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. Δπ and ΔSASA 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 likeness (http://creativecommons.org/licenses/by/4.0/).

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 Δπ and ΔSASA 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 (lipophilicity of the substituent of the drug), π (lipophilicity of the substituent of the receptor), SASA (solvent accessible surface area of the substituent of the drug) and SASA (solvent accessible surface area of the substituent of the receptor), π and SASA 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.
Drug-receptor interaction in term of $\Delta \pi_{dr}$ and $\Delta \text{SASA}_{dr}$ are defined as:

$$\Delta \pi_{dr} = \pi_{dr} - \pi$$  

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

$$\Delta \text{SASA}_{dr} = \text{SASA}_{rd} - \text{SASA}_{sr}$$  

where SASA$_{rd}$ is the SASA of the substituent of drug (HIV-1-PRI), SASA$_{sr}$ the SASA of the substituent of receptor and $\Delta \text{SASA}_{dr}$ is their change (higher - lower).

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

$$\pi = \log P_{\text{deriv}} - \log P_{H}$$  

$$\text{SASA}_{S} = \text{SASA}_{\text{deriv}} - \text{SASA}_{H}$$

where log $P_{\text{subs}}$ ($\pi$) is the log P of the substituent of the drug/receptor, log $P_{\text{deriv}}$ is the log P of the derivative and log $P_{H}$ is the log P of the lead compound, SASA$_{\text{subs}}$ (or SASA$_{S}$) is the SASA of the substituent of the drug/receptor, SASA$_{\text{deriv}}$ 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 | R  | X      | Y      | Z   | o(log1/C) |
|----------|----|--------|--------|-----|-----------|
| 1        | Cbz\(^a\) | H    | CHMe\(_2\) | Me  | 5.82 |
| 2        | Cbz   | H    | CHMe\(_2\) | n-Bu | 6.03 |
| 3        | Qua\(^b\) | H    | CHMe\(_2\) | n-Bu | 6.90 |
| 4        | Cbz   | H    | CHMe\(_2\) | n-Pr | 6.29 |
| 5        | Cbz   | H    | CHMe\(_2\) | Et  | 6.48 |
| 6        | Cbz   | H    | CHMe\(_2\) | 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\(_2\)CHMe\(_2\) | t-Bu | 7.89 |
| 10       | Qua   | H    | CH\(_2\)CHMe\(_2\) | t-Bu | 8.52 |
| 11       | Cbz   | H    | C\(_6\)H\(_5\) | t-Bu | 7.54 |
| 12       | Qua   | H    | C\(_6\)H\(_5\) | t-Bu | 8.30 |
| 13       | Cbz   | H    | C\(_6\)H\(_5\) | t-Bu | 7.72 |
| 14       | Qua   | H    | C\(_6\)H\(_5\) | t-Bu | 8.52 |
| 15\(^c\) | Cbz   | Me   | C\(_6\)H\(_5\) | t-Bu | 5.19 |
| 16\(^d\) | Cbz   | Me   | C\(_6\)H\(_5\) | t-Bu | 5.29 |
| 17       | Cbz   | H    | 4-Py | t-Bu | 6.98 |
| 18       | Qua   | H    | 4-Py | t-Bu | 7.72 |

\(^a\)Carbobenzyloxy, \(^b\)Quinolinyl-2-carboxamide, \(^c\)CHXY in R-configuration, \(^d\)CHXY in S-configuration

