Medicinal Chemistry Name:_____
CHEM 515
Mid-term Exam
March 6, 2025

There are 12 lucky questions on the exam. You should complete any 10 of the 12 questions.
Each question is worth 10 points. You are encouraged to answer the questions where you feel you have the greatest understanding or competence. You may use blank paper provided to write your answers. Please label the additional paper with your name and the question number. You can staple the answers to this exam at the end. If you answer additional questions beyond the 10 requested, then bonus points *may* be awarded.

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.

1. Lead compound development

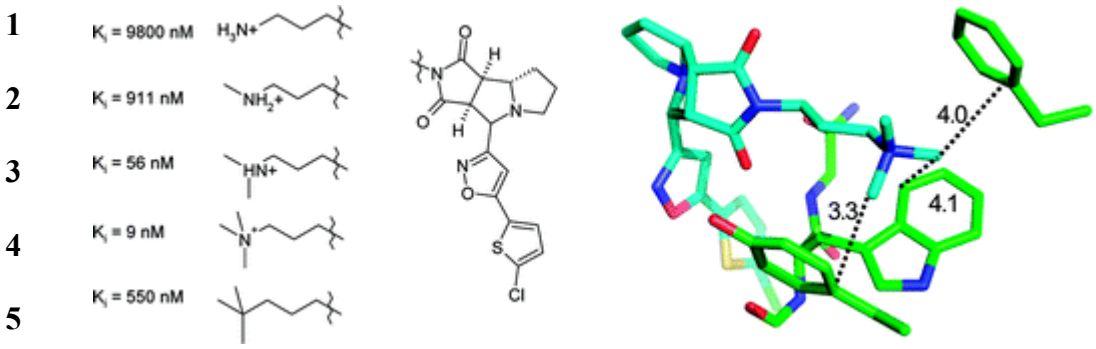
Pick three of the six most common methods for finding new drug leads to begin a therapy program and briefly (one to three sentences or phrases) describe what these three involve. (10 pts.)

Six most common methods for lead drug discovery:

(1) Random screen or high throughput screen (HTS)
(2) Directed screen
(3) Structure-based drug design (SBDD)
(4) Fragment screen or Fragment based lead generation (FBLG):
(5) DNA-encoded library screening (DEL):
(6) Known compounds

2. Molecular interactions

The following figure and K_i values for factor X_a inhibitors were described in the article entitled, "A Medicinal Chemist's Guide to Molecular Interactions" (*J. Med. Chem*. **2010**, *53*, 5061-5084).



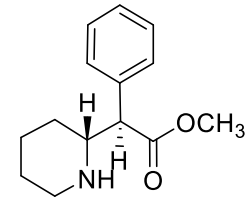
a) What is the name of the intermolecular interaction shown in the picture for the most potent of the inhibitors in the list? (3 pts.)

b) The trend demonstrated in the first four inhibitors (**1-4**) highlights the impact of desolvation on drug potency. Explain. Your answer should include a description of drug desolvation. (4 pts.)

c) What is learned from the fifth inhibitor (**5**) with a K_i= 550 nM? (3 pts.)

3. Metabolism of Ritalin

Methylphenidate (Ritalin) is the most commonly prescribed treatment for attention deficit hyperactivity disorder (ADHD). Based on our discussions of drug metabolism, propose three potential metabolic products of methylphenidate. You must have at least one example of a Phase I metabolic product and at least one example of a Phase II metabolic product. You may show a Phase II step that occurs after one of your Phase I metabolic reactions. Each metabolic reaction should be titled with the type of reaction and the Phase (I or II). Reactions catalyzed by cytochrome P-450 should be noted with a 'CYP' designation. (10 pts.)

