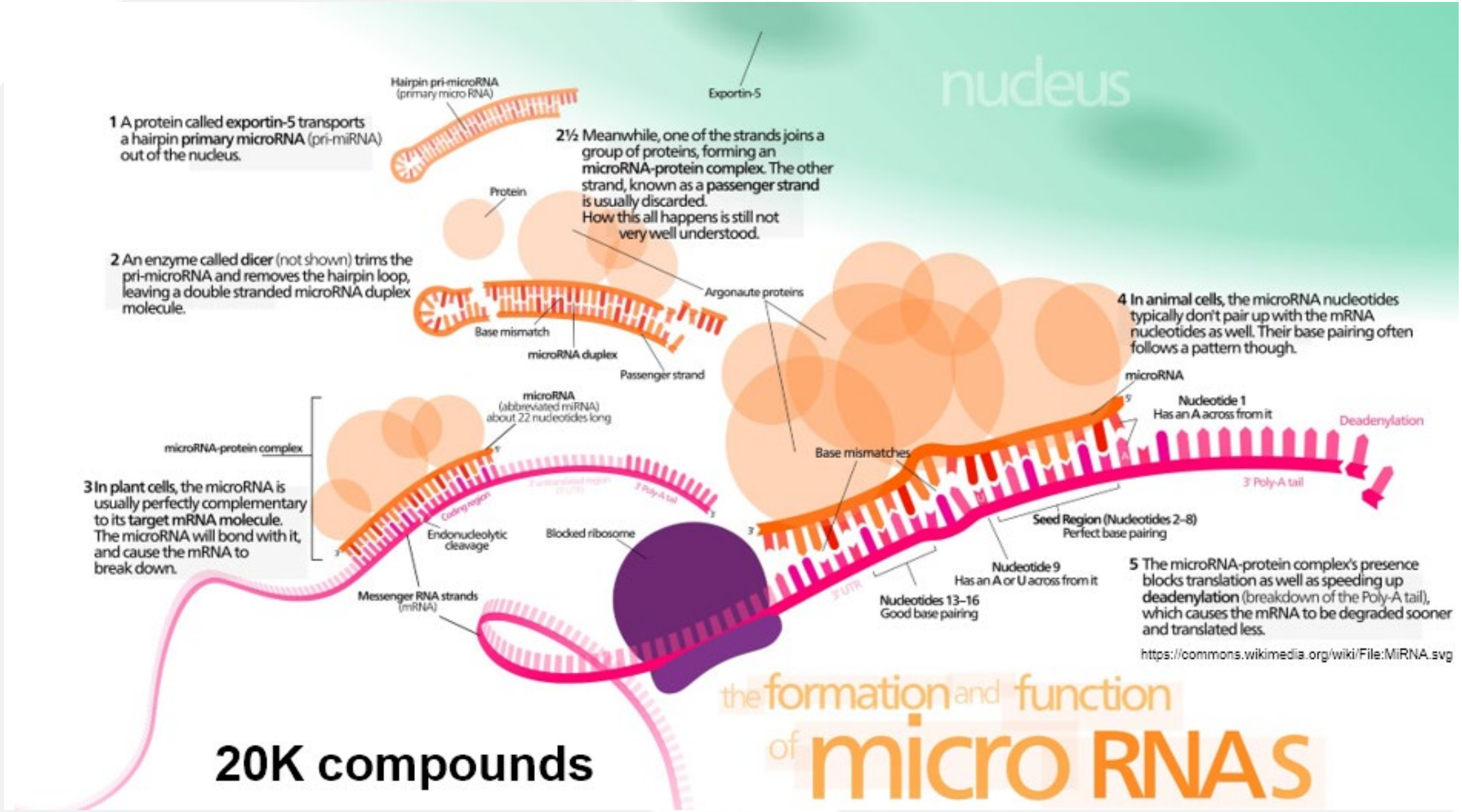


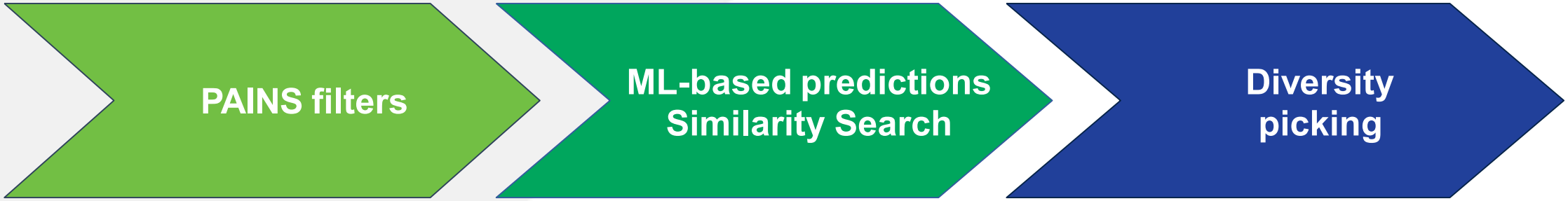
We improve the quality of life by creating new medicines

mi-RNA — New Druggable Targets

- microRNAs (miRs) are small (~18e25 nucleotides), noncoding RNAs, involved in regulation of cell division, proliferation, and death.
- miRs can have a role in a wide range of diseases including cancer, neurologic disorders, autoimmune diseases, metabolic diseases, and cardiovascular diseases.
- Since their discovery in 1993, over 2500 human mature miRs have been found; their mechanism of action and functions are focus for the ongoing research [1, 2].
- Despite the fact that numerous small molecules have been discovered over the last decade, research into miR targeted small molecules has just started. We share CheDiv's miR-targeted library in hope to help this field continue to thrive.

1. Alles J, Fehlmann T, Fischer U, Backes C, Galata V, Minet M, Hart M, Abu-Halima M, Grässer FA, Lenhof HP, Keller A, Meese E. An estimate of the total number of true human miRNAs. Nucleic Acids Res. 2019 Apr 23;47(7):3353-3364. doi: 10.1093/nar/gkz097
