innovative science • intuitive software

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

Paolo Tosco

What causes selectivity?

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

3D Property

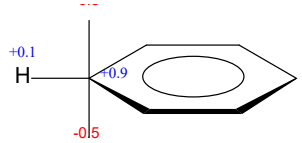
- Shape
  - Smaller / Larger residues
  - Alternative protein conformations

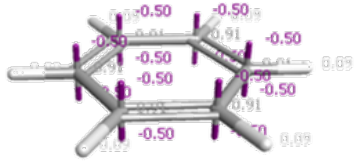
3D Property

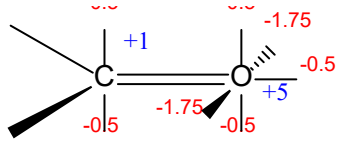
- Biological processes
  - E.g. Compartmentalization of targets

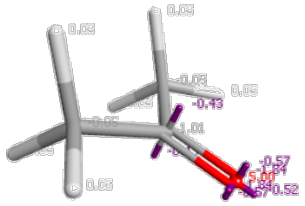
The XED force field

- XED force field – eXtended Electron Distribution
  - Multipoles via additional monopoles

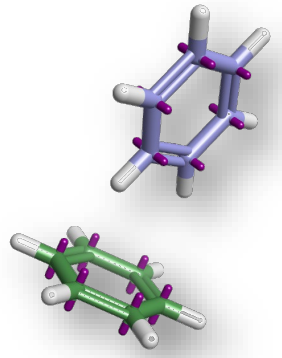








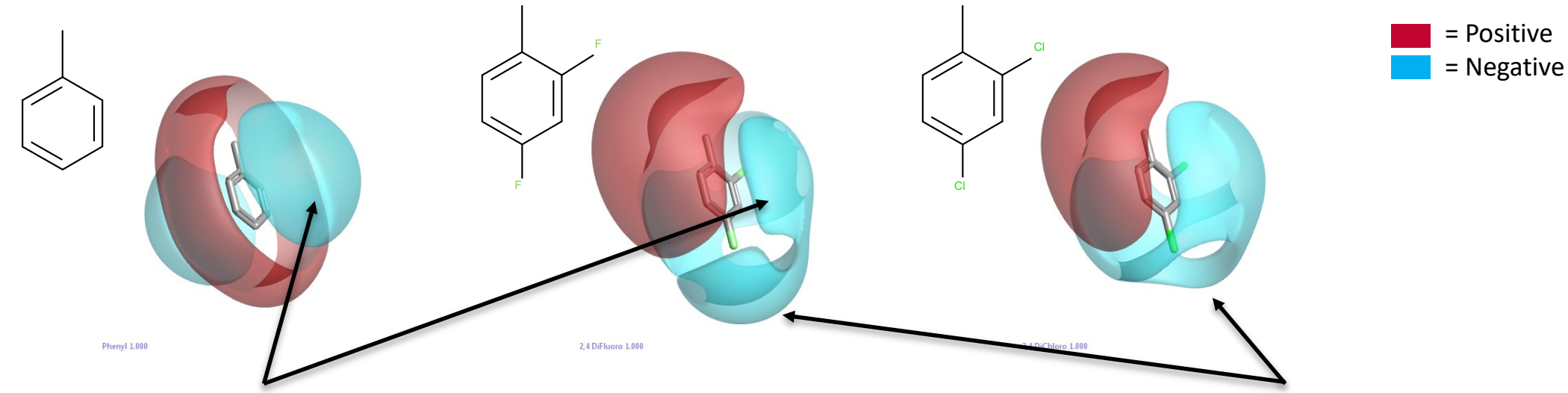
  - Huckel
    - separation of π and σ components of partial charges
      - π charges added to ‘xed’ atoms
      - σ charges added to nuclei
      - Excellent modeling of substituent effects



  - Full molecular mechanics force field with excellent coverage of organic chemistry, water and proteins
    - Minimization, conformations etc.
    - Not a dynamics force field

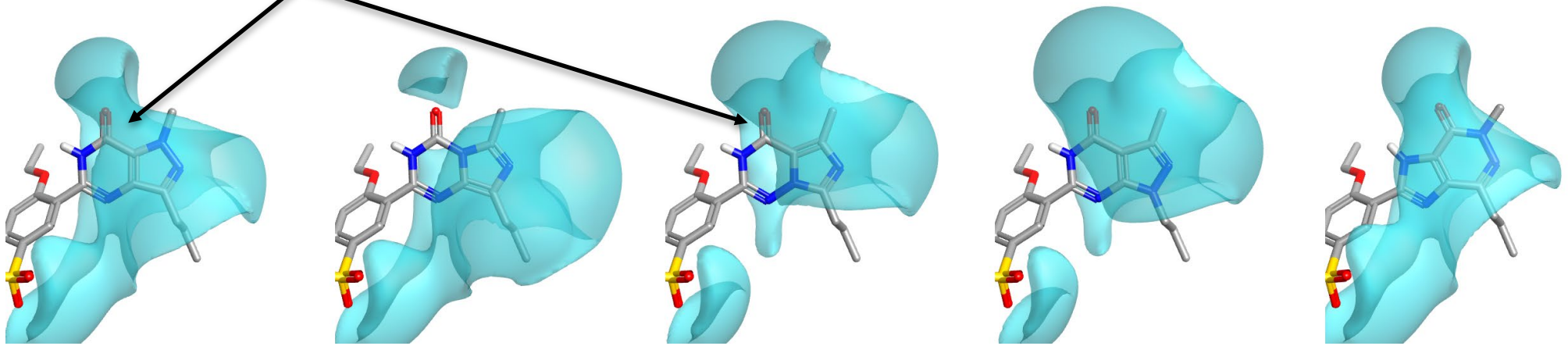
Vinter, *J. Comput.-Aided Mol. Des.*, **1994**, 8, 653-668

XED electrostatics generate detailed ligand interaction patterns

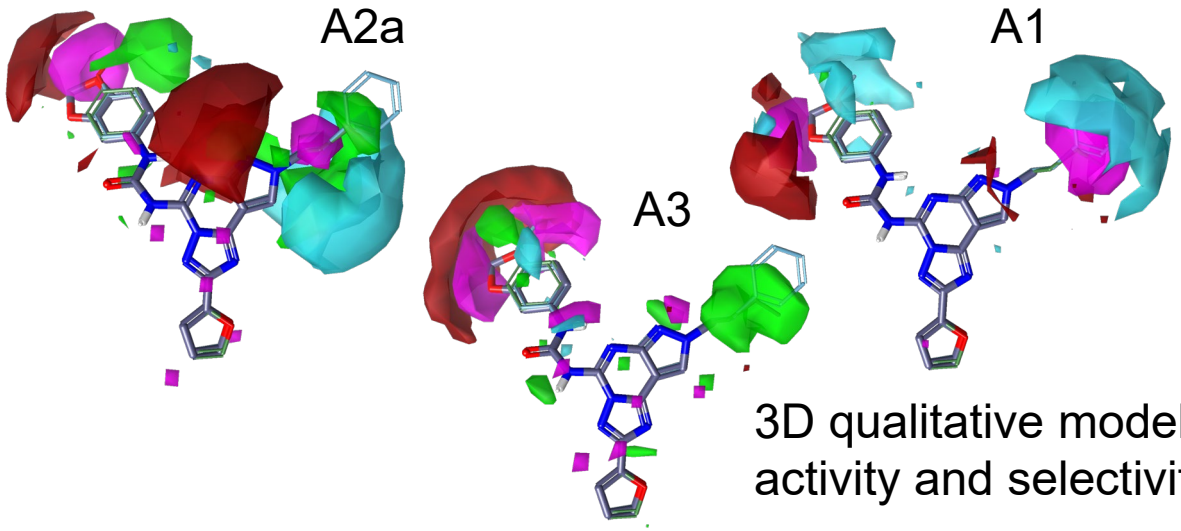


Detailed simulation of electron density changes

Detailed description of halogens

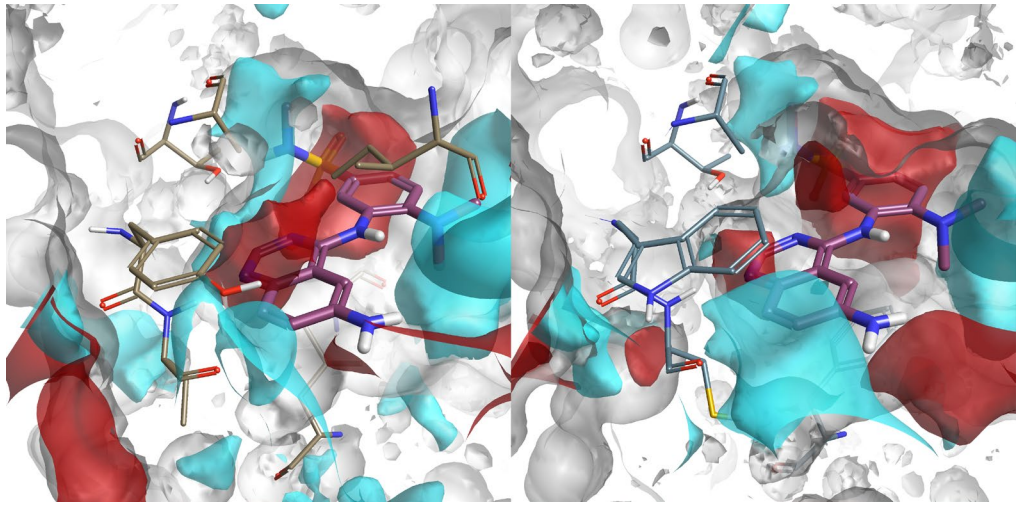


Designing for selectivity in Cresset applications



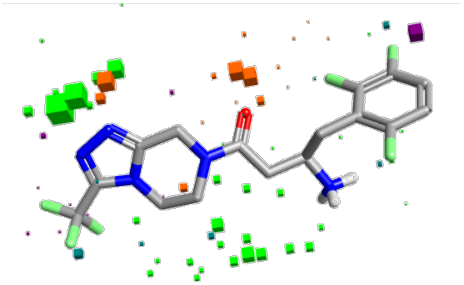
3D qualitative models of activity and selectivity

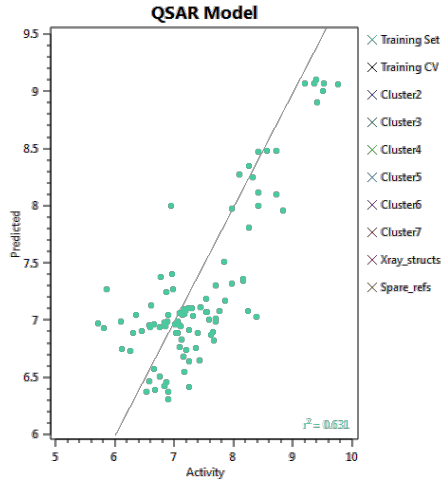
TNNI3K vs b-RAF



Protein electrostatics and protein – ligand electrostatic complementarity

3D qualitative models of activity and selectivity





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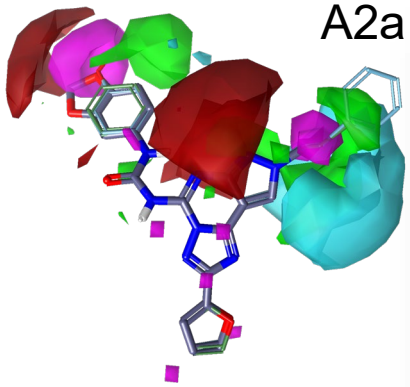
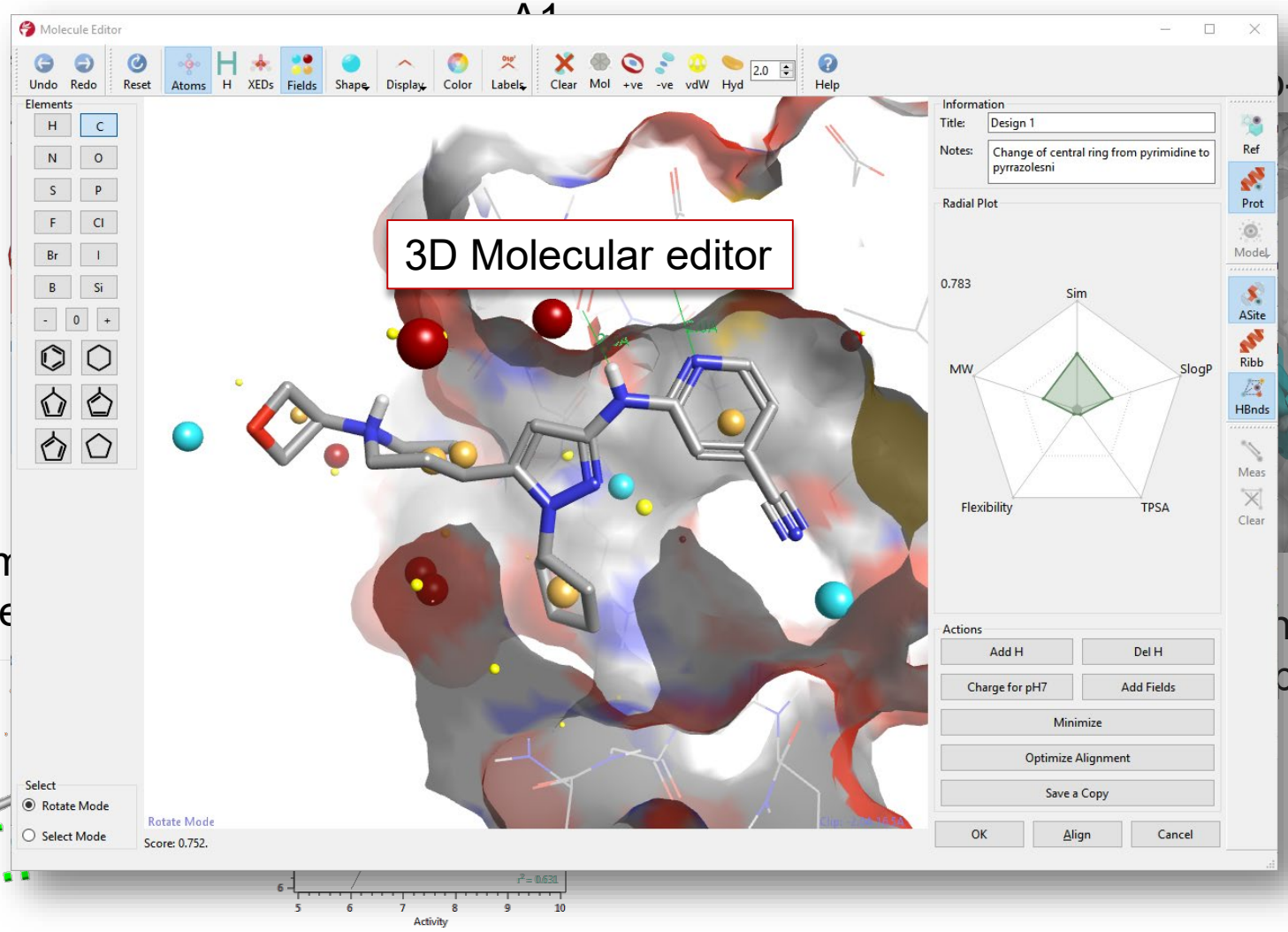
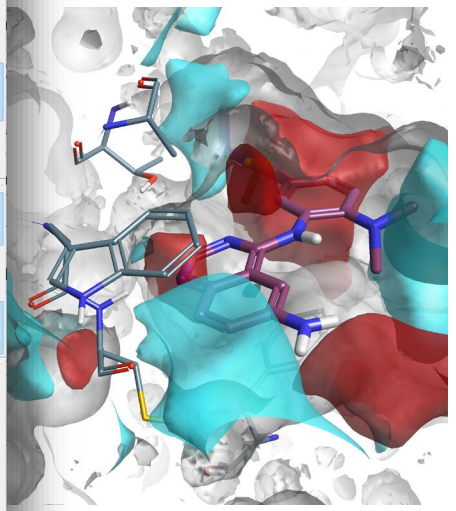
Designing for selectivity in Cresset applications



A2a



-RAF



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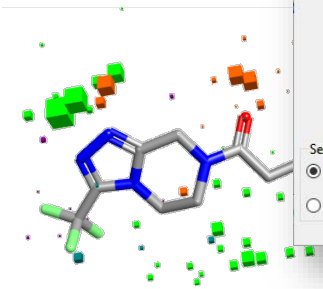

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Torch™ – Molecule design using ligand alignment

Customer requests:

Can I draw with ChemDraw?

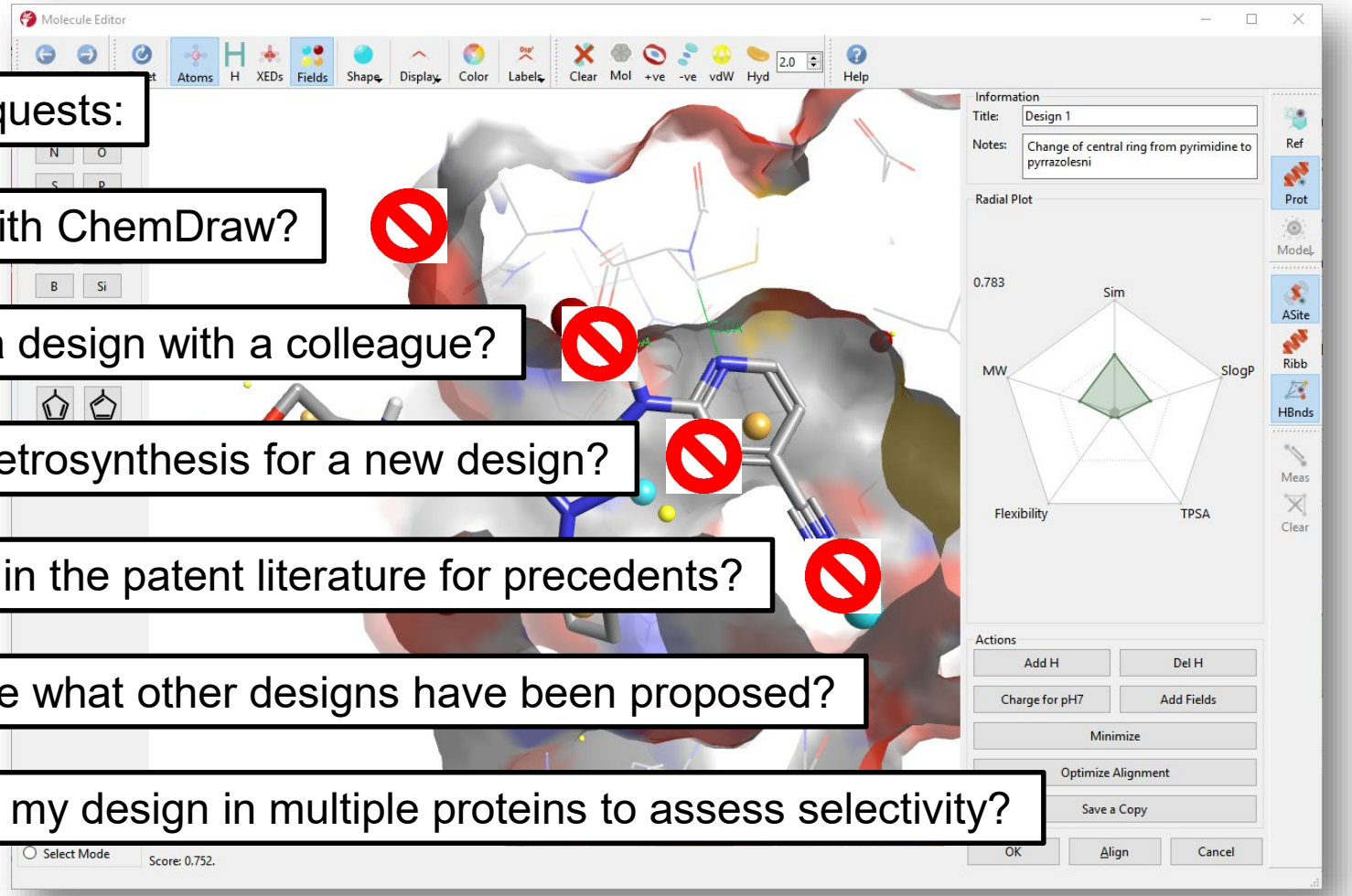
Can I share a design with a colleague?

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?



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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

Article

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

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[†,§]

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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

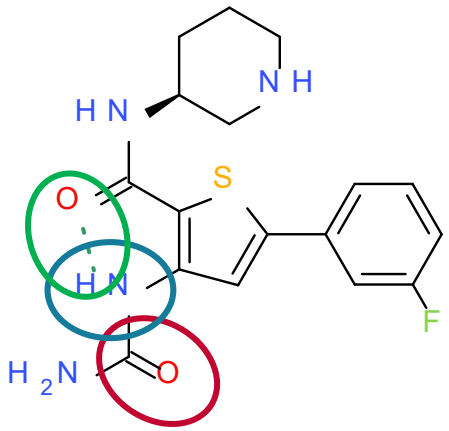
> CHK1 is a promising target to improve the therapeutic index of DNA-damaging anti-cancer agents

> 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

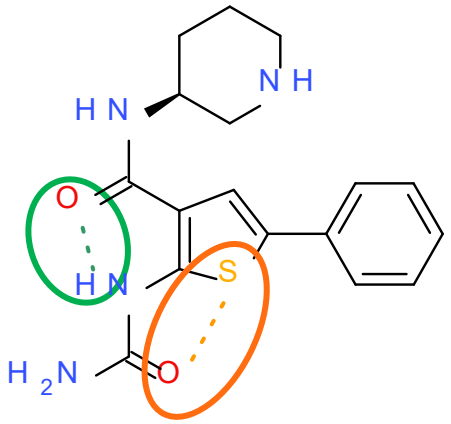
TCU and TZQ leads



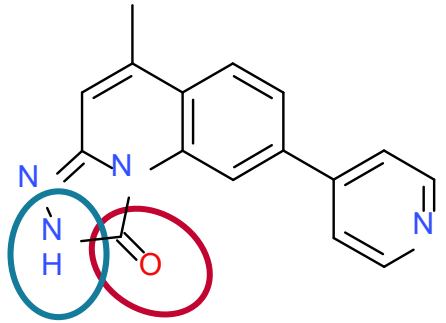
1 (AZD7762)
Thiophene carboxamide urea (TCU)
Clinical candidate

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

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



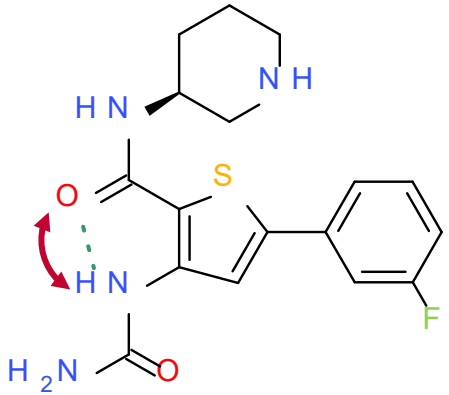
3
Thiophene carboxamide urea (TCU)
Matched pair with **1**



2
Triazoloquinolone (TZQ)

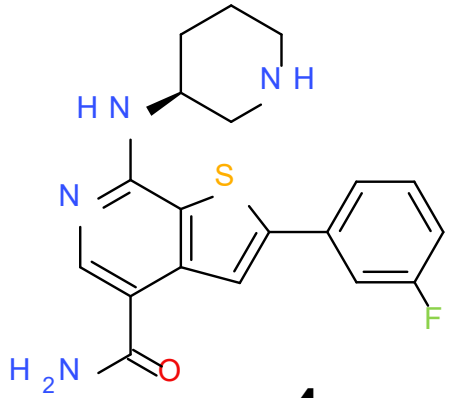
Both **1** and **3** feature an intramolecular hydrogen bond which stabilizes the bioactive conformation

Ring closure, ring opening



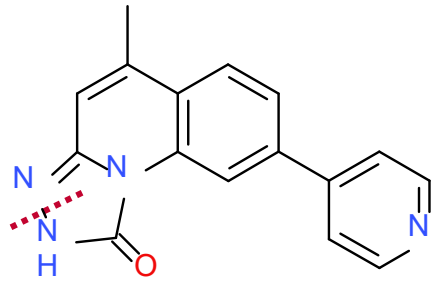
1 (AZD7762)
Thiophene carboxamide urea (TCU)
Clinical candidate

Ring closure

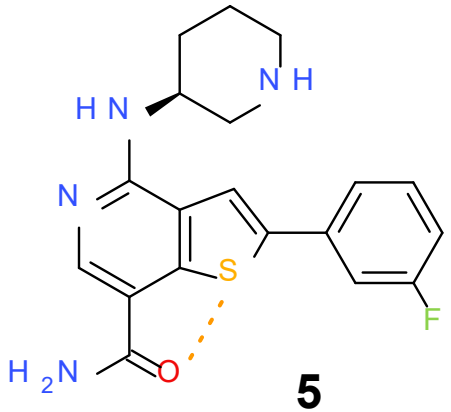


4
4-Carboxamide thienopyridine (4-CTP)

Ring opening



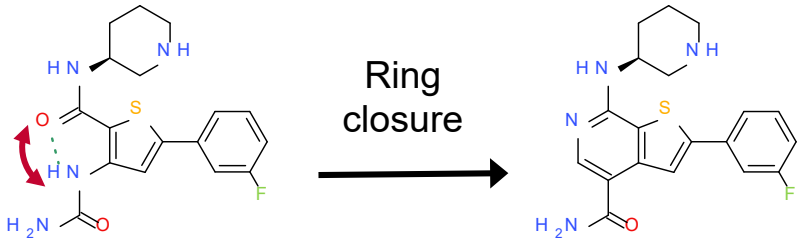
2
Triazoloquinolone (TZQ)



5
7-Carboxamide thienopyridine (7-CTP)

