UK-QSAR Autumn Meeting 2014
Uni of Cambridge, Cambridge, UK

Evidence-based medicinal chemistry

…using matched molecular series

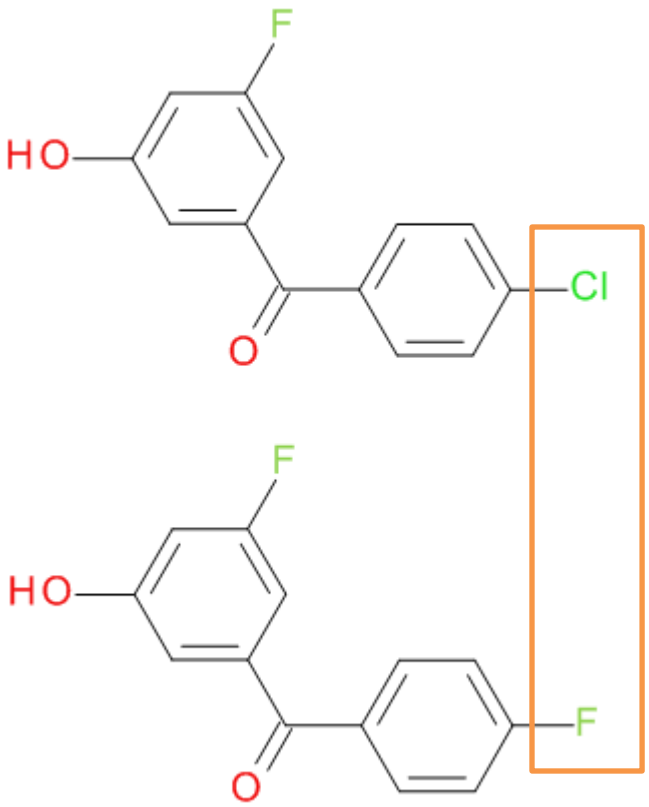
Noel O'Boyle and Roger Sayle

NextMove Software

Jonas Boström

AstraZeneca

MATCHED (MOLECULAR) PAIRS



1.6

3.5

[Cl, F]

Coined by Kenny and Sadowski in 2005*

Easier to predict **differences** in the values of a property than it is to predict the value itself

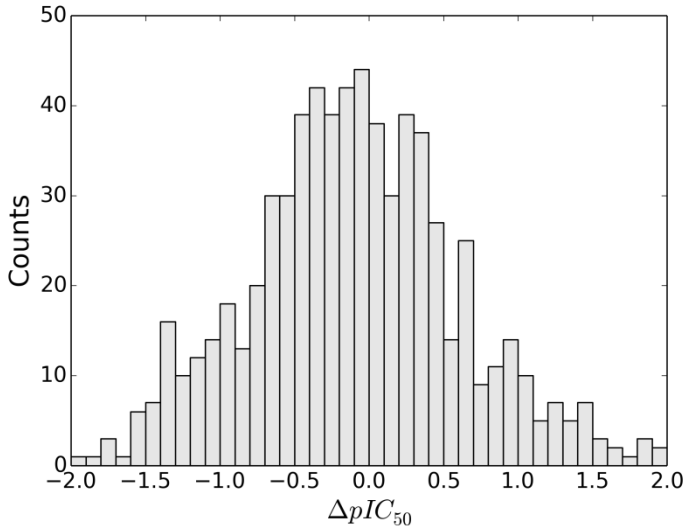
* Chemoinformatics in drug discovery, Wiley, 271–285.

MATCHED PAIR USAGE

- Successfully used for:
  - Rationalising and predicting physicochemical property changes
  - Finding bioisosteres
- Not very successful in improving activity
  - Activity changes dependent on binding environment
- Hajduk, Sauer. *J. Med. Chem.* **2008**, *51*, 553
  - Data from 30 protein targets at Abbott
  - Most R group transformations led to potency changes normally distributed around 0

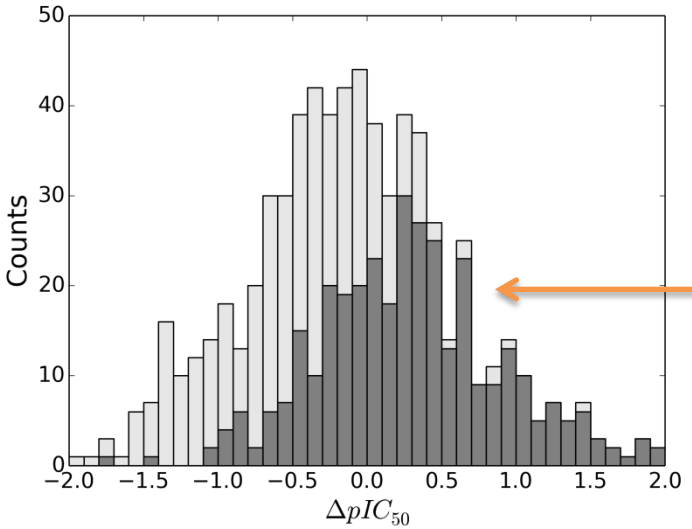
MATCHED PAIRS AND ACTIVITY

$pIC_{50}(CC)$-$pIC_{50}(CCCC)$



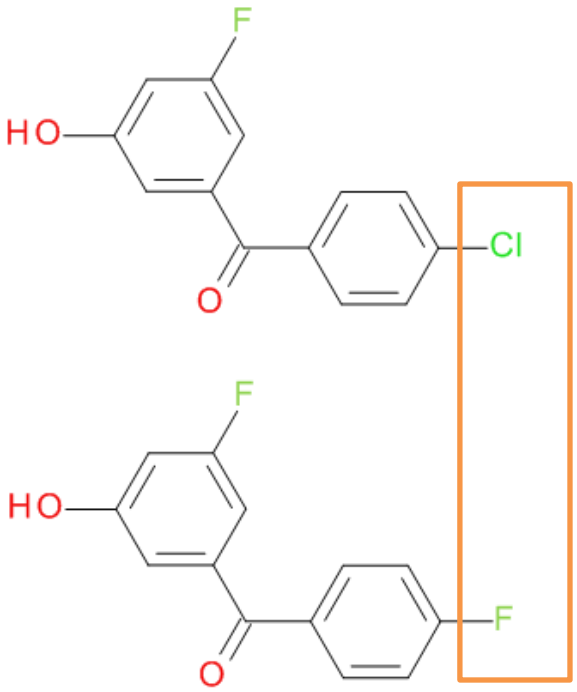
MATCHED PAIRS AND ACTIVITY

$pIC_{50}(CC)-pIC_{50}(CCCC)$



For those cases where:
[CCC > CCCC]

