Tuberculosis remains a social and medical issue. It has been a highly contagious disease, caused by the bacteria *Mycobacterium tuberculosis (Mtb),* very often with severe course, which results in over one million deaths worldwide yearly.

Chemotherapy for drug-susceptible TB includes the four first-line TB drugs, namely isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (EMB) for the first 2 months of treatment, followed by INH and RIF for the next 4 months of treatment. A growing phenomenon is the drug resistance of mycobacteria. An alarming problem is multidrug resistant tuberculosis (MDR-TB, *multidrug resistant tuberculosis*), defined as resistance to at least isoniazid and rifampicin, and in recent years, multidrug resistant tuberculosis with extended mycobacterial resistance (XDR-TB, *extensively drug resistant tuberculosis*) to isoniazid, rifampicin, and fluoroquinolones, as well as totally drug-resistant tuberculosis (TDR-TB, *totally drug-resistant tuberculosis*).

A four-drug treatment regiment was introduced 40 years ago but the emergence of multidrug-resistance and more recently TDR necessitates the identification of new targets and drugs for the cure of *Mtb* infection. For almost five decades the TB drug development process remained stagnant. The last 10 years have made sudden progress giving some new drugs including bedaquline (Sirturo®, trial phase 3), delamanid (Deltyba®, trial phase 3), pretomanid (trial phase 3), sutezolid (trial phase 2). Each class of drug has a specific target. These targets are either involved in cell wall biosynthesis, protein synthesis, DNA/RNA synthesis, or metabolism. The new drugs, unfortunately, have several side effects; Sirturo and Deltyba have the potential to induce arrhythmia. It is recommended that both Sirturo and Deltyba are utilized only in patients for whom the other treatments failed.

Organic synthesis plays a major role in the development of novel drugs, due to the possibility of modifying the chemical structure of active biological compounds and therefore, their biological activity. Chemical modification on the active molecules may results in an increase, decrease, modification of the biological response, or development of novel molecules that may target sites different to those present in unmodified counterpart. From this basic idea, a broad range of different structures can be derived, leading to the development of better and more effective therapeutic agents.

In this project, we will be modifying the structure of known antituberculosis drugs, according to the words of Sir James Whyte Black, winner of the 1988 Nobel Prize in Medicine: *"The most fruitful basis for the discovery of a new drug is to start with and an old drug."* Therefore, the main goal of the project is to modify isoniazid and rifamycin. For modification, we will use boron and its polyhedral structures - boron clusters - carboranes, and metallacarboranes.

The general formula of carboranes is $C_2B_{n-2}H_n$. The cage containing 10 boron atoms $C_2B_{10}H_{12}$ (dicarba-*closo*-dodecaborane) is the most frequently used in the modification of molecules and biomolecules. Carborane derivatives containing metal ions (e.g. Co, Fe, Cr) are metallacarboranes. These two groups of compounds show great pharmaceutical potential: a rigid geometry that keeps the substituents in a specific position, the unique non-covalent interaction ability, lipophilicity, chemical stability, bioorthogonality, and abiotic origin. The rich and diverse chemistry of these compounds enables researchers to use boron clusters to synthesize molecules with interesting physicochemical and biological properties.

Our project is supported by the promising results of preliminary studies, in which we developed methods for the synthesis of 12 isoniazid-carboranyl cluster conjugates. The selected conjugate was active against the pathogenic *Mtb* H37Rv strain at a concentration as isoniazid, and the most important all conjugates were active against the *Mtb* Δ*katG* mutant that was not isoniazid active. In this project, we will increase the library of isoniazid-carboranyl cluster conjugates, and also with metallacarboranes as well as obtain rifamycin-boron cluster conjugates for the first time. We will define their physicochemical properties (lipophilicity, solubility, ability to permeate biological membranes) that may affect their biological activity. In extensive *in vitro* biological studies, we will investigate whether selected compounds will inhibit the growth of the wild *Mtb* strain as well as INH/RIF resistant mutants. We will also investigate whether the selected compounds inhibit the activity of INH/RIF target proteins as well as other essential *Mtb* enzymes.

This is an interdisciplinary project that combines organic, inorganic chemistry, and microbiology. Its implementation may contribute to the identification of new active substances against *Mtb* as well as drug-resistant strains. Additionally, the conducted research will contribute to the enrichment of knowledge on boron clusters and their use in medicinal chemistry for the development of new biologically active substances.