Emerging patterns mining and automated detection of contrasting chemical features

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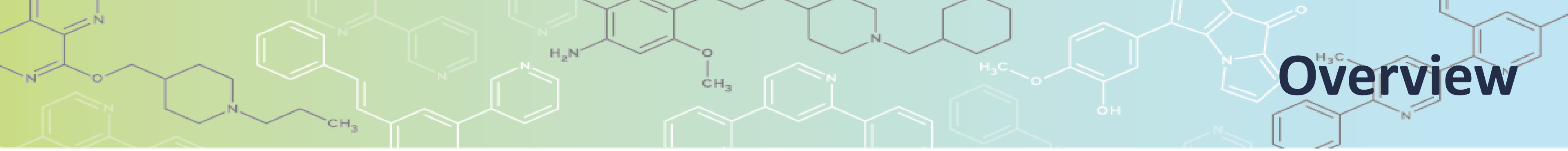


Overview

- Emerging Pattern (EP) mining
  - Generalities
  - Our contributions

- Case study I : Detection of structural alerts for the mutagenicity endpoint

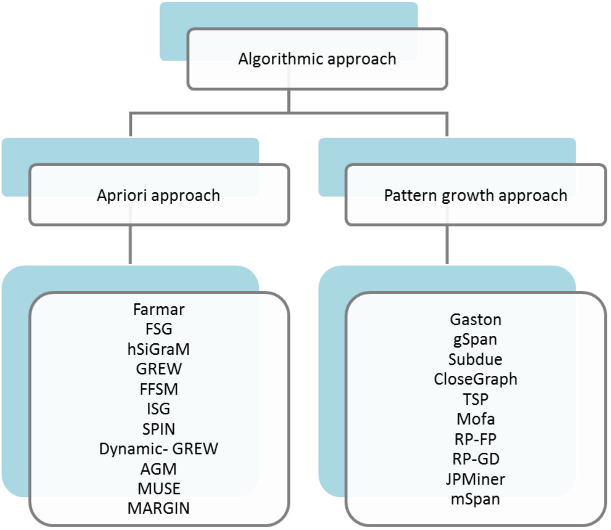
- Case study II : Polypharmacology of kinases

Data mining in chemoinformatics

- With the explosion of the availability of data, we need new methods to identify structure-activity relationships in large databases
  - LeadScope, ChEMBL, PubChem, …

- The calculation of the frequency of a descriptor is often at the core of the process

- Algorithms for the calculation of frequent descriptors often lead to the generation of myriads of such descriptors



Algorithmic approach

Apriori approach

Farmar
FSG
hSiGraM
GREW
FFSM
ISG
SPIN
Dynamic- GREW
AGM
MUSE
MARGIN

Pattern growth approach

Gaston
gSpan
Subdue
CloseGraph
TSP
Mofa
RP-FP
RP-GD
JPMiner
mSpan

Emerging patterns mining

- To limit the number of generated descriptors, methods have been proposed for finding representative and significant subsets
- Emerging pattern mining is a data mining technique introduced by Dong and Li [1,2] that captures differentiating features between 2 classes of data

Descriptors

	d1	d2	d3	d4	d5
mol1	X				X
mol2	X	X	X		X
mol3				X	
mol4	X	X			
mol5	X	X		X	
mol6	X	X			X
mol7					X
mol8			X		
mol9	X		X		X
mol10	X		X		

[1] Dong G. & Li J. Efficient mining of Emerging Patterns: Discovering trends and differences. *Proc. ACM SIGKDD Int. Conf. Knowl. Discovery Data Min., 5th* **1999**, 43-52.
[2] *Contrast Data Mining: Concepts, Algorithms, and Applications*; Dong G. & Bailey J., Eds.; CRC Press: Boca Raton, FL, **2013**.

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Descriptors

	d1	d2	d3	d4	d5
mol1	X				X
mol2	**X**	**X**	X		X
mol3				X	
mol4	**X**	**X**			
mol5	**X**	**X**		X	
mol6	**X**	**X**			X
mol7					X
mol8			X		
mol9	X		X		X
mol10	X		X		

Emerging Pattern (EP)

{d1,d2}
is supported by
molecules [2,4,5]
and molecule [6]

Growth-rate
$\rho = 3$

[1] Dong G. & Li J. Efficient mining of Emerging Patterns: Discovering trends and differences. *Proc. ACM SIGKDD Int. Conf. Knowl. Discovery Data Min., 5th* **1999**, 43-52.
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Descriptors

	d1	d2	d3	d4	d5
mol1	X				X
mol2	X	X	X		X
mol3				**X**	
mol4	X	X			
mol5	X	X		**X**	
mol6	X	X			X
mol7					X
mol8			X		
mol9	X		X		X
mol10	X		X		

Jumping Emerging Pattern (JEP)

{d4}
is supported by
molecules [3,5]

Growth-rate
$\rho = \infty$

[1] Dong G. & Li J. Efficient mining of Emerging Patterns: Discovering trends and differences. *Proc. ACM SIGKDD Int. Conf. Knowl. Discovery Data Min., 5th* **1999**, 43-52.
[2] *Contrast Data Mining: Concepts, Algorithms, and Applications*; Dong G. & Bailey J., Eds.; CRC Press: Boca Raton, FL, **2013**.

Applications of EP mining in chemoinformatics

- Auer and Bajorath were the firsts to apply EP mining in chemoinformatics [3,4]
  - Particularly, they introduced the notion of emerging chemical patterns (ECPs) for molecular classification

[3] Auer J. & Bajorath J. Emerging Chemical Patterns: A new methodology for molecular classification and compound selection. *J. Chem. Inf. Model.* **2006**, *46*, 2502-2514.
[4] Namasivayam V.et al. Classification of compounds with distinct or overlapping multi-target activities and diverse molecular mechanisms using Emerging Chemical Patterns. *J. Chem. Inf. Model.* **2013**, *53*, 1272–1281.

- Sherhod and co-workers also applied EP mining for the identification of toxicophores for various toxicological endpoints [5,6]
  - Their method has been successfully used to implement new structural alerts for mutagenicity in the Derek Nexus expert system [7]

[5] Sherhod R.et al. Automating knowledge discovery for toxicity prediction using Jumping Emerging Pattern mining. *J. Chem. Inf. Model.* **2012**, *52*, 3074-3087.
[6] Sherhod R. et al. Emerging Pattern mining to aid toxicological knowledge discovery. *J. Chem. Inf. Model.* **2014**, *54*, 1864-1879.
[7] Coquin L. et al. New structural alerts for Ames mutagenicity discovered using Emerging Pattern mining techniques. *Toxicol. Res.* **2015**, *4*, 46- 56.

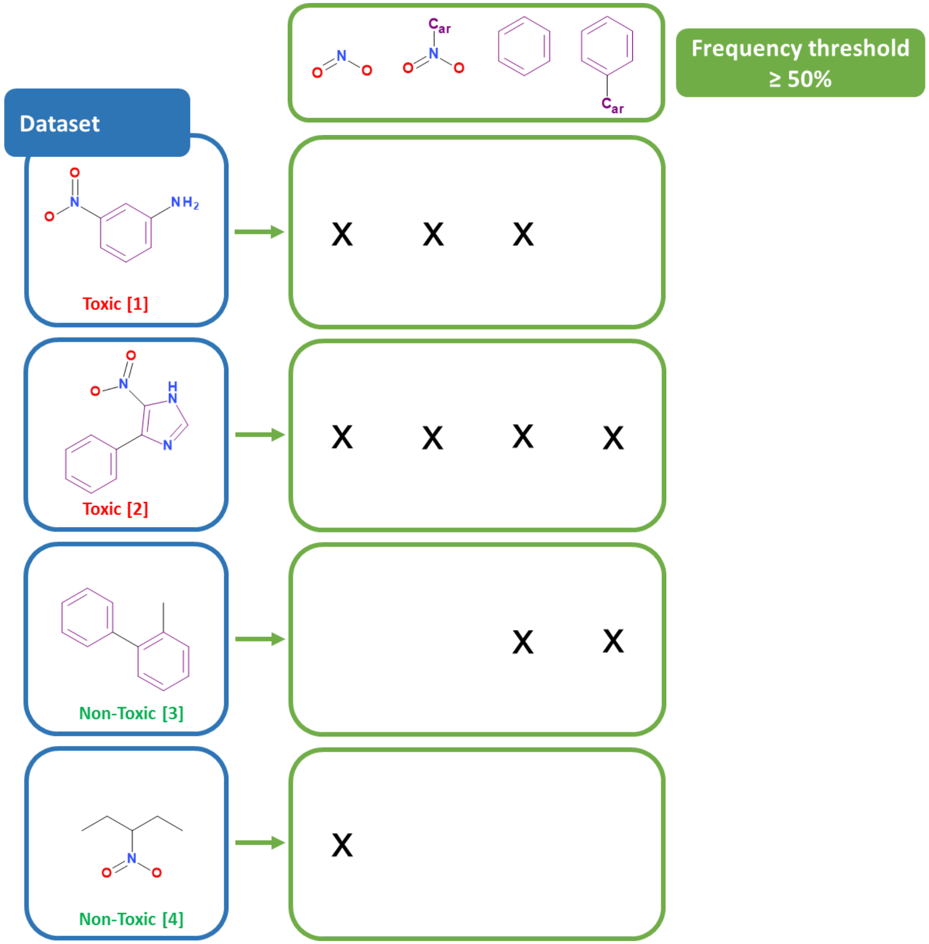
- Our contributions
  - We related the occurrences of jumping fragments to aquatic toxicity data [8]
  - We introduced the enumeration of combinations of chemical fragments [9,10]

[8] Lozano S. et al. Introduction of jumping fragments in combination with QSARs for the assessment of classification in ecotoxicology. *J. Chem. Inf. Model.* **2010**, *50*, 1330–1139.
[9] Poezevara G. et al. Extracting and summarizing the frequent emerging graph patterns from a dataset of graphs. *J. Intel. Inf. Syst.* **2011**, *37*, 333–353.
[10] Cuissart B. et al. Emerging Patterns as Structural Alerts for Computational Toxicology. In *Contrast Data Mining: Concepts, Algorithms and Applications*; Dong, G., Bailey, J., Eds.; Chapman and Hall/CRC, **2013**; pp 269–281.

