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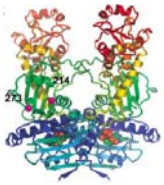
Integrated Information
Speeding Drug Discovery

HSP90 Ligands Chemical Diversity of Known Molecules and Discovery of New Potential Hits by Virtual Screening

ChemAxon

ChemAxon 2008 European User Group Meeting
May 7th and 8th, 2008, Visegrad, Hungary

Davide Audisio



Heat Shock Protein 90

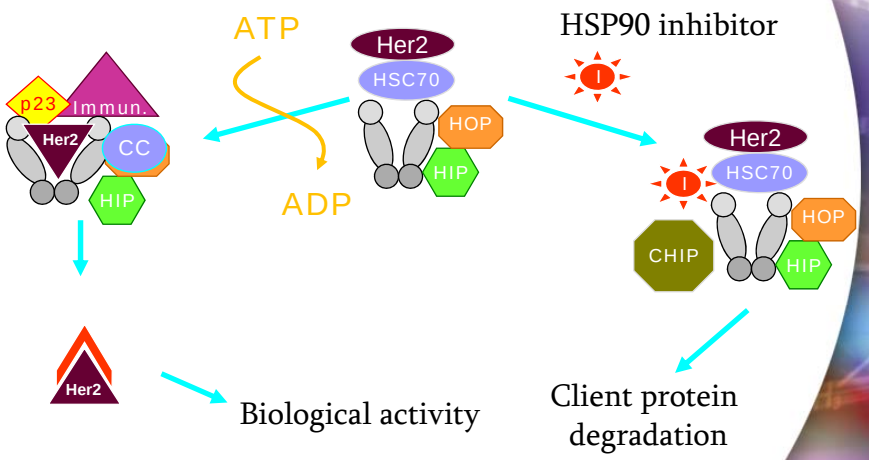
✓ Molecular chaperone responsible for folding, stability and function of « client » proteins involved in the developement and progression of cancer

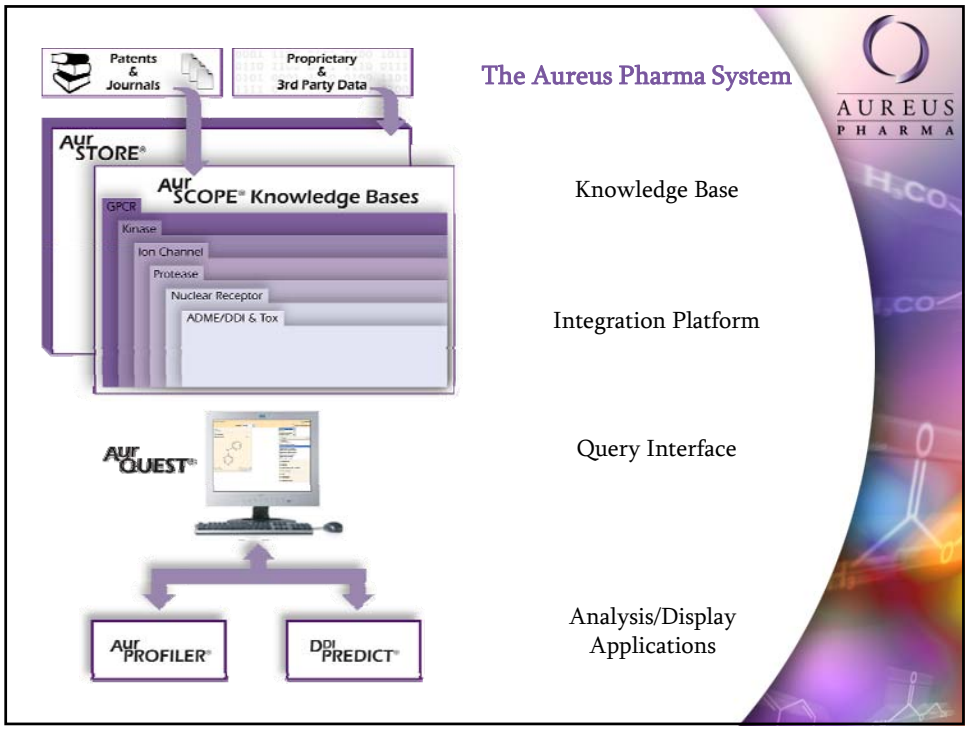
✓ Function is regulated by ATP binding pockets in the C- and N-terminal regions of the protein

