האוניברסיטה
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THE HEBREW
UNIVERSITY
OF JERUSALEM

PROGRESS AND CHALLENGES IN LIGANDS DISCOVERY FOR BITTER TASTE RECEPTORS

Masha Niv

The Hebrew University

Drugs will only work if you take them

1.7 million children under the age of 15 live with HIV.
Just over 50% take antiretroviral treatment compared to 76% of adults living with HIV

13/7/2023 Gilead Sciences, Inc. announced collaboration to design pediatric formulations to eliminate bitterness in these two drugs

TAF (tenofovir)

SOF (sofosbuvir)

Regulatory agencies ask companies for taste evaluation

Since 2018 FDA expects that all medicines with the potential to be given to children should be assessed for palatability.

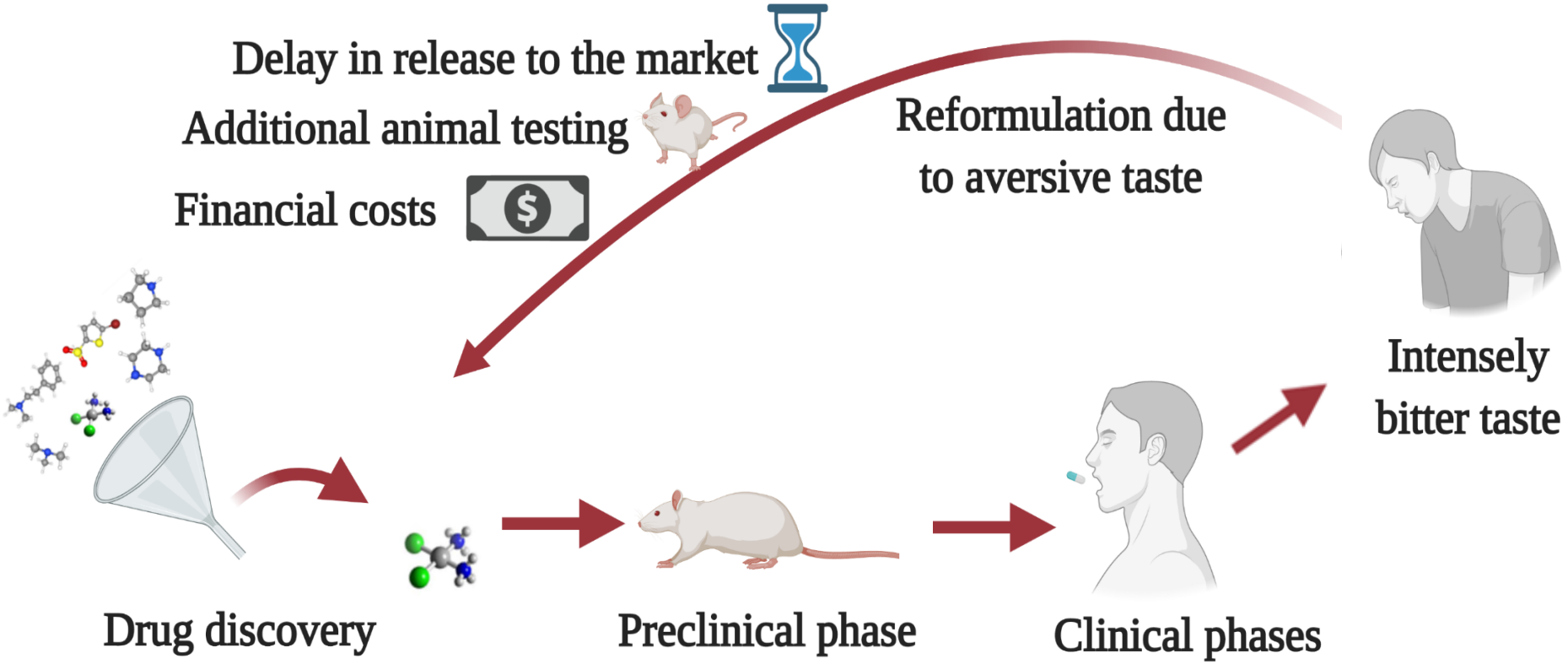
European Medicines Agency (EMA) lists taste as a key consideration for medicine development for the geriatric population.

https://www.fda.gov/files/drugs/published/E11%28R1%29-Addendum--Clinical-Investigation-of-Medicinal-Products-in-the-Pediatric-Population.pdf

Brouwer, Adriaen (1605–1638)
“The bitter potion”

Many drugs are bitter

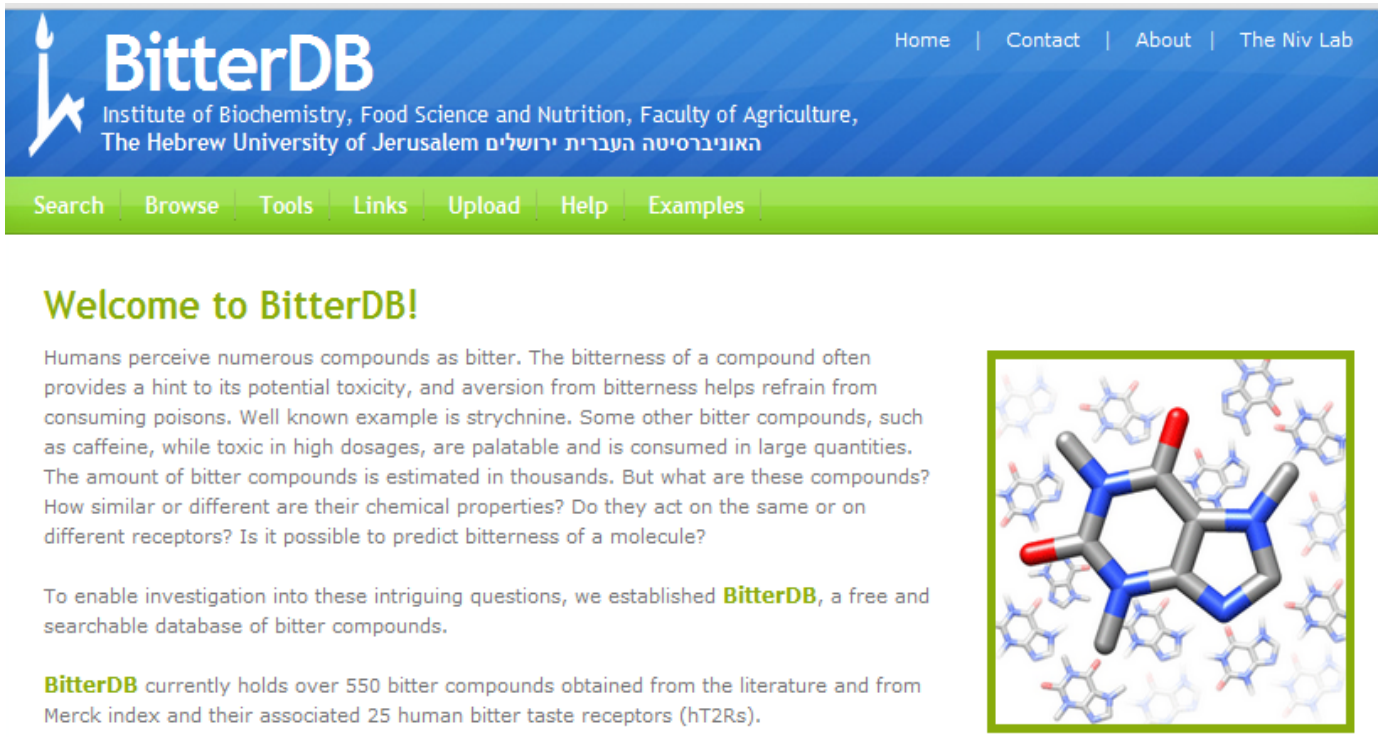
Typical process in pharma



Can we do better?

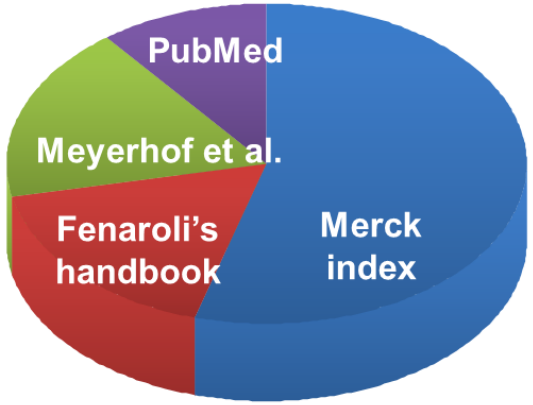
Margulis et al., *CSBJ* 2021

Knowing and predicting bitter molecules



over 1000 known bitter molecules

~60k users http://bitterdb.agri.huji.ac.il/



Wiener et al *Nucleic Acids Res* 2012 Dagan-Wiener et al *Nucleic Acids Res* 2018

Dagan-Wiener et al, **Bitter or not? BitterPredict, a tool for predicting taste from chemical structure,** *Sci Reports* 2017

We want to predict intensely bitter molecules

Data for the model (positive and negative sets):

BitterDB
Institute of Biochemistry, Food Science and Nutrition, Faculty of Agriculture,
The Hebrew University of Jerusalem האוניברסיטה העברית ירושלים

