Today's slides

I. Anticoagulants

A. Oral anticoagulants

- Coumarin derivatives
- 1,3-indandione and 1,3-indandione-derived drugs

B. Parenteral anticoagulants

- Heparins

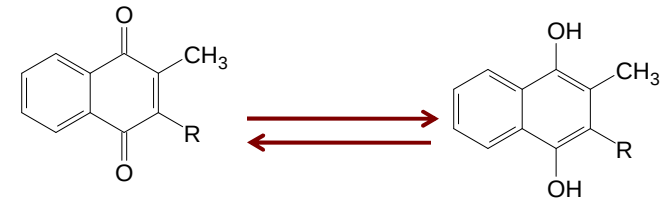
A. Oral anticoagulants-

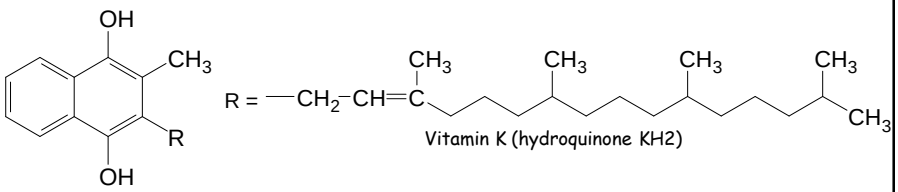
1). Coumarin derivatives

a. Vitamin K-"Koagulations"-Coagulants

b. MOA of courmarin derivatives

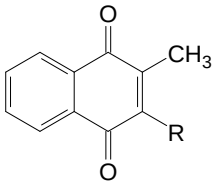
c. SARs for courmarin





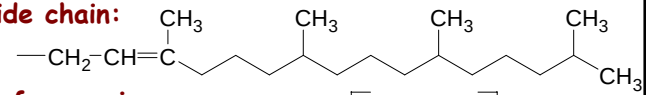
Vitamin K (hydroquinone KH2)

- Vitamin K
  - Natural products
    - Vitamin K1 and Vitamin K2
      - Hydrophobic
      - K2 is produced by the bacteria in human intestine
  - Synthetic forms
    - K3, K4, and K5

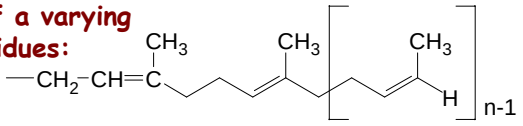


Vitamin K (Naphthoquinone)

For K1, R is a phytyl side chain:

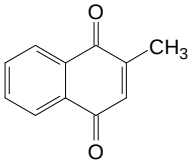


For K2, R is composed of a varying number of isoprenoid residues:



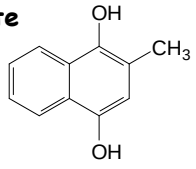
Vitamin K3

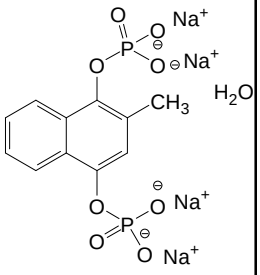
- Menadione,
- 1,4-naphthoquinone



Vitamin K4

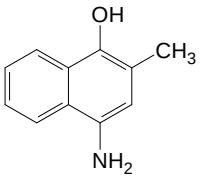
- Menadiol and Mendiol diphosphate
- 2-methylnaphthalene-1,4-diol
- Water-soluble





