DNA Encoded Libraries

ARTICLES

nature
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Design, synthesis and selection of DNA-encoded small-molecule libraries

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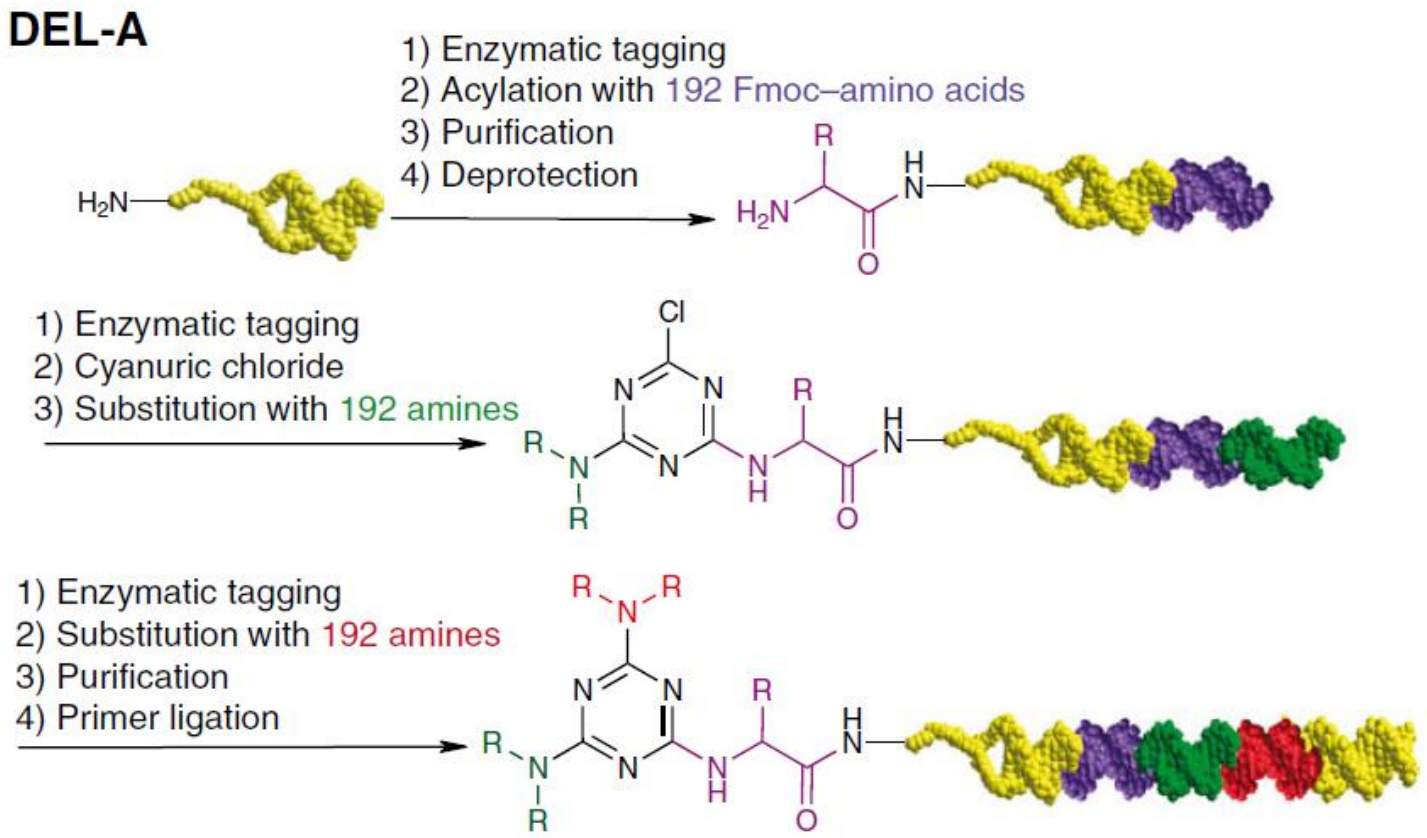
Biochemical combinatorial techniques such as phage display, RNA display and oligonucleotide aptamers have proven to be reliable methods for generation of ligands to protein targets. Adapting these techniques to small synthetic molecules has been a long-sought goal. We report the synthesis and interrogation of an 800-million-member DNA-encoded library in which small molecules are covalently attached to an encoding oligonucleotide. The library was assembled by a combination of chemical and enzymatic synthesis, and interrogated by affinity selection. We describe methods for the selection and deconvolution of the chemical display library, and the discovery of inhibitors for two enzymes: Aurora A kinase and p38 MAP kinase.

