NAME_____ 4-Digit ID:_____

Heterocyclic Chemistry

Prof. Phil S. Baran
Department of Chemistry
Scripps Research



OPENING!
VERY Therapeutics™*
"Laughter is the best medicine"

Congratulations! You are just about to earn your PhD in chemistry from Wow Research. Invigorated by all of the content in heterocycles, you have decided to go to industry and interview on site at VERY Therapeutics. Your industry hosts, Max and Tucker have an action-packed schedule where you will interact with all departments at VERY Therapeutics. They heard how miserably challenging your classes (especially heterocycles) at Wow research were and are eager to grill you. In order to protect intellectual property, the legal department of the company requests that you provide only your FINAL answers in the most LEGIBLE handwriting possible. Take synthetic routes back to SIMPLE starting materials

You have until 5:00 pm PDT before they bring in the next candidate.

Question 1 : _____/ 45

Question 2 : _____/ 45

Question 3 : _____/ 60

Question 4 : _____/ 40

Question 5 : _____/ 60

Question 6 : _____/ 30

Question 7 : _____/ 15

Question 8 : _____/ 55

BONUS QUESTION :_____/ 45

TOTAL : _____/ 350 + 45

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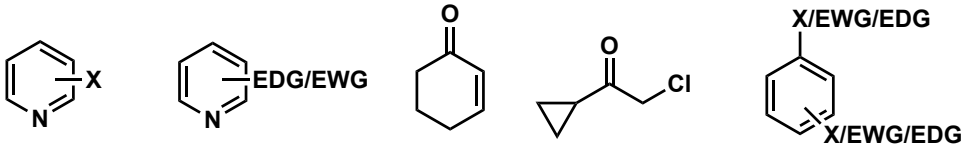
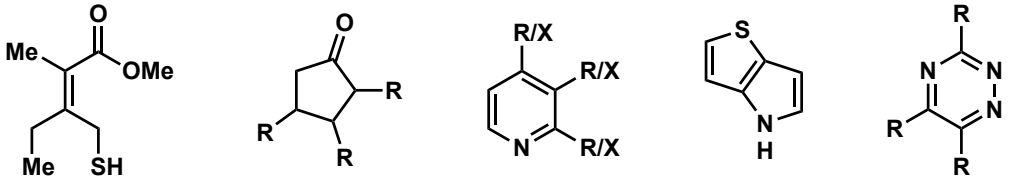
Examples of simple starting materials (not limited to):



Examples of not simple starting materials (not limited to):



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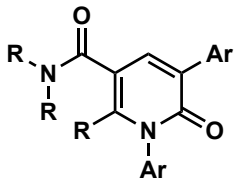
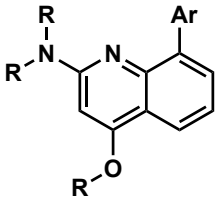
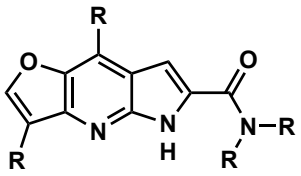
Question #1: (45 points total, 15 points each) Medicinal Chemistry – The MedChem team at VERY Therapeutics is working to study anti-aging in the context memes so that memes never die. They have identified the following hits and want to perform SAR studies at the specified positions to hopefully advance one to lead status. **Provide a Med Chem FORWARD ROUTE WITH SUGGESTED REAGENTS to the following cores that allows for diverse R groups. Ar groups are aryl/hetaryl and R can be either alkyl or aryl. Cross coupling is allowed in Med Chem.**



