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**XVII CONVEGNO NAZIONALE  
DELLA DIVISIONE DI CHIMICA FARMACEUTICA  
DELLA SOCIETÀ CHIMICA ITALIANA**

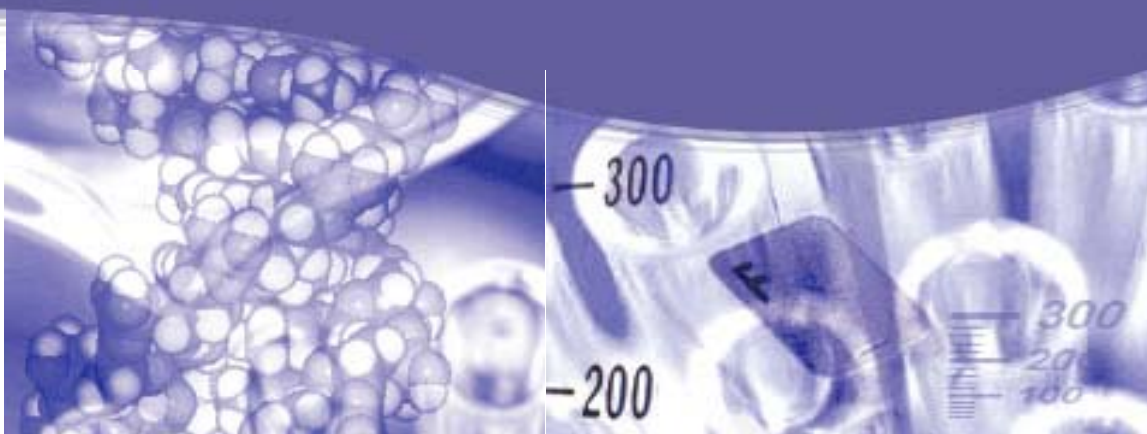


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- ▣ INFOMETRICS
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# Induced fit and virtual docking applied to PPAR $\alpha$ and PPAR $\gamma$ agonists

**Elena Fioravanzo**

**S-IN Soluzioni Informatiche, Vicenza**

## ■ What is “Induced Fit”?

- Protocol

## ■ PPARs

- PPAR- $\alpha$
- PPAR- $\gamma$

## ■ Results

- Structures
- Enrichment Factor

# 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

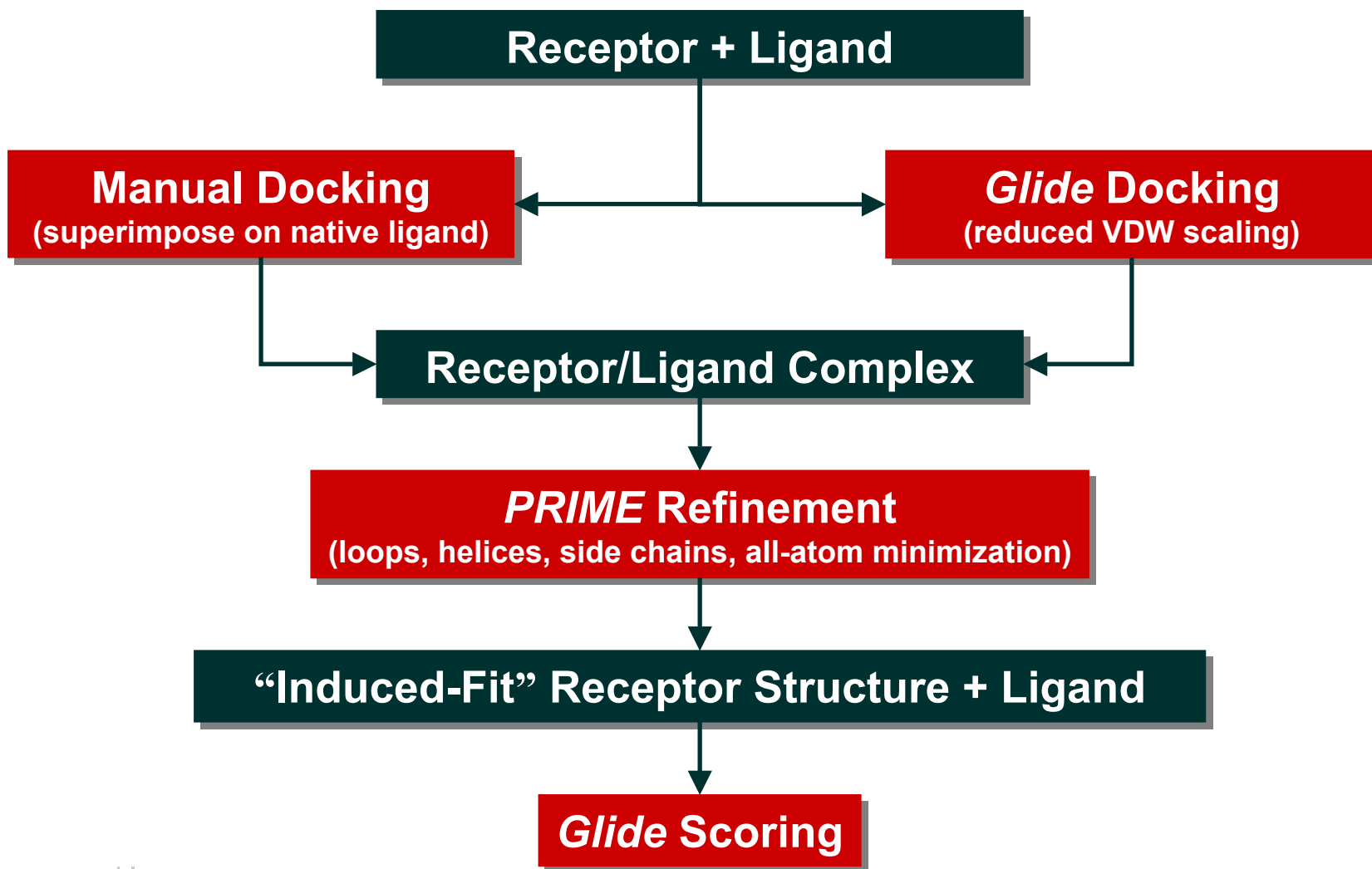
“induce” adjustments in one receptor structure  
to obtain an alternative receptor structure

