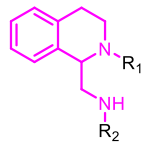
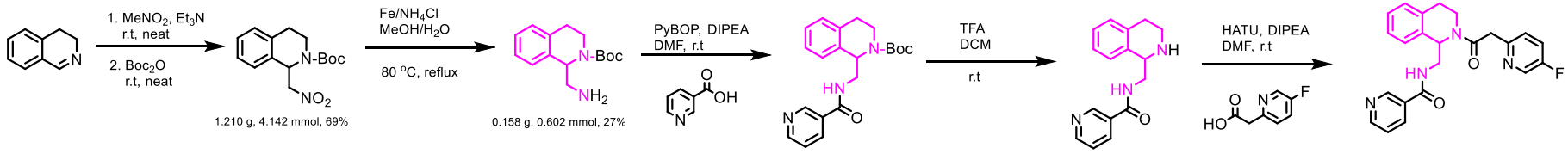
3,4-dihydroisoquinoline synthesis and core (Andy and Kangping)

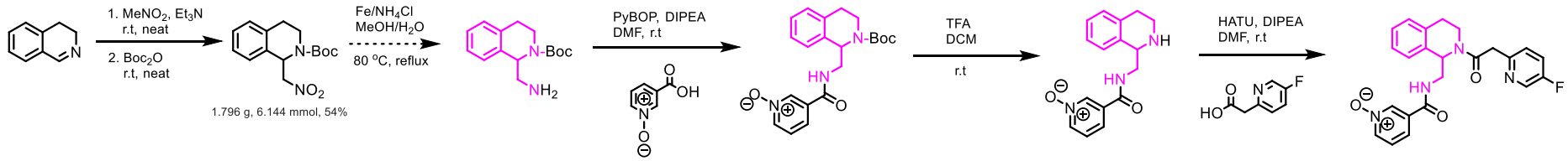
Core:



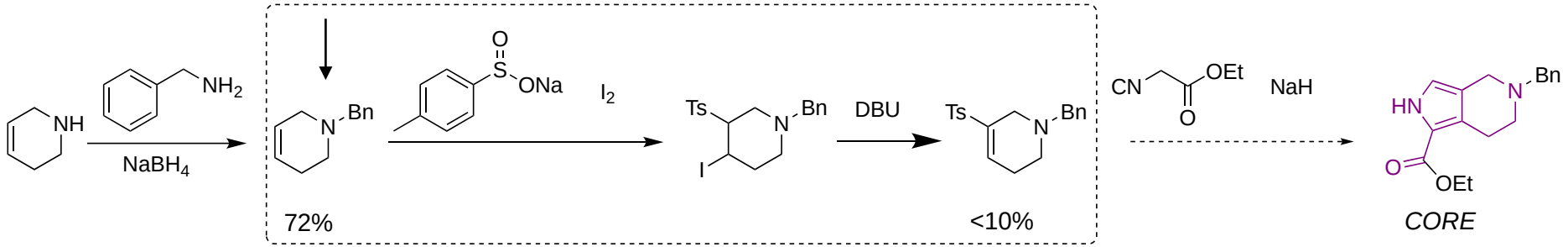
Compound A

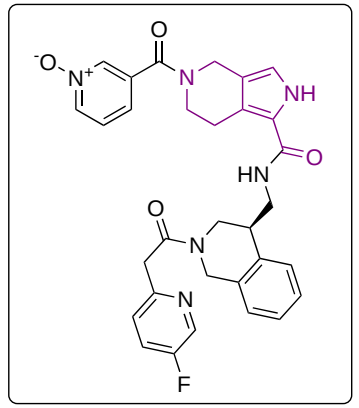


Compound B



Trying different protecting groups

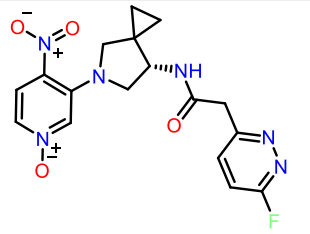




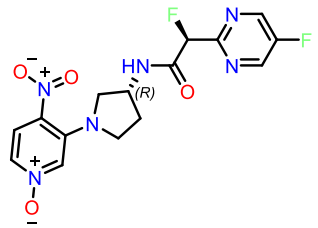
1) https://doi.org/10.1016/j.tetlet.2020.152719

