

Medicinal Chemistry

CHEM 515

Final Exam

Tuesday, May 2 and Thursday, May 4, 2023

Name: _____

Read each question carefully before answering. Be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

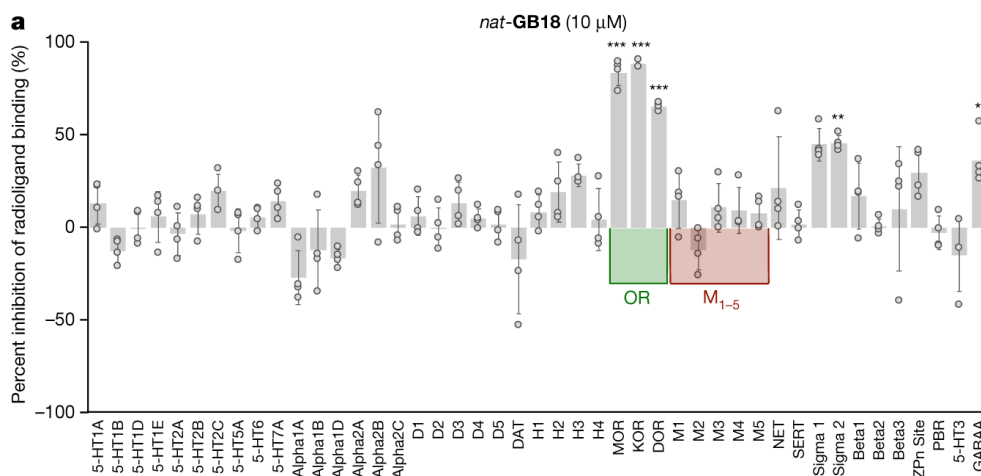
In medicinal chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Don't forget to include formal charges when appropriate.

The exam is worth a total of 150 points. It has 13 fifteen-point questions on the exam and you need to answer at least 10 of the 13 questions. You can answer 11, 12 or 13 questions and I will only count your 10 answers with the most points. *Bonus points may be awarded for correct answers on your lower performing question.*

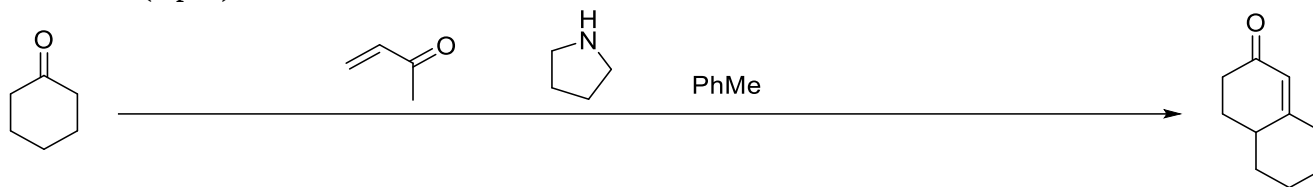
1. “Synthesis and target annotation of the alkaloid GB18”, *Nature* 2022, Vol. 606, pp. 917–921. S. Woo and R. A. Shenvi (*Angelina and Shiraz, February 28*)

a) We saw several examples of alkaloid molecules discussed over the course of the semester. What are alkaloids and why are they important in medicinal chemistry? (3 pts.)

b) Figure 4a from the article is reproduced here. What were the researchers doing with GB18 in this assay and what did they discover? Your answer should address the items listed along the x-axis of the graph, what the y-axis is measuring and how that was accomplished. (4 pts.)



c) Show the mechanism of the following reaction, a Robinson annulation, which was a key step in the synthesis of GB-18. (8 pts.)



2. “Diversity-oriented synthesis yields novel multistage antimalarial inhibitors”. *Nature* 2016, Vol. 538, pp. 344-349. S. L. Schreiber et al. (*Hannah and Lana, March 16*)

a) What is diversity-oriented synthesis and how was it used in the research reported to achieve a new antimalarial drug? (3 pts.)

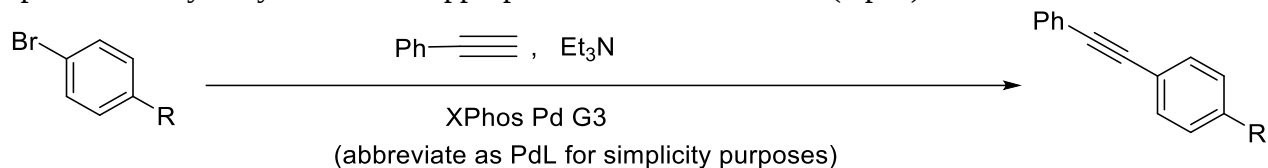
b) Describe the anti-malarial mechanism of action of BRD7929 by answering the following four questions. One sentence should suffice for each.(5 pts.)

(i) What was the parasite target of the bicyclic azetidine drug BRD7929 and what does that target protein normally do?

(ii) Where does the BRD7929 bind on the target?

(iii) How was this report of BRD7929 binding to the parasite target a seminal discovery?

c) Show the mechanism of the Heck alkynylation reaction used in the synthesis of BRD7929. Be sure to label each step of the catalytic cycle with the appropriate mechanistic name. (7 pts.)

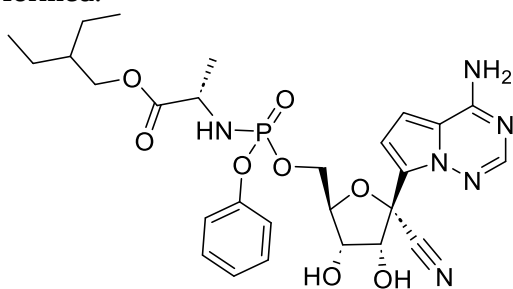


3. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016, volume 531, pp. 381–385. Travis K. Warren, Sina Bavari, et al. (Jacqueline and Rosie, March 21)

a) Remdesivir (structure below) isn't the active therapeutic agent. (6 pts.)

