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CCC: 0377-8282/2001

Melagatran and Ximelagatran

Anticoagulant
Thrombin Inhibitor

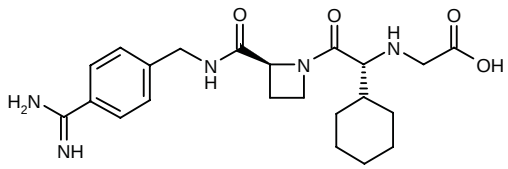
Melagatran

Prop INN

4-[1-[*N*-(Carboxymethyl)-D-cyclohexylglycyl]azetidin-2(*S*)-ylcarboxamidomethyl]benzamidine

N-[2-[2(*S*)-[*N*-(4-Amidinobenzyl)carbamoyl]azetidin-1-yl]-1(*R*)-cyclohexyl-2-oxoethyl]glycine

H-319/68
Exanta®



$C_{22}H_{31}N_5$ Mol wt: 429.5230

CAS: 159776-70-2

EN: 233311

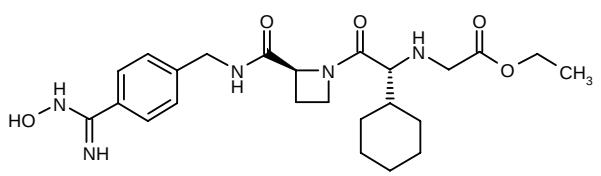
Ximelagatran

Prop INN

2-[1(*R*)-Cyclohexyl-2-[2(*S*)-[*N*-[4-(*N*^{2}-hydroxyamidino)benzyl]carbamoyl]azetidin-1-yl]-2-oxoethylamino]acetic acid ethyl ester

N-[2-[1(*R*)-Cyclohexyl-2-[2(*S*)-[*N*-[4-(*N*^{2}-hydroxyamidino)benzyl]carbamoyl]azetidin-1-yl]-2-oxoethyl]glycine ethyl ester

H-376/95
Exanta®



$C_{24}H_{35}N_5O_5$ Mol wt: 473.5770

CAS: 192939-46-1
CAS: 260790-58-7 (as monohydrate)
CAS: 260790-59-8 (as monohydrobromide)
CAS: 260790-60-1 (as monomethanesulfonate)

EN: 254767

Synthesis of Melagatran

Melagatran can be synthesized by several related ways:

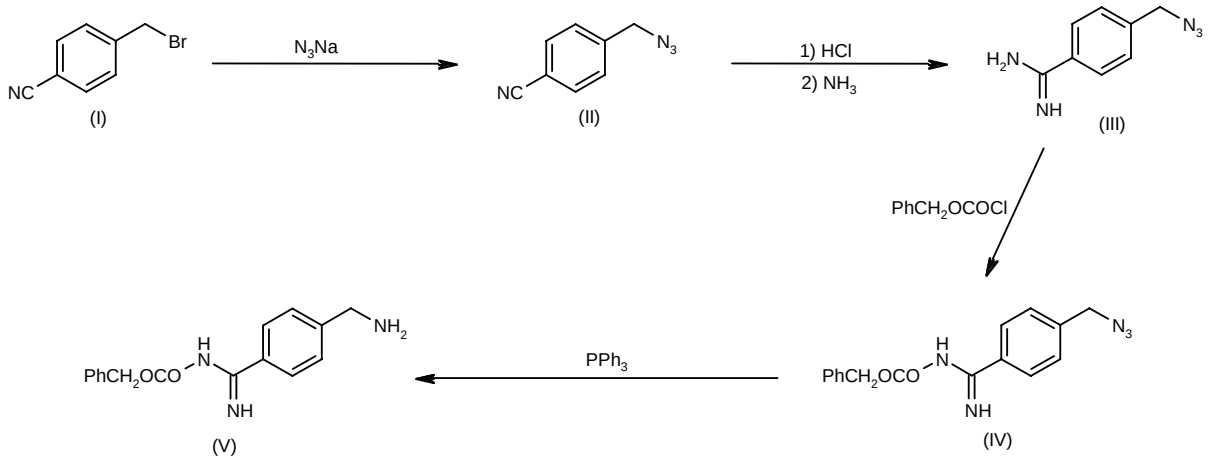
a) The reaction of 4-cyanobenzyl bromide (I) with NaN_3 in DMF gives 4-cyanobenzyl azide (II), which is treated first with HCl and then with ammonia to yield 4-(azidomethyl)benzamidine (III). Protection of the amidino group of (III) with benzyl chloroformate affords the protected compound (IV), which is finally reduced at the azido group with PPh_3 in THF to provide 4-(benzyloxycarbonylamidino)benzylamine (V) (1). Scheme 1.

