

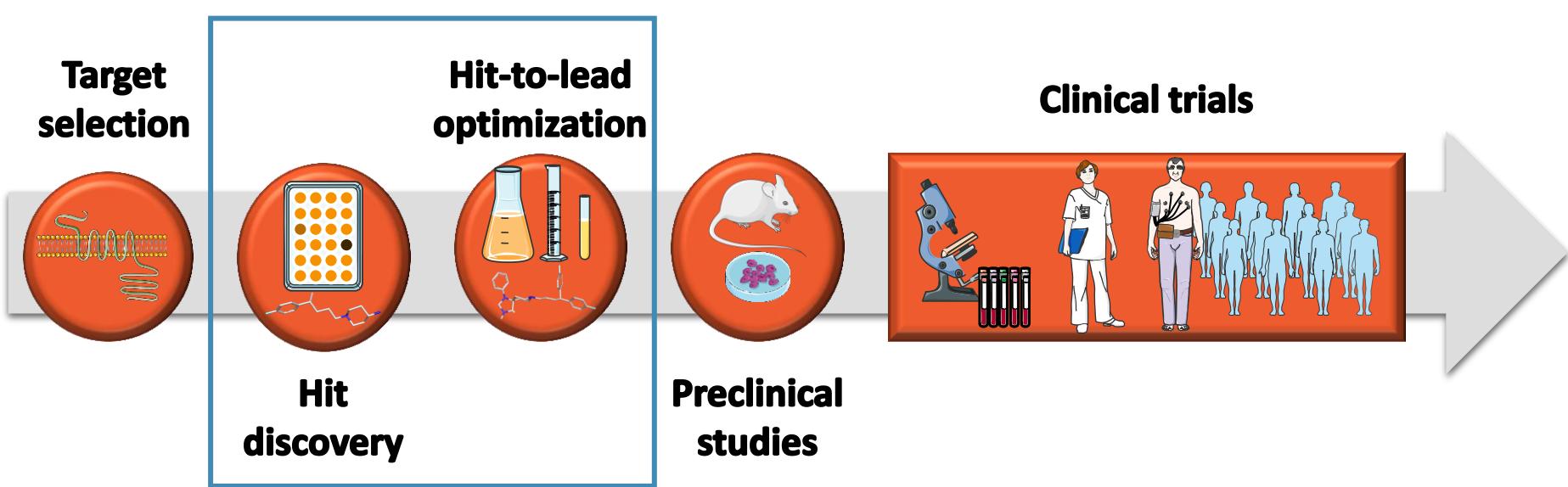
Online structure-based screening of purchasable approved drugs and natural compounds

*retrospective examples of drug repositioning on cancer
targets*

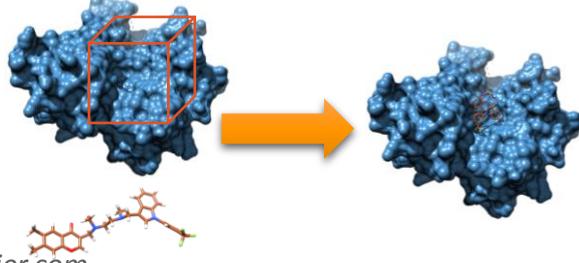
N. Lagarde – B. Villoutreix
28.06.2018

Background

Drug discovery



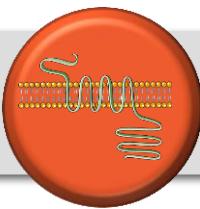
Virtual screening methods



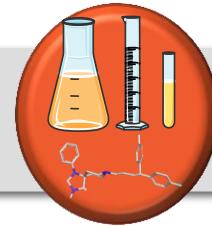
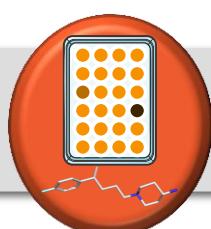
Background

