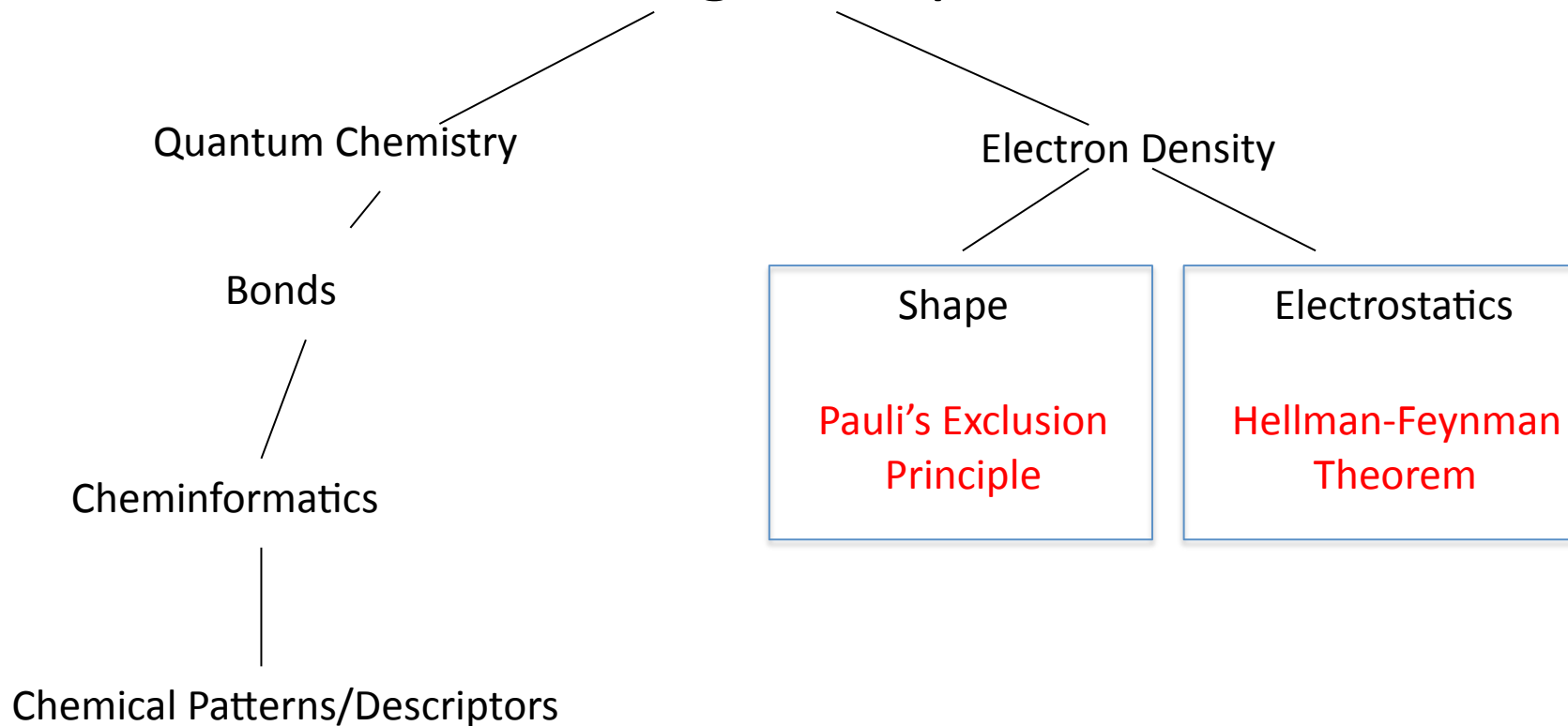


Electrostatics

Why I continue to bother

I: Physics

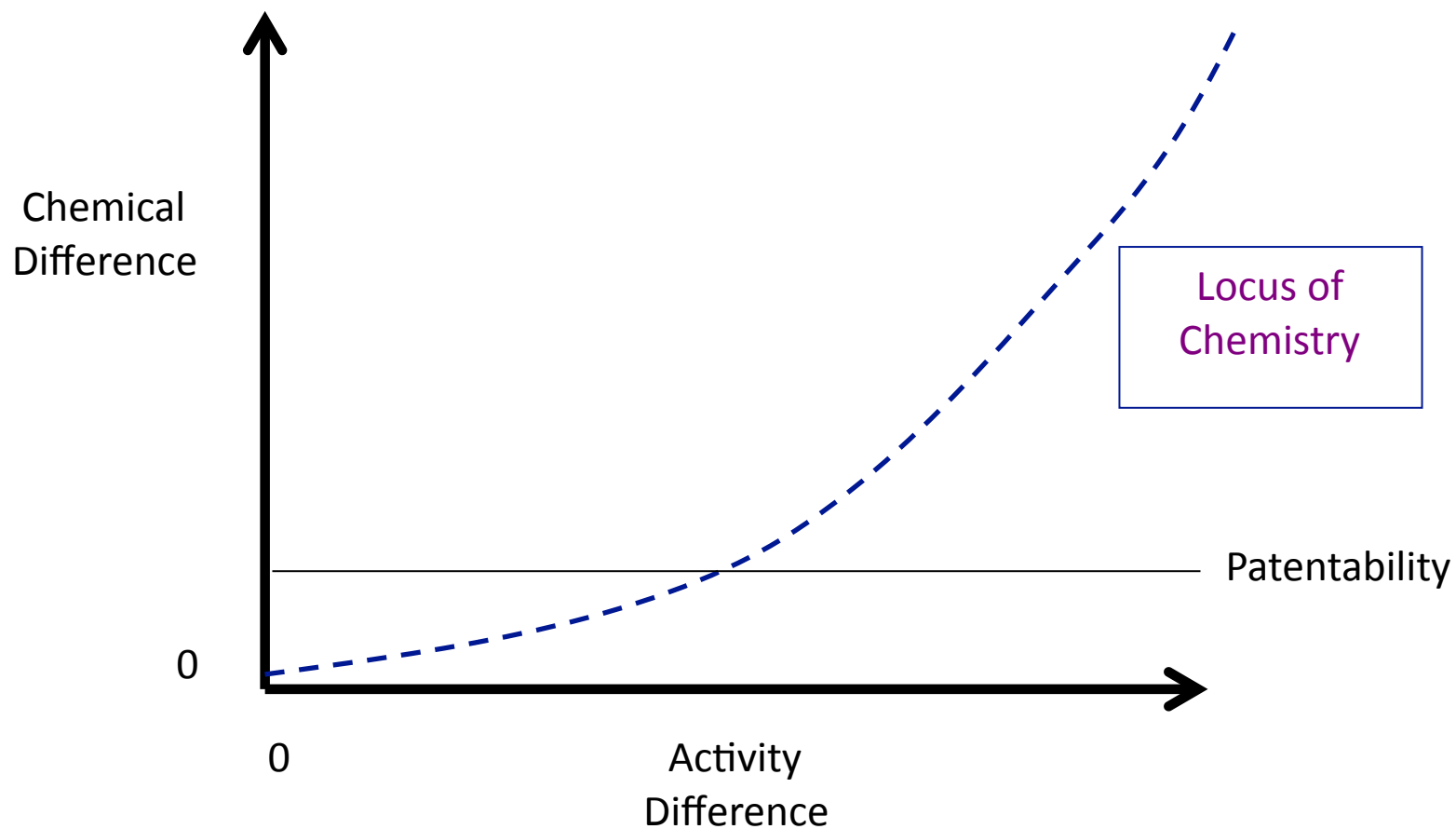
Schrödinger's Equation



