
CHAPTER 1
General Introduction

1.1 General Introduction

Drugs are defined as chemical substances that are used to prevent or cure diseases in humans and animals. Drugs can also act as poisons if taken in excess. For example paracetamol overdose causes coma and death. Apart from the curative effect of drugs, most of them have several unwanted biological effects known as side effects. Aspirin which is commonly used as an analgesic to relieve minor aches and pains, as an antipyretic to reduce fever and as an anti-inflammatory medication, may also cause gastric irritation and bleeding. Also many drugs, such as antibiotics, when over used develop resistance to the patients, microorganisms and virus which are intended to control by drug. Resistance occurs when a drug is no longer effective in controlling a medical condition.¹ Thus, new drugs are constantly required to surmount drug resistance, for the improvement in the treatment of existing diseases, the treatment of newly identified disease, minimise the adverse side effects of existing drugs etc. Drugs are classified in number of different ways depending upon their mode of action such as antithrombotic drugs, analgesic, antianxiety, diuretics, antidepressant and antibiotics etc.²

Antithrombotic drugs are one of the most important classes of drugs which can be shortly defined as “drugs that reduce the formation of blood clots”. The blood coagulation, also known as haemostasis is a physiological process in which body prevents blood loss by forming stable clot at the site of injury. Clot formation is a coordinated interplay of two fundamental processes, aggregation of platelets and formation of fibrin. Platelet aggregation involves association of platelets through physical forces following their activation, whereas fibrin formation involves the chemical synthesis of fibrin polypeptide through the action of several enzymes and cofactor. The clot which forms at unwanted place and blocks the blood flow is known as thrombus and the phenomenon is known as thrombosis. Thrombosis can be treated by either preventing thrombus formation or dissolving existing thrombus. Thus, there are three classes of antithrombotic agents—antiplatelets, anticoagulants and thrombolytic drugs (**Figure 1.1**). Antiplatelet molecules block the physical process (traditionally referred as the cellular process), anticoagulants inhibit the chemical process (also referred as the humoral process) whereas thrombolytic drugs dissolves the blood clot by a process of thrombolysis.³

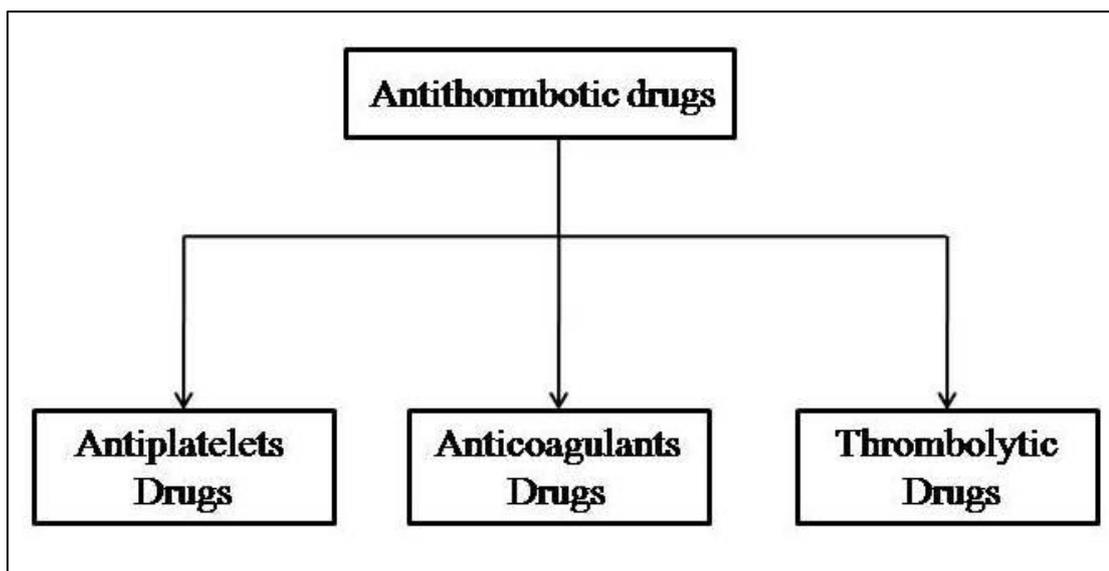


Figure 1.1 Classification of Antithrombotic drugs

Blood flow is a complex and highly regulated physiological process, with multiple complementary and opposing mechanisms of control. Normally in the vasculature, a precise balance is achieved, permitting free flow while also allowing the trigger of nearly instantaneous clot formation at sites of vascular injury to prevent hemorrhage. Indeed, blood coagulation evolved in humans and animals as a protective mechanism against bleeding. As protective blood clots (hemostatic plugs) form and grow after injury, mechanisms exist to maintain or dissolve them as needed (known as fibrinolysis) while allowing normal flow in the remainder of the vasculature.

Understanding of Haemostasis and Fibrinolysis

A thorough understanding of the haemostatic system is essential in order to design and develop a new anticoagulant agent. Many theories were suggested by ancient researchers in order to understand the mechanism of blood clotting. Plato in *Omnia divini Platonis opera*, Hippocrates in *De Carnibus* and Aristotle in *Meteorology* mentioned that when blood leaves the body there is drop in temperature and this result into haemostasis. In the 18th century, physicians became aware that blood clotting is a natural mechanism to prevent the blood loss from an injury. Jean-Louis Petit a French surgeon in the 1730s first recognized that bleeding after amputation was controlled by clotting.⁴

According to current understanding haemostasis consists of two stages primary and secondary. Primary haemostasis begins immediately after endothelial damage and involves blood vessel constriction followed by the activation and adhesion of platelets to form a soft aggregate plug. While the secondary haemostasis consists of the complex assembly in which serine proteases gather at the cell membrane receptors where they arrange into complexes with cofactors leading to a series of regulated enzymatic reactions that ultimately result in the formation of a stable fibrin blood clot at the site of injury.⁵ The secondary haemostasis was presented as a coagulation/waterfall model in 1964 by Ratnoff and Davie and very soon after that McFarlane presented the cascade theory of coagulation which explains the modern concept of coagulation.⁶ The coagulation cascade can be divided into two pathways; 1) Initiation and 2) Propagation (**Figure 1.2**).

