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Real Time 3D Design in 2D!

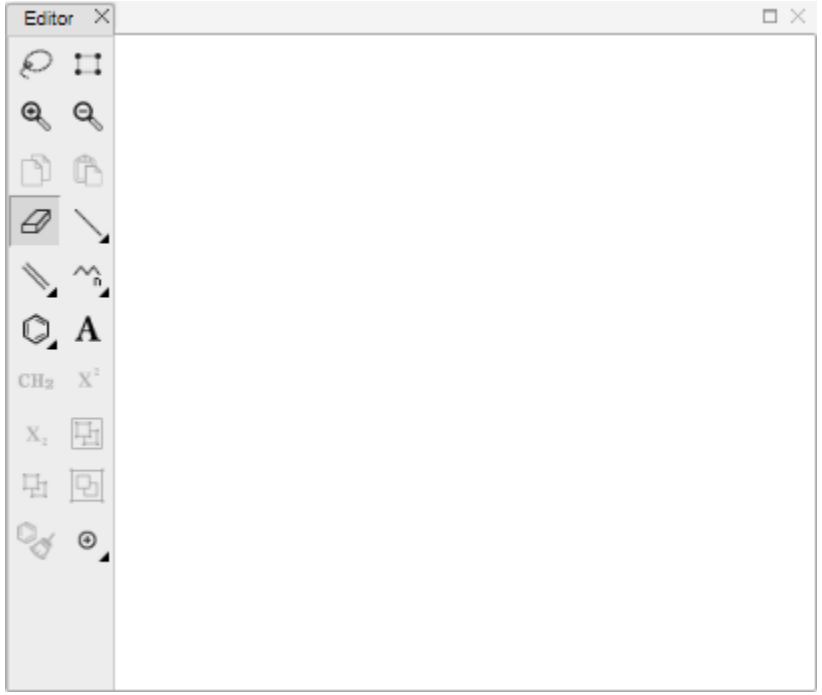
Paolo Tosco

How nice would it to be…

…to draw a molecule in the 2D sketcher and see it grow sensibly within the active site in the 3D viewport?

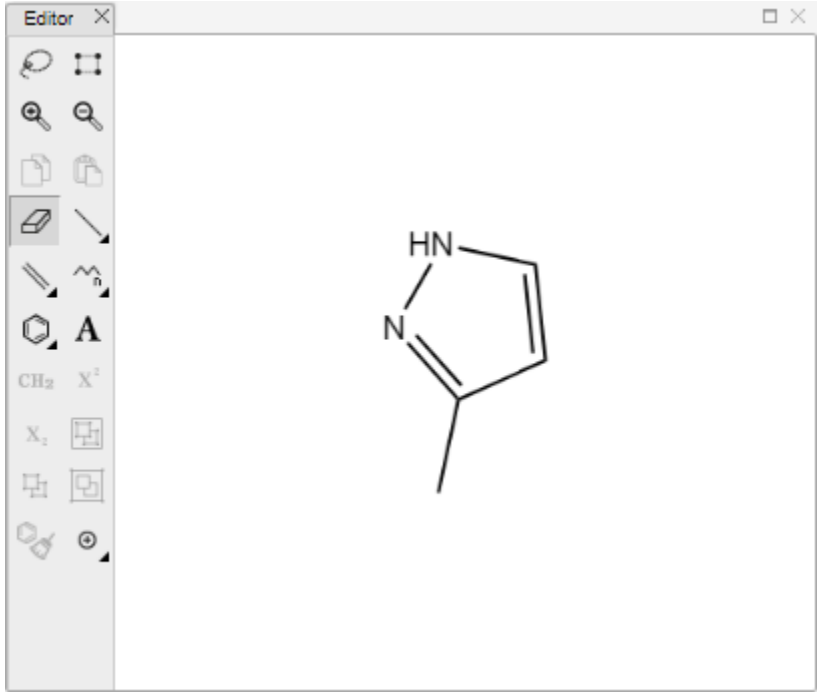
How hard can it to be?

> Start from a blank 2D sketcher canvas



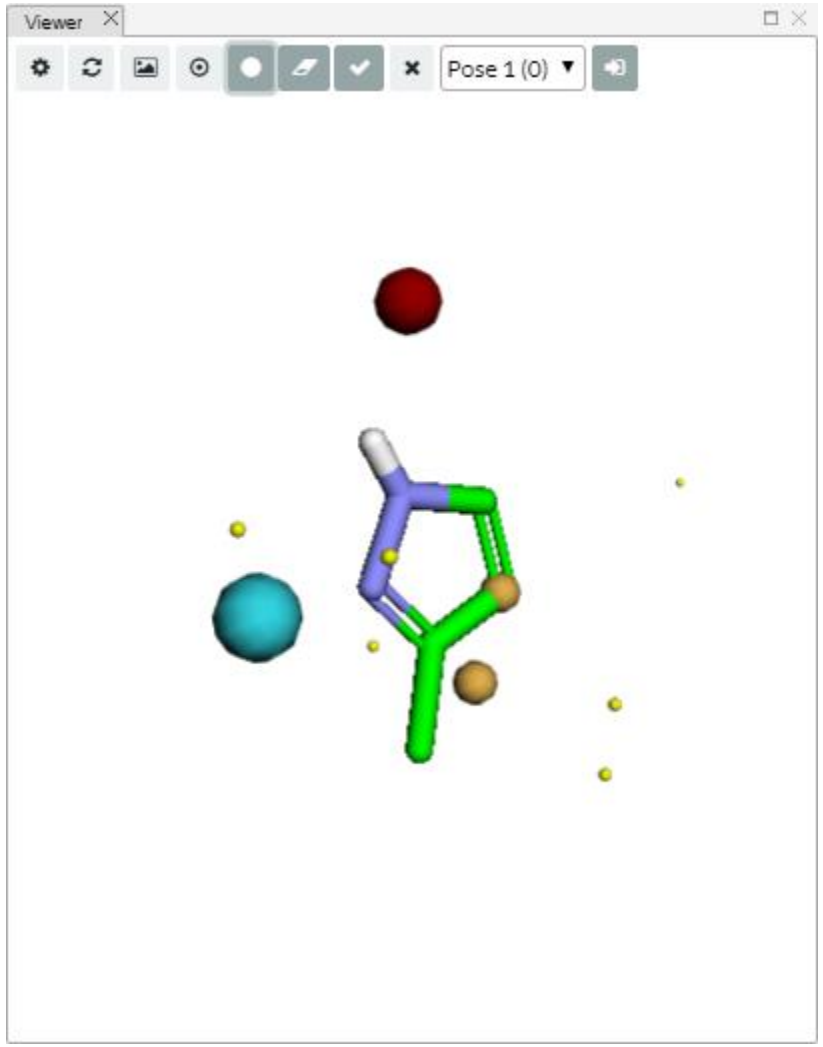
How hard can it to be?

