Bis(Pyrrolide-imine) Gold(III) Macrocycles and Chelates: Repurposed Anticancer Compounds Become a Novel Class of Antimicrobials Targeting Mycobacterium Tuberculosis and Mycobacterium Abscessus

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Bis(pyrrolide-imine) gold(III) macrocycles and chelates: repurposed anticancer compounds become a novel class of antimicrobials targeting *Mycobacterium tuberculosis* and *Mycobacterium abscessus*

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*Mycobacterium tuberculosis* (*Mtb*) and the fast-growing *Mycobacterium abscessus* (*Mab*) are two important human pathogens causing persistent pulmonary infections that are difficult to cure and require long treatment times. The emergence of drug resistant *Mtb* strains and the high level of intrinsic resistance of *Mab* calls for novel drug scaffolds that effectively target both pathogens. In this study, we have evaluated the activity of bis(pyrrolide-imine) gold(III) macrocycles and chelates, originally designed as DNA intercalators capable of targeting human topoisomerase I and II, against *Mab* and *Mtb*. We identified a total of 5 non-cytotoxic compounds active against both mycobacterial pathogens under replicating *in vitro* conditions. We chose one of these hits, 14, for detailed analysis due to its potent bactericidal mode of action, ease of crystallization, and ready availability (scalable synthesis). This compound exhibited activity superior to rifampicin (RIF) against phenotypically drug tolerant non-replicating bacilli in a multistress dormancy model. The clinical relevance of this compound is further demonstrated by its ability to inhibit several phylogenetically diverse *Mtb* clinical isolates. Prompted by previous data suggesting that 14 may target topoisomerase/gyrase enzymes, we demonstrated that it lacked cross-resistance with fluoroquinolones, which target the *Mtb* gyrase, as well as with the front-line drug RIF which implies a novel mechanism of action. Drugs like compound 14 that inhibit not only replicating and dormant *Mtb* bacilli, but also *M. abscessus* represent a promising starting point for the development of novel therapeutics for infections by pathogenic mycobacteria.

Key words: gold macrocycle, tuberculosis, mycobacterium, topoisomerase