Drug discovery

Target selection



Hit-to-lead optimization



Hit discovery

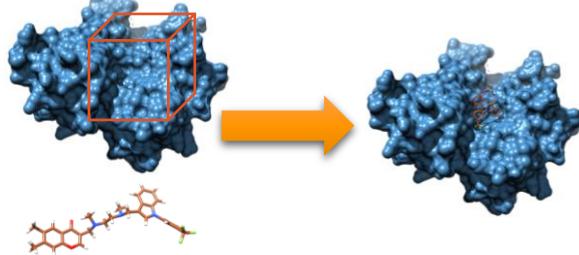
Preclinical studies



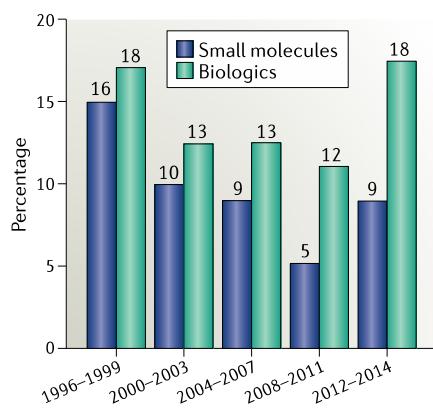
Clinical trials

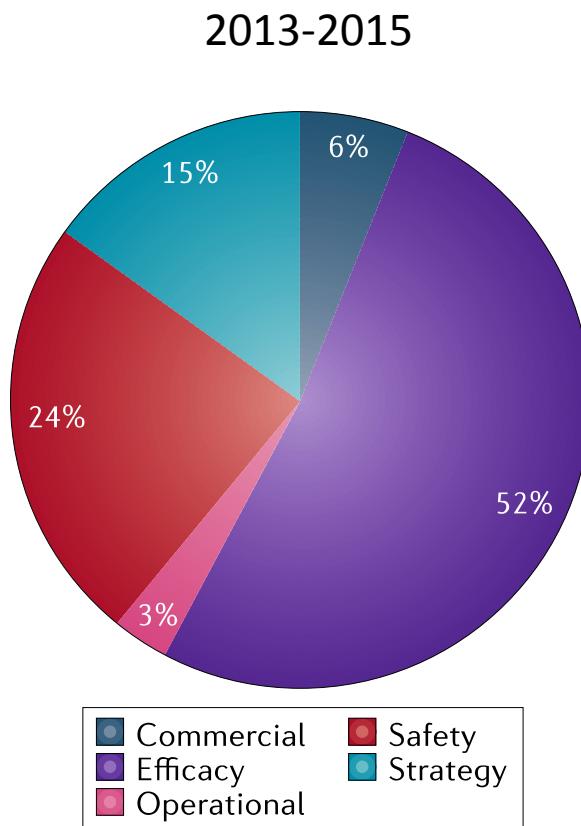


Virtual screening methods

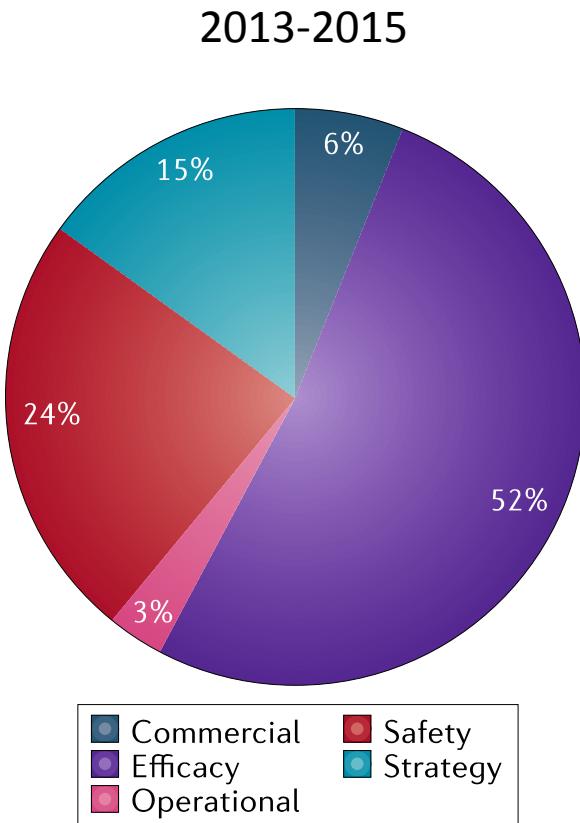


Success rate ~ 10%



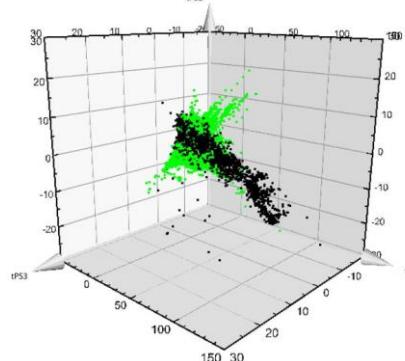


Harrison, R.K. *Nat Rev Drug Discov*, 2016



Harrison, R.K. *Nat Rev Drug Discov*, 2016

Inspired by natural products



Rosen, J. *J Med Chem*, 2009

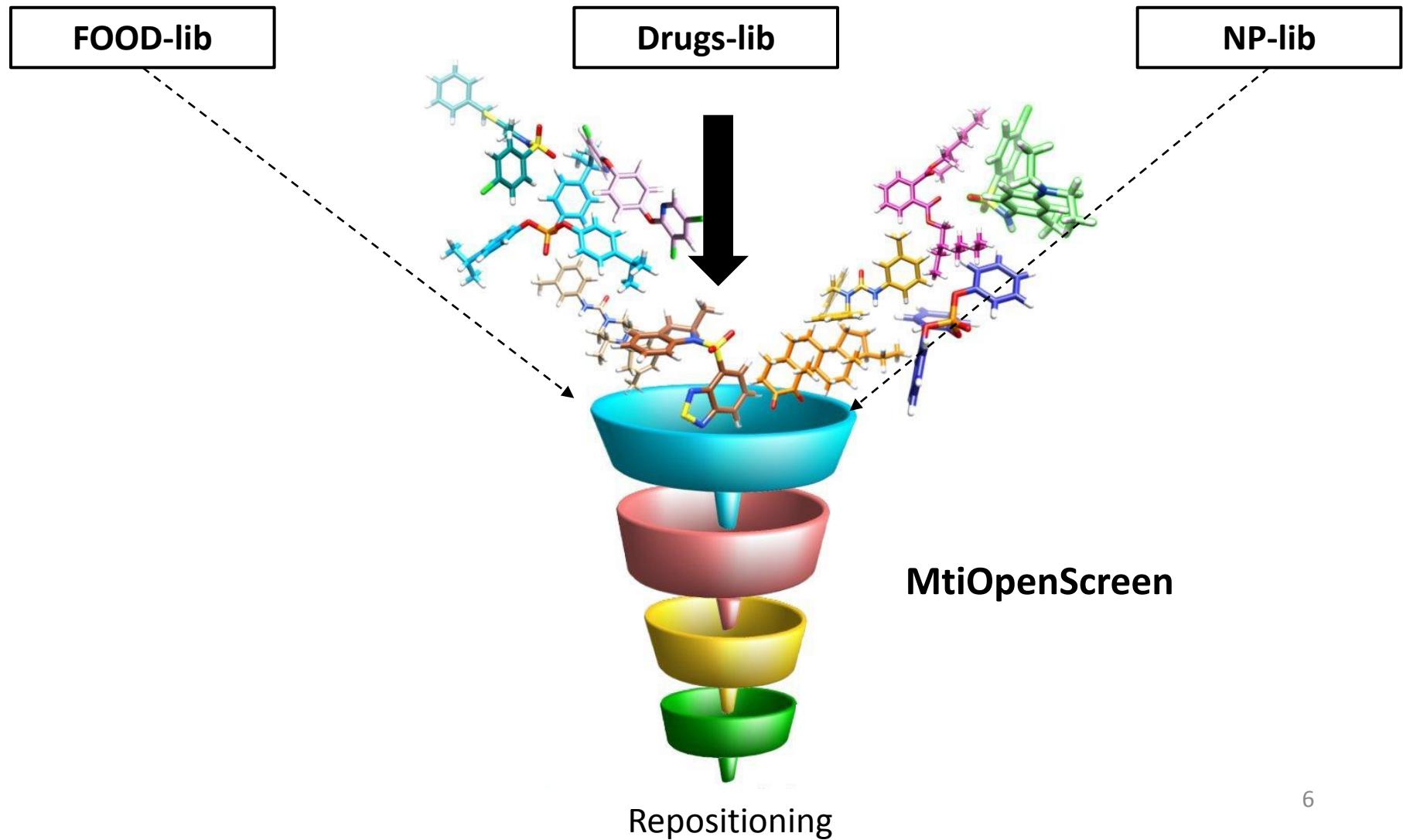
natural metabolite
bioavailability

Drug repositioning



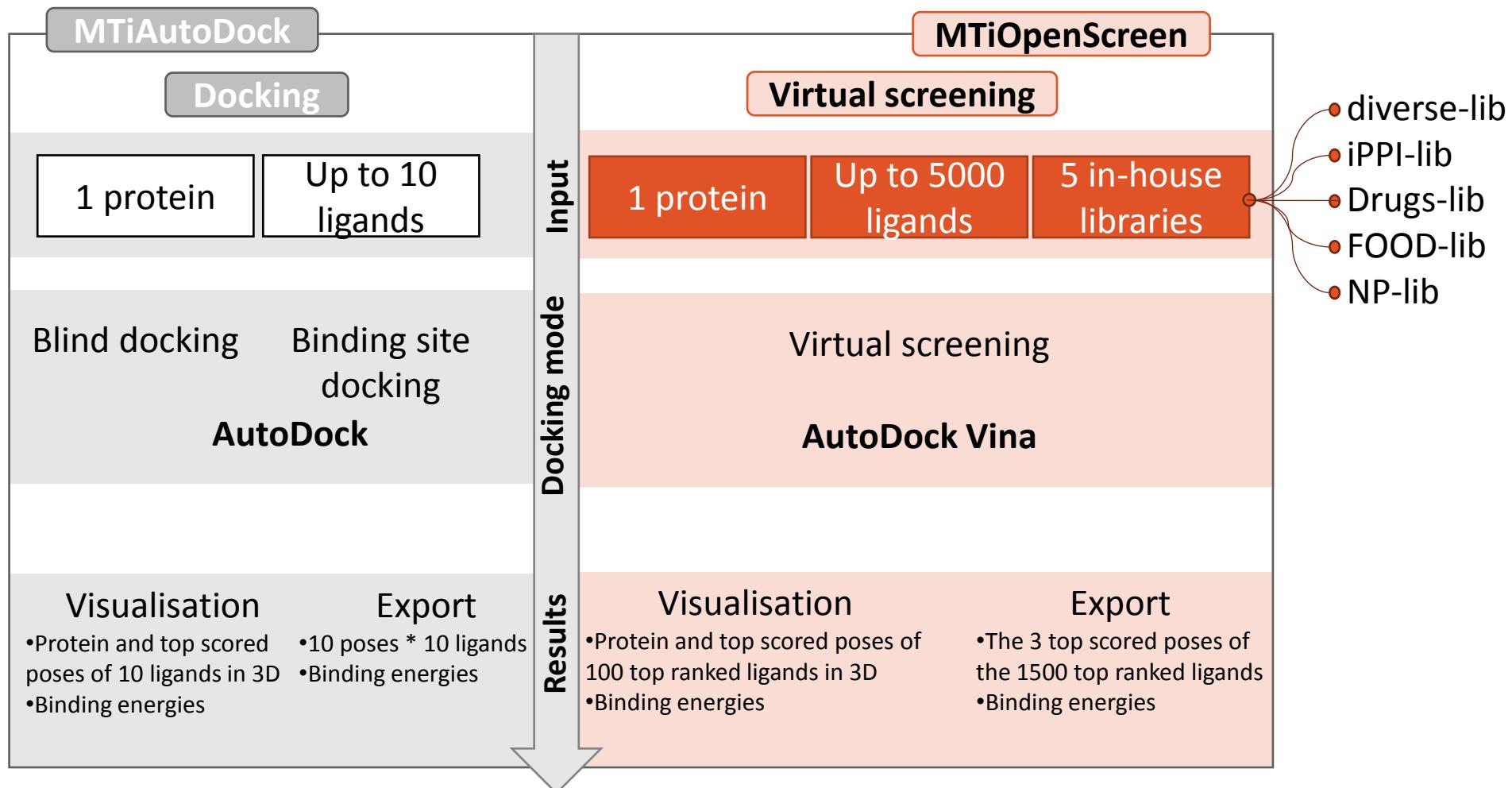
Nosengo, N. *Nature*, 2016

User-friendly structure-based virtual screening protocol combined with prepared and purchasable approved drug and natural compound collections



