Vernalis

York Structural Biology Laboratory

The University of York

HYMS THE HULL YORK MEDICAL SCHOOL

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# Current Perspectives in Fragment-Based Discovery

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Vernalis (R&D) Ltd, Cambridge
YSBL & HYMS, Univ of York, UK

Philadelphia, 11th Oct 2010

# Overview

Vernalis

- Why?
  - some history
- How?
  - finding fragments that bind
- Some success stories
  - and some that were halted - lessons learnt
- Some issues and discussion points
  - challenging targets
  - which fragments to optimise
  - fragments and chemical space
- Main points and what's next?

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- Trying to find compounds that bind to target
  - Compounds need to have required shape and chemistry

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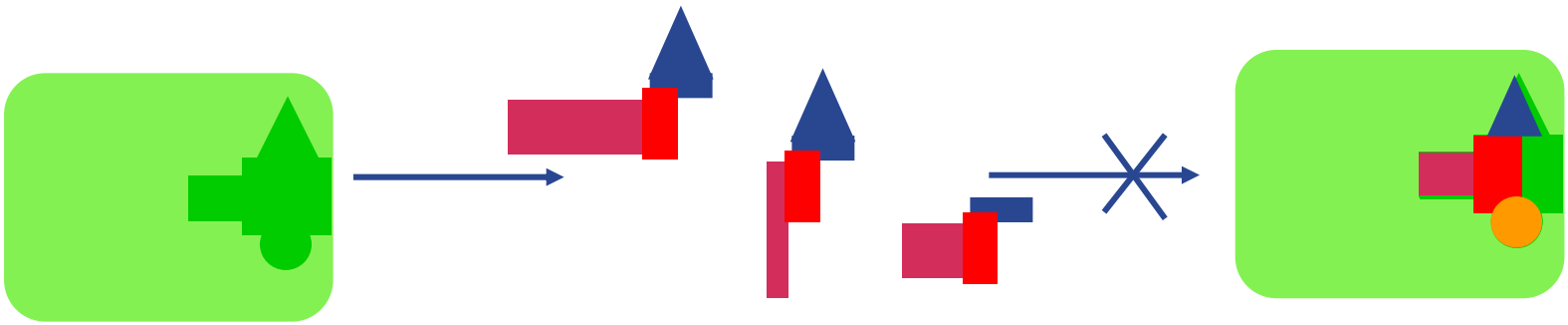
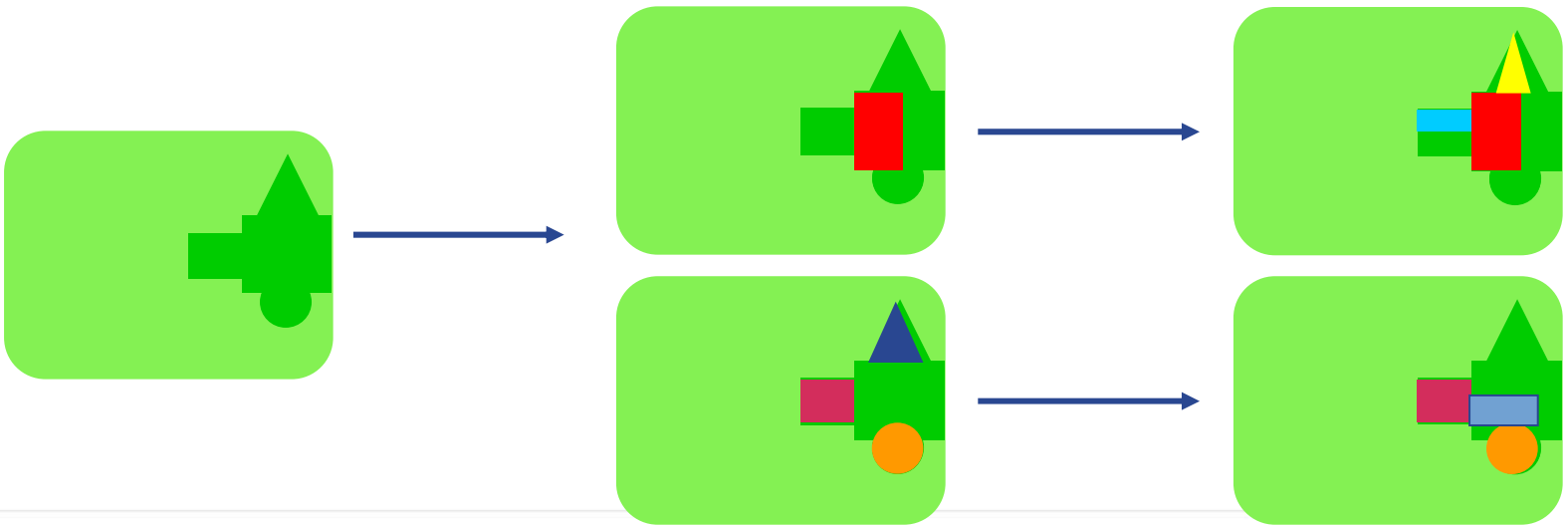
- Trying to find compounds that bind to target
  - Compounds need to have required shape and chemistry
- High Throughput Screening
  - Compounds decorated in the wrong way
  - Particularly a problem with new target classes



# Why fragments?



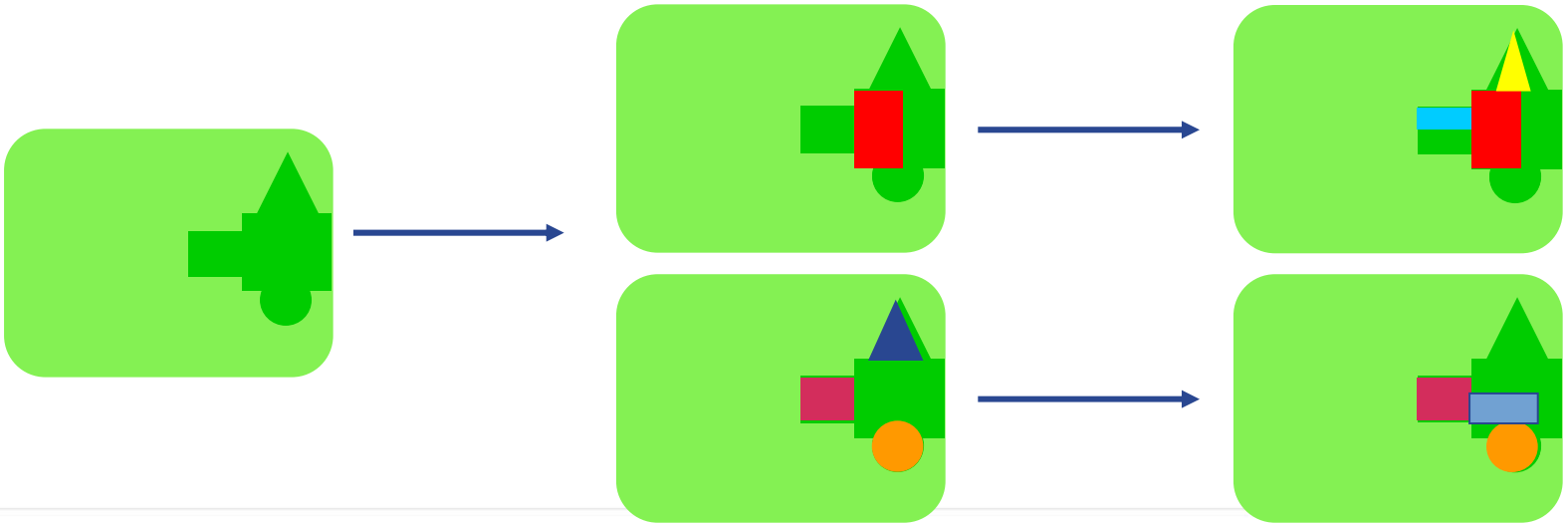
- Hits from fragments
  - Find small parts that bind
  - Then grow or merge fragments to create hit compound



# Why fragments?



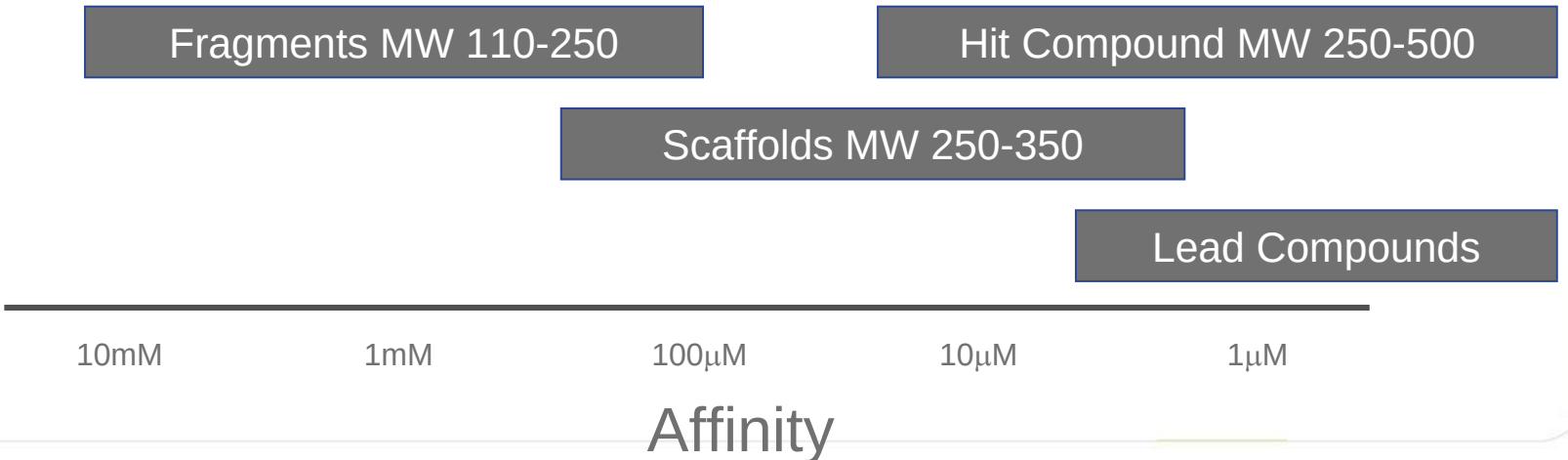
- Hits from fragments
  - Find small parts that bind
  - Then grow or merge fragments to create hit compound
- Can also provide ideas
  - Hit / lead optimisation
  - Scaffold hopping



# Why are fragments different?



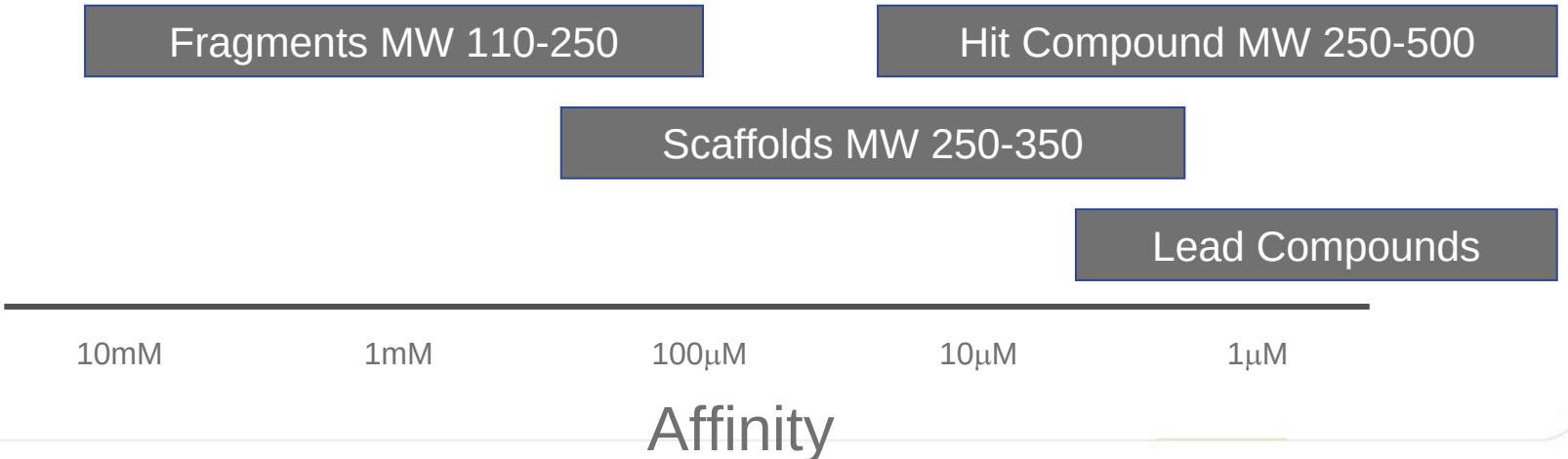
- A fragment is just a small weak hit



# Why are fragments different?



- A fragment is just a small weak hit
- Requires assay(s) that can detect binding reliably
- Methods for evolving fragments (libraries and/or design)
- Design of library includes constraints of assay / evolution
- Requires structure to get hits on scale of assay
  - to generate SAR that drives medicinal chemistry
  - Track the ligand efficiency – binding energy per heavy atom



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# Origin of the ideas



- By early 1980s
  - Jencks “On the Attribution and Additivity of Binding Energies”
    - *Proc. Nat. Acad. Sci. USA* 1981 78(7): 4046-4050
    - $\Delta G = -RT\ln K$ => twice the energy – square the affinity

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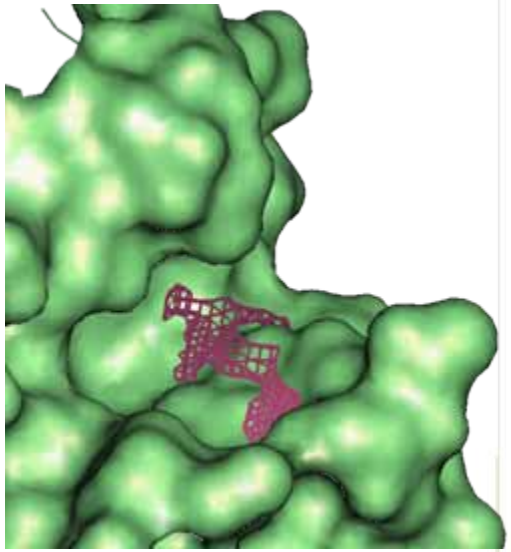
- Early 1980s
  - Peter Goodford and GRID – computation to map where functional groups could bind to active sites
    - Goodford, *J Med Chem* **1985**, *28,* 849
    - Example of OH probe on surface of lysozyme



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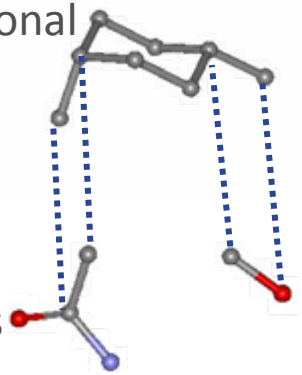

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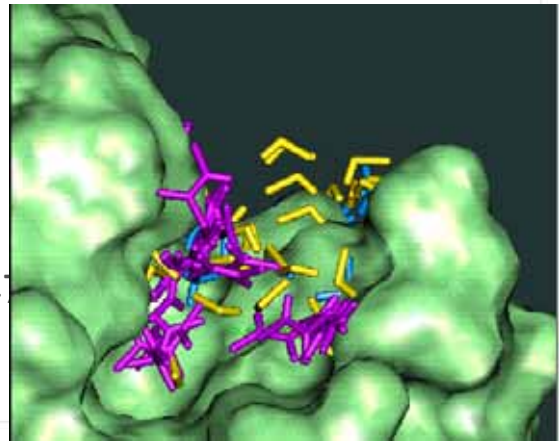
  - Karplus, Miranker, Eisen, Hubbard – MCSS / Hook
    - Karplus and Miranker, *Proteins* **1991,** *11***,** 29
    - Eisen et al *Proteins* **1994***, 19*, 119
    - English, Groom & Hubbard, *Prot Eng*, **2001**, *14*, 4



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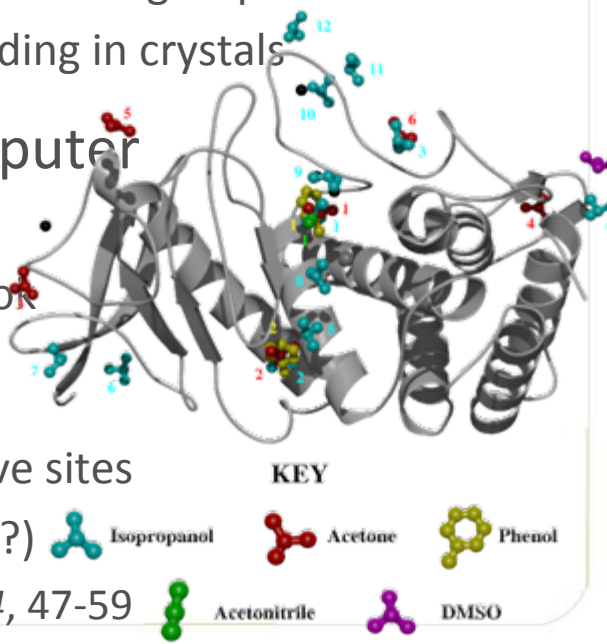
- 1990s
  - Ringe – Xray mapping of solvent binding to active sites
  - Extended to other systems and titrated (affinity?)
    - English, Groom & Hubbard, *Prot Eng*, **2001**, *14*, 47-59



# Implementation of the ideas



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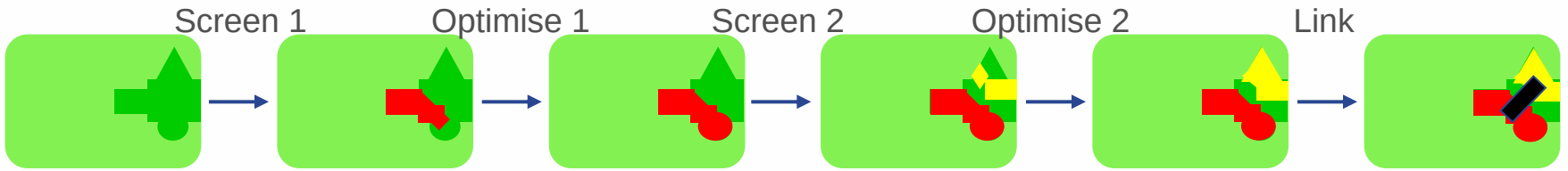

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    - Roche, Novartis, AZ
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- Additional conceptual framework developed
  - Hann et al analysis of compound size, complexity and finding hits
    - *J. Chem. Inf. Comp. Sci.* **2001**, *41*, 856-864
  - Ligand efficiency
    - Kuntz and maximal affinity – *PNAS,* **1999**, *96,* 9997-10002
    - Ligand Efficiency – $\Delta G$ / HAC – *Drug Disc Today*, **2004,** *9*, 430-431

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- Mid-2000s
  - A number of fragment-derived compounds selected for clinical trials
  - Unlike many other technologies – methods developed and relevance understood (with minimal hype) before large-scale takeup

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# Screening fragment libraries

Hubbard & Murray (2010), Meth Enzymology, in press

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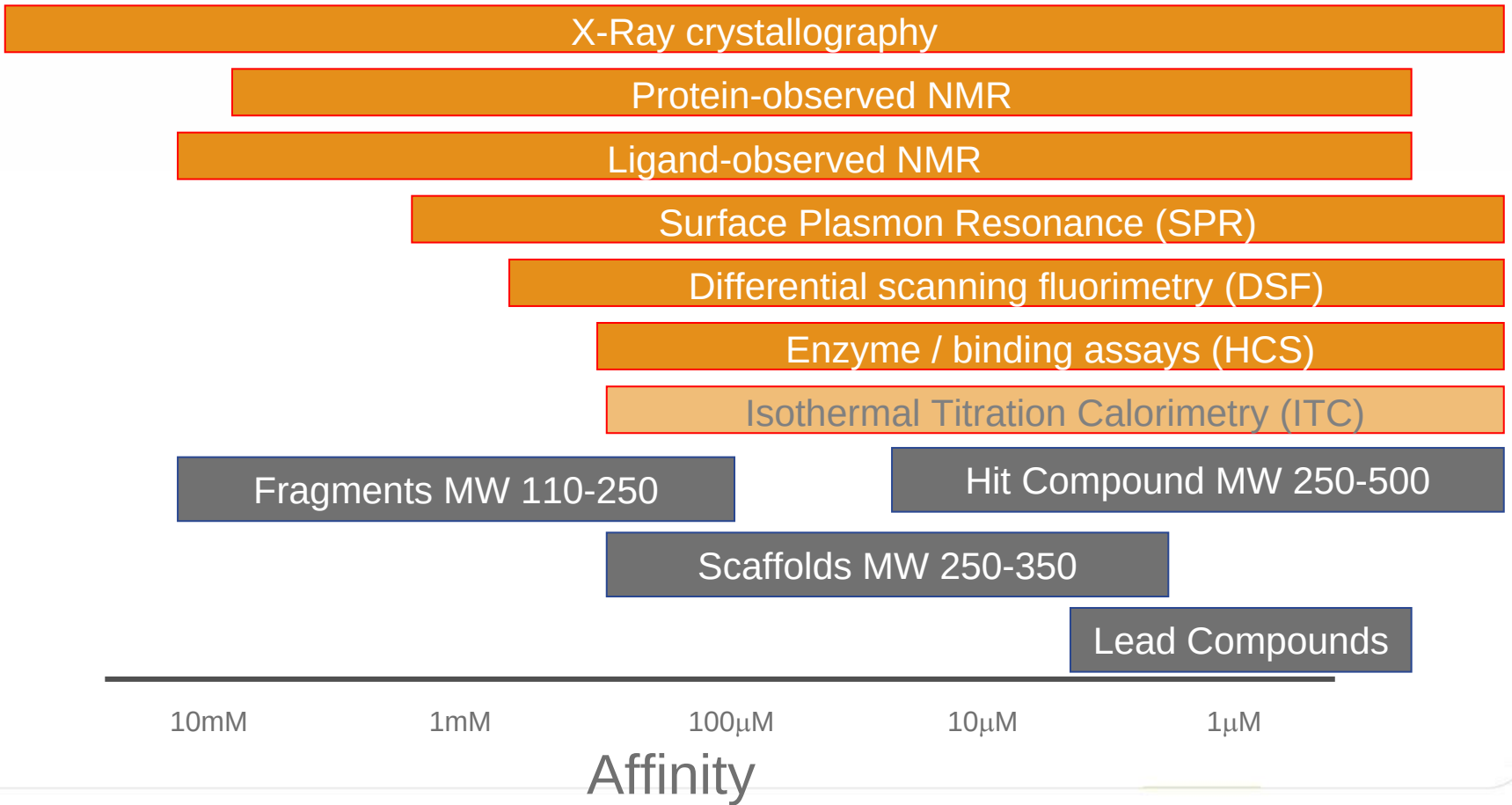
FBLD 2010

- Different experimental approaches have different strengths and limitations



# Vernalis experience



- For “good” active sites:
  - If assays configured correctly
    - Pay attention to quality of the library – solubility / aggregation etc
    - Same hits identified by ligand observed NMR and SPR
    - High percentage of validated hits give crystal structures

# Vernalis experience



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    - And it is a lot of redundant work

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    - But high concentrations can confound the assay
  - Calorimetry (ITC) not yet for screening

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  - “Wet” assays can work sometimes
    - But high concentrations can confound the assay
  - Calorimetry (ITC) not yet for screening
  - Thermal melt methods
    - Measure temperature at which protein unfolds
    - Unreliable - weak fragments can bind without stabilizing protein
    - Can find cryptic / allosteric sites (sometimes)

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- For “challenging” sites:
  - Can get “over-binding” / anamolous results
  - Cross-validate binding by different techniques

# Vernalis experience

Hubbard & Murray (2010), Meth Enzymology, in press



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- For “challenging” sites:
  - Cross-validate binding by different techniques
- Need for faster, more sensitive, less resource intensive methods
  - e.g. see Pharmadiagnostics poster

# Detect binding by ligand based NMR

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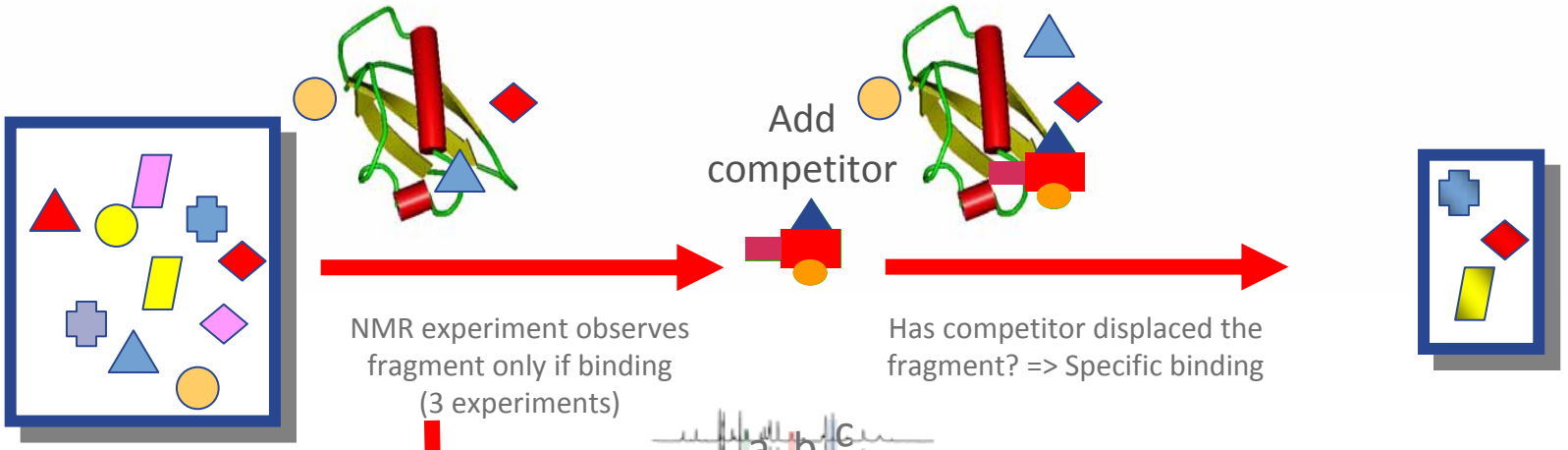
FBLD 2010

Target + fragments

Target + fragments
+ competitor ligand



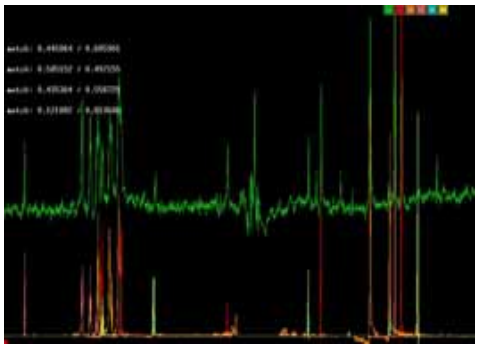

NMR experiment observes fragment only if binding (3 experiments)

