Option D: Medicinal Chemistry

Semantics

Date No.

→ Drug: a chemical that affects how the body works [good and bad effects]

→ Medicine: a chemical that improves health

→ Both of them do the following → ① Alters physiological state [consciousness / activity level / coordination] ② Alters incoming sensory information ③ Alters mood, emotions

Administration

① Oral → pills, liquids

② Inhalation → nicotine (vapour form)

③ Rectal → suppositories

④ Parenteral → injections

Parenteral

→ Intravenous → deposited directly into bloodstream, for ~~vaccin~~ local anaesthetics

→ Intramuscular → injected into muscle, for vaccines

→ Subcutaneous → just under skin, into adipose tissue [subcutaneous tissue], for dental injections

Bioavailability

Def: Fraction of administered dosage that reaches the target part of the body

→ hence drugs administered by intravenous parenterals have 100% Bioavailability and are used as a metric for comparison

→ Very important as it determines dosage

First Pass Effect

→ When medicine administered orally, not all will enter the bloodstream because in the digestive system, enzymes act as biological catalysts, breaking down the drug in the stomach, liver or small intestine. The liver is the site of further metabolic breakdown

Factors affecting Bioavailability

① Administration: intravenous avoids first pass effect; morphine administered intravenously because low bioavailability of 30% when administered orally because the remainder is ~~administered~~ metabolised by the liver

② Polarity: Non-polar, lipid soluble drugs are more effective at ~~enterin~~ passing through the phospholipid bilayers in the brain. However, polar drugs can dissolve in the aqueous blood plasma. Take heroin as an example, has less polar ester groups that crosses blood-brain barrier effectively, unlike morphine, which has polar hydroxyl groups

③ Functional groups: Acid Base groups can determine charge on drugs at different pH values and hence affect its reactivity and solubility. Look at pK_a and pK_b

Drug Action

→ dependent on interactions with receptors, enzymes, fibrous proteins in the p.l bilayer. The binding prevents or disrupts biological activity → interrupts disease

→ The greater the chemical fit between the drug and the receptor, the greater the drug activity

→ forms supramolecular complexes by LDFs, H-bonding or ionic bonding

Physiological Effects

Date No.

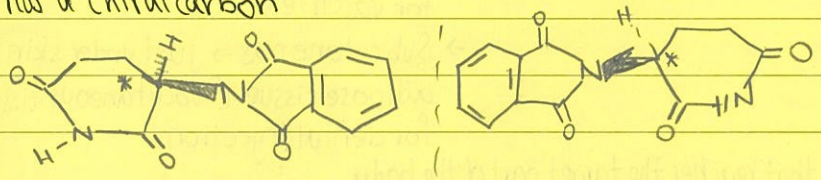
1. Therapeutic – beneficial, either intentional or not
2. Adverse – harmful outcome, intentional or not
3. Side effects → non-intended physiological effects that can be positive or negative

Example – diphenhydramine

Therapeutic → dries mucous membranes } swapped when treating insomnia
Side Effect → drowsiness

~~Shadow of Thalidomide~~ Children of Thalidomide

Recall: Optical isomerism is when a compound can exist as 2 non-superimposable mirror images or has a chiral carbon



- The enantiomer used to combat morning sickness was non mutagenic but because it was sold as a racemate, R and S variants were present, the S was teratogenic, inducing severe deformities in the fetus

Tolerance and Addiction

- Tolerance: reduced response to drug of same dose → why? Body becomes more efficient at metabolising the drug [↓ bioavailability], drug receptors become less effective. Hence, increased doses are required for a therapeutic effect → dangerous, as approaches toxic dose levels
- Addiction: ask Sugi. ~~Needs~~ Patient becomes dependent on the drug to stay normal and suffers withdrawal symptoms if not taken. Minor for caffiene (headaches) but serious for opiates, alcohol and barbituates

Therapeutic Index (TI)

- used in reference to dosing regime → which aims to maintain constant level of [drug]. We need to keep the [drug] within safe levels but enough to induce therapeutic physiological effects
- The therapeutic window is the range of doses between the minimum amounts of the drug to produce the desired effect and medicinally unacceptable adverse effects.
- Quantified as TI
- ED_{50} → minimum effective dose that produces the therapeutic effect in 50% of the population
- LD_{50} → dose that is lethal to 50% of population
- TD_{50} → dose that is toxic to 50% of the population

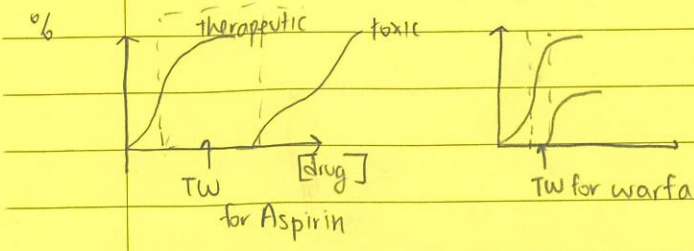
$TI\ (animals) = \frac{LD_{50}}{ED_{50}}$

$TI\ (humans) = \frac{TD_{50}}{ED_{50}}$ (not ethical to kill humans)

Date No.

Danger of a Low TI

→ e.g warfarin → lower margin between toxic and effective doses, correct dosage is crucial, not safe if taken in slightly higher doses



Things to account for with dosage

1) Sex
2) Age
3) weight
4) Diet
5) Environment
6) Side Effects, tolerance, addiction

→ hence blood plasma concentrations must be monitered

Development of Drugs

① Identifying Needs → it is a major investment, hence industry is selective in focus, ∴ lots into cardiovascular disease, obesity and cancer. Context: control of licensing of drugs – average dev time from identification → market is 10 - 12 years. Less focus on serendipity, use of rational drug design [identifying molecular target and designing drug to interact].

