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University of Modena
and Reggio Emilia
Department of
Pharmaceutical Sciences



Italian Chemical Society
Division of
Medicinal Chemistry



EFMC

SECOND JOINT
ITALIAN-SWISS MEETING
ON MEDICINAL CHEMISTRY

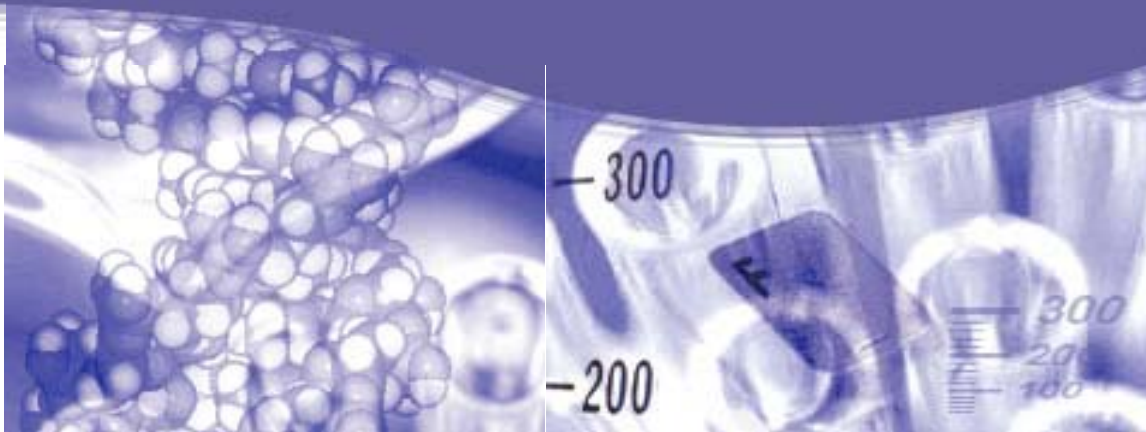


S.IN Soluzioni
Informatiche
for Chemistry and Pharmaceutical Chemistry



S.IN Soluzioni
Informatiche

- ▣ CHEMINFORMATICS
- ▣ INFOMETRICS
- ▣ BIOINFORMATICS



Induced Fit and Pharmacophore generation approach applied to A_{2A} Adenosine Receptor Antagonists.

Marco Parenti

S-IN Soluzioni Informatiche, Vicenza

■ A_{2A} receptors

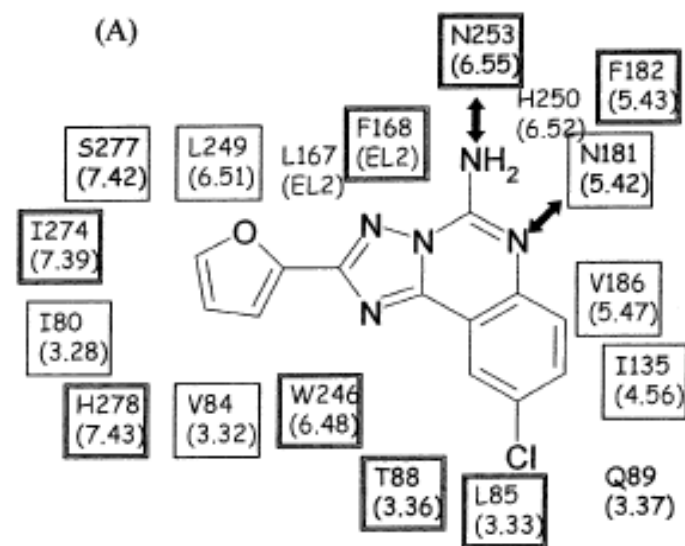
- Are densely distributed in the central nervous system (striatum, nucleus accumbens and olfactory tubercles)
- play an important role in the regulation of mood and motor activity.
- selective A_{2A} adenosine receptor antagonists can be useful for the treatment of Parkinson's Disease.

■ Our approach

- Since an x-ray structure of A_{2A} receptor is not available, to explore the binding properties of some adenosine-like antagonists, we have set up two different approaches:
 - **Structure based design**
 - Induced fit protocol applied to a published homology building model (pdb code 1upe), using [Glide](#) and [Prime](#)
 - **Ligand based design**
 - 3D pharmacophore generation procedure using [Phase](#)

■ Our work is based on:

- A 3D model of the human A2A adenosine receptor built by homology modeling from rhodopsin and validated with site-directed mutagenesis published on the PDB (code 1UPE)
- An assumption of binding mode for antagonists, published on literature and well consistent with the experimental results*



*Kim et al, J.Med.Chem. 2003, 46, 4847-4859

What is “Induced Fit”?

The receptor changes shape as it binds to a ligand

BUT

usually the receptor is held rigid and
the ligand is free to move

“induce” adjustments in one receptor structure
to obtain an alternative receptor structure

?

