# CReM-dock: de novo design of chemical reasonable compounds guided by molecular docking

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The objective of this study is the development of a tool to design compounds de novo and decorate co-crystallized ligands with the special focus on synthetic accessibility. This tool employs the CReM approach [1] to generate ligand structures and control their synthetic feasibility and molecular docking by EasyDock [2] to assess their binding to a target protein. The developed tool offers two modes: i) iterative growth of a fragment co-crystallized with a protein preserving the position of the parent part of a molecule and ii) de novo compound generation starting from a custom set of fragments, which are subsequently docked and iteratively expanded. CReM-dock offers an optional augmentation of docking score and bias physicochemical properties of generated compounds, e.g. the fraction of sp3 carbon atoms. CReM-dock was benchmarked on de novo generation of ligands of targets belonging to different families to investigate dependency of diversity, synthetic accessibility, docking score and other properties of generated structures from chosen settings. We compared CReM-dock with REINVENT4 [3] and demonstrated that both tools result in comparable docking and synthetic accessibility scores of generated molecules, while CReM-dock compounds have higher novelty. The developed tool offers predictable control over synthetic feasibility of generated molecules and great flexibility to perform pure de novo generation as well as fragment expansion or scaffold decoration. This work was funded by the Ministry of Education, Youth and Sports of the Czech Republic through INTER\_EXCELLENCE II grant LUAUS23262, the e-INFRA CZ (ID:90254), and CZ-OPENSCREEN project (LM2023052).

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