

# Topic 7

## Presentations

### 7.1 Day 1 (1-6)

- 3/11:
- Nate's presentation.
    - Figure out what IC<sub>50</sub> means, and why nanomolar (including single-digit) is good!
    - Explain bio terms (but I'm already planning this).
      - Make sure I have oncometabolite definition right!
    - Make sure all mechanistic/synthetic details are right and explainable (but I'm already planning this).
      - “You should be able to right a mechanism for any reaction you're going to present” - Steve.
      - “If you're in a job interview, you have to be able to have some answer if someone asks how the reaction goes.”
      - “Sometimes I know and sometimes I don't, and then I have to look up a bunch of papers. And then sometimes I can figure it out and sometimes I can't, but at least I have something to say then.” Sweet!
  - Steve to Dennis: “All of these presentations should have been downloaded ahead of time.”
  - Frank's (Harvard) presentation.
    - Vadadustat.
    - “Slow down, breathe, and don't read from the slide.”
    - “You gonna walk us through that scheme? Because otherwise, it's useless.”
      - Make sure I explain all figures, including crystal structures!! Learn the hydrogen bonds.
    - Make sure I can explain ambiguous selectivity, too!!
    - HBr works to hydrolyze *activated* (e.g., phenyl) methyl ethers (and can do nitrile hydrolysis at the same time).
      - Explain selectivity for chloro S<sub>N</sub>Ar on *s*-triazene vs. *ortho*-pyridine.
      - More activated/under more mild conditions. Look up typical conditions for pyridine S<sub>N</sub>Ar and look to differentiate temperature, acid, etc. from the used conditions.
  - Minh's presentation.
    - Voydeya.
    - Appreciating structural/retrosynthetic challenges is probably a good idea!
    - Make sure I know what the biuret test is (a protein test — like the functional group tests Steve discussed that day — that does not contain biuret, but gives a positive result to the peptide-like bonds in biuret).

- Check timing: Make sure I get everything in in 10 minutes, and don't linger on the bio!
- Sleep well both of the next two nights!
- Alexander's presentation.

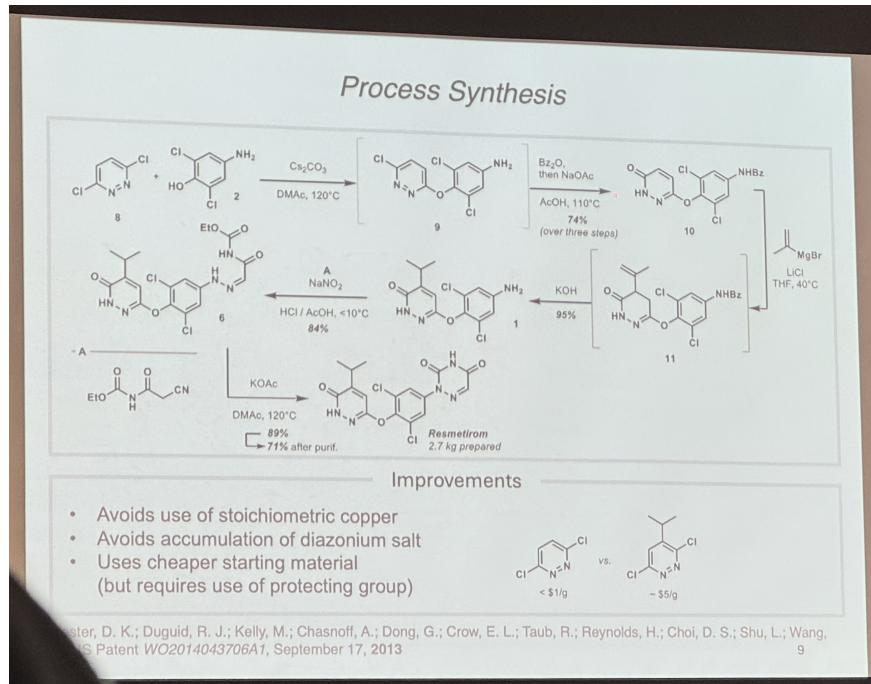


Figure 7.1: Alexander Müller's graphic design.

