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Exercises Part 1

SCS Spring School on Digital Chemistry –
Applied to Drug & Crop Protection Discovery

Les Diablerets

16.-20.04.2023

Exercise 1.1

Two fragment hits are presented to you by a newly formed project team.
Which of the two would you prioritise to follow-up and why?

- Fragment 1: 1.92 Å resolution, R: 19.8%, Rfree: 24.1% (ligand ID and name: 1001 UH4)
- Fragment 2: 1.88 Å resolution, R: 20.2%, Rfree: 26.6% (ligand ID and name: 1101 LIG)

Tasks (15 min):

- Open both pdbs and electron density maps in coot and analyse for both ligands.
  Caveat: it's a homodimer! (more than one ligand may be bound)
- Discuss the electron density in your group. What can you see, what can't you see? Is the binding pose realistic or could there be doubts? What happens, if you decrease sigma levels of both, the 2FoFc and the FoFc density maps?
- Open both pdbs in PyMol and superpose the binding sites, compare the binding of the two fragments. Which interactions do you see, which ones look favourable/important? Discuss the small molecule conformations, the orientations of the surrounding amino acid side chains and their protonation sites (e.g. His 41, Ser 144, Cys 145, His 163, Glu 166, His 172, Gln 189)
- Bonus: look at side chain orientations in the pdb and scroll the sigma levels of their electron densities

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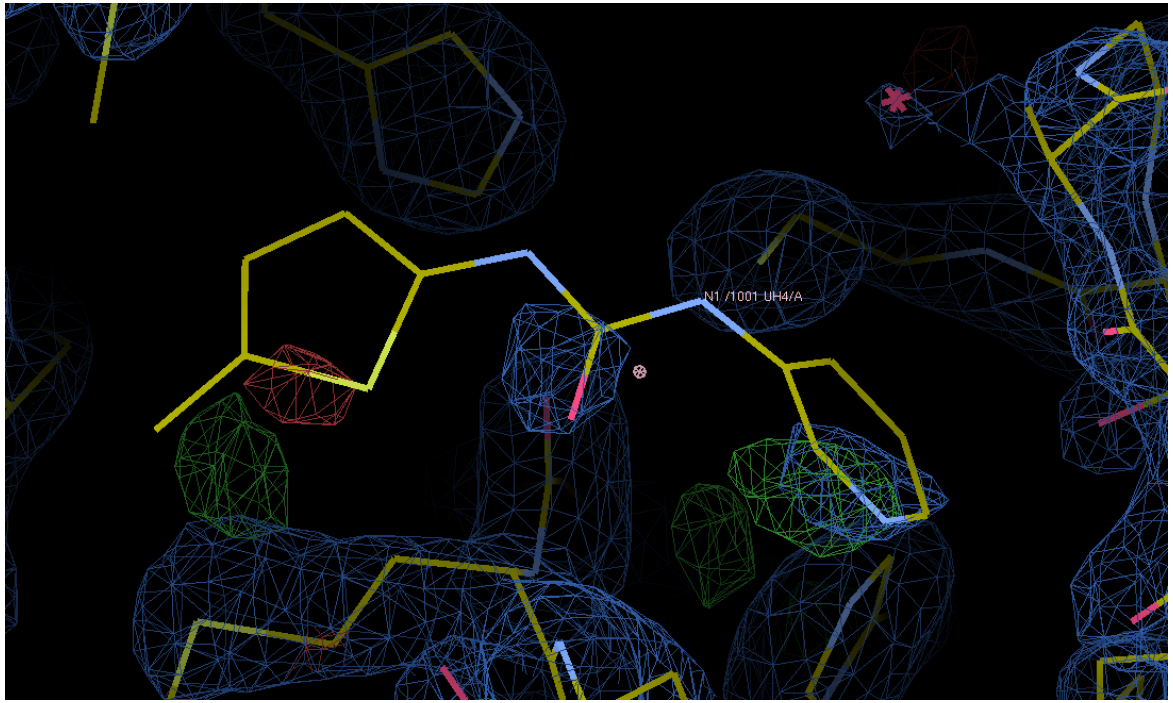
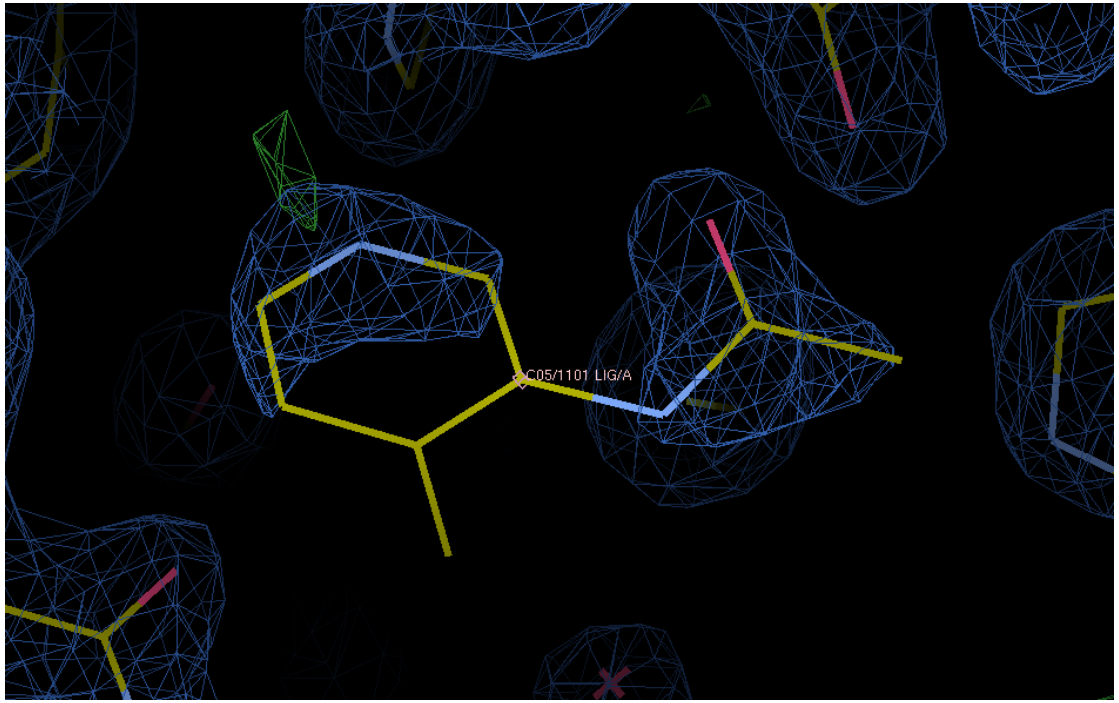
Exercise 1.1

