Patchreenart Saparpakorn 2006: Structure-Based Inhibitor Design of New Potent HIV-1 Reverse Transcriptase, Active Against Mutant Type. Doctor of Philosophy (Physical Chemistry), Major Field: Physical Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 156 pages.
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The reverse transcriptase (RT) of human immunodeficiency virus type-1 (HIV-1) is the essential enzyme converting the single-stranded viral RNA genome into double-stranded proviral DNA prior to its integration into the host genomic DNA. Nevirapine (Viramune®) was the first generation of non-nucleoside reverse transcriptase inhibitors (NNRTIs) that has been approved by the FDA for the treatment of HIV-1 infection. Unfortunately, nevirapine showed a lack of affinity upon two important mutations, the K103N and Y181C mutations. Virtual screening method is used to screen the compounds active against K103N and Y181C HIV-1 RT from a set of 500k commercially available drug-like compounds. GOLD program is the best possible docking/scoring strategy in this study. The compounds in the database were filtered by using pharmacophore searching. The 3D pharmacophore models were constructed based on the known important interactions between the amino acid in the binding pocket and NNRTIs. 45k compounds are found to match the phamacophore models and they are applied to molecular docking using the GOLD program. The hits from docking were selected and classified. Finally, the 32 selected compounds from the classification were tested for HIV-1 RT inhibition. Three compounds, BIO5935, BSP12957, and CHE63164, are found that their %inhibition are higher than 50. In order to find novel nevirapine analogues insensitive to the K103N and Y181C HIV-1 RT, 360 nevirapine derivatives are designed using a combinatorial library design approach. These derivatives are docked into the binding pocket of K103N and Y181C HIV-1 RT, using the GOLD program. Post-docking process by using topological analysis is applied to the 124 selected docked-compounds with SILVER program to retrieve 31 compounds presenting a significant percentage of their surface buried upon binding (>80%) and exhibiting H-bonds to either N103 or C181 residues of the HIV-RT. To ensure that these compounds have H-bonding interaction to either N103 or C181 residues, the interaction energies are calculated by quantum chemical calculations. 3 of 31 compounds are filtered out because of their repulsive interaction with N103. These indicated that quantum chemical calculations can be useful as an alternative method for post processing of docking results.

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