N = 411 compounds

gsk
GlaxoSmithKline

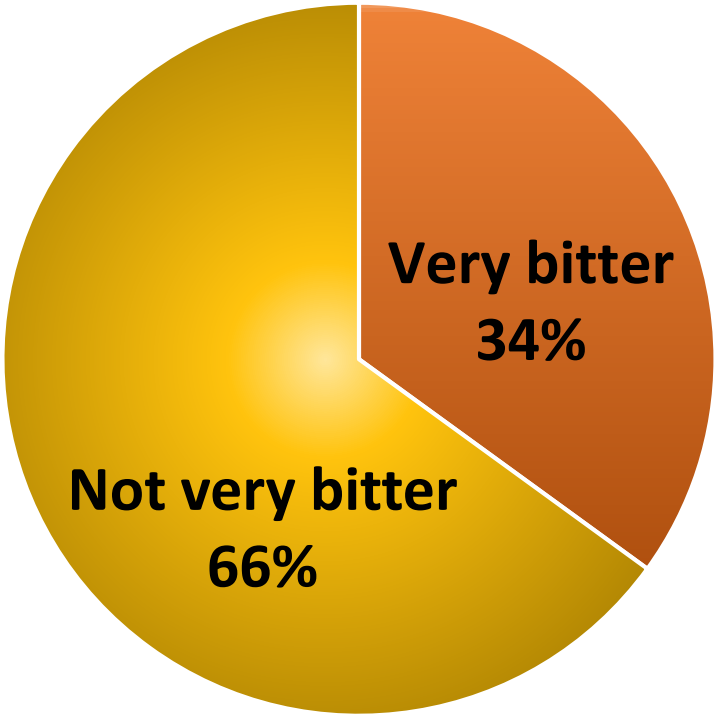
N = 34 compounds

AnalytiCon discovery

N = 145 compounds

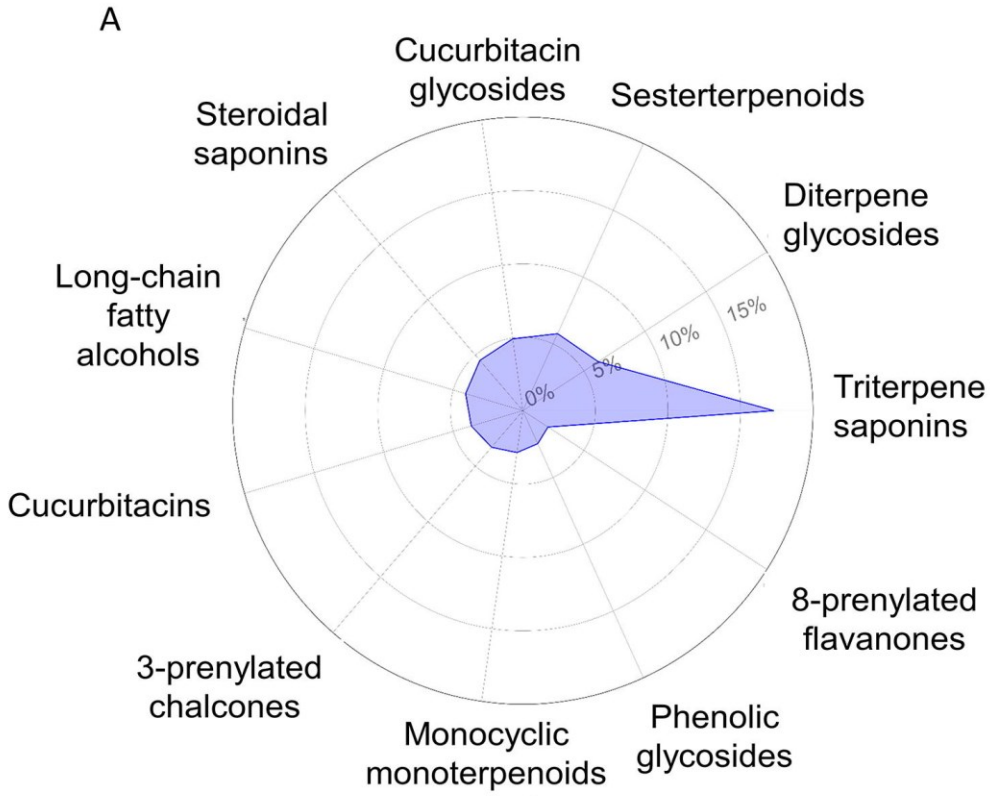
Non-bitter dataset

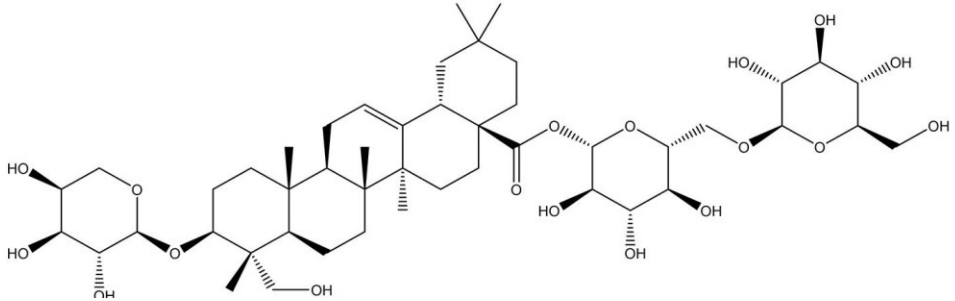
N = 140 compounds



Margulis, E., et al. (2021) *CSBJ*

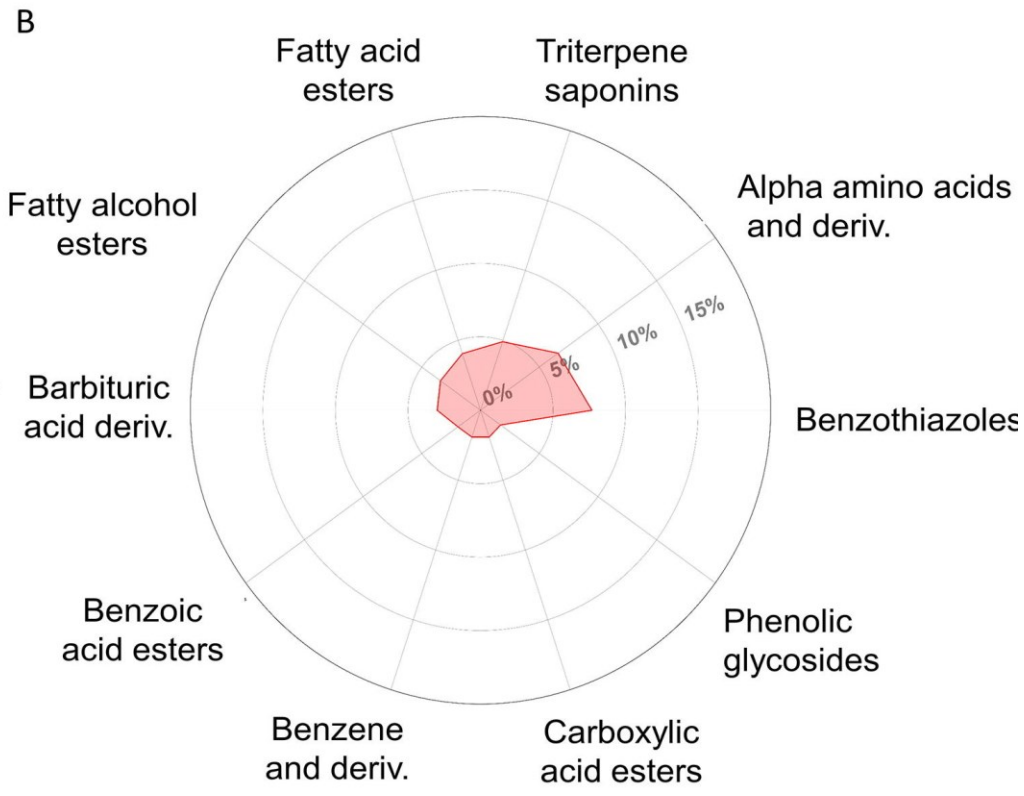
Top families of intensely bitter

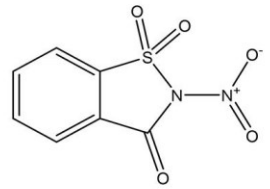




Example: Asperosaponin VI

Top families of not very bitter





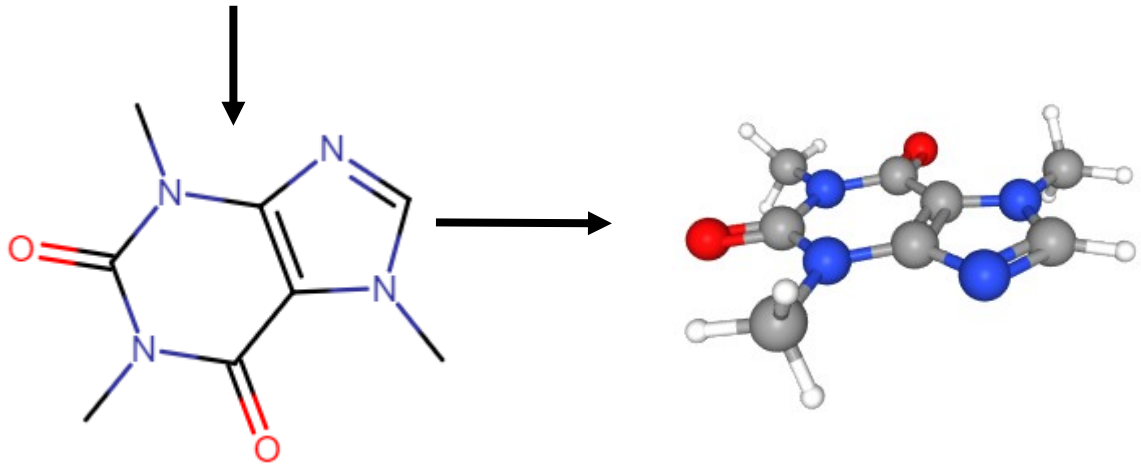
Example: Nitrosaccharin

Margulis et al. (2021) *CSBJ*

Data preparation for training

Collection of SMILES strings

CN1C=NC2=C1C(=O)N(C(=O)N2C)C



Ligand preparation (2D to 3D structure)

Descriptors calculation

Physicochemical properties (MW, AlogP, Charge, etc..)

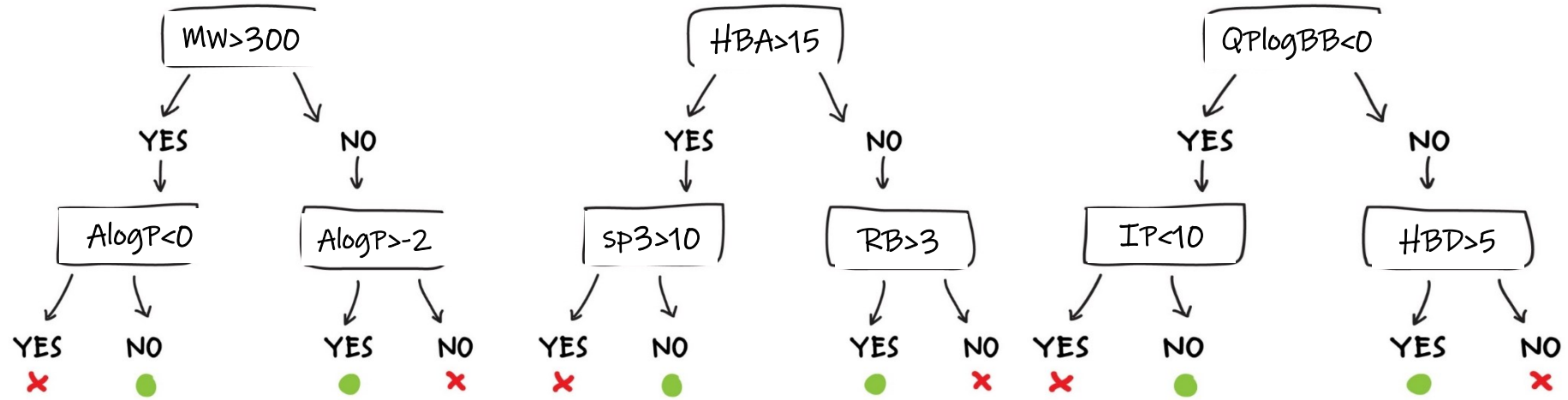
Ligfilter properties (OH groups, Amines, sp3 carbons, etc..)

QikProp properties (QPlogBB, QPlogHERG, QPlogKp, etc..)

Margulis, E., et al. (2021) *CSBJ*

BitterIntense constructed using XGBoost algorithm

Extreme Gradient Boosting (XGBoost) was used - learning from the mistakes in previous iteration, works well with small and unbalanced data.



Based on Chen, T., et al. (2016) *Proc. 22nd acm sigkdd Int. Conf. Knowl. Discov. data Min*.

BitterIntense reaches accuracy of over 80%

	Training set (493 compounds)	Test set (123 compounds)	Hold-out set (105 compounds)
Accuracy (%)	87±5	83	80
Precision (%)	80±8	71	63
Recall (%)	85±4	86	77

$$100 * \frac{Tp + Tn}{Tp + Tn + Fp + Fn}$$

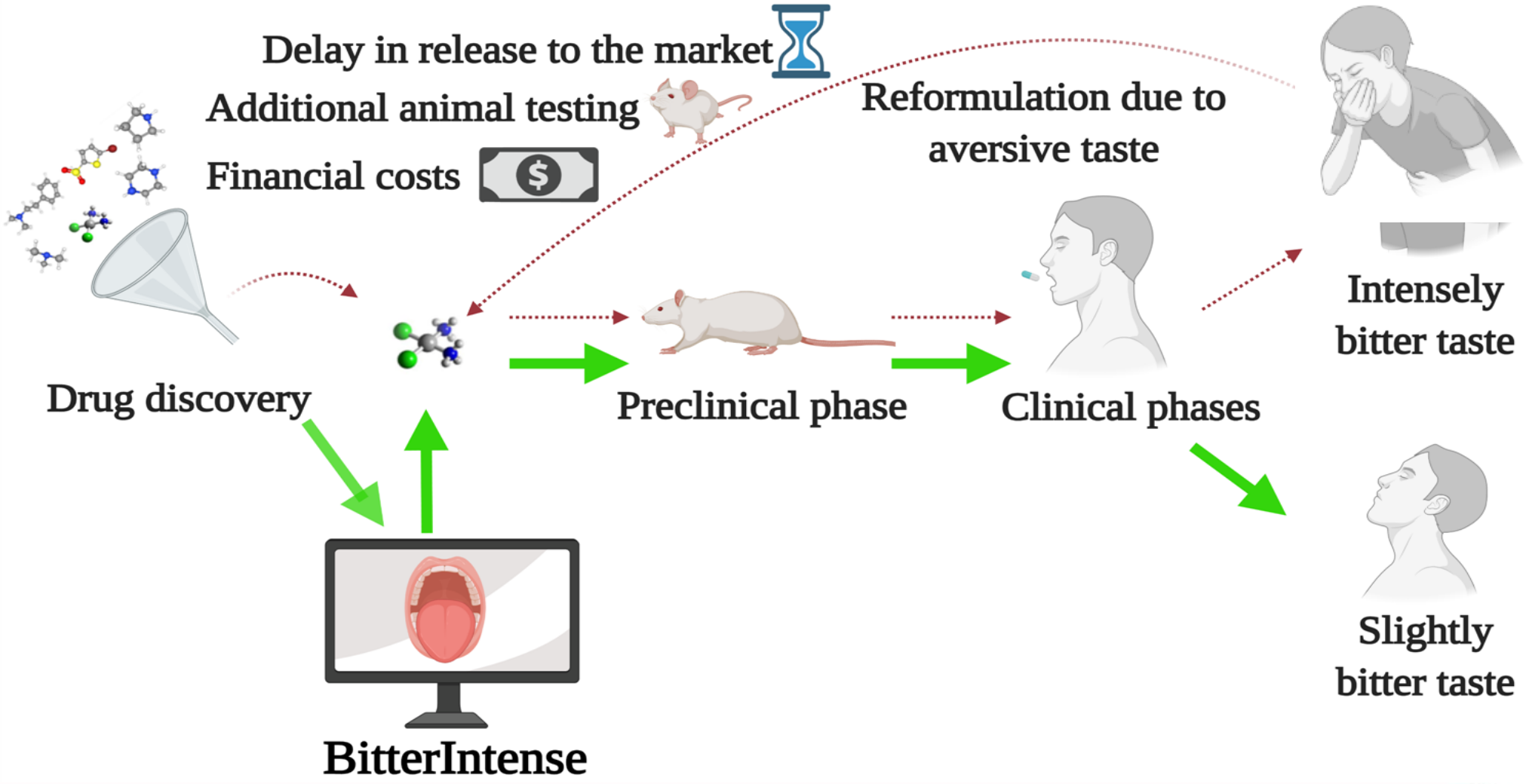
$$100 * \frac{Tp}{Tp + Fp}$$

$$100 * \frac{Tp}{Tp + Fn}$$

Tp – True positives
Tn – True negatives
Fp – False positives
Fn – False negatives

