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flare

Electrostatic Complementarity™ as a New Approach to Visualize and Predict Activity

Sylvie Sciammetta

Outline

- Introduction
- Electrostatic Complementarity (EC) calculations
- Case studies
  - Series of XIAP inhibitors - EC and activity correlation
  - Series of mGLU5 negative allosteric modulators - molecular design
  - Imatinib - selectivity
- Summary and future outlook

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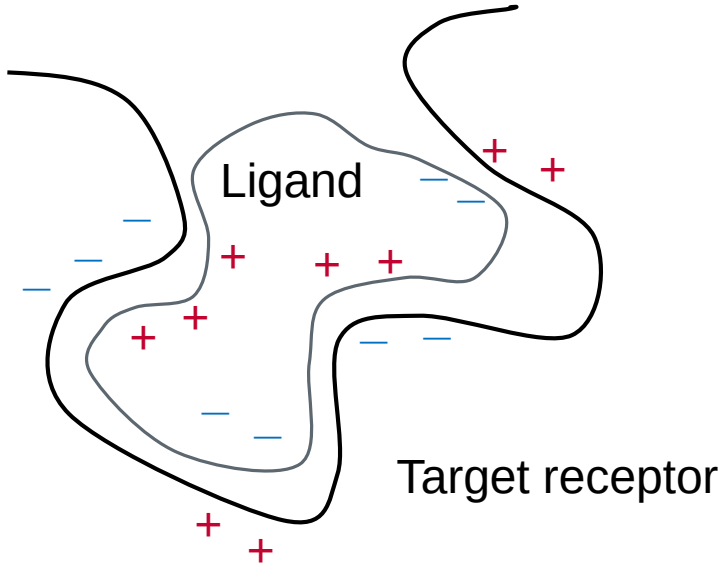
Electrostatic interactions and complementarity

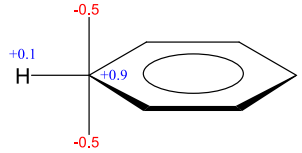
- Electrostatic interactions between ligands and their receptors is an important factor (e.g. H-Bonding, ionic, cation-π, π-π, lone-pair-sigma hole (halogen-bonding) & orthogonal multipolar interactions (e.g. Fluorine bonding).
  - Molecular recognition
  - Binding free energy

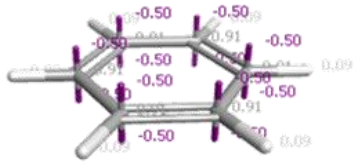


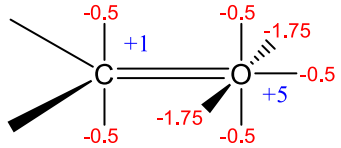
- Assessing Electrostatic Complementarity (EC)
  - Insight of why ligand bind
  - Inform molecular design
  - Predict activity

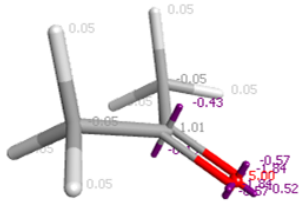
Cresset electrostatics - the XED molecular mechanics force field

- eXtended Electron Distributions – “XED”
  - Multipoles via additional monopoles

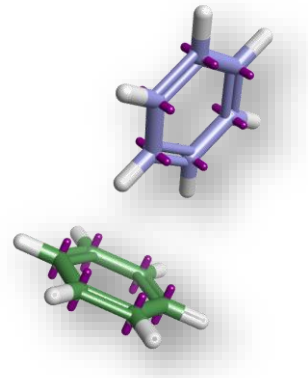








  - Huckel
    - separation of π and σ components of partial charges
      - π charges added to ‘xed’ atoms
      - σ charges added to nuclei
      - Excellent modeling of substituent effects
    - find bond orders and assign hybridization
      - Analogue N(sp^3) atoms – pyramidal to planar



  - Full molecular mechanics force field with excellent coverage of organic chemistry, water and proteins
    - Minimization, conformations etc.
    - Not a dynamics force field