- Start from a blank 2D sketcher canvas
  - sketch something



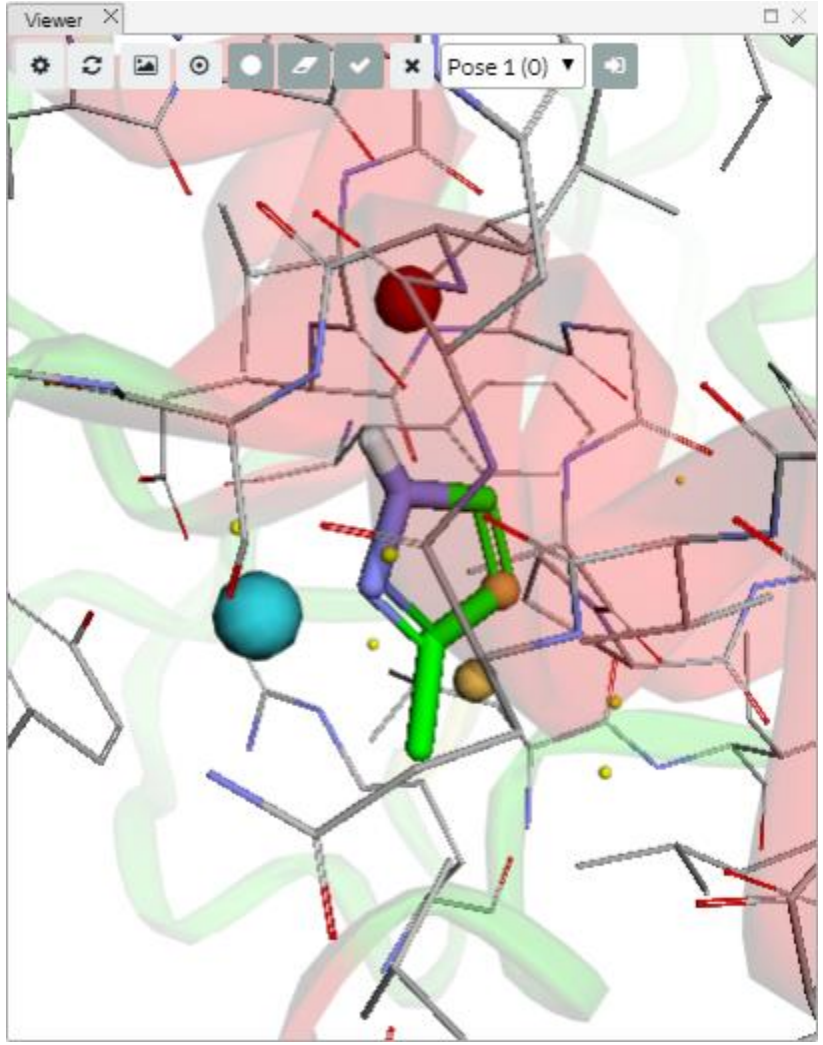
How hard can it to be?

- Start from a blank 2D sketcher canvas
  - sketch something
  - the largest 2D fragment is popped to a 3D conformation…



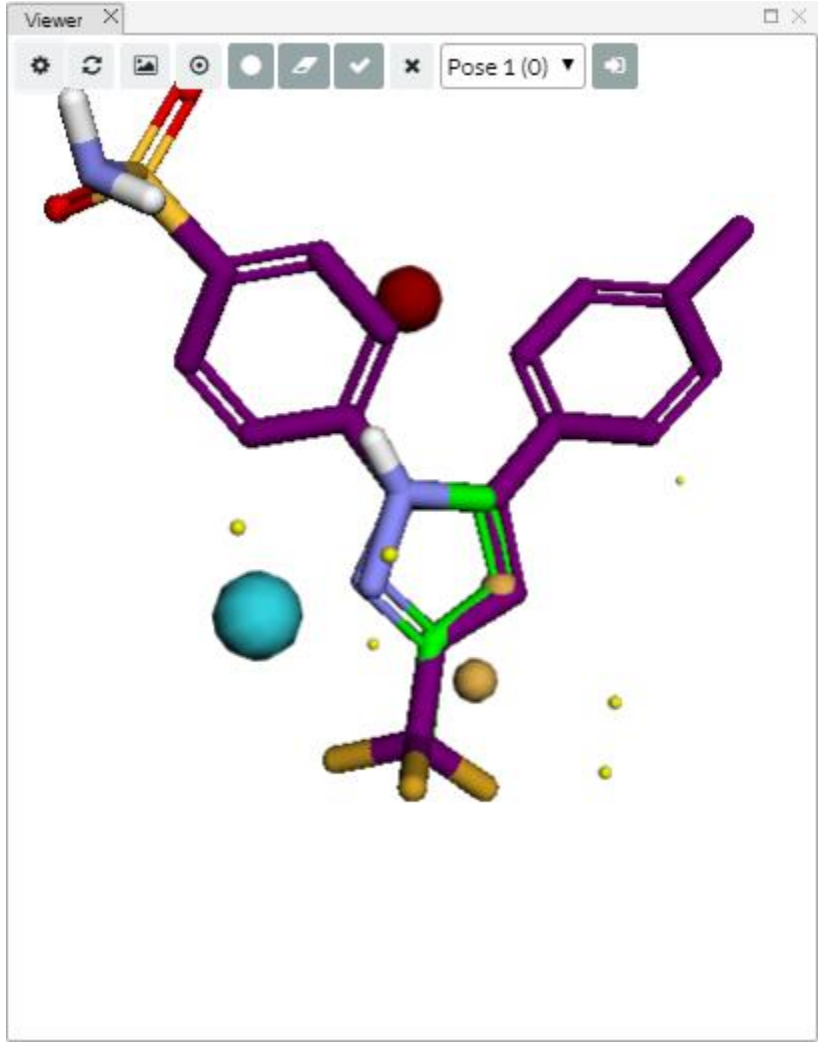
How hard can it to be?

- Start from a blank 2D sketcher canvas
  - sketch something
  - the largest 2D fragment is popped to a 3D conformation…
  - …and docked into the protein's active site



How hard can it to be?

- Start from a blank 2D sketcher canvas
  - sketch something
  - the largest 2D fragment is popped to a 3D conformation…
  - …and docked into the protein's active site
  - …or aligned against a reference using the Forge™ Align algorithm



