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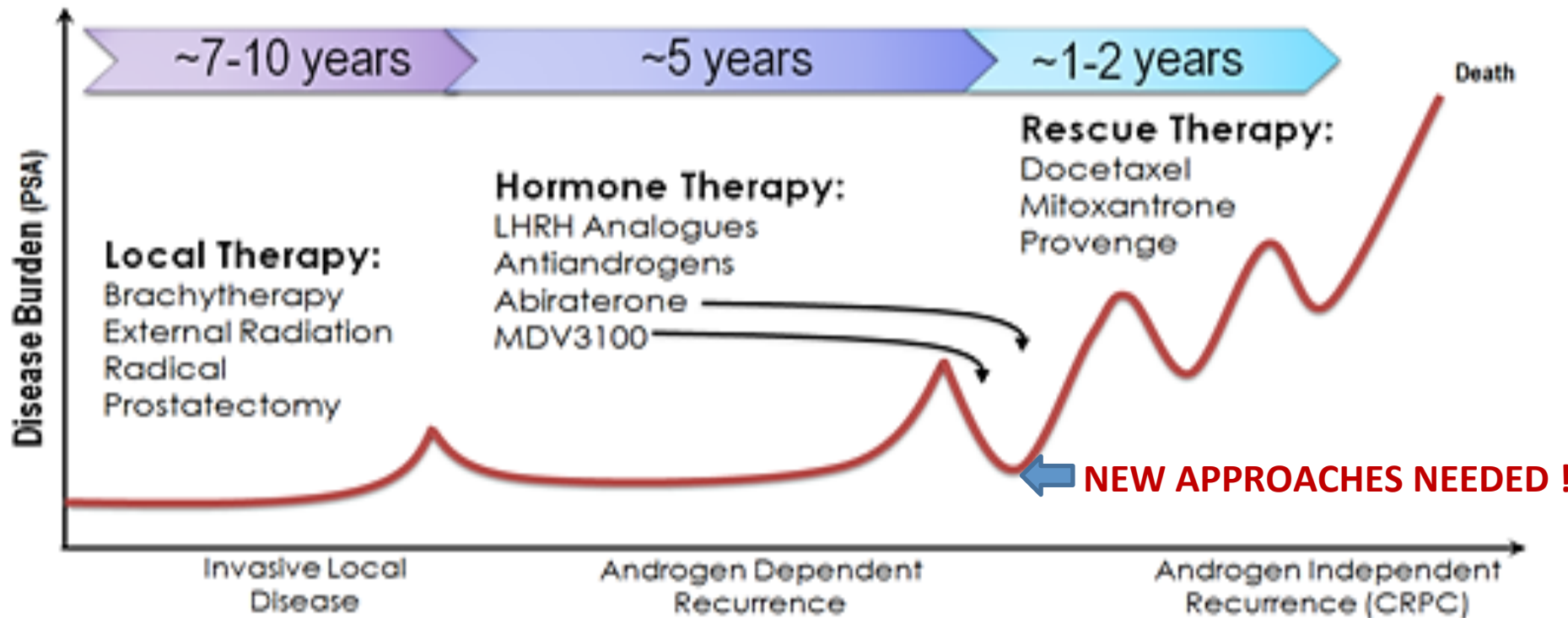
# Addressing the Problem of Drug Resistance. Application of Network Theory for Identification of Novel Drug Targets

Artem Cherkasov  
UBC

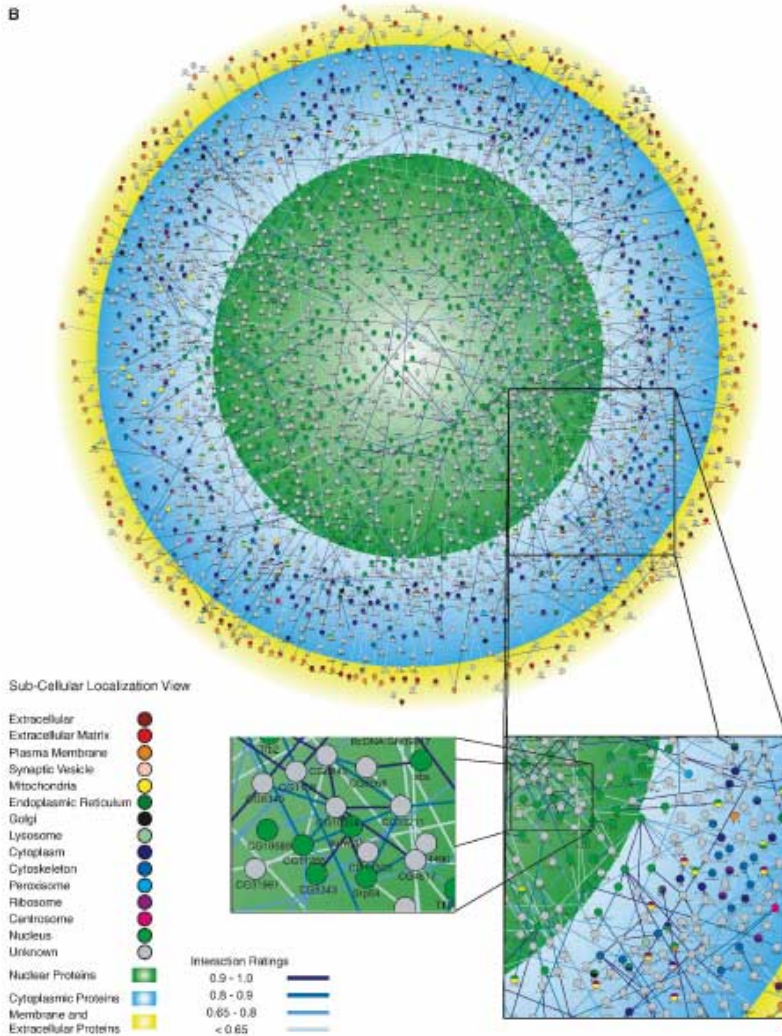
June. 26, 2014



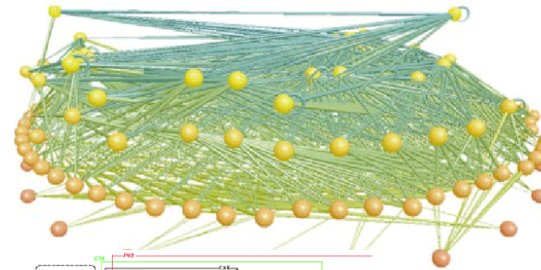
# The problem of resistance



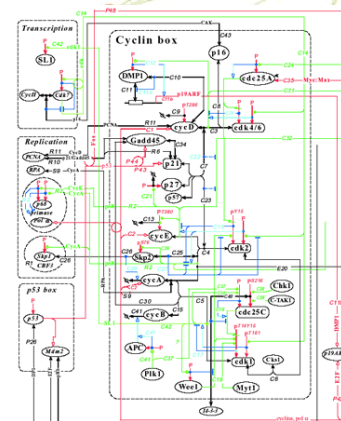
# Protein interaction networks – Targets Source



*The web of human sexual contacts*  
(Liljeros et al., Nature, 411 (2001) 907.)



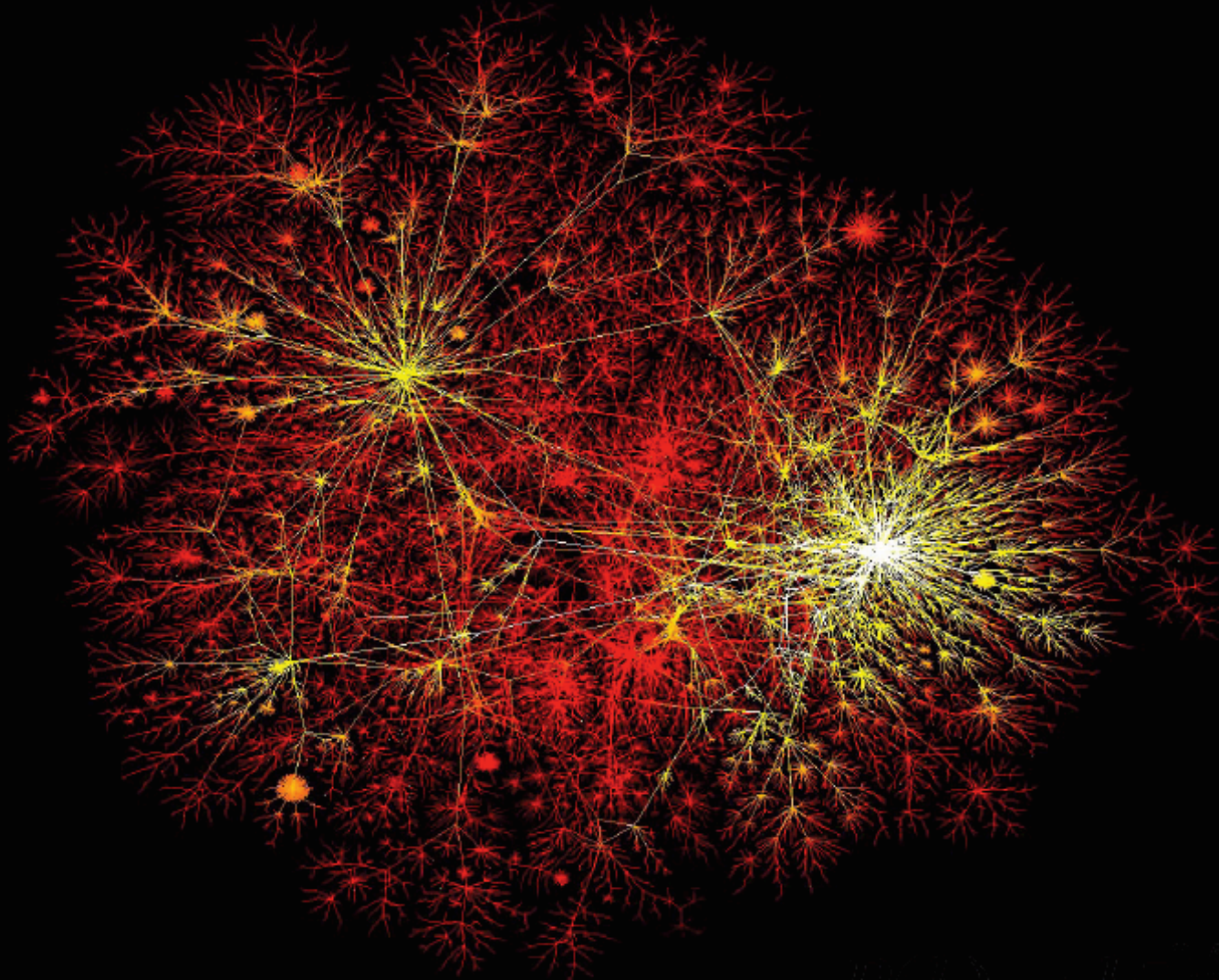
*The Food Network*



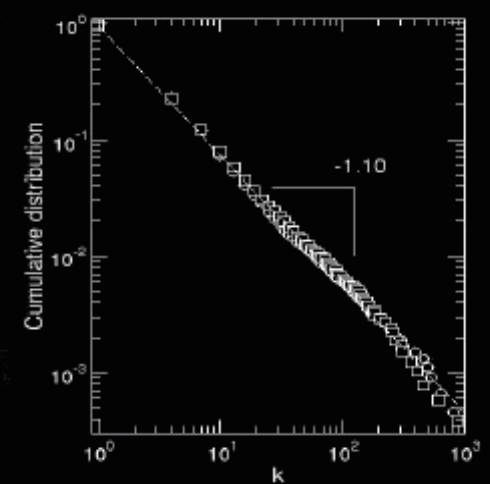
*Neurons connections*

*Metabolic networks*

# Complex networks are **scale-free**

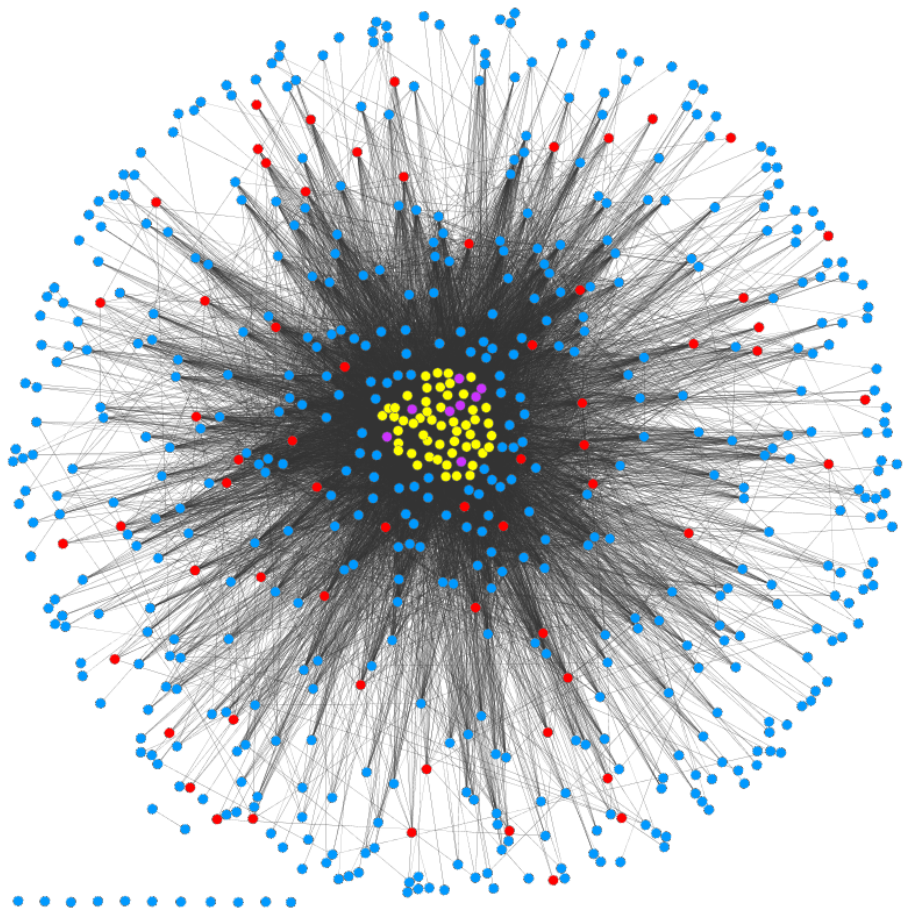


$$P(k) \sim k^{-\gamma} \phi(k/\xi)$$



Barabási, Albert-László (2004). *Linked: How Everything is Connected to Everything Else*

