

## Copper Related Toxicity of 1-Hydroxy-2-Thiopyridines

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**Abstract :** With the emergence of primary resistance to the current drugs and wide distribution of latent tuberculosis infection, a need for new compounds with a novel mode of action is growing steadily. Copper-mediated innate immunity and antibacterial toxicity propose novel strategies in TB drug discovery and development. Transcriptome of *M. tuberculosis* was obtained by RNA-seq, intracellular copper content was measured by ICP MS and complexes of 1-hydroxy-2-thiopyridines with copper were detected by HPLC. 1-hydroxy-2-thiopyridine derivatives were found to be highly active in vitro against both actively growing and dormant non-culturable *M. tuberculosis*. Transcriptome response to 1-hydroxy-2-thiopyridines revealed signs of copper toxicity in *M. tuberculosis* bacilli. Indeed, Cu was found to accumulate inside cells treated with 1-hydroxy-2-thiopyridines. These compounds were found to form stable charged lipophilic complexes with  $\text{Cu}^{2+}$  ions which transport into mycobacterial cell. Subsequent metabolic destruction of the complex led to transformation of 1-hydroxy-2-thiopyridines into 2-methylmercapto-2-ethoxycarbonylpyridines, which did not possess antitubercular activity and releasing of free  $\text{Cu}^{2+}$  in the cytoplasm. 1-hydroxy-2-thiopyridines are a potent class of Cu-dependent inhibitors of *M. tuberculosis* which may control *M. tuberculosis* infection by impairment of copper homeostasis. Acknowledgment: This work was financially supported by the Ministry of Education and Science of the Russian Federation (Agreement No 14.616.21.0065; unique identifier RFMEFI61616X0065).

**Keywords :** copper toxicity, drug discovery, *M. tuberculosis* inhibitors, 2-thiopyridines

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