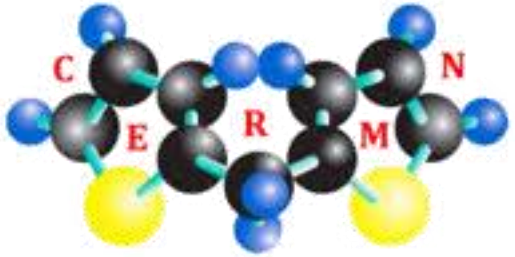


SCHISM

Supporting chemoinformatics via interactive unsupervised and semi-supervised data mining

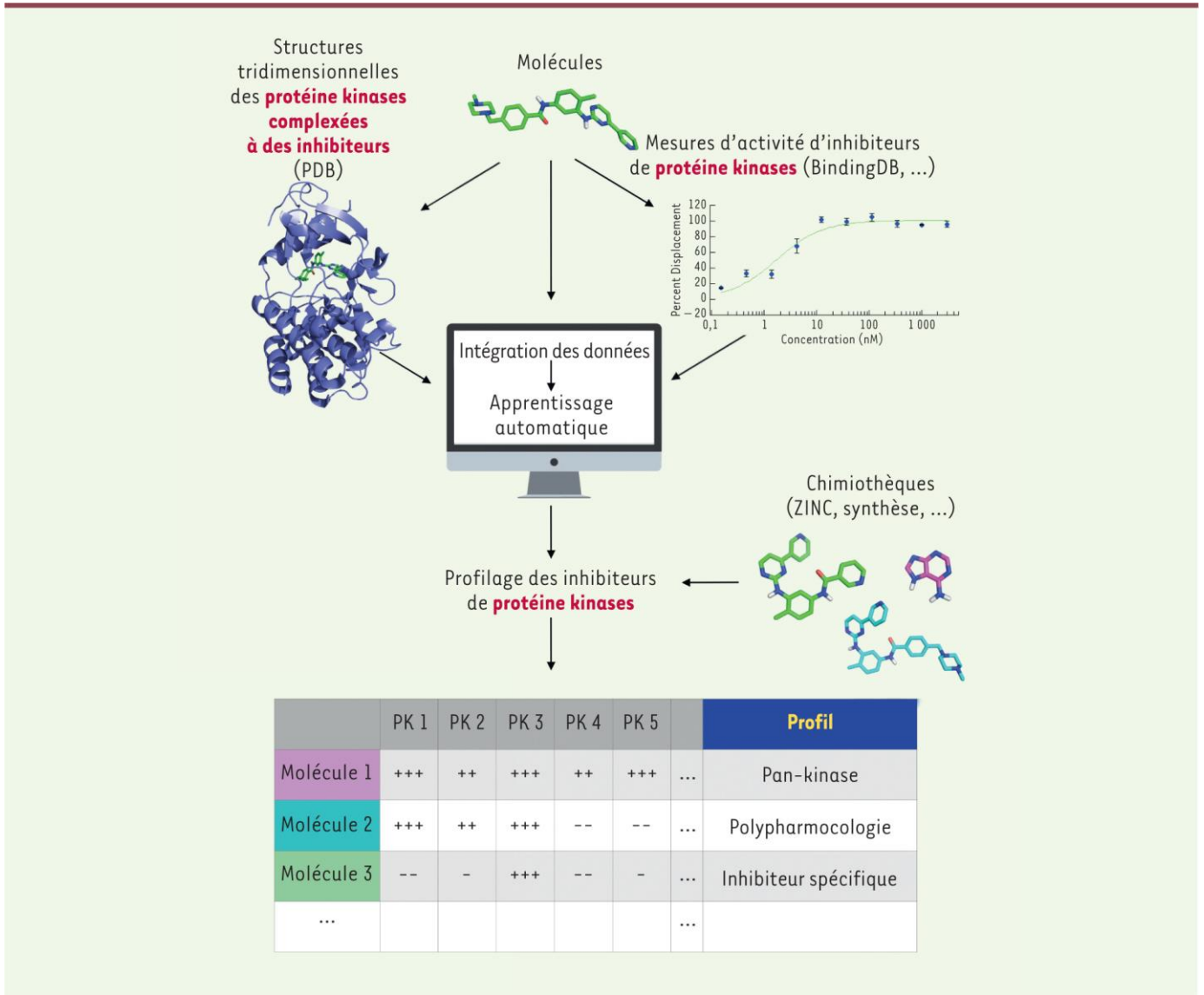
Ronan Bureau, Alban Lepailleur, Jean-Luc Manguin, Jean-Luc Lamotte, Bertrand Cuissart

Le projet SCHISM est financé par l'Union européenne dans le cadre du programme opérationnel FEDER/ FSE 2014-2020."/"The European project "SCHISM" is funded by the European Union within the framework of the Operational Programme ERDF/ESF 2014-2020

RÉGION NORMANDIE

UNION EUROPÉENNE
Fonds européen de développement régional

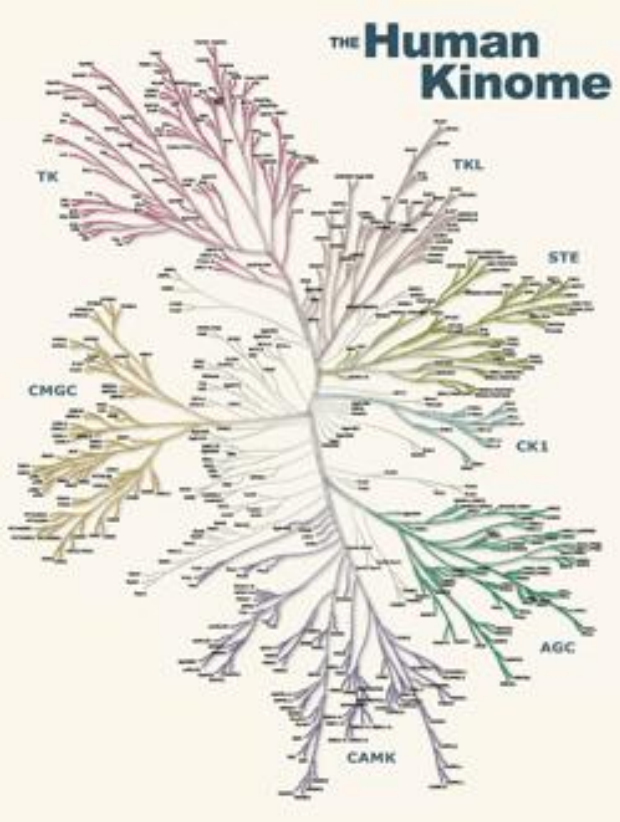
DATA : Kinome (535 kinases humaines)



	PK 1	PK 2	PK 3	PK 4	PK 5		Profil
Molécule 1	+++	++	+++	++	+++	...	Pan-kinase
Molécule 2	+++	++	+++	--	--	...	Polypharmocologie
Molécule 3	--	-	+++	--	-	...	Inhibiteur spécifique
...						...	

