Drugs of the Future 2009, 34(11): 861-872

CCC: 0377-8282/2009
DOI: 10.1358/dof.2009.34.11.1445298

EDOXABAN TOSILATE

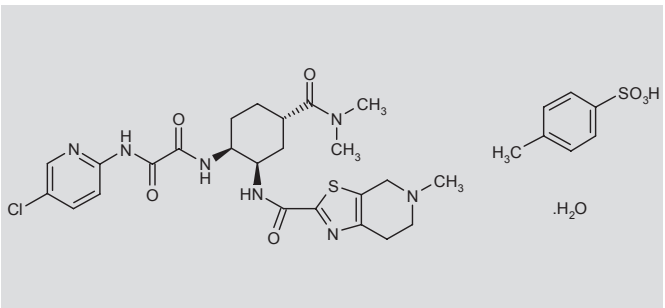
Prop INNM

Direct Factor Xa Inhibitor
Prevention of Post-operative Venous Thromboembolism
Treatment of Atrial Fibrillation

DU-176b

N^1-(5-Chloropyridin-2-yl)-N^2-[(1*S*,2*R*,4*S*)-4-(*N*,*N*-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-ylcarboxamido)cyclohexyl]oxamide *p*-toluenesulfonate monohydrate

InChI= 1S/C24H30ClN7O4S.C7H8O3S.H2O/c1-31(2)24(36)13-4-6-15(27-20(33)21(34)30-19-7-5-14(25)11-26-19)17(10-13)28-22(35)23-29-16-8-9-32(3)12-18(16)37-23;1-6-2-4-7(5-3-6)11(8,9)10;/h5,7,11,13,15,17H,4,6,8-10,12H2,1-3H3,(H,27,33)(H,28,35)(H,26,30,34);2-5H,1H3,(H,8,9,10);1H2/t13-,15-,17+;;/m0../s1



$C_{31}H_{40}ClN_7O_8S_2$
Mol wt: 739.274
CAS: 912273-65-5
CAS: 480448-29-1 (monohydrochloride)
CAS: 480449-70-5 (anhydrous, free base)
CAS: 480449-71-6 (anhydrous)
EN: 386638

ABSTRACT

Deep vein thrombosis and related complications are important contributors to mortality and morbidity and represent a major public health concern. New orally active small molecules with powerful and reliable antithrombotic actions are being developed as currently available anticoagulant strategies have limitations. Factor Xa has emerged as a particularly promising target for effective anticoagulation because it acts at the convergence point of the intrinsic and extrinsic coagulation pathways. Edoxaban tosilate (DU-176b), an oral, direct and highly specific inhibitor of activated factor Xa, has no effect on the enzymatic activities of other serine proteases. The antithrombotic action of edoxaban has been demonstrated both in vitro and in vivo, in experimental models of arterial and venous thrombosis in different animal species. A 10-fold dissociation between antithrombotic and bleeding effects was predicted from different animal models. Edoxaban has a favorable pharmacokinetic profile in humans, reaching a maximal concentration 1-2 h after oral administration with an elimination half-life of 9-11 h, and is predominantly renally secreted. Data from early clinical studies indicate that edoxaban is safe and effective in preventing thrombotic events in patients after elective total knee arthroplasty and unilateral hip replacement. Phase II studies have investigated safety, efficacy and dose response relationships in patients with nonvalvular atrial fibrillation with encouraging results. Phase III studies are currently underway to confirm the safety and effectiveness of edoxaban versus the standard treatment warfarin in patients with atrial fibrillation.

SYNTHESIS**

Edoxaban tosilate has been prepared by the following synthetic strategies:

1) By conjugation of the cyclohexanediamine (I) with lithium 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylate (II) by means of EDC and HOBt in DMAc (1) or DMF (2, 3). Scheme 1.

2) By conjugation of diamine (I) with the HCl salt of 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine-2-carboxylic acid (III) in the presence of EDC, HOBt and Et_3N (4). Scheme 1.

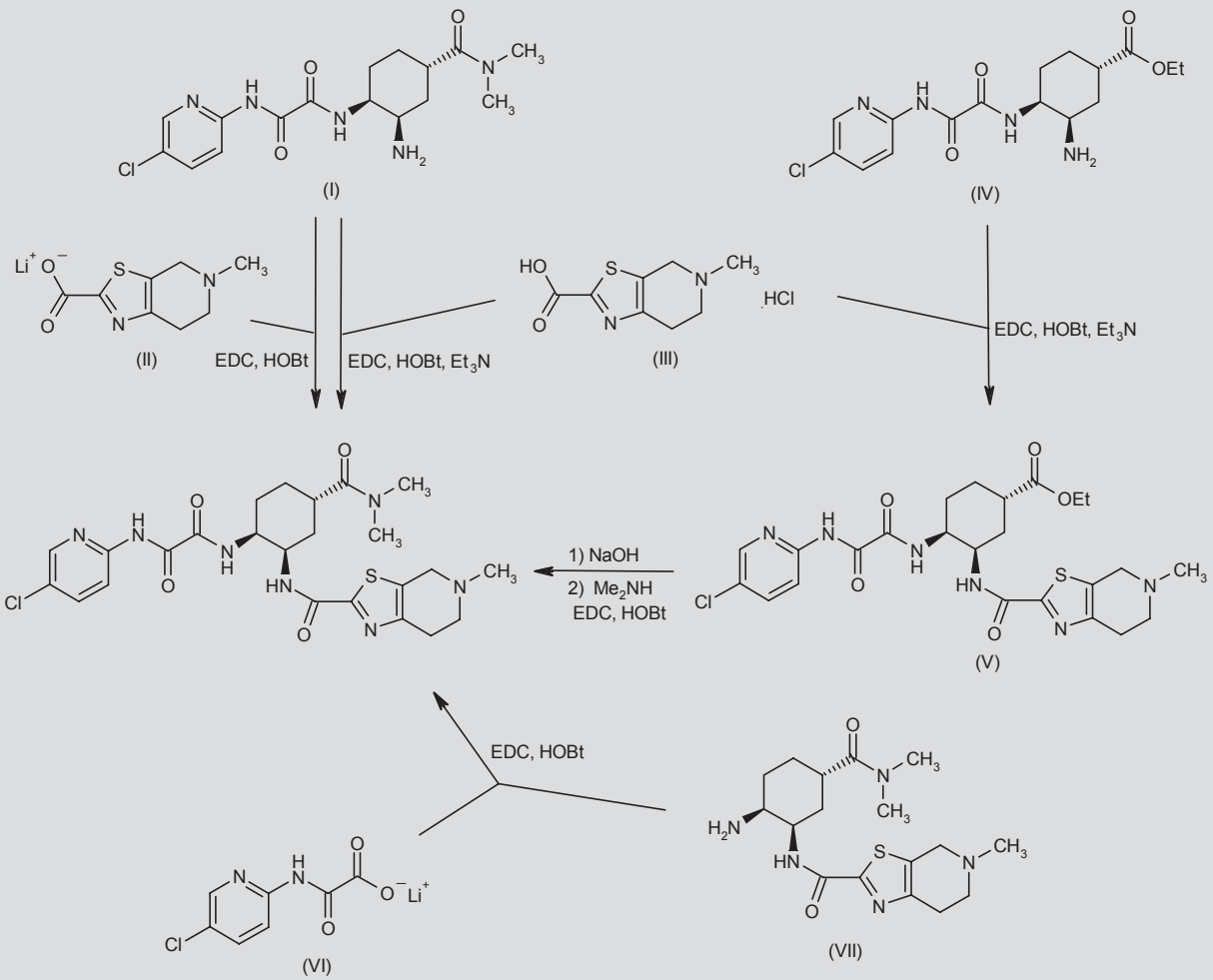
3) By conjugation of the thiazolopyridinecarboxylic acid (III) with the aminocyclohexanecarboxylic acid ethyl ester (IV) using EDC, HOBt and Et_3N to provide diamide ester (V) (5), which is then hydrolyzed with NaOH in H_2O/DMSO, followed by coupling of the resultant carboxylic acid with dimethylamine in the presence of EDC and HOBt in aqueous acetonitrile (1, 6). Scheme 1.