Our method

- What makes our method [10] original:
  - We operate directly from the molecular graphs

[11] Metivier, J.P. et al. Discovering structural alerts for mutagenicity using Stable Emerging Molecular Patterns. *J. Chem. Inf Model.* **2015**, *55*, 925-940



Toxic [1]	X	X	X	
Toxic [2]	X	X	X	X
Non-Toxic [3]			X	X
Non-Toxic [4]	X			

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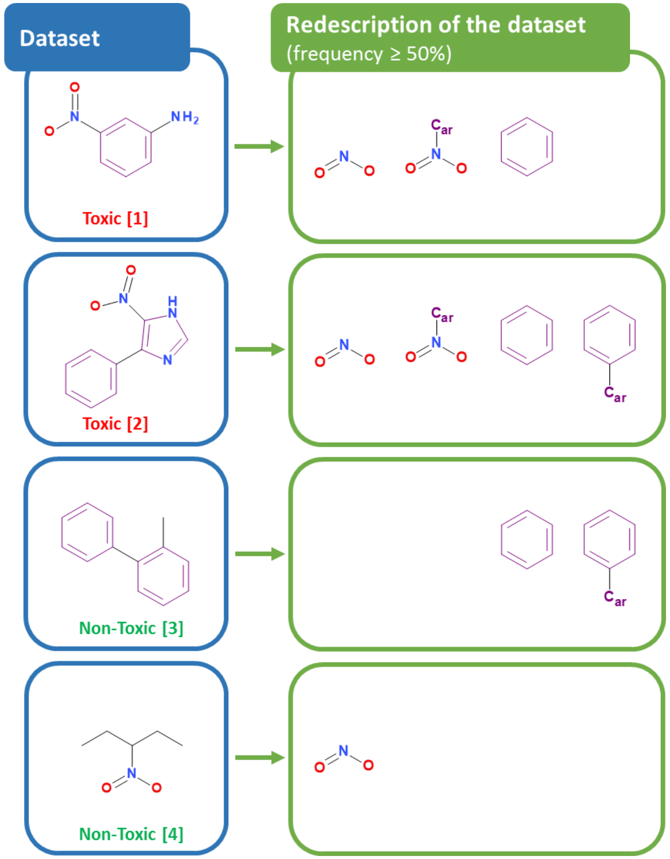

Dataset

Redescription of the dataset
(frequency ≥ 50%)

Toxic [1]

Toxic [2]

Non-Toxic [3]

Non-Toxic [4]

Our method

- What makes our method[11] original:
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  - We enumerate the frequent closed patterns

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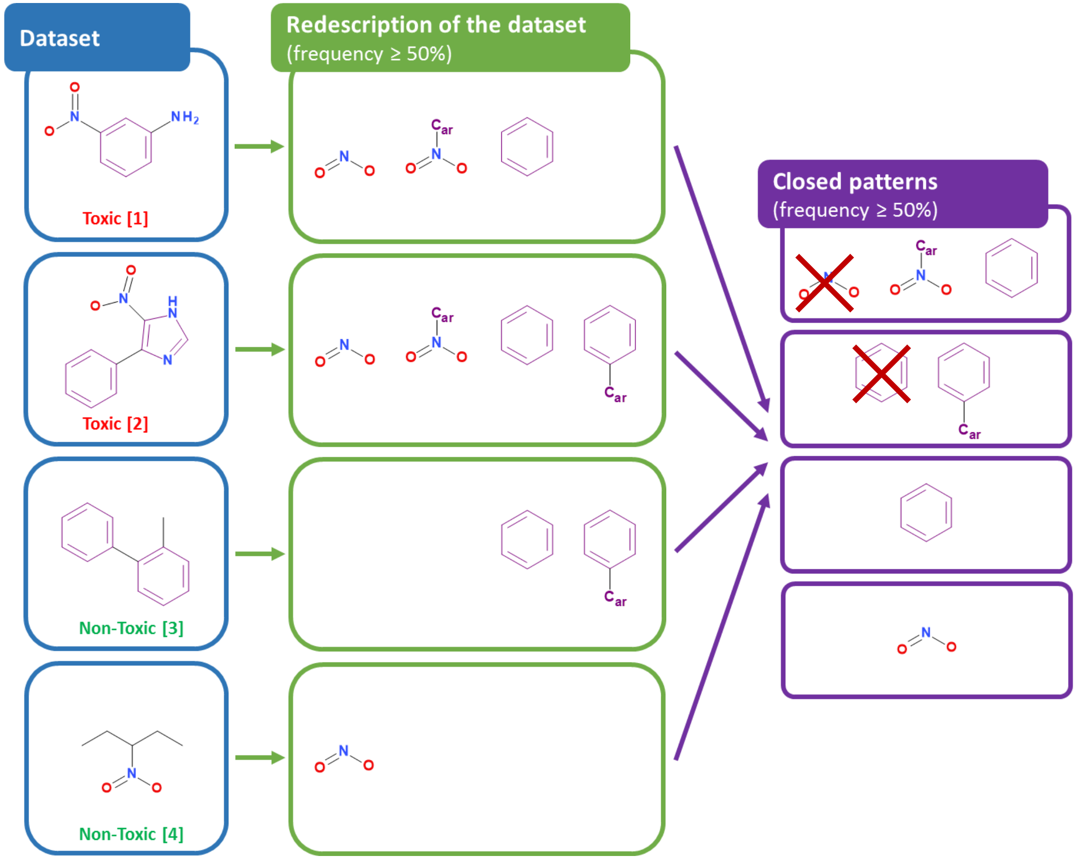
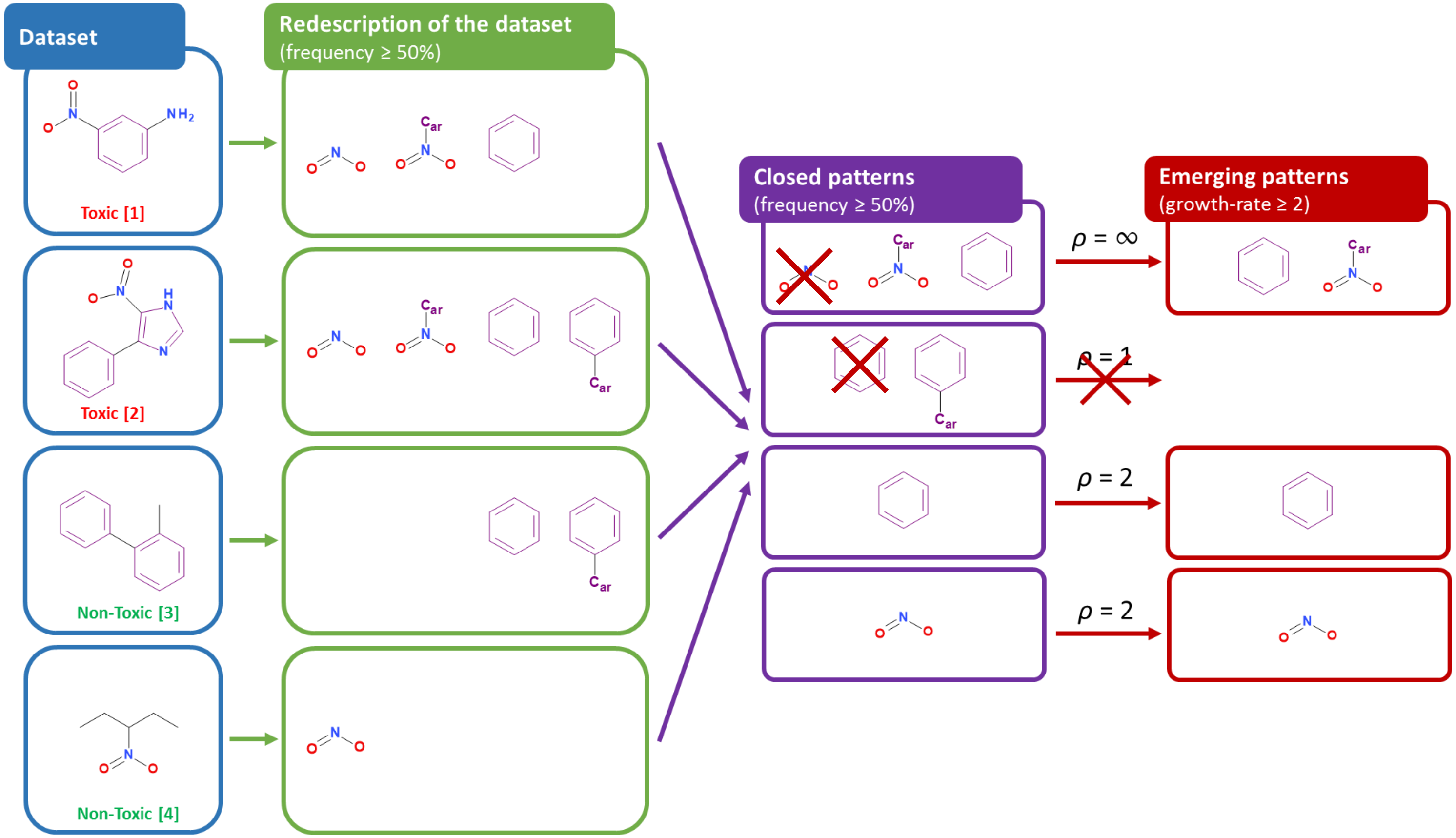