Reduction of the phenyl ring of *N*-(*tert*-butoxycarbonyl)-(*R*)-phenylglycine (VI) with H_2 over Rh/Al_2O_3 in methanol gives the protected (*R*)-cyclohexylglycine (VII), which is condensed with azetidine (VIII) by means of EDC in acetonitrile to yield the dipeptide (IX). Hydrolysis of the ester group of (IX) affords the carboxylic acid (X), which is condensed with the amino group of the previous intermediate (V) by means of EDC and DMAP in acetonitrile (1) or ethyl acetate/acetonitrile (2) to provide adduct (XI). Cleavage of the Boc-protecting group of (XI) with HCl (1) or methanesulfonic acid (2) gives (XII) with a terminal amino group that is condensed with benzyl 2-(2-nitrophenylsulfonyloxy)acetate (XIII) (1) or benzyl 2-bromoacetate (XIV) (2) by means of K_2CO_3 in the same solvent to yield the melagatran precursor (XV). Finally, this compound is deprotected by hydrogenation with H_2 over Pd/C in methanol (1, 2). Scheme 2.

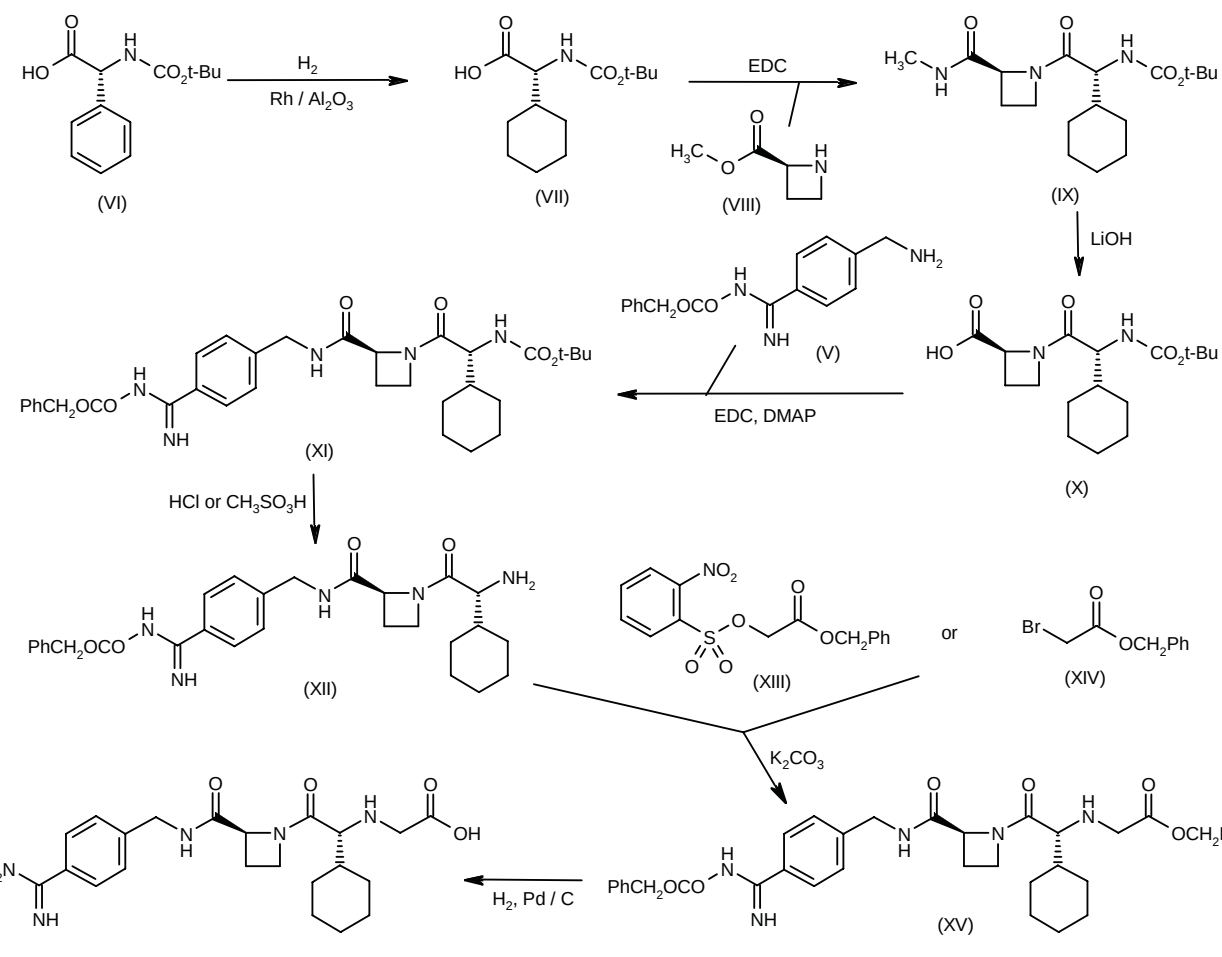
