3rd RDKit Meeting
Merck, Darmstadt, Oct 2014

Using RDKit for Matched Molecular Series Analysis

When two are not enough

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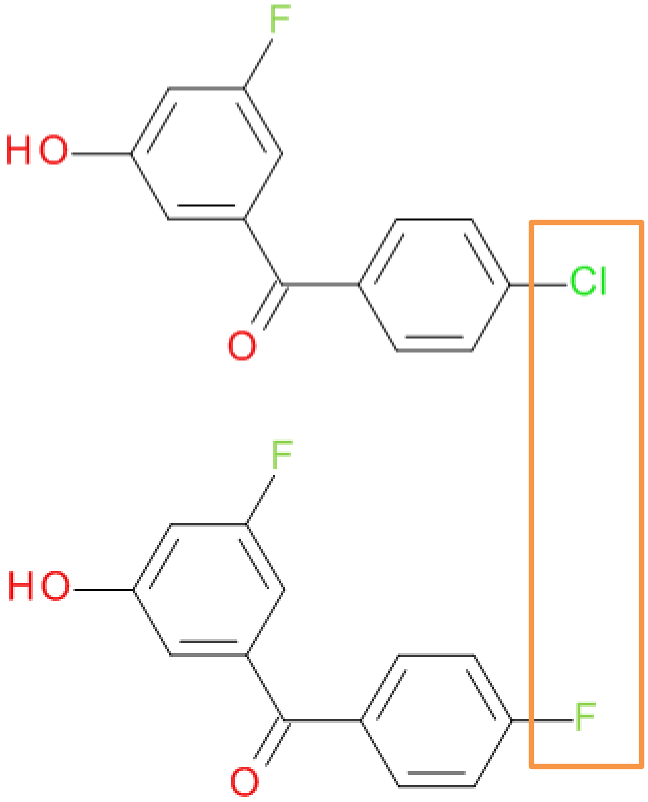
NextMove Software

HOW TO CHOOSE WHAT COMPOUND TO MAKE NEXT?

- Based on experience on related projects
  - What worked last time?
- By observing an activity trend, inferring a SAR relationship, and extrapolating
  - Aka ‘chemical intuition’
- Our additional suggestion:
  - Take advantage of the wealth of experience and trends contained in 57K med chem papers
  - ‘evidence-based medicinal chemistry’

MATCHED PAIRS & SERIES

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

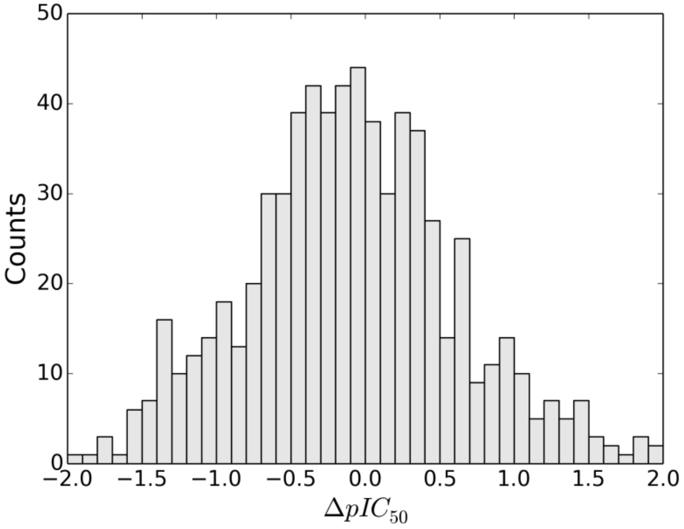
* Chemoinformatics in drug discovery, Wiley, 271–285.

MATCHED PAIR USAGE

- Successfully used for:
  - Predicting physicochemical property changes
  - Finding bioisosteres
- Not very successful in improving activity
  - Activity changes dependent on binding environment
  - Need to use matched pair data only for a particular binding pocket for a particular protein
- 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

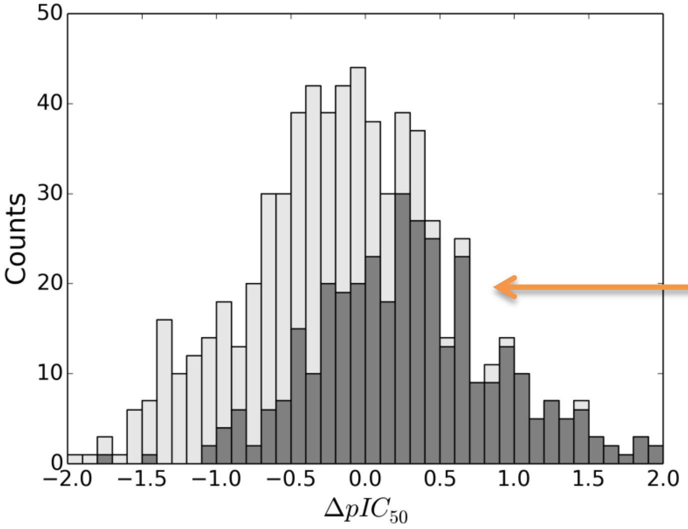
MATCHED PAIRS AND ACTIVITY

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



MATCHED PAIRS AND ACTIVITY

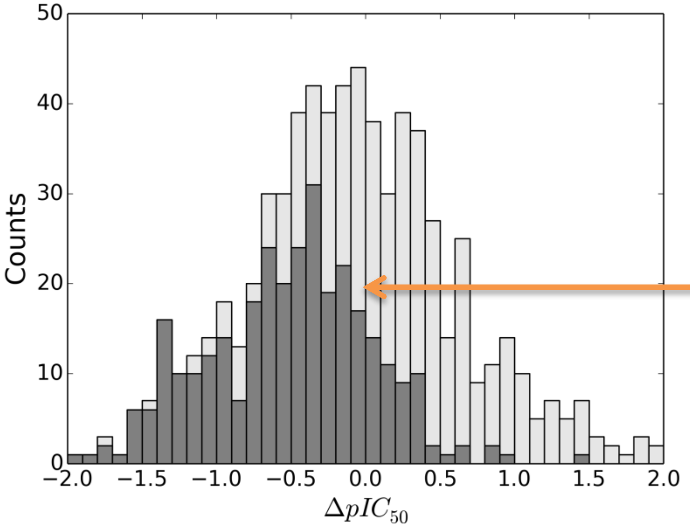
$pIC_{50}(CC)-pIC_{50}(CCCC)$



For those cases where:
[CCC > CCCC]

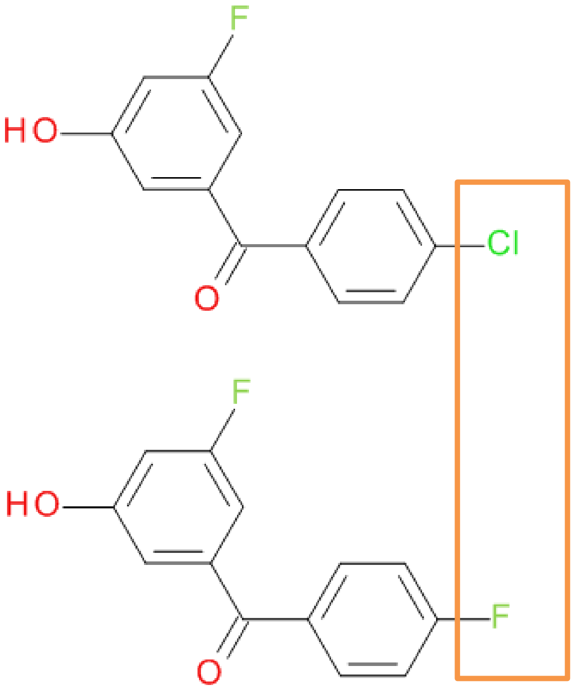
MATCHED PAIRS AND ACTIVITY

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



For those cases where:
[CCC < CCCC]

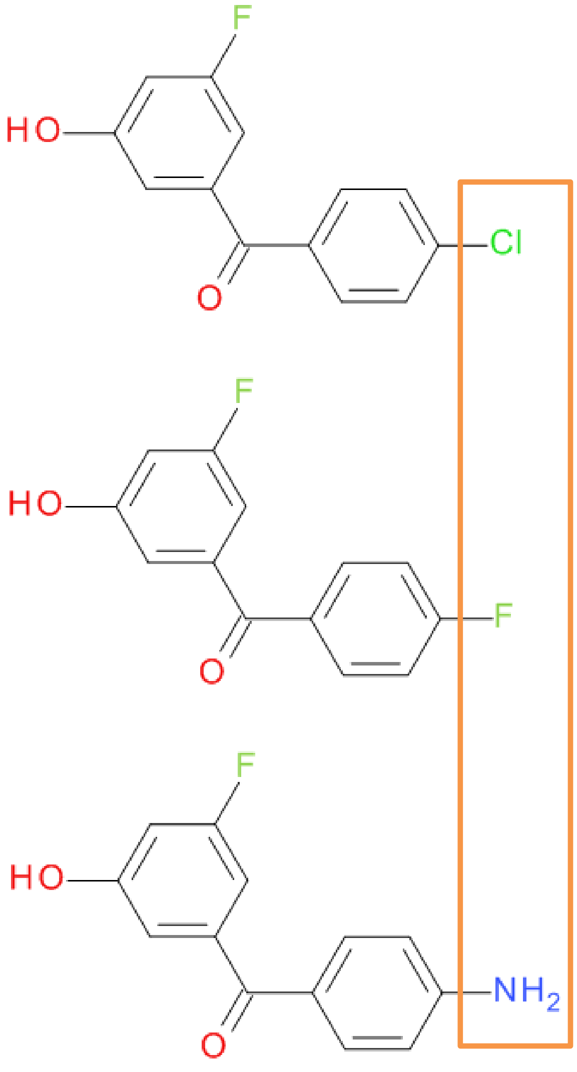
Matched series of length 2 = matched pair



[Cl, F]

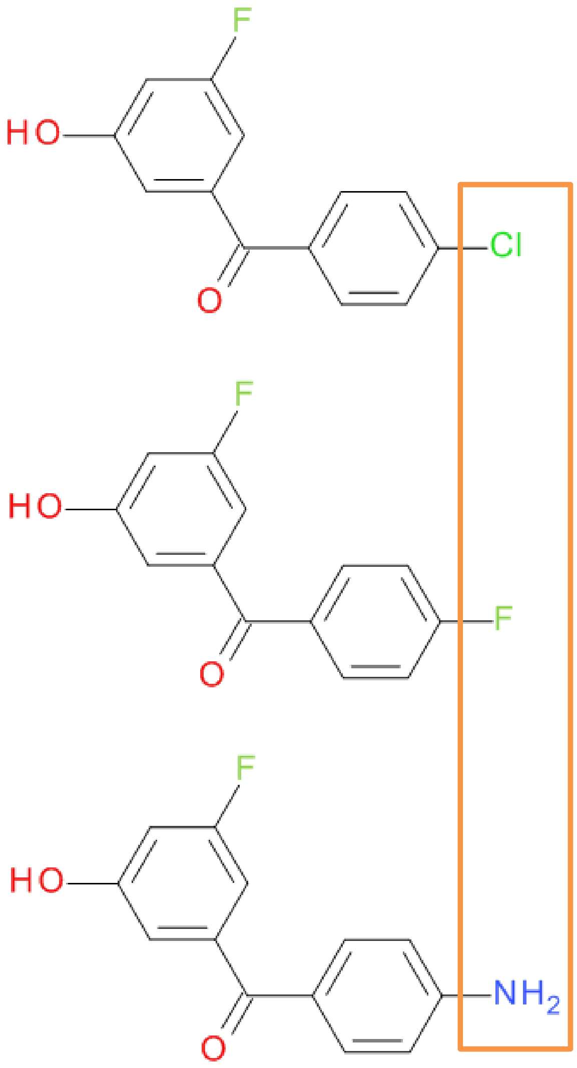
“Matching molecular series” introduced by Wawer and Bajorath, *J. Med. Chem.* **2011**, *54*, 2944

