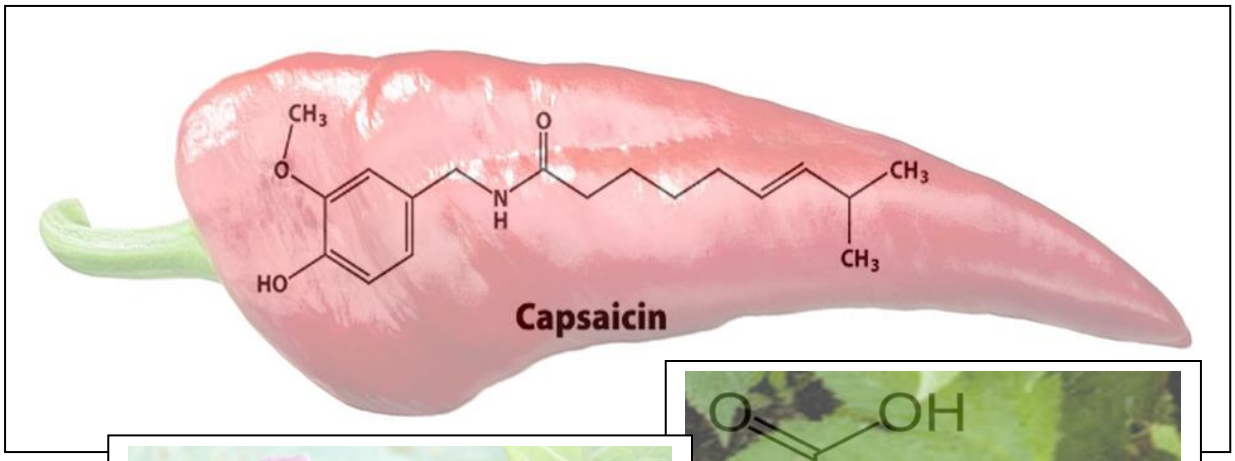
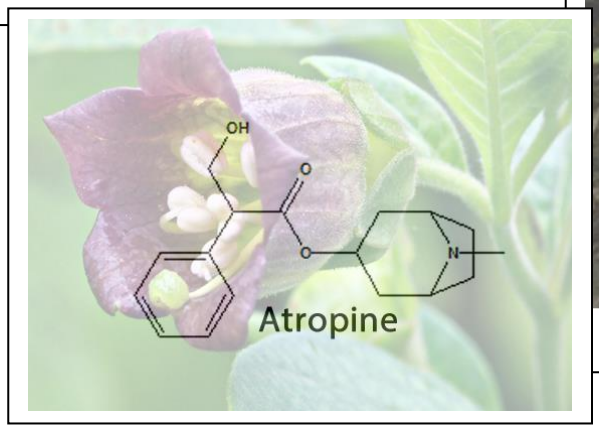
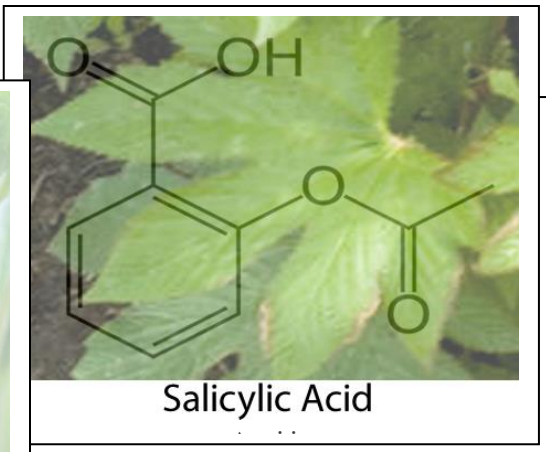
MEDICINES-STRUCUTURE AND FUNCTION







Medicines derived from nature have played a pivotal role in addressing various health concerns, offering therapeutic benefits that have been harnessed for centuries. Two such noteworthy compounds are atropine and capsaicin, each sourced from distinct botanical origins. Atropine, is derived from the deadly nightshade plant (Atropa belladonna) and related species. Widely recognized for its ability to block responses to stimuli of smooth muscle in the body, atropine has been employed in medicine to dilate pupils, treat bradycardia, and alleviate spasms in the digestive tract. On the other hand, capsaicin, the fiery component of chili peppers (Capsicum species), holds unique pharmacological qualities. Known for its analgesic properties, capsaicin is utilized topically to relieve pain and is being explored for its potential role in treating various conditions, including neuropathic pain and arthritis. These compounds showcase the richness of medicinal resources in nature.