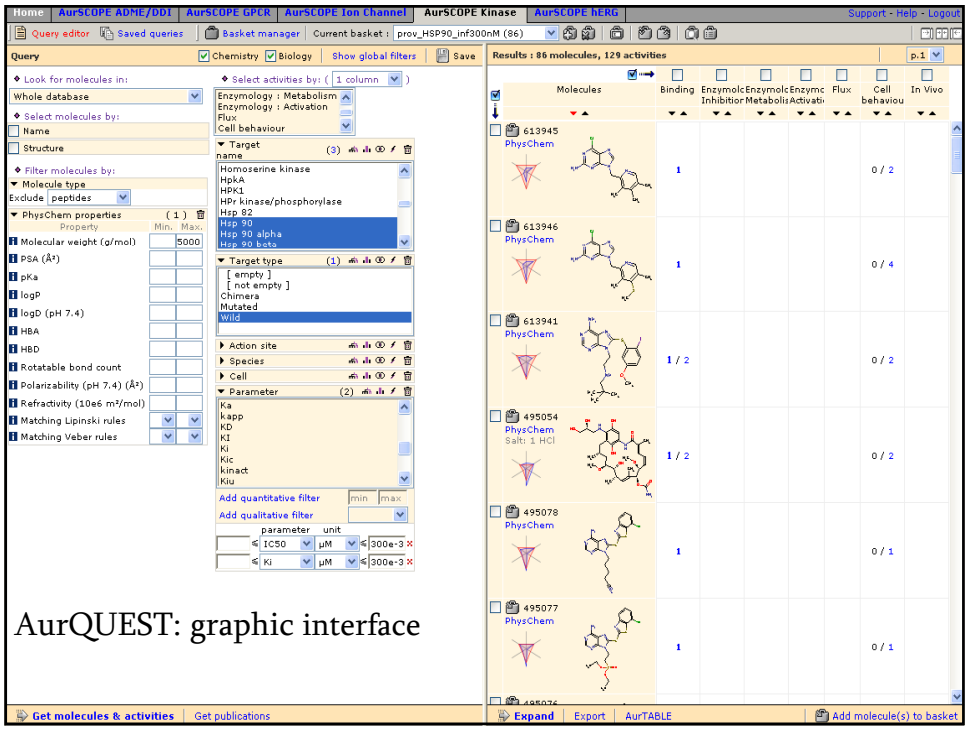
✓ Inhibition of HSP90 leads to degradation of client proteins and subsequently cell growth arrest and apoptosis in cancer cells

HSP90 → Exciting Target for Cancer Therapy

HSP90 : activity and inhibition





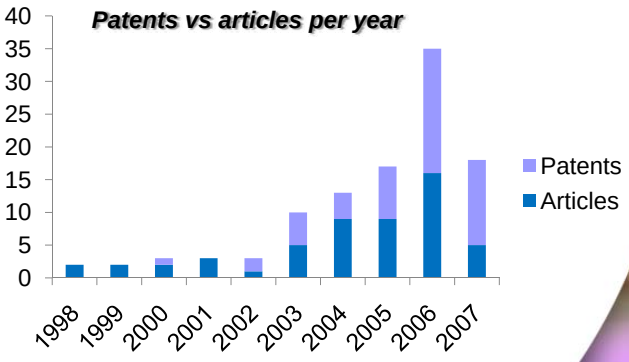


AurQUEST: graphic interface

HSP90 Knowledgebase content

March 2008 release

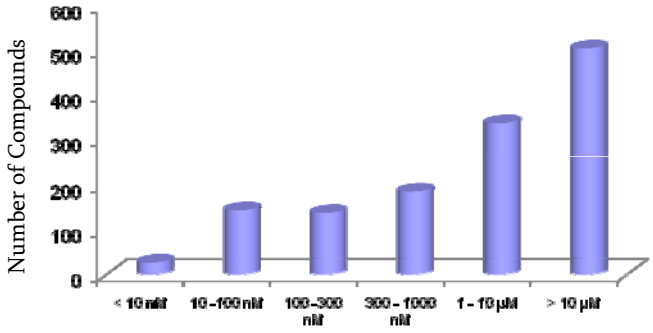
- 106 documents (54 articles & 52 patents)
- 1 576 compounds
- 2 907 Biological Activities



