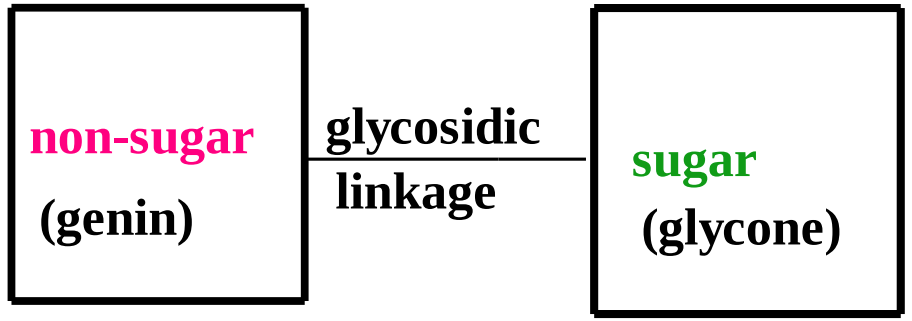
Glycosides

Cardioactive glycosides

LEC. 2

D. AMANI A. TAWFEEQ

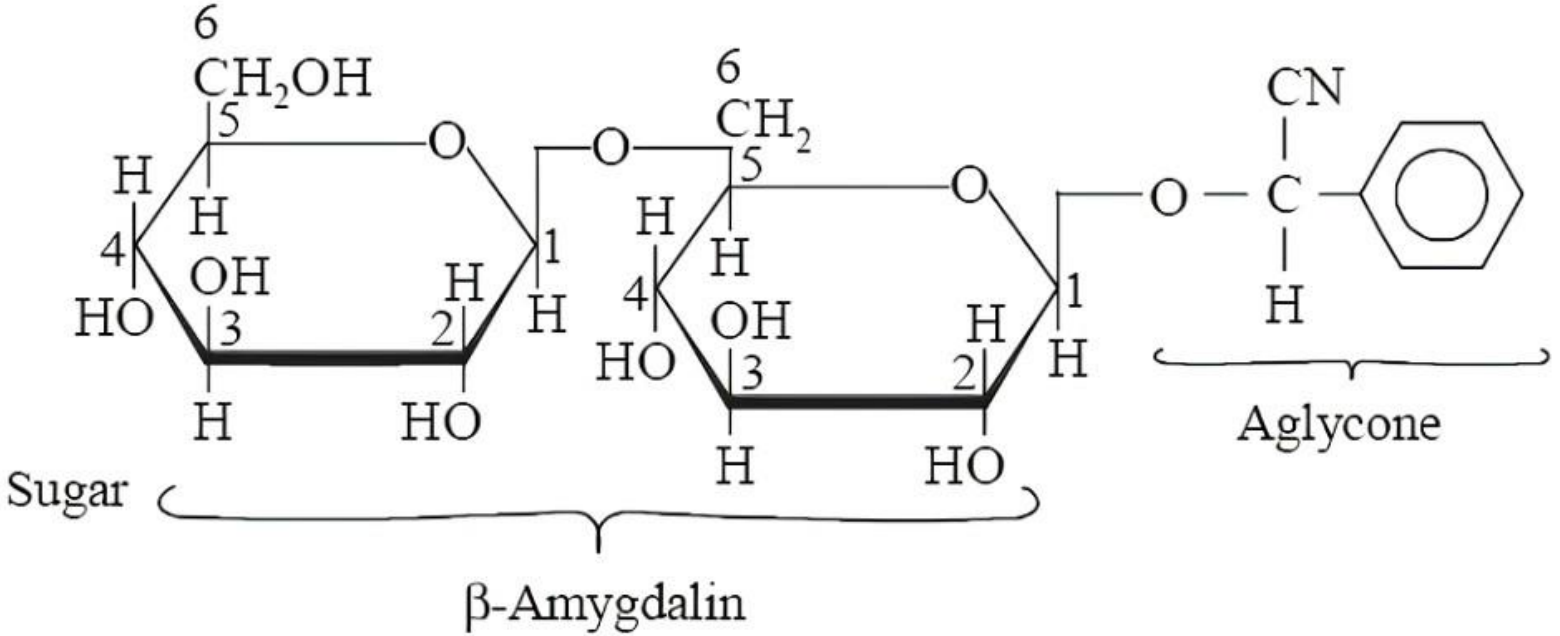
Glycosides

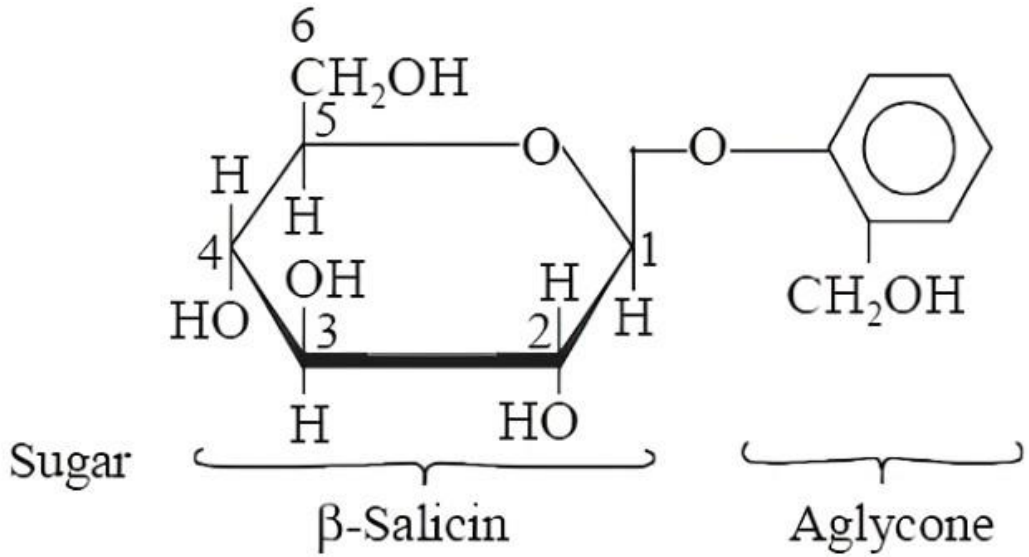


- Glycosides are compounds that contain a sugar molecule (glycone) bound to a non-sugar molecule (aglycone).Chemically, it is an acetal formed from the condensation of hemiacetal (hydroxyl gp. Of sugar) with hydroxyl gp. Of other sugar