2. Van Meter EN, Onyango JA, Teske KA. A review of currently identified small molecule modulators of microRNA function. Eur J Med Chem. 2020 Feb 15;188:112008. doi: 10.1016/j.ejmech.2019.112008

Virtual Screening Strategy



Key steps:

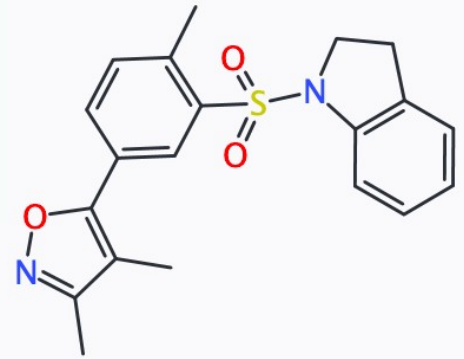
- Removal of compounds with undesirable properties:
  - Substructure filters for removal of PAINS [1].
  - Filters using non MedChem-friendly SMARTS [2].
- Virtual screening guided by Machine learning models and Similarity search:
  - Machine learning models on ECFP fingerprints built using data from ChEMBL29 database.
- Structural diversity picking (Hierarchical clustering; Min-Max algorithm [3]; Dice Similarity / ECFP2048)

1. Baell JB, Holloway GA. New substructure filters for removal of pan assay interference compounds (PAINS) from screening libraries and for their exclusion in bioassays. J Med Chem. 2010; 53(7):2719-40. doi: 10.1021/jm901137j.
2. Sushko I, Salmina E, Potemkin VA, Poda G, Tetko IV. ToxAlerts: a Web server of structural alerts for toxic chemicals and compounds with potential adverse reactions. J Chem Inf Model. 2012; 52(8):2310-6. doi: 10.1021/ci300245q.
3. Ashton, M. et. al., Quant. Struct.-Act. Relat., 21 (2002), 598-604.

