COAGULANTS AND ANTICOAGULANTS

Learning outcomes

At the end of topic , students are able to …

1. Explain the process of coagulation
2. Classify coagulant and anticoagulant drugs.
3. Explain the chemistry and SAR of anticoagulant drugs
4. Differentiate between coagulant and anticoagulant drugs.
5. Write the synthetic route of warfarin

COAGULANT

Haemostasis (arrest of blood loss) and blood coagulation involve complex interactions between the injured vessel wall, platelets and coagulation factors.

The coagulation factors (proteins) are manufactured by the liver.

- Ionized calcium (Ca++) is available in the blood and from intracellular sources.

- Phospholipids are prominent components of the cellular and platelet membranes.

- They provide a surface on which the chemical reactions of coagulation can take place.

Coagulation factors

Factor I—Fibrinogen
Factor II—Prothrombin
Factor III—Tissue thromboplastin (tissue factor)
Factor IV—Ionized calcium (Ca++)
Factor V—Labile factor or proaccelerin
Factor VI—Unassigned
Factor VII—Stable factor or proconvertin
Factor VIII—Antihaemophilic factor
Factor IX—Plasma thromboplastin component, Christmas factor
Factor X—Stuart–Prower factor
Factor XI—Plasma thromboplastin antecedent
Factor XII—Hageman factor
Factor XIII—Fibrin stabilizing factor

Mechanism of Blood Clotting

Coagulation can be initiated by either of the two distinct pathways

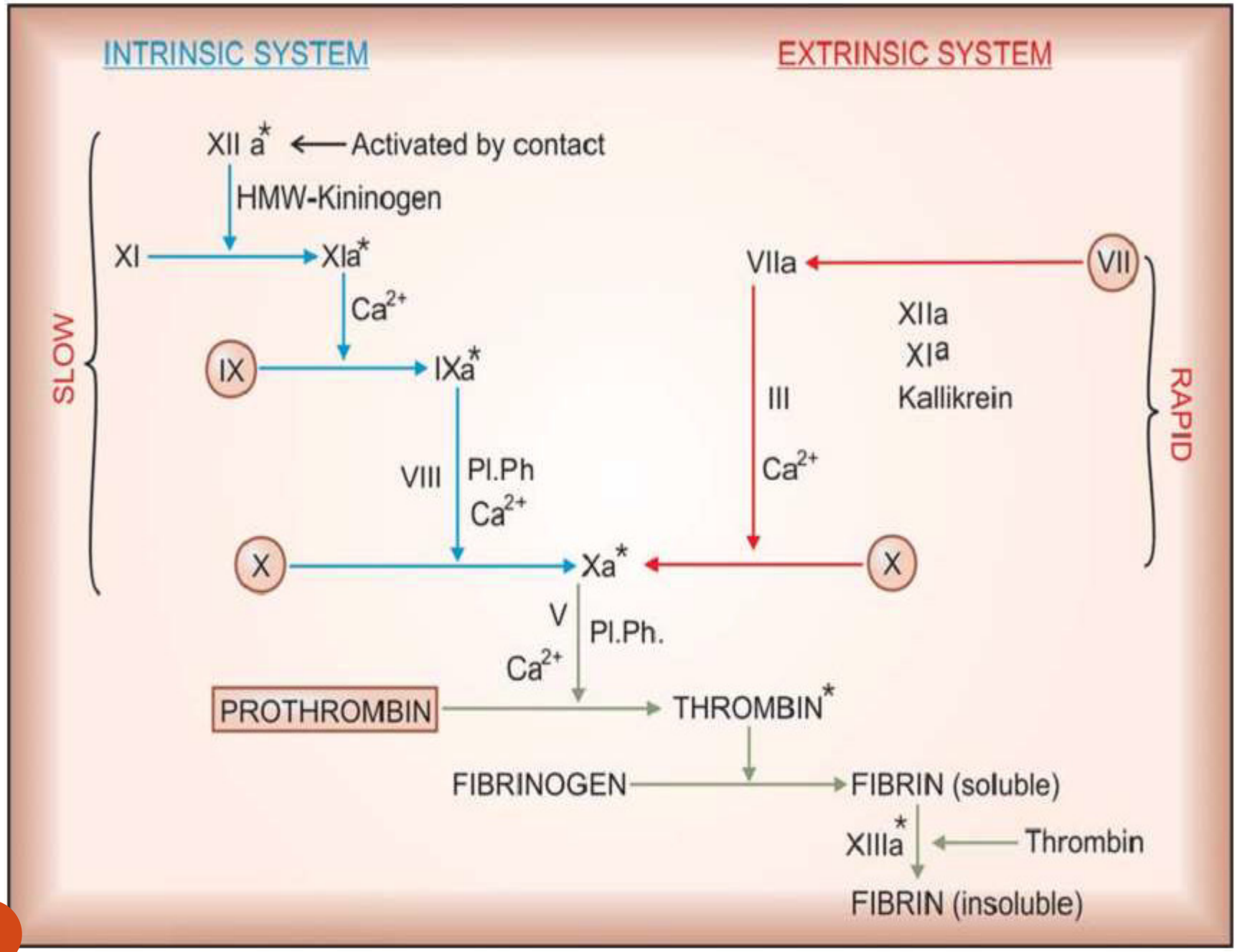
1. **The intrinsic pathway** can be initiated by events that take place within the lumen of blood vessels.

