Drugs affecting blood clotting

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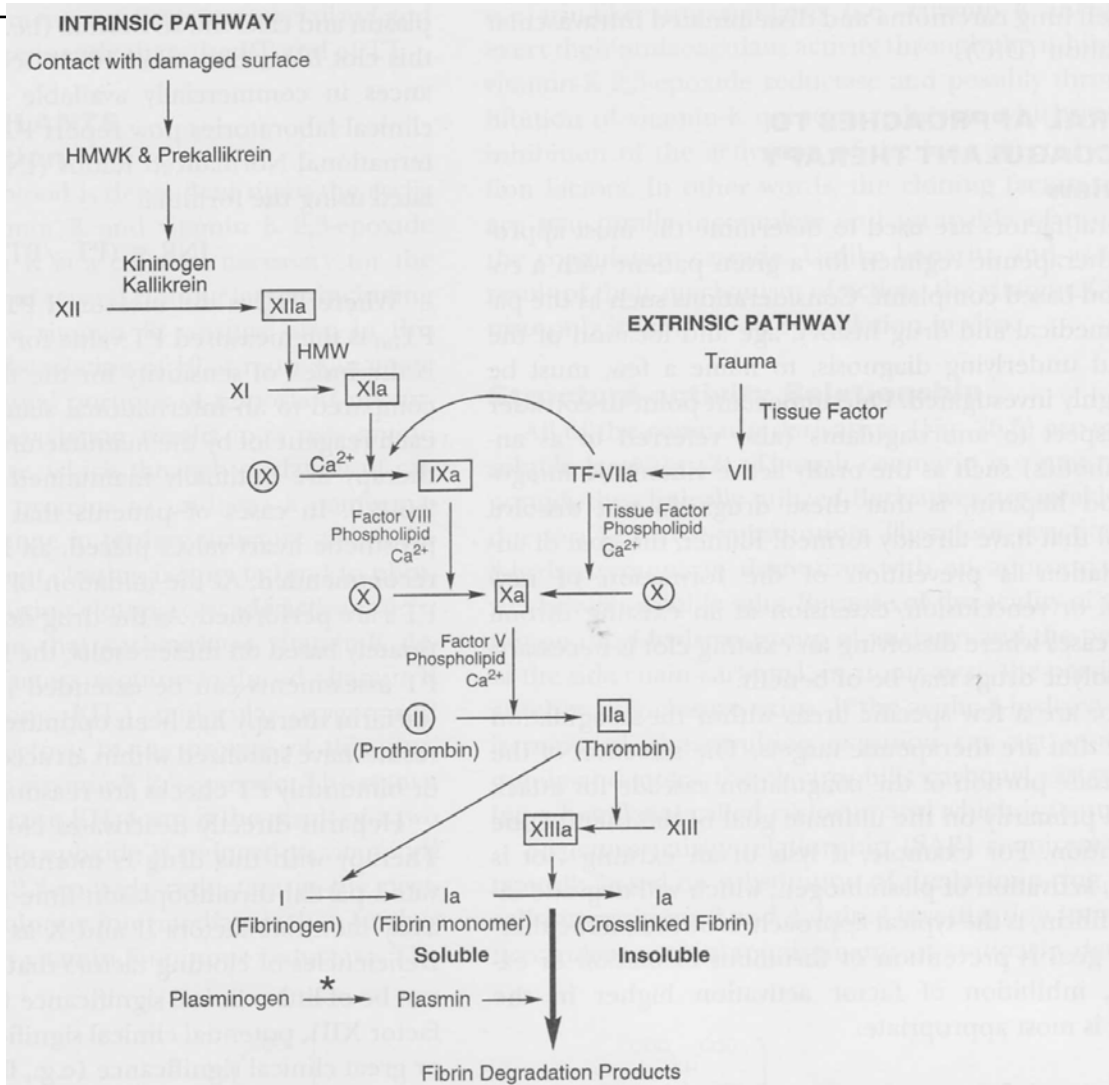
Blood clot

- stops bleeding
- necessary for homeostasis at physiological conditions

Blood clot formation - coagulation



Formed Clot

- Thrombus – fixed on surface (vessel wall)
- Embolus – free-floating clot
- both can occlude vessels and cause ischaemia with necrosis of the tissue

Thrombotic conditions

- often due to atherosclerotic vessel changes
- anticoagulant therapy – prevention of clot forming
- thrombolytic therapy – dissolving of already formed clots

