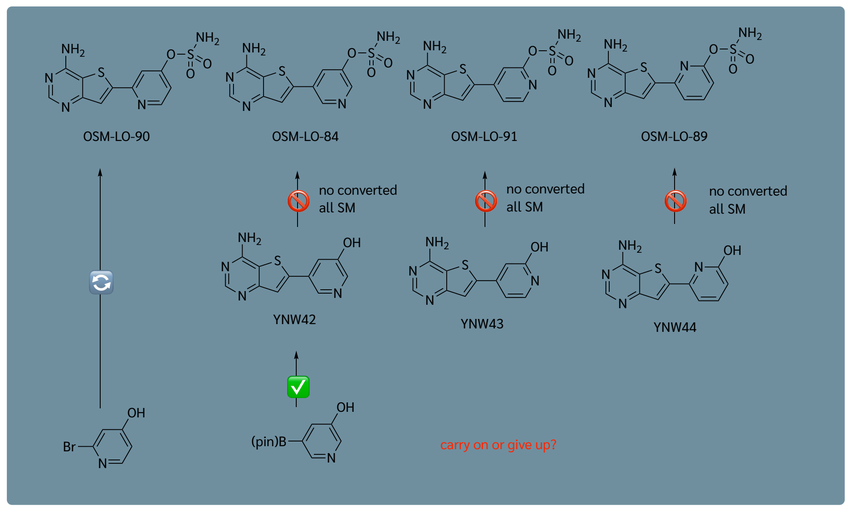
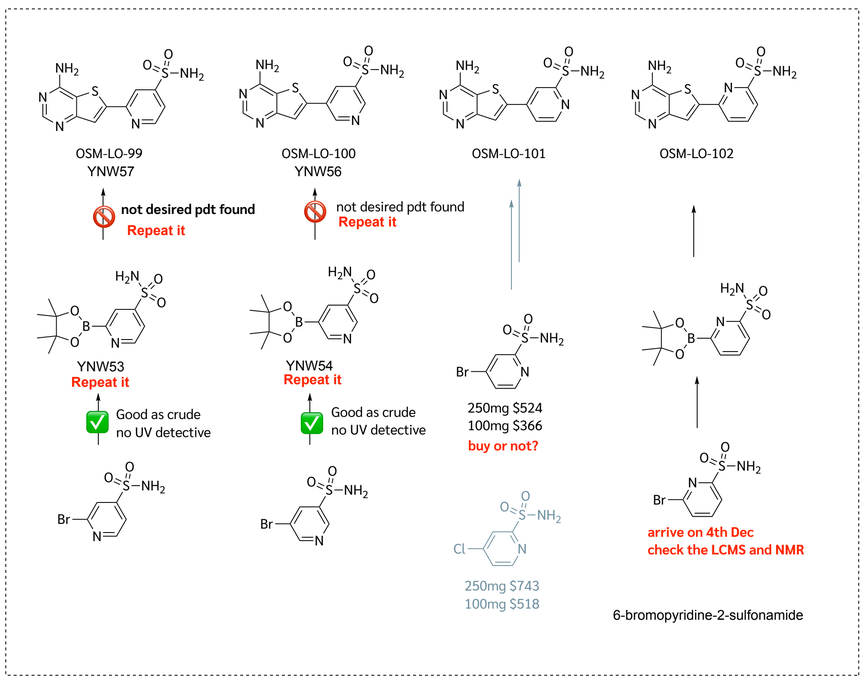
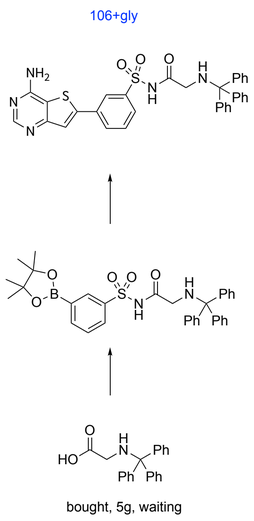
Pyridyl sulfamates (stopped):



