Research Article

Extended Rule of Five and Prediction of Biological Activity of Peptidic HIV-1-PR Inhibitors

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Abstract: In this research work, we have applied “Lipinski’s RO5” for pharmacokinetics (PK) study and to predict the activity of peptidic HIV-1 protease inhibitors. Peptidic HIV-1-PRIs have been taken from literature with their observed biological activities (OBAs) in term of IC50. The logarithms of the inverse of IC50 have been used as biological end point (log1/C) in the study. For calculation of physicochemical parameters, the molecular modeling and geometry optimization of all the derivatives have been carried out with CAChe Pro software using semiempirical PM3 method. Prediction of the biological activity of the inhibitors has shown that the best QSAR model is constructed from pharmacokinetic properties, molecular weight and hydrogen bond acceptor. This also proved that these properties play important role to describe the PKs of the drugs. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the compounds of the same series.

Keywords: Lipinski’s RO5; peptidic HIV-1-PRIs; QSAR; PM3

1. Introduction

Our body is a wonder machine and is composed of various systems and each system is a complex of various organs and each organ is composed of different tissues and each tissue is composed of same types of cells and uncountable reactions is responsible for vitality of the cell. Optimal function of each organ is regulated by innumerable reactions and each reaction is specific with respect to reactants, reaction conditions, enzymes, co-enzymes, co-factor, etc. Thus, systems and finally our body are also directly and or indirectly affected by these too [1]. When optimal level and function of any above mentioned chemical species is changed this led to abnormal body function. To maintain the normal body function some specific chemicals are required and these chemicals are called medicines [2]. The branch of chemistry which deals with design, development, mode of action, effect, side effects, etc. is known as medicinal chemistry. Medicinal chemist was, is, and will be play important role in design and development of drugs of maximum efficiency and no or minimum side effects along with low cost and minimum efforts [3]. The time course of drugs and their effects in the body is mathematically quantified by pharmacokinetics (PKs) study. PKs include absorption (A), distribution (D), metabolism (M), excretion (E) and toxicity (T) of drugs i.e., ADMET. Designing of an appropriate drug regimen is based on these ADMET parameters [4]. Lipinski states that most "drug-like" molecules have log P ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10, and number of hydrogen bond donors ≤ 5. Molecules violating more than one of these rules may have problems with bioavailability [5-9]. The rule is called "Rule of 5", because the border values are 5, 500, 2 × 5, and 5. In this research work, first of all we have applied Lipinski’s rule of five (RO5) in extended form on peptidic HIV-1 protease inhibitors (peptidic HIV-1-PRIs) for PKs study. And secondly, prediction of the activity of the inhibitor has also been made using these PKs properties as descriptors.
2. Materials and methods

The study materials of the present research work are a series of fifty one urea isostere derivatives as peptidic HIV-1-PRIs listed in Scheme-1 [10]. Out of fifty one compounds under study, the 18 compounds (compound no. 1-18) have the parent skeleton of Figure 1A, out of the remaining thirteen, the seventeen compounds (compound no. 19-35) have the parent skeleton of Figure 1B, while the remaining sixteen compounds (compound no. 36-51) have the parent skeleton of Figure 1C. These inhibitors have been taken from literature with their observed biological activities (OBAs) in term of IC<sub>50</sub> (the concentration of compound leading to 50% effect and expressed in mol L<sup>-1</sup> or mol g<sup>-1</sup>) [11,12]. The logarithms of the inverse of IC<sub>50</sub> have been used as biological end point (log1/C) in the study. For calculation of physicochemical parameters, the molecular modeling and geometry optimization of all the compounds have been carried out with CAChe Pro software using semiempirical PM3 method [13]. The molecular mass of the each compound was calculated by internal procedure from the molecular formula. The log P of each compound was calculated by atom-typing scheme of Ghose and Crippen [14]. The number of hydrogen bond donors in each compound was counted by counting the sum of NH and OH groups while the number of hydrogen bond acceptors in each compound was counted by counting the sum of N and O atoms from their structure formula [15,16].