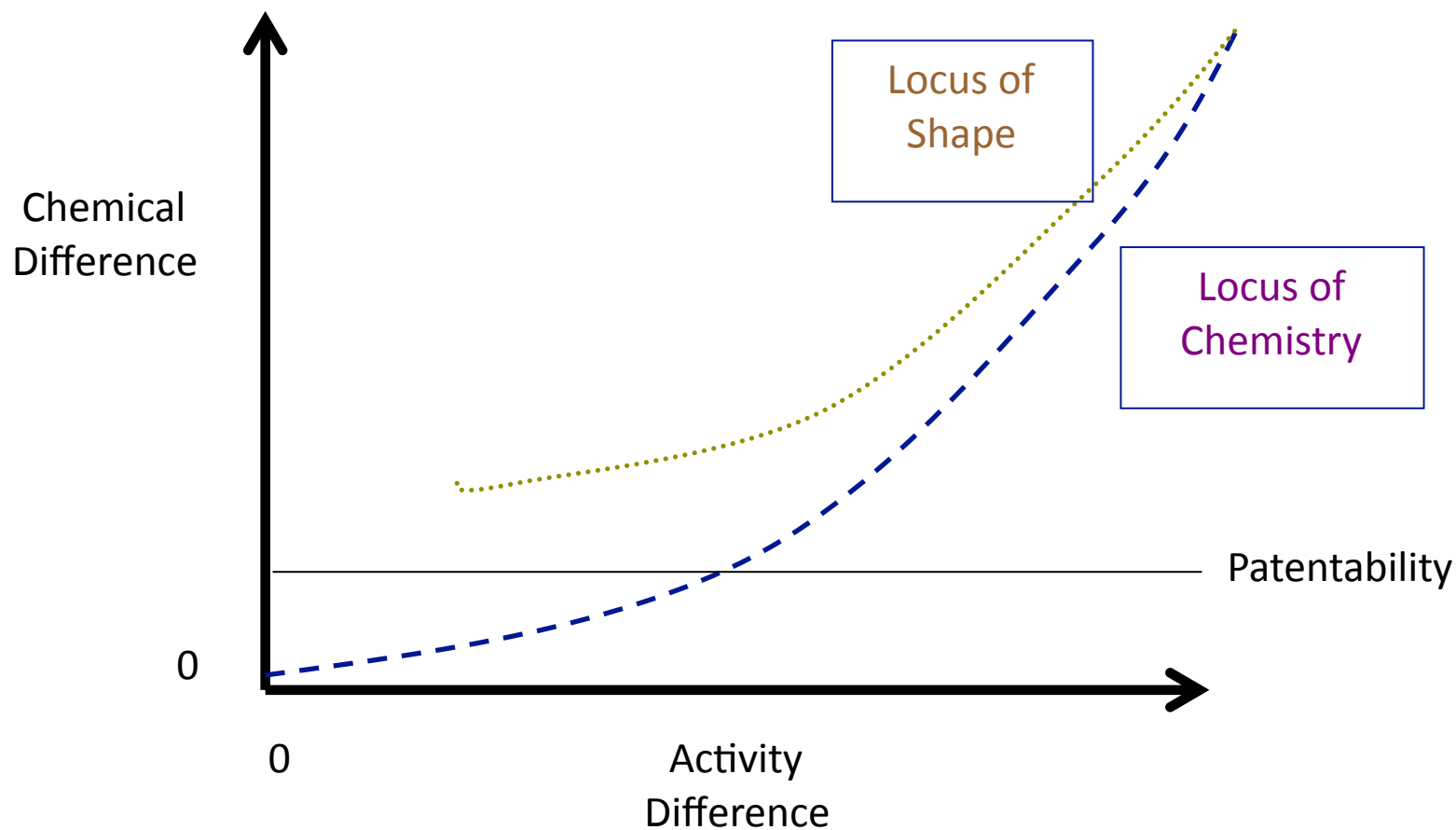
II: Progress

- Jean-Francois' EPIC
- SAMPL2
- Andy's work on dipoles
- Mike's work on SZMAP
- Electrostatic Similarity

