Lipids are a class of biological molecules defined by low solubility in water and high solubility in nonpolar solvents.

As molecules that are largely hydrocarbon in nature, lipids represent highly reduced forms of carbon and, upon oxidation in metabolism, yield large amounts of energy. Lipids are thus the molecules of choice for metabolic energy storage.

Classification

By structure:

1. Simple: fats, oils, waxes, steroids.
2. Complex: phospholipids, sphingolipids, glycolipids.
3. The derivatives: hormones, fat-solubility vitamins
4. On the basis of whether they undergo hydrolysis reactions in alkaline solution:
   I. Saponifiable **lipids** can be hydrolyzed under alkaline conditions to yield salts of fatty acids.
   II. Nonsaponifiable **lipids** do not undergo hydrolysis reactions in alkaline solution.

Biological functions

- The most important role of lipids is as a fuel. Thus fat is the most concentrated form in which potential energy can be stored.
- Since fat is a bad conductor of heat, it provides excellent insulation.
- Fat may also provide padding to protect the internal organs.
- Some compounds derived from lipids are important building blocks of biologically active materials.
- Lipoproteins are constituents of cell walls.
- One more important function of dietary lipids is that of supplying the so-called essential fatty acids

Fatty acids

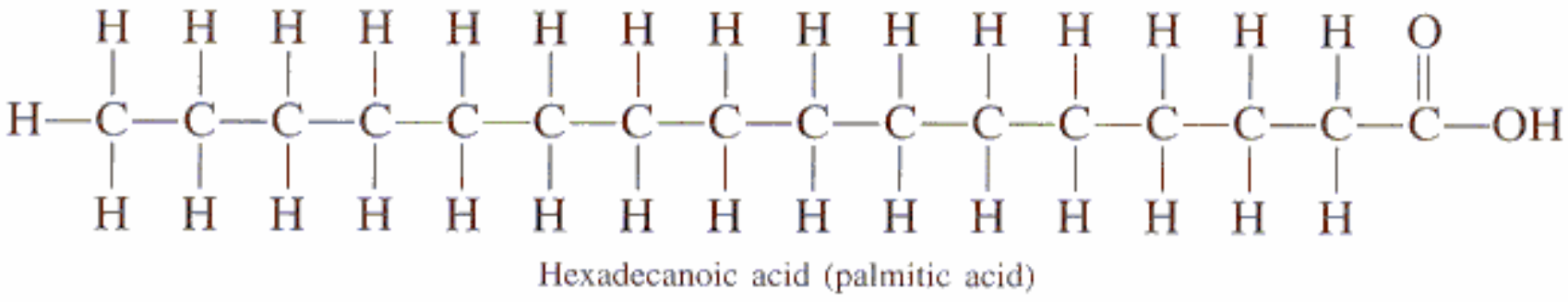
– are saponifiable lipid building blocks.

Fatty acids are naturally occurring carboxylic acids with an unbranched carbon chain and an even number of carbon atoms. The pathway by which fatty acids are biosynthesized they almost always contain an even number of carbon atoms. Long-chain fatty acids (12 to 26 carbon atoms) are found in meats and fish; medium-chain fatty acids (6 to 10 carbon atoms) and short-chain fatty acids (fewer than 6 carbon atoms) occur primarily in dairy products.

There are saturated and unsaturated Fatty acids.

Saturated fatty acid

- Fatty acid chains that contain only carbon-carbon single bonds are referred to as **saturated.**
- Palmitic acid:

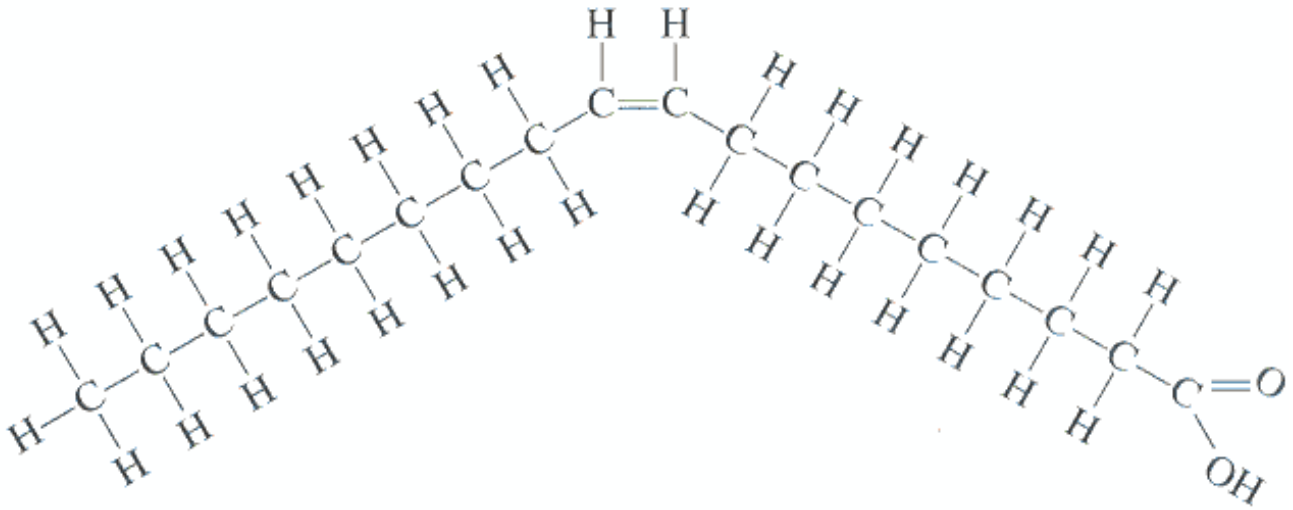


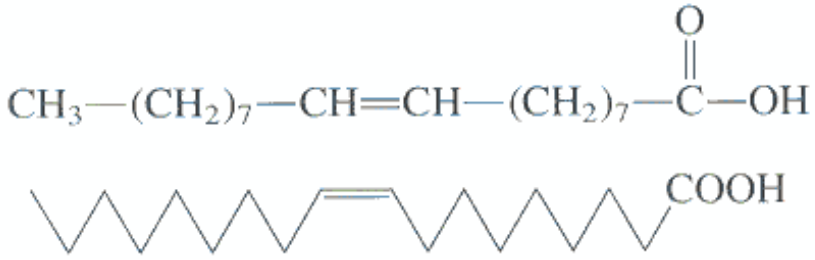
Hexadecanoic acid (palmitic acid)

Unsaturated fatty acid

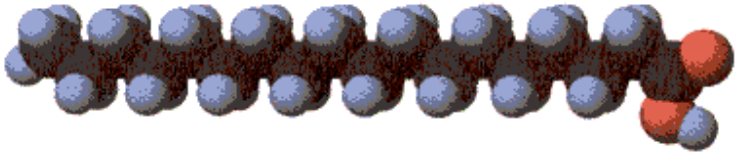
- Those molecules that contain one or more double bonds are said to be **unsaturated.**
- There are mono- and polyunsaturated fatty acids.

Oleic acid:

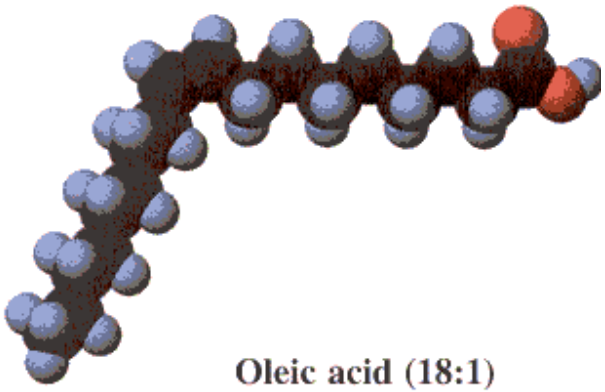




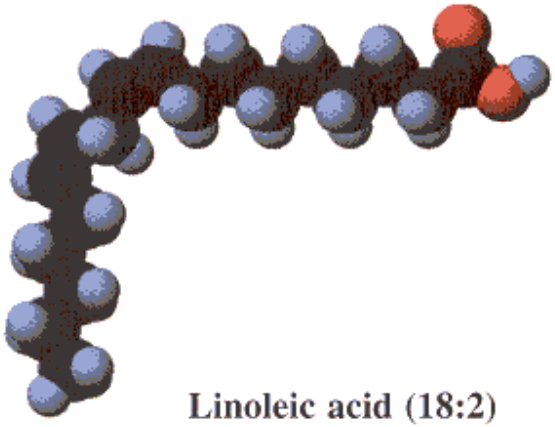
Structure of fatty acids



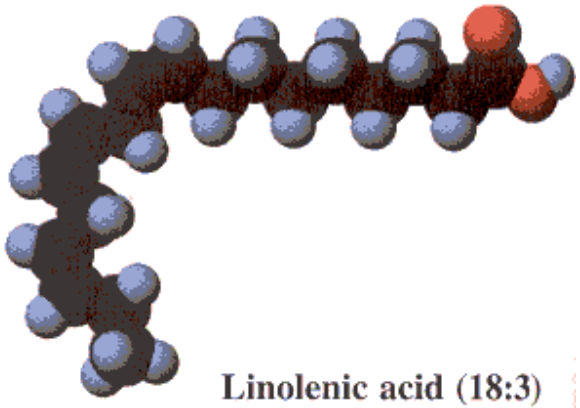
Stearic acid (18:0)



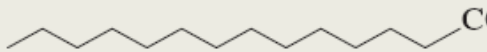
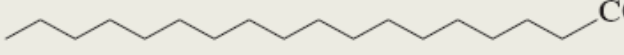
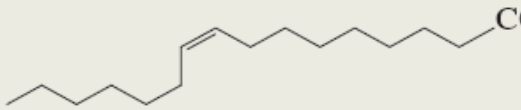
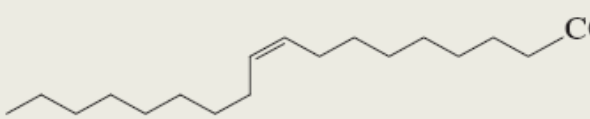
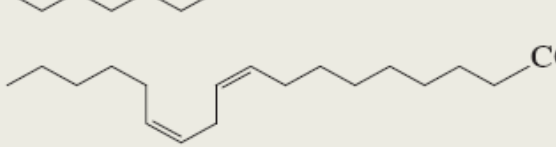
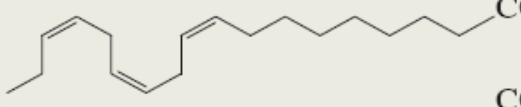
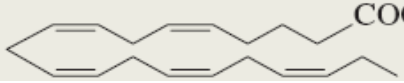
Oleic acid (18:1)

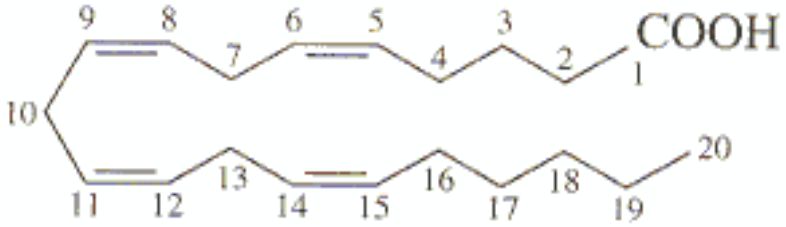


Linoleic acid (18:2)

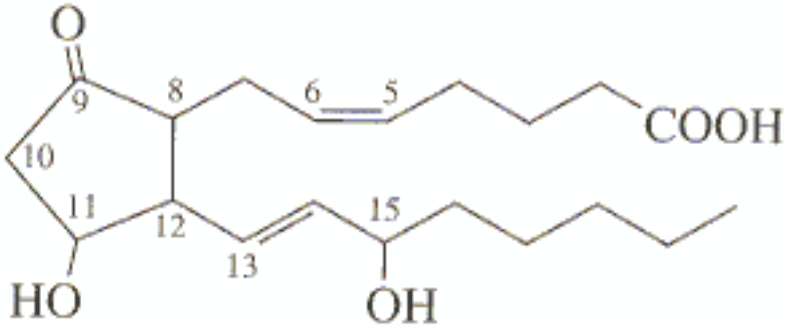


Linolenic acid (18:3)

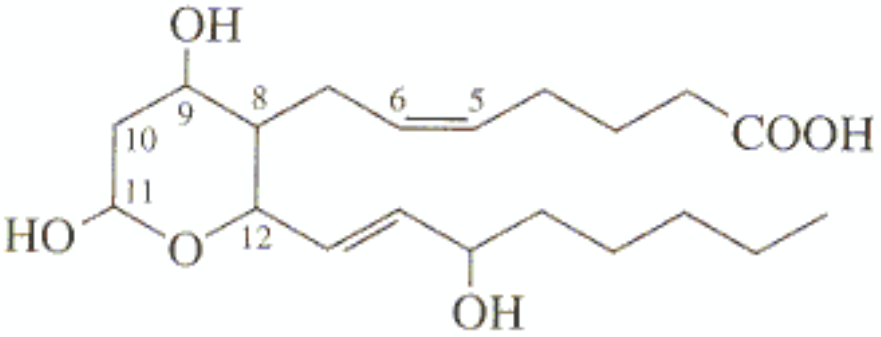
Number of carbons	Common name	Systematic name	Structure	Melting point °C
Saturated				
12	lauric acid	dodecanoic acid		44
14	myristic acid	tetradecanoic acid		58
16	palmitic acid	hexadecanoic acid		63
18	stearic acid	octadecanoic acid		69
20	arachidic acid	eicosanoic acid		77
Unsaturated				
16	palmitoleic acid	(9*Z*)-hexadecenoic acid		0
18	oleic acid	(9*Z*)-octadecenoic acid		13
18	linoleic acid	(9*Z*,12*Z*)-octadecadienoic acid		−5
18	linolenic acid	(9*Z*,12*Z*,15*Z*)-octadecatrienoic acid		−11
20	arachidonic acid	(5*Z*,8*Z*,11*Z*,14*Z*)-eicosatetraenoic acid		−50
20	EPA	(5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-eicosapentaenoic acid		−50



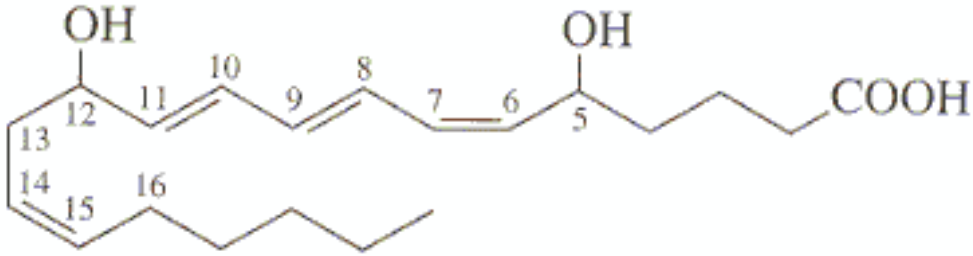
(a) Arachidonic acid



(b) Prostaglandin E_2

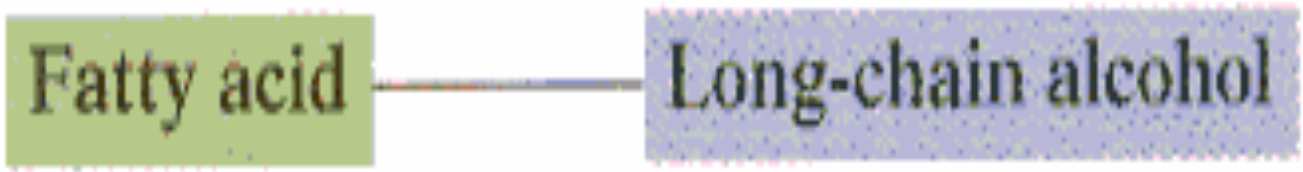


(c) Thromboxane B_2

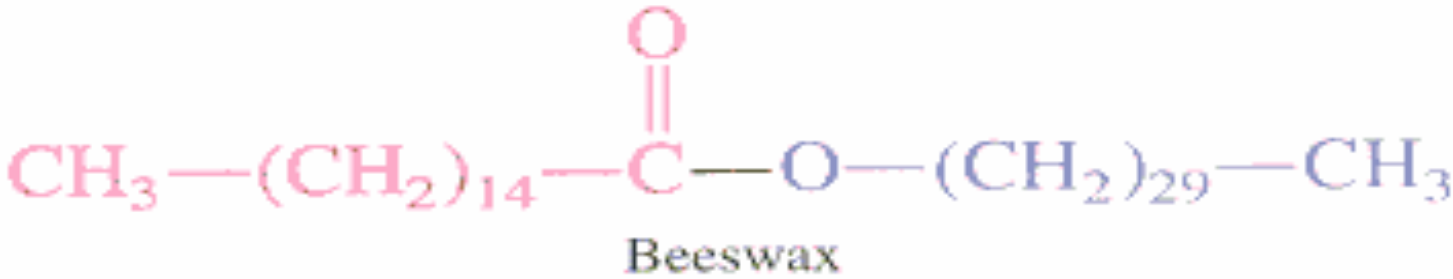


(d) Leukotriene B_4

A wax is a monoester formed from the reaction of a long-chain monohydroxy alcohol with a fatty acid molecule.

The block diagram: 

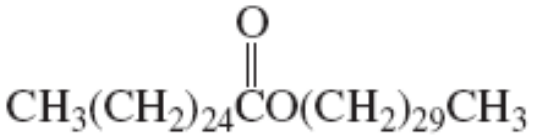
Example



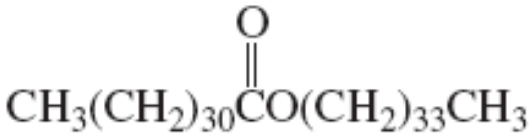
Beeswax

Biological role: They serve as protective coatings on leaves, stems, and fruit of plants and the skin and fur of animals.

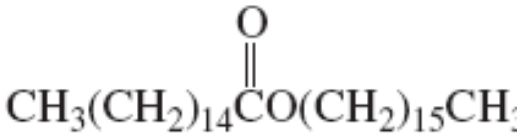
Layers of honeycomb in a beehive



a major component of beeswax
structural material of beehives



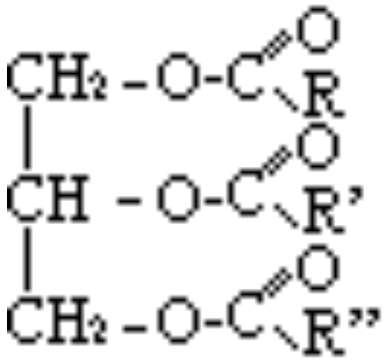
a major component of carnauba wax
coating on the leaves of a Brazilian palm



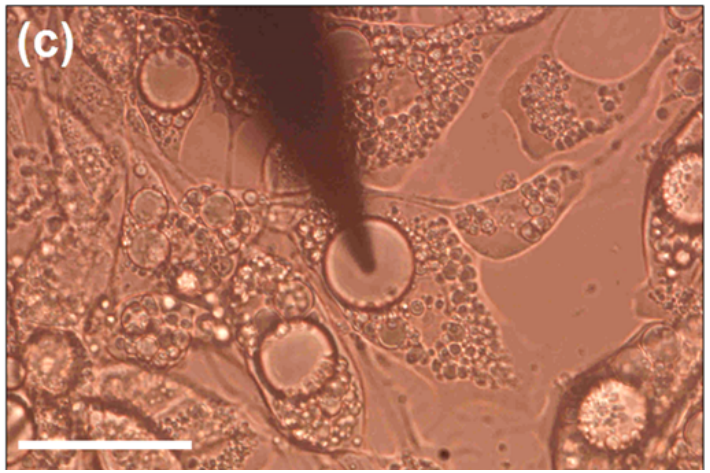
a major component of spermaceti wax
from the heads of sperm whales

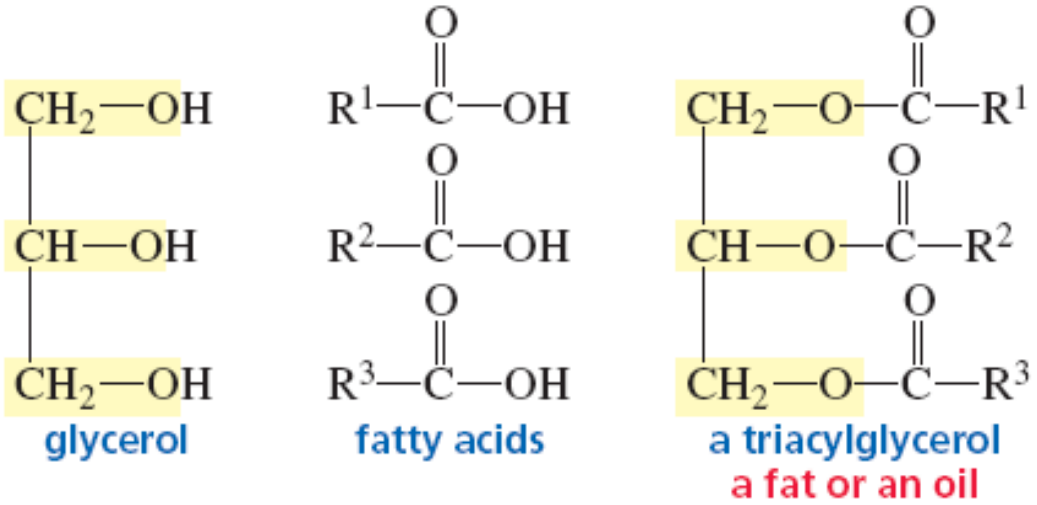
Oils and fats

- Fatty acid esters of the trihydric alcohol – glycerol are called acylglycerol or glycerides; “neutral fat”