This requires only elements (clotting factors, Ca++ platelet surface, etc) found within or intrinsic to the vascular system.

2. **The extrinsic pathway** is the other route to coagulation.

It requires tissue factor (tissue thromboplastin), a substance that is extrinsic to or not normally cumulating in the vessel.

Tissue factor is released when the vessel wall is ruptured.


INTRINSIC SYSTEM
EXTRINSIC SYSTEM
XII a* ← Activated by contact
HMW-Kininogen
XI
XIa*
Ca2+
IX
IXa*
VIII
Pl.Ph
Ca2+
X
Xa*
V
Ca2+
Pl.Ph.
PROTHROMBIN
THROMBIN*
FIBRINOGEN
FIBRIN (soluble)
XIIIa*
Thrombin
FIBRIN (insoluble)
SLOW
VIIa
VII
XIIa
XIa
Kallikrein
III
Ca2+
X
RAPID

Classification of Coagulants

1) Vitamin K derivatives :

1. K1 (from plants, : Phytonadione fat-soluble) (Phylloquinone)
2. K3 (synthetic)

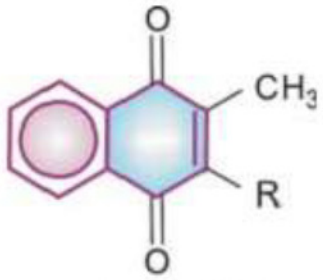
a) Fat-soluble : Menadione, Acetomenaphthone

b) Water-soluble : Menadione sod. Bisulfite

2) Miscellaneous :

- Fibrinogen (human),
- Antihaemophilic factor
- Desmopressin,
- Rutin, Ethamsylate

Chemistry of Vit.K



VITAMIN K

•Chemically, all vitamin Ks are 2-methyl 1,4-naphthoquinone derivatives containing variable aliphatic side chains at C3.

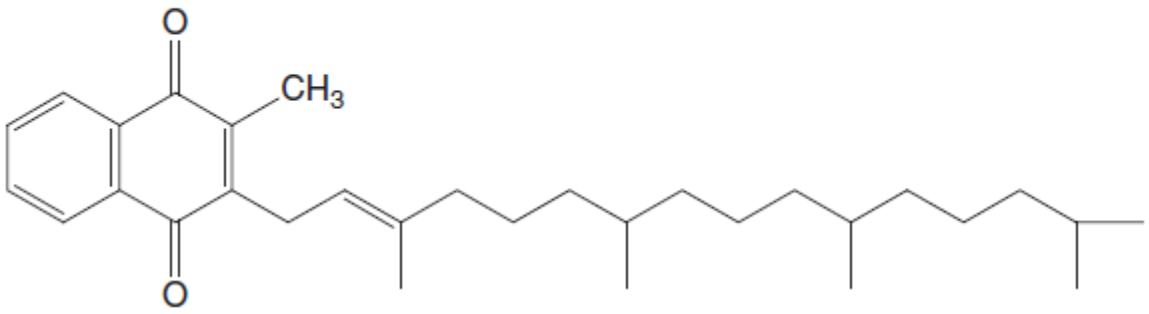
•Phylloquinone invariably contains a phytyl side chain.