MATCHED SERIES OF LENGTH 3



[Cl, F, NH_2]

ORDERED MATCHED SERIES OF LENGTH 3



pIC_{50}

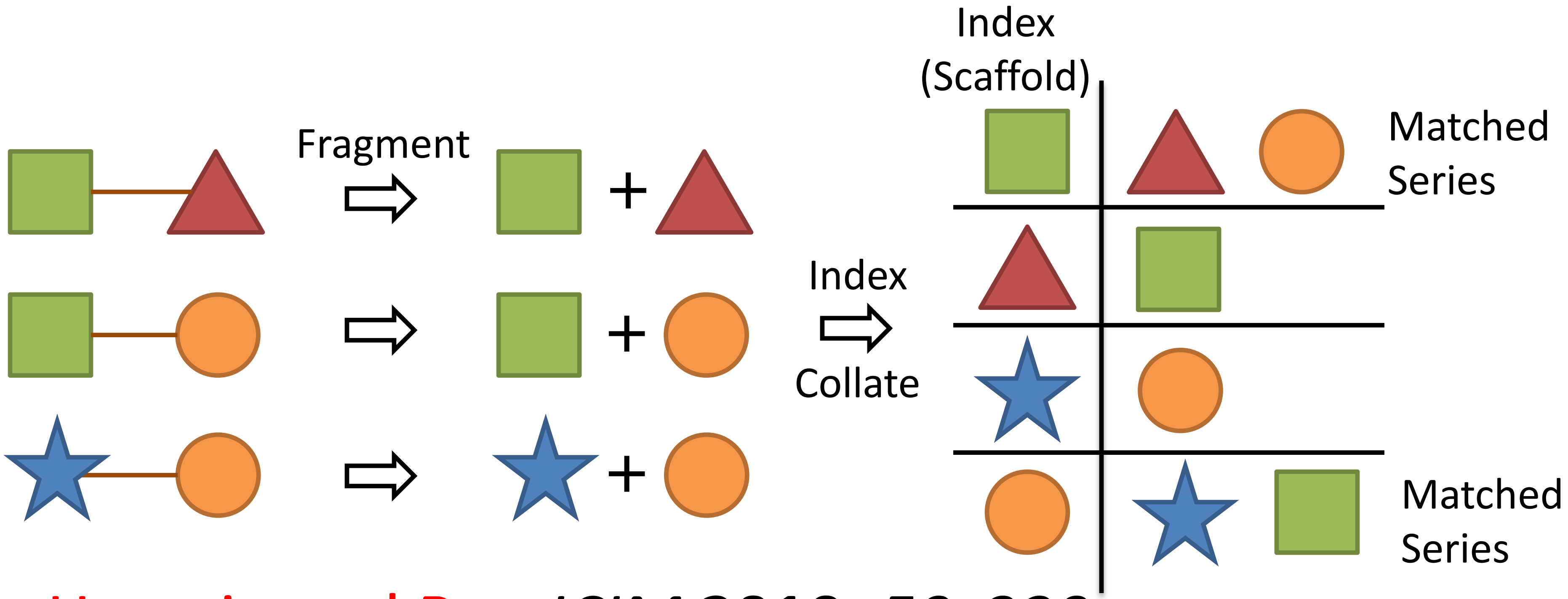
3.5

2.1

1.6

[Cl > F > NH_2]

ALGORITHM TO FIND MATCHED SERIES



- <span>Hussain and Rea</span> *JCIM* **2010**, *50*, 339
  - Fragment molecules at acyclic single bonds
    - Single-cut only, scaffold >= 5, R group <= 12, preserve stereochemistry at break point
  - Index each fragment based on the other
    - A matched series will be indexed together

FIND MATCHED SERIES IN JAMEED'S FRAGMENTS

```
import rdk
import sys
from collections import namedtuple
Frag = namedtuple('Frag', ['id', 'scaffold', 'rgroup'])

class Series():
    def __init__(self):
        self.rgroups = []
        self.scaffold = ""

def getFrags(filename):
    frags = []
    for line in open(filename):
        broken = line.rstrip().split(",")
        if broken[2]: # should be blank for single-cut
            continue
        smiles = broken[-1].split(".")
        mols = [rdk.readstring("smi", smi) for smi in smiles]
        numAtoms = [mol.Mol.GetNumAtoms() for mol in mols]

        if numAtoms[0] > 5 and numAtoms[1] < 12:
            frags.append(Frag(broken[1], smiles[0], smiles[1]))
        if numAtoms[1] > 5 and numAtoms[0] < 12:
            frags.append(Frag(broken[1], smiles[1], smiles[0]))
    frags.sort(key=lambda x:(x.scaffold, x.rgroup))
    return frags
```

```
def getSeries(frags):
    oldfrag = Frag(None, None, None)
    series = Series()
    for frag in frags:
        if frag.scaffold != oldfrag.scaffold:
            if len(series.rgroups)>=2:
                series.scaffold = oldfrag.scaffold
                yield series
            series = Series()
        series.rgroups.append( (frag.rgroup, frag.id) )

        oldfrag = frag
    if len(series.rgroups)>=2:
        series.scaffold = oldfrag.scaffold
        yield series

if __name__ == "__main__":
    filename = sys.argv[1]

    frags = getFrags(filename)
    it = getSeries(frags)

    for series in it:
        print "# %s" % series.scaffold
        for rgroup in sorted(series.rgroups):
            print "%s %s" % (rgroup[0], rgroup[1])
```

FIND MATCHED SERIES IN JAMEED'S FRAGMENTS

sample_fragmented.txt

```
# [*:1]CNc1ncnc2sccc21
[*:1]c1ccccc1 2139597
[*:1]c1cccnc1 2531831
# [*:1]Cn1nc(C)cc1C
[*:1]c1ccc(C(=O)O)cc1 615212
[*:1]c1ccc(C(=O)O)o1 658387
# [*:1]NC(=O)C1COc2ccccc2O1
[*:1]c1ccc(C(=O)O)cc1 2881039
[*:1]c1ccc(C(N)=O)cc1 2787356
....
```

pickett_fragmented.txt

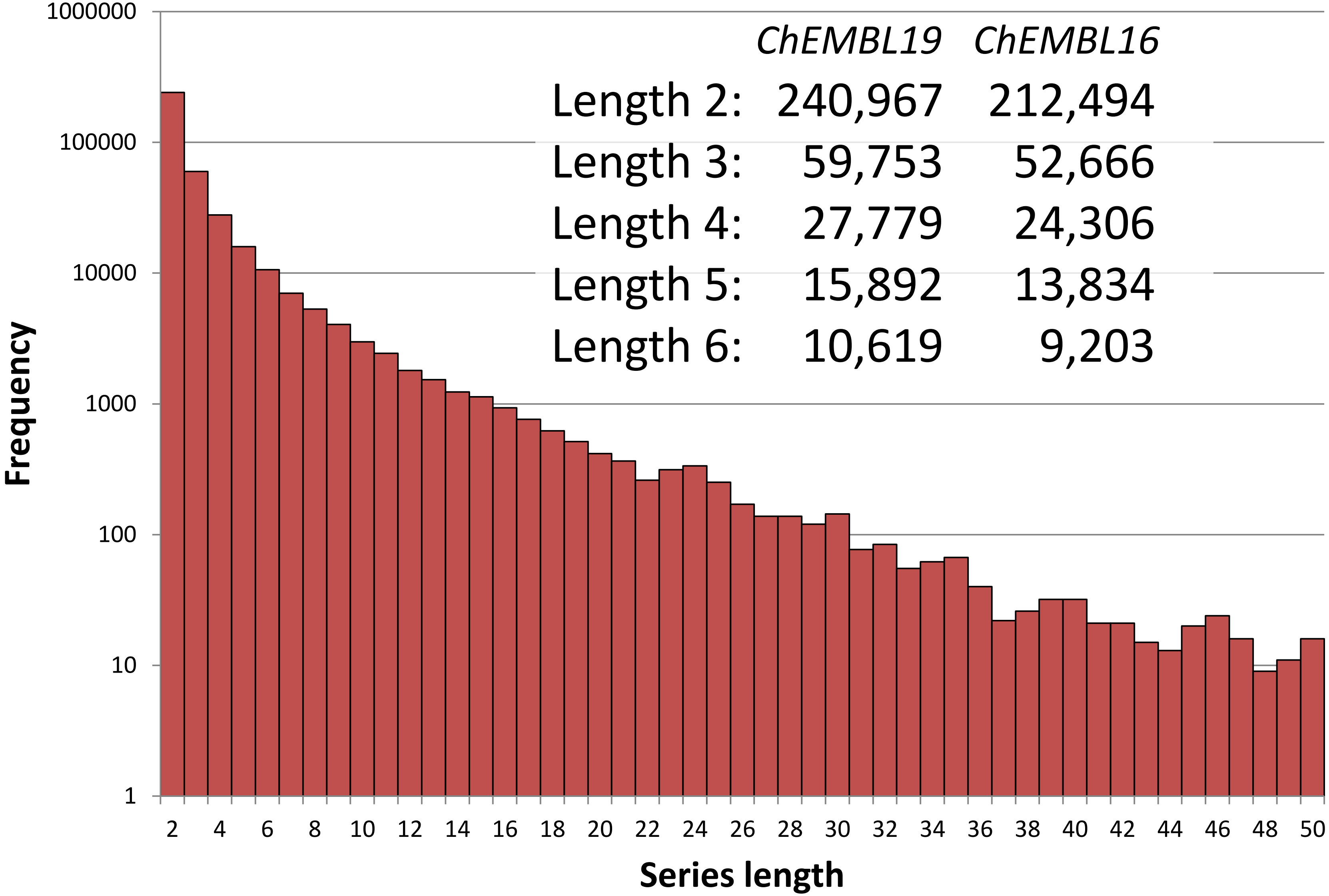
```
# [*:1]C[C@H](NS(=O)(=O)c1ccc(-c2c(C)cccc2C)cc1)C(=O)O
[*:1]C(=O)OC(C)(C)C A18B22
[*:1]C(C)C A04B22
[*:1]C(N)=O A29B22
[*:1]C1CC1 A42B22
[*:1]CC(=O)NC(C)C A41B22
[*:1]CC(=O)OC(C)(C)C A19B22
[*:1]CC(=O)OCC A14B22
[*:1]CCC A31B22
[*:1]CCCNC(C)=O A06B22
[*:1]CS(C)=O A24B22
[*:1]NC(N)=O A09B22
[*:1]OC(C)(C)C A33B22
[*:1]OCc1ccccc1 A32B22
[*:1]SC A02B22
[*:1]SCCc1ccncc1 A17B22
[*:1]SCc1ccccc1 A03B22
[*:1]Sc1ccccc1 A43B22
[*:1]Sc1cccs1 A50B22
[*:1]Sc1nccs1 A49B22
[*:1]c1c[nH]c2ccccc12 A28B22
[*:1]c1ccc(O)cc1 A01B22
[*:1]c1cccc(C#N)c1 A44B22
[*:1]c1ccccn1 A39B22
[*:1]c1cccs1 A27B22
[*:1]n1cccn1 A46B22
[*:1]n1cncn1 A47B22
```

