

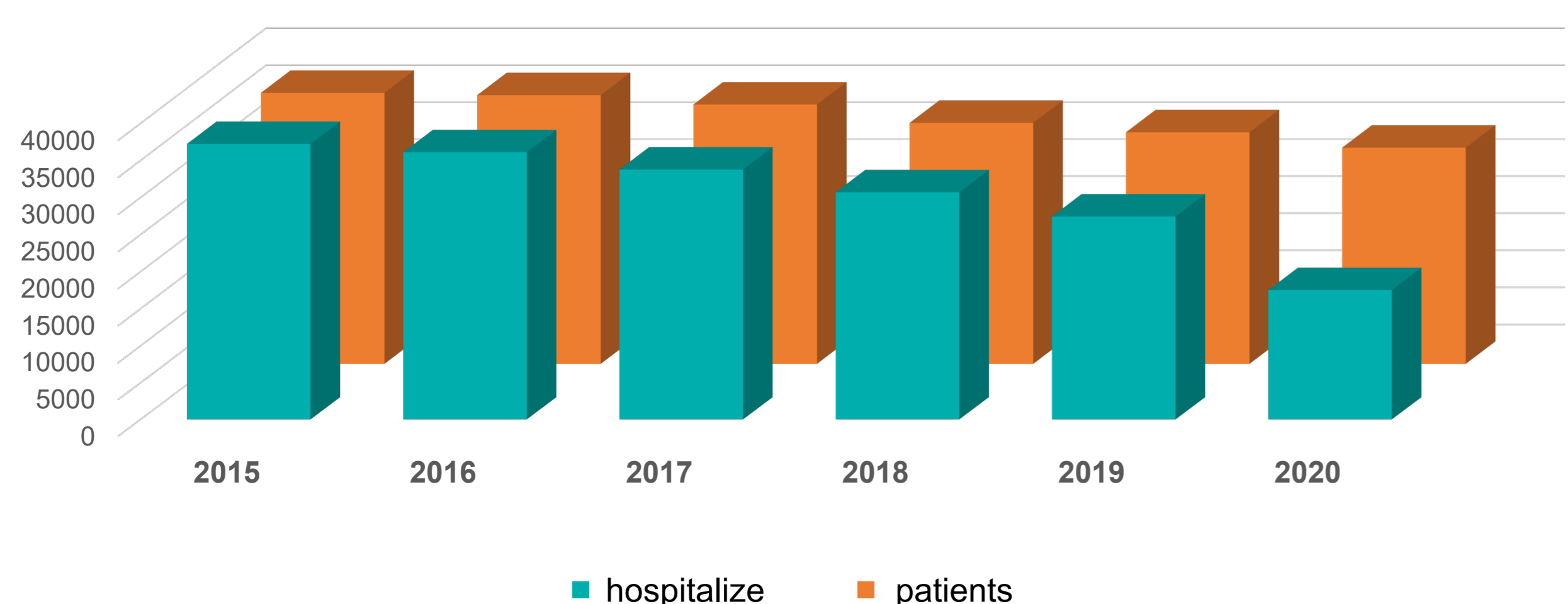
# IDENTIFICATION OF NOVEL POTENTIAL INHIBITORS OF DPRE1 FROM MYCOBACTERIUM TUBERCULOSIS AND MYCOBACTERIUM BOVIS