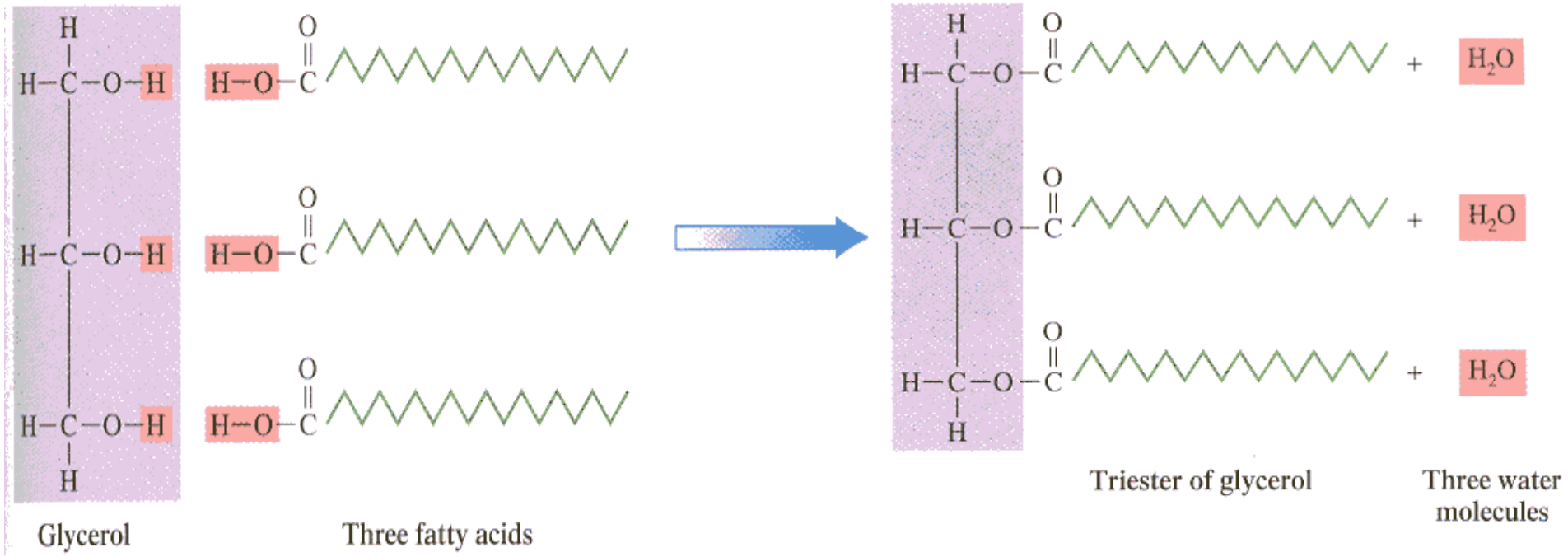


- Reaction formation of triacylglycerol's





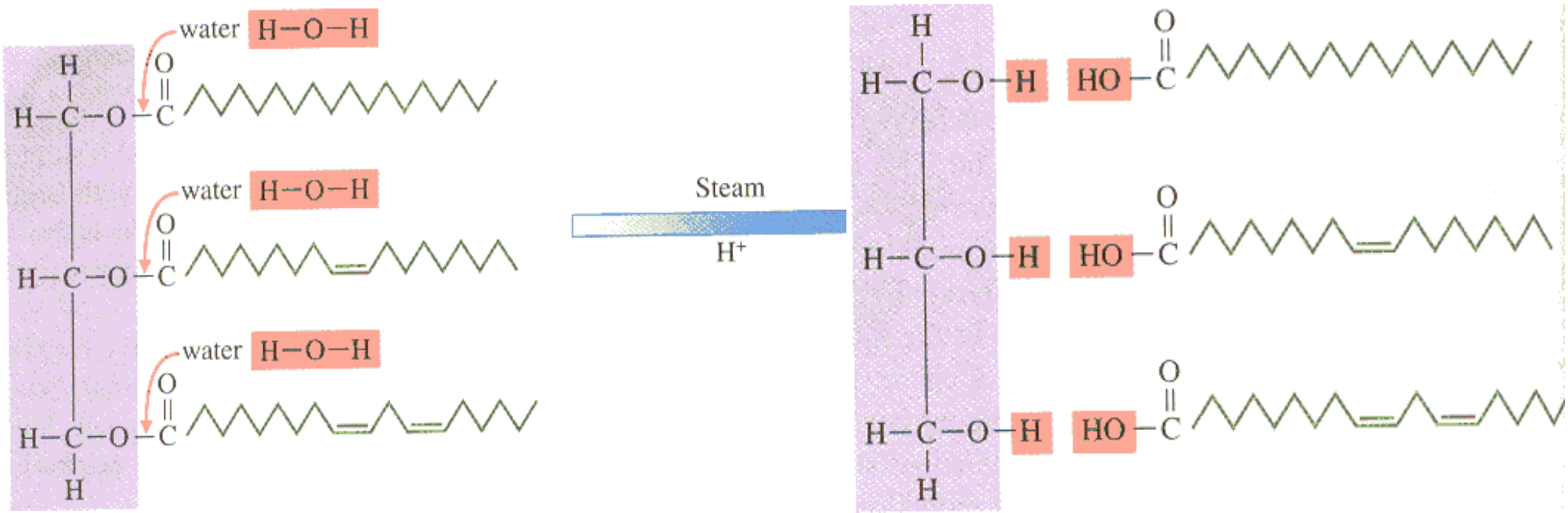
Reaction formation of triacylglycerol



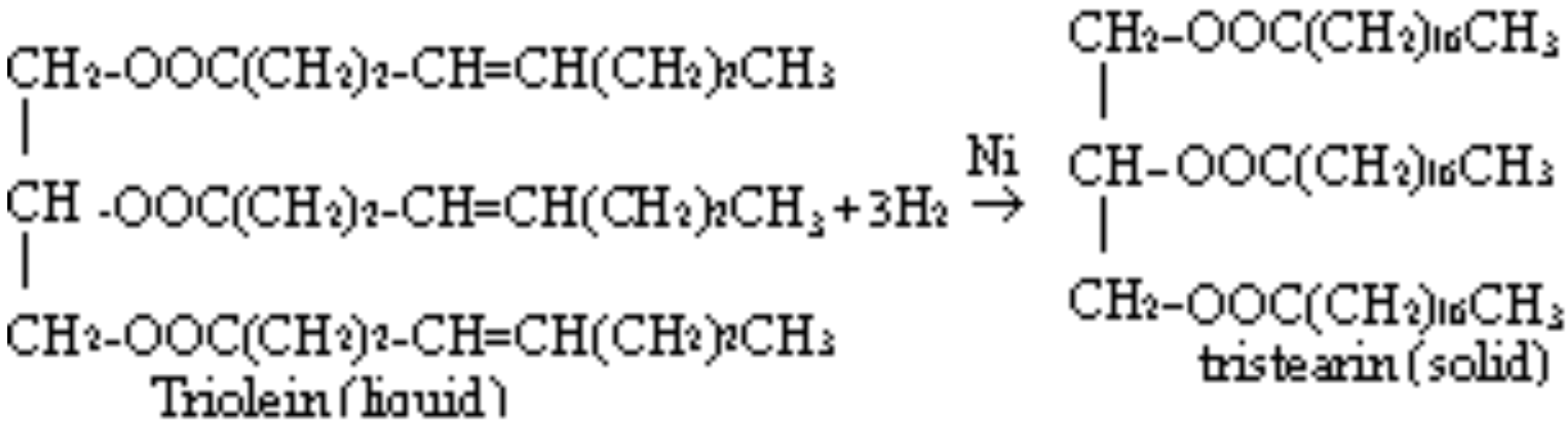
- **Acid number**. It is the number of milligrams of potassium hydroxide required to neutralize the free fatty acids in 1 g of the oil or fat.
- **Saponification number.** It is number of milligrams of potassium hydroxide required to completely saponify l00 g of the oil or fat.
- **Iodine number.** It is the number of grams of iodine that combine with 100 g of oil or fat. It is a measure of the degree of unsaturation of a fat or oil; a high iodine number indicates a high degree of unsaturation of the fatty acids of the fat.
- **Reichert -Meissl number**. (R. M. number). It is the number of milliliters of potassium hydroxide required to neutralize the distillate (obtained by saponification, acidification and steam distillation of the fat) of 5 g of the fat.

Chemical properties

- **Hydrolysis.** There is acidic, basic and enzyme's hydrolysis.
- Acidic and enzyme:



Hydrogenation.



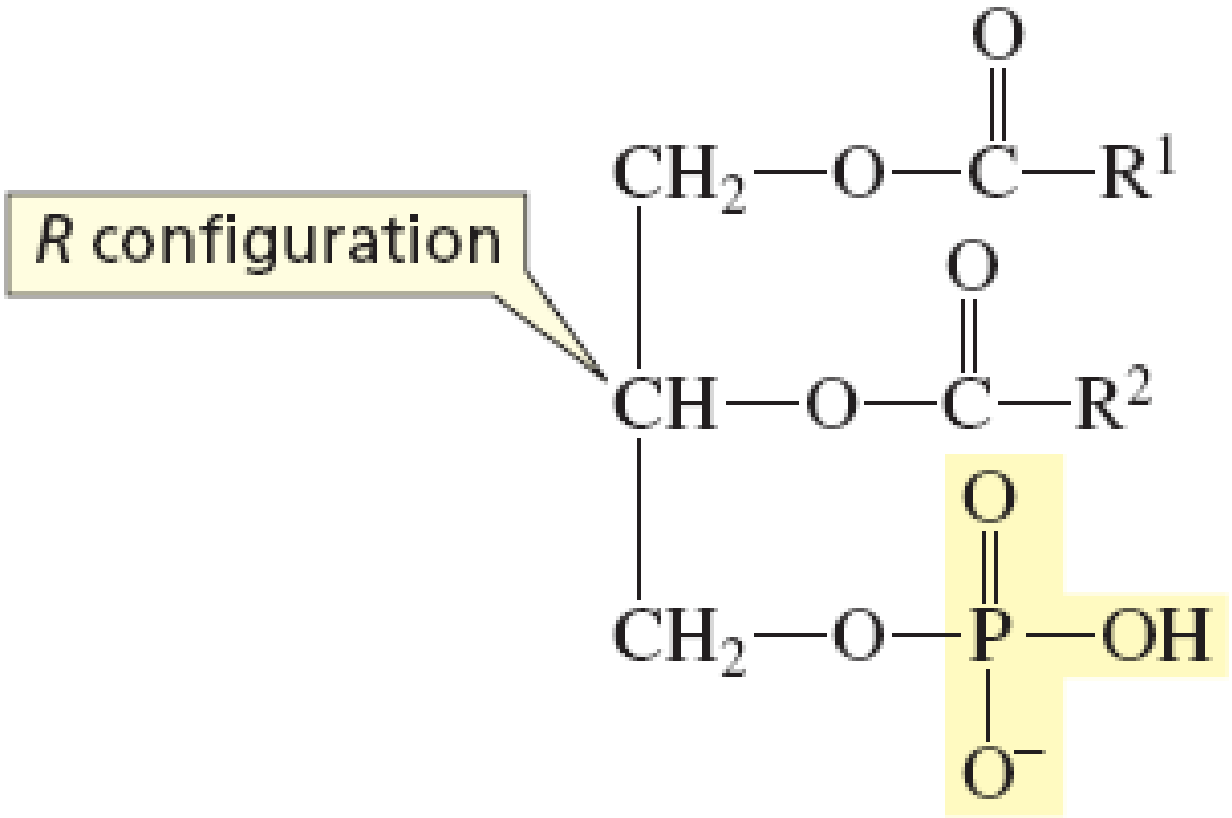
- **Phosphoacylglycerols** are triesters of glycerol in which two -OH groups are esterified with fatty acids and one the third is esterified with phosphofic acid, which in turn is esterified to an alcohol.

a)Phosphatidylethanolamines

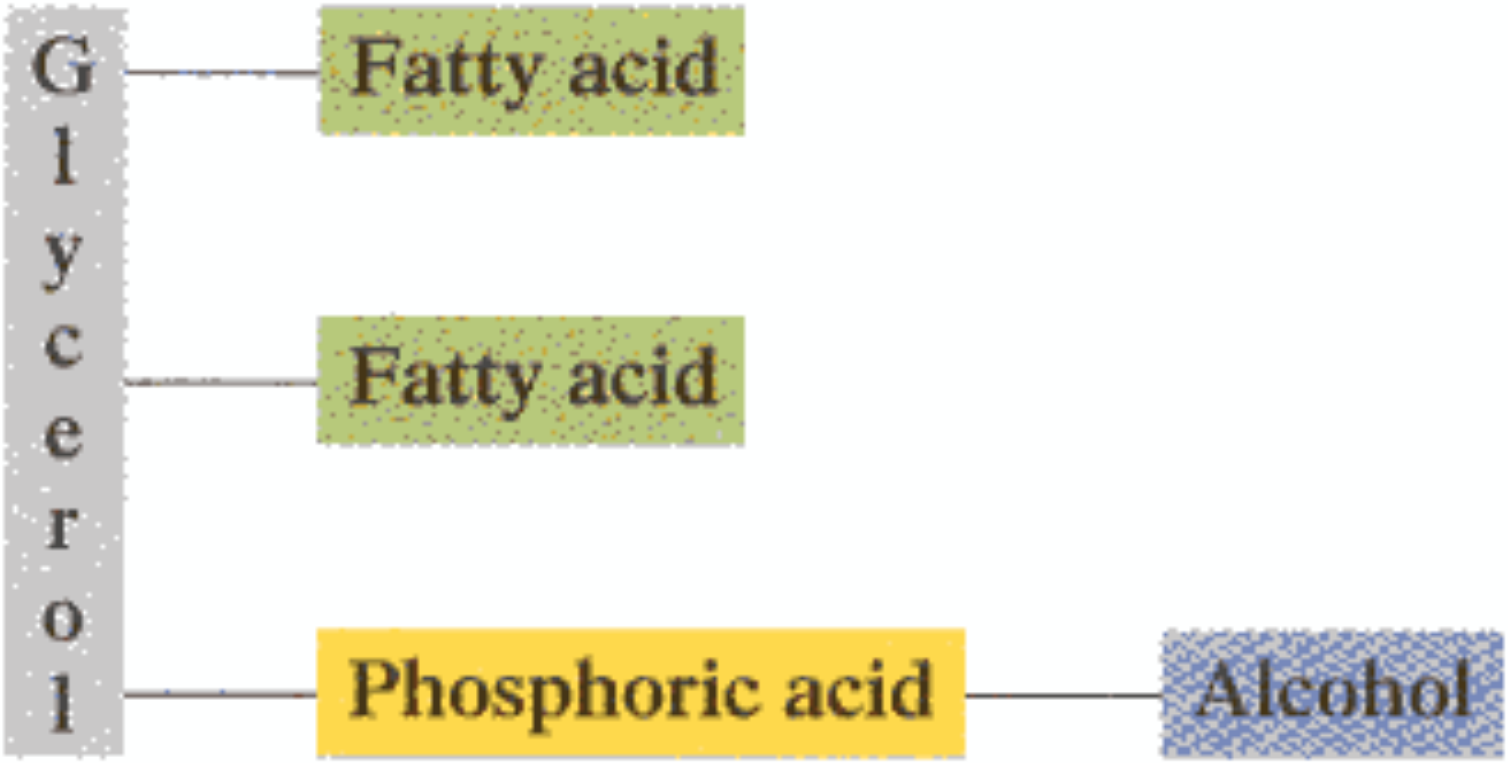
b)Phosphatidylcholines

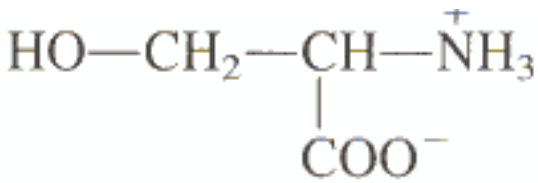
c)Phosphatidylserines

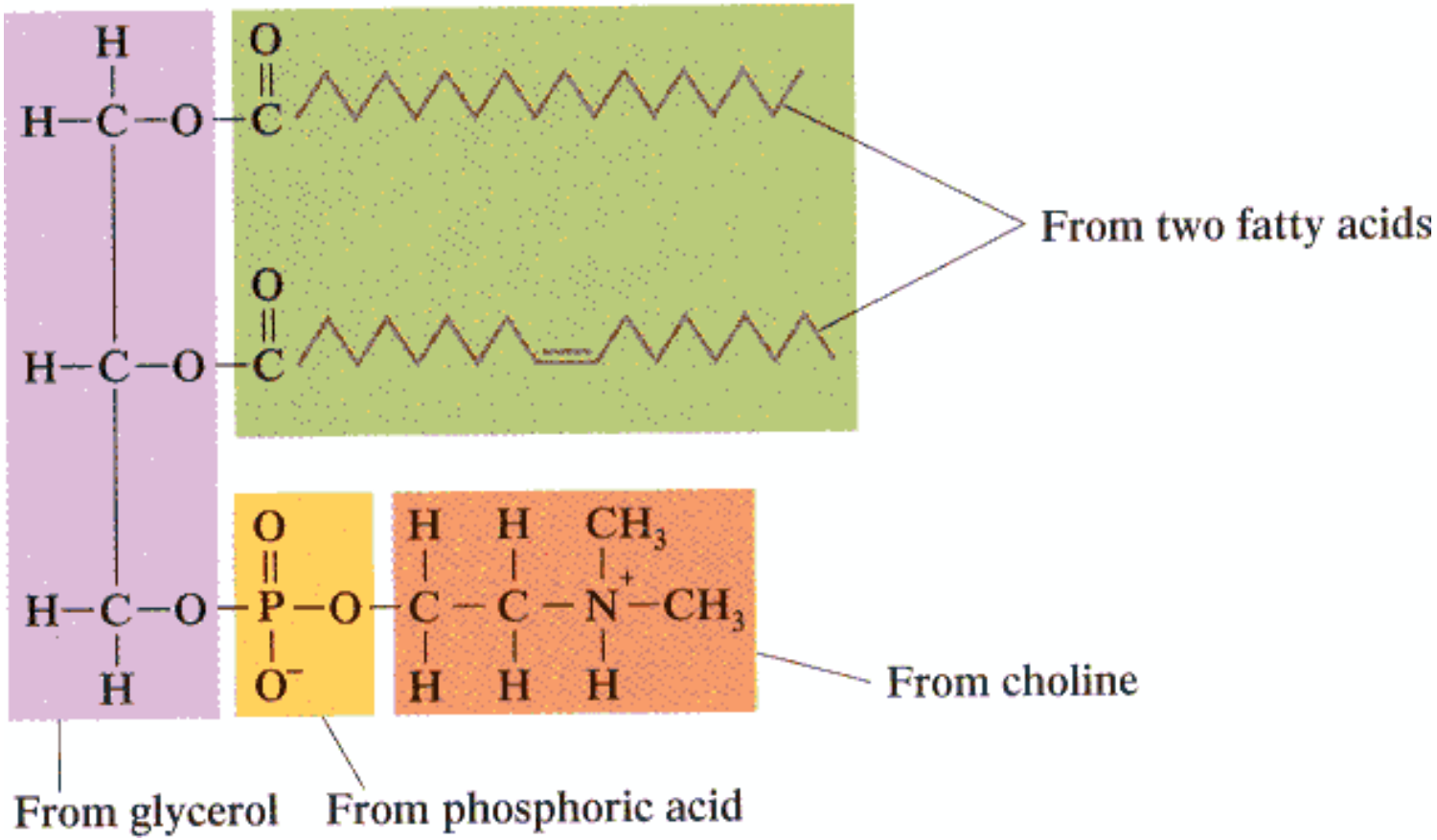
- **Phosphosphingolipid** are esters of dialcohol sphingosine in which a fatty acid in amide linkage on the amino group and the phosphorylcholine group attached by way of the terminal alcohol group.