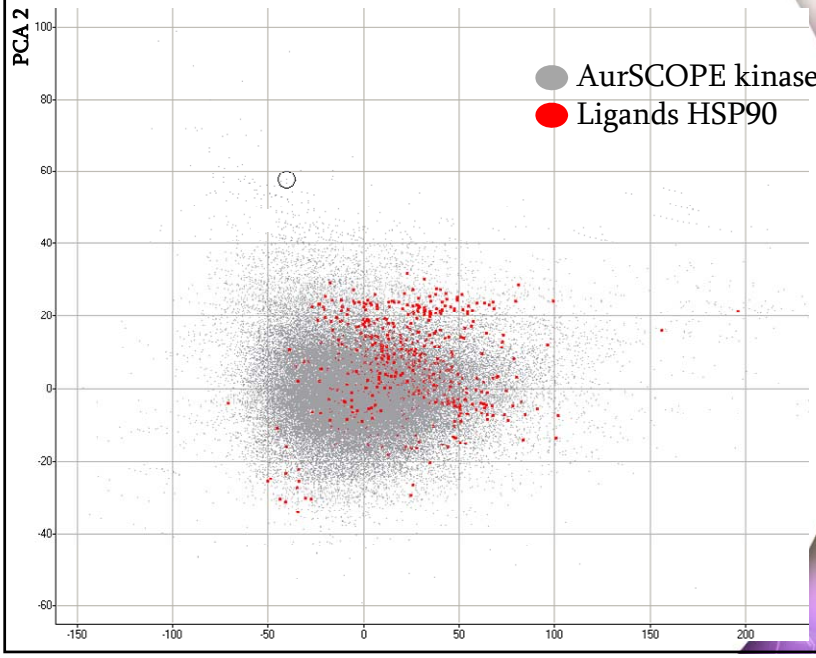
Activity Distribution

2 305 IC_{50}s for 1 203 compounds

- 361 < 100 nM (150 cpds)
- 454 > 100 nM & < 1 µM (265 cpds)
- 1 208 > 1 µM (720 cpds)



Chemical Diversity



Chemical diversity of HSP90 inhibitors

- Creation of molecule sets with different thresholds :
  IC_{50} < 300 nM (actives compounds)
  IC_{50} > 80 µM (inactive compounds)
  AurQUEST

- 2D molecular descriptors calculation
  Calculator Module

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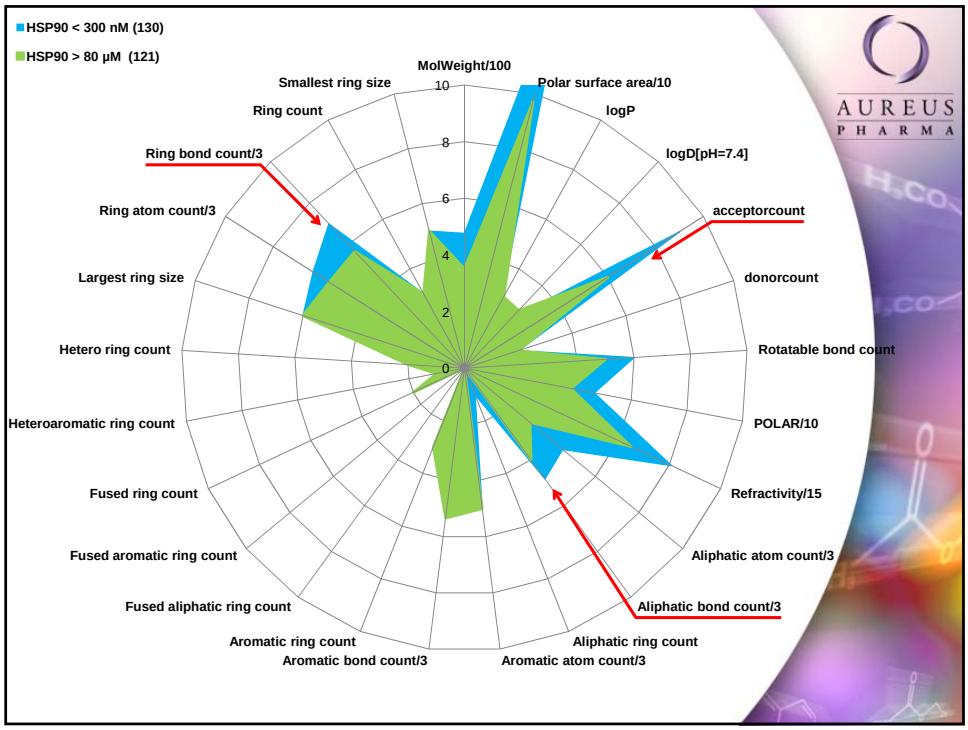
- Radar graphical representation