Margulis, E., et al. (2021) *CSBJ*

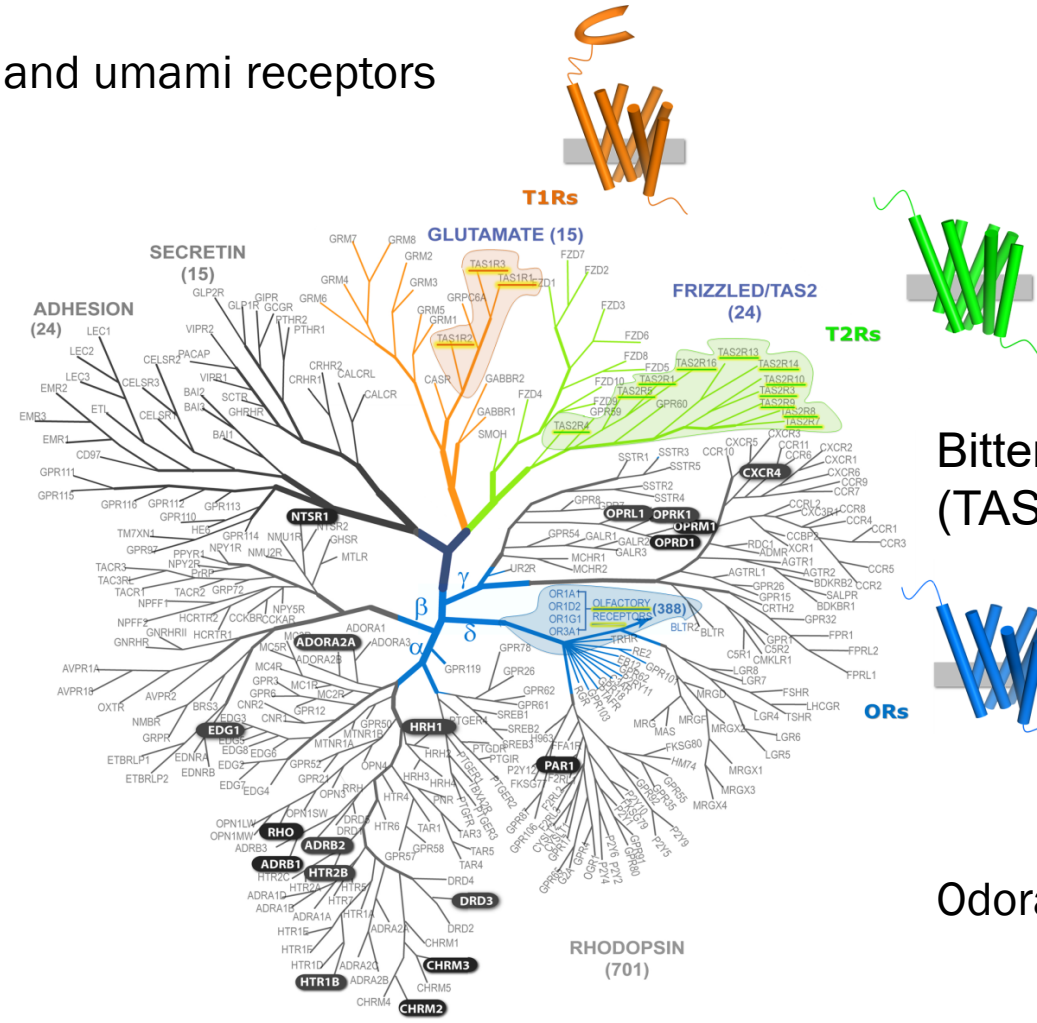
BitterIntense for expediting drug discovery



Margulis, E., et al. (2021) *CSBJ*

Bitter, sweet and umami taste receptors of vertebrates are GPCRs

Sweet and umami receptors



25 3 30

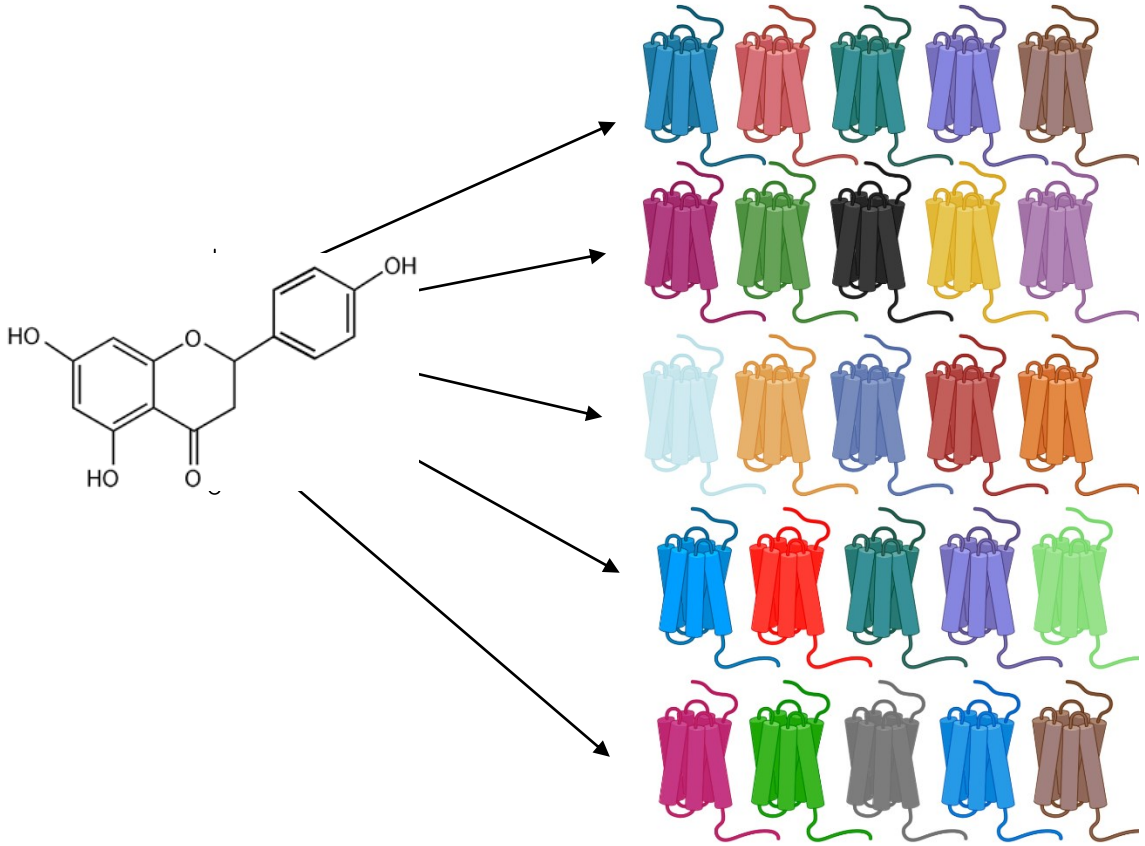
Bitter taste receptors (TAS2Rs or T2Rs)

Odorant receptors

Di Pizio and Niv, *Isr J Chem* 2014

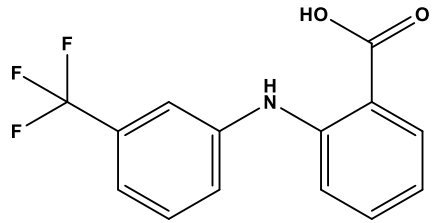
Di Pizio, Levit et al, Methods in Cell Biol 2016

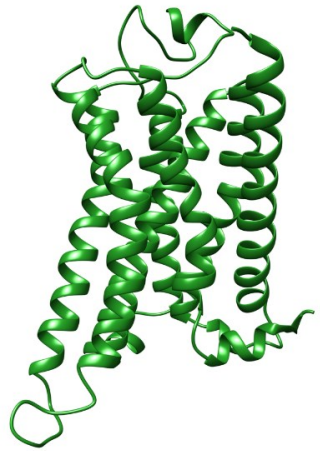
Which T2Rs are responsible for particular compounds bitterness?



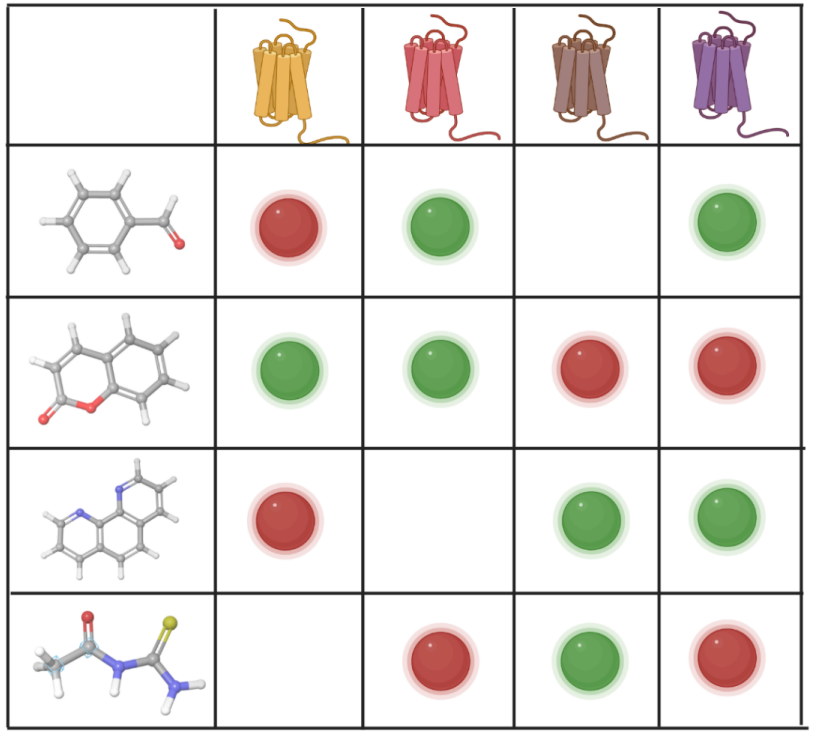
Humans have 25 bitter taste receptor subtypes
One ligand can activate many receptors
One receptor can have many ligands

Can we match ligands to receptors?





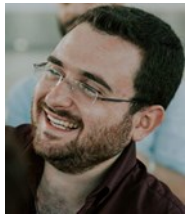
BitterMatch – matchmaking ligands and bitter taste GPCRs



1. Similarity-based recommendation system

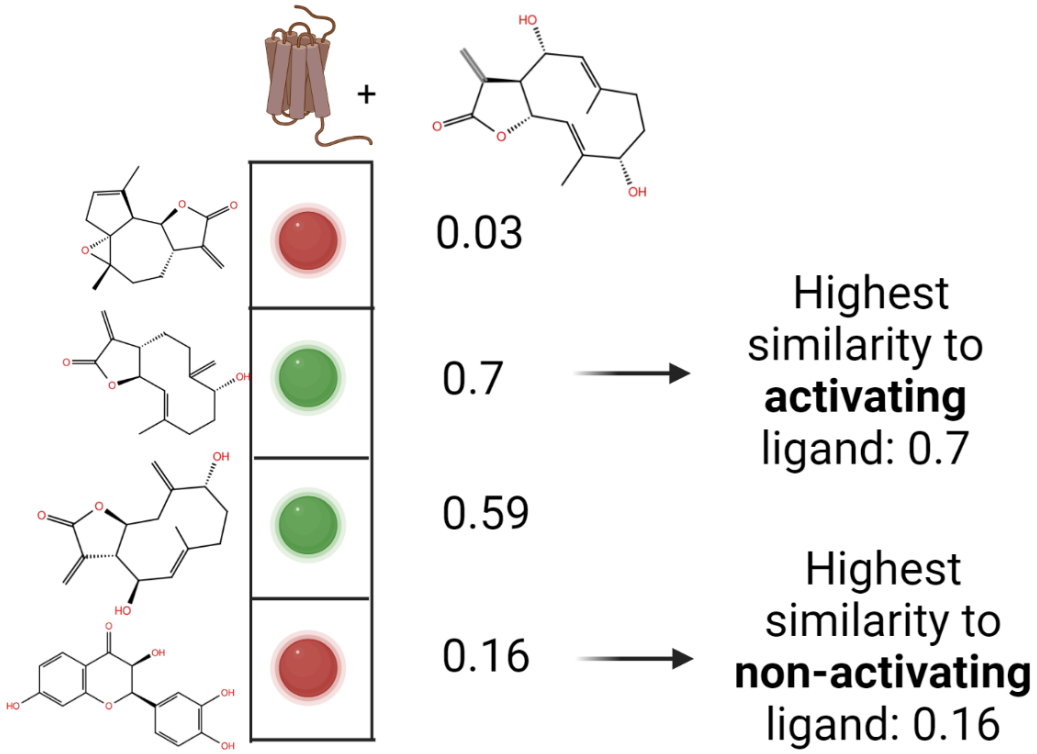
Activating

Not Activating



Margulis, E., Slavutsky, et al *J Cheminform* 2022

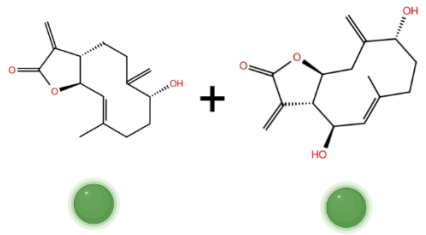
Neighbor-informed chemical features



Highest similarity to **activating** ligand: 0.7

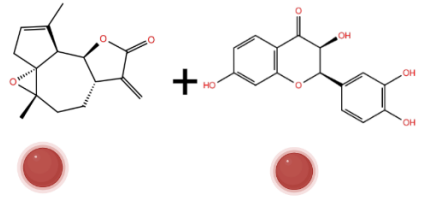
Highest similarity to **non-activating** ligand: 0.16