Induced fit has two main applications:

generation of the complex structure for a ligand known to be active but
that cannot be docked in an existing (rigid) structure of the receptor

rescue of false negative: instead of screening against a single
conformation of the receptor, additional conformations obtained via
induced fit are used

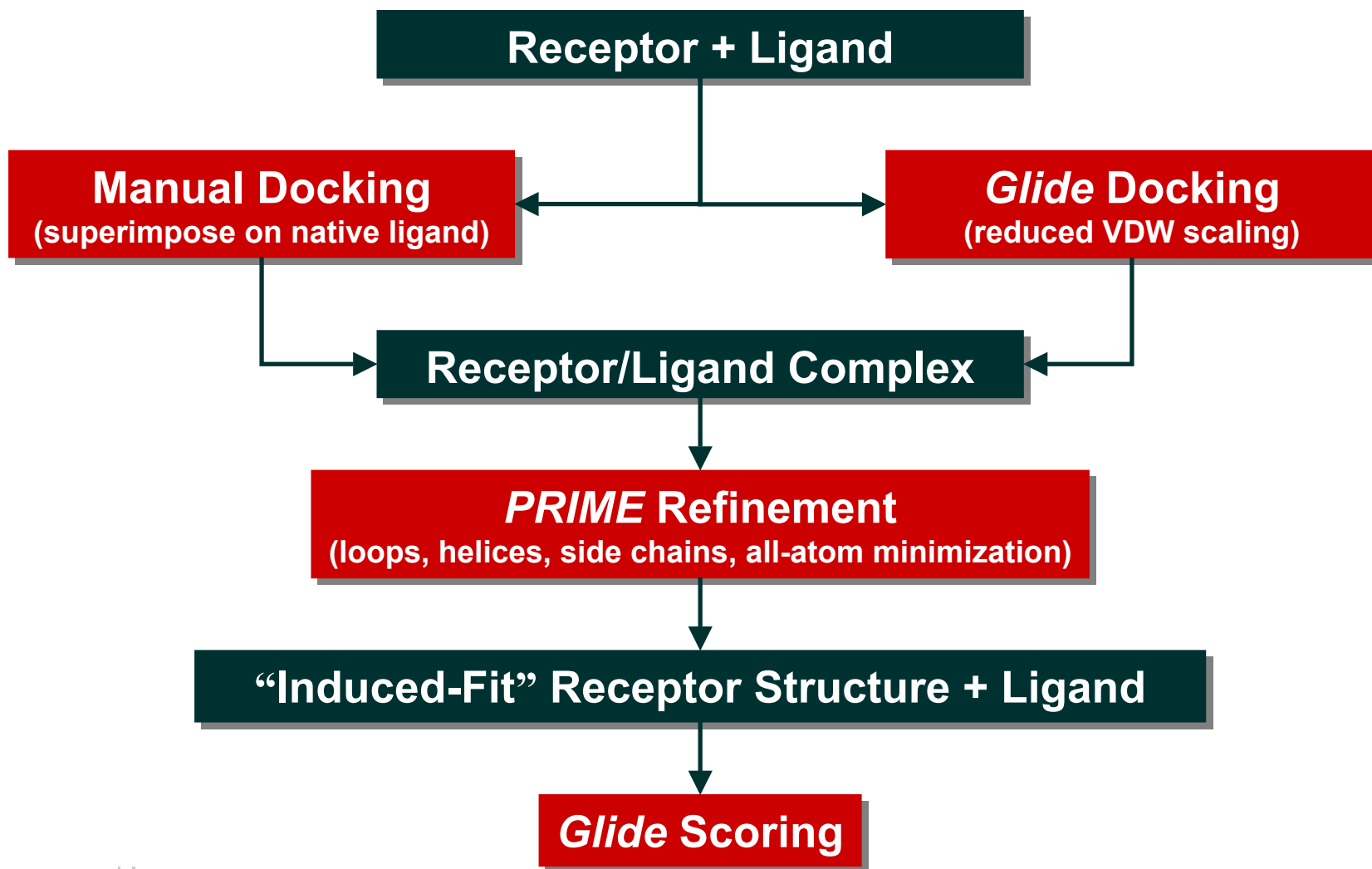
■ Glide: A complete solution for ligand-receptor docking

- Glide offers the full spectrum of speed and accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode predictions, providing consistently high enrichment at every level.

■ Prime: a powerful and innovative package for accurate protein structure predictions

