Introductory medicinal chemistry course for pharmacy students: an assignment-based assessment strategy

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Section 1: Detailed Course Description:

The medicinal chemistry section was 1/3 of a 6 credit hour course. Only the medicinal chemistry syllabus is listed below.

MEDICINAL CHEMISTRY

Overview: The fundamental goal of this class section is to provide pharmacy students with the necessary understanding of the molecular interactions that occur between drugs and their targets (i.e. receptors and enzymes). They will have a general understanding of how drugs are discovered and developed, structure activity relationships and how a drug can be modified chemically to improve drug action and/or reduce adverse effects, while maintaining activity. The principles of drug metabolism at a molecular level are also discussed. Weekly case studies will be discussed to exemplify key points.

Section 2: Lecture topics and Learning objectives

Lecture 1. Drug discovery: hit and lead identification

Understand the concept of hits and leads in the context of drug discovery.
Describe drug discovery projects
Describe various sources of hits and leads.

Lecture 2. Lead optimization: drug-target interactions and the pharmacophore

Identify properties evaluated and improved during lead optimization.
Recognize the molecular interactions involved in drug-target binding.
Describe some historical and current methods to evaluate structure-activity relationships.
Understand how pharmacophores are identified and utilized.
Learn the principles of ligand-based and structure-based drug design.

Lecture 3. Lead optimization: properties optimized and medicinal chemistry strategies
Understand the specific properties that are targeted during lead optimization.
Become familiar with lead optimization assays and their target values.
Apply common rules used during lead optimization.
Learn multiple strategies that are applied during the lead optimization process.
Recognize when specific medicinal chemistry strategies should be applied.

Lecture 4. The process of developing a drug from an optimized lead
Develop an understanding of the historical evolution of the drug approval process.
Summarize the different types of patents important for drug discovery and development.
Identify the characteristics of process chemistry synthesis.
Learn the various phases of clinical trials and what is evaluated in each.
Summarize aspects of formulations that are critical for a drug development project.

Lecture 5. Drug metabolism
Become familiar with the pharmacokinetic parameters that are evaluated during the drug development stage.
Understand aspects of toxicity testing undertaken during the drug development stage.
Become familiar with the phases of drug metabolism.
Recognize and apply the sites of potential drug metabolism
Know and apply the classes of enzymes responsible for drug metabolism and conjugation

Lecture 6. Receptors, ion channels, and transporters as drug targets
Describe the basic structural features of different classes of receptors, ion channels, and transporters.
Understand the various ways small molecules can affect the activity of receptors, ion channels, and transporters.
Develop a basic understanding of receptor theory.
Learn examples of various drugs that act at G protein-coupled receptors, nuclear receptors, ion channels, and transporters.

Lecture 7. Enzymes As Drug Targets Part 1
Learn general mechanisms of several classes of enzymes including esterases, proteases, and kinases.
Understand the use of enzyme kinetics to characterize inhibition.
Recognize when to apply specific medicinal chemistry strategies according to the class of enzyme being targeted.
Learn examples of drugs that target various enzyme classes

Lecture 8. Enzymes As Drug Targets Part 2

Learn general mechanisms of several classes of enzymes including polymerases, oxygenases, and reductases
Understand the use of enzyme kinetics to characterize inhibition.
Recognize when to apply specific medicinal chemistry strategies according to the class of enzyme being targeted.
Learn examples of drugs that target various enzyme classes.

Lecture 9. Protein-protein and lipid structure interactions as drug targets
Understand why atypical drug targets, such as protein-protein interactions and lipid structures, are more challenging than traditional receptor and enzyme targets.
Gain familiarity with the general strategies used for hit identification for these targets.
Understand several design strategies and concepts that have been successfully applied to find modulators of protein-protein interactions.
Identify several different mechanisms by which small molecules can modulate protein-protein interactions.
Learn examples of drugs that work by interrupting or mimicking protein-protein interactions and by interacting with lipids and cell membranes.

Lecture 10. DNA and RNA as drug targets
Explain the rationale for targeting DNA and RNA.
Name and describe the various ways small molecules can make noncovalent interactions with DNA.
Identify several different mechanisms by which small molecules can cause modifications to nucleic acids.
Describe how antisense oligonucleotides work.
Recognize drugs that function by targeting DNA and RNA.

Section 3: Textbooks

Highly recommended is Dunlap and Huryn as the Medicinal Chemistry in PHAR1040 closely mirrors early Chapters in that book.

1. Norma Dunlap, Donna M. Huryn, *Medicinal Chemistry*, Garland Science, 1st Ed. 2018.
2. Benjamin E. Blass, *Basic Principles of Drug Discovery and Development,* Academic Press, Elsevier, 1st Ed. 2015
3. Foye's Introduction to Medicinal Chemistry, LWW
4. Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, LWW
5. Patrick's Introduction to Medicinal Chemistry, OUP

At the end of each lecture there are review questions and application questions, in addition to the required assignment on drug design to be submitted (see below).

Secion 4: Course evaluation

9 weekly assignments (2% each), Final video assignment 18 %, total 33 % of course.