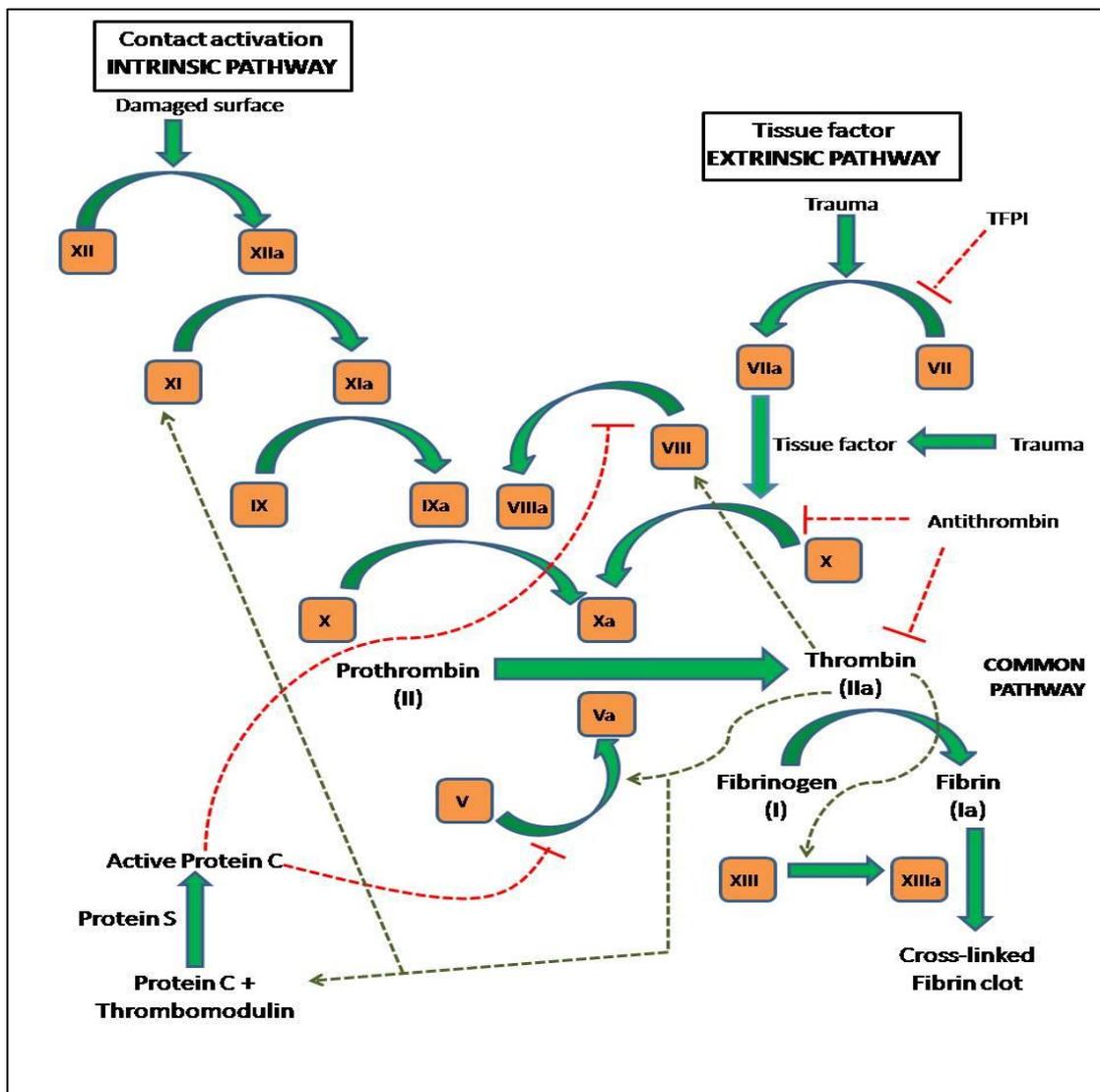


Figure 1.2 Blood Coagulation Cascade Model

The primary and most important pathway for the initiation of blood coagulation is the tissue factor (TF) pathway that takes only three steps to activate thrombin. In this pathway factor VII gets converted to its active form factor VIIa by trauma. The cascade is triggered when the factor X gets activated by factor VIIa, which leads to the generation of small amount of thrombin (factor IIa). However factor VIIa gets rapidly deactivated by tissue factor pathway inhibitor. The small amount of thrombin generated is the first phase of initiation. When the prothrombin (factor II) is activated (factor IIa), it initiates the propagation of factor V and factor XIII, as well as factor VIII and XI in contact activation pathway. The propagation phase is mediated by contact activation pathway. This pathway is also activated by factor XII providing an alternative route for fXI activation. Fibrin cleaved by this pathway is slower than the extrinsic pathway. The *Hageman factor* (factor XII), factor XI, *prekallikrein* and *high molecular weight kininogen* (HMWK) are involved in this pathway of activation. Thus this pathway provides a further interrelationship between the various enzyme cascade systems in plasma. The first step is binding of factor XII to sub-endothelial surface exposed by an injury. A complex of *prekallikrein* and HMWK also interacts with the exposed surface in close proximity to the bound factor XII, which becomes activated. During activation, the single chain protein of the factor XII is cleaved into two chains (50 and 28 kDa). The light chain (28 kDa) contains the active site and the molecule is referred to as activated factor XIIa. *Hageman factor* can auto activate, thus the pathway is self-amplifying once triggered. Factor XIIa in the presence of HMWK converts factor XI to factor XIa. Factor XIa then cleaves factor IX to factor IXa. Factor IXa combines with factor VIIIa, activated by either thrombin or fXa, in the presence of calcium and phospholipids, to form the tenase complex. This complex in turn converts factor X to fXa.⁷

Factor Va along with fXa, calcium and anionic phospholipids form the prothrombinase complex consist of common pathway. Factor Va derives from several sources, including activated platelets adhering at injury sites, as well as from plasma, where fV can be activated by fXa. The prothrombinase complex then cleaves prothrombin (fII) to generate small amounts of thrombin (fIIa), the final coagulation enzyme responsible for clot formation. Factor Xa can cleave prothrombin in the absence of factor Va, anionic phospholipids and calcium, however this activation is approximately 300,000 folds less as compared within the prothrombinase complex.⁸

Meanwhile, the thrombin proteins also feed back to activate more platelets to stop further bleeding. Thus, thrombin converts fibrinogen to soluble fibrin. This soluble fibrin then polymerizes to cross linked fibrin by factor XIIIa on the surface of activated platelets and forms a permeable haemostatic plug. This provides positive feedback and ensures efficient generation of burst of thrombin and fibrin, so that haemostasis can occur.⁶ The enzymes responsible for blood coagulation are all serine protease except fV, fVII which are glycoprotein and fXIII a transglutaminase. All these enzymes are secreted as inactive zymogene and are sequentially activated by other serine proteases.