b) Reaction of 4-cyanobenzyl bromide (I) with bis(*tert*-butoxycarbonyl)imine (XVI) by means of NaH in THF gives the protected benzylamine (XVII), which is treated with hydroxylamine and Na_2CO_3 in ethanol/water to yield the *N*-hydroxybenzamidine (XVIII). Reduction of compound (XVIII) with H_2 over Pd/C in $AcOH/Ac_2O$ affords the protected benzamidine (XIX), which is treated with benzyl chloroformate and NaOH in THF in order to obtain the fully protected compound (XX). Selective deprotection of (XX) with HCl gives 4-(benzyloxycarbonylamidino)benzylamine (V), which is condensed with the protected azetidine-2-carboxylic acid (XXI) to afford the corresponding amide (XXII). Boc-deprotection of (XXII) provides azetidine (XXIII), which is condensed with *N*-Boc-(*R*)-cyclohexylglycine (VII) to give the protected dipeptide (XI). Boc-deprotection of (XI) affords intermediate (XII), which is condensed with benzyl 2-bromoacetate (XIV) to give the melagatran precursor (XV). Finally, this compound is debenzylated by hydrogenation with H_2 over Pd/C as before (3). Scheme 3.

L.A. Sorbera, M. Bayès, J. Castañer, J. Silvestre. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