(i) Show the key intermediate that forms on the path to the active therapeutic agent and describe the process that occurs to form the intermediate. You do NOT need to show the curved arrow electron flow mechanism, such as required on the mid-term exam.

(ii) Show the structure of the active therapeutic agent that forms from remdesivir. Briefly describe how it is formed.



Remdesivir (GS-5734)

b) The process by which the active nucleoside found in remdesivir is delivered to the body is a common drug design strategy. (5 pts.)

(i) What's the name of this general strategy used in drug design? _____

(ii) What's the name of the technology or substituents added to remdesivir that enables the delivery of the nucleoside? Circle this group on the structure of remdesivir shown above and write the name on the line below.

(iii) In the specific case of remdesivir, what is this technology overcoming that normally undermines the delivery of the active nucleoside in remdesivir?

c) What is the actual mechanism of action of remdesivir once the active agent is delivered? Be as specific as possible. (4 pts.)

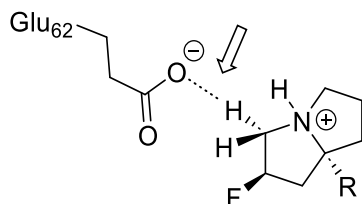
4. “Identification of MRTX1133, a Noncovalent, Potent, and Selective KRASG12D Inhibitor”. *J. Med. Chem.* **2022**, Vol. **65**, pp. 3123–3133. X. Wang, M. A. Marx et al. (Christina and Diana, March 23)

a) KRAS and cancer. (4 pts.)

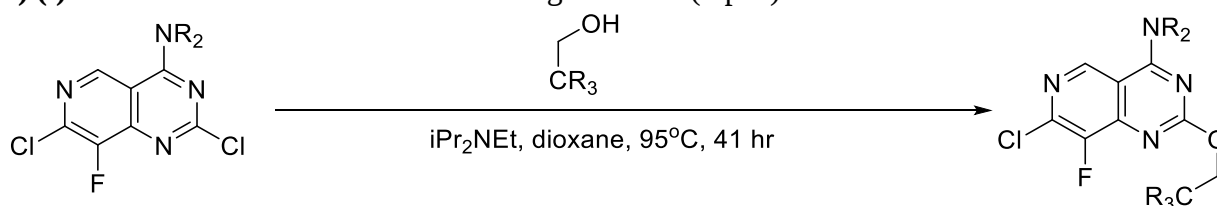
(i) Why is KRAS an important target in cancer treatment?

(ii) What is the natural ligand or substrate for KRAS and what challenges are faced in trying to compete with that substrate or ligand?

b) In the article, the researchers report the intermolecular interaction below, between the protonated pyrrolizidine ring of the drug and the KRAS protein (see arrow). Provide the name of the intermolecular force and explain the basis for the interaction that is occurring. (3 pts.)



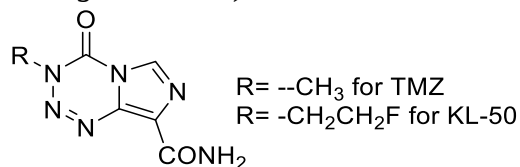
c) (i) Show the mechanism of the following reaction. (6 pts.)



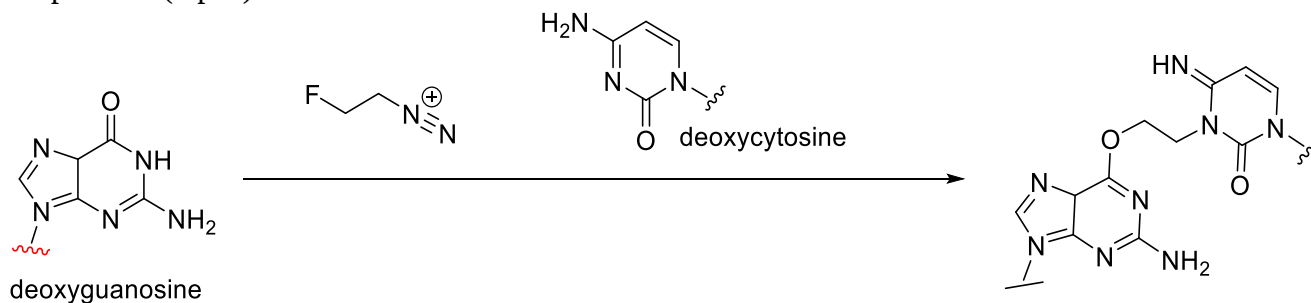
(ii) Suggest an explanation for the regioselectivity in the reaction at only one of the two C-Cl bonds. (2 pts.)

5. “Mechanism-based design of agents that selectively target drug-resistant glioma”. Science 2022, Vol. 377, pp. 502-511. R. Bindra, S. Herzon et al. (Chloe and Greg, March 30)

As you may recall, the primary focus of the article was the development of KL-50 as an improved version of temozolomide (TMZ) for the treatment of glioblastoma's that are O⁶-methylguanine methyl transferase deficient (MGMT-) tumors.

