Adaptable online Team-Based Learning in a capstone simulation "Hit-to-Lead" Drug Discovery exercise

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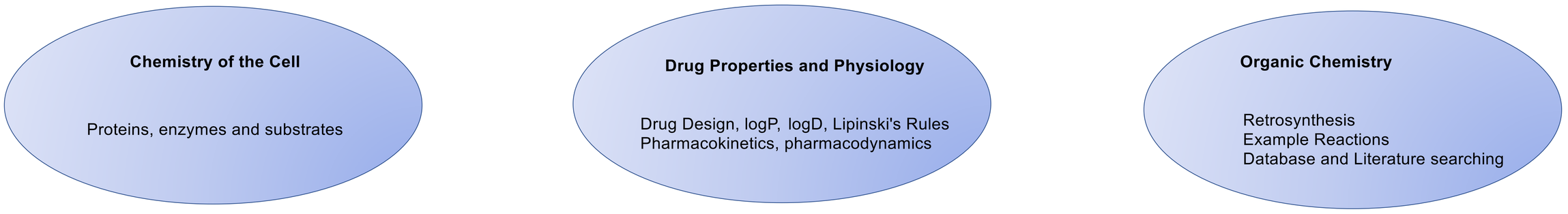
Drug discovery, particularly at the early stages, involves an understanding of both the chemistry of the potential drug molecule and the biological environment with which it interacts. This exercise aims to bring together all these different components that they have been taught across their degree programme into one capstone coursework exercise over eight weeks.



- Students are placed in groups of 4-6 depending on numbers
- Five different disease targets available to use depending on number of groups
- Weekly 2-hour workshop
- Week 1 – initial setup: to design an orally active Lead Compound with a given activity (target IC_{50}) for a given disease target from data on 4 Hit Compounds
- Teams agree a code of conduct, team name and logo
- Initial data for each compound: FW, logP, $logD_{7.4}$, logS and IC_{50}
- Weeks 2-5 – pre-reading and TBL exercises
- Teams review data a propose new compounds in an iterative process
- Each week teams submit 4 new compounds to "test"
- Weeks 6-8 – Teams develop a synthesis of their lead compound using retrosynthesis and databases such as Reaxys and SciFinder to plan the forward synthesis
- Week 11 – students submit an individual report in the form of a patent application
- During the pandemic the exercise was run entirely online
- Each team had a dedicated Microsoft Teams channel with their files and data. These were used to facilitate live discussion

Assessment has 3 components:

Team-based assessment (40%)

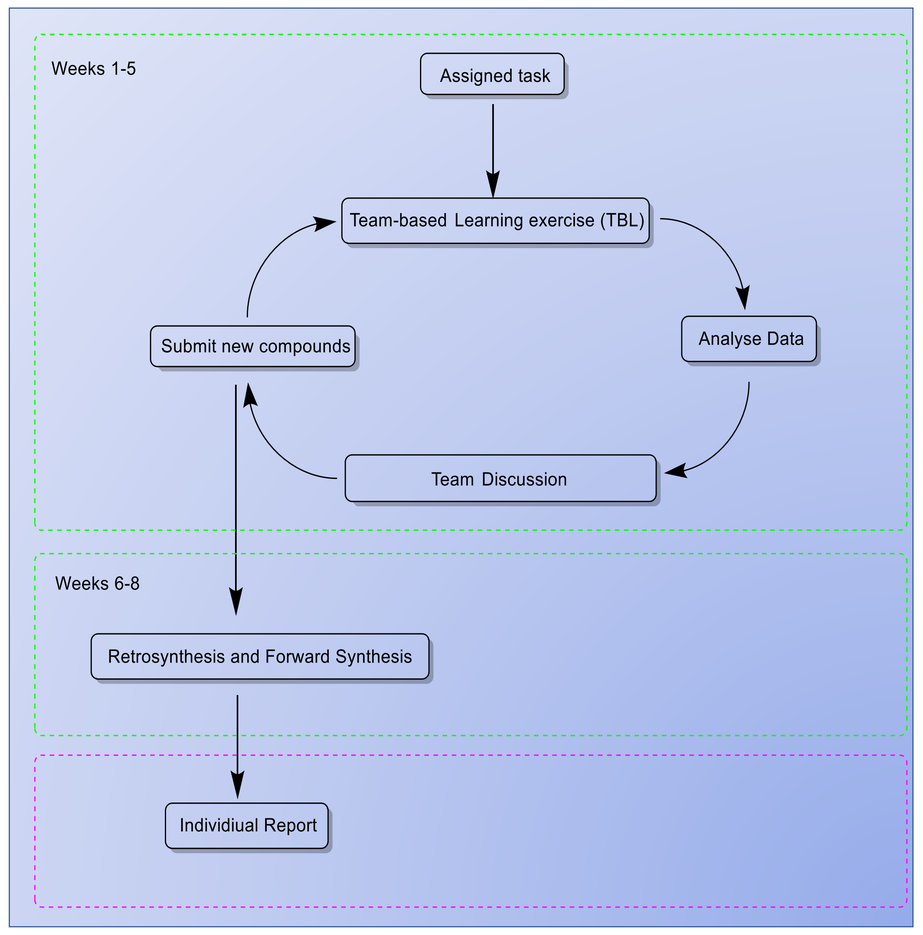
- They are assessed on how they have justified their changes based on the results they have obtained.