Our method

- What makes our method [11] original:
  - We operate directly from the molecular graphs
  - We enumerate the frequent closed patterns to extract the emerging patterns

[11] Metivier, J.P. et al. Discovering structural alerts for mutagenicity using Stable Emerging Molecular Patterns. *J. Chem. Inf Model.* **2015**, *55*, 925-940



Our method

- What makes our method[11] original:
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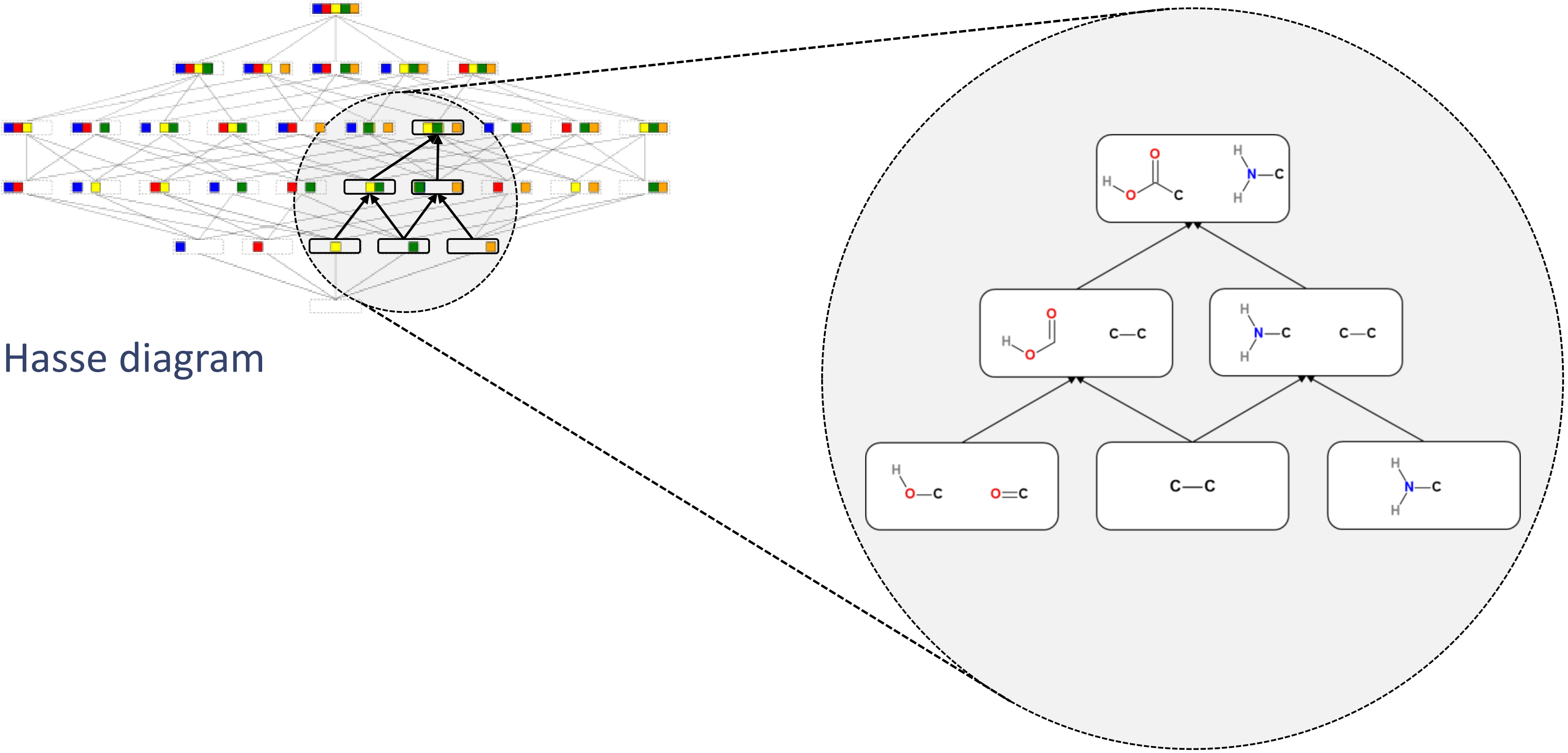
  - We enumerate the frequent closed patterns to extract the emerging patterns
  - We organize the patterns in a Hasse diagram

[11] Metivier, J.P. et al. Discovering structural alerts for mutagenicity using Stable Emerging Molecular Patterns. *J. Chem. Inf Model.* **2015**, *55*, 925-940



Hasse diagram

Case study (I): Structural alerts

- Search of structural alerts
  - One of the most interesting approach of predictive toxicology
  - Define the key features of a molecule that are required to initiate a toxicological pathway
  - Examples of domain experts rules
    - The Tennant and Ashby’s set for DNA reactivity
    - The Benigni and Bossa’s set for mutagenic and carcinogenic potential
    - ToxAlerts
  - The updating of a knowledge base is very time consuming since it requires strong investment of domain experts and a detailed analysis of the scientific literature

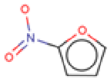
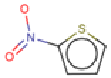
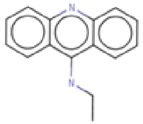
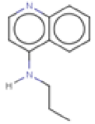
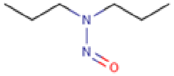
EP mining should reduce the time and efforts needed to identify new structural alerts

Case study (I): Structural alerts

❍ Search of structural alerts for mutagenicity

- The Hansen benchmark dataset (http://doc.ml.tu-berlin.de/toxbenchmark/)
  - □ 6512 compounds from the literature annotated with Ames mutagenicity data
    - ▪ 3503 Ames ⊕ and 3009 Ames ⊖
  - □ Use of a 0.36% frequency threshold (support of 20 molecules) → 15000 Eps

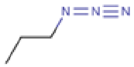
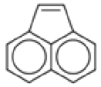
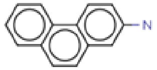
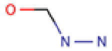
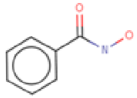
- 10 JEPs → only present in the mutagens

	JEPs	Support	ρ
MF_945		83	∞
MF_954		31	∞
MF_1666		27	∞
MF_991		32	∞
MF_252		27	∞

Nitro aromatic groups: MF_945, MF_954

Polycyclic aromatic amines: MF_1666, MF_991

Nitrosamine group: MF_252

	JEPs	Support	ρ
MF_4		28	∞
MF_1616		26	∞
MF_1211		25	∞
MF_87		25	∞
MF_414		37	∞

Azide group: MF_4

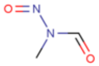
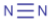
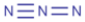
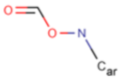
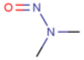
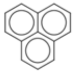
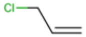
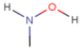
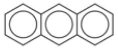
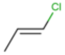
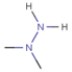
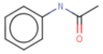
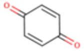
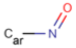
Polycyclic planar hydrocarbon system: MF_1616

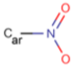
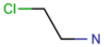
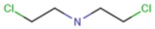
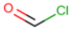
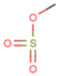
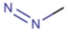
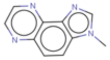
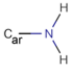
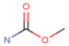
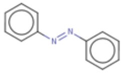
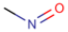
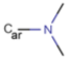
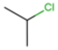
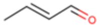
Generalized toxicophores: MF_1211, MF_87, MF_414