?

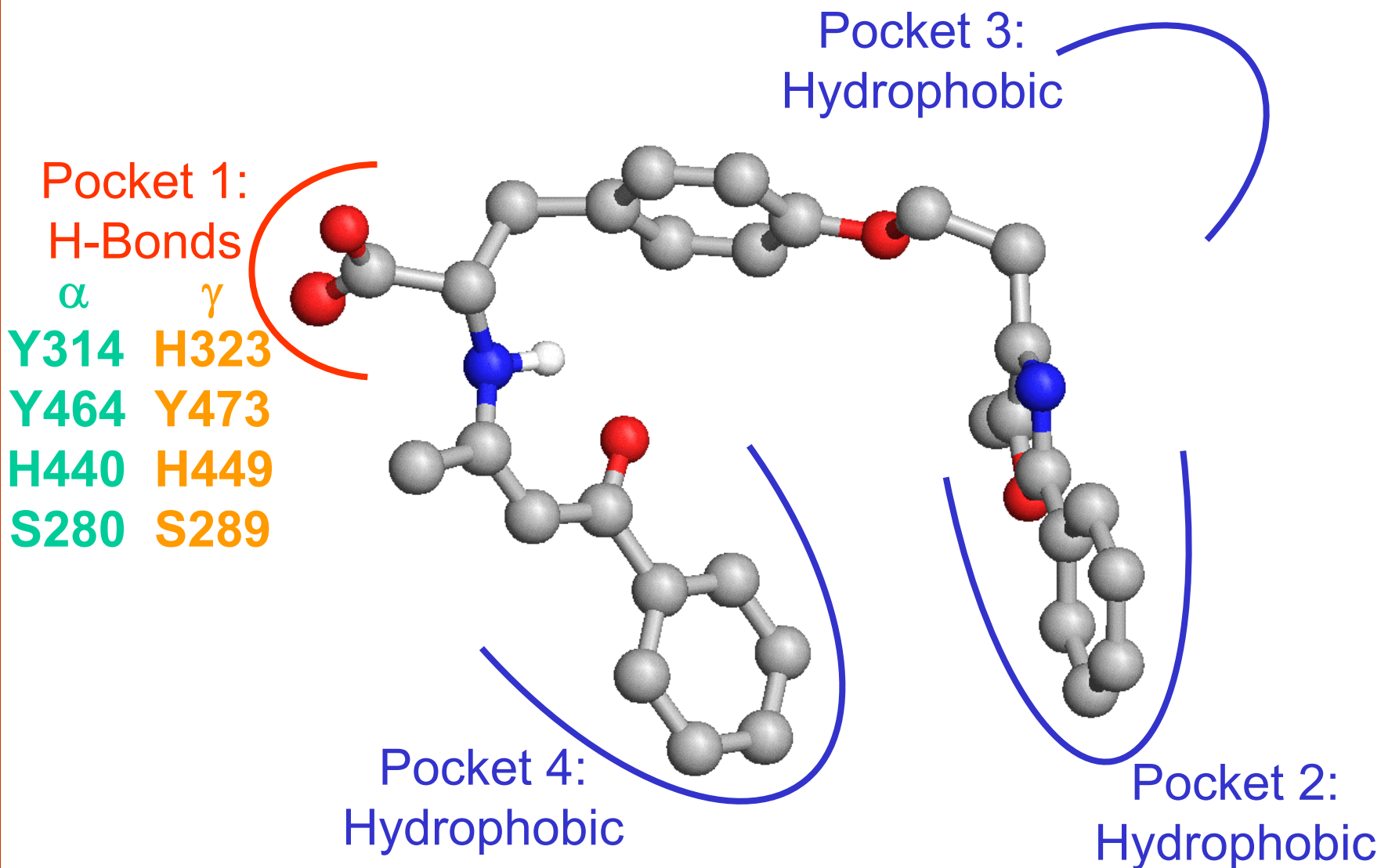
Induced fit has two main applications:

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



# PPAR: binding site



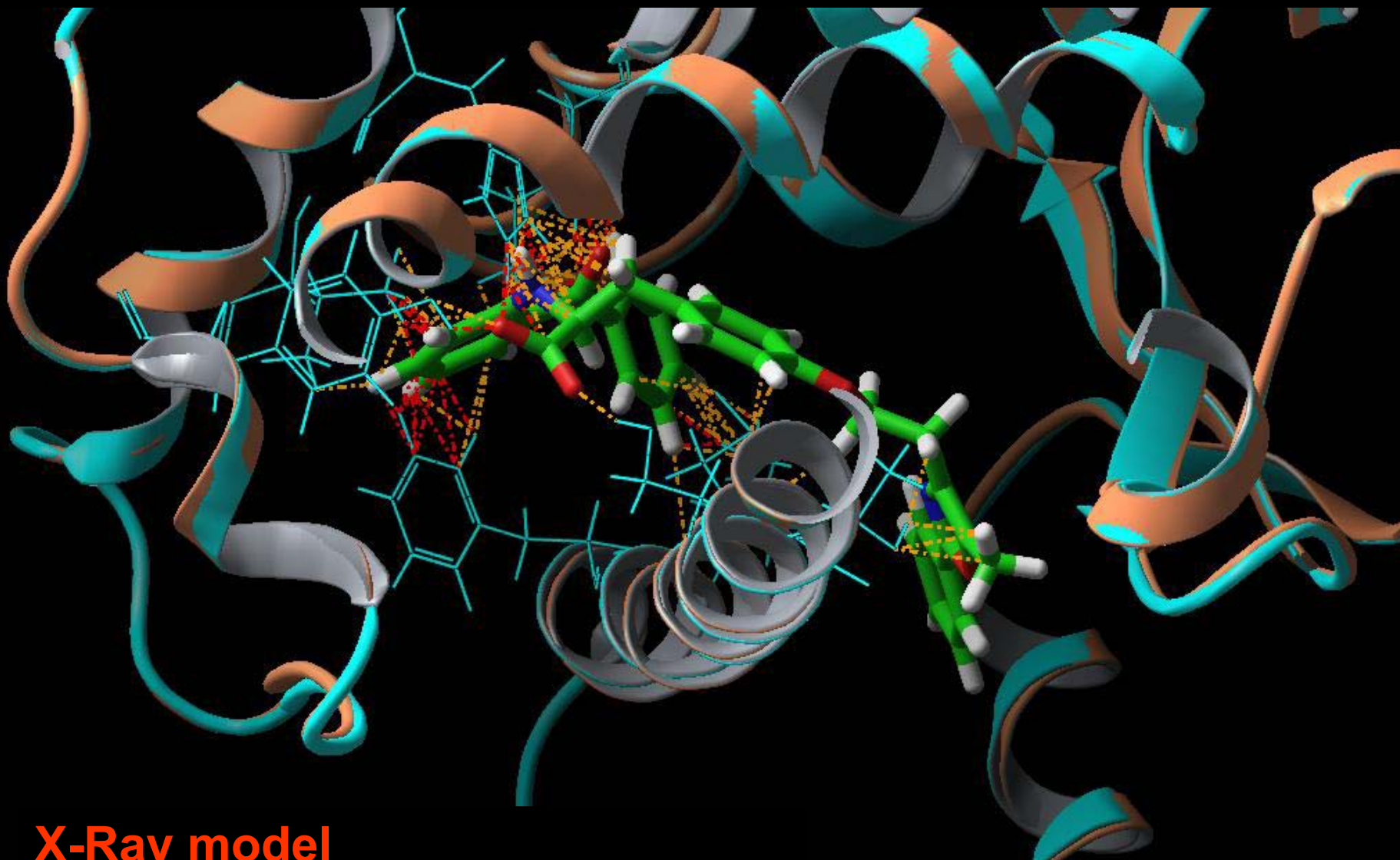
## ■ PPAR- $\alpha$

- 1KE7 => IF receptor structure
- 60 known agonist (pIC<sub>50</sub> 4.3 – 8.7)
- 1000 decoy ligands (Rognan database)

## ■ PPAR- $\gamma$

- 1FM6 => IF receptor structure
- 1FM9
- 42 known agonist (pIC<sub>50</sub> 4.2 – 9.5)
- 1000 decoy ligands (Rognan database)

