Docking-Derived Pharmacophores

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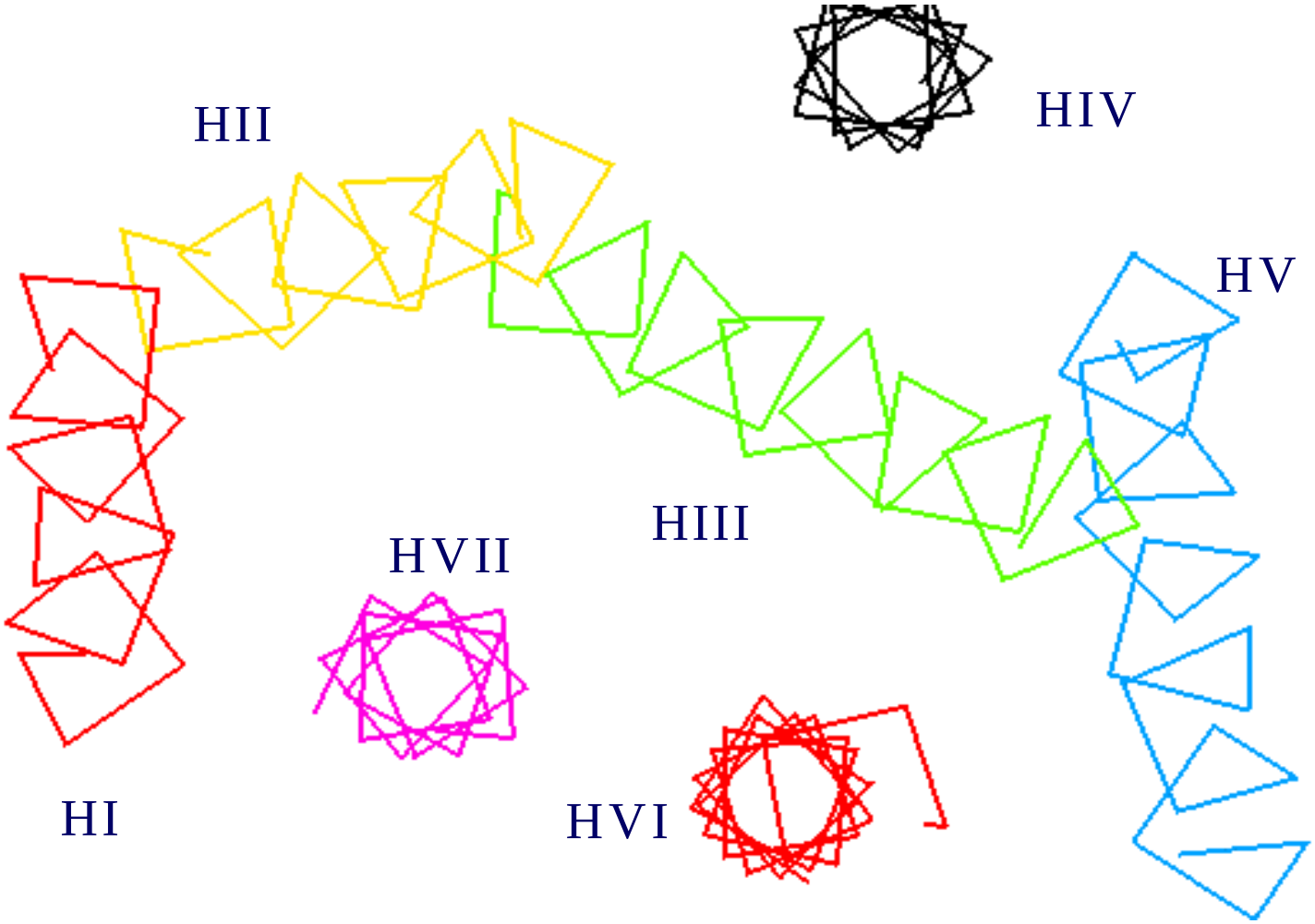
α_1-Adrenoceptors

- members of G-protein coupled receptor superfamily (GPCRs)
- range of subtypes, no really selective ligands available for some subtypes
- no high resolution 3D structure for any GPCR
- GPCR model constructed on the basis of rhodopsin electron diffraction structure and sequence homology studies by Baldwin *et al.*