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  - sketch something
  - the largest 2D fragment is popped to a 3D conformation…
  - …and docked into the protein's active site
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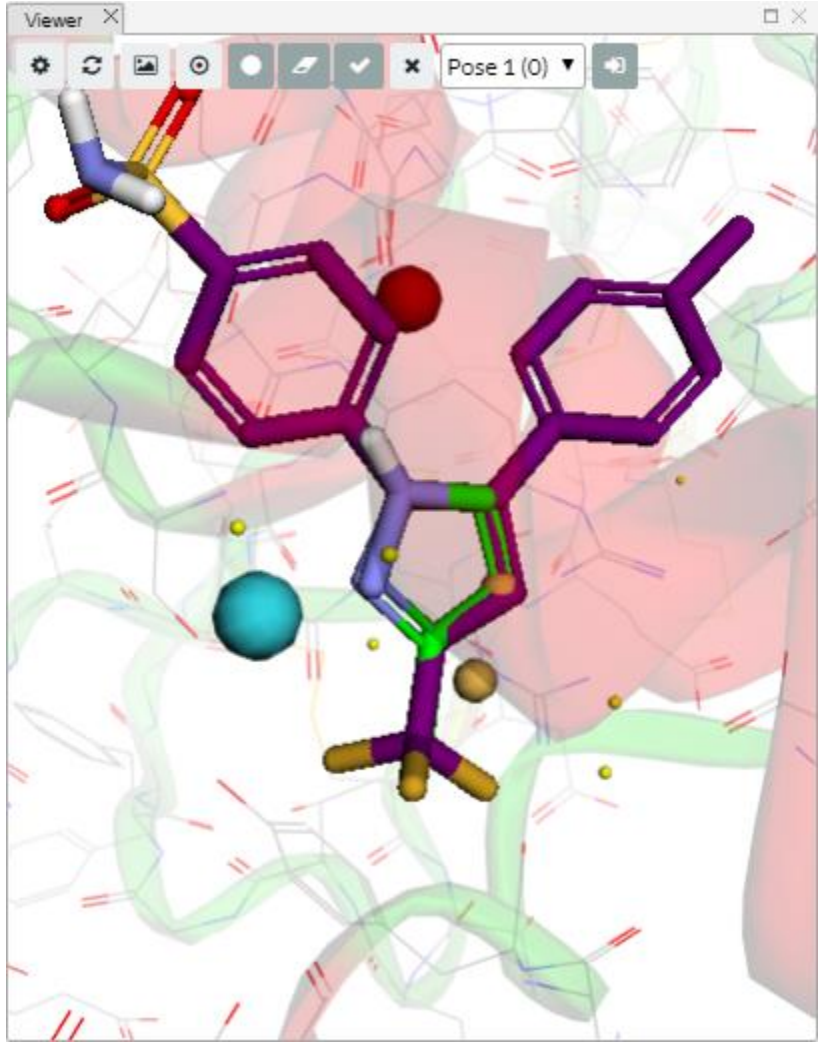
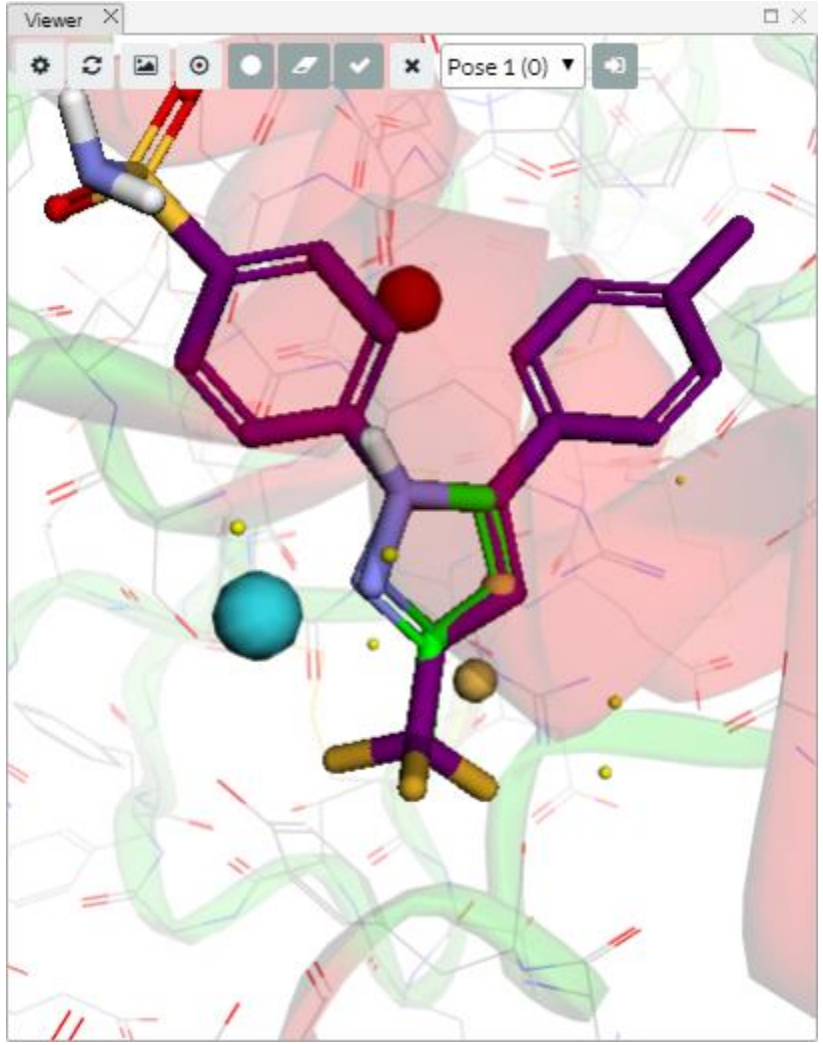
  - using the protein as excluded volume (if available)



How hard can it to be?

- Start from a blank 2D sketcher canvas
  - sketch something
  - the largest 2D fragment is popped to a 3D conformation…
  - …and docked into the protein's active site
  - …or aligned against a reference using the Forge™ Align algorithm
  - using the protein as excluded volume (if available)
  - then the *grow3D* process begins



A simple flow chart will help: start from blank

Look at disconnected fragments which make up the sketch

Has the number of 2D frags changed?

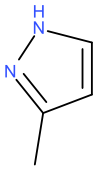
YES

Are there more frags than before?