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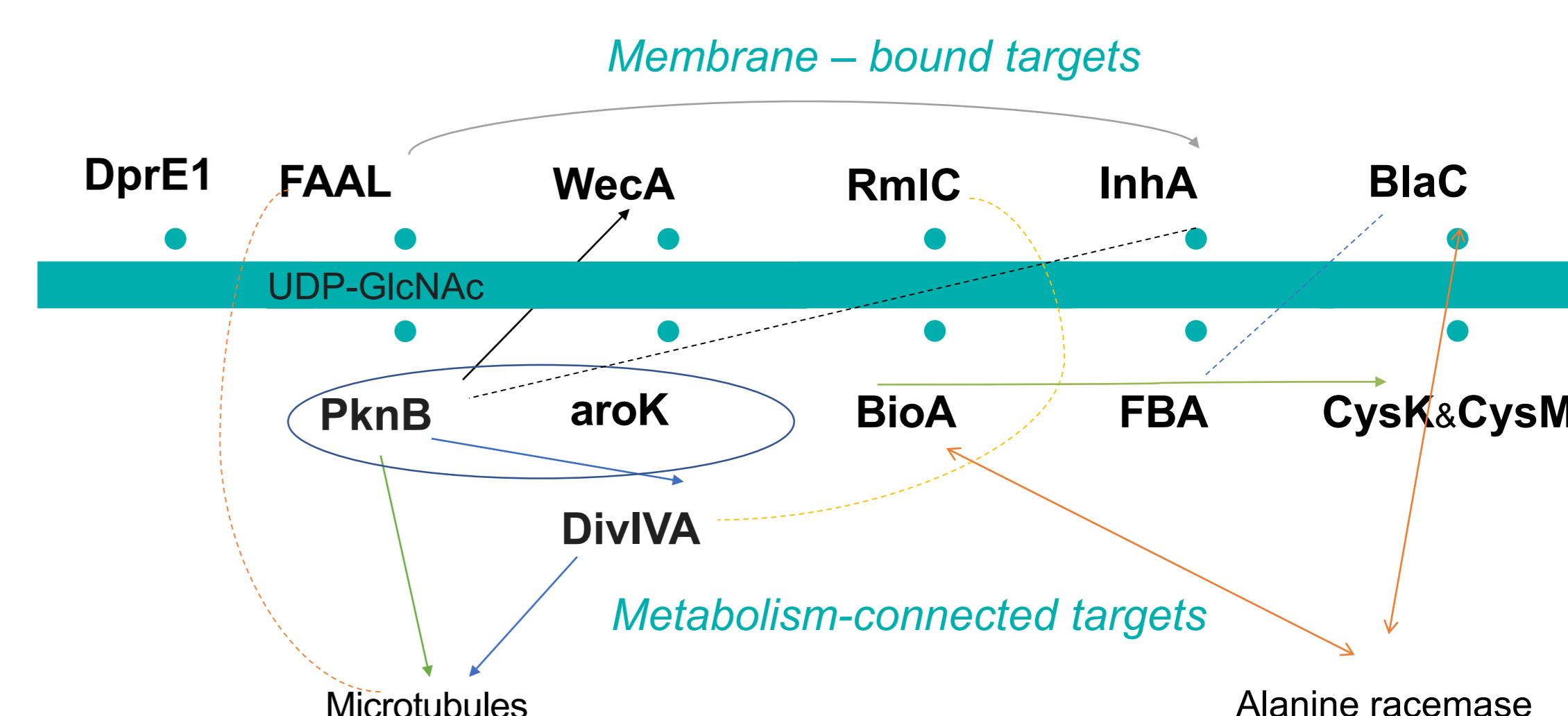
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Tuberculosis is a well-known bacterial infectious disease that has gradually acquired all the hallmarks in social status around the world. From the pharmacological point of view, one of the best approaches in defeating it is the identification and development of the novel inhibitors targeting unique proteins of the genus *Mycobacterium*. Such molecular targets, being essential and conservative in respect of mycobacteria genus, lack obvious homologues in humans and animals, therefore limited side toxic effects in patients are expected.



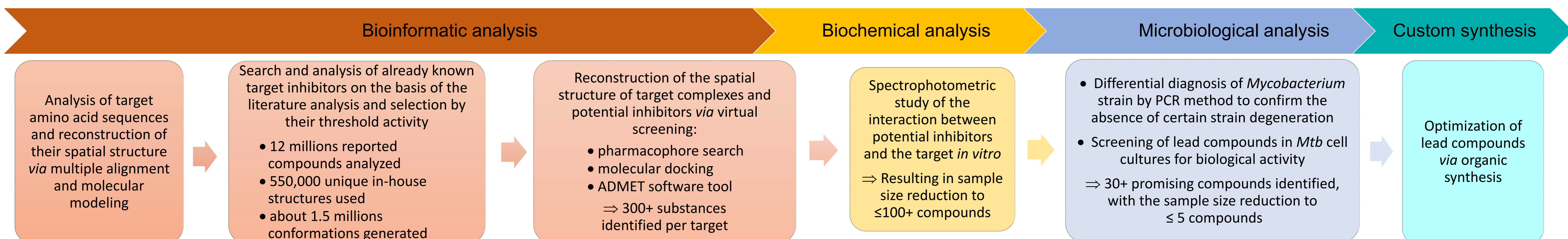
Incidence statistics in the Ukraine by years