Sum of **activating** ligands similarities



= 1.29

Sum of **non-activating** ligands similarities

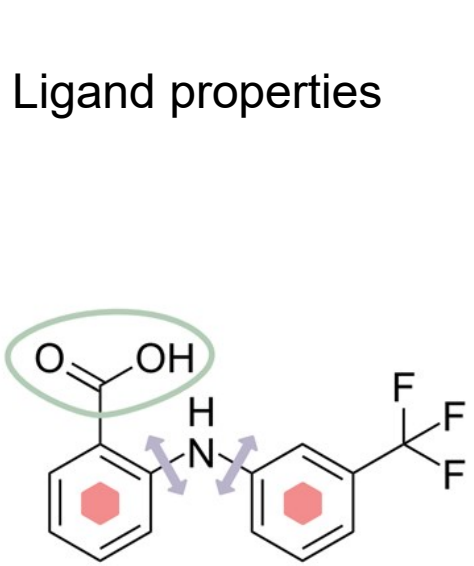


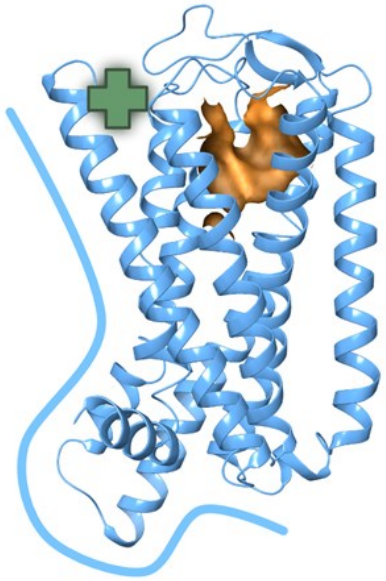
= 0.19

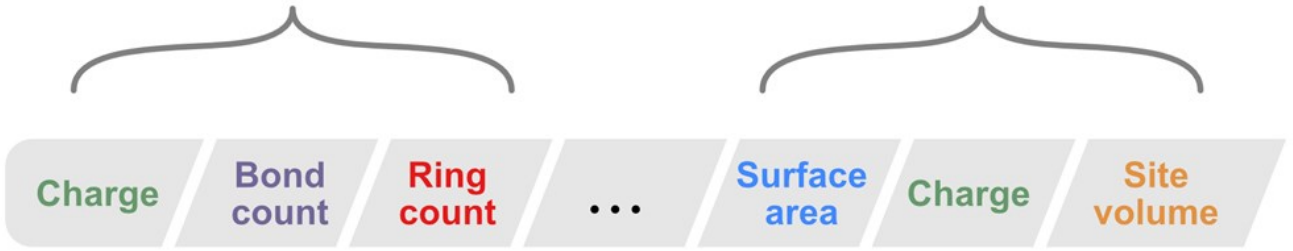
Ligand and receptor properties as additional features

3. Receptor properties
(sequence-based, structure-based)

2. Ligand properties







BITTER MATCH

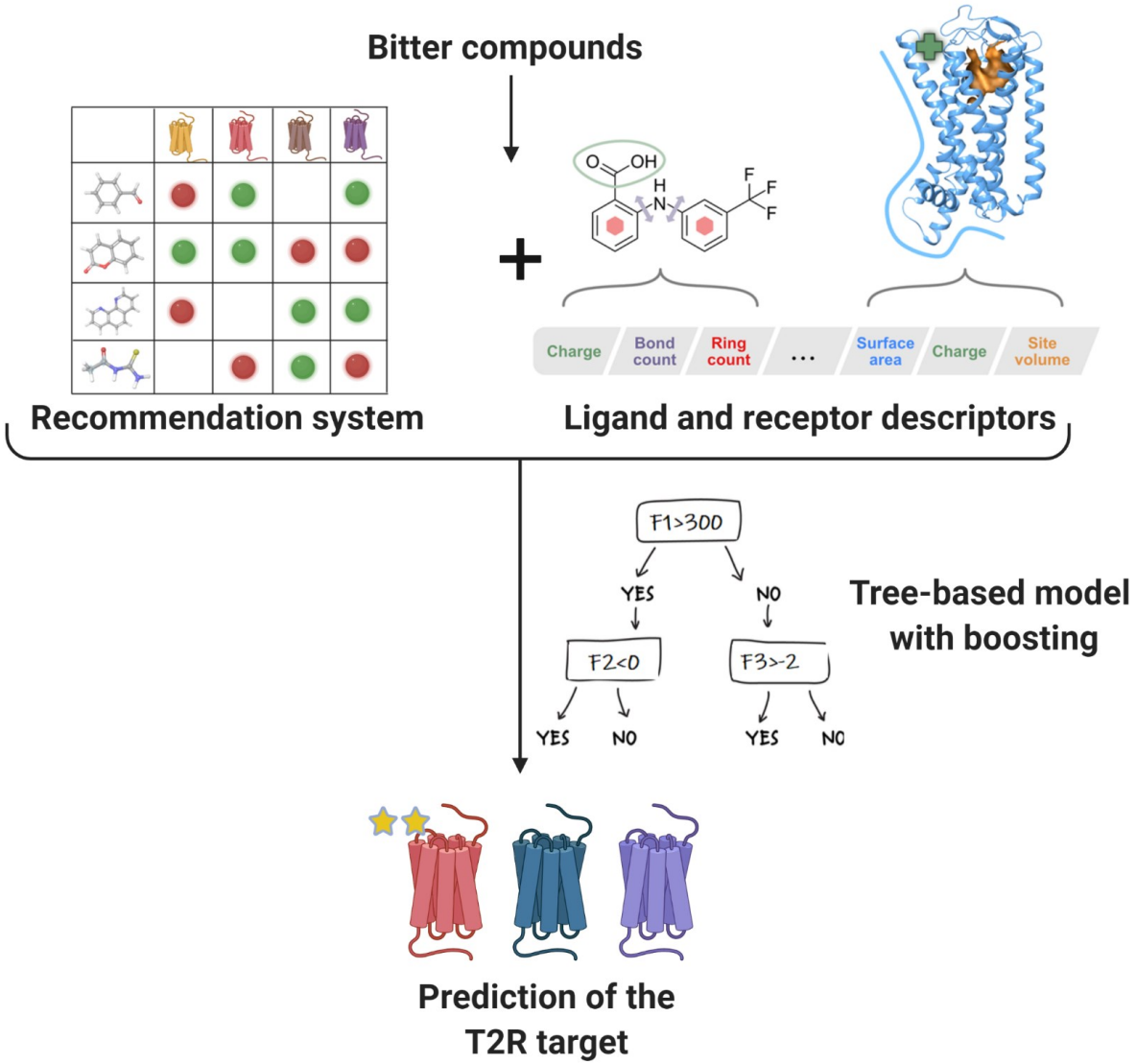
Data curation
303 ligands
21 human and 20 mice T2Rs

Challenges

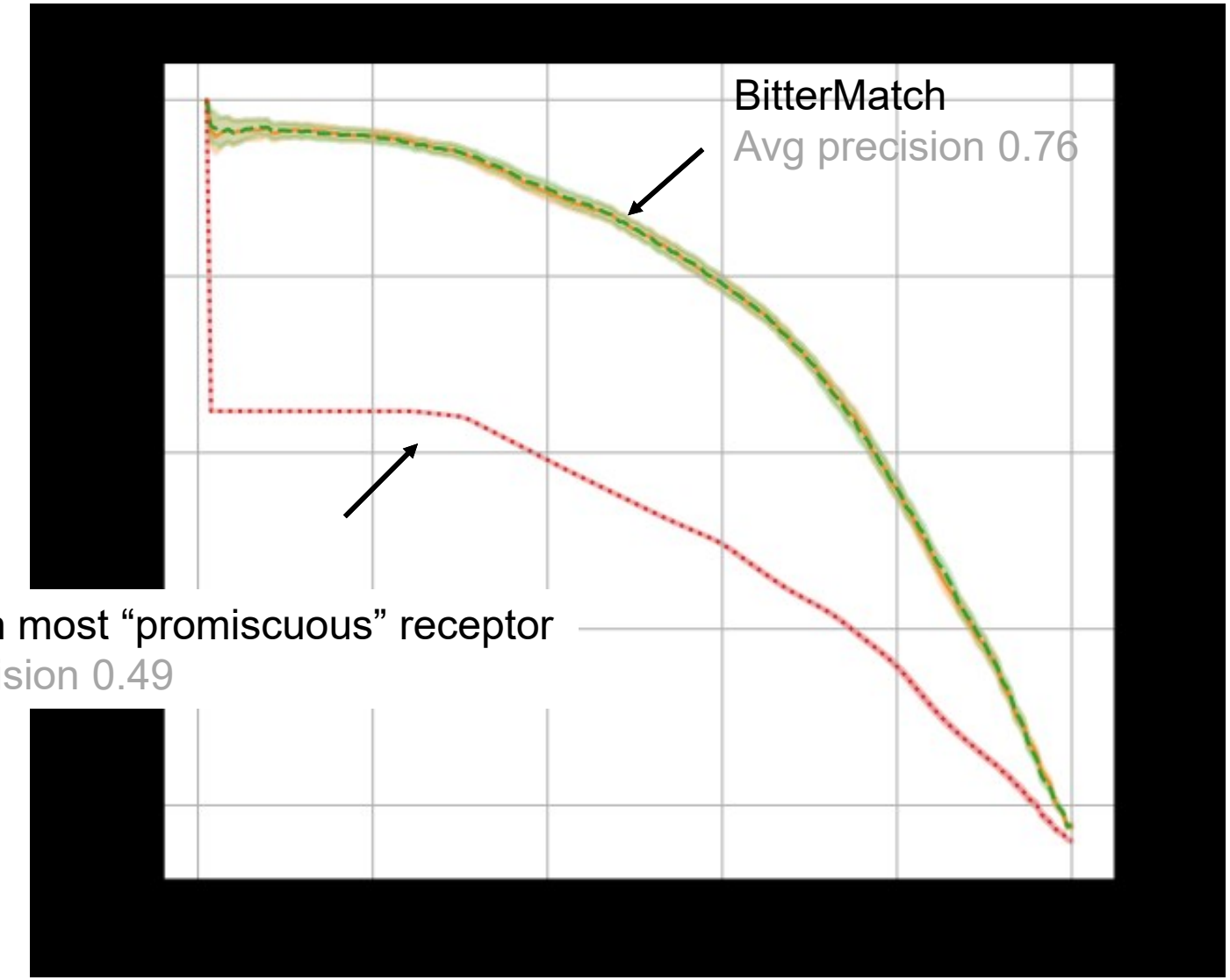
Sparse dataset (gaps in the matrix)
4500 of 12423 pairs known

Unbalanced data

Low resolution 3D models;
functional assays (no binding data)



Precise and tunable tool for predicting bitter receptor targets



Margulis, Slavutsky, et al *J Cheminform* 2022

Prospective predictions and in-vitro validation of BitterMatch

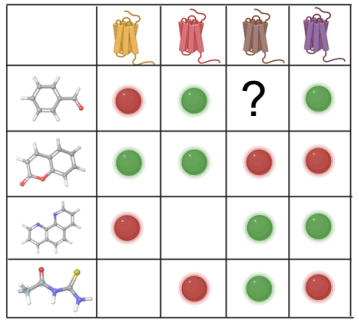
12 compounds “BitterMatched” to 21 human T2Rs and tested *in-vitro* (252 ligand-receptor pairs)

