Medicinal Chemistry Name:_Kelly Bleasby_____
CHEM 515
Final Exam
Tuesday, May 2 and Thursday, May 4, 2023

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.)

Alkaloids are natural products with at least one nitrogen atom, and are molecules created by plants or certain animals in nature. They often demonstrate bioactivity that can be used for therapeutic purposes or serve as a lead compound for the development of therapeutic treatments.

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.)

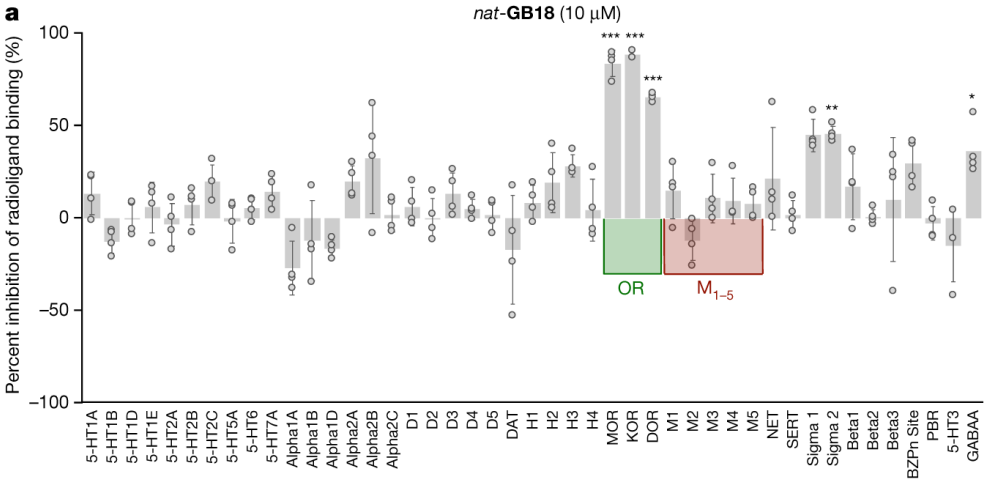
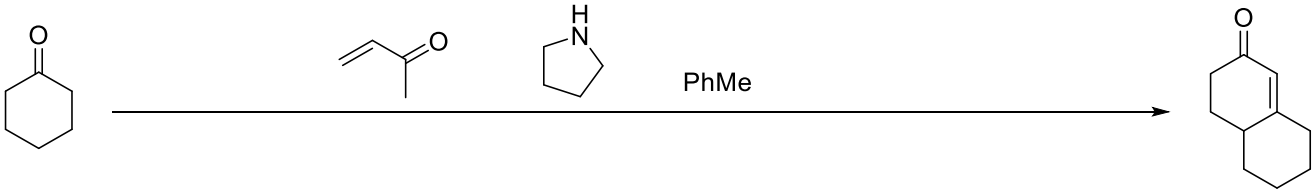
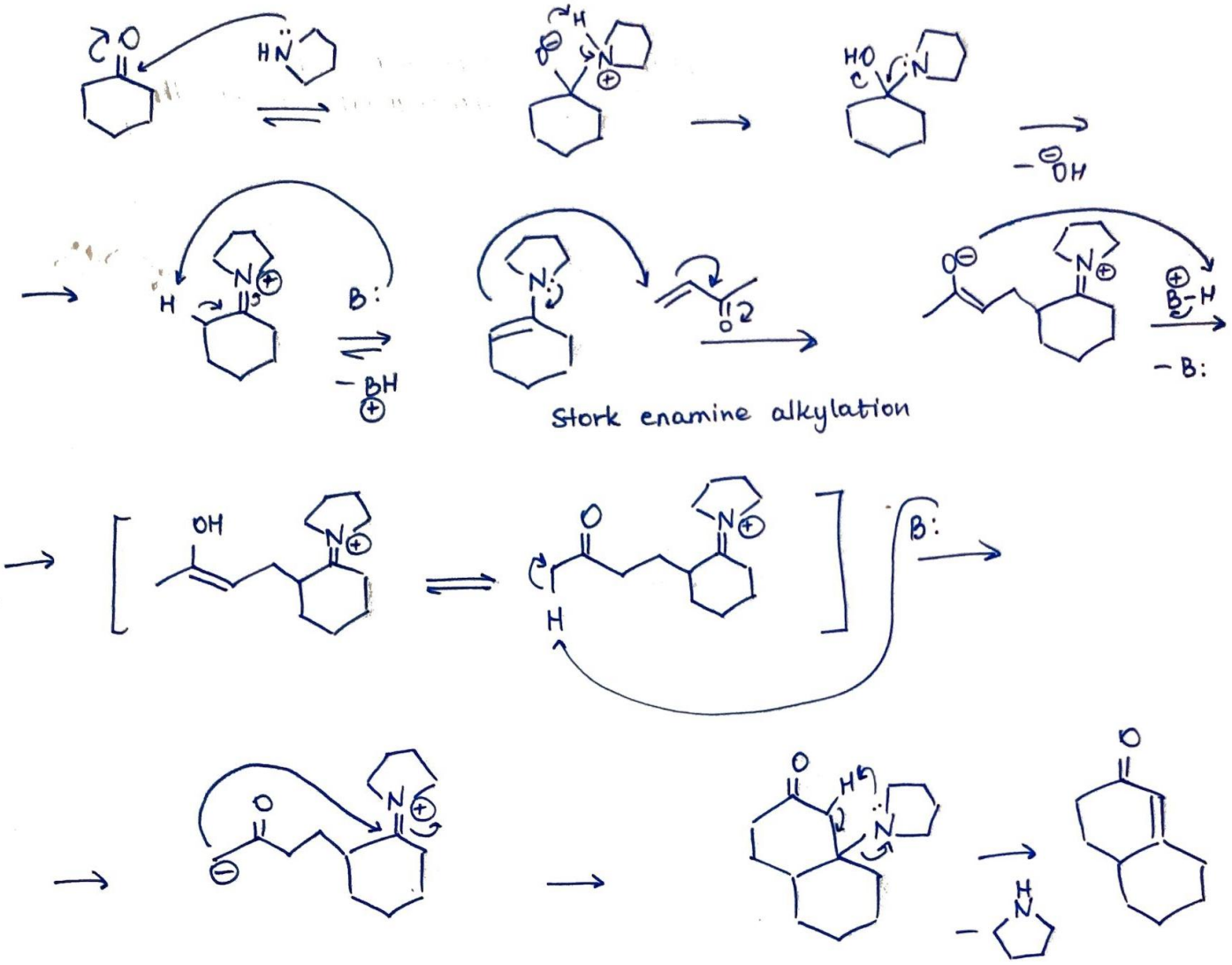


Figure 4a shows a screen done to analyze the receptors that GB-18 can bind. The different neurological receptors analyzed in the extensive screen are listed along the x-axis. The y-axis measures the impact GB-18 has on each of the different receptors relative to the binding of the natural ligand. A radioactive natural ligand was used and allowed for a quantitative assessment of GB-18 binding. The amount of radioactive ligand displaced or inhibited from binding by GB-18 determines the affinity and potency of GB-18 for each of the different receptors.

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.)

Diversity oriented synthesis is a strategy to use synthetic chemistry tools to create a large variety of structurally different and complex (natural product-like) molecules quickly with the goal of analyzing a large amount of chemical space and discovering new bioactive or therapeutically active molecules.

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?

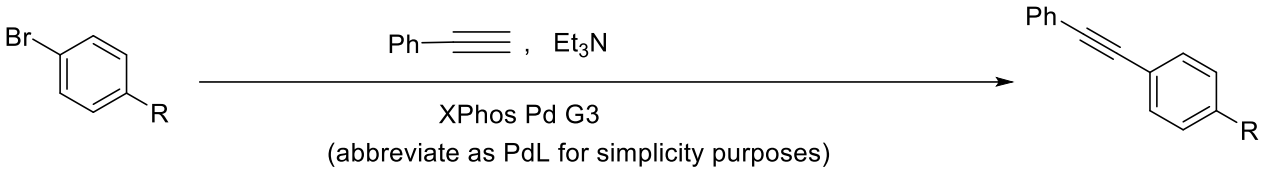
The target of BRD7929 was phenylalanine tRNA synthetase, which is responsible for the synthesis of phenylalanine-tRNA that is critical for the construction of proteins with phenylalanine amino acids.

