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Molecular Dynamic Simulation of a DABO Analogue: a Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitor

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Palavras-Chave: *AIDS/HIV-1*, *Reverse Transcriptase, Non-Nucleoside Inhibitors, Molecular Dynamic Simulation*.

Introduction

In the research for anti-AIDS (Acquired Immune Deficiency Syndrome) agents, non-nucleoside HIV-1 (Human Immunodeficiency Virus - type 1) reverse transcriptase (RT) inhibitors (NNRTIs) have gained a definitive and important place due to their unique antiviral profile, being highly potent, selective, and with low toxicity.[1]

Several chemical classes of compounds have been described as NNRTIs, but only three compounds (i.e., nevirapine, delavirdine, and efavirenz) have been approved for clinical use. NNRTIs are effective drugs in current use in combination antiretroviral therapies along with nucleoside RT inhibitors (NRTIs) and/or protease inhibitors (PIs) to treat HIV-1/AIDS patients.[1]

However, since NNRTIs have a low genetic barrier to resistance, the need for novel NNRTIs active against drug-resistant mutants selected by current therapies is still a goal.[2] Dihydro-alkoxy-benzyl-oxopyrimidines (DABOs), a class of potent NNRTIs developed in the past decade,[3] does not have yet a conformational profile, therefore we decide to investigate the dynamic behavior of a potent new DABO analogue, F_2-NH-DABO (Fig.1a), which was highly potent against both the wild type and the Y181C HIV-1 mutant type.[3]

Methodology

The three-dimensional (3D) structure of F_2-NH-DABO was constructed (Spartan program, Wavefunction, Inc.) using the 3D coordinates of a reference compound (MKC-442) co-crystallized with the HIV-1 RT (PDB code: 1RT1)[3] and the geometry optimizations were carried out with the AM1 semiempirical method (Spartan). The molecular dynamic simulation (MDS) was carried out in GROMACS v. 3.2 program during 5 ns in a box of water (Fig.1b) at a constant temperature of 300K using the GROMOS87 force field.[4]

Results and Discussion

The MDS energy results of the F_2-NH-DABO compound shows that Total Energy of the system was conserved during the 5 ns simulation in *c.a.* -29.000 KJ·mol^{-1}; Potential Energy also kept stable around -35.000 KJ·mol^{-1}, with little fluctuations around this value. Although little conformational variance could be observed in the MDS, according to the RMSD variation profile during the 5 ns of simulation (Fig.2), the MDS showed that other stable conformers may exist at 300K, apart from the starting conformer considered (Fig.1b).

The main differences observed in the conformational profile of the F_2-NH-DABO structure, taking the initial one as reference (Fig.1b), were around the main rotatable bonds in the system, namely, the 2,6-F_2-benzyl group, that fluctuates behind and back to the pyrimidinone ring; and the cyclopentyl ring attached to the amino (NH) group, that adopted envelope and twist conformations.

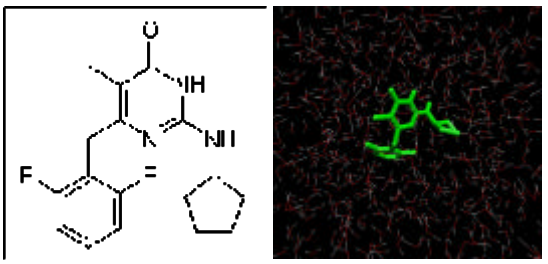

Fig. 1. (a) Chemical structure of the simulated DABO analogue (F_2-NH-DABO) and (b) its initial conformation in a box of water before the molecular dynamic simulation.

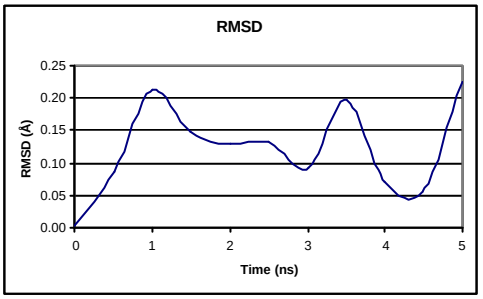

Fig. 2. RMSD variation of F_2-NH-DABO in the 5 ns MDS.

Conclusions

Although conformational analysis may be assessed in different ways, in this work, it was performed using MDS in order to study the dynamic behavior of a NNRTI of a DABO series. The MDS showed little variation in the conformational profile of the F_2-NH-DABO derivative in comparison with the initial structure. However, the MDS showed that other stable conformers may exist at 300K, apart from the one considered, suggesting that they could be considered in a further MDS study of the inhibitor-enzyme complex.

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