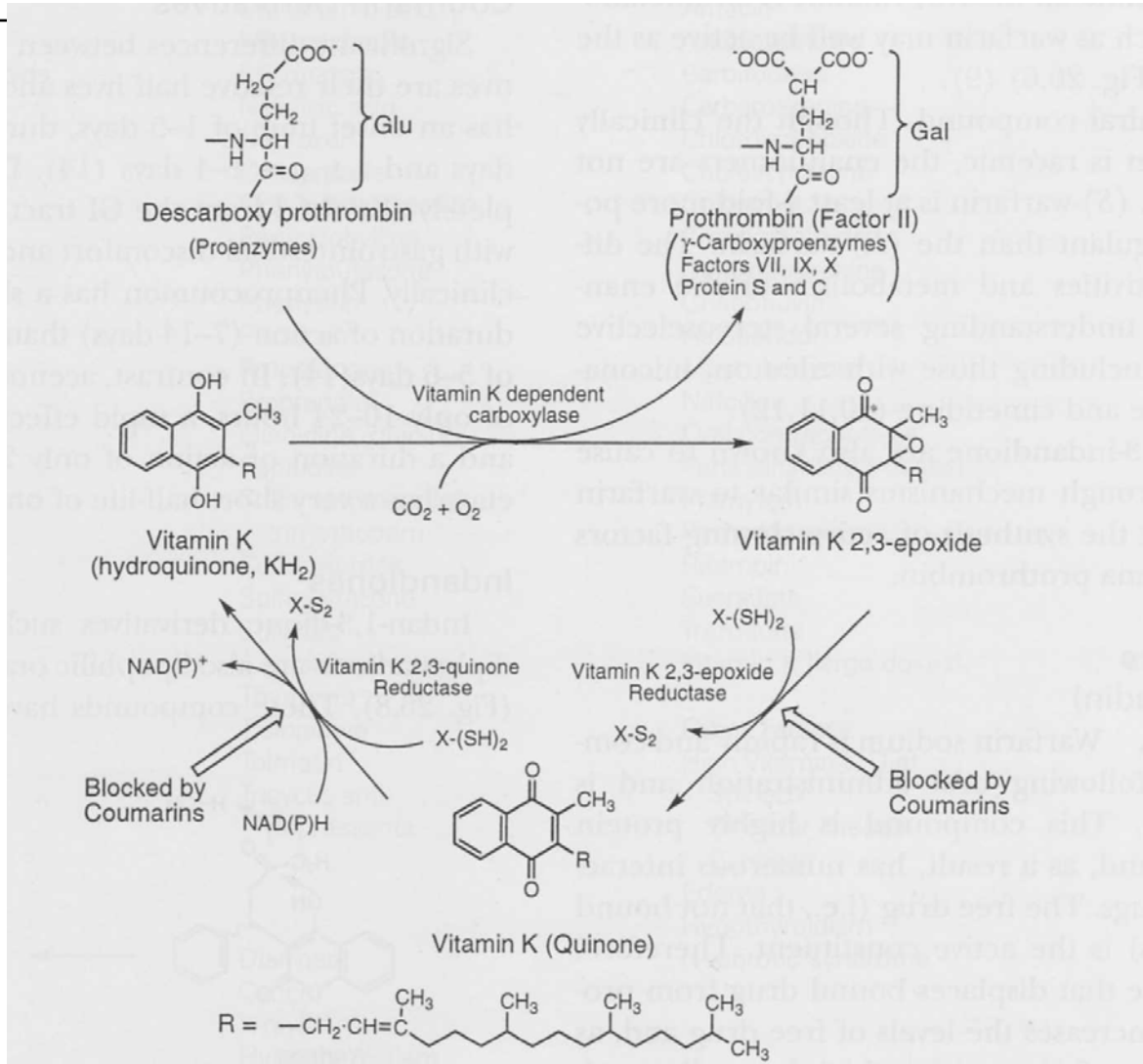
Diseases connected with thrombotic conditions:

- myocardium infarction
- valvular hearth disease
- angina pectoris
- pulmonary embolism
- cerebrovascular accident (stroke)