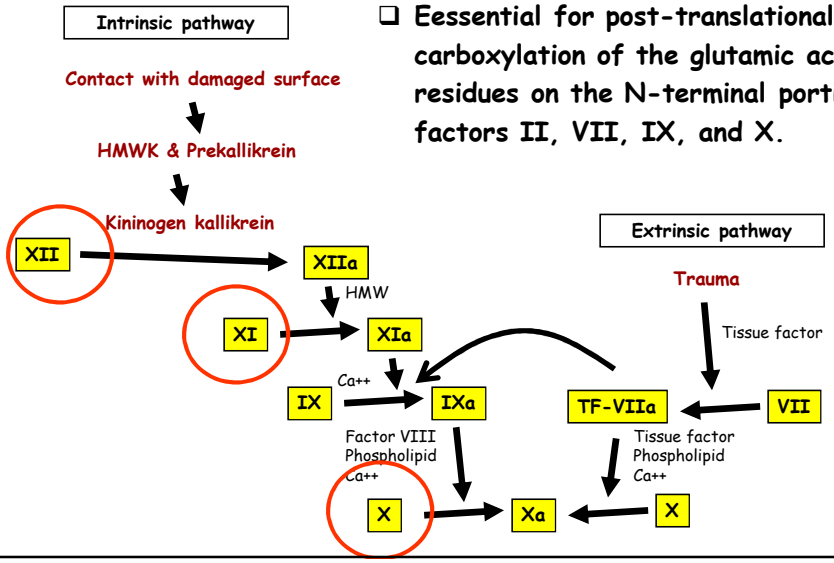
Vitamin K5

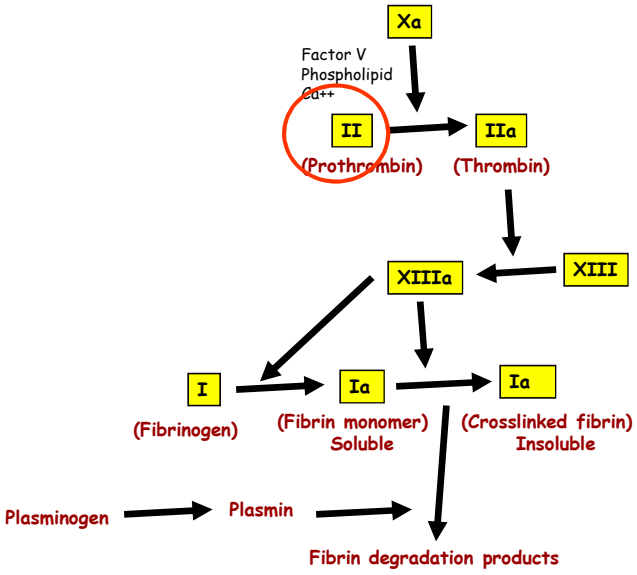
- 4-amino-2-methyl-1-naphthol
- Anti-fungi agent