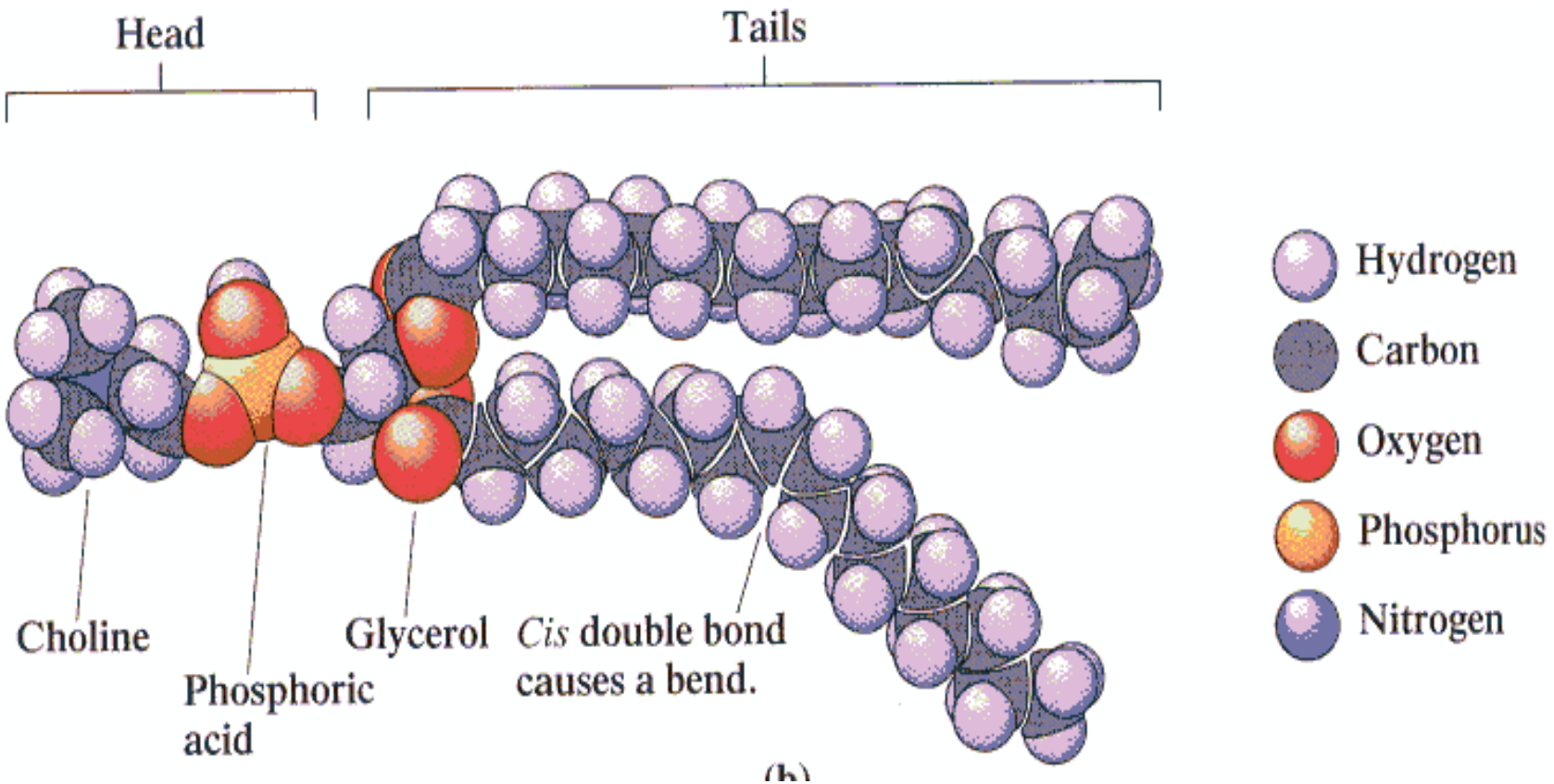


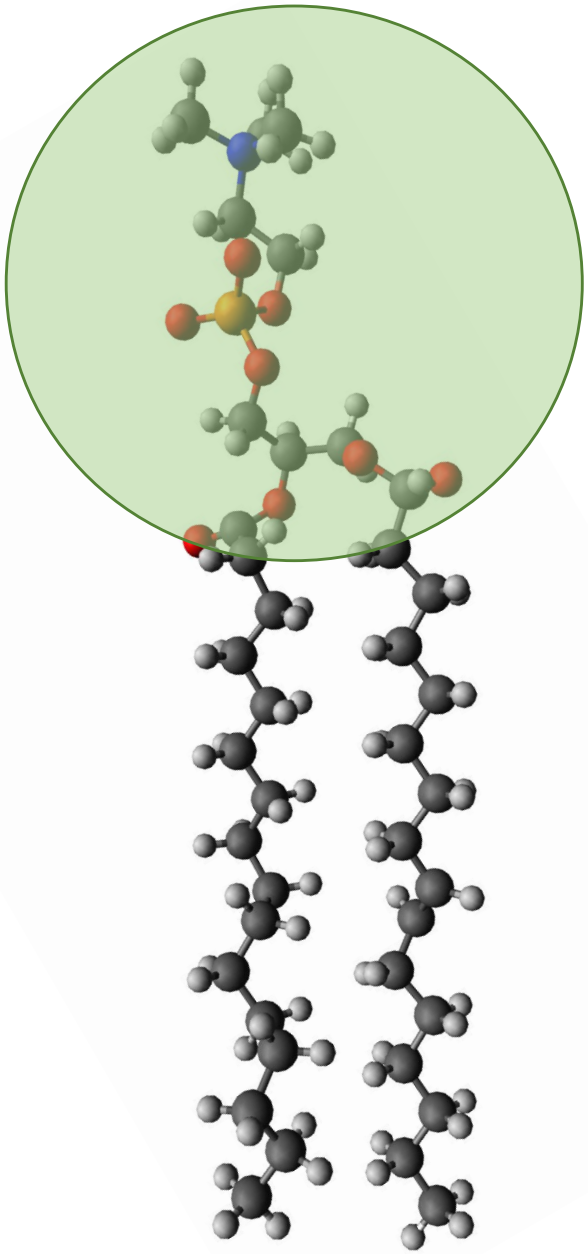
a phosphatidic acid

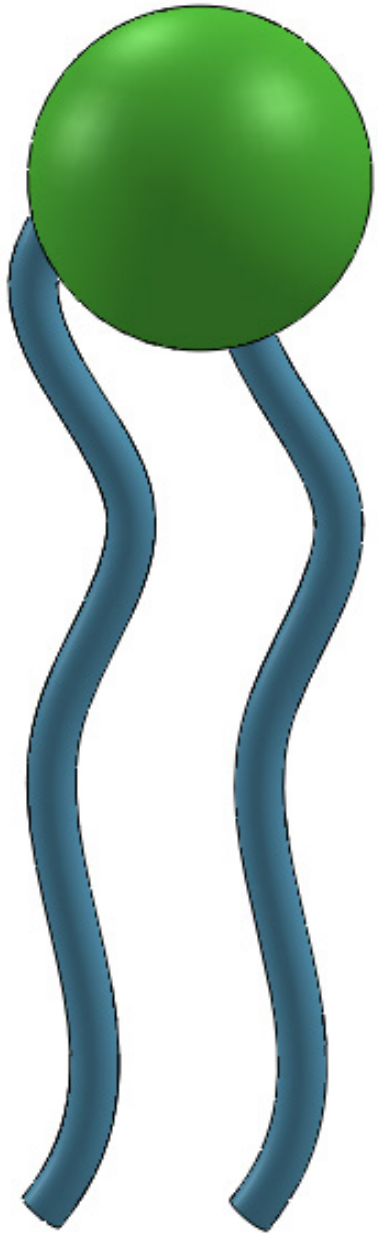

Glycerol
Fatty acid
Fatty acid
Phosphoric acid
Alcohol

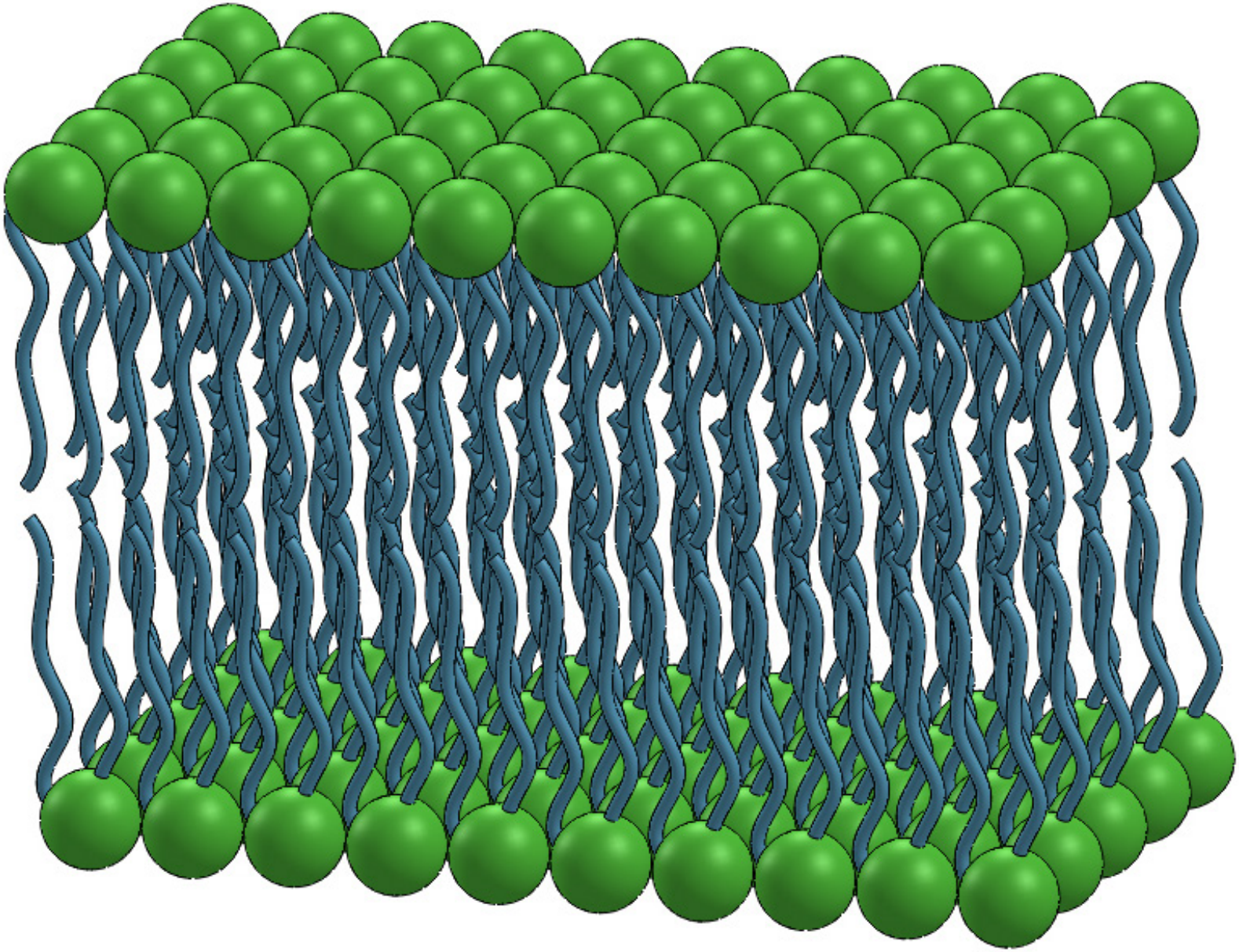


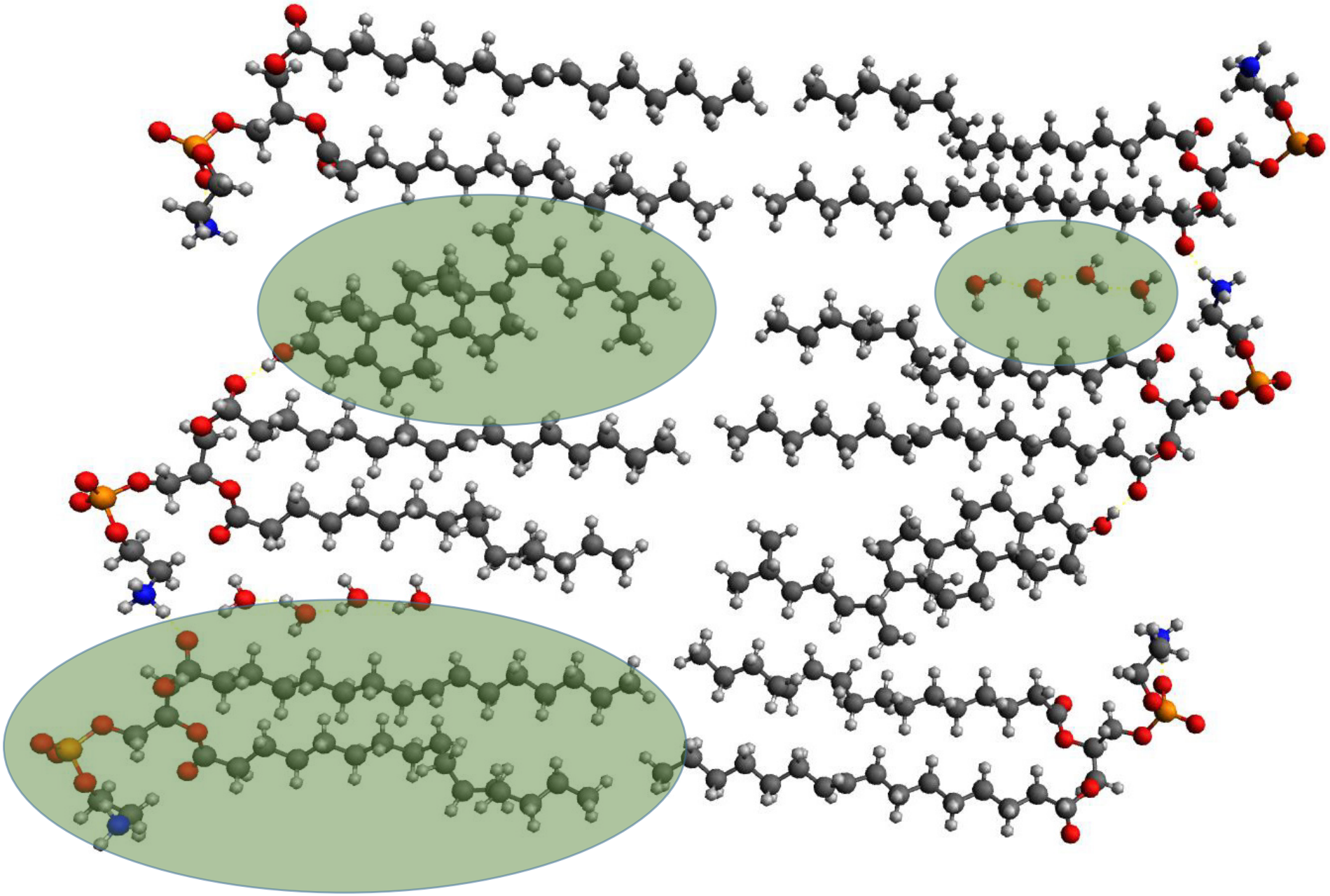

From two fatty acids
From choline
From glycerol
From phosphoric acid

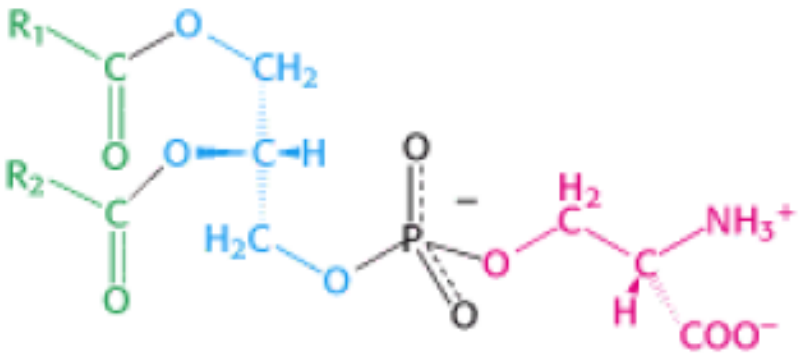

Head
Tails
Choline
Phosphoric acid
Glycerol
Cis double bond causes a bend.
Hydrogen
Carbon
Oxygen
Phosphorus
Nitrogen



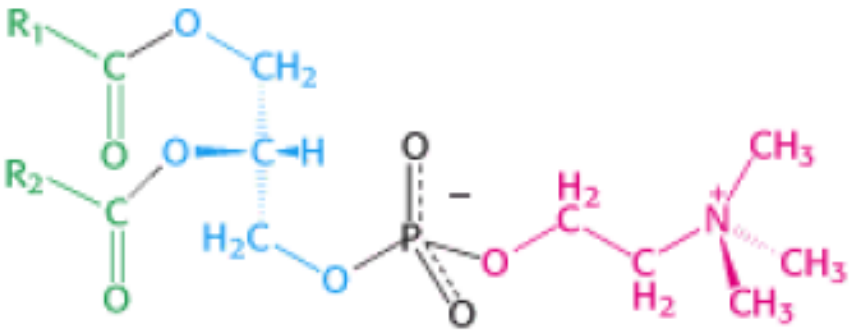




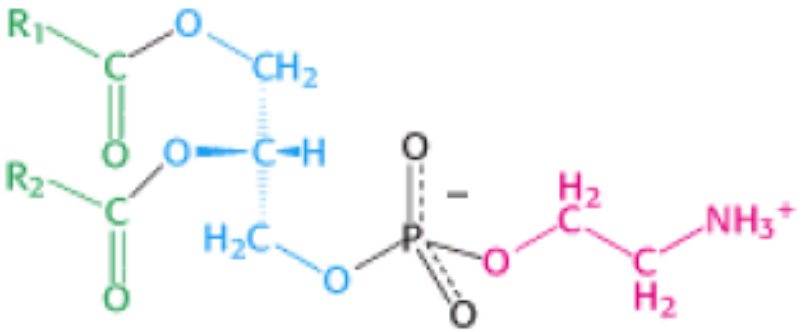




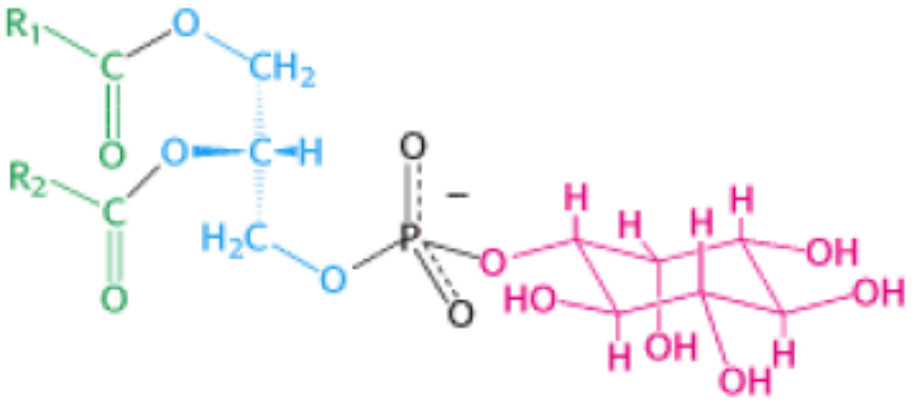
Phosphatidyl serine



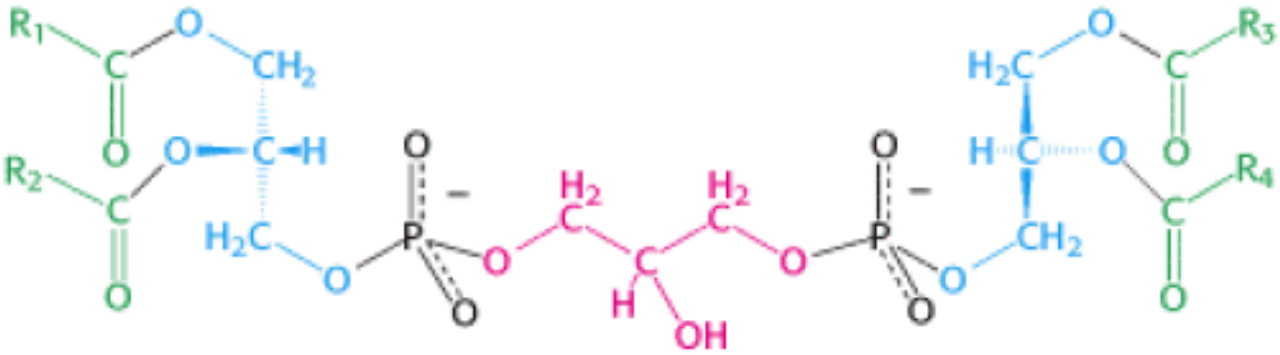
Phosphatidyl choline



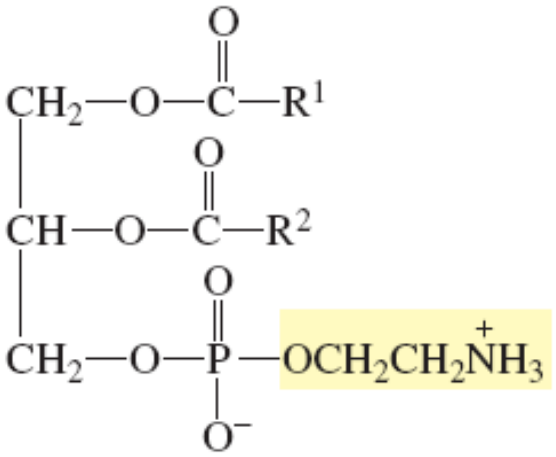
Phosphatidyl ethanolamine



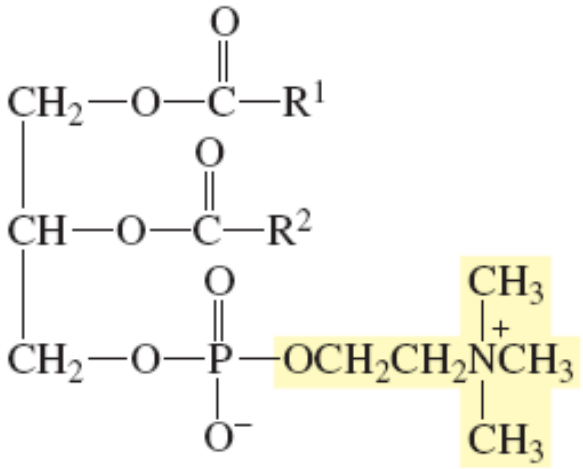
Phosphatidyl inositol



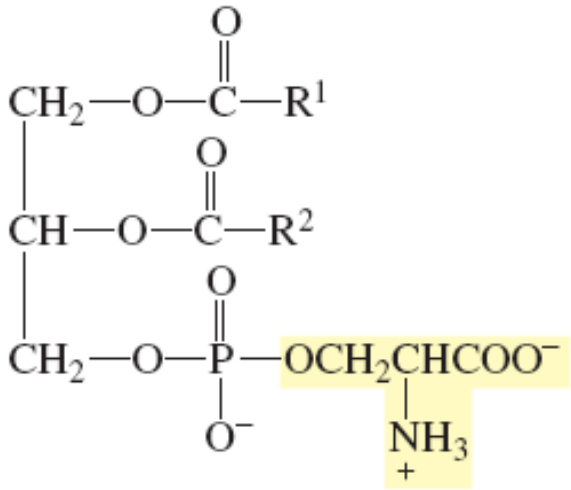
Diphosphatidyl glycerol (cardiolipin)