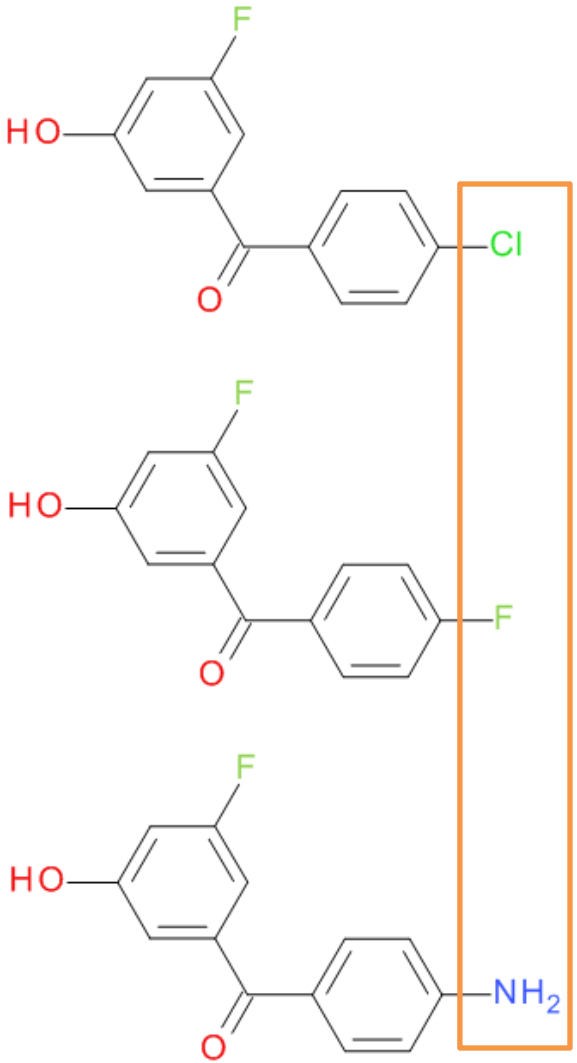
MATCHED SERIES OF LENGTH 2 = MATCHED PAIR



[Cl, F]

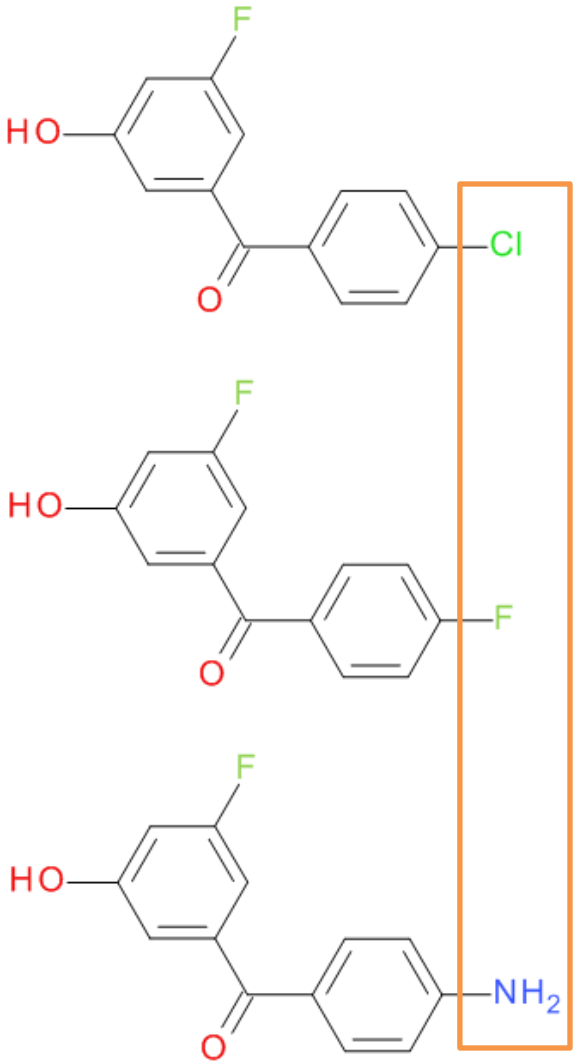
"Matching molecular series" introduced by Wawer and Bajorath, *J. Med. Chem.* **2011**, *54*, 2944

MATCHED SERIES OF LENGTH 3



[Cl, F, NH_2]

ORDERED MATCHED SERIES OF LENGTH 3



	pIC_{50}
Cl	3.5
F	2.1
NH_2	1.6

[Cl > F > NH_2]

PREFERRED ORDERS: HALIDES (N=2)

For an ordered matched series (i.e. A>B>C>…), there are N! ways of arranging the R Groups:

Series	Observations*
F > H	9761
H > F	8685

Would expect 9223 for each assuming the order is random

- We can calculate enrichment

*Dataset is ChEMBL19 IC_{50} data for binding assays (transformed to pIC_{50} values)

PREFERRED ORDERS: HALIDES (N=2)

For an ordered matched series (i.e. A>B>C>…), there are N! ways of arranging the R Groups:

Series	Enrichment	Observations
F > H	1.06*	9761
H > F	0.94*	8685

Would expect 9223 for each assuming the order is random

- We can calculate enrichment

*Significant at 0.05 level according to binomial test after correcting for multiple testing (Bonferroni with N-1)

PREFERRED ORDERS: HALIDES (N=3)

Series	Enrichment	Observations
Cl > F > H	1.90*	1478
H > F > Cl	1.08	838
F > Cl > H	0.86*	673
F > H > Cl	0.78*	607
Cl > H > F	0.76*	589
H > Cl > F	0.63*	490

PREFERRED ORDERS: HALIDES (N=4)

Series	Enrichment	Observations
Br > Cl > F > H	5.43*	263
Cl > Br > F > H	3.22*	156
H > F > Cl > Br	**1.59***	**77**
Br > Cl > H > F	1.43	69
F > Cl > Br > H	1.40	68
Cl > Br > H > F	0.85	41
…	…	…
H > F > Br > Cl	**0.76**	**37**
…	…	…
H > Br > F > Cl	**0.50***	**24**
Cl > H > F > Br	0.48*	23
Cl > F > H > Br	0.45*	22
H > Cl > F > Br	0.43*	21
Br > F > H > Cl	0.41*	20
F > H > Br > Cl	0.41*	20
H > Cl > Br > F	0.41*	20
F > Br > H > Cl	0.35*	17
Br > H > F > Cl	**0.23***	**11**

N=2: Max = 1.06, Min = 0.94
N=3: Max = 1.90, Min = 0.63
N=4: Max = 5.43, Min = 0.232

Longer series exhibit greater preferences

If [H>F>Cl] is observed, will Br increase activity further?
149 observations of [H>F>Cl]
but only 11 where [Br>H>F>Cl]