# MRSA Proteins Interactions Network, 13,219 interactions, 608 proteins

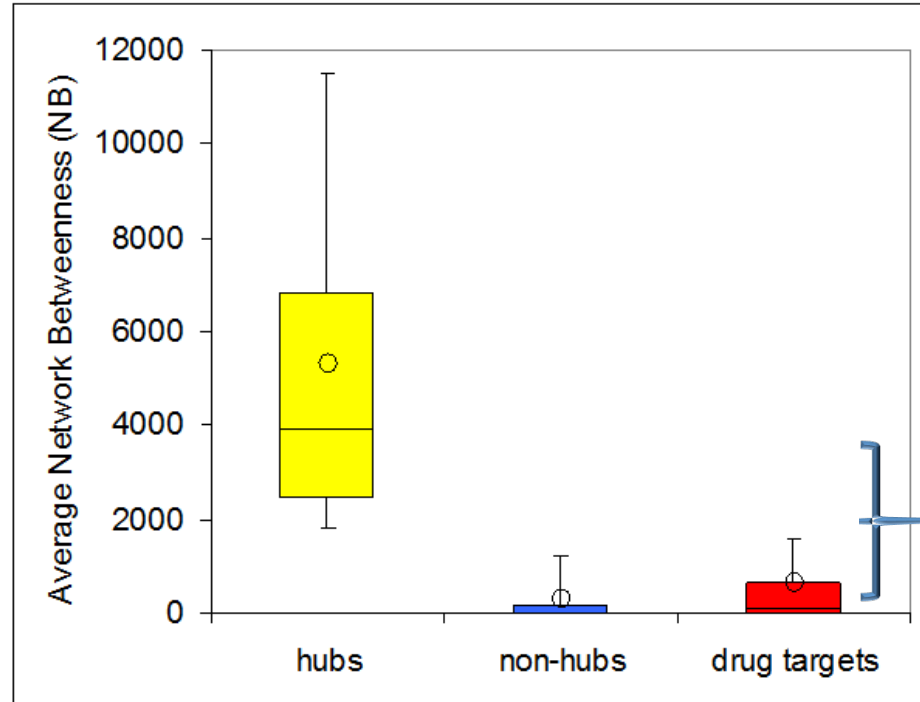
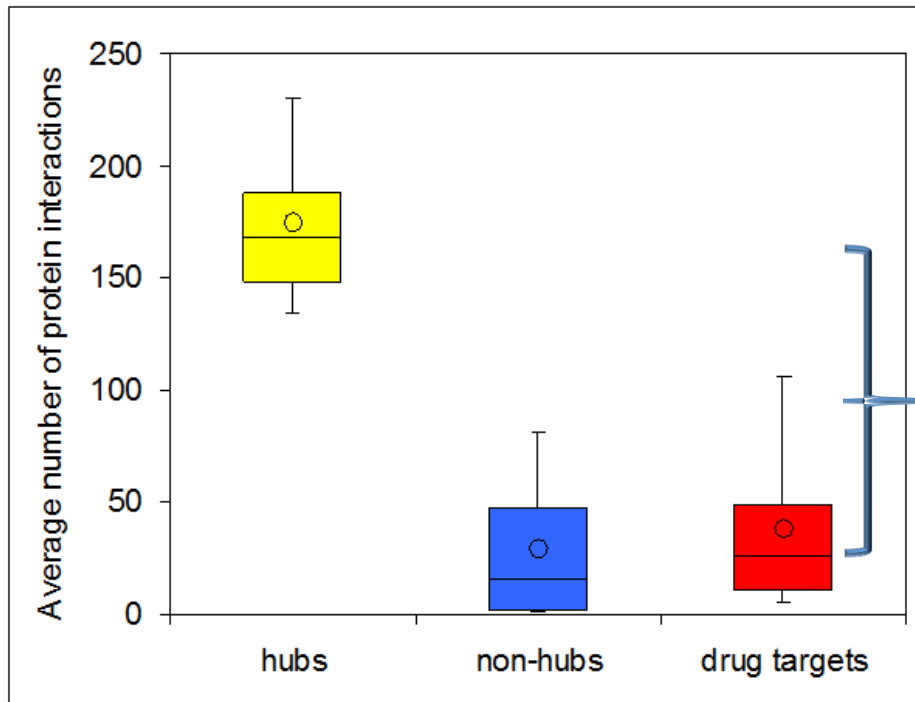


2D representation of the MS-MS derived MRSA PIN. Hub proteins are marked in yellow

The conventional antimicrobial targets are marked in red and they are NON-hubs!



# Results: MRSA PIN analysis



Average number of protein interactions among drug targets, hubs and non-hubs (left panel). **Network Betweenness (NB)** values for drug targets, hubs and non-hubs (right panel).

**The conventional antimicrobial targets are NOT hubs!**

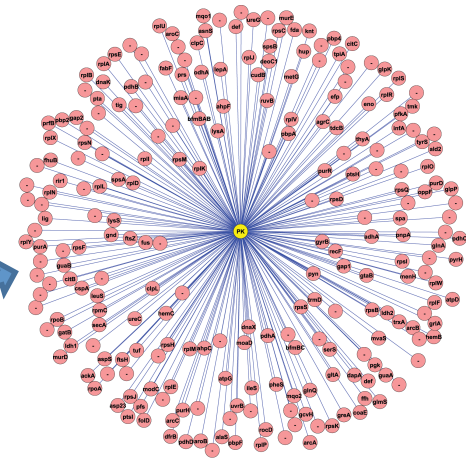
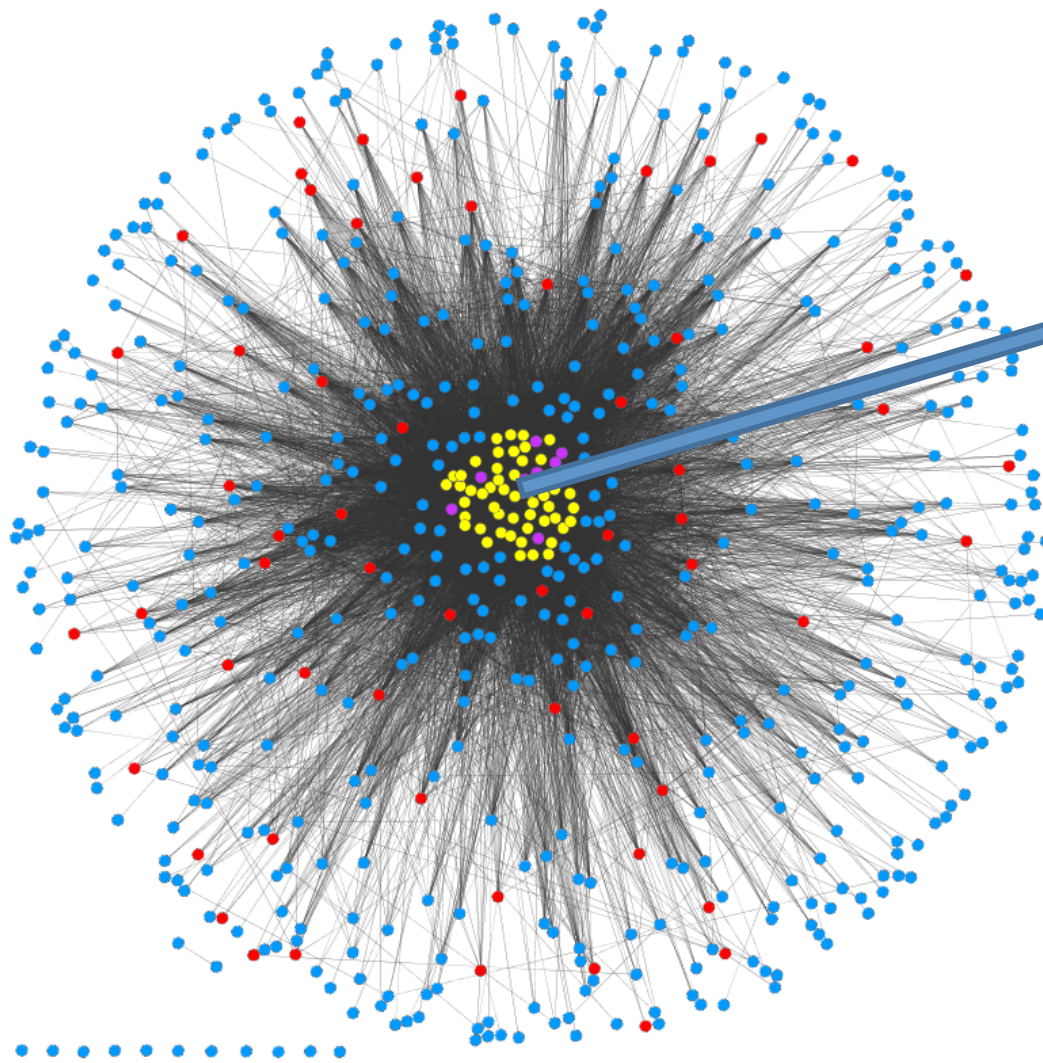
## WHY HUBS COULD BE BETTER TARGETS?

- MOST ESSENTIAL
- LESS ADAPTIVE (LOWER RATES OF MUTATION, SLOWER EVOLVING HOUSE-KEEPING GENES)

## WHY HUBS COULD BE BAD TARGETS?

- MOST CONSERVED
- HOUSE-KEEPING PROTEINS WITH ORTHOLOGUES (CANCER) AND PARALOGUES (ANTIBIOTICS)



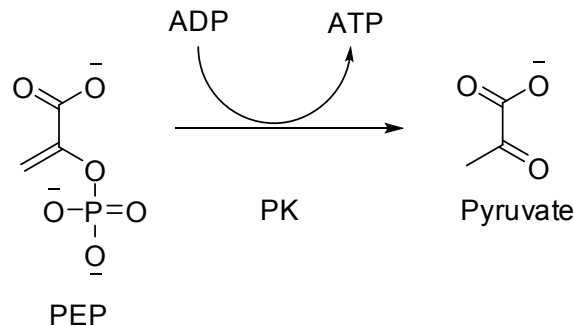






# Pyruvate Kinase

- Pyruvate kinase (PK) was identified as a highly connected hub protein in MRSA.
  - Essential for *S. aureus* viability.
  - Pyruvate is used in a number of biosynthetic pathways, placing PK at a pivotal metabolic intersection.