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

| Compd.No | R\(_1\) | R2 | R3 | o(log1/C) |
|----------|--------|----|----|-----------|
| 19       | CH\(_2\)Ph | H | H | 9.6 |
| 20       | CH\(_2\)Ph | H | H | 8.11 |
| 21       | CH\(_2\)CH\(_3\)Ph | H | OH | 9.72 |
| 22       | CH\(_2\)-4-CF\(_3\)Ph | H | H | 9.59 |
| 23       | CH\(_2\)CH=CHPh | H | H | 9.64 |
| 24       | CH\(_2\)C\(_6\)F\(_3\) | H | H | 9.22 |
| 25       | CH\(_2\)-4-CH\(_3\)Ph | H | H | 9.54 |
| 26       | CH\(_2\)-4-NH\(_2\)Ph | H | H | 9.51 |
| 27       | CH\(_2\)-4-NO\(_2\)Ph | H | H | 9.57 |
| 28       | H    | H  | H  | 5.53 |
| 29       | CH\(_2\)-4-OHPh | H | H | 9.8 |
| 30       | CH\(_2\)CH=CH\(_2\) | H | H | 7.56 |
| 31       | CH\(_2\)-4-IPh | H | H | 9.14 |
| 32       | CH\(_2\)C(O)Ph | H | H | 8.27 |
| 33       | CH\(_2\)-4-Pyridyl | H | H | 9.28 |
| 34       | CH\(_2\)Ph | H | H | 9.60 |
| 35       | CH\(_2\)-4-CMe\(_3\)Ph | 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         | ![Image](image1) | 6.94      | 44         | ![Image](image2) | 9.16      |
| 37         | ![Image](image3) | 8.02      | 45         | ![Image](image4) | 9.75      |
| 38         | ![Image](image5) | 7.47      | 46         | ![Image](image6) | 7.39      |
| 39         | ![Image](image7) | 6.16      | 47         | ![Image](image8) | 4.52      |
| 40         | ![Image](image9) | 6.79      | 48         | ![Image](image10) | 6.89      |
| 41         | ![Image](image11) | 7.18      | 49         | ![Image](image12) | 6.84      |
| 42         | ![Image](image13) | 6.67      | 50         | ![Image](image14) | 10.00     |
| 43         | ![Image](image15) | 6.91      | 51         | ![Image](image16) | 7.41      |

3. Results and Discussion:

Survey of literatures exposed that HIV-1 PR is a viral encoded homodimeric aspartyl protease with C2 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 (πR, πX, πY, and πZ) and its interactions (ΔπR) with the substituents of receptor amino acids (π) 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 πR and substituent-X has the lowest value. The decreasing order of substituent hydrophobicity has the sequence πR > πX > πZ > πY. 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 (ΔπR) 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 ΔπR has the sequence ΔπR(Asp) > ΔπR(Thr) > ΔπR(Val) > ΔπR(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 ΔπR. The values of (ΣΔπR)binding-site and (ΣΔπR)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 ΣΔπR. Among the binding site, Ile has maximum interaction with the drug than Val, as it has lower value of ΔπR.

3.1.2. Second Set

This set comprises of seventeen inhibitors (Table 2) [5]. The log P, πR1, πR2, πR3, π and ΔπR 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 (ΔπR) between substituent-R1 and receptor amino acid have been evaluated and are also presented in Table 5. The decreasing order of ΔπR has the order ΔπR(Asp) > ΔπR(Thr) > ΔπR(Val) > ΔπR(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 ΔπR. The values of (ΣΔπR)binding-site and (ΣΔπR)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 ΣΔπR. Among the binding site, substituent-R1 has maximum interaction with the Ile than Val, as this interaction has lower value of ΔπR.

3.1.3. Third Set:

This set comprises of sixteen peptidic inhibitors (Table 3) [5]. The log P, πR and π have been evaluated and are presented in Table 6. The hydrophobic interactions (ΔπR)
between substituent-X and receptor amino acid have been evaluated and are also presented in Table 6. The decreasing order of $\Delta \pi_{As}$ has the order $\Delta \pi_{As}$(Asp) > $\Delta \pi_{As}$(Thr) > $\Delta \pi_{As}$(Val) > $\Delta \pi_{As}$(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 $\Delta \pi_{As}$. The values of ($\Sigma \Delta \pi_{R}$)\text{binding-site} and ($\Sigma \Delta \pi_{R}$)\text{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 $\Sigma \Delta \pi_{As}$. Among the binding site, substituent-X has maximum interaction with the Ile than Val, as this interaction has lower value of $\Delta \pi_{As}$.