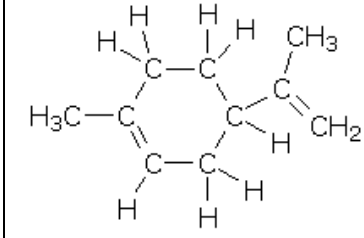
Solvent extraction

Solvent extraction involves the suspension of plant materials within organic solvents, followed by heating, filtration and solvent evaporation to isolate a filtrate that is composed of concentrated target solute mainly, a fragrant oil.

Considering how a number of medicinal molecules undergo thermal decomposition, it is important to extract them with mild techniques such as solvent extraction. Not only does solvent extraction offer an extraction procedure using relatively mild temperatures but also a selective approach to extracting bioactive molecules. Selectivity and yield can be achieved with the selection of appropriate solvents.

Solvents with a polarity similar to a given target solute often result in better extraction. There is also the consideration of the use of **green** solvents from renewable resources.

Consider limonene, shown on the right in fig.1. It is used as a solvent to extract other plant based bioactive molecules. Limonene, however, is also extensively used in the pharmaceutical industry as a flavouring to mask the taste of certain medications, as well as showing promise in cancer treatment and as an antioxidant and anti-inflammatory agent.



Limonene

Figure 1

1. When considering the solvent extraction of limonene two solvents are top of the list for use. These solvents are hexane and ethanol.

   a. With reference to structure and intermolecular bonding discuss why hexane is an ideal solvent .

   Hexane is a hydrocarbon and hence non-polar that will interact with the non-polar limonene molecule via dispersion forces.

   b. With consideration of the green chemistry principles, discuss why ethanol is used over hexane to purify limonene from plant matter.

   Hexane is toxic ethanol is non-toxic.

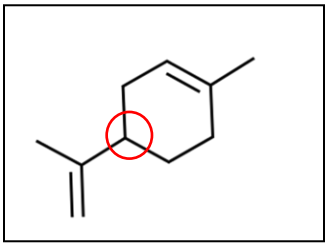
   Hexane comes from the petrochemical industry and hence is non-renewable whereas ethanol is renewable via the fermentation of plant matter.

   c. In the box provided on the right :

      i. Draw the skeletal structure of limonene.

      ii. Use the image drawn to circle all the chiral carbons present in limonene.

      iii. How many enantiomers of limonene exist? *2*

   d. Solvent extraction is enhanced by an increase in temperature and decrease in plant matter particle size. Explain why.

   Increased temperature increases the kinetic energy of molecules which helps break bonds between the solute and the plant matter thus facilitating the solute's interaction with the solvent. This will increase the solubility of the solute in the given solvent.

   A smaller particle size increases the surface area of plant matter exposed to the solvent which causes a faster rate of transfer of solute into the solvent.

e. Explain one advantage and one disadvantage of using large volumes of solvent to extract solute from plant mass.

Advantage – the greater the volume of solvent the greater the amount of solute that can dissolve.
– the greater the volume the greater the efficiency of dissolving large comnplex solute molecules.
– large volumes of solvents dilutes the solutions and creates a safer environment especially when dealing with toxic or flammable solutes.

Disadvantage – creates large amount of waste.
– extra cost as some of the solvents are expensive.

Steam distillation

Steam distillation is a separation technique used to purify or isolate plant-based compounds with relatively high boiling temperatures and prone to thermal decomposition. Plant oils are compounds that are generally purified by steam distillation. Water is heated to produce steam (A), which rises through the plant matter vapourising the volatile oils (B) and carrying them through to the condensing chamber (C). The distilled liquid (D) is a mixture of water and oils. Since the oils are non-polar they will separated from the water and form a layer floating on the surface of the water and therefore easily collected.

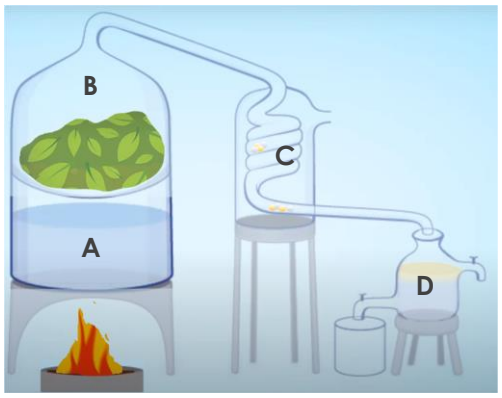


Figure 2 – steam distillation unit

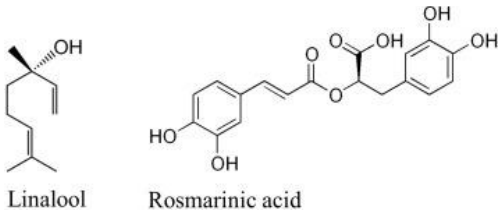


Figure 3

1. Consider the molecular structures of linalool and rosmarinic acid, shown in fig 2. These molecules are components of lavender oil. Linalool has established sedative, antidepressant and anticonvulsant effects.

