ABSTRACT

People living with HIV/AIDS (PLWHA) have a higher risk of developing tuberculosis (TB). When compared with people without HIV infection there is an estimated rate of 26 to 31 times greater risk of developing tuberculosis (TB) in PLWHA. So there is a necessity to develop a single drug regimen for HIV-TB co-infection. Previous literature reports on piperidine derivatives with anti-TB and anti-HIV activities and the well known antitubercular drug, isoniazid (INH), with pyridine scaffold prompted us for the research on piperidine. In the present study, the series of 1-(1H-benzimidazol-2-ylmethyl)piperidin-4-substituted imines (PB1 - PB25), 1-(1H-benzimidazol-2-ylmethyl)-3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines (B1 – B25) and 3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines (R1 - R25) have been designed by using molecular docking studies. The pKa values of the designed compounds were calculated and all the compounds were evaluated for drug-likeness based on Lipinski’s and Veber’s rule by using chemspider software. The above designed compounds were synthesized by various synthetic methods like dehydrohalogenation, Schiff’s reaction and aldol condensation. All the synthesized compounds were characterized by using TLC, IR, NMR and Mass spectroscopic methods. The compounds were screened for in-vitro antitubercular activity against Mycobacterium tuberculosis H37Rv by agar dilution method, and Anti-HIV activity by single-cycle infection assay and multi-cycle infection assay. The safety profile of all the compounds were evaluated by cytotoxicity screening against Vero cell lines by using MTT assay method. Among the three series, the compounds R1 – R25, showed good and energetically favourable binding interactions with both EACP reductase (1ZID.pdb) and Integrase enzymes(1BI4.pdb). The binding interactions revealed the importance of
furylidene, piperidine scaffold and its substitution at 4th position for the inhibition of both the target enzymes. Many ionization states were found for all compounds since various ionisable substituents are present in the molecules. All the test compounds complies the rule-of-five except PB17, PB21 and B9, B15, B17, B21, B25, which showed one violation and the compounds B8, B11, B18, B20 and R20, which showed two violations. All other test compounds complies with the polar surface area based on Veber’s rule except the compounds B4, B5, B20 and B21 and R20 which showed the polar surface area more than 140 Å². All the test compounds comply with the number of rotatable bonds from Veber’s rule. It has been observed that % absorption, which has been calculated from polar surface area, was between 65.37% to 92.09% for 1-(1H-benzimidazol-2-ylmethyl)piperidin-4-substituted imines (PB1 - PB25) 48.89% and 84.65% for 1-(1H-benzimidazol-2-ylmethyl)-3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines (B1 – B25) and 55.75% and 91.51% for 3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines (R1 - R25). All the compounds were found to possess antitubercular activity at various concentrations. The compounds R7, R12, R17, R18, R19, R20, B12, B17 and B20 were found to be more potent than ethambutol. The compounds B20, R17 and R20 were found to be most promising antitubercular agents with MIC 0.39 µg/ml. Among all compounds, R17 could be good oral drug candidate for further lead optimization. Almost all active compounds were found to be less toxic with the selectivity index > 10. All the compounds showed negligible anti-HIV activity, but the compound R7 was found to be moderately active with the IC₅₀ 2.1±0.04 µM in multi-cycle infection assay compared with the standard drug, zidovudine (IC₅₀ 5.7 nM). The cytotoxicity of the compound was found to be >58 µM. R7 was also found to be more potent
antitubercular agent compared with the standard drug, ethambutol. So, R7 could be a good oral drug candidate for HIV/TB co-infection and can be a better lead compound for further structural modification.