•Menaquinones are a series of compounds that have a longer side chain with more unsaturation.

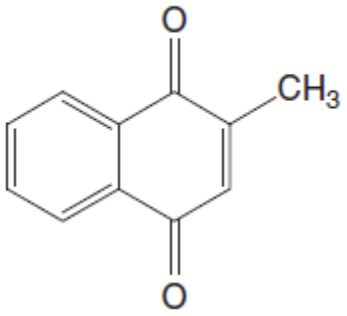
•This side chain may be composed of 1 to 13 prenyl (isoprenyl) units

Examples of Vit.K

Vitamin K (Synonym: Vitamin K_1-Phytomenadione)



Vitamin K_3 (Menadione)



Vit. K .

- Vit. K is a fat-soluble dietary principle required for the synthesis of clotting factors.
- **Daily requirement:** Vit. K produced by colonic bacteria and 3–10 µg/day external source may be sufficient. The total requirement of Vit. K for an adult has been estimated to be 50–100 µg/day.

MOA:

Vit K acts as a cofactor at a late stage in the synthesis by liver of coagulation proteins - prothrombin, factors VII, IX and X.

Use: The only use of vit K is in prophylaxis and treatment of bleeding due to deficiency of clotting factors.

Toxicity

Rapid i.v. injection of emulsified vit K produces flushing, breathlessness, a sense of constriction in the chest, fall in BP;

MISCELLANEOUS COAGULANTS :

1. FIBRINOGEN

The fibrinogen fraction of human plasma is employed to control bleeding in haemophilia, antihaemophilic globulin (AHG) deficiency and acute afibrinogenemic states; 0.5 g is infused i.v.

2. ANTIHAEMOPHILIC FACTOR

It is concentrated human AHG prepared from pooled human plasma. It is indicated (along with human fibrinogen) in haemophilia and AHG deficiency. It is highly effective in controlling bleeding episodes, but action is short-lasting (1 to 2 days).

3. DESMOPRESSIN

It releases factor VIII and von Willebrand's factor from vascular endothelium and checks bleeding in haemophilia and von Willebrand's disease.

MISCELLANEOUS COAGULANTS :

4. RUTIN

It is a plant glycoside claimed to reduce capillary bleeding. It has been used in a dose of 60 mg oral BD–TDS along with vit C which is believed to facilitate its action. Its efficacy is uncertain.

5.ETHAMSYLATE

It reduces capillary bleeding when platelets are adequate; probably exerts antihyaluronidase action—improves capillary wall stability, but does not stabilize fibrin(not an antifibrinolytic). Ethamsylate has been used in the prevention and treatment of capillary bleeding in menorrhagia

Reflection Questions

1. Classify coagulants with suitable examples and write the mechanism of action of Vit.k.

2. Enumerate pathways for coagulation process.

ANTICOAGULANT

➢**Anticoagulants**, commonly known as **blood thinners**, are chemical substances that prevent or reduce coagulation of blood, prolonging the clotting time.

CLASSIFICATION:

1. **In vitro anticoagulants:** Heparin, Sodium oxalate, and Sodium citrate.
2. **In vivo anticoagulants.**

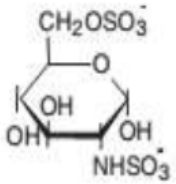
a) Injectable anticoagulants :Heparin

a) Oral anticoagulants

1. **Coumarin derivatives:** Warfarin, Bishydroxycoumarin.

2. **Indandiones:** Phenindione, Diphenadion.

