Lékařská fakulta

IMTM

XXVIII Symposium on Bioinformatics and Computer-Aided Drug Discovery

Molecular Dynamic Pharmacophore and its application to Design Novel MARK4 Inhibitors

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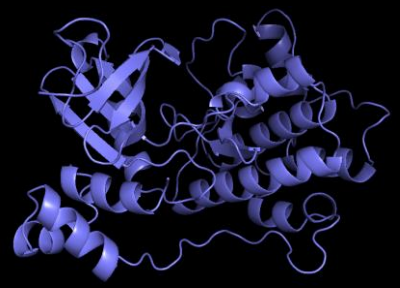
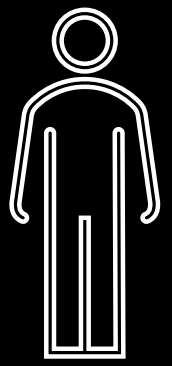
Way2Drug
2022

MARK4

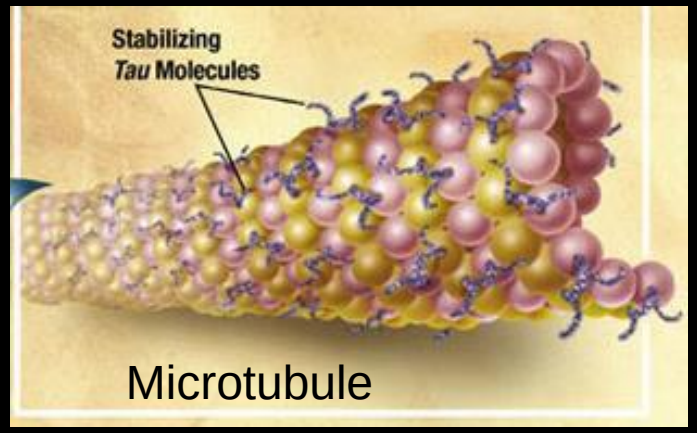


Microtubule Affinity-Regulating Kinase 4 (MARK4)