Has competitor displaced the fragment? => Specific binding

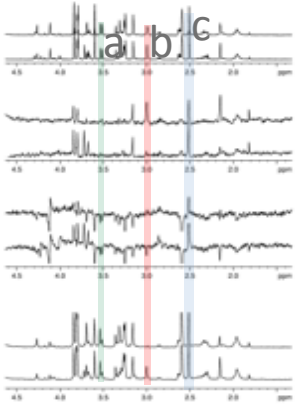
**Fragment Library**

**1200 + fragments**
**Assayed in mixtures of 12**

**5 – 100 Hit Fragments**



Internal QC – protein & fragments

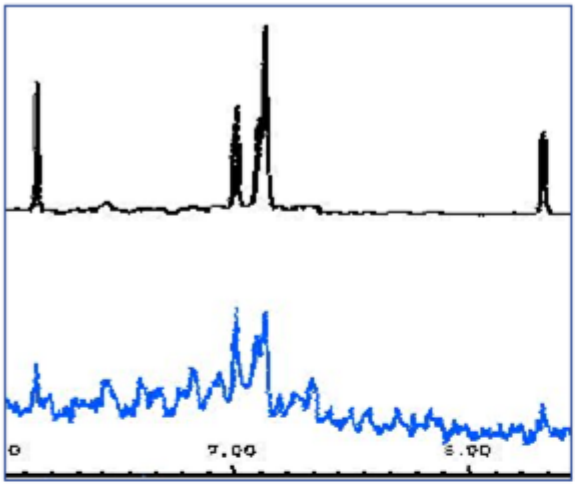


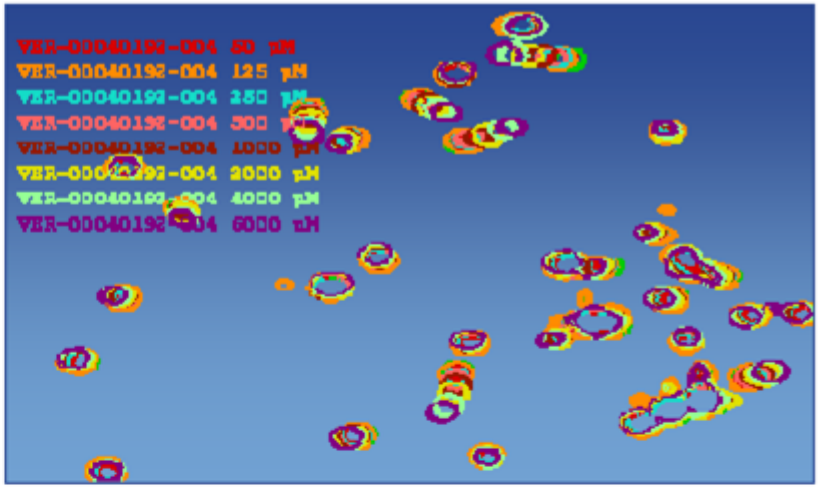

Has the advantage can monitor ligand and protein in each experiment

Ben Davis speaking later today

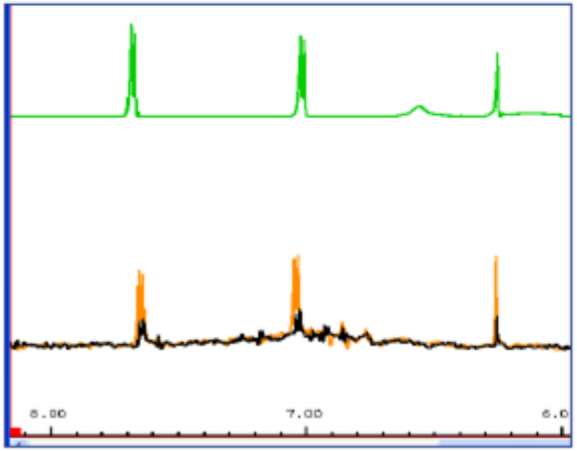
# NMR Sensitivity

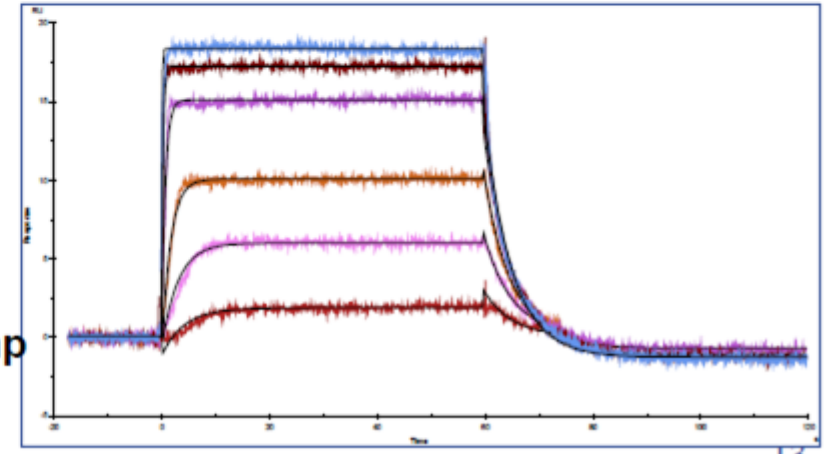





PPI fragment: NMR $K_D$ 3.8 mM



13

Potent Kinase fragment: SPR $K_D$ 90 nM; Enz $cK_I$ 130 nM

# The Vernalis process

Vernalis

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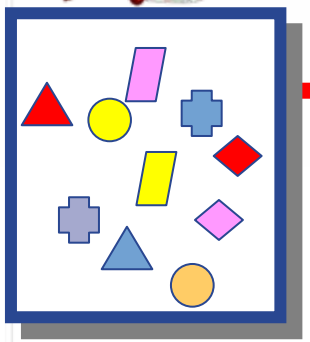
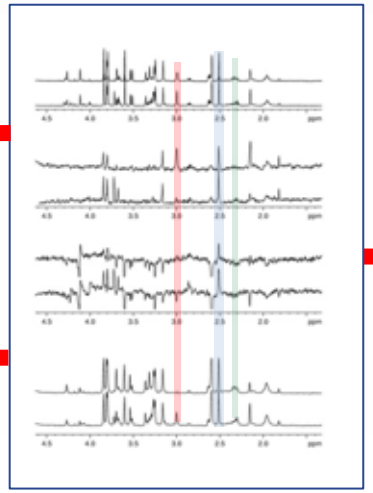
SeeDs - Structural Exploitation of Experimental Drug Startpoints*

*Hubbard et al (2007), Curr Topics Med Chem, 7, 1568

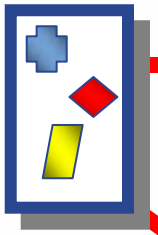
Target



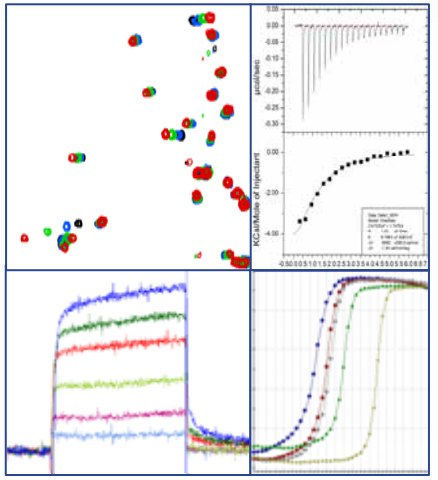
Fragment Library ~
1200 compounds



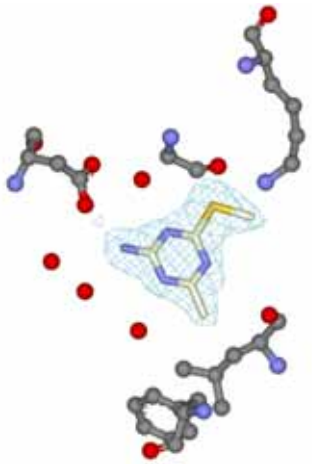
Library screened in mixtures of 10-12



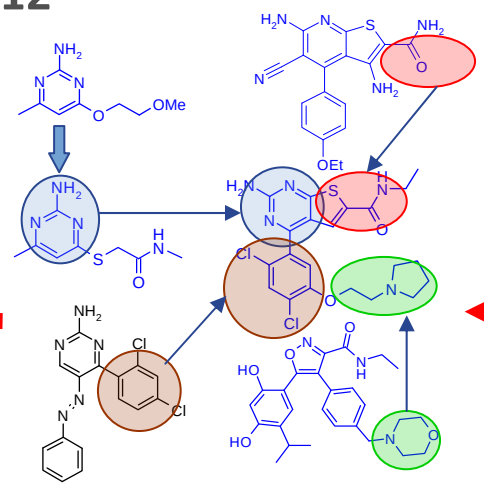
Hits



Characterisation

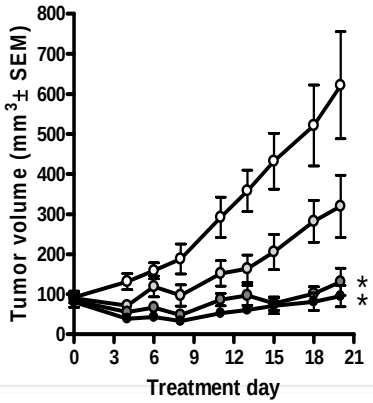


Structure Determination



Design, Build & Test

Drug?



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# Fragment based discovery



- Vernalis has disclosed examples in:
  - ATPases: Hsp90 and Hsp70
  - Kinases: CDK2, Chk1, PDPK1 (PDK1)
  - Protein-protein interactions: Pin1
- Undisclosed examples in:
  - Other ATPases
  - Other kinases
  - Other protein-protein interactions
- A growing literature of examples
  - See Congreve et al (2008), J Med Chem and Schulz and Hubbard (2009), Curr Opin Phar for overview

# Can find hits for most targets

Chen & Hubbard (2009), JCAMD, **23,** 603

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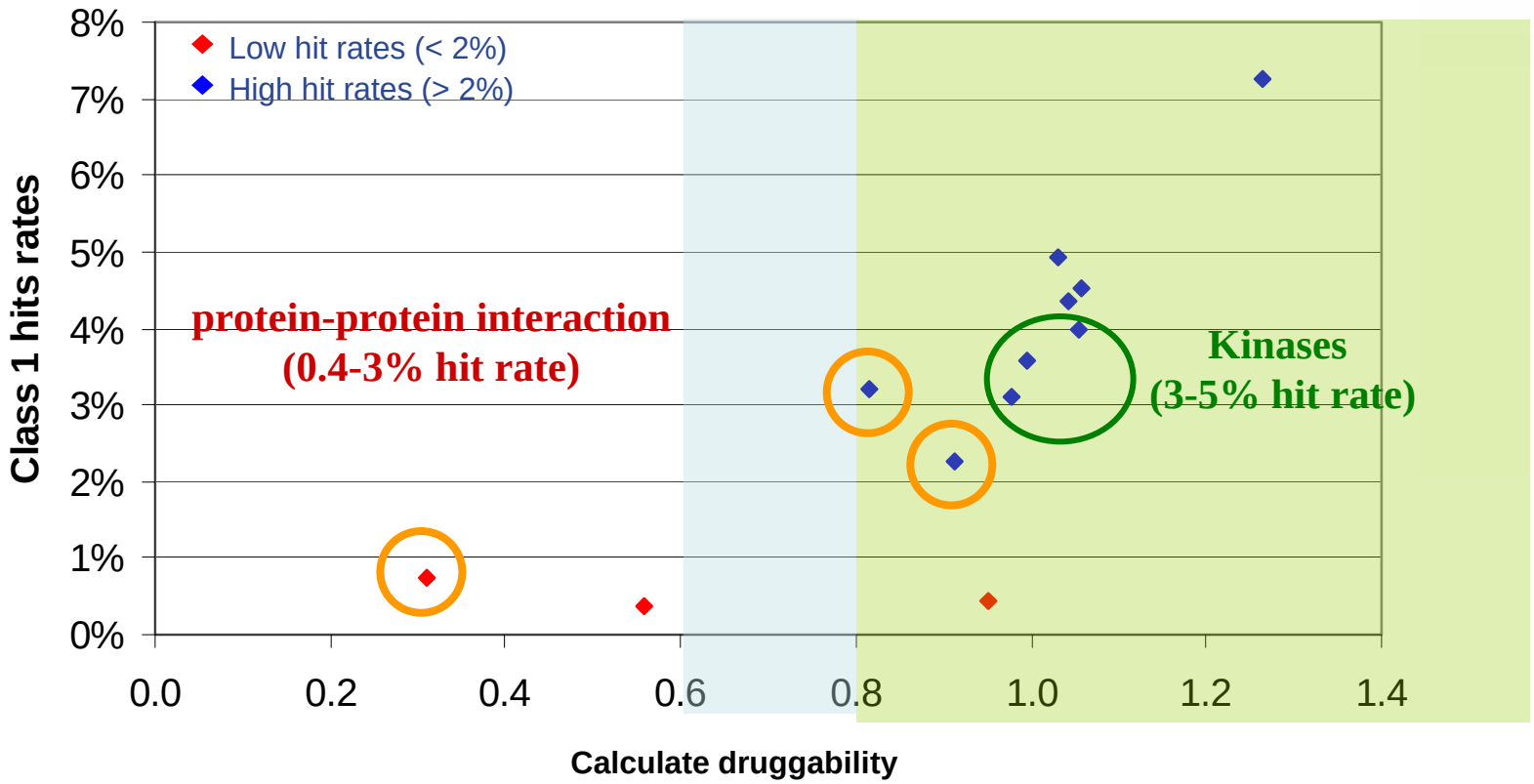
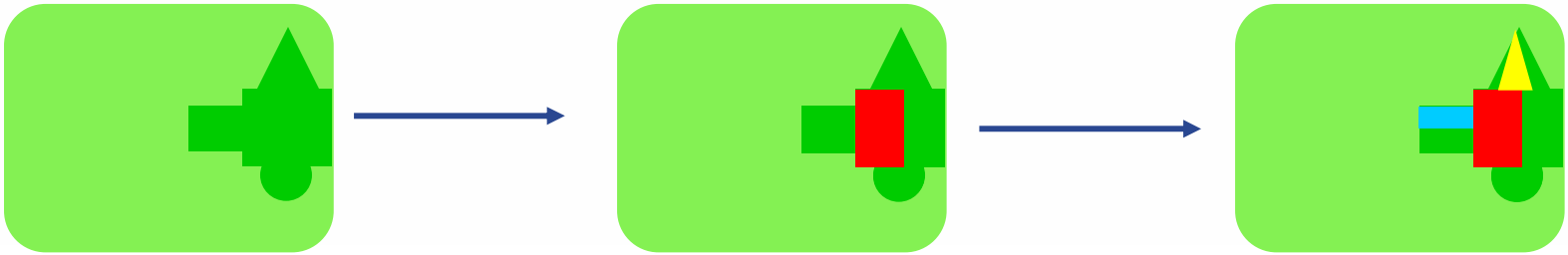



- "Druggability" is calculated from shape of binding site using the SiteMap algorithm
- General trend is hit rate increases with druggability – but see later

# A kinase example – Chk1



- Growing fragments



# Chk1 – Fragment hit

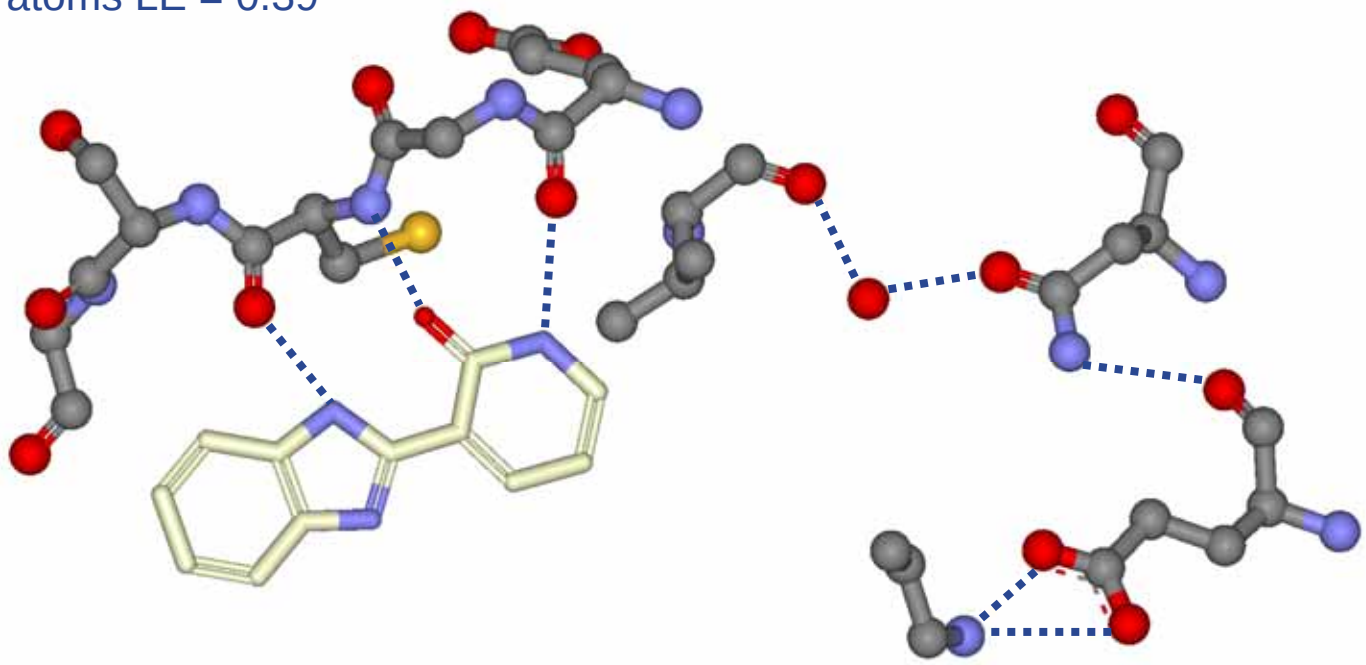


- Compound 1 “designed” fragment targeting kinases

Chk-1 $IC_{50}$ >100$\mu$M

100$\mu$M and 15 Heavy atoms LE = 0.39

**Bound structure in Chk1 ATP binding site**



K38 CG to NZ only; D55, N59, V68;

D85–G89, - side chain of Y86

Water 37

# Chk1 – initial growth



- Compound 2 - amide “fixes” binding site waters

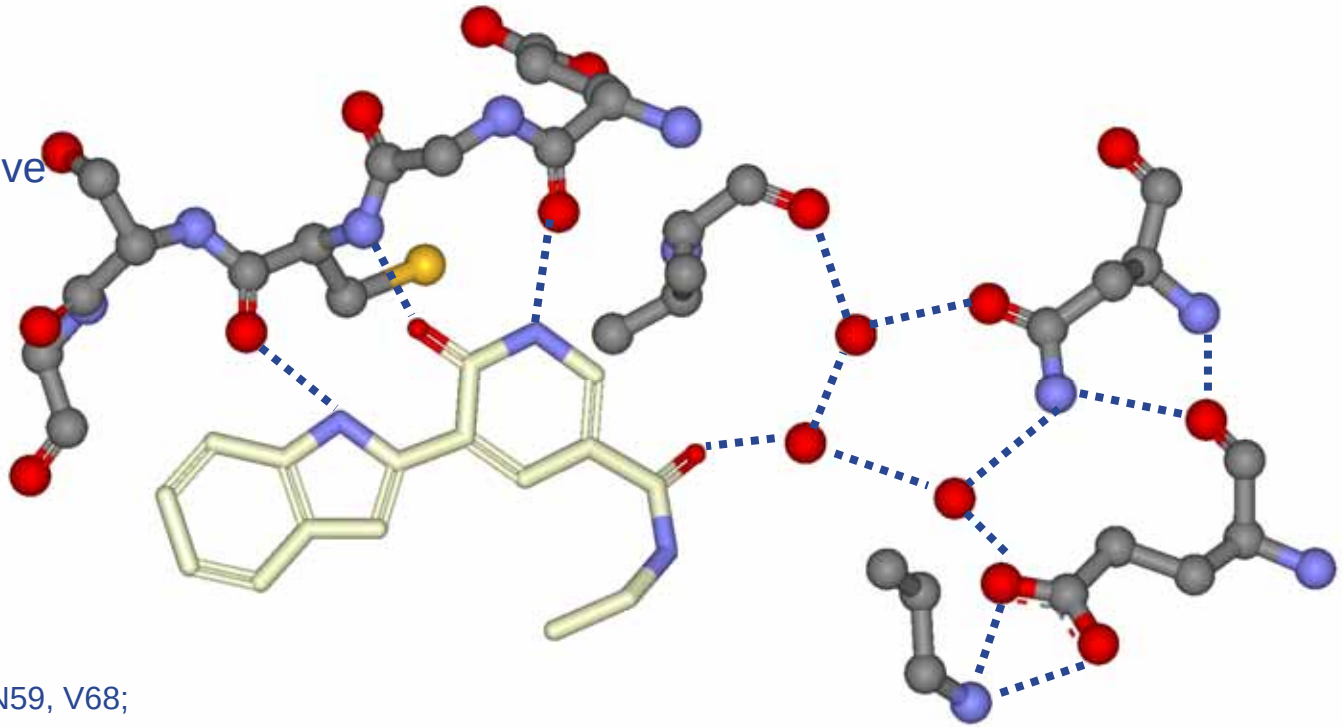
Chk-1 $IC_{50}$ 5$\mu$M

LE 0.39

$GI_{50}$ HCT116 >80$\mu$M

pH2AX (MEC) – inactive

**Bound structure in Chk1 ATP binding site**



K38 CG to NZ only; D55, N59, V68;

D85–G89, - side chain of Y86

Water 16, 31, 85

# Chk1 – second growth

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- Compound 3 – targets further interactions

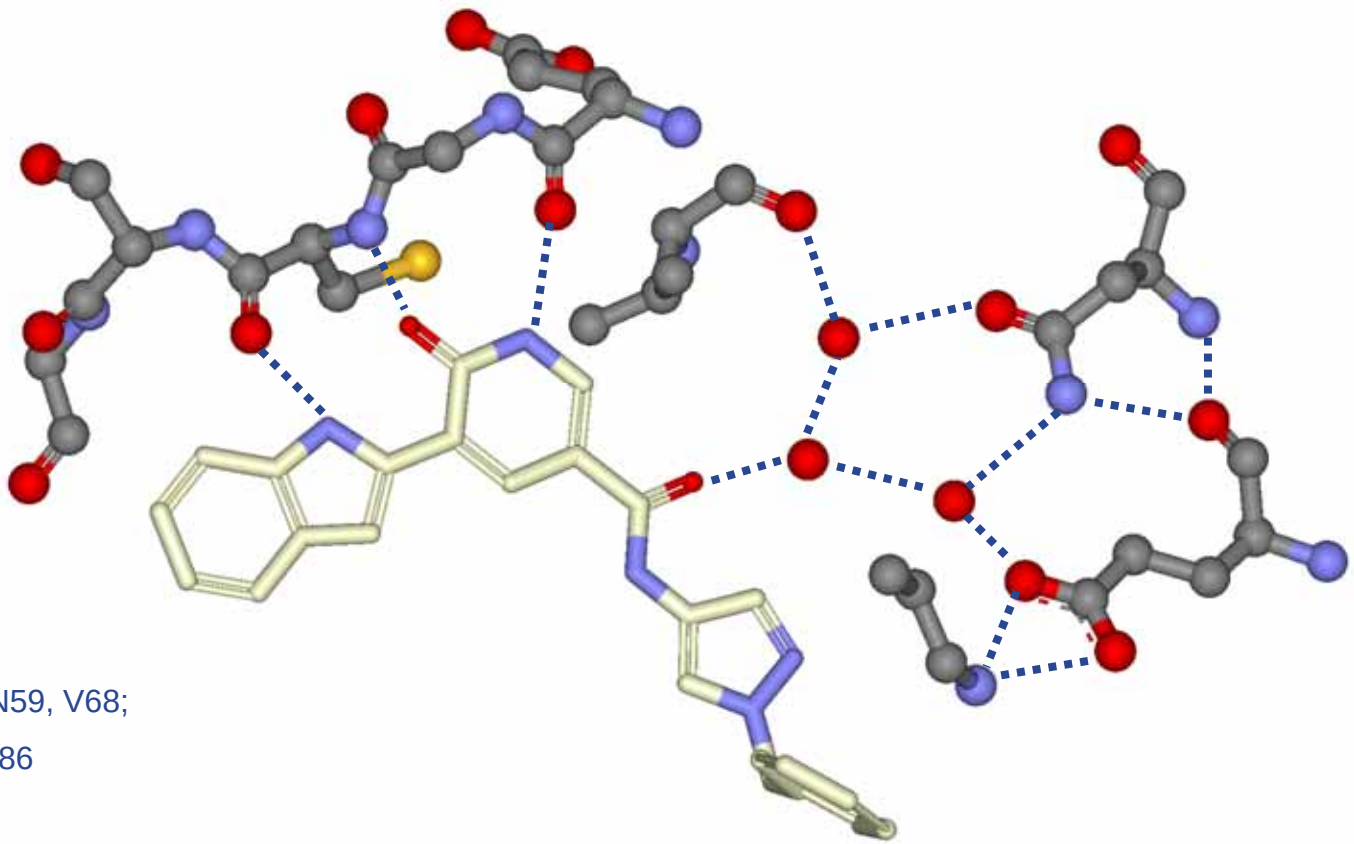
Chk-1 $IC_{50}$ 0.2$\mu$M

LE 0.33

$GI_{50}$ HT29 4$\mu$M

pH2AX (MEC) – 7$\mu$M

**Bound structure in Chk1 ATP binding site**



K38 CG to NZ only; D55, N59, V68;

D85–G89, - side chain of Y86

Water 91, 123, 136

# Chk1 – 1st optimisation



- Compound 4 – amide reversed - interactions optimised

Chk-1 $IC_{50}$ 0.013μM

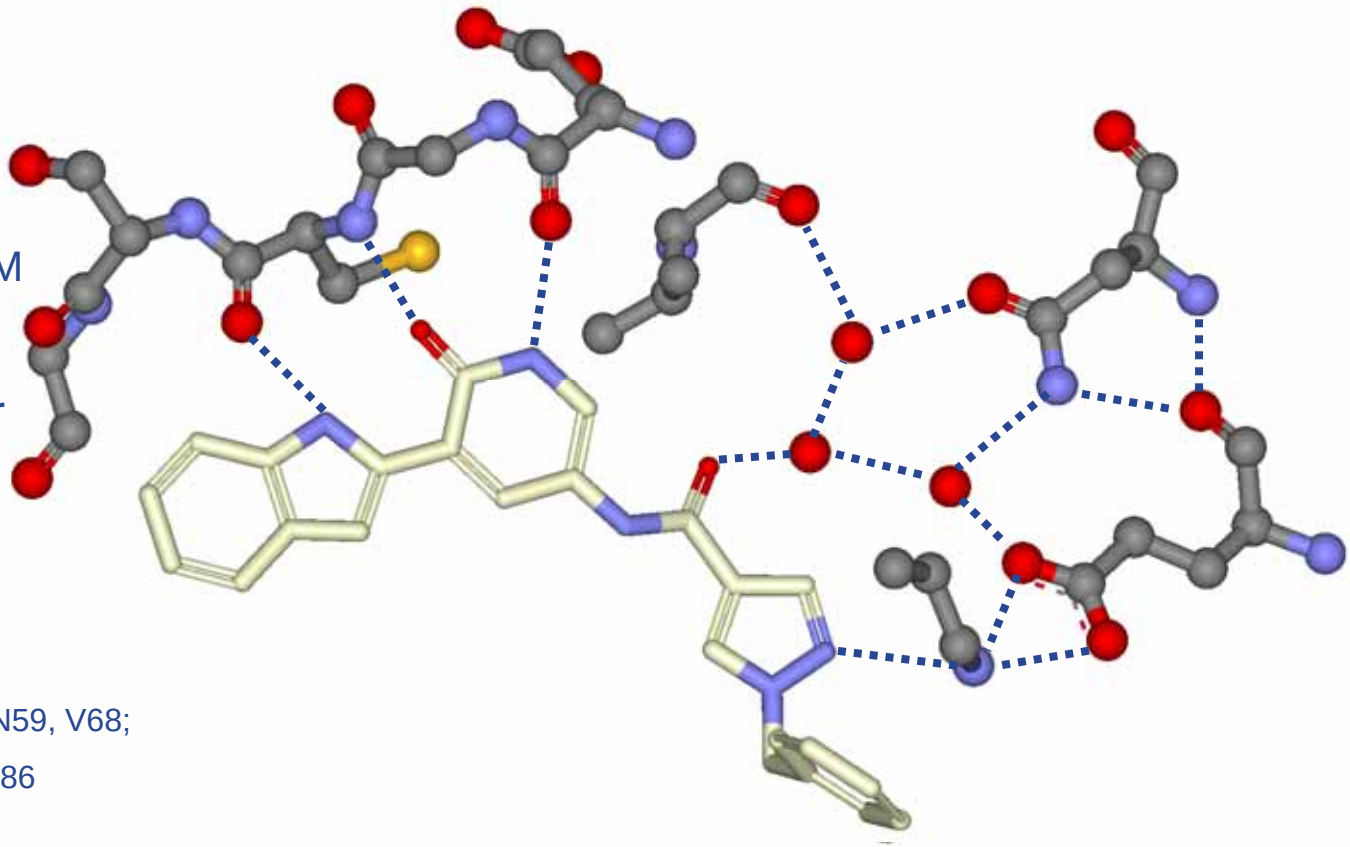
**LE 0.39**

$GI_{50}$ HT29 1.8μM

pH2AX (MEC) – 0.2μM

**Series members further optimised to identify Candidate V158411**

**Bound structure in Chk1 ATP binding site**



K38 CG to NZ only; D55, N59, V68;