Methods

MTiOpenScreen: A service to dock small compounds



Chemical libraries generation



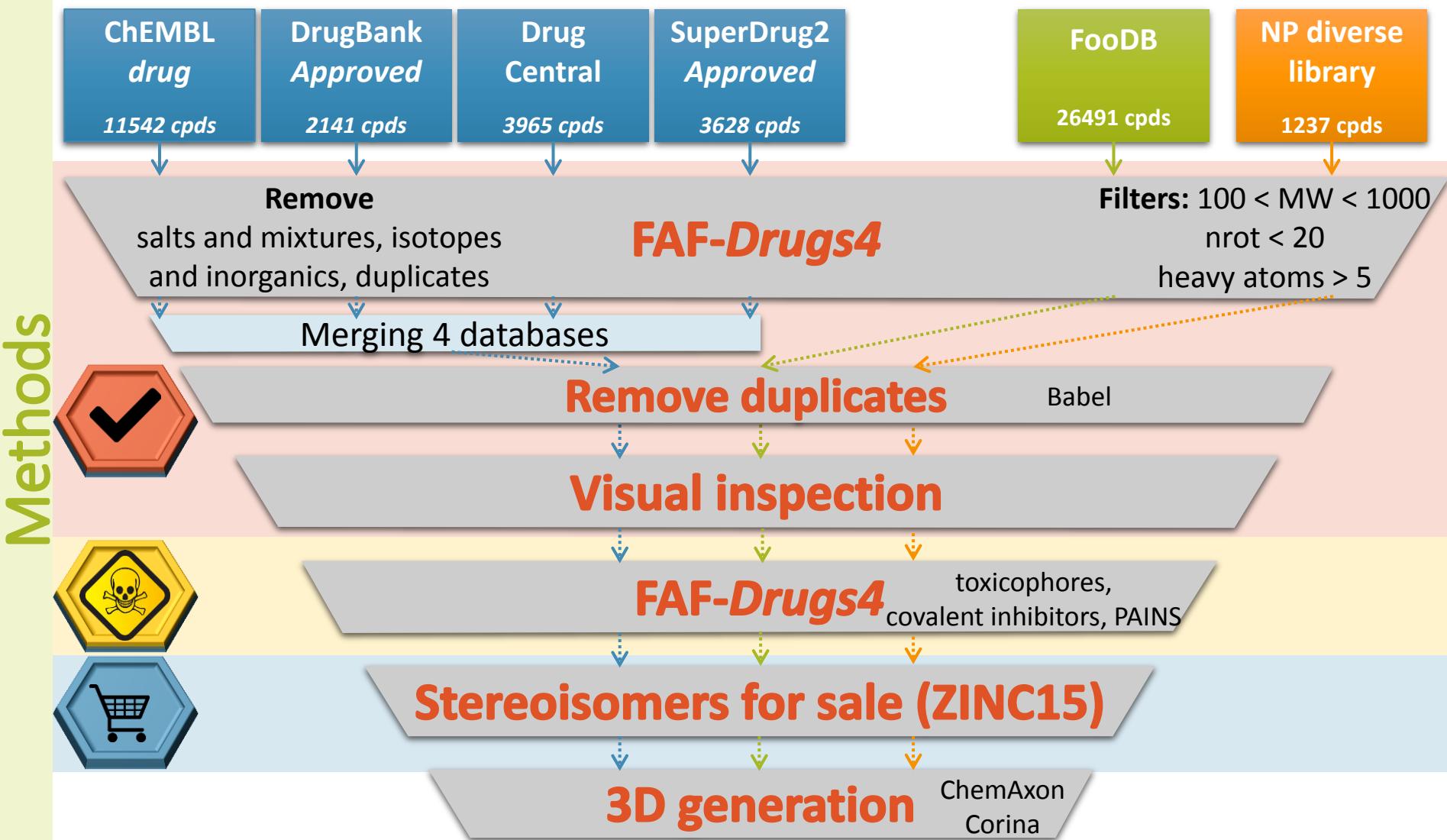
Suitable for docking computations



No major documented toxicophores



Purchasable



ChEMBL: Gaulton A et al. *Nucleic Acids Res*, 2012

DrugBank: Wishart DS et al. *Nucleic Acids Res*, 2018

DrugCentral: Ursu O et al. *Nucleic Acids Res*, 2017

SuperDrug2: Siramshetty VB et al. *Nucleic Acids Res*, 2018

FooDB: <http://www.foodb.ca>

NP: O'Hagan S and Kell DB *Biotechnol Lett*, 2018

FAF-Drugs4: Lagorce D et al. *Bioinformatics*, 2017

ChEMBL
drug

11542 cpds

DrugBank
Approved

2141 cpds

Drug
Central

3965 cpds

SuperDrug2
Approved

3628 cpds

FooDB

26491 cpds

NP diverse
library

1237 cpds

Remove

salts and mixtures, isotopes
and inorganics, duplicates

FAF-Drugs4

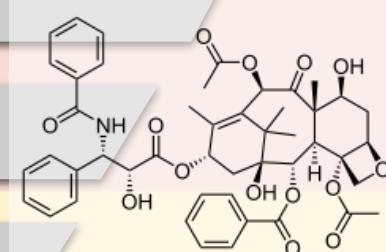
Filters: 100 < MW < 1000
nrot < 20
heavy atoms > 5

Merging 4 databases

Remove duplicates

Babel

Visual inspection



FAF-Drugs4

toxicophores,
covalent inhibitors, PAINS

Stereoisomers for sale (ZINC15)