② Identify a compound → called a lead compound, used to start design of drug. Usually from plants e.g lead compound from yew trees lead to Taxol. Analogues now created (chemically related compound) Done using combinatorial chemistry → produces and tests many potential medicines

③ Testing → Animals first ~~the humans~~ → ethics and safety say this should be minimised. From here, therapeutic index calculated

④ Human Testing → Phase I: 50-100, Phase II: 200-400, Phase III 3000+, then with placebo to provide basis for comparison

For the drug, need to also find structure, possible synthesis, extraction and yield

D2 → Aspirin and Penicillin

Analgesics

→ Painkillers, interfere with transmission of pain signals

→ Strong: Only available on prescription, interact with receptors in brain that reduce the transmission of pain signals in the brain and spinal cord. They bind to receptor sites of neurons, hence preventing the chemical neurotransmitter that has passed through the synapse from binding to a new neuron. Target Organ = Brain. E.g heroin, morphine

→ Mild/Weak: intercept pain stimulus at the source. Hence, target organ is the site of pain. They act as a competitive inhibitors and bind to the active side of prostaglandin synthase, interfering with the production of prostaglandins, which transmit pain signals to the brain + causes fever + swelling

Aspirin

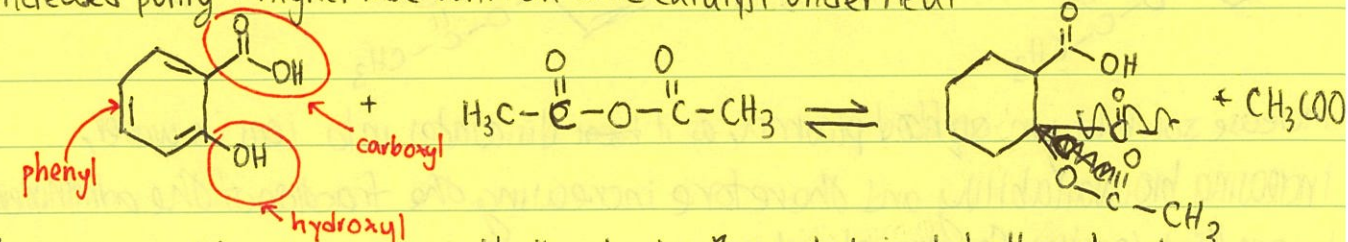
~~Prop~~ [Medical Profile]

Therapeutic Effects: prophylactic [preventative] blood thinner (anti coagulant) to prevent strokes or heart attacks. Because it blocks productions of prostaglandins, it is a mild analgesic. → also antipyretic

Side Effect: Bleeding in stomach lining [amplified by synergistic effect of taking alcohol with aspirin]. Due to carboxyl functional group, can cause acidosis (↓ blood pH)

[Preparation]

(1) salicylic acid is reacted with ethanoic anhydride (condensation of 2 CH_3COOHs) to provide increased purity + higher rate with an acid catalyst under heat

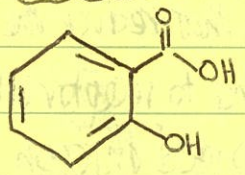


(2) *Aspirin is acetyl-salicylic acid. We then dissolve the products in hot ethanol, such that aspirin dissolves but impurities do not, allowing aspirin to recrystallise, increasing yield and purity. Cold water is then used to prevent complete dissolution in ethanol

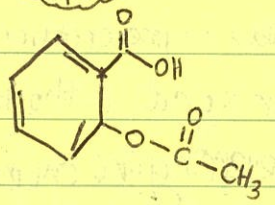
Characterisation by IR

Note

Salicyclic Acid



Aspirin



Similarities

1) carboxyl group ∴ broad absorption for $2500_{cm} \leq x \leq 3500 cm^{-1}$
2) Ester group → each registers at least 1 C=O
3) C-H bonding for $500_{cm} - 1800_{cm^{-1}}$

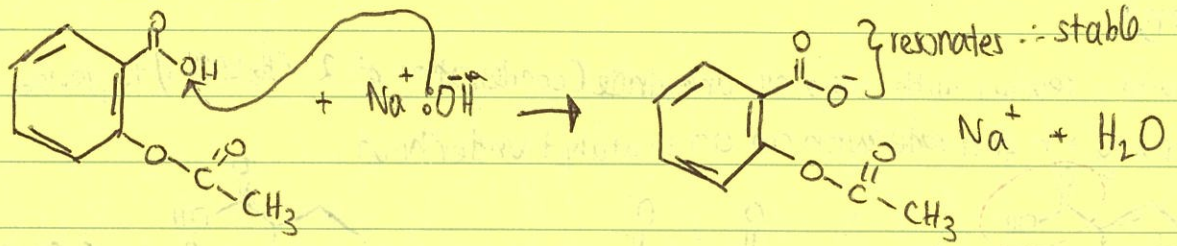
Differences

1) 2 C=O peaks for Aspirin, as 2 C=Os, 1 higher in cm^{-1}, because of increased polarity
2) No alcohol C-O-H absorption

Testing

→ use m.p, aspirin is 138-140°C. Impurities ↓ m.p + cause wider range

Increasing Solubility



- increase solubility in aq blood plasma, as it ~~beco~~ dissociates into ions in water, increasing bioavailability and therefore increasing the fraction of the administered dosage that reaches the target site, hence more effective
- Once in the strongly acidic environment, it reverts to its unionised form (e.g stomach)

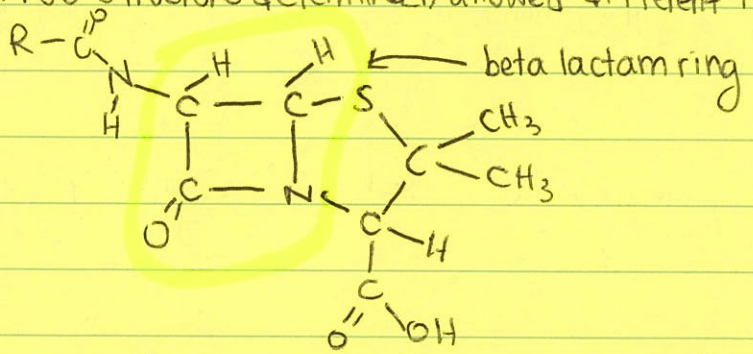
Synergistic Effect with Alcohol

Penicillin

→ Serendipity at play; Alexander Fleming discovered an area on a bacteria sample that was left bare, near a fungi that had grown.

→ Penicillin G [original] was produced by penicillinsum notatum (fungi)

→ 1950 structure determined, allowed different types to be produced.



beta lactam ring

→ Normally, the ring would be have angles of 109.5° due to the sp^3 hybridisation of the atoms but has 90° angles due to restrictions. It is naturally produced, no chemical explanation as to why as of now.

