	-345.02	0.72	0.72	0.68	0.68	0.67	0.82	0.77	0.62	0.76
16	-344.25	-344.94	-344.95	-344.91	-344.95	-344.97	-345.07	-345.05	-344.96	-345.09	0.69	0.70	0.66	0.70	0.72	0.82	0.80	0.71	0.84
17	-339.25	-339.97	-339.92	-339.91	-339.92	-339.90	-340.04	-340.01	-339.88	-340.03	0.72	0.67	0.66	0.67	0.65	0.79	0.76	0.63	0.78
18	-345.69	-346.41	-346.38	-346.39	-346.39	-346.33	-346.50	-346.52	-346.43	-346.55	0.72	0.69	0.70	0.70	0.64	0.81	0.83	0.74	0.86

N = nitrogen atom and O = oxygen atom

Table 1B. Evaluation of energy of protonation of second set inhibitors

S. N.	Total energy of neutral compd.	Total energy at respective acceptor sites of protonated derivatives							Energy of protonation at respective acceptor sites						
		O2	**O23**	**O31**	**O32**	**O33**	**N4**	**N10**	**O2**	**O23**	**O31**	**O32**	**O33**	**N4**	**N10**
19	-291.93	-292.19	-292.71	-292.56	-292.77	-292.66	-292.60	-292.64	0.26	0.78	0.63	0.84	0.73	0.67	0.71
20	-299.07	-299.33	-299.86	-299.74	-299.90	-299.80	-299.74	-299.78	0.26	0.79	0.67	0.83	0.73	0.67	0.71
21	-311.24	-311.53	-312.06	-311.96	-312.06	-311.99	-311.93	-311.93	0.29	0.82	0.72	0.82	0.75	0.69	0.69
22	-346.83	-347.15	-347.61	-347.46	-347.67	-347.56	-347.49	-347.54	0.32	0.78	0.63	0.84	0.73	0.66	0.71
23	-304.44	-304.77	-305.21	-305.07	-305.27	-305.17	-305.10	-305.15	0.33	0.77	0.63	0.83	0.73	0.66	0.71
24	-371.49	-371.76	-372.30	-372.20	-372.31	-372.27	-372.20	-372.22	0.27	0.81	0.71	0.82	0.78	0.71	0.73
25	-299.12	-299.38	-299.90	-299.76	-299.96	-299.85	-299.78	-299.83	0.26	0.78	0.64	0.84	0.73	0.66	0.71
26	-301.38	-301.64	-302.17	-302.02	-302.22	-302.11	-302.05	-302.10	0.26	0.79	0.64	0.84	0.73	0.67	0.72
27	-323.73	-324.03	-324.51	-324.36	-324.56	-324.47	-324.40	-324.45	0.30	0.78	0.63	0.83	0.74	0.67	0.72
28	-248.57	-248.84	-249.38	-248.58	-249.40	-249.32	-249.25	-249.30	0.27	0.81	0.01	0.83	0.75	0.68	0.73
29	-304.16	-304.47	-304.95	-304.79	-304.99	-304.89	-304.82	-304.87	0.31	0.79	0.63	0.83	0.73	0.66	0.71
30	-268.22	-268.49	-269.02	-268.86	-269.05	-268.96	-268.89	-268.94	0.27	0.80	0.64	0.83	0.74	0.67	0.72
31	-300.75	-301.06	-301.52	-301.37	-301.58	-301.47	-301.41	-301.45	0.31	0.77	0.62	0.83	0.72	0.66	0.70
32	-309.37	-309.68	-310.24	-310.06	-310.20	-310.12	-310.06	-310.10	0.31	0.87	0.69	0.83	0.75	0.69	0.73
33	-294.09	-294.34	-294.86	-294.75	-294.88	-294.78	-294.76	-294.73	0.25	0.77	0.66	0.79	0.69	0.67	0.64
34	-301.09	-301.35	-301.88	-301.74	-301.93	-301.84	-301.78	-301.82	0.26	0.79	0.65	0.84	0.75	0.69	0.73
35	-320.61	-320.87	-321.39	-321.24	-321.44	-321.35	-321.27	-321.33	0.26	0.78	0.63	0.83	0.74	0.66	0.72

N = nitrogen atom and O = oxygen atom

Table 1C. Evaluation of energy of protonation of third set inhibitors

S. N.	Total energy Of neutral compd.	Total energy at respective acceptor sites of protonated derivatives					Energy of protonation at respective acceptor sites				
		O2	O13	O21	O29	N4	O2	O13	O21	O29	N4
36	-266.85	-267.11	-267.63	-267.48	-267.68	-267.51	0.26	0.78	0.63	0.83	0.66
37	-268.22	-268.48	-269.02	-268.85	-269.05	-268.88	0.26	0.80	0.63	0.83	0.66
38	-279.75	-280.00	-280.53	-280.38	-280.58	-280.41	0.25	0.78	0.63	0.83	0.66
39	-293.34	-293.68	-294.12	-293.97	-294.18	-293.99	0.34	0.78	0.63	0.84	0.65
40	-281.84	-282.11	-282.63	-282.48	-282.67	-282.51	0.27	0.79	0.64	0.83	0.67
41	-316.60	-316.88	-317.41	-317.37	-317.42	-317.27	0.28	0.81	0.77	0.82	0.67
42	-299.07	-299.35	-299.88	-299.74	-299.89	-299.75	0.28	0.81	0.67	0.82	0.68
43	-277.20	-277.44	-277.98	-277.83	-278.03	-277.87	0.24	0.78	0.63	0.83	0.67
44	-299.10	-299.34	-299.87	-299.73	-299.91	-299.74	0.24	0.77	0.63	0.81	0.64
45	-304.09	-304.38	-304.90	-304.77	-304.92	-304.77	0.29	0.81	0.68	0.83	0.68
46	-304.09	-304.36	-304.92	-304.76	-304.90	-304.76	0.27	0.83	0.67	0.81	0.67
47	-272.19	-272.45	-272.99	-272.82	-273.04	-272.85	0.26	0.80	0.63	0.85	0.66
48	-279.75	-280.08	-280.53	-280.38	-280.57	-280.41	0.33	0.78	0.63	0.82	0.66
49	-279.33	-279.60	-280.13	-280.00	-280.17	-280.01	0.27	0.80	0.67	0.84	0.68
50	-304.08	-304.36	-304.89	-304.76	-304.90	-304.77	0.28	0.81	0.68	0.82	0.69
51	-286.19	-286.43	-286.95	-286.82	-287.02	-286.84	0.24	0.76	0.63	0.83	0.65

N = nitrogen atom and O = oxygen atom

Table 2. Evaluation of energy of protonation of receptor protein

S.N.	Amino Acid	Total energy of neutral compd.	Total energy at respective acceptor sites of protonated derivatives		Energy of protonation at respective acceptor sites	
			N7	**O6**	**N7**	**O6**
1	Val-32	-69.17	-69.93	-69.98	0.76	0.81
2	Ile-47	-76.33	-77.10	-77.13	0.77	0.80
2	Ile-50	-76.33	-77.10	-77.13	0.77	0.80
2	Ile-84	-76.33	-77.10	-77.13	0.77	0.80