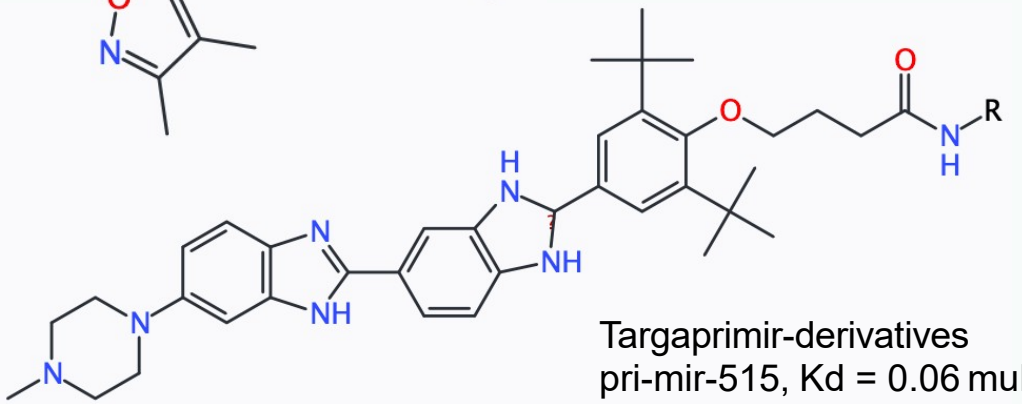
Known miR Inhibitors: similarity search

Similarity search (ECFP-Tanimoto, shape similarity) to select novel miR-modulators

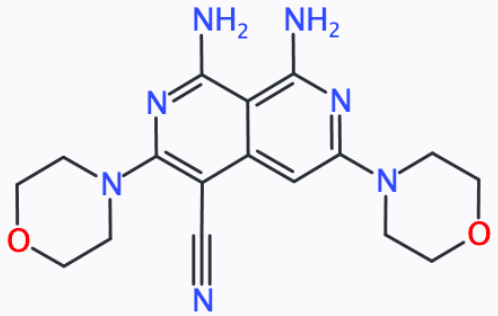
Known binders (examples)



Comp17
mir-31 inhibitor [1]