Electron densities 2FoFc @ σ 1.5, FoFc @ σ ±3.0

Fragment 1



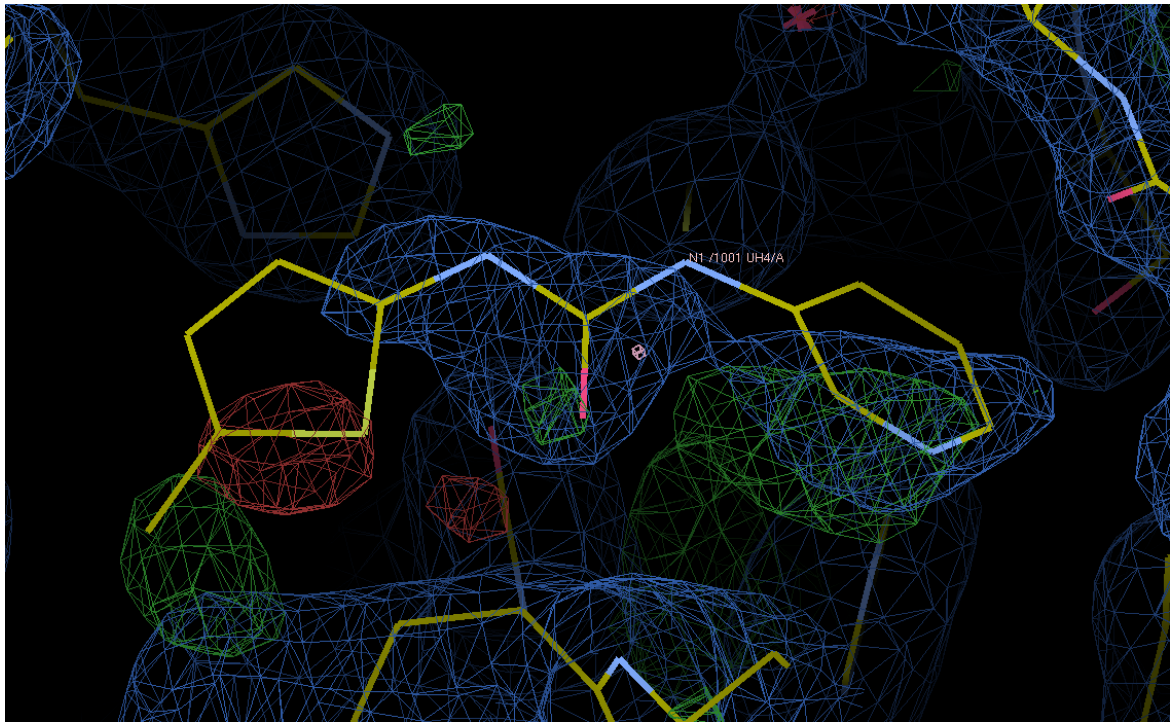
Fragment 2



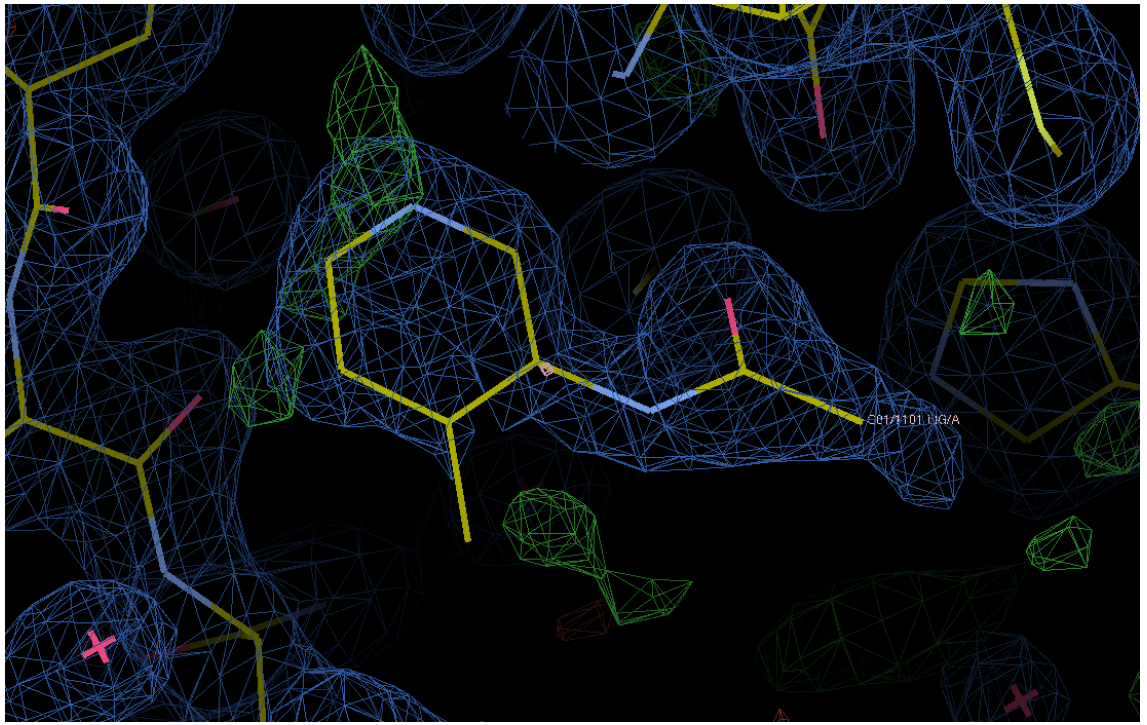
Exercise 1.1

Electron densities 2FoFc @ σ 1.0, FoFc @ σ ±2.5

Fragment 1

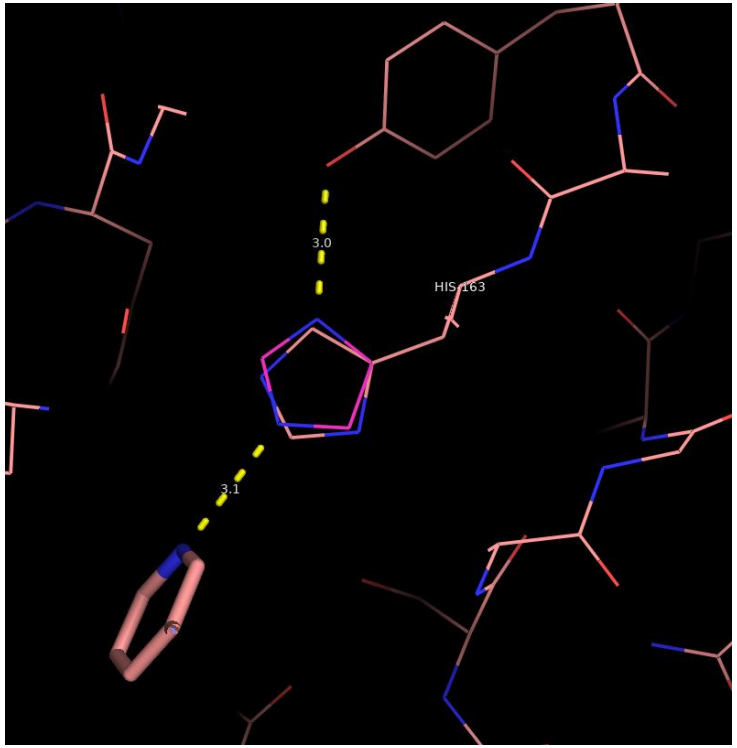


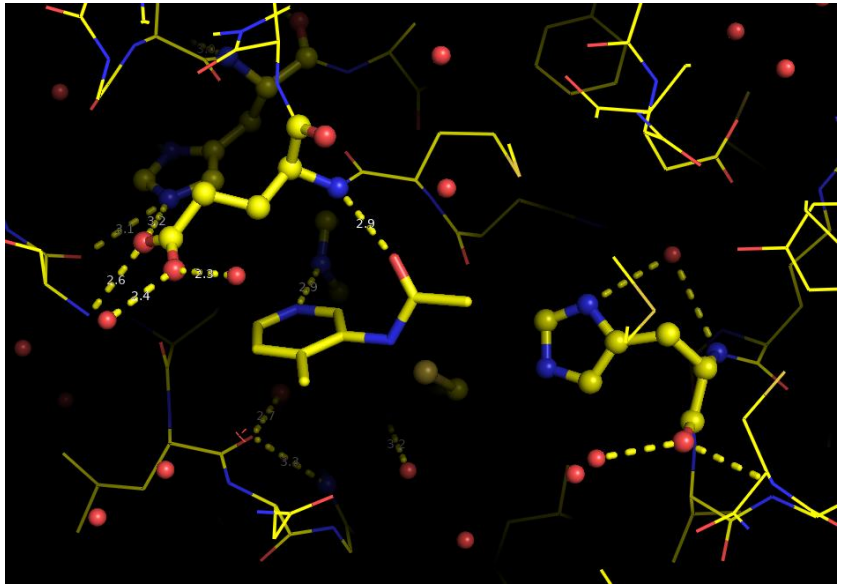
Fragment 2

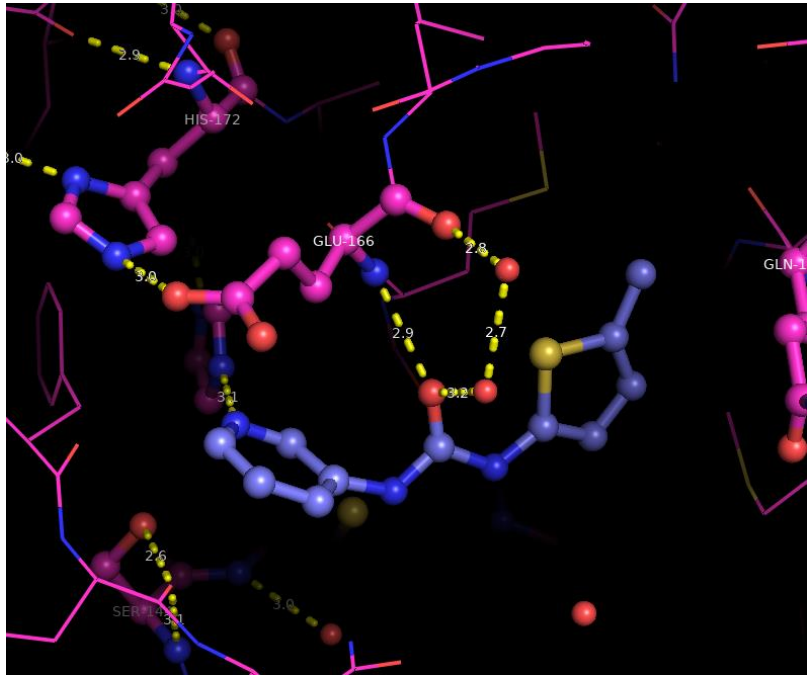


