

XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2026)



LIGAND-RECEPTOR INTERACTION INSIGHTS FROM IN SILICO REVERSE FRAGMENT BASED DRUG DISCOVERY (R-FBDD) FOR KNOWN DRUGS AND LEAD COMPOUNDS

Dmitry A. Shulga

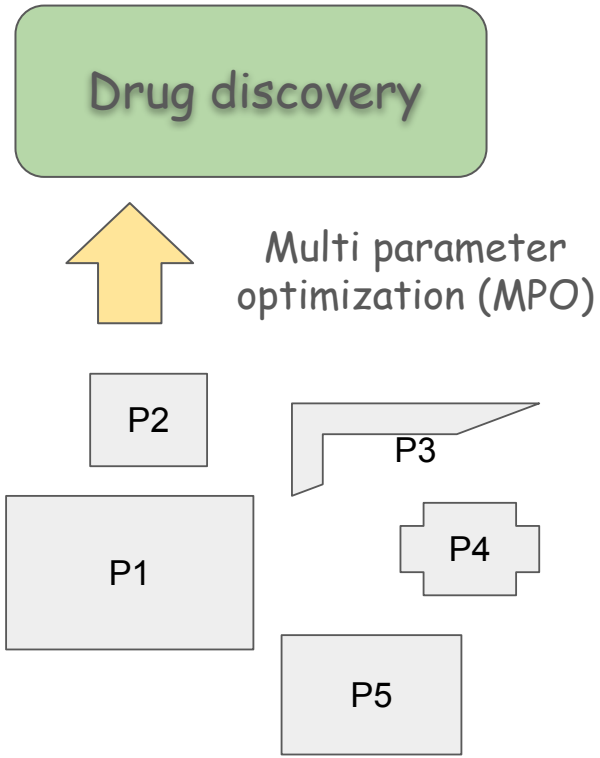
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Outline

1. the drug discovery and CADD scenes
2. enter R-FBDD… its basics
3. R-FBDD at different stages of early drug discovery
4. what can R-FBDD show from scratch for a real drug?
5. thoughts and future directions

Drug discovery and CADD scenes… (1)

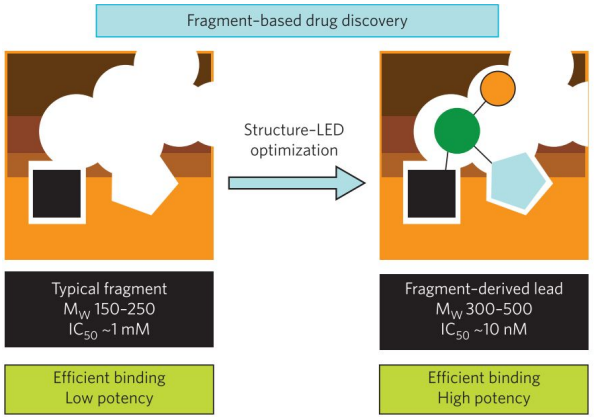


1. high risks
2. high attrition rates
3. high expenses
4. not guaranteed success

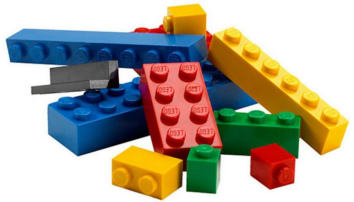
Unmet requirement for cure

Drug discovery and CADD scenes… (2)

… **Fragment based drug discovery/design (FBDD)** → Promising approach to overcome certain difficulties



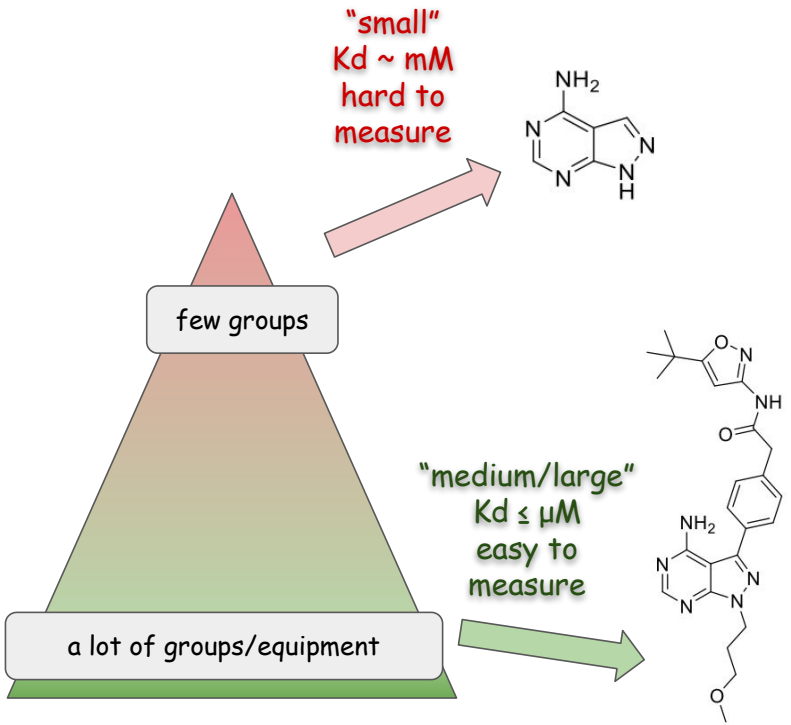
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1. better chemical space coverage with smaller libraries
   a. less risks to find a hit
   b. fewer compounds to screen
2. highly efficient binding patterns (in terms of LE)
   a. higher chances to get a drug
   b. shorter optimization path
3. phys-chem properties control - less risks of lead attrition in clinical Phases
4. direct link to SBDD and subsequent rational design
5. alternative scaffolds for the same target - lower risks of 'bad' series
6. proven source of lead and approved drug compounds by 2020-ies - 8 approved/40 clin.trials