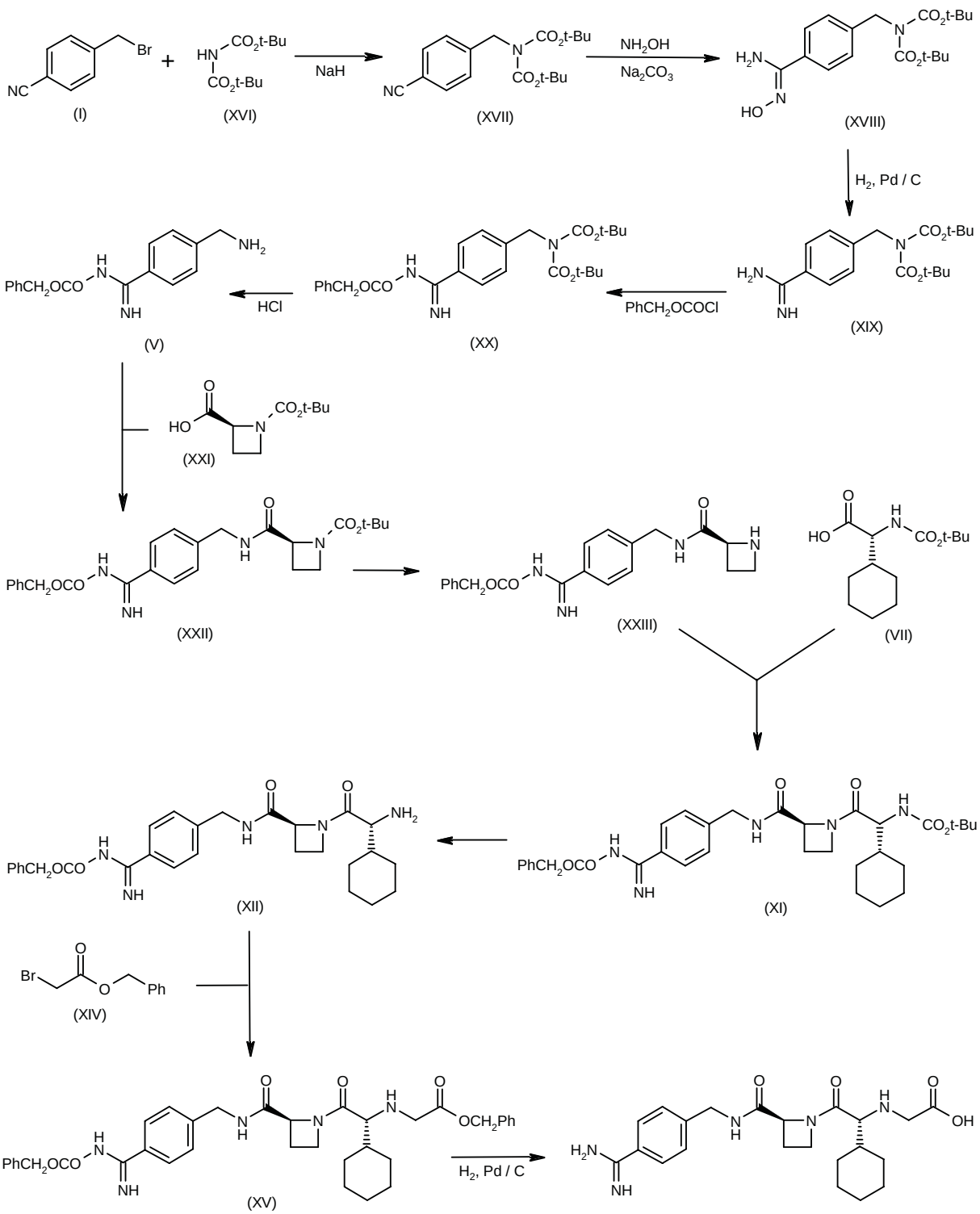
Scheme 1: Synthesis of Intermediate (V)