CHEMBL BIOACTIVITY DATABASE

- ChEMBL 19 – July 2014
  - 57k papers
    - 94% from *Bioorg. Med. Chem. Lett.*, *J. Med. Chem.*, *J. Nat. Prod.*, *Bioorg. Med. Chem.*, *Eur. J. Med. Chem.*, *Antimicrob. Agents Chemother.*, *Med. Chem. Res.*
  - 1.4 million compounds with 12 million activities
  - 1.1 million assays against 10k targets

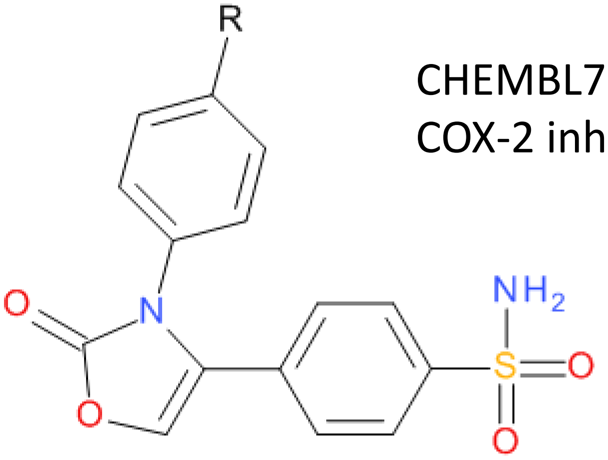
Gaulton et al. *Nucleic Acids Res.* **2012**, *40*, D1100

Matched series in ChEMBL19 IC50 binding assays

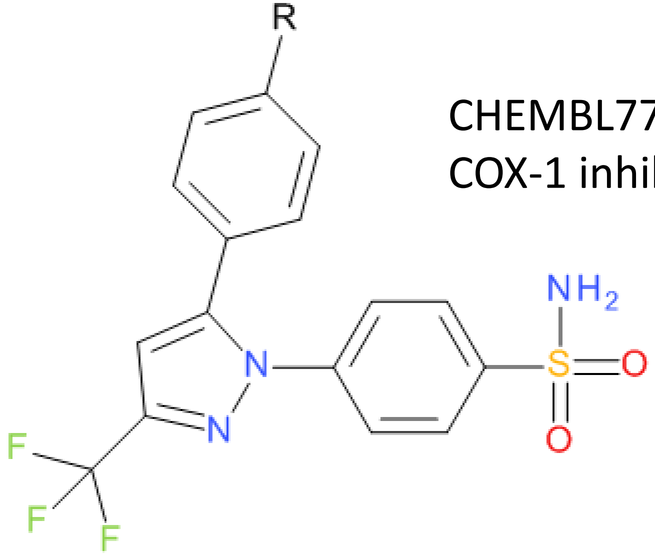


	ChEMBL19	*ChEMBL16*
Length 2:	240,967	212,494
Length 3:	59,753	52,666
Length 4:	27,779	24,306
Length 5:	15,892	13,834
Length 6:	10,619	9,203

SAR TRANSFER



CHEMBL768956
COX-2 inhibition



CHEMBL772766
COX-1 inhibition

R Group	CHEMBL768956 (pIC$_{50}$)	CHEMBL772766 (pIC$_{50}$)
SMe	??	5.92
NH_2	??	5.88
OMe	6.68	5.59
Me	6.10	4.82
Cl	5.92	4.75
F	5.82	4.59
Et	5.81	4.54
CF_3	5.70	<4.00
H	5.62	4.26
COOH	4.23	<3.60

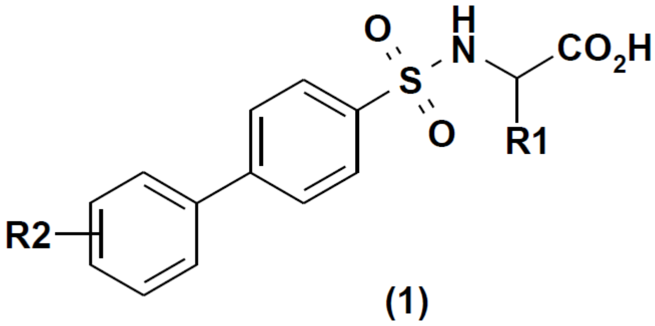
Rank order

Potential SAR transfer

0.93 rank order correlation

50x50 Matrix from Pickett et al.

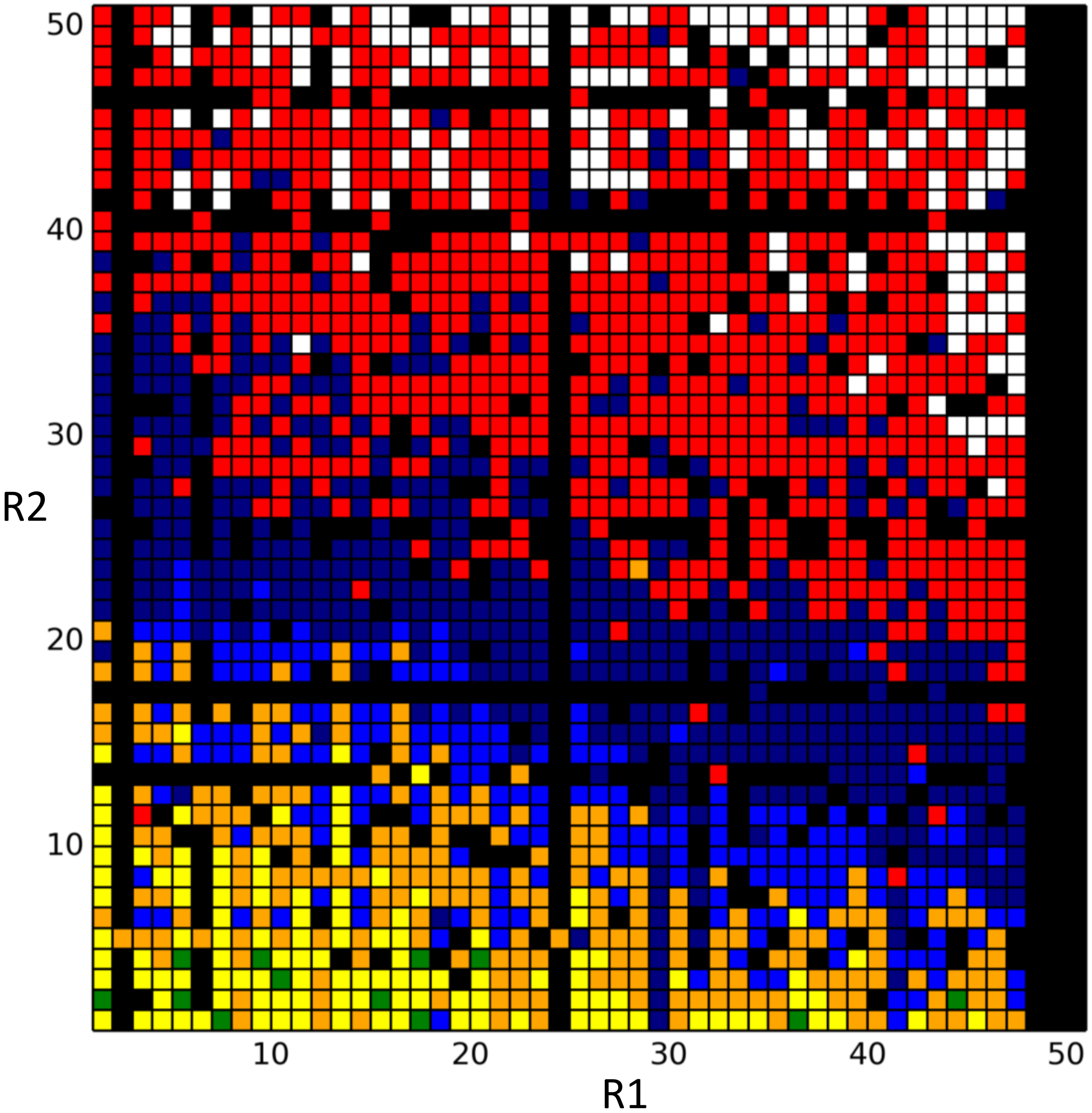
Pickett, Green, Hunt, Pardoe, Hughes. *ACS Med. Chem. Lett.* **2011**, *2*, 28.



(1)