Ile = isoleucine amino acid, Val = valine amino acid, N = nitrogen atom and O = oxygen atom

Table 3. Properties of hydrogen bonds

Properties	Very strong bonds	Moderate and weak bonds
Type of bonds	F—H…..F$^-$ O—H…..O$^-$ +O—H…..O Only two-center bonds	D—H…..A (A is an electronegative atom) Two-, three- and four-center bonds
Bond length	Narrow range H…..A 1.2 to 1.5Å H…..A ≈ D—H	Broad range H…..A 1.5 to 3.0Å H…..A > D—H
Bond angles	Strongly directional D—H…..A ≈ 180˚	Weakly directional D—H…..A ≈ 160±20˚

Table 4A1. Calculation of bond properties of H-bond formed between oxygen at site-25 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length (Å)	Bond Order	Bond Angle (˚) C=O····H
1	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.480	0.100	1.881	0.018	150.96
2	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.491	0.101	1.850	0.023	132.19
3	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.447	0.104	1.833	0.022	150.17
4	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.509	0.101	1.840	0.021	165.26
5	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.489	0.104	1.884	0.021	138.83
6	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.511	0.101	1.852	0.020	151.32
7	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.529	0.094	1.841	0.026	138.88
8	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.488	0.098	1.868	0.020	146.72
9	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.470	0.112	1.843	0.025	109.19
10	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.424	0.110	1.855	0.022	148.38
11	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.475	0.109	1.850	0.022	125.52
12	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.541	0.095	1.855	0.025	112.51
13	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.464	0.115	1.844	0.023	141.88
14	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.505	0.093	1.856	0.022	133.62
15	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.488	0.086	1.861	0.022	126.08
16	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.475	0.085	1.877	0.021	122.82
17	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.533	0.094	1.869	0.019	121.27
18	$^{\delta-}O\cdots\cdots H^{\delta+}$	-0.484	0.096	1.850	0.023	149.35

Table 4A2. Calculation of bond properties of H-bond formed between oxygen at site-15 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	O$^{\delta-}$	H$^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) C=O····H
1	$^{\delta-}$O·········H$^{\delta+}$	-0.442	0.094	1.847	0.022	141.48
2	$^{\delta-}$O·········H$^{\delta+}$	-0.453	0.095	1.836	0.027	122.59
3	$^{\delta-}$O·········H$^{\delta+}$	-0.432	0.088	1.862	0.019	152.65
4	$^{\delta-}$O·········H$^{\delta+}$	-0.454	0.084	1.878	0.020	131.92
5	$^{\delta-}$O·········H$^{\delta+}$	-0.467	0.086	1.872	0.020	144.62
6	$^{\delta-}$O·········H$^{\delta+}$	-0.466	0.093	1.857	0.024	124.88
7	$^{\delta-}$O·········H$^{\delta+}$	-0.451	0.089	1.848	0.022	145.99
8	$^{\delta-}$O·········H$^{\delta+}$	-0.433	0.093	1.883	0.019	153.60
9	$^{\delta-}$O·········H$^{\delta+}$	-0.495	0.089	1.849	0.025	132.84
10	$^{\delta-}$O·········H$^{\delta+}$	-0.483	0.100	1.855	0.019	162.56
11	$^{\delta-}$O·········H$^{\delta+}$	-0.466	0.090	1.850	0.021	165.19
12	$^{\delta-}$O·········H$^{\delta+}$	-0.460	0.089	1.865	0.019	165.63
13	$^{\delta-}$O·········H$^{\delta+}$	-0.469	0.087	1.871	0.022	118.03
14	$^{\delta-}$O·········H$^{\delta+}$	-0.460	0.087	1.880	0.018	155.90
15	$^{\delta-}$O·········H$^{\delta+}$	-0.461	0.095	1.856	0.021	149.20
16	$^{\delta-}$O·········H$^{\delta+}$	-0.462	0.088	1.869	0.019	148.50
17	$^{\delta-}$O·········H$^{\delta+}$	-0.446	0.088	1.862	0.023	118.95
18	$^{\delta-}$O·········H$^{\delta+}$	-0.429	0.090	1.861	0.019	149.01

Table 4A3. Calculation of bond properties of H-bond formed between oxygen at site-13 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	O$^{\delta-}$	H$^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) C=O····H
1	$^{\delta-}$O·········H$^{\delta+}$	-0.539	0.094	1.859	0.022	139.57
2	$^{\delta-}$O·········H$^{\delta+}$	-0.550	0.092	1.848	0.025	119.83
3	$^{\delta-}$O·········H$^{\delta+}$	-0.536	0.097	1.843	0.027	121.62
4	$^{\delta-}$O·········H$^{\delta+}$	-0.571	0.090	1.855	0.025	126.42
5	$^{\delta-}$O·········H$^{\delta+}$	-0.505	0.096	1.844	0.025	132.49
6	$^{\delta-}$O·········H$^{\delta+}$	-0.505	0.091	1.844	0.022	150.52
7	$^{\delta-}$O·········H$^{\delta+}$	-0.533	0.096	1.839	0.027	114.29
8	$^{\delta-}$O·········H$^{\delta+}$	-0.336	0.315	1.017	0.670	114.55
9	$^{\delta-}$O·········H$^{\delta+}$	-0.550	0.098	1.856	0.025	127.61
10	$^{\delta-}$O·········H$^{\delta+}$	-0.508	0.098	1.855	0.025	128.34
11	$^{\delta-}$O·········H$^{\delta+}$	-0.547	0.094	1.875	0.022	121.10
12	$^{\delta-}$O·········H$^{\delta+}$	-0.489	0.095	1.855	0.021	145.89
13	$^{\delta-}$O·········H$^{\delta+}$	-0.558	0.095	1.857	0.024	131.82
14	$^{\delta-}$O·········H$^{\delta+}$	-0.493	0.102	1.841	0.025	129.86
15	$^{\delta-}$O·········H$^{\delta+}$	-0.572	0.100	1.839	0.028	124.79
16	$^{\delta-}$O·········H$^{\delta+}$	-0.498	0.096	1.858	0.025	120.46
17	$^{\delta-}$O·········H$^{\delta+}$	-0.525	0.095	1.854	0.024	129.57
18	$^{\delta-}$O·········H$^{\delta+}$	-0.583	0.088	1.867	0.023	125.77

Table 4A4. Calculation of bond properties of H-bond formed between nitrogen at site-10 of the inhibitor and hydrogen of Val moiety of receptor protein

