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Fakulteta za kemijo
in kemijsko tehnologijo

Inverse Molecular Docking as a New Powerful Tool for Drug-Repurposing

Laboratory of Physical Chemistry and Chemical Thermodynamics
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Kleefstra Syndrome Scientific Conference
Ljubljana, June 1st 2023

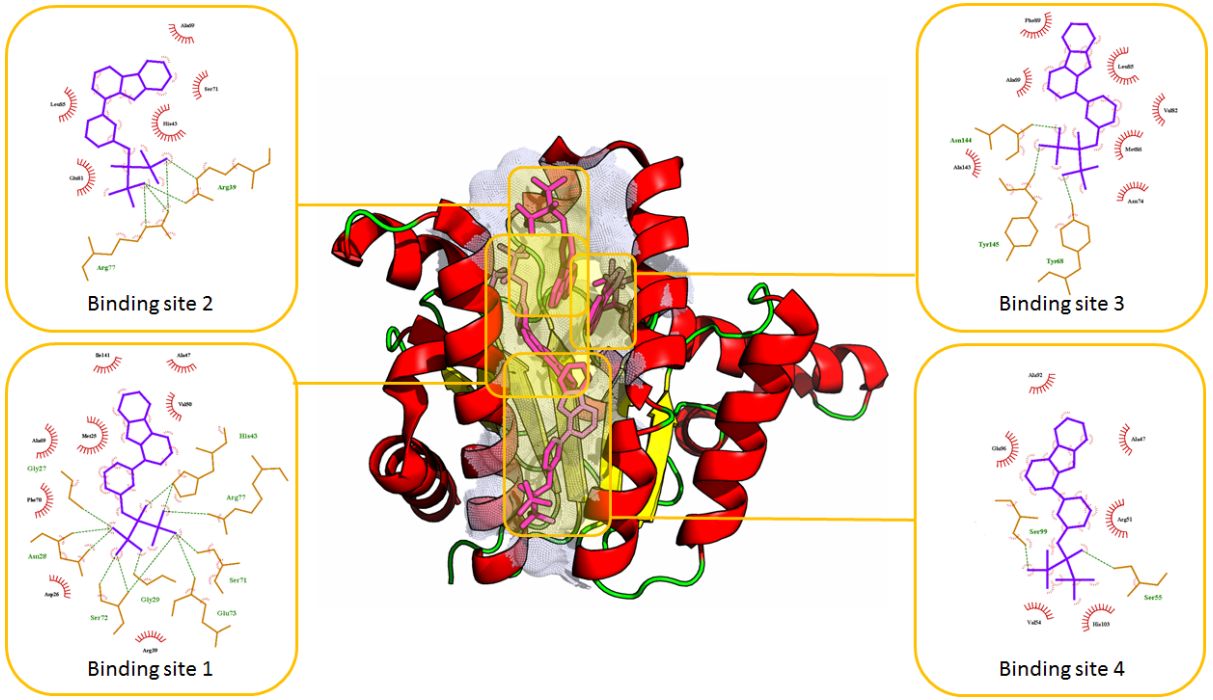
Presentation structure:

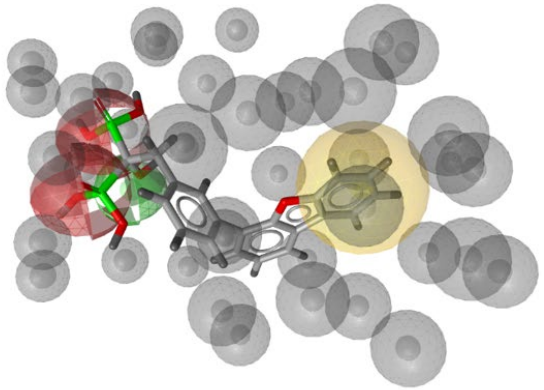
- molecular docking
- inverse docking
- drug repurposing
- inverse docking for drug repurposing
- inverse docking fingerprints

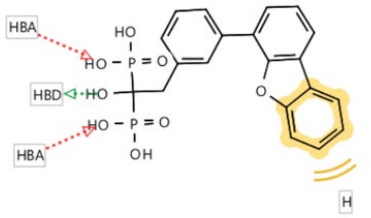
Typical molecular docking application in an HTVS scenario

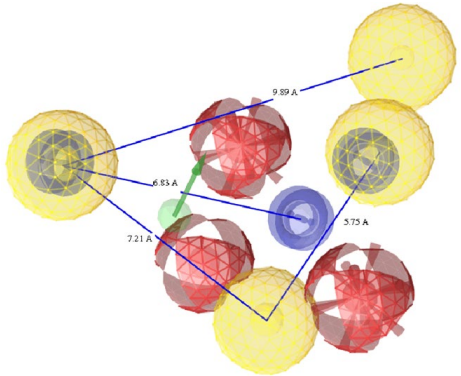
Workflow:

molecular docking





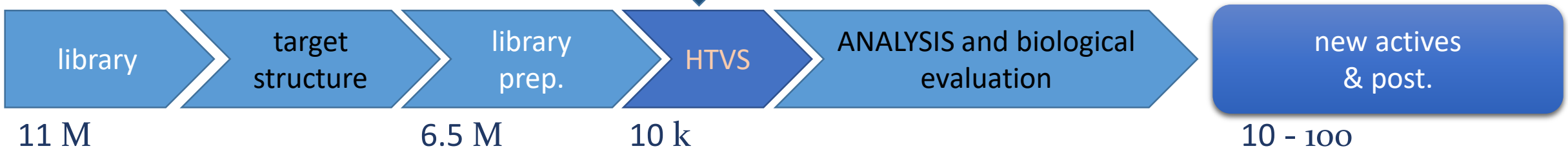


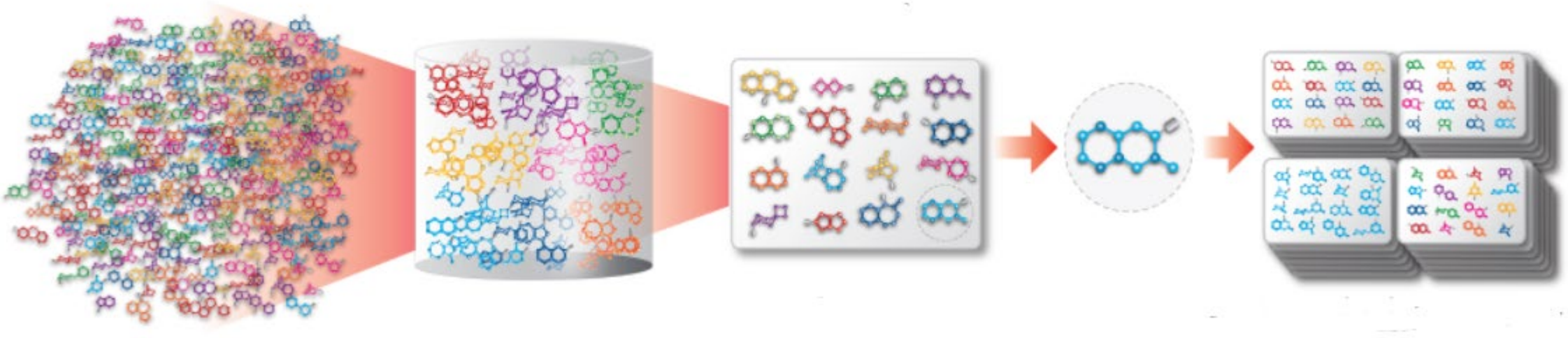


Typical molecular docking application in an HTVS scenario

Workflow:

molecular docking

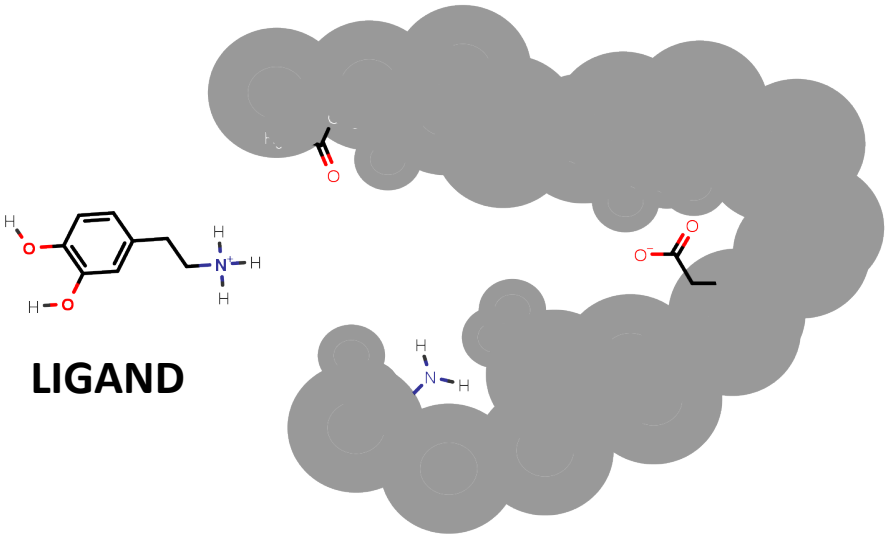




What is molecular docking?

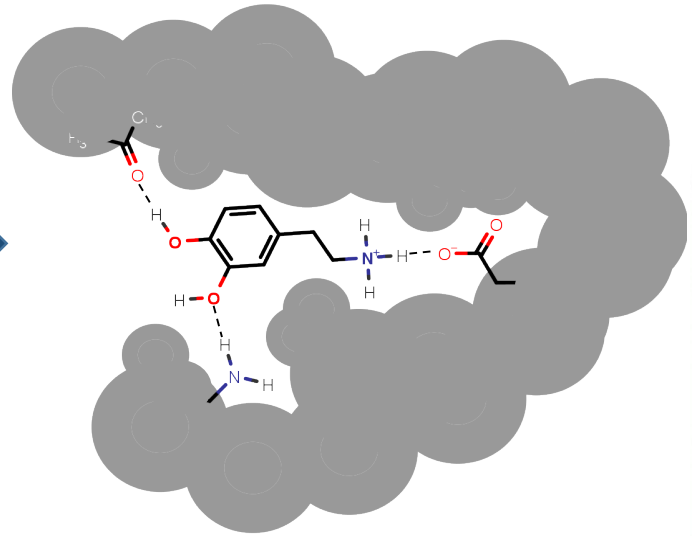
DOCKING + SCORING

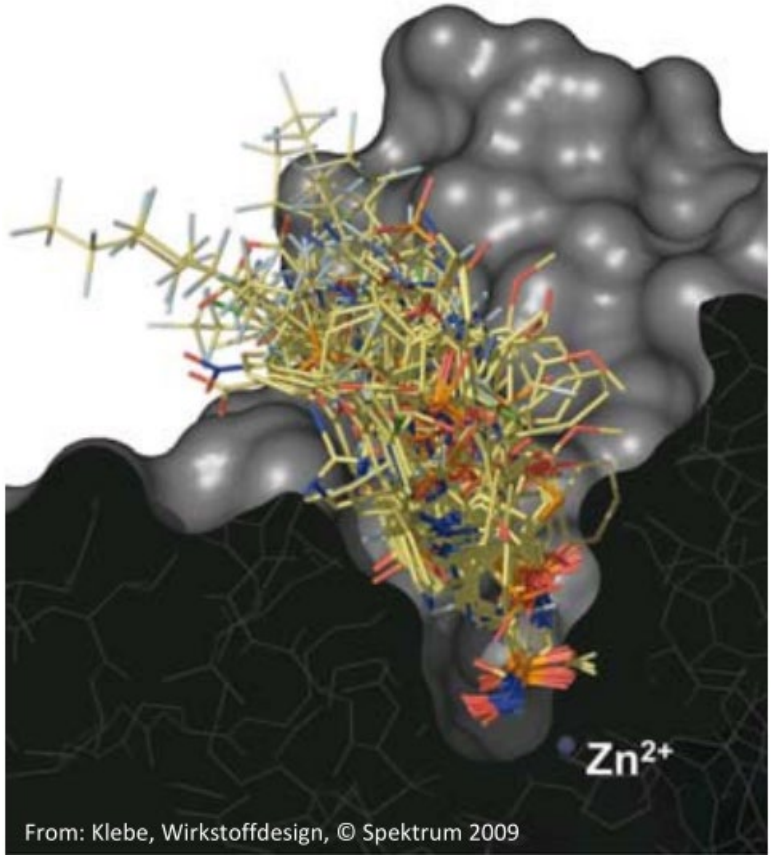
Large molecule
"target"



LIGAND

Large-molecule (protein)
-ligand complex

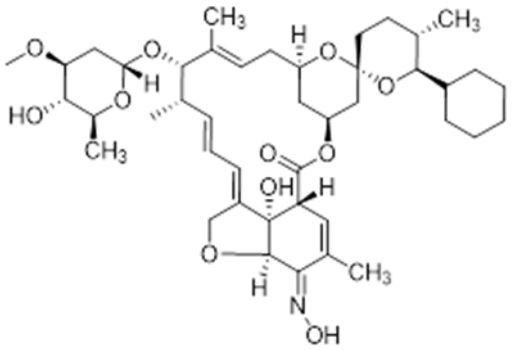




Can this be turned around ?

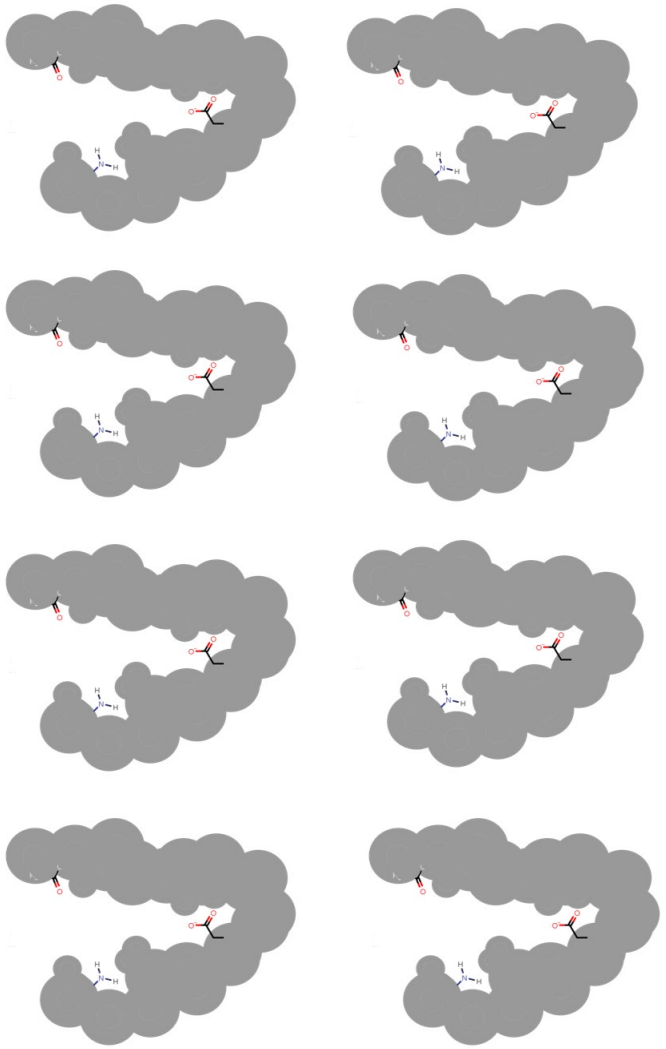
Inverse molecular docking

One ligand against many
Binding "targets" ?