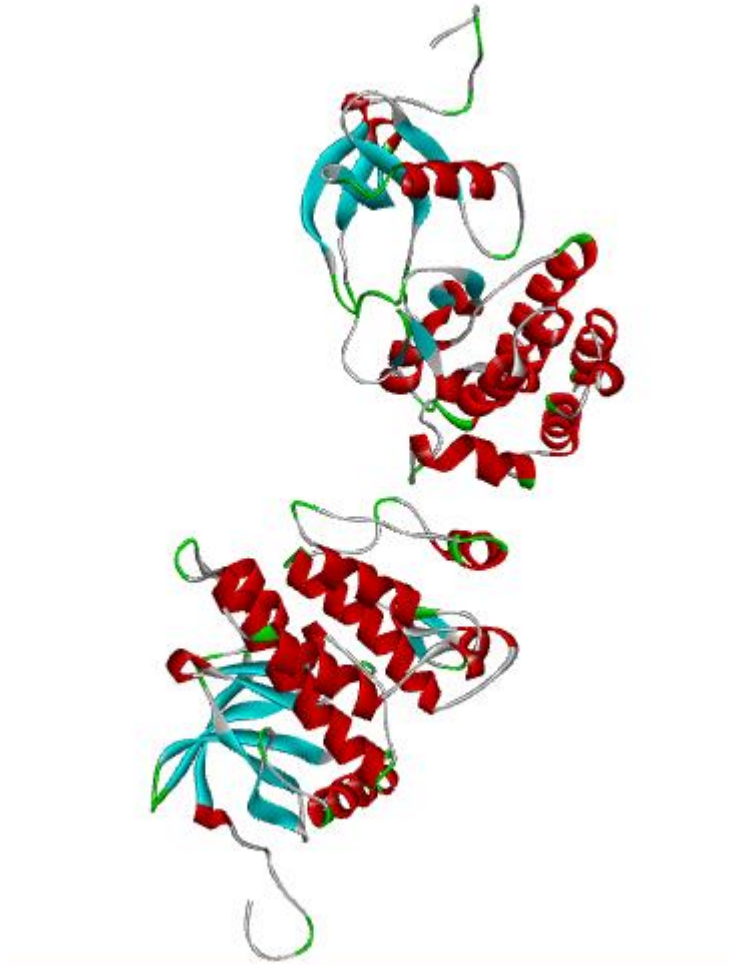
Victor Reys et Gilles Labesse. Profilage in silico des inhibiteurs de protéine kinases. Med Sci (Paris) 2020; 36 (Hors série n° 1) : 38–41

DATA : Kinome (535 human kinases)



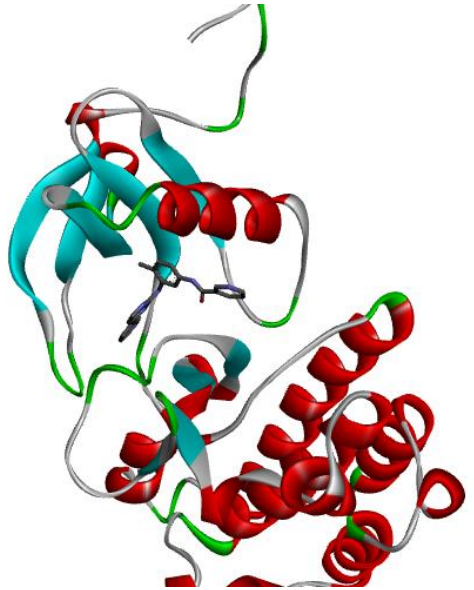
The Protein Kinase Complement of the Human Genome
G Manning, DB Whyte, R Martinez, T Hunter, S Sudarsanam
(2002). Science 298:1912-1934

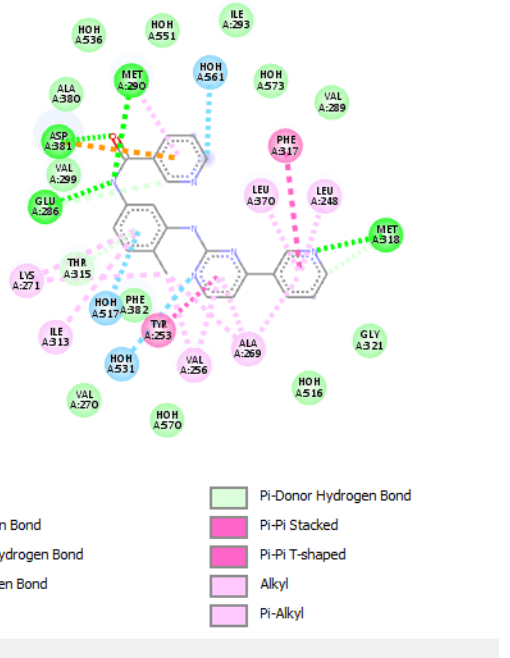
Kinases are divided into 9 main groups, and each group is then split into families, and often subfamilies.
Voir : http://kinase.com/classification/



1FPU (PDB)

More than 95% of current kinase inhibitors target the largely conserved ATP (cofactor) binding site (type I)



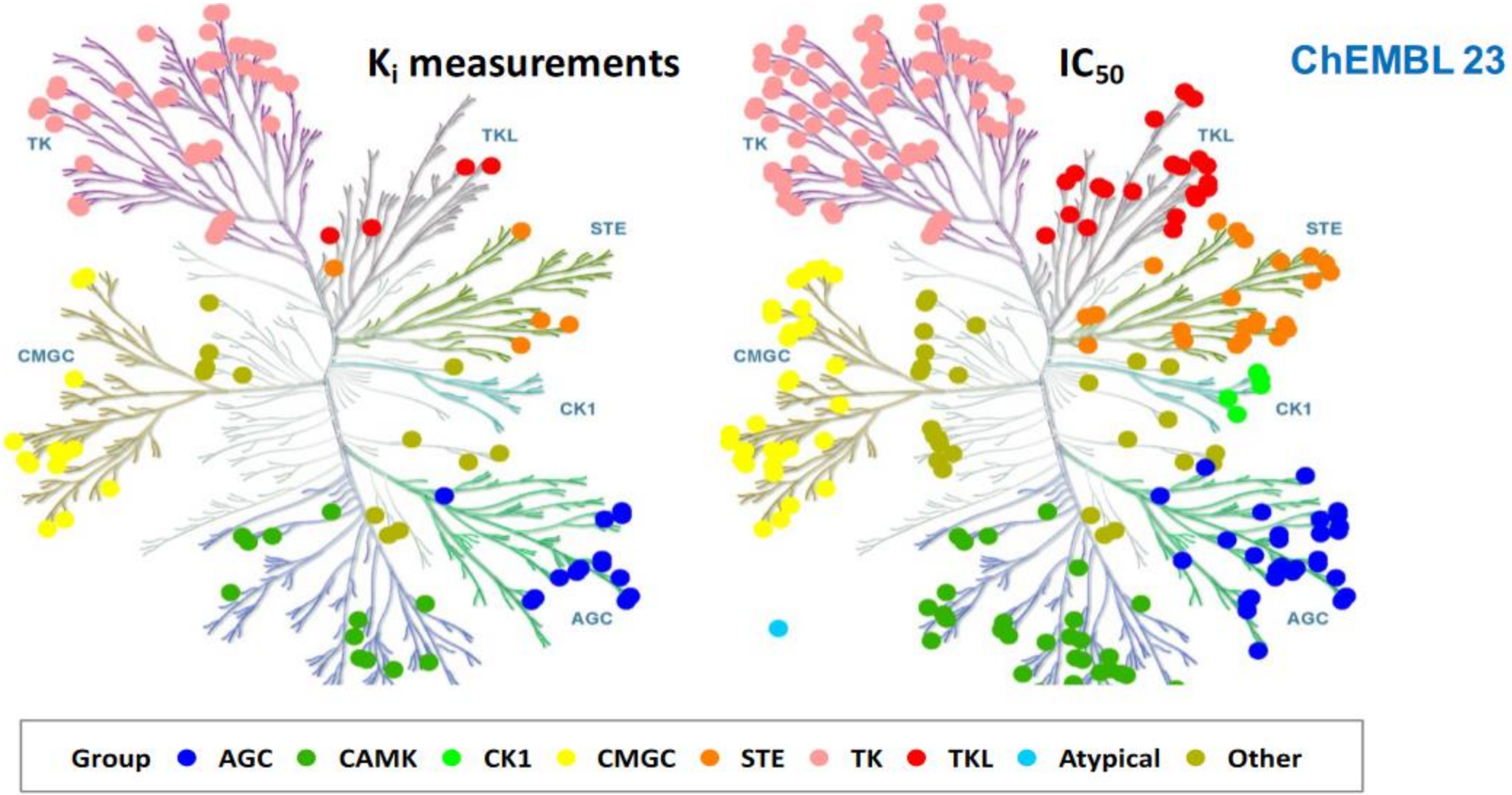


Kinase inhibitors with **high-confidence** activity data

ChEMBL 23 **2017**	ChEMBL 18 **2015**
• **45,728** kinase inhibitors • 286 kinases • 12 kinase groups	• **18,951** kinase inhibitors • 266 kinases • 10 kinase groups