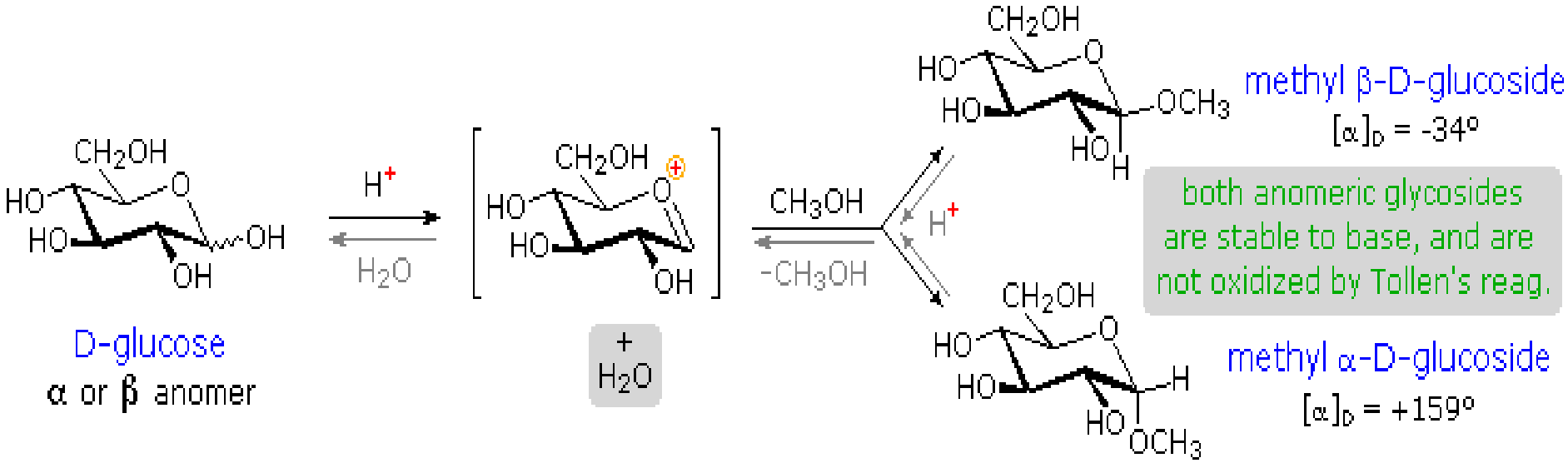
- The aglycon may be a secondary metabolite: a terpene, flavonoid, coumarine, or other natural product. Glycoside showed extra chemical diversity.

- The glycan, Among the sugars found in natural glycosides, D glucose is the most abundant one, L rhamnose and L-fructose also occur quite frequently. Of the pentoses : L-arabinose is more common than D-xylose.


Sugar
Aglycone
β-Amygdalin


Sugar
Aglycone
β-Salicin

Because of the cyclic structure of the sugar, two diastereoisomers of the glycoside exist depending on the configuration of the anomeric carbon. These diastereoisomers are called anomers and are designated as α and β. This classification depends on the glycosidic linkage (above the linkage is β), below the linkage is α.

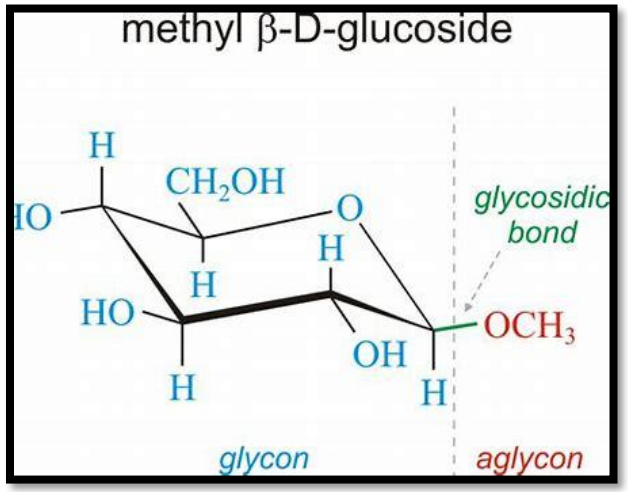


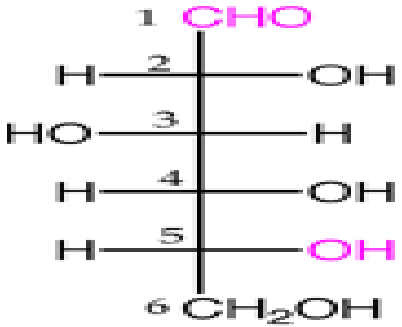
D-glucose
α or β anomer

methyl β-D-glucoside
$[\alpha]_D$ = -34°

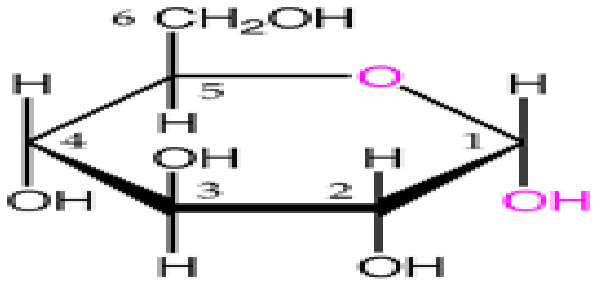
both anomeric glycosides are stable to base, and are not oxidized by Tollen's reag.

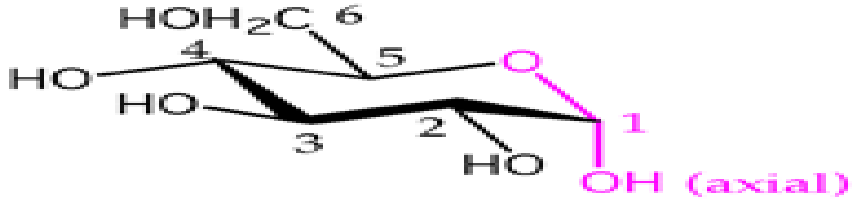
methyl α-D-glucoside
$[\alpha]_D$ = +159°



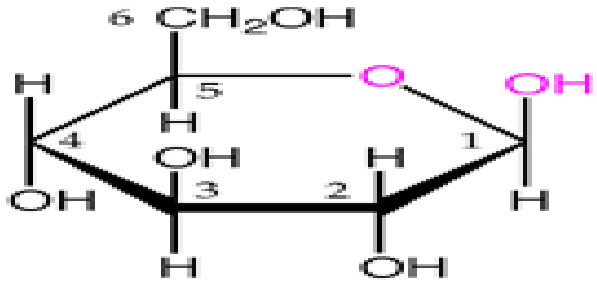


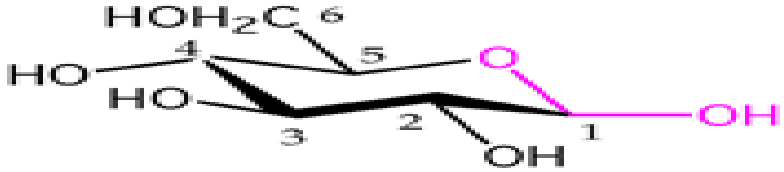
D-Glucose
(An aldohexose)



