SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF THE 3-NITRO ISOMER OF BIOREDUCTIVE TB DRUG PRETOMANID (PA-824)

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INTRODUCTION: TUBERCULOSIS
• Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (M. tb), a small, aerobic, slow-dividing, non-motile bacillus whose cell walls contain high levels of lipids, e.g., mycolic acid. TB usually affects the lungs, and the infection is in most cases latent (no symptoms), with ~10% progressing to the active disease.
• TB is one of the leading causes of death worldwide, with 10.4 million people falling ill with TB and 1.4 million dying from the disease in 2015. About one third of the population has latent TB. TB is a major killer of HIV positive people, with ~35% dying from TB in 2015 (1).
• Drug-susceptible TB can be treated with a standard 6 month course of four antimicrobial drugs, isoniazid, rifampicin, ethambutol and pyrazinamide. The spread of multi- and extensively drug resistant (MDR/XDR) TB is becoming a major health crisis.

PRETOMANID
• Bicyclic nitromidazoles such as PA-824 show aerobic activity, by inhibition of cell wall mycolic acid biosynthesis in actively replicating M. tb, as well as anaerobic killing of nonreplicating bacteria, by release of nitric oxide.
• The anaerobic activity of PA-824 involves bioreductive activation by a Deazaflavin (F420) dependent nitroreductase (Ddn). PA-824 is converted to several metabolites, including a des-nitro derivative. Derivatives shown in the figure are potentially the most exciting, as they display different mechanisms of action to the existing treatments and are active against both drug-susceptible and drug-resistant TB (2). Novel regimens including these new anti-TB drugs together with repurposed antibiotics, such as Linezolid or Moxifloxacin, are currently undergoing clinical trials.

SYNTHESIS OF THE 3-NITRO ISOMER OF PRETOMANID
• The synthesis of 1 was challenging, with difficulties arising from a key nitration reaction on alcohol 3 to give the nitrated product 4. Optimization of the synthetic route allowed the preparation of gram quantities of the desired target material 1.

PRETOMANID SYNTHESIS SIDE PRODUCTS
• Recently, two very minor side products were isolated from the process synthesis of PA-824. One was postulated to be the 3-nitro isomer (1) of PA-824, while the other was thought to be a 3'-methyl derivative (2). The syntheses of both targets were carried out to confirm their structures and evaluate their biological activities.

REFERENCE