S.No.	**H-Bond**	**N$^{\delta-}$**	**H$^{\delta+}$**	**Bond Length**	**Bond Order**	**Bond Angle (˚) H–N····H**
1	$^{\delta-}N \cdots H^{\delta+}$	-0.065	0.041	3.197	0	78.67
2	$^{\delta-}N \cdots H^{\delta+}$	-0.067	0.054	3.326	0	34.53
3	$^{\delta-}N \cdots H^{\delta+}$	-0.056	0.068	5.826	0	66.27
4	$^{\delta-}N \cdots H^{\delta+}$	-0.026	0.063	2.764	0.002	136.13
5	$^{\delta-}N \cdots H^{\delta+}$	-0.020	0.058	3.576	0	131.81
6	$^{\delta-}N \cdots H^{\delta+}$	-0.028	0.063	3.802	0	96.69
7	$^{\delta-}N \cdots H^{\delta+}$	0.016	0.044	………	………	………
8	$^{\delta-}N \cdots H^{\delta+}$	-0.042	0.061	3.724	0	56.08
9	$^{\delta-}N \cdots H^{\delta+}$	-0.046	0.065	3.211	0	76.59
10	$^{\delta-}N \cdots H^{\delta+}$	-0.051	0.056	2.719	0.002	77.92
11	$^{\delta-}N \cdots H^{\delta+}$	-0.058	0.053	3.373	0	57.04
12	$^{\delta-}N \cdots H^{\delta+}$	0.030	0.060	………	………	………
13	$^{\delta-}N \cdots H^{\delta+}$	-0.028	0.063	2.635	0.003	103.59
14	$^{\delta-}N \cdots H^{\delta+}$	-0.045	0.067	3.292	0	122.88
15	$^{\delta-}N \cdots H^{\delta+}$	-0.007	0.051	3.591	0	123.84
16	$^{\delta-}N \cdots H^{\delta+}$	-0.038	0.062	3.993	0	160.12
17	$^{\delta-}N \cdots H^{\delta+}$	0.063	0.052	………	………	………
18	$^{\delta-}N \cdots H^{\delta+}$	-0.043	0.053	3.365	0	59.91

Table 4B1. Calculation of bond properties of H-bond formed between oxygen at site-32 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	**H-Bond**	**O$^{\delta-}$**	**H$^{\delta+}$**	**Bond Length**	**Bond Order**	**Bond Angle (˚) C=O····H**
19	$^{\delta-}O \cdots H^{\delta+}$	-0.476	0.089	1.887	0.021	122.69
20	$^{\delta-}O \cdots H^{\delta+}$	-0.440	0.095	1.869	0.021	128.07
21	$^{\delta-}O \cdots H^{\delta+}$	-0.415	0.091	1.884	0.022	127.47
22	$^{\delta-}O \cdots H^{\delta+}$	-0.441	0.090	1.858	0.021	120.88
23	$^{\delta-}O \cdots H^{\delta+}$	-0.502	0.087	1.852	0.023	140.49
24	$^{\delta-}O \cdots H^{\delta+}$	-0.480	0.086	1.854	0.024	118.01
25	$^{\delta-}O \cdots H^{\delta+}$	-0.508	0.090	1.871	0.024	138.64
26	$^{\delta-}O \cdots H^{\delta+}$	-0.471	0.066	2.637	0.001	151.56
27	$^{\delta-}O \cdots H^{\delta+}$	-0.424	0.092	1.851	0.023	135.60
28	$^{\delta-}O \cdots H^{\delta+}$	-0.527	0.081	1.864	0.023	121.32
29	$^{\delta-}O \cdots H^{\delta+}$	-0.467	0.092	1.857	0.023	133.06
30	$^{\delta-}O \cdots H^{\delta+}$	-0.444	0.099	1.857	0.024	136.55
31	$^{\delta-}O \cdots H^{\delta+}$	-0.455	0.091	1.842	0.023	152.73
32	$^{\delta-}O \cdots H^{\delta+}$	-0.349	0.080	3.016	0	146.94
33	$^{\delta-}O \cdots H^{\delta+}$	-0.444	0.090	1.852	0.021	150.07
34	$^{\delta-}O \cdots H^{\delta+}$	-0.452	0.088	1.873	0.021	116.90
35	$^{\delta-}O \cdots H^{\delta+}$	-0.435	0.092	1.849	0.021	139.06

Table 4B2. Calculation of bond properties of H-bond formed between oxygen at site-23 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) C=O····H
19	$^{\delta-}O\cdots H^{\delta+}$	-0.492	0.093	1.852	0.021	143.91
20	$^{\delta-}O\cdots H^{\delta+}$	-0.465	0.093	1.884	0.018	165.48
21	$^{\delta-}O\cdots H^{\delta+}$	-0.474	0.099	1.876	0.019	157.05
22	$^{\delta-}O\cdots H^{\delta+}$	-0.464	0.092	1.878	0.023	123.73
23	$^{\delta-}O\cdots H^{\delta+}$	-0.496	0.061	5.149	0	63.14
24	$^{\delta-}O\cdots H^{\delta+}$	-0.481	0.101	1.860	0.022	61.18
25	$^{\delta-}O\cdots H^{\delta+}$	-0.463	0.097	1.850	0.024	117.08
26	$^{\delta-}O\cdots H^{\delta+}$	-0.460	0.088	1.868	0.021	133.78
27	$^{\delta-}O\cdots H^{\delta+}$	-0.452	0.094	1.858	0.024	121.64
28	$^{\delta-}O\cdots H^{\delta+}$	-0.465	0.091	1.848	0.022	154.25
29	$^{\delta-}O\cdots H^{\delta+}$	-0.472	0.058	2.414	0.003	143.37
30	$^{\delta-}O\cdots H^{\delta+}$	-0.461	0.100	1.867	0.023	119.50
31	$^{\delta-}O\cdots H^{\delta+}$	-0.489	0.095	1.854	0.023	147.30
32	$^{\delta-}O\cdots H^{\delta+}$	-0.449	0.089	1.863	0.021	138.31
33	$^{\delta-}O\cdots H^{\delta+}$	-0.476	0.091	1.853	0.023	132.53
34	$^{\delta-}O\cdots H^{\delta+}$	-0.464	0.090	1.864	0.023	128.52
35	$^{\delta-}O\cdots H^{\delta+}$	-0.486	0.095	1.855	0.024	126.31

