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CARE – Corona Accelerated R&D in Europe

WP3 – Hits to Leads

D3.4 Coordinated AI - platform

Lead contributor	IKTOS

Other contributors	Dundee University Nuvisan Takeda Merck Servier

Document History

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Abstract

The goal is to identify and develop potent SARS-CoV antivirals by prosecuting drug discovery strategies, in parallel, target-based and phenotypic-based approaches. Develop a rapid and effective medicinal chemistry, computational chemistry, and AI combinatorial approaches.
For the target-based approach, AI-driven Ligand-Based and Structured-Based technology from Iktos deliver novel compounds, which are expected to have optimized activity. On top of that, Medicinal Chemistry and Computational Chemistry expertise are also provided by Iktos and Dundee University. Unfortunately, many compounds were inactive (pIC_{50} < 4.0), although one compound showed pIC_{50} = 5.47. The active compounds were not significantly more potent than the input set of GRL molecules (a compound that has been studied for SARS-CoV-2; Ratia et al., 2008).
For the phenotypic approach, novel chemical structures were proposed, and synthetic accessibility was assessed by AI technology. Synthesis and biological assay testing are ongoing.

Methods

For the target-based approach, Iktos applied the Ligand-Based (LB) drug design technology "Makya" and Structured-Based (SB) AI technology. "Makya" is an innovative *de novo* design AI platform that uses deep learning-based generative AI. On top of the LB approach, Iktos also applied an SB design method, a "Fragment Growing algorithm" which was developed by Iktos. The "Fragment Growing algorithm" takes into account the protein-ligand interactions and optimizes the docking score and physchem parameters simultaneously. Thanks to the integration with Iktos "retrosynthesis routes prediction technology" "Spaya" which predicts retrosynthesis routes, the synthetic feasibility of the generated compounds is controlled, with a predicted number of steps and routes based on known reactions and building blocks.

Results

For the target-based approach, about 174 compounds were designed using the AI-driven Structure-Based technology. Optimization of the synthesis accessibility was conducted to accelerate the DMTA (Design, Make, Test, Analyze) cycles. One compound showed pIC_{50} = 5.47.
For the phenotypic approach, six scaffolds were proposed and around 20 analogues were created in each scaffold with a Medicinal Chemistry rationale (synthetic accessibility, fsp3 (fraction of sp3 carbons) and removal of litigious scaffolds). Synthesis and biological assay testing are ongoing.

Discussion

Target-based approach: Four different approaches for the design of the molecules have been performed. There is still some room to modify the hit compound in order to increase its potency. However, due to the limitation of the project resources and budget, further exploration was stopped. Takeda shared new hit compounds and additional datasets in

1Q 2023 but it could not provide significant improvement of the Machine learning algorithm performance for the compound's design. Tight SAR, IP profile and limited chemical synthesis resources meant that Iktos' proprietary technology could not be used at its fullest potential.
Phenotypic-approach: Novel chemical structures have been proposed with a Medicinal Chemist rationale. Due to changes in resource allocation, no experimental results have been obtained yet, but once assay results are obtained, Iktos will run Structure Activity Relationship analysis and incorporate it in the AI-driven compounds design. Deconvolution studies are ongoing and once the target is known, a Structure-Based approach might also be put in place at Iktos (pending available crystal structures of the target protein).

Conclusion

Target based approach: The initial assessment and structure preparation to apply Itkos Structured-Based AI technology were successfully conducted. Diverse and novel chemical structures have been designed through Iktos AI platform. Iktos AI pipeline delivered compounds with easy synthetic accessibility. About 142 compounds were designed by the AI-driven Ligand-Based and Structure-Based technologies. Optimization of the synthetic accessibility was conducted to accelerate the DMTA cycles. One compound showed pIC_{50} = 5.47.

Phenotypic approach: The target parameters/rewards setting for the AI-driven generation was completed. Novel scaffolds were proposed aiming at diversifying the structure and investigating a wider chemical space. Synthetic accessibility was also well-secured by Iktos AI retrosynthesis tool to help ensure a timely DMTA cycle.

In conclusion, for the CARE Consortium, Iktos is committed to the design of new compounds through the Makya *de novo* design AI platform and "Fragment Growing algorithm". With its unique integration of deep generative AI and retrosynthesis analysis, Iktos AI platform enables to acceleration of the drug discovery process and optimize the delivery of lead compounds.

Reference

Kiira Ratia, et al. (2008) A noncovalent class of papain-like protease/deubiquitinase inhibitors blocks SARS virus replication. PINAS 105: 16119-16124