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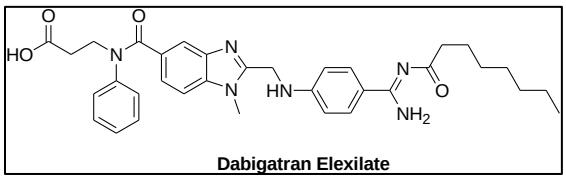
Discovery and development of dabigatran

Preetpal S. Sidhu
Department of Chemistry and Biochemistry, University of Wisconsin, 2200 E. Kenwood Blvd., Milwaukee, WI 53201-0413, USA
Email: Sidhup@uwm.edu

Abstract
Thrombin is key protease involved in regulation of coagulation cascade and thus, highly targeted to design the newer anticoagulant. Various direct and allosteric inhibitors of thrombin were designed but few made their way to clinic. Dabigatran is direct inhibitors of thrombin approved by FDA for clinical use. This article highlights the discovery and development of dabigatran as newer anticoagulant drug.

Keywords: allosteric inhibitors, anticoagulant, dabogatran, coagulation cascade, thrombin

Thromboembolic disorders are a major cause of death in the modern society due to life-style changes [1]. Current therapies include indirect thrombin inhibitors (heparin and low molecular weight heparin), Vitamin K antagonist (warfarin), and direct thrombin inhibitors (argatroban and bivalirubin) [2, 3]. Recently the focus has been on the discovery of selective and safer inhibitors of thrombin targeting the active site and exosites of thrombin [4-8]. Thrombin is the main effector protease involved in the coagulation cascade. Thrombin is activated upon contact with tissue factor on exposed extravascular tissues [3]. Thrombin activates upstream factors in the coagulation cascade to initiate and propagate coagulation thereby enhancing its own generation. The procoagulant activity of thrombin is inhibited by circulating anticoagulant biomolecules such as antithrombin, heparin cofactor II and protein C. Thrombin also induces many cellular effects via a family of G-protein coupled pro-tease activated receptors (PAR), PAR1, PAR3, and PAR4 [9].



Dabigatran Elexilate

The work summarized the discovery and development of anticoagulant drug dabigatran [10]. Dabigatran is a synthetic, reversible DTI with high affinity and specificity for its target, binding both free and clot-bound thrombin, and offers a favorable pharmacokinetic profile [11]. Based on X-ray crystal structure of a bovine thrombin complex with peptide-like benzamidine based inhibitor NAPA, a lead compound was identified because of its favorable selectivity profile and strong *in vitro* and *in vivo* activity, exhibited prolonged anticoagulant effect and high dose tolerance in rats after i.v. administration [12]. However, it was not orally active due to its polarity. The compound was converted into an orally active prodrug dabigatran etexilate. Based on its promising profile, dabigatran etexilate was selected for clinical development [13].

Dabigatran is a reversible competitive inhibitor with a *Ki* of 4.5 nM. It inhibits both clot-bound and free thrombin. Dabigatran inhibits both thrombin induced platelet aggregation and tissue factor induced thrombin generation [13]. Dabigatran has fast onset of action (peak plasma concentration in 2-3 hours) with half-life of 12-14 hours. Contrary to current antithrombotic therapies, dabigatran does not require routine coagulation monitoring. It is not metabolized by cytochrome P450 and does not have drug-drug interactions. It has low plasma protein binding and undergoes about 80% renal excretion. One of the most common side

effects of dabigatran is bleeding [14]. Dabigatran etexilate is contra-indicated in severe renal impairment, paediatric populations, pregnancy, and lactation due to inadequate evidence of safety and efficacy. It also inhibits or induces both CYP3A4. Dabigatran do not require formal therapeutic drug monitoring but by their nature they can lead to increased bleeding and thus monitoring Hb may be advised. Dabigatran etexilate can also lead to epistaxis, anaemia, nausea and gastrointestinal discomfort, including diarrhoea. [14].

Preclinical investigations reveal that dabigatran is effective in both venous and arterial models. In clinical trial program, dabigatran has shown good safety profile. Dabigatran is also shown to be effective in the prevention of venous thrombosis after orthopedic surgery, acute thrombosis, and secondary prevention of VTE with no increased risk of bleeding [14, 15]. It has been studied in more than 10,000 patients in clinical trials for treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis in major orthopedic surgery [16]. In clinical trial RE-LY, there was a significantly higher risk of gastrointestinal bleeding with dabigatran 150 mg bid compared with warfarin [17]. No statistical significant difference was seen when using the 110 mg BID dabigatran dose. Mild to moderate dyspepsia related to dabigatran was also reported. The side effect tended to be transient, and may be managed by giving dabigatran with a large glass of water, with food, or a proton-pump inhibitor [18, 19]. In the treatment of VTE, dabigatran etexilate was compared to standard warfarin treatment [20-22]. Dabigatran demonstrated the same efficacy in thrombosis prevention with significantly less minor bleeding and similar major bleeding [23, 24]. Dabigatran also demonstrated efficacy in atrial fibrillation similar to standard warfarin therapy [17]. Dabigatran is approved for prevention of stroke and systemic embolism associated with nonvalvular atrial fibrillation with dosage of 150 mg PO BID. The cost of dabigatran ($3000/year) is substantially higher than those of warfarin ($48/year), but reduces the cost associated with regular clinical monitoring.

There is a significant unmet need to develop anticoagulation treatment that is effective, easy and safe. More than 50 years after the discovery of warfarin, the development of dabigatran is considered as breakthrough achievement for the treatment of thromboembolic disease including the prevention of catastrophic strokes in patients [15].

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