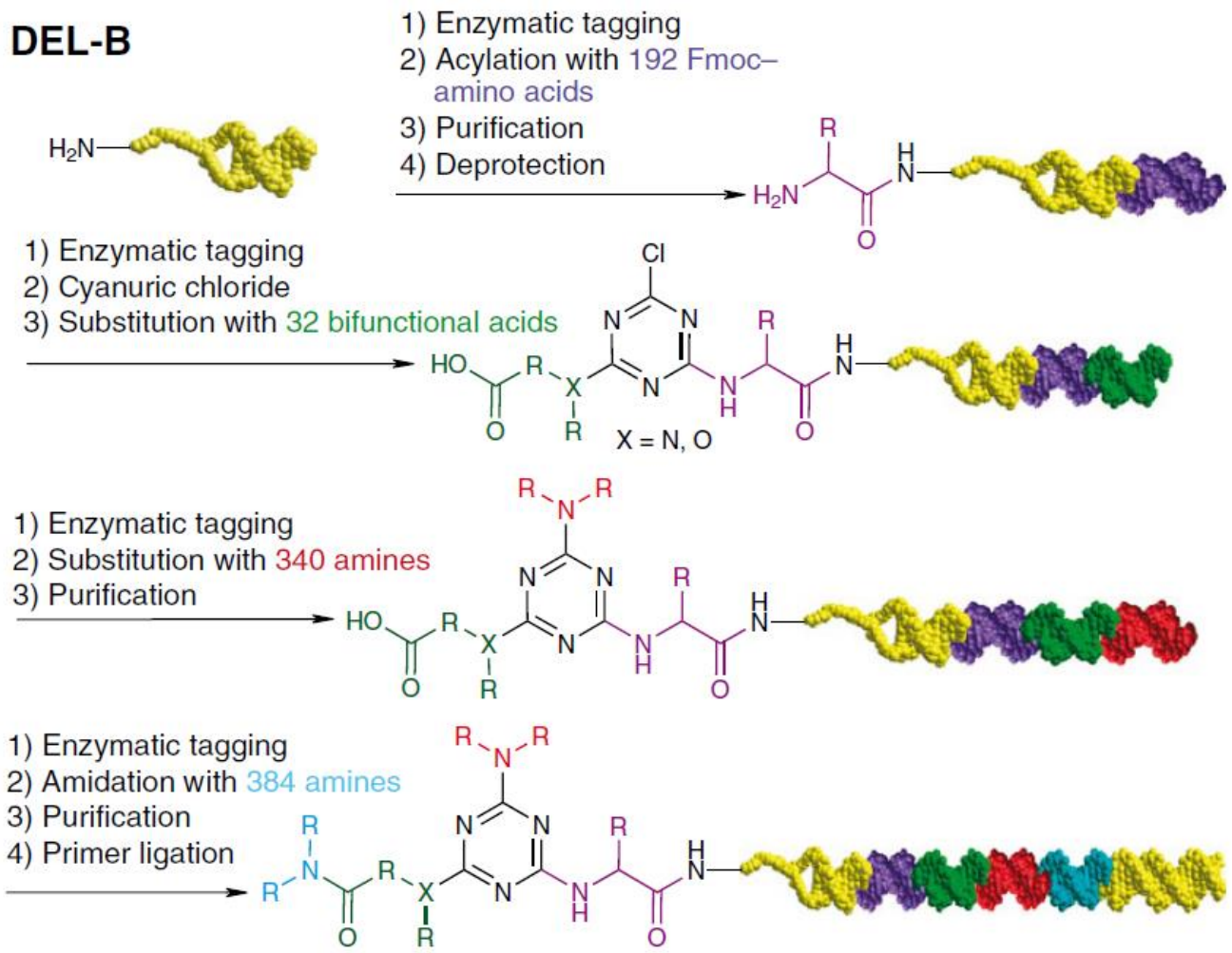
Relevant for exam: Figures 1 to 4, and Scheme 1

Figure 1 (upper panel)



- Why DNA tagging?
- Library size?
- What is «split and pool»?
- Which building blocks?
  Which chemical reactions?
- Number building blocks?
- Purification?

Figure 1 (lower panel)



- What is different compared to library A?
- Number building blocks? Library size?
- Why do amines not react with two positions of cyanuric acid?

SI Figure 1

“Headpiece.” Sequence: 5′-/5Phos/GAGTCA/iSp9/iUniAmM/iSp9/TGACTCCC-3′

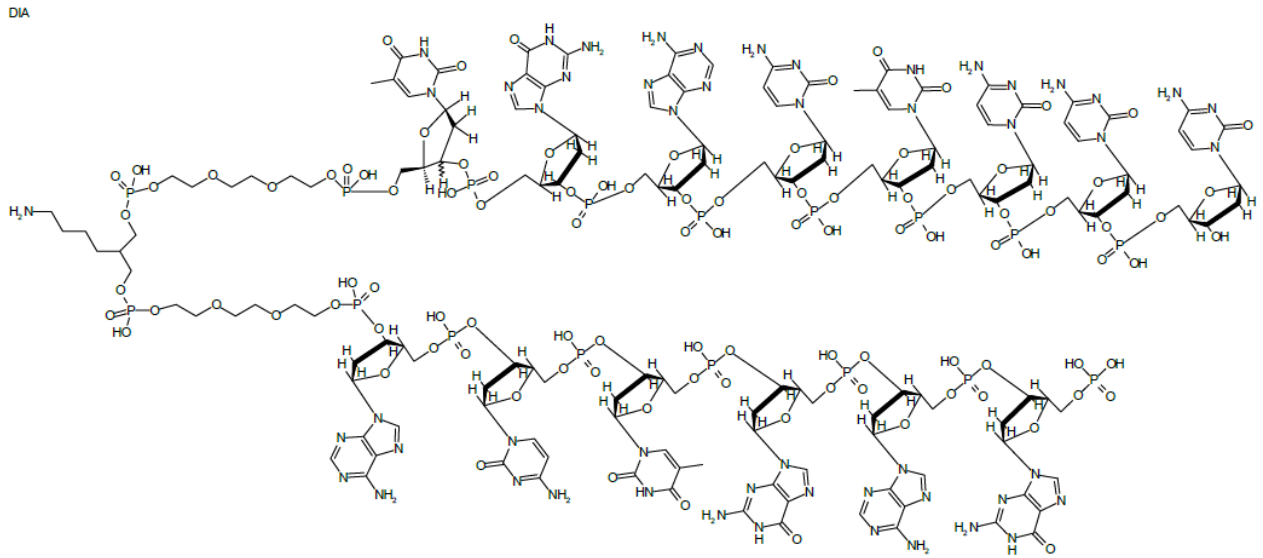
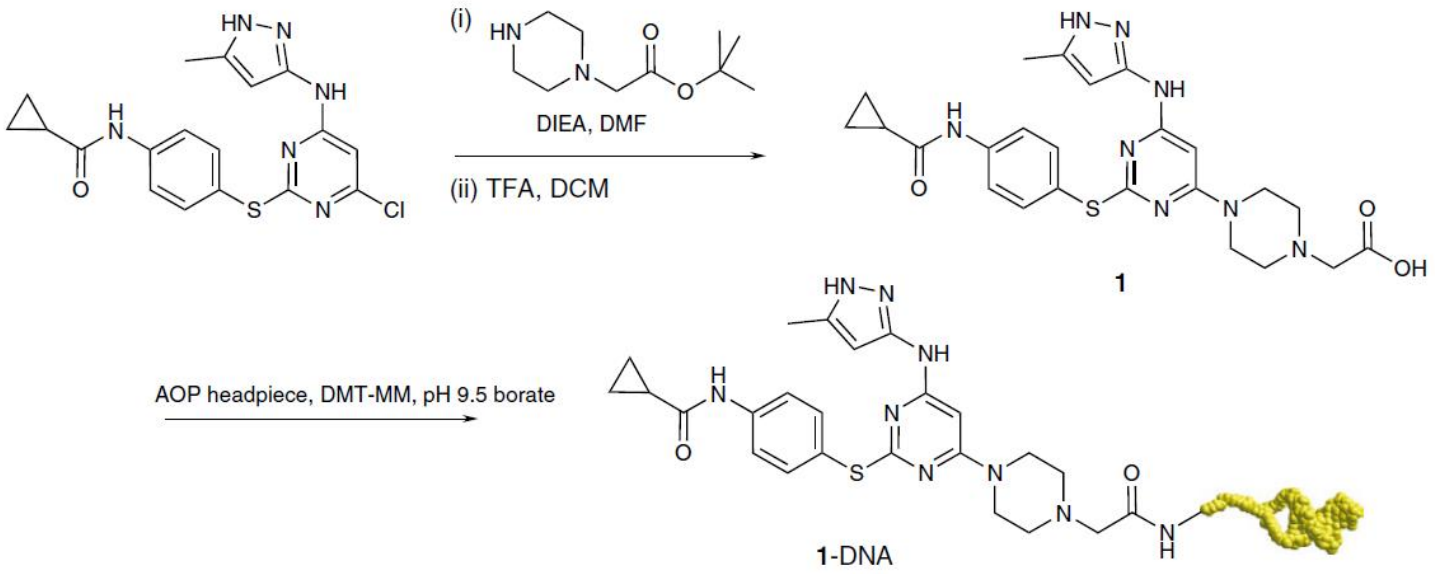


