# Screening of Commercial Compound Library for Novel Catalytic Inhibitors of DPP3

**Luka Petohleb**,[a] **Antonia Matić**[b] **and Antonija Tomić**[b]

*lukapetohleb97@gmail.com*

[a]*Faculty of Science, Horvatovac 102A, Zagreb, Croatia*
[b]*Division of organic chemistry and biochemistry Ruđer Bošković Institute, Bijenička cesta 54, Zagreb, Croatia*

Dipeptidyl peptidase III (DPP3) is a zinc-dependent metalloprotease that cleaves dipeptides from the N-terminus of oligopeptide substrates. It is found in almost all human tissues and is thought to contribute to protein degradation, blood pressure regulation [1], protection against oxidative stress, and pain modulation [2]. Although DPP3 is implicated in several physiological and pathological processes, including oxidative stress response and cancer progression [3], only a few strong DPP3 inhibitors are known, and even the most potent ones lack specificity, targeting multiple metallopeptidases [4]. Identifying specific DPP3 inhibitors would provide valuable tools for a more detailed investigation of its role in human health and disease.

In this study, we applied a virtual high-throughput screening (vHTS) approach using the Glide program from Schrödinger to identify novel and more selective inhibitors of DPP3's enzymatic activity from the Enamine compound library. Out of 460 160 compounds in the Hit Locator Library, 12 candidates showing the most favorable docking scores and binding geometries with DPP3's active site were selected for further analysis. These were subjected to molecular dynamics (MD) simulations of at least 400 ns. Compound selected for experimental validation was chosen based on stable binding interactions and favorable binding free energy calculated using the MM-PBSA method.

**References:**

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