	TP	TN	FP	FN
# of pairs	16	210	4	22

Precision = 0.8

Recall = 0.42

Dr. Maik Behrens



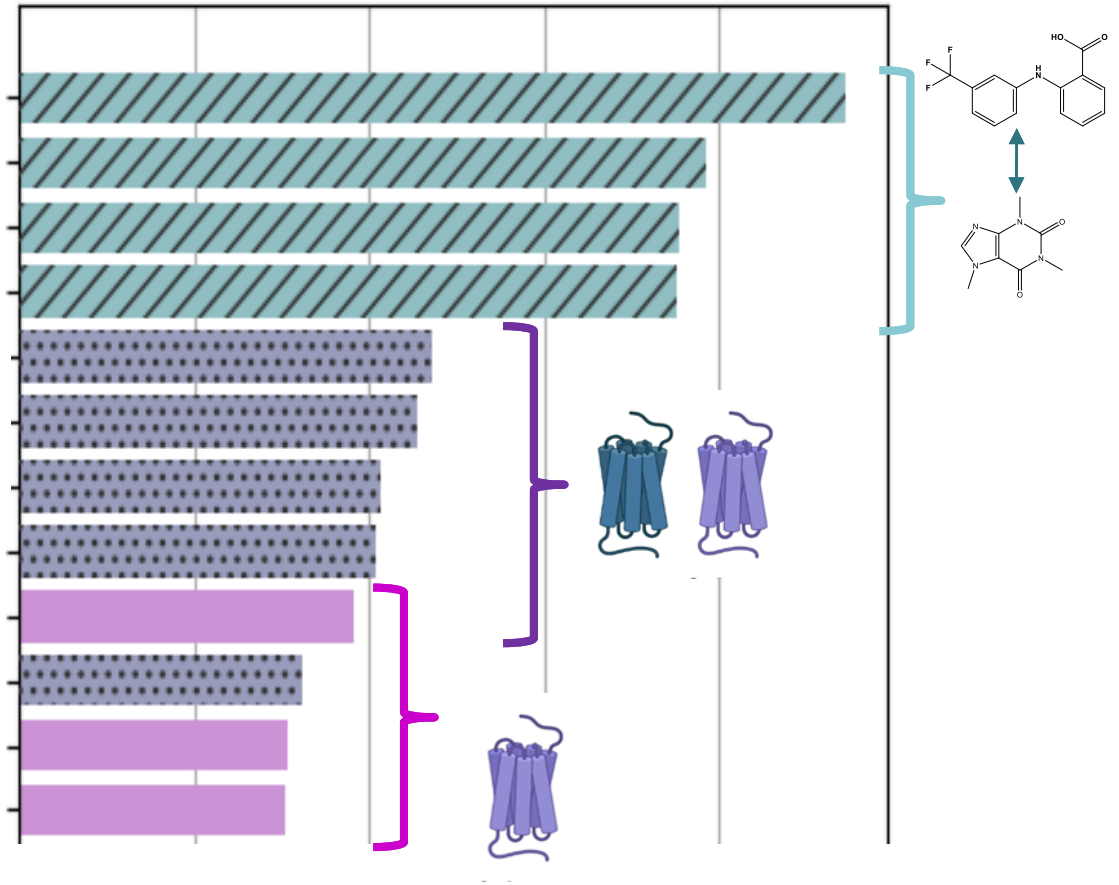
Important features

Chemical similarity to ligands that do **not** activate the receptor

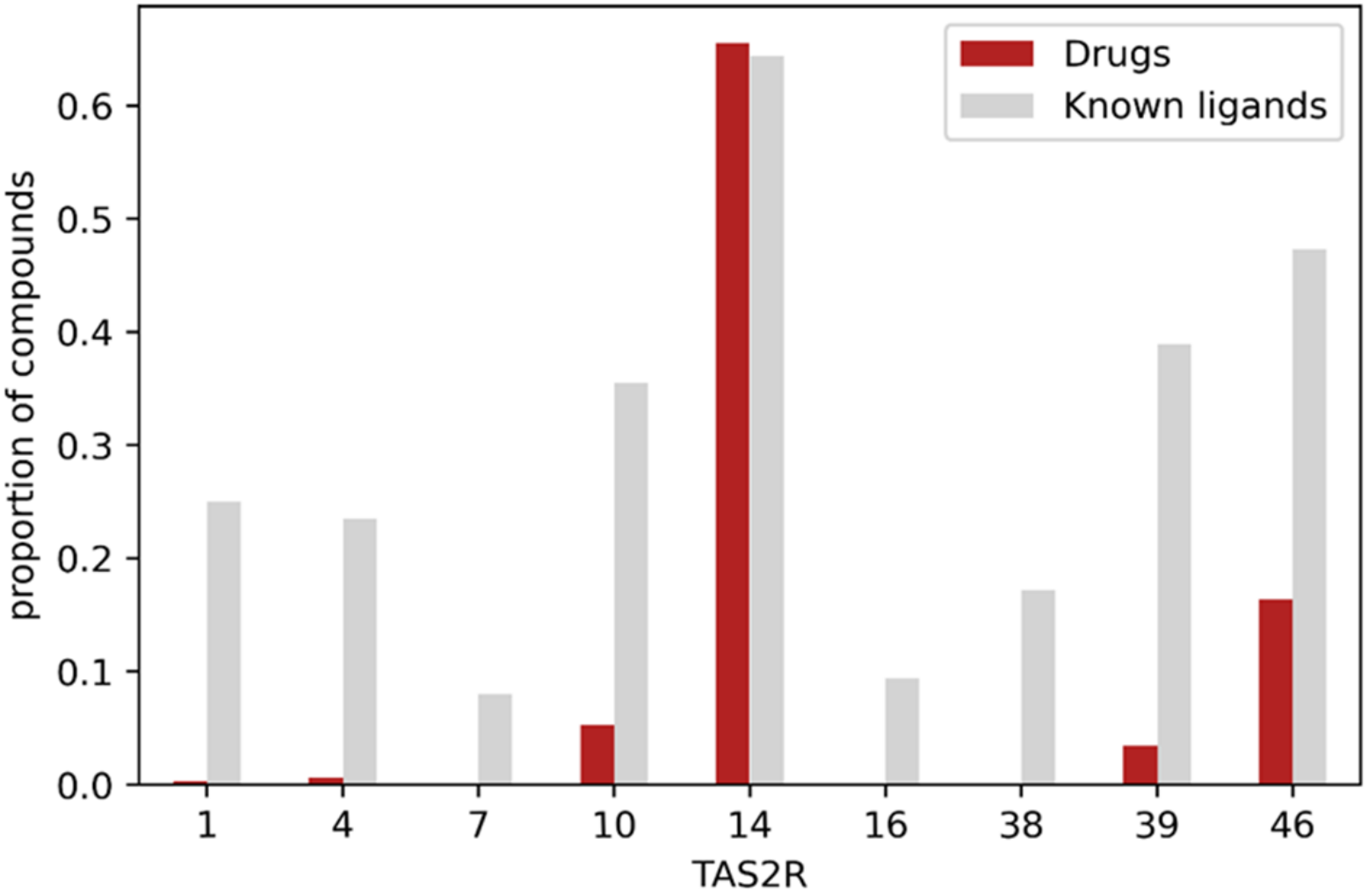
Chemical similarity to ligands that **do** activate the receptor

Identity and similarity of binding sites of receptors activated by the ligand

Receptor features (total hydrophobic SASA, radius of gyration)



BitterMatch for DrugBank

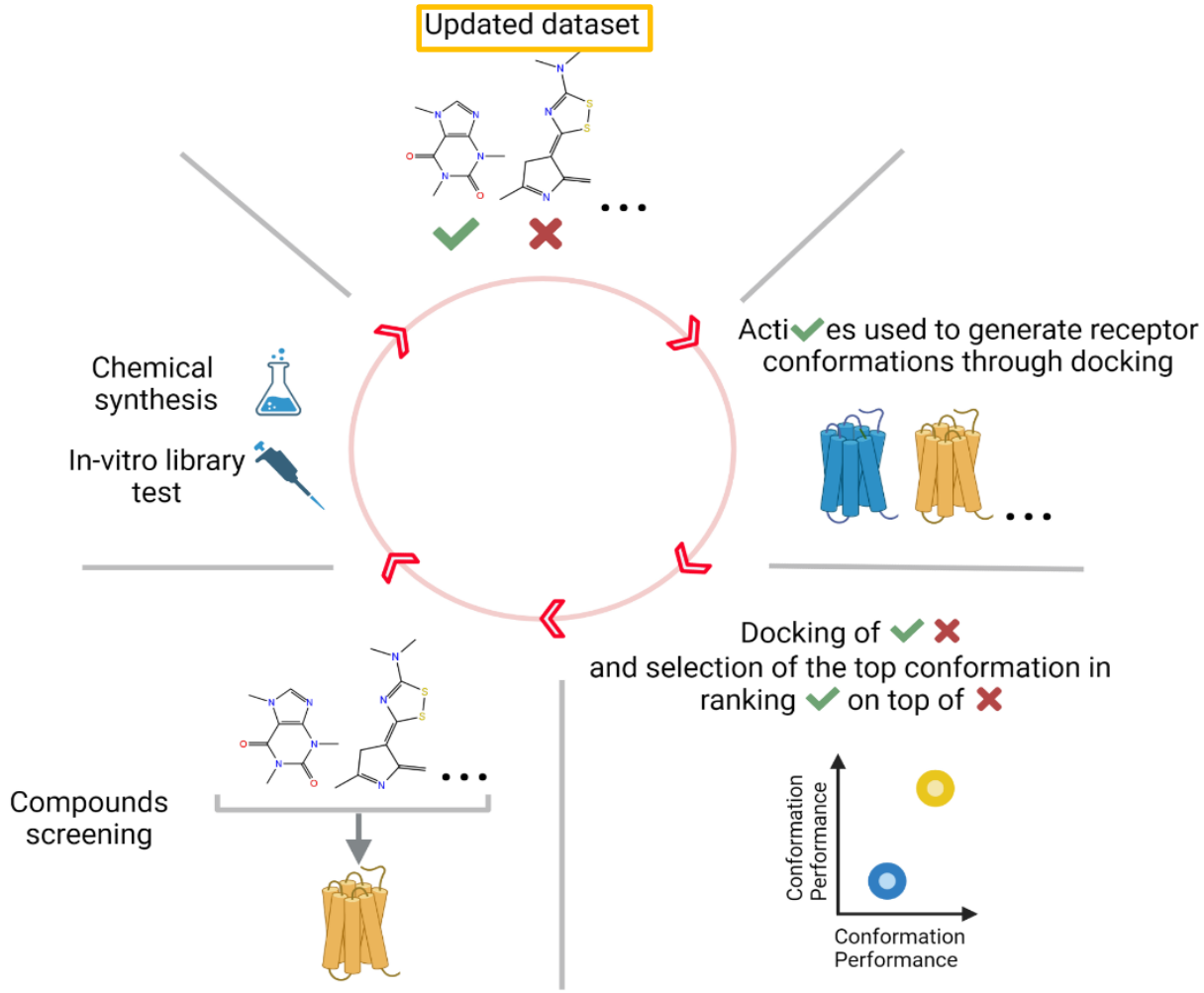


T2R14 is activated
by many drugs

1. Can we inhibit it?
2. What's the physiological relevance?

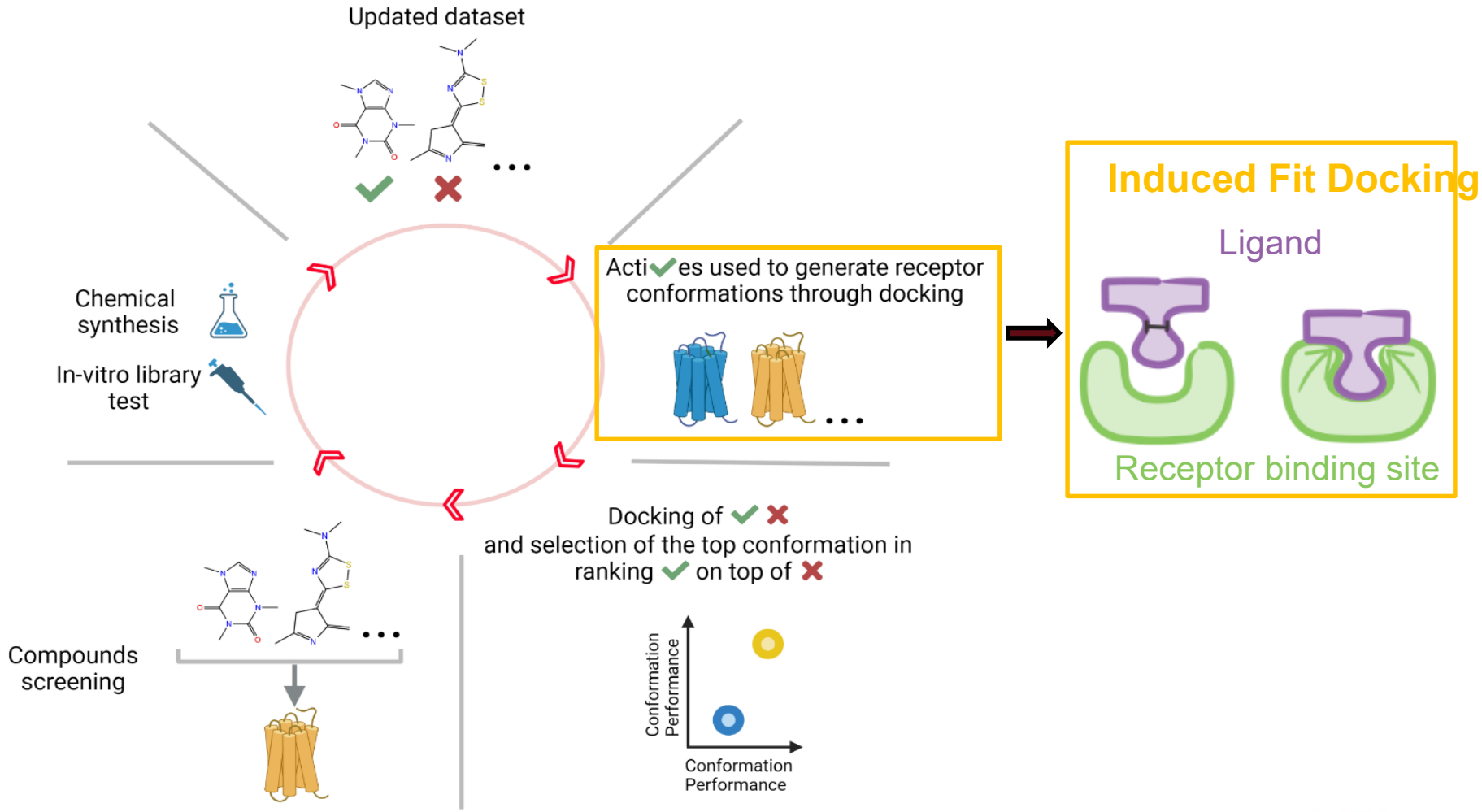
Margulis, E., Slavutsky, et al *J Cheminform* 2022