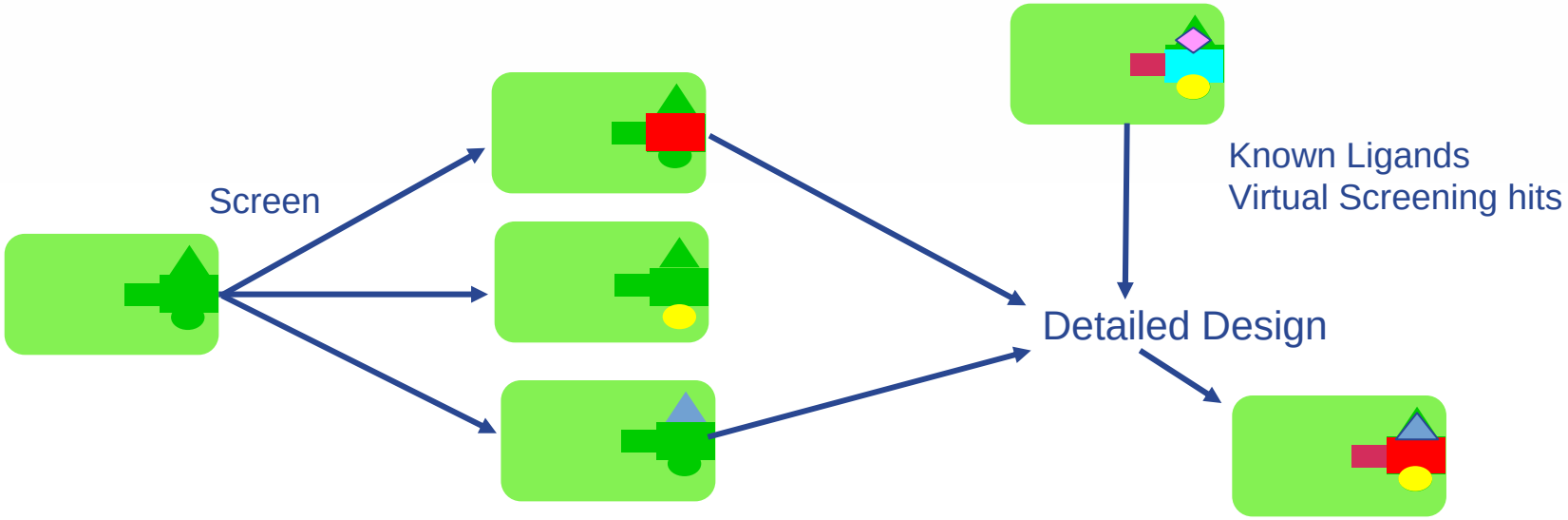
D85–G89, - side chain of Y86

Water 16, 31, 85, 179

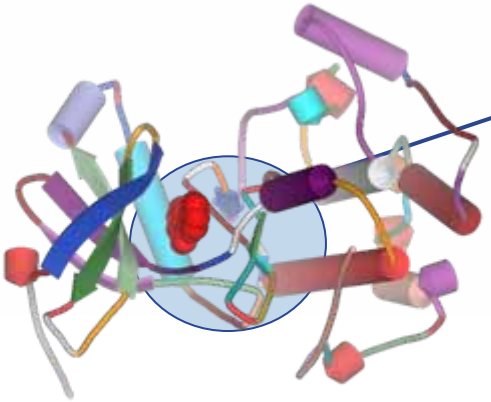
# A kinase example – PDPK1 (PDK1)



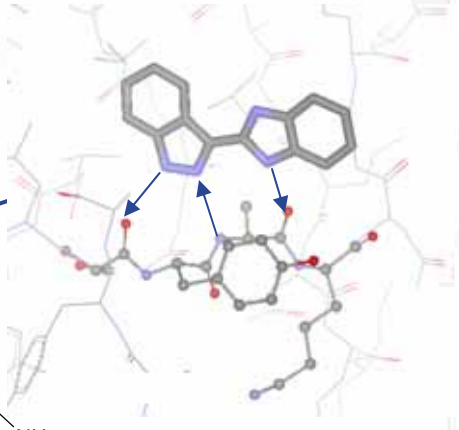
- Structure-guided merging of fragments and literature compounds

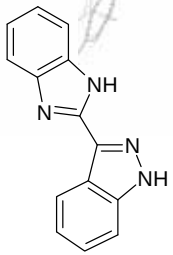


# PDPK1 – finding fragments



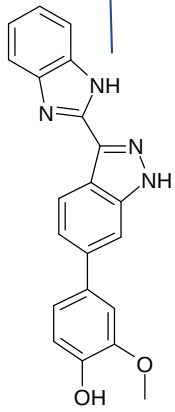
Structure in PDPK1



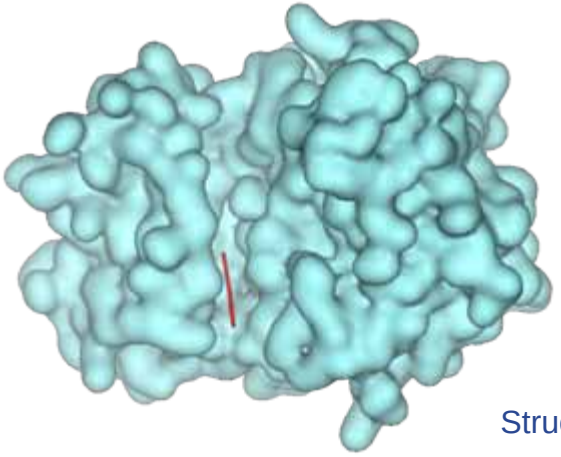



7μM in Chk1
3μM in PDPK1

Structure bound to Chk1 used to design minimal scaffold




Agouron (promiscuous) Chk1 inhibitor



Structure in PDPK1

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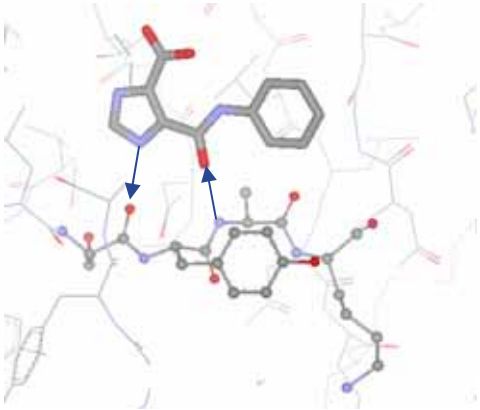
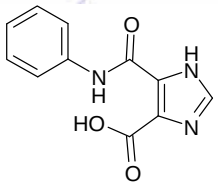
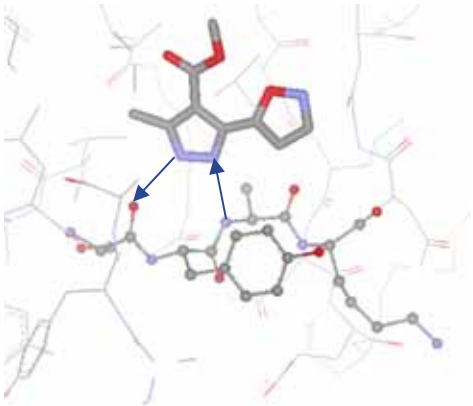
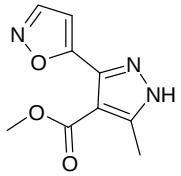




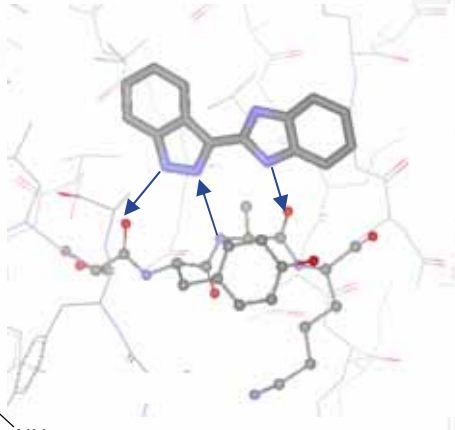
180μM

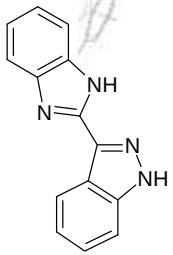
SeeDs identified by NMR that competitively bind to kinase active site (displaced by staurosporine). >80 SeeDs identified – structures determined for >50.





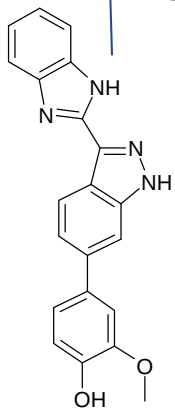
150μM





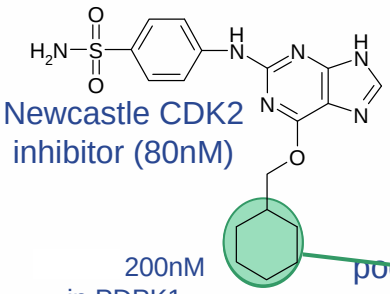
3μM

Structure bound to Chk1 used to design minimal scaffold



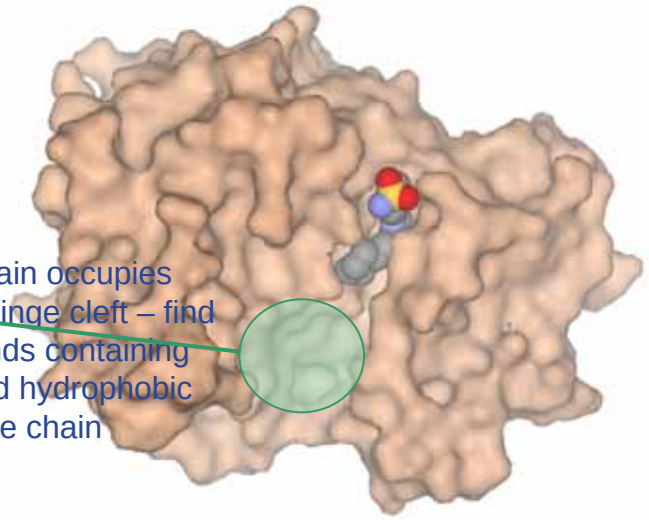
Agouron (promiscuous) Chk1 inhibitor

# PDPK1 – evolving fragments

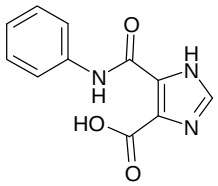


Newcastle CDK2 inhibitor (80nM)

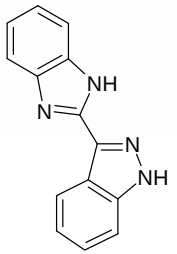
200nM in PDPK1



Side chain occupies pocket in hinge cleft – find compounds containing SeeD and hydrophobic side chain



180μM



3μM

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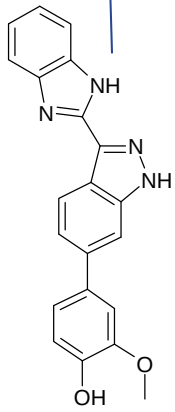

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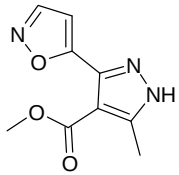
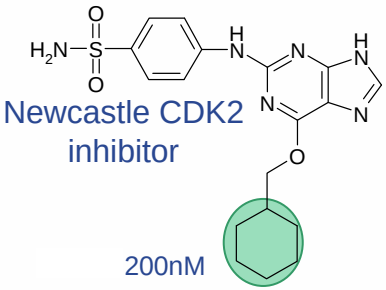


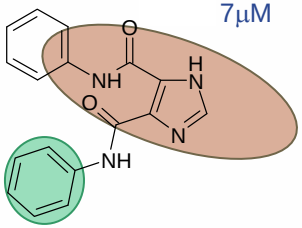
150μM

# PDPK1 – evolving fragments

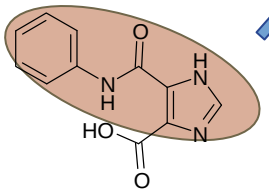


Newcastle CDK2 inhibitor

200nM



7μM



180μM

rCat

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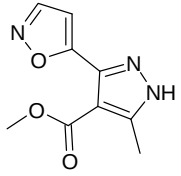
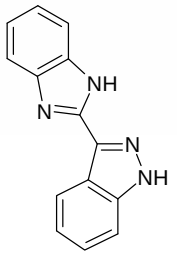
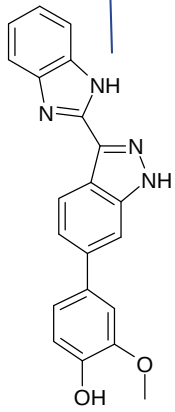


150μM



3μM

Structure bound to Chk1 used to design minimal scaffold

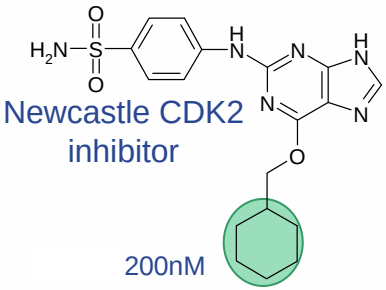


Agouron (promiscuous) Chk1 inhibitor



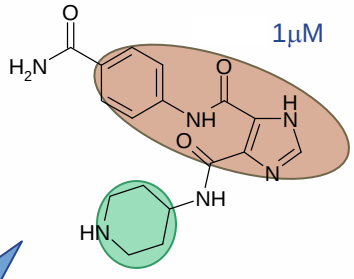
rCat – catalogue of available compounds, JCICS, **44** 643

# PDPK1 – evolving fragments



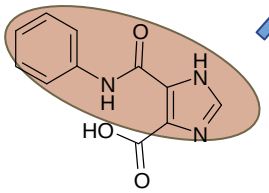
Newcastle CDK2 inhibitor

200nM



1μM

Chemistry around side chains to explore affinity and solubility



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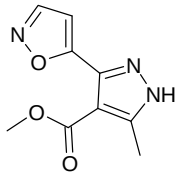
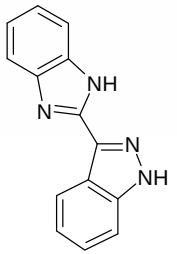


150μM



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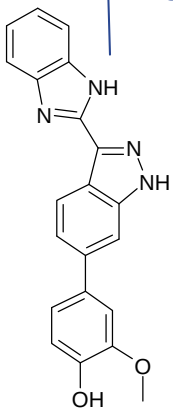
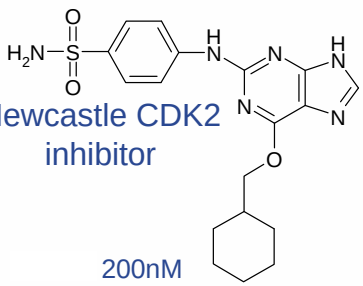


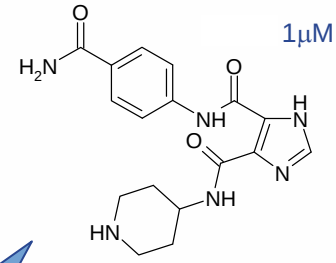
Agouron (promiscuous) Chk1 inhibitor

# PDPK1 – merging fragments

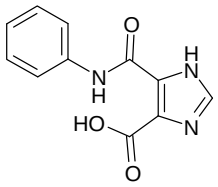


Newcastle CDK2 inhibitor

200nM

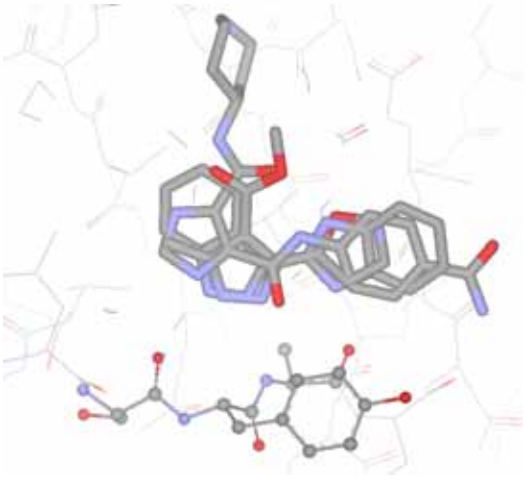


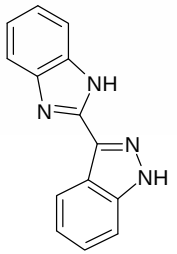
1μM



180μM

Structures of compounds bound to PDPK1





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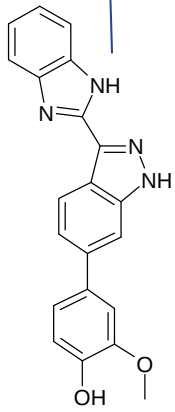

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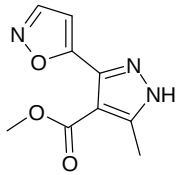
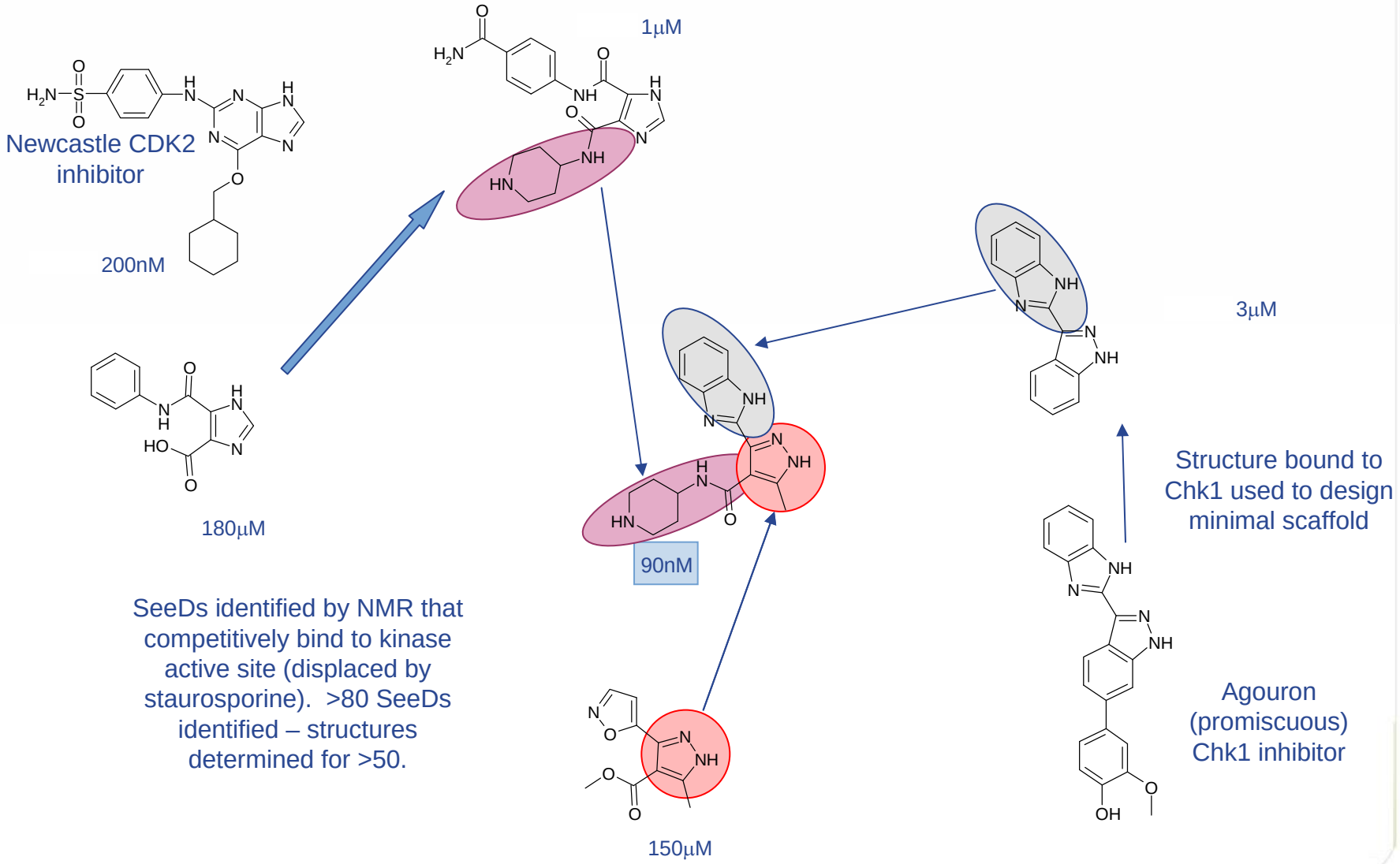


150μM

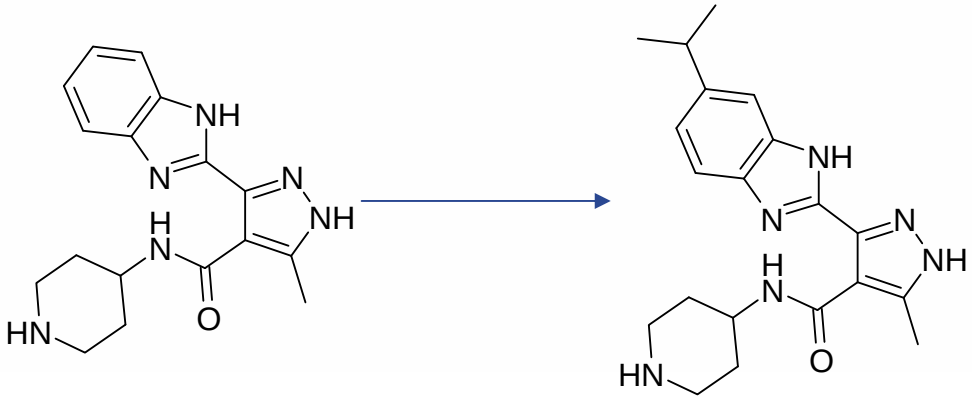
# PDPK1 – merging fragments



# PDPK1 – lead generation



- Series optimisation




- PDPK1 $IC_{50}$ = 15nM
  - Selective vs several important kinases
  - Potent on cells; HCT116 $GI_{50}$ = 80nM
  - Also active on a wide cancer panel
- Appropriate PD marker changes seen *in vivo*
- Aurora kinase activity confounded establishing proof of concept on the biology
  - Lee Walmsley, Jon Moore, Chris Torrance, Stuart Ray, Ijen Chen
  - see Hubbard (2008) J Synch Rad **15** 227

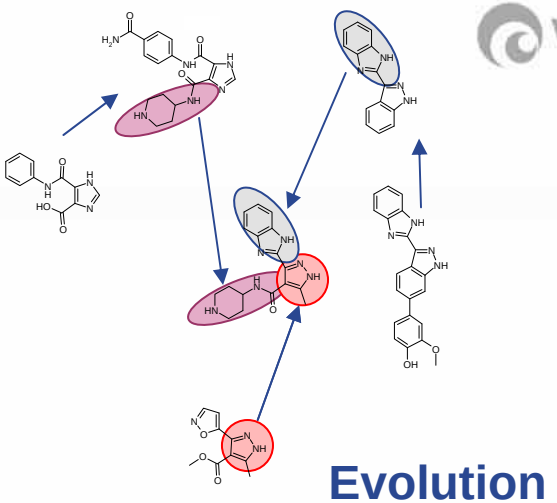
# Overview

Vernalis

- Why?
  - some history
- How?
  - finding fragments that bind
- Some success stories
  - and some that were halted - lessons learnt
- Some issues and discussion points
  - challenging targets
  - which fragments to optimise
  - fragments and chemical space
- Main points and what's next?

# Projects that halted I

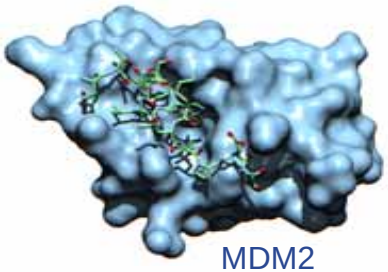





- PDPK1
- Aurora activity of compounds confounding
  - Confidence in the biology put on hold
- LESSON LEARNT
  - Fragment methods can rapidly generate tool compounds to probe biology of new targets

# Projects that halted I

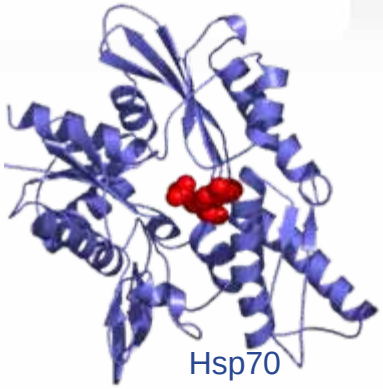



MDM2

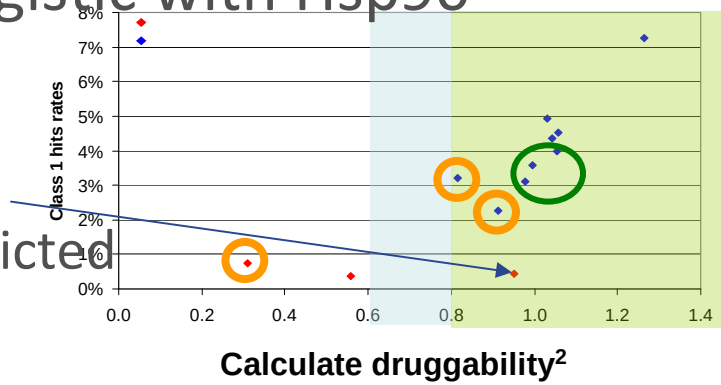
- MDM2
  - An early project (at same time as Hsp90)
  - Required P53 peptide for crystal structure
  - Some nice hits from fragment screen (about 40)
  - Never able to obtain crystal structure with fragment bound
  - Preliminary library chemistry gave flat SAR
  - Mapping of binding by HSQC could not differentiate
  - Other priorities
- LESSON LEARNT
  - A robust model of fragment binding can help evolution
  - Subsequent development of NMR-guided models

# Projects that halted III






- Hsp70
  - Up-regulated in response to Hsp90 inhibition
  - Another ATPase – but active site very different
- Attractive as potentially synergistic with Hsp90 inhibitors
- Not many fragment hits
  - The target that falls off the predicted druggability scale




- Evidence that active site quite mobile
- LESSON LEARNT
  - Low hit rate from experimental screening should raise a flag for potential issues

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# Challenging Targets



- Can find fragments that bind
  - Orthogonal biophysical methods can validate and characterise fragment binding

# Challenging Targets

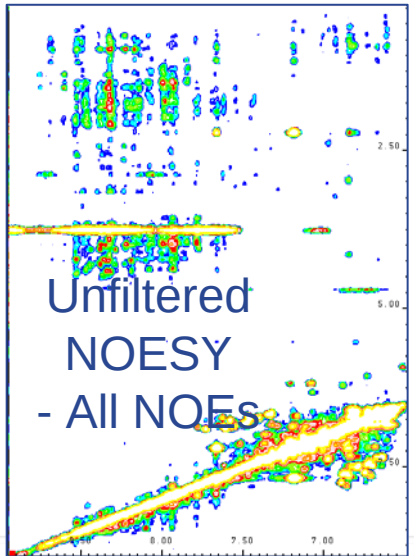


- Can find fragments that bind
- Evolution requires robust model of fragment binding
- Best model is from X-ray structure
  - But sometimes high affinity ligand required for structure

# Challenging Targets



- Can find fragments that bind
- Evolution requires robust model of fragment binding
- Best model is from X-ray structure
- NMR methods can provide sufficient quality of model
  - Experiments can be filtered to reveal just the interactions between protein and ligand