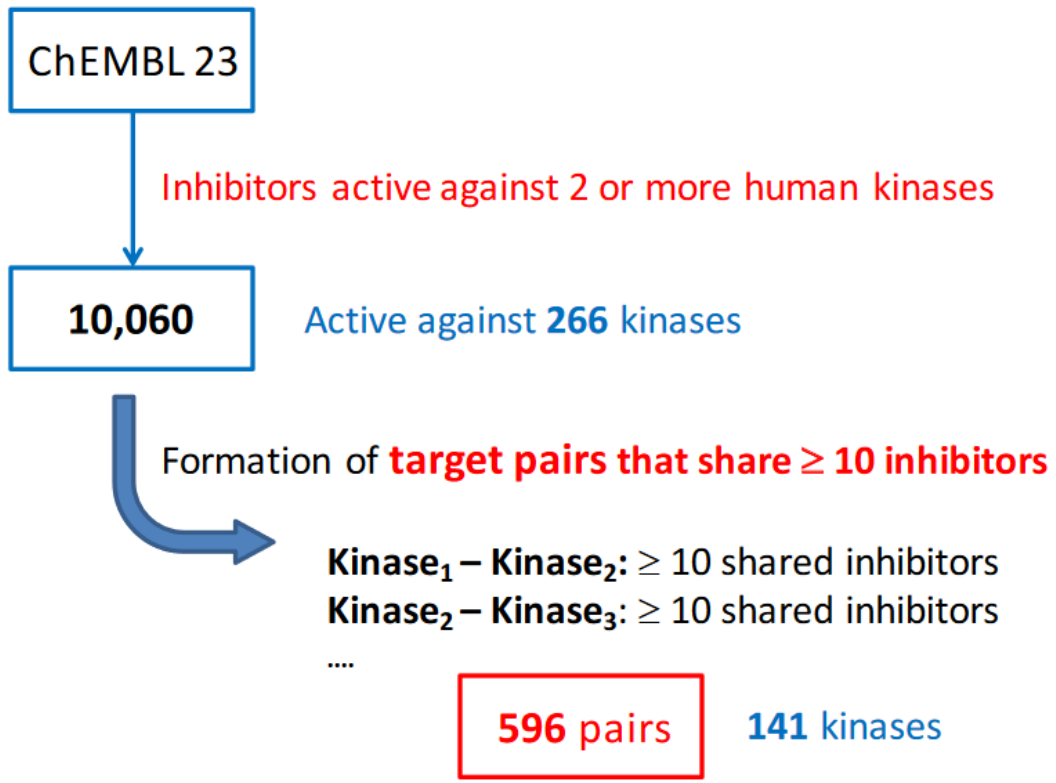
Jürgen Bajorath (University of Bonn). Emerging Big Data: Chemoinformatics-Driven View of Kinase Drug Discovery

CHEMBL27	May 2020	10.6019/CHEMBL.database.27
CHEMBL26	March 2020	10.6019/CHEMBL.database.26
CHEMBL25	March 2019	10.6019/CHEMBL.database.25
CHEMBL24.1	June 2018	10.6019/CHEMBL.database.24.1
CHEMBL24	May 2018	10.6019/CHEMBL.database.24
CHEMBL23	May 2017	10.6019/CHEMBL.database.23


K_i measurements
IC_{50}
ChEMBL 23
TK
TKL
STE
CMGC
CK1
AGC
Group
AGC
CAMK
CK1
CMGC
STE
TK
TKL
Atypical
Other

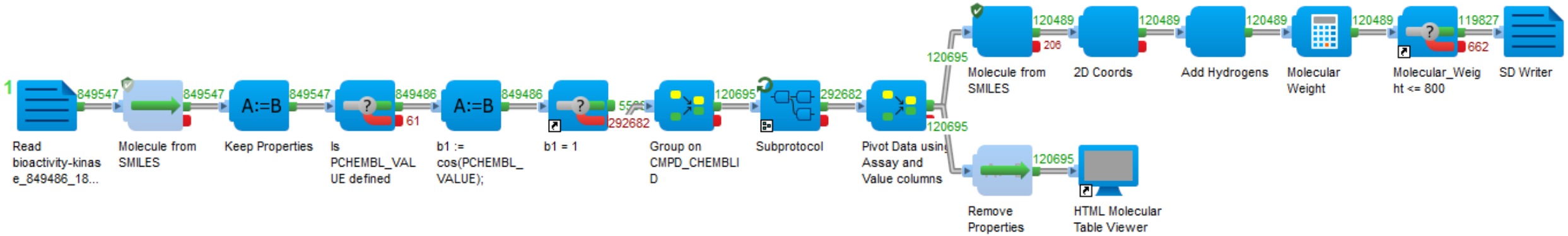
Kinase Inhibitors - Selectivity

- **Promiscuous** human kinase inhibitors with high-confidence data



Jürgen Bajorath (University of Bonn). Emerging Big Data: Chemoinformatics-Driven View of Kinase Drug Discovery

Compilation des données kinases / ChEMBL24

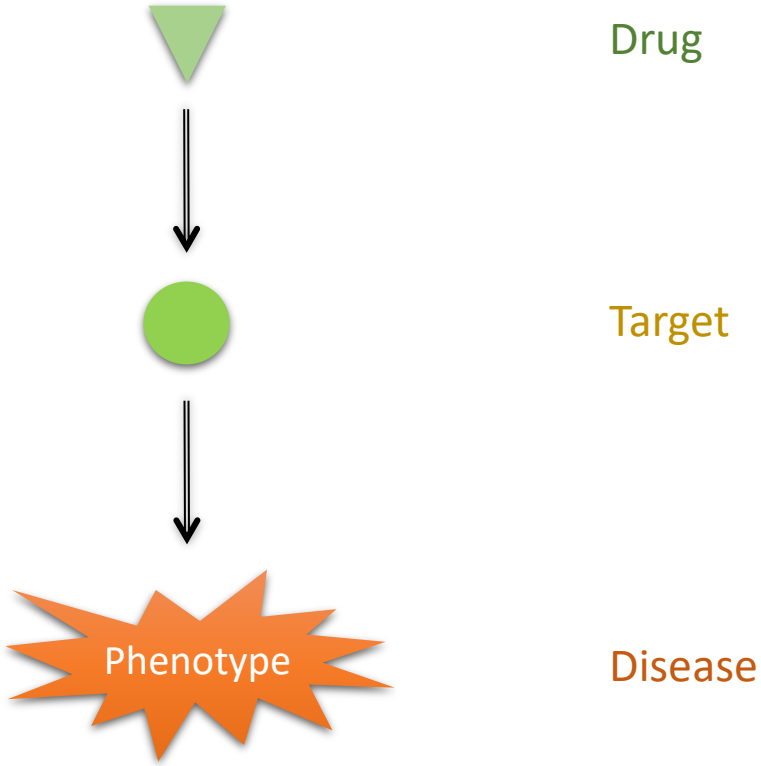


Compilation des données kinases (ChEMBL)

