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MEDICINAL CHEMISTRY - II

UNIT 3

TOPIC :

- **Coagulant & Anticoagulants :** Menadione, Acetomenadione, Warfarin*,Anisindione, clopidogrel

Coagulants and Anticoagulants

Coagulants (Hemostatic Agents):

- Coagulants are drugs that **promote blood clotting** and **control bleeding**.
- Used in conditions of **excessive bleeding**, **hemorrhages**, or **deficiency of clotting factors**.
- They act by **enhancing the coagulation cascade** or **stabilizing clot formation**.

Anticoagulants:

- Anticoagulants are drugs that **inhibit blood clot formation** to prevent **thrombosis and embolism**.
- They are used in conditions such as **deep vein thrombosis (DVT), pulmonary embolism, atrial fibrillation, myocardial infarction**, and **stroke prevention**.
- These drugs act by **inhibiting clotting factors**, **blocking platelet aggregation**, or **antagonizing vitamin K**.

Classification

A. Coagulants

1. **Vitamin K and Derivatives:**
    - **Examples:** Phytonadione (Vitamin K_1), Menadione (Vitamin K_3)
    - **Mechanism:** Promote γ-carboxylation of **clotting factors II, VII, IX, X** → restores coagulation.
    - **Uses:** Vitamin K deficiency, hemorrhagic disease of newborn, anticoagulant overdose.
2. **Hemostatic Agents (Synthetic/Topical):**
    - **Examples:** Tranexamic acid, Aminocaproic acid, Fibrin sealants
    - **Mechanism:** Inhibit **plasminogen → plasmin conversion** → reduces fibrinolysis.

- **Uses:** Surgical bleeding, trauma, heavy menstrual bleeding.

3. **Blood Coagulation Factor Concentrates:**
   - **Examples:** Factor VIII, Factor IX concentrates
   - **Mechanism:** Replace **deficient clotting factors** in hemophilia.
   - **Uses:** Hemophilia A & B, congenital clotting factor deficiencies.
4. **Other Coagulants:**
   - **Calcium salts ($CaCl_2$, Ca gluconate):** Essential cofactor in coagulation cascade.

B. Anticoagulants

1. **Vitamin K Antagonists (VKAs):**
   - **Example:** Warfarin
   - **Mechanism:** Inhibits **vitamin K epoxide reductase** → ↓ γ-carboxylation of **II, VII, IX, X** → prevents clot formation.
   - **Uses:** Prevention of DVT, pulmonary embolism, atrial fibrillation.
2. **Heparins:**
   - **Examples:** Unfractionated heparin (UFH), Low molecular weight heparin (LMWH: Enoxaparin, Dalteparin)
   - **Mechanism:** Enhances **antithrombin III activity** → inhibits thrombin (IIa) and factor Xa.
   - **Uses:** DVT, pulmonary embolism, acute coronary syndrome, perioperative prophylaxis.
3. **Direct Oral Anticoagulants (DOACs):**
   - **Examples:**
     - Direct thrombin inhibitors: Dabigatran
     - Factor Xa inhibitors: Rivaroxaban, Apixaban, Edoxaban
   - **Mechanism:** Directly inhibit thrombin or factor Xa → prevent fibrin formation.
   - **Uses:** Stroke prevention in atrial fibrillation, treatment and prevention of DVT and PE.
4. **Other Anticoagulants:**
   - **Fondaparinux:** Synthetic pentasaccharide → selective factor Xa inhibitor

- **Argatroban, Bivalirudin:** Direct thrombin inhibitors (parenteral, for heparin-induced thrombocytopenia)

Therapeutic Uses

Coagulants:

- **Vitamin K deficiency**
- **Hemophilia A & B**
- **Surgical bleeding**
- **Excessive menstrual bleeding**
- **Overdose of anticoagulants**

Anticoagulants:

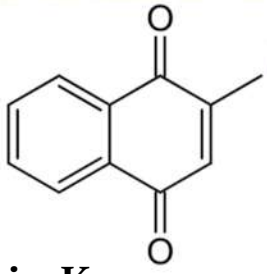
- **Deep vein thrombosis (DVT)**
- **Pulmonary embolism (PE)**
- **Atrial fibrillation (stroke prevention)**
- **Myocardial infarction & unstable angina**
- **Post-operative thromboprophylaxis**

Menadione (Vitamin K3)

- **Menadione** is a **synthetic derivative of Vitamin K**, also known as **Vitamin K3**.
- It belongs to the **naphthoquinone class** of compounds.
- Menadione acts as a **provitamin**, which can be converted in vivo to **active Vitamin K2 (menaquinone)**.
- It plays a key role in **blood coagulation**, **bone metabolism**, and other physiological processes that require **γ-carboxylation of glutamate residues**.
- Unlike natural Vitamin K1 (phylloquinone), menadione is **water-soluble** and can be used in certain formulations, but its **toxicity limits clinical use**.

