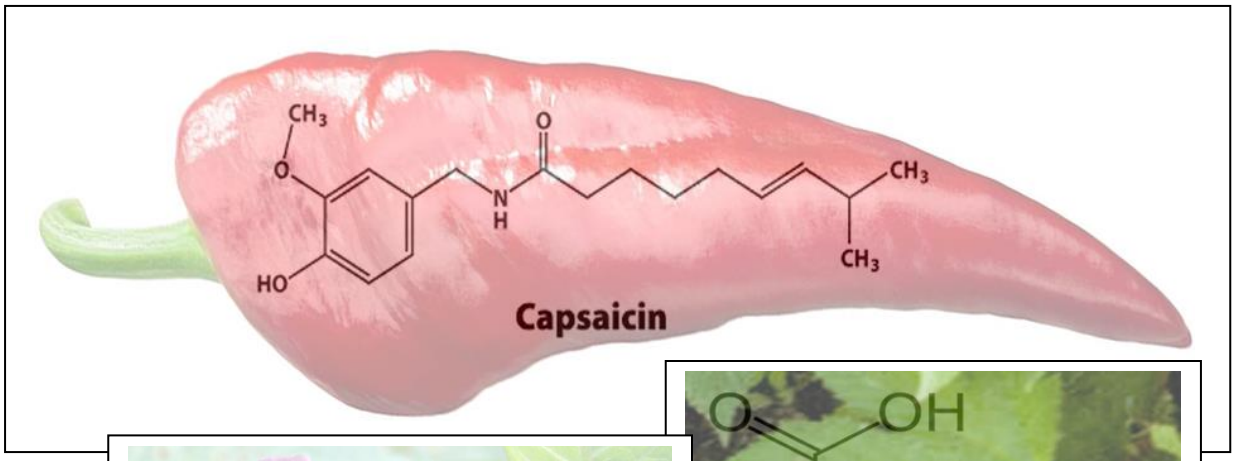
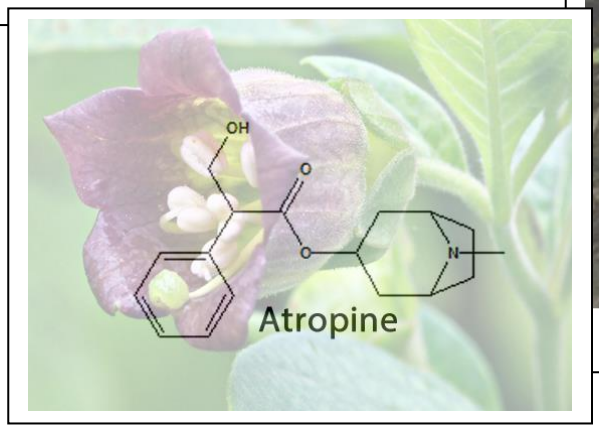
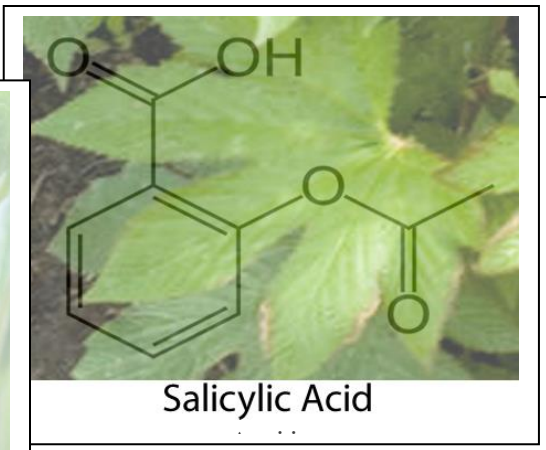
MEDICINES-STRUCUTURE AND FUNCTION







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.

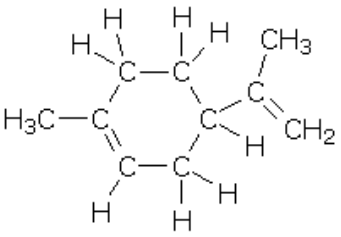
Solvent extraction

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 .