Table 4B3. Calculation of bond properties of H-bond formed between oxygen at site-33 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) H–O····H
19	$^{\delta-}O\cdots H^{\delta+}$	-0.380	0.088	1.876	0.025	84.75
20	$^{\delta-}O\cdots H^{\delta+}$	-0.369	0.092	1.872	0.022	110.78
21	$^{\delta-}O\cdots H^{\delta+}$	-0.335	0.083	1.871	0.023	108.96
22	$^{\delta-}O\cdots H^{\delta+}$	-0.348	0.084	1.863	0.024	129.26
23	$^{\delta-}O\cdots H^{\delta+}$	-0.383	0.094	1.877	0.022	137.89
24	$^{\delta-}O\cdots H^{\delta+}$	-0.359	0.085	1.863	0.025	96.75
25	$^{\delta-}O\cdots H^{\delta+}$	-0.374	0.095	1.848	0.024	108.99
26	$^{\delta-}O\cdots H^{\delta+}$	-0.350	0.088	1.877	0.024	116.42
27	$^{\delta-}O\cdots H^{\delta+}$	-0.332	0.092	1.854	0.025	131.40
28	$^{\delta-}O\cdots H^{\delta+}$	-0.349	0.087	1.866	0.025	119.81
29	$^{\delta-}O\cdots H^{\delta+}$	-0.346	0.088	1.872	0.020	111.70
30	$^{\delta-}O\cdots H^{\delta+}$	-0.356	0.087	1.874	0.024	112.90
31	$^{\delta-}O\cdots H^{\delta+}$	-0.376	0.091	1.857	0.022	104.64
32	$^{\delta-}O\cdots H^{\delta+}$	-0.349	0.080	1.872	0.023	118.14
33	$^{\delta-}O\cdots H^{\delta+}$	-0.355	0.084	1.857	0.021	94.53
34	$^{\delta-}O\cdots H^{\delta+}$	-0.372	0.084	1.866	0.022	83.36
35	$^{\delta-}O\cdots H^{\delta+}$	-0.360	0.089	1.860	0.024	109.62

Table 4B4. Calculation of bond properties of H-bond formed between oxygen at site-33 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) H–O····H
19	$^{\delta-}$N·········H$^{\delta+}$	0.006	0.057	·········	·········	·········
20	$^{\delta-}$N·········H$^{\delta+}$	-0.017	0.088	3.757	0	122.54
21	$^{\delta-}$N·········H$^{\delta+}$	-0.045	0.064	4.739	0	81.70
22	$^{\delta-}$N·········H$^{\delta+}$	-0.025	0.070	3.740	0	89.27
23	$^{\delta-}$N·········H$^{\delta+}$	0.019	0.058	·········	·········	·········
24	$^{\delta-}$N·········H$^{\delta+}$	0.013	0.045	·········	·········	·········
25	$^{\delta-}$N·········H$^{\delta+}$	0.027	0.048	·········	·········	·········
26	$^{\delta-}$N·········H$^{\delta+}$	-0.014	0.063	3.395	0	62.89
27	$^{\delta-}$N·········H$^{\delta+}$	-0.004	0.092	3.529	0	133.56
28	$^{\delta-}$N·········H$^{\delta+}$	0.022	0.045	·········	·········	·········
29	$^{\delta-}$N·········H$^{\delta+}$	0.001	0.059	·········	·········	·········
30	$^{\delta-}$N·········H$^{\delta+}$	-0.022	0.053	3.679	0	117.40
31	$^{\delta-}$N·········H$^{\delta+}$	-0.013	0.059	4.870	0	99.98
32	$^{\delta-}$N·········H$^{\delta+}$	-0.033	0.065	5.110	0	30.97
33	$^{\delta-}$N·········H$^{\delta+}$	-0.042	0.056	3.687	0	59.47
34	$^{\delta-}$N·········H$^{\delta+}$	-0.015	0.049	4.528	0	94.00
35	$^{\delta-}$N·········H$^{\delta+}$	-0.036	0.089	5.613	0	109.30

Table 4C1. Calculation of bond properties of H-bond formed between oxygen at site-29 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) C=O····H
36	$^{\delta-}$O·········H$^{\delta+}$	-0.439	0.097	1.864	0.022	133.76
37	$^{\delta-}$O·········H$^{\delta+}$	-0.471	0.106	1.856	0.024	128.39
38	$^{\delta-}$O·········H$^{\delta+}$	-0.517	0.102	1.853	0.024	129.15
39	$^{\delta-}$O·········H$^{\delta+}$	-0.447	0.102	1.857	0.025	126.96
40	$^{\delta-}$O·········H$^{\delta+}$	-0.438	0.093	1.862	0.018	165.20
41	$^{\delta-}$O·········H$^{\delta+}$	-0.400	0.099	1.876	0.018	165.88
42	$^{\delta-}$O·········H$^{\delta+}$	-0.443	0.097	1.859	0.021	143.85
43	$^{\delta-}$O·········H$^{\delta+}$	-0.486	0.100	1.843	0.024	142.11
44	$^{\delta-}$O·········H$^{\delta+}$	-0.433	0.099	1.856	0.021	154.77
45	$^{\delta-}$O·········H$^{\delta+}$	-0.506	0.099	1.863	0.022	137.97
46	$^{\delta-}$O·········H$^{\delta+}$	-0.467	0.098	1.868	0.02	153.09
47	$^{\delta-}$O·········H$^{\delta+}$	-0.467	0.104	1.843	0.022	151.04
48	$^{\delta-}$O·········H$^{\delta+}$	-0.438	0.099	1.859	0.02	126.65
49	$^{\delta-}$O·········H$^{\delta+}$	-0.480	0.101	1.842	0.023	133.87
50	$^{\delta-}$O·········H$^{\delta+}$	-0.419	0.110	1.855	0.021	129.66
51	$^{\delta-}$O·········H$^{\delta+}$	-0.453	0.096	1.846	0.023	141.68

Table 4C2. Calculation of bond properties of H-bond formed between oxygen at site-13 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	**H-Bond**	**O$^{\delta-}$**	**H$^{\delta+}$**	**Bond Length**	**Bond Order**	**Bond Angle (˚) C=O····H**
36	$^{\delta-}$O·········H$^{\delta+}$	-0.494	0.091	1.856	0.024	129.64
37	$^{\delta-}$O·········H$^{\delta+}$	-0.485	0.054	3.168	0	138.82
38	$^{\delta-}$O·········H$^{\delta+}$	-0.485	0.099	1.857	0.021	76.30
39	$^{\delta-}$O·········H$^{\delta+}$	-0.488	0.095	1.861	0.019	164.33
40	$^{\delta-}$O·········H$^{\delta+}$	-0.454	0.090	1.881	0.018	147.40
41	$^{\delta-}$O·········H$^{\delta+}$	-0.475	0.095	1.875	0.018	164.00
42	$^{\delta-}$O·········H$^{\delta+}$	-0.519	0.096	1.835	0.025	125.77
43	$^{\delta-}$O·········H$^{\delta+}$	-0.425	0.102	1.883	0.018	151.77
44	$^{\delta-}$O·········H$^{\delta+}$	-0.426	0.095	1.860	0.021	144.87
45	$^{\delta-}$O·········H$^{\delta+}$	-0.469	0.106	1.864	0.019	147.24
46	$^{\delta-}$O·········H$^{\delta+}$	-0.488	0.097	1.847	0.021	175.08
47	$^{\delta-}$O·········H$^{\delta+}$	-0.448	0.094	1.898	0.02	130.67
48	$^{\delta-}$O·········H$^{\delta+}$	-0.447	0.096	1.882	0.018	154.72
49	$^{\delta-}$O·········H$^{\delta+}$	-0.434	0.094	4.055	0	149.71
50	$^{\delta-}$O·········H$^{\delta+}$	-0.452	0.110	1.834	0.024	124.70
51	$^{\delta-}$O·········H$^{\delta+}$	-0.453	0.098	1.869	0.018	148.09