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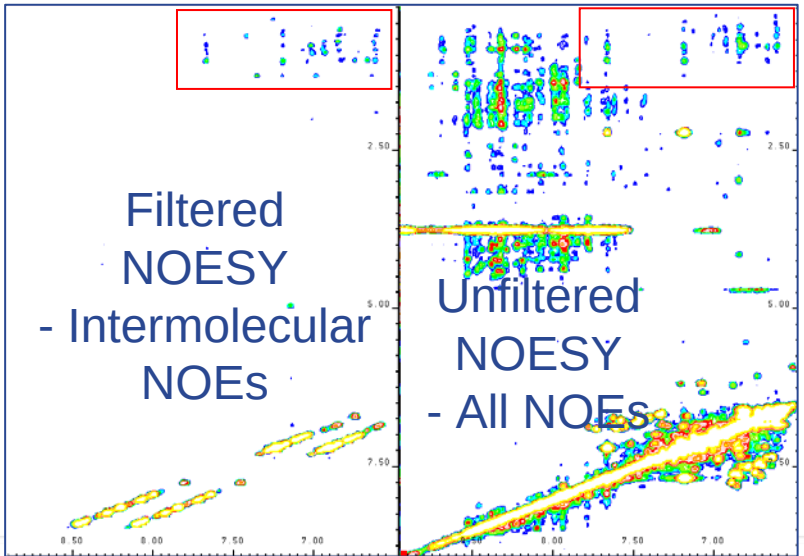


Protein/ligand

# Challenging Targets



- Can find fragments that bind
- Evolution requires robust model of fragment binding
- Best model is from X-ray structure
- NMR methods can provide sufficient quality of model
  - Experiments can be filtered to reveal just the interactions between protein and ligand
  - Have developed leads from fragments using NMR models
  - High affinity ligands give X-ray structures that confirm model
- Hear Ben Davis later today

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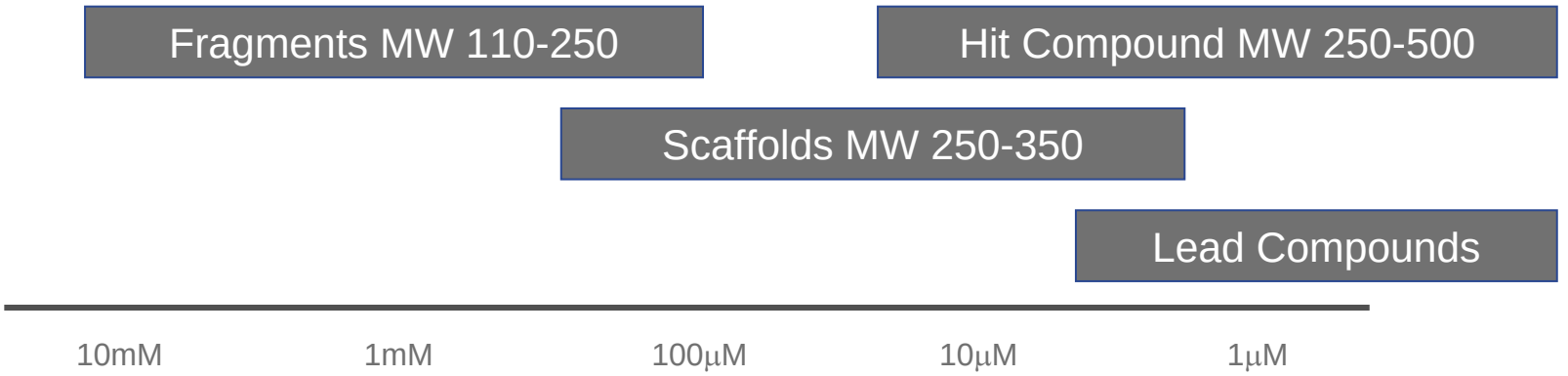
# Why size matters

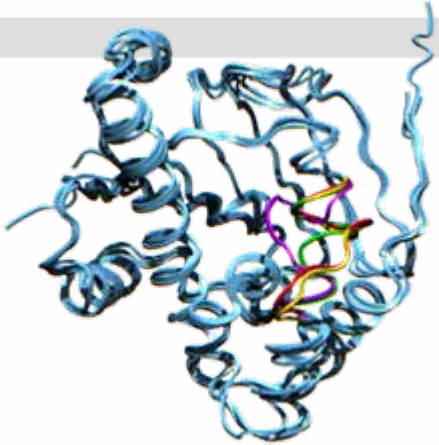


- A small number of fragments can sample a large chemical space
- Fink and Reymond estimate that available chemical space increases 8.3x per heavy atom (JCIM, 2007. 47:342)
  - $10^3$ fragments of ave MW 190 are equivalent to $10^{18}$ compounds of ave MW 450
  - This is equivalent to $>10^9$ compounds of ave MW 280
- Beware the super-sized fragment !!



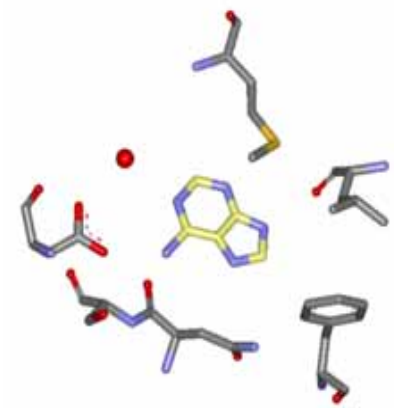
# Fragments and chemical space

# Hsp90: Fragment screen

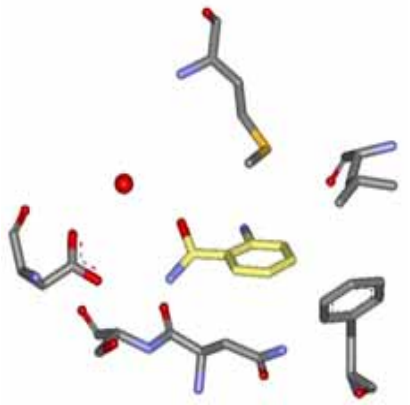


Vernalis
FBLD 2010

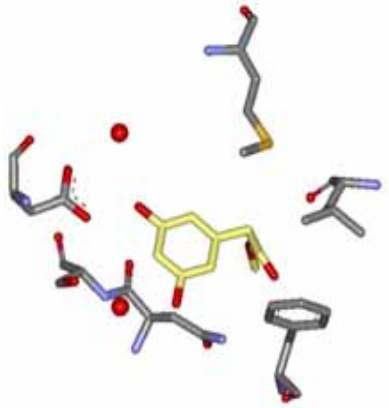
- Targetting the N-terminal domain – an ATPase
- FBLD programme began in early 2002
  - - screened library of 729 fragments by NMR
- 17 fragments identified
  - Crystal structures for most fragments binding to Hsp90



Adenine



Amide



Resorcinol

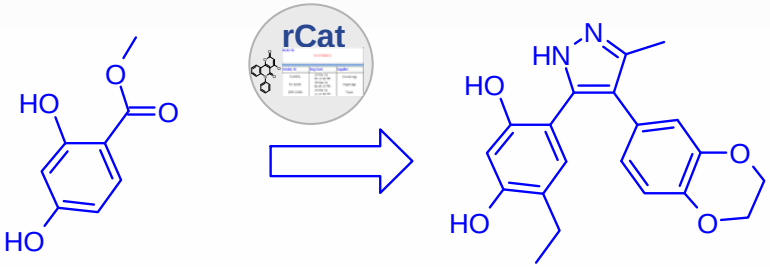
# Hsp90 example I



- Growing fragments

# Hsp90 – AUY922 story





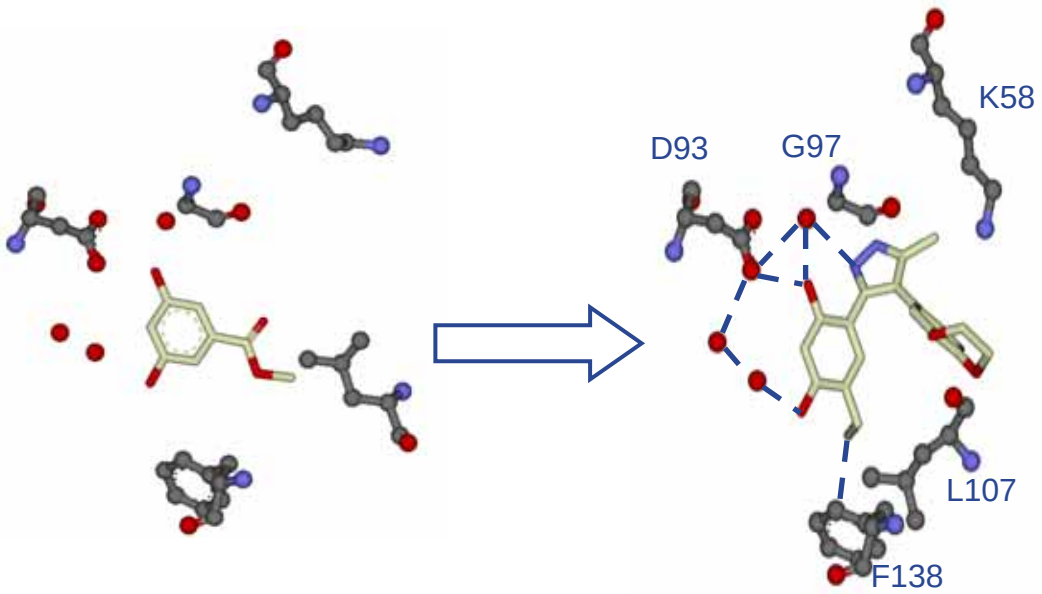

FP $IC_{50}$ = ~1mM

Starting fragment

FP $IC_{50}$ = 0.28µM
$GI_{50}$ = 6µM

Hit from SAR by catalogue

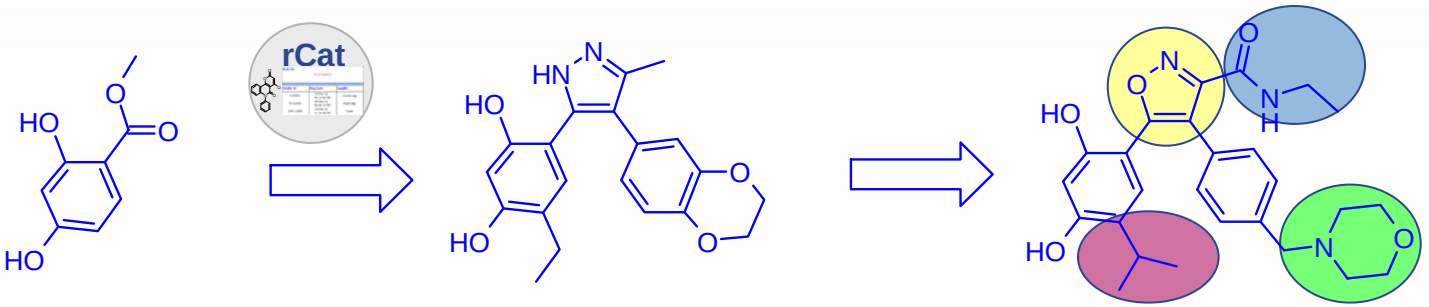
See poster from Michele Schulz on designing fragment library to maximally represent a compound collection




- $GI_{50}$ in HCT116 colon cell line

# Hsp90 – AUY922 story

Vernalis
FBLD 2010




FP $IC_{50}$ = ~1mM

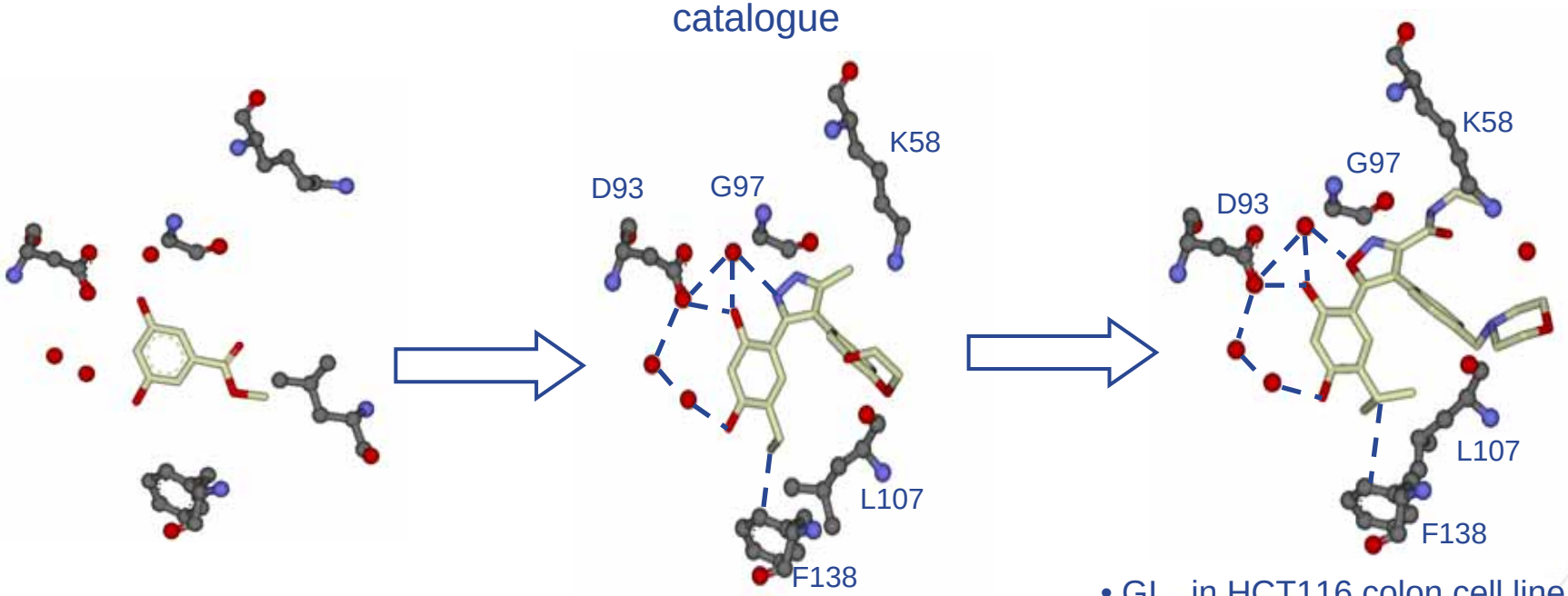
Starting fragment

FP $IC_{50}$ = 0.28μM
$GI_{50}$ = 6μM

Hit from SAR by catalogue

FP $IC_{50}$ = 0.009μM
$GI_{50}$ = 0.014μM

Phase II Candidate




- $GI_{50}$ in HCT116 colon cell line

# Hsp90 example II

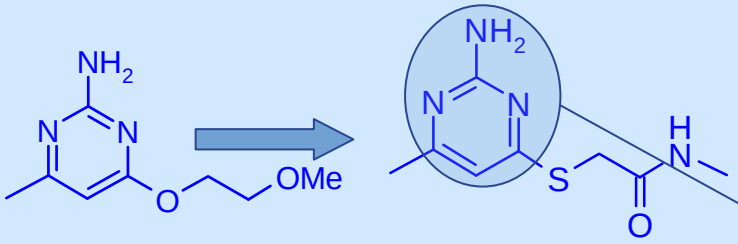


- Merging information from virtual screening, existing compounds and other fragment hits to design oral backup

# Hsp90 – BEP800 story

Vernalis
FBLD 2010

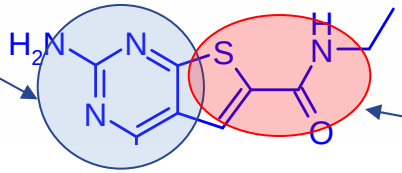
**Fragment** **Evolved fragment**



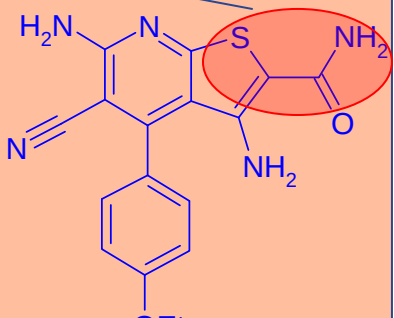
VER-26734
FP $IC_{50}$>5mM

VER-52959
FP $IC_{50}$=535µM

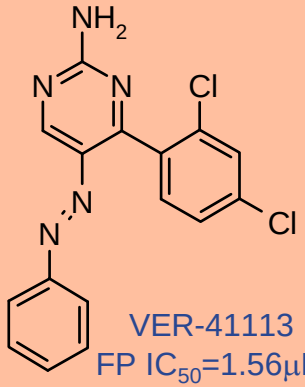
VER-82576
NVP-BEP800
FP $IC_{50}$=0.058µM
HCT116 $GI_{50}$=0.161µM
BT474 $GI_{50}$=0.057µM



**Virtual Screening Hit**

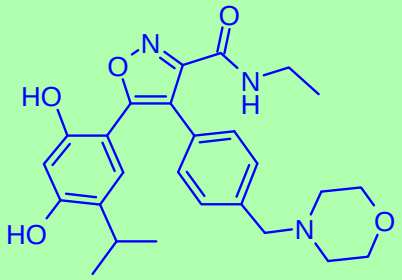


VER-45616
FP $IC_{50}$=0.9µM



VER-41113
FP $IC_{50}$=1.56µM

**Virtual Screening Hit**

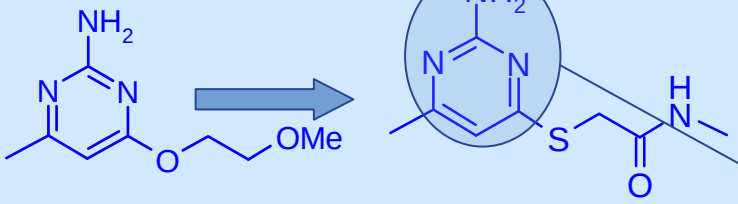


NVP-AUY922

# Hsp90 – BEP800 story

Vernalis
FBLD 2010

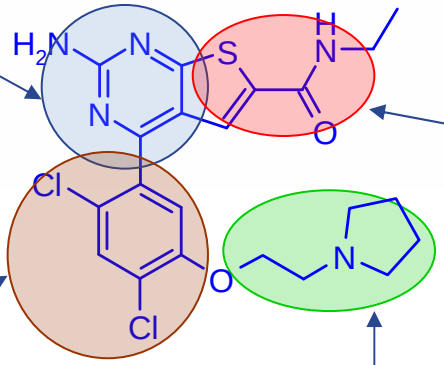
**Fragment** **Evolved fragment**



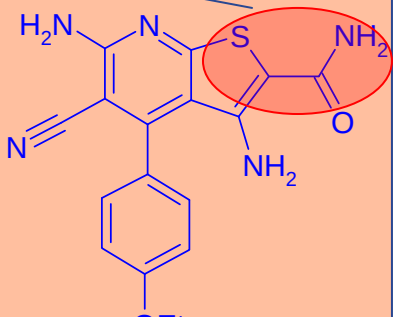
VER-26734
FP $IC_{50}$>5mM

VER-52959
FP $IC_{50}$=535µM

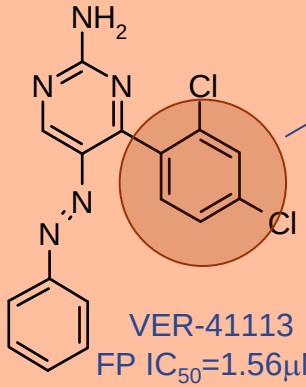
VER-82576
NVP-BEP800
FP $IC_{50}$=0.058µM
HCT116 $GI_{50}$=0.161µM
BT474 $GI_{50}$=0.057µM



**Virtual Screening Hit**

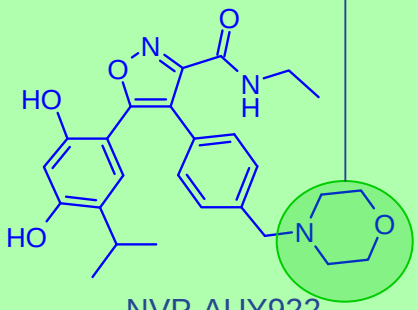


OEt
VER-45616
FP $IC_{50}$=0.9µM



VER-41113
FP $IC_{50}$=1.56µM

**Virtual Screening Hit**



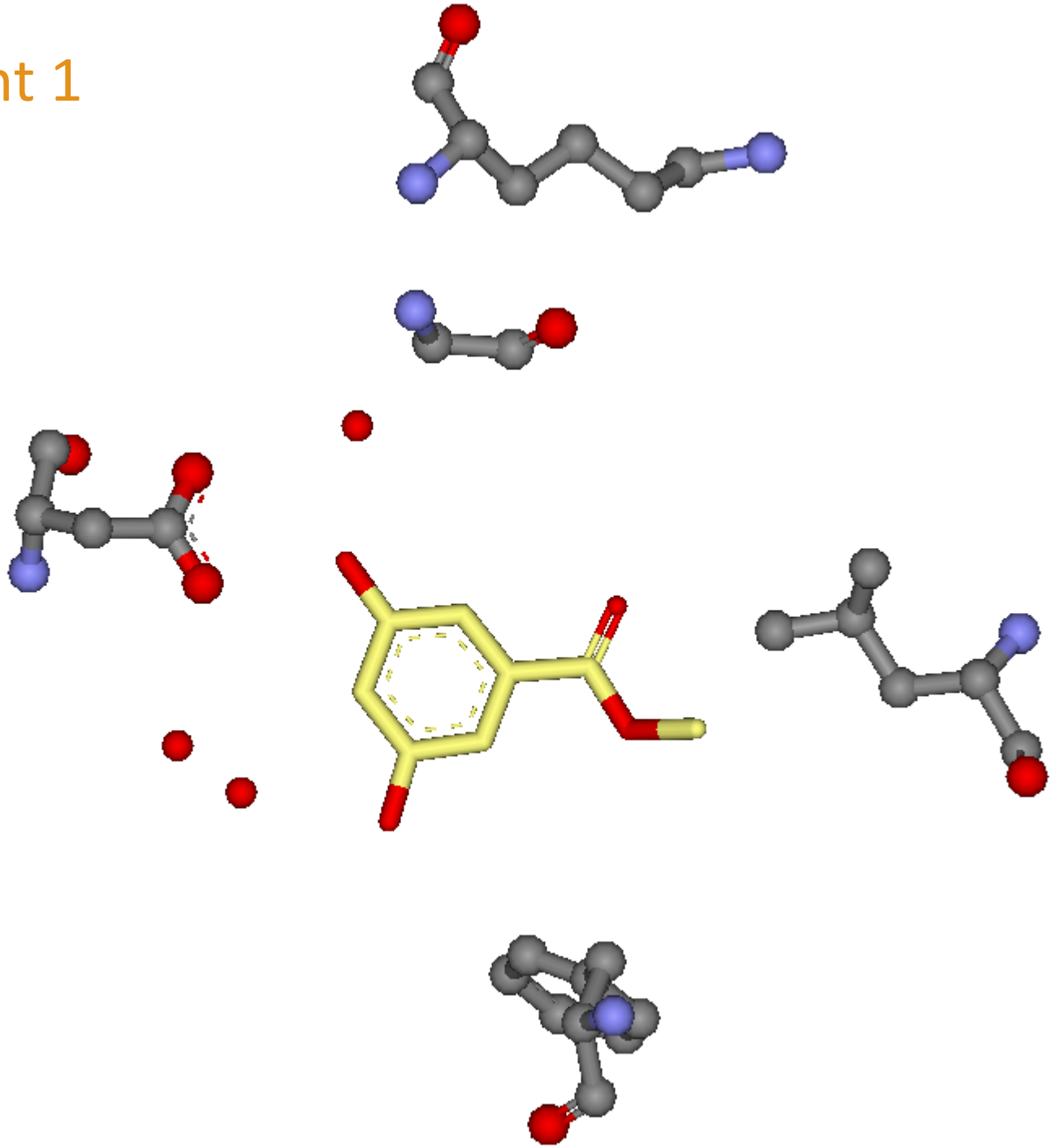
NVP-AUY922

# Fragments and Chemical Space

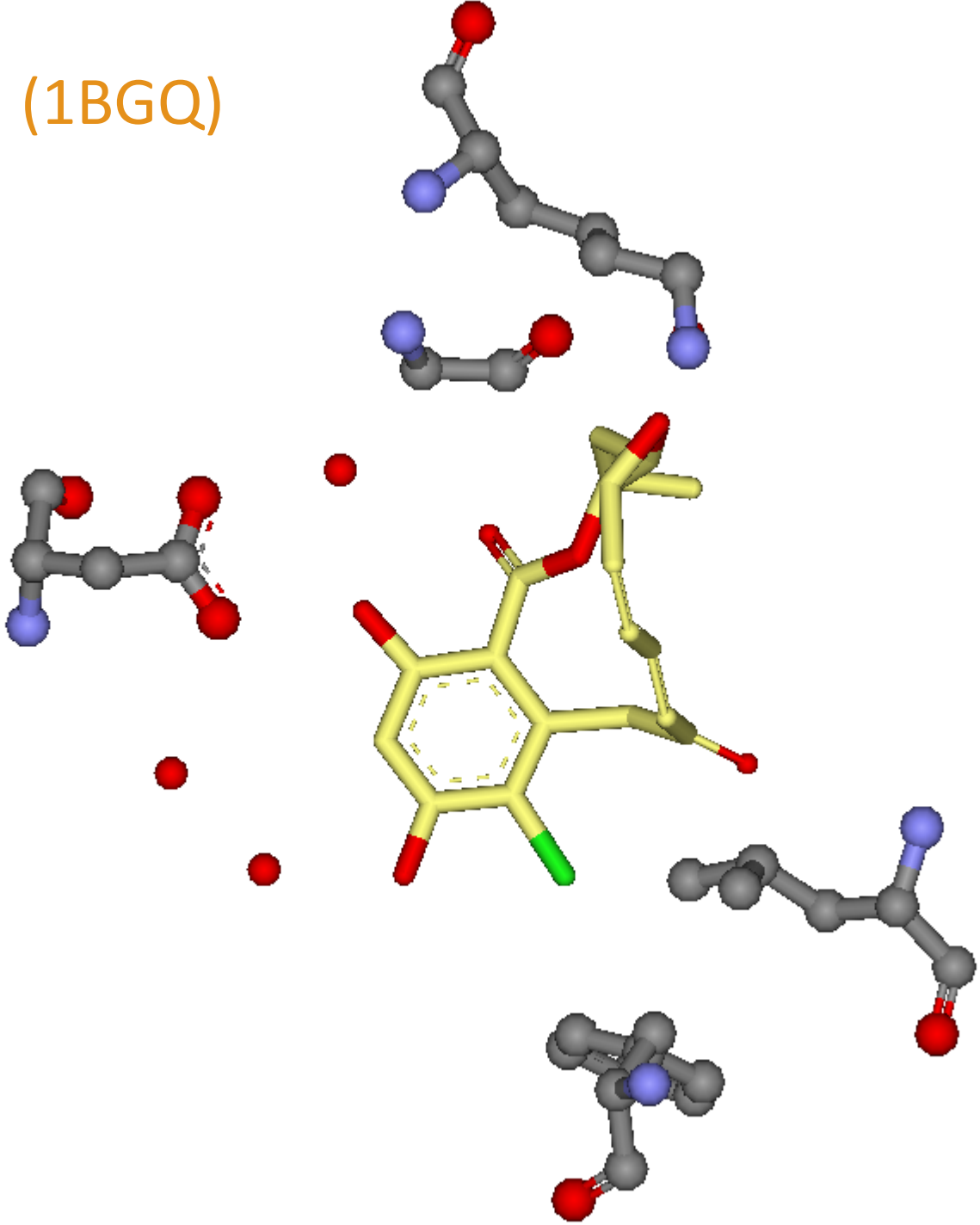


- The following is a survey of published HSP90 inhibitors for which crystal structures released
  - 4 letter code is deposited PDB code
- Comparison with results of first fragment screen in 2002 which identified 17 (23) fragments
- Four classes of inhibitors
  1. Resorcinol analogues (AUY922)