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

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

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

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.

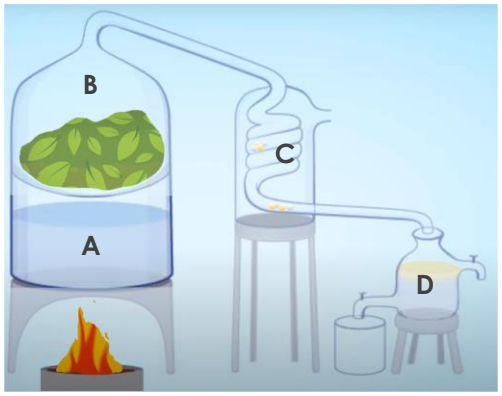


Figure 2 – steam distillation unit

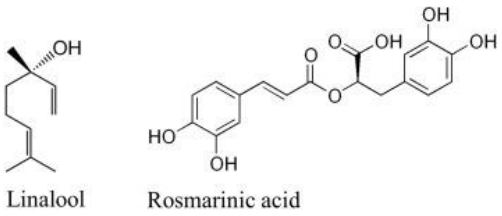


Figure 3

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.

   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.

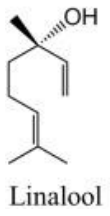


Figure 4

   c. A mixture of limonene and linalool was separated using reverse phase HPLC. The chromatogram obtained is shown in fig 5.
      i. Identify peaks A and B. Justify your choice.

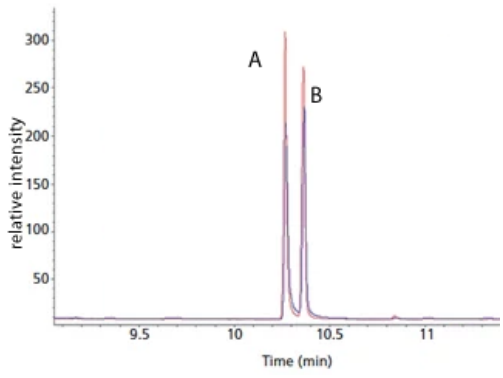


Figure 5

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

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.

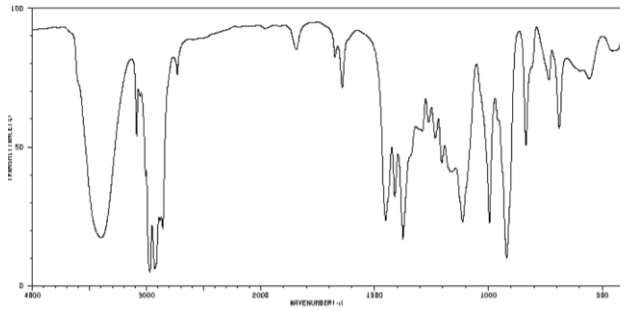


Figure 6

iv. Give the IUPAC name for linalool.

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.

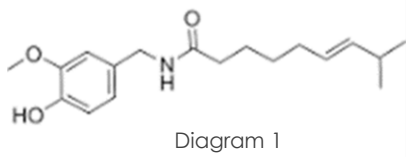


Diagram 1

   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.

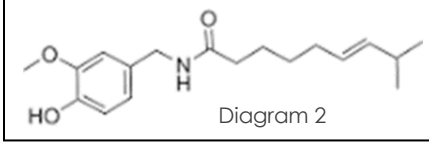


Diagram 2

   c. Consider the capsaicin molecule, diagram 2.
      i. Define what is meant by the term "chiral carbon" .

      ii. Define an enantiomer?

      iii. Describe the relationship between chiral carbons and optical isomers.

      iv. How many optical isomers can be found for the capsaicin molecule?

   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.

