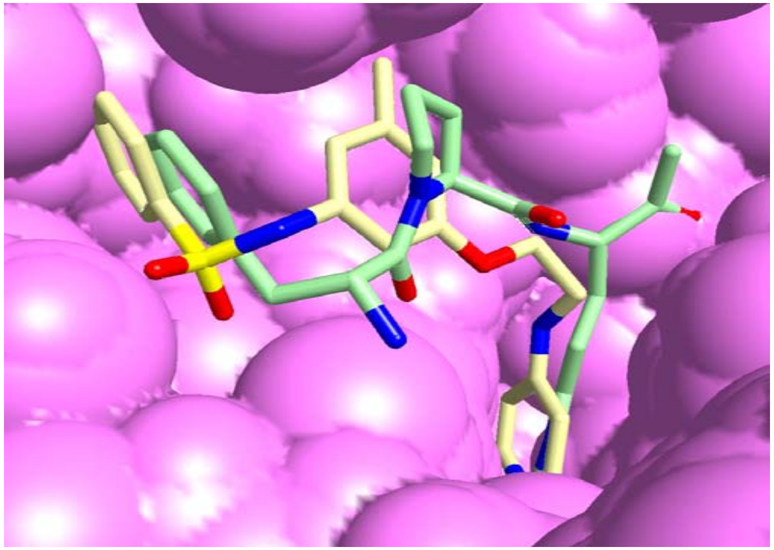
Where it all started

MGMS
25 Years

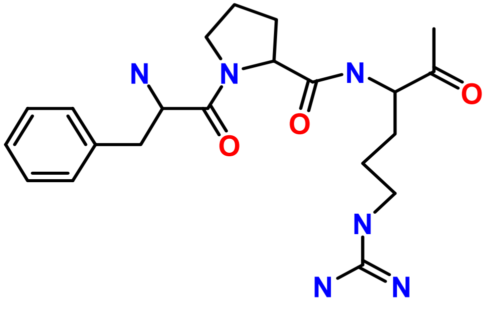
Balls Park
Hertford

Defining SIMILARITY for Structural Diversity

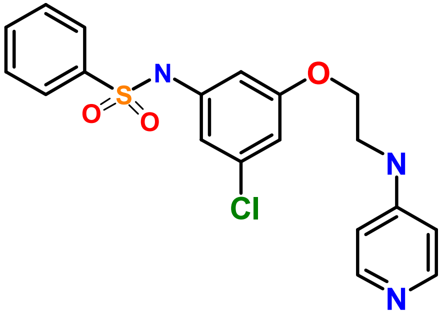
Structurally different molecules can bind at the same protein site and create the same biological response



THROMBIN ACTIVE SITE



PEPTIDE



NON-PEPTIDE

- What makes these compounds look the same to the protein?

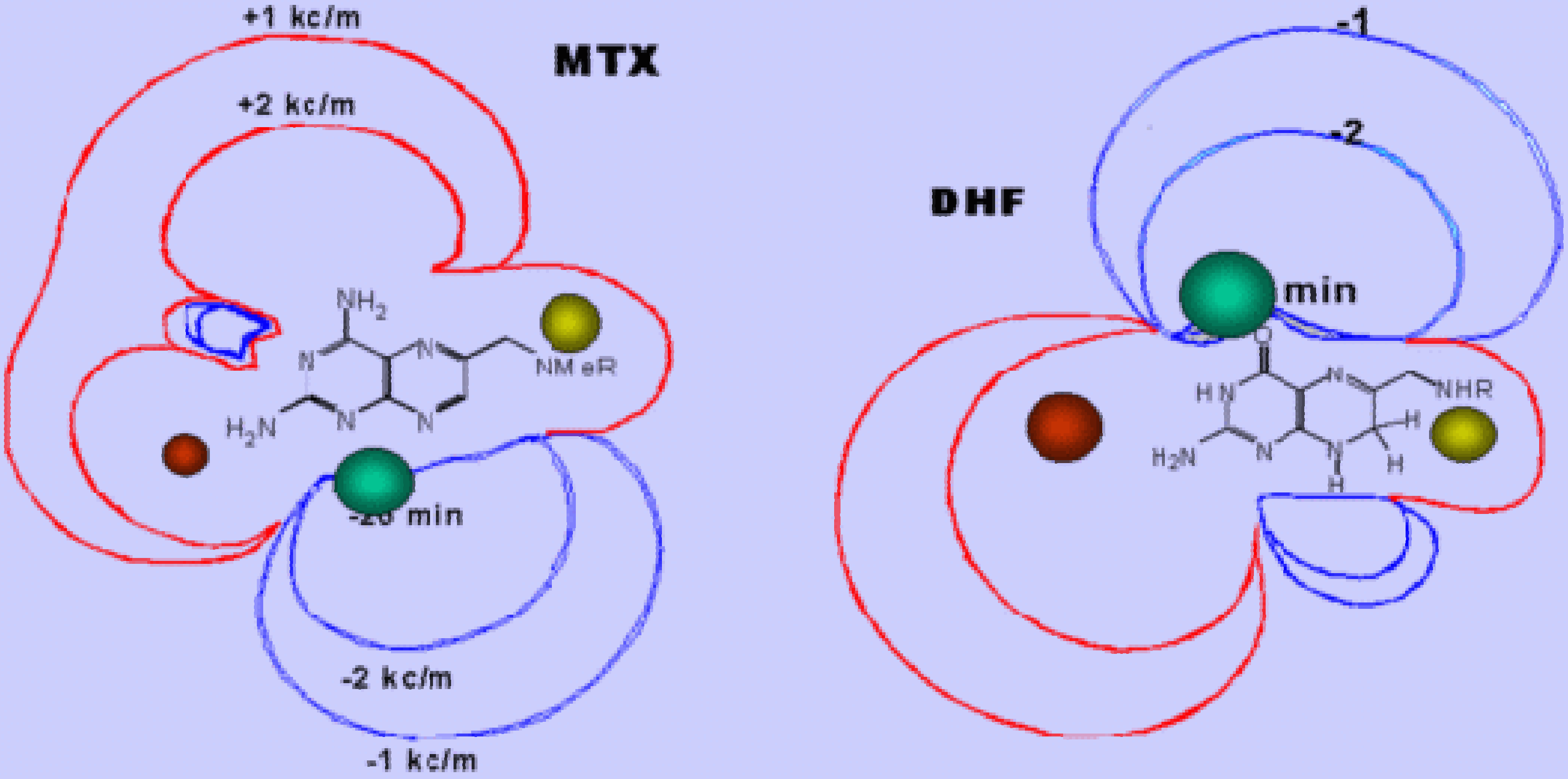
  If it cannot be their atom and bond structure

  Can we find Similarity Beyond the Molecular Structure?

Early observations that MEP maxima and minima might help

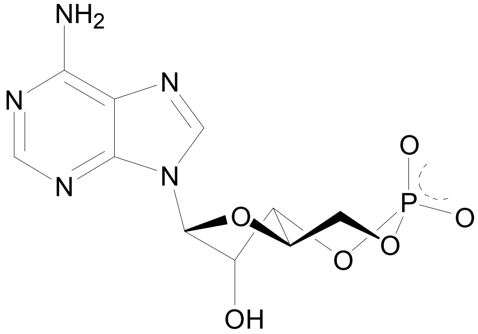
Early Hint that the MEP might be Useful

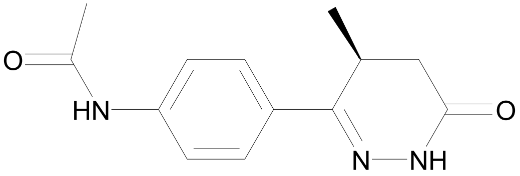
Distillation of Field Contours to Manageable Field Extrema

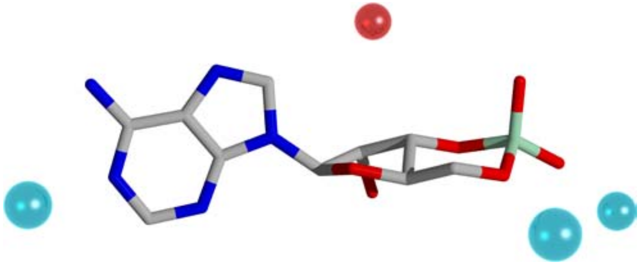


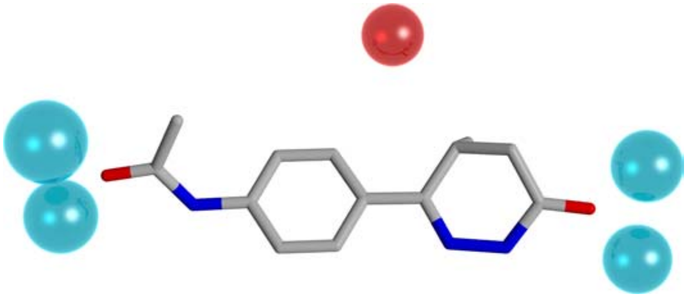
Wellcome Foundation (1980) unpublished

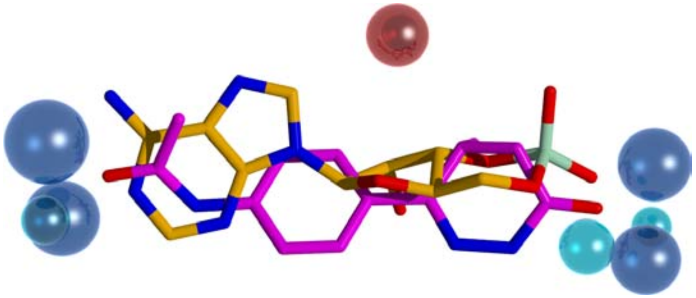
Early PDE III Modelling with MEP Extrema







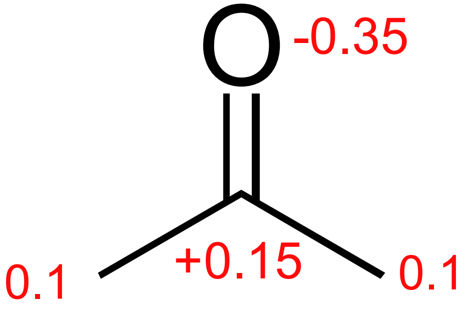




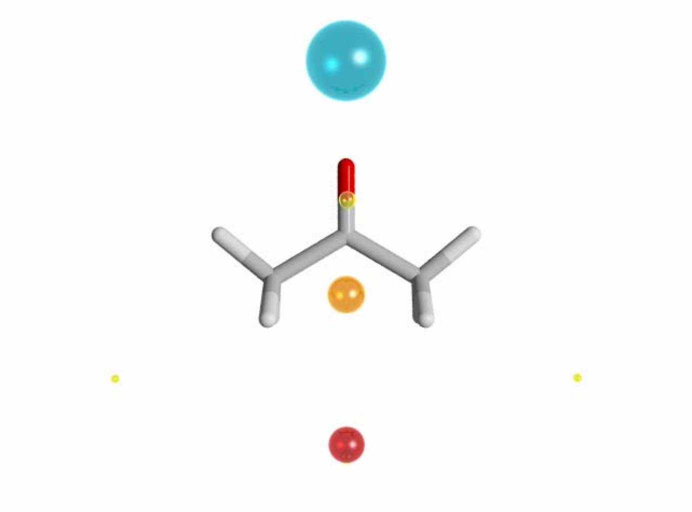
A Davis, B Warrington and J G Vinter,(1987)
Strategies in Drug Design II- Modelling studies on phosphodiesterase substrates and inhibitors
J Comp-Aid Mol Design, 1, 97-120

