Med Chem spring 2025 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, although I might allow longer if students are struggling to finish.

General topics to know for all lectures:
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. You'll be expected to know amino acid side chains and the types of intermolecular forces they might have with various functional groups in a drug.
3. State of ionization of functional groups (mostly amines and carboxylic acids) at physiological pH (e.g. PS7, qu. 3b)
4. Be able to identify important medicinal chemistry concepts: pharmacophores; pro-drugs; reversible vs. irreversible drugs; isosteres; general structure-activity principles and analysis (know electron-releasing groups, electron-withdrawing groups, resonance, inductive/polar effect, etc.); log P (or clog P), log D
5. Purpose of different phases of clinical trials (1=safety; 2=efficacy; 3=larger efficacy)

General reaction mechanisms to know:
Synthetic mechanisms: Suzuki cross-coupling reaction; amide bond synthesis (HATU, EDC); nucleophilic aromatic substitution.
Enzyme mechanisms: serine proteases; metalloproteases.
Some presentations included examples of these. See early problem sets for the correct mechanisms.
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.
-Drug metabolism and pharmacokinetics (PK or ADME) information would be questions that you might also see. Know the following terms that we've seen: Cl, F, P(permeability), V_d or V_{ss}, C_{max}, AUC, $T_{1/2}$, etc.
-**Drugs and receptors lecture** will likely have a set of questions and many course student presentations discussed CNS drugs, so there might be overlapping content.

Problem set questions will likely be an important source of final exam questions.

Focused content from student presentations:

Date and presenters	Drug class	Article	Med Chem topics for final exam
March 18 **Carmen and Juanita**	Early drug development	A chemical approach for identifying O-GlcNAcmodified proteins in cells, C. Bertozzi et al. Proc. Natl. Acad. Sci. July 21, 2003, 100 (16) 9116-9121 A chemical approach for identifying O-GlcNAc-modified proteins in cells | PNAS	Reactions to know: Staudinger reaction and related (intermediates in process), Fig. 2 Bioassays or figures to understand: Figures 1A, 3, 4B,C,E,F/G. Table 1 (enzyme parameters Km and Vmax).

			Important concepts: -overall goal of the project -structure of O-Glc-NAc and NAz and their attachment to Ser/Thr (but not the entire conjugate piece nor biotin) -role of hexosamine salvage pathway -role of streptavidin-biotin binding and horseradish peroxidase (HRP) use
March 20 **Chi and Sahana**	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 mechanism: Fischer indole synthesis Bioassays to understand: Figure 2a/2b, 3f, and 4a/4b. Important concepts: clogP; lipophilicity and neurological agents; cardiotoxicity (hERG); pharmacophore; serontonin receptors
March 25 **Dr. Kelly Bleasby** (BMS)		Optimizing Blood-Brain-Barrier Penetration: Considerations for Drug Design, Delivery and Translation Harnessing Preclinical Data as a Predictive Tool for Human Brain Tissue Targeting | ACS Chemical Neuroscience	-effects of transport proteins in controlling drug access to the brain and CNS (be familiar with this cycle and system) -free drug theory -impact of frequency of P-gp and BRCP transporter proteins in different animal models and comparison with human drug BBB penetration.
March 27 **Stirling and Gabriela**	Schizophrenia and potential Alzheimer's disease 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: CYP mechanism of oxidation of xanomeline (mechanism shown at beginning of course) Bioassays to understand: Table 1 (a radioligand assay) and Figure 1 (an example of drug metabolism) Important concepts: receptor agonism; cholinergic hypothesis; drug metabolism; orthosteric vs. allosteric inhibitors/agonists/antagonists; isosteres
April 1 **Dr. Trevor Sherwood** (BMS)		Discovery of afimetoran, a first-in-class small molecule dual antagonist of TLR7/8 for the treatment of lupus Identification of 2-Pyridinylindole-Based Dual Antagonists of Toll-like Receptors 7	-general med chem structure-activity principles including isosteres, steric and electronic considerations of different substituents -V_{ss} or V_d meaning and importance; Cl meaning and importance