LIGAND
(selamectin)

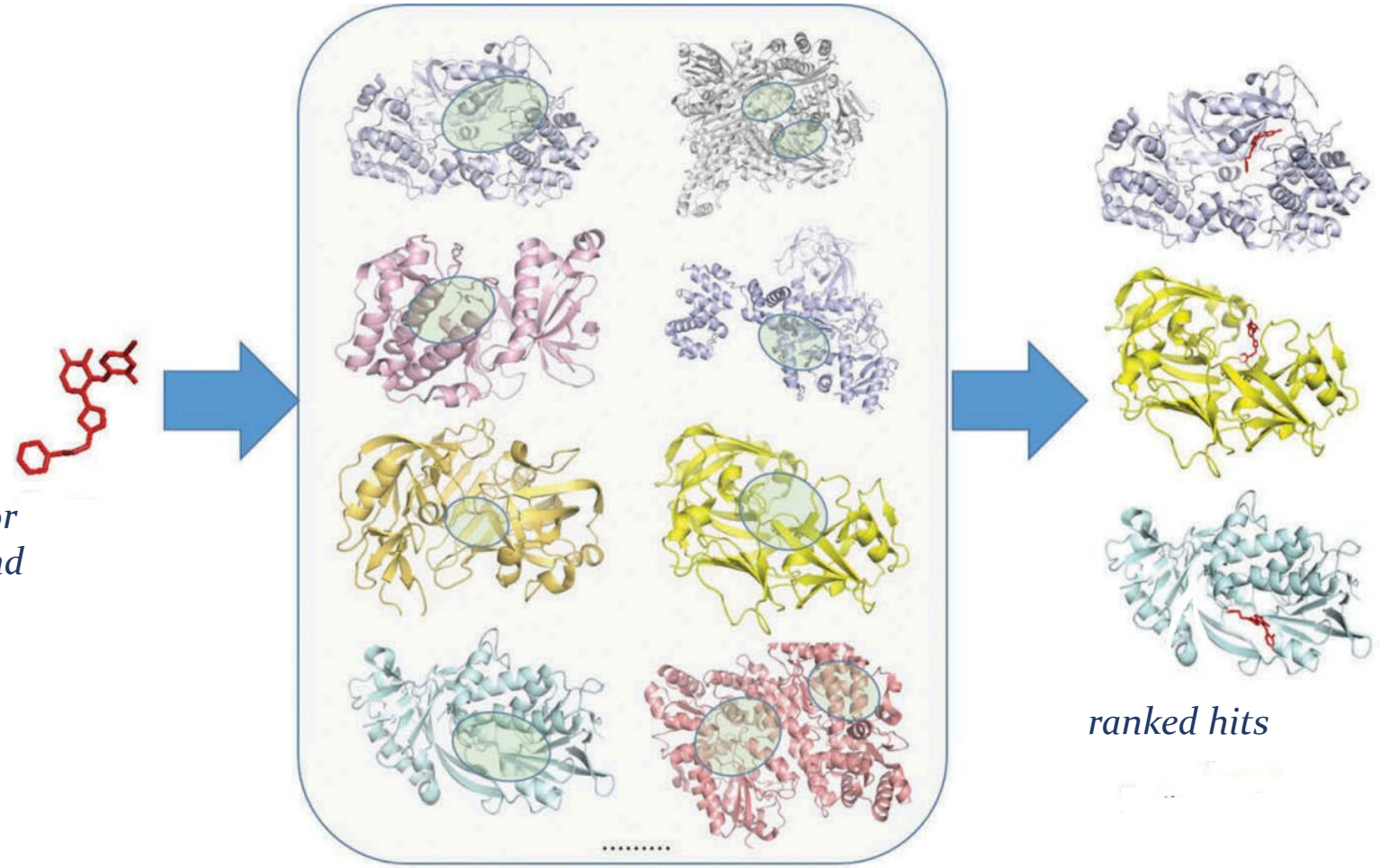
molecular docking



Inverse molecular docking

Docking a small-molecule drug/ligand in the potential binding cavities of a set of macromolecular targets.

Typical experimental preparation.

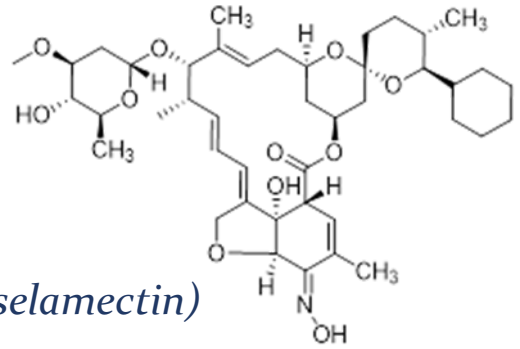


Ligand (or also ligand library)

Library of "targets"

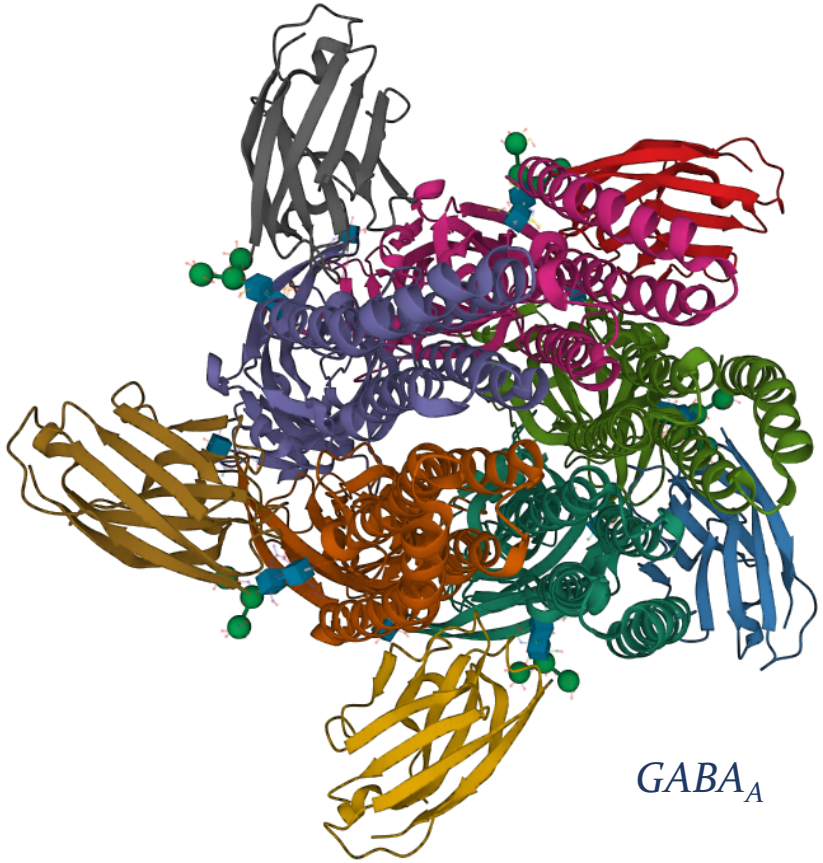
ranked hits

Inverse docking applications



Ligand (selamectin)

binding partners?