GLIDE docking predictions: Pyrrolidines and nitro-N-oxides

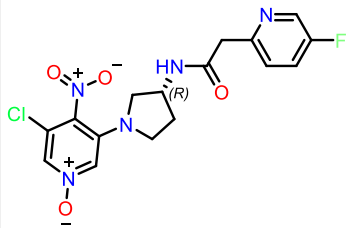
Glide scores → **Check docking poses with AutoDock Vina / DS** → **Modification to structure and re-check binding score.**



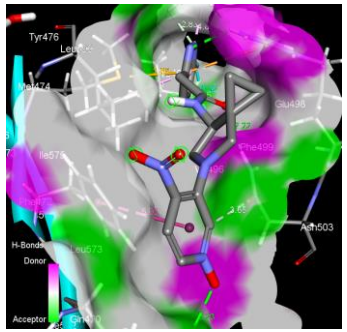
GLIDE docking score: -7.16 kcal mol^{-1}
VINA docking score: -7.16 kcal mol^{-1}

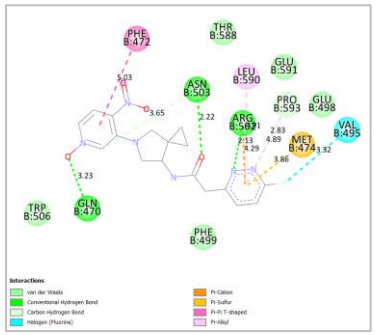


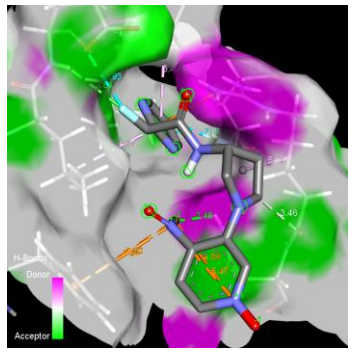
GLIDE docking score: -7.50 kcal mol^{-1}
VINA docking score: -5.8 kcal mol^{-1}

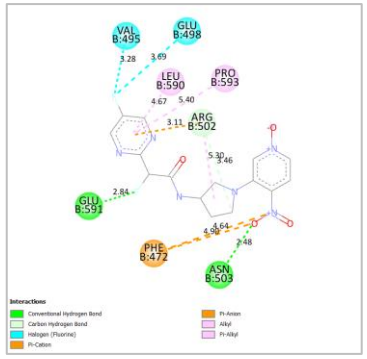


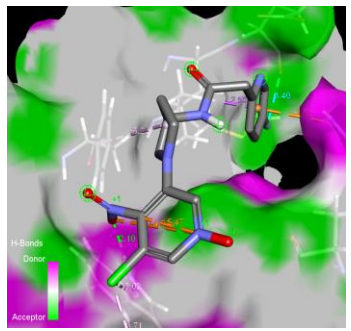
GLIDE docking score: -7.61 kcal mol^{-1}
VINA docking score: -5.30 kcal mol^{-1}

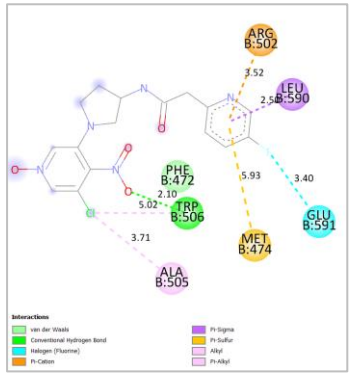




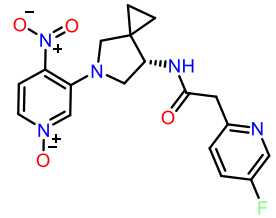






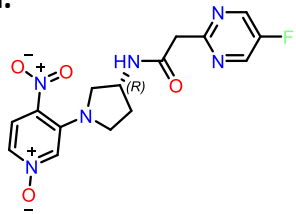


- **Substitute pyridazine for pyridine.**



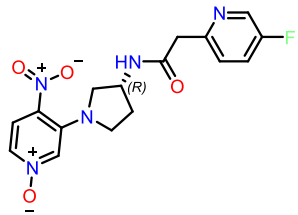
SMILES: FC(C=C1)=NN=C1CC(N[C@H]2C3(CC3)CN(C(C=[N+]4[O-])=C(C=C4)[N+]([O-])=O)C2)=O
VINA docking score: -7.16 kcal mol^{-1}