- Resmetirom.
- Electron-rich arenes easily oxidize in the body, leading to redox cycling. Causes safety/toxicity issues.
  - Good discussion of design principles; keep doing the same!
- Good retrosynthesis, followed by synthesis.
- Dives into mechanisms of key steps.
- Good graphic design: Boxes. Very clean and clear. Citations in light grey at bottom left.
- Numbering chemicals and compounds is a good idea.
- Explaining selectivity is definitely needed!
- Angel's presentation.
  - Ceftobiprole: Staph antibiotic.
  - Starts with retrosynthetic analysis of moieties.
  - Gives a total nitrogen count; I could/should, too!
  - Gives a discovery timeline.
  - Know the mutations.
  - Drawing out arrow-pushing mechanisms is not inappropriate.
  - Make changes clear in large molecules moving from one to the next with colored bonds, as Steve does! Otherwise, you just get lost as to what's changing...

- On Thursday, we'll start at 9:00 instead of 9:05.
- Kwanwoo's presentation.

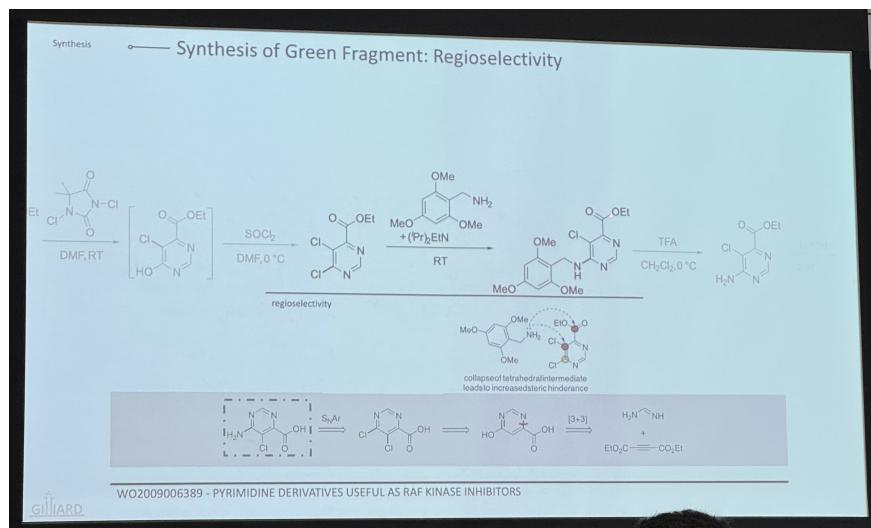


Figure 7.2: Kwanwoo Park's graphic design.

- Ojemda.
- Also uses MIT/Gilliard slide template!
- Also discussing a glioma; could give him a shoutout in my presentation!
- Slides are too cluttered and he's reading off the slides.
- Good retrosynthetic analysis. Color-coded fragments (using pastel-colored boxes might be better, then keeping them on each slide).
- Points out Hantzsch; I should make a fuss about names as well.
- Know the names of functional groups! Know the carbon numbering in my molecule.
- Graphic design.
  - Mechanism in pop-up box is a good approach.
  - Keeping the general scheme at the bottom of each slide, being progressively highlighted, as you move through bigger synthetic details up top.
  - Chemoselectivity with circles in popup box.
- Know reagent names, and functional group names.

## 7.2 Day 2 (7-14)

3/13:

- Jasmin's presentation.
  - Xolremdi.
  - Also does limitations of ok med chem synthesis!
  - Does retrosynthetic analysis separately from forward synthesis; would have been a good idea, as Christine suggested.
  - Uses a table beneath a larger, marked up scheme to show screened conditions for one reaction.
  - “Silica gel pad” means filtration, not chromatography, which is why they can get away with it.
  - Catalytic KI and bulky base can do Finkelstein-type chloride/iodide exchange *in situ* before S<sub>N</sub>2 displacement with the other reaction.