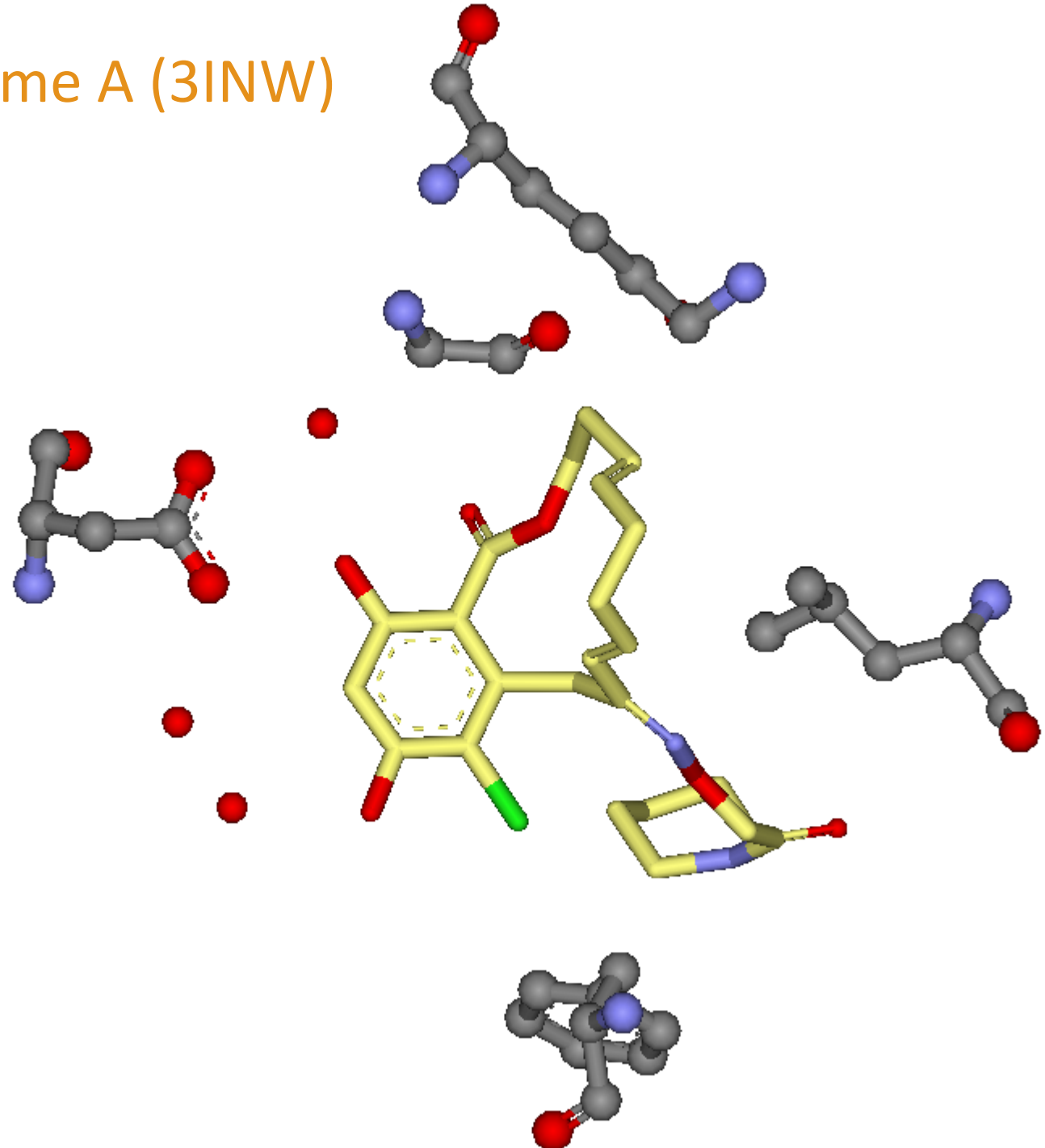
# Fragment 1



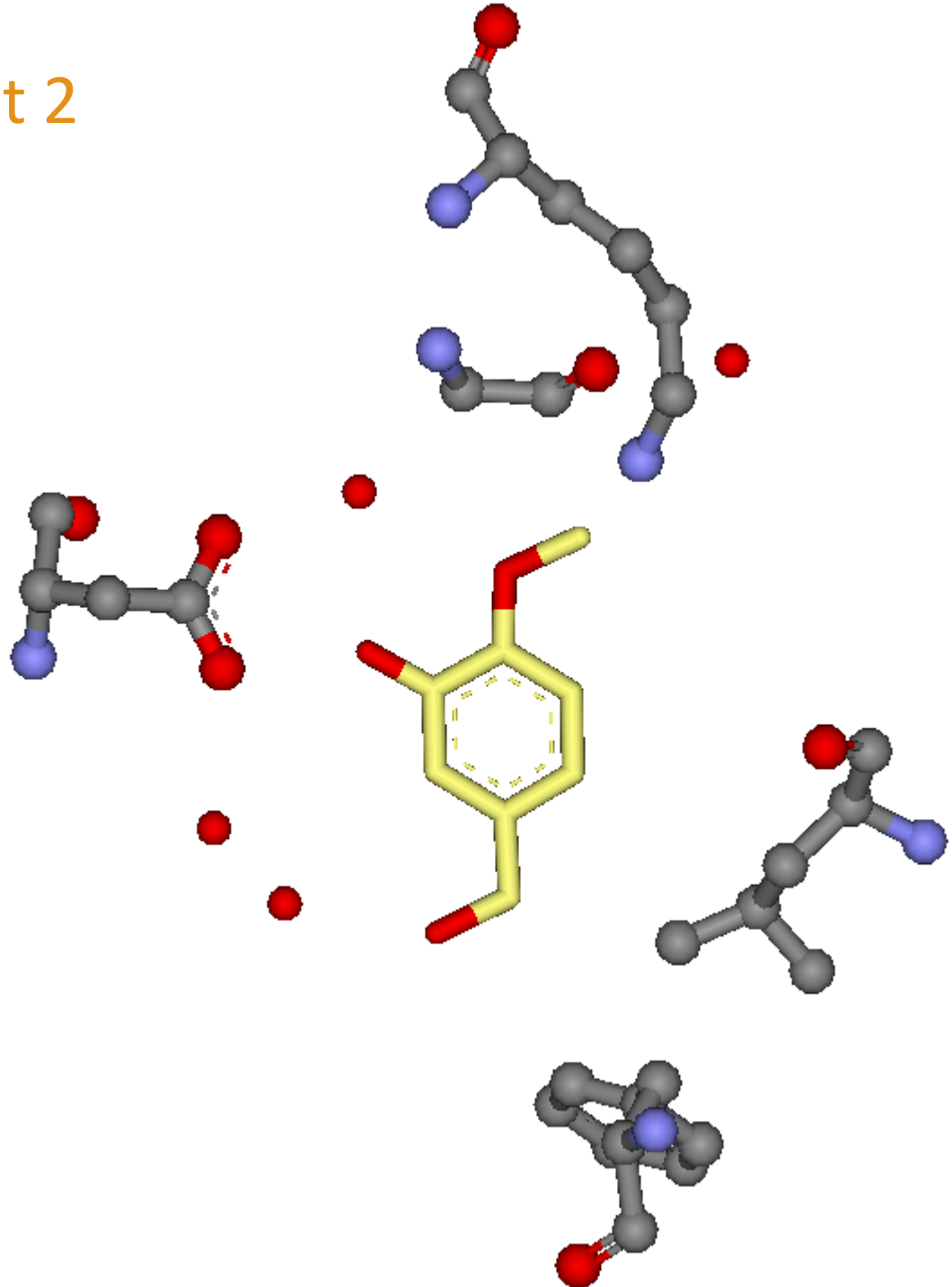
# Radicicol (1BGQ)



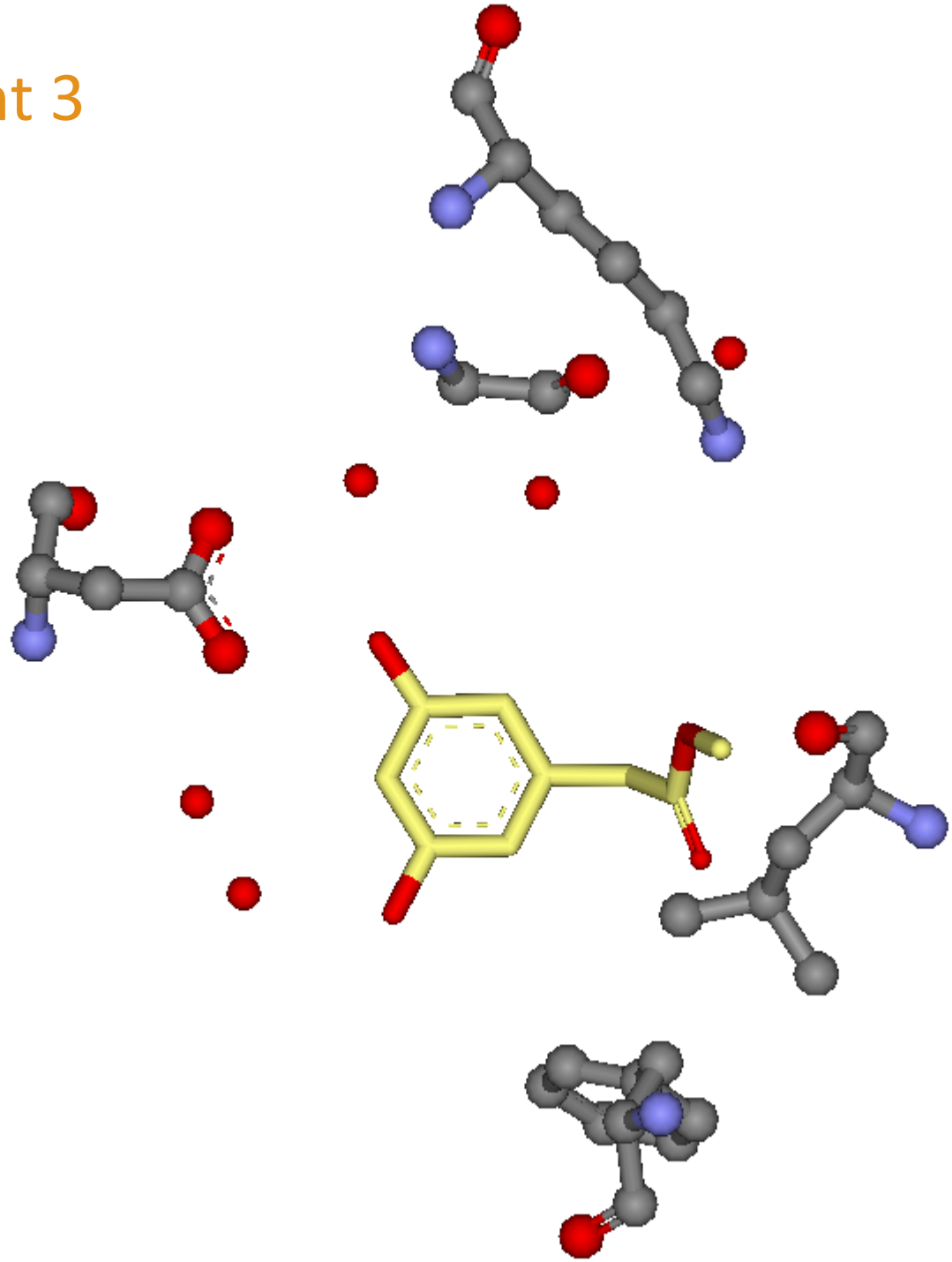
# Pochoxime A (3INW)



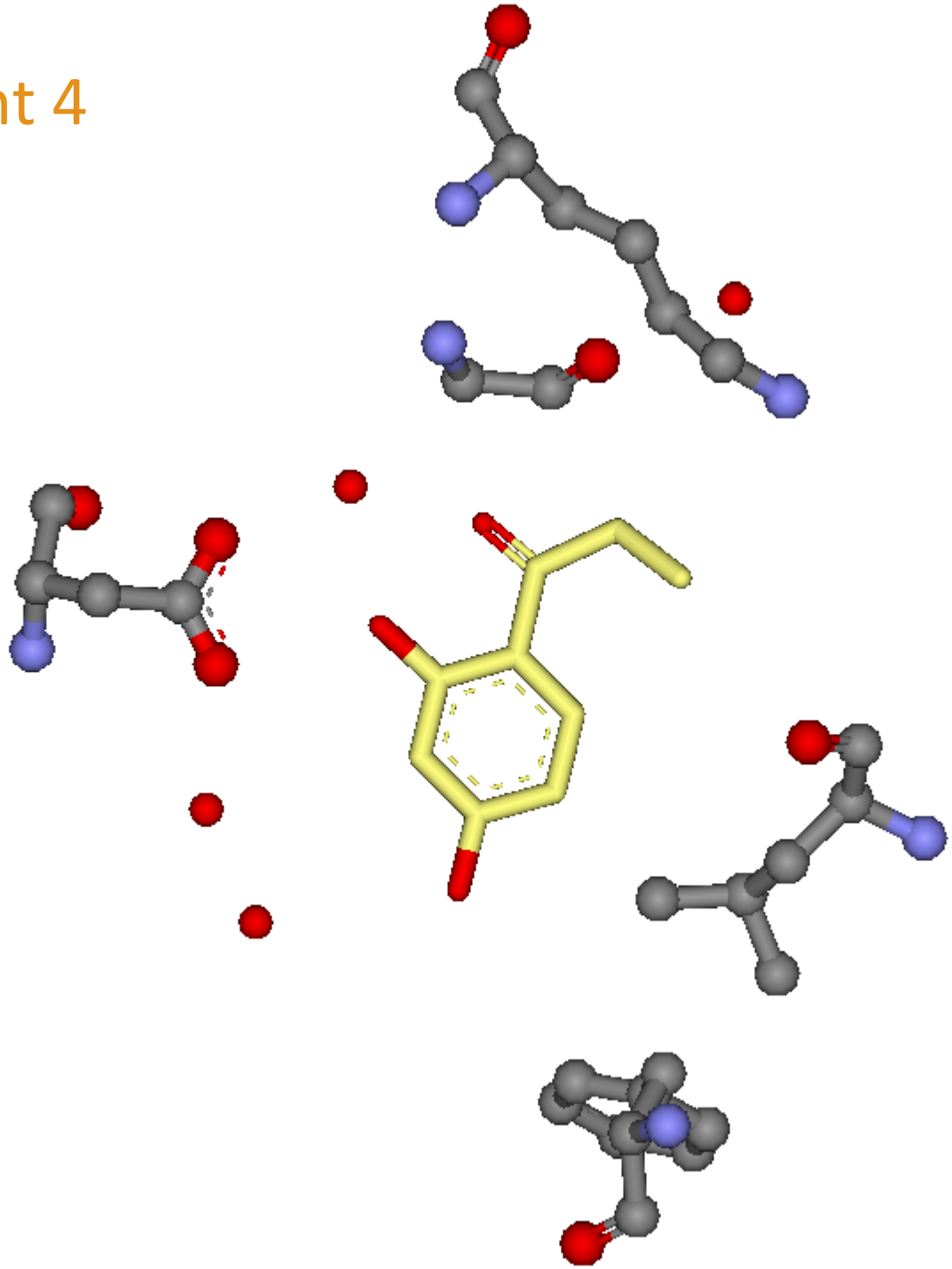
# Fragment 2



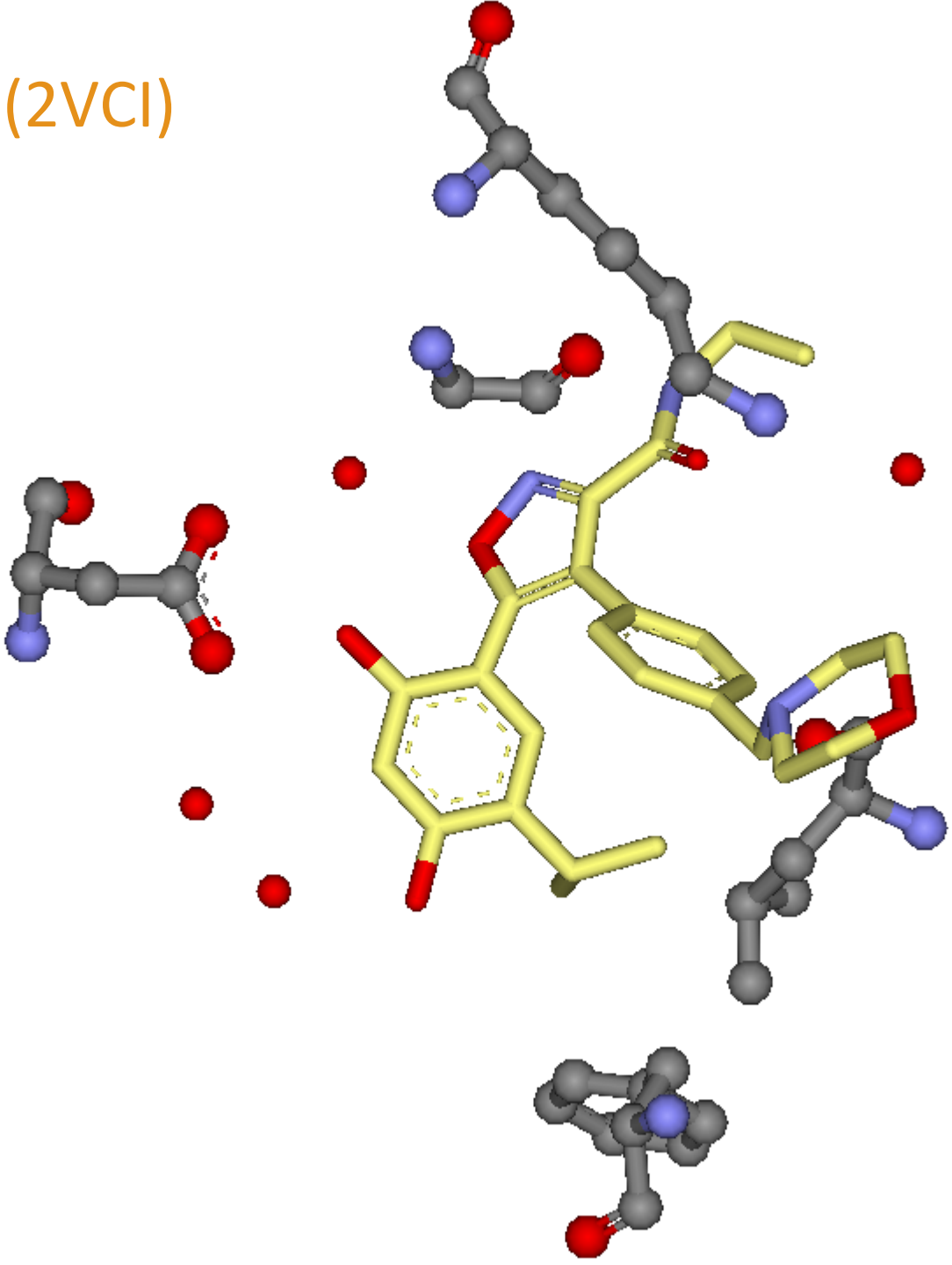
# Fragment 3



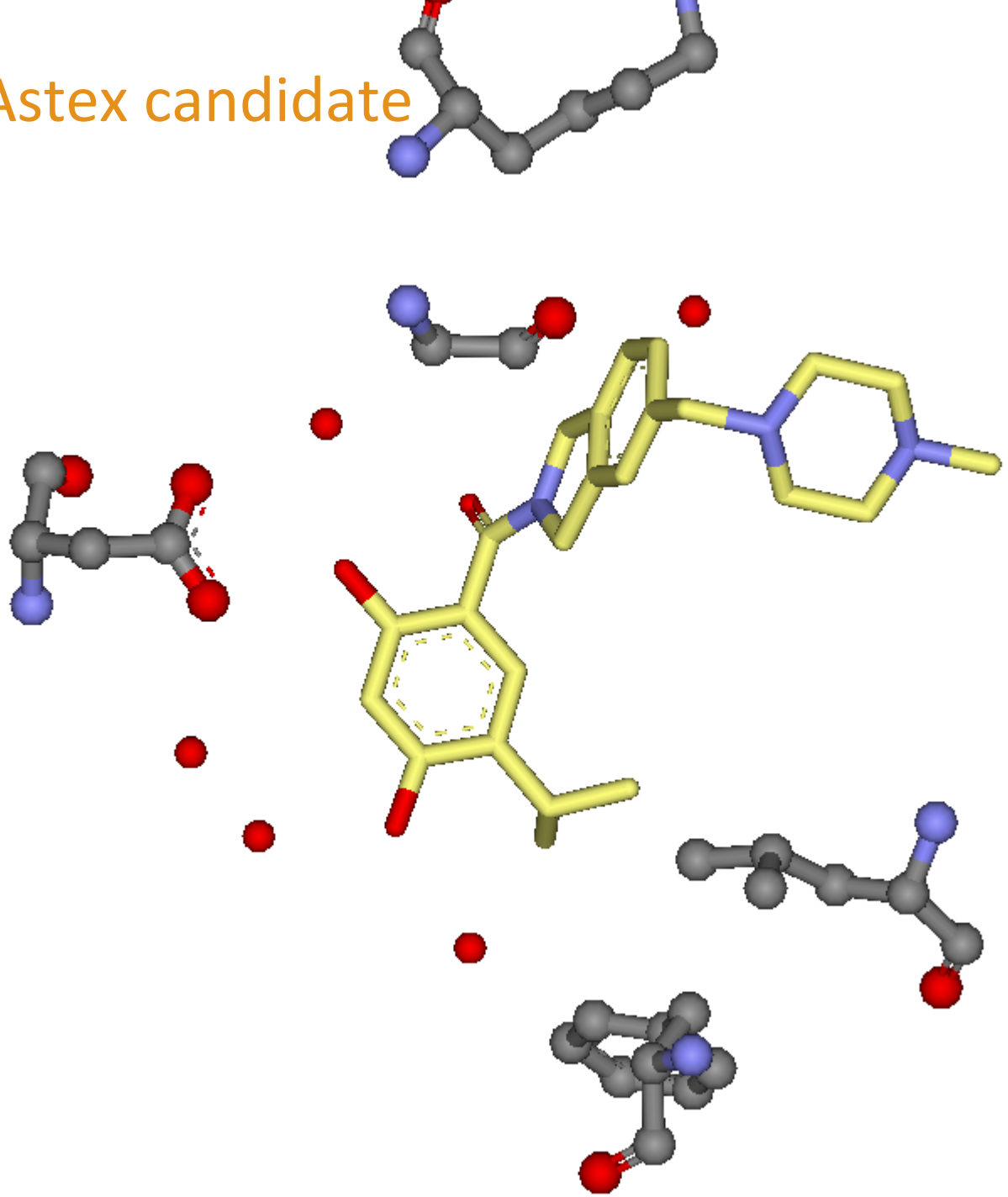
# Fragment 4



# AUY922 (2VCI)



# 2XJX – Astex candidate



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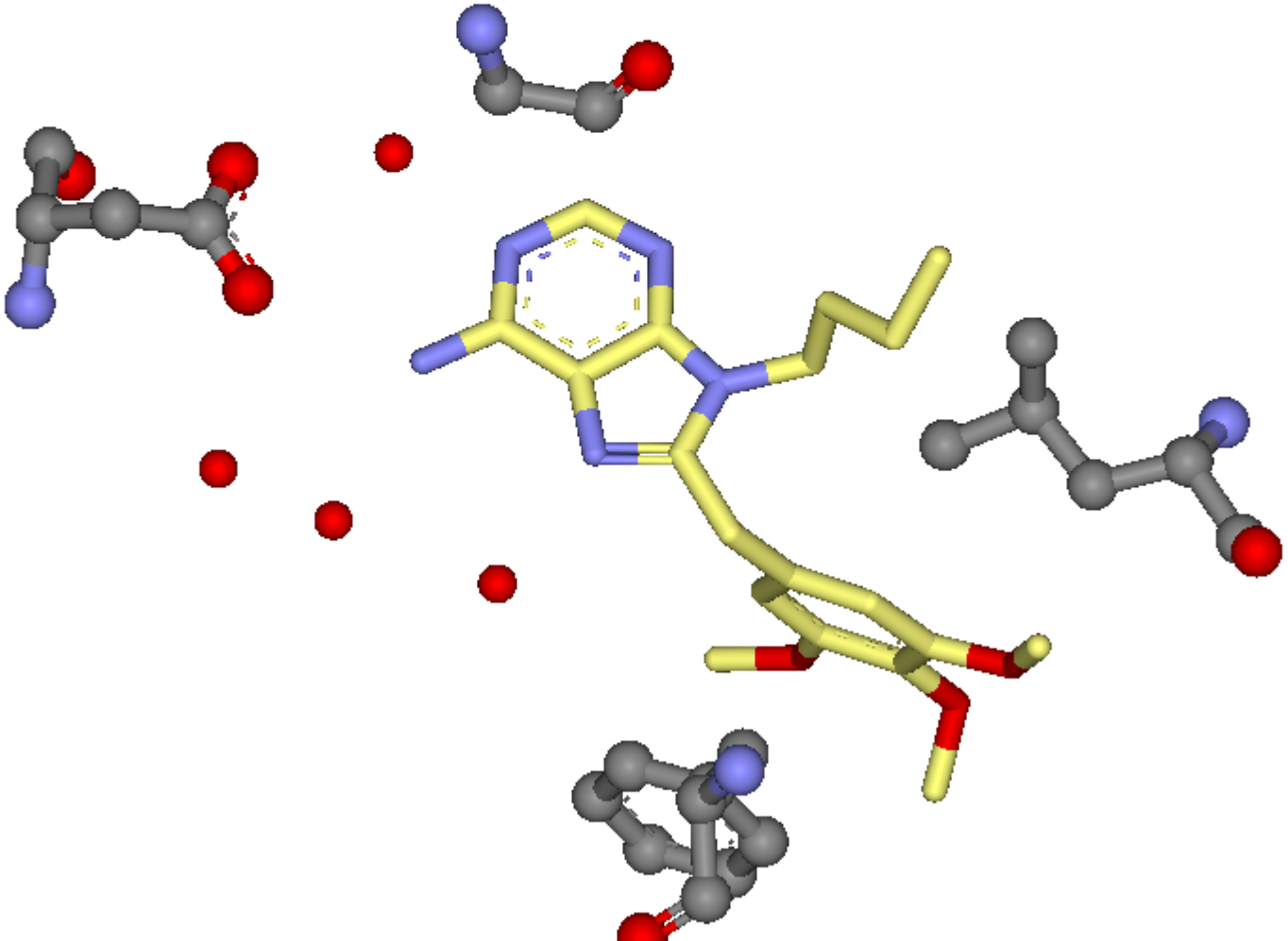
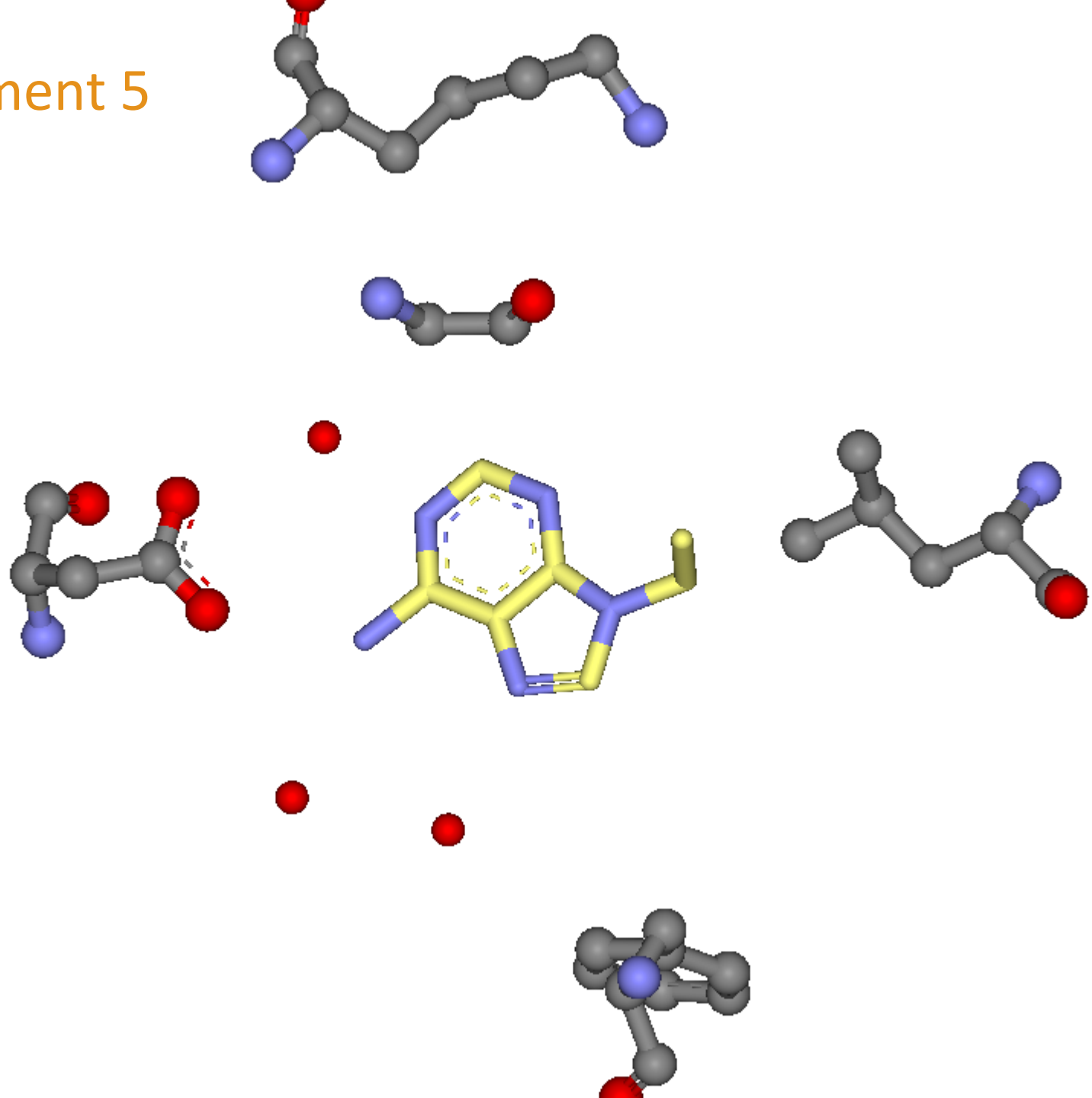
  2. Purine analogues (BEP800)