Vinter, *J. Comput.-Aided Mol. Des.*, **1994**, 8, 653-668

Ligand and protein molecular interaction potentials

2006 →

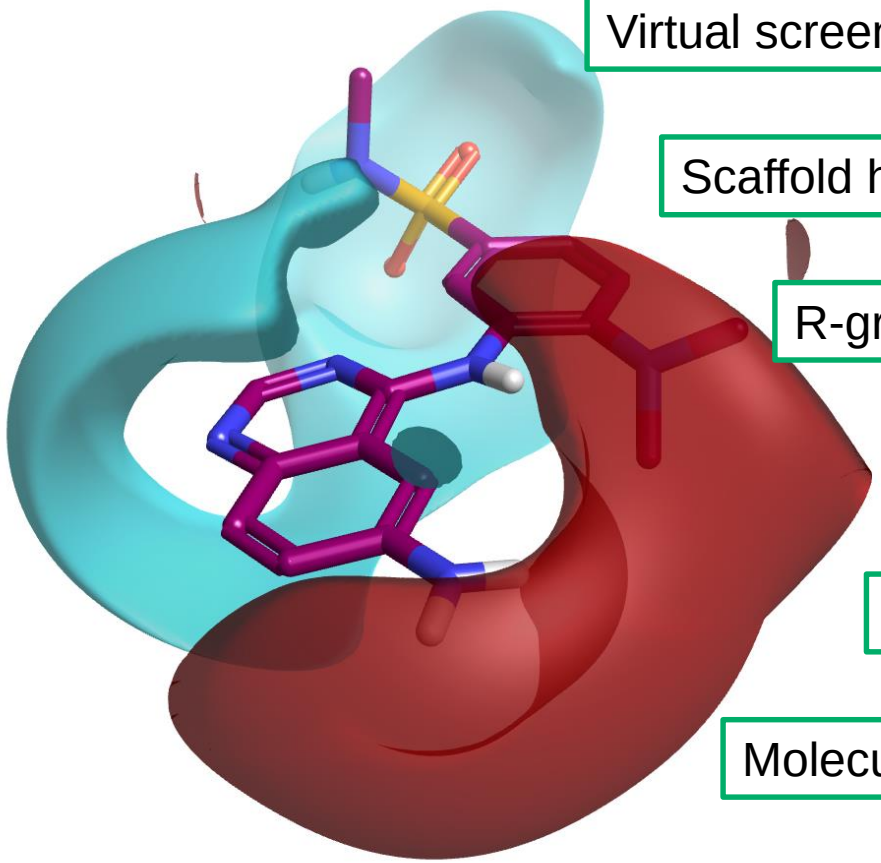
Virtual screening

Scaffold hopping

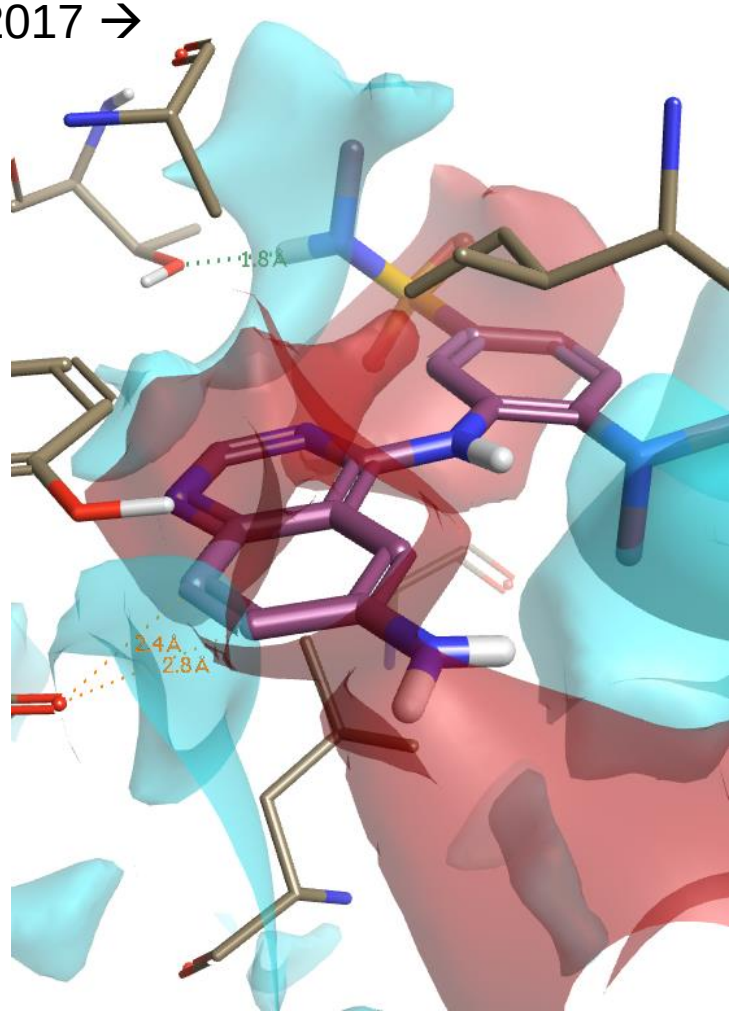
R-group selection

SAR analysis

Molecule design



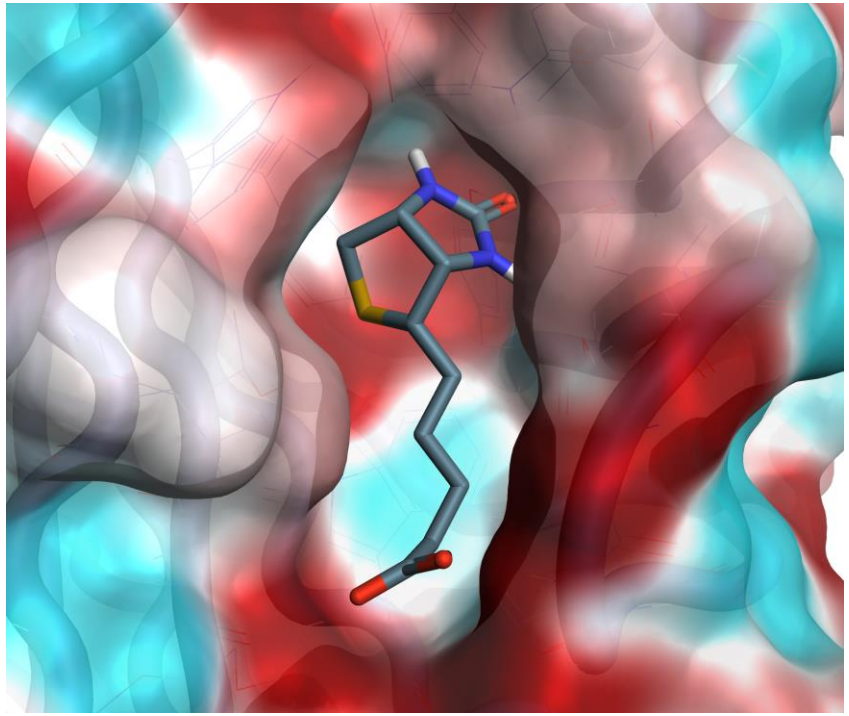
2017 →



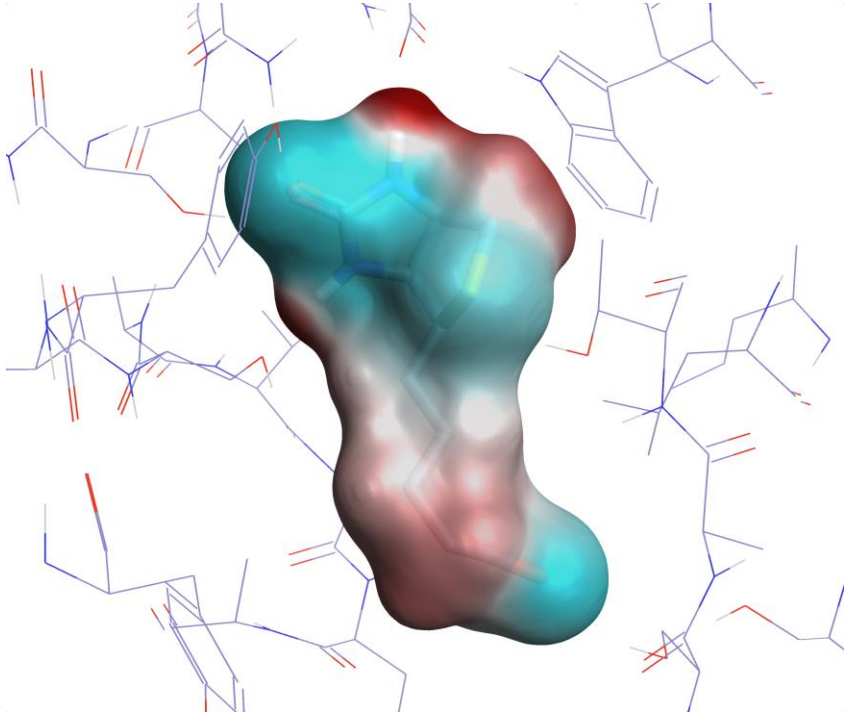
Positive potential

Negative potential

Biotin-Streptavidin electrostatics



180˚ rotation



XED ESP surface of Streptavidin

XED ESP surface of Biotin

Positive potential

Negative potential

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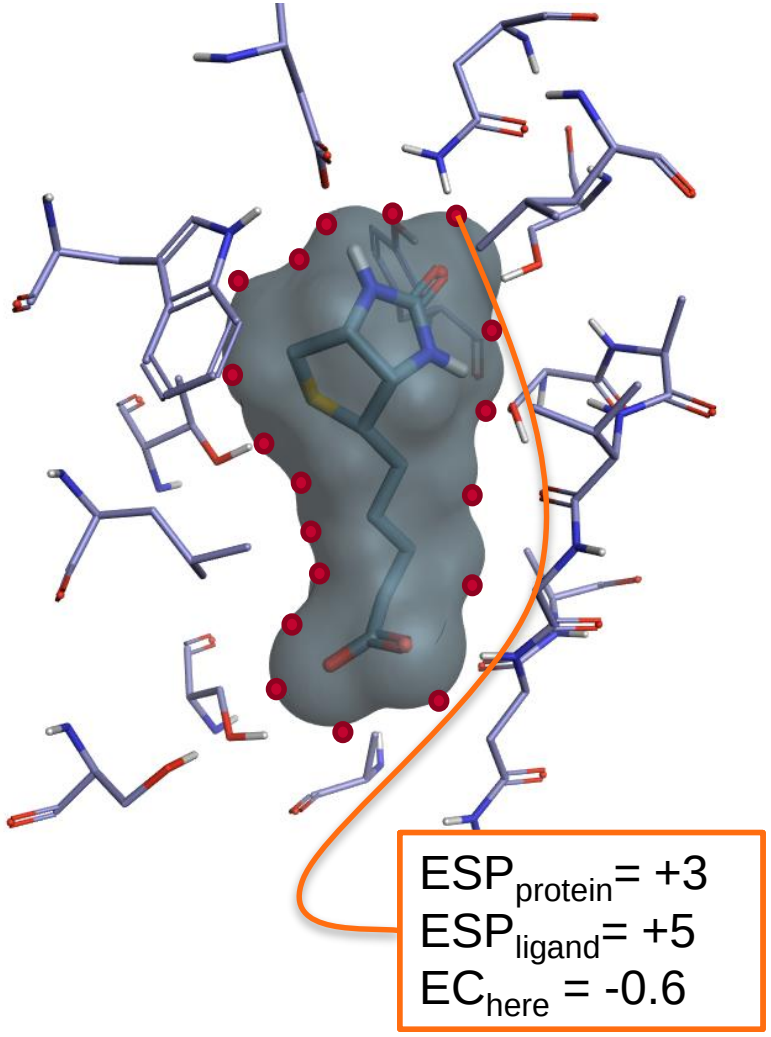
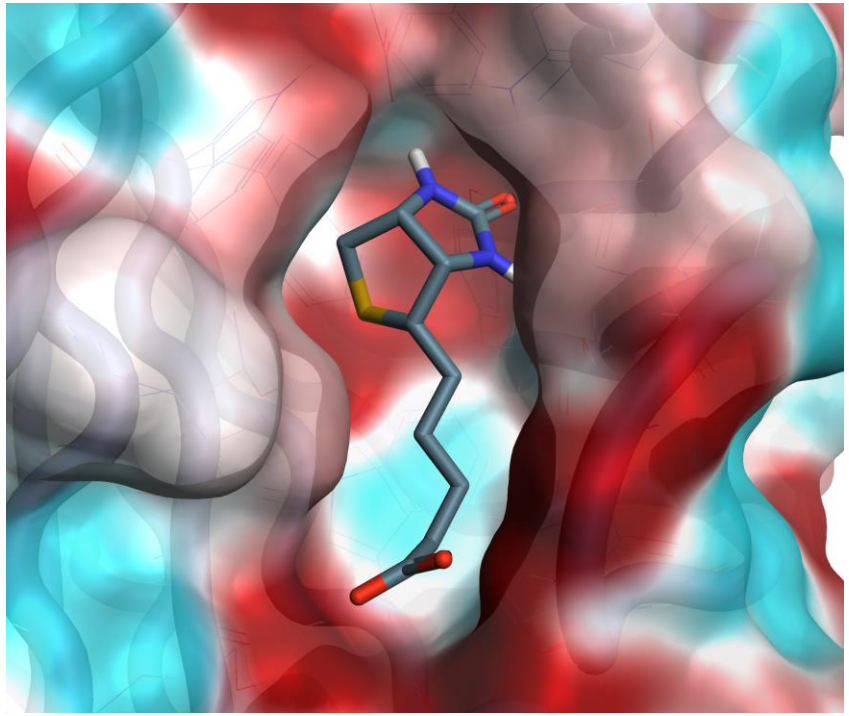
Calculating Electrostatic Complementarity