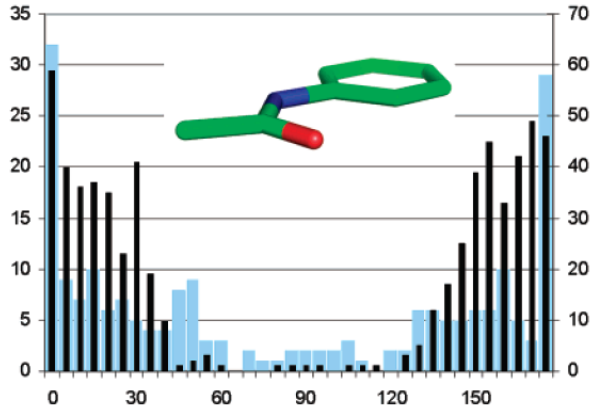
Exercise 1.1

His 163 & conformation



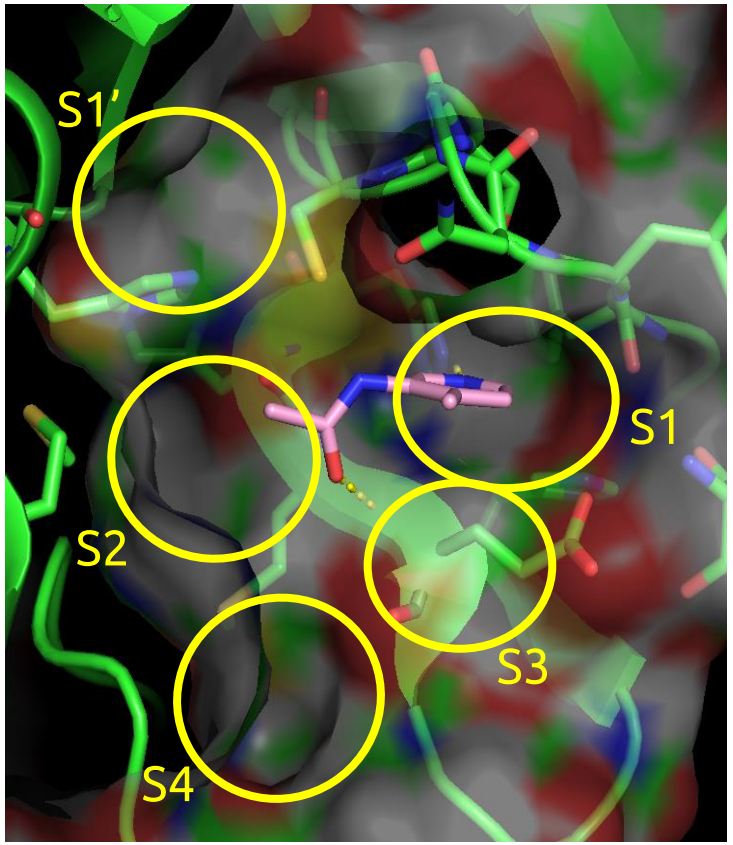






Exercise 1.2

The team has selected the Aminopyridine

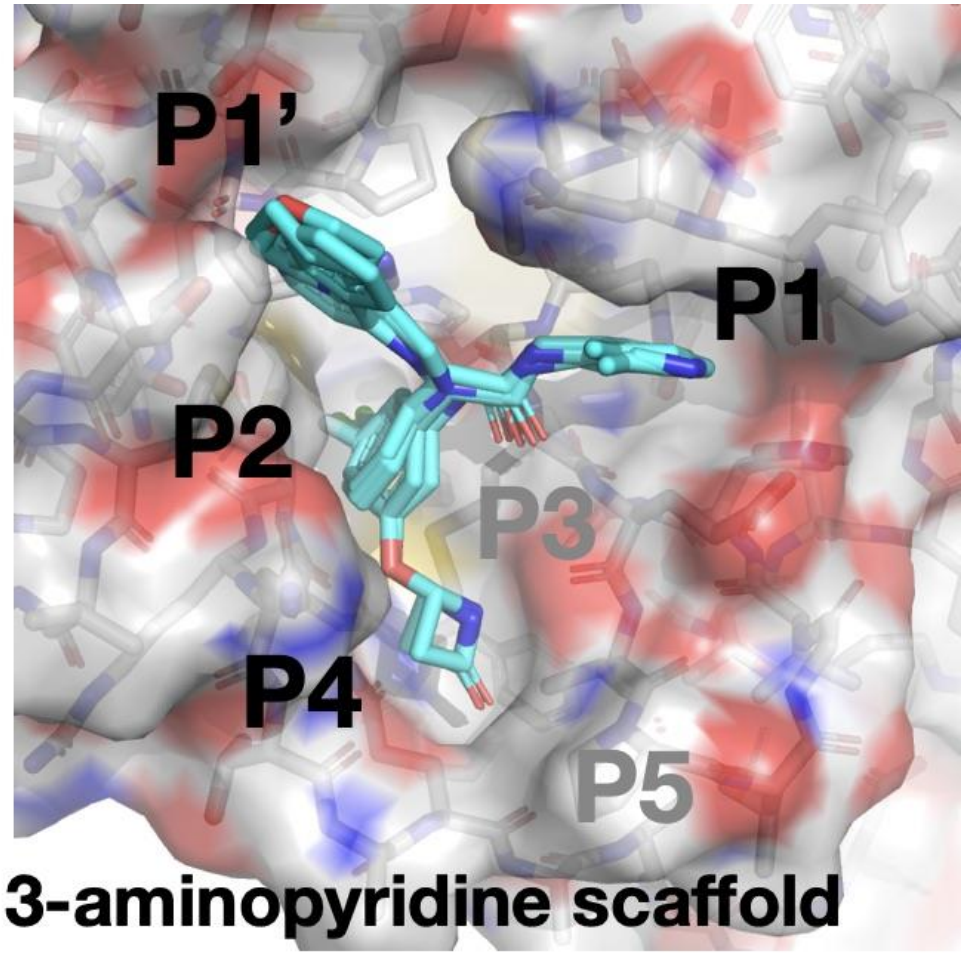


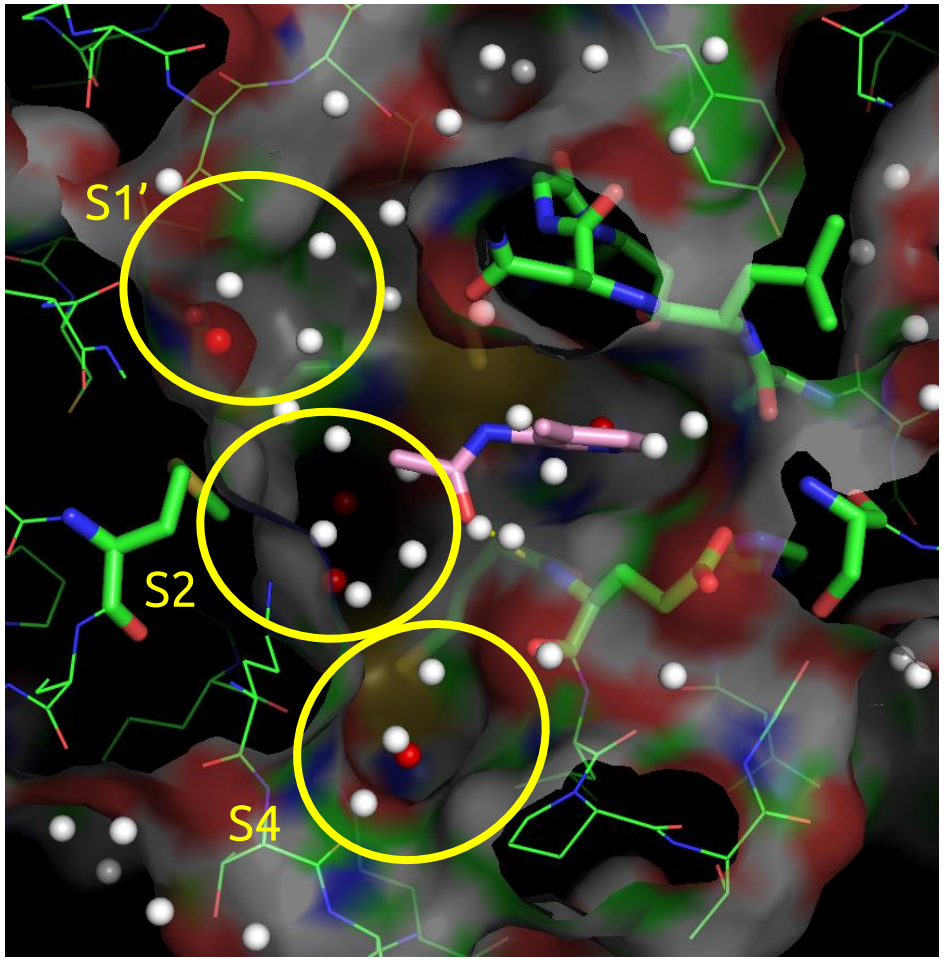
Tasks (10 min):

- The affinity will need to be improved. Analyse the fragment and discuss:
  In which subpocket will you extend the fragment first to improve its affinity?
  Which potential interactions will you try to make?
  How large will the resulting molecule become?
- Open the pymol session in Exercise_1/1.2, showing the result of a water network analysis.
  Red waters are classified "unhappy" waters. What would you conclude? Is your analysis from before confirmed? What properties would your molecule need in this subpocket?