HSP90 < 300 nM (130)
HSP90 > 80 µM (121)
MolWeight/100
Polar surface area/10
logP
logD[pH=7.4]
acceptorcount
donorcount
Rotatable bond count
POLAR/10
Refractivity/15
Aliphatic atom count/3
Aliphatic bond count/3
Aliphatic ring count
Aromatic atom count/3
Aromatic bond count/3
Aromatic ring count
Fused aliphatic ring count
Fused aromatic ring count
Fused ring count
Heteroaromatic ring count
Hetero ring count
Largest ring size
Ring atom count/3
Ring bond count/3
Ring count
Smallest ring size
0
2
4
6
8
10
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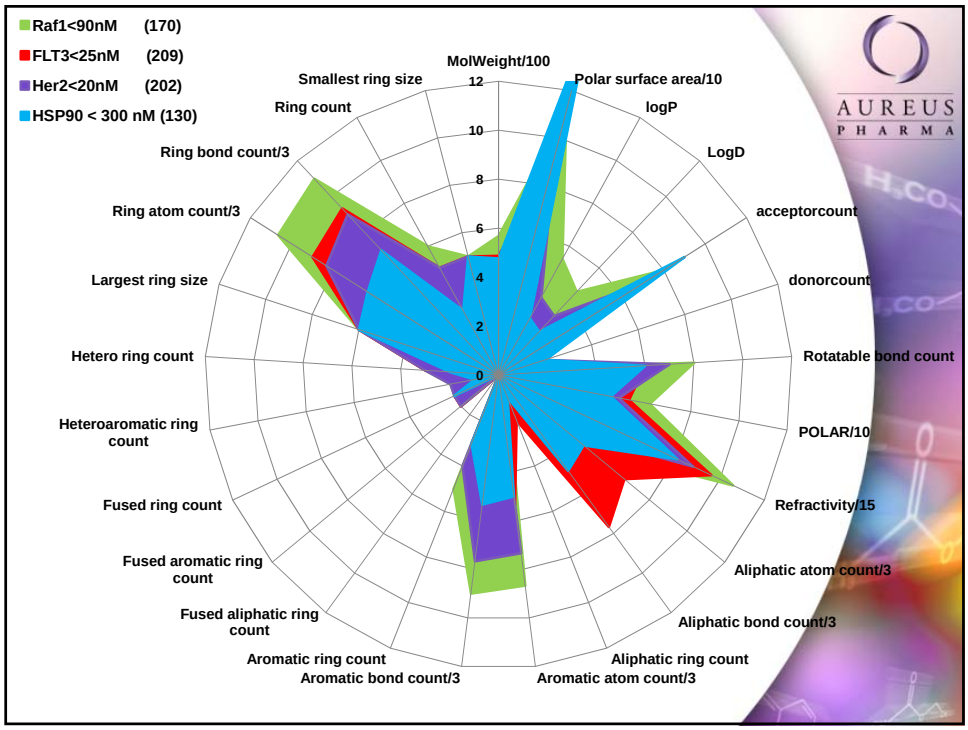
Raf1<90nM (170)
FLT3<25nM (209)
Her2<20nM (202)
HSP90 < 300 nM (130)
MolWeight/100
Polar surface area/10
logP
LogD
acceptorcount
donorcount
Rotatable bond count
POLAR/10
Refractivity/15
Aliphatic atom count/3
Aliphatic bond count/3
Aliphatic ring count
Aromatic atom count/3
Aromatic bond count/3
Aromatic ring count
Fused aliphatic ring count
Fused aromatic ring count
Fused ring count
Heteroaromatic ring count
Hetero ring count
Largest ring size
Ring atom count/3
Ring bond count/3
Ring count
Smallest ring size
0
2
4
6
8
10
12
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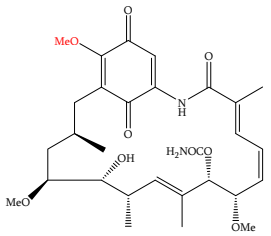
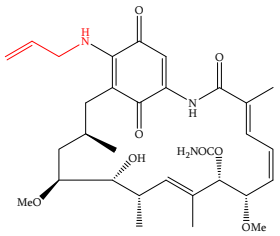
Ligand families chemical diversity

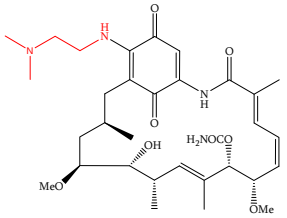
1. Geldanamycine-derived inhibitors :
   IC_{50} < 300 nM



