

TOXICOLOGICAL SAFETY ASSESSMENT OF NOVEL CARBOHYDRAZIDES: AN ANTITUBERCULAR AGENT

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ABSTRACT

Nowadays multidrug-resistan tuberculosis strain which is unaffected by the major anti-tuberculosis drugs currently on the market. That's why there is an urgency to develop new drugs and strategies to fight against tuberculosis or a tragedy may occur. A novel series of 5,6-dihydropyridazine-1 (4*H*)-carbohydrazides and its analogs was synthesized and characterized spectroscopically. All the compounds were characterized and screened for in vitro anti-tuberculosis (anti-TB) activity against Mycobacterium tuberculosis H37Rv strains by using resazurin assay utilizing microtiter-plate method. These compounds also showed good antitubercular. Thus, the high level of activity shown by the compounds (7a, 7e) suggests that these compounds could serve as leads for development of novel synthetic compounds with enhanced anti-TB activity. After that, a toxicological safety assessment was conducted on 5,6-dihydropyridazine-1(4*H*)-carbohydrazides, to predict safety with oral consumption by rats. Two genotoxicity studies were conducted and no evidence of mutagenicity or genotoxicity was observed in the presence or absence of a rat liver S9 metabolic activation system at concentrations up to 5,000 µg of compound/plate in a chromosomal aberration assay. Studies conducted in Wistar rats included a 14-day acute oral toxicity study, and a 90-day repeated oral toxicity study. A 6-month repeated oral toxicity study was conducted in rats. In the 14-day study, the NOAEL was determined to be 5 g/kg body weight. While a few statistically significant ($p < 0.05$) findings were observed in the 90-day Wistar rat study, it was considered to be a sound basis for conducting a 6-month study. In the 6-month rat study, the no observed effect level was concluded as 1,000 mg/kg bw/d, the highest dose group tested. Finally, in a developmental toxicity study in rats no fetal abnormalities related to administration of the test article were observed.

Keywords: Carbohydrazides Antitubercular activity Genotoxicity.

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