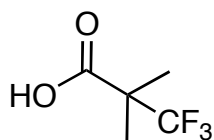


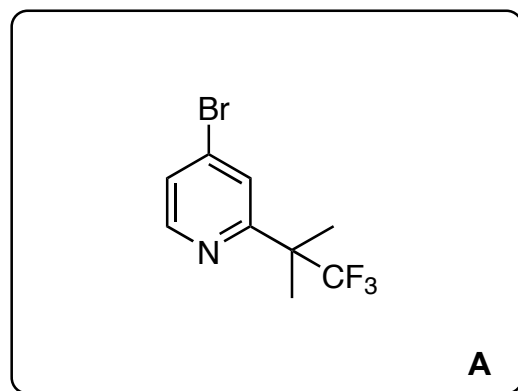
**Discovery of NVP-BYL719 a potent and selective phosphatidylinositol-3 kinase alpha inhibitor selected for clinical evaluation (+ Heterocycles Quiz)**

Furet, P.; Guagnano, V.; Fairhurst, R. A.; Imbach-Weese, P.; Bruce, I.; Knapp, M.; Fritsch, C.; Blasco, F.; Blanz, J.; Aichholz, R.; Hamon, J.; Fabbro, D.; Caravatti, G.

*Bioorg. Med. Chem. Lett.* **2013**, *23*, 3741-3748.



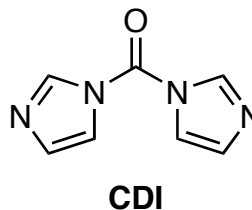
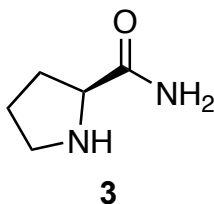
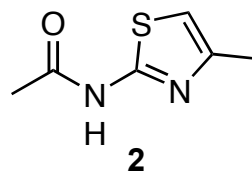
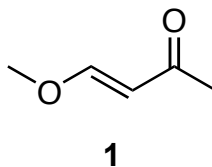
1-4



5-8

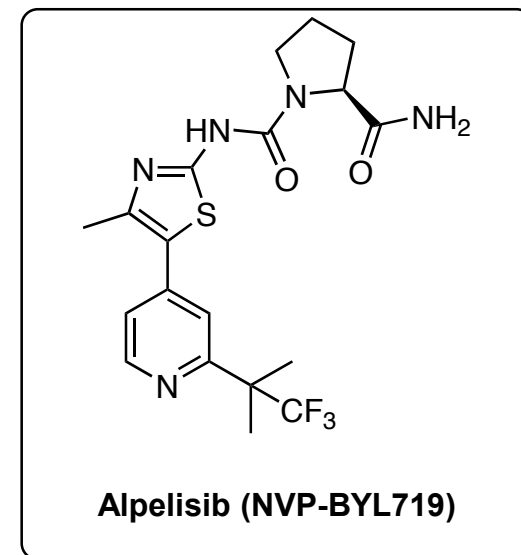
**Alpelisib (NVP-BYL719)**

- 1) oxalyl chloride
- 2) **1**, LiHMDS, -78 °C, then substrate, then TFA
- 3) NH<sub>3</sub> (aq.)
- 4) POBr<sub>3</sub>



- 5) **2**, Pd(OAc)<sub>2</sub>/*t*-Bu<sub>3</sub>P<sup>y</sup> HBF<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>
- 6) 6 N HCl, EtOH
- 7) CDI
- 8) **3**, Et<sub>3</sub>N

- 2) what heterocycle is formed?  
*pyrone*  
please provide a mechanism
- 3) what heterocycle is formed?  
*pyridone*
- 5) which heterocycle is introduced?  
*thiazole*  
How would you make **2**?
- 7) what is the structure of CDI? what is the heterocycle? *imidazole*
- 8) what is the amino acid analog of **3**?  
*proline*  
what heterocycle is in **3**? *pyrrolidine*