Coagulation cascade is regulated at different stages. When factor VII is activated by tissue factor released from trauma, it is almost immediately inhibited by the tissue factor pathway inhibitor protein (TFPI). The most important physiological inhibitor of the coagulation cascade is Antithrombin. Its anticoagulant activity is focused on the regulation of thrombin, fXa and fIXa.⁹ Activated protein C is the third inhibitor of coagulation cascade which inactivates fVa and fVIIIa. It is activated by thrombomodulin-thrombin complex in presence of protein S.¹⁰

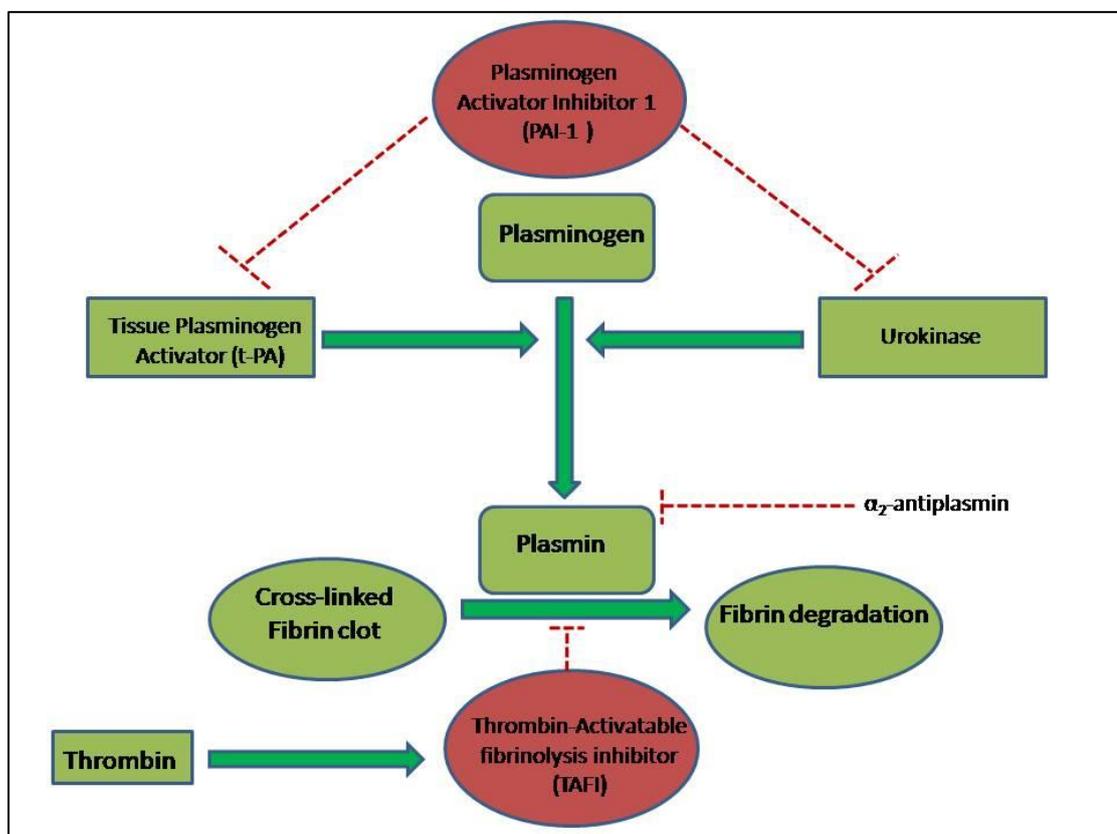


Figure 1.3 Fibrinolysis pathway

Once haemostasis is restored and the tissue is repaired, the clot or thrombus must be removed from the injured tissue, restoring normal blood flow to that area. This is achieved by fibrinolytic pathway (**Figure 1.3**). Dissolving fibrin and the eventual removal of the blood clot¹¹ is achieved by fibrinolytic system. The pro-enzyme plasminogen is converted to plasmin in the presence of fibrin and an enzyme tissue plasminogen activator (t-PA). Urokinase plasminogen activator is also able to catalyze this conversion. However exact role of urokinase in vascular fibrinolysis is less clear¹² instead it is majorly involved in cell migration and tissue remodeling through extravascular activation of plasminogen.¹³ Thus t-PA is the main plasminogen activator in fibrinolysis pathway. Plasmin breaks fibrin into small soluble fractions known as fibrin degradation products (FDPs). There are several types of FDPs, since plasmin cleaves at multiple sites in the fibrin structure. Like coagulation, fibrinolysis is also carefully regulated. This process is regulated by α -2-antiplasmin, a protein that binds to and inactivate plasmin,¹⁴ plasminogen activator inhibitor (PAI-1) and thrombin activable fibrinolysis inhibitor (TAFI) also known as carboxypeptidase U (CPU)¹⁵ (**Figure 1.3**).

Cause of Thrombosis and Thrombotic disorders

Imbalances in the complex regulatory network of coagulation and anticoagulation, however, can lead to a variety of pathological consequences. Thrombosis is a pathological consequence of haemostasis. It takes place when the haemostatic response surpasses the normal regulatory counterbalance by anticoagulant factors or due to failure of fibrinolytic pathway, which are supposed to limit and localize thrombus formation to the injured area.¹⁶ Thrombus which travels within the body is known as embolus and the phenomenon is known as embolism. Abnormal formation of thrombus in arteries and veins in the body results into set of thrombotic disorders which leads to a wide range of cardiovascular diseases. These conditions may develop due to aging, hereditary causes, acquired disease conditions (e.g., atheromatous disease, cancer, antiphospholipid syndrome) and use of drugs (e.g., oral contraceptive).¹⁷ Cardiovascular disease is the class of diseases that affects circulatory system which includes heart and blood vessels (arteries, capillaries and veins). Thus there are two types of thrombotic disorders arterial thromboembolism and venous thromboembolism (VTE).