$GABA_A$

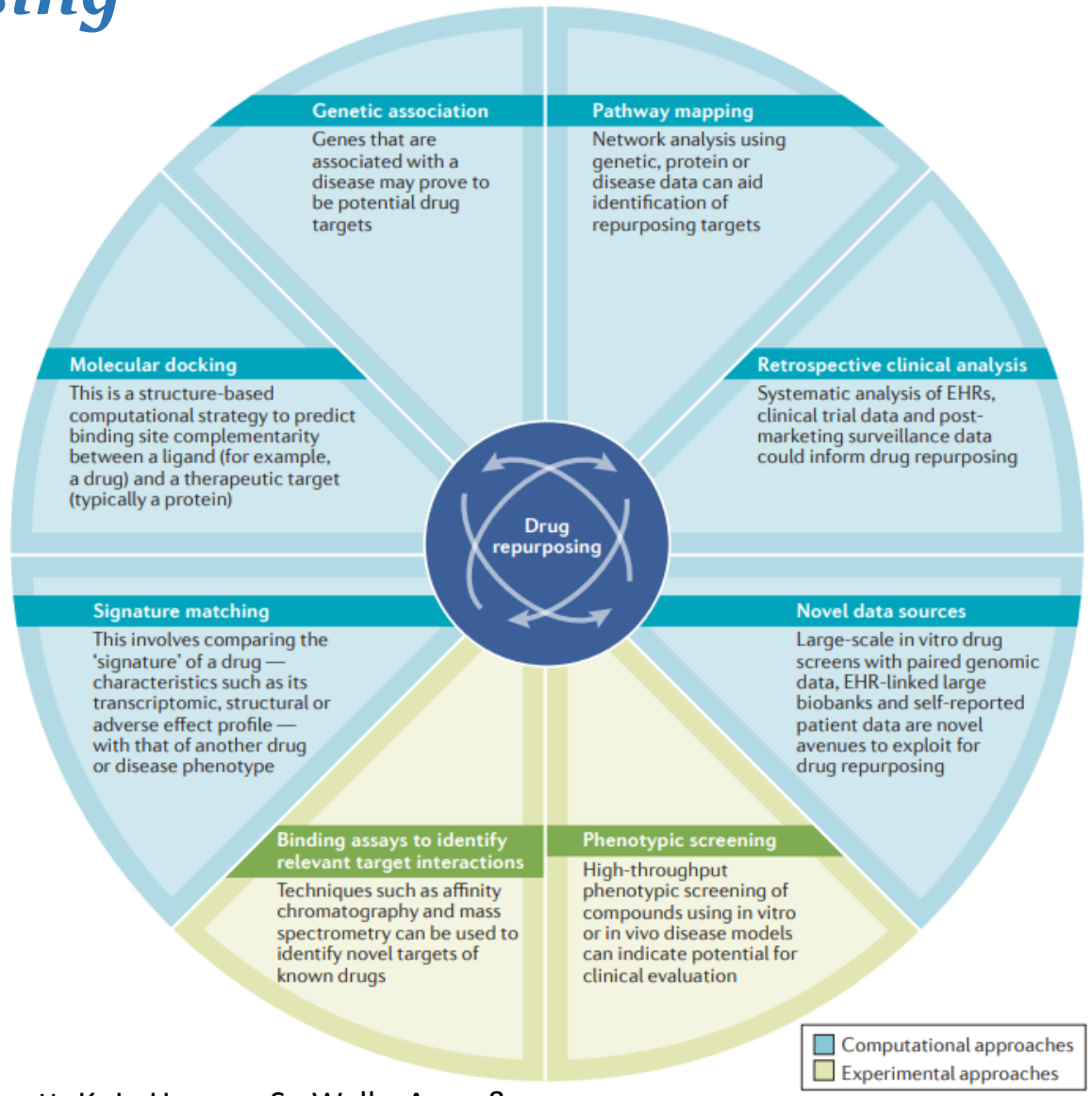
- *MOA studies*
- *Target fishing*
- *Selectivity studies*
- *Off-target studies*
- *Target or Binding partner engineering*
- *Drug repurposing*

Drug Repurposing

Due to high attrition rates, costs and invested time in new drug discovery and development, repurposing of known drugs to treat novel diseases is an attractive alternative.
Namely, it involves the use of de-risked compounds, resulting in lower overall development costs and shorter development timelines.

Drug name	Original indication	New indication	Date of approval	Repurposing approach used	Comments on outcome of repurposing
Zidovudine	Cancer	HIV/AIDS	1987	In vitro screening of compound libraries	Zidovudine was the first anti-HIV drug to be approved by the FDA
Minoxidil	Hypertension	Hair loss	1988	Retrospective clinical analysis (identification of hair growth as an adverse effect)	Global sales for minoxidil were US$860 million in 2016 (Questale minoxidil sales report 2017; see Related links)
Sildenafil	Angina	Erectile dysfunction	1998	Retrospective clinical analysis	Marketed as Viagra, sildenafil became the leading product in the erectile dysfunction drug market, with global sales in 2012 of $2.05 billion[8]
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	1998 and 2006	Off-label usage and pharmacological analysis	Thalidomide derivatives have achieved substantial clinical and commercial success in multiple myeloma
Celecoxib	Pain and inflammation	Familial adenomatous polyps	2000	Pharmacological analysis	The total revenue from Celebrex (Pfizer) at the end of 2014 was $2.69 billion (Pfizer 2014 financial report; see Related links)
Atomoxetine	Parkinson disease	ADHD	2002	Pharmacological analysis	Strattera (Eli Lilly) recorded global sales of $855 million in 2016