Exercise 1.2

Subpockets





Exercise 1.3

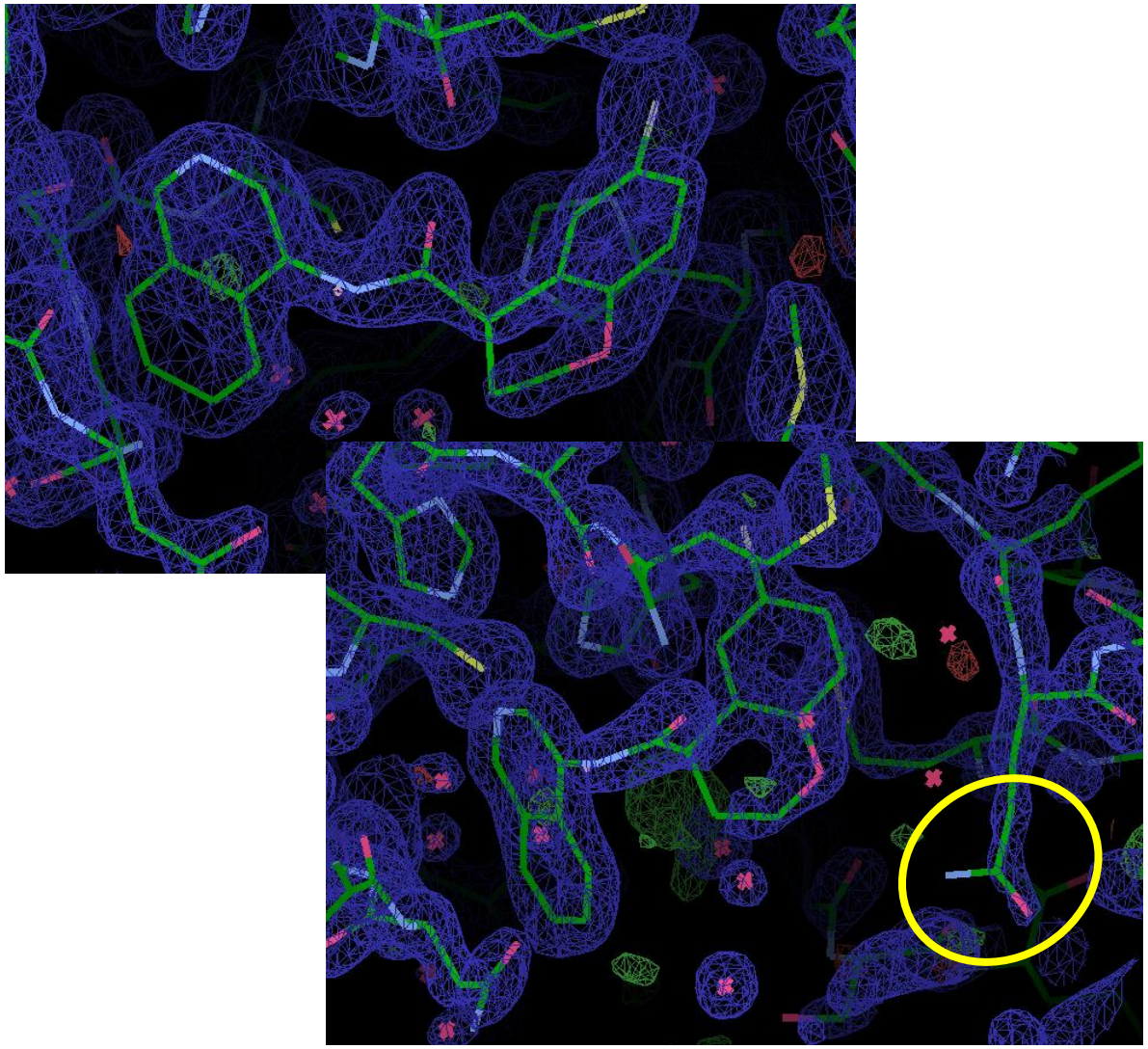
The team has selected the Aminopyridine

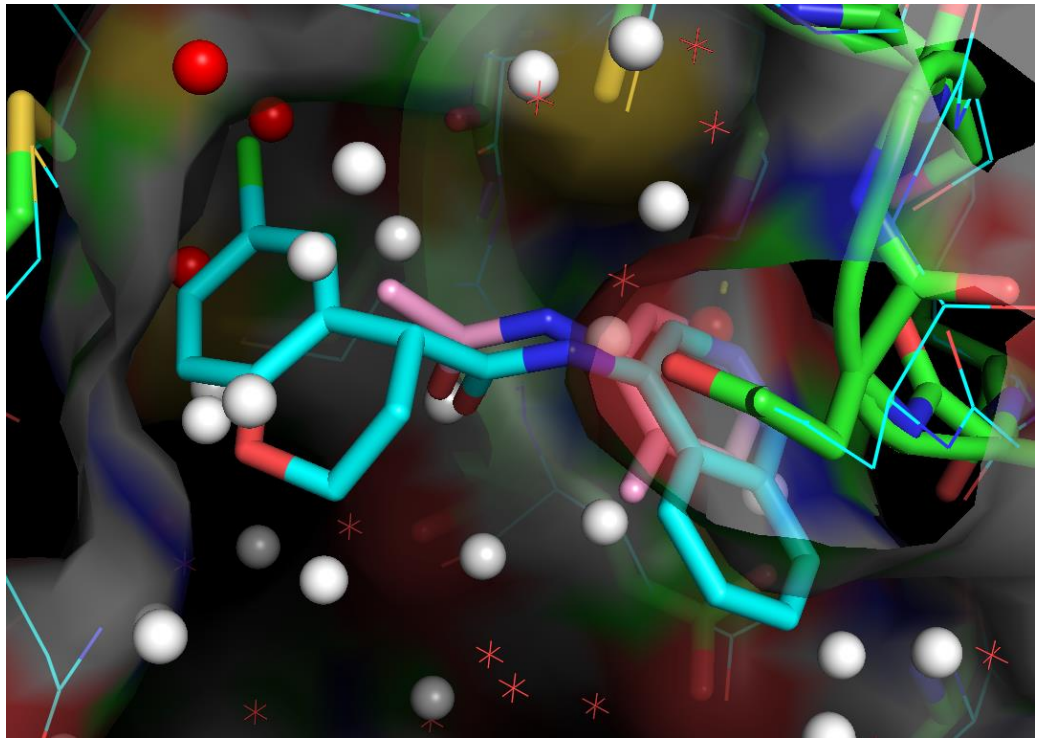
Tasks (10 min):