I. In vitro anticoagulants-Heparin



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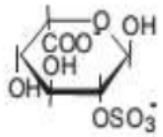

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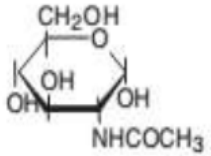

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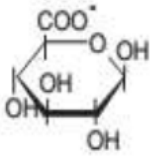

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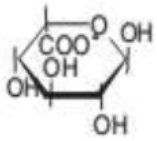

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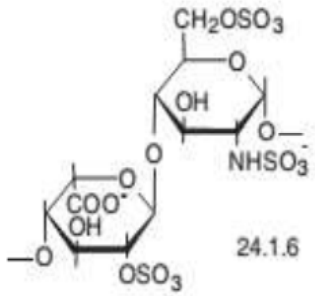
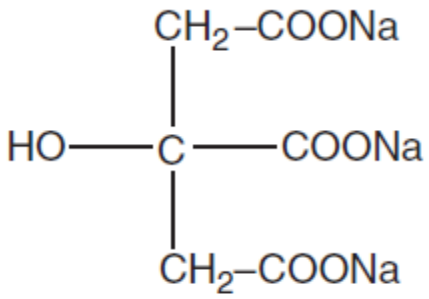
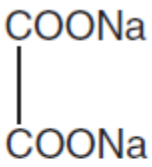


24.1.6

Heparin Derivatives



Sodium citrate



Sodium oxalate

Chemistry and occurrence-Heparin

1. Heparin is a non-uniform mixture of straight chain mucopolysaccharides with MW 10,000 to 20,000.
2. It contains polymers of two sulfated disaccharide units: Dglucosamine- Liduronic acid D-glucosamine-D-glucuronic acid.
3. It carries strong electronegative charges and is the strongest organic acid present in the body.
4. It occurs in mast cells as a much bigger molecule(MW ~75,000) loosely bound to the granular protein.
5. Thus, heparin is present in all tissues containing mast cells; richest sources are lung, liver and intestine

Mechanism of action

Mechanism of action:It acts indirectly by activating plasma antithrombin III (AT III, a serine proteinase inhibitor) and may be other similar cofactors.

1. Heparin-AT III complex inactivates clotting factors - Xa, IIa, IXa, XIIa and XIIIa, but not VIIa (extrinsic pathway)
2. Acts only by interfering with Xa – inducing conformational change in AT III – smaller effect on a PTT – whole blood clotting time

Adverse effects :

1. Bleeding due to overdose – haematuria
2. Thrombocytopenia – aggregation of platelets
3. Hypersensitivity – urticaria, rigor, fever and anaphylaxis etc.
4. Alopecia and osteoporosis

Marketed Heparin Derivatives .

They differ in composition, pharmacokinetics and dosage.

- Enoxaparin,
- Reviparin,
- Nadroparin,
- Dalteparin: for treatment of deep vein thrombosis
- Pamparin: for unstable angina and prophylaxis of DVT;
- Ardeparin

HEPARINOIDS

1.Heparan sulfate

It is a heparin-like natural substance found on cell surface and intercellular matrix in many tissues. It is a less potent anticoagulant than heparin, but may have a more favourable profile of action.

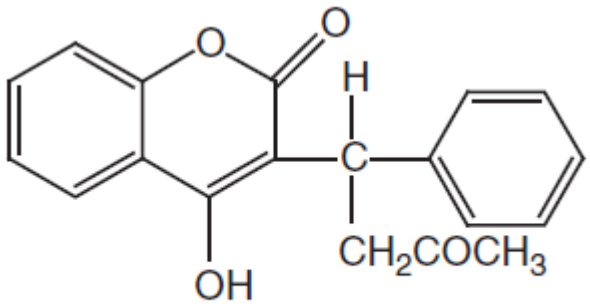
2. Danaparoid

It is a preparation containing mainly heparin sulfate, obtained from pig gut mucosa, which is used in cases with heparin induced thrombocytopenia.

3. Heparin antagonist Protamine Sulfate, USP.

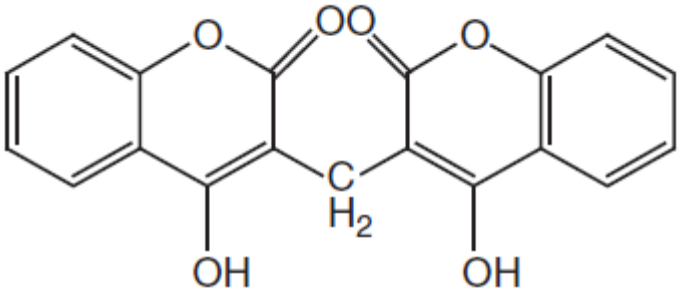
Protamine sulfate has an anticoagulant effect, but if used in the proper amount, it counteracts the action of heparin and is used as an antidote for the latter in cases of over dosage. I