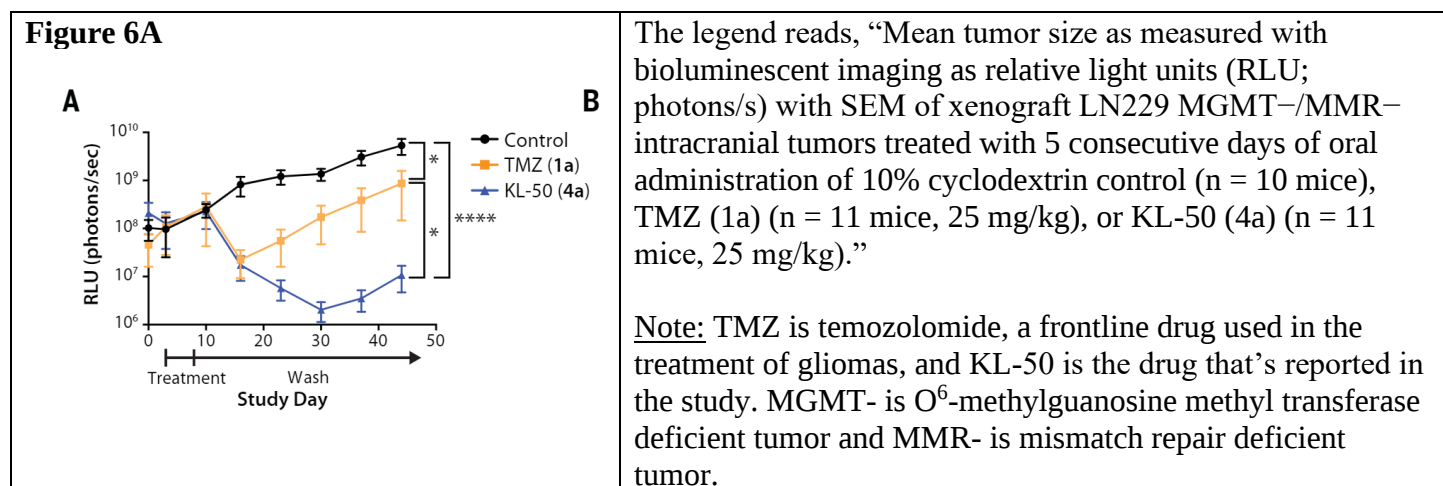


a) Show the curved arrow electron flow mechanism for the reaction of KL-50's 2-fluoroethyl diazonium ion, liberated after hydrolysis and decarboxylation of KL-50, in forming interstrand cross-links (ICL's) between a guanosine and a cytosine as described in the article. You may assume acids and bases are available to facilitate the process. (8 pts.)



b) What is the reaction of temozolomide with DNA, which serves as a treatment for glioblastoma? (2 pts.)

c) **Figure 6A** from the article is reproduced below. What does the figure tell us about TMZ and KL-50? Be sure to address why the study was done specifically on an MGMT-/MMR- intracranial tumor. (5 pts.)

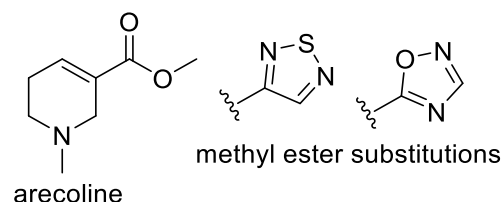


6. “Classics in Chemical Neuroscience: Xanomeline” ACS Chemical Neuroscience, 2017, Vol. 8, pp. 435-443. Craig W. Lindsley et al. (*Yael and Kalyn, April 4*)

a) What is the mechanism of action of xanomeline and how is this thought to benefit treatment of Alzheimer’s disease and schizophrenia? (3 pts.)

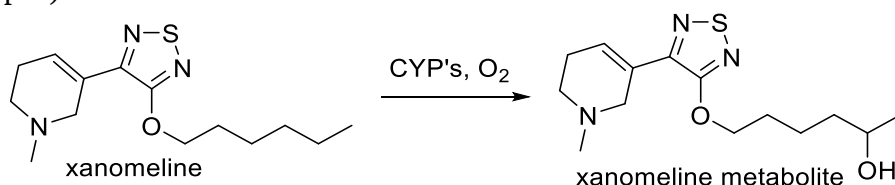
b) Arecoline was the natural product inspiration for xanomeline. Two methyl ester substitutions made to the arecoline lead structure are shown.

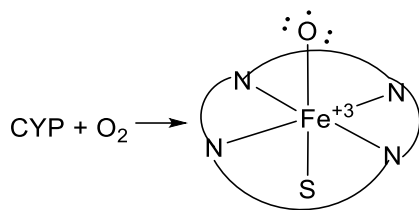
(i) In medicinal chemistry, what is the term used for these types of changes to a particular functional group? (2 pts.)



(ii) Name two benefits that might be realized by changing the methyl ester to either of the heteroaromatic rings shown. (2 pts.)

c) One of xanomeline’s metabolic products as reported in the article is shown below. Draw the mechanism of cytochrome P-450’s (CYP’s) reaction with xanomeline to cause the metabolite formation. You are encouraged to abbreviate xanomeline’s structure to only show the relevant alkyl chain piece in drawing your mechanism. (5 pts.)



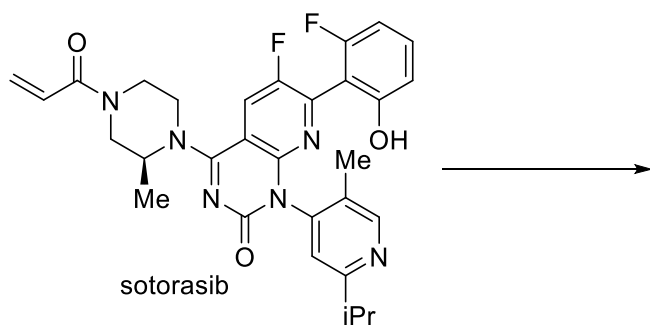


d) As represented in the metabolic reaction shown in part c, what is the body's general goal in conducting metabolic reactions with drugs? How is this occurring with the xanomeline metabolite? (3 pts.)

