



innovative science • intuitive software



Is using a 2D drawing application to design for kinase selectivity an oxymoron?

Paolo Tosco

What causes selectivity?

> Electrostatics

3D Property

- > E.g. Alternative H-bond pattern
- > Differing electrostatic expectations – electron rich vs electron poor

> Shape

3D Property

- > Smaller / Larger residues
- > Alternative protein conformations

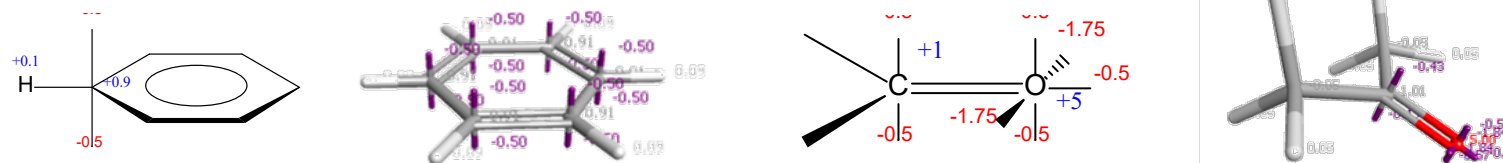
> Biological processes

- > E.g. Compartmentalization of targets

The XED force field

> XED force field – eXtended Electron Distribution

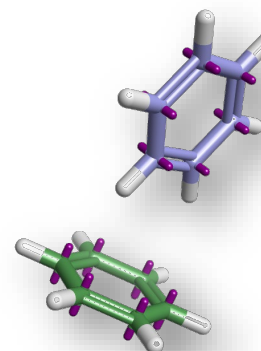
> Multipoles via additional monopoles



> Huckel

> separation of π and σ components of partial charges

- > π charges added to 'xed' atoms
- > σ charges added to nuclei
- > Excellent modeling of substituent effects

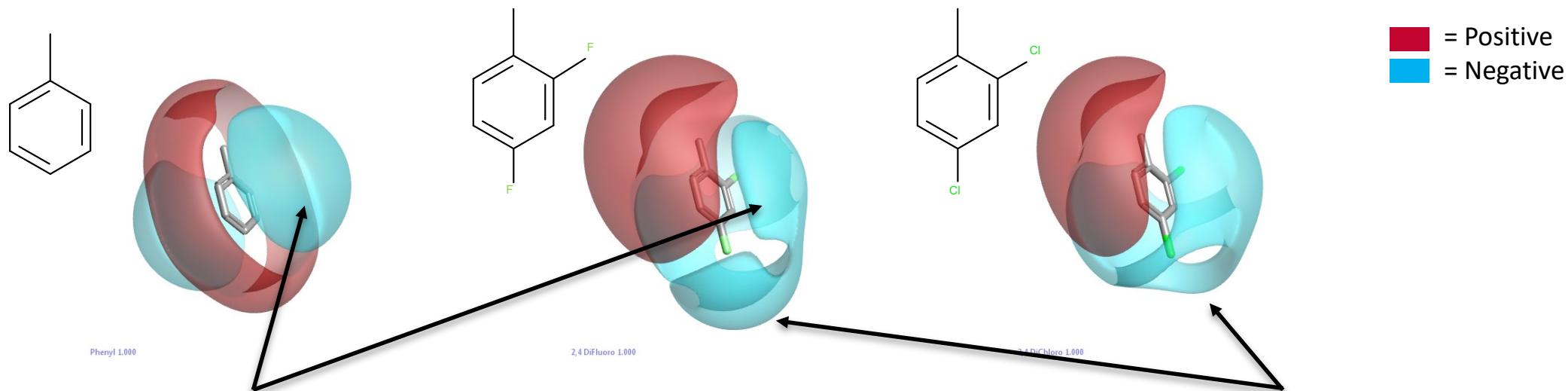


> Full molecular mechanics force field with excellent coverage of organic chemistry, water and proteins

- > Minimization, conformations etc.
- > Not a dynamics force field

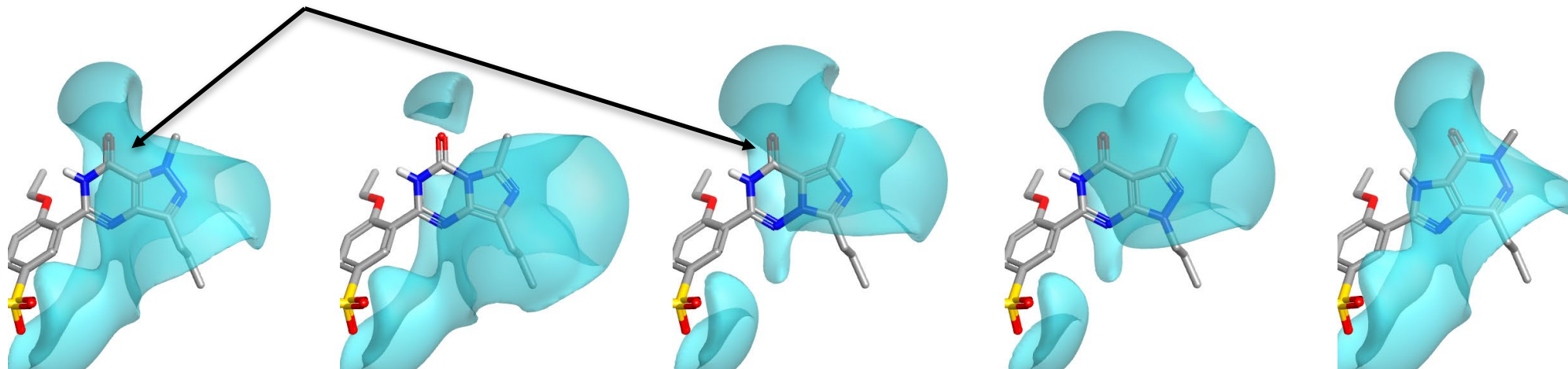
Vinter, *J. Comput.-Aided Mol. Des.*, **1994**, 8, 653-668

XED electrostatics generate detailed ligand interaction patterns

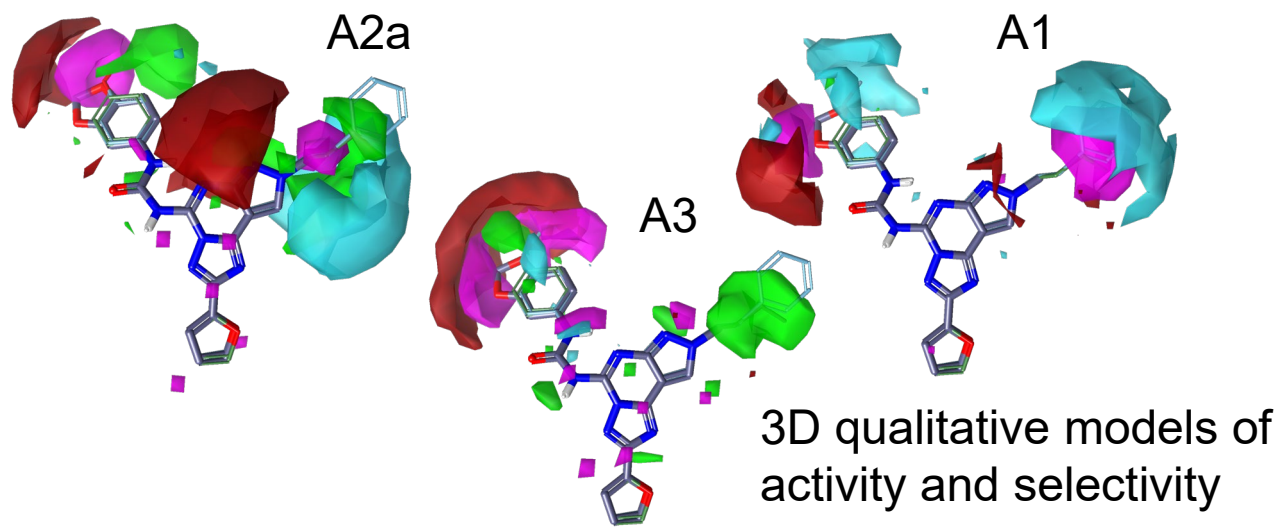


Detailed simulation of electron density changes

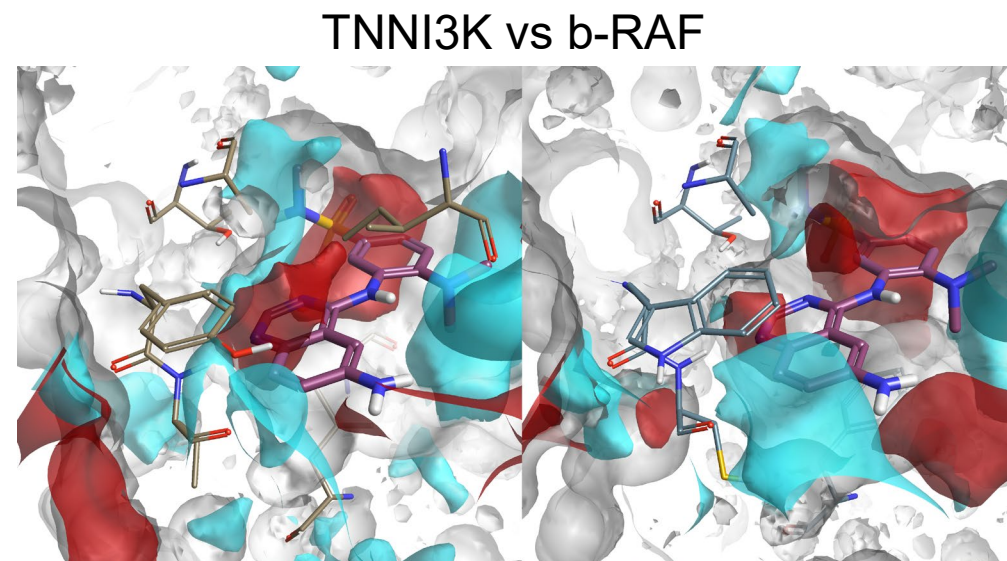
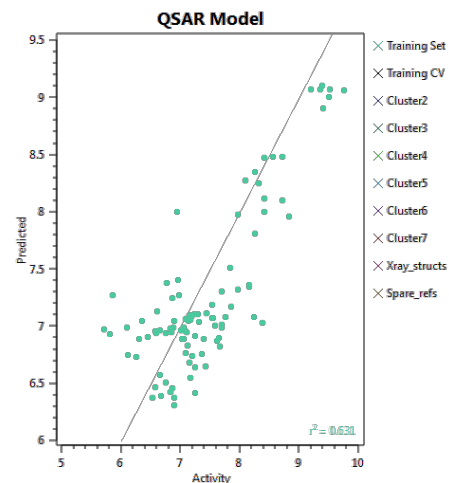
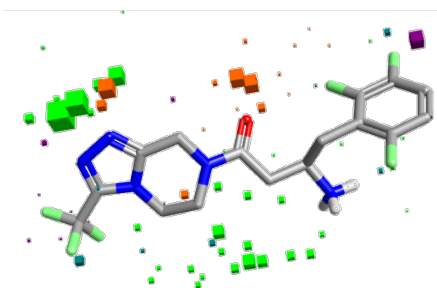
Detailed description of halogens



Designing for selectivity in Cresset applications



3D qualitative models of activity and selectivity



Protein electrostatics and protein – ligand electrostatic complementarity

Designing for selectivity in Cresset applications

A2a

3D Molecular editor

RAF

3D qualitative molecular activity and selectivity

and protein – ligand complementarity

Score: 0.752

Activity

$r^2 = 0.631$

Radial Plot

Metric	Value
Sim	0.783
MW	
Flexibility	
TPSA	
SlogP	

Torch™ – Molecule design using ligand alignment

Customer requests:

Can I draw with ChemDraw? 

Can I share a design with a colleague? 

Can I see a retrosynthesis for a new design? 

Can I search in the patent literature for precedents? 

How can I see what other designs have been proposed?

How do I see my design in multiple proteins to assess selectivity?

Molecule Editor

Atoms H XEDs Fields Shape Display Color Labels Clear Mol +ve -ve vdW Hyd 2.0 Help

Information
Title: Design 1
Notes: Change of central ring from pyrimidine to pyrazolesni

Radial Plot

0.783 Sim SlogP
MW Flexibility TPSA

Actions
Add H Del H
Charge for pH7 Add Fields
Minimize
Optimize Alignment
Save a Copy
OK Align Cancel

Select Mode Score: 0.752

Rethinking the design process and application

Accessible 3D design

- > Combine the best of 2D and 3D
- > You draw in 2D but see the result in 3D 'live'
- > Express your ideas
- > Eliminate the duds

Collaborative environment

- > Conversation tool
 - > No technological artefacts
- > No inhibition to collaboration
- > No idea is missed
- > Easy communication across project teams

Generating live 3D feedback

- > Docking too slow for “live”
 - > Remains a failsafe
- > Created a “Grow3D” approach where new molecules are compared to the old and the change is applied intelligently
 - > Full algorithmic details in COMP 191,
[Gallery 3A, Omni San Diego Hotel](#), 2:20pm
- > Multiple 3D coordinates are possible, which one is relevant?
 - > Consider selectivity case with similar proteins – dock to both targets or just one?
 - One 3D pose for each design easier to understand and use

The Grow3D methodology applied to CHK1 inhibitors


Journal of
**Medicinal
Chemistry**

Cite This: *J. Med. Chem.* 2018, 61, 1061–1073

Article

pubs.acs.org/jmc

Adventures in Scaffold Morphing: Discovery of Fused Ring Heterocyclic Checkpoint Kinase 1 (CHK1) Inhibitors

Bin Yang,^{*,†}  Melissa M. Vasbinder,[†] Alexander W. Hird,[†] Qibin Su,[†] Haixia Wang,[†] Yan Yu,[†] Dorin Toader,^{†,||} Paul D. Lyne,[†] Jon A. Read,[‡] Jason Breed,[‡] Stephanos Ioannidis,[†] Chun Deng,^{†,⊥} Michael Grondine,[†] Nancy DeGrace,[†] David Whitston,[†] Patrick Brassil,^{†,#} and James W. Janetka^{†,\$}

[†]Oncology Chemistry, IMED Biotech Unit, AstraZeneca, 35 Gatehouse Drive, Waltham, Massachusetts 02451, United States

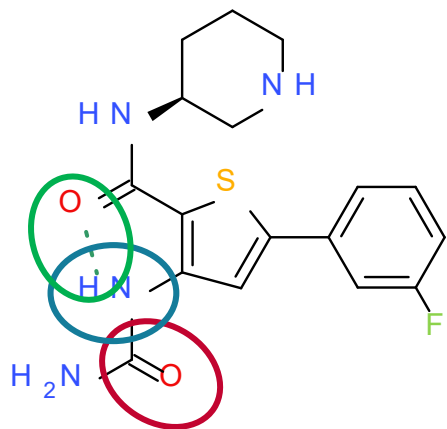
[‡]Discovery Sciences, IMED Biotech Unit, AstraZeneca, Building 310, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, U.K.