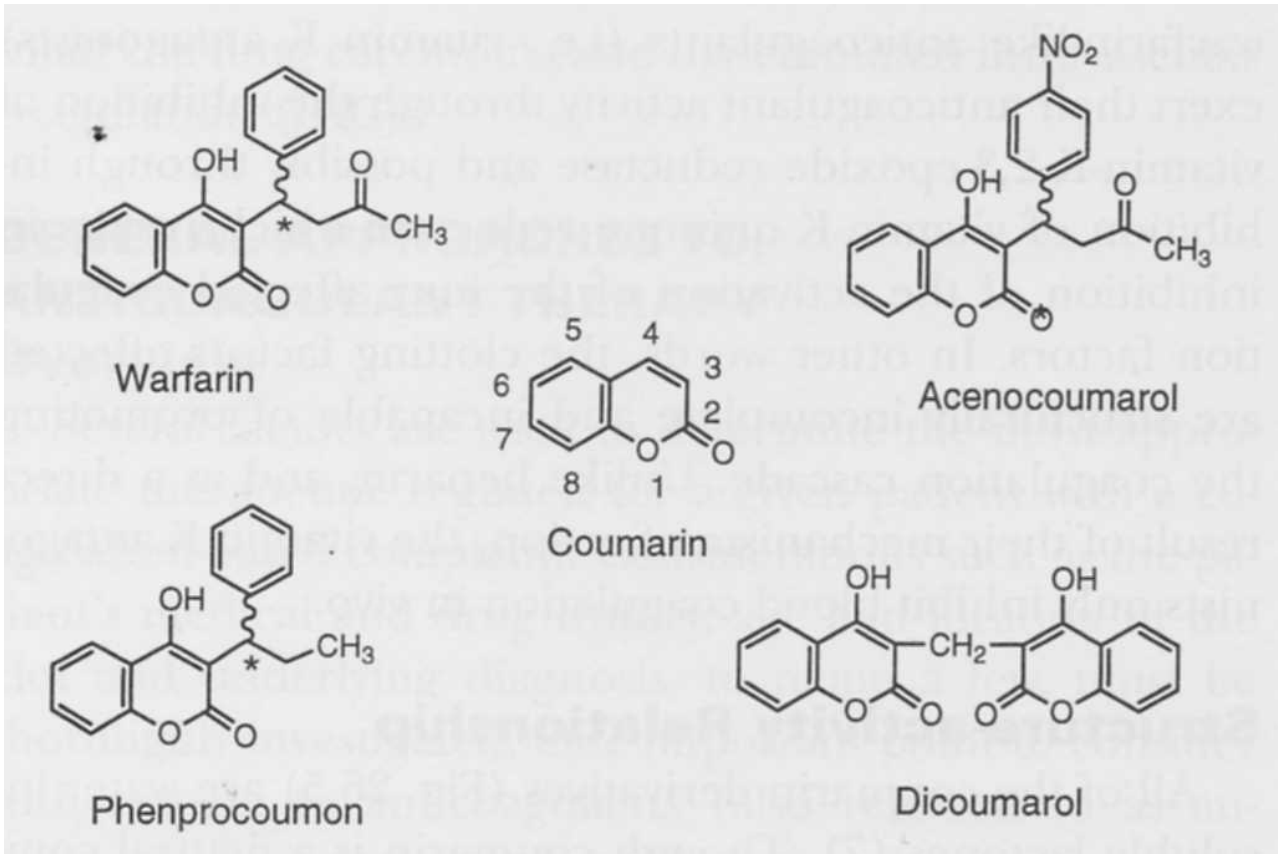
Oral anticoagulants

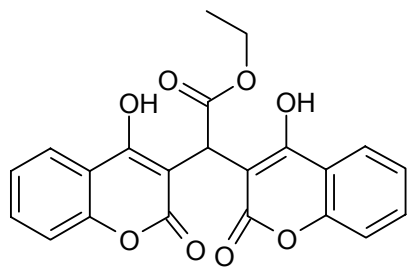
- vitamin K antagonists
- heparins
- antiplatelet drugs

Vitamin K antagonists - coumarins



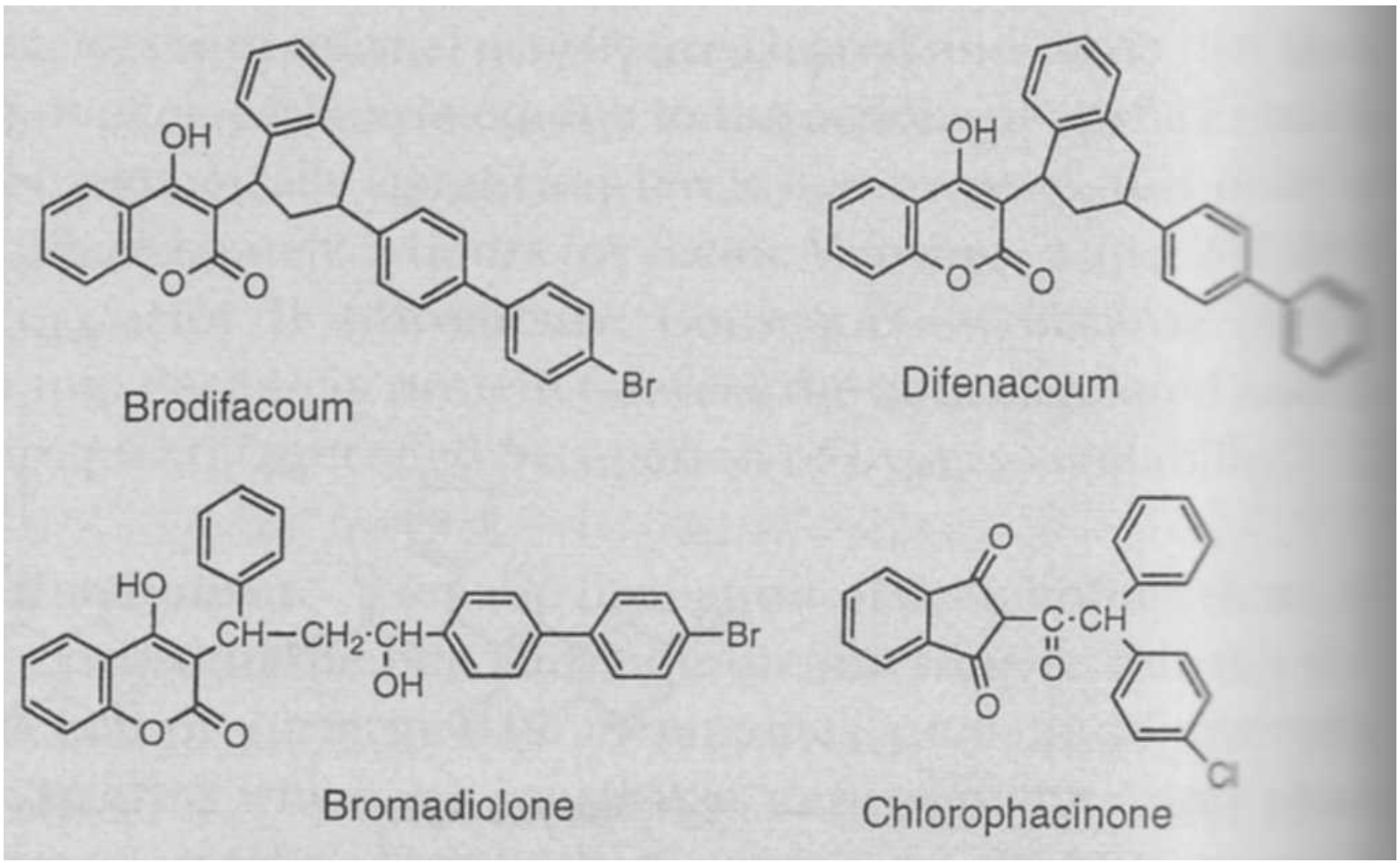
Coumarins: Structure-activity relationships