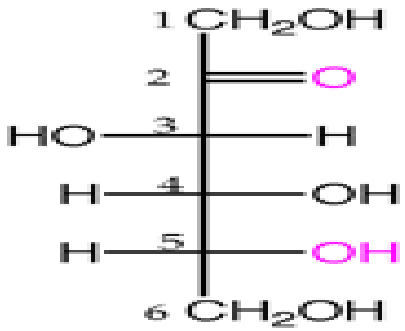


α-D-Glucopyranose
(The α anomer of Glucose, which is a six-membered ring, also called just α-D-Glucose)

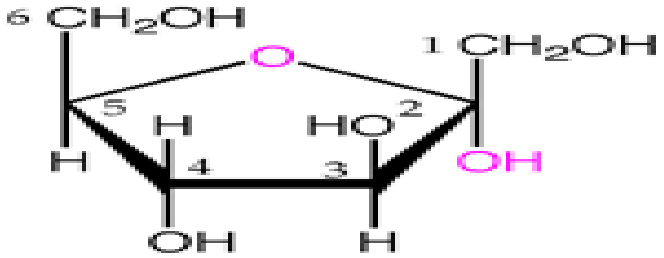




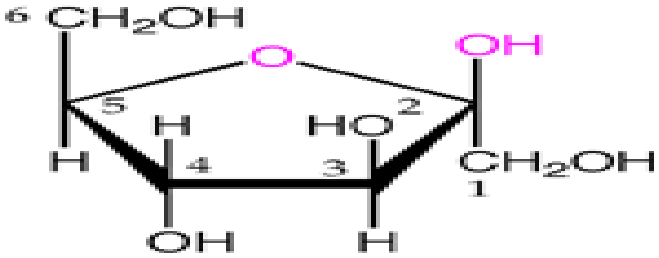
β-D-Glucopyranose
(The β anomer of Glucose, which is a six-membered ring, also called just β-D-Glucose)



D-Fructose
(A ketohexose)



α-D-Fructofuranose
(α-D-Fructose)

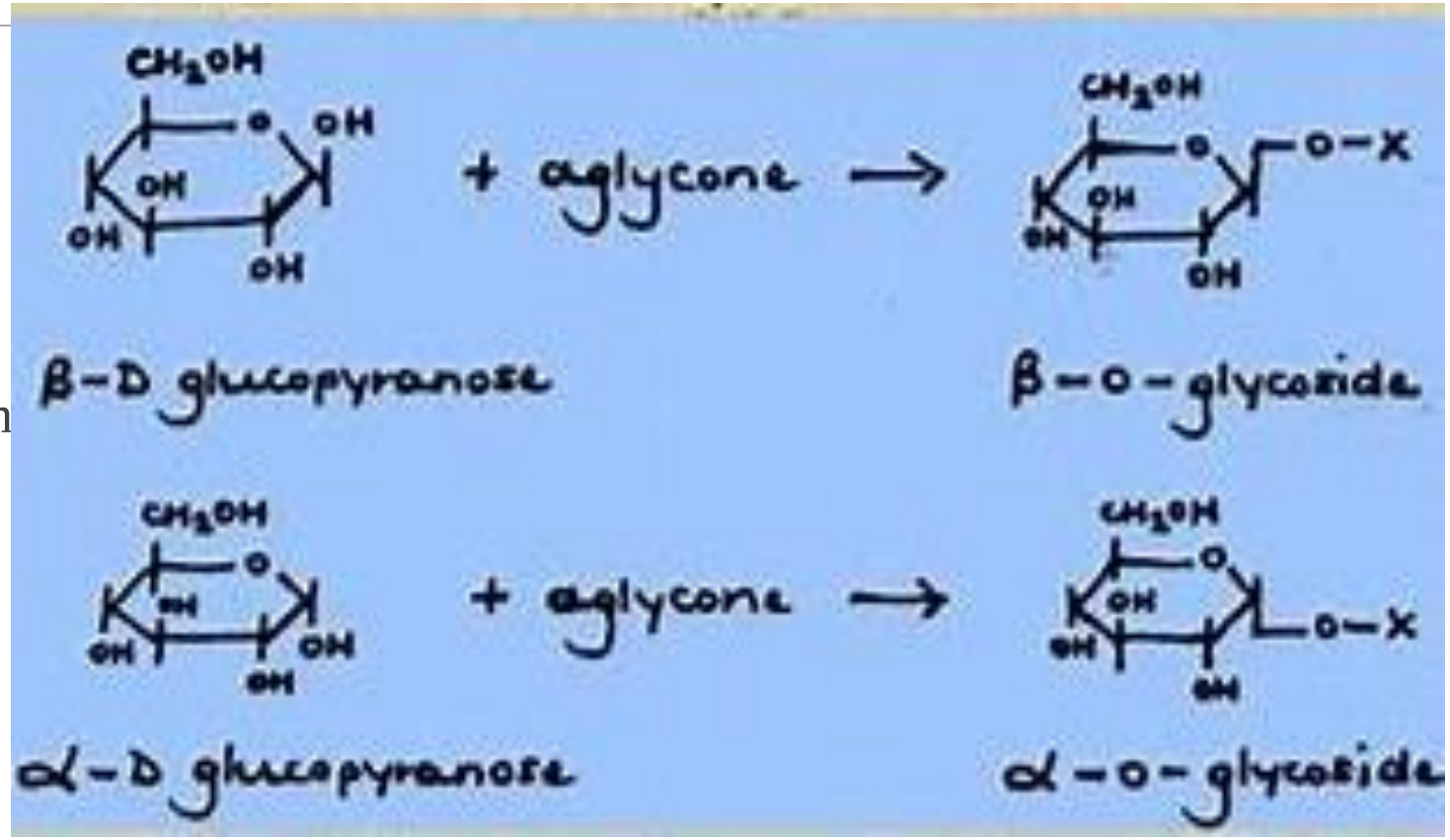


β-D-Fructofuranose
(β-D-Fructose)

sugar moiety of a glycoside can be joined to the aglycone via

- Oxygen atom (O-glycosides)
- Carbon atom (C-glycosides)
- Nitrogen atom (N-glycosides- Sulfur atom

(S-glycosides)