ChemAxon
Corina

3D generation

ChEMBL: Gaulton A et al. Nucleic Acids Res, 2012

DrugBank: Wishart DS et al. Nucleic Acids Res, 2018

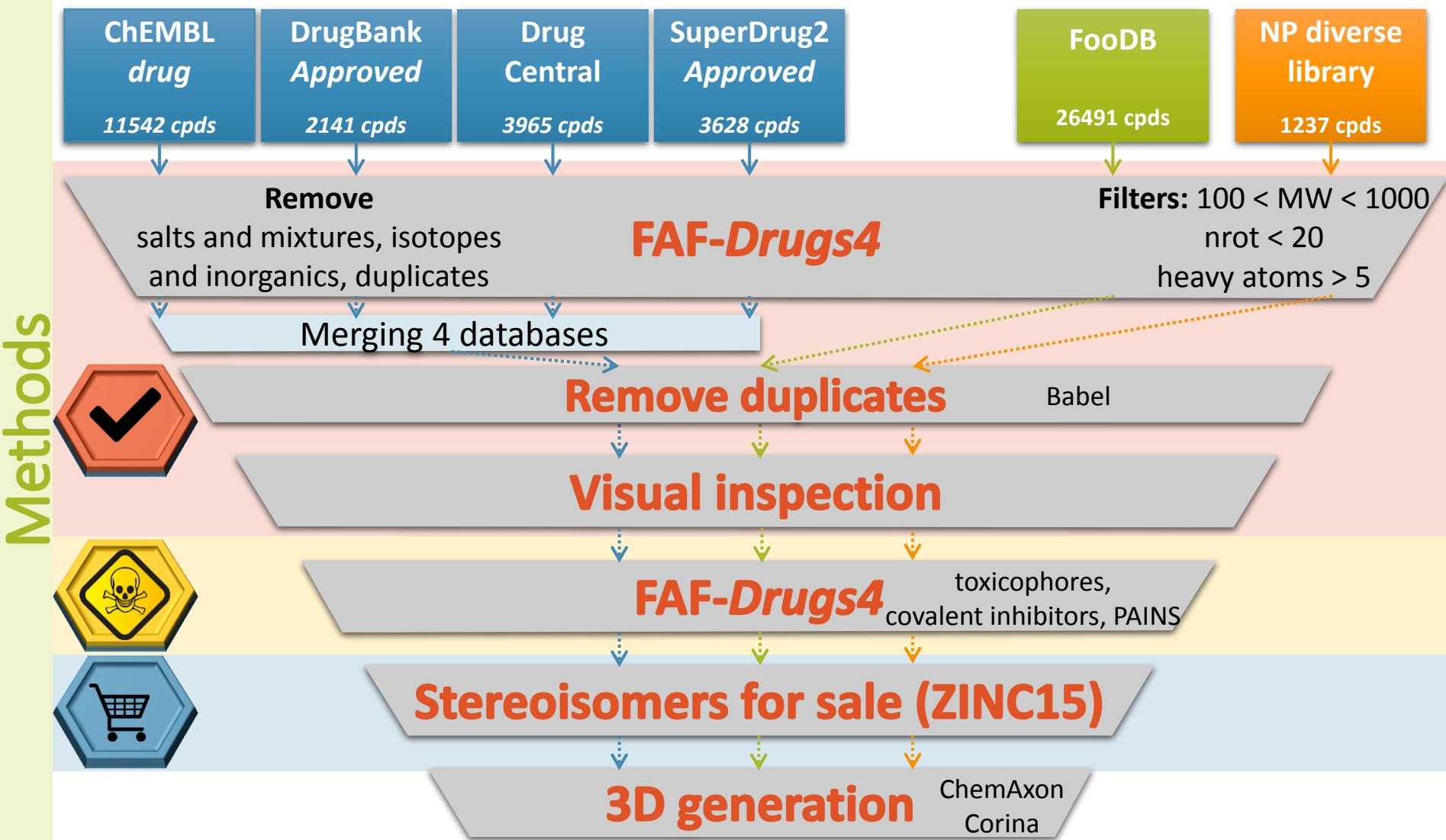
DrugCentral: Ursu O et al. Nucleic Acids Res, 2017

SuperDrug2: Siramshetty VB et al. Nucleic Acids Res, 2018

FooDB: <http://www.foodb.ca>

NP: O'Hagan S and Kell DB Biotechnol 10, 2018

FAF-Drugs4: Lagorce D et al. Bioinformatics, 2017



ChEMBL: Gaulton A et al. *Nucleic Acids Res*, 2012

DrugBank: Wishart DS et al. *Nucleic Acids Res*, 2018

DrugCentral: Ursu O et al. *Nucleic Acids Res*, 2017

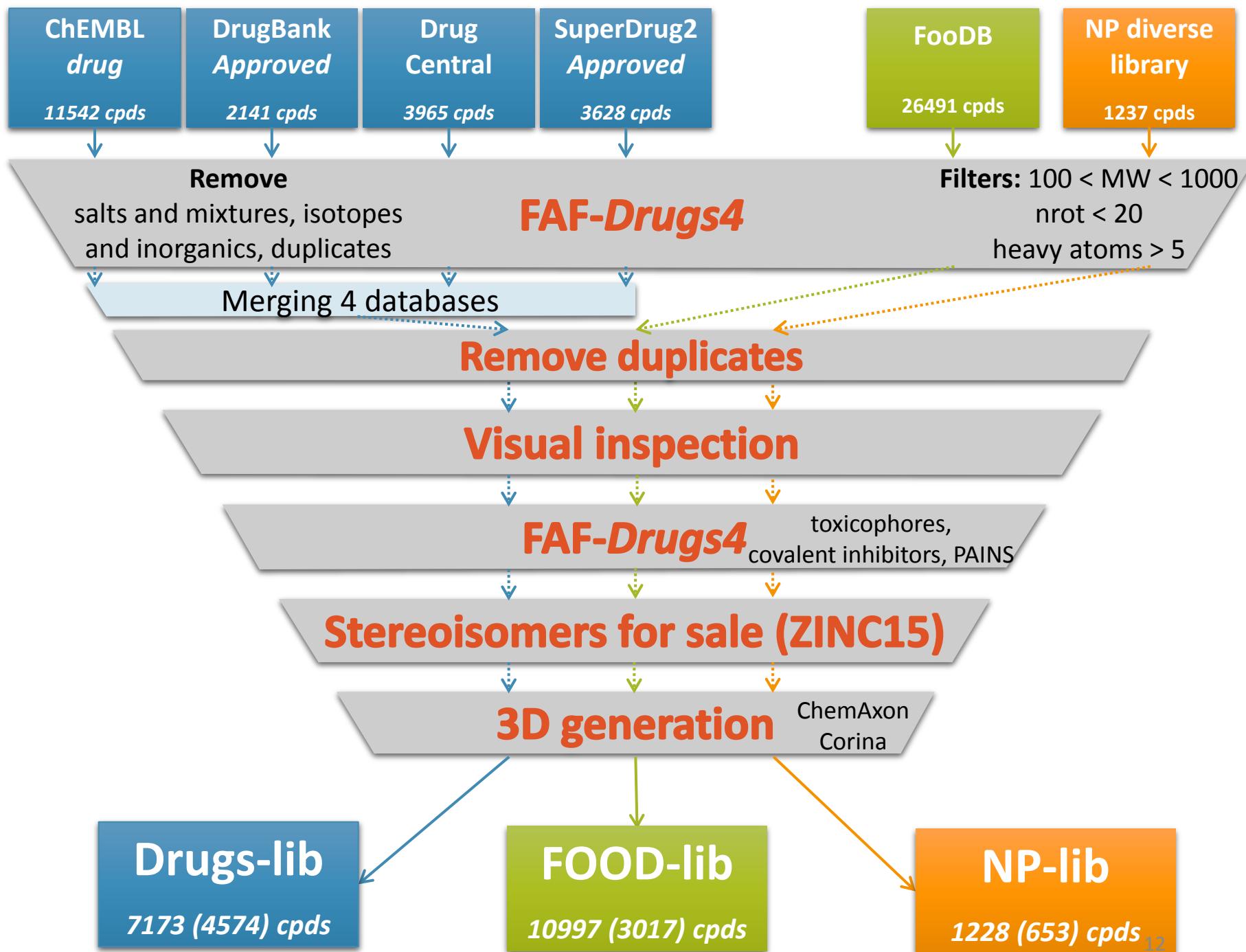
SuperDrug2: Siramshetty VB et al. *Nucleic Acids Res*, 2018