## Heterocycle Quiz!



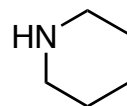
aziridine



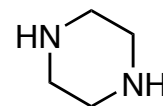
2*H*-azirine



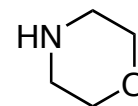
azetidine



piperidine



piperazine



morpholine



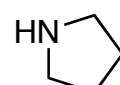
oxirane



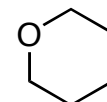
oxetane



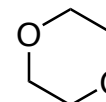
tetrahydrofuran



pyrrolidine



tetrahydro-2*H*-pyran



1,4-dioxane



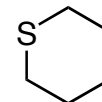
thiirane



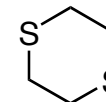
thietane



tetrahydrothiophene



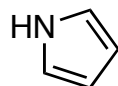
tetrahydro-2*H*-thiopyran



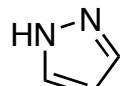
1,4-dithiane



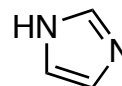
furan



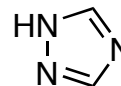
1*H*-pyrrole



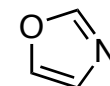
1*H*-pyrazole



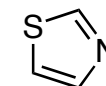
1*H*-imidazole



1*H*-1,2,4-triazole



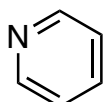
oxazole



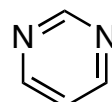
thiazole



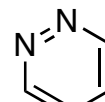
thiophene



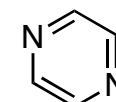
pyridine



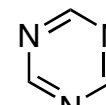
pyrimidine



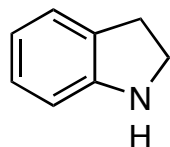
pyridazine



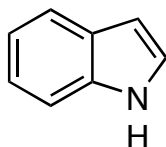
pyrazine



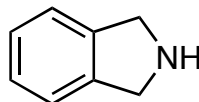
1,3,5-triazine



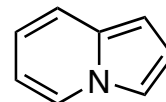
indoline



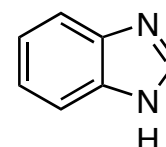
1*H*-indole



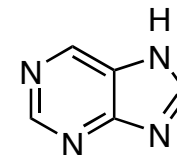
isoindoline



indolizine

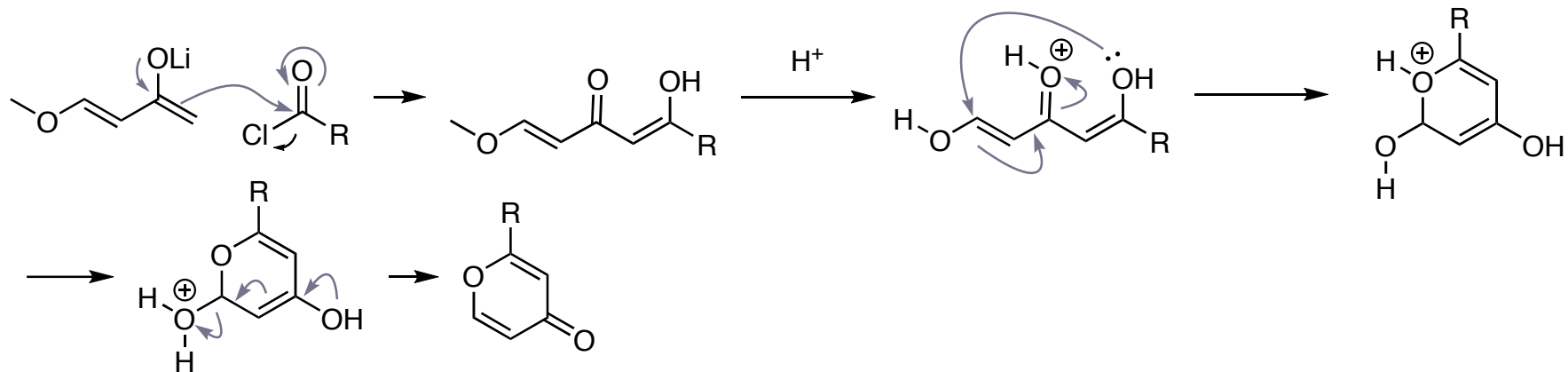


benzimidazole

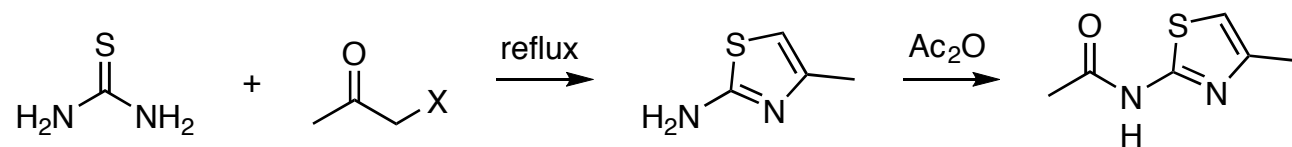


7*H*-purine

solution step 2:



synthesis of **2**: *Hantzsch Thiazole Synthesis*



Additional References for Heterocycles:

<https://www.scripps.edu/baran/heterocycles/Essentials1-2009.pdf>

[https://www.youtube.com/watch?v=H7Zil8IIUK0&list=PLZ0nxZgbV3vYHmafX7YDDAFHsfy\\_PpNp4](https://www.youtube.com/watch?v=H7Zil8IIUK0&list=PLZ0nxZgbV3vYHmafX7YDDAFHsfy_PpNp4)