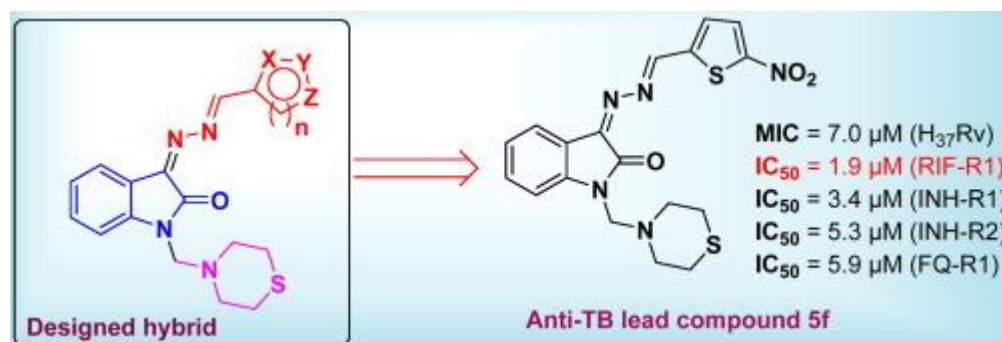


Novel chemotherapeutic agents against multidrug resistant-tuberculosis (MDR-TB) are urgently needed at this juncture to save the life of TB-infected patients. In this work, we have synthesized and characterized novel isatin hydrazones 4(a-o) and their thiomorpholine tethered analogues 5(a-o). All the synthesized compounds were initially screened for their anti-mycobacterial activity against the H₃₇Rv strain of *Mycobacterium tuberculosis* (MTB) under level-I testing. Remarkably, five compounds 4f, 4h, 4n, 5f and 5m (IC₅₀ = 1.9 μ M to 9.8 μ M) were found to be most active, with 4f (IC₅₀ = 1.9 μ M) indicating highest inhibition of H₃₇Rv. These compounds were further evaluated at level-II testing against the five drug-resistant strains such as isoniazid-resistant strains (INH-R1 and INH-R2), rifampicin-resistant strains (RIF-R1 and RIF-R2) and fluoroquinolone-resistant strain (FQ-R1) of MTB. Interestingly, 4f and 5f emerged as the most potent compounds with IC₅₀ of 3.6 μ M and 1.9 μ M against RIF-R1 MTB strain, followed by INH-R1 MTB strain with IC₅₀ of 3.5 μ M and 3.4 μ M, respectively. Against FQ-R1 MTB strain, the lead compounds 4f and 5f displayed excellent inhibition at IC₅₀ 5.9 μ M and 4.9 μ M, respectively indicating broad-spectrum of activity. Further, molecular docking, ADME pharmacokinetic and molecular dynamics simulations of the compounds were performed against the DNA gyrase B and obtained encouraging results.

Graphical abstract



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