1) Submission of any assignment is an acceptance of, and adherence to, the academic integrity policy of the College of Pharmacy, Faculty of Health and Dalhousie University.
2) There are no written exams for the medicinal chemistry section. The medicinal chemistry is 33% of your grade for the course.
3) Associated with each lecture there is **one application question to be completed and submitted using the online form link on the PDF lecture slides**. The question will be related to the drug discovery example covered each week. Each completed submission is worth **2%** of your final grade for the course.
4) The remaining 15% of your grade will be the screen capture video and audio of a specific drug and how it binds to its target (~3 min duration). Each student will be able to select a drug from a pre-defined list. It is suggested to use the Molsoft browser (see tutorial video for assistance) https://youtu.be/KehX3gQft50. Discussion with the course instructor is welcomed for those who seek clarity on the process.
5) Creativity and originality are welcomed alongside chemically relevant scientific information.
6) Submission of a link for each screen recording / video will be via the Microsoft form in the medicinal chemistry PDF slides on Brightspace.
7) **Failure to submit assignments by due dates, without written documentation, as approved by Dalhousie, will result in zero for that assignment**.

Assignment	Grade %	Drug design topic	Due date
1	2	Artemisinin	Wed Sept 13th
2	2	Imatinib	Wed Sept 20th
3	2	Rivaroxaban	Wed Sept 27th
4	2	Linezolid	Wed Oct 18th
5	2	Fluoxetine	Wed Oct 25th
6	2	Ramelteon	Wed Nov 1st
7	2	Enalapril	Wed Nov 8th
8	2	Vorinostat	Wed Nov 20th
8	2	Maraviroc	Wed Nov 28th
10	15	Video / screen recording Complete assignment week 13 – 17 Nov	Wed Dec 6th

Assignment 1

Use the molecule drawing website https://www.molsoft.com/2dto3d.html or other online drawing software, use the Chemical dictionary search to retrieve the artemether structure, explore the shape of the molecule in 3D. Change the structure using the drawing tools to artemisinin and dihydroartemisin and explore the 3D nature of each molecule.

- Open http://molsoft.com/2dto3d.html
- Use the Chemical Dictionary Search (on the top right) to find the molecule of interest
- Modify the structure as required
- Export the Isomeric SMILES code use the Export button and then Show SMILES
- Copy (right click for copy) and paste the ascii string into the online form for assignment one.
- Note. Isomeric SMILES codes contain stereochemical information whereas canonical SMILES codes do not.

- Note. You do not have to use the suggested website, but it is one that is efficient.

Assignments 2 – 9

Use the molecule drawing website https://www.molsoft.com/2dto3d.html.

- Use the Chemical dictionary search to retrieve the drug structure.
- Design your own analogue to target the drug target. Paste the Isomeric SMILES codes for the analogue, and your rationale to this form:
- The quality (strength) of the interaction between analogue and target is not part of the grading.
- Kudos may be given for novel analogues with great insight.

Rubric

- SMILES codes generates relevant structure
- Chemical structure is different to parent drug in meaningful manner
- Stable chemical structure
- Written statement identifies appropriate structural feature(s) on chemical structure and on target
- Written statement identifies relevant molecular interactions
- Written statement grammatically and scientifically sound
- Written statement links to chemical structure

Paste the Isomeric SMILES code and the written statement onto the online form for submission.

Assignment 10 rubric

- PDB code selection after thanksgiving
- Using the molsolft browser (http://www.molsoft.com/icm_browser.html) use the MolsoftBrowserTutorial video (https://youtu.be/KehX3gQft50) and online tools to explain how to use the software.
- Develop a presentation using the software to explain how the drug interacts with its target. Explore textbook / literature / web resources to provide background depth of knowledge.
- The rubric for evaluation is based on the level of competency describing the following points:
  The drug structural features
  The drug target
  Whether it is a natural product or synthetic drug
  Functional groups that are involved in binding the drug target
  Types of molecular interactions between drug and target
  Potential structure-activity relationships
  Potential sites of metabolism
  Potential sites of reactivity
  Other pertinent information about the drug-target interaction, mechanism of action, drug properties
- Creativity and original approaches are encouraged alongside scientific rigor.
- Not all of the above points are expected to be covered, it is recognized each drug is different.
- The length of the recording should be no more than 3 minutes.

Section 5: Web-based Medicinal Chemistry Resources for Pharmacy (and beyond)

1. CISCO VPN server – software so your computer appears from within Dalhousie – search Dalhousie ITS CISCO
2. Dalhousie library website
3. Structure drawing – 2D to 3D https://www.molsoft.com/2dto3d.html
4. Protein Data Bank: http://www.rcsb.org to look up / for PDB codes (drug-enzyme interactions)
5. ICM-Browser http://www.molsoft.com/icm_browser.html https://youtu.be/KehX3gQft50 (video assistance)
6. To calculate molecular properties http://molsoft.com/mprop/ or https://www.molinspiration.com/cgi-bin/properties
7. Pubchem (chemical searches) : https://pubchem.ncbi.nlm.nih.gov
8. Drugbank (drug data): https://www.drugbank.ca
9. SciFinder (best chemical / structural information): https://scifinder.cas.org/scifinder/view/scifinder/scifinderExplore.jsf
10. Chemdraw software (https://sitesubscription.cambridgesoft.com/#D)
11. Wikipedia: a great resource for non-clinical drug information

Section 6: List of drugs and PDB codes for assignment 10.

