Article

Drug-Receptor Interaction of Peptidic HIV-1 Protease: The Hydrophobic Effect-I

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Abstract: When a drug interacts with its receptor, the nonpolar substituent of drug and receptor proteins attract each other because they have opposite magnitude with respect to each other. X-rays structure studies reflected that the S2/S2' pocket in HIV-1 protease enzyme are essentially hydrophobic. 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. $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ have been used to measure the extent of hydrophobic interaction between peptidic protease inhibitors and receptor proteins (binding site: valine–isoleucine; and catalytic site: glycine–aspartic acid–threonine) on the HIV-1 protease enzyme. For measurement of hydrophobic interaction, the molecular modeling and geometry optimization of all the inhibitors and the receptor amino acids have been carried out with CAChe Pro software by opting semiempirical PM3 methods. Log P was calculated using the atom-typing scheme of Ghose and Crippen, while solvent accessible surface area by conductor likes screening model. π_d, π_r, $SASA_{Sd}$ and $SASA_{Sr}$ well describe the hydrophobicities of the substituents and play the effective role for site selectivity for interaction of the drug with the receptor. Comparative study of values of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ show the order of hydrophobic interaction with respect to amino acids: Asp > Thr > Val > Ile and Thr > Val > Asp > Ile, respectively. Further, comparative study of the values of $(\Sigma\Delta\pi_{dr})_{binding-site}$, $(\Sigma\Delta\pi_{dr})_{catalytic-site}$, $(\Sigma\Delta SASA_{dr})_{binding-site}$, $(\Sigma\Delta SASA_{dr})_{catalytic-site}$ shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta\pi_{dr}$ and $\Sigma\Delta SASA_{dr}$. Among the binding site, Val has maximum interaction than Ile, as it has lower vale of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$.

Keywords: Hydrophobicity, Solvent Accessible Surface Area, PM3

1. Introduction

Interactions between the hydrophobic regions of a binding site and those of a complementary ligand are often observed to provide the driving force for binding [1]. In this work $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ have been used to measure the extent of hydrophobic interaction between peptidic HIV-1 protease inhibitors (HIV-1-PRIs) and receptor proteins (binding and catalytic site) on the HIV-1 protease enzyme (HIV-1-PR). These approaches have been parametrized using π_d (lipophilicity of the substituent of the drug), π_r (lipophilicity of the substituent of the receptor), $SASA_{Sd}$ (solvent accessible surface area of the substituent of the drug) and $SASA_{Sr}$ (solvent accessible surface area of the substituent of the receptor). π and $SASA_S$ have been used to identify those groups/substituents that are more likely have a strong hydrophobic interaction with nonpolar regions [2]. These consider not only atom type but also the non-additive effects arising from the shape and extent of a nonpolar region. When a drug interacts with its receptor, the nonpolar substituent of drug and receptor proteins attract each other because they have opposite magnitude with respect to each other as shown in Figure 1.
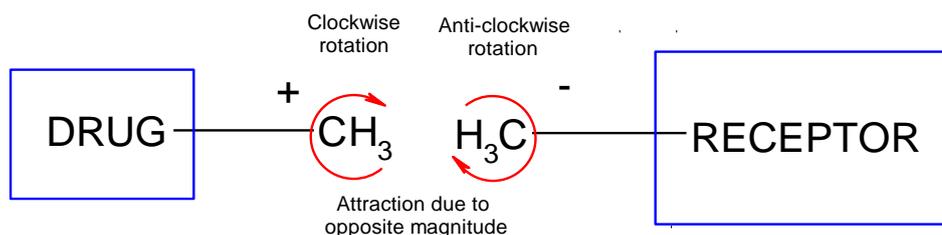
Figure 1. Hydrophobic interaction between drug and receptor.

Drug-receptor interaction in term of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ are defined as:

$$\Delta\pi_{dr} = \pi_d - \pi \tag{1}$$

where π_d is the log P of the substituent of drug (peptidic HIV-1-PRI), π_r the log P of the substituent of receptor (amino acids) and $\Delta\pi_{dr}$ is their change (higher - lower).

$$\Delta SASA_{dr} = SASA_{Sd} - SASA_{Sr} \tag{2}$$

where $SASA_{Sd}$ is the $SASA_S$ of the substituent of drug (HIV-1-PRI), $SASA_{Sr}$ the SASA of the substituent of receptor and $\Delta SASA_{dr}$ is their change (higher - lower).

Lower the values of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ higher will the interaction. The log P and SASA of the substituent have been evaluated by solving the following equations [3].

$$\pi = log\ P_{derivt} - log\ P_H \tag{3}$$

$$SASA_S = SASA_{derivt} - SASA_H \tag{4}$$

where log P_{subs} (π) is the log P of the substituent of the drug/ receptor, log P_{derivt} is the log P of the derivative and log P_H is the log P of the lead compound, $SASA_{subs}$ (or $SASA_S$) is the SASA of the substituent of the drug/ receptor, $SASA_{derivt}$ is the SASA of the derivative and $SASA_H$ is the SASA of the lead compound. In this work, we have studied the hydrophobic interaction governing the drug-receptor interaction of fifty-one HIV-1-PRIs with their receptor on HIV-1-PR.