Geldanamycine



17 - AAG



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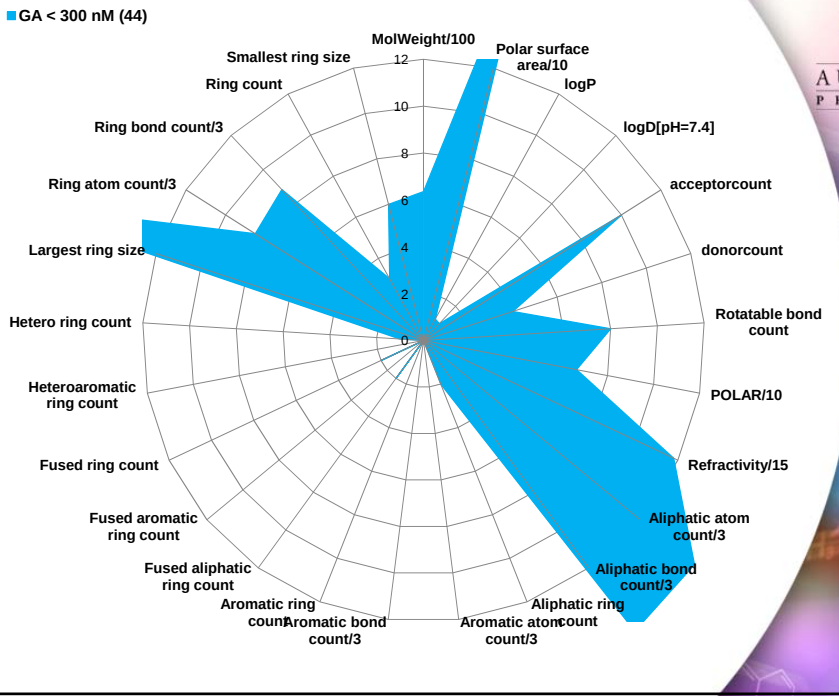
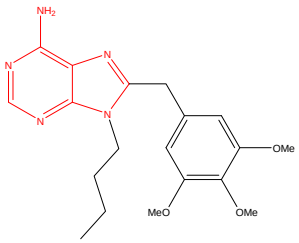
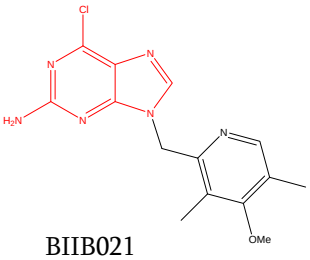


Ligand families chemical diversity

2. **Purine-like family inhibitors :**
   IC_{50} < 1 µM



PU3



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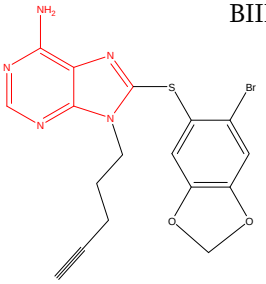
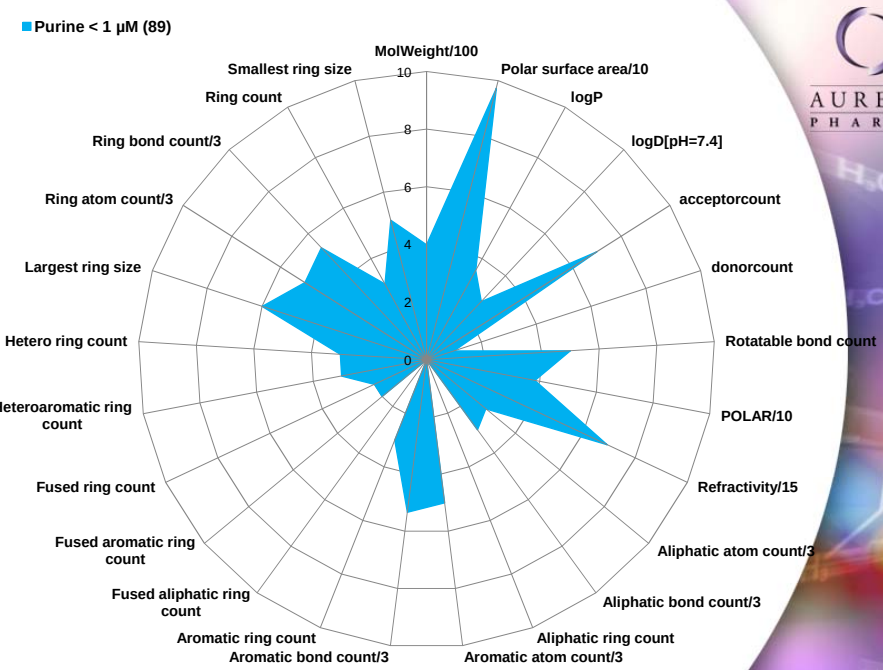
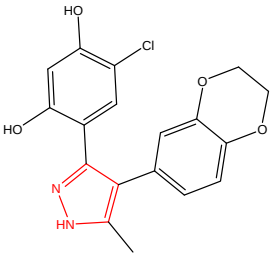


