

Molecules, 2018, vol.23, N12

Ligand-based pharmacophore modeling using novel 3D pharmacophore signatures

Kutlushina A., Khakimova A., Madzhidov T., Polishchuk P.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2018 by the authors. Pharmacophore modeling is a widely used strategy for finding new hit molecules. Since not all protein targets have available 3D structures, ligand-based approaches are still useful. Currently, there are just a few free ligand-based pharmacophore modeling tools, and these have a lot of restrictions, e.g., using a template molecule for alignment. We developed a new approach to 3D pharmacophore representation and matching which does not require pharmacophore alignment. This representation can be used to quickly find identical pharmacophores in a given set. Based on this representation, a 3D pharmacophore ligand-based modeling approach to search for pharmacophores which preferably match active compounds and do not match inactive ones was developed. The approach searches for 3D pharmacophore models starting from 2D structures of available active and inactive compounds. The implemented approach was successfully applied for several retrospective studies. The results were compared to a 2D similarity search, demonstrating some of the advantages of the developed 3D pharmacophore models. Also, the generated 3D pharmacophore models were able to match the 3D poses of known ligands from their protein-ligand complexes, confirming the validity of the models. The developed approach is available as an open-source software tool: <http://www.qsar4u.com/pages/pmapper.php> and <https://github.com/meddwl/psearch>.

<http://dx.doi.org/10.3390/molecules23123094>

Keywords

3D pharmacophore hash, 3D pharmacophore signatures, Ligand-based modeling, Pharmacophore modeling

References

- [1] Schuster, D.; Nashev, L.G.; Kirchmair, J.; Laggner, C.; Wolber, G.; Langer, T.; Odermatt, A. Discovery of Nonsteroidal 17 β -Hydroxysteroid Dehydrogenase 1 Inhibitors by Pharmacophore-Based Screening of Virtual Compound Libraries. *J. Med. Chem.* 2008, 51, 4188-4199. [CrossRef] [PubMed]
- [2] Hinsberger, S.; Hüsecken, K.; Groh, M.; Negri, M.; Hauptenthal, J.; Hartmann, R.W. Discovery of Novel Bacterial RNA Polymerase Inhibitors: Pharmacophore-Based Virtual Screening and Hit Optimization. *J. Med. Chem.* 2013, 56, 8332-8338. [CrossRef] [PubMed]
- [3] Krautscheid, Y.; Senning, C.J.Å.; Sartori, S.B.; Singewald, N.; Schuster, D.; Stuppner, H. Pharmacophore Modeling, Virtual Screening, and in Vitro Testing Reveal Haloperidol, Eprazinone, and Fenbutrazate as Neurokinin Receptors Ligands. *J. Chem. INF* 2014, 54,1747-1757. [CrossRef] [PubMed]

- [4] Polishchuk, P.G.; Samoylenko, G.V.; Khristova, T.M.; Krysko, O.L.; Kabanova, T.A.; Kabanov, V.M.; Kornyllov, A.Y.; Klimchuk, O.; Langer, T.; Andronati, S.A.; et al. Design, Virtual Screening, and Synthesis of Antagonists of α_1 as Antiplatelet Agents. *J. Med. Chem.* 2015, 58, 7681-7694. [CrossRef] [PubMed]
- [5] Vuorinen, A.; Schuster, D. Methods for generating and applying pharmacophore models as virtual screening filters and for bioactivity profiling. *Methods* 2015, 71, 113-134. [CrossRef] [PubMed]
- [6] Jones, G. GAPE: An Improved Genetic Algorithm for Pharmacophore Elucidation. *J. Chem. INF* 2010, 50, 2001-2018. [CrossRef] [PubMed]
- [7] Korb, O.; Monecke, P.; Hessler, G.; Stützle, T.; Exner, T.E. pharmACophore: Multiple Flexible Ligand Alignment Based on Ant Colony Optimization. *J. Chem. INF* 2010, 50, 1669-1681. [CrossRef] [PubMed]
- [8] Patel, Y.; Gillet, V.J.; Bravi, G.; Leach, A.R. A comparison of the pharmacophore identification programs: Catalyst, DISCO and GASP. *J. Comput. Aid. Mol. Des.* 2002, 16, 653-681. [CrossRef]
- [9] Martin, Y.C.; Bures, M.G.; Danaher, E.A.; DeLazzer, J.; Lico, I.; Pavlik, P.A. A fast new approach to pharmacophore mapping and its application to dopaminergic and benzodiazepine agonists. *J. Comput. Aid. Mol. Des.* 1993, 7, 83-102. [CrossRef]
- [10] Wolber, G.; Dornhofer, A.A.; Langer, T. Efficient overlay of small organic molecules using 3D pharmacophores. *J. Comput. Aid. Mol. Des.* 2006, 20, 773-788. [CrossRef] [PubMed]
- [11] Richmond, N.J.; Abrams, C.A.; Wolohan, P.R.N.; Abrahamian, E.; Willett, P.; Clark, R.D. GALAHAD: 1. Pharmacophore identification by hypermolecular alignment of ligands in 3D. *J. Comput. Aid. Mol. Des.* 2006, 20, 567-587. [CrossRef] [PubMed]
- [12] Schneidman-Duhovny, D.; Dror, O.; Inbar, Y.; Nussinov, R.; Wolfson, H.J. PharmaGist: A webserver for ligand-based pharmacophore detection. *Nucleic Acids Res.* 2008, 36, W223-W228. [CrossRef] [PubMed]
- [13] Schreyer, A.M.; Blundell, T. USRCAT: Real-time ultrafast shape recognition with pharmacophoric constraints. *J. Cheminformatics* 2012, 4, 27. [CrossRef] [PubMed]
- [14] Koes, D.R.; Camacho, C.J. Pharmer: Efficient and Exact Pharmacophore Search. *J. Chem. INF* 2011, 51, 1307-1314. [CrossRef] [PubMed]
- [15] Morgan, H.L. The Generation of a Unique Machine Description for Chemical Structures-A Technique Developed at Chemical Abstracts Service. *J. Chem. Documentation* 1965, 5, 107-113. [CrossRef]
- [16] Butina, D. Unsupervised Data Base Clustering Based on Daylight's Fingerprint and Tanimoto Similarity: A Fast and Automated Way To Cluster Small and Large Data Sets. *J. Chem. Inf. Comput. Sci.* 1999, 39, 747-750. [CrossRef]
- [17] Halgren, T.A. Merck molecular force field. I. Basis, form, scope, parameterization, and performance of MMFF94. *J. Comput. Chem.* 1996, 17, 490-519. [CrossRef]