FIND R GROUPS THAT INCREASE ACTIVITY

ChEMBL

In-house

Query

A > B

A > B > C

C > **A** > **B**

D > **A** > **B** > C

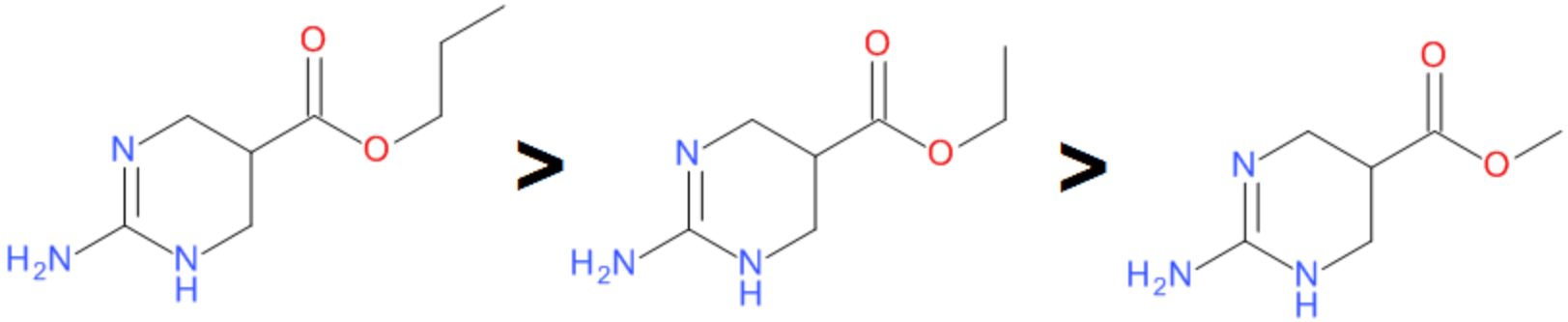
D > **A** > C > **B**

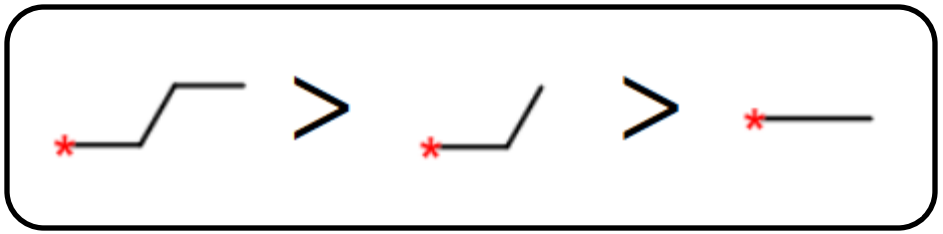
E > D > **A** > **B**

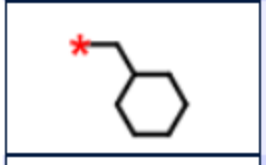
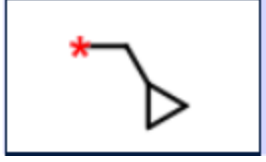
…

R Group	Observations	Obs that increase activity	% that increase activity
D	3	3	**100**
E	1	1	**100**
C	4	1	**25**
…	…		…