2. Materials and Methods:

The study materials of the present research work are fifty-one peptidic HIV-1-PRIs and receptor proteins. The inhibitors have been taken from literatures [4, 5] and are listed in Table 1 to 3 with their observed bioactivities in term of IC$_{50}$ [6]. The logarithms of the inverse of IC$_{50}$ have been used as biological end point (log1/C) in the study. Interaction sites on receptor proteins are amino acids. These are valine and isoleucine amino acids on binding site, while aspartic acid, threonine and glycine amino acids on catalytic site, and are shown in Figure 2. For measurement of hydrophobic interaction, the molecular modeling and geometry optimization of all the inhibitors and the receptor amino acids have been carried out with CAChe Pro software by opting PM3 methods [7]. Log P is calculated using the atom-typing scheme of Ghose and Crippen [8], while SASA by conductor like screening model (COSMO) [9]. The majority of HIV research is done with cells and these studies tend to overestimate log P for animal system. A study of their database revealed that log P for cells is about 1 log unit higher than for whole organisms [10].

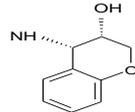**Table 1. First set of peptidic HIV-1-PRIs with observed biological activities**

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*

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

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

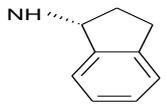**Table 3. Third set of fifty one peptidic HIV-1-PRIs with observed biological activities**
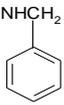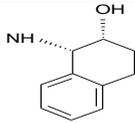
Compd. No.	X	o(log1/C)	Compd. No.	X	o(log1/C)
36		6.94	44		9.16
37		8.02	45		9.75
38		7.47	46		7.39
39		6.16	47		4.52
40		6.79	48		6.89
41		7.18	49		6.84
42		6.67	50		10.00
43		6.91	51		7.41
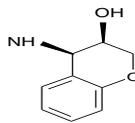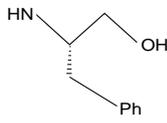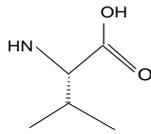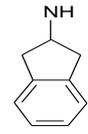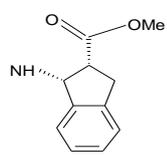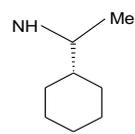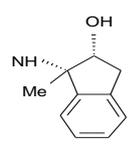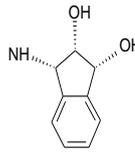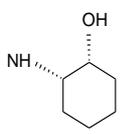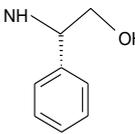
3. Results and Discussion:

Survey of literatures exposed that HIV-1-PR is a viral encoded homodimeric aspartyl protease with C_2 symmetry [11, 12], and a catalytic triad of Asp-Thr-Gly contributed by each monomer that comprises the active site of the enzyme. Literatures also showed that all protease inhibitors bind to the protease binding site pocket that has a considerable number of hydrophobic residues and the X-rays structure indicates that the S2/S2' pocket in HIV-1-PR are essentially hydrophobic [11-13]. 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 [13]. The importance of hydrophobic residues in the bonding pocket reconfirms the contribution of the hydrophobicity of inhibitors on anti-HIV activity. Since Val and Ile are hydrophobic in nature, they must be playing a decisive role in hydrophobic interaction. In this article, we have studied hydrophobic interaction governing the drug-receptor

interaction of fifty-one peptidic HIV-1-PRIs with their receptor on HIV-1-PR. All the fifty-one inhibitors have been divided in three sets on the basis of their structural similarities (Figure 3). The first, second and third set comprises of eighteen, seventeen and sixteen inhibitors, respectively [4, 5].

Figure 2. Structure of receptor proteins: (1) Valine, (2) Isoleucine, (3) Aspartic Acid, (4) Threonine and (5) Glycine

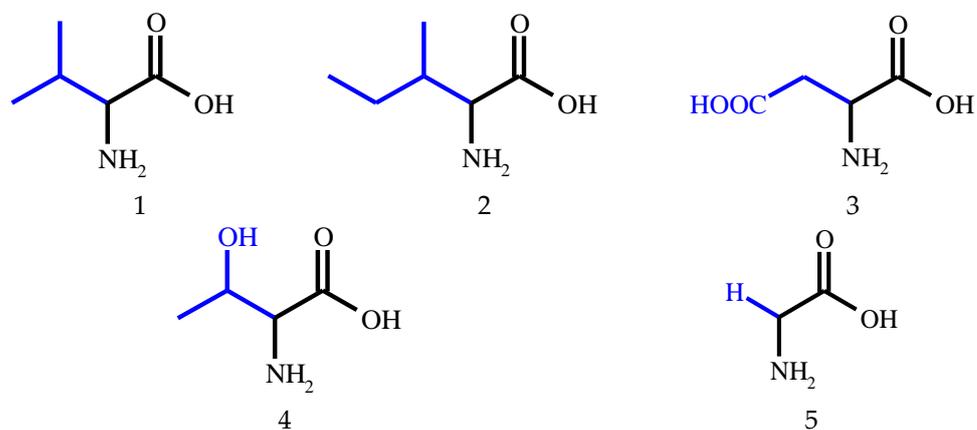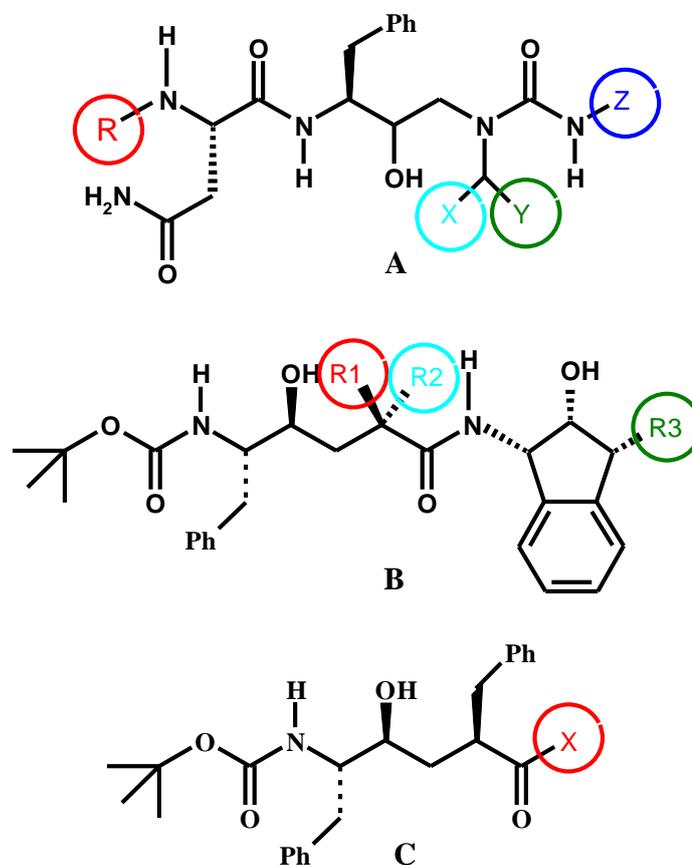**Figure 3.** Parent skeleton of peptidic HIV-1-PRIs: (A) first set, (B) second set and (C) third set