a. Write the semi-structural formula of linalool.
$(CH_3)_2CCH(CH_2)_2C(CH_3)(OH)CHCH_2$

b. How many optical isomers of linalool are expected to exist in nature. Using the structure of linalool, shown in fig 4, Justify your answer.
2 optical isomers
Linalool has 1 chiral carbon as circled in fig. 4 hence 2 optical isomer (2^1)

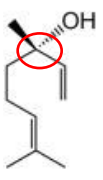


Figure 4

c. A mixture of limonene and linalool was separated using reverse phase HPLC. The chromatogram obtained is shown in fig 5.

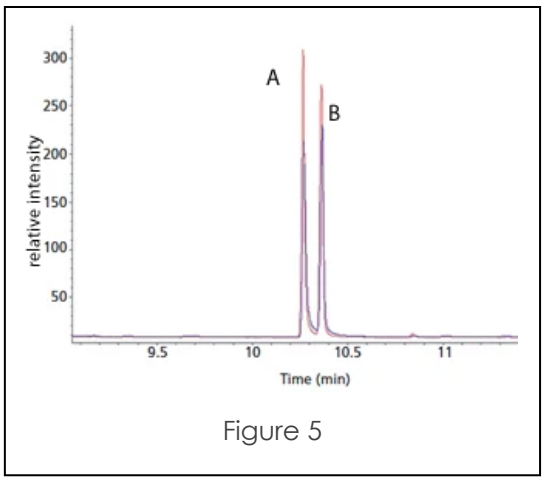


Figure 5

i. Identify peaks A and B. Justify your choice.

Reverse phase chromatography uses a non-polar stationary phase. The more non-polar a molecule is the longer its retention time. Hence B is limonene as limonene is non-polar hydrocarbon whilst linalool has a hydroxyl group hence is a polar molecule that can form hydrogen bonds as intermolecular forces hence will interact more with the mobile phase than the stationary phase.

ii. Which compound is present in the highest concentration? Justify your answer.

Compound A is present in the highest concentration as it has the greatest peak area.

iii. Which of the two peaks A or B in fig 5 above will produce the IR spectrum shown in fig 6? Justify your answer.

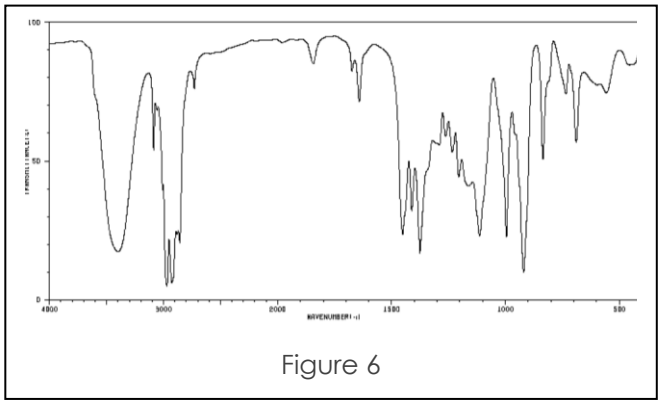


Figure 6

The peak that is associated with linalool, as answer to ci. An alcohol (OH) group is present as its absorbance at around 3400 cm^{-} indicates.

iv. Give the IUPAC name for linalool.

3,7-dimethyl-1,6-octadiene-3-ol or 3,7-dimethylocta-1,6-diene-3-ol

1. The skeletal structure of capsaicin is shown on the right.
   a. Aside from the C=C double bond, circle and name four other functional groups present in the structure.

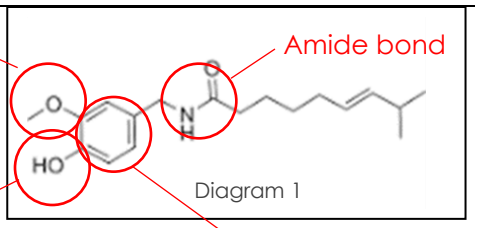


Diagram 1

   b. Capsaicin can be absorbed directly through the skin.
   It is highly lipophilic (dissolves in non-polar substances) and hence able to penetrate the cell membrane to interact with its target receptor.
   Circle two sections of the molecule in diagram 2 that are responsible for its lipophilic properties.