FooDB: <http://www.foodb.ca>

NP: O'Hagan S and Kell DB *Biotechnol* 11, 2018

FAF-Drugs4: Lagorce D et al. *Bioinformatics*, 2017

Methods

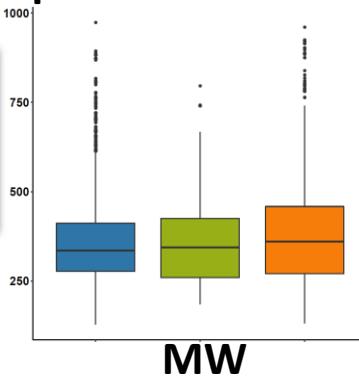


Results

Compounds libraries composition and diversity

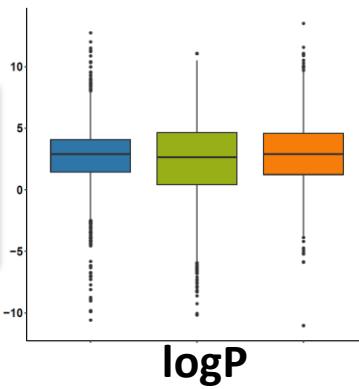
Drugs-lib

7173 cpds



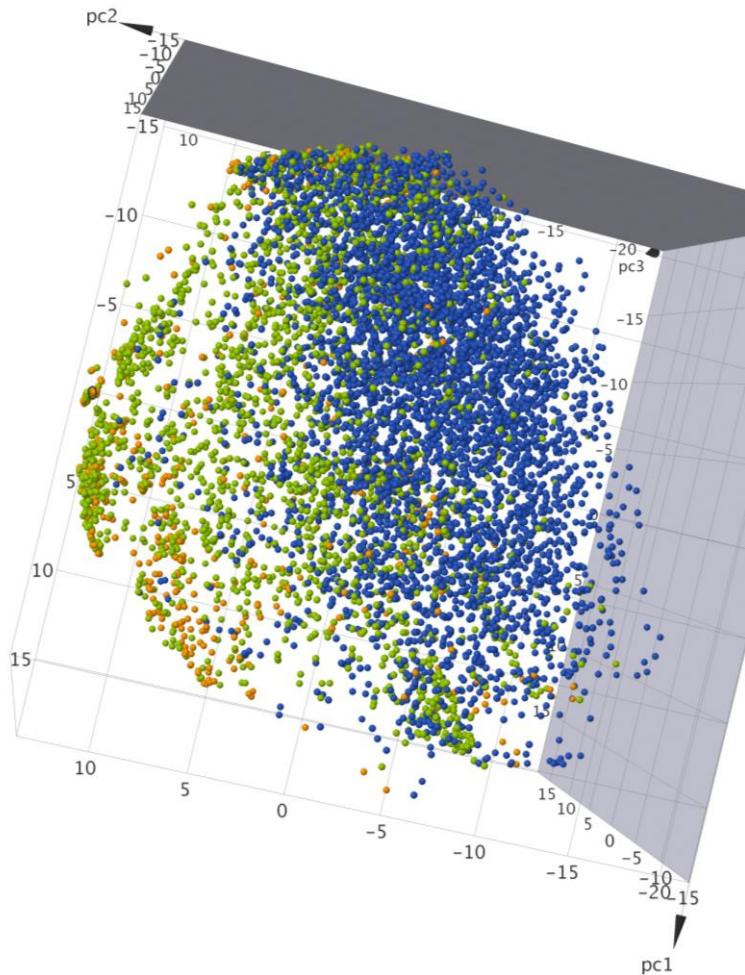
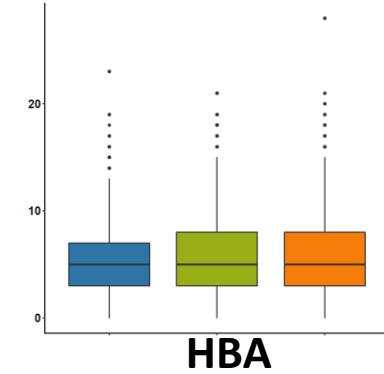
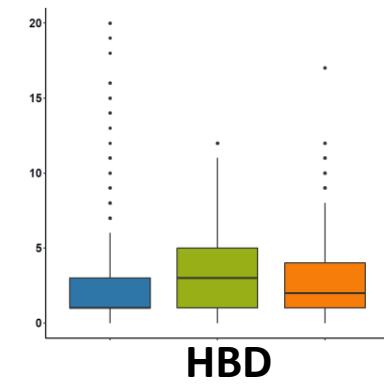
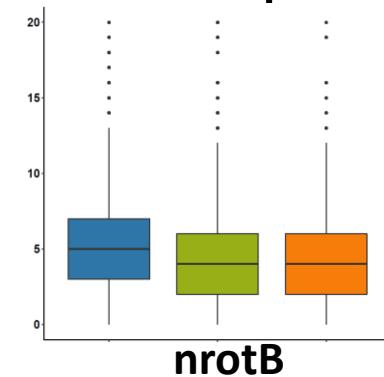
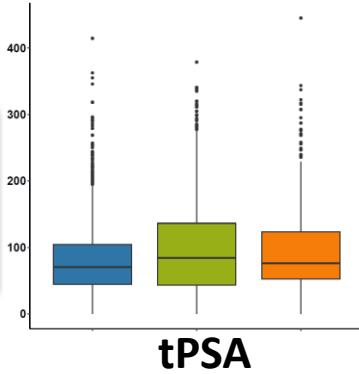
FOOD-lib

