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Application of linear combination of pharmacophore models in modeling and screening of UDP-N-acetylmuramoylalanine glutamate ligase inhibitors

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UDP-N-acetylmuramoylalanine glutamate ligase (MurD) is one of the most promising biological targets in the development of next-generation anti-bacterial compounds. Along with other members of the amide ligases (MurC–F), MurD inhibits the synthesis of peptidoglycan (PG) – a 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 agents.
A set of 87 MurD ligase inhibitors available in ChEMBL database (Feb, 2016) and in the literature enables application of *in silico* aproaches for the discovery of new ligands. Here, we applied a linear combination of pharmacophore models as described previously [1]. All MurD inhibitors were hierarchically clustered using Canvas software [2] with some manual refinements ensuring appropriate chemical classification. Next, for each cluster multiple hypotheses were generated. After initial evaluation on DUD-like test set [3], one hpothesis per cluster, with the best statistical parameters, was selected to form the linear combination of pharmacophore models, i.e. the first, general pharmacophore hypothesis of MurD ligase inhibitors.
This collection was used as part of a multistep virtual screening protocol for narrowing down of ca. 8M compounds from commercial databases as well as 100K compounds from combinatorial library of easy-to-synthesize compounds.

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

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