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–Richards molecular surface [20]. Shrake and Rupley 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$_{R}$) 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$_{R}$ and substituent-X has the lowest value. The decreasing order of substituent hydrophobicity has the sequence: SASA$_{X}$ > SASA$_{Y}$ > SASA$_{Z}$ > SASA$_{R}$. Thus, substituent-R has maximum probability to interact with receptor amino acids. The hydrophobic interactions ($\Delta$SASA$_{R}$) 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$_{R}$ has the sequence $\Delta$SASA$_{R}$(Thr) > $\Delta$SASA$_{R}$(Asp) > $\Delta$SASA$_{R}$(Val) > $\Delta$SASA$_{R}$(Ile). The values of ($\Sigma \Delta$SASA$_{R}$)\text{binding-site} and ($\Sigma \Delta$SASA$_{R}$)\text{catalytic-site} (Table 10) shows that peptidic HIV-1-PRLs interact with binding site rather than catalytic site as binding site have lower value of $\Sigma \Delta$SASA. A comparative study of $\Delta$SASA$_{R}$ reveals that Ile amino acid of binding sites has lowest values of $\Delta$SASA$_{R}$ 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$_{R}$ of each compound of second set have been evaluated and are presented in Table 8.
Table 4. log P, π<sub>R</sub>, π<sub>i</sub>, and Δπ<sub>dr</sub> of compounds of the first set.

| S.N. | log P | Substituent-R | Substituent-X | Substituent-Y | Substituent-Z | Binding Site | Catalytic Site | Δπ<sub>dr</sub> | Δπ<sub>dr</sub> | Δπ<sub>dr</sub> | Δπ<sub>dr</sub> |
|------|-------|---------------|---------------|---------------|---------------|--------------|---------------|----------------|----------------|----------------|----------------|
| 1    | 1.79  | -0.44         | 2.23          | 1.79          | 0.00          | 0.58         | 1.21          | 1.54           | 0.25           | 0.82          | 0.43          |
| 2    | 3.00  | 0.77          | 2.23          | 3.00          | 0.00          | 1.78         | 1.22          | 1.54           | 1.46           | 0.82          | 0.43          |
| 3    | 3.00  | 0.77          | 2.23          | 3.00          | 0.00          | 1.78         | 1.22          | 1.54           | 1.46           | 0.82          | 0.43          |
| 4    | 2.60  | 0.37          | 2.23          | 2.60          | 0.00          | 1.39         | 1.21          | 1.54           | 1.06           | 0.82          | 0.43          |
| 5    | 2.13  | -0.10         | 2.23          | 2.13          | 0.00          | 0.92         | 1.21          | 1.54           | 0.59           | 0.82          | 0.43          |
| 6    | 2.55  | 0.32          | 2.23          | 2.55          | 0.00          | 1.33         | 1.22          | 1.54           | 1.01           | 0.82          | 0.43          |
| 7    | 2.62  | 0.40          | 2.22          | 2.62          | 0.00          | 1.41         | 1.21          | 1.54           | 1.08           | 0.81          | 0.42          |
| 8    | 2.62  | 0.40          | 2.22          | 2.62          | 0.00          | 1.41         | 1.21          | 1.54           | 1.08           | 0.81          | 0.42          |
| 9    | 2.95  | 0.40          | 2.55          | 2.95          | 0.00          | 1.41         | 1.54          | 1.87           | 1.08           | 1.14          | 0.75          |
| 10   | 2.95  | 0.72          | 2.23          | 2.95          | 0.00          | 1.41         | 1.54          | 1.87           | 1.08           | 0.82          | 0.43          |
| 11   | 3.31  | 1.08          | 2.23          | 3.31          | 0.00          | 1.41         | 1.90          | 2.23           | 1.08           | 0.82          | 0.43          |
| 12   | 3.31  | 1.08          | 2.23          | 3.31          | 0.00          | 1.41         | 1.90          | 2.23           | 1.08           | 0.82          | 0.43          |
| 13   | 3.19  | 0.96          | 2.23          | 3.19          | 0.00          | 1.41         | 1.78          | 2.11           | 1.08           | 0.82          | 0.43          |
| 14   | 3.19  | 0.96          | 2.23          | 3.19          | 0.00          | 1.41         | 1.78          | 2.11           | 1.08           | 0.82          | 0.43          |
| 15   | 3.60  | 1.37          | 2.23          | 3.19          | 0.41          | 1.75         | 1.85          | 2.52           | 1.08           | 0.82          | 0.43          |
| 16   | 3.60  | 1.37          | 2.23          | 3.19          | 0.41          | 1.75         | 1.85          | 2.52           | 1.08           | 0.82          | 0.43          |
| 17   | 1.88  | -0.35         | 2.23          | 1.88          | 0.00          | 1.41         | 0.47          | 0.80           | 1.08           | 0.82          | 0.43          |
| 18   | 1.88  | -0.35         | 2.23          | 1.88          | 0.00          | 1.41         | 0.47          | 0.79           | 1.09           | 0.82          | 0.43          |