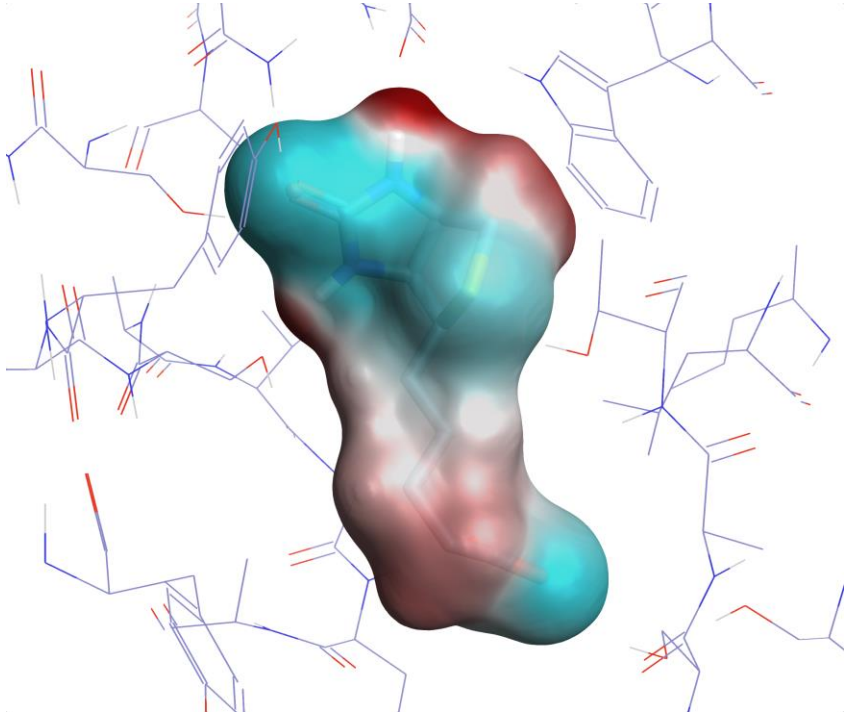
1. Place a solvent-accessible surface on the ligand
2. For each vertex on the surface, compute the electrostatic potential due to the ligand and to the protein
3. Scale down points on the ligand surface which are too far away from any protein atom (≥ 3 Å)
4. Cap values to a maximum (roughly corresponding to the maximum potential of a water molecule)
5. Complementarity(vertex) = $(1 - \frac{ESP_{ligand} + ESP_{protein}}{MAX\ (ESP_{ligand,protein})})$
6. Color vertices according to complementarity
   - → *perfect electrostatic complementarity = 1 (green)*
   - → *both potentials zero = 0 (white)*
   - → *perfect electrostatic clash = -1 (red)*



Biotin-Streptavidin electrostatics



180˚ rotation



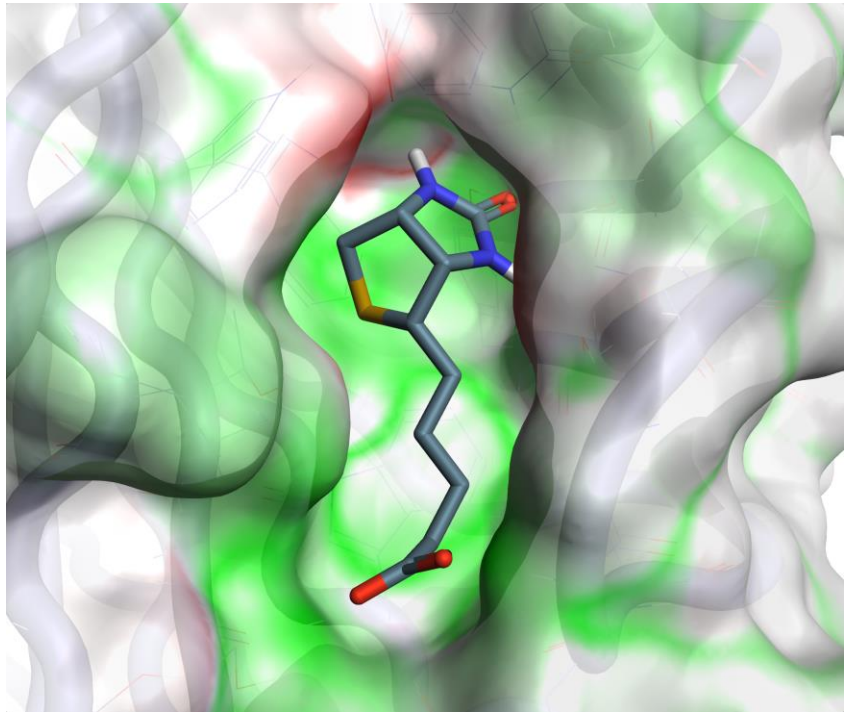
XED ESP surface of Streptavidin

XED ESP surface of Biotin

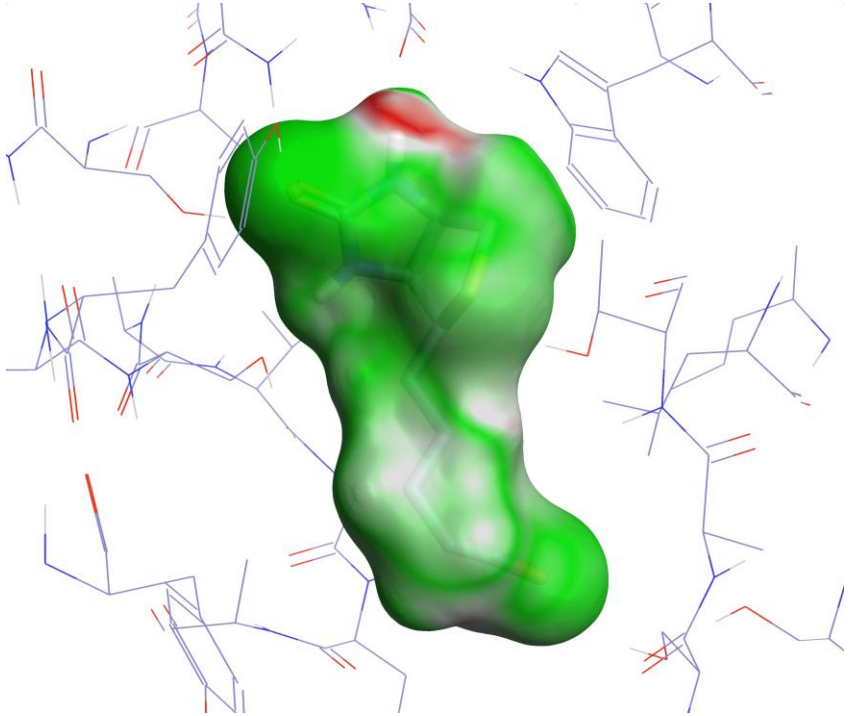
Positive potential

Negative potential

Biotin-Streptavidin Electrostatic Complementarity



180˚ rotation



EC surface of Streptavidin

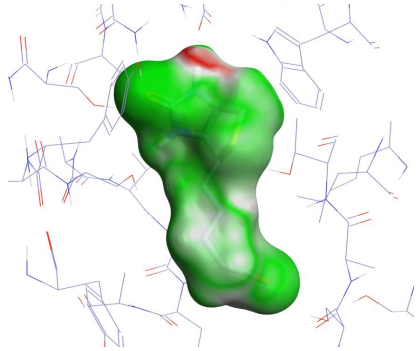
EC surface of Biotin

Good EC

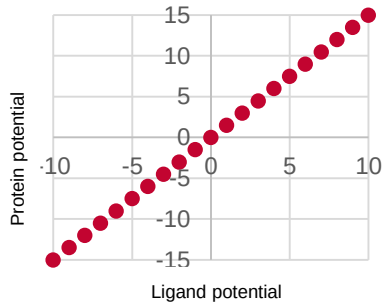
Poor EC

Converting Electrostatic Complementarity colors to scores

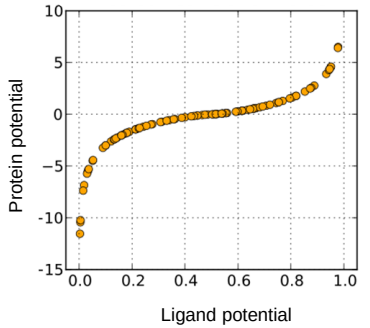
- Complementarity score (-1,1)
  - Normalized surface integral of the complementarity score described before
  - Includes some compensation for desolvation effects (capping of electrostatic potential values), and so may be more robust when these are significant
- Complementarity r (-1,1) or Pearson
  - Pearson correlation coefficient of protein and ligand electrostatic potentials sampled on the surface vertices
  - Can provide a better indication of ligand activity in some cases but is susceptible to noise
- Complementarity rho (-1,1) or Spearman
  - Spearman rank correlation coefficient of protein and ligand electrostatic potentials sampled on the surface vertices
  - More robust against background electric fields (useful if the computed protein electric potential is being biased by a large net charge on the protein)



Pearson



Spearman



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Application to a series of XIAP inhibitors

