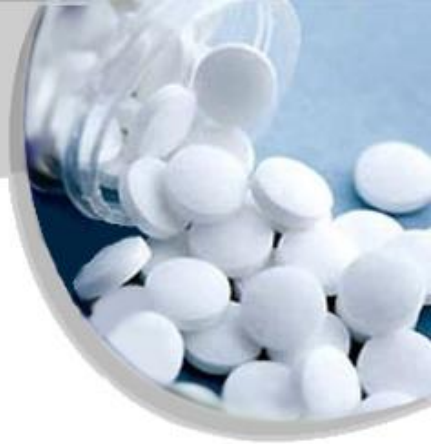


Applications of Prodrugs

Shuaib Alahmad

1.5 Prodrugs

Definition:

Inactive compounds which are converted to active compounds in the body.

Uses:

- **Improving membrane permeability**
- **Prolonging activity**
- **Masking toxicity and side effects**
- **Varying water solubility**
- **Drug targeting**
- **Improving chemical stability**
- **‘Sleeping agents’**

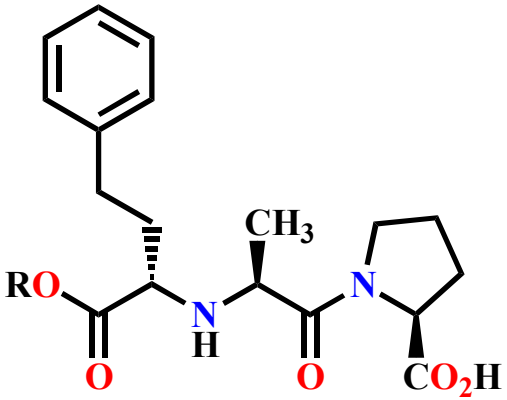
1.5.1 Prodrugs to improve membrane permeability

1.5.1.1 Esters

- Used to mask polar and ionisable carboxylic acids
- Hydrolysed in blood by esterases
- Used when a carboxylic acid is required for target binding
- Leaving group (alcohol) should ideally be non toxic

Example:

Enalapril for enalaprilate (antihypertensive)



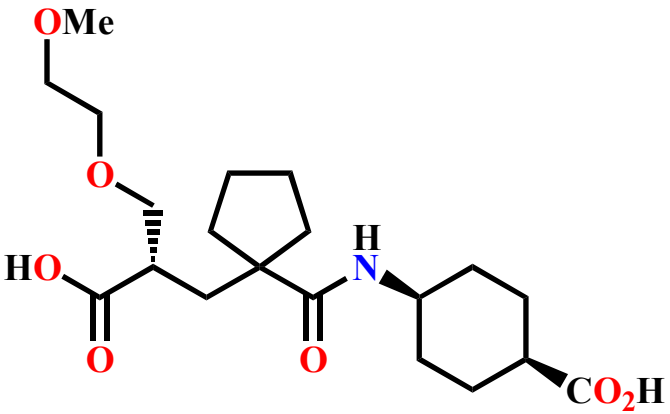
R=Et Enalapril
R=H Enalaprilit

1.5.1 Prodrugs to improve membrane permeability

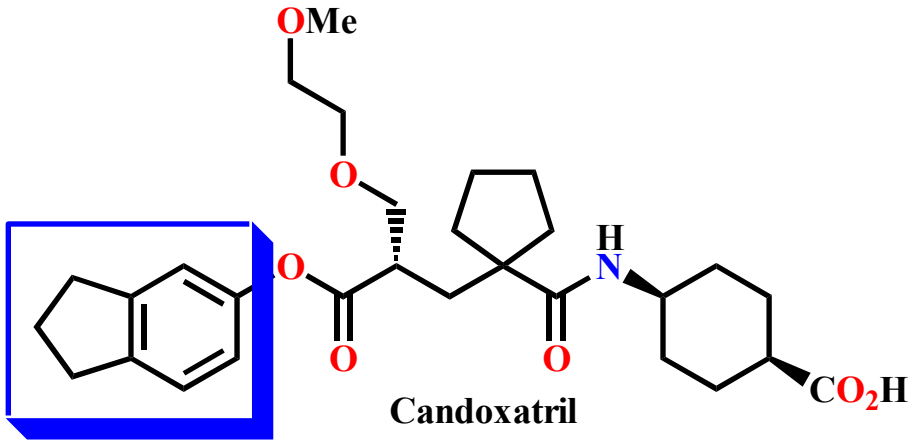
Example:

Candoxatril for Candoxatrilat (protease inhibitor)

Protease inhibitors (PIs) are medications that act by interfering with enzymes that cleave proteins. Some of the most well known are antiviral drugs widely used to treat HIV/AIDS and hepatitis C.



Candoxatrilat



Candoxatril

5-indanyl group

- **Varying the ester varies the rate of hydrolysis**
- **Electron withdrawing groups increase rate of hydrolysis (e.g. 5-indanyl)**
- **Leaving group (5-indanol) is non toxic**

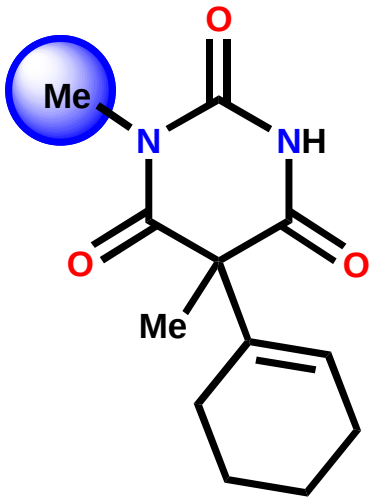
1.5.1 Prodrugs to improve membrane permeability

1.5.1.2 *N*-Methylation of amines

- **Used to reduce polarity of amines**
- **Demethylated in liver**

Example:

Hexobarbitone



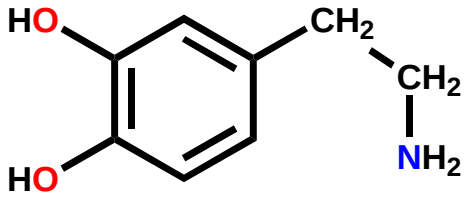
Hexobarbital is a barbiturate derivative having hypnotic and sedative effects.

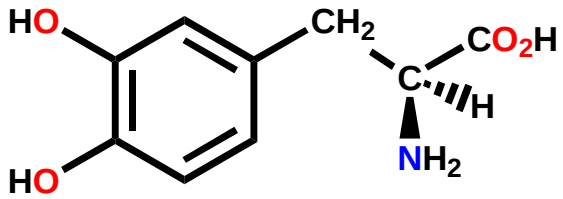
1.5.1 Prodrugs to improve membrane permeability

1.5.1.3 Trojan Horse Strategy

- **Prodrug designed to mimic biosynthetic building block**
- **Transported across cell membranes by carrier proteins**