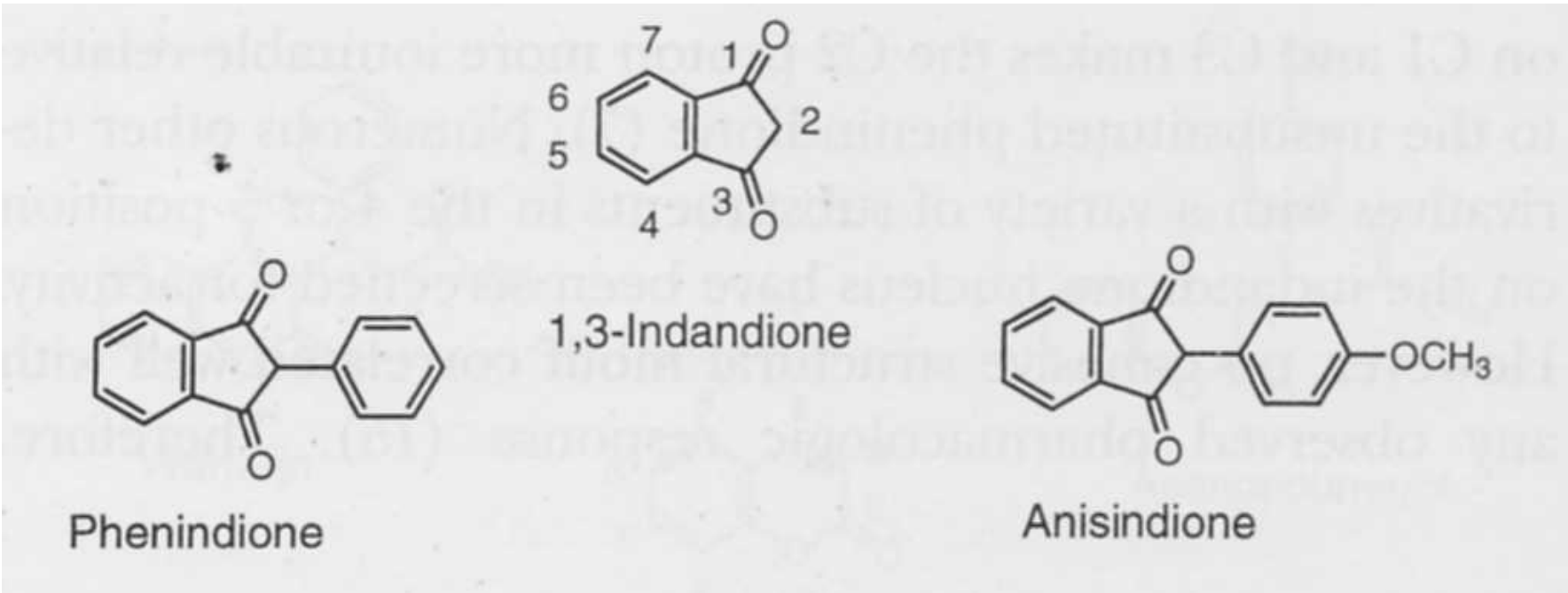


Ethylbiscoumacetate

Superwarfarin analogues-rhodenticides



Indandiones



Heparins

- accelerates binding of antithrombin III (protease inhibitor) to activated IX, X, XI, XII factors, kallikrein and thrombin
- chemically a mixture of sulfated mucopolysacharides

Forms of Heparins

- High molecular weight heparin (HMWH) – unfractionated. Mr 5-30 kD. Individual response for therapy, monitoring necessary
- Low molecular weight heparin (LMWH) – fraction of Mr 4-6 kD isolated from HMWH. Higher selectivity for Xa factor, better pharmacological properties