CMPD_CHEMBLID	TARGET_CHEMBLID	CANONICAL_SMILES	MOL_PREF_NAME	PROTEIN_ACCESSION	b1	Vascular endothelial growth factor receptor 1	Tyrosine-protein kinase receptor RET	Platelet-derived growth factor receptor beta	Tyrosine-protein kinase receptor FLT3	Fibroblast growth factor receptor 1	ALK tyrosine kinase receptor	Tyrosine-protein kinase ABL	Glycogen synthase kinase-3 alpha	Glycogen synthase kinase-3 beta	Glycogen synthase kinase-3	Tyrosine-protein kinase FYN	CDK9/cyclin T1
CHEMBL86943	CHEMBL3516	CCOC(=O)c1c(C)[nH]c(\C=C\2/C(=O)Nc3ccccc23)c1C		P35969	0,63960	7.16	6.12	5.4	5.37	5.3	5.27	4.72					
CHEMBL296586	CHEMBL2850	Brc1ccc2[nH]c3c(CC(=O)Nc4ccccc34)c2c1	KENPAULLONE	P49840	-0,24354	6.4			5.8			6.8	8.1	7.7	7.64	7.2	7.19
CHEMBL298445	CHEMBL301	Cc1nc(N)sc1c2ccnc(Nc3cccc(c3)[N+](=O)[O-])n2		P24941	-0,74865							6.8		7.7			8.4
CHEMBL298813	CHEMBL1862	CC[C@H](NC(=O)[C@H](Cc1ccc(cc1)C(F)(F)P(=O)(O)O)NC(=O)C)C(=O)N(C)CCCC2CCCCC2		P00519	0,88552							5.8					
CHEMBL299477	CHEMBL267	CC[C@H](C)[C@H](NC(=O)[C@H](CCC(=O)O)NC(=O)[C@H](CCC(=O)O)NC(=O)[C@H](Cc1ccc(OP(=O)(O)O)cc1)NC(=O)C)C(=O)N[C@@H](CCC(=O)O)C(=O)O		P12931	0,99986							5.1				5.96	
CHEMBL299707	CHEMBL299	COc1ccccc1C(=O)Nc2cccc(Nc3nccc(n3)c4ccccn4)c2		P17252	0,97659							5.72					
CHEMBL300817	CHEMBL1862	Clc1cccc(Nc2nccc(n2)c3cccnc3)c1		P00519	0,89463							5.82					
CHEMBL301845	CHEMBL267	CC[C@H](NC(=O)[C@H](Cc1ccc(OP(=O)(O)O)cc1)NC(=O)C)C(=O)N(C)CCCC2CCCCC2		P12931	0,52065							4.82					
CHEMBL306380	CHEMBL4223	Cc1ccc(cc1)c2nn(c3ncnc(N)c23)C(C)(C)C		P42685	-0,60201	6.8	8		5.7	6.5		6.83				7.57	
CHEMBL312214	CHEMBL267	CCCNc1nc(SC)nc2c1cnn2CC(Cl)c3ccccc3		P12931	0,98327							5.32					
CHEMBL1092754	CHEMBL262	Cn1cc(\C=C\2/Oc3cccc(O)c3C2=O)c4c(ccnc14)c5ccc(cc5)C(=O)NCCO		P49841	-0,36722					7.3		8.01	7.97	8.23			
CHEMBL1092926	CHEMBL2971	Fc1cc(cc(F)c1CN2CCOCC2)c3cccc4ncc(nc34)c5cnn(c5)C6CCNCC6		O60674	-0,28213							7.1					
CHEMBL1097700	CHEMBL3587	CNc1cc(O)c2C(=O)O[C@@H](C)[C@H](C)\C=C/C(=O)[C@@H](O)[C@@H](O)C\C=C\c2c1		Q02750	-0,64117				7.04			6.67				7.33	
CHEMBL1163016	CHEMBL279	CC1(C)CC(CC(C)(C)N1[O])N=C(O)c2cccc(c2)c3cc4nccc(Nc5cccc(O)c5)n4n3		P35968	-0,58592							8.3				8.3	
CHEMBL1164180	CHEMBL4247	CN1CCN(CC1)c2ccc(cn2)c3cnc4NCCN(Cc5cc(Cl)ccc5C(F)(F)F)c4c3		Q9UM73	-0,14550	5.8	6.2	6.2	5.9	5.9	8	6.1					
CHEMBL1164265	CHEMBL5627	CN1CCN(CC1)c2ccc(cn2)c3cnc4NCCN(Cc5c(F)ccc(F)c5Cl)c4c3		P29376	-0,74865		6		6.9	6.1	7.96	7					
CHEMBL1949855	CHEMBL5903	Clc1cccc2C(=O)NC=Nc12		Q04771	0,97659	5	5.3	4.6		5	4.4	4.4	4.6	4.7			
CHEMBL1964441	CHEMBL2007	CNCC#Cc1cnc(N)c2c(csc12)c3ccc(NC(=O)Nc4cccc(C)c4)cc3		P16234	-0,67872	7.4	7.6	8.5	7.9	6.7	5.6	6.8				5.6	
CHEMBL1964718	CHEMBL4203	CC1=CN2CC(=O)NN=C2C=C1		Q9HAZ1	0,70867		4.3					4					
CHEMBL1965169	CHEMBL4036	Cc1ccc(cc1)c2cc3nc(Br)cnc3[nH]2		Q00535	-0,24354		5.6					6.1					
CHEMBL1965170	CHEMBL1913	COc1ccc(NC(=O)Nc2ccc(cc2)c3csc4c(cnc(N)c34)c5cnn(CC(O)CO)c5)cc1		P09619	-0,99223	8.2	9	9.3	8	6.3	5.6	8.7		5.6		6	
CHEMBL1965570	CHEMBL1868	Nc1ncc(c2cocc2)c3scc(c4ccc(NC(=O)Nc5ccccc5F)cc4)c13		P17948	-0,74865	8.7	7.6			6.7		7				6.9	
CHEMBL2003657	CHEMBL4179	CC(C)S(=O)(=O)n1c(N)nc2ccc(cc12)c3c(nc4sccn34)c5ccc(F)cc5		P45984	0,15337					5.7		6.3				7.1	
CHEMBL2003785	CHEMBL4203	Fc1cccc(CNc2ncnc3[nH]cnc23)c1		Q9HAZ1	0,88552	4.1	4.9	4.9		4.6	4.2	4.3	4.3	4.3			
CHEMBL2004025	CHEMBL2147	COCOc1cccc(OCOC)c1c2ccc(NS(=O)(=O)C)cc2C(=O)OC		P11309	0,86940		5.7	6.2		6.2	5.8	5.7	6.2	6.4		5.8	
CHEMBL2004118	CHEMBL1075104	CCc1nc(Nc2ccc(N3CCOCC3)c(Cl)c2)nc4[nH]ccc14		Q5S007	0,053955		6.3				5.4	5.8					
CHEMBL2004290	CHEMBL1913	COc1ccc(NC(=O)Nc2ccc(cc2)c3csc4c(cnc(N)c34)c5cnn(CC(C)(C)O)c5)cc1		P09619	-0,86544	8.37	8.5	8.9	8.71	6.8	5.9	8.5				6.6	
CHEMBL2004311	CHEMBL4895	Cc1cc(C)cc(NC(=O)Nc2ccc(c(C)c2)c3cccc4C(=O)NCc34)c1		P30530	0,053955	7.1	7		7.6	5.5	6.8	6.2					
CHEMBL2004515	CHEMBL4203	C1Oc2ccc(cc2O1)c3ncnc4[nH]ccc34		Q9HAZ1	0,52608	5.3	5.6		4.6	4.8	5.3	5.1	5	4.6			
CHEMBL2004637	CHEMBL2007	CCN(CCN)C(=O)c1cccc(c1)n2nc(cc2NC(=O)Nc3cccc4ccccc34)C(C)(C)C		P16234	0,86940	5.5	6.3	6.4			5.5	5.8	5.6	5.7		5.4	
CHEMBL2004716	CHEMBL1868	CCN(CC)CCNC(=O)C=Cc1cnc(N)c2c(csc12)c3ccc(NC(=O)Nc4cccc(C)c4)cc3		P17948	-0,99969	9.4	8.3		7.3	7.5	6.2	8.6				7.6	
CHEMBL3884319	CHEMBL5600	CC1(C)C(=O)N([C@H]2CCc3c(O)cccc23)c4nc(Nc5ccccc5)ncc14		P27448	-0,87528				8.1			5.94	5.48	5.53			5.8
CHEMBL3889746	CHEMBL1862	FC(F)(F)Oc1ccc(NC(=O)c2cncc(c2)c3cccnc3)cc1		P00519	-0,20456							8.06					
CHEMBL3890053	CHEMBL1862	Fc1ccc(cc1c2cncnc2)C(=O)Nc3ccc(OC(F)(F)F)cc3		P00519	-0,59400							8.49					
CHEMBL3890055	CHEMBL1862	O[C@H]1CCN(C1)c2ncc(cc2c3cnc(Cl)c(F)c3)C(=O)Nc4ccc(OC(F)(F)F)cc4		P00519	-0,99969							9.4					
CHEMBL3890279	CHEMBL1862	N[C@H]1CCN(C1)c2ncc(cc2c3cncnc3)C(=O)Nc4ccc(OC(F)(F)F)cc4		P00519	-0,83931							8.85					
CHEMBL3890327	CHEMBL1862	O[C@@H]1CN(C[C@@H]1O)c2ncc(cc2c3cncc(F)c3)C(=O)Nc4ccc(OC(F)(F)F)cc4		P00519	-0,77456							8.74					
CHEMBL3890630	CHEMBL1862	CCN(CCO)c1ncc(cc1c2cncnc2)C(=O)Nc3ccc(OC(F)(F)F)cc3		P00519	-0,79318							8.77					
CHEMBL3890658	CHEMBL1862	CN(CCO)c1ccc(cc1c2cncs2)C(=O)Nc3ccc(OC(F)(F)F)cc3		P00519	-0,43138							8.3					
CHEMBL3891044	CHEMBL1862	NC12CC1CN(C2)c3ncc(cc3c4cncnc4)C(=O)Nc5ccc(OC(F)(F)F)cc5		P00519	-0,76176							8.72					
CHEMBL3891109	CHEMBL1862	O[C@H]1CCN(C1)c2ncc(cc2c3cccc(F)c3)C(=O)Nc4ccc(OC(F)(F)F)cc4		P00519	-0,97911							9.22					
CHEMBL3891624	CHEMBL1862	O[C@H]1CCN(C1)c2ncc(cc2c3cncnc3)C(=O)Nc4ccc(OC(F)(F)C(F)(F)F)cc4		P00519	-0,70755							8.64					