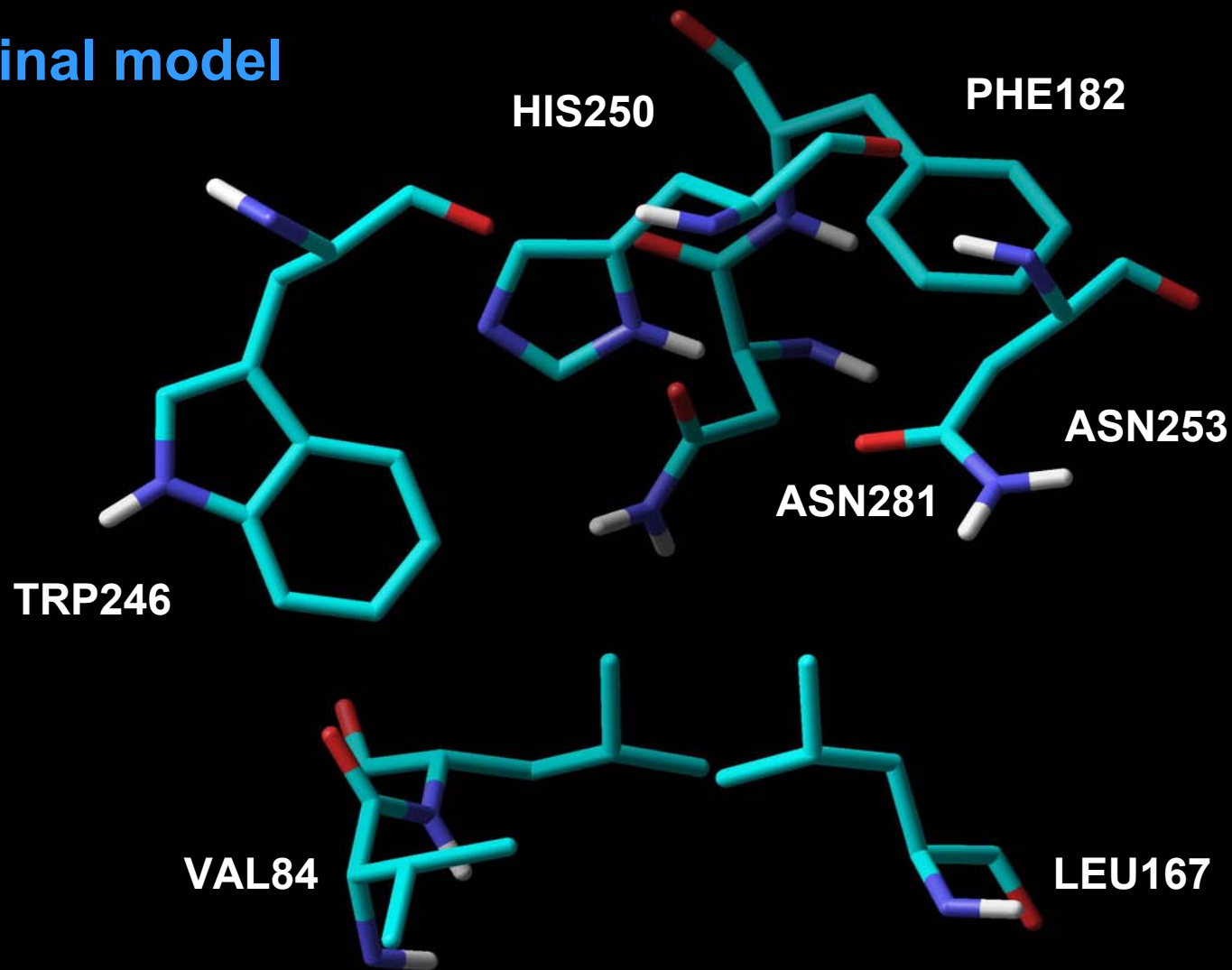
- Prime is a fully-integrated protein structure prediction program. It provides an easy-to-use interface that takes a novice user intuitively from sequence to alignment to refined structure.

