Our previous research works have shown high *in vitro* antituberculotic activity of pyridine derivatives. Some of the obtained compounds showed a significant tuberculostatic activity against *M. tuberculosis* $H_{37}Rv$ standard strain and clinical isolates from patients of the Institute of Tuberculosis and Pulmonary Diseases in Warsaw. This project is a continuation of that research direction. Its main aim is the synthesis of novel 2,4-disubtituted derivatives of pyridine containing in their structure thiosemicarbazide moiety or imino group. We will examine their suitability as potential anti-TB drugs.

Nitrile moiety present in the starting material is characterized by a significant chemical reactivity. It can be converted in many ways by treating it with various chemical agents. We want to use it in the synthesis of new derivatives of this compound. All obtained compounds will be tested for tuberculostatic activity at the Institute of Tuberculosis and Pulmonary Diseases in Warsaw. On this basis, the selection of the most and least active compounds will be made. These substances will then be characterized by the Group of X-ray Crystallography and Crystal Chemistry, Technical University of Lodz for physicochemical properties (electrostatic potential distribution, lipophilicity, pKa) and their molecular structure will be determined by the methods of X-ray crystallography in order to determine the structural factors responsible for their tuberculostatic activity For the most active compounds we plan genetic studies in the Laboratory of Genetics and Physiology of Mycobacterium, Institute of Medical Biology of the Polish Academy of Science in Lodz. They allow predicting potential molecular targets for these compounds in the cells of *M. tuberculosis* and suggest the mechanism of anti-tuberculosis activity. Furthermore, these compounds will be also tested for cytotoxicity and antimicrobial activity against other types of bacteria, to demonstrate their specificity against *Mycobacterium* genus.

Within presented project we plan the synthesis of approx. 200 new chemical substances which will be picolinonitrile derivatives and selection of the most promising as the potential anti-tuberculosis drugs. Tuberculosis is an infectious disease caused by acid-fast aerobic bacteria belonging to the *Mycobacteriaceae* family. It occupies a leading position in the reports of the incidence and mortality of the world's population. It is estimated that in the period 2000-2020 approx. 1 billion people in the world will be infected, of which 20% will develop the active form, while 4% will die because of it. As the cause of global threat of Mycobacterium an increase in the number of new strains of multi-drug resistant MDR-TB (multidrug-resistant tuberculosis), pre-XDR-TB (pre-extensively resistant tuberculosis) and XDR-TB (extensively drug-resistant tuberculosis) is mentioned. Treatment of MDR-TB requires a long period, and the cure is achieved in only 50% of newly diagnosed patients, and among patients previously treated only in 29%. Resistant strains of pathogenic microorganisms are a serious threat, especially for immunocompromised patients, and infections caused by them are the most common complication in people taking immunosuppressive drugs, and HIV-positive. TB is the most often direct reason of deaths of AIDS patients. Lowering the resistance increases susceptibility cases up to 50%. In 2014, it recorded approx. 1.2 million cases of tuberculosis in HIV-positive patients, with 30% of those infected died. The emergence of resistant strains has created an urgent need for more effective and safe drugs for tuberculosis. Among the leading anti-tuberculosis chemotherapeutic drugs currently used isoniazid (INH), pyrazinamide (PZA), ethionamide (ETA) should be mentioned. Unfortunately, the most effective chemotherapeutic agents, as well as antibiotics, for example rifampicin (RMP), produce numerous serious side effects in the internal organs, eg. liver, central nervous system, pancreas, and cause hypersensitivity reactions. For this reason, the development of new medicinal substances possessing antituberculotic activity is still a present question. Significant impact on the science development may be the cognitive aspect of the project, the implementation of which will contribute to the understanding of new molecular targets and mechanisms of tuberculostatics action. Deepening our knowledge in this area is particularly important in view of the immigration problem currently affecting the European Union. Poland, as a member country, may soon face the problem of increasing the number of people infected with the most resistant form of active tuberculosis.