1. Murray, C. W., & Rees, D. C. (2009) // *Nature chemistry*, *1*(3), 187-192., doi: 10.1038/nchem.217
2. Murray, C. W., Verdonk, M. L., & Rees, D. C. (2012). // *Trends in pharmacol. sci.*, *33*(5), 224-232., doi: 10.1016/j.tips.2012.02.006
3. Joseph-McCarthy, D., Campbell, A. J., Kern, G., & Moustakas, D. (2014) // *JCIM*, 54(3), 693-704., doi: 10.1021/ci400731w
4. Erlanson, D. A., Fesik, S. W., Hubbard, R. E., Jahnke, W., & Jhoti, H. (2016) // *Nat. Rev. Drug Disc.*, *15*(9), 605-619., doi: 10.1038/nrd.2016.109

FBDD limitations





FBDD limitations - unfairness no more!

Fragment Based Drug Discovery/Design - FBDD

Democratize FBDD!



few groups

a lot of groups/equipment

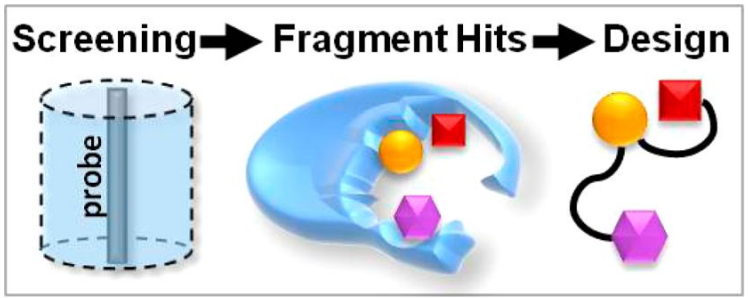
Mission: make benefits of FBDD accessible to many scientists!

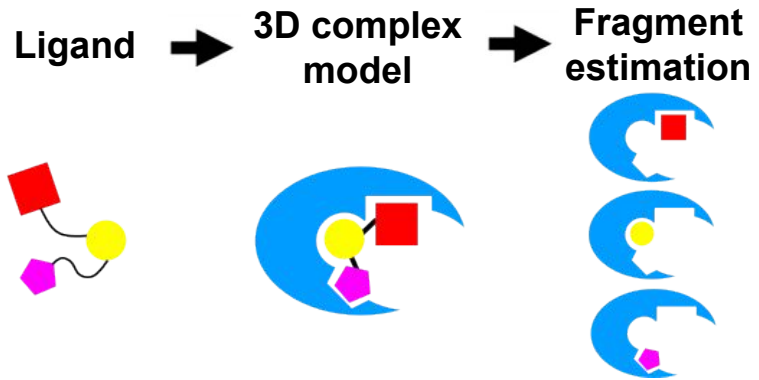
Corollary: large and medium sized molecules as input

Enter R-FBDD (1)

Fragment approach (FBDD): find the most active/affine fragments -> combine/grow into a new lead molecule.

***Reverse* fragment approach (R-FBDD)**: split a molecule into fragments -> estimate energetic contribution of each fragment



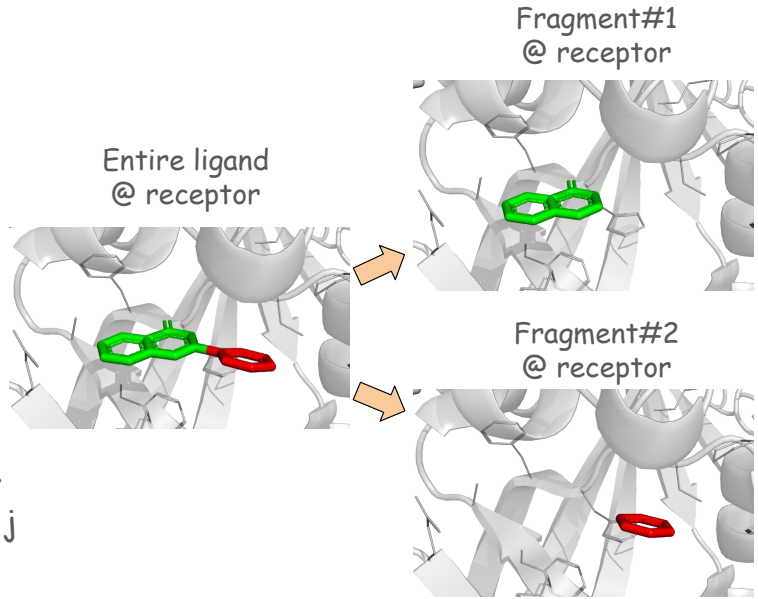


Joseph-McCarthy, D., Campbell, A. J., Kern, G., & Moustakas, D. (2014) // *JCIM*, 54(3), 693-704., doi: 10.1021/ci400731w