Glide / Prime Protocol



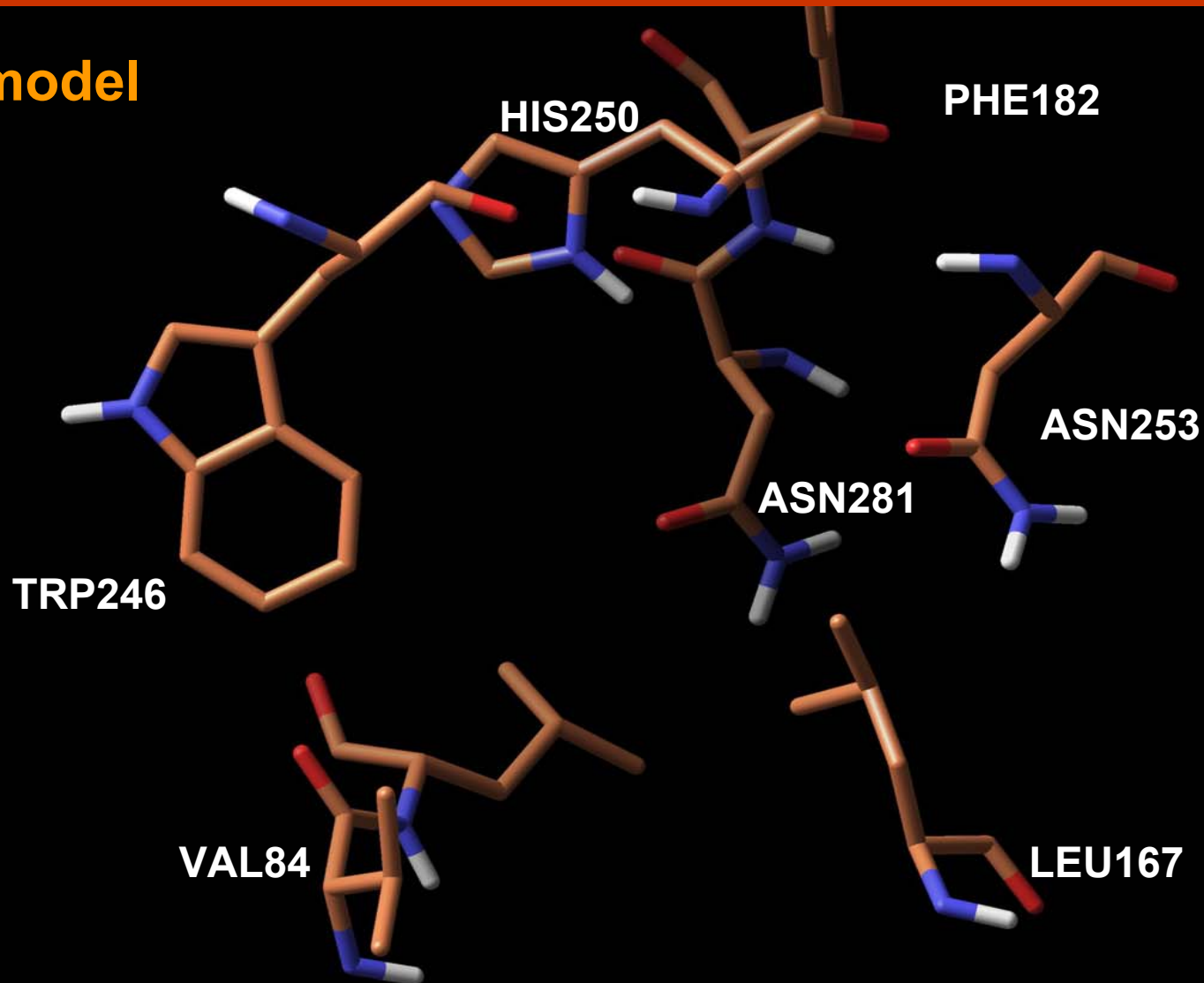
Induced Fit Model

Original model



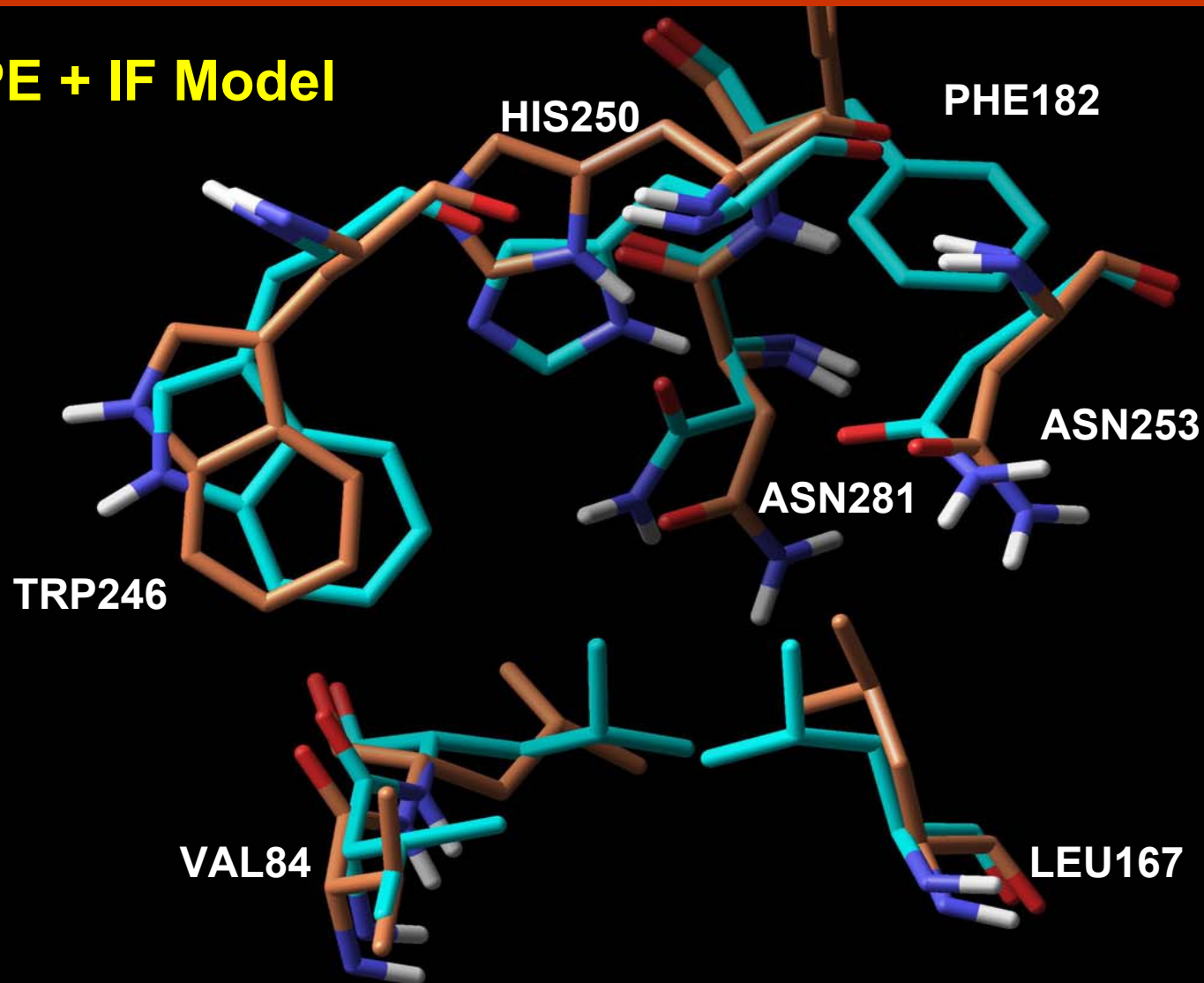
Induced Fit Model

IF model



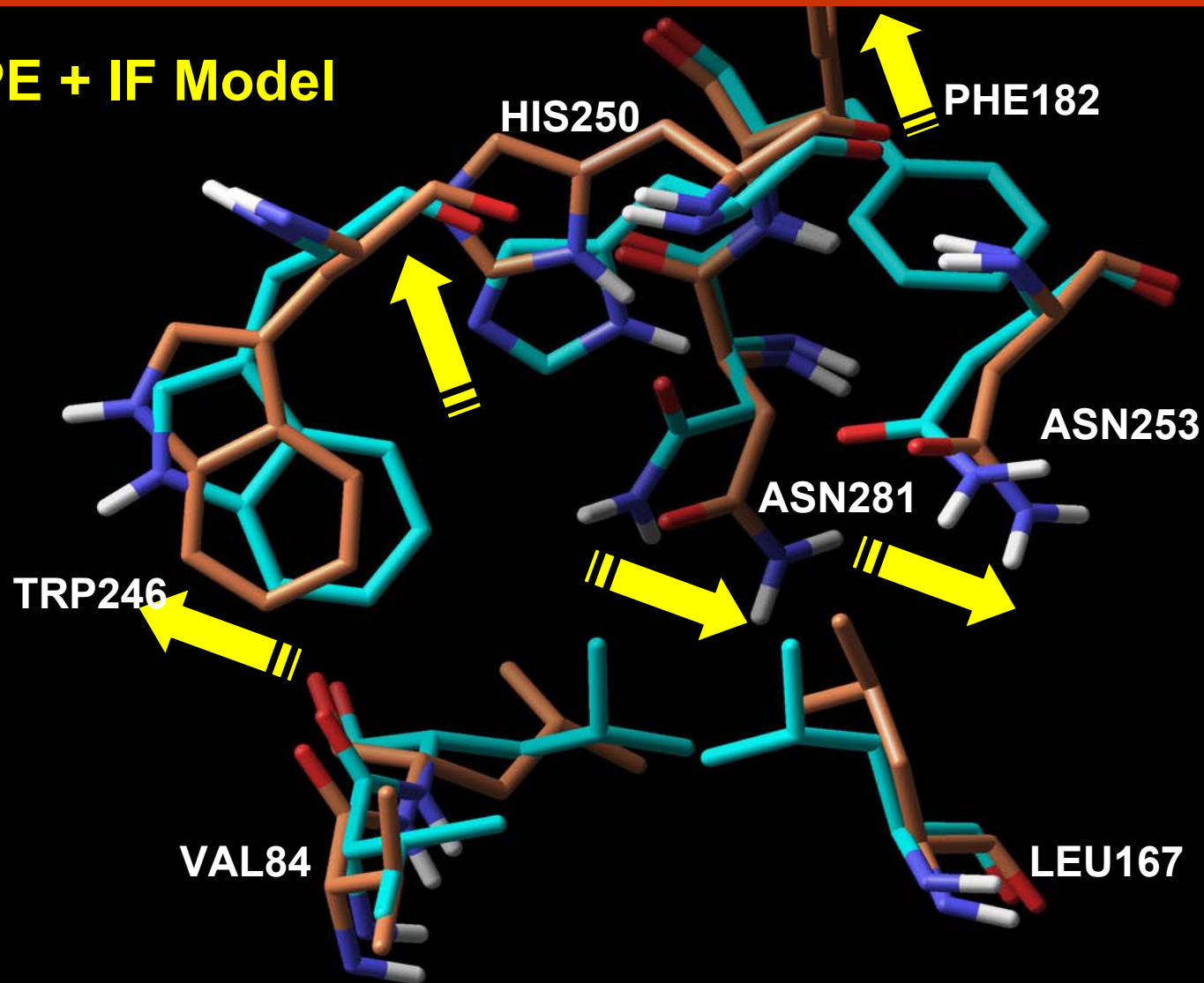
Induced Fit Model

1UPE + IF Model



Induced Fit Model

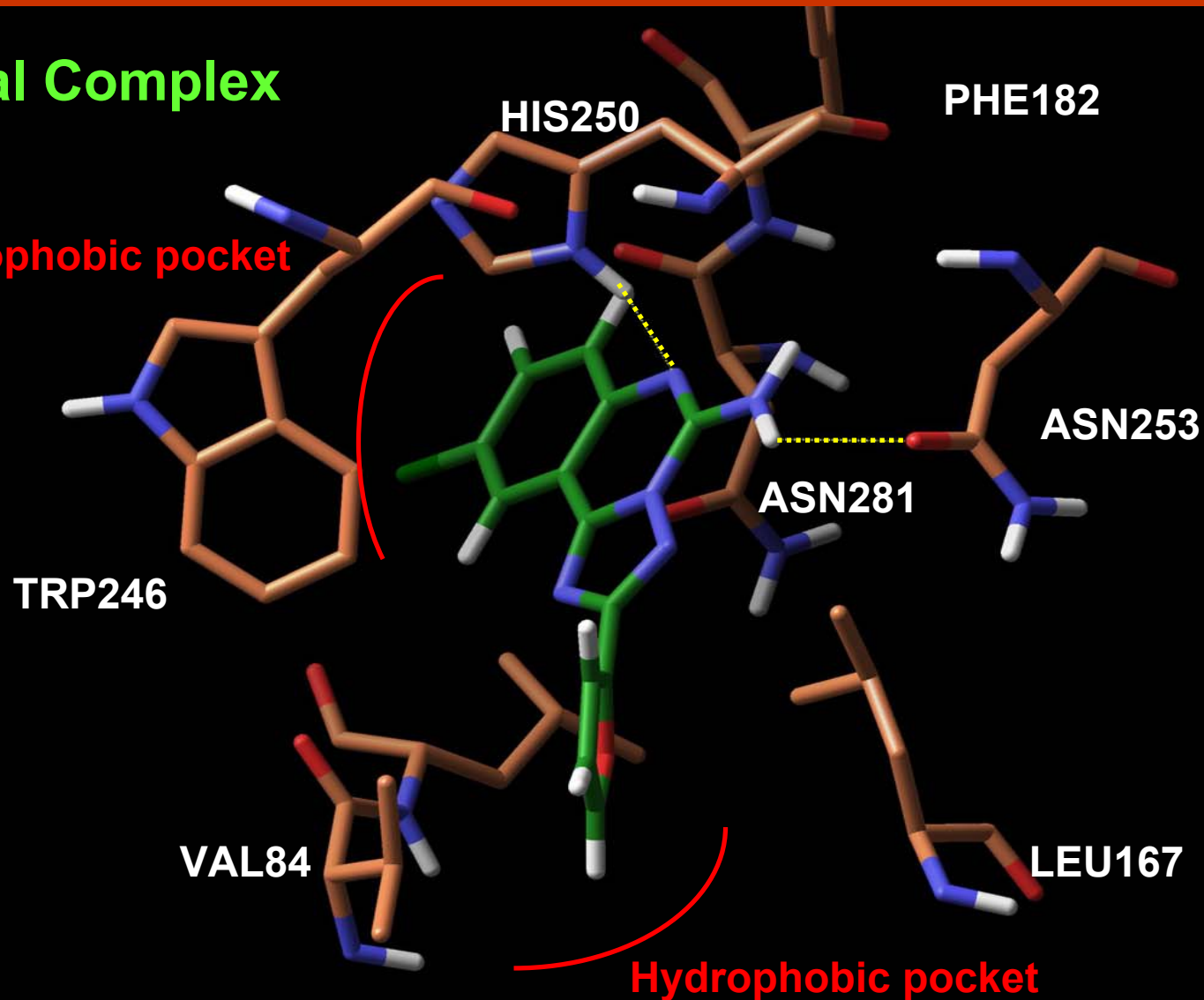
1UPE + IF Model



Induced Fit Model

Final Complex

Hydrophobic pocket



- Phase: A high-performance program for ligand-based drug design
 - Phase is a complete package of pharmacophore modeling tools that offers scientists an unparalleled level of control at each step. Fast, accurate, and highly configurable, Phase is a powerful tool for hit generation and lead hopping.

■ 320 A_{2A} antagonist taken from literature

J.Med.Chem 2002, 45, 115-126

J.Med.Chem 2003, 46, 1229-1241

J.Med.Chem 2004, 47, 1031-1043

J.Med.Chem 2004, 47, 1434-1447

J.Med.Chem 2004, 47, 4291-4299

J.Med.Chem 2004, 47, 6218-6229

J.Med.Chem 2004, 47, 663-672

J.Med.Chem 2005, 48, 2009-2018

Bioorg.Med.Chem.Lett. 2004, 14, 4831-4834

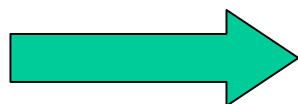
Bioorg.Med.Chem.Lett. 2004, 14, 4835-4838

