DEEP LEARNING FOR LIGAND-BASED DE NOVO DESIGN IN LEAD OPTIMIZATION: A REAL LIFE CASE STUDY

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Introduction

Multi-Parameter Optimization (MPO) is a major challenge in New Chemical Entity (NCE) drug discovery projects, and the inability to identify molecules meeting the Target Product Profile (TPP) in lead optimization (LO) is an important cause of NCE project failure or delay. Several ligand- and structure-based de novo design methods have been published over the past decades, some of which have proved useful for multi-objective optimization (MPO) (ref 1-7). However, there is still need for improvement to better address the chemical feasibility of generated compounds as well as increasing the explored chemical space while tackling the MPO challenge. Recently, promising results have been reported for deep learning generative models applied to de novo molecular design (ref 8), but until now, to our knowledge, no report has been made of the value of this new technology for addressing MPO in an actual drug discovery project. Our objective in this study was to evaluate the potential of a ligand-based de novo design technology using deep learning generative models to accelerate the discovery of an optimized lead compound meeting the TPP LO criteria.

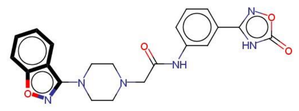
Can AI help to design optimal compounds matching simultaneously all the objectives of the LO project?

1 Initial data distribution

Objectives	Activity	5-HT2A	5-HT2B	α1	D1	Na_V 1.2	hERG	RLM	HLM	Caco-2 FAbs	Caco-2 Efflux
Concentration	30 nM	10 µM	10 µM	10 µM	10 µM	10 µM	10 µM	-	-	-	-
Filled %	29%	28%	26%	33%	28%	30%	59%	90%	90%	87%	77%
Blueprint Threshold	≥30%	≤50%	≤50%	≤50%	≤50%	≤50%	≤30%	≥50%	≥50%	≥90%	≤15
In blueprint rate	59%	29%	35%	33%	53%	68%	45%	49%	35%	61%	80%
Best compound	194	20	18	1	4	0	19	82	63	89	26

The project data set comprised 880 molecules tested on 11 biological assays: 1 activity criteria (phenotypic assay), 6 off-target activity (selectivity criteria), 4 DMPK criteria (microsomal stability and permeability assays). The data set was sparse with 10-70% missing data rates. **No molecule in the initial data set was meeting simultaneously the 11 objectives of the project:** 6 active molecules were meeting a maximum of 9 objectives.

Presence of a 1,2-benzoxazole moiety which appears in 61% of cases in the whole dataset and in 78% of the last 50 molecules.



Best compound in the initial dataset
9 objectives out of 11 (Active 9/11)

48 molecules out of 880 had been measured against all the objectives. **In average those molecules reached 6.4 objectives.**

2 QSAR models development

All data were binned according to the project TPP (1=In, 0=Out). QSAR models were developed for all 11 objectives, using logistic regression models or ensemble models on morganFP with a random split (80/20). Probability thresholds to predict 1 were selected in cross validation on the train set to maximize precision to the detriment of accuracy and recall, in order to reduce the risk of false positives.

Activity	Pred 0	Pred 1
Measured 0	22	0
Measured 1	23	3
Precision		100%
Recall		12%

5-HT2A	Pred 0	Pred 1
Measured 0	31	0
Measured 1	4	1
Precision		100%
Recall		20%

5-HT2B	Pred 0	Pred 1
Measured 0	21	3
Measured 1	3	6
Precision		67%
Recall		67%

a1	Pred 0	Pred 1
Measured 0	38	0
Measured 1	7	1
Precision		100%
Recall		13%

D1	Pred 0	Pred 1
Measured 0	21	0
Measured 1	1	14
Precision		100%
Recall		93%

Na_V 1.2	Pred 0	Pred 1
Measured 0	19	2
Measured 1	8	12
Precision		86%
Recall		60%

hERG	Pred 0	Pred 1
Measured 0	63	1
Measured 1	17	6
Precision		86%
Recall		26%

RLM	Pred 0	Pred 1
Measured 0	75	2
Measured 1	24	46
Precision		96%
Recall		66%

HLM	Pred 0	Pred 1
Measured 0	105	3
Measured 1	30	9
Precision		75%
Recall		23%

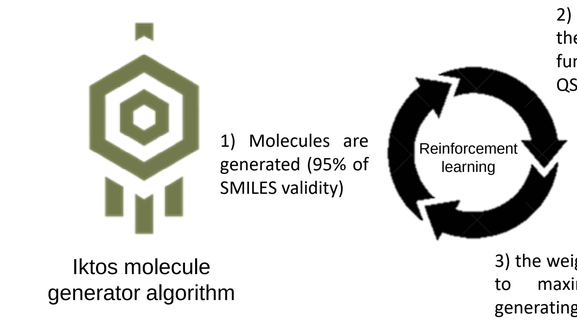
Caco-2 FAbs	Pred 0	Pred 1
Measured 0	69	0
Measured 1	65	7
Precision		100%
Recall		10%

Caco-2 Efflux	Pred 0	Pred 1
Measured 0	34	2
Measured 1	48	40
Precision		95%
Recall		45%

On average, the QSAR predictive models performed well with high precision in the test sets, except for 5-HT2B (precision 67%). Interpretability of the results was difficult for Activity, Alpha and 5-HT2A due to the small number of positive compounds in the test set.