Matched pairs

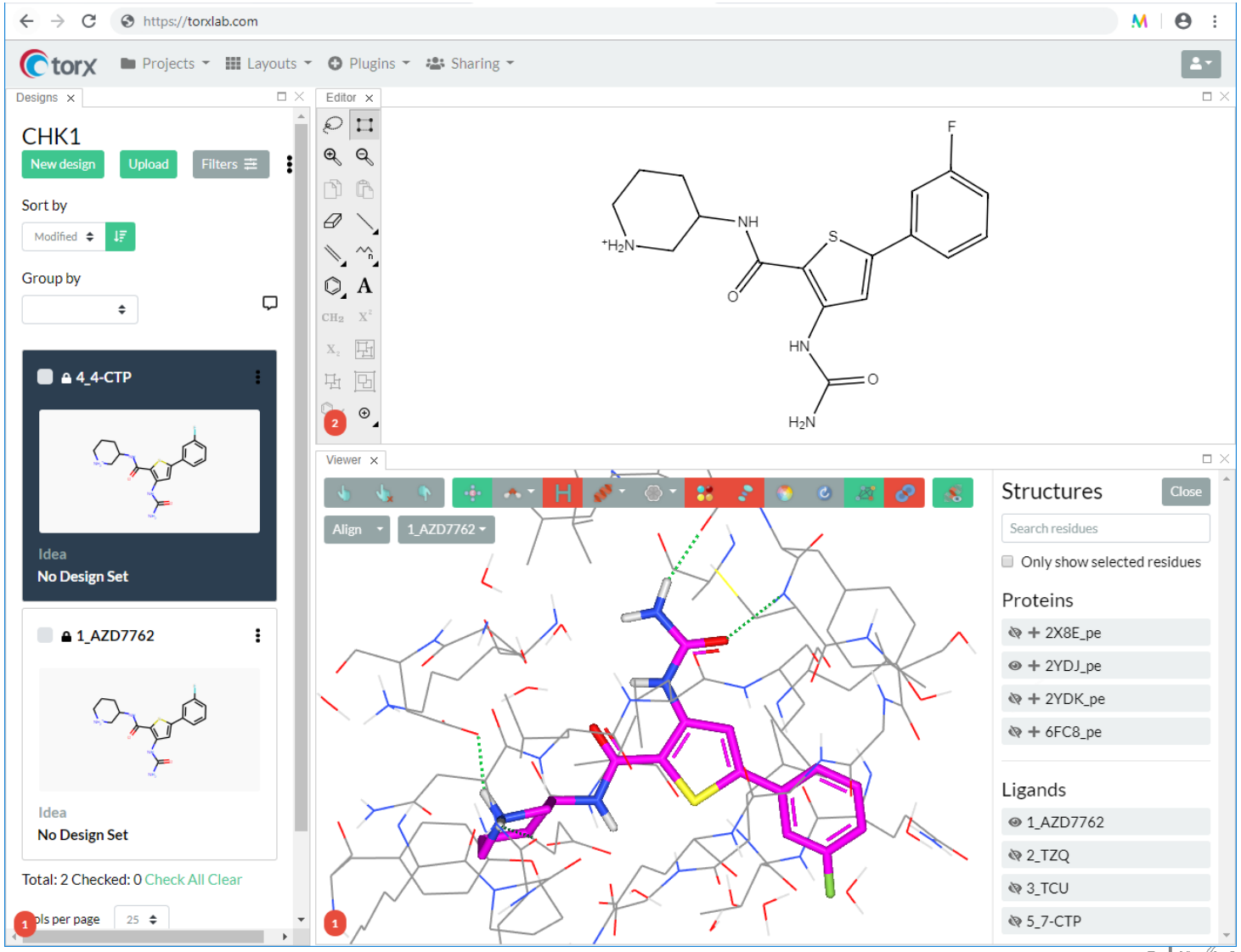
Ring closure in *grow3D*



1 (AZD7762) **4** (4-CTP)

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



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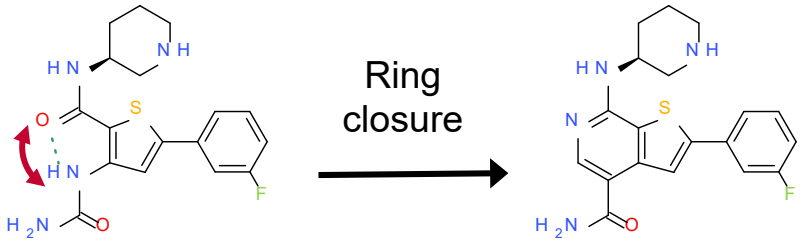
Positioning the initial 3D structure

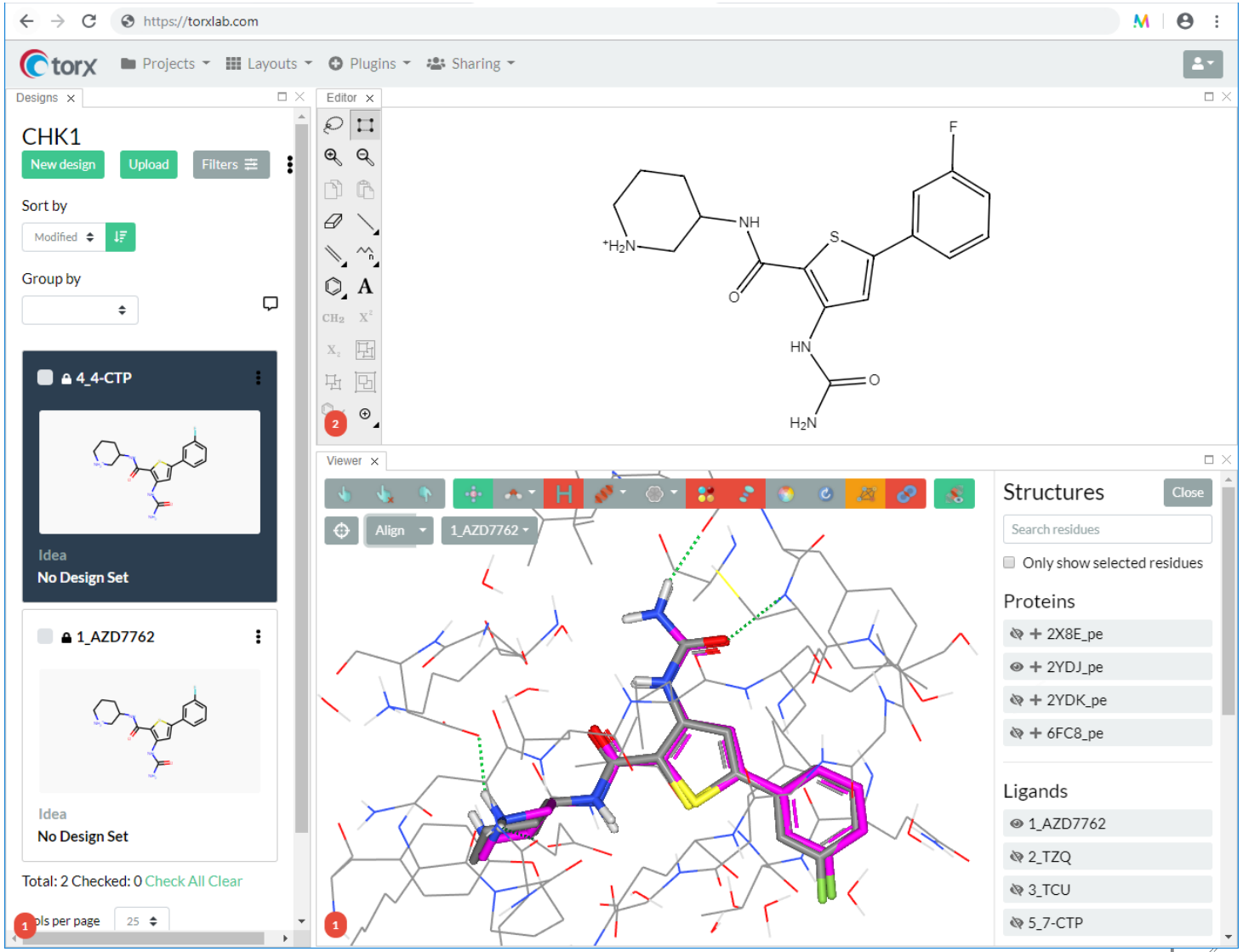


1 (AZD7762)

4 (4-CTP)

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



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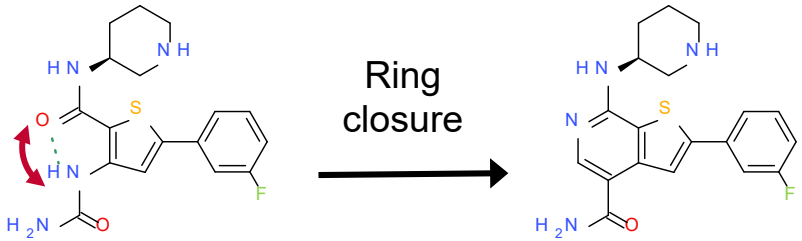
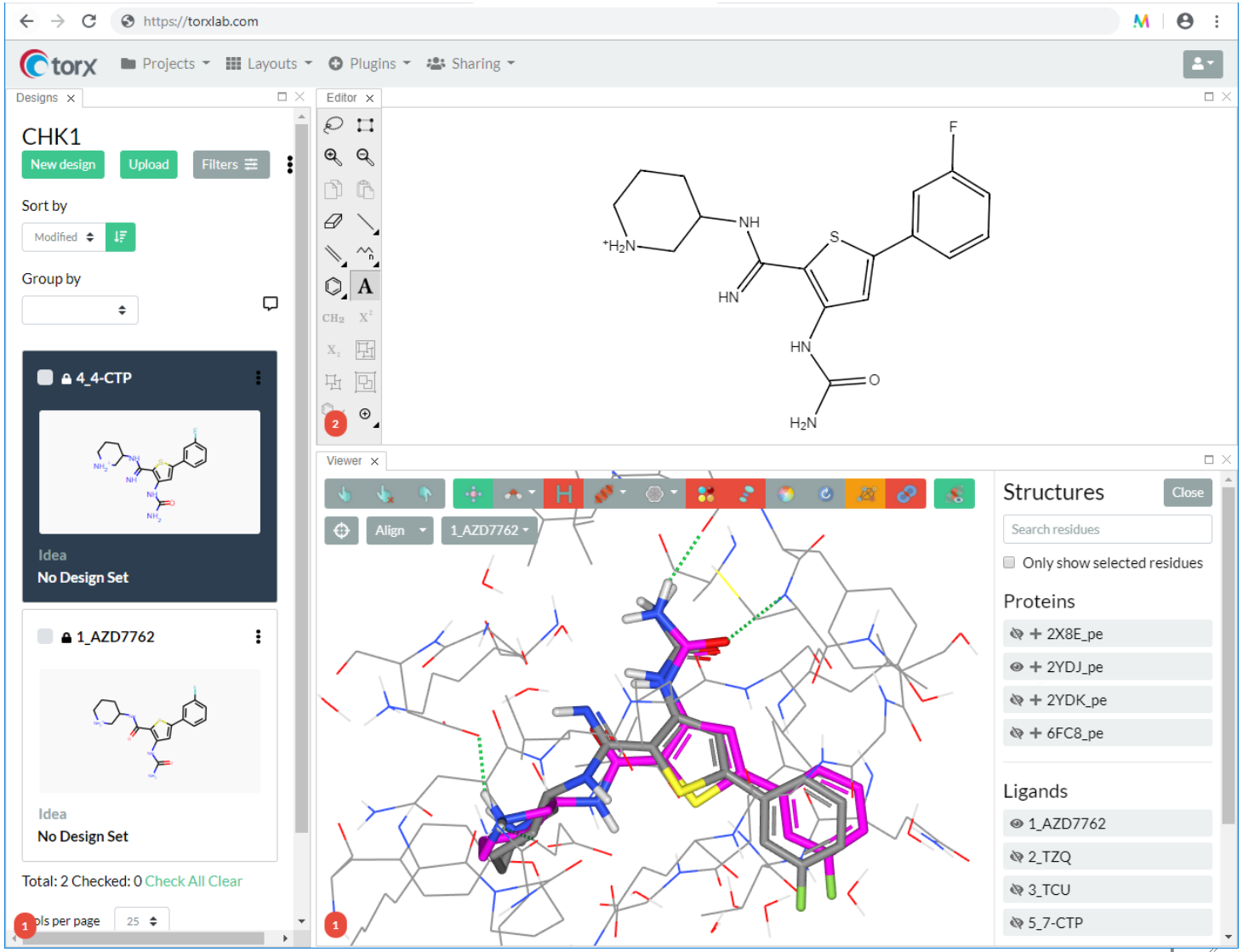
Scaffold morphing begins



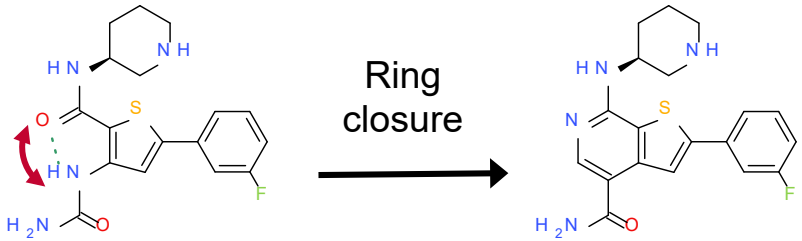
1 (AZD7762)

4 (4-CTP)

Then I turn the carbonyl group into an imine…



Scaffold morphing begins

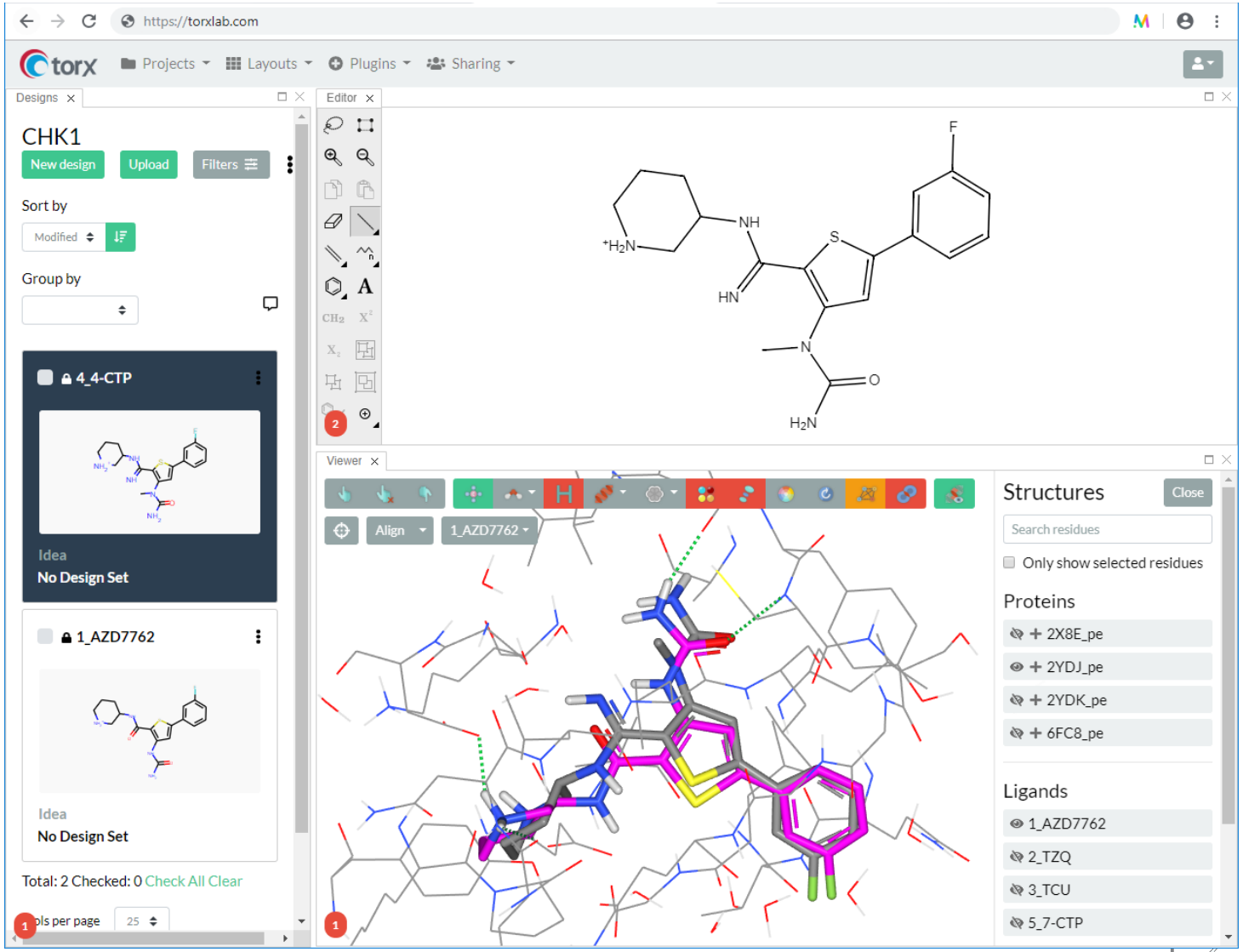


1 (AZD7762) **4** (4-CTP)

Then I turn the carbonyl group into an imine…

…the urea into an *N*-methylurea…

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



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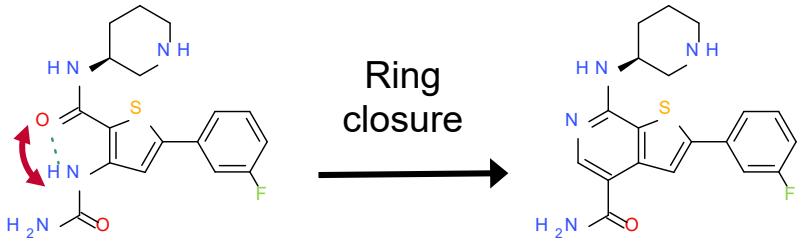
Scaffold morphing begins



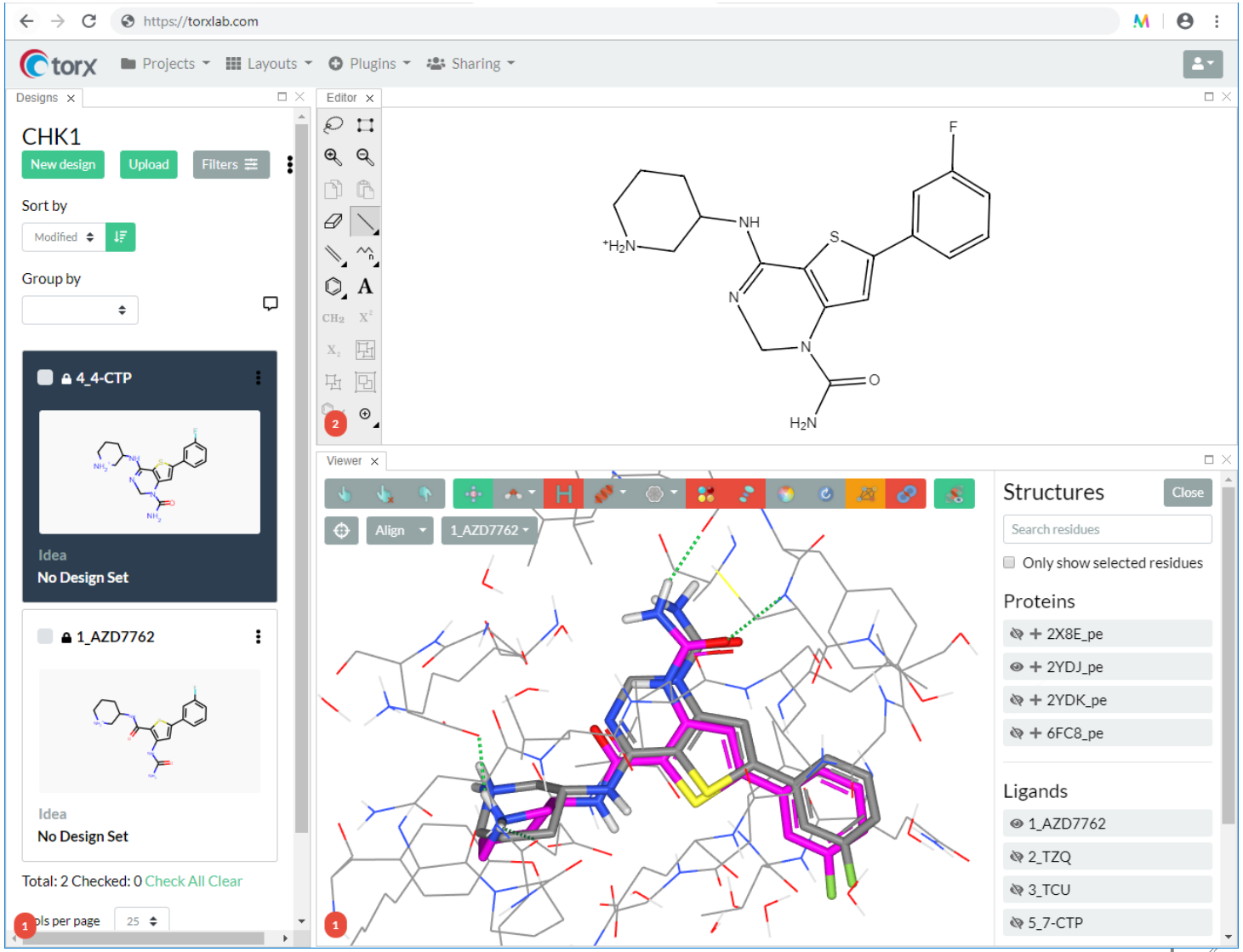
1 (AZD7762)

4 (4-CTP)

Then I turn the carbonyl group into an imine…

…the urea into an *N*-methylurea…

Whoa, that worked!



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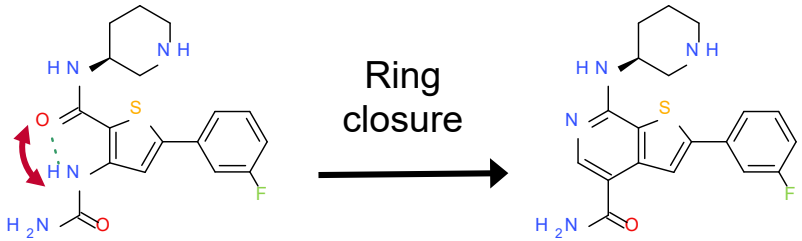
Scaffold morphing begins

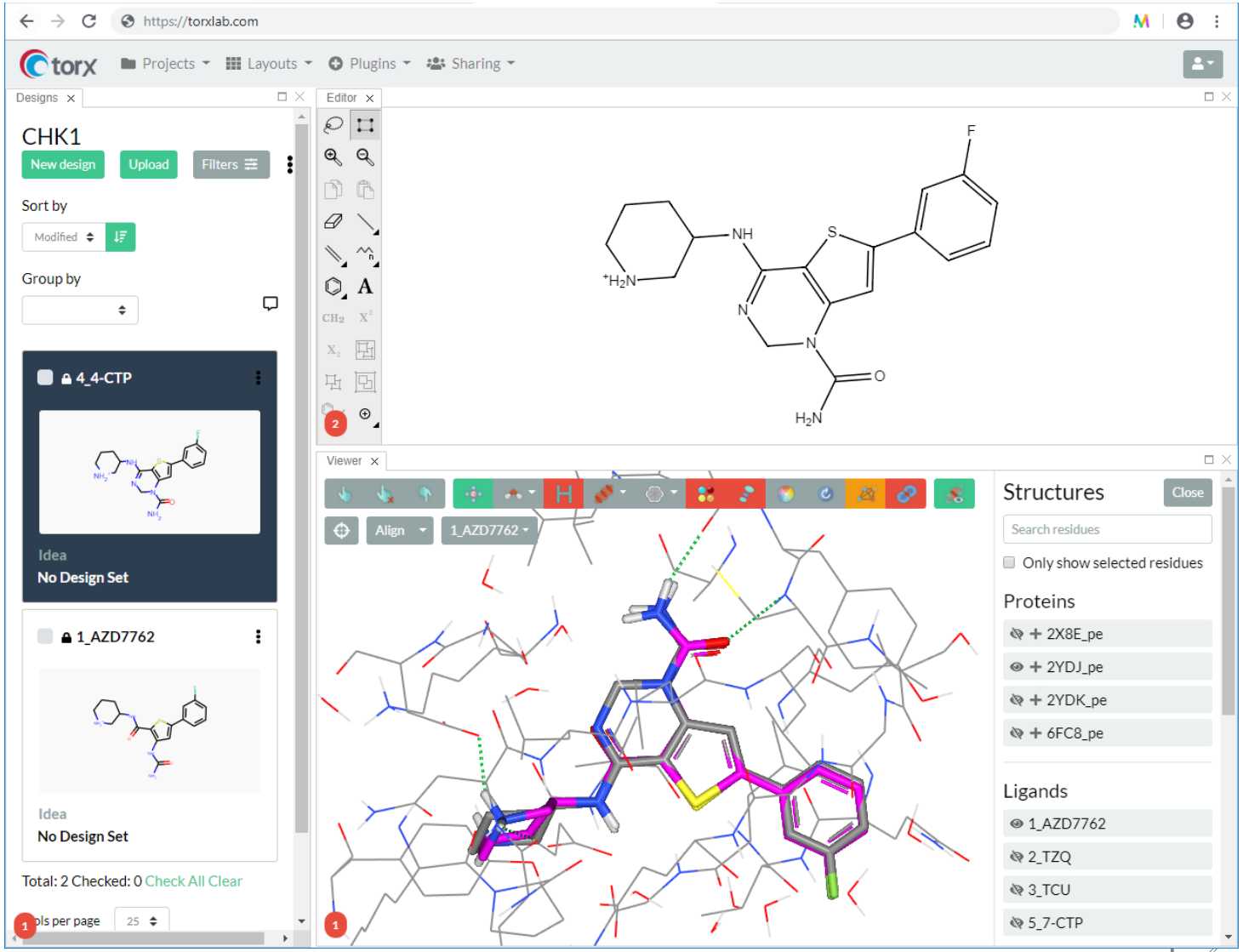


1 (AZD7762) **4** (4-CTP)

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)…



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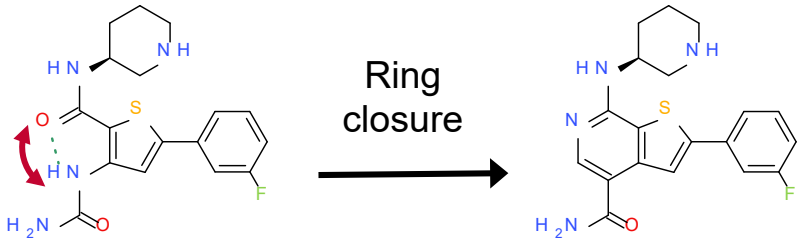