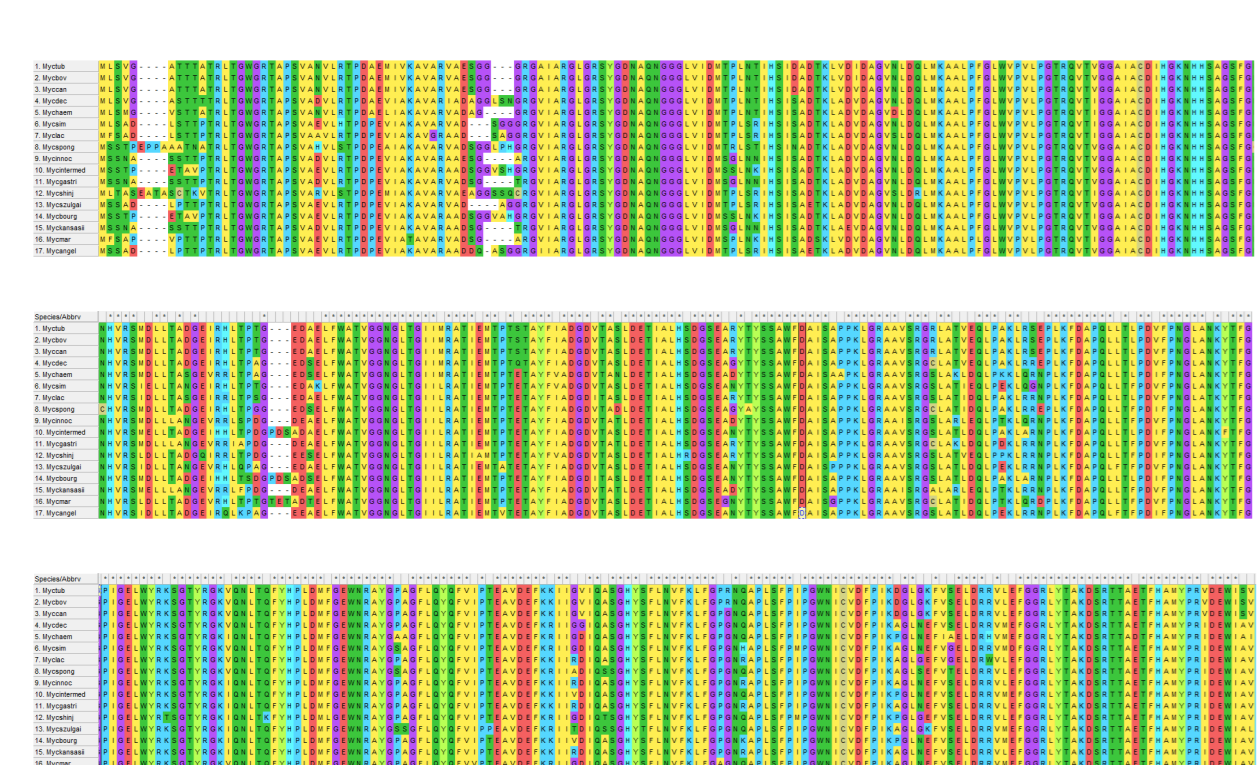
Protein-protein interaction analysis

Our project "Creation of new effective inhibitors of Z-ring formation to obtain new anti-tuberculosis drugs with antimetabolic action" was focused on a large-scale examination of different microorganism functions and possibilities of their inhibition in search for novel inhibitors of *M.tuberculosis* and *M.bovis*. PPI and statistic analysis have been performed starting from the known protein targets, already employed in the reported tuberculosis treatments, followed by molecular docking studies.