Figure 1. Sequence and structure of the “headpiece.” MW = 4937 D

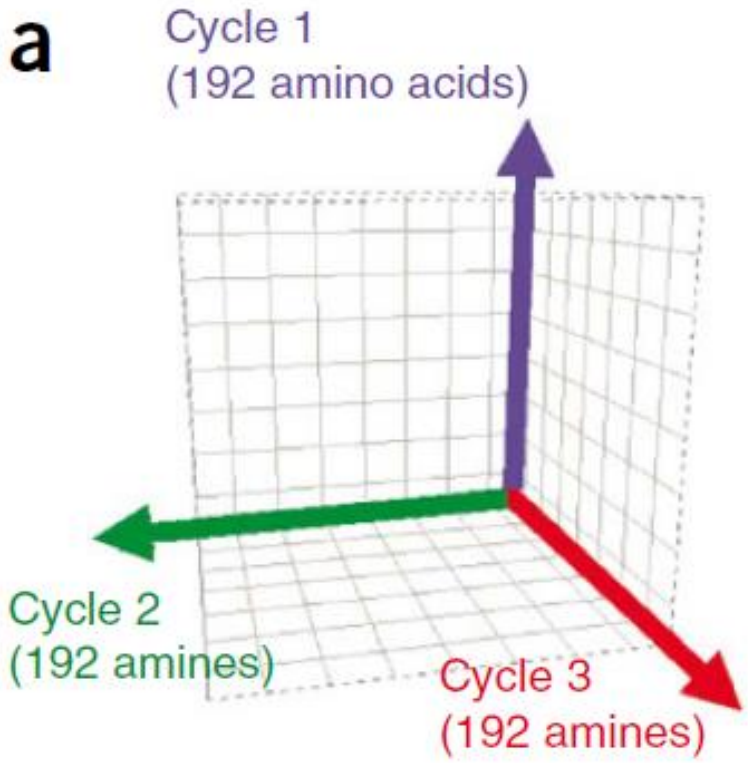
- What is «headpiece»
- To which chemical group are the building blocks linked?
- How are «DNA» codes linked?

Scheme 1



- What is «1»
- For which control experiment was «1» used in this work?
- What was the outcome of the control experiment?
- How were selection experiments performed (Method A and B)?

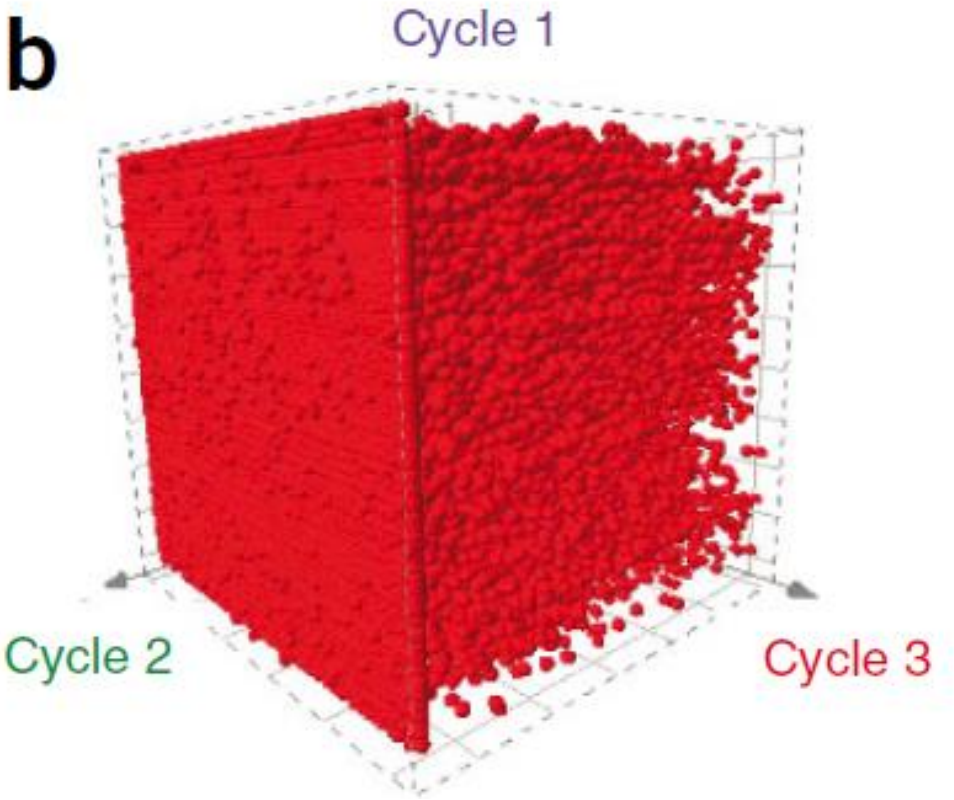
Figure 2a



The sequencing data of a selection was presented in «cubic scatter plots» :

- Which «pattern» was expected for a library before a selection?
- Which «pattern» was expected for a library after a selection?