Bioorg.Med.Chem.Lett. 2005, 15, 511-515

Bioorg.Med.Chem.Lett. 2005, 15, 1333-1336

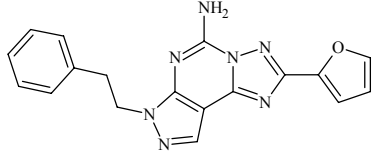
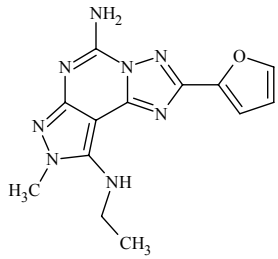
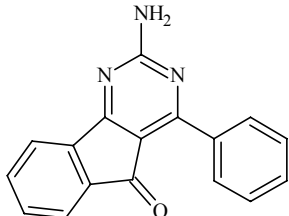
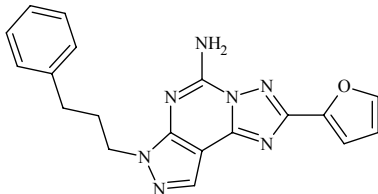
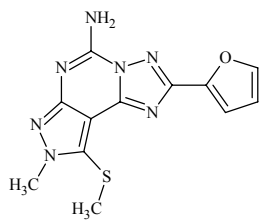
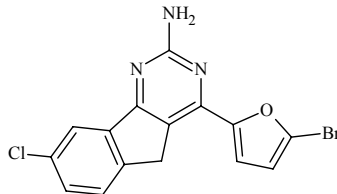
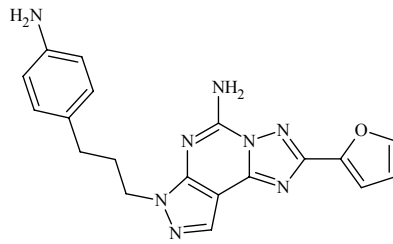
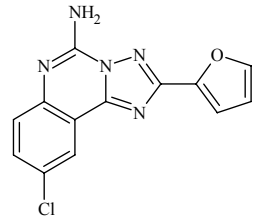
■ Preliminary selection criteria:

- Binding data measured on human receptor
- Molecules with undefined chiral centers and non-significative data (e.g. $K_i > 500$) were excluded