4) By conjugation of the monoacylated cyclohexanediamine (VII) with *N*-(5-chloro-2-pyridyl)oxamic acid lithium salt (VI) by means of EDC and HOBt in DMF (2, 3). Scheme 1.

G. Escolar*, M. Díaz-Ricart.
Servicio de Hemoterapia y Hemostasia, Hospital Clínic, Universitat de Barcelona, Villarroel 170, 08036 Barcelona, Spain. *Correspondence: gescolar@clinic.ub.es

**Synthesis prepared by R. Pandian, R. Castañer, J. Bolós. Thomson Reuters, Provenza 388, 08025 Barcelona, Spain.

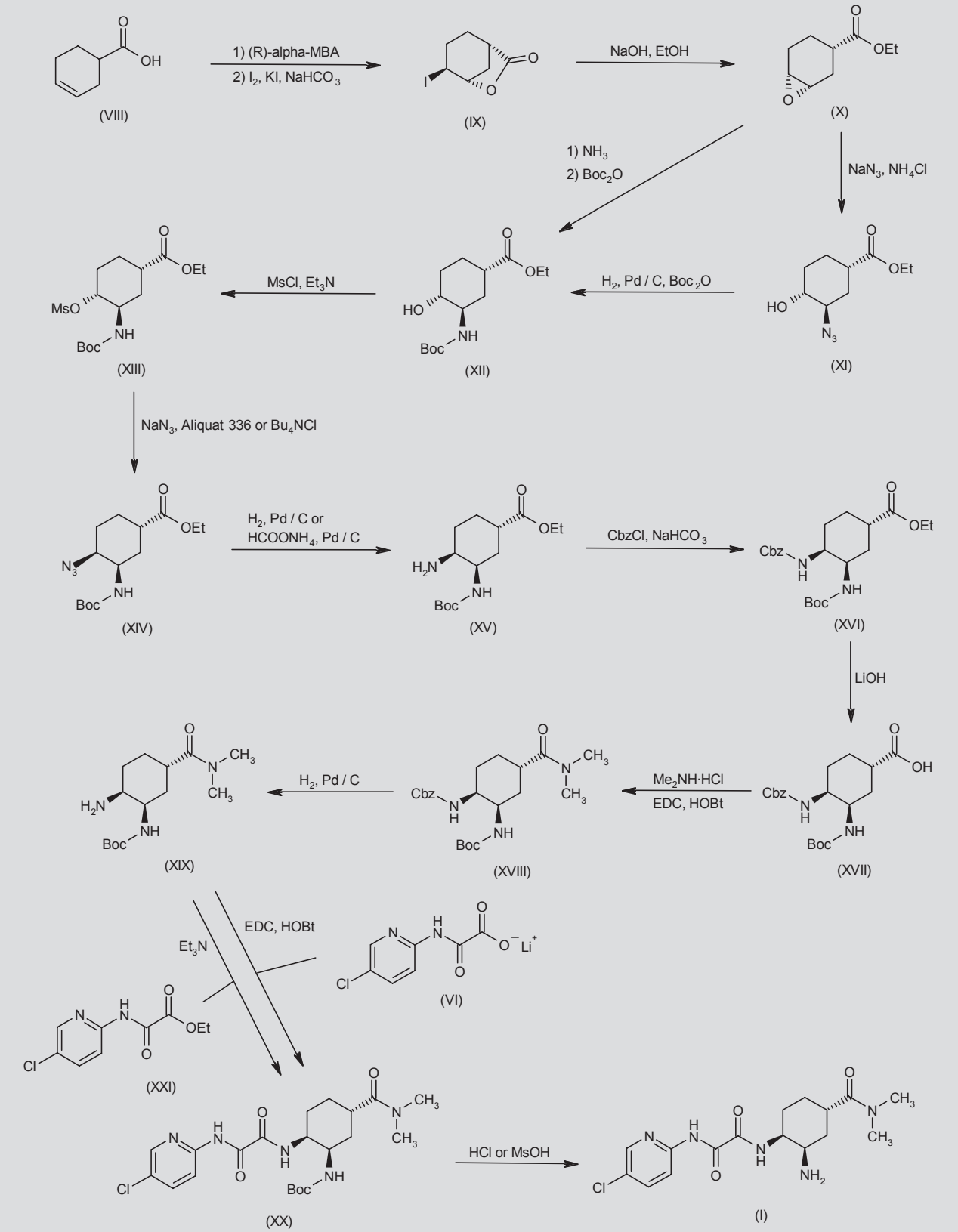
Scheme 1. Synthesis of Edoxaban



The tosilate salt has been obtained by treatment with *p*-toluenesulfonic acid in EtOH (4) or H_2O/EtOH/CH_2Cl_2 (2, 3).