Strained structure

→ Makes carboxyamide group highly reactive, can cause ring to open.

→ Bacteria require a cell wall to prevent it bursting and prevent entry of unwanted substances, they use the enzyme transpeptidase to maintain their cell walls [cross-linkages]

→ The β-lactam ring breaks in contact with it and acts as a competitive inhibitor, blocking the action of the enzyme

→ ∴ cell wall production fails due to preventing cross-linking

→ Water floods in due to Δosmolarity (concentration of osmotically active solutes), leading to bursting

Resistance to Penicillins

→ some bacteria, by natural selection, develop genes that code for the production of β-lactamase or penicillinase as it is known colloquially.

Reasons – ① Overprescription → lead to increased number of bacteria exposed to penicillin, more mutations per unit time, leading to greater proportion developing resistance genes. ② Patient Compliance

→ modify side chain to reduce the ability of β-lactamase to break the β-lactam ring before contact with transpeptidase, ie. e.g a phenyl group [additional]

D.3 : Opiates

Opiates

- narcotic analgesics derived from the opium poppy
- directly interfere with brain (interfere with transmission of pain impulses in the brain's relay neurons)
- bind to opoid receptors located at the synaptic cleft on both pre and post synaptic neurones
- blockes transmission of pain impulses between brain cells
- ergo, ~~if~~ strong analgesics such as opiates interfere with the perception of pain without depressing the central nervous system
- only available on prescription, given to relieve pain from serious injuries or disease (heart attacks, cancer...

Side Effects

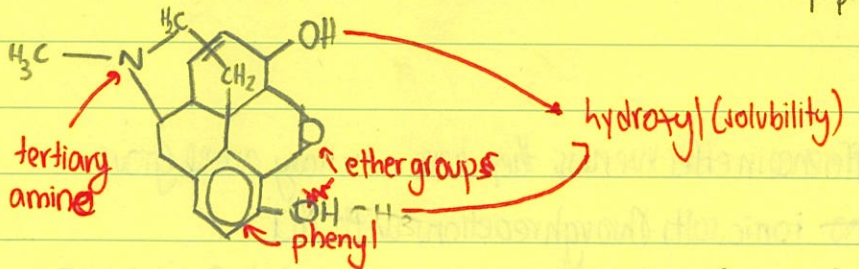
Short Term	Long Term
~~E~~urophia Euphoria	Constipation
Dulling of pain	Disrupt menstrual cycle
Depress nervous system	Addiction
slower breathing + heart rate	Social problems
inhibit cough reflex (why Jane from Breaking Bad died)	↑ risk of HIV/AIDS
~~nau~~ nausea + death	

The Blood brain barrier

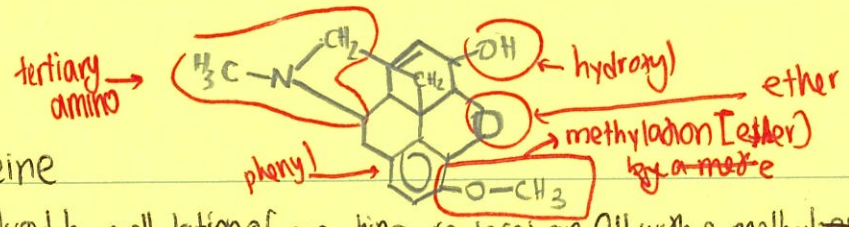
→ brain surrounded by a non-polar ~~ph~~ membrane
→ protects brain by restricting entry of substances that can enter from the blood (e.g pathogens)
→ Lipid based, hence non-polar
→ polar molecules have limited capacity to diffuse across
→ Drug must be non-polar and lipid soluble to easily pass through
→ but solubility in water is still important → transported by blood to the brain
→ lipophillic molecules pass through best

Specific Opiates

(1) Morphine → naturally found in raw opium



→ in cough medication and ST treatment of diarrhoea (as opoid receptors are associated with conoractions of smooth muscle in the gastrointestinal tract)
→ used to produce heroin and codeine through semi-synthetic routes

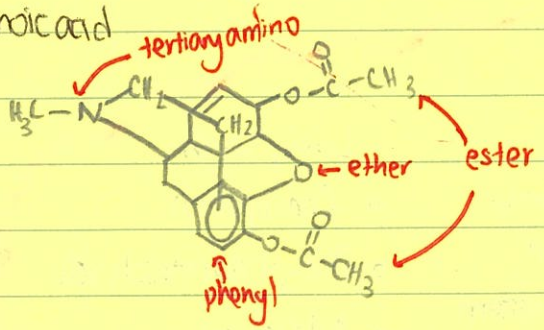


Codeine

- produced by methylation of morphine, replaces an OH with a methyl ~~ester~~ ether
- less polar, can cross BBB better
- drop in binding capacity to opoid receptors, weaker analgesic than morphine
- Codeine's active metabolite is morphine (broken down into morphine by metabolic reactions) (CYP206)
- This metabolic reaction is glucuronidation

3) Diamorphine [Heroin]

- produced by an esterification reaction with morphine, replacing both OHs with ester groups
- reagent: ethanoic anhydride or ethanoic acid
- decrease polarity significantly
- can cross BBB more efficiently
- Context: brain is target organ
- greater binding to opoid receptors per unit time
- reaches brain faster and in higher concentrations



Interesting: 6-acetylmorphine more potent than heroin, not hydrolysed by esterases

NOTE: Codeine and Diamorphine are semi-synthetic drugs, (obtained by a synthetic reaction to a naturally occuring compound). They are prodrugs, meaning their metabolites, mainly morphine, are the compounds that bind to opoid receptors. E.g heroin broken down by esterases. Administered via intravenous parenteral

Heroin v Morphine

- apart from the previously explained difference in effectiveness, they have a tertiary amine group
- allows conversion into ~~tertiary amino~~ ionic salts through reactions with HCl
- Heroin can be administered as diamorphine hydrochloride, reverts to undissociated form at BBB
- ↑ Bioavailability

Advantages and Disadvantages

WHO Pain treatment assignment

1. Pain Persisting or increasing - mild analgesic (e.g aspirin)
2. Greater pain persisting or increasing - use weak opoid (e.g codeine)
3. Complete pain relief - strong opoid e.g morphine

Intravenous morphine is most commonly used in cases of severe pain.