- Yifan's presentation.

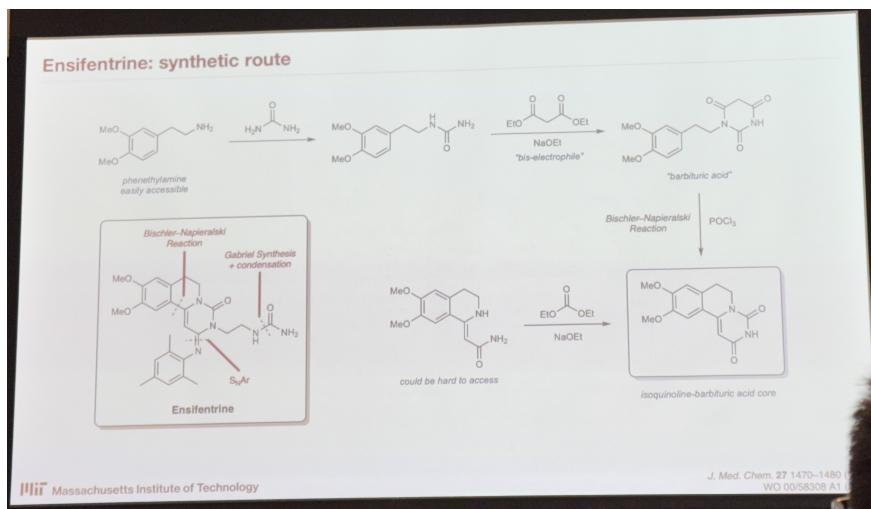


Figure 7.3: Yifan's graphic design.

- Emphasizing first-in-class and novel mechanisms of action may be a good idea.
- Graphic design: Disconnections labeled with reactions in a popup box!
- Finkelstein again: NaI, K<sub>2</sub>CO<sub>3</sub>, and 2-butanone (like W. S. Johnson!).
- Yuzhe's presentation.
  - Deyryxikutubub.
  - Talks about mental health effects of having a disease, too!
  - Numbering compounds with different numbers for different protecting groups (variables), as papers often do!
- My presentation.
  - C–F–O bonds aren't really a thing; it's more of an interaction.
  - We did actually talk about *s*-triazines in class (oops); Steve made fun of the name.
  - TFA, HC(OMe)<sub>3</sub> is a common drying agent, an alternative to a Dean-Stark apparatus.
    - Both things I put up are plausible, but drying is more common.
  - Steve points out that Cyanamid was acquired by another company, then bought by Pfizer (like everything else).
- Jordan Bench's presentation.
  - Lazertinib.
  - Steve points out a number of things in the reactions that would be hard to tell from patents.
    - Formate is for transfer hydrogenation.
  - Patent authors use patent generics a lot, because otherwise people will make a slight improvement, repatent, and sell more cheaply.
  - You have to do a certain number of the examples in the patent in order to justify it, but not all of them.
- Georgia's presentation.

- Miplyffa.
- Rare disease (only 300 people in the US), so test cases to justify the approval were only on 4-5 people.
- Process synthesis at 50 g scale, but maybe that makes sense with the small number of people affected.
- Elizabeth's presentation.