Journal of Medicinal Chemistry

Article

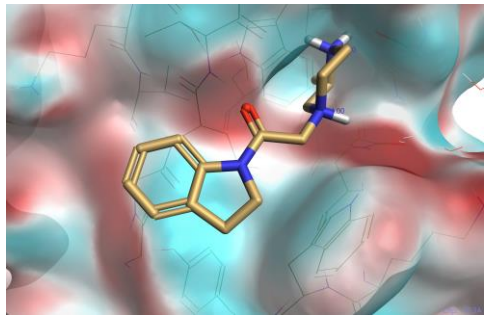
pubs.acs.org/jmc

Fragment-Based Drug Discovery Targeting Inhibitor of Apoptosis Proteins: Discovery of a Non-Alanine Lead Series with Dual Activity Against cIAP1 and XIAP

Gianni Chessari,* Ildiko M. Buck, James E. H. Day, Philip J. Day, Aman Iqbal, Christopher N. Johnson, Edward J. Lewis, Vanessa Martins, Darcey Miller, Michael Reader, David C. Rees, Sharna J. Rich, Emiliano Tamanini, Marc Vitorino, George A. Ward, Pamela A. Williams, Glyn Williams, Nicola E. Wilsher, and Alison J.-A. Woolford

Astex Pharmaceuticals, 436 Cambridge Science Park, Milton Road, Cambridge, CB4 0QA, United Kingdom

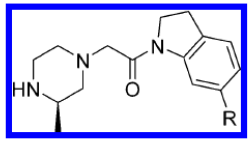
> Investigation of the electronegative pocket of XIAP-BIR3 by modulating the functionality of the indole C6 with a range of electron withdrawing and electron donating substituents.



Negative potential

Positive potential

Table 2. XIAP-BIR3 Affinity of Substituted Indolines 7−16

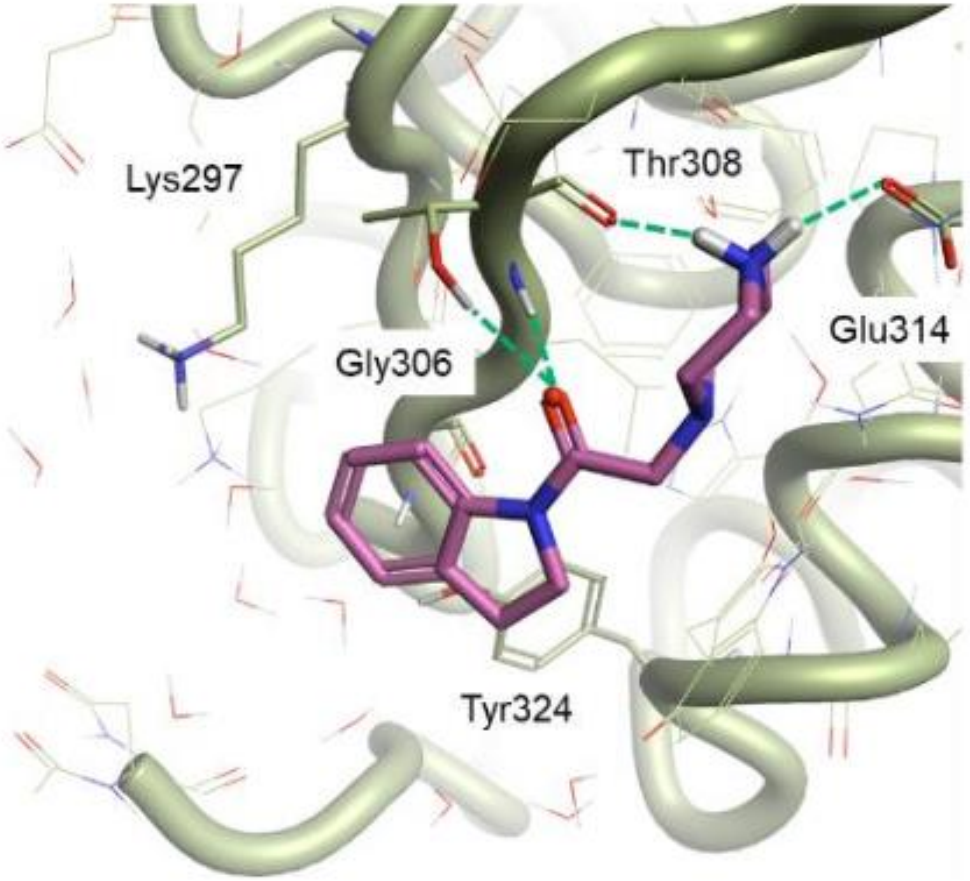


compd	R	Hammett σ_p	XIAP-BIR3[a] IC_{50} (μM) or %I	XIAP-BIR3 LE[b] (kcal mol^{-1} per non-H atom)
7	−H	0.00	52% @ 495 μM	~0.24
8	$-NH_2$	−0.66	56% @ 1000 μM	~0.20
9	−OMe	−0.27	49% @ 155 μM	~0.25
10	−Me	−0.17	46	0.30
11	−iPr	−0.15	59	0.26
12	−F	0.06	51	0.29
13	−Cl	0.23	13	0.33
14	−Br	0.23	9.8	0.34
15	$-CF_3$	0.54	5.9	0.31
16	$-SO_2Me$	0.72	4.1	0.32

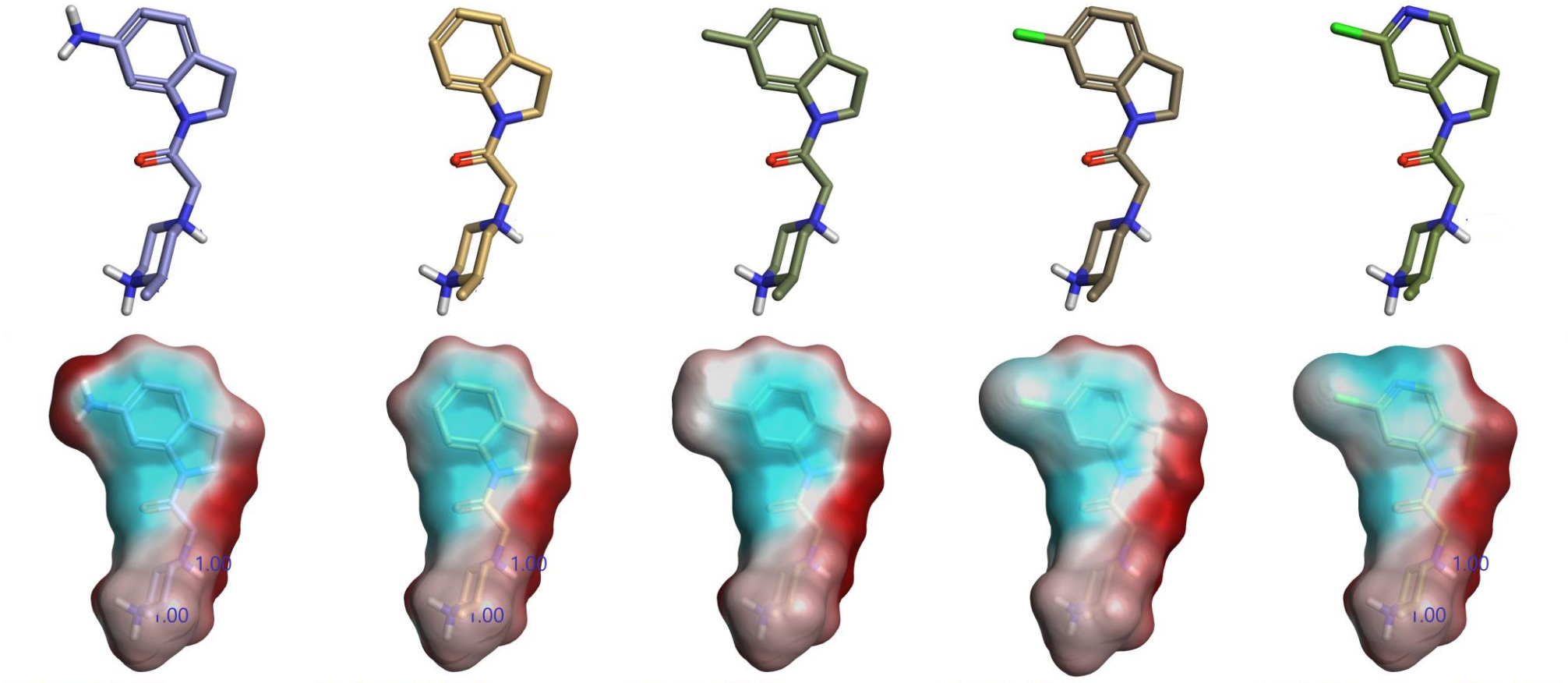
[a]Values were determined by fluorescence polarization assay (see Experimental Section). Potency data are reported as the mean of at least two runs. [b]Values calculated according to the Hopkins formula.[17]

Data set and experimental set-up

- Table 2 compounds compared to 5C7A protein
- The side chain atoms were minimized with the XED force field for each ligand as many modelled binding modes clash with the flexible side chain of Lys297.
- Retained water have at least 2 H-bond contacts to the protein or at least 1 H-Bond to ligand and protein.
- Manual building of ligands
  - Substructure alignment of the indoline scaffold to the 5C7A ligand using Forge