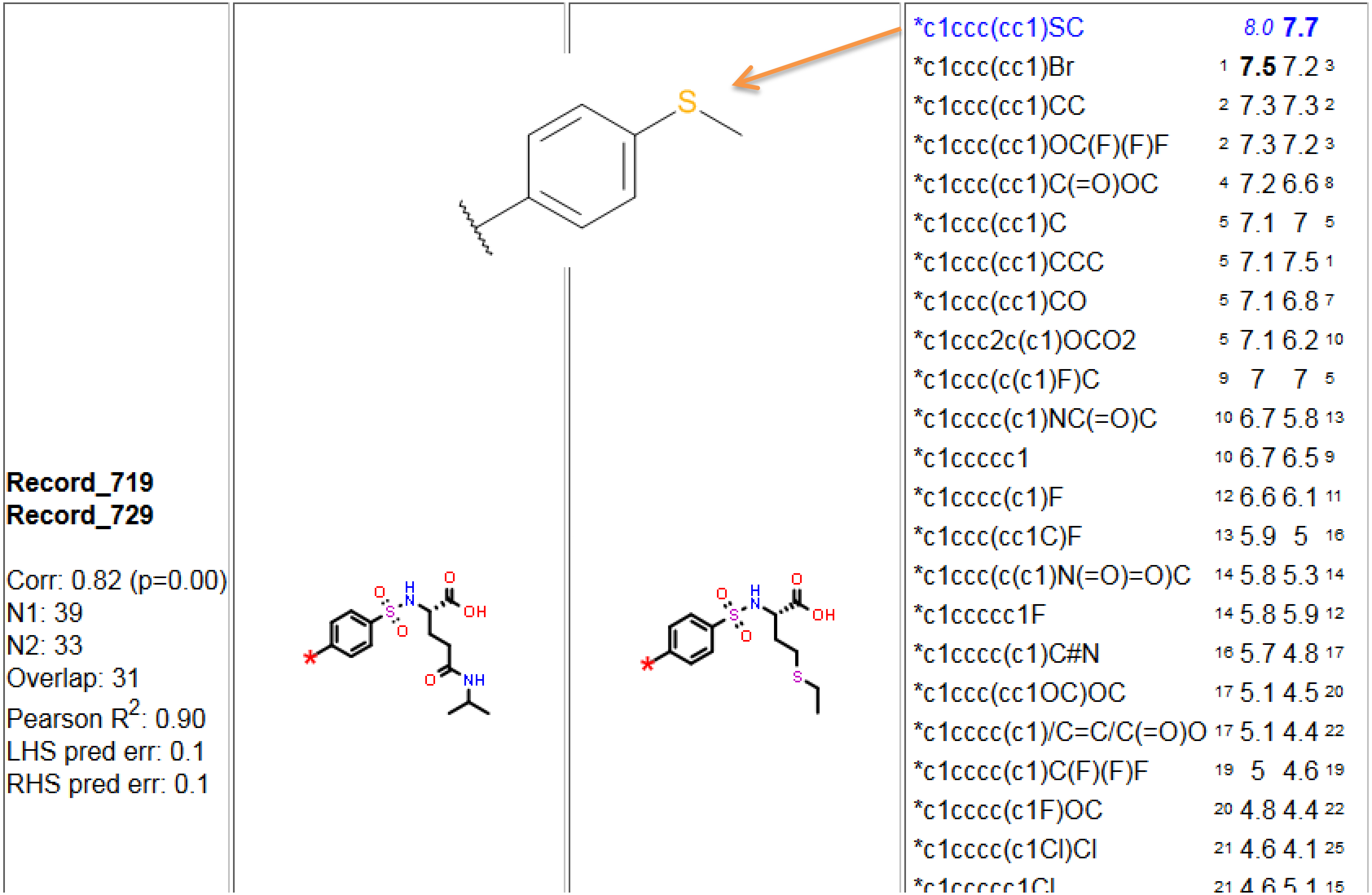
MMP-12 pIC50

- ⬛ Null
- ⬜ Inact
- 🟥 <5
- 🟦 5-6
- 🟦 6-6.5
- 🟧 6.5-7
- 🟨 7-7.5
- 🟩 >7.5



INTERNAL SAR TRANSFER

Do an all-against-all comparison of the series



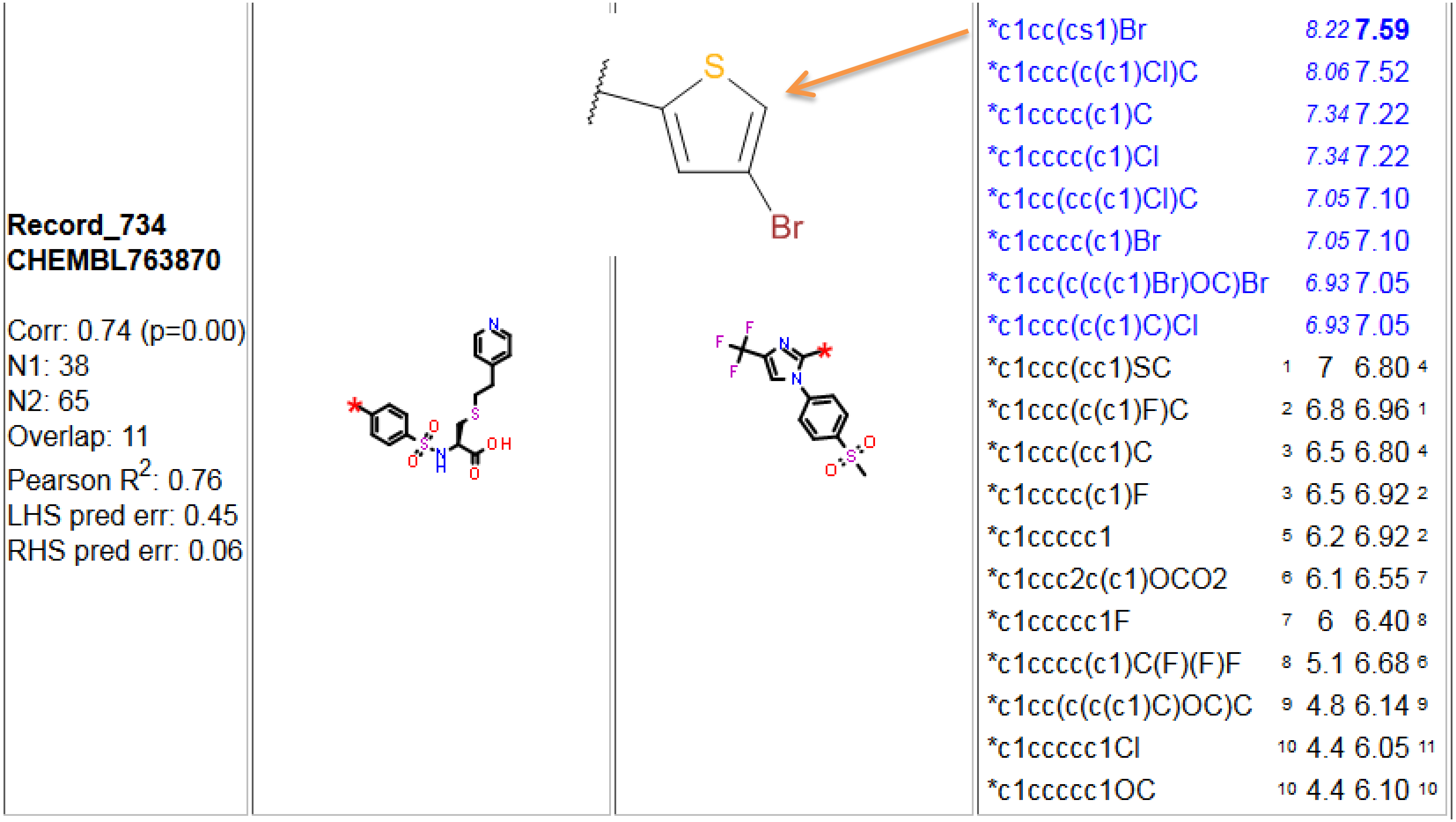
Record_719
Record_729

Corr: 0.82 (p=0.00)
N1: 39
N2: 33
Overlap: 31
Pearson R^2: 0.90
LHS pred err: 0.1
RHS pred err: 0.1

*c1ccc(cc1)SC		*8.0*	**7.7**	
*c1ccc(cc1)Br	1	**7.5**	7.2	3
*c1ccc(cc1)CC	2	7.3	7.3	2
*c1ccc(cc1)OC(F)(F)F	2	7.3	7.2	3
*c1ccc(cc1)C(=O)OC	4	7.2	6.6	8
*c1ccc(cc1)C	5	7.1	7	5
*c1ccc(cc1)CCC	5	7.1	7.5	1
*c1ccc(cc1)CO	5	7.1	6.8	7
*c1ccc2c(c1)OCO2	5	7.1	6.2	10
*c1ccc(c(c1)F)C	9	7	7	5
*c1cccc(c1)NC(=O)C	10	6.7	5.8	13
*c1ccccc1	10	6.7	6.5	9
*c1cccc(c1)F	12	6.6	6.1	11
*c1ccc(cc1C)F	13	5.9	5	16
*c1ccc(c(c1)N(=O)=O)C	14	5.8	5.3	14
*c1ccccc1F	14	5.8	5.9	12
*c1cccc(c1)C#N	16	5.7	4.8	17
*c1ccc(cc1OC)OC	17	5.1	4.5	20
*c1cccc(c1)/C=C/C(=O)O	17	5.1	4.4	22
*c1cccc(c1)C(F)(F)F	19	5	4.6	19
*c1cccc(c1F)OC	20	4.8	4.4	22
*c1cccc(c1Cl)Cl	21	4.6	4.1	25
*c1ccccc1Cl	21	4.6	5.1	15

EXTERNAL SAR TRANSFER

Do an all-against-ChEMBL comparison



Record_734
CHEMBL763870

Corr: 0.74 (p=0.00)
N1: 38
N2: 65
Overlap: 11
Pearson R^2: 0.76
LHS pred err: 0.45
RHS pred err: 0.06

*c1cc(cs1)Br		8.22	**7.59**	
*c1ccc(c(c1)Cl)C		8.06	7.52	
*c1cccc(c1)C		7.34	7.22	
*c1cccc(c1)Cl		7.34	7.22	
*c1cc(cc(c1)Cl)C		7.05	7.10	
*c1cccc(c1)Br		7.05	7.10	
*c1cc(c(c(c1)Br)OC)Br		6.93	7.05	
*c1ccc(c(c1)C)Cl		6.93	7.05	
*c1ccc(cc1)SC	1	7	6.80	4
*c1ccc(c(c1)F)C	2	6.8	6.96	1
*c1ccc(cc1)C	3	6.5	6.80	4
*c1cccc(c1)F	3	6.5	6.92	2
*c1ccccc1	5	6.2	6.92	2
*c1ccc2c(c1)OCO2	6	6.1	6.55	7
*c1ccccc1F	7	6	6.40	8
*c1cccc(c1)C(F)(F)F	8	5.1	6.68	6
*c1cc(c(c(c1)C)OC)C	9	4.8	6.14	9
*c1ccccc1Cl	10	4.4	6.05	11
*c1ccccc1OC	10	4.4	6.10	10

STRENGTHS AND WEAKNESSES

- High confidence in predictions if sufficiently long series with correlated activities (or their rank order)
  - Not always able to find such a series
  - For short series will typically find 10s/100s/1000s of matching series with low confidence
- Suited to pairwise comparison within focused dataset
  - Dense SAR matrix from target with well-explored SAR

PREFERRED ORDERS IN MATCHED SERIES

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**

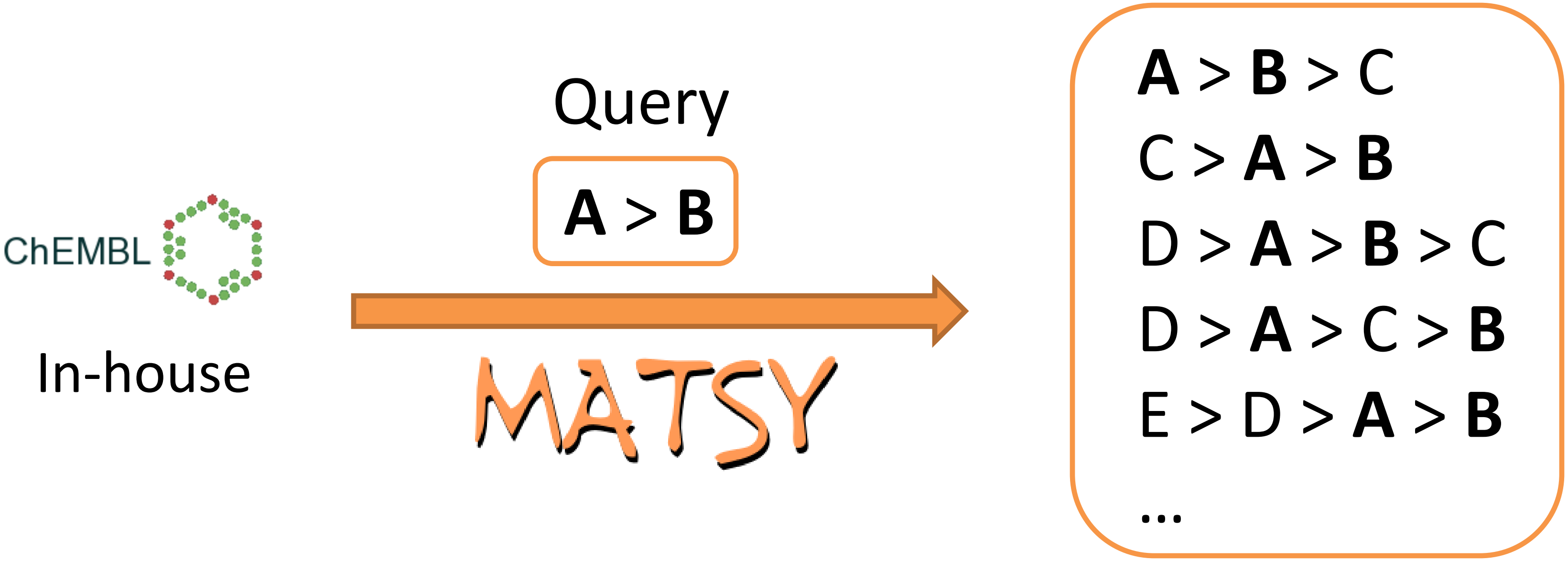
N=2: Max = 1.06, Min = 0.94
N=3: Max = 1.90, Min = 0.63
N=4: Max = 5.43, Min = 0.232

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]