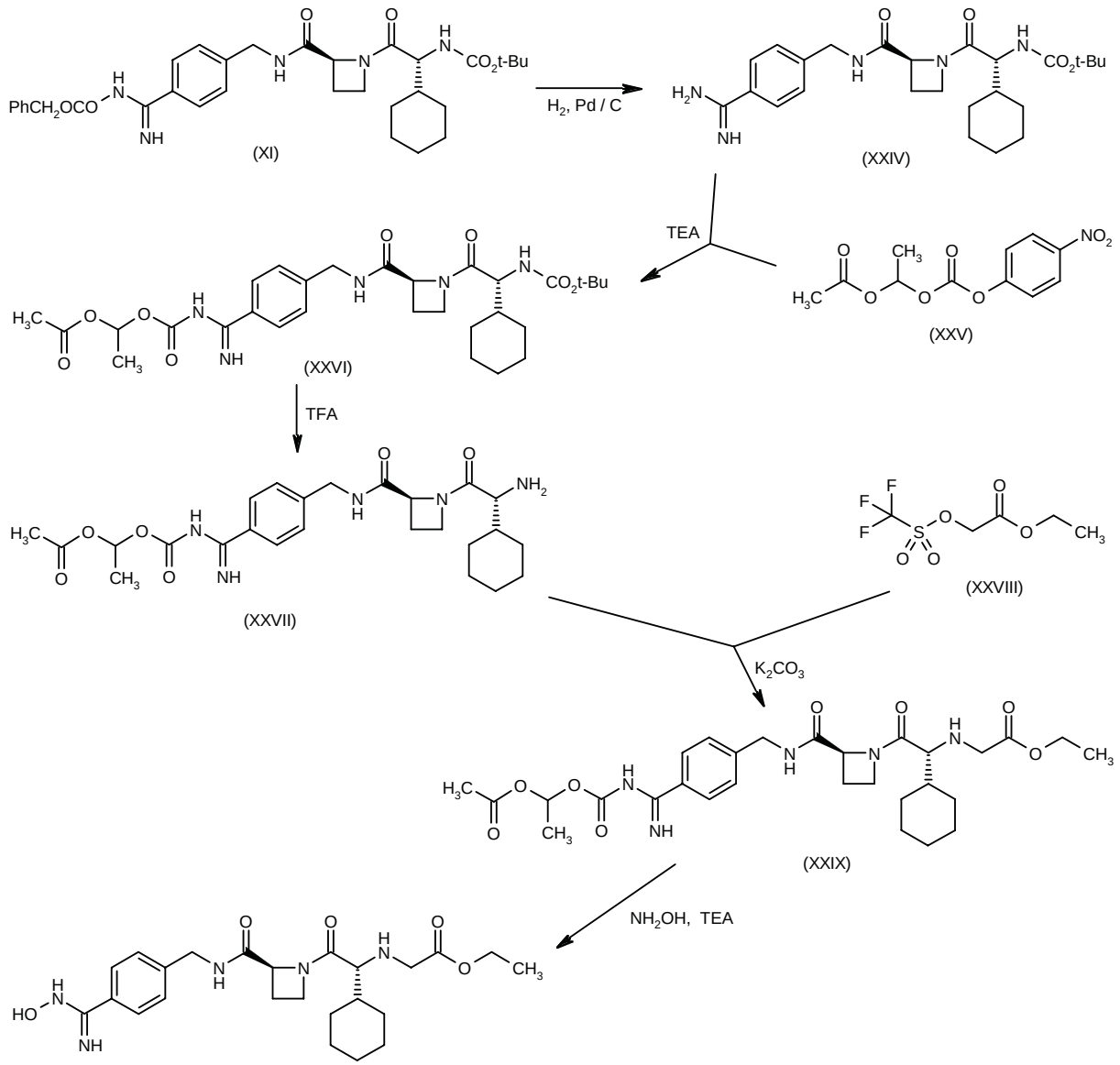
Scheme 2: Synthesis of Melagatran



Scheme 3: Synthesis of Melagatran



Scheme 4: Synthesis of Ximelagatran



Synthesis of Ximelagatran

Removal of the benzyl-protecting group of compound (XI) by hydrogenation over Pd/C in EtOH/H_2O provides the benzamidine derivative (XXIV), which by reaction with 1-(acetoxyethyl) 4-nitrophenyl carbonate (XXV) by means of TEA in dichloromethane provides the *N*-protected benzamidine derivative (XXVI). Treatment of (XXVI) with trifluoroacetic acid in the same solvent allows elimination of the Boc group to yield compound (XXVII), which by condensation with 2-(trifluoromethanesulfonyloxy)acetic acid ethyl ester (XXVIII) in the presence of K_2CO_3 in the same solvent affords the ximelagatran precursor (XXIX). Finally, compound (XXIX) is treated with hydroxylamine and TEA in ethanol in order to deprotect and to oxidize the amidino group, yielding ximelagatran (4). Scheme 4.

Introduction

Coagulation, anticoagulation and fibrinolysis are the 3 processes that must be carefully controlled in order for normal homeostasis to occur. When the balance of regulation of these processes is dysfunctional, the result is the formation of intravascular thrombi leading to reduced blood flow and eventual tissue damage and cell death.