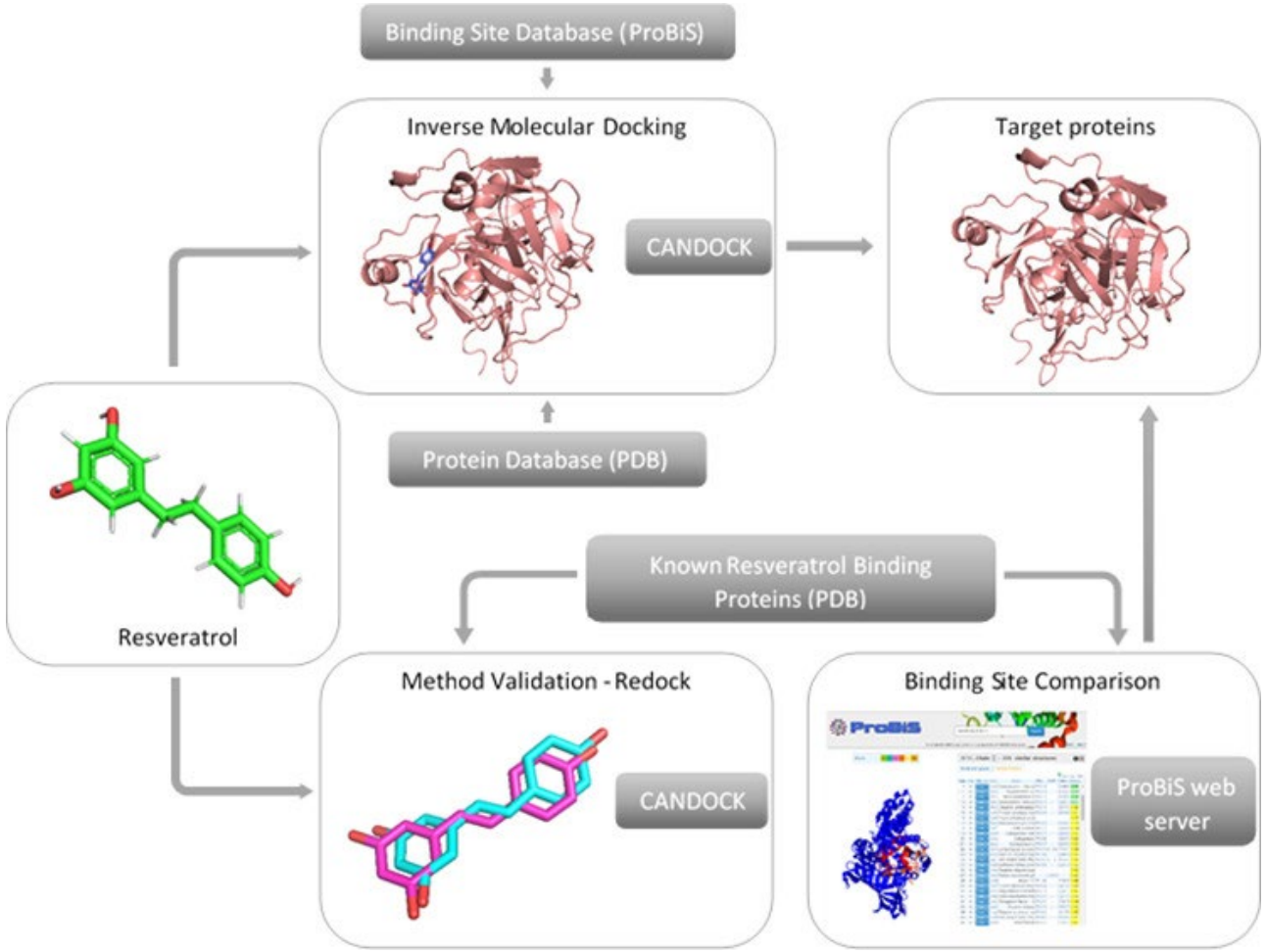
Drug Repurposing



Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., ... & Pirmohamed, M. (2019). Drug repurposing: progress, challenges and recommendations. Nature reviews Drug discovery, 18(1), 41-58.

Inverse docking applications in drug repurposing

Discovery of Novel Potential Human Targets of a Known Molecule



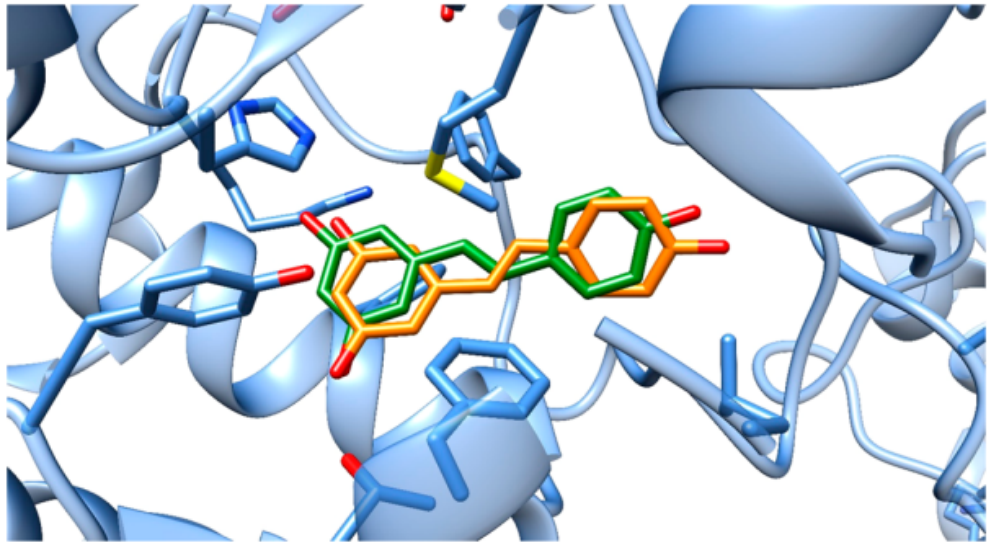


Figure 5. Comparison of the redocked and the cocrystallized resveratrol poses in the sulfotransferase family cytosolic 1B member 1 protein (PDB ID 3ckl). Docked resveratrol (green) overlaps well with the cocrystallized resveratrol (orange) with the RMSD value of 1.25 Å. Protein is presented as blue cartoon model.

Kores, K., Lesnik, S., Bren, U., Janezic, D., & Konc, J. (2019). Discovery of novel potential human targets of resveratrol by inverse molecular docking. *Journal of Chemical Information and Modeling*, *59*(5), 2467-2478.

Inverse docking applications in drug repurposing

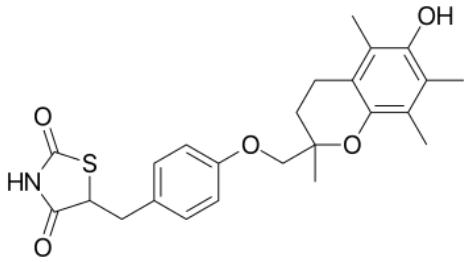
Discovery of Novel Potential Human Targets of a Known Molecule

PDB ID with chain	protein name	predicted binding energy [arbitrary units[a]]	protein function and reported connection with diseases	known experimental correlation with resveratrol	references
3h5cB	vitamin K-dependent protein Z	−47.2125	plasma glycoprotein, that plays an important role in blood coagulation; cofactor for inhibition of factor X	no	48, 49
			protein Z/ZPI system connected with thrombosis, coronary syndromes, stroke, nephrotic syndrome		
5ab2A	endoplasmic reticulum aminopeptidase 2 (ERAP2)	−46.2235	regulation of the antigenic peptide repertoire, influencing cytotoxic immune responses, shaping epitope immunodominance	no	50
			potential link with resistance to HIV infection and association with predisposition to cancer and other MHC-connected diseases		
5e1dA	N-terminal methyltransferase 1 (NTMT1)	−45.1385	catalyst of the N-terminal methylation of various proteins	no	51
			knockdown of NTMT1 leads to hypersensitivity or intolerance of breast cancer cells to etoposide and γ-irradiation treatments, also higher mortality rate and premature aging of mice		
3zmvA	lysine-specific histone demethylase 1A	−44.4614	catalyst of the removal of mono- or dimethyl groups from proteins	yes[52]	53
			involvement in cancer, neurodegeneration, and viral infection		
3fedA	glutamate carboxypeptidase III	−44.2817	metalloenzyme, homologue to glutamate carboxypeptidase II, which is a transmembrane metallopeptidase, found in brain, small intestine, and prostate	no	54
			biological significance is not yet known		
1i3oE	baculoviral IAP repeat-containing protein 4	−43.9549	antiapoptotic protein, potent caspase inhibitor, potential approach for treatment of human glaucoma	no	55, 56
			connection with glaucoma, Wilson disease		
4cqlE	estradiol 17-beta-dehydrogenase 8	−42.9049	short-chain alcohol dehydrogenase, enzyme, catalysator of reversible interconversion of 17beta-estradiol and estrone, reduction of 16alpha-hydroxyestrone to estriol (estrogen in human pregnancy) and the oxidation−reduction of some androgens and progesterone	no	57, 58
			dysfunctions result in disorders in reproduction and neuronal diseases, also found in cancers		
2hyvA	annexin A2	−42.7037	important in various processes, like membrane trafficking, cell signaling apoptosis and inflammation	no	10, 59

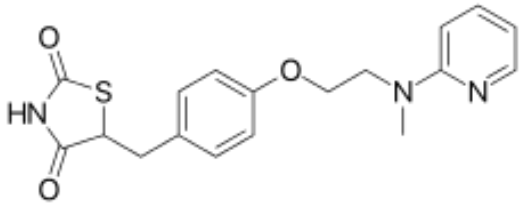
Kores, K., Lesnik, S., Bren, U., Janezic, D., & Konc, J. (2019). Discovery of novel potential human targets of resveratrol by inverse molecular docking. *Journal of Chemical Information and Modeling*, *59*(5), 2467-2478.

