APPLICATION CHEMISTRY:

MATERIALS & DESIGN

(Medicinal Chemistry & Drug Delivery)

By: Mr. Chan M.H., Lucas

Medicinal Chemistry and Drug Delivery

- Two of the ways in which chemists are trying to combat disease:

- Developing and synthesising new drugs to **target specific diseases**.

- One way of doing this is to **start from natural products** – molecules that are **synthesised by plants and other organisms** - that have been shown to have beneficial effects, for example, the drug **Taxol®,found in yew tree leaves**.

- Taxol® has been found to be **effective against some cancers**.

Medicinal Chemistry and Drug Delivery

- Secondly, chemists are investigating means of **getting drugs to the specific part of the body where they need to act**.

- Such methods can **reduce side effects and the quantities** of drugs needed.

- One involves **liposomes**, where, in effect, the drug is delivered in a “bag” to the diseased body site.

Designing drugs

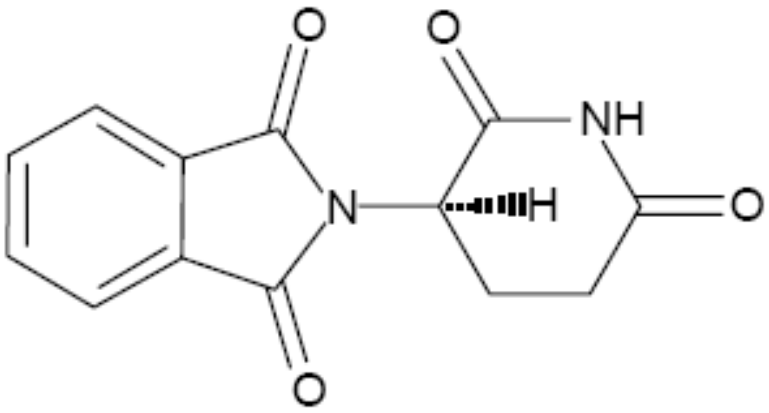
- When a molecule is to be used as a drug it is important that it is **effective in achieving its desired effect** *and* that **undesirable side effects are avoided**.

- **Thalidomide** was, at this time(1960s), the preferred **sedative during pregnancy** as the alternatives, such as Valium, were addictive.

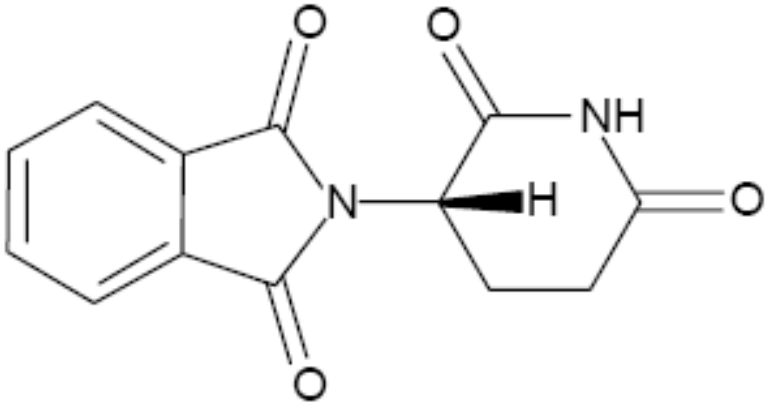
- At that time the **thalidomide produced was a mixture of two optical isomers**.

- one of the isomers of thalidomide have disastrous **side-effects, causing babies to be born with congenital deformities** such as shortened limbs

Designing drugs



(R) – Thalidomide desirable properties: sedative and antinausea drug



(S) – Thalidomide teratogenic: causes birth defects

Figure 3.1 – the two enantiomers of thalidomide

Designing drugs

- **Drug molecules act by binding to receptors**, and in many cases these receptors are **enzymes**.

- Drugs can be competitive inhibitors of enzymes and if a drug has optical isomers, only the **isomer that is complementary to the shape of the enzyme active site will fit**.