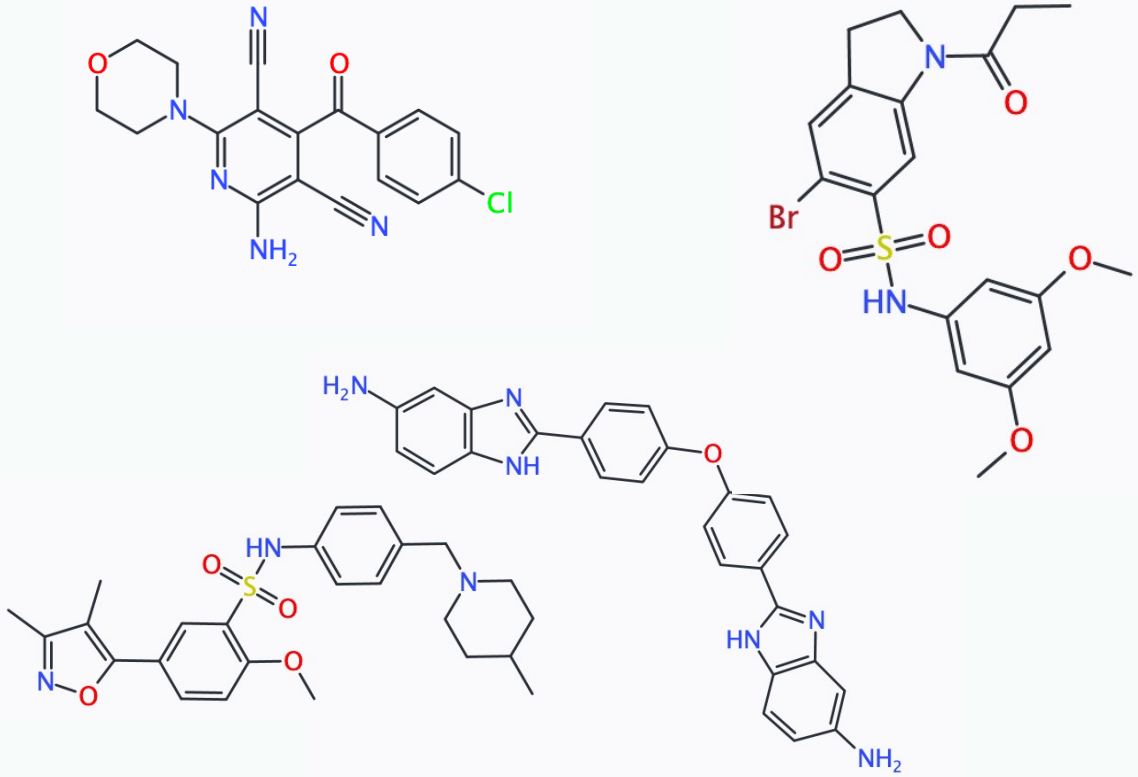


Targaprimir-derivatives
pri-mir-515, Kd = 0.06 muM



Comp35
Targets UU internal loop binding motif of miR-544 hairpin structure [2]

VS-hits (examples)



1. Im K, Song J, Han YT, Lee S, Kang S, Hwang KW, Min H, Min KH. Identification of aminosulfonylarylisoxazole as microRNA-31 regulators. PLoS One. 2017 Aug 4;12(8):e0182331.
2. Haga CL, Velagapudi SP, Strivelli JR, Yang WY, Disney MD, Phinney DG. Small Molecule Inhibition of miR-544 Biogenesis Disrupts Adaptive Responses to Hypoxia by Modulating ATM-mTOR Signaling. ACS Chem Biol. 2015 Oct 16;10(10):2267-76.