Table I: Inhibition of human thrombin (α-thrombin) and other trypsin-like serine proteases and selectivity index [serine protease/thrombin] for selected thrombin inhibitors launched or under active development (from Prous Science Integrity).

Compound (Ref.)	Thrombin inhibition	Trypsin inhibition	Factor Xa inhibition	Plasmin inhibition	tPA inhibition	Kallikrein inhibition
	K_i (nM)			K_i (μM)		
Argatroban (76)	21.0	5.04 [240]	30.0 [1430]	>372 [>17710]	>777 [>37000]	>355 [>16900]
CVS-1123 (77, 85)	1.42*	–	0.26* [183]	0.32* [225]	>25* [17600]	–
Desirudin (78)	0.00006	>1000* [>1.6 x 10^{10}]	>1000* [>1.6 x 10^{10}]	>1000* [1.6 x 10^{10}]	>1000* [1.6 x 10^{10}]	>1000* [1.6 x 10^{10}]
Melagatran (15, 37)	2.0	0.004 [2]	2.80 [1400]	0.70 [350]	0.90 [450]	0.60 [300]
Napsagatran (76)	0.036	0.48 [13333]	1.90 [52777]	>360 [>1.0 x 10^{7}]	68.4 [1.9 x 10^{6}]	2.00 [55556]
S-18326 (79, 80)	4.0*	0.006* [1.5]	1.25* [313]	0.37* [93]	0.044* [11]	0.074* [19]
UK-156406 (81)	0.46	0.026 [57]	–	–	–	–

*IC_{50}

Hypercoaguability may result in venous thrombosis, which can lead to pulmonary embolism and arterial thrombosis. These conditions, in turn, can cause unstable angina and peripheral arterial occlusion, both potential inducers of myocardial infarction or thrombotic stroke (5, 6). Thus, considerable attention has been given to the search for antithrombotic agents.

Particular attention has been paid to the development of inhibitors of thrombin. Thrombin, a trypsin-like serine protease, is the final enzyme in the coagulation cascade formed from prothrombin via the serine protease factor Xa. Thrombin plays several key roles in the coagulation cascade. It induces platelet aggregation and, through positive feedback and activation of factors Va, VIIIa and XI, it enhances its own production. On the surface of endothelial cells, thrombin complexed with thrombomodulin activates protein C complexed with protein S and inactivates factor Va and factor VIIIa, resulting in inactivation of thrombin generation. Thrombin's primary role is to catalyze the reaction which transforms fibrinogen to fibrin. Fibrin will then polymerize, forming the matrix of the developing clot. In addition, thrombin also activates the generation of factor XIIIa from factor XIII. Factor XIIIa covalently links fibrin strands within the clot, thus stabilizing it. Thrombin also stimulates tissue plasminogen activator (tPA) release, which contributes to the dissolution of clots (7-10).

Current antithrombotic therapies include heparin and warfarin. However, these compounds indirectly inhibit thrombin via suppression of precursor coagulation proteins (11, 12). Although these agents are the mainstays of antithrombotic treatment, they are associated with adverse properties such as bleeding and interpatient dosing variabilities. Moreover, although low-molecular-weight heparins display a reduction in plasma protein binding and less interpatient variability, they are ineffective against clot-bound thrombin and may cause thrombocytopenia (13). The research response has been increased interest in developing small-molecule inhibitors that selectively bind to the active site of thrombin and thus directly inhibit the enzyme. These compounds can penetrate the thrombus and inhibit clot-bound thrombin and may result in a more predictable anticoagulatory response (14). Several direct thrombin inhibitors currently under development and their pharmacological activities are shown in Tables I and II.