Table 4C3. Calculation of bond properties of H-bond formed between nitrogen at site-4 of the inhibitor and hydrogen of Val moiety of receptor protein

S.No.	**H-Bond**	**N$^{\delta-}$**	**H$^{\delta+}$**	**Bond Length**	**Bond Order**	**Bond Angle (˚) H–N····H**
36	$^{\delta-}$N·········H$^{\delta+}$	-0.020	0.045	3.374	0	111.16
37	$^{\delta-}$N·········H$^{\delta+}$	-0.005	0.060	4.597	0	17.57
38	$^{\delta-}$N·········H$^{\delta+}$	-0.014	0.065	5.715	0	30.63
39	$^{\delta-}$N·········H$^{\delta+}$	-0.032	0.062	4.846	0	55.61
40	$^{\delta-}$N·········H$^{\delta+}$	-0.030	0.052	4.369	0	30.35
41	$^{\delta-}$N·········H$^{\delta+}$	-0.028	0.057	3.064	0	42.84
42	$^{\delta-}$N·········H$^{\delta+}$	-0.001	0.041	3.381	0	52.46
43	$^{\delta-}$N·········H$^{\delta+}$	-0.039	0.047	3.138	0	69.56
44	$^{\delta-}$N·········H$^{\delta+}$	-0.036	0.059	3.991	0	105.28
45	$^{\delta-}$N·········H$^{\delta+}$	-0.022	0.049	4.274	0	44.77
46	$^{\delta-}$N·········H$^{\delta+}$	-0.003	0.059	3.670	0	122.15
47	$^{\delta-}$N·········H$^{\delta+}$	-0.019	0.051	3.547	0	21.11
48	$^{\delta-}$N·········H$^{\delta+}$	-0.035	0.055	3.921	0	28.72
49	$^{\delta-}$N·········H$^{\delta+}$	-0.027	0.080	4.055	0	39.47
50	$^{\delta-}$N·········H$^{\delta+}$	-0.021	0.063	3.201	0	91.92
51	$^{\delta-}$N·········H$^{\delta+}$	-0.017	0.058	3.953	0	29.19

Table 4C4. Calculation of bond properties of H-bond formed between oxygen at site-21 of the inhibitor and hydrogen of Ile moiety of receptor protein

S.No.	H-Bond	$O^{\delta-}$	$H^{\delta+}$	Bond Length	Bond Order	Bond Angle (°) H–O···H
36	$^{\delta-}O\cdots H^{\delta+}$	-0.334	0.084	1.876	0.020	127.00
37	$^{\delta-}O\cdots H^{\delta+}$	-0.349	0.083	1.853	0.022	37.57
38	$^{\delta-}O\cdots H^{\delta+}$	-0.364	0.055	4.311	0	98.33
39	$^{\delta-}O\cdots H^{\delta+}$	-0.340	0.084	1.876	0.020	123.86
40	$^{\delta-}O\cdots H^{\delta+}$	-0.339	0.084	1.885	0.022	102.23
41	$^{\delta-}O\cdots H^{\delta+}$	-0.368	0.086	1.858	0.024	103.95
42	$^{\delta-}O\cdots H^{\delta+}$	-0.338	0.084	1.850	0.022	120.85
43	$^{\delta-}O\cdots H^{\delta+}$	-0.330	0.081	1.865	0.022	126.96
44	$^{\delta-}O\cdots H^{\delta+}$	-0.324	0.078	1.901	0.020	26.83
45	$^{\delta-}O\cdots H^{\delta+}$	-0.336	0.080	1.878	0.020	115.63
46	$^{\delta-}O\cdots H^{\delta+}$	-0.354	0.082	1.885	0.019	107.21
47	$^{\delta-}O\cdots H^{\delta+}$	-0.345	0.087	1.892	0.020	111.01
48	$^{\delta-}O\cdots H^{\delta+}$	-0.329	0.085	1.876	0.022	111.48
49	$^{\delta-}O\cdots H^{\delta+}$	-0.333	0.090	1.859	0.024	121.20
50	$^{\delta-}O\cdots H^{\delta+}$	-0.359	0.056	3.238	0	103.34
51	$^{\delta-}O\cdots H^{\delta+}$	-0.333	0.058	3.204	0	107.71

The site-N10 forms weak H-bond ranging from 3.395 to 5.613Ǻ with H-atom (—NH—) of Val moiety of receptor protein. Compounds no.-19, 23, 24, 25, 28 and 29 form only three H-bonds and it is the nitrogen atom of site-10 which fails to form H-bond because of low electron density and have small positive charge of 0.006, 0.019, 0.013, 0.027, 0.022 and 0.001, respectively. All the weak H-bonds have zero bond order, except compounds no.-4, 10 and 13, which have bond order 0.002, 0.002 and 0.003, respectively. All these weak H-bonds have zero bond order.

3.2. *Non-bonding Interaction*

In all previous studies of our research group the donors were organic molecules and acceptors were metal salts [17, 18]. But in this work, both parts of the system under investigation are organic molecules. For this, using absolute electronegativity (χ) [15], firstly each compound has been classified as acid or base with respect to each receptor amino acid and is presented in Table 5.

The intermolecular interaction can be explained by using electron flux. The ΔN represents electron flux and is defined as: $\Delta N = (\chi_A - \chi_B)/ 2(\eta_A - \eta_B)$, whose negative value represents spontaneous process. In spontaneous process electron will flow from molecule B to A. If two systems under investigation (drug/ inhibitor and receptor/ enzyme) are brought together the electron will flow system of lower χ to that of system of higher χ. And this electron flow will end up by equalization of chemical potential [15b]. It has been established that electronegativity (χ) is the negative of the chemical potential (-μ) [15]. The spontaneous electron flows resulted in lowering of energy of the system [15a]. The lowering of energy of the system is represented by ΔE. Which can be defined as: $\Delta E = -(\chi_A - \chi_B)^2/ 4(\eta_A - \eta_B)$. Herein, η_A and η_B are absolute hardness of the system A and system B. The values of ΔN and ΔE are presented in Table 6. ΔN refracted that binding site on receptor protein has higher values of charge transfer for Val amino acids than Ile amino acids. ΔE shows that binding site on receptor protein has higher value of energy lowering for Val amino acids than Ile amino acids, too.