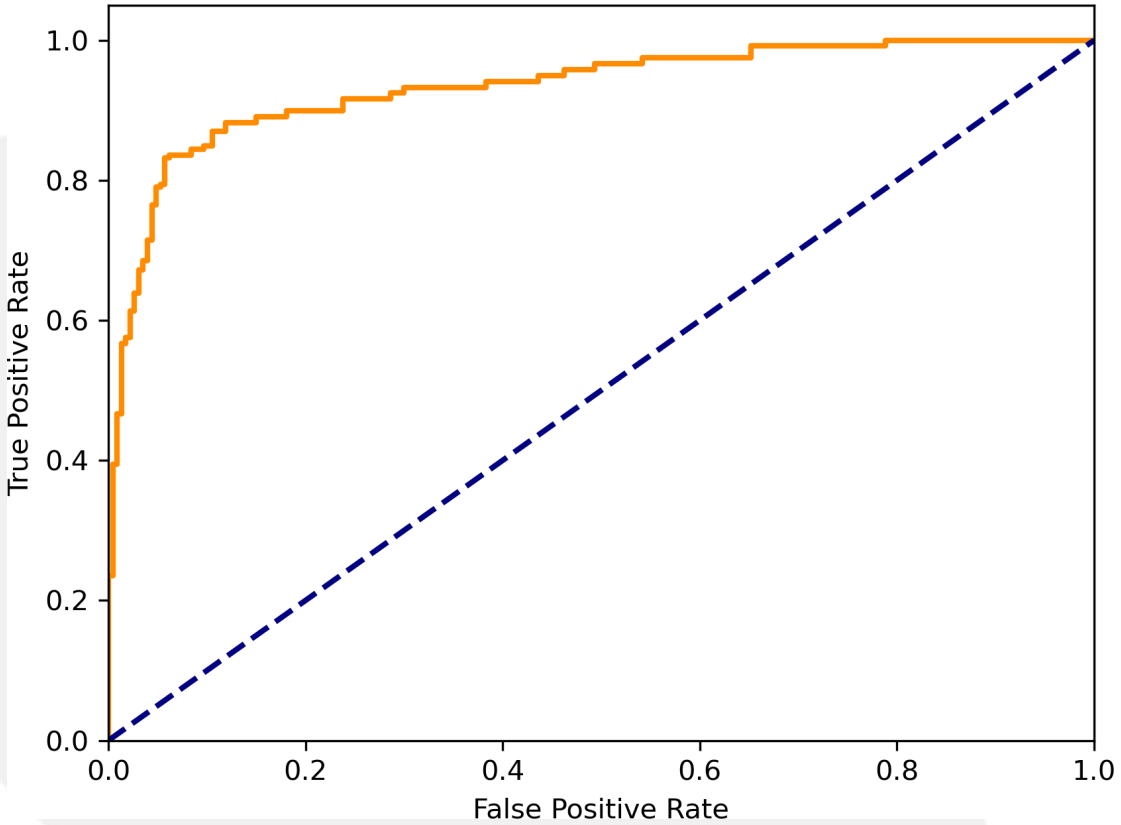
miR-21 inhibitors

Machine Learning based virtual screening to select novel miR-21 inhibitors

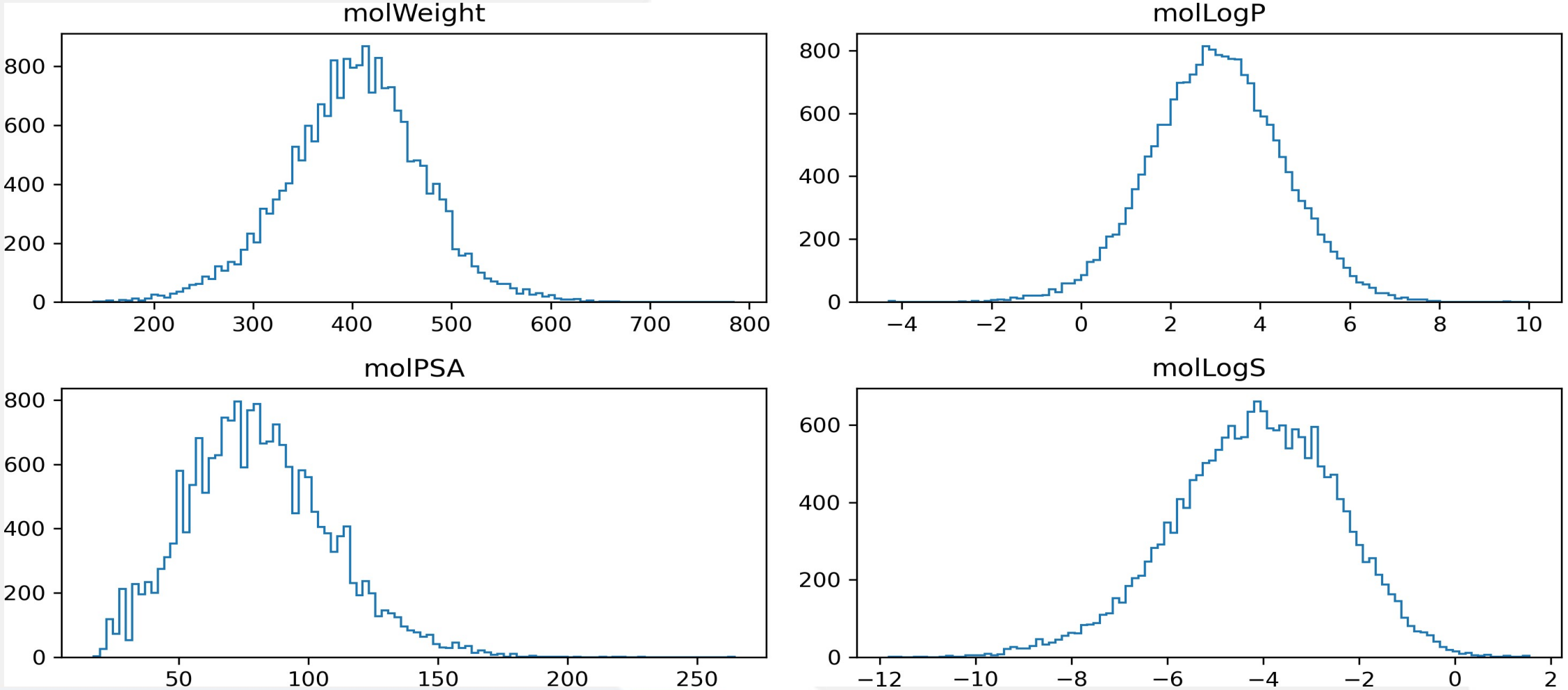
ML-models

- ChEMBL29 & PubChem: known
- miR-21 inhibitors
  PubChem BioAssay: confirmed
- inactive compounds
  XGBoost, Random Forest using ECFP2048 fingerprints
- AUC ROC on the external test set ~ 0.92

