Biocatalysis towards industry scale synthesis of isoindolone drug derivatives

Project Lead: Prof. Debabrata Maiti

Specific problem being addressed: Recently we have employed biocatalysis, especially artificial metalloenzyme catalysis, towards asymmetric synthesis of bioactive small molecules. In this context, we want to scale up our already developed protocols to synthesize bioactive as well as commercial drug molecules. Large scale protein expression and whole cell reaction conditions are already achieved and we are going to apply them for robust synthesis of small drug molecules. The main issue that will be addressed here is the achievement of high turnover numbers (TON). Additionally, use of organic solvents will be significantly minimized.

Project Summary: Although asymmetric catalysis has long been a challenge for chemists, nature has been able to perform such reactions on highly complex molecules rather robustly using a variety of enzymes. However, these enzymes do have limitations in terms of the types of reaction that can be performed, the flexibility of the enzyme, and the specificity of the substrates. Learning from it, we envisioned that by combining the two strategies, we would be able to perform non-biological reactions in an enantioselective manner while having minimal impact on the environment as our method does not require any external oxidants. In addition, as the protein can be easily extracted using cell colonies, it is both economical for production and easily scalable and does not require additional efforts like chiral ligands. The enzyme system also provides better turnover numbers and lower catalyst loading making it highly efficient compared to its synthetic counterparts. ***Currently we are at TRL 5.***

Specific milestones of the project are the following

- Milestone 1: Express the mutant protein in 100mg scale and in multiple batches (0-10 months)
- Milestone 2: Incorporating multiple functional groups (0-12 months)
- Milestone 3: Enzyme testing in large scale synthesis (0-12 months)
- Milestone 4: Pilot-scale production of the enzyme (12-24 months)
- Milestone 5: Synthesis of the target molecules (12-24 months)

Impact of this innovation: Isoindolone and its derivatives are common moieties that are present in various natural products some of which are being utilized for therapeutic treatment. As such, its synthesis has attracted the interest of various groups and a number of protocols for its synthesis can be readily found. Isoindolone is one such derivative that is present in various pharmaceuticals. As many of the drug molecules and natural products that contain isoindolone scaffold have an aromatic substituent, we propose that our methodology would be a good fit for the synthesis of such molecules and provide value to industries that perform their large-scale synthesis. Their applications and impact of the isoindolone-based drugs are captured in the table.

Budget amount (INR): 50 Lakhs

Duration of project: 3 years