Chemical Structure

- **Chemical name:** 2-Methyl-1,4-naphthoquinone
- **Molecular formula:** $C_{11}H_8O_2$
- **Molecular weight:** 172.18 g/mol
- **Chemical class:** Naphthoquinone; synthetic vitamin K derivative
- **Structural**



Mechanism of Action

- Menadione serves as a **vitamin K precursor**, participating in the **γ-carboxylation of glutamate residues** in **vitamin K-dependent proteins**.

Stepwise Mechanism:

1. Menadione is **reduced to menadiol** in the body.
2. Menadiol participates in the **carboxylation of glutamate residues** to form γ-carboxyglutamate in **coagulation factors II, VII, IX, X, protein C, and protein S**.
3. This reaction is catalyzed by **γ-glutamyl carboxylase** in the presence of **vitamin K epoxide cycle**.

4. The γ-carboxylation allows **calcium binding**, essential for **activation of clotting factors**.

Synthesis of Menadione

1. **Starting material:** 1,4-naphthalenedione or naphthalene derivatives
2. **Methylation:**
    - Introduction of **methyl group at C2 position** using **methylating agents** (e.g., methyl iodide) → forms 2-methyl-1,4-naphthoquinone
3. **Purification:**
    - Crystallization or distillation yields **pure menadione**.

Uses

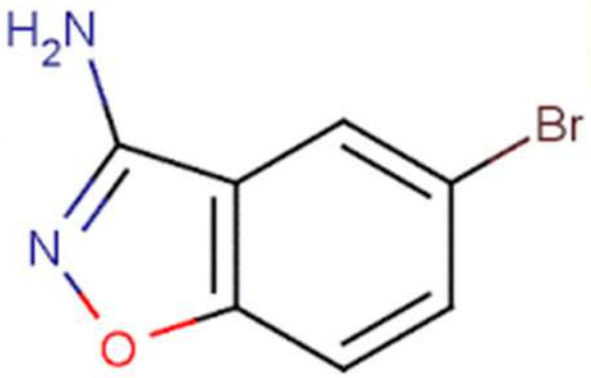
- **Therapeutic Uses:**
    1. **Vitamin K deficiency:** Supplementation in cases of deficiency
    2. **Prevention of hemorrhagic disease in newborns** (historically; now replaced by Vitamin K1)
    3. **Rodenticide poisoning:** Used in combination with anticoagulant rodenticides for antidote studies
    4. **Research:** Studying vitamin K metabolism

Acetomenadione (Vitamin K4)

- **Acetomenadione**, also known as **Vitamin K4**, is a **synthetic, water-soluble derivative of Vitamin K**.
- Unlike natural fat-soluble vitamins K1 and K2, Vitamin K4 is **water-soluble**, making it easier to administer orally or parenterally.
- It is a **provitamin**, which is **converted in vivo into active Vitamin K2 (menaquinone)**.
- Primarily used in **prevention and treatment of Vitamin K deficiency**, especially when fat absorption is impaired.

Chemical Structure

- **Chemical name:** 2-(Acetylamino)naphthalene-1,4-dione
- **Molecular formula:** $C_{12}H_9NO_3$
- **Molecular weight:** 207.21 g/mol
- **Chemical class:** Synthetic naphthoquinone derivative; water-soluble Vitamin K analog
- **Structural**



Mechanism of Action

- Acts as a **Vitamin K precursor**, converted in vivo to **active Vitamin K2**.

Stepwise Mechanism:

1. **Reduction to menadiol derivative** in the body.
2. Participates in **γ-carboxylation of glutamate residues** in **Vitamin K-dependent clotting factors** (II, VII, IX, X) and proteins C & S.