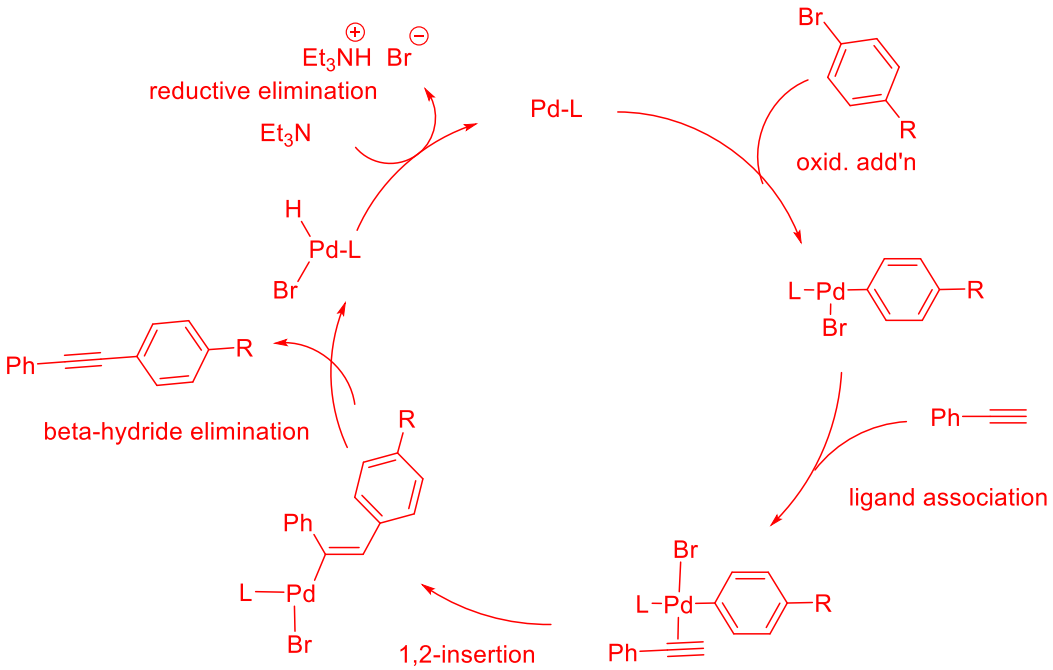
(ii) Where does the BRD7929 bind on the target?

BRD7929 binds in both the ATP pocket and the phenylalanine amino acid binding pocket of tRNA synthetase.

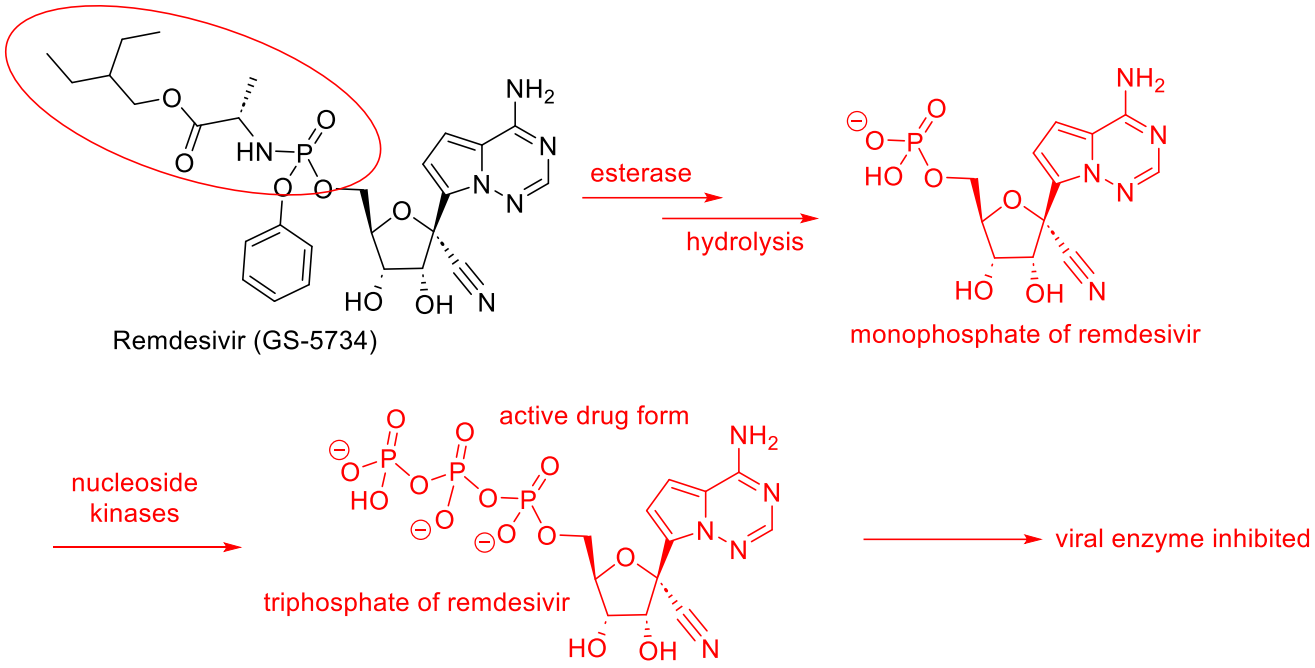
(iii) How was this report of BRD7929 binding to the parasite target a seminal discovery?
The parasite's phenylalanine tRNA synthetase was never previously recognized as a potential target, so BRD7929 was able to identify a new malaria parasite therapeutic target.

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 undergoes metabolic activation through the action of esterases, amidases and hydrolysis reactions to afford the monophosphate form of remdesivir. The monophosphate form then reacts with nucleoside kinases to become phosphorylated and form the triphosphate derivative of remdesivir, which is the active therapeutic agent.

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? ___Prodrug____

(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.

____Pro-tide_____

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

Most nucleoside drugs need to be transformed into their triphosphate form to be an active therapeutic agent. With remdesivir and many other nucleoside analogs, the conversion to the monophosphate is quite slow. The pro-drug technology, Pro-Tide, adds the nucleoside as a mono-phosphate form, which then gets phosphorylated twice more in rapid succession, thereby avoiding the slow first phosphorylation step.

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

Remdesivir is a delayed chain terminator meaning it gets incorporated by RNA polymerase into the viral RNA during replication, but the nucleoside of remdesivir eventually ends the RNA polymerization process. The termination is the result of the cyano group colliding with a serine amino acid in the polymerase enzyme.

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.)

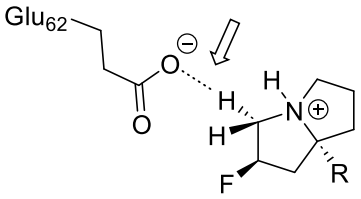
(i) Why is KRAS an important target in cancer treatment?

KRAS is the most commonly mutated protein in human cancers and is responsible for signaling cell growth and cell proliferation.

