Multicriteria Decision Aiding in the service of Drug Discovery

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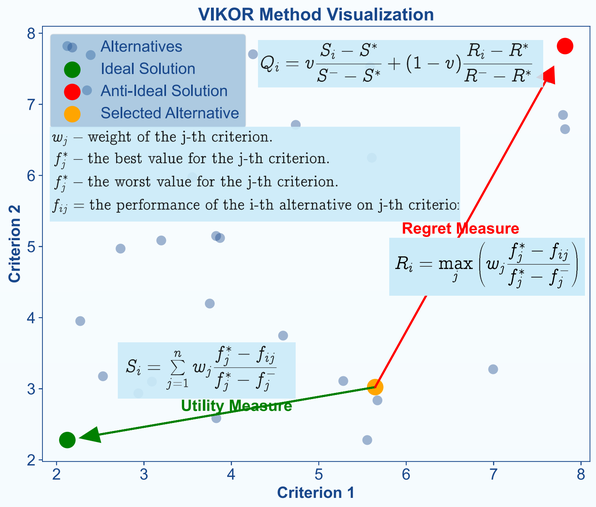
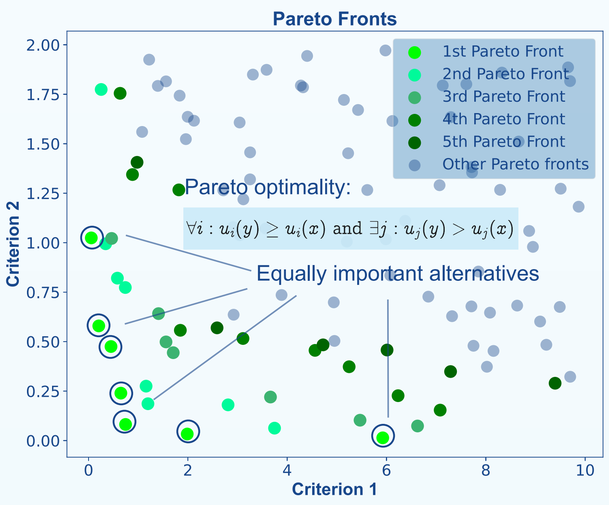
Abstract

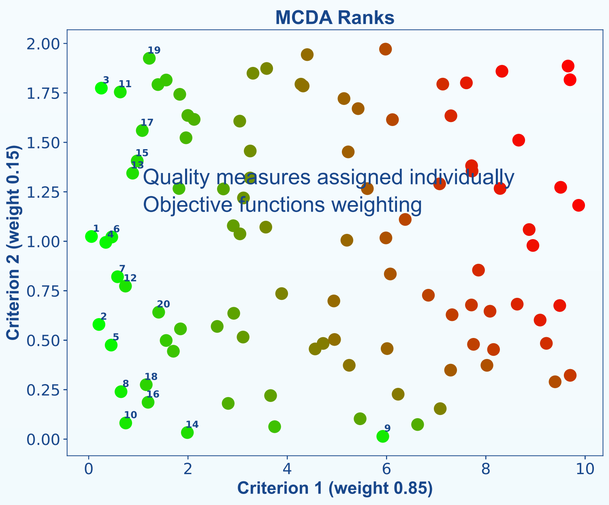
Drug discovery is inherently a multicriteria optimization problem. In the first instance, it involves a tremendously large chemical space where each compound can be characterized by multiple molecular and biological properties. Modern computational approaches try to efficiently explore chemical space in search of molecules with the desired combination of properties. For example, Pareto optimizers identify a so-called “Pareto front”, a set of non-dominated solutions. From qualitative perspective all solutions on the front are potentially equally desirable, each expressing a trade-off between the goals. However, often there is a need to weight the objectives differently, depending on their perceived importance. To address this, we have recently implemented a new Multicriteria Decision Aiding/Analysis (MCDA) method as a part of our AI-powered Drug Design (AIDD™) technology initiative [1]. This allows the user to differently weight various objective functions, which, in turn, efficiently directs the generative chemistry process towards the desired areas in chemical space.