Example: Levodopa for dopamine



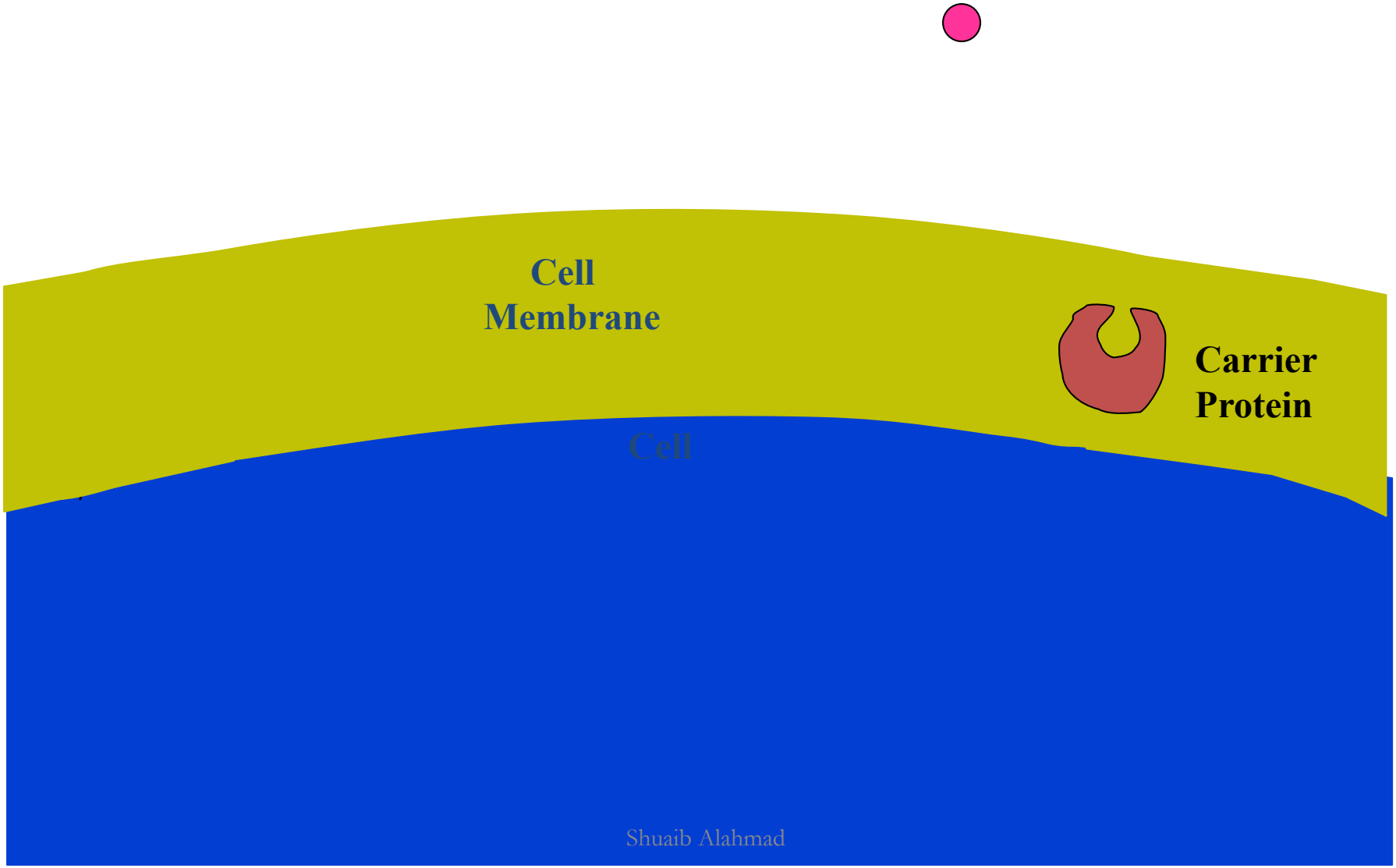


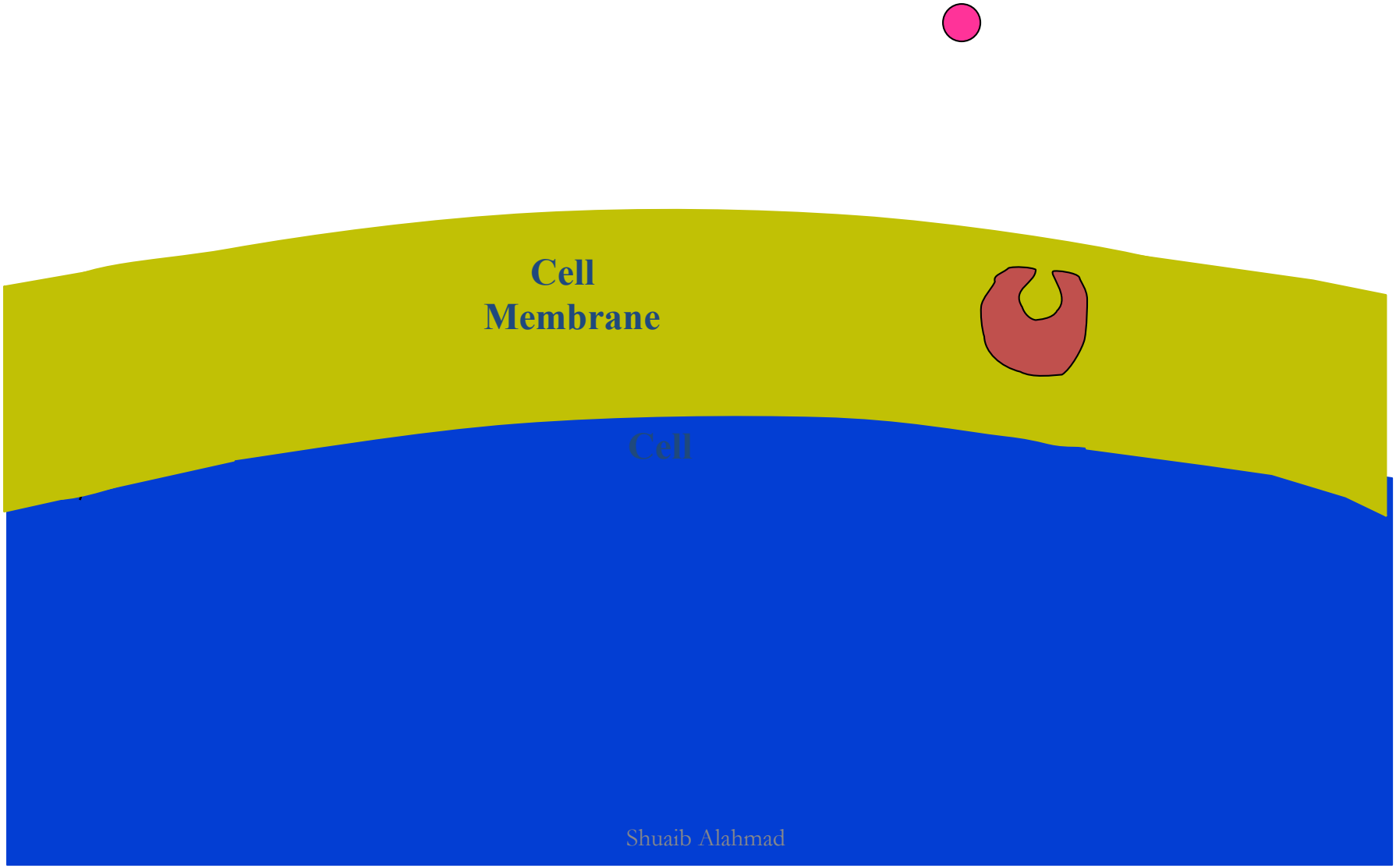
Dopamine

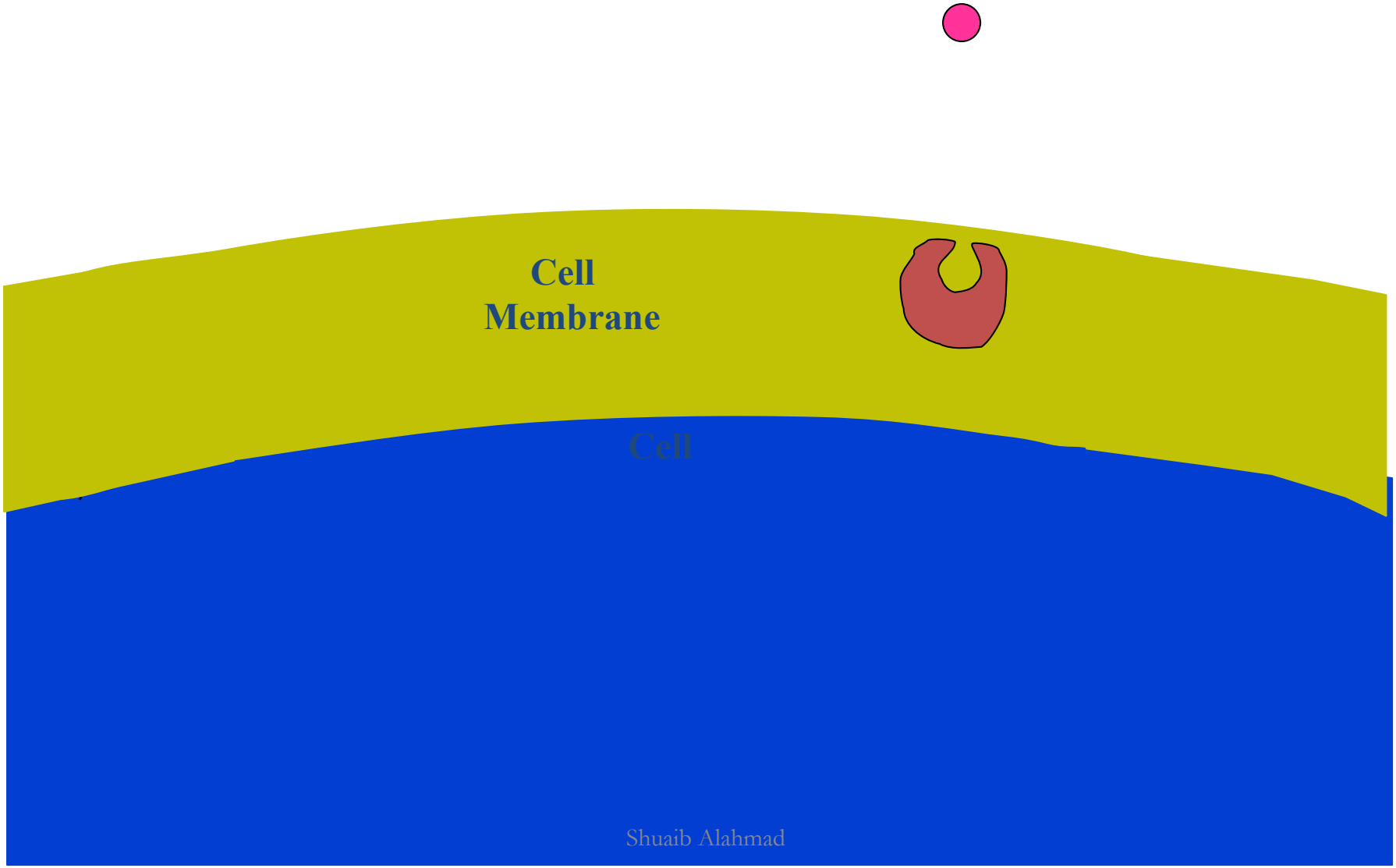
- **Useful in treating Parkinson's Disease**
- **Too polar to cross cell membranes and BBB**

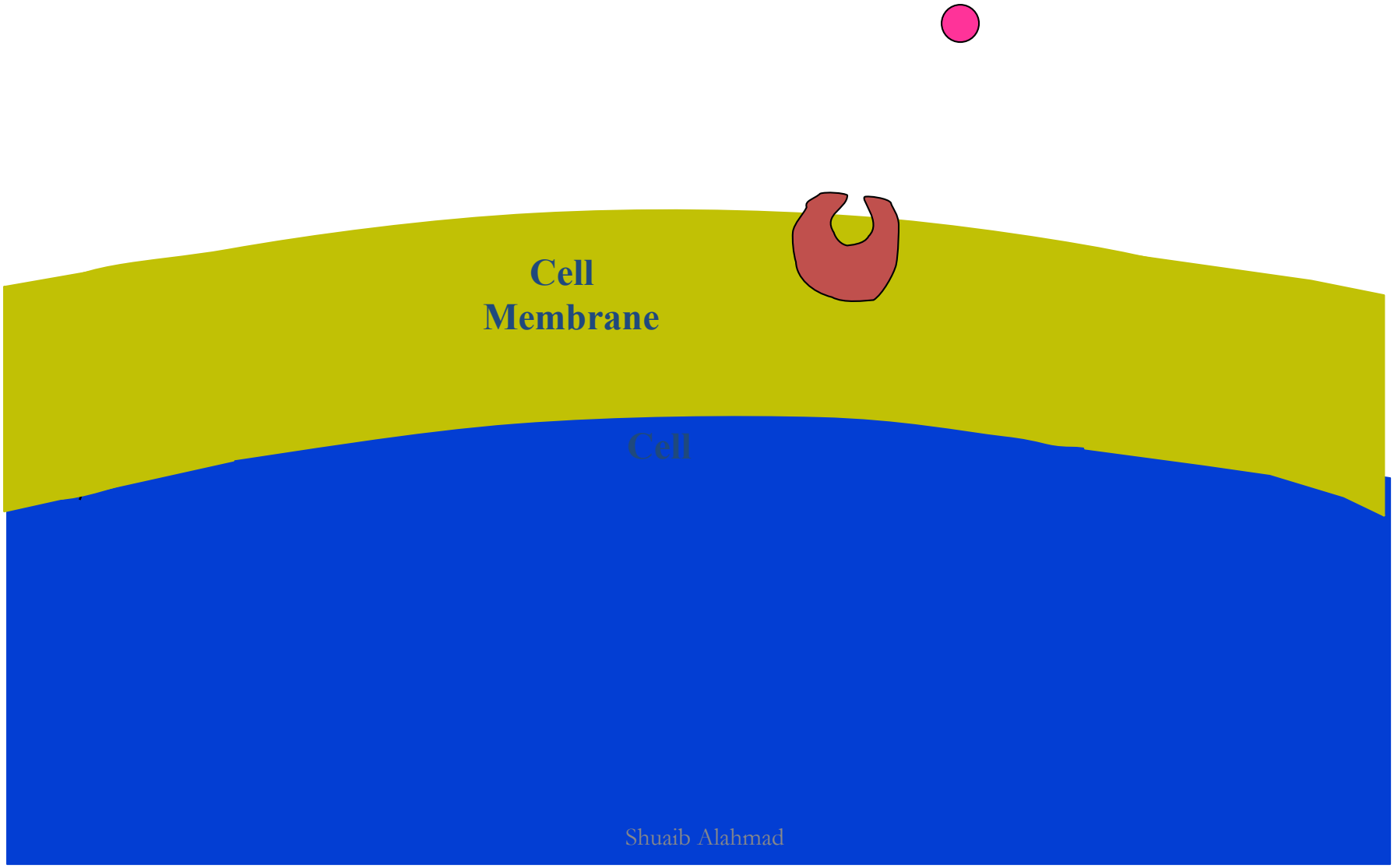
Levodopa

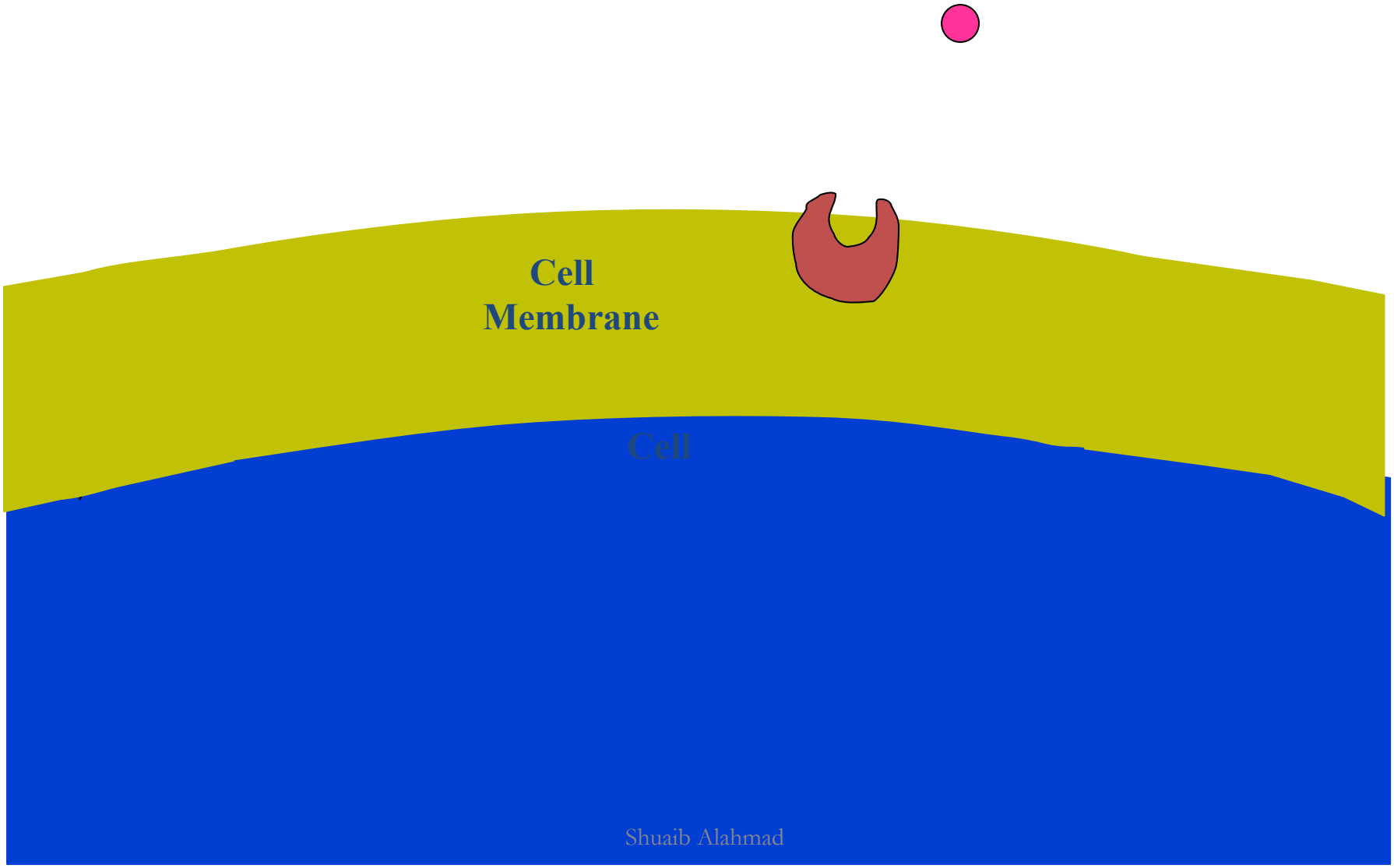
- **More polar but is an amino acid**
- **Carried across cell membranes by carrier proteins for amino acids**
- **Decarboxylated in cell to dopamine**