Case study (I): Structural alerts

❍ Search of structural alerts for mutagenicity

- Comparison with ToxAlerts (https://ochem.eu/) → 32 out of 50 toxicophores

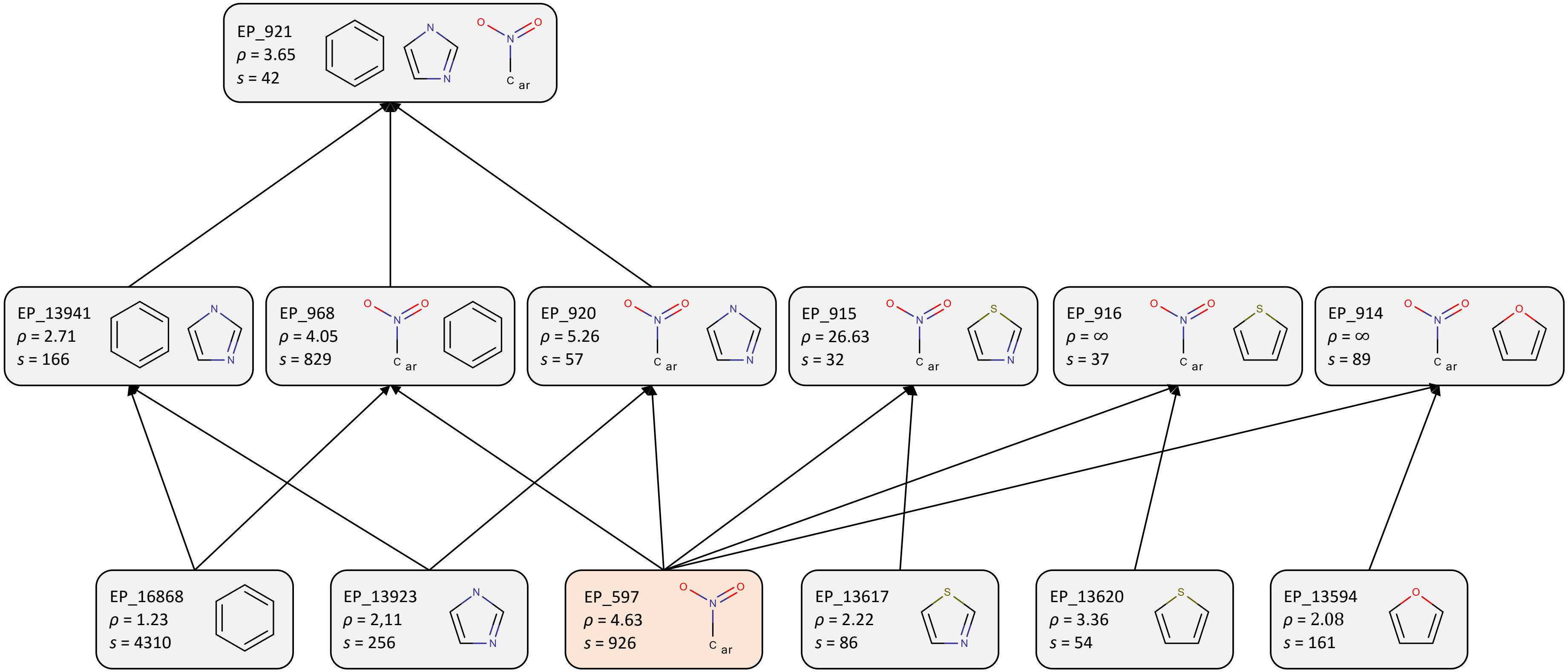
	EPs	Support	ρ	Structural Alert in ToxAlerts
MF_73		44	36.94	N-nitroso-N-alkylamides N-nitroso-N-alkylureas N-nitroso-N-alkylcarbamates
MF_0		67	27.92	Diazo
MF_1		55	22.76	Azide
MF_125		52	21.47	Aromatic and aliphatic aziridinyl derivatives
MF_156		47	12.60	Aromatic hydroxylamine ester
MF_72		27	9.09	Nitrosamine
MF_1651		178	6.79	Polycyclic aromatic hydrocarbons
MF_1841		26	6.59	Allylic halides
MF_824		48	6.01	Hydroxyl amine
MF_1667		226	5.84	Polycyclic aromatic hydrocarbons
MF_1831		36	5.33	Monohaloalkene
MF_75		162	5.19	Unsubstituted heteroatom-bonded heteroatom
MF_927		35	5.16	Aromatic N-acyl amine
MF_1298		27	4.94	Quinones
MF_920		964	4.70	Nitrosoarenes

	EPs	Support	ρ	Structural Alert in ToxAlerts
MF_134		926	4.63	Aromatic nitro groups
MF_444		93	4.47	Nitrogen mustard
MF_212		35	4.15	N mustard
MF_2188		29	4.12	Acyl halides
MF_2107		40	4.05	Alkyl ester of sulfonic and sulfuric acids
MF_34		74	3.68	Aliphatic azo
MF_1317		26	3.61	Heterocyclic polycyclic aromatic hydrocarbons
MF_1883		308	2.33	Aliphatic and aromatic epoxides
MF_916		656	2.17	Primary aromatic amine
MF_432		50	1.83	Alkyl carbamate
MF_41		151	1.54	Aromatic azo
MF_153		51	1.33	Aliphatic nitroso
MF_169		182	1.25	Tertiary aromatic amine
MF_2197		26	1.17	Aliphatic halogens
MF_1836		59	1.17	α,β-unsaturated carbonyl

Case study (I): Structural alerts

❍ Search of structural alerts for mutagenicity

- Extract of the Hasse diagram
  - □ Example: stimulation[12] of aromatic rings by the addition of a nitro group

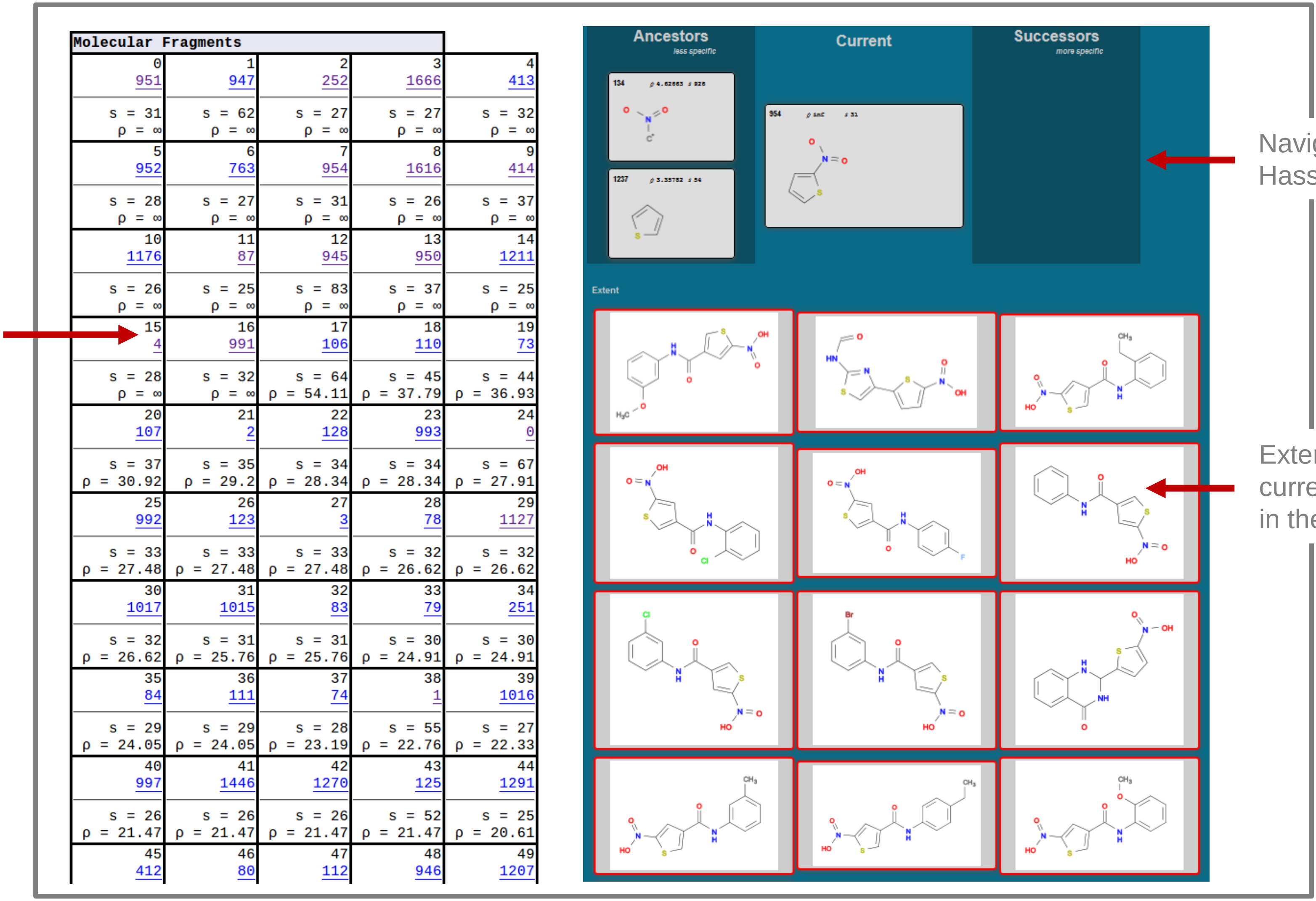


[12] Bissell-Siders R.et al. On the stimulation of patterns. *Lect. Notes Comput. Sci.* **2010**, *6208*, 56-69.