3.1. Hydrophobicity/ Lipophilicity

Hydrophobicity or lipophilicity (ratio of octanol solubility to water solubility) measured through log P. The molecular lipophilic potential (MLP) was the first method designed to calculate the hydrophobic profile of a molecule in three dimensions [14, 15]. The development of the MLP was based on the finding that the partition coefficient (P) of a molecule, which represents its relative distribution over an octanol/water boundary, could be estimated from its chemical structure [16]. From the assumption that the log P is an additive property of the molecular fragments that make up a molecule, values for a wide variety of atom types and groups have been calculated. The receptor pocket may not be completely homogeneous (hydrophobic), so that log P does not perform a very good job for a large molecule with multiple position of substitution where as hydrophobicity of substituent (π) is more appropriate in such cases. For sake of simplicity each set has been studied separately as described below.

3.1.1. First Set

This set comprises of eighteen inhibitors (Table 1) [4]. The hydrophobicity of the each compound (log P), hydrophobicities of its substituents (π_R, π_X, π_Y, and π_Z) and its interactions ($\Delta\pi_{dr}$) with the substituents of receptor amino acids (π_r) of this set have been evaluated and are presented in Table 4. A reference to the table shows that among the four substituents R, X, Y and Z, substituent-R has the highest value of π_d and substituent-X has the lowest value. The decreasing order of substituent hydrophobicity has the sequence $\pi_R > \pi_Y > \pi_Z > \pi_X$. Thus, substituent-R has maximum probability to interact hydrophobically with receptor amino acids: valine (Val), isoleucine (Ile), aspartic acid (Asp), threonine (Thr) and glycine (Gly). Val and Ile constituting the receptor amino acids of binding site, while Asp, Thr and Gly that of catalytic site of the enzyme, HIV-1-PR. The hydrophobic interactions ($\Delta\pi_{dr}$) between substituent-R and receptor amino acid have been evaluated by solving Eq.1 and are also presented in Table 4. The decreasing order of $\Delta\pi_{dr}$ has the sequence $\Delta\pi_{dr}(Asp) > \Delta\pi_{dr}(Thr) > \Delta\pi_{dr}(Val) > \Delta\pi_{dr}(Ile)$. A reference to these data shows that substituent-R has maximum interaction with the Ile amino acids as this interaction has lowest value of the $\Delta\pi_{dr}$. The values of $(\Sigma\Delta\pi_{dr})_{binding-site}$ and $(\Sigma\Delta\pi_{dr})_{catalytic-site}$ (Table 10) shows that peptidic HIV-1-PRIs of this set interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta\pi_{dr}$. Among the binding site, Ile has maximum interaction with the drug than Val, as it has lower value of $\Delta\pi_{dr}$.

3.1.2. Second Set

This set comprises of seventeen inhibitors (Table 2) [5]. The log P, π_{R1}, π_{R2}, π_{R3}, π_r and $\Delta\pi_{dr}$ have been evaluated and are presented in Table 5. A reference to the table shows that among the three substituents R1, R2 and R3, substituent-R1 has the highest value of π. Thus, substituent-R1 has maximum probability to interact hydrophobically with receptor amino acids of the HIV-1-PR enzyme. The hydrophobic interactions ($\Delta\pi_{dr}$) between substituent-R1 and receptor amino acid have been evaluated and are also presented in Table 5. The decreasing order of $\Delta\pi_{dr}$ has the order $\Delta\pi_{dr}(Asp) > \Delta\pi_{dr}(Thr) > \Delta\pi_{dr}(Val) > \Delta\pi_{dr}(Ile)$. A reference to these data shows that substituent-R1 has maximum interaction with the Ile amino acids as this interaction has lowest value of the $\Delta\pi_{dr}$. The values of $(\Sigma\Delta\pi_{dr})_{binding-site}$ and $(\Sigma\Delta\pi_{dr})_{catalytic-site}$ (Table 10) shows that inhibitors of this set interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta\pi_{dr}$. Among the binding site, substituent-R1 has maximum interaction with the Ile than Val, as this interaction has lower value of $\Delta\pi_{dr}$.