II. In vivo anticoagulants- a. Coumarin Derivatives



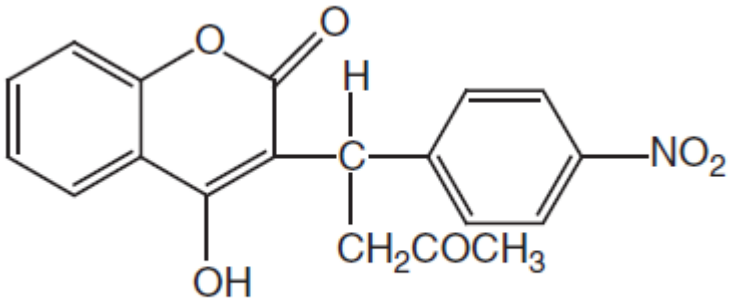
Warfarin

Warfarin, 3-(α-acetonylbenzyl) -4-hydroxycoumarin,



Dicoumarol

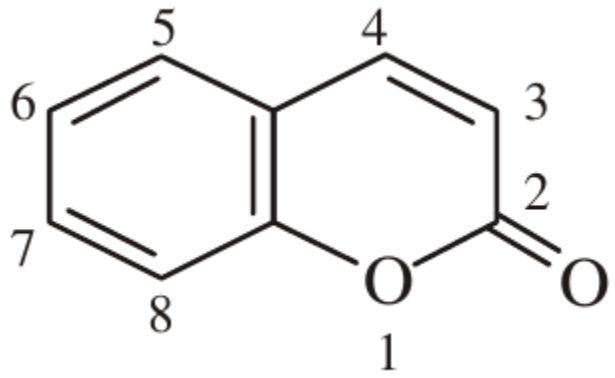
Dicoumarol, 3,3′-methylene-bis(4-hydroxycoumarin),