MCDA vs Pareto pruning for generative chemistry

- **VIKOR method[2] (VIseKriterijumska Optimizacija I Kompromisno Resenje)**
- **Multi-criteria decision analysis (MCDA) technique**
- **Ranking from among alternatives in the presence of conflicting criteria**
- **Regret and Utility measures**
- **Each alternative ranked individually**
- **Incorporation of user preferences**

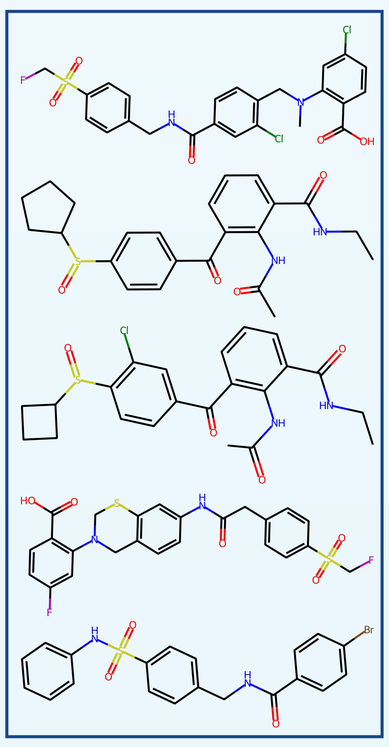






AIDD™

AIDD is a generative chemistry engine coupled with Multi-Parametr Optimization (MPO) algorithms, and exists as a module within ADMET Predictor®. It applies set of chemical transformation rules expressed in SMIRKS language. New compounds, created within the evolutionary loop, are subject to quality estimation with certain objective functions. The best trade-off molecules, chosen within the Pareto or MCDA pruning, are systematically improved as the optimization evolves. Here we use AIDD to demonstrate the added advantage of MCDA in two tasks: (1) Rediscovery of a PXR ligand from a crystal structure, and (2) PXR lead optimization.



Initialize with **K** randomly generated analogs. **SMIRKS**

Evaluate properties: e.g. ADMET_Risk, SynthDiff, Activities, HTPK, 3D similarity.

Prune molecules: Pareto or **MCDA**.

Generate **M** more analogs. **SMIRKS**

Potentially involve scaffold definition or drug-like filter. **SMARTS**

Repeat **N** times

References

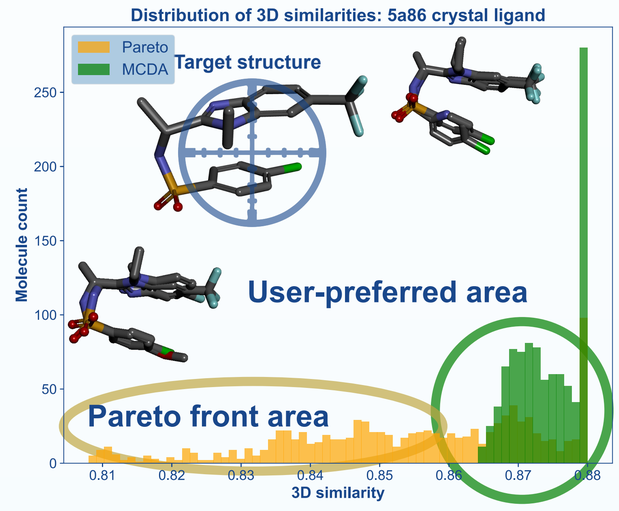
1.Jones J, Clark RD, Lawless MS, Miller DW, Waldman M, The AI-driven Drug Design (AIDD) platform: an interactive multi-parameter optimization system integrating molecular evolution with physiologically based pharmacokinetic simulations. J Comput Aided Mol Des 2024;38(1):14.
2.Opricovic S, Multicriteria Optimization of Civil Engineering Systems. PhD Thesis. Faculty of civil engineering, Belgrade, 1998, 2(1), 5-21.