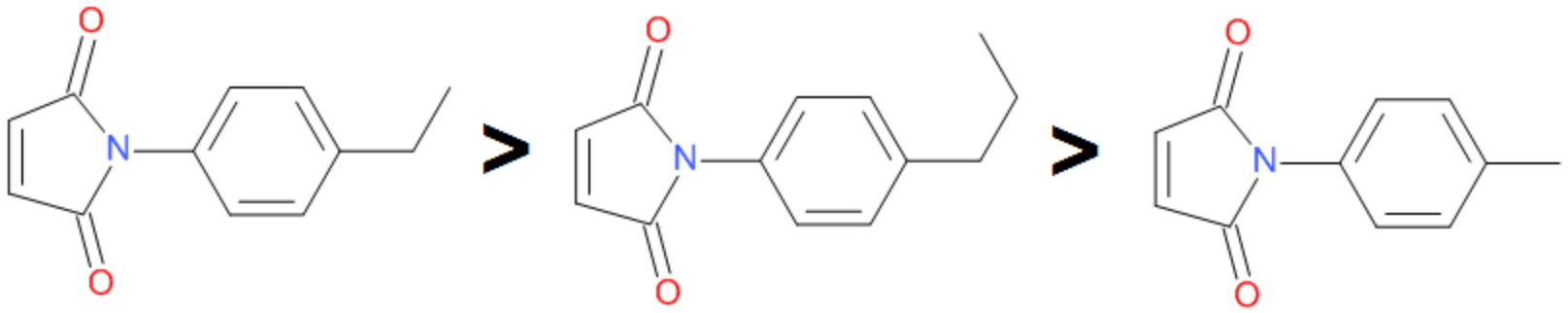
EXAMPLE

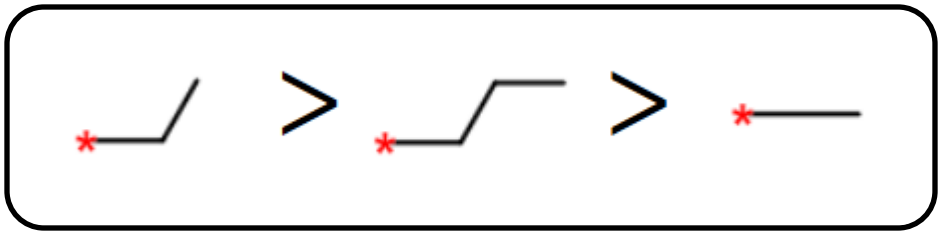




	% >	Counts	ΔLogP
	90	21	+3.3
	72	60	+1.7
	69	32	+2.8
	63	27	+1.6
	60	40	-0.1

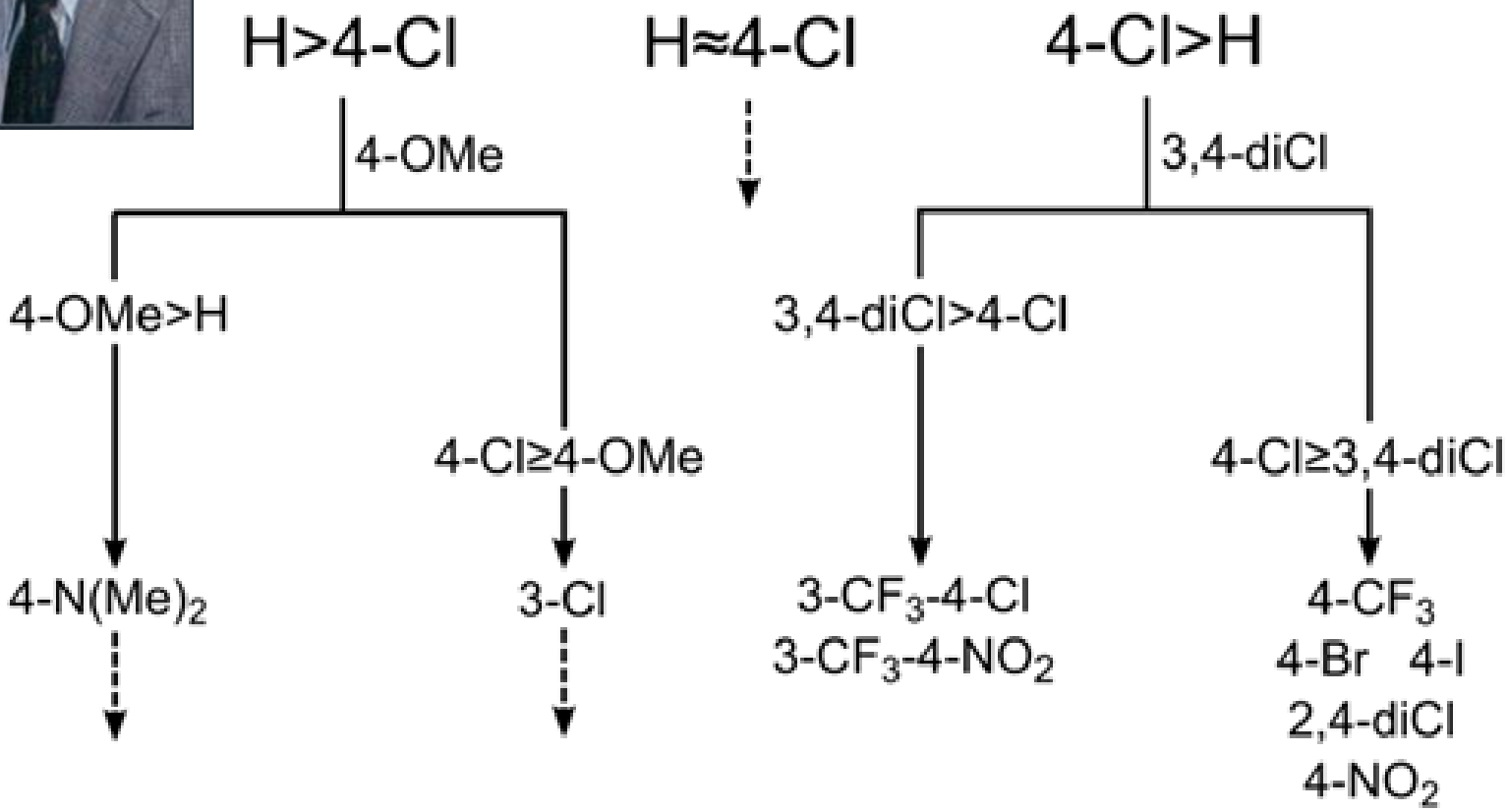
EXAMPLE II





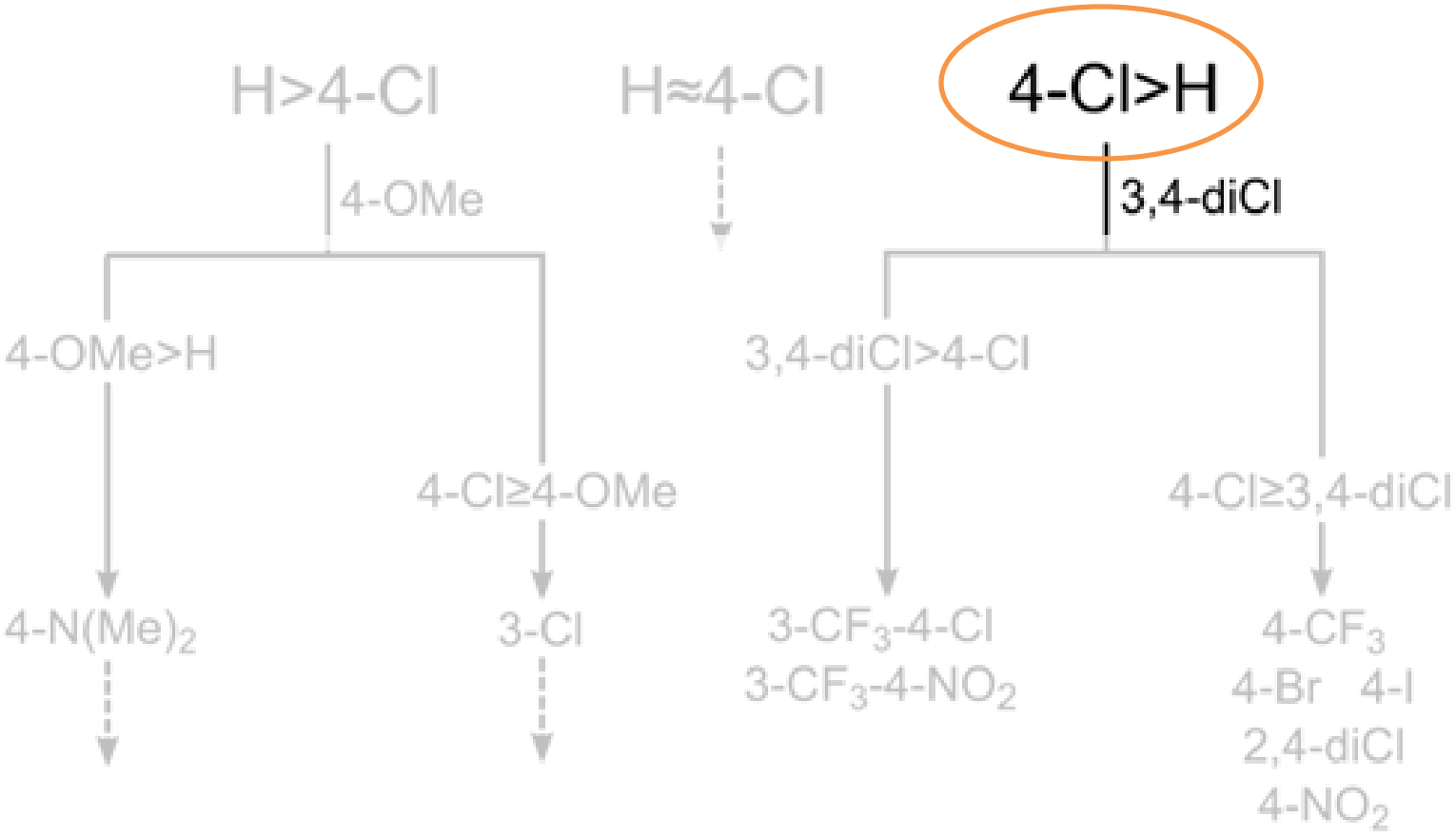
	% >	Counts	ΔLogP
*—Br	38	21	**-0.8**
*	37	27	+0.9
*	33	**111**	+0.3
*	33	27	+1.0
*—OH	33	21	**-1.6**