Shulga D. A., Ivanov N. N., & Palyulin V. A. (2021) // *Mend. Comm.*, *31*(3), 291-293, doi: 10.1016/j.mencom.2021.04.004

Enter R-FBDD (2)

Input
- 3D ligand-receptor complex
- reference energy, ΔE_{mol}
- fragments of interest



1. Estimate binding energy of each fragment, E_j
2. Stockholders' share $\omega_j = \frac{E_j}{\sum_{i=1}^{N} E_i}$
3. Scaled energy $E_j^{Scaled} = \omega_j \cdot \Delta E_{mol}$
4. Energy share of each fragment $Share_j = 100\% \cdot \omega_j$
5. Ligand efficiency of j-th fragment $\mathrm{LE(GE)} = E_j^{Scaled}/\mathrm{NH}$

NB $\sum_{i=1}^{N} E_i \neq \Delta E_{mol}$

R-FBDD at different stages of DD (general)

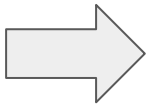
#	DD Stages	Goals	R-FBDD assistance
1.	**Initial analysis**	next- or best-in-class; grasp what's known	estimate value of different fragments in known actives [1,2], estimation of IP
2.	**Hit finding**	find new molecules with initial activity	"**anchor**" and "**ballast**" groups for **affinity** [1,2]; **select promising series of molecules** [3]; composition of focused virtual libraries
3.	**Hit-to-lead**	optimize activity, initial ADMET optimization	**recommender system to grow from a hit [in press]**; composition of focused virtual libraries
4.	**Lead optimization**	selectivity, ADMET	per fragment estimation and optimization of lipophilicity, solubility, selectivity (ADMET)

1. Shulga D. A., Ivanov N. N., & Palyulin V. A. (2021) // *Mend. Comm.*, *31*(3), 291-293, doi: 10.1016/j.mencom.2021.04.004
2. Shulga D. A., Ivanov N. N., & Palyulin V. A. (2022) // *Molecules*, *27*(6), 1985, doi: 10.3390/molecules27061985
3. Myazin V.D., Shulga D.A., Ivanov N.N. & Palyulin V. A. (2026) // *Mol. Divers*, doi: 10.1007/s11030-026-11620-4

What can R-FBDD elucidate from scratch for known drugs/drug candidates?

Design

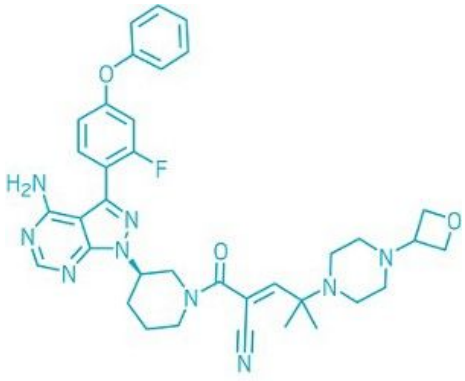
F-FBDD for known drug/candidate



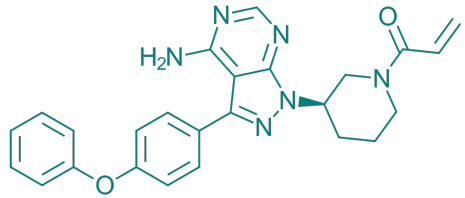
Evaluate results retrospectively

Rilzabrutinib (Wayrilz) and BTK

- FDA approved on 2025 and first-in-class
- To treat immune thrombocytopenia
- Covalent Bruton's tyrosine kinase (BTK) inhibitor