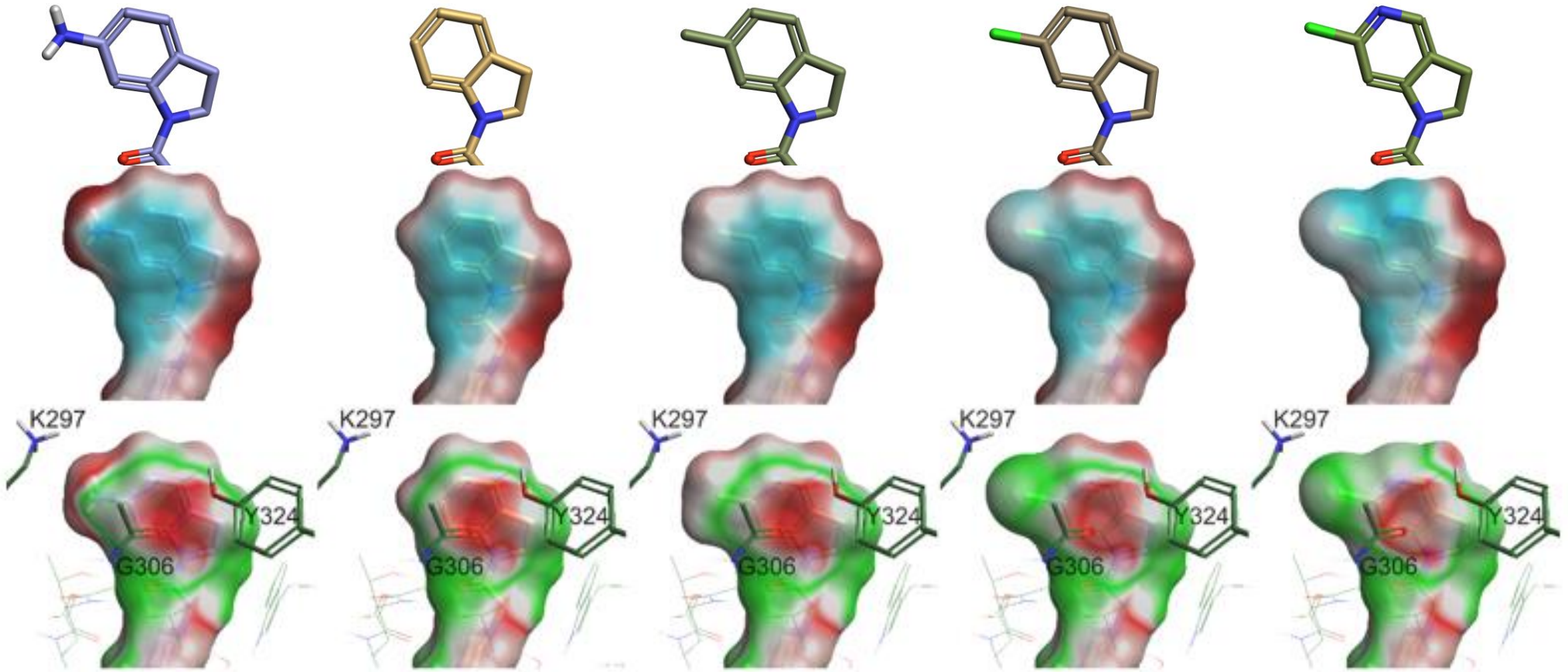
Electrostatic potential of five XIAP inhibitors



Compound 8	Compound 7	Compound 10	Compound 13	Compound 17
pIC_{50} = 3.0	3.3	4.3	4.5	5.1

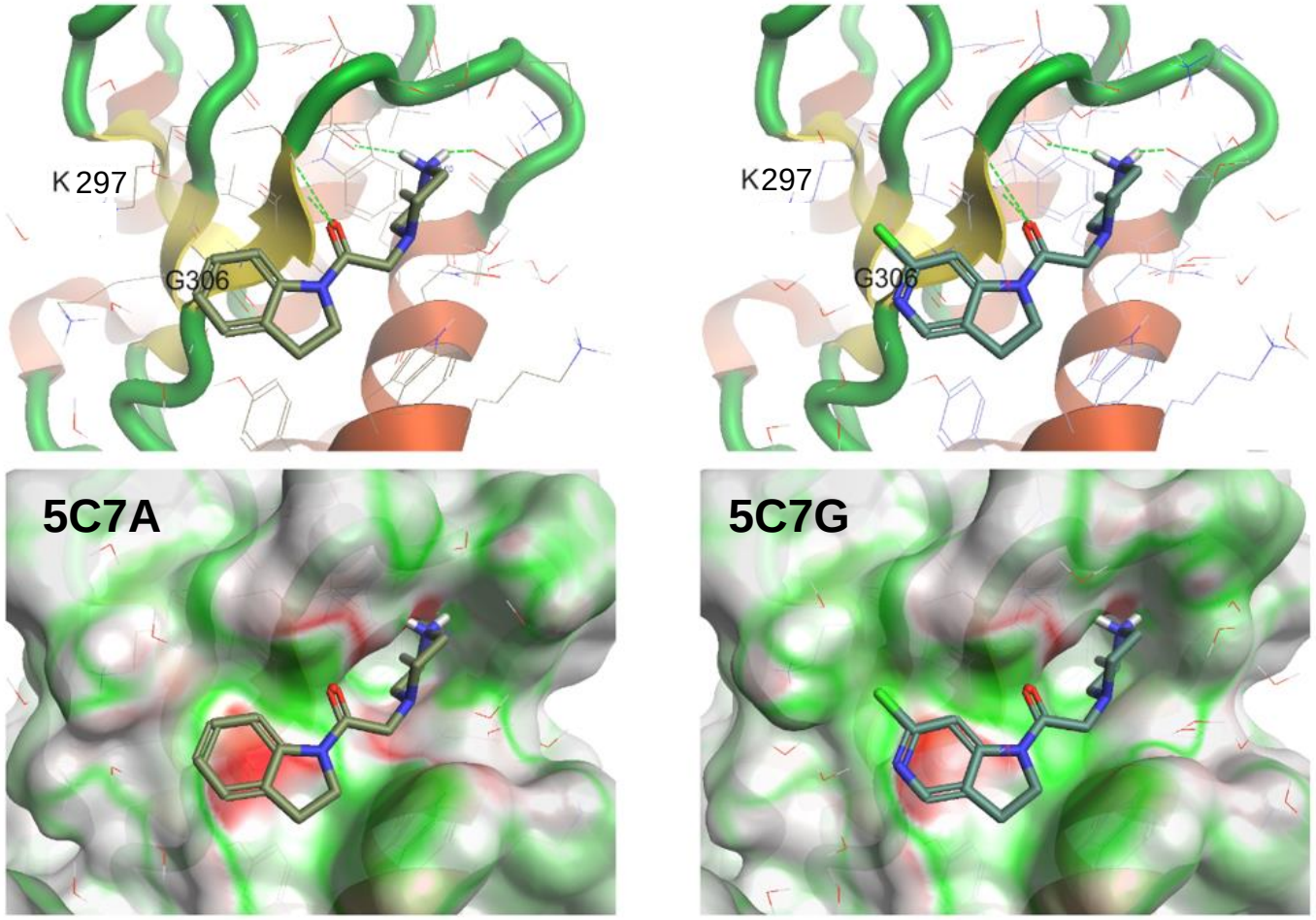
→ Increase electron withdrawing effect

Electrostatic Complementarity of five XIAP inhibitors



EC to XIAP binding site

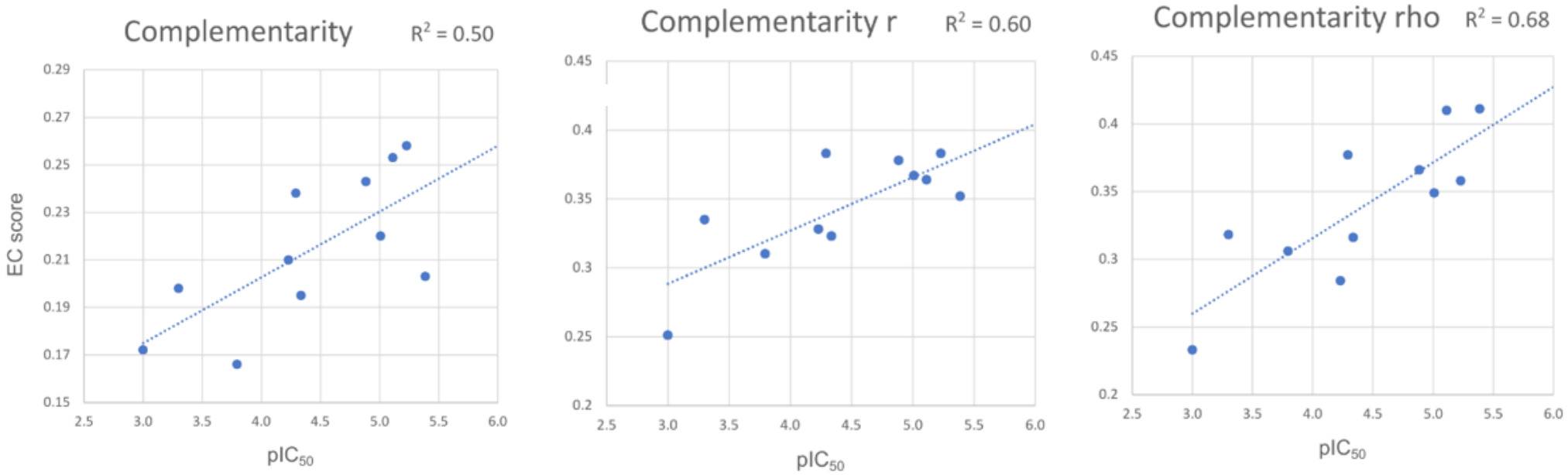
- The EC maps show improved EC
  - Around Lys297 side chain
  - Around Gly306 backbone