Preparation of the cyclohexanediamine (I):
Resolution of racemic 3-cyclohexene-1-carboxylic acid (VIII) with (*R*)-α-methylbenzylamine (6) results in the target (*S*)-enantiomer, which undergoes intramolecular iodolactonization to compound (IX) by means of I_2, KI and $NaHCO_3$ in H_2O/CH_2Cl_2. The bicyclic iodolactone (IX) then rearranges to epoxy ester (X) by treatment with NaOH in EtOH/H_2O. Ring opening of epoxide (X) with NaN_3 in the presence of NH_4Cl in DMF at 76 °C affords the *trans*-azido alcohol (XI), which is converted to the *tert*-butyl carbamate (XII) by catalytic hydrogenation in the presence of Pd/C and Boc_2O in EtOAc (2, 3). Carbamate (XII) can also be obtained by reaction of epoxide (X) with ethanolic ammonia at 50 °C, followed by protection of the resultant amino alcohol with Boc_2O in EtOH (4). After conversion of alcohol (XII) to the corresponding mesylate (XIII) by means of methanesulfonyl chloride and Et_3N in CH_2Cl_2 (2, 3) or EtOAc (4), substitution of the mesylate group with NaN_3 in the presence (4, 5) or the absence (2-4) of phase transfer catalysts, including Aliquat 336, Hex_4NCl, $PhCH_2NEt_3Cl$, Me_4NCl (4), or Bu_4NCl or Et_4NCl (4, 5), in NMP at 60 °C affords the *cis*-azido-carbamate (XIV) (2-5). Reduction of azide (XIV) by either hydrogenation with H_2 and Pd/C in EtOH/EtOAc (2, 3) or transfer hydrogenation with ammonium formate and Pd/C in EtOH/H_2O (4, 5) gives amine (XV), which is optionally converted to the corresponding oxalate salt (4). Subsequent protection of the free amine group in compound (XV) (2, 3) or its oxalate (4) with benzyl chloroformate in the presence of $NaHCO_3$ in THF/H_2O (2, 3) or EtOAc/H_2O (4) yields the fully protected diamine (XVI), which undergoes ester hydrolysis by means of LiOH in H_2O/THF (2, 3) or H_2O/EtOH (4) to furnish the carboxylic acid (XVII). After condensation of carboxylic acid (XVII) with dimethylamine hydrochloride by means of EDC and HOBt in CH_2Cl_2 (2, 3) or DMF (4), the resulting *N*,*N*-dimethylcarboxamide (XVIII) is

Scheme 2. Synthesis of Intermediate (I).



selectively deprotected by catalytic hydrogenolysis over Pd/C in MeOH (2, 3) or EtOH (4) yielding amine (XIX), which is optionally isolated as the oxalate salt by precipitation with oxalic acid in EtOAc (4). Coupling of the cyclohexylamine (XIX) with *N*-(5-chloro-2-pyridyl)oxamic acid lithium salt (VI) by means of EDC and HOBt in CH_2Cl_2 then leads to amide (XX) (2, 3), which can be alternatively obtained by condensation of the corresponding oxalate salt of (XIX) with ethyl *N*-(5-chloro-2-pyridyl)oxamate (XXI) in the presence of Et_3N in acetonitrile (4). Finally, subsequent deprotection of amide (XX) by means of HCl in ethanol (2, 3) or MsOH in acetonitrile (4) provides the target cyclohexanediamine (I). Scheme 2.

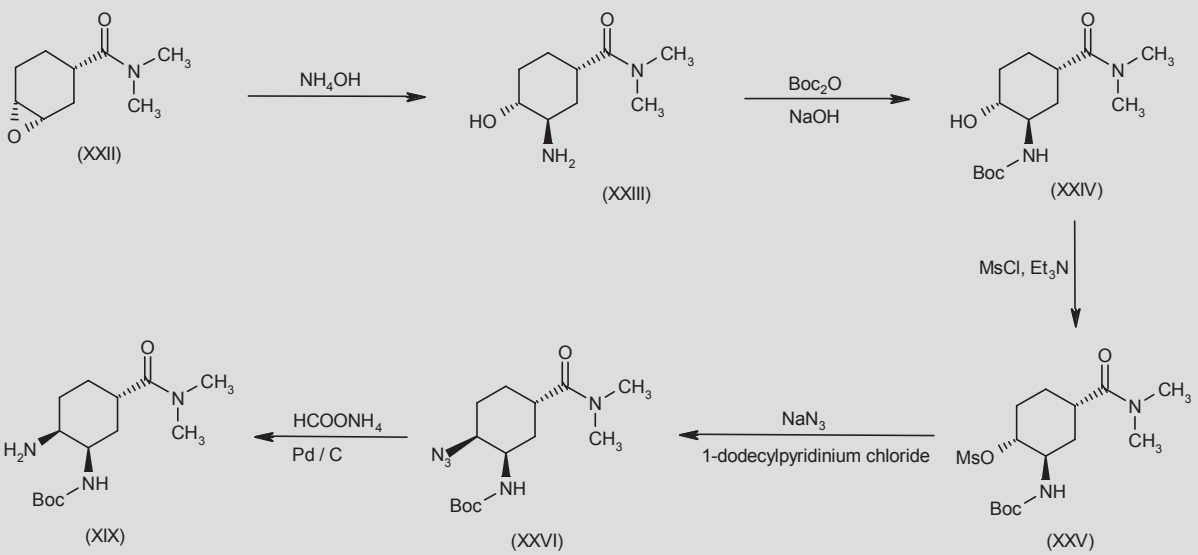
Alternatively, the monoprotected cyclohexanediamine (XIX) can be prepared as follows. Ring opening of *N*,*N*-dimethyl-3,4-epoxycyclohexanecarboxamide (XXII) with ammonium hydroxide at 40 °C, followed by protection of the resultant amino alcohol (XXIII) with Boc_2O in aqueous NaOH provides the *N*-Boc-protected amino alcohol (XXIV). After conversion of alcohol (XXIV) to the corresponding mesylate (XXV) by means of methanesulfonyl chloride and Et_3N in 4-methyl-2-pentanone, substitution with NaN_3 in the presence of 1-dodecylpyridinium chloride in DMAc or toluene at 60 °C furnishes azide (XXVI). Finally, azide (XXVI) is reduced by transfer hydrogenation with ammonium formate and Pd/C in MeOH at 40 °C (4). Scheme 3.

Aminocyclohexanecarboxylic acid ethyl ester (IV) and some synthetic precursors are prepared as follows. Acylation of 2-amino-5-chloropyridine (XXVII) with either potassium ethyl oxalate (XXVIII) by means of EDC and HOBt in DMF (2, 3, 5) or with methyl oxalyl chloride (XXIX) in the presence of $NaHCO_3$ in THF or CH_2Cl_2 (2, 3) or Et_3N in CH_2Cl_2 (5) provides the corresponding *N*-(5-chloro-2-pyridyl)-oxamic acid esters (XXI) and (XXX), respectively. The lithium oxamate (VI) has been prepared by hydrolysis of the methyl ester (XXX) with LiOH in aqueous THF (2, 3, 5). Coupling of the ehtyl pyridyloxamate (XXI) with the monoprotected diamine (XV) (previously derivatized as the corresponding malate or oxalate salt) in the presence of Et_3N in acetonitrile at 65-70 °C yields oxamide (XXXI), which is finally deprotected to give intermediate (IV) by removing the *N*-Boc-protecting group by means of methanesulfonic acid in acetonitrile (5). Scheme 4.