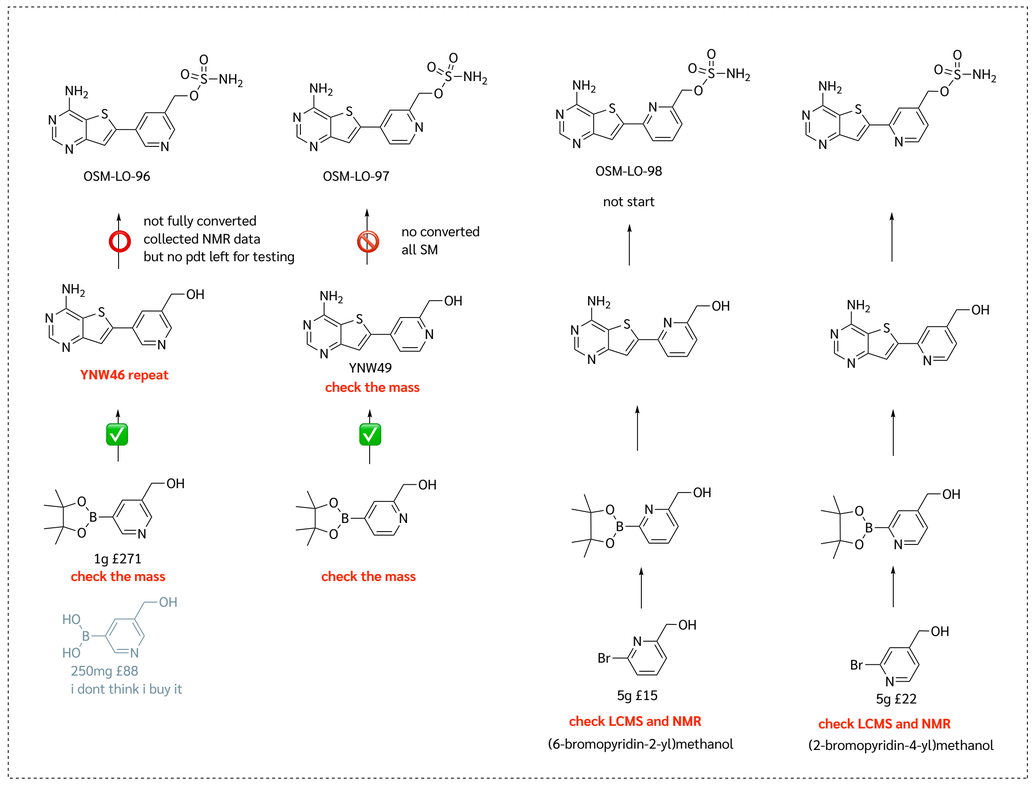
Pyridyl sulfonamide:



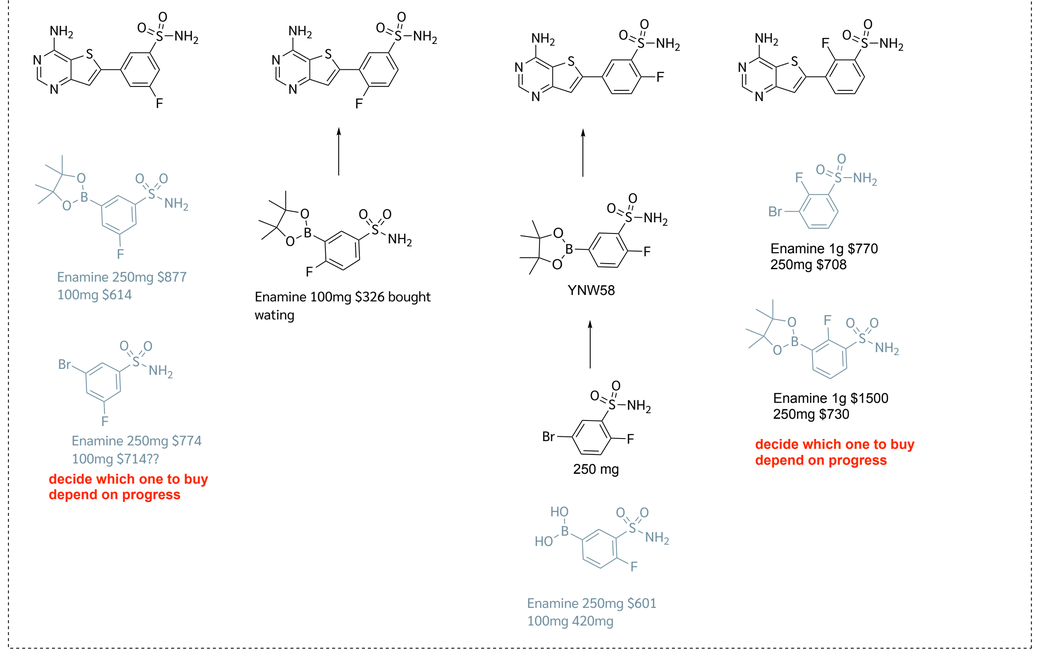
106 + aa adduct:



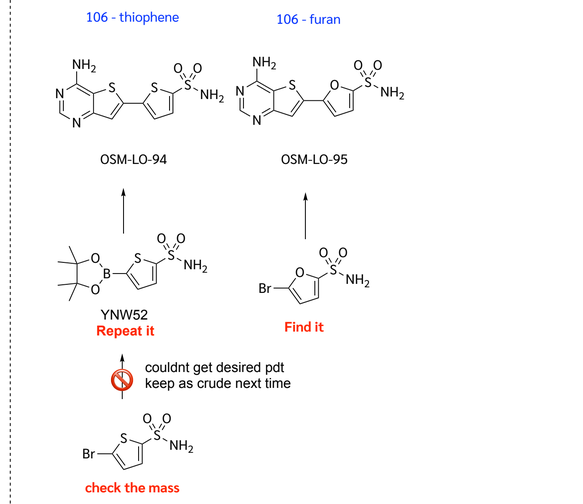
Pyridyl benzyl sulfamates:



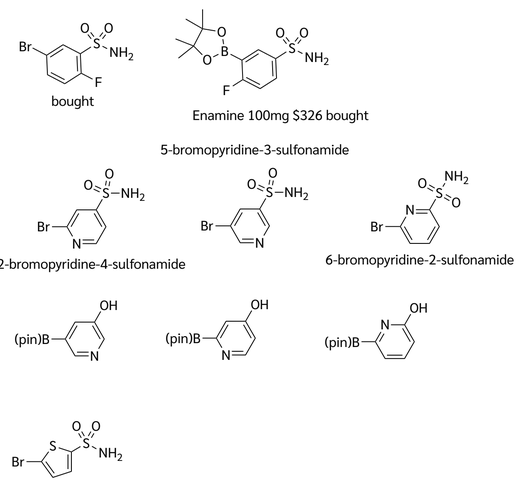
106 + F sulfonamde:



Aryl ring replace:



chemicals bought:

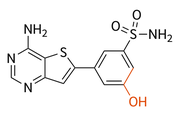


Hey. I guess we don't really know much about the reactivity of sulfonamides and sulfamates with activated esters -
what makes the reaction faster or slower. What about we plan a standalone study of an in vitro assessment of reactivity of sulfonamide/sulfamate nucleophiles on a range of activated esters?
Can we tune the reactivity usefully?
Not a current priority, but have a general think about how we might do this? I would imagine we'd need something we can easily follow by NMR on the minute/hour timescale cleanly.
What kind of reaction might that be? Has anyone done this before with some model activated ester?
This is the kind of thing that could be i) a standalone little chapter of your PhD and a nice paper, leading to ii) better design of reaction hijacking inhibitors.

make sure what is activated esters means. like nitophenyl ester ? or N-hydroxysuccinimide? normal chemical stucture ester or need a protein environment for generate ester?
It will be good if i can do it in SoP (ask Nikita), but if it involve protein then i need to think protein purchase and temperature setting more carefully. **SEARCH IT**

metabolism idea, jeremy said the -OH will add into meta position in metabolism progress

Need to use metasite to see where the metabolism will happen. if P450 will oxidised in meta positon (right pic) of aryl sulfonamide. Then changing H to F will block the metabolism and 106 will have longer half life in theory. **(awating download approval)**



1) Do we have efficacy vs resistant strains? (Yinuo, let's check).

2) Yinuo, what's the molarity for our existing solubility measurements (rather than mg/mL etc)? Ideally want 100 uM. Let's add to the GH site.

5) Note that human mics is actually < 3.5 according to more recent measurement in Science Cloud (Yinuo do we have the raw data anywhere?)

13) Yinuo. Analogs are still needed because of the drive for better potency, physicochem, PK.
Other potential targets:
OSM-LO-80 with N linking ring to S.
106 with N on the ring linking the S.
NH2 variant of 87
Connect N as part of fused ring, though getting trajectory right will be hard.
Try to reduce PSA.

In terms of evaluating these molecules vs other pathogens, should we try to find the orthologues closest to Pfal? Or we just make them all - Yinuo is starting with the GLY adduct.