Pharmacophore modeling of UDP-N-acetylmuramoylalanine glutamate ligase inhibitors – methodology and application for virtual screening

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UDP-N-acetylmuramoylalanine glutamate ligase (MurD) is one of the most promising biological targets in development of next-generation of anti-bacterial compounds. Along with other members of the amide ligases (MurC-F), MurD inhibits the synthesis of peptidoglycan (PG) – key bacterial metabolite, crucial for bacterial growth. Anti-bacterial action of MurC-F is indeed very promiscuous, given that this metabolic pathway is common for bacteria and inhibitors of a single enzyme may be multipotent antibacterial agent.

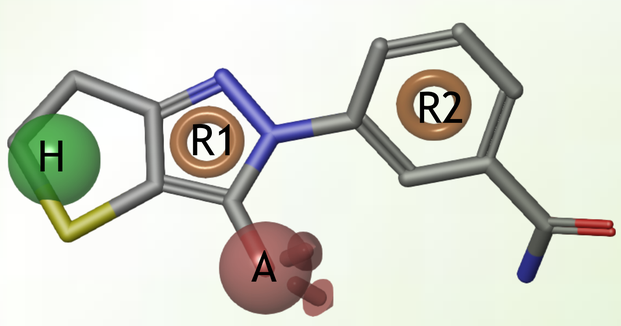
Due to the increasing numbers of published MurD inhibitors (87 structures in February 2016) some standard *in silico* approaches, such as pharmacophore modelling, may be utilized for the discovery of new ligands. In this study, all known MurD inhibitors were hierarchicaly clustered using Canvas [1] with manual refinements to ensure proper chemotypes classification. Multiple hypotheses were developed for each cluster, employing the previously utilized approach [2]. After aplication of DUD-like test set [3], one model per cluster was selected (according to Yourden's statistics value, Figure 1.) to form the linear combination of pharmacophore models, i.e. the first, general pharmacophore hypothesis of MurD inhibitors (Figure 2.).

$$Y = \frac{TP \cdot TN - FN \cdot FP}{(TP + FN) \cdot (TN + FN)}$$

Figure 1. Yourden's statistic formula. TP is the number of true positives (actives labeled as actives), TN the number of true negatives (inactives labeled as inactives), FP the number of false positives (inactives labeled as actives) and FN the number of false negatives (actives labeled as inactives).

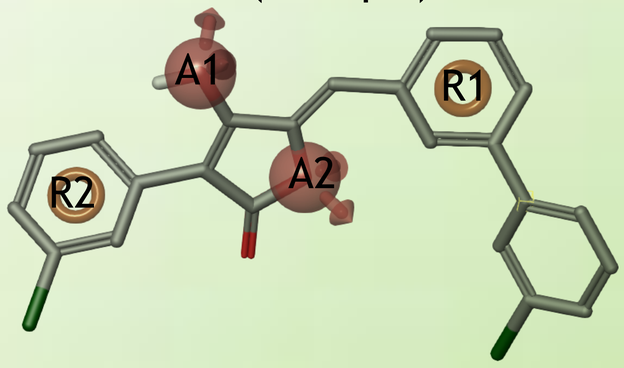
Developed combination of pharmacophore models was applied as one of the steps in the virtual screening protocol reducing space of 4.9M of compounds from six commercial databases (Lifechem, Enamine, Chemdiv, Chembridge, Keyorganic and Maybridge) to ~114K structures for further investigation (Figure 3). In the next step these compounds are docked to models of MurD enzymes developed on diffrent crystal structures. The best performing compounds from docking studies will be purchased and evaluated in *in vitro* tests.

Cluster 1 (14 cmpds) - ADDH



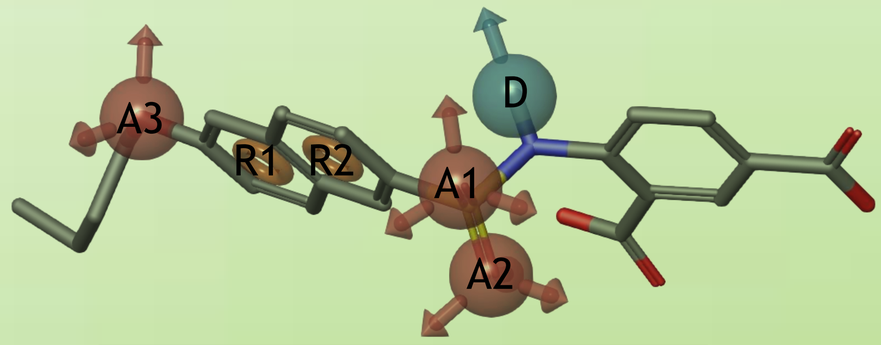
	H	R1	R2
A	4.21	2.55	4.09
H		2.65	6.61
R1			3.96