In arterial thrombosis, thrombi are mainly platelet rich and fibrin poor (so called white clots) and are formed under high shear stress. The primary trigger of arterial thrombosis is rupture of atherosclerotic plaque.¹⁸ When this rupture takes place platelets become activated and gathered rapidly at the site by platelet aggregation process which results in the rapid growth of the thrombus. This process is followed by activation of coagulation factors in coagulation cascade resulting into generation of fibrin the main protein component of the thrombus and this cascade operates in both arterial and venous thrombosis. Arterial thrombosis leads to heart disease such as myocardial infarction (MI), arterial fibrillation (AF) and stroke (**Figure 1.4**).¹⁹ There is an important association between myocardial ischemia commonly known as acute coronary syndrome (ACS) and AF with an estimated relative risk for AF of 2.8 for angina and 3.6 for MI.²⁰ Most acute myocardial infarctions are caused by thrombosis developed on a coronary atherosclerotic plaque. Unstable angina is a consequence of thrombosis, which is the major initiating factor. A thrombus that is fibrin-rich often fully blocks artery and results in ST-elevated myocardial infarction (STEMI), whereas a platelet-rich arterial thrombus is often partially occlusive, resulting in unstable angina and non-ST-elevated myocardial infarction.

Patients suffering from AF are having high risk of stroke in brain because the thrombi developed in the atria can move into the cerebral blood vessel from heart (**Figure 1.4**). Stroke has symptoms such as inability to understand, inability to move limbs on one side of the body, vision impairment of one side of the visual field, permanent damage to nervous system and death.²¹ An estimated 5-14% of all strokes are caused by cerebral emboli. Due to arterial emboli there is insufficient supply of oxygen to tissue resulting into its death and confiscation of the affected limb if not treated effectively within hours.²²

Coronary artery thrombosis is responsible for acute myocardial infarction which is the common cause of death in the developed world. The World Health Organization (WHO) reports that more than 70 % of coronary deaths occur in subjects older than 70 yrs in North America and Western Europe. In India and other developing countries 70 % deaths occur in subjects less than 70 yrs of age.²³ About 12 million people affect every year and causes 5 million deaths by ischemic stroke which

is the third leading cause of death in developed countries.²⁴ As per WHO report in 2009, the incidence of stroke in India is around 130 per 100,000 people every year. Epidemiological studies from various parts of India have reported the rising trends and a high burden in the levels of conventional risk factors such as diabetes, hypertension and metabolic syndrome which are largely determined by urbanization as evident from the urban-rural difference in the risk factors observed in India.^{25, 26}

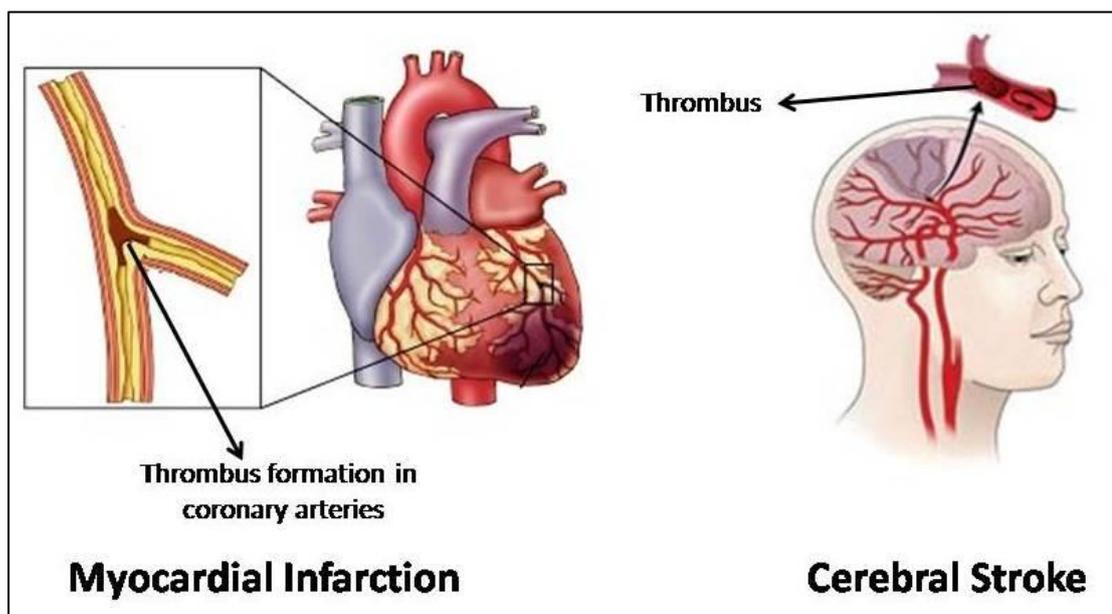


Figure 1.4 Schematic representation of Arterial thromboembolism

Thrombi that forms in veins are rich in fibrin and trapped red blood cells and are referred to as red clots. Venous thromboembolism (VTE) is a collective term used to describe a number of medical conditions that result from abnormal thrombosis formation in veins including deep vein thrombosis (DVT) and pulmonary embolism. VTE is the third leading cause of cardiovascular-associated death, after myocardial infarction and stroke. Deep vein thrombosis occurs in large veins of the legs and it leads to pulmonary embolism when the part thrombus breaks away and travels to the lungs to block pulmonary artery, resulting in obstruction of blood flow.²⁷ Change in the composition of the blood that promotes thrombosis, changes that reduce blood flow and changes to the vessel wall results into deep vein thrombosis.

