AI-driven platform discovers PHD inhibitor for anemia treatment

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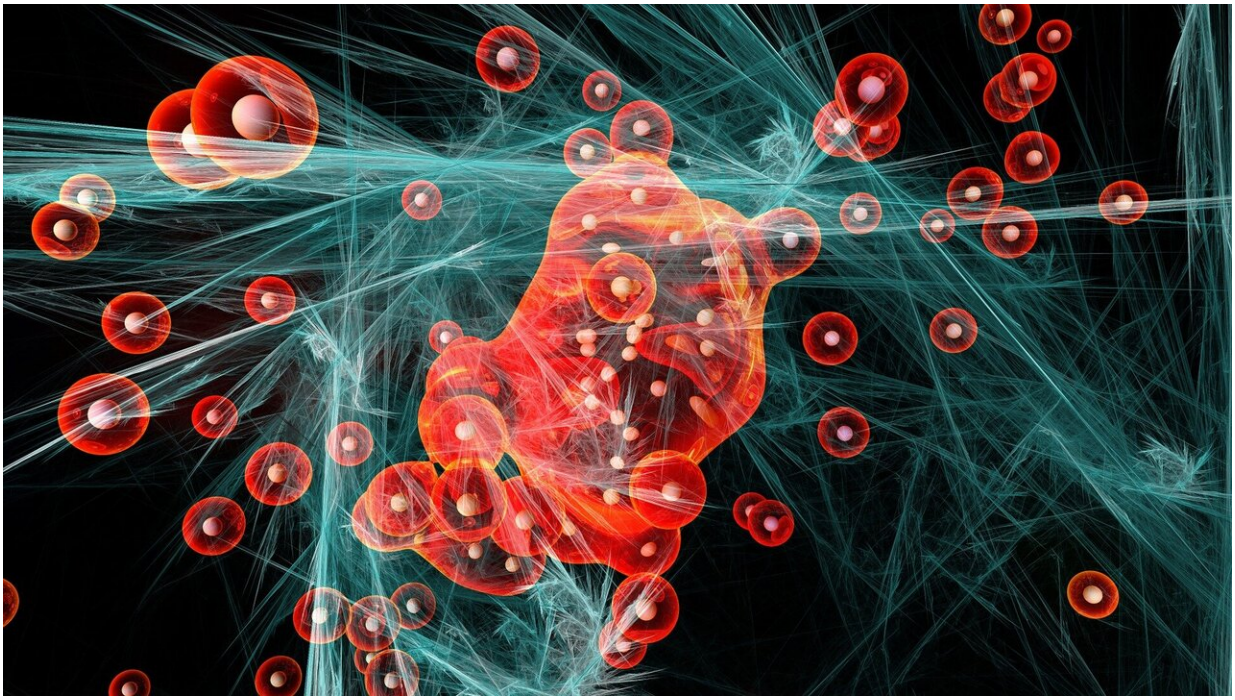

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A study published in the *Journal of Medicinal Chemistry* reports the discovery of a novel PHD inhibitor for the treatment of anemia.

The academic breakthrough is powered by Chemistry42, InSilico Medicine's proprietary generative chemistry platform consisting of more than 40 selected generative models.

As suggested in previous studies, the inhibition of prolyl hydroxylase domain enzymes (PHD) influences fundamental biological processes, including red blood cell production, by regulating the HIF-α pathway, thus indicating the potential for the treatment of CKD-induced anemia.

Guided by a structure-based drug discovery (SBDD) strategy, Insilico's scientists gathered structure information on the PHD target and known molecules and generated a series of molecule candidates with the help of Chemistry42. Utilizing built-in filters covering drug-likeness, pharmacophore clues, synthesis evaluation, and more, the AI-generated candidates were ranked and prioritized before a hit compound was produced for further optimization.

"Thanks to Chemistry42, we had end-to-end assistance from molecule generation to hit compound selection," said Xiaoyu Ding, the computational chemist sharing first authorship. "With the power of generative artificial intelligence, we could accelerate the drug discovery process without compromises in novelty or quality."

Afterward, several rounds of synthesis test optimization yielded lead compound 15, which demonstrated a favorable in vitro/in vivo ADMET profile, a clean safety profile, and promising PK properties in multiple species. Moreover, the compound was proven to alleviate anemia in a rat disease model with relatively simple synthesis steps.

"Given that more than 10% of the global population suffers from CKD, Insilico's novel molecule could be meaningful for further investigations and patients worldwide," said Jianyu Xu, the medicinal chemist who co-authored the paper. "After comprehensive research into PHD inhibitors already available on the market, we hope to develop a novel noncarboxylic acid molecule for better permeability and PK profiles."

More information: Jianyu Xu et al, Discovery of Novel and Potent

Prolyl Hydroxylase Domain-Containing Protein (PHD) Inhibitors for The Treatment of Anemia, *Journal of Medicinal Chemistry* (2024). DOI: 10.1021/acs.jmedchem.3c01932