		and 8 (TLR7/8) | ACS Medicinal Chemistry Letters Discovery of Potent and Orally Bioavailable Small Molecule Antagonists of Toll-like Receptors 7/8/9 (TLR7/8/9) | ACS Medicinal Chemistry Letters	-Toll-like receptor antagonism therapeutic mechanism of action to address autoimmune diseases -2020 ACS Med Chem Letters article: Figure 5A and B (crystal structure of 17c bound to TLR8). -I will focus questions on the two lecture references given the absence of slides or a recording.
April 3 **Alex and Sidney**	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	Reactions: Be able to complete the synthesis by providing intermediate products (know what reagents do), if I gave you a fill-in-the-box synthetic pathway -show reactivity of functional groups in GB-18 (PS8) Bioassays to understand: Figure 4a (radioligand assay) and 4b TANGO assay (also see slide no. 33 in presentation) Important concepts: G-protein coupled opioid receptors (know the basics of operation); natural product alkaloid drugs; structure-reactivity analysis (see PS8)
April 8 **Dr. Denise Grunenfelder** (BMS)	anti-cancer via T-cell activation	The Frontier of T Cell Checkpoint Therapies: Discovery of Dual Inhibitors of Diacylglycerol Kinases α and ζ Discovery of Potent, Dual-Inhibitors of Diacylglycerol Kinases Alpha and Zeta Guided by Phenotypic Optimization | ACS Medicinal Chemistry Letters	Reactions: diazirine photoaffinity labeling Important concepts: phenotypic drug screening; understand the mechanism of action of the DG kinase inhibitor (Fig. 1)
April 10 **Rio and Simone**	antiviral	Discovery of JNJ-1802, a First-in-Class Pan-Serotype Dengue Virus NS4B Inhibitor | Journal of Medicinal Chemistry Tim H.M. Jonckers et al. *J. Med. Chem.* 2024, 67, 5, 4063–4082	Reaction mechanisms: Bioassays to understand: Table 3 and 9 Important concepts: phenotypic screens; dengue virus treatment (role of serotypes); effects of methoxy vs. glycol vs. sulfone group; chiral center issues;

April 15 **Nuha and Kyra**	antibacterial	Discovery of Taniborbactam (VNRX-5133): A Broad-Spectrum Serine- and Metallo-β-lactamase Inhibitor for Carbapenem-Resistant Bacterial Infections | Journal of Medicinal Chemistry B. Liu, C. J. Burns et al. (Venatorx Pharmaceuticals in Malvern, PA) *J. Med. Chem.* 2020, 63, 6, 2789–2801	Reaction mechanisms: serine and metalloproteases as beta-lactamases; mechanism of penicillin inhibition of cell wall biosynthesis; mechanism of boronic acid inhibition of serine and metallo- beta-lactamases (Fig. 4) Bioassays to understand: Table 2 and 3 Important concepts: 4 mechanisms of bacterial resistance to beta-lactams
April 17 **Paige and Taylor**	potential anti-parasitic	Cyanotriazoles are selective topoisomerase II poisons that rapidly cure trypanosome infections | Science S. P. S. Rao et al. Science, 29 Jun 2023, Vol 380, Issue 6652, pp. 1349-1356	Reaction mechanisms: 5-Ethynyl-2′-deoxyuridine (EdU) reaction mechanism with Cu click chemistry Bioassays to understand: Figure 4A, i.e. role of mutation studies. Figure 5A-I (assays and crystal structures)
April 22 **Dr. Dipa Kalyani** (Merck)	coronary artery disease (cholesterol lowering)	Cyclic peptides and drug development Series of Novel and Highly Potent Cyclic Peptide PCSK9 Inhibitors Derived from an mRNA Display Screen and Optimized via Structure-Based Design | Journal of Medicinal Chemistry	Reaction mechanisms: HATU peptide coupling/amide synthesis Concepts: basics of the mechanism of cholesterol lowering through PCSK9 inhibition; peptide synthesis (Merrifield), including macrocyclic peptides; peptide drug strategies;
April 24 **Chelsea and Bernie**	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: Heck alkynylation, reductive amination Bioassays to understand: Fig. 3 Important concepts: diversity-oriented synthesis; natural product-like drugs, phenotypic screening practices, hERG issues

April 29 **Sonja and Elaine**	antibacterial	A novel antibiotic class targeting the lipopolysaccharide transporter | Nature *volume 625*, pages 566–571, (2024); C. Zampaloni, M. A. Lobritz, K. A. Bradley et al. (Hoffman-La Roche Pharmaceutical Company)	Reaction mechanisms: Suzuki cross-coupling reaction, HATU peptide coupling. Bioassays to understand: Important concepts: CRAB resistance; lipopolysaccharide transporter system and the mechanism of action of Zosurabalpin (ZAB, Fig. 3ab); solid phase peptide synthesis (Merrifield); macrocyclic peptide synthetic strategies; plasma precipitation
May 1 **Gabby, Joseph and Spencer**	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: TMZ and KL-50 mechanism of action (e- flow); KL-50 synthesis (slide 17, 57+58→4a); Bioassays to understand: Figure 2B, 5AB, and 6A. Important concepts: TMZ and KL-50 mechanism of action (general principles);