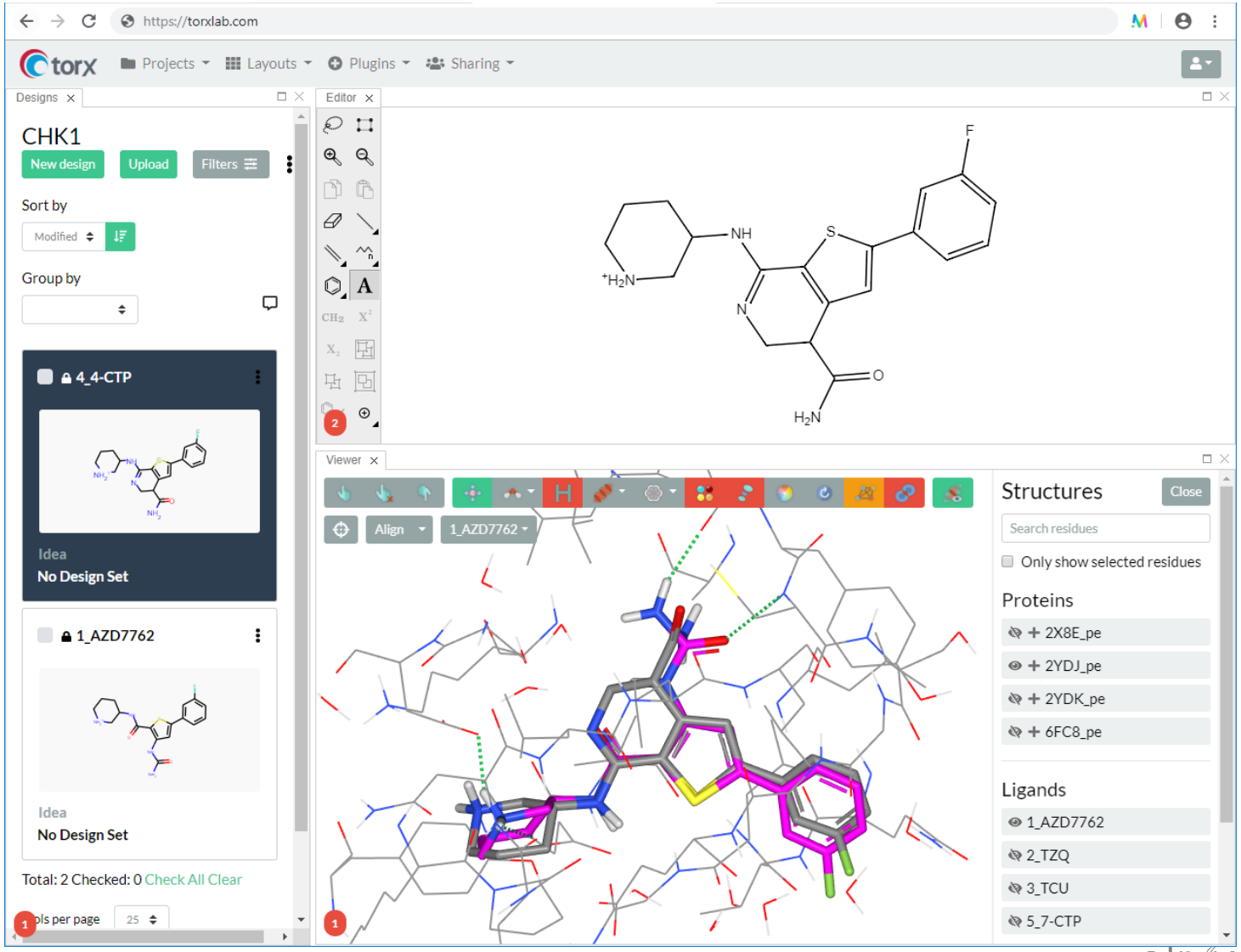
1 (AZD7762) **4** (4-CTP)

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…



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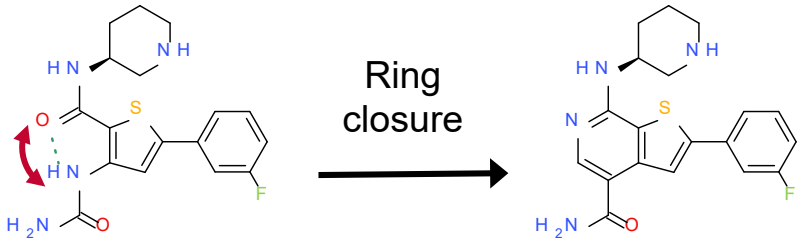
Scaffold morphing: done!



1 (AZD7762) **4** (4-CTP)

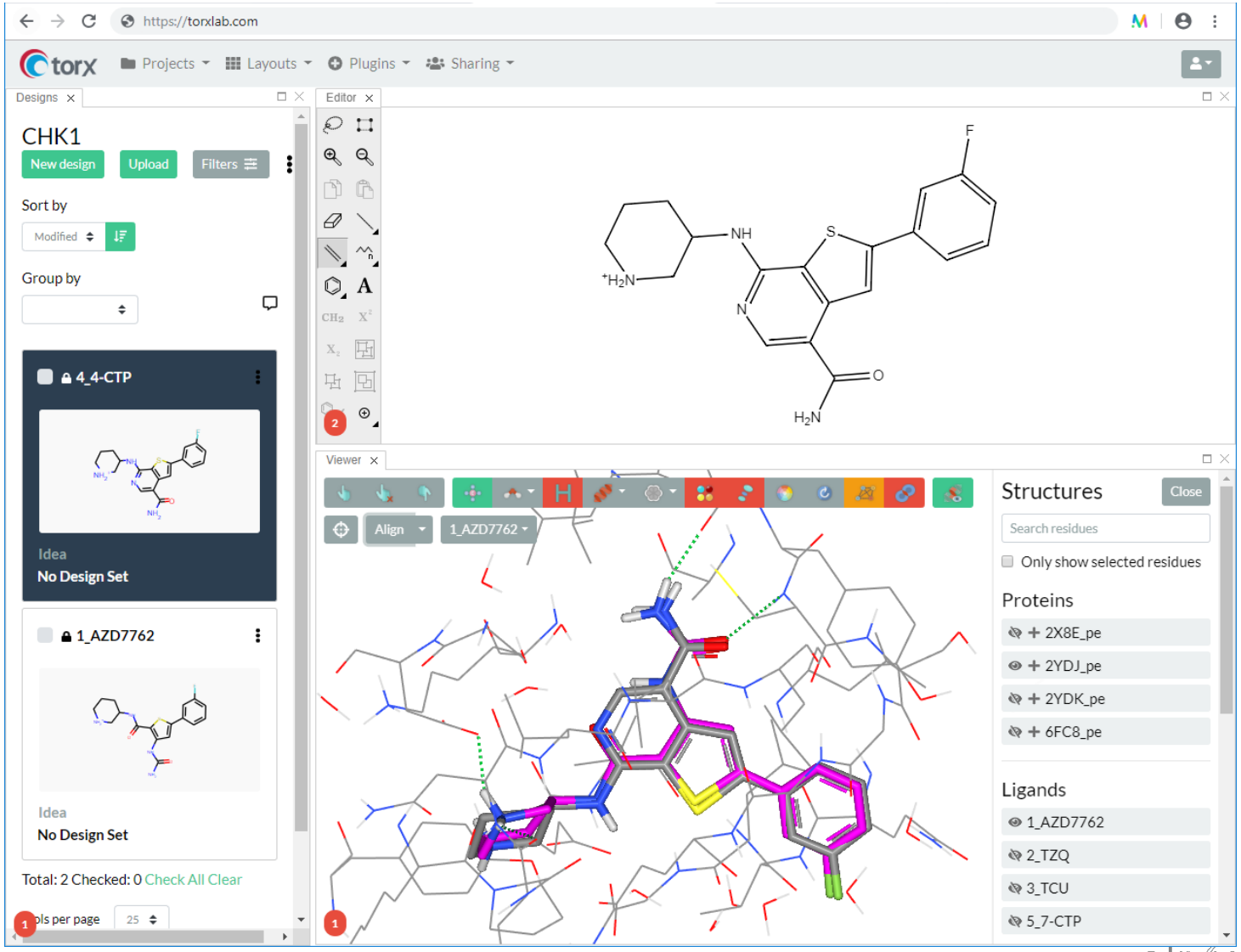
Then I turn the carbonyl group into an imine…

…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!



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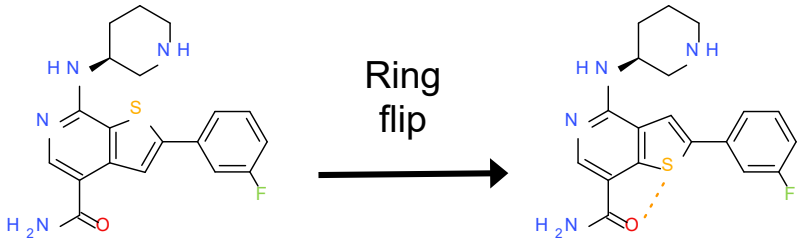
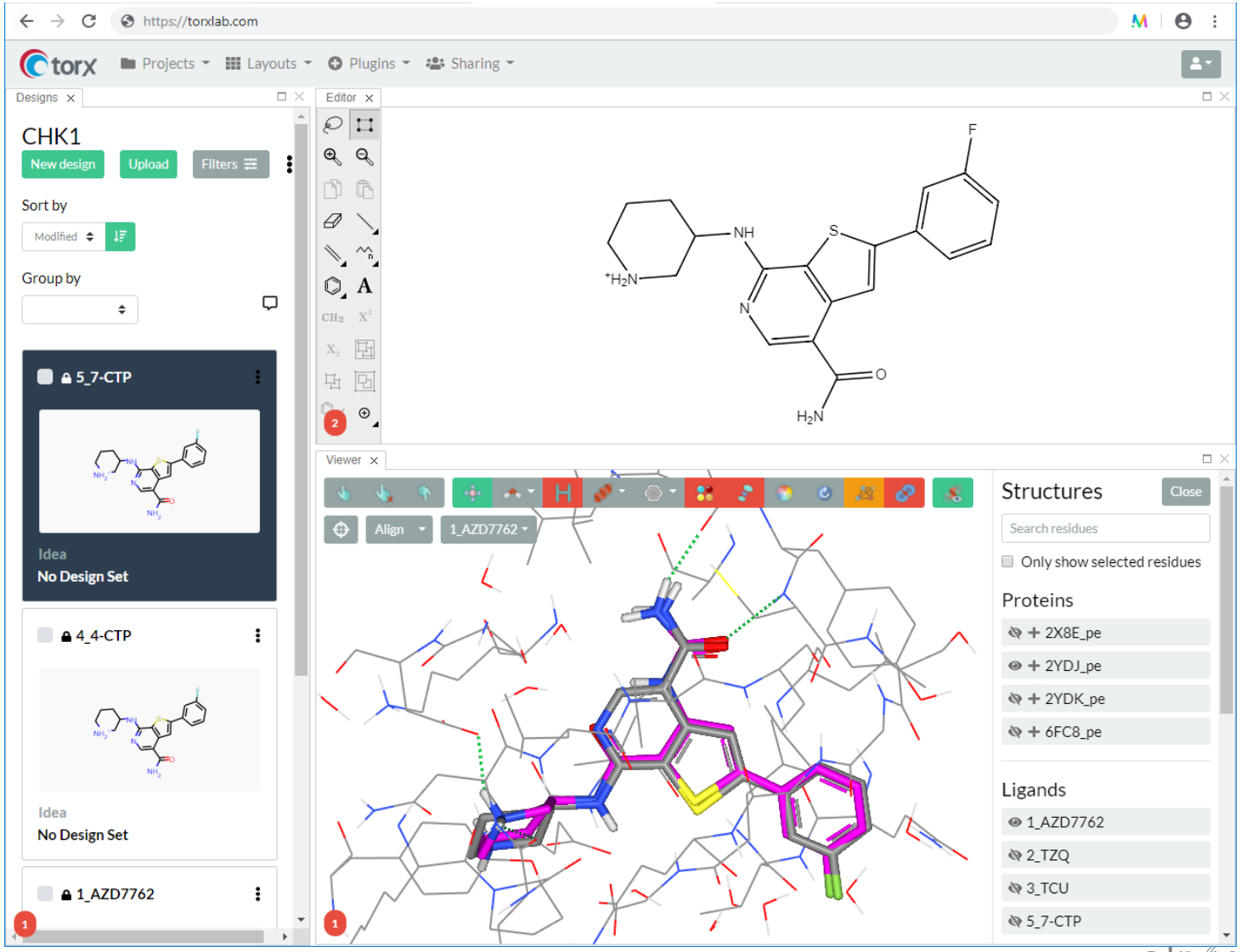
More transformations at constant #atoms



4 (4-CTP) **5** (7-CTP)

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



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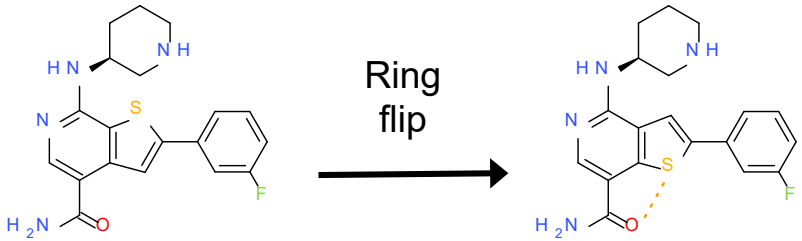
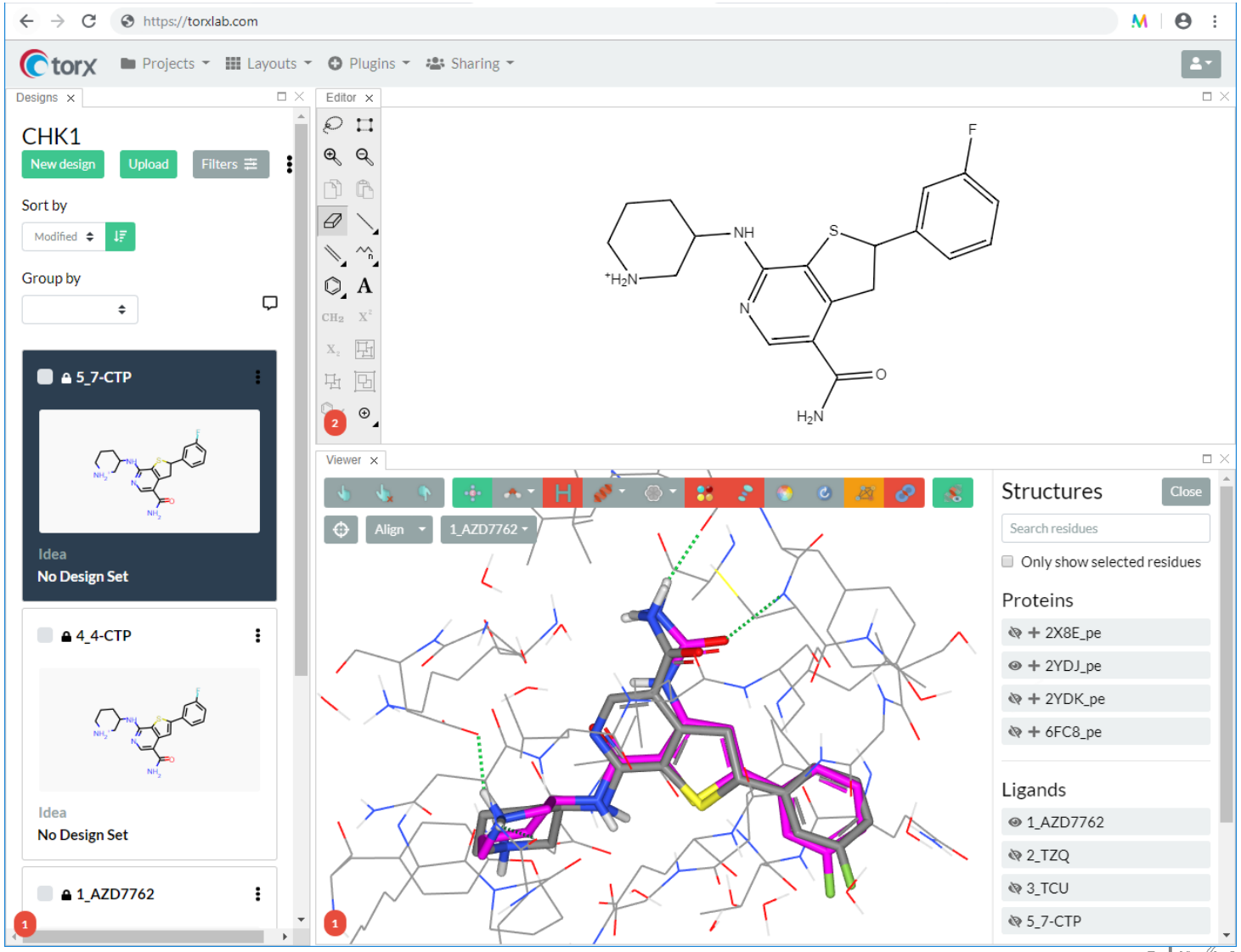
More transformations at constant #atoms



4 (4-CTP) **5** (7-CTP)

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

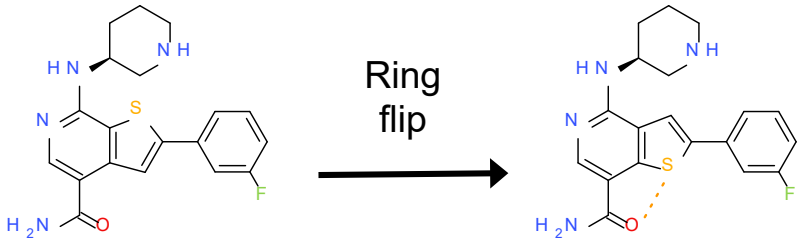
1. Hydrogenate the thiophene…



cresset software

elixir

More transformations at constant #atoms

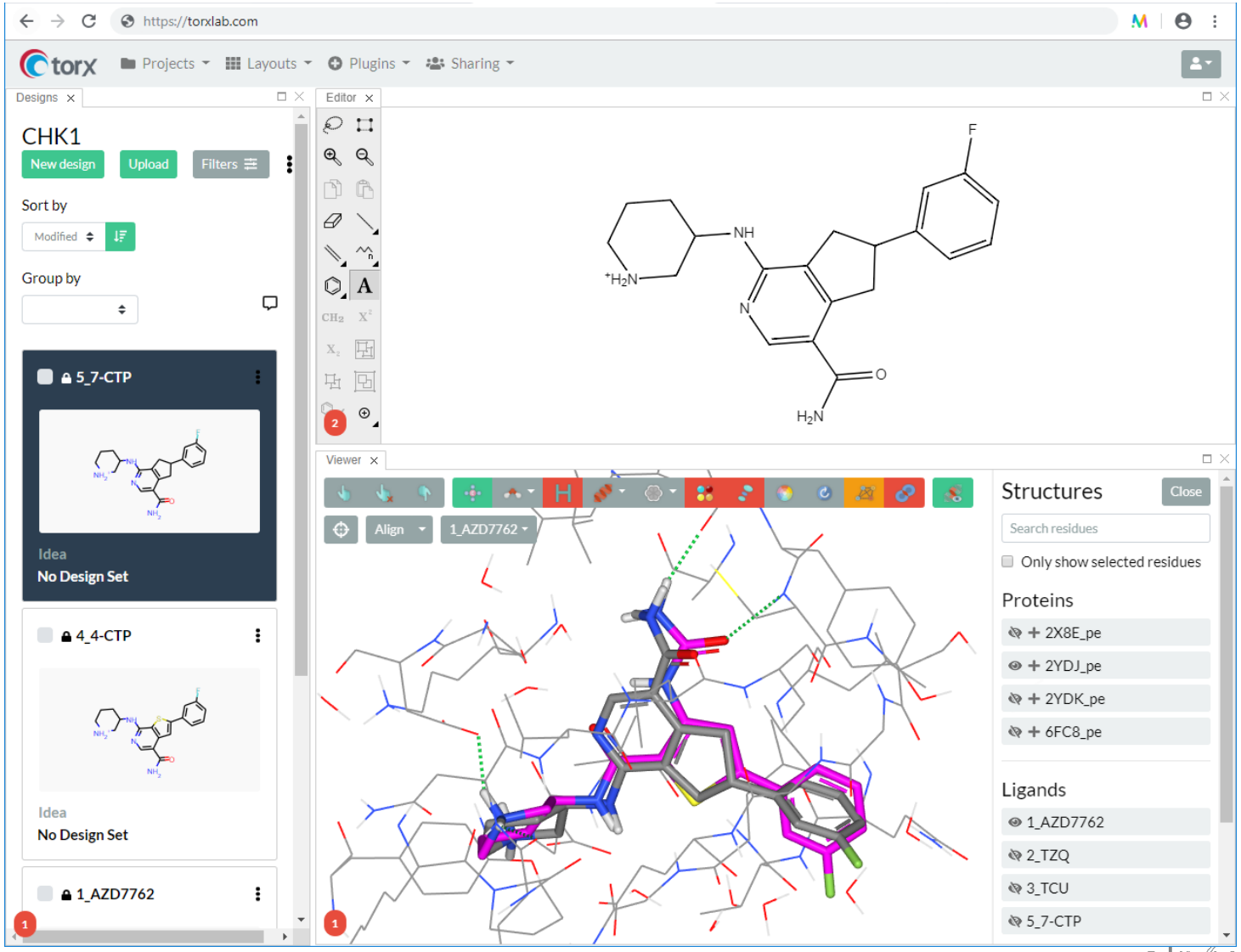


4 (4-CTP) **5** (7-CTP)

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

1. Hydrogenate the thiophene…

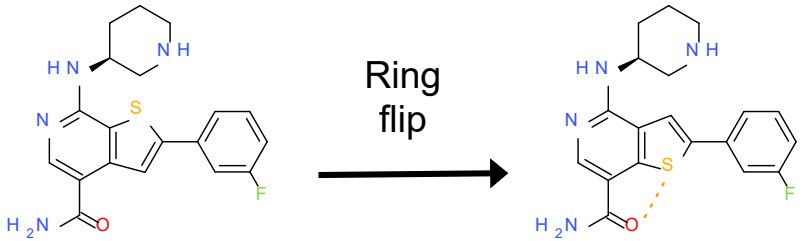
2. Turn it into a cyclopentene…



cresset software

elixir

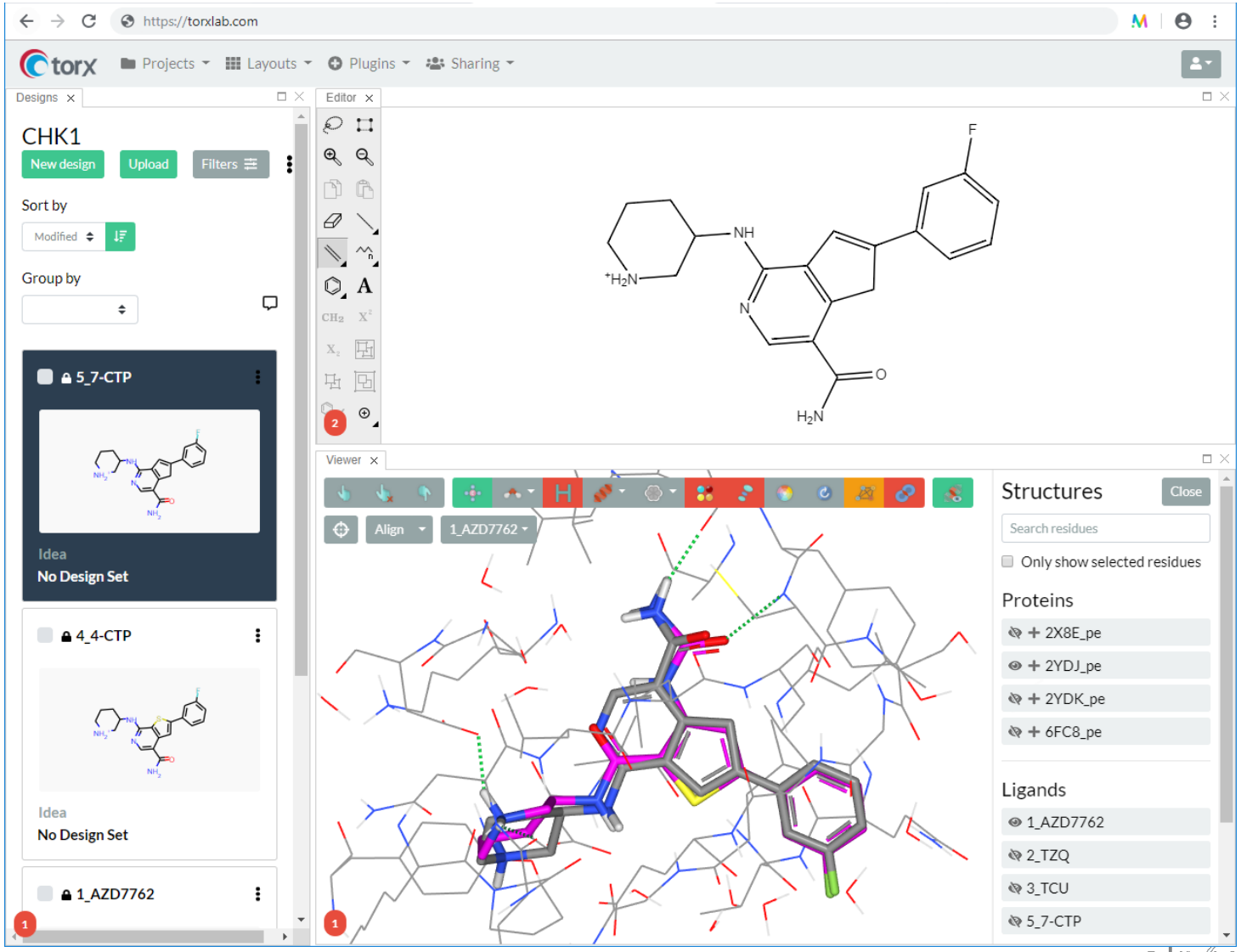
More transformations at constant #atoms



4 (4-CTP) **5** (7-CTP)