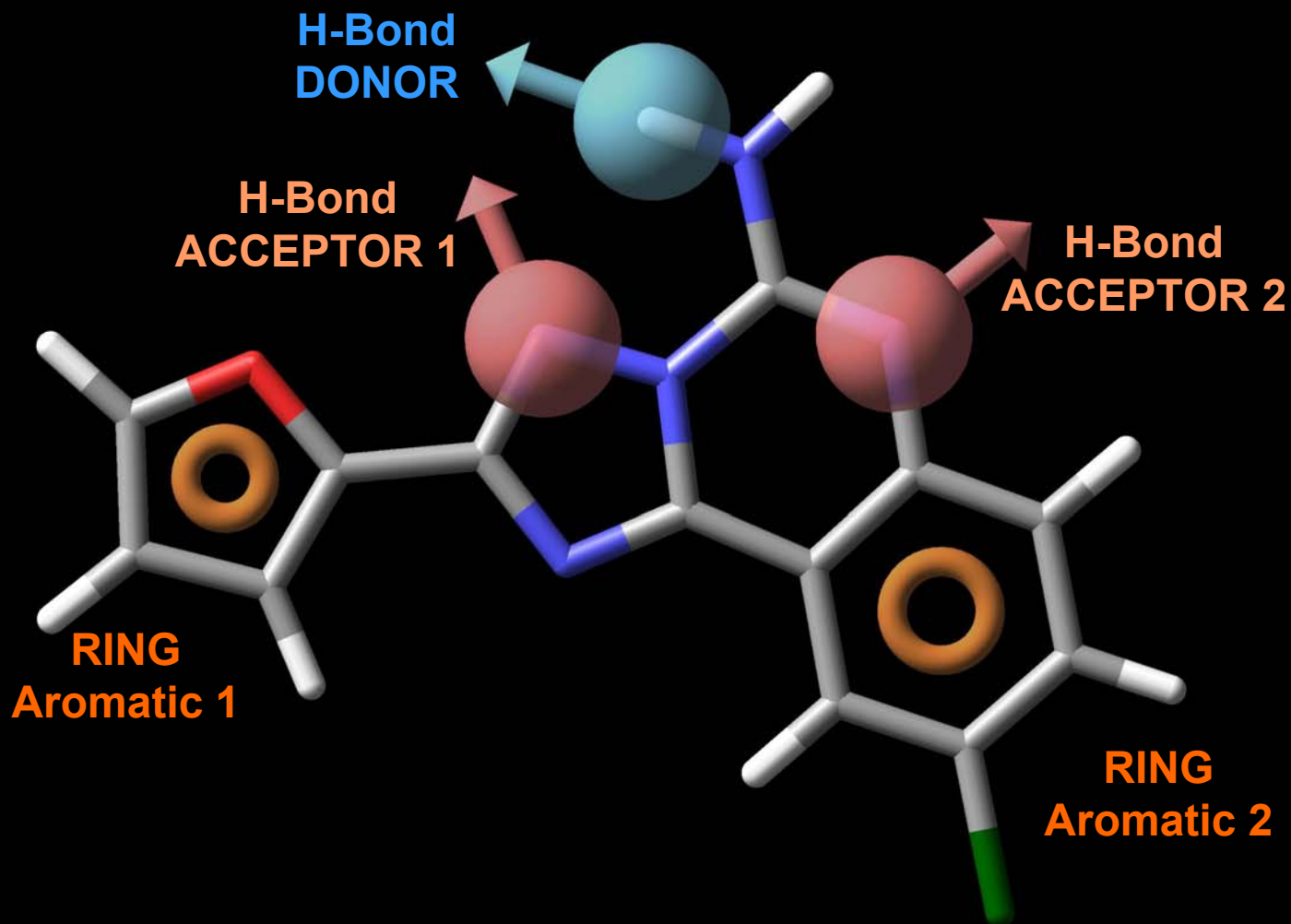


Training set: 68 molecules

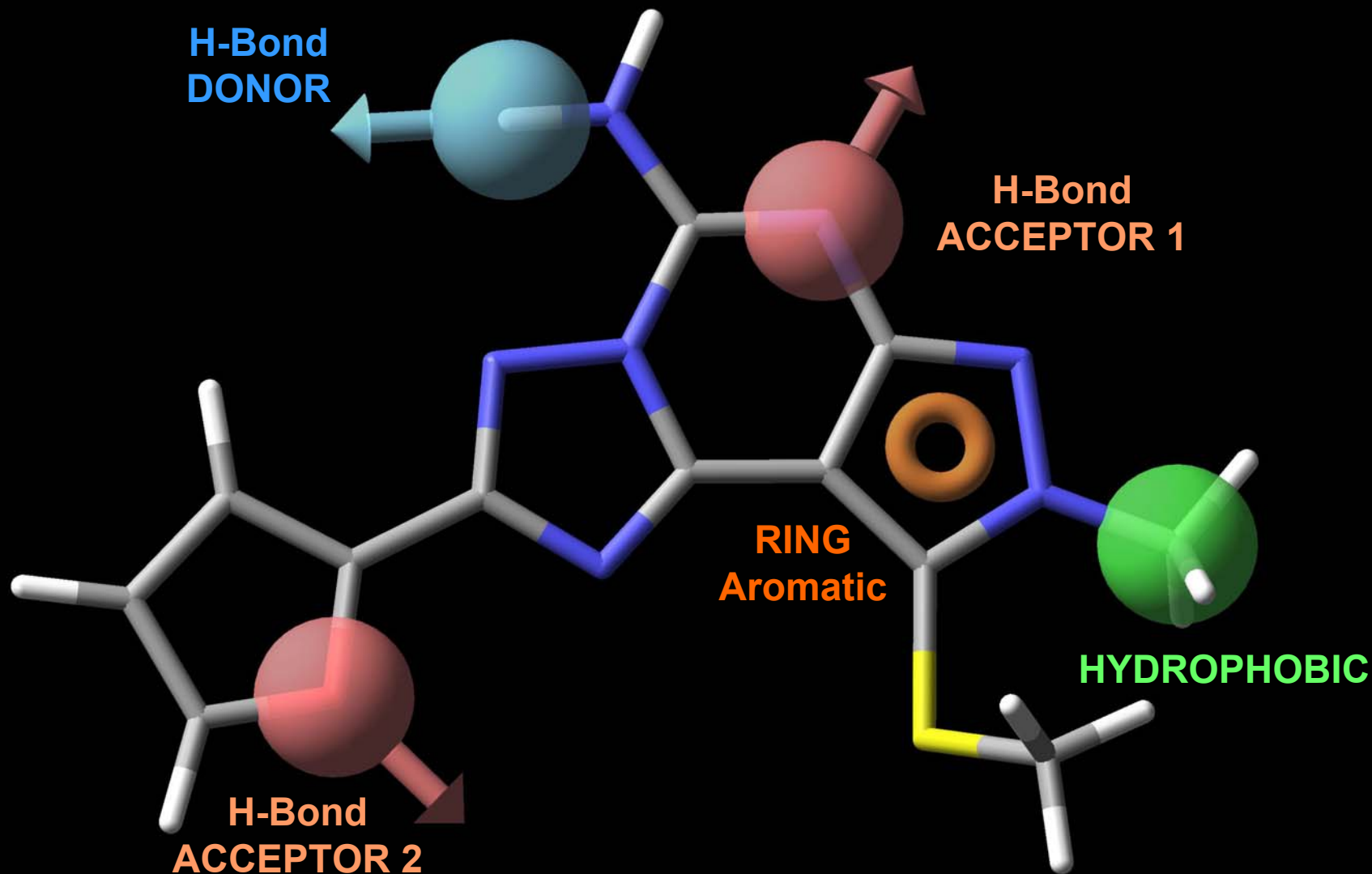
Active Set

N°	Structure	A2A Activity Ki (nM)	N°	Structure	A2A Activity Ki (nM)	N°	Structure	A2A Activity Ki (nM)
1		1.1	4		10	7		1.7
2		1.2	5		1.2	8		1
3		0.22	6		1.2			

Pharmacophore 1



Pharmacophore 2



- The IF protocol leads to an alternative structure of the receptor able to bind adenosine-like antagonist, and that can be used in future docking studies
- Two different pharmacophore were generated, both suggesting a binding mode similar to original working hypothesis.
 - Predictive power of pharmacophores are still under investigation...

■ S-IN Soluzioni Informatiche

- Elena Fioravanzo
- Massimo Mabilia

■ Sigma-Tau

- Grazia Gallo
- Andrea Ciacci