Case study (I): Structural alerts

❍ Our interactive visualization tool https://chemoinfo.greyc.fr/2014_Metivier/

List of patterns



Molecular Fragments

0
951
s = 31
ρ = ∞
	1
	947
	s = 62
	ρ = ∞
		2
		252
		s = 27
		ρ = ∞
			3
			1666
			s = 27
			ρ = ∞
				4
				413
				s = 32
				ρ = ∞

5
952
s = 28
ρ = ∞
	6
	763
	s = 27
	ρ = ∞
		7
		954
		s = 31
		ρ = ∞
			8
			1616
			s = 26
			ρ = ∞
				9
				414
				s = 37
				ρ = ∞

10
1176
s = 26
ρ = ∞
	11
	87
	s = 25
	ρ = ∞
		12
		945
		s = 83
		ρ = ∞
			13
			950
			s = 37
			ρ = ∞
				14
				1211
				s = 25
				ρ = ∞

15
4
s = 28
ρ = ∞
	16
	991
	s = 32
	ρ = ∞
		17
		106
		s = 64
		ρ = 54.11
			18
			110
			s = 45
			ρ = 37.79
				19
				73
				s = 44
				ρ = 36.93

20
107
s = 37
ρ = 30.92
	21
	2
	s = 35
	ρ = 29.2
		22
		128
		s = 34
		ρ = 28.34
			23
			993
			s = 34
			ρ = 28.34
				24
				0
				s = 67
				ρ = 27.91

25
992
s = 33
ρ = 27.48
	26
	123
	s = 33
	ρ = 27.48
		27
		3
		s = 33
		ρ = 27.48
			28
			78
			s = 32
			ρ = 26.62
				29
				1127
				s = 32
				ρ = 26.62

30
1017
s = 32
ρ = 26.62
	31
	1015
	s = 31
	ρ = 25.76
		32
		83
		s = 31
		ρ = 25.76
			33
			79
			s = 30
			ρ = 24.91
				34
				251
				s = 30
				ρ = 24.91

35
84
s = 29
ρ = 24.05
	36
	111
	s = 29
	ρ = 24.05
		37
		74
		s = 28
		ρ = 23.19
			38
			1
			s = 55
			ρ = 22.76
				39
				1016
				s = 27
				ρ = 22.33

40
997
s = 26
ρ = 21.47
	41
	1446
	s = 26
	ρ = 21.47
		42
		1270
		s = 26
		ρ = 21.47
			43
			125
			s = 52
			ρ = 21.47
				44
				1291
				s = 25
				ρ = 20.61

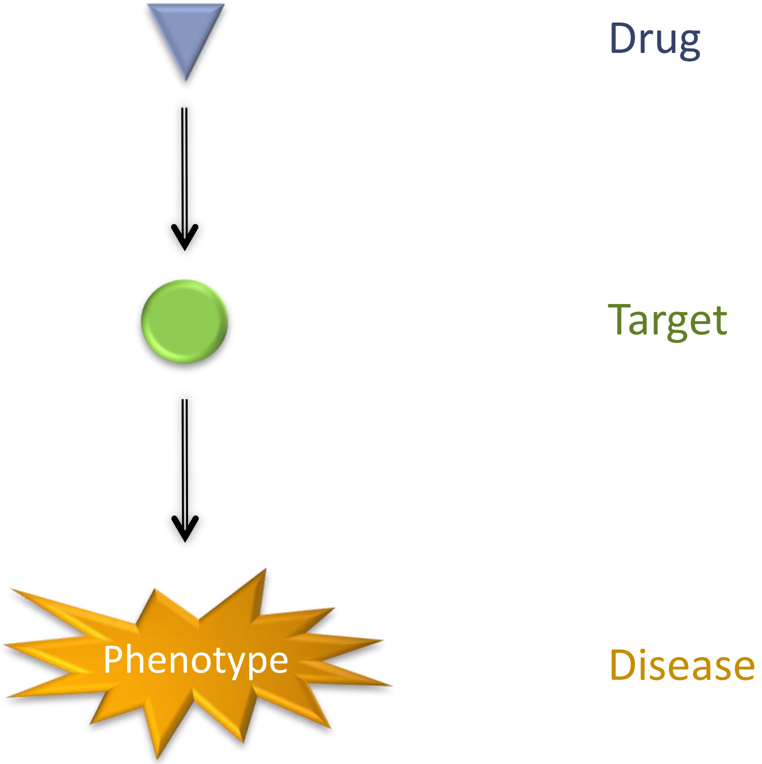
45 412	46 80	47 112	48 946	49 1207

Navigation in the Hasse diagram

Extent of the current pattern in the dataset

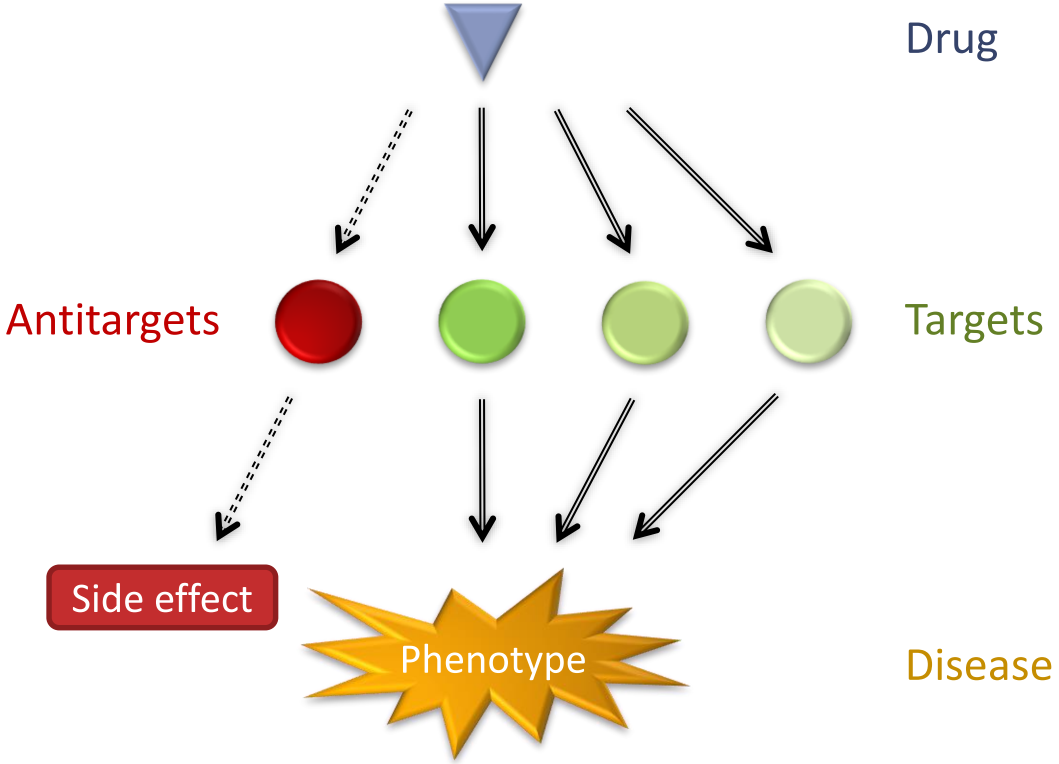
Case study (II): Polypharmacology

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



Case study (II): 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

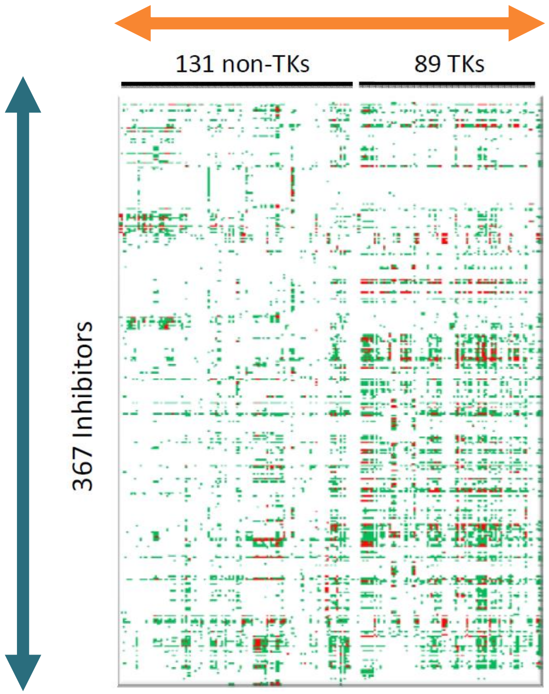


Case study (II): Polypharmacology

- Polypharmacology of kinases [13,14]
  - Most tumors can escape from the inhibition of any single kinase
  - The GSK Published Kinase Inhibitor Set (PKIS) as a source of knowledge

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

367 small molecules ATP-competitive kinase inhibitors



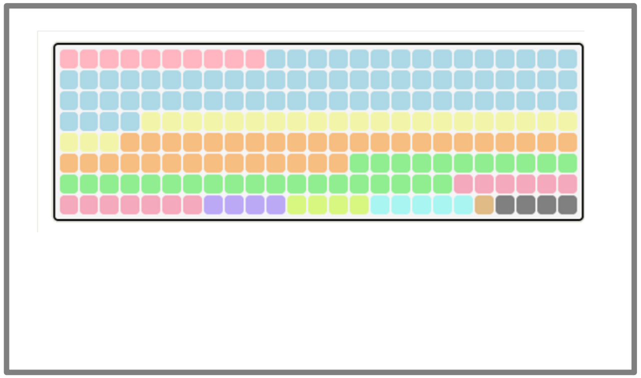
Data available from

ChEMBL

[13] Knight, Z.A. et al. Targeting the Cancer Kinome through Polypharmacology. *Nat. Rev. Cancer* **2010**, *10*, 130–137.
[14] Wu, P. et al. Small-Molecule Kinase Inhibitors: An Analysis of FDA-Approved Drugs. *Drug Discovery Today* **2016**, *21* (1), 5–10.