- During hit to lead optimization, the aminopyridine has been modified and affinity is improved. There is a new xray structure.
- Open the .pdb file and the .map files in Exercise_1/1.3 and discuss the structure. Are there any new interactions? How different are the amino acid side chain conformations? How certain are they? Does the ligand conformation look favourable?
- Bonus: superpose this structure with the water network analysis from the last exercise.
- Starting from this molecule: which reaction could be applied to further explore the S2 pocket? Discuss possible drawbacks or advantages of each reaction.

Exercise 1.3

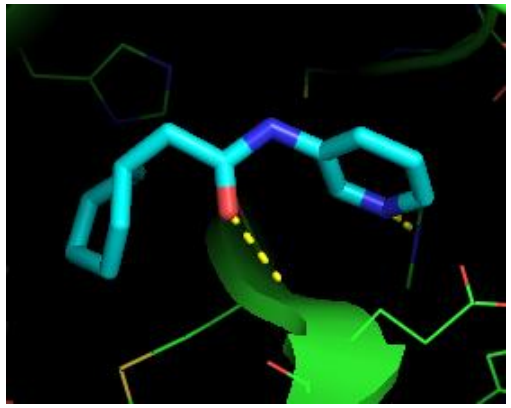
Electron densities 2FoFc @ σ 1.5, FoFc @ σ ±3.0



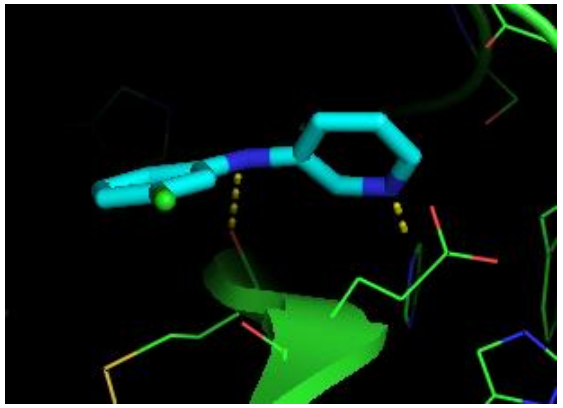


Exercise 1.3

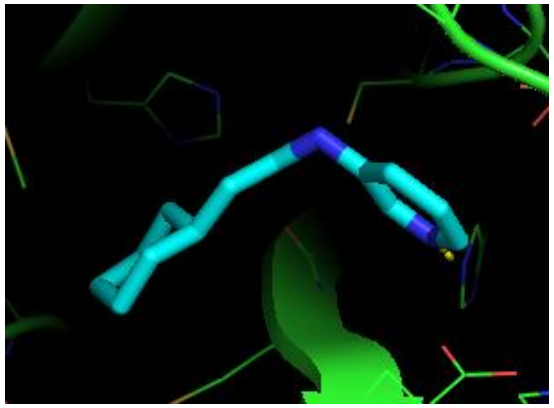
Possible reaction products (examples from Covid Moonshot)