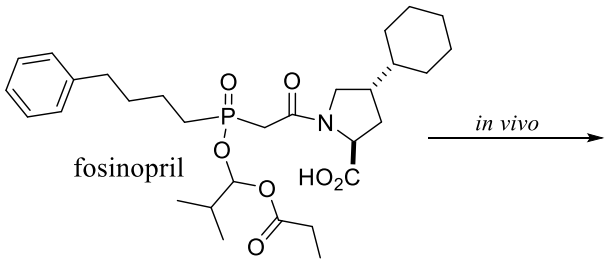


methylphenidate

4. Angiotensin-converting enzyme (ACE) inhibitors

In class we talked about ACE inhibitors such as captopril and enalapril, which are used for the treatment of hypertension. Another example of an ACE drug is fosinopril (structure shown below). *In vivo* fosinopril is converted into fosinoprilat, the active drug and an inhibitor of ACE by the action of an esterase, which releases both propanoic acid and 2-methylpropanal.

a) Provide the structure of fosinoprilat in the box below based on the description of the in vivo transformation of fosinopril. (3 pts.)



fosinopril

in vivo

fosinoprilat, the active drug

b) What is the general medicinal chemistry name applied to fosinopril given that it is transformed in vivo into the active drug? (1 pt.)

c) Fosinopril binds in the active site of the metalloprotease ACE in a manner similar to captopril and enalaprilat, the active form of enalapril. Draw a picture of this interaction. You only need include the critical potions of fosinopril and the ACE. (3 pts.)

d) Unlike captopril and enalapril, fosinopril's inhibition of the ACE enzyme can also be considered a "transition state analog" inhibition event. How is fosinopril acting as a transition state analog and why is this a useful mode of inhibition of enzymes? Pictures might assist in your explanation. (3 pts.)

5. HIV protease inhibitors

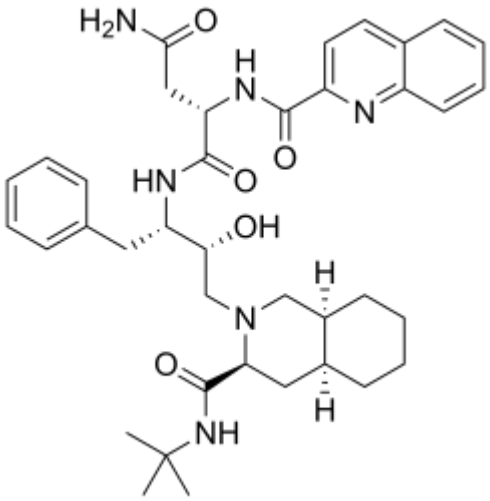
Saquinavir is an HIV protease inhibitor developed by Roche pharmaceutical company with the structure shown below. It has many of the same properties as the two other HIV protease inhibitors, ritonavir and indinavir, that were discussed in class.

a) Sketch the key interaction between saquinavir and the amino acids involved in catalysis in the HIV protease active site. (5 pts.) You should abbreviate your structures but be sure to:

(i) Show the side chains of the key enzyme amino acids involved in catalysis.

(ii) Show the portion of saquinavir interacting with these catalytic amino acids.

(iii) Identify key intermolecular forces involved in the interaction between the amino acids and saquinavir.



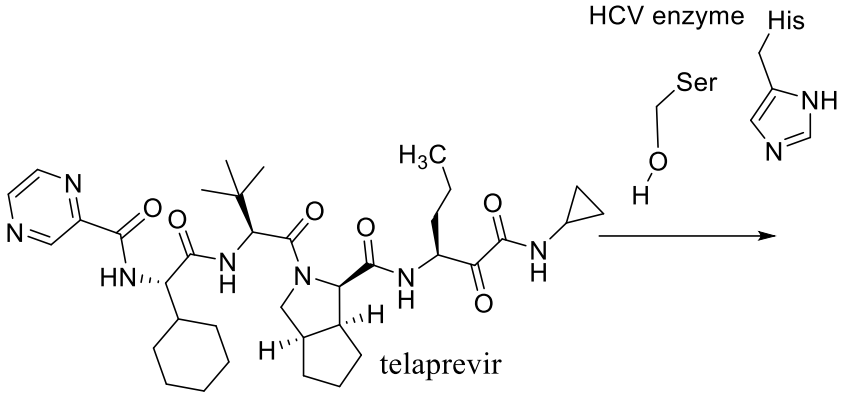
saquinavir

b) On the structure of saquinavir drawn above, identify the approximate location of the components of saquinavir in the subsites S_1, S_1', S_2, S_2', and S_3. (5 pts.)