3.1.3. Third Set:

This set comprises of sixteen peptidic inhibitors (Table 3) [5]. The log P, π_X and π_r have been evaluated and are presented in Table 6. The hydrophobic interactions ($\Delta\pi_{dr}$)

between substituent-X and receptor amino acid have been evaluated and are also presented in Table 6. The decreasing order of $\Delta\pi_{dr}$ has the order $\Delta\pi_{dr}(Asp) > \Delta\pi_{dr}(Thr) > \Delta\pi_{dr}(Val) > \Delta\pi_{dr}(Ile)$. A reference to these data shows that substituent-X has maximum interaction with the Ile amino acids as this interaction has lowest value of the $\Delta\pi_{dr}$. The values of $(\Sigma\Delta\pi_{dr})_{binding-site}$ and $(\Sigma\Delta\pi_{dr})_{catalytic-site}$ (Table 10) shows that inhibitors of this set interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta\pi_{dr}$.Among the binding site, substituent-X has maximum interaction with the Ile than Val, as this interaction has lower value of $\Delta\pi_{dr}$.

The strength of the hydrophobic interaction is thus influenced not only by the polarity but also by the shape and extent of the exposed molecular surface [17]. It was also reported by Wang et al. that at least two additional factors are important in the binding of a compound to HIV-1-PR [16].The first one is the conformational inhibitor molecule, and the second one is the hydrophobic interaction between an inhibitor and the enzyme. As reported that HIV-1-PR has four hydrophilic pockets near its active sites, and it has also been shown that favorable hydrophobic interactions with these pockets are driblet for an inhibitor to achieve nanomolar potency [19]. The work of Wang et al. is also able to rationalize differences in binding affinity for enzyme-inhibitor complexes with largely hydrophobic binding sites.

3.2. *Solvent accessible surface area*

Solvent accessible surface area (SASA) is used to compute surface properties. SASA was first described by Lee and Richards in 1971 and is also known as Lee–Richard molecular surface [20]. Shrake and Ruplet in 1973 developed the rolling ball algorithm to calculate solvent accessible surface area [20]. SASA also provides a useful tool to gain insight into the overall extent of a hydrophobic region on a molecule or in the binding site of a protein, but unable for any real account of the particular atom types that make up the binding site or their positions relative to one another. Besides, it provides no means of assessing the shape of the binding site because it only calculates the relative accessibility of the contributing atoms [21]. Here, we studied hydrophobic interaction with respect to SASA and for the sake of simplicity each set has separately been described below.

3.2.1. First Set

The solvent accessible surface area (SASA) of each compound, solvent accessible surface area of its substituents ($SASA_R$, $SASA_X$, $SASA_Y$, and $SASA_Z$) and its interactions ($\Delta SASA_{dr}$) with the substituents of receptor amino acids ($SASA_r$) of the first set have been evaluated and are presented in Table 7. A reference to the table shows that among the four substituents R, X, Y and Z, substituent-R has the highest value of $SASA_d$ and substituent-X has the lowest value. The decreasing order of substituent hydrophobicity has the sequence: $SASA_R > SASA_Z > SASA_Y > SASA_X$. Thus, substituent-R has maximum probability to interact with receptor amino acids. The hydrophobic interactions ($\Delta SASA_{dr}$) between substituent-R and receptor amino acid have been evaluated by solving Eq.2 and are also presented in Table 7. The decreasing order of $\Delta SASA_{dr}$ has the sequence $\Delta SASA_{dr}(Thr) > \Delta SASA_{dr}(Asp) > \Delta SASA_{dr}(Val) > \Delta SASA_{dr}(Ile)$. The values of $(\Sigma\Delta SASA_{dr})_{binding-site}$ and $(\Sigma\Delta SASA_{dr})_{catalytic-site}$ (Table 10) shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta SASA$. A comparative study of $\Delta SASA_{dr}$ reveals that Ile amino acid of binding sites has lowest values of $\Delta SASA_{dr}$ than remaining amino acids. Thus, inhibitors of this set interact with Ile amino acid of binding site.

3.2.2. Second Set:

The SASA, $SASA_{R1}$, $SASA_{R2}$, $SASA_{R3}$, $SASA_r$ and $\Delta SASA_{dr}$ of each compound of second set have been evaluated and are presented in Table 8.

Table 4. log P, π_d, π_r, and $\Delta\pi_{dr}$ of compounds of the first set.