# PU3 (1UY6)

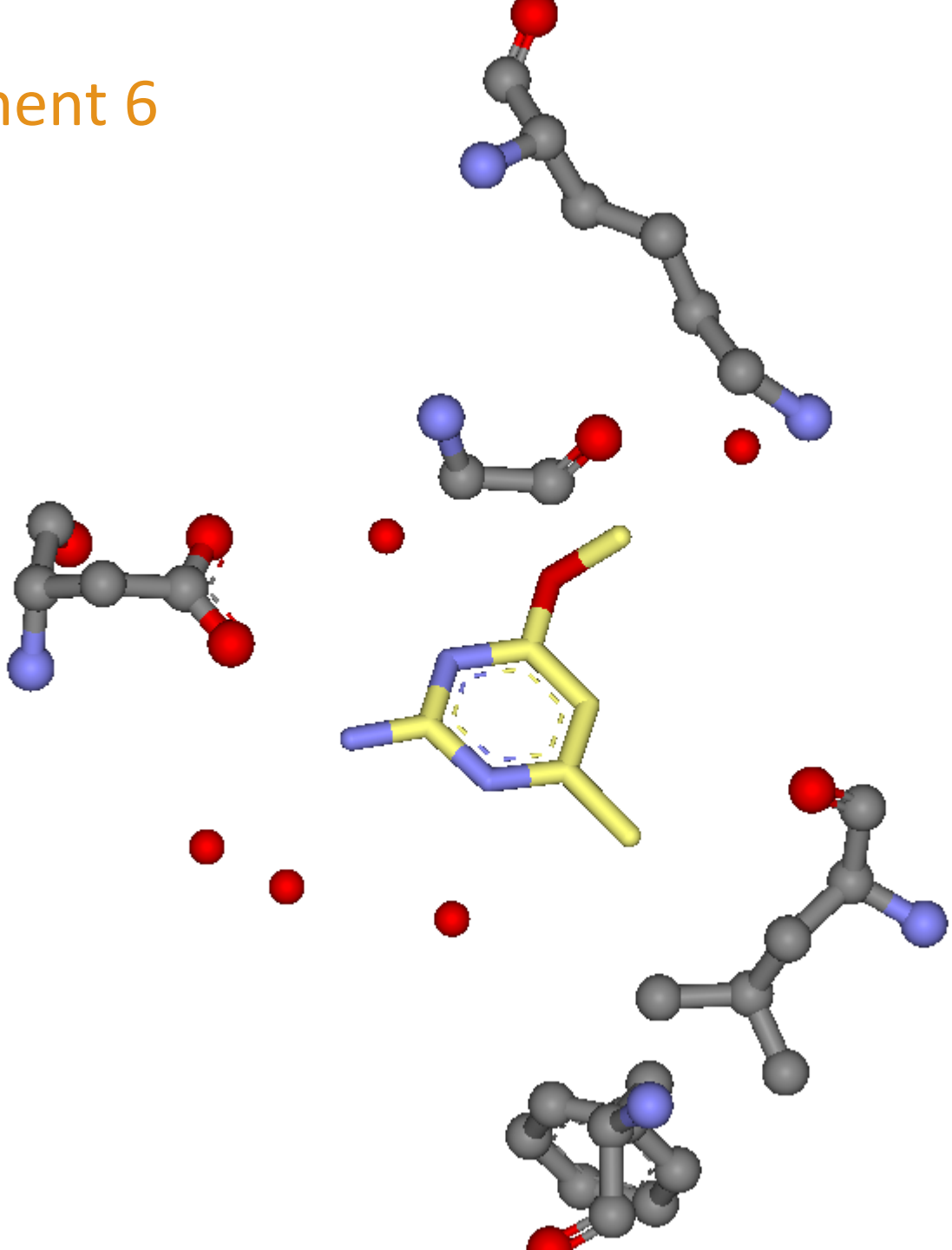
- Ligand-based design based on purine scaffold