Accepted Electrostatic Models Get Unintuitive MEP Extrema

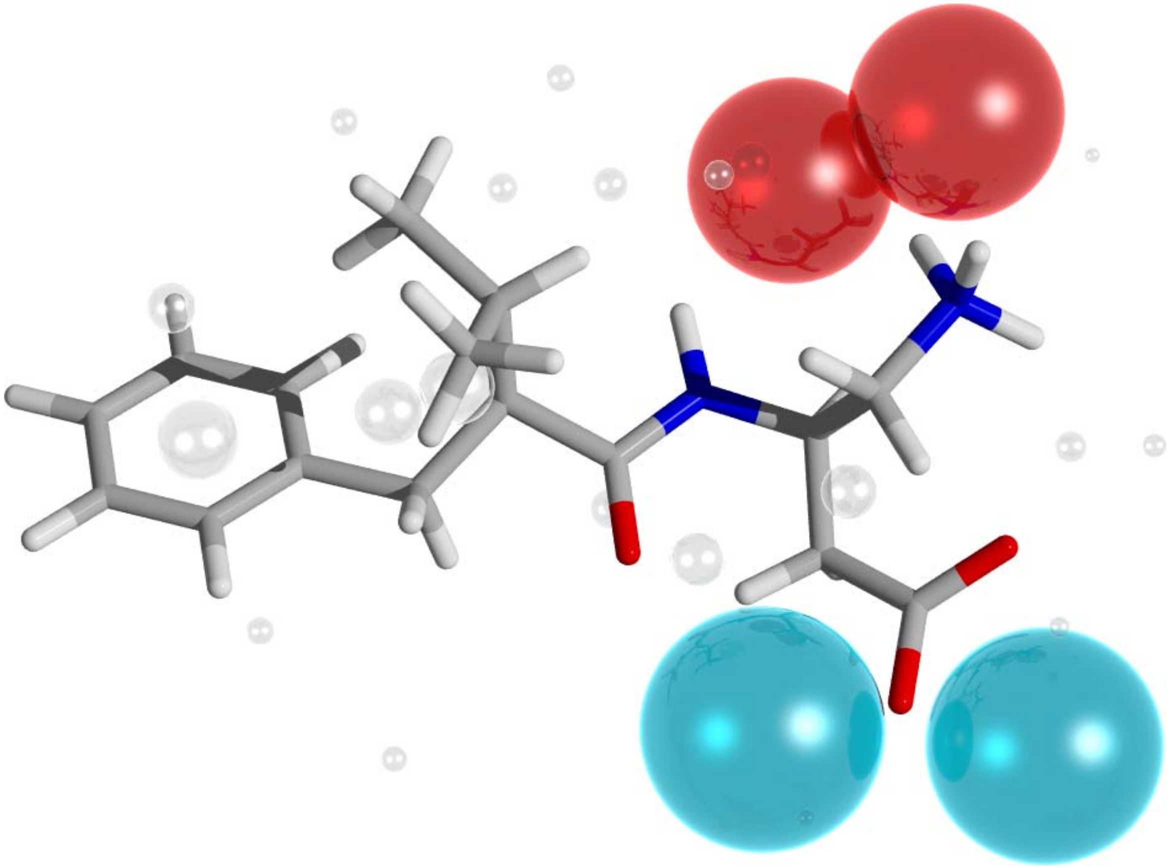
Atom-centred
charges (ACCs)

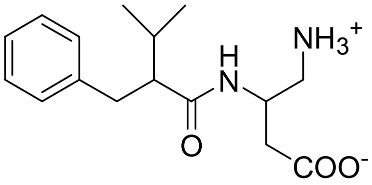


Fields from
ACC's



The ACC Electrostatic Model gives Unintuitive MEP Extrema





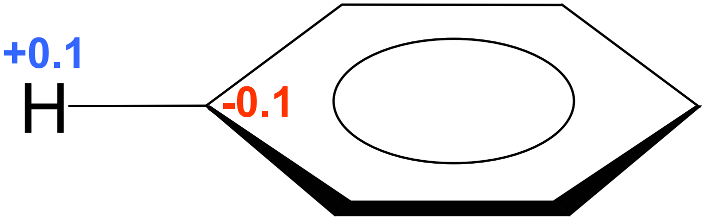
……so

Can the quality of MEP Extrema be improved with a new Molecular Mechanics FORCE FIELD with better electrostatic descriptors?

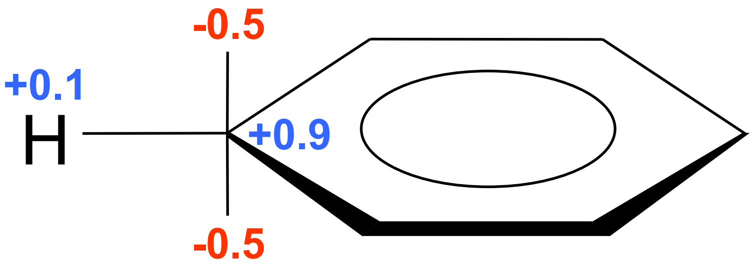
Extending π Electrons Away from the Nucleus

Would the description of electrostatics be improved?

ACCs



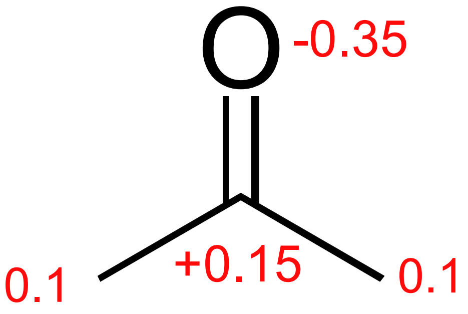
XEDs

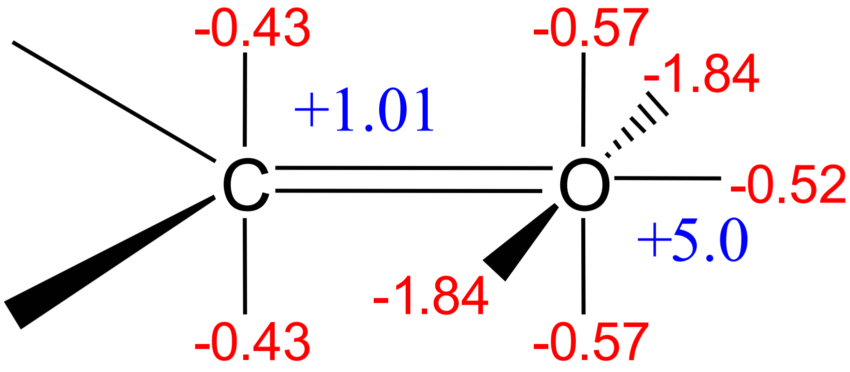


C. A. Hunter, J. K. M. Sanders, (1990)
The nature of π-π interactions
J. Am. Chem. Soc. 1990, **112**, 5525-5534

e**X**tended **E**lectron **D**istributions

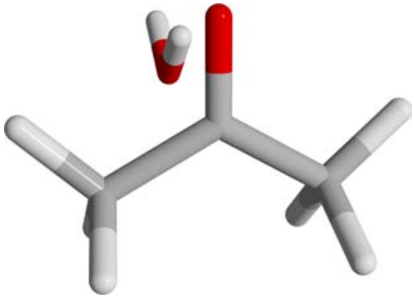
The XED patterns reflect the electron arrangement of an atom and combine to form integrated π networks. Each XED has its own set of force field parameters.


ACCs

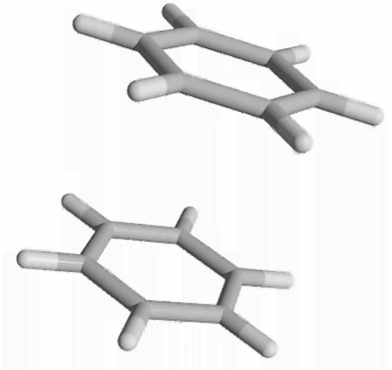

XEDs

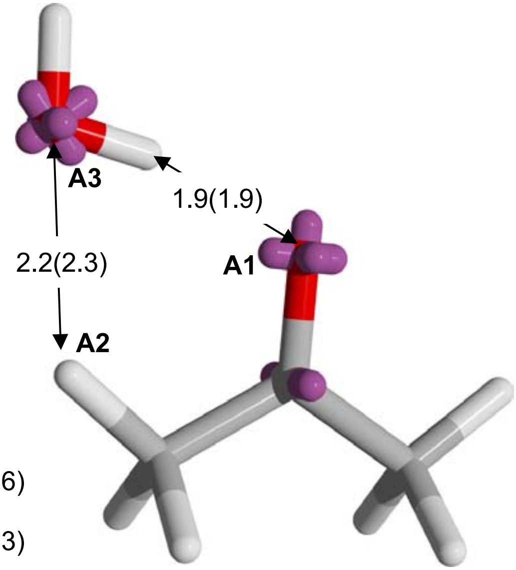
J. G. Vinter, (1994)
Extended electron distributions applied to the molecular mechanics of intermolecular interactions
J Comp-Aid Mol Design, **8**, 653-668

Intermolecular Interactions

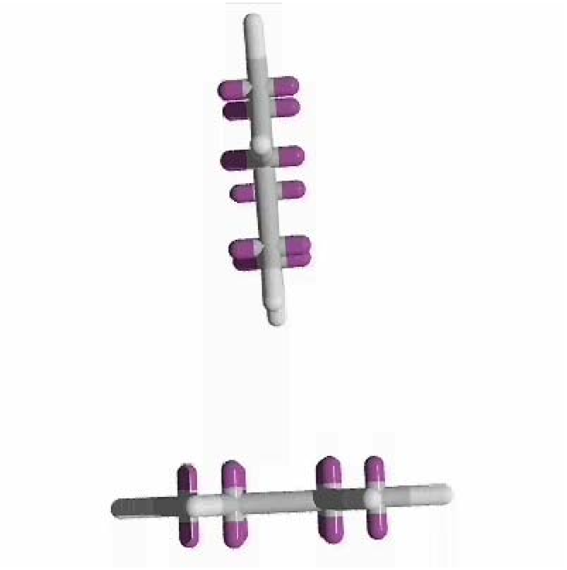


ACCs





XEDs



A1=114(116)

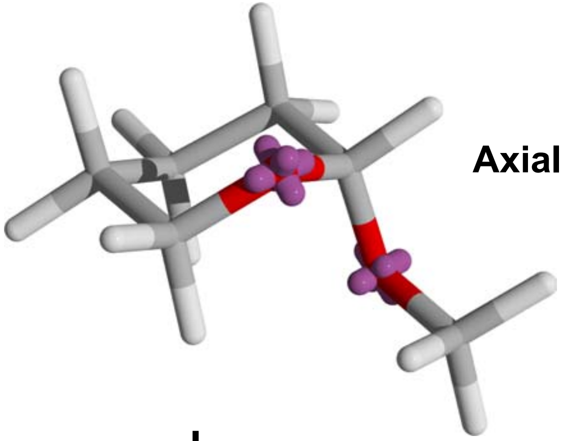
A2=137(143)

A3=74(69)