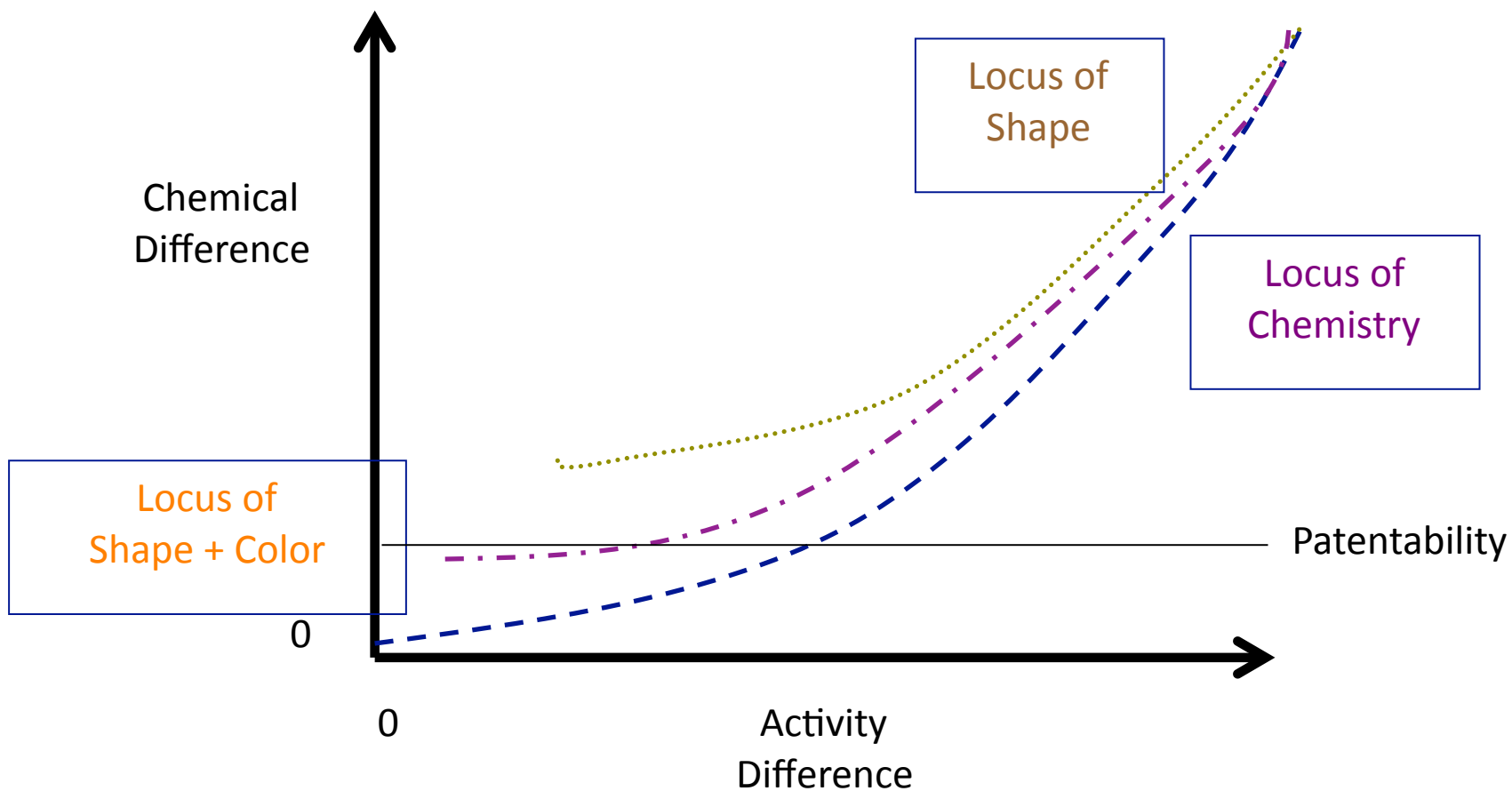
Design & Similarity



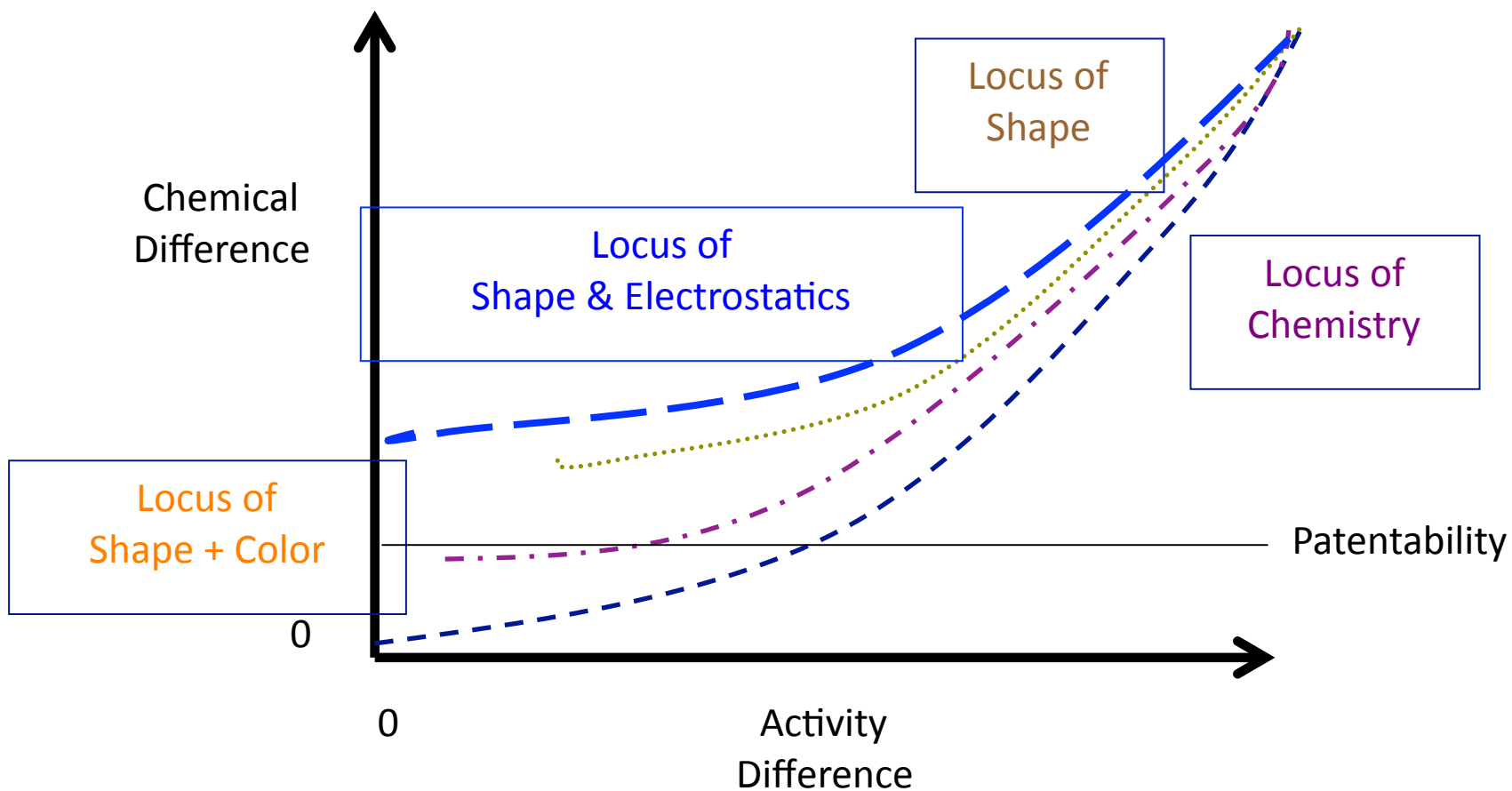
Design & Similarity



Design & Similarity



Design & Similarity



Shape & Electrostatics

$$\Delta^2 = \int_{\text{all space}} (\chi_1 - \chi_2)^2 dv$$

ROCS

$$\Theta^2 = \int_{\text{all space}} (\phi_1 - \phi_2)^2 dv$$

EON

χ_n = steric field {n}

ϕ_m = potential field {m}

Δ, Θ = *Shape / Electrostatic Distance*

Schnecke & Boström, 2006

Cilomilast vs. Piclamilast

DDT • Volume 11, Number 1/2 • January 2006