Iterative discovery

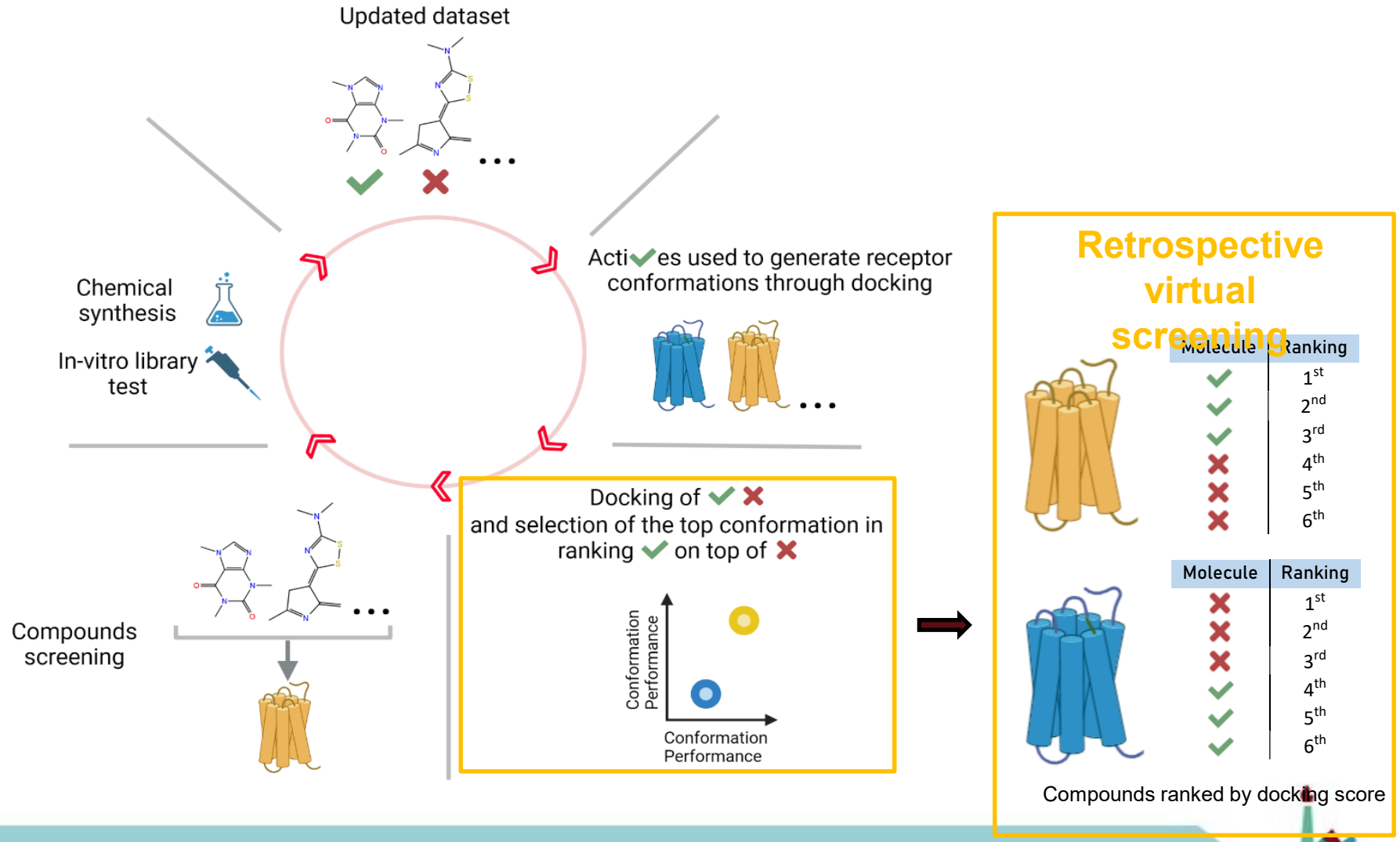


Fierro F, Peri L, et al. *Cell Mol Life Sci*. 2023

Iterative discovery



Iterative discovery



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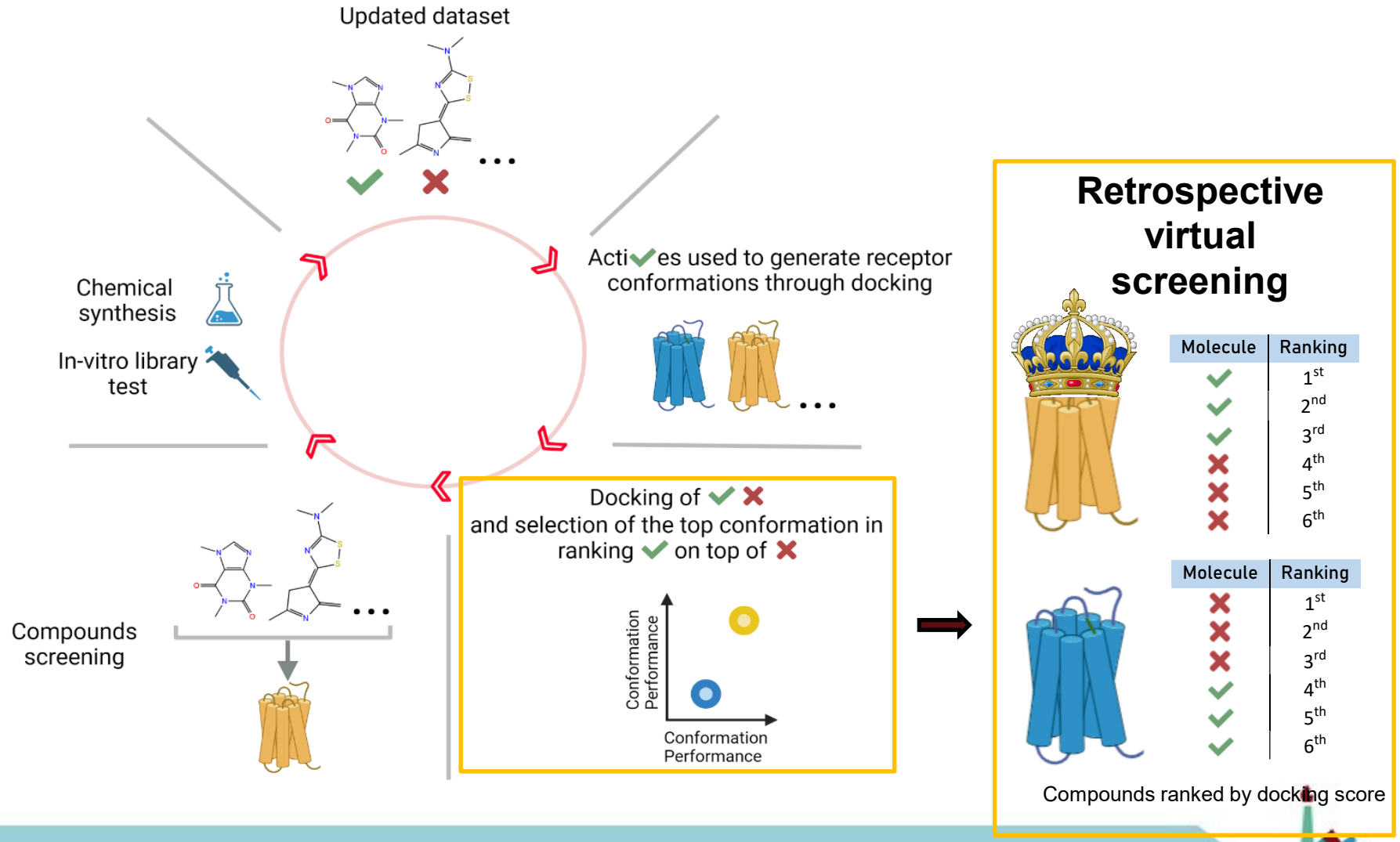
Iterative discovery



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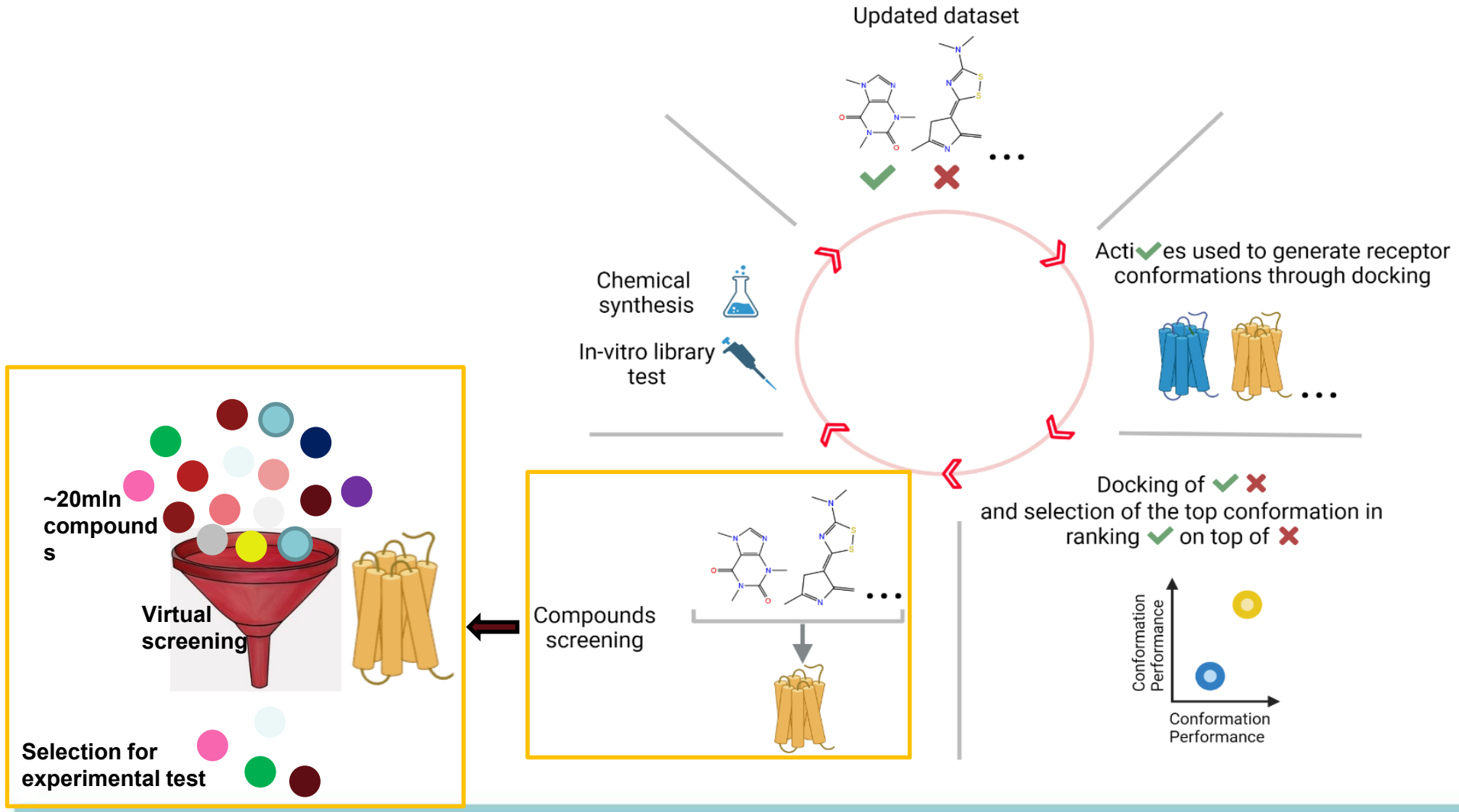
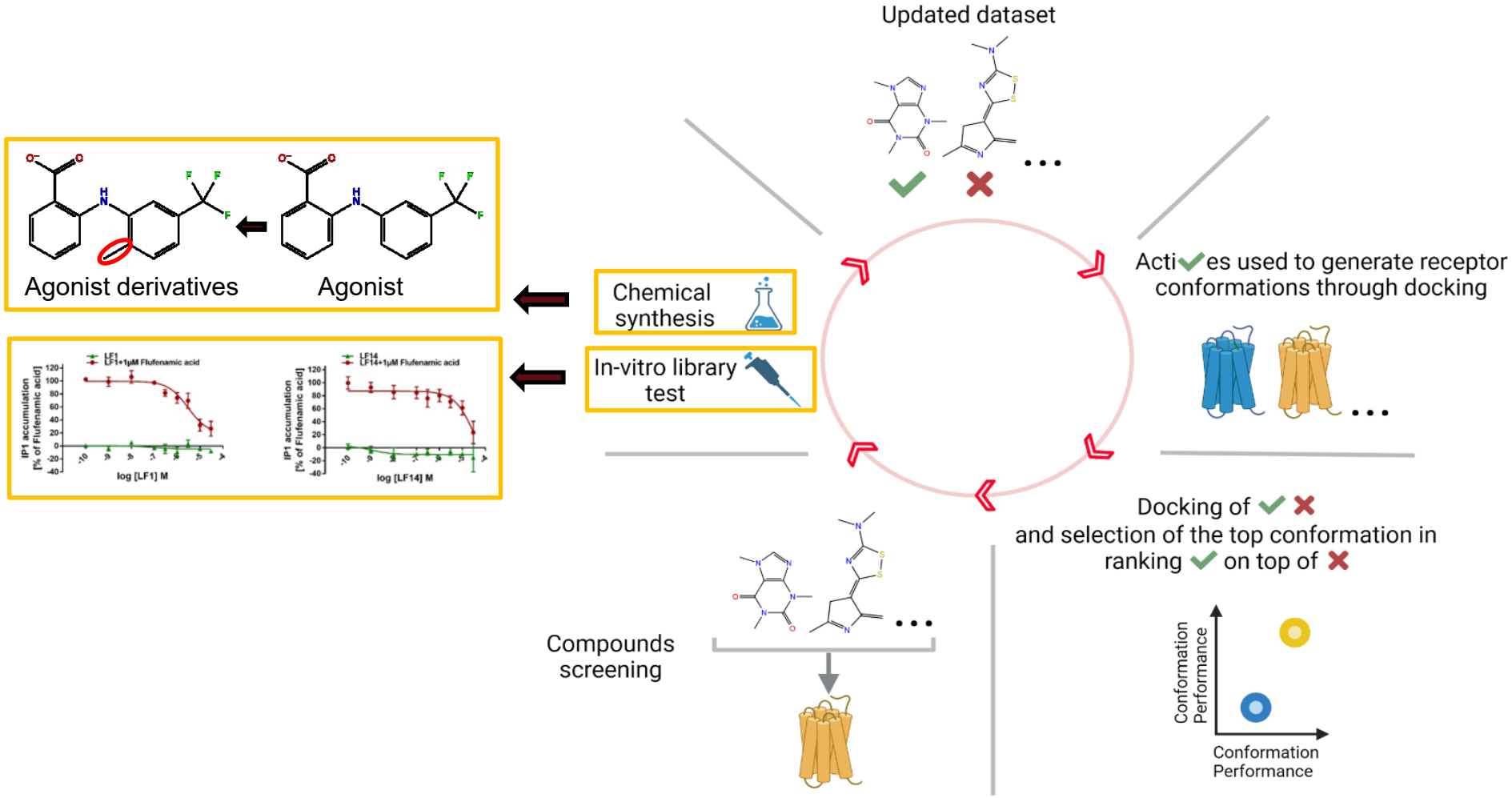
Iterative discovery