Inverse docking applications in drug repurposing

Study of drug side effects



Troglitazone
(withdrawn)



Rosiglitazone
(Avandia)

Glitazones are a class of heterocyclic compounds consisting of a five-membered thiazolidinedione ring used in the treatment of diabetes mellitus type 2.

withdrawn due to increased incidence of drug-induced hepatitis

Kores, K., Konc, J., & Bren, U. (2021). Mechanistic insights into side effects of troglitazone and rosiglitazone using a novel inverse molecular docking protocol. Pharmaceutics, 13(3), 315.

Inverse docking applications in drug repurposing

Identified targets for troglitazone

PDB ID with Chain	Docking Score [Arbitrary Units [1]]	Protein Name	Protein Function and Connection with Diseases	References
3uzxA [2]	−68.2	3-oxo-5-beta-steroid 4-dehydrogenase	Catalyzes the reduction of the Δ4 double bond of bile acid intermediates and steroid hormones carrying the Δ4-3-one structure in the A/B cis configuration.	[44]
5fyyA [2]	−68.0	Lysine-specific demethylase 5B	A member of the KDM5 sub-family, acting as a histone 3 lysine 4 trimethyl demethylase, regulating proliferation, stem cell self-renewal, and differentiation. Connected with various forms of cancer.	[45,46]
2wtvA	−66.1	Aurora kinase A	Involved in the regulation of centrosomes and segregation of chromosomes. Associates with the centrosome and the spindle microtubules during mitosis and plays a critical role in several mitotic events. Known connections to various forms of cancer.	[47,48]
4gs4A [3]	−64.7	Alpha-tubulin *N*-acetyltransferase 1	Acetylates K40 on α-tubulin at the lumenal side of microtubules. Connections with neurological disorders, cancer, heart diseases.	[49,50]
1mncA	−64.0	Neutrophil collagenase	A member of the matrix metalloproteinase family. Degrades fibrillar type I, II, and III collagens. Implicated in several degenerative diseases with a slow matrix degradation rate, such as osteoporosis and Alzheimer's disease.	[51,52]

Kores, K., Konc, J., & Bren, U. (2021). Mechanistic insights into side effects of troglitazone and rosiglitazone using a novel inverse molecular docking protocol. Pharmaceutics, 13(3), 315.

Inverse docking applications in drug repurposing

Identified targets for rosiglitazone

PDB ID with Chain	Docking score [Arbitrary Units [1]]	Protein Name	Protein Function and Connection with Diseases	References
4jijA	−60.5	Matrix metalloproteinase 9	Degrades components of the extracellular matrix, mostly collagens. Known connections with cancer, neurological disorders, and cardiovascular diseases.	[66–69]
4lk3A	−59.9	UDP-glucuronic acid decarboxylase 1	Catalyzes the formation of UDP-xylose from UDP-glucuronate. No known connections with human diseases.	[70,71]
3f9zA	−59.8	*N*-lysine methyltransferase KMT5A	Monomethylates lysine 20 of histone H4 (H4K20), proliferating cell nuclear antigen (PCNA) and p53. Potential connections with cancer tumorigenesis and neurodegenerative diseases.	[72,73]
4u7pA	−58.8	DNA (cytosine-5)-methyltransferase 3A	Responsible for the de novo methylation of 5-methylcytosine during embryogenesis for the establishment of the somatic methylation pattern, which is crucial for embryonic development. Known connections with hematological malignancies, that is tumors of the hematopoietic and lymphoid tissues, as well as with defects in brain development or neurological defects.	[74–77]

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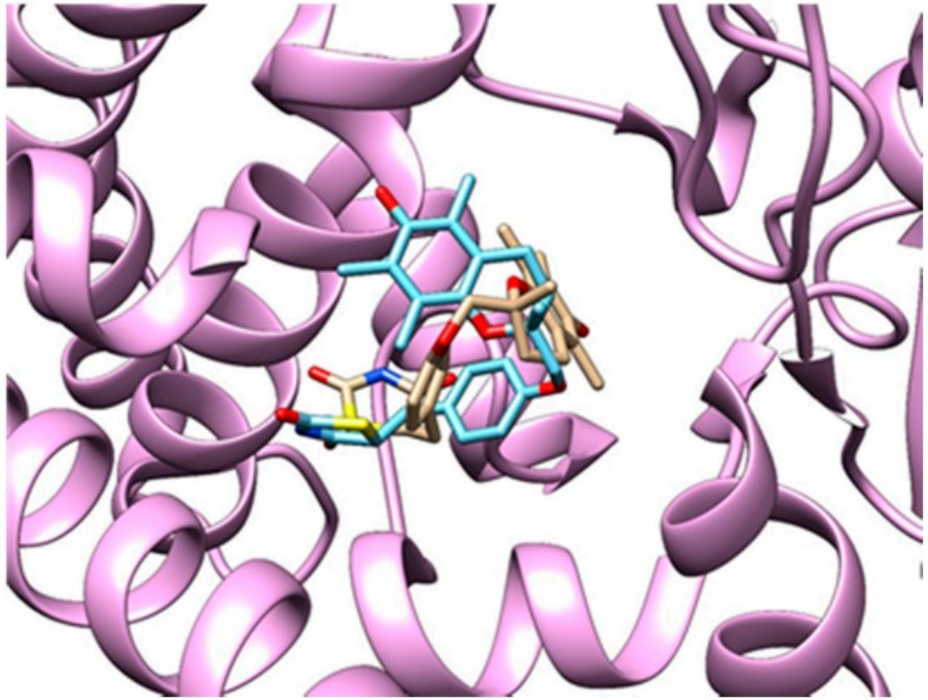
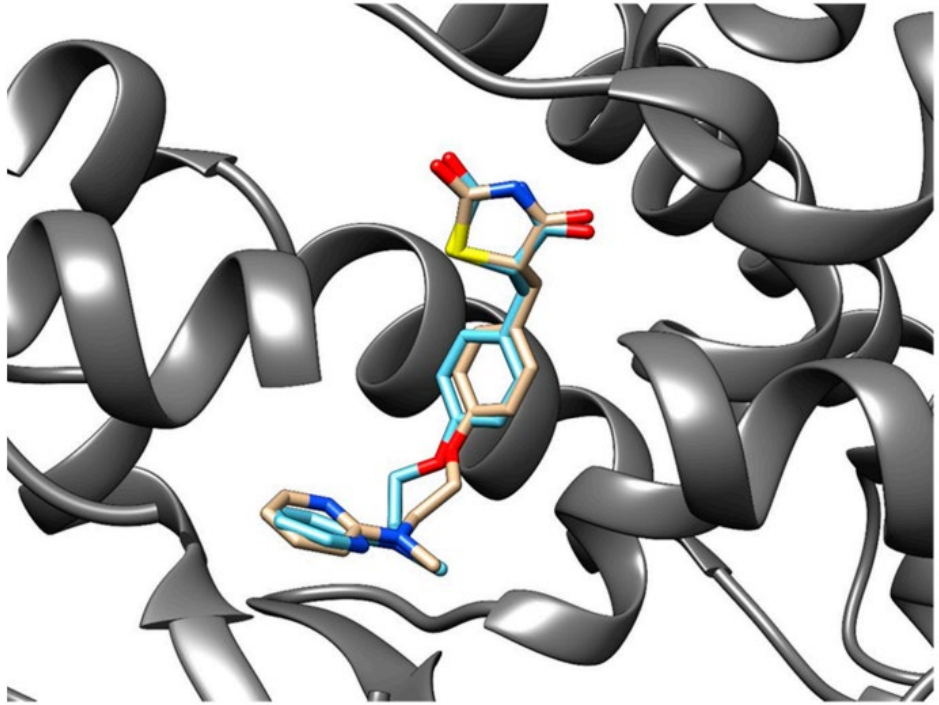
Inverse docking applications in drug repurposing