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Table 5. \( \log P \), \( \pi_r \), and \( \Delta \pi_{dr} \) of compounds of the second set.

| S.N. | log P |
|------|-------|
|      |       |
|      |       |
|      |       |
|      |       |

| S.N. | log P |
|------|-------|
|      |       |
|      |       |
|      |       |
|      |       |

|         | Substituent-R1 | Substituent-R2 | Substituent-R3 | Binding Site | Catalytic Site |
|---------|---------------|---------------|---------------|--------------|----------------|
|         | \( \log P_H \) | \( \pi_{R1} \) | \( \log P_H \) | \( \pi_{R2} \) | \( \log P_H \) | \( \pi_{R3} \) | \( \Delta \pi_{dr} \) | \( \Delta \pi_{dr} \) | \( \Delta \pi_{dr} \) | \( \Delta \pi_{dr} \) |
| 19      | 5.39         | 3.21          | 2.18          |              |                |                | 0.77         | 0.38         | 2.26         | 2.02         |
| 20      | 6.05         | 3.78          | 2.27          |              |                |                | 0.86         | 0.47         | 2.35         | 2.11         |
| 21      | 5.16         | 2.59          | 2.57          |              |                |                | 1.16         | 0.77         | 2.65         | 2.41         |
| 22      | 6.27         | 3.21          | 3.06          |              |                |                | 1.65         | 1.26         | 3.14         | 2.90         |
| 23      | 5.92         | 3.21          | 2.71          |              |                |                | 1.30         | 0.91         | 2.79         | 2.55         |
| 24      | 6.09         | 3.21          | 2.88          |              |                |                | 1.47         | 1.08         | 2.96         | 2.72         |
| 25      | 5.86         | 3.21          | 2.65          |              |                |                | 1.24         | 0.85         | 2.73         | 2.49         |
| 26      | 4.61         | 3.21          | 1.40          |              |                |                | 0.01         | 0.40         | 1.48         | 1.24         |
| 27      | 5.34         | 3.21          | 2.13          |              |                |                | 0.72         | 0.33         | 2.21         | 1.97         |
| 28      | 3.21         | 3.21          | 0.00          |              |                |                | 1.41         | 1.80         | 0.08         | 0.16         |
| 29      | 5.10         | 5.10          | 0.00          |              |                |                | 1.41         | 1.80         | 0.08         | 0.16         |
| 30      | 4.35         | 3.21          | 1.14          |              |                |                | 0.27         | 0.66         | 1.22         | 0.98         |
| 31      | 6.65         | 3.21          | 3.44          |              |                |                | 2.03         | 1.64         | 3.52         | 3.28         |
| 32      | 4.46         | 3.21          | 1.25          |              |                |                | 0.16         | 0.55         | 1.33         | 1.09         |
| 33      | 4.08         | 3.21          | 0.87          |              |                |                | 0.54         | 0.93         | 0.95         | 0.71         |
| 34      | 5.18         | 3.21          | 1.97          |              |                |                | 0.56         | 0.17         | 2.05         | 1.81         |
| 35      | 7.02         | 3.21          | 3.81          |              |                |                | 2.40         | 2.01         | 3.89         | 3.65         |
Table 6. log P, πₐ, πᵣ, and Δπᵣₐ of compounds of the third set.

