[P11]Application of automated machine learning in search for multi-target-directed ligands blocking PDE4B, PDE8A and TRPA1 ion channel with potential use in the treatment of asthma and COPD

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Asthma and COPD are characterized by complex pathophysiology associated with chronic inflammation, bronchoconstriction, and bronchial hyperresponsiveness resulting in airway remodeling. The currently available therapeutic strategies do not address all of the most important pathological processes in the course of both diseases. Therefore, it is an urgent need to work out comprehensive solutions that fully affect the pathological processes of both diseases. As a possible solution for the enhanced treatment of asthma and COPD, we propose the rationally designed multi-target-directed ligands (MTDLs), combining PDE4B and PDE8A inhibition with TRPA1 ion channel blockade. This approach allows forobtaining synergistic bronchodilatory, anti-inflammatory, and additional anti-remodeling activity.

The aim of the study is to develop AutoML models to search for MTDL blocking PDE4B, PDE8A and TRPA1, which will allow the selection of novel MTDL chemotypes.

Using "mljar-supervised" - Automated Machine Learning Python package [1], there were regression models developed for each of the biological targets (PDE4B, PDE8A, TRPA1). For this purpose, libraries of inhibitors derived from CHEMBL database and collected from scientific articles were used. Each inhibitor was represented by a set of calculated molecular descriptors (PADEL software) and IC_{50} values. Ensemble systems combining various modeling tools like artificial neural networks, decision trees and i.e. XGBoost were found as the best models for each of the biological targets. On their basis, virtual screenings of commercially available compounds derived from the ZINC15 database, were performed. A common group of compounds placed within the top results were selected as potential novel chemotypes of multifunctional ligands.

Further studies, carried out after the purchase of selected compounds, will be focused on in vitro activity tests providing reliable results to aid the discovery of MTDLs blocking PDE4B, PDE8A and TRPA1.

The study was financially supported by the National Science Centre, Poland (grant no. 2020/37/N/NZ7/02365). Calculations were performed partially with use of computers co-financed by the qLIFE Priority Research Area under the program "Excellence Initiative Research University" at Jagiellonian University and Polish Operating Programme for Intelligent Development POIR4.2 project no. POIR.04.02.00-00-D023/20.

Bibliography :

[1] Aleksandra Płońska and Piotr Płoński ; MLJAR: State-of-the-art Automated Machine Learning Framework for Tabular Data. Version 0.10.3 ; 2021; https://github.com/mljar/mljar-supervised

APPLICATION OF AUTOMATED MACHINE LEARNING IN SEARCH FOR MULTI-TARGET-DIRECTED LIGANDS BLOCKING PDE4B, PDE8A AND TRPA1 ION CHANNEL WITH POTENTIAL USE IN THE TREATMENT OF ASTHMA AND COPD

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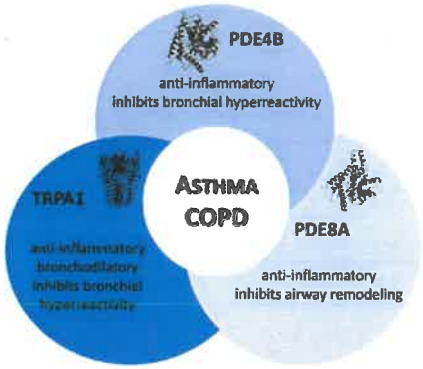
INTRODUCTION

Chronic respiratory diseases constitute a serious and challenging problem facing modern science. 650 million people suffer from chronic obstructive pulmonary disease (COPD) worldwide and over 330 million contend with asthma (1). Additionally, both diseases are the third- and fourth-largest cause of deaths in the world population (2).

Asthma and COPD are characterized by complex pathophysiology associated with chronic inflammation, bronchoconstriction, and bronchial hyperresponsiveness resulting in airway remodeling.

The currently available therapeutic strategies do not address all of the most important pathological processes in the course of both diseases. **Therefore, it is an urgent need to work out comprehensive solutions that fully affect the pathological processes of both diseases.**



As a possible solution for the enhanced treatment of asthma and COPD, we propose the rationally designed **multi-target-directed ligands (MTDLs), combining PDE4B and PDE8A inhibition with TRPA1 ion channel blockade.** This approach allows for obtaining synergistic bronchodilatory, anti-inflammatory, and additional anti-remodeling activity.

AIM OF THE STUDY

The aim of the study is to develop AutoML models to search for multi-target-directed ligands blocking PDE4B, PDE8A and TRPA1, which will allow the selection of novel MTDL chemotypes.

RESULTS

Using "mljar-supervised" - Automated Machine Learning Python package (3), there were regression models developed for each of the biological targets (PDE4B, PDE8A, TRPA1). For this purpose, libraries of inhibitors derived from CHEMBL database and collected from scientific articles and patents were used. Each inhibitor was represented by a set of calculated molecular descriptors (PaDEL software) and pIC_{50} values. Ensemble systems combining various modeling tools like artificial neural networks, decision trees and i.e. XGBoost were found as the best models for each of the biological targets. On their basis, virtual screenings of commercially available compounds derived from the ZINC15 database, were performed. Based on the combined ranking of top active compounds from each biological target a common group of compounds was selected as potential novel chemotypes for multifunctional ligands.

