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New lipophilic isoniazid derivatives and their 1,3,4-oxadiazole analogues: synthesis, antimycobacterial activity and investigation of their mechanism of action

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Abstract

The development of novel drugs is essential for the treatment of tuberculosis and other mycobacterial infections in future. A series of *N*-alkyl-2-isonicotinoylhydrazine-1-carboxamides was synthesized from isoniazid (INH) and then cyclized to *N*-alkyl-5-(pyridin-4-yl)-1,3,4-oxadiazole-2-amines. All derivatives were characterised spectroscopically. The compounds were screened for their *in vitro* antimycobacterial activity against susceptible and multidrug-resistant *Mycobacterium tuberculosis* (*Mtb.*) and nontuberculous mycobacteria (NTM; *M. avium*, *M. kansasii*). The most active carboxamides were substituted by a short *n*-alkyl, their activity was comparable to INH with minimum inhibitory concentrations (MICs) against *Mtb.* of 0.5-2 μM. Moreover, they are non-toxic for HepG2, and some of them are highly active against INH-resistant NTM (MICs ≥4 μM). Their cyclization to 1,3,4-oxadiazoles did not increase the activity. The experimentally proved mechanism of action of hydrazine-1-carboxamides consists of the inhibition of enoyl-ACP-reductase (InhA) in a way similar to INH, which is blocking the biosynthesis of mycolic acids. *N*-Dodecyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine as the most efficacious oxadiazole inhibits growth of both susceptible and drug-resistant *Mtb.* strains with uniform MIC values of 4-8 μM with no cross-resistance to antitubercular drugs including INH. The mechanism of action is not elucidated but it is different from INH. Obtained results qualify these promising derivatives for further investigation.

Highlights

•2-Isonicotinoylhydrazine-1-carboxamides and 1,3,4-oxadiazoles were synthesised.
•Activity against *M. tuberculosis* and nontuberculous mycobacteria (MIC ≥0.5 μM).
•Low or no cytotoxicity for HepG2 cells.
•2-Isonicotinoyl-*N*-methylhydrazine-1-carboxamide targets InhA identical to isoniazid.
•5-(Pyridin-4-yl)-1,3,4-oxadiazol-2-amines inhibit multidrug-resistant strains.