Disadvantages (see first page of D3 for more)

1. Addiction → dependence on drug to ~~rem~~ maintain a normal psychological and physiological state (withdrawal symptoms (e.g cold sweats, anxiety, cramps) may manifest if the drug is not taken regularly. Compounded by increasing tolerance, ~~more~~ higher doses to bring about therapeutic effect, more exposure. Leads to (apparently, in most cases, this is an acceptable answer) thieving, prostitution and ~~drug~~ other crimes)

Treating Addiction → slow + difficult. Using an alternative analgesic such as methadone works. Reduces craving and halt withdrawal symptoms → but does not produce euphoria

D4: pH regulation of the stomach

D4 : pH Regulation in the Stomach

Date No.

The Stomach

→ low pH (1-2) as this is the optimum for pepsin, an exopepsidase in the stomach that breaks down polypeptides into dipeptides

→ HCl secreted by parietal cells in gastric glands within the stomach lining

→ Aside from establishing optimum conditions, kills any pathogens that enter

Active Metabolites

- active forms of a drug after it has been metabolised (processed by body)
- The effect of the active metabolite may be stronger than the drug, e.g morphine is the active metabolite of codeine.
- ∴ may be responsible for therapeutic effects

Excess Acidity

- may be caused by the following factors
  - → excess alcohol
  - → stress
  - → drugs
  - → microorganisms e.g heliobacter pylori, which results in ulcer formation by burrowing into mucus lining, (inflammation)
- Results in the following
  - → discomfort in stomach (dyspepsia)
  - → heartburn
  - → acid reflux
  - → ulceration
- eats away at mucus lining

H-2 Receptor Antagonists

- histamines are produced by enterochromaffin-like cells (ECL cells)
- bind to H-2 receptors on the membranes of parietal cells, stimulating the release of acid
- H-2 receptor antagonists (e.g ranitidine, a.k.a Zantec) bind to the H-2 receptor and block histamine binding, thus preventing / reducing the release of HCl from parietal cells, inhibiting H^+ production
- The data booklet has this molecule's structure
- Developed from histamine analogues, over the counter drug as well

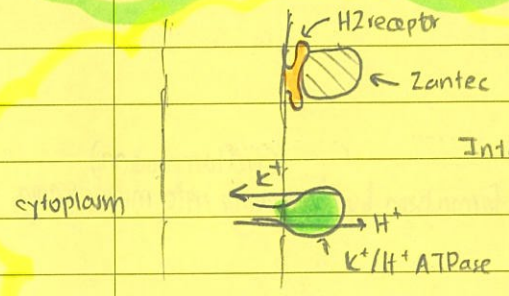
Side Effects

→ diarrhoea
→ headaches
→ dizziness

Proton Pump Inhibitors (PPIs)

Date No.

- Gastric H^+ secretion involves the use of the K^+/H^+ ATPase proton pump
- Uses energy from ATP hydrolysis to use active transport to bring K^+ from ~~intes~~ intestinal lumen into cytoplasm. The energy released by ATP hydrolysis is also used to actively transport H^+ from the cytoplasm into the intestinal lumen
- Ensures electrochemical neutrality
- inhibits acid secretion
- Omeprazole (Prilosec) and esomeprazole (Nexium), both competitive inhibitors of K^+/H^+ ATPase
- Nexium is ~~a~~ an enantiomer of prilosec
- Prilosec is a racemate and ~~shifts~~ undergoes a chiral shift (on Sulfur) into active enantiomer
- Hence, prilosec's active metabolite is Nexium.



A diagram showing a cross-section of a parietal cell membrane

Antacids

→ neutralise acid directly (non specific reactions)
→ weak bases
→ Cannot use strong as they are caustic and could harm the stomach
→ prevent acid from attacking ~~damaged~~ / exposed stomach lining
→ allow ulcers to heal
→ e.g milk of magnesia ($Mg(OH)_2$ and MgO) milk because of white precipitate.
→ Recall acid-base neutralisation reactions
→ Al slower dissolving, longer effect, constipation
→ Mg fast acting, laxative

Syllabus Stated Antacids

i) $Mg(OH)_2(s) + 2HCl(aq) \rightarrow MgCl_2(aq) + 2H_2O(l)$
2) $Ca(OH)_2(s) + 2HCl(aq) \rightarrow CaCl_2(aq) + 2H_2O(l)$
3) $Al(OH)_3(s) + 3HCl(aq) \rightarrow AlCl_3(aq) + 3H_2O(l)$
4) $Na_2CO_3(s) + 2HCl(aq) \rightarrow 2NaCl(aq) + CO_2(g) + H_2O(l)$
5) $NaHCO_3(s) + HCl(aq) \rightarrow NaCl(aq) + CO_2(g) + H_2O(l)$

Side Effects

PPIs and H2 Antagonists

→ diarrhoea, headaches, dizziness
→ ↑ risk of osteoporosis + allergy dev

Antacids

→ Al linked to Alzheimers
→ flatulence + stomach bloating ($[CO_2(g)]$)
→ Alter absorption of other drugs

Buffers

K_a = for $HA(aq) + H_2O(l) \rightleftharpoons A^-(aq) + H_3O^+(aq)$

$K_a = \frac{[H_3O^+][A^-]}{[HA]}$, we assume $[HA]_{initial} = [HA]_{equilibrium}$, $[H_2O]$ same ~~cancel~~

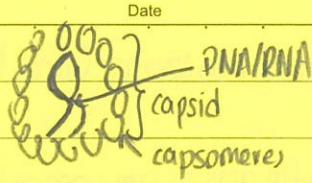
$pH = pK_a - \log_{10}\left(\frac{[acid]}{[salt]}\right)$

SEE CHAPTER 8 NOTES

D5: Antiviral Medications

Date No.

Viruses



→ sub microscopic pathogens
→ not classified as living organisms, lack a metabolism
→ only reproduce in host cell, take over metabolism by carrying genes into cytoplasm
→ Host cells assemble viral components using ribosomes, when the host dies, these new viruses are released into the fluid environment of the organism

Bacteria	Viruses
→ complex prokaryotes	→ simple, lack structures for metabolism
→ specific bacterial processes e.g building up cell wall, can be blocked by antibiotics	→ no structures/processes for antibiotics to target (v. little targets for drugs)
→ reproduce by binary fission	→ reproduce using host cell, DNA/RNA replication
→ cell membrane and cell wall	→ protein coat, no cell wall or membrane (capsomeres are constituent proteins)

Why are viruses a big problem?