3. γ-Carboxylation allows **calcium binding**, essential for **activation of clotting factors**.

Synthesis

1. **Starting material:** 1,4-naphthoquinone
2. **Amination:**
    - Introduce an amino group at position 2 via nucleophilic substitution
3. **Acetylation:**
    - Convert the amino group to **acetylamino** using **acetic anhydride or acetyl chloride**
4. **Purification:**
    - Crystallization yields **acetomenadione**

Uses

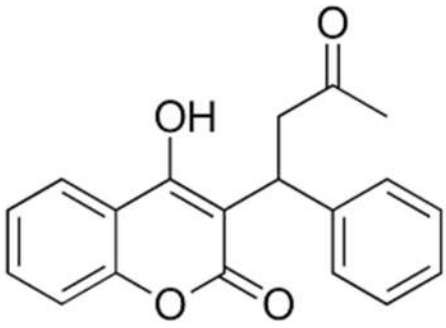
- **Therapeutic Uses:**
    1. **Vitamin K deficiency:** Oral or parenteral supplementation
    2. **Prevention and treatment of hemorrhagic disease in neonates**
    3. **Antidote for overdosage of anticoagulants** (e.g., warfarin)
    4. **Patients with malabsorption** (e.g., liver disease, biliary obstruction)

Warfarin

- **Warfarin** is an **oral anticoagulant** belonging to the **coumarin derivative class**.
- It is widely used to **prevent and treat thromboembolic disorders**, such as **deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation-associated stroke**, and **mechanical heart valve thrombosis**.
- Warfarin was initially developed as a **rat poison** but is now used therapeutically at controlled doses.
- It is **highly protein-bound**, metabolized in the liver, and has a **narrow therapeutic index**, requiring **regular INR monitoring**.

Chemical Structure

- **Chemical name:** 4-hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one
- **Molecular formula:** $C_{19}H_{16}O_4$
- **Molecular weight:** 308.33 g/mol
- **Chemical class:** 4-hydroxycoumarin derivative; vitamin K antagonist
- **Structural**



Mechanism of Action

- **Warfarin is a vitamin K antagonist** that inhibits the **vitamin K epoxide reductase complex (VKORC1)**.

Stepwise Mechanism:

1. Vitamin K is required for **γ-carboxylation of glutamate residues** on clotting factors II, VII, IX, X, and proteins C & S.
2. Warfarin **inhibits VKORC1**, preventing regeneration of active **vitamin K hydroquinone**.

3. Without active vitamin K, the liver produces **inactive clotting factors**, reducing coagulation.
4. **Onset of action is delayed** (36–72 hours) because existing clotting factors have to degrade.

Synthesis of Warfarin

1. **Starting materials:** 4-hydroxycoumarin and benzylideneacetone (or derivatives)
2. **Condensation reaction:**
    - 4-hydroxycoumarin reacts with benzylideneacetone under **base catalysis** → forms **Warfarin**
3. **Purification:**
    - Crystallization or recrystallization yields pure warfarin

Uses

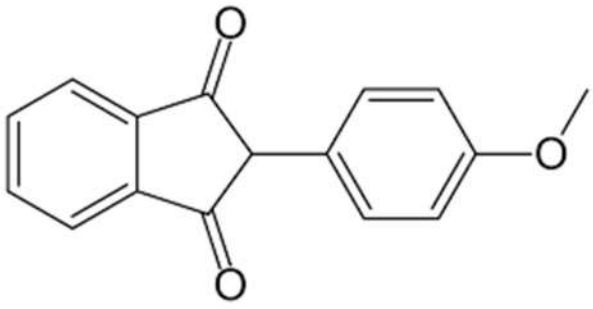
- **Therapeutic Uses:**
    1. **Prevention and treatment of venous thromboembolism** (DVT, PE)
    2. **Prevention of thromboembolism in atrial fibrillation**
    3. **Prevention of thrombus formation in mechanical heart valves**
    4. Occasionally used in **myocardial infarction prophylaxis**

Anisindione

- **Anisindione** is an **oral anticoagulant** belonging to the **1,3-indandione class**.
- It is used to **prevent and treat thromboembolic disorders**, similar in effect to warfarin.
- Acts as a **vitamin K antagonist**, inhibiting the synthesis of active clotting factors.
- Less commonly used today compared to warfarin due to **narrow therapeutic index** and need for frequent **monitoring of prothrombin time (PT/INR)**.