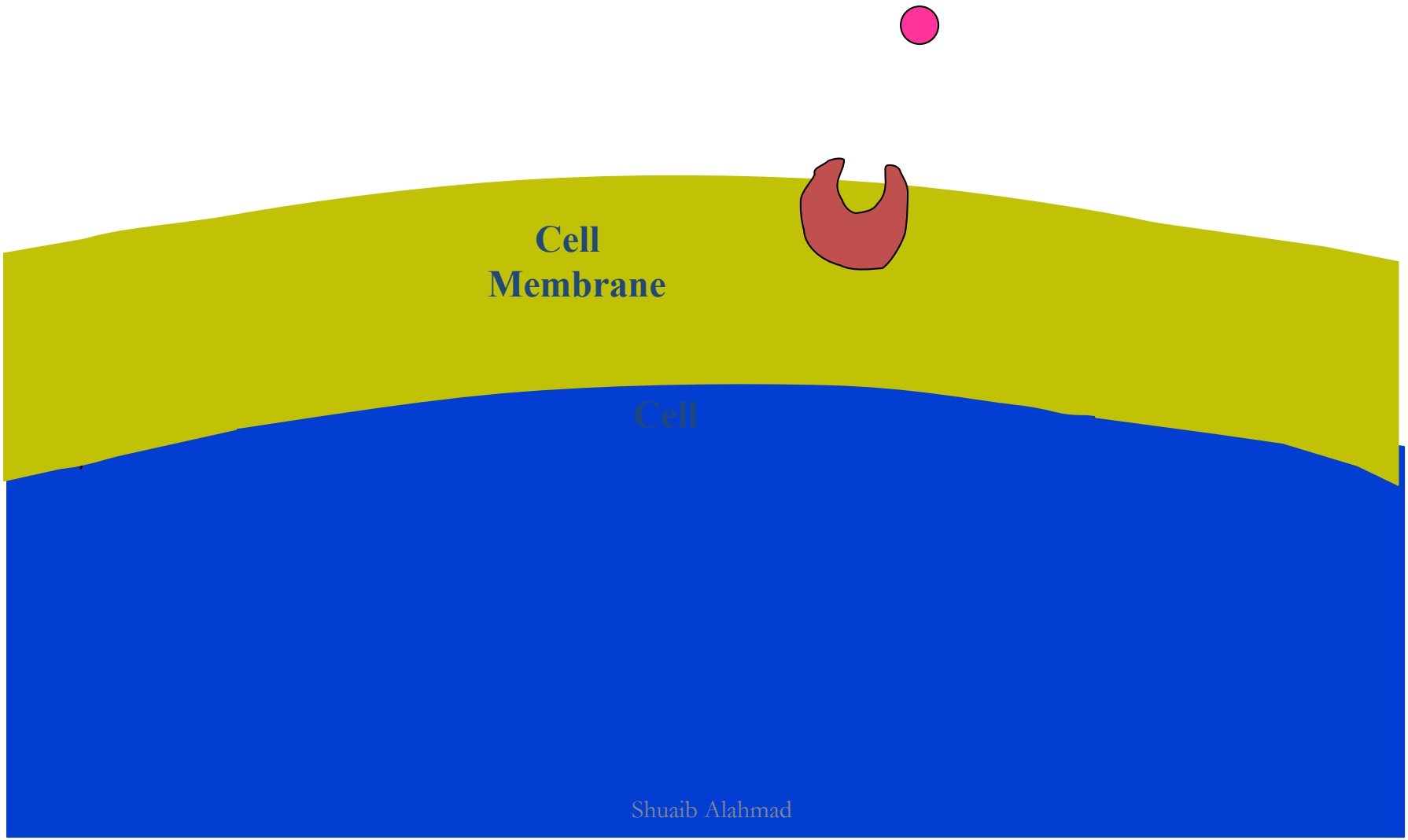


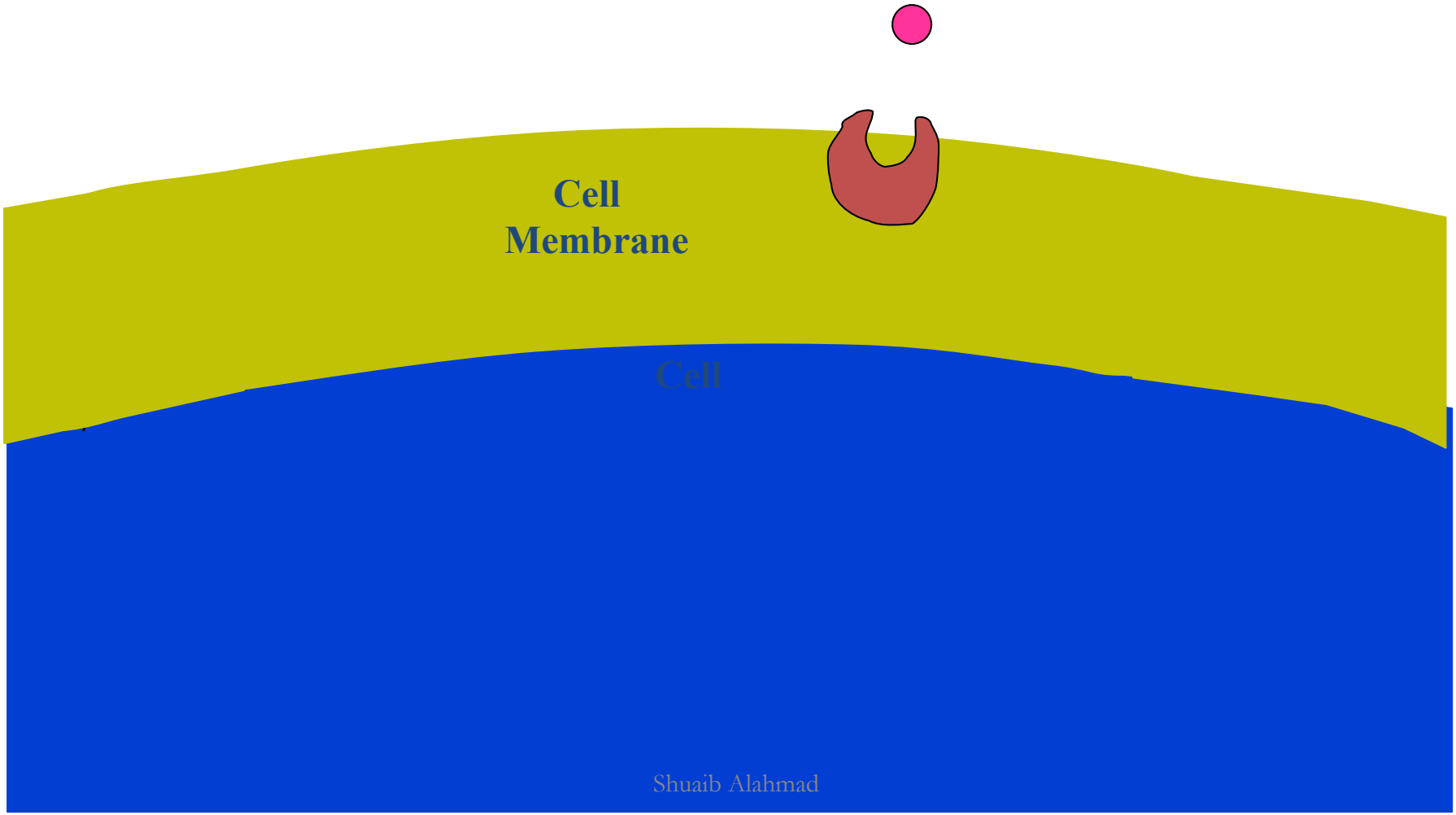


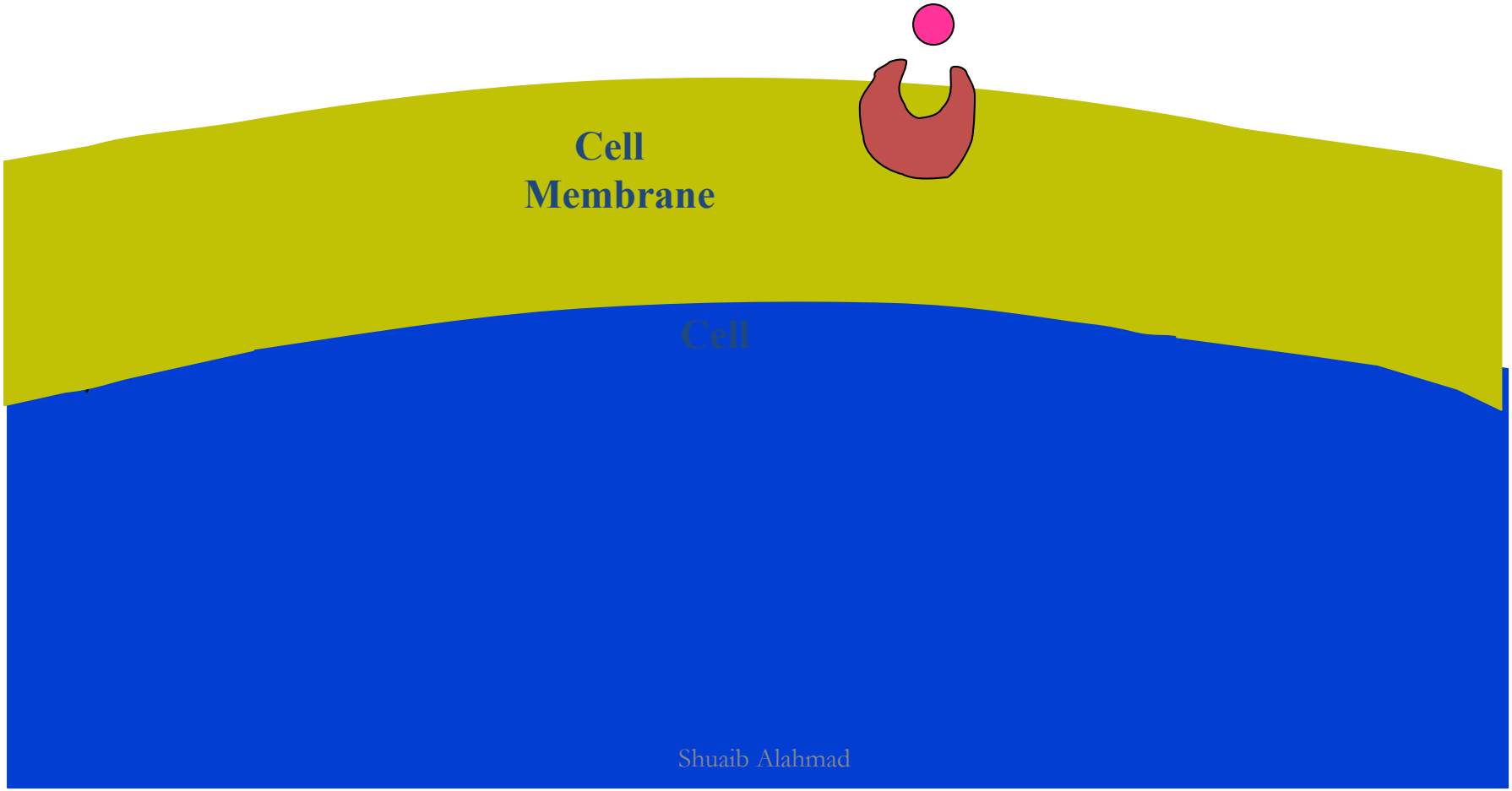


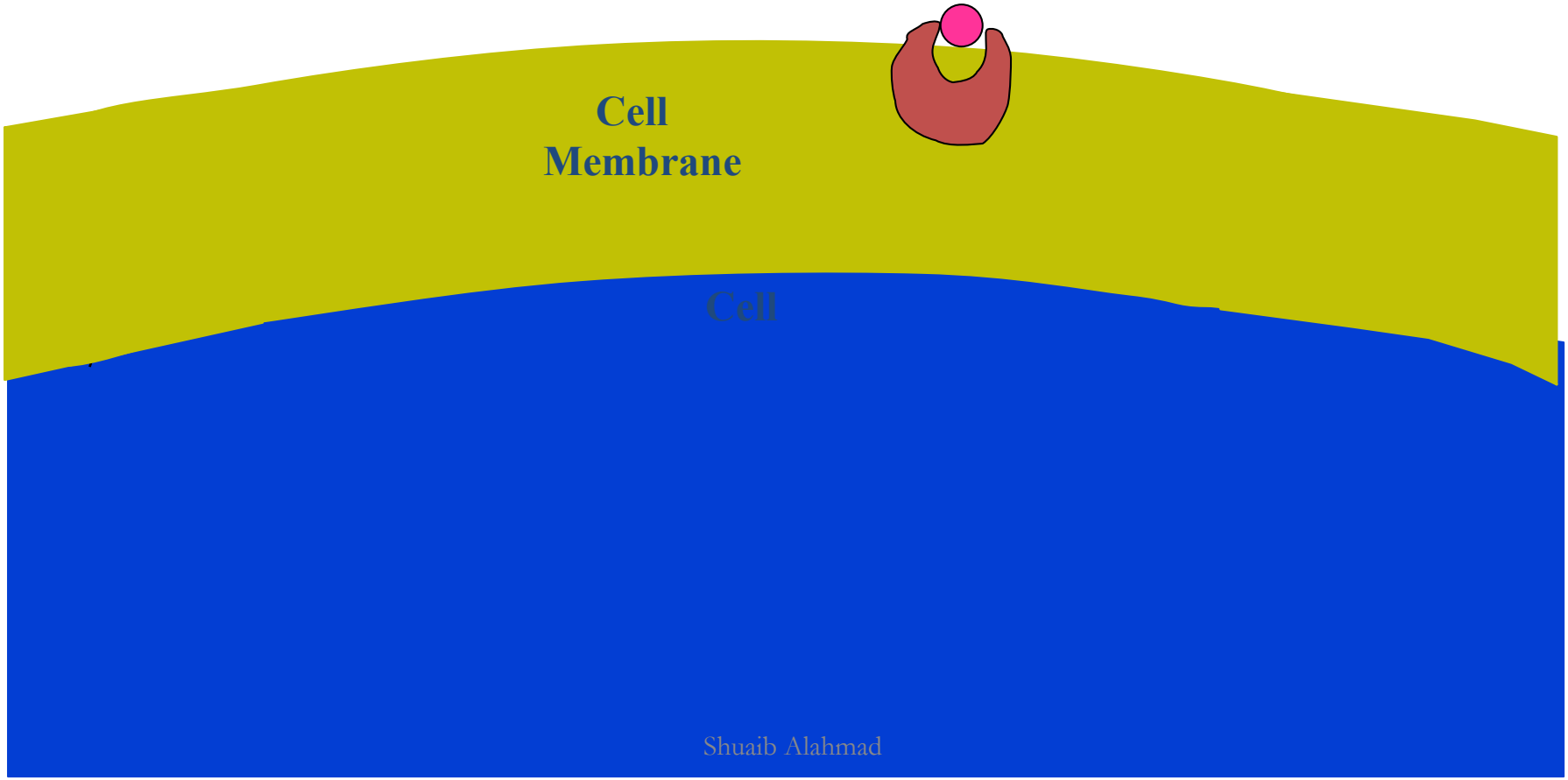


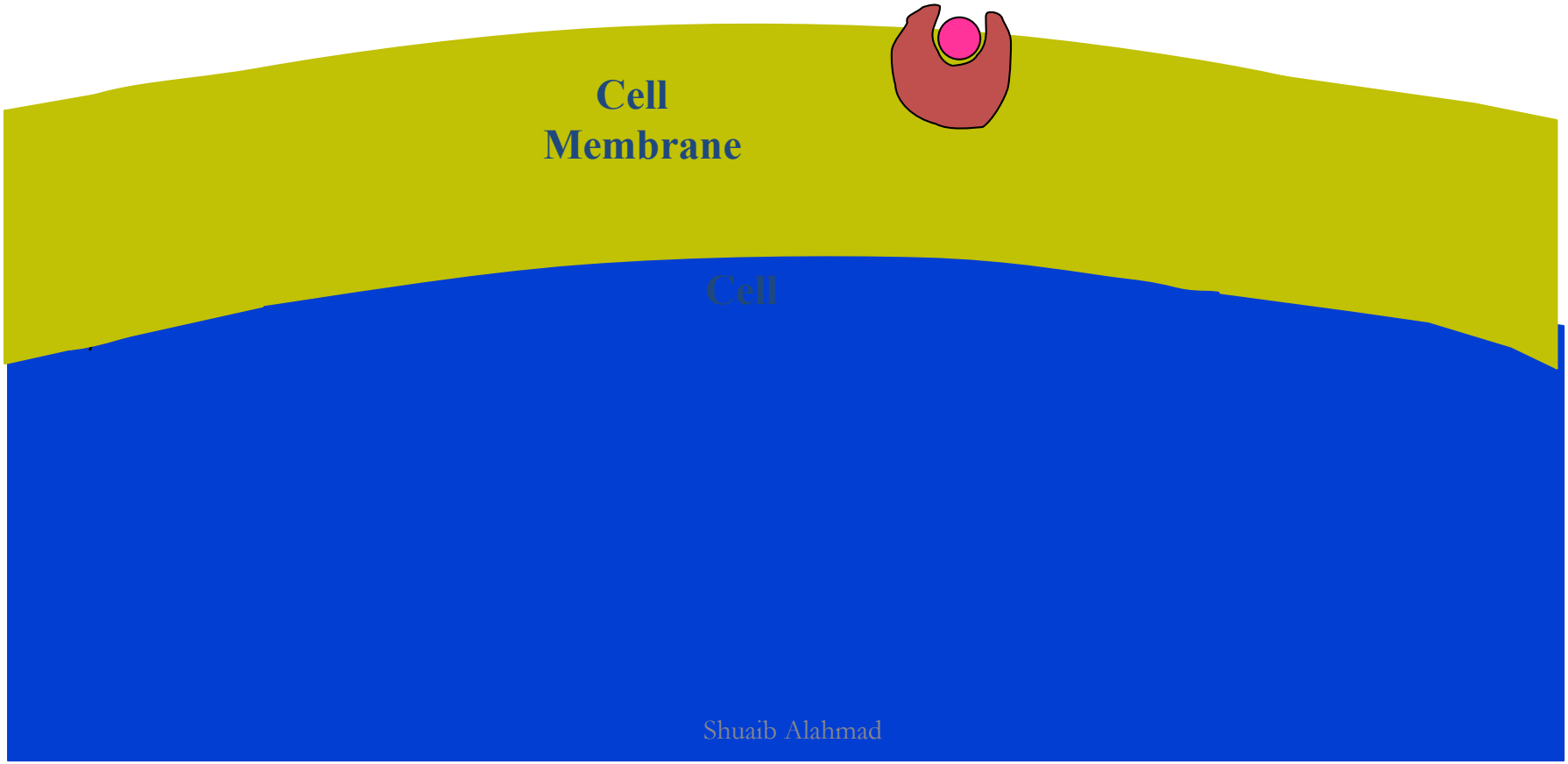


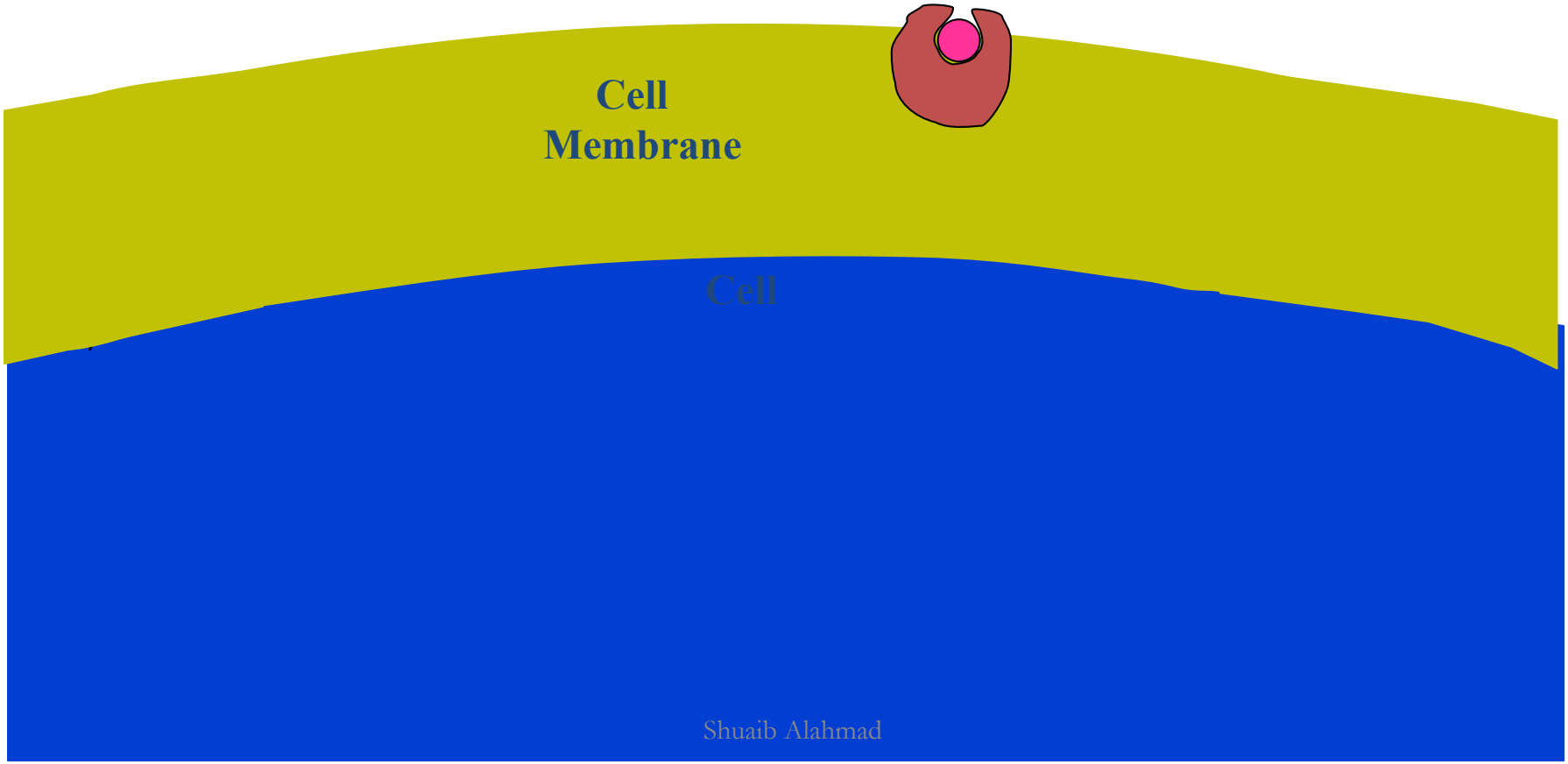


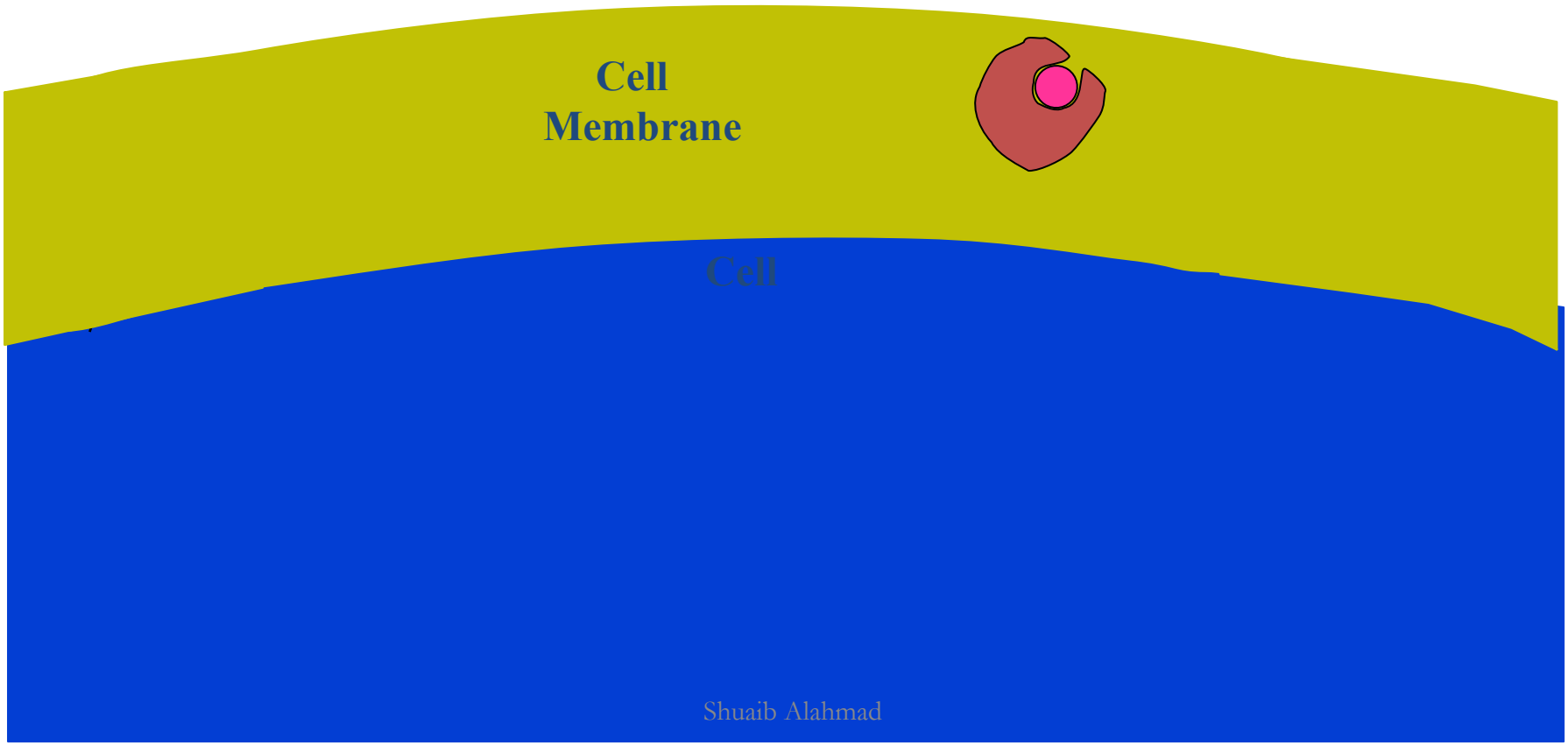


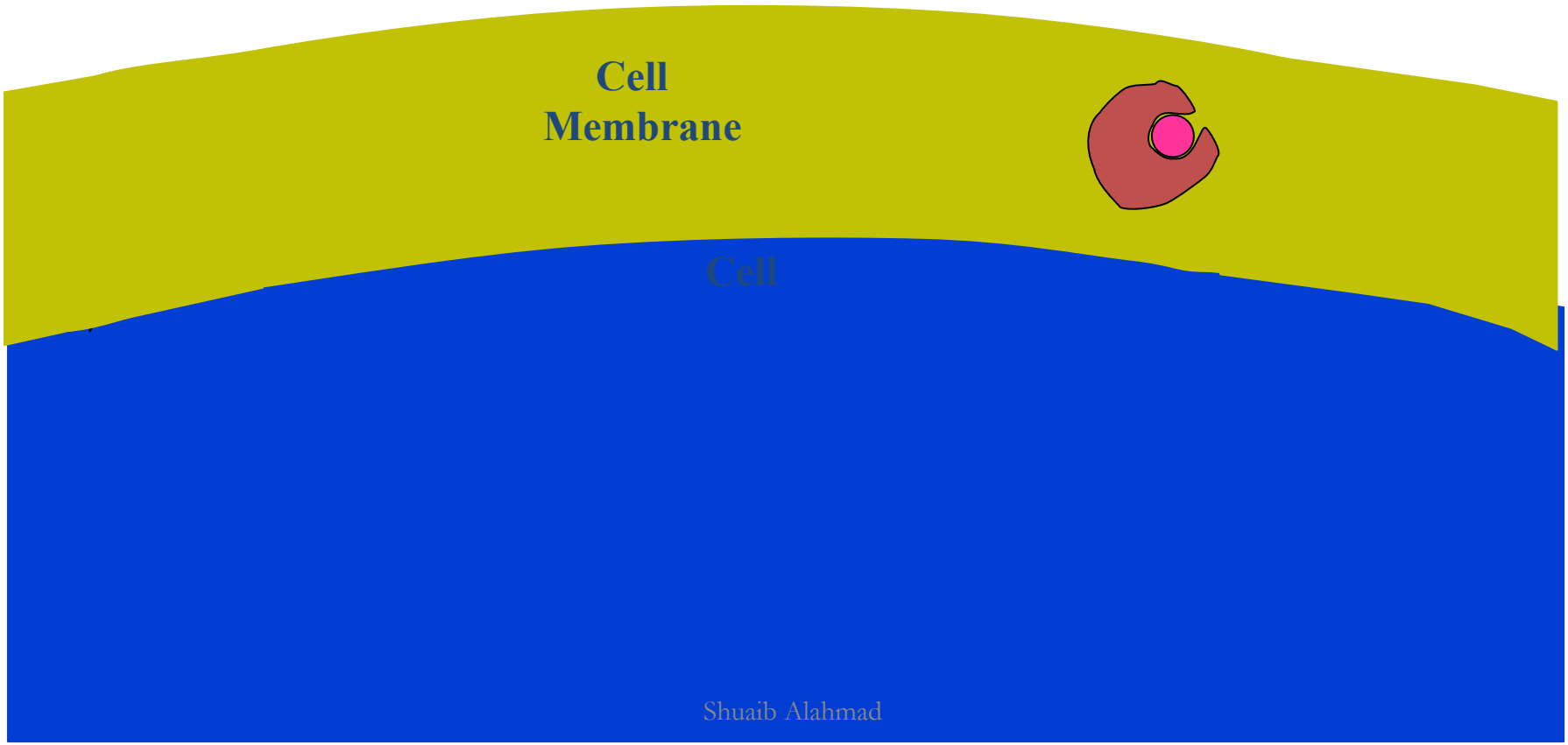


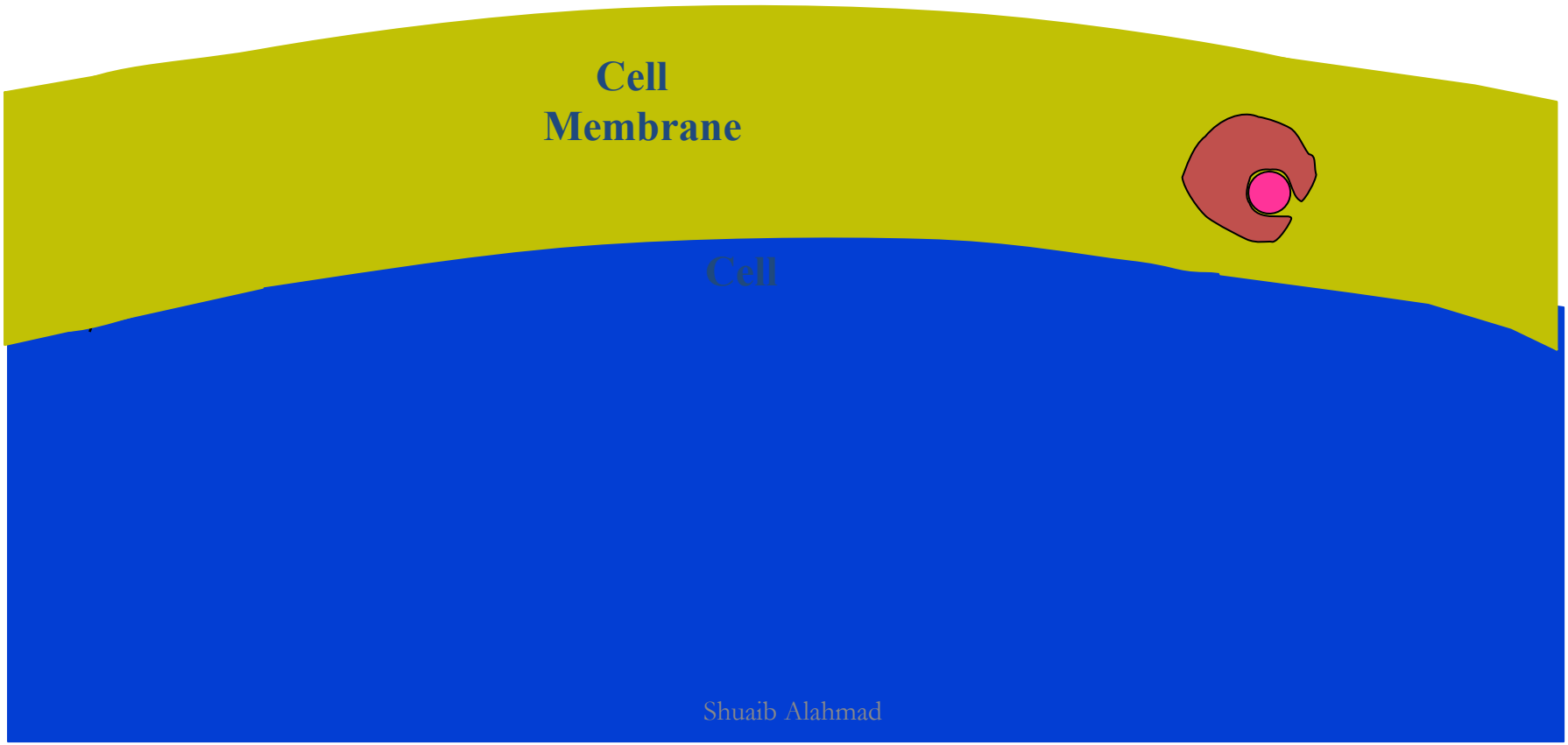


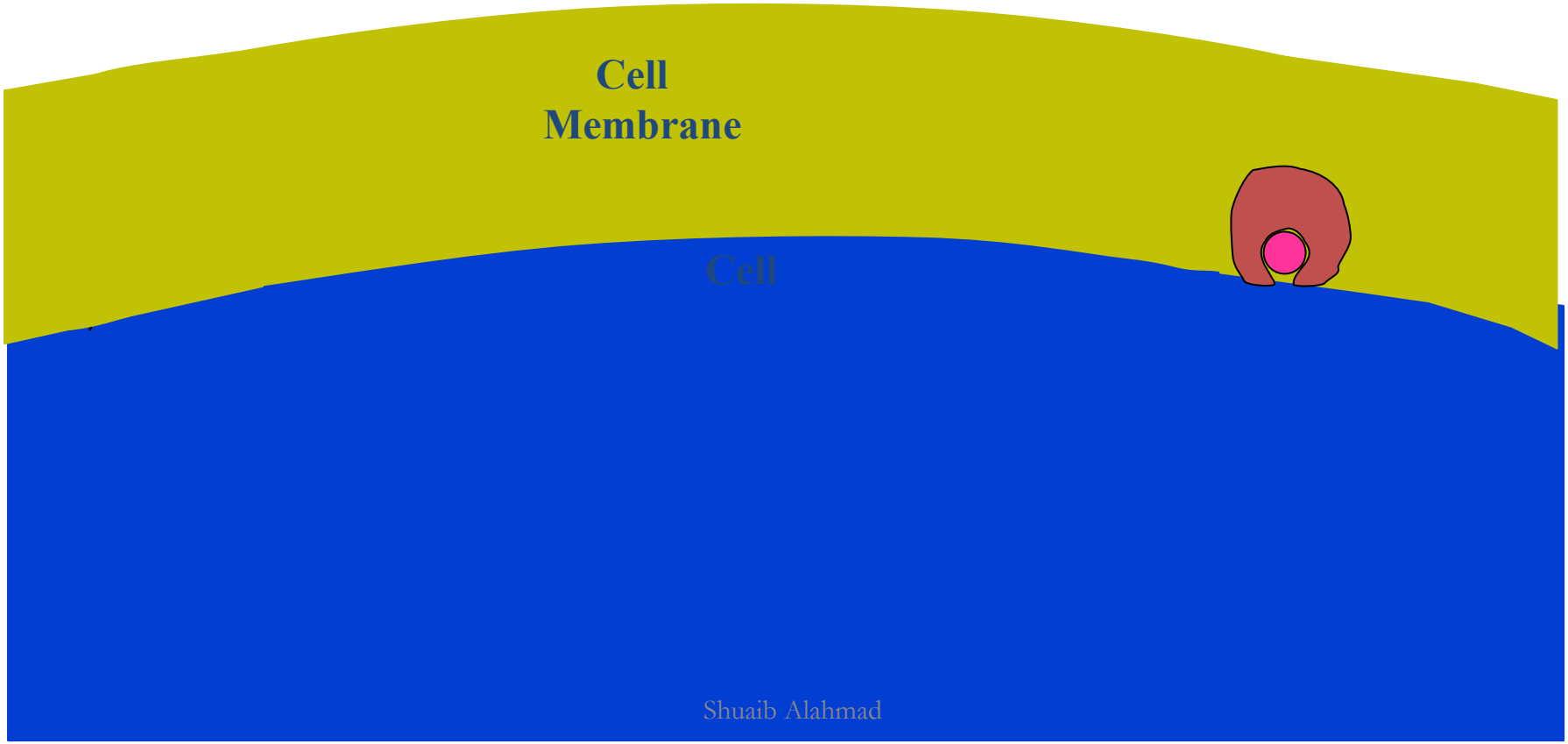


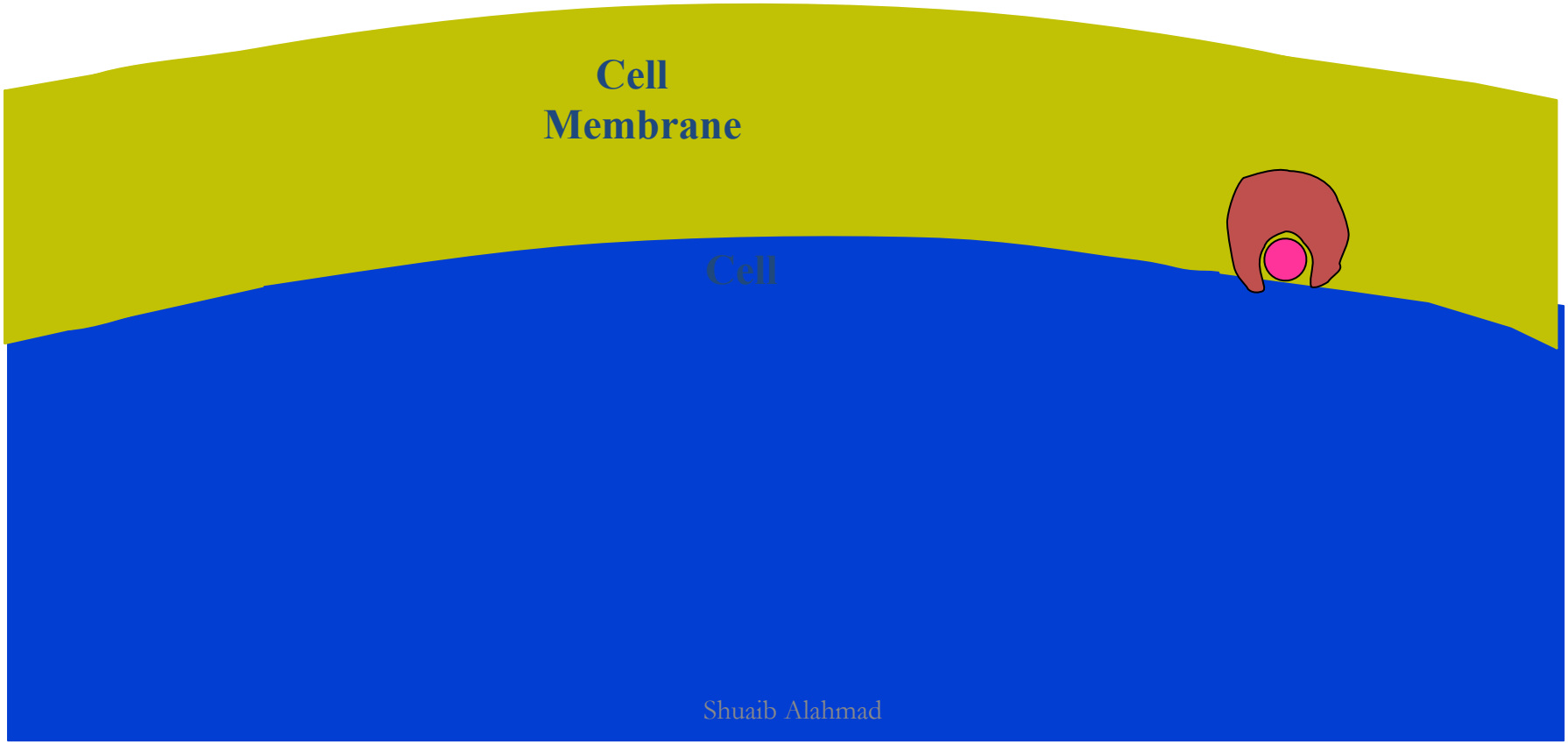