A



B



C

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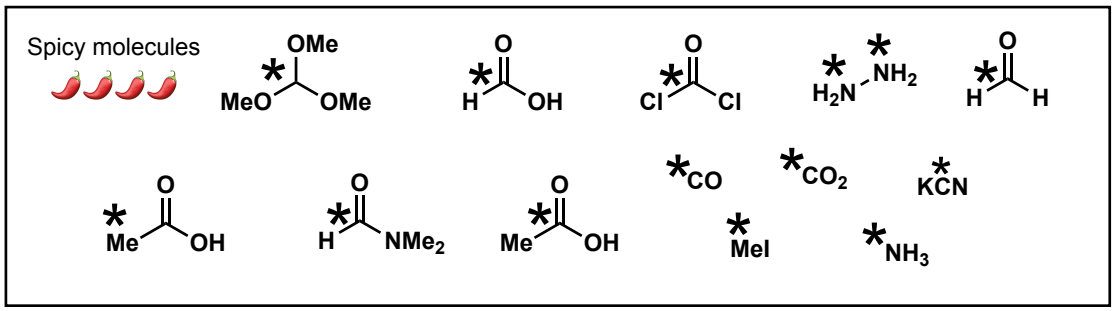
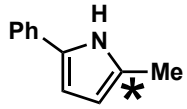
Question #2: (45 points total, 5 points each) Radiochemistry Group – The radiochemistry group is studying ADME properties of several different molecules. Specifically, they want to see whether or not these compounds have a long $t_{1/2}$ in the funny bone. **Provide quick FORWARD ROUTES WITH SUGGESTED REAGENTS to the following radiolabeled compounds using the building blocks below:**



A)



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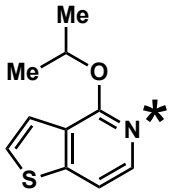

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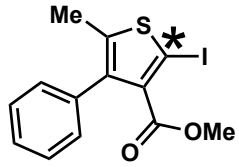
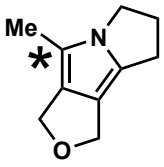
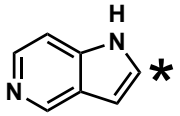


D)



E)



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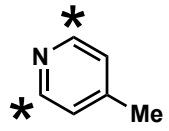
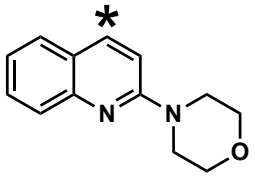
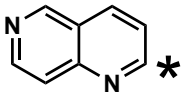


G)



H)



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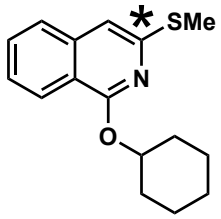
I)



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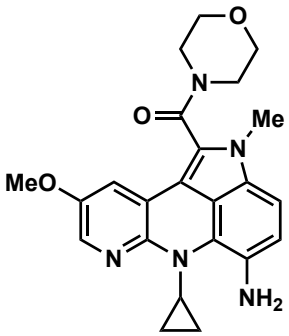
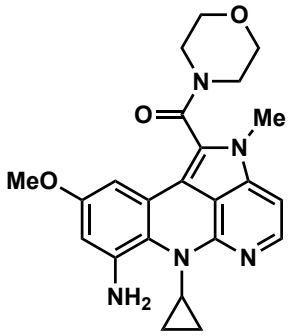
Question #3: (60 points total, 20 points each) Medicinal Chemistry – The Med Chem team at Very Therapeutics is in the early stages of a new program directed towards relieving stress in students taking hard exams. They have identified the following molecule from a library screen as being uniquely effective in reducing stress, so much so that simply proposing a synthesis of it has therapeutic effects.

Part A: Please provide a FORWARD ROUTE WITH SUGGESTED REAGENTS to the compound below.



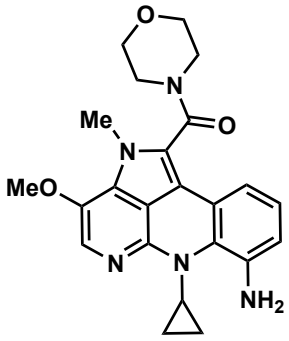
Question #3 (continued):

Part B: Oops. That appeared to have the opposite effect… The computational chemists have suggested that adjusting the scaffold slightly will turn the compound from an agonist to an antagonist of the biological target. **Please provide a FORWARD ROUTE WITH SUGGESTED REAGENTS to the compound below.**



Question #3 (continued):

Part C: Oh jeez. That still didn't work. In vivo studies failed to demonstrate efficacy. Academic consultant, Bill Pharan, thinks making some scaffold changes, yet again, may solve this conundrum. He also thinks that the aniline may lead to tox problems… but we will cross that bridge when we get there. **Please provide a FORWARD ROUTE WITH SUGGESTED REAGENTS to the compound below.**