- **Removal of alkyl fluorine atom.**



SMILES: FC(C=N1)=CN=C1CC(N[C@H](CC2)CN2C(C=[N+]3[O-])=C(C=C3)[N+]([O-])=O)=O
VINA docking score: -5.8 kcal mol^{-1}

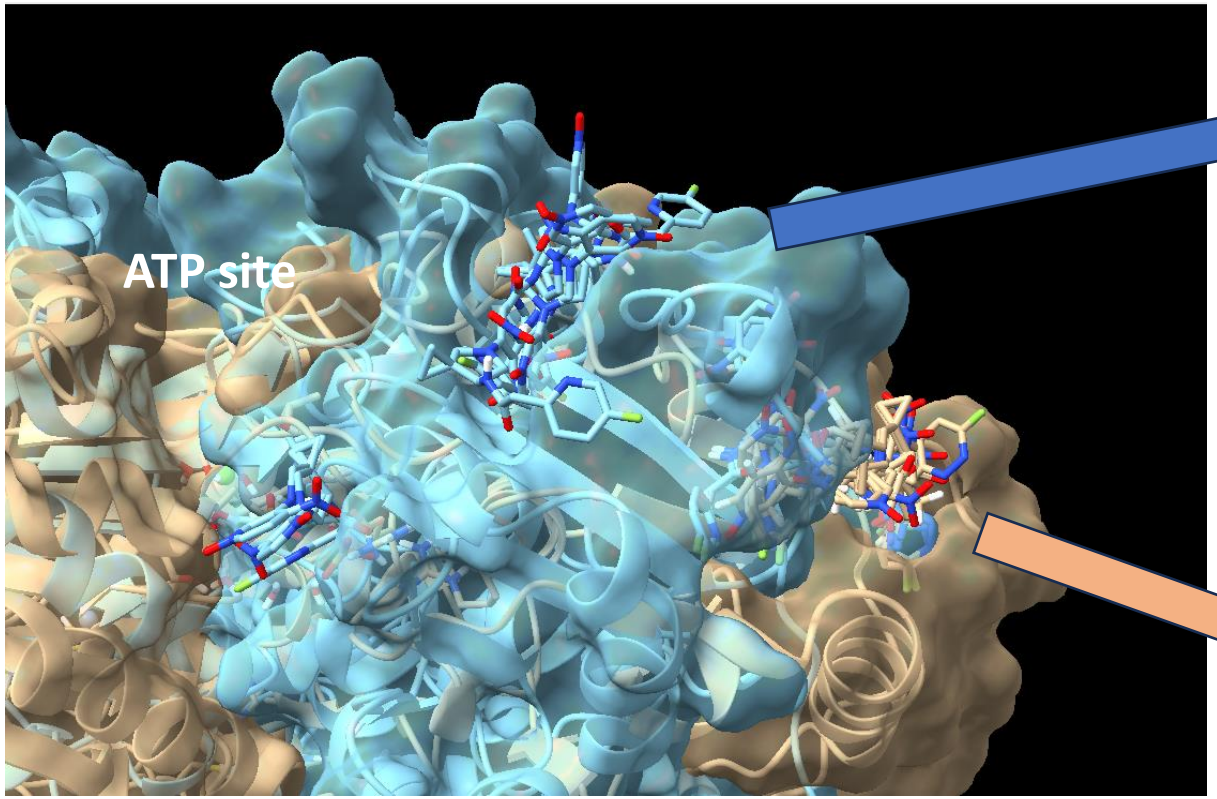
- **Removal of chlorine atom.**



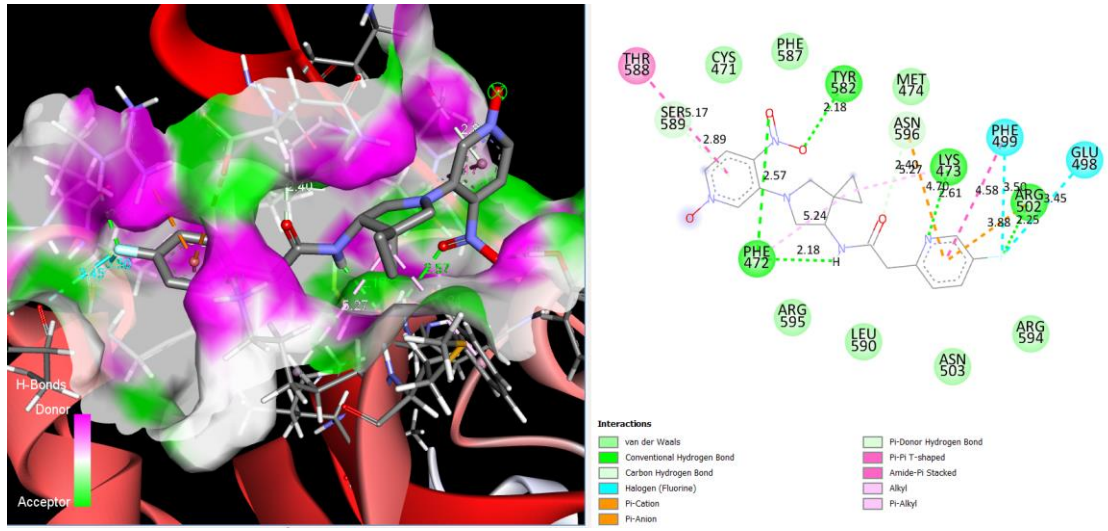