Polypharmacology

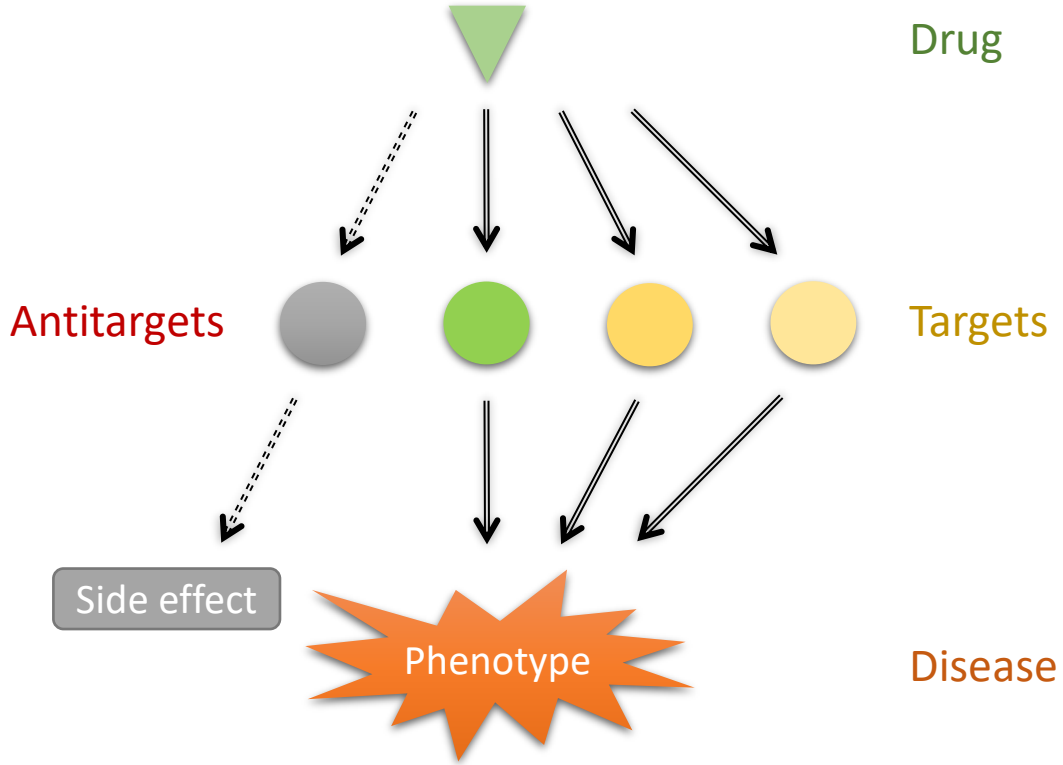
- The “one drug – one target – one disease” paradigm



Polypharmacology

❍The “one drug – one target – one disease” paradigm

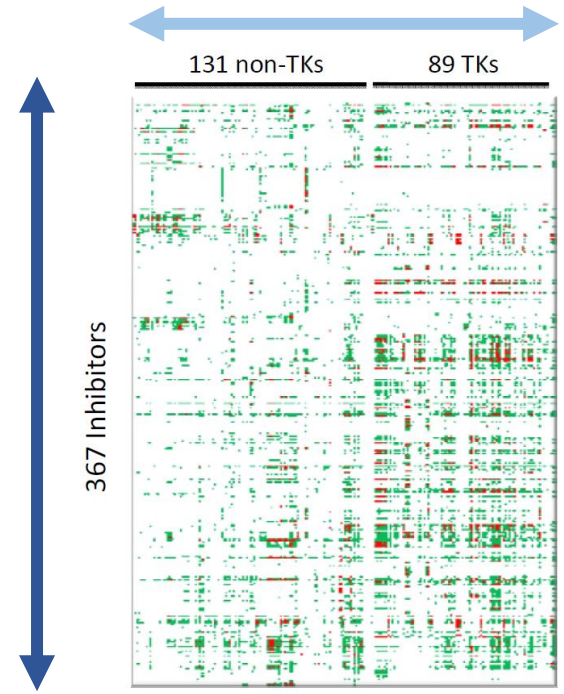
- Polypharmacological drug behavior
  - Many known drugs elicit their therapeutic effects by acting on multiple targets
  - But such drugs can also bind antitargets responsible for side effects



Case study : PKIS

- Polypharmacology of kinases
  - Most tumors can escape from the inhibition of any single kinase
  - The GSK Published Kinase Inhibitor Set (PKIS) as a source of knowledge [1]

Annotation of the kinase inhibitors using affinity data for 220 kinases (active/inactive)



367 small molecules
ATP-competitive kinase inhibitors

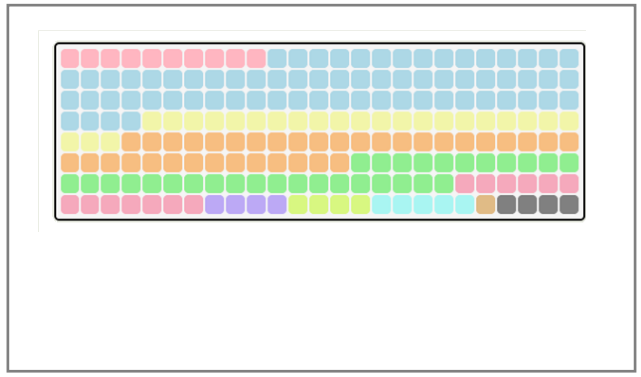
31 diverse chemotypes

PKIS2 [2]
406 kinases
645 inhibitors

[1] Drewry DH et al. Seeding collaborations to advance kinase science with the GSK Published Kinase Inhibitor Set (PKIS). Curr Top Med Chem. 2014;14(3):340-2.
[2] Drewry DH et al. Progress towards a public chemogenomic set for protein kinases and a call for contributions. PLoS One. 2017 Aug 2;12(8):e0181585.

