Defining the 3D Active Site Requirements for GPCRs via Molecular Field Technology: CCK2 Ligands Case Study

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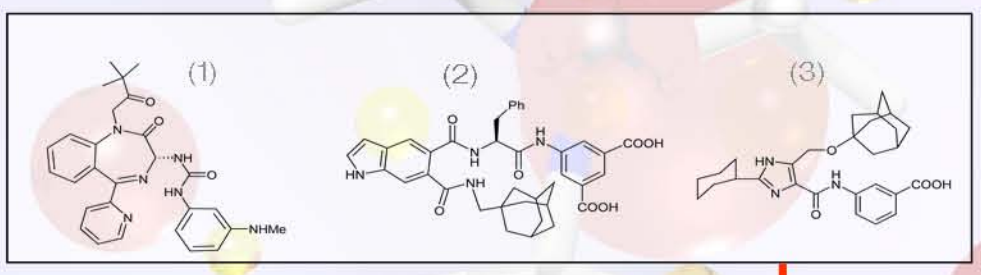
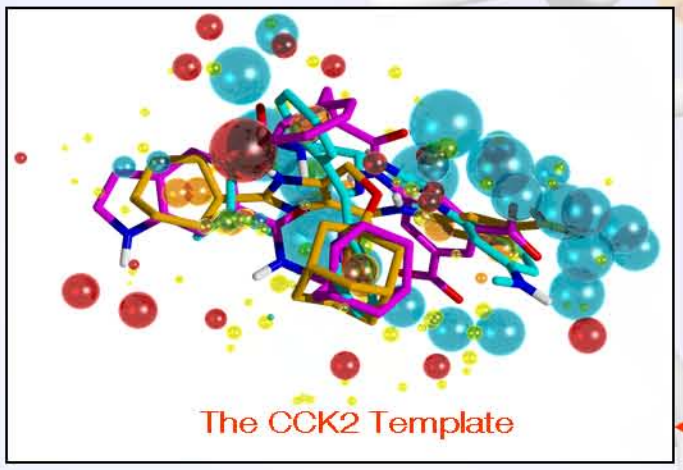
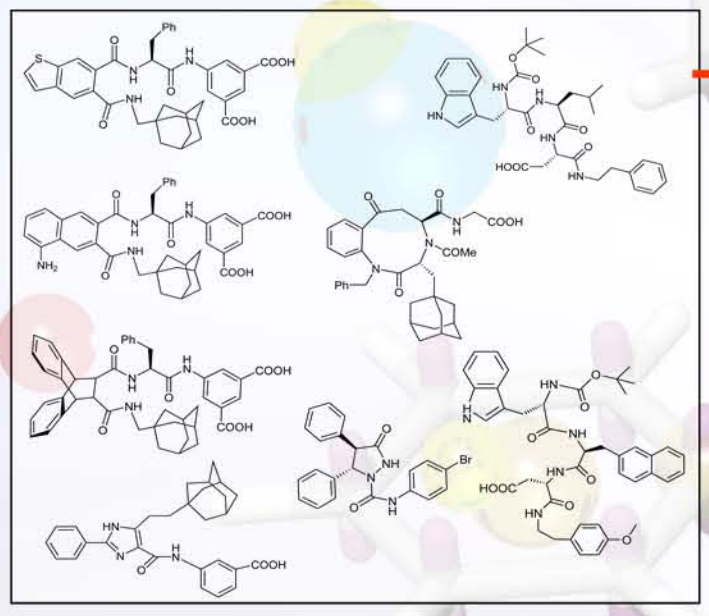
Introduction

Structure-based drug design is widely accepted as a valuable tool to aid lead optimisation for targets with an x-ray structure. However, designing ligands for GPCR receptors, such as CCK2, presents a greater challenge due to the lack of good 3D structural data on the targets. Certain groups have found homology models based on rhodopsin useful, but there can be large errors in these models. We have therefore approached this problem from the ligands' viewpoint.

Cresset's molecular fields [1] model the binding characteristics of a ligand. They have been extensively validated for virtual screening by us and some of the major pharma companies. We have now applied fields to create a model to predict bioactive conformations of ligands in the absence of x-ray data. Our reasoning is that if a set of diverse ligands can adopt a conformation in which they all display the same field pattern, then this alignment must be an hypothesis for their bioactive conformation.