Case study (II): Polypharmacology

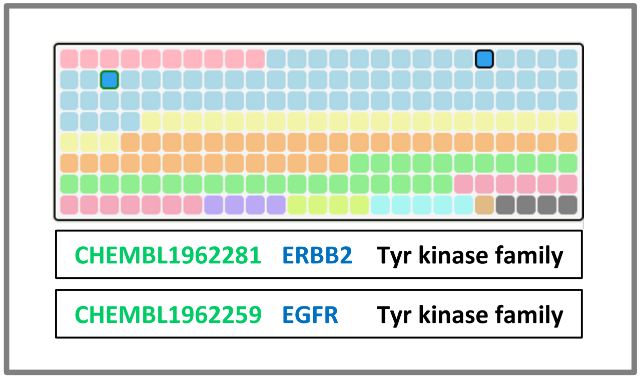
- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases



Case study (II): Polypharmacology

❍ Kinase Miner

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



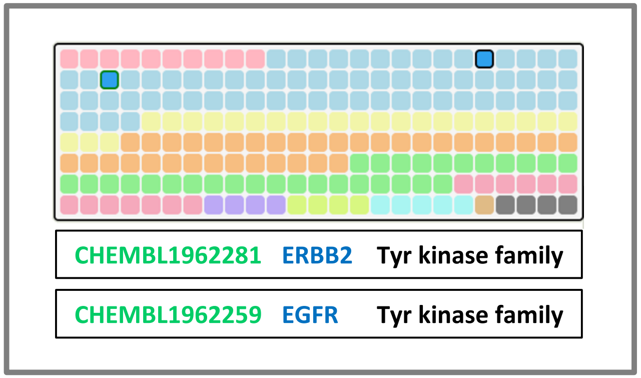
CHEMBL1962281 ERBB2 Tyr kinase family

CHEMBL1962259 EGFR Tyr kinase family

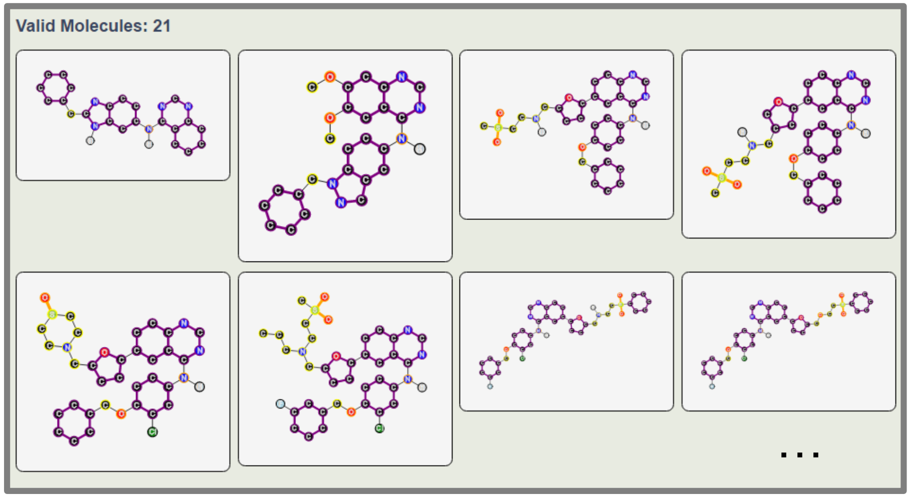
Case study (II): Polypharmacology

❍ Kinase Miner

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



CHEMBL1962281	ERBB2	Tyr kinase family
CHEMBL1962259	EGFR	Tyr kinase family



Valid Molecules: 21

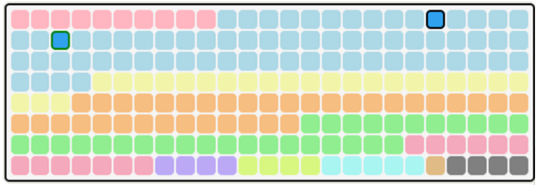
. . .

Molecules in agreement with the dual ERBB2 and EGFR inhibition

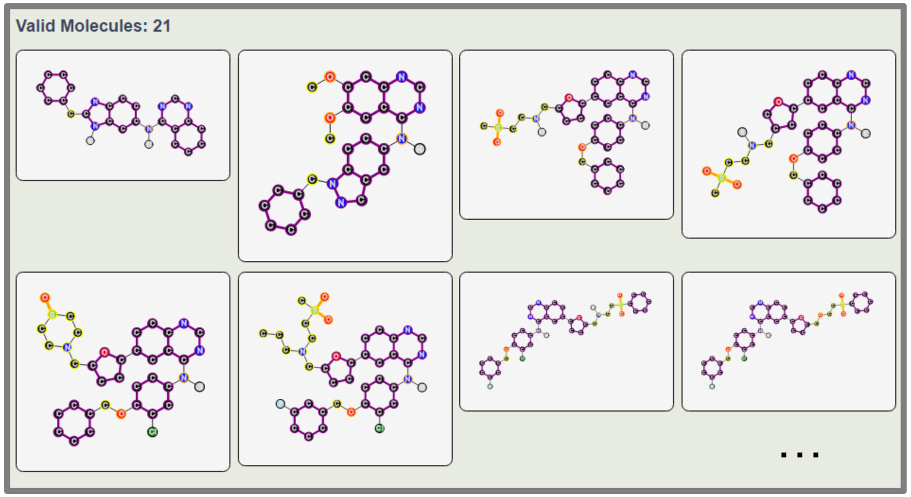
Case study (II): Polypharmacology

❍ Kinase Miner

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

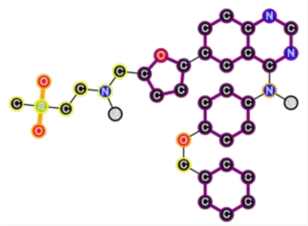


CHEMBL1962281	ERBB2	Tyr kinase family
CHEMBL1962259	EGFR	Tyr kinase family

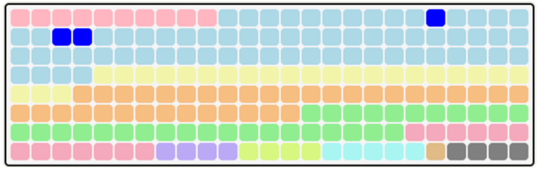


Valid Molecules: 21

. . .



CHEMBL529066

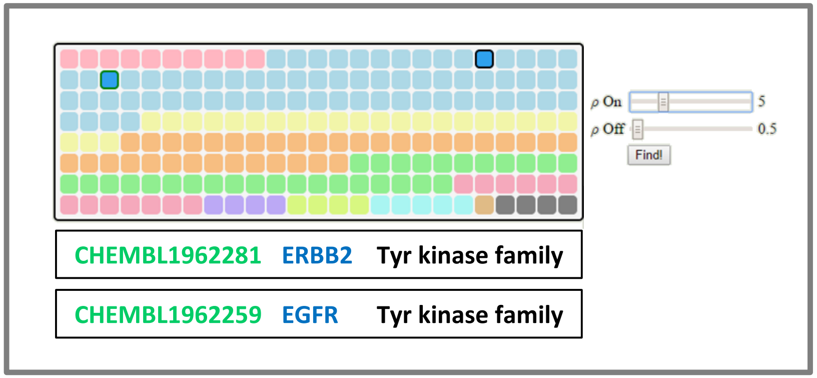


ERBB2	73.03 % inh @ 1µM
ERBB4	96.64 % inh @ 1µM
EGFR	94.13 % inh @ 1µM

Case study (II): Polypharmacology

❍ Kinase Miner

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



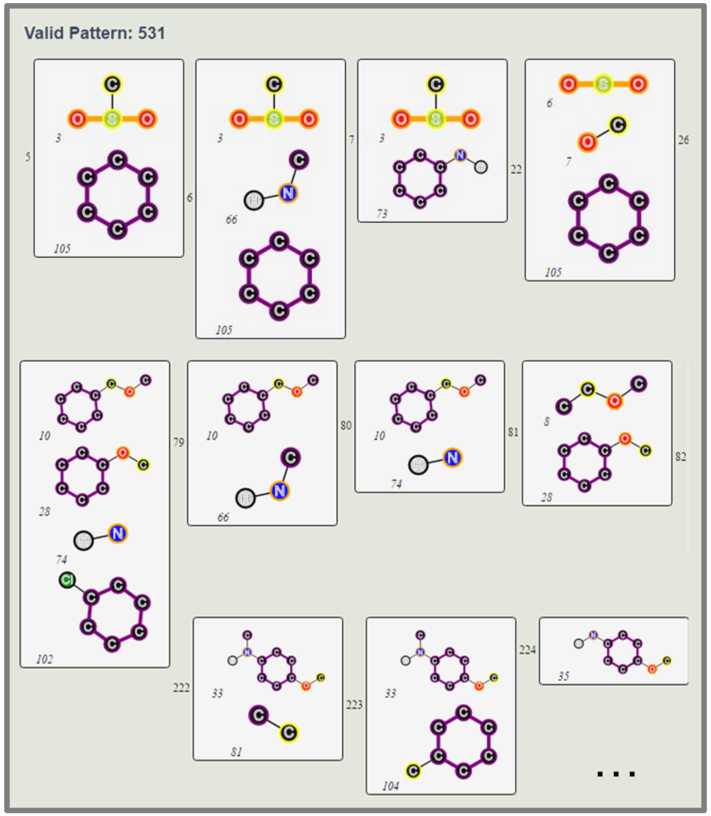
ρ On 5

ρ Off 0.5

Find!

