NAME_____ 4-Digit ID:_____

Heterocyclic Chemistry

Prof. Phil S. Baran
Department of Chemistry
Scripps Research



In the year 2050, after a long and fulfilling career at VERY Therapeutics, you finally decided to step down from your position as Vice President to establish a consulting firm, The Consulting Corner LLC. It's a high-stake game as your trademark is that you personally bet a vital organ on each suggestion. If you wish to keep your business and bodily functions working properly then you must respond to the following consulting questions from your top 7 clients. For insurance reasons provide only your FINAL answers in the most LEGIBLE handwriting possible.

You have 4 hours until you want to get back to enjoying retirement and stop risking vital organs on consulting questions. We are getting too old for this.

Email 1 : _____/ 40

Email 2 : _____/ 40

Email 3 : _____/ 60

Email 4 : _____/ 50

Email 5 : _____/ 40

Email 6 : _____/ 25

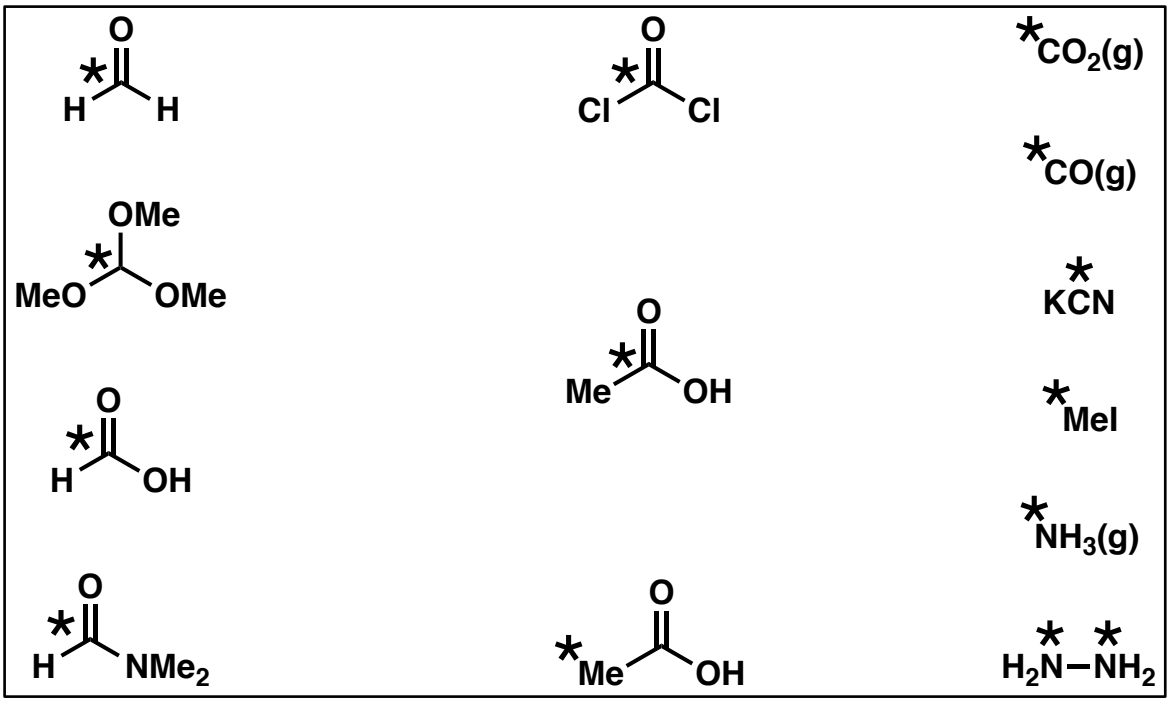
Email 7 : _____/ 30

Text message BONUS QUESTION :_____/ 30

TOTAL : _____/ 285 + 30

NAME_____ 4-Digit ID:_____

ATTENTION: For any radiolabeling questions, the only available radiolabeled starting materials are show here.