7. "Discovery of a Covalent Inhibitor of KRASG12C (AMG 510) for the Treatment of Solid Tumors"
J. Med. Chem. 2020, Vol. 63, pp. 52–65, B. A. Lanman et al. (Jim, April 6)

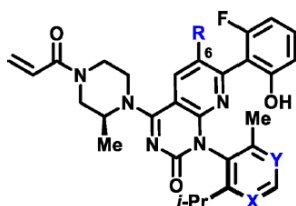
a) The researchers chose to use a covalent inhibitor against KRASG12C. Why did they choose a covalent inhibitor while the researchers inhibiting KRASG12D chose a non-covalent inhibitor? (3 pts.)

b) Show the key covalent reaction between KRASG12C and the drug, sotorasib. (5 pts.)



c) Table 5 from the article is shown below. Answer the following questions based on your understanding of the parameters shown and the associated structural properties.

Table 5. Biopharmaceutical Optimization of (R)-24 Significantly Enhances Bioavailability



compd	R	X	Y	log <i>D</i> (pH 7.4) ^a PSA (Å ²) ^a	p-ERK IC ₅₀ MIA PaCa-2 (μM) ^b	viability IC ₅₀ MIA A549 (μM) ^c	MulH hep CL _{int} (μL/min)/10 ⁶ cells	MDCK permeability A-B (μcm/s)	HT solubility (μM, PBS/ FaSSIF/ 0.01 N HCl)	mouse CL (L h ⁻¹ kg ⁻¹) V _{ss} (L/kg) t _{1/2} (h) F (%) ^d
(R)-24	Cl	CH	CH	3.6 89	0.028	0.002 11.9	102 30	15	12 204 9	1.4 0.8 0.9 4–12 ^e
(R)-34	Cl	N	CH	2.4 102	0.011	0.001 34.1	75 11	1	46 381 500	3.9 1.4 0.4 < 0.5
(S)-35 ^f	Cl	CH	N	2.4 102	0.065	0.003 32.4	96 5	2	335 435 534	1.4 0.4 0.4 < 0.5
(R)-36	Cl	N	N	1.7 115	0.038	0.003 >50	139 5	1	499 500 421	3.5 1.1 0.3 < 0.5
(R)-37	F	CH	CH	3.0 89	0.090	0.011 11.6	111 37	22	41 164 24	2.0 1.0 0.5 < 0.5
(R)-38	F	N	CH	2.0 102	0.068	0.005 36.5	36 9	6	423 492 499	1.6 0.7 0.5 22–40
(S)-39 ^f	F	CH	N	2.0 102	0.142	0.016 49.1	100 9	1	426 477 484	3.7 1.1 0.3 15
(R)-40	F	N	N	1.2 115	0.128	0.009 >50	65 5	<1	495 500 500	4.7 1.7 0.3 10

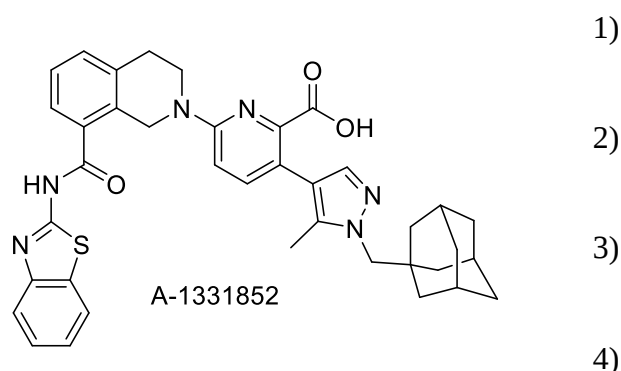
^alog *D* (pH 7.4) and PSA (polar surface area) calculated using ACD/Percepta (ACD/Labs, Toronto, Canada). ^bp-ERK1/2 immunoassay (MSD), 2 h incubation. ^cViability assessed at 72 h by CellTiter-Glo luminescence assay (Promega) in MIA PaCa-2 (p.G12C) and A549 (p.G12S) cell lines. All data represent *n* ≥ 2. ^div/po dosing in BALB/c mice (vehicle: iv, 1 mg/kg, DMSO; po, 10 mg/kg, 1% Tween 80, 2% HPMC, 97% water). ^eCrystalline polymorphs. ^fPresence of the pyridyl nitrogen changes IUPAC substituent priority for naming purposes; the isopropyl substituent remains oriented toward the cryptic pocket, as in other analogues.

(i) What does log *D* mean and what does the value say about the difference between compound **24** and **38**? (2 pts.)

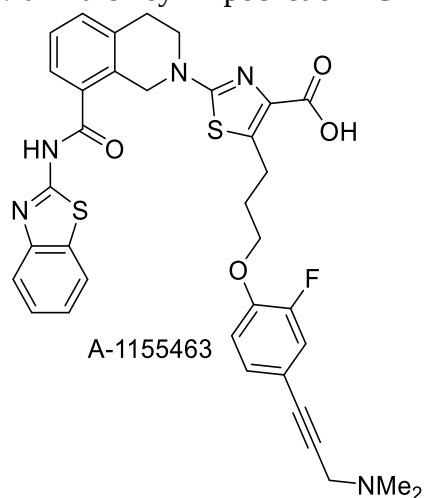
(ii) Cite two other pharmacokinetic (PK) parameters identified in Table 5 that made compound **38** a better drug candidate than **24**? Briefly explain why the parameters you cite are better for drug action. (5 pts.)