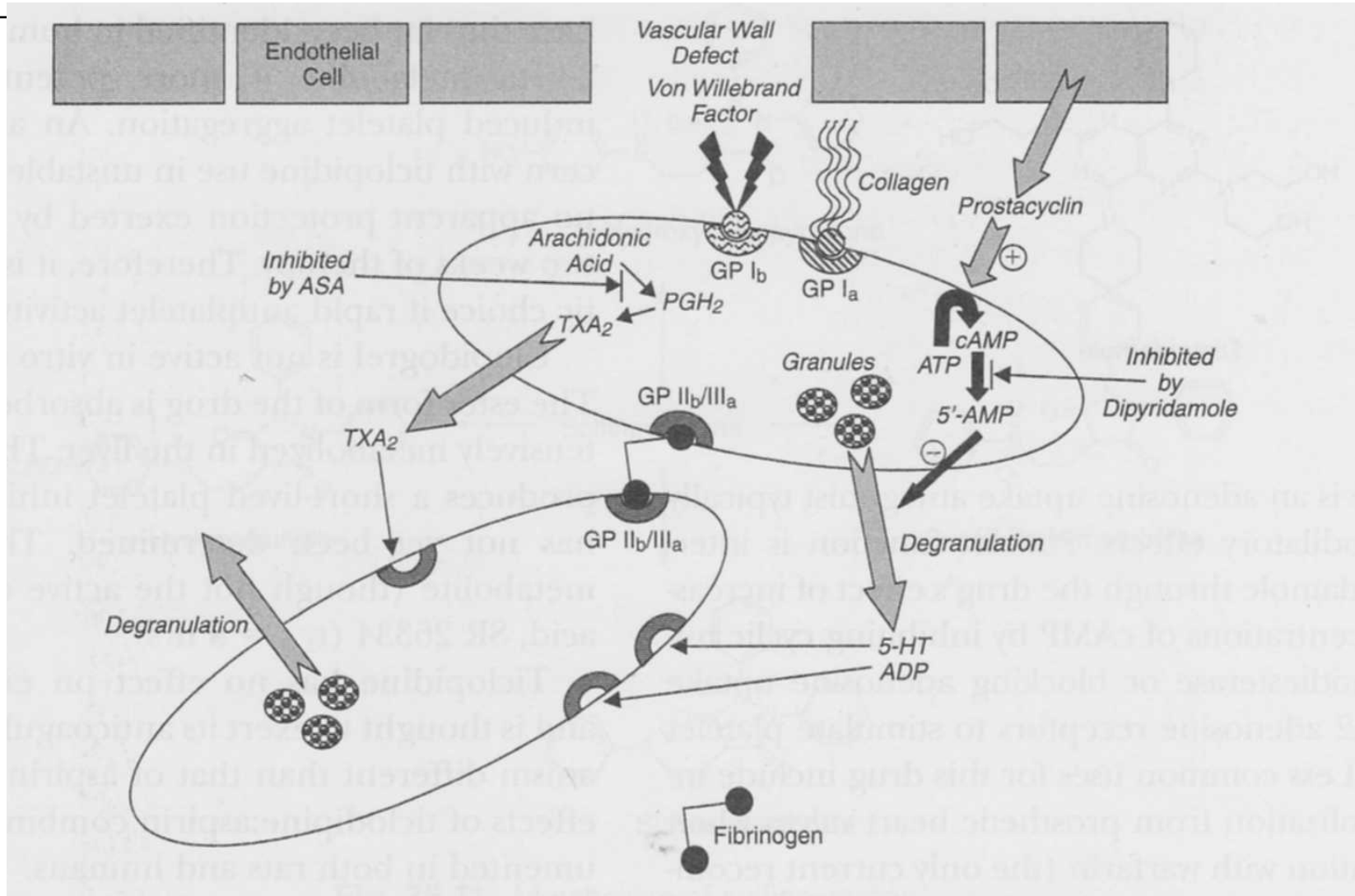
Heparinoids

- synthetic analogues of heparin
- sulfatated polysacharides of similar Mr
- only external use (unguents, creams, gels) due to high system toxicity

Hirudin

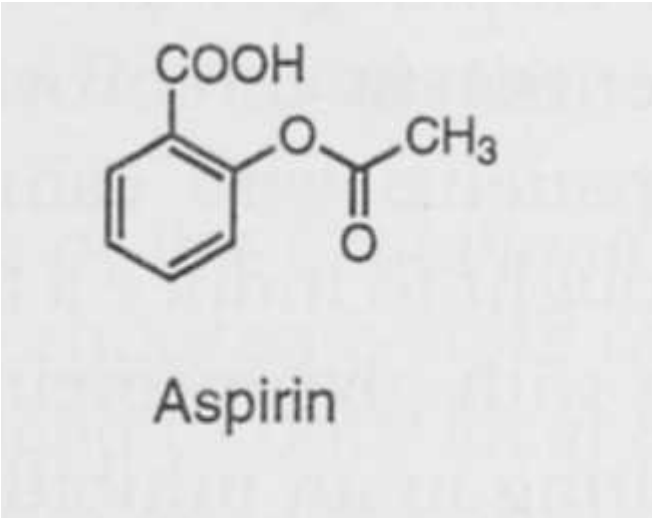
- protein of 65 aminoacids
- originally isolated from medicinal leech, now used recombinant form
- forms complex with thrombin