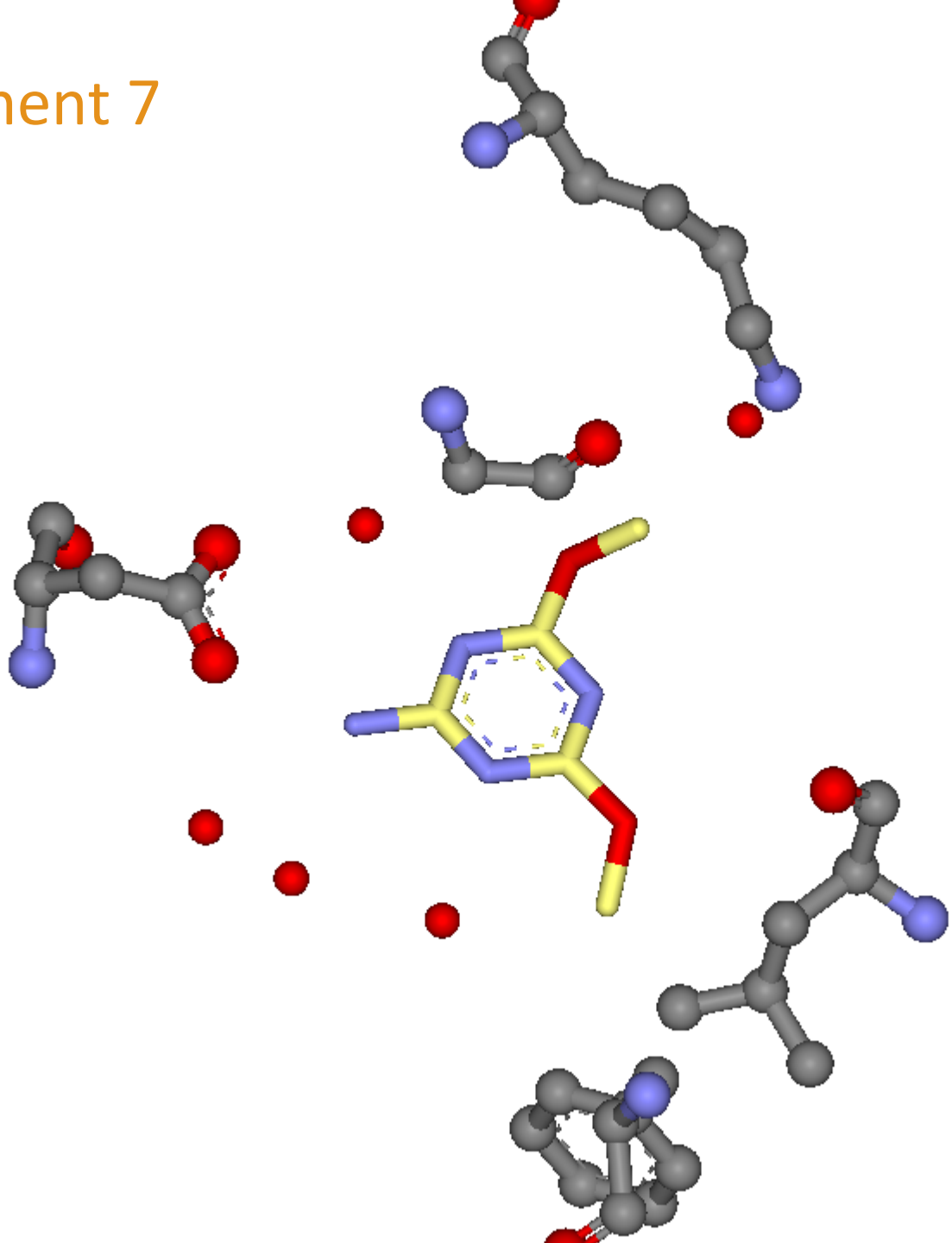
Fragment 5



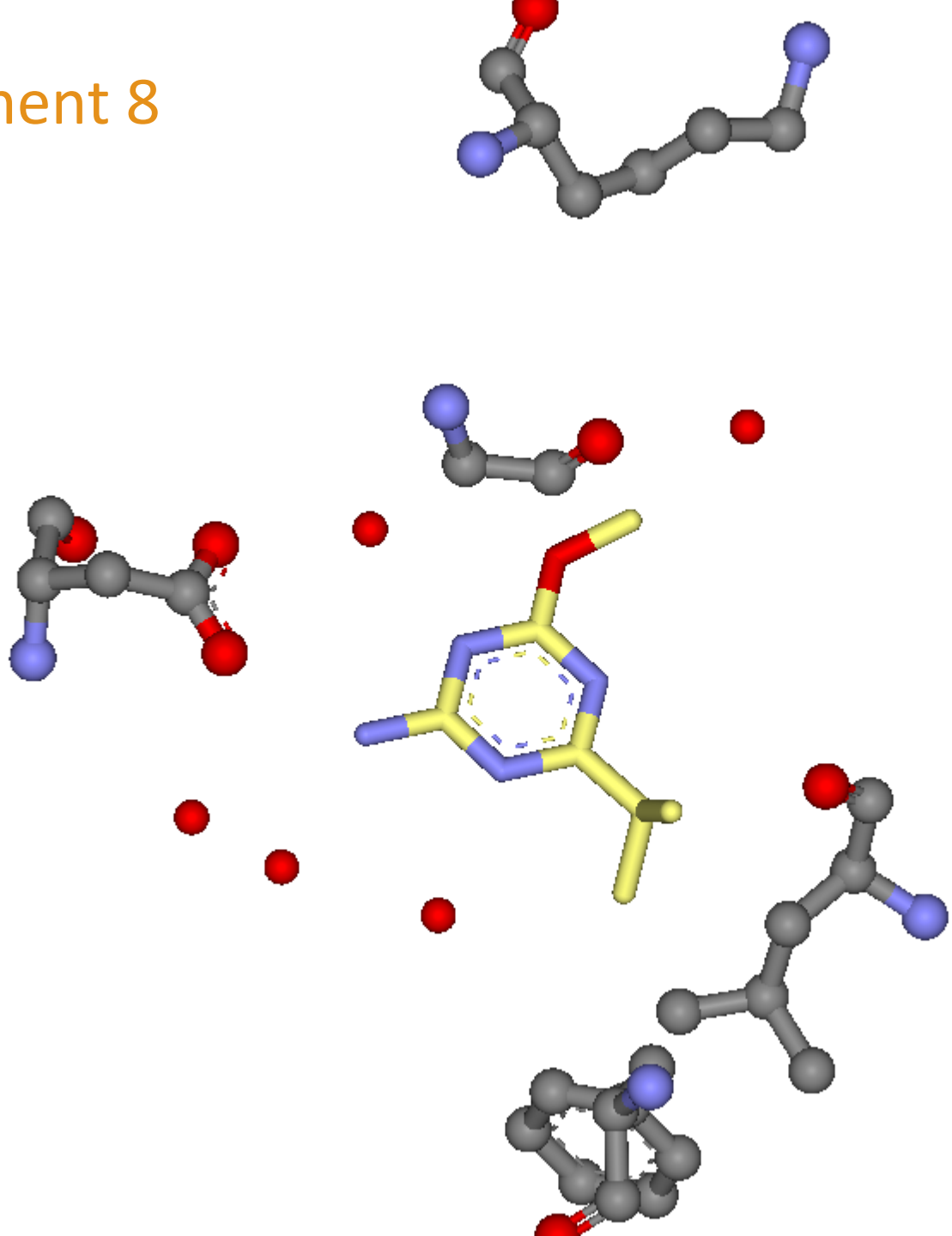
# Fragment 6



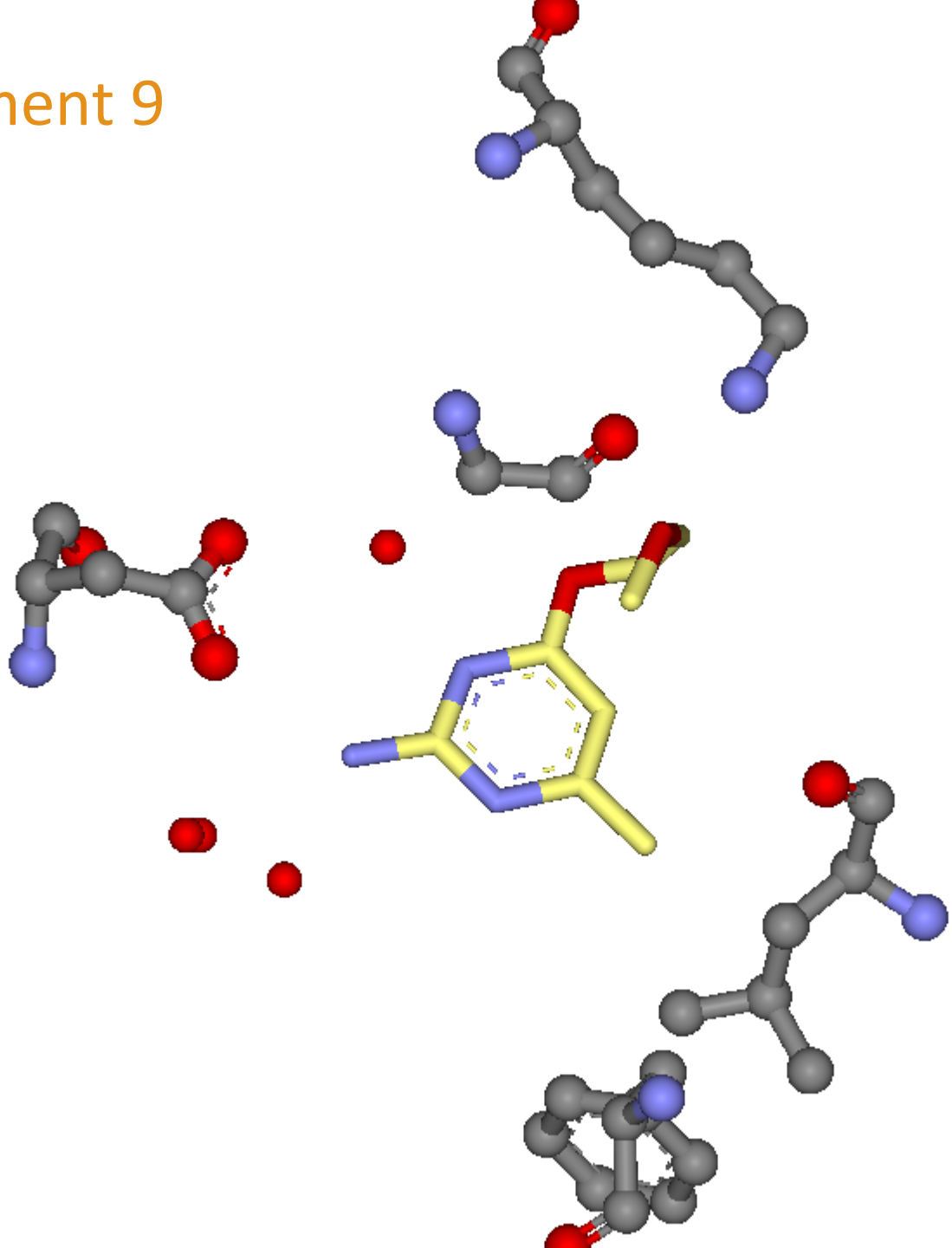
# Fragment 7



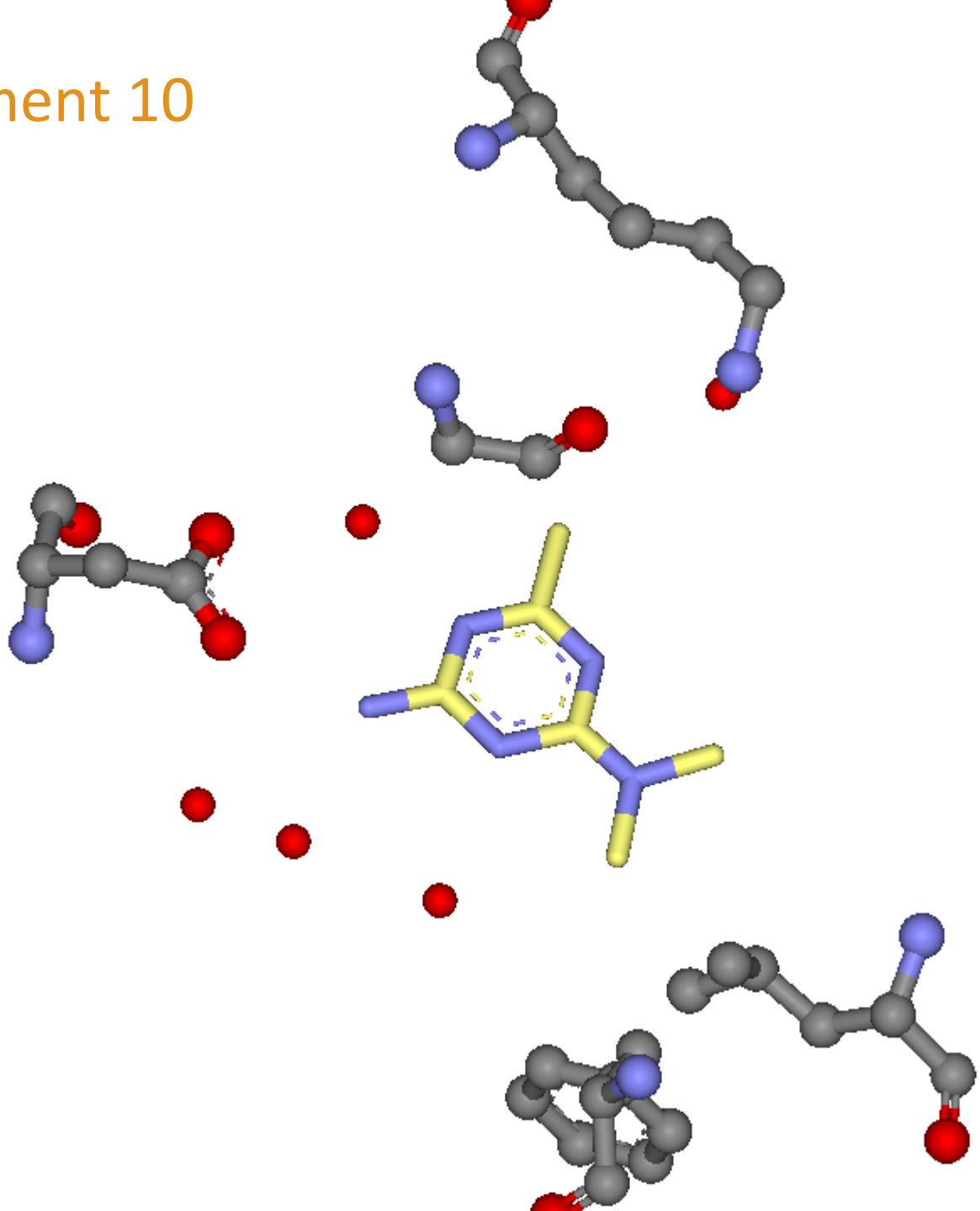
# Fragment 8



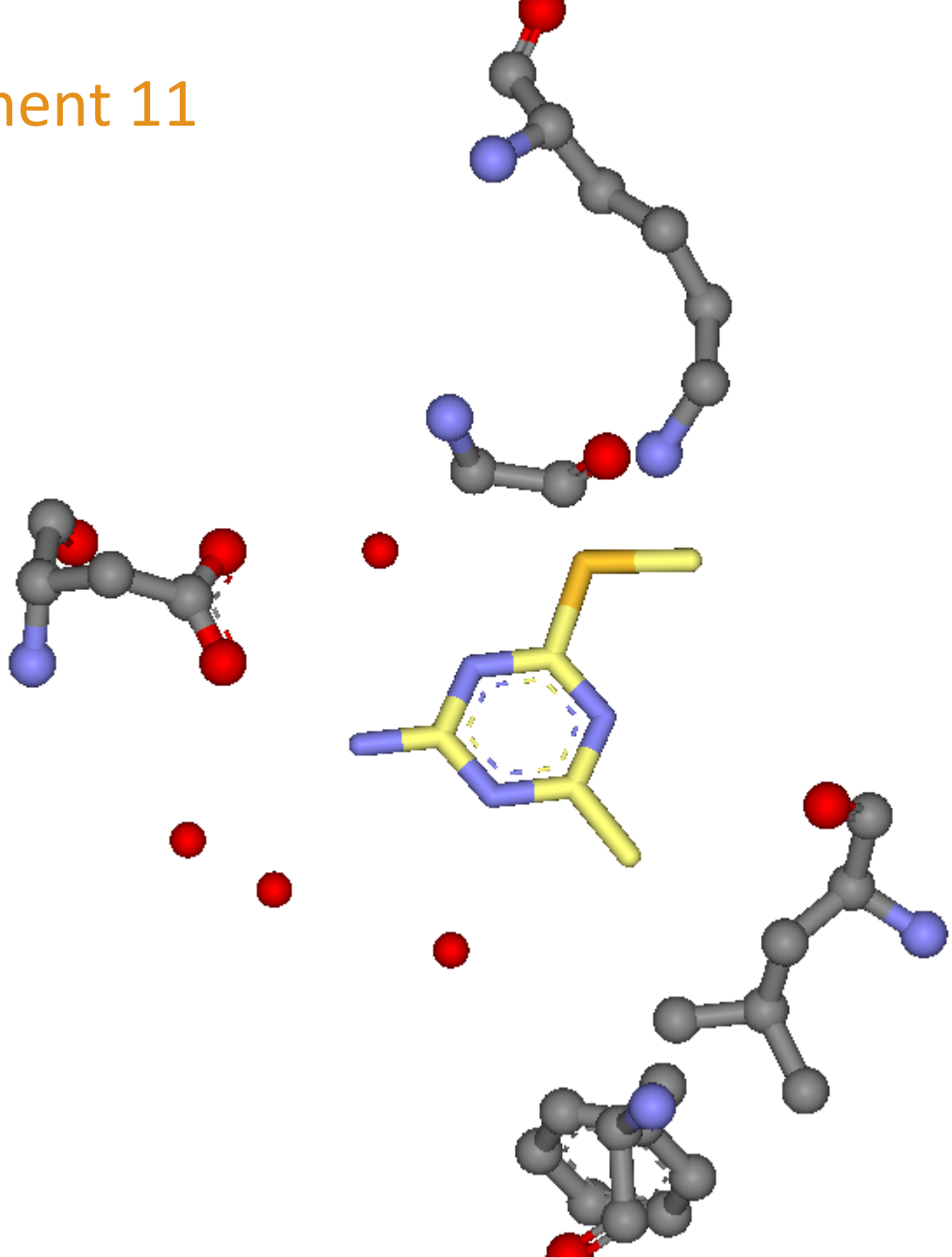
# Fragment 9



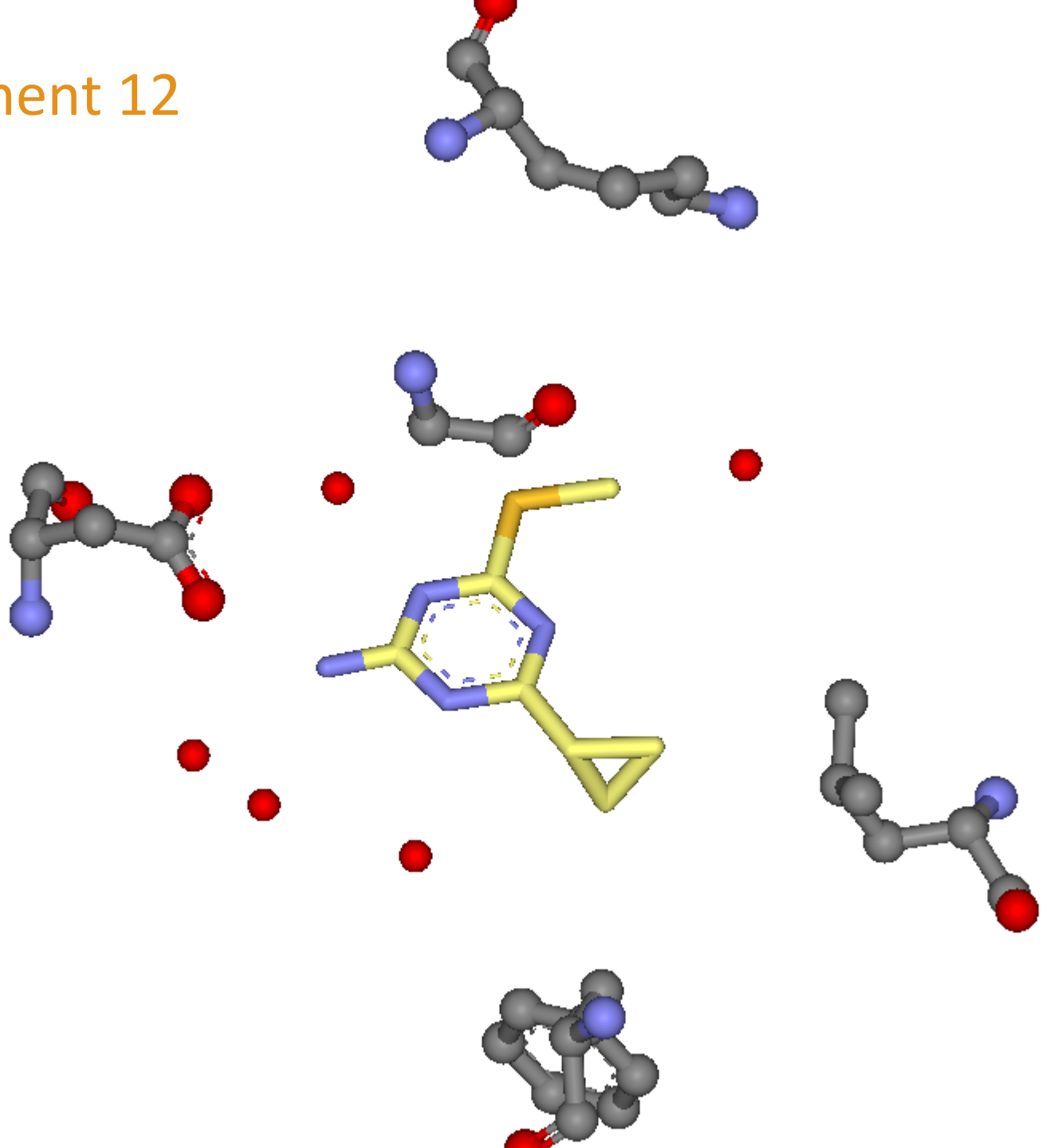
# Fragment 10



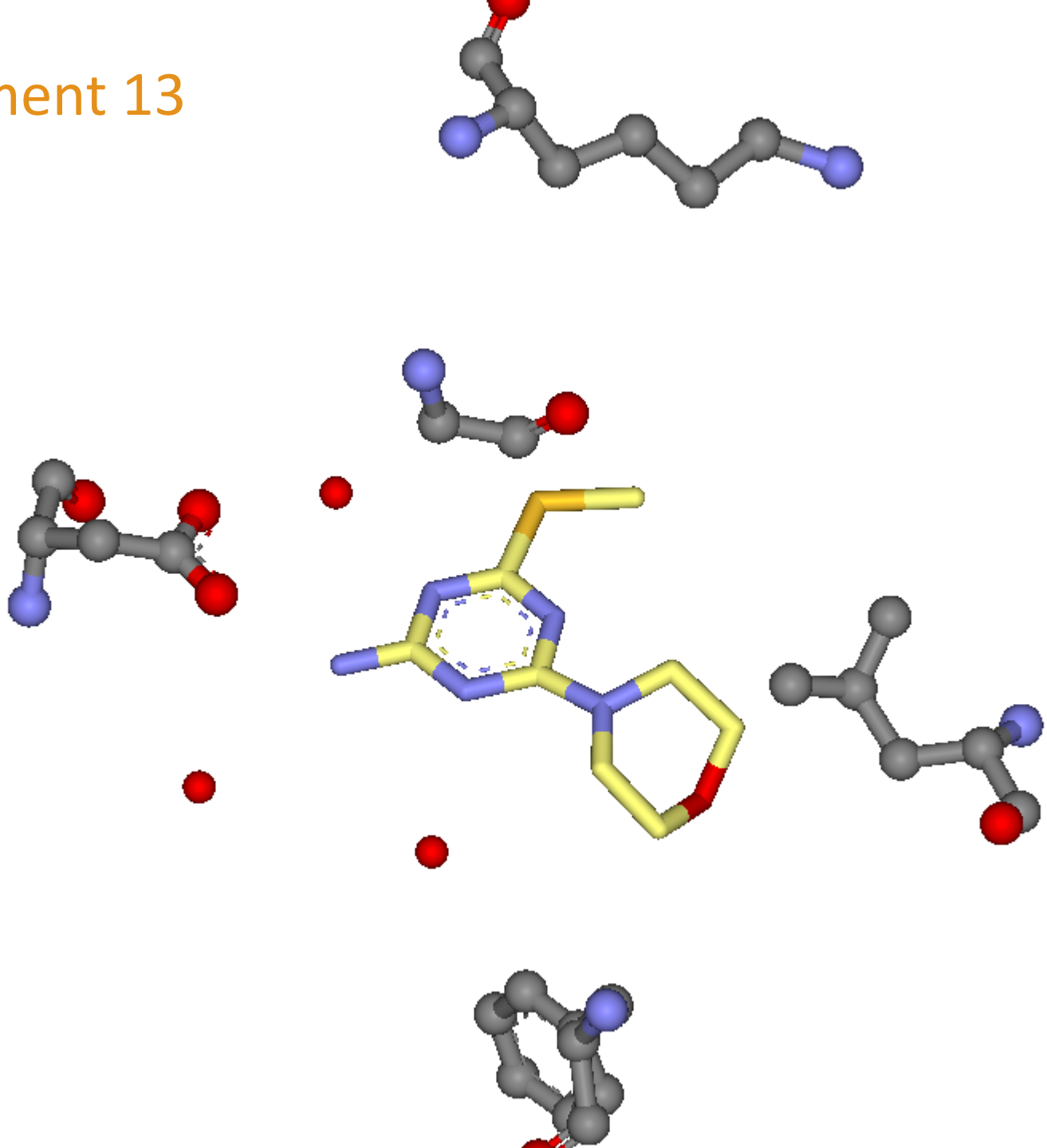
# Fragment 11



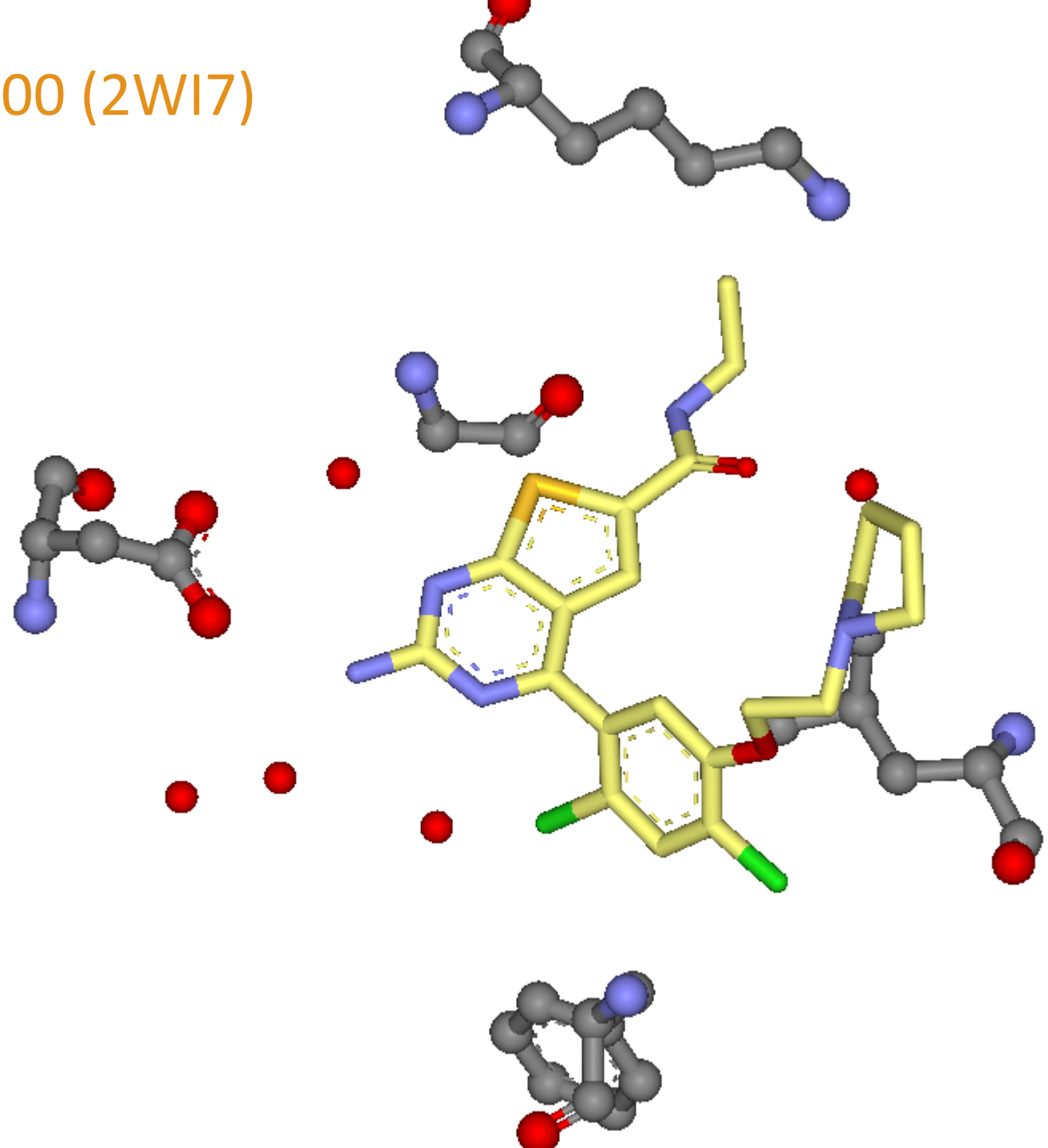
# Fragment 12



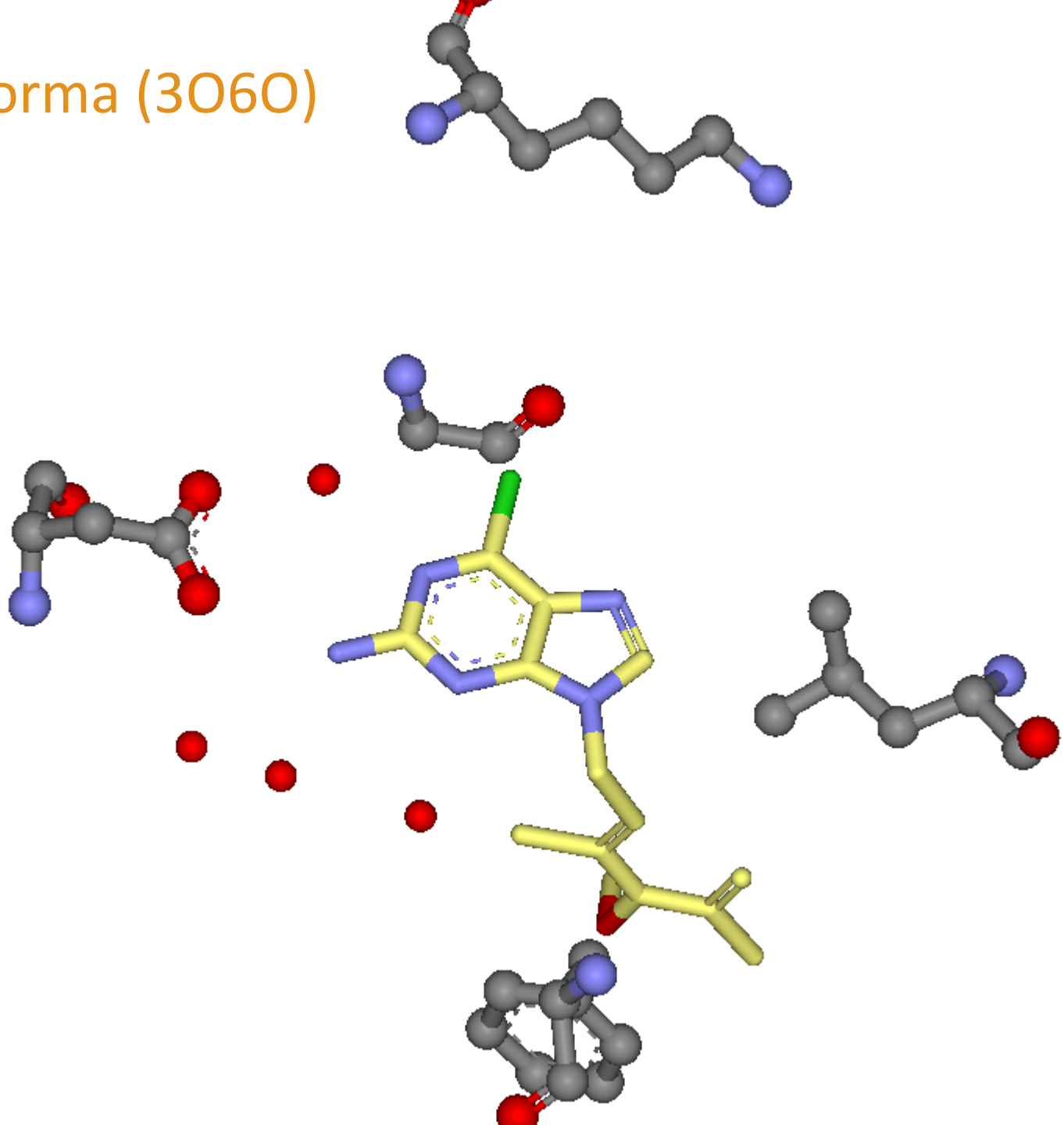
Fragment 13



BEP800 (2WI7)



# Conforma (3O6O)



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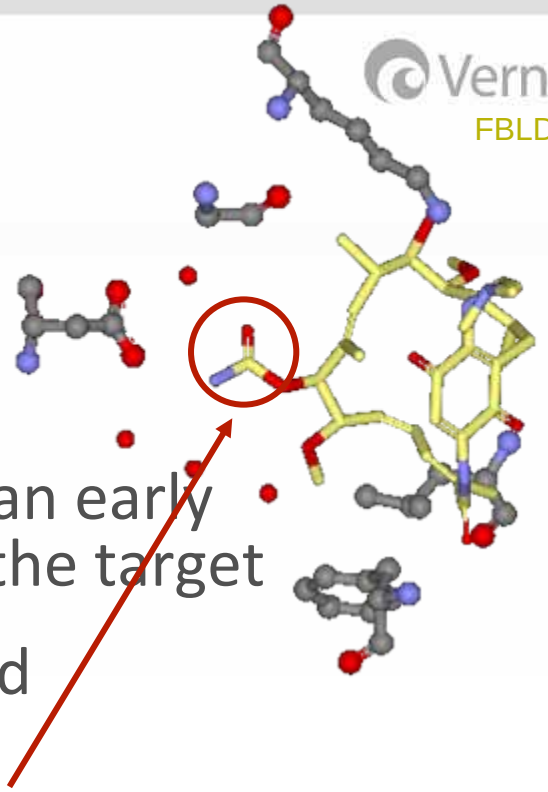
- Comparison with results of first fragment screen in 2002 which identified 17 (23) fragments
- Four classes of inhibitors
  1. Resorcinol analogues (AUY922)
  2. Purine analogues (BEP800)
  3. Amide containing

# Amide containing

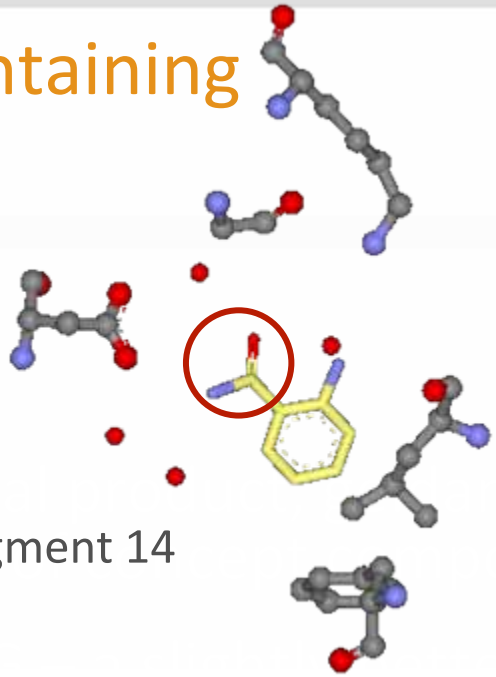




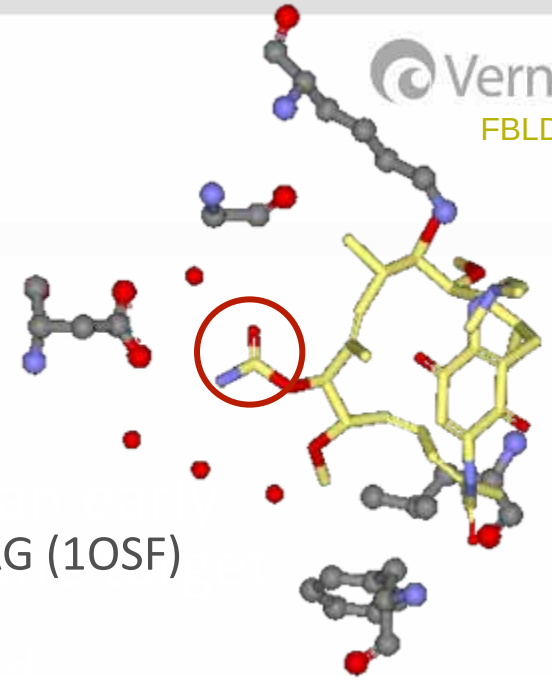
- Natural product, geldanamycin, an early proof of concept compound for the target
- DMAG – a slightly better behaved compound (1OSF)
- Amide – a key interaction motif

# Amide containing





Fragment 14



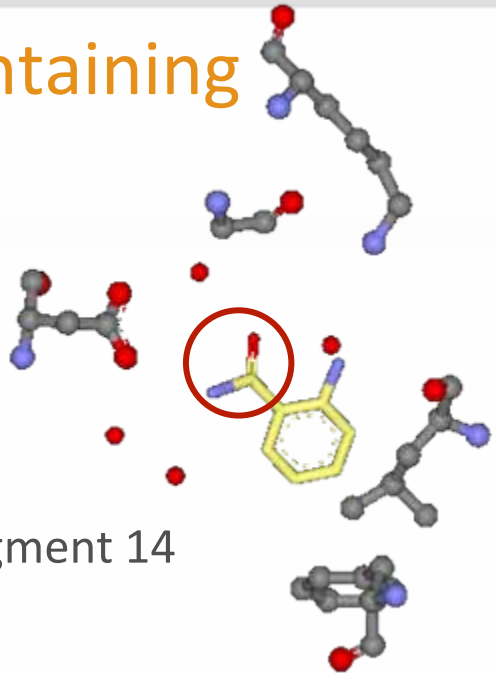
DMAG (1OSF)

- Amide – a key interaction motif
- Seen in one fragment
- But also in published candidates (Serenex)

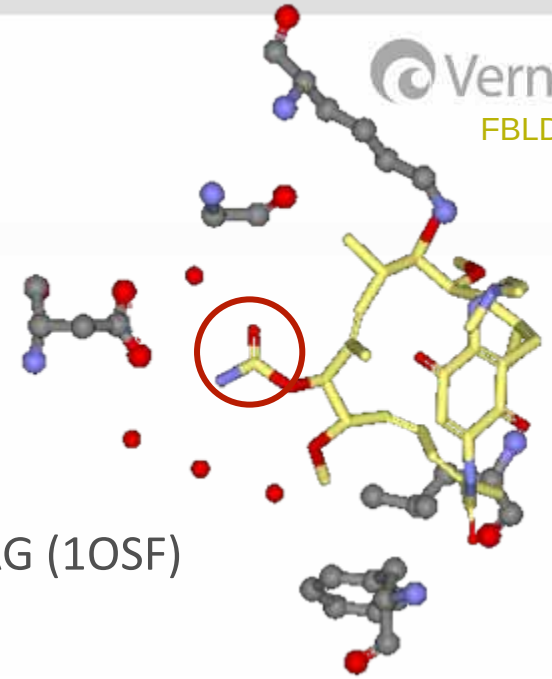
# Amide containing



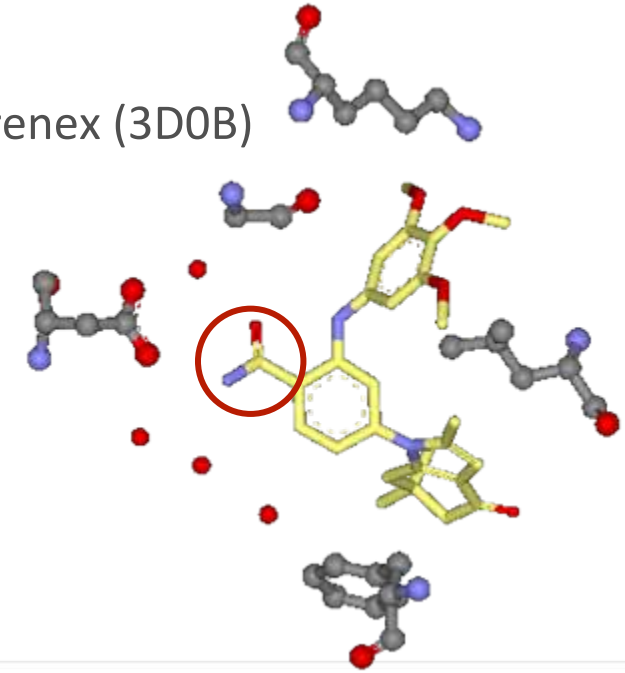
Fragment 14



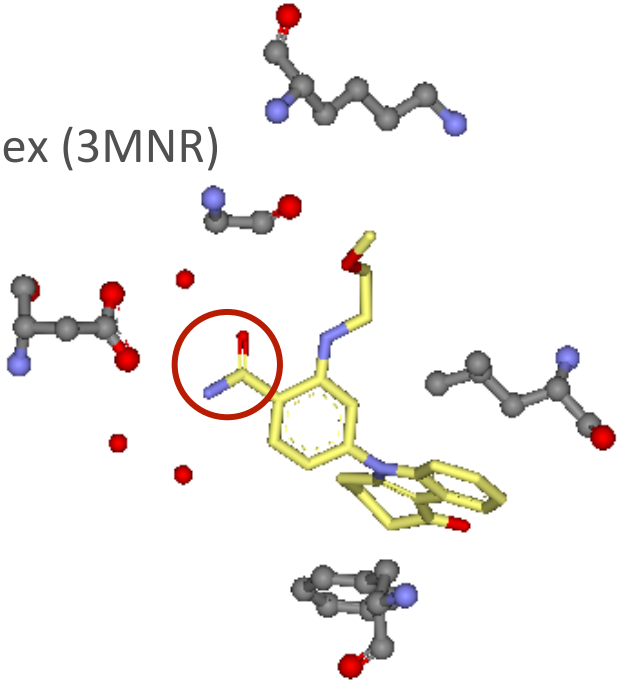
DMAG (1OSF)



Serenex (3D0B)



Serenex (3MNR)



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- Comparison with results of first fragment screen in 2002 which identified 17 (23) fragments
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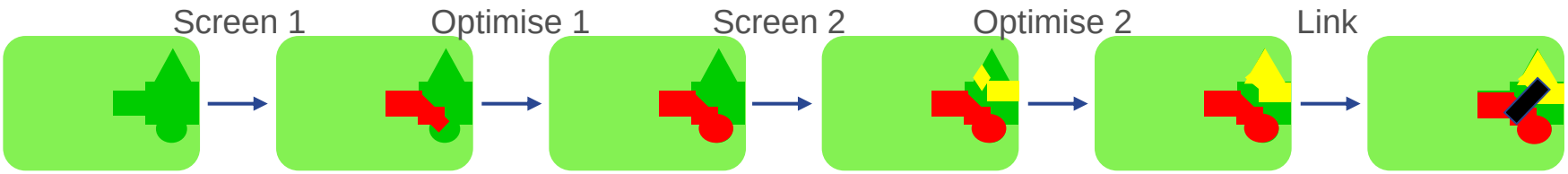
  1. Resorcinol analogues (AUY922)
  2. Purine analogues (BEP800)
  3. Amide containing
  4. Second site binders

# Second site binders



- Early aspiration in FBLD was to identify fragments binding to two sites
  - Then link them together to gain potency

1996 - SAR by NMR from Abbott group (Fesik and Hajduk) - *Science* **1996**, *274*, 1531-1534



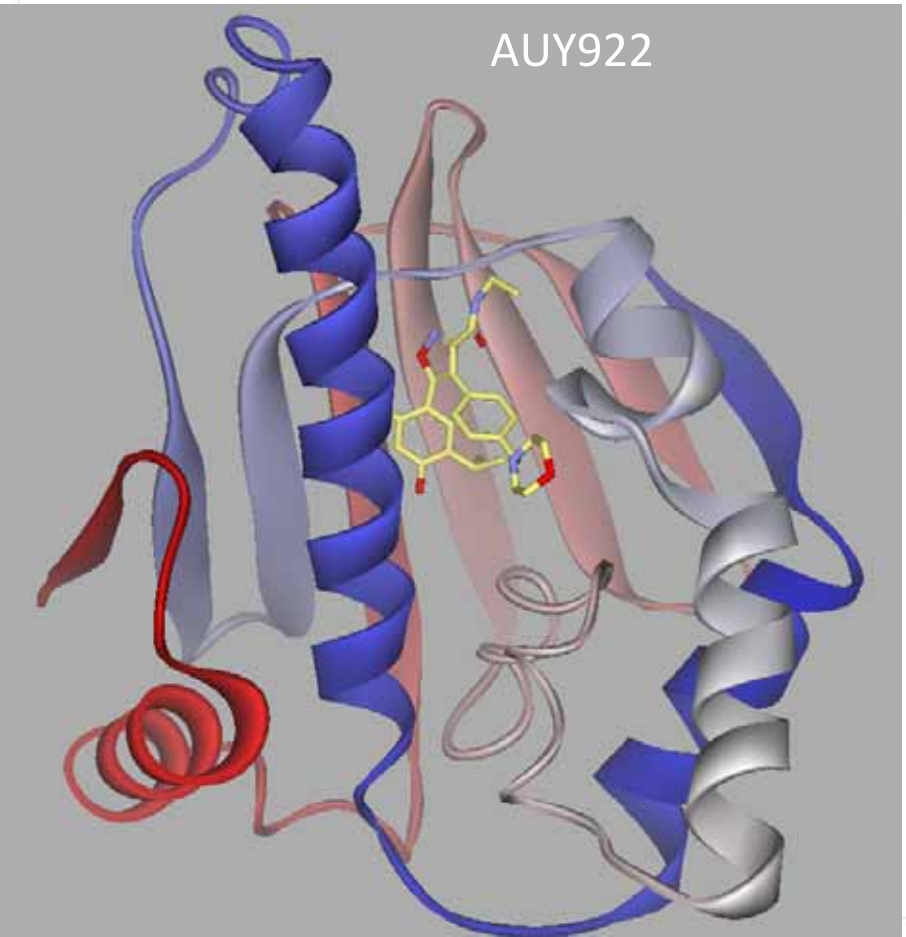
# Conformational change in HSP90

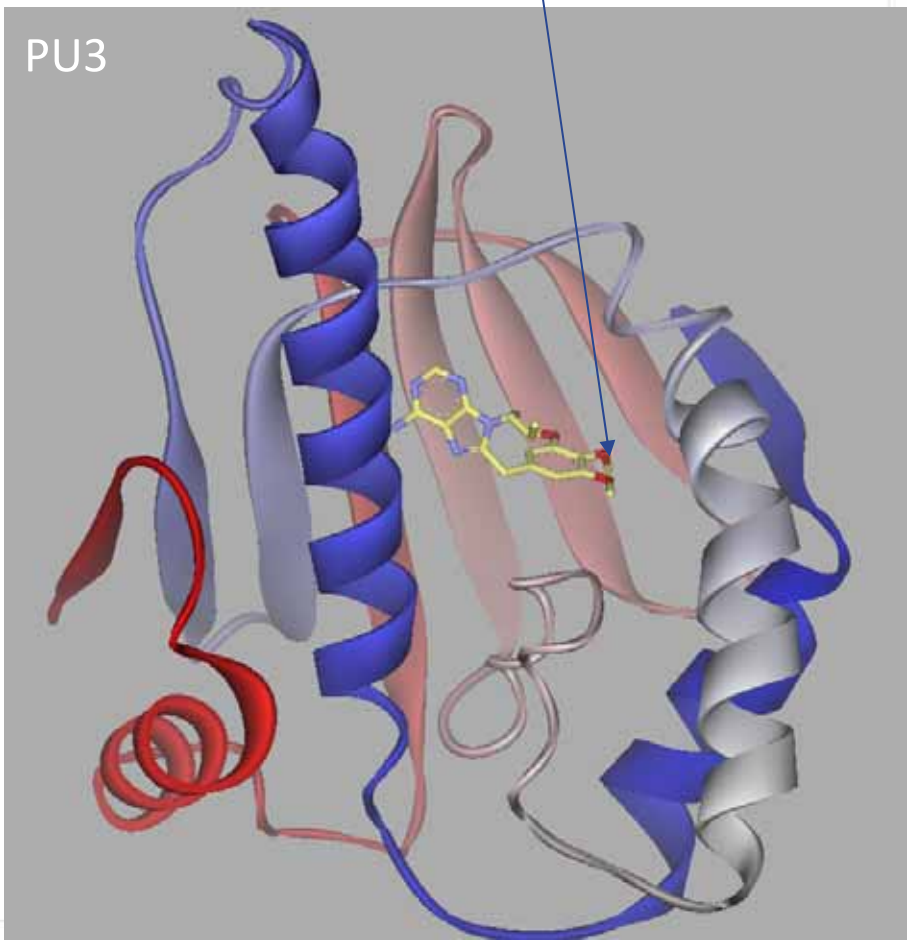
Wright et al (2004), Chem & Biol **11,** 775