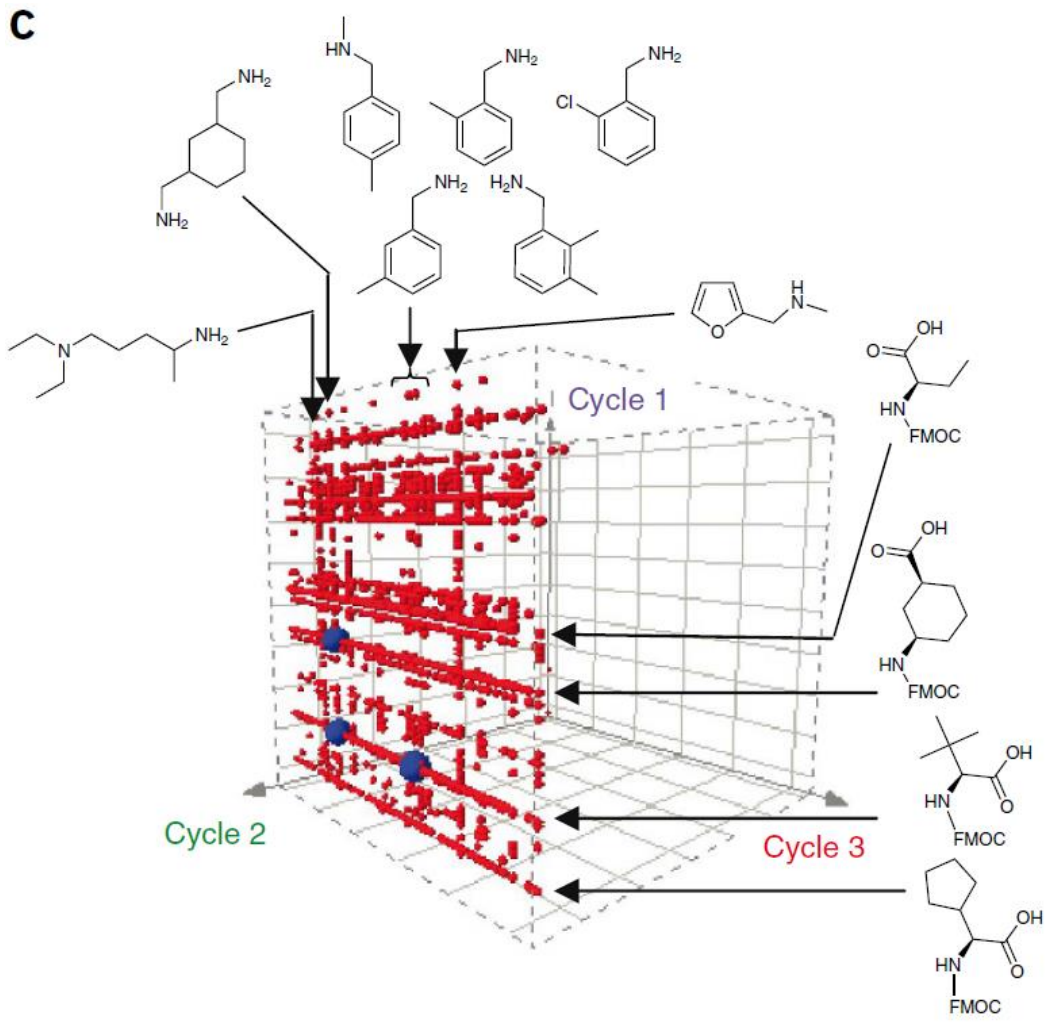
Figure 2b



Selection with p38 MAPK and Library A:

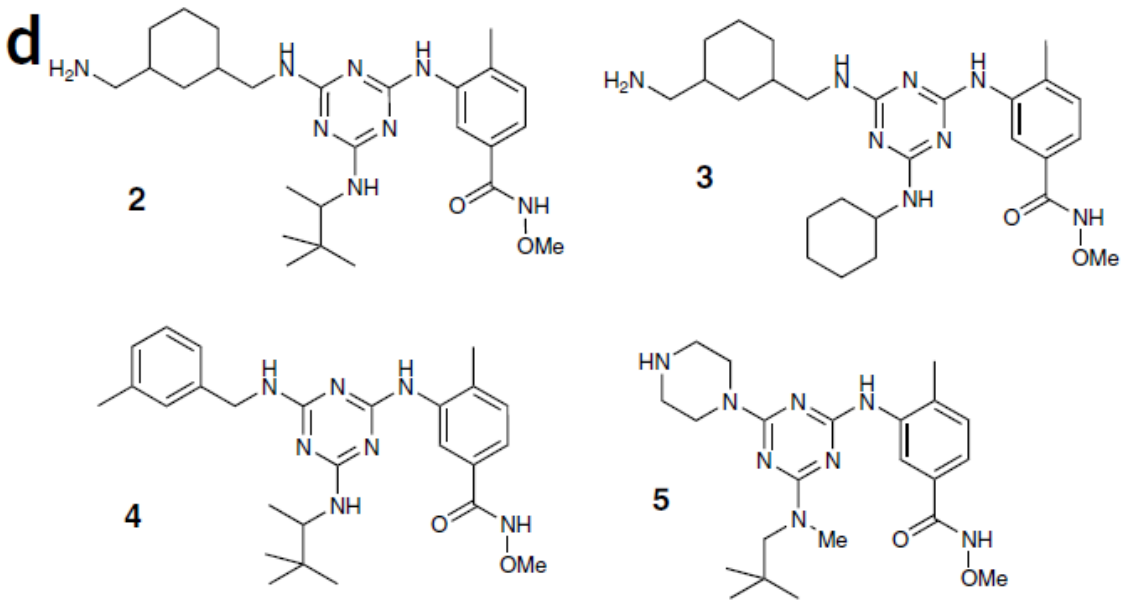
- What data is this «cubic scatter plot» showing?

Figure 2c



- What is the difference compared to the plot in Figure 2b?
- Which building block position (cycle) is most important for the enriched ligands?
- What are the «blue» dots?