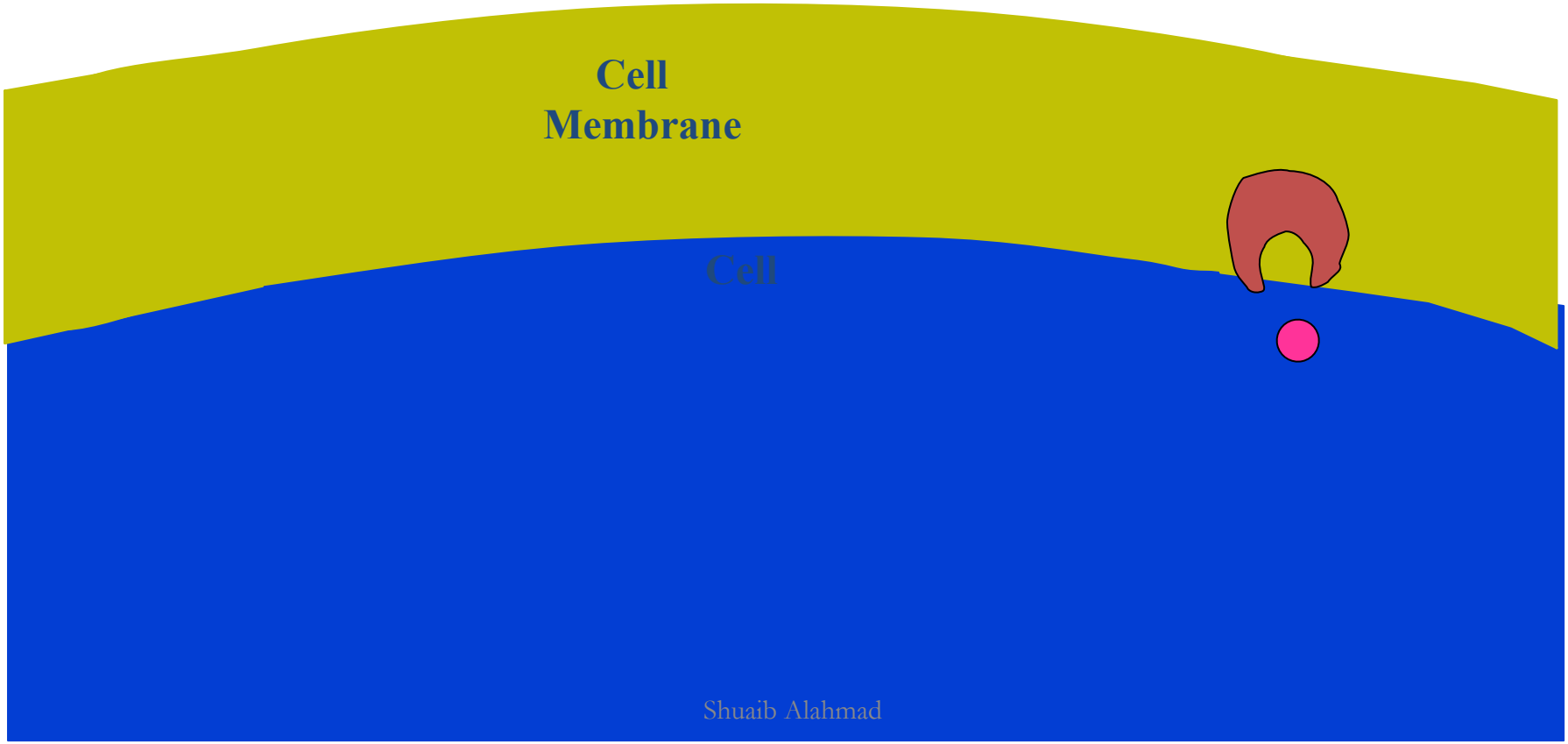


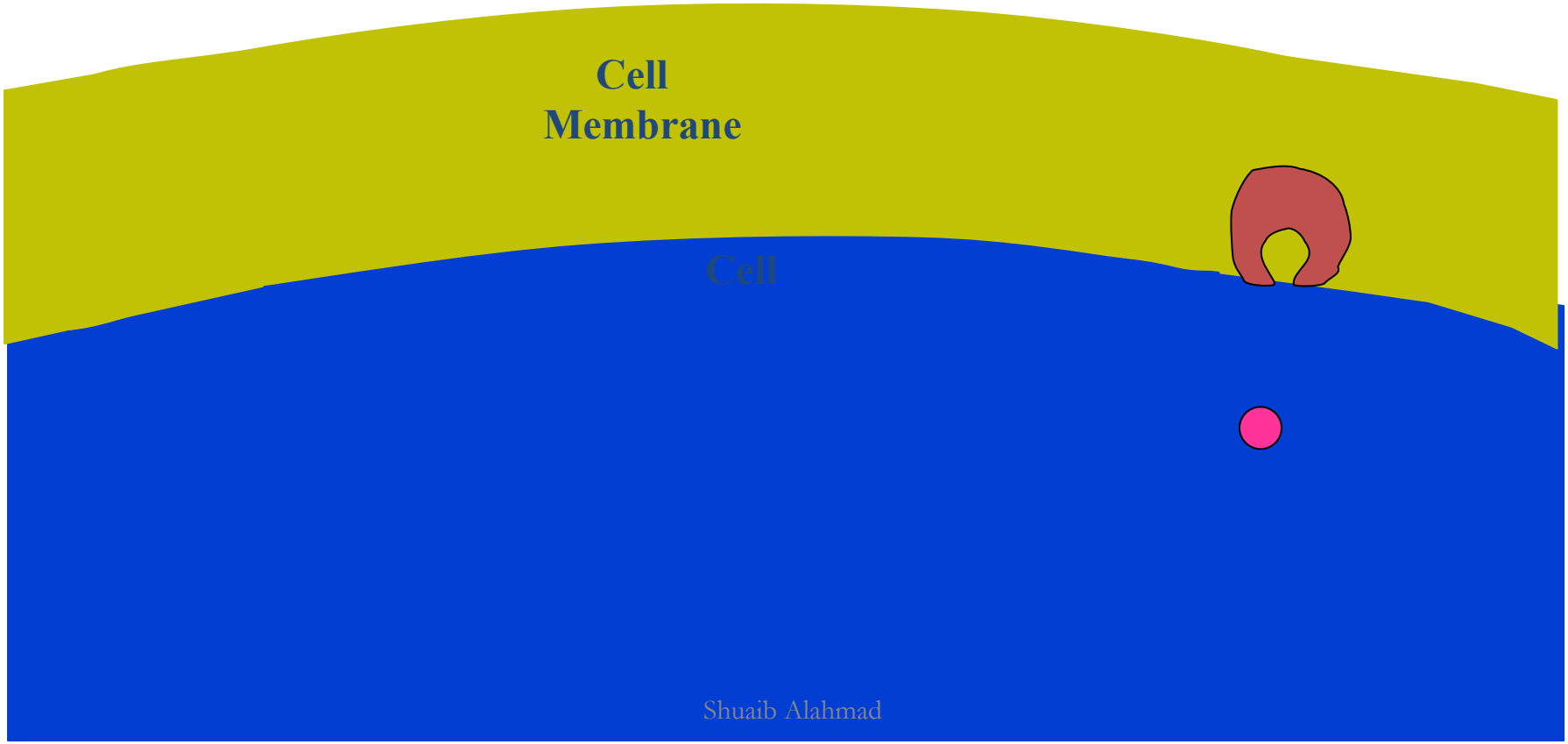


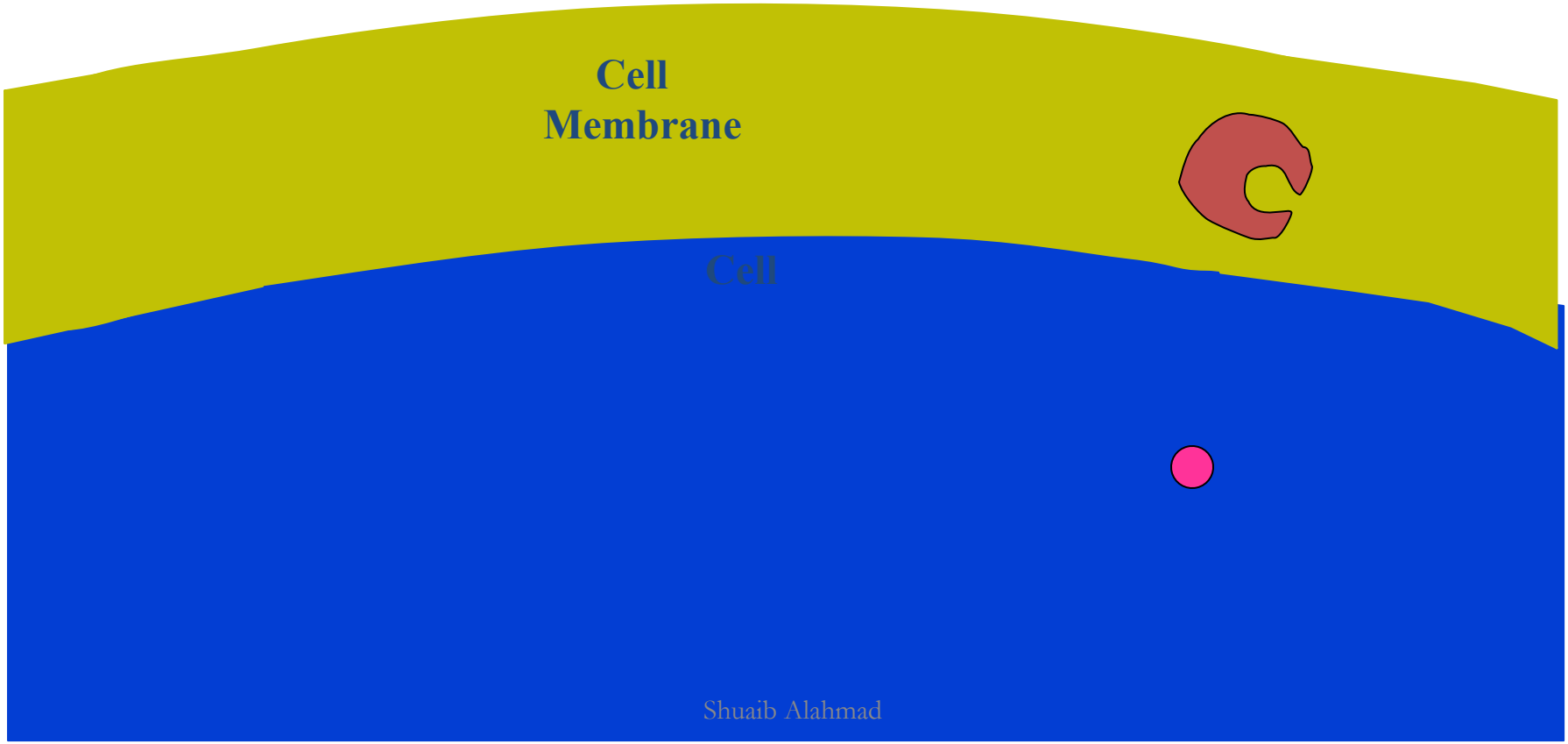




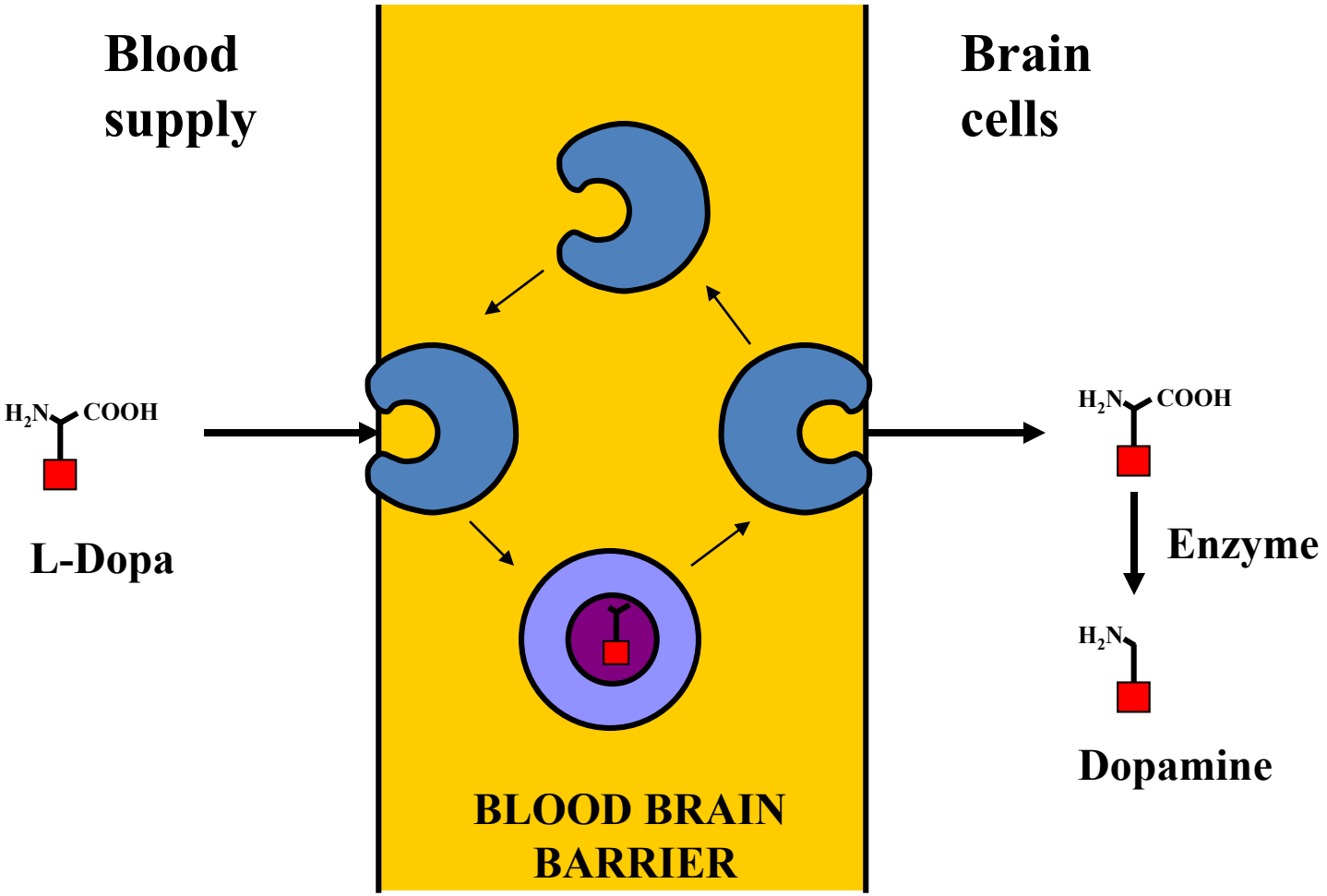








1.5.1 Prodrugs to improve membrane permeability



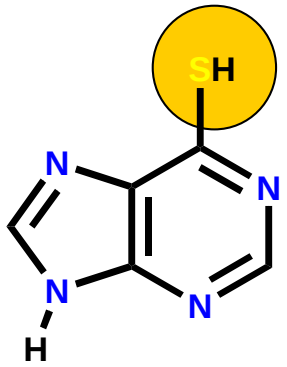
1.5.2 Prodrugs to prolong activity

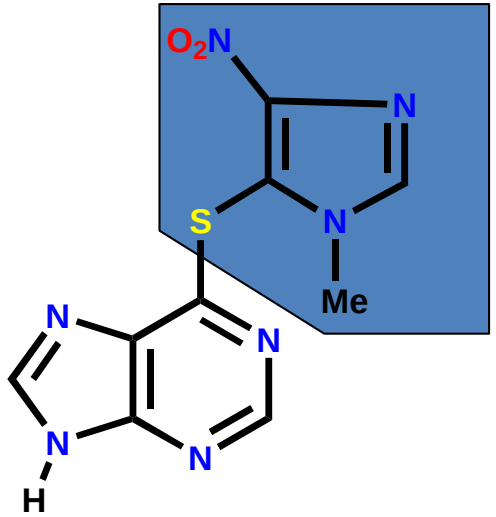
1.5.2.1 Mask polar groups

- **Reduces rate of excretion**

Example:

Azathioprine for 6-mercaptopurine