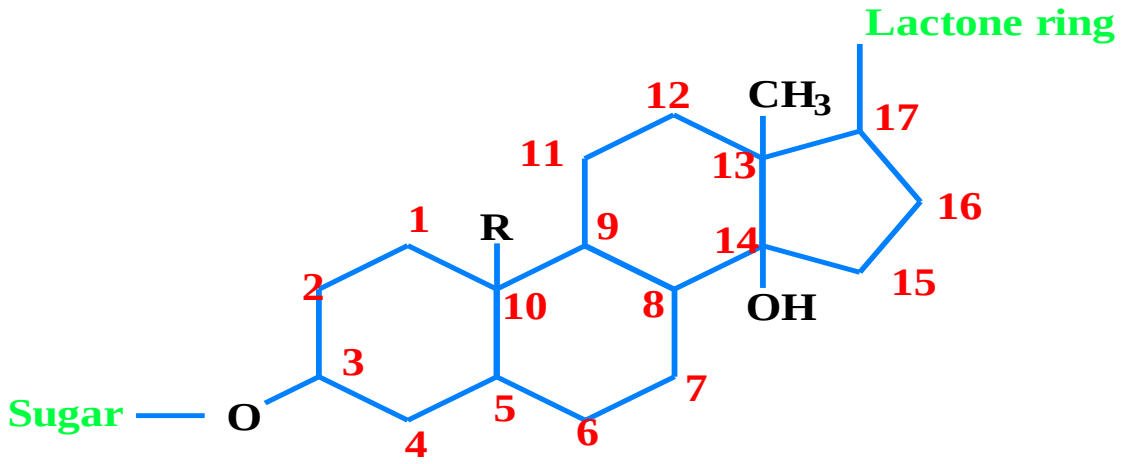
Classification:

- **Atom from the aglycone involved in the glycosidic linkage:**
  - Aglycone- O- Sugar — O-glycosides
  - Aglycone- C- Sugar — C-glycosides
  - Aglycone- S- Sugar — S-glycosides
  - Aglycone- N- Sugar — N-glycosides
- **Number of sugars:**
  - One sugar — monosides — e.g. Salicin.
  - Two sugar — Biosides — e.g. Diosmin.
  - Three sugars — Triosides — e.g. Digoxin.
- **Nature of the glycoside:**
  - Primary glycosides: Originally present in the plant — e.g. Purpurea A
  - Secondary glycosides: Resulted from removal of one sugar from the primary glycosides — e.g. Digitoxin

1- Cardioactive glycosides

The members of this group are characterized by their highly specific action on the cardiac muscle, increasing tone, excitability & and contractility.

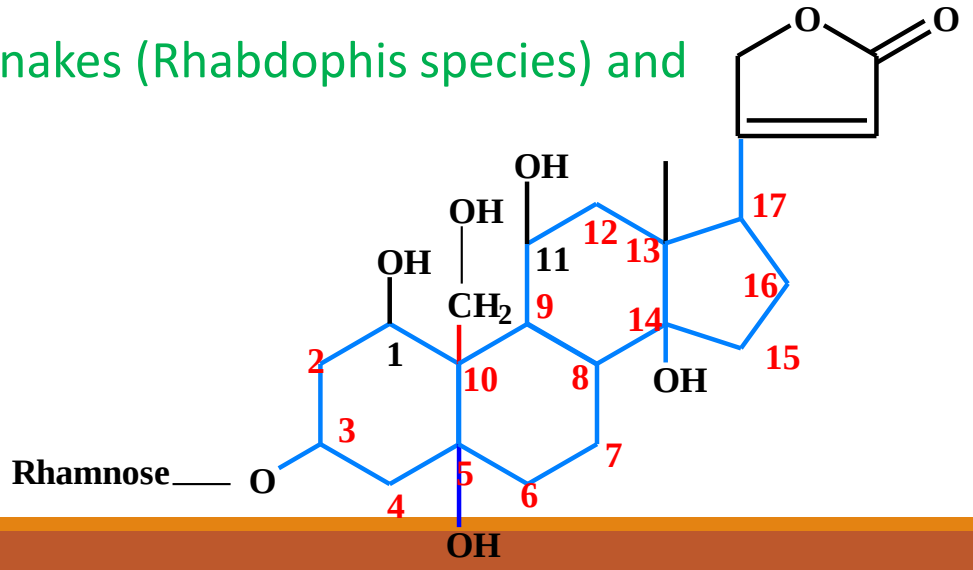
The aglycones of these glycosides are referred to as "cardiac genins". These aglycones are steroidal in nature, specifically, they are derivatives of cyclopenta-phenanthrene containing an unsaturated lactone ring at C_{17}.



- Chemically, two major groups of cardiac glycosides, namely **the cardenolides and bufadienolides, .**

- **1-Bufadienolides** are C-24 steroids and their glycosides and are characterized by a doubly unsaturated bond, six-membered (pentadienolide) lactone ring located at C-17β .

2-The lactone ring of the cardenolides is a single unsaturated bond, five-membered (butenolide) ring at that position . Numerous bufadienolides and their metabolites have been isolated, mainly from plants across the world, but also from toads of the genus Bufo, colubrid snakes (Rhabdophis species) and fireflies (Photinus species).

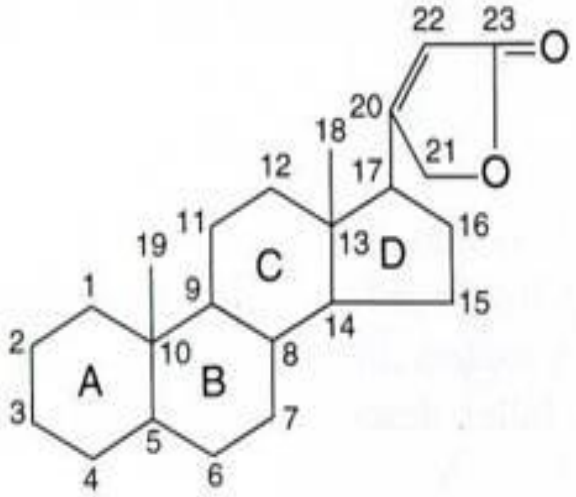


All cardio active glycosides are characterized by the following structural features:

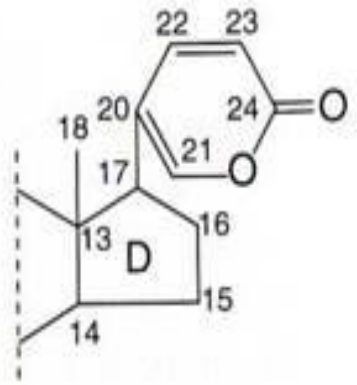
1. The presence of ***β*-OH** at position **C-3**, which is always involved in glycosidic linkage to a mono, di, tri, OR tetra saccharide.
2. The presence of another ***β*-OH** group at **C-14**.
3. The presence of unsaturated **5 or 6-** membered **lactone ring** at position **C-17**, also in the ***β*** configuration.
4. Additional **OH groups** may be present at **C-5, C-11** and **C-16.**
5. The **A/B** ring junction is usually **(cis),** while the **B/C** ring junction is always **(trans)** and the **C/D** ring junction is in all cases **(cis).**

This applies the word CATSC, where A means anti (trans not between two rings, & S means sin (cis not between two rings).

The rings are lettered and the carbon atoms are numbered.