MRSA Pyruvate Kinase (PK) might be a good HUB target, BUT highly similar to human PKs

```
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[HUMAN PK] 359 IMLSGETAKGDYPLEAVRMQHLLIAREAEAAIYHQLFEELELRLAPITSDPTEATAVGAVEASFKCCSGA 427
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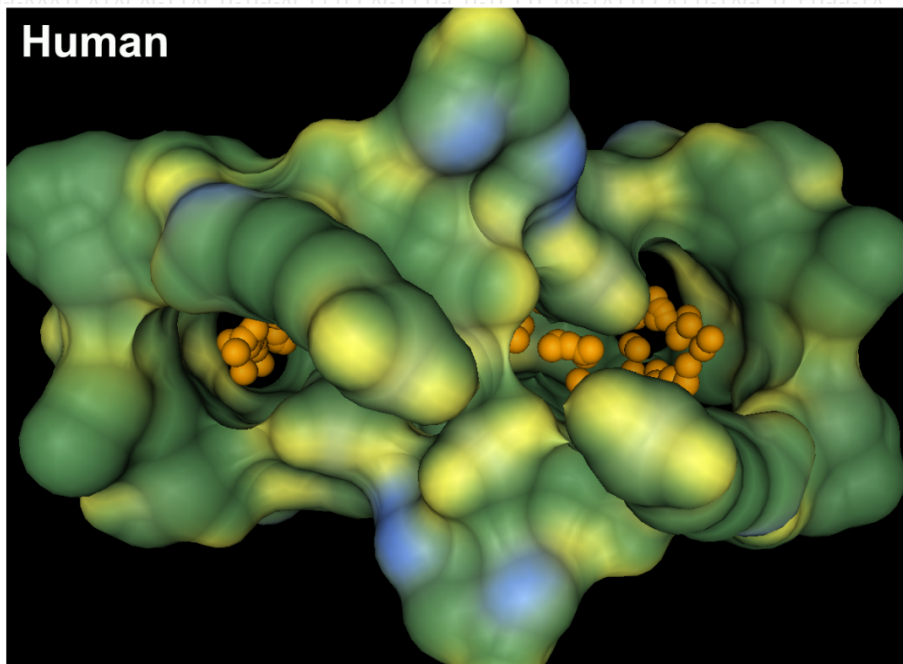
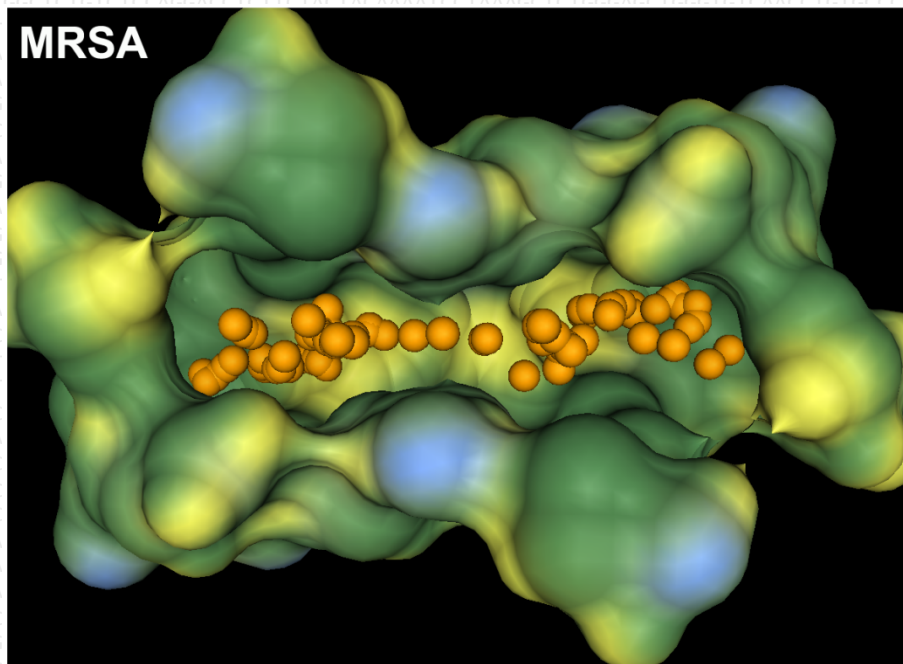
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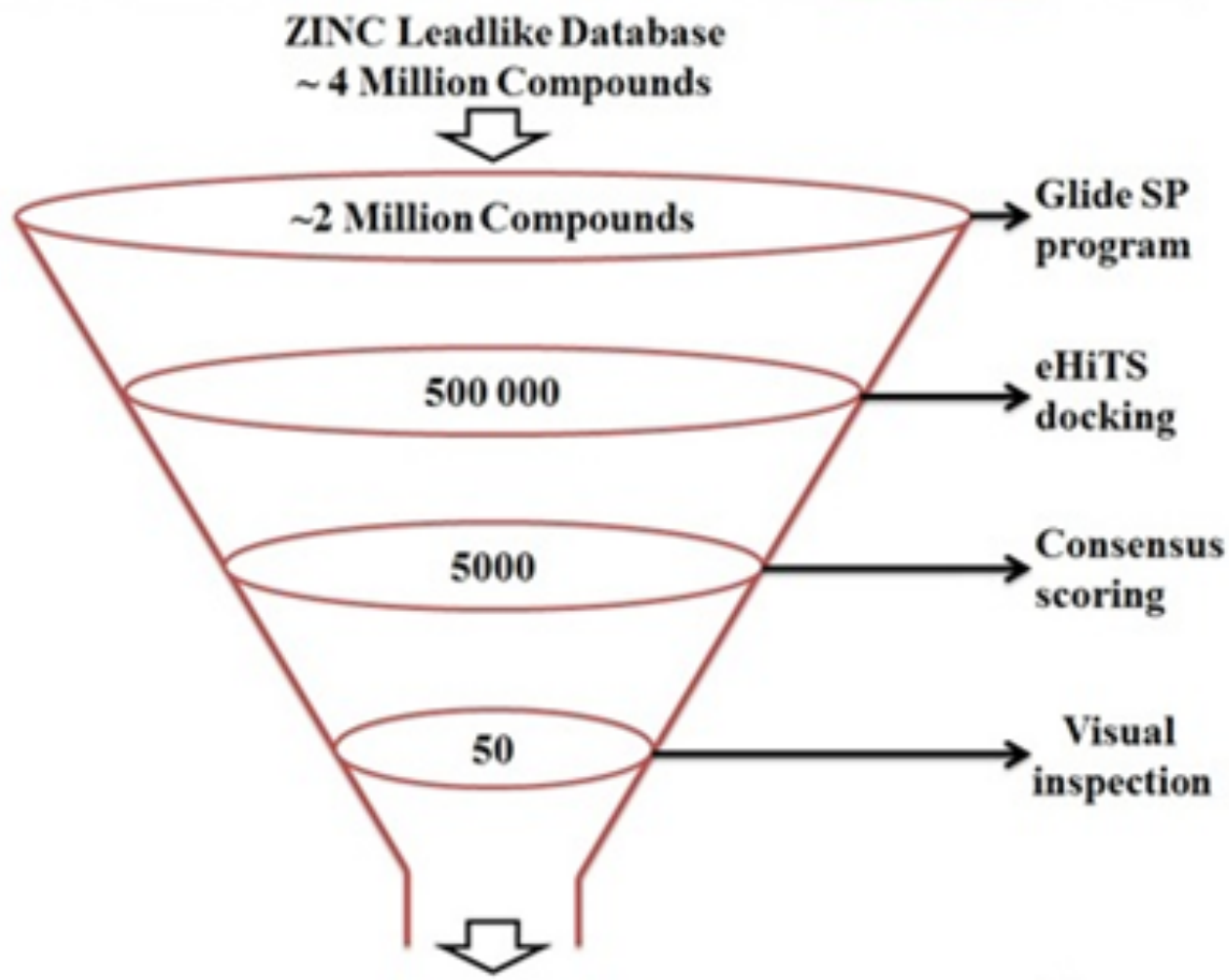
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Structural model of the interface-binding site for MRSA and human PK. Orange spheres show the interface cavity in MRSA and human.

The MRSA PK model shows an assessable binding pocket located at the interface of two PK monomers. Whereas, the pocket in human PK is partially closed by five amino acid residues (Glu418-B, Arg399-A, B and Arg400-A, B).

# VIRTUAL SCREENING PIPELINE



## Can ‘Bacterial-Metabolite-Likeness’ Model Improve Odds of ‘in Silico’ Antibiotic Discovery?

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Received November 1, 2005

‘Inductive’ QSAR descriptors have been used to develop the series of QSAR models enabling ‘in silico’ distinguishing between antimicrobial compounds, conventional drugs, and druglike substances. The constructed neural network-based models operating by 30 ‘inductive’ parameters have been validated on an extensive set of 2686 chemical structures and resulted in up to 97% accurate separation of the three types of molecular activities. The demonstrated ability of ‘inductive’ parameters to adequately capture molecular features determining ‘antibiotic-like’ and ‘druglike’ potentials have been further utilized to construct a model of ‘Bacterial-Metabolite-Likeness’ (BML). The same ‘inductive’ descriptors have been used to train a neural network that could very accurately recognize substances involved into bacterial metabolism (that have been experimentally identified). When the developed model has been applied to the mixed set of antimicrobials, drugs, and