6-Mercaptopurine

(suppresses immune response)

- **Short lifetime - eliminated too quickly**

Azathioprine

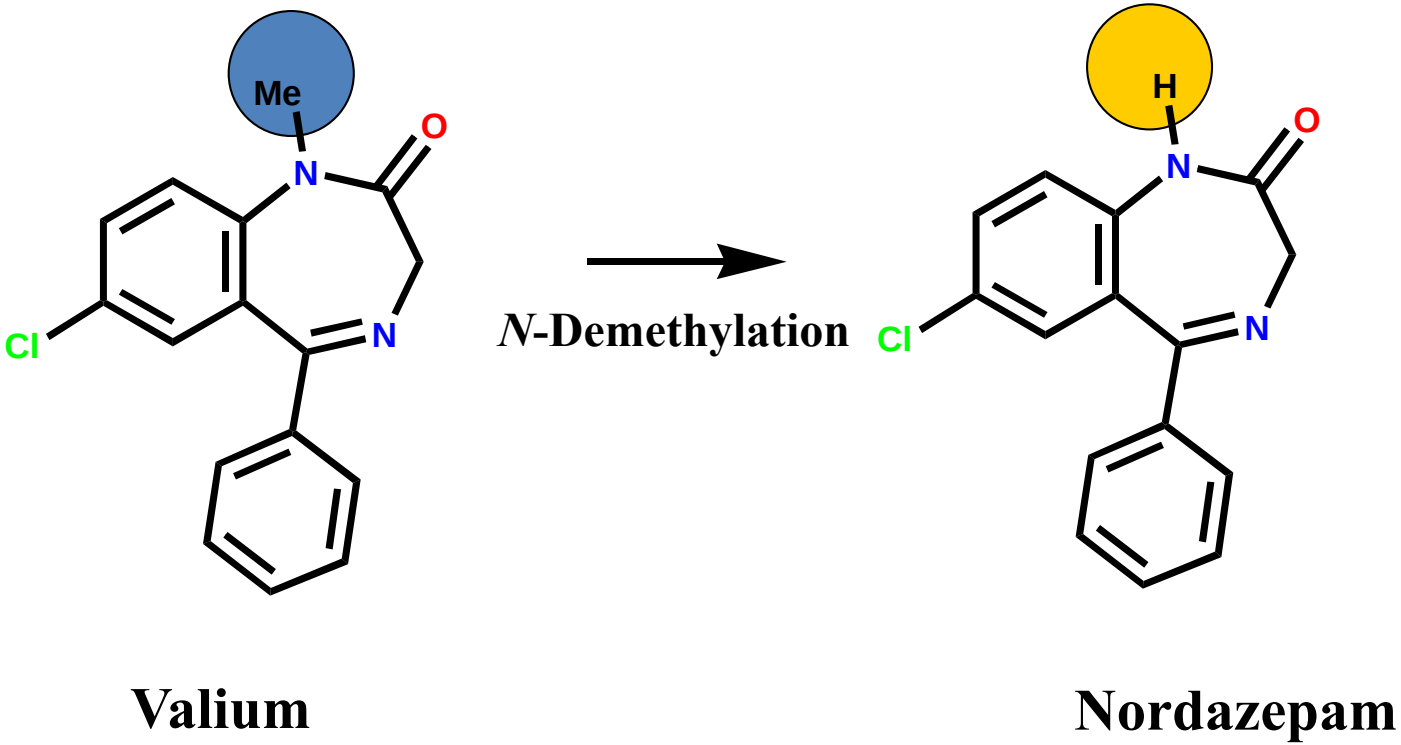
- **Slow conversion to 6-mercaptopurine**
- **Longer lifetime**

1.5.2 Prodrugs to prolong activity

Example:

Valium for nordazepam

Sustained Action



Valium **Nordazepam**

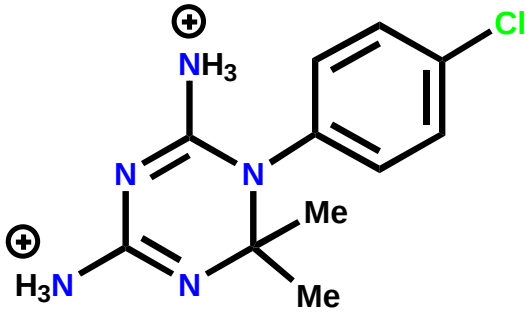
1.5.2 Prodrugs to prolong activity

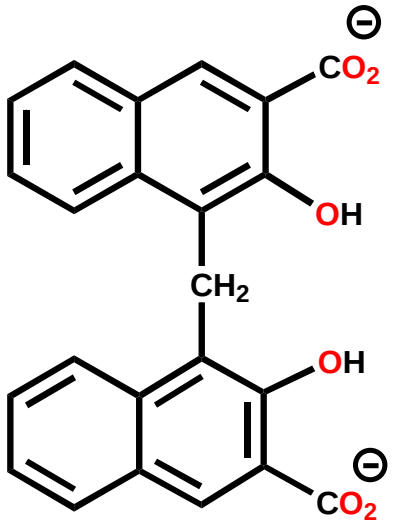