3 Iktos molecule generator

Iktos molecule generator, a proprietary algorithm using deep learning LSTM generative models with reinforcement learning inspired by similar architecture (ref 9), was then used to design virtual molecules fulfilling all 11 objectives according to a proprietary multi-objective fitness function built from the predictive QSAR models, as described in the adjacent figure. In the reinforcement learning setting, the molecule generator is the policy and the multi-objective function is the reward. It is optimised using a policy gradient algorithm adjusting the weights of the LSTM towards regions of high rewards in the chemical space.



Iktos molecule generator algorithm

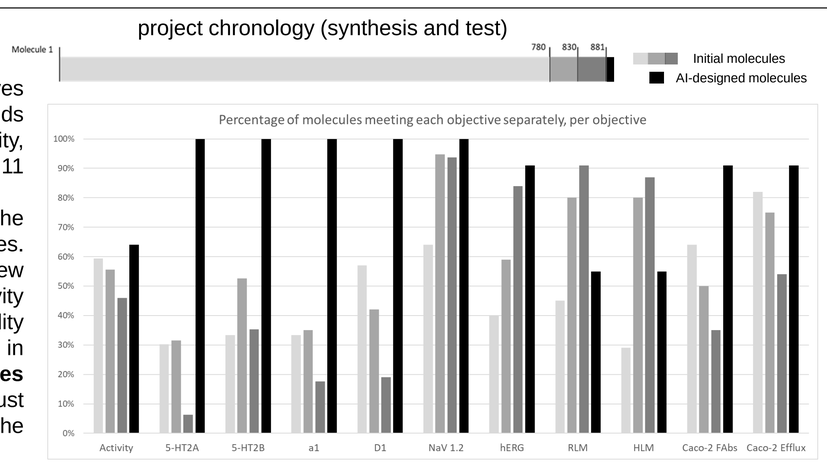
A. Illustration of the reinforcement taking place at each iteration of the algorithm

B. Visualization of the convergence of the model towards molecules maximizing the individual scores on each QSAR models (x axis: nb of iterations; y axis: average score of the molecules generated on each QSAR model)

4 Results

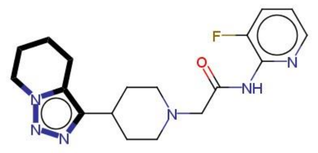
150 virtual compounds predicted to meet all 11 objectives simultaneously were proposed by Iktos algorithm. 20 compounds were selected based on synthetic accessibility, structural diversity, and score confidence. For 9 molecules the synthesis failed so 11 compounds were finally tested.

For most of the objectives, the new molecules outperformed the molecules of the initial dataset, including the 50 most recent ones. The average number of objectives hit was 9.5 for the new molecules vs. 6.4 previously. Hit rate was >90% for all selectivity and permeability targets and 65% for activity. Metabolic Stability however was decreased with a 55% hit rate. More importantly, in the 11 new compounds, **1 met simultaneously all 11 objectives of the project**, and 2 were good on 10/11 objectives, and just below the required threshold, within the margin of error of the assay, on the missed objective.



Objectives	Activity	5-HT2A	5-HT2B	α1	D1	Na_V 1.2	hERG	RLM	HLM	Caco-2 FAbs	Caco-2 Efflux
Best AI designed compound	83	7	18	7	-9	2	3	57	75	97	7

Presence of a [1,2,3]triazolo[1,5-a]pyridine moiety which appears 6 times in the initial dataset.