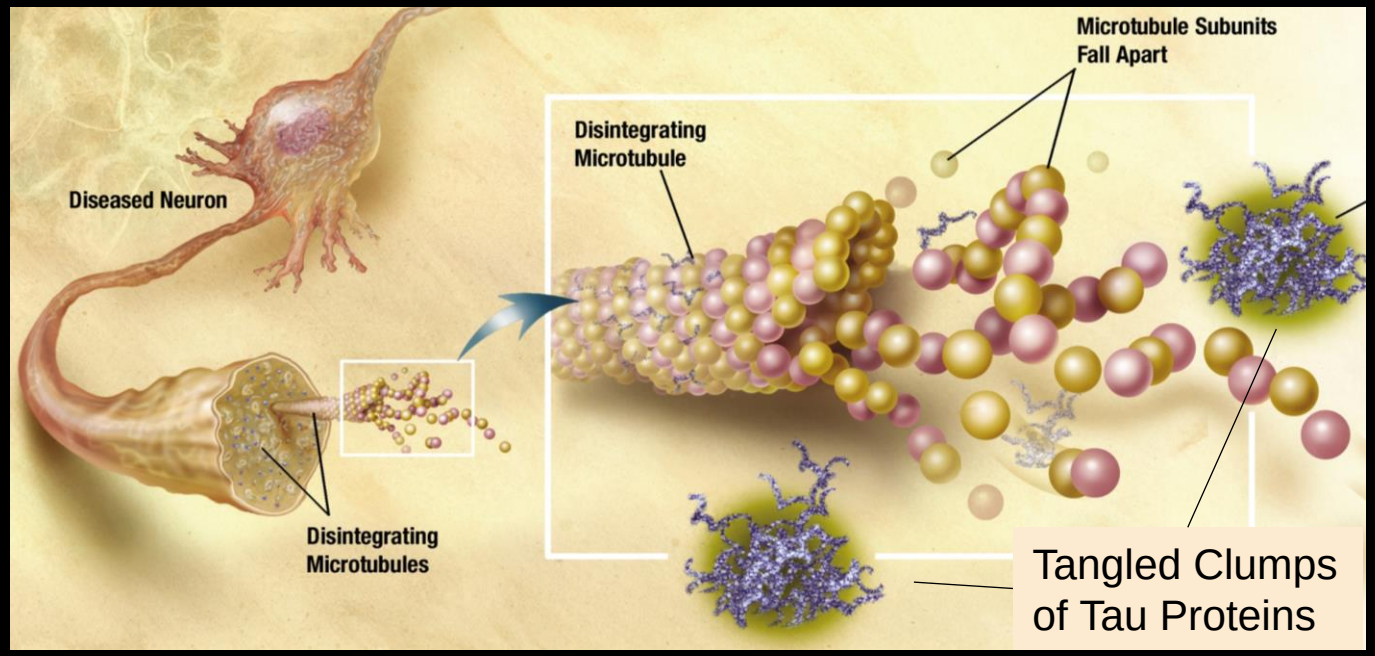


Tau protein

Microtubule-Associated Protein 2 (MAP2) and MAP4



Cell regulation



Neurodegenerative Disorders

Cancer

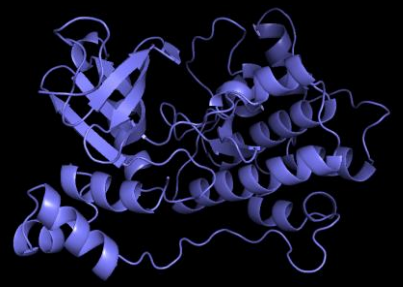
Diabetes

and other metabolic diseases

[Trinczek at al., JBC, 2004]

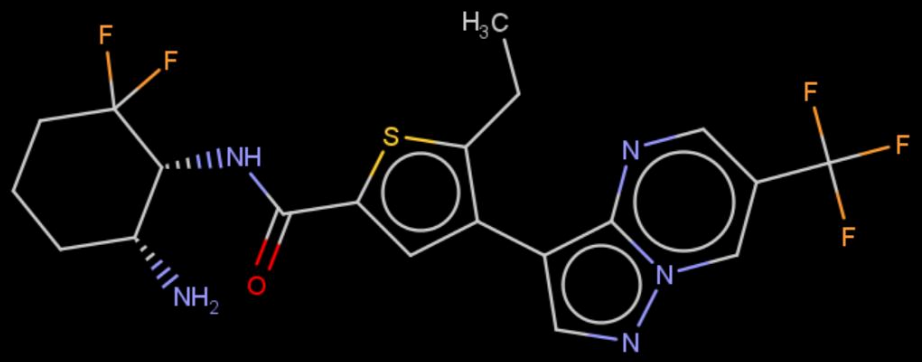