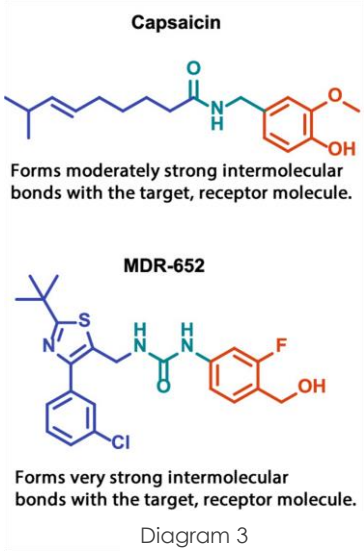


Diagram 3

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.

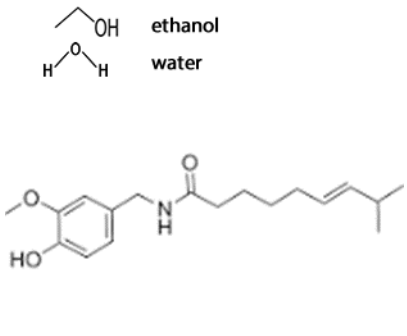
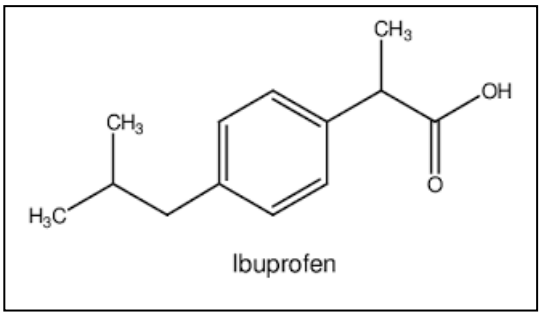


Diagram 4

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.

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.



Ibuprofen

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

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

   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. Identify which graph represents the rate of a reaction catalysed by an enzyme in the presence of a competitive inhibitor.

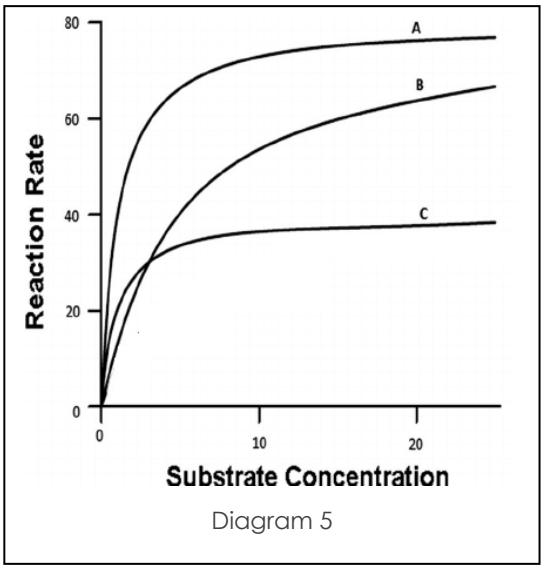


Diagram 5

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

      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.

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.

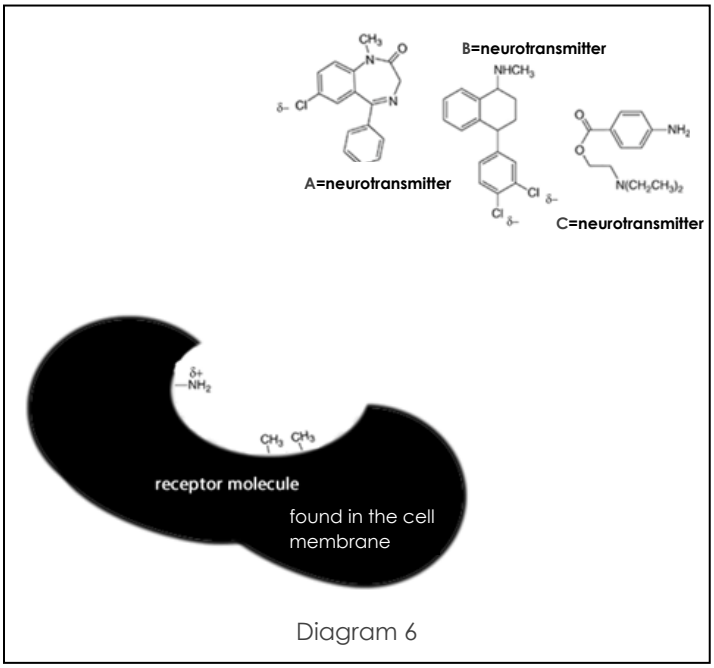
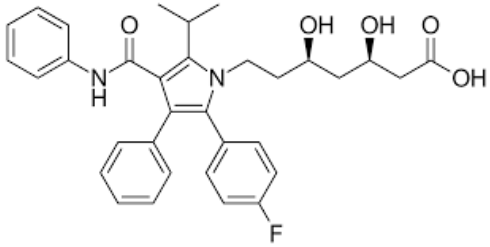


