Med Chem final exam content guidance

Format of final exam: ~12-15 fifteen-point questions and you will need to answer 10. You'll have three hours and maybe longer if I see that the exam is taking too long (like the mid-term).

General topics to know:
1. A drug's target and its mechanism of action
e.g. GB18 is a mu and kappa opioid receptor (MOR/KOR) antagonist
-see article title and abstract for this information—presenters also described this
2. Intermolecular forces in a variety of examples—I'll give you drug structures and/or crystal structures and you need to identify key interactions

General reaction mechanisms to know: Suzuki cross-coupling reaction, amide bond synthesis (HATU, EDC), nucleophilic aromatic substitution. The Suzuki and Nu aromatic subst. are represented in the list below. Amide bond synthesis is a general Nu acyl subst. also represented below. I would give you reactant, reagent and product structures, . You'd need to show all curved electron flow arrows and intermediates.

Other types of questions that you might see:
-I might ask about differences in activity between two different derivatives (not necessarily from a table noted below) and the basis for the difference. I would be looking for general medicinal chemistry structure-activity principles (e.g. N's cause molecules to be polar; F's are electronegative and electron-withdrawing) and I would provide an appropriate amount of background information (e.g. PS #10, qu. 1c with the table data shown).
-Drug metabolism and pharmacokinetics (PK or ADME) information would be questions that you might also see.
-**Iboxamycin and penicillin lecture** material will have a set of questions
-**Heteroaromatics lecture**: There will likely be questions about heteroaromatics. Know the mechanism from PS #8, qu. 3.
-**Dr. Bleasby's lecture** might have questions
-**Dr. Worm's lecture** will only have questions if I provide structures and ask about general med chem structure-activity principles
-**Dr. Luo's lecture** will have questions about med chem principles in drug development. There also were several Heck reactions shown and they are near and dear to my heart.

Focused content from student presentations:

Article	Drug class	Article	Med Chem topics for final exam
Feb. 28 **Angelina and Shiraz**	opioid receptor antagonist	Synthesis and target annotation of the alkaloid GB18 Nature 2022, Vol. 606, pp. 917–921 S. Woo and R. A. Shenvi https://www.nature.com/articles/s41586-022-04840-9	Reaction mechanisms: 1. Robinson annulation with pyrrolidine (*note:* This was updated and corrected.) 2. Danheiser annulation Bioassays to understand: Figures 4a and 4b

March 16 **Hannah and Lana**	potential anti-malarial	Diversity-oriented synthesis yields novel multistage antimalarial inhibitors Nature 2016, Vol. 538, pp. 344-349. S. L. Schreiber et al. https://www.nature.com/articles/nature19804 -synthesis details from J. Am. Chem. Soc. 2017, 139, 32, 11300–11306 https://pubs.acs.org/doi/10.1021/jacs.7b06994	Reaction mechanisms: 1. Heck alkynylation reaction (catalytic cycle) 2. Reductive amination Bioassays to understand: Figures 3 and 4
March 21 **Jacqueline and Rosie**	antiviral	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. https://www.nature.com/articles/nature17180	Reaction mechanisms: 1. Grignard reaction (1+2→3) 2. Cyano group installation (3→4) Bioassays to understand: Figure 1c, 1e and 1f
March 23 **Diana and Christina**	anti-cancer	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. https://pubs.acs.org/doi/10.1021/acs.jmedchem.1c01688	Reaction mechanisms: 1. Nu aromatic substitution (40→41 and 41→42) 2. Suzuki coupling reaction (42→43 or another similar example from another article—see below) Bioassays to understand: Table 3, Figure 14
March 30 **Chloe and Greg**	anti-cancer	Mechanism-based design of agents that selectively target drug-resistant glioma Science 2022, Vol. 377, pp. 502-511 R. Bindra, S. Herzon et al. https://www.science.org/doi/10.1126/science.abn7570	Reaction mechanisms: 1. 2-Fluoroethyl diazonium (**4c**) reactions with nucleotides (PS #9) 2. 57+58→4a, a series of Nu acyl substitutions followed by an amine reaction with diazo group. Bioassays to understand: Figure 2B and 6A.
April 4 **Yael and Kalyn**	potential Alzheimer's and schizophrenia treatment	Classics in Chemical Neuroscience: Xanomeline ACS Chemical Neuroscience, 2017, Vol. 8, pp. 435-443. Craig W. Lindsley et al. https://pubs.acs.org/doi/10.1021/acschemneuro.7b00001	Reaction mechanisms: 1. $NaBH_4$ reduction of pyridine 2. **CYP mechanism of oxidation of xanomeline (mechanism shown at beginning of course) Bioassays to understand: Table 1 and Figure 1 (only as it demonstrates oxidative metabolism)

April 6 **Jim**	anti-cancer	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. https://pubs.acs.org/doi/10.1021/acs.jmedchem.9b01180	Reaction mechanisms: 1. Covalent drug reaction (see PS #10) 2. "Step 3 cyclization" (Nu aromatic substitution) *note: there was also a Suzuki coupling reaction used (Step 6) Bioassays to understand: Table 5 (PK parameters) and Figure 8
April 11 **Lucy and Ebrar**	anti-cancer	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. https://pubs.acs.org/doi/10.1021/acsmedchemlett.9b00568	Reaction mechanisms: 1. Synthesis of S-10: Methoxy-carbonylation catalytic cycle 2. Amide bond formation using CDI *note: there was also another Suzuki cross coupling to make S-18 Bioassays to understand: Table 6 and Figure 5
April 13 **Jenna and Yui**	anti-cancer	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. https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.2c01422	Reaction mechanisms: 1. Ullman reaction to couple aryl halides with nitrogen compounds Bioassays to understand: Table 3 and 4
April 18 ***Charli and Reece**	anti-addictive	A non-hallucinogenic psychedelic analogue with therapeutic potential Nature 2021, Vol. 589, pp. 474–479 D. E. Olson et al. https://www.nature.com/articles/s41586-020-3008-z	Reaction mechanisms: 1. Fischer indole synthesis Bioassays to understand: Figure 2a/2b and 3f
April 25 **Kim**	potential antimalarial	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. https://www.science.org/doi/10.1126/science.abn0611	Reaction mechanisms: 1. Three-step reaction hijacking mechanism with ML-901 (see also Supplementary Figure 1) Bioassays to understand: Figure 1D and 4C