| S.N. | log P | Substituent-R | | Substituent-X | | Substituent-Y | | Substituent-Z | | Binding Site | | Catalytic Site | | |
| | | | | | | | | | | Val $\pi_r = 1.41$ | Ile $\pi_r =1.8$ | Asp $\pi_r =0.08$ | Thr $\pi_r =0.16$ | Gly $\pi_r =0$ |
		log P$_H$	π_R	log P$_H$	π_X	log P$_H$	π_Y	log P$_H$	π_Z	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$
1	1.79	-0.44	2.23	1.79	0.00	0.58	1.21	1.54	0.25	0.82	0.43	2.15	2.07	-----
2	3.00	0.77	2.23	3.00	0.00	1.78	1.22	1.54	1.46	0.82	0.43	2.15	2.07	-----
3	3.00	0.77	2.23	3.00	0.00	1.78	1.22	1.54	1.46	0.82	0.43	2.15	2.07	-----
4	2.60	0.37	2.23	2.60	0.00	1.39	1.21	1.54	1.06	0.82	0.43	2.15	2.07	-----
5	2.13	-0.10	2.23	2.13	0.00	0.92	1.21	1.54	0.59	0.82	0.43	2.15	2.07	-----
6	2.55	0.32	2.23	2.55	0.00	1.33	1.22	1.54	1.01	0.82	0.43	2.15	2.07	-----
7	2.62	0.40	2.22	2.62	0.00	1.41	1.21	1.54	1.08	0.81	0.42	2.14	2.06	-----
8	2.62	0.40	2.22	2.62	0.00	1.41	1.21	1.54	1.08	0.81	0.42	2.14	2.06	-----
9	2.95	0.40	2.55	2.95	0.00	1.41	1.54	1.87	1.08	1.14	0.75	2.47	2.39	-----
10	2.95	0.72	2.23	2.95	0.00	1.41	1.54	1.87	1.08	0.82	0.43	2.15	2.07	-----
11	3.31	1.08	2.23	3.31	0.00	1.41	1.90	2.23	1.08	0.82	0.43	2.15	2.07	-----
12	3.31	1.08	2.23	3.31	0.00	1.41	1.90	2.23	1.08	0.82	0.43	2.15	2.07	-----
13	3.19	0.96	2.23	3.19	0.00	1.41	1.78	2.11	1.08	0.82	0.43	2.15	2.07	-----
14	3.19	0.96	2.23	3.19	0.00	1.41	1.78	2.11	1.08	0.82	0.43	2.15	2.07	-----
15	3.60	1.37	2.23	3.19	0.41	1.75	1.85	2.52	1.08	0.82	0.43	2.15	2.07	-----
16	3.60	1.37	2.23	3.19	0.41	1.75	1.85	2.52	1.08	0.82	0.43	2.15	2.07	-----
17	1.88	-0.35	2.23	1.88	0.00	1.41	0.47	0.80	1.08	0.82	0.43	2.15	2.07	-----
18	1.88	-0.35	2.23	1.88	0.00	1.41	0.47	0.79	1.09	0.82	0.43	2.15	2.07	-----

Table 5. log P, π_d, π_r, and $\Delta\pi_{dr}$ of compounds of the second set.

								Binding Site		Catalytic Site		
								Val	Ile	Asp	Thr	**Gly**
S.N.	log P	Substituent-R1		Substituent-R2		Substituent-R3		$\pi_r = 1.41$	$\pi_r = 1.8$	$\pi_r = 0.08$	$\pi_r = 0.16$	$\pi_r = 0$
		log P$_H$	π_{R1}	log P$_H$	π_{R2}	log P$_H$	π_{R3}	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$
19	5.39	3.21	2.18	5.39	0.00	5.39	0.00	0.77	0.38	2.26	2.02	-----
20	6.05	3.78	2.27	6.05	0.66	6.05	0.00	0.86	0.47	2.35	2.11	-----
21	5.16	2.59	2.57	5.16	0.00	5.78	-0.62	1.16	0.77	2.65	2.41	-----
22	6.27	3.21	3.06	6.27	0.00	6.27	0.00	1.65	1.26	3.14	2.90	-----
23	5.92	3.21	2.71	5.92	0.00	5.92	0.00	1.30	0.91	2.79	2.55	-----
24	6.09	3.21	2.88	6.09	0.00	6.09	0.00	1.47	1.08	2.96	2.72	-----
25	5.86	3.21	2.65	5.86	0.00	5.86	0.00	1.24	0.85	2.73	2.49	-----
26	4.61	3.21	1.40	4.61	0.00	4.61	0.00	0.01	0.40	1.48	1.24	-----
27	5.34	3.21	2.13	5.34	0.00	5.34	0.00	0.72	0.33	2.21	1.97	-----
28	3.21	3.21	0.00	3.21	0.00	3.21	0.00	1.41	1.80	0.08	0.16	-----
29	5.10	5.10	0.00	5.10	0.00	5.10	0.00	1.41	1.80	0.08	0.16	-----
30	4.35	3.21	1.14	4.35	0.00	4.35	0.00	0.27	0.66	1.22	0.98	-----
31	6.65	3.21	3.44	6.65	0.00	6.65	0.00	2.03	1.64	3.52	3.28	-----
32	4.46	3.21	1.25	4.46	0.00	4.46	0.00	0.16	0.55	1.33	1.09	-----
33	4.08	3.21	0.87	4.08	0.00	4.08	0.00	0.54	0.93	0.95	0.71	-----
34	5.18	3.21	1.97	5.18	0.00	5.18	0.00	0.56	0.17	2.05	1.81	-----
35	7.02	3.21	3.81	7.02	0.00	7.02	0.00	2.40	2.01	3.89	3.65	-----

Table 6. log P, π_d, π_r, and $\Delta\pi_{dr}$ of compounds of the third set.