- **In order to bind** to its receptor a drug must not only have the shape to fit, but **must also be able to interact with the groups on the receptor** molecule **by hydrogen bonds, ionic interactions or dipole-dipole interactions**.

Designing drugs

- Computational methods have proved very powerful both in designing new medicines and in understanding how drugs act.

- Chemists seek a route that produces only the active molecule that is desired. This process is called **asymmetric synthesis**.

- A key reason for this change is that when two chiral molecules are produced, they are produced in equal quantities, so half of the reactants are wasted.

- Asymmetric synthesis therefore **saves on resources and costs**.

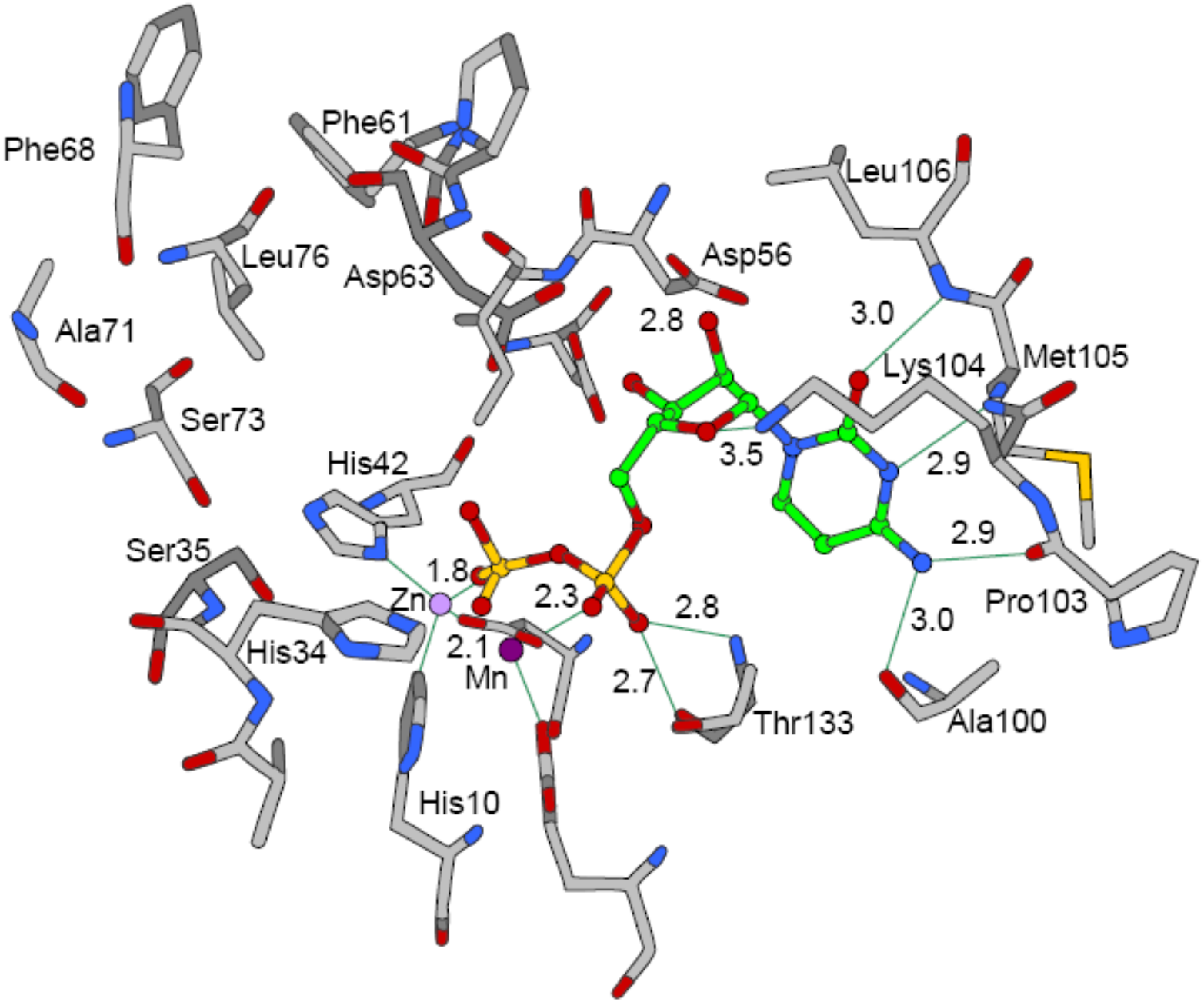


Figure 3.2 – Computer-generated model of a drug in the active site of an enzyme, showing hydrogen bonds

Designing drugs

- A successful example of asymmetric synthesis is in the treatment of Parkinson's disease.

- a molecule called **L-dopa** (the L enantiomer of dopa) can alleviate the symptoms.

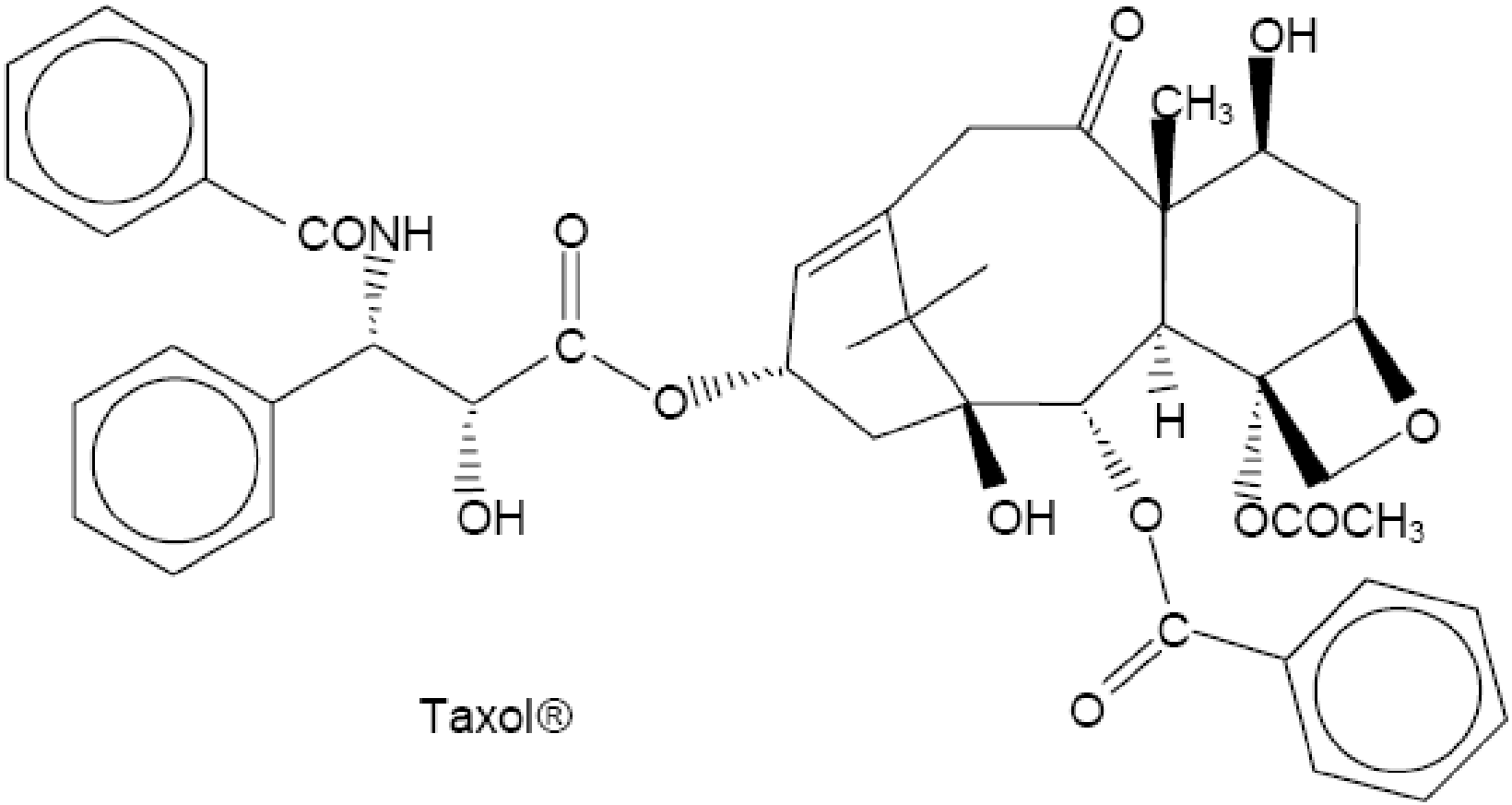
- The L-dopa must be free of D-dopa, as the latter has many unpleasant side effects. Chemists now make pure L-dopa for use by patients.