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

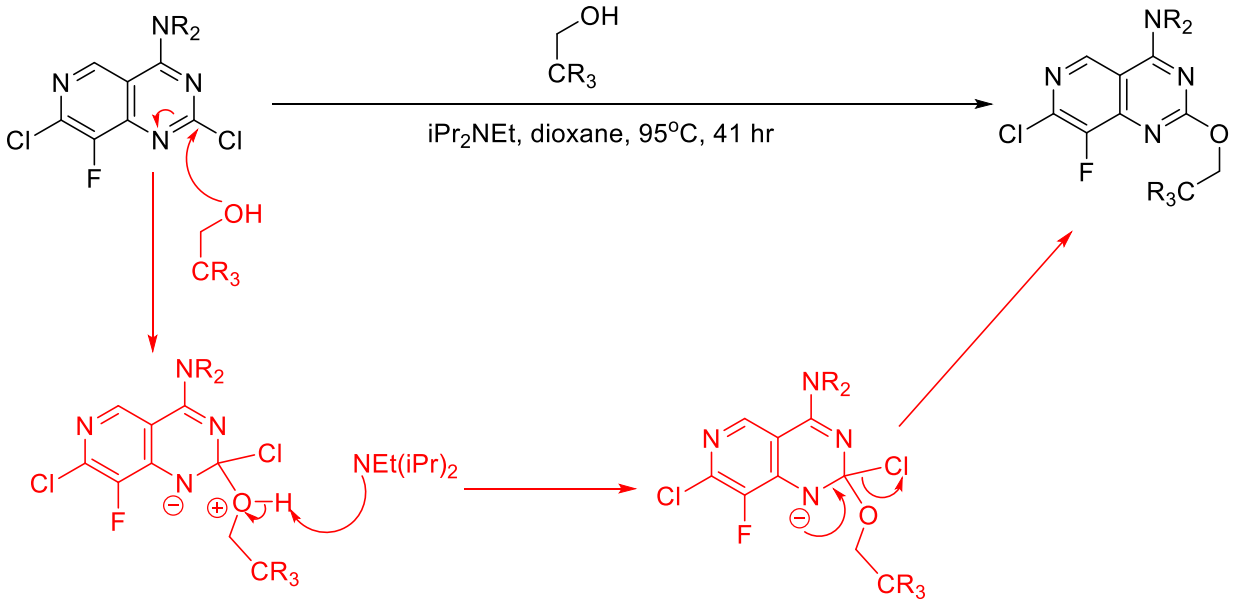
GTP and GDP are the natural ligands or substrates of KRAS and they have picomolar level affinity for KRAS making it quite challenging to make a molecule that could compete with GTP or GDP and have higher affinity for KRAS.

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.)



The interaction between the glutamate carboxylate anion oxygens and the pyrrolizidine proton is a non-classical hydrogen bond. The electron rich carboxylate anion electrons are bonding or associating with the electron deficient H on the pyrrolizidine ring. It is electron deficient due to the adjacent ammonium cation and the adjacent electronegative fluorine atom both withdrawing electron density from the carbon that holds the H. This makes the H more acidic and capable of forming an H-bond with the carboxylate anion.

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

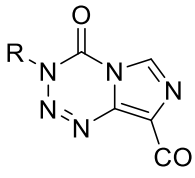


(ii) Suggest an explanation for the regioselectivity in the reaction at only one of the two C-Cl bonds. (2 pts.)

The position that reacts is more activated to nucleophilic aromatic substitution with the two electronegative nitrogens present on the same carbon of the C-Cl bond in the pyrimidine ring versus only one nitrogen atom on the C-Cl bond in the pyridine ring.

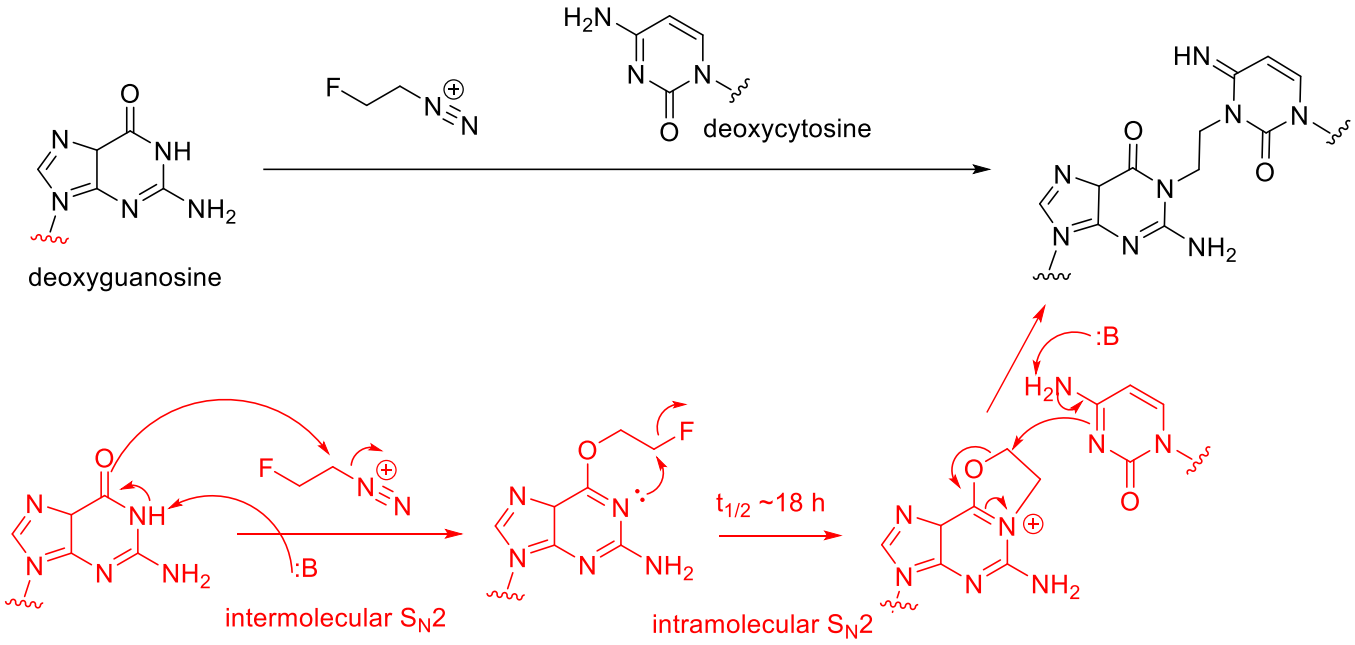
5. "Mechanism-based design of agents that selectively target drug-resistant glioma". Science 2022, Vol. 377, pp. 502-511. R. Bindra, S. Herzon et al. *(Chloe and Greg, March 30)*

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 O^6-methylguanine methyl tranasferase deficient (MGMT-) tumors.



R= --CH_3 for TMZ
R= -CH_2CH_2F for KL-50

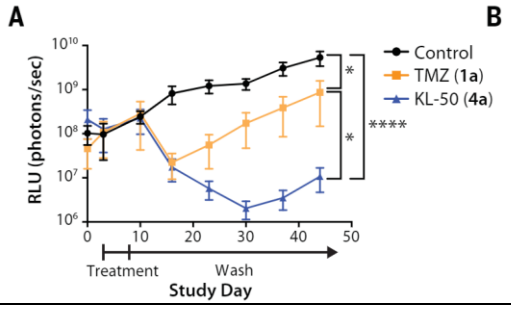
a) Show the curved arrow electron flow mechanism for the reaction of KL-50's 2-fluoroethyl diazonium ion, liberated after hydrolysis and decarboxylation of KL-50, in forming interstrand cross-links (ICL's) between a guanosine and a cytosine as described in the article. You may assume acids and bases 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.)
Temozolomide causes the methylation of DNA at a variety of sites. The methylation initially leads to DNA repair mechanisms fixing problems and attacking glioblastomas.

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.)

Figure 6A	The legend reads, "Mean tumor size as measured with bioluminescent imaging as relative light units (RLU; photons/s) with SEM of xenograft LN229 MGMT−/MMR− intracranial tumors treated with 5 consecutive days of oral administration of 10% cyclodextrin control (n = 10 mice), TMZ (1a) (n = 11 mice, 25 mg/kg), or KL-50 (4a) (n = 11 mice, 25 mg/kg)." Note: TMZ is temozolomide, a frontline drug used in the treatment of gliomas, and KL-50 is the drug that's reported in



	the study. MGMT- is O^6-methylguanosine methyl transferase deficient tumor and MMR- is mismatch repair deficient tumor.