![Figure 1A](image1.png)

![Figure 1B](image2.png)

![Figure 1C](image3.png)

Figure 1. Parent skeleton of peptidic HIV-1-PRIs

3. Results and discussion

Lipinski exposed that RO5 was associated with 90% of orally active drugs that achieved phase-II status [5-9] and this help to reduce attrition during clinical development [17,18]. Veber et al. (2002) extended Lipinski’s RO5 by adding fifth and sixth rules that is most drug like molecules have the sum of H-bond donors and acceptor (HD + HA) ≤ 12 and the number of rotatable bond (Rot.Bond) ≤ 10, respectively (Figure 2) [19]. Graphical representation of above criteria for each compound under study has been drawn and is presented in Scheme 2. It was found that molecules violating these rules also show poor oral bioavailability.
Figure 2. Graphical representation of Lipinski’s RO5 with extension

3.1. Molecular Weight (Criteria-1)

Absorption of a drug in our body takes place from intestinal epithelium to blood vessel and from there to action point. It was experimentally scaled that drugs having molecular weight higher than 500Da show a decrease in absorption [7, 20]. The molecular mass of the each compound was calculated by internal procedure from the molecular formula and has been presented in Table 1. A reference to data reveals that compound no. 28, 30 and 37 follow criteria-1. These compounds have molecular mass less than 500Da while the rest of the compounds have molecular mass greater than 500Da ranging from 502 to 670Da. Drug candidates that disobey criteria-1 are likely to have low solubility and to only pass through cell membranes with difficulty [21]. Thus, out of fifty one compounds, only three compounds: compound no. 28, 30 and 37, have reliable solubility and to pass through cell membranes.

Table 1. Values of pharmacokinetic descriptors with observed biological activity of inhibitors

| No. | MW   | log P | HD | HA | HD+HA | Rot. Bond | o(log1/C) |
|-----|------|-------|----|----|-------|-----------|----------|
| 1   | 541.65 | 1.79  | 6  | 11  | 17    | 19        | 5.82     |
| 2   | 583.73 | 3.00  | 6  | 11  | 17    | 22        | 6.03     |
| 3   | 604.75 | 3.00  | 6  | 11  | 17    | 20        | 6.90     |
| 4   | 569.70 | 2.60  | 6  | 11  | 17    | 21        | 6.29     |
| 5   | 555.67 | 2.13  | 6  | 11  | 17    | 20        | 6.48     |
| 6   | 569.70 | 2.55  | 6  | 11  | 17    | 21        | 6.59     |
| 7   | 583.73 | 2.62  | 6  | 11  | 17    | 22        | 7.46     |
| 8   | 604.75 | 2.62  | 6  | 11  | 17    | 20        | 8.22     |
| 9   | 597.75 | 3.02  | 6  | 11  | 17    | 23        | 7.89     |
| 10  | 618.78 | 2.95  | 6  | 11  | 17    | 21        | 8.52     |
| 11  | 623.79 | 3.31  | 6  | 11  | 17    | 20        | 7.54     |
| 12  | 644.81 | 3.31  | 6  | 11  | 17    | 18        | 8.30     |
### 3.2. Log P (Criteria 2)

Limit for lipophilicity is log P ≤ 5. The log P of each compound was calculated by atom-typing scheme of Ghose and Crippen and is presented in Table 1 [14]. A reference to these data reveal that compound no. 1-18, 26, 28-30, 32, 33, 37, 40, 43, 45, 46 and 50 follow criteria-2, while compound no. 19-25, 27, 31, 34-36, 41, 42, 44, 47-49 and 51 disobey criteria-2 are likely to be poorly soluble in aqueous solution and hence unable to gain access to membrane surfaces [5, 7]. Thus, out of fifty one compounds, only twenty one compounds: compound no. 1-18, 26, 28-30, 32, 33, 37, 40, 43, 45, 46 and 50, have reliable lipophilicity and hence able to gain access to membrane surfaces. If a compound is too