SMILES: O=[N+]([O-])C(C=C[N+]([O-])=C1)=C1N(CC2)C[C@@H]2NC(CC3=CC=C(F)C=N3)=O
VINA docking score: -5.30 kcal mol^{-1}

Truncated MD simulation and docking:
Fragment-bound vs ATP/ssRNA bound states (Geoff Wells + Tom)

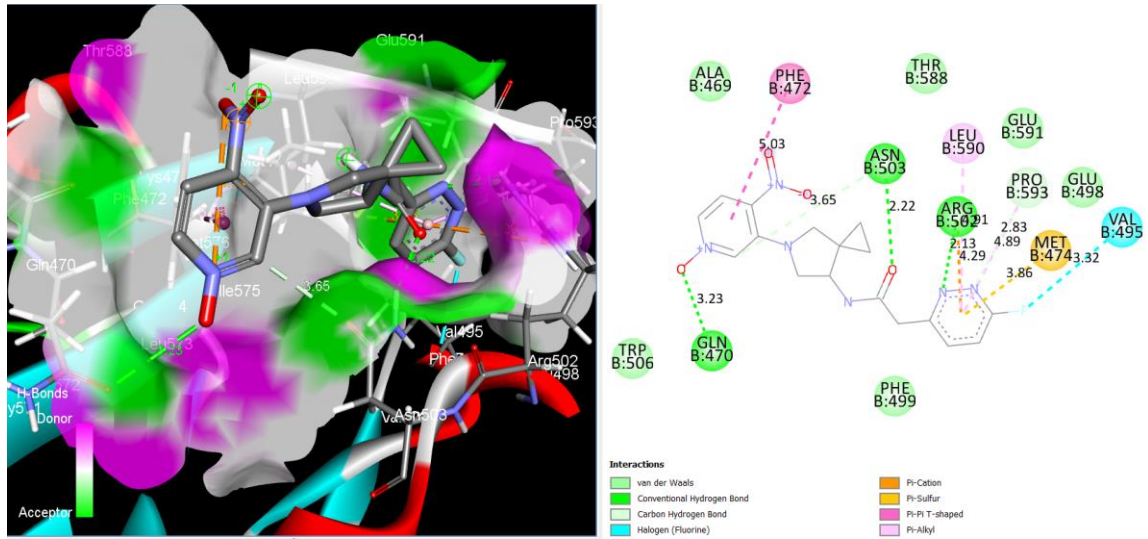
- Pdb: 7cxm (nsp13-ATP-ssRNA)
- Pdb: 5rm9 (fragment-nsp13)