Cardenolide

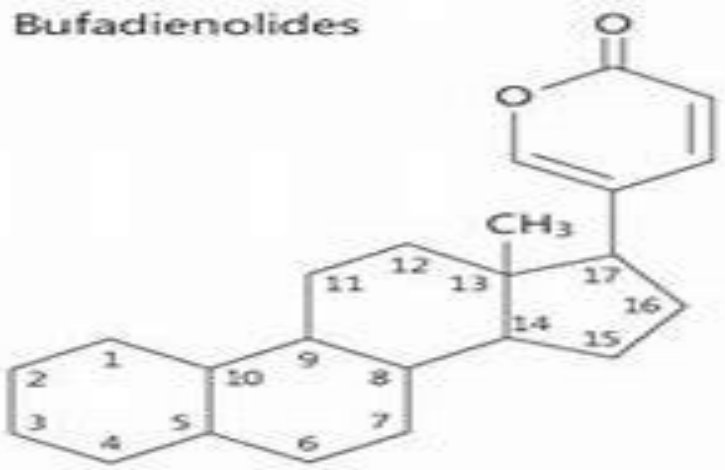


Bufadienolide

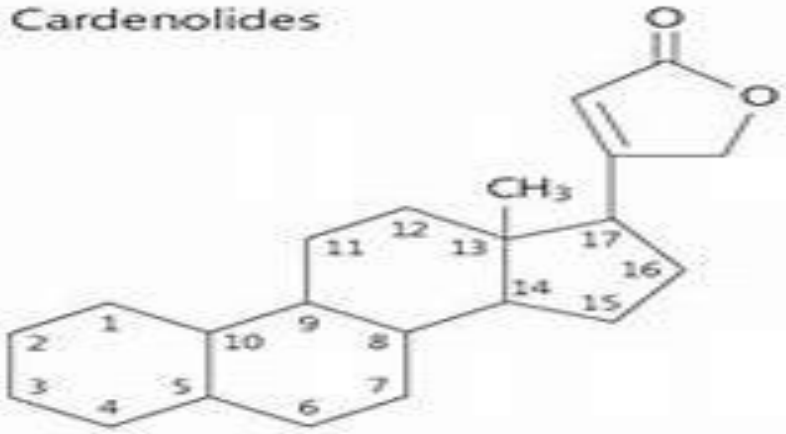
Cardio active Glycosides

The glycone portion at position **C-3** of cardiac glycosides may contain **four monosaccharide molecules** linked in series. Thus, from a single genin one may have a monoside, a bioside, a trioside or a tetroside.

Bufadienolides



Cardenolides

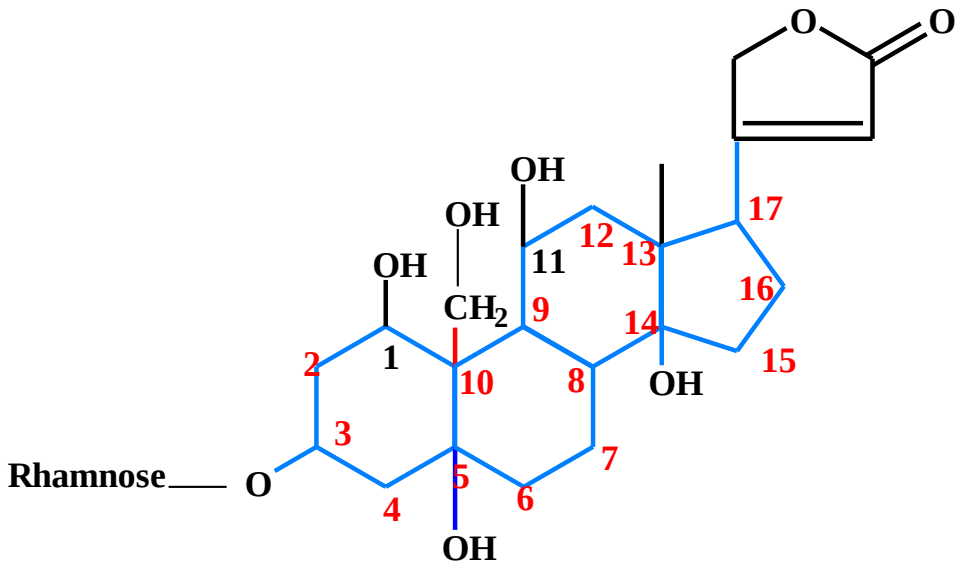


	1	3	5	10	11	12	14	16
Cardenolides								
Digoxin		$(Dig)_3$				OH	OH	
Digitoxin		$(Dig)_3$					OH	
Ouabain	OH	Rhamnose	OH	CH_2OH	OH		OH	

Nomenclature of cardioactive glycosides

- The sequence of systematic nomenclature is as follows:
- Arrange the functional groups starting from the least number & denote their configuration.
- Denote 5 whether α or β
- Denote the type of glycoside
- Denote the position & number of the double bonds

1β,3β, 5, 11β, 14, 19-hexa hydroxyl- 5β-card- 20(22)-en- 3-rhamnoside



General properties of Cardiac glycosides :

- ✓Amorphous powder
- ✓bitter taste
- ✓sol. In H2O
- ✓Insol. In Org. solvents
- ✓Very toxic compounds
- ✓ Odorless

Drugs (plants)containing cardioactive glycosides

1.Digitalis (Foxglove):

- It Is the dried leaf of ***Digitalis purpurea*** F: Scraphulariaceae. Digitalis is from the Latin digitus, meaning finger and refers to the finger-shaped corolla, purpurea is Latin & refers to the purple color of the flower

- The drug contains a large number of glycosides of which the most important from a medicinal viewpoint are: **digitoxin, gitoxin, & gitalxin.** The average concentration is about 0.16%. Nearly 30 other glycosides have been identified in the drug ex: purpura glycoside

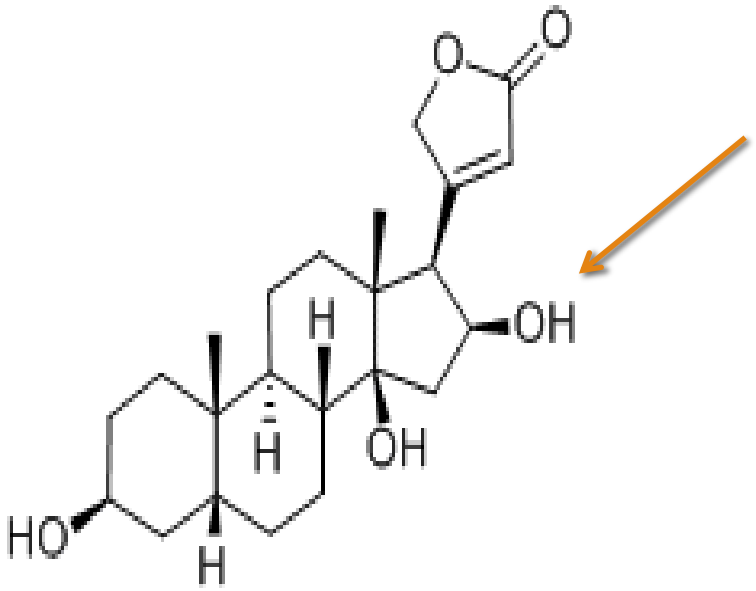
- Note: **Digitalis glycosides** contain angular methyl group at **C-10,** while **strophanthus glycoside** are characterized by the presence of either an **aldehydic** (CHO) or **primary alcoholic** ($C`H_2OH$) group at **C-10**