Small-molecule thrombin inhibitors are classified into 2 subtypes: tripeptide and peptide mimetics of the fibrinogen cleavage site and nonpeptide inhibitors. One of the most advanced compounds is the small-molecule double prodrug ximelagatran (H-376/95), an inactive anticoagulant developed from the non-covalent peptide thrombin inhibitor melagatran (H-319/68), which exhibits poor bioavailability and absorption upon oral dosing. Following oral administration, the prodrug ximelagatran is rapidly hydrolyzed and reduced to the active thrombin inhibitor melagatran. Due to the predictable pharmacokinetics and the antithrombotic activity of melagatran, ximelagatran has been selected for further development for the prevention and treatment of venous thrombosis and for the prevention of stroke in individuals with atrial fibrillation.

Pharmacological Studies

An *in vitro* study showed that melagatran, the active compound of ximelagatran, potently and competitively

Table II: Pharmacological activities of selected thrombin inhibitors in assays predictive of antithrombotic activity (from Prous Science Integrity).

Compound	Platelet aggregation inhibition[a]	Thrombosis inhibition[b]	TT	APTT Time prolongation[f]	PTT
Argatroban	3.5-13 (81, 83)	0.20[c] (84)	0.16[g] (86)	1.40[h] (86)	1.90[h] (86)
CVS-1123	–	0.50[d] (22)	–	–	–
Desirudin	64 (78)	–	0.016[i] (78)	0.11[i] (78)	–
Melagatran	1.9 (15)	0.016[e] (22)	0.01[i] (15, 37)	0.59[i] (15, 37)	2.20[i] (15, 37)
S-18326	–	–	0.25[i] (80)	0.63[i] (80)	2.44[i] (80)
Ximelagatran	–	–	1.30[i] (37)	25.0[i] (37)	130[i] (37)

[a]Inhibition of thrombin-induced human platelet aggregation (IC_{50}, nM); [b]Inhibition of thrombus formation in rats (ED_{50}, mg/kg/h i.v.) induced by [e]thrombin; [d]arteriovenous shunt or [e]vein ligation; TT: thrombin time prolongation; APTT: activated partial thromboplastin time prolongation; PTT: prothrombin time prolongation; [f]Concentration required to double the prolongation time with respect to control values (EC_{200}, μM) in human plasma except when otherwise indicated: [g]rabbit plasma; [h]rat plasma. (References are in parentheses).

inhibited human α-thrombin with a K_i value of 0.002 ± 0.0003 μmol/l. The action of melagatran was selective since, although the agent was effective in inhibiting other serine proteases with the exception of trypsin, the concentrations required were at least 300 times greater than that required for thrombin inhibition. Similarly, melagatran (1, 3 or 10 μmol/l) concentration-dependently inhibited thrombin-induced human washed platelet aggregation with an IC_{50} value of 0.0019 μmol/l; the agent had no effect on ADP- or collagen-induced aggregation. Results from thrombin time (TT), activated partial thromboplastin time (APTT) and prothrombin time (PT) coagulation assays using pooled human platelet-poor plasma from 20-30 healthy volunteers showed that low concentrations of melagatran (0.010, 0.59 and 2.2 μmol/l for the respective assays) doubled clotting time as compared to control values. Melagatran was also effective in inhibiting fibrinolysis in 2 *in vitro* global fibrinolysis models which examined the formation and lysis of clots from the euglobulin plasma fraction or plasma obtained from pooled human platelet-poor plasma. Melagatran (1.1 μmol/l) concentration-dependently decreased fibrinolysis time and prolonged clotting time in both assays. However, although a concentration of 1.1 μmol/l was effective in the euglobulin plasma fraction model, concentrations greater than 10 μmol/l were required for inhibition of fibrinolysis in the plasma model (15).

Several *in vitro* studies have been conducted to further characterize the melagatran-induced inhibition of thrombin. In a study using an *in vitro* model of thrombin generation (*i.e.*, the endogenous thrombin potential [ETP] method) that employs human, rabbit and rat platelet-poor plasma and measures amidolytic activity over time, melagatran (0.6 μM) prolonged the lag-time (6.32 *vs.* 2.12 min) of thrombin generation and almost completely inhibited thrombin production. Further analysis revealed that the agent inhibited thrombin-induced feedback activation of factor V, resulting in prevention of formation of the active prothrombinase complex and further thrombin generation (16, 17).