Iterative discovery



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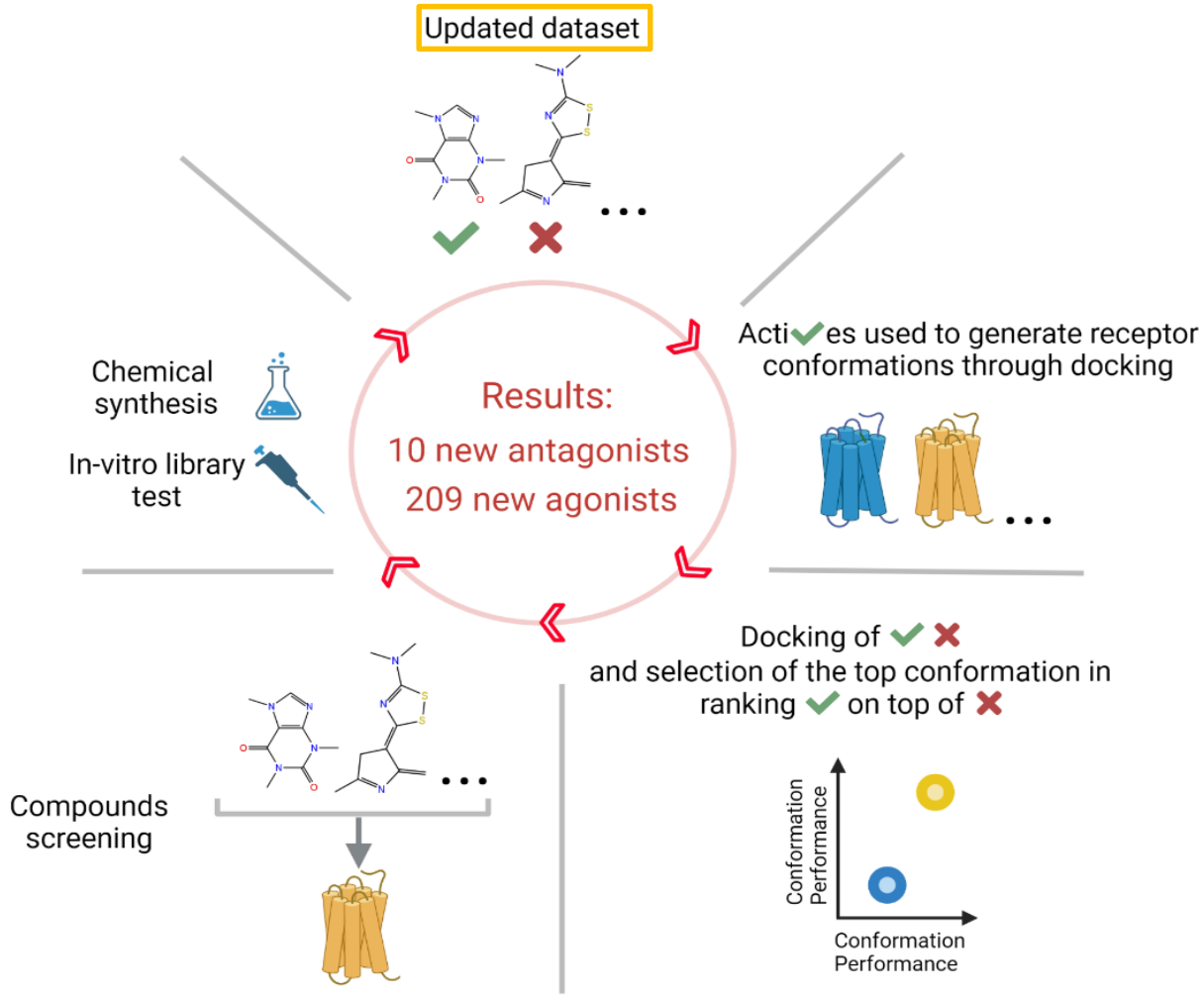

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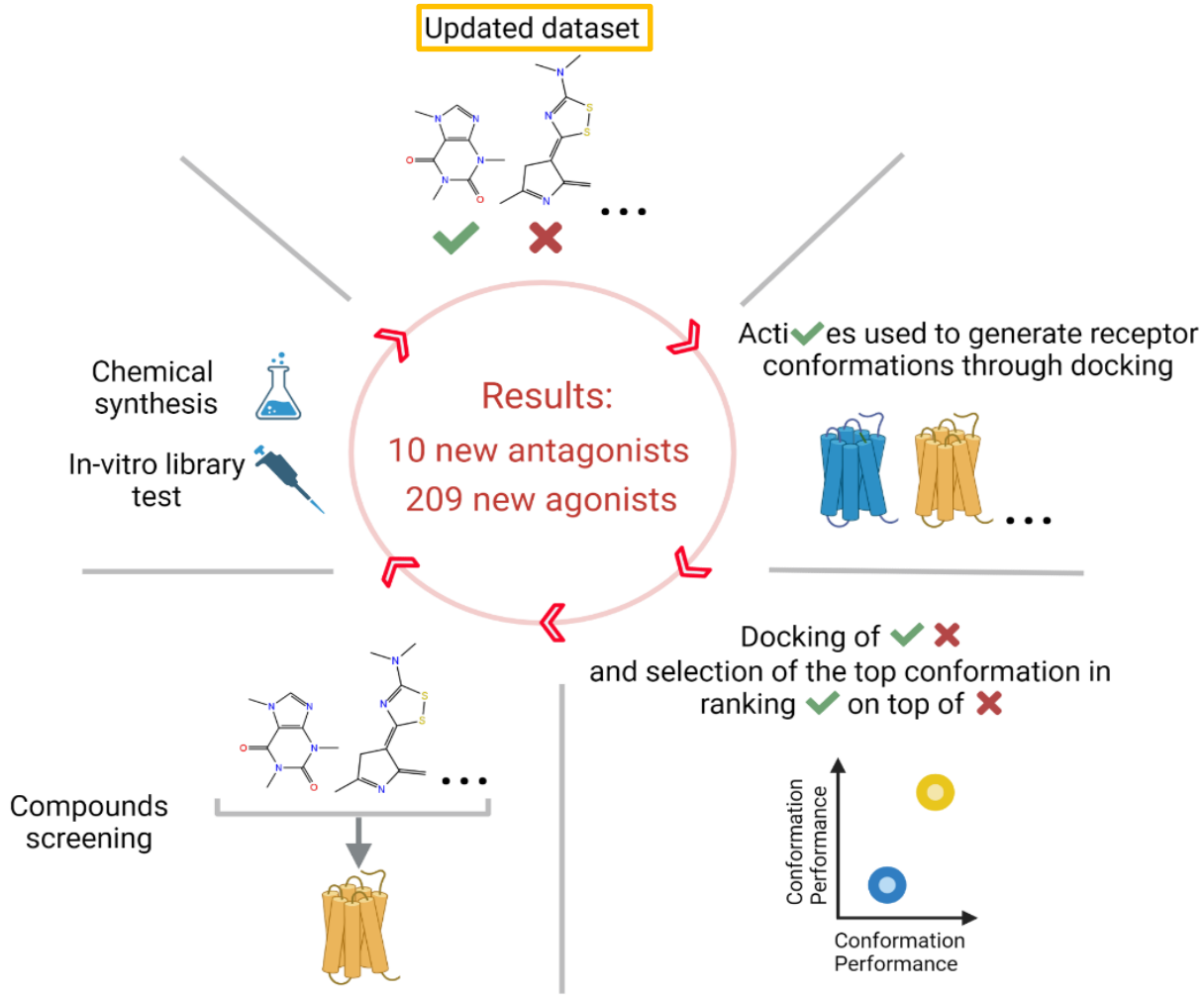
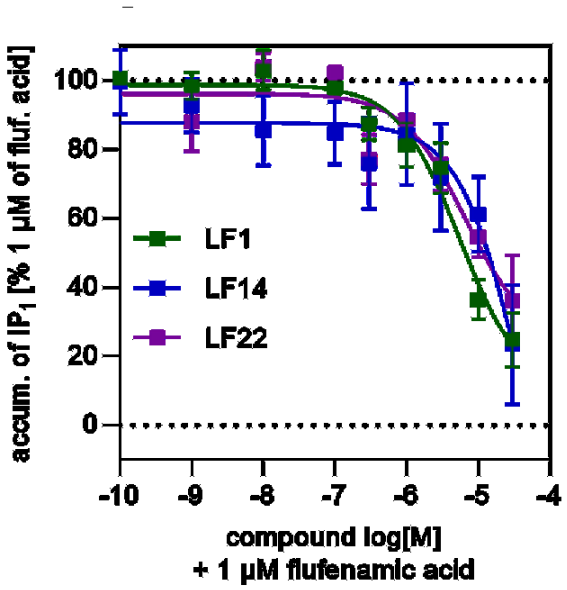


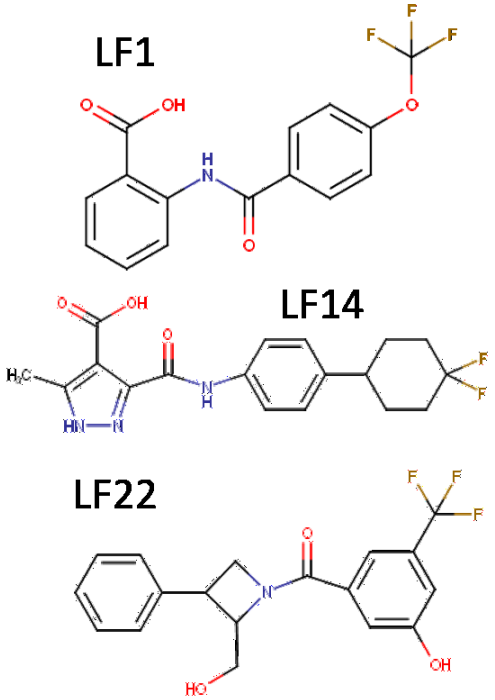
BitterMatch:
10 antagonists and 130 agonists predicted to be selective for T2R14 over other T2Rs

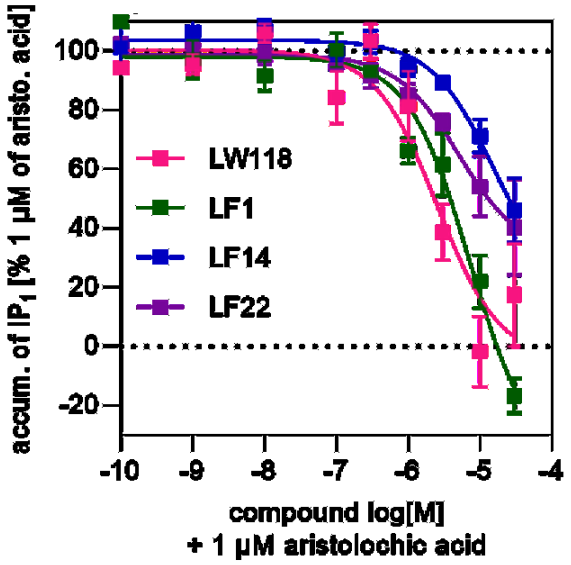
Fierro F, Peri L, et al. *Cell Mol Life Sci*. 2023

Screen of Enamine - 30 purchased, 3 confirmed as antagonists in-vitro (+3 agonists)