NAME_____ **4-Digit ID:**_____

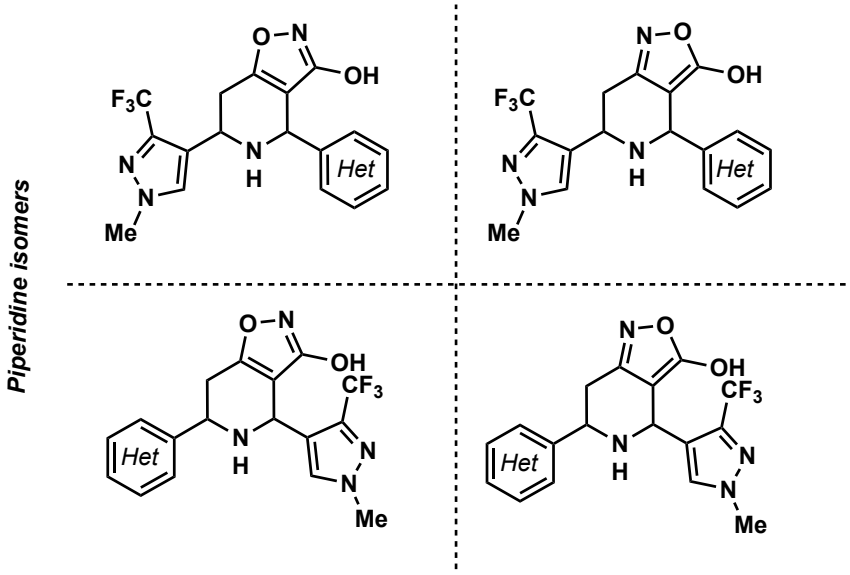
Email #1: Dear Consulting Corner,

We are in the early stages of developing a FUN-8675309 agonist. We are unsure about what the final structure ought to be but we know that an isoxazole is important on the northern part of the molecule and an N-methyl trifluoromethyl pyrazole is critical on either the southwest or southeastern portion of the molecule. We also need to be able to perform SAR with heteroaromatic subsitutents on the central piperidine ring. Unfortunately, **ALL CROSS COUPLINGS TO INSTALL THE PYRAZOLE AND HET-Ar HAVE FAILED.** Please help us design a flexible route to the following compounds. **Propose a FORWARD MED CHEM SYNTHESIS with reagents to each of the following molecules that allows for various Het substituents. No cross coupling allowed. (40 POINTS, 10 EACH).**