Using the process which occurs in brain as an example
The pictures were taken from [Wikipedia: Alzheimer's disease]

MARK4



MARK4

PDB code: 5es1



PDB code: 5RC

Macromolecule Content

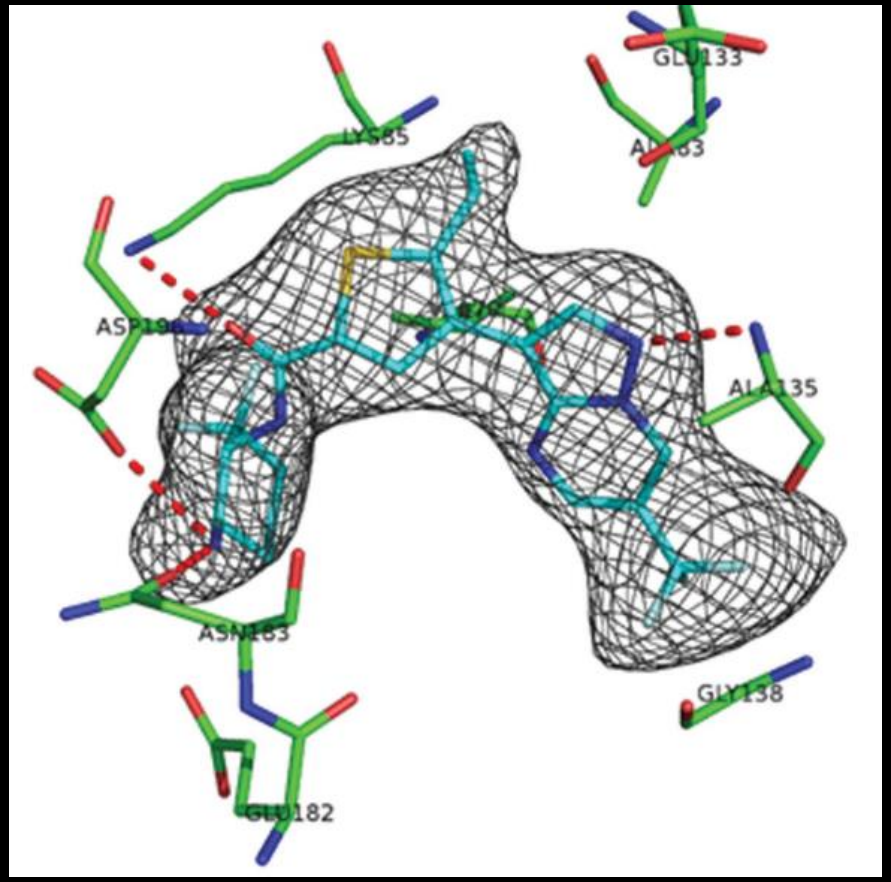
Chains: A
Sequence Length: 328
Organism: Homo sapiens