In the western world, the incidence is one case of DVT and 0.5 cases of PE per 1000 population per year.²⁸ Autopsy studies have shown the incidence of VTE in hospitalized patients to be as high as 34.7% with fatal pulmonary embolism in 9.4%

of cases.²⁹ VTE contributes substantially to patient morbidity, mortality and cost of management. VTE is prevalent throughout the world. In a recent global epidemiological study, 52% (42% medical and 64% surgical) of 68183 (55% medical and 45% surgical) patients in 358 hospitals across 32 countries were found to be at risk for developing VTE. India contributed 2058 patients (46% medical and 54% surgical), where 54% (45% medical and 61% surgical) of hospitalized patients had risk factors for VTE.^{30,31}

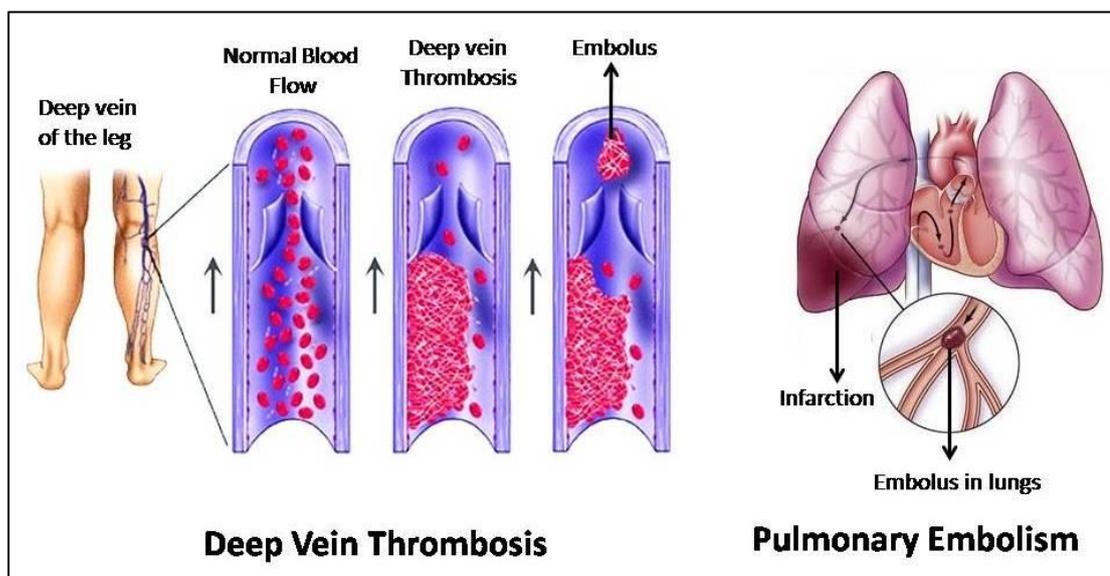


Figure 1.5 Schematic representation of Venous thromboembolism

Antithrombotic Therapy

Antithrombotic agents are divided into three main groups depending upon their mechanism of action as antiplatelets, anticoagulants and thrombolytic drugs (*vide infra*).

Antiplatelet drugs prevent activation and aggregation of platelet and are generally used for the treatment and the prevention of arterial thrombosis (because arterial clots are platelet-rich and fibrin-poor).^{32,33} Therefore there are two pathways, platelet activation (ADP receptor signaling, PAR1 signaling and TXA2 signaling) and platelet aggregation (phosphodiesterase and α IIb β 3 integrin) which are found to be beneficial in targeting at the time of antiplatelet therapies. Thus, there are four classes of antiplatelet drugs (a) thromboxane/cyclooxygenase inhibitors, (b) ADP-receptor antagonist (c) GPIIb/IIIa or α IIb β 3-integrin inhibitors and (d) cyclic nucleotide phosphodiesterase (PDEIII inhibits PYP12-mediated cAMP pathway of platelet aggregation) antagonists depending on their mode action. Aspirin is the first and most

widely used antiplatelet drug which inhibits platelets activation by irreversible inhibition of cyclooxygenase-1 (COX-1).³⁴ Some examples of antiplatelet drugs are Aspirin (1), ticlopidine (2), clopidogrel (3), prasugrel (4), dipyridamole (5) and cilostazol (6) (**Figure 1.6**).

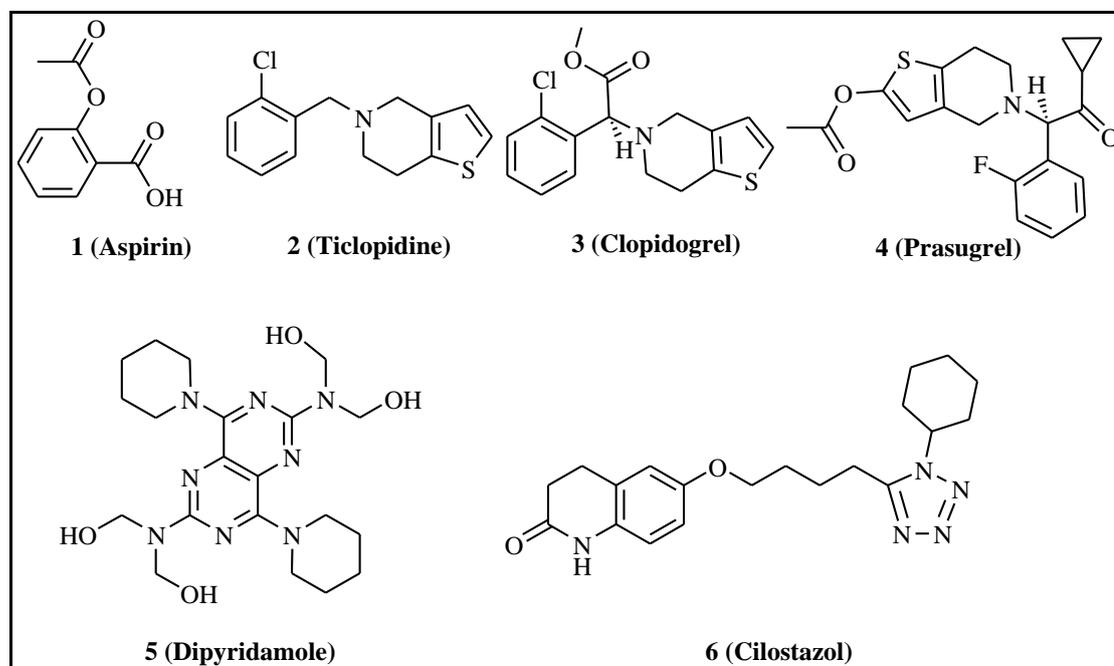


Figure 1.6 Antiplatelet drugs

Thrombolytic drugs accelerate the transition of plasminogen to active enzyme plasmin which degrades fibrin clot.¹⁹ Streptokinase and recombinant tissue plasminogen activator (rt-PA) (Alteplase, Reteplase and Tenecteplase, etc.) are activators of fibrinolytic system and major thrombolytic drugs in this category. The major drawback associated with thrombolytic therapy is bleeding due to fibrinolysis at the site of injury. However as compared to streptokinase, recombinant tissue plasminogen activator (rt-PA) causes less extensive fibrinogenolysis but bleeding occurs with similar incidence for all agents.³⁵ Plasminogen activator inhibitor-1 (PAI-1) and activated thrombin activatable fibrinolysis inhibitor (TAFIa) are now days new target for thrombolytic therapy without and without t-PA. Inhibition of both indirectly inhibit fibrinolysis thus leading to reduced bleeding complications.³⁶