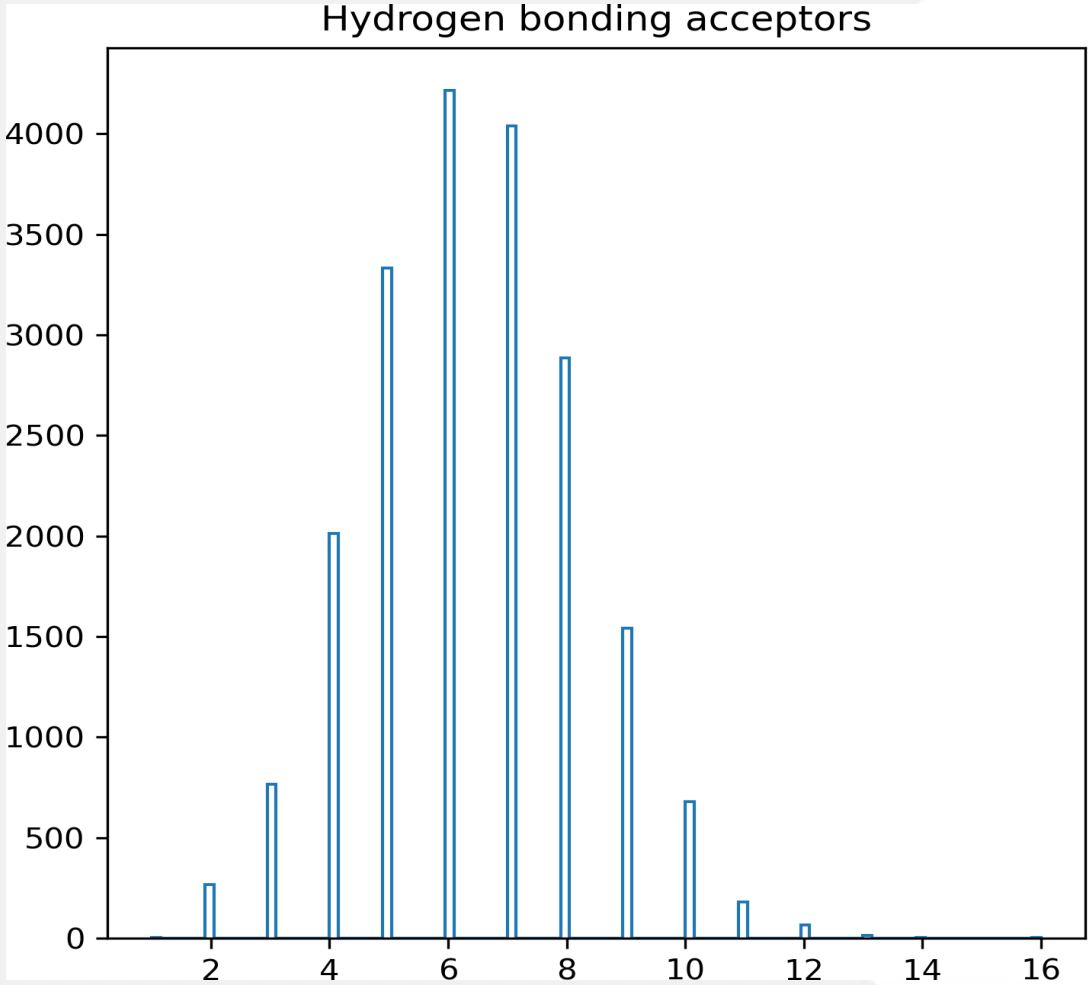
ROC-curve

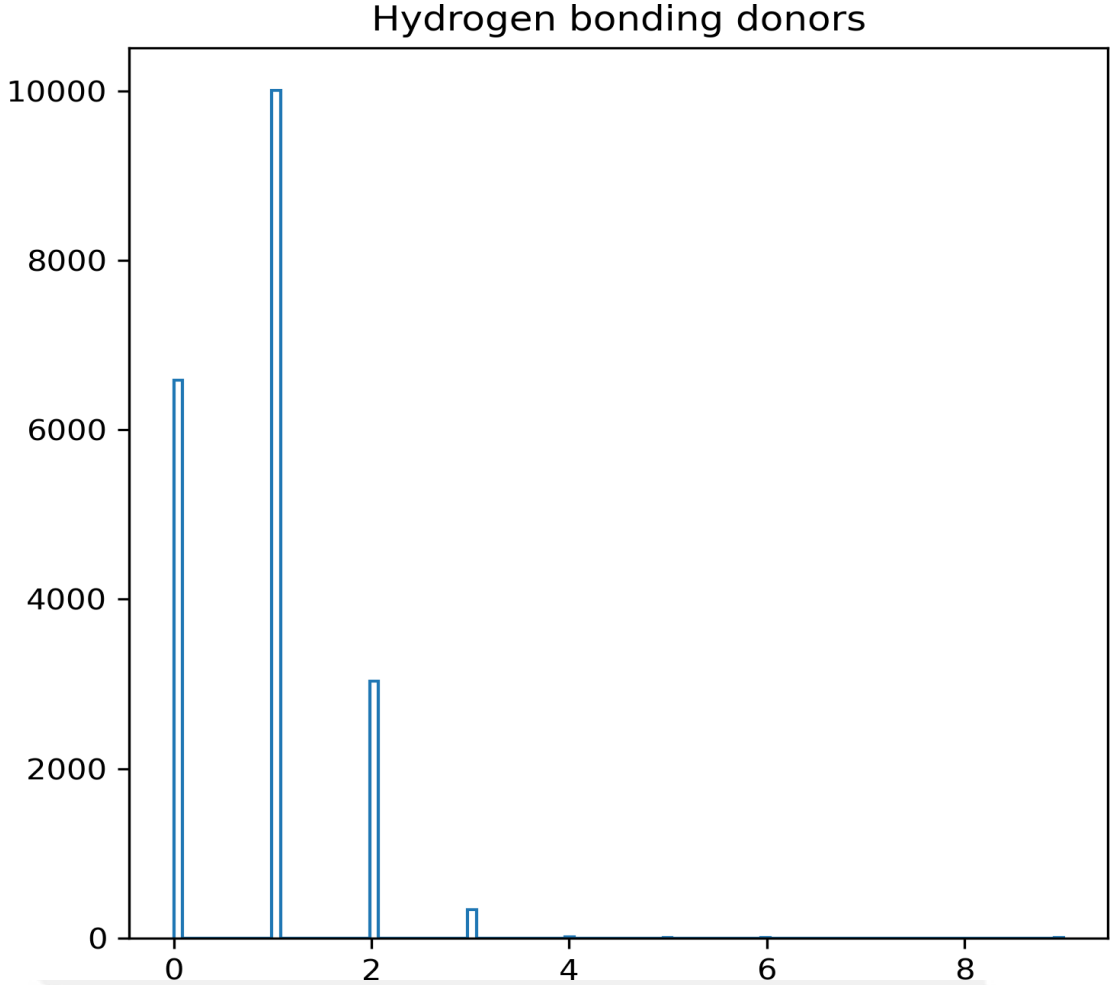


Property space of the selected 20K compounds



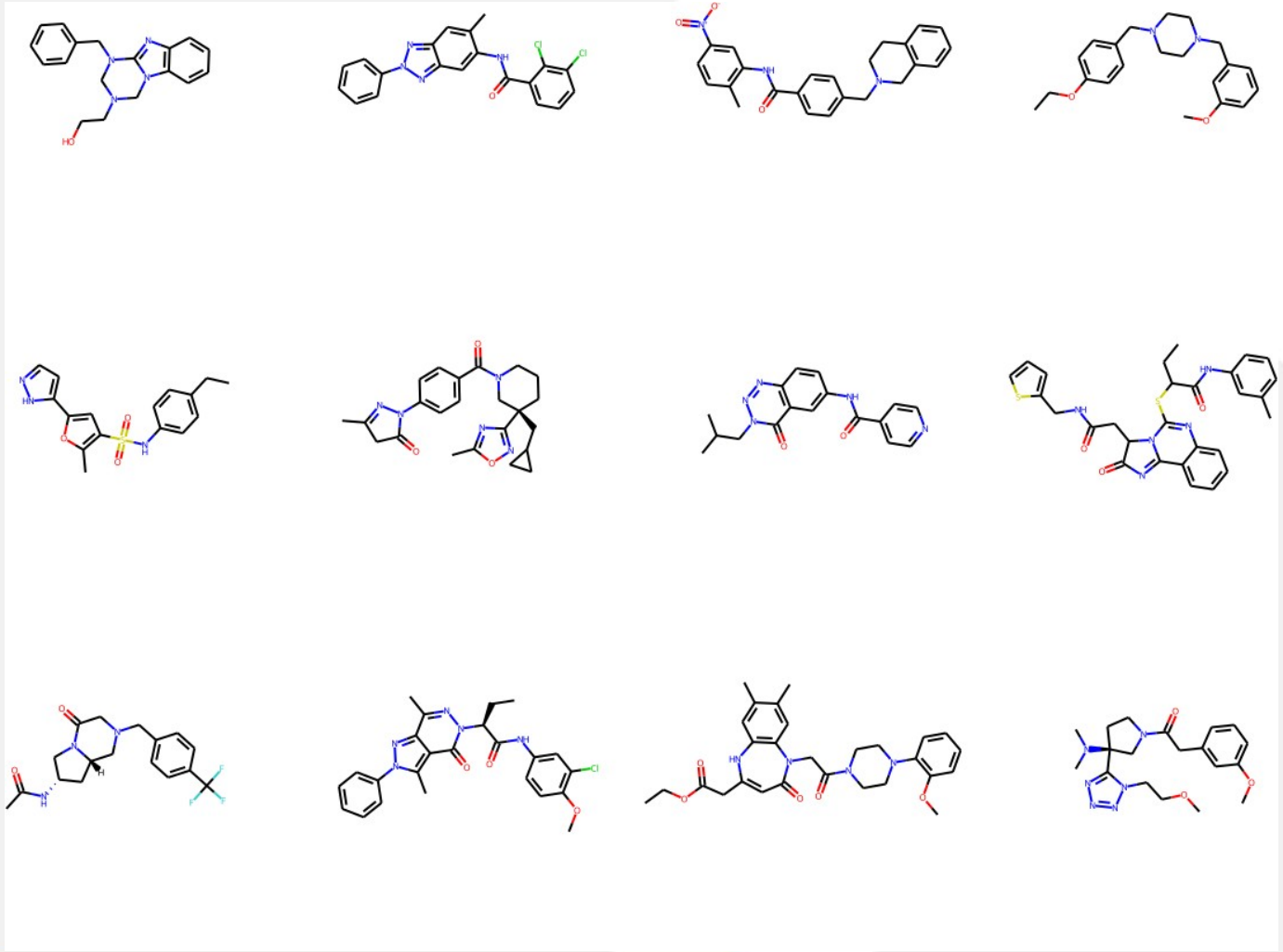
Property space of the selected 20K compounds





Virtual Screening Results – Analysis and Summary (Examples of compounds)

CHEMRAR group of companies



CHEMRAR
group of companies

Благодарим за внимание

Инструкция по заказу соединений из библиотеки «ХимРар»:

Наш сайт: https://chemrar.ru/library-full-list/

Направьте список интересующих соединений на email: vvk@chemrar.ru

В соответствии с вашим запросом менеджер выполнит подборку соединений и направит информацию о наличии. Имеется возможность сделать поиск по структуре/буквенному идентификатору (ID, CAS, MFCD), а также импортировать файл в различных форматах: SMILE, sdf, txt.