

Using molecular fields for rational drug design against GPCRs: Application to CCK2 antagonists

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1. The importance of 3D protein-ligand structural information in drug discovery

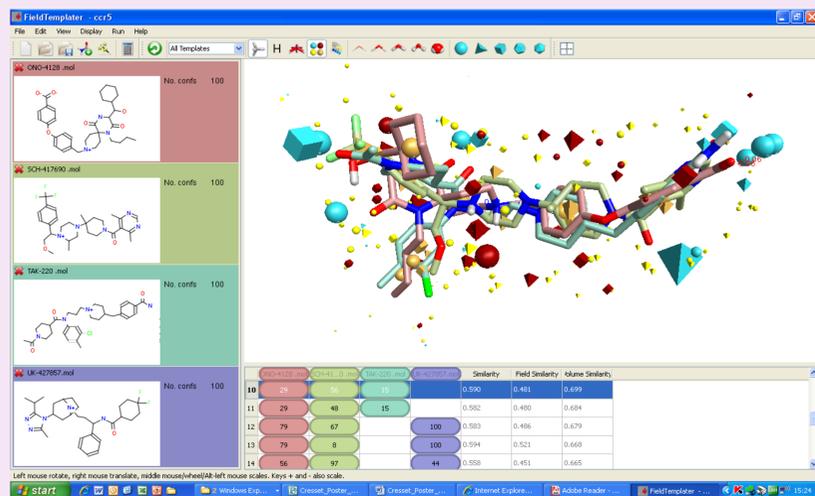
It is widely accepted that having the 3D structure of a protein co-crystallized with an active ligand is a highly valuable tool in drug discovery. It allows an understanding of the shape and key molecular features required for activity and can be used to guide a discovery project through hit-finding and lead optimisation.

2. What if I don't have a protein x-ray structure?

Many important drug targets, including GPCRs and ion channels lack accurate 3D structures. Molecular field technology can be used for these targets to create a **bioactive conformation model** from active ligands alone.

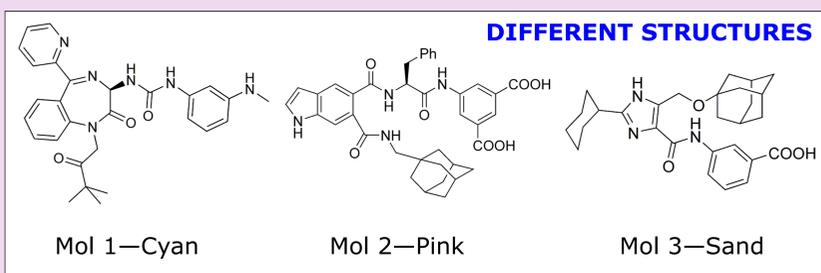
3. How is this achieved?

- ⇒ Cresset's molecular fields [1] encode electrostatic, steric and hydrophobic properties in a quantitative way
- ⇒ The field of an active molecule in its 3D bioactive conformation generates a **molecular surface pharmacophore** that depicts the binding properties which compliment the protein active site
- ⇒ The field pattern of a ligand depends on its conformation, so
- ⇒ We use FieldTemplater to find those conformations of a small set of diverse active ligands that can all express a highly similar molecular surface



Screenshot of FieldTemplater™ which runs under Windows or Linux on a PC or workstation