→ mutate quickly, different antigens, no secondary immune response by memory cells.
→ May lay dormant, and the mutated form may cause a flare up
→ e.g Chicken pox, herpes, HIV/AIDS
→ lie in host cells, no significant change to antigens, so difficult to target cells
→ Divide and spread rapidly → begets more mutations per unit time
→ Render vaccines mute to an extent, new mutations: different antigens [see Biology 11.1 Notes]

Antivirals

(1) Alter cells genetic material so the virus cannot insert its own genes in
(2) Block enzyme activity in the host cell, so virus cannot multiply or leave

Oseltamivir (Tamiflu)

→ acts as a competitive inhibitor on neuroaminidase, an antigen enzyme on the influenza virus
→ CONTEXT (for non-biologists): Neuroaminidase is an enzyme on the influenza virus that catalyses the degredation of linkages between a virus and the cell that has released it. It's reverse, hemagglutinin, is another glycoprotein that enables docking. Neuroaminidase catalyses a cleavage reaction that allow new virus particles to escape. Snips of a sugar molecule or glycoprotein link to the phospholipid bilayer.

Date No.

→ influenza has several forms that may or may not have the same antigens → not a universal fix!

→ Tamiflu acts as a competitive inhibitor that binds to neuroaminidase's active site

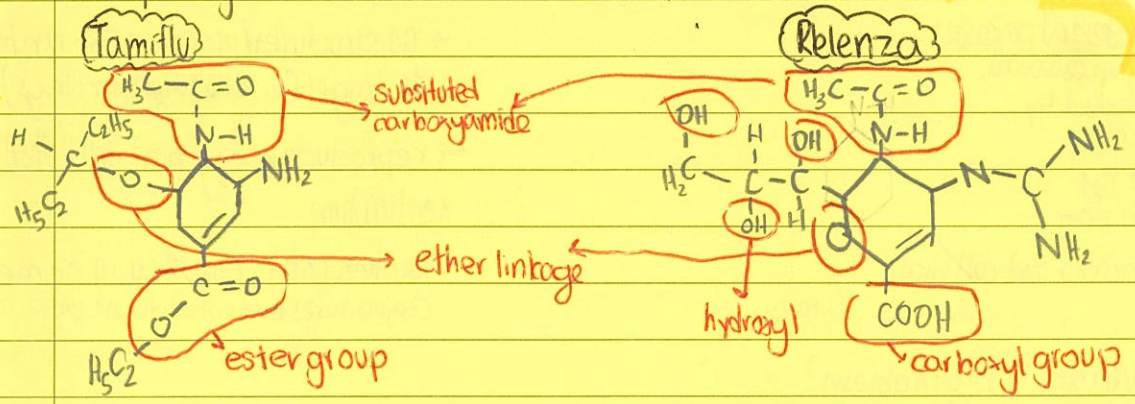
→ Inhibits breakdown of the links, hence prevent release of new viral particles

→ This is a prophylactic treatment

→ Relenza acts in the same way, both have similar structure to sialic acid.

→ Tamiflu is hydrolysed to its carboxylate anion, which is its active metabolite

Comparing the structures of Tamiflu and Relenza



→ oral administration	→ inhalation
→ resistance observed	→ no observed resistance YET
→ nausea, vomiting	→ possible asthma

HIV and AIDs

→ human immunodeficiency virus and acquired immuno deficiency syndrome

→ AIDs is a syndrome, characterised by a very weak immune system → succumb to diseases like pneumonia

→ HIV's antigens bind to receptors on $CD4^+$ T lymphocytes, allowing it to penetrate the cell

→ Retrovirus, has RNA, which it converts into cDNA in the cell by reverse transcriptase. Integrates cDNA into the cell's genome

Why is HIV so difficult to treat?

(1) Attacks helper-T lymphocytes, hence can no longer activate B lymphocytes to stimulate immunoresponse

(2) Rapid accumulation of mutations - variations mean memory cells no longer effective

(3) Virus lies dormant - difficult for immune system to detect

(4) Easily transmitted - body fluids, needles, via placenta

Antiretroviral Drugs

Date No.

- interrupt stages of HIV life cycle

(1) Virus antigens bind to receptors on the CD4+ T-lymphocyte's plasma membrane

Possible Treatment: Antagonist molecule could be introduced to block binding, stop virus docking

(2) Virus enters host cell by endocytosis

Possible Treatment: Alter cell membrane's fluidity

(3) Virus loses protective coat and releases reverse transcriptase and RNA, the former converts RNA → cDNA

Possible Treatment: Drugs that stop loss of capsid. More effective: AZT, a competitive inhibitor of reverse transcriptase. As only retroviruses use reverse transcriptase, does not affect normal cells

Stops integration of virus DNA into the cell's genome

(4) New viral RNA and proteins synthesised

Possible Treatment: Alter genome to inhibit production

(5) Virus particles exit the cell

Possible Treatment: Use drugs that prevent exit, e.g Oseltamivir's action as a competitive inhibitor on neuroaminidase

Date No.

FALCON

D6: Environmental Impacts

Date No.

Nuclear Waste

→ produced from nuclear medicine
→ High Level Waste: gives off large amounts of ionising radiation over a long period of time (high $t_{\frac{1}{2}}$)
→ Low Level Waste: gives off small amounts of ionising radiation over a short period of time (low $t_{\frac{1}{2}}$)
→ LLW: e.g protective clothing, gloves, towels, implements contaminated with radiation
→ LLW stored in sealed containers [radiation emission ends in a few days], then disposed off in landfills or sea
→ ^{99}Tc is LLW, short half life
→ HLW stored underwater in reinforced cooling ponds for 5 - 10 years or vitrified
→ Then, it is transfered to heavily shielded underground storage, e.g concrete bunkers, prevent contamination of water bodies
→ Innovation
- extracting uranium from ash using supercritical $CO_2(l)$
- replacing radionuclides with fluorescent dyes (w.r.t diagnostic medicine)

Solvent waste

→ synthesis and extraction of drugs involve the use of solvents
→ Why is it dangerous?
① incineration may release toxins into the environment (environmental impact) → deplete O_3 layer or add to enhanced GE
② contaminate soil/water
③ Toxic to workers (e.g carcinogenic)
④ Safety w.r.t use (flammable, explosive)
→ chlorinated compounds should be avoided → must be incinerated at high Ts to prevent the formation of carcinogenic dioxins
→ ditto for aromatic compounds
→ H_2O and supercritical $CO_2(l)$ best solvents (least harm to environment)
→ We want to limit environmental waste and reduce the use of auxillaries.
→ Recycle non-chlorinated solvents

Note: GE: greenhouse effect

Antibiotic Waste

Date No.