Experimental Data Snapshot

Method: X-RAY diffraction
Resolution: 2.80 Å

Acta Cryst F
ISSN 2053-230X

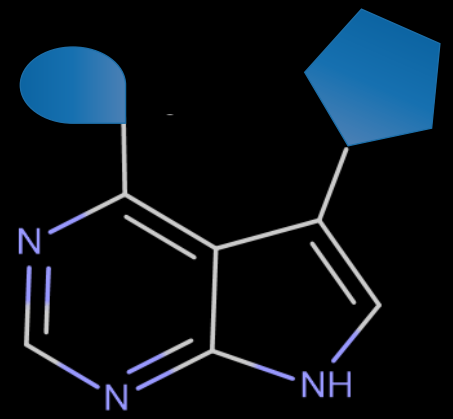
Sack at al., 2016

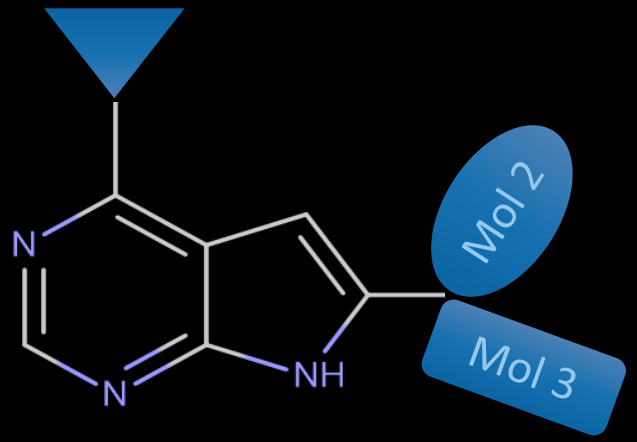


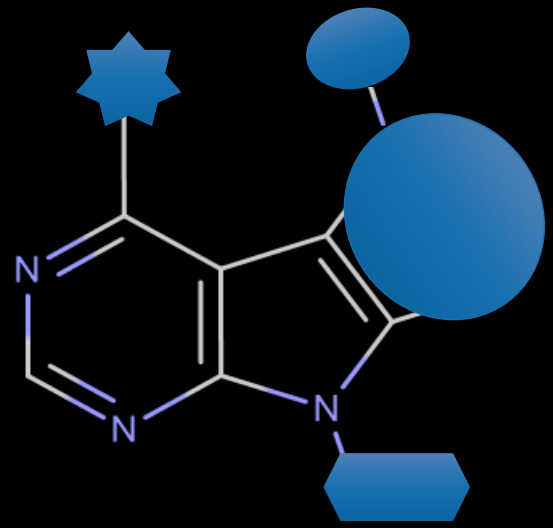
5RC	MARK1	MARK2	MARK3	MARK4
IC50, µM	0.0041	0.0025	0.0039	0.0046

Initial ligands

From the proprietary database







Mol 1	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	>50	>50	0.95
docking	-6.7	-7.4	-7.0	-8.0

Mol 2	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	>50	38.8	0.59
docking	-7.5	-8.9	-7.7	-9.5

Mol 3	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	>50	>50	0.47
docking	-7.7	-8.1	-7.8	-9.1

Mol 4	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	>50	>50	1.29
docking	-8.1	-7.8	-8.1	-8.6

Aim

Discover selective MARK4 inhibitors of new chemotypes
to extend structural diversity of compounds for further selection and optimization

MD representative pharmacophores

MD snapshot timeline

[Polishchuk at al., Int J Mol Sci, 2019]

A	B	C	D	E	F	G

MD pharmacophores

b36..87 53b..ef 53b..ef e4f..ce 53b..ef 4af..f3 79f..31

3D pharmacophore hashes

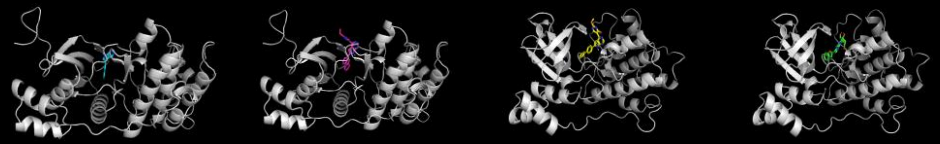
[Kutlushina at al., Molecules, 2018]