| S.N. | log P | Substituent-X | Binding Site | Catalytic Site |
|------|-------|---------------|--------------|---------------|
|      |       | log Pᵣ | πᵣ | Δπᵣₐ | πᵣ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ | Δπᵣₐ |
| 36   | 5.71  | 3.69   | 2.02 | 0.61 | 0.22 |       |       |       |       |       |       |       |       |       |
| 37   | 4.24  | 3.69   | 0.55 | 0.86 | 1.25 |       |       |       |       |       |       |       |       |       |
| 38   | 6.16  | 3.69   | 2.47 | 1.06 | 0.67 |       |       |       |       |       |       |       |       |       |
| 39   | 5.59  | 3.69   | 1.90 | 0.49 | 0.10 |       |       |       |       |       |       |       |       |       |
| 40   | 4.88  | 3.69   | 1.19 | 0.22 | 0.61 |       |       |       |       |       |       |       |       |       |
| 41   | 5.66  | 3.69   | 1.97 | 0.56 | 0.17 |       |       |       |       |       |       |       |       |       |
| 42   | 5.47  | 3.69   | 1.78 | 0.37 | 0.02 |       |       |       |       |       |       |       |       |       |
| 43   | 4.75  | 3.69   | 1.06 | 0.35 | 0.74 |       |       |       |       |       |       |       |       |       |
| 44   | 5.78  | 3.69   | 2.09 | 0.68 | 0.29 |       |       |       |       |       |       |       |       |       |
| 45   | 4.98  | 3.69   | 1.29 | 0.12 | 0.51 |       |       |       |       |       |       |       |       |       |
| 46   | 4.98  | 3.69   | 1.29 | 0.12 | 0.51 |       |       |       |       |       |       |       |       |       |
| 47   | 5.83  | 3.69   | 2.14 | 0.73 | 0.34 |       |       |       |       |       |       |       |       |       |
| 48   | 6.01  | 3.69   | 2.32 | 0.91 | 0.52 |       |       |       |       |       |       |       |       |       |
| 49   | 6.24  | 3.69   | 2.55 | 1.14 | 0.75 |       |       |       |       |       |       |       |       |       |
| 50   | 4.76  | 3.69   | 1.07 | 0.34 | 0.73 |       |       |       |       |       |       |       |       |       |
| 51   | 5.34  | 3.69   | 1.65 | 0.24 | 0.15 |       |       |       |       |       |       |       |       |       |
Table 7. SASA, SASA_r, SASA_v and ΔSASA_dr of compounds of the first set