- These changes alone **would not have had an effect on the thalidomide story**, as the **molecule can switch between enantiomers at the pH of the blood**.

Designing drugs

- Seeking a new pharmaceutical - start from a natural product molecule
- Recent example - anticancer drug Taxol®
- Taxol® is found in yew trees. It acts by binding to protein molecules in the cell and preventing the cell from dividing.
- Only small amounts of Taxol® can be isolated from yew trees, so it became important to find ways of synthesising Taxol®.

Designing drugs



Taxol®

Figure 3.3 – structure of Taxol®

Designing drugs

- Synthesising a molecule as large and complex as Taxol® is a major challenge

- To do this requires chemists to firstly, know the structure of the Taxol®, and then work out ways of making the drug.

- The structures of such molecules can be worked out by the NMR and X-ray techniques

Designing drugs

- The first groups achieved their goal in 1994, but research continues as chemists are keen to minimise the number of reactions needed

- Keen to make similar molecules with slightly different shapes and functional groups in order to try and find a molecule that is even more effective with fewer side effects.

Delivering drugs

- Get the drug molecule to that target site. This process is termed “**drug delivery**”.

- There are many problems with delivering drugs, one of which is how to get the drug to its target in one piece and **avoid it being broken down by enzymes or degrading in extremes of pH**.

- One successful method of delivery involves the use of liposomes. These are **artificial microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers**.

Delivering drugs

- A phospholipid is a molecule that is **hydrophilic** (water-loving) **at one end** and **hydrophobic** (water-hating) **at the other end**.

- In water-based solutions such as blood, lipids group together to form double layers with their **hydrophilic groups on the outside**, forming polar interactions with the water, and their **hydrophobic groups on the inside**, away from the water.

