CHEM3115/CHEM3915

Synthetic Medicinal Chemistry

(Updated September 2017)

6 credit points. **Session:** Semester 2. **Classes:** Two 1hr lectures & 4 hrs prac. **Prerequisites:** CHEM (2001 or 2101 or 2301 or (2311 and 2312) or 2401 or 2901 or 2903 or 2911 or 2915) and CHEM (2302 or 2402 or 2902 or 2912 or 2916 or ((2403 or 2913) and MOBT2102)). **Assessment:** 1 x 2hr exam (48%), laboratory 3115 (40%), laboratory 3915 (33%), assignment (12%), assignment 3915 (7%).

The development of new pharmaceuticals relies on the ability to design and synthesize new organic compounds. *Synthesis is the fundamental enabling discipline for medicinal chemistry* – without it, the development of new drugs cannot progress from design to implementation, and ultimately to a cure. This unit will tackle important factors in drug design, and will highlight the current arsenal of methods used in the discovery of new drugs, including rational drug design, high throughput screening and combinatorial chemistry. We will develop a logical approach to planning a synthesis of a particular target structure. The synthesis and chemistry of heterocycles, which comprise some 40% of all known organic compounds and are particularly common in pharmaceuticals, will be outlined. Examples will include important ring systems present in biological systems, such as pyrimidines and purines (DNA and RNA), imidazole (amino acids and vitamins) and porphyrins (the oxygen-carrying component of blood). Throughout the course, the utility of synthesis in medicinal chemistry will be illustrated with cases studies such as anti-influenza (Relenza), anaesthetic (benzocaine), anti-inflammatory (Vioxx), antihypertensive (pinacidil) and cholesterol-lowering (Lovastatin) drugs.

**Lecturers:** Dr Yu Heng LAU, Prof Maxwell Crossley and Dr Chris McErlean

**Timetable:** Mondays and Tuesdays at 10am
Lecture Plan

Weeks 1 - 5 (Monday): Medicinal Chemistry & Retrosynthetic Analysis (Yu Heng)

- Introduction to Medicinal Chemistry: definitions, drugs and drug targets, what makes a good drug (ADMET and Lipinski), where do drugs come from?
- The Making of a New Drug: drug discovery, structure-activity relationships, lead optimisation and process development.
- Retrosynthesis: making molecules backwards, the Legends of Synthesis, definitions and key concepts.
- The Tools of Retrosynthetic Analysis: disconnections, synthons and functional group interconversions.
- Taking the Disconnection Approach Further: multi-step disconnections, two-group disconnections, umpulong and convergence.
- Selectivity: chemo-, regio- and stereoselectivity, selectivity in synthetic planning, selectivity vs specificity.
- Protecting Groups: concepts, groups that need protecting, orthogonality, examples from the literature.
- The Art and Science of Synthesis: examples from modern medicinal chemistry and the recent literature.
- Workshop Problems; Recap & Review

Weeks 5 (Tuesday) - 9: Heterocyclic Chemistry (Crossley)

- Tautomerism. Examples of key heterocycles: pyridine, pyrrole, pyrimidine and imidazole. The central role of tautomerism.
- Everything You Ever Wanted to Know about Pyridine. Imine/enamine chemistry, synthesis of pyridine.
- DNA. Nucleotide structure, role of tautomerism in DNA’s structure. Mechanisms drugs use to interact with DNA, e.g. oligopyrroles, actinomycin, camptothecin, topotecan acyclovir, AZT.
- Combinatorial chemistry. The solid phase as a synthetic aid and protecting group. Solid phase peptide synthesis, and split-and-mix synthesis. Small molecule solid phase synthesis and drug discovery, e.g. ciprofloxacin. Solid phase reagents and scavengers.
- Workshop Problems; Recap & Review
Weeks 9 (Tuesday) - 13: Selectivity in Synthesis at sp² Centres (McErlean)

- Carbonyl chemistry. Discuss the need for stereoselective synthesis. Reducing reagents: Chemo- and diastereoselectivity; Introduction to the Felkin–Anh model. Palytoxin.
- Carbonyl chemistry. Organometallics: formation and reactivity; 1,2- vs 1,4-additions; Felkin-Anh vs chelation control. Resiniferatoxin.
- Carbonyl chemistry. Enolates: formation, regioselectivity; silylenol ethers; thermodynamic vs kinetic control; enolate geometry with LDA. Norzoanthamine.
- Carbonyl chemistry. Enolates: Aldol reactions; predicting diastereoselectivity using the Zimmerman-Traxler model; Auxillary approach to enantioselectivity. Discodermolide.
- The chemistry of other sp² centres. Alkenes: synthesis via Wittig, Julia and metathesis reactions (ring closing metathesis and cross metathesis). Gambieric acid A.
- The chemistry of other sp² centres. Palladium in contemporary synthesis; general overview; Suzuki, Stille, Negeshi, Sonogashira and Heck reactions; Hydroxypalladation–carbonylation–lactonisation. Multiple examples.
- Workshop Problems; Recap & Review.