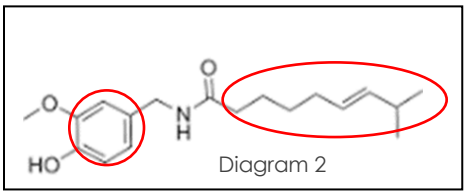


Diagram 2

   The long hydrocarbon tail is hydrophobic or lipophilic. The benzene ring is also a lipophilic structure.

   c. Consider the capsaicin molecule, diagram 2.
      i. Define what is meant by the term "chiral carbon" .
      A chiral carbon, is bonded to four different atoms or groups of atoms to create two non-superimposable mirror image structures, known as enantiomers
      ii. Define an enantiomer?
      An enantiomer is one of a pair of molecules that are non-superimposable mirror images of each other. Enantiomers are a type of stereoisomer, meaning they have the same molecular formula and connectivity of atoms but differ in their three-dimensional arrangement.
      iii. Describe the relationship between chiral carbons and optical isomers.
      For each chiral carbon present in a molecule two enantiomers are produced. A molecule with n chiral carbons will have 2^n enantiomers.
      iv. How many optical isomers can be found for the capsaicin molecule?
      Since capsaicin has no chiral carbons it has no enantiomers (optical isomers)

   d. Compare the two molecules shown in diagram 3. Give a valid explanation as to why the intermolecular bonds are stronger between MDR-625 and its protein receptor with a very polar binding site when compared to the intermolecular bonds between
   capsaicin and the same protein receptor as MDR-625 binds to.

   Since it's a polar site on the receptor molecule that both molecules will bond to the amide links circled will become critical. Capsaicin has one amide link but yMDR-652 has two N-H sites with which to form hydrogen bonds. So more hydrogen and or dipole-dipole bonds can be formed by MDR-652 and the receptor.

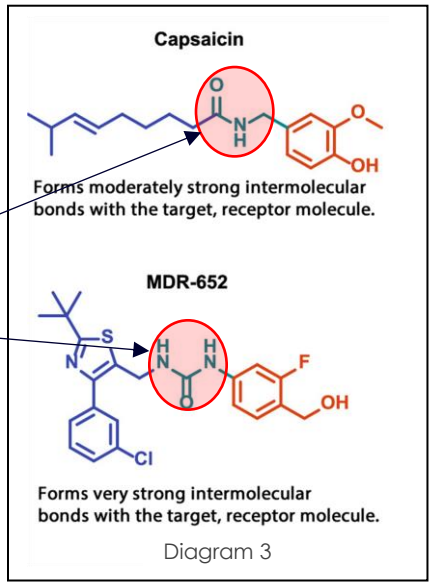


Diagram 3

e. Capsaicin has a boiling point around 220 °C but starts to undergo thermal degradation at temperatures around 200 °C. Capsaicin is sparingly soluble in water but highly soluble in solvents such as acetone and ethanol as well as hexane.

i. Using the diagram of capsaicin, shown on the right in diagram 4, discuss why capsaicin is soluble in ethanol but not in water.

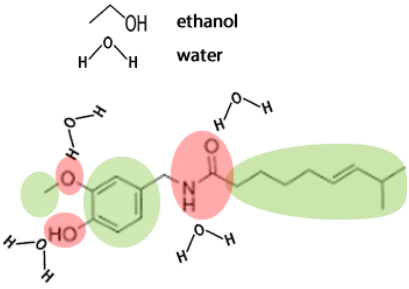


Diagram 4

Water is a polar molecule and hence interacts via Hydrogen and dipole-dipole bonds to the polar sections of capsaicin, labelled in red. This leaves the majority of the molecule unable to form significant interactions with the polar water molecule.

Ethanol has both polar and nonpolar sections and hence can form intermolecular interactions comprised of dispersion, dipole-dipole and hydrogen bonds with the entire molecule of capsaicin, as shown in the diagram 4a on the right.

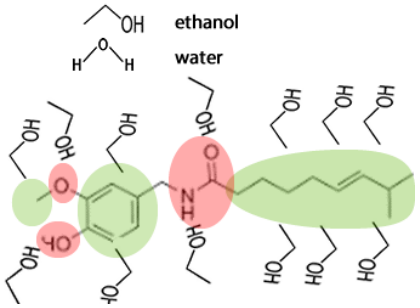
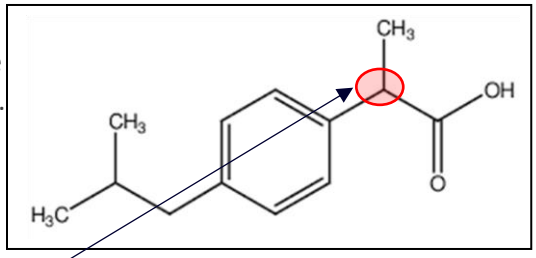


Diagram 4a

ii. Which of one of the two separating techniques, solvent extraction or distillation, should be used to isolate capsaicin from a mixture of organic compounds. Explain your reasoning.
Since in undergoes thermal decomposition at temperatures below its boiling point distillation can not be used. Solvent extraction takes place at much milder temperatures and hence is the only viable separating technique. An appropriate solvent needs to be used, one in which capsaicin is selectively dissolved.