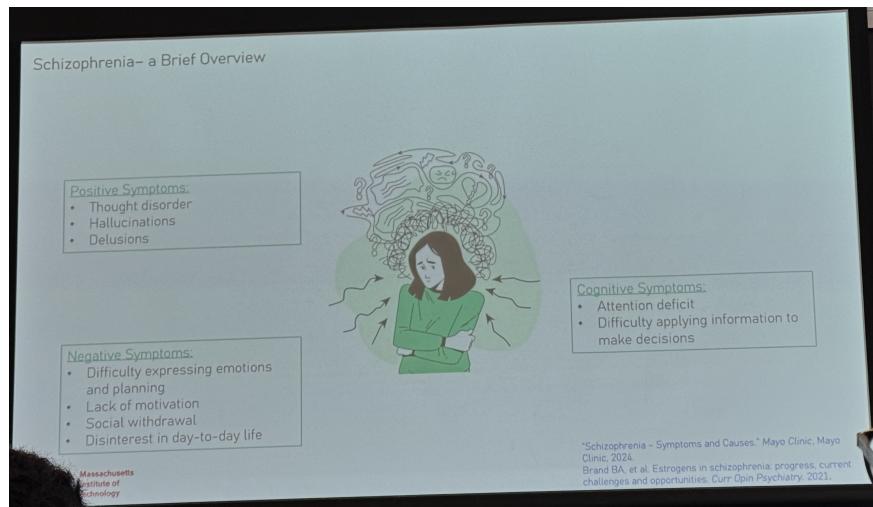


Figure 7.4: Elizabeth's graphic design.

- Cobenfy: Combination drug of xanomeline and trospium chloride.
- Graphic design: Boxes around an image to identify different aspects. Hard lines, good font, and color are all useful, though the color is a bit light and hard to read...
- TMSCN is an alternate nucleophilic cyanide equivalent to KCN.
- Thiadiazole synthesis from  $S_2Cl_2$ , and a nitrile/amine. Mechanistically pretty complicated, per Steve.
- Eva Bayer's (Harvard) presentation.
  - Has radioactive  $^{18}F$ .
  - Higher image resolution (for PET) among competitors. Goes *very specifically* to mitochondria.
  - Good that a precursor was approved in pesticides, because it flushes out of humans super quickly, so no long-term toxicity. But hangs around long enough for imaging.
  - Time really matters in the synthesis (it's 110 minutes, 35% yield) because the  $^{18}F$  decays so rapidly!
  - You basically need a cyclotron on site to produce this stuff and get it into a patient ASAP.

### 7.3 Day 3 (15-21)

3/18:

- Jonah's presentation.
  - Itovebi.
  - Buchwald-Ullmann-type cross-coupling; because Steve consults for Genentech, so they acknowledged him in the patent and publication.
  - Graphic design.

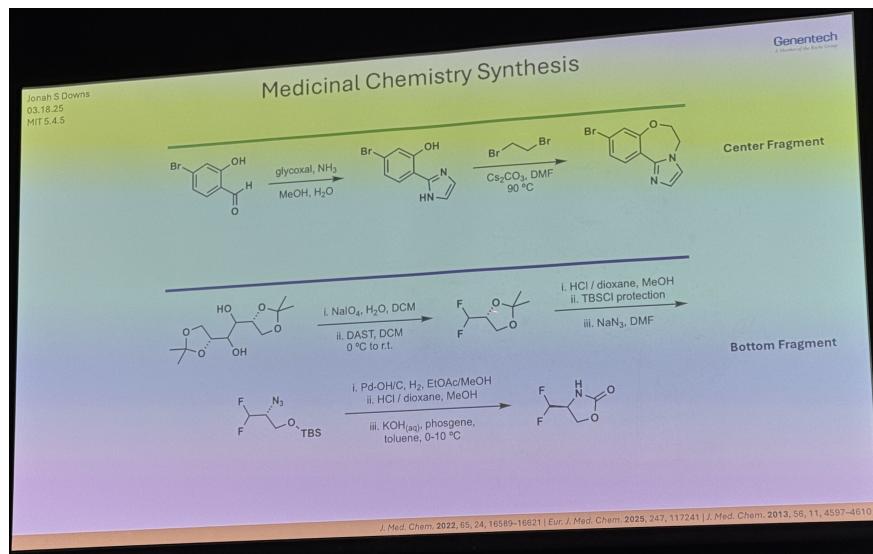


Figure 7.5: Jonah's graphic design.