Antiplatelet drugs



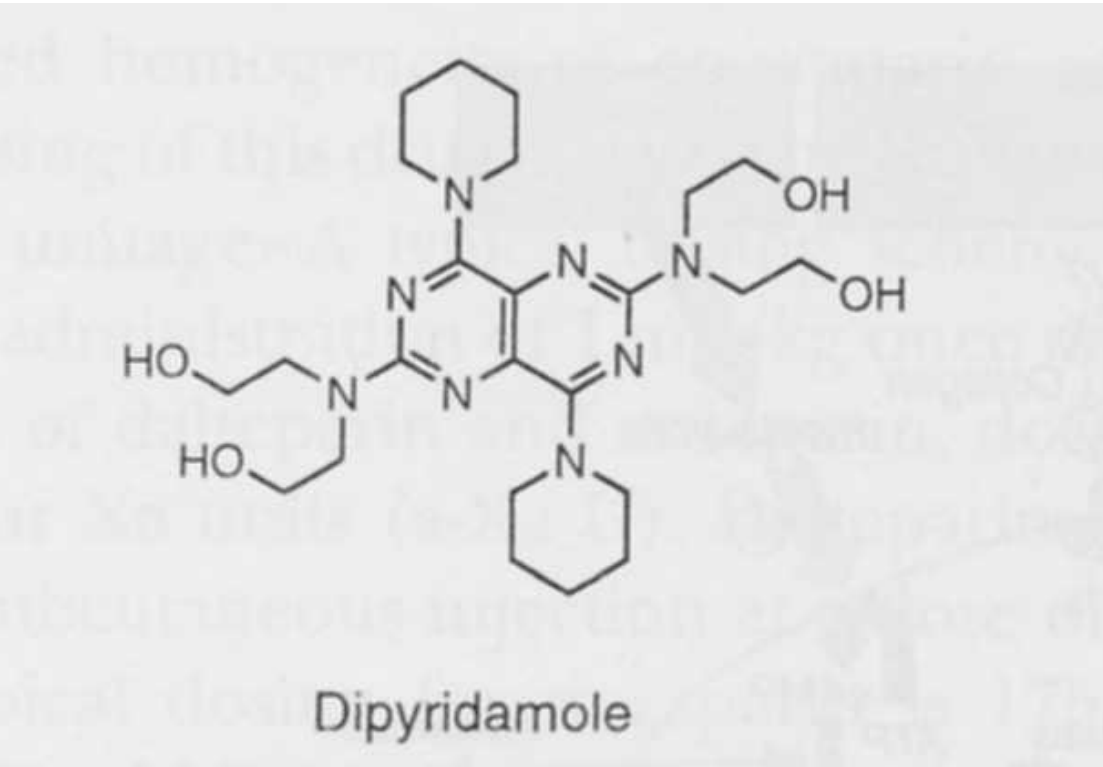
Acetylosalicylic acid (aspirin)

- cyclooxygenase inhibitor



Dipyridamole

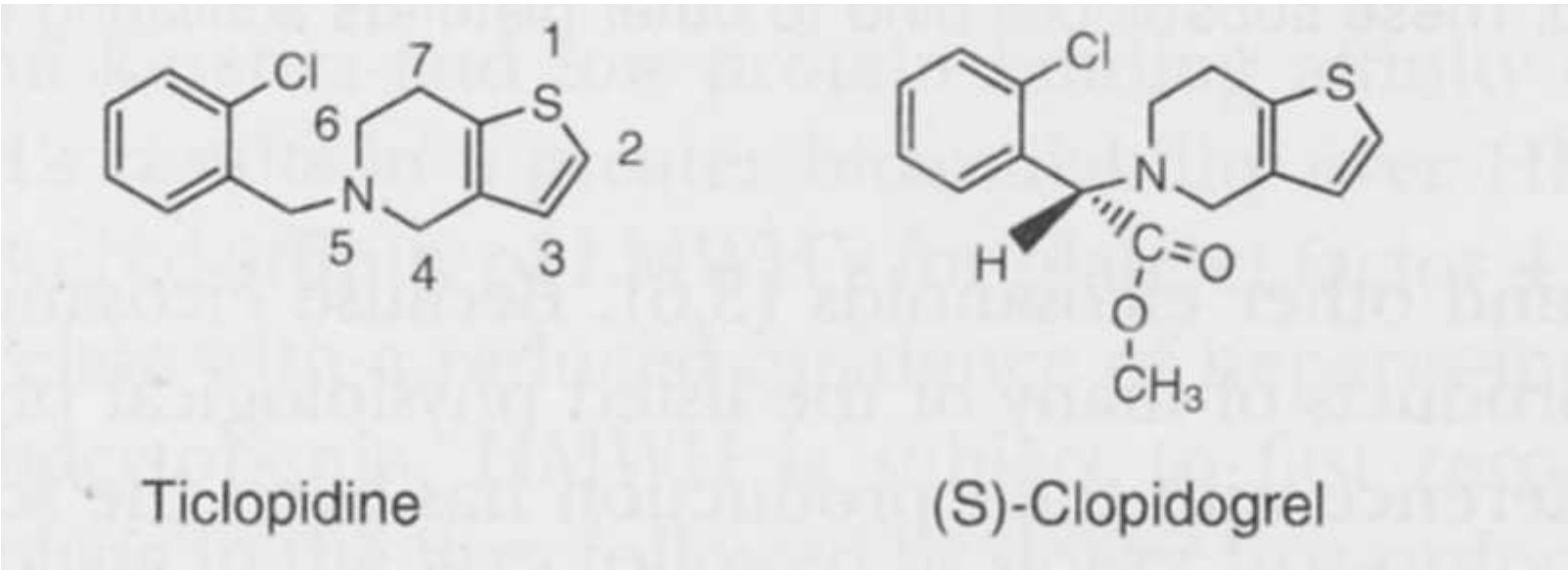
- adenosine uptake antagonist
- in combination with warfarin