S.N.	log P			Binding Site		Catalytic Site		
				Val	Ile	Asp	Thr	Gly
		Substituent-X		$\pi_r = 1.41$	$\pi_r = 1.8$	$\pi_r = 0.08$	$\pi_r = 0.16$	$\pi_r = 0$
		log P_H	π_X	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$	$\Delta\pi_{dr}$
36	5.71	3.69	2.02	0.61	0.22	2.10	1.86	-----
37	4.24	3.69	0.55	0.86	1.25	0.63	0.39	-----
38	6.16	3.69	2.47	1.06	0.67	2.55	2.31	-----
39	5.59	3.69	1.90	0.49	0.10	1.98	1.74	-----
40	4.88	3.69	1.19	0.22	0.61	1.27	1.03	-----
41	5.66	3.69	1.97	0.56	0.17	2.05	1.81	-----
42	5.47	3.69	1.78	0.37	0.02	1.86	1.62	-----
43	4.75	3.69	1.06	0.35	0.74	1.14	0.90	-----
44	5.78	3.69	2.09	0.68	0.29	2.17	1.93	-----
45	4.98	3.69	1.29	0.12	0.51	1.37	1.13	-----
46	4.98	3.69	1.29	0.12	0.51	1.37	1.13	-----
47	5.83	3.69	2.14	0.73	0.34	2.22	1.98	-----
48	6.01	3.69	2.32	0.91	0.52	2.40	2.16	-----
49	6.24	3.69	2.55	1.14	0.75	2.63	2.39	-----
50	4.76	3.69	1.07	0.34	0.73	1.15	0.91	-----
51	5.34	3.69	1.65	0.24	0.15	1.73	1.49	-----

Table 7. SASA, SASA$_d$, SASA$_r$ and ΔSASA$_{dr}$ of compounds of the first set

S.N.	SASA	Substituent-R		Substituent-X		Substituent-Y		Substituent-Z		Binding Site Val SASA$_r$ = 17.28	Binding Site Ile SASA$_r$ = 24.16	Catalytic Site Asp SASA$_r$ = 20.69	Catalytic Site Thr SASA$_r$ = 15.66	Catalytic Site Gly SASA$_r$ = 0
		SASA$_H$	SASA$_R$	SASA$_H$	SASA$_X$	SASA$_H$	SASA$_Y$	SASA$_H$	SASA$_Z$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$
1	220.62	174.78	45.85	220.62	0.00	212.52	8.10	212.54	8.08	28.57	21.69	25.16	30.19	-----
2	234.86	192.21	42.65	234.86	0.00	226.78	8.08	208.27	26.59	25.37	18.49	21.96	26.99	-----
3	247.04	195.96	51.08	247.04	0.00	239.18	7.86	218.10	28.94	33.80	26.92	30.39	35.42	-----
4	247.07	192.35	54.72	247.07	0.00	237.92	9.15	226.11	20.96	37.44	30.56	34.03	39.06	-----
5	233.90	191.55	42.36	233.90	0.00	217.06	16.84	219.56	14.34	25.08	18.20	21.67	26.70	-----
6	230.66	190.56	40.09	230.66	0.00	227.66	3.00	211.84	18.82	22.81	15.93	19.40	24.43	-----
7	231.08	188.72	42.36	231.08	0.00	226.30	4.78	206.95	24.13	25.08	18.20	21.67	26.70	-----
8	240.17	191.60	48.57	240.17	0.00	232.63	7.54	216.63	23.54	31.29	24.41	27.88	32.91	-----
9	244.21	192.96	51.24	244.21	0.00	230.23	13.98	220.44	23.77	33.96	27.08	30.55	35.58	-----
10	257.24	208.38	48.86	257.24	0.00	230.84	26.40	236.43	20.81	31.58	24.70	28.17	33.20	-----
11	249.78	207.76	42.02	249.78	0.00	220.52	29.26	235.09	14.69	24.74	17.86	21.33	26.36	-----
12	251.20	196.86	54.34	251.20	0.00	237.28	13.92	223.30	27.90	37.06	30.18	33.65	38.68	-----
13	257.99	210.81	47.17	257.99	0.00	225.50	32.49	232.14	25.85	29.89	23.01	26.48	31.51	-----
14	264.17	202.17	62.00	264.17	0.00	239.92	24.25	240.75	23.42	44.72	37.84	41.31	46.34	-----
15	249.16	213.92	35.24	249.30	-0.14	221.87	27.29	232.86	16.30	17.96	11.08	14.55	19.58	-----
16	261.52	216.47	45.05	253.96	7.56	232.31	29.21	236.48	25.04	27.77	20.89	24.36	29.39	-----
17	245.27	202.48	42.80	245.27	0.00	231.08	14.19	223.11	22.16	25.52	18.64	22.11	27.14	-----
18	247.64	205.52	42.11	247.64	0.00	228.85	18.79	228.50	19.14	24.83	17.95	21.42	26.45	-----

Table 8. SASA, SASA$_d$, SASA$_r$ and ΔSASA$_{dr}$ of compounds of the second set.