a phosphatidylethanolamine
a cephalin

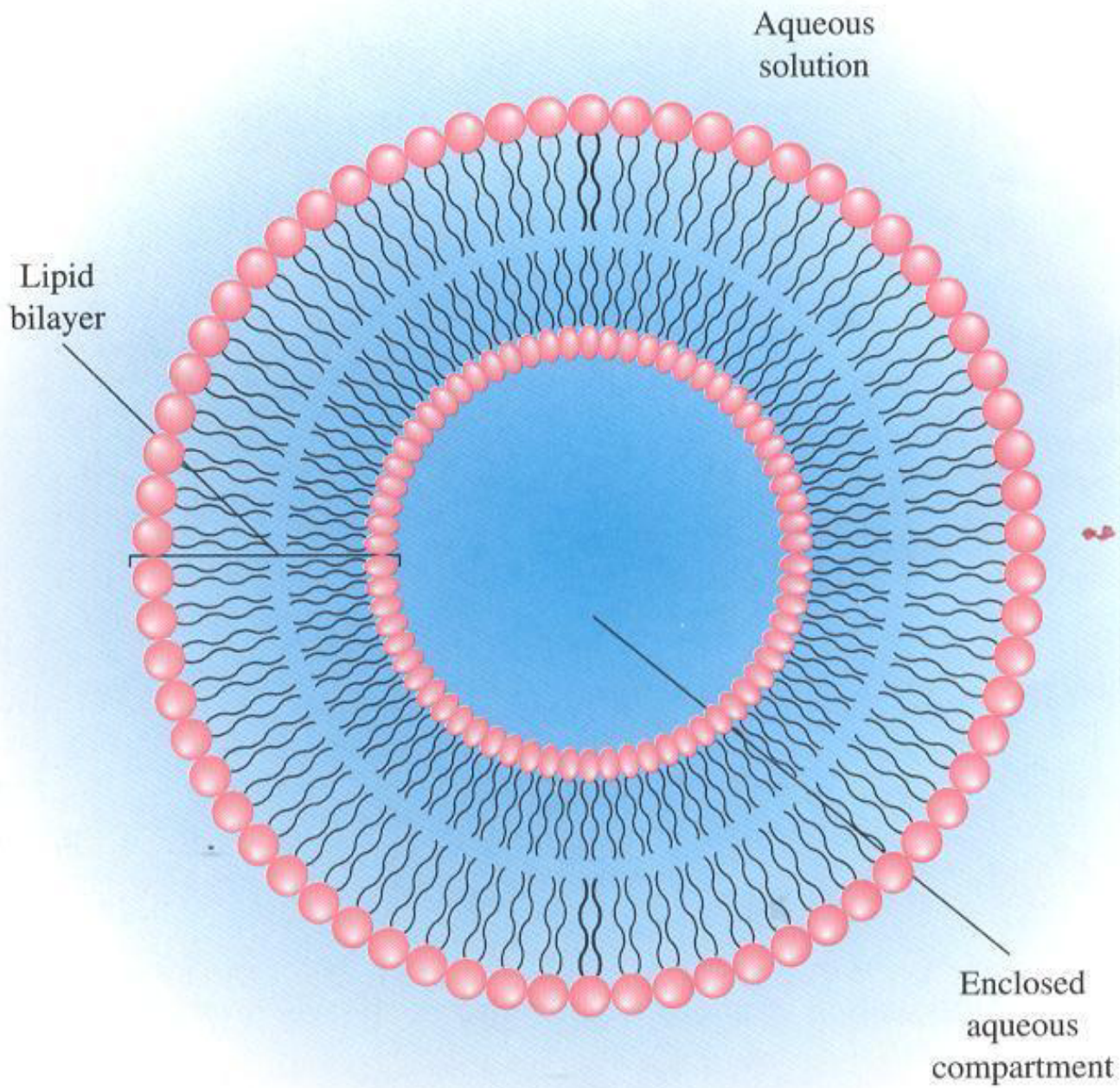


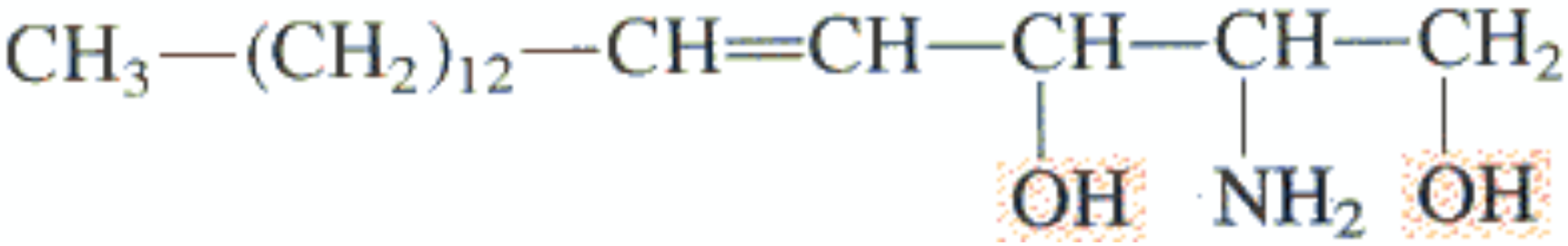
a phosphatidylcholine
a lecithin



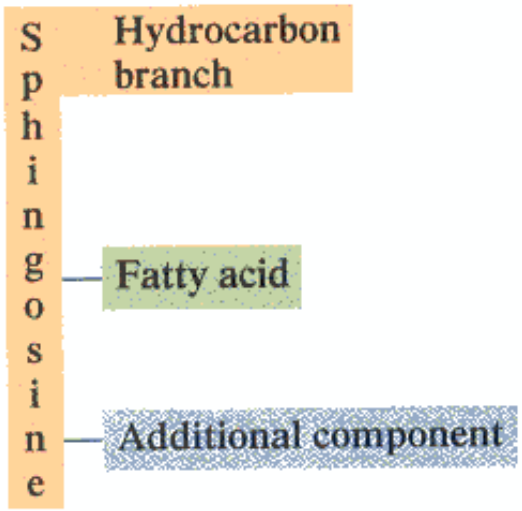
a phosphatidylserine

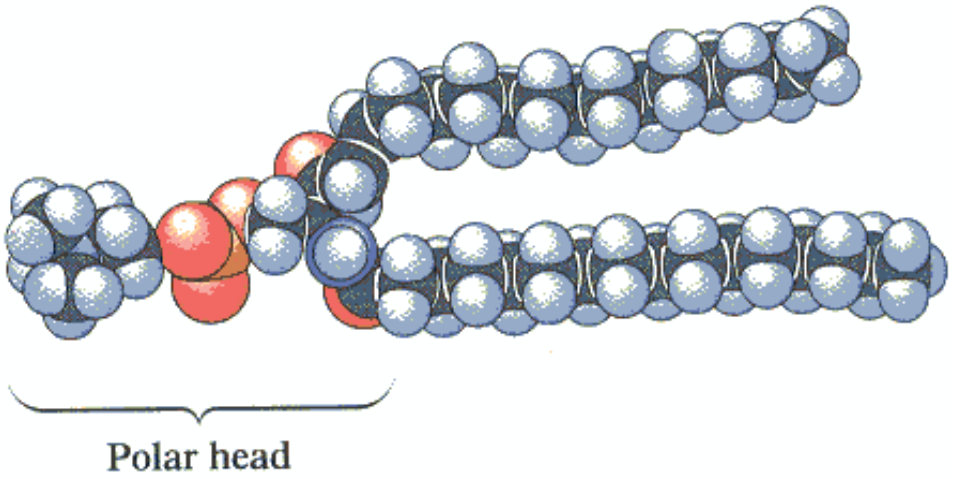
Liposome


Aqueous solution
Lipid bilayer
Enclosed aqueous compartment



Sphingosine

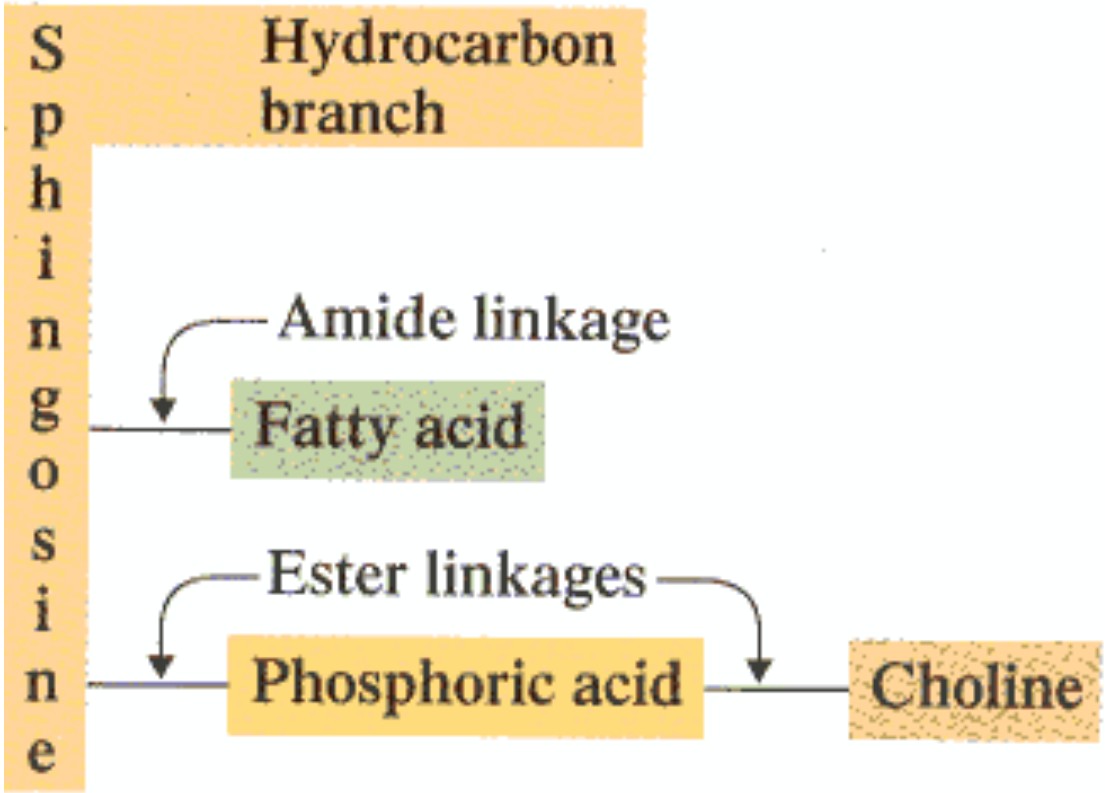


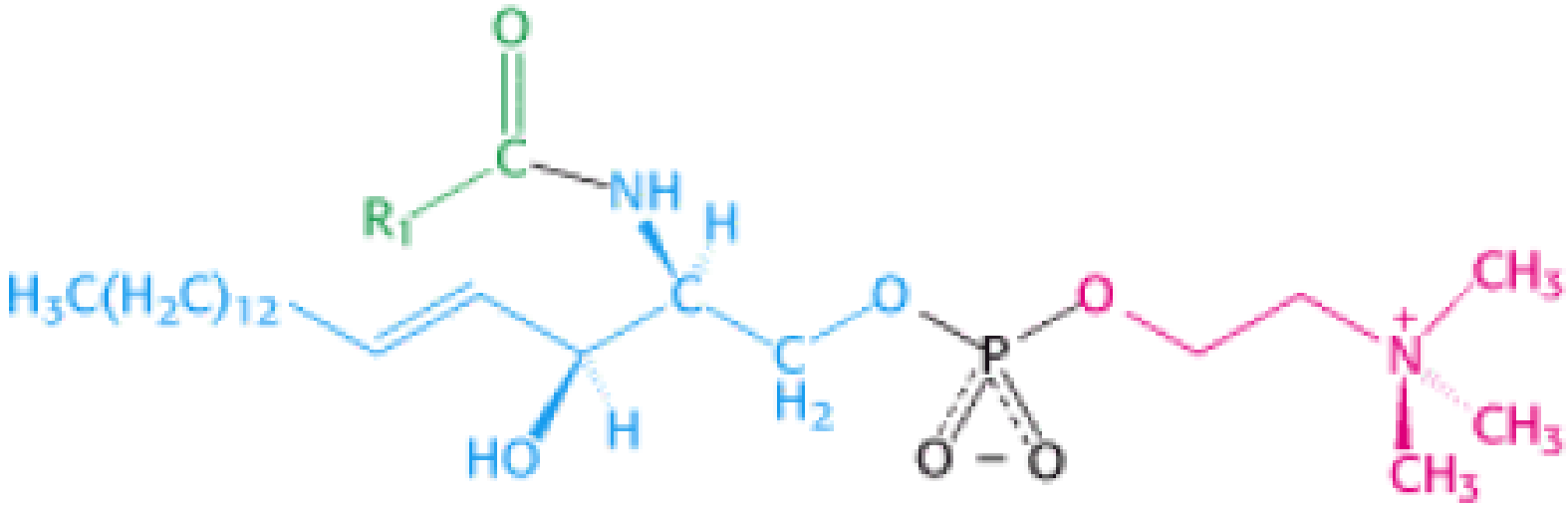


sphingornyelins.

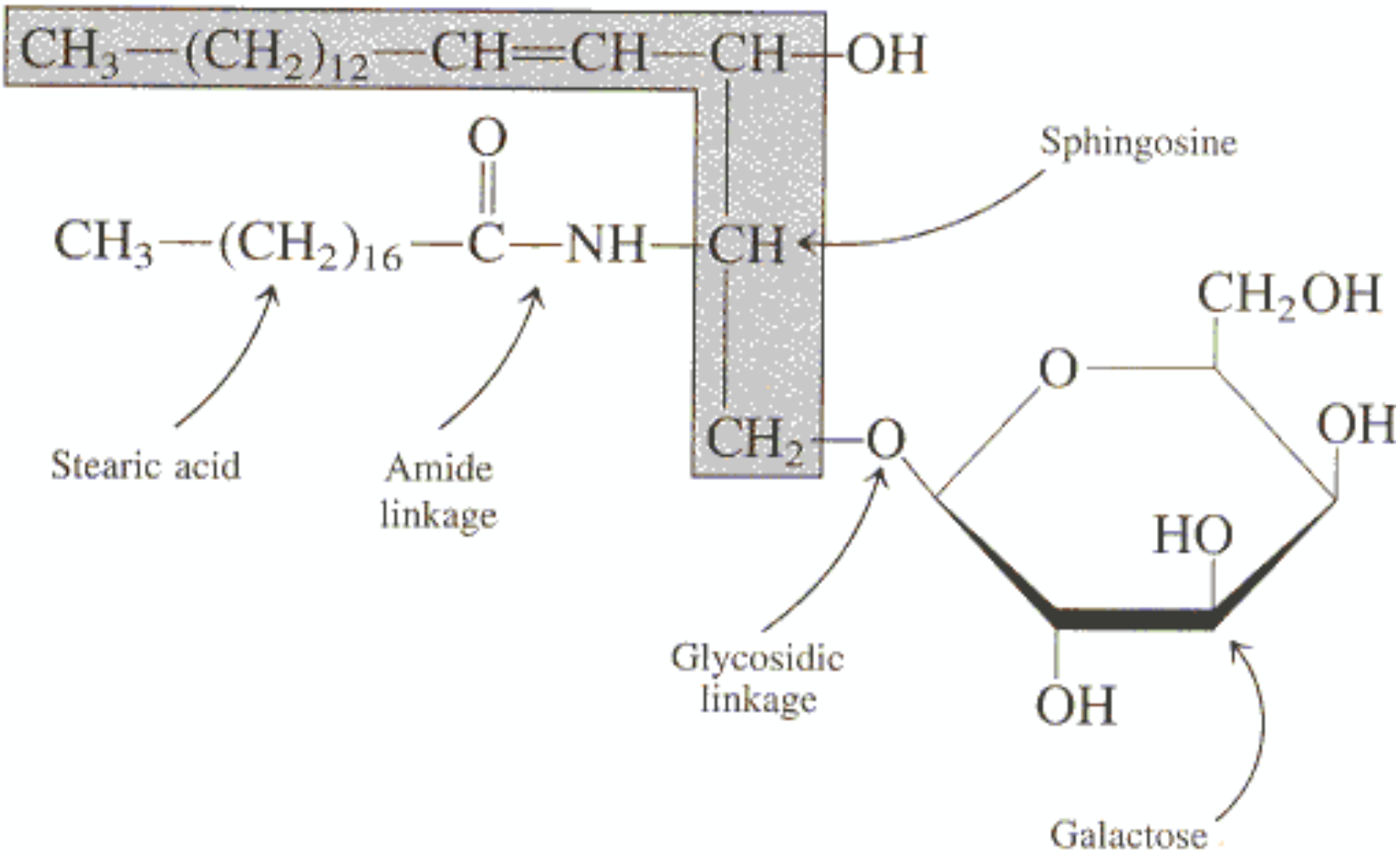
Sphingomyelins are found in all cell membranes and are important structural components of the myelin sheath, the protective and insulating coating that surrounds nerves

Sphingornyelins

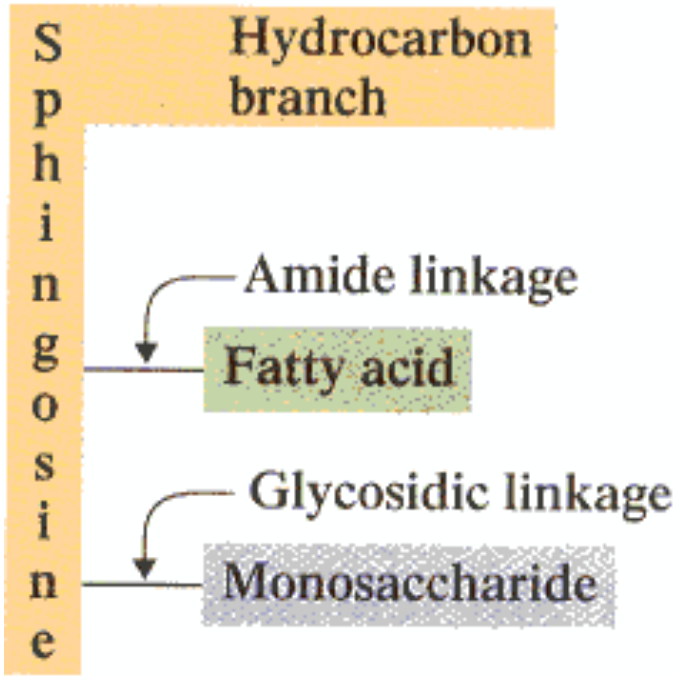


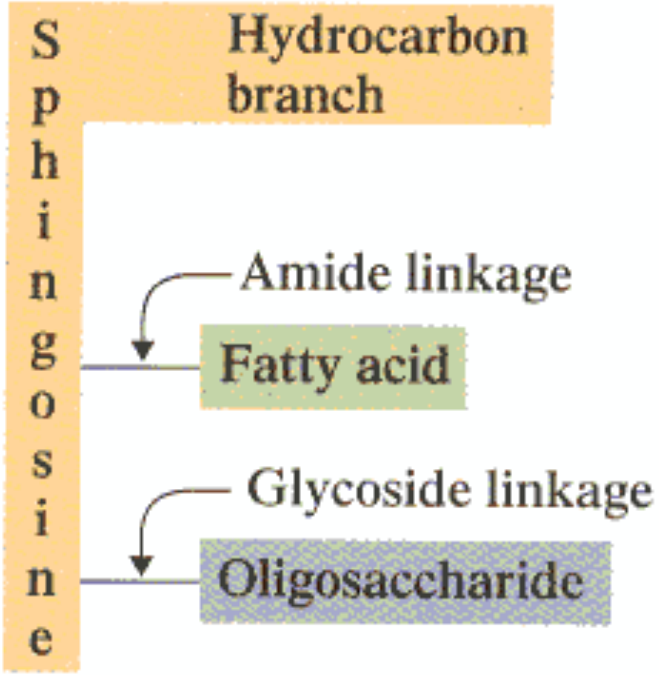


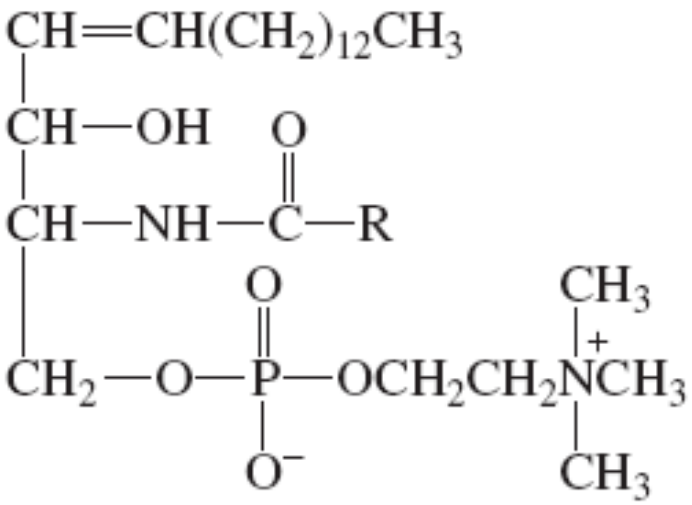
Sphingomyelin


CH3—(CH2)12—CH=CH—CH—OH
O
CH3—(CH2)16—C—NH—CH
Sphingosine
CH2OH
O
OH
CH2—O
HO
OH
Stearic acid
Amide linkage
Glycosidic linkage
Galactose

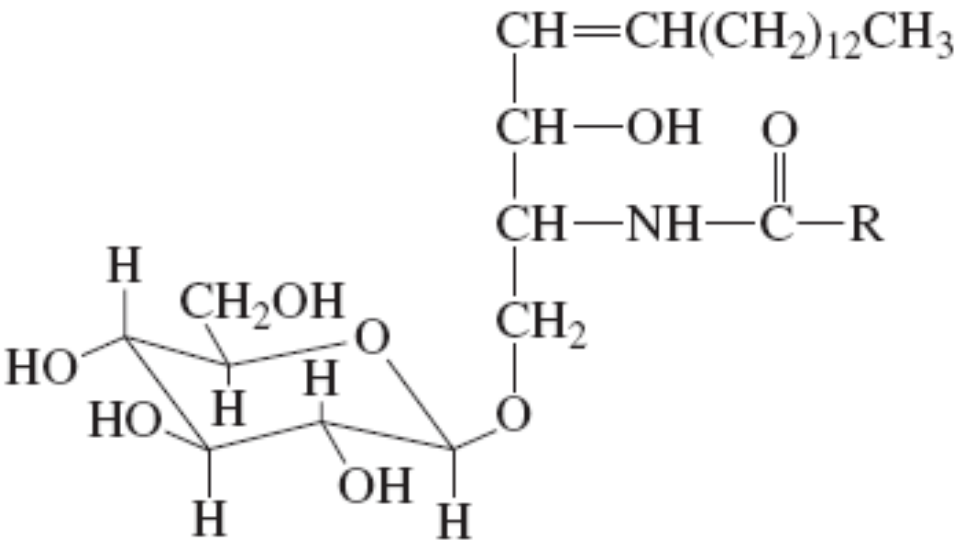
- **Cerebrosides,** the simplest of such carbohydrate-containing lipids, usually have a glucose or galactose as the carbohydrate unit.
- **Gangliosides** contain more complex carbohydrate heads; up to seven monosaccharide units are present.