Anticoagulant agents target proteins of the coagulation cascade thus establishing their role in the treatment and the prevention of venous thrombosis (because venous clot are fibrin-rich and platelet-poor). However the arterial clot

contains fibrin so they are also used in prevention of arterial thrombosis.^{19,37} Anticoagulants are generally divided into four main categories a) heparins and its derivatives b) vitamin K antagonists (VKAs) c) direct thrombin inhibitors (DTIs) d) direct fXa inhibitors.

Conventional anticoagulant therapy includes animal derived unfractionated heparin (UFH), chemically fractionated low-molecular-weight heparins, Fondaparinux and VKAs. McLean was the first to discover the anticoagulant property of heparin in 1916.³⁸ Heparin binds to the antithrombin and enhances its ability to inhibit fXa and thrombin. UFH is a mixture of glycosaminoglycans and polysaccharides composed of a long chain of repeated disaccharide unit with variable composition and length with species of molecular weights ranging from 3 to 30 kDa (most in the range 12-15 kDa).³⁹ LMWHs are the fractionated heparin derived chemically or enzymatically from UFH. Their molecular weight ranges from 4371 Da to 5866 Da. Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin and Tinzaparin examples of LMWHs.⁴⁰ They are administered subcutaneously once or twice daily. Heparins have several limitations like inability to neutralize fibrin-bound thrombin, binding to various plasma proteins and unpredictable dose-dependent anticoagulant response. Therefore, anticoagulant monitoring and routine dose adjustments is required for UFH and LMWHs.⁴¹

Fondaparinux an indirect factor Xa inhibitor is a pentasachharide and is chemically related to low molecular weight heparins. It is a selective and reversible fXa inhibitor. As compared to UFH and LMWH it has minimal side effects. Use of fondaparinux has been approved as an alternative to LMWH in certain types of surgery, such as orthopedic.⁴²

VKA as for example warfarin (**7**), dicoumarol (**8**), acenocoumarol (**9**), phenprocoumon (**10**), tecarfarin (**11**) (**Figure 1.7**) inhibits the enzyme vitamin-K epoxide reductase (VKORC1) and thus restrict γ -carboxylation of vitamin K. This further inhibits the activation of several enzymes responsible for coagulation such as fII, fVII, fIX and fX as well as the naturally occurring endogenous anticoagulant proteins C and S. Of all the VKAs warfarin is the good standard for oral anticoagulants therapy from last 60 years. VKAs are also associated with side effects such as increased bleeding risk, narrow therapeutic window, food-drug interaction and

variability in dose-response. Also a strict monitoring of the international normalized ratio (INR) is required for patients on VKAs therapy.^{43,44} These disadvantages of traditional anticoagulant therapy have led the foundation for the researchers to look for new promising alternatives to overcome these drawbacks. Therefore a new approach has been adopted by targeting a single coagulation factor directly. The development of target-specific anticoagulants has mainly focused on components of the common pathway that is thrombin and fXa. However enzymes of intrinsic pathway such as fIXa, fXIa and fXIIa are also targeted for development of new anticoagulant drugs.

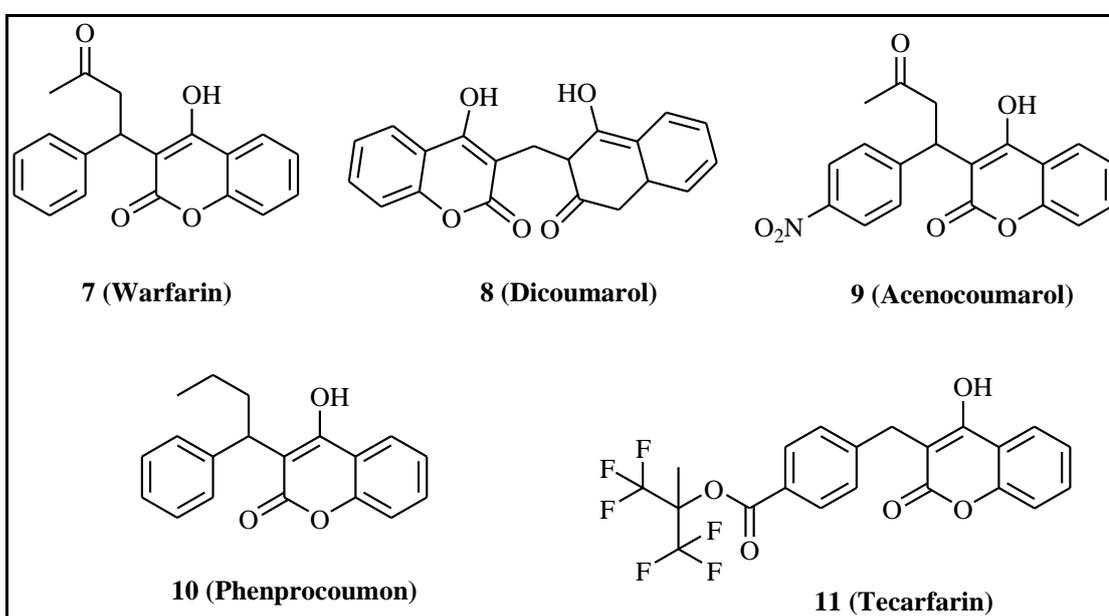


Figure 1.7 Vitamin K antagonist anticoagulant drugs

Thrombin is responsible for the conversion of fibrinogen to fibrin; also it activates various coagulation factors like fV and fVIII (**Figure 1.2**). Direct thrombin inhibitors (DTIs) inhibits free thrombin and clot-bound thrombin therefore it very effective and predictive anticoagulant therapy. Ximelagartran was the first orally available DTI with a good anticoagulant activity but was withdrawn from the market in 2006 due to its hepatotoxicity. Dabigatran etexilate (**18**) was the next oral DTI which is the prodrug that is rapidly converted to dabigatran. Argatroban (**17**), recombinant hirudin and its derivatives bivalirudin, desirudin, and lepirudin are parental DTIs. These are reversible inhibitors of thrombin having less bleeding than the irreversible direct thrombin inhibitors (**Figure 1.8**). However its lab monitoring and parental administration makes them less useful as compared to dabigatran.⁴⁵