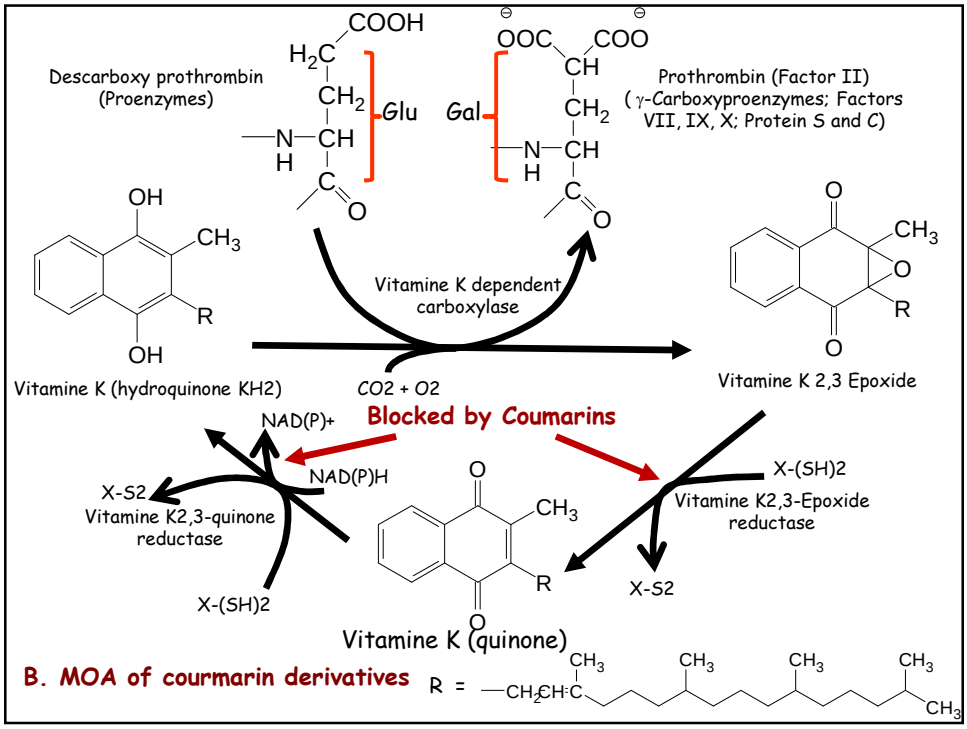


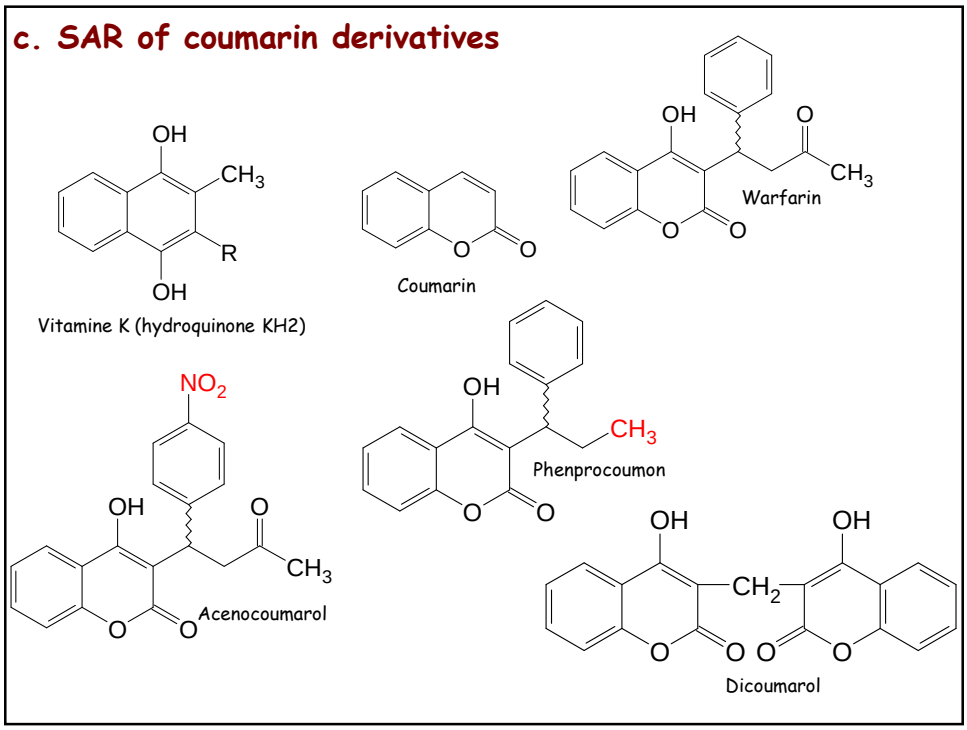
MOA and therapeutic uses of Vitamin K

- ❑ Coenzyme
- ❑ Coagulant
- ❑ Prosthetic
- ❑ Eessential for post-translational carboxylation of the glutamic acid residues on the N-terminal portions of factors II, VII, IX, and X.

