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Abstract:

The primary challenge of most early stage hit-discovery and development projects is to identify novel chemical matter with Freedom to Operate (FTO), while simultaneously optimizing the physico-chemical properties that are crucial for robust activity. This is a multi-parameter optimization (MPO) problem that is difficult to solve and makes the drug discovery process expensive, complex, and time-consuming. To overcome the shortcomings of the traditional screening approaches, Iktos has developed a 3D structure-based generative Artificial Intelligence (AI) pipeline, focused on MPO, where the goal is to identify new, easily accessible molecules with drug-like characteristics and high activity on the protein target. The technology uses deep-learning based de novo design algorithms to generate molecules. The generation process is optimized by Reinforcement Learning based on diversity, novelty, quality, synthetic accessibility, and maximizing of 3D scores of the generated molecules, thus ensuring ligand interactions with key atoms within the protein pocket. This is an iterative AI-based chemical space exploration aimed at designing new chemical structures with optimal 3D scores and physico-chemical properties. Here we demonstrate this technology by identifying compounds with high affinity for an oncology target of known structure (PIM1- kinase). Using a combination of 3D-structure based techniques, parameters, and generative AI pipeline, we successfully identified novel active compounds that are outside the chemical space of the known PIM1-kinase inhibitors. No prior knowledge of existing PIM1-kinase inhibitors was used during the generation. Experimentally, one of the novel Iktos compounds was found to have IC50<1µM and good preliminary ADME properties (logD, solubility, and clearance). Our approach represents a fundamental shift in tackling MPO in early stage drug discovery projects to the chances for success.