The Baldwin α-carbon GPCR template



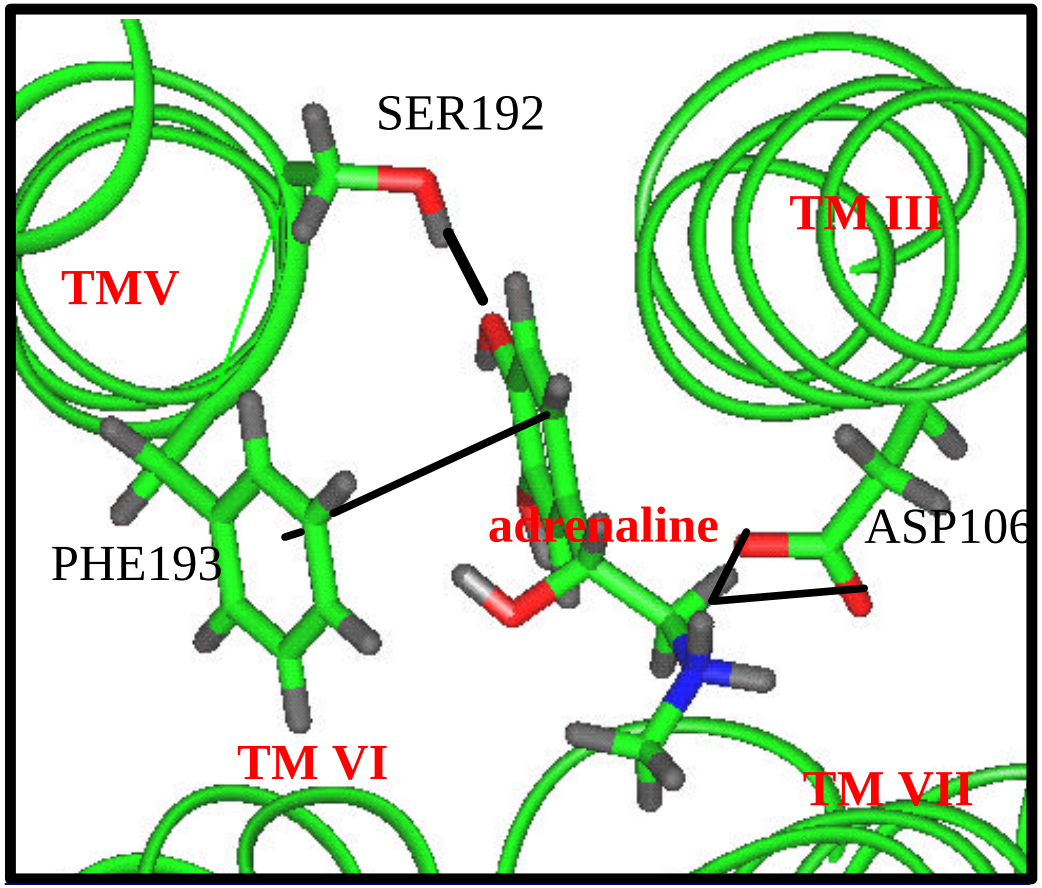
Construction of Receptor Models

- determine size and location of transmembrane helices by homology methods
- build helices as α helices in InsightII, MSI
- pack helices according to template, aligning helices *via* conserved residues
- constrain backbone *i*,*i*+*4* hydrogen bonds
- minimize thoroughly

Validation of Models

- docking of adrenaline
- protonated agonist manually docked into binding site, keeping N^+ atom 2 to 4 Å from the conserved Asp residue in TM3
- after minimisation, observed receptor-ligand interactions in agreement with experimental data
- binding energies: BE=IE+ER+EL