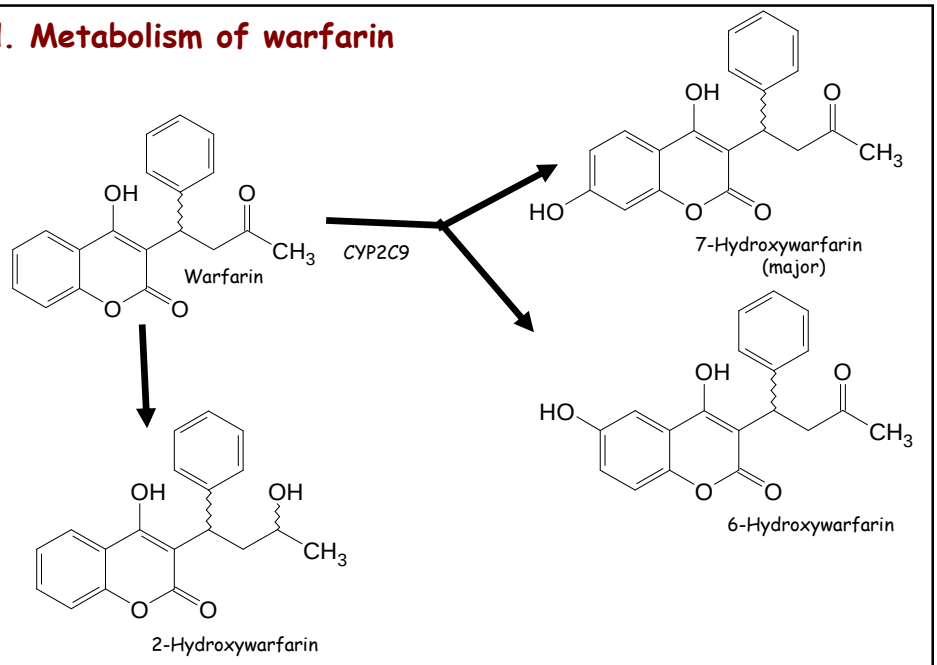




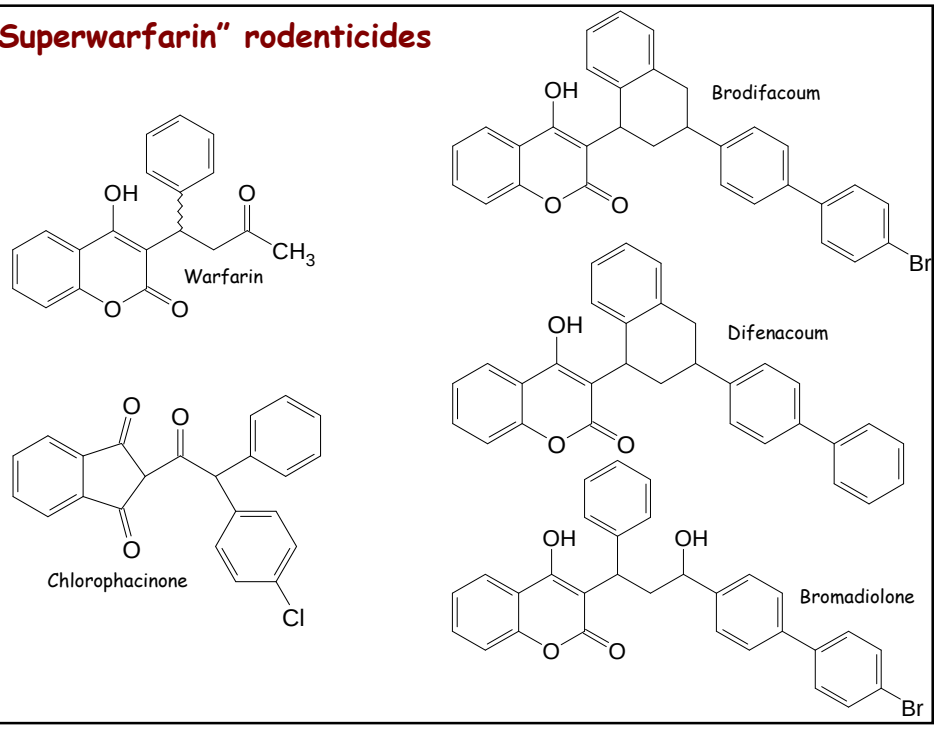

Descarboxy prothrombin
(Proenzymes)
Glu
Gal
Prothrombin (Factor II)
(γ-Carboxyproenzymes; Factors
VII, IX, X; Protein S and C)
Vitamine K dependent
carboxylase
Vitamine K (hydroquinone KH2)
CO2 + O2
Vitamine K 2,3 Epoxide
NAD(P)+
Blocked by Coumarins
NAD(P)H
X-S2
Vitamine K2,3-quinone
reductase
X-(SH)2
X-(SH)2
Vitamine K2,3-Epoxide
reductase
X-S2
Vitamine K (quinone)
B. MOA of courmarin derivatives
R =