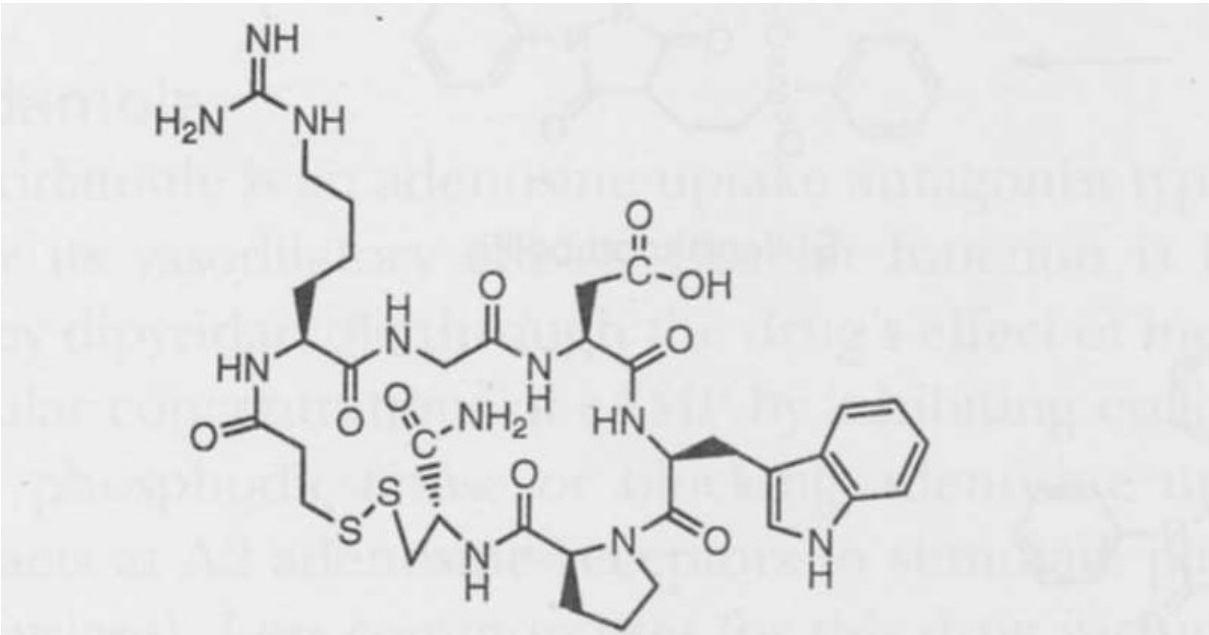
Dipyridamole

Ticlopidine and Clopidogrel

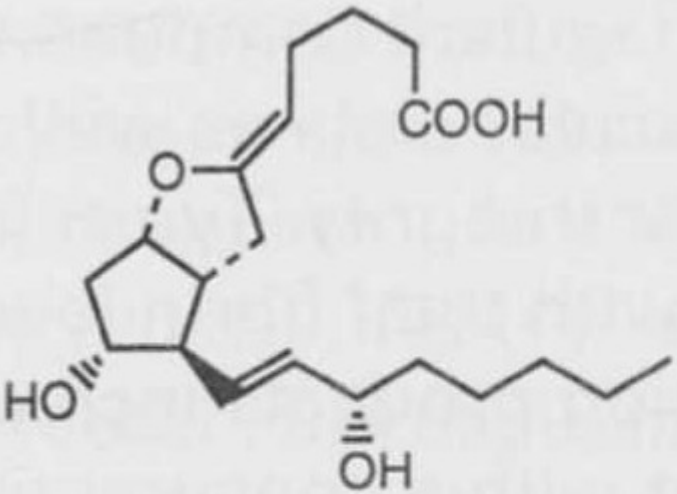
inhibitors of tromboxan-synthase



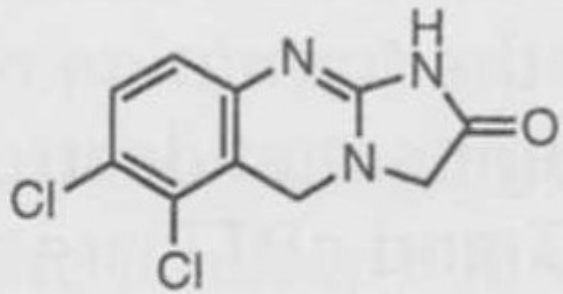
Glycoprotein receptor antagonists



Thromboxan antagonists



Epoprostenol



Anagrelide

Thrombolytic drugs

- physiological fibrinolytic agent – plasmin – non-specific protease enzyme digesting fibrin
- activated from proenzyme plasminogen

Streptokinase

- protein purified from haemolytic streptococcus bacteria
- forms complex with plasminogen – active catalyzator of plasminogen to plasmin conversion
- short biological half-time (30min)
- often hypersensitivity reaction (from rash to anaphylaxis)

Anistreplase

- prodrug of streptokinase with anisoyl groups acylated on lysine fragments
- prolonged biological half-time (90min)

Urokinase

- isolated from human fetal kidney cells
- directly degrade fibrin and fibrinogen
- very short half-time (15min)
- no hypersensitive reactions

