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Antimycobacterial active oxyphosphorus acids derivatives

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Tuberculosis (TB) is an infection disease with high mortality worldwide. Rapid emergence and spread of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis (M. tbc.)* requires novel alternatives to the treatment. These facts stimulate the development of new effective anti-tuberculosis drugs acting by new or different mechanism of action, attacking on the latent (dormant) forms which may become active and when are mutated, may cause incurable pandemic. Based on our previous results of salicylanilide diethyl (thio)phosphates showing an increased antimycobacterial activity against both tuberculous and non-tuberculous mycobacteria, including drug-resistant strains, we have synthesized and evaluated other substituted 2-(phenyl-carbamoyl)phenyl phosphenite derivatives. Parent compounds, i.e., the most active salicylanilides from previous studies, prepared by microwave assistance from substituted salicylic acids and anilines in the presence of PCl3, were esterified via chlorides of appropriate oxyphosphorus acids in the presence of triethylamine. Using dichlorides of phosphorus-based acids, substituted 3-phenyl-3-hydrobenzo[*e*][1,3,2]oxazaphosph-inin-4-one 2-oxides were synthesized. Some derivatives were obtained by a reaction of substituted salicylanilides with phosphite in the presence of tertiary base, 4-(dimethylamino) pyridine and tetrachloromethane (Atherton-Todd reaction). All the prepared compounds were investigated for their *in vitro* activity in Sula's semisynthetic medium to determine their minimum inhibitory concentrations (MICs). The antimycobacterial activity was evaluated against *Mycobacterium tuberculosis* CNCTC (Czech National Collection of Type Cultures) 331/88 ($H_{37}Rv$), CNCTC nontuberculous mycobacteria: *Mycobacterium avium* 330/88 and *Mycobacterium kansasii* 235/80 and a clinically isolated strain of *M. kansasii* 6509/96. The most active derivatives having MIC ≤ 1 μmol.L^{-1} underwent additional evaluation against MDR-TB strains clinically isolated from patients. Both synthesis and biological evaluation results have been patented. Their mechanism of action is under investigation.

Biography

Prof. Jarmila Vinsova is Head of Development of new potential drugs with antimicrobial activity research group in Charles University in Prague. She is Member of the Scientific Council, Charles University in Prague, Faculty of Pharmacy in Hradec Kralove (since 2014). She have got Honorary member of Slovak Pharmaceutical Society (2013) and Weber price – award for notable teaching activity, scientific research and organization in pharmacy - granted by Slovak Pharmaceutical Society (2014).

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