|   | Log P |     |     |     |     |     |
|---|------|-----|-----|-----|-----|-----|
| 13 | 617.74 | 3.19 | 6   | 11  | 17  | 20  | 7.72 |
| 14 | 638.77 | 3.19 | 6   | 11  | 17  | 18  | 8.52 |
| 15a| 631.77 | 3.6  | 6   | 11  | 17  | 21  | 5.19 |
| 16a| 631.77 | 3.6  | 6   | 11  | 17  | 21  | 5.29 |
| 17 | 618.73 | 1.88 | 6   | 12  | 18  | 20  | 6.98 |
| 18 | 639.75 | 1.88 | 6   | 12  | 18  | 18  | 7.72 |
| 19 | 544.69 | 5.39 | 4   | 7   | 11  | 17  | 9.60 |
| 20 | 558.72 | 6.05 | 4   | 7   | 11  | 18  | 8.11 |
| 21 | 574.72 | 5.16 | 5   | 7   | 12  | 19  | 9.72 |
| 22 | 612.69 | 6.27 | 4   | 8   | 12  | 18  | 9.59 |
| 23 | 570.73 | 5.92 | 4   | 7   | 11  | 18  | 9.64 |
| 24 | 634.64 | 6.09 | 4   | 7   | 11  | 17  | 9.22 |
| 25 | 558.72 | 5.34 | 4   | 9   | 13  | 18  | 9.57 |
| 26a| 559.70 | 4.61 | 6   | 8   | 14  | 18  | 9.51 |
| 27a| 589.69 | 5.34 | 4   | 9   | 13  | 18  | 9.57 |
| 28 | 454.57 | 3.21 | 4   | 7   | 11  | 15  | 5.53 |
| 29a| 560.69 | 5.1  | 5   | 8   | 13  | 18  | 9.8  |
| 30 | 494.63 | 4.35 | 2   | 7   | 9   | 17  | 7.56 |
| 31a| 670.59 | 6.65 | 2   | 7   | 9   | 17  | 9.14 |
| 32 | 572.70 | 4.46 | 2   | 8   | 10  | 18  | 8.27 |
| 33 | 545.68 | 4.08 | 2   | 7   | 9   | 17  | 9.28 |
| 34 | 576.75 | 5.18 | 2   | 7   | 9   | 18  | 9.60 |
| 35 | 600.80 | 7.02 | 2   | 7   | 9   | 21  | 9.77 |
| 36 | 502.65 | 5.71 | 3   | 6   | 9   | 17  | 6.94 |
| 37 | 494.63 | 4.24 | 3   | 7   | 10  | 17  | 8.02 |
| 38 | 528.69 | 6.16 | 3   | 6   | 9   | 16  | 7.47 |
| 39a| 546.71 | 5.59 | 4   | 7   | 11  | 20  | 6.16 |
| 40 | 512.65 | 4.88 | 4   | 8   | 12  | 21  | 6.79 |
| 41a| 586.73 | 5.66 | 3   | 8   | 11  | 18  | 7.18 |
| 42a| 558.72 | 5.47 | 4   | 7   | 11  | 18  | 6.67 |
| 43 | 510.67 | 4.75 | 4   | 7   | 12  | 17  | 6.91 |
| 44 | 558.72 | 5.78 | 4   | 7   | 12  | 17  | 9.16 |
| 45a| 560.69 | 4.98 | 4   | 8   | 12  | 17  | 9.75 |
| 46 | 560.69 | 4.98 | 4   | 8   | 12  | 17  | 7.39 |
| 47a| 508.70 | 5.83 | 3   | 6   | 9   | 17  | 4.52 |
| 48 | 528.69 | 6.01 | 3   | 6   | 9   | 16  | 6.89 |
| 49 | 522.73 | 6.24 | 3   | 6   | 9   | 18  | 6.84 |
| 50a| 560.69 | 4.76 | 5   | 8   | 13  | 18  | 10.00 |
| 51 | 532.68 | 5.34 | 4   | 7   | 11  | 19  | 7.41 |

*Data points not included in deriving regression equation*
hydrophobic (log P >>5), it will remain in the first membrane it contacts and if it is too hydrophilic, it will never cross cell membranes to get to its site of action [22-24].

3.3. Hydrogen bonding

The numbers of hydrogen bond donors and acceptors are known to affect the physicochemical properties (solubility, adsorption, distribution) of a molecule and hence the efficacy of a drug. RO5 states that for better permeation and absorption, the number of donors and acceptors in a ligand should be less than 5 and 10, respectively [25].