Students were provided access to an online list after the third lecture and told to select their drug of choice. This is the data used for fall 2023.

Drug	Disease	Mechanism of action	Method of discovery	PDB	Approximate year approved	Subtype of disease
Abemaciclib	Cancer	CDK6 inhibitor	med chem	5L2S	2017	To treat certain advanced or metastatic breast cancers
Abrocitinib	Atopic dermatitis	JAK1 inhibitor	med chem	6BBU	2022	To treat atopic dermatitis
Abrocitinib	Atopic dermatitis	JAK1 inhibitor	med chem	6BBU	2022	To treat atopic dermatitis
Alectinib	Cancer	ALK kinase domain inhibitor	med chem	3AOX	2015	To treat ALK-positive lung cancer
Aliskiren	Hypertension	Renin inhibitor	med chem	2V0Z	2008	?
Alpelisib	Cancer	PI3K alpha inhibitor	med chem	4JPS	2019	To treat breast cancer
Ampicillin	Antibacterial	Penicillin binding protein	NP - semisynthesis	3ITA		
Artesunate	malaria	Artemisinin antimalarial	NP - semisynthesis	6FGC	2020	To treat severe malaria
Asciminib	cancer	ABL kinase	med chem	5MO4	2021	To treat CML
Avacopan	anti-inflamatory	Complement 5a receptor antagonist	med chem	6C1R	2021	To treat immune ANCA-associated vasculitis
AZT	HIV	DNA replication	repurposing	1E99		
Aztreonam	Antibacterial	Beta-lactamase	NP - semisynthesis	1FR1		

Baloxavir Marboxil	Influenza	Cap-endonuclease inhibitor	med chem	6FS6	2018	To treat acute uncomplicated influenza in patients who have been symptomatic for no more than 48 hours.
Baricitinib	Rheumatoid arthritis	BMP-2 inducible kinase	med chem	4W9X	2018	To treat moderately to severely active rheumatoid arthritis
Belinostat	Cancer	HDAC	med chem	5EEN	2014	
Bictegravir	HIV	Integrase strand-transfer inhibitors	med chem	6RWM	2018	To treat infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen
Brigatinib	Cancer	ALK	med chem	6MX8	2017	To treat patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib
Calcipotriol	Psoriasis	Vitamin D Receptor agonist	med chem	1S19		
Carbenicillin	Antibacterial	Penicillin binding protein	NP - semisynthesis	3OCL		
Carfilzomib	Cancer	Proteasome inhibitor	NP	4R67	2012	
Ceftazidime	Antibacterial	Penicillin binding protein	NP - semisynthesis	3OCN		
Cephalothin	Antibacterial	Penicillin binding protein	NP - semisynthesis	1CEG		
Clavulanic Acid	Antibacterial	Beta-lactamase	NP	1BLC		
Cobimetinib	Cancer	MEK1 protein kinase inhibitor	med chem	4LMN	2015	To be used in combination with vemurafenib to treat advanced melanoma that has spread to other parts of the body or can't be removed by surgery, and that has a certain type of abnormal gene (BRAF V600E or V600K mutation)
Copanlisib	Cancer	PI3K alpha / delta inhibitor	med chem	5G2N	2017	To treat adults with relapsed follicular lymphoma
Dabrafenib	Cancer	BRAF V600E	med chem	4XV2	2013	
Daclatasvir	HCV	NS5A inhibitor	med chem	4CL1		
Dacomitinib	Cancer	EGFR kinase inhibitor	med chem	4I23	2018	To treat metastatic non-small-cell lung cancer
Daridorexant	Insomnia	Orexin 1/2 receptor antagonist	med chem	6TP3	2022	To treat insomnia
Dolutegravir	HIV	Integrase strand-transfer inhibitors	med chem	3S3M		
Donepezil	Alzheimer's	AChE inhibitor	med chem	4EY7		
Doravirine	HIV	Non-nucleoside reverse transcriptase inhibitor	med chem	4NCG	2018	To treat HIV-1 infection in adult patients
Elvitegravir	HIV	Integrase strand-transfer inhibitors	med chem	3L2U	2015	For use as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Emtricitabine	HIV	Nucleoside reverse transcriptase inhibitor	med chem	2NO6	2015	For use as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older