YES

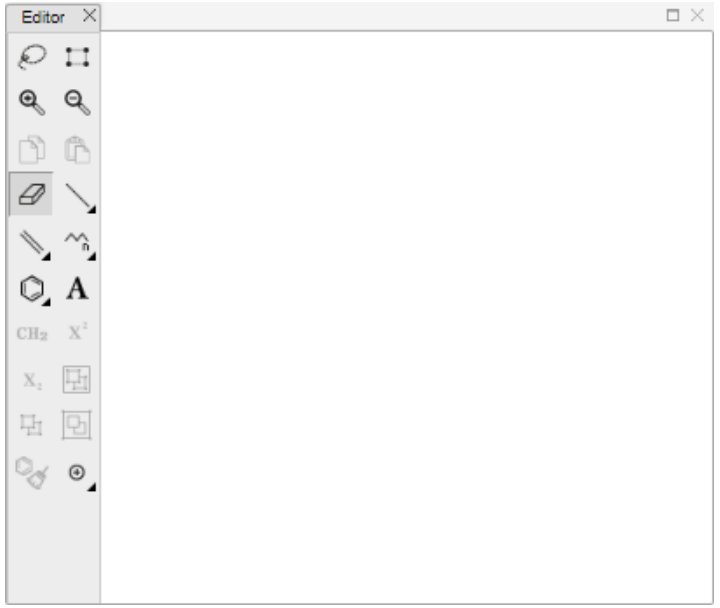
NO

No fragments

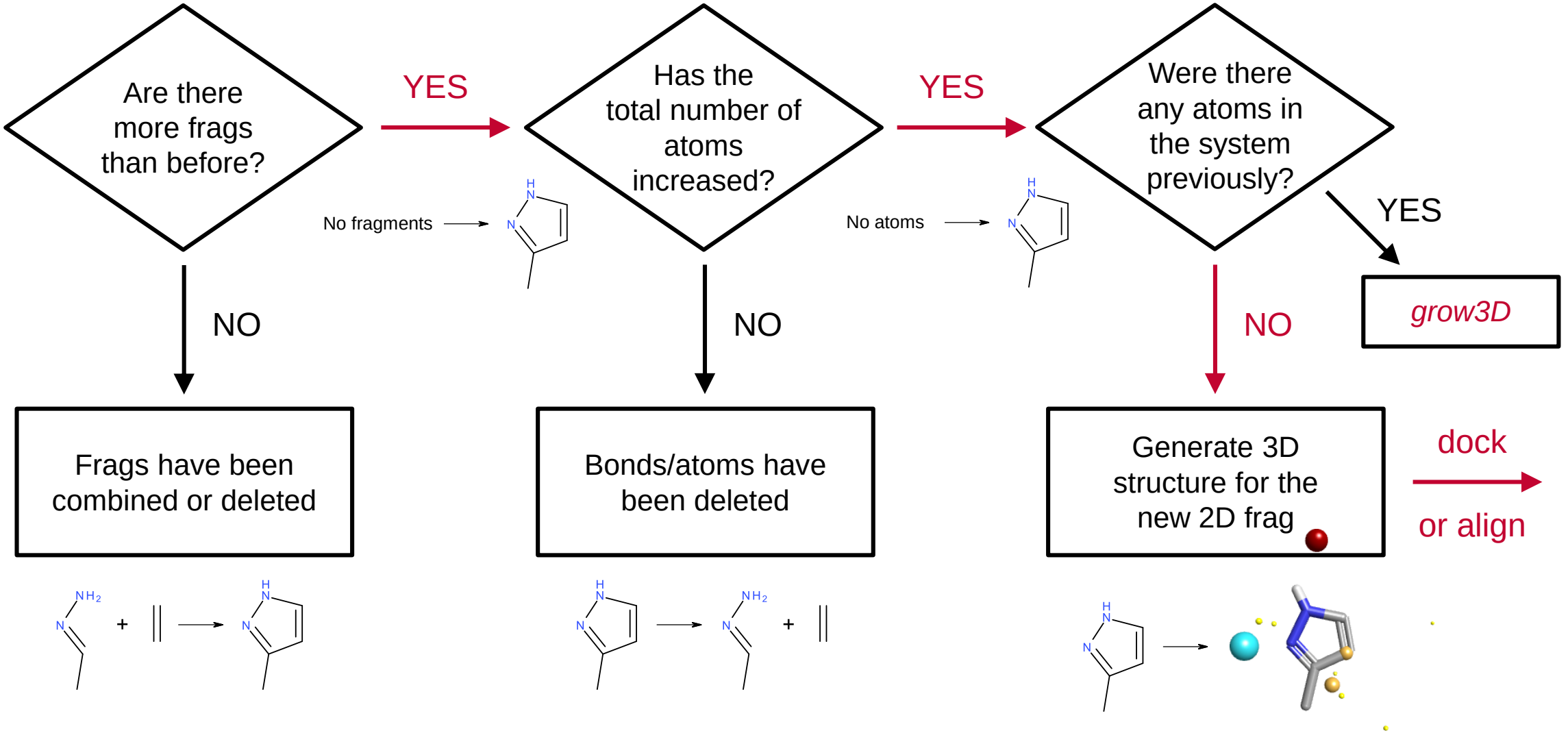


NO

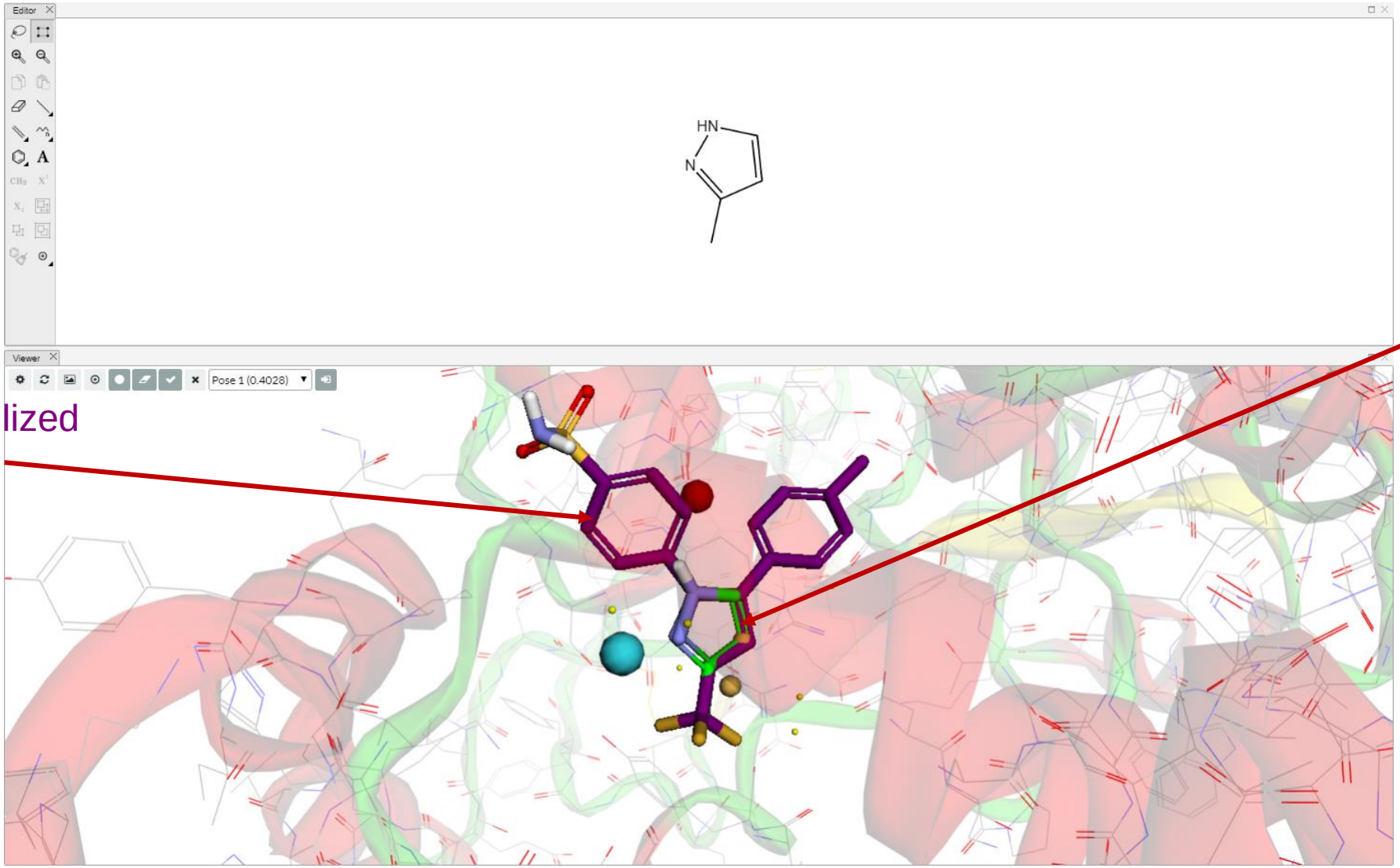
We'll keep it simple and start from a single fragment added to a blank 2D canvas



A simple flow chart will help: initial 3D design generation



Initial placement of the first 3D design in the 3LN1 pocket

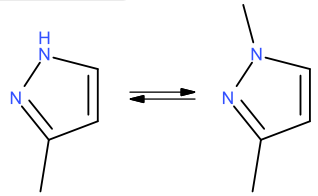


Co-crystallized celecoxib (purple)

Aligned 3-methyl-pyrazole (green)

A simple flow chart will help: growing the 2D design

Map current 2D frags to previous 2D frags

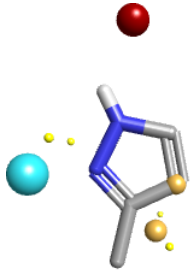


Loop over 2D frags: does this frag have 3D coords?