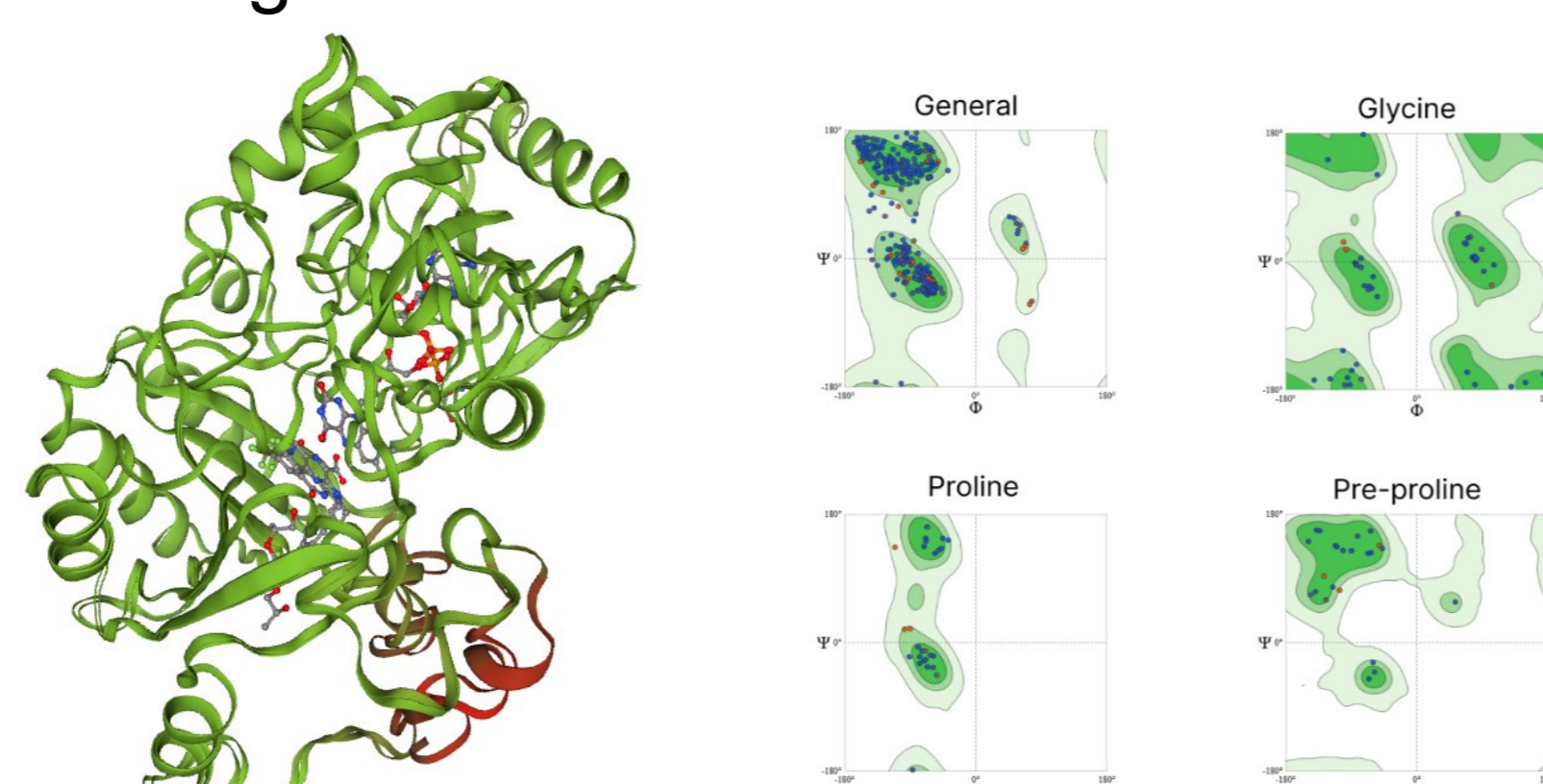
## General methodology of project



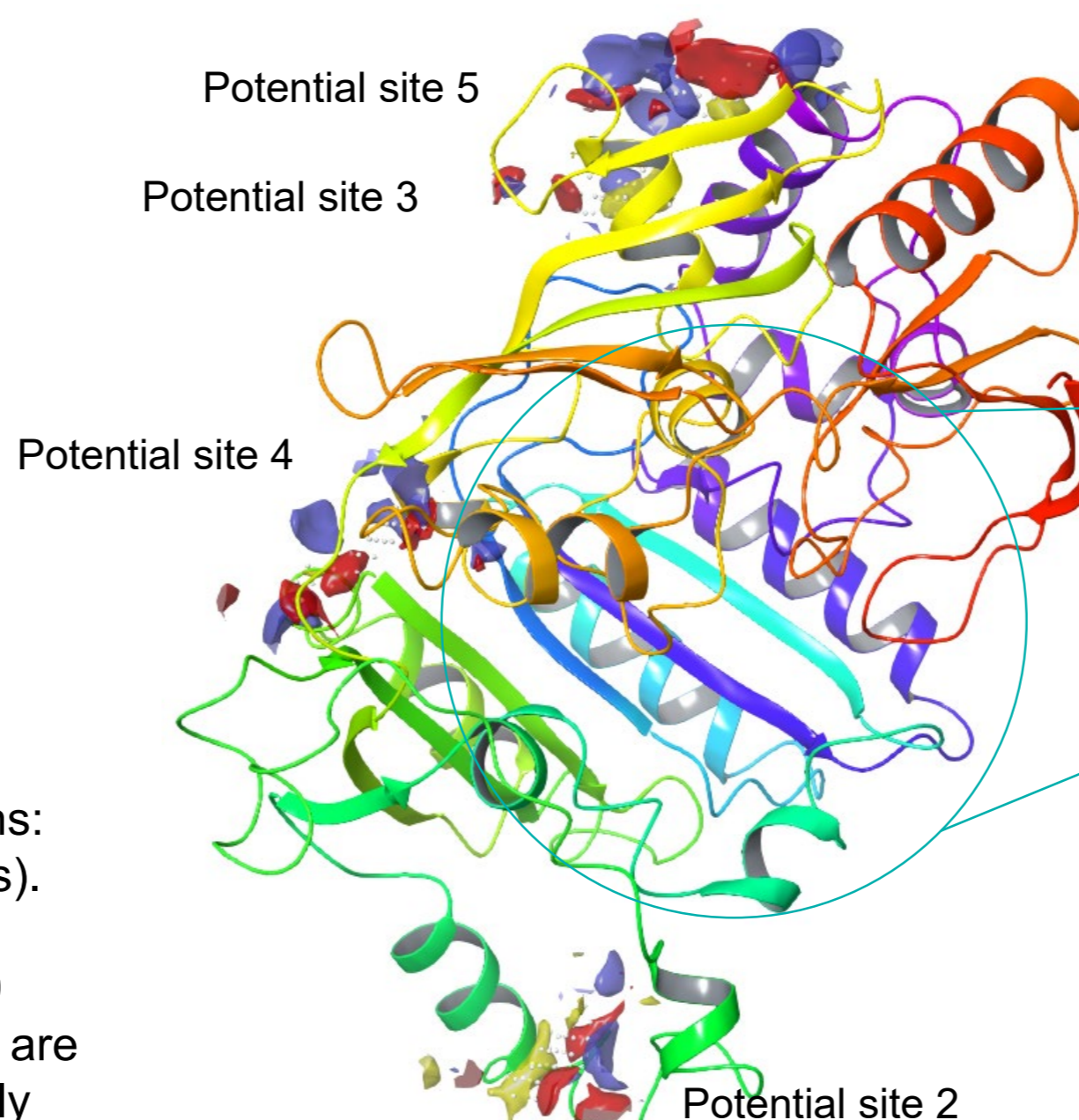
Enzymes, involved in the biosynthesis of fatty acids and peptidoglycans that compose the *Mycobacterium* cell wall, were considered highly attractive targets in the frame of this project. *In silico* structural and biological studies of essential molecular targets related to the mitotic apparatus and cell wall biosynthesis have been carried out. Based on the bioinformatics analysis of the known sites