Delivering drugs

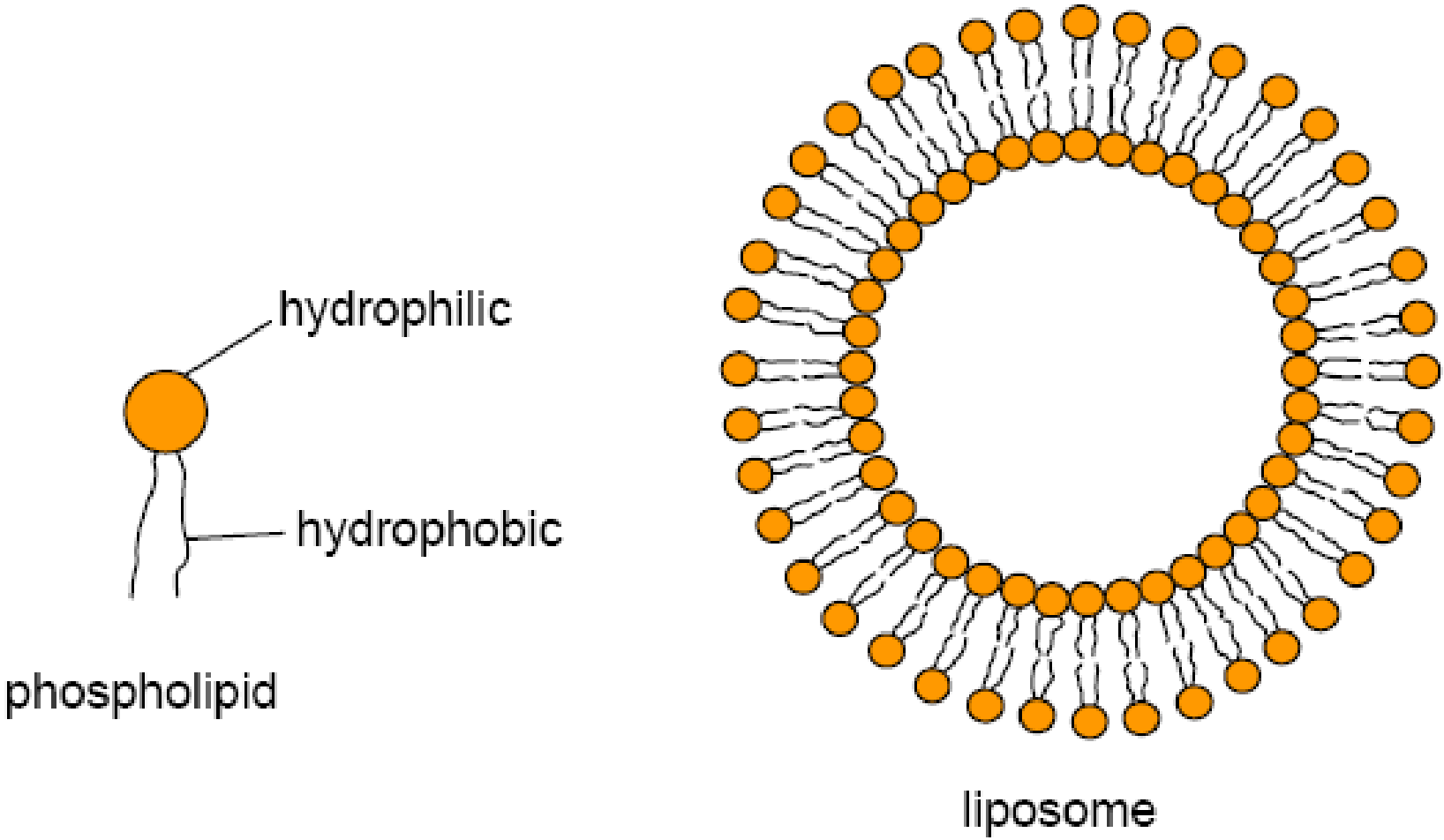
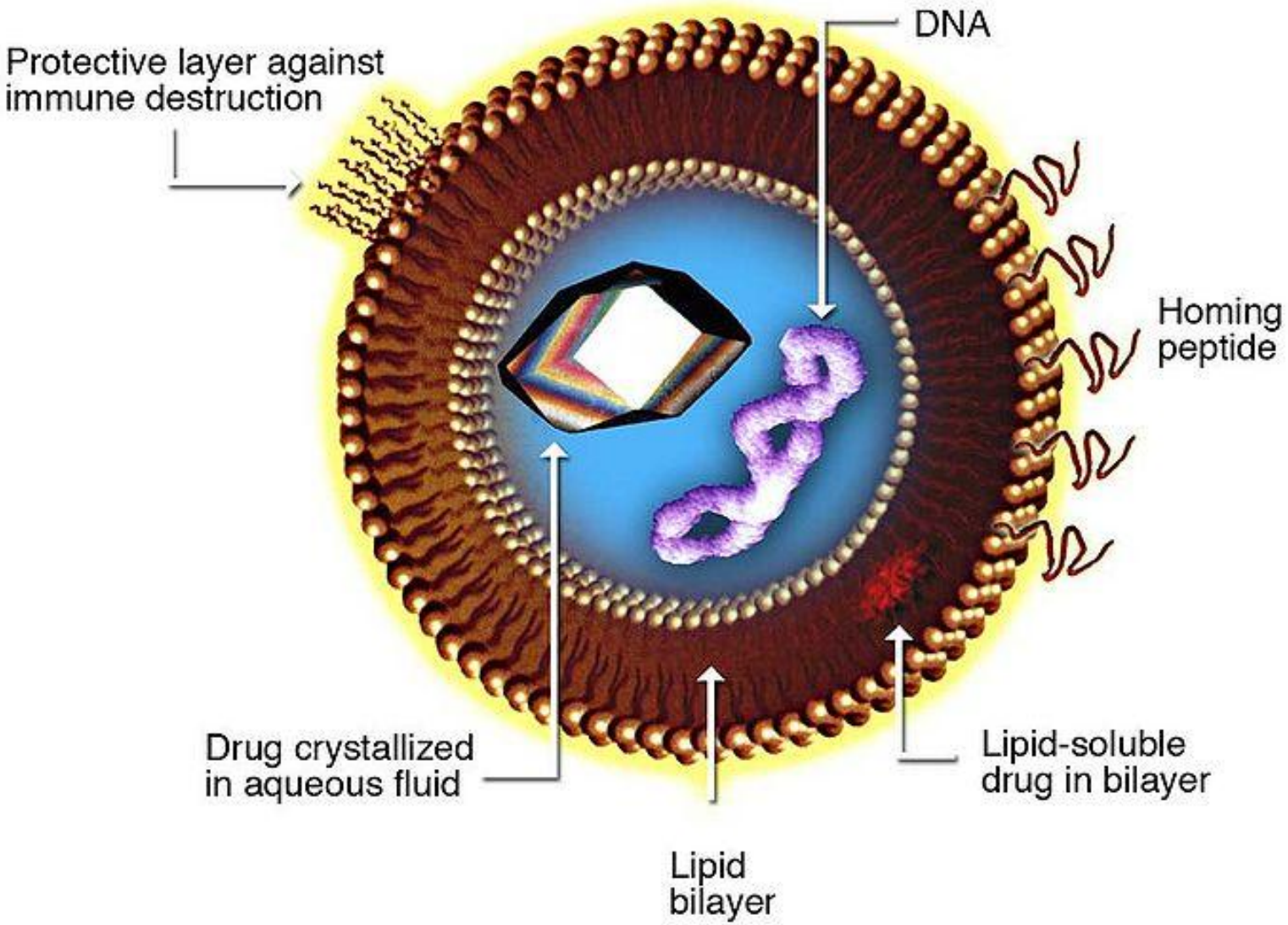


Figure 3.4 – a phospholipid and a cross-section of a liposome

Liposome for Drug Delivery



Delivering drugs

- Liposomes are **biodegradable and non-toxic** and can be **used to carry vaccines, drugs, enzymes,** or other substances to target cells or organs.

- They **can carry both *hydrophilic* molecules** (polar molecules **that form hydrogen bonds with water and hence dissolve**) and ***hydrophobic* molecules** (non-polar molecules that do not dissolve in water).

Delivering drugs

- Modifying surface of liposomes biochemists have developed long-circulating liposomes, which do not degrade quickly and have a better chance of reaching their target.

- **Once the liposome reaches its target, the drug will be transferred to the target.**

Delivering drugs

- A second method of protecting drugs while they are circulating in the bloodstream is to attach them to polymers. A popular polymer to use is polyethylene glycol, or PEG.
- PEG is soluble in water
- Disadvantage of PEG compared with a liposome is that it can only carry two drug molecules.
- To improve the number of drug molecules that a polymer can deliver, different polymers can be made where some of the monomers have side chains that can link to the drug molecules.

-
- http://www.youtube.com/watch?v=1QwyMWM0Jjg&feature=related