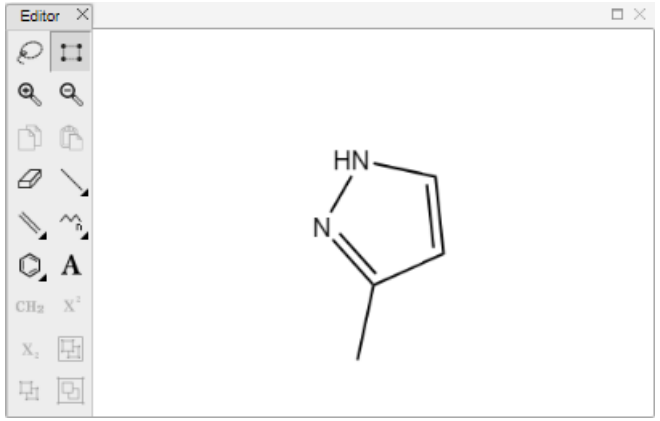
YES

NO

No action



Pair current frag 2D indices to previous

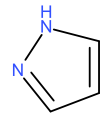


Let's add a methyl group in position 1 on the pyrazole system

Compare # indices of current frag with previous

<

Atoms were deleted



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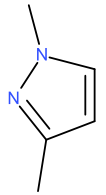
Atoms were added



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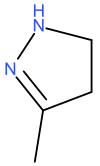
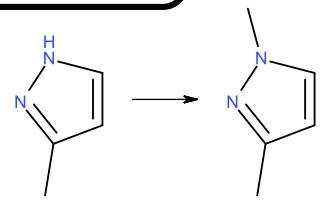


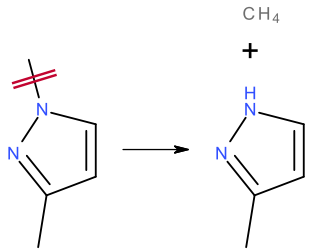
Check:
- Element
- Bonds
- Bond order
- Hybridization
- Formal charge
- Stereo

A simple flow chart will help: growing the 3D design

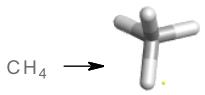
A methyl group was added



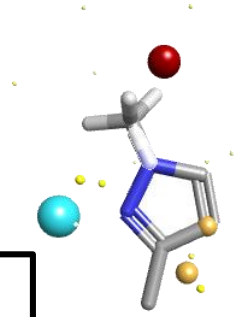
- Find bonds to added atoms
- Delete those bonds and cap with hydrogens



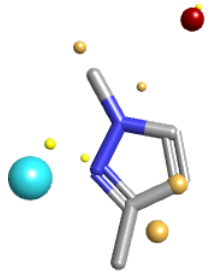
Generate 3D coords for newly added 2D frags



Align frag Hs with parent's heavy atoms and vice versa



Bond to parent with appropriate bond order

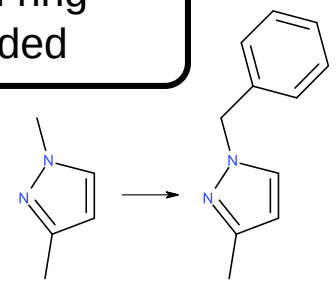


Ready for next 3D growth iteration!

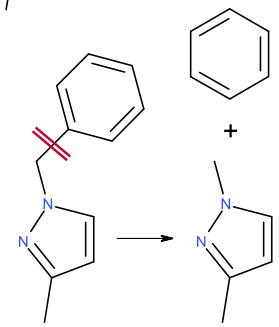
Methyl was easy, can I have more of those, please?

A simple flow chart will help: scoring 3D designs

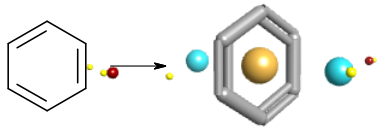
A phenyl ring was added



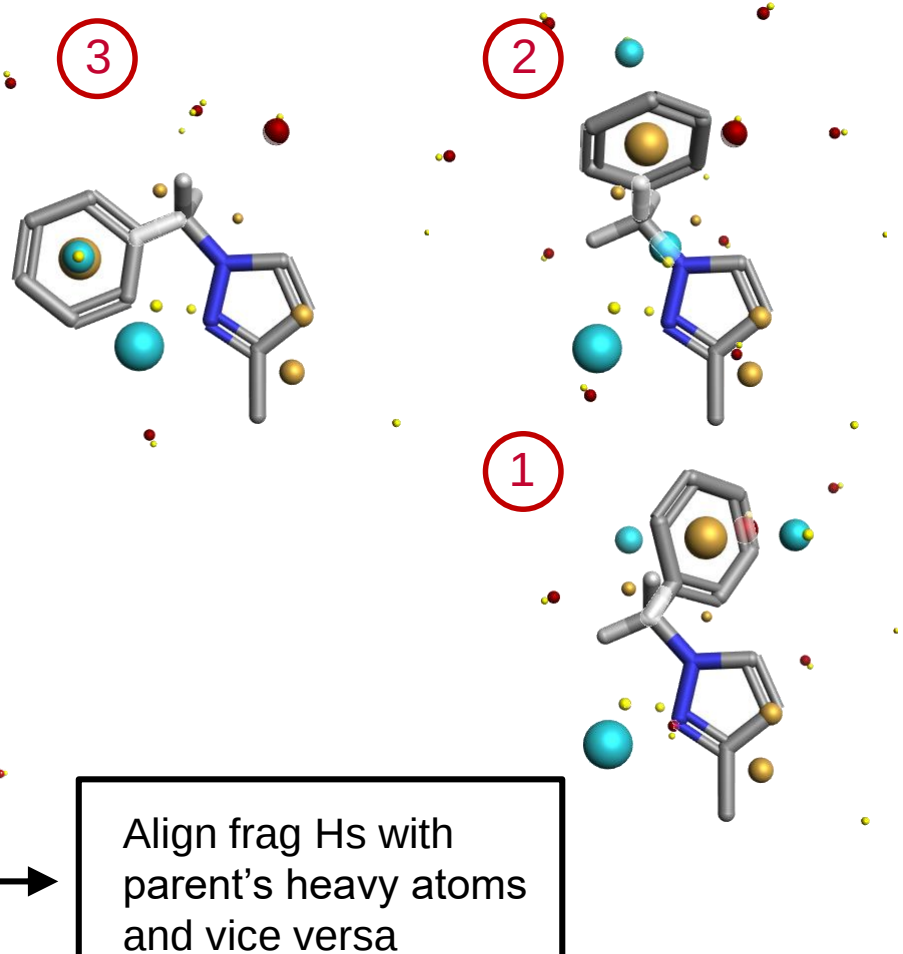
- Find bonds to added atoms
- Delete those bonds and cap with hydrogens