The figure shows a study of the effects of the drugs TMZ and KL-50 on a tumor. The control is the experiment without any drug and allows a comparison of the effects of TMZ and KL-50. From the graph, TMZ causes an initial decrease in the tumor size during treatment, but the tumor growth returns approximately 10 days after treatment. KL-50 demonstrates much stronger tumor suppression over a longer period of time, but the tumor does start to regrow roughly 20 days after treatment. The study was conducted with MGMT-/MMR- tumors because those are difficult to treat and the purpose of developing the new drug, KL-50. KL-50 has a new mechanism of action that not only O-alkylates guanosine, but also, over time, forms interstrand cross-links between guanosine and cytosine as shown in the mechanism of part a. After interstrand cross-links are formed, the DNA is damaged enough (i.e. lesions) to prevent the tumor DNA from replicating and the tumor growth is suppressed.

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)*

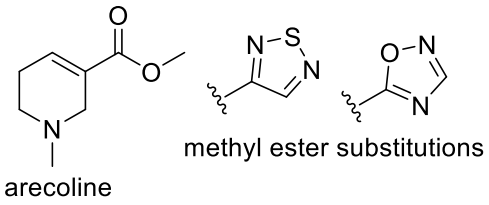
a) What is the mechanism of action of xanomeline and how is this thought to benefit treatment of Alzheimer's disease and schizophrenia? (3 pts.)

Xanomeline is a muscarinic acetylcholine receptor agonist, which means upon binding at a receptor it will elicit a biological effect consistent with acetylcholine binding at the same receptor. Decreased acetylcholine activity is believed to be the cause of Alzheimer's disease, schizophrenia, and other neurological disorders (the cholinergic hypothesis of neurodegenration).

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.)

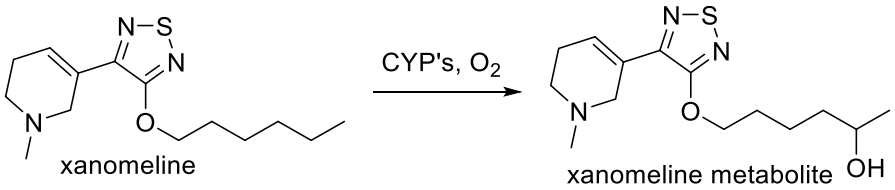
These represent "isosteric changes" as the groups have similar shape and electronics as the ester.

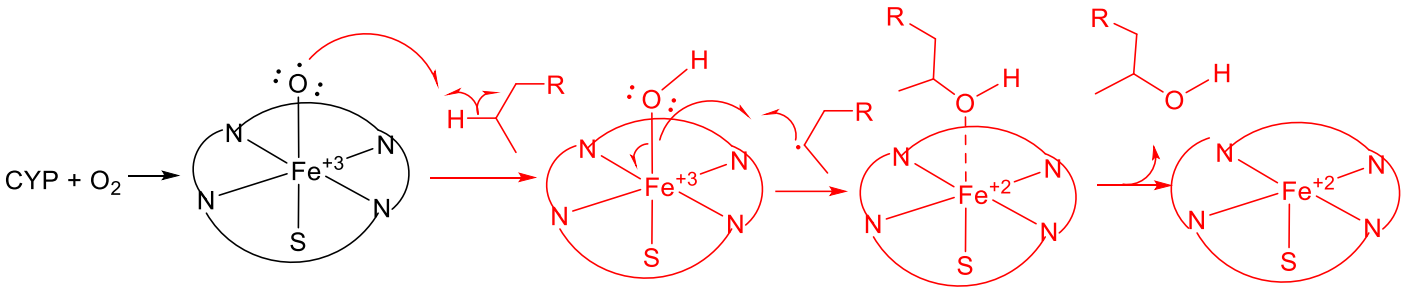


(ii) Name two benefits that might be realized by changing the methyl ester to either of the heteroaromatic rings shown. (2 pts.)

The heteroaromatic rings would likely be more stable to hydrolysis or esterases and they would enhance solubility by introducing more polar heteroatoms capable of hydrogen bonding.

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.)

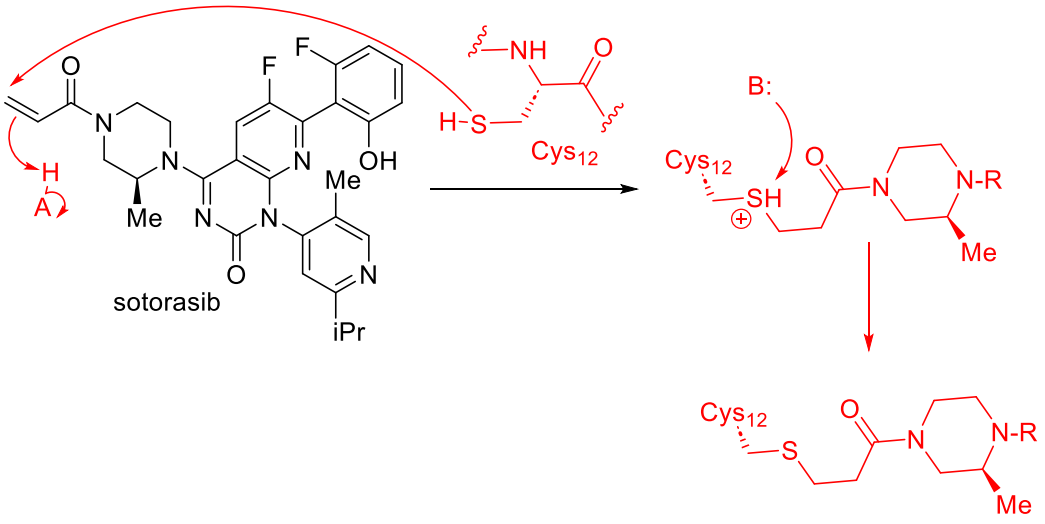




d) As represented in the metabolic reaction shown in part c, what is the body's general goal in conducting metabolic reactions with drugs? How is this occurring with the xanomeline metabolite? (3 pts.)
The body is trying to polarize drugs or any foreign substances to allow their rapid removal or excretion from the body through promoting their ability to dissolve in aqueous solutions. By adding a hydroxyl group to the alkyl chain of xanomeline, the metabolite is now more polar and would be more soluble in water.

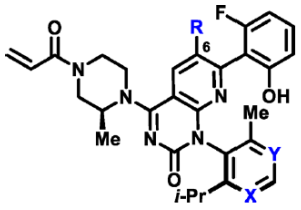
7. "Discovery of a Covalent Inhibitor of KRASG12C (AMG 510) for the Treatment of Solid Tumors" J. Med. Chem. 2020, Vol. 63, pp. 52−65, B. A. Lanman et al. *(Jim, April 6)*
a) The researchers chose to use a covalent inhibitor against KRASG12C. Why did they choose a covalent inhibitor while the researchers inhibiting KRASG12D chose a non-covalent inhibitor? (3 pts.)
The mutation for G12C has glycine replaced by cysteine, which is quite nucleophilic. G12D substitutes the glycine with an aspartic acid, which is much less nucleophilic. Having a good thiol nucleophile allowed for the researchers, B. A. Lanman et al., to make a drug with an electrophile that could react with the thiol nucleophile of cysteine and destroy the mutant KRASG12C target protein.

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



cmpd	R	X	Y	log *D* (pH 7.4)| PSA (Å^2)[a]	p-ERK IC_{50} MIA PaCa-2 (μM)[b]	viability IC_{50} MIA PaCa-2| 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

[a]log *D* (pH 7.4) and PSA (polar surface area) calculated using ACD/Percepta (ACD/Labs, Toronto, Canada). [b]p-ERK1/2 immunoassay (MSD), 2 h incubation. [c]Viability 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 $n \geq 2$. [d]iv/po dosing in BALB/c mice (vehicle: iv, 1 mg/kg, DMSO; po, 10 mg/kg, 1% Tween 80, 2% HPMC, 97% water). [e]Crystalline polymorphs. [f]Presence 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.)