DIGITALIS PURPUREA

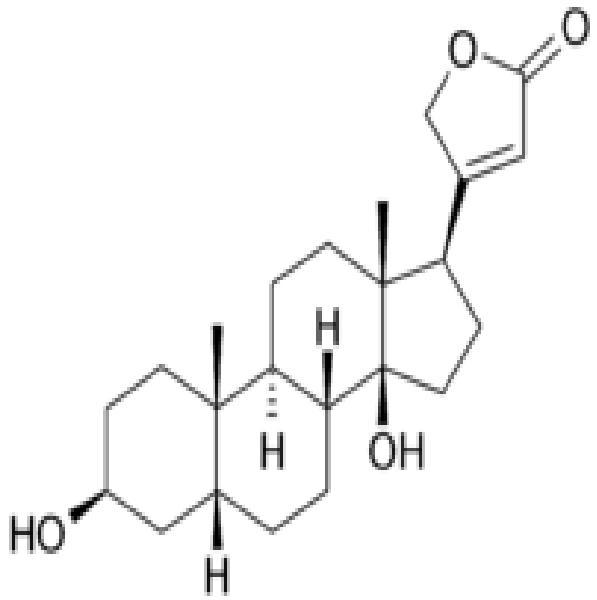
DIGITALIS LANATA

FAMILY PLANTAGINACEAE

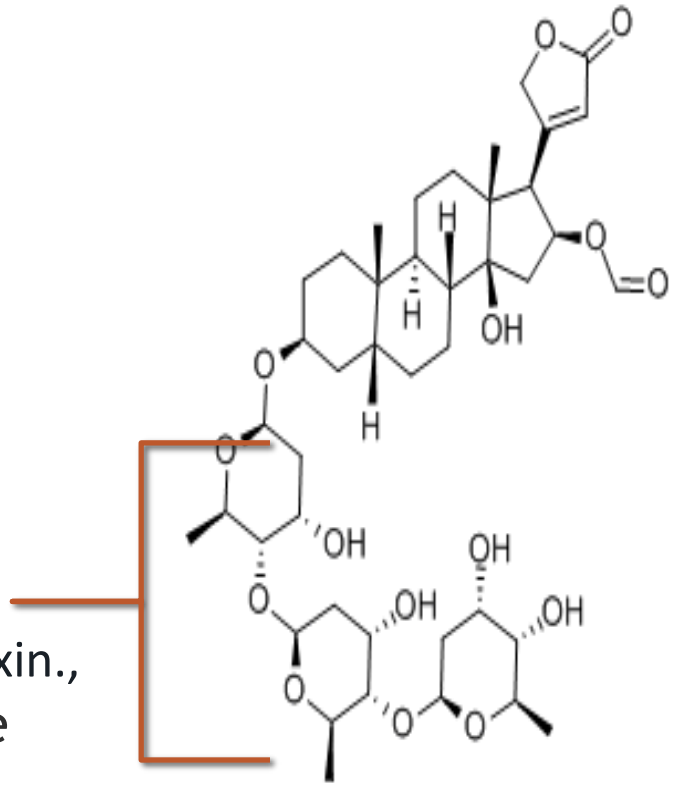
Gitoxigenin



Digitoxigenin



Gitaloxin



is a cardenolide which is the aglycon of digoxin.,
The steroid aglycon of digoxin, a lactone steroid containing a furan-2-one moiety

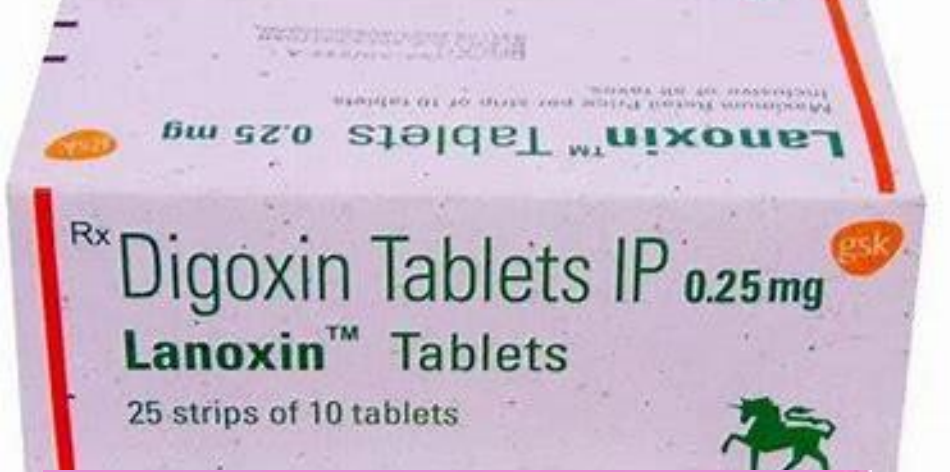
Digitalis lanata:

Nearly 70 different glycosides have been detected in the leaves of *Digitalis lanata*. All are derivatives of five different aglycones three of which (**digitoxigenin, gitoxin, & gitaloxin**) also occur in *D. purpurea*. The other two types of glycosides are derived from digoxigenin & diginatigenin occur in *D. lanata* but not in *D. purpurea.*

Digoxin

- Digoxin is a cardiac glycoside used as a drug in case of heart problems**, including congestive heart failure, atrial fibrillation or flutter, and certain cardiac arrhythmias**. It has a very narrow therapeutic window of the medication. Digoxin is a toxic substance with well well-known cardiotoxic effect.
- increase the force and speed of contraction of the heart.

{increase in cardiac output, an increase in cardiac work capacity without any increase in oxygen consumption}


Rx Digoxin Tablets IP 0.25 mg
Lanoxin™ Tablets
25 strips of 10 tablets


actavis
Digoxin Tablets
125 micro-grams
28 tablets
For oral use


NDC 49884-494-01 100 Tablets
Digoxin Tablets, USP
250 mcg (0.25 mg)
LA494-01-3
Rx only
Each scored tablet contains
250 mcg (0.25 mg).
Distributed by Par Pharmaceutical
Chestnut Ridge, NY 10977 U.S.A.
Mfd. by
Patheon Manufacturing Services LLC.
Greenville, NC 27834
Made in Germany
017152
PAR


NDC 0641-1410-35
Digoxin Injection, USP
500 mcg/2 mL
Rx only
0.5 mg/2 mL (250 mcg/mL)
FOR SLOW INTRAVENOUS OR
DEEP INTRAMUSCULAR USE
DILUTION IS NOT REQUIRED
25 x 2 mL Ampuls
WEST-WARD


DIGOXIN :
Indications :
Atrial fibrillation
Heart failure
Contraindications :
Ventricular fibrillation
Ventricular tachycardia
Arrhythmia

Mechanism of Action of Digoxin:

Digitoxin and digoxin inhibit sodium–potassium activated adenosine triphosphatases (i.e., Na+/K+-ATPase) in the myocardium, which results in a concurrent efflux of potassium and an influx of sodium to the cells.(The glycosides are thought to act at the membrane level, by inhibition of the Na-K ATPase, which would result in an increase of the intracellular calcium ion concentration.)