X K Zhang *et al* (1992) Science **257** 942

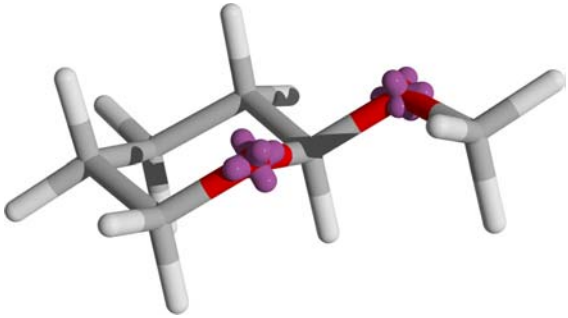
Intramolecular Interactions

The Anomeric Effect

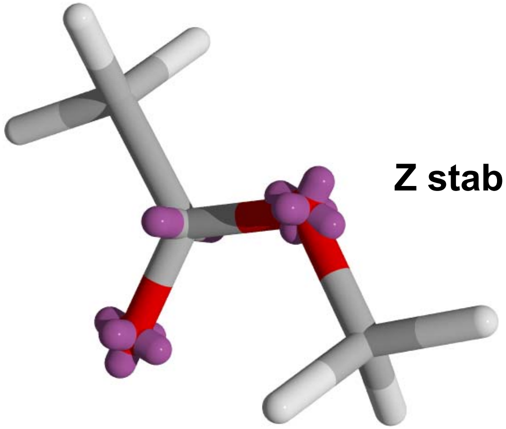


Axial stable

XED	**EXP**	ACC
1.4	**1.1**	0.2

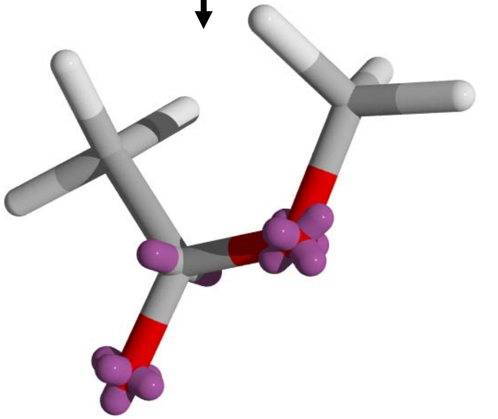


The E-Z Barrier



Z stable

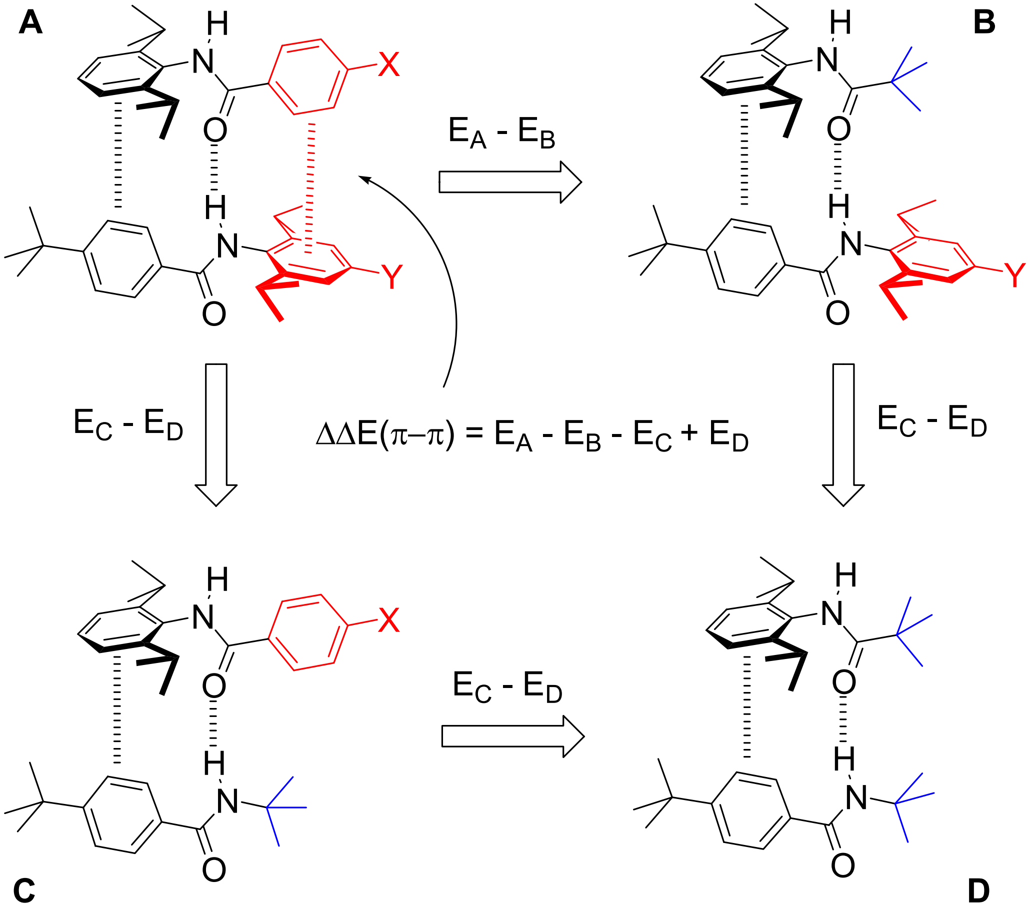
XED	**EXP**	ACC
8.3	**8.5**	3.7



K Gundertofte *et al* (1996) J Comp Chem **17** 429-449

Measuring the Ar/Ar Binding Energy of ‘Hunter Zippers’

using Double-mutant Cycles

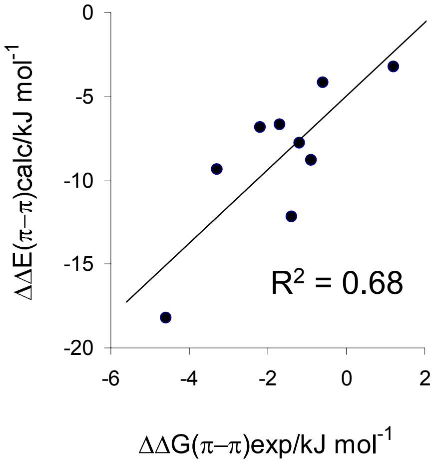


$$\Delta\Delta E(\pi\text{–}\pi) = E_A - E_B - E_C + E_D$$

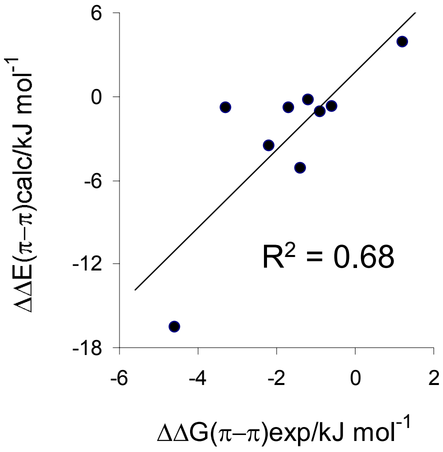
G. Chessari, C. A. Hunter, C. M. R. Low, M. J. Packer, J. G. Vinter and C. Zonta. (2002)
An Evaluation of Force Field Treatments of Aromatic Interactions
Chem. Eur. J., **8**, No 13, 2860-2867