c. SAR of coumarin derivatives
Vitamine K (hydroquinone KH2)
Coumarin
Warfarin
Phenprocoumon
Acenocoumarol
Dicoumarol

d. Metabolism of warfarin



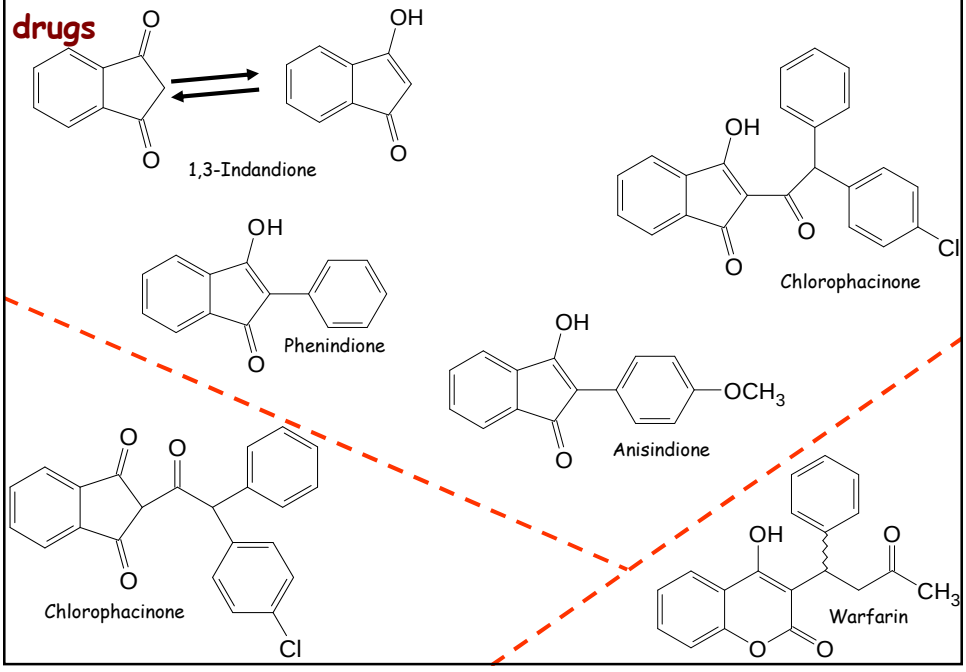
"Superwarfarin" rodenticides



2). 1,3-indandione and 1,3-indandione-derived drugs

- Structural similarity to wafarin
- MOA and pharmaceutical properties are similar to wafarin
- Cross-allergic reactions between wafarin and indandione-derived drugs
- More renal and hepatic toxicity

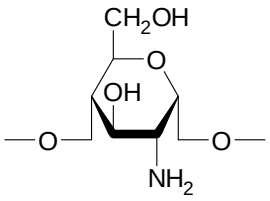
2). 1,3-indandione and 1,3-indandione-derived drugs

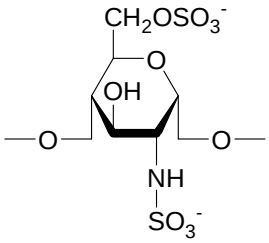


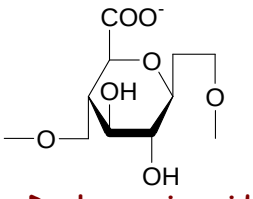
B. Parenteral anticoagulants (Heparin-based)

- High-molecular-weight heparin
  - Unfractionated
  - 5-30 kDa (mean 15 kDa)
- Low-molecular-weight heparin
  - 4-6 kDa