6. Hepatitis C virus (HCV) protease inhibitors

Telaprevir was an HCV protease drug developed by Vertex pharmaceutical company. It has a mechanism of action similar to boceprevir, which was discussed in problem set 5.

a) On the structure below, draw the curved electron flow arrows and the product that results from the interaction of telaprevir with the HCV serine protease, called NS3/4A. You are encouraged to abbreviate your product structure but be sure to include the key components of the reaction outcome. (6 pts.)



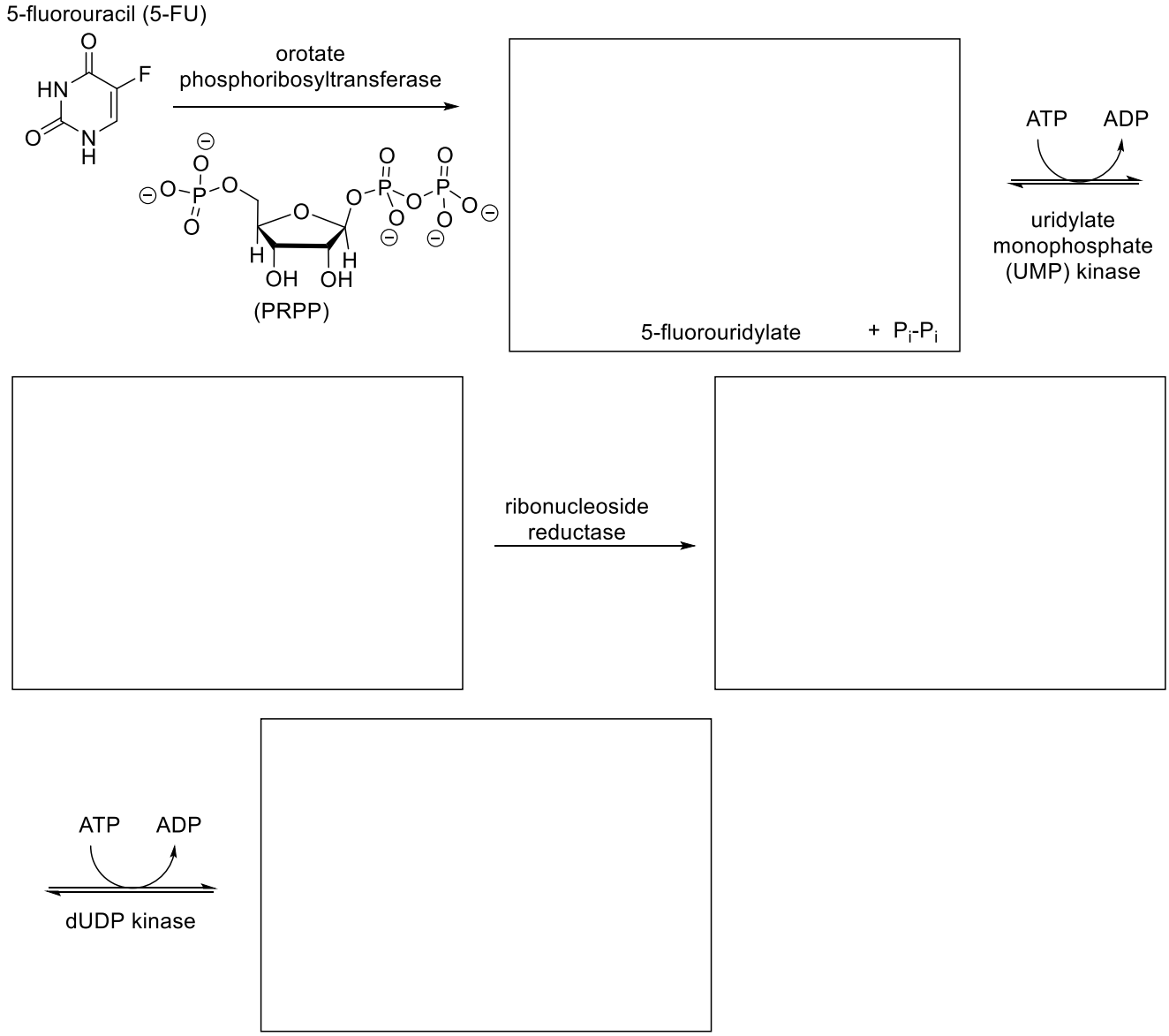
b) Based on the reaction that you showed between telaprevir and the HCV serine protease, what general class of inhibitors does telaprevir represent? (2 pts.)

c) On the structure above, circle the substituent or group that would likely occupy the S_3 subsite of the HCV protease. (2 pts.)