| S.N. | SASA | Substituent-R | Substituent-X | Substituent-Y | Substituent-Z |
|------|------|---------------|---------------|---------------|---------------|
|      |      | SASA_H SASA_R | SASA_H SASA_X | SASA_H SASA_V | SASA_H SASA_Z |
| 1    | 220.62 | 174.78 45.85 | 220.62 0.00 | 212.52 8.10 | 212.54 8.08 | 28.57 21.69 |
| 2    | 234.86 | 192.21 42.65 | 234.86 0.00 | 226.78 8.08 | 208.27 26.59 | 33.80 26.92 |
| 3    | 247.04 | 195.96 51.08 | 247.04 0.00 | 239.18 7.86 | 218.10 28.94 | 37.44 30.56 |
| 4    | 247.07 | 192.35 54.72 | 247.07 0.00 | 237.92 9.15 | 226.11 20.96 | 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 |
| 6    | 230.66 | 190.56 40.09 | 230.66 0.00 | 227.66 3.00 | 211.84 18.82 | 22.81 15.93 |
| 7    | 231.08 | 188.72 42.36 | 231.08 0.00 | 226.30 4.78 | 206.95 24.13 | 25.08 18.20 |
| 8    | 240.17 | 191.60 48.57 | 240.17 0.00 | 232.63 7.54 | 216.63 23.54 | 31.29 24.41 |
| 9    | 244.21 | 192.96 51.24 | 244.21 0.00 | 230.23 13.98 | 220.44 23.77 | 33.96 27.08 |
| 10   | 257.24 | 208.38 48.86 | 257.24 0.00 | 230.84 26.40 | 236.43 20.81 | 31.58 24.70 |
| 11   | 249.78 | 207.76 42.02 | 249.78 0.00 | 220.52 29.26 | 235.09 14.69 | 24.74 17.86 |
| 12   | 251.20 | 196.86 54.34 | 251.20 0.00 | 237.28 13.92 | 223.30 27.90 | 37.06 30.18 |
| 13   | 257.99 | 210.81 47.17 | 257.99 0.00 | 225.50 32.49 | 232.14 25.85 | 29.89 23.01 |
| 14   | 264.17 | 202.17 62.00 | 264.17 0.00 | 239.92 24.25 | 240.75 23.42 | 44.72 37.84 |
| 15   | 249.16 | 213.92 35.24 | 249.30 -0.14 | 221.87 27.29 | 232.86 16.30 | 17.96 11.08 |
| 16   | 261.52 | 216.47 45.05 | 253.96 7.56 | 232.31 29.21 | 236.48 25.04 | 27.77 20.89 |
| 17   | 245.27 | 202.48 42.80 | 245.27 0.00 | 231.08 14.19 | 223.11 22.16 | 25.52 18.64 |
| 18   | 247.64 | 205.52 42.11 | 247.64 0.00 | 228.85 18.79 | 228.50 19.14 | 24.83 17.95 |

Binding Site

| | Val | Ile |
|-----------------|-----|-----|
| SASA_v = 17.28  | SASA_v = 24.16 |
| ΔSASA_dr | ΔSASA_dr |
| 25.16 | 30.19 |
| 21.96 | 26.99 |
| 30.39 | 35.42 |
| 34.03 | 39.06 |

Catalytic Site

| | Asp | Thr | Gly |
|-----------------|-----|-----|-----|
| SASA_v = 20.69 | SASA_v = 15.66 | SASA_v = 0 |
| ΔSASA_dr | ΔSASA_dr | ΔSASA_dr |
| 21.67 | 26.70 |
| 19.40 | 24.43 |
| 21.67 | 26.70 |
| 27.88 | 32.91 |
| 30.55 | 35.58 |
| 28.17 | 33.20 |
| 21.33 | 26.36 |
| 33.65 | 38.68 |
| 26.48 | 31.51 |
| 41.31 | 46.34 |
| 14.55 | 19.58 |
| 24.36 | 29.39 |
| 22.11 | 27.14 |
| 21.42 | 26.45 |
Table 8. SASA, SASA$_{dr}$, SASA$_{r}$ and ΔSASA$_{dr}$ of compounds of the second set.

| S.N. | SASA    |   |   |   |   | Binding Site | Catalytic Site |
|------|---------|---|---|---|---|--------------|----------------|
|      | SASA$_{H}$ | SASA$_{R1}$ | SASA$_{H}$ | SASA$_{R2}$ | SASA$_{H}$ | SASA$_{R3}$ | SASA$_{dr}$ | SASA$_{dr}$ | SASA$_{r}$ | SASA$_{r}$ | 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 | 19.35 | 24.38 | ----- |       |
| 22   | 226.19  | 186.15 | 40.04 | 226.19 | 0.00 | 226.19 | 0.00 | 22.16 | 15.28 | 18.75 | 23.78 | ----- |       |
| 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, SASA₄, SASA₅ and ΔSASAₑ of compounds of the third set.