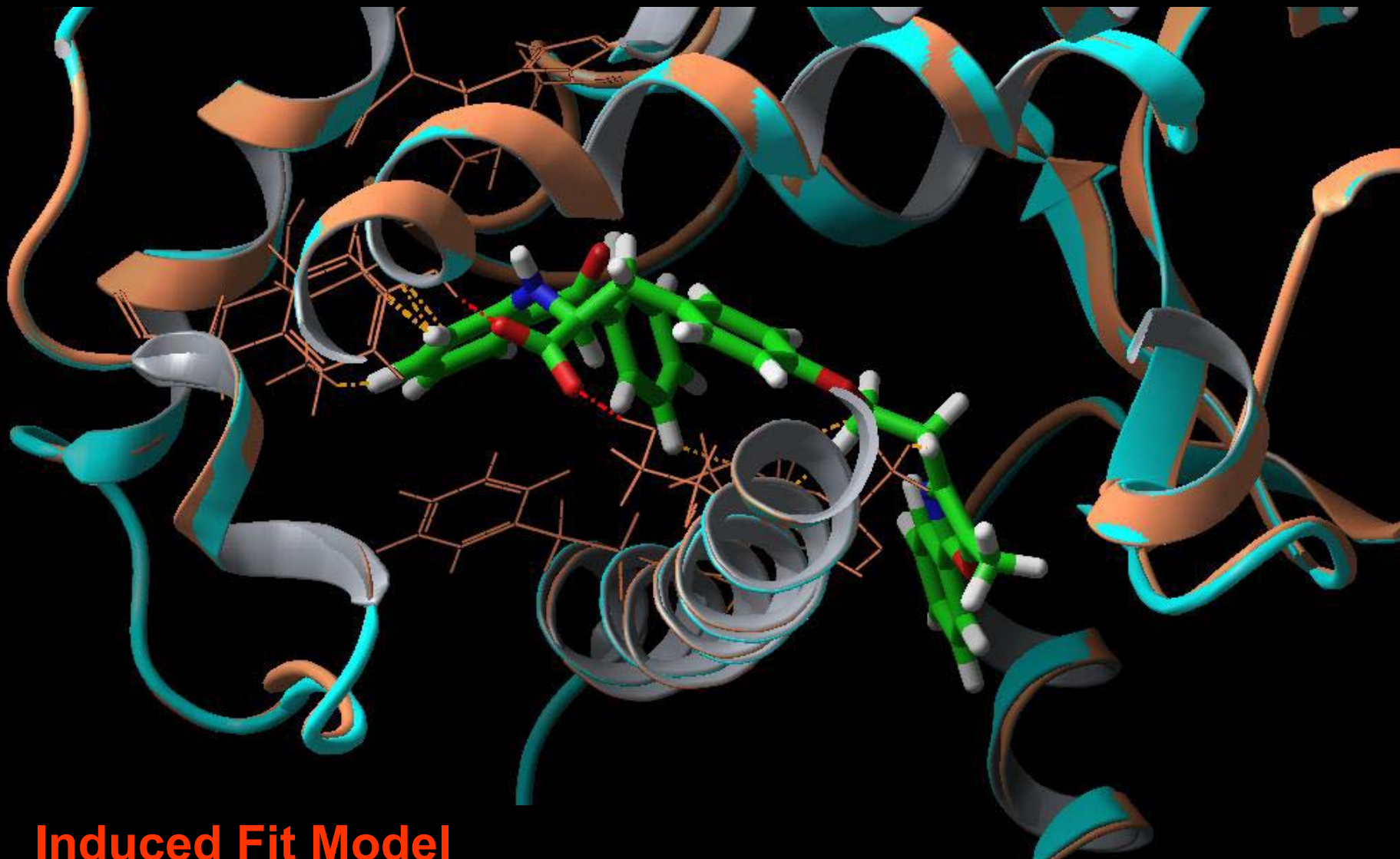
# Results: PPAR- $\alpha$



**X-Ray model**

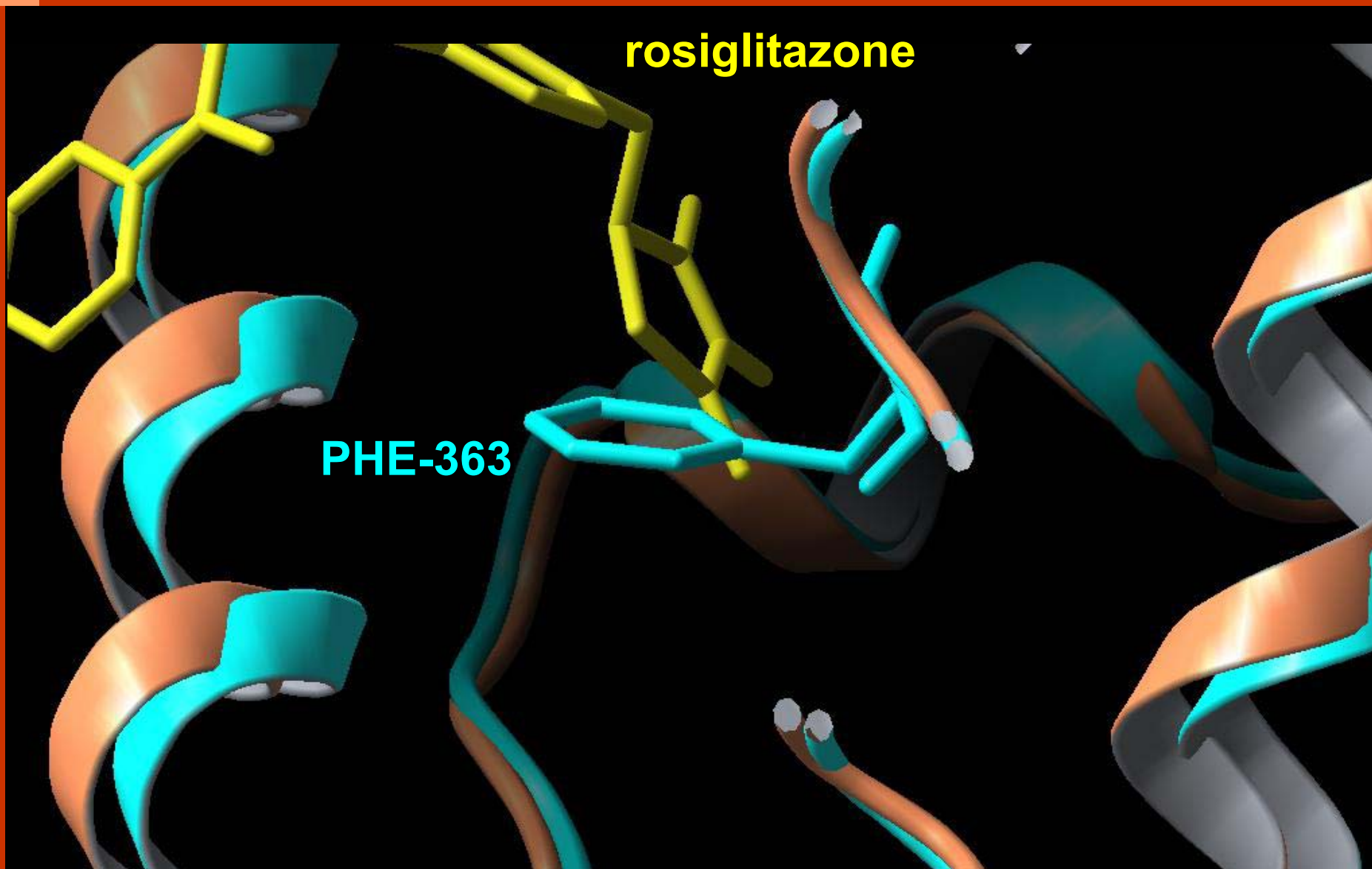
GI262570 pIC<sub>50</sub>( $\alpha$ ) = 6.3