Rilzabrutinib



Ibrutinib

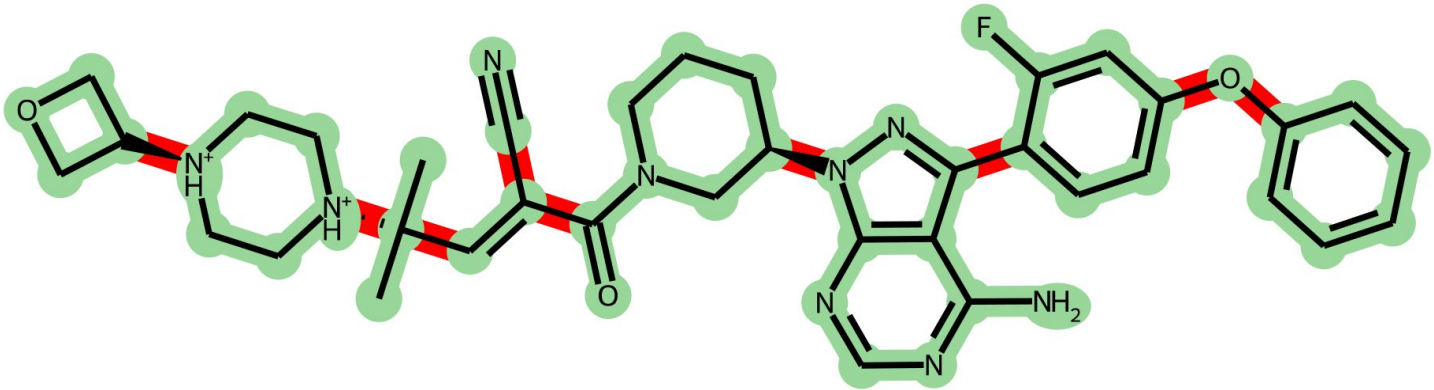
Pros

1. more selective across kinases
2. partially reversible covalent binding

more efficient + less toxic

Blind R-FBDD analysis of Rilzabrutinib@BTK

Fragmentation - slightly modified
MedChemFrag [1,2] rules



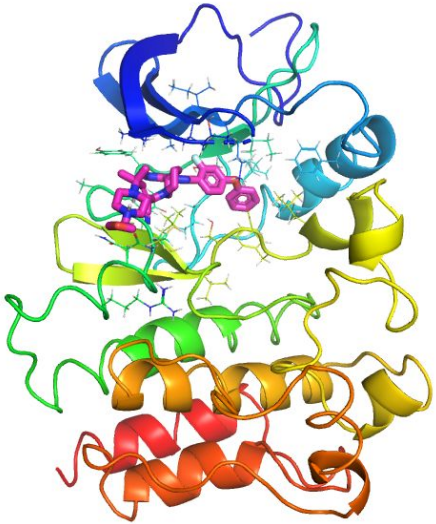
1. Ivanov, N. N., Shulga, D. A., & Palyulin, V. A. (2023) // Biophysica, 3(2), 362-372., doi: 10.3390/biophysica3020024
2. Our hg repo for MedChemFrag https://molmodel.com/hg/medchem_fragment_splitter/

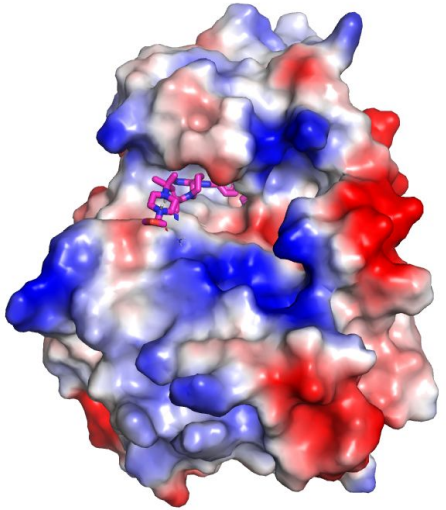
Blind R-FBDD analysis of Rilzabrutinib@BTK

Complex structure source

PDB:7L5O

1. PDB for better reliability of 3D geometry
2. non-covalent complex - more relevant for analysis
3. prepare the complex as for MD modeling: protonation, hydrogens, etc.



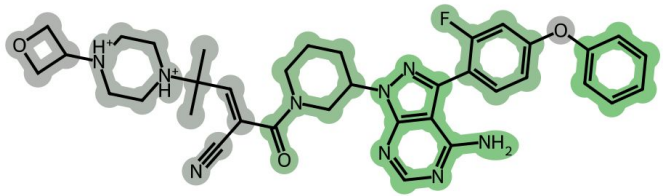


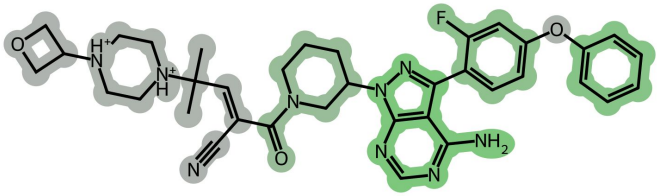
Blind R-FBDD analysis of Rilzabrutinib@BTK

Different Scoring Functions to assign fragment weights

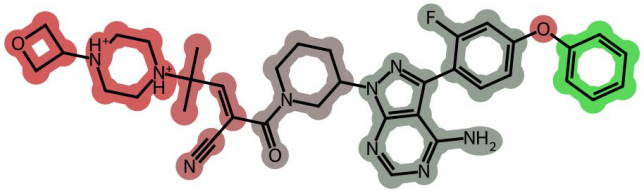
ΔE_{mol} = -12.55 kcal/mol

Energy share

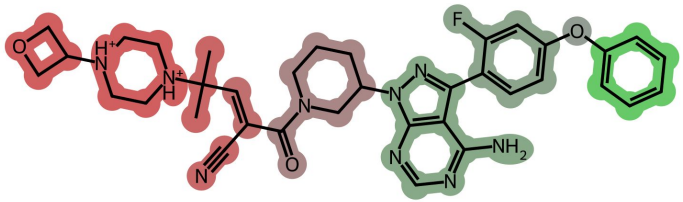




LE (0.3)