Validation of the XED Force Field Interatomics

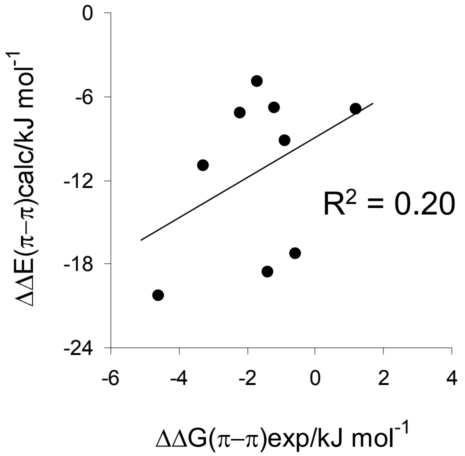
MM2



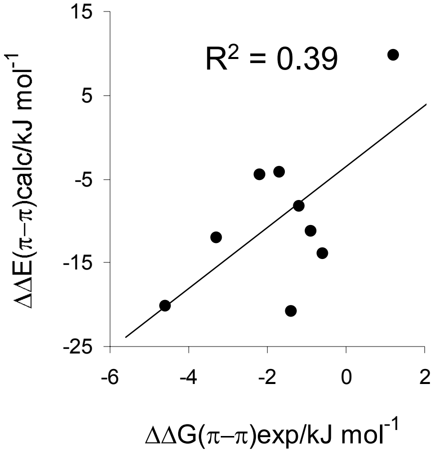
MM3

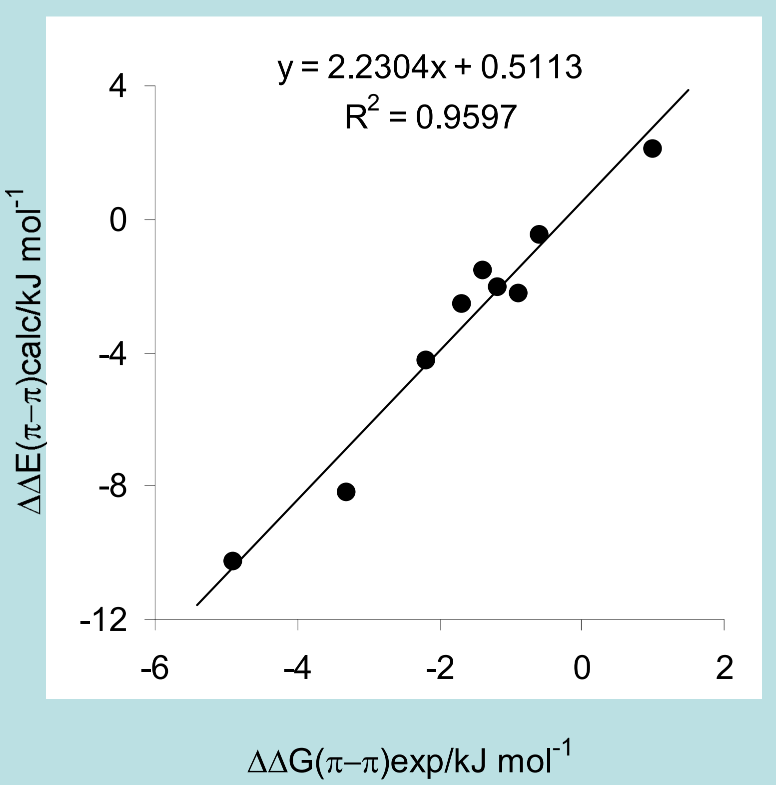


AMBER



OPLS

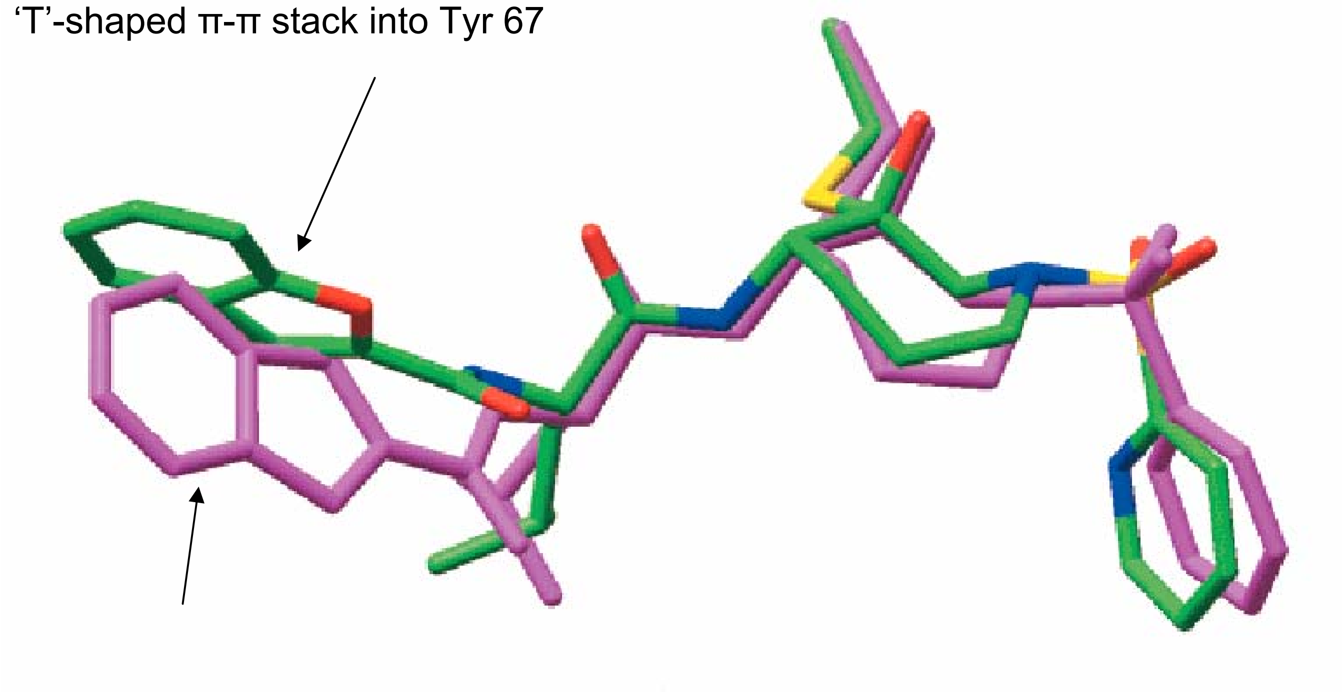




Aromatic - Aromatic Interactions

Cathepsin K inhibitors

X-ray binding data (green) indicating a
'T'-shaped π-π stack into Tyr 67



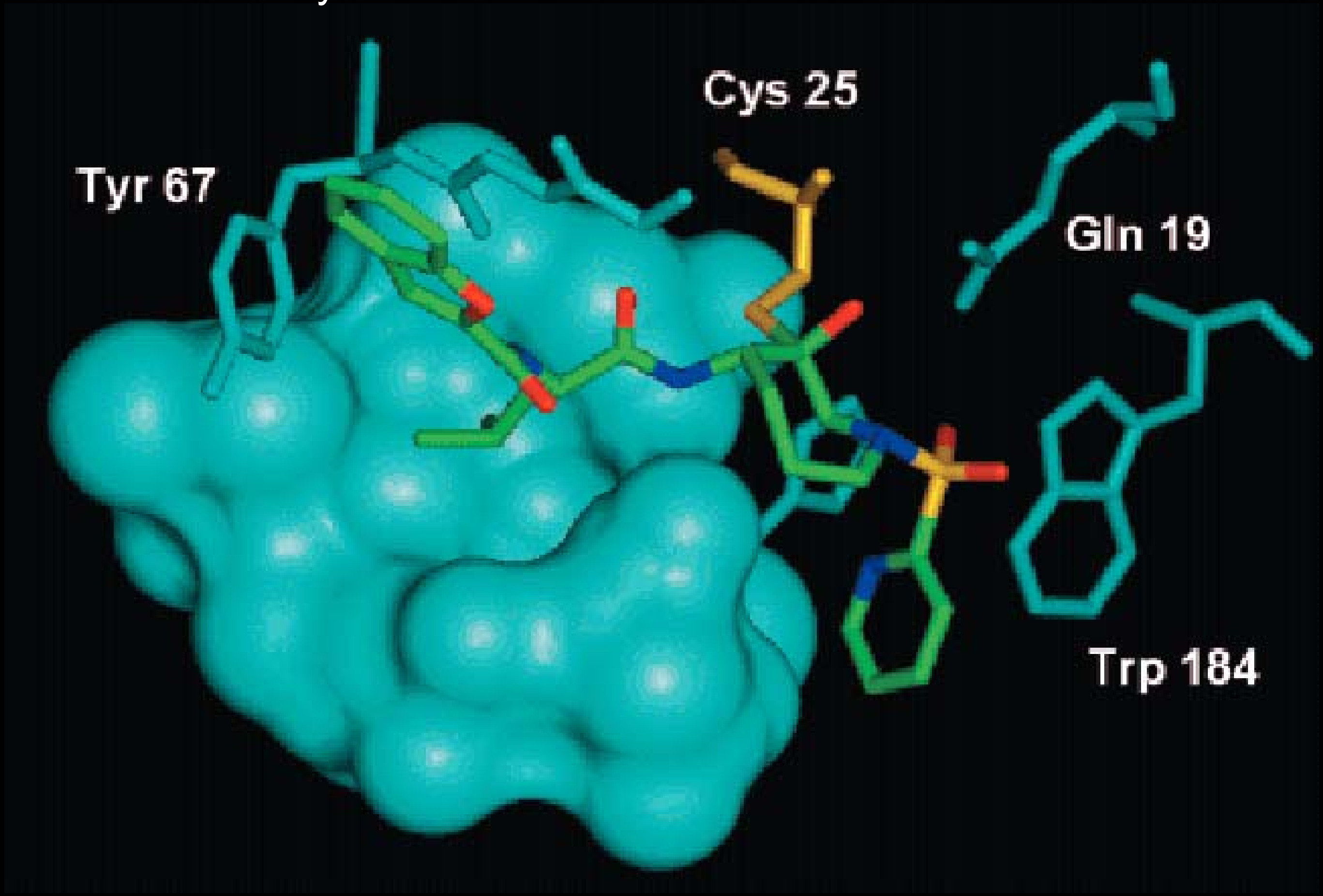
Predicted binding (magenta) mode, using the MMFF force field, preferred a parallel π-π stack
Parallel stacking is rarely found unless slanted and offset
T-stacking is common and slanted or at 90^o.

R. W. Marquis et. al. (2001)
Azepanone-Based Inhibitors of Human and Rat Cathepsin K
J Med Chem **44** (9) 1380-1395

Aromatic - Aromatic Interactions

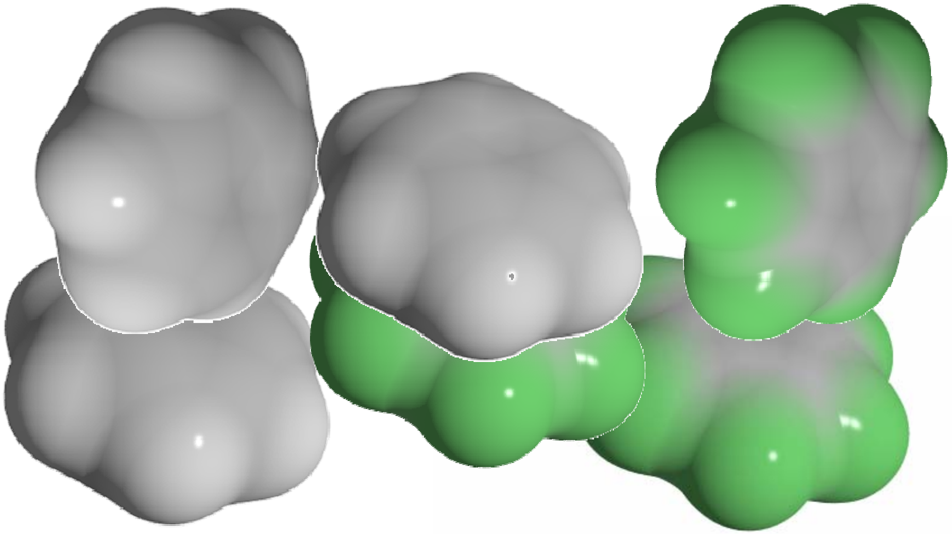
Cathepsin K inhibitors

X-ray binding data (green) showing the preferred 'T'-shaped π-π stack of the benzofuran into the face of Tyr 67



Aromatic - Aromatic Interactions

Fluorination

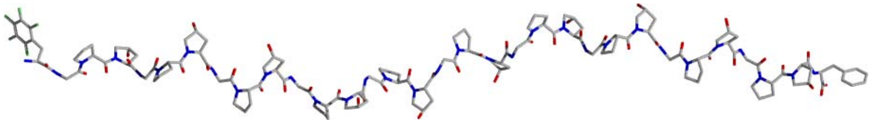


Method	Separation Ǻ	ΔE Kcal/mole
Experiment	3.4-3.6	~-7
XEDs	3.6	-5.6
ACCs	3.3	-4.2
CP-MP2/6-31G**	3.6	-3.7
HF/6-31G**	4.1	-1.5
AM1	4.7	-0.5
PM3	4.5	-0.5

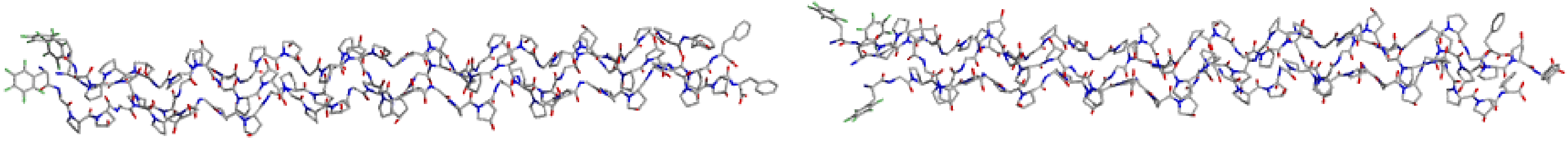
O. R. Lozman, R. J. Bushby, J. G. Vinter, (2001)
Complementary polytopic interactions (CPI) as revealed by molecular modelling using the XED force field
J. Chem. Soc. Perkin **2**, 9, 1446-1453

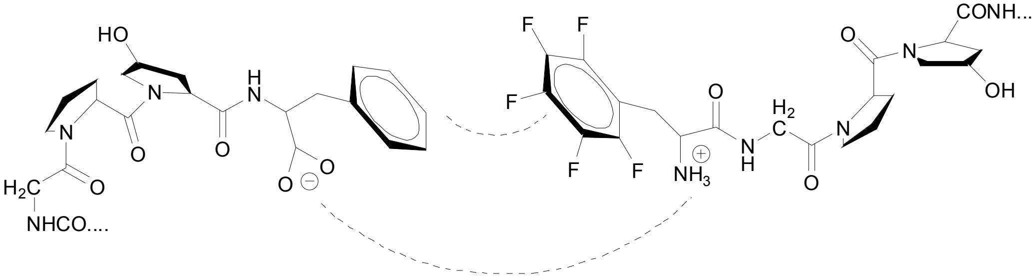
Aromatic - Aromatic Interactions

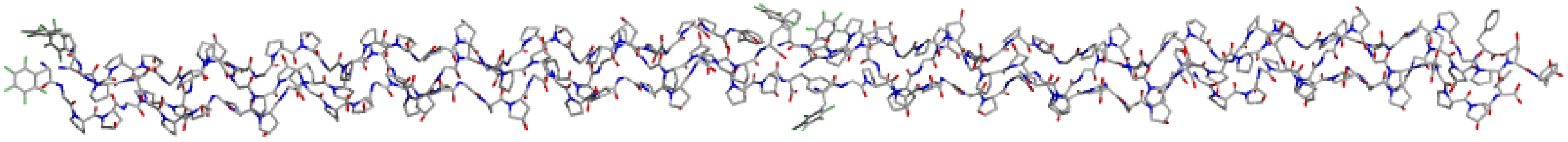
Fluorination



1 unit = 3 x 32mer (Gly-Pro-Hyp) triple helix







Final aggregation to fibres 7000nM long x 260nM wide (i.e. ~750 units)

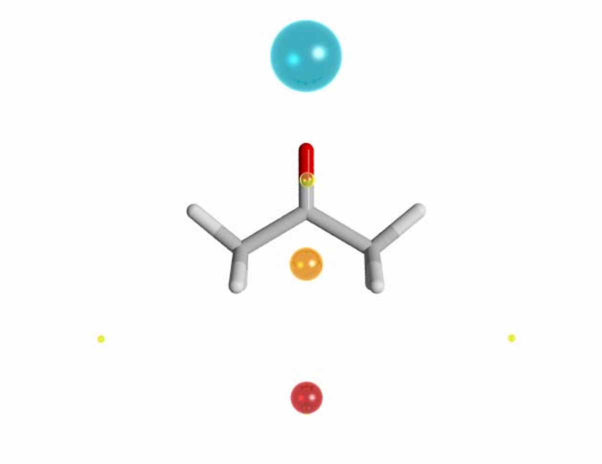
M. A. Cejas, W. A. Kinney, C. Chen, G. C. Leo, B. A. Tounge, J. G. Vinter, P. P. Joshi, B. E. Maryanoff. (2007) Collagen-Related Peptides: Self-Assembly of Short, Single Strands into a Functional Biomaterial of Micrometer Scale. J. Am. Chem. Soc. **129**, 2202-2203

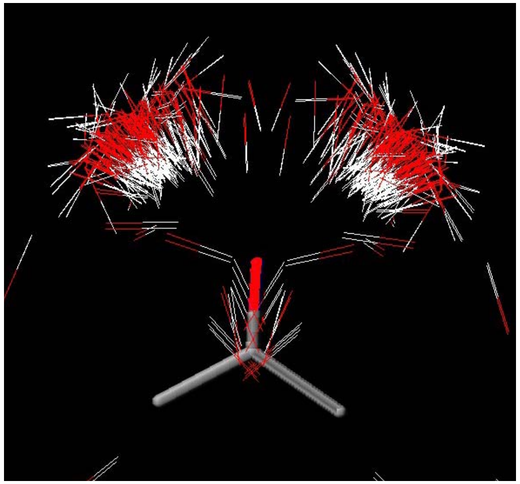
……so much for the force field.

Has it improved the quality of MEPs?