of ligand-protein interaction, the reconstruction of target proteins in complex with reference compounds was done and models for pharmacophore search and docking were built.



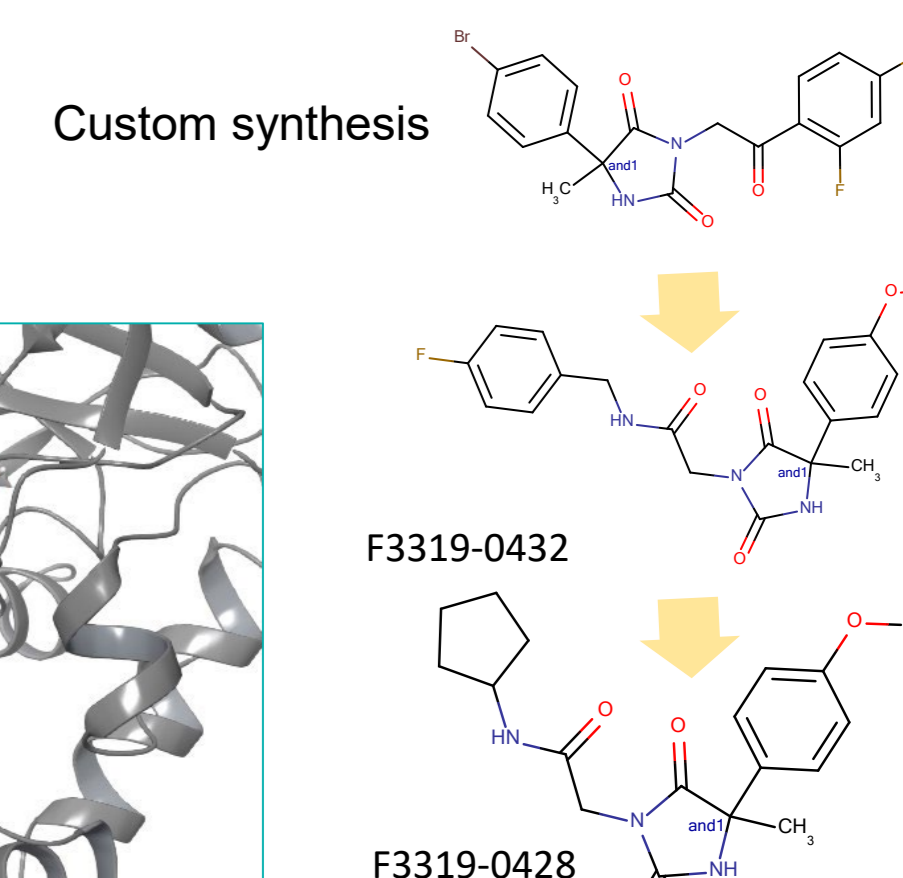
DrpE1 *Mycobacterium* specificity was established based on the results of multiple alignment, the sequences identity of DRPE1 *M.tuberculosis* ranges from 87.88 % (*M.shinjukuense*) to 100 % (*M.bovis*). In mammals, the homology was found only with 24-dehydrocholesterol reductase sequence (29.17 %)



