

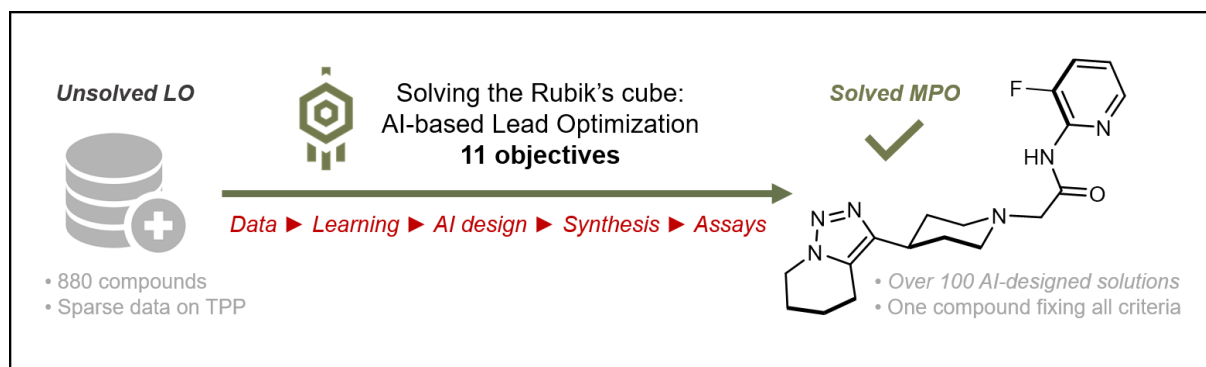
Deep Learning Applied To Ligand-Based De Novo Design: A Real-Life Lead Optimization Case Study

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Despite existing ligand- and structure-based de novo design methods, Multi-Parameter Optimization (MPO) remains a major challenge in New Chemical Entity (NCE) drug discovery projects, and the inability to identify molecules meeting all the criteria of lead optimization (LO) is an important cause of NCE project failure.[1]-[2] Lately, promising results have been reported for deep learning generative models applied to de novo molecular design.[3] Yet, to our knowledge, no report to date has been made of the value of this new technology for addressing MPO in a complex, real life drug discovery project.

Starting from a data set of 880 molecules tested on 11 bioassays, single task QSAR models were developed. Then, our deep generative algorithm has been used to design virtual molecules fulfilling all 11 objectives according to a multi-objective fitness function built from the predictive QSAR models. From 150 AI-designed compounds, 11 have been synthesized & assessed in vitro. Amongst them, one met simultaneously all objectives of the project, and 2 met 10/11 objectives just below the required threshold, within the margin of error of the assay, regarding the last objective. To our knowledge, this is the first successful application of deep learning to de novo design, to solve an MPO issue in an actual drug discovery project, moreover on a large number of objectives.

Bibliography :

[1] Firth N.C. *et al.* MOARF, an Integrated Workflow for Multiobjective Optimization: Implementation, Synthesis, and Biological Evaluation. *J. Chem. Inf. Model.* **2015**, *55*, 1169–1180.

[2] Nicolaou, C. A., Brown, N. Multi-Objective Optimization Methods in Drug Design. *Drug Disc. Today Technol.* **2013**, *10*, e427-e435.

[3] Chen, H. *et al.* The rise of deep learning in drug discovery *Drug Disc. Today* **2018**, *23*, 1241-1250.