Acenocoumarol

3-(α-acetonyl-*p-nitrobenzyl)-4-hydroxycoumarin*

SAR-Coumarin Derivatives



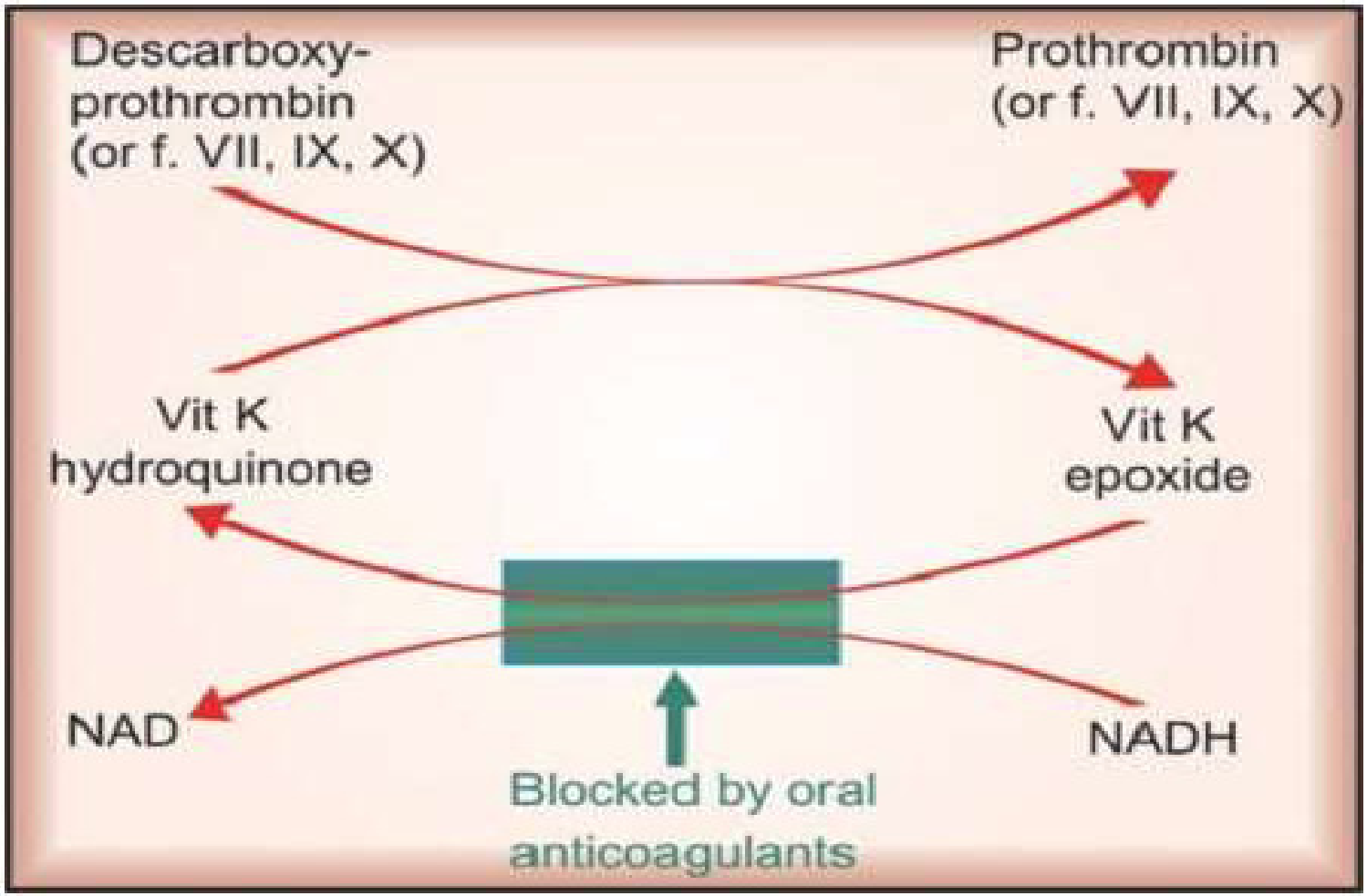
1. The coumarin ring system has an easy acceptability in the biological system compared to its isomeric form.
2. Nature of substituent at position 3 affects the duration of action and activity spectrum.
3. Increase in Molecular weiht increases the aanticiagulant activity.
4. No substitution is allowed at 5,6,7, and 8 position.

Mechanism of action : Coumarin Derivatives

•**Coumarin derivatives** (4-hydroxycoumarin compounds) are oral **anticoagulants** (OA) that prevent vitamin K from acting as a cofactor in the hepatic synthesis of the vitamin K-dependent coagulation factors II, VII, IX, and X (as well as the **anticoagulants**, proteins C and S). They are also called vitamin K antagonists (VKA).

•Competitive antagonist of Vit.K – lowers the plasma level of vit. K dependent clotting factors

Mechanism of action : oral anticoagulant



Therapeutic uses and ADR: Coumarin Derivatives

Uses:

DVT, Pulmonary embolism and atrial fibrillation

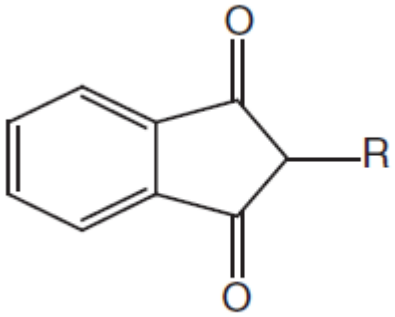
ADRs:

Bleeding – epistaxis, haematuria,
bleeding GIT Intracranial haemorrhage – Minor bleeding – Vit K (takes long) – Fresh blood transfusion or blood factors –

Other ADRs:

Alopecia,
dermatitis and
diarrhoea

b. Indnedione Derivatives



1,3-Indandione (**indanedione**) is an organic compound with the molecular formula $C_9H_6O_2$. Chemically, it is a β-diketone.

Name	R_1
Phenindione	$-C_6H_5$
Anisindione	$H_3CO-C_6H_4-$
Bromindione	$Br-C_6H_4-$
Diphenadione	$-COCH(C_6H_5)_2$

SAR:

1. Increase in the size of R from phenyl to substituted phenyl groups increase anticoagulant activity

Chemistry of Indnedione Derivatives

Chemistry: indanedione are a cyclic beta-diketone consisting of indane 1,3-dione having a substituted yphenyl substituent
It is a vitamin K antagonist.
It is a beta-diketone and an aromatic ketone.