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

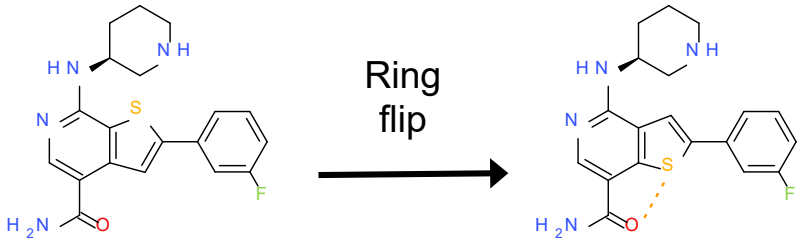
1. Hydrogenate the thiophene…
2. Turn it into a cyclopentene…
3. Dehydrogenate cyclopentene…



cresset software

elixir

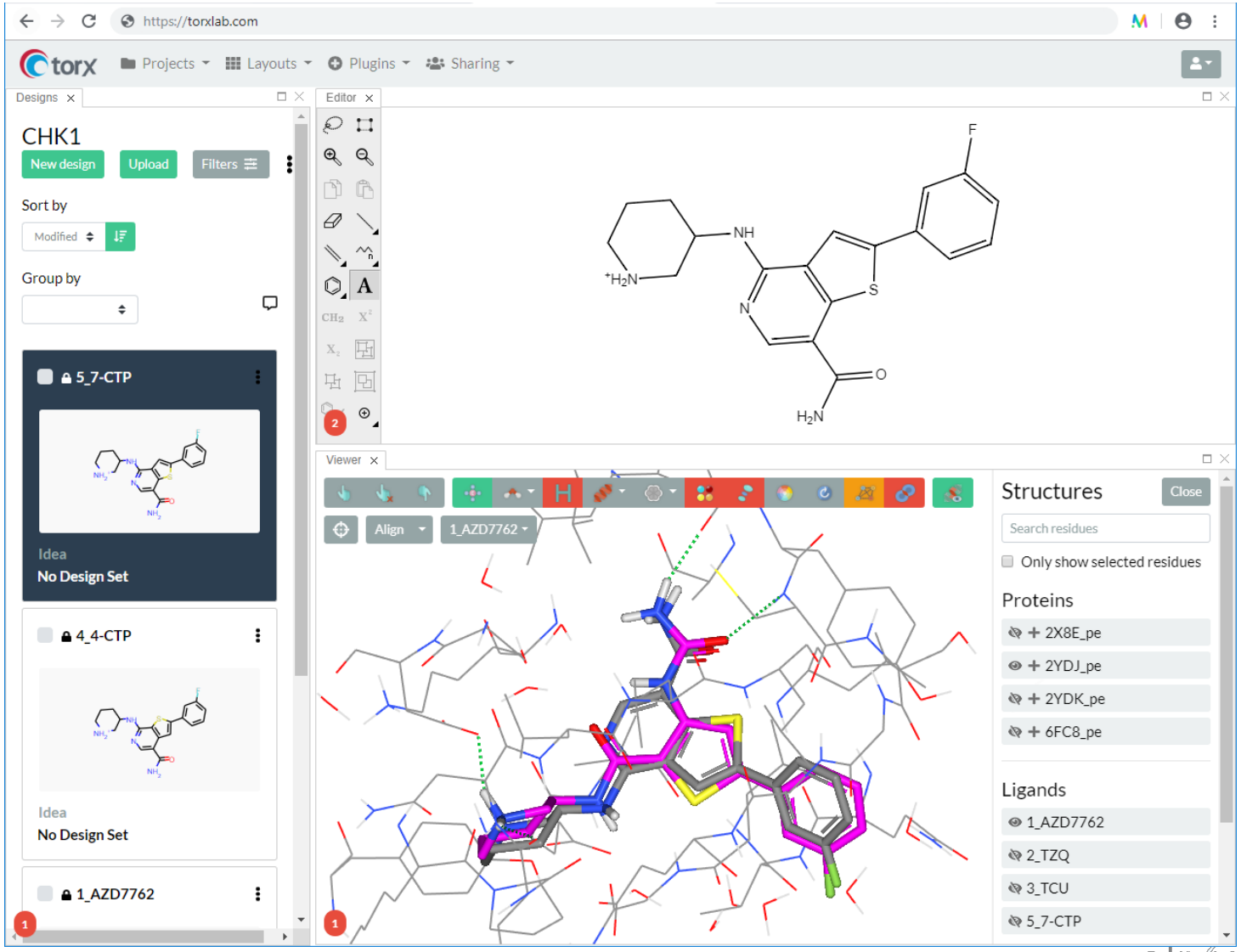
More transformations at constant #atoms



4 (4-CTP) **5** (7-CTP)

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

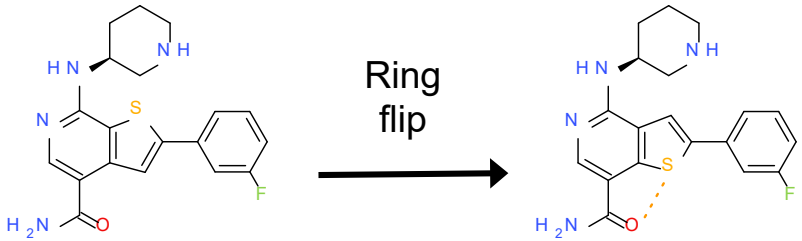
1. Hydrogenate the thiophene…
2. Turn it into a cyclopentene…
3. Dehydrogenate cyclopentene…
4. Turn cyclopentadiene into thiophene…



cresset software

elixir

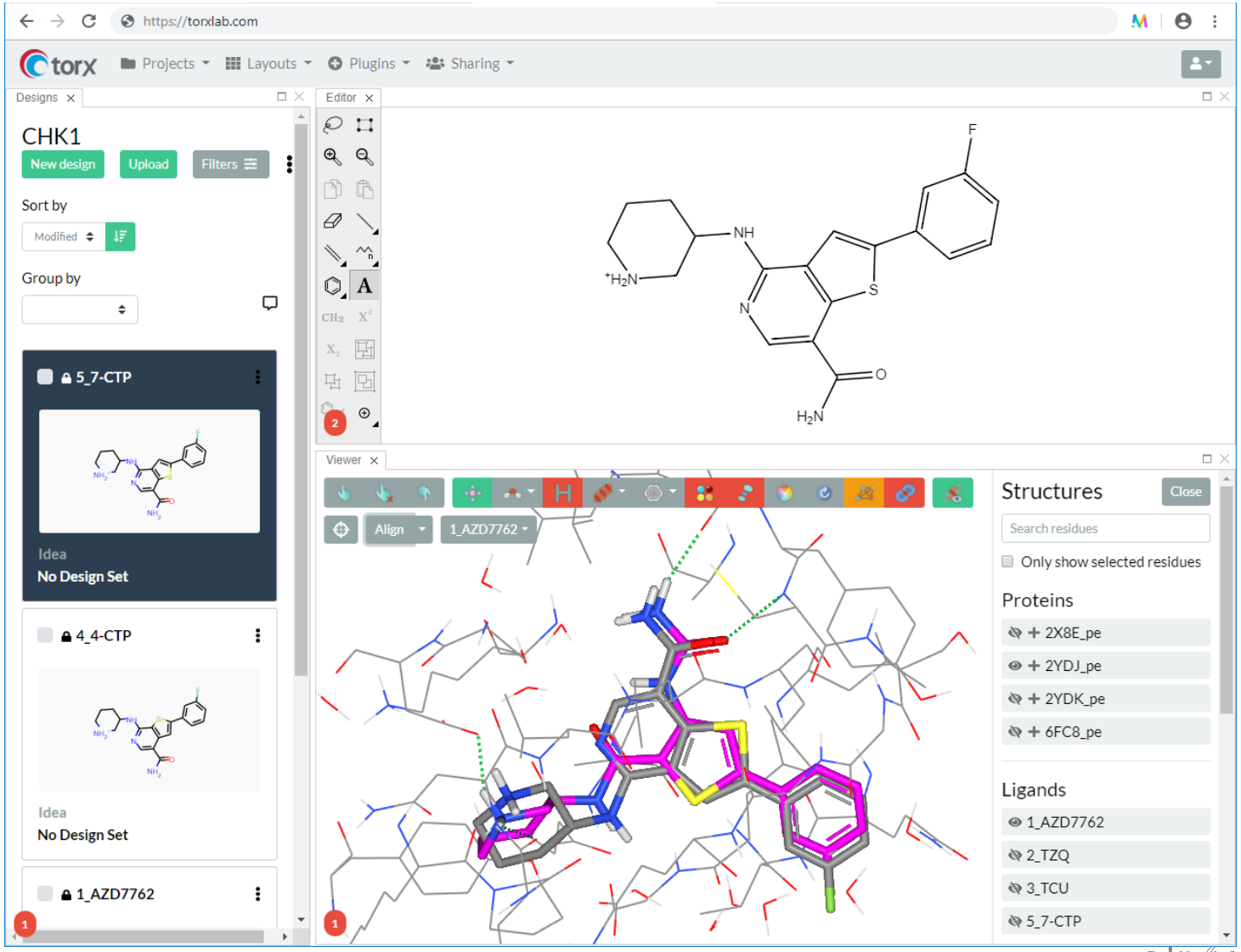
More transformations at constant #atoms



4 (4-CTP) **5** (7-CTP)

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



cresset software

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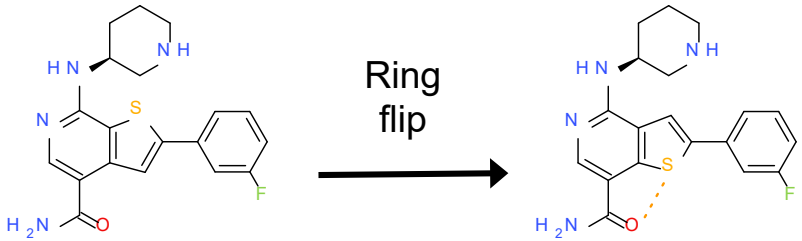
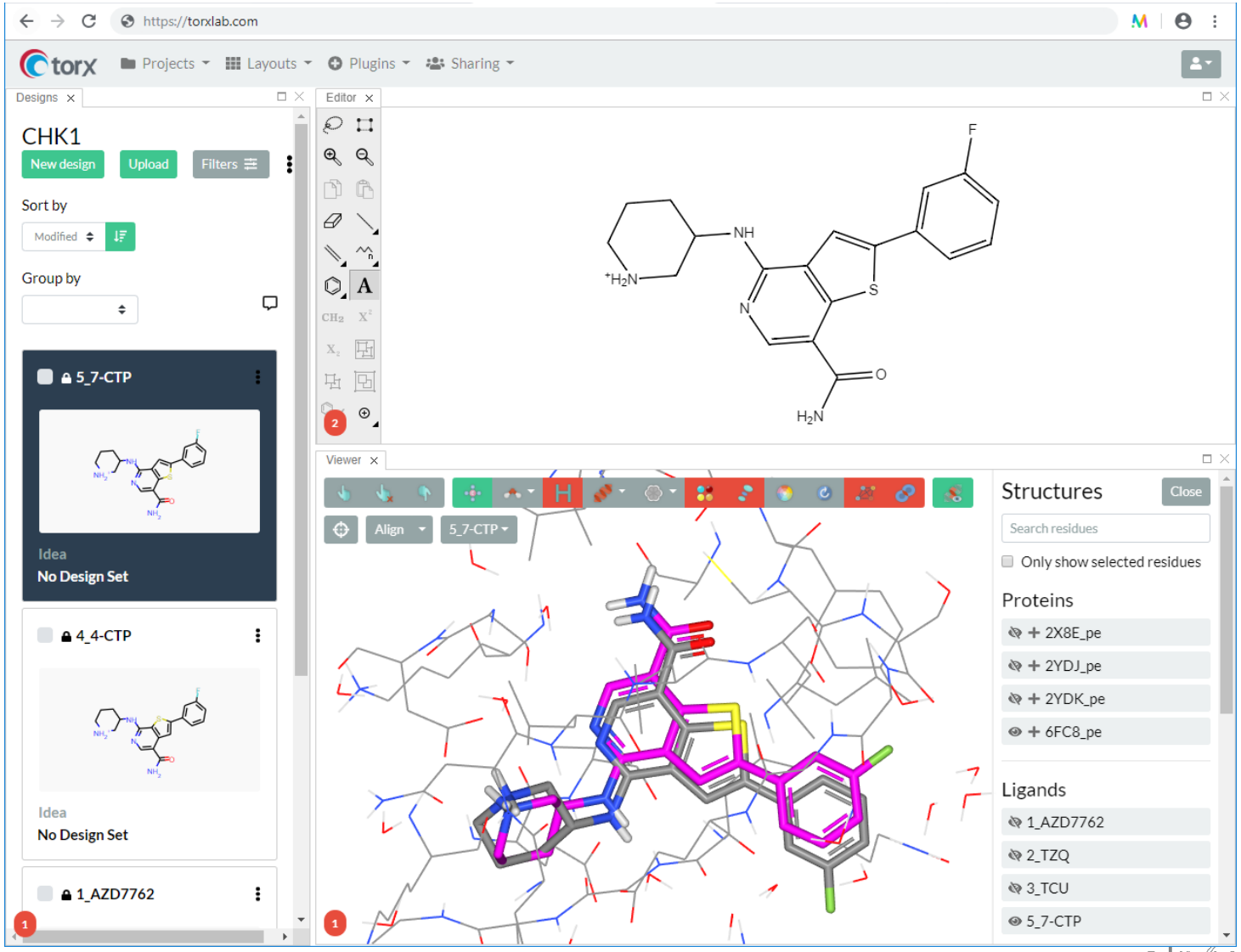
More transformations at constant #atoms: how did we do?



4 (4-CTP) **5** (7-CTP)

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



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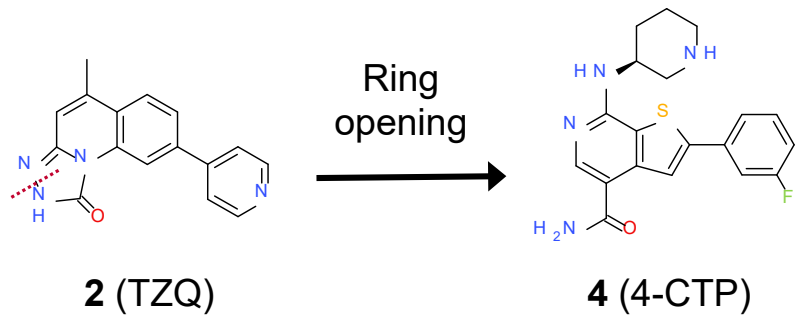
Ring opening in *grow3D*



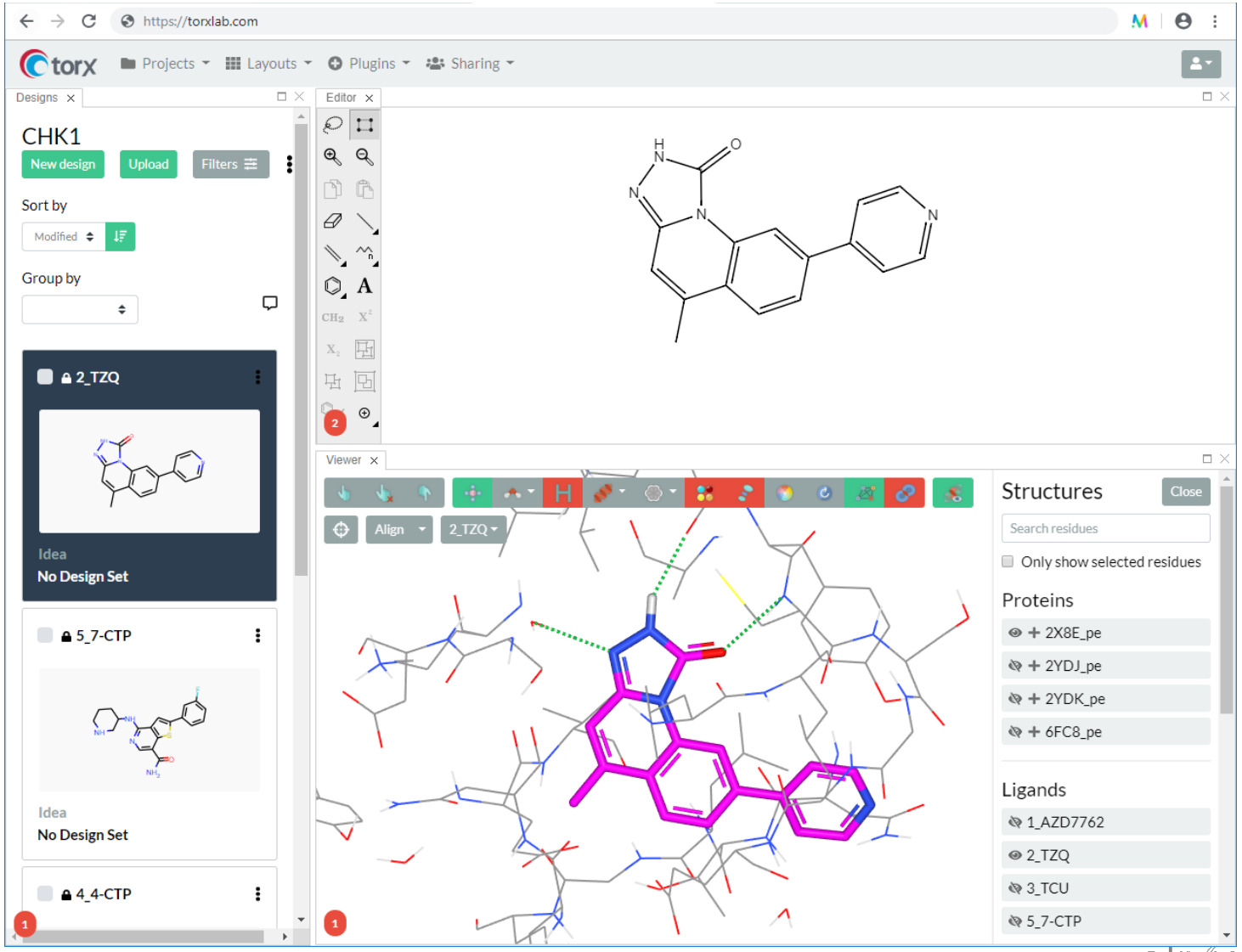
2 (TZQ)

4 (4-CTP)

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

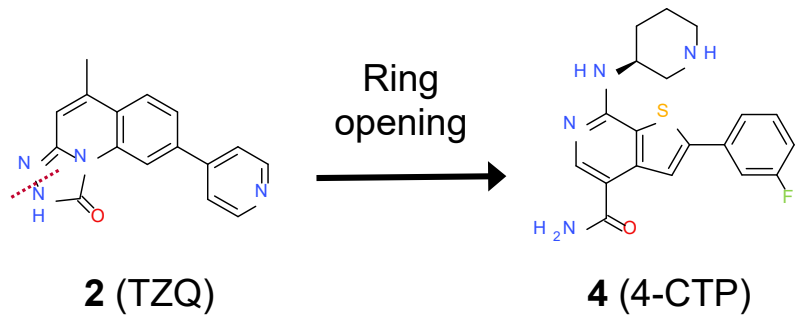
This morphing involves far more changes to the scaffold than the previous one



cresset software

elixir

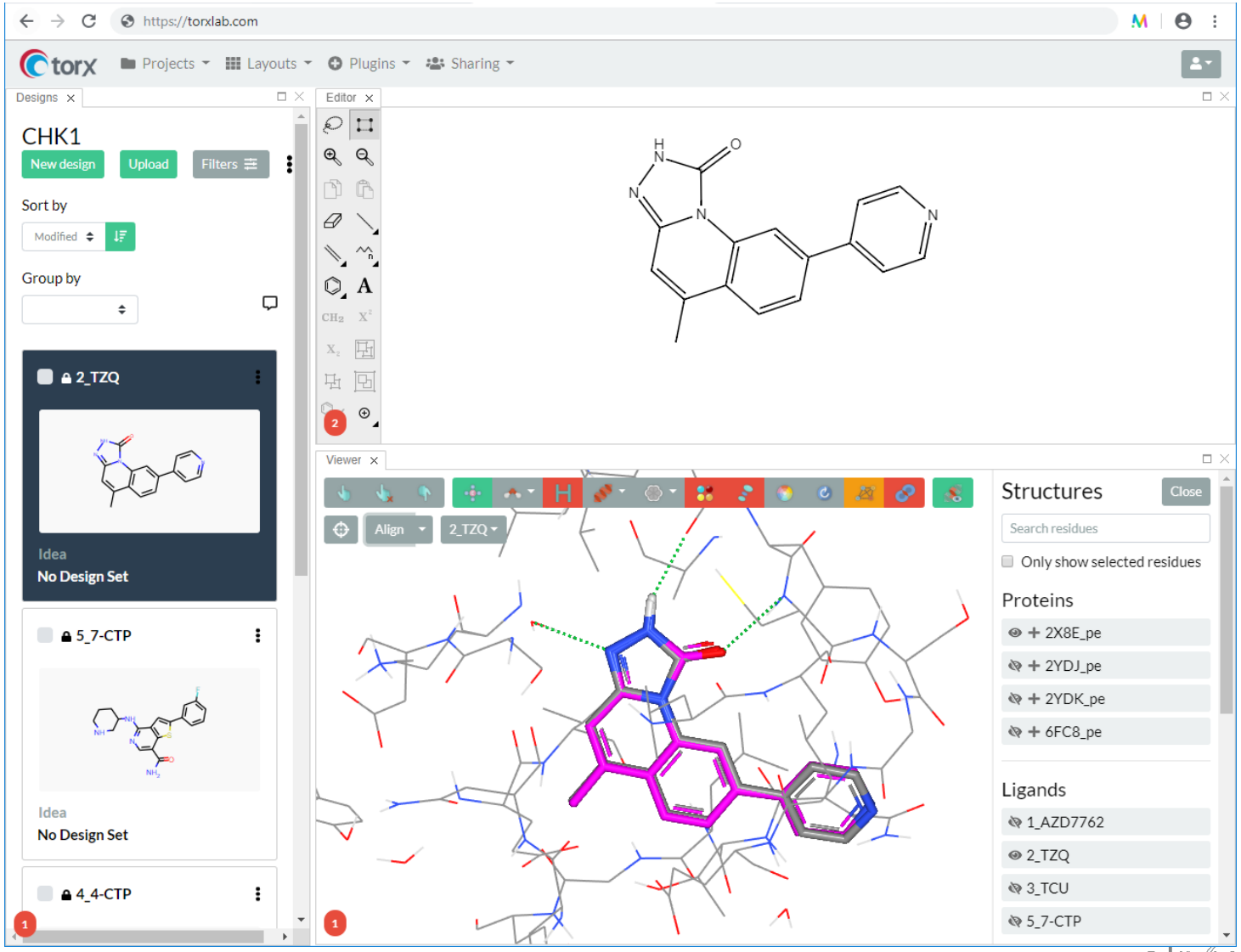
A more complicated design case



2 (TZQ)

4 (4-CTP)

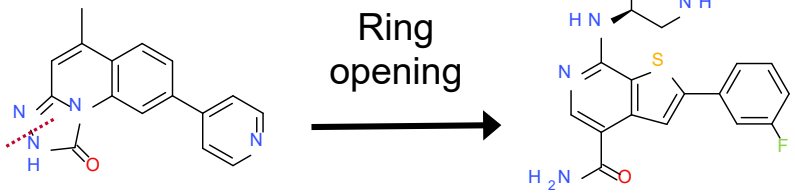
As previously, I start by aligning my 2D design to the X-ray reference



cresset software

elixir

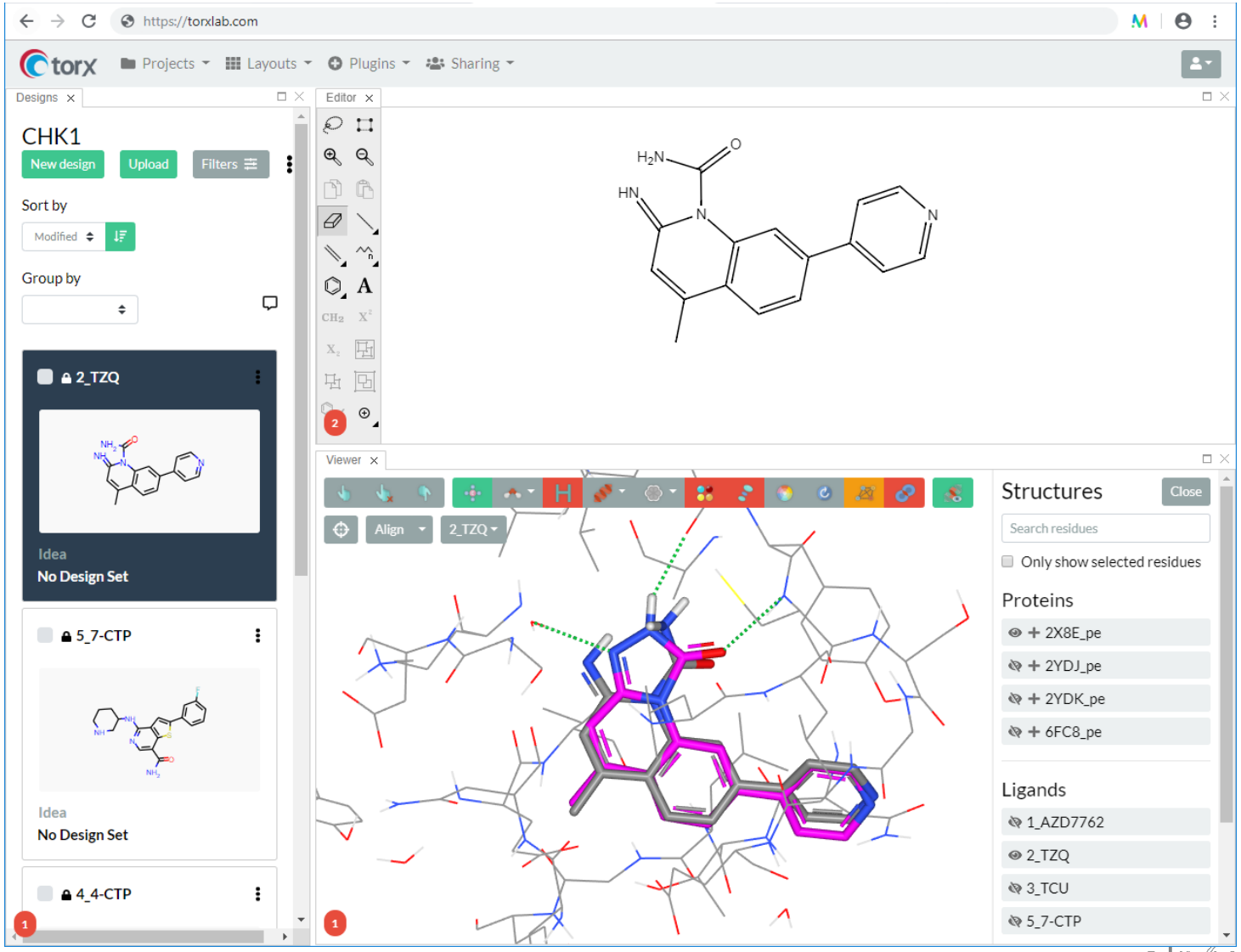
A more complicated design case



2 (TZQ) **4** (4-CTP)

