CONCLUSION

In this work, structure-based inhibitor design by using virtual screening approach was applied to an ‘in house’ commercial database (Chapter I) and a library of nevirapine derivatives (Chapter II) to search for the novel compounds and novel nevirapine derivatives insensitive to K103N and Y181C HIV-1 RT mutants.

From the results in Chapter I, the GOLD method is the best possible docking/scoring strategy to reproduce the orientation of nevirapine and PNU-142721 into their K103N binding pockets and that of nevirapine into Y181C binding pocket. Therefore, the GOLD method is used in the further docking step. The first step of virtual screening procedure is pharmacophore-based filtering of a set of 500k commercially available drug-like compounds by using 3 and 2 of 3D-pharmacophore models for K103N and Y181C, respectively. The pharmacophore models are derived from the important interaction of nevirapine and some NNRTIs in K103N and Y181C binding pockets. There are 20,200 and 3,733 compounds found to match pharmacophore models 1 and 2 and model 3 of K103N, respectively. 19,761 compounds are found to match the Y181C pharmacophore models. The second step is to dock the matching compounds from the first step into K103N and Y181C binding pockets and select two hitlists (GoldScore higher than 45 and GoldScore higher than 50) for each protein mutant. Then, 7k virtual hits from the second step were selected and classified by scaffold diversity and 50 compounds are selected. Finally, 32 compounds are purchased and tested the HIV-1 inhibition to wild-type, K103N and Y181C by using enzyme assay. Three compounds, BIO5935, BSP12957, and CHE63164, are found that their %inhibition are higher than 50. BIO5935, has 75.85% of wild-type inhibition with an IC_{50} = 7.84 mM. BSP12957, has 58.66% of K103N inhibition with an IC_{50} = 15.64 mM for K103N HIV-1 RT. CHE63164, has 51.16% wild-type inhibition with an IC_{50} = 6.15 mM and 55.90 % of K103N inhibition with an IC_{50} = 5.63 mM. This virtual screening procedure is an alternative method to screen and select the compounds in the rational way.

In Chapter II, virtual screening approach is applied to the library of nevirapine derivatives with the aim of finding new nevirapine derivatives having the interaction with N103 and C181. 360 nevirapine derivatives are designed using a combinatorial library design approach by adding or replacing the fragments consist of the necessary functional groups for drug-like compound to nevirapine. The GOLD method is used to dock these compounds into K103N and Y181C binding pockets. 124 compounds having a GoldScore higher than that of nevirapine (55.00 and 52.00 for K103N and Y181C mutants, respectively) were firstly retrieved and submitted to a topological analysis with the SILVER program. Finally, 31 compounds presenting a significant percentage of the surfaces buried upon binding (>80%) and exhibiting hydrogen bonds to either N103 or C181 residues of the HIV-RT were selected. To ensure that these compounds have hydrogen bonding interaction to either N103 or C181 residues, quantum chemical calculations were applied to calculate the interaction energies between the hits and N103 or C181. There are 3 of 31 compounds having repulsive interaction with N103 because of the steric hindrance with N103. These indicated that quantum chemical calculations can be useful as an alternative method for post processing of docking results. Not only the topological analysis of the hits, but also the interaction energy calculation of the hits is a challenge approach to prioritize the hits before performing the experimental testing.