Individual assessment (50%)

- Final report includes Abstract, State of the Art (Introduction), Development (Results and Discussion) and Synthesis (Experimental)

Peer assessment (10%)

- Each student evaluates their team peers on research and preparation, cooperation and work ethic.



Paper-based

- Originally run as a paper-based exercise – everything "2D"
- Physicochemical data is generated using the online RSC ACD/iLab tool
- In week 3 teams are given a ChemDraw schematic of the protein target site showing the position and arrangement of the important amino acids
- In addition to the physicochemical data, IC_{50} data can then be decided upon to guide teams towards more druglike molecules
- Paper-based implementation is quicker and easier for large cohorts
- Currently being trialled by University of Leicester

Computational

- Adaptations have incorporated computational techniques: GOLD, PyMOL and PoseView (ProteinsPlus), to allow a more realistic simulation
- The teams submitted compounds are docked using GOLD. Using the ProteinsPlus website 2D representations showing the important interactions are generated. Students are taught how to use PyMOL to view their docked compounds in 3D, how to generate the PoseView and finally how to dock their compounds in GOLD
- IC_{50} values are decided upon by the rank order of the highest ranked poses
- Students access much higher-level Drug Discovery concepts
- More time-consuming to generate data for teams

Examples from individual student reports showing self-generated images to explain their teams decision-making process

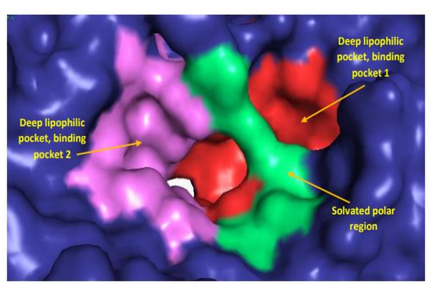


Figure 3 – The binding site of the 26S proteasome shown using surface visualisation in PyMOL. The 2 deep lipophilic pockets are shown in red (binding pocket 1) and violet (binding pocket 2), with the solvated bridging polar region shown in green. The rest of the protein (non-binding region) is shown in dark blue.

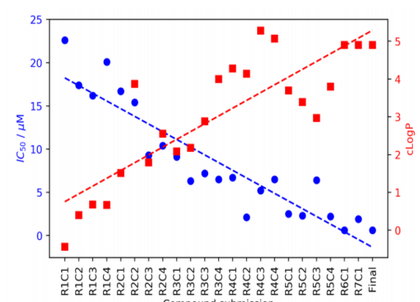


Figure 6 – The evolution of IC_{50} (clue circles) and cLogP (red squared) with compound submissions. The general trend as a linear regression for each parameter is shown as a dashed line.