Entrectinib	Cancer	ALK kinase domain	med chem	5FTO	2019	To treat adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive, To treat adult and pediatric patients 12 years of age and older with solid tumors
Erdafitinib	Cancer	FGFR inhibitor	med chem	5EW8	2019	To treat adult patients with locally advanced or metastatic bladder cancer
Eribulin	Cancer	Tubulin binder	NP - semisynthesis	5JH7	2010	
Ertapenem	Antibacterial	Beta-lactamase	NP - semisynthesis	3M6B		
Fedratinib	Cancer	Bromodomane BRD4 inhibitor	med chem	4OGJ	2019	To treat adult patients with intermediate-2 or high-risk primary or secondary myelofibrosis
Flurbiprofen	Pain	COX2 inhibitor	med chem	3PGH		
Fluticazone Fluroate	Inflammation	Glucocorticoid nuclear receptor LBD	med chem	3CLD		
Futibatinib	cancer	ibroblast growth factor receptor kinases	med chem	6MZW	2022	Intrahepatic cholangiocarcinoma (bile duct cancer)
Gilteritinib	Cancer	FLT3 inhibitor	med chem	6JQR	2018	To treat patients who have relapsed or refractory acute myeloid leukemia (AML)
Grazoprevir	HCV	NS3/4A protease inhibitor	med chem	3SUD	2016	To treat patients with chronic hepatitis C virus (HCV) genotypes 1 and 4 infections in adult patients.
Haloperidol	Antipsychotic	DRD2 dopamine receptor	med chem	6LUQ		
Ibrutinib	Cancer	BTK kinase	med chem	5P9I	2013	
Indomethacin	Pain	COX2 inhibitor	med chem	4COX		
Infigratinib	cancer	FGFR2 kinase inhibitor	med chem	3TT0	2021	To treat FGFR2-mutated bile duct cancer
Ivacaftor	Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	med chem	6O2P	2018	To treat cystic fibrosis in patients age 12 years and older
Ixazomib	Cancer	Proteasome inhibitor	med chem	5LF7	2015	To treat people with multiple myeloma who have received at least one prior therapy
Lemborexant	Insomnia	Orexin-1 receptor	med chem	6TOT	2019	To treat insomnia
Lenacapavir	antiviral HIV	HIV-1 capsid	med chem	6VKW	2022	To treat HIV-1 infection
Lenvatinib	Cancer	VEGFR1 inhibitor	med chem	5ZV2	2015	To treat patients with progressive, differentiated thyroid cancer (DTC) whose disease progressed despite receiving radioactive iodine therapy (radioactive iodine refractory disease).
Linagliptin	NIDDM	DPP4	med chem	2RGU		
Lorlatinib	Cancer	ALK / ROS1 inhibitor	med chem	4CLI	2018	To treat patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer
Meropenem	Antibacterial	Beta-lactamase Oxa-13	NP - semisynthesis	1H8Y		
Midostaurin	Cancer	Multi-targeted protein kinase	NP - semisynthesis	4NCT	2017	To treat acute myeloid leukemia, advanced systemic mastocytosis
Migalastat	Fabry disease	Human alpha-N-acetylgalactosaminidase	med chem	4DO5	2018	To treat treat adults with Fabry disease.
Mocifloxacin	Antibiotic	DNA gyrase	med chem	5CDQ		

Mu-Opioid antagonist	Pain	mu-opioid	NP - semisynthesis	4DKL		morphinan antagonist
Neratinib	Cancer	EGFR kinase inhibitor	med chem	2JIV	2017	To reduce the risk of breast cancer returning
Niraparib	Cancer	PARP1	med chem	4R6E	2017	For the maintenance treatment for recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers
Obeticholic Acid	Liver disease	Nuclear receptor FXR agonist		1OSV	2016	To treat rare, chronic liver disease
Olutasidenib	cancer	Isocitrate dehydrogenase I	med chem	6U4J	2022	To treat refactory acute myeloid leukemia
Orlistat	Weight loss	Human fatty acid synthase	med chem	2PX6		? maybe not original target
Oseltamivir	Influenza	Neuraminidase	med chem	6HEB		
Osilodrostat		Cortisol synthesis inhibitor	med chem	7m8v	2020	To treat cushing disease
Osimertinib	Cancer	EGFR T790M inhibitor	med chem	6JX4	2015	To treat certain patients with non-small cell lung cancer
Oteseconazole	Antifungal infection	sterol 14-alpha demethylase (CYP51)	med chem	5TZ1	2022	To treat Candidiasis
Pacritinib	cancer	FLT3 and JAK2 inhibitor	med chem	5LBZ	2022	To treat Myelofibrosis, but the structure here is not the kinase ihibitor, but another previously unknown target quinon reductase 2
Palbociclib	Cancer	CDK6 inhibitor	med chem	5L2I	2015	To treat advanced (metastatic) breast cancer
Panobinostat	Cancer	Histone deacetylase inhibitor	med chem	5EF8	2015	To treat patients with multiple myeloma
Pemigatinib	Cancer	FGFR1-3 kinase inhibitor	med chem	7wcl	2020	To treat Cholangiocarcinoma
Pexidartinib	Cancer	FMS kinase	med chem	4R7H	2019	To treat adult patients with symptomatic tenosynovial giant cell tumor
Piperacillin	Antibacterial	Penicilin binding protein	NP - semisynthesis	6Q9N		
Pomalidomide	Cancer	E3 ubiquitin ligase	drug repurposing /med chem	6H0F	2013	
Pralsetinib	Cancer	RETkinaseinhibitor	med chem	7ju5	2020	To treat RETfusion-positiveNSCLC
Relebactam	Antibiotic	Beta-lactamase	med chem	6QW7	2019	To treat complicated urinary tract and complicated intra-abdominal infections
Remdesivir	antiviral	RNA polymerase inhibitor	med chem	7BV2	2020	To treat COVID19
Ribociclib	Cancer	CDK6 inhibitor	med chem	5L2T	2017	To treat postmenopausal women with a type of advanced breast cancer
Ripretinib	Cancer	KIT1 protein kinase inhibitor	med chem	6MOB	2020	To treat advanced gastrointestinal-stromal tumors
Ripretinib	cancer	KITandPDGFRAkinaseinhibitor	med chem	6MOB	2020	To treat GIST
Ritonavir	HIV	CYP3A	med chem	3NXU		(similar to cobicistat)
Rivastigmine	Alzheimer's	AChE inhibitor	NP - semisynthesis	1GQR		
Rosiglitazone	NIDDM	PPARgamma agonist	animal model, later discovered to be PPAR	5YCP		
Rosuvastatin	Cholesterol lowering	HMG CoA reductase inhibitor	med chem	1HWL	2003	To treat cardivascular disease
Rucaparib	Cancer	PARP inhibitor	med chem	4RV6	2016	To treat women with a certain type of ovarian cancer
Sacubitril	Heart failure	Neprilysin inhibitor	med chem	5JMY		To treat heart failure