1.5.2.2 Add hydrophobic groups

- Drug concentrated in fat tissue
- Slow removal of hydrophobic group
- Slow release into blood supply

Example:

Cycloguanil pamoate (antimalarial)





Cycloguanil **Pamoate**

Lipophilic

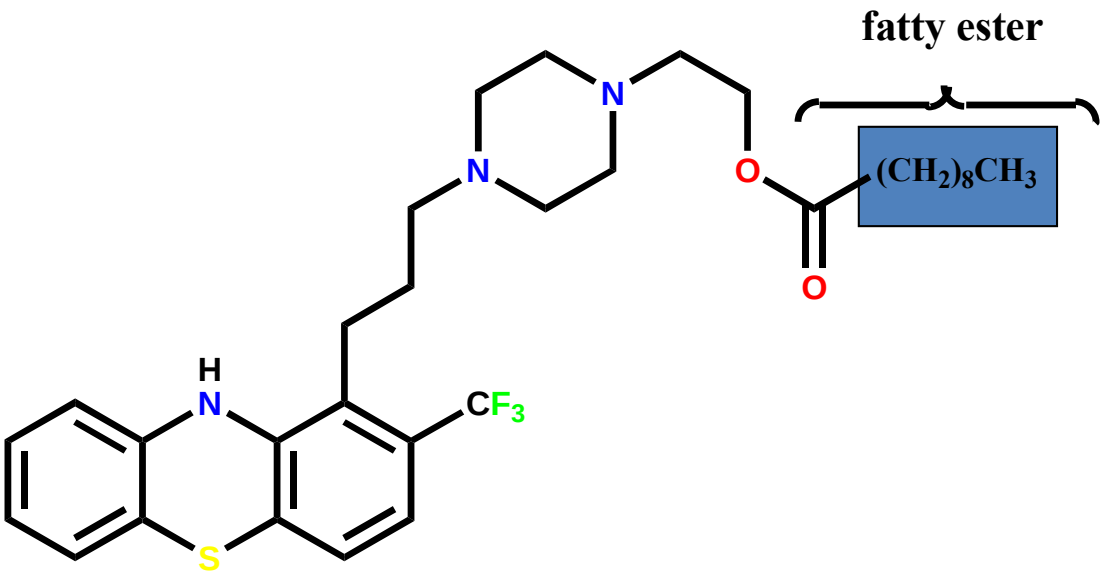
1.5.2 Prodrugs to prolong activity

1.5.2.2 Add hydrophobic groups

Example:

Hydrophobic esters of fluphenazine (antipsychotic)

Fluphenazine is a medication that treats schizophrenia.