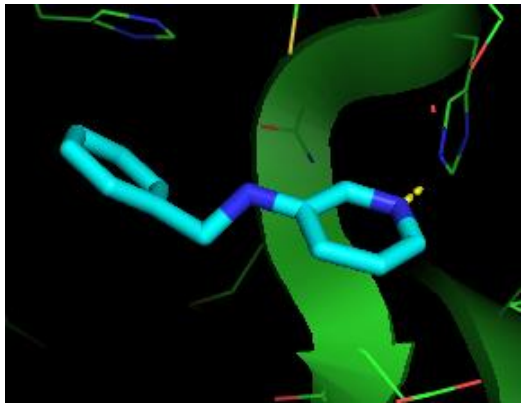
Amide



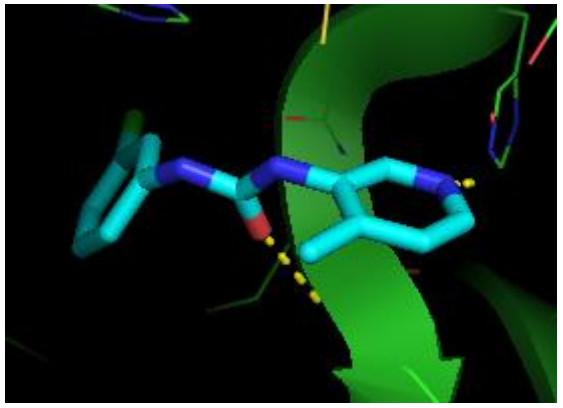
Buchwald



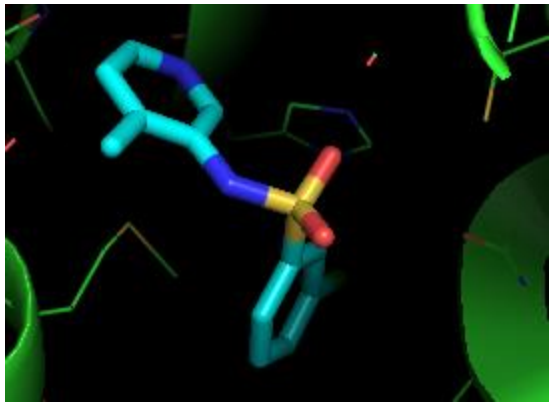
N-alkylation



Reductive amination



Urea



Sulfonamide

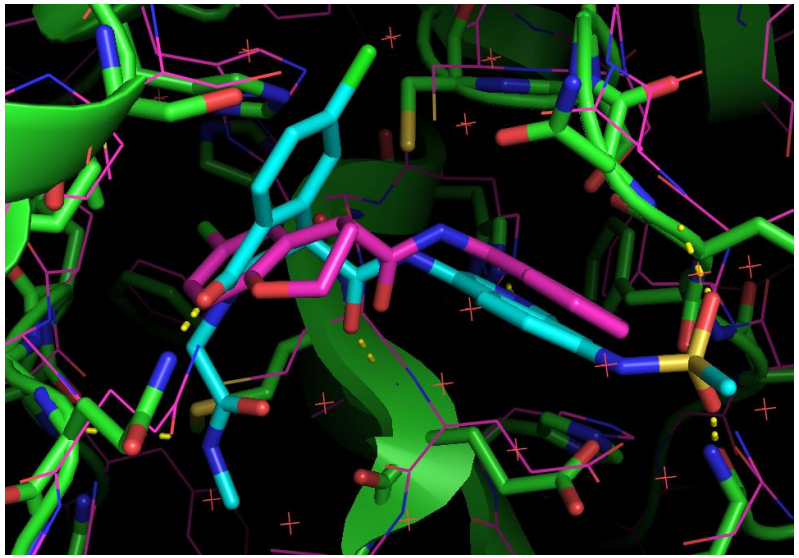
Exercise 1.4

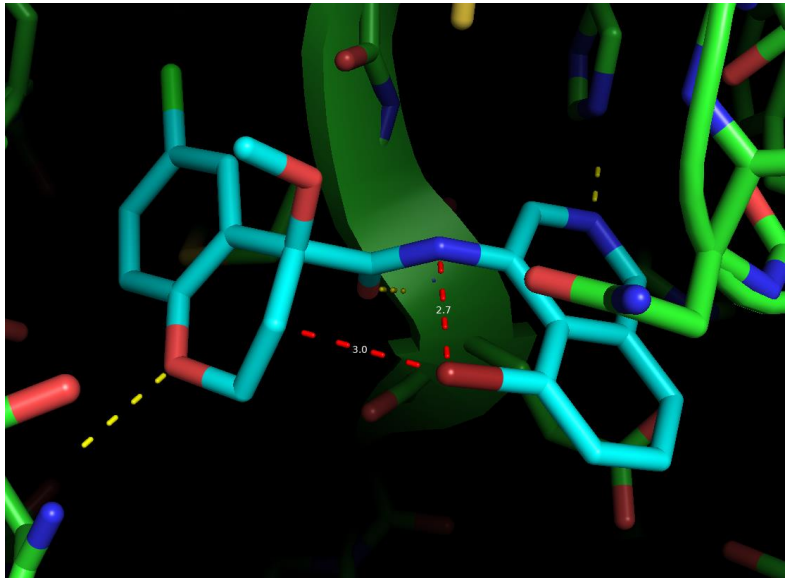
Amide coupling

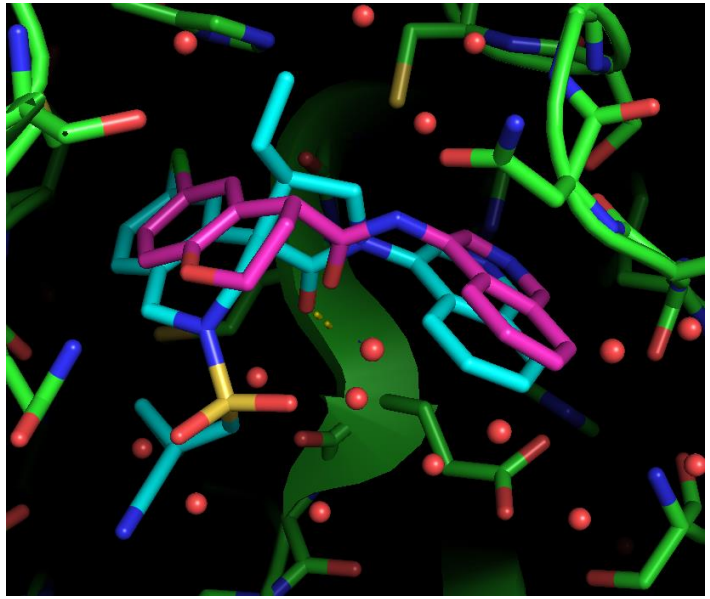
Tasks (10 min):

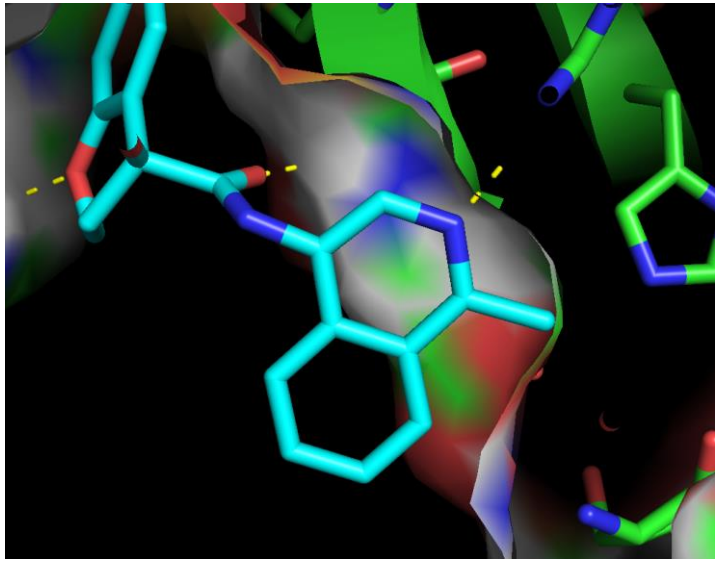
- The team has decided to create an amide library. Some ideas are presented in the pymol session in folder 1.4. Analyse these virtual products. Which docking poses look good? How do the ligand conformations look? How well is the original binding mode conserved? Which molecules make sense? What else would you try to make?

Exercise 1.4









Exercise 1.5

Patent alert!