druglike chemicals (not used for training the BML model), it exhibited a 2–5-fold recognition preference toward antimicrobial compounds compared to general drugs and an 18- to 45-fold preference when compared to a druglike substance (depending on the model stringency). These results illustrate immanent similarity between conventional antimicrobials and native bacterial metabolites and suggest that the developed BML model can be an effective classification tool for ‘in silico’ antibiotic studies.

### INTRODUCTION

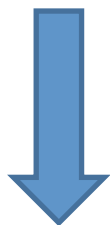
In the series of our previous works we reported the development of 3D-sensitive QSAR descriptors called ‘inductive’ and demonstrated their successful application in a number of molecular modeling studies including quantification of antibacterial activity of organic compounds<sup>1</sup> and cationic peptides,<sup>1,2</sup> computation of partial charges in small molecules<sup>3</sup> and proteins,<sup>4</sup> and in comparative docking analysis<sup>4,5</sup> as well as in ‘in silico’ lead discovery.<sup>4,5</sup> The detailed description of ‘inductive’ QSAR descriptors and their rationale can be found in the recent review.<sup>1</sup>

In summary, all ‘inductive’ QSAR parameters are related to atomic electronegativity ( $\chi$ ), covalent radii ( $R$ ), and

$$\begin{aligned} \sigma_{j \rightarrow N-1}^* &= \beta \sum_{i \neq j} \frac{N-1(\chi_j^0 - \chi_i^0)R_j^2}{r_{j-i}^2} \\ \sigma_{G \rightarrow j}^* &= \beta \sum_{i \in G, i \neq j} \frac{n(\chi_i^0 - \chi_j^0)R_i^2}{r_{i-j}^2} \quad (2) \\ \chi_{N-1 \rightarrow j}^0 &= \frac{\sum_{i \neq j} \chi_i^0 (R_i^2 + R_j^2)}{\sum_{i \neq j} \frac{N-1R_i^2 + R_j^2}{r_{i-j}^2}} \quad \chi_{N-1 \rightarrow j}^0 = \frac{\sum_{i \neq j} \chi_i^0 (R_i^2 + R_j^2)}{\sum_{i \neq j} \frac{N-1R_i^2 + R_j^2}{r_{i-j}^2}} \quad (3) \end{aligned}$$

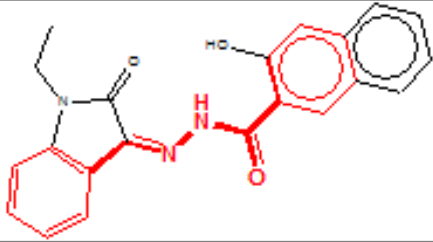
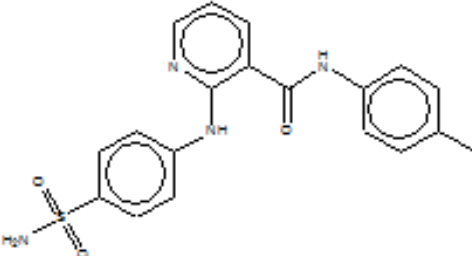
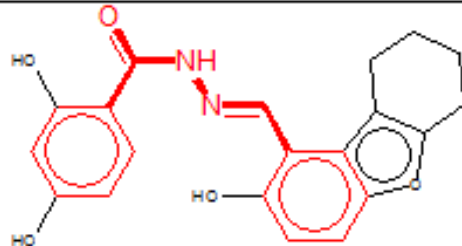
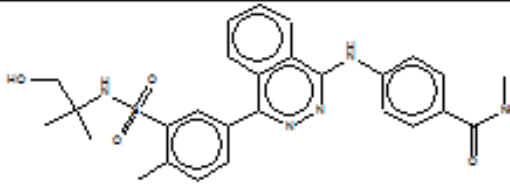