3.4. H-bond Donors (Criteria 3)

The number of hydrogen bond donors in each compound was counted by counting the sum of NH and OH groups from their structure formula and is also presented in Table 1 [15]. A reference to these data reveals that compound no. 1-18 and 26 disobey criteria-3, while compound no. 19-25 and 27-51 follow criteria-3. Thus, out of fifty one compounds, only thirty two compounds: compound no. 19-25, and 27-51, have reliable polarity for better permeation and absorption.

3.5. H-bond Acceptors (Criteria 4)

The number of hydrogen bond acceptors in each compound was counted by counting the sum of N and O atoms from their molecular formula and is also presented in Table 1 [16]. A reference to these data reveals that compound no. 1-18 disobey Criteria 4, while compound no. 19-51 follow criteria-4. Thus, out of fifty one compounds, only thirty three compounds: compound no. 19-51, have reliable polarity for better permeation and absorption. Drug candidates that disobey criteria-3 and or 4 are likely to be too polar to pass through cell membranes [26].

3.6. Sum of H-bond donors and acceptors (Criteria 5)

The number of HD+HA in each compound was counted by counting the sum of HD and HA and is also presented in Table 1. A reference to these data reveals that compound no. 1-18, 26, 27, 29 and 51 disobey criteria-5, while compound no. 19-25, 28, 30-49 and 50 follow criteria-5. Thus, out of fifty one compounds, only thirty two compounds (compound no. 1-18, 26, 27, 29 and 51) have reliable polarity for better permeation and absorption [18].

3.7. Number of Rotatable Bonds (Criteria 6)

Rotatable bond (Rot.Bond) is defined as any single non-ring bond, bounded to non-terminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier. This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [18]. The percentage of the dose reaching the circulation is called the bioavailability. The number of Rot.Bond in each compound is also presented in Table 1. A reference to these data reveals that all the compounds disobey criteria-6 as the Rot.Bond is beyond the limits. Thus, all these compounds show poor oral bioavailability of drugs.

The above study indicates that compound no. 1-18 obey only criteria-2 and disobey criteria-1, 3, 4, 5 and 6. Compound no. 19-25, 31, 34-36, 38, 39, 41, 42, 44, 47-49 and 51 obey criteria-3, 4 and 5 but disobey criteria-1, 2 and 6. Compound no. 26 obeys criteria-2 and 4, while compound no. 27 obeys only criteria-3. Compound no. 29 obeys criteria-3 and 4. Compound no. 50 obeys criteria-2 to 4. Compound no. 28 (OBA=5.53), 30 (OBA=7.56) and 37 (OBA=8.02) obey criteria-1 to 5 and only disobey criteria-6. Compound no. 32, 33, 40, 43, 45 and 46 obey criteria-2 to 5 but disobey criteria-1 and 6. Thus, out of fifty one peptidic HIV-1-PRIs only three (Compound no. 28, 30 and 37) obey above criteria except criteria-6. Thus, the clinical development of peptide-derived compounds has been hindered by
their poor PKs, including low oral bioavailability and rapid excretion and complex and expensive synthesis as concluded by earliest researchers [27-29].

3.8. Prediction of Activity

From the above study, we have observed that out of fifty one peptidic HIV-1-PRIs only three (Compound no. 28, 30 and 37) obey above criteria except criteria-6. All physicochemical parameters examined in this study well describe the PKs of the drugs. Taking these observations, we have selected, MW, logP, HD, HA, HD+HA and Rot.Bond, as PK descriptors to predict the activity of the peptidic HIV-1-PRIs. For prediction of the activity of the peptidic HIV-1-PRIs, QSAR model have been developed [30]. In developing QSAR models, MW, logP, HD, HA, HD+HA and Rot.Bond used as independent variables and the log1/C values as dependent variable. Multiple linear regression analysis has been made by Project Leader software associated with CAChe, using the above descriptors (Table 1) in different combinations as described in our previous work [31]. A large number of models were developed, but only top five models are reported here (Eqs.1-5). The predicted activities p(log1/C) as obtained Eqs.1-5 are incorporated in the Table 2. The reliability of these models is very clear from their reliable values of correlation coefficient r² and cross-validated correlation coefficient r²CV. The trends of observed and predicted activities are presented in Figure 3 in the form of correlation matrix plot, while the normal probability plots of residuals in Figures. 4, 5, 6, 7 and 8.