→ extensive use of antibiotics (broad-spectrum) enables bacteria to develop resistance
→ e.g MRSA (variant of tuberculosis bacteria)
→ ↑exposure, ↑P(resistance developing)
→ Disposal of unused antibiotics
- Used as prophylactic for animal lifestock → excreted into water bodies / remains in tissues → enters food chain, increasing exposure of bacteria to the antibiotics
- Sanitizers increase exposure of bacteria to antibiotics
- Expired unused antibiotics are discarded → contaminate water, soil → increase exposure [when you don't complete a course of antibiotics]
- urine of people on Antibody → discharged into rivers → ↑exposure

→ What ways are there to handle it?
- minimise release into environment (destruction)
- Complete prescribed dose
- Do not overuse

Green Chemistry

Principles

1) High Atom Economy, Low Environmental Impact
- Atom Economy = $\frac{\text{Mr of desired products}}{\text{Mr of all products}}$
- ↑ sustainability, reduce production of unwanted products

2) Minimise steps in synthesis
- ↑ separate steps, ↓ % yield, ↑ waste products + E used

3) Greener reactants + Solvents
- catalysts, lower operating Ts

Case Study: Oseltamivir

- precursor for synthesis is shikimic acid or shikimate [c. base]
- found in low [ ]s in many plants, e.g Chinese star anise [used as food source as well]
- Extracted in lengthy process - low yield, used LiN_3 (unsafe)
- New Methods - ①: fermentation of genetically modified bacteria to produce shikimate
  ②: Harvesting from pine trees, more abundant resource
  ③: Extract from suspension cultures of Indian sweetgum trees

D7: Taxol

Date No.

~~How is it obtained?~~

What is Taxol?

- anti cancer drug (chemotherapeutic agent)
- binds to tubulin, a key part of microtubules
- Stop the breakdown of mitotic spindles in telophase, halting division
- has 11 chiral centres, hence 22 possible enantiomers - only 1 works as a chemotherapeutic drug

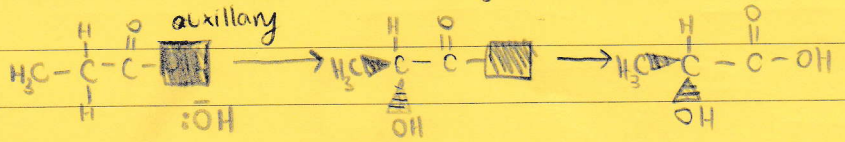
Synthesis

(1) Obtaining lead compounds

- pure form could be obtained from yew trees (bark) but only 0.0.004% is taxol
- stripping the bark kills the tree → not environmentally friendly
- now, lead compound taken from leaves of yew ~~or pine~~ trees → more sustainable, no damage to plant
- This is therefore semi-synthetic synthesis (as we use a naturally occuring lead compound to prod Taxol)
- synthetic route - 30 steps + inefficient

(2) Synthesis using lead compounds

- We use asymmetric synthesis / enantioselective synthesis
- cannot produce racemates; enantiomers may have harmful physiological effects
- waste of money to extract single enantiomer from a racemate → low yield [by in-vitro]
- We utilise a chiral auxillary: an optically active substance that is temporarily incorporated into organic synthesis so it can be carried out asymmetrically.
- binds to a site on a molecule and blocks it by steric hinderence, so the reaction can only occur with one side (forced to use a single enantiomer) (stereospecific)
- once the enantiomer has been produced, the auxillary is recycled and reused
- E.g synthesis of lactic acid (2-hydroxy-propanoic acid)



- conversion of leaf compound (10-DAB) to taxol takes 13 solvents + lots of organic reagents
- Fungi produce taxol in fermentation reactions
- New plant fermentation technology: extracted from plant cell cultures and extracted by chromatography → Green Chemistry (no solvents, harmful ones anyway)

Revisit the use of polarimeters!

D8: Nuclear Medicine

Date No.

Ionisation Density: $\alpha > \beta > \gamma$

Penetrating Power: $\gamma > \beta > \alpha$

Radiation

(1) α radiation

- ejection of $^4_2\alpha$ from unstable nuclei
- written as ^4_2He or $^4_2\alpha$.
- decrease in mass by 4, decrease in proton number by 2

Example

$^{238}_{92}U \rightarrow {}^{234}_{90}Th + {}^4_2\alpha$

(2) Beta Radiation (β)

- conversion of a neutron to proton and subsequent ejection of an electron and neutrino
- no change in mass number, ↑ proton number by 1
- written as $^0_{-1}\beta$

Example

$^{234}_{90}Th \rightarrow {}^{234}_{91}Pa + {}^0_{-1}\beta$

(3) Gamma (γ) Radiation

- emission of energy as photons
- short wavelengths
- usually accompanies α or β decay [Lutetium-177]
- when partides and antiparticles meet
- no change in mass or atomic number

Ionisation

- radiation provides energy for the removal of electrons
- lead to formation of unstable ~~radicals~~ radicals which may react immediately via oxidation reaction
- e.g $H^\bullet$ or $OH^\bullet$, acts on DNA to initiate apoptosis
- Ionisation Density → energy released along a unit length, highest for α due to +2 charge, then β as -1
- Higher ID, energy release more localised, for instance, a small region in a cell

Half Lives

- follow a first order rate reaction

Rate = $k[N]$ but as it decays with a half life: $N_T = N_0 e^{-\lambda t}$ where N_T is amount at time t, N_0 is initial, λ is the decay constant

↓ ln of both side)

PROOF →

$$\ln(N_T) = \ln(N_0) - \lambda t$$

$$\ln\left(\frac{N_T}{N_0}\right) = -\lambda t$$

- To find the decay constant / half life, we use the following derivation

let $N_T = \frac{1}{2}N_0$

NOTE that λ is in (unit time)$^{-1}$

$$\ln\left(\frac{1}{2}\right) = -\lambda t_{\frac{1}{2}}$$

$$\ln(2) = \lambda t_{\frac{1}{2}} \quad \therefore \quad \lambda = \frac{\ln(2)}{t_{\frac{1}{2}}} \text{ and } t_{\frac{1}{2}} = \frac{\ln(2)}{\lambda}$$

FALCON

Date No.