10997 cpds



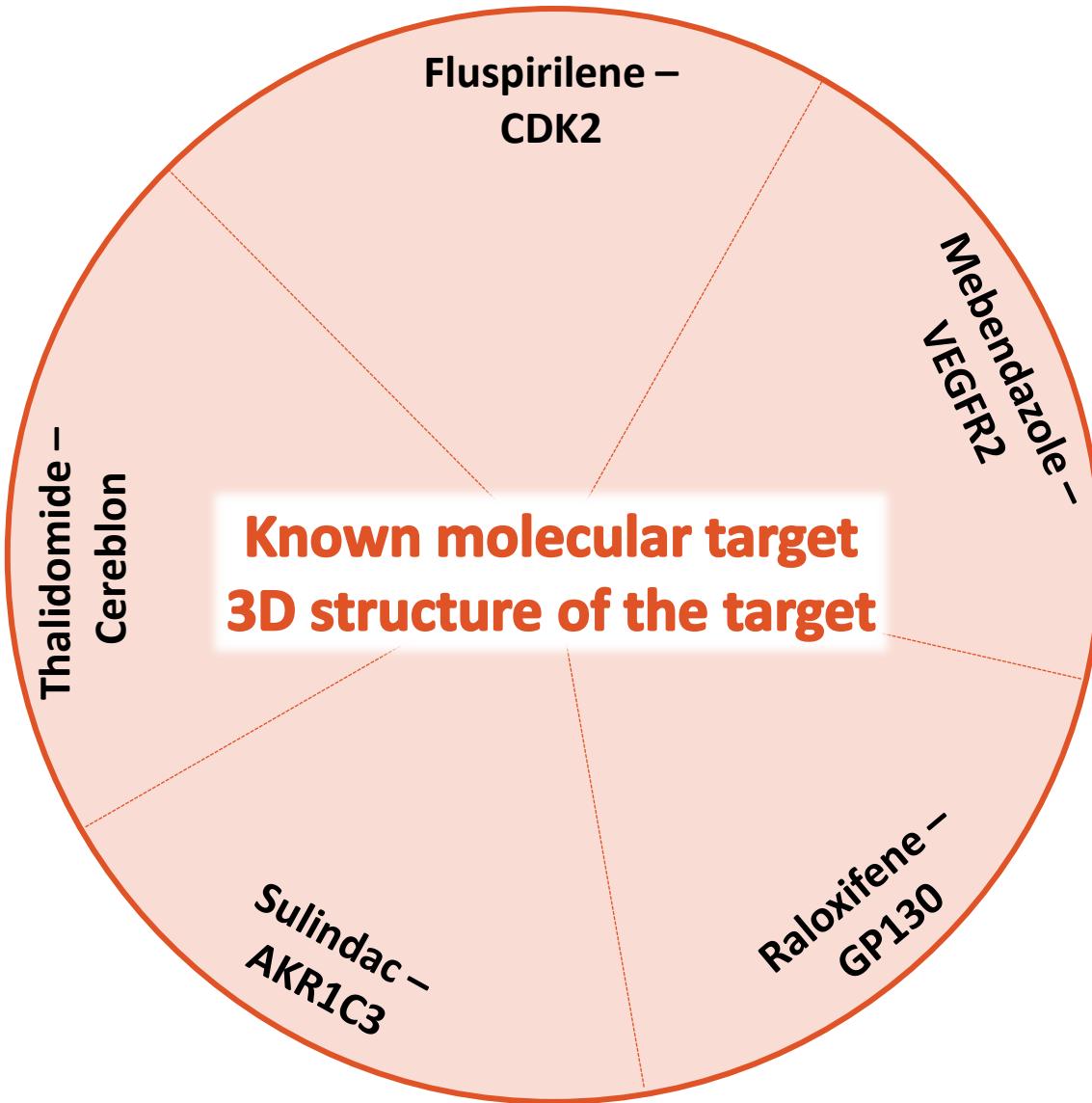
NP-lib

1228 cpds



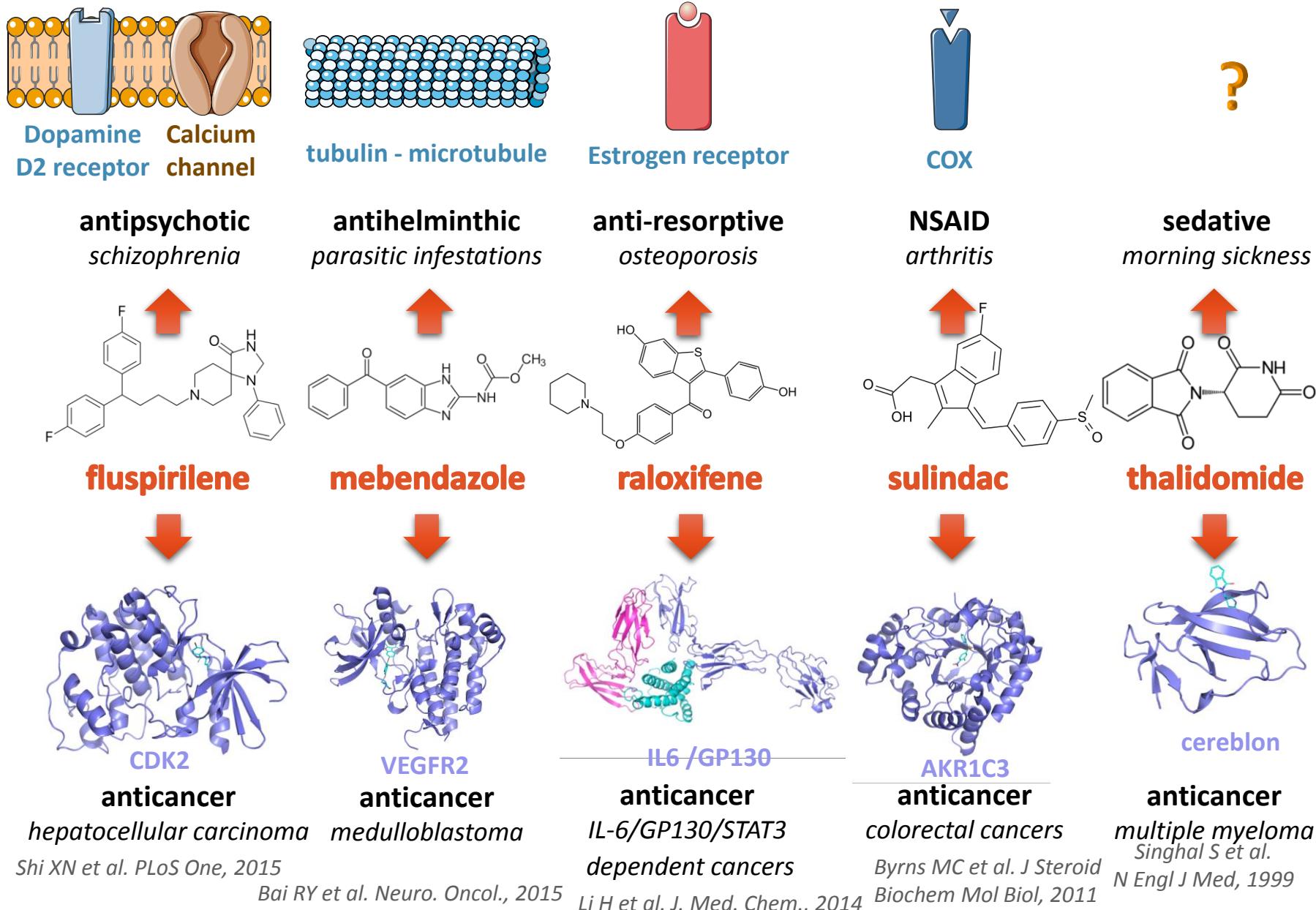
Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Results



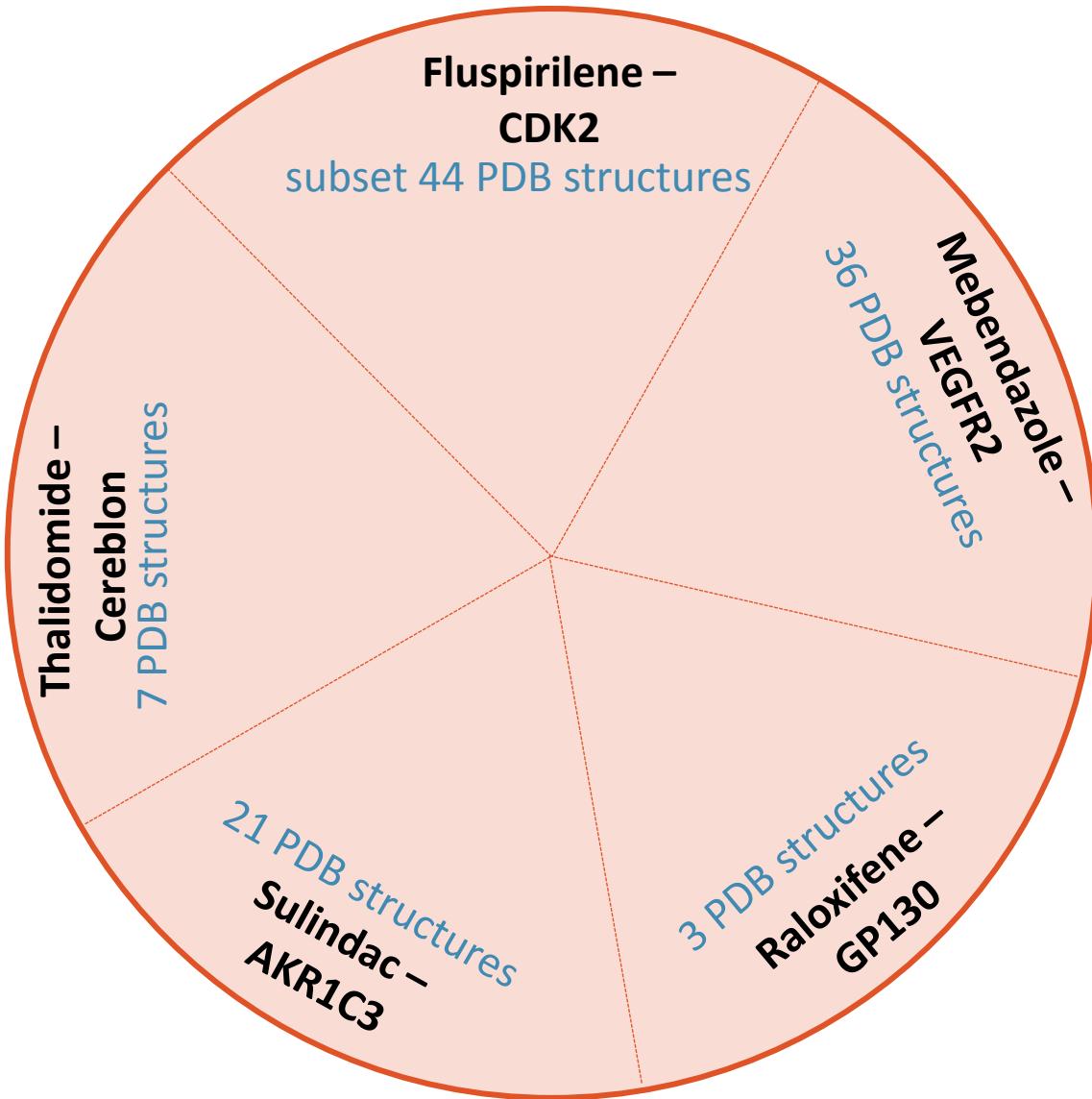
Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Results



Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Results

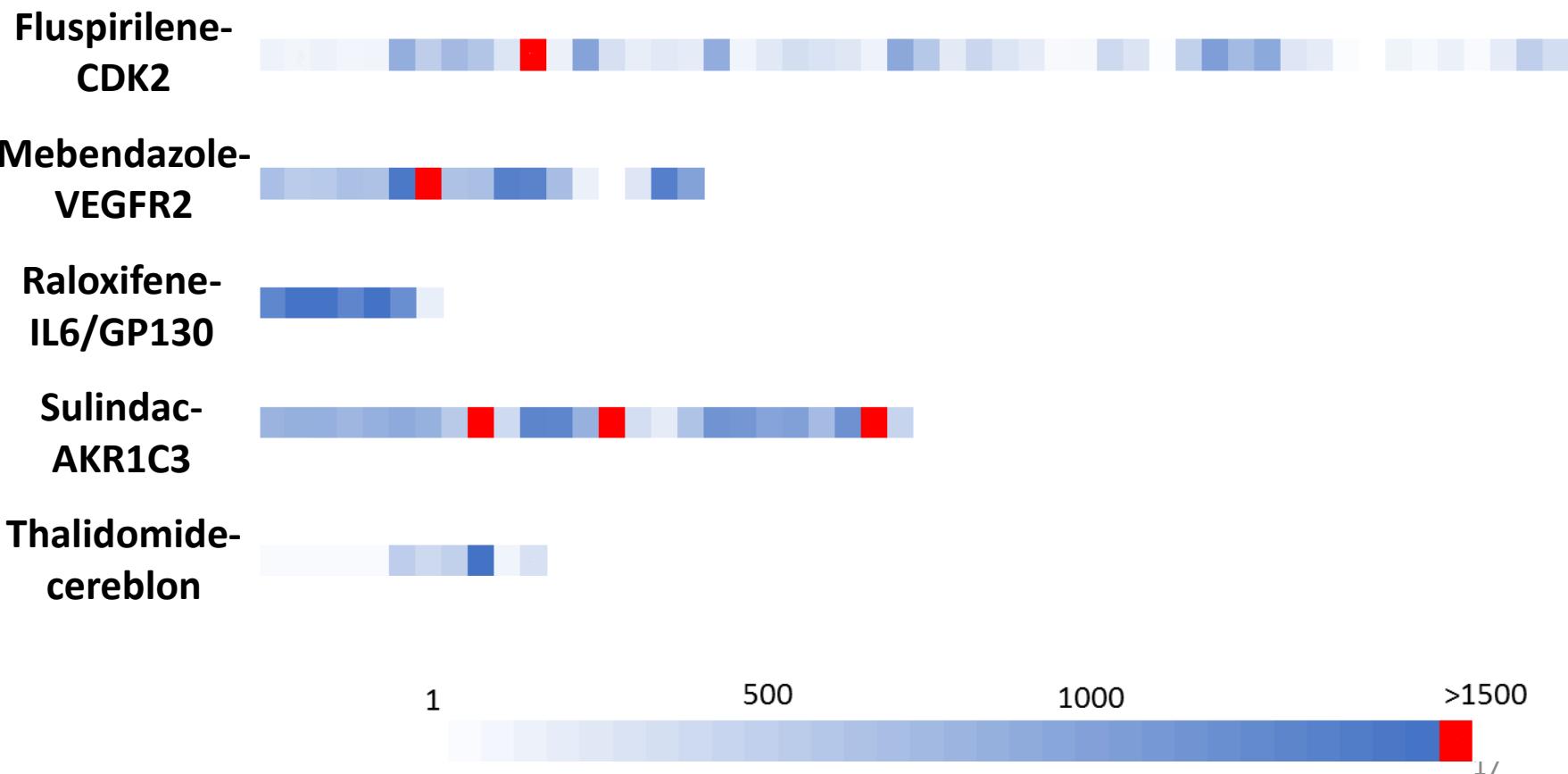


holo X-Ray PDB structures
without missing residues
in the binding site

Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Hit = compound ranked within the 1500 best scored drugs