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cmps



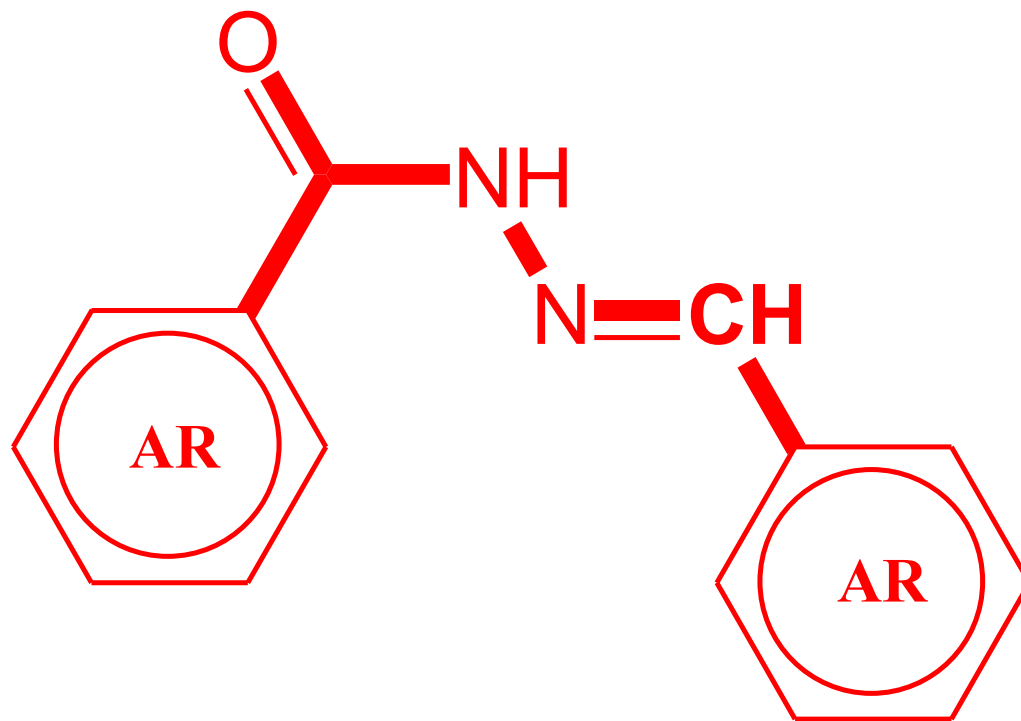
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ID	structure	IC <sub>50</sub> MRSA PK, $\mu\text{M}$	MIC MRSA $\mu\text{M}$	I	II	III	IV	V
IS-63		0.911	>500	83.9	15	1.3	13.5	22.2
IS-168				79.5	17.6	12.6	30.6	24.7
IS-53				77.8	39.3	57.5	78.1	87.8
IS-165				54.6	25.8	8.3	15.3	9.4

ID	structure	IC <sub>50</sub> MRSA PK, $\mu$ M	MIC MRSA $\mu$ M	I	II	III	IV	V
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IS-165				54.6	25.8	8.3	15.3	9.4



# TOPOLOGICAL QUERRY

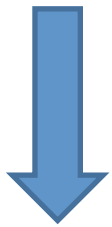


# LIGAND-BASED SEARCH

IS-130

structure	IC50 MRSA PK, $\mu\text{M}$	MIC MRSA $\mu\text{M}$	I	II	III	IV	V	Tanimoto to IS-63
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			78.8	10.9	10.2	7.3	-4.7	0.72
			78.3	22.8	26.7	15.7	20.8	0.76
			71.1	-1.7	2.2	9.8	0.9	0.60
			66.4	13.0	11.8	7.1	-1.0	0.76
			60.6	3.6	25.3	5.6	12.3	0.64
			50.0	10.4	10.2	0.4	0.8	0.70

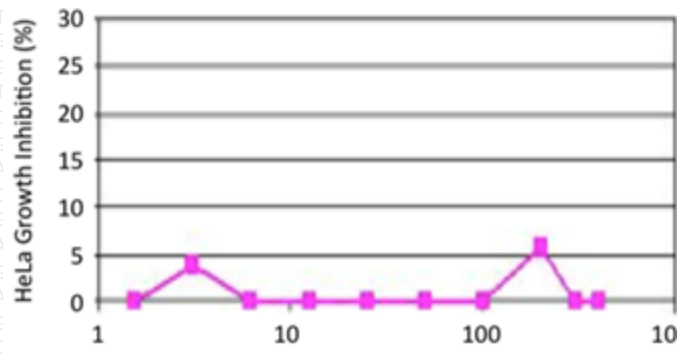
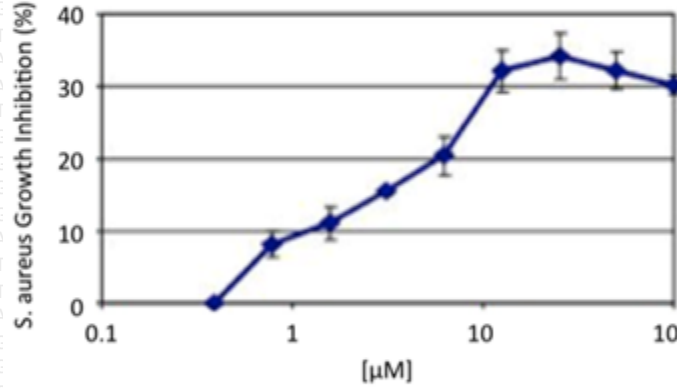
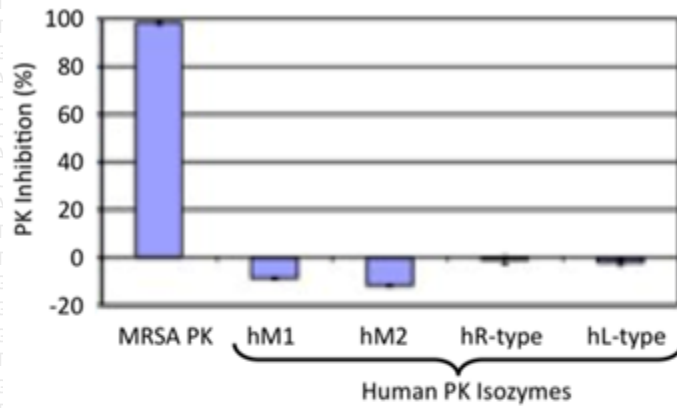
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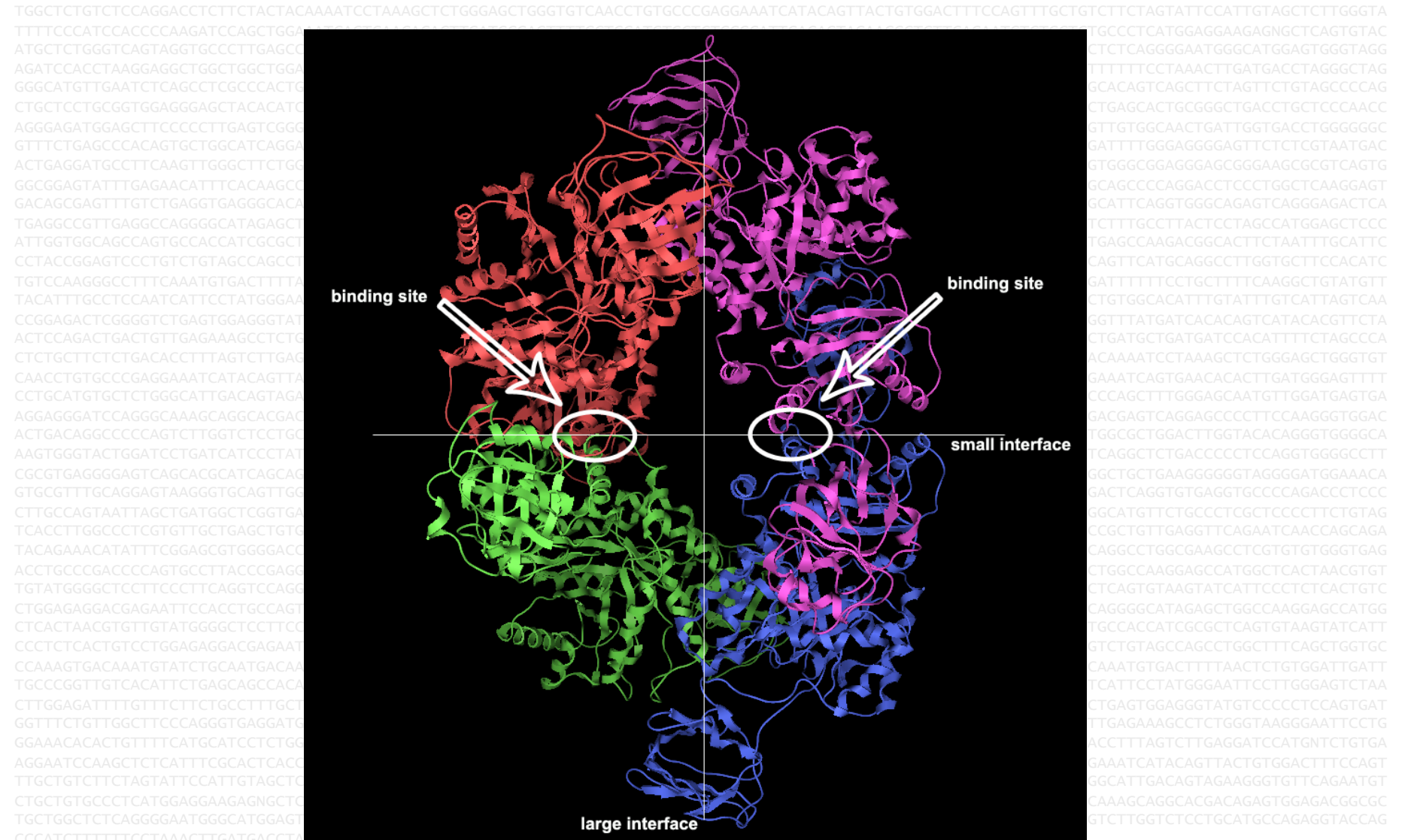


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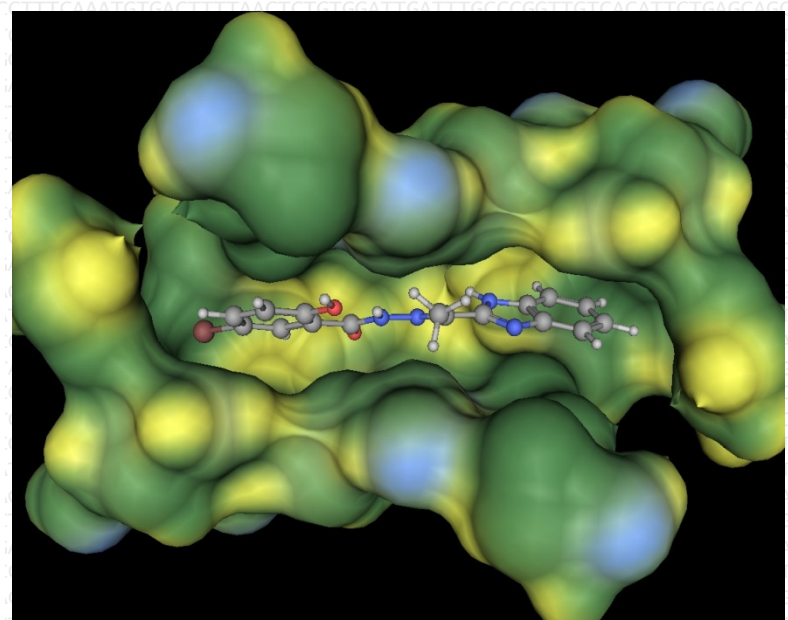
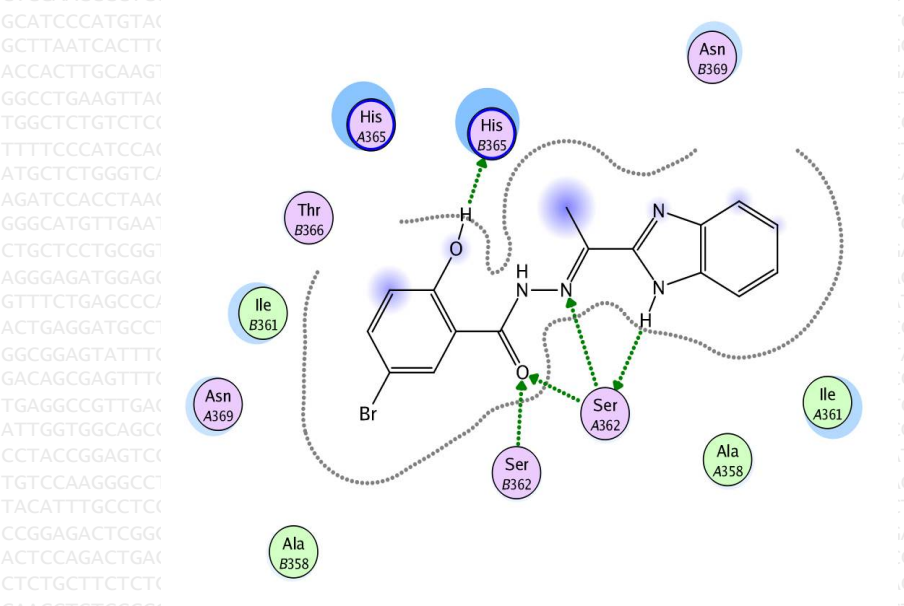
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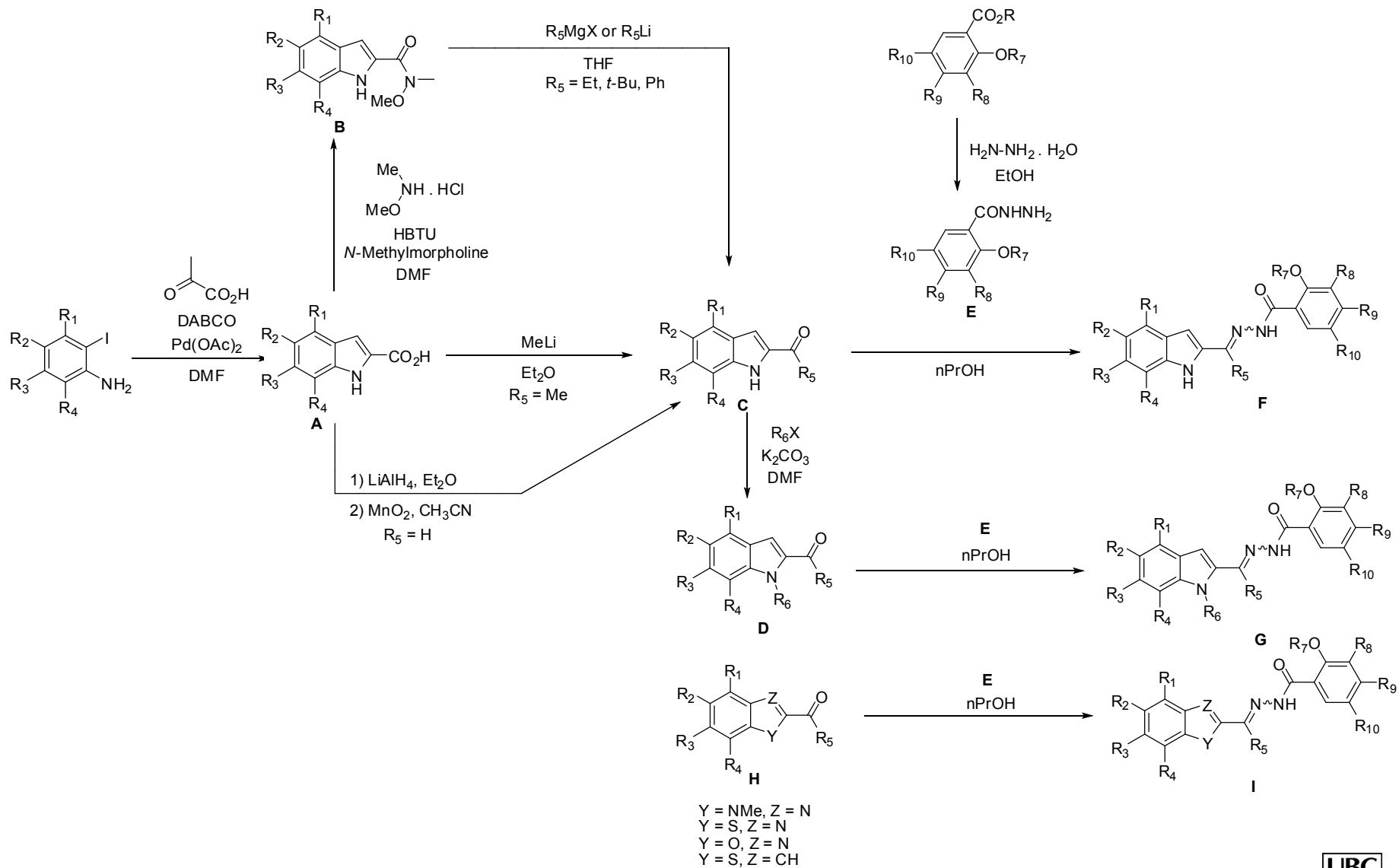
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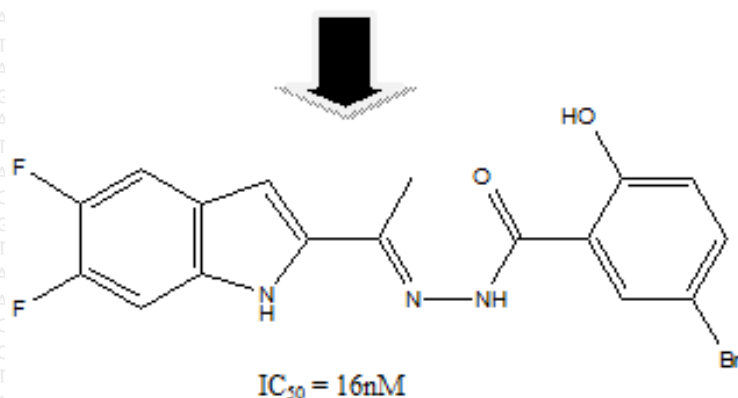
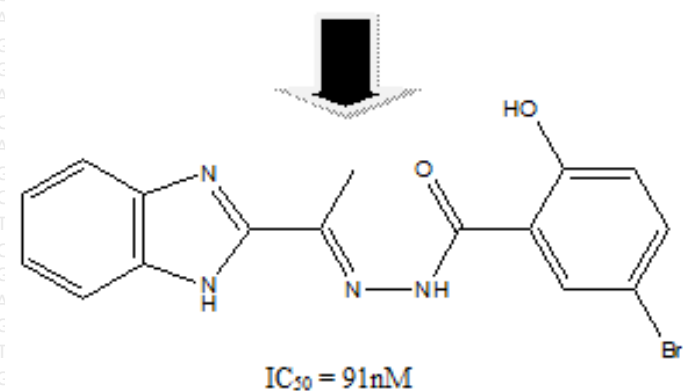
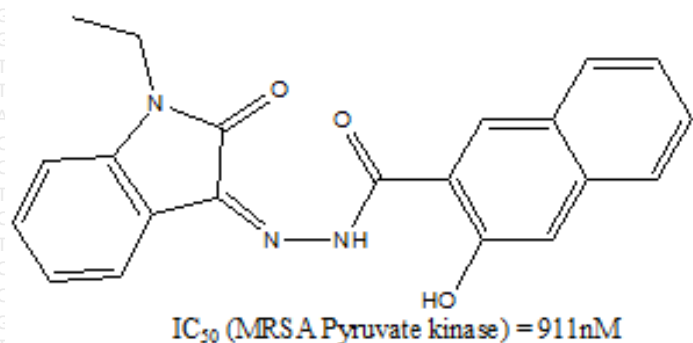
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Binding mode of IS-130 at the interface binding site a) A two-dimensional map of the binding interactions between IS-130 and the interface site based on its co-crystallization with MRSA PK. Green arrows depict hydrogen-accepting interactions between IS-130 and MRSA PK residues from the interface. b) Binding orientation of IS-130 within the interface-binding pocket based on the protein-ligand crystallized structure. The protein surface is rendered where green protein surface depicts the hydrophobic interface and yellow depicts the hydrophilic surface.