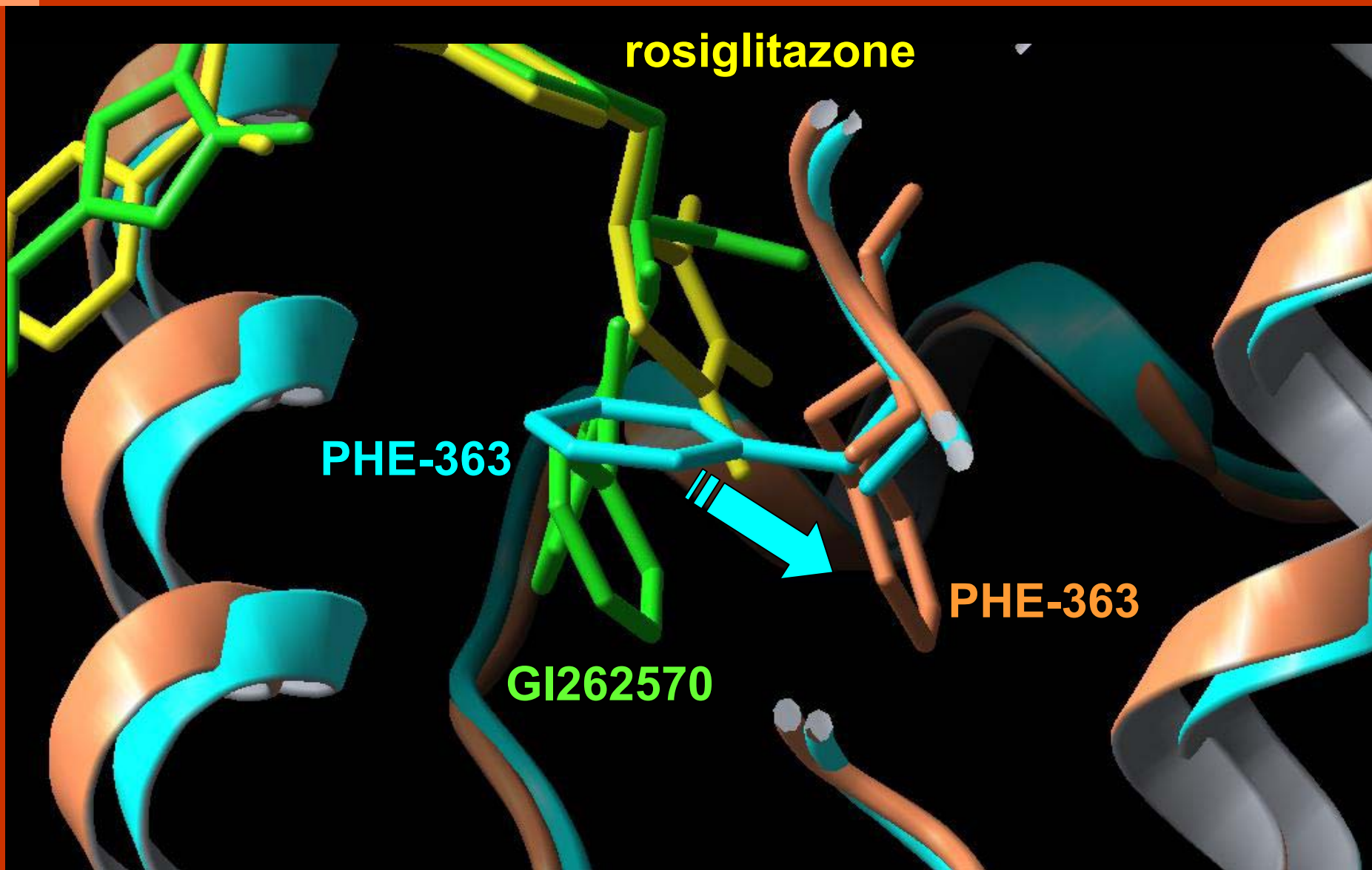
# Results: PPAR- $\alpha$