2. Ibuprofen, shown on the right, is used as a non-steroidal anti-inflammatory drug. It works to inhibit the synthesis of prostaglandins via the enzyme cyclo-oxygenase. It works as a competitive inhibitor of cyclo-oxygenase.



a. Discuss how ibuprofen inhibits the synthesis of prostaglandins by cyclo-oxygenase.

Ibuprofen can interact with the active site of cyclo-oxygenase similar to the substrate by forming temporary bonds. As such it competes with the substrate for the active site and so minimises the interaction between the enzyme and the substrate.

b. How many enantiomers does ibuprofen have that must be tested for their pharmacological impact? Justify your answer. *2*

One chiral carbon

c. A non-competitive enzyme inhibitor is one that binds to the enzyme at a site other than the active site and in doing so changes the shape of the enzyme so it no longer functions to catalyse a given reaction.

i. Consider the graphs shown in diagram 5. Graph A represents the rate of an enzyme catalysed reaction. Identify which graph represents the rate of a reaction catalysed by an enzyme in the presence of a competitive inhibitor.

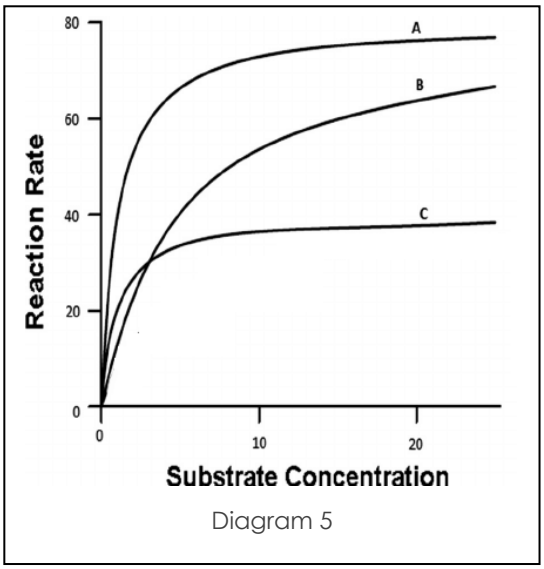


Diagram 5

B

ii. With reference to collision theory explain your answer to question i. above.

With a high concentration of substrate, the rate of collision between the enzyme and substrate is high. This high collision frequency increases the likelihood of successful collisions that lead to product formation. The impact of the competitive inhibitor is reduced because the substrate outcompetes the inhibitor for the active sites.

iii. Identify the graph that represents the rate of a reaction catalysed by an enzyme in the presence of a non-competitive inhibitor. Explain your choice.

Non-competitive inhibitors bind to the enzyme at a site distinct from the active site. This binding does not compete with the substrate for the active site; instead, it alters the enzyme's conformation, making it less effective in catalyzing the reaction or unable to catalyse the reaction at all.

3. Consider the image of a receptor molecule and three molecules that act as neurotransmitters in diagram 6. Neurotransmitters are biological, chemical messengers that fit perfectly onto target proteins called receptors to induce a predetermined response from the cell.

   a. Which molecule or molecules can interact with the receptor in order to induce the appropriate response from the cell? Justify your answer with specific reference to chemical structure and bonding.