Compound 7 pIC_{50}= 3.3
LE = 0.24

Compound 17 pIC_{50} = 5.1
LE = 0.35

EC scores and pIC_{50} correlation for the XIAP series



- Nice correlation between the XIAP-BIR3 pIC_{50} and the EC scores
- EC maps provide a visual insight into ligand - protein binding and activity prediction
- Calculations of EC scores are fast - just over 1 second per molecule

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Application to a series of mGLU5 negative allosteric modulators

Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Fragment and Structure-Based Drug Discovery for a Class C GPCR: Discovery of the mGlu$_5$ Negative Allosteric Modulator HTL14242 (3-Chloro-5-[6-(5-fluoropyridin-2-yl)pyrimidin-4-yl]benzonitrile)

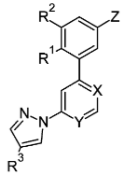
John A. Christopher,* Sarah J. Aves, Kirstie A. Bennett, Andrew S. Doré, James C. Errey, Ali Jazayeri, Fiona H. Marshall, Krzysztof Okrasa, Maria J. Serrano-Vega, Benjamin G. Tehan, Giselle R. Wiggin, and Miles Congreve

Heptares Therapeutics Ltd., BioPark, Welwyn Garden City, Hertfordshire AL7 3AX, U.K.

> Two ligand-bound X-ray structures with 2.6 and 3.1 A resolution (clear density for ligands)

PDB: 5CGC

Table 1. In Vitro Profile of Compounds 6−17

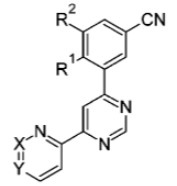


	X	Y	Z	R^1	R^2	R^3	mGlu$_5$ pK_i	mGlu$_5$ pIC$_{50}$	RLM $t_{1/2}$ (min)
6	N	N	CN	H	F	H	7.2	6.4	25
7	N	N	CN	F	H	H	6.6	nd[a]	6
8	N	N	CN	H	H	H	6.1	nd	nd
9	N	N	H	H	F	H	5.1	nd	nd
10	N	N	OMe	H	F	H	<4.2	nd	nd
11	N	N	$CONH_2$	H	F	H	<4.2	nd	nd
12	N	N	CN	H	Me	H	8.4	7.9	10
13	N	N	CN	H	Cl	H	8.4	8.3	12
14	N	N	CN	F	Cl	H	9.3	8.6	20
15	N	CH	CN	H	Me	H	7.6	7.4	51
16	CH	N	CN	H	Me	H	7.7	7.7	43
17	N	N	CN	H	Cl	F	7.7	7.1	52

[a]nd = not determined.

PDB: 5CGD

Table 2. In Vitro Profile of Compounds 21−30

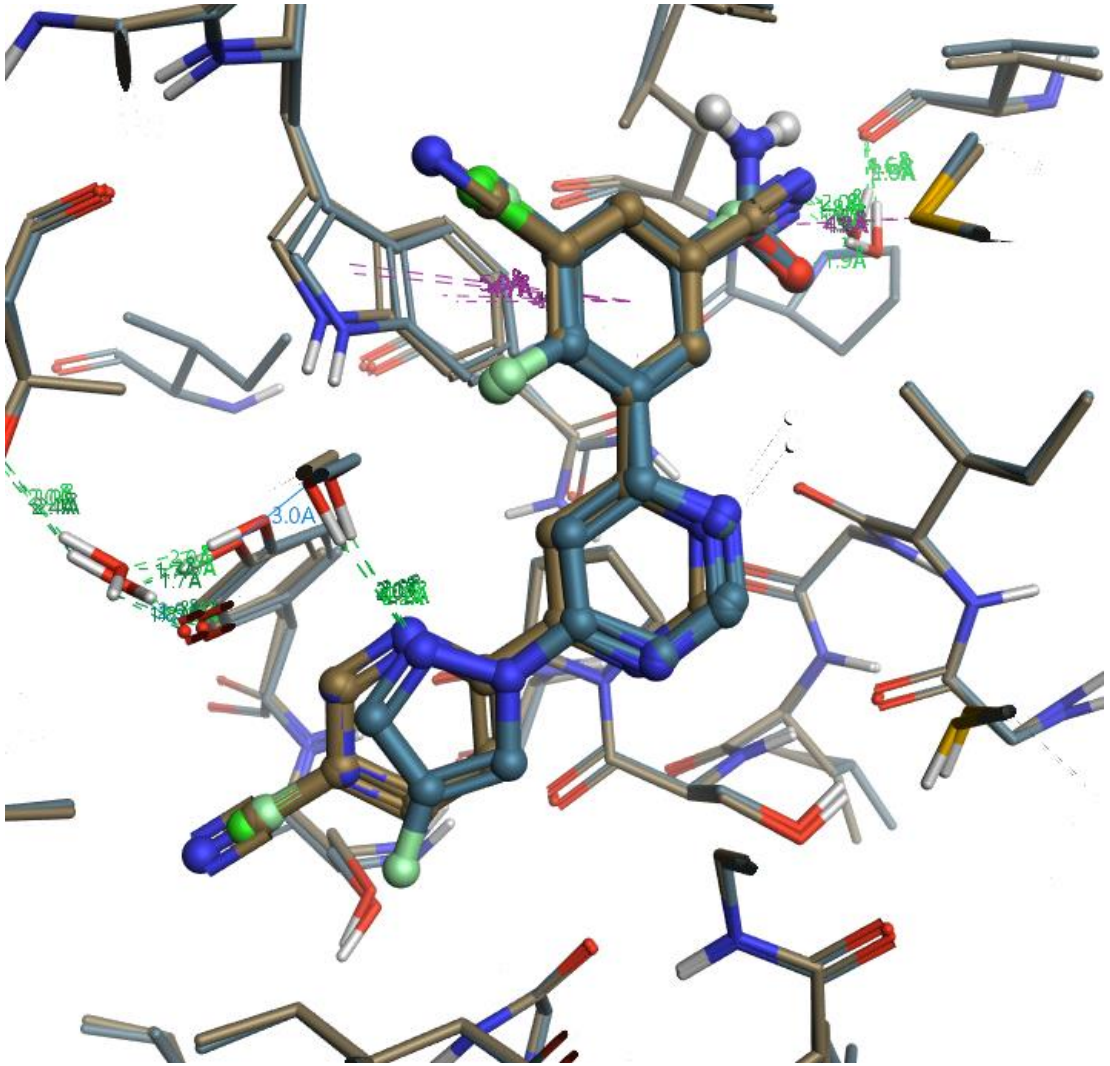


	X	Y	R^1	R^2	mGlu$_5$ pK_i	mGlu$_5$ pIC$_{50}$	RLM $t_{1/2}$ (min)
21	CH	CH	H	Cl	8.5	8.6	43
22	CH	CH	F	Cl	8.9	8.8	31
23	CH	CMe	H	Cl	8.6	8.3	19
24	CH	CF	H	CN	8.8	8.6	>100
25	CH	CF	H	Cl	9.3	9.2	44
26	CH	CCN	H	Cl	9.2	9.2	>100
27	CH	CCl	H	Cl	8.8	8.5	35
28	CH	CF	F	Cl	9.1	9.4	87
29	N	CH	H	Cl	8.0	6.7	nd[a]
30	CH	N	H	Cl	8.3	7.5	nd