8. “Discovery of A-1331852, a First-in-Class, Potent, and Orally-Bioavailable BCL-XL Inhibitor”, ACS Med. Chem. Lett. 2020, Vol. 11, pp. 1829–1836. A. S. Judd et al. (*Lucy and Ebrar, April 11*)

a) The final drug candidate’s structure is shown below. Identify four key bond disconnections that were used to construct this molecule in an efficient manner with roughly equal size pieces. Describe the type of reaction that was used for each of your bond disconnections. (8 pts.)



b) The researchers report in the abstract, “Key design elements included rigidification of the A-1155463 pharmacophore and introduction of sp^3 -rich moieties capable of generating highly productive interactions within the key P4 pocket of BCL-XL.” For reference, the structure of A-1155463 is shown below.



(i) Circle the part of A-1155463 that was rigidified. What benefit can generally be achieved in the “rigidification” of a drug structure? What are the dangers of rigidifying a structure? Your answer should include consideration of the thermodynamic parameters impacted. (4 pts.)

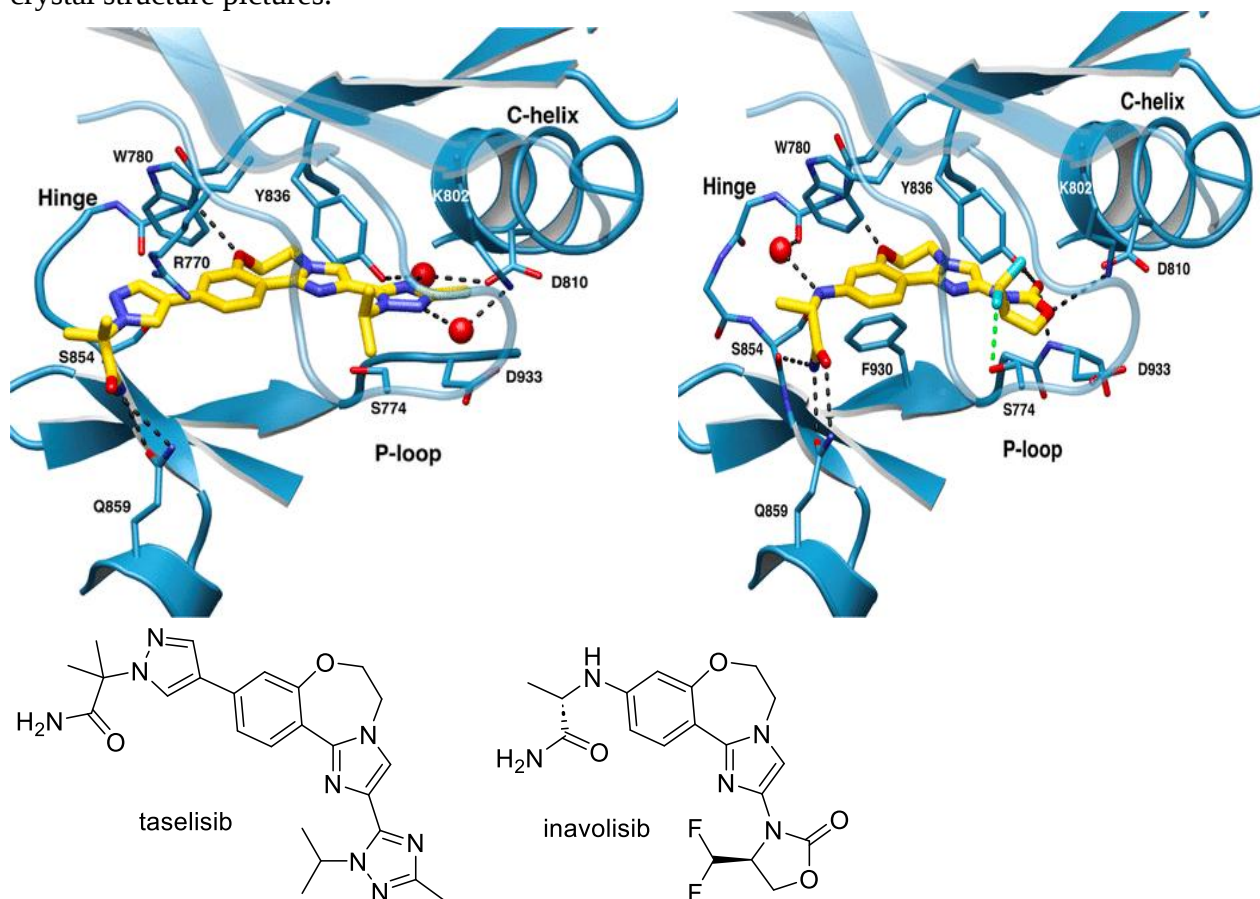
(ii) On A-1331852 shown in part a, circle the part of A-1331852 that was the “introduction of sp^3 -rich moieties capable of generating highly productive interactions within the key P4 pocket”. What types of intermolecular forces were formed with these interactions? (3 pts.)

9. “Discovery of GDC-0077 (Inavolisib), a Highly Selective Inhibitor and Degradator of Mutant PI3K α ”

J. Med. Chem. 2022, 65, pp. 16589–16621, E. J. Hanan et al. (Jenna and Yui, April 13)

a) What does PI3K α (phosphatidylinositol 3-kinase alpha) do in cells, what co-factor does it use and why is it a target of anti-cancer research? (4 pts.)

b) The crystal structures of tasisib (left), the initial drug lead, and inavolisib (right), the optimized PI3K α inhibitor developed and described in the article are shown below. The two drug structures are shown below their crystal structure pictures.

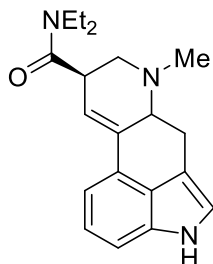


Identify three differences between tasisib and inavolisib binding in the PI3K α protein and briefly describe the differences. Identify the interaction that is considered critical to the (300-fold) isoform selectivity (PI3K α versus PI3K δ). (8 pts.)

