TB and HIV both are harmonized by each other. PLWHA are 26-31 times more prone to TB infection. TB is the leading cause of death in HIV infected people, especially in sub-Saharan Africa, where 50% of AIDS deaths were caused by TB. This co-infection is also increasing in other parts of the world like China, Western Asia and Eastern Europe. As long as TB cannot be controlled, TB related HIV deaths cannot be stopped. Even though ART is effective, the complication increases because of the interactions with the TB drug regimen. The present anti-TB drug rifampin also inhibits the effectiveness of ART by inducing the enzyme cytochrome which metabolizes the ARV drugs too quickly. In order to tackle these problems single drug regimens for the treatment of HIV-TB co-infection are very much essential. Even though WHO taken various steps to stop this dual terror, it is possible to minimize only the number of new infections and number of deaths, but this dual terror could not be eradicated completely. Complete eradication would be possible only if an effective new single drug regimen or an effective vaccine is developed for the treatment of both HIV and TB without toxicity and with affordable cost. By keeping this in mind in the present study we have attempted to develop a single drug regimen for HIV-TB co-infection.

Previous literature reports on piperidine derivatives, effect of furan and benzimidazoles as an effective anti-TB and anti-HIV agents, and Isoniazid (INH), the antitubercular drug with pyridine scaffold prompted us for the research on piperidine moiety. Based on this, we have designed 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 \((B1 \text{ – } B25)\) and 3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines \((R1 \text{ – } R25)\) for antitubercular and anti-HIV activity using molecular docking studies by targeting the enzymes EACP reductase (1ZID.pdb) and Integrase (1BI4.pdb), respectively by using V.Life MDS 4.2 software. The docking results of 1-(1H-benzimidazol-2-ylmethyl)piperidin-4-substituted imines \((PB1-PB25)\) revealed that all the compounds were energetically favourable in terms of dock score, ranging from -46.99 to -67.62 against EACP reductase and -50.99 to -77.95 against integrase enzyme. These binding interactions revealed the importance of N1- and phenyl ring of benzimidazole and also N- of aliphatic side chain moiety for favourable binding interaction for EACP reductase inhibition, but there was no hydrogen bonding interaction found with the integrase enzyme.

In order to get good dual activity the second series of compounds were designed. The docking results of 1-(1H-benzimidazol-2-ylmethyl)-3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines \((B1 \text{ – } B25)\) revealed that all the compounds were energetically favourable in terms of dock score, ranging from -4.83 to -73.5 against EACP reductase and -30.41 to -70.96 against integrase enzyme. These binding interactions revealed the importance of furan ring, substitution at the 4\(^{th}\) position of the piperidine ring, piperidine ring, and methylene group present in between benzimidazole and piperidine for favourable binding interactions. Even though the binding interaction was favourable the dock score of the most of the compounds were found to be less, so that better EACP reductase inhibitory activity was not expected. The binding interactions with integrase enzyme revealed that the O- of furan ring and the N- of piperidine showed hydrogen bonding and charge transfer interaction with the amino acid residues...
TYR99A and GLU170B, respectively. There is a pi-stacking interaction of furan ring with the amino acid residues TYR99A, GLN95A and HIS171B of the receptor. These interactions insisted the importance of furylidene substitution and piperidine ring for integrase inhibitory activity. Since there was no binding interaction with benzimidazole ring while docking against integrase enzyme and also there was no hydrogen bonding interaction against EACP reductase as well as the dock score against EACP reductase was found to be less. So it was assumed that removing the benzimidazole substitution at N- of the piperidine nucleus could have beneficial effect against both the enzymes. Based on these results, another series of compounds were designed without benzimidazole nucleus.

The docking results of 3,5-bis(furan-2-ylmethylidene)piperidin-4-substituted imines (R1 - R25) revealed that all the compounds were energetically favourable in terms of dock score which is ranging from -35.79 to -61.55 against EACP reductase and -44.79 to -56.48 against integrase enzyme. The N-of piperidine ring and the furan ring of the compounds showed binding interaction with ALA128A and TYR182A through hydrogen bonding and p – p stacking, respectively. Hydrophobic and van der Waal’s interaction was found with various amino acid residues of the receptor. These binding interactions revealed the importance of furan ring and the piperidine ring for favourable binding interactions. Since all the active compounds showed favourable binding so that the better EACP reductase inhibitory activity was expected. While targeting the enzyme integrase, the N- of piperidine ring and the phenyl ring of phenyl hydrazone substituted at 4\textsuperscript{th} position of piperidine (R7) showed hydrogen bonding interactions through THR174B and HIS171B, respectively. Furan ring and N-of piperidine ring of the compound R7 showed charge transfer and p – p stacking interaction with the amino acid residues
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TYR99A and GLU170B, respectively. These interactions revealed the importance of phenyl hydrazine substitution, furylidene substitution and piperidine ring for integrase inhibitory activity. Since third series of compounds showed favourable dock score as well as favourable binding interactions with both the target enzymes, better dual activity was expected.

Since various ionisable groups present in the molecule to enhance the biological activity, the pKa values of all the compounds were calculated using Marvin sketch software. All the I-, II- and III-series of compounds were found to possess many pKa values, which is responsible for the solubility, lipophilicity and permeability of the compounds.

To find out the pharmacokinetic profile and drug-likeness of the compounds all the compounds were evaluated for Lipinski’s and Veber’s rule using chemspider software. In this study, all the test compounds complies the rule-of-five, except PB17, PB21, B9, B15, B17, B21, B25 and R6 - R12, R14, R15, R17, R18, R21, R25, 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, B21 and R20, which showed the polar surface area more than 140 Å². All the test compounds comply with the number of rotatable bonds based on Veber’s rule. It has been observed that % absorption, which has been calculated (Raj 2015; Zhao 2002) from polar surface area, was between 65.37% to 92.09% for I series, 48.89% and 84.65% for II series and 55.75% and 91.51% for III series. So good oral drug candidate can be expected.
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The above designed compounds were synthesized by simple methods in good yield and characterized by spectroscopic methods like IR, NMR and Mass. These compounds were evaluated for their *in-vitro* antitubercular and anti-HIV activity. In the I series, the compounds **PB4, PB5, PB13** and **PB20** showed the most promising antitubercular activity with MIC 6.25 µg/ml. In the II series, the compounds **B7, B11, B18**, and **B19** showed equipotent activity with MIC 3.125 µg/ml compared with the standard drug ethambutol. The compounds **B12, B17, & B20** were found to be more potent compared with ethambutol with MIC 1.56 µg/ml, 0.78 µg/ml, and 0.39 µg/ml, respectively. In the III series, the compounds **R4, R5, R6, R10, R11, R21** and **R25** showed equipotent activity with MIC 3.125 µg/ml compared with the standard drug ethambutol. The compounds **R7, R12, R17, R18, R19** and **R20** were found to be more potent compared with ethambutol. The compounds **B20, R17** and **R20** were found to be most promising antitubercular agents with MIC 0.39 µg/ml. Among all the test compounds, **R17** could be good oral drug candidate for further lead optimization. All the active compounds were found to be less toxic with the selectivity index > 10.

The anti-HIV activity of I and II series were found to be negligible, but in the III series, the compound **R7** was found to be moderately active with the *IC*$_{50}$ 2.1±0.04 µM compared with the standard drug, zidovudine (*IC*$_{50}$ 5.7nM). The cytotoxicity of the compound was found to be >58 µM. This results gave us the insight for the further structural modification of these compounds to get potent anti-HIV agents and also **R7** could be a good oral drug candidate for HIV-TB co-infection and can be a better lead compound for further structural modification.