Chemical Structure

- **Chemical name:** 2-(4-methoxyphenyl)indene-1,3-dione
- **Molecular formula:** $C_{16}H_{12}O_3$
- **Molecular weight:** 252.26 g/mol
- **Chemical class:** 1,3-indandione derivative; vitamin K antagonist
- **Structural**



Mechanism of Action

- Acts as a **vitamin K antagonist**, similar to warfarin.

Stepwise Mechanism:

1. **Inhibition of Vitamin K epoxide reductase (VKORC1):**
   - Prevents regeneration of active vitamin K hydroquinone.
2. **Reduction in γ-carboxylation** of glutamate residues in clotting factors II, VII, IX, X, and proteins C & S.
3. Production of **inactive clotting factors** → decreased coagulation.
4. **Delayed onset** of anticoagulant effect (36–72 hours) due to existing active clotting factors.

Synthesis of Anisindione

1. **Starting materials:** Phenylacetic acid derivative and phthalic anhydride
2. **Cyclization reaction:**
    - Phenylacetic acid condenses with phthalic anhydride → forms indandione core
3. **Substitution:**
    - Introduction of **4-methoxyphenyl group** at position 2 via electrophilic substitution
4. **Purification:**
    - Crystallization or recrystallization to yield pure anisindione

Uses

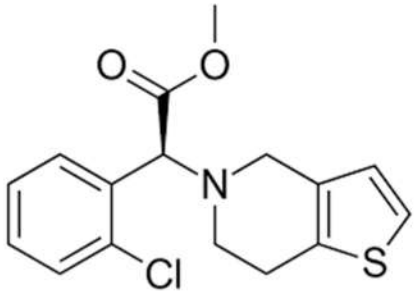
- **Therapeutic Uses:**
    1. **Prevention of venous thromboembolism** (DVT, PE)
    2. **Prevention of stroke** in atrial fibrillation patients
    3. **Management of mechanical heart valve thrombosis risk**
    4. **Adjunct therapy** in patients prone to thrombosis

Clopidogrel

- **Clopidogrel** is an **oral antiplatelet agent** belonging to the **thienopyridine class**.
- It **prevents platelet aggregation** by irreversibly inhibiting the **P2Y12 subtype of ADP receptors** on platelets.
- It is a **prodrug**, requiring hepatic metabolism (mainly by CYP2C19) to form its **active metabolite**.
- Widely used in **cardiovascular disease** to prevent **thrombotic events**, such as **myocardial infarction (MI), stroke, and stent thrombosis**.
- Often used in **combination with aspirin** (dual antiplatelet therapy).

Chemical Structure

- **Chemical name:** Methyl (2S)-2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)acetate
- **Molecular formula:** $C_{16}H_{16}ClNO_2S$
- **Molecular weight:** 321.82 g/mol
- **Chemical class:** Thienopyridine derivative; prodrug
- **Structural**



Mechanism of Action

- **Target:** P2Y12 ADP receptor on platelet surface

Stepwise Mechanism:

1. Clopidogrel is a **prodrug**, metabolized in the liver by **CYP enzymes** (mainly CYP2C19) to an **active thiol metabolite**.
2. The active metabolite **irreversibly binds to P2Y12 receptors** on platelets.

3. Inhibition of P2Y12 → **prevents ADP-mediated activation of glycoprotein IIb/IIIa complex**.
4. Result: **Reduced platelet aggregation** and thrombus formation.

Synthesis

Stepwise Overview:

1. **Starting materials:** 2-chlorophenylacetic acid and 6,7-dihydrothieno[3,2-c]pyridin-5(4H)-one
2. **Condensation:**
   - React 2-chlorophenylacetic acid derivative with thienopyridine ketone to form **intermediate**
3. **Esterification:**
   - Conversion to methyl ester yields **Clopidogrel**
4. **Purification:**
   - Crystallization to obtain pure compound

Uses

- **Therapeutic Uses:**
  1. **Prevention of atherosclerotic events** in patients with **recent MI, stroke, or peripheral arterial disease**
  2. **Acute coronary syndrome (ACS):** In combination with aspirin
  3. **Prevention of stent thrombosis** after coronary stent placement
  4. Alternative in patients intolerant to **aspirin**