Docking of Adrenaline into the α_{1A} Receptor

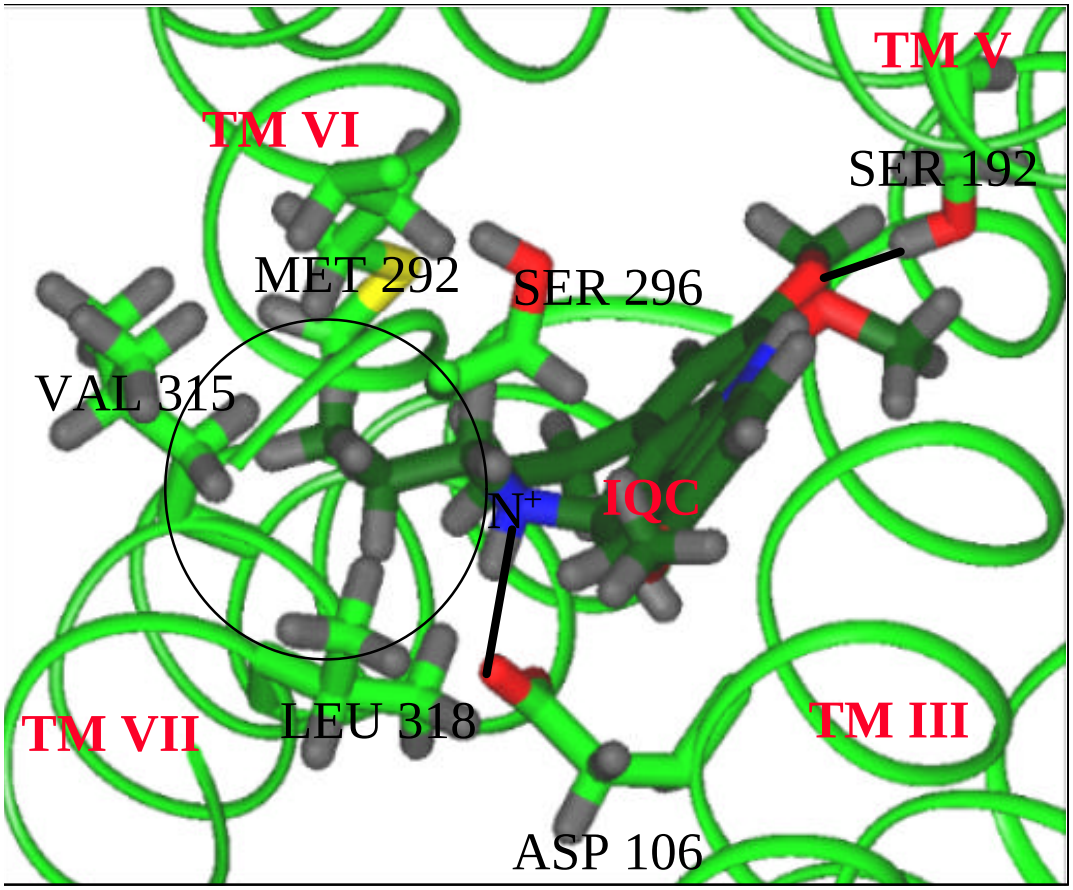


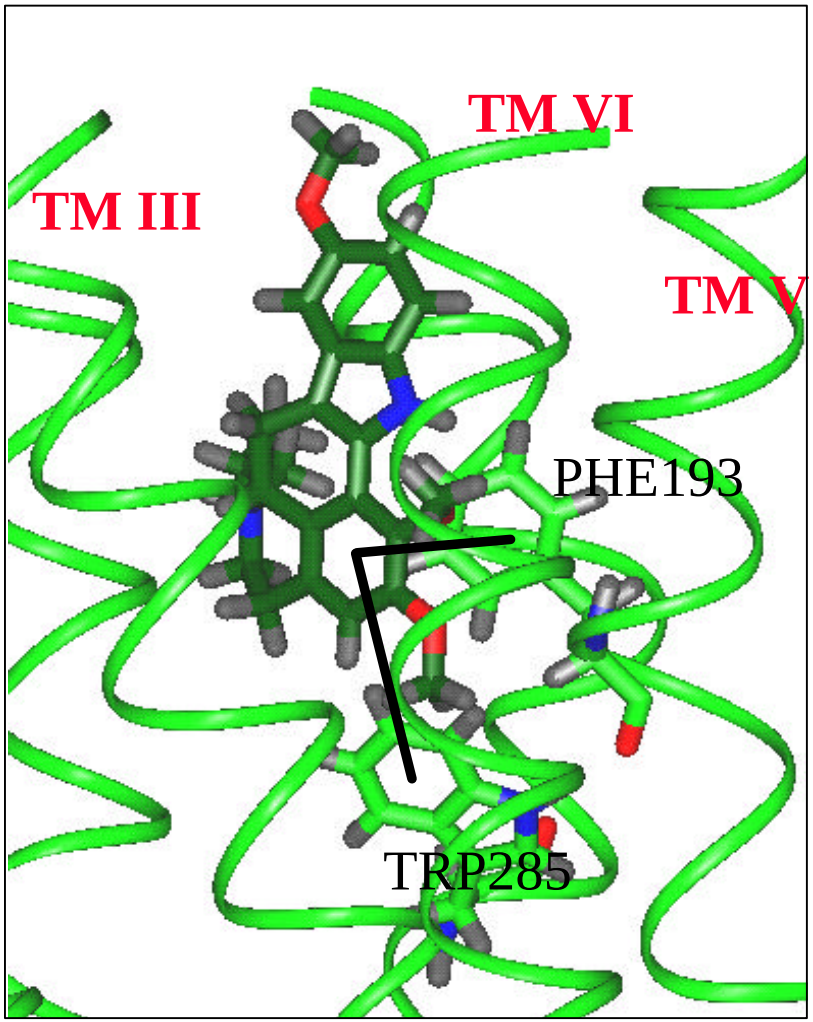
Docking of a Rigid Antagonist

- IQC
- assumption: same binding site as adrenaline
- binding data (pK_is, racemate)