REVIEWS

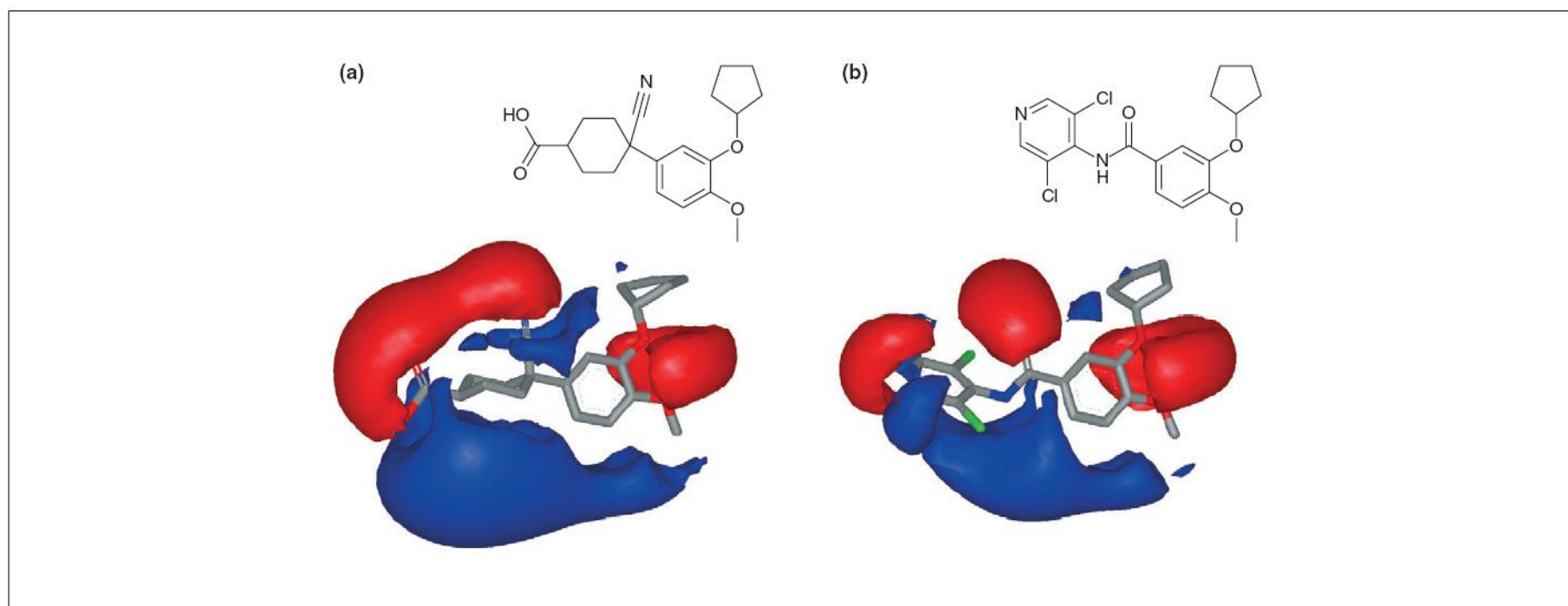
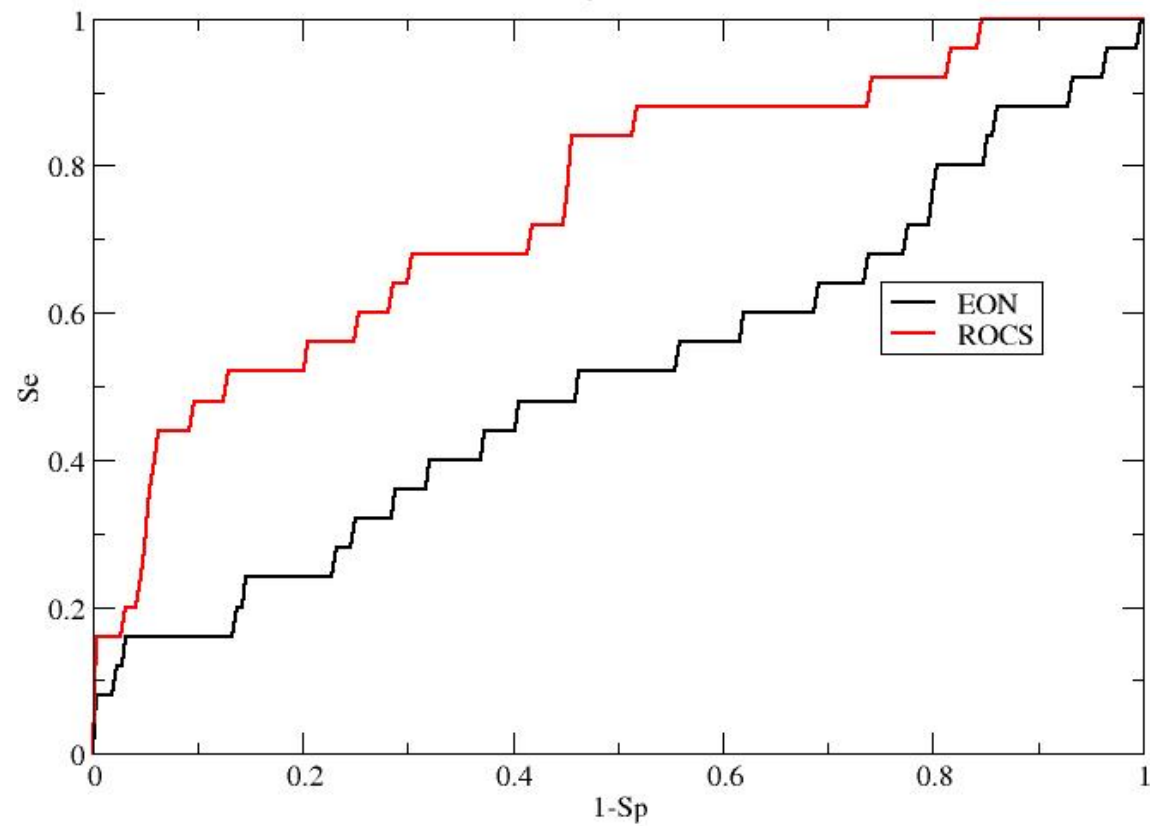


FIGURE 4

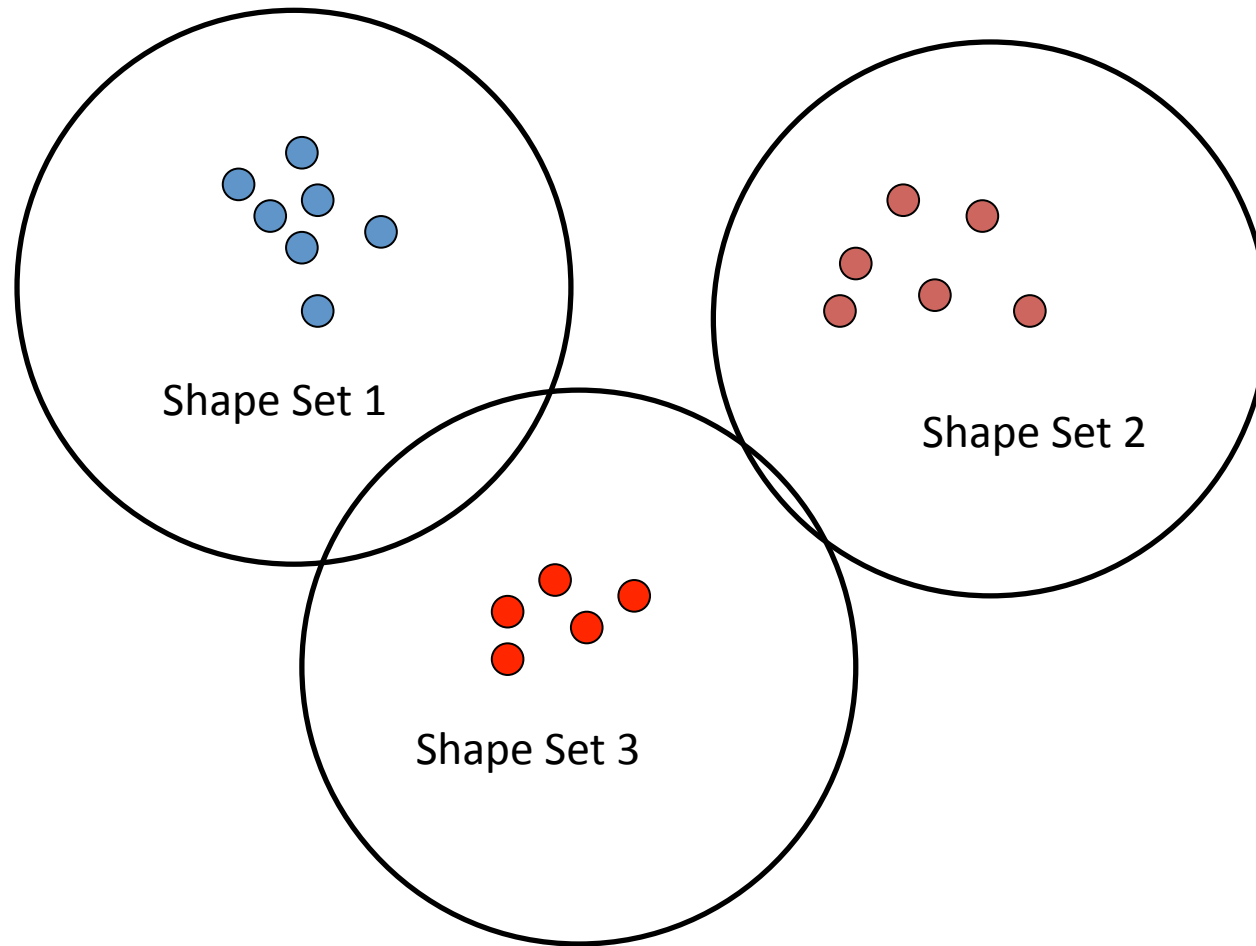
Database search based on shape and electrostatic similarity can identify structures that have similar chemical properties (electrostatics) to a template molecule but are structurally dissimilar. The two inhibitors of Phosphodiesterase 4B, (a) cilomilast and (b) piclamilast, are structurally different but have high shape and electrostatic similarity.