a sphingomyelin

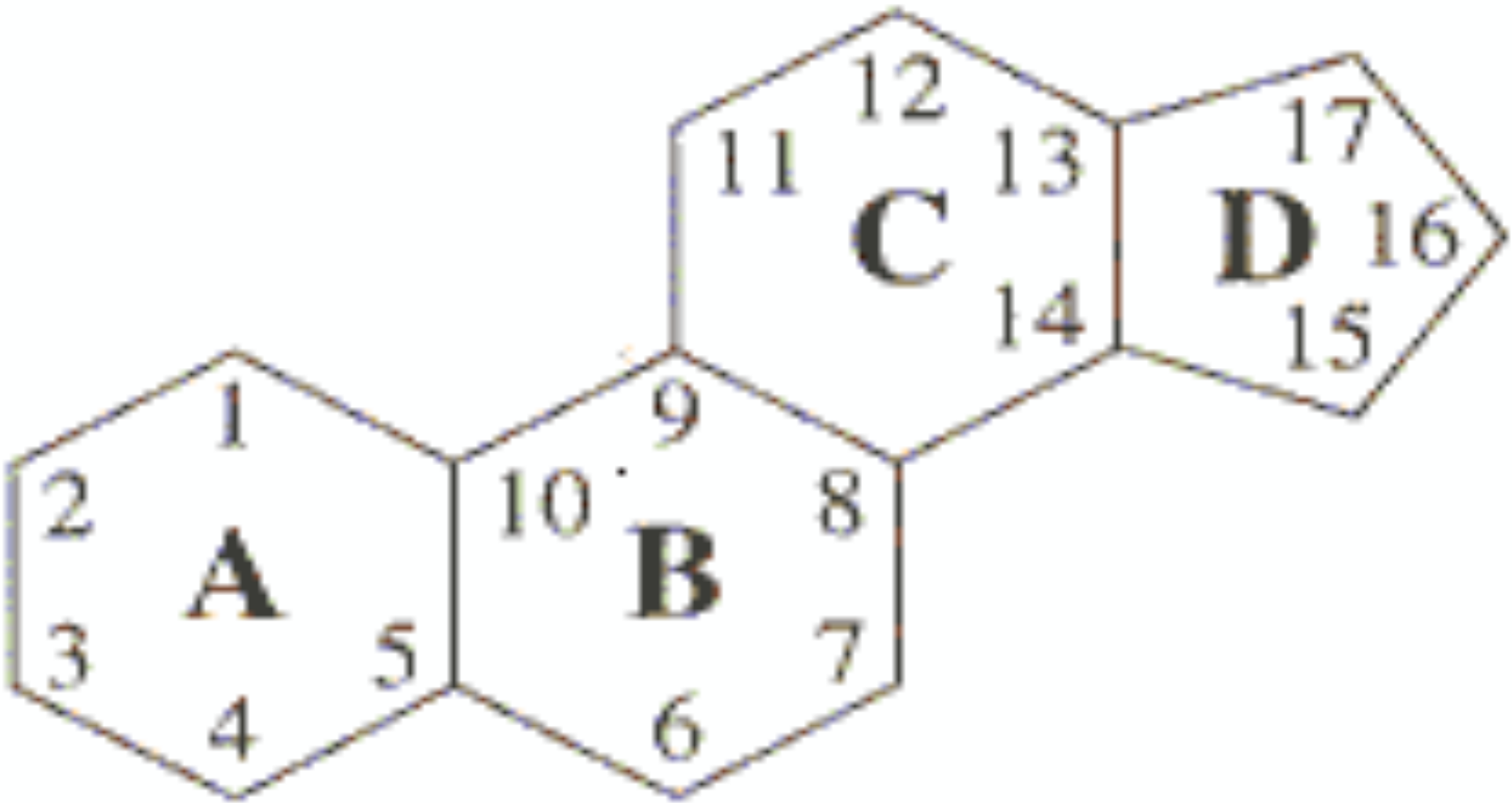


a glucocerebroside

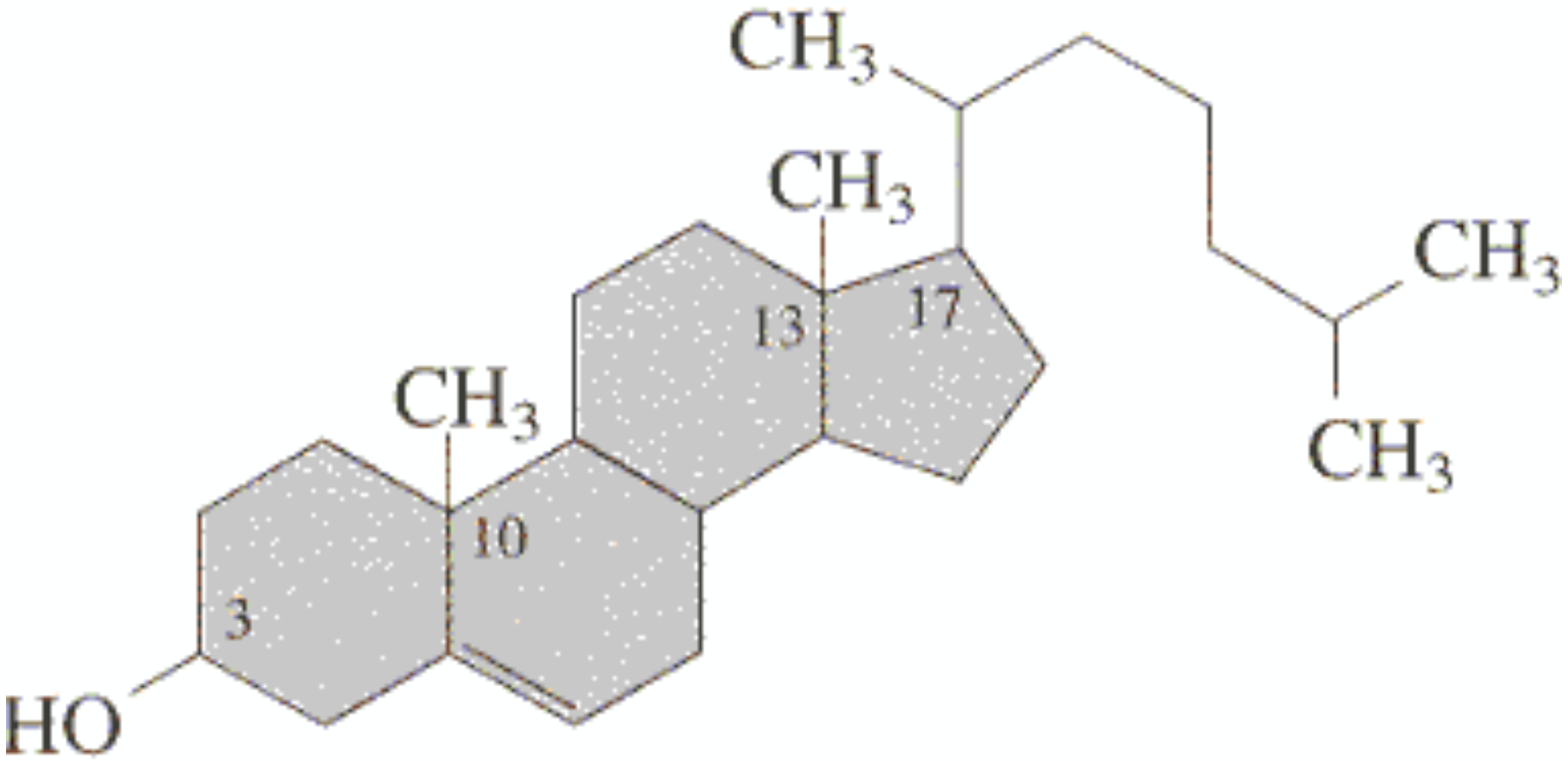
Nonsaponifiable Lipids

- **Lipids** do not undergo hydrolysis in alkaline solution.
- **Nonsaponifiable** Lipids: steroids, eicosanoids, terpenes, pheromones, fat-soluble vitamins
- A **steroid** is a lipid whose structure is based on the tetracyclic (four-ring) system shown in the following examples. Three of the rings are six-membered, while the fourth is five-membered. Steroids have many diverse roles throughout both the plant and animal kingdoms.

Pentahydrofenantrene (sterane)

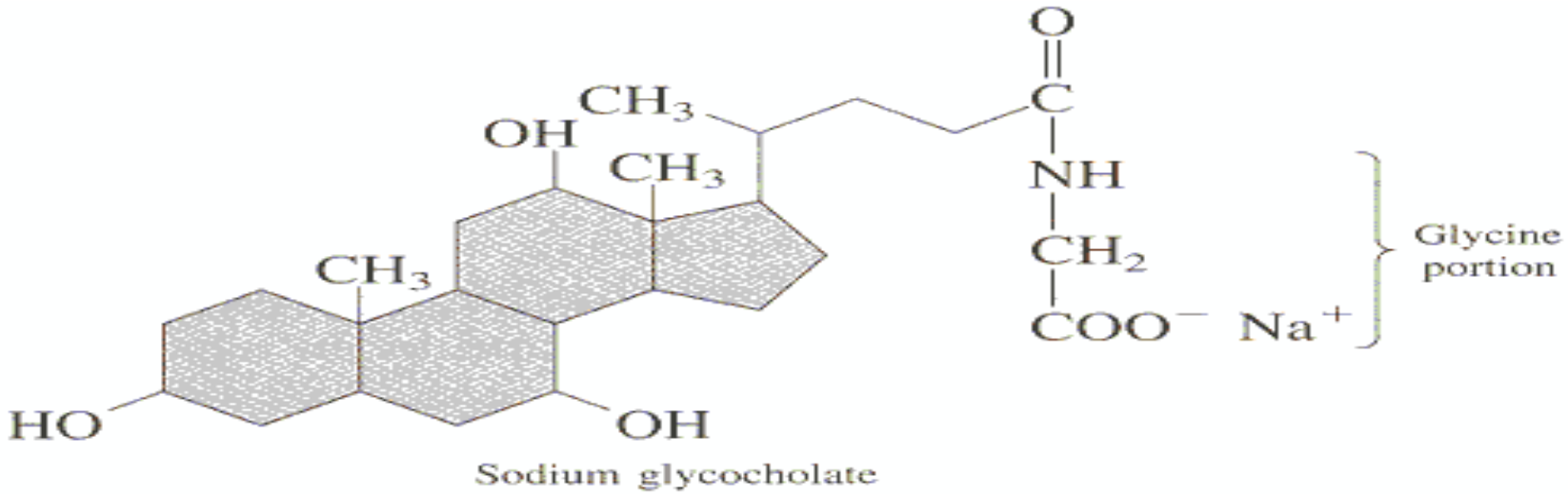


Cholesterol is the most abundant steroid in the human body

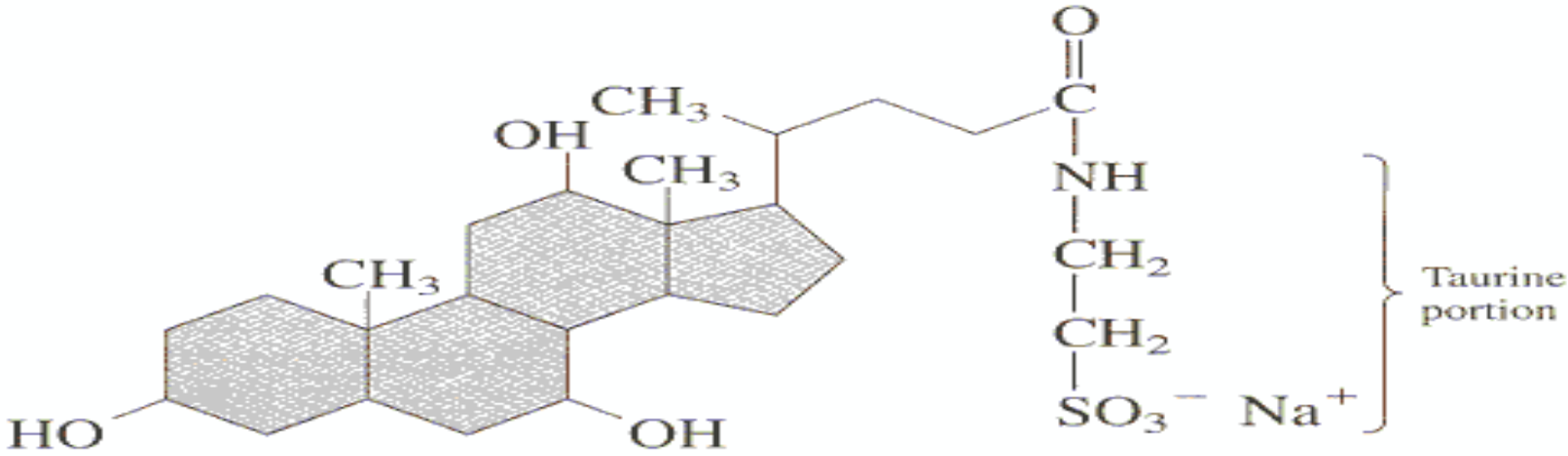


- Cholesterol, an unsaturated alcohol whose structure is the most abundant animal steroid. It has been estimated that a 60 kg person has a total of about 175 g of cholesterol distributed throughout the body. Much of this cholesterol is bonded through ester links to fatty acids, but some is found as the free alcohol. Gallstones, for example, are nearly purecholesterol.
- Cholesterol serves two important functions in the body. First, it is a minor component of cell membranes, where it helps to keep the membranes fluid. Second, it serves as the body's starting material for the synthesis of all other steroids, including the sex hormones.

Bile acids



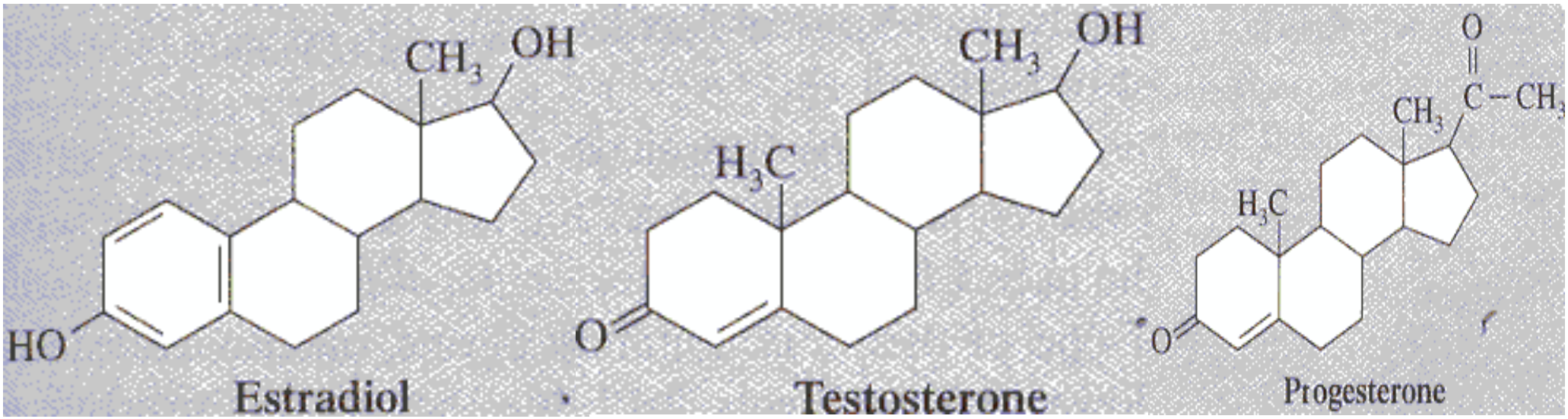
Sodium glycocholate



Sodium taurocholate

The liver secretes a clear, golden-yellow, viscous fluid known as bile. It is stored in the gall bladder and is mainly useful for digestive system.

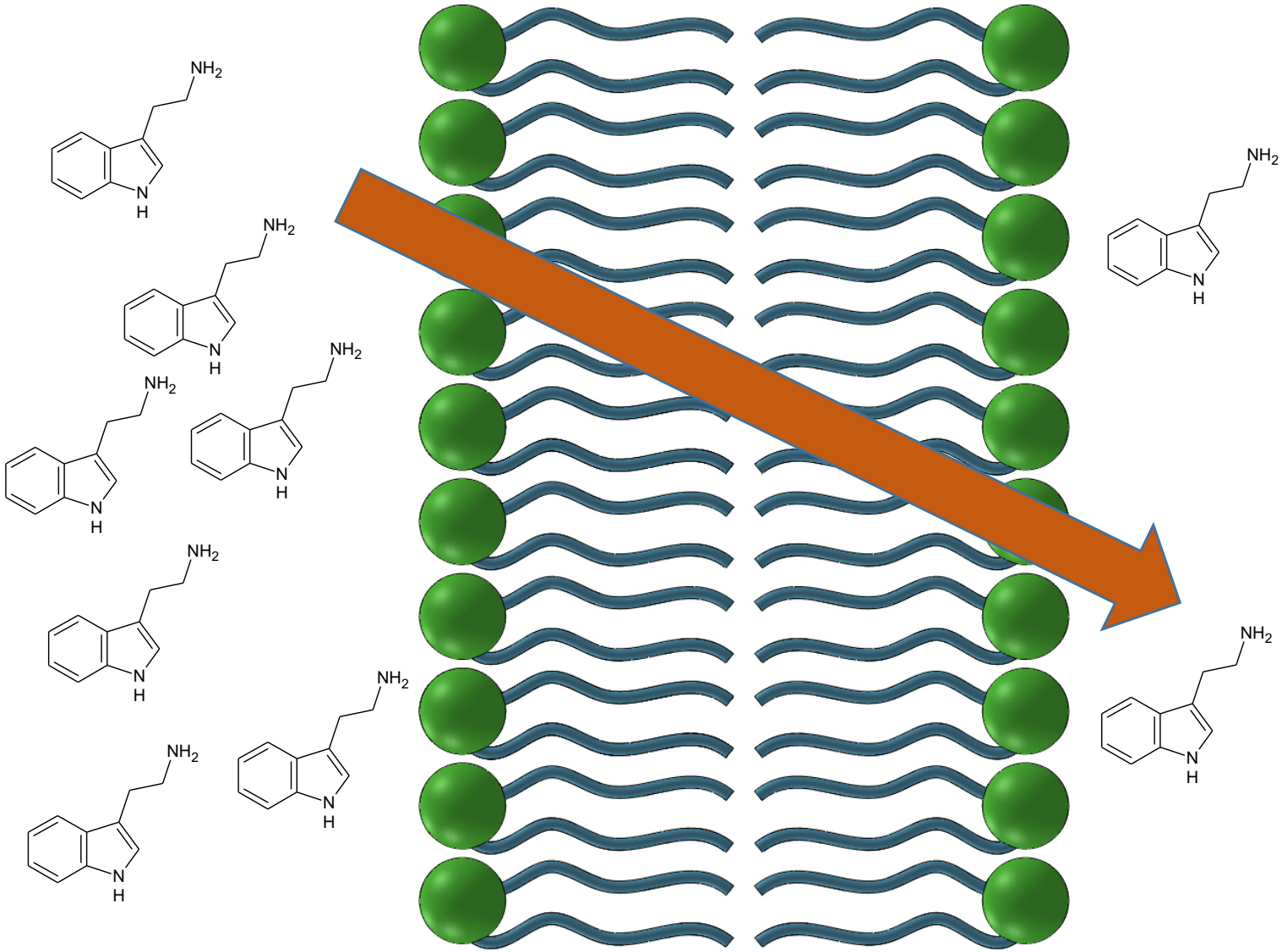
Steroids hormones.



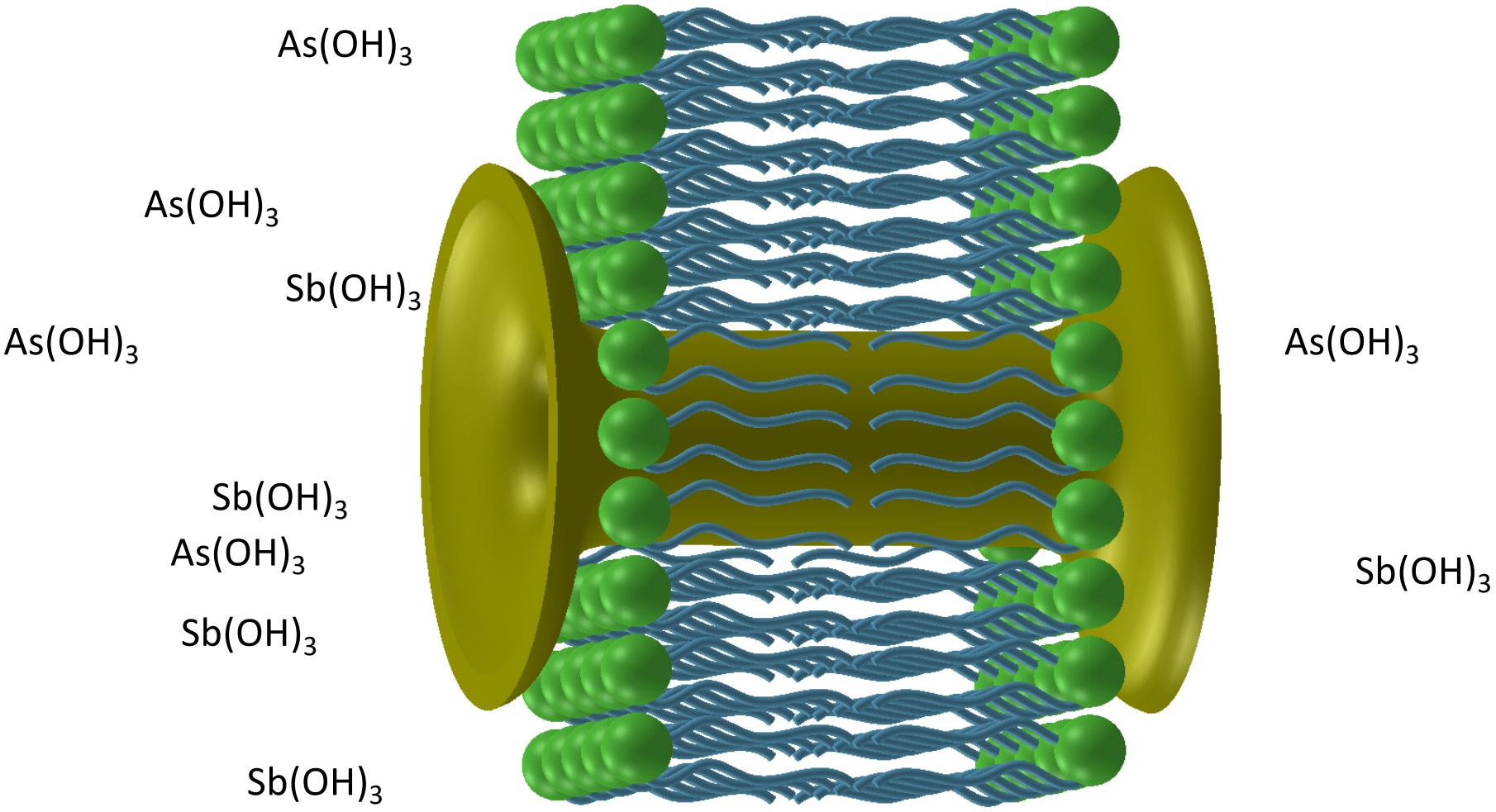
Hormones are chemical messengers produced by ductless glands.