α_{1A}	α_{1B}	α_{1D}
8. 4	6. 6	7. 0

Docking of IQC into the α_{1A} Receptor

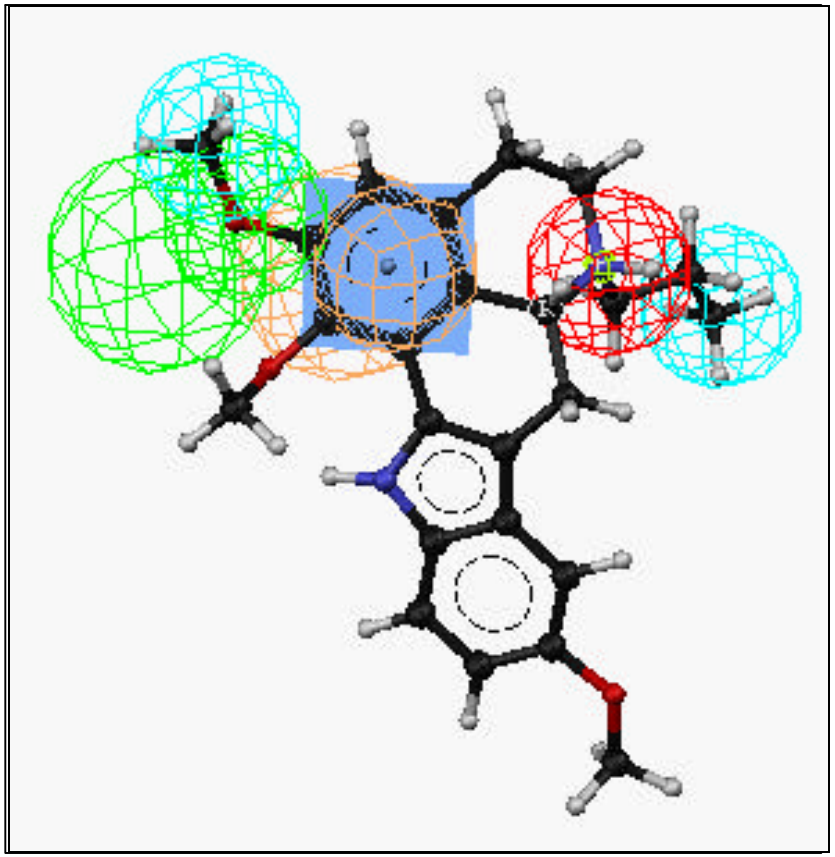


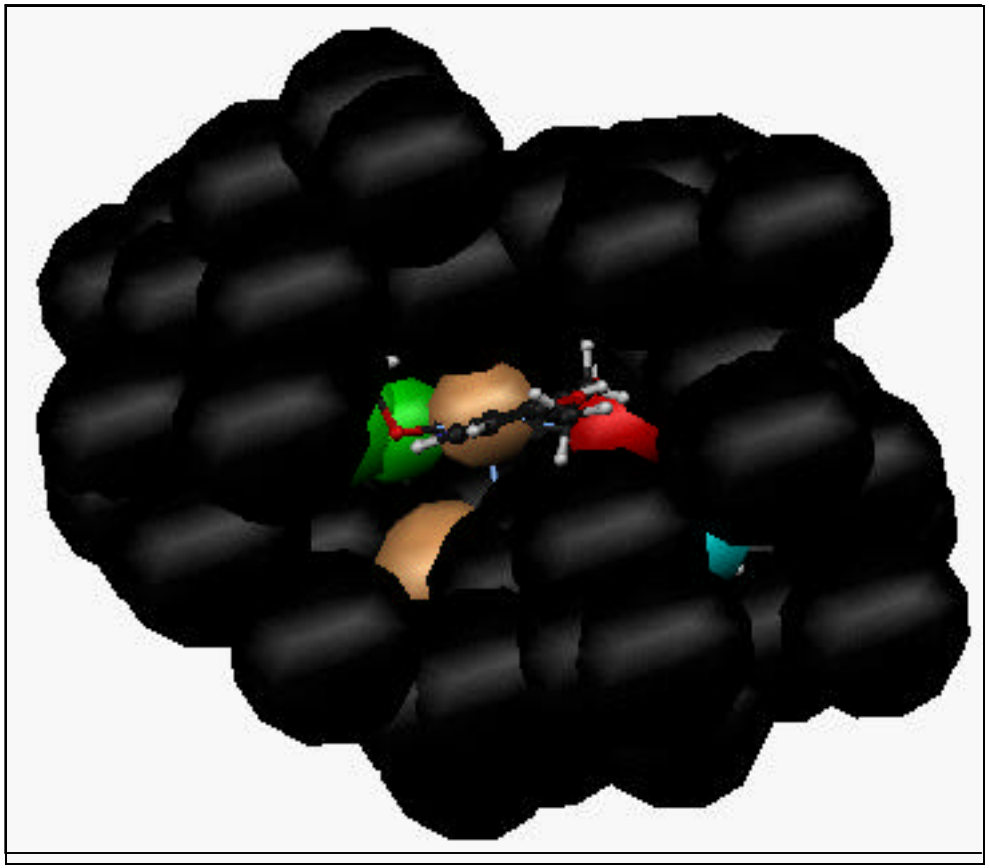


Docking-Derived Pharmacophores

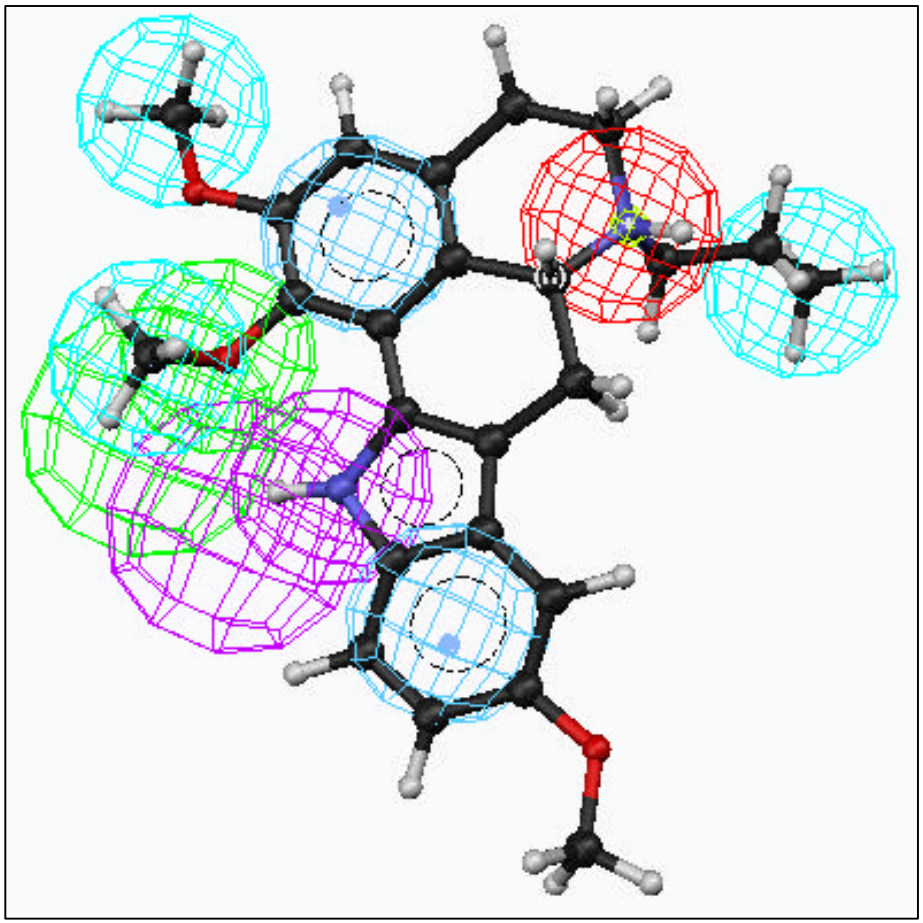
- from model of ligand-receptor complex
  - using Catalyst (MSI)
  - method according to Greenidge *et al.* (J. Med. Chem., 41 (1998), 2503)
  - determine ligand atoms involved in interactions with receptor, determine nature of interaction
  - place features onto template according to above
  - determine coordinates of residues surrounding the ligand, use to define large number (80-100) of excluded volume features