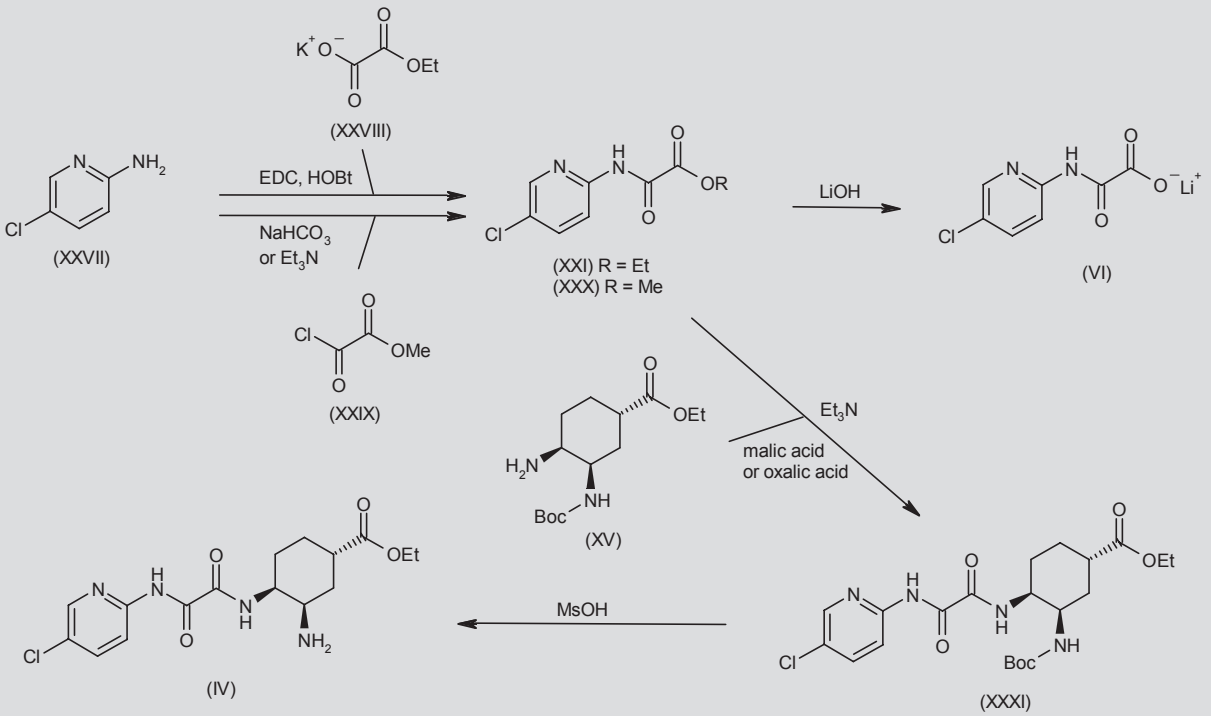
Intermediate (VII) is prepared as follows. Hydrolysis of *cis*-azido-carbamate (XIV) using aqueous LiOH gives the corresponding carboxylic acid (XXXII), which is converted into carboxamide (XXXIII) by reaction with dimethylamine hydrochloride in the presence of EDC, HOBt and NMM in CH_2Cl_2. *N*-deprotection of carboxamide (XXXIII) with HCl in EtOH/CH_2Cl_2, followed by condensation of the resultant amine (XXXIV) with the lithium thiazolopyridinecarboxylate derivative (II) by means of EDC and HOBt in DMF provides amide (XXXV), which is finally reduced at the azido moiety by catalytic hydrogenation over Pd/C in MeOH (2, 3). Scheme 5.

The thiazolopyridine derivatives (II) and (III) can be obtained in several ways. Treatment of *N*-Boc-4-piperidinone (XXXVI) with pyrrolidine in the presence of *p*-TsOH·H_2O in refluxing cyclohexane, followed by cyclization of the resulting enamine with cyanamide and elemental sulfur in MeOH gives 2-amino-5-Boc-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (XXXVII), which by Sandmeyer reaction with $CuBr_2$ and *t*-BuONO in DMF at 40 °C affords the 2-bromo compound (XXXVIII). After removal of the *N*-Boc-protecting group of intermediate (XXXVIII) with TFA, reductive methylation of the deprotected amine (XXXIX) with formaldehyde and $NaBH(OAc)_3$ in the presence of AcOH and Et_3N in CH_2Cl_2 yields 2-bromo-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (XL) (2, 3, 5), optionally isolated as the corresponding tosylate salt (1). Alternatively, cyclization of 1-methyl-4-piperidinone (XLI) with cyanamide and sulfur in

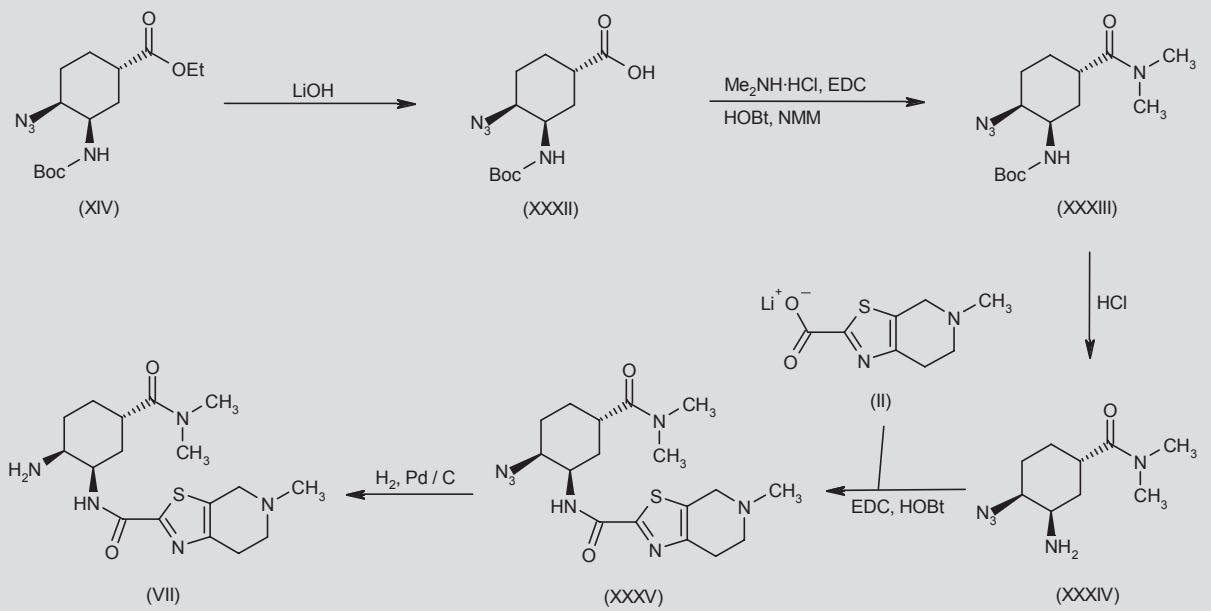
Scheme 3. Synthesis of Intermediate (XIX).