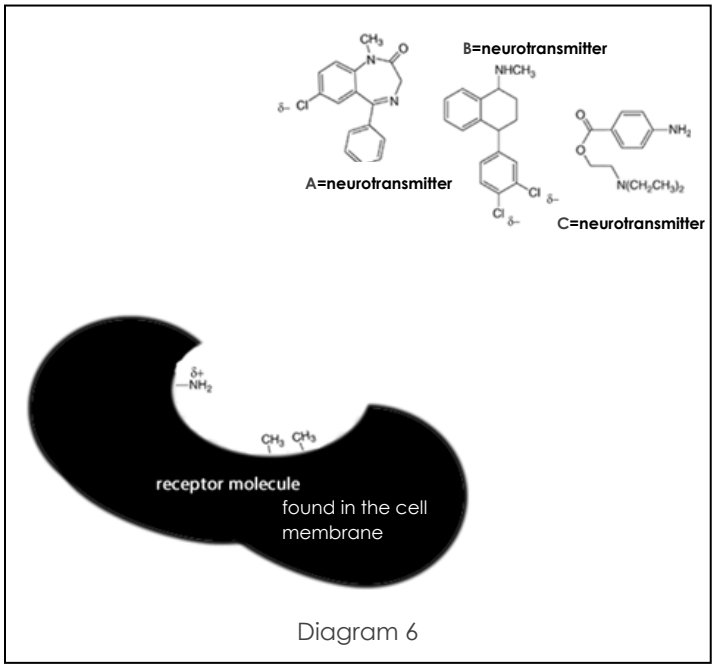
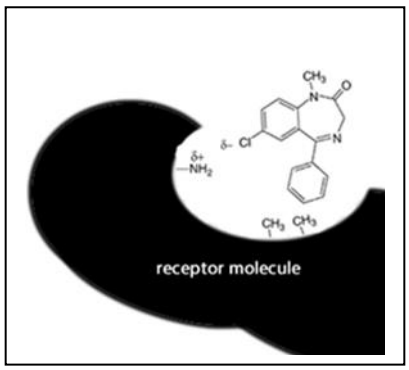
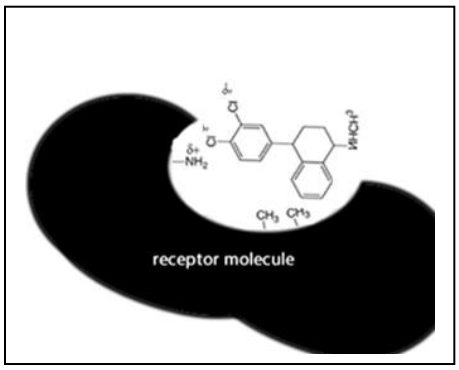
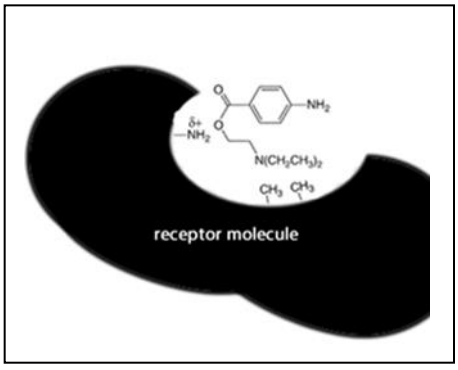


Diagram 6







All three neurotransmitters look as though they are capable of forming weak intermolecular bonds with the receptor. The stereospecificity of each transmitter enables the polar and non-polar ends of the receptor to align well and form dipole-dipole bonds in the polar regions and dispersion forces in the non-polar regions.

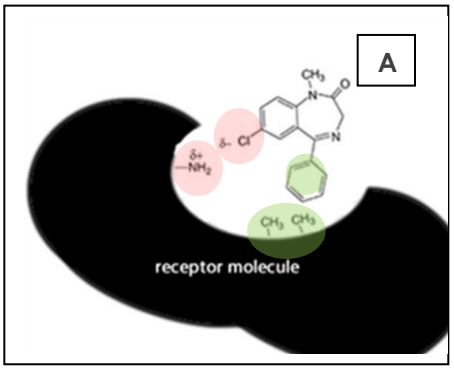
b. Using the three molecules and the receptor molecule shown in diagram 6 above as examples, discuss how an understanding of the stereochemistry of drugs is crucial in designing compounds with desired therapeutic effects.

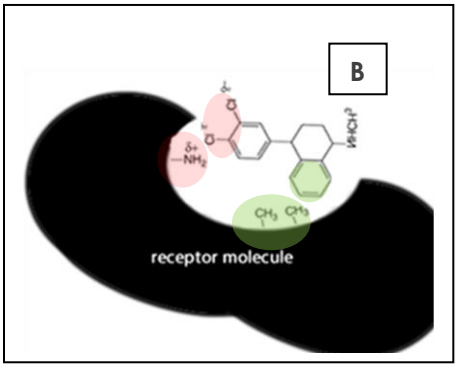
Often receptors and enzymes are large three-dimensional molecular structures that have specific three-dimensional binding sites that recognize specific stereochemical arrangements.

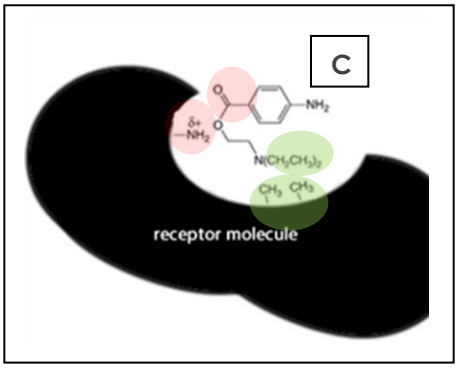
As seen in the three examples shown on the right polar and non-polar regions of both the receptor and transmitter overlap. Depending on the nature of these regions the molecules can bind strongly or weakly which impacts on their pharmacological efficacy. Scientists manipulate the functional groups at different regions of the molecule to increase or decrease the affinity of the molecules with the receptor. For example, molecule A has one chlorine atom in the polar region whereas B has two giving it a greater affinity to bind more strongly with the polar region. Molecule C, on the other hand may not be as good at binding to the non-polar section with two ethyl groups (CH_2CH_3) as the flat benzene ring.