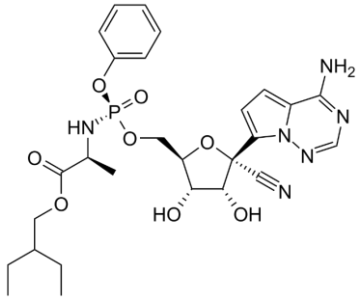
7. Nucleic acid drugs

Most nucleic acid drugs that interact with DNA or RNA polymerase require the activation process shown below for the well-known anti-cancer drug, 5-fluorouracil.

a) Provide the products for the four reactions shown. (8 pts.)



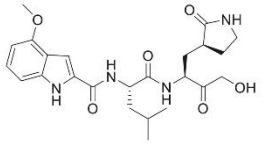
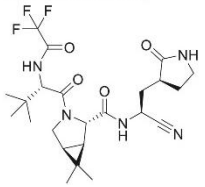
b) Which step in this process is often the slowest or rate-limiting and the reason for the Pro-tide technology used with the COVID-19 anti-viral remdesivir? (2 pts.)



remdesivir

8. Paxlovid drug development

The table below shows important drug pharmacodynamic (PD) and pharmacokinetic (PK) parameters of the COVID-19 Pfizer drug called nirmatrelvir (PF-07321332) and the lead compound 1 (PF-00835231). Answer the questions below based on the table's data and our class discussions. Your answers should identify the data that you are using to draw your conclusions (i.e. the table column). (10 pts.)

Number/Structure	SARS-CoV2 M^{pro} K_i (nM)[*]	VeroE6-enACE2 CPE EC_{50} (nM)[†]	MDCK-LE P_{app} (x 10^{-6} cm/sec)[‡]	HLM CL_{int} (μl/min/mg)[§]	Rat CL_p (mL/min/kg)[¶]	Oral F (%)[¶#]	F_u x F_g (%)[¶††]
1 (PF-00835231) 	0.271 (0.155 – 0.471, n=6)	231 (158 – 338, n=8)	< 0.207 ± 0.048 (n=6)	7.47 ± 0.88	27.0 ± 3.1	1.4 ± 0.8	3.3
6 (PF-07321332) 	3.11 (1.47 – 6.59, n=6)	74.5 (66.5 – 83.4, n=20)	1.71 ± 0.28 (n=4)	24.5 ± 0.2	27.2 (22.5, 31.9)	50 (30, 71), 34 ±19[**]	95, 65[**]

a) Is nirmatrelvir more potent than the lead compound in isolated enzyme assays or cell-based assays? Approximately how different are the values, i.e. five-times, ten-times, one-hundred-times?

b) Which compound has better bioavailability and by approximately how much?

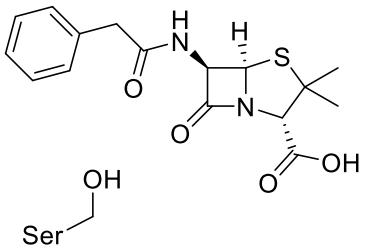
c) Which compound is better able to penetrate cells and by approximately how much?

d) Which compound is degraded most rapidly and removed from the system? Estimate the difference.

9. Penicillin mechanism of action

Penicillin is another antibacterial that we discussed. It reacts with the bacterial transpeptidase enzyme, a serine protease.

a) Show the curved arrow electron flow mechanism of penicillin's interaction with bacteria in the space below. The necessary starting components, penicillin and the important side chain of the bacterial transpeptidase enzyme, are given. Be sure to include any important intermediates. You may use generic acids and bases to accomplish the reaction. (7 pts.)