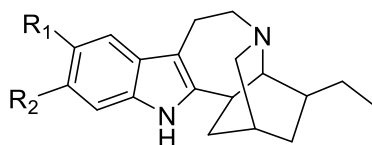
c) Both drugs are competitive with a reactant or substrate of the PI3K α catalytic reaction. What is that component? (3 pts.)

10. “A non-hallucinogenic psychedelic analogue with therapeutic potential”, Nature 2021, Vol. 589, pp. 474–479, D. E. Olson et al. (Charli and Reece, April 18)

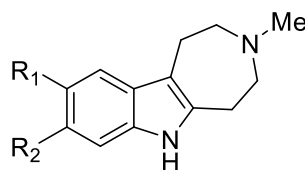
a) Identify the common pharmacophore for the following neuroactive agents by circling it. (3 pts.)



lysergic acid diethylamide (LSD)

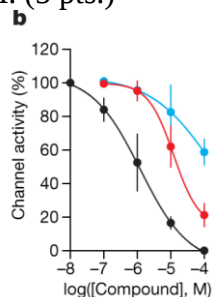


ibogaine



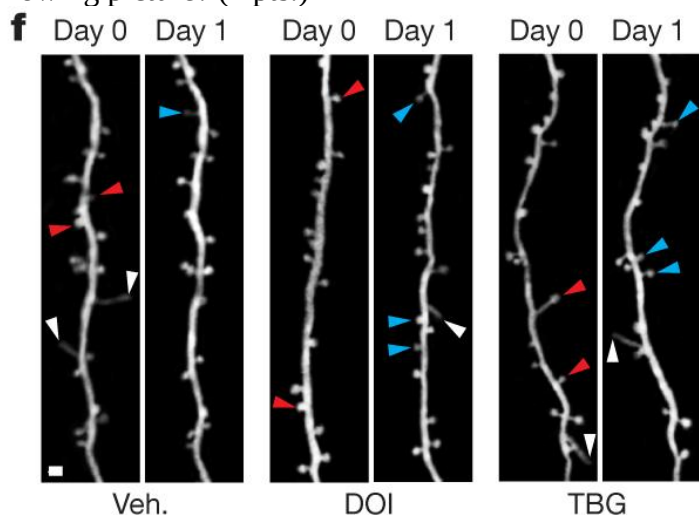
tabernanthalog (TBG)

b) Figure 2b is shown below. Why were the researchers concerned with hERG channels and which compound showed the least amount of inhibition? Approximate the IC₅₀ values of each to the nearest tens digit in molarity, M. (5 pts.)



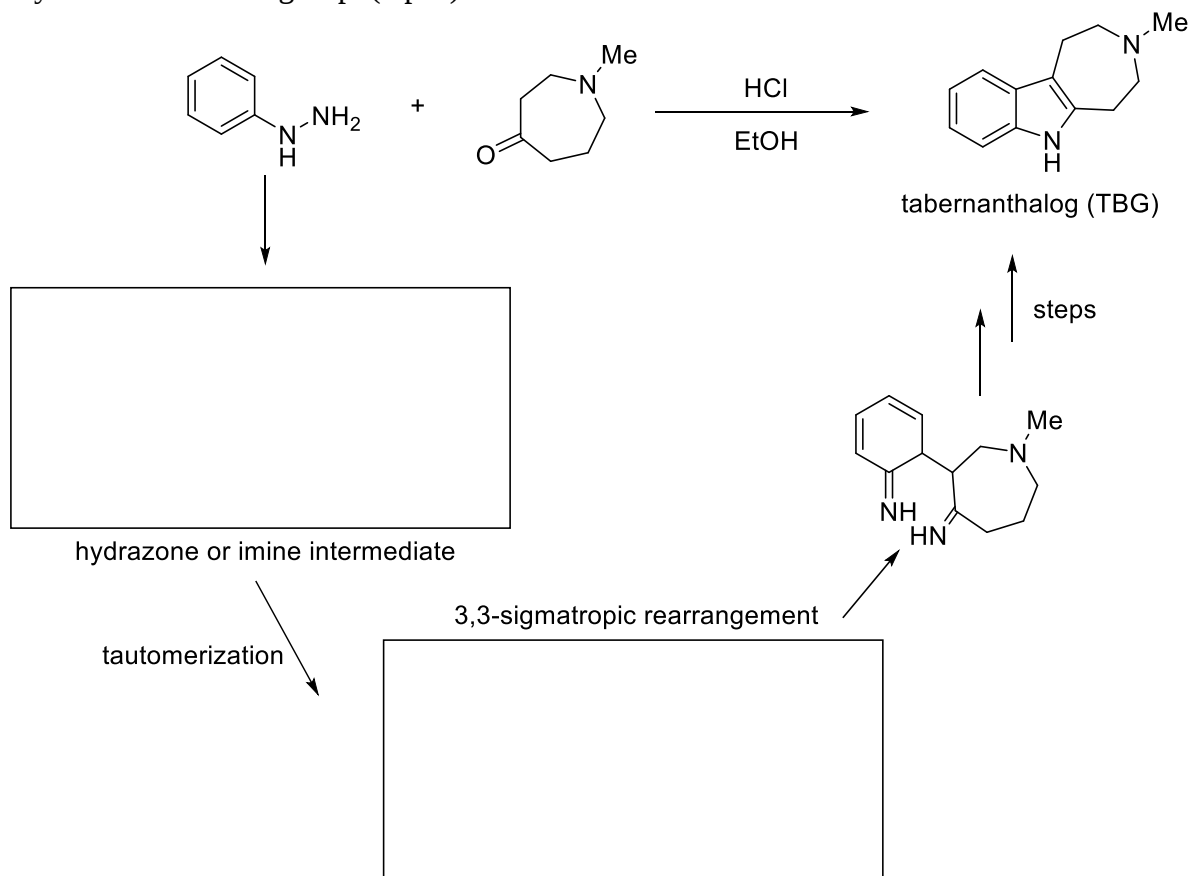
Legend text: Inhibition of hERG channels expressed in HEK293 cells. Data are mean $\pm$ s.d. IBO, ibogaine (black); IBG, ibogainalog (red); TBG, tabernanthalog (blue)

c) Figure 3f is shown below. What important outcome did the researchers argue was demonstrated in the following picture? (2 pts.)



