# ePharmaLib: A Versatile Library of e-Pharmacophores to Address Small-Molecule (Poly-)Pharmacology

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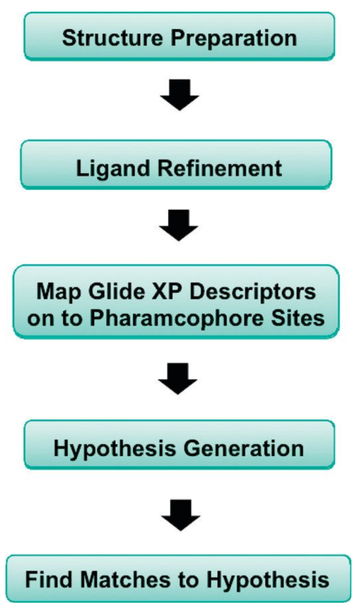
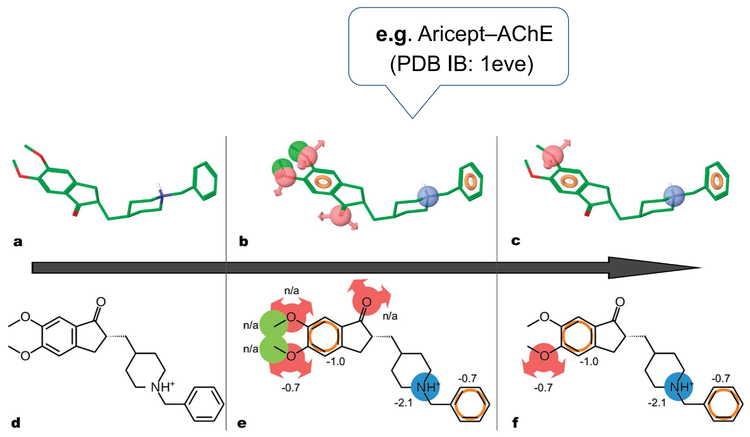
## Introduction

- Pharmacology operates on the axiom: "*corpora non agunt nisi fixata*", famously stated by Paul Ehrlich in 1909 [1].
- Nowadays, it is widely acknowledged that bioactive compounds oftentimes bind to several target proteins thereby exhibiting polypharmacology [2].
- Experimentally determining drug–target interactions (DTIs) is however laborious and costly, whereas computational methods are faster and cheaper.
- To this end, we created ePharmaLib [3], an open-access library of e-pharmacophores modeled from the solved cocrystal structures of 17,594 therapeutically relevant protein–ligand complexes from the scPDB [4].

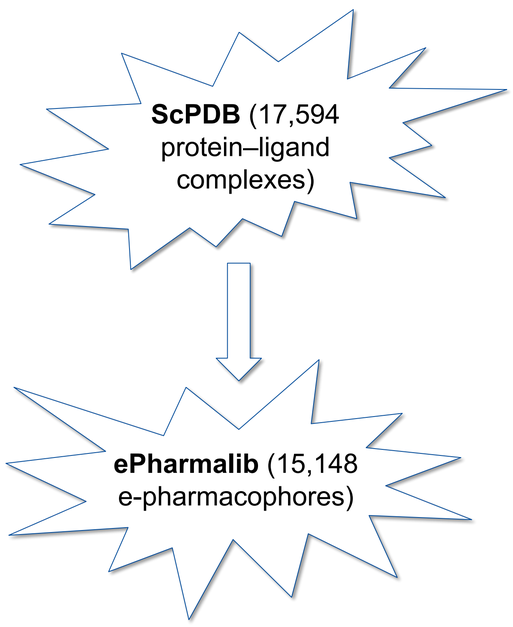

## ePharmaLib Development

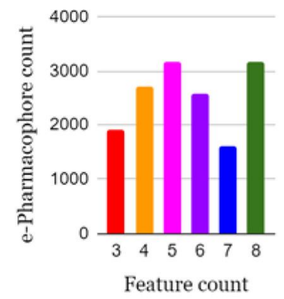



Schrodinger Software Suite [5]

## ePharmaLib Statistics

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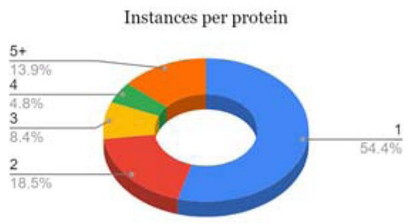
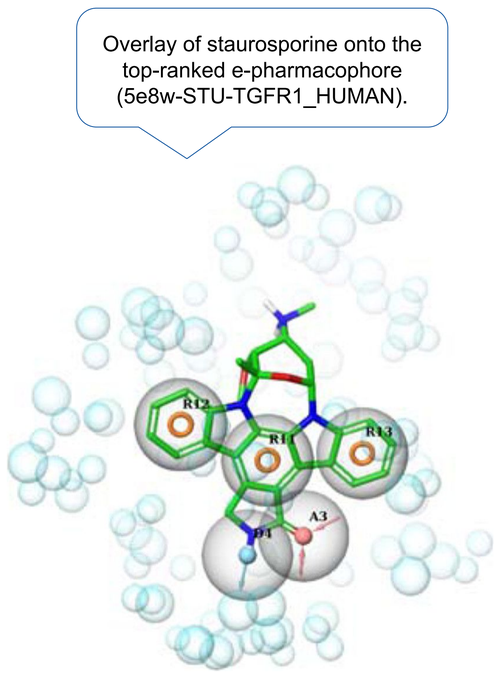