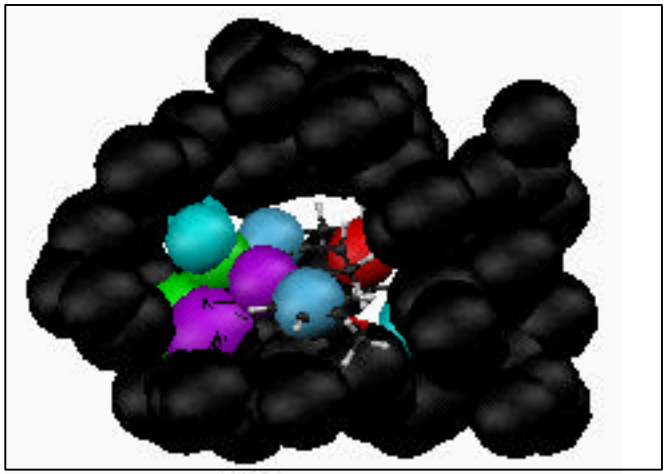
α_{1A} Docking Derived Pharmacophore



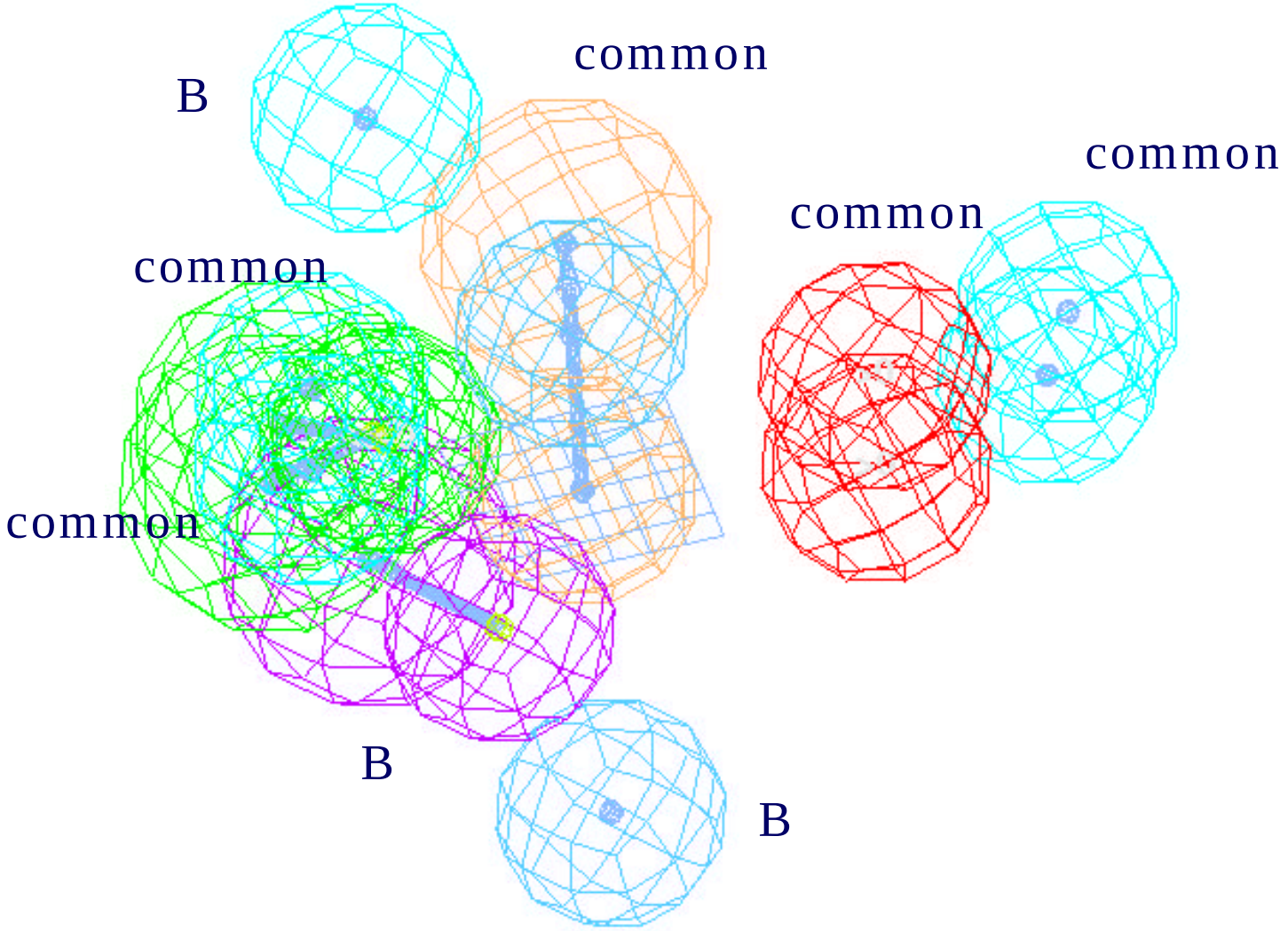


α_{1B} Docking Derived Pharmacophore





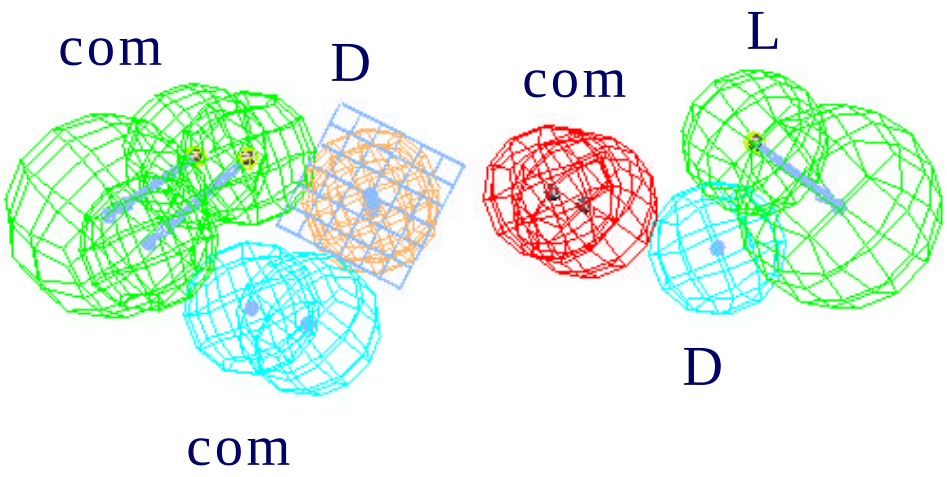
Comparison of the α_{1A} and α_{1B} Docking Derived Pharmacophores

