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Production of Nitric Oxide by Thienopyrimidine TP053

Authors : Elena G. Salina, Laurent R. Chiarelli, Maria R. Pasca, Vadim A. Makarov

Abstract : Tuberculosis is one of the most challenging threats to human health, confronted by the problem of drug resistance. Evidently, new drugs for tuberculosis are urgently needed. Thienopyrimidine TP053 is one of the most promising new antitubercular prodrugs. Mycothiol-dependent reductase Mrx2, encoded by rv2466c, is known to be a TP053 activator; however, the precise mode of action of this compound remained unclear. Being highly active against both replicating and non-replicating tuberculosis bacilli, TP053 also revealed dose-escalating activity for M. tuberculosis-infected murine macrophages. The chemical structure of TP053 is characterized by the presence of NO_2 group which was suggested to be responsible for the toxic effects of the activated compound. Reduction of a nitroaromatic moiety of TP53 by Mrx2 was hypothesized to result in NO release. Analysis of the products of enzymatic activation of TP053 by Mrx2 by the Greiss reagent clearly demonstrated production of nitric oxide in a time-dependent manner. Mass-spectra of cell lysates of TP-treated M. tuberculosis bacilli demonstrated the transformation of TP053 to its non-active metabolite with Mw=261 that corresponds NO release. The mechanism of NO toxicity for bacteria includes DNA damage and degradation of iron-sulfur centers, especially under oxygen depletion. Thus, TP-053 drug-like scaffold is prospective for further development of novel anti-TB drug. This work was financially supported by the Russian Foundation for Basic Research (Grant 17-04-00342).

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