- The **isoprenoids** are a vast array of biomolecules that contain repeating fivecarbon structural units known as **isoprene units**.
- **Terpenes** are an enormous group of molecules that are found largely in the “essential oils” of plants. Steroids are derivatives of complex hydrocarbon ring system.
- Examples of these biomolecules, referred to as **mixed terpenoids**, include vitamin E (α-tocopherol), ubiquione, vitamin K, and some cytokinins (plant hormones).

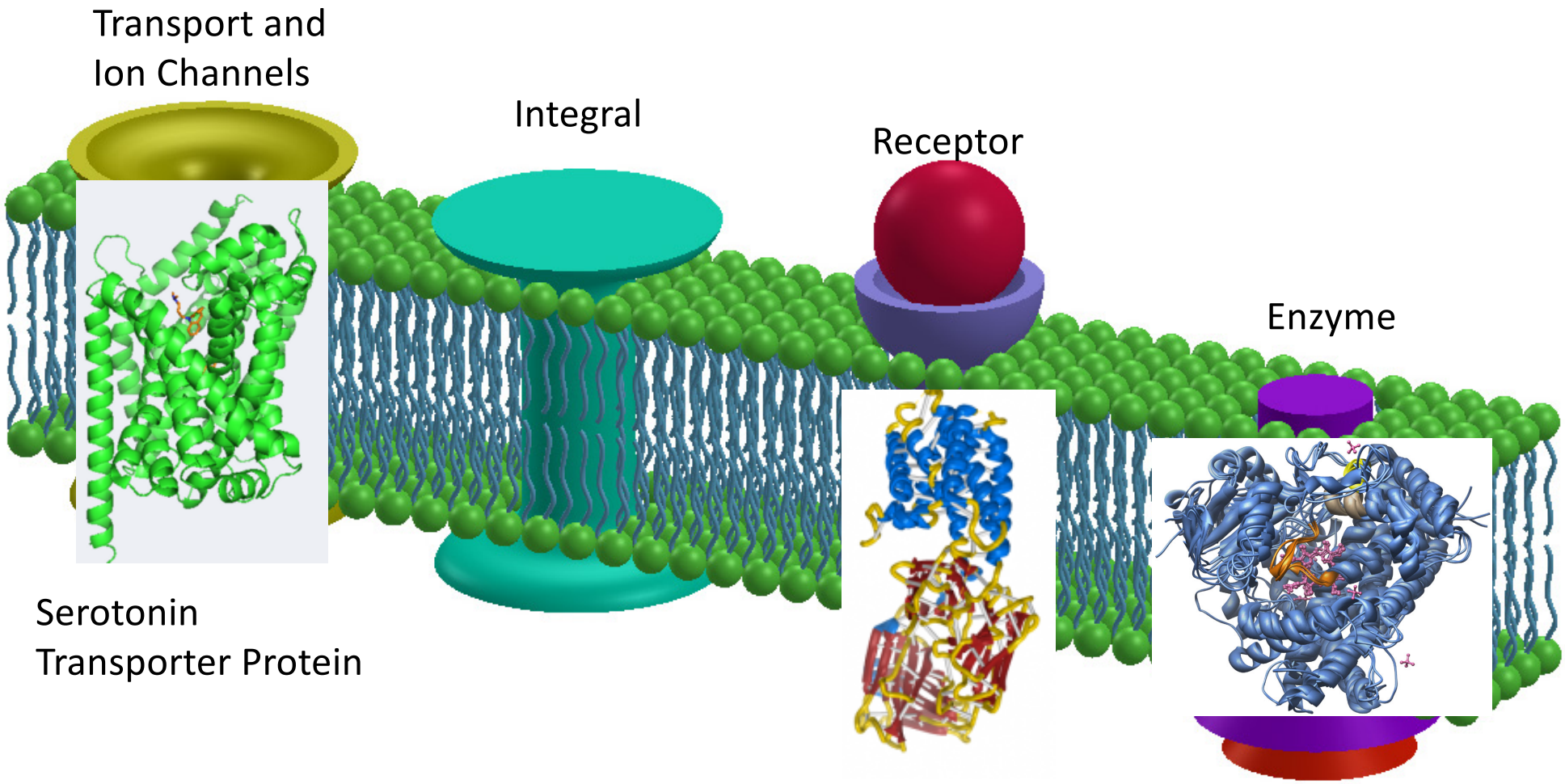
Passive Diffusion

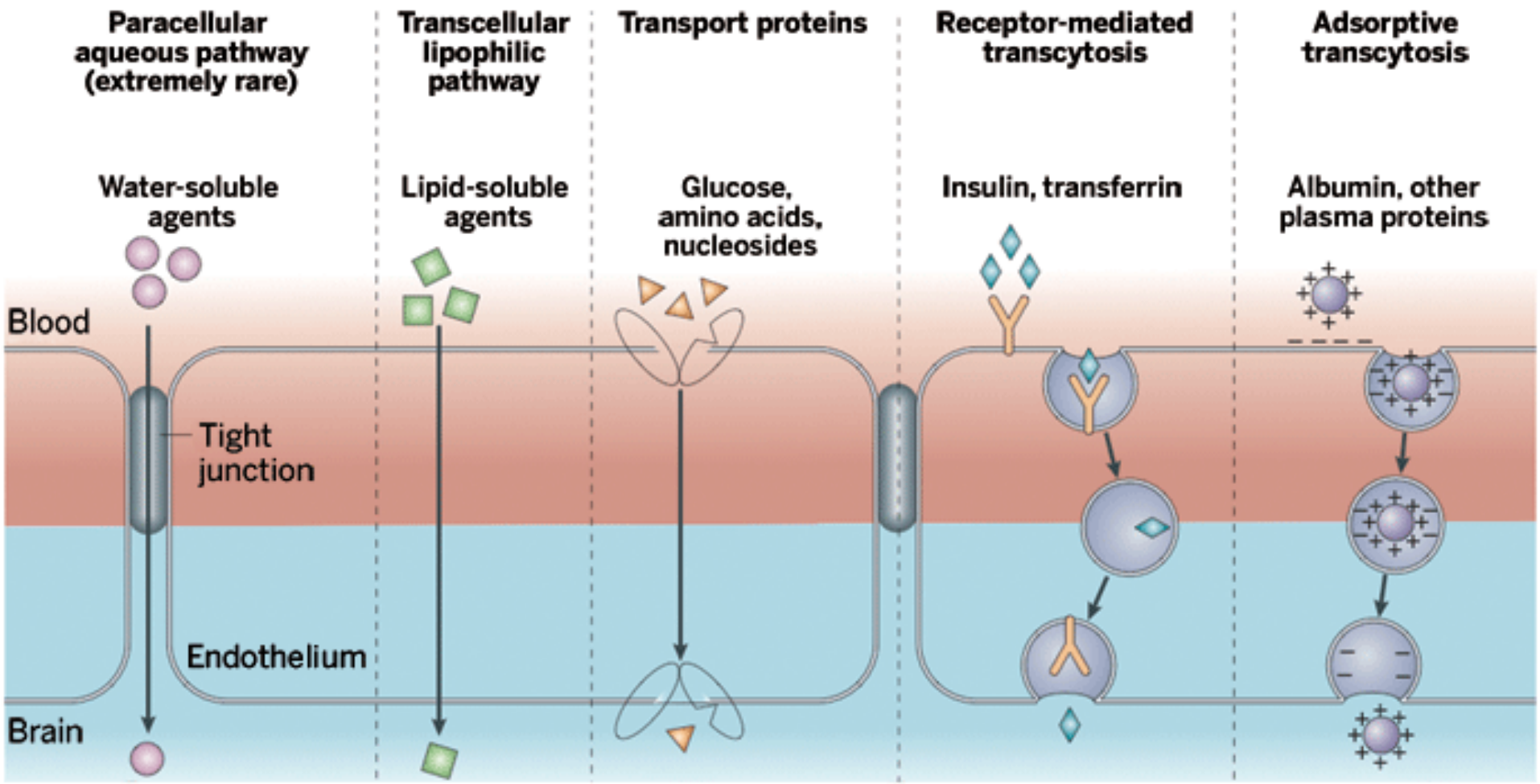


Active Transport



Membrane Protein Function





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A SIMPLE METHOD FOR THE ISOLATION AND PURIFICATION OF TOTAL LIPIDES FROM ANIMAL TISSUES

BY JORDI FOLCH, M. LEES, AND G. H. SLOANE STANLEY
(From the McLean Hospital Research Laboratories, Waverley, and the Department of Biological Chemistry, Harvard Medical School, Boston, Massachusetts)
(Received for publication, August 23, 1956)

1. Homogenize 1 x 10e6 cells or ~10 mg tissue into either 200 uL chloroform-methanol (v/v 2:1) or 200 uL hexane-isopropanol (v/v 3:2).
2. Centrifuge for 5-10 min at 14,000 rpm in a microcentrifuge.
3. Transfer the organic phase to a clean tube and vacuum dry. Store the material in the freezer (<20oC), desiccated and protected from air, i.e., under anaerobic conditions to minimize oxidation.
4. Re-dissolve the vacuum-dried lipids/cholesterol into a suitable assay buffer prior to use.

A COMPARATIVE ANALYSIS OF NINE POPULAR SOLVENT-BASED LIPID EXTRACTION METHODS TO IDENTIFY LIPID SPECIFIC AFFINITY FOR DIRECT EXTRACTION AND INJECT MASS SPECTROMETRY TECHNIQUES

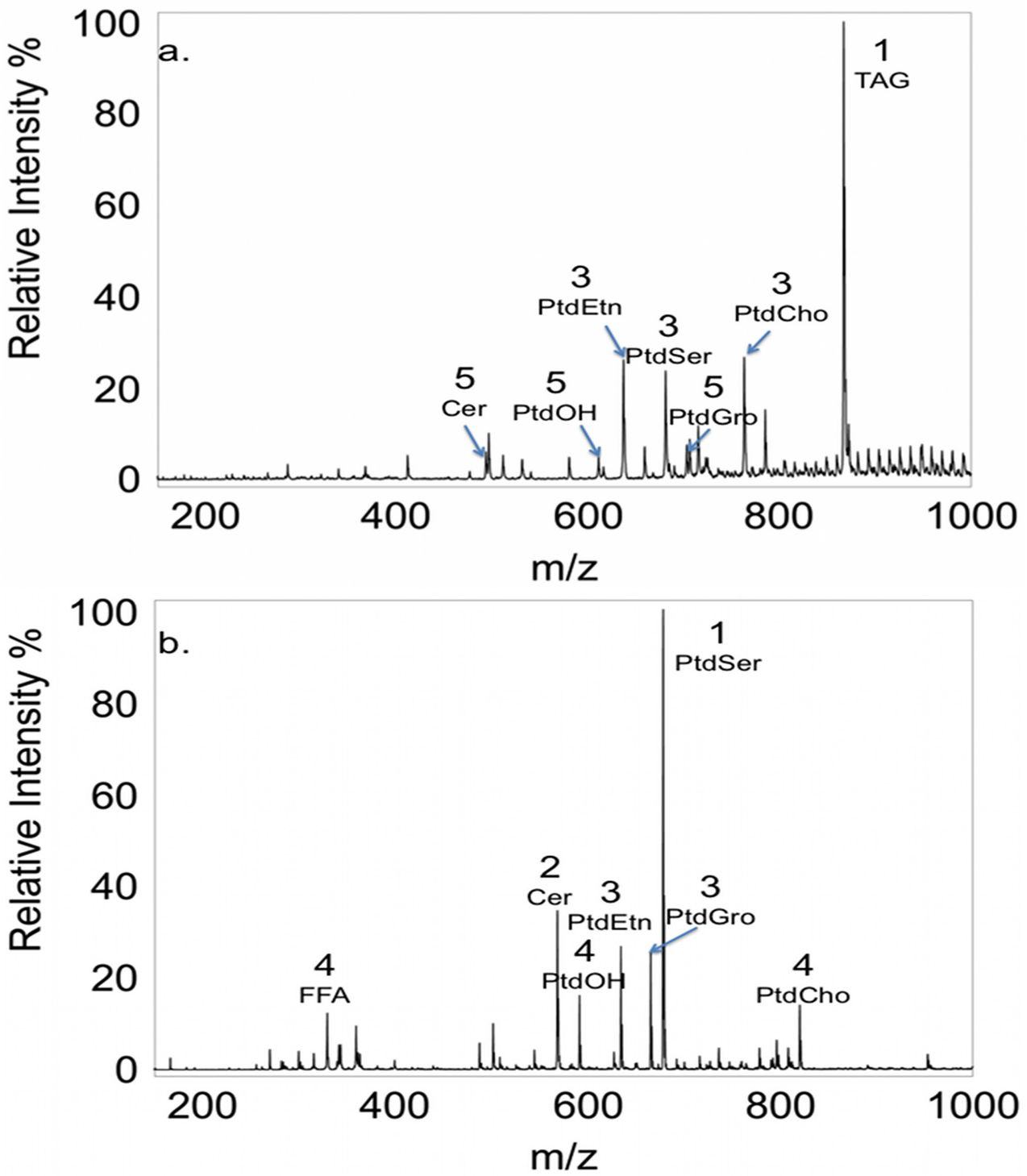
Jason Hamilton, Guido Verbeck

Table 1. The tabulated positive and negative mode lipid extraction efficiency scores for all solvent systems evaluated.

	1:1		1:1		1:1		2:1		1:1		1:1		1:2		3:2		1:1	
	IPA:$CHCl_3$		IPA:CH_2Cl_2		CH_2Cl_2:MeOH		$CHCl_3$:MeOH		$CHCl_3$:MeOH		EA:IPA		$CHCl_3$:MeOH		IPA:Hexane		EA:EtOH	
Lipid Standard	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)	(-)	(+)
FFA	3	5	3	5	2	3	3	3	3	3	4	5	3	2	2	5	4	5
Cer	1	4	1	4	2	4	2	4	2	4	1	5	3	5	2	4	2	5
PA	3	4	4	4	5	4	5	4	5	4	4	5	5	5	5	3	5	5
PC	3	2	4	2	4	2	5	3	5	3	3	3	5	3	5	3	4	3
PE	2	2	3	2	4	2	5	2	5	3	3	3	5	3	5	5	5	3
PG	3	3	3	3	5	5	5	5	5	5	3	5	5	5	5	5	5	5
PS	1	2	1	2	3	2	5	2	4	2	4	5	5	3	5	2	5	5
TG	5	1	5	1	5	1	5	1	5	1	5	1	5	1	5	3	5	1
Total	**21**	**23**	**24**	**23**	**30**	**23**	**35**	**24**	**34**	**25**	**27**	**32**	**36**	**27**	**34**	**30**	**35**	**32**
Efficiency Score	**44**		**47**		**53**		**59**		**59**		**59**		**63**		**64**		**67**	

Rating System: 1 - excellent, 2 - good, 3 - fair, 4 - poor, 5 - absent from spectrum

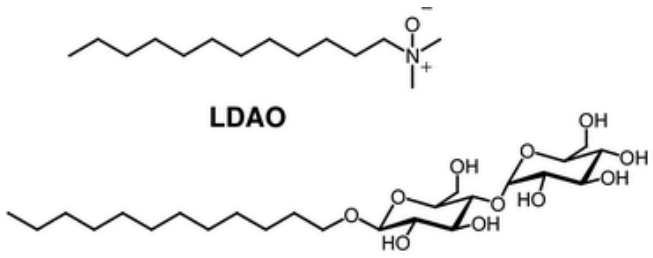
Phosphatidic acid (PA14:0/14:0), phosphatidylcholine (PC 14:0/14:0), phosphatidylethanolamine (PE 14:0/14:0), triglyceride (TG 17:0/17:0:17:0) and free fatty acid (FFA) (16:0) were purchased from Sigma Aldrich. Phosphatidylglycerol (PG) (14:0/14:0), phosphatidylserine (PS) (14:0/14:0), and ceramide (Cer d18:1/14:0),


a.
Relative Intensity %
100
80
60
40
20
0
200
400
600
800
1000
m/z
1
TAG
3
PtdEtn
3
PtdSer
3
PtdCho
5
Cer
5
PtdOH
5
PtdGro
b.
Relative Intensity %
100
80
60
40
20
0
200
400
600
800
1000
m/z
1
PtdSer
2
Cer
3
PtdEtn
3
PtdGro
4
PtdOH
4
FFA
4
PtdCho

Membrane Protein Extraction: The Basics

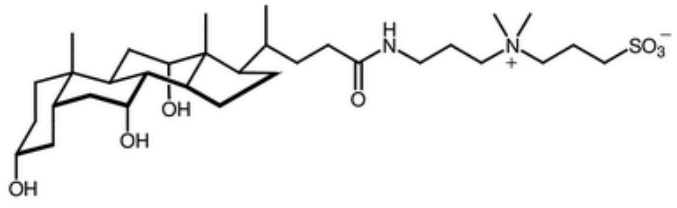
A. Extraction and Solubilization: The source of the proteins (mammalian cells, tissues, bacterial cells) are homogenized in a suitable buffer containing protease inhibitors (kits, Thermo). A detergent containing buffer is used to extract membrane proteins from the lipid bilayer. Different types of detergents, such as ionic detergents, non-ionic detergents, bile salts detergents, and zwitterionic detergents, are available

Reconstitution Methods	Advantages	Disadvantages
Ionic detergents (such as SDS)	perfect for solubilization of membrane proteins	cause some denaturation of proteins
Bile acid salts	Mild and does not deactivate easily	some protein denatures with these detergents
Non-ionic detergents (such as DDM, DM or OG)	Non-denaturing and mildly stringent	short chains get deactivated
Zwitterionic detergents (such as CHAPS, PIPES, MES, TES)	good for structural studies	more deactivating than non-ionic detergents
amphiphilic polymers	less viscosity problems, does not require traditional detergents	applicable on limited proteins
Tripod amphiphiles	give high efficiency of extraction for certain proteins	limited use

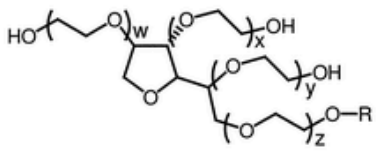


LDAO

DDM



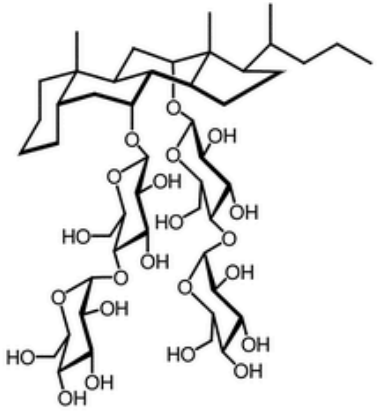
CHAPS



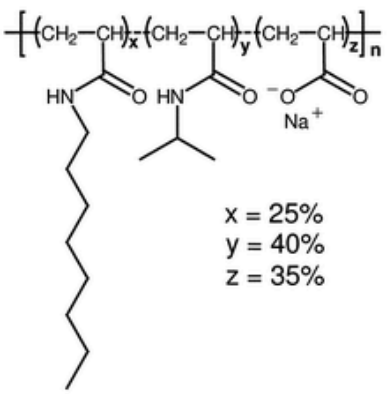
w+ x + y + z = 20

R = $C_nH_{2n-1}C(O)$

Tween series



Deoxycholate-based amphiphile

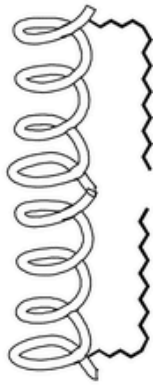


x = 25%

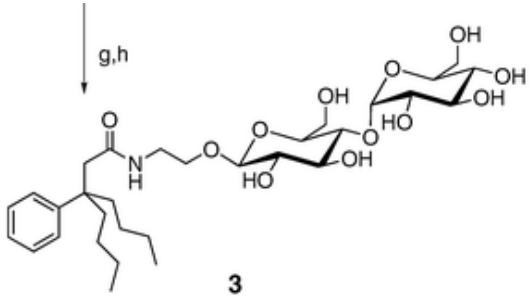
y = 40%

z = 35%

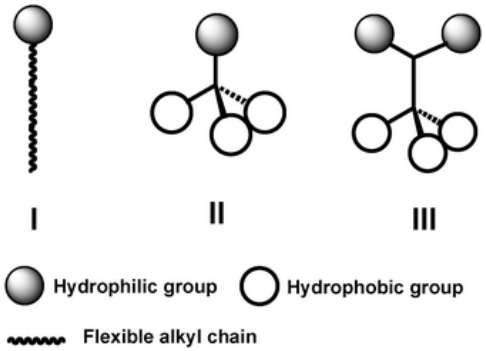
Amphipol (A8-35)



