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NSC 18725, a Pyrazole Derivative Inhibits Growth of Intracellular *Mycobacterium tuberculosis* by Induction of Autophagy

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The increasing incident rates of drug-resistant tuberculosis (DR-TB) is a global health concern and has been further complicated by the emergence of extensive and total drug-resistant strains. Identification of new chemical entities which are compatible with first-line TB drugs, possess activity against DR-, and metabolically less active bacteria is required to tackle this epidemic. Here, we have performed phenotypic screening of a small molecule library against *Mycobacterium bovis* BCG and identified 24 scaffolds that exhibited MIC_{99} values of at least 2.5 μM. The most potent small molecule identified in our study was a nitroso containing pyrazole derivative, NSC 18725. We observed a significant reduction in viable bacilli load of starved *Mycobacterium tuberculosis* upon exposure to NSC 18725. The action of NSC 18725 was "synergistic" with isoniazid (INH) and "additive" with other drugs in our checkerboard assays. Structure-activity relationship (SAR) studies of the parent compound revealed that pyrazole derivatives without a functional group at fourth position lacked anti-mycobacterial activity *in vitro*. The derivative with *para*-chlorophenyl substitution at the first position of the pyrazole ring was the most active scaffold. We also demonstrate that NSC 18725 is able to induce autophagy in differentiated THP-1 macrophages. The induction of autophagy by NSC 18725 is the major mechanism for the killing of intracellular slow and fast-growing mycobacteria. Taken together, these observations support the identification of NSC 18725 as an antimycobacterial compound, which synergizes with INH, is active against non-replicative mycobacteria and induces autophagy in macrophages.

Keywords: *Mycobacterium tuberculosis*, phenotypic screening, pyrazole scaffold, NSC-18725, autophagy

INTRODUCTION

Tuberculosis (TB), is responsible for the highest number of annual deaths among the infectious diseases (Glaziou et al., 2018). Furthermore, approximately 1.7 billion individuals are estimated to be latently infected with *Mycobacterium tuberculosis*. These individuals are asymptomatic, non-infectious but at a risk of developing disease during their lifetime (Glaziou et al., 2018). The