MD representative pharmacophores

A	B	D	F	G

[github.com/ci-lab-cz/pharmd]

MD pharmacophores generation

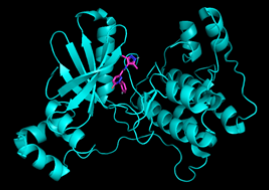


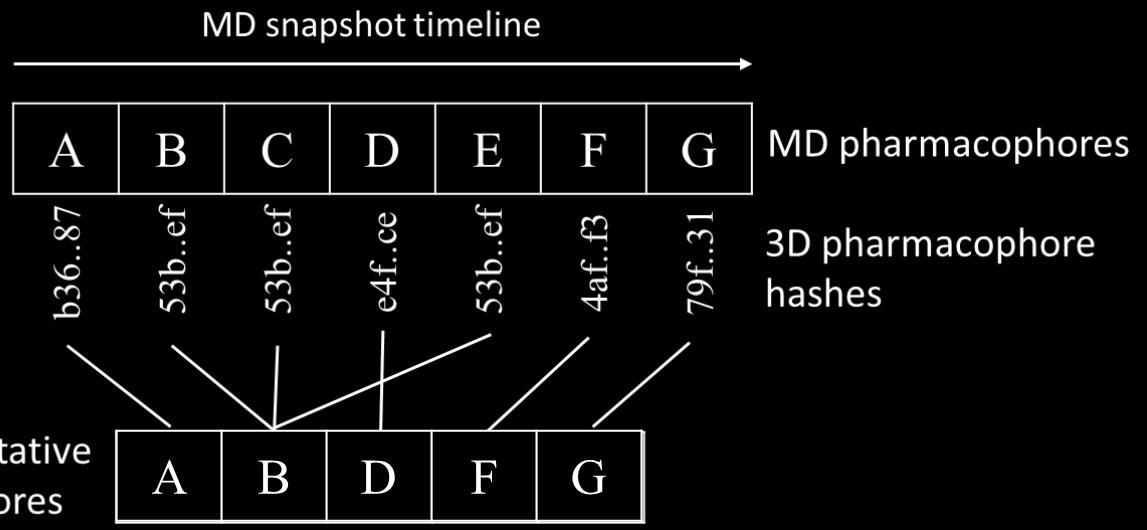
MD snapshot timeline

150 ns

MD representative pharmacophores

Mol 1	Mol 2	Mol 3	Mol 4
4015	2532	5221	5965





github.com/ci-lab-cz/pharmd

Validation of MD pharmacophores

MD snapshot timeline

150 ns

MD representative pharmacophores

Mol 1	Mol 2	Mol 3	Mol 4
4015	2532	5221	5965

ChEMBL + proprietary

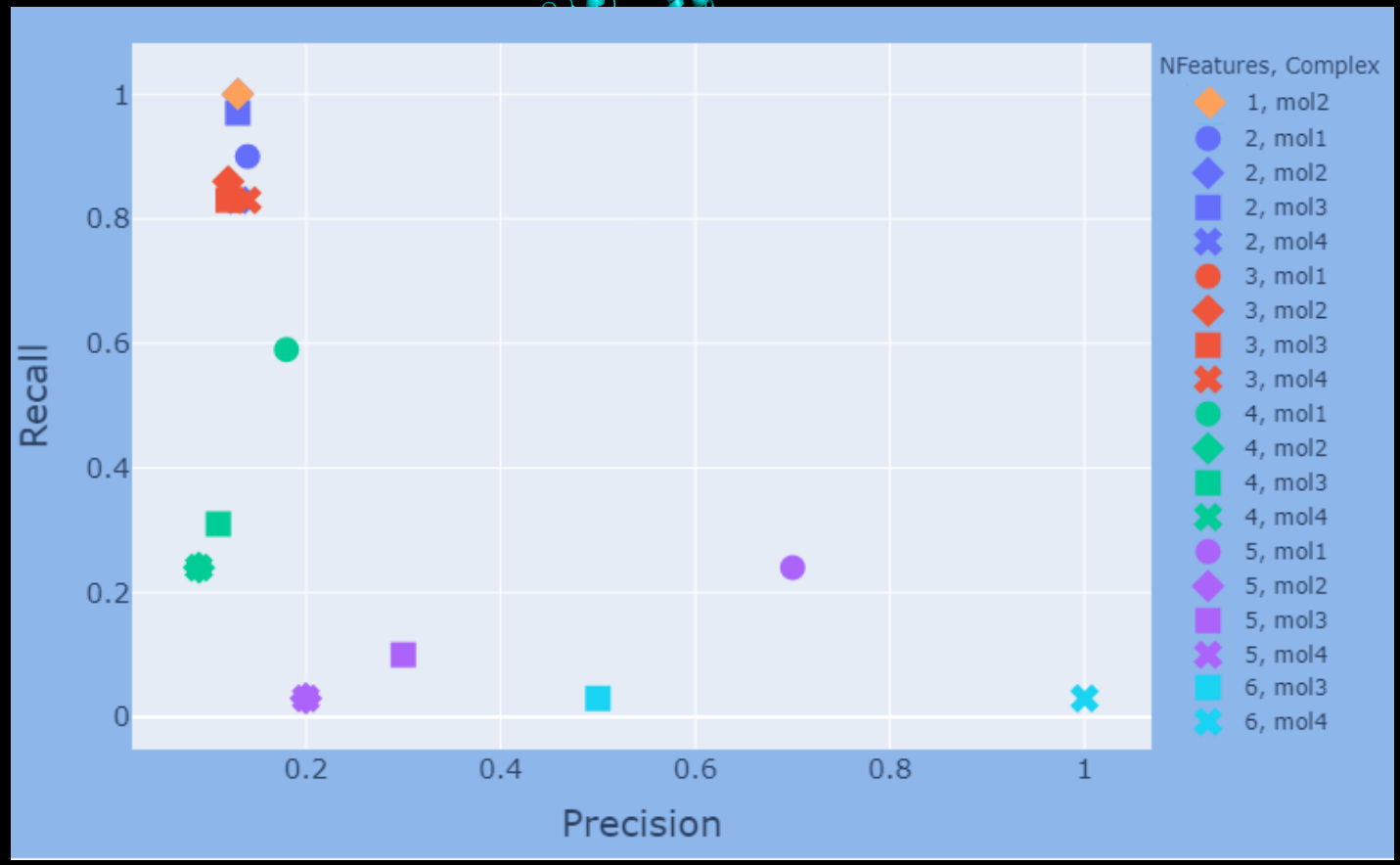
190 inactive molecules

29 active molecules

up to 50 conformers

Virtual screening of validation set

Quality assessment of the MD representative pharmacophores



Primary VS of Enamine by MD pharmacophores

MD snapshot timeline 150 ns

5+ features MD representative pharmacophores

Mol 1 3938 | Mol 2 2331 | Mol 3 4989 | Mol 4 5876

up to 50 conformers 1783794 molecules

Virtual screening of Enamine

68337 molecules

RTB <= 5
MW <= 500 Da

Enamine datasets	Premium	Advanced	HTS	Total
Number of molecules	36929	376097	1370768	**1783794**
Number of Murcko scaffolds	26852	246940	714851	988643