Scheme 4. Synthesis of Intermediates (IV) and (VI)



Scheme 5. Synthesis of Intermediate (VII).



the presence of pyrrolidine in *i*-PrOH at 50 °C yields 2-amino-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (XLII), which is converted to the corresponding bromide (XL) by diazotization with $NaNO_2$ in the presence of HBr in H_2O. Metalation of the bromo derivative (XL) with BuLi in THF at –78 °C, followed by quenching with CO_2 affords the lithium carboxylate (II) (1-3, 5), which is converted to the carboxylic acid (III) by treatment with HCl in EtOH. Alternatively, cyanation of bromide (XL) with NaCN/CuCN in DMAc at 150 °C yields nitrile (XLIII), which is hydrolyzed to carboxylate (II) using LiOH in EtOH (1). In one further method, deamination of intermediate (XXXVII) by diazotization with $NaNO_2$ and H_2SO_4 in the presence of hypophosphorous acid in H_2O gives 5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine (XLIV) (1), which is carboxylated to compound (II) by metalation with BuLi in THF at –78 °C and subsequent quenching with CO_2 (1-3, 5), or by acylation with trichloroacetyl chloride and Et_3N in toluene, followed by haloform reaction of the resultant trichloromethyl ketone in the presence of LiOH (1). Scheme 6.

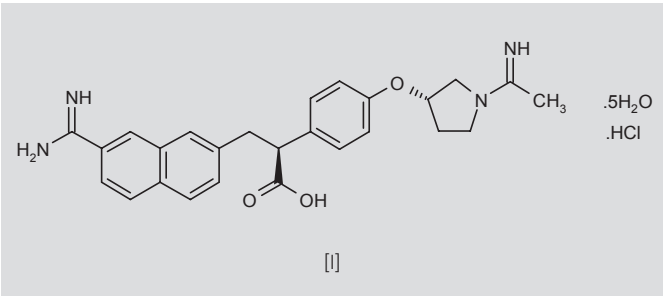
The tetrahydrothiazolopyridine intermediate (XLIV) can also be prepared by a different procedure. After protection of 4-aminopyridine (XLV) as the *N*-Boc derivative (XLVI) with Boc_2O in THF, treatment with BuLi in cold THF, followed by elemental sulfur yields the 3-sulfanylpyridine (XLVI). Cyclization of the Boc-protected amino thiol (XLVI) with formic acid at reflux, followed by KOH in H_2O or Et_2O leads to thiazolo[5,4-*c*]pyridine (XLVII), which is converted to the target intermediate (XLIV) by quaternization with iodomethane in DMF at 80 °C and then reduction with $NaBH_4$ in MeOH (2, 3, 5). Scheme 6.

BACKGROUND

Deep vein thrombosis (DVT) and related complications are an important public health issue as they are a leading cause of morbidity and mortality and may result in disability. There were an estimated 900,000 venous thromboembolism (VTE) events in the US in 2005 (7). These data are similar to those reported in Europe (8) and suggest that safe and effective prophylaxis could significantly reduce incidence of VTE and related mortality (9). Social and economic burdens and the treatment of thrombotic complications related to atrial fibrillation are also significant (10).

Thrombotic complications are the result of hypercoagulable congenital or acquired conditions converging on an altered vascular wall. Anticoagulant drugs are currently used in the prophylaxis and treatment of these complications. Research is currently focused on new anticoagulants that do not require parenteral administration (heparins do and are costly and inconvenient) or repeated monitoring and dose adjustment, as is the case with classic oral vitamin K antagonists (11). The new generation of oral anticoagulants is expected to possess a favorable pharmacokinetic profile, rapid onset, predictable action, wider therapeutic range, better safety profile and fewer pharmacological interactions than classic oral anticoagulants.

Inhibition of either thrombin (FIIa) or activated factor X (FXa) has become the main target of new anticoagulant strategies. Inhibitors of FXa, a serine protease that converts prothrombin to thrombin, have shown great promise as anticoagulant therapy without the limitations inherent in traditional agents (11, 12). One molecule of FXa results in the generation of thousands of thrombin molecules;



[I]

inhibiting FXa may block this burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation and platelets. Edoxaban tosilate (DU-176b) is a new oral anticoagulant with a direct and specific inhibitory action on FXa; it is 10,000 fold selective for FXa over thrombin (FIIa).

PRECLINICAL PHARMACOLOGY

Edoxaban was a product of the research of Daiichi-Sankyo Inc. on a prototype FXa inhibitor, initially named DX-9065a [I]. In 1994, DX-9065a was considered a promising direct, selective, synthetic inhibitor of FXa (13) with potent anticoagulant and antithrombotic effects in experimental (14) and clinical settings (15, 16). However, DX-9065a had a low oral bioavailability and required parenteral administration (17). A basic amidine moiety as an arginine side chain mimetic, used to achieve a higher anticoagulant potency for DX-9065a, was implicated in its low oral bioavailability (18). The evolution of DX-9065 into the orally active molecule edoxaban required extensive studies of structure-activity relationships and modifications of the original molecule involving the replacement of the amidine moiety with less basic moieties (19, 20) to improve its oral absorption (21). Relevant information on the pharmacology of this new anticoagulant is summarized in Table I.

The anticoagulant properties of edoxaban have been investigated in vitro in different animal species (22). The effects of edoxaban on activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) were tested in human, rat, cynomolgus monkey and rabbit plasma. Anticoagulant activity was expressed as the concentration of edoxaban required to double the initial coagulation time, estimated by regression analysis from dose response curves. Edoxaban prolonged the PT and APTT of human plasma in a concentration-dependent manner, doubling PT and APTT at concentrations equivalent to 0.256 and 0.508 μM, respectively. The concentration of edoxaban required to double the coagulation time for TT was much higher (4.95 μM), suggesting that a direct antithrombin effect is not the main mechanism for its anticoagulant action. The effects on PT prolongation were similar in human, monkey and rabbit plasma, whereas higher concentrations were required to double coagulation times in rat plasma (22). Edoxaban inhibits thrombin generation in human platelet rich or poor plasma and the extent of the inhibition can be monitored by means of calibrated automated thrombinography (23).

