ABSTRACT

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Tuberculosis (TB) is a serious infectious disease caused by obligately pathogenic rods of *Mycobacterium tuberculosis* complex (*Mtb.*), and it is still among the ten most common causes of death worldwide. One of the main complications of TB therapy is the ever-increasing resistance of mycobacterial strains to conventional drugs. Therefore, the development of new antimycobacterial compounds is crucial to overcome this issue.

Research and development of new potential antimycobacterial agents often involve structure modifications of clinically used drugs – frequently the first-line drug, isoniazid (INH). The starting point of this work is also the structure of the already mentioned INH.

First, a series of 2-alkyl-5-(pyridine-4-yl)-1,3,4-oxadiazoles and *N*'-acylisonicotinohydrazides as their synthetic precursors were prepared and evaluated with very promising activity (expressed as minimal inhibitory concentration – MIC) against several mycobacterial strains (MIC *Mtb.* $H_{37}Rv$ of 1-8 μM). Furthermore, the most active compounds were tested against selected multidrug- and extensively drug-resistant strains of *Mtb.* (MDR- and XDR-TB) with MIC values of 4-8 μM. No cross-resistance with clinically used antituberculosis agents has been reported. Compounds from these series did not show any significant *in vitro* toxicity against HepG2 cell line in the used concentration range.

Based on our previous findings, another series of modified 2-alkyl-5-heteroaryl-1,3,4-oxadiazoles and their precursors were prepared and evaluated. The modification concerned the heterocyclic core (replacing the isonicotinohydrazide with an isomeric nicotinohydrazide or picolinohydrazide) or the alkyl chain (its different branching, introduction of a double bond). These compounds showed in some cases very promising activities that were better than the original series of compounds (MIC *Mtb*. $H_{37}Rv$ of 0.5-4 μM; MIC *M. kansasii* 6509/96 of 1-8 μM).

Asymmetric 1,2-diacylhydrazines, as precursors to the abovementioned derivatives, were prepared by two various synthetic routes. The first method was based on the reaction of INH with the appropriate acyl chloride (commercially available or in-house prepared) in the presence of potassium carbonate as a base, using anhydrous tetrahydrofuran as a solvent. The second synthetic way was based on carbodiimide C-N coupling using *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate as a catalyst. All of the prepared 2-alkyl-5-heteroaryl-1,3,4-oxadiazoles were obtained directly by dehydrative cyclization of 1,2-diacylhydrazines. This was carried out by reaction with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane as a solvent.

Key words

N'-acylheteroarylhydrazides; 2-alkyl-5-heteroaryl-1,3,4-oxadiazoles; antimycobacterial resistance; cytotoxicity; *in vitro* antimycobacterial activity; isoniazid; 1,3,4-oxadiazole; tuberculosis