TRPA1

455 active and 139 inactive TRPA1 antagonists represented by 1444 PaDEL 2D descriptors and pIC_{50} values

„mljar-supervised" Automated Machine Learning Python package

mljar

R^2	0.6457
RMSE	0.6646
NRMSE	16.02%

PDE4B

1705 active and 54 inactive PDE4B inhibitors represented by 1444 PaDEL 2D descriptors and pIC_{50} values

„mljar-supervised" Automated Machine Learning Python package

mljar

R^2	0.8571
RMSE	0.6059
NRMSE	9.93%

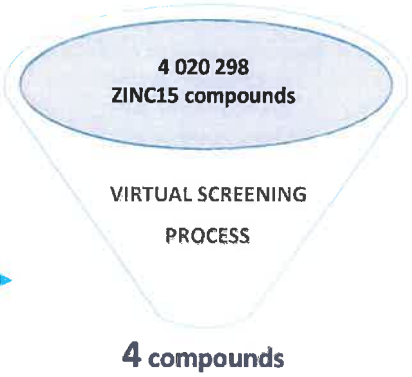
PDE8A

83 active and 86 inactive PDE8A inhibitors represented by 1444 PaDEL 2D descriptors and pIC_{50} values

„mljar-supervised" Automated Machine Learning Python package

mljar

R^2	0.8737
RMSE	0.3415
NRMSE	8.28%



4 compounds

with the highest predicted PDE4B/PDE8A/TRPA1 inhibitory activity

	TRPA1 pIC_{50}	PDE4B pIC_{50}	PDE8A pIC_{50}
ZINC000186997245	5.6321	5.3937	5.5871
ZINC000007826462	5.4722	5.7422	5.3079
ZINC001875259283	5.9901	6.5273	5.3351
ZINC000263618997	**6.2079**	**6.5813**	**5.5365**

CONCLUSION

The developed empirical models allowed to select the most promising MTDLs blocking PDE4B/PDE8A/TRPA1. The obtained models limited the number of the most important descriptors for each prediction, and indicated 240 common descriptors for the three biological targets.

Further studies, carried out after the purchase of selected compounds, will be focused on *in vitro* activity tests providing reliable results to aid the discovery of MTDLs blocking PDE4B, PDE8A and TRPA1.

Literature:

1) Ferrante, G.; La Grutta, S. The Burden of Pediatric Asthma. Frontiers in Pediatrics 2018, 6.
2) Masoli, M.et al., Global Initiative for Asthma (GINA) Program. The Global Burden of Asthma: Executive Summary of the GINA Dissemination Committee Report. Allergy 2004, 59 (5), 469–478. https://doi.org/10.1111/j.1398-9995.2004.00526.x.
3) Aleksandra Płońska and Piotr Płoński ; MLJAR: State-of-the-art Automated Machine Learning Framework for Tabular Data. Version 0.10.3 ; 2021 ; https://github.com/mljar/mljar-supervised

AutoML icon - image: Flaticon.com

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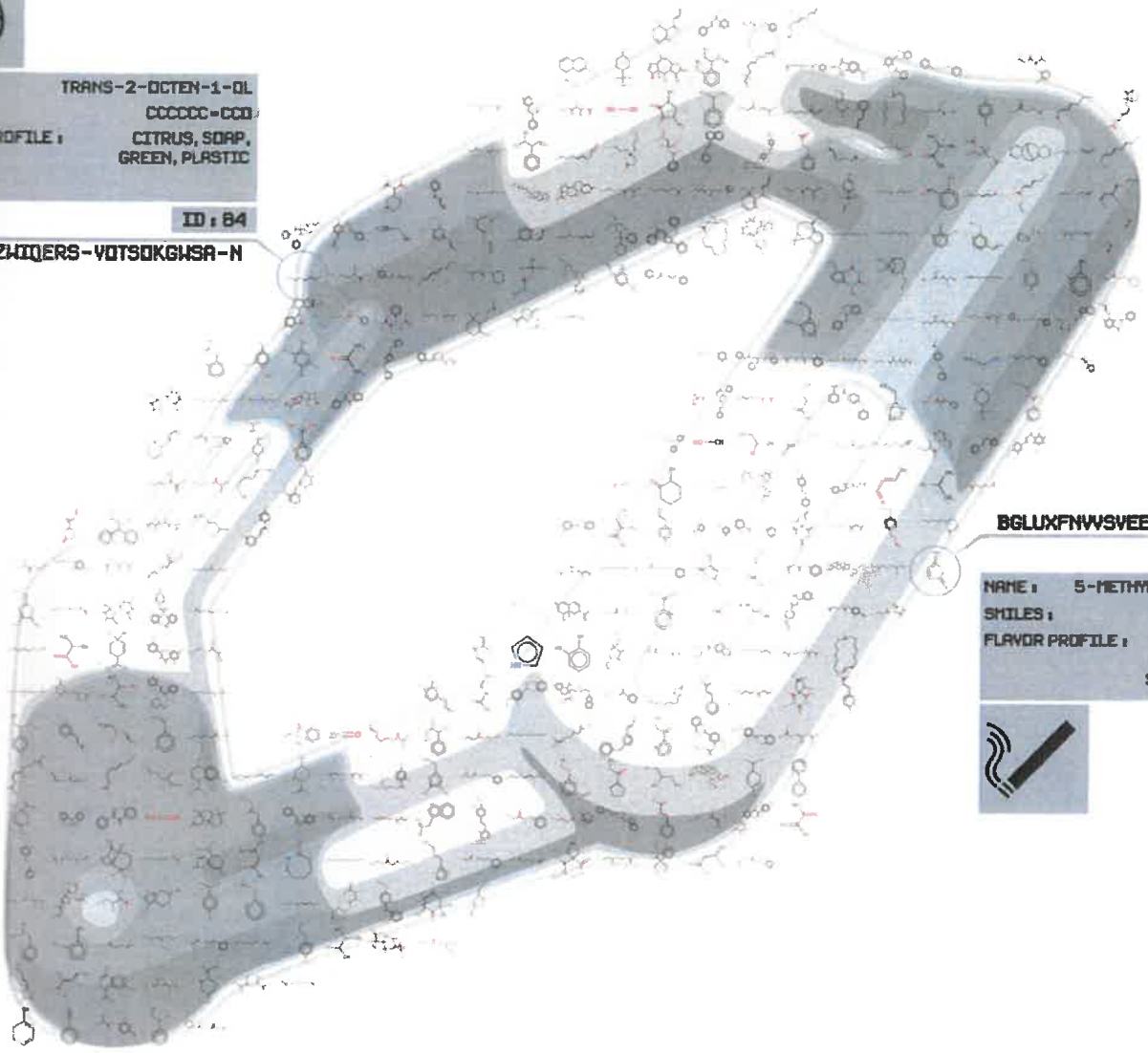
Chem'info's 3