Vernalis

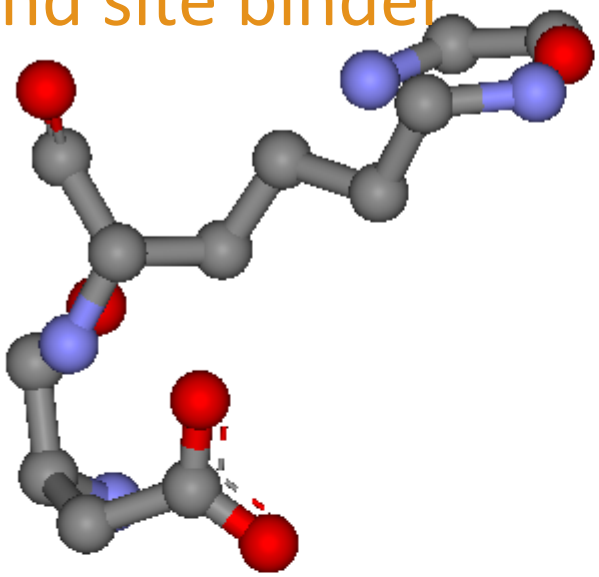
FBLD 2010

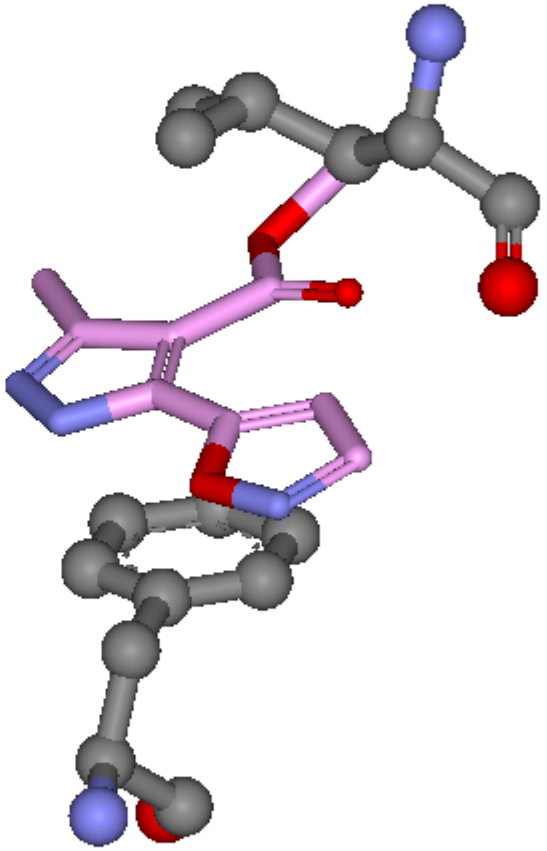
- Tri-OMe-benzene occupies hydrophobic pocket under helix
- Helix at lid of ATP site is flexible



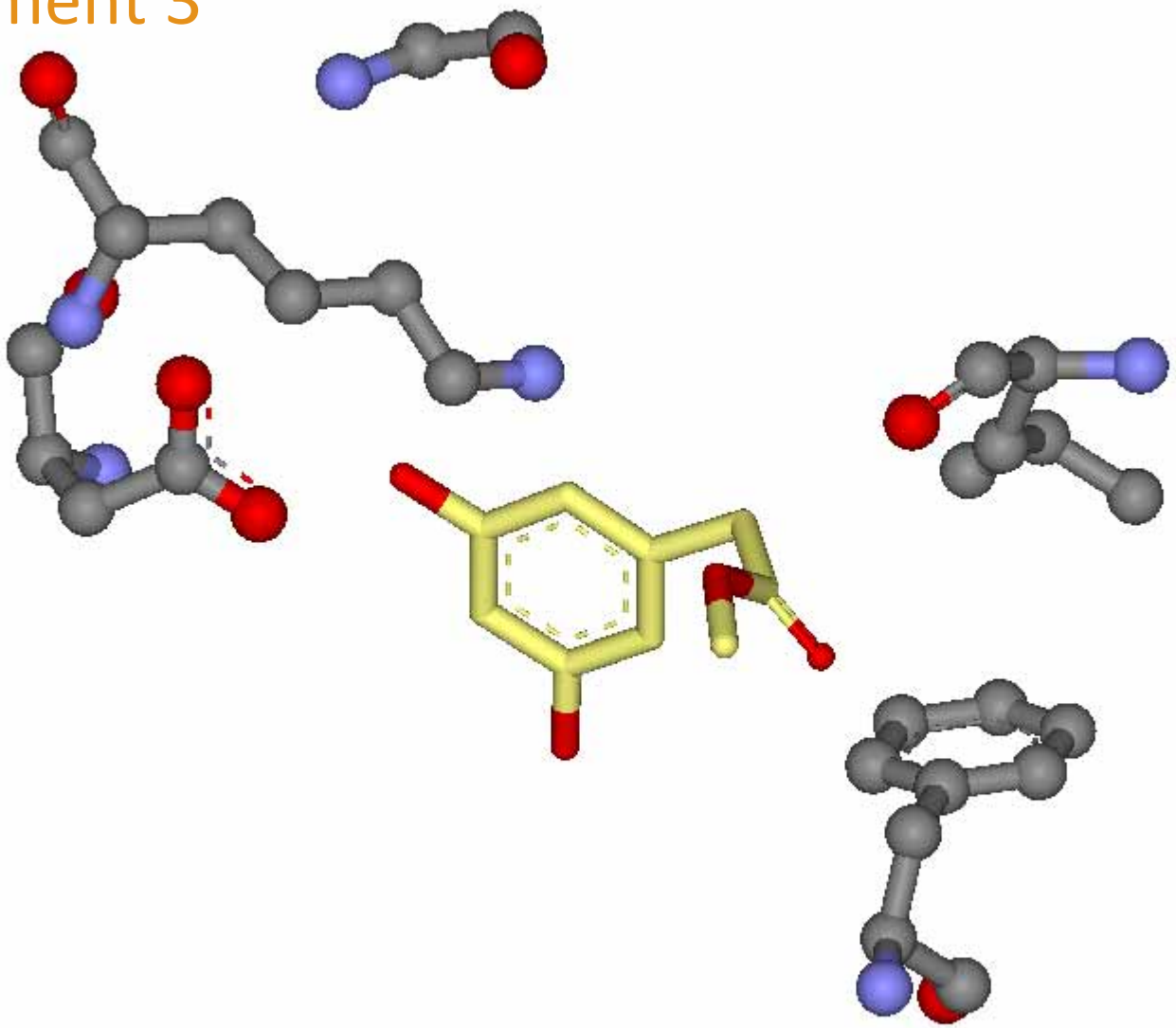
# Second site binder



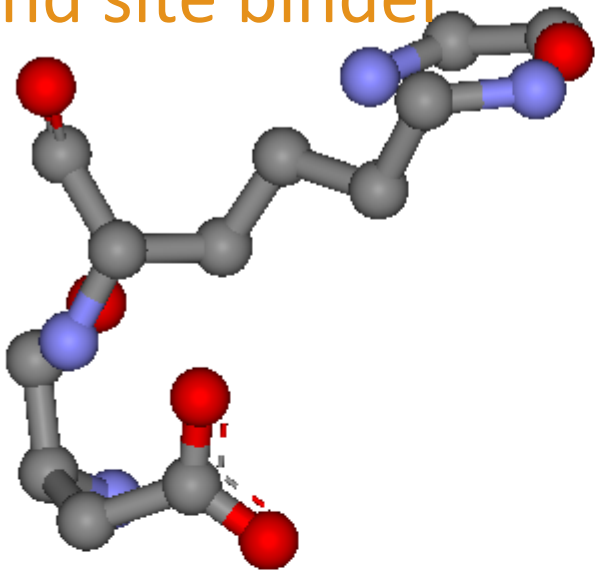


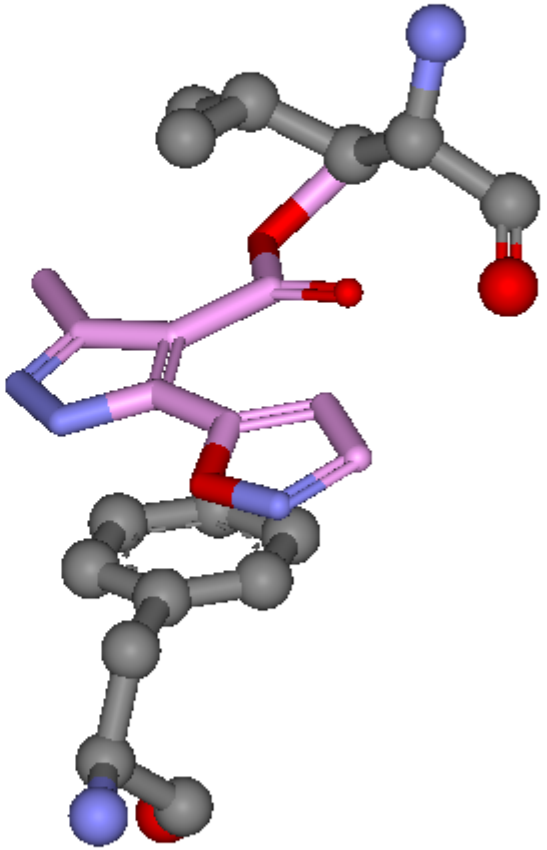
- Fragment 15 can bind into the same pocket – conformation changes in the crystal

# Fragment 3

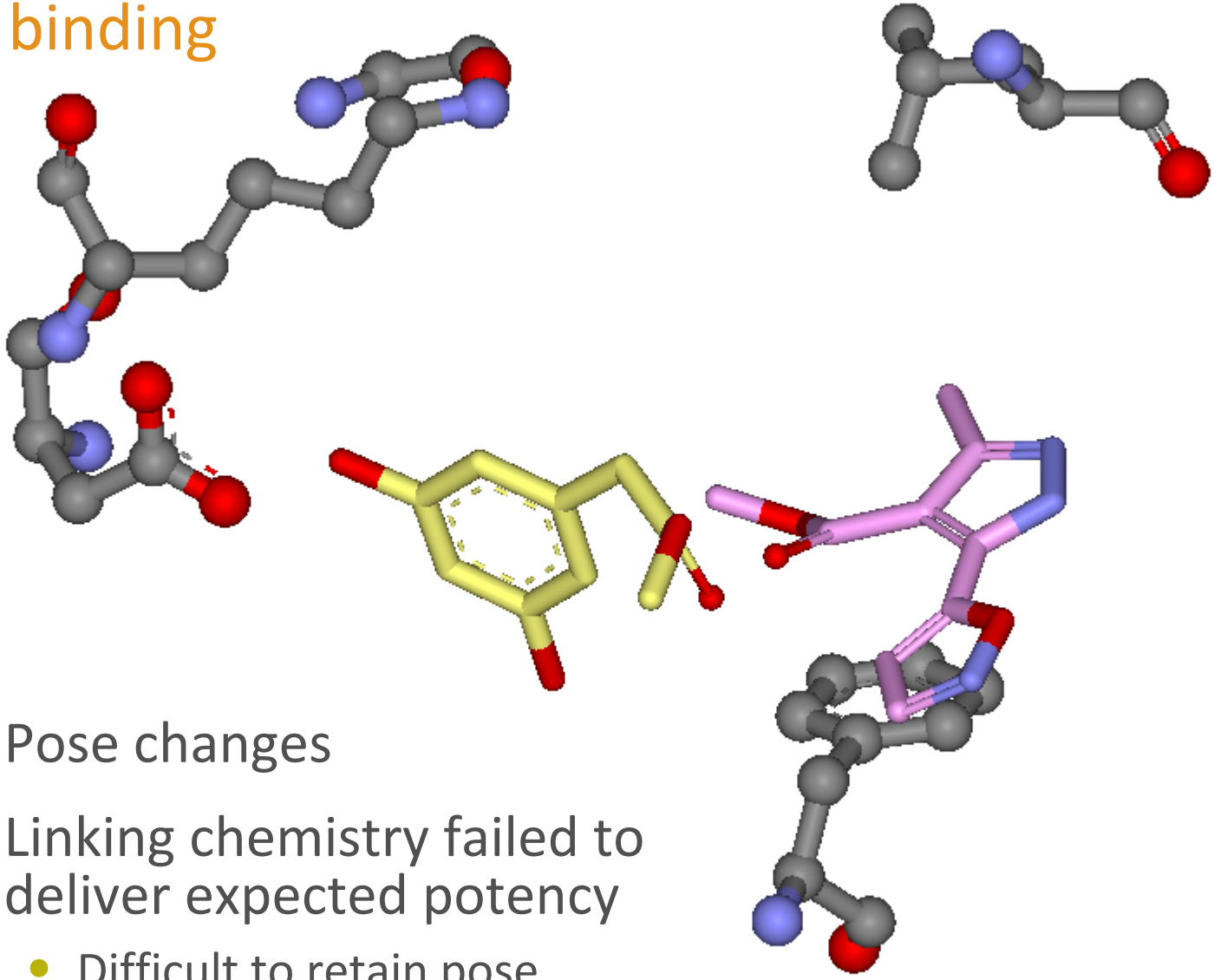


# Second site binder



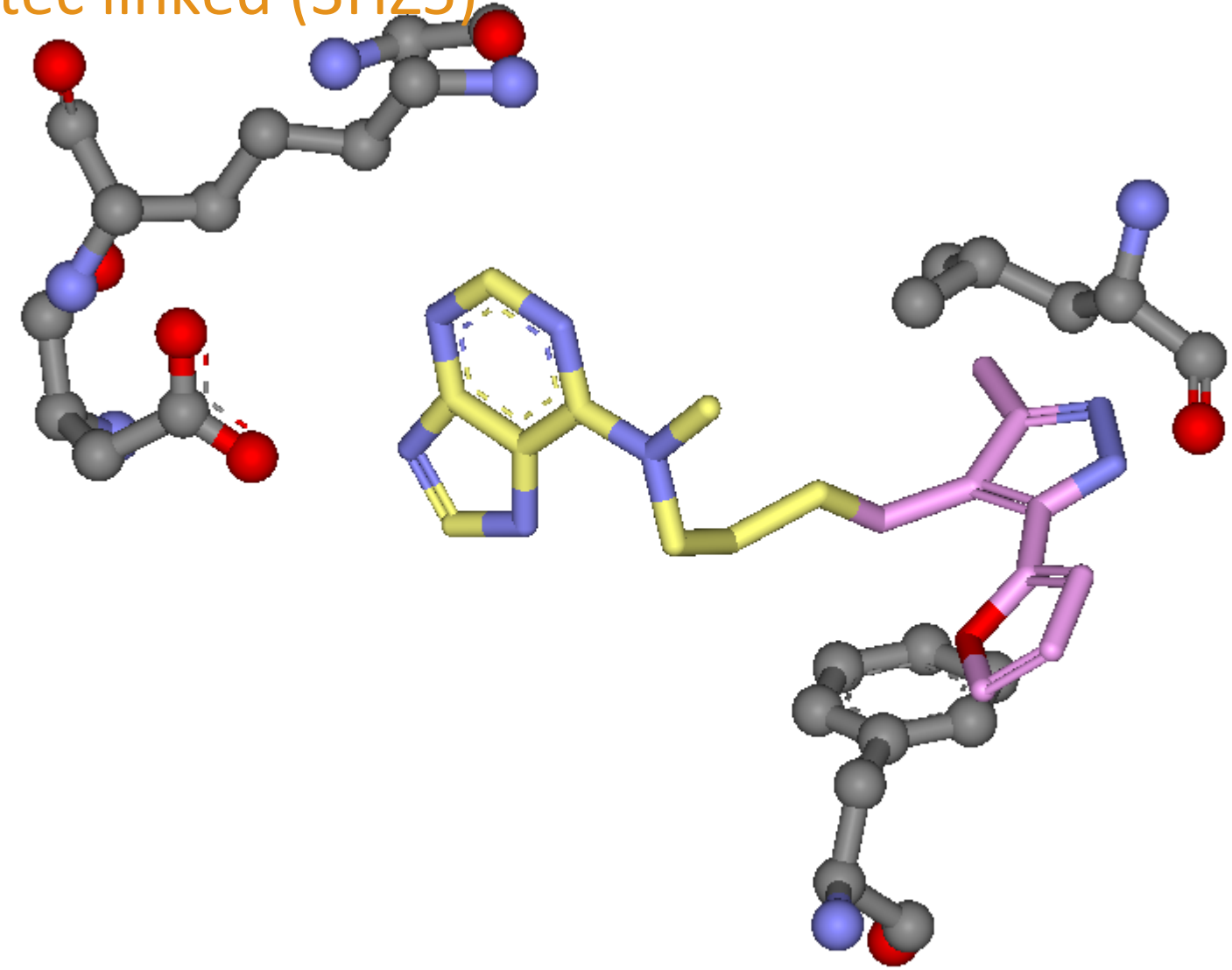


# Both binding

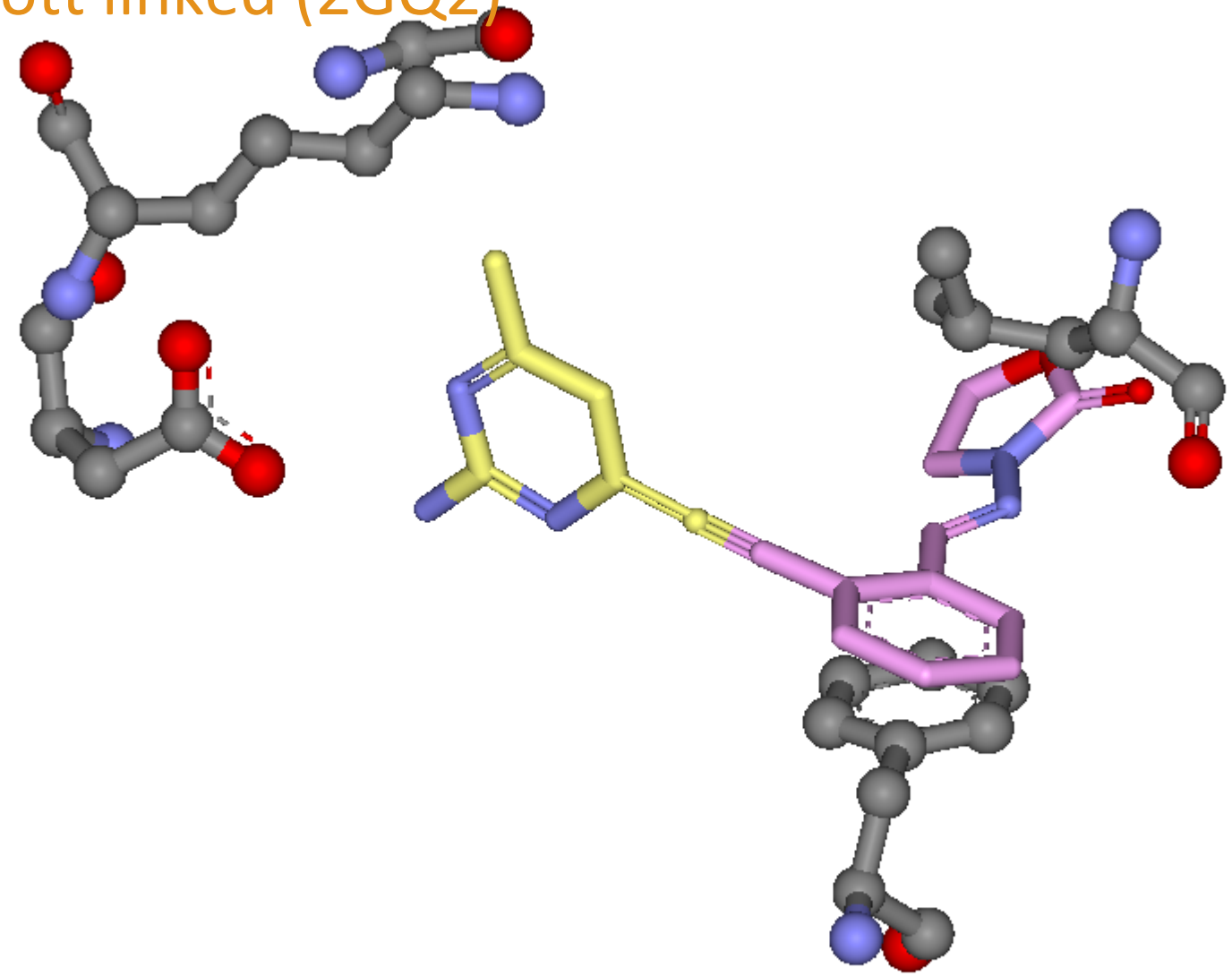


- Pose changes
- Linking chemistry failed to deliver expected potency
  - Difficult to retain pose

# Evotec linked (3HZ5)



# Abbott linked (2GQ2)



- Also another compound (2GQ0)

# Fragments and Chemical Space



- The following is a survey of published HSP90 inhibitors for which crystal structures released
- Comparison with results of first fragment screen in 2002 which identified 17 (23) fragments
- Four classes of inhibitors
  1. Resorcinol analogues (AUY922)
  2. Purine analogues (BEP800)
  3. Amide containing
  4. Second site binders
- And some fragments left over unused
  - And 25 from second screen with larger library

# Overview

Vernalis

- Why?
  - some history
- How?
  - finding fragments that bind
- Some success stories
  - and some that were halted - lessons learnt
- Some issues and discussion points
  - challenging targets
  - which fragments to optimise
  - fragments and chemical space
- Main points and what's next?

# Fragments – main points



- Finding fragments that bind is straightforward
  - For well behaved active sites – 3-5% hit rates
  - Even for challenging protein-protein sites – 0.5-3%
  - Faster, more sensitive and robust methods would help (education)
- Fragments are just small, weak hits
  - Small number of compounds sample large chemical diversity
  - Design of library crucial
    - Properties, diversity, vectors, QC
    - Baurin et al (2004), JCICS, **44**, 2157; Hubbard et al (2007),CODD, **10**, 289; CODD, Chen & Hubbard (2009), JCAMD, **23**, 603

# Fragments – main points



- Finding fragments that bind is straightforward
  - For well behaved active sites – 3-5% hit rates
  - Even for challenging protein-protein sites – 0.5-3%
  - Faster, more sensitive and robust methods would help (education)
- Fragments are just small, weak hits
  - Small number of compounds sample large chemical diversity
  - Design of library crucial - properties, diversity, vectors, QC
- Challenge is deciding what to do with the fragments
  - Fragments provide inspiration / guidance for design of novel compounds that may require ambitious chemistry
  - Critical is integration of structure, modelling and chemistry
  - Doesn't necessarily speed up the hit discovery process
- Provide opportunity for chemists to be "good"
  - Main benefit is choice in discovery

# What's next for fragments?



- Many are adopting fragments alongside HTS
  - Use to mine corporate collection
    - (GSK, Pfizer, Novartis, Abbott ….)
- Fragments in absence of structure
  - Structure gives chemistry direction before on scale in assay
  - NMR can provide low resolution information if X-ray fails
    - Particularly relevant for some protein-protein interaction targets
- Designing new fragments
  - 3D - Vectors, shape, functionality distribution
- Tools to help the chemist make decisions
  - which fragments to evolve?

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THE UNIVERSITY of York
H·Y·M·S THE HULL YORK MEDICAL SCHOOL

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  - James Murray – structure, biophysics and chemistry
  - James Davidson – chemistry and modelling
- At this meeting – York
  - Michele Schulz – library design
- For a copy of presentation
  - r.hubbard@vernalis.com

# Company Overview

Vernalis
FBLD 2010

- Vernalis - a small pharmaceutical company
  - Recognised for innovation and delivery in structure and fragment-based drug discovery
    - Six development candidates generated in the past five years
    - Research collaborations with large and small pharma
  - Significant pre-clinical and clinical development capabilities
    - See http://www.vernalis.com/ver/rdc2/pipeline for clinical trial pipeline
- ~ 60 in research, based in Cambridge, UK (Granta Park)
  - Structure-based drug discovery since 1997
- Portfolio of discovery projects
  - Protein structure, fragments and modelling integrated with medicinal chemistry
  - Internal projects in oncology
  - Collaborations with large and small pharma
- Aim to establish additional collaborations during 2010

# Recent Research Achievements

Six development candidates in the past five years

- V24343 (CB1 antagonist for obesity / diabetes)
  - – successfully completed Phase I
- AUY922 (Hsp90 inhibitor iv for cancer) partnered with Novartis
  - – currently in Phase I
- Oral Hsp90 inhibitor partnered with Novartis
- V81444 (A2a antagonist for Parkinson's)
  - - backup for programme partnered with Biogen Idec
- V158866 FAAH inhibitor for the management of pain
- V158411 Chk1 inhibitor for oncology

- External endorsement of Vernalis SBDD
  - Hsp90 – FTE support + milestones for phase1 i.v and oral
  - Servier – FTE support + milestone; extended to two targets
  - GSK – upfront cash and equity investment + milestones for progress

# Research: Key highlights I

Vernalis
FBLD 2010

- Proprietary approach to fragment-based discovery (SeeDs) which others are now attempting to emulate.
  - Pragmatic application of the most appropriate biophysical methods to enable structure-based drug discovery
  - >9 years experience as one of the first to apply fragment methods – recognised as a world leader
- >95% success rate in establishing and optimising routine, high throughput determination of previously published crystal structures.
  - Over 2,400 ligand bound structures determined to date.
  - Novel crystal structures for some important target classes, for example protein-protein interactions

# Research: Key highlights II

Vernalis
FBLD 2010

- Demonstrated capability to generate multiple lead series against a wide variety of drug targets
  - Disclosed targets include kinases such as CDK2, Chk1 and PDPK1, as well as ATPases such as DNA gyrase and Hsp90
- Novel crystal structures of challenging targets, including protein-protein interactions and the proline isomerase, Pin1
- NMR spectroscopy has been used recently to derive ligand binding modes where it is difficult to determine crystal structures of protein-fragment complexes
- Demonstrated productivity in lead optimisation
  - Six development candidates in the past five years

# Selected publications 2007-

Vernalis
FBLD 2010

- Structure-guided design of alpha-amino acid-derived Pin1 inhibitors.
  - Potter AJ et al, Bioorg Med Chem Lett. 2009 Nov 22. [Epub ahead of print]
- Combining hit identification strategies: fragment-based and in silico approaches to orally active 2-aminothieno[2,3-d]pyrimidine inhibitors of the Hsp90 molecular chaperone.
  - Brough PA et al J Med Chem. 2009 Aug 13;52(15):
- Discovery and functional evaluation of diverse novel human CB(1) receptor ligands.
  - Foloppe N et al Bioorg Med Chem Lett. 2009 Aug 1;19(15):4183-90.
- Conformational sampling and energetics of drug-like molecules.
  - Foloppe N, Chen IJ Curr Med Chem. 2009;16(26):3381-413.
- Lessons for fragment library design: analysis of output from multiple screening campaigns.
  - Chen IJ, Hubbard RE.J Comput Aided Mol Des. 2009 Jun 3. [Epub ahead of print]
- Novel adenosine-derived inhibitors of 70 kDa heat shock protein, discovered through structure-based design.
  - Williamson DS et al J Med Chem. 2009 Mar 26;52(6):1510-3.
- Recent progress in Fragment Based Discovery
  - Schulz, M, Hubbard RE Curr Topics Pharmacology, 2009, 9, 615-621
- Fragment Based Ligand Discovery
  - Fischer, M, Hubbard RE Mol Interv. 2009, 9, 22-30
- Conformational sampling of druglike molecules with MOE and catalyst: implications for pharmacophore modeling and virtual screening.
  - Chen IJ, Foloppe N.J Chem Inf Model. 2008 Sep;48(9):1773-91.
- Medicinal chemistry of Hsp90 inhibitors.
  - Drysdale MJ, Brough PA.Curr Top Med Chem. 2008;8(10):859-68.
- Fragment approaches in structure-based drug discovery.
  - Hubbard RE. J Synchrotron Radiat. 2008;15,:227-30.
- Discovery of a novel class of selective human CB1 inverse agonists.
  - Foloppe N et al Bioorg Med Chem Lett. 2008 Feb 1;18(3):1199-206.
- 4,5-diarylisoxazole Hsp90 chaperone inhibitors: potential therapeutic agents for the treatment of cancer.
  - Brough PA et al J Med Chem. 2008 Jan 24;51(2):196-218.
- The SeeDs approach: integrating fragments into drug discovery.
  - Hubbard RE, Davis B, Chen I, Drysdale MJ. Curr Top Med Chem. 2007;7(16):1568-81.
- Discovery of a potent CDK2 inhibitor with a novel binding mode, using virtual screening and initial, structure-guided lead scoping.
  - Richardson CM et al, Bioorg Med Chem Lett. 2007 Jul 15;17(14):3880-5.
- Informatics and modeling challenges in fragment-based drug discovery.
  - Hubbard RE, Chen I, Davis B. Curr Opin Drug Discov Devel. 2007 May;10(3):289-97.