TOPLISS DECISION TREE

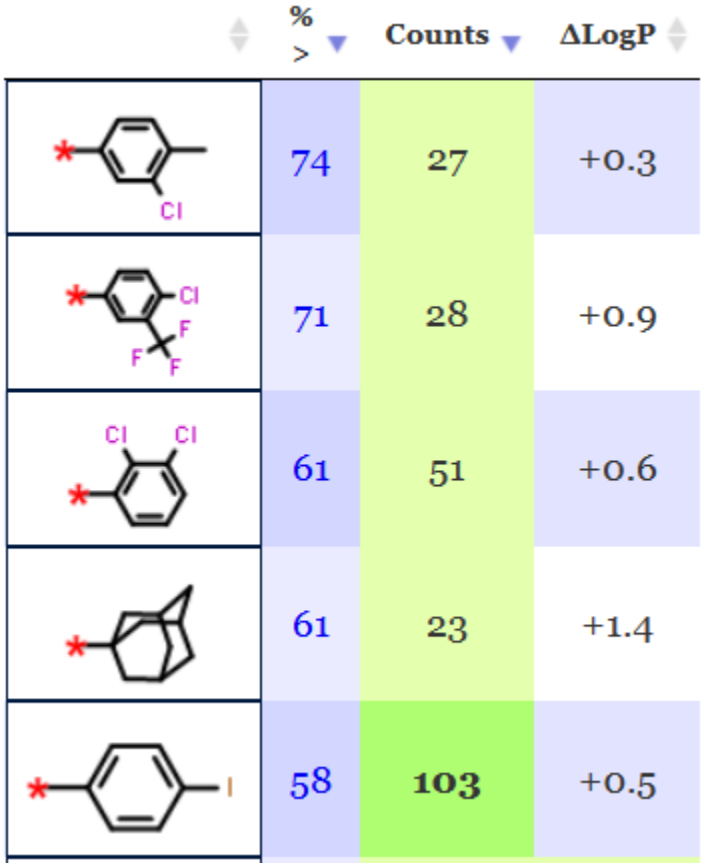


Topliss, J. G. Utilization of Operational Schemes for Analog Synthesis in Drug Design. *J. Med. Chem.* **1972**, *15*, 1006–1011.

TOPLISS DECISION TREE



TOPLISS DECISION TREE



4-Cl>H

3,4-diCl

4-OMe

4-N(Me

diCl>4-Cl

CF_3-4-Cl

CF_3-4-NO_2

4-Cl≥3,4-diCl

4-CF_3

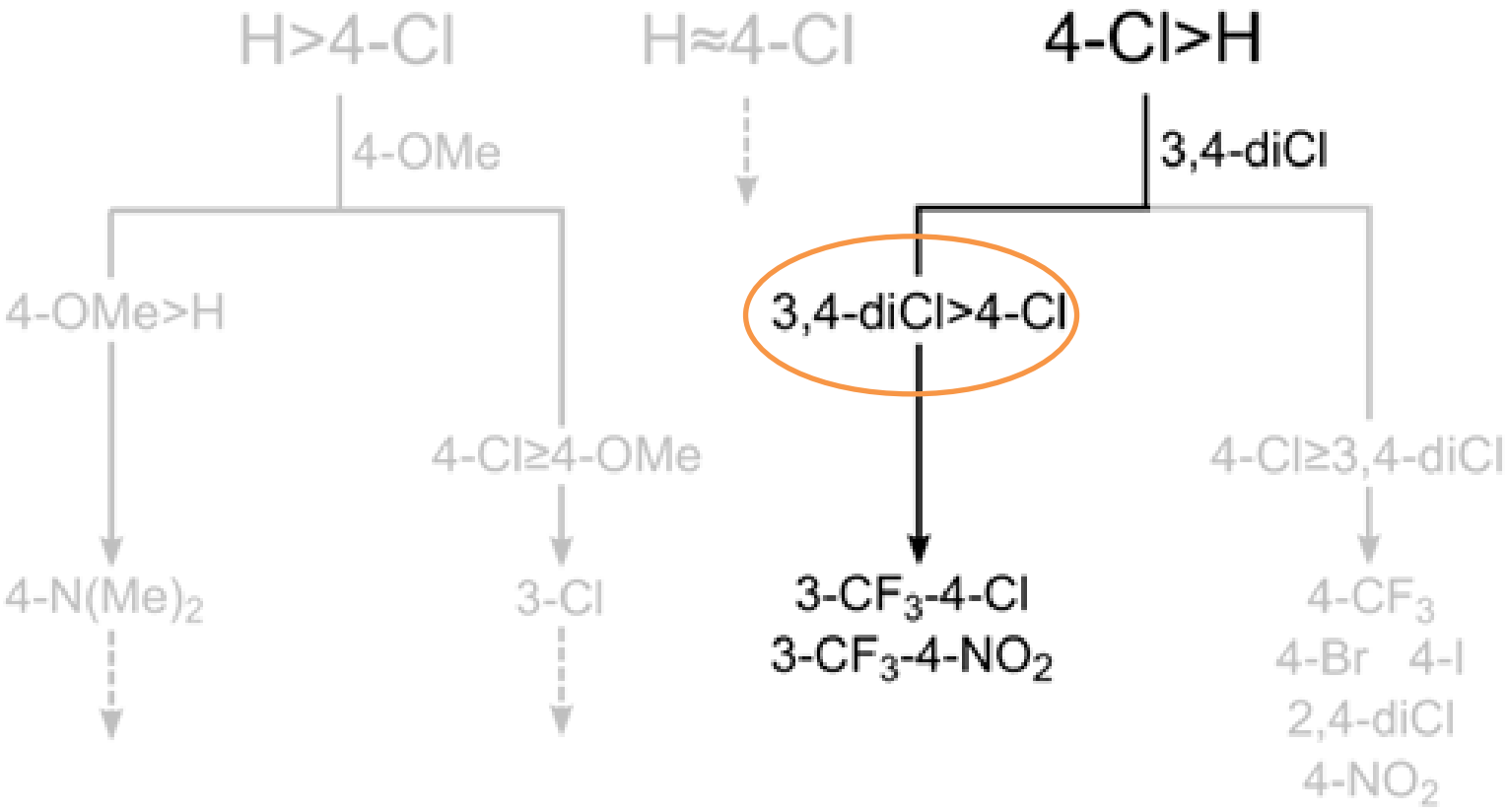
4-Br 4-I

2,4-diCl

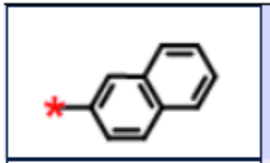
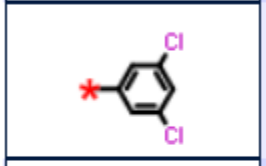
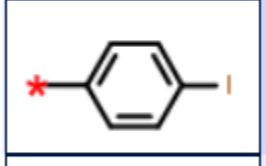
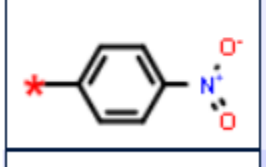
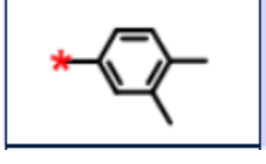
4-NO_2

