Pittfall-ridden process of designing TrmD inhibitors

4EU+ TrmD competition

Tomáš Jelínek, Marek Tobiáš, Anna Gregušová, Aneta Tranová, Tomáš Preisler

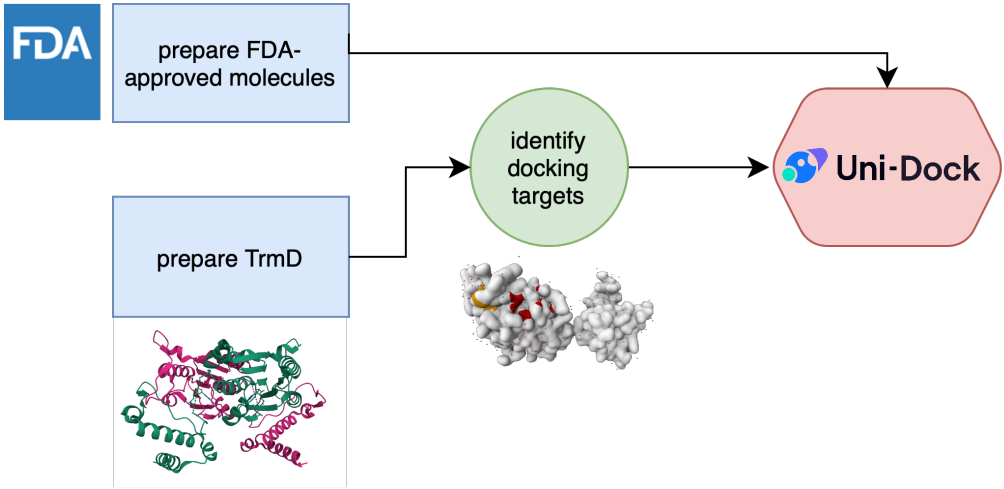
Charles University

January 25, 2025

Introduction

- Overview of the challenges encountered during the docking into TrmD.
- Objectives of the presentation:
  - FDA-approved molecules docking
  - Docking of uncommon FDA-approved molecules.
  - EvoFLOPA - why and how?.
  - Evolution-based lead optimization results.
- Relevance of TrmD as antibiotic target.

Workflow of FDA-approved molecule docking approach



Uncommon FDA-Approved molecules

1 Hydrotalcite

- ID: CHEMBL3833351
- Max Phase: Approved
- Molecular Formula: CH24Al2Mg6O23
- Molecular Weight: 603.97
- Vinardo score: ≈16 kcal/mol

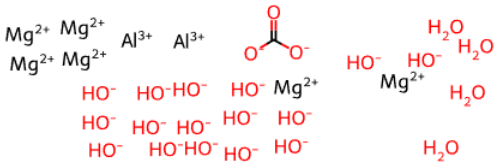


Figure 1: Hydrotalcite - structure from ChEMBL

Docking of wierd molecules

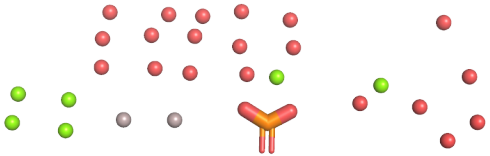


Figure 2: Hydrotalcite ChEMBL's SDF file visualized in PyMOL

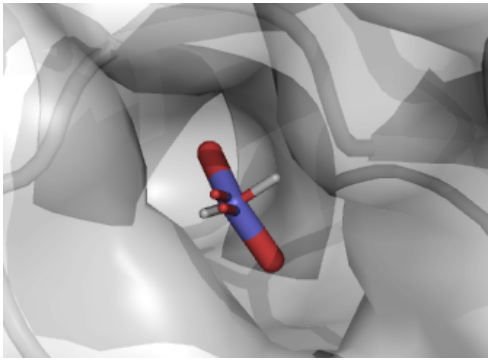


Figure 3: Hydrotalcite docket into trmD AdoMet pocket - completely wrong

No need to start from zero

TrmD as a potential antibiotic target has attracted the interest of several people

- Vlasov et al. [2022] have designed novel 4-methylthienopyrimidines and validated them in vitro.
- Wilkinson et al. [2023] have created and also validated in vitro nicotineamide analogs and have reached single-digit nM IC_{50}.
- Zhong et al. [2019] have screened circa hundred thousand compounds and found pyridine-pyrazole-piperidine molecules with strong binding

No need to start from zero

- Advantages of stealing
  - One can avoid long process of virtual screening of random compounds
  - Molecules presented in papers are not patented, so why not use them...
- So lets start with existing mols and optimize!
- Where to start? Read a nice review! Pang et al. [2024], Hu et al. [2023]

What algorithm to chose?

There are already many great options to use for molecular optimization, so we have decided to create a new one from scratch...