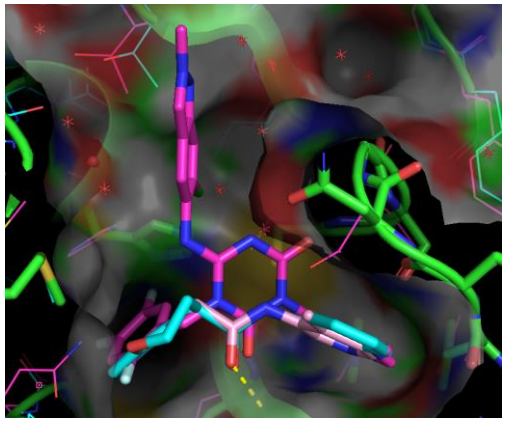
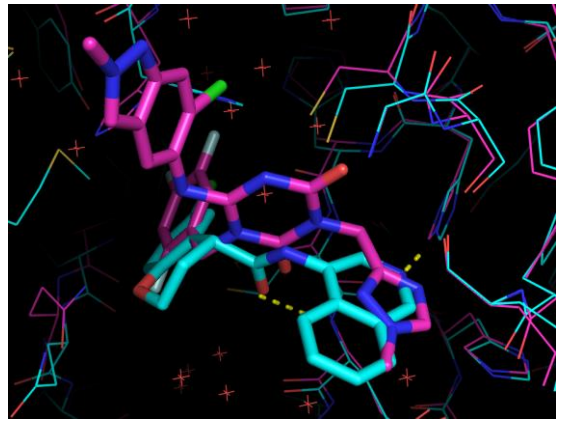
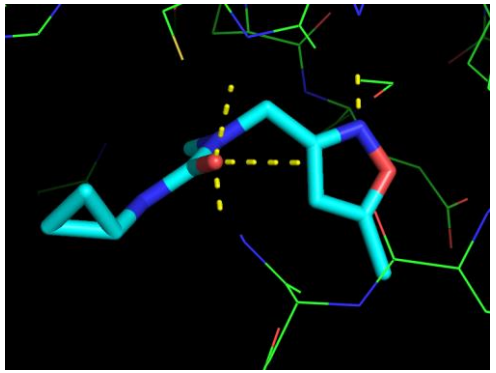
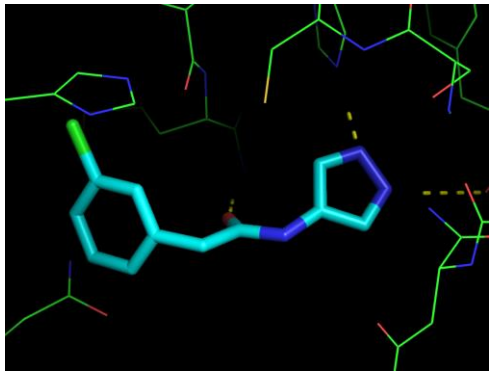
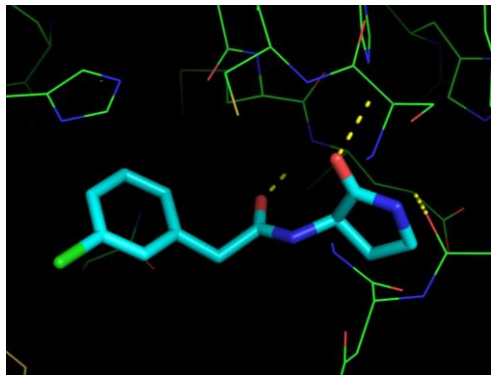
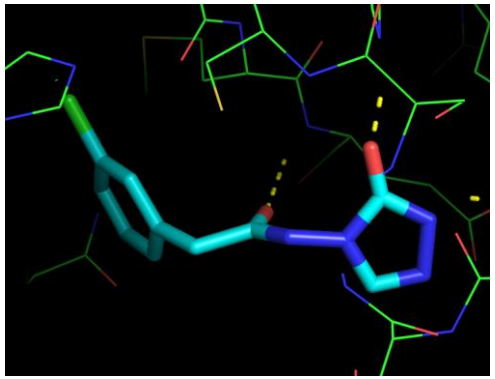
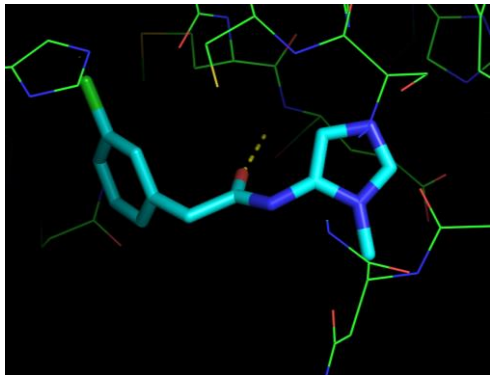
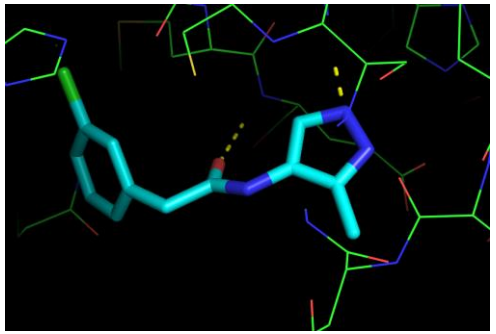
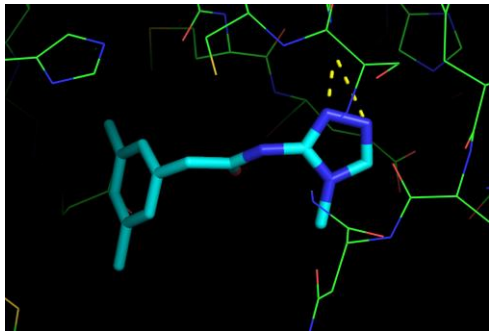
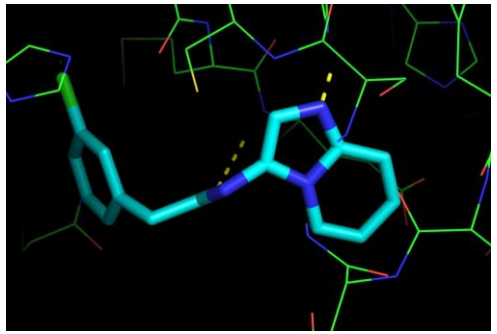
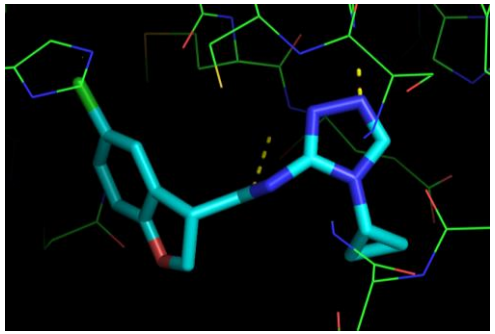
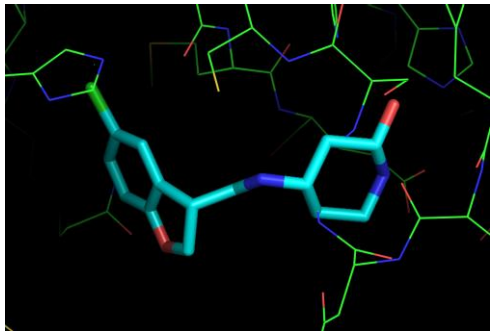
Tasks (10 min):

- The pyridine has been patented. Find a replacement for this part of your molecule, draw your ideas in 2D on paper.

Exercise 1.5

Examples from Covid Moonshot

& Ensitrelvir (Shionogi)

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