# Development of Novel Inhibitors for Rifamycin-resistant RNA Polymerase of *Mycobacterium tuberculosis*

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Medicinal Chemistry Student Seminar
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Tuberculosis (TB) is an infectious pulmonary disease caused by the pathogen *Mycobacterium tuberculosis* (MTB) and is the second leading cause of death due to a single infectious agent. In 2015 alone, the disease claimed the lives of about 1.8 million people and is estimated to be carried in its latent form by one third of the world's population. Rifampin, a semi-synthetic derivative of the rifamycin natural product, is the lead drug used in modern anti-TB treatment. It works by binding to a pocket within the β subunit of MTB RNA polymerase, directly blocking the path of elongating RNA when the transcript becomes 2-3 nucleotides long. Although highly potent, treatment of tuberculosis using rifampin has its limitations. The structure of MTB RNAP is susceptible to frequent mutations which cause resistance of the enzyme to rifampin. The long treatment time required by the current medication regimen has contributed to the occurrence of rifamycin-resistant (Rif[R]) MTB RNAP. Rifampin is also an agonist of the human pregnane X receptor (hPXR), causing over-induction of CYP 3A4 leading to drug-drug interactions. TB-HIV coinfection has a high mortality rate due to this activation, since most anti-HIV drugs are substrates of CYP 3A4.
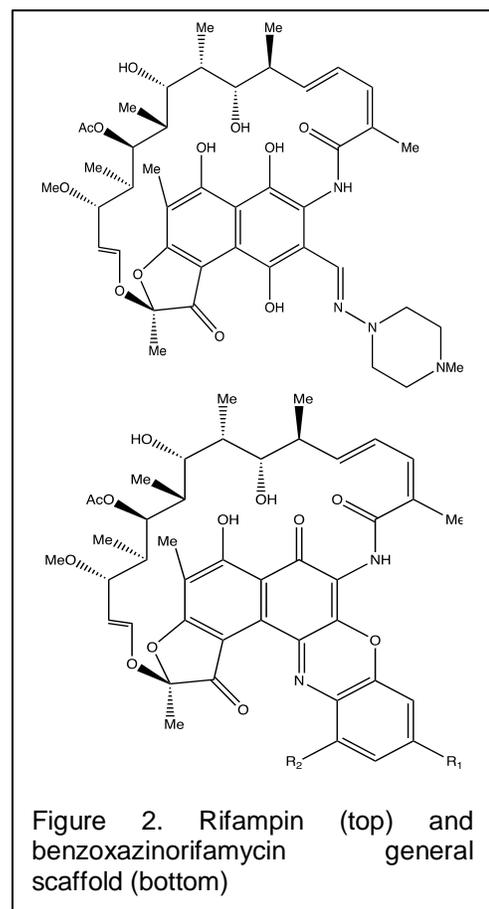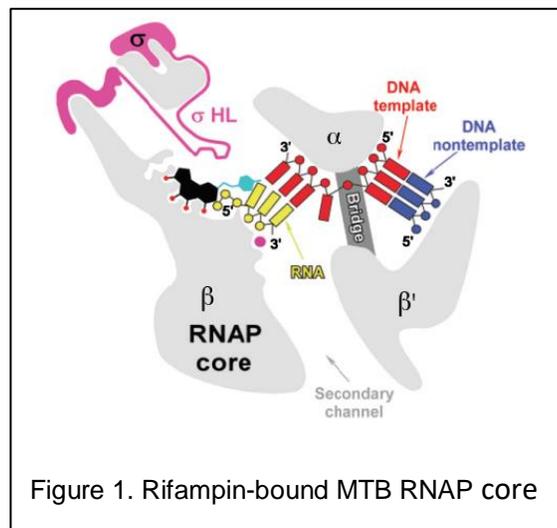
Figure 1. Rifampin-bound MTB RNAP core

Figure 2. Rifampin (top) and benzoxazinorifamycin general scaffold (bottom)

In an attempt to alleviate the global TB burden, this research project aims at developing novel inhibitors of MTB RNAP by two main approaches: identification of novel scaffolds by high-throughput screening and the structure based design of novel benzoxazinorifamycins (bxRif's). A library of diverse natural product extracts is being screened for inhibitory activity against one of the most clinically relevant Rif[R] MTB RNAP mutants and its hits will be followed up for the development of lead scaffolds. Leads from a screen of ~150,000 small molecules are also being studied and developed further based on initial SAR collected. A library of synthesized bxRif derivatives is being evaluated biochemically and, using the currently available crystal structures of MTB RNAP and hPXR, computationally observed interactions between the molecules and the protein binding sites are being used to guide further modification and design of novel bxRif's. The dual goal of increasing Rif[R] MTB RNAP inhibition while simultaneously decreasing hPXR activation is being pursued. This work is expected to yield novel inhibitors of Rif[R] MTB RNAP that could lead to a more efficient treatment regimen and decreased drug-drug interactions in the fight against TB.