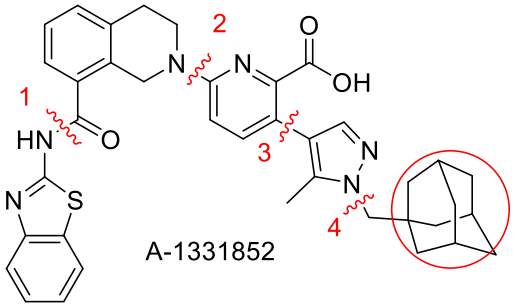
Log D is a measure of a molecule's lipophilicity or hydrophilicity. Compound **24** with a log D of 3.6 would be more lipophilic than compound **38** with a log D of 2.0.

(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.)

The drug hepatic clearance (MulH hep Cl_{int}) for 38 became lower (36|9) versus 24 (102|30). If a drug clearance is lower, then the drug remains in the blood longer. Secondly, the bioavailability (F%) became higher for 38 (22-40%) versus 24 (4-12%). The higher the bioavailability, the more drug circulating in the body and available to exert a therapeutic effect. As a third example, HT solubility increases for 38 (423|492|499) versus 24 (12|204|9) and solubility in aqueous media is critical for drugs to travel to and reach their target after administration.

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.)



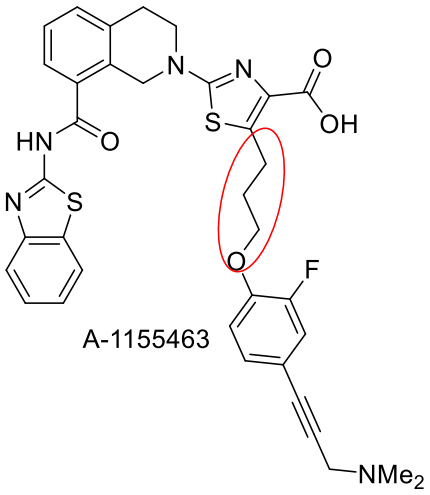
1) amide bond formation

2) nucleophilic aromatic substation

3) Suzuki cross-coupling reaction

4) S_N2 alkylation

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.



A-1155463

(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.)

The rigidification of A-1155463 lead to the formation of an inhibitor that bound more precisely and favorably in the desired orientation and location of the BCL-XL protein pocket. Generally this can improve drug potency if the correct conformation is achieved since it reduces the degrees of freedom of the structure and reduces the entropy penalty from binding in a fixed conformation. However, if an incorrect conformation is installed, then the rigidification can undermine drug binding and lose necessary interactions, which is an enthalpy penalty from lost intermolecular force interactions with the protein.

(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.)

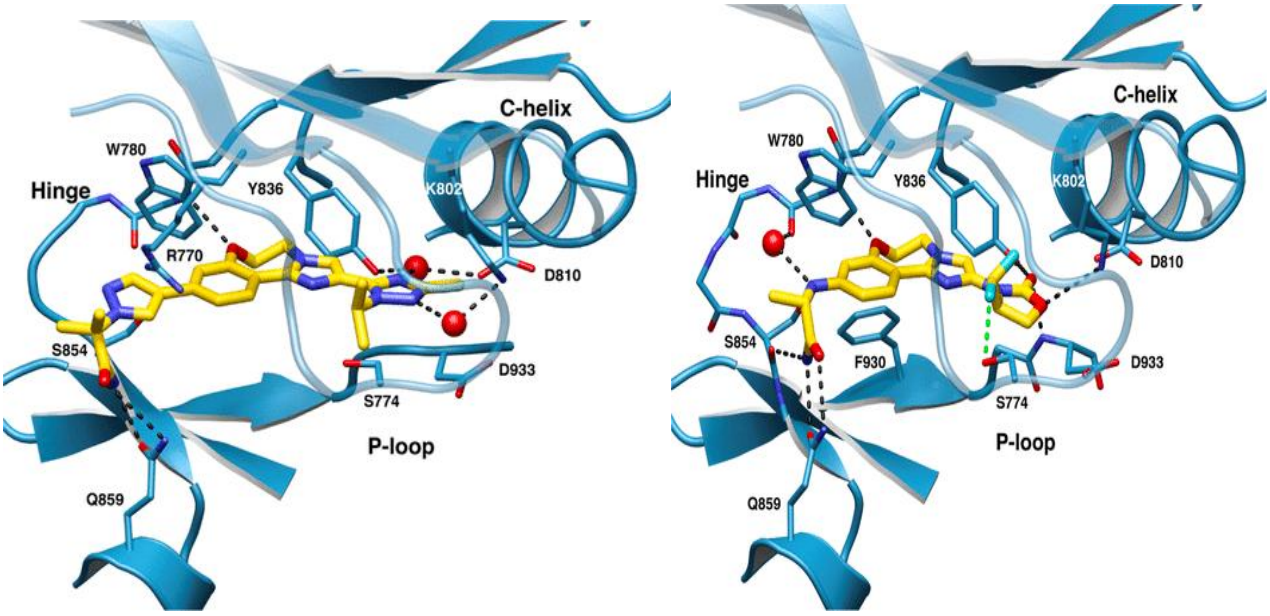
The lipophilic alkane piece (adamantyl unit) had lipophilic interactions in the lipophilic P4 pocket, which would be happening with van der Waals force interactions.

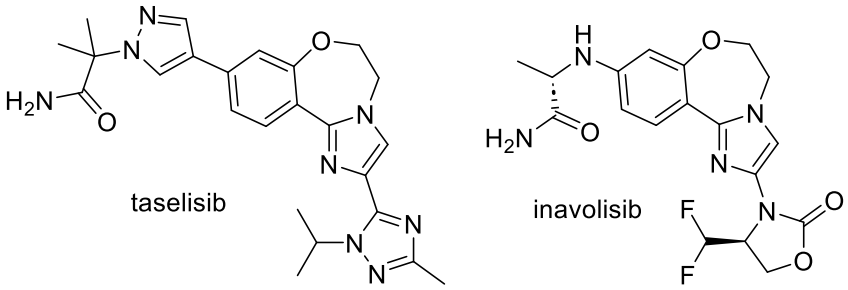
9. "Discovery of GDC-0077 (Inavolisib), a Highly Selective Inhibitor and Degrader of Mutant PI3Kα" J. Med. Chem. 2022, 65, pp. 16589−16621, E. J. Hanan et al. *(Jenna and Yui, April 13)*

a) What does PI3Ka (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.)

PI3Kα phosphorylates various proteins leading to cell growth and survival. It needs ATP as the source of phosphate groups in its catalytic reaction. Overexpression of PI3Kα leads to cancer due to excess cell growth.

b) The crystal structures of taselisib (left), the initial drug lead, and inavolisib (right), the optimized PI3Ka 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 taselisib and inavolisib binding in the PI3Ka protein and briefly describe the differences. Identify the interaction that is considered critical to the (300-fold) isoform selectivity (PI3Kα versus PI3Kδ). (8 pts.)

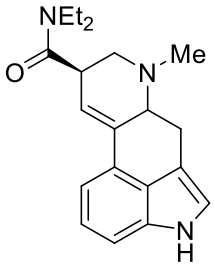
a) Inavolisib has an additional H-bond between S854 and the primary amide on the left side of the structure.
b) Inavolisib has a direct H-bond between the oxygen in the oxazolidinone ring on the lower right of the structure with D810, while taselisib has that H-bond connection to D810 through two water molecules.
c) One of inavolisib's fluorine atoms is H-bonded to S774. The F atom H-bond to S774 is believed to be the reason for the significant selectivity between PI3Kα and PI3Kδ.
d) NH of inavolisib has an H-bond with H_2O and a main chain C=O near W780 that doesn't exist in taselisib.

c) Both drugs are competitive with a reactant or substrate of the PI3Kα catalytic reaction. What is that component? (3 pts.)