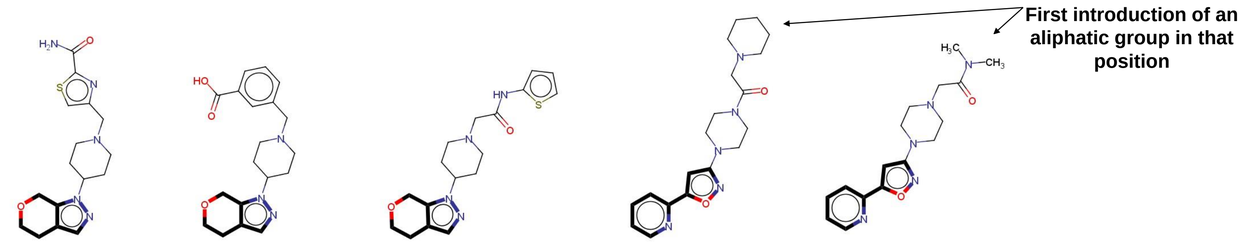


The 11 AI designed molecules were measured against all the objectives. **In average those molecules were found to reach 9.5/11 objectives in average.**

Best AI designed compound, active and meeting 11 objectives out of 11 (Active 11/11)

5 Analysis

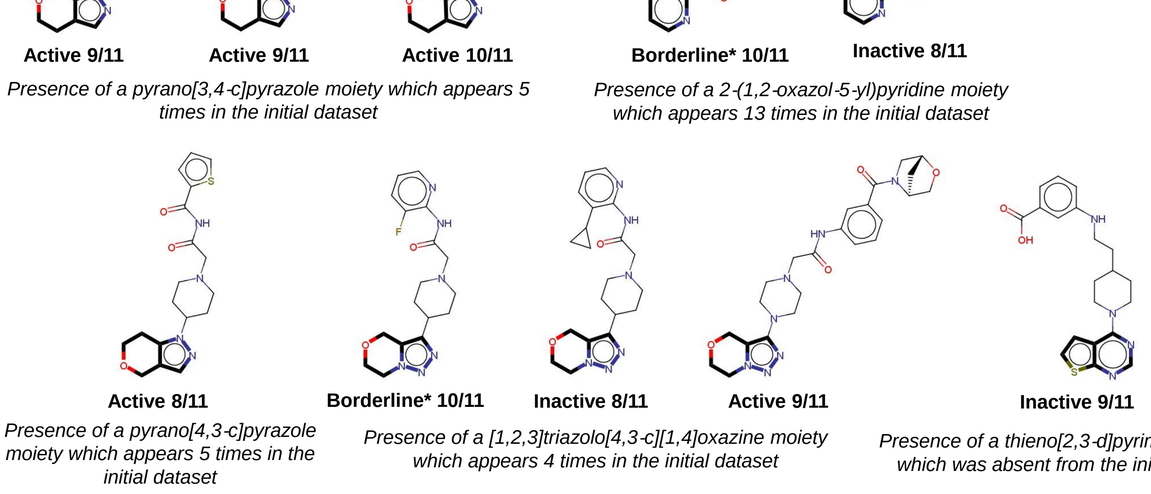
As shown below, the 11 compounds generated by the AI algorithm displayed functional groups that were rare in the initial dataset or that were never tried before in the project, showing the ability to identify favorable modifications with few data and to propose successful innovations, including introducing an aliphatic group at a place where only aromatic moieties had been tried before.



Active 9/11 | **Active 9/11** | **Active 10/11** | **Borderline* 10/11** | **Inactive 8/11**

Presence of a pyrano[3,4-c]pyrazole moiety which appears 5 times in the initial dataset

Presence of a 2-(1,2-oxazol-5-yl)pyridine moiety which appears 13 times in the initial dataset

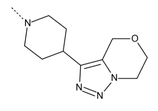


Active 8/11 | **Borderline* 10/11** | **Inactive 8/11** | **Active 9/11** | **Inactive 9/11**

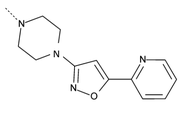
Presence of a pyrano[4,3-c]pyrazole moiety which appears 5 times in the initial dataset

Presence of a [1,2,3]triazolo[4,3-c][1,4]oxazine moiety which appears 4 times in the initial dataset

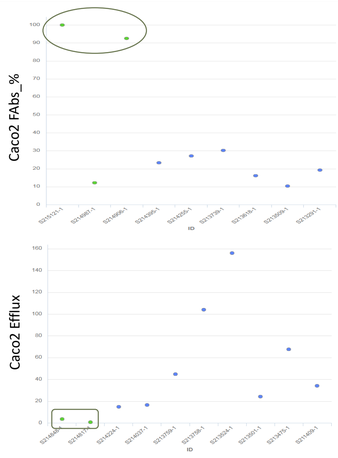
Presence of a thieno[2,3-d]pyrimidine moiety which was absent from the initial dataset

