APPLICATION OF MOLECULAR MODELING FOR PREDICTING NEW STRUCTURES OF POTENTIAL DRUGS

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Abstract:

Quinones containing one, two, and three aromatic rings were identified as a class of micromolar non-peptidic inhibitors of HIV-1 proteinase, an enzyme required for HIV (Human Immunodeficiency Virus) replication and an important target for AIDS treatment (Acquired immunodeficiency syndrome). Anthrarufin (1,5-dihydroxy-9,10-anthraquinone) is an anthraquinone that has been identified as an compound with antimalaric and antioxidative properties. In this study are presented results of molecular docking simulations in active binding sites of the HIV-1 reverse transcriptase (RT) with anthrarufin, antrarufin derivatives and 9-chloro-TIBO. The molecular docking simulation is performed using the MolAICal software. According to the obtained values of free energy of binding (ΔG_{bind}) antrarufin derivatives can be considered as a potential inhibitors of HIV-1 RT, since it possesses similar inhibitory potency as already recognized inhibitor.

Keywords: Reverse transcriptase (RT), Anthrarufin derivatives, Molecular docking

1. Introduction

The human immunodeficiency virus (HIV) is a virus that targets the body's immune system. Acquired immunodeficiency syndrome (AIDS) can be developed if HIV is not treated. Although there is no effective cure for HIV at this time, it can be managed with good medical care. HIV patients who get proper therapy can have long, healthy, and fulfilling lives. The first attempt to stop HIV from spreading is to block viral enzymes that are only expressed by the virus and are not found in the human DNA. The key target of anti-AIDS therapy is HIV reverse transcriptase (RT). Structural investigations of HIV-1 RT, both unliganded and in complex with various nonnucleoside inhibitors (NNIs), have revealed a similar method of binding and inactivation using NNIs with two hinged rings distorting the polymerase catalytic site. Quinones consist of one, two, and three aromatic rings were identified as a class of micromolar non-peptidic inhibitors of HIV-1 proteinase, an enzyme required for HIV replication, and thus an important treatment target for AIDS. Later, it has been discovered that simple hydroxyquinones inhibit HIV-1 proteinase at the micromolar level, which was a promising target for HIV treatment development. The inclusion of hydroxyl groups on one or two rings in the structure of these compounds has been demonstrated to increase their inhibitory efficacy. Because of the hydroxyl groups and the polycyclic aromatic π -electron structure, polyhydroxy anthraquinones can bind to proteins in a variety of ways. It is thought that the observed inhibition of HIV-1 proteinase by anthraquinones is due to these binding interactions. Anthrarufin (1,5-dihydroxy-9,10-anthraquinone) is a three-ringed molecule with two hydroxyl groups, and it is structurally comparable to already the known HIV-1 RT inhibitors. In this paper, results of molecular docking simulations which study the interactions

between the active binding site of the HIV-1 RT and anthrarufin , as well as with antrarufin derivatives are presented.

2. Methods

For a better understanding of the binding potential of the investigated ligands, the deep learning model of binding affinity prediction was employed. Before molecular docking simulations, the pockets and binding sites of HIV-1 RT receptor were determined. The three-dimensional crystal structure of HIV-1 RT is downloaded from the Protein Data Bank (PDB IDs: 1REV) [1]. UCSF Chimera was used to prepare the HIV-1 RT structure for virtual screening [2]. Molecules of water and cofactor were removed and the purified structure of HIV-1 RT was saved as a pdb format. The same software, UCSF Chimera, was used to prepare the native ligand. Also using Chimera, a binding pocket of HIV-1 RT was generated. Furthermore, a chemically reasonable mutations base (CReM) was used to modify anthrarufin and 20 different synthetically acceptable anthrarufin derivatives were obtained [3]. For virtual screening, the MolAICal software was utilized. MolAICal software combines neural networks (artificial intelligence) and classical programming for design 3D ligands in the pocket of disease targets [4]. The Autodock Vina molecular docking software is implemented in MolAICal [5]. Following the screening, 10 compounds with a lower binding energy values were chosen.

3. Results and discussion

In this study, the deep learning model of binding affinity prediction was used to virtually screen de novo drugs based on molecular docking results. This was accomplished using the MolAICal. The native bound ligand of HIV-1 RT was extracted and a binding pocket analysis was performed. After that, re-docking was performed with the screened compounds, which are presented in Figure 1. This was performed with aim to generate the same docking pose found in its co-crystallized form. Also, molecular docking simulations have been done with antarufin as the starting compound and with the native bound ligand (9-chloro-TIBO). The antrarufin derivatives were chosen so that multiple structural characteristics, such as the presence of halogen atoms, different numbers of aromatic rings, amino and other groups, can be investigated.