Chemistry

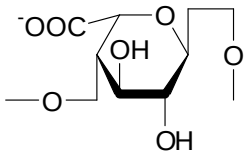


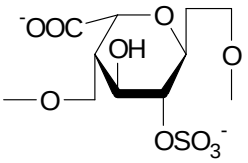




D-glucuronic acid

N-Acetyl-D-glucosamine and it sulfated derivative

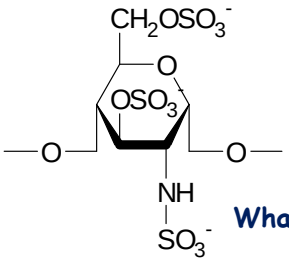


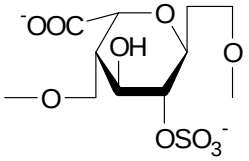


L-iduronic acid and its sulfated derivative

Chemistry

3-O-sulfate and 2-O-sulfate derivatives

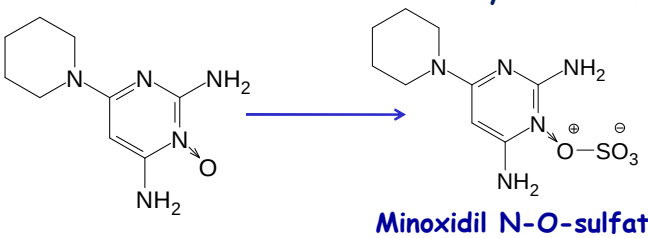




What has been transferred, sulfate or sulfonate?