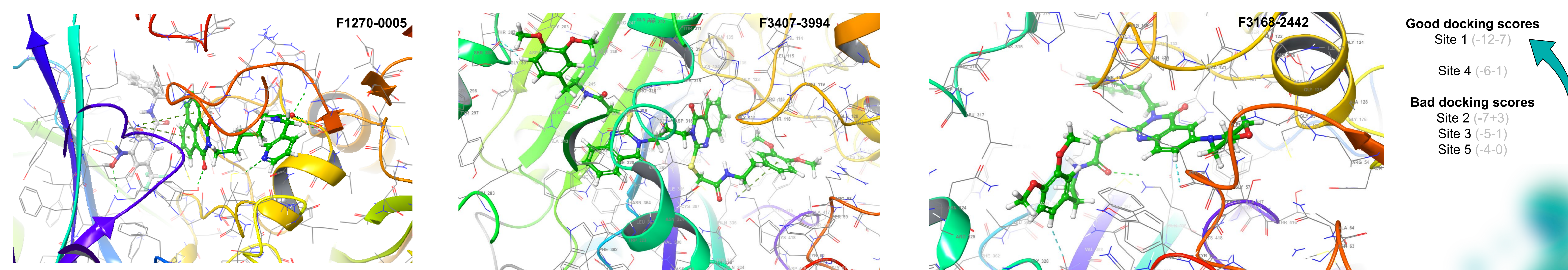
Structure of the DrpE1 is 461 amino acids long and contains two domains: FAD- and substrate-binding domains (22 %  $\alpha$ -helices and 26 %  $\beta$ -sheets). Ramachandran map of the DrpE1 *M.bovis* reconstructed structure demonstrates significant differences in 2 amino acid residues: LYS260 THR311. *M.tuberculosis* and *M.bovis* DRPE1 similarity scores for LYS260 are 0.79 and 0.92, respectively, and, for THR311, 0.79 and 0.86, respectively



Pharmacophore models based on X-ray data were used for molecular docking of known inhibitors to DrpE1 potential sites. As the result, hydrophobic interactions of the binding site amino acids (Ile 276, Ala280, Val284, Ala297, Leu311, Ile312, Val328, Met344, Tyr346, Leu396, Phe410, Pro428, Tyr429, Trp430, Leu465), hydrogen bond acceptors (Glu274, Ile276, Gln278, Asp354, Asp389, Asp393, Asp407) and hydrogen bond donors (Gln278, Ser281, Arg299, Tyr346, Lys391) were found.



Presented in this poster are the results of docking the Life Chemicals proprietary HTS Compound Collection against *Mtb* DprE1. Inhibition of DprE1 interrupts the cell wall biosynthesis in mycobacteria, leading to cell death. In total, 649 potential DprE1 inhibitors and modifiers were identified. They have become a starting point for the synthesis of new derivatives and analogues and their biochemical evaluation. Moreover, as shown by our previous research, some representatives belong to the compound families already reported in the literature as potent DprE1 inhibitors (Balabon O. et al., 2020).



The Pi-pi stacking system and hydrogen bonds are a common feature of the identified potential inhibitors and the target binding site