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An in-silico approach aimed to clarify the role of Y181C and K103N HIV-1 reverse transcriptase mutations versus Indole Aryl Sulphones

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ABSTRACT

The emergence of HIV-1 drugs resistant stains remains of pivotal interest in relation to drugs development. Non nucleoside reverse transcriptase inhibitors proven to be very effective versus HIV-1 wild type but, with the only exception of diarylpyrimidines (e.g., etravirine, **1**), were featured by high-level resistance versus mutated RT.

The effects of two of the most clinically relevant RT mutations (Y181C; K103N) were studied by a computational approach. This involved molecular dynamics, principal components analysis (PCA) and residue interactions networks (RINs). The methodology was applied to **1** and to Indolyl Aryl Sulphones (IASs **2** and **3**), a class of potent RT inhibitors active also versus mutated RT forms. The molecular insight from this study was in accordance with the proposed mechanism of resistance for studied mutations and it might be useful in the design of novel RT inhibitors with high ligand efficacy on resistant strains.

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1. Introduction

HIV the causative agent of AIDS, was identified over 30 years ago and it is still one of the most challenging organism to defeat. Over the years, research efforts have led to the development of many anti HIV drugs (35 approved drugs) that resulted in the implementation of effective therapies able to control HIV propagation/replication and to span the life expectancy of patients [1]. Despite the important achievement, challenges like discovery of a complete AIDS cure and an effective way to overcame drug resistance remain an open question. Indeed the UNAIDS estimation for 2014 are about 36.9 million people living with AIDS; 2 million people newly infected and 1.2 million people died for AIDS and AIDS-related illness worldwide [1].

The current regimen against AIDS called Highly Active Antiretroviral Therapy (HAART) comprises a drugs cocktail containing different classes of target specific antiretrovirals [2]. Nonetheless, the acquisition and transmission of HIV drug resistance poses a major risk to the success of HAART. Drugs resistance can be acquired through drug selection pressure or transmitted by person to person. The HIV-1 Reverse Transcriptase (RT) is an error prone enzyme that introduces one misincorporation per 10^4 nucleotide incorporation [3]. Although individuals are infected with only few original clones [4] the HIV-1 high mutation rate soon led to the generation of many HIV variants that could include drug resistant strains.

Many steps that have proven to be effective for controlling viral replication feature the HIV-1 life cycle. The transcription of the viral sRNA to dDNA by RT sounds to be one of the most important steps [5]. Indeed about half of anti HIV-1 approved drugs target RT. These are mainly divided in Nucleoside Reverse Transcriptase inhibitors (NRTI) and Non-Nucleoside Reverse Transcriptase inhibitors (NNRTI). The first have to be phosphorylated in-vivo than compete with substrate acting as terminator of DNA synthesis [6]. NNRTIs do not require an activation step, they bind to an allosteric site causing conformational changes that impair the DNA biosynthesis [7,8]. The NNRTI-binding pocket is less well conserved than the dNTP-binding site, thus it is intrinsically resistant to most NNRTIs [9].

Among NNRTI the diarylpyrimidines (DAPYs), which include etravirine (ETV, **1**) are representatives of conformationally flexible inhibitors designed to bind the RT in different conformations by means of "wiggling" and "jiggling" of flexible moieties [10,11]. Thus the DAPY plasticity might minimize the loss in binding stabilization caused by mutations providing additional contacts [10].

In the NNRTI field we have already reported the Indolyl Aryl Sulfones (IAS) [12]. This class of NNRTI is able to impair the WT RT activity at nanomolar concentration [13,14]. They also have proven

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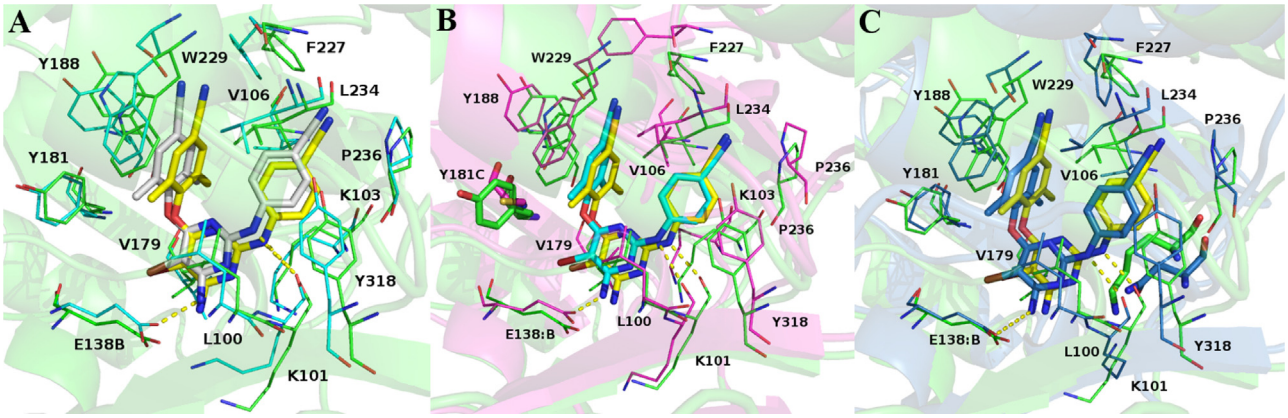

Fig. 1. Compound **1** molecular dynamics snapshots. Molecular dynamics pose of WT RT/**1** in white (A), Y181C RT/**2** in cyan (B) and K103N RT/**2** in blue (C). Co-crystallized **1** binding mode is shown in yellow, RTs are reported as ribbon while binding site as lines and H-bonds are reported as yellow dot lines. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to be very effective versus most of clinically relevant HIV-1 mutant strains [15–17].