AutoDock4.2



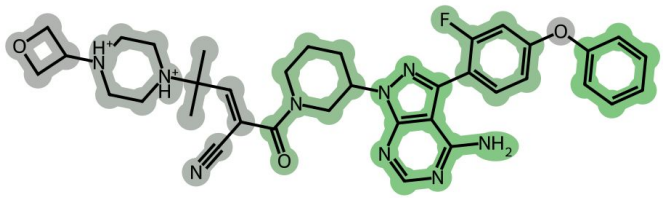
Vina

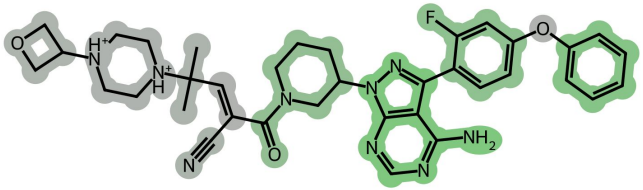
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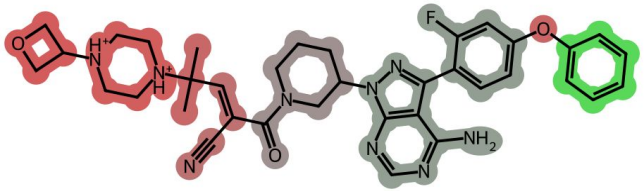
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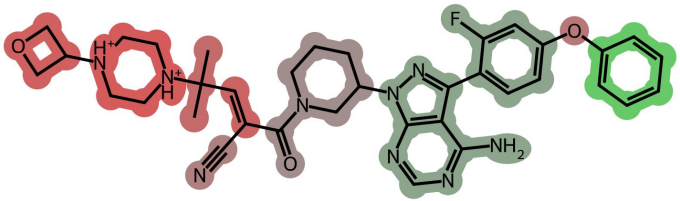
Energy share





LE (0.3)





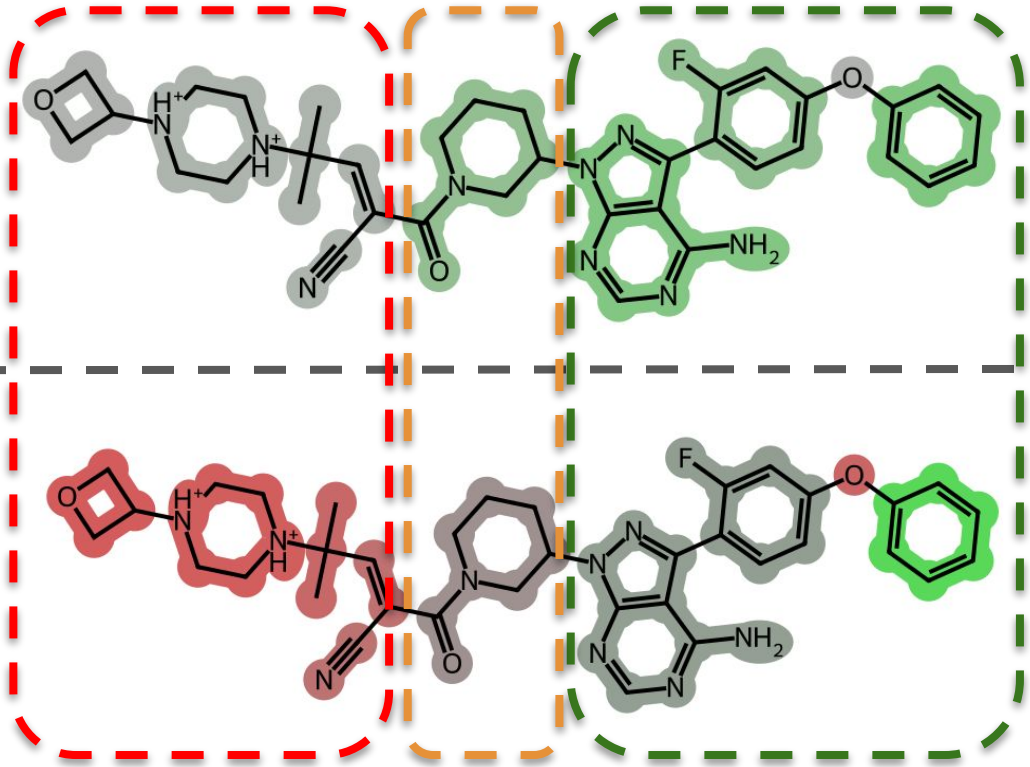
AutoDock4.2

DrugScoreX

Blind R-FBDD analysis of Rilzabrutinib@BTK

General results

Energy share



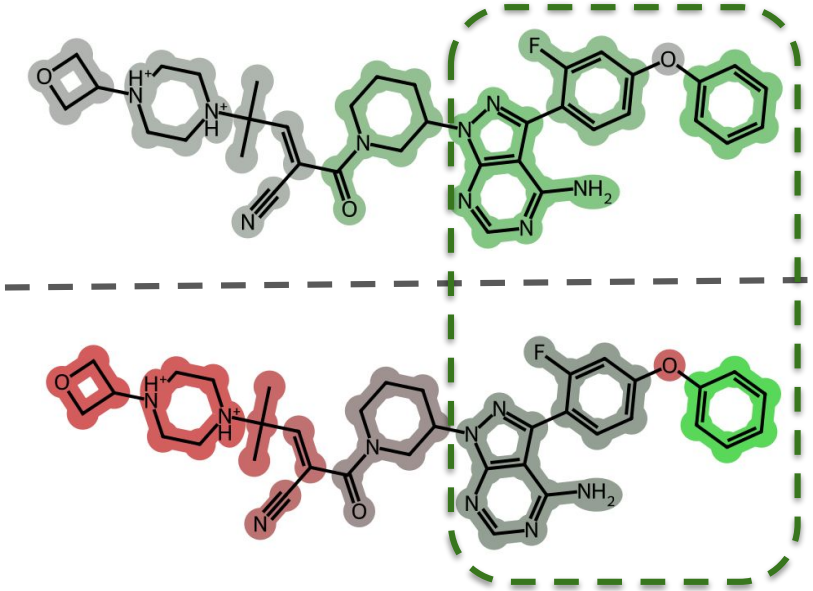
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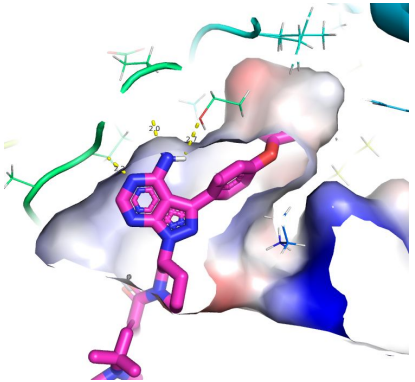
LE (0.3)