Rank filtered molecules by CCA score

MD snapshot timeline

150 ns

5+ features MD representative pharmacophores

Mol 1	Mol 2	Mol 3	Mol 4
3938	2331	4989	5876

up to 50 conformers

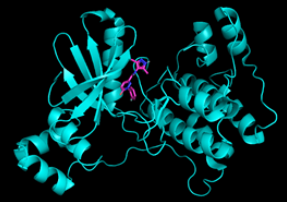
1783794 molecules

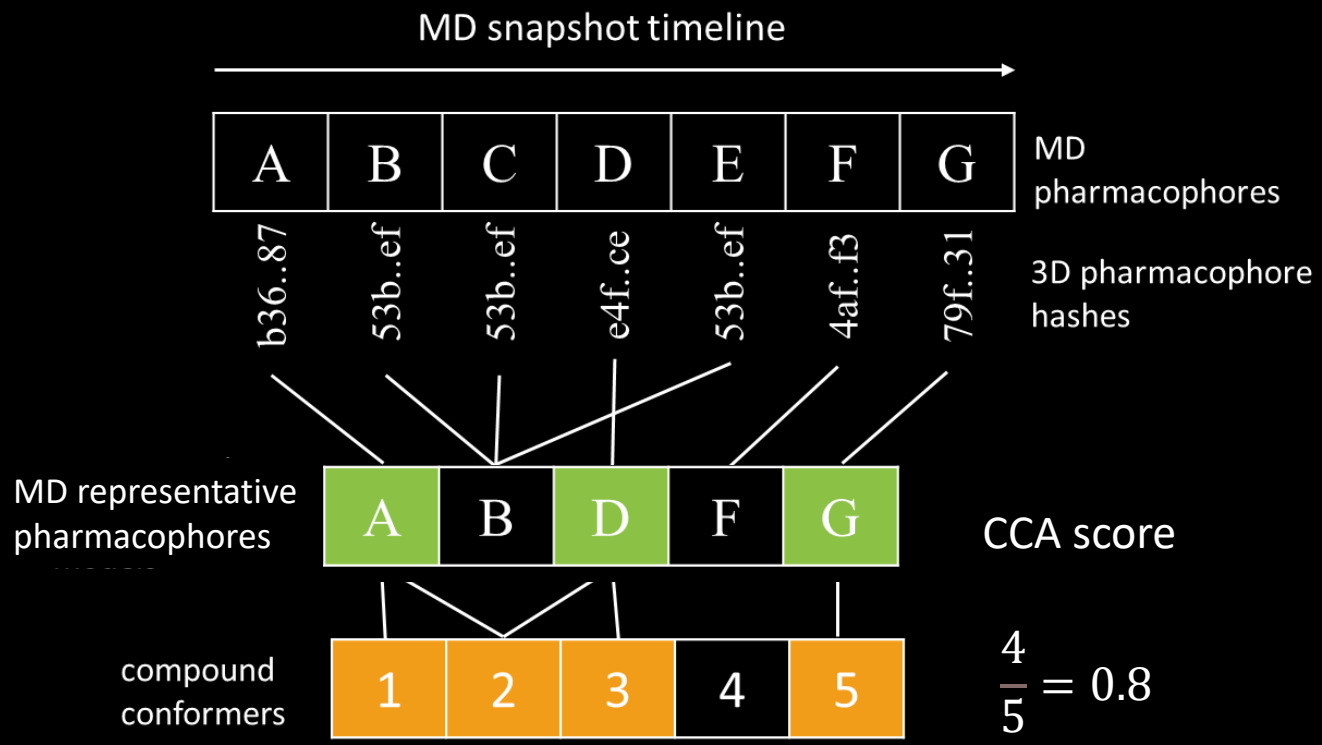
Virtual screening of Enamine

68337 molecules

Conformers coverage Approach (CCA)

618 molecules





Polishchuk at al., Int J Mol Sci, 2019

github.com/ci-lab-cz/pharmd

Selecting hits by docking

MD snapshot timeline

150 ns

5+ features MD representative pharmacophores

Mol 1
3938

Mol 2
2331

Mol 3
4989

Mol 4
5876

up to 50 conformers

1783794 molecules

Virtual screening of Enamine

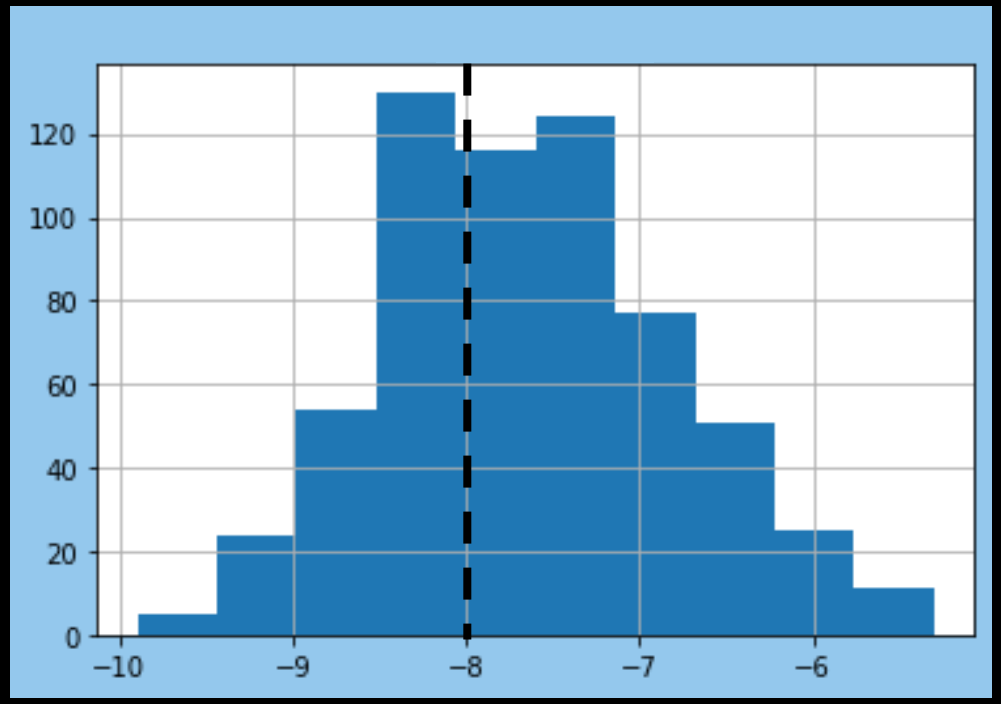
68337 molecules

Conformers coverage Approach (CCA)