Regards,
Rezipf Therapuetics

Isoxazole isomers

Piperidine isomers



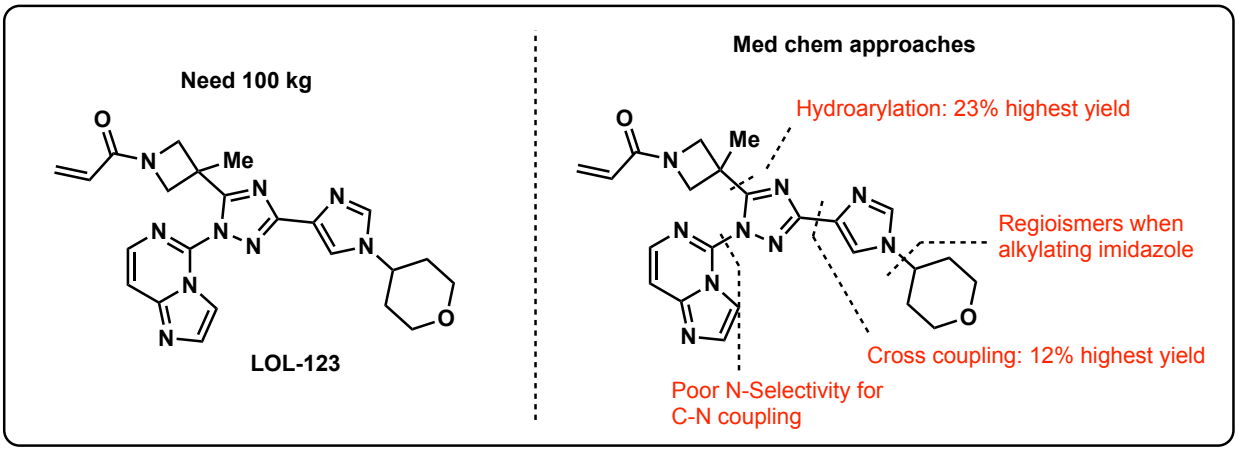
NAME_____ **4-Digit ID:_____**

NAME_____ 4-Digit ID:_____

Email #2: Dear Consulting Corner,

We are looking to scale up the synthesis of LOL-123, an irreversible inhibitor of old joke recognition. The medicinal chemistry route, while allowing interrogation of the biological hypotheses, is hardly scalable. We have highlighted the shortcomings in the box below. **We need a process route that does not rely on the tactics/strategies used in the medicinal chemistry campaign as this chemistry is NOT FIT FOR PROCESS. Provide a process friendly forward route with reagents. NO CROSS COUPLING WILL WORK (40 points).**

Kind regards,
Smistol Qyers Mibb



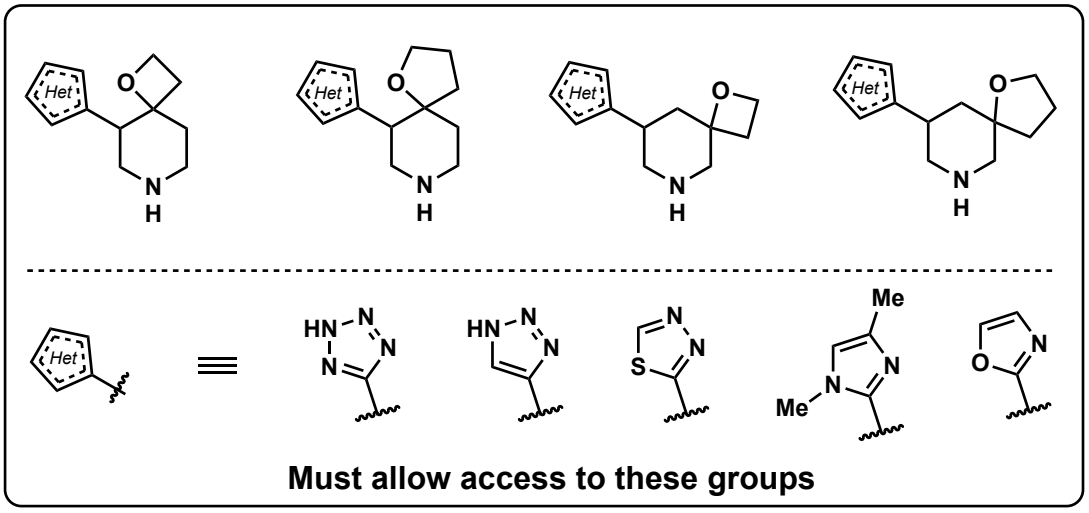
NAME_____ **4-Digit ID:_____**

NAME_____ 4-Digit ID:_____

Email #3: Dear Consulting Corner,

Help! Urgent! We have a deadline for making the following compounds coming in a few weeks. Unfortunately, we only took 2019 heterocycles and only know how to make unsaturated systems. **We need a route to ALL of the following spirocyclic compounds that allows for the installation of ALL of the following 5-membered heterocycles at the same position on the piperidine core**. **Provide FORWARD routes with reagents to each of the following compounds. Your route must include the synthesis of all of the heterocycles in the box. (60 points, 15 points each).**