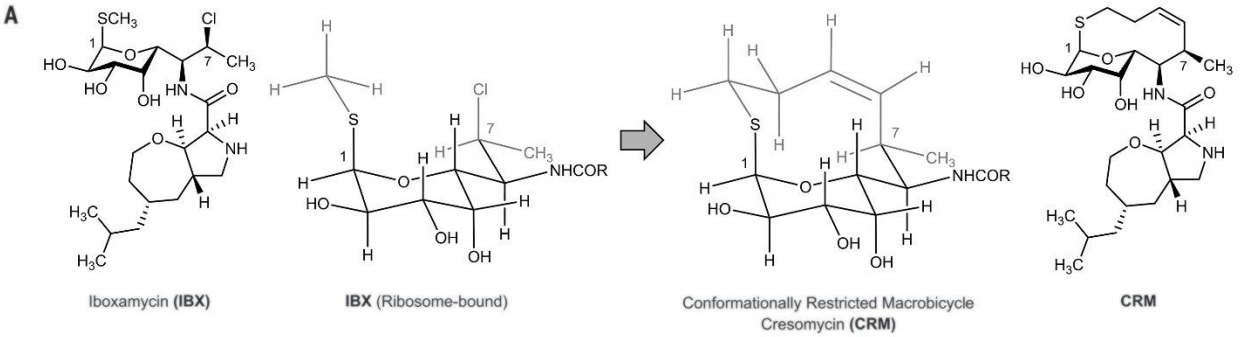
(Ser of transpeptidase enzyme)

b) How does this reaction with the bacterial transpeptidase enzyme kill the bacteria? (3 pts.)

10, Iboxamycin antibacterial drug

A 2024 report in *Science* described a second generation of an iboxamycin drug, which further evolved the antibacterial drug structure by the addition of an alkyl/alkenyl bridge that restricted the conformation of the iboxamycin molecule. This new antibacterial, called cresomycin (CRM), was found to further enhance the potency of the antibacterial drug, IBX.

(An antibiotic preorganized for ribosomal binding overcomes antimicrobial resistance | Science)



a) Cresomycin, like IBX and clindamycin, interacts with bacteria by inhibiting the same critical operation of the bacteria. Where did IBX and clindamycin bind and how did that kill the bacteria? (3 pts.)

b) What benefits would the conformational restriction shown for CRM provide, in terms of enthalpy and entropy, in binding to the ribosome in the same location as IBX? (7 pts.)

11. Antibacterial drug properties

An article published in the Journal of Medicinal Chemistry offered an analysis of antibacterials and their unique properties in an effort to facilitate the successful development of new antibacterials. The results are reported in the table below. Review the data in the table and answer the following questions based on our discussions of similar drug properties in other molecules.

Table 1. Comparison of Average (Mean) Compound Property Values of Three Drug Data Sets Representing General (CMC, Excluding Antibiotics) and Antibacterial Drugs

parameter	CMC data set	antibacterials (only Gram-positive activity)	antibacterials (Gram-negative activity)
MW	338	813	414
clogp	2.7	2.1	−0.1
$clogD_{7.4}$	1.6	−0.2	−2.8
PSA ($Å^2$)	70	243	165
rel PSA (%)	22	30	42
H-donor	1.6	7.1	5.1
H-acceptor	4.9	16.3	9.4

CMC= comprehensive medicinal chemistry, which is all drugs that are not antibacterials

a) Compare the general properties of drugs with those of the antibacterials, both gram positive and gram negative. Which properties are different and what do these properties represent, i.e. your answer should include a description of what these properties mean. It would be appropriate for you to define acronyms that are used in the list of parameters. (5 pts.)

b) Are there any properties of the antibacterials that break Lipinski's rule of five? Are there any properties that adhere to Lipinski's rule of five? (5 pts.)

12. Suzuki-Miyaura reaction mechanism

Provide a mechanism for the following cross-coupling reaction. Be sure to include intermediate structures and the mechanistic name of the steps in the catalytic cycle. You are encouraged to abbreviate the intermediate structures but be sure the key components of the molecules are shown. (10 pts.)