| S.N. | SASA | Substituent-X | Binding Site | Catalytic Site |
|------|------|---------------|--------------|----------------|
|      |      |               | Val          | Asp            |
|      |      |               | Ile          | Thr            |
|      |      |               | Gly          |                |
| S.N. | SASA | SASA₄ | SASA₅ | ΔSASAₑ | ΔSASAₑ | ΔSASAₑ | ΔSASAₑ | ΔSASAₑ | ΔSASAₑ |
|------|------|-------|-------|--------|--------|--------|--------|--------|--------|
| 36   | 204.14 | 173.54 | 30.60 | 13.32 | 6.44  | 20.69 | 15.66 | ----   | -----  |
| 37   | 196.90 | 173.54 | 23.36 | 6.08  | 0.80  | 16.01 | 21.04 | -----  | -----  |
| 38   | 210.24 | 173.54 | 36.70 | 19.42 | 12.54 | 14.91 | 19.94 | -----  | -----  |
| 39   | 209.14 | 173.54 | 35.60 | 18.32 | 11.44 | 6.06  | 11.09 | -----  | -----  |
| 40   | 200.29 | 173.54 | 26.75 | 9.47  | 2.590 | 44.69 | 49.72 | -----  | -----  |
| 41   | 238.92 | 173.54 | 65.38 | 48.10 | 41.22 | 41.92 | 46.95 | -----  | -----  |
| 42   | 236.15 | 173.54 | 62.61 | 45.33 | 38.45 | 41.24 | 7.27  | -----  | -----  |
| 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 | 35.60 | 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 ΣΔπdr and ΣΔSASAdr of binding site and catalytic site of all the three sets.