Golgi associated sulfotransferases

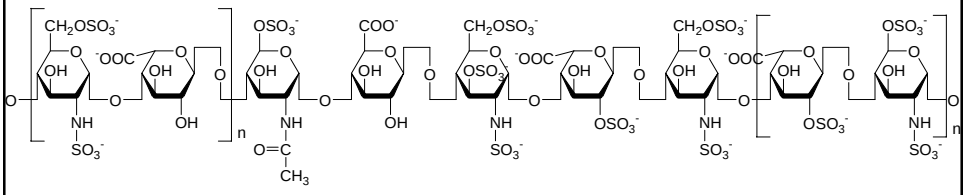
Cytosolic sulfotransferases

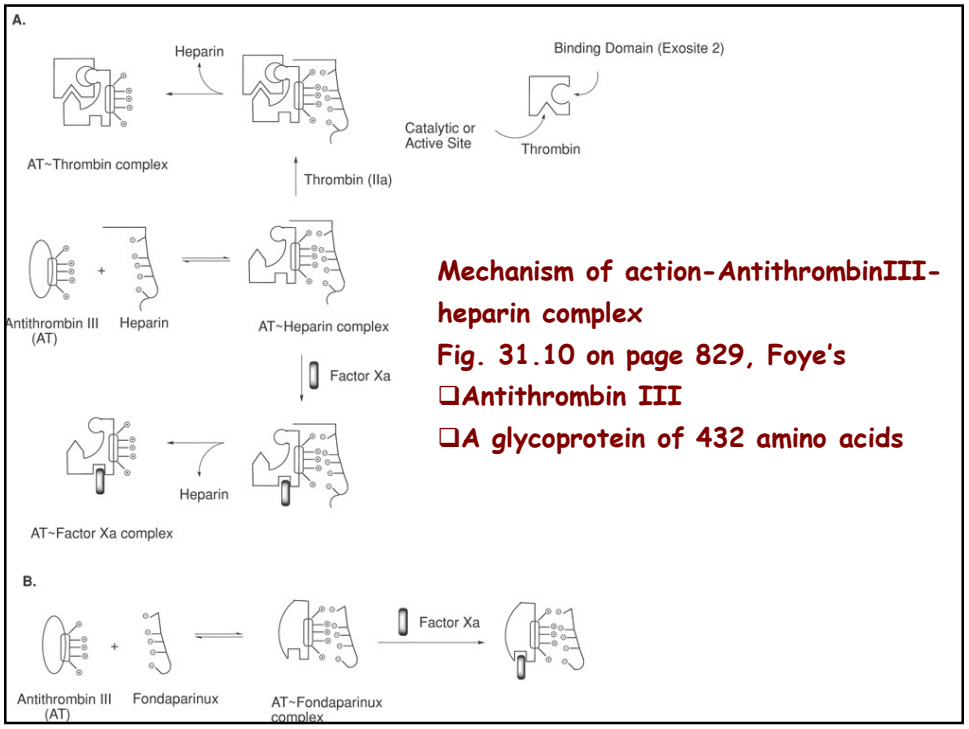


Minoxidil N-O-sulfate

Heparin and heparin sulfate

- Endogenous substance
  - Polymers
- Biosynthesis
  - Glycosyltransferases
  - Sulfotransferases
  - Epimerase





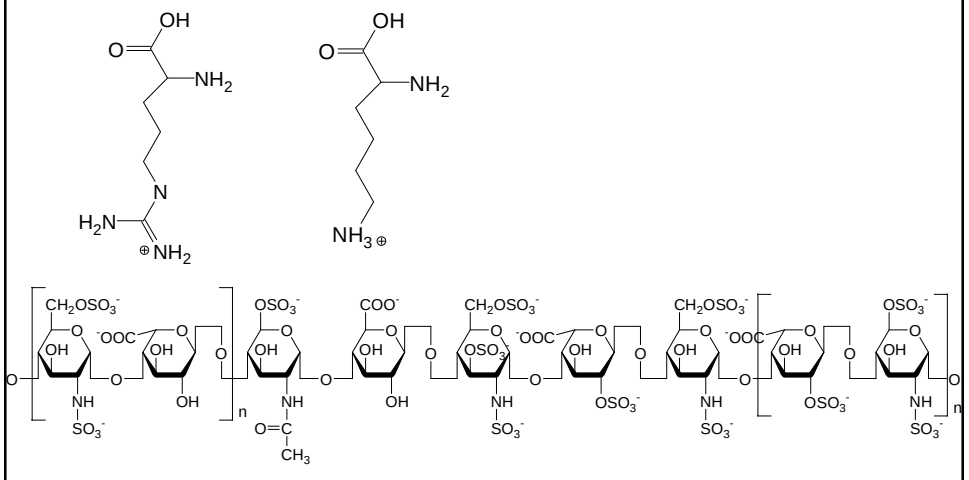
Mechanism of action-AntithrombinIII-heparin complex

Fig. 31.10 on page 829, Foye's

- **Antithrombin III**
- **A glycoprotein of 432 amino acids**

Mechanism of action-Antithrombin III-heparin complex

Ionic binding between sulfate and carboxylate anions in heparin and arginine and lysine cations in Antithrombin III



Pharmacokinetics

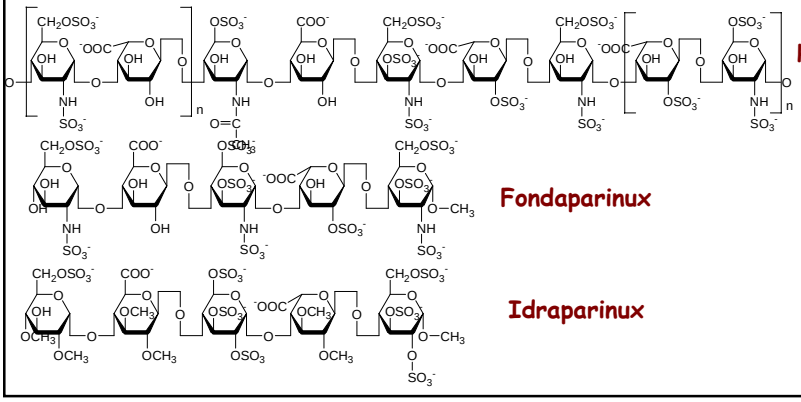
- Unfractionated heparin, or HMWH, and Low molecular weight heparin, or LMWH
  - Nonspecific binding of HMWH results in a low absorption rate.