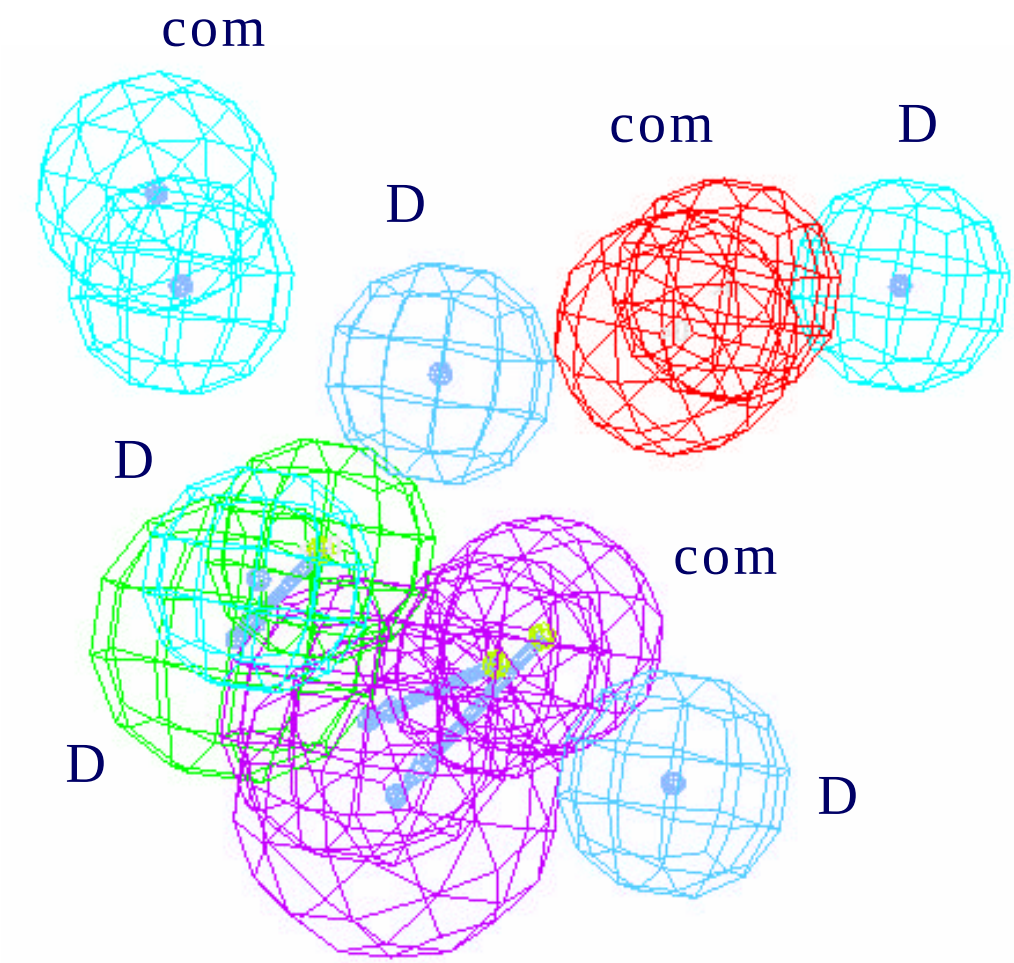


Ligand Based Drug Design for Selective Antagonists of α_1-AR Subtypes

- pharmacophores developed for training sets including only selective antagonists for each subtype
- IQC not included in these pharmacophore training sets

Comparison of Ligand- and Docking-Derived Pharmacophores



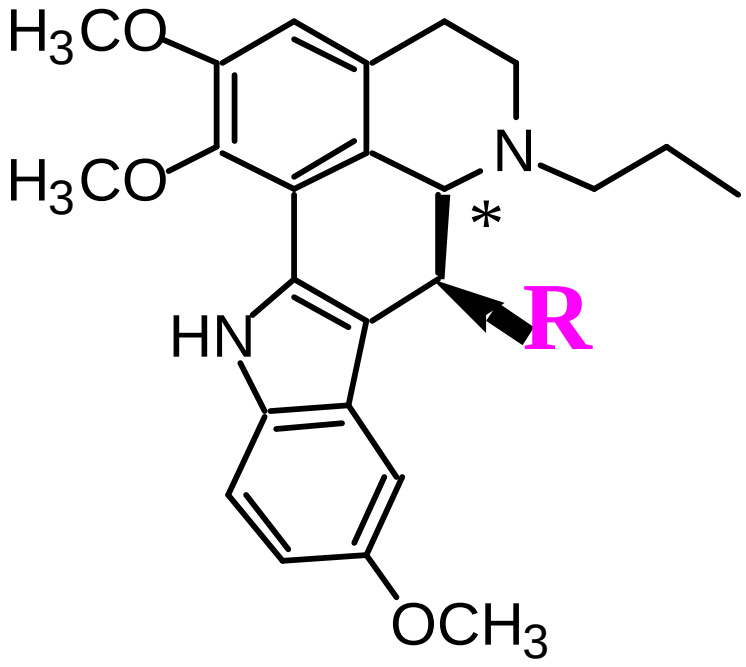


α_{1A} (left) and α_{1B} (right)