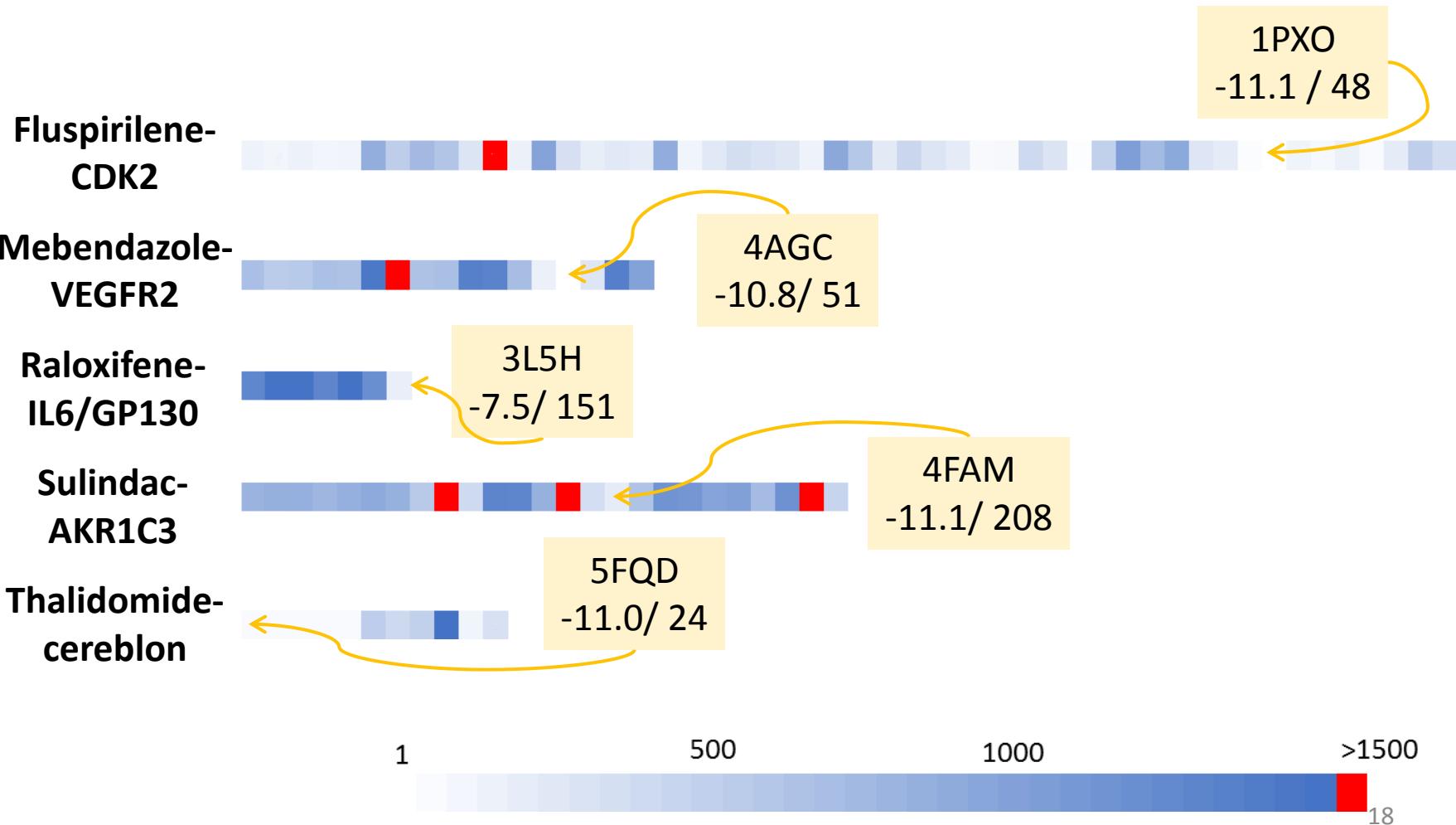
Results



Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Results

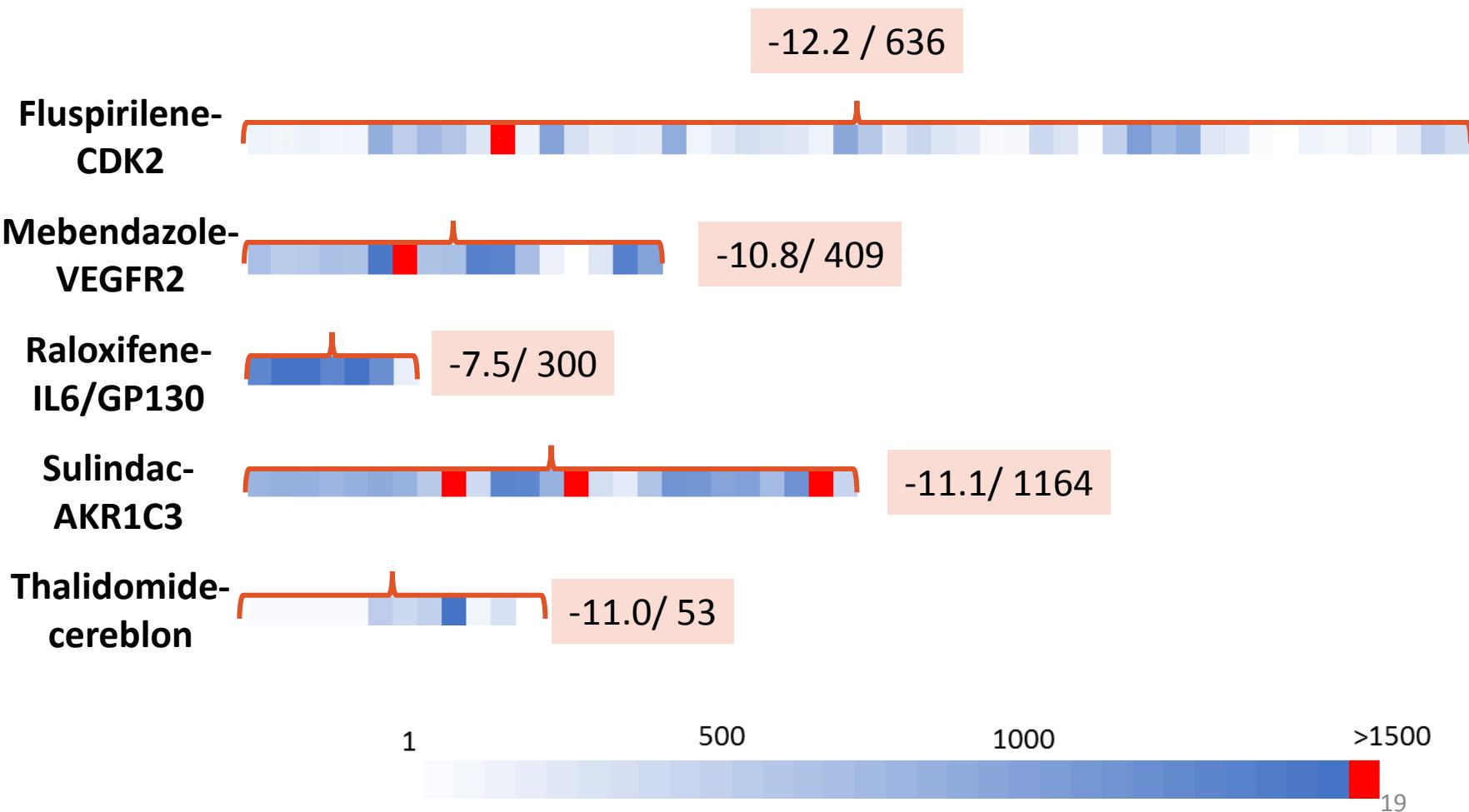
Hit = compound ranked within the 1500 best scored drugs



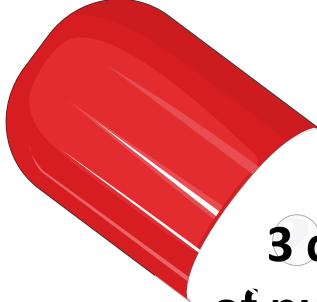
Retrospective examples of the use of the Drugs-lib for drug repositioning on cancer targets

Results

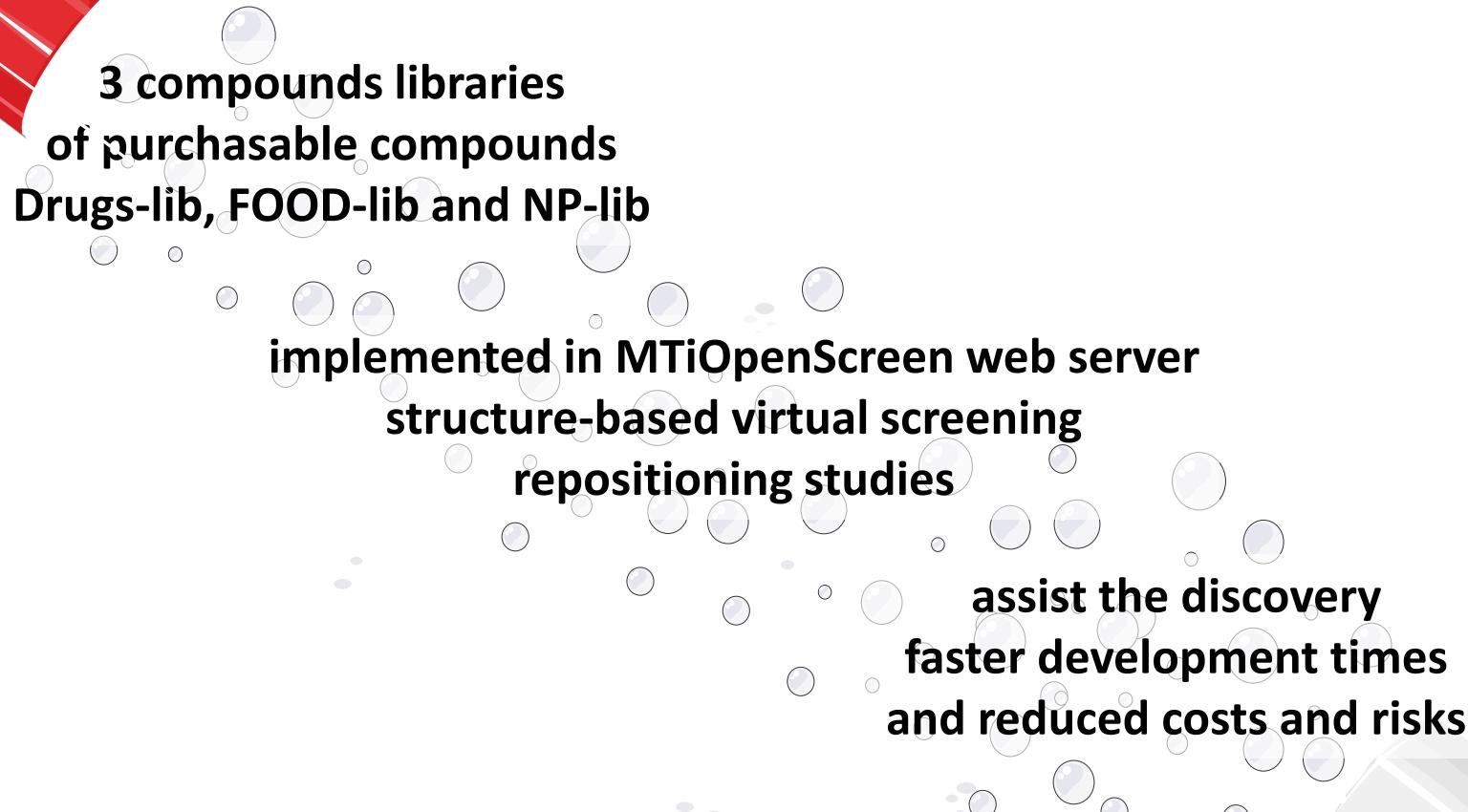
Hit = compound ranked within the 1500 best scored drugs



Conclusion



**3 compounds libraries
of purchasable compounds
Drugs-lib, FOOD-lib and NP-lib**



**implemented in MTiOpenScreen web server
structure-based virtual screening
repositioning studies**



**assist the discovery
faster development times
and reduced costs and risks**

Acknowledgements



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