Case study : PKIS

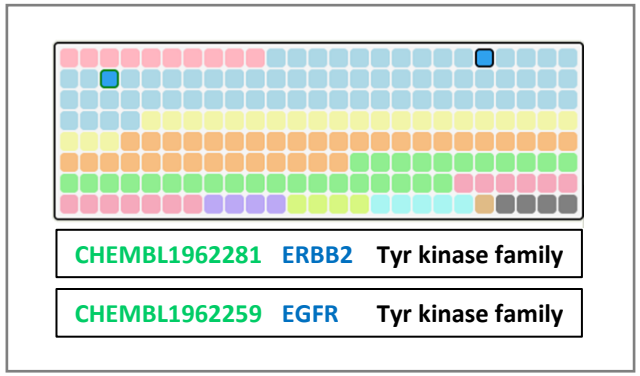
- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases



https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases
  - Example: dual inhibition of ERBB2 and EGFR



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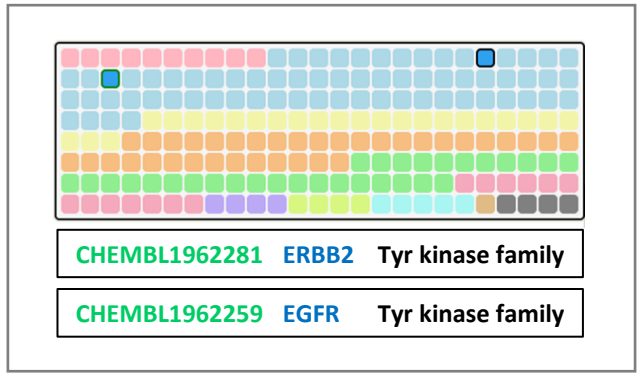

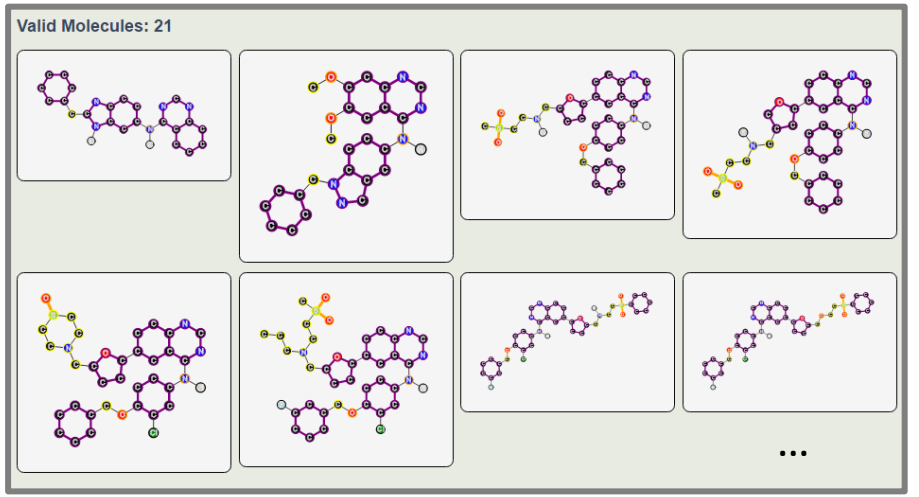

Molecules in agreement with the dual ERBB2 and EGFR inhibition

https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

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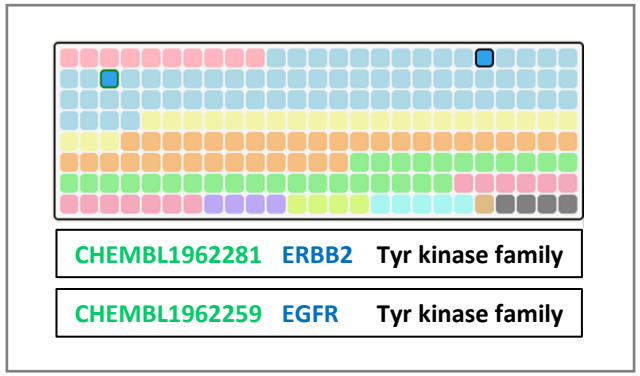
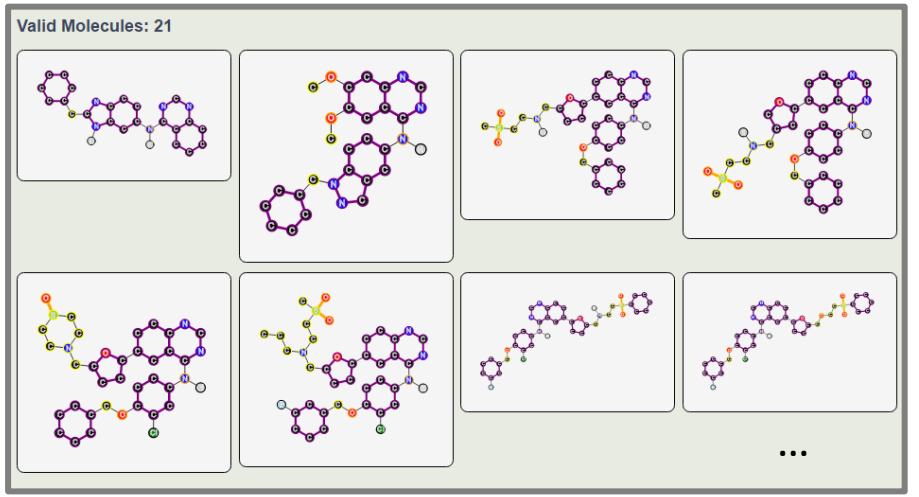
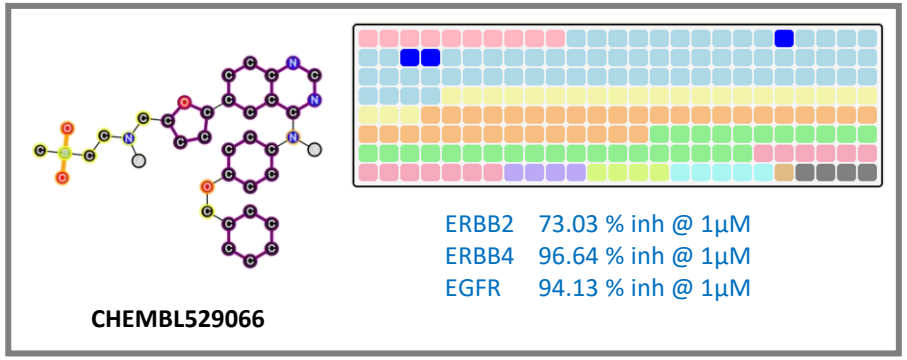
  - Example: dual inhibition of ERBB2 and EGFR