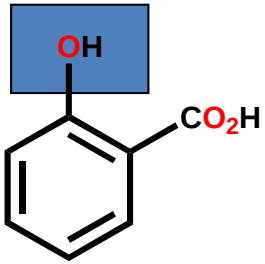
- **Given by intramuscular injection**
- **Concentrated in fatty tissue**
- **Slowly released into the blood supply**
- **Rapidly hydrolysed in the blood supply**

1.5.3 Prodrugs to mask toxicity and side effects

- **Mask groups responsible for toxicity/side effects**
- **Used when groups are important for activity**

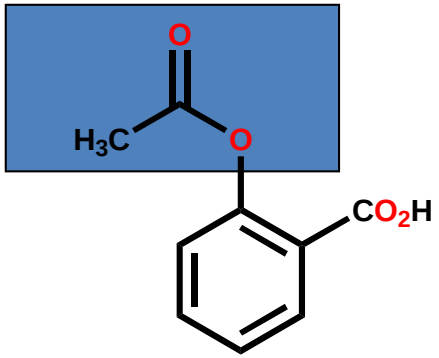
Example:

Aspirin for salicylic acid



Salicylic acid

- **Analgesic, but causes stomach ulcers due to phenol group**



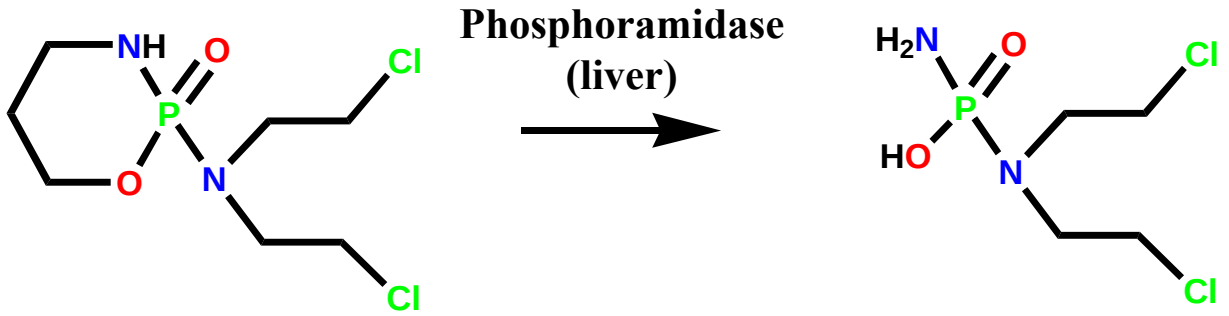
Aspirin

- **Phenol masked by ester**
- **Hydrolysed in body**

1.5.3 Prodrugs to mask toxicity and side effects

Example:

Cyclophosphoramide for phosphoramide mustard (anticancer agent)



Cyclophosphoramide

- **Non toxic**
- **Orally active**

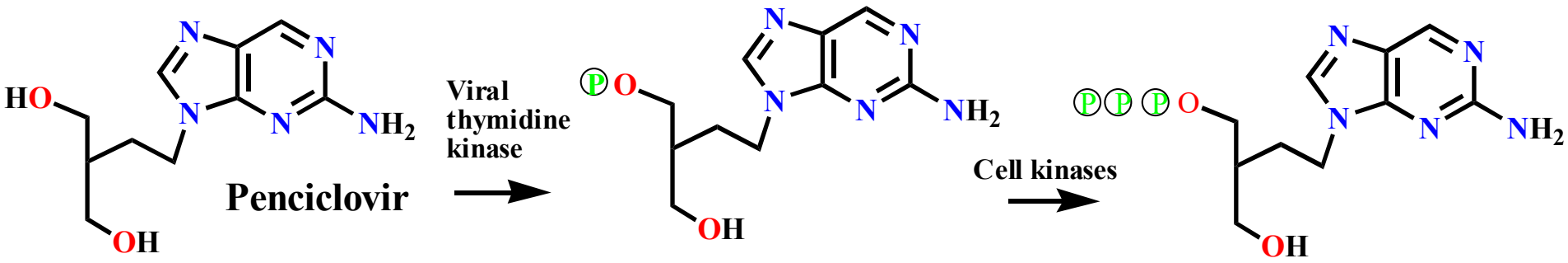
Phosphoramide mustard

- **Alkylating agent**

1.5.3 Prodrugs to mask toxicity and side effects

Example:

Antiviral drugs



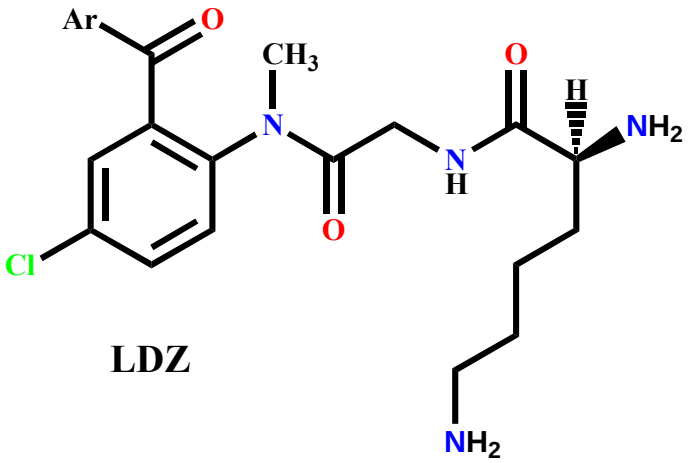
Phophorated penciclovir

- First phosphorylation requires viral thymidine kinase
- Only activated in virally infected cells
- Non-toxic to uninfected cells

1.5.3 Prodrugs to mask toxicity and side effects

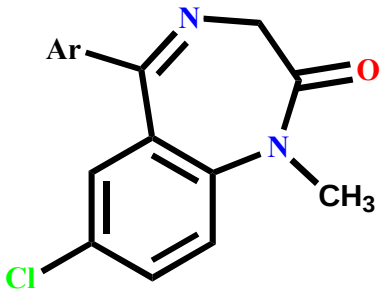
Example:

LDZ (Avizafone) for diazepam



LDZ

a) Aminopeptidase
b) Cyclisation



Diazepam

LDZ

- **Avoids drowsy side effects of diazepam**

1.5.4 Prodrugs to lower water solubility

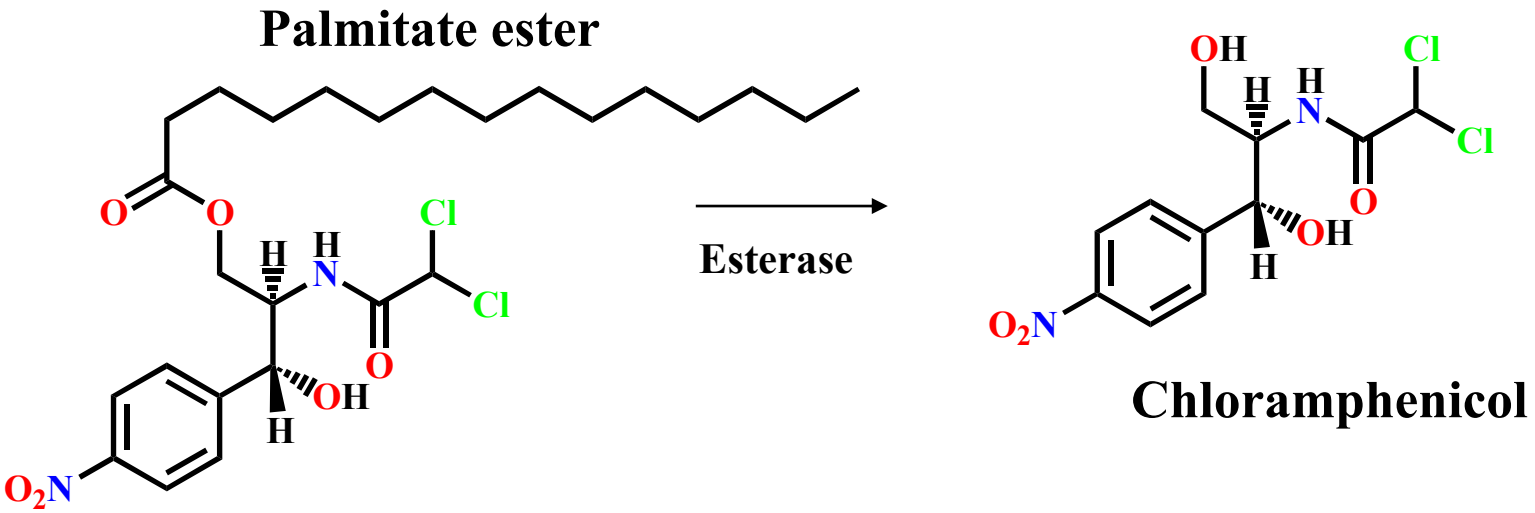
- The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors, which can be solved by lowering the solubility of drug or prodrug in saliva.
- Chloramphenicol, an extremely bitter drug has been derivatized to chloramphenicol palmitate, a sparingly soluble ester.
- It possesses low aqueous solubility which makes it tasteless and later undergoes in vivo hydrolysis to active chloramphenicol by the action of pancreative lipase

1.5.4 Prodrugs to lower water solubility

- Used to reduce solubility of foul tasting orally active drugs
- Less soluble on tongue
- Less revolting taste

Example:

Palmitate ester of chloramphenicol (antibiotic)

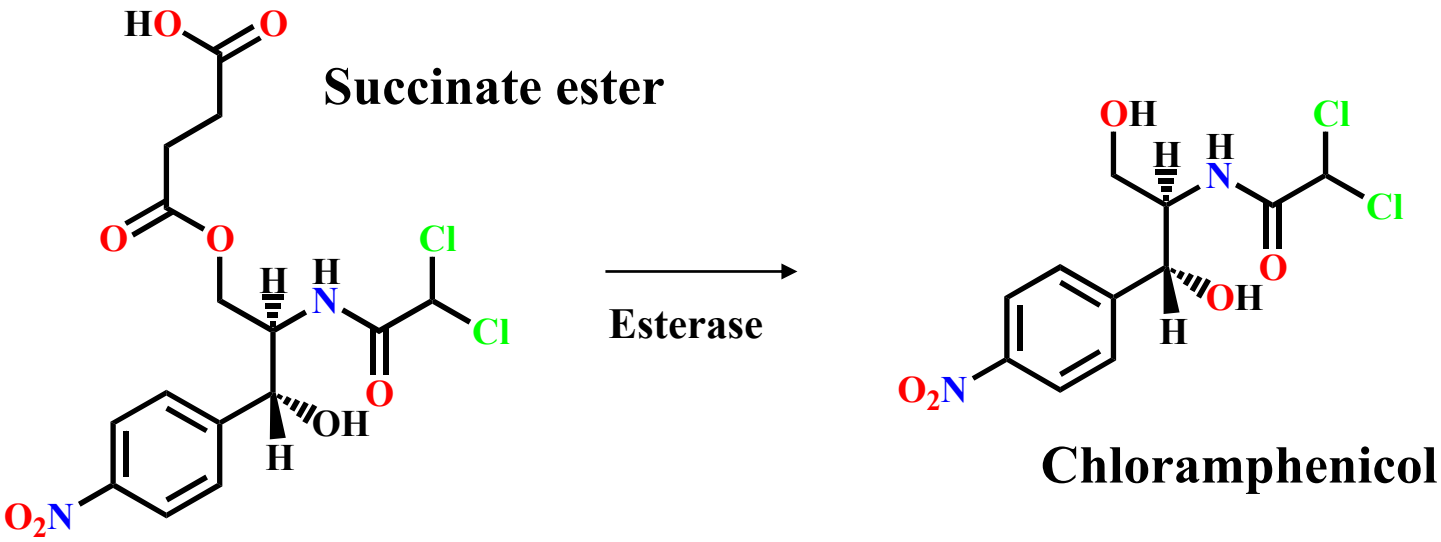


1.5.5 Prodrugs to increase water solubility

- Often used for i.v. drugs
- Allows higher concentration and smaller dose volume
- May decrease pain at site of injection

Example:

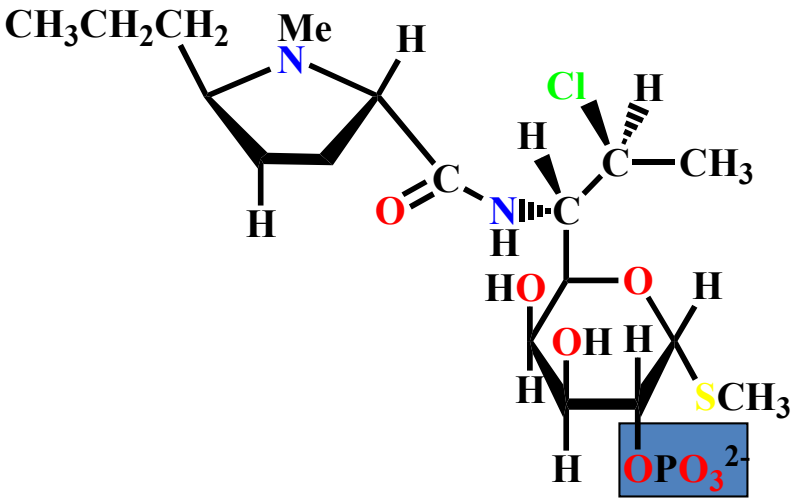
Succinate ester of chloramphenicol (antibiotic)