Generate 3D coords for newly added 2D frags



Align frag Hs with parent's heavy atoms and vice versa



A simple flow chart will help: scoring 3D designs

A phenyl ring was added

- Find bonds to added atoms
- Delete those bonds and cap with hydrogens

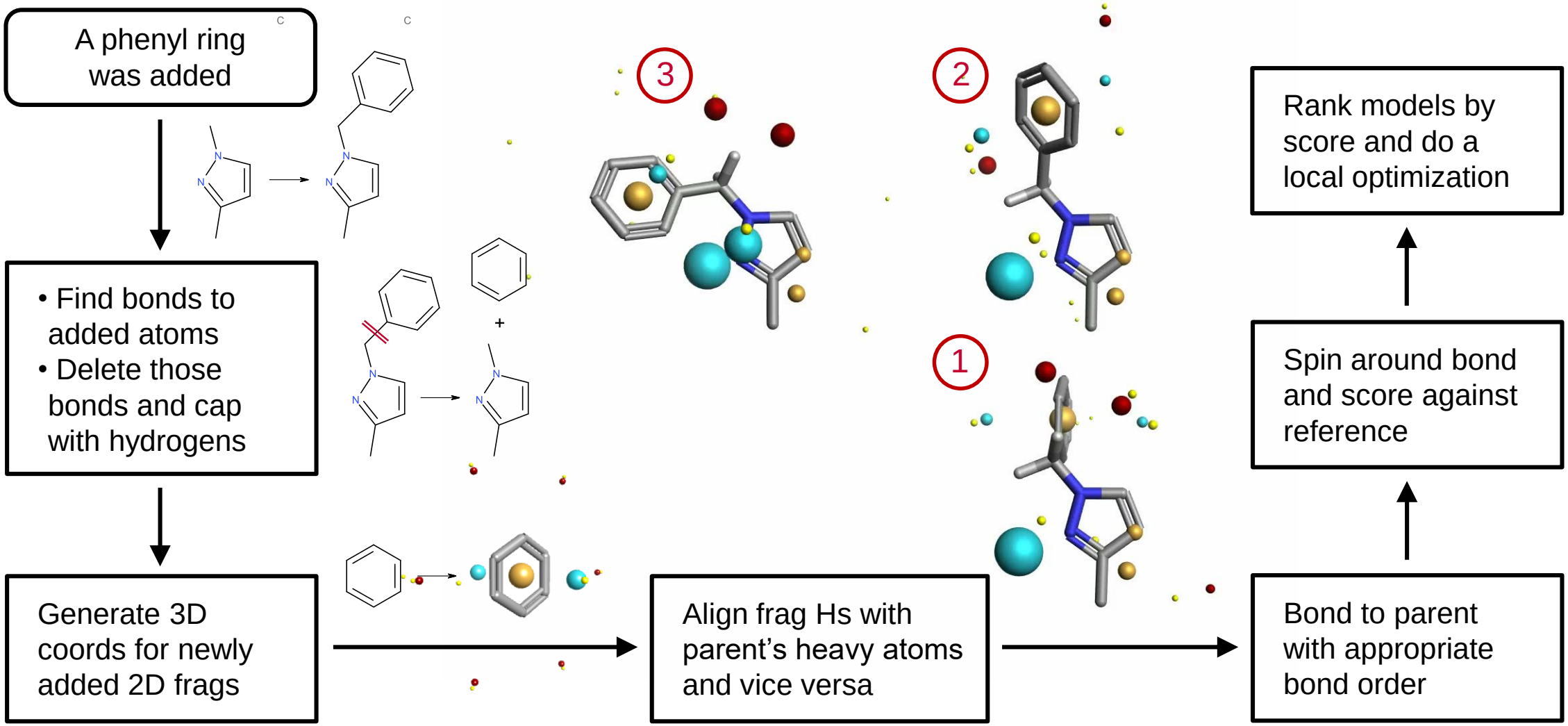
Generate 3D coords for newly added 2D frags

Align frag Hs with parent's heavy atoms and vice versa

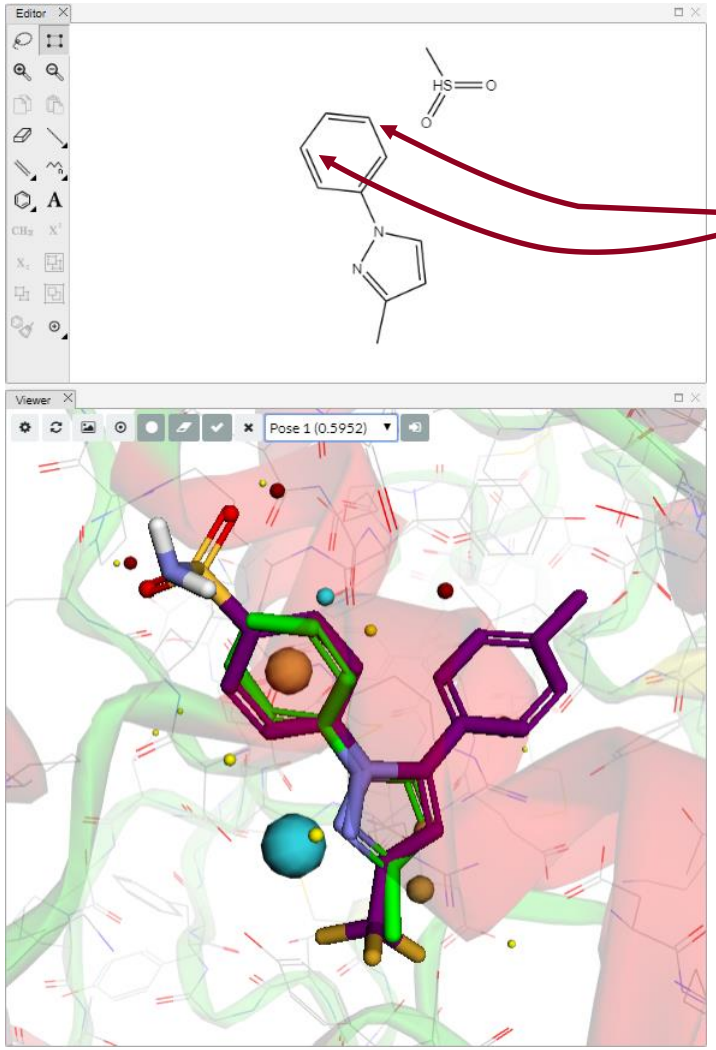
Bond to parent with appropriate bond order