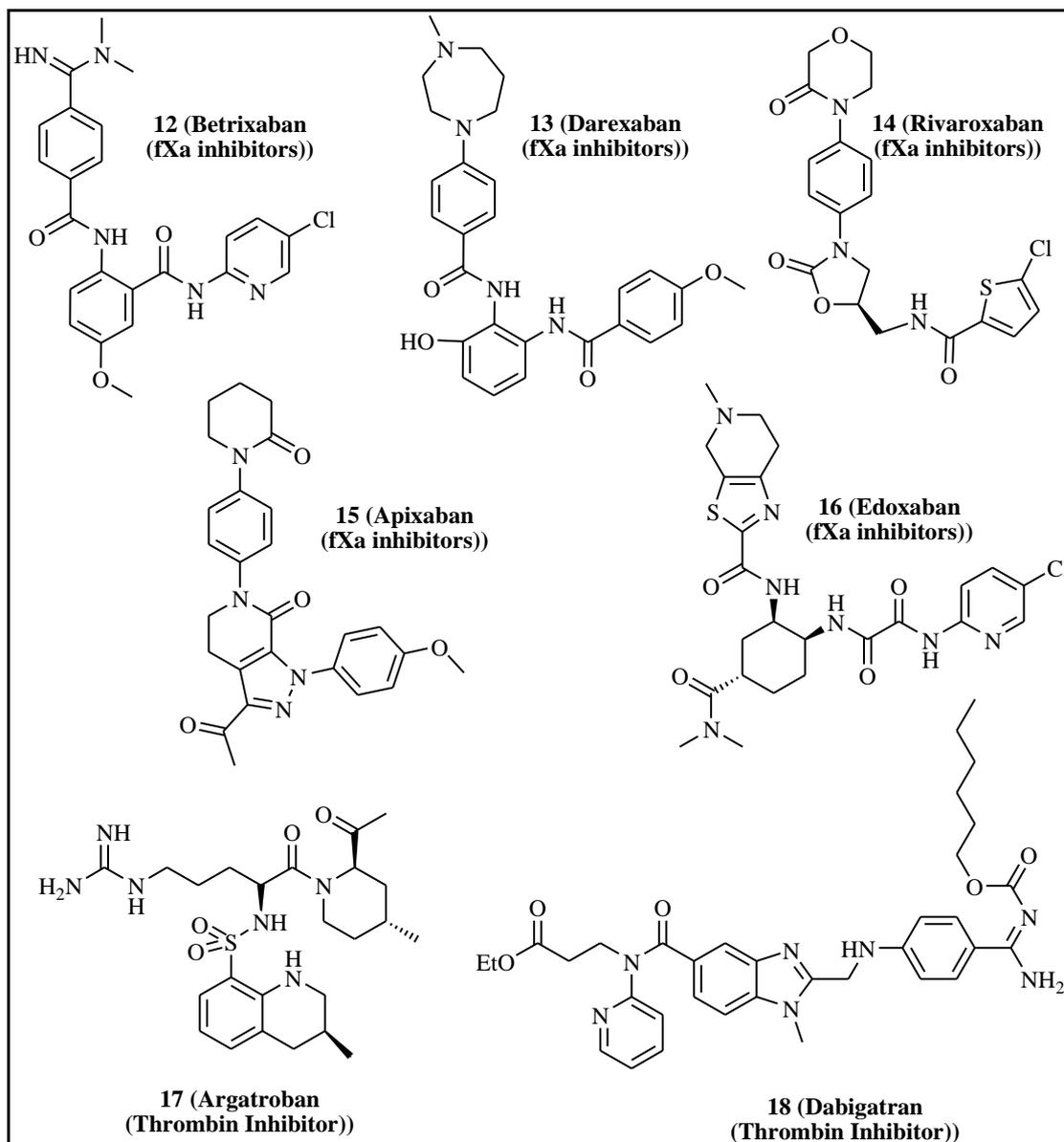


Figure 1.8 Anticoagulants inhibiting Factor Xa and thrombin

Factor Xa has a unique position in blood coagulation cascade at the juncture of the intrinsic and extrinsic pathways, which catalyzes the formation of thrombin from prothrombin via prothrombinase complex (**Figure 1.2**). It is known that thrombin is responsible for fibrin clot formation in the cascade and also has several thrombotic functions, including activation of platelets and feedback activation of several coagulation factors.⁴⁶ Inhibition of fXa should safely interrupt blood coagulation and prevent production of new thrombin without affecting its basal level. Hence fXa inhibitors are predicted to cause less mutilation of hemostasis than direct thrombin inhibitors, leading to a higher therapeutic ratio.⁴⁷⁻⁵⁰ Therefore, extensive research have

been carried out during the last few decades to develop novel orally administered fXa inhibitors. In this direction many small molecule fXa inhibitors having different scaffolds have been reported.⁵¹ Rivaroxaban (**14**) is the first oral factor Xa inhibitor available in market. Also betrixaban (**12**), darexaban (**13**), apixaban (**15**) and edoxaban (**16**) are some of the examples of most active fXa inhibitors⁵²⁻⁵⁴ (**Figure 1.8**).