The specificity of the inhibitory effect of edoxaban on the enzymatic activity of different serine proteases was evaluated using chromogenic substrata. Edoxaban possessed a high specific affinity to

Scheme 6. Synthesis of Intermediates (II) and (III).

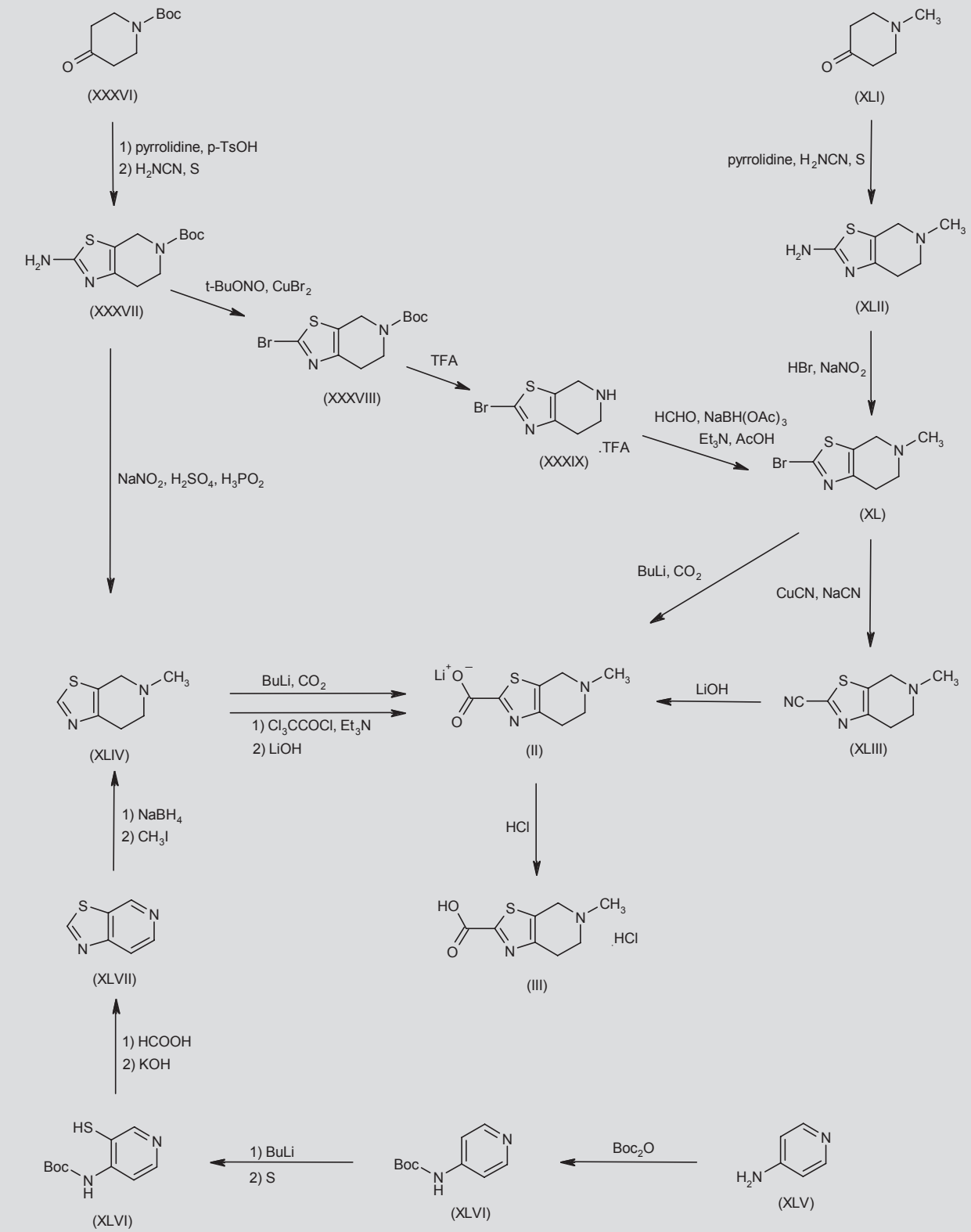


Table I. *Pharmacodynamics and pharmacokinetics of Edoxaban tosilate.*

Experimental conditions	Dose	Comments
Anticoagulant activity in vitro in human plasma	0.256 and 0.508 μM	Doubles PT and APTT (22) Reversed by recombinant Factor VIIa, recombinant Factor VIIIa, activated prothrombin complex (38,39)
Anti-Factor Xa activity (K_i value)	0.457 nM rabbits 0.715 nm monkeys 0.561 nM human	10,000 fold lower than K_i value for Factor IXa (22)
Pharmacokinetics: Maximum activity and duration of anticoagulant effects	Peak at 0.5 h, sustained for 4 h (rat) Peak at 4 h sustained for 24 h (monkey) Peak at 1.5 h sustained for 5 h (human)	Good correlation between plasma concentration and pharmacodynamics. Renal excretion. (22, 33, 34)
Antithrombotic action in vivo	0.5-12.5 mg/kg	(25, 26, 28-30, 33)
Antithrombotic action ex vivo	60 mg, single dose	(34)

competitively inhibit human FXa with a K_i value of 0.561 nM (13, 22). It also inhibited cynomolgus monkey and rabbit FXa with similar potency (K_i values of 0.715 and 0.457 nM, respectively), whereas the K_i value for rat FXa was higher (6.98 nM) (22). Edoxaban had very weak direct inhibitory action on thrombin and FIXa, with K_i values of 6.00 and 41.7 μM, respectively, more than 10,000-fold higher than the K_i for FXa (22). The antithrombotic effects of edoxaban are independent of plasma levels of antithrombin (AT) as demonstrated in studies in AT-deficient mice (24).

The antithrombotic properties of edoxaban have been evaluated in several models of venous and arterial thrombosis (25, 26). Oral administration of edoxaban significantly inhibited thrombus formation in models of venous stasis in rats and rabbits. Similar results were observed in a platinum wire-induced venous thrombosis model in rats: thrombus formation was significantly reduced by doses of edoxaban equivalent to 2.5 mg/kg (22). Antithrombotic effects elicited by edoxaban paralleled increased PT and anti-FXa activities in the plasma of these animals. Edoxaban also had a significant anticoagulant effect in a rat model of tissue factor-induced disseminated intravascular coagulation (27). The combined effects of edoxaban and ticlopidine or tissue plasminogen activator (t-PA) were investigated in rat models of arterial, venous and arterial-venous shunt thrombosis. Data from these studies revealed that edoxaban administered with ticlopidine or t-PA had an additive antithrombotic effect compared with each compound administered alone (25).