Poor EON VS performance

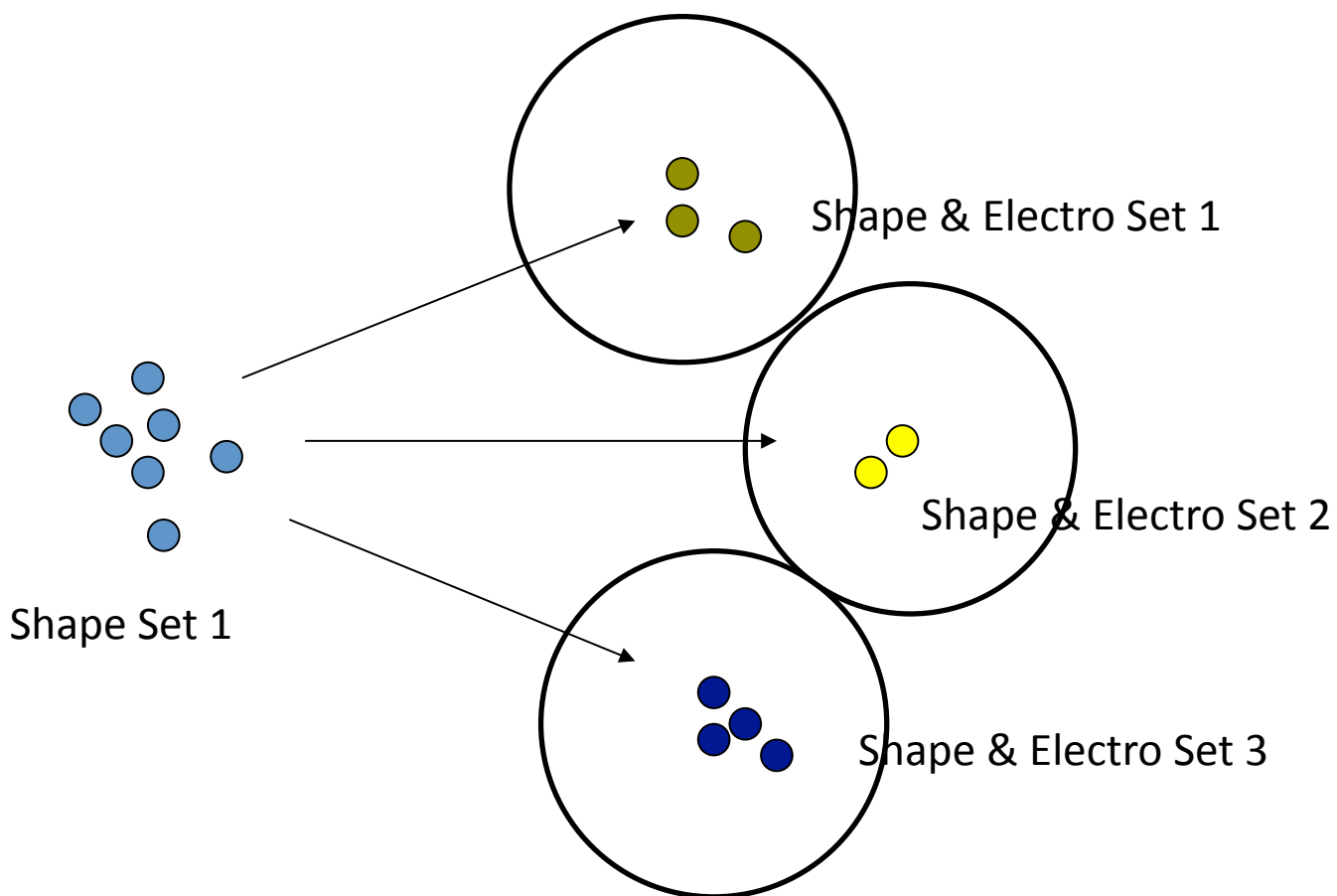
ROCS v. EON, Inh 41; PDE5
Shape/colour



Multiple Shape Models



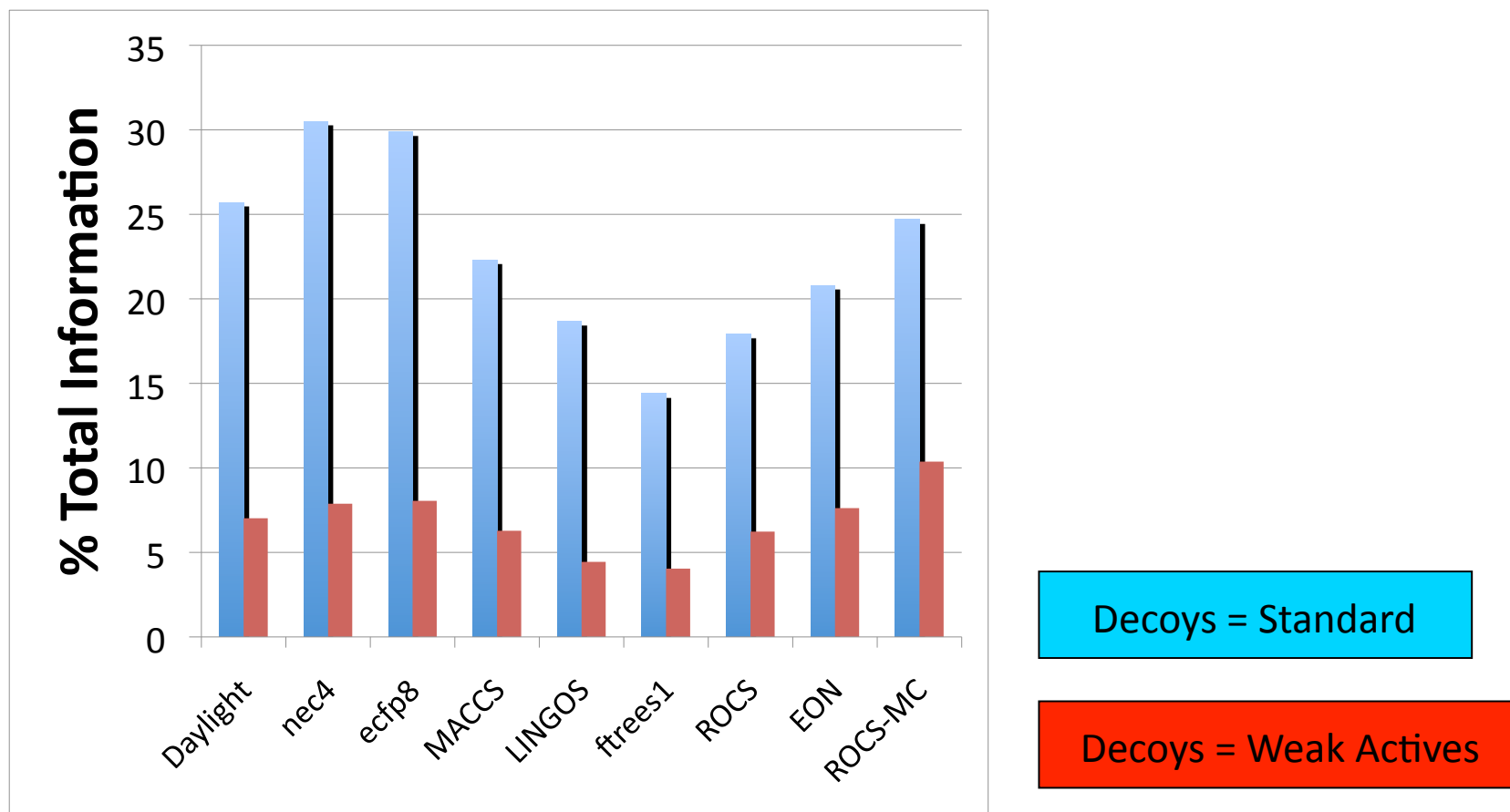
Multiple Shape and Electrostatic Models



Improvements in EON 2.0

- 1) Use of salt
- 2) Optimized 'strike zone'
- 3) Flexible terminal rotors
- 4) pKa normalization
- 5) Optimized grid resolution: faster

Abbott Pair Data



Between strong and weakly actives, 3D has most information

Shape & Electrostatics -EON

Best Practices:

1. Run ROCS
2. Take top ~500 hits
3. Rescore with EON

Prospective Success

- J & J
1. Abbott Labs
 2. U. Innsbruck
 3. U. Kyoto
 4. Oxford U.

JnJ: Scaffold Replacement