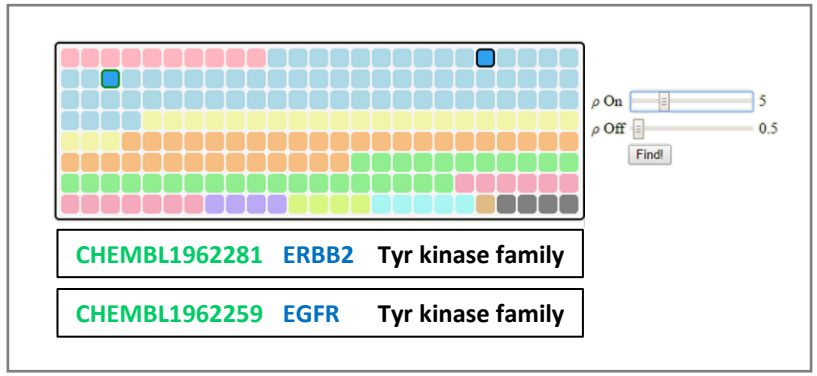


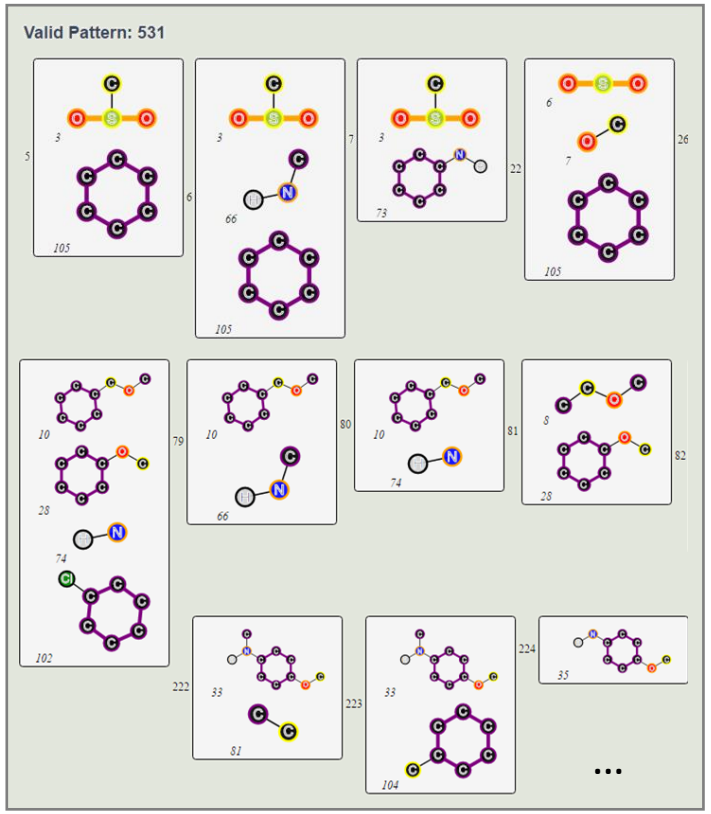


https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases
  - Example: dual inhibition of ERBB2 and EGFR





https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

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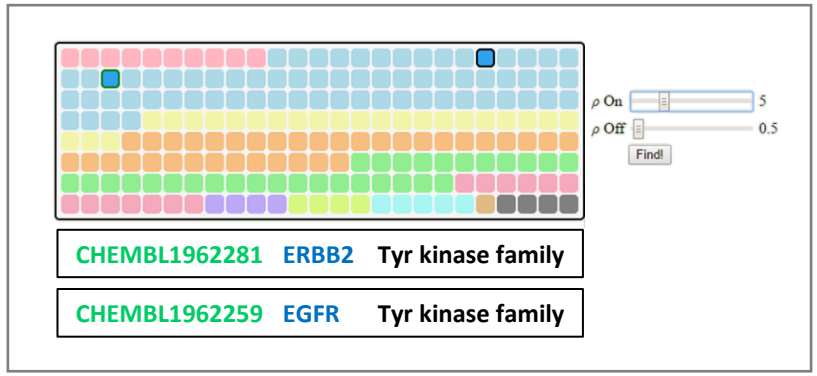
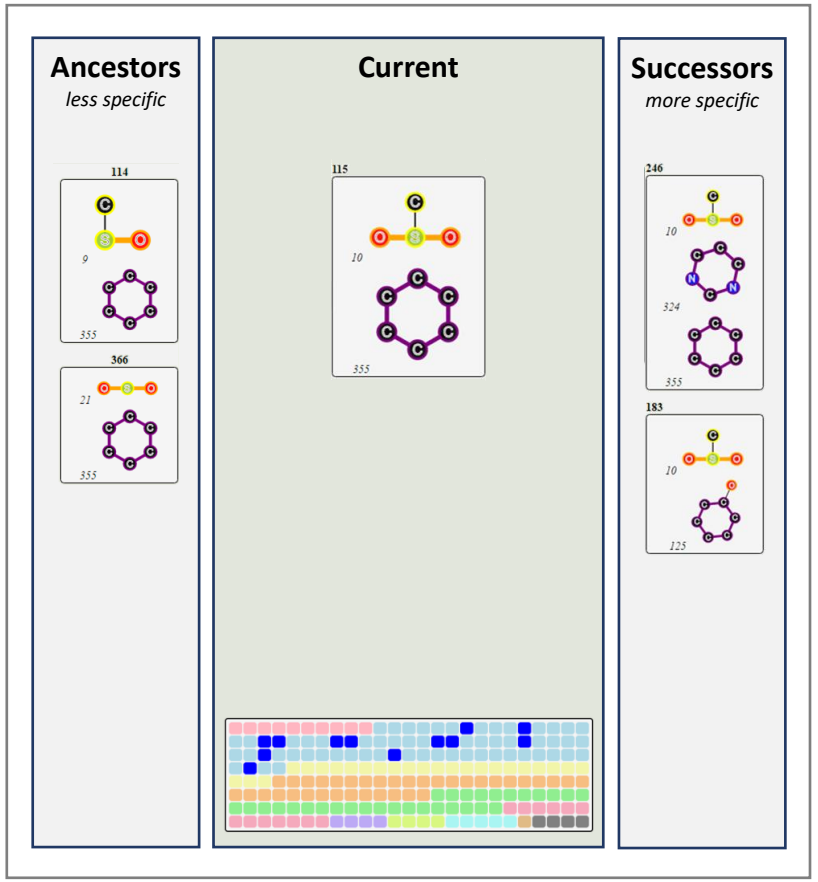
  - Example: dual inhibition of ERBB2 and EGFR