LPD



3



I II III

Hydrophilic group

Hydrophobic group

Flexible alkyl chain

tripod amphiphiles

Tripod amphiphiles for membrane protein manipulation

Pil Seok Chae Philip D. Laible and Samuel H. Gellman

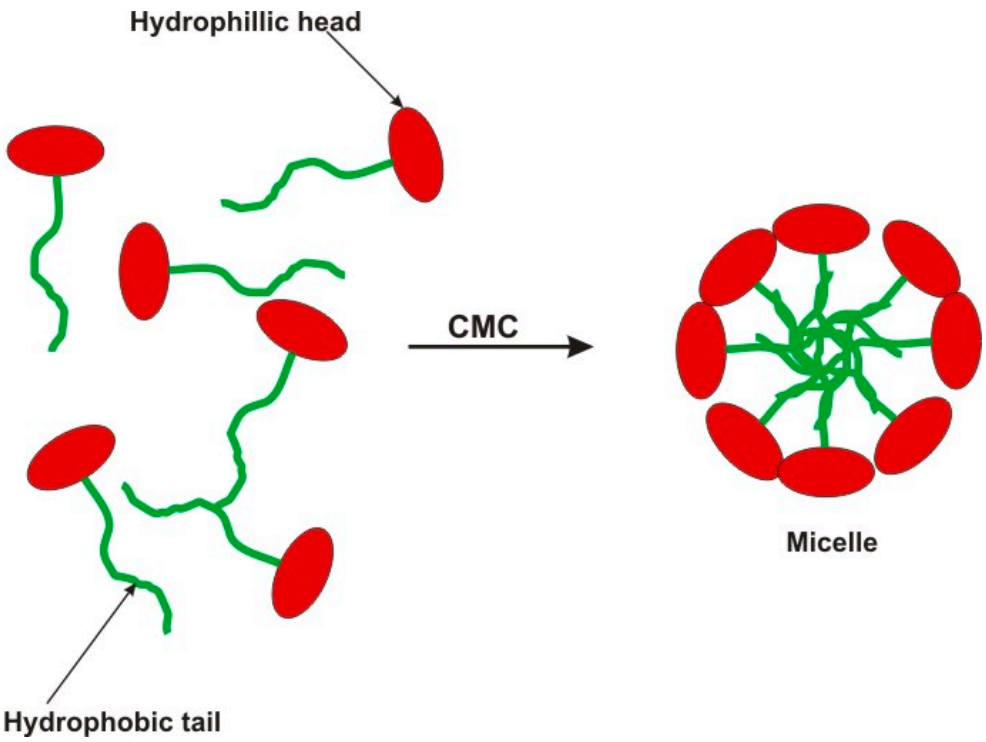
Mol. BioSyst., 2010, **6**, 89-94

Membrane Protein Extraction: The Basics

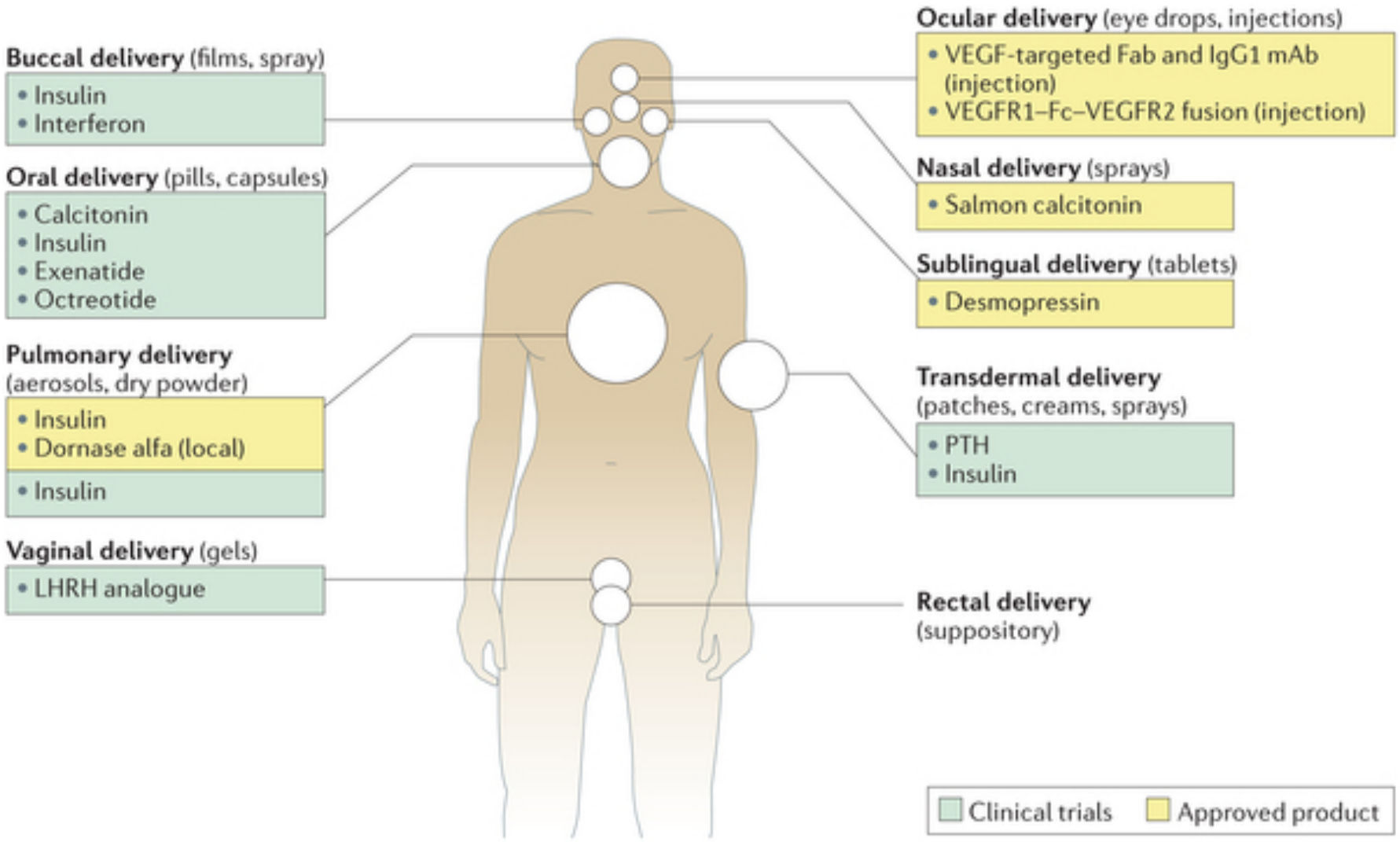
B. Removal of detergent:

During the process of extraction to solubilize membrane proteins, an excess of detergents and salts are used, which can create disruption in the further experimental layout. Hence, the detergents and salts have to be cleared to make a purified concoction of the extracted membrane proteins.

1. CMC isolation
2. Hydrophobic adsorption: Hydrophobic resins or beads
3. Gel Chromatography
4. Ion-exchange chromatography



Drug Delivery



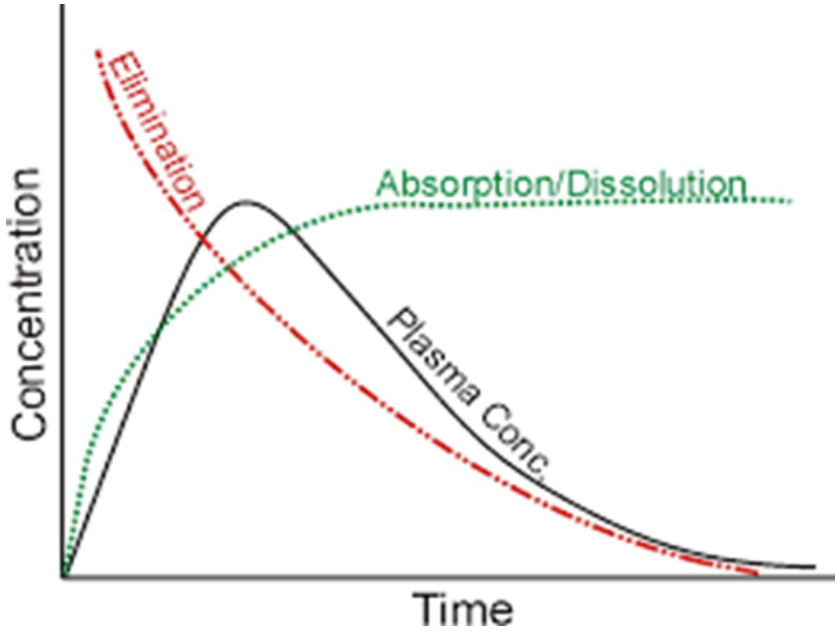
Nature Reviews Drug Discovery 13, 655–672 (2014) doi:10.1038/nrd4363

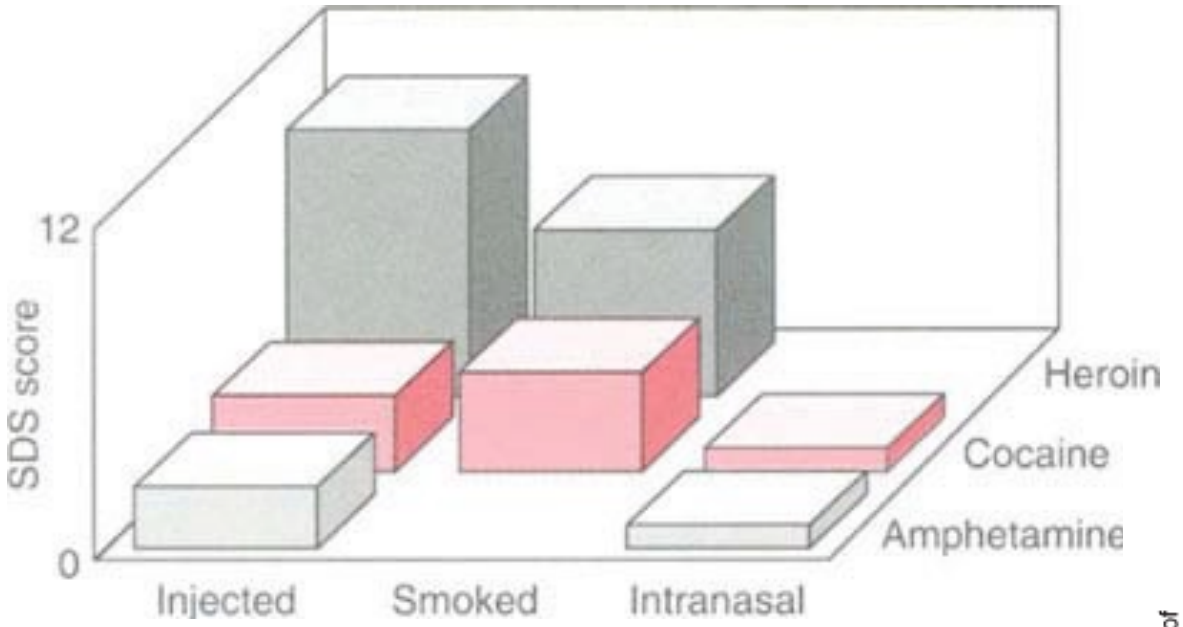
Bioavailability

Examples of <100% Availability

- Incomplete absorption
- Decomposition
- First-pass metabolic inactivation
- Poor transport

$$Absolute\ bioavailability\ (F) = \frac{AUC_{\ po}}{AUC_{\ iv}} \times \frac{Dose_{iv}}{Dose_{po}} \times 100$$





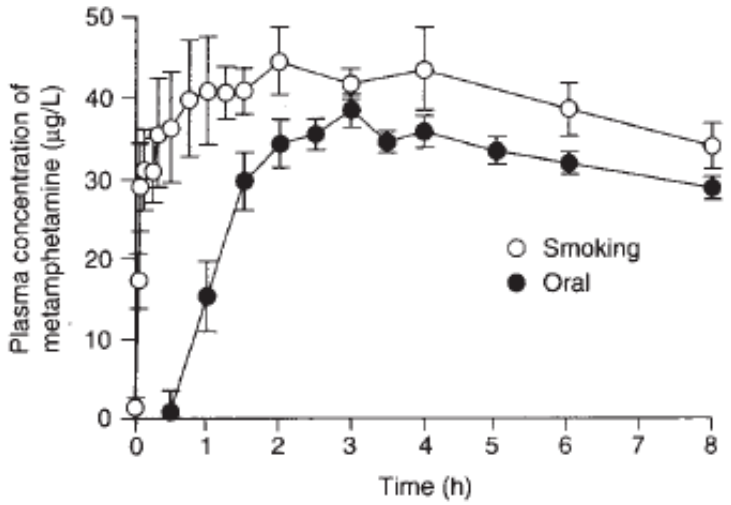
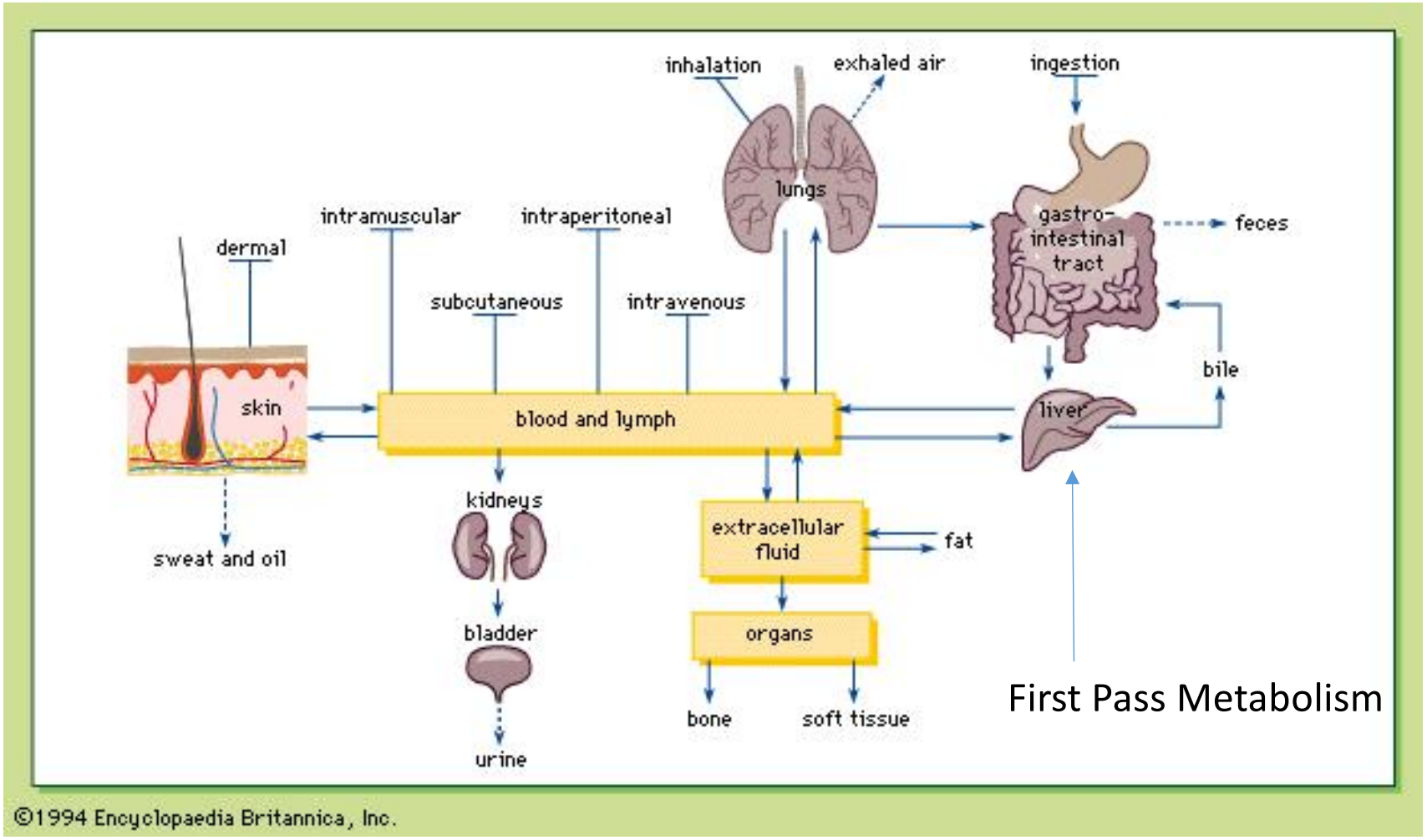


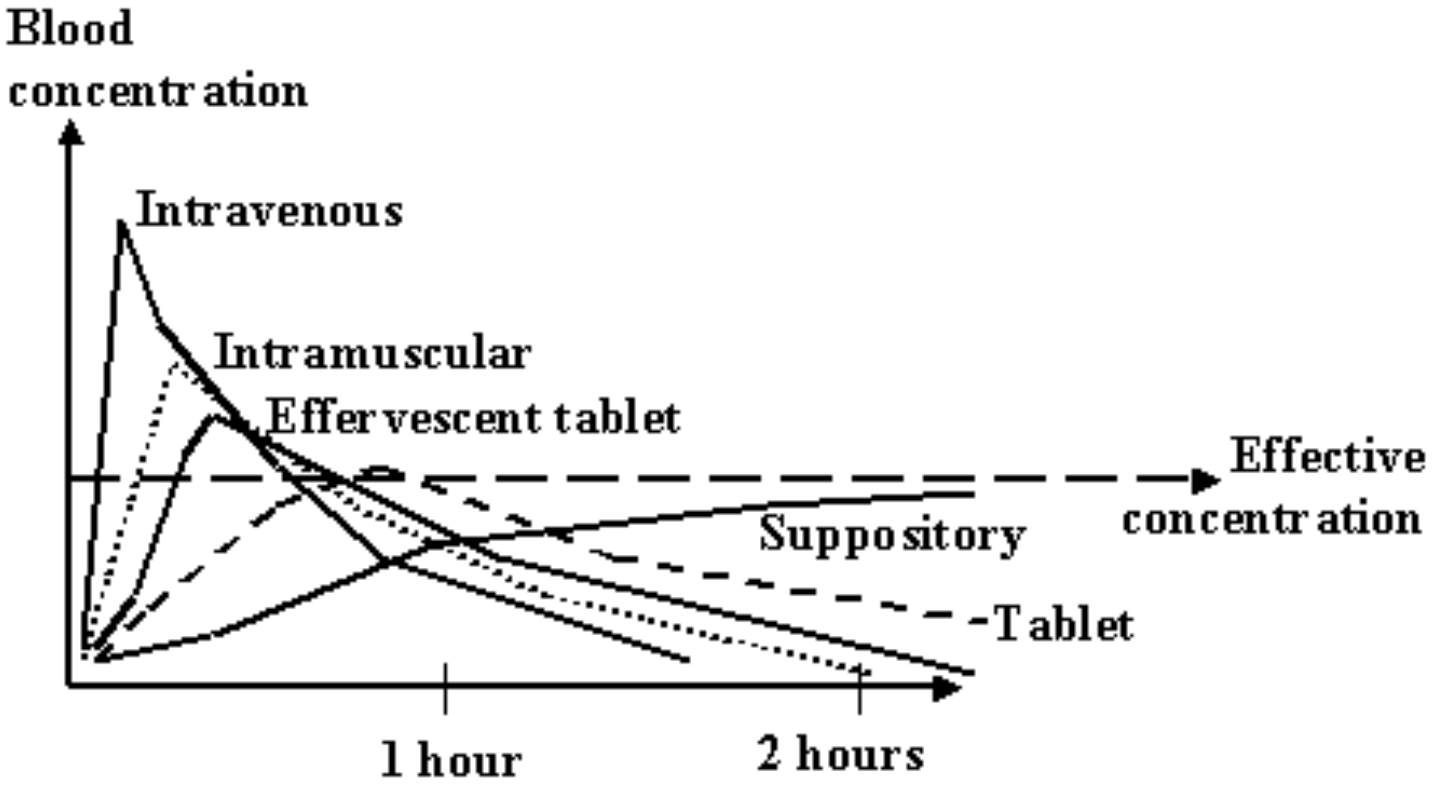
Fig. 2. Comparison of plasma concentration profiles of metamphetamine after oral administration and smoking, the oral dose given was 0.25 mg/kg. The smoked dose was approximately 21 mg per individual, which was slightly higher than the oral dose. The mean result of 6 individuals (± SEM) is shown. Smoking produces a more rapid rise in plasma methamphetamine concentrations than oral administration but plateau phase concentrations and half-life of elimination are similar for both routes (from Cook et al.,[595] with permission).

Clin. Pharmacokinet. 1997 Nov;33 (5) 344-400
0312-5963/97/001

Method of Entry:

1. Pulmonary (High Surface area – Many Capillaries)
2. Gastrointestinal
3. Dermal
4. IV
5. Muscle Injection





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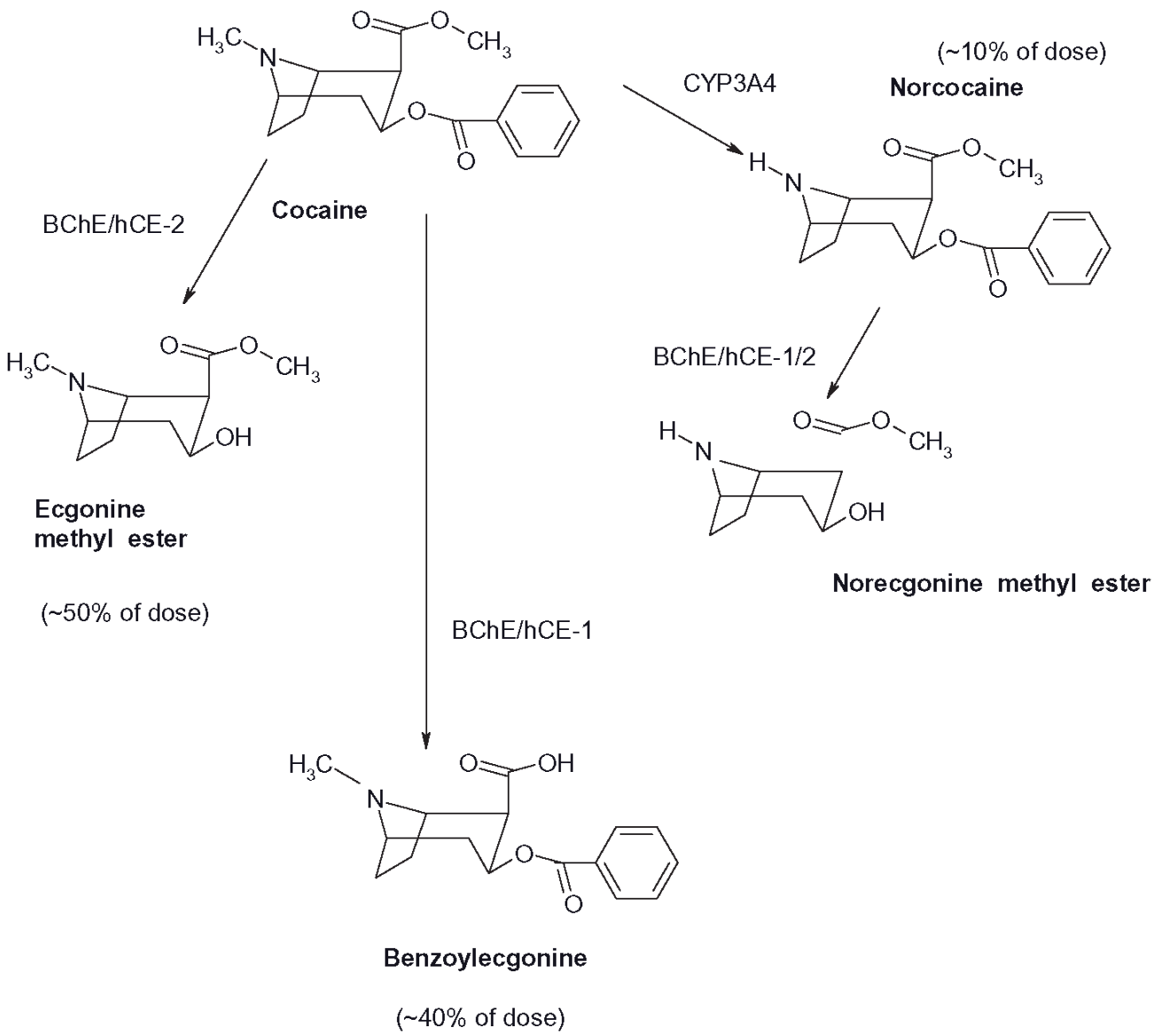
Cocaine (Metabolism of Major Illicit Drugs) (Human Drug Metabolism)
http://what-when-how.com/human-drug-metabolism/cocaine-metabolism-of-major-illicit-drugs-human-drug-metabolism/



Cocaine metabolism, showing the role of CYP3A4 in demethylation (toxic pathway) and human carboxylesterases (hCE-1 and 2) and butyrylcholinesterase (BChE). Esterases are found in virtually every tissue, clearing cocaine extremely rapidly.