PU - H58



Ligand families chemical diversity

3. Diarylpyrazoles-family inhibitors : IC_{50} < 10 µM



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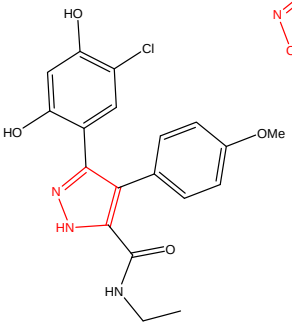
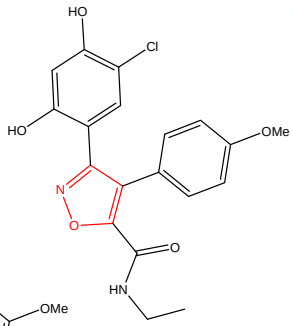
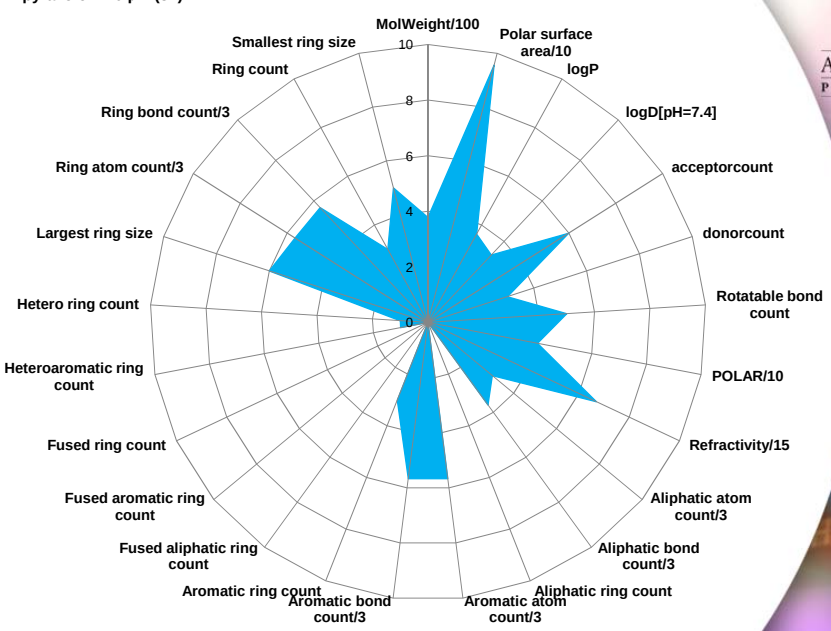