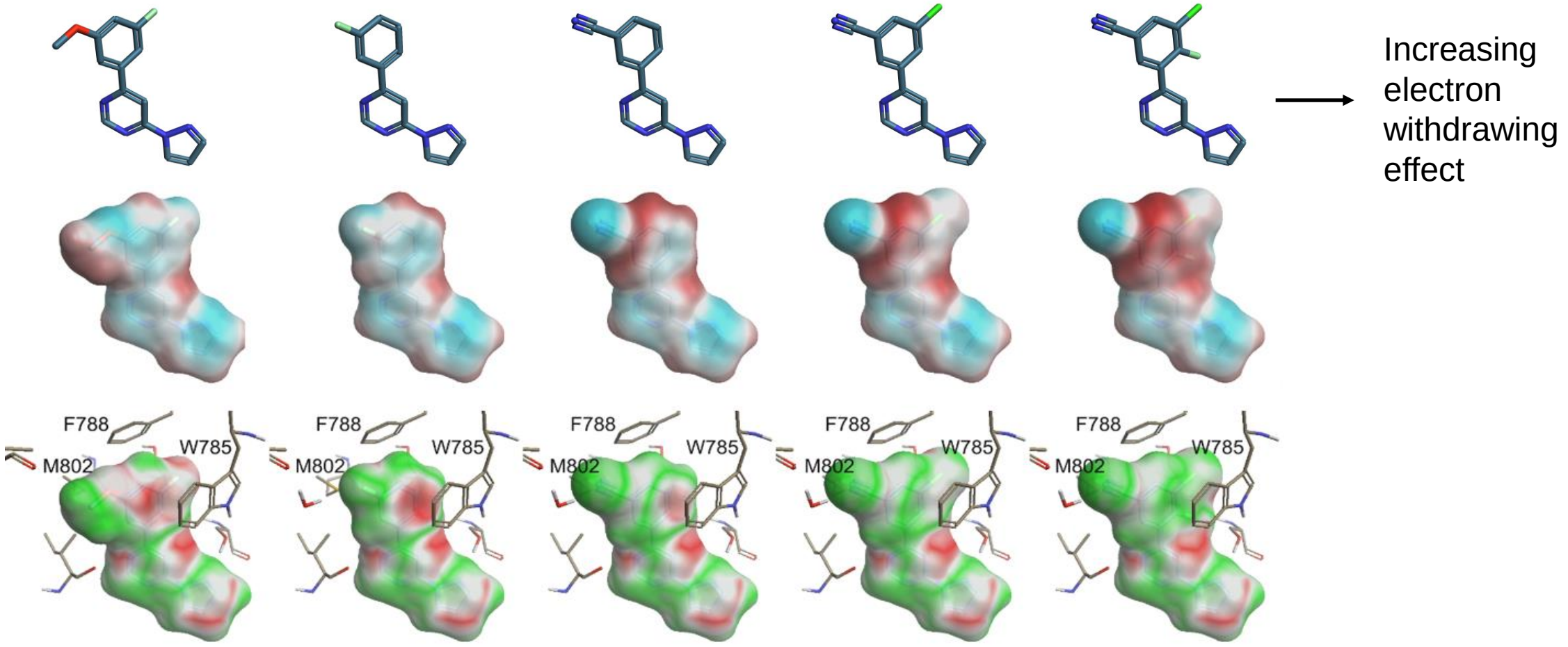
[a]nd = not determined.

Data set and experimental set-up

- Table 1 compounds compared to 5CGC protein
- Table 2 compounds compared to 5CGD protein
- Only minor changes in structure
- Retained “stable” water from 3D RISM calculation (same waters in each structure)
- Manual mutation of ligands
  - No optimization of binding
  - Manual orientation of groups

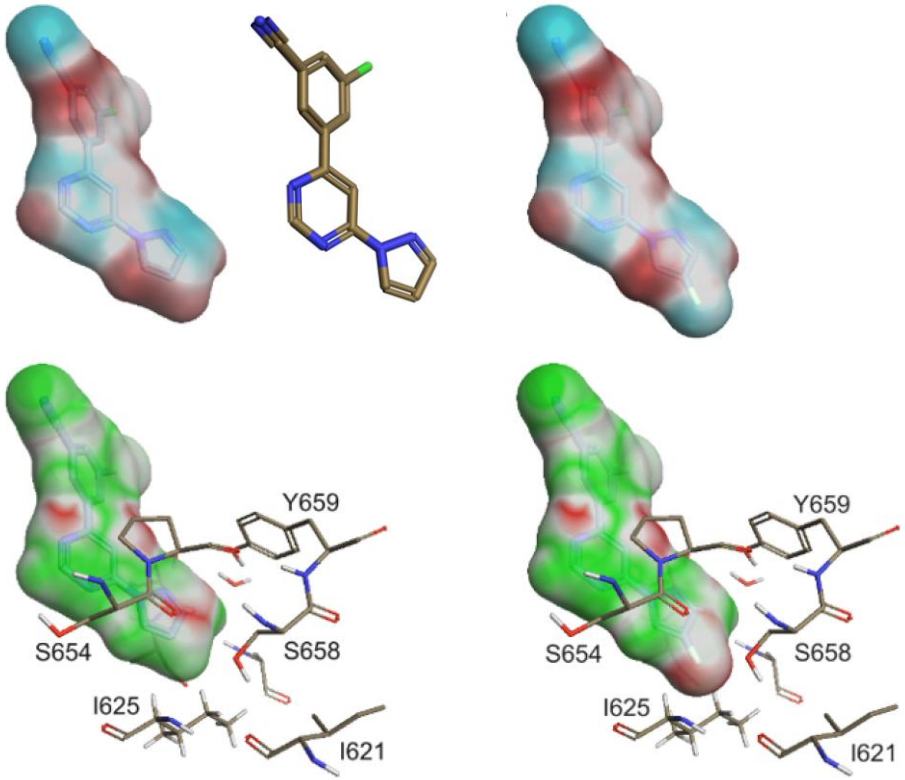


Electrostatic Complementarity of five mGLU5 NAMs

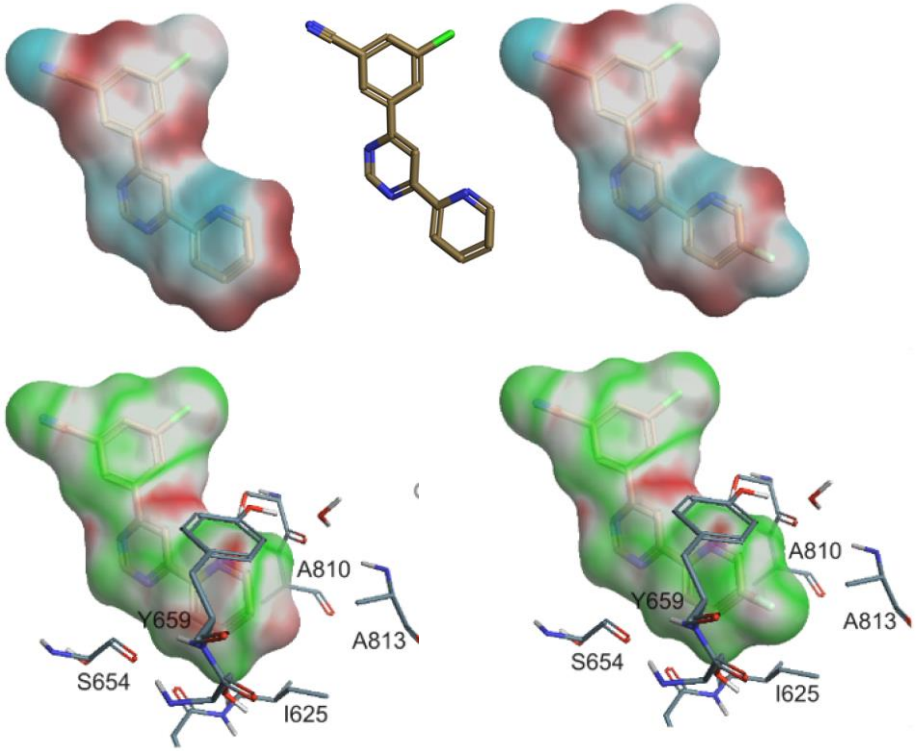


Impact of fluorination on EC and activities

A



B



	Compound 13	Compound 17	Compound 21	Compound 25
	pKi = 8.4	7.7	pKi = 8.5	9.3
	SCI = 0.40	0.38	SCI = 0.40	0.46
	R = 0.57	0.47	R = 0.58	0.62
	Rho = 0.52	0.48	Rho = 0.56	0.61

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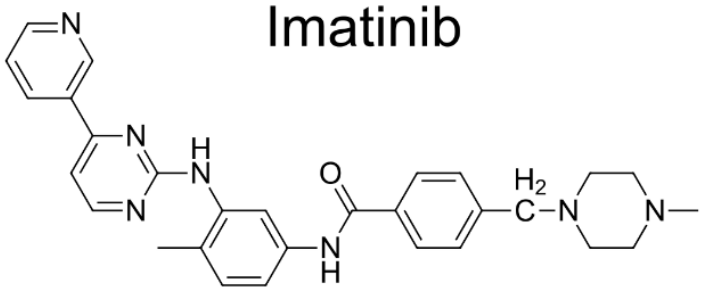
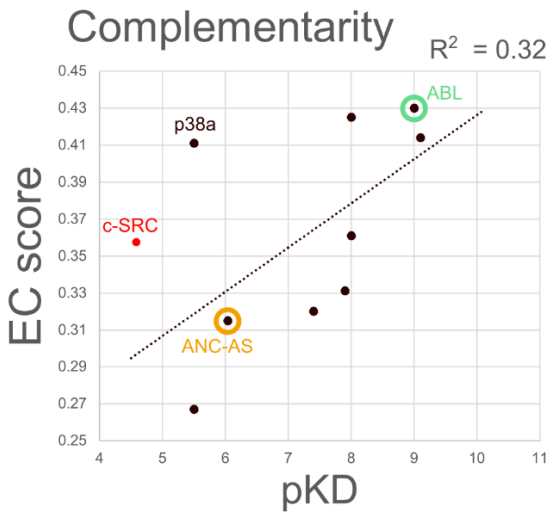
- Summary and future outlook