It is also crucial to investigate the different enantiomers of each transmitter molecule for their affinity for the receptor. All three transmitters here have no enantiomers.

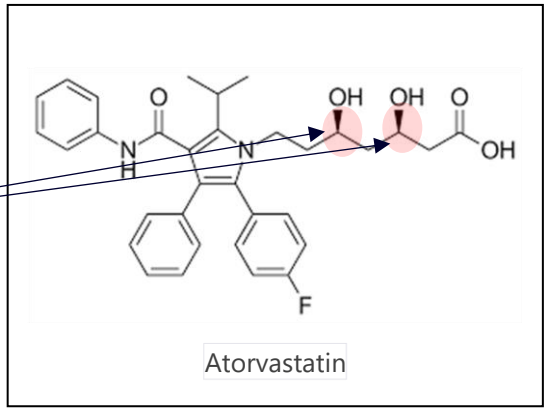
The environment in which the receptor is found in is also critical to the design of pharmacologically active molecules. For example if the receptor is inside a cell then the drug must pass through the lipophilic cell membrane, hence the drug must also possess a significant hydrophobic section as to interact, via dispersion forces, with the membrane.







4. The structure of Atorvastatin is shown on the right. This molecule acts as a competitive inhibitor to the enzyme HMG-CoA reductase, which plays a crucial role in cholesterol biosynthesis.



Atorvastatin

   a. How many enantiomers of atorvastatin have to be tested for safety before it can be approved by the medical authorities?

      2 chiral carbons => $2^2 = 4$ enantiomers

   b. A mixture of different enantiomers of Atorvastatin was to be separated into the different components so that a pure sample of the active enantiomer was to be collected. HPLC was decided as being the separating technique to be used. Which of the following options is most suitable as the stationary phase? Justify your answer as to why you decided on your preferred option and why the other would not be suitable.

      i. Alumina beads coated with an amino acid with a basic Z group such as arginine.

      ii. Alumina beads coated with protein HMG-CoA reductase.

      iii. Alumina beads coated with an acidic amino acid such as glutamic acid and run at SLC.

      Enantiomers have identical chemical and physical properties. Only when interacting with other stereospecific molecules, such as enzymes, do they exhibit different properties. So a HPLC methode using a chiral stationary phase will be successful.
      Options i. and ii. Will not cause separation as the enantiomers behave in an identical manner chemically. Option iii, however, involves an enzyme that is very specific to binding one particular enantiomer only and this method will differentiate between the enantiomers and slow the rate of movement of the active enantiomer though the column.

5. A tablet of ibuprofen ($C_{13}H_{18}O_2$, 206.3 g/mol) was crushed, placed in a 200mL conical flask and dissolved in 100 mL of water and several drops of 0.1 M H_2SO_4 added. It was then titrated against a standard solution of 1.00 M $KMnO_4$, a pink coloured solution. During the titration ibuprofen is completely oxidised and clear Mn^{2+} ions are formed. The end point was reached when the solution turned a permanent pink colour at which point a titre of 10.01 mL was recorded.

   a. Write the balanced half equation for the oxidation reaction, states included.
   $24H_2O(l) + C_{13}H_{18}O_2(aq) + \rightarrow 13CO_2(g) + 66H^+(aq) + 66e$

   b. Write the balanced half equation for the reduction reaction, states included.

   $5e + 8H^+(aq) + MnO_4^-(aq) + \rightarrow Mn^{2+}(aq) + 4H_2O(l)$

   c. Write the balanced chemical equation, states included, for the overall reaction.

   $198H^+(aq) + 5C_{13}H_{18}O_2(aq) + 66MnO_4^-aq) \rightarrow 65CO_2(g) + 144H_2O(l) + 66Mn^{2+}(aq)$

   d. Calculate the amount, in mg, of ibuprofen in the tablet.