Warm and kind regards,
X Æ A-12
Chem-X



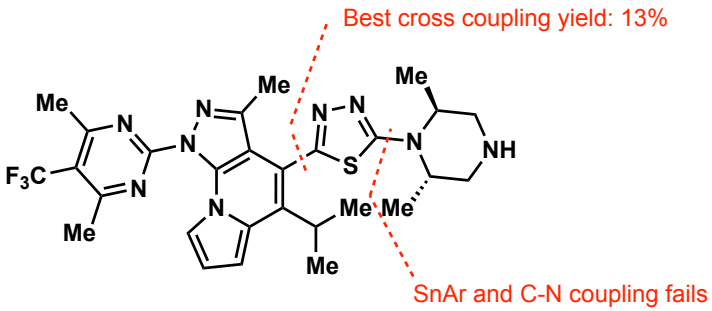
NAME_____ **4-Digit ID:_____**

NAME_____ **4-Digit ID:**_____

Email #4: Dear Consulting Corner,

The following structure has been identified as a promising lead. We need to scale this up for a Phase 1 study. In this case, cross coupling strategies are acceptable. We have a very good catalysis team that can work with us to develop good coupling reactions. That being said, the team has concluded that cross coupling **CANNOT** be used to install the piperazine or the thiadiazole portions of the molecule. SnAr also fails with the piperazine. **Metal mediated couplings are acceptable on other portions of the molecule. Propose a FORWARD SYNTHESIS with reagents that does not cross couple the piperazine and the thiadiazole (50 points).**

Warmer and kinder regards,
Maydup Neyem



NAME_____ **4-Digit ID:_____**

NAME_____ 4-Digit ID:_____

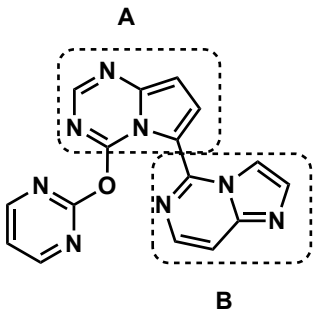
Email #5: Dear Consulting Corner

We have recently been interested in a new field of therapeutics called "drug-drug conjugates." We have identified this Frankenstein of a molecule as being a good conjugate of several different reported pharmacophores. In order to make it a true drug-drug conjugate, we need to link it to another equally efficacious molecule. We also need to be able to study ADME through radio labelling a part of the molecule that does NOT also have the linker. **Propose a structure that places a linker anywhere on either A or B. Additionally your structure must include a ^{14}C label at any carbon in the ring you did not choose. THEN, propose a forward route with reagents to that structure (40 points).**

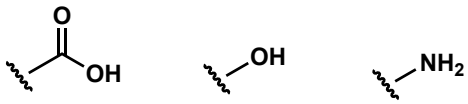
(Example: propose a structure with an acid somewhere on B and a carbon label somewhere on A).

Warmest and kindest regards,
Bob

Proposed Structure



Appropriate Linkers

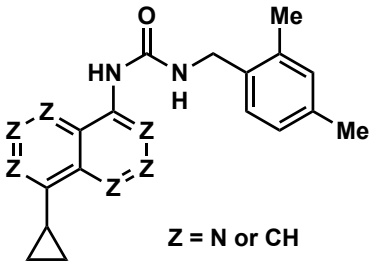


NAME_____ **4-Digit ID:_____**

NAME_____ 4-Digit ID:_____

Email #6: Dear Consulting Corner,

We have disclosed the following Markush structure in a recent patent. Our boss told us that we have to reach out to you for some sort of consulting, but our lawyers really don't want us to do so. So just take a look at this Markush structure and if you ever get bored, just make up a compound that fits it and propose a retro. **Propose a structure where at least 3 of the Z's are nitrogen. Then proposed a RETROSYNTHESIS of that structure (25 points).**