Drug	Dose (mg)	half-life (h)	Bioavalability			Source
			Nasal	Smoking	Oral	
Heroin		0.1				NHTSA
Acetylsalicylic Acid		0.25				PfC
GHB	2000-4000	0.5				NHTSA
Cocaine	40-100	0.8	57%	70%		NHTSA
Morphine	5-30	1.9			30%	PfC
Acetaminophen		2				PfC
Ketamine		2.3	40%		20%	NHTSA
LSD		3				NHTSA
Oxycodone	2.5-30	5				NDAA
MDMA		7				NHTSA
Caffeine		8				NDAA
Methamphetamines	2.5-15	10.1				NHTSA
PCP		21		50%		NHTSA
Methadone	20-200	40			75%	NHTSA
Diazepam	4-40	43			99%	NHTSA
THC	2.5-10	72				NHTSA
Phenobarbital		100				NDAA

Clearance:

$$CL_{system} = CL_{renal} + CL_{hepatic} + CL_{excretion} + CL_{other}$$

$$CL_{renal} = \frac{C_{urinary} * V_{urinary}}{C_{plasma}}$$

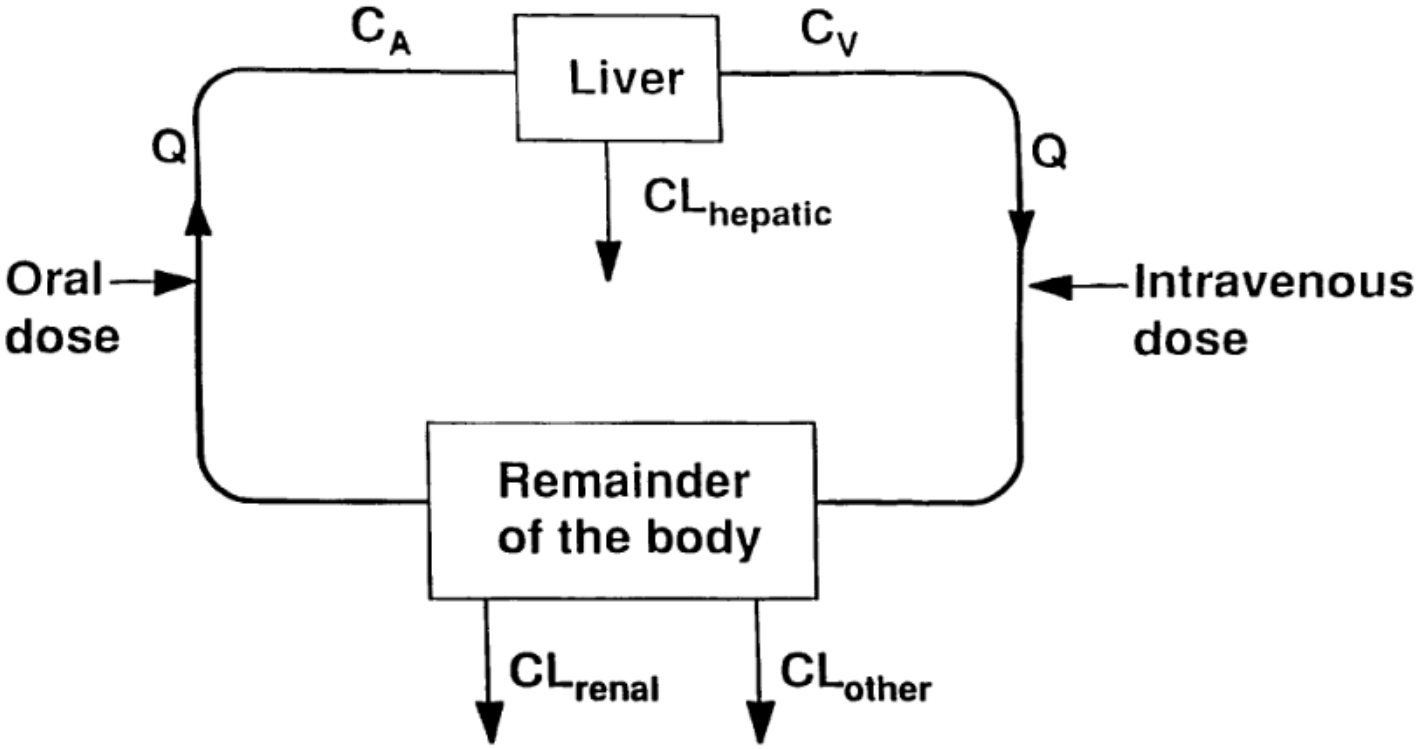


FIG. 1.—A schematic representation of the concentration–clearance relationship.

Benet, L.Z.; Zia-Amirhosseini, P., "Basic Principles of Pharmacokinetics", *Toxicologic Pathology*, 23 (1995) 115-123.

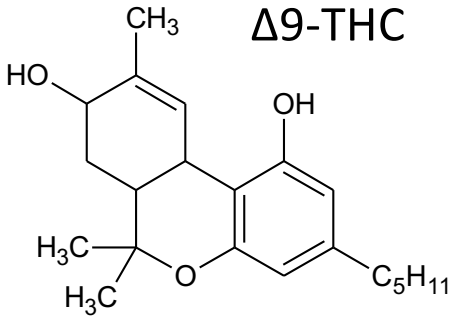
What makes a good drug candidate:

RO5 – Rule of Five – Lipinski's Rule of Five

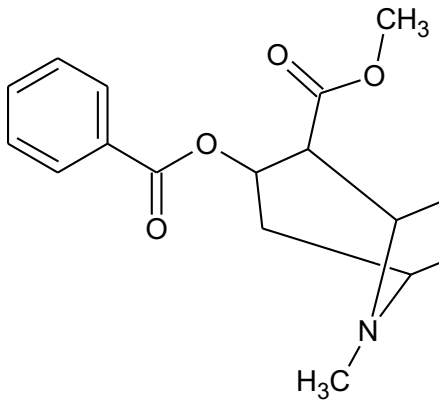
1. No more than 5 H-bond donors
2. No more than 10 H-bond acceptors
3. <500 amu molecular mass
4. Octanol:H_2O partition coefficient < 5

Modified Rules:

1. Octanol:H_2O partition coefficient -.04 < P < +5.6
2. Molar Refractivity from 40 to 130
3. Polar Surface Area < 140 $Å^2$
4. 10 or fewer Rotatable Bonds

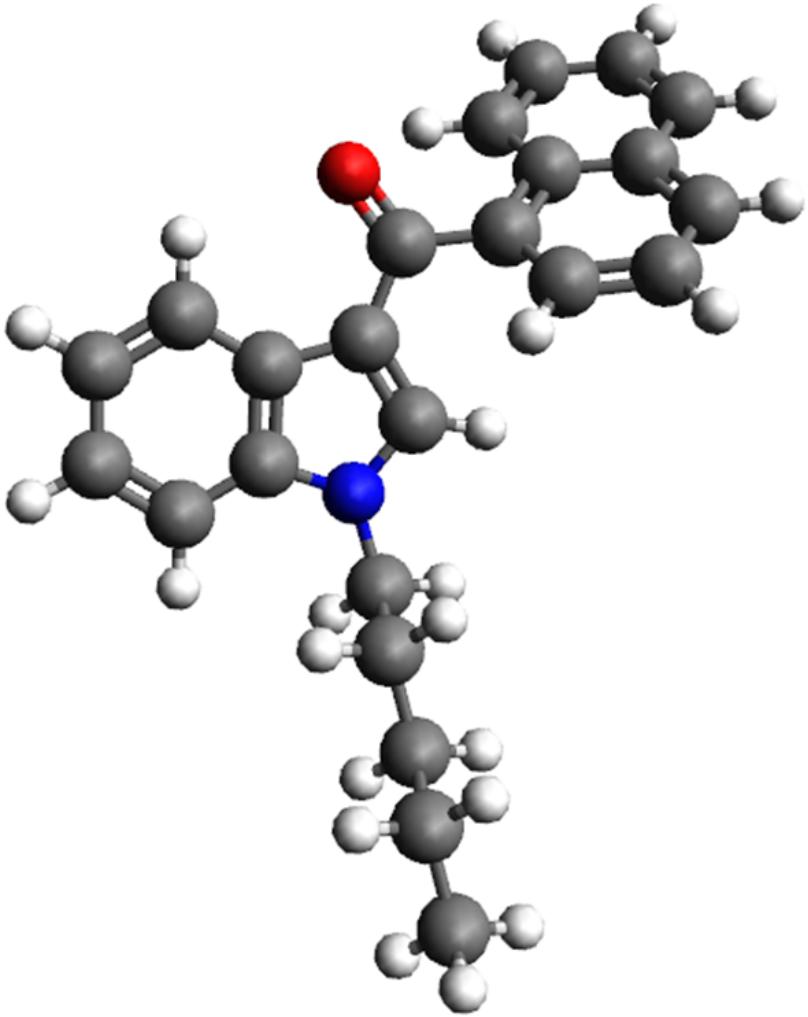


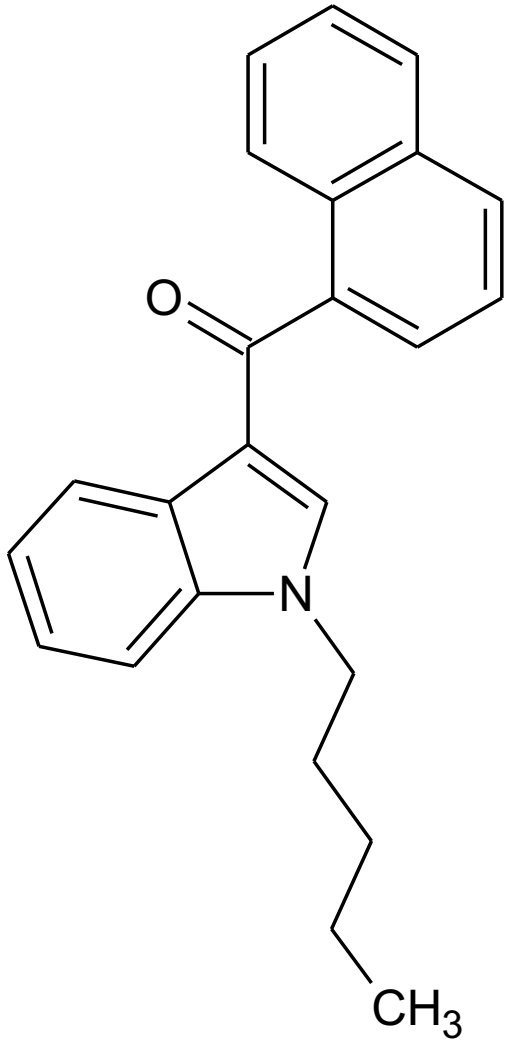
Δ9-THC



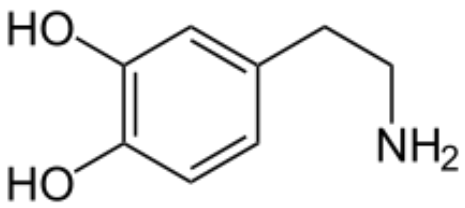
Cocaine

JWH-018

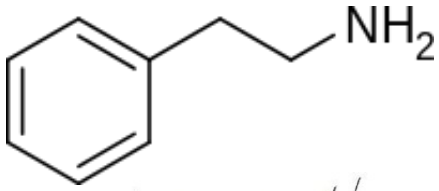


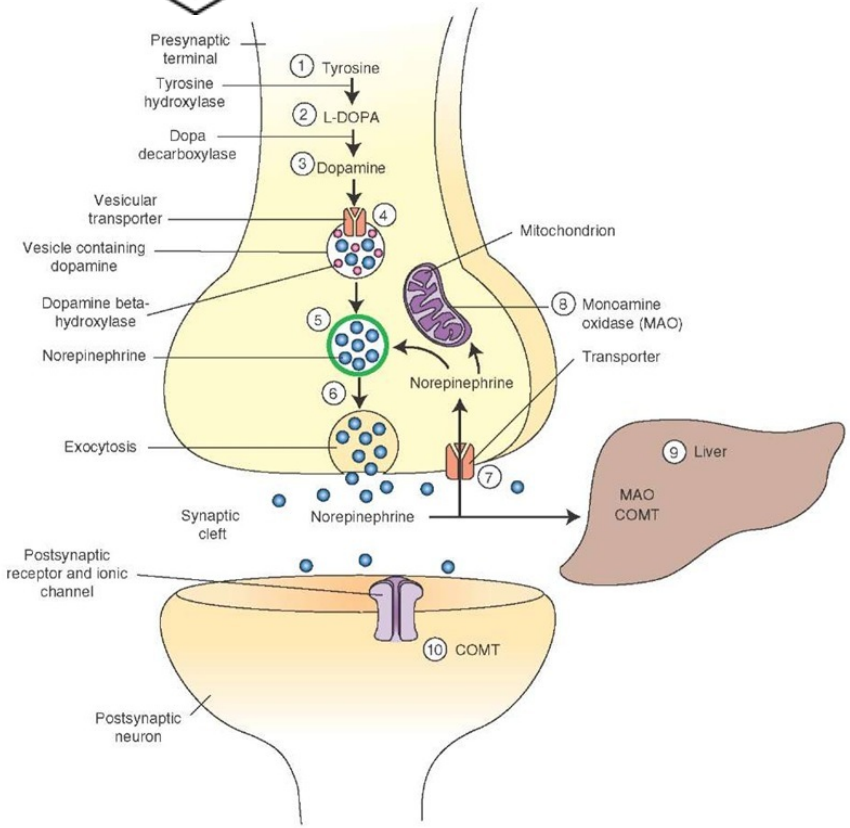


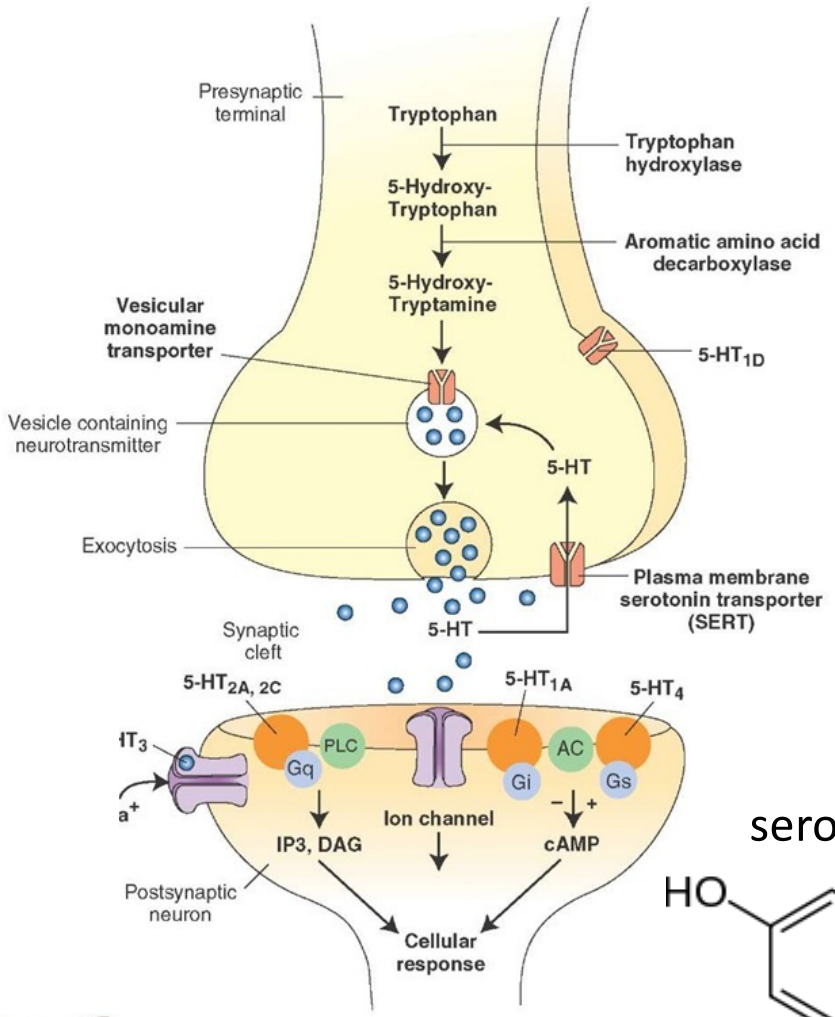
dopamine



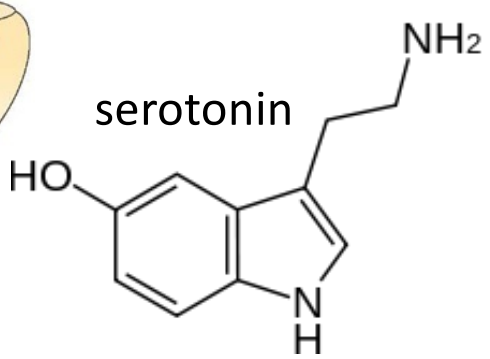
phenethylamine



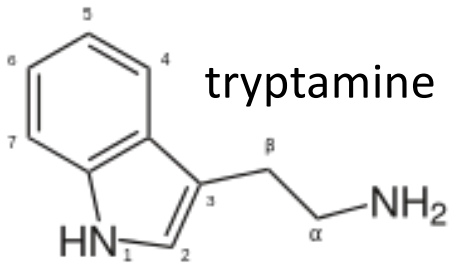




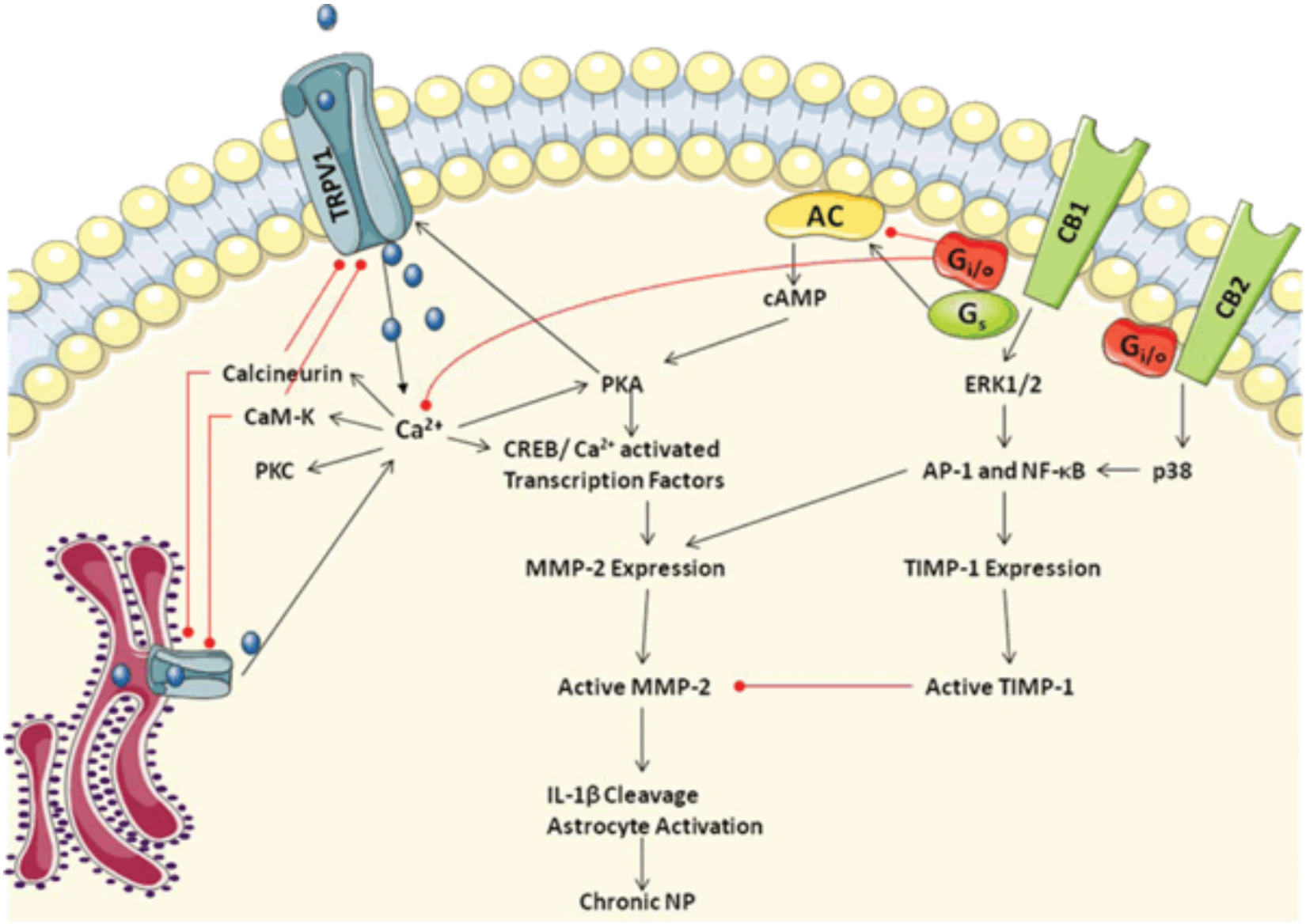
serotonin



tryptamine



http://what-when-how.com/neuroscience/neurotransmitters-the-neuron-part-4/



Pain modulation
Appetite modulation
Anti-inflammatory Response
Immune Response

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