Alteplase, Reteplase

- produced using recombinant technology
- analogues of human plasminogen activator
- specifity for already formed clots
- extremely short half-time (5min)
- administrated via continuous infusion

Ancrod, Batroxobin

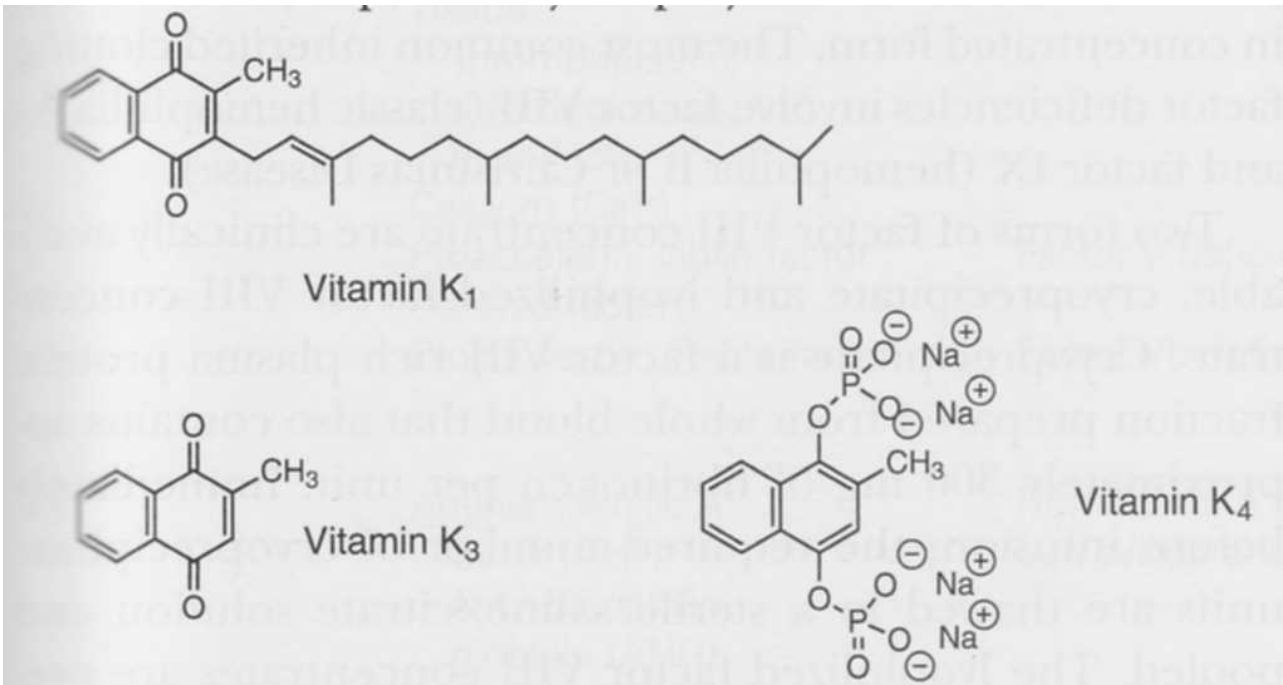
- snake poison proteases
- non-specific effect by digesting both fibrin and coagulation factors

Coagulants

- used in states with excessive bleeding caused by insufficient coagulation

Vitamin K

- Vitamin K1(phytonadion), K3 (menadion), water soluble K4 (menadione sodium diphosphate)



Vitamin K

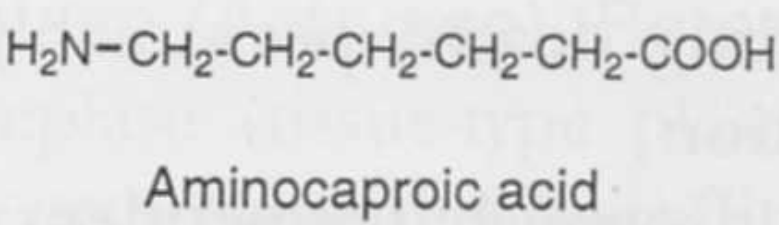
- used in avitaminose states
- therapy of bleeding caused by vitamin K antagonists (including rhodenticides)

Protamine

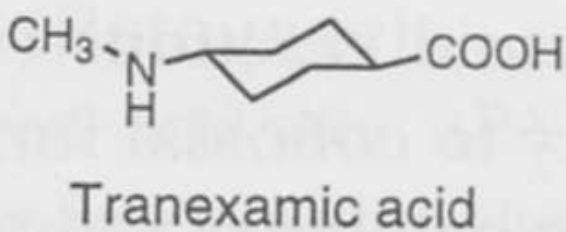
- group of simple proteins
- specific antagonists of heparin
- isolated from salmon sperm
- often hypersensitive reactions

Aminocapronic and Tranexamic acid

- completely inhibits plasminogen activation



Aminocaproic acid



Tranexamic acid

Aprotinin

- protease inhibitor blocking kallikrein and plasmin
- useful in postoperative bleeding

Clotting factors

- recombinant factors substituting physiological factors
- used in chronical diseases like haemophylia

Plasma extenders

- Physiological solution (0.9 % NaCl)
- Ringer solutions (some additive minerals and lactate)
- protein colloids (albumin, plasma protein fraction)
- dextran polymers (branched glucose polymers produced by bacteria)