MATSY: PREDICTION USING MATCHED SERIES

FIND R GROUPS THAT INCREASE ACTIVITY



ChEMBL

In-house

Query

A > **B**

MATSY

A > **B** > C

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

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

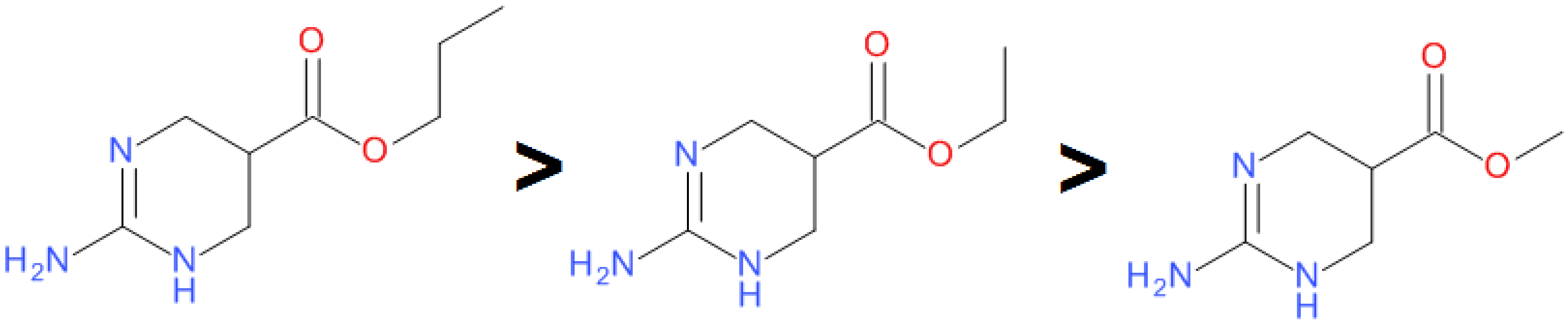
D > **A** > C > **B**

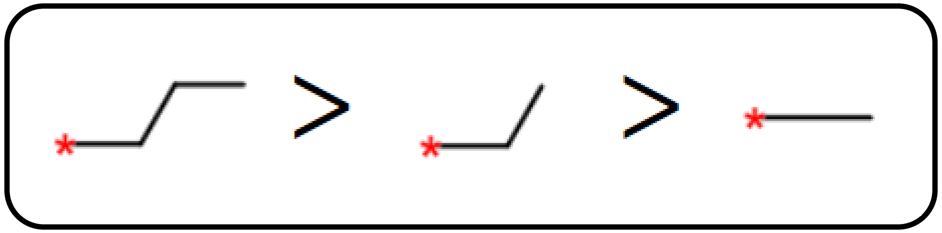
E > D > **A** > **B**

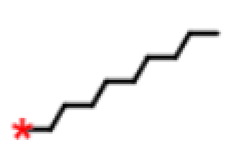
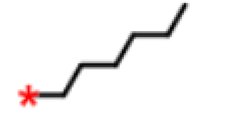
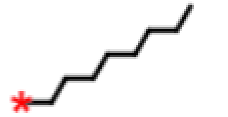
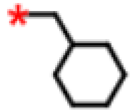
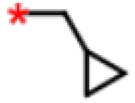
…

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

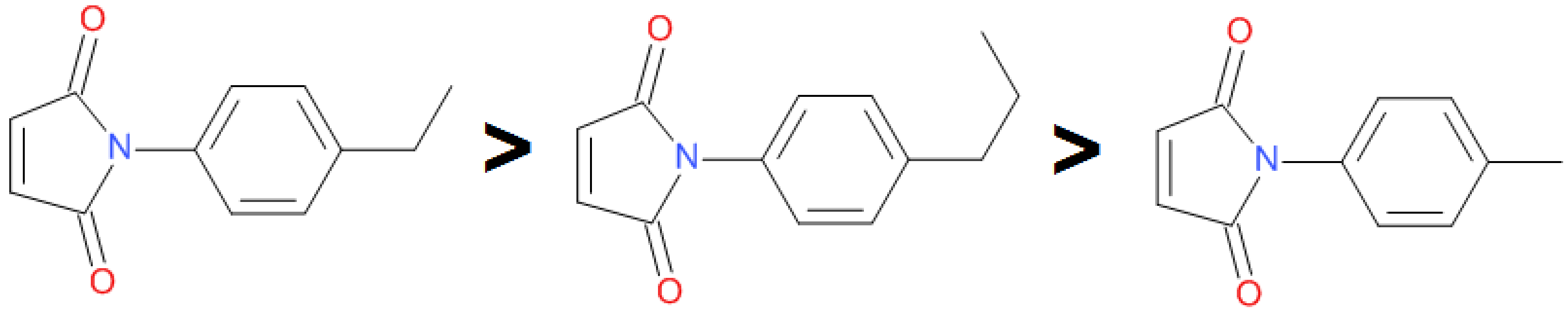
EXAMPLE

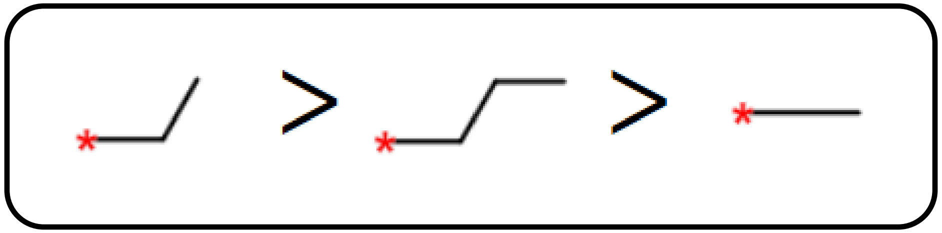


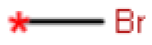
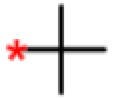
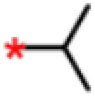
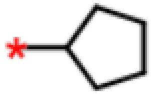
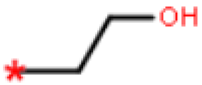