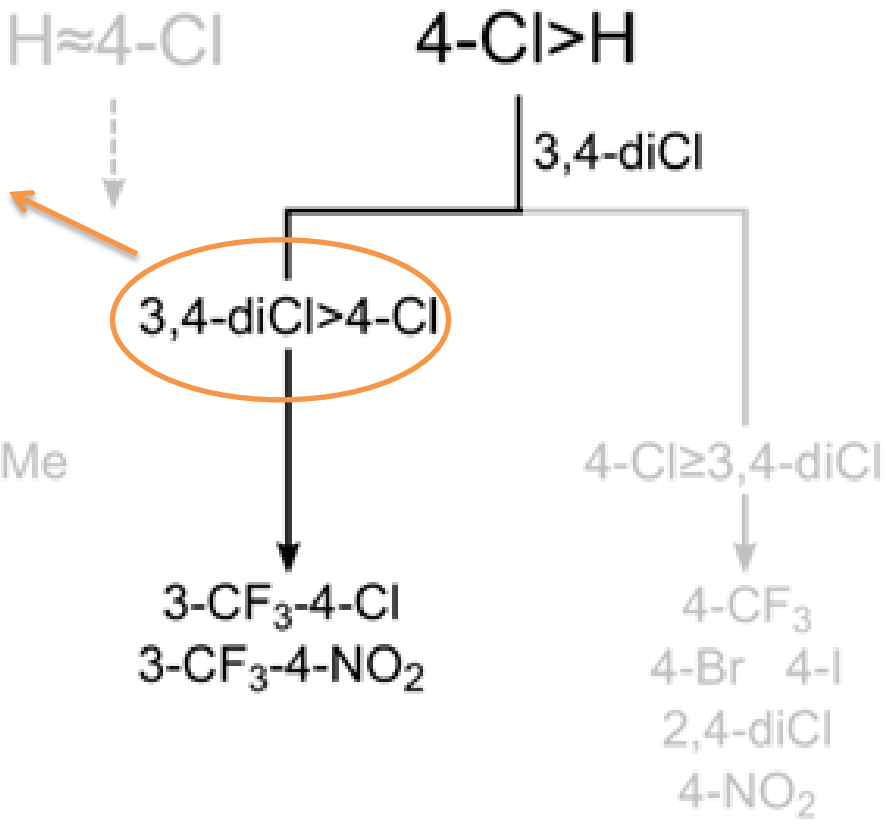
(11th)

TOPLISS DECISION TREE

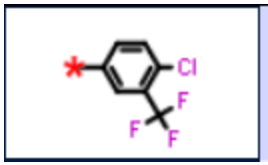


TOPLISS DECISION TREE

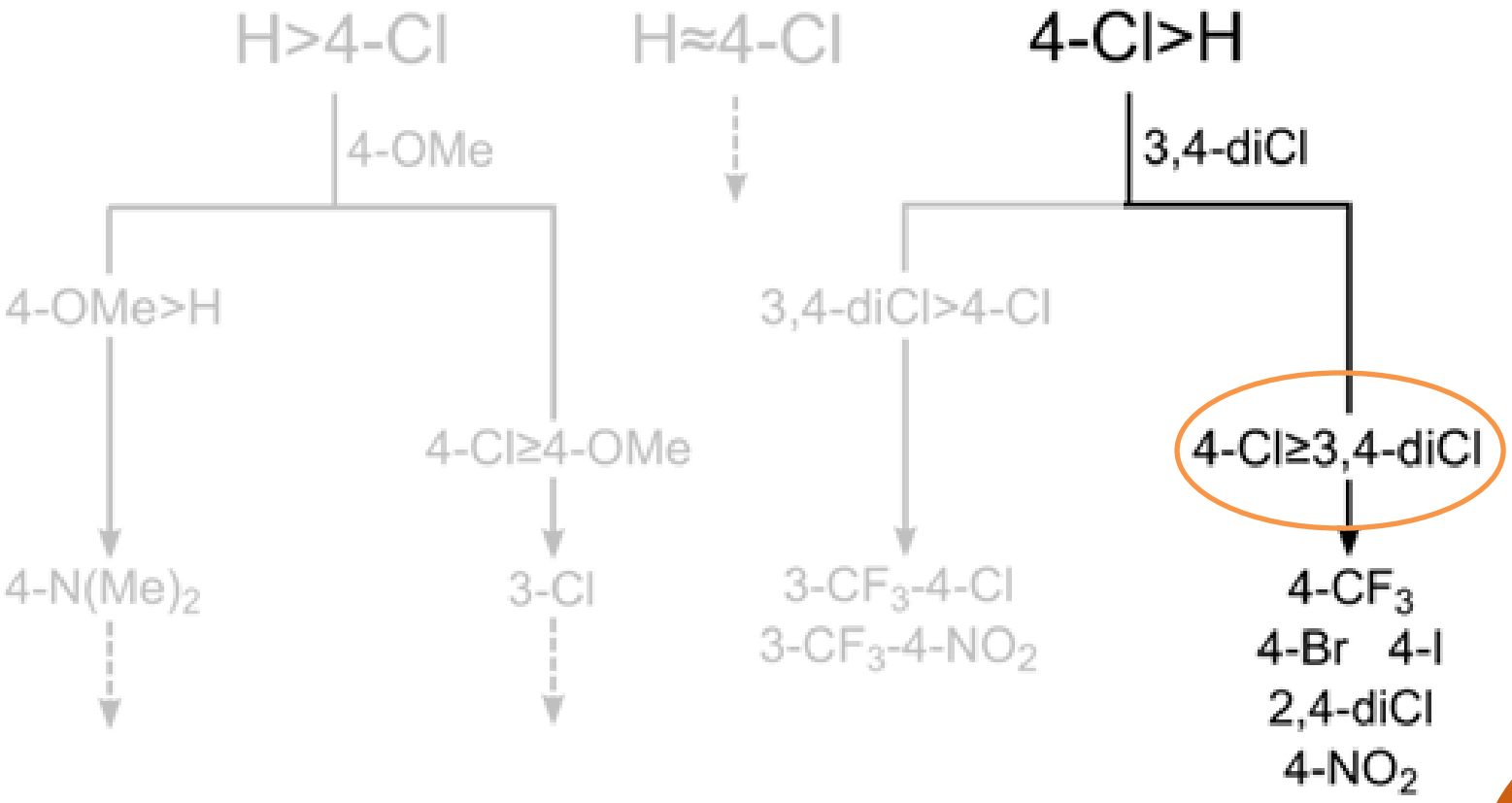
	% >	Counts	ΔLogP
	32	57	+0.4
	24	37	0.0
	22	23	-0.1
	21	47	**-2.9**
	20	20	-0.1