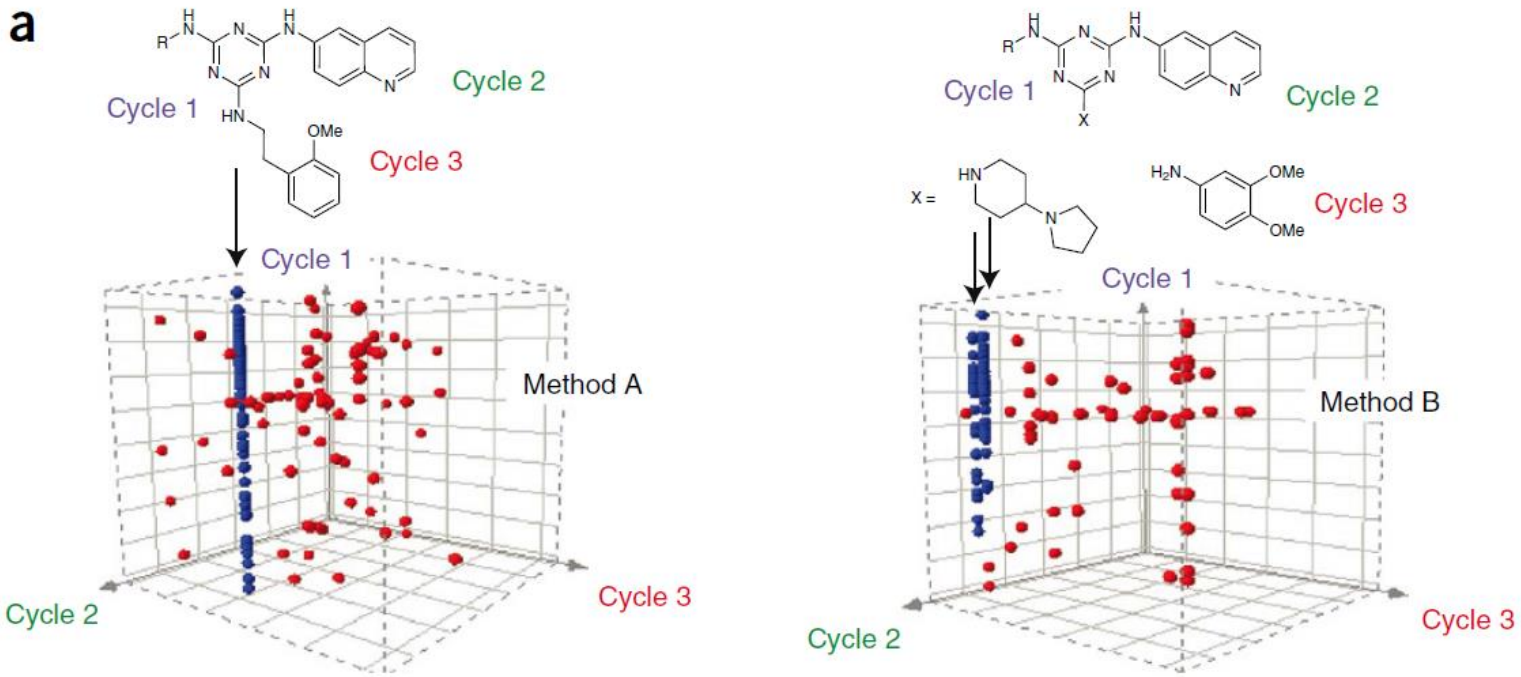
Figure 2d



Compound	IC_{50} (nM)
2	≤2
3	≤2
4	15
5	18

- Which four chemical structures are shown here?
- Which building block is most important (cycle 2)?
- Which building blocks were added in cycle 1 and cycle 3?
- What is compound «5»?
- To which position was DNA linked?

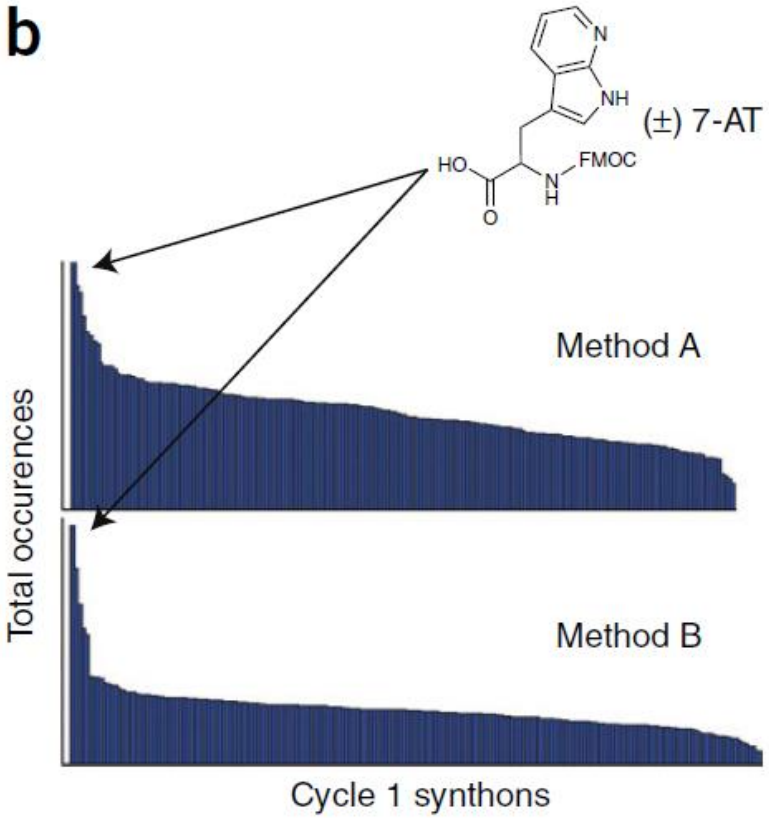
Figure 3a



Selection with auroara A kinase:

- What are «method A» and «method B»?
- Which building block position (cycle) is not important for compounds in «blue»?
- Which building block position (cycle) is most important for the enriched ligands in «blue»?

Figure 3b



Compound with the 7-azatryptophan (7-AT) building block was enriched in both methods (A and B):

- Where are these compounds seen in the «cubic scatter plots»? In which cycle was 7-AT added?

