Fragment-Based Chemogenomics

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Introduction

We have created a **proprietary** and **structurally diverse fragment library** (Fig. 1-2) and screened it for a variety of G-protein coupled receptors (**GPCRs**) and a number of **other drug targets** (Fig. 3). The resulting data allows for a **fragment-based chemogenomics** study (Fig. 4-5) to interrogate the **interactions** of GPCRs and their ligands (Fig. 6).

Diverse Fragment Library

Fig. 1

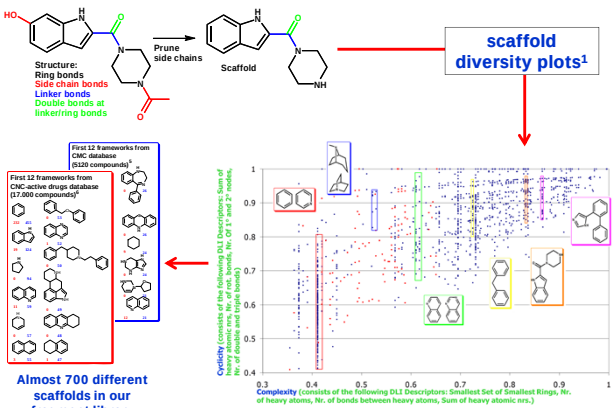
Proprietary database

Fragment rules

- ✓ Heavy atoms ≤22
- ✓ Log P, H-bond acceptors & H-bond donors ≤3
- ✓ Rotatable bonds ≤5
- ✓ No reactive functional groups

1010 Fragments

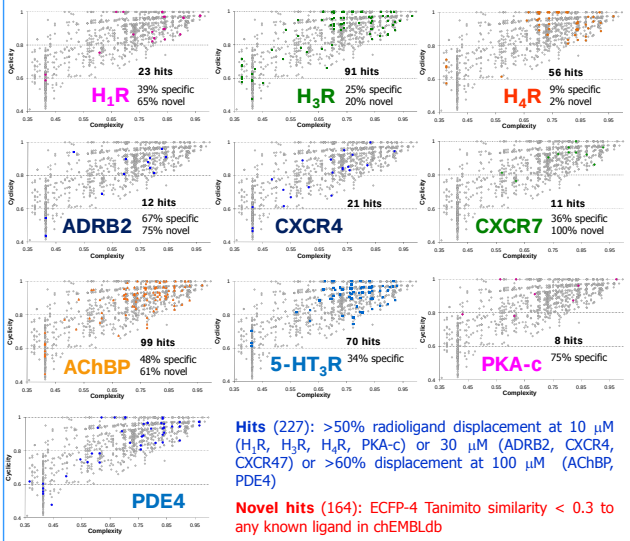
Fig. 2 **Fragment diversity analysis**



Almost 700 different scaffolds in our fragment library

Diverse & Novel Fragment Hits

Fig. 3: Screening of 1010 **fragments** against a variety of proteins, incl. **GPCRs** (H_1R, H_3R, H_4R, ADRB2, CXCR4, CXCR7) and **other targets** (AChBP, 5-HT_3R, PKA-c, PDE4B) yielded **diverse** sets of **novel** and **target-specific hits** (color coded).



Hits (227): >50% radioligand displacement at 10 μM (H_1R, H_3R, H_4R, PKA-c) or 30 μM (ADRB2, CXCR4, CXCR47) or >60% displacement at 100 μM (AChBP, PDE4)

Novel hits (164): ECFP-4 Tanimito similarity < 0.3 to any known ligand in chEMBLdb

Fragment-based chemogenomics

Fig. 4: Fragment bio-affinity profiles illustrate **binding site differences** and **similarities,** some of which are **anticipated** while others are **surprising**:

- Anticipated differences: GPCRs vs. kinase (PKA-c) + phosphodiesterase (PDE4)
- Anticipated similarities: histamine receptors H_1R, H_3R, and H_4R
- Surprising differences: bioaminergic GPCRs ADRB2 vs. H_1R, H_3R, and H_4R
- Surprising similarities: H_4R (GPCR) and 5-HT_3R (ion channel)

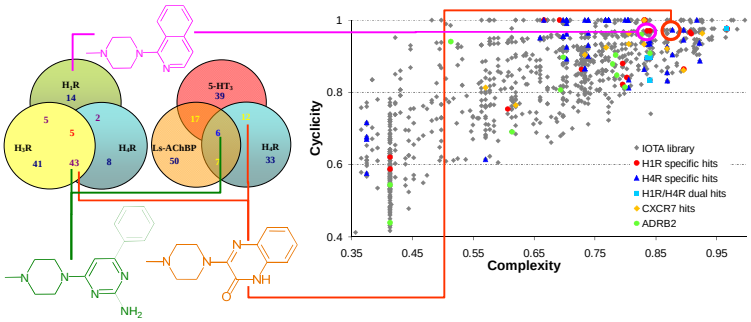
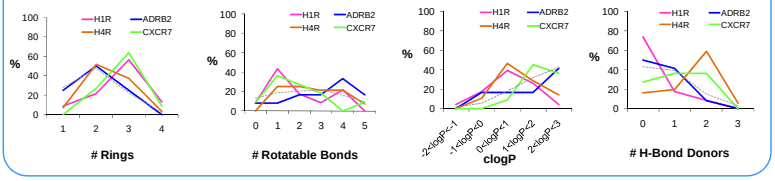


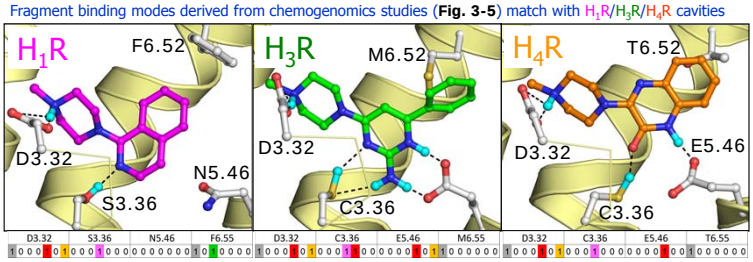
Fig. 5: Similarities/differences between **target binding sites** are reflected by similarities/differences in physical chemical **properties** of **fragment hits**.



Fragment-protein interactions

Fig. 6: Fragment bio-affinity profiles (Fig. 3-5) are used to optimize structural models and define **protein-ligand interaction fingerprints**[2] that aid target-selective **structure-based virtual screening**[3] and **ligand design**[4] methods.

Fragment binding modes derived from chemogenomics studies (**Fig. 3-5**) match with H_1R/H_3R/H_4R cavities



1) contact; 2) face-to-face stacking; 3) edge-to-face stacking; 4) HB acc.-HB don.; 5) HB don.-HB acc.; 6) neg.-pos.; 7) pos.-neg.

Conclusions and Perspectives

- We have created a proprietary and diverse fragment library that has been screened for a variety of GPCRs and other protein targets.
- All screens have resulted in unique and novel fragment hits.
- The use of fragments in chemogenomics approaches results in higher resolution interaction fingerprints and leads to improved structural understanding and novel insights in ligand binding characteristics.
- These studies can support the design of novel ligands with specified activity profiles.

References

1) J.Xu et al., *J Chem Inf Comput Sci* (2000) 40:1177; 2) C. de Graaf et al., *J Med Chem* (2008) 51:4978; 3) C. de Graaf et al. *Curr Pharm Des* (2009) 15:4026; 4) Smits et al. *J Med Chem* (2008) 51:2457

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