In 2018 AZ published an interesting scaffold morphing exercise on some Checkpoint kinase 1 (CHK1) inhibitors they had previously identified

A (very) quick introduction to CHK1

- > CHK1 is a promising target to improve the therapeutic index of DNA-damaging anti-cancer agents
- > DNA damage triggers CHK1 activation, which in turn arrests the cell cycle, thus allowing DNA repair to take place
- > Inhibiting CHK1 abrogates the cell cycle arrest, causing apoptosis
- > CHK1 inhibitors would thus sensitize tumour cells to the action of DNA-damaging drugs

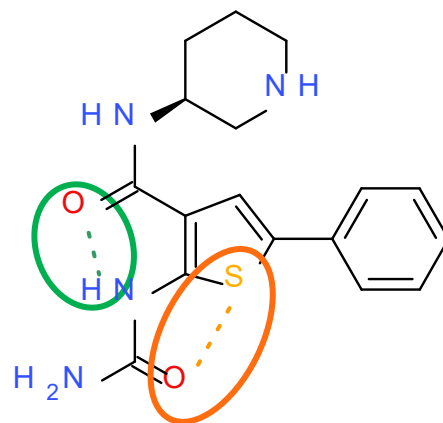
TCU and TZQ leads



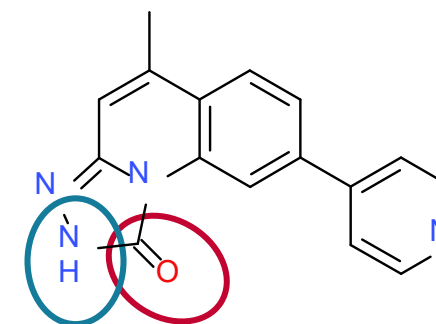
1 (AZD7762)
Thiophene carboxamide
urea (TCU)
Clinical candidate

The **carbonyl** group interacts with
the backbone N-H of Cys-87

The **amino** group interacts with
the backbone C=O of Glu-85



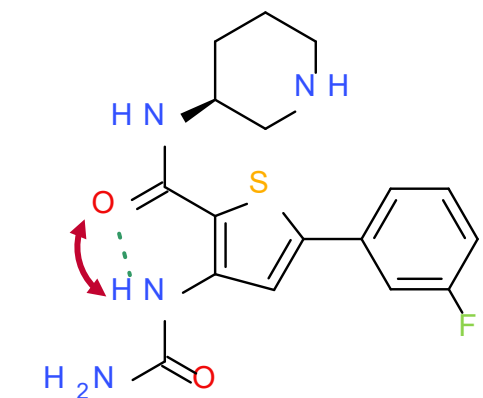
3
Thiophene carboxamide
urea (TCU)
Matched pair with **1**



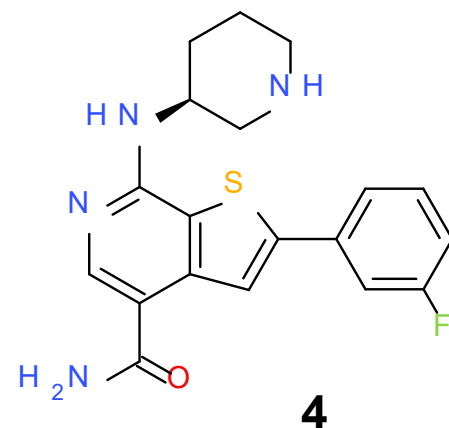
2
Triazoloquinolone
(TZQ)

Both **1** and **3** feature an
intramolecular **hydrogen bond**
which stabilizes the bioactive
conformation

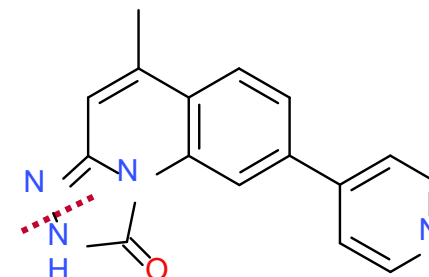
Ring closure, ring opening



Ring
closure



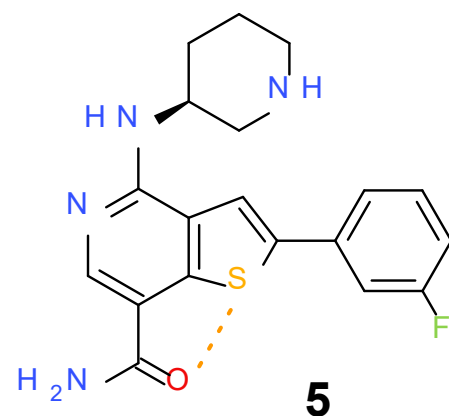
Ring
opening



1 (AZD7762)
Thiophene carboxamide
urea (TCU)
Clinical candidate

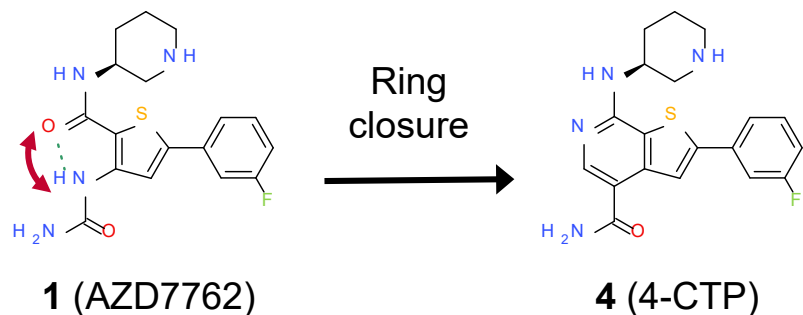
4
4-Carboxamide
thienopyridine (4-CTP)

2
Triazoloquinolone
(TZQ)



Matched pairs

Ring closure in *grow3D*



Let's see what *grow3D* can do about the ring closure of **1** to **4**

I'll use the 2YDJ PDB structure (CHK1 co-crystallized with **1**) as a reference

torx

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

4_4-CTP

Idea No Design Set

1_AZD7762

Idea No Design Set

Total: 2 Checked: 0 Check All Clear

1 25

Viewer x

Align 1_AZD7762

Structures

Search residues

Only show selected residues

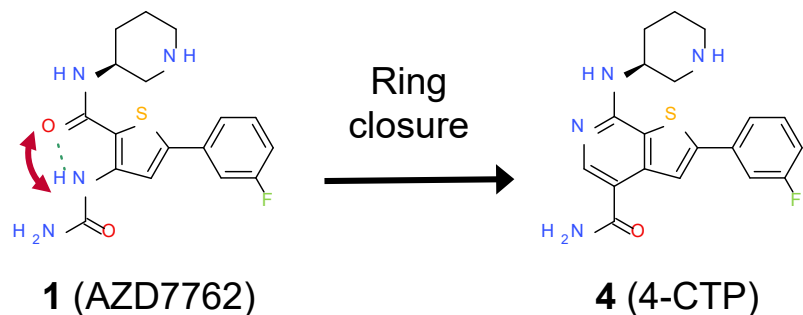
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

Positioning the initial 3D structure



I'll start by generating a 3D conformation of **1** and aligning it to the X-ray reference

In the background, multiple 3D conformations of **1** are generated, and the one with the highest field/shape similarity score to the reference is chosen

torxlab.com

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

4_4-CTP

Idea No Design Set

1_AZD7762

Idea No Design Set

Total: 2 Checked: 0 Check All Clear

Align 1_AZD7762

Structures

Search residues

Only show selected residues

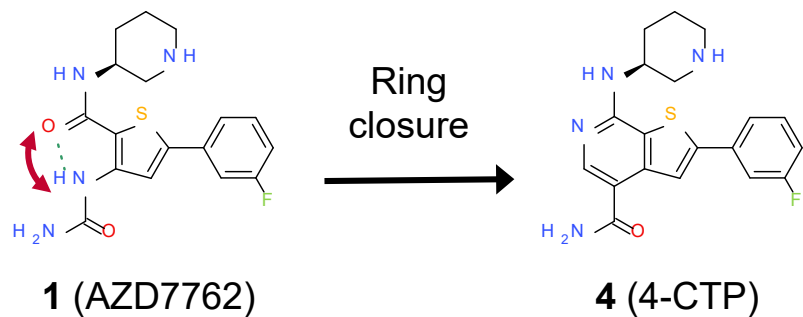
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

Scaffold morphing begins



Then I turn the carbonyl group into an imine...

torxlab.com

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

4_4-CTP

Idea No Design Set

1_AZD7762

Idea No Design Set

Total: 2 Checked: 0 Check All Clear

1 items per page 25

Viewer x

Align 1_AZD7762

Structures

Search residues

Only show selected residues

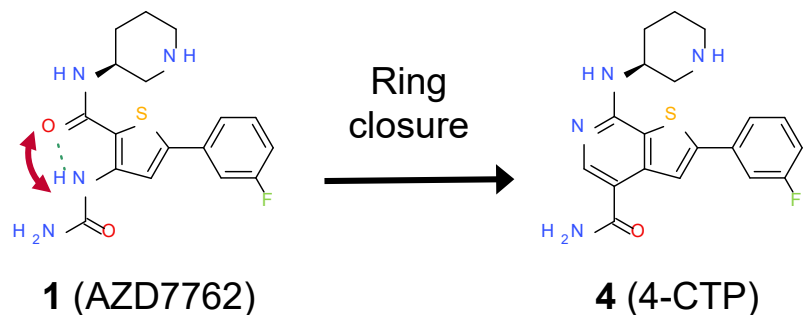
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

Scaffold morphing begins



Then I turn the carbonyl group into an imine...

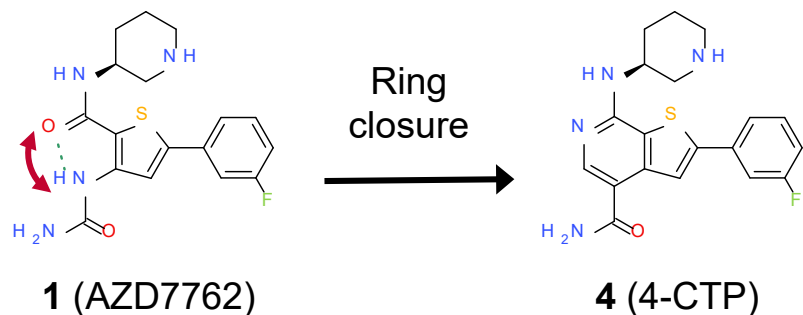
...the urea into an *N*-methylurea...

...now the difficult bit: ring closure!
(holding my breath)...

The screenshot displays the Torxlab web interface. The top navigation bar includes 'torx', 'Projects', 'Layouts', 'Plugins', and 'Sharing'. The main workspace is divided into several panels:

- Editor:** Shows the chemical structure of molecule 4 (4-CTP) with a piperidine ring, a thiophene ring, and a fluorophenyl group.
- Viewer:** Shows the 3D docking of molecule 4 into a protein structure, with various interaction types highlighted in different colors.
- Designs:** A list of designs including 'CHK1' and '4_4-CTP'. The '4_4-CTP' design is selected, showing its structure and 'No Design Set' status.
- Structures:** A list of protein structures including '2X8E_pe', '2YDJ_pe', '2YDK_pe', and '6FC8_pe'.
- Ligands:** A list of ligands including '1_AZD7762', '2_TZQ', '3_TCU', and '5_7-CTP'.

Scaffold morphing begins



Then I turn the carbonyl group into an imine...

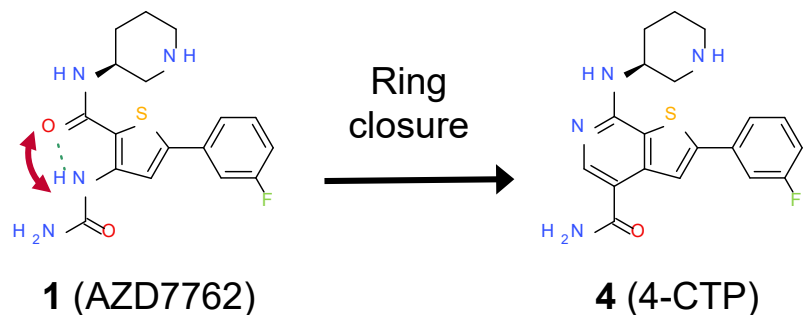
...the urea into an *N*-methylurea...