Usual the XED Electrostatic Model gives Intuitive MEP Extrema

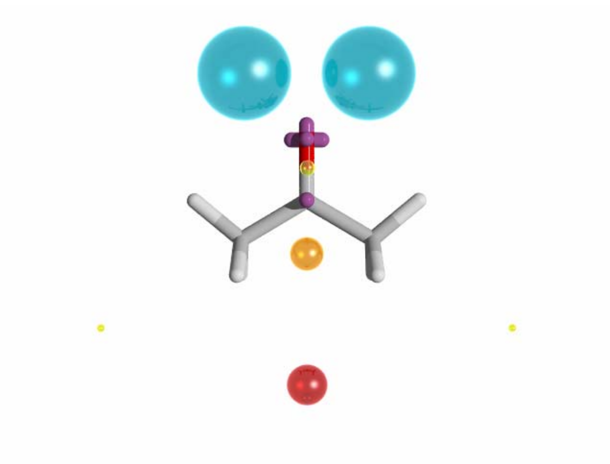
Fields from ACCs





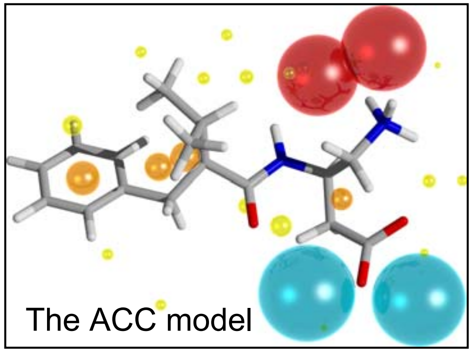
Interaction of Carbonyl and
Any-OH from CCDCs
Isostar

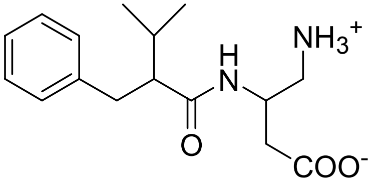
Fields from XEDs

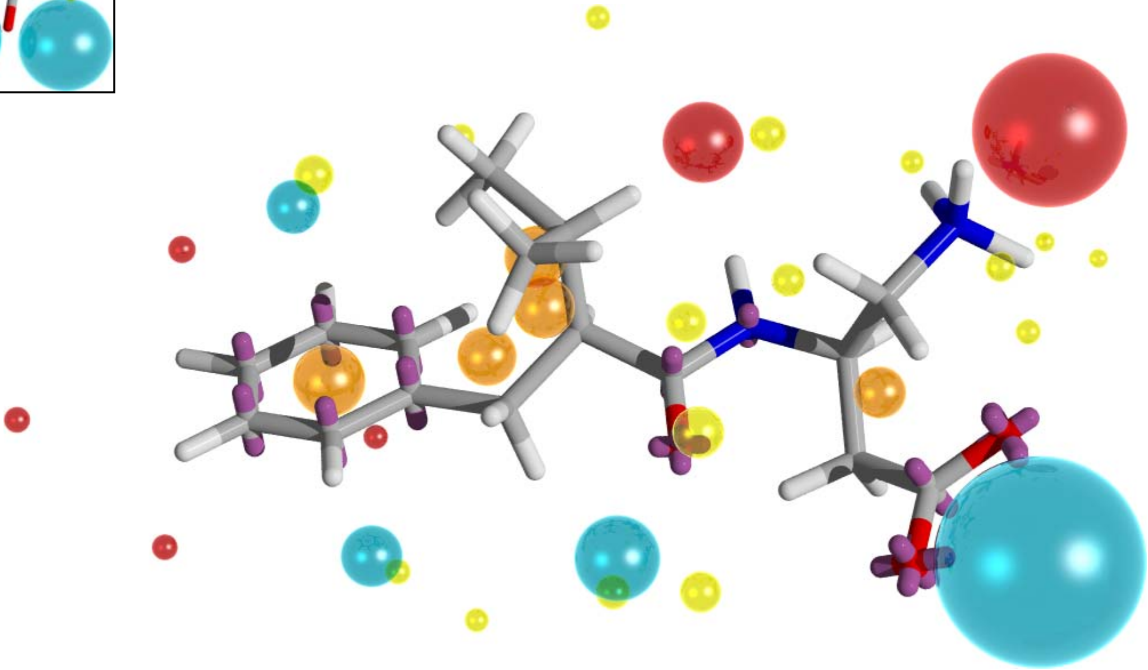


J. G. Vinter and K. I. Trollope, (1995)
Multi-conformational Composite Molecular Fields in the Analysis of Drug Design
J. Comp-Aid. Mol Design, 9, 297-307

Usual the XED Electrostatic Model gives Intuitive MEP Extrema



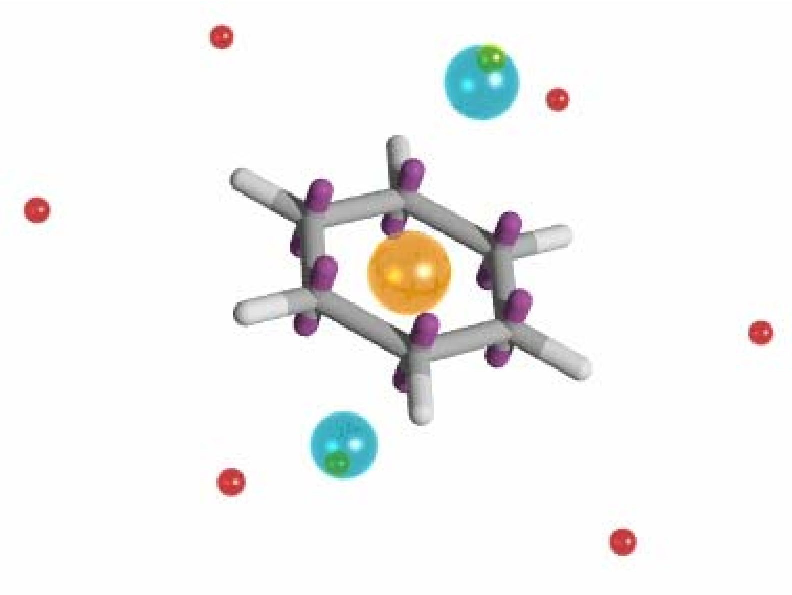




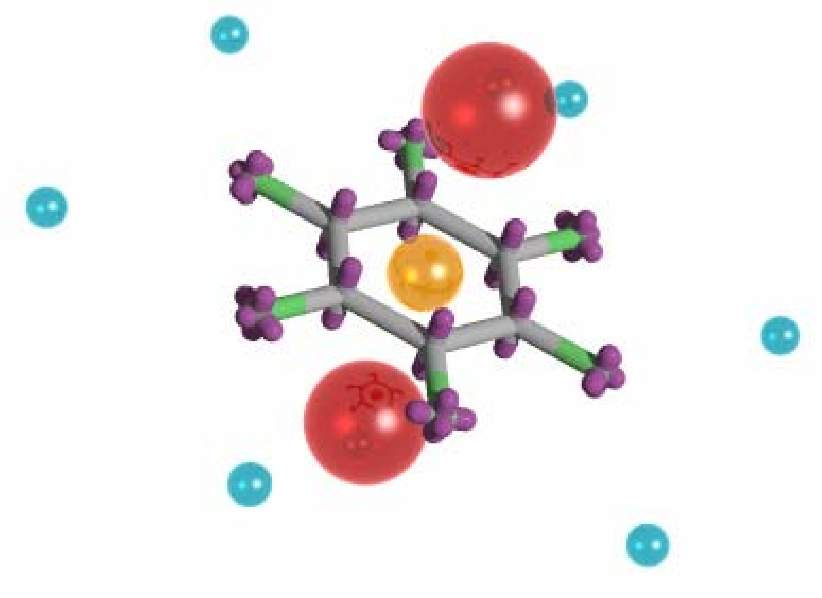
R. P. Apaya, B. Lucchese, S. L. Price and J. G. Vinter, (1995)
The matching of electrostatic extrema: A useful method in drug design? A study of phosphodiesterase III inhibitors
J. Comp-Aid. Mol. Design, **9**, 33-43