Figure 4: 100% logical thing to do

EvoFLOPA
Evolutionary Fast Lead Optimization Algorithm

- EvoFLOPA uses k-beam simulated annealing to improve lead molecules using mutations and breeding.
- Uses SELFIES [Nigam et al., 2021] as molecular representation.
  - It is basically SMILES 2.0

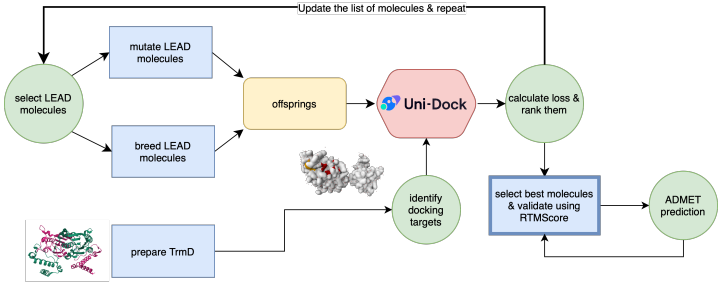


Figure 5: EvoFLOPA workflow

EvoFLOPA found something, is it good?

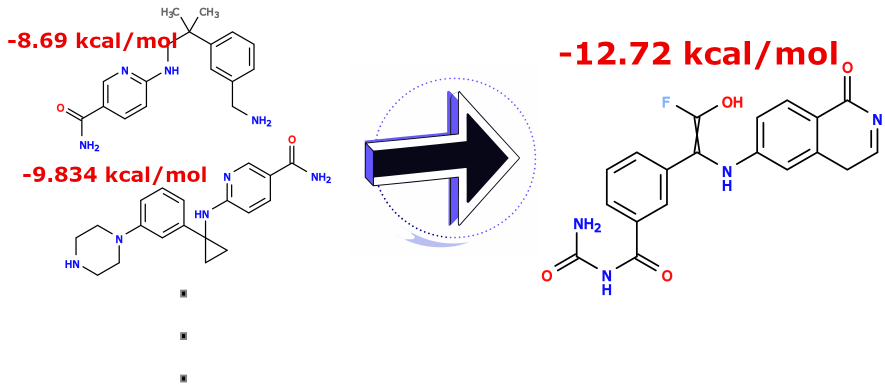


Figure 6: Compound YF found by EvoFLOPA

VINA sucks
So what to do?