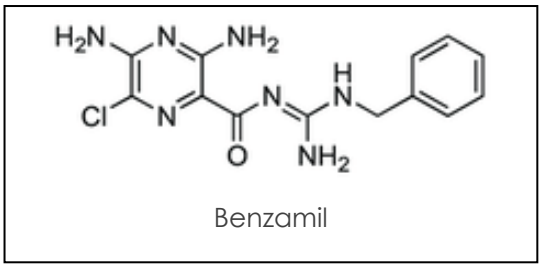
   Step 1 mol of MnO_4^- per titre = C X V =1.00 X 0.01001 = 1.001×10^{-2}
   Step 2 mol of ibuprofen per tablet = $1.001 \times 10^{-2} \times 5/66 = 7.58 \times 10^{-4}$
   Step 3 find the mass in grams of ibuprofen per tablet $7.58 \times 10^{-4} \times 206.3 = 0.156$ grams
   Step 4 find the mass in mg of ibuprofen in the tablet = 156

6. Conformational changes refer to the alterations in the three-dimensional arrangement or shape of a molecule, particularly in the arrangement of its atoms or functional groups. These changes are often reversible and result from the rotation of single bonds within the molecule, leading to different spatial arrangements or conformations. Conformational changes are common in flexible molecules, where certain rotations around single bonds allow the molecule to adopt multiple shapes or conformations. Benzene rings enable molecules to be more rigid and maintain a 3D fixed structure. Cyclohexane, however will undergo conformational changes as it bends and flexes to adopt different 3D shapes.

   a. With relevance to the way drugs interact with enzymes and receptors within the body discuss the importance of benzene as a necessary part of the molecular structure of most medications.

      Bioactive molecules used in medicines are stereospecific, that is they align perfectly with the surface of the receptors or active site of enzymes. Benzene is molecule that has a rigid planar structure which does not undergo conformational changes, unlike cyclohexane. This means that the functional groups attached to the ring structure remains in a permanent position in 3D space so that it will always be in the right place to interact with the receptor and active site.

   b. Consider the molecule of benzamil shown on the right. It is a diuretic that acts on specific receptors in the kidney to increase urine production.



Benzamil

      Cyclohexane and benzene ring structures, shown on the right in diagram 7, are hydrophobic structures.

      i. Describe the nature of the binding sites that these structures will have the highest affinity with on a protein and identify the type of bonding that takes place between these structures and the binding site.
      Non-polar hydrophobic structures interacting via dispersion forces.

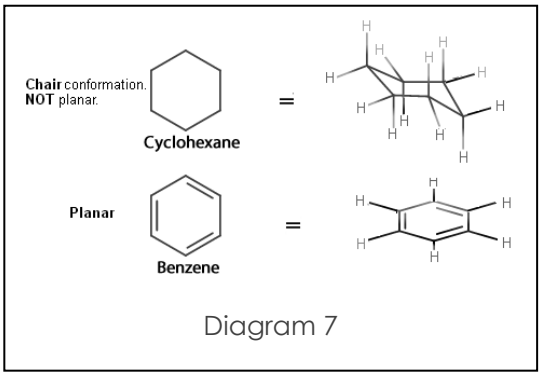


Diagram 7

      ii. Steric hindrance refers to the obstruction of two molecular structures coming in close proximity to each other, caused by the presence of bulky groups or atoms around a particular site in a molecule.
      Describe how the effectiveness or potency of Benzamil will change if the benzene ring was replaced with cyclohexane and explain why with reference to steric hinderance.
      - Bioactive molecules generally act by a close interaction between complementary shaped sites on molecules such as receptors and active sites. The better the interaction between the medicinal molecules and the target structure the greater the potency or effectiveness. Benzene is planar molecule that can get close to its target structure in the body. Cyclohexane, however, will be impacted by steric hinderance due to the extra hydrogens coming of the ring structure and will not form a strong bond with its target.

c. Label the functional groups shown in diagram 8.

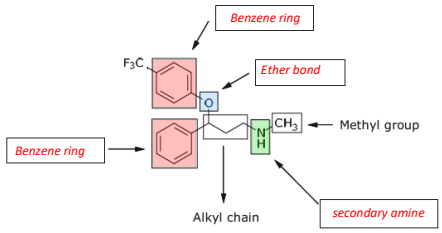


Diagram 8

7. A component of eucalyptus oil, called methyl cinnamate, has the chemical structure shown in diagram 9.

a. Name three functional groups forming the molecular structure of methyl cinnamate.

C=C

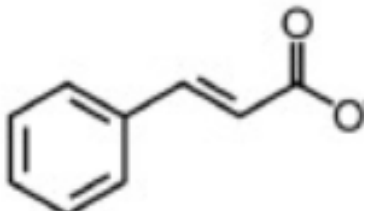
ester

benzene ring

b. Methyl cinnamate can be formed in the lab by reacting an organic acid with an alcohol. Name the alcohol used and identify the type of reaction taking place. *Methanol, esterification reaction or condensation reaction*

c. Given a benzene ring is written as C_6H_5, write the semi-structural formula for methyl cinnamate.

$C_6H_5CHCHCOOCH_3$



methyl cinnamate

Diagram 9