→ we can find the amount of substance remaining after t units time by this formula

$$N_t = N_0\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}}$$ ← incidentally, this is the percentage remaining

e.g Find the amount of $^{99}_{43}Tc$ left after 8 hours if it had an initial mass of 5.00g and has a half life of 6.01 hours.

Context: $^{99}_{43}Tc \longrightarrow {}^{99}_{43}Tc + \gamma$

Applying

$N_t = (N_0)\left(\frac{1}{2}\right)^{\frac{t}{t_{\frac{1}{2}}}} \rightarrow (5.00)\left(\frac{1}{2}\right)^{\frac{8}{6.01}} = 1.99g$ (3.sf)

Diagnostic Medicine

Technetium-99m ($^{99}_{43}Tc$)

- metastable radioactive isotope used in tracing (radiopharmaceutical) + artificial
- Half life of 6 hours and biological half life of 24 hours → long enough for gamma camera to detect, leaves fast enough to prevent/minimise side effects.
- generated in hospitals by decay of molybdenum-99 (B)
- releases gamma rays, penetrating (easy to detect), low ionisation (∴ low damage)
- can bind to biological molecules : allows activity of specific organs/organ systems to be studied

Iodine-131 (^{131}I)

- beta + gamma emitter
- 8 hour half life + taken up by thyroid gland as thyroxin produced has 4 I atoms
- mostly used to kill thyroid tissue

Positron Emission Tomography (PET)

- administered ~~as~~ radionuclide emits positrons
- accumulates in target tissue, in which emitted positrons combine with electrons, releasing γ rays
- gamma camera allows determination of origin
- e.g ~~Flourin~~ Fluorine-18, ~~taken up~~ bonded to glucose in administered radionuclide, taken up more rapidly by cancer cells → visible on scan
- combined with computerised tomography (CT) to create PET CT to increase range of possible ~~dig~~ diagnosis.

Magnetic Resonance Imaging (MRI)

Date No.

- applies HNMR
- uses shift in proton spin, uses radiowaves to induce antiparallel shift
- Computer can used to create 2 or 3-D images.
- Very useful as H atoms in water → 70% of body by mass

Radionuclide Therapy

→ the rapid division of cancer cells increase their susceptibility to ionising radiation, as DNA that codes
for replication and mitosis are primarily affected
→ Can be external (teletherapy) or internal

External Radiotherapy

- Primarily gamma rays, directed from an external source
- $^{60}_{27}Co \rightarrow {}^{60}_{28}Ni + {}^{0}_{-1}B + \gamma$
- Linear Accelerator: Microwave technology accelerate e^-, which are aimed at heavy metals, in order to produce high energy X-rays
- Gamma Knife Radiosurgery: 200 different Co-60s produce γ rays, which converge to produce a high dose

Internal Radiotherapy

- radionuclide enters body → solid (implant) or liquid
- implant can be introduced → patient needs to be isolated → radiation may have adverse effects on others

Targeted Alpha Therapy (TAT)

- can treat metastasis: inhibits production of secondary tumours
- α emitting ~~nucleotides~~ radionuclides attached to antibodies which bind to cancer antigens → specific targets.
- $^{4}_{2}\alpha$s have high ionisation density, high energy dispersed over small area - limit effect on non-target cells while killing target cells
- uses $^{212}_{82}Pb$-212 → alpha decay

Boron Neutron Capture Therapy

- high dose of ~~normal~~ B-10 (non radioactive) administered, collected mainly by cancer cells (R & Mitosis ↑)
- Irradiated with neutrons to produce unstable B-11. Occurs in cell, high ionisation density
- Higher p of being taken up by cancer cells, limit effects on somatic, healthy cells
- $^{10}_{5}B + {}^{1}_{0}n \rightarrow {}^{11}_{5}B \rightarrow {}^{4}_{2}\alpha + {}^{7}_{3}Li$
- Whoever came up with this is a genius.

FALCON

Side Effects of Radiotherapy

Date No.

1) Hair loss → acts on rapidly dividing follicle cells
2) Fatigue
3) Nausea
4) Sterility
5) Damage to DNA / growing / regenerating tissue

Yttrium-90 and Lutetium-177

- Yt-90 is a β emitter, but Lu-177 is β and γ
- Lu-177 has shorter penetration : ideal for smaller tumours + limit exposure of healthy cells
- Lu-177 can bind to the carrier DOTA-TATE, which attaches to specific tumours such as neuroendocrine tumours and certain thyroid cancers.

D9: Drug Detection and Analysis

Date / No.

Isolation and Purification

RECAP: Solubility

- ↑ solubility if favourable interactions can form between solute + solvent
- For n.p solvents, n.p solutes can dissolve, as LDFs can form
- For p. solvents, p. solutes can dissolve, hydrogen bonds form (or dipole-dipole interactions)

Isolation (by solubility)

→ can be done by solubility differences

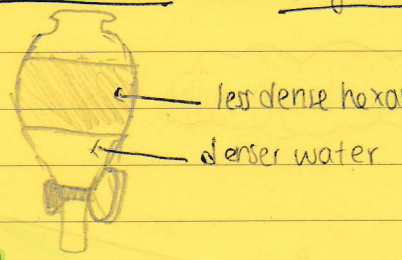
→ e.g choosing a solvent that selectively dissolves one substance over another

→ coffee beans being decaffeinated by extracting caffeine with $CO_2(l)$ is a good example

→ Solvent extraction: when one solute shows a significant difference in solubility between 2 immiscible solvents.

→ Leads to unequal distribution

→ We use a separating funnel (see RHS)



→ ① Add a solvent that a known solute A dissolves in to a ~~known~~ aqueous solution of A in a separating funnel

② Shake vigorously and let it settle to allow immiscible layers to form

③ A dissolves more in the new solvent (e.g hexane) than water

④ The lower layer can therefore be drained away; it has little of solute A

⑤ Recover A by evaporation / crystallisation.