| S.N. | First Set | | | | Second Set | | | | Third Set | | | |
|------|-----------|----------|----------|----------|-----------|----------|----------|----------|-----------|----------|----------|
|      | Binding Site | Catalytic Site | Binding Site | Catalytic Site | Binding Site | Catalytic Site | Binding Site | Catalytic Site | Binding Site | Catalytic Site | Binding Site | Catalytic Site |
|      | ΣΔπdr | ΣΔπdr | ΣΔSASAdr | ΣΔSASAdr | ΣΔπdr | ΣΔπdr | ΣΔSASAdr | ΣΔSASAdr | ΣΔπdr | ΣΔπdr | ΣΔSASAdr | ΣΔSASAdr |
| 1    | 1.25   | 4.22   | 50.26    | 55.35    | 1.15   | 4.28   | 7.88     | 12.97    | 0.83   | 3.96   | 19.76     | 24.85    |
| 2    | 1.25   | 4.22   | 43.86    | 48.95    | 1.33   | 4.46   | 16.26    | 21.35    | 2.11   | 4.86   | 31.96     | 37.05    |
| 3    | 1.25   | 4.22   | 60.72    | 65.81    | 1.93   | 5.06   | 29.76    | 34.85    | 1.73   | 4.86   | 31.96     | 37.05    |
| 4    | 1.25   | 4.22   | 68.00    | 73.09    | 2.91   | 6.04   | 38.64    | 43.73    | 0.59   | 3.72   | 29.76     | 34.85    |
| 5    | 1.25   | 4.22   | 43.28    | 48.37    | 2.21   | 5.34   | 37.44    | 42.53    | 0.83   | 2.3    | 12.06     | 17.15    |
| 6    | 1.25   | 4.22   | 38.74    | 43.83    | 2.55   | 5.68   | 40.54    | 45.63    | 0.73   | 3.86   | 89.32     | 94.41    |
| 7    | 1.23   | 4.20   | 43.28    | 48.37    | 2.09   | 5.22   | 18.66    | 23.75    | 0.39   | 3.48   | 83.78     | 88.87    |
| 8    | 1.23   | 4.20   | 55.70    | 60.79    | 0.41   | 2.72   | 19.74    | 24.83    | 1.09   | 2.04   | 6.88      | 9.51     |
| 9    | 1.89   | 4.86   | 61.04    | 66.13    | 1.05   | 4.18   | 43.48    | 48.57    | 0.97   | 4.1    | 35.46     | 40.55    |
| 10   | 1.25   | 4.22   | 56.28    | 61.37    | 3.21   | 0.24   | 40.48    | 35.39    | 0.63   | 2.5    | 91.64     | 96.73    |
| 11   | 1.25   | 4.22   | 42.60    | 47.69    | 3.21   | 0.24   | 40.34    | 35.25    | 0.63   | 2.5    | 72.94     | 78.03    |
| 12   | 1.25   | 4.22   | 67.24    | 72.33    | 0.93   | 2.2    | 18.42    | 13.33    | 1.07   | 4.2    | 11.28     | 16.37    |
| 13   | 1.25   | 4.22   | 52.90    | 57.99    | 3.67   | 6.8    | 56.08    | 61.17    | 1.43   | 4.56   | 29.88     | 34.97    |
| 14   | 1.25   | 4.22   | 82.56    | 87.65    | 0.71   | 2.42   | 48.42    | 53.51    | 1.89   | 5.02   | 42.24     | 47.33    |
| 15   | 1.25   | 4.22   | 29.04    | 34.13    | 1.47   | 1.66   | 7.52     | 12.61    | 1.07   | 2.06   | 31.08     | 36.17    |
| 16   | 1.25   | 4.22   | 48.66    | 53.75    | 0.73   | 3.86   | 46.52    | 51.61    | 0.39   | 3.22   | 27.2      | 32.29    |
| 17   | 1.25   | 4.22   | 44.16    | 49.25    | 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. Thus, substituent-R1 has maximum probability to interact hydrophobically with receptor amino acids of the HIV-1 protease enzyme. The hydrophobic interactions (ΔSASA) between substituent-R1 and receptor amino acid have been evaluated and are also presented in Table 8. The hydrophobic interactions in term of ΔSASA 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 ΔSASA and Thr has the highest value of ΔSASA. The decreasing order of ΔSASA has the sequence: ΔSASA(Thr) > ΔSASA(Val) > ΔSASA(Asp) > ΔSASA(Ile). The values of (ΣΔSASA)binding-site and (ΣΔSASA)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 ΣΔSASA. A comparative study of ΔSASA reveals that Ile amino acid of binding sites has lowest values of ΔSASA 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, SASAx and SASA of each compound of the third set have been evaluated and are presented in Table 9. The hydrophobic interactions in term of ΔSASA 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 ΔSASA and Thr has the highest value of ΔSASA. The decreasing order of ΔSASA has the sequence: ΔSASA(Thr) > ΔSASA(Val) > ΔSASA(Asp) > ΔSASA(Ile). The values of (ΣΔSASA)binding-site and (ΣΔSASA)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 ΣΔSASA. A comparative study of ΔSASA reveals that Ile amino acid of binding sites has lowest values of ΔSASA than remaining amino acids. Thus, inhibitors of this set interact with Ile amino acid of binding site.

4. Conclusions

1. Analysis of π and SASA shows that among the four substituents R, X, Y and Z of the first set, substituent-R has the highest value of both π and SASA. Among the three substituents R1, R2 and R3 of the second set, substituent-R1 also has the highest value of both π and SASA. Among the receptor amino acids (Val, Ile, Asp, Thr and Gly), Ile has the highest value of both π and SASA. Thus, π, π, π, SASA and SASA 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 Δπ and ΔSASA of all the three sets shows that they have the same order of hydrophobic interaction with respect to amino acids, Δπ(Asp) > Δπ(Thr) > Δπ(Val) > Δπ(Ile) and ΔSASA(Thr) > ΔSASA(Val) > ΔSASA(Asp) > ΔSASA(Ile). A comparative study of the values of (ΣΔπ)binding-site, (ΣΔπ)catalytic-site, (ΣΔSASA)binding-site and (ΣΔSASA)catalytic-site shows that peptidic HIV-1-PRIs interact with binding site rather than catalytic site as binding site have lower value of ΣΔπ and ΣΔSASA. Among the binding site, Val has maximum interaction than Ile, as it has lower value of Δπ and ΔSASA. Thus, Δπ, ΔSASA, ΣΔπ and ΣΔSASA well describe the extent of hydrophobic interaction of the drug with the receptor.

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