Spin around bond and score against reference

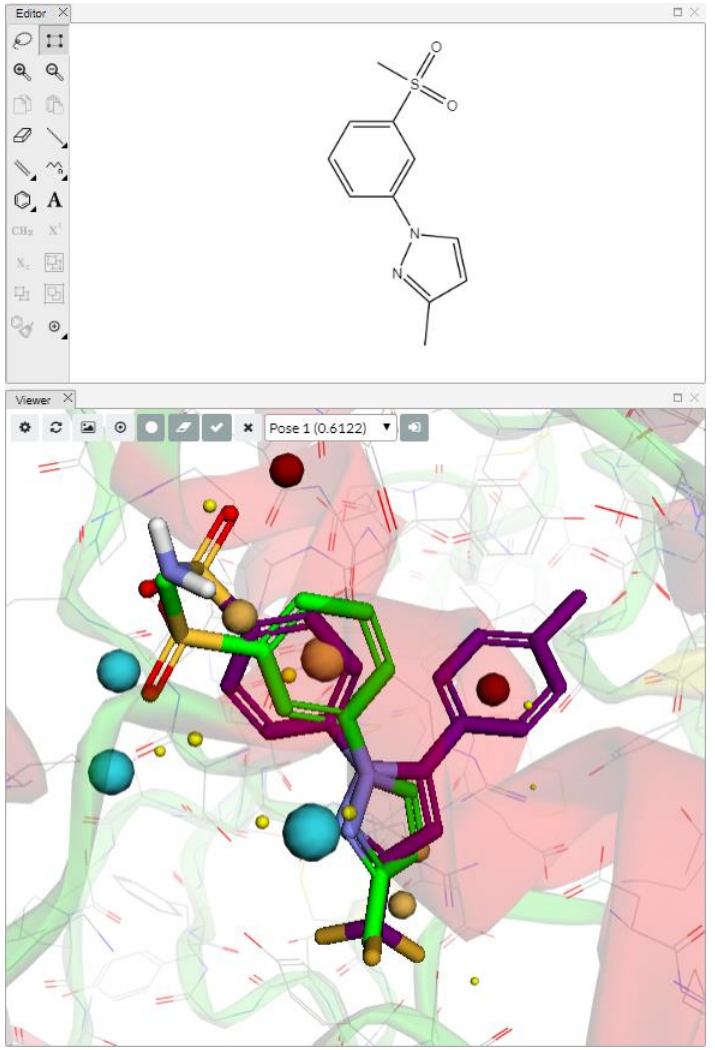
Rank models by score and do a local optimization



The devil is in the details: symmetries



When adding a *m*-methyl-sulfonyl substituent in 2D, there are actually two symmetry-equivalent positions it might fit in 3D