B

## Retrospective Validation

- A target fishing study was carried out with ligands from the StreptomeDB [6], notably staurosporine (STU), an indolocarbazole displaying highly potent pan-kinase inhibition.
- Predicted targets are ranked in terms of an RMSD-based metric known as *Fitness*. It ranges between 3 (perfect alignment) and −1 (non-alignment).
- In total, 490 PDB protein hits (253 unique proteins) were retrieved. Strikingly, out of the top-50 protein hits, 41 (first 13 in a row) are STU-bound proteins, i.e., "known–known" DTI pairs.
- The general observation that can be made from this ranking of protein hits is the high self-retrieval rate of known targets.



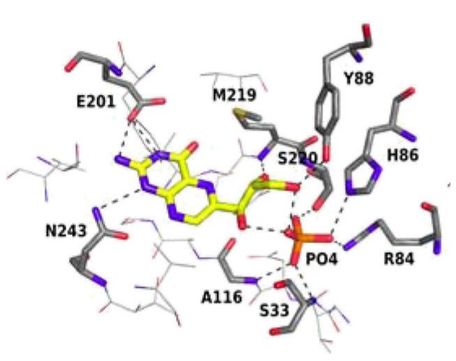

Top-10 ranking of "known-known" DTI pairs of staurosporine (STU)

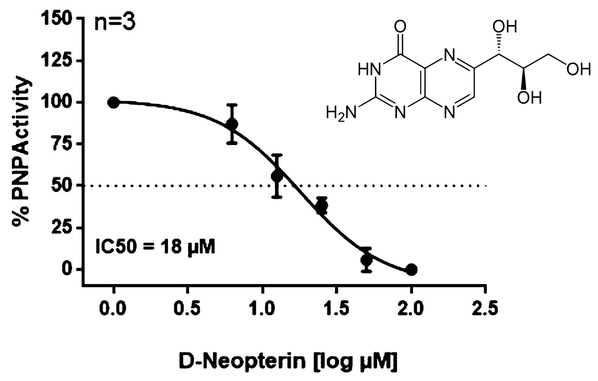
| Rank | Target ID[a] | Target Name | Feature types[b] | Feature count | Fitness |
|---|---|---|---|---|---|
| 1 | 5e8w-STU-TGFR1_HUMAN | TGF-beta receptor type-1 | ADRRR | 5 | 2.901 |
| 2 | 1u59-STU-ZAP70_HUMAN | Tyrosine-protein kinase ZAP-70 | ADHRRR | 6 | 2.898 |
| 3 | 3ckx-STU-STK24_HUMAN | Serine/threonine-protein kinase 24 | ADHPRRR | 7 | 2.895 |
| 4 | 1e8z-STU-PK3CG_HUMAN | Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform | AHRRR | 5 | 2.891 |
| 5 | 2buj-STU-STK16_HUMAN | Serine/threonine-protein kinase 16 | ADHRRR | 6 | 2.889 |
| 6 | 1q3d-STU-GSK3B_HUMAN | Glycogen synthase kinase-3 beta | ADHRRR | 6 | 2.886 |
| 7 | 4u97-STU-IRAK4_HUMAN | Interleukin-1 receptor-associated kinase 4 | ADHRRR | 6 | 2.886 |
| 8 | 3bkb-STU-FES_HUMAN | Tyrosine-protein kinase Fes/Fps | ADHRRR | 6 | 2.885 |
| 9 | 1aq1-STU-CDK2_HUMAN | Cyclin-dependent kinase 2 | ADHRRR | 6 | 2.883 |
| 10 | 3a62-STU-KS6B1_HUMAN | Ribosomal protein S6 kinase beta-1 | ADHRRR | 6 | 2.883 |

[a]PDBID-hetID-UniProtEntryName.
[b]A: H-bond acceptor; D: H-bond donor; R: aromatic; H: hydrophobe.

## Prospective Validation

- A scaffold hopping study was carried out with 7735 DrugBank ligands against 27 e-pharmacophores of the human purine nucleoside phosphorylase (hPNP), a validated cancer drug target with no FDA-approved drugs. Four hits (neopterin, tiazofurin, CAN-508, and pseudouridine) were selected for *in vitro* validation by means of a colorimetric assay. Only neopterin (endogenous biomarker) showed significant inhibition of hPNP.




## Summary and Outlook

- ePharmaLib is an open-access library of 15,148 medicinally relevant e-pharmacophores, for use in diverse virtual screening scenarios.
- A good balance was obtained between computational efficiency and predictive accuracy, with an average runtime of an hour/molecule/processor.
- Of note, pharmacophore screening should be combined with molecular docking and/or molecular (meta)dynamics simulations prior to experimental validation.
- The mechanism of action of neopterin (an endogenous immunomodulator) was elucidated to stem from its inhibition of hPNP. Therefore, neopterin could serve as a starting point for the development of a new class of hPNP inhibitors.

http://www.pharmbioinf.uni-freiburg.de/epharmalib

https://training.galaxyproject.org/training-material/topics/computational-chemistry/tutorials/**zauberkugel**/tutorial.html

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## Acknowledgments

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