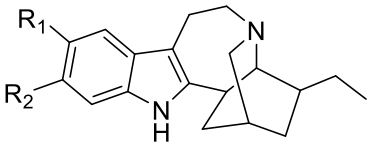
ATP, adenosine triphosphate.

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)*

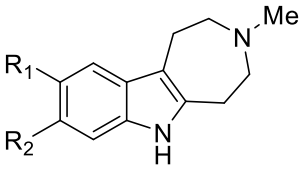
a) Identify the common pharmacophore for the following neuroactive agents by circling it. (3 pts.)



lysergic acid diethylamide (LSD)

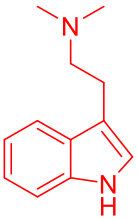


ibogaine

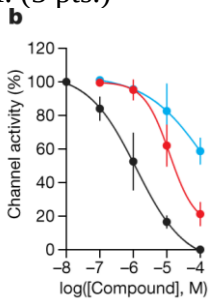


tabernanthalog (TBG)

pharmacophore



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 IC_{50} values of each to the nearest tens digit in molarity, M. (5 pts.)

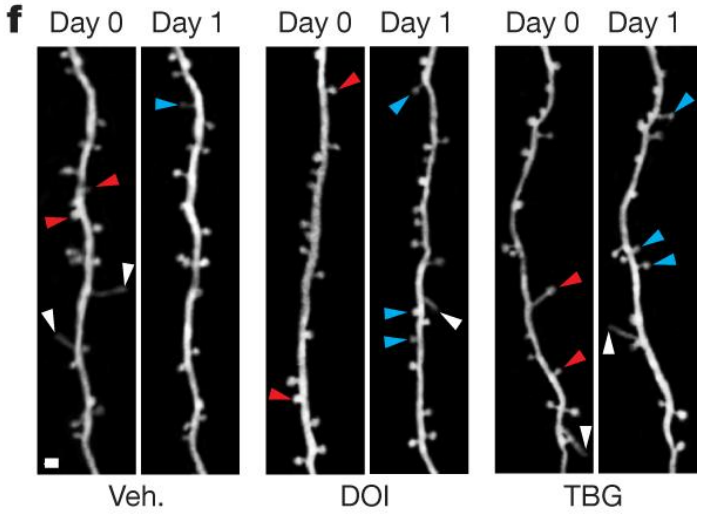


Legend text: Inhibition of hERG channels expressed in HEK293 cells. Data are mean ± s.d. IBO, ibogaine (black); IBG, ibogainalog (red); TBG, tabernanthalog (blue)

hERG (human ether-a-go-go) is a receptor in the heart and inhibition of it can cause serious cardiac problems or cardiotoxicity. All drugs need to be screened for hERG activity.

TBG showed the least hERG inhibition at roughly ~10^{-3} or 10^{-4} M, while IBG was next at ~10^{-5} M and IBO showed the most at ~10^{-6} M.

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

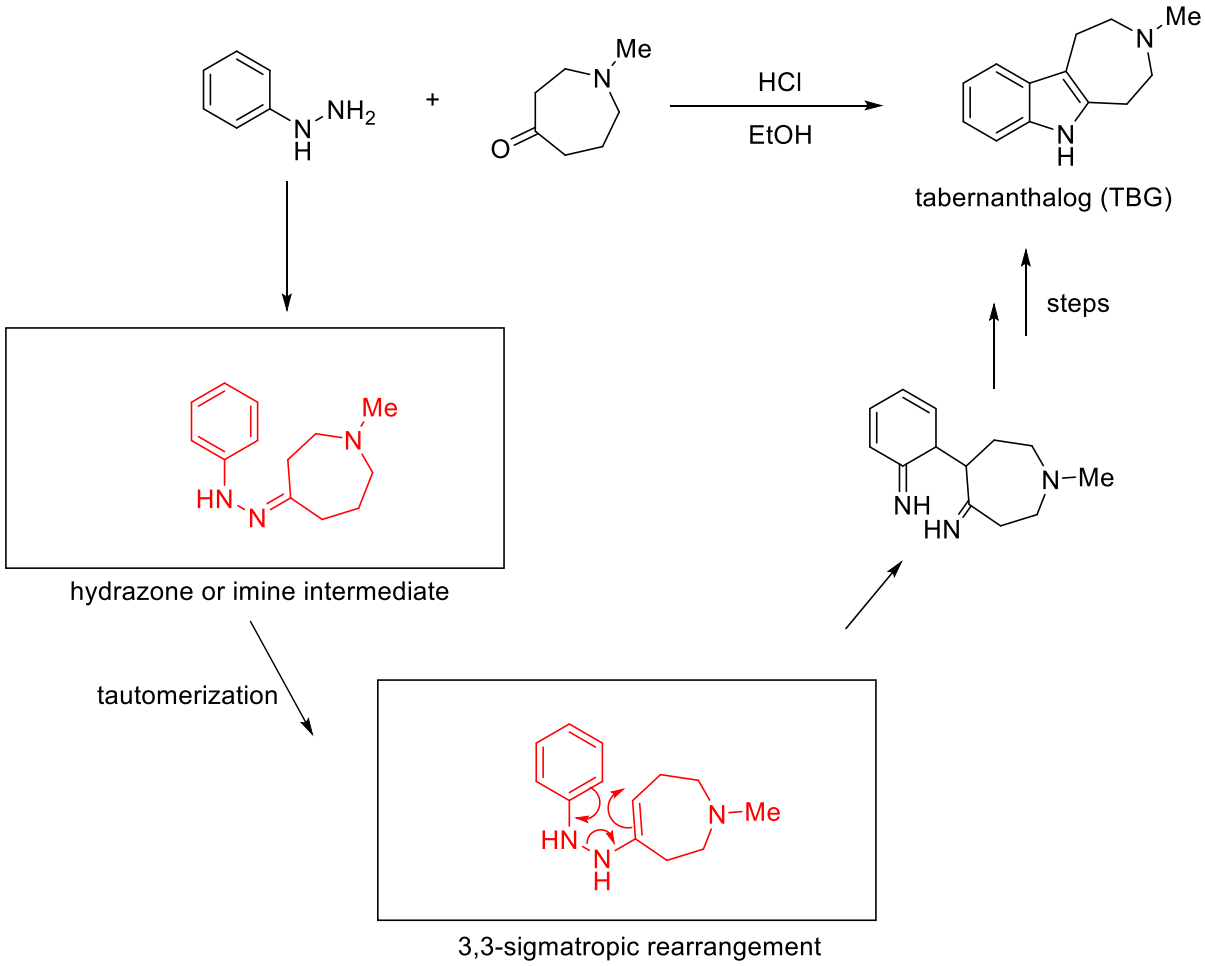


Representative images of the same dendritic segments from the mouse primary sensory cortex before (day 0) and after (day 1) treatment. Blue, red and white arrowheads represent newly formed spines, eliminated