Safinamide	Parkinsons	MAO B inhibitor	med chem	2V5Z	2017	To treat Parkinson's disease
Salbutamol	Asthma	Beta2-adrenergic receptor	med chem	2Y04		but beta 1 receptor
Salmeterol	Asthma	Beta2-adrenergic receptor	med chem	6MXT		
Selpercatinib	Cancer	RETkinaseinhibitor	med chem	7ju6	2020	To treat RETfusion-positiveNSCLCand P,O,B,A thyroid cancer
Selumetinib	Cancer	MEK1 protein kinase inhibitor	med chem	4U7Z	2020	To treat neurofibromatosis type 1, a genetic disorder of the nervous system causing tumors to grow on nerves
Selumetinib	cancer	MEK1/2 kinase inhibitor	med chem	7jut	2020	To treat acute myeloid leukemia, advanced systemic mastocytosis
Sildenafil	Erectile disfunction	PDE5	med chem	1UDT		
Sofosbuvir	HCV	NS5B	med chem	4WTG	2017	To treat adults with chronic hepatitis C virus
Tafamidis Meglumine	Heart disease	TTR complex	med chem	3TCT	2019	To treat heart disease (cardiomyopathy) caused by transthyretin mediated amyloidosis (ATTR-CM) in adults
Talazoparib	Cancer	PARP inhibitor	med chem	4UND	2018	To treat locally advanced or metastatic breast cancer patients with a germline BRCA mutation.
Telmisartan	Blood pressue / Heart failure	PPARgamma agonist	med chem	3VN2		
Tepotinib	Cancer	MET kinase inhibitor	med chem	4R1V	2021	To treat non-small cell lung cancer (NSCLC)
Timolol	Glaucoma	Beta2-adrenergic receptor	med chem	3D4S		
Tivozanib	Cancer	VEGFR kinase inhibitor	med chem	4ASE	2021	To treat Renal cell carcinoma
Trifarotene	Acne	RAR gamma agonist	med chem	6FX0	2019	For the topical treatment of acne vulgaris in patients 9 years of age and older
Valacyclovir	HCV	Transporter uptake	med chem, prodrug	6GZ9		
Vancomycin	Antibiotic	D-Ala-D-Ala PBP substrate	NP	1FVM		
Venetoclax	Cancer	BCL-2 inhibitor	med chem	6O0K	2016	For chronic lymphocytic leukemia in patients with a specific chromosomal abnormality
Vismodegib	Cancer	Hedgehog signaling pathway antagonist	med chem	5L7I		
Vonoprazan	Bacterial infection	gastric proton pump	med chem	5YLU	2022	To treat Helicobacter pylori infections in combination with amoxicillin and clarithromycin
Voxilaprevir	HCV	NS3/4A protease	med chem	6NZT	2017	To treat adults with chronic hepatitis C virus
Zanamivir	Influenza	Neuraminidase	med chem	3TI5		
Zanubrutinib	Cancer	BTK kinase	med chem	6J6M	2019	To treat certain patients with mantle cell lymphoma, a form of blood cancer

Table S1. Instructor item relating to the course materials. These followed the standardized institutional questions (not provided).

Item	*Instructor Item*
1	The online medicinal chemistry assignments (assignments 1 - 9) involving drug design gave opportunities to apply course concepts including drug-target interactions

2 The online medicinal chemistry assignment, (assignment 10) investigating a single drug and preparing an online video, gave opportunities to apply course concepts including exploring the mechanism of action of the drug?
3 After completing the online medicinal chemistry assignments, I feel more confident for the medicinal chemistry components of the integrated problem-based learning cases?
4 Would you prefer to take another course with this type of assessment?
5 The online medicinal chemistry assignments involving drug design were preferable to traditional classroom-based written exams (e.g. MCQ / short answer)?