Table 5. Classification of compounds (acid/A or base/B) with respect to receptor amino acids

No.	χ_D	**Val**	**Ile**	**No.**	χ_D	**Val**	**Ile**
		$\chi_R = 4.71$	$\chi_R = 4.88$			$\chi_R = 4.71$	$\chi_R = 4.88$
1	4.97	A	A	27	5.47	A	A
2	5.01	A	A	28	4.97	A	A
3	5.36	A	A	29	4.74	A	B
4	5.01	A	A	30	4.92	A	A
5	4.98	A	A	31	4.93	A	A
6	5.02	A	A	32	5.16	A	A
7	5.06	A	A	33	5.10	A	A
8	5.34	A	A	34	5.19	A	A
9	4.94	A	A	35	4.88	A	A
10	5.33	A	A	36	4.96	A	A
11	4.93	A	A	37	4.89	A	A
12	5.37	A	A	38	4.89	A	A
13	5.03	A	A	39	4.85	A	B
14	5.33	A	A	40	4.90	A	A
15	4.97	A	A	41	4.99	A	A
16	5.12	A	A	42	4.94	A	A
17	5.33	A	A	43	4.87	A	B
18	4.92	A	A	44	4.95	A	A
19	4.90	A	A	45	4.83	A	B
20	4.93	A	A	46	4.82	A	B
21	5.02	A	A	47	4.89	A	A
22	5.17	A	A	48	4.80	A	B
23	4.88	A	A	49	4.90	A	A
24	5.40	A	A	50	4.99	A	A
25	4.84	A	B	51	4.97	A	A
26	4.53	B	B				

χ: electronegativity, R: receptor amino acid, D stand for drug (HIV-1-PRIs), Val: valine, Ile: isoleucine, A: acid and B: base.

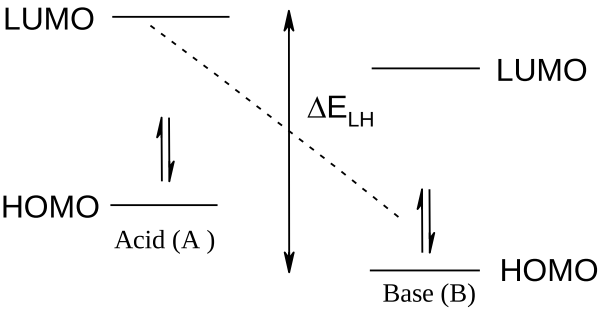


Figure 4. HOMO-LUMO Energy Gaps and their change, ΔE_{LH}

Table 6. Calculation of ΔE_{LH}, ΔN and ΔE of EI-complexes formed, when HIV-1-PRIs interact with binding site on HIV-1-PR

No.	χ_D	η_D	**Val**		**Ile**		**No.**	χ_D	η_D	**Val**		**Ile**	
			χ_R =4.71 η_R = 5.38		χ_R =4.88 η_R = 5.34					χ_R =4.71 η_R = 5.38		χ_R =4.88 η_R = 5.34	
			ΔN	**ΔE**	**ΔN**	**ΔE**				**ΔN**	**ΔE**	**ΔN**	**ΔE**
1	4.97	4.75	0.0128	-0.0020	0.0045	-0.0002	27	5.47	4.27	0.0394	-0.0150	0.0307	-0.0091
2	5.01	4.76	0.0148	-0.0020	0.0064	-0.0004	28	4.97	4.80	0.0128	-0.0020	0.0044	-0.0002
3	5.36	4.21	0.0339	-0.0110	0.0251	-0.0060	29	4.74	4.60	0.0015	0.0000	0.0070	-0.0005
4	5.01	4.77	0.0148	-0.0020	0.0064	-0.0004	30	4.92	4.78	0.0103	-0.0010	0.0020	0.0000
5	4.98	4.80	0.0133	-0.0020	0.0049	-0.0002	31	4.93	4.31	0.0114	-0.0010	0.0026	-0.0001
6	5.02	4.79	0.0152	-0.0020	0.0069	-0.0005	32	5.16	4.56	0.0226	-0.0050	0.0141	-0.0020
7	5.06	4.76	0.0173	-0.0030	0.0089	-0.0008	33	5.10	4.60	0.0195	-0.0040	0.0111	-0.0012
8	5.34	4.19	0.0329	-0.0100	0.0241	-0.0056	34	5.19	4.23	0.0250	-0.0060	0.0162	-0.0025
9	4.94	4.69	0.0114	-0.0010	0.0030	-0.0001	35	4.88	4.72	0.0084	-0.0010	0.0000	0.0000
10	5.33	4.20	0.0324	-0.0100	0.0236	-0.0053	36	4.96	4.81	0.0123	-0.0020	0.0039	-0.0002
11	4.93	4.72	0.0109	-0.0010	0.0025	-0.0001	37	4.89	4.89	0.0088	-0.0010	0.0005	0.0000
12	5.37	4.15	0.0346	-0.0110	0.0258	-0.0063	38	4.89	4.79	0.0088	-0.0010	0.0005	0.0000
13	5.03	4.82	0.0157	-0.0030	0.0074	-0.0006	39	4.85	4.86	0.0068	0.0000	0.0015	0.0000
14	5.33	4.20	0.0324	-0.0100	0.0236	-0.0053	40	4.90	4.89	0.0093	-0.0010	0.0010	0.0000
15	4.97	4.73	0.0129	-0.0020	0.0045	-0.0002	41	4.99	4.78	0.0138	-0.0020	0.0054	-0.0003
16	5.12	4.55	0.0206	-0.0040	0.0121	-0.0015	42	4.94	4.82	0.0113	-0.0010	0.0030	-0.0001
17	5.33	4.11	0.0327	-0.0100	0.0238	-0.0054	43	4.87	4.89	0.0078	-0.0010	0.0005	0.0000
18	4.92	4.77	0.0103	-0.0010	0.0020	0.0000	44	4.95	4.80	0.0118	-0.0010	0.0035	-0.0001
19	4.90	4.78	0.0094	-0.0010	0.0010	0.0000	45	4.83	4.67	0.0060	0.0000	0.0025	-0.0001
20	4.93	4.79	0.0108	-0.0010	0.0025	-0.0001	46	4.82	4.67	0.0055	0.0000	0.0030	-0.0001
21	5.02	4.82	0.0152	-0.0020	0.0069	-0.0005	47	4.89	4.89	0.0088	-0.0010	0.0005	0.0000
22	5.17	4.52	0.0232	-0.0050	0.0147	-0.0021	48	4.80	4.79	0.0044	0.0000	0.0039	-0.0002
23	4.88	4.39	0.0087	-0.0010	0.0000	0.0000	49	4.90	4.86	0.0093	-0.0010	0.0010	0.0000
24	5.40	4.38	0.0353	-0.0120	0.0267	-0.0070	50	4.99	4.82	0.0137	-0.0020	0.0054	-0.0003
25	4.84	4.69	0.0065	0.0000	-0.0020	0.0000	51	4.97	4.81	0.0128	-0.0020	0.0044	-0.0002
26	4.53	4.38	0.0092	-0.0010	0.0180	-0.0032							