Aromatic - Aromatic Interactions

Fluorination



$Q= -16.7eA^2$

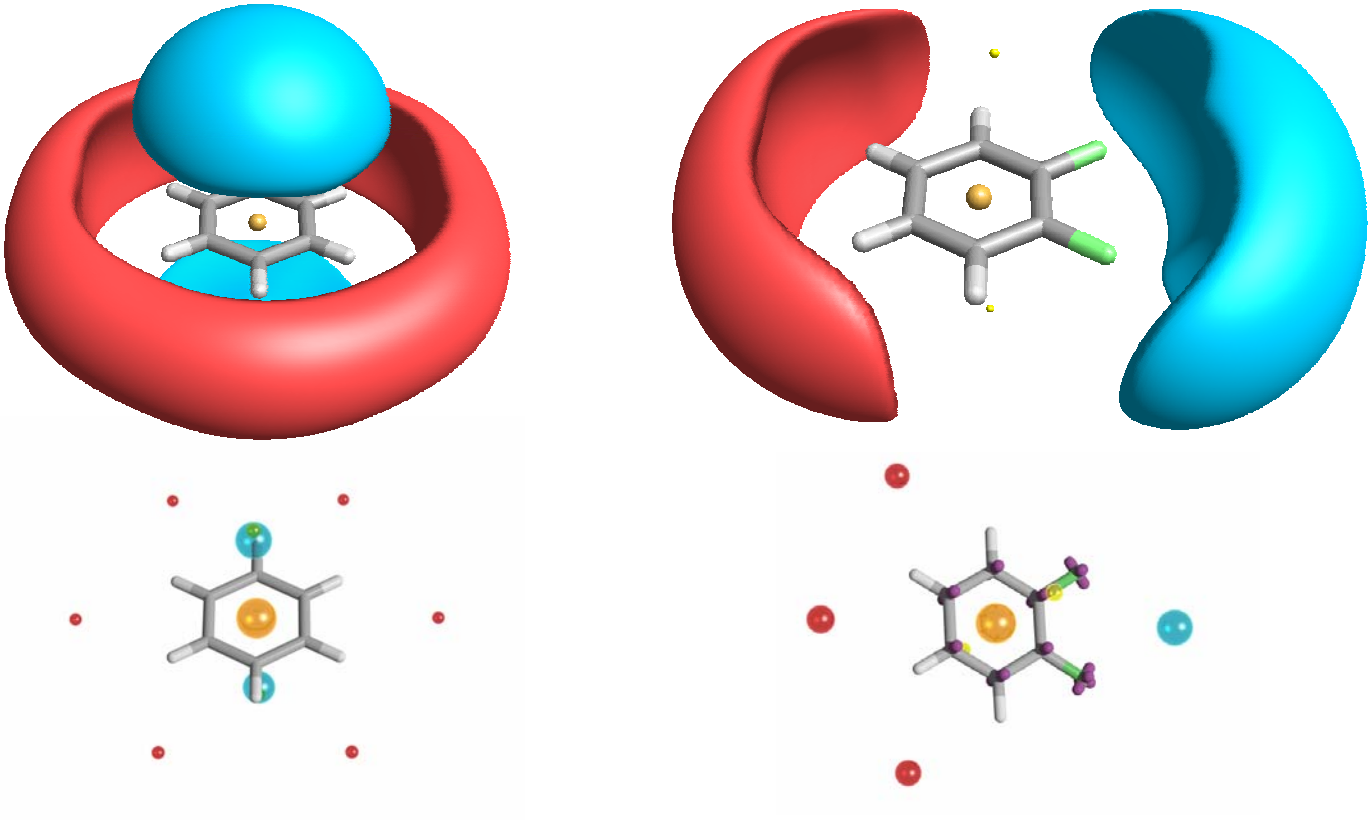


$Q= +17.8eA^2$

Aromatic Interactions

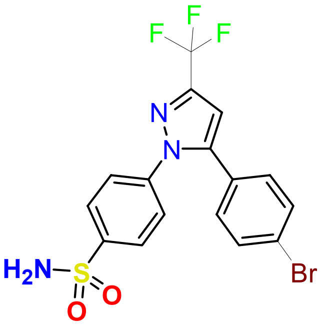
Fluorination

A real medicinal chemistry case

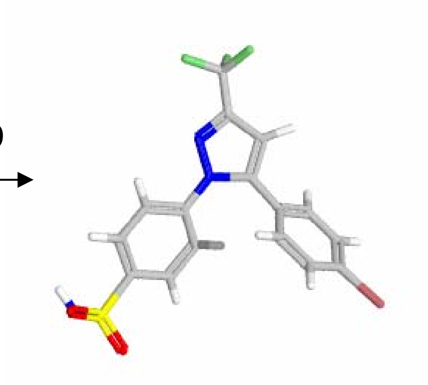


A. Matsushima et al. (2000)
J. Biochem. **128**, 225-232

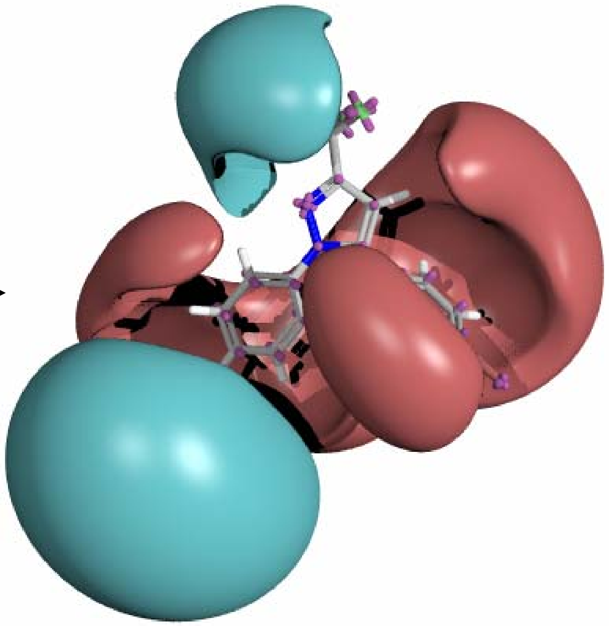
MEP, Surface and 'Hydrophobic' Extrema



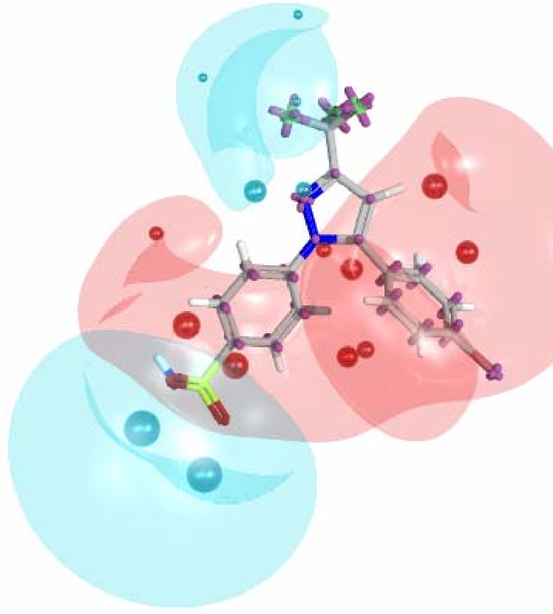
2D to 3D



Adding the MEP



Distil the MEP down to extrema



Remove structure

Blue: negative
Red: positive
Yellow: steric
Orange: hydrophobic

T. Cheeseright, M. Mackey, S. Rose, A. Vinter, (2006)
Molecular field extrema as descriptors of biological activity: Definition and validation.
J. Chem. Inf. Model. **46**, No 2, 665-676

The proposition is that:

If two or more molecules bind to the same active site, then their fields in the bioactive conformation must be similar

Put another way:

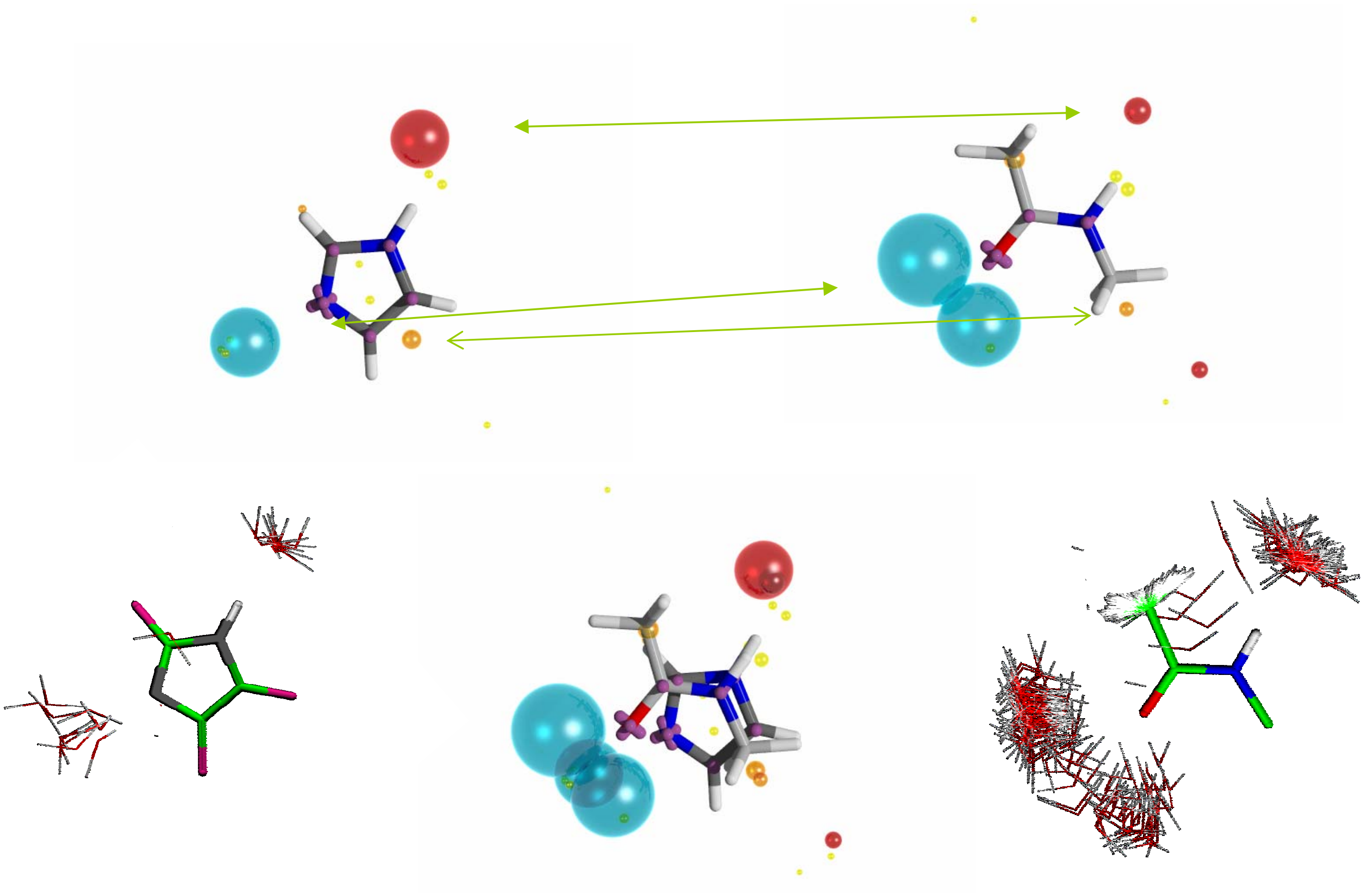
If two or more molecules can generate similar field patterns, they are likely to act at the same biological site

now –

can the comparison of the improved MEP Extrema on the **Outside** of two molecules be used to indicate **Molecular Similarity**?

Molecular Similarity from the Outside In – Fields to Structures

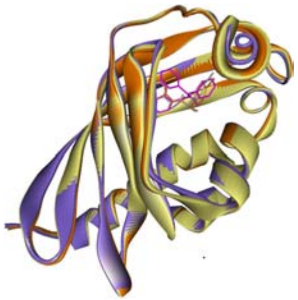
The Field Overlay Principle

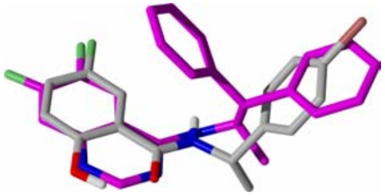


T. Cheeseright, M. Mackey, S. Rose, A. Vinter, (2006)
Molecular field extrema as descriptors of biological activity: Definition and validation.
J. Chem. Inf. Model. **46**, No 2, 665-676

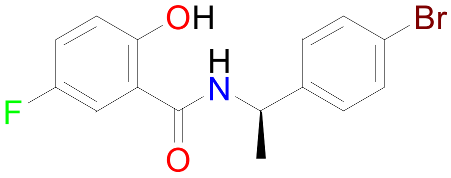
Does the Field Overlay Principle Work?

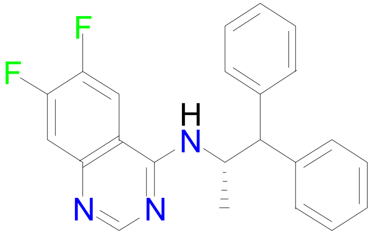
The Field Overlay of Two Ligands in their Bioactive Conformations find the Common Pose in the Target