Whoa, that worked!

The screenshot shows the Torxlab web interface. The top navigation bar includes 'torx', 'Projects', 'Layouts', 'Plugins', and 'Sharing'. The main workspace is divided into several panels:

- Designs:** Shows a list of designs for 'CHK1'. Design '4_4-CTP' is selected and highlighted in dark blue. Below it, design '1_AZD7762' is visible. A status bar at the bottom indicates 'Total: 2 Checked: 0 Check All Clear'.
- Editor:** Displays the chemical structure of 4-CTP. The structure features a piperidine ring connected to a thiazole ring, which is further substituted with a fluorophenyl group and a methylurea group.
- Viewer:** Shows a 3D ball-and-stick model of the molecule docked into a protein binding pocket. The protein backbone is shown in grey, and the ligand is highlighted in various colors (blue, yellow, green, red).
- Structures:** A panel on the right side of the viewer showing a list of structures. Under 'Proteins', there are entries for 2X8E_pe, 2YDJ_pe, 2YDK_pe, and 6FC8_pe. Under 'Ligands', there are entries for 1_AZD7762, 2_TZQ, 3_TCU, and 5_7-CTP.

Scaffold morphing begins



Then I turn the carbonyl group into an imine...

...the urea into an *N*-methylurea...

...let's clean it up a little bit (both 2D and 3D)...

torxlab.com

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

4_4-CTP

Idea No Design Set

1_AZD7762

Idea No Design Set

Total: 2 Checked: 0 Check All Clear

1 25

Viewer x

Align 1_AZD7762

Structures

Search residues

Only show selected residues

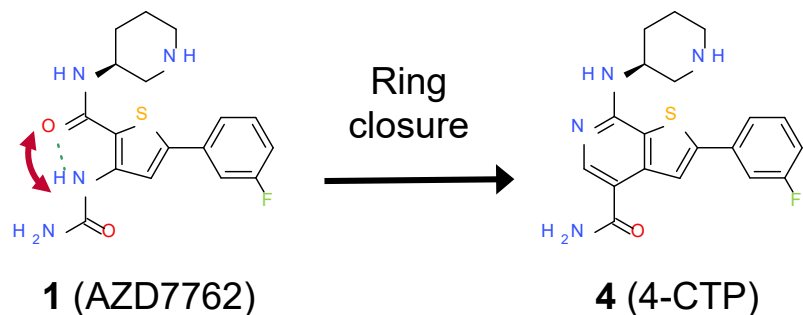
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

Scaffold morphing begins



Then I turn the carbonyl group into an imine...

...the urea into an *N*-methylurea...

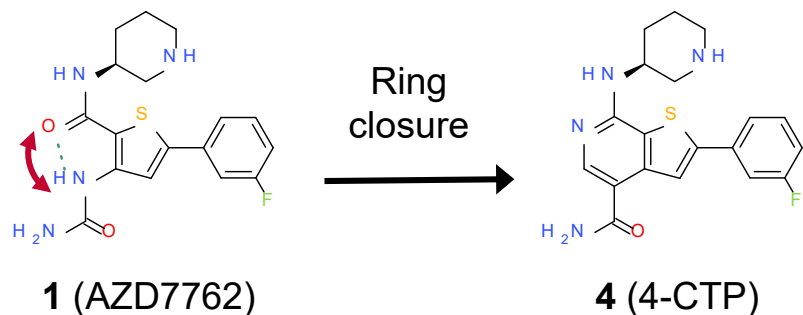
...let's clean it up a little bit (both 2D and 3D)...

...now I turn the dihydropyrimidine into a dihydropyridine...

The screenshot shows the Torx software interface. The top navigation bar includes 'torx', 'Projects', 'Layouts', 'Plugins', and 'Sharing'. The main workspace is divided into several panels:

- Editor:** Displays the 2D chemical structure of molecule 4 (4-CTP). The structure features a dihydropyridine ring system fused to a thiophene ring, which is further substituted with a piperidine ring, a methylurea group, and a 4-fluorophenyl group.
- Viewer:** Shows a 3D ball-and-stick model of the molecule docked into a protein binding pocket. The protein backbone is shown in grey, and the molecule is highlighted in various colors (blue, yellow, pink, green) to show its interaction with the protein.
- Structures Panel:** Lists the structures in the current design set, including '1_AZD7762' and '4_4-CTP'. It also shows a list of proteins (2X8E_pe, 2YDJ_pe, 2YDK_pe, 6FC8_pe) and ligands (1_AZD7762, 2_TZQ, 3_TCU, 5_7-CTP).
- Designs Panel:** Shows a list of designs with a 'Total: 2 Checked: 0 Check All Clear' status.

Scaffold morphing: done!



Then I turn the carbonyl group into an imine...

...the urea into an *N*-methylurea...

...let's clean it up a little bit (both 2D and 3D)...

...now I turn the dihydropyrimidine into a dihydropyridine...

...and aromatize to pyridine: done!

torx

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by

Modified

Group by

4_4-CTP

Idea No Design Set

1_AZD7762

Idea No Design Set

Total: 2 Checked: 0 Check All Clear

1

Viewer x

Align 1_AZD7762

Structures

Search residues

Only show selected residues

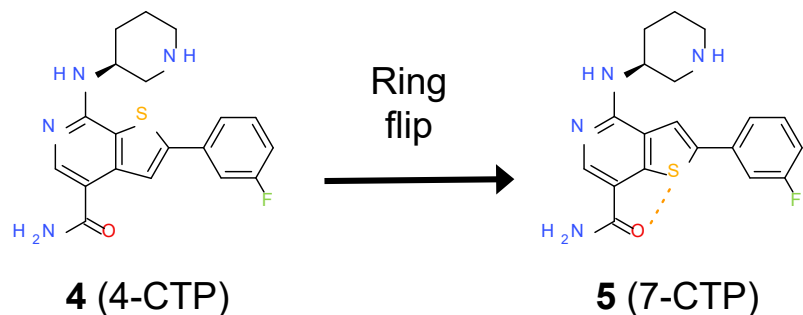
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

More transformations at constant #atoms



I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

torxlab.com

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

5_7-CTP

Idea No Design Set

4_4-CTP

Idea No Design Set

1_AZD7762

Structures

Search residues

Only show selected residues

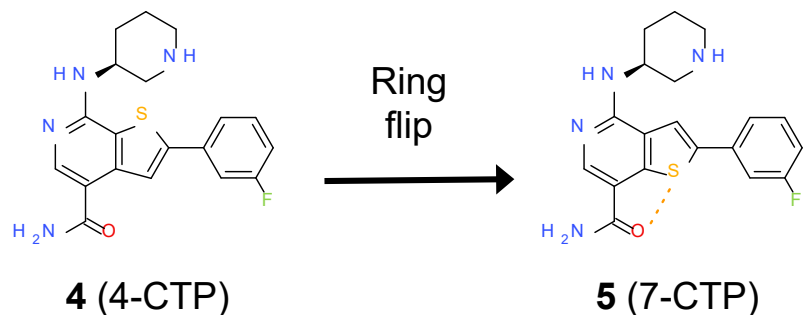
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

More transformations at constant #atoms



I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

1. Hydrogenate the thiophene...

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torx Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by

Modified

Group by

5_7-CTP

Idea No Design Set

4_4-CTP

Idea No Design Set

1_AZD7762

Viewer x

Align 1_AZD7762

Structures Close

Search residues

Only show selected residues

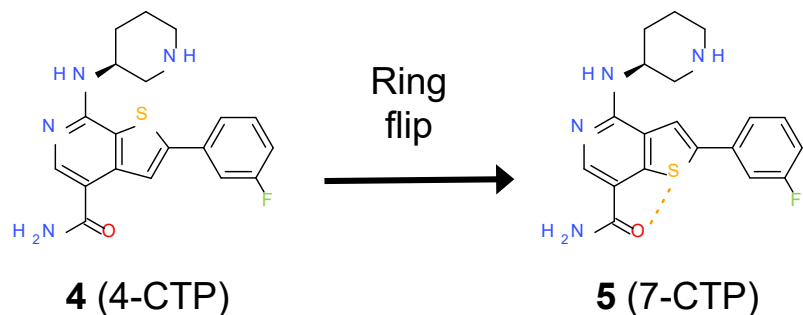
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

More transformations at constant #atoms



I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

1. Hydrogenate the thiophene...
2. Turn it into a cyclopentene...

torxlab.com
Projects Layouts Plugins Sharing

Designs x Editor x

CHK1
New design Upload Filters

Sort by
Modified

Group by

5_7-CTP
Idea
No Design Set

4_4-CTP
Idea
No Design Set

1_AZD7762

Viewer x

Align 1_AZD7762

Structures Close

Search residues

Only show selected residues

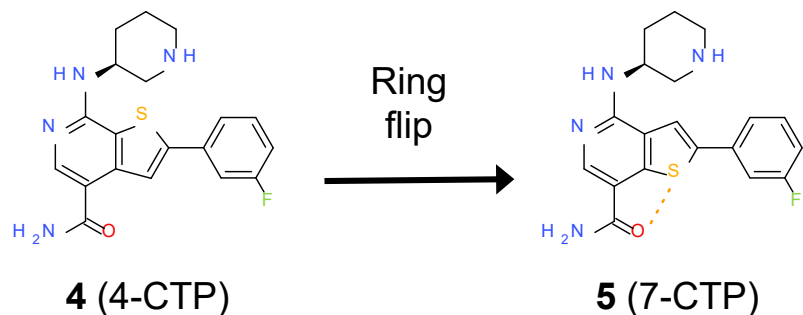
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

More transformations at constant #atoms



I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

1. Hydrogenate the thiophene...
2. Turn it into a cyclopentene...
3. Dehydrogenate cyclopentene...

torxlab.com

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

5_7-CTP

Idea No Design Set

4_4-CTP

Idea No Design Set

1_AZD7762

Structures

Search residues

Only show selected residues

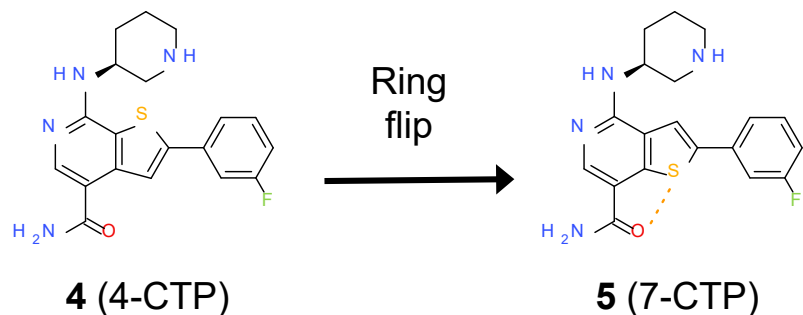
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

More transformations at constant #atoms



I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

1. Hydrogenate the thiophene...
2. Turn it into a cyclopentene...
3. Dehydrogenate cyclopentene...
4. Turn cyclopentadiene into thiophene...

torx
Projects Layouts Plugins Sharing

Designs x Editor x

CHK1
New design Upload Filters

Sort by
Modified

Group by

5_7-CTP
Idea
No Design Set

4_4-CTP
Idea
No Design Set

1_AZD7762

Viewer x

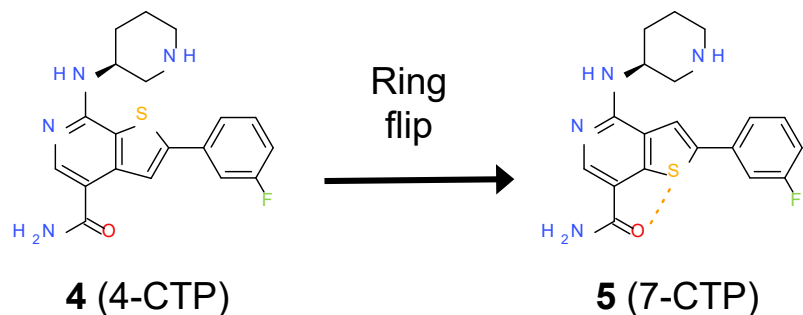
Align 1_AZD7762

Structures
Search residues
Only show selected residues

Proteins
+ 2X8E_pe
+ 2YDJ_pe
+ 2YDK_pe
+ 6FC8_pe

Ligands
1_AZD7762
2_TZQ
3_TCU
5_7-CTP

More transformations at constant #atoms

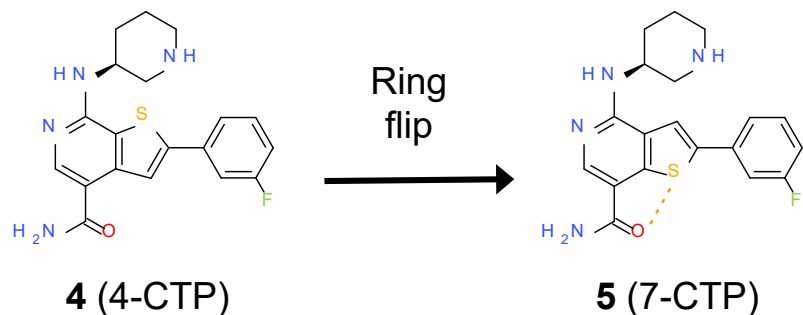


I will now flip the thiophene ring to turn **4** into **5** in 4 moves:

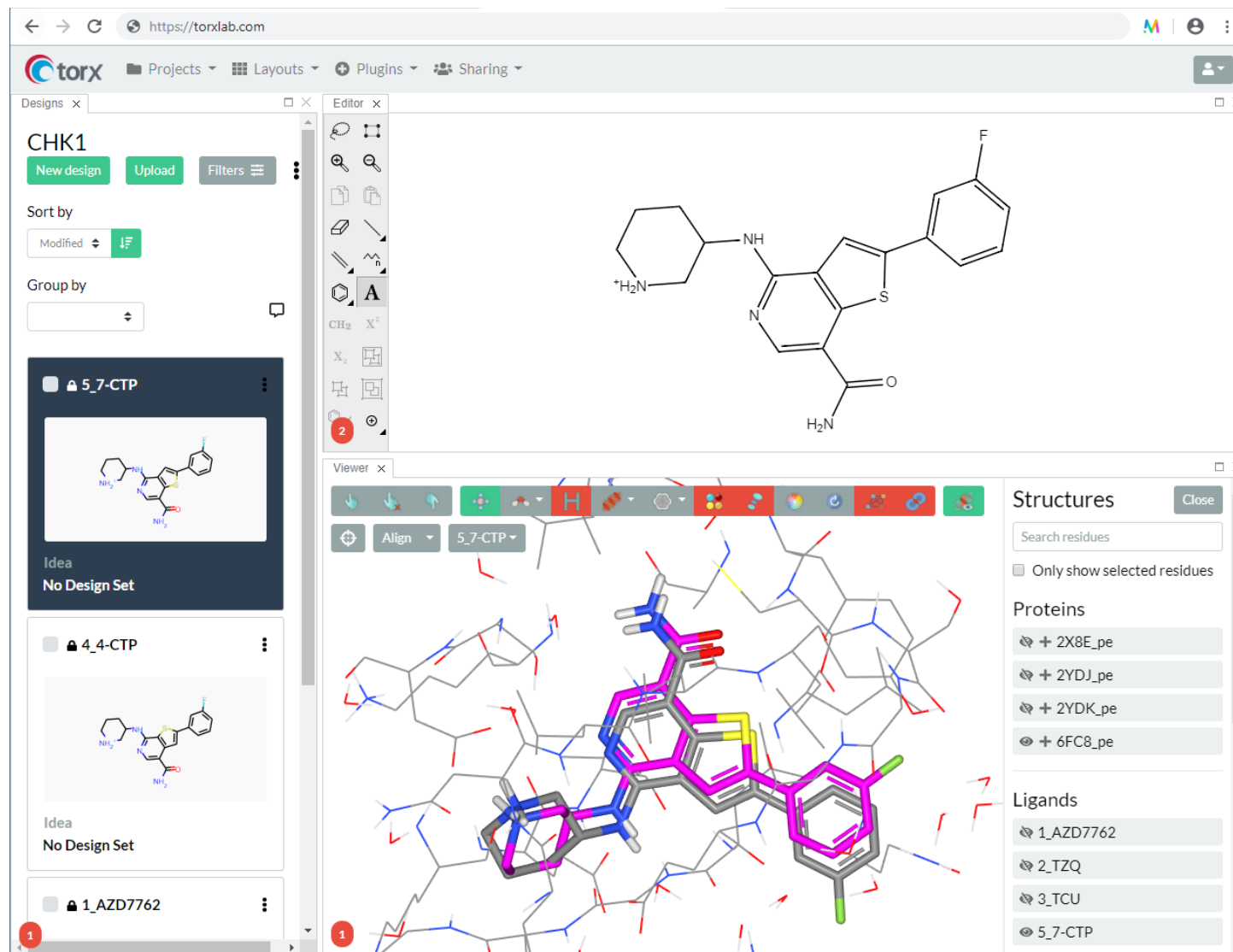
1. Hydrogenate the thiophene...
2. Turn it into a cyclopentene...
3. Dehydrogenate cyclopentene...
4. Turn cyclopentadiene into thiophene...and clean it up

The screenshot displays the Torx software interface. The top navigation bar includes 'torx', 'Projects', 'Layouts', 'Plugins', and 'Sharing'. The main editor window shows the chemical structure of molecule 5 (7-CTP). The left sidebar contains a design list with three entries: '5_7-CTP', '4_4-CTP', and '1_AZD7762'. The bottom viewer window shows a 3D representation of the molecule docked in a protein binding site, with various atoms highlighted in different colors.

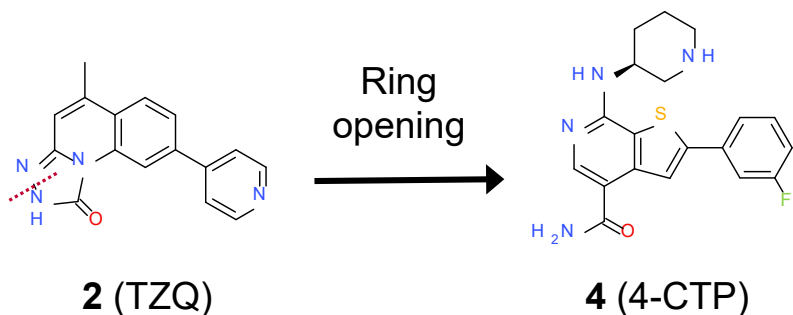
More transformations at constant #atoms: how did we do?



This is how our designed **5** compares against its experimental X-ray structure **6FC8**



Ring opening in *grow3D*



Let's try and get to **4** through a ring opening approach starting from **2**

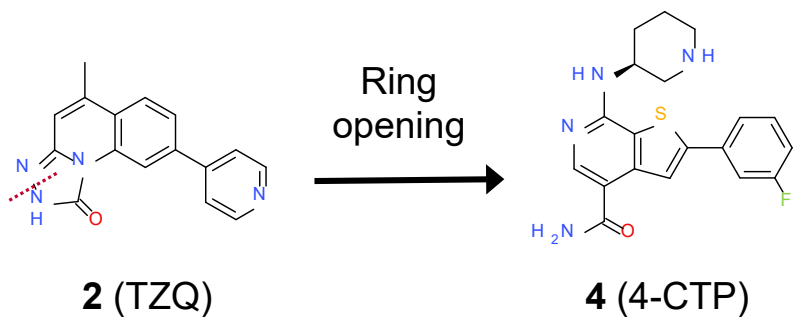
I'll use the 2X8E PDB structure (CHK1 co-crystallized with **2**) as a reference

This morphing involves far more changes to the scaffold than the previous one

Screenshot of the Torx software interface showing a molecular design project. The interface includes a browser window at the top displaying the URL <https://torxlab.com>. The main workspace is divided into several panels:

- Editor:** Shows the chemical structure of molecule **2 (TZQ)** in a 2D representation.
- Viewer:** Shows a 3D molecular model of molecule **2 (TZQ)** docked into a protein structure (CHK1). The protein is shown in a grey stick representation, and the ligand is shown in a magenta stick representation. The viewer includes a toolbar with various manipulation tools.
- Designs:** A sidebar on the left shows a list of designs. The current design is **CHK1**. Below it, there are three design ideas: **2_TZQ**, **5_7-CTP**, and **4_4-CTP**. Each idea has a small thumbnail image and the text "Idea No Design Set".
- Structures:** A panel on the right shows a list of structures. It includes a search bar and a checkbox for "Only show selected residues". The list contains:
 - Proteins:
 - + 2X8E_pe
 - + 2YDJ_pe
 - + 2YDK_pe
 - + 6FC8_pe
 - Ligands:
 - 1_AZD7762
 - 2_TZQ
 - 3_TCU
 - 5_7-CTP

A more complicated design case



As previously, I start by aligning my 2D design to the X-ray reference

torx

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by

Modified

Group by

2_TZQ

Idea No Design Set

5_7-CTP

Idea No Design Set

4_4-CTP

Viewer x

Align 2_TZQ

Structures

Search residues

Only show selected residues

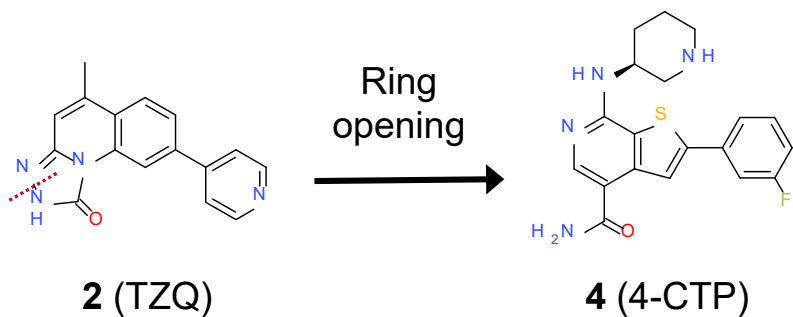
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

A more complicated design case



As previously, I start by aligning my 2D design to the X-ray reference

Then I cleave the hydrazide bond

torx

Projects Layouts Plugins Sharing

Designs x Editor x

CHK1

New design Upload Filters

Sort by Modified

Group by

2_TZQ

Idea No Design Set

5_7-CTP

Idea No Design Set

4_4-CTP

Viewer x

Align 2_TZQ

Structures

Search residues

Only show selected residues

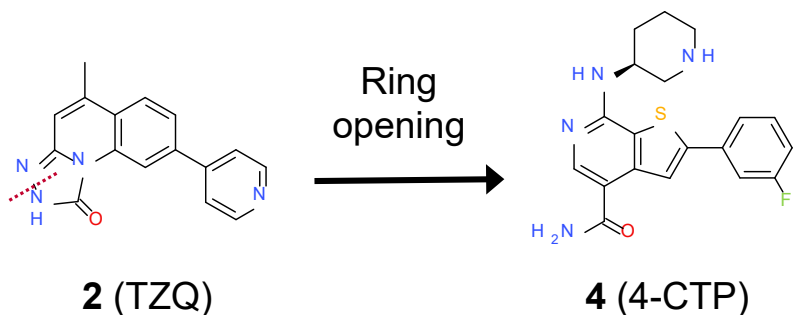
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

A more complicated design case



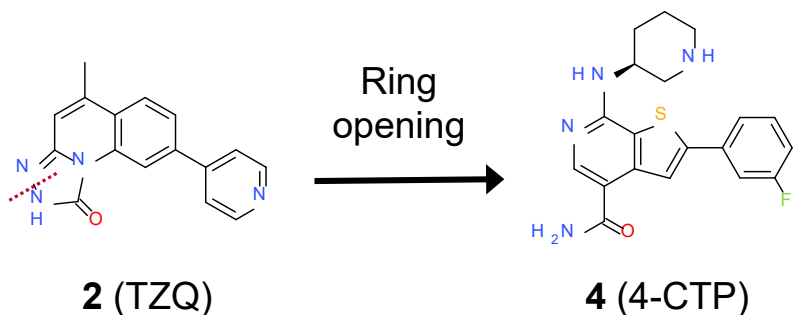
As previously, I start by aligning my 2D design to the X-ray reference

Then I cleave the hydrazide bond

Get rid of the imino substituent

Screenshot of the Torx software interface. The main window displays a 3D molecular model of a protein-ligand complex. The protein structure is shown in grey, and the ligand is highlighted in pink and blue. The interface includes a top navigation bar with 'torx' logo and menu items like 'Projects', 'Layouts', 'Plugins', and 'Sharing'. Below the navigation bar, there are tabs for 'Designs' and 'Editor'. The 'Designs' tab shows a list of designs: 'CHK1', '2_TZQ', '5_7-CTP', and '4_4-CTP'. The 'Editor' tab shows a 2D chemical structure of the ligand. The 'Viewer' tab shows a 3D molecular model of the protein-ligand complex. The right sidebar contains a 'Structures' panel with a search bar and a list of structures: '2X8E_pe', '2YDJ_pe', '2YDK_pe', '6FC8_pe', '1_AZD7762', '2_TZQ', '3_TCU', and '5_7-CTP'. The interface also includes a 'Sort by' dropdown menu and a 'Group by' dropdown menu.

A more complicated design case



As previously, I start by aligning my 2D design to the X-ray reference

Then I cleave the hydrazide bond

Get rid of the imino substituent

torx
Projects Layouts Plugins Sharing

Designs x Editor x

CHK1
New design Upload Filters

Sort by
Modified

Group by

2_TZQ
Idea
No Design Set

5_7-CTP
Idea
No Design Set

4_4-CTP

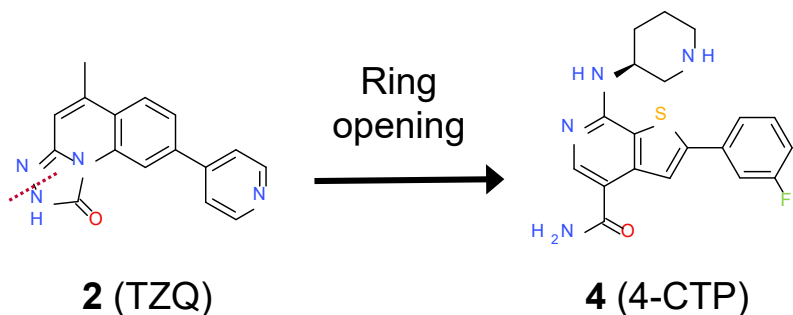
Viewer x
Align 2_TZQ

Structures
Search residues
Only show selected residues

Proteins
+ 2X8E_pe
+ 2YDJ_pe
+ 2YDK_pe
+ 6FC8_pe

Ligands
1_AZD7762
2_TZQ
3_TCU
5_7-CTP

A more complicated design case



As previously, I start by aligning my 2D design to the X-ray reference

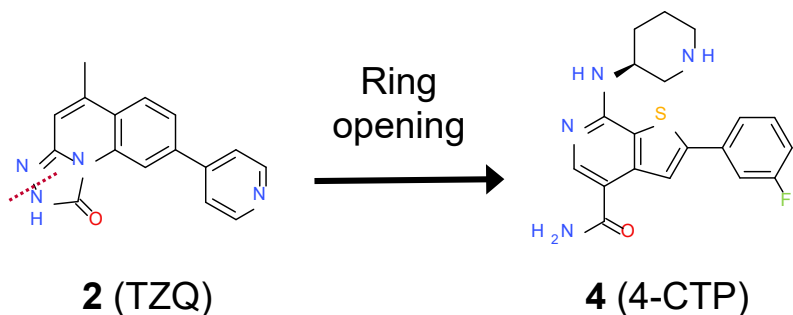
Then I cleave the hydrazide bond

Get rid of the imino substituent

Re-aromatize the system

Screenshot of the Torx software interface. The main window displays a 2D chemical structure of a molecule. The interface includes a top navigation bar with "torx" logo, "Projects", "Layouts", "Plugins", and "Sharing" menus. Below the navigation bar, there are tabs for "Designs" and "Editor". The "Designs" tab shows a list of designs: "CHK1", "2_TZQ", "5_7-CTP", and "4_4-CTP". The "Editor" tab shows a 3D molecular model of the molecule, with a "Viewer" window below it. The "Viewer" window shows a 3D representation of the molecule, with a "Align" button and a dropdown menu showing "2_TZQ". On the right side, there is a "Structures" panel with a search bar and a list of structures: "2X8E_pe", "2YDJ_pe", "2YDK_pe", "6FC8_pe", "1_AZD7762", "2_TZQ", "3_TCU", and "5_7-CTP".