Pregnane X Receptor

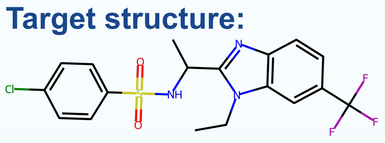
The Pregnane X Receptor (PXR) is a nuclear receptor that regulates the expression of genes involved in drug metabolism and transport. It is important to target PXR, because it plays a critical role in protecting the body from toxic substances by activating the expression of detoxifying enzymes and transporters upon binding with various endogenous and exogenous ligands.

Crystal structure rediscovery

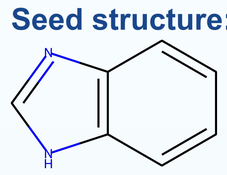
- **Known 3D geometry: PDB ID 5a86**
- **Main objective: 3D similarity to crystal structure**
- **OBJ_Sim3D weight: 70% (max)**
- **OBJ_SynthDiff+ weight: 15% (min)**
- **OBJ_ADMET_Risk weight: 15% (min)**
- **Pareto vs. MCDA pruning**
- **Pareto pruning: uniform coverage**
- **MCDA pruning: covers the user-preferred area**



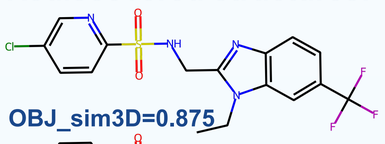
Target structure:



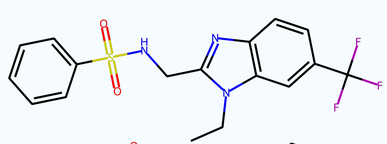
Seed structure:



Rediscovered structures:



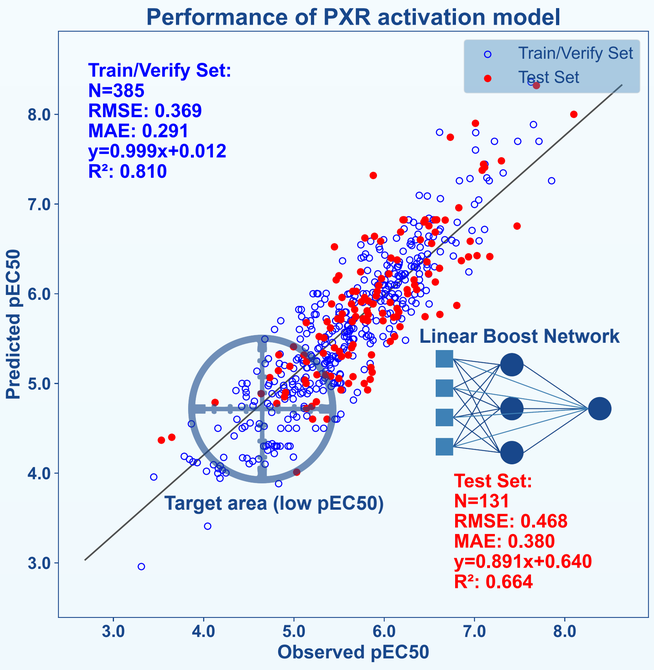
Other structures:



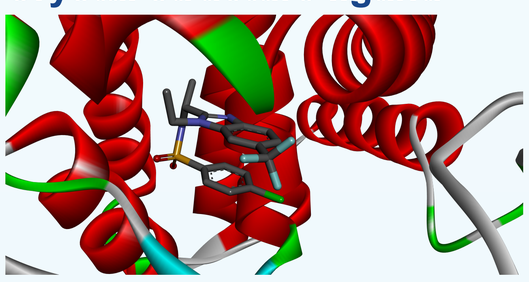
- **The MCDA pruning directs the generative chemistry process**
- **Objective weights as user preference elicitation method**
- **Desired chemical space exploration**
- **More flexible than Pareto pruning**
- **Each molecule ranked individually**
- **Any number of objectives**