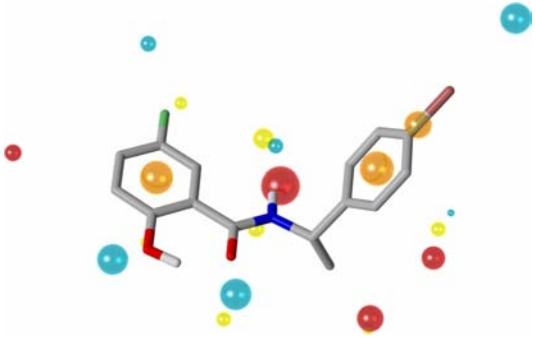


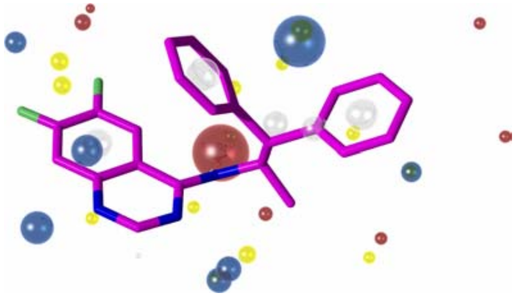
X-ray poses

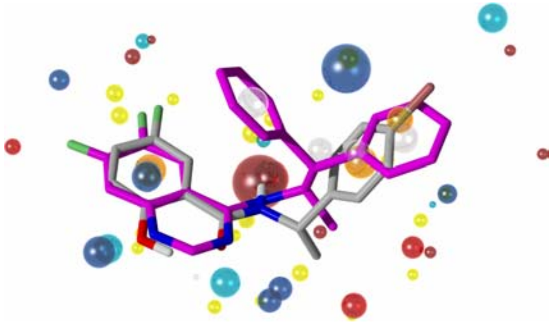




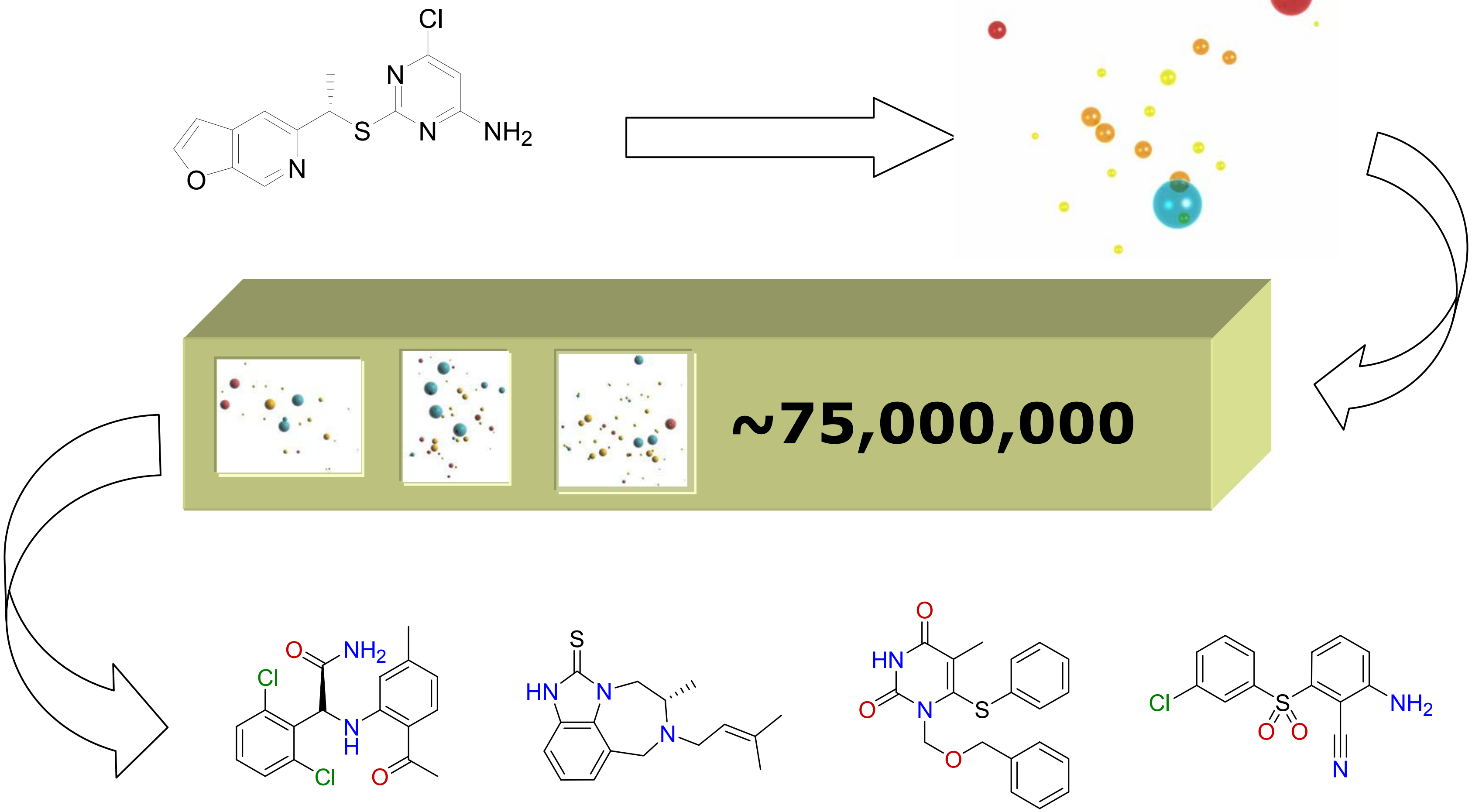
Field overlay





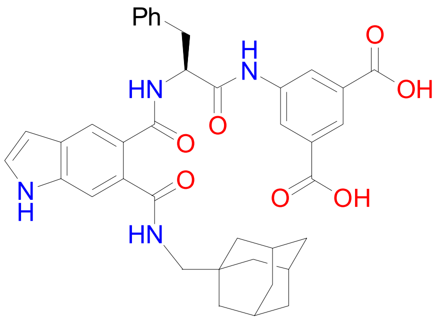


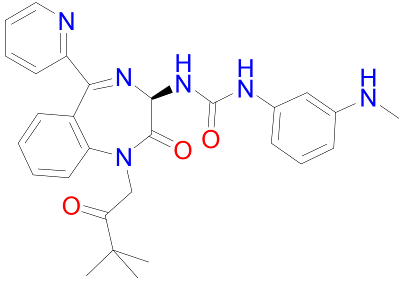
Virtual Field Screening. The Field Search Principle



T. Cheeseright, M. Mackey, S. Rose, A. Vinter, (2007)
Molecular field technology applied to virtual screening and finding the bioactive conformation
Expert Opin. Drug Discov. **2**, 131-144

Virtual Field Screening on a Class A GPCR – CCK_2



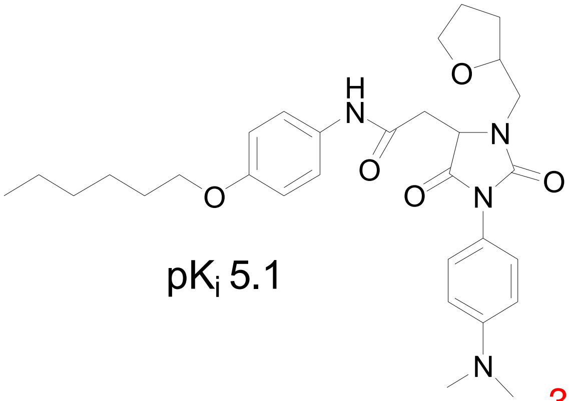


Search the commercial compounds database (50 conformations per compound)

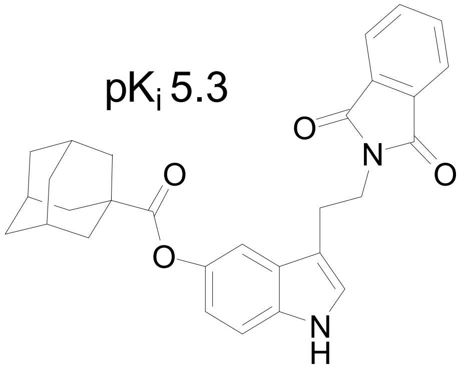
Distilled to 1000 Compounds
Visual inspection to 100
88 Purchased and tested

27 had $pK_b > 5$ (better than 10uM)
4 had $pK_b > 6$ (better than 1uM)

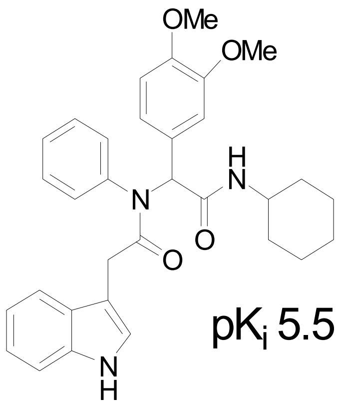
MW range 350-600



pK_i 5.1



pK_i 5.3



pK_i 5.5

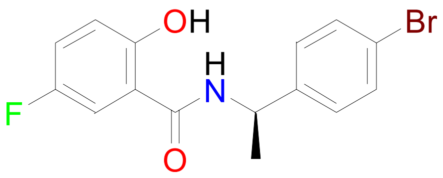
3 of the 27 actives found

- **If we can overlay two ligands known to act at the same site, can we -**

- **overlay three and increase the chance of finding their bioactive ligand conformers from searching for the unique field pattern that satisfies the needs of the protein active site -**

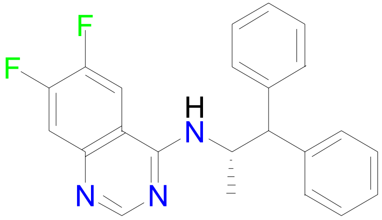
- **without having any X-ray data?**

Overlaying the Fields of Conformational Sets to find the Common Field Pattern



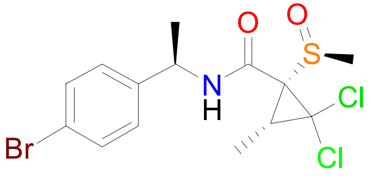
A

24 conformers



B

50 conformers



C

50 conformers

Overlay Fields of all conformers in pairs to create duos
(keep 100 best duos from each set)

AB
100 duos

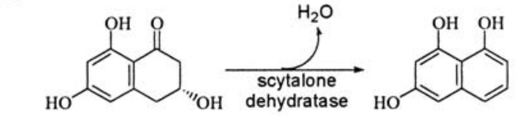
BC
100 duos

CA
100 duos

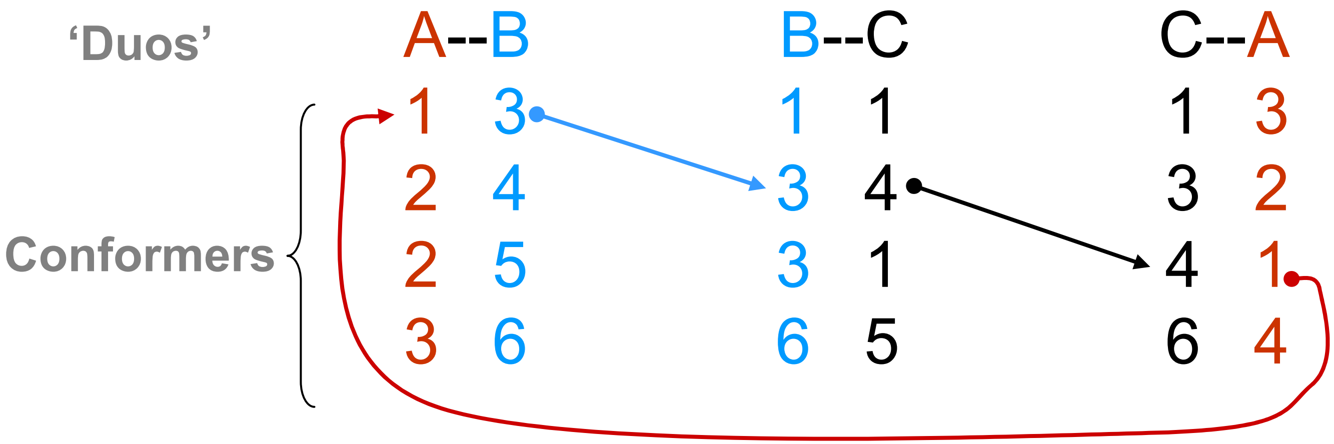
100 duos for each pair ordered by best overlay score

A--B		B--C		C--A	
1	3	1	1	1	3
2	4	3	4	3	2
2	5	3	1	4	1
3	6	6	5	6	4
	.		.		.
	.		.		.

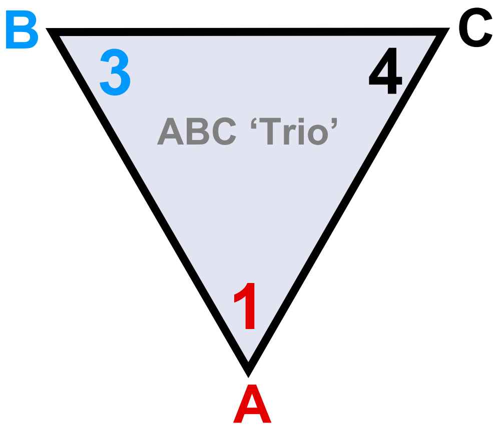
Scytalone Dehydratase; found only in fungi, and as the major determinant of rice blast disease



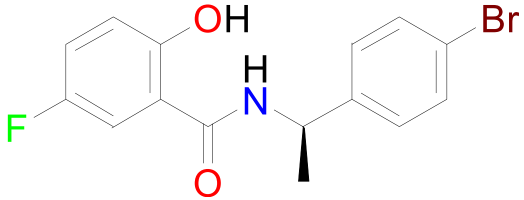
Trio Field Overlays

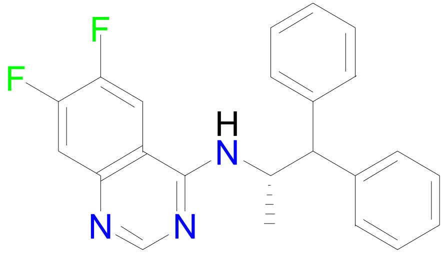


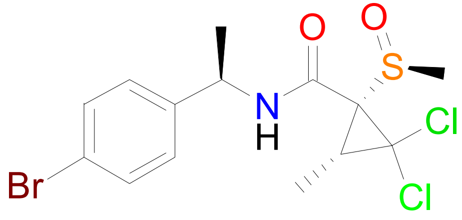
‘Duos’	A--B		B--C		C--A	
Conformers	1	3	1	1	1	3
	2	4	3	4	3	2
	2	5	3	1	4	1
	3	6	6	5	6	4



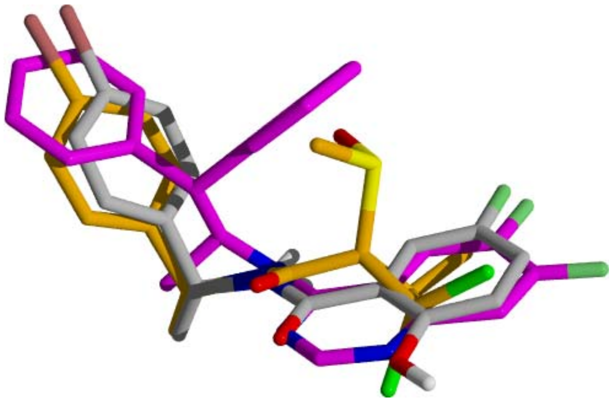
Finding the X-ray poses from Trio Field Overlays without X-ray Data