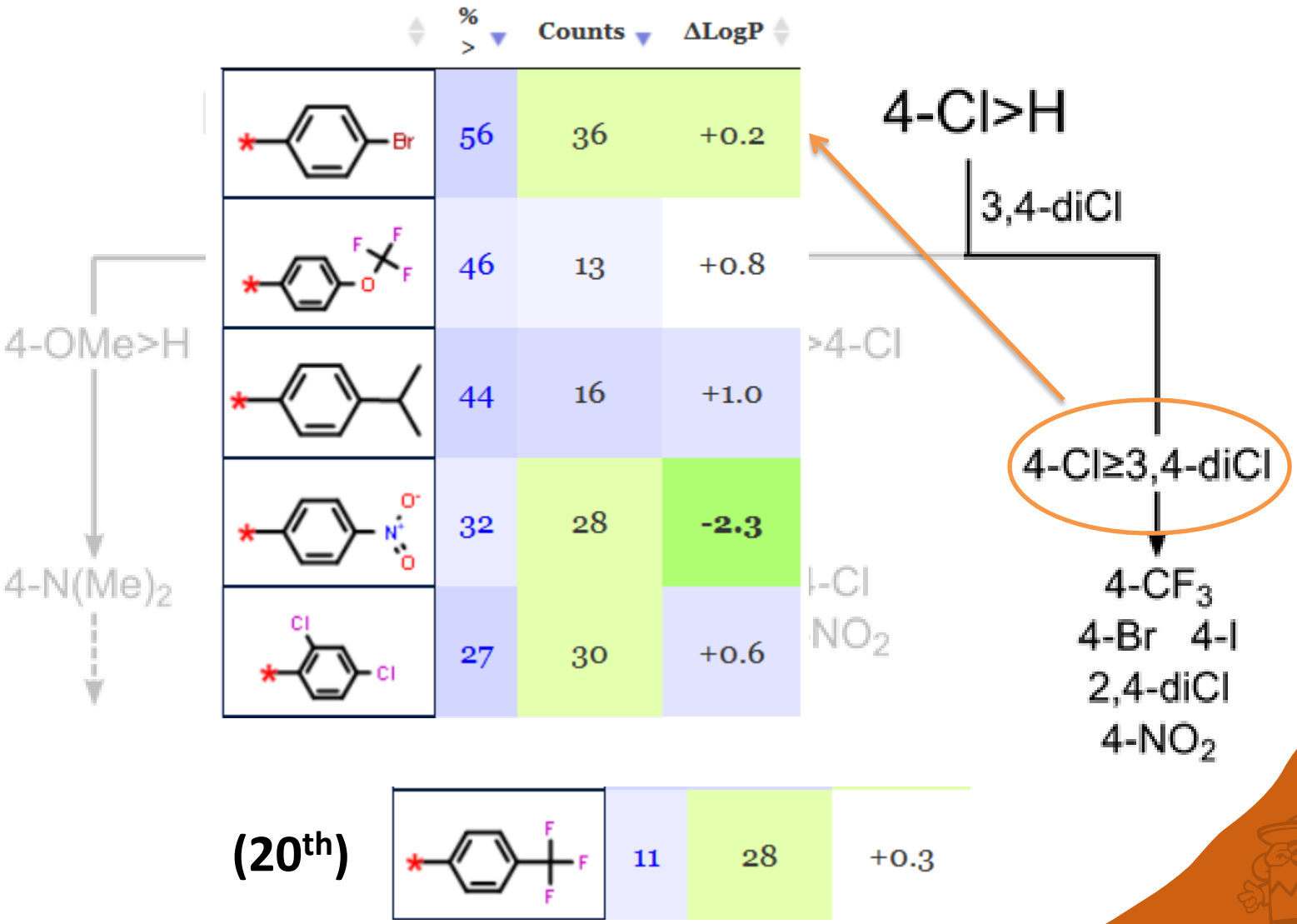
(1st if lower cutoff)

	33	5.00	15	+0.3

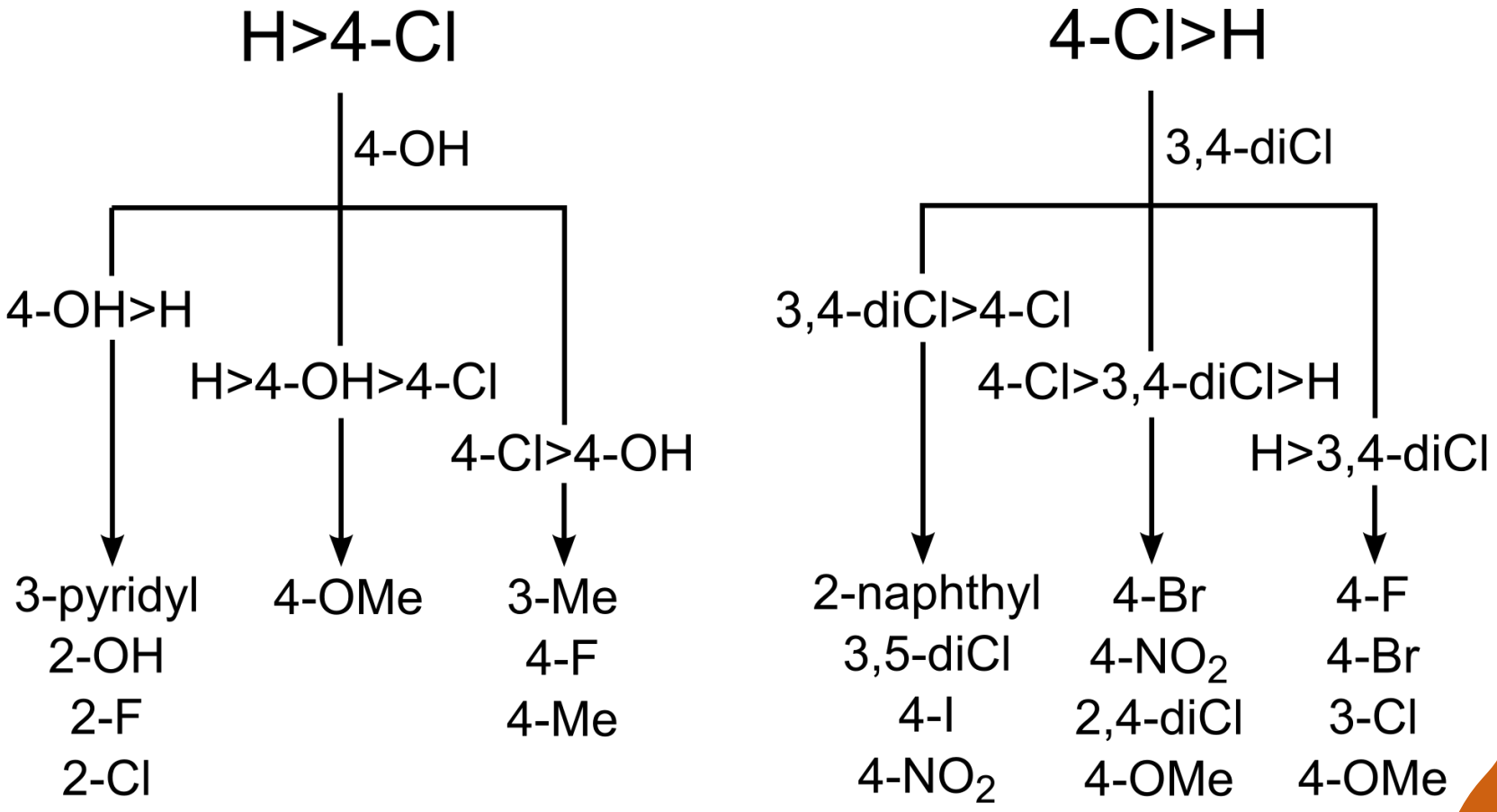
TOPLISS DECISION TREE



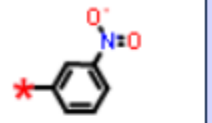
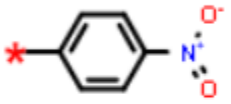
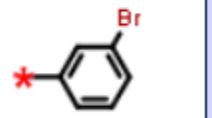
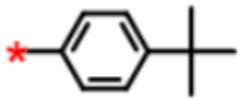
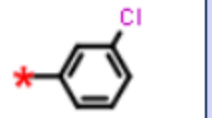
TOPLISS DECISION TREE