QSAR model

- **PXR agonist activity model**
- **Based on 516 compounds from ChEMBL**
- **Created with ADMET Modeler**
- **Based on Linear Boost Network**
- **Reasonable performance**
- **Applied to optimize the ligand**

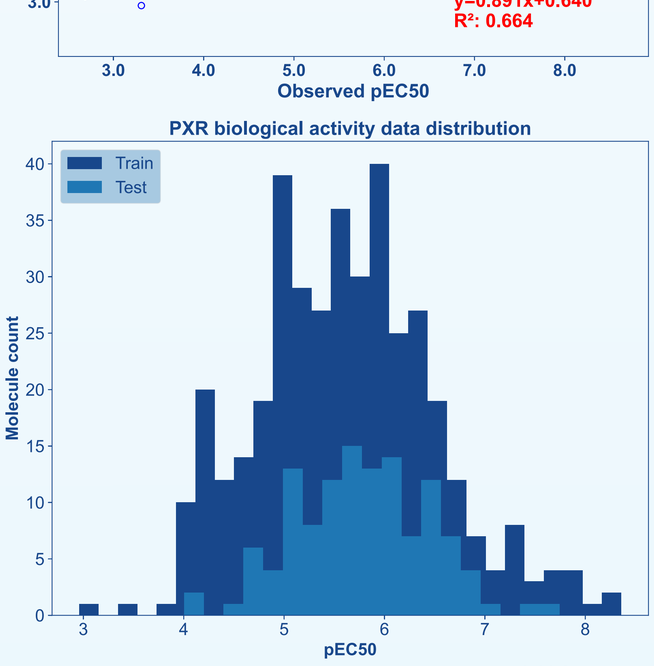


Crystal structure ligand

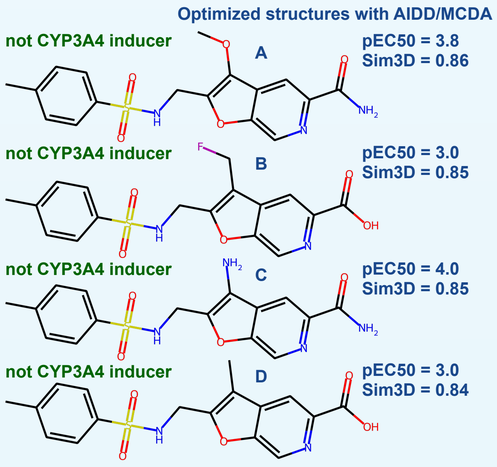


Ligand optimization

- **The 5a86 ligand induces CYP3A4**
- **PXR activator (predicted pEC50=6.2)**
- **Key objective 1: lower the pEC50 of the ligand**
- **Key objective 2: maintain the 3D similarity to reference structure**
- **Key objective 3: keep the organic synthesis difficulty level low**
- **Method: AIDD with MCDA pruning**
- **OBJ_PXR weight: 50% (min)**
- **OBJ_Sim3D weight: 30% (max)**
- **OBJ_SynthDiff weight: 20% (min)**

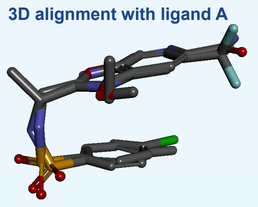


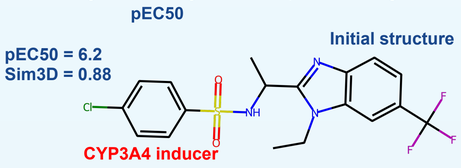
Optimized structures with AIDD/MCDA



CYP3A4 induction predictions obtained with an in-house SLP model

3D alignment with ligand A





- **New ligands designed**
- **Reduced pEC50**
- **Maintained 3D similarity**
- **Predicted CYP3A4 induction was negative**
- **AIDD with MCDA pruning**
- **User preferences successfully elicited**

Grab the poster

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