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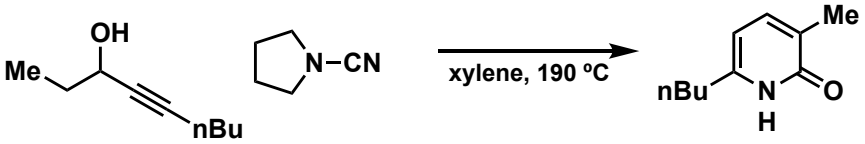
Question #4: (40 points total, 10 points each). During your lunch break, you overhear a few Very Therapeutics scientists, Hucker and Pax, discussing some bizarre reactions they found on the internet. Intrigued, and looking to make a killer impression, you go out of your way to insert yourself into their conversation and tell them exactly how these reactions work. **PLEASE PROVIDE REASONABLE MECHANISMS FOR THE FOLLOWING REACTIONS.**

Part A:



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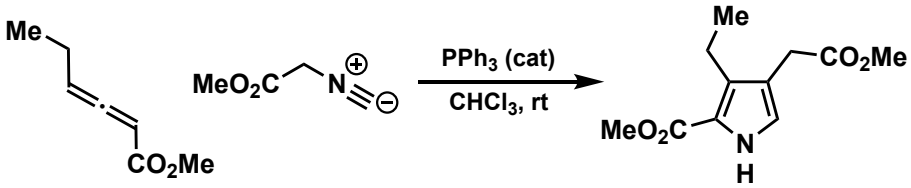
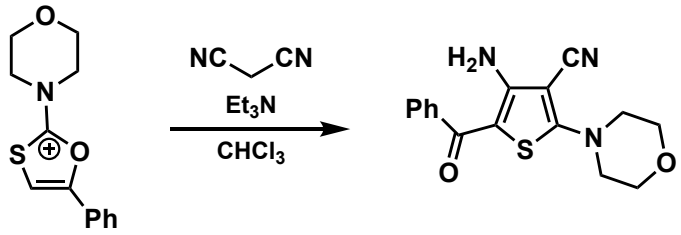
Part B:



Part C:



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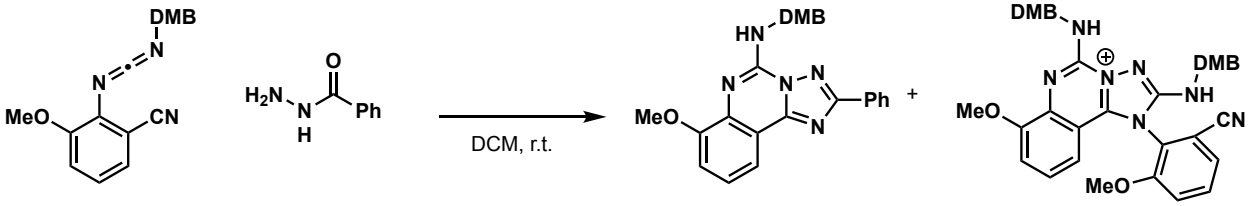
Part D:



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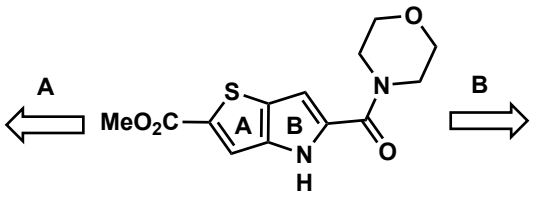
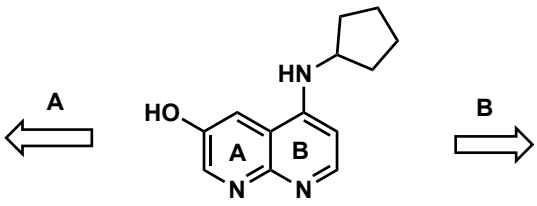
Question #5. **(60 points total, 15 points each)**. Medicinal Chemistry – At Very Therapeutics, fused heterocycles are no laughing matter. Isolated from dead crickets at comedy clubs, such molecules have been shown to improve the delivery of terrible jokes. Unfortunately, no one at Very Therapeutics knows how to make them. Show them who is boss by demonstrating you know how to make these systems by breaking either ring!
Propose TWO RETROSYNTHESES for each of the following compounds. **One that disconnects ring A and one that disconnects ring B.** Please take your retrosyntheses back to mono or difunctionalized heterocycles with SIMPLE substituents (ex: Halogen, Nitrile, Ester, Hydroxyl, Methyl, etc).

