Discovery of Novel Inhibitors of PIM-1 Kinase Enabled by Generative AI

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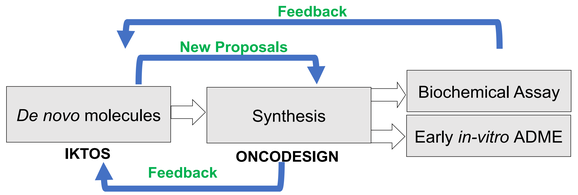
BACKGROUND

- Proto-oncogene serine/threonine-protein (PIM-1) kinase is implicated in multiple human cancers and is an attractive therapeutic target
- Small-molecule inhibitors for this target have shown promising anti-cancer activity in clinical trials. However, side effects due to insufficient selectivity have proven problematic; further research is needed to overcome these issues
- **Oncodesign and Iktos** have collaborated on the *de novo* design of novel PIM-1 kinase inhibitors, utilizing **Oncodesign's** expertise with PIM-1 and implementing **Iktos's** structure-based generative artificial intelligence (AI) technology



OBJECTIVES

- Use **generative AI** to generate and identify new PIM-1 kinase inhibitor hits with **activity ≤1 μM**, freedom-to-operate (FTO), and good *in vitro* ADME properties
- Use this as a case-study to demonstrate the benefits and capabilities of the generative AI technology developed by Iktos

STRUCTURE-BASED (SB) GENERATIVE AI

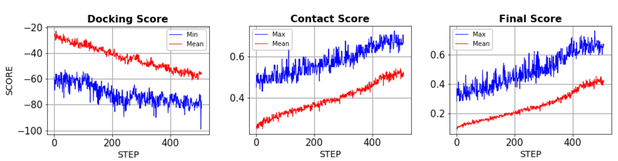
Iktos has developed a state-of-the-art SB generative AI pipeline with the goal of overcoming the shortcomings of traditional virtual screening processes. This pipeline generates new molecules with high predicted activity on the protein target while also maintaining critical drug-like characteristics. By maximizing 3D scores and/or interactions with key pocket residues, this technology increases the odds of identifying novel molecules with desired properties earlier in a drug discovery project

AI Generation
- Batch of 128 SMILES

Score
- Pose filtering, clustering, scoring
- Proprietary Contact Score
- Overall score computation

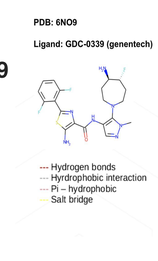
Ligand Prep
- Chirality check
- Protonation

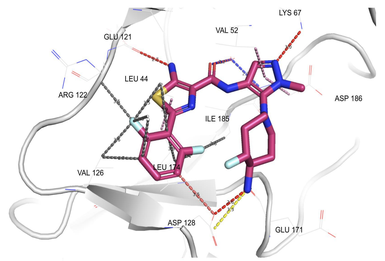
3D Production
- Molecular docking
- MM-GB/SA Rescoring



GENERATIVE AI SETUP

- Generator (LSTM) trained on CHEMBL dataset
- Reference PDB structure for docking: **6NO9**
- Murcko scaffolds of known PIM-1 inhibitors forbidden during generation
- Reward functions:
  - Molecular descriptors (MW, cLogD, TPSA, HBD/HBA, QED, PFI)
  - 3D scores: Docking and Contact

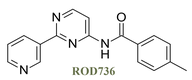




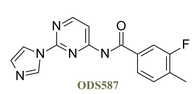
GENERATION AND SYNTHESIS

First Generation Synthesis

- 5 molecules synthesized; 2 actives + 3 inactives. Tested on PIM-1 and co-target PIM-3
- From scratch → **~ 5 μM** activity within first round of generation and synthesis of 5 molecules

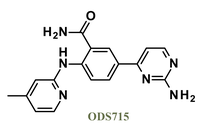


	Inhibition			
	PIM-1		PIM-3	
	@10μM	@1μM	@10μM	@1μM
ROD736	69%	32%	88%	22%
ODS587	45%	–	71%	69%



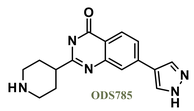
Next Generation Synthesis

- 4 molecules synthesized; 2 actives + 2 inactives. Tested on PIM-1 and co-target PIM-3. Early *in vitro* ADME data generated
- **~ 5 μM → ~ 1 μM** activity with synthesis of total 9 molecules

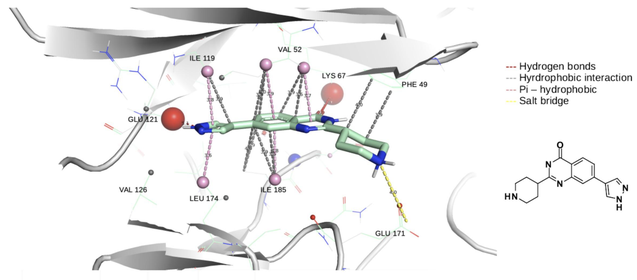


	Inhibition			
	PIM-1		PIM-3	
	@10μM	@1μM	@10μM	@1μM
ODS715	72%	37%	82%	26%
ODS785	88%	50%	90%	54%

	ADME Data		
	ChromlogD	Sol. PBS/Fassif	Clint r/h
ODS715	1.9	218/228	<5/9
ODS785	0	221/250	54/27



Binding Mode of ODS785 Identified



- Binding mode reveals that this compound does not explore the sub-pocket of PIM-1 which is explored by the crystal ligand
- New generations and synthesis launched to achieve this

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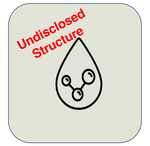
NEW HITS IDENTIFIED

- **We have identified a new hit** using this approach which is active against PIM-1 and PIM-3 and has good ADME properties
- Binding mode analysis revealed that this molecule explores the same sub-pocket as the crystal ligand but has a different scaffold
- Further analysis of this compound is ongoing

IC_{50} = 1.08 μM (PIM-1)
IC_{50} = 535 nM (PIM-3)



ChromlogD = 2.7
Sol. PBS/Fassif = 205/239
Clint r/h = 103/53

CONCLUSIONS AND TAKEAWAYS

Hit discovery
- Compound with activity ≤ 1μM from new scaffolds identified
- Good preliminary ADME properties (logD, solubility, stability)

Technology: Generative AI
- Patent busting: Forbid multiple scaffolds during generation
- Multi Parameter Optimization (MPO)
- Easy to create diversity around a hit
- Iterative Design-Make-Test (DMT) cycle crucial to success

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IKTOS PRODUCTS

Makya is a chemist-friendly SaaS platform for AI-driven *de novo* 2D drug design focused on MPO. Ask us about its features or visit **makya.ai**

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