Off-target MOA

Our results successfully explained the side effects of troglitazone and rosiglitazone, and we also predicted additional ones, that could occur after the long-term application of these two drugs. With further development of computational methods and in conjunction with experimental research, these results can be further analyzed to better explain the side effects of both drugs and to help mitigate or even eliminate them.

CYP-2C8





PPAR-gamma

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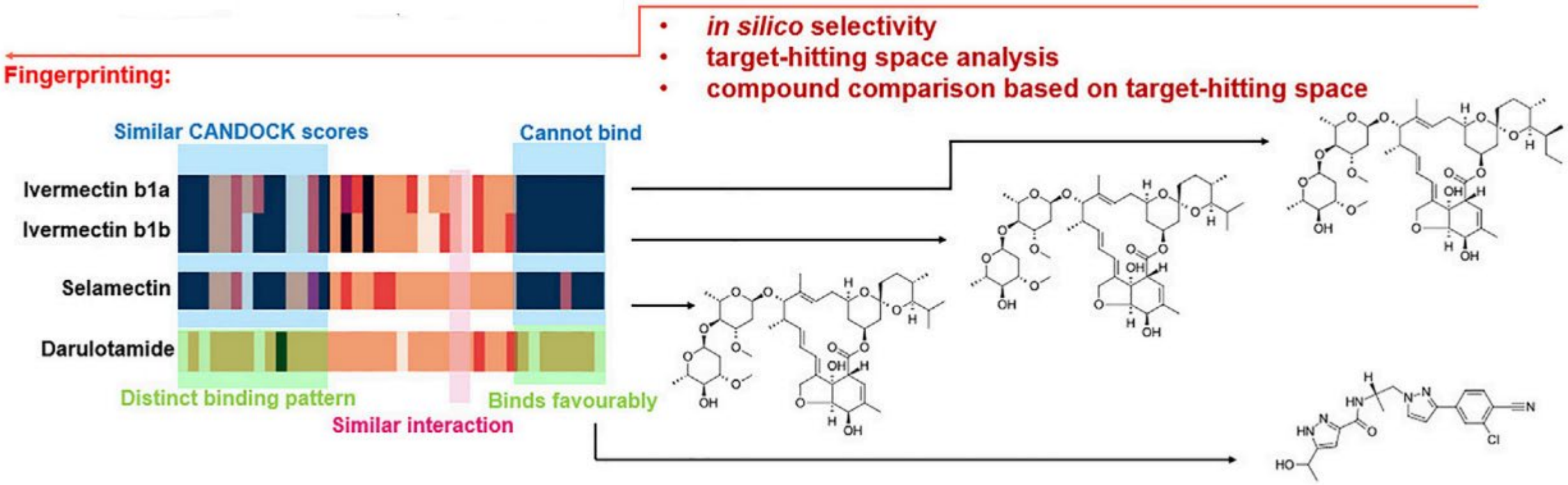
Inverse docking applications in drug repurposing

Novel approach of inverse fingerprinting for large scale analysis



Jukič, M., Kores, K., Janežič, D., & Bren, U. (2021). Repurposing of drugs for SARS-CoV-2 using inverse docking fingerprints. *Frontiers in Chemistry*, 1059.

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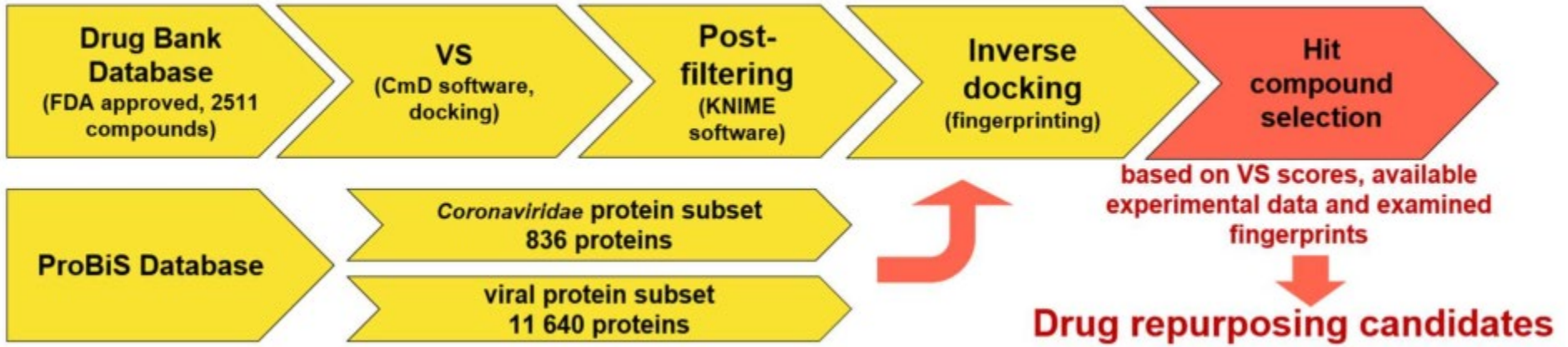
Inverse docking applications in drug repurposing

Many ligands against proteome approaches



Using inverse fingerprinting we can circumvent typical inverse docking problems and use the proteome data to our advantage