Cluster 2 (11 cmpds) - AARR



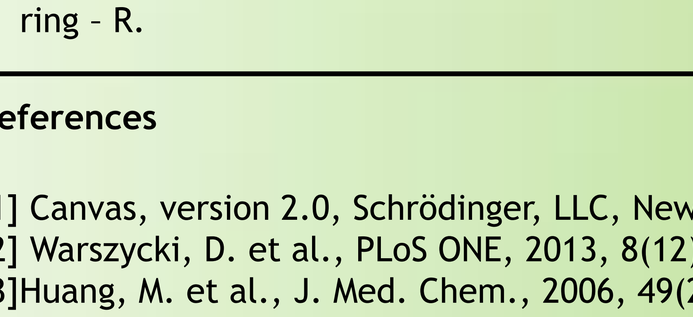
	A2	R1	R2
A1	3.56	5.90	4.08
A2		4.11	5.12
R1			8.97

Cluster 3 (26 cmpds) - AAADRR



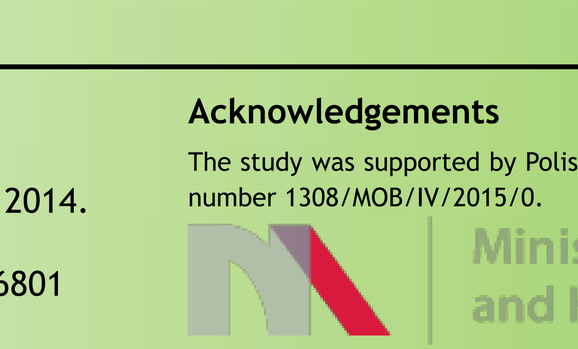
	A2	A3	D	R1	R2
A1	2.57	8.96	2.87	6.36	3.94
A2		8.62	3.44	5.83	3.93
A3			8.37	2.80	5.04
D				5.82	3.79
R1					2.45

Cluster 4 (28 cmpds) - AANN



	A2	N1	N2
A1	3.38	8.87	7.66
A2		5.53	5.31
N1			4.88

Cluster 5 (8 cmpds) - AAADD



	A2	A3	D1	D2
A1	2.39	6.05	4.72	2.39
A2		3.71	3.27	4.56
A3			3.14	8.12
D1				6.48

Figure 2. The additive model of pharmacophore models of MurD inhibitors. For each hypothesis the best fitting compound is presented, along with a matrix of distances (in angstroms) between features. The feature abbreviations used are: hydrogen bond acceptor – A, hydrogen bond donor – D, hydrophobic group – H; positevely ionized group – P, aromatic ring – R.

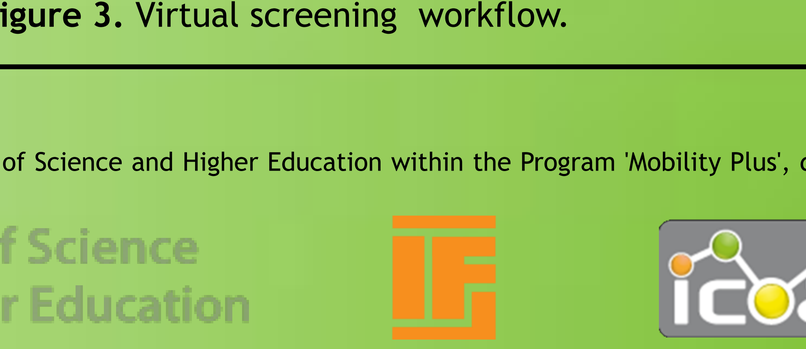


Figure 3. Virtual screening workflow.

References

[1] Canvas, version 2.0, Schrödinger, LLC, New York, NY, 2014.
[2] Warszycki, D. et al., PLoS ONE, 2013, 8(12), e84510.
[3]Huang, M. et al., J. Med. Chem., 2006, 49(23), 6789-6801

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