εHOMO: energy of highest occupied molecular orbital, εLUMO: energy of lowest unoccupied molecular orbital, $\Delta E_{LH} = \varepsilon LUMO - \varepsilon HOMO$, *χ: electronegativity, η: hardness, Val: valine, Ile: isoleucine, ΔN: shift in charge, ΔE: lowering of energy, and. R: receptor amino acid, D stand for drug (HIV-1-PRIs),*

After that strength of interaction can be studied by using interaction energy, which is represented by ΔE_{int} and defined as $\Delta E_{int} = \Delta E_v - \Delta E_\mu$ [12]. This equation involves two processes one is charge transfer process represent by ΔE_v and other process is reshuffling of charge distribution and is represent by ΔE_μ. Both can be defined respectively as: $\Delta E_v \approx -(\mu_A - \mu_B)^2 S_A{\cdot}S_B / 2(S_A + S_B)$ and $\Delta E_\mu \approx -\lambda/2(S_A + S_B)$. Herein, S_A and S_B are the global softness of system A and system B, respectively [11]. It has been established that global softness (S) is the half of the absolute hardness (½η) [15]. Interaction energy for enzyme-inhibitor interaction between HIV-1-PR and HIV-1-PRIs has been evaluated and is presented in Table 7. ΔE_{int} values show higher values of interaction energy for Ile amino acids than Val amino acids.

Frontier orbitals (HOMO and LUMO) as reported can help to describe intermolecular interaction. This interaction involves HOMO of donor (B) and LUMO of acceptor (A) to come close with same symmetry (Figure 4).

Table 7. Calculation of ΔE_v, ΔE_μ and ΔE_{int} of EI-complexes formed, when HIV-1-PRIs interact with binding site on HIV-1-PR

S.No.	μ_D	S_D	N_D	λ	**Val**			**Ile**		
					μ_R =-4.71, S_R = 0.093, and N_R = 48			**μ_R =-4.88, S_R = 0.094 andN_R =54**		
					ΔE_v	ΔE_μ	ΔE_{int}	ΔE_v	ΔE_μ	ΔE_{int}
1	-4.97	0.11	176	50.18	16.48	-126	-110.00	1.89	-133	-130.98
2	-5.01	0.11	194	58.56	22.82	-148	-125.03	4.34	-155	-150.38
3	-5.36	0.12	206	64.52	88.27	-152	-64.00	47.89	-159	-111.14
4	-5.01	0.10	188	55.70	23.22	-141	-117.58	4.49	-148	-143.03
5	-4.98	0.10	182	52.90	18.14	-134	-116.07	2.40	-141	-138.40
6	-5.02	0.10	188	55.70	24.40	-141	-116.62	4.99	-148	-142.77
7	-5.06	0.11	194	58.56	30.85	-148	-116.99	8.16	-155	-146.55
8	-5.34	0.12	206	64.52	83.65	-152	-68.34	44.60	-159	-114.14
9	-4.94	0.11	194	58.56	12.82	-147	-133.88	0.85	-154	-152.67
10	-5.33	0.12	212	67.60	80.09	-159	-79.30	41.98	-166	-124.29
11	-4.93	0.11	210	66.56	11.73	-167	-155.56	0.57	-175	-173.98
12	-5.37	0.12	222	72.90	89.73	-171	-80.94	49.34	-178	-128.42
13	-5.03	0.10	204	63.50	27.35	-161	-133.99	6.30	-169	-162.22
14	-5.33	0.12	216	69.70	82.16	-164	-82.20	43.47	-171	-127.88
15	-4.97	0.11	210	66.56	16.67	-168	-150.84	1.98	-175	-172.80
16	-5.12	0.11	198	60.52	39.59	-149	-109.49	13.56	-156	-142.34
17	-5.33	0.12	210	66.56	77.49	-155	-77.47	40.66	-162	-121.07
18	-4.92	0.10	210	66.56	11.19	-168	-157.06	0.43	-176	-175.11
19	-4.90	0.10	182	52.90	9.31	-134	-124.55	0.13	-140	-140.30
20	-4.93	0.10	188	55.70	12.30	-141	-128.86	0.65	-148	-147.26
21	-5.02	0.10	188	55.70	24.37	-142	-117.21	4.91	-148	-143.43
22	-5.17	0.11	206	64.52	48.84	-158	-109.53	19.26	-165	-146.11
23	-4.88	0.11	192	57.60	6.66	-139	-132.56	0.00	-146	-145.77
24	-5.40	0.11	212	67.60	108.01	-163	-55.19	61.37	-170	-108.88
25	-4.84	0.11	188	55.70	3.82	-140	-135.70	0.48	-146	-145.71
26	-4.53	0.11	188	55.70	7.80	-135	-126.69	27.90	-141	-113.04
27	-5.47	0.12	186	54.76	126.94	-130	-3.33	76.63	-137	-59.96
28	-4.97	0.10	148	38.42	17.07	-97	-80.31	2.03	-103	-101.03
29	-4.74	0.11	182	52.90	0.15	-131	-130.96	4.92	-138	-132.64
30	-4.92	0.10	164	44.94	11.56	-114	-102.20	0.50	-120	-119.37
31	-4.93	0.12	188	55.70	10.73	-133	-122.58	0.62	-140	-139.09
32	-5.16	0.11	186	54.76	48.70	-135	-86.38	19.01	-142	-122.60
33	-5.10	0.11	182	52.90	36.18	-131	-94.88	11.47	-138	-126.05
34	-5.19	0.12	182	52.90	49.99	-125	-75.30	21.12	-131	-110.36
35	-4.88	0.11	206	64.52	7.06	-162	-155.17	0.00	-169	-169.39
36	-4.96	0.10	172	48.40	15.84	-123	-107.00	1.61	-129	-127.56
37	-4.89	0.10	164	44.94	8.71	-115	-106.42	0.04	-121	-121.26
38	-4.89	0.10	182	52.90	8.42	-134	-125.55	0.04	-141	-140.51
39	-4.85	0.10	184	53.82	4.95	-137	-132.48	0.25	-144	-143.86
40	-4.90	0.10	166	45.80	9.14	-117	-108.15	0.08	-124	-123.43
41	-4.99	0.10	186	54.76	20.33	-139	-118.27	3.27	-145	-142.02
42	-4.94	0.10	188	55.70	13.75	-142	-127.77	0.99	-148	-147.29
43	-4.87	0.10	172	48.40	6.87	-124	-117.09	0.01	-130	-130.34
44	-4.95	0.10	182	52.90	14.29	-134	-119.80	1.16	-141	-139.52
45	-4.83	0.11	182	52.90	3.65	-132	-128.50	0.53	-139	-138.13
46	-4.82	0.11	178	51.08	2.76	-128	-124.91	0.96	-134	-133.11