618 molecules

Docking

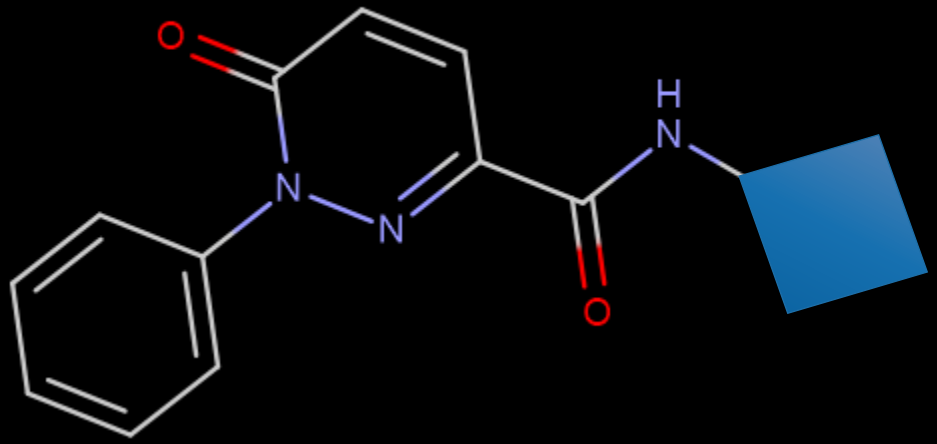
AutoDock Vina

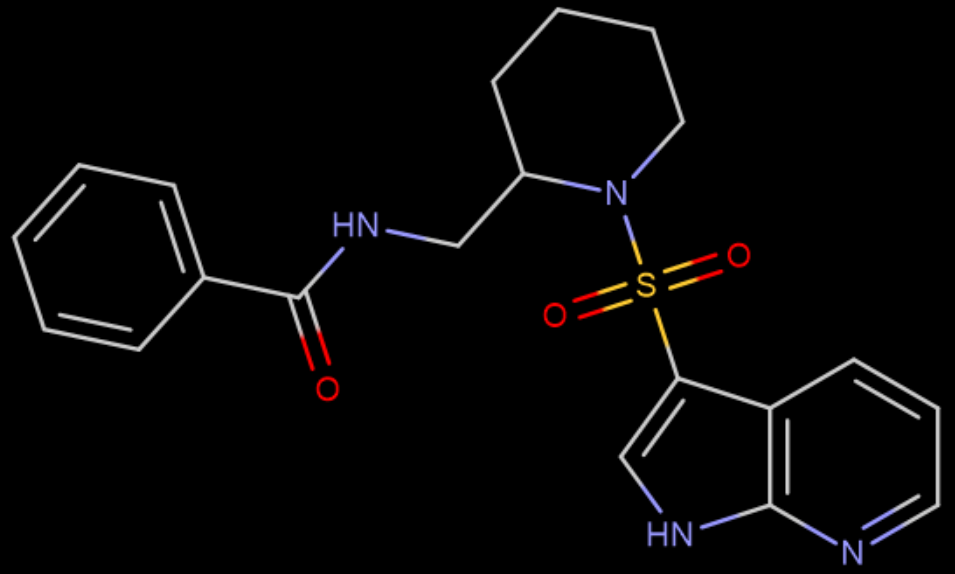


235 molecules

24 hits

The found inhibitors





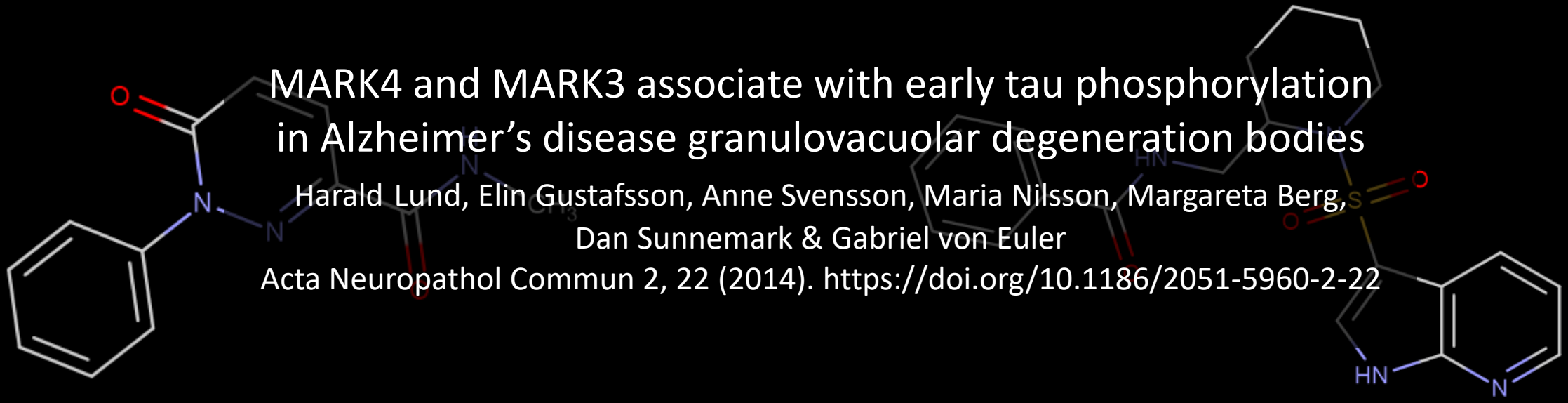
Hit1	mol 1	mol 2	mol 3	mol 4
Tanimoto	0.37	0.32	0.33	0.3