Table S2. Quantitative response to instructor items

Year	2022	2021	2022	2021	2022	2021	2022	2021	2022	2021
Item	1	1	2	2	3	3	4	4	5	5
Response count	46 / 69	32 / 64	46 / 69	32 / 64	45 / 69	32 / 64	45 / 69	32 / 64	46 / 69	31 / 64
Mean	3.6	4.1	3.8	4.3	3.9	3.6	2.9	3.9	3.5	4.5
S.D.	1.3	0.8	1.1	0.8	1.0	0.9	1.2	0.8	1.2	0.1
Interpolated Median	3.9	4.2	4.0	4.0	4.0	3.7	2.9	4.0	3.6	4.8
S. Disagree (%)	7	0	4	0	2	3	13	0	7	0
Disagree (%)	20	3	7	3	7	6	27	3	17	3
Neutral (%)	11	13	20	13	20	31	24	28	22	10
Agree (%)	35	53	43	41	44	50	24	41	33	19
S. Agree (%)	28	31	26	44	27	9	11	28	22	68

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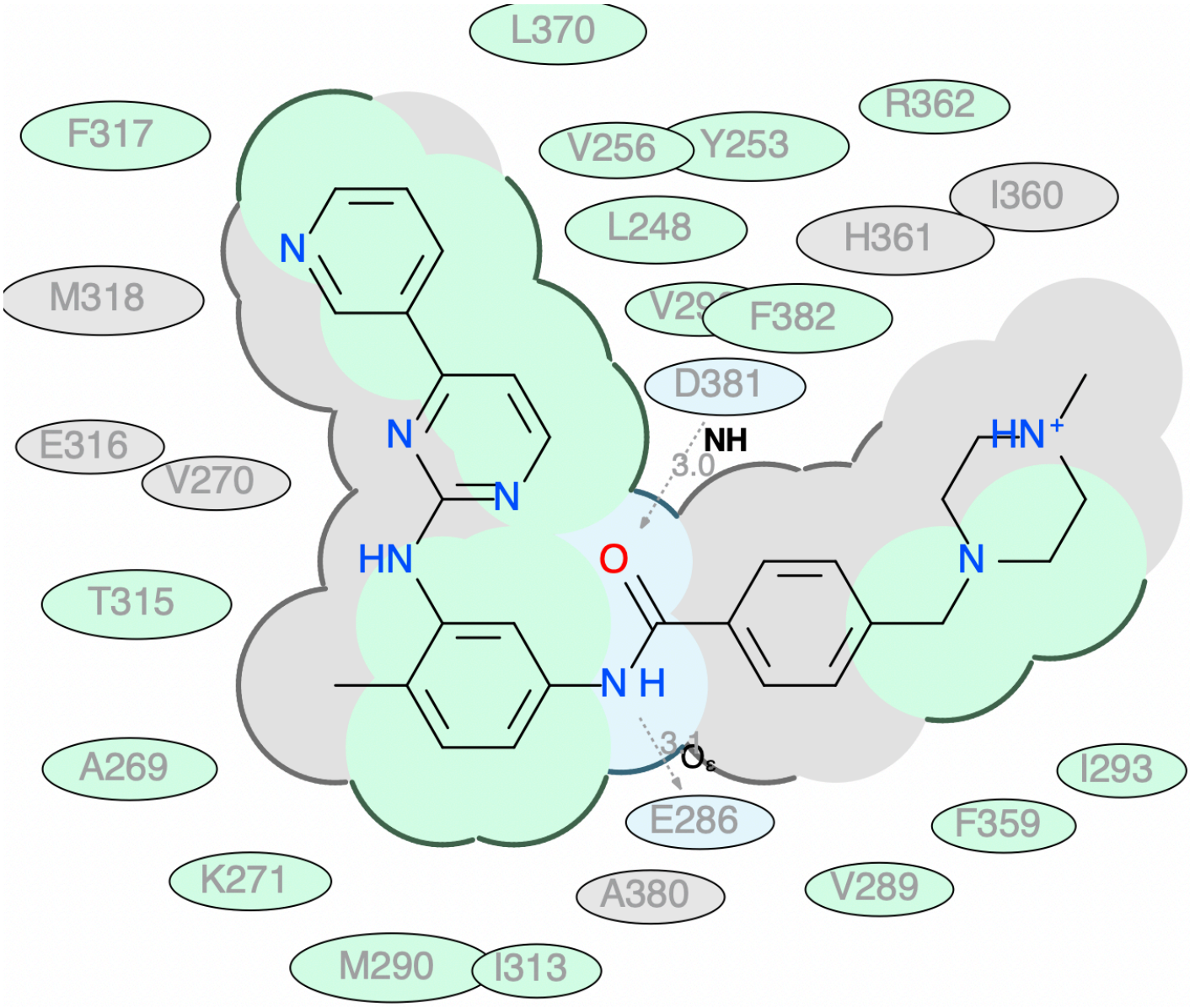
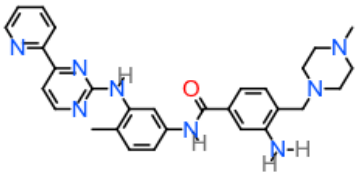
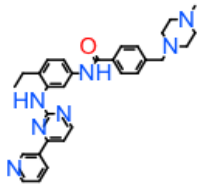
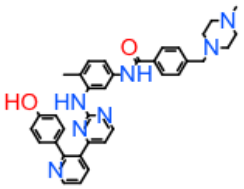
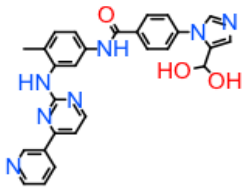
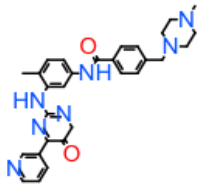
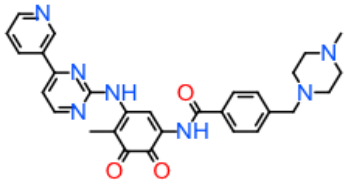
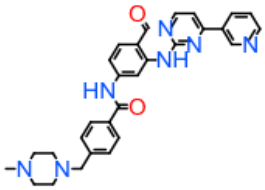
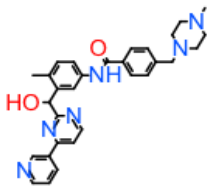
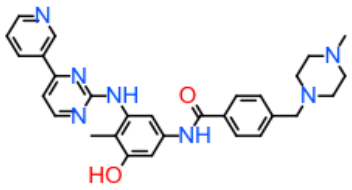
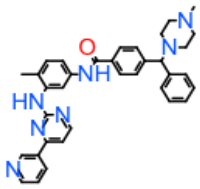
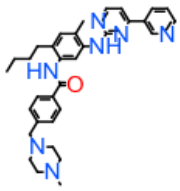
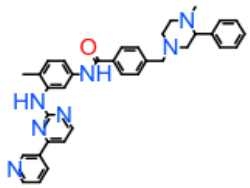
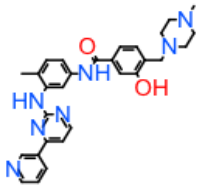
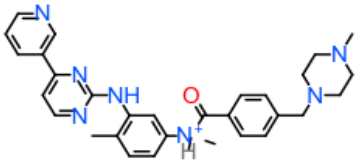
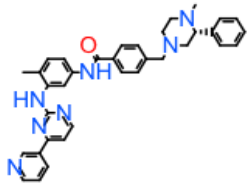
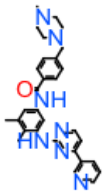
Figure 1. Larger version.