Scaffold hopping from pyridones to imidazo[1,2-*a*]pyridines. New positive allosteric modulators of metabotropic glutamate 2 receptor

Gary Tresadern^{a,*}, Jose María Cid^b, Gregor J. Macdonald^c, Juan Antonio Vega^b, Ana Isabel de Lucas^b, Aránzazu García^b, Encarnación Matesanz^b, María Lourdes Linares^b, Daniel Oehlrich^c, Hilde Lavreysen^d, Ilse Biesmans^d, Andrés A. Trabanco^{b,*}

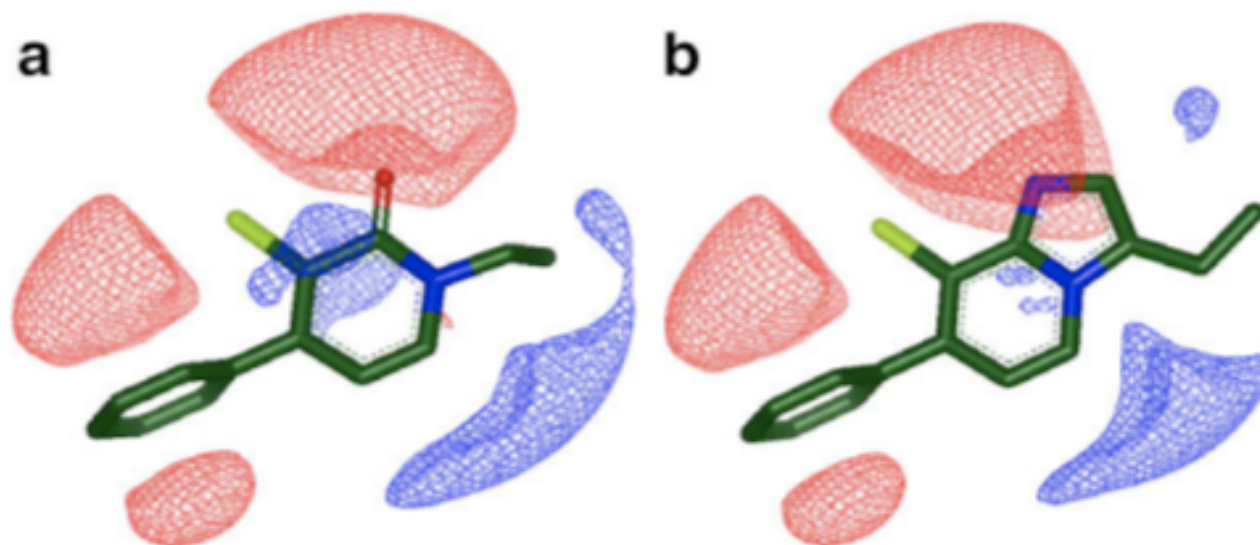
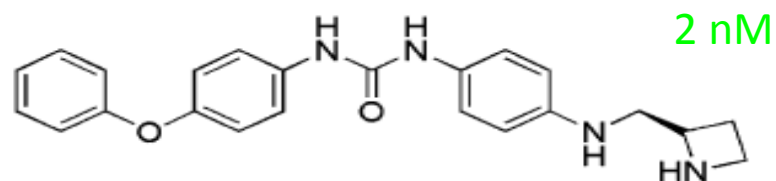
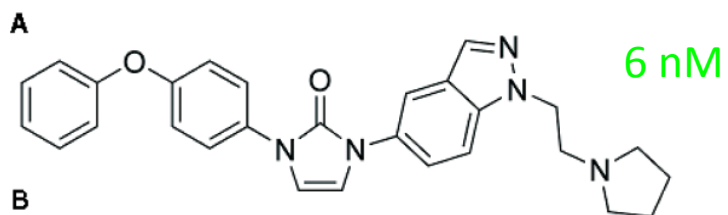
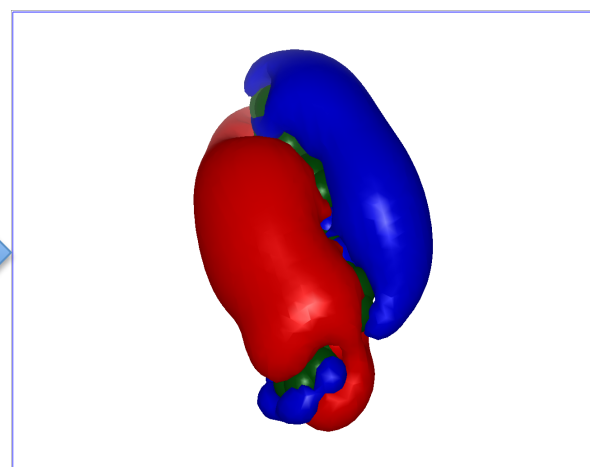
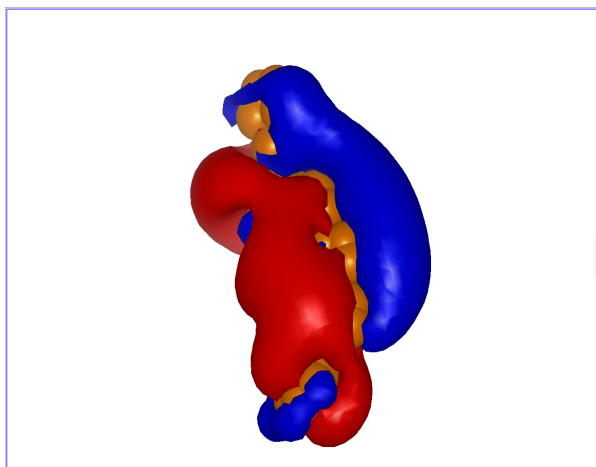


Figure 4. Electrostatic fields of (a) pyridone query and (b) imidazopyridine hit fragment. Negative field is red and positive blue.