S.N.	SASA	Substituent-R1		Substituent-R2		Substituent-R3		Binding Site		Catalytic Site		
								Val	Ile	Asp	Thr	Gly
								SASA$_r$ = 17.28	SASA$_r$ = 24.16	SASA$_r$ = 20.69	SASA$_r$ = 15.66	SASA$_r$ = 0
		SASA$_H$	SASA$_{R1}$	SASA$_H$	SASA$_{R2}$	SASA$_H$	SASA$_{R3}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$
19	210.51	185.85	24.66	210.51	0.00	210.51	0.00	7.38	0.50	3.97	9.00	-----
20	218.59	189.74	28.85	218.59	8.08	218.59	0.00	11.57	4.69	8.16	13.19	-----
21	242.44	206.84	35.60	242.44	0.00	235.54	6.90	18.32	11.44	14.91	19.94	-----
22	226.19	186.15	40.04	226.19	0.00	226.19	0.00	22.76	15.88	19.35	24.38	-----
23	225.17	185.73	39.44	225.17	0.00	225.17	0.00	22.16	15.28	18.75	23.78	-----
24	228.42	187.43	40.99	228.42	0.00	228.42	0.00	23.71	16.83	20.30	25.33	-----
25	218.71	188.66	30.05	218.71	0.00	218.71	0.00	12.77	5.89	9.36	14.39	-----
26	218.47	187.88	30.59	218.47	0.00	218.47	0.00	13.31	6.43	9.90	14.93	-----
27	228.16	185.70	42.46	228.16	0.00	228.16	0.00	25.18	18.30	21.77	26.80	-----
28	188.58	188.10	0.48	188.58	0.00	188.58	0.00	16.80	23.68	20.21	15.18	-----
29	217.28	216.73	0.55	217.28	0.00	217.28	0.00	16.73	23.61	20.14	15.11	-----
30	199.57	188.06	11.51	199.57	0.00	199.57	0.00	5.77	12.65	9.18	4.15	-----
31	234.50	185.74	48.76	234.50	0.00	234.50	0.00	31.48	24.60	28.07	33.10	-----
32	227.80	182.87	44.93	227.80	0.00	227.80	0.00	27.65	20.77	24.24	29.27	-----
33	210.34	185.86	24.48	210.34	0.00	210.34	0.00	7.20	0.32	3.79	8.82	-----
34	233.55	189.57	43.98	233.55	0.00	233.55	0.00	26.70	19.82	23.29	28.32	-----
35	226.76	187.28	39.48	226.76	0.00	226.76	0.00	22.20	15.32	18.79	23.82	-----

Table 9. SASA, SASA$_d$, SASA$_r$ and ΔSASA$_{dr}$ of compounds of the third set.

S.N.	SASA	Substituent-X		Binding Site		Catalytic Site		
				Val	Ile	Asp	Thr	Gly
				SASA$_r$ = 17.28	SASA$_r$ = 24.16	SASA$_r$ = 20.69	SASA$_r$ = 15.66	SASA$_r$ = 0
		SASA$_H$	SASA$_X$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$	ΔSASA$_{dr}$
36	204.14	173.54	30.60	13.32	6.44	9.91	14.94	-----
37	196.90	173.54	23.36	6.08	0.80	2.67	7.70	-----
38	210.24	173.54	36.70	19.42	12.54	16.01	21.04	-----
39	209.14	173.54	35.60	18.32	11.44	14.91	19.94	-----
40	200.29	173.54	26.75	9.47	2.590	6.06	11.09	-----
41	238.92	173.54	65.38	48.10	41.22	44.69	49.72	-----
42	236.15	173.54	62.61	45.33	38.45	41.92	46.95	-----
43	196.47	173.54	22.93	5.65	1.230	2.24	7.27	-----
44	211.99	173.54	38.45	21.17	14.29	17.76	22.79	-----
45	240.08	173.54	66.54	49.26	42.38	45.85	50.88	-----
46	230.73	173.54	57.19	39.91	33.03	36.50	41.53	-----
47	199.90	173.54	26.36	9.08	2.200	5.67	10.70	-----
48	209.20	173.54	35.66	18.38	11.50	14.97	20.00	-----
49	215.38	173.54	41.84	24.56	17.68	21.15	26.18	-----
50	209.80	173.54	36.26	18.98	12.10	15.57	20.60	-----
51	207.86	173.54	34.32	17.04	10.16	13.63	18.66	-----

Table 10. Values of $\Sigma\Delta\pi_{dr}$ and $\Sigma\Delta SASA_{dr}$ of binding site and catalytic site of all the three sets.

	First Set					Second Set					Third Set			
S.N.	Binding Site	Catalytic Site	Binding Site	Catalytic Site	S.N.	Binding Site	Catalytic Site	Binding Site	Catalytic Site	S.N.	Binding Site	Catalytic Site	Binding Site	Catalytic Site
	$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta SASA_{dr}$	$\Sigma\Delta SASA_{dr}$		$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta SASA_{dr}$	$\Sigma\Delta SASA_{dr}$		$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta\pi_{dr}$	$\Sigma\Delta SASA_{dr}$	$\Sigma\Delta SASA_{dr}$
1	1.25	4.22	50.26	55.35	19	1.15	4.28	7.88	12.97	36	0.83	3.96	19.76	24.85
2	1.25	4.22	43.86	48.95	20	1.33	4.46	16.26	21.35	37	2.11	1.02	6.88	10.37
3	1.25	4.22	60.72	65.81	21	1.93	5.06	29.76	34.85	38	1.73	4.86	31.96	37.05
4	1.25	4.22	68.00	73.09	22	2.91	6.04	38.64	43.73	39	0.59	3.72	29.76	34.85
5	1.25	4.22	43.28	48.37	23	2.21	5.34	37.44	42.53	40	0.83	2.3	12.06	17.15
6	1.25	4.22	38.74	43.83	24	2.55	5.68	40.54	45.63	41	0.73	3.86	89.32	94.41
7	1.23	4.20	43.28	48.37	25	2.09	5.22	18.66	23.75	42	0.39	3.48	83.78	88.87
8	1.23	4.20	55.70	60.79	26	0.41	2.72	19.74	24.83	43	1.09	2.04	6.88	9.51
9	1.89	4.86	61.04	66.13	27	1.05	4.18	43.48	48.57	44	0.97	4.1	35.46	40.55
10	1.25	4.22	56.28	61.37	28	3.21	0.24	40.48	35.39	45	0.63	2.5	91.64	96.73
11	1.25	4.22	42.60	47.69	29	3.21	0.24	40.34	35.25	46	0.63	2.5	72.94	78.03
12	1.25	4.22	67.24	72.33	30	0.93	2.2	18.42	13.33	47	1.07	4.2	11.28	16.37
13	1.25	4.22	52.90	57.99	31	3.67	6.8	56.08	61.17	48	1.43	4.56	29.88	34.97
14	1.25	4.22	82.56	87.65	32	0.71	2.42	48.42	53.51	49	1.89	5.02	42.24	47.33
15	1.25	4.22	29.04	34.13	33	1.47	1.66	7.52	12.61	50	1.07	2.06	31.08	36.17
16	1.25	4.22	48.66	53.75	34	0.73	3.86	46.52	51.61	51	0.39	3.22	27.2	32.29
17	1.25	4.22	44.16	49.25	35	4.41	7.54	37.52	42.61					
18	1.25	4.22	42.78	47.87										