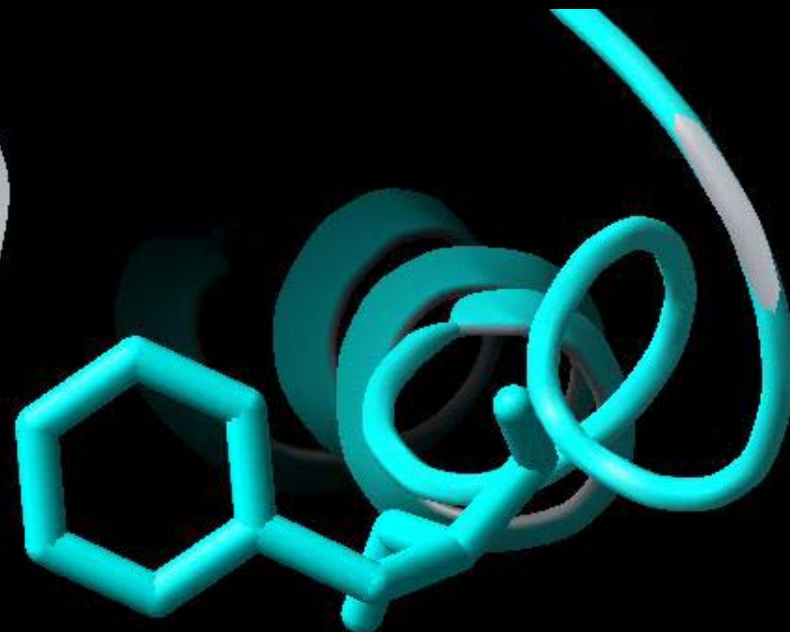
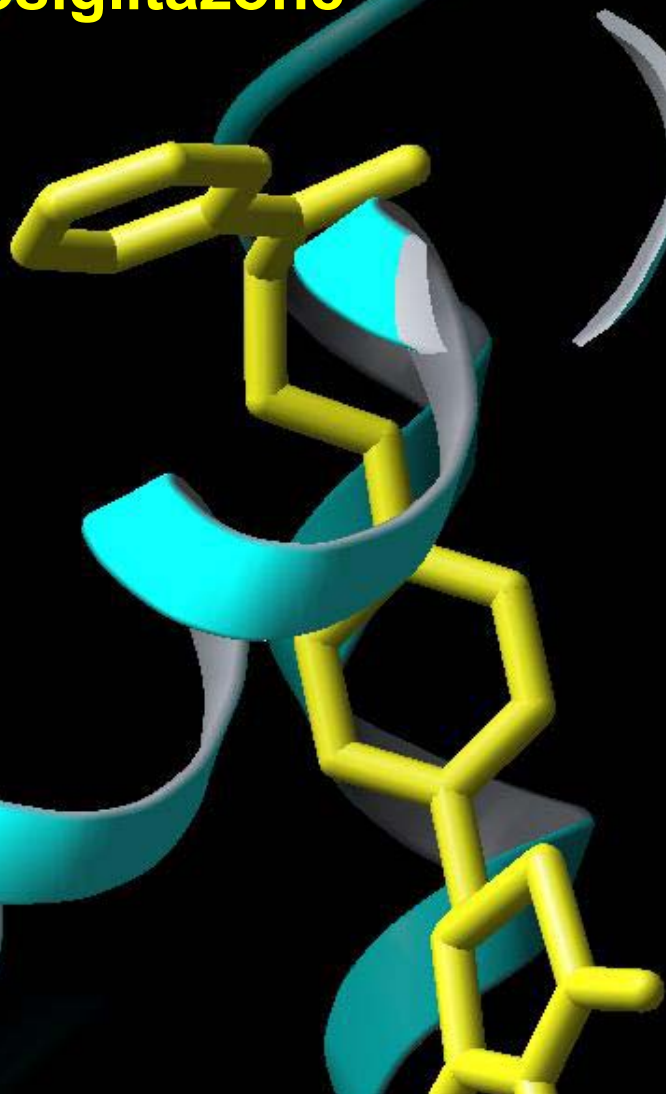
**Induced Fit Model**

