Title

Can we harness AI to optimize our FAAH hits?

Authors

Frans ter Brake, Martin Sicho, Patrick Rehorst, Lisa Hunink, Mario van der Stelt, Anthe Janssen

Poster presentation

The discovery of new therapeutic drugs is increasingly benefiting from advances in computational drug discovery. The integration of machine learning, particularly techniques based on large language models and reinforcement learning, into the drug discovery process has opened new avenues for the de novo design of drug-like molecules.[1] In this research, we used a newly developed gel-based multiplexed activity-based protein profiling workflow to screen 823 urea-based compounds against fatty acid amide hydrolase, a key enzyme in the endocannabinoid system which is associated with the regulation of neurochemical pathways involved in anxiety, inflammation, depression, and pain.[2,3] This resulted in the identification of three hits. We then trained an in silico generator based on DrugEx to design analogues, using literature data and the discovered hits. The generated analogues were scored using the QED metric and a QSAR model that was trained on literature data. Analogues with a pIC_{50} of more than 8 and favourable physiochemical properties were curated by docking and synthesizability. A selection of these compounds are currently being synthesized and screened using chemical proteomics in order to evaluate the implementation of AI in our hit optimization strategy.

References (*max 3*)

Last name of first author, Initials., et al., *Title of publication.* Name of journal, year of publication. **volume number**: p. xx-xx.

1. Liu X., et al., *DrugEx v3: scaffold-constrained drug design with graph transformer-based reinforcement learning*, Journal of Cheminformatics, 2023. 15(1): 24
2. Esbroeck A.C.M., et al., *Activity-based protein profiling reveals off-target proteins of the FAAH inhibitor BIA 10-2474*, Science, 2017. 356(6342): 1084-1087.
3. Janssen A.P.A., et al., *Development of a Multiplexed Activity-Based Protein Profiling Assay to Evaluate Activity of Endocannabinoid Hydrolase Inhibitors*, ACS Chemical Biology, 2018. 13(9): 2406-2413