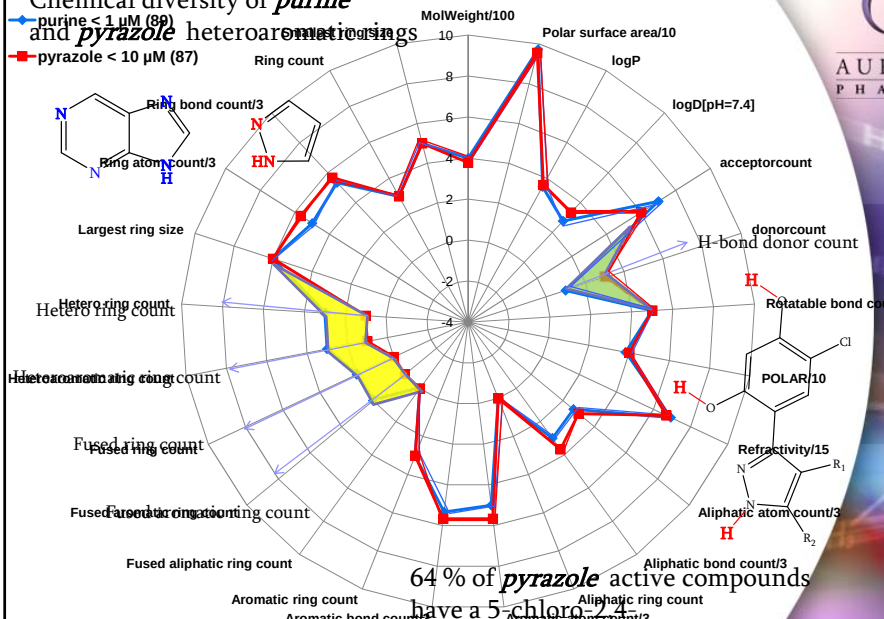
VER-49009



VER-50589

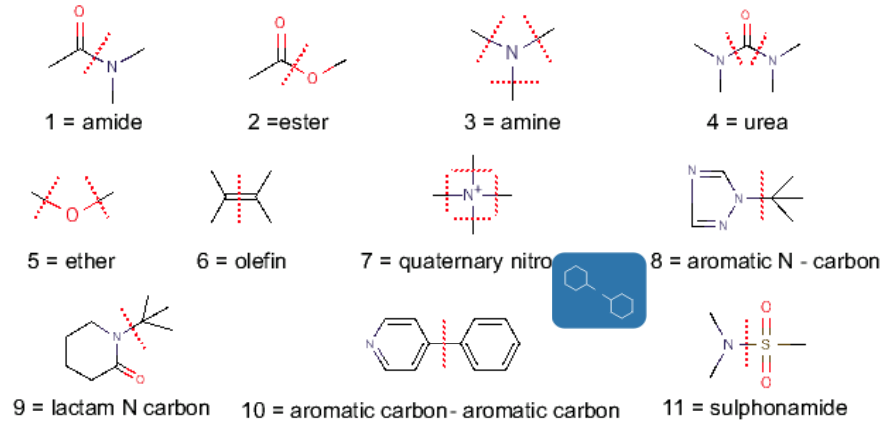


Chemical diversity of ***purine*** and ***pyrazole*** heteroaromatic rings

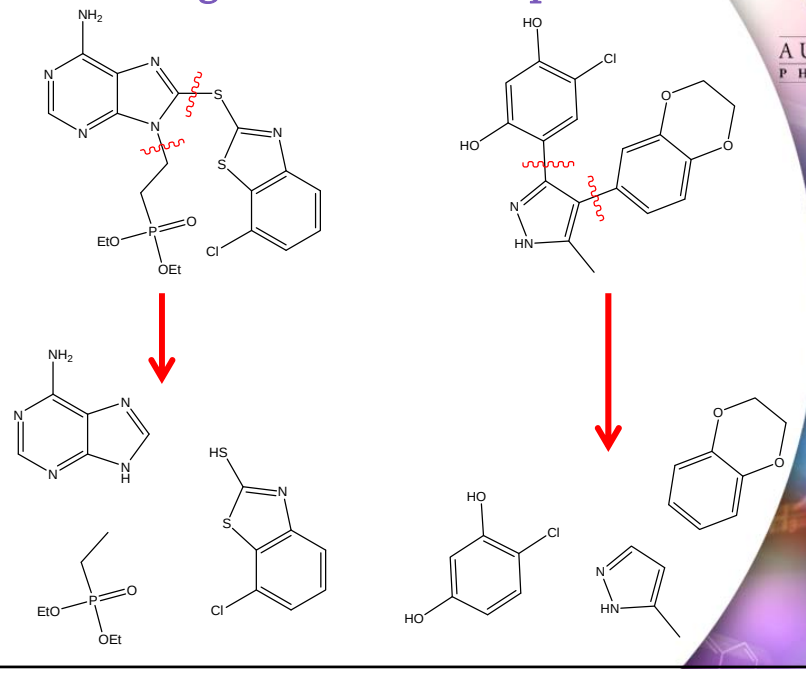


64 % of ***pyrazole*** active compounds have a 5-chloro-2,4-dihydroxyphenyl substituent

Chemical fragmentation : understanding the HSP90 target space

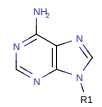
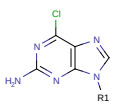
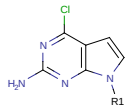
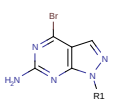
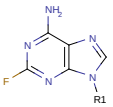
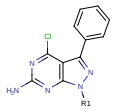
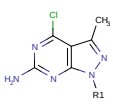
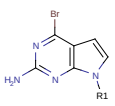
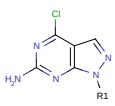
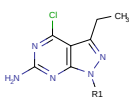
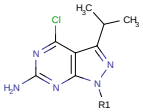
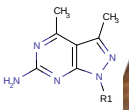


Fragmentation : examples



Purine-like family :

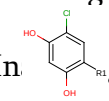
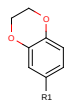
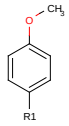
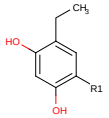
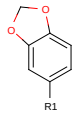
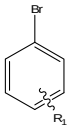
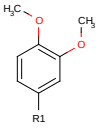
• Occurance of purine-like scaffold (IC_{50} < 1 µM) :

	33		13		7		6
	6		5		4		3
	3		2		1		1

Diarylpyrazole family :

✓ Active group (IC_{50} < 10 µM)

✓ Inactive group (IC_{50} > 30 µM)

N°	Fragment	Active	Inactive	N°	Fragment	Active	Inactive
A		64%	34%	E		6%	23%
B		29%	11%	F		5%	4%
C		8%	4%	G		3%	3%
D		7%	4%	H		3%	3%