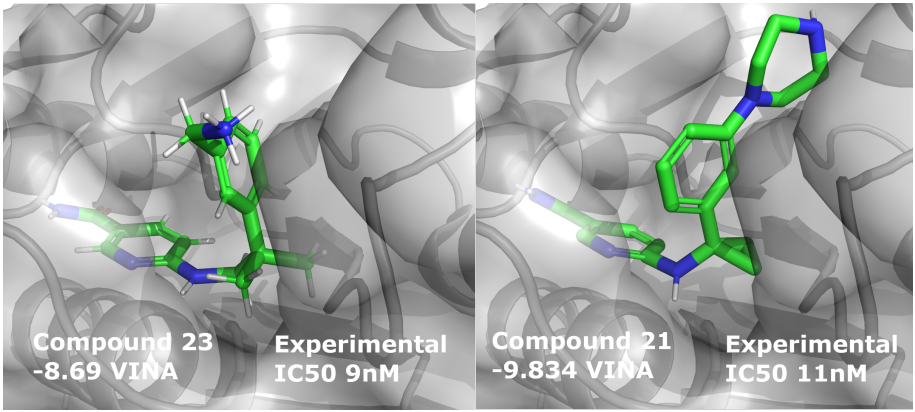


Figure 7: VINA doesn't match wet lab results

RTMScore to the rescue

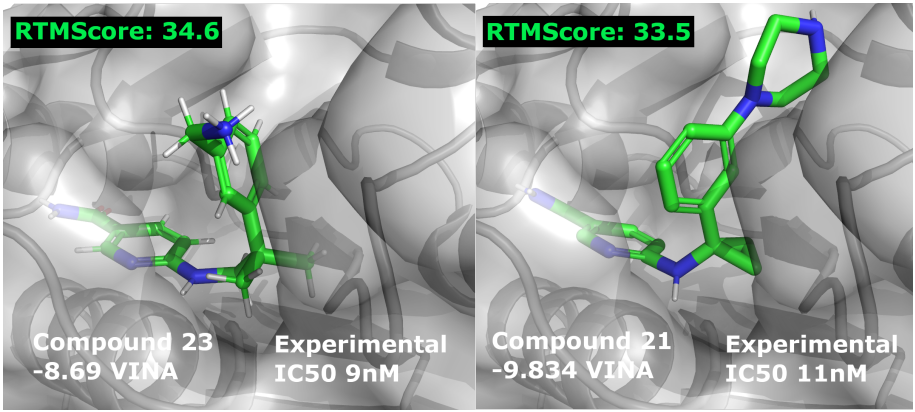


Figure 8: RTMScore matches

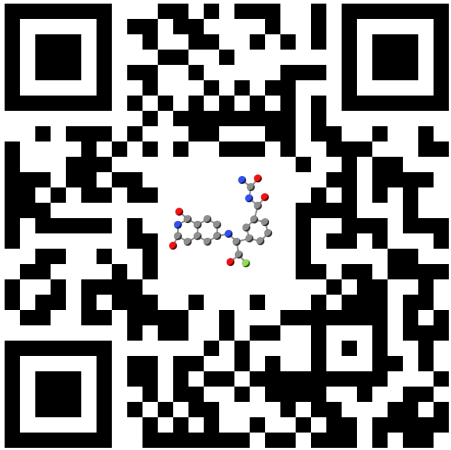
Mols overview

Ligand Name	Vina Score	QED	SA Score	RTMScore
Adomet	-8.69	0.29	4.74	27.6
Compound 23	-8.61	0.76	2.30	34.57
Compound Y	-13.10	0.62	3.01	38.6
Compound YF	-12.72	0.60	3.06	42.8
Compound YOH	-13.06	0.51	3.06	40.2
Ravicti	-13.50	0.16	3.16	32.2

Table 1: Comparison of Ligands Based on Various Scores

Results

Come visit our poster!



Reference I

Wenhao Hu, Yingying Liu, Xuanyu Chen, Wenhao Chai, Hangyue Chen, Hongwei Wang, and Gaoang Wang. Deep learning methods for small molecule drug discovery: A survey. (arXiv:2303.00313), March 2023. doi: 10.48550/arXiv.2303.00313. URL http://arxiv.org/abs/2303.00313. arXiv:2303.00313 [cs].

AkshatKumar Nigam, Robert Pollice, Mario Krenn, Gabriel Dos Passos Gomes, and Alán Aspuru-Guzik. Beyond generative models: superfast traversal, optimization, novelty, exploration and discovery (stoned) algorithm for molecules using selfies. *Chemical Science*, 12(20):7079–7090, 2021. ISSN 2041-6520, 2041-6539. doi: 10.1039/D1SC00231G.

Chao Pang, Jianbo Qiao, Xiangxiang Zeng, Quan Zou, and Leyi Wei. Deep generative models in de novo drug molecule generation. *Journal of Chemical Information and Modeling*, 64(7): 2174–2194, April 2024. ISSN 1549-9596, 1549-960X. doi: 10.1021/acs.jcim.3c01496.

Sergiy Vlasov, Konstantin Krolenko, Hanna Severina, Olena Vlasova, Oleksandr Borysov, Pavlo Shynkarenko, Vitaliy Vlasov, and Victoriya Georgiyants. Novel 4-methylthienopyrimidines as antimicrobial agents: synthesis, docking study and in vitro evaluation. *Journal of Applied Pharmaceutical Science*, 2022. ISSN 2231-3354. doi: 10.7324/japs.2023.102631. URL http://dx.doi.org/10.7324/japs.2023.102631.

Reference II

Andrew J. Wilkinson, Nicola Ooi, Jonathan Finlayson, Victoria E. Lee, David Lyth, Kathryn S. Maskew, Rebecca Newman, David Orr, Keith Ansell, Kristian Birchall, Peter Canning, Peter Coombs, Lucia Fusani, Ed McIver, João Pisco, Philip M. Ireland, Christopher Jenkins, Isobel H. Norville, Stephanie J. Southern, Richard Cowan, Gareth Hall, Catherine Kettleborough, Victoria J. Savage, and Ian R. Cooper. Evaluating the druggability of trmd, a potential antibacterial target, through design and microbiological profiling of a series of potent trmd inhibitors. *Bioorganic amp; Medicinal Chemistry Letters*, 90:129331, June 2023. ISSN 0960-894X. doi: 10.1016/j.bmcl.2023.129331. URL http://dx.doi.org/10.1016/j.bmcl.2023.129331.

Wenhe Zhong, Ann Koay, Anna Ngo, Yan Li, Qianhui Nah, Yee Hwa Wong, Yok Hian Chionh, Hui Qi Ng, Xiaoying Koh-Stenta, Anders Poulsen, Klement Foo, Megan McBee, Meng Ling Choong, Abbas El Sahili, Congbao Kang, Alex Matter, Julien Lescar, Jeffrey Hill, and Peter Dedon. Targeting the bacterial epitranscriptome for antibiotic development: Discovery of novel trna-(n1g37) methyltransferase (trmd) inhibitors. *ACS Infectious Diseases*, 5(3): 326–335, January 2019. ISSN 2373-8227. doi: 10.1021/acsinfecdis.8b00275. URL http://dx.doi.org/10.1021/acsinfecdis.8b00275.

Thank you for Listening

It’s time for Q & A