The antithrombotic action of edoxaban has been compared with that of other anticoagulant agents in different experimental conditions. In rats, the antithrombotic effect of edoxaban was compared with that of fondaparinux, an indirect FXa inhibitor (28, 29). Edoxaban effectively prevented both arterial and venous thrombosis in these models in the same dose range; fondaparinux required higher doses to inhibit arterial thrombosis and was less efficacious under conditions of high shear rates. Edoxaban has also been compared with unfractionated, low molecular weight heparins and warfarin (30, 31, 33). The antithrombotic response to edoxaban was similar to that of the other anticoagulants tested.

The antithrombotic effects of edoxaban have been compared with those of melagatran, an oral thrombin inhibitor, in a tissue factor-induced model of hypercoagulation in anesthetized rats (32). Both edoxaban (0.3 mg/kg i.v. bolus) and melagatran (2 mg/kg i.v. bolus) effectively inhibited hypercoagulation in this model. Melagatran enhanced platelet consumption and thrombin-antithrombin complex generation 2 and 4 h after induction of hypercoagulation, indicating that it may aggravate hypercoagulation.

PHARMACOKINETICS

Edoxaban is rapidly absorbed, reaching a maximal concentration 1-2 h after oral administration (33). Once absorbed, edoxaban is predominantly renally excreted with an elimination half life of 9-11 h. In studies in rats, edoxaban (2.5 and 5 mg/kg) showed a maximal inhibition of FXa activity in plasma 0.5 h after oral administration and this effect was maintained for up to 4 h. Anti-FXa activity was rapidly achieved in monkeys, reaching a peak at 4 h (93%) and lasting for 24 h (11%) after dosing. The area under the curve (AUC) of plasma concentration and maximum concentration (C_{max}) after 1 mg/kg were 852 ± 284 ng.h/mL and 175 ± 74 ng/mL (22). Absorption of edoxaban in humans is rapid, with a median time to C_{max} (t_{max}) ranging from 1.0 to 1.5 h and a plasma half life of 8–11 h. A peak plasma level of 240 ± 16 ng/mL was reached at 1.5 h after a single 60 mg dose. At 5 h the level had dropped to a mean of 127 ± 6 ng/mL and at 12 h mean plasma drug level was 37 ± 3 ng/mL (34). Food intake did not have a significant effect on the AUC or C_{max} of edoxaban in Caucasian or Japanese healthy volunteers. T_{max} was slightly later in the fed than the fasted state for both cohorts and renal clearance was generally similar in both states (35).

SAFETY

Data indicate that edoxaban may have a low prohemorrhagic potential. A 10-fold dissociation between antithrombotic and bleeding effects was predicted from different animal models of thrombosis or hemorrhage (30). Edoxaban appeared to have minimal impact on primary hemostasis. Human platelet aggregation induced by ADP, collagen or a thromboxane A_2 receptor agonist was slightly affected at concentrations of edoxaban used to inhibit coagulation. Higher concentrations of edoxaban were required to inhibit thrombin-

induced platelet aggregation, reflecting its weak anti-FIIa activity (36).

Edoxaban at 3 mg/kg was not significantly different from control in a model of tail bleeding time in the rat. At the highest doses (10 and 30 mg/kg) bleeding times were significantly prolonged 1.9-fold compared with the corresponding controls (22). Edoxaban may have a wider safety margin than unfractionated or low molecular weight heparins, as inferred from the dissociation between doses required to achieve antithrombotic and bleeding actions (30, 33). The prohemorrhagic potential of edoxaban has also been compared with that of melagatran (37). Intracerebral hemorrhage was induced by the administration of 0.1 U collagenase solution through a 29-gauge needle into the striatum of rats. Doses required for 50% inhibition of thrombosis were 0.045 and 0.14 mg/kg/h for edoxaban and melagatran, respectively. The safety margin between antithrombotic effects and exacerbation of intracerebral hemorrhage was wider for edoxaban than melagatran (133 vs. 7) in this experimental setting.

The prolongation of PT induced by edoxaban in human plasma was concentration dependently reversed by addition of recombinant FVIIa (rFVIIa). In an in vivo study in rats, edoxaban (1 mg·kg/h) administered intravenously for 2 h significantly prolonged plantar bleeding time; rFVIIa dose dependently reversed the prolongation of bleeding time at doses of 1 and 3 mg/kg (38). Other studies have investigated the neutralizing effects of activated prothrombin complex concentrate (Feiba), recombinant factor VIII (rFVIII) and factor IX on the anticoagulant effects of edoxaban in human plasma and animal models (39). Data from these studies demonstrated that rFVIIa, Feiba, rFVIII and factor IX significantly antagonised the anticoagulant action of edoxaban, indicating that they may be useful as antidotes for edoxaban if serious bleeding occurs.

CLINICAL STUDIES

Clinical studies with edoxaban are summarized in Table II. A phase I study explored the antithrombotic action of edoxaban by comparing the size of ex vivo platelet rich thrombus formation and other biomarkers of coagulation at 1.5, 5 and 12 h post-dose vs. baseline. Twelve healthy subjects received a single oral 60 mg dose of edoxaban (34). Edoxaban significantly reduced ex vivo thrombus formation at venous and arterial shear rates. The antithrombotic effects in perfusion tests were maximal at 1 h, significant at 5 h and had disappeared by 12 h. Under venous flow after 1.5 and 5 h the thrombus was 28% and 21% smaller versus baseline, respectively ($P < 0.05$). Under arterial condition, the reduction was 26% and 17%, respectively ($P < 0.05$). Thrombin generation decreased by 28% at 1.5 h and 10% at 5 h. Effects on clotting parameters and thrombin generation and levels of antifactor X activity paralleled the data from the perfusion tests (34).

The effects of edoxaban (60 mg twice daily) and other anticoagulants on a panel of biomarkers of blood coagulation and platelet responses were evaluated in an open-label, randomized, non-treatment and active-controlled multiple dose study in elderly patients aged 64 to 75 years (40). Blood samples were collected predose and 1.5, 4, 12 and 24 h after dosing on day 1 then on day 4 predose and 12, 24, 48 and 72 h after last drug administration. No significant modifications of platelet or endothelium biomarkers were evident. Interestingly, antiFXa activities at peak levels were approximately 10 times higher after edoxaban than after dalteparin. Plasma drug concentrations correlated with blood test results after dalteparin, ximelagatran and edoxaban. Overall, there was no evidence of hypercoagulation or rebound effect following cessation of these three agents. No significant adverse events were observed and all subjects received all doses of study medication as planned (40).