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

Then I cleave the hydrazide bond



cresset software

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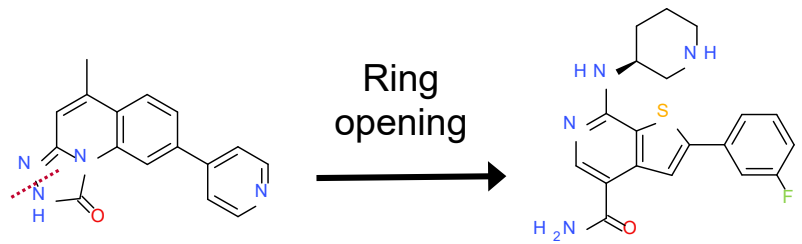
A more complicated design case



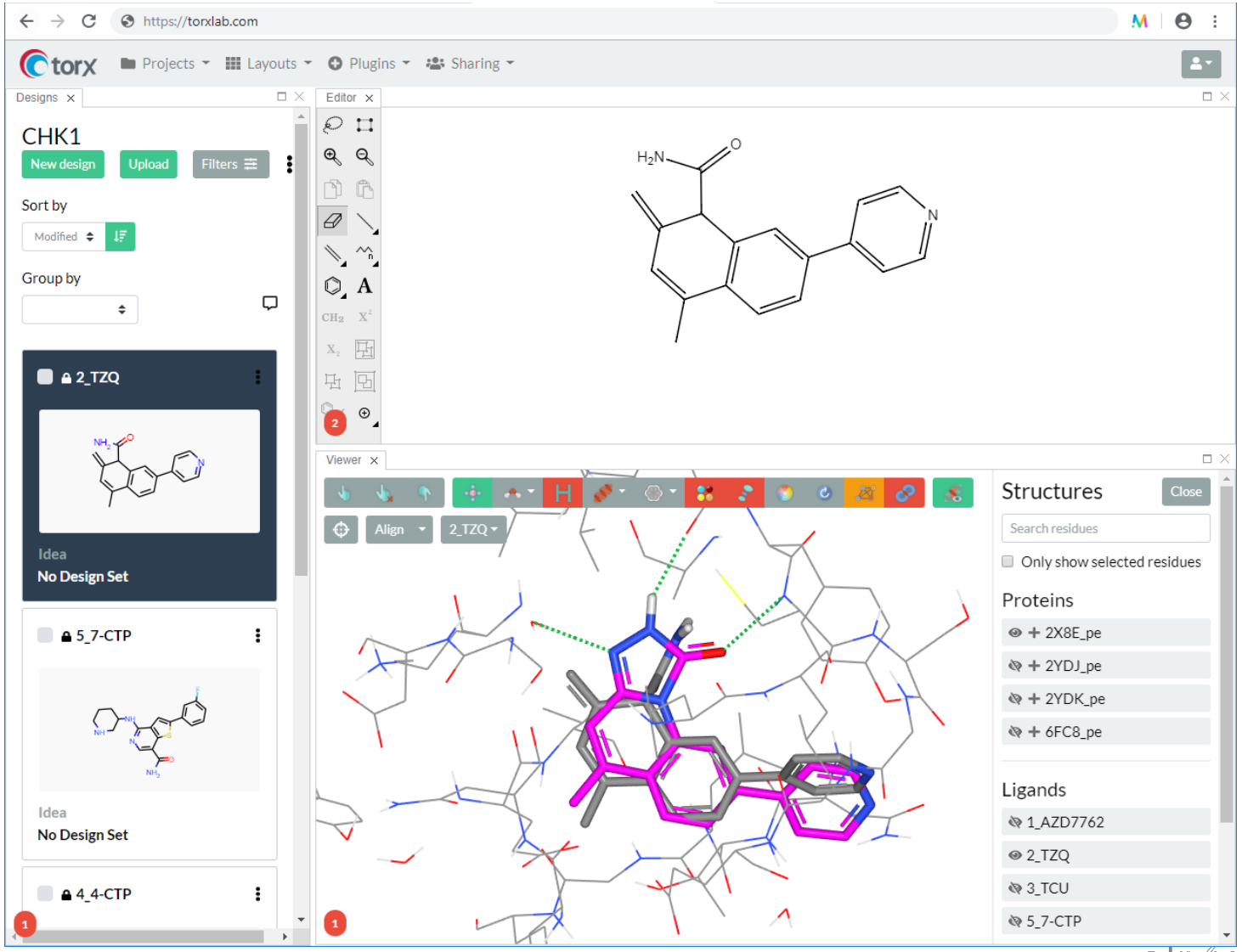
2 (TZQ)

4 (4-CTP)

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

Then I cleave the hydrazide bond

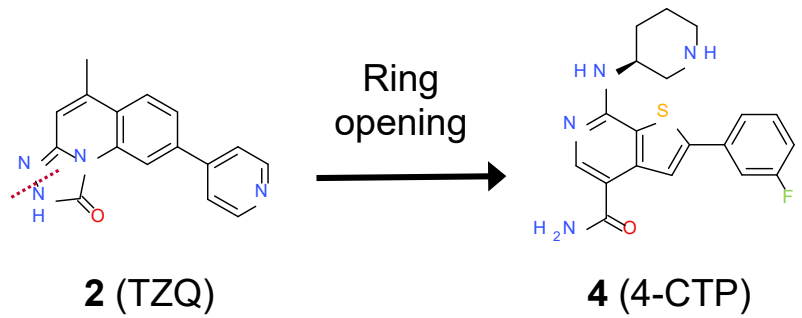
Get rid of the imino substituent



cresset software

elixir

A more complicated design case



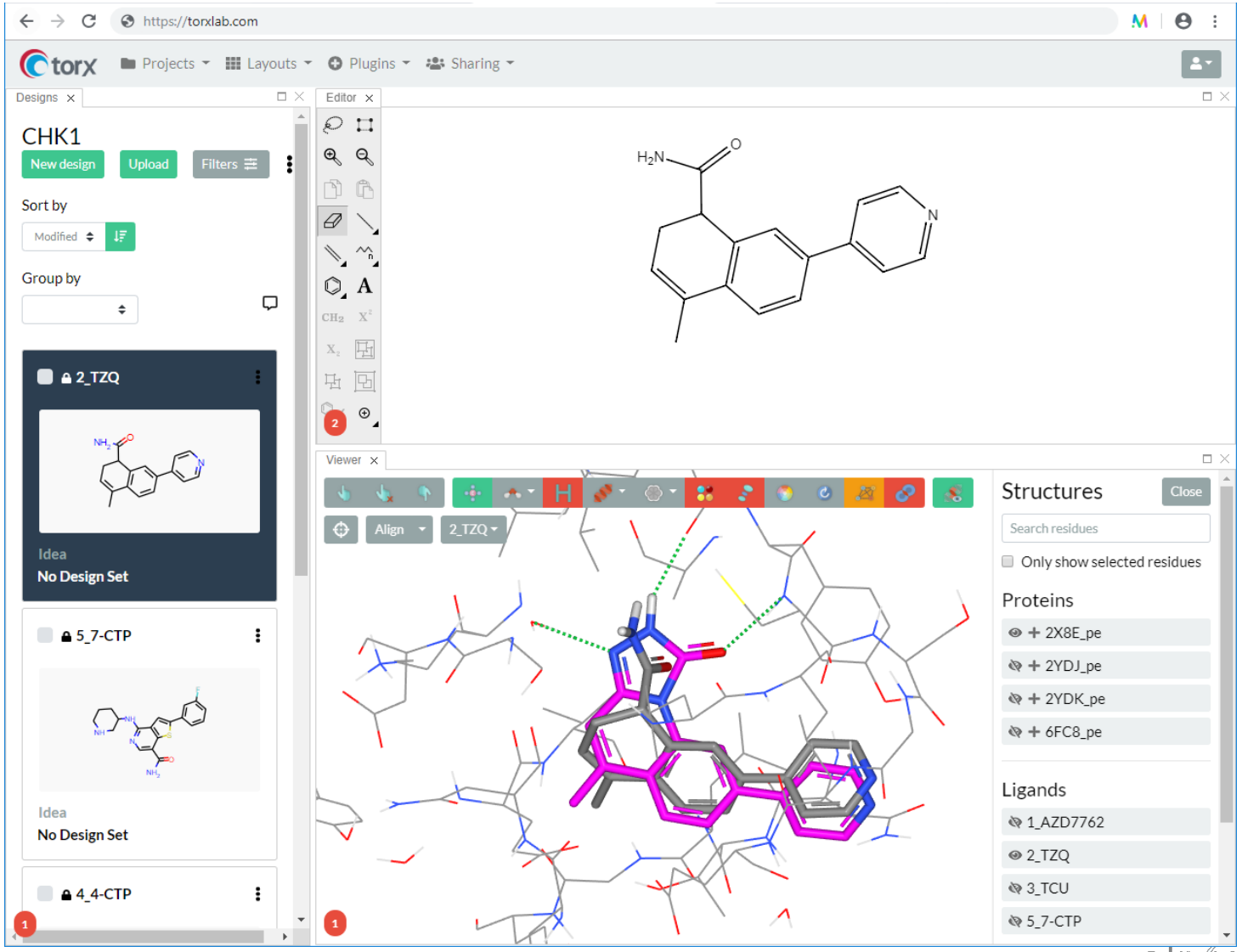
2 (TZQ)

4 (4-CTP)

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

Then I cleave the hydrazide bond

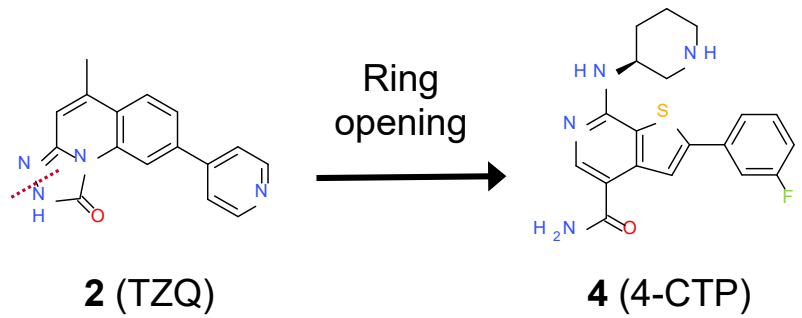
Get rid of the imino substituent



cresset software

elixir

A more complicated design case



2 (TZQ)

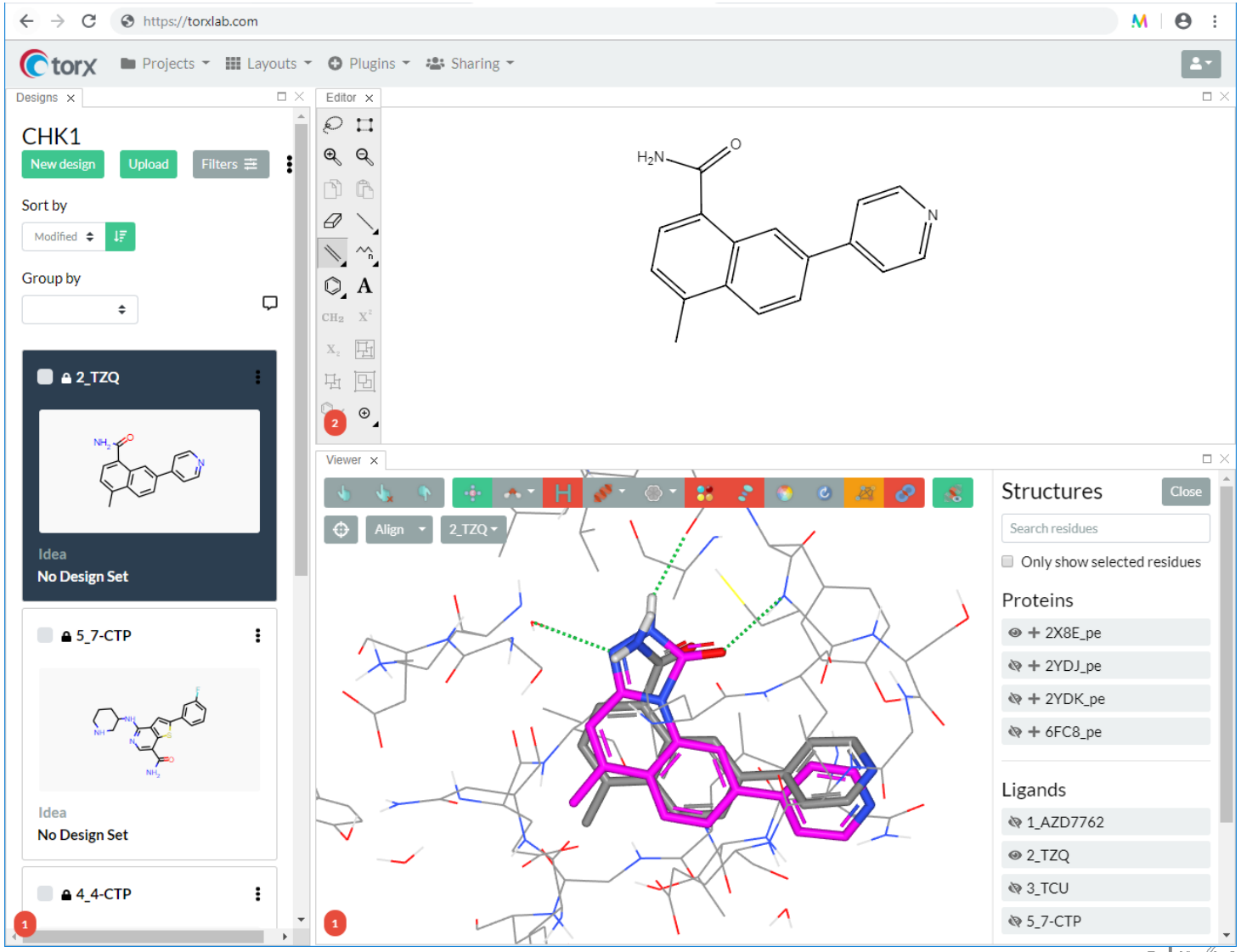
4 (4-CTP)

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

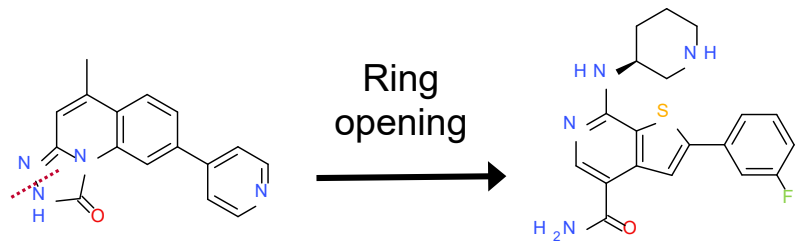
Re-aromatize the system



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

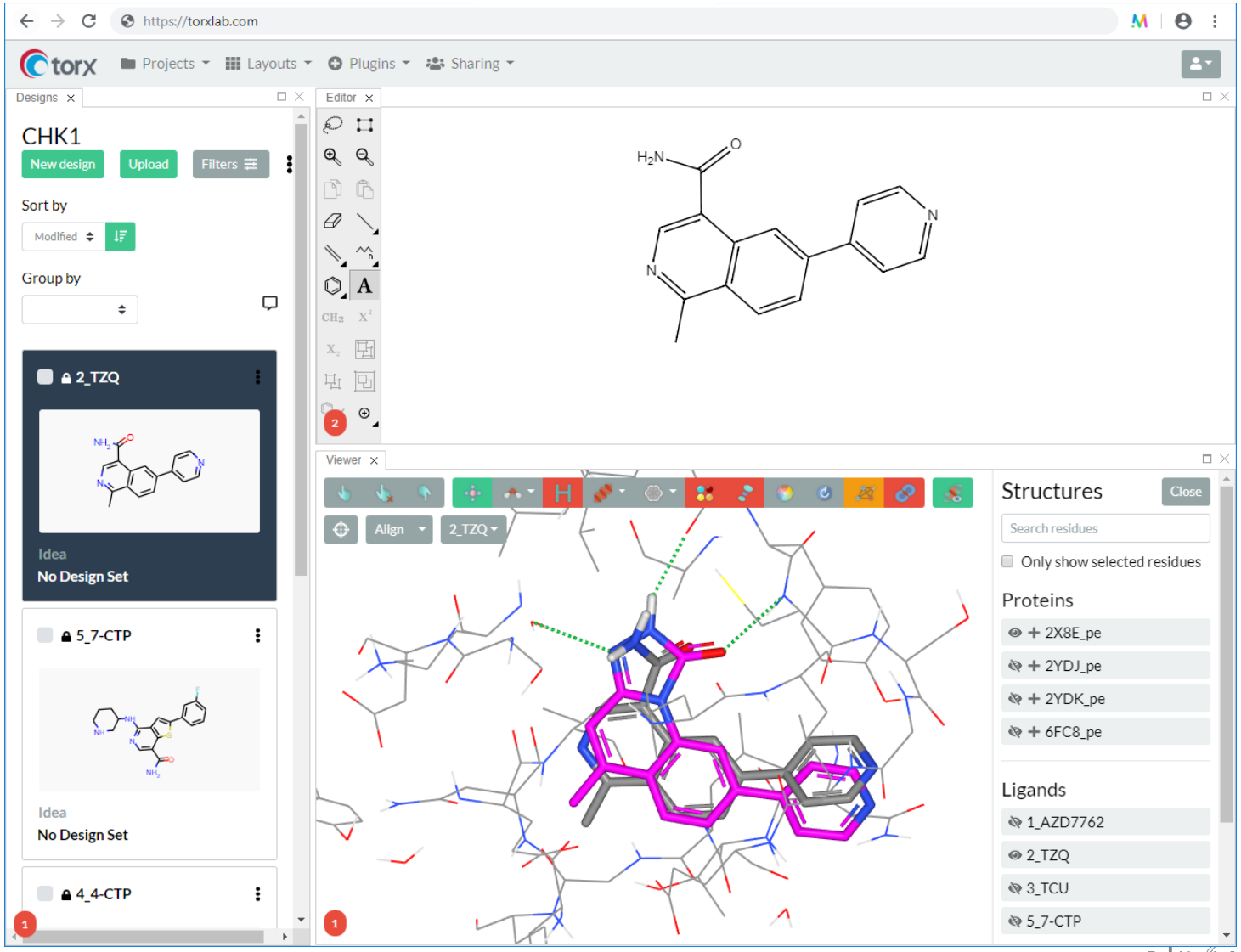
As previously, I start by aligning my 2D design to the X-ray reference

Then I cleave the hydrazide bond

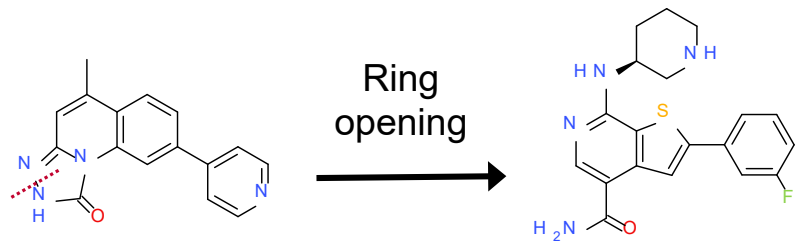
Get rid of the imino substituent

Re-aromatize the system

Turn the naphthalene into an isoquinoline



A more complicated design case



2 (TZQ)

4 (4-CTP)

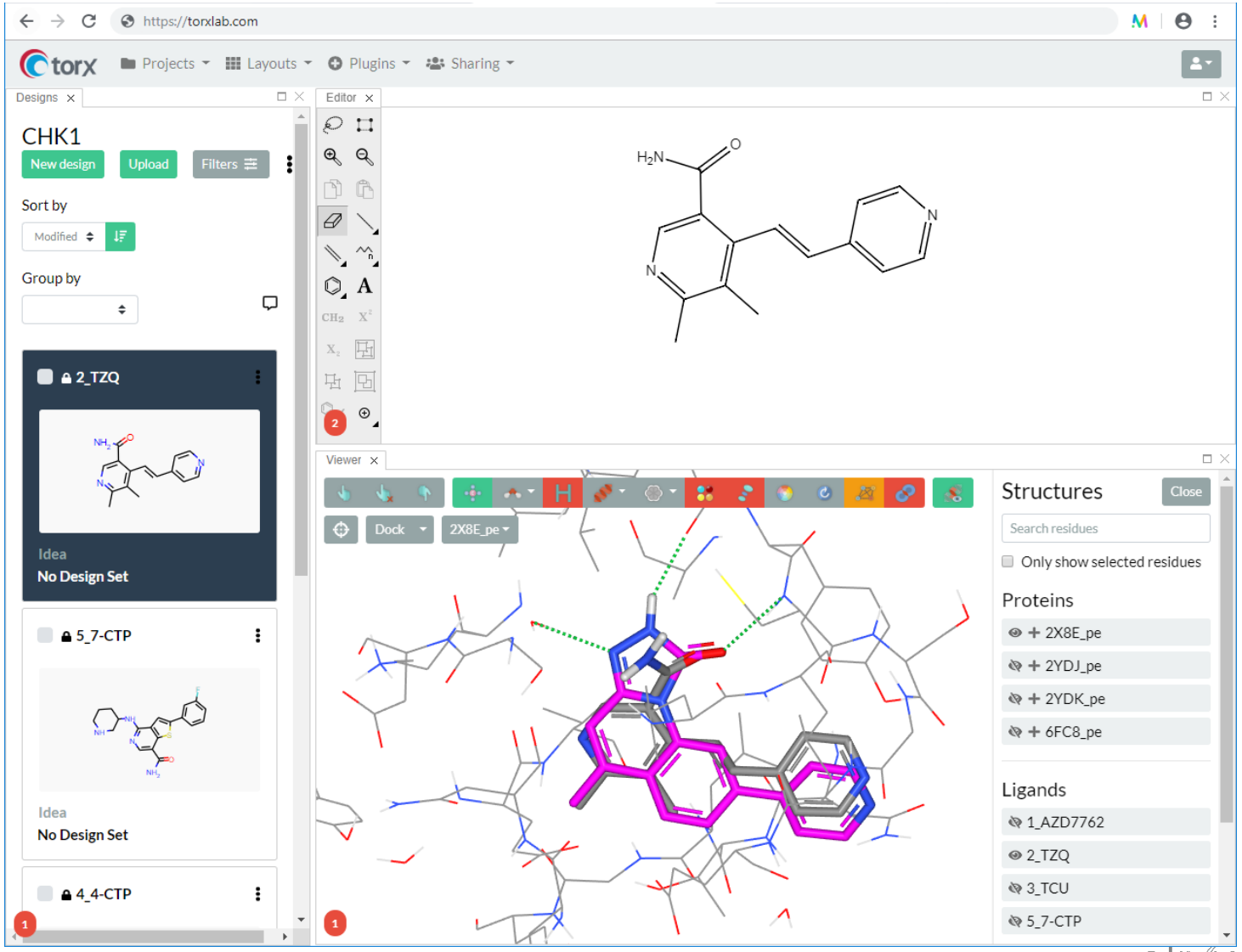
Then I cleave the hydrazide bond

Get rid of the imino substituent

Re-aromatize the system

Turn the naphthalene into an isoquinoline

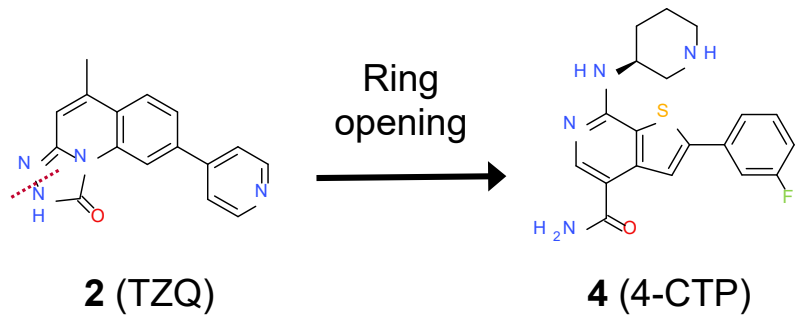
Break the phenyl ring as I need to make it 5-term



