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Short Communication

Analysis of binding energy activity of TIBO and HIV-RT based on simple consideration for conformational change

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Tetrahydro-imidazo[4,5,l-jk][1,4]-benzodiazepin-2 (1 H)one (TIBO) is a noncompetitive non nucleotide antiretroviral drug with a specific allosteric binding site of HIV-1 RT. The conformational analysis shows that the effect of the drug depends on the potential energy which varied due to the beta rotatable dihedral angles (N6 - C15 - C16 = C17) of the TIBO side chain. The change of binding energy between TIBO and HIV-RT due to the variation in beta rotatable dihedral angles was determined. The theoretical simulation for a step size of 30 degrees variation from 0 to 90 degree changes was performed. The derived binding energies range from 0 to 8 kcal/mol. Changes in the beta dihedral angle conformation critically affects the binding energy. TIBO derivatives that affect the beta angle can change the binding energy between drug and HIV-RT and this can affect drug activity.

Key words: TIBO, HIV-RT, angle.

INTRODUCTION

Human immunodeficiency virus (HIV) inhibitors targeted at the virus-associated reverse transcriptase (RT) can be divided into two groups, depending on whether they are targeted at the substrate or nonsubstrate binding site. To the first group belong the dideoxynucleosides, dioxolane derivatives, oxetanocin analogues and carbocyclic derivatives which need to be phosphorylated intra-cellularly to their triphosphate forms before they act as competitive inhibitors or alternate substrates (chain terminators) of HIV RT (De Clercq, 1992). The second group consists of drugs that interact noncompetitively with a specific allosteric binding site of HIV-1 RT (De Clercq, 1992). The tetrahydro-imidazo[4,5,l-jk][1,4]-benz-odiazepin-2 (1 H)one (TIBO) is an important member of this group (De Clercq, 1992; White et al., 1991; Pauwels et al., 1992).

TIBO blocks the chemical reaction, but does not interfere with nucleotide binding or the nucleotide-induced conformational change (Spence et al., 1995). Rather, in the presence of saturating concentrations of the inhibitors, it is bound tightly (Kd, 100 nM), but non-productively (Spence et al., 1995). According to the study of Gupta and Garg (1996), the anti-HIV activity of the derivatives of TIBO that have been found to elicit their action through the allosteric inhibition of the enzyme viral RT is analysed in relation to the physicochemical properties of the molecules and significant correlations are obtained between the activity and the hydrophobic constant and some dummy parameters of substituents Gupta and Garg (1996). The main action of TIBO occurs after the complex formation between TIBO and HIV-RT. The intermolecular binding energy between the active side chain of TIBO and binding pocket of HIV-RT is about 8 kCal/mol (Saen-oon et al., 2005). However, the conformational analysis shows that the effect of the drug depends on the potential energy which varied due to the beta rotatable dihedral angles (N6 - C15 - C16 = C17) of the TIBO side chain. In this work, the change of binding energy between TIBO and HIV-RT due to the variation in beta rotatable dihedral angles was determined.

MATERIALS AND METHODS

Basic concepts in binding between TIBO and HIV-RT

As previously mentioned, binding between the active side chains of TIBO and binding pocket of HIV-RT is the main reaction. The active side chain of TIBO posed two important parts for the reaction, alpha (C5 - N6 - C15 - C16) and beta (N6 - C15 - C16 = C17) dihedral angles. The alpha angle is fixed and beta is variable.

Quantum chemical analysis for binding energy

This is a calculation-based study. Basically, each chemical reaction poses it specific required reaction energy. The primary assumption in this study is the required reaction energy for the pharmacological reaction between TIBO and HIV-RT is equal to 8 kCal/mol when occurred within a planar angle (interphase angle = 90 degree) (Saen-oon et al., 2005). In this work, the theoretical simulation for a step size of 30 degrees variation from 0 to 90 degree changes was performed. Calculation for the energy in each binding scenario was done based on physical theory of force.

Table 1. Changing in binding energy due to the variation of beta dihedral angle.

Variation angle	Binding energy (kCal/mol)
0	8
30	6
60	2
90	0

RESULTS AND DISCUSSION

The stepwise changing in binding energy corresponding to the variation of beta dihedral angle is presented in Table 1. The derived binding energies range from 0 kcal/mol to 8 kcal/mol

Inhibitors of HIV-RT are important drugs for the treatment of acquired immuno-deficiency syndrome (AIDS) (Arnold et al., 1996). Numerous potent inhibitors of RT have been described including all of the drugs that have been currently licensed for the treatment of AIDS. Failure of antiretroviral drug therapy can be resulted from both of the viral mutants and the conformation of antiretroviral drug. TIBO derivatives exert their effects by binding to a hydrophobic pocket in the RT heterodimer and that mutations which give rise to drug resistance directly interfere with the interactions between the TIBO and HIV-1 RT (Boyer et al., 1994). There are some researches to clarify the structure of TIBO-HIV-RT complex (Ren et al., 1995, 1999). In this theoretical research, the energy change corresponding to the conformational change within TIBO was investigated.

It was observed that change in the beta dihedral angle conformation critically affects the binding energy. Decreased biding energy can be observed. This implies the difficulties for occurrence of reaction and further implies the drug resistance. Based on the results in this study, it seems that any TIBO derivatives that affect the beta angle can change the binding energy between drug and HIV-RT and this can affect drug activity. Proper modifications to the TIBO group of inhibitors might enhance their binding and hence, potentially, their therapeutic efficacy (Ren et al., 1995). This explains some derivatives are highly active while the others are not. Also, it can reveal the fact that the same drug is effective for sometimes but not at all times.

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