A)



B)



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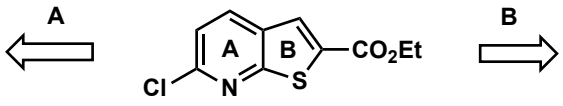
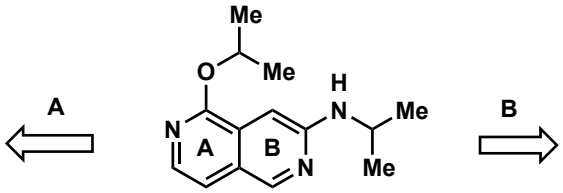
Question #5 (continued):

C)



D)



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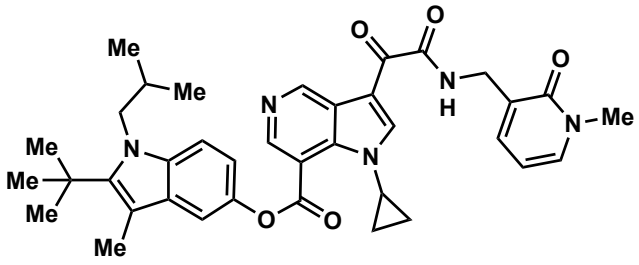
Question #6: (30 points) Process Chemistry – The process team, exhausted from a long and brutal cage match with the medicinal chemists, are unable to come up with a manufacturing route to the following clinical candidate. Eager to help, you check your pockets for some transition metals to make it easy but unfortunately you spent it all on late-stage stoichiometric couplings in your PhD. Desperate to make a good impression, you still jump at the opportunity to help! **Propose a process friendly RETROSYNTHESIS for the following molecule. No metal mediated cross coupling reactions allowed.**



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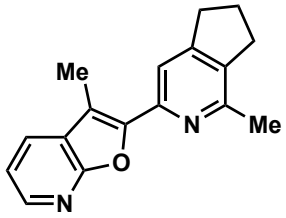
Question #7: (15 points total) Awkward hallway encounter – On your way out of the process team interview, you bump into someone who graduated from your current lab. Gee, chemistry *is* a small world! Pretending like all those times they grilled you on mechanisms totally didn't happen you stop and chat for a bit. Quickly, you find yourself drawn into a deep discussion about what the best way to build their scaffold is. Now it is your turn to teach them a lesson in synthetic strategy. **Please provide a FORWARD ROUTE WITH SUGGESTED REAGENTS to the compound below.**



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WOW! Great news! You have been hired by Very Therapeutics. You have blown them away with your creative answers and quick thinking.

In fact, they were so impressed that they have made you Vice President of Chemistry right away!

As VP, you must oversee the following project from start to finish.

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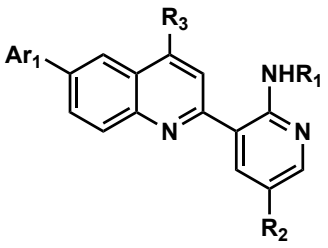
Question #8: (55 points total)

Part A: (10 points) Medicinal Chemistry – Your medicinal chemistry team has identified the following scaffold as being a potent FUN-1 agonist. Help them make it in a modular way. **Please provide a FORWARD ROUTE WITH SUGGESTED REAGENTS to the compound below. The route should allow for rapid diversification at the variable positions (Ar_1, Ar_2, Ar_3, and R).**



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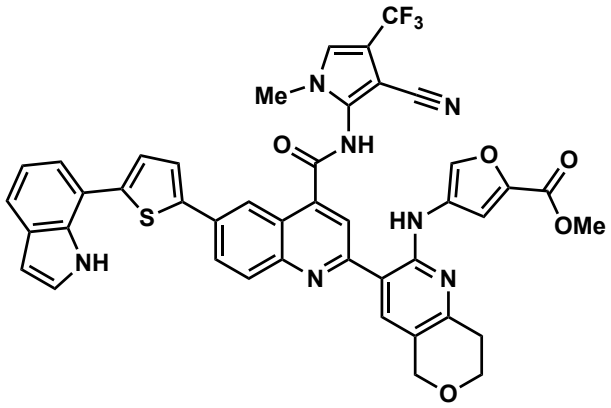
Question #8 (continued):