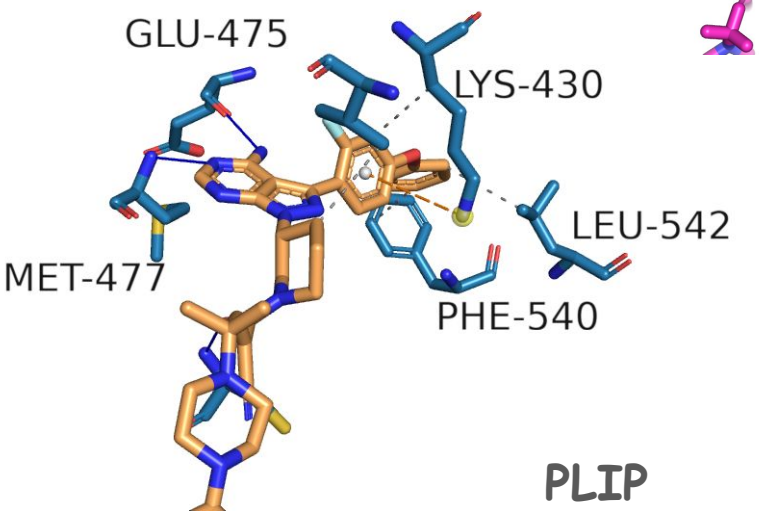
AutoDock4.2

Blind R-FBDD analysis of Rilzabrutinib@BTK

"Anchor" groups



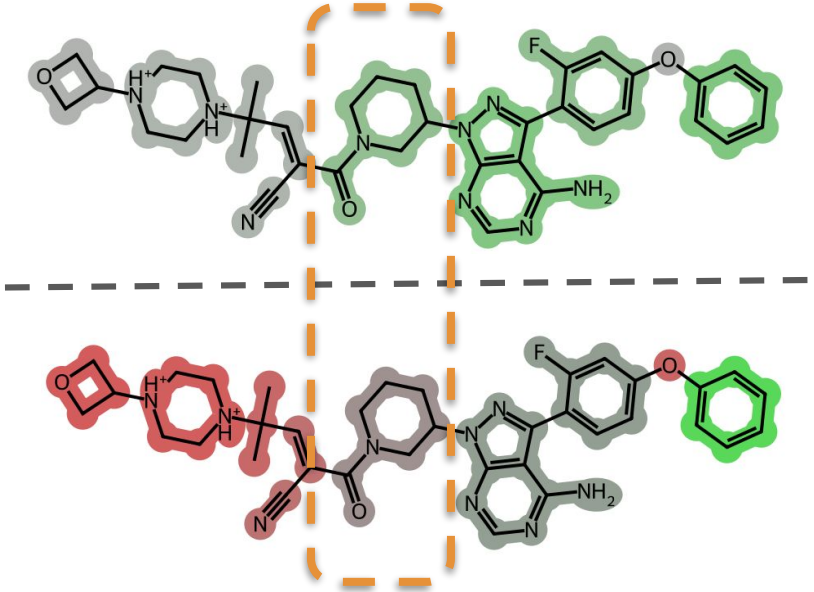


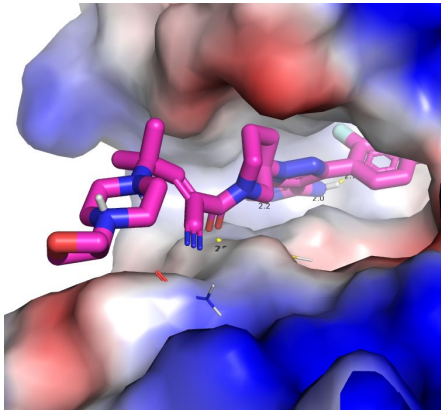


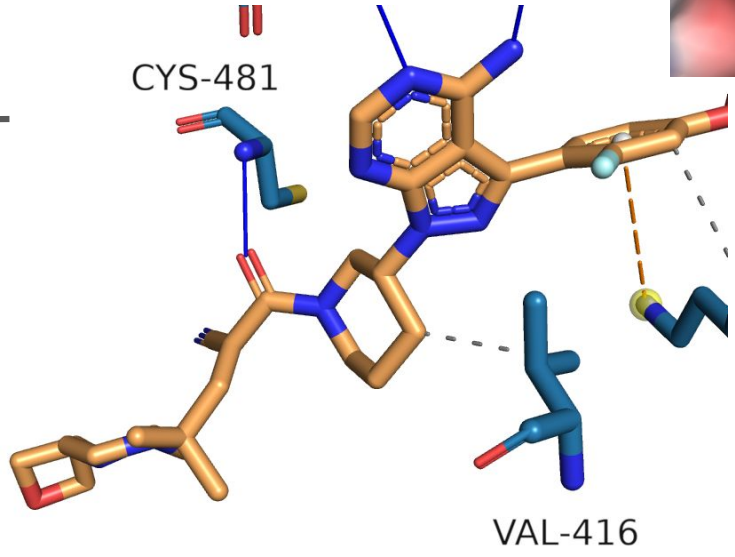
PLIP

Blind R-FBDD analysis of Rilzabrutinib@BTK