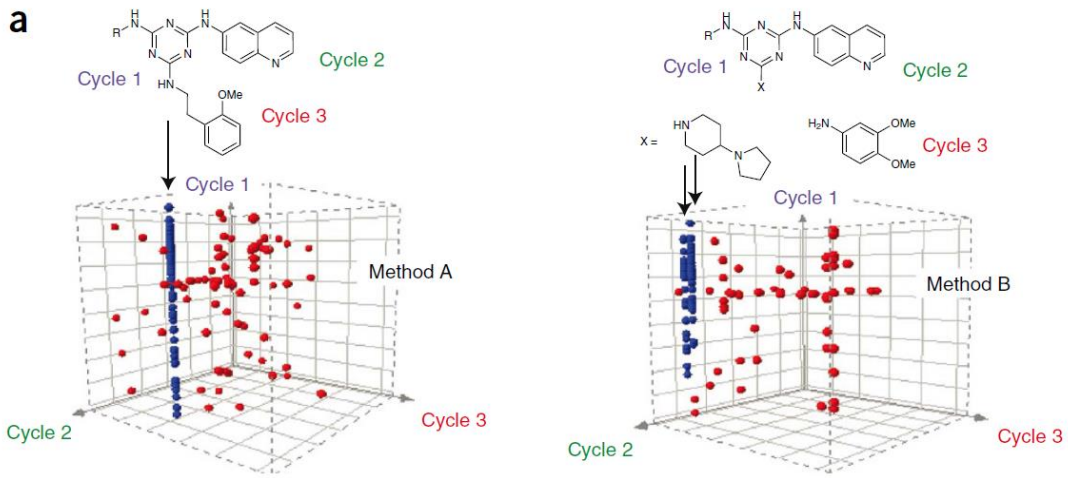
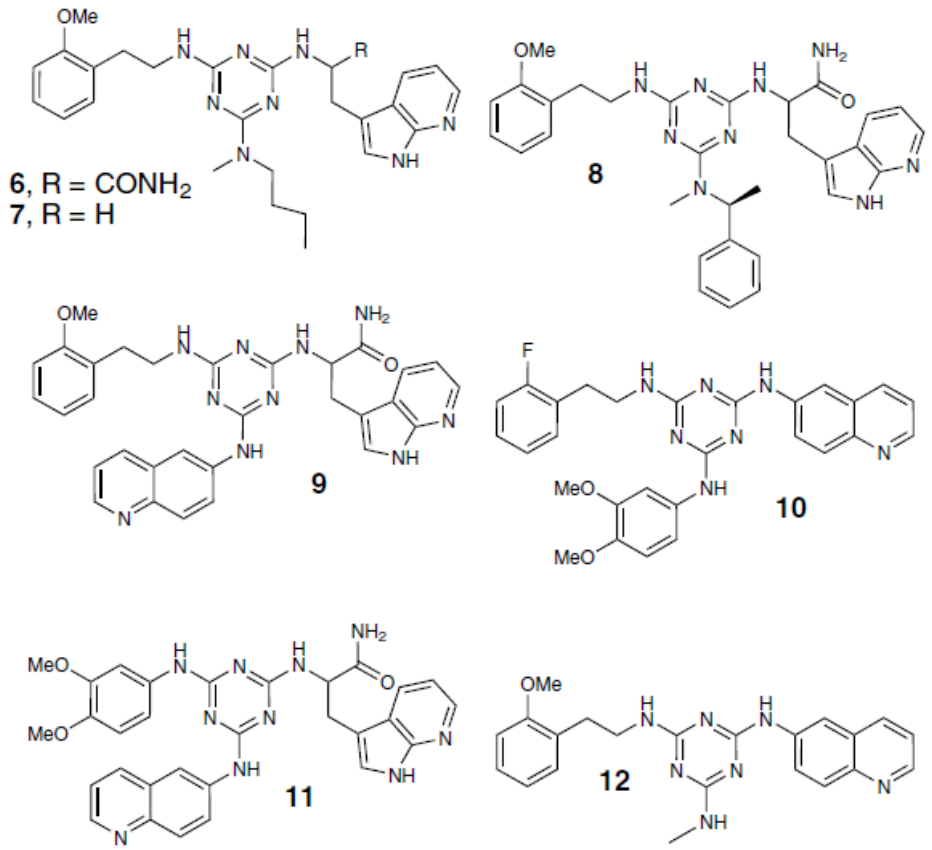


Figure 3c

c

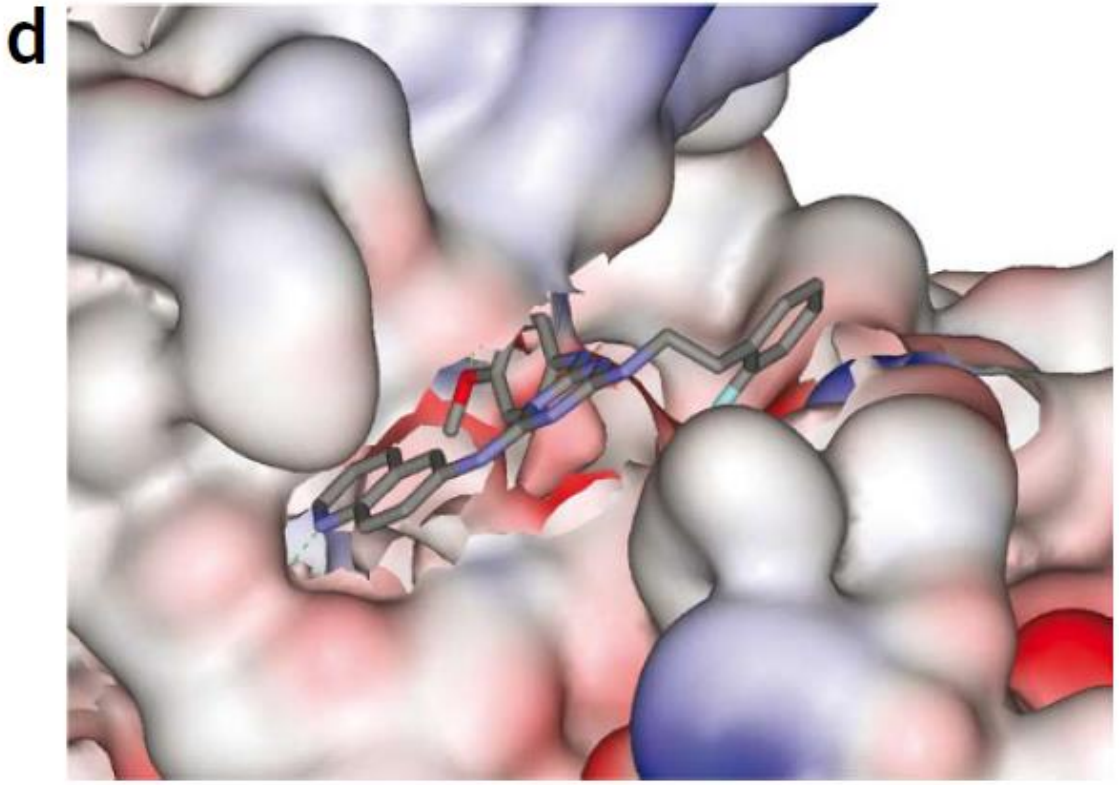


Compound	IC_{50} (μM)
6	3.8
7	1.2
8	6.3
9	3.7
10	2.1
11	0.27
12	5.1

Selection with auroara A kinase:

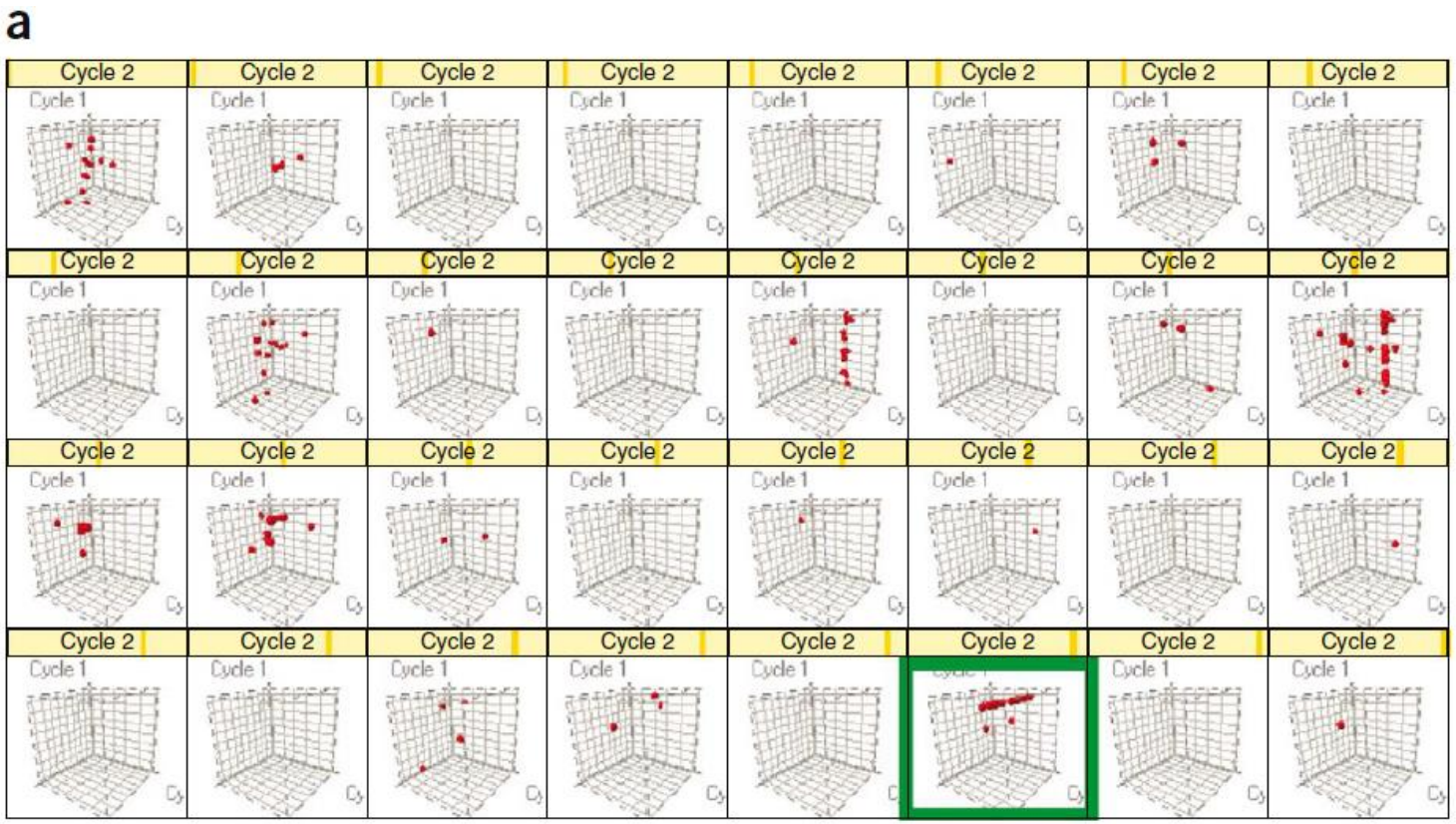
- Which compounds were chosen for re-synthesis & characterization?
- Were the observed binding affinities good?

Figure 3d



- Which experiment was performed here?
- Which compound is shown?
- Which building block is solvent-exposed? Does this make sense?

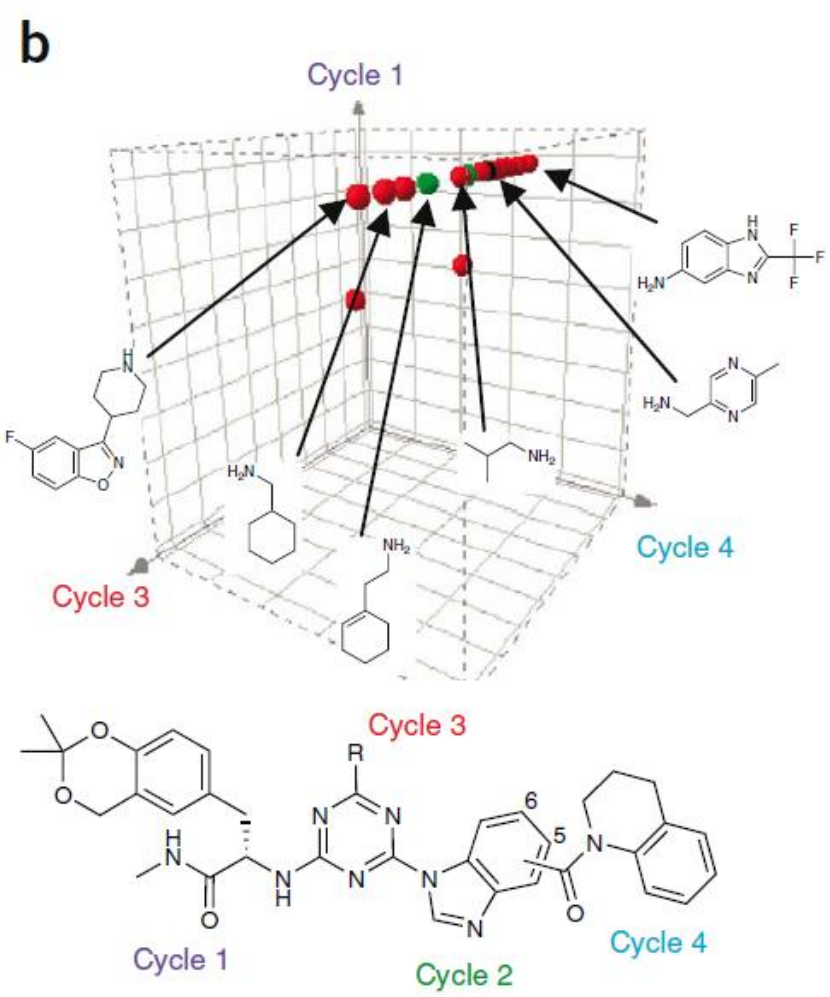
Figure 4a



Selection of p38 MAPK inhibitors:

- Why are there 32 cubes?
- Which library was screened?