1.5.5 Prodrugs to increase water solubility

Example:

Phosphate ester of clindamycin (antibacterial)

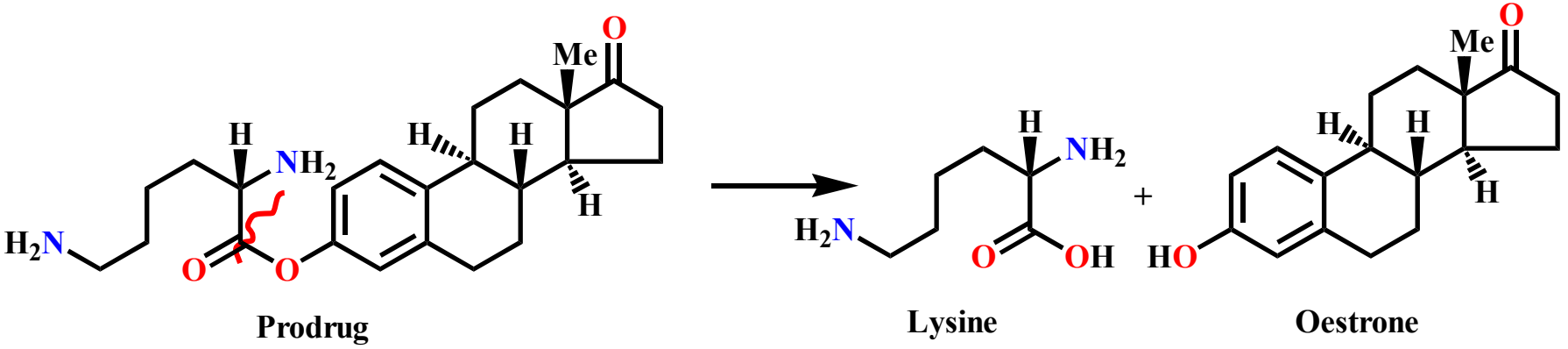


- **Less painful on injection**

1.5.5 Prodrugs to increase water solubility

Example:

Lysine ester of oestrone

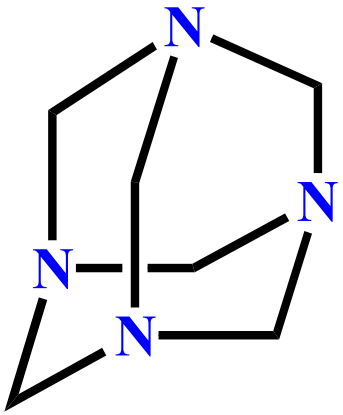


- Lysine ester of oestrone is **better absorbed** orally than oestrone
- Increased water solubility prevents formation of fat globules in gut
- Better interaction with the gut wall
- Hydrolysis in blood releases oestrone and a non toxic amino acid

1.5.6 Prodrugs used to target drugs

Example:

Hexamine



- **Stable and inactive at pH>5**
- **Stable at blood pH**
- **Used for urinary infections where pH<5**
- **Degrades at pH<5 to form formaldehyde (antibacterial agent)**

1.5.7 Prodrugs to increase chemical stability

Chemical stability is necessary parameter for every therapeutic agent to elicit its pharmacological activity for a longer duration.

A shelf life of at least 2 years is desirable except for vaccines, cytotoxic agents and other life saving drugs.

Although chemical unstability can be solved to a greater extent by appropriate formulations, its failure necessitates the use of prodrug approach.

The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable

1.5.7 Prodrugs to increase chemical stability

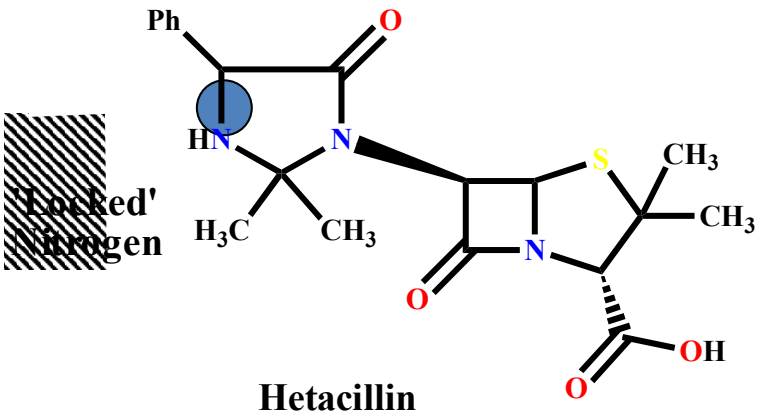
This approach was successfully used to inhibit the auto aminolysis, which occur due to capability of NH2 group of side chain to attach β–lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin.

By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin „ties up" the amine group and thus inhibits auto aminolysis.

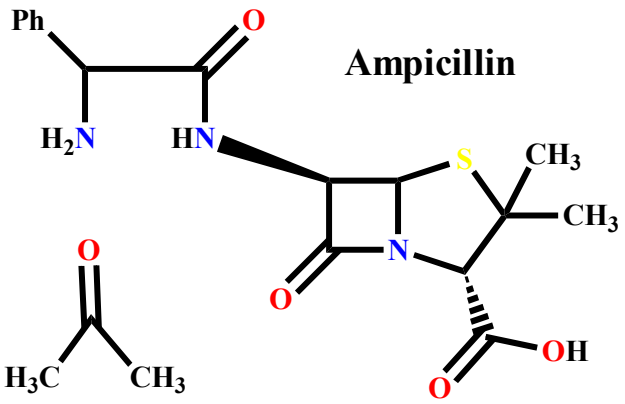
1.5.7 Prodrugs to increase chemical stability

Example:

Hetacillin for ampicillin



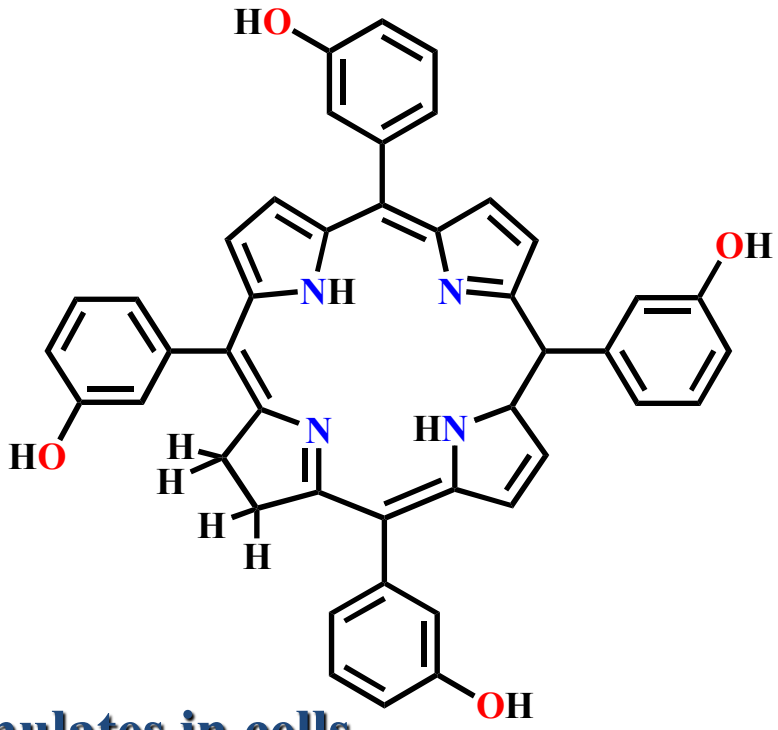
Hetacillin



- **Ampicillin is chemically unstable in solution due to the α-NH_2 group attacking the β-lactamse ring**
- **'N' in heteacillin is locked up within a heterocyclic ring**

1.5.8 Prodrugs activated by external influences -sleeping agents

Example: **Photodynamic therapy - Foscan**



- **Inactive and accumulates in cells**
- **Activated by light - method of targeting tumour cells**
- **Foscan is excited and reacts with oxygen to produce toxic singlet oxygen**
- **Cell destruction is caused by singlet oxygen**

1.6 Drug alliances - synergism

Definition:

Drugs which have a benefical effect on the activity or pharmacokinetic properties of another drug

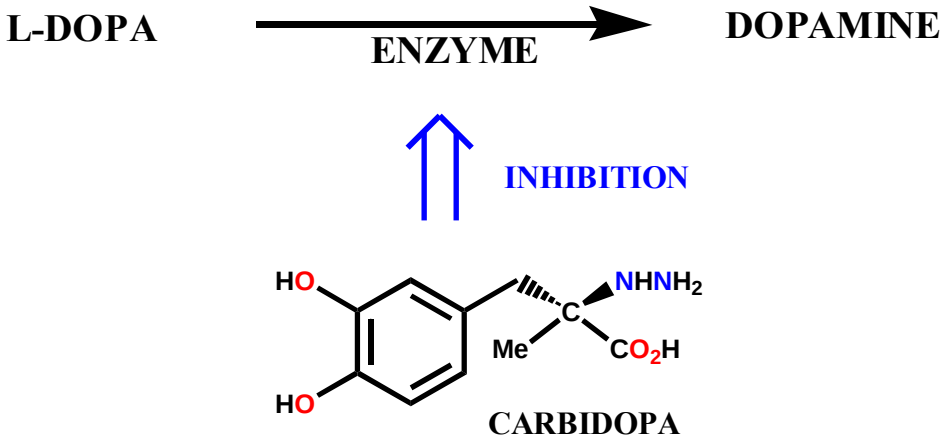
1.6.1 Sentry Drugs

Definition:

A drug that is added to 'protect' another drug

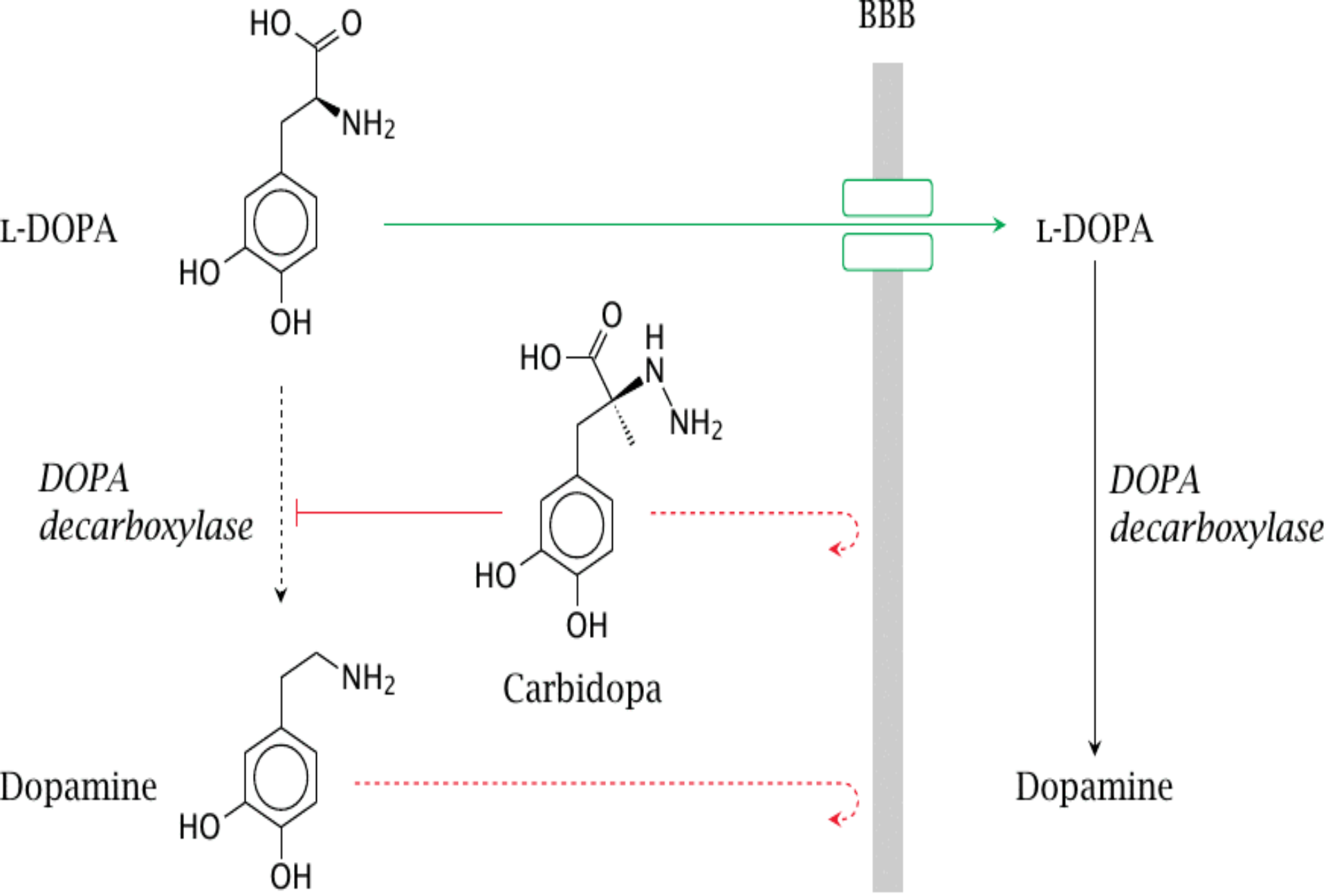
Example:

Carbidopa



- **Carbidopa protects L-dopa**
- **It inhibits the decarboxylase enzyme in the peripheral blood supply**
- **It is polar and does not cross the blood brain barrier**
- **It has no effect on the decarboxylation of L-Dopa in the CNS**
- **Smaller doses of L-dopa can be administered - less side effects**

Other examples: **Clavulanic acid**



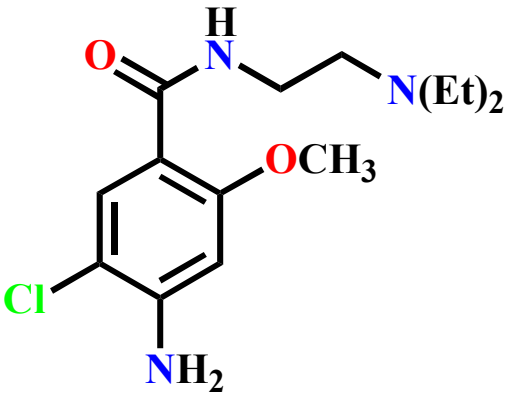
1.6.2 Localizing drugs to a target area

Example: Adrenaline and procaine (local anaesthetic)

- Adrenaline constricts blood vessels at the injection area
- Procaine is localised at the injection area

1.6.3 Increasing absorption

Example: Metoclopramide



- Administered with analgesics in the treatment of migraine
- Increases gastric motility and causes faster absorption of analgesics
- Leads to faster pain relief

Thank You!