Representative images of the same dendritic segments from the mouse primary sensory cortex before (day 0) and after (day 1) treatment. Blue, red and white arrowheads represent newly formed spines, eliminated spines and filopodia, respectively. 2,5-Dimethoxy-4-iodoamphetamine (DOI) and TBG (tabernanthalog).

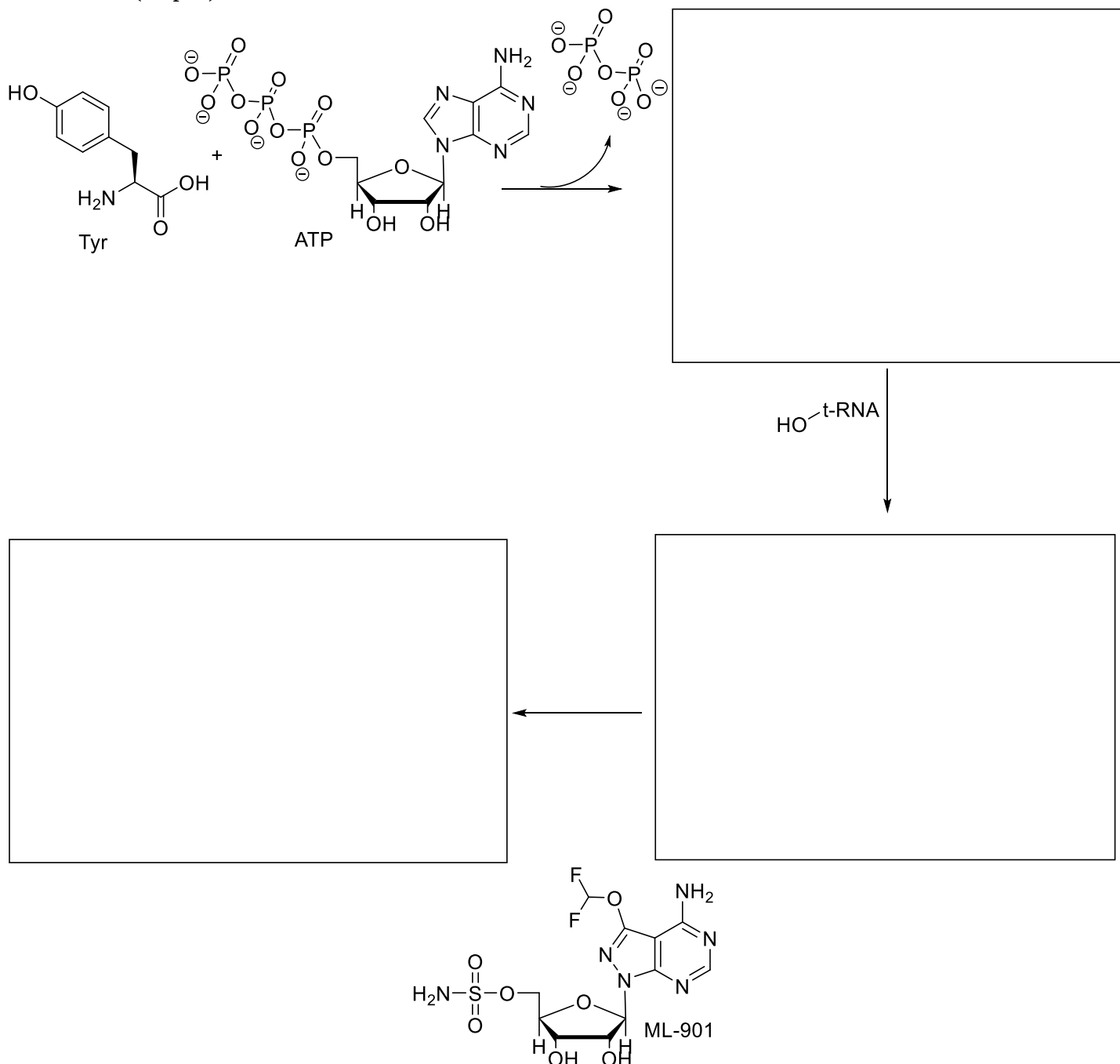
d) Shown below is the key reaction to form the TBG drug structure. Complete the sequence by showing the intermediates and providing the curved electron flow arrows for the 3,3-sigmatropic rearrangement that is the key C-C bond forming step. (5 pts.)



11. “Reaction hijacking of tyrosine tRNA synthetase as a new whole-of-life-cycle antimalarial strategy”

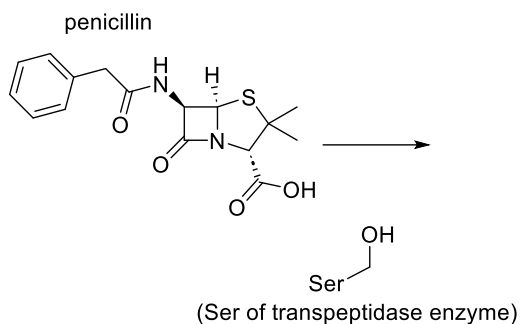
Science 2022, Vol 376, pp. 1074-1079, A. E. Gould, L. Tilley et al. (Kim, April 25)

Show the mechanism of the reaction hijacking process that is the mechanism of action for ML-901. Provide the key intermediates and side products in the boxes provided. Show all curved electron flow arrows for the steps in the reaction. (15 pts.)