Table 2. Predicted activities of the compounds as obtained by Eqs.1-5.

| No. | o(log1/C) | Eq.1 | p(log1/C) | Eq.2 | p(log1/C) | Eq.3 | p(log1/C) | Eq.4 | p(log1/C) | Eq.5 | p(log1/C) |
|-----|-----------|------|-----------|------|-----------|------|-----------|------|-----------|------|-----------|
| 1   | 5.82      | 5.96 | 6.27      | 6.26 | 6.22      | 6.21 |
| 2   | 6.03      | 7.03 | 7.08      | 7.08 | 7.15      | 7.15 |
| 3   | 6.90      | 7.57 | 7.54      | 7.53 | 7.53      | 7.52 |
| 4   | 6.29      | 6.67 | 6.81      | 6.80 | 6.84      | 6.84 |
| 5   | 6.48      | 6.32 | 6.54      | 6.54 | 6.54      | 6.54 |
| 6   | 6.59      | 6.67 | 6.81      | 6.81 | 6.85      | 6.85 |
| 7   | 7.46      | 7.03 | 7.11      | 7.11 | 7.21      | 7.21 |
| 8   | 8.22      | 7.57 | 7.57      | 7.56 | 7.58      | 7.58 |
| 9   | 7.89      | 7.39 | 7.38      | 7.38 | 7.51      | 7.52 |
| 10  | 8.52      | 7.92 | 7.84      | 7.90 | 7.91      | 7.91 |
| 11  | 7.54      | 8.05 | 7.92      | 7.92 | 7.91      | 7.91 |
| 12  | 8.30      | 8.58 | 8.38      | 8.38 | 8.29      | 8.28 |
| 13  | 7.72      | 7.90 | 7.80      | 7.79 | 7.79      | 7.79 |
| 14  | 8.52      | 8.43 | 8.26      | 8.26 | 8.17      | 8.16 |
| 15a | 5.19      | 7.91 | 7.91      | 7.91 | 7.91      | 7.91 |
| 16a | 5.29      | 7.91 | 7.91      | 7.91 | 7.91      | 7.91 |
| 17  | 6.98      | 7.39 | 7.44      | 7.45 | 7.43      | 7.44 |
| 18  | 7.72      | 7.93 | 7.90      | 7.91 | 7.81      | 7.81 |
| 19  | 9.60      | 8.15 | 8.07      | 8.05 | 8.04      | 8.01 |
| 20  | 8.11      | 8.51 | 8.32      | 8.30 | 8.32      | 8.29 |
| 21  | 9.72      | 8.92 | 8.71      | 8.67 | 8.83      | 8.80 |
| 22  | 9.59      | 9.35 | 8.98      | 8.97 | 8.93      | 8.91 |
| 23  | 9.64      | 8.81 | 8.59      | 8.57 | 8.61      | 8.58 |
| 24  | 9.22      | 10.44| 9.97      | 9.95 | 9.98      | 9.96 |
| 25  | 9.57      | 8.24 | 8.07      | 8.07 | 7.96      | 7.95 |
|    |   9.51 |  7.86 |  7.86 |  7.86 |  7.86 |  7.86 |
|----|--------|-------|-------|-------|-------|-------|
| 26a|        |       |       |       |       |       |
| 27a|  9.57  |  7.99 |  7.99 |  7.99 |  7.99 |  7.99 |
| 28 |  5.53  |  5.86 |  6.29 |  6.27 |  6.22 |  6.18 |
| 29a|  9.8   |  7.88 |  7.88 |  7.88 |  7.88 |  7.88 |
| 30 |  7.56  |  6.88 |  7.14 |  7.14 |  7.12 |  7.12 |
| 31a|  9.14  | 10.43 | 10.43 | 10.43 | 10.43 | 10.43 |
| 32 |  8.27  |  8.34 |  8.33 |  8.34 |  8.35 |  8.36 |
| 33 |  9.28  |  8.18 |  8.27 |  8.27 |  8.32 |  8.32 |
| 34 |  9.60  |  8.97 |  8.85 |  8.85 |  8.91 |  8.92 |
| 35 |  9.77  |  9.58 |  9.22 |  9.23 |  9.34 |  9.35 |
| 36 |  6.94  |  7.61 |  7.66 |  7.63 |  7.65 |  7.62 |
| 37 |  8.02  |  6.88 |  7.11 |  7.10 |  7.11 |  7.09 |
| 38 |  7.47  |  8.27 |  8.19 |  8.16 |  8.13 |  8.09 |
| 39a|  6.16  |  8.06 |  8.06 |  8.06 |  8.06 |  8.06 |
| 40 |  6.79  |  6.81 |  6.93 |  6.91 |  7.01 |  7.00 |
| 41a|  7.18  |  8.38 |  8.38 |  8.38 |  8.38 |  8.38 |
| 42a|  6.67  |  8.29 |  8.29 |  8.29 |  8.29 |  8.29 |
| 43 |  6.91  |  7.29 |  7.39 |  7.55 |  7.37 |  7.57 |
| 44 |  9.16  |  8.51 |  8.34 |  8.52 |  8.31 |  8.51 |
| 45a|  9.75  |  7.88 |  7.88 |  7.88 |  7.88 |  7.88 |
| 46 |  7.39  |  8.03 |  7.96 |  7.95 |  7.89 |  7.87 |
| 47a|  4.52  |  7.78 |  7.78 |  7.78 |  7.78 |  7.78 |
| 48 |  6.89  |  8.27 |  8.20 |  8.18 |  8.15 |  8.12 |
| 49 |  6.84  |  8.12 |  8.05 |  8.03 |  8.08 |  8.05 |
| 50a| 10.00  |  7.88 |  7.88 |  7.88 |  7.88 |  7.88 |
| 51 |  7.41  |  7.85 |  7.82 |  7.79 |  7.88 |  7.85 |