CHEMBL1962281 ERBB2 Tyr kinase family

CHEMBL1962259 EGFR Tyr kinase family



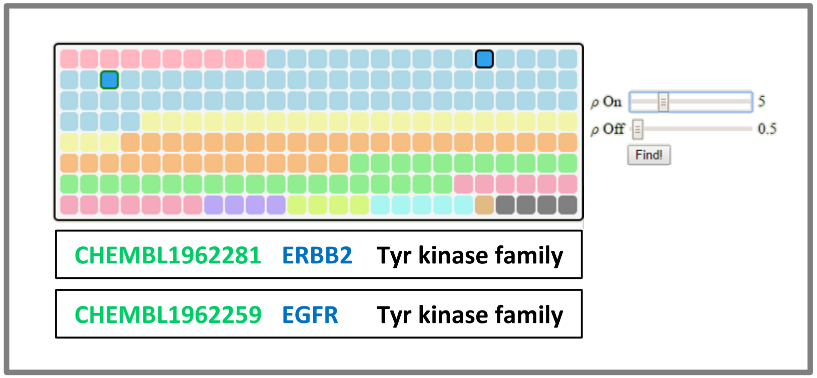
Valid Pattern: 531

. . .

Case study (II): Polypharmacology

❍ Kinase Miner

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

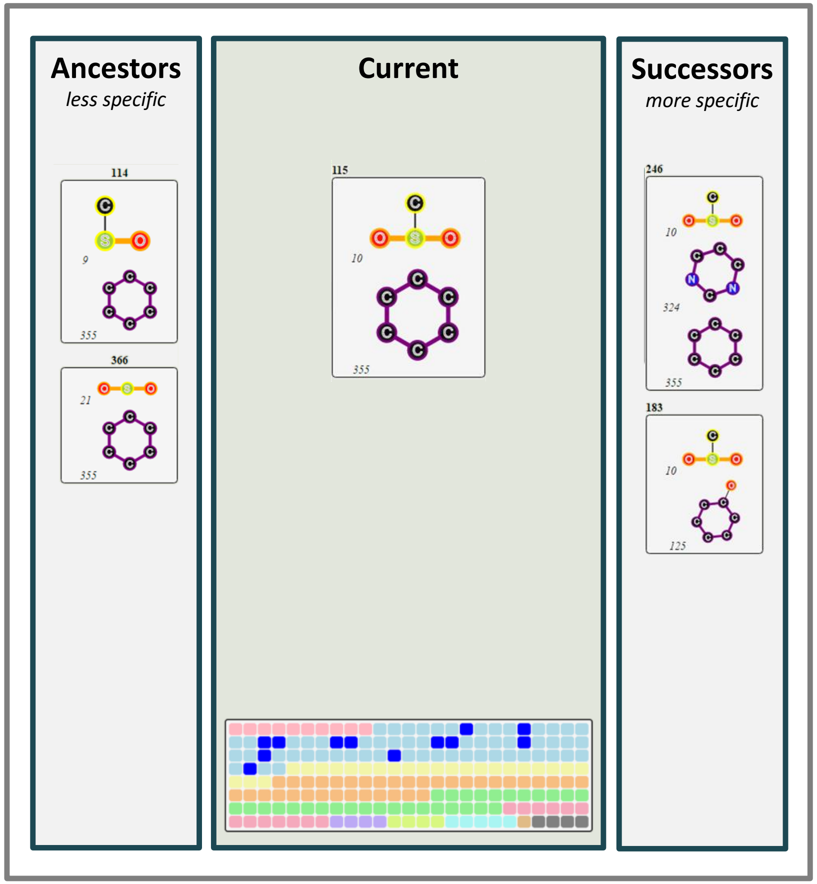


ρ On 5

ρ Off 0.5

Find!

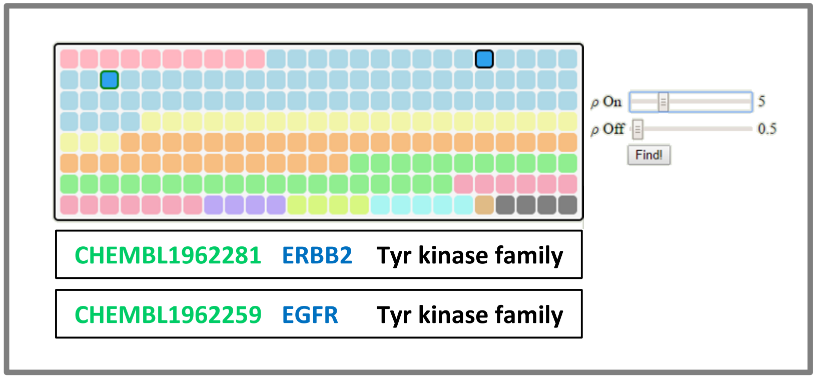
CHEMBL1962281	ERBB2	Tyr kinase family
CHEMBL1962259	EGFR	Tyr kinase family



Case study (II): Polypharmacology

❍ Kinase Miner

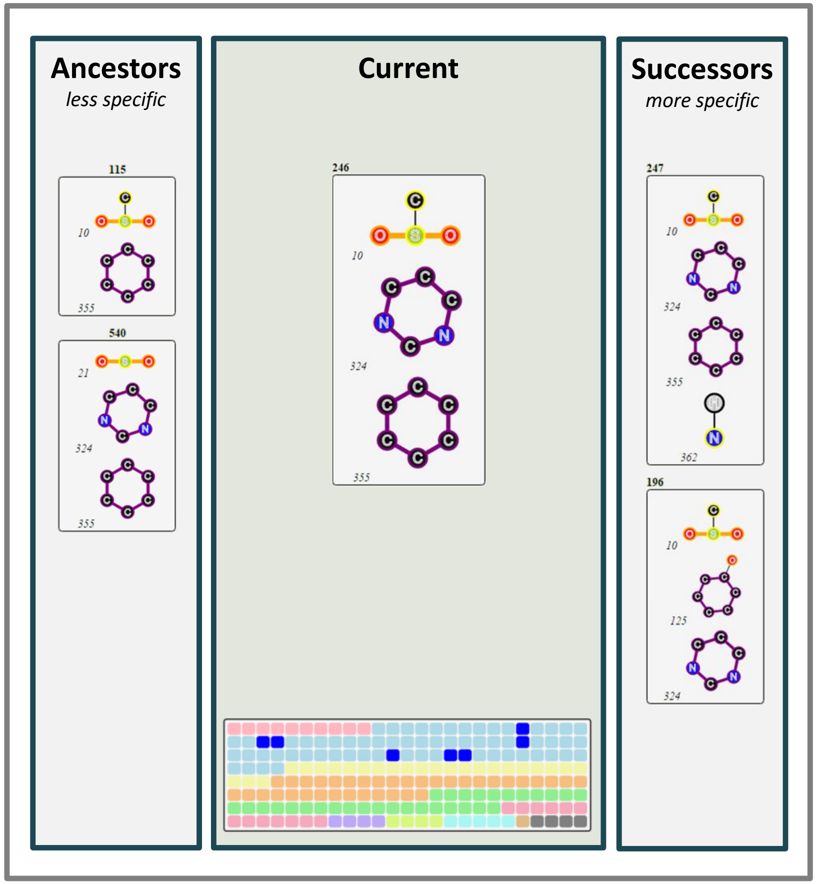
- Interactive tool dedicated to polypharmacology of kinases
- Example: dual inhibition of ERBB2 and EGFR



