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Structure-based design of some isonicotinic acid hydrazide analogues as potential antitubercular agents

Atta, A.[a], Fahmy, S.[a], Rizk, O.[a,b], Sriram, D.[c], Mahran, M.A.[a], Labouta, I.M.[a]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Alexandria University, Alexandria, 21521, Egypt

[b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Pharos University in Alexandria, 21311, Egypt

[c] Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology and Science, Pilani, 33031, India

Abstract:

New pyridine derivatives were designed and synthesized as Isonicotinic acid hydrazide (INH) analogues. The synthesized compounds were evaluated for their antitubercular activity against Mycobacterium tuberculosis strain $H_{37}R_v$. Ten compounds (3c, 3e-g, 5a-c, 6h, 10 and 11b) showed promising antitubercular activity with MIC range 7.30 µM–19.39 µM. Compounds 3e, 3g, 5b and 11b were the most potent analogues, with MIC 7.30–8.74 µM. They were equipotent to the standard drug Ethambutol (MIC 7.64 µM) and more active than the standard drug Pyrazinamide (MIC 50.77 µM). They were further examined for cytotoxicity in human embryonic kidney (HEK) cell line at the concentration of 50 µg/mL using MTT assay. Results declared that most compounds showed acceptable safety margin. Molecular Docking studies into 2-trans-enoyl-acyl carrier protein reductase, called InhA have been conducted for compounds 3e, 3g, 5b and 11b using Molecular Operating Enviroment software (MOE 2016.0802), where reasonable binding interactions have been identified and effective overall docking scores have been recorded. Their drug-likeness has been assessed using Molinspiration and Osiris software.

Reference:

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