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# Synthesis of IS-130 Analogues





DOCKING

SUBSTRUCTURE SEARCH

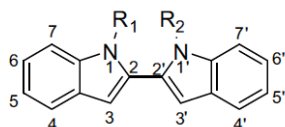
MED CHEM OPTIMIZATION



bisIndoles with  
 $IC_{50} < 1nM$

**Table 1**

PK inhibitory activity and antimicrobial activity of substituted bis-indoles



Analogs	IC <sub>50</sub> <sup>a</sup> (nM)	MIC <sup>b</sup> (μg/ml)	R <sub>1</sub>	R <sub>2</sub>	Substitutions
<b>10a</b>	21.4	2.0	H	H	6-Bromo
<b>10b</b>	7.0	16.0	H	H	6,6'-Dibromo
<b>10c</b>	2.2	0.3 (3)	H	H	6,5'-Dibromo
<b>10d</b>	2.0	0.3	H	H	6-Bromo-5'-chloro
<b>10e</b>	2.8	0.3	H	H	6-Bromo-5'-fluoro
<b>10f</b>	2.5	>64	H	H	6-Bromo-5'-methoxy
<b>10g</b>	2.2	>64	H	H	6-Bromo-5'-phenyl
<b>10h</b>	36% @ 10 μM	ND	H	H	5-Bromo
<b>10i</b>	3.0	>64 (2)	H	H	5,5'-Dibromo
<b>10j</b>	39% @ 10 μM	ND	H	H	5,6-Dibromo
<b>10k</b>	1.5	0.5	H	H	5,6,6'-Tribromo
<b>10l</b>	2.0	>64	H	H	5,5',6,6'-Tetrabromo
<b>10m</b>	1.6	1.0	H	H	5,6,5'-Tribromo
<b>12a</b>	1.0	>64 (2)	H	CH <sub>3</sub>	6,5'-Dibromo
<b>12b</b>	25% @ 10 μM	ND	CH <sub>3</sub>	H	6,5'-Dibromo
<b>12c</b>	1.9	>64	H	CH <sub>2</sub> OCH <sub>3</sub>	6,5'-Dibromo
<b>14</b>	11.1	>64	H	CH <sub>2</sub> COOH	6,5'-Dibromo
<b>15</b>	6.0	>64	H		6,5'-Dibromo
<b>17</b>	1.3	2.0	H	CH <sub>2</sub> CH <sub>2</sub> OH	6,5'-Dibromo
<b>20a</b>	2.0	4.0	H		6,5'-Dibromo
<b>20b</b>	1.2	>64	H		6,5'-Dibromo

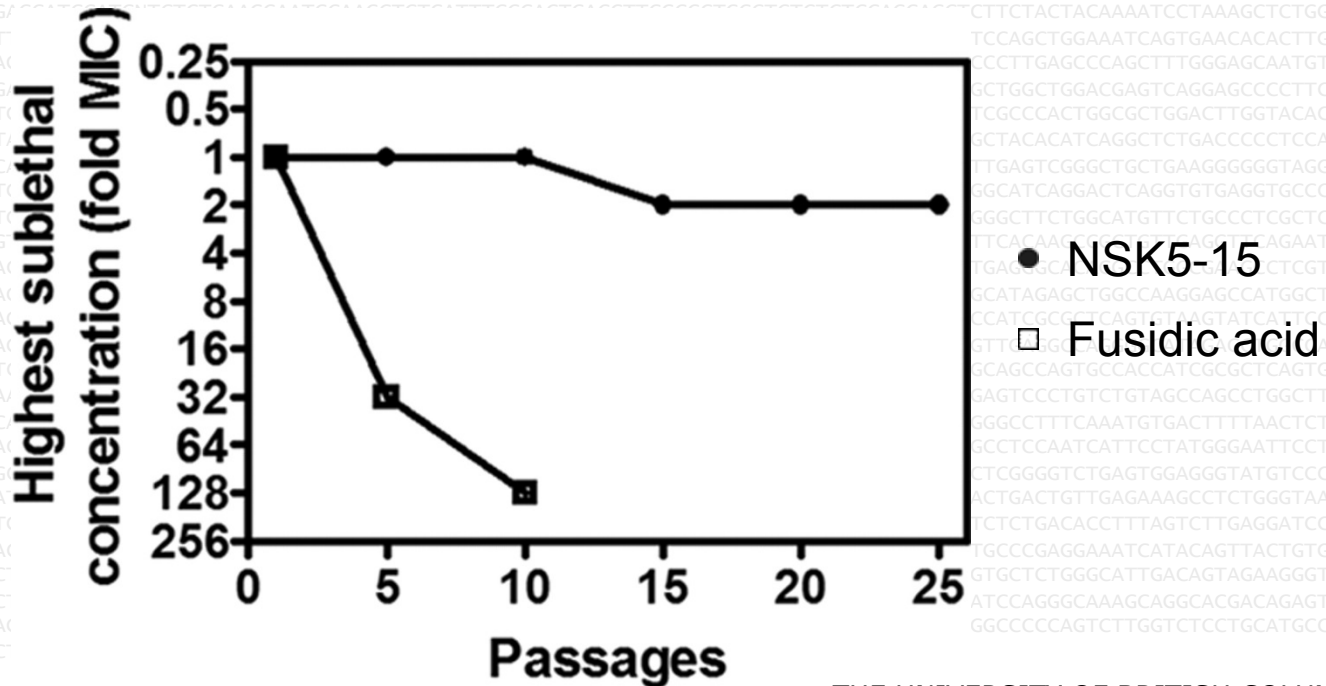
<sup>a</sup> IC<sub>50</sub> values are calculated from a triplicate 15-point titration. Alternatively the % inhibition at the highest concentration tested is presented.<sup>b</sup> Minimum concentration to give >98% inhibition of growth of *S. aureus* ATCC 29213 (single determination or average of (n) determinations). Control MIC (vancomycin) is