ρ On 5

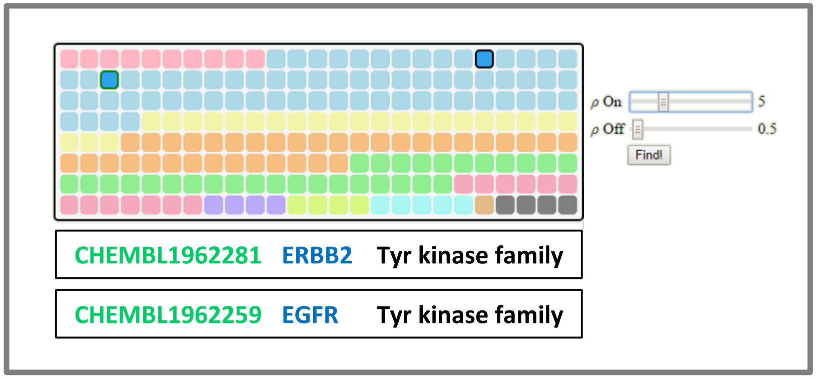
ρ Off 0.5

CHEMBL1962281	ERBB2	Tyr kinase family
CHEMBL1962259	EGFR	Tyr kinase family

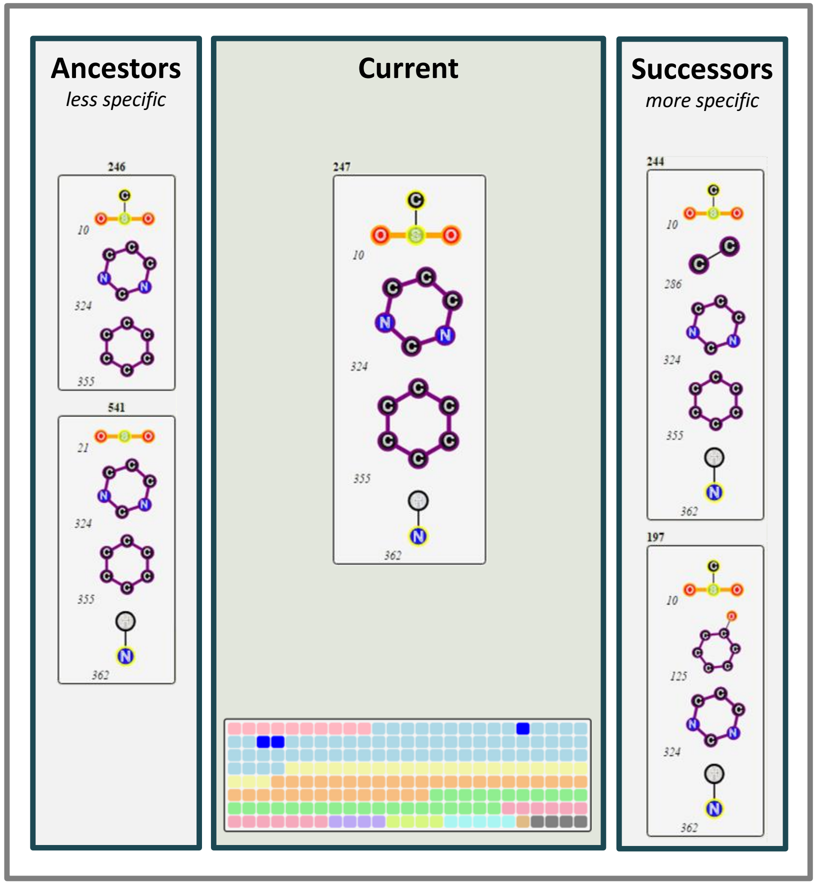


Case study (II): Polypharmacology

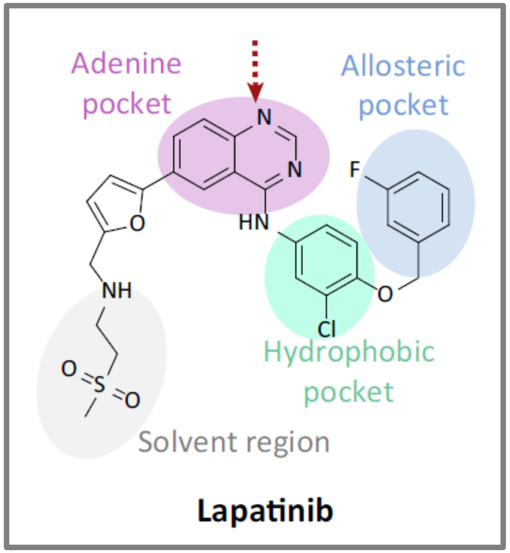
- Kinase Miner
  - Interactive tool dedicated to polypharmacology of kinases
  - Example: dual inhibition of ERBB2 and EGFR



CHEMBL1962281	ERBB2	Tyr kinase family
CHEMBL1962259	EGFR	Tyr kinase family

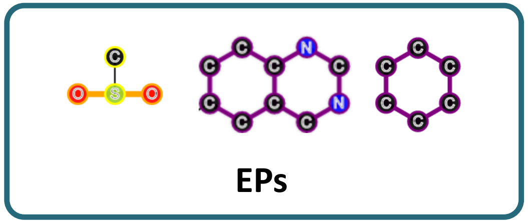


Last development



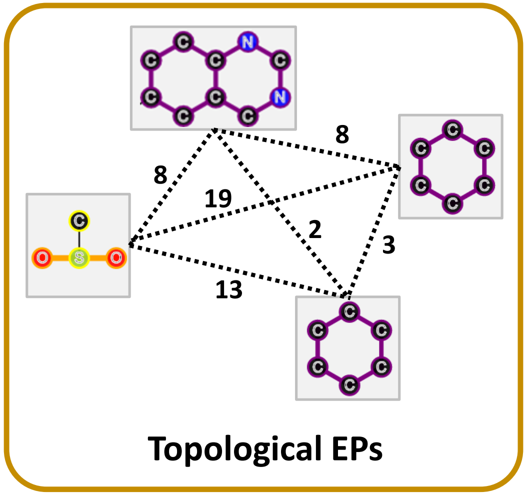
Lapatinib

1 Initial method



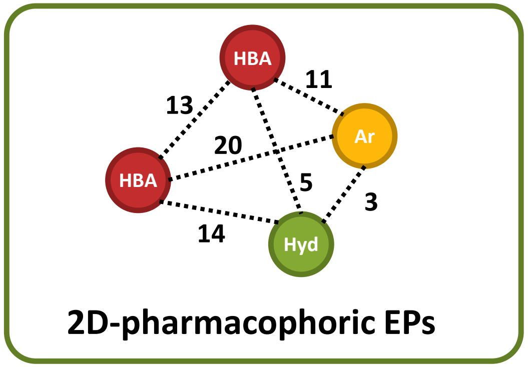
EPs

2 Addition of the distances



Topological EPs

3 Pharmacophoric definitions



2D-pharmacophoric EPs

Conclusion and perspectives

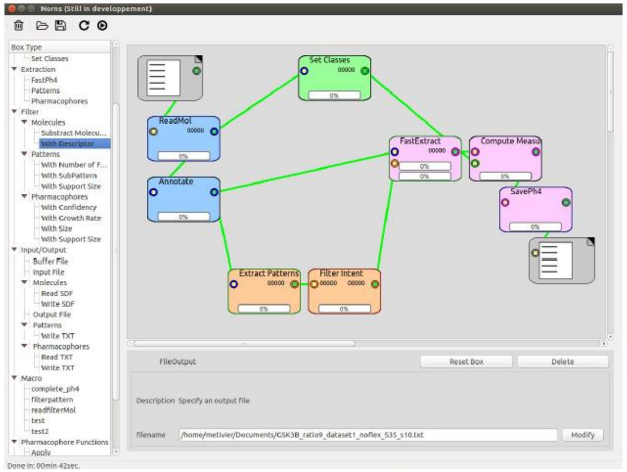
- The aim of the EP mining described here is to support the knowledge discovery in large and multidimensional data sets

- Validation
  - Identification of toxicophores
  - Understanding of the polypharmacological profile of kinase inhibitors

- Development of a workflow tool

Poster P17

Métivier et al.
Automated Generation of 2D-Pharmacophores from Large Datasets

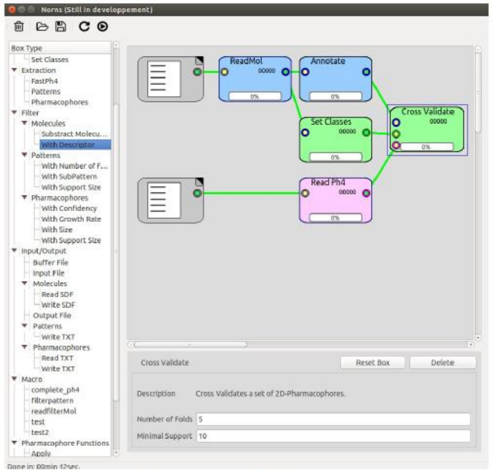


FileOutput

Description Specify an output file

filename /home/metivier/Documents/GSK3B_ratio9_dataset1_noflex_S35_s10.txt

2D-Pharmacophore Extraction



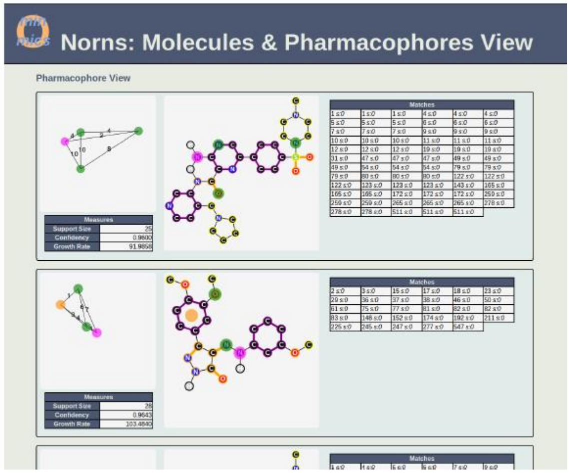
Cross Validate

Description Cross Validates a set of 2D-Pharmacophores.

Number of Folds 5

Minimal Support 10

Cross-validation



Measures	
Support Size	25
Confidency	0.9600
Growth Rate	91.9856

Measures	
Support Size	28
Confidency	0.9643
Growth Rate	103.4840

Results as webpages

Acknowledgments

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Guillaume Poezevara
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Sergei Kuznetsov

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INCUBATION

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ANR