Mechanism of action:
Anisindione is a synthetic anticoagulant and an indanedione derivative.
It prevents the formation of active procoagulation factors II, VII, IX, and X, as well as the anticoagulant proteins C and S, in the liver by inhibiting the vitamin K-mediated gamma-carboxylation of precursor proteins.

Therapeutic uses and ADR: Indanedione Derivatives

Theurapeutic use:

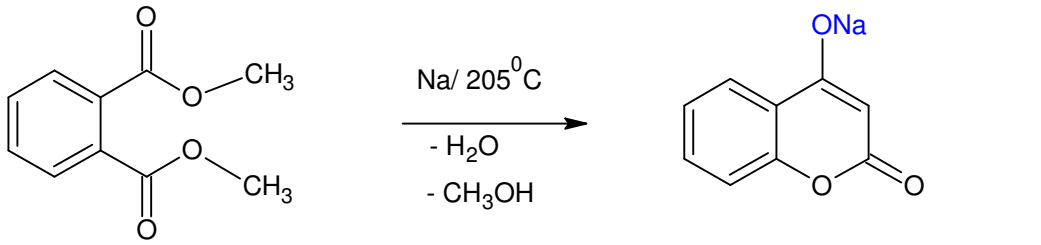
It is used for preventing and treating thrombosis, thrombophlebitis, and thromboembolism.

ADR:

Nausea, diarrhea, pyrexia, dermatitis or exfoliative dermatitis, urticaria, alopecia, and sore mouth or mouth ulcers

SYNTHESIS OF WARFARIN

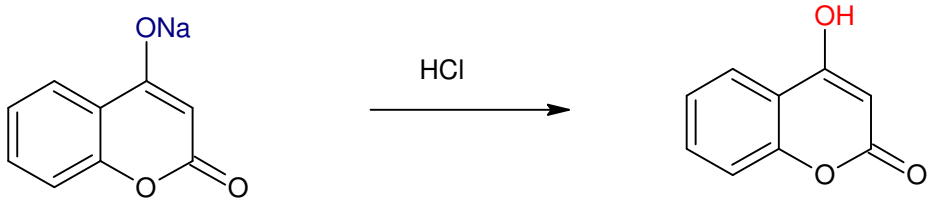
Step I:



Methyl ester of acetyl salicylic acid

sodium 2-oxo-2*H*-chromen-4-olate

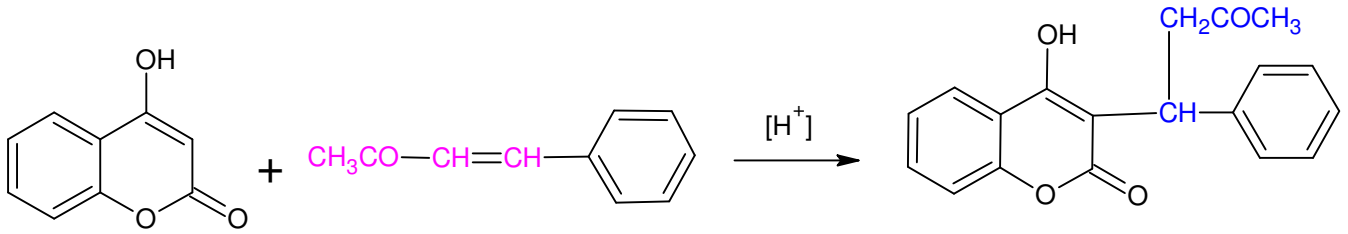
Step II:



sodium 2-oxo-2*H*-chromen-4-olate

4 - Hydroxy coumarin

Step III:



4 - Hydroxy coumarin

Benzalactone

Warfarin

IUPAC Name: 4-hydroxy-3-(3-oxo-phenylbutyl)-2H-Chromen-2-one

Category: Oral anticoagulant

Reflection Questions

1. Classify anticoagulants with suitable examples and write the synthesis of coumarin.

2. Enumerate the coumarin derived anticoagulants.

3. Write a note on indanedione derivatives

4. Write the synthetic route of warfarin

Thank you