The CCK2 Template



Work Flow

Take 3 **structurally-diverse ligands** highly active in the CCK2 in vitro rat stomach functional assay [2]

Use **FieldTemplater** to derive a bioactive conformation model: **The CCK2 Template**

Use **FieldAlign** to align 8 diverse molecules with a range of CCK2 activities to the template

Plot the **field similarity** value of each molecule to the template **against** the **biological activity**

Fields and Field Points

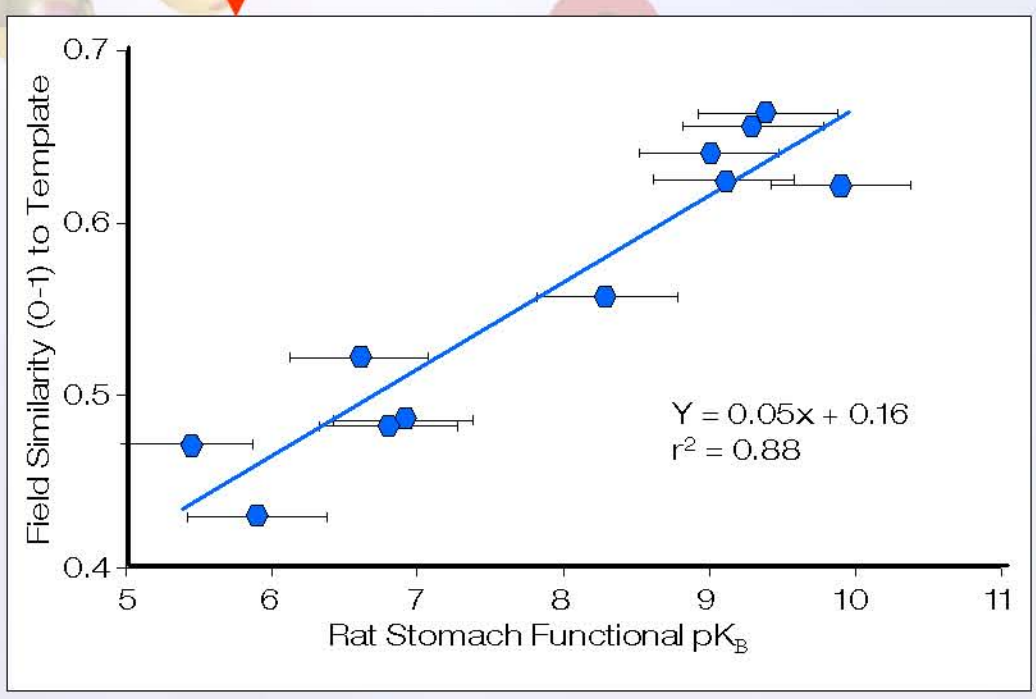
Cresset describes molecules by 4 molecular fields: electrostatic (+ve and –ve), hydrophobic and steric. The fields model the binding properties of compounds. We place fieldpoints (coloured spheres) at the sites where the fields are strongest. Molecules with similar field point patterns are expected to show similar binding characteristics to an active site, irrespective of their atomic structure.

FieldTemplater

FieldTemplater takes 3 or more structurally-diverse 2D molecules and finds those conformations that can display a common field
pattern. This pattern is an hypothesis for the binding features required for activity and the molecules' conformations are an hypothesis for their bioactive conformation.

FieldAlign

FieldAlign takes 2D molecular structures and aligns them to a 3D reference molecule (here, the CCK2 template) using molecular fields. A similarity value is generated for each molecule's field to the template field. The more similar the molecular fields, the higher the similarity value (1 = identical).



Conclusions

1. A CCK2 template model for activity has been constructed from 3 active compounds, starting from their 2D structure, by looking for a set of conformations in which they all display a common field pattern.
2. The template correctly predicts the activity of a set of test compounds using a field similarity measure.

References

1. T. Cheeseright et al, J. Chem. Inf. Model.; **46**, 665-676 (2006)
2. I.M. Buck et al, J. Med. Chem.; **48**, 6803-6812 (2005)

Note: It is advantageous to use highly active compounds to create the template, since they have the optimal field for activity. Use of low activity compounds will result in a poorly predictive model.

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