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

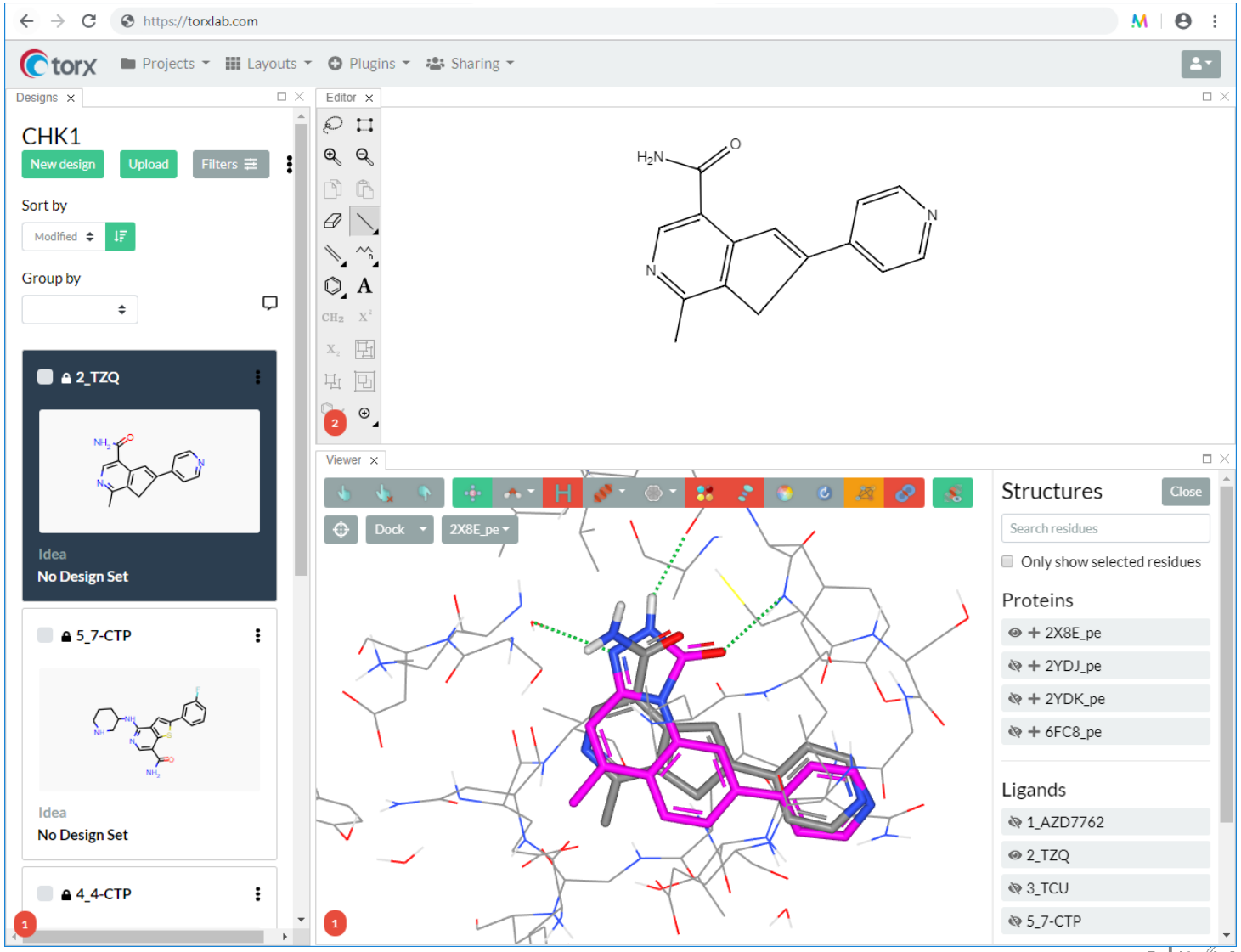
Get rid of the imino substituent

Re-aromatize the system

Turn the naphthalene into an isoquinoline

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

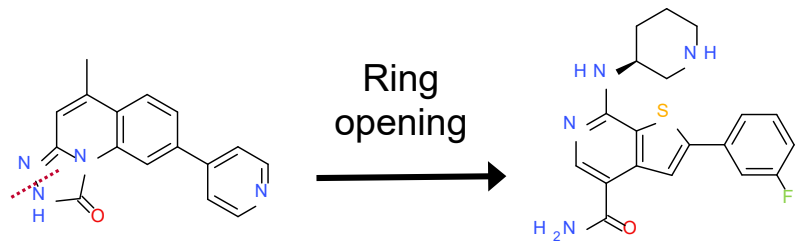
Close to a cyclopentadiene ring



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

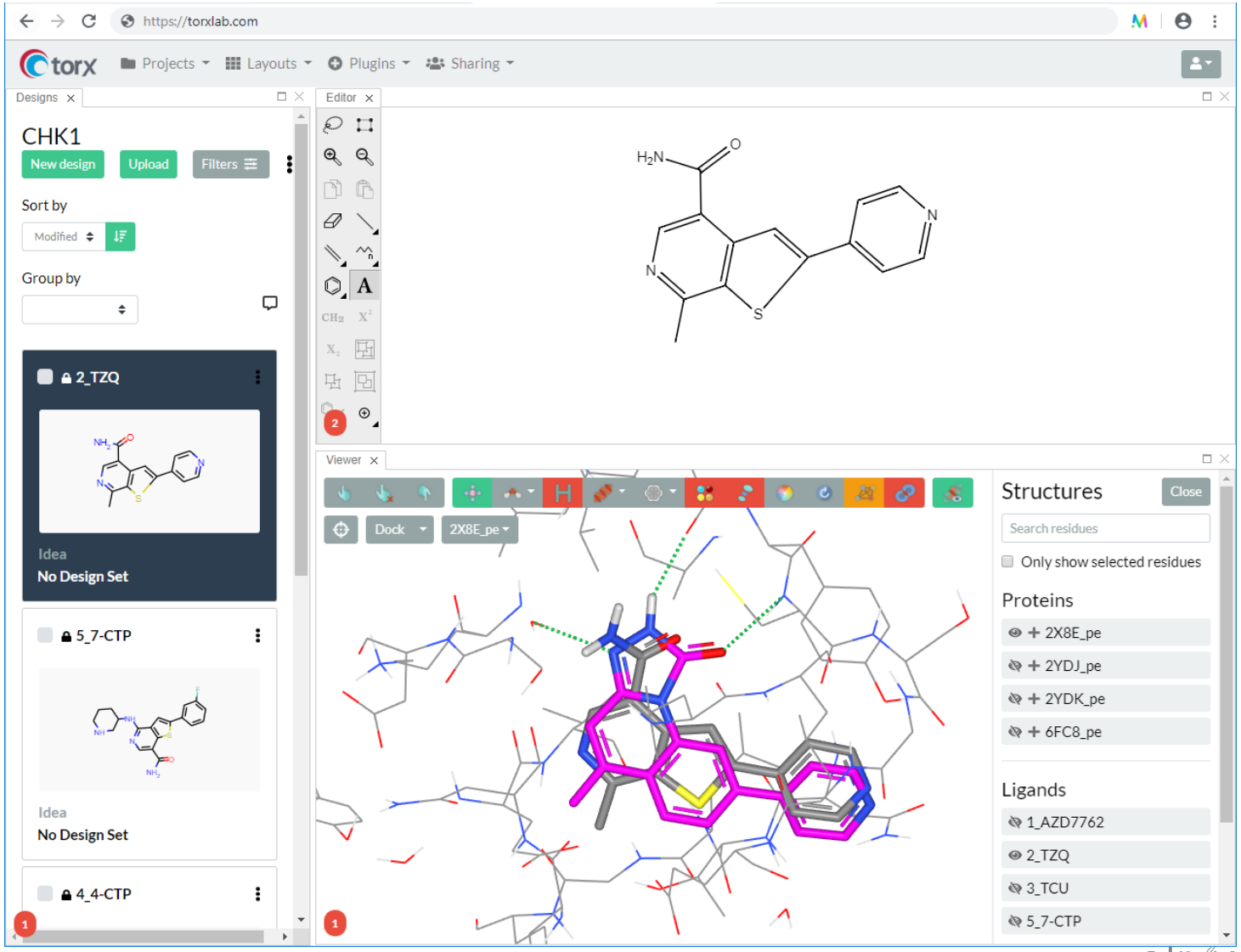
Re-aromatize the system

Turn the naphthalene into an isoquinoline

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

Close to a cyclopentadiene ring

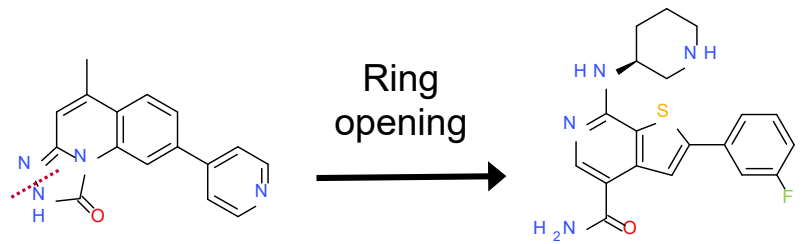
Turn cyclopentadiene into thiophene



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

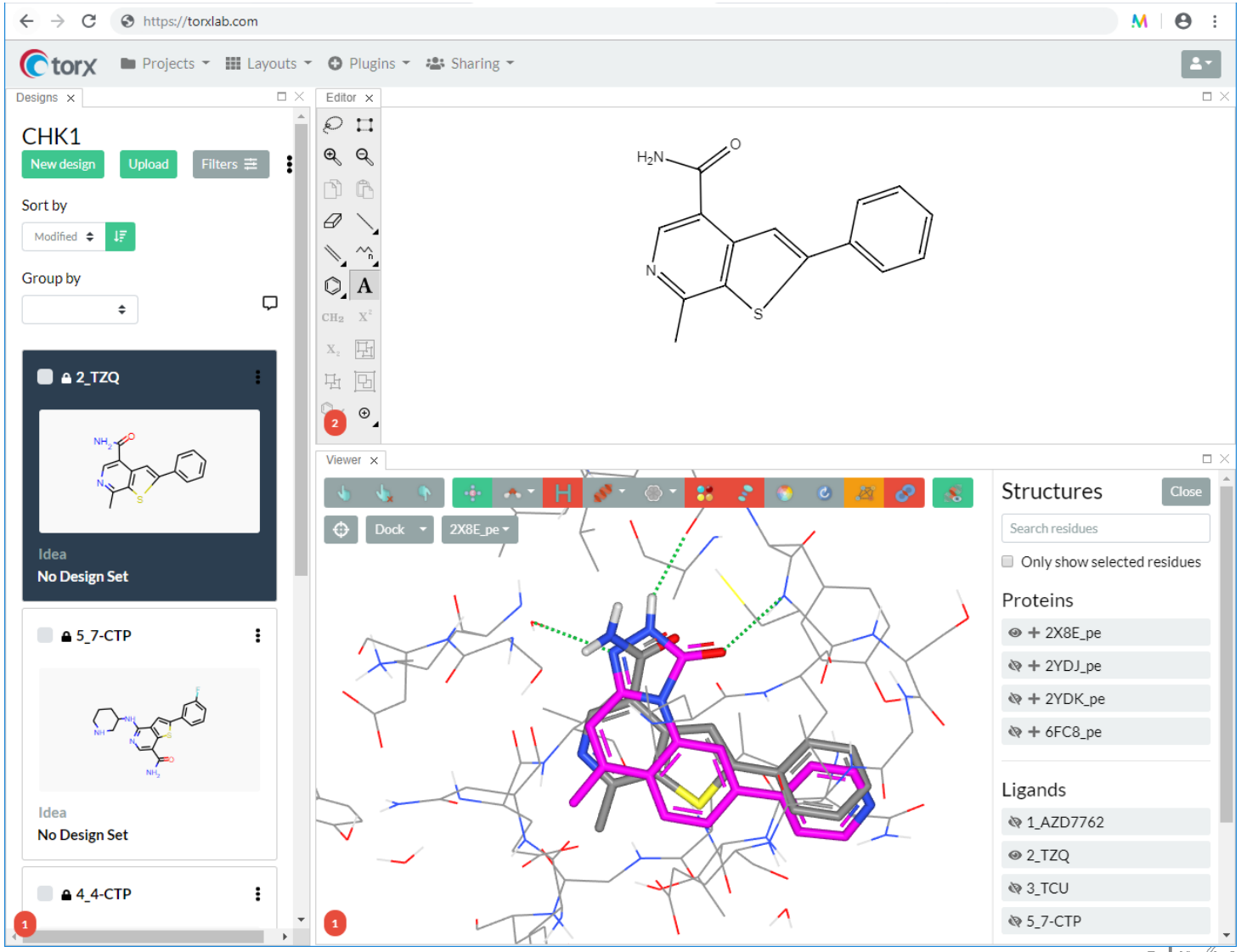
Turn the naphthalene into an isoquinoline

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

Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

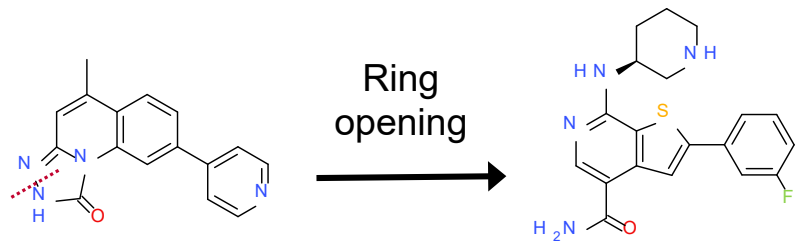
Turn pyridine into benzene



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

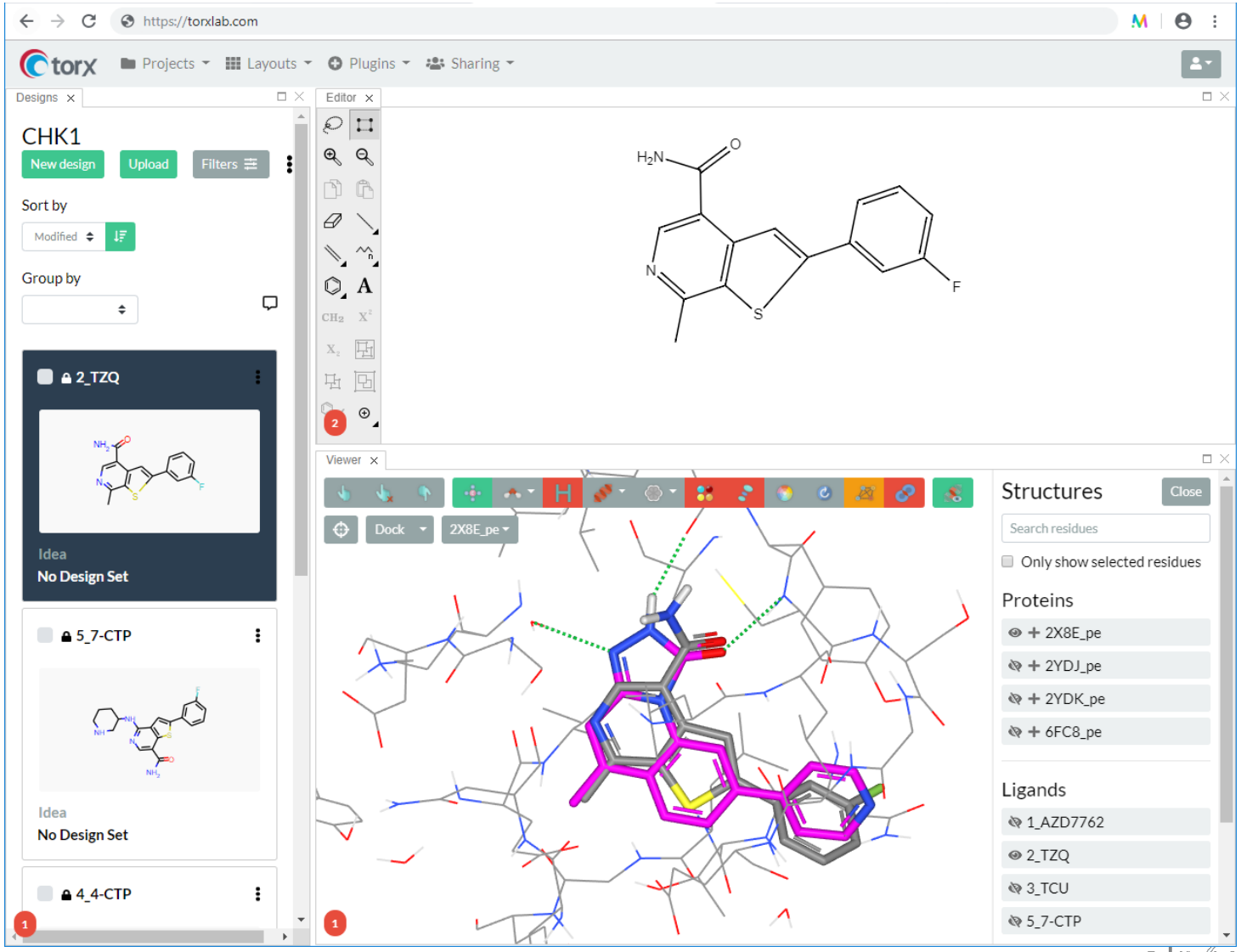
Break the phenyl ring as I need to make it 5-term

Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Add *m*-fluorine to benzene



cresset software

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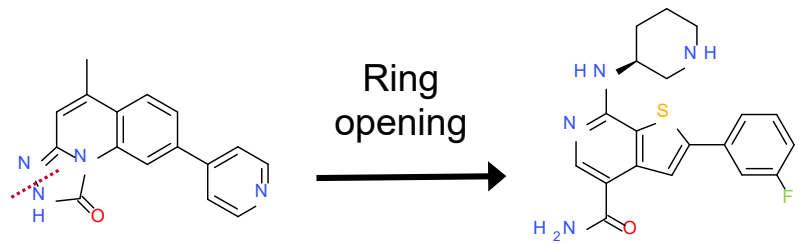
A more complicated design case



2 (TZQ) **4** (4-CTP)

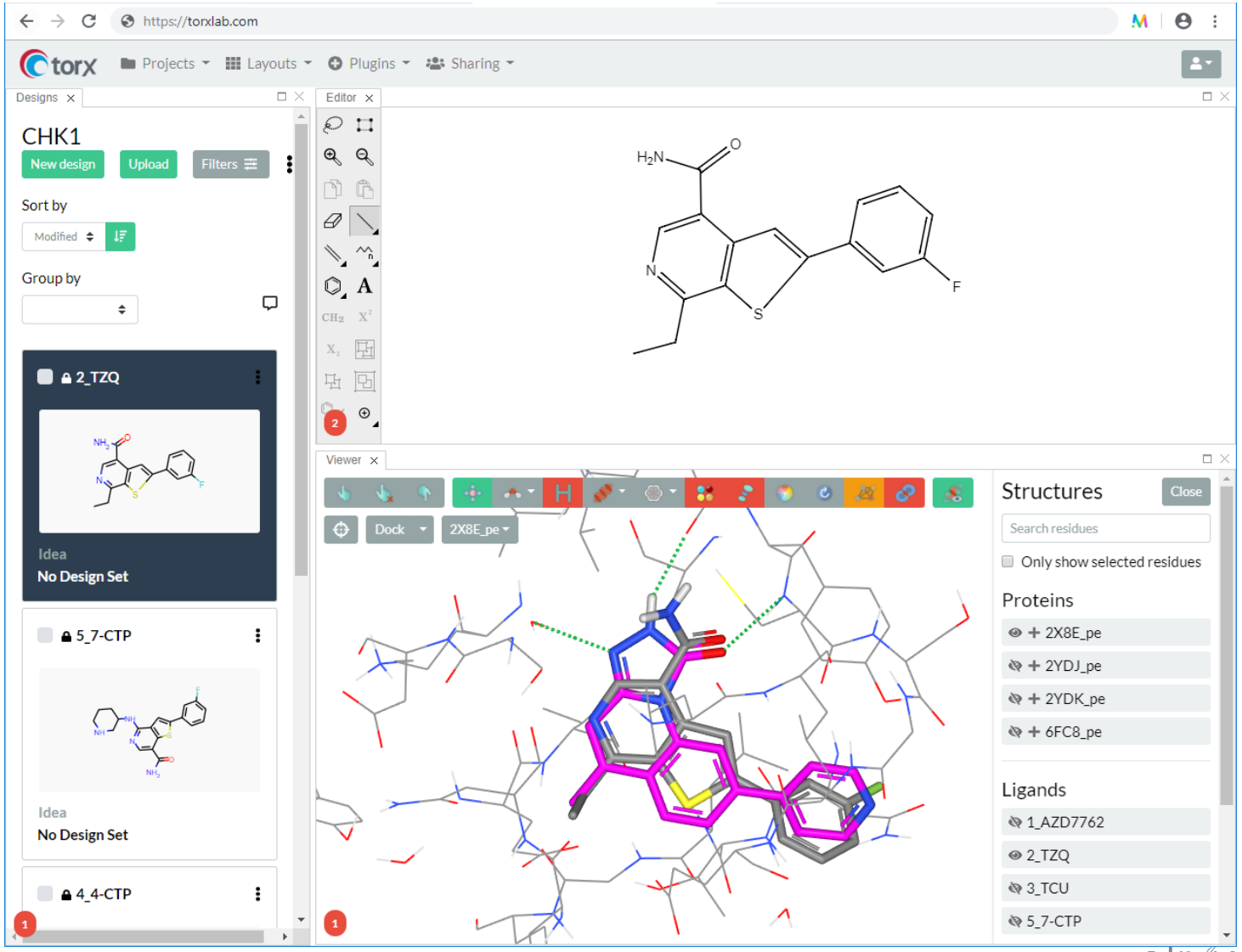
Close to a cyclopentadiene ring

Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Add *m*-fluorine to benzene

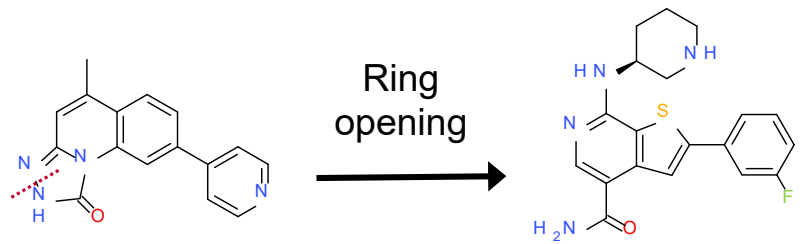
Grow methyl into an ethyl



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

Close to a cyclopentadiene ring

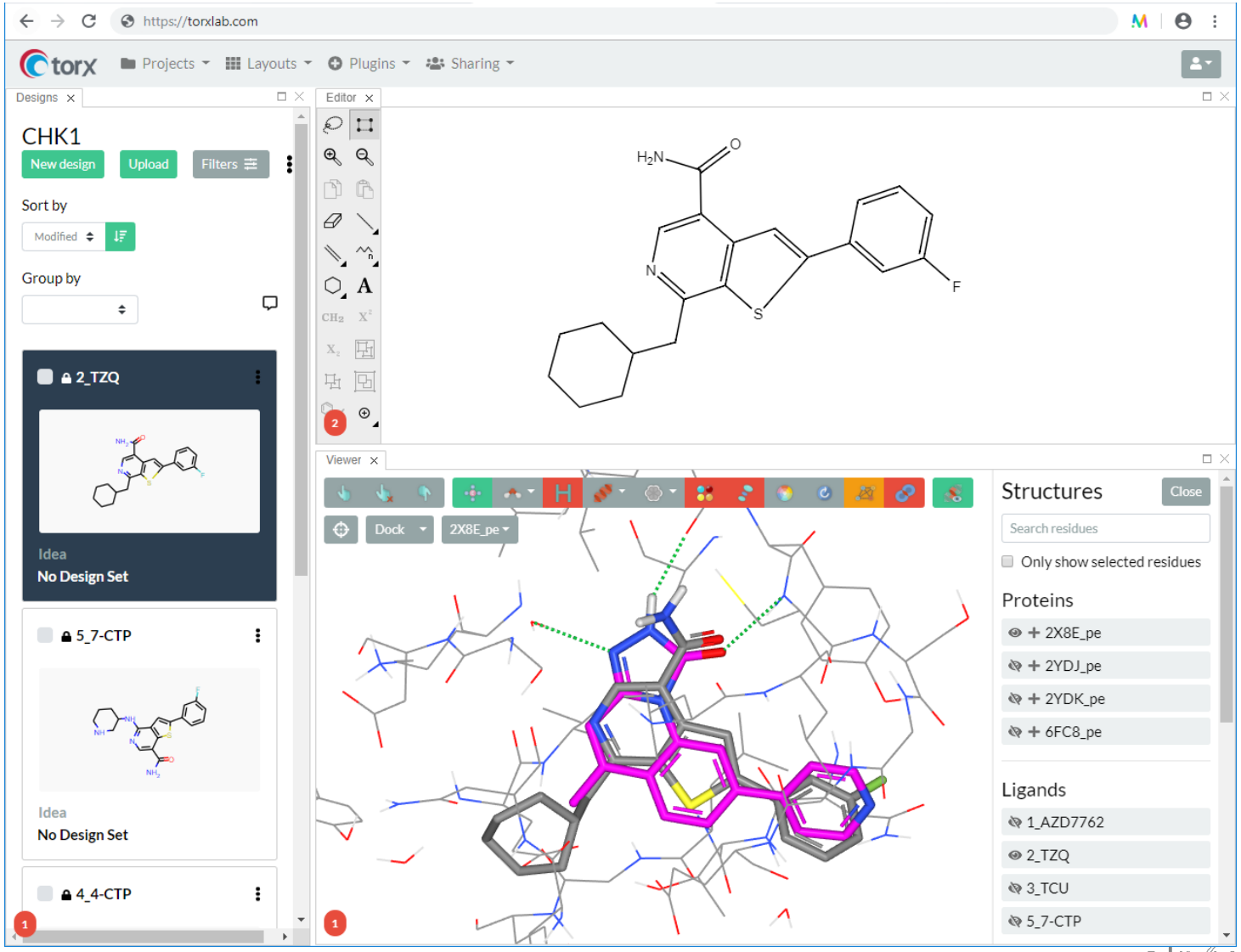
Turn cyclopentadiene into thiophene

Turn pyridine into benzene

Add *m*-fluorine to benzene

Grow methyl into an ethyl

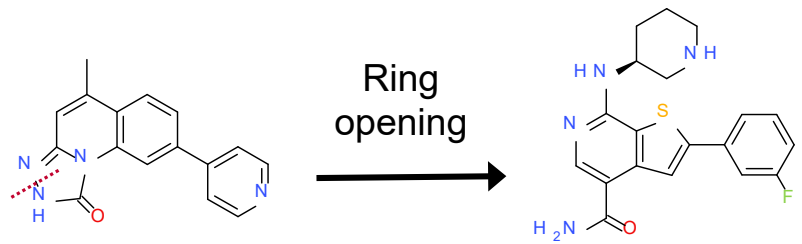
Attach a cyclohexyl to the ethyl



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

Turn cyclopentadiene into thiophene

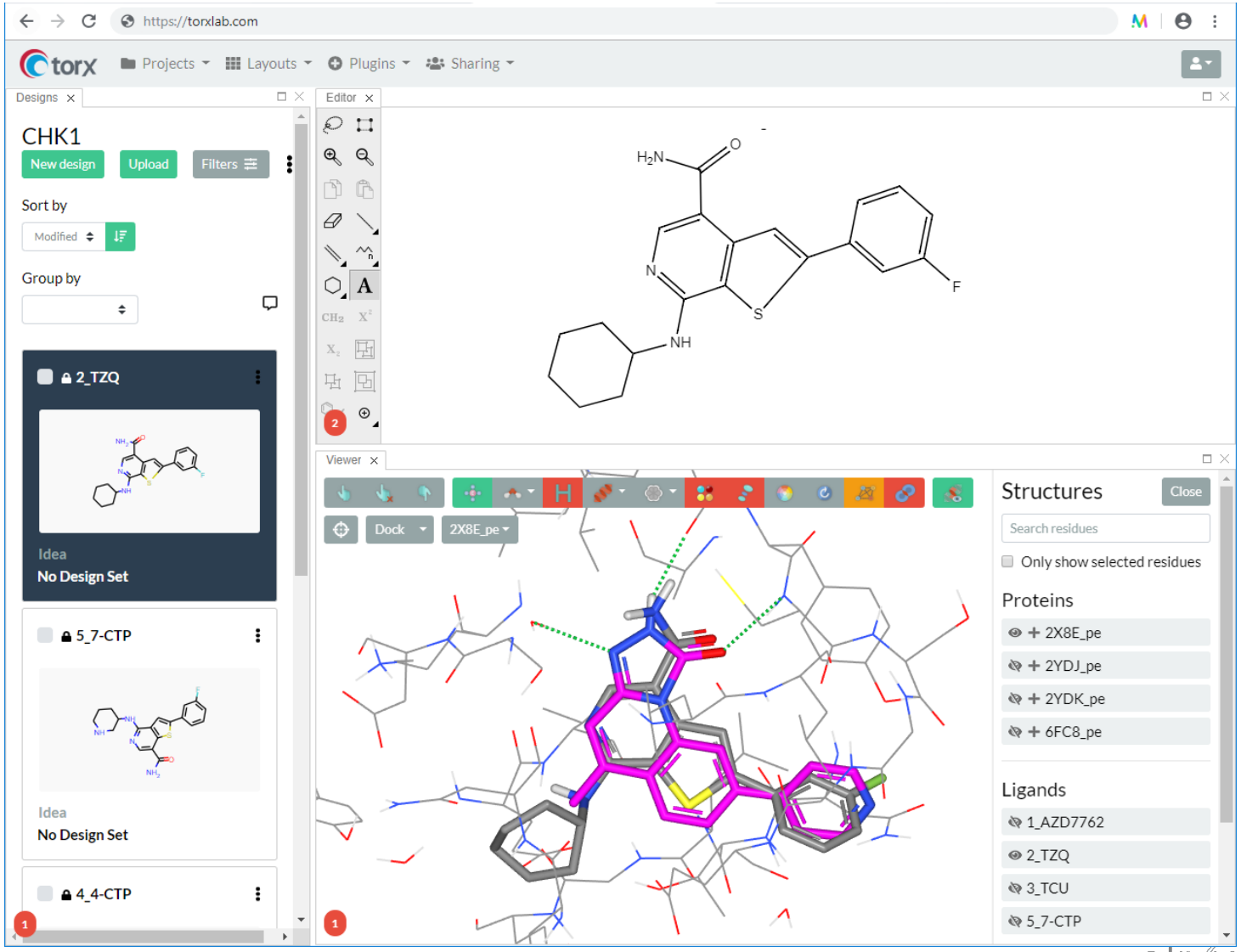
Turn pyridine into benzene

Add *m*-fluorine to benzene

Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

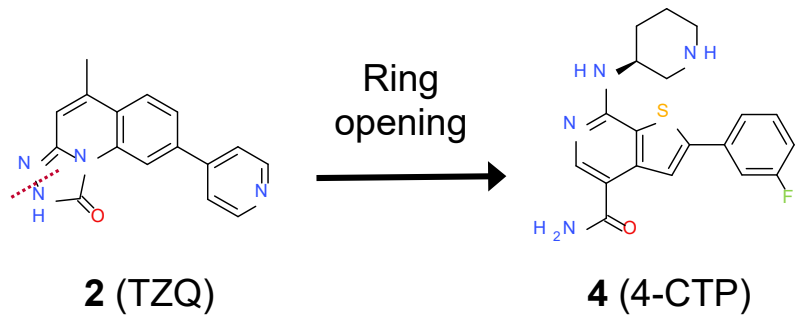
Turn methylene into amino



cresset software

elixir

A more complicated design case



2 (TZQ)