Pdb: 7cxm (nsp13-ATP-ssRNA) at 0ns/1000ns



Pdb: 5rm9 (fragment-nsp13)

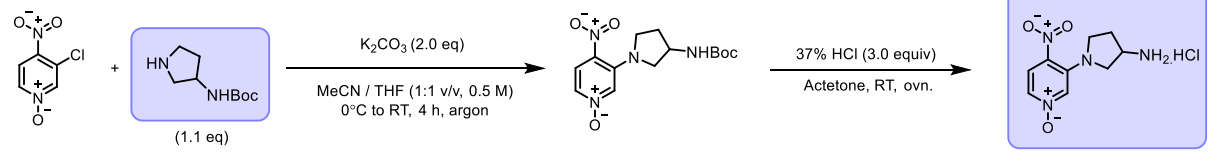


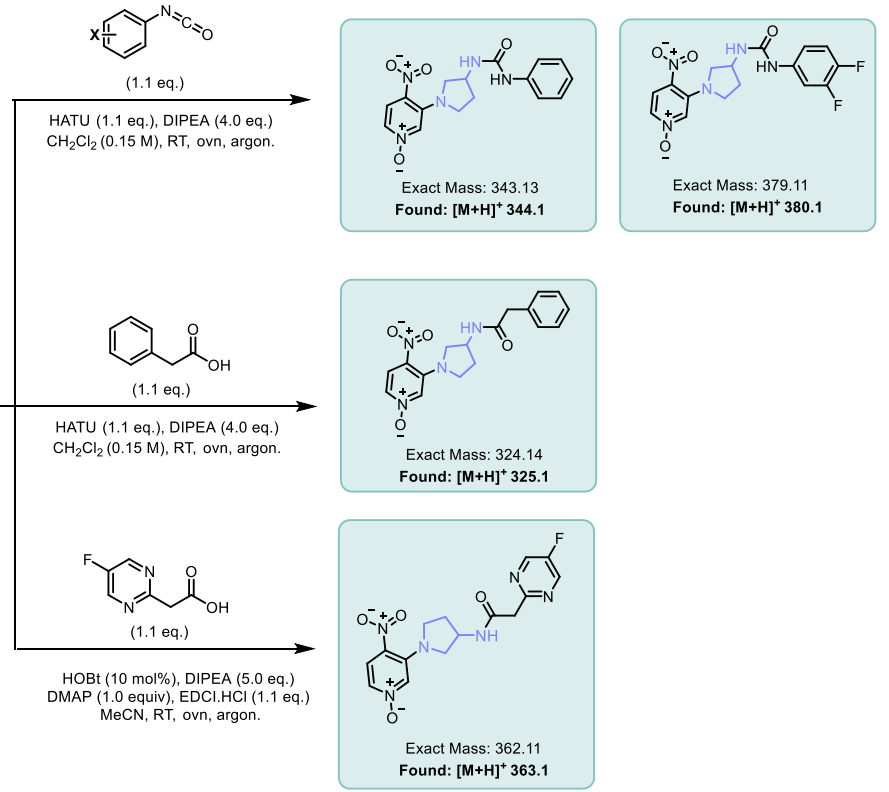
Modelling the active SARS-CoV-2 helicase complex as a basis for structure-based inhibitor design DOI: 10.1039/D1SC02775A *Chem. Sci.*, 2021, **12**, 13492-13505

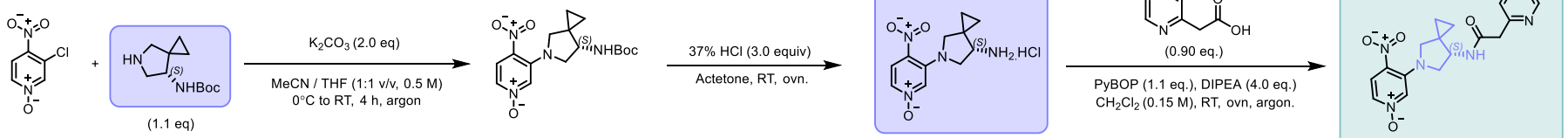
Pyrrolidines and nitro-N-oxides (Tom)

Building block in hand

Made







Benzoazepines (Tom)