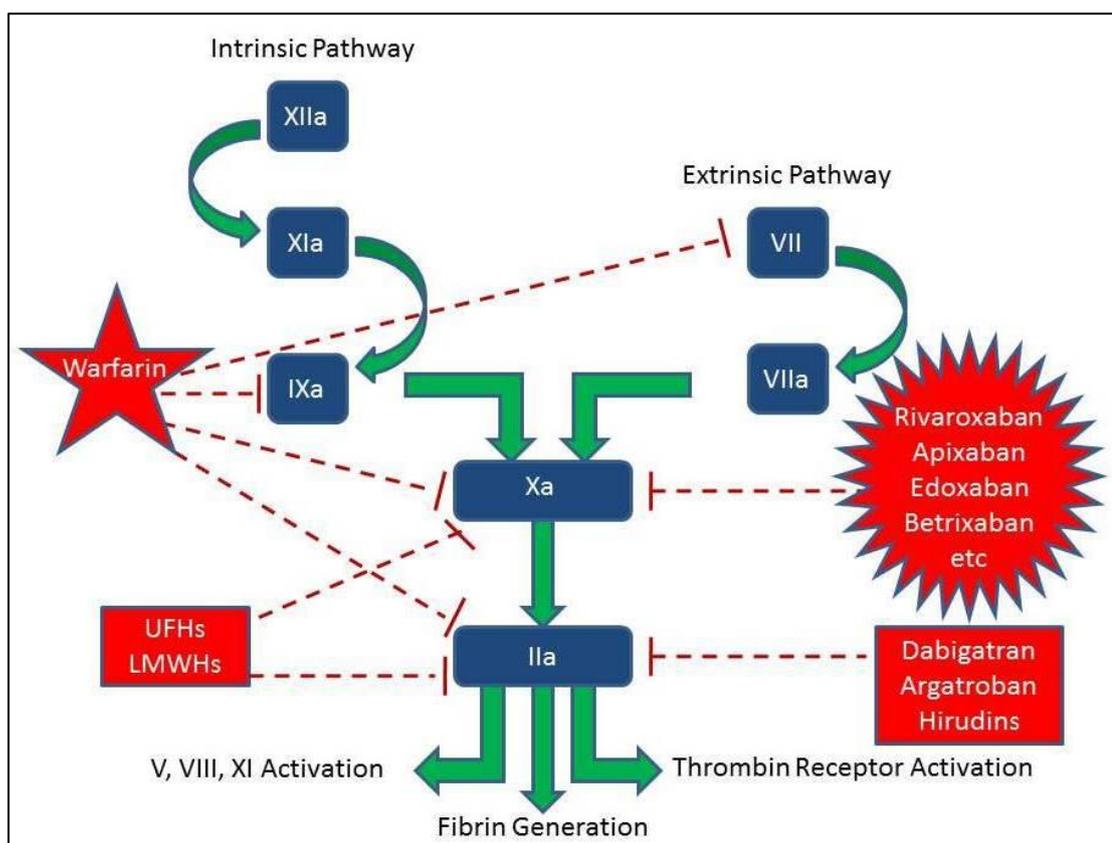


Figure 1.9 Some examples of anticoagulants targeting coagulation cascade enzymes.

Several protease enzymes in extrinsic and intrinsic pathway are targeted by various anticoagulant drugs as discussed above. **Figure 1.9** shows few examples of the anticoagulants inhibiting various enzymes.

Thus various antithrombotic drugs for the treatment of thrombotic disorders are available in market **Tables 1.1** shows some of the examples.

Table 1.1 Prescribed antithrombotic drugs

Classification	Biological function	Marketed name
Glycoprotein Iib/IIIa inhibitors	Preventing platelet aggregation and thrombus formation	Abciximab; Eptifibatide; Tirofiban
Other platelet aggregation inhibitors	Preventing platelet aggregation and thrombus formation	Acetylsalicylic acid/Aspirin; Aloxiprin; Ditazole; Carbasalate calcium; Cloricromen; Clopidogrel; Dipyridamole; Indobufen; Picotamide; Prasugrel; Ticlopidine; Triflusal; prostaglandin analogue
Plasminogen activators	Activating plasminogen	Alteplase/Retepase/Tenecteplase, Streptokinase, Urokinase/Saruplase, Anistreplase
Vitamin K antagonists	Antagonising the effects of vitamin K and prevent the activation of vitamin K dependant protein	Acenocoumarol; Clorindione; Coumatetralyl; Dicumarol (Dicoumarol); Diphenadione; Ethyl biscoumacetate; Phenprocoumon; Phenindione; Tiocloamarol; Warfarin
Heparins	Activating antithrombin III which block thrombin from clotting	Antithrombin III; Danaparoid; Heparin; Sulodexide; low molecular weight heparin (Bemiparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin)
Direct thrombin inhibitors (DTIs)	Inhibiting thrombin	Argatroban; Bivalirudin; Dabigatran; Desirudin; Hirudin; Lepirudin; Melagatran; Ximelagatran
Factor Xa Inhibitor	Inhibiting factor Xa	Rivaroxaban, Apixaban, Edoxaban

Presently there are several antithrombotic drugs for treatment of thromboembolic diseases however most of them are associated with drawbacks and do not fulfill the definition of the ideal anticoagulant. Ideal anticoagulant should not require routine monitoring of coagulation or platelet counts, have low rate of bleeding, administered orally with fixed dosage, should have wide therapeutic window, less interaction with food and other drugs and effective in reducing thromboembolic events. As described earlier thromboembolic diseases are associated with high mortality and morbidity. Current therapeutic options to treat thrombotic disorders are effective but not adequate enough to meet the patient's requirements. Among the novel anticoagulant drugs, orally administered direct thrombin inhibitors and factor Xa inhibitors display better efficiency and improved safety profile. Inhibition of fXa should prevent production of new thrombin without affecting its basal level, which should ensure primary hemostasis. Hence, fXa inhibitors are predicted to have lower risk of bleeding than heparins and warfarin, and even higher therapeutic ratio than direct thrombin inhibitors (DTIs). This provides a rationale to develop new and improved fXa inhibitors as anticoagulants.

Chapter 2 describes the design, synthesis and characterization of some novel neutral 2-substituted benzamidobenzene derivatives as factor Xa inhibitors.

Chapter 3 is devoted to molecular docking study and biological activities of 2-substituted benzamidobenzene derivatives (synthesized in chapter 2) as factor Xa inhibitors along with thrombin, activated partial thromboplastin time (APTT) and prothrombin time (PT) of most active molecules

In continuation of our research in the development of novel anticoagulants we sought an oxidant which could selectively oxidize sulfide to sulfoxide. Thus **chapter 4** is subject matter of development of novel reagent, Cetyltrimethyl ammonium Periodate (CTAPI), for selective oxidation of sulfide to sulfoxide.

While **chapter 5** explores the application of CTAPI in diastereoselective oxidation of (-) and (+) S-Phenyl-S-Neomenthyl sulfides to corresponding sulfoxides.

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