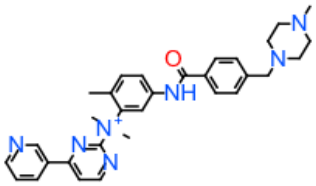
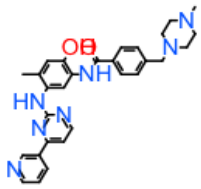
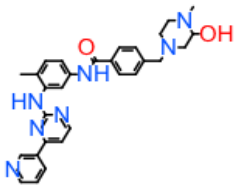
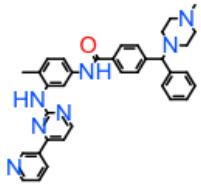
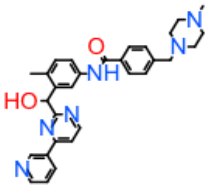
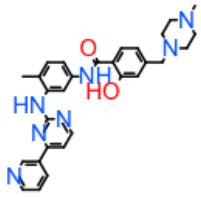


Section 7: Example assignment two responses

The student class was contacted by email to ask if their previously marked assignment could be used anonymously as example work for this manuscript. The first twenty positive responses were used (there were no negative responses). This data is from a subsequent class rather than from the classes whose survey data is included in Figure 2 and the table above.

Compound	What is your rationale for the structural modification?	Score	Comments
	I added a primary amine to the meta position of the DFG motif of imatinib. The hydrogens on the nitrogen atom would act as H-bond donors with the lone pairs on the oxygen atoms that make up the carboxylic acid side chain of the D381 residue.	2	Clear description linking chemical functionlity to target
	I increased the hydrocarbon branching from the central aromatic ring from a methyl group to an ethyl group, thereby increasing the potential for van der Waals forces with the active site of the Bcr-Abl enzyme.	1.5	Lacks target identification
	Adding this tyrosine amino acid in this position improves the binding of the structure in this binding site because of potential pi stacking interactions between the added benzene and the Phe317 of the hinge region. The OH of the tyrosine could also contribute to H bonding with the Thr315	1.6	Careful with the language - you didn't add tyrosine
	I made structural changes on the five ring structure, it previously had a methyl group and I added isopropyl alcohol, it increases hydrogen bonding and also enhances binding interactions. The strong electronegativity difference between hydrogen and oxygen leads to a strong attraction and finally making it an better drug efficacy.	1.5	Structure in equilibrium with aldehyde and description lacks linking to target residues
	I added an Oxygen double bond to the pyramidine ring, where this oxygen would bind through hydrogen bonding to the hydrogen attached to the secondary amine group of Aspartic amino acid in Bcr-Abl kinase.	1.7	Needed details on which aspartic acid and be careful with chemical language - do you mean an amide instead of secondary amine?
	I have decided to add two ketone (double bond oxygen) groups to the linker benzene ring of the linker module. This theoretically should improve the connection of imatinib to Bcr-Abl kinase, as the addition of the ketones will add the possibility of two more hydrogen bonds. Also, I believe the above-mentioned changes will increase the stability of imatinib's connection to the target molecule because the linker has the least bonds compared to other modules in imatinib.	1.5	The dicarbonyl is usually a reactive functionality and you don't mention where the H-bonds will be formed on the kinase
	I added a carbonyl group; originally where there was a methyl group, I added it to the carbon which was originally a methyl group. The O on the carbonyl group could hydrogen bond with the hydrogens on an Alanine.	1.4	You need more clarity in terms of which hydrogens.
	I have created this analogue of Imatinib by changing the secondary amine that connected two aromatic rings to a carbon then adding a hydroxyl group to that carbon. The hydroxyl group added will still act as a Hydrogen bond donor to Thr 315 but the reason for this using Oxygen instead is because it is more electronegative then Nitrogen causing the Hydrogen bond/interaction to Thr 315 to be stronger and bind better to the Bcr-Abl kinase.	1.7	Good rationale, but remember that the structure has become chiral