Lior Peri





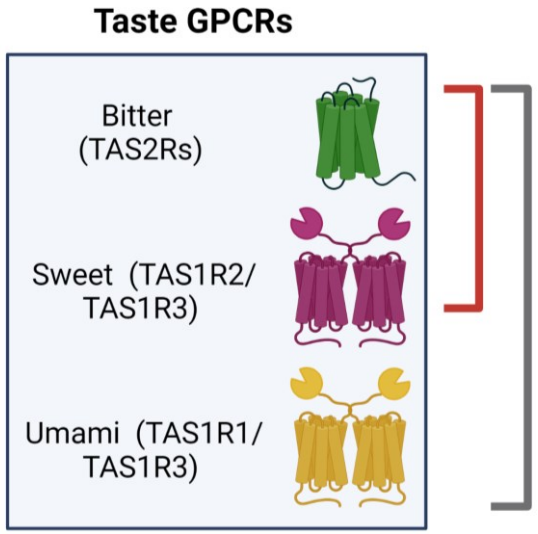


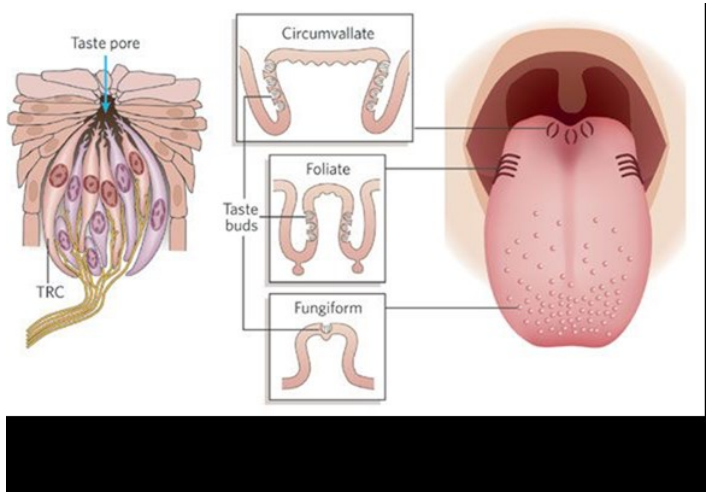
Antagonists already used by other labs

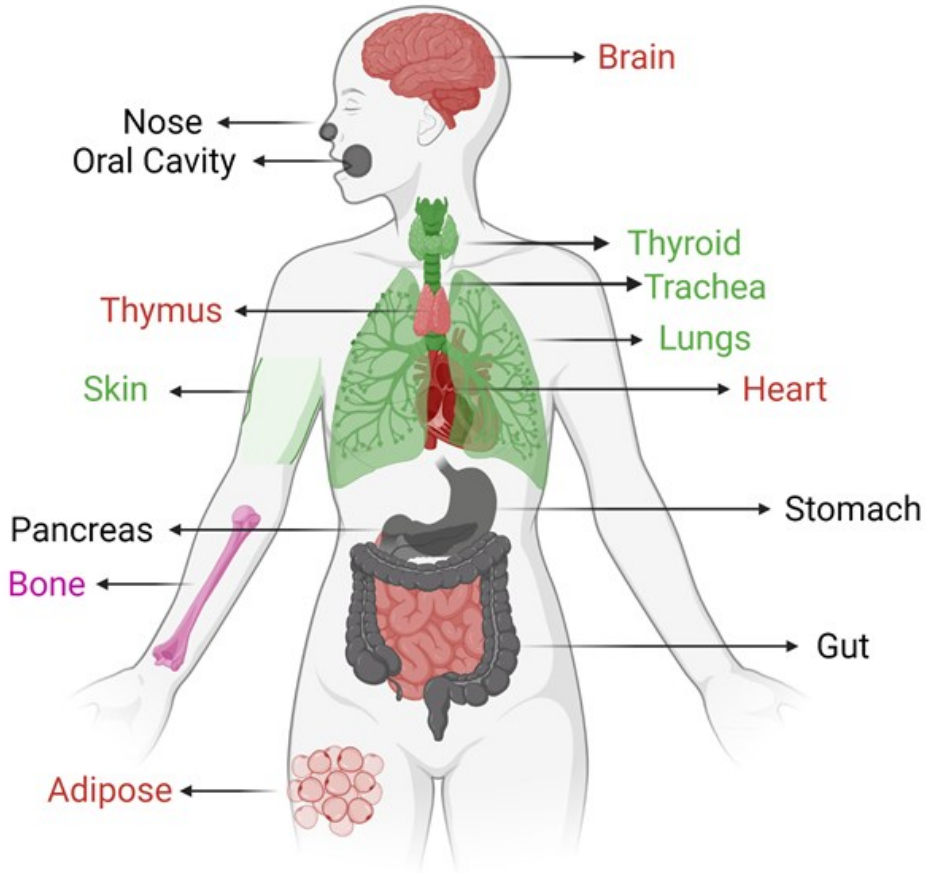
BitterMatch predicts TAS2R14-selectivity

Fierro F, Peri L, et al. *Cell Mol Life Sci*. 2023

Taste receptors expression



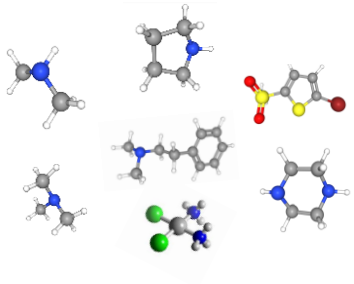




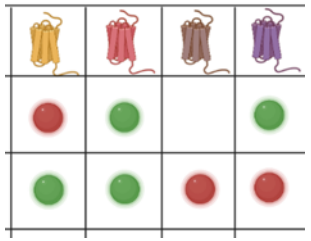
review Dubovski et al, PMBTS

Probes for understanding physiology? Opportunity for polypharmacology?

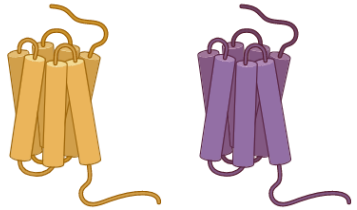
Bitterness masking pipeline

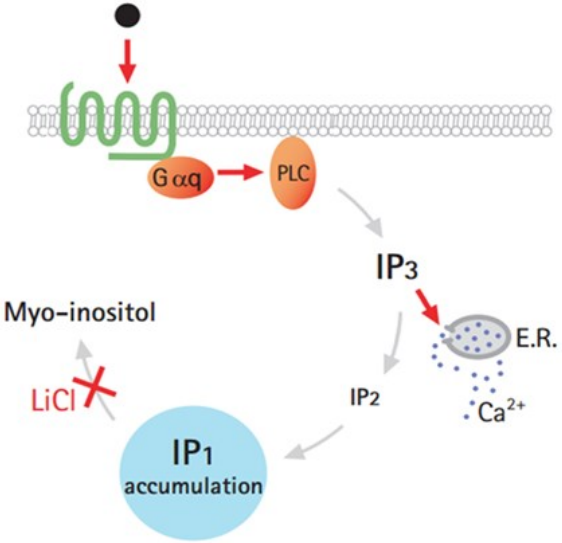


BitterIntense
Identifying very bitter compounds
(Margulis et al 2021)



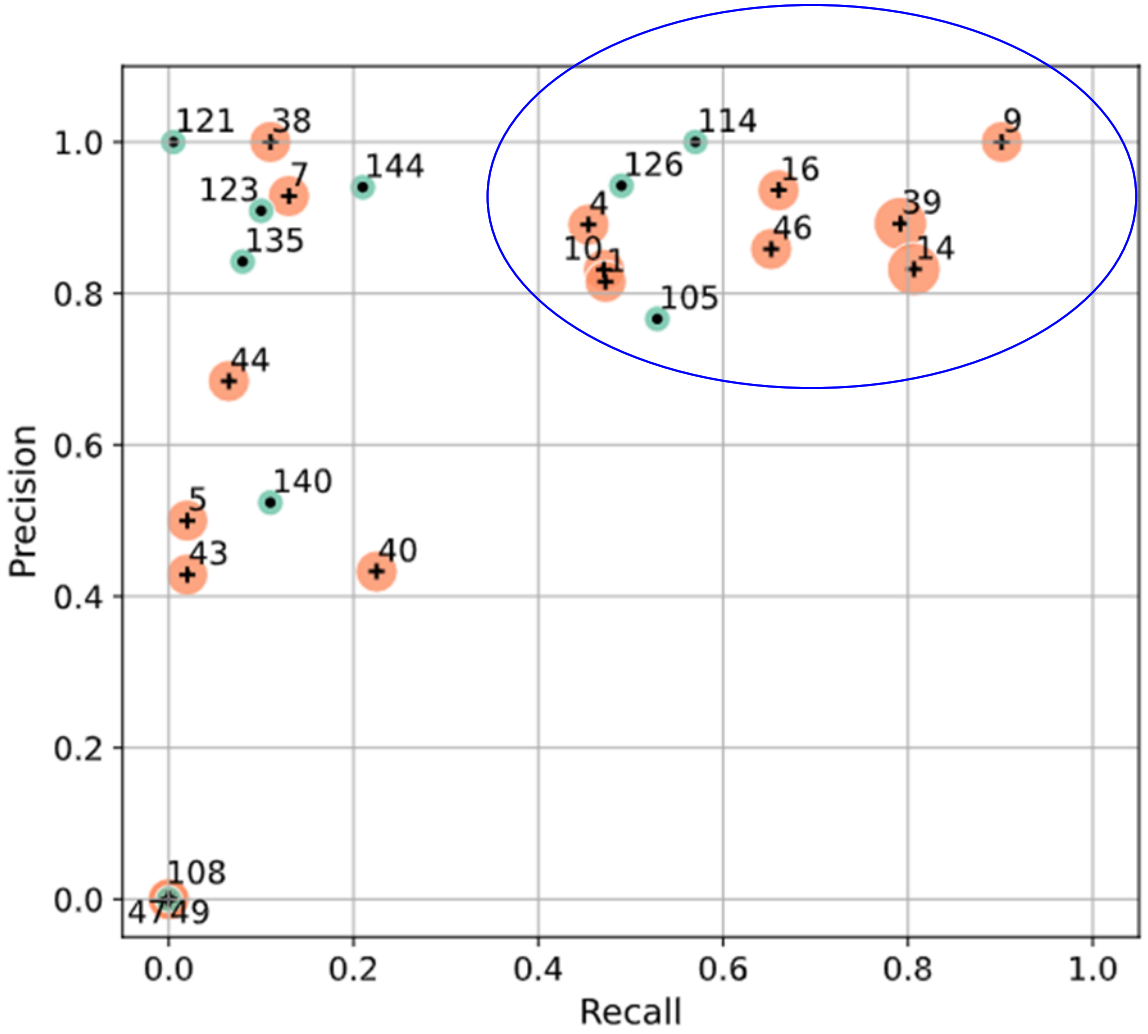
BitterMatch

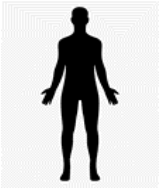


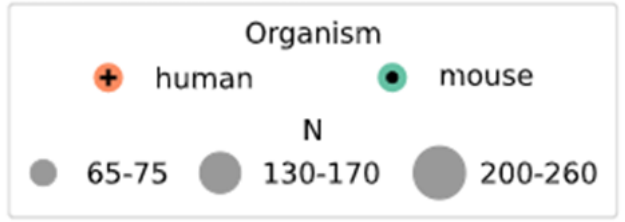


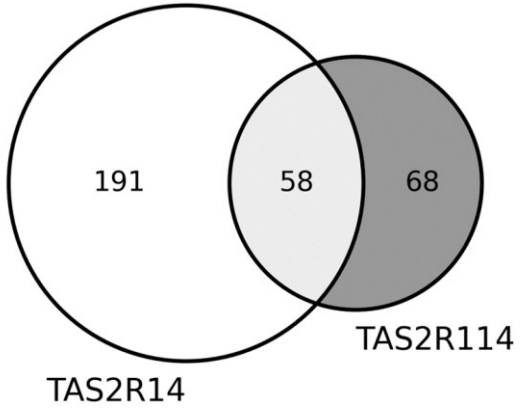
antagonists

Progress and challenges









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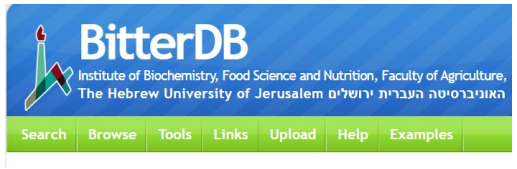
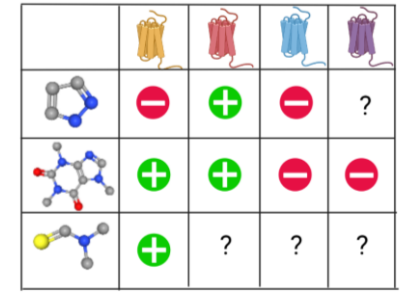
Summary

BitterDB

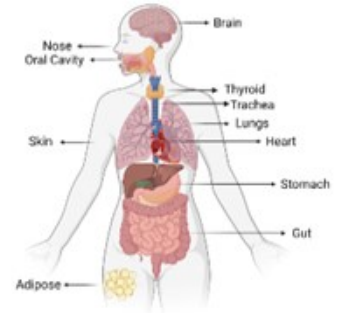


BitterPredict, BitterIntense

BitterMatch ligands to receptors



Bitter taste antagonists to mask bitterness and study ectopic taste receptors



Data! neighbor-informed features, 3D refinement and evaluation with known ligands

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CIDR Center for Interdisciplinary Data Science Research

ChemAxon

DFG Deutsche Forschungsgemeinschaft German Research Foundation

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Regarding positions