NAME : TRANS-2-OCTEN-1-OL
SMILES : CCCCCC=CCO
FLAVOR PROFILE : CITRUS, SOAP, GREEN, PLASTIC

ID : 84

RMOMPFZWIQERS-VOTSOKGWSA-N



BGLUXFNWVSVEET-UHFFFAOYSA-N

ID : 305

NAME : 5-METHYL-2(5H)-FURANONE
SMILES : CC1C=CC(=O)O1
FLAVOR PROFILE : SOLVENT, TOBACCO, COUMARIN, OILY, SWEET, NUTTY, TONKA

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Poster session

1	AKHMETSHIN Tagir	HyFactor: Hydrogen-count labelled graph-based defactorization autoencoder
2	ASGARKHANOVA Farah	Computer-aided design of selective chemical probes of angiotensin-converting enzyme 2
3	BAYBEKOV Shamkhal	Prediction of DMSO solubility for fragment-based screening
4	BORT William	Harnessing the "creativity" of AI to generate novel chemical reactions
5	CHEN Ya	Cheminformatic Analysis of Ring Systems in Natural Products
6	CHIESA Luca	A new machine learning based method for ADRB2 agonist detection using single-ligand dynamic interaction data
7	BENKAIDALI Lydia	Visualization and analysis of metabolomic space of Alzheimer's disease using Generative topographic mapping
8	LEGEHAR Ashenafi	Drugmapper: a Web Resource to Explore Active Pharmaceutical Ingredients (Apis)
9	MERVEILLE KOSSIWA Eguida	Protein subpocket cloud comparison revealed similarity between HIV-1 reverse transcriptase and tumor necrosis factor binding sites
10	GAMBACORTA Nicola	PLATO: a user-friendly web platform for target fishing and bioactivity prediction
11	GAWALSKA Alicja	Application of automated machine learning in search for multi-target-directed ligands blocking PDE4B, PDE8A and TRPA1 ion channel with potential use in the treatment of asthma and COPD
12	GESLIN Damien	Deciphering a pharmacophore network generated from BCR-ABL data
13	LEHEMBRE Etienne	Towards DAG-based interactive pharmacophore exploration
14	IWATA Michio	Dynamic sensitivity analysis to predict time-course drug transcriptomic responses of the cellular system
15	JAMROZIK Marek	Computer-aided search for new anthracycline antibiotic reductases inhibitors with a potential to support anticancer therapy
16	JONCZYK Jakub	Molecular modelling and machine learning techniques in search for novel SARS-CoV-2 main protease inhibitors
17	KAITOH Kazuma	Scaffold-Retained Structure Generator to Extensively Produce Molecules with Unique Chemical Substructures
18	LAMANNA Giuseppe	DeLA-Drug: A Deep Learning Algorithm for Automated Design of Drug-like Analogues
19	HANDA Koichi	Prediction of Compound Plasma Concentration Time Profiles after Oral Administration in Mice Using Random Forests
20	OUDAHMANE Mehdi	Flexible Protein-Ligand Docking Protocol: a Case Study on the Androgen Receptor
21	PEREBYINIS Mariana	Assessment of the overlap between the 'on-the-shelf' drug-like space and ultra-large 'on-demand' combinatorial libraries