Abbott Labs: MCH Receptor



HTS



**Virtual
Screen**

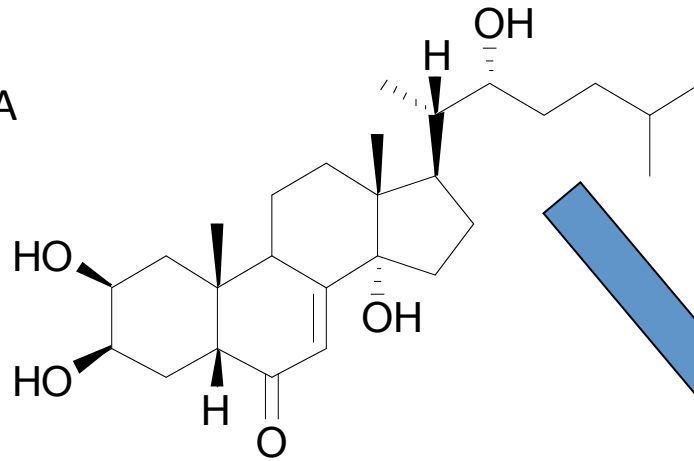
Shape Tanimoto = 0.84
Electro Tanimoto = 0.56
Daylight Tanimoto = 0.25

Kyoto University

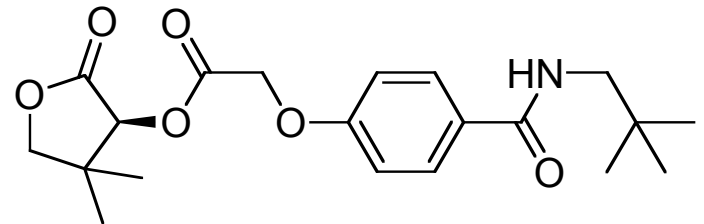
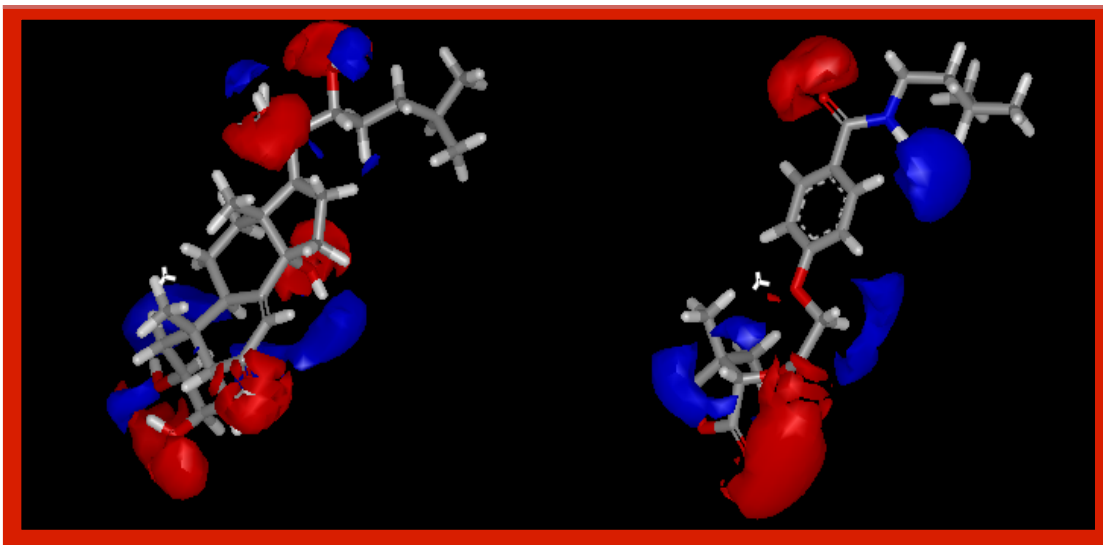
Insect Molting Hormone Agonist, Harada *et al*, 2008

Ponasterone A

0.2 μM



ST=0.73
ET=0.35



10 μM

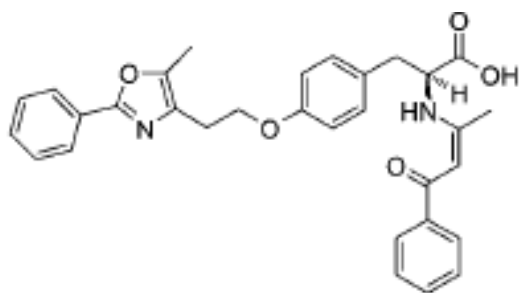
University of Innsbruck

Discovery of Novel PPAR Ligands by a Virtual Screening Approach Based on Pharmacophore Modeling, 3D Shape, and Electrostatic Similarity Screening

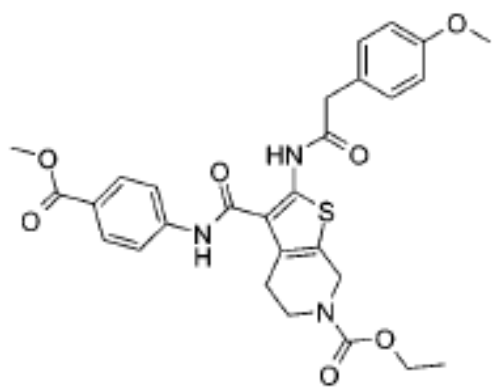
Patrick Markt,[†] Rasmus K. Petersen,[‡] Esben N. Flindt,[‡] Karsten Kristiansen,[§] Johannes Kirchmair,^{||} Gudrun Spitzer,[⊥] Simona Distinto,[†] Daniela Schuster,^{†,||} Gerhard Wolber,^{||} Christian Laggner,[†] and Thierry Langer^{*,†,||}

- 4 PPAR query compounds
 - 3 from PDB complexes, one unknown structure
- ROCS 1063848 compounds v. each query
- Rerank best 1500 by EON
- Select and test 10 compounds