12. Antibiotics lecture: Penicillin and iboxamycin. “A synthetic antibiotic class overcoming bacterial multidrug resistance”, Nature 2021, Vol. 599, pp. 507–512. A. G. Myers et al. (Dr. Mal, March 2)

a) Shown below is the structure of penicillin which has served as an iconic antibiotic for the treatment of a variety of bacterial infections for nearly a century. Show the reaction of penicillin with the bacterial enzyme, transpeptidase, which utilizes a serine amino acid to catalyze its reaction. Be sure to draw all important **intermediates** in the reaction. You may use general acids and bases to assist in your mechanism. (5 pts.)

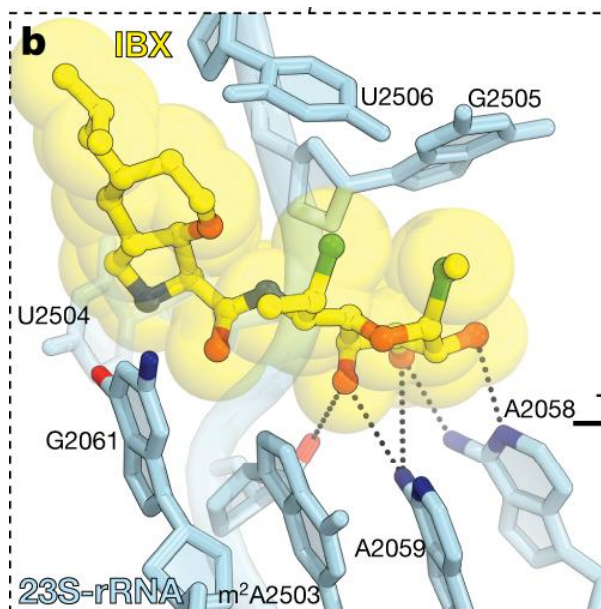
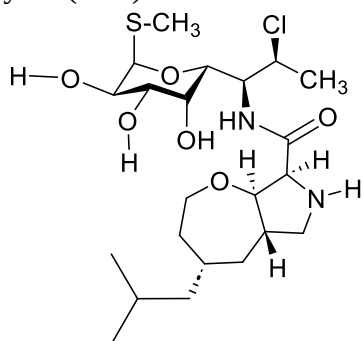


b) Briefly describe how the reaction you've shown in part a relates to the antibacterial activity of penicillin. Your answer should describe what happens to the bacteria after the reaction shown (with all the gory details). (2.5 pts.)

c) Iboxamycin's structure is shown below and its interaction with bacteria is illustrated in the portion of X-ray crystal structure to the right.

(i) Where is iboxamycin binding and how does this exert an antibacterial effect? (2.5 pts.)

iboxamycin (IBX)

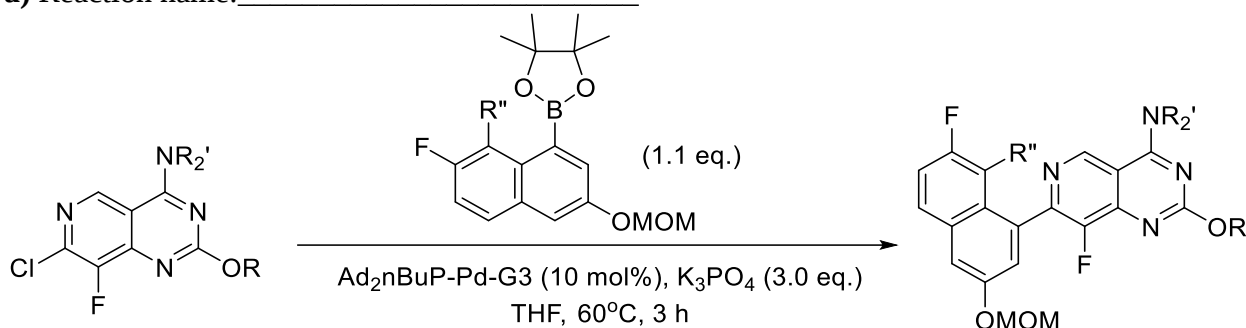


(ii) Annotate the structure of iboxamycin above, by identifying the three different intermolecular forces (IMF's) quoted below from the article. Using the crystal structure information and the information in the quotes, you should list the bacteria target groups (e.g. G2505) involved in the IMF you identify. You should show an appropriate fragment of the bacteria target structure that is involved in the IMF. (5 pts.)

- 1) "...a network of hydrogen bonds anchors the amino-octose moiety of IBX to NPET nucleotides..."
- 2) "...the cationic aminoacyl residue of IBX occupies a hydrophilic pocket formed by the PTC residues G2061 and U2504, displacing a divalent magnesium ion..."
- 3) "...presents the 7'-isobutyl group for interaction with the A-site cleft formed by....residues A2451 and C2452"

13. Organometallic mechanisms. Choose one of the two reactions below and show the mechanism of the catalytic cycle. Identify all the steps by the type of organometallic mechanistic process. You are encouraged to abbreviate structures but be sure to show the key components. Provide the name of the reaction that you choose for demonstrating the catalytic cycle. (15 pts.)

a) Reaction name: _____



--OR--

b) Reaction name: _____