Hit1	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	14.72	0.0088	0.032
docking	-8.026	-7.754	-7.164	-8.628

Hit2	mol 1	mol 2	mol 3	mol 4
Tanimoto	0.34	0.31	0.31	0.26

Hit2	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	19.79	>50	12.01
docking	-8.169	-7.755	-8.121	-8.863

The found inhibitors



MARK4 and MARK3 associate with early tau phosphorylation in Alzheimer's disease granulovacuolar degeneration bodies

Harald Lund, Elin Gustafsson, Anne Svensson, Maria Nilsson, Margareta Berg, Dan Sunnemark & Gabriel von Euler

Acta Neuropathol Commun 2, 22 (2014). https://doi.org/10.1186/2051-5960-2-22

Hit1	mol 1	mol 2	mol 3	mol 4
Tanimoto	0.37	0.32	0.33	0.3

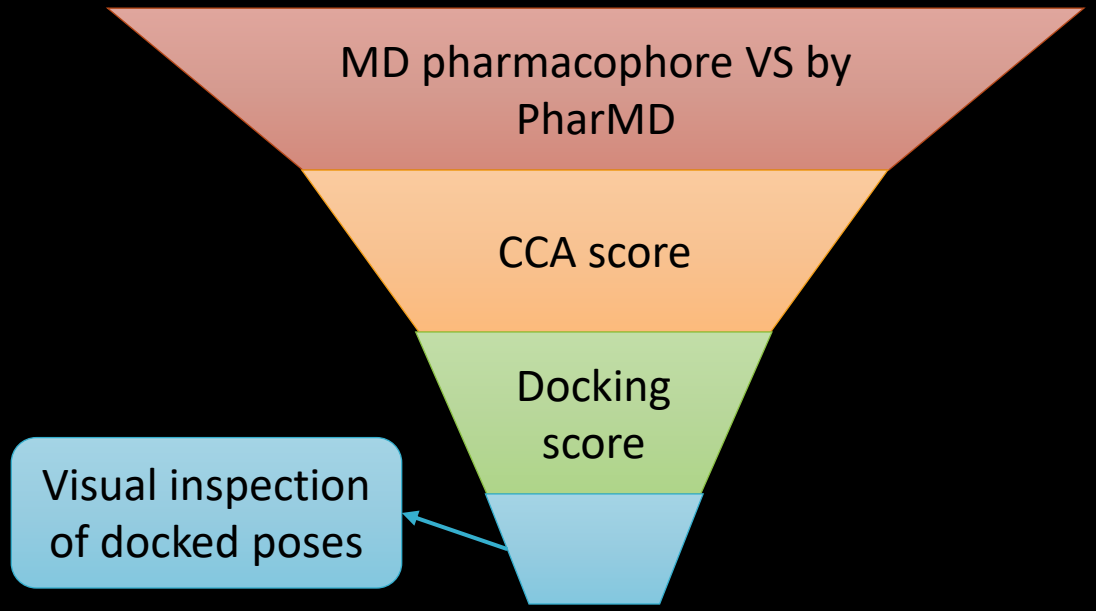
Hit1	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	14.72	0.0088	0.032
docking	-8.026	-7.754	-7.164	-8.628

Hit2	mol 1	mol 2	mol 3	mol 4
Tanimoto	0.34	0.31	0.31	0.26

Hit2	MARK1	MARK2	MARK3	MARK4
IC50, µM	>50	19.79	>50	12.01
docking	-8.169	-7.755	-8.121	-8.863

Conclusions

- A workflow for virtual screening based on our previous implementation of MD pharmacophores and molecular docking was developed and validated
- We were able to find a novel MARK inhibitor which was selective over 1 and 2 subtypes and can be promising for further research



Acknowledgements

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PhD Petr Džubák, doc. Marian Hajduch

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And thank you for watching… ☺ Question?