"Medium affinity" groups



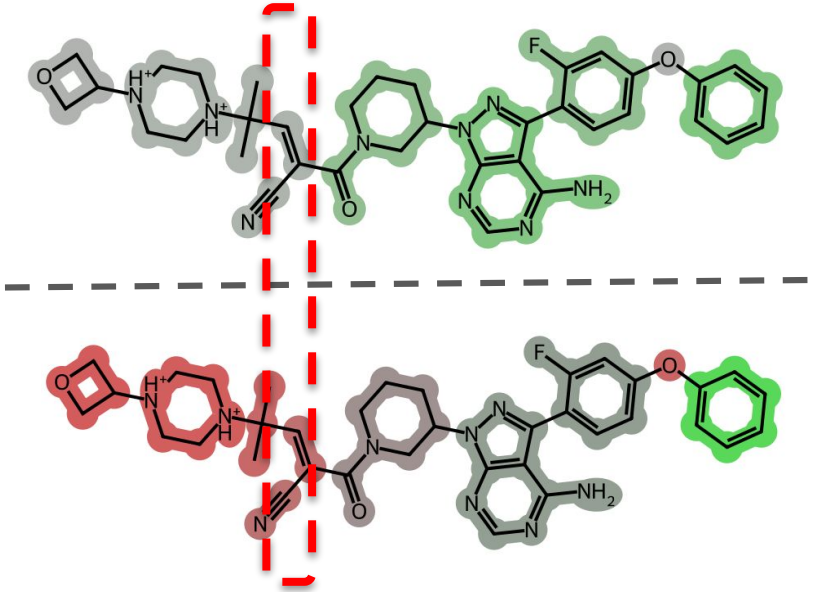


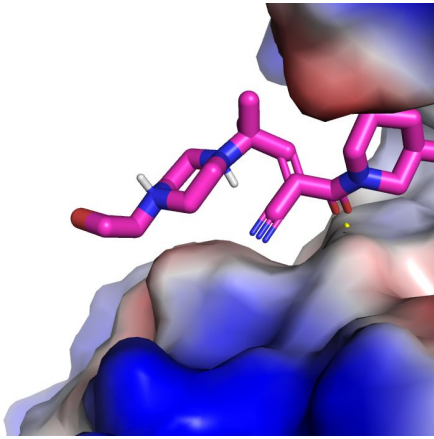


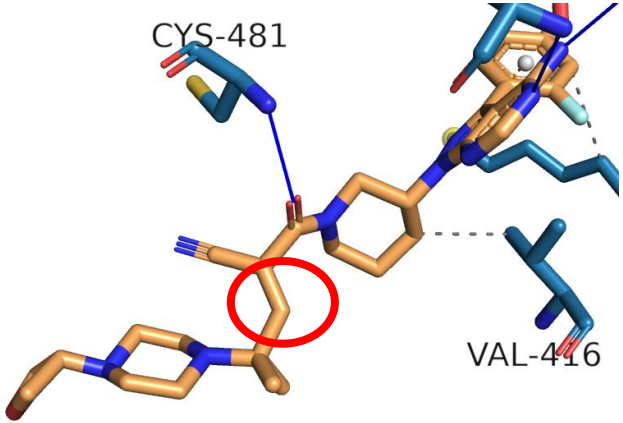
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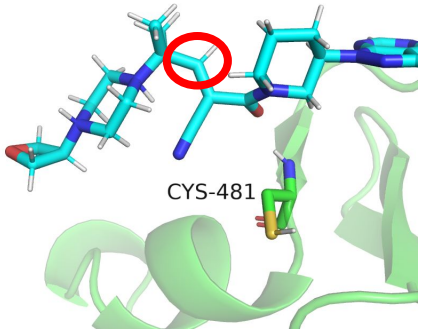
Blind R-FBDD analysis of Rilzabrutinib@BTK