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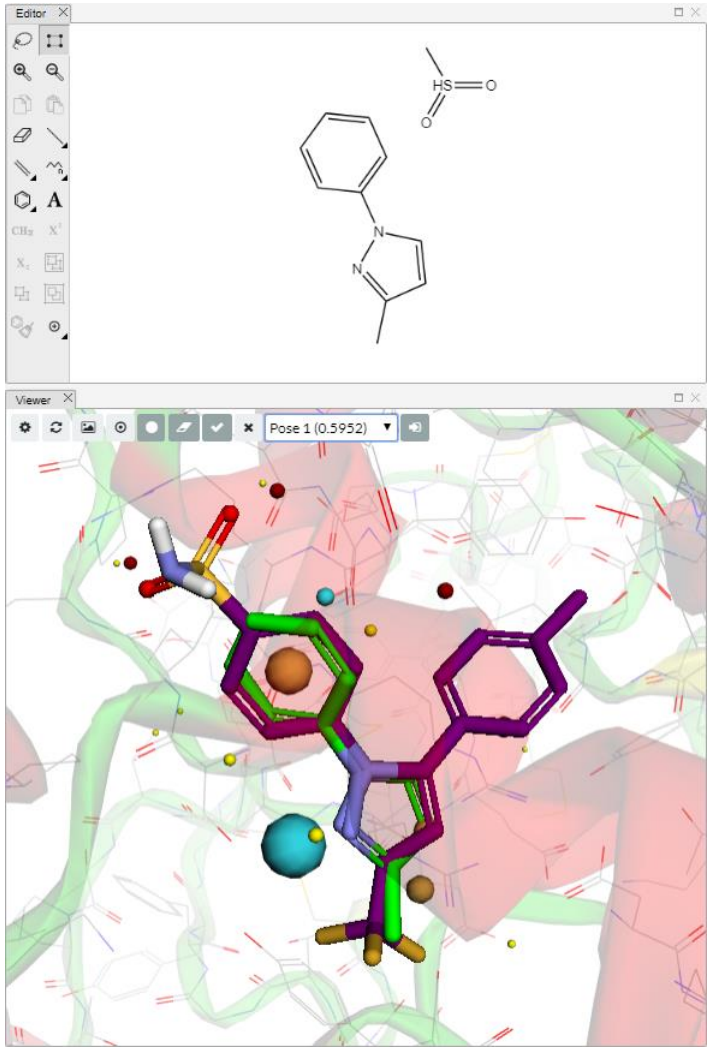
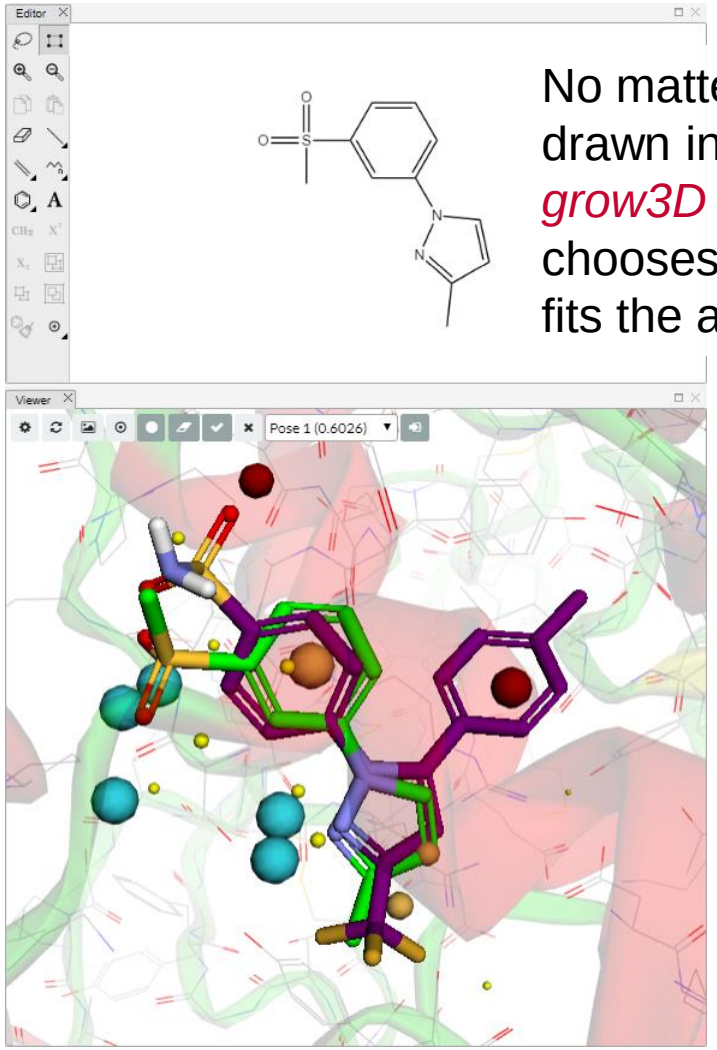
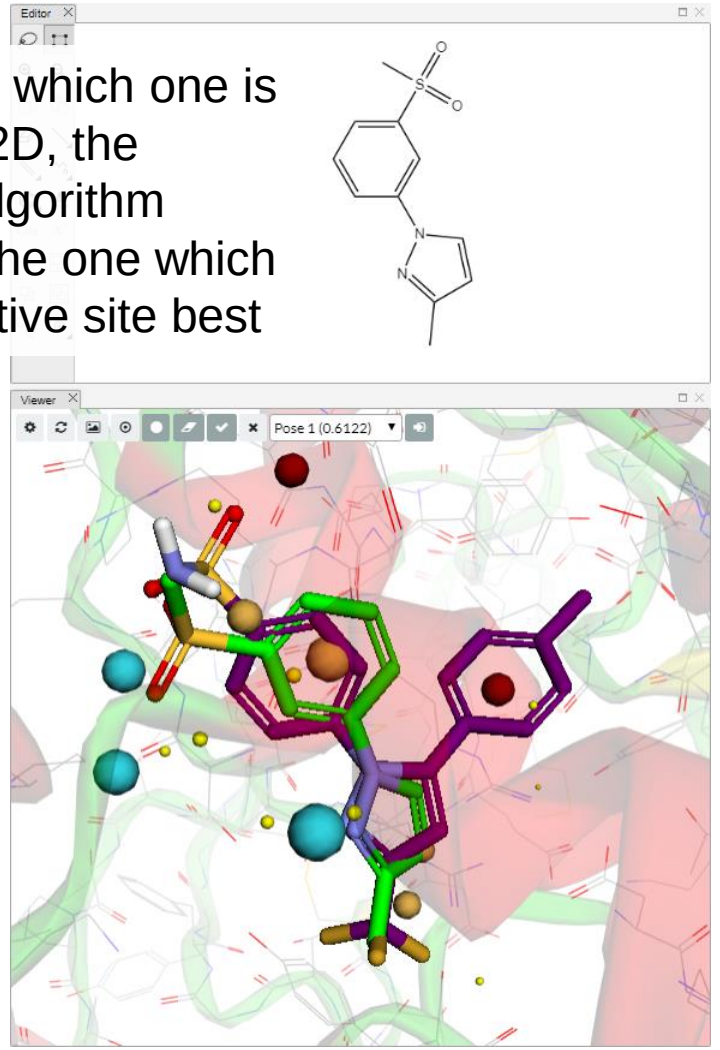
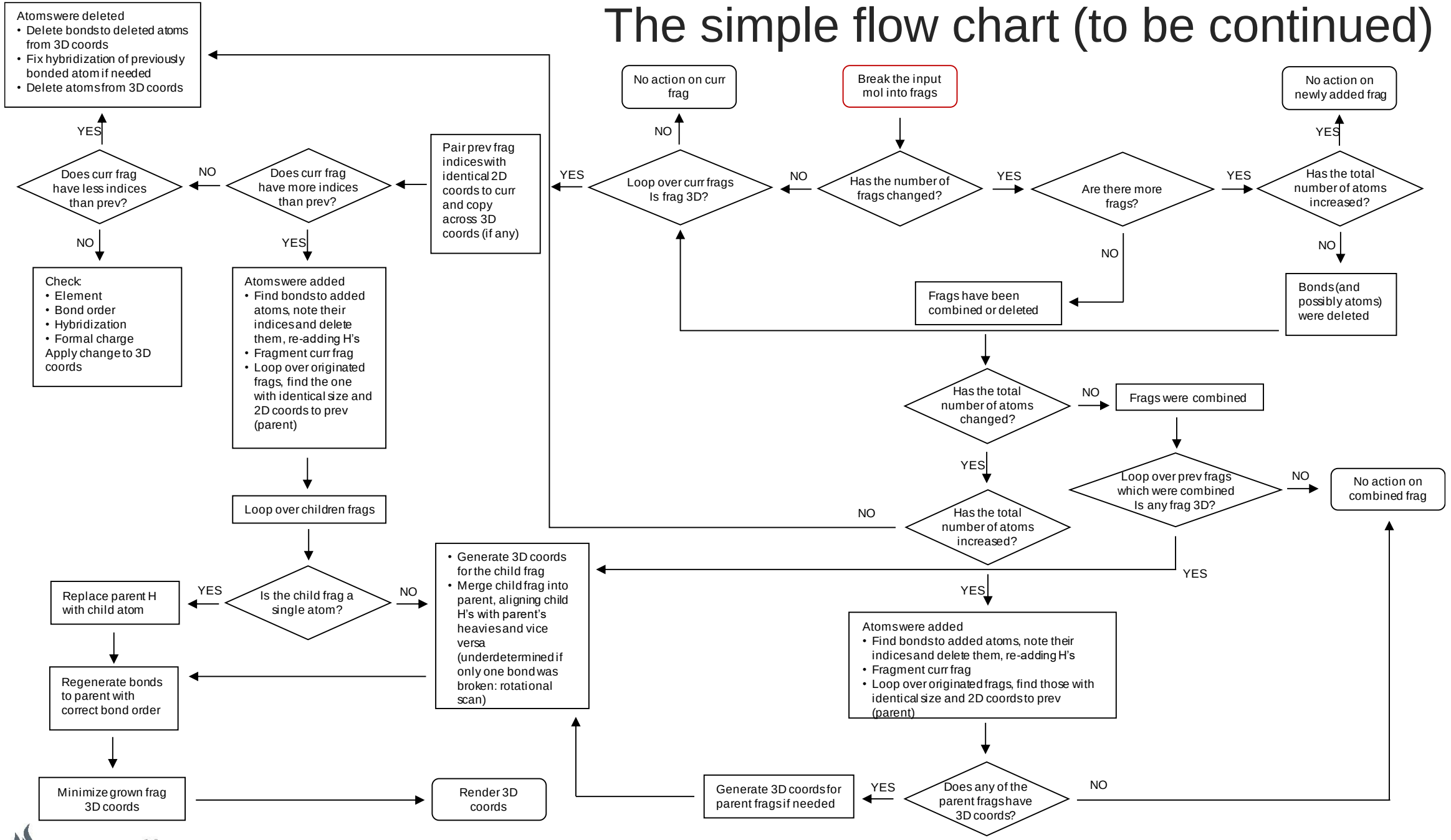




No matter which one is drawn in 2D, the *grow3D* algorithm chooses the one which fits the active site best



The simple flow chart (to be continued)



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Thank you for your attention

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Acknowledgments

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The RDKit community

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