**GI262570 pIC<sub>50</sub>( $\alpha$ ) = 6.3**





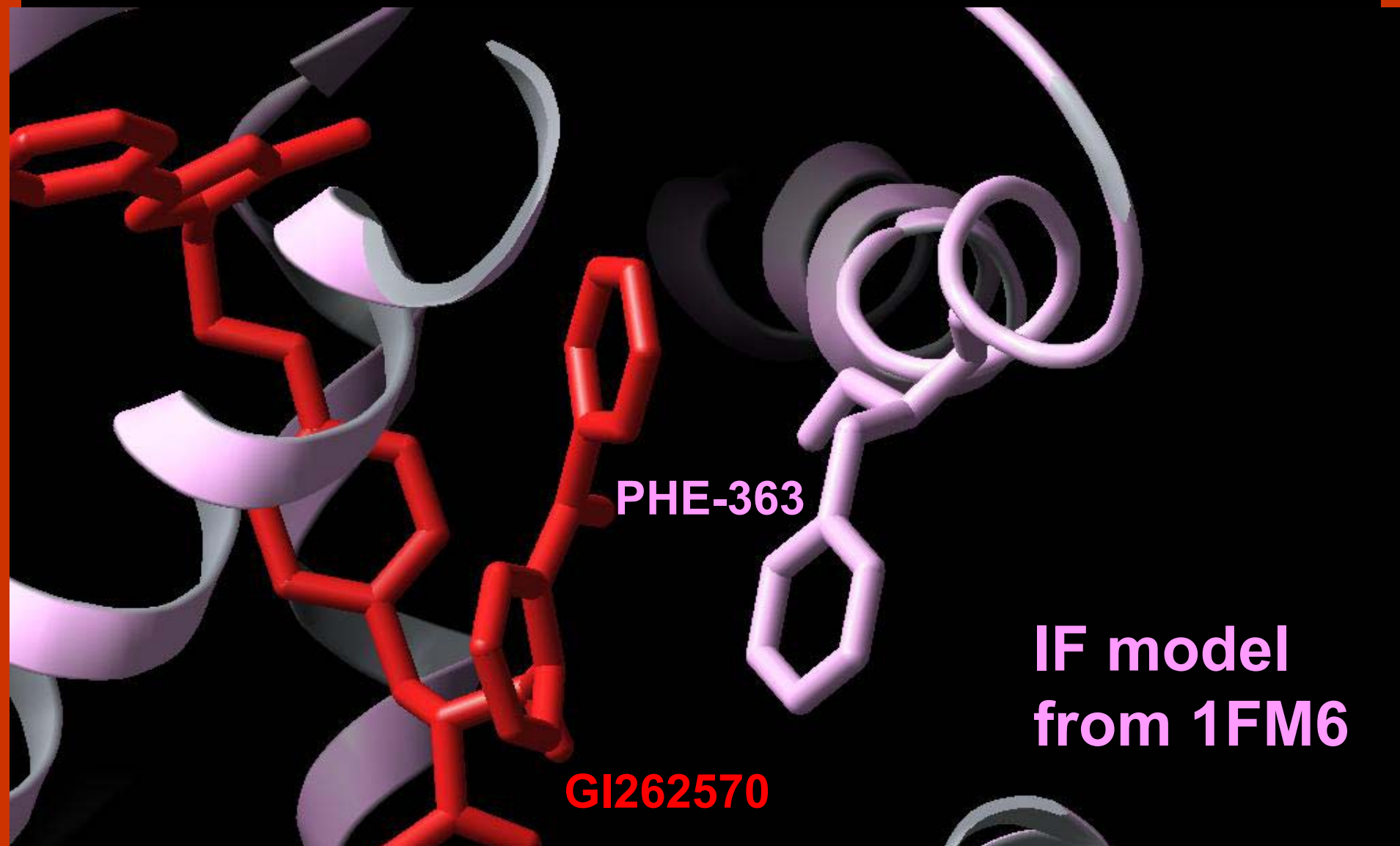
**rosiglitazone**



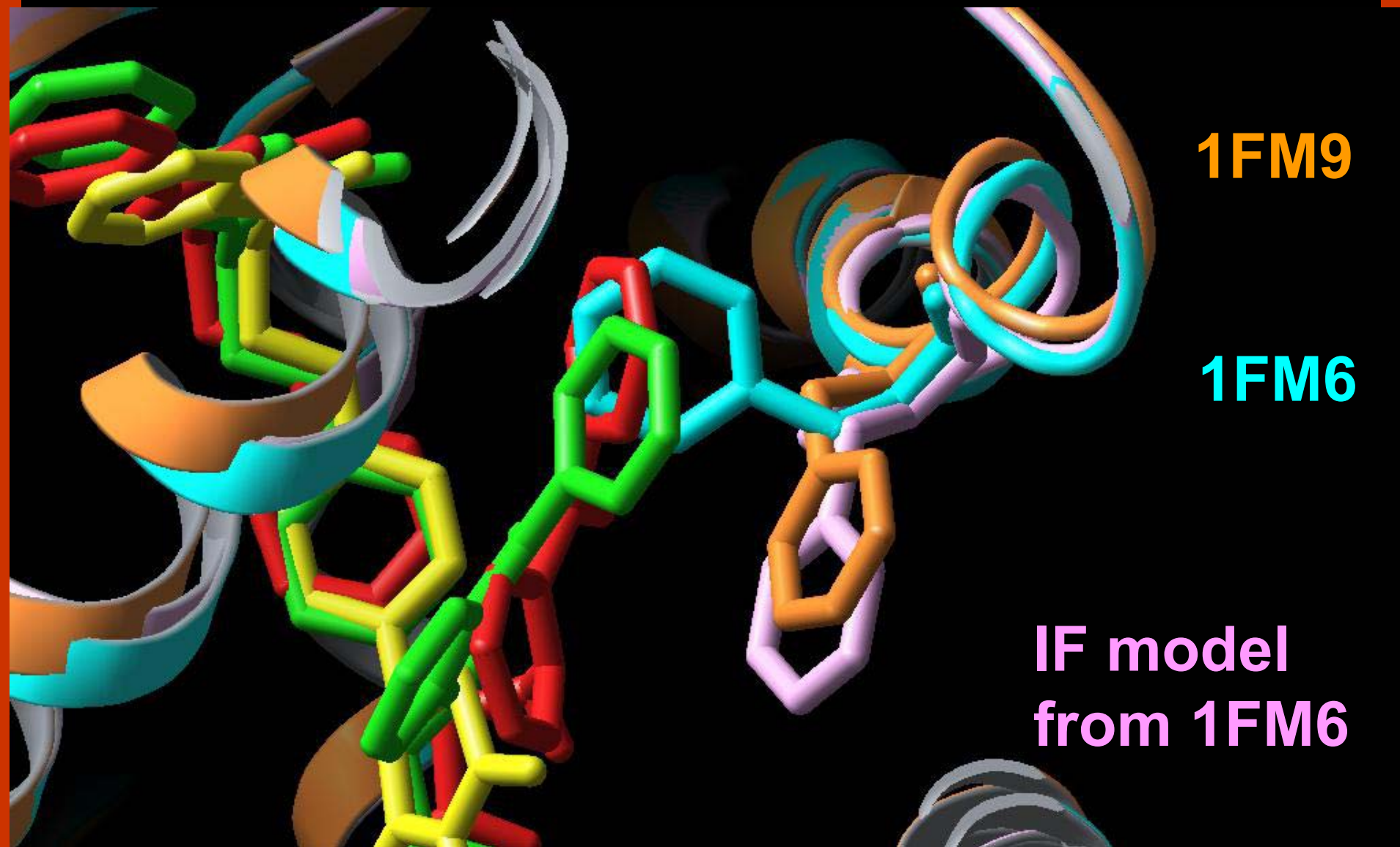
**PHE-363**

**1FM6**

# Results: PPAR- $\gamma$

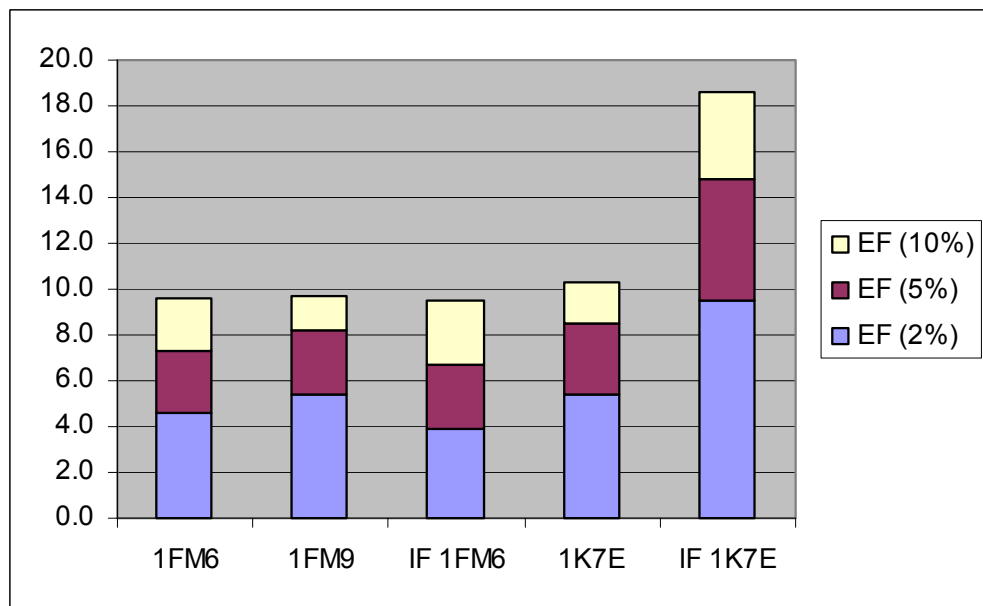


# Results: PPAR- $\gamma$



# Results: EF

Receptor	EF (2%)	EF (5%)	EF (10%)
1FM6	4.6	2.8	2.3
1FM9	5.4	2.7	1.5
<b>IF 1FM6</b>	<b>3.9</b>	<b>2.8</b>	<b>2.8</b>
1K7E	5.4	3.1	1.8
<b>IF 1K7E</b>	<b>9.5</b>	<b>5.3</b>	<b>3.8</b>



Receptor	EF' (70%)
1FM6	1.5
1FM9	1.0
<b>IF 1FM6</b>	<b>1.7</b>
1K7E	1.8
<b>IF 1K7E</b>	<b>2.9</b>

## ■ S-IN Soluzioni Informatiche

- Dott. Massimo Mabilia
- Dott. Marco Parenti
- Dott.ssa Cristina Ferrari

## ■ Database

- Dott. D.Rognan from University of Strasbourg