MATSY DECISION TREE (ONE OF MANY)

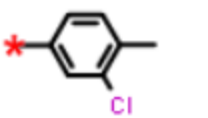
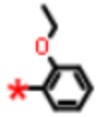
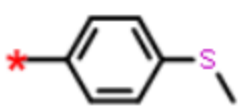
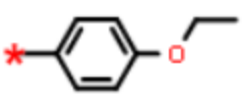
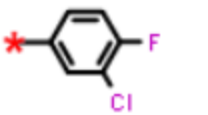


MODIFYING THE PREDICTIONS FOR **4-Cl > H**

	% >	Counts
	67	30
	47	30
	46	24
	44	25
	42	77

Kinases

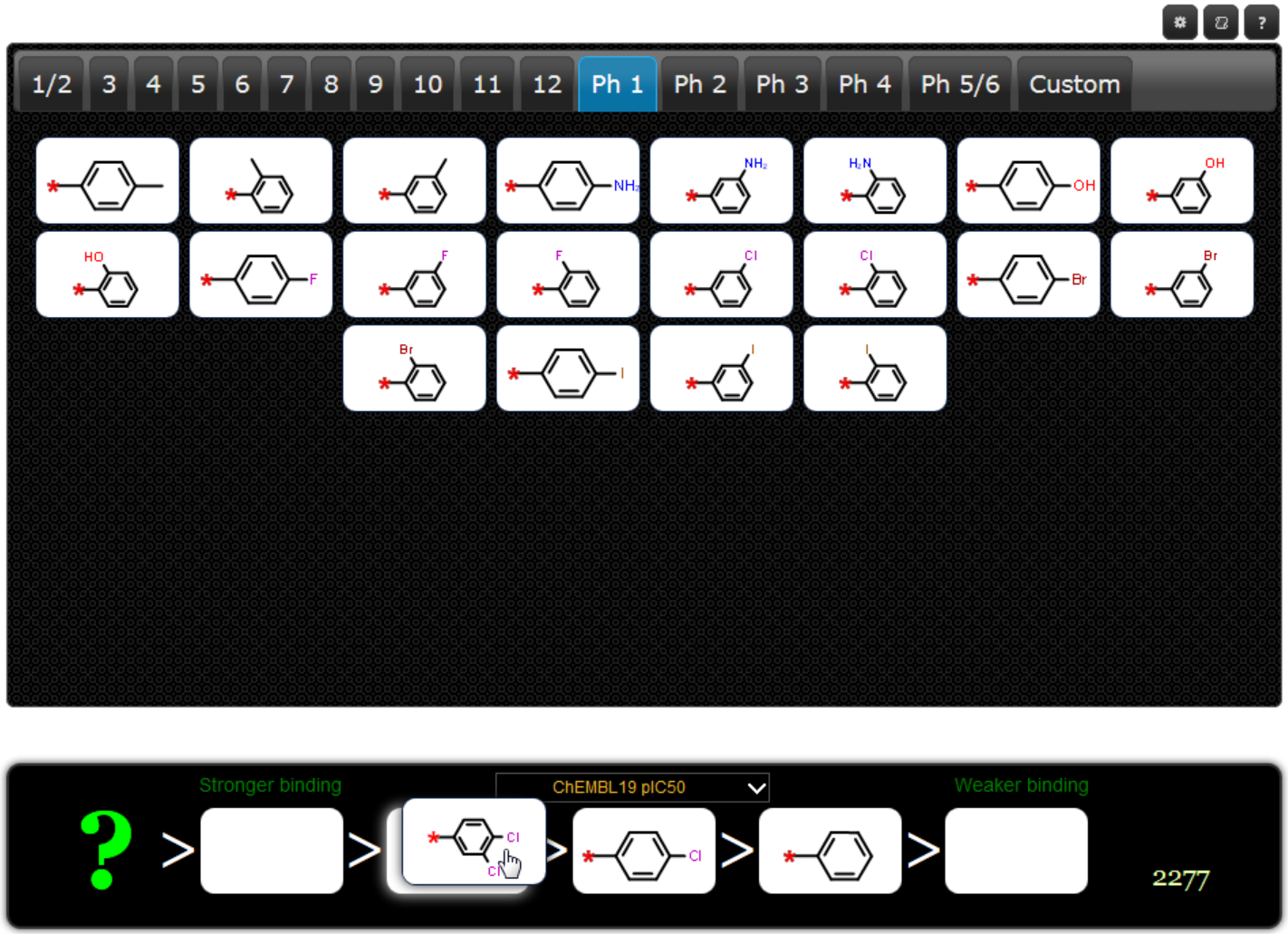
Target-specific

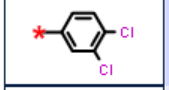
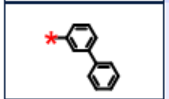
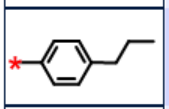
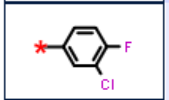
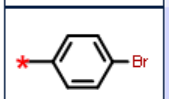
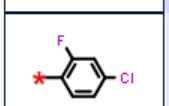
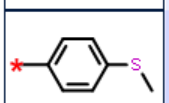
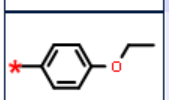
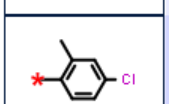
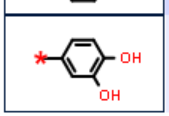
	% >	Counts	ΔLogP
	63	27	+0.3
	55	20	-0.4
	49	63	0.0
	48	46	-0.4
	48	46	+0.1

ΔLiPE > 0

Incorporate metrics

DRAG-AND-DROP INTERFACE TO MATSY



	% >	Counts	ΔLogP
	54	391	+0.6
	54	37	+2.0
	53	30	+1.1
	52	46	+0.1
	50	521	+0.2
	50	32	+0.1
	49	63	0.0
	48	46	-0.4
	48	25	+0.3
	48	21	-2.2

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EVIDENCE-BASED MEDICINAL CHEMISTRY

- Take advantage of the wealth of experience contained in 57k med chem papers

- Synthetic decisions backed by experimental data
  - Can drill-down into the data, look at targets, scaffolds
  - Can restrict experimental data used to particular targets, use in-house data rather than ChEMBL

- Does not explain why, only that it happens
  - Lots of interesting scientific questions (hint hint)

Evidence-based medicinal chemistry

…using matched molecular series

noel@nextmovesoftware.com

Using Matched Molecular Series as a Predictive Tool To Optimize Biological Activity
J. Med. Chem. **2014**, *57*, 2704.

Slides (soon!) at
http://slideshare.net/nextmovesoftware