# Resistance Studies

To assess the potential for cells to become resistance to NSK5-15, we tried to generate resistant mutants by using *S. aureus* RN4220.

Cells were passaged for up to 25 consecutive generations in the presence of sublethal concentration of NSK5-15 or for 10 generation with fusidic acid.

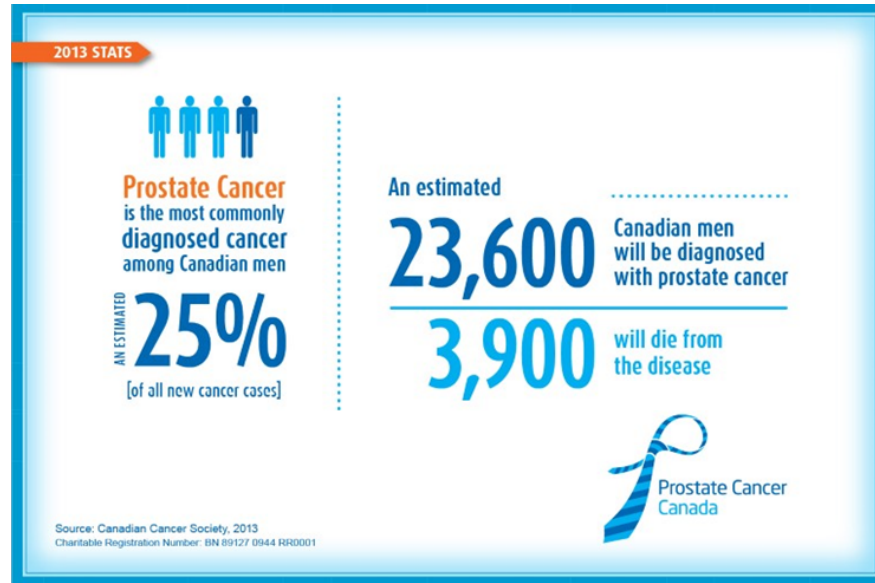


DON'T HUBS ADOPT?

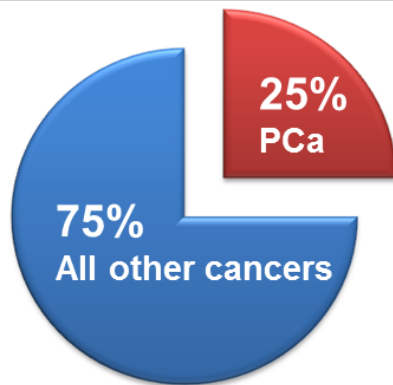
THEY PROBABLY DO... EVENTUALLY



# Prostate Cancer



Total estimated cases

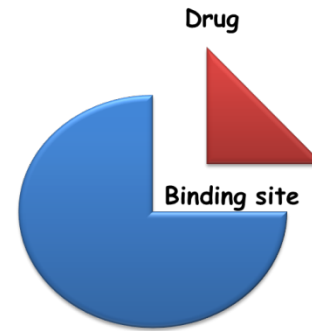


PCa deaths



# Limitations of Conventional Anti-Androgens

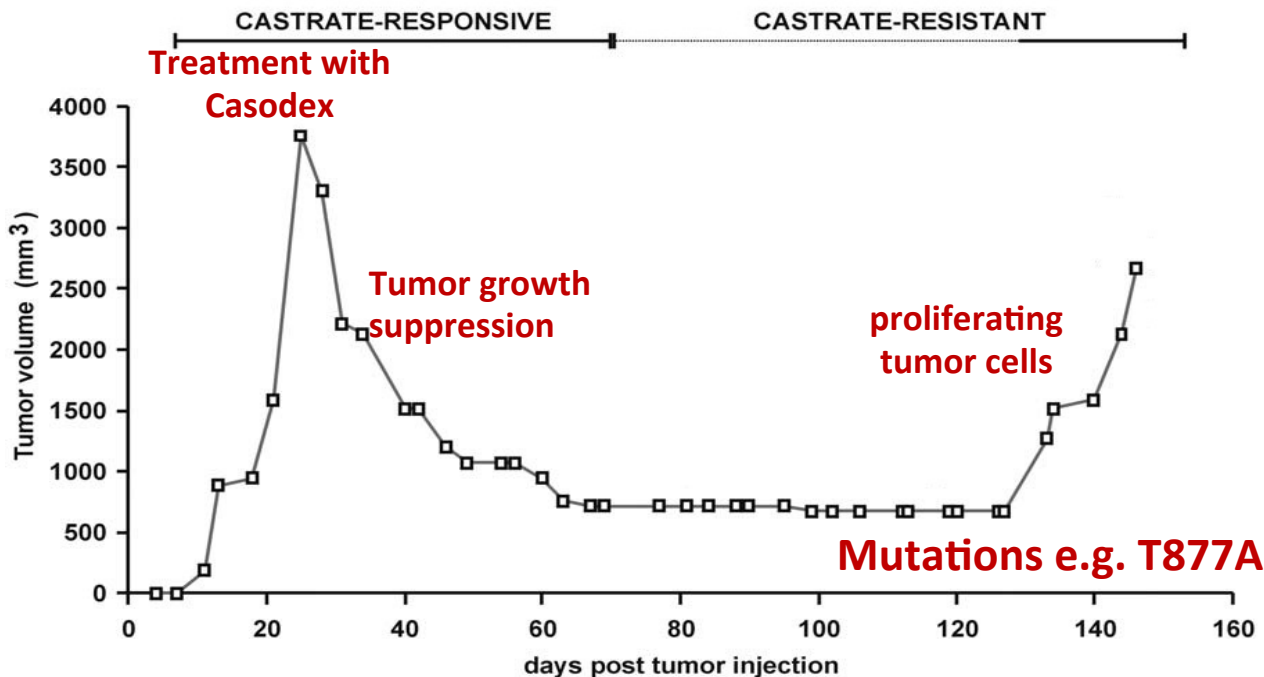
## ❖ Mutations in the protein



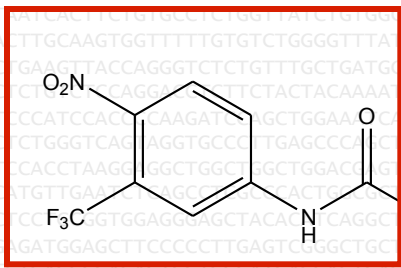
Normal AR



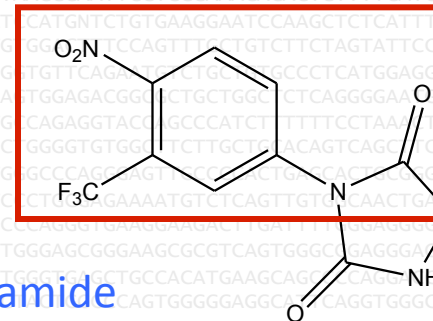
Mutated AR



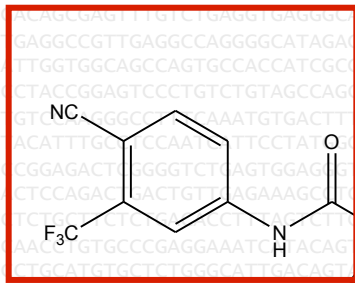
# Existing anti-androgens



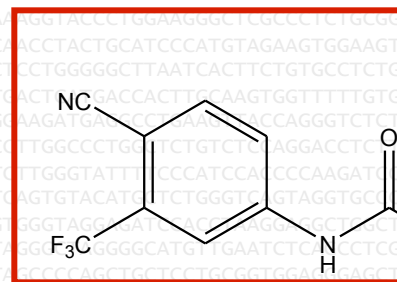
Flutamide



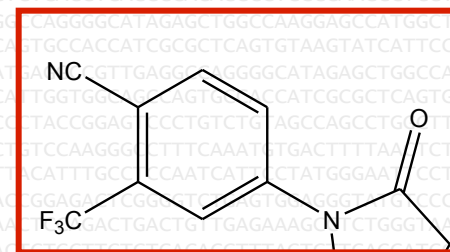
Nilutamide



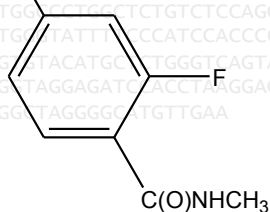
Biglutamide (Casodex)



MDV3100 (Enzalutamide)



RU56187

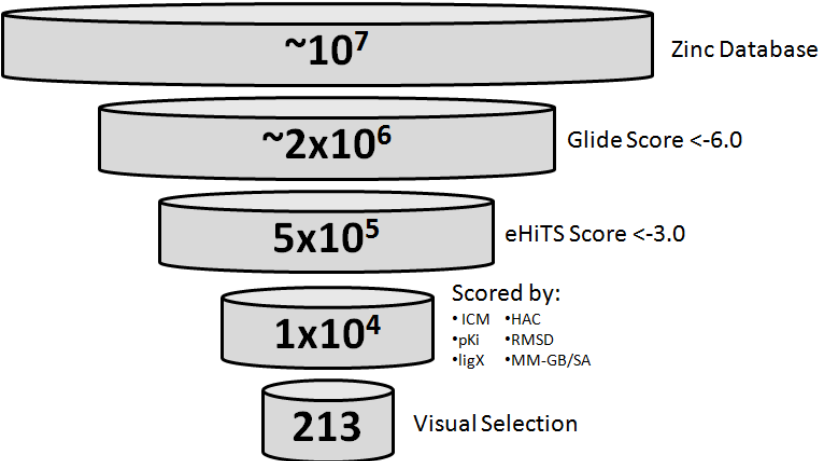






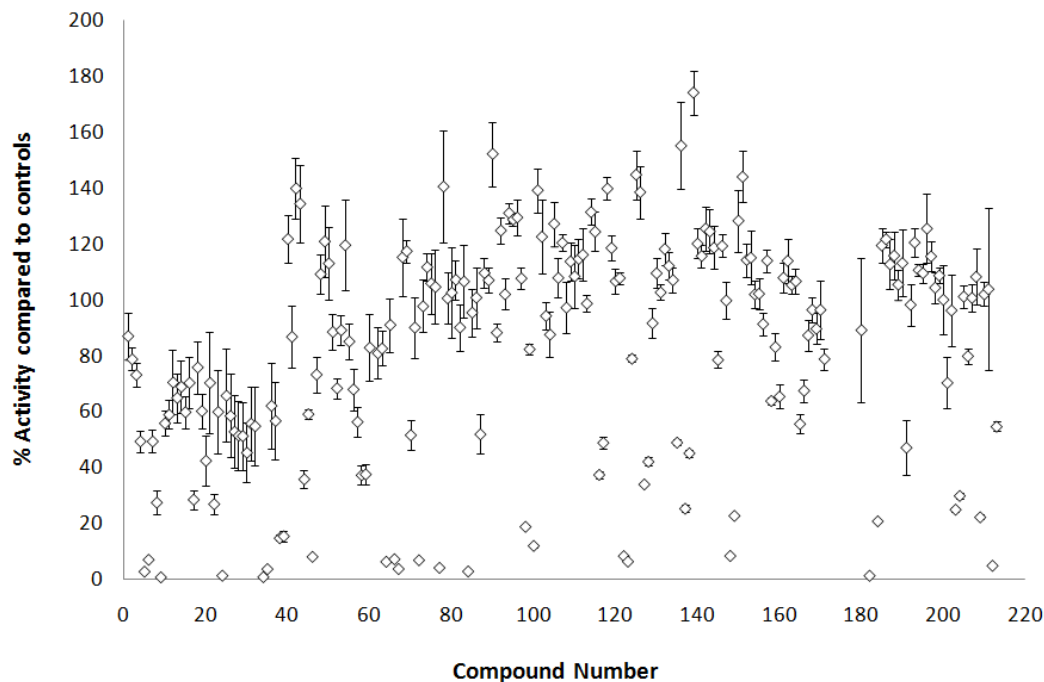
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## Number of compounds



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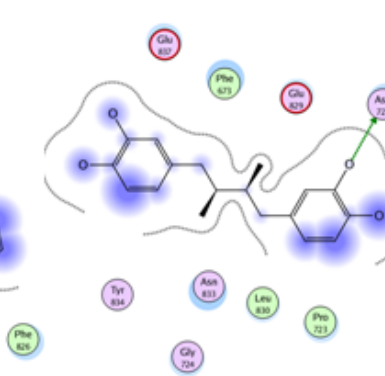
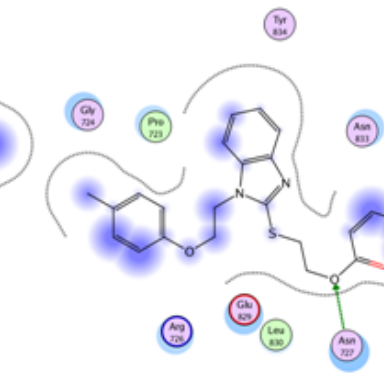
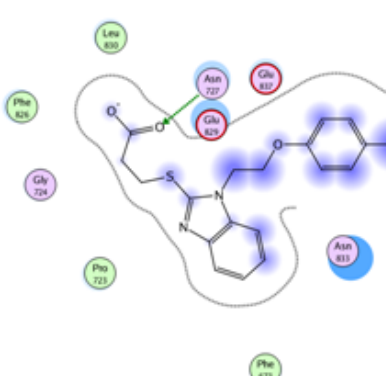
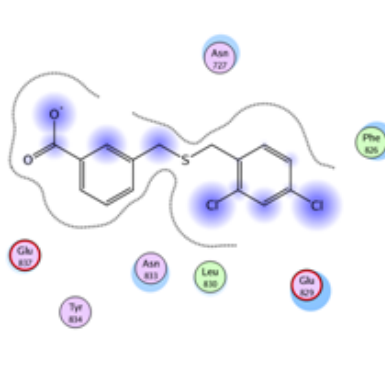
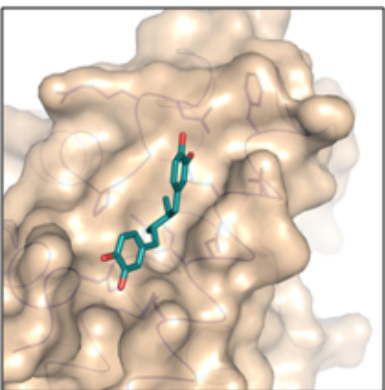
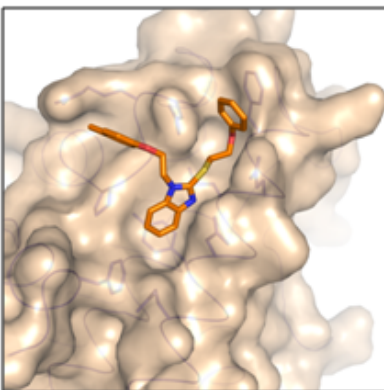
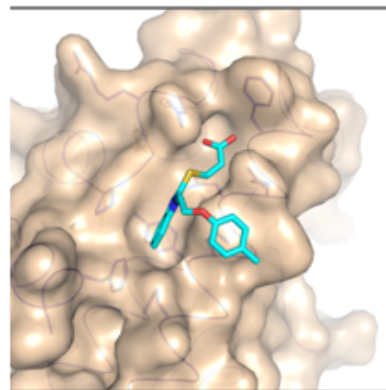
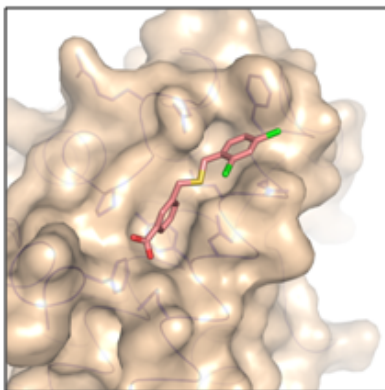
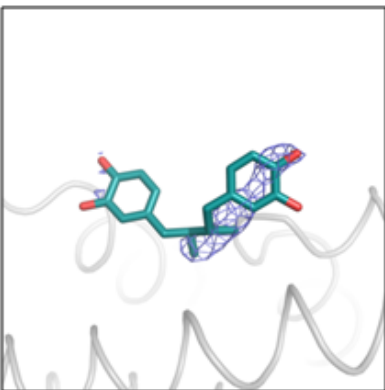
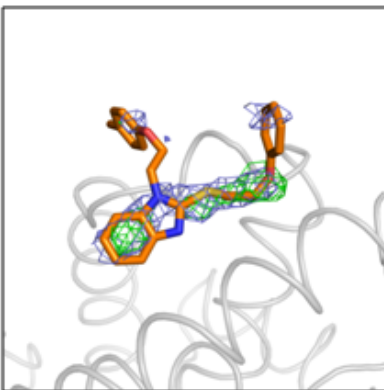
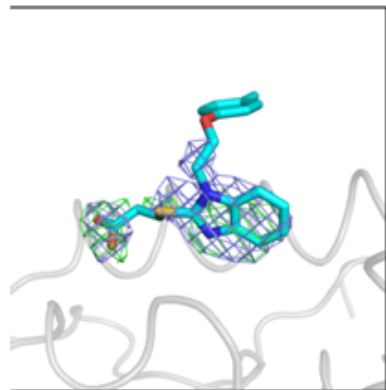
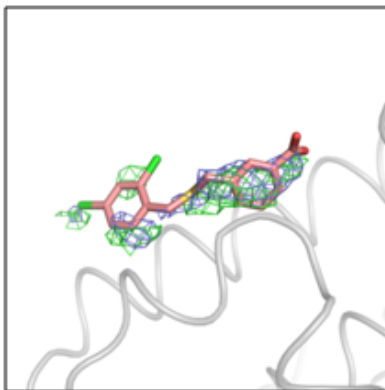
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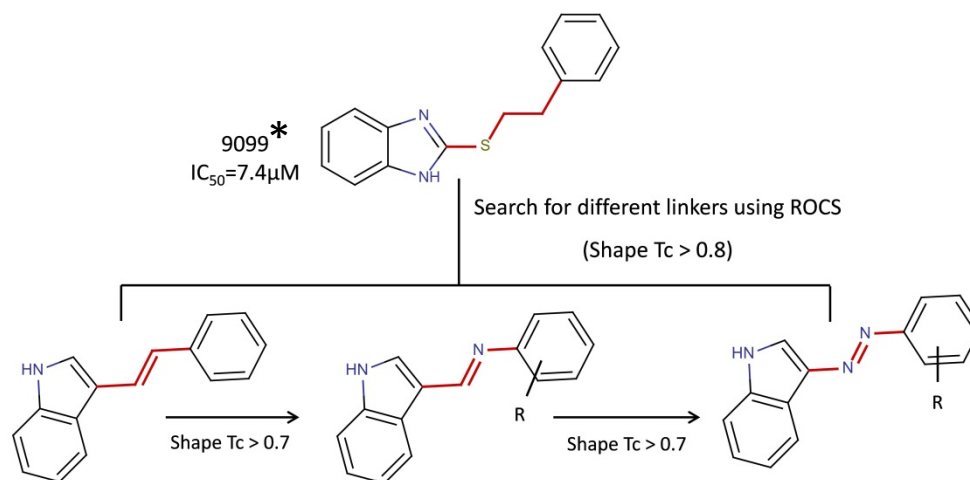
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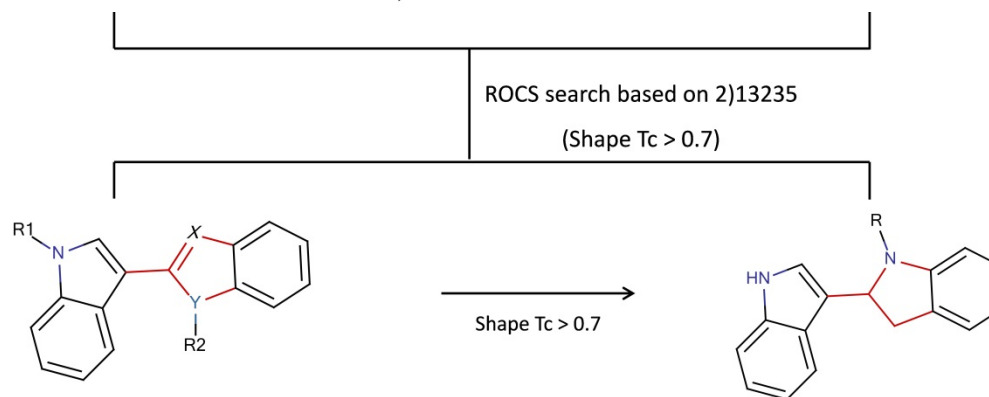
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# Identification of Potent BF3 Inhibitors



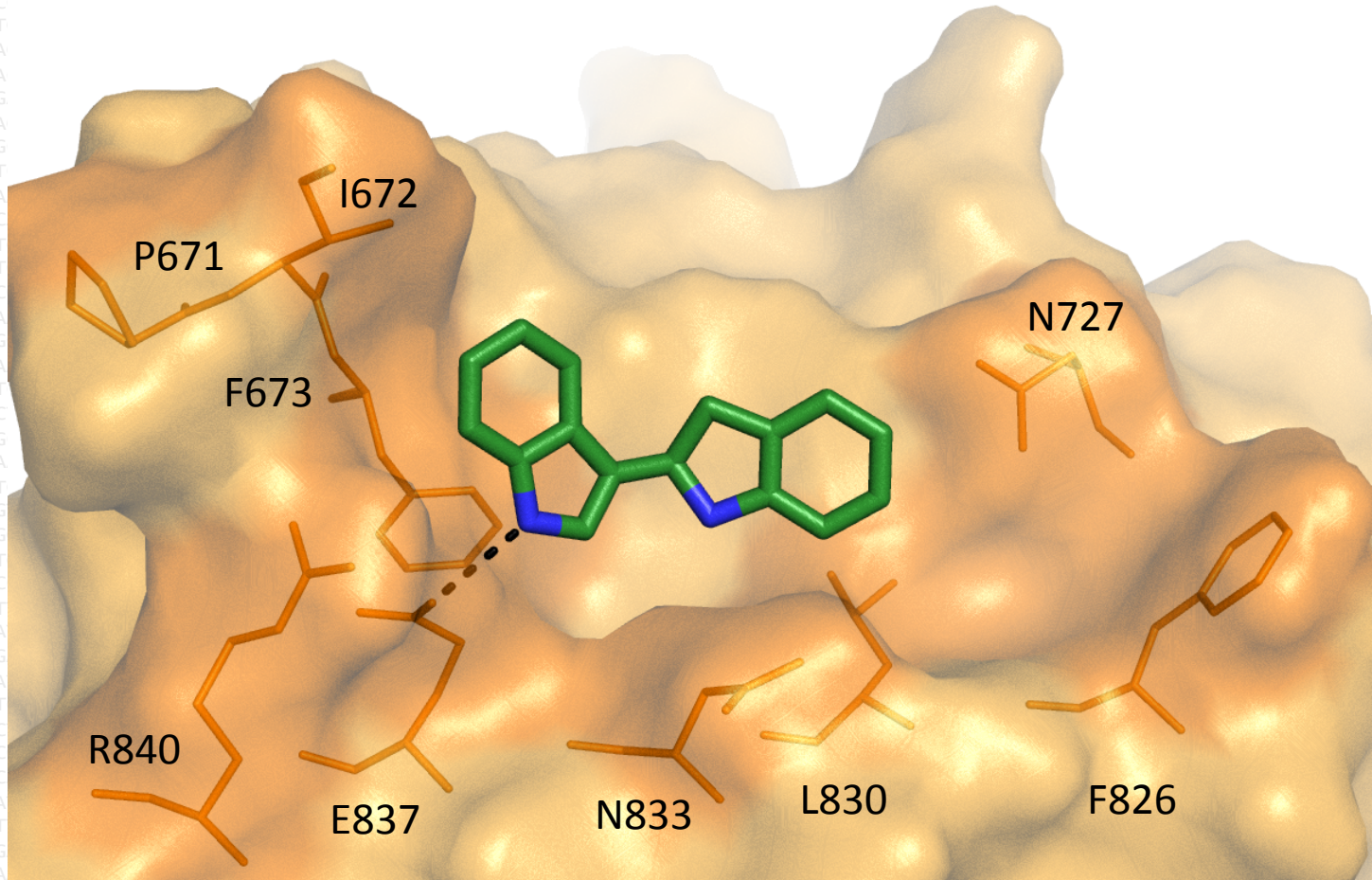