A reference to the table shows that among the three substituents R1, R2 and R3, substituent-R1 has the highest value of $SASA_d$. Thus, substituent-R1 has maximum probability to interact hydrophobically with receptor amino acids of the HIV-1 protease enzyme. The hydrophobic interactions ($\Delta SASA_{dr}$) between substituent-R1 and receptor amino acid have been evaluated and are also presented in Table 8. The hydrophobic interactions in term of $\Delta SASA_{dr}$ of substituent-R1 with respect to each amino acid have been evaluated and are also presented in Table-5. A reference to these data shows that among the five amino acids Ile has lowest value of the $\Delta SASA_{dr}$ and Thr has the highest value of $\Delta SASA_{dr}$. The decreasing order of $\Delta SASA_{dr}$ has the sequence $\Delta SASA_{dr}(Thr) > \Delta SASA_{dr}(Val) > \Delta SASA_{dr}(Asp) > \Delta SASA_{dr}(Ile)$. The values of $(\Sigma\Delta SASA_{dr})_{binding-site}$ and $(\Sigma\Delta SASA_{dr})_{catalytic-site}$ (Table 10) shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta SASA$. A comparative study of $\Delta SASA_{dr}$ reveals that Ile amino acid of binding sites has lowest values of $\Delta SASA_{dr}$ than remaining amino acids. Thus, peptidic HIV-1-PRIs of this set interact with Ile amino acid of binding site.

3.2.3. Third Set

The SASA, $SASA_X$ and $SASA_r$ of each compound of the third set have been evaluated and are presented in Table 9. The hydrophobic interactions interm of $\Delta SASA_{dr}$ of substituent-X with respect to each amino acid have been evaluated and are also presented in Table 9. A reference to these data shows that among the five amino acids Ile has lowest value of the $\Delta SASA_{dr}$ and Thr has the highest value of $\Delta SASA_{dr}$. The decreasing order of $\Delta SASA_{dr}$ has the sequence: $\Delta SASA_{dr}(Thr) > \Delta SASA_{dr}(Val) > \Delta SASA_{dr}(Asp) > \Delta SASA_{dr}(Ile)$. The values of $(\Sigma\Delta SASA_{dr})_{binding-site}$ and $(\Sigma\Delta SASA_{dr})_{catalytic-site}$ (Table 10) shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta SASA$. A comparative study of $\Delta SASA_{dr}$ reveals that Ile amino acid of binding sites has lowest values of $\Delta SASA_{dr}$ than remaining amino acids. Thus, inhibitors of this set interact with Ile amino acid of binding site.

4. Conclusions

1. Analysis of π_d and $SASA_d$ shows that among the four substituents R, X, Y and Z of the first set, substituent-R has the highest value of both π_d and $SASA_d$. Among the three substituents R1, R2 and R3 of the second set, substituent-R1 also has the highest value of both π_d and $SASA_d$. Among the receptor amino acids (Val, Ile, Asp, Thr and Gly), Ile has the highest value of both π_d and $SASA_d$. Thus, π_d, π_r, $SASA_{Sd}$ and $SASA_{Sr}$ well describe the hydrophobicities of the substituents and play the effective role for site selectivity for interaction of the drug with the receptor.

2. Comparative study of values of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$ of all the three sets shows that they have the same order of hydrophobic interaction with respect to amino acids, $\Delta\pi_{dr}(Asp) > \Delta\pi_{dr}(Thr) > \Delta\pi_{dr}(Val) > \Delta\pi_{dr}(Ile)$ and $\Delta SASA_{dr}(Thr) > \Delta SASA_{df}(Val) > \Delta SASA_{dr}(Asp) > \Delta SASA_{dr}(Ile)$. A comparative study of the values of $(\Sigma\Delta\pi_{dr})_{binding-site}$, $(\Sigma\Delta\pi_{dr})_{catalytic-site}$, $(\Sigma\Delta SASA_{dr})_{binding-site}$, $(\Sigma\Delta SASA_{dr})_{catalytic-site}$ and shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma\Delta\pi_{dr}$ and $\Sigma\Delta SASA_{dr}$. Among the binding site, Val has maximum interaction than Ile, as it has lower vale of $\Delta\pi_{dr}$ and $\Delta SASA_{dr}$. Thus, $\Delta\pi_{dr}$, $\Delta SASA_{dr}$, $\Sigma\Delta\pi_{dr}$ and $\Sigma\Delta SASA_{dr}$ well describe the extent of hydrophobic interaction of the drug with the receptor.

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