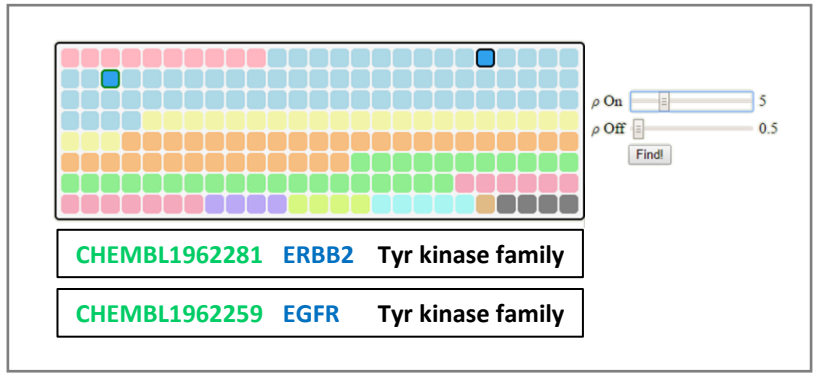


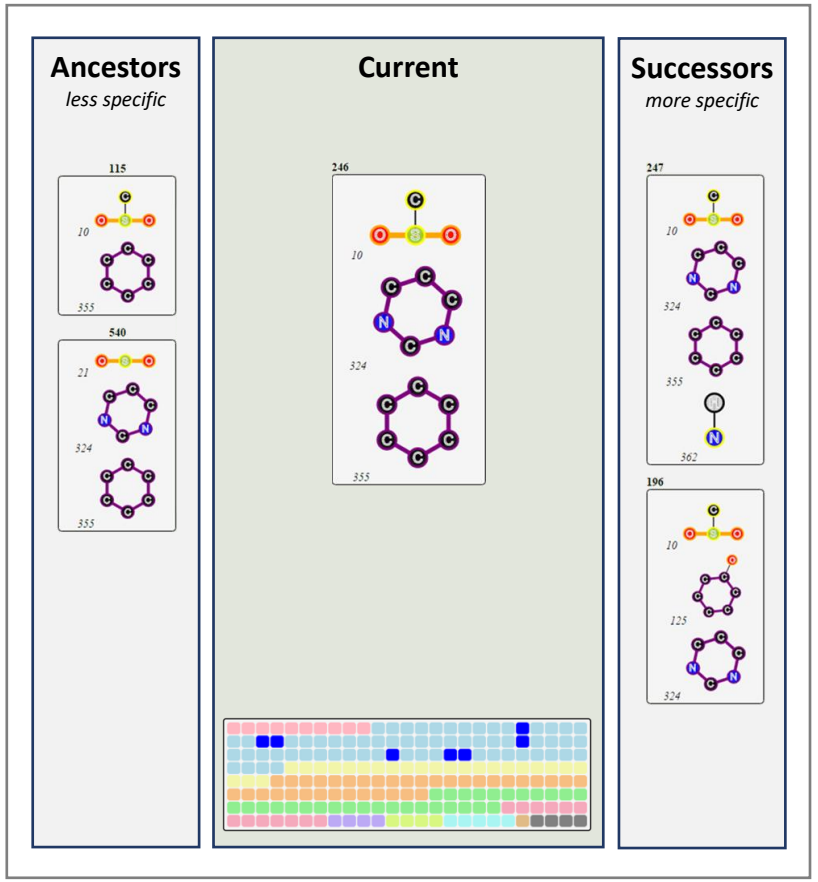


https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases
  - Example: dual inhibition of ERBB2 and EGFR





https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

Case study : PKIS

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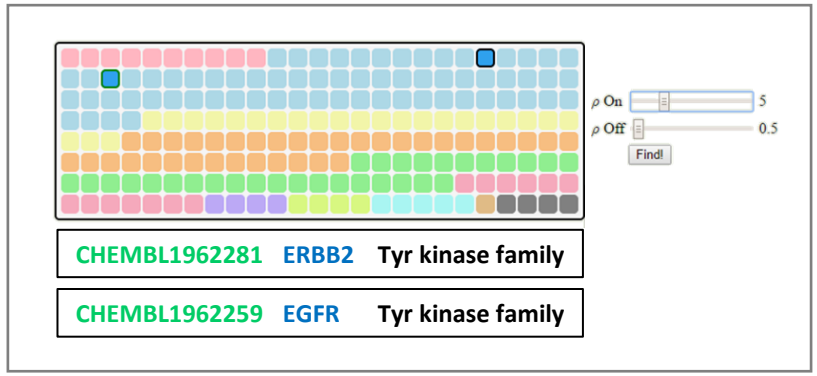
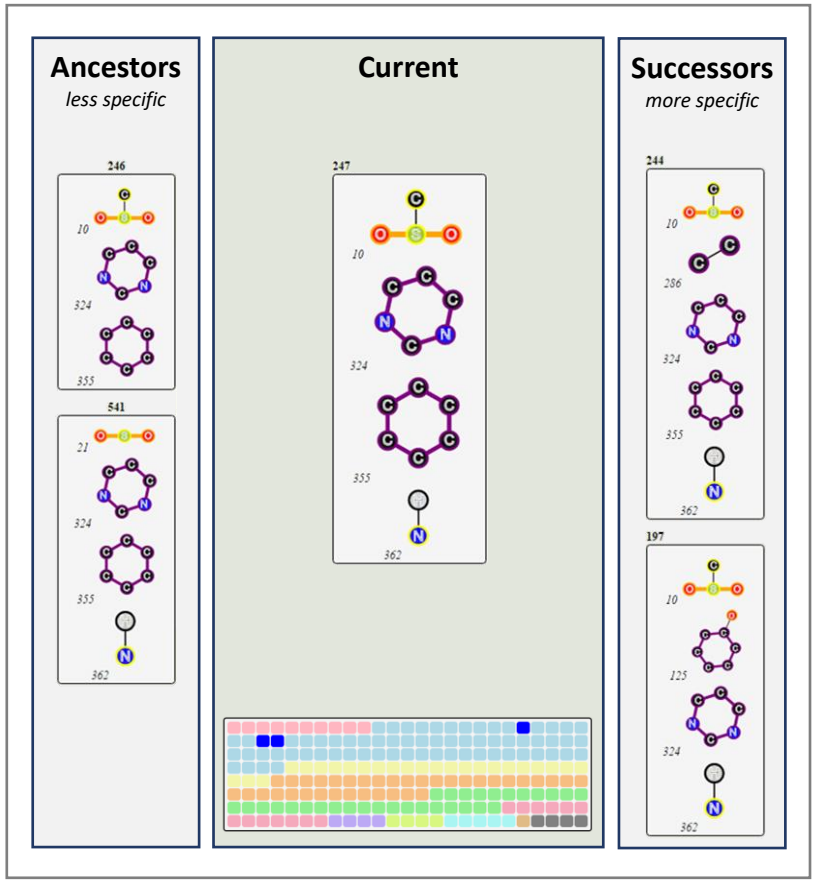
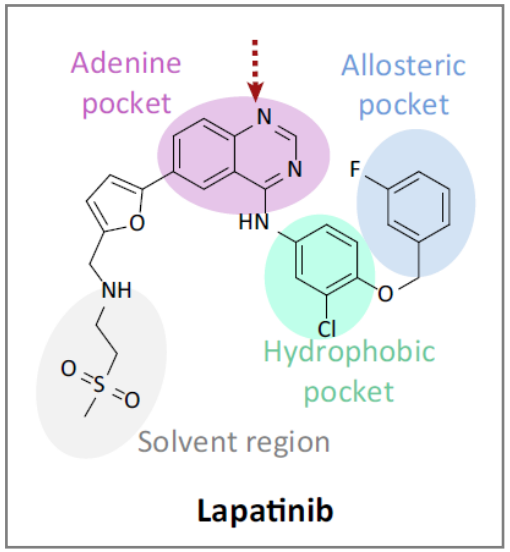


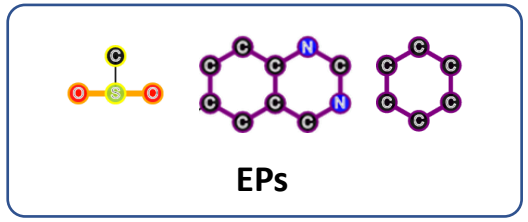


https://chemoinfo.greyc.fr/metivier/kinase_miner/finder.html

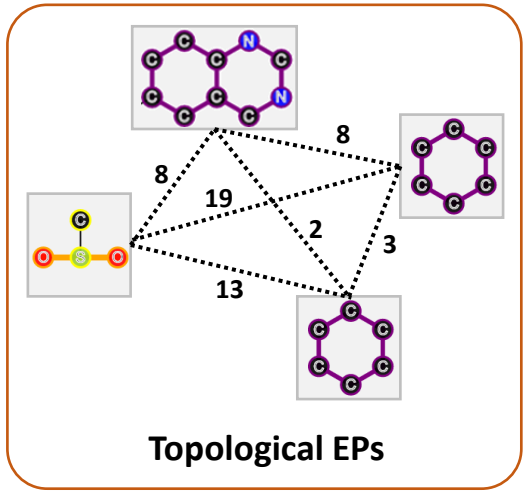
Last development



1 Initial method



2 Addition of the distances



3 Pharmacophoric definitions