ID	IC <sub>50</sub> (μM)	ID	R	IC <sub>50</sub> (μM)	ID	R	IC <sub>50</sub> (μM)
13235	2.21	13303	2-CF3	4.46	13259	1-CF3	0.31
		13304	2,4-Cl	7.27	13256	-	0.38
		13299	3-Me	8.16	13255	1-Cl	0.52
		13300	3-OMe	9.33	13225	1,3-Me	0.70
		13310	2,3-Me	10.31	13254	3-Cl	1.20
		13345	1,6-Cl	13.89	13257	3-Me	4.18
		13320	2-OMe	25.23	13258	1-Ph	6.78
		13321	2,3-Cl	25.78			
		13309	1,3-Br	27.21			



ID	Group	IC <sub>50</sub> (μM)	ID	R	IC <sub>50</sub> (μM)
13127	X=C, Y=N	0.60	<b>13163</b>	-	<b>0.31</b>
13166	X=C, Y=N, R <sub>1</sub> R <sub>2</sub> =Me	1.69	13164	Me	0.43
13167	X=N, Y=C, R <sub>2</sub> =NO	1.91			
13221	X=N, Y=N	>25			

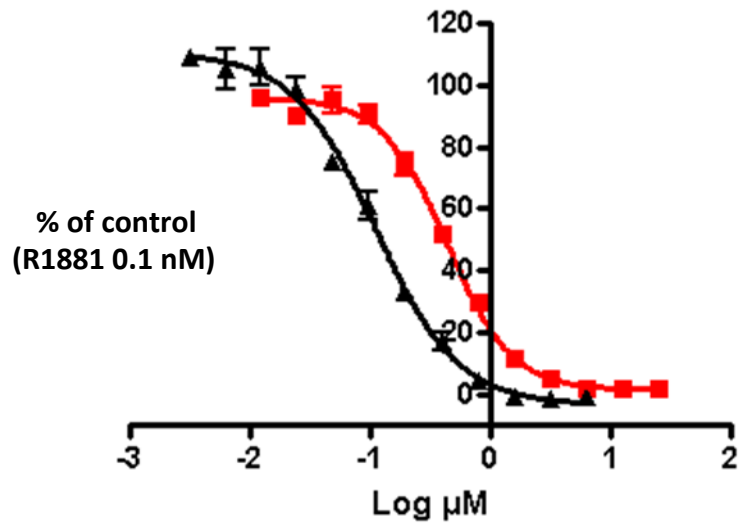
\*Munuganti RS *et al*, J Med Chem, **2013**, 56, 1136

# Binding Pose of 13163

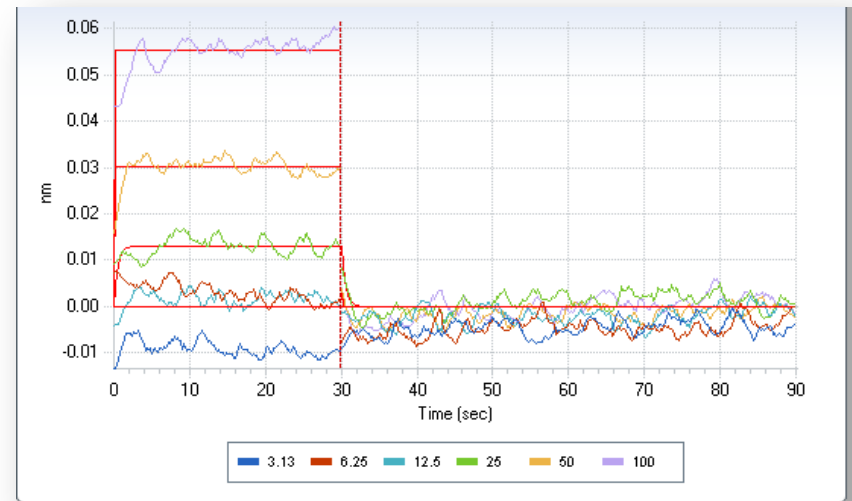


# *In vitro* characterization of 13163

Inhibition of AR  
translational activity



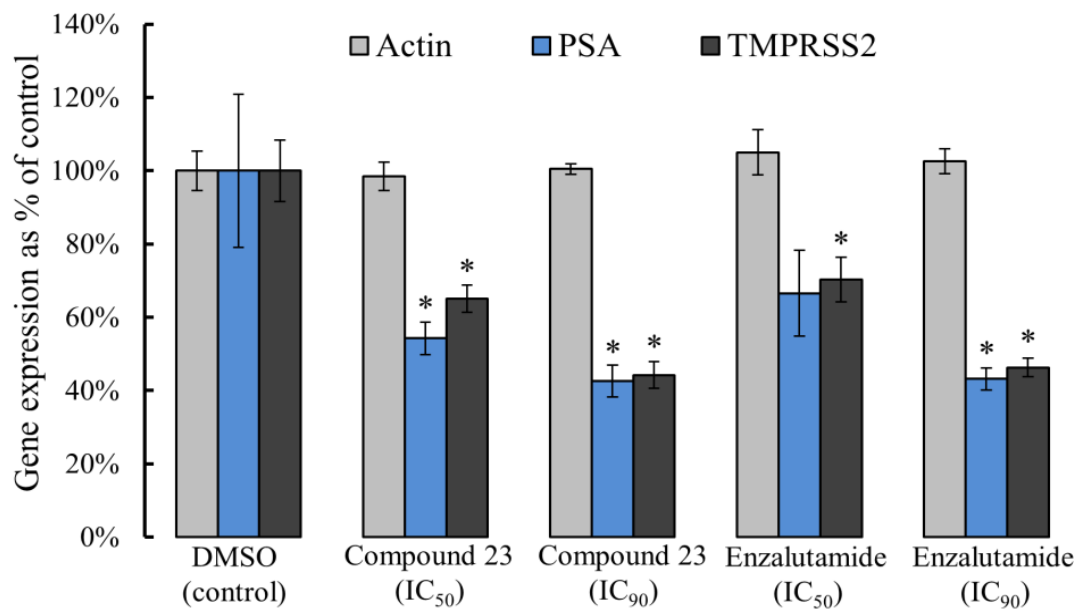
Binding of 13163 to AR LBD



AR eGFP  $\text{IC}_{50}$

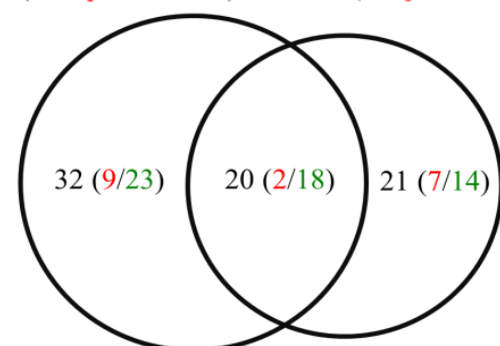
**13163:** 0.31  $\mu\text{M}$   
MDV3100: 0.090  $\mu\text{M}$

# Vpc13163(CMP23 on the chart) and Enzalutamide affect different genes



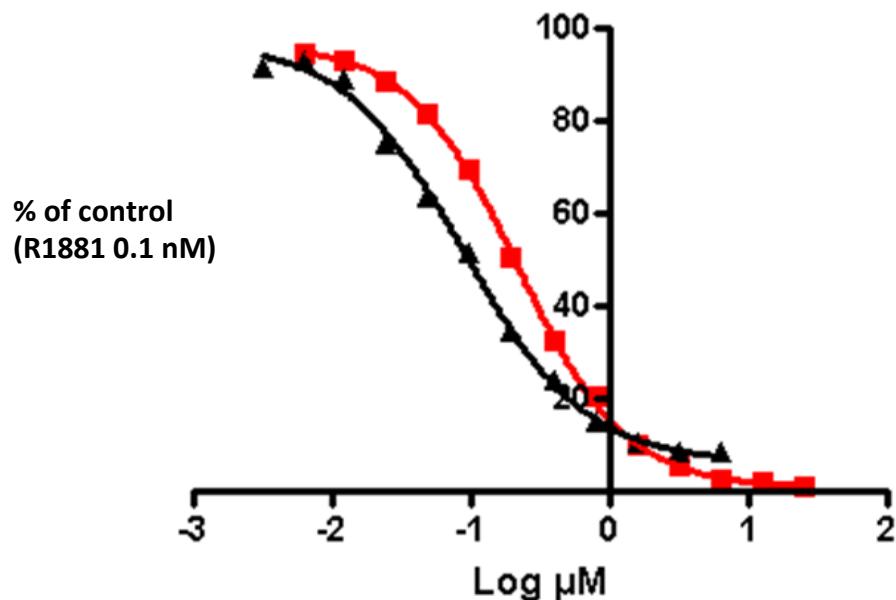
Compound 23 (IC<sub>90</sub>)  
52 (11 Up/ 41 Down)

Enzalutamide (IC<sub>90</sub>)  
41 (9 Up/ 32 Down)



# Effect of 13163 on PSA Secretion in LNCaP and Enzalutamide resistant cell line

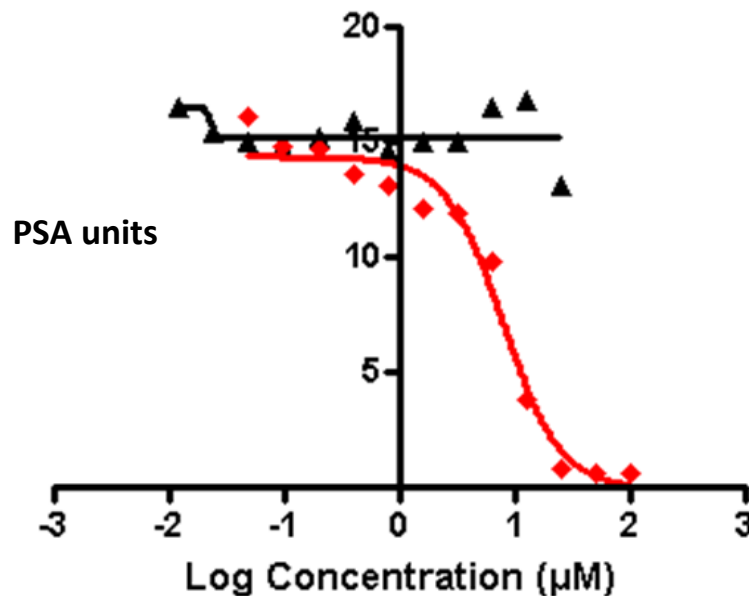
LNCaP



13163:  
Enza:

0.216  $\mu\text{M}$   
0.090  $\mu\text{M}$

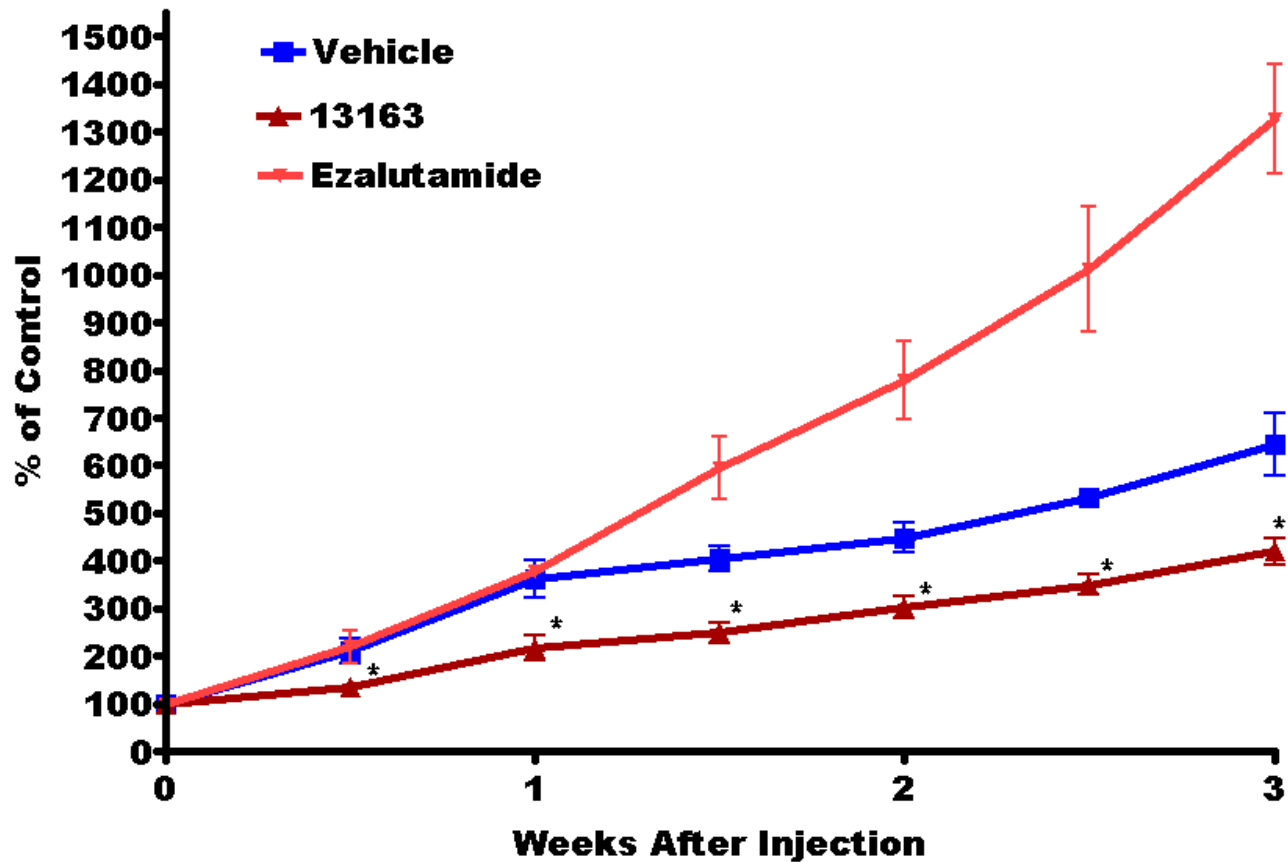
MR49F cell line



13163:  
Enza:

7.031  $\mu\text{M}$   
Inactive

# Effect of 13163 in Enzalutamide Resistant Mouse Model (tumor volume)



# CONCLUSIONS

**Hubs PPI represent attractive drug targets,**  
associated with lower chances of resistance development  
(example 1)

such PPI inhibitors also help overcoming existing resistance  
(example 2)





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, Ravi Munuganti, Huifang Li  
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