7 CONCLUSIONS

7.1 HIV-1 protease drugs *viz.*, tipranavir, nelfinavir, lopinavir and atazanavir exhibit different binding modes with CYP3A4, whereas ritonavir, amprenavir, indinavir, saquinavir, fosamprenavir and darunavir exhibit similar binding modes, which indicate that these two groups of drugs could be co-formulated.

7.2 Ritonavir, being a booster drug, can be co-formulated with any of tipranavir, nelfinavir, lopinavir or atazanavir for ritonavir-boosted protease inhibitor therapy.

7.3 The non-nucleoside reverse transcriptase inhibitor (NNRTIs), efavirenz and etravirine, displayed diverse binding modes with CYP3A4 when compared to most of HIV-1 protease drugs. This indicates that efavirenz and etravirine are the most suitable drugs to combine with HIV-1 protease drugs for combination therapy in AIDS.

7.4 Delavirdine and maraviroc docking produced large number of cluster conformers which indicates that these two drugs possess high flexibility in binding to CYP3A4. This would lead to competitive binding with the co-administered HIV-1 protease drugs, altering their plasma concentration by interfering with same binding site residues in CYP3A4.

7.5 The core regimen anti-tuberculosis (anti-TB) drugs, rifampin, isoniazid and pyrazinamide, displayed similar binding modes by interacting with Arg212 of CYP3A4. Of these, the inhibitory effect of isoniazid would be negated by the induction effect of rifampin during competitive binding for metabolic clearance. This makes core anti-TB drugs suitable for combination treatment with other drug substrates of CYP3A4.
7.6 The aforementioned core regimen anti-TB drugs also shares similar binding mode with HIV-1 protease inhibitors *viz.*, ritonavir, amprenavir, indinavir, saquinavir, fosamprenavir and darunavir, and also with entry inhibitor *viz.*, maraviroc. Hence, co-administration of core anti-TB drugs with these antiretroviral drugs could lead to severe contraindications.

7.7 Three NNRTIs *viz.*, delavirdine, efavirenz and etravirine displayed different binding modes with CYP3A4 when compared to core anti-TB drugs. Hence, the combinations of NNRTIs and core anti-TB drugs are the most suitable regimens for the treatment of HIV-related tuberculosis.

7.8 Although ritonavir and rifampin bind to the same residue Arg212, the inhibitory effect of ritonavir would be negated by inducing effect of rifampin during combination therapy. Hence, these two drugs could be co-administered with other anti-HIV or anti-TB drugs possessing a different binding mode for their metabolism.

7.9 Based on drug–drug interaction profiles, Ser119, Arg212 and Arg372 were identified as the major drug binding residues in CYP3A4. In addition, heme moiety and phenylalanine cluster (Phe57, Phe108, Phe215 and Phe304) play crucial role in drug binding to CYP3A4.