*Data points not included in deriving regression equation*

**Figure 3.** Correlation matrix plot between predicted activities p(log1/C) and observed biological activities log1/C (OBA) of peptidic HIV-1 protease inhibitors.
Figure 4. Normal probability plot of residual from Eq. 1

Figure 5. Normal probability plot of residual from Eq. 2

Figure 6. Normal probability plot of residual from Eq. 3
The following is a textual representation of the content in the image:

**Figure 7.** Normal probability plot of residual from Eq. 4

\[ p(\log 1/C) = 0.0228638 \times MW - 0.14613 \times \log P - 0.0301332 \times HD - 0.579332 \times HA + 0.0496907 \times \text{RotBond} - 0.193275 \]

\[ R^2 = 0.646, \quad R^2 CV = 0.616, \quad n = 39, \quad k = 2, \quad df = 36, \quad p = 0.000, \quad f = 26.86 \]

**Figure 8.** Normal probability plot of residual from Eq. 5

\[ p(\log 1/C) = 0.028288 \times MW - 0.151666 \times \log P - 0.275988 \times HD - 0.80627 \times HA + 0.231955 \times \text{HD} + 0.054194 \times \text{RotBond} - 0.32974 \]

\[ R^2 = 0.541, \quad R^2 CV = 0.407, \quad n = 39, \quad k = 4, \quad df = 34, \quad p = 0.000, \quad f = 13.87 \]

**Figure 8.** Normal probability plot of residual from Eq. 5

\[ p(\log 1/C) = 0.0217326 \times MW - 0.0821632 \times \log P - 0.0341481 \times HD - 0.492033 \times HA + 0.26834 \]

\[ R^2 = 0.541, \quad R^2 CV = 0.407, \quad n = 39, \quad k = 4, \quad df = 34, \quad p = 0.000, \quad f = 13.87 \]

**Figure 8.** Normal probability plot of residual from Eq. 5

\[ p(\log 1/C) = 0.0217606 \times MW - 0.0819599 \times \log P - 0.241383 \times HD - 0.676382 \times HA + 0.195232 \times HD + HA + 0.188692 \]

\[ R^2 = 0.542, \quad R^2 CV = 0.377, \quad n = 39, \quad k = 5, \quad df = 33, \quad p = 0.000, \quad f = 10.89 \]
\[ p(\log{1/C}) = 0.0226838 \times MW - 0.14613 \times \log{P} - 0.0301332 \times HD - 0.579332 \times HA + 0.0496907 \times \]