ROCS + EON: PPAR- α

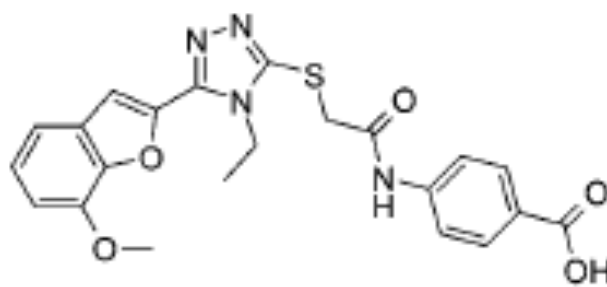


Query



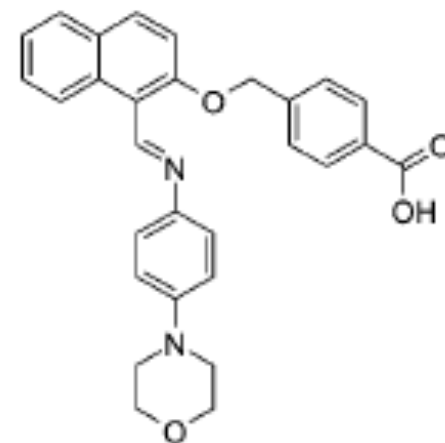
1.5 μ M

5



1.0 μ M

7

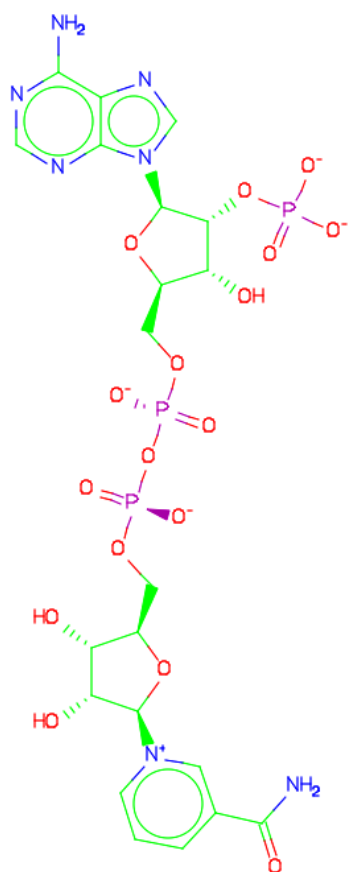


43 μ M

8

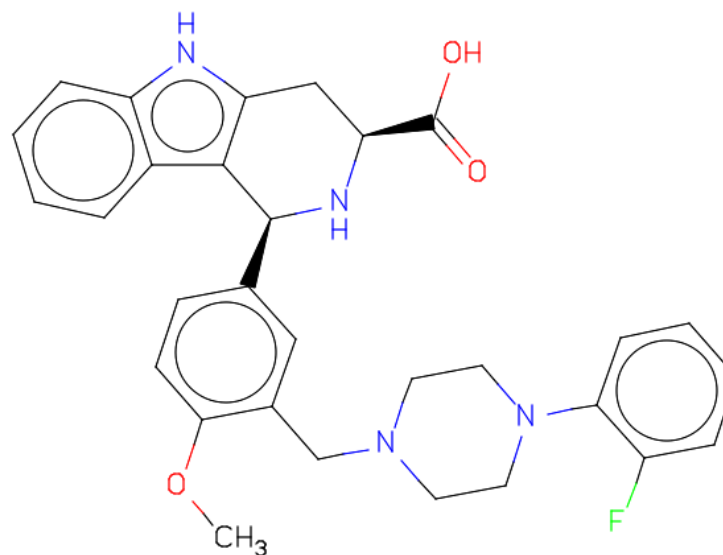
Churchill *et al*, Nature Chem. Biol. Feb. 2009

Ligand_20



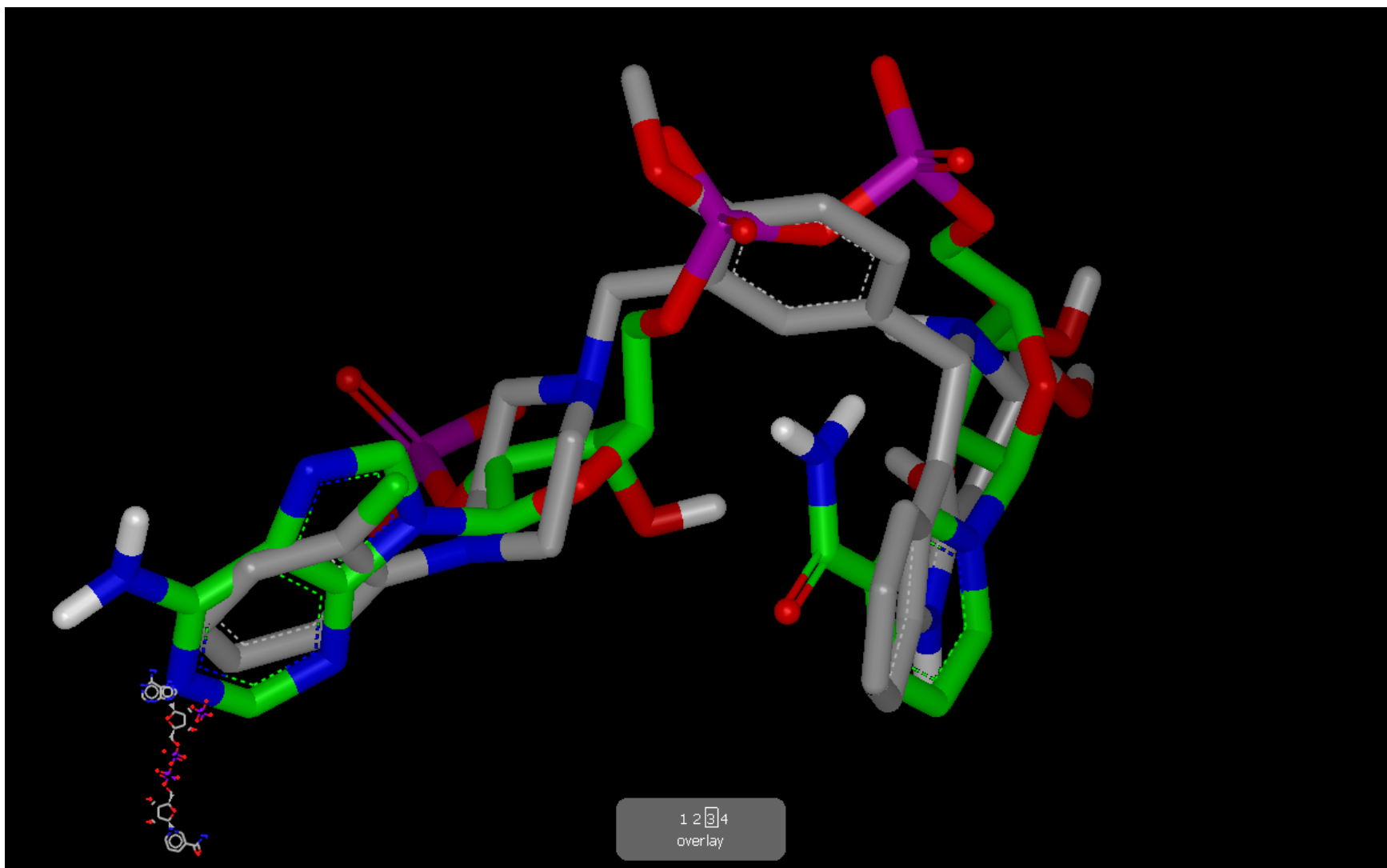
Query: NAADP

untitled-dbase-1_61



Hit: NED14

Surprisingly 3D Overlap



NED14

- First nanomolar drug-like competitive antagonist for NAADP
- Patented by Oxford
- Used as a chemical genomics tool

EON 3.0

- Much, much faster.
- Gradients
- Terminal hydroxyl search
- Partial matching

Progress!