	% >	Counts	ΔLogP
	90	21	+3.3
	72	60	+1.7
	69	32	+2.8
	63	27	+1.6
	60	40	-0.1

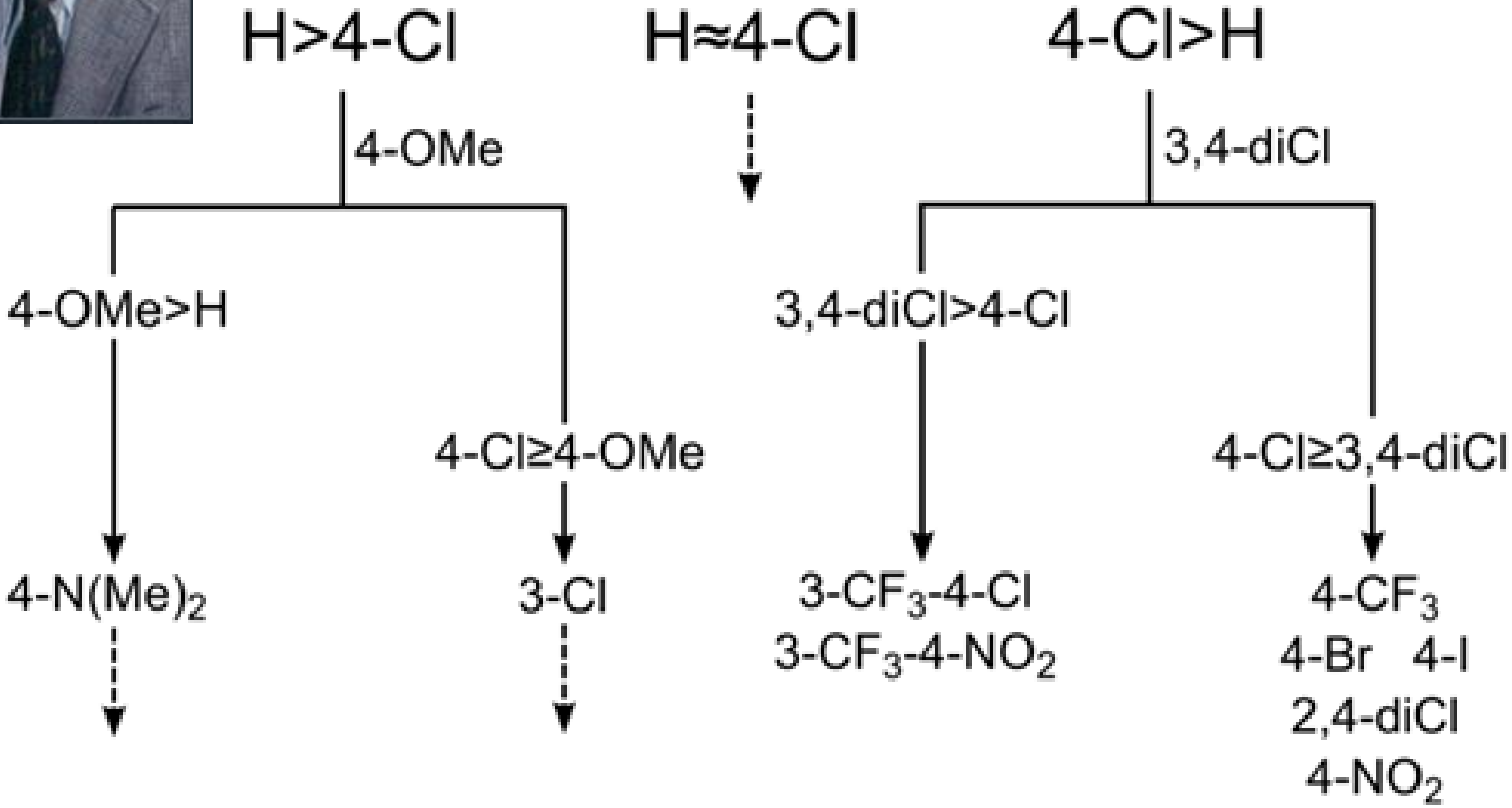
EXAMPLE II





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

Topliss Decision Tree



H>4-Cl

H≈4-Cl

4-Cl>H

4-OMe

3,4-diCl

4-OMe>H

4-Cl≥4-OMe

3,4-diCl>4-Cl

4-Cl≥3,4-diCl

4-N(Me)$_2$

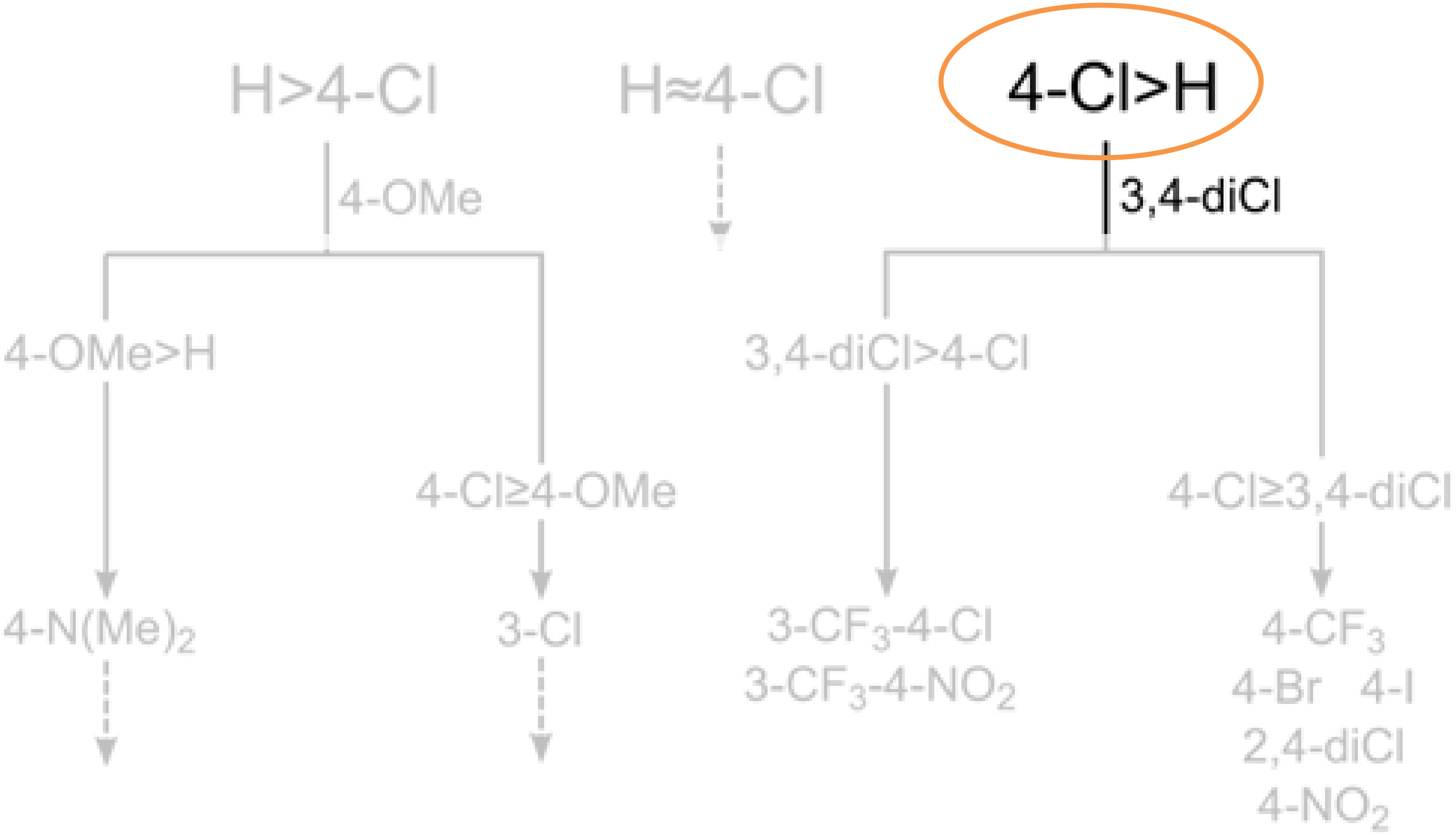
3-Cl

3-CF$_3$-4-Cl
3-CF$_3$-4-NO$_2$

4-CF$_3$
4-Br 4-I
2,4-diCl
4-NO$_2$

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

TOPLISS DECISION TREE



H>4-Cl

H≈4-Cl

4-Cl>H

4-OMe

3,4-diCl

4-OMe>H

4-Cl≥4-OMe

3,4-diCl>4-Cl

4-Cl≥3,4-diCl

4-N(Me)$_2$

3-Cl

3-CF$_3$-4-Cl

3-CF$_3$-4-NO$_2$

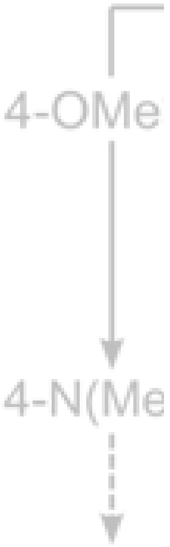
4-CF$_3$

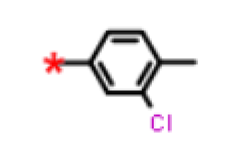
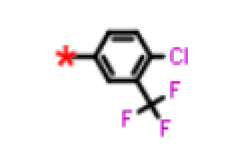
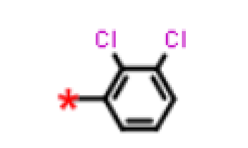
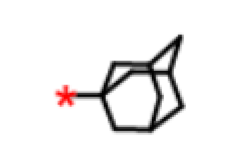
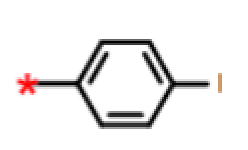
4-Br 4-I

2,4-diCl

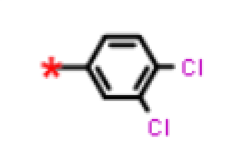
4-NO$_2$

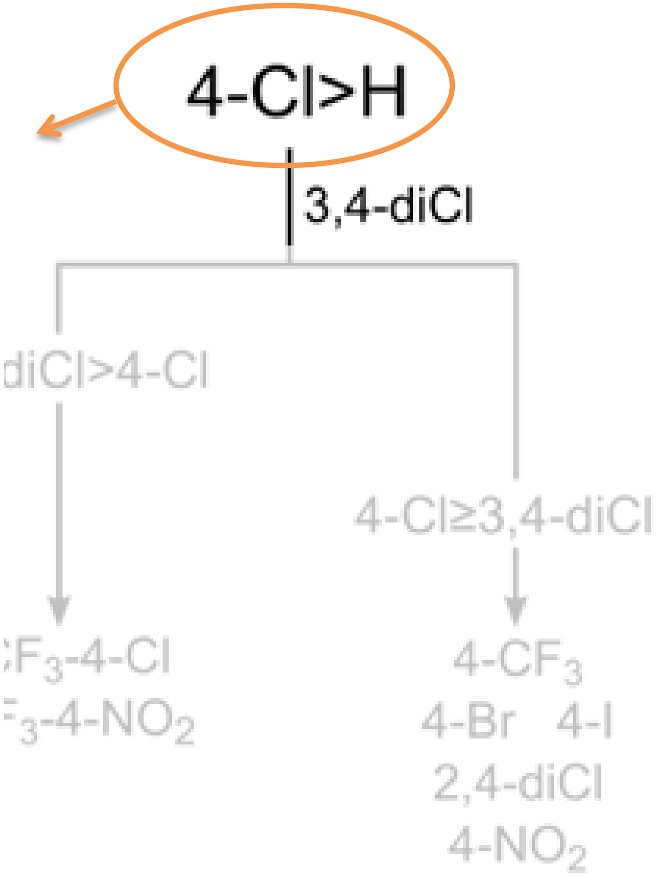
TOPLISS DECISION TREE



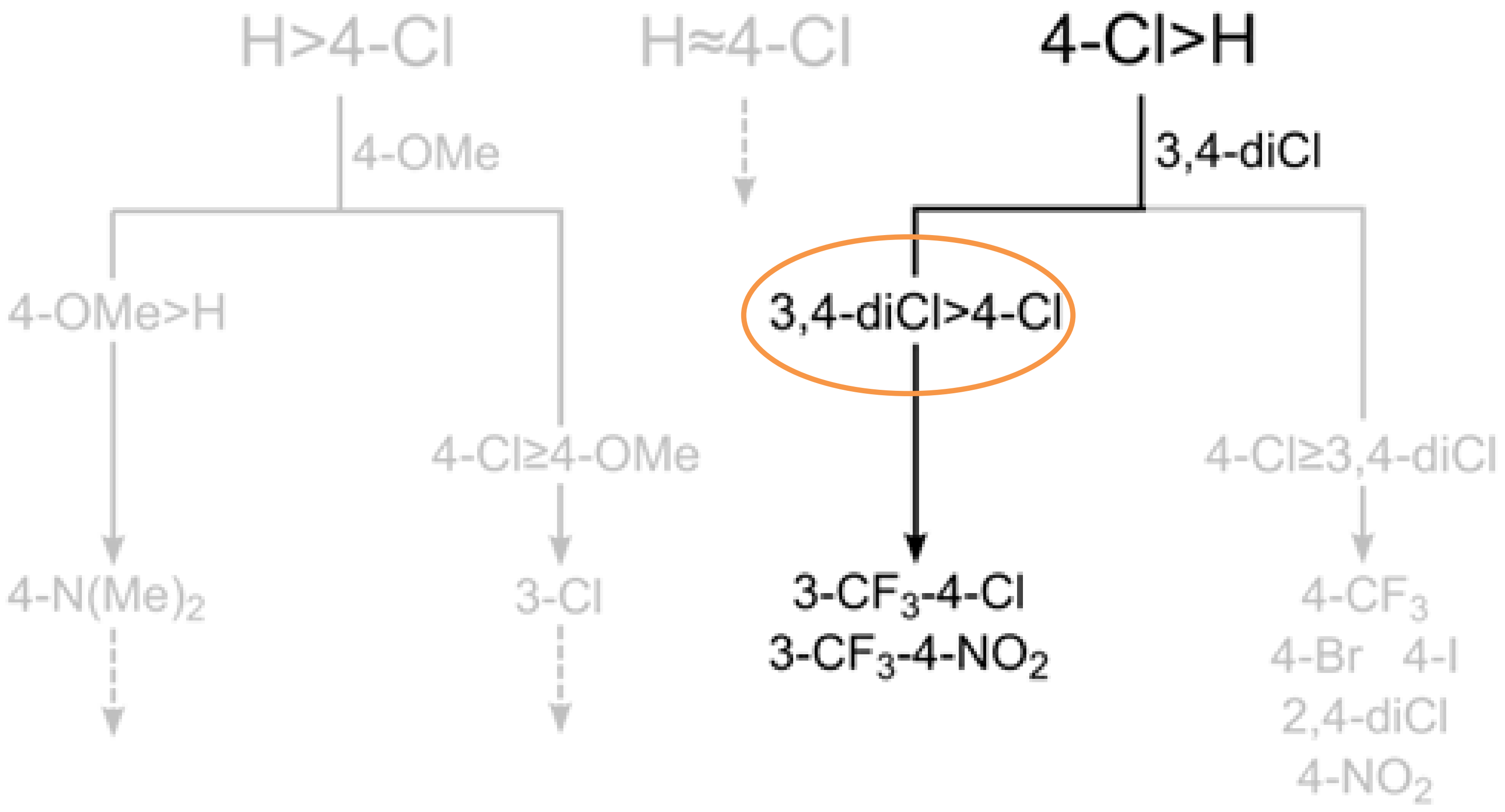
	% >	Counts	ΔLogP
	74	27	+0.3
	71	28	+0.9
	61	51	+0.6
	61	23	+1.4
	58	103	+0.5

(11th)

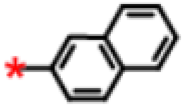
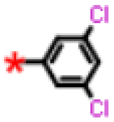
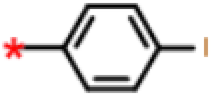
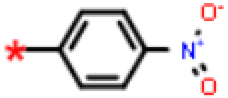
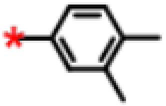
	54	391	+0.6

