CHIRALITY: A HIDDEN DRIVING FORCE IN PROTEIN–DRUG RECOGNITION

Xavier Lucas and Stefan Günther

Pharmaceutical Bioinformatics, Institute of Pharmaceutical Sciences, University of Freiburg, Germany

xavier.lucas@pharmazie.uni-freiburg.de

Introduction

We have recently shown that high-throughput virtual screening is a suitable approach do identify **epigenetic inhibitors** among millions of molecules [1]. Yet, a rule of thumb allowing for the discrimination of molecules incorporating target properties prior to docking is missing.

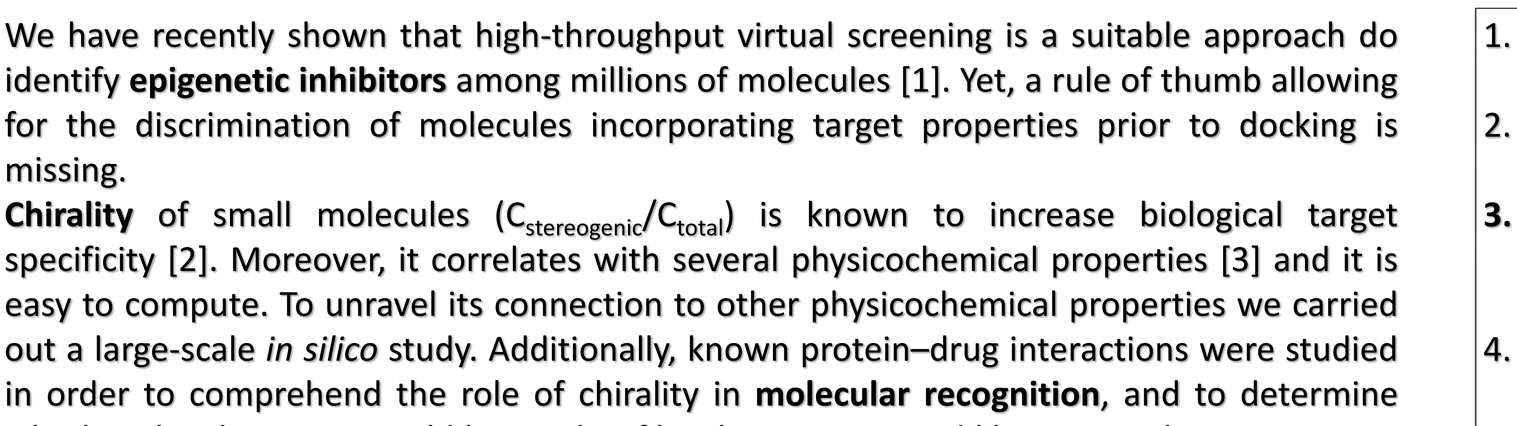
Chirality of small molecules ($C_{stereogenic}/C_{total}$) is known to increase biological target specificity [2]. Moreover, it correlates with several physicochemical properties [3] and it is easy to compute. To unravel its connection to other physicochemical properties we carried out a large-scale *in silico* study. Additionally, known protein–drug interactions were studied in order to comprehend the role of chirality in **molecular recognition**, and to determine whether this descriptor could be used to filter large compound libraries applying target site information [4].

Conclusions

1. The content of chiral carbons can be used to **estimate** other physicochemical properties, such as **solubility**.
2. Chirality can be used to **pre-filter** large compound libraries incorporating target information.
3. **Rule of thumb**: simple drugs bind to hydrophobic, druggable active sites; whereas complex drugs are attracted to hydrophilic, low-druggable pockets.
4. Increasing chirality might enable addressing **low-druggable targets**.
5. Protein families have three **distinct recognition patterns** towards substrates' chirality.

Results

By exploring thousands of **protein–drug complexes** we discovered that hydrophobic, druggable binding sites recognize achiral or simple molecules, whereas hydrophilic, low-druggable pockets attract drugs with many stereogenic carbon atoms:

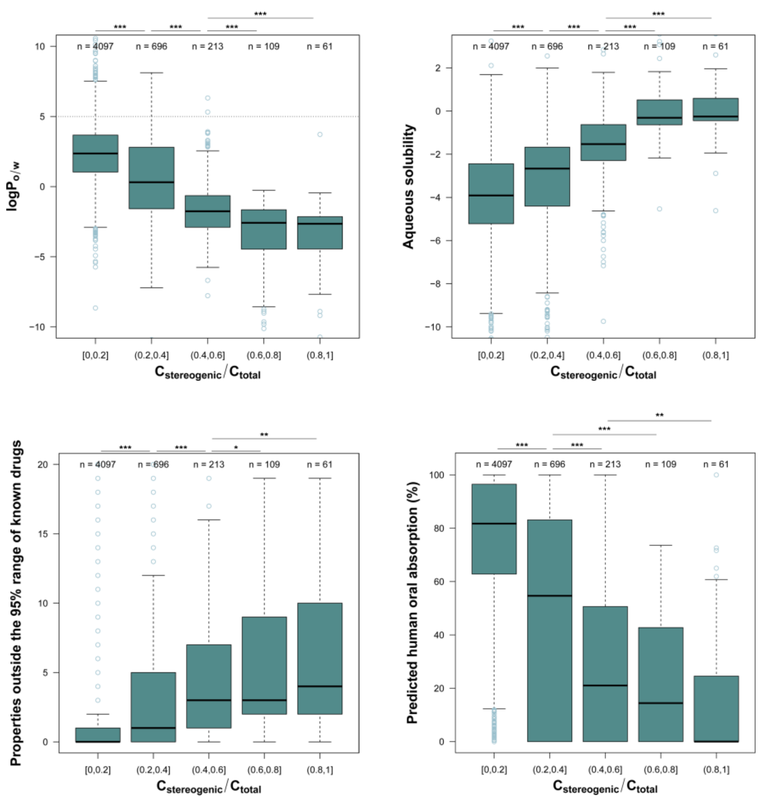


$C_{stereogenic}/C_{total}$ = 0.00
Druggability score = 1.07
Hydrophobic/hydrophilic = 1.29

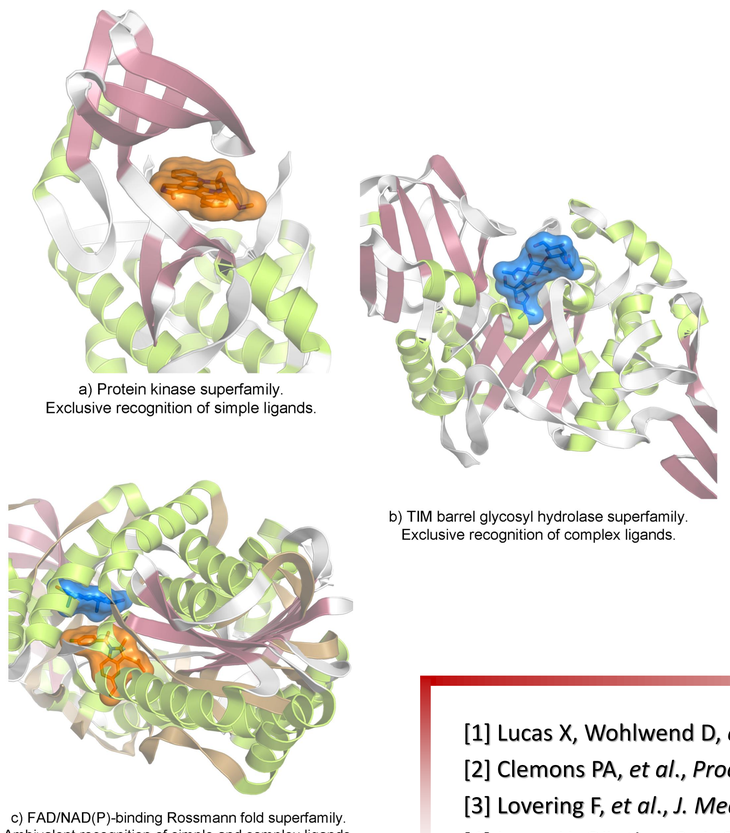
$C_{stereogenic}/C_{total}$ = 0.44
Druggability score = 0.90
Hydrophobic/hydrophilic = 0.76

$C_{stereogenic}/C_{total}$ = 0.82
Druggability score = 0.80
Hydrophobic/hydrophilic = 0.00

The binned chirality content of drugs correlates with several physicochemical properties, including **hydrophobicity,** aqueous **solubility**, and **drug-likeness**:



3 distinct **protein family-behaviors** towards recognition of chiral substrates were additionally observed:



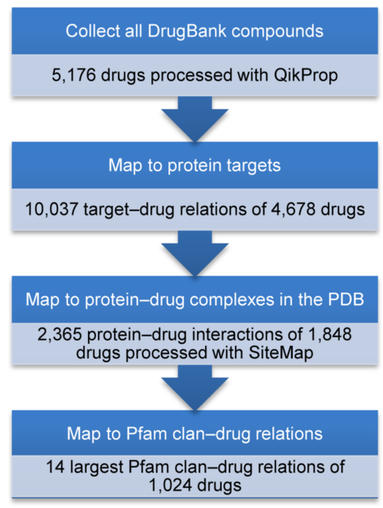
a) Protein kinase superfamily.
Exclusive recognition of simple ligands.

b) TIM barrel glycosyl hydrolase superfamily.
Exclusive recognition of complex ligands.

c) FAD/NAD(P)-binding Rossmann fold superfamily.
Ambivalent recognition of simple and complex ligands.

Methods

Aiming at studying protein–drug recognition, drugs and their targets were extracted from the **DrugBank** database :



Outlook

The correlation of chirality with other physicochemical properties of drugs and their targets will allow to **re-organize chemical libraries** based on this descriptor.

The presented rule, and the libraries derived thereof, will be used to preselect small molecules for low-druggable targets.

[1] Lucas X, Wohlwend D, *et al.*, *Angew. Chem. Int. Ed.*, 2013, *52*(52):14055–9.
[2] Clemons PA, *et al.*, *Proc. Natl. Acad. Sci. U S A*, 2010, *107*(44):18787–92.
[3] Lovering F, *et al.*, *J. Med. Chem.*, 2009, *52*(21):6752–6.
[4] Lucas X, Günther S, *J. Comput. Chem.* (in press).

http://pharmaceutical-bioinformatics.org

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