Rot.Bond - 0.193275\]  
\[ r^2 = 0.543, \quad r^2_{CV} = 0.380, \quad n = 39, \quad k = 5, \quad df = 33, \]

\[ p = 0.000, \quad f = 10.80 \]

\[ p(\log{1/C}) = 0.0228288 \times MW - 0.151686 \times \log{P} - 0.275986 \times HD - 0.80627 \times HA + 0.231955 \times HD + HA + 0.054194 \times \]

\[ \text{Rot.Bond} - 0.32974 \]

\[ r^2 = 0.545, \quad r^2_{CV} = 0.270, \quad n = 39, \quad k = 6, \quad df = 32, \]

\[ p = 0.000, \quad f = 8.84 \]

In the above QSAR models, Eq.1 is best model. The descriptors of the model are MW (molecular weight) and HA (hydrogen bond acceptor), the correlation coefficients and cross-validation are 0.646 and 0.616, respectively, and the predicted activity is presented in Table 2. The best model has been selected on the basis of values of correlation coefficient \( r^2 \) followed by other statistical parameters as shown above.

4. Conclusions

All physicochemical parameters examined in this study well describe the PKs of the drug. Prediction of the biological activity of the inhibitors has shown that the best QSAR model, “\( p(\log{1/C}) = 0.0254183 \times MW - 0.528322 \times HA - 1.99507 \)” is constructed from PK properties, molecular weight and hydrogen bond acceptor. This also proves that these properties are the prerequisite to describe the PKs of the drugs. On the basis of the derived models one can build up a theoretical basis to access the biological activity of the compounds of the same series.

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Appendix

Scheme 1. Structure of peptidic HIV-1 protease inhibitors
Scheme 2. Graphical representation of rule of five of peptidic HIV-1 protease inhibitors

1. Compound-1
2. Compound-2
3. Compound-3
4. Compound-4
5. Compound-5
6. Compound-6
7. Compound-7
8. Compound-8
9. Compound-9
| Compound | MW | log P | HD | HA | HD+HA | Rot. Bond | OBA |
|----------|-----|-------|----|----|-------|-----------|-----|
| Compound 7 | 7.46 | 22 | 17 | 11 | 6 | 2.62 | 583.73 |
| Compound 8 | 8.22 | 20 | 17 | 11 | 6 | 2.62 | 604.75 |
| Compound 9 | 7.89 | 23 | 17 | 11 | 6 | 3.02 | 597.75 |
| Compound 10 | 8.52 | 21 | 17 | 11 | 6 | 2.95 | 618.78 |
| Compound 11 | 7.54 | 20 | 17 | 11 | 6 | 3.31 | 623.79 |
| Compound 12 | 8.3 | 18 | 17 | 11 | 6 | 3.31 | 644.81 |
| Compound 13 | 7.72 | 20 | 17 | 11 | 6 | 3.19 | 617.74 |
| Compound 14 | 8.52 | 18 | 17 | 11 | 6 | 3.19 | 638.77 |
| Compound 15 | 5.19 | 21 | 17 | 11 | 6 | 3.60 | 631.77 |
| Compound 16 | 7.4 | 17 | 11 | 6 | 3.60 | 631.77 |
| Compound 17 | 8.52 | 18 | 17 | 11 | 6 | 3.19 | 638.77 |
| Compound 18 | 5.19 | 21 | 17 | 11 | 6 | 3.60 | 631.77 |
| Compound | MW | log P | HD  | HA  | HD+HA | Rot. Bond | OBA |
|----------|----|------|-----|-----|-------|-----------|-----|
| 25       |    |      |     |     |       |           |     |
| 26       |    |      |     |     |       |           |     |
| 27       |    |      |     |     |       |           |     |
| 28       |    |      |     |     |       |           |     |
| 29       |    |      |     |     |       |           |     |
| 30       |    |      |     |     |       |           |     |
| 31       |    |      |     |     |       |           |     |
| 32       |    |      |     |     |       |           |     |
| 33       |    |      |     |     |       |           |     |
| 34       |    |      |     |     |       |           |     |
| 35       |    |      |     |     |       |           |     |
| 36       |    |      |     |     |       |           |     |