A more complicated design case



As previously, I start by aligning my 2D design to the X-ray reference

Then I cleave the hydrazide bond

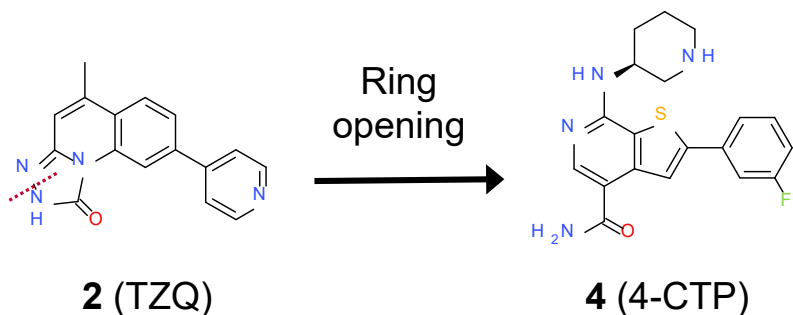
Get rid of the imino substituent

Re-aromatize the system

Turn the naphthalene into an isoquinoline

Screenshot of the Torx software interface. The main window displays a 2D chemical structure of a naphthalene derivative. The interface includes a sidebar with a list of designs (2_TZQ, 5_7-CTP, 4_4-CTP) and a viewer window showing a 3D molecular model of the structure docked into a protein binding site. The protein structure is shown in grey, and the ligand is shown in magenta. The viewer window also displays a list of structures and ligands.

A more complicated design case



Then I cleave the hydrazide bond

Get rid of the imino substituent

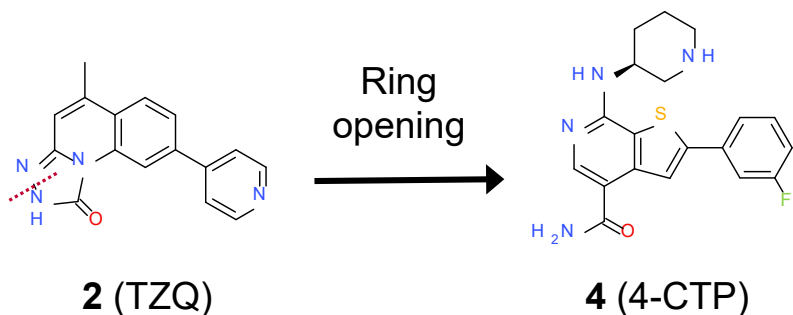
Re-aromatize the system

Turn the naphthalene into an isoquinoline

Break the phenyl ring as I need to make it 5-term

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a browser window at the top with the URL <https://torxlab.com>. The main workspace displays a chemical structure of a ligand (2-TZQ) and a protein structure (2X8E_pe). The left sidebar shows a list of designs, including 2-TZQ, 5-7-CTP, and 4-4-CTP. The right sidebar shows a list of structures and ligands, including 2X8E_pe, 2YDJ_pe, 2YDK_pe, 6FC8_pe, 1_AZD7762, 2_TZQ, 3_TCU, and 5-7-CTP.

A more complicated design case



Get rid of the imino substituent

Re-aromatize the system

Turn the naphthalene into an isoquinoline

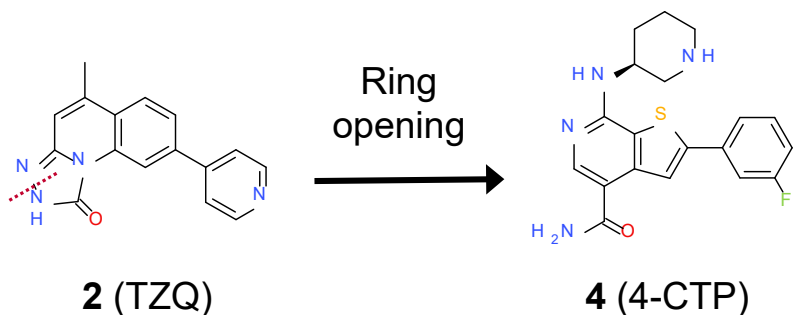
Break the phenyl ring as I need to make it 5-term

Close to a cyclopentadiene ring

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a top navigation bar with 'torx' logo, 'Projects', 'Layouts', 'Plugins', and 'Sharing' menus. The main workspace is divided into several panels:

- Designs:** Shows a list of designs including 'CHK1' with buttons for 'New design', 'Upload', and 'Filters'. It also has 'Sort by' (Modified) and 'Group by' options.
- Editor:** Displays the chemical structure of the target molecule, 4 (4-CTP), in a 2D representation.
- Viewer:** Shows a 3D molecular model of the target molecule docked into a protein structure (2X8E_pe). The protein structure is shown in a stick representation, and the target molecule is highlighted in magenta.
- Structures:** A sidebar panel with a search bar and a list of structures: '2X8E_pe', '2YDJ_pe', '2YDK_pe', and '6FC8_pe'. It also has a 'Close' button.
- Proteins:** A sidebar panel with a list of proteins: '1_AZD7762', '2_TZQ', '3_TCU', and '5_7-CTP'. It also has a 'Close' button.
- Ligands:** A sidebar panel with a list of ligands: '1_AZD7762', '2_TZQ', '3_TCU', and '5_7-CTP'. It also has a 'Close' button.

A more complicated design case



Re-aromatize the system

Turn the naphthalene into an isoquinoline

Break the phenyl ring as I need to make it 5-term

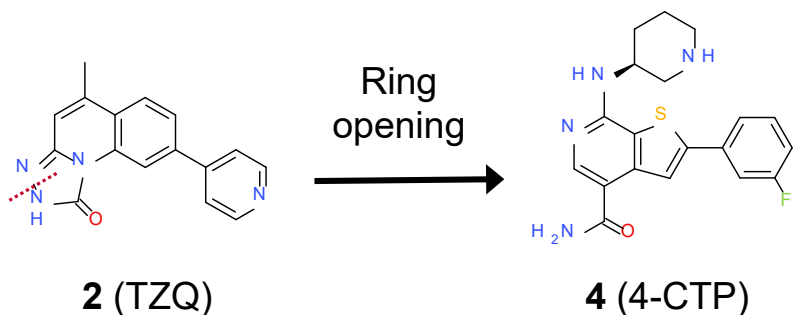
Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a browser window at the top with the URL <https://torxlab.com>. The main workspace is divided into several panels:

- Editor:** Displays the chemical structure of the ligand 2 (TZQ) in a 2D representation.
- Viewer:** Shows a 3D molecular model of the ligand docked into the protein structure of CHK1. The protein is shown in a grey stick representation, and the ligand is highlighted in pink and yellow.
- Structures:** A sidebar on the right lists the structures currently loaded in the viewer, including proteins (2X8E_pe, 2YDJ_pe, 2YDK_pe, 6FC8_pe) and ligands (1_AZD7762, 2_TZQ, 3_TCU, 5_7-CTP).
- Designs:** A sidebar on the left shows a list of designs, including 2_TZQ, 5_7-CTP, and 4_4-CTP. Each design entry includes a small thumbnail of the molecule and the text "Idea No Design Set".

A more complicated design case



Turn the naphthalene into an isoquinoline

Break the phenyl ring as I need to make it 5-term

Close to a cyclopentadiene ring

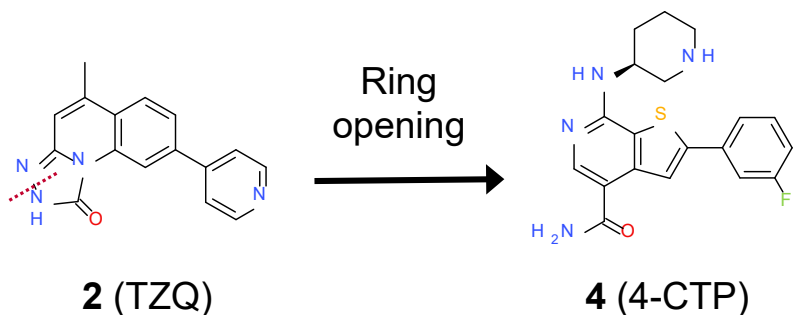
Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a top navigation bar with "torx" logo, "Projects", "Layouts", "Plugins", and "Sharing" menus. The main workspace is divided into several panels:

- Editor:** Displays the chemical structure of the ligand, 4 (4-CTP), with a toolbar for editing.
- Viewer:** Shows a 3D molecular model of the ligand bound to the protein structure, with a toolbar for viewing and docking.
- Structures:** A sidebar panel with a search bar and a list of structures: "2X8E_pe", "2YDJ_pe", "2YDK_pe", and "6FC8_pe".
- Ligands:** A sidebar panel with a list of ligands: "1_AZD7762", "2_TZQ", "3_TCU", and "5_7-CTP".
- Designs:** A sidebar panel showing a list of designs: "2_TZQ", "5_7-CTP", and "4_4-CTP". Each design has a thumbnail image and the text "Idea No Design Set".

A more complicated design case



Break the phenyl ring as I need to make it 5-term

Close to a cyclopentadiene ring

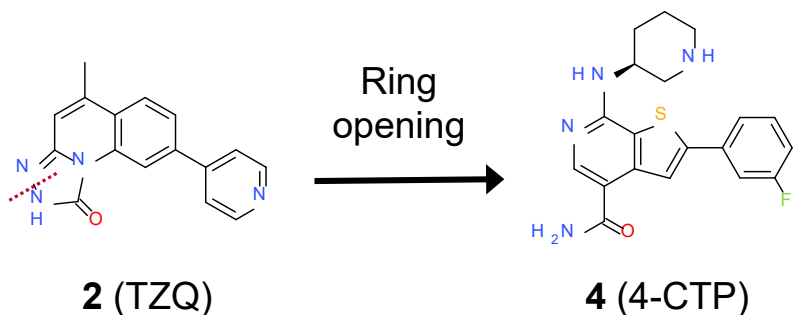
Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Add *m*-fluorine to benzene

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a browser window at the top with the URL <https://torxlab.com>. The main workspace is divided into several panels: a top-left panel with "CHK1" and buttons for "New design", "Upload", and "Filters"; a top-right panel showing a 2D chemical structure of a ligand; a bottom-left panel with a "Viewer" showing a 3D molecular model of the ligand bound to a protein structure; and a bottom-right panel with a "Structures" sidebar listing various residues and ligands. The sidebar lists "Proteins" (2X8E_pe, 2YDJ_pe, 2YDK_pe, 6FC8_pe) and "Ligands" (1_AZD7762, 2_TZQ, 3_TCU, 5_7-CTP). The interface also features a "Designs" list on the left with entries for "2_TZQ", "5_7-CTP", and "4_4-CTP".

A more complicated design case



Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

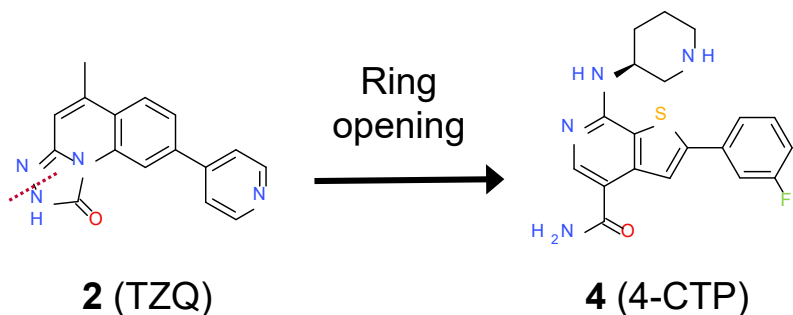
Turn pyridine into benzene

Add *m*-fluorine to benzene

Grow methyl into an ethyl

Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a browser address bar (https://torxlab.com), navigation menus (Projects, Layouts, Plugins, Sharing), and a main editor area displaying the chemical structure of 4 (4-CTP). The left sidebar shows a list of designs (2_TZQ, 5_7-CTP, 4_4-CTP) and a viewer area showing a 3D molecular model of the ligand bound to the protein structure. The right sidebar displays a list of structures and ligands, including 2_TZQ and 5_7-CTP.