- Different colored lines to separate different fragment syntheses.
- Colored bar at bottom with citations.
- Rachel's presentation.

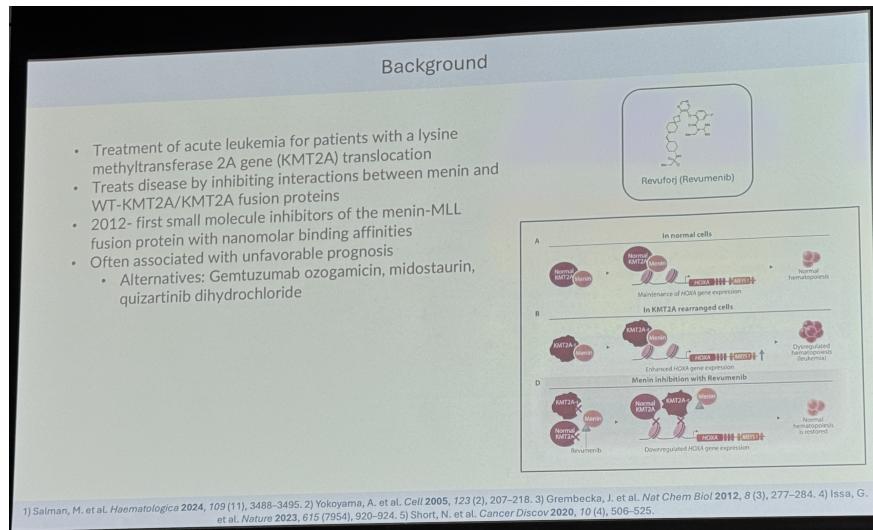


Figure 7.6: Rachel's graphic design.

- Revuforj.
- Graphic design.
  - Also has colored bar at bottom with citations, matched by colored title bar at top. Bottom bar grows and shrinks if 2nd line is needed; font size is fixed.
  - There are known procedures for taking *N*-oxides and going directly to substitution without going through the 2-chloro derivative with  $\text{POCl}_3$ .
- Christina's presentation.

- Attruby.
- Frank's presentation.
  - Crenessity.
  - Synthesis on hundreds of kilograms scale.
  - Hydroxyls are sometimes incorporated so that you can make a prodrug; they're good linkers, like with JJ!
- Nicolás Manno's presentation.
  - Ensartinib.
  - Drew an auxiliary reaction scheme on the board in no time flat!
- Ismael Wane's presentation.
  - Zavzpret.
  - **Jeffery modification** of the Heck reaction (ligand free, but often limited to aryl chlorides).
  - DuPhos used for asymmetric hydrogenation.
    - Developed by Mark Burk at DuPont.
  - Dianion cyclizes.
  - **Erlenmeyer synthesis** (with Hippuric acid).
- Andrew Yue's presentation.
  - Graphic design.
    - Highlights the bonds that are formed, and it does help.
    - It is also very important to conserve the relative orientation of moieties between steps as much as possible!
    - Animation idea: When you have to do a synthesis across multiple slides, have everything but the last compound fade away, then have the last compound slide to the top-left corner of the next slide.
  - **Molander salts** in a Suzuki-type coupling.
  - **Chiral supercritical fluid chromatography** (chiral SFC) can resolve atropisomers.
  - Fluoride limits reactor size (it etches glass and stainless steel); you have to use **Hastelloy reactors**, which are much more expensive.
  - Steve: This has got to be an incredibly expensive molecule. There's much less price pressure as oncology drugs because people will pay to save their lives.
- 2nd exam on Thursday.
  - 2023 practice exam is a final exam.
  - 2024 exam is more like this one.
  - Try to be here a bit before 9:00 AM.
- Notes on presentations.
  - It's harder to do biocatalytic processes in discovery, but they're great in long-term process routes.