Specific drugs and their pharmacokinetics

- HMWH
  - 5-30 kDa
  - b.i.d.; q.i.d.
  - Nonspecific binding
    - High plasma protein binding affinity
  - A low absorption rate.
- LMWH
  - 2-7 kDa
  - q.d.
  - Relatively low protein binding affinity
  - Better bioavailability

Specific drugs and their pharmacokinetics

- Newer heparin development
  - Fondaparinux and idraparinux
    - Synthetic
    - The antithrombin III complex binds only to Factor Xa but not thrombin
    - Excellent bioavailability
    - Little or no protein binding affinity



Heparin

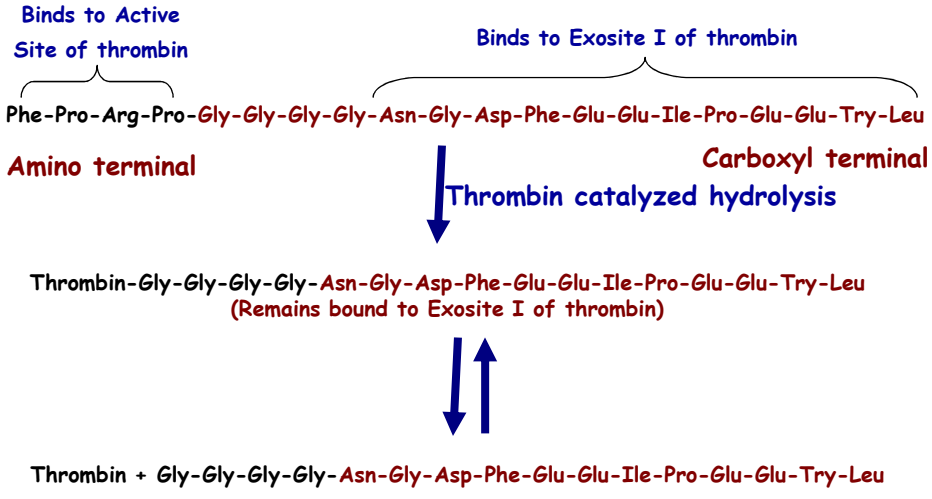
Fondaparinux

Idraparinux

II. Direct thrombin inhibitors

- Direct thrombin inhibitors
  - History of drug development
  - Lead compound
    - Hirudin, a small protein (65 amino acids) isolated from the salivary glands of the medicinal leech (Hirudo medicinalis)
    - Recombinant proteins is used for anti-coagulant therapy and research
  - Lead modification
    - Hirulogs, small peptidomimetric analogues of Hirudin
      - Recombinant analogues
        - Lepirudin
        - Desirudin
      - Bivlirudin (20 amino acids)

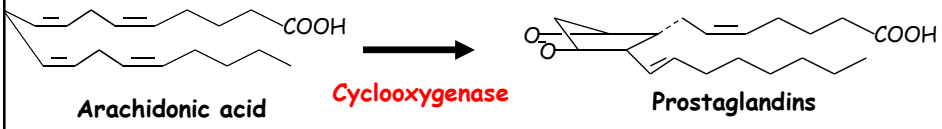
Bivlirudin-Chemical structure, binding sites to thrombin, and release from thrombin



III. Aspirin (Antiplatelet).

Cell membrane phospholipids

↓ PhospholipaseA2



Classification of non-steroidal anti-inflammatory drugs (NSAIDs) by chemical structure

- **Pyrazolones**
  - Phenylbutazone
- **Carboxylic acids**
  - **Salicylates**
    - Acetylsalicyclic acid (Aspirin)
  - **Arylalkanoic acids**
    - Ibuprofen, Naproxen, Fenorpofen, Fenbufen, Ketoprofen, Flurbiprofen
    - **Indolacetic acids**
      - Indomethacin
    - **Pyrrolacetic acids**
      - Ketorolac
    - **Phenylacetic acids**
      - Diclofenac
  - **Anthranilic acids**
    - Mefenamic acid, Floctafenine
- **Oxicams**
  - Piroxicams

Wall and Melzack's Textbook of Pain