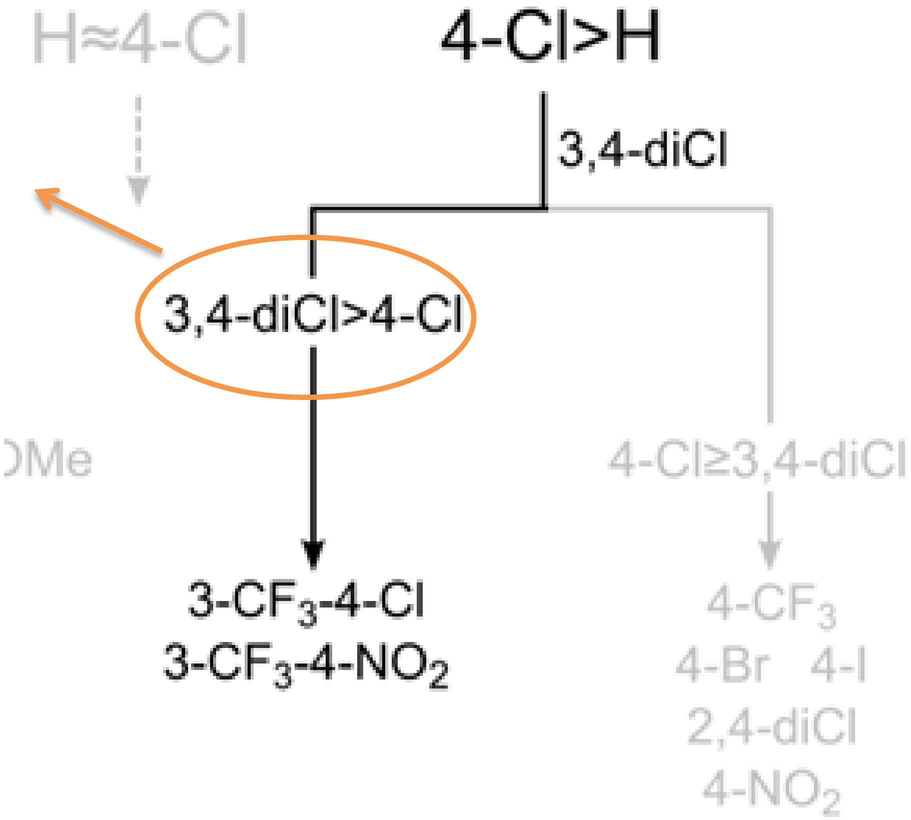


TOPLISS DECISION TREE

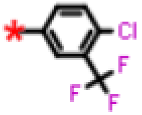


TOPLISS DECISION TREE

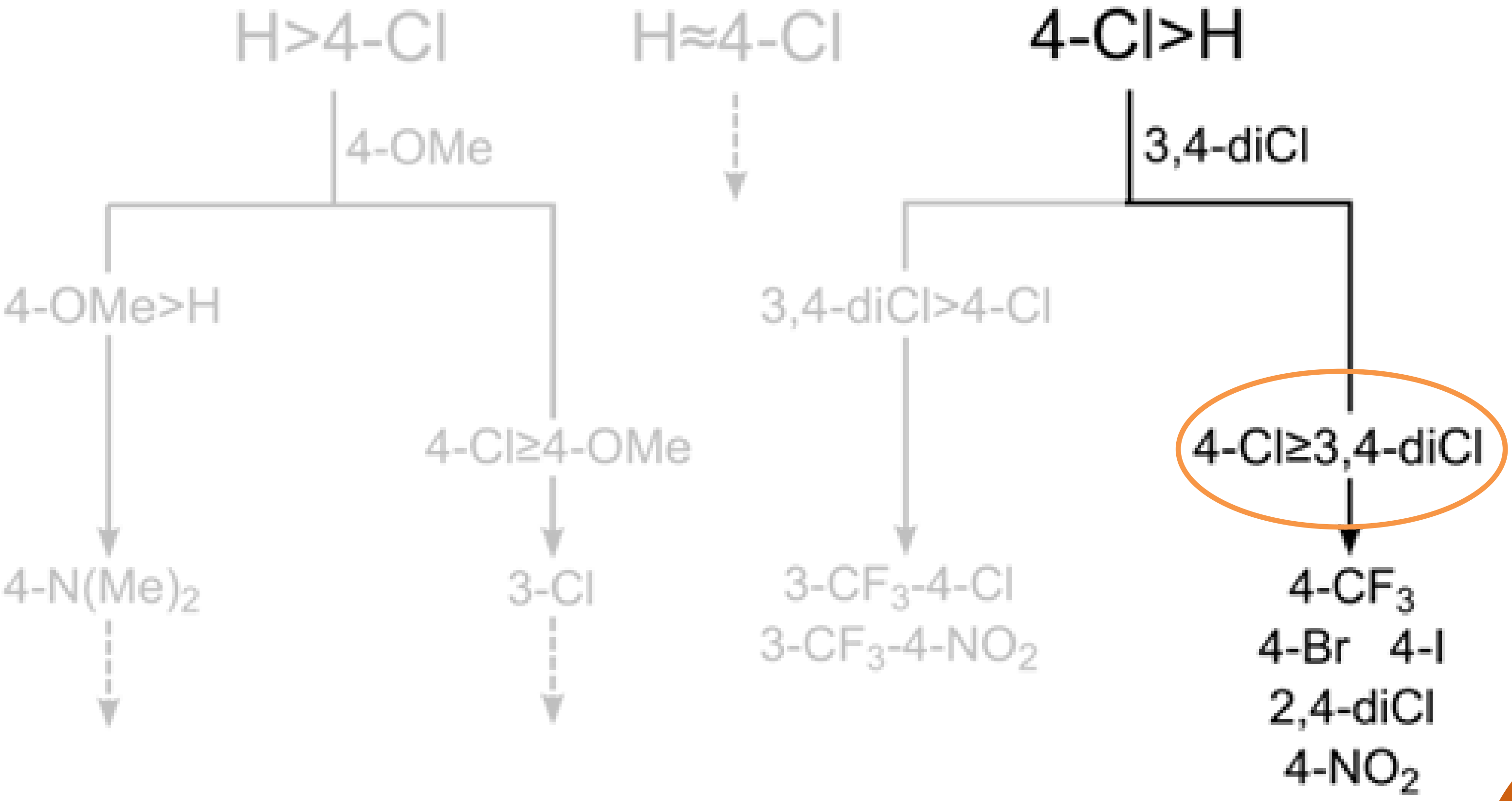
	% >	Counts	ΔLogP
	32	57	+0.4
	24	37	0.0
	22	23	-0.1
	21	47	-2.9
	20	20	-0.1



(1st if lower cutoff)

	33	5.00	15	+0.3

TOPLISS DECISION TREE



H>4-Cl

4-OMe

4-OMe>H

$4\text{-}N(Me)_2$

4-Cl≥4-OMe

3-Cl

H≈4-Cl

4-Cl>H

3,4-diCl

3,4-diCl>4-Cl

$3\text{-}CF_3\text{-}4\text{-}Cl$

$3\text{-}CF_3\text{-}4\text{-}NO_2$

4-Cl≥3,4-diCl

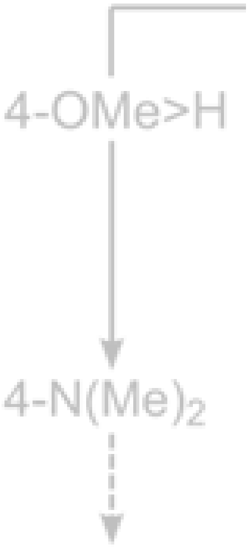
$4\text{-}CF_3$

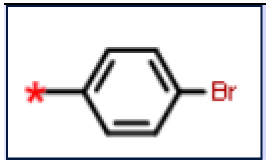
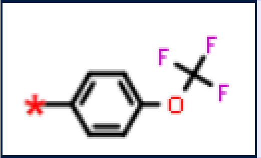
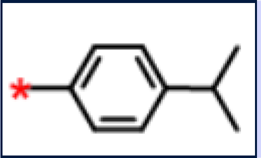
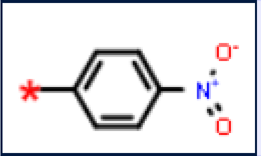
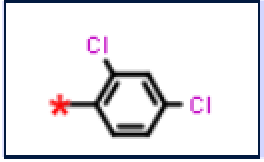
4-Br 4-I

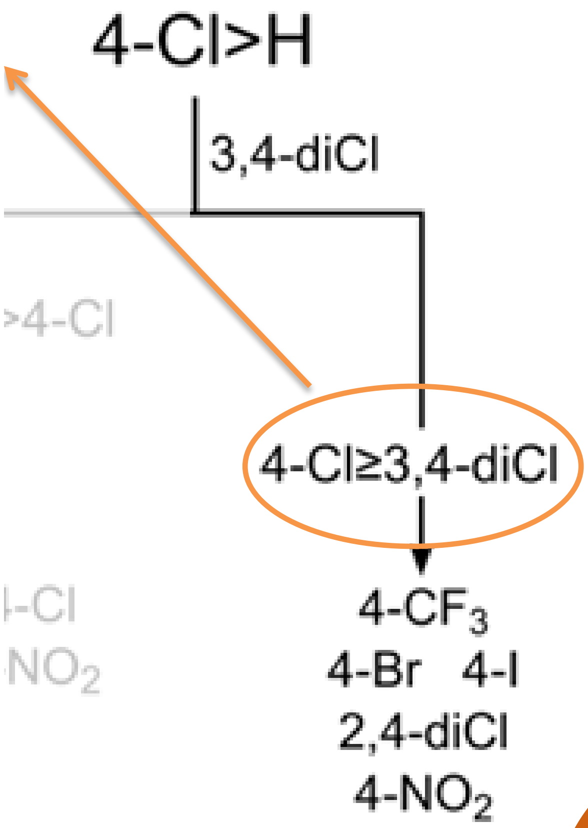
2,4-diCl

$4\text{-}NO_2$

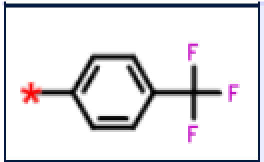
TOPLISS DECISION TREE



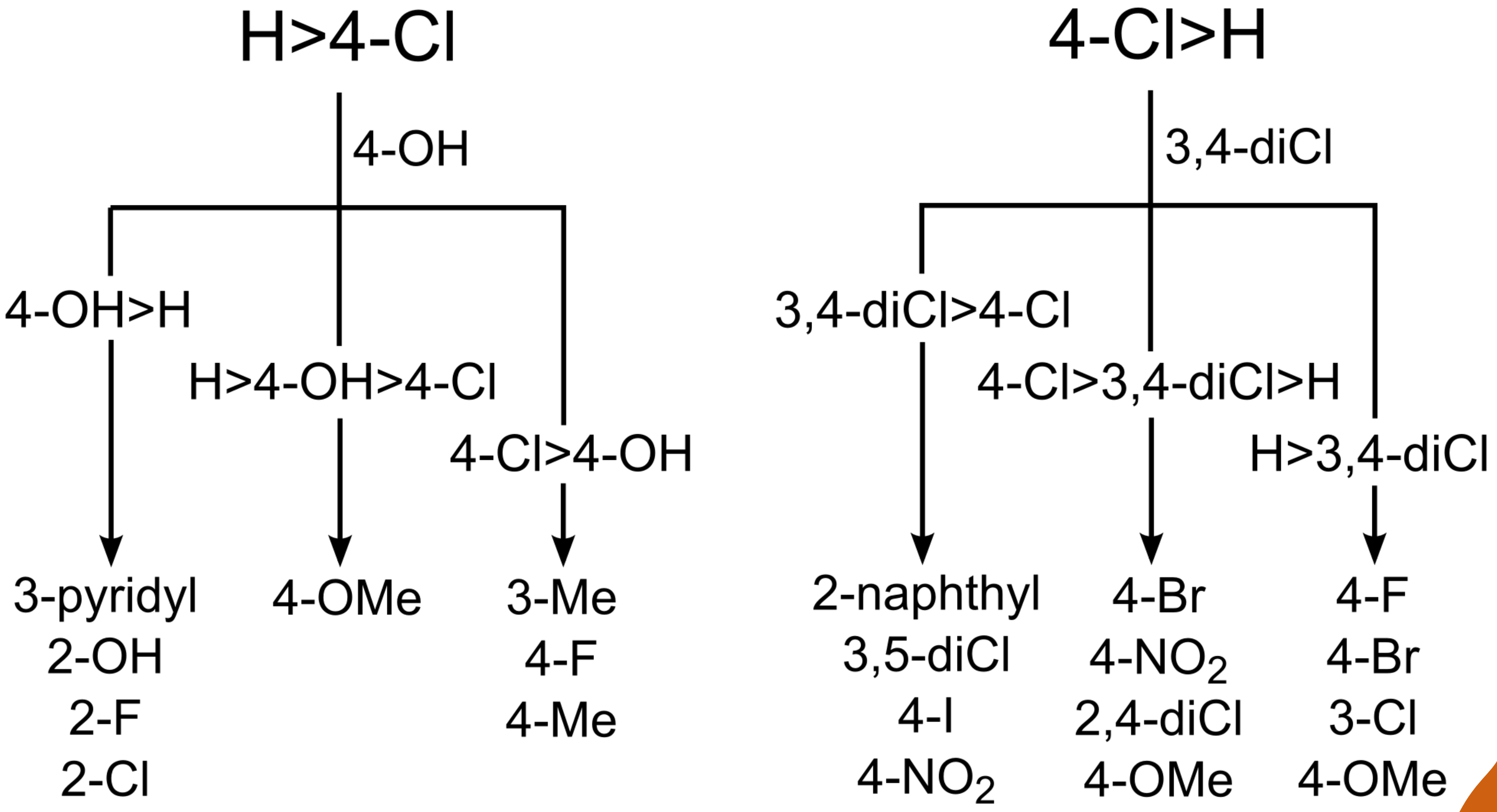
	% >	Counts	ΔLogP
	56	36	+0.2
	46	13	+0.8
	44	16	+1.0
	32	28	-2.3
	27	30	+0.6