The safety, efficacy and pharmacodynamics of edoxaban for the prevention of VTE were assessed in Japanese patients (N = 523) after elective total knee arthroplasty in a randomized, parallel-group, placebo-controlled, double-blind, double-dummy, multicenter study (41). Edoxaban was administered at doses ranging from 5 to 60 mg for 11 to 14 days and the incidence of VTE was compared with that after placebo. Patients who received edoxaban at any dose had significantly lower rates of VTE than patients who received placebo and a dose related response was observed ($P < 0.001$). The incidence of major and clinically relevant bleeding was comparable across all groups with no significant differences between doses or between edoxaban and placebo. No serious adverse effects or modifications in liver enzymes were observed during the study.

The efficacy and safety of edoxaban in the prevention of VTE was also assessed in patients undergoing elective unilateral hip replacement (42) in a randomized, parallel-group, multiple-dose, double-blind, double-dummy, multicenter trial. A total of 774 patients was randomly allocated to receive standard doses of dalteparin or edoxaban (15 to 90 mg/day) started 6 to 8 h postoperatively for 7 to 10 days. Rates of symptomatic or positive venographies or major bleeding events were similar among the different groups indicating that edoxaban could be as effective and safe as the conventional low molecular weight heparin used for comparison.

Different dose regimens of edoxaban (30 mg/day, 30 mg twice daily, 60 mg/day or 60 mg twice daily) compared with standard warfarin treatment in patients with nonvalvular atrial fibrillation were assessed in a randomized, parallel-group, multicenter, multinational, double-blind, phase II study (43). Patients (N = 1146) were randomly assigned to receive either one of the fixed dose regimens of edoxaban or warfarin dose adjusted to a target international normalized ratio (INR) of 2.0-3.0 and were followed for 12 weeks. The incidence of major and clinically relevant non-major bleeding events was significantly higher in both the edoxaban 30 mg and 60 mg twice daily groups than in those receiving warfarin. The incidence of major and clinically relevant non-major bleeding events in the edoxaban 30 mg or 60 mg/day groups was similar to that in warfarin-treated patients. The incidence of stroke was similar across treatment groups. Edoxaban 30 mg/day and 60 mg/day dose regimens had a safety profile similar to warfarin in patients with atrial fibrillation. There were no significant differences in the number of patients with persistently elevated liver enzymes across the treatment groups. Results from this clinical trial suggest that the edoxaban 30 mg/day and 60 mg/day regimens were well tolerated in this patient population.

A recent randomized, parallel-group, multinational safety phase IIb clinical trial evaluated the relationship between pharmacokinetic responses and the probability of bleeding events in patients with atrial fibrillation under treatment with edoxaban using warfarin as a comparator (44). A total of 1145 patients were randomized to either double-blind edoxaban or open-label warfarin (INR 2.0-3.0) for 3 months. The study concluded that bleeding events strongly correlat-

Table II. *Clinical trials of edoxaban tosilate.*

Objective or clinical condition	Phase	No. of patients	Duration of the study	Results	Ref.
Antithrombotic action ex vivo	I	12	12 h	Antithrombotic effects after a single dose of 60 mg were maximal at 1 h, significant at 5 h and had disappeared by 12 h.	34
Modification of a panel of biomarkers in elderly patients administered different anti-Factor Xa therapies	I	10	72 h	Prothrombin time and thrombin generation tests are suitable for the evaluation of Factor Xa inhibitors	40
Prevention of venous thromboembolism after total knee arthroplasty	II	523	11-14 days	Dose dependent efficacy observed with doses from 5 to 60 mg/day	41
Prevention of venous thromboembolism after hip replacement vs. low molecular weight heparin	II	774	7-10 days	Dose dependent efficacy observed with doses from 15 to 90 mg/day	42
Nonvalvular atrial fibrillation vs. warfarin: Dose optimization, safety	II	1146	12 weeks	Safe at 30 and 60 mg/day. Increased bleeding after 30 or 60 mg twice daily	43
Atrial fibrillation vs. warfarin	IIb	1145	3 months	Bleeding correlated with Cminss and was less frequent with doses of 30 and 60 mg/day	44
Nonvalvular atrial fibrillation: Dose optimization	II	536	12 weeks with 8 weeks' follow up	Populations with body weight ? 60 mg may have a higher bleeding risk	45
Atrial fibrillation vs. warfarin	III	16,500	24 months	Recruiting patients. Expected to finish by 2011.	46

ed with edoxaban levels (C_{minss}; $P = 0.01$ for major bleeds and major plus clinically relevant bleeds; $P < 0.0001$ for minor bleeds and $P < 0.00001$ for all bleeds). A similar phase II study evaluated the safety of different dose regimens of edoxaban (30, 45 and 60 mg/day) in Japanese patients (N = 536) with nonvalvular atrial fibrillation using standard warfarin treatment as comparator (45). There was a trend for a dose dependent increase in bleeding with edoxaban, although there were no statistically significant differences between warfarin and any of the edoxaban doses. Patients with low body weight (≤ 60 kg) had a higher bleeding risk. These data suggest that doses of edoxaban should be slightly lowered for patients below 60 kg. A phase III trial is underway to determine whether edoxaban may be a suitable replacement for warfarin in patients with atrial fibrillation (Engage AF TIMI 48) (46).

Future management of patients with thrombotic complications will require a transition from approved antivitamin K anticoagulants to the newly developed oral drugs. Mendell et al. explored the safety and pharmacokinetics of edoxaban in healthy subjects bridging from warfarin therapy (47). Participants in the study received open label warfarin titrated to INR 2.0–3.0 for 3 days; 24 h after discontinuation, subjects were randomized to receive edoxaban 60 mg/day or placebo for 5 days. Administration of edoxaban was associated with a rapid effect on the INR, which increased to a peak of 3.8 at 2 h and returned to baseline within 12 h. At 24 h INR values were not significantly different between edoxaban and placebo. Edoxaban may be safely administered to healthy subjects 24 h after the last dose of warfarin (INR 2.0-3.0).

CONCLUSION

In conclusion, edoxaban tosilate should be considered a potential new treatment for the prevention of both arterial and venous thromboembolism. Studies currently being run may provide further data to support the use of edoxaban for these indications. Future studies may reveal the potential of this drug for the prevention and treatment of arterial thrombosis.

SOURCE

Daiichi Sankyo Co., Ltd. (JP).

DISCLOSURE

The authors have no potential conflict of interest to declare.

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