→ Depends on relative solubilities in 2 immiscible solvents

Isolation and Purification (by volatility)

RECAP: M.P + B.P

- ↑ m.p, b.p with H.b > p.d-p.d > p.d-induced d > LDFs
- ↑ M.p/b.p with Mr for LDFs

Fractional Distillation

→ exploits difference in volatilities

→ uses a fractionating column with glass beads to facilitate condensation, produces fractions of liquids which boil within a small range of Ts

→ isolate drug products from liquid mixtures

→ used to separate chemical feedstock

Raoult's Law

Date No.

χ_A (mole fraction / chi) $= \frac{n(A)}{n(A)+n(B)}$ for a mixture of A and B

Qualitative: number of moles of A divided by the total number of moles of A and B.

Context

liquid $\underset{\text{condense}}{\overset{\text{evap/boil}}{\rightleftharpoons}}$ gas

→ If equilibrium lies to RHS, then higher vapour pressure, more gas molecules exerting a force on liquid surface

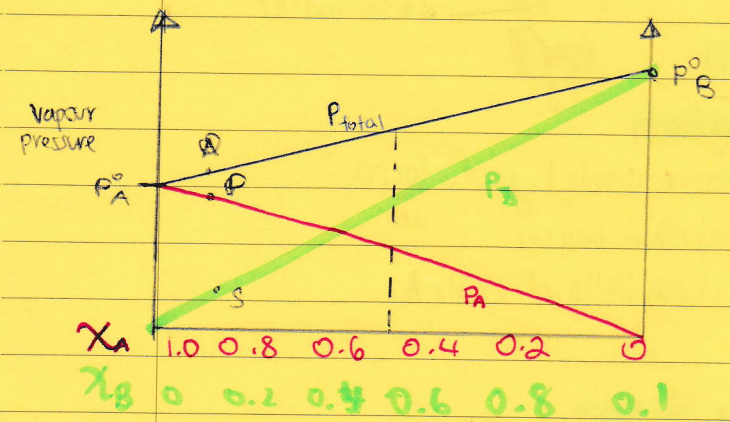
→ ∴ if we have a more volatile substance, ↑ vapour pressure

→ Total vapour pressure (P) = vapour pressure of A (P_A) + vapour pressure of B (P_B)

→ $P_A = P^\circ_A \cdot \chi_A$, where P°_A is the vapour pressure of the pure substance

→ Assumptions: fully miscible substances (ideal solution) ergo form similar intermolecular forces.

Interpreting graphs



Q = P + S

○ At 0.5 each (for χ), $P_B > P_A$, ∴ higher P°_B + ↑ proportion of B relative to A

Purification

→ we can also carry out purification with fractional distillation

→ e.g. for a ~~solution~~ mixtures with $P_B > P_A$, the vapour initially produced by boiling a 0.6 : 0.4 ratio of A to B is enriched with B (more volatile), leading to a shift in χ_A and χ_B

→ Can repeat over several cycles

→ vapour rises up column, condenses and falls back down, reboiled by rising vapour

→ ∴ end ~~liquid~~ vapour condensed to form enriched solution with high [volatile substance]

Drug Detection

Date No.

Context

→ need methods to check on presence and [drugs] in body
→ must adhere to legal limits

Steroid Detection

→ has 4 fused rings → steroidal backbone
→ e.g male hormones (androgens)
→ anabolic steroids promote tissue growth
→ synthesised from testosterone, e.g nandrolone
→ ↑ strength + endurance but toxic to the liver + can cause cancer
→ disturb hormone balance, affect secondary sexual characteristics (hair placement + fertility)
→ we can analyse urine samples for metabolites/drugs by gas chromatography – mass spectrometry

GC-MS

→ ~~As for~~ Stationary phase: liquid coated onto a solid support (long capillary tube)
→ Mobile Phase: inert gas such as $He_{(g)}$ or $N_{2(g)}$
→ separation of components in a mixture is reliant on their rates of movement
→ More volatile + less soluble, ↑ rate, vice versa
→ injected in first and boiled
→ mixes with inert gas and passes into column; some may dissolve into solvent (s. phase)
→ Each component is eluted (exits from column into detector) at different time intervals (retention time)
→ Passage of each compound represented as a peak → ergo ∝ $\int$peak = ~~for~~ concentration relative to a standard
→ The eluted sample is then passed to a mass spec (no need to purely use retention times)
→ vaporised, ionised, passed into magnetic field, deflected + accelerated
→ RECALL* = put a +ve charge on fragment → $[C_3H_5O]^+$

Ethanol

→ polar, H-bonds with water, passes from gut via blood to several body parts
→ Hence, effects very quickly manifest in drunks.
→ Depressants: inhibit neuron transmission in the CNS, s.t changes in behaviour, possible dependency
→ judgement can become impaired.

Testing for Ethanol

Date No.

NOTE: $C_2H_5OH(aq) \rightleftharpoons C_2H_5OH(l)$
(blood) (exhaled breath)

1. Basic Breathalyser
   - use redox reaction to measure $[C_2H_5OH]$ and determine $[C_2H_5OH]_{blood}$
   - $C_2H_5OH(aq) + [O] \rightarrow CH_3COOH + H_2O$
   - $Cr_2O_7^{2-}(aq)$ reduced from [+6] to [+3] in $Cr^{3+}(aq)$.
   - Orange → Green [crystal colour change]
   - Photocell determines extent of colour change
   - Finds $[C_2H_5OH]_{exhaled}$, uses K_c to find $[C_2H_5OH]_{blood}$

2. Intoximeters
   - has a porous disk with Pt(s) electrodes, both saturated with acidic electrolyte
   - C_2H_5OH from breath is oxidised at anode - $C_2H_5OH(aq) + H_2O(l) \rightarrow CH_3COOH(aq) + e^- + H_2$
   - e^- released flow from anode to cathode and H^+ used to reduce $O_2(g)$ to $H_2O(l)$
   - $O_2(g) + 4H^+(aq) + 4e^- \rightarrow 2H_2O(l)$
   - Movement of e^- through electrical (external) circuit + movement of ions in electrolyte generate a current
   - I used to calculate $[C_2H_5OH]_{blood}$