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QSAR Study of Cyclic Urea Type HIV-1 Protease Inhibitors Using *Ab Initio* Fragment MO Calculation of Their Complex Structures with HIV-1 Protease

*Tatsusada YOSHIDA and Hiroshi CHUMAN

Institute of Health Biosciences, The University of Tokushima, 1-78 Shomachi, Tokushima, 770-8505, JAPAN
*tyoshida@ph.tokushima-u.ac.jp

1. Introduction

Although a number of QSAR studies using the Hansch−Fujita approach have been reported and have indicated various degrees of success in drug discovery, descriptors often used in the classical QSAR equations are derived from the chemical structures of ligands. Three-dimensional structural information on ligands and their target proteins is not often considered. The three-dimensional descriptors derived from protein–ligand complex structures can reflect the interaction directly and are considered to be more suitable for studying the variation in the inhibitory potency. In this paper, we performed QSAR analyses on a series of cyclic urea type inhibitors (CUIs) (shown in Figure 1) of HIV-1 protease (PR) using descriptors obtained form molecular dynamics and *ab initio* fragment molecular orbital (FMO) [1] calculations [2].

2. Methods

2-1. Molecular Modeling of HIV-1 PR−CUI complexes

Thirteen CUIs were selected from those used in the classical QSAR study reported by Garg *et al* [3]. The MD calculations were performed on each HIV-1 PR−CUI complex at 298 K using AMBER 8 [4]. Ten snapshot structures of each HIV-1 PR−CUI complex during 500 ps MD production run were extracted. Then energy minimization was done on each snapshot structure. Each minimized structure of the HIV-1 PR−CUI complex was used to derive structure-dependent QSAR descriptors.
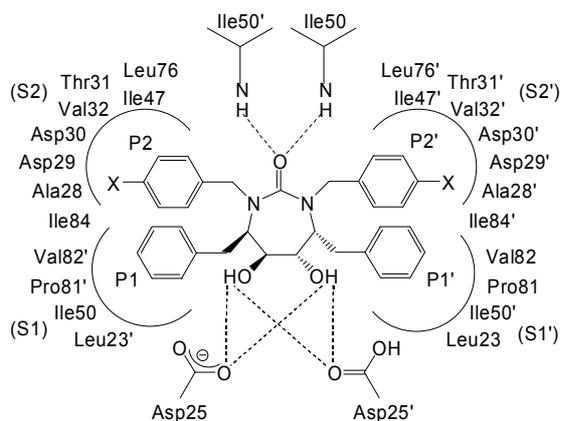

Figure 1. Schematic representation of the binding sites in the HIV-1 PR−CUI complex.

2-2. Accessible Surface Area

The water Accessible Surface Area (*ASA*) has been often utilized as a quantitative descriptor of hydrophobic interaction energy in QSAR studies [6]. The average value of change in *ASA* (ΔASA) upon complex formation with HIV-1 PR for the ten snapshot structures was calculated with a water probe radius of 1.4 Å and Bondi's van der Waals atomic radii for each element.

2-3. QSAR Descriptors for Electronic Contribution

We carried out *ab initio* FMO calculations of the complex structure of HIV-1 PR with each CUI by using the ABINIT-MP [5]. The average values for the ten snapshot structures of ligand binding energy (ΔE_{ligand}), inter-fragment interaction energy (IFIE) between CUI and each amino acid residue of the HIV-1 PR, and the atomic charge difference induced by complex formation were estimated

by the HF/6−31G level in order to identify important electronic features responsible for the variations in the inhibitory potencies.

3. QSAR Study Based on Interaction with HIV-1 PR

The three-dimensional and electronic descriptors obtained through the MD and FMO calculations were used to describe the variation of the inhibition constants (pK_i). We formulated Eq. 1 as a linear combination of $\Delta E_{\mathrm{ligand}}$ and ΔASA.

$$pK_i = -0.0445\ \Delta E_{\mathrm{ligand}} + 8.75 \cdot 10^{-3} \Delta ASA + 16.1,\ n = 13,\ r = 0.881,\ s = 0.555,\ F = 17.3 \qquad (1)$$

From the IFIE analysis, the major contributions to the total electronic interaction energy were found to be from Asp25 (25'), Asp30 (30'), and Ile50 (50'). In fact, the sum of IFIEs with these six residues was nicely correlated with the total interaction energy ($r = 0.978$) and Eq. 1 can be transformed as the following Eq. 2.

$$pK_i = -0.0377\ [\mathrm{IFIE}(25) + \mathrm{IFIE}(30) + \mathrm{IFIE}(31) + \mathrm{IFIE}(50)] + 9.50 \cdot 10^{-3}\ \Delta ASA + 16.2,$$
$$n = 12,\ r = 0.931,\ s = 0.446,\ S_{\mathrm{cv}} = 0.513,\ F = 29.1 \qquad (2)$$

Among the all compounds, the variances of IFIE(30) and IFIE(31) which represent the interaction energy with Asp30 (30') were found to be higher than those of the other residues (Figure 2), indicating that the interaction with Asp30 (30') which is in close contact with the substituted moiety in each CUI determine the variations in the inhibitory potency dominantly.

We also carried out principal component analysis of the charge differences in order to explored a "certain pattern" of charge redistribution induced by the complex formation, and confirmed a considerable amount of charge redistribution occurred between each CUI and surroundings of Asp30 (30'). Introduction of the first principle component score Z_1 instead of $\Delta E_{\mathrm{ligand}}$ in Eq. 1 gives Eq. 3.
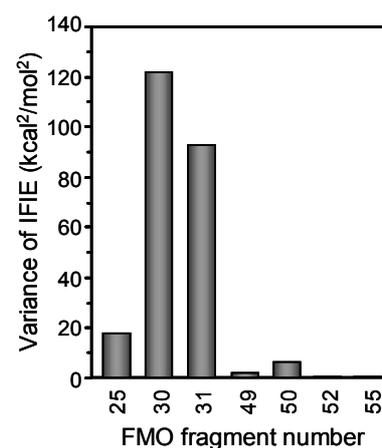

Figure 2. Variance of IFIE.

$$pK_i = -10.8\ Z_1 + 9.65 \cdot 10^{-3}\ \Delta ASA + 19.0,\ n = 13,\ r = 0.867,\ s = 0.584,\ F = 15.1 \qquad (3)$$

Eq. 3 indicates that the variations in the inhibitory potency are governed by the charge redistribution and the ΔASA term.

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