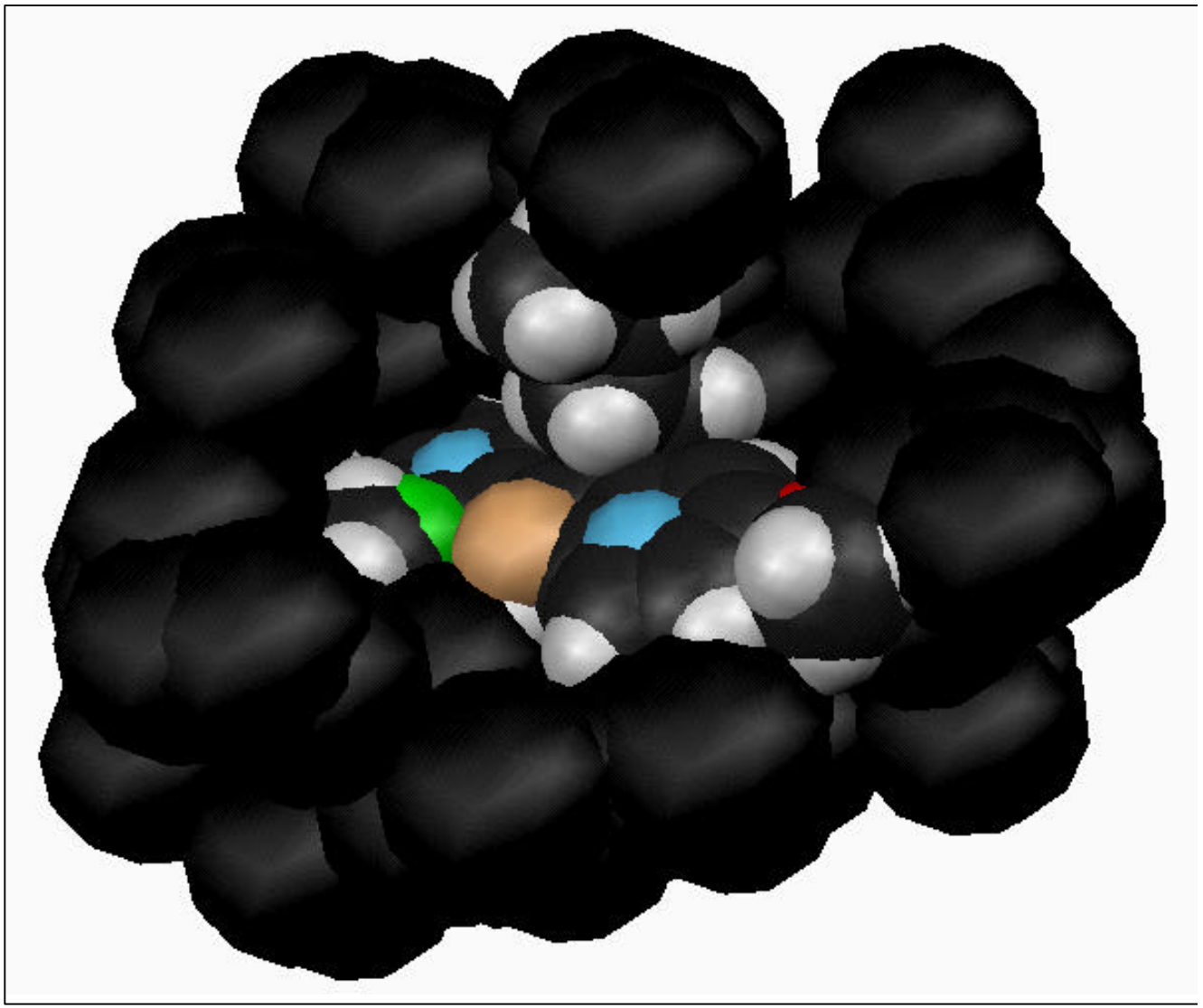
Ligand Design using the Docking-Derived Pharmacophores

- utilising the "free space" above IQC in the α_{1B} binding pocket

R	α_{1A} fit	α_{1B} fit
Me	0.52	0.51
Ethyl	0.60	0.39
n-Propyl	no fit	0.42
n-Butyl	no fit	0.59
Isopropyl	0.63	0.02
Isobutyl	0.26	0.49



Target Ligand Mapped on to α_{1B} Pharmacophore



Summary

- α_{1A} and α_{1B} adrenoceptor models built and evaluated
- novel rigid antagonist docked and receptor-ligand interactions studied
- pharmacophores constructed by placing those interactions onto the rigid IQC template
- excluded volumes from receptor-ligand complexes included into pharmacophores
- docking derived pharmacophores give new insights for ligand design