4 (4-CTP)

Turn pyridine into benzene

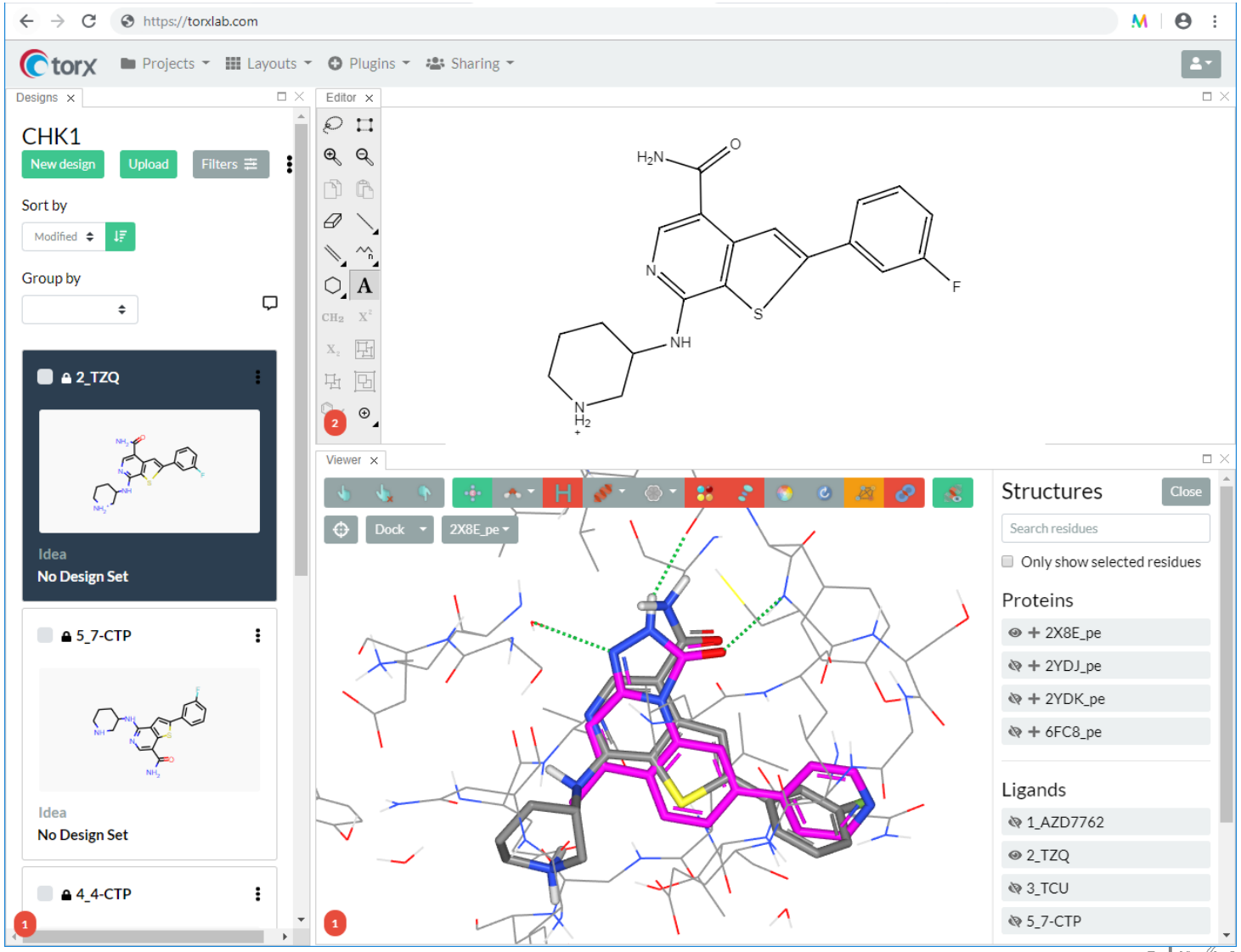
Add *m*-fluorine to benzene

Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

Turn methylene into amino

Turn cyclohexyl into 3-piperidyl



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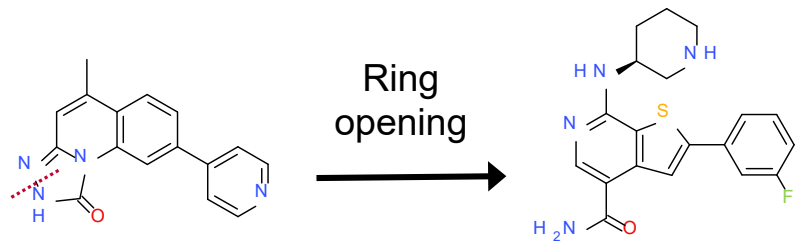
A more complicated design case



2 (TZQ)

4 (4-CTP)

Add *m*-fluorine to benzene

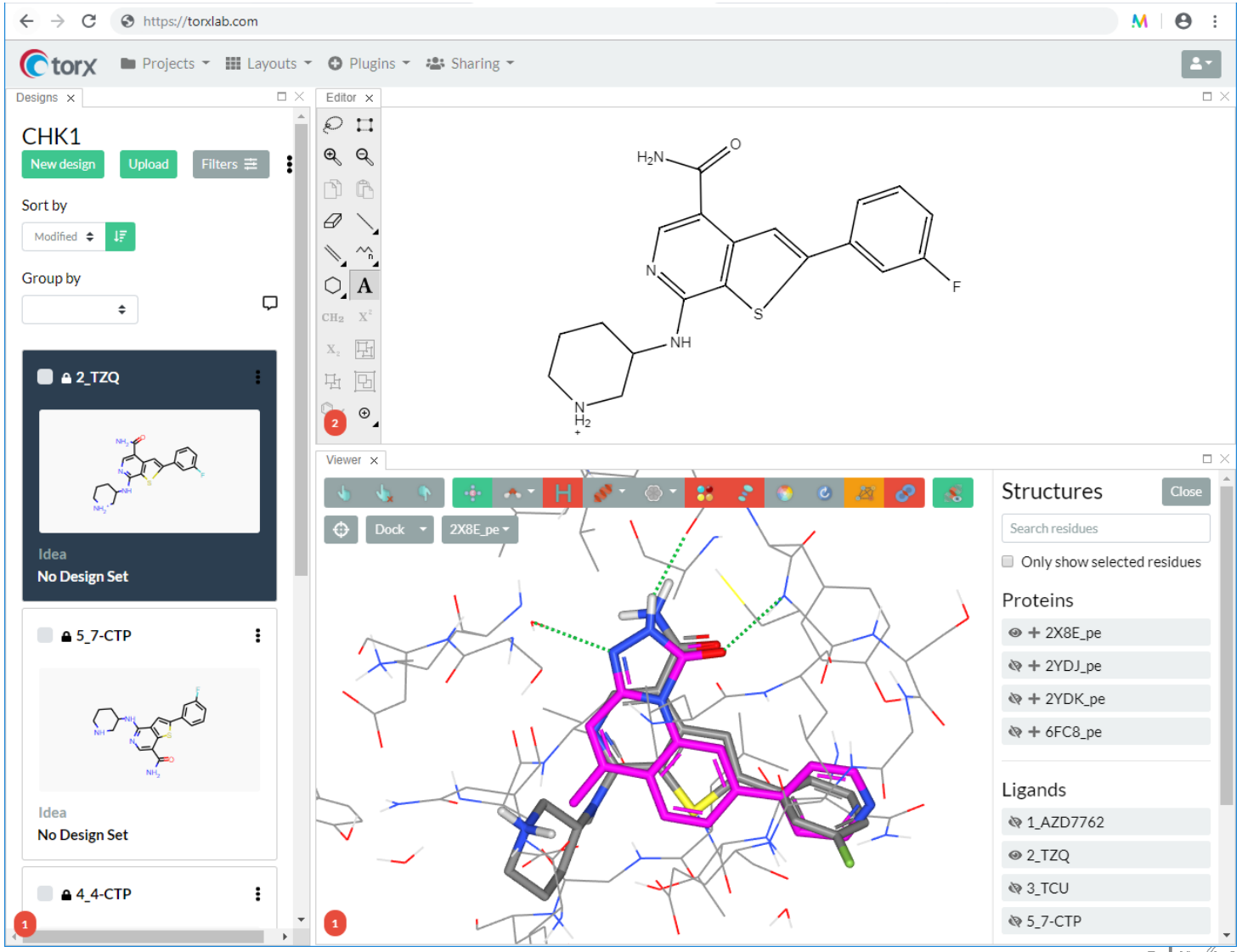
Grow methyl into an ethyl

Attach a cyclohexyl to the ethyl

Turn methylene into amino

Turn cyclohexyl into 3-piperidyl

Final clean-up, and we're done!



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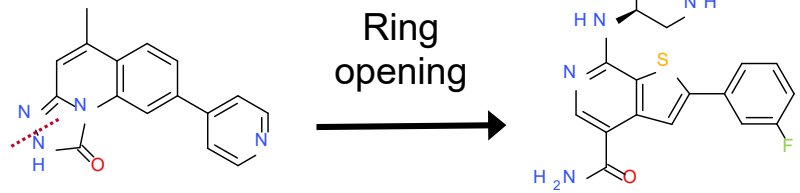
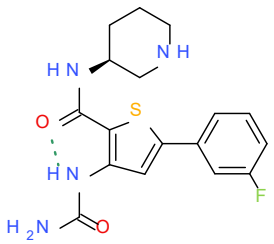
A more complicated design case



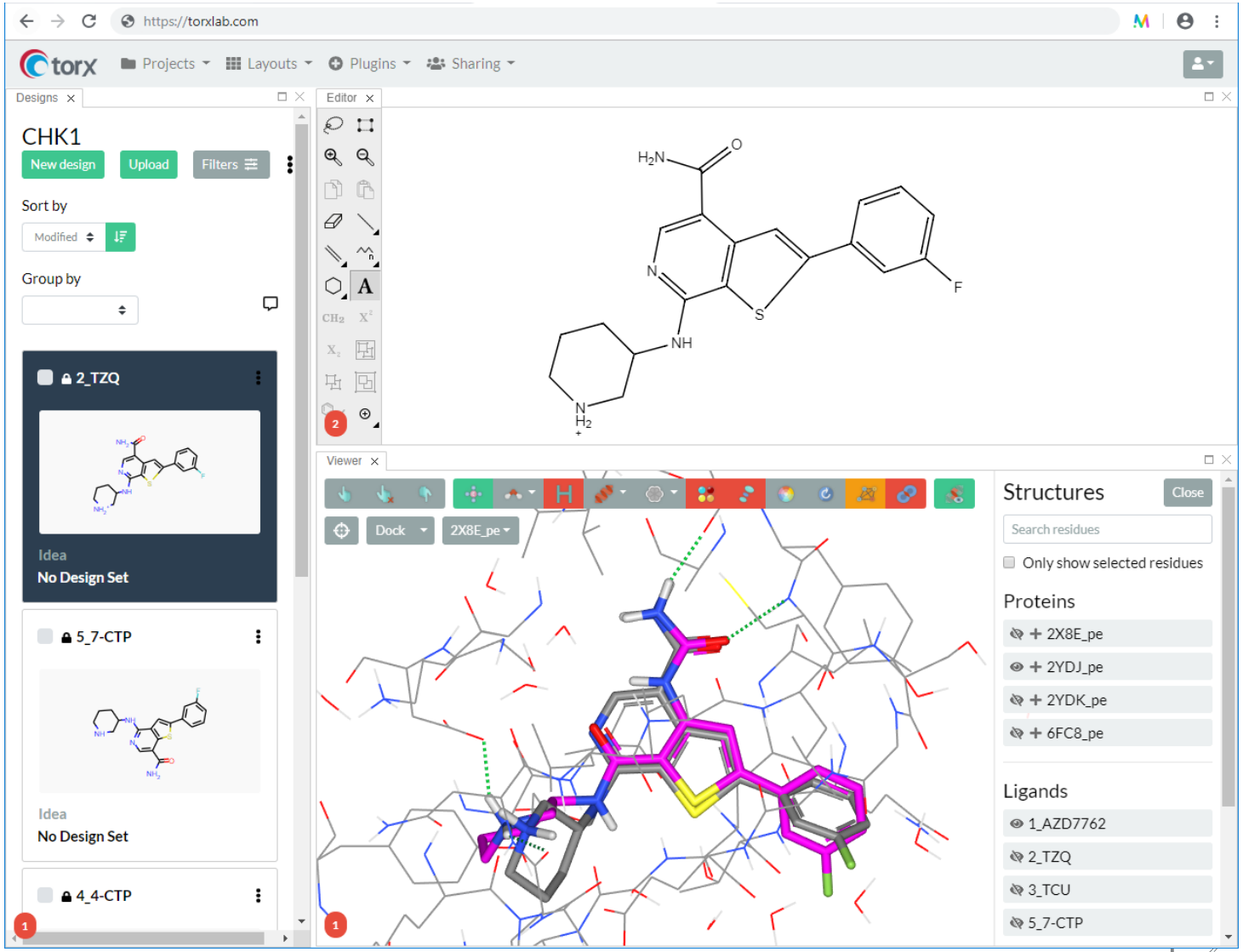
2 (TZQ)

4 (4-CTP)

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



1 (AZD7762)



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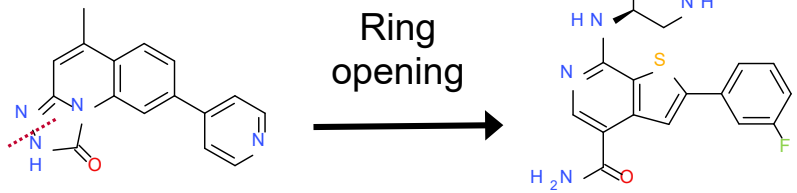
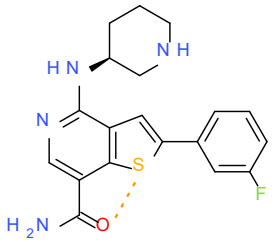
A more complicated design case



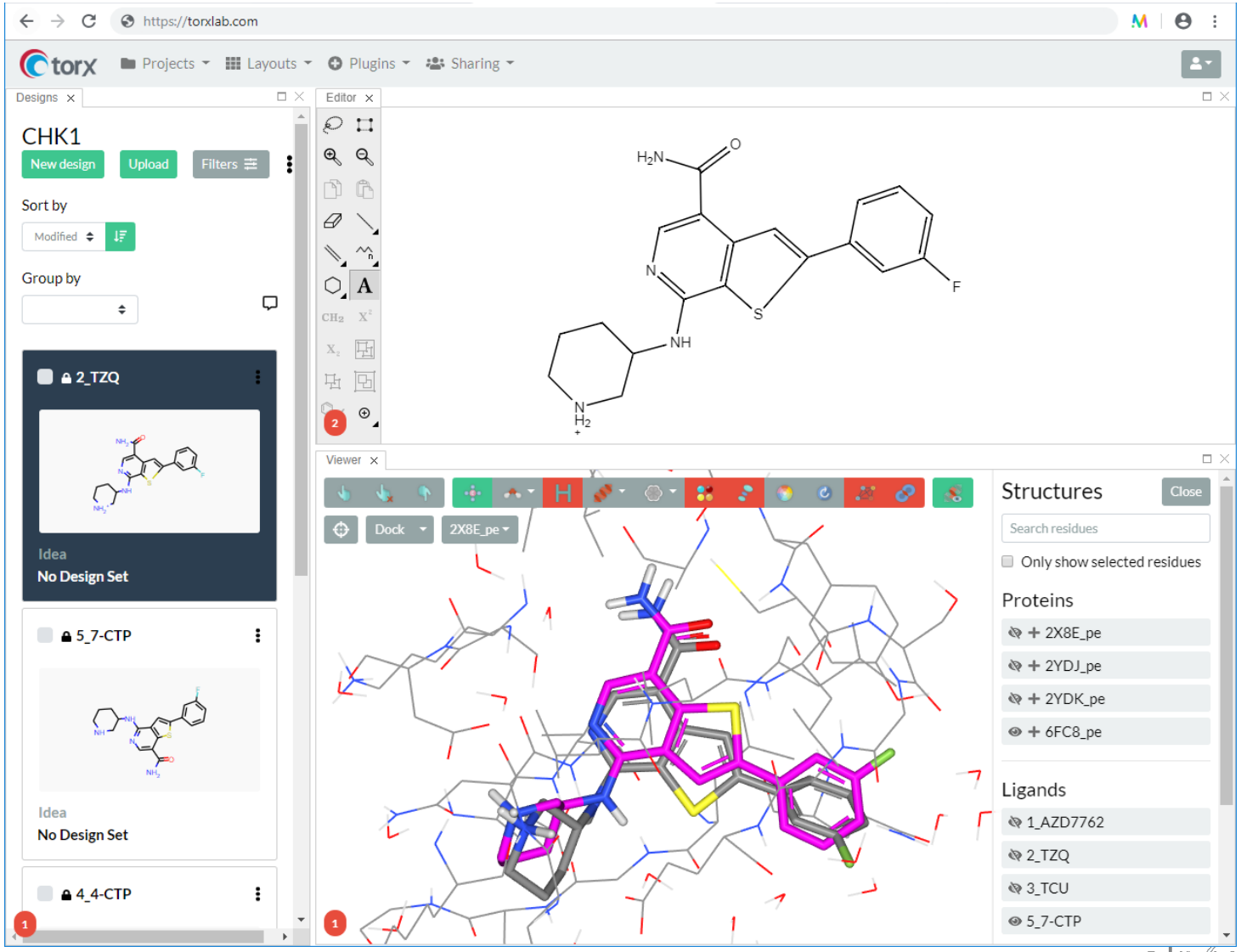
2 (TZQ)

4 (4-CTP)

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



5 (7-CTP)



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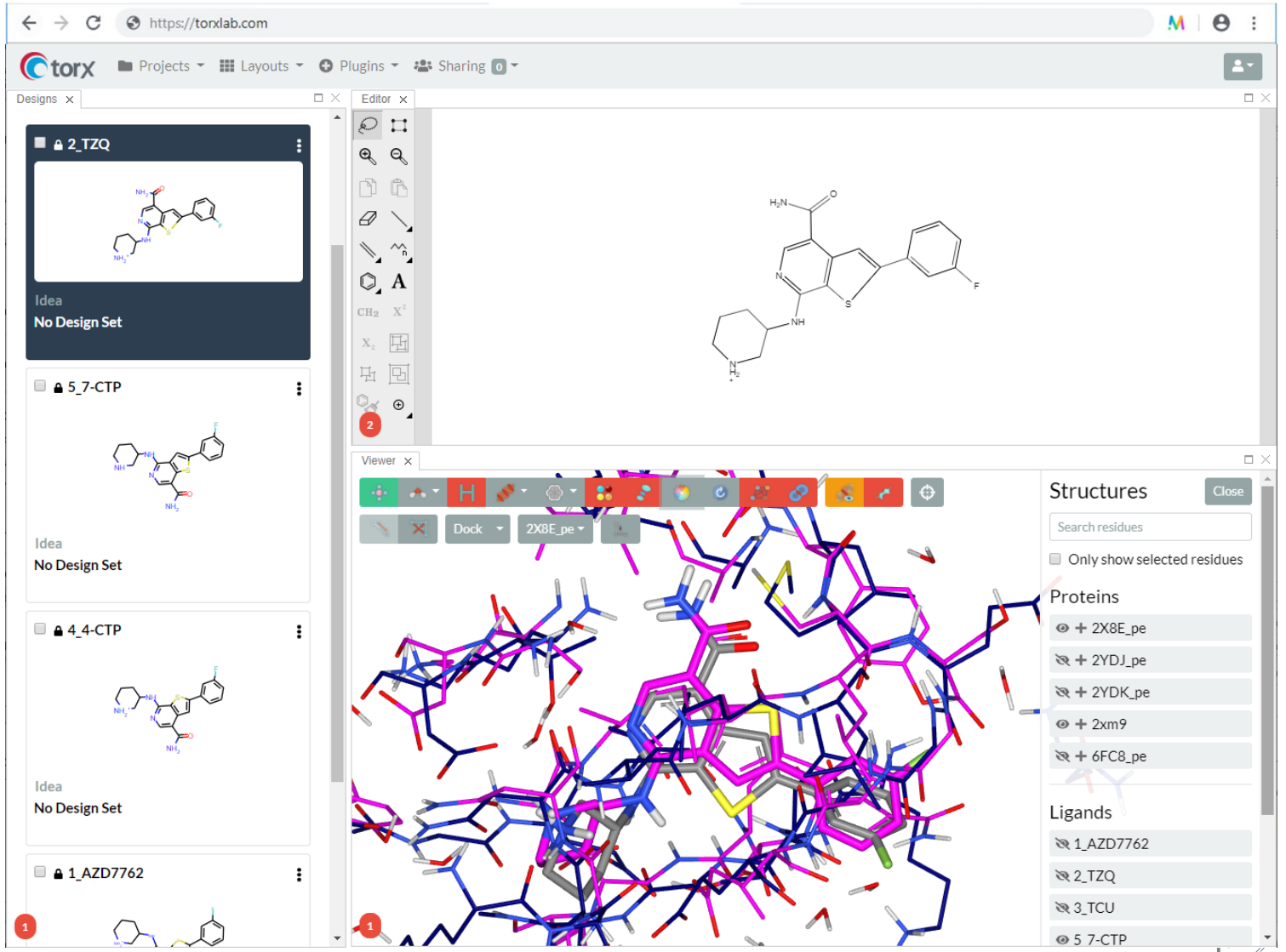
Adding in selectivity – traditional view