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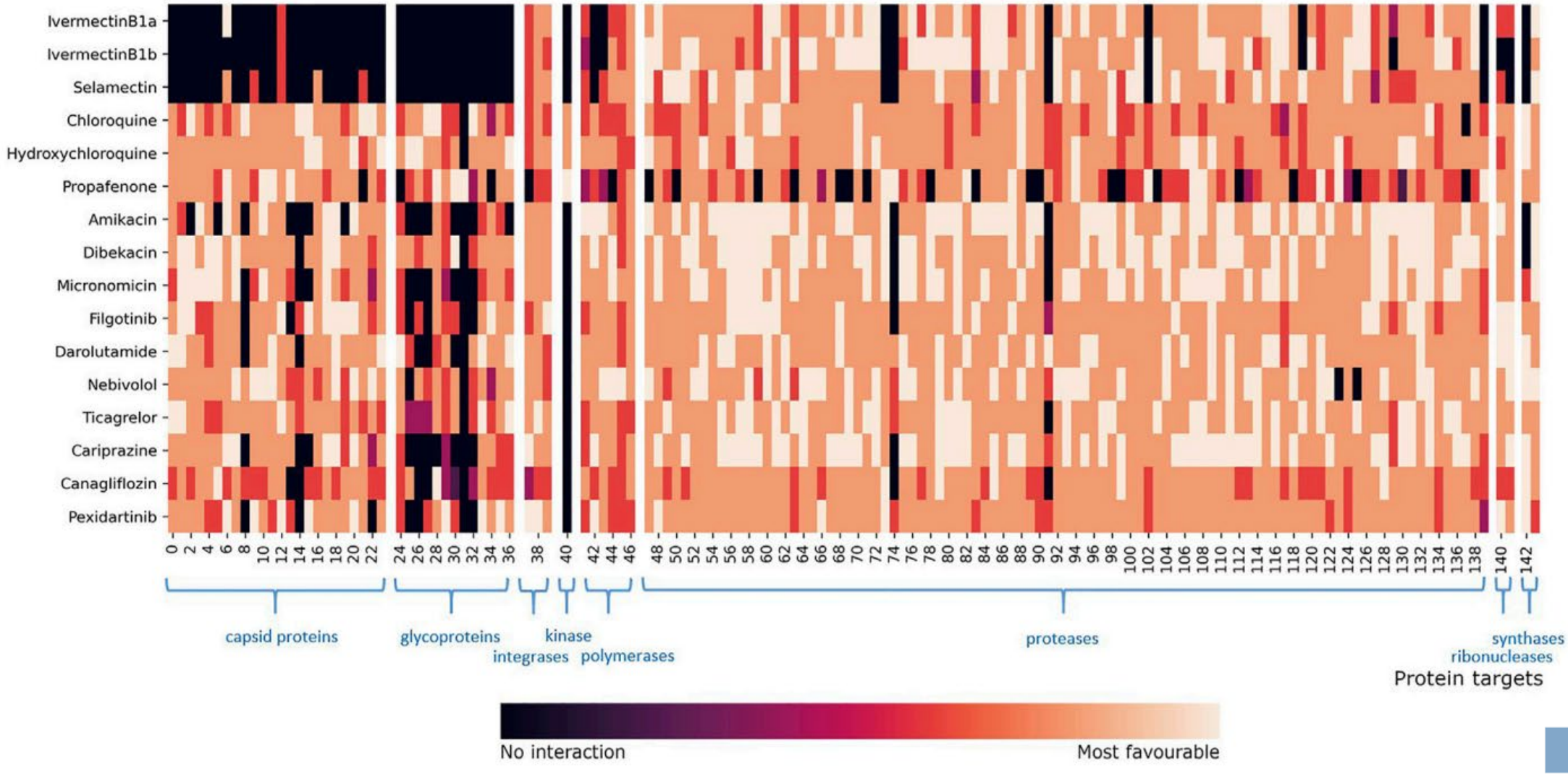
Inverse docking applications in drug repurposing

Many ligands against proteome approaches



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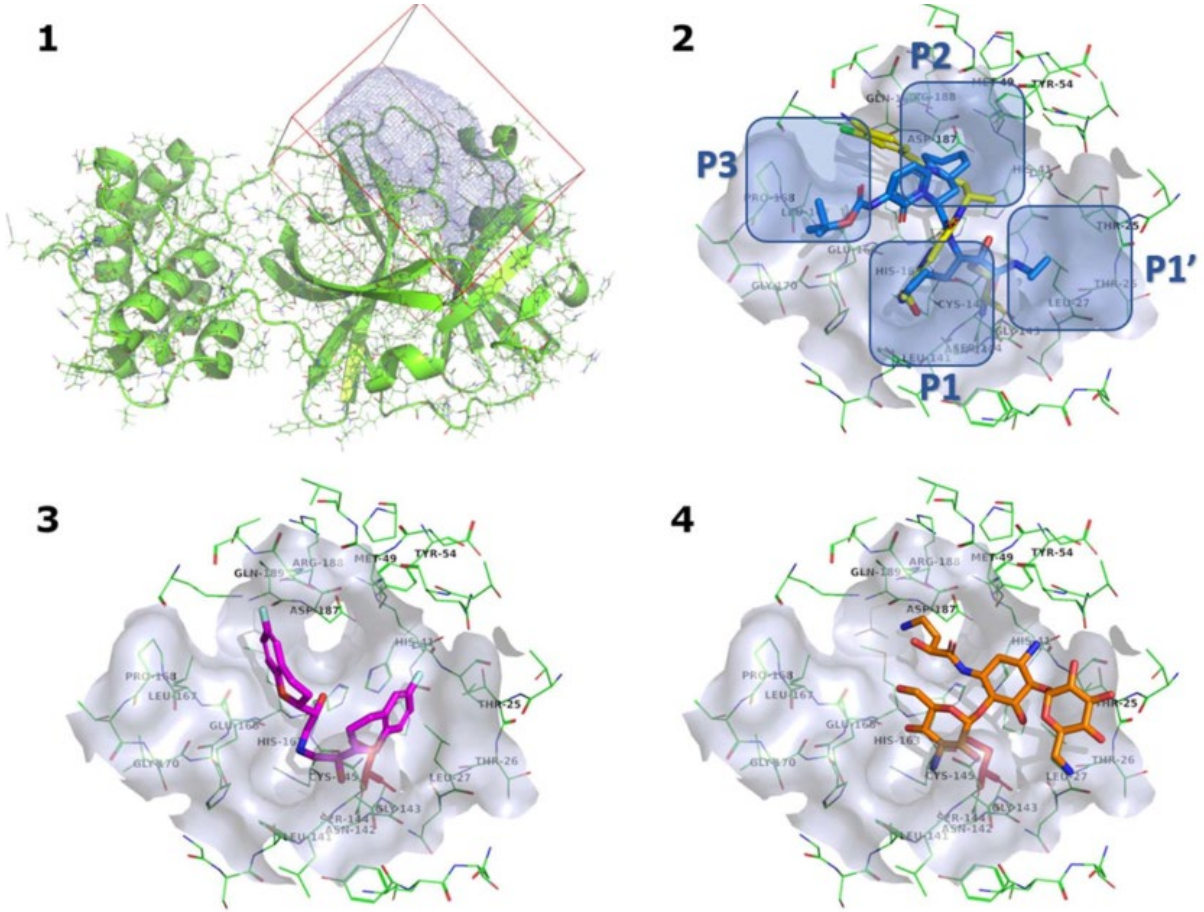
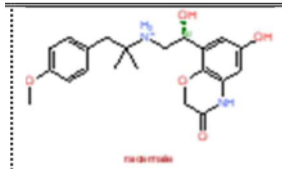
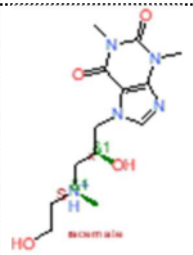
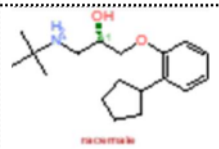
Inverse docking applications in drug repurposing

Repurposing for SARS-CoV-2 3CL^{pro}



structure	*Mr (g/mol)*	*Name (INN)*	*CmDock docking score (1)*	*Classification (2)*	*Phospholipidosis potential in silico (3)*
	386.5	Olodaterol	-25.8	*beta2-adrenergic agonist*	no
	311.3	Xanthinol	-24.5	*vasodilatator*	no
	291.4	Penbutolol	-24.4	*beta-adrenergic antagonist*	no

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Our computational resources:

VEGA HPC

HPC RIVR

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Thank You for Your attention!

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