"Covalent warhead" group





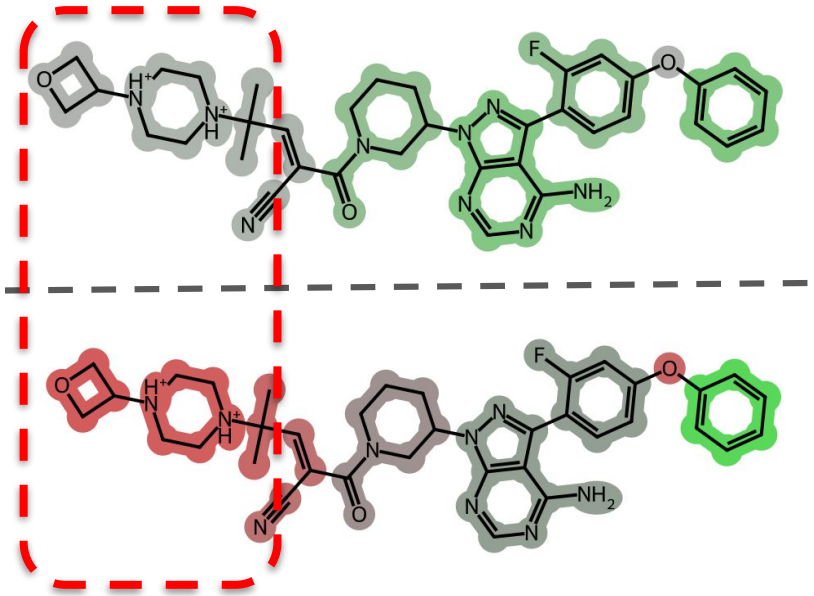




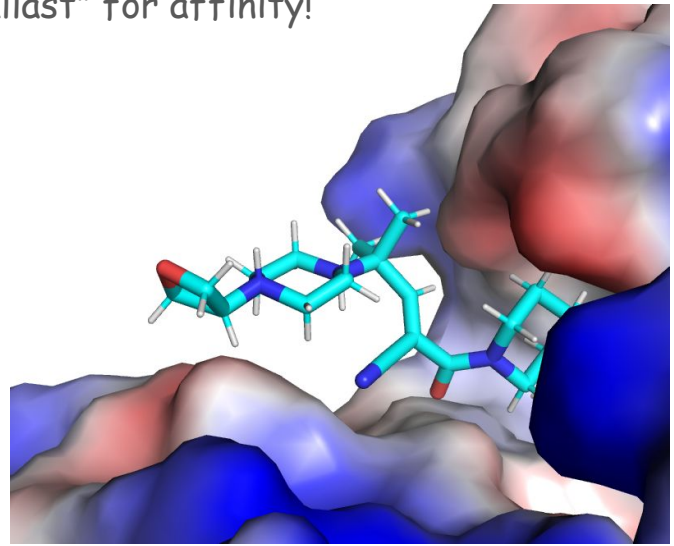
PLIP

Blind R-FBDD analysis of Rilzabrutinib@BTK

"Selectivity/ADMET" groups



"Ballast" for affinity!



BUT:

1. charged and polar groups - ADMET
2. particular shape - selectivity

PLIP - no apparent interactions

Takeaway from R-FBDD analysis of Rilzabrutinib@BTK

1. the "**anchor**" and "**ballast**" groups (for affinity) are detected correctly
2. specific **selectivity/ADMET** groups made clear
3. R-FBDD **supplements** the expert analysis and CADD results

Where R-FBDD is better suited?

1. R-FBDD well **supplements** the existing tools and CADD expertise in rational drug design - it gives **a new layer of information** to build strong and useful **hypotheses** for their subsequent creative implementation and ultimate experimental check

2. R-FBDD approach finds its place at essentially all early stages drug discovery - with emphasis on
   a. the **specific objectives** of the stage
   b. the **inherent risks** of the stage

3. R-FBDD approach is **NOT** the "**magic bullet**" but a useful **new layer** on top of **accessible data and existing tools** - so the best application is within the iterative discovery via Deming's **Design-Make-Test-Analyze** (DMTA) **cycle**

Perspective of R-FBDD and future directions

- better **tool implementation** - more intuitive usage
- more **use cases** - better define pros and cons, **applicability domain**
- more flexible (partially defined by user) **molecule splitting** scheme based on **QC MEP** conservation - **MedChemFrag2.0** - WIP!
- integration of R-FBDD as a tool in **AI agentic system** (MCP) - as fully "**interpretable AI**"

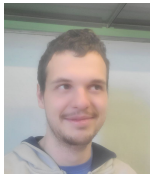
Acknowledgement



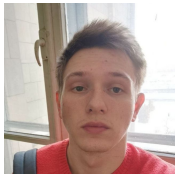
Nikita Ivanov - R-FBDD developer - almost PhD



Arslan Shaimardanov - SF/electrostatic interaction contribution - almost PhD



Vasily Myazin - graduate student - use of R-FBDD in hit finding



Mikhail Rybkin - graduate student - use of R-FBDD in hit-to-lead opt



Vladimir Palyulin - general supervision, scientific expertise



Daniil Chernov - MS 2025 - R-FBDD within MM/GBSA



Ilyas Zhanataev - MS 2025 - MEP based splitting of conjugated fragments



Denis Zverev - graduate student - MEP based splitting - MedChemFrag2.0



Nikita Kholod - diploma student - MEP based splitting - MedChemFrag2.0

“Modes” of collaboration

Dmitry A. Shulga,
PhD, MBA

academic

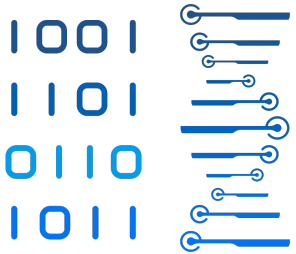


applied/contract

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XXXII Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2026)



Thank you!