At the state of the art two RT mutations are well known to be the most frequent and the most conferring drug resistance to NNRTIs: Y181C and K103N [18].

The Y181C mutation is selected in vivo primarily by Nevirapine (NVP) [19], Efavirenz and **1** [20]. It causes >50-fold reduced susceptibility to NVP [21], about 5-fold reduced susceptibility to **1** [22]. The 181 residue is located within the NNBS doing direct interactions with most of the known NNRTIs. The resistance driven by this mutation is based on the loss/change of inhibitors interactions at the NNBS binding pocket.

The K103N RT mutation is selected very frequently by numerous non-nucleoside RT NNRTIs [12] and is also commonly seen in patients receiving HAART [23]. The location of residue 103 at the outer rim of the NNRTI binding bind implies that it is very seldom involved in direct interactions with the bound drugs [24,25]. It was already reported that this kind of mutation did not affect the inhibitors binding stability but it stabilizes the RT in a "closed-form" avoiding the inhibitor binding [24].

In this work we compared the molecular dynamics trajectories for WT and mutated RTs (Y181C and K103N) of **1** and two selected ATIs (**2** and **3**) by principal components analysis (PCA) and residue interactions networks (RINs). The aim was to evaluate if the wiggling and jiggling movements that ensure broad spectrum to **1** featured also ATIs, given that studied compounds had comparable inhibitory concentrations. Furthermore, since compounds **2** and **3** had very similar structures but **3** was inactive versus K103N RT mutation (Table 1), we aimed to clarify if there were differences in the **2** and **3** binding mode that may cause the loss of **3** inhibitory activity

2. Result and discussion

2.1. Compound 1 analysis

The well described interactions of **1** in the NNBS provided us the possibility to evaluate the reliability of our in silico approach. **1** was also used as reference to compare the IASs trajectories. The crystal structure of WT RT/**1** (PDB code: 3MEC [11]) showed as **1** was stabilized into WT NNBS by a series of interactions: the pyrimidine group formed contact with L100and V179; benzonitrile moiety lay in a hydrophobic pocket mainly formed by V106, P236, Y318, and L234 doing also interaction with the dimethylcyanophenyl substituent was accounted of extensive aromatic contacts with the Y181, Y188, W229, and F227 side chains. Thus starting from crystal structure we carried out 50 ns of molecular dynamic by Amber suite [27]. The trajectory analysis showed that **1** retained its starting conformation and all described interactions (Fig. 1A). In advance, during the simulation we observed another H-bond between secondary amine group and acid moiety of E138. The **1** root mean square fluctuation (RMSF) was 0.66 Å with torsion angles ($\tau_1 - \tau_4$) shifting no larger than 10° (Table 2) compared with crystallized conformation (Fig. S1).

Then we repeated the analyses for the Y181C RT/**1** complex (pdb code: 1UWB [28]). The trajectory analysis of Y181 RT/**1**, according to the ability of **1** to wiggling into the NNBS showed a slightly different binding pose compared with WT RT/**1** complex (Fig. 1B). By modifying $\tau_1 - \tau_3$ dimethylbenzonitrile moiety of **1** retained contact with the Y188 and W229 forming additional contact with C181, which might compensate the loss of interaction with Y181. The $\tau_2 - \tau_4$ repositioning allowed benzonitrile of **1** to retain its stabilizing contacts. Lastly the H-bond between primary amine and K101

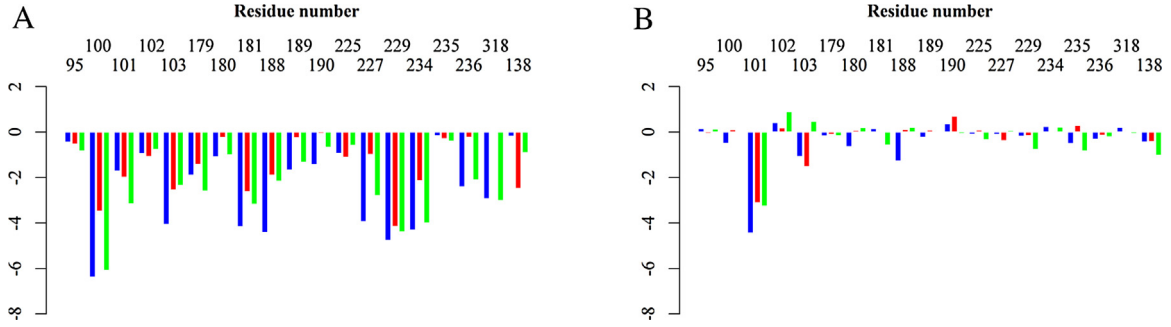

Fig. 2. Residue decomposition energy of all RT/**1** complexes: (A) van der Waals contribution and (B) Coulomb contribution. X axes are residue numbers; Y axes Glide computed energy (kcal/mol). WT, Y181C and K103N are depicted in blue, red and green respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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