- **Effects:**

- Ingestion may cause nausea, abdominal pain, vomiting, cardiac dysrhythmias, and hyperkalemia.
- The cardiac glycosides are gastrointestinal irritants, may be responsible for a variety of cardiac arrhythmias (e.g., irregular pulse, bradycardia, rapid thready pulse, ventricular fibrillation), and can be fatal

Drug-drug and food interactions

- Your body may not absorb this drug as well if you also eat foods that are high in fiber or if you take certain medications. Take this medication at least 2 hours before or after eating food products that are high in fibre (such as bran).

- If you are taking antacids, kaolin-pectin, milk of magnesia, metoclopramide, sulfasalazine, or aminosalicylic acid, take them as far apart from your digoxin dose as possible.
- Other medications can affect the removal of digoxin from your body, which may affect how digoxin works. Examples include azole antifungals (such as itraconazolemacrolide antibiotics (such as clarithromycin, erythromycin.

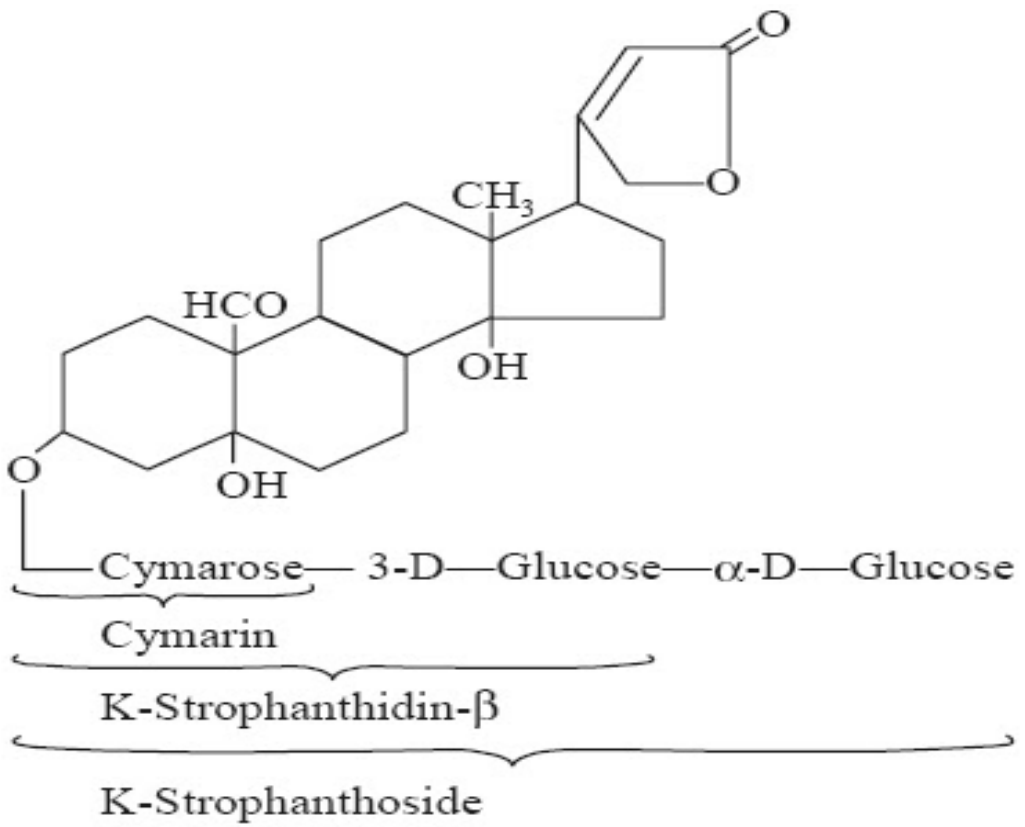
2.*Strophanthus:*

Is the dried ripe seeds of *Strophanthus kombe* or *Strophanthus hispidus* F: Apocyanaceac. Strophanthus is from the Greek meaning " a tune or twist " & refer to the twisted lobes of the corolla; hispidus means hairy, referring to the hairy character of the plant.

Kombe is a native African name for the seed.

strophanthoside

Structure of K-strophanthoside
Strophanthoside is used as a cardiac stimulant and diuretic.

