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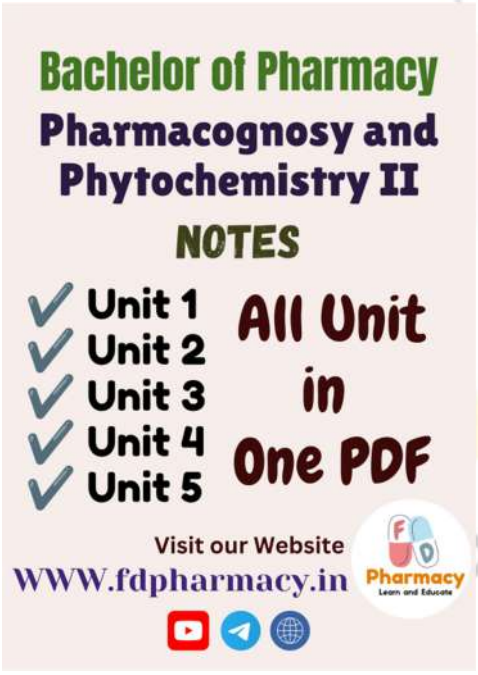
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MEDICINAL CHEMISTRY - II

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:

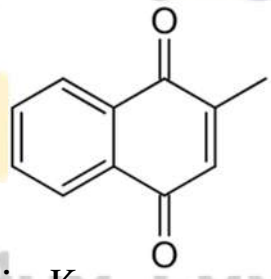
- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Atrial fibrillation (stroke prevention)
- Myocardial infarction & unstable angina
- Post-operative thromboprophylaxis

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

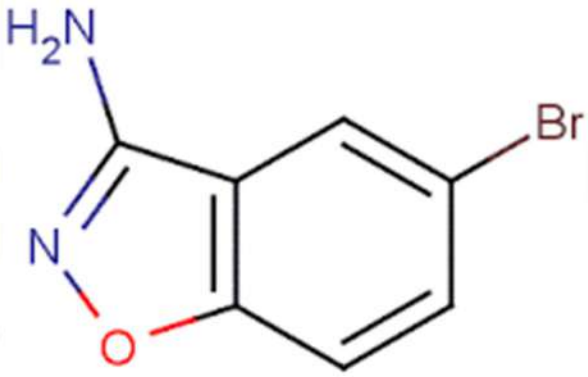
- Therapeutic Uses:
    1. Vitamin K deficiency: Supplementation in cases of deficiency
    2. Prevention of hemorrhagic disease in newborns (historically; now replaced by Vitamin K1)
    3. Rodenticide poisoning: Used in combination with anticoagulant rodenticides for antidote studies
    4. Research: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

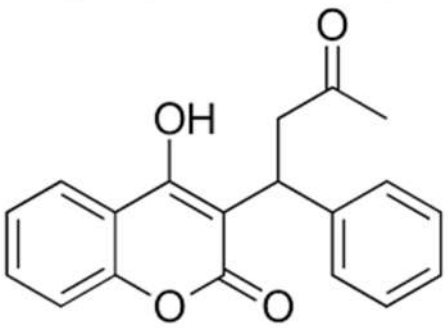
- Therapeutic Uses:
    1. Vitamin K deficiency: Oral or parenteral supplementation
    2. Prevention and treatment of hemorrhagic disease in neonates
    3. Antidote for overdosage of anticoagulants (e.g., warfarin)
    4. Patients with malabsorption (e.g., liver disease, biliary obstruction)

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

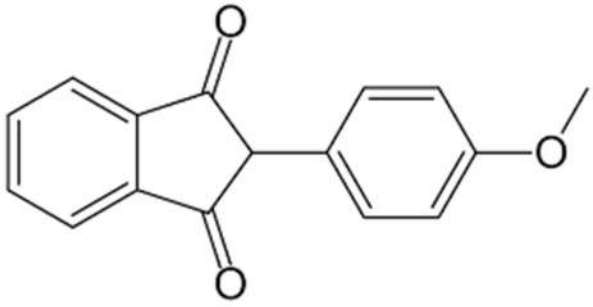
- Therapeutic Uses:
    1. Prevention and treatment of venous thromboembolism (DVT, PE)
    2. Prevention of thromboembolism in atrial fibrillation
    3. Prevention of thrombus formation in mechanical heart valves
    4. Occasionally used in myocardial infarction prophylaxis

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

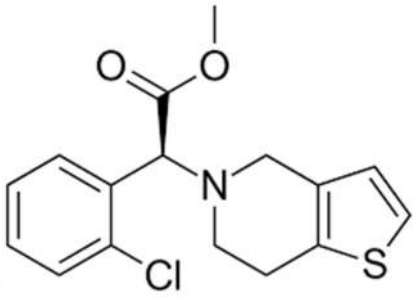
- Therapeutic Uses:
    1. Prevention of venous thromboembolism (DVT, PE)
    2. Prevention of stroke in atrial fibrillation patients
    3. Management of mechanical heart valve thrombosis risk
    4. Adjunct therapy in patients prone to thrombosis

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