Figure 4b

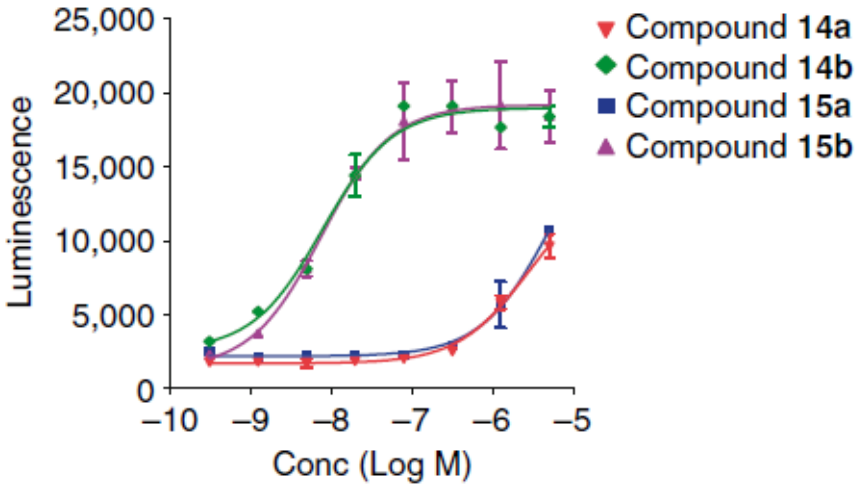


- Which building block position(s) (cycle) is/are most important?
- Which building block position (cycle) is the least important?

Figure 4c

c

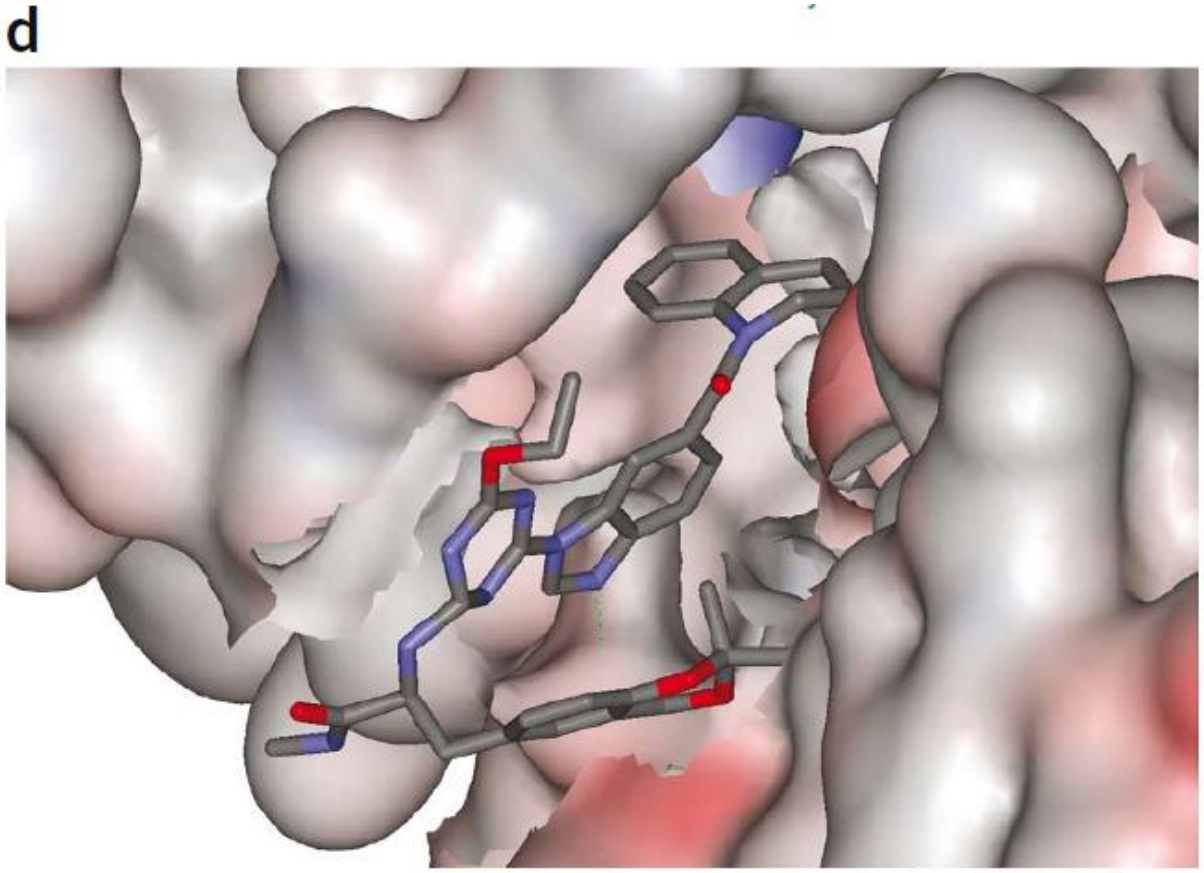
Compound	R	EC_{50} (μM)
13	$NH^{i}Bu$ (mixture)	0.25
14a	OEt (5-isomer)	2.7
14b	OEt (6-isomer)	≤0.008
15a	OH (5-isomer)	5.2
15b	OH (6-isomer)	≤0.007



Suddenly, highly active p38 MAPK inhibitors 14b and 15b were found.

- How were they found?
- Were the –OH and –OEt groups present in the library/selection?

Figure 4d



The cycle 1 building block points to the solvent.

- Is this expected? Why?