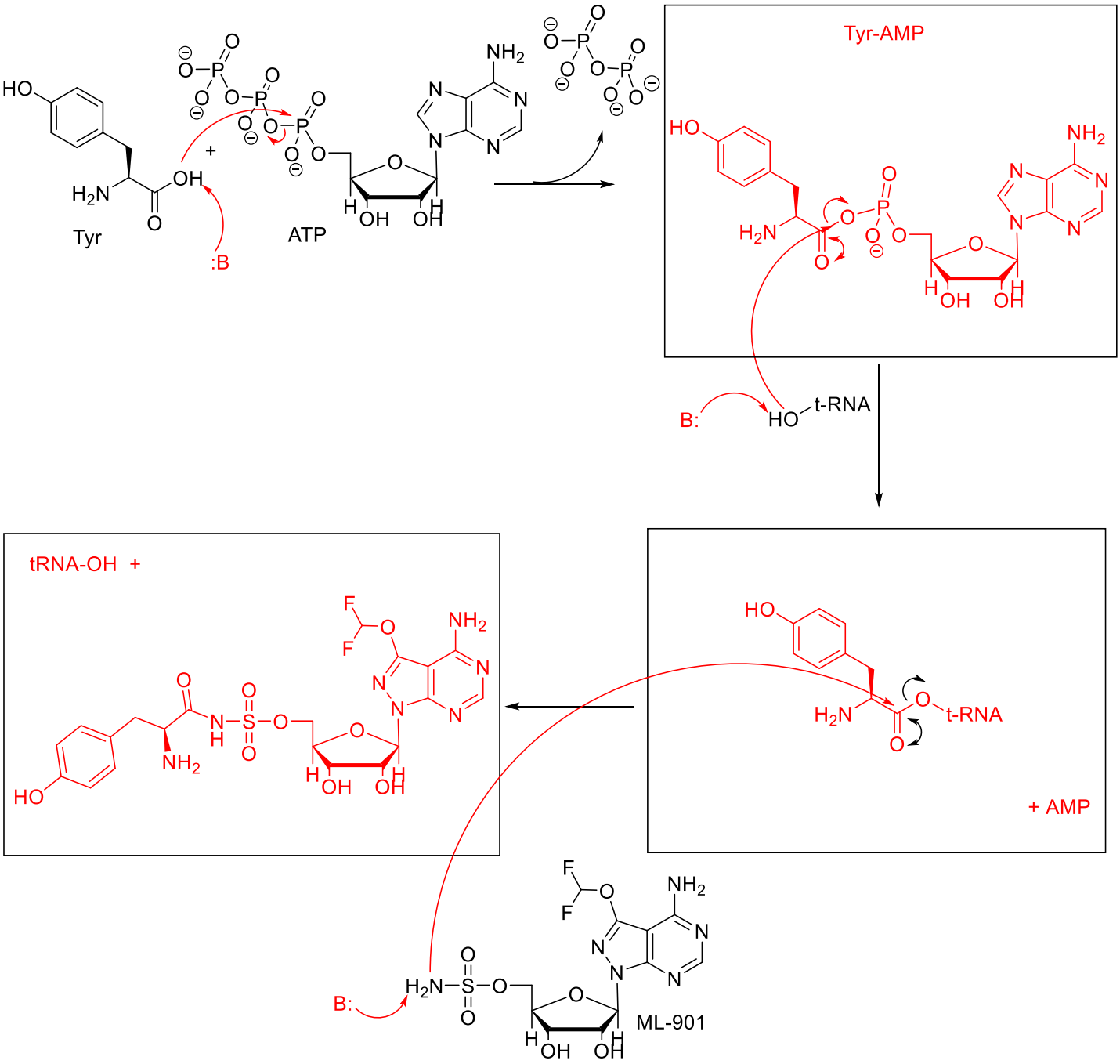
The researchers argued that the picture of the nerve dendrites showed nerve growth and illustrated neural plasticity generated by treatment with the TBG.

spines and filopodia, respectively. 2,5-Dimethoxy-4-iodoamphetamine (DOI) and TBG (tabernanthalog).

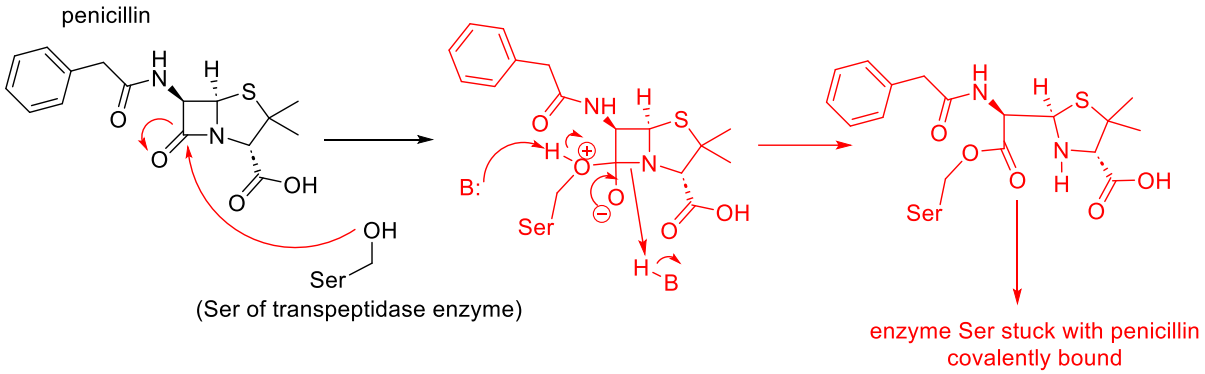
d) Shown below is the key reaction to form the TBG drug structure. Complete the sequence by showing the intermediates and providing the curved electron flow arrows for the 3,3-sigmatropic rearrangement that is the key C-C bond forming step. (5 pts.)



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.)



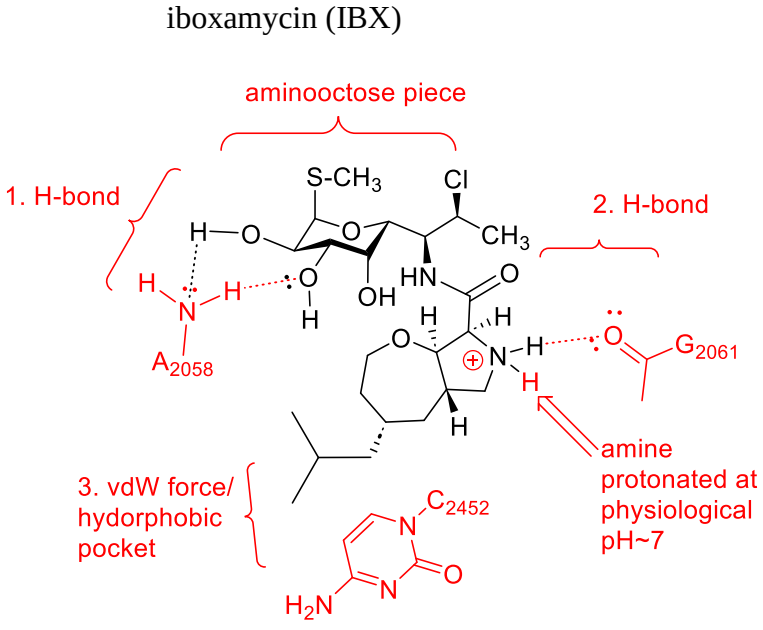
b) Briefly describe how the reaction you've shown in part a relates to the antibacterial activity of penicillin. Your answer should describe what happens to the bacteria after the reaction shown (with all the gory details). (2.5 pts.)

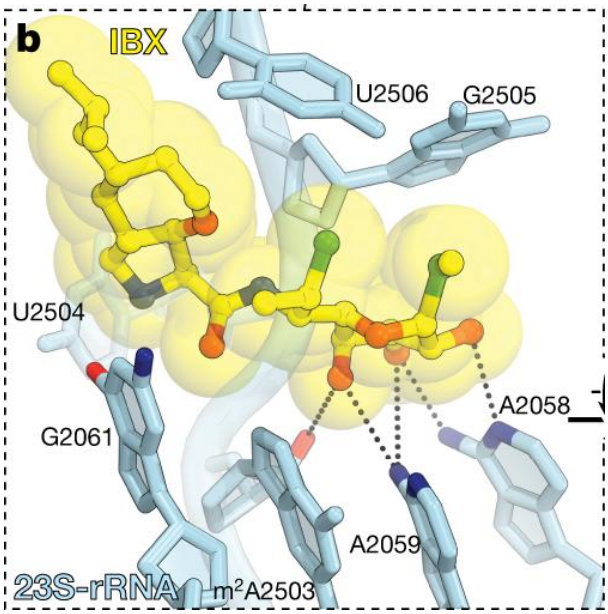
Penicillin reacts with the transpeptidase enzyme which is a critical enzyme used by the bacteria to synthesize cell walls, which are essential to protect it from its external environment. By intercepting the transpeptidase serine protease, the penicillin has blocked cell wall biosynthesis and the bacteria guts are spilled out. Bacteria cell synthesis is aborted and the bacteria cell dies.