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



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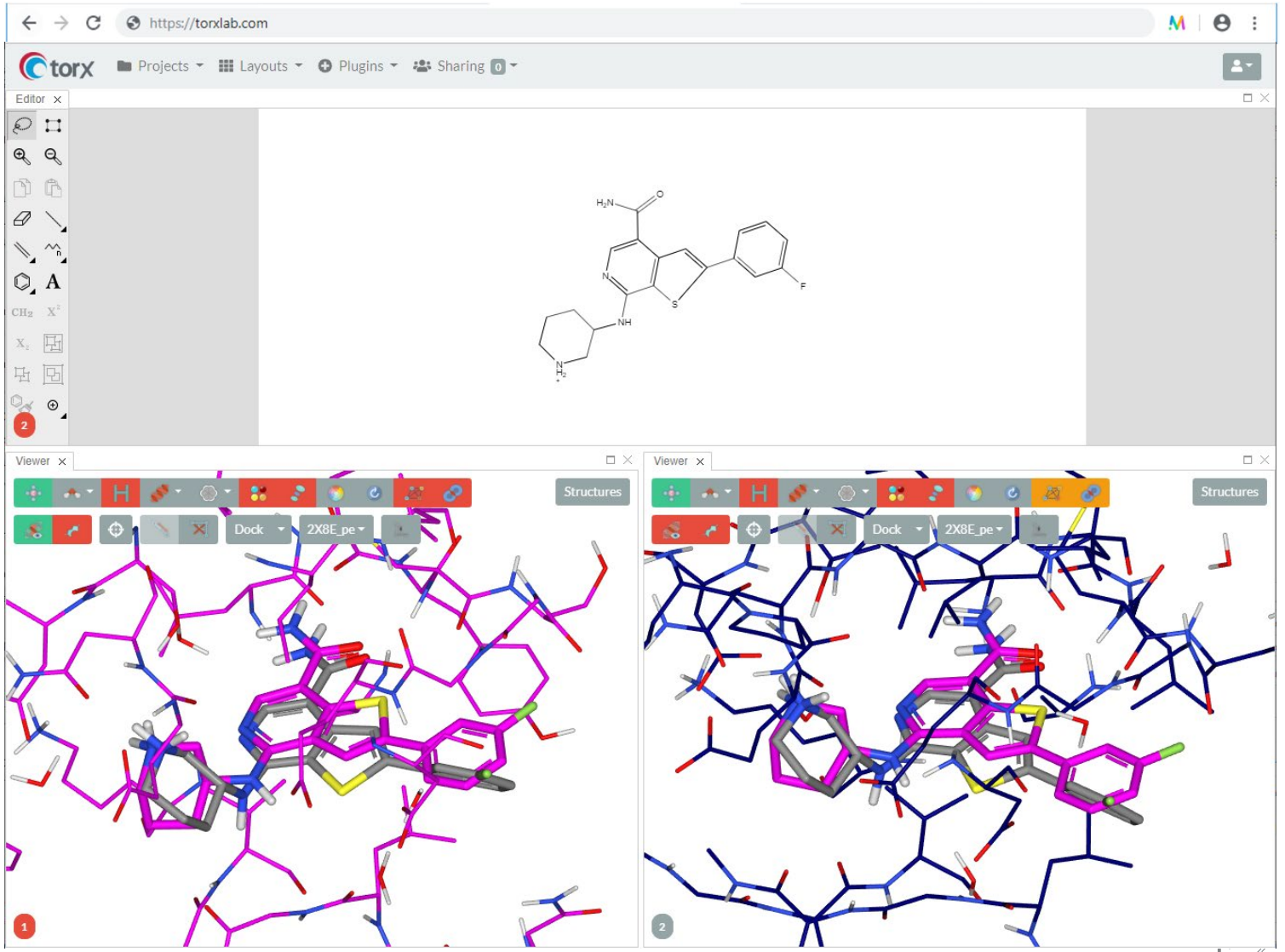
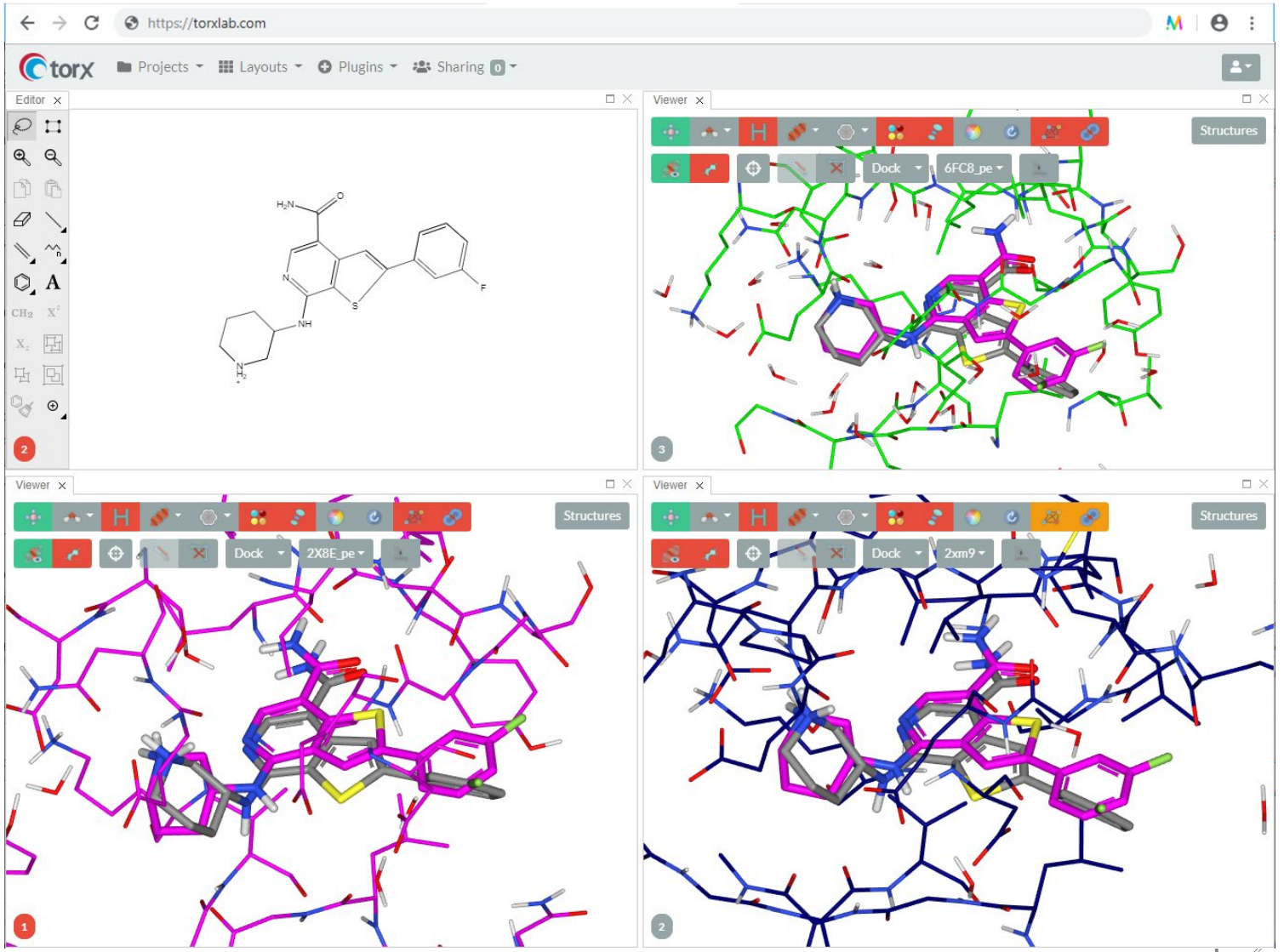
Adding in selectivity – side by side visualization

- 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



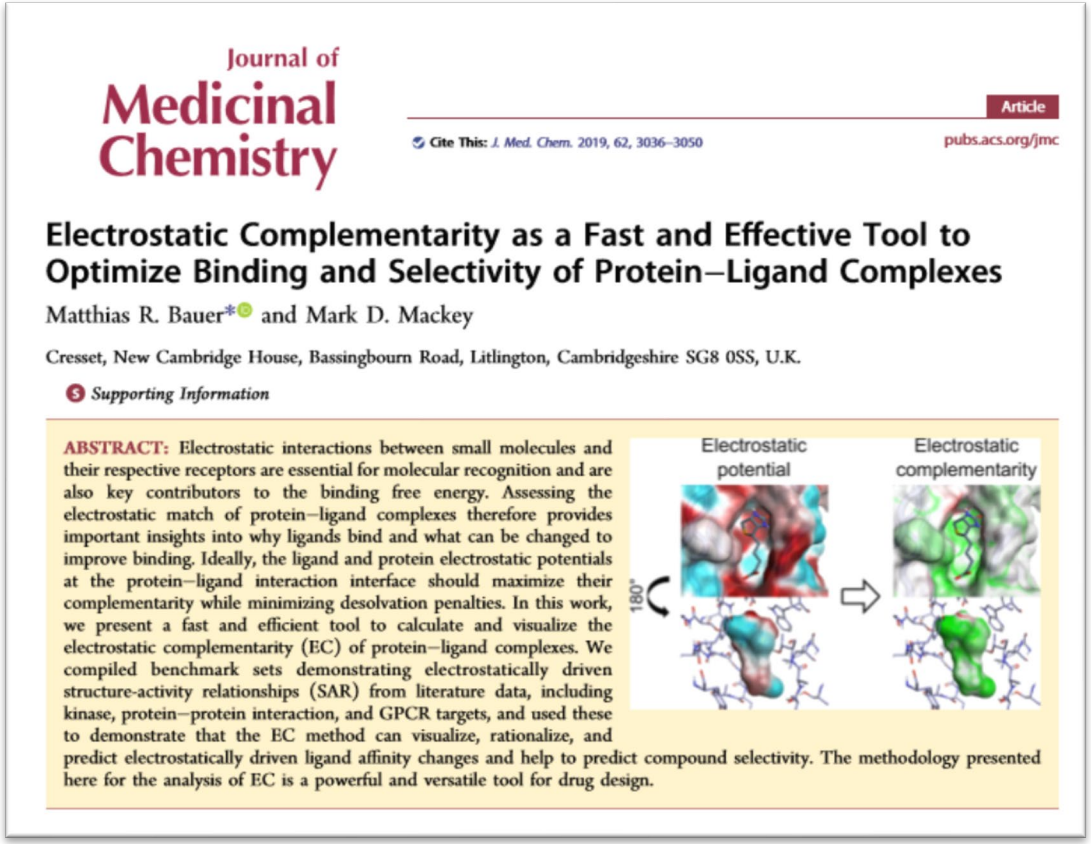
Looking ahead – more advanced modelling techniques

> 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

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

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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.

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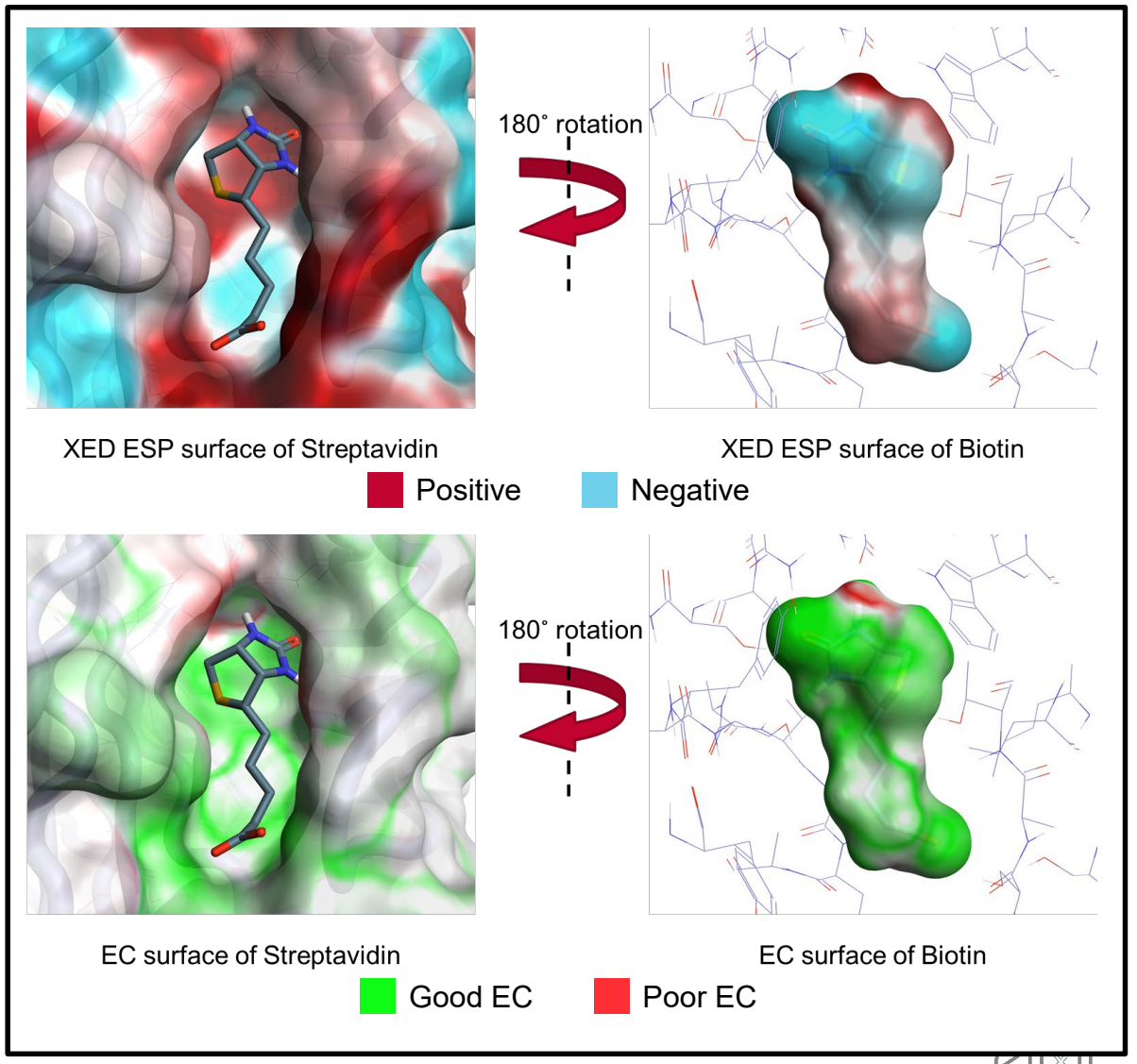
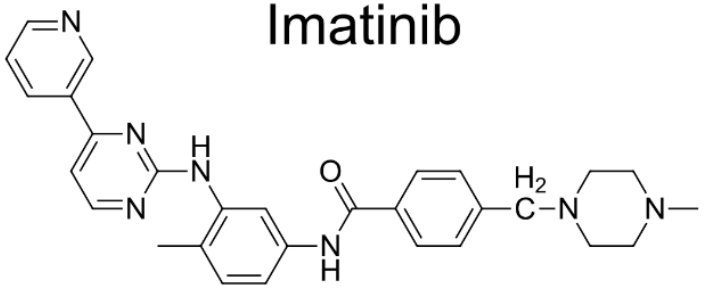
Electrostatic Complementarity as a guide for molecule design

- 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

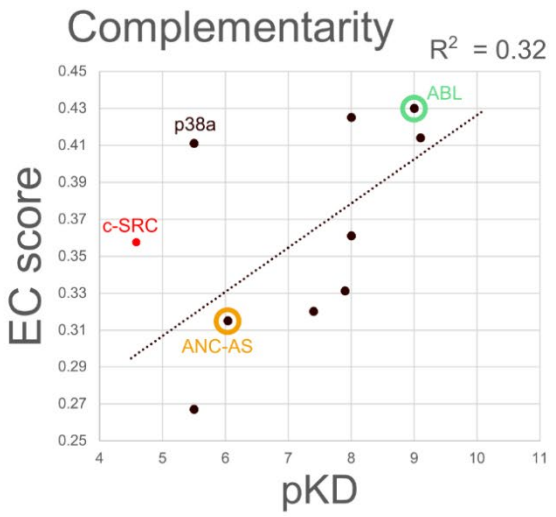


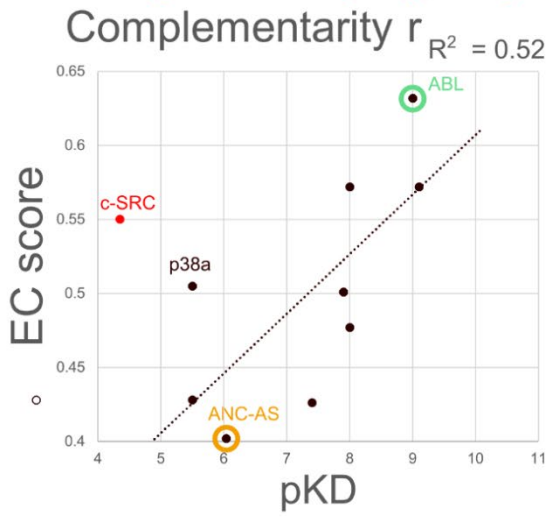
Imatinib – EC and selectivity

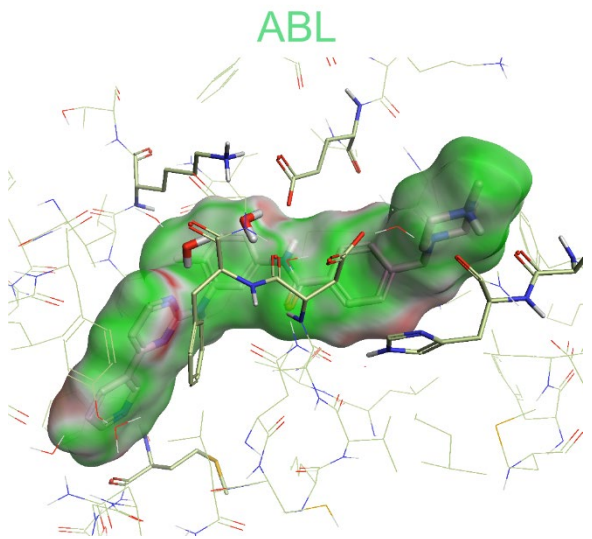


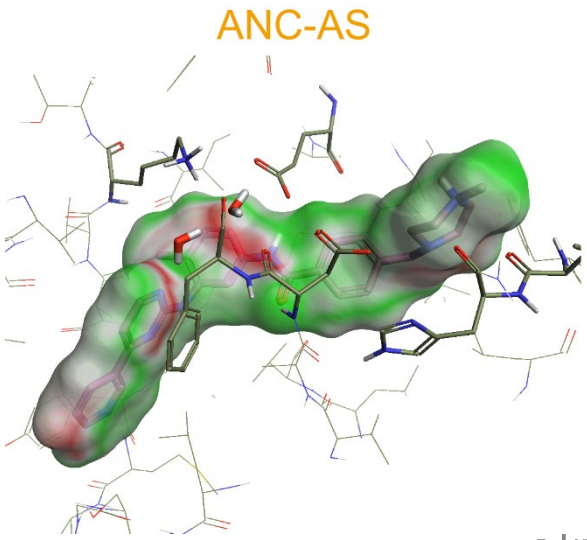
target	pdb	pKD	Complementarity	Complementarity r
c-SRC [a]	2OIQ	4.4	0.36	0.55
p38a	3HEC	5.5	0.41	0.51
SYK	1XBB	5.5	0.27	0.43
ANC-AS	4CSV	6.0	0.32	0.40
LCK	2PL0	7.4	0.32	0.43
KIT	1T46	7.9	0.33	0.50
CSF1	4R7I	8.0	0.36	0.48
ABL2	3GVU	8.0	0.43	0.57
ABL	1OPJ	9.0	0.43	0.63
DDR1	4BKJ	9.1	0.41	0.57

[a] Imatinib binding decreased due to conf. penalty upon binding









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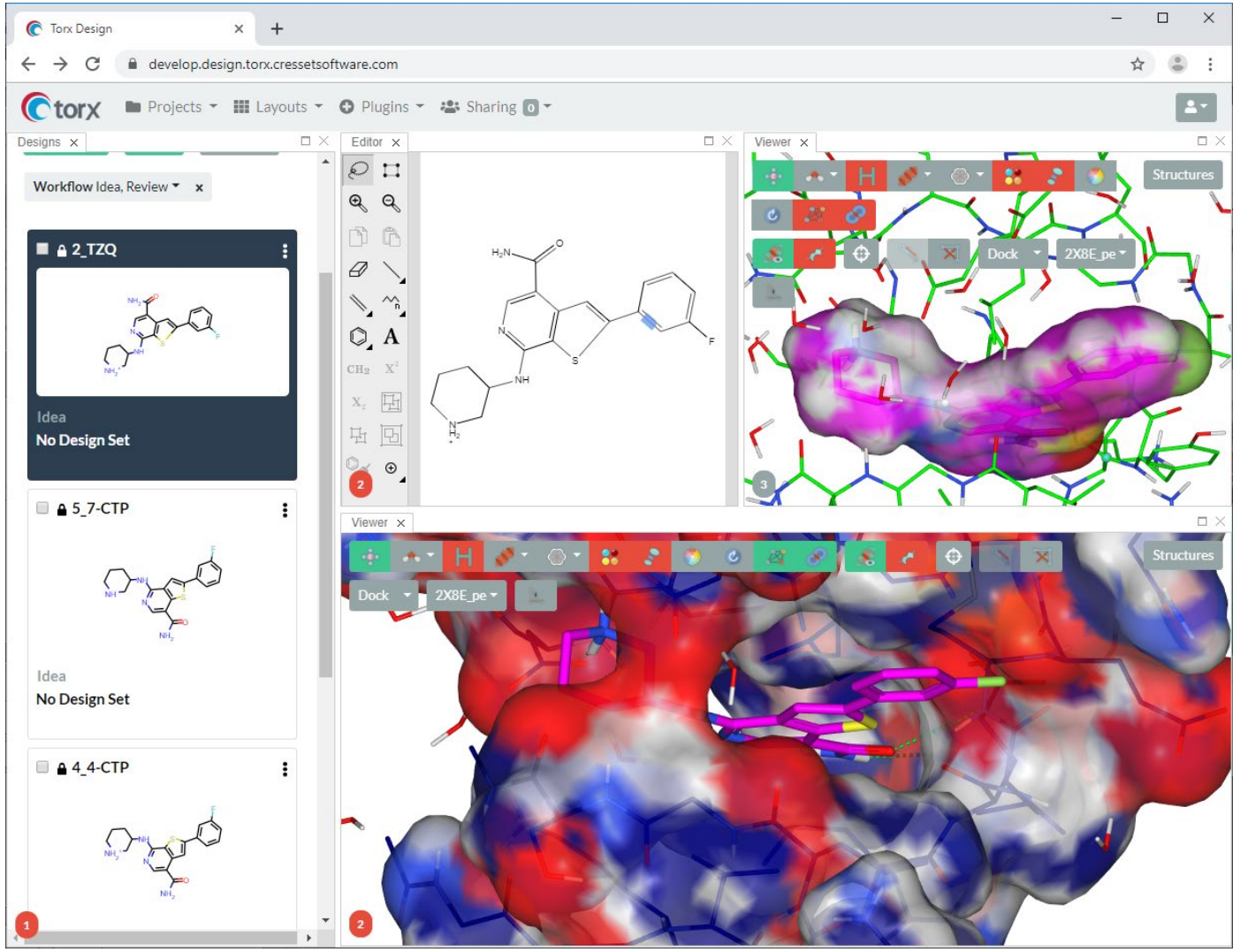
EC Implementation into Torx

- > Surfaces on
  - > Ligands
  - > Proteins
- > Minimization of ligand in binding site
- > Color by EC
- > Z-clipping



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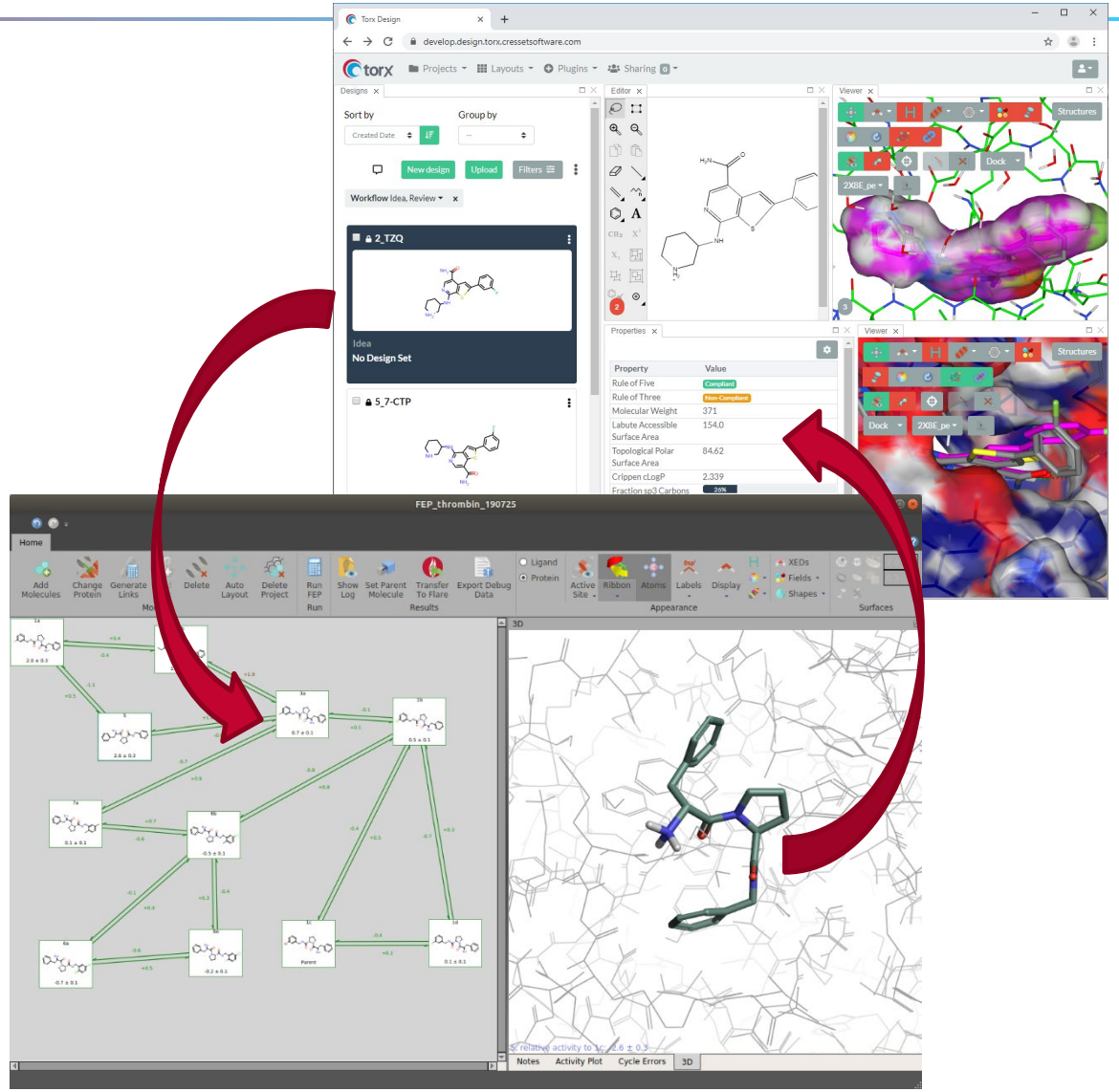
What about FEP?

- 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



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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

Thank you for your attention

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Acknowledgments

@Cresset: Mark Mackey, Tim Cheeseright

The RDKit