3 Z's MUST BE NITROGEN

Proposed Structure

The categorical most warm and kind regards,
Gaul Soodman

NAME_____ **4-Digit ID:_____**

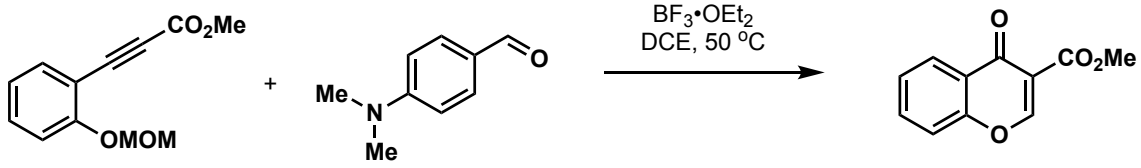
NAME_____ 4-Digit ID:_____

Email #7: Dear Consulting Corner,

We came across these interesting reactions. What is going on here? **Propose a reasonable mechanism for the following reaction (30 points, 15 each).**

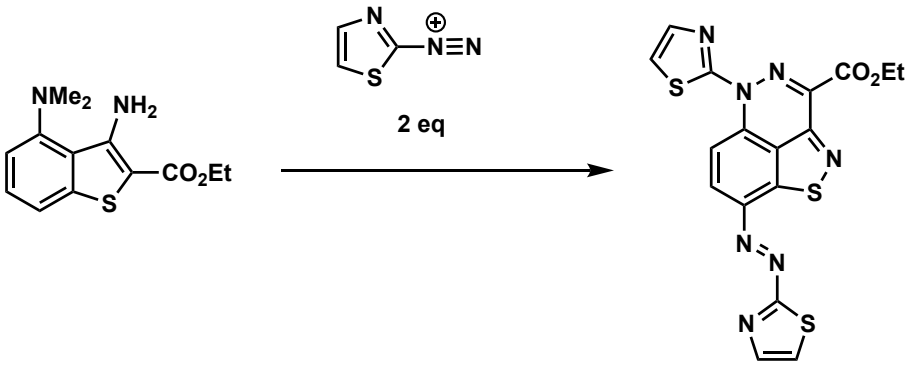
-$Scifinder^{n^n}$

A)



NAME_____ 4-Digit ID:_____

B)



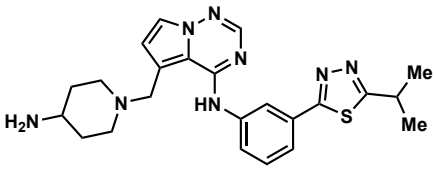
NAME_____ 4-Digit ID:_____

BONUS Text Message:

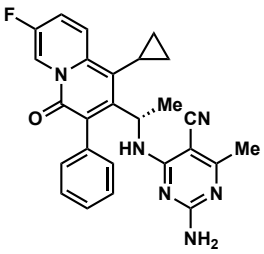
Hey consulting corner! What's up! I don't know if you remember me from when we took heterocycles together back in 2025 but I remember you and all the great answers you gave in class. Hey if it's not too much to ask, can you help me fill in these blank spots in my notes from all those years ago? How were these made again?

Propose a RETROSYNTHESIS of each molecule (30 points total, 5 points each).

A)

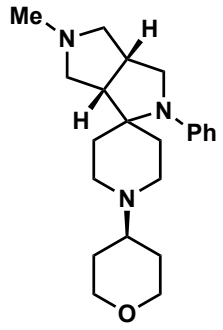


B)

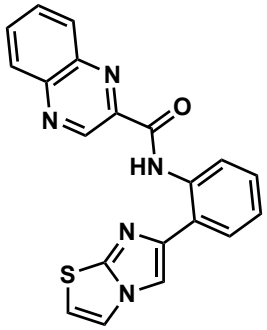


NAME_____ 4-Digit ID:_____

C)

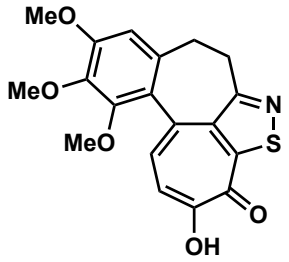


D)



NAME_____ 4-Digit ID:_____

E)



F)