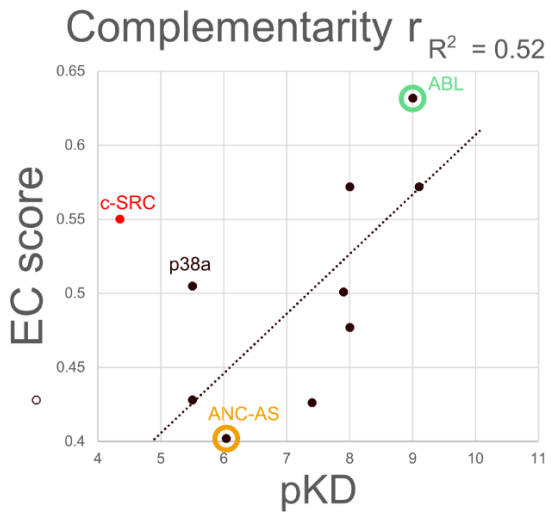
Imatinib – EC and selectivity

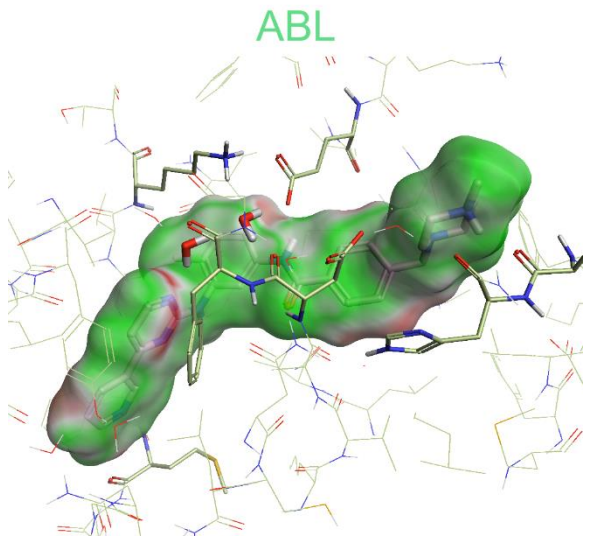


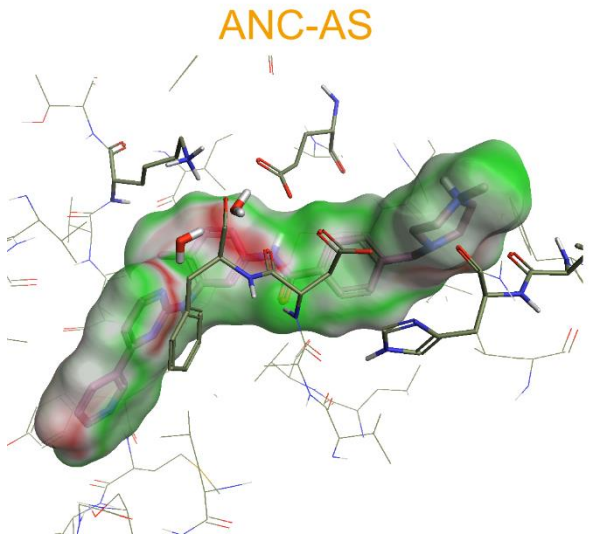
target	pdb	pKD	Complementarity	Complementarity r
c-SRC [a]	2OIQ	4.4	0.36	0.55
p38a	3HEC	5.5	0.41	0.51
SYK	1XBB	5.5	0.27	0.43
ANC-AS	4CSV	6.0	0.32	0.40
LCK	2PL0	7.4	0.32	0.43
KIT	1T46	7.9	0.33	0.50
CSF1	4R7I	8.0	0.36	0.48
ABL2	3GVU	8.0	0.43	0.57
ABL	1OPJ	9.0	0.43	0.63
DDR1	4BKJ	9.1	0.41	0.57

[a] Imatinib binding decreased due to conf. penalty upon binding



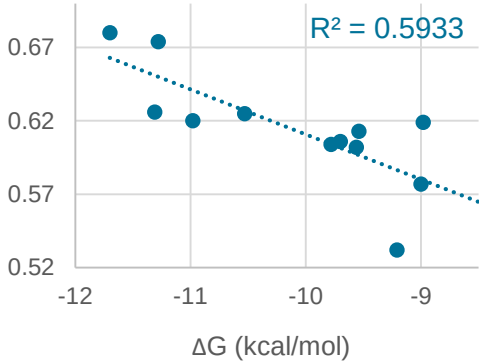




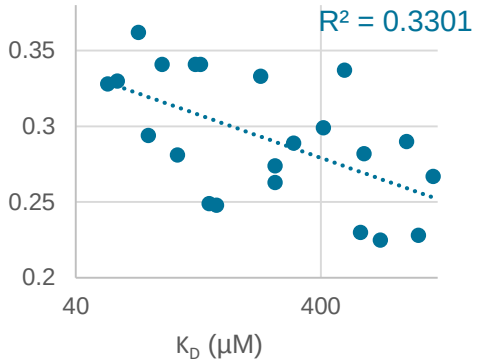


Application to additional data sets

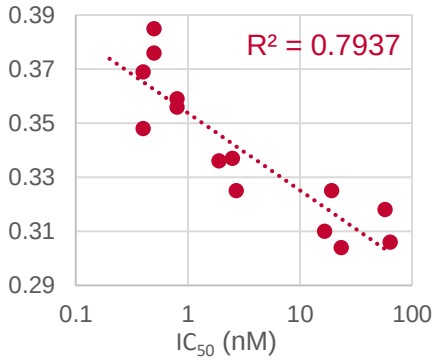
TYK2



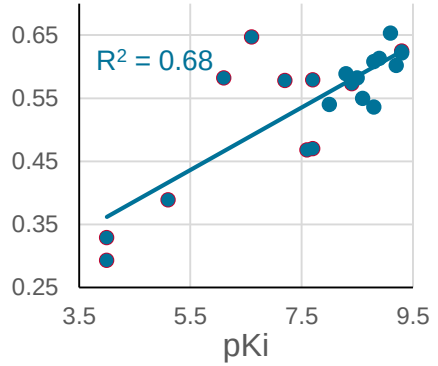
RPA70N



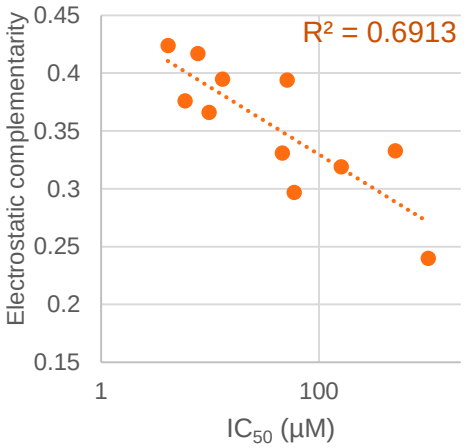
PERK



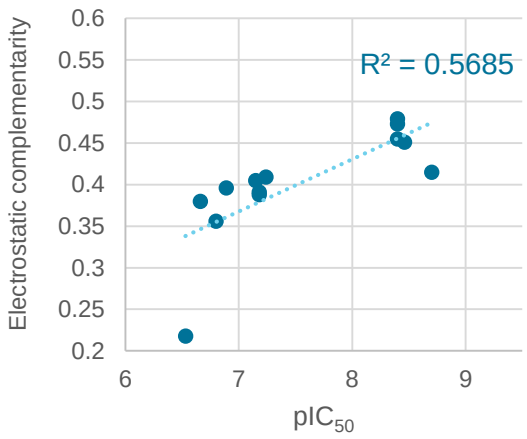
mGlu5



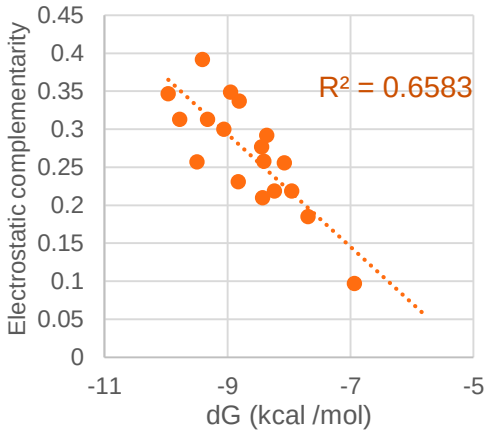
XIAP



DPP4



MCL1



Complementarity; Complementarity r; Complementarity rho

Summary and future outlook

- Meaningful assessment of electrostatic complementarity at low computational cost (< 1 second per molecule on a desktop workstation)

- Possible to rank bioactivities of ligands (provided electrostatics play a main role in affinity changes)
  - Caveats: does not calculate free energy of binding ΔG (desolvation, cavity term and space filling, entropic contributions, conformational effects missing); orthogonal multipolar interactions (fluorine bonding)

- Additional validation and future research: Improved handling of solvent exposed areas, rescoring of docking results

Try EC on your dataset using Flare:
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Cresset team (summer 2018)

Questions welcomed

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