Diagram 6

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.

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.

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?

   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.

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.

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

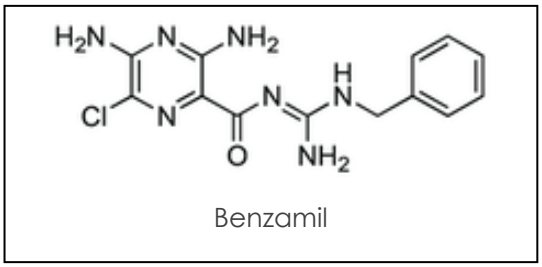
   c. Write the balanced chemical equation, states included, for the overall reaction.

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

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. Using the information above and with relevance to the way drugs interact with enzymes and receptors within the body, discuss the importance of benzene over cyclohexane in drug design.

   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.

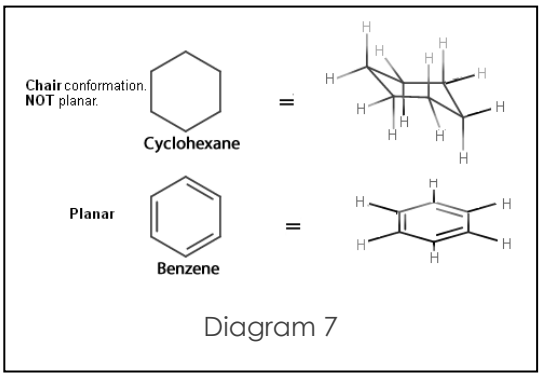


Diagram 7

   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.

c. Label the functional groups shown in diagram 8.

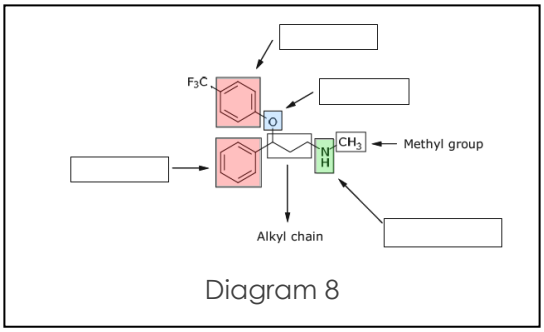
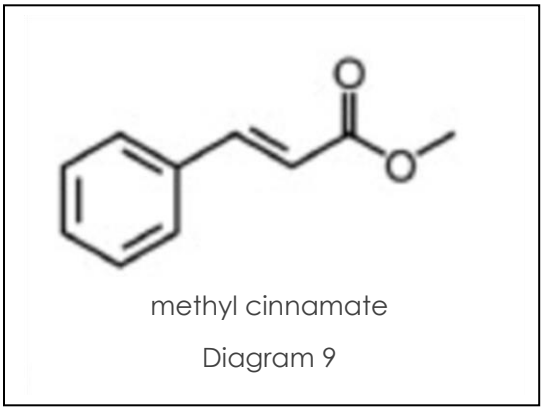


Diagram 8

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.



methyl cinnamate

Diagram 9

   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.

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