Part B: (35 points) Process Chemistry – Congratulations, your FUN-1 agonist has been moved up to Phase III by the FDA after demonstrating efficacy and safety in a small patient population. The advisory panel also loved how the structure has one of each heterocycle. Pretty as it is, the required dose is quite high as we did not hear any laughing during this exam. As a result, the manufacturing route needs to be incredible scalable and not reliant on costly cross coupling chemistry (say that 5 times fast). **Propose a process friendly FORWARD SYNTHESIS WITH SUGGESTED REAGENTS. You may not use any metal mediated cross coupling reactions.**



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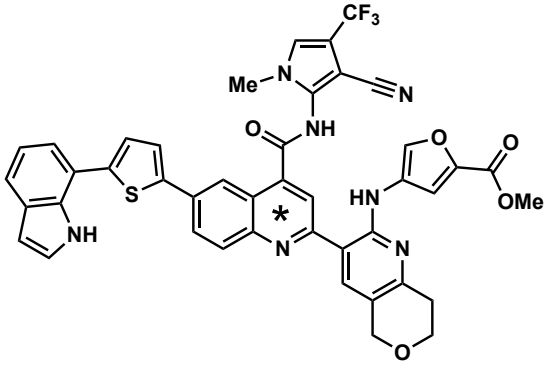
Part C: (10 points) Radio Chemistry – Quantitative biology wants to track ADME of your FUN-1 agonist. The radiochemistry team has a bit of an unorthodox definition of what fun means and suggested ^{14}C labelling the pyridine OR the quinoline. Exercising good executive leadership skills, you kindly listen to their suggestion and trust their judgement. **Propose a RETROSYNTHESIS ONLY for each of the following <u>CARBON</u> labelled compound below. You only have to label ONE ring carbon on either ring at any position. You pick. You may only use molecules in the box from problem 2.**



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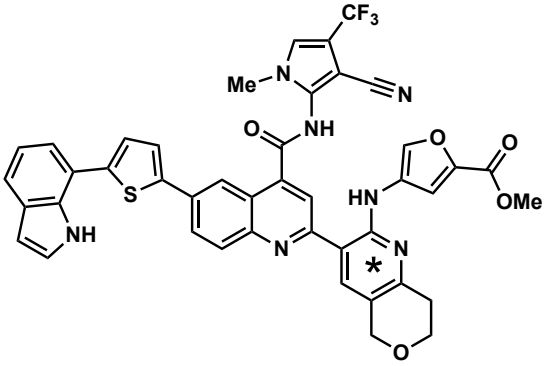

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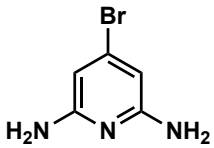
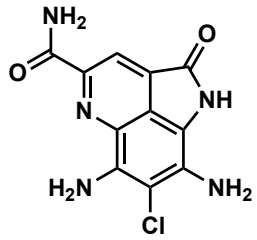
BONUS: (45 points total, 5 points each) Wow what a day. Like Gilgamesh standing on the city wall, you ponder whether or not the journey was worth it all. Turns out it was because you are the VP of Very Therapeutics in your late 20's. While you are waiting for your brand new Tesla to charge, you think back to heterocycles and wonder if you still got it. You also wonder you even are remembering the structures correctly… **Propose RETROSYNTHESES of the following molecules.**

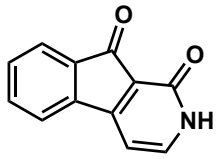
A)



B)



C)



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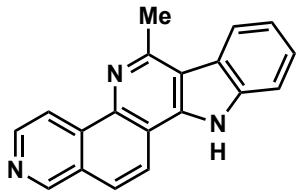
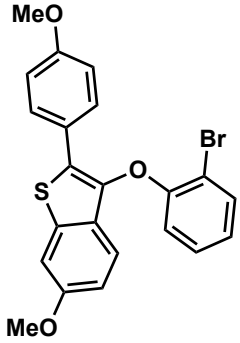
D)



E)



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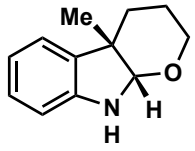

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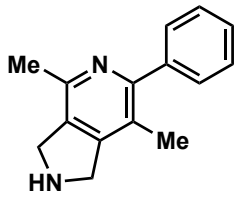
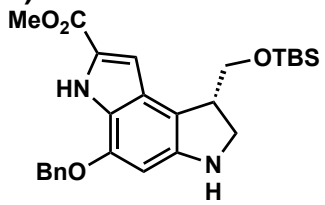
G)



H)



I)