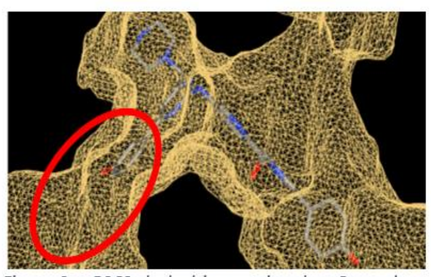


Figure 9 – R3C3 docked in proteins.plus. Occupying the side pocket was the aim of the R4C4 structure.

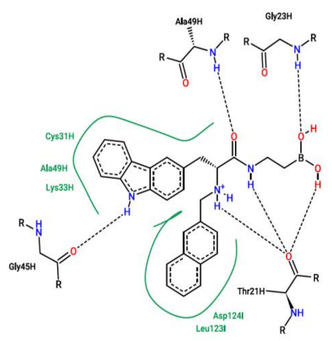


Figure 5 – The binding interactions observed for R4C2. The green lines represent hydrophobic interactions, the dotted lines represent polar or ionic interactions.

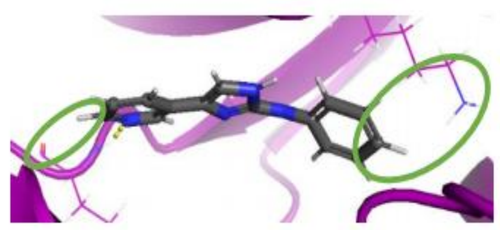


Figure 9: R1C2 is docked, with interactions aimed to be made by R2C3 highlighted

Team-based Learning aspects (TBL)

- Each week students were given pre-reading on a subject relevant to the workshop. Students undertook TBL assessments in the form of iRATs and tRATs (individual and team Readiness Assessment Tests) – in the tRAT the team answers the same questions the were asked in the iRAT but can discuss the answer as a team
- In all cases the team scores were higher than any score by an individual team member
- Tests were carried out using Microsoft Forms during the live sessions in Microsoft Teams – students submitted iRATs in the main session then went into their team channel to complete the tRAT
- The TBL concept is extremely useful for reinforcing the team nature of the exercise – prior to introduction were more likely to see more individual behaviour and even exclusion
- After the RATs time is allowed for discussion of the questions and concepts before the teams receive their data form the previous week

Student Feedback

"This exercise forced me to look over my previous drug discovery notes and put them into practice for the first time which helped me to understand it better. I learnt a lot through doing this exercise which was a nice change to traditional lectures."

"This coursework was quite good fun, and I really enjoyed using the computational visualisation software. This was the only group work I have ever done for an assessed unit, but it was enjoyable and worked really well. It was really interesting being able to explore a protein in this way, and I think this has been a really valuable experience for any chemistry student hoping to go into drug design."

"This has definitely been the most exciting module we've had this semester and the LOIL I looked forward to the most. I enjoyed the practical aspect of it and the way we all learned new things or were reminded of older stuff that we don't get to practice very often. The rest of my team and I got really invested in the Design-a-Drug exercise and spent a good few hours every week trying to come up with modifications to our structures. We met up every week, in person (before lockdown) and on Zoom, and had heated debates over whose modifications are more suitable and which ones we should incorporate into our new drugs."

"I found this coursework to be extremely useful and good way to apply the knowledge of what we had learnt over the years of this drug discovery course. It was good to be able to get a grasp of how to think about what aids drug design and how to go about thinking of ways to improve the drug from ways I feel I couldn't have picked up by just watching lectures alone. The coursework exercise also allowed for development of new skills such as an introduction to molecular docking."

"The coursework was fun overall – the software we used was excellent to get used to and the whole concept was greatly enjoyable, making us feel like we were designing from scratch all by ourselves!!"

"I have really enjoyed this exercise, both working as part of a group and because it has been so different to any previous modules I've taken. I found it really interesting and also think that this experience will be very useful for people who want to go into the pharmaceutical industry – especially those who didn't do relevant placements."