	I added a hydroxyl group to the linker aromatic ring of Imatinib so that it could hydrogen bond with lysine 271 and increase the overall binding afinity of Imatinib to Bcr-Abl kinase.	2	Very clear
	I decided to add a phenol group to a carbon that was next to the piperazine group. I believe Placing a Phenol group here will help to improve the solubility of the molecule. My phenol group will interact with the Phe359 in the base Bcr-Abl kinase and undergo non-covalent pi-stacking which overall increases the stability of the molecule	1.7	This makes the molecule chiral
	I added a hydrocarbon chain to the “linker” portion of the Imatinib molecule to incur some van der Waals forces between the new hydrocarbon chain and ILE 313 of the Bcr-Abl kinase and possibly desolvate the active site and the new molecule.	2	Good description
	I added a phenyl ring to the structure to allow for Pi bonding between the drug molecule and the amino acid F139 (phenylalanine). This will allow for a stronger bonding between the two.	2	Nice and clear
	I added an hydroxyl group to create a hydrogen bond between the drug and D381 (Aspartic Acid), specifically with an oxygen in aspartic acid. The hydrogen bond in this example will allow for a stronger bond between the two.	1.5	D381 is already involved in a key H-bonding interaction, so you need to be more specific.
	I connected the methyl group to the secondary amide's nitrogen to make it positively charged. This will increase solubility, which will improve drug absorption. Also, the positively charged nitrogen can have an ionic interaction with a negatively charged receptor, decreasing the Kd value due to higher energy, meaning there would be a tighter binding between the drug and receptor/protein.	1.3	You've removed a key H-bonding feature of the drug. Be specific with which particular residue will interact
	By adding this phenyl group to imatinib, it should interact with the F359 (phenylalanine 359) in the Bcr-Abl Kinase via pi stacking, allowing the drug to target this enzyme more specifically. This might also help the drug better be absorbed when taken orally, as the increased lipophilicity may facilitate diffusion into the enterocyte membranes of the stomach and GI tract.	2	Nice and clear
	I added another methyl group to the "linker" part of imatinib. I did this so that there would be additional hydrogen bonding with Bcr-ABl Kinase and they would be better linked.	1.3	How would this methyl substituent be involved in hydrogen bonding?

	I added two methyl substituents onto the nitrogen that is sandwiched in between two aromatic rings. This gives the nitrogen a positive charge allowing it to have a cation-pi binding interaction with Phe 317 instead of Thr 315 (the amino acid it usually binds to).	1.7	An audacious change. Switching binding modes will likely not improve binding affinity.
	I added a hydroxyl group onto the third aromatic ring of the imatinib analogue. This addition will increase the protein kinase activity by targeting the met 290 amino acid creating hydrogen bonding between the alcohol and the met group.	1.7	Be specific about which part of Met will be involved in H-bonding
	I added a hydroxyl group on the piperazine of the drug imatinib. The hydrogen of the added hydroxyl group will form a hydrogen bond with the oxygen of the carbonyl group, located on the histidine residue, His 361. This will strengthen the binding of the drug to the bcr-abl kinase.	1.5	Structure unstable. Introduces chirality.
	I added the addition of a benzene ring to the structure. With the addition of the benzene there would be increased π-π binding interactions with the target of Bcr-Abl Kinase. Possible interactions could be with Phe(359 or 382) target residues.	1.7	This change does make the molecule chiral
	I decided to change the nitrogen which is hydrogen bonded to the Thr 315 residue to a carbon atom covalently bonded to an alcohol (OH). This is because oxygen is more electronegative than nitrogen, where oxygen will enforce a greater pull of bonded electrons than nitrogen, giving hydrogen a larger partial positive charge. Therefore, stronger hydrogen bonding will occur between imatinib and threonine-315.	1.7	Good rationale, but remember that the structure has become chiral
	the fluoride substituent added to the pyrimidine ring creates more hydrogen bonding with the kinase/enzyme while the ethyl and hydroxyl groups on the aromatic ring adjacent to the piperazine ring form van der waals forces and more hydrogen bonds with Bcr-Abl respectively	1.4	Make only one change and be specific about where and how it will interact.
	The OH group I have added on the DFG motif (benzene ring) will perform a hydrogen bond interaction with the oxygen on Asp381	1.7	D381 is already involved in a key H-bonding interaction, so you need to be more specific.