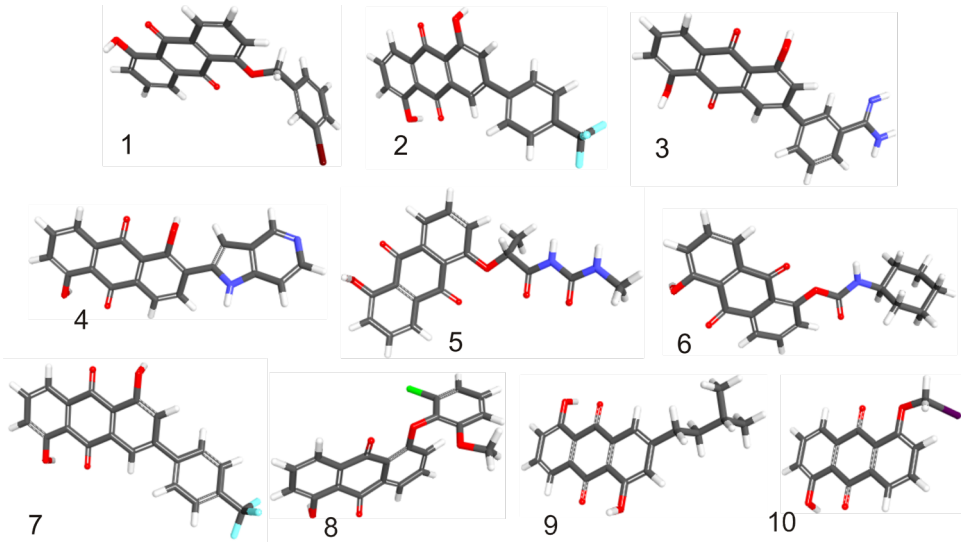

Fig. 1. 10 compounds with lower binding energy values were chosen by virtual screening.

The calculated values of the free energy of binding (ΔG_{bind}) for all examined ligands, are collected in Table 1. The lowest values of ΔG_{bind} indicate better binding affinity. The results

presented in Table 1 indicate that some derivatives of antarufin possess potentially better binding affinity than antrarufin, which was accepted. It is interesting and significant that some antarufin derivatives, actually derivatives 1 and 2, possess higher binding affinity to HIV-1 RT than its native bound ligand 9-chloro-TIBO (Table 1). It should be noticed that the obtained values of ΔG_{bind} of antrarufin and 9-chloro-TIBO are very similar. Because of this, the inhibitory potency of the series of 10 potential derivatives of antrarufin are investigated. The compounds for which lower values of ΔG_{bind} are obtained could be subjected to further examination as possible inhibitors of HIV-1 RT.

	ΔG_{bind} (kcal/mol)
9-chloro-TIBO	-13.01
anthrarufin	-12.81
derivate 1	-14.32
derivate 2	-14.16
derivate 3	-13.97
derivate 4	-13.76
derivate 5	-13.31
derivate 6	-13.04
derivate 7	-13.00
derivate 8	-12.80
derivate 9	-12.51
derivate 10	-12.29

Table 1. The calculated values of free energies of binding

4. Conclusions

The majority of HIV treatment is focused on the use of medicines that prevent virus cells from multiplying. The HIV-1 reverse transcriptase (RT) is one of the most crucial proteins in the virus cells' proliferation. The job of HIV-1 RT is to allow the virus's RNA genomes to be converted into DNA, allowing retroviral replication to take place. Finding potent HIV-1 RT inhibitors might lead to the most effective HIV treatment. For this aim, the inhibitory potency of anthrarufin and its derivatives is estimated. Their inhibitory potency is compared to the inhibitory potency of 9-chloro-TIBO. The results of molecular docking simulations show that almost all of the studied compounds can inhibit HIV-1 RT. The most important ones are derivatives 1 and 2. The obtained values of the free energy of binding show that derivatives 1 and 2 have the strongest inhibitory potency. Inconclusion, , all compounds with lower values of binding energies than 9-chloro-TIBO could be further investigated as prospective HIV-1 RT inhibitors.

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