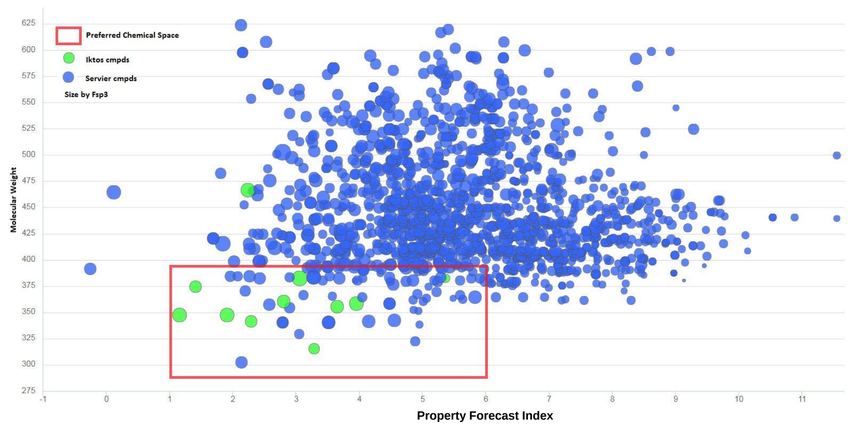


The AI algorithm was able to identify the only permeable compounds within the 6,7-dihydro-4H-triazolo[5,1-c][1,4]oxazine series while maintaining safety and stability



The AI algorithm was able to identify compounds with reduced efflux within the pyridoisoxazole series while maintaining safety and stability





Most of the 11 compounds generated by the AI algorithm were situated in a favorable chemical space regarding Molecular Weight, Property Forecast Index (Ref 10) and the fraction of sp3 carbon atoms.

* In the margin error of the Activity assay

6 Conclusion

Using a large dataset of 880 molecules, Iktos DL-based de novo design algorithm was able to identify 150 virtual compounds meeting the project TPP in silico. The hit rate of the 11 compounds tested was impressive compared to the previous molecules and 3 of those 11 compounds were found to be "in" the TPP (2 being slightly below the limit on 1 objective out of 11). The algorithm was able to suggest functional groups that were rare or absent in the initial dataset and that proved very beneficial for the MPO.

To our knowledge, this is the first report of a successful application of deep learning for de novo design to solve an MPO issue in an actual drug discovery project, moreover on a large number of objectives. This is a demonstration of the potential of this technology to bring substantial improvements to medicinal chemistry. The use of such approach in the earlier phases (hit to lead, early LO) is under investigation. Improvement needs have been identified and are being addressed regarding increasing the synthetic accessibility and diversity of the suggested structures.

1) Firth N.C. et al. MOARF, an Integrated Workflow for Multiobjective Optimization: Implementation, Synthesis, and Biological Evaluation. *J. Chem. Inf. Model*. **2015**; 2) Nicolaou, C. A., Brown, N. Multi-Objective Optimization Methods in Drug Design. *Drug Disc. Today Technol*. **2013**; Brown, N., McKay, B., Gilardoni, F., Gasteiger, J. A Graph-Based Genetic Algorithm and its Application to the Multiobjective Evolution of Median Molecules. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1079−1087; 3) Ertl, P., Lewis, R. IADE: a System for Intelligent Automatic Design of Bioisosteric Analogs. *J. Comput.-Aided Mol. Des.* **2012**, *26*, 1207−1215; 4) Ertl, P., Lewis, R. Evaluation of a Semi-Automated Workflow for Fragment Growing. *J. Chem. Inf. Model*. **2015**, *55*, 180−193; 5) Segall, M. D. Multi-Parameter Optimization: Identifying High Quality Compounds With a Balance of Properties. *Curr. Drug Metab*. **2012**, *18*, 1292−1310; 6) Nicolaou, C. A., Joannis, A., Costas, S. P. de novo Drug Design Using Multiobjective Evolutionary Graphs. *J. Chem. Inf. Model*. **2009**, *49*, 295−307; 7) Van der Horst, E.,Marqués-Gallego, P.,Mulder-Krieger, T., van Veldhoven, J., Kruisselbrink, J., Aleman, A., Emmerich, M. T. M., Brussee, J., Bender, A., IJzerman, A. P. Multi-Objective Evolutionary Design of Adenosine Receptor Ligands. *J. Chem. Inf. Model.* **2012**, *52*, 1713−1721; 8) Chen, H. et al. The rise of deep learning in drug discovery *Drug Disc. Today* **2018**; 9) Segler, M.H.S., Kogej, T., Tyrchan, C., Waller M.P. Generating Focussed Molecule Libraries for Drug Discovery with Recurrent Neural Networks. *ACS Cent Sci.* **2018,** *4(1)*, 120–131. 10) Robert J. Young, Darren V.S. Green, Christopher N. Luscombe and Alan P. Hill, *Drug Discovery Today,* **2011**,16, 17/18, 822-830.