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 binds in the bacteria ribosome. By binding it prevents protein synthesis by the bacteria, thereby preventing bacterial survival.



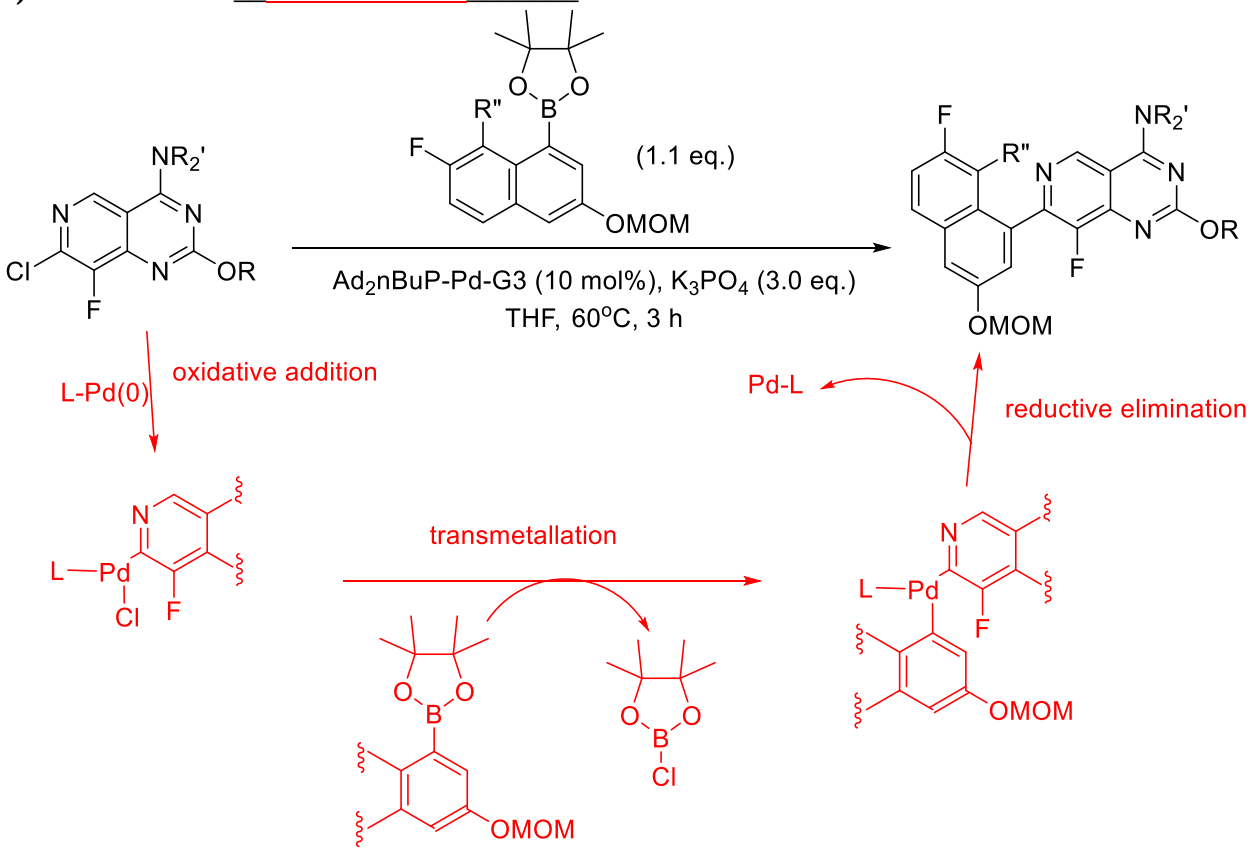


(ii) Annotate the structure of iboxamycin above, by identifying the three different intermolecular forces (IMF's) quoted below from the article. Using the crystal structure information and the information in the quotes, you should list the bacteria target groups (e.g. G2505) involved in the IMF you identify. 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 aminooctose 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"

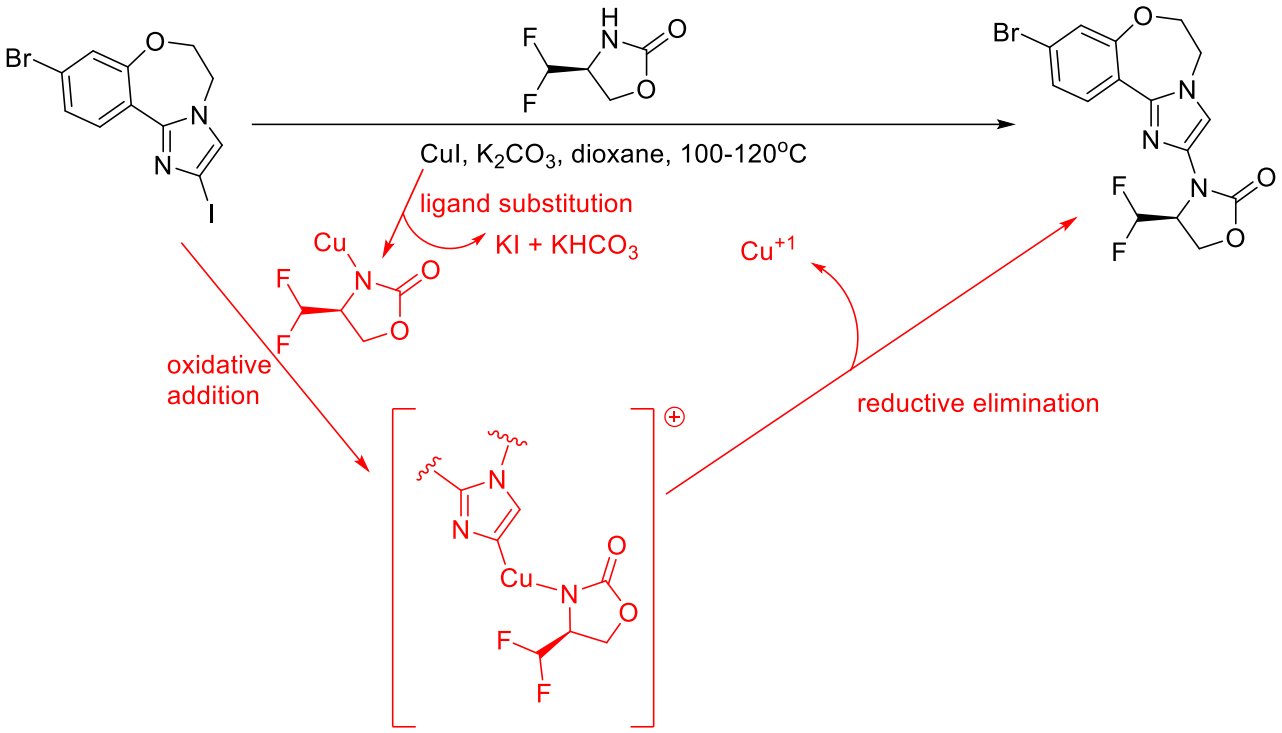
13. Organometallic mechanisms. Choose **<u>one</u>** of the two reactions below and show the mechanism of the catalytic cycle. Identify all the steps by the type of organometallic mechanistic process. You are encouraged to abbreviate structures but be sure to show the key components. Provide the name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

a) Reaction name:__Suzuki reaction_____



--OR--

b) Reaction name:__Ullman reaction_____


Br
O
N
N
I
F
F
H
N
O
O
CuI, K2CO3, dioxane, 100-120°C
ligand substitution
KI + KHCO3
Cu
F
F
N
O
O
oxidative
addition
Cu+1
reductive elimination
Br
O
N
N
F
F
N
O
O
N
N
Cu
N
O
O
F
F
⊕