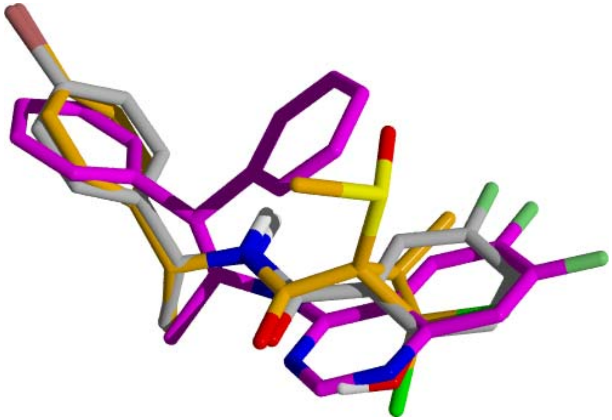




X-ray Overlay



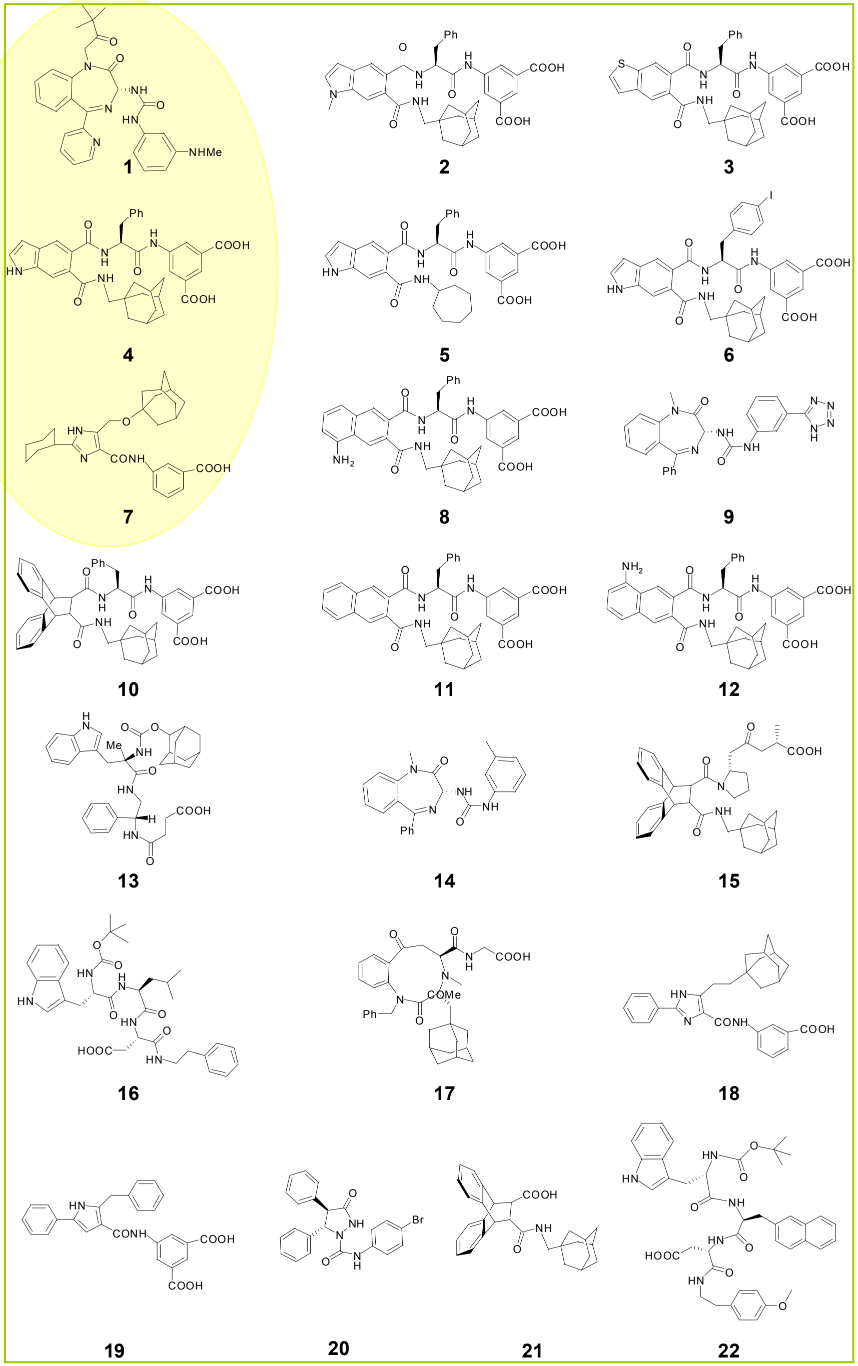
‘FieldTemplating’ Overlay



finally -

Is there ANY correlation between
Similarity Score and Biological Activity?

Applying Field Ideas to a Real Case History

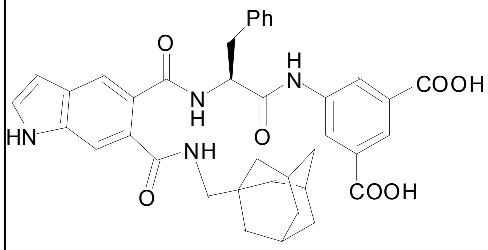


CCK$_2$ Correlations

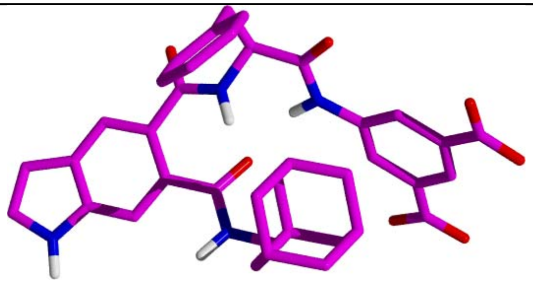
Compound number (Identifier)	CCK$_2$ Bioassay		CCK$_1$ Bioassay
	RSpK$_B$	RSpK$_B$ s.e†	pK$_i$
1	9.9	0.3	6.4
2	9.8	0.3	5.4
3	9.4	0.3	6.1
4	9.3	0.2	5.4
5	9.3	0.2	5.5
6	9.1	0.2	5.7
7	9.1	-	-
8	9.0	0.2	5.6
9	8.4	0.2	6.5
10	8.3	0.2	5.7
11	8.2	0.1	6.1
12	8.2	0.2	5.6
13	7.9	0.2	6.2
14	7.6	0.1	6.5
15	7.3	0.2	4.6
16	6.9	0.2	5.1
17	6.8	0.3	5.1
18	6.6	0.3	5.9
19	6.3	0.4	5.1
20	5.9	1.4	4.7
21	5.6	-	-
22	5.4	0.2	7.2

All act as simple competitive antagonists in the rat stomach (RS) functional in vitro assay

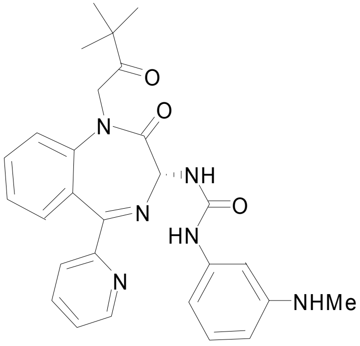
Best Template from 1, 4 and 7



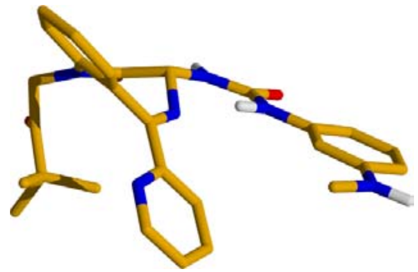
4



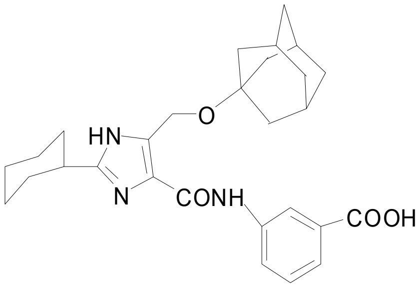
4 (conformation 1)



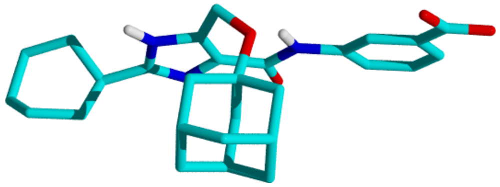
1



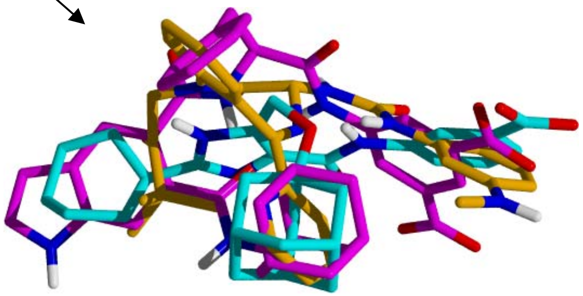
1 (conformation 4)



7

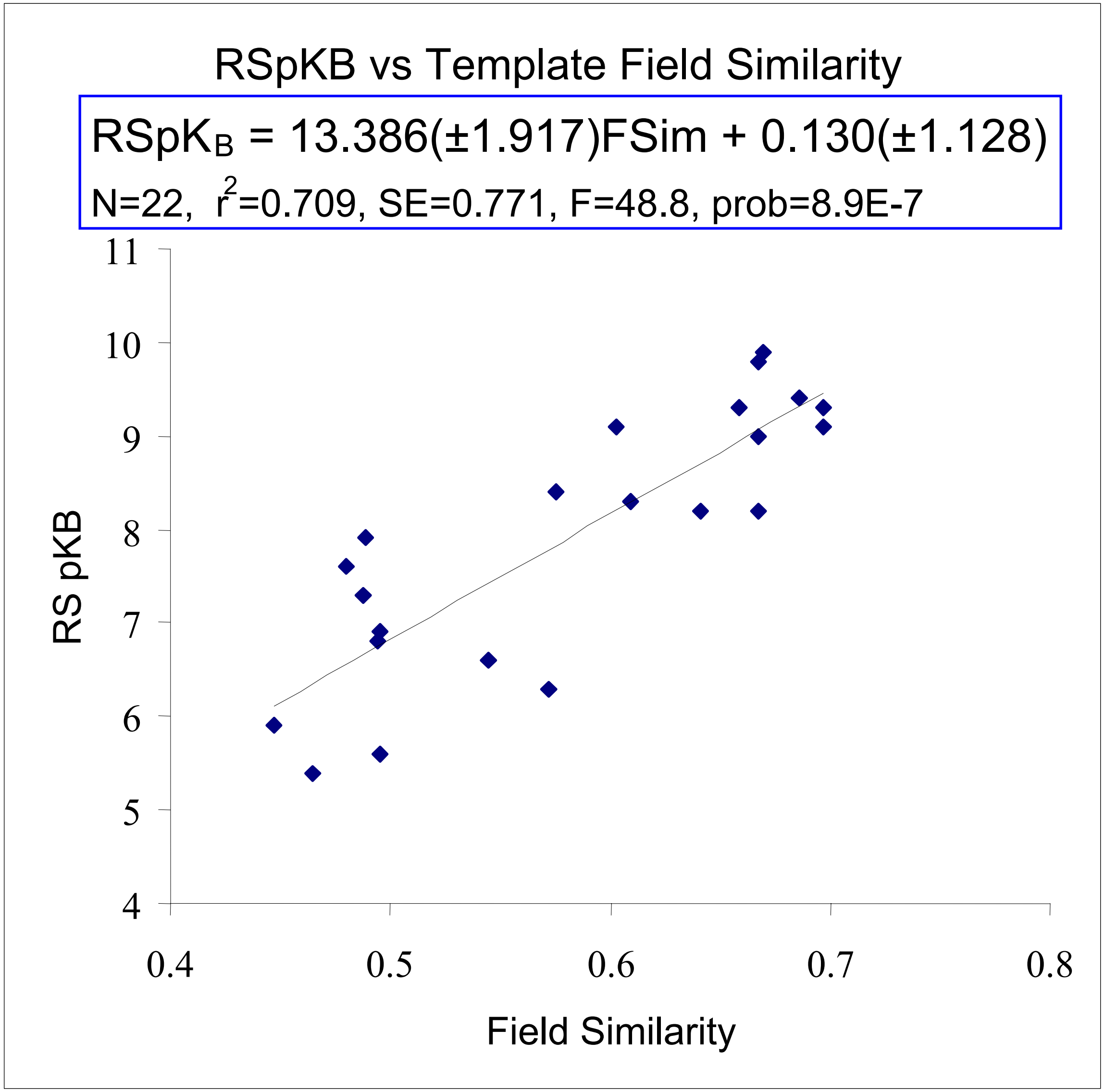


7 (conformation 18)



Best Template

CCK_2 Activity is Correlated with Field Similarity



RSpKB vs Template Field Similarity

$RSpK_B = 13.386(\pm1.917)FSim + 0.130(\pm1.128)$

N=22, r^2=0.709, SE=0.771, F=48.8, prob=8.9E-7

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