A more complicated design case



Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

Turn pyridine into benzene

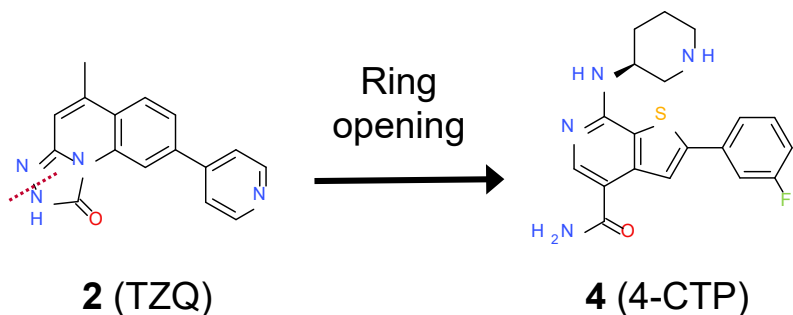
Add *m*-fluorine to benzene

Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

Screenshot of the Torx software interface showing the design process for compound **4 (4-CTP)**. The interface displays the chemical structure of the target molecule in the Editor view. The left sidebar shows a list of designs, including **2_TZQ**, **5_7-CTP**, and **4_4-CTP**. The bottom right panel shows the Structures list, including **2_TZQ** and **5_7-CTP**. The interface also shows a protein structure (2X8E_pe) and a ligand (1_AZD7762) docked into the protein binding site.

A more complicated design case



Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Add *m*-fluorine to benzene

Grow methyl into an ethyl

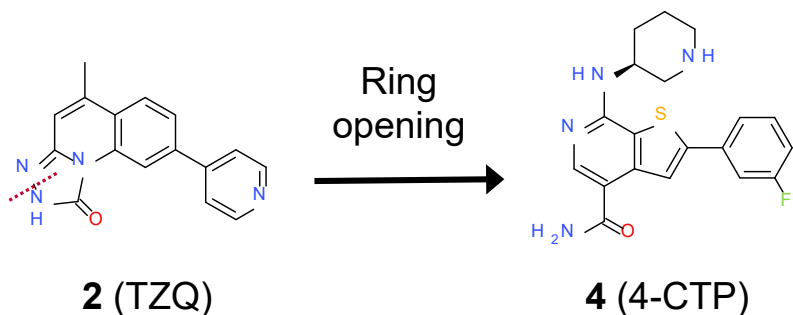
Attach a cyclohexyl to the ethyl

Turn methylene into amino

Screenshot of the Torx software interface showing the design process for CHK1. The interface includes a browser window at the top with the URL <https://torxlab.com>. The main workspace is divided into several panels:

- Editor:** Displays the chemical structure of the target molecule, CHK1, which is a complex heterocyclic molecule with a thiophene ring, a benzene ring (with a fluorine atom at the para position), an ethyl group, and a cyclohexyl ring.
- Viewer:** Shows a 3D molecular model of the target molecule docked into a protein structure, with various interaction points highlighted.
- Structures:** A sidebar panel listing the structures used in the design process, including 2X8E_pe, 2YDJ_pe, 2YDK_pe, 6FC8_pe, 1_AZD7762, 2_TZQ, 3_TCU, and 5_7-CTP.
- Designs:** A sidebar panel showing the design process, including the starting material 2_TZQ and the final product 4_4-CTP.

A more complicated design case



Turn pyridine into benzene

Add *m*-fluorine to benzene

Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

Turn methylene into amino

Turn cyclohexyl into 3-piperidyl

Screenshot of the Torx software interface showing the design process for 4 (4-CTP). The interface includes a browser window at the top with the URL <https://torxlab.com>. The main workspace displays the chemical structure of 4 (4-CTP) in a 2D representation. Below the structure, there is a 3D molecular model showing the ligand docked into a protein structure. The interface also features a sidebar with design options, a viewer window, and a panel on the right showing the list of structures and ligands.

Structures

- Search residues
- Only show selected residues

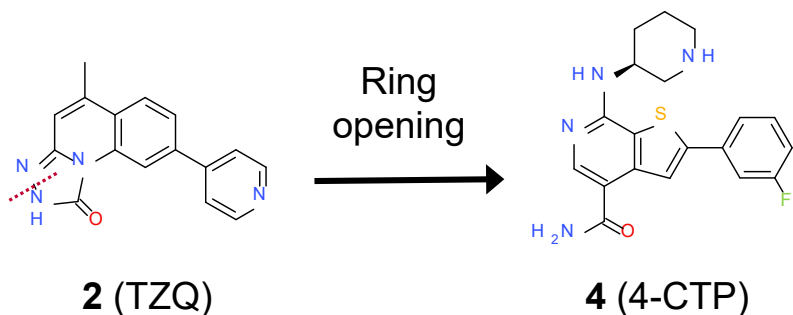
Proteins

- + 2X8E_pe
- + 2YDJ_pe
- + 2YDK_pe
- + 6FC8_pe

Ligands

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

A more complicated design case



Add *m*-fluorine to benzene

Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

Turn methylene into amino

Turn cyclohexyl into 3-piperidyl

Final clean-up, and we're done!

The screenshot shows the Torx software interface. The main window displays the chemical structure of 4-CTP. The interface includes a sidebar with a list of designs, a central editor area with various tools, and a bottom panel showing the protein structure and a list of structures and ligands.

Designs: CHK1

Sort by: Modified

Group by: [Dropdown]

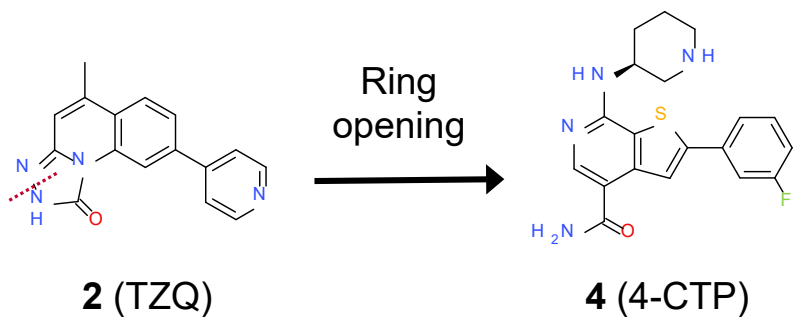
Structures:

- 2X8E_pe
- 2YDJ_pe
- 2YDK_pe
- 6FC8_pe

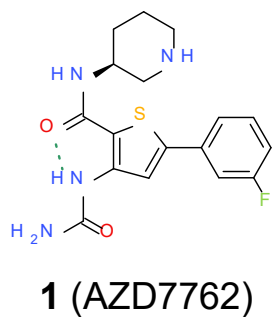
Ligands:

- 1_AZD7762
- 2_TZQ
- 3_TCU
- 5_7-CTP

A more complicated design case



This is how our designed **4** compares against the experimental X-ray structure of **1** (2YDJ)...



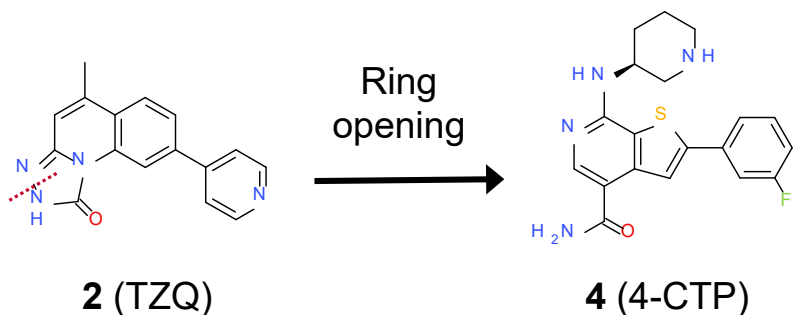
Screenshot of the Torx software interface showing a design project for CHK1. The interface includes a design list on the left, a central editor window, and a 3D viewer window.

The design list shows three designs:

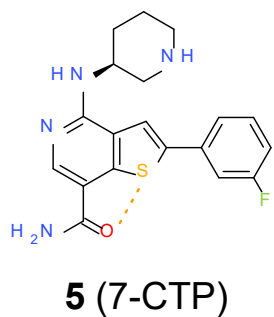
- 2_TZQ
- 5_7-CTP
- 4_4-CTP

The 3D viewer shows the protein structure (2X8E_pe) and the designed ligand (4_4-CTP) docked in the binding pocket. The protein structure is shown in grey, and the ligand is shown in a stick representation with a color gradient.

A more complicated design case



...and against the experimental X-ray structure of its close analogue 5 (6FC8)



Screenshot of the Torx software interface showing a molecular design project for CHK1. The interface includes a design list on the left, a central editor window, and a viewer window displaying the protein structure and ligands.

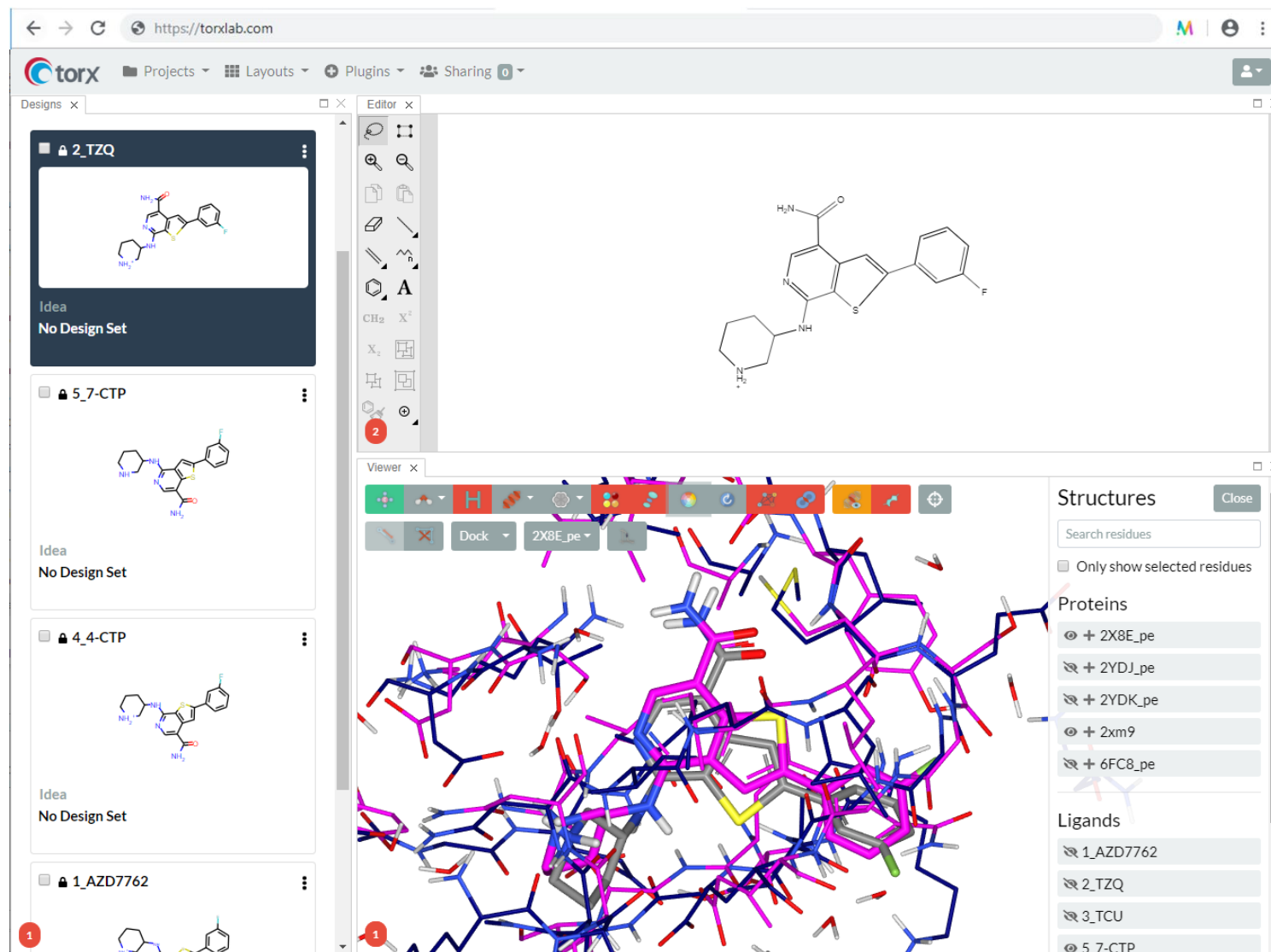
The design list shows:

- 2_TZQ
- 5_7-CTP
- 4_4-CTP

The viewer window displays the protein structure (2X8E_pe) and the ligands (2_TZQ, 3_TCU, 5_7-CTP).