47	-4.89	0.10	182	52.90	8.79	-135	-126.64	0.05	-142	-142.02
48	-4.80	0.10	184	53.82	2.15	-136	-134.25	1.50	-143	-141.54
49	-4.90	0.10	182	52.90	9.16	-135	-125.81	0.09	-142	-141.51
50	-4.99	0.10	178	51.08	20.31	-130	-109.56	3.19	-136	-133.18
51	-4.97	0.10	178	51.08	17.70	-130	-112.00	2.23	-136	-133.96

μ: chemical potential, S: softness, N: number of valence electrons, λ: constant, Val: valine, Ile: isoleucine, ΔE_v: corresponds to the charge transfer process and ΔE_μ: corresponds to a reshuffling of the charge distribution., and ΔE_{int}: interaction energy

Table 8. Calculation of ΔE_{LH}, ΔN and ΔE of EI-complexes formed, when HIV-1-PRIs interact with binding site on HIV-1-PR

No.	**$^{D}\varepsilon$HOMO**	**$^{D}\varepsilon$LUMO**	**Val**	**Ile**	**No.**	**$^{D}\varepsilon$HOMO**	**$^{D}\varepsilon$LUMO**	**Val**	**Ile**
			$^{R}\varepsilon$HOMO =-10.09 $^{R}\varepsilon$LUMO =0.67	**$^{R}\varepsilon$HOMO =-10.22 $^{R}\varepsilon$LUMO =0.46**				**$^{R}\varepsilon$HOMO =-10.09 $^{R}\varepsilon$LUMO =0.67**	**$^{R}\varepsilon$HOMO =-10.22 $^{R}\varepsilon$LUMO =0.46**
			ΔE_{LH}	**ΔE_{LH}**				**ΔE_{LH}**	**ΔE_{LH}**
1	-9.711	-0.220	10.378	9.996	27	-9.743	-1.207	10.409	9.008
2	-9.769	-0.250	10.436	9.965	28	-9.764	-0.172	10.431	10.043
3	-9.563	-1.148	10.229	9.067	29	-9.335	-0.139	10.001	9.791
4	-9.783	-0.240	10.449	9.975	30	-9.706	-0.140	10.372	10.075
5	-9.779	-0.172	10.446	10.044	31	-9.247	-0.618	9.913	9.597
6	-9.804	-0.233	10.470	9.983	32	-9.720	-0.602	10.387	9.613
7	-9.817	-0.299	10.483	9.916	33	-9.692	-0.501	10.359	9.714
8	-9.533	-1.146	10.200	9.069	34	-9.427	-0.960	10.094	9.255
9	-9.628	-0.248	10.294	9.968	35	-9.603	-0.155	10.269	10.061
10	-9.525	-1.126	10.191	9.089	36	-9.766	-0.150	10.432	10.065
11	-9.646	-0.207	10.313	10.008	37	-9.785	0.001	10.451	10.216
12	-9.515	-1.221	10.181	8.994	38	-9.680	-0.104	10.346	10.111
13	-9.852	-0.218	10.518	9.997	39	-9.711	0.014	10.377	10.168
14	-9.535	-1.132	10.201	9.083	40	-9.787	-0.006	10.454	10.209
15	-9.699	-0.237	10.365	9.979	41	-9.775	-0.209	10.442	10.007
16	-9.664	-0.571	10.331	9.644	42	-9.759	-0.123	10.425	10.092
17	-9.433	-1.220	10.099	8.995	43	-9.764	0.020	10.430	10.221
18	-9.690	-0.150	10.357	10.065	44	-9.742	-0.150	10.408	10.065
19	-9.682	-0.122	10.348	10.094	45	-9.500	-0.167	10.166	9.957
20	-9.724	-0.135	10.391	10.081	46	-9.489	-0.146	10.155	9.945
21	-9.838	-0.195	10.504	10.020	47	-9.780	-0.006	10.447	10.209
22	-9.682	-0.648	10.348	9.567	48	-9.597	-0.009	10.263	10.054
23	-9.274	-0.492	9.941	9.723	49	-9.754	-0.042	10.420	10.174
24	-9.784	-1.019	10.450	9.196	50	3.855	4.990	-3.189	15.205
25	-9.526	-0.145	10.192	9.983	51	-9.784	-0.160	10.451	10.056
26	-8.911	-0.143	9.948	9.368					

εHOMO: energy of highest occupied molecular orbital, εLUMO: energy of lowest unoccupied molecular orbital, ΔE_{LH} = εLUMO – εHOMO, χ: electronegativity, η: hardness, Val: valine, Ile: isoleucine, ΔN: shift in charge, ΔE: lowering of energy, and. R: receptor amino acid, D stand for drug (HIV-1-PRIs)

The energy for such interaction for each complex has been calculated by the equation, ΔE_{LH} = (εLUMO – εHOMO). ΔE_{LH} has been used to measure the weak electrostatic attractions that strengthen the formation of enzyme-inhibitor (EI) complex [13, 14b]. We have calculated eigenvalues of LUMO and HOMO of receptor amino acids and HIV-1-PRIs and placed them in Table 8 Their change ΔE_{LH} have also been evaluated and are also placed in same table. A lower value of this will support strong and effective drug-receptor interaction. ΔE_{LH} shows that receptor protein has maximum attraction for Ile amino acids than Val amino acids. As there are three isoleucine residues at positions, 47, 50 and 84 respectively i.e. Ile-47, Ile-50, and Ile-84 and one valine residue at position 32 i.e. Val-32. Results of orbital based study have also been found to supports the results as abstracted from interaction energy.

4. Conclusion

1. Energy of protonation did good job for correct location of most favorable H-bond acceptor sites. (i) All the compounds of first set form moderate H-bonds ranging from 1.833 to 1.883Å with H-atom (—NH—) of Ile moieties of receptor protein, except compound no.-8 which form strong H-bond (1.017Å) with site-O13. (ii) All the compounds of second set form moderate H-bonds ranging from 1.833 to 1.883Å with H-atom (—NH—) of Ile moieties of receptor protein, except compound no.-8 which form strong H-bond (1.017Å) with site-O13. (iii) All the compounds of the third set form moderate H-bonds ranging from 1.834 to 1.901Å with H-atom (—NH—) of Ile moieties of receptor protein, except compound no.-37 (site-O13), 38 (site-O21), 49 (site-O13), 50 (site-O21) and 51 (site-O21) which form weak H-bond. The site-N4 forms weak H-bond ranging from 3.064 to 5.715Å with H-atom (—NH—) of Val moiety of receptor protein. All these weak H-bonds have zero bond order.

2. (i) Charge transfer followed by energy lowering reflected maximum interaction with valine amino acids than isoleucine. (ii) While results of interaction energy shows maximum interaction with isoleucine amino acids than valine. (iii) The result of interaction energy is also supported by ΔE_{LH} that shows receptor protein has maximum attraction for Ile amino acids than Val amino acids. This may be due to contribution of isoleucine amino acids is much higher (three in number) than the contribution of valine amino acid (one in number).

3. All the parameters used in this study did good job that judging their selection and can also be used in intermolecular interactions of different nature of compounds.

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