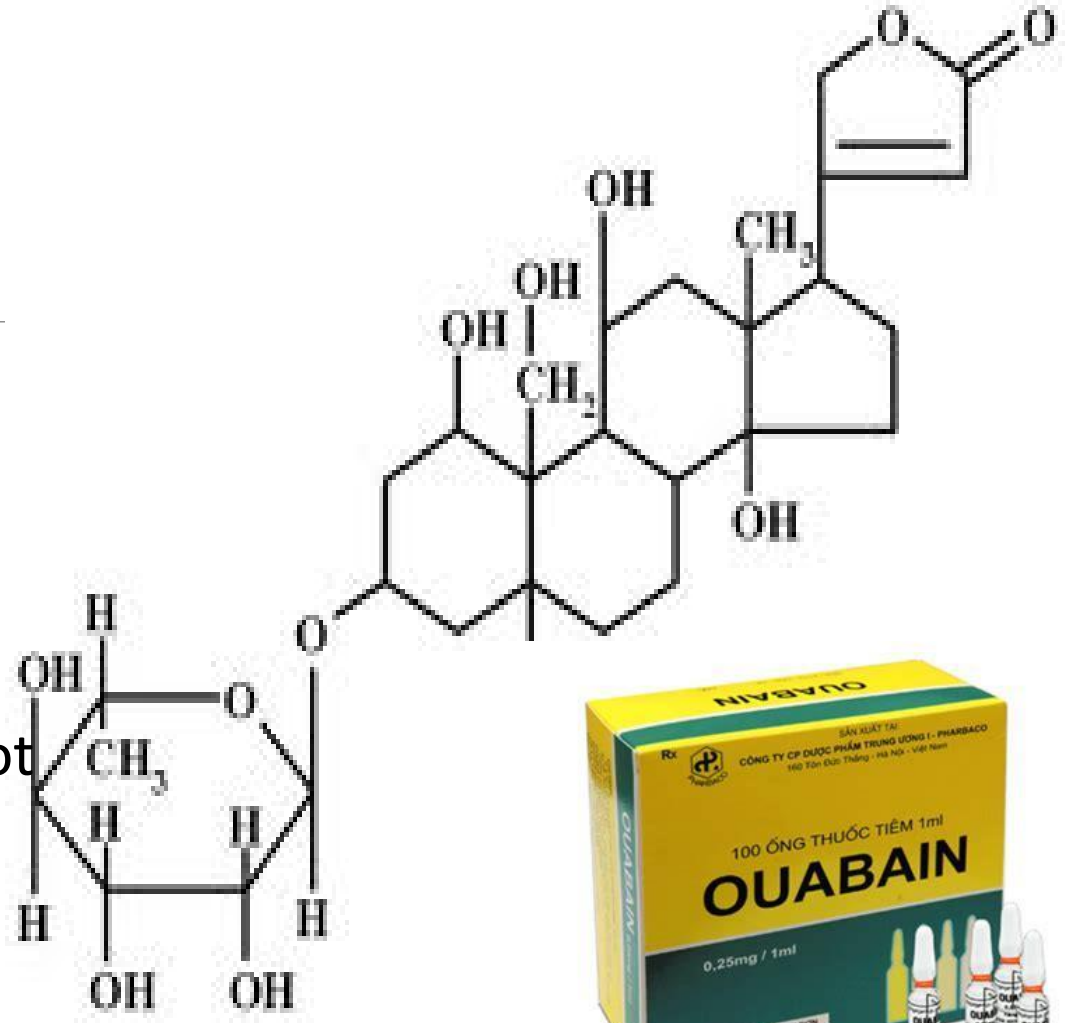


ouabain

Ouabain (G-strophanthin) is obtained from S. gratus

Ouabain is a cardio tonic used i.v. for prompt therapeutic effect. It is absorbed so slowly & so irregularly from the GIT that oral administration is not recommended & is even considered un safe.

- Ouabain is a steroid hormone that is a multi-hydroxylated alpha-L-rhamnosyl cardenoloide (consisting of rhamnose and ouabagenin).



Structure of ouabain (sugar is rhamnose)

3. Squill:

Is the cut & dried fleshy inner scales of the bulb of the white variety of *Urginea maritima* known in commerce as white or Mediterranean squill, or of *Urginea indica* known in commerce as Indian squill F: Liliaceae.

- It is a very variable plant, the bulb differing greatly in size and colour, and the leaves of the flower presenting similar varieties, which has led to the formation of several species, about twenty-five species having been described. Two varieties of Squill, termed respectively *white* and *red*.
- contain the three bitter glucosidal substances Scillitoxin, Scillipicrin and Scillin
- Squill stimulates the bronchial mucous membrane and is given in bronchitis after subsidence of the acute inflammation.

4. Oleander:

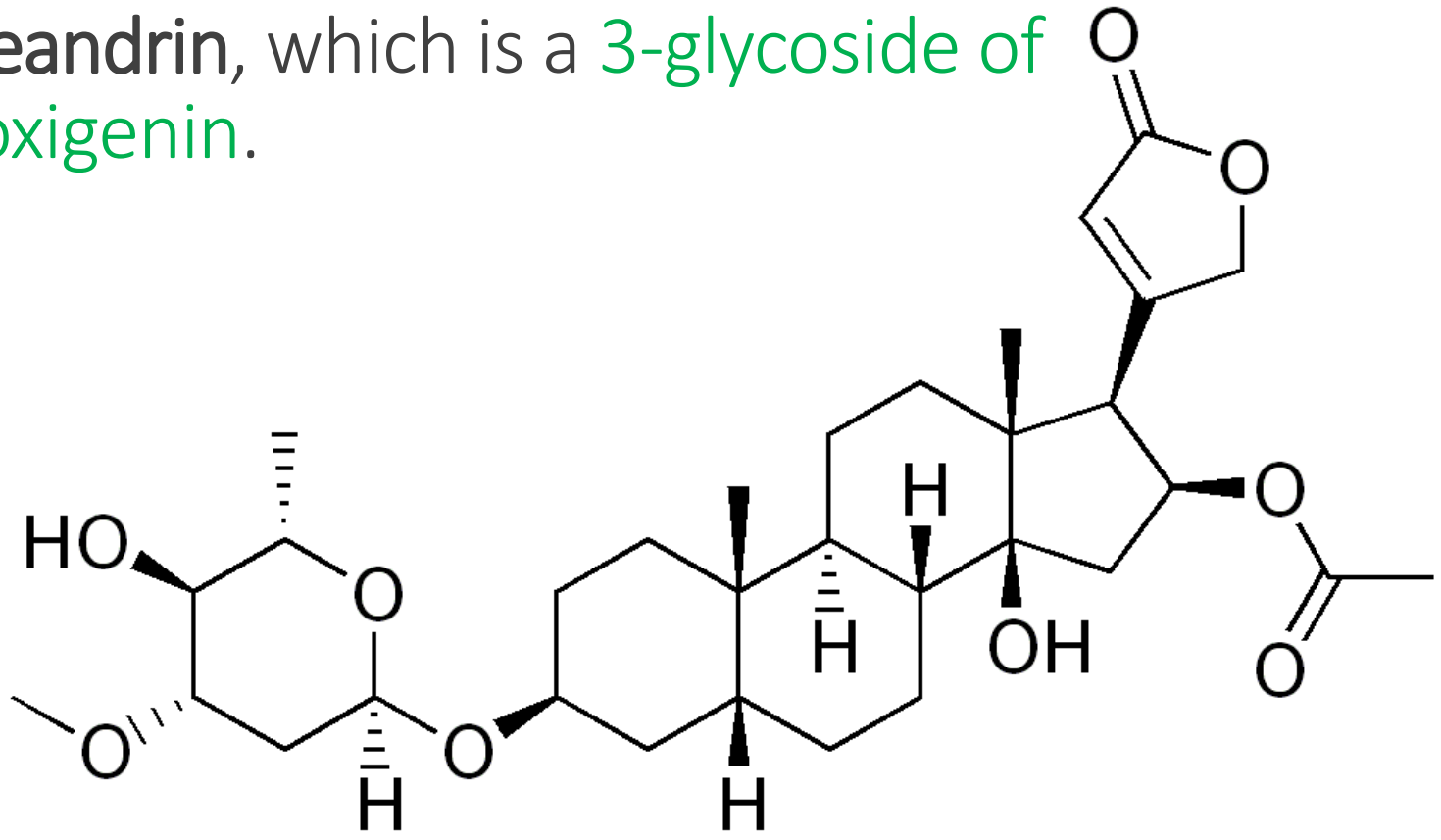
Is the dried leaves of *Nerium oleander* F: Apocyanaceae. It has been used to treat cardiac insufficiency

oleandrin

Uses: as an expectorant but it also possesses emetic, cardio tonic & diuretic properties. The usual dose is 100mg .

Note: For oleander, all parts of the leaf are poisonous; a single well-chewed leaf has been reported to be lethal. Foxglove leaves and seeds are toxic

- The main constituent is **oleandrin**, which is a 3-glycoside of 16-acetyl derivative of gitoxigenin.



The End