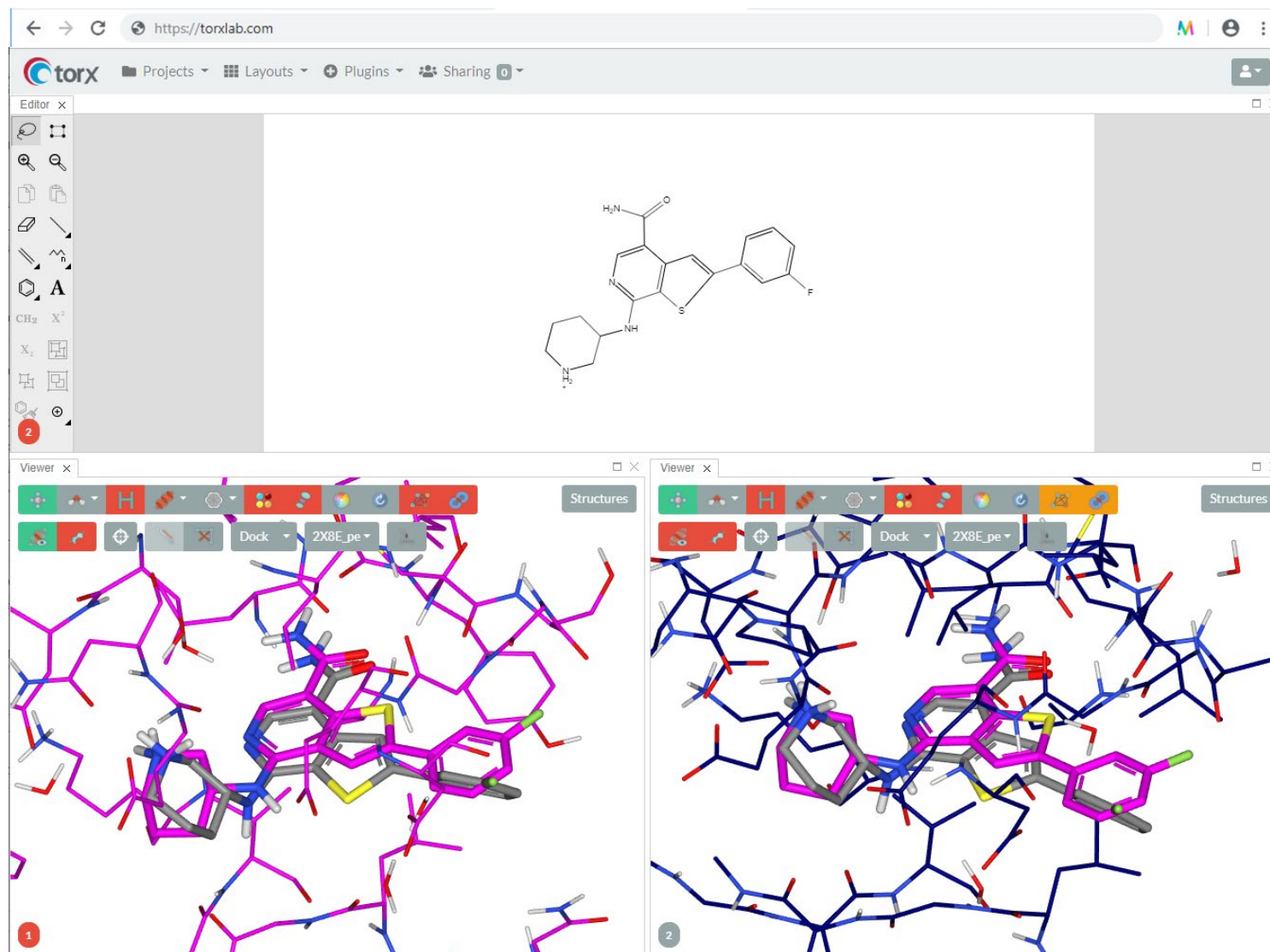
Adding in selectivity – traditional view

- > How to design for selectivity?
 - > One 3D pose or multiple?
- > Focus on simplicity → one pose
- Visualize against alternative targets
 - As with many other applications



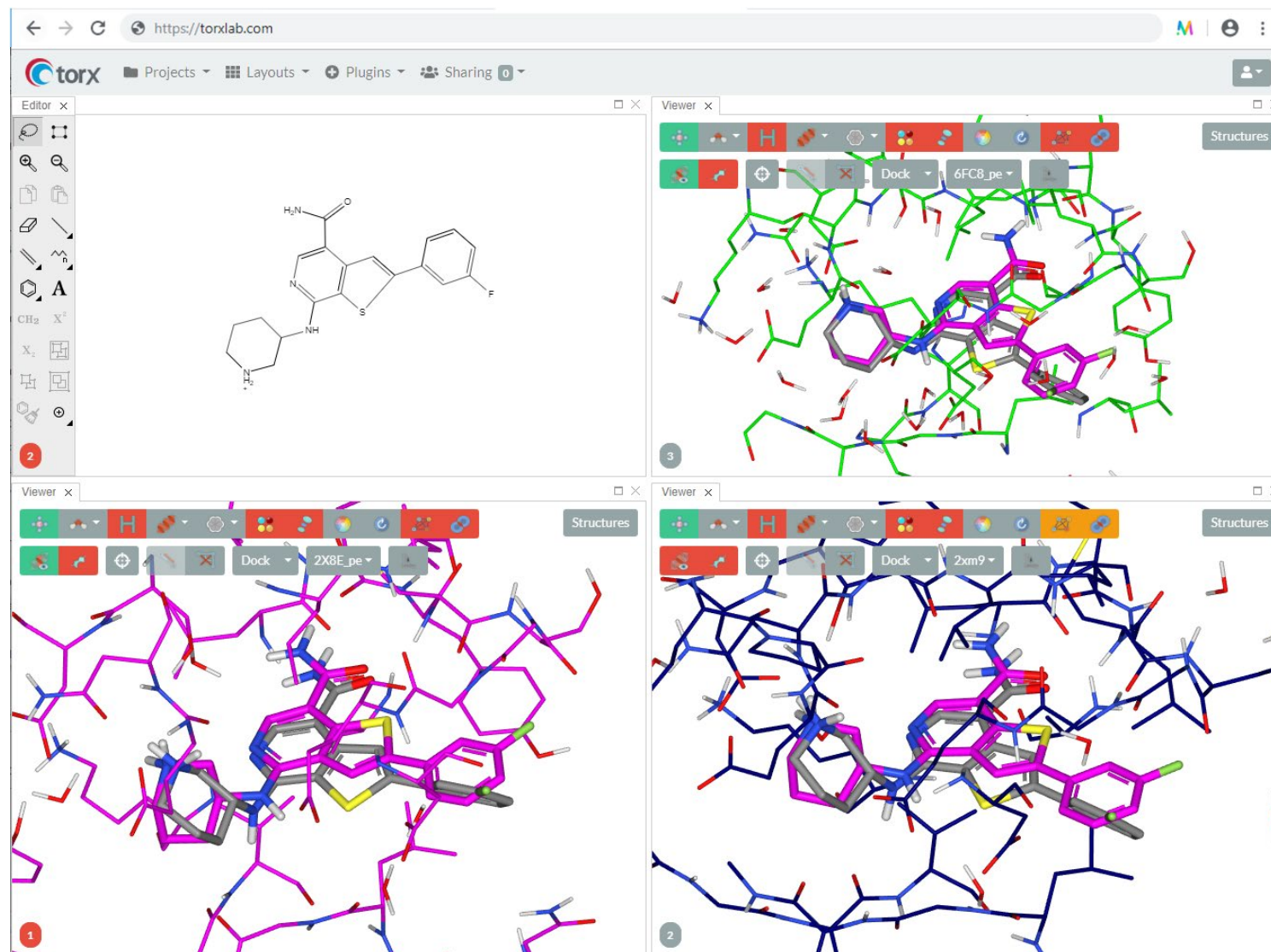
Adding in selectivity – side by side visualization

- > Traditional view creates difficulties in viewing interactions and clashes
- > By using separate viewers we can assess the ligand against each protein independently



Adding in selectivity – Multiple 3D views

- > There is no limit on the number of viewers
 - > Except screen space
- > All respond to changes in the 2D structure



Looking ahead – more advanced modelling techniques

- > Currently we are limited to viewing structures
- > More advanced modelling techniques provide quantitation

> Electrostatic complementarity

> FEP

Journal of
**Medicinal
Chemistry**

Article
Cite This: *J. Med. Chem.* 2019, 62, 3036–3050
pubs.acs.org/jmc

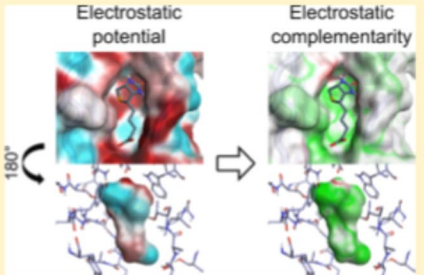
Electrostatic Complementarity as a Fast and Effective Tool to Optimize Binding and Selectivity of Protein–Ligand Complexes

Matthias R. Bauer* and Mark D. Mackey

Cresset, New Cambridge House, Bassingbourn Road, Litlington, Cambridgeshire SG8 0SS, U.K.

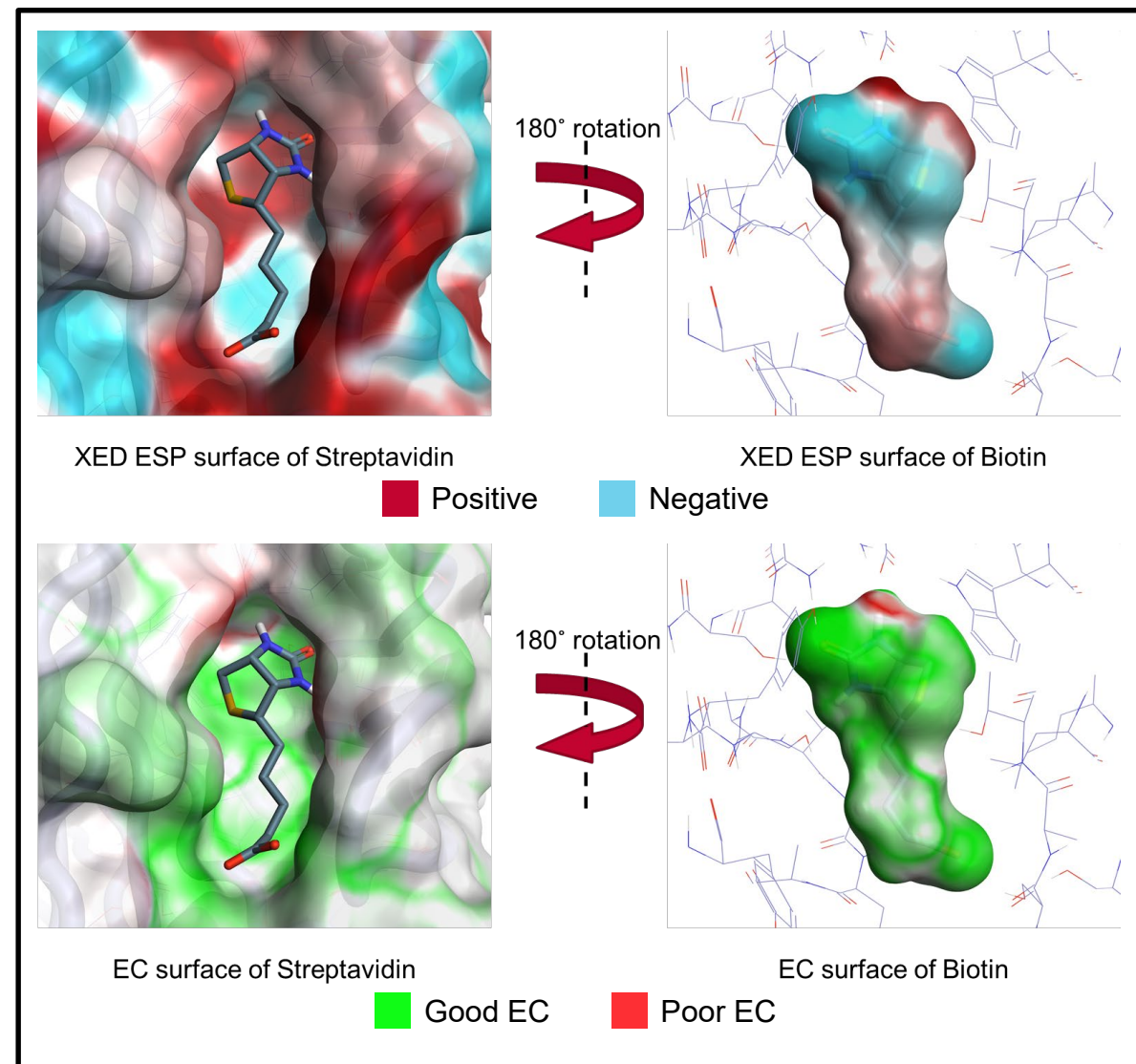
Supporting Information

ABSTRACT: Electrostatic interactions between small molecules and their respective receptors are essential for molecular recognition and are also key contributors to the binding free energy. Assessing the electrostatic match of protein–ligand complexes therefore provides important insights into why ligands bind and what can be changed to improve binding. Ideally, the ligand and protein electrostatic potentials at the protein–ligand interaction interface should maximize their complementarity while minimizing desolvation penalties. In this work, we present a fast and efficient tool to calculate and visualize the electrostatic complementarity (EC) of protein–ligand complexes. We compiled benchmark sets demonstrating electrostatically driven structure–activity relationships (SAR) from literature data, including kinase, protein–protein interaction, and GPCR targets, and used these to demonstrate that the EC method can visualize, rationalize, and predict electrostatically driven ligand affinity changes and help to predict compound selectivity. The methodology presented here for the analysis of EC is a powerful and versatile tool for drug design.