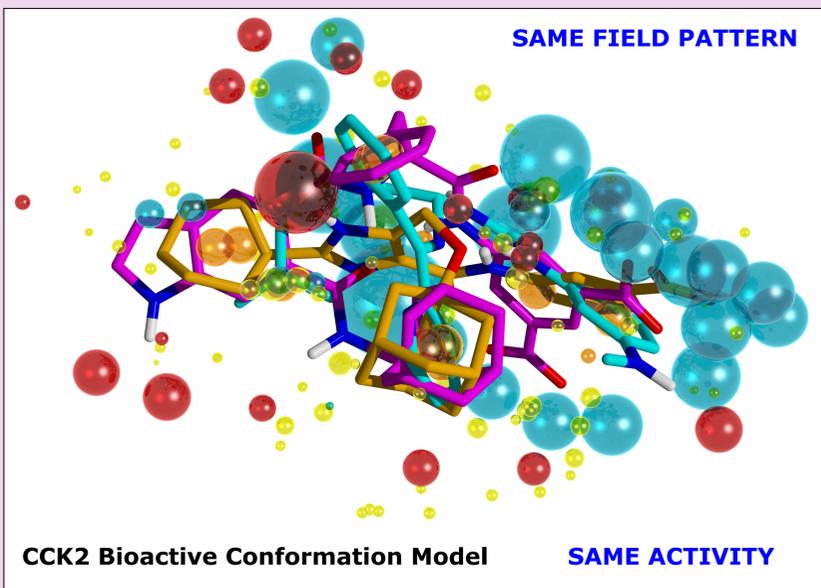
Application to CCK2 antagonists



Input 3 diverse active CCK2 ligands to FieldTemplater in 2D

FieldTemplater Technology

- Converts 2D structure to 3D
- Generates 100 diverse conformations of each
- Adds molecular fields to each conformation
- Hunts for common field patterns across the conformation population of each molecule



FieldTemplater outputs 3D bioactive conformation alignment hypotheses

Use FieldAlign to test the model

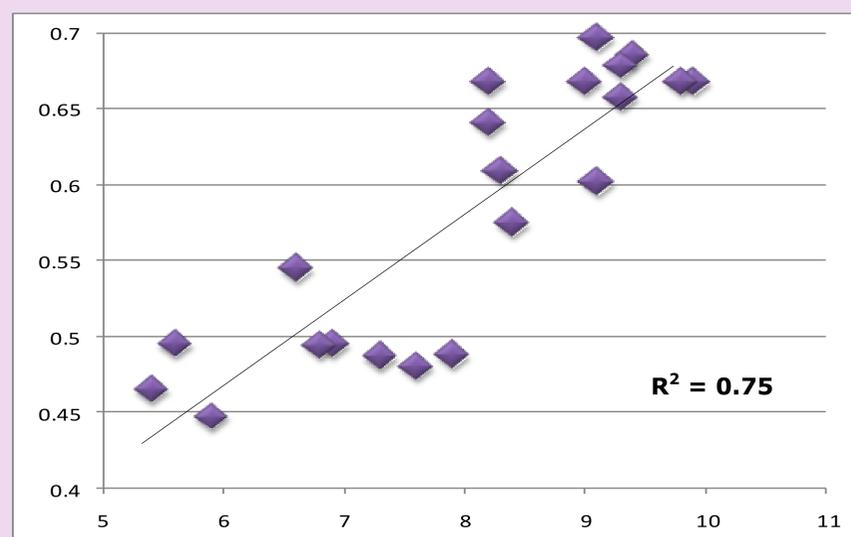
Validation

We fitted 18 active ligands drawn in 2D to the model from 7 highly diverse chemotypes [2] using our FieldAlign software and calculated their field similarity to the model

We plotted field similarity against activity (rat stomach functional pKb)

We obtained a linear relationship between biological activity and field similarity, so validating the predictivity of the model.

Plot of Field Similarity vs Rat Stomach pKb



Conclusions

- ⇒ We found a bioactive conformation hypothesis using just three active CCK2 antagonists, so it is suitable for use early in the drug discovery process and the model can be refined as more information becomes available
- ⇒ The model correctly predicted the activity of 18 highly diverse structures (these can be found in [2]) using just similarity of their field to the model.
- ⇒ Doing conventional QSAR on this diversity of structures would not be feasible
- ⇒ This approach does not require protein structural information
- ⇒ The FieldTemplater and FieldAlign software can be run by a medicinal chemist or molecular modeller using a standard desktop PC

References

- Cheeseright, T. et al, J. Chem. Inf. Model., (2006) 46, 665-676
- Low, CMR and Vinter JG, J Med Chem, (2008) 51, 565-573