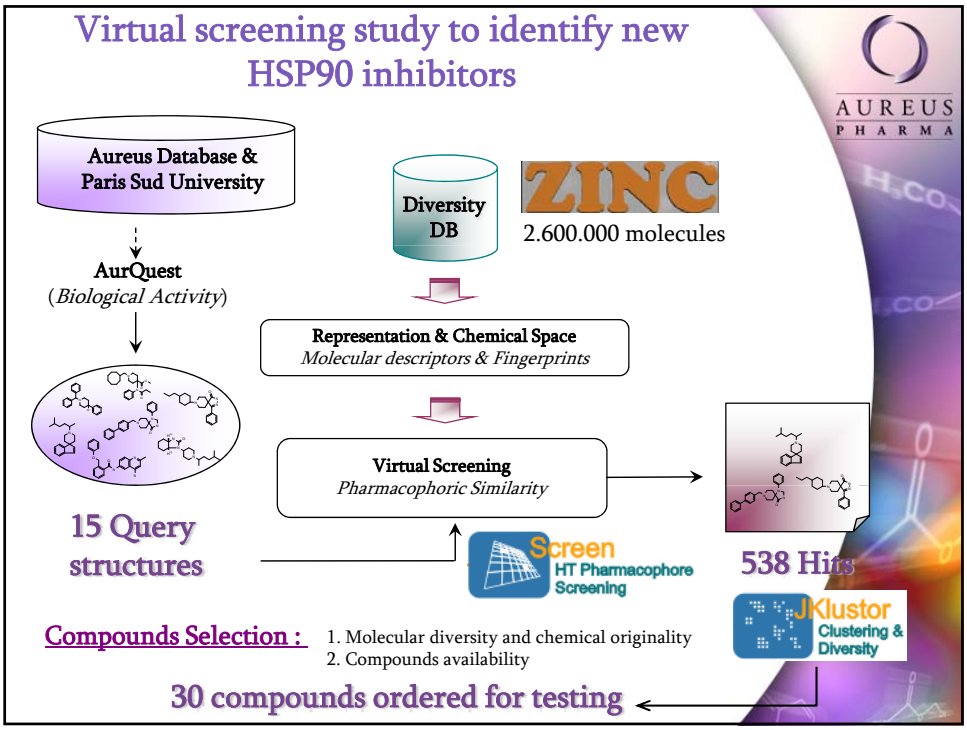
Chemical database searching :
looking for novel drug leads

✓Apply analysis output in an experimental strategy

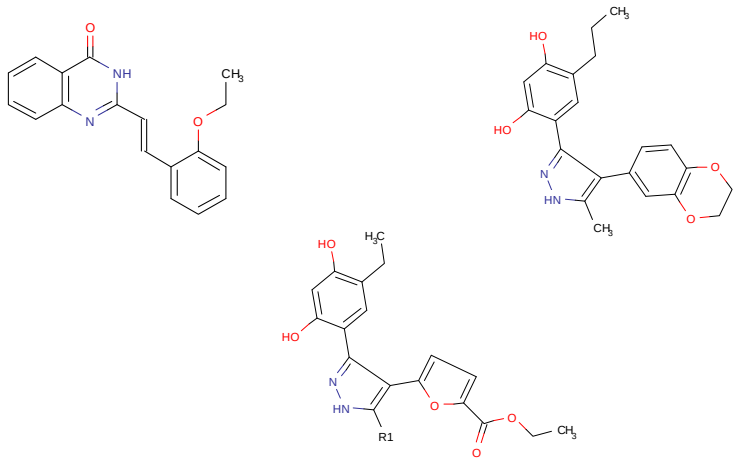
✓ Use the HSP90 knowledge database for drug discovery

Ligand Based Virtual Screening

Virtual screening study to identify new HSP90 inhibitors

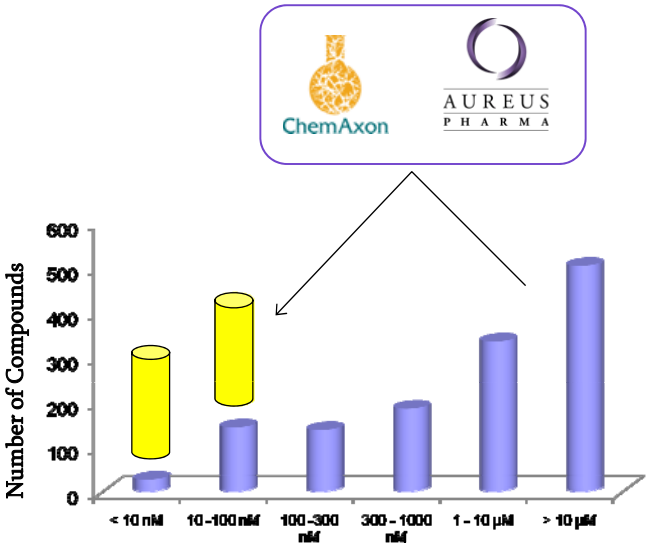


Identified Virtual Screening hits already known as HSP90 inhibitors :



Park et al. Bioorg.Med.Chem.Lett. 17 (2007) 6345-6349
Workman et al. Bioorg.Med.Chem.Lett. 15 (2005) 3338 – 3343
WO 03/055860 (2003) P. Workman,

Conclusions :



Activity distribution of HSP90 ligands

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