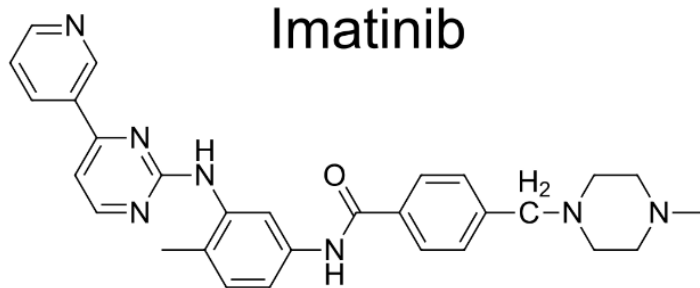


Electrostatic Complementarity as a guide for molecule design

- > Electrostatic interactions between ligands and proteins are an important factor in recognition and binding energetics
- > Assessing Electrostatic Complementarity (EC) provides
 - > Insight of why ligand bind
 - > Inform molecular design
 - > Predict activity
- > Dedicated algorithm to calculate and display where electrostatics are complementary

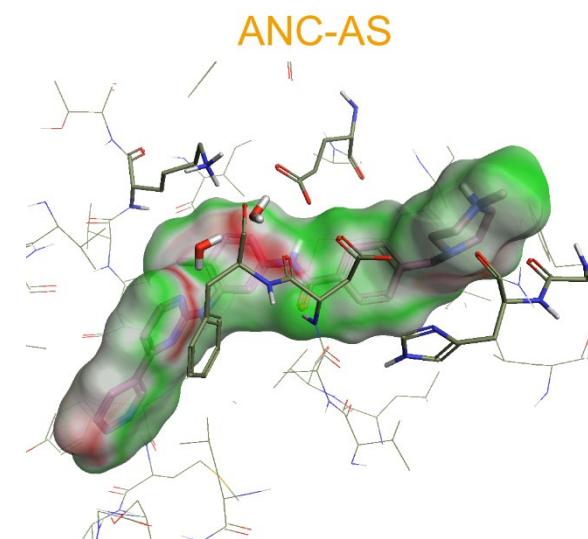
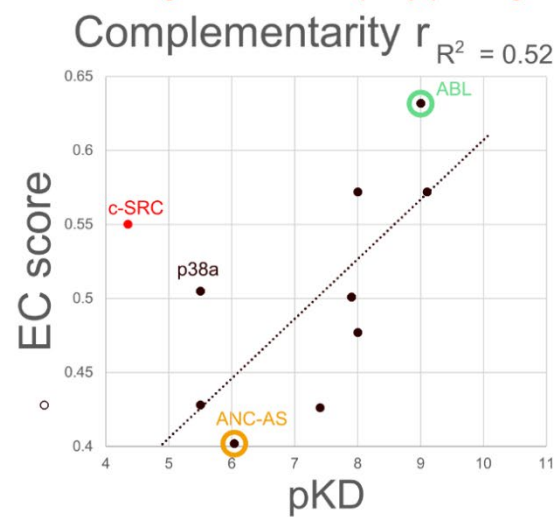
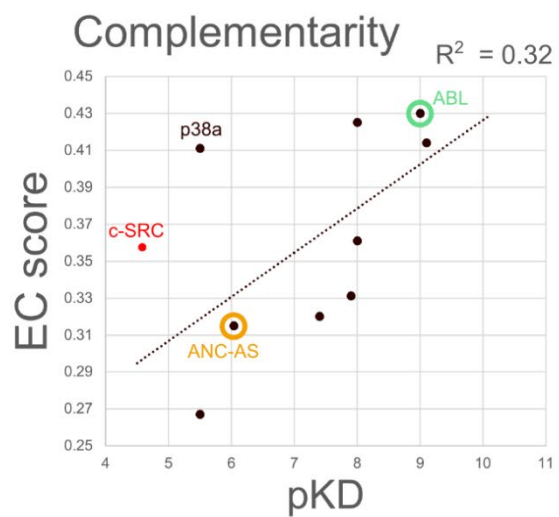
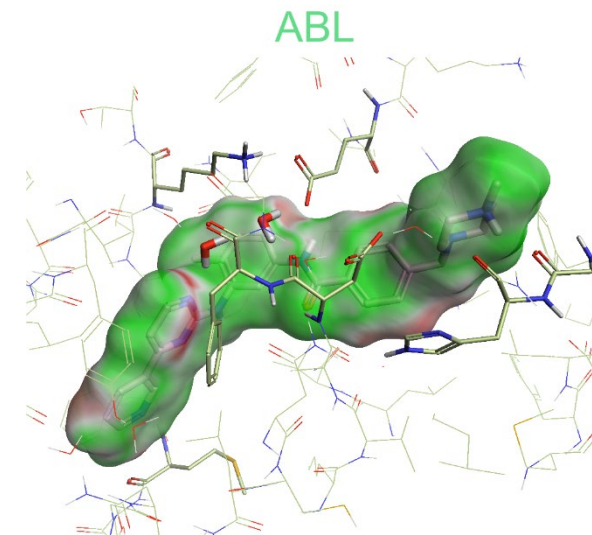


Imatinib – EC and selectivity



target	pdb	pKD	Complem entarity	Complem entarity r
c-SRC ^a	2OIQ	4.4	0.36	0.55
p38a	3HEC	5.5	0.41	0.51
SYK	1XBB	5.5	0.27	0.43
ANC-AS	4CSV	6.0	0.32	0.40
LCK	2PLO	7.4	0.32	0.43
KIT	1T46	7.9	0.33	0.50
CSF1	4R7I	8.0	0.36	0.48
ABL2	3GVU	8.0	0.43	0.57
ABL	1OPJ	9.0	0.43	0.63
DDR1	4BKJ	9.1	0.41	0.57

^a Imatinib binding decreased due to conf. penalty upon binding



EC Implementation into Torx

✓ ✓ ✓
> Surfaces on

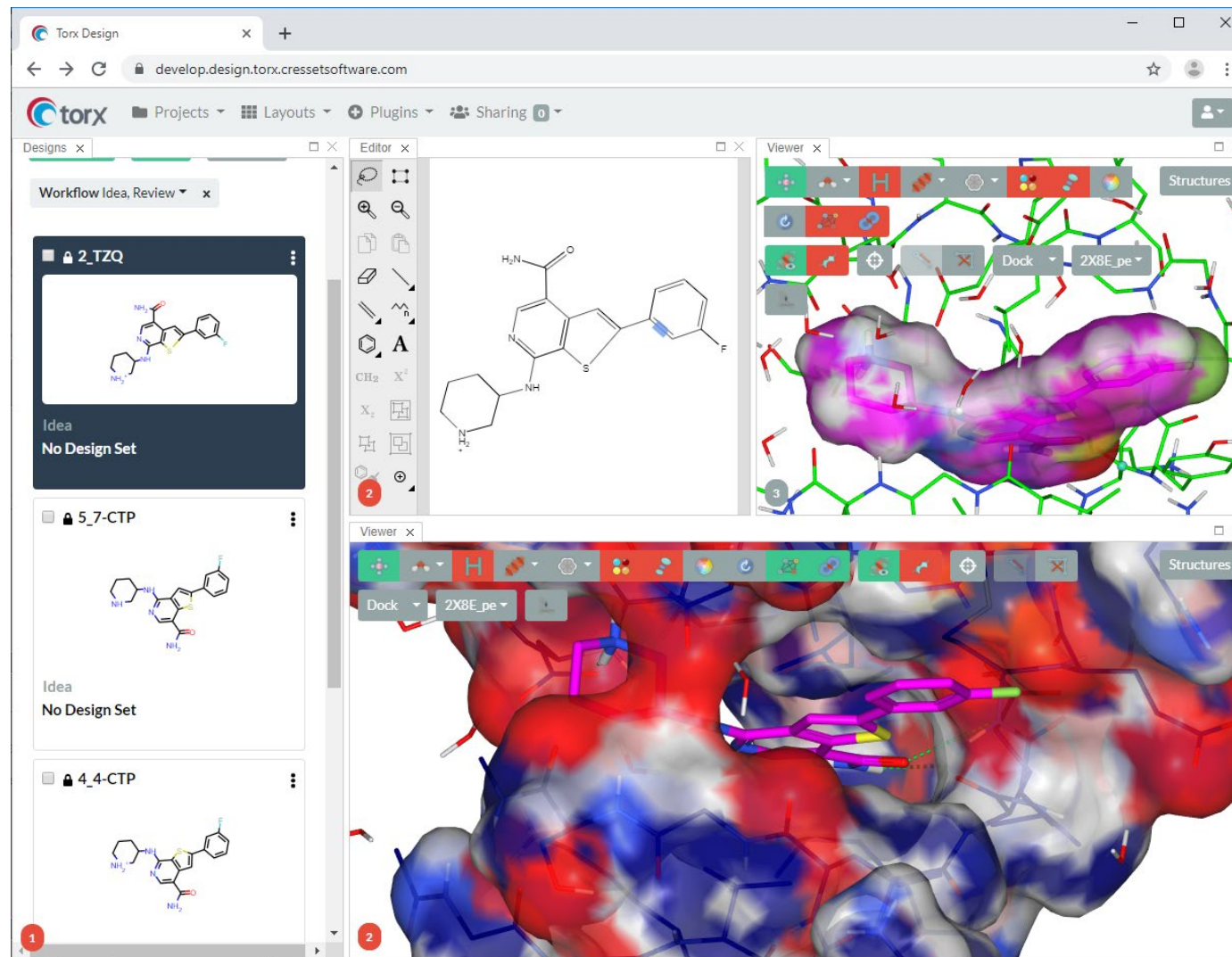
> Ligands

> Proteins

> Minimization of ligand
in binding site

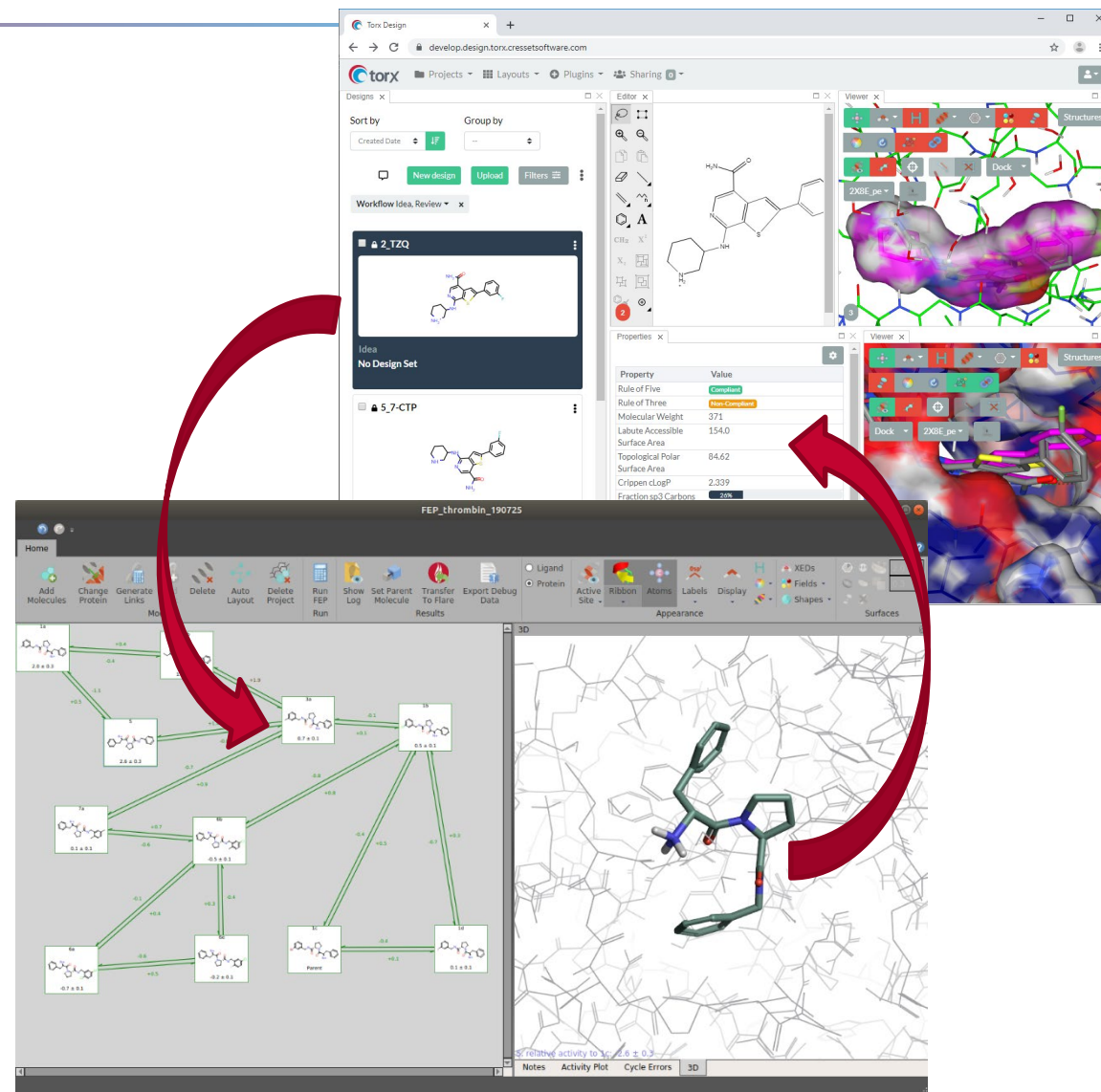
> Color by EC

> Z-clipping



What about FEP?

- > FEP calculations generally require skilled intervention
- > Calculations slow and expensive – too slow for automation?
- > Certainly too slow for interactive feedback
- > Alternative solution is to enable easy transfer of designs to specialist modelling application



Conclusions

- > Using Grow3D enables real-time conversion of 2D sketches to 3D designs
- > Full-fledged docking or alignment protocol as a failsafe
- > Implementation in web interface enables flexible display options
- > Future development to add quantitation – Electrostatic complementarity and FEP



innovative science • intuitive software



Thank you for
your attention

paolo@cresset-group.com

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@Cresset: Mark Mackey, Tim Cheeseright

The RDKit