(20th)

	11	28	+0.3

MATSY DECISION TREE (ONE OF MANY)



H>4-Cl

4-OH

4-OH>H

3-pyridyl
2-OH
2-F
2-Cl

H>4-OH>4-Cl

4-OMe

4-Cl>4-OH

3-Me
4-F
4-Me

4-Cl>H

3,4-diCl

3,4-diCl>4-Cl

2-naphthyl
3,5-diCl
4-I
4-NO_2

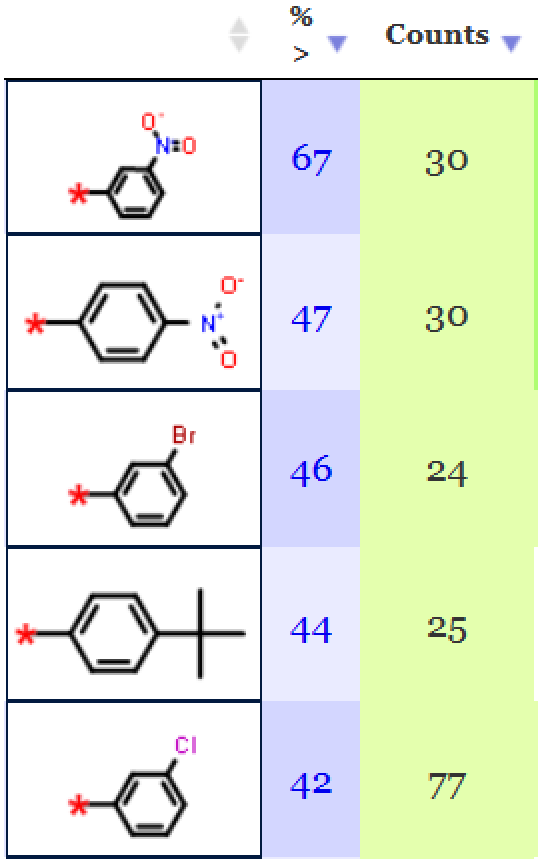
4-Cl>3,4-diCl>H

4-Br
4-NO_2
2,4-diCl
4-OMe

H>3,4-diCl

4-F
4-Br
3-Cl
4-OMe

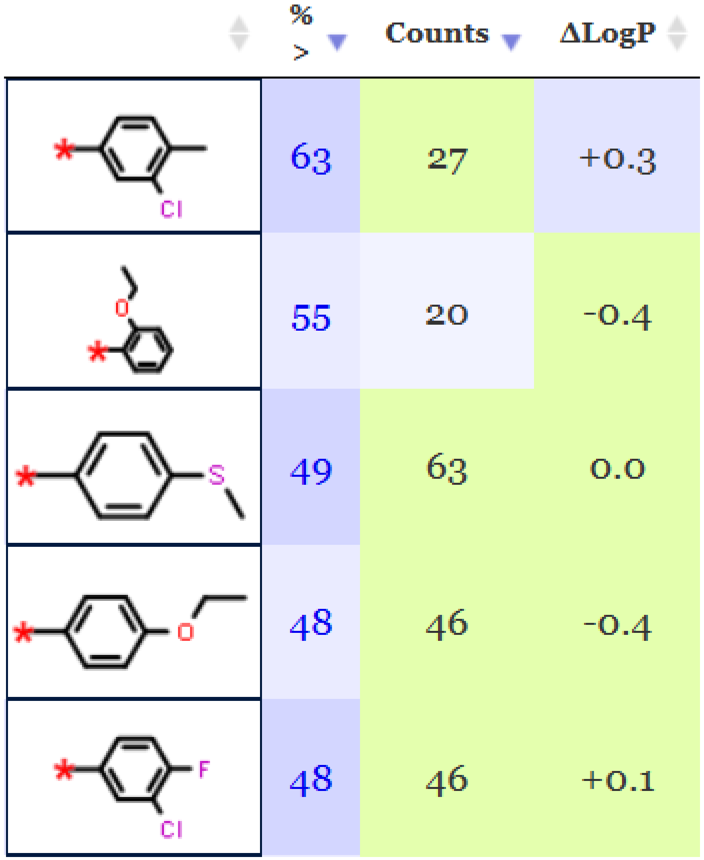
MODIFYING THE PREDICTIONS FOR 4-Cl > H



	% >	Counts
O^- N^+=O	67	30
O^- N^+ O	47	30
Br	46	24
	44	25
Cl	42	77

Kinases

Target-specific

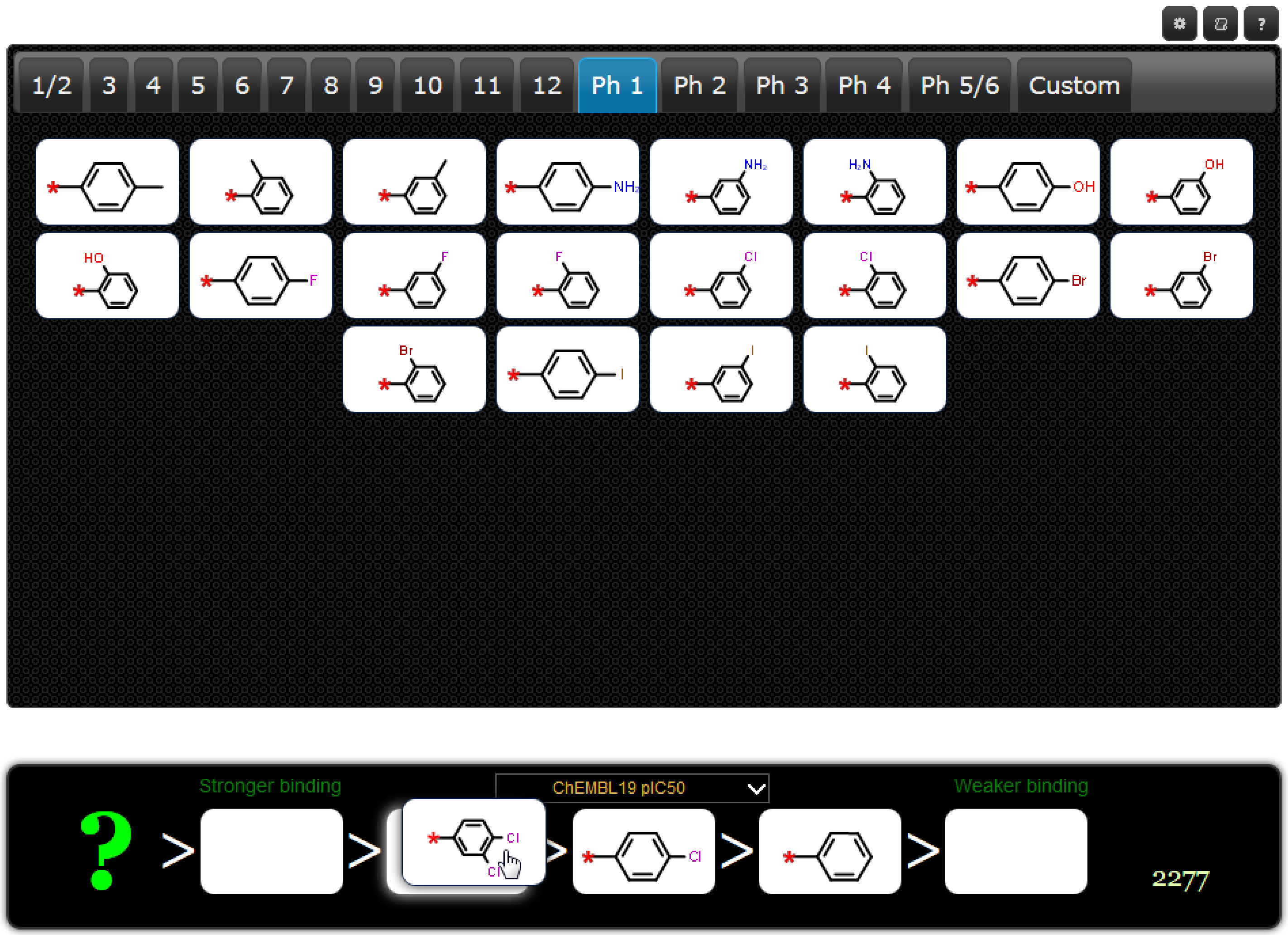


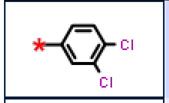
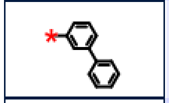
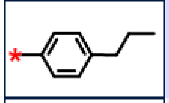
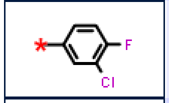
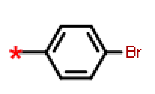
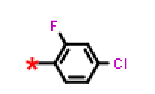
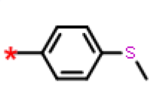
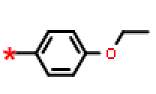
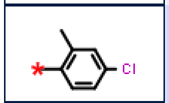
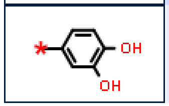
	% >	Counts	ΔLogP
Cl	63	27	+0.3
O	55	20	-0.4
S	49	63	0.0
O	48	46	-0.4
F Cl	48	46	+0.1

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**

Showing 11 to 20 of 111 entries

Previous Next

IN SUMMARY

- Longer matched series (N>2) show an increased preference for particular activity orders
- This can be exploited to predict R groups that will increase activity
  - Predictions are typically based on data from a range of targets and structures
- Completely knowledge-based
  - Can link predictions to particular targets/structures
  - Predictions refined based on new results

Using RDKit for Matched Molecular Series Analysis

When two are not enough

noel@nextmovesoftware.com

Acknowledgements

Roger Sayle

Jonas Bostrom, AstraZeneca

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