Results from a study using human platelet-poor plasma clots from 5 healthy volunteers demonstrated that melagatran was also effective against clot-bound thrombin. The agent at concentrations of 0.1 and 0.5 mM significantly inhibited clot-bound thrombin by 21 and 36%, respectively (IC_{50} = ~ 1 mM) (18). Melagatran exhibited an increased affinity for the active thrombin binding site (K_i = 1.8 ± 0.1 *vs.* 0.8 ± 0.1 nM) when α-thrombin was complexed to thrombomodulin. It was hypothesized that this was due to a conformational change occurring when thrombin binds to thrombomodulin (19).

An *in vitro* study using human kidney cells transfected with cDNA for human thrombomodulin and incubated with human thrombin and human protein C showed that treatment with melagatran concentration-dependently inhibited protein C activation (IC_{50} = 5.4 ± 3 nmol/l). Although inogatran (IC_{50} = 23 ± 15 nmol/l) and recombinant hirudin (r-hirudin; IC_{50} = 5 ± 0.7 nmol/l) were also effective in this assay, heparin alone at doses up to 2 IU/ml had no effect (20).

When the action of melagatran was examined on thrombin- and thrombin receptor-activating peptide (TRAP)-induced platelet activation in an *in vitro* assay using human whole blood, results showed that the agent concentration-dependently inhibited thrombin- but not TRAP-induced platelet CD62P (P-selectin, a marker of platelet activation) expression (IC_{50} = 13 nmol/l). Heparin and dalteparin were more active against thrombin-induced CD62P expression, with IC_{50} values of 0.04 and 0.08 IU/ml, respectively, indicating the higher antithrombin activity of these indirect thrombin inhibitors (21).

The antithrombotic activity of melagatran has been demonstrated in several *in vivo* models. In a study using a rat occlusion model of caval vein thrombosis, melagatran exhibited dose-dependent antithrombotic effects, with greater than 90% inhibition of thrombus weight observed at a dose of 145 μg/kg/h i.v. Melagatran was more potent than inogatran and twice as potent as dalteparin (ED_{50} = 16 ± 1 *vs.* 24 ± 2 and 33 ± 2 μg/kg/h, respectively). However, although none of the compounds (infused at concentrations similar to ED_{50} values)

prolonged APTT *in vitro*, when given at doses resulting in complete thrombus inhibition, APTT was slightly prolonged 1.3-fold for melagatran and inogatran and 1.2-fold for dalteparin (22). Melagatran was similarly effective in a nonocclusive rat model of deep venous thrombosis (involving administration of [^{125}I]-fibrinogen to determine clot size), where the agent was more potent than heparin in reducing thrombus accretion; results suggest that melagatran was more effective against clot-bound thrombin and/or thrombin-induced platelet aggregation than the indirect thrombin inhibitor (23).

Prophylactic administration of ximelagatran (1-20 μmol/kg p.o. for 4 days) was demonstrated to be as effective as warfarin (0.063-0.63 mg/kg p.o. for 4 days) in the prevention of thrombus formation in a study using a rat model of venous thrombosis. Animals were treated with the agents for 4 days prior to surgery to induce thrombosis (*i.e.*, partial stenosis and topical application of ferric chloride to the wall of the abdominal vena cava). Dose-dependent decreases in thrombus weight were observed in both ximelagatran- and warfarin-treated animals as compared to placebo and almost complete prevention of thrombus formation was observed with the higher doses of the agents. However, the hemoglobin content of abdominal swabs was found to be higher in warfarin-treated animals as compared to animals treated with ximelagatran, indicating reduced bleeding with the latter agent. Moreover, ximelagatran treatment resulted in dose-dependent increases in TT with no effects on PT while warfarin dose-dependently increased PT but had no effects on TT (24).

Melagatran (0.1-0.3 μmol/kg i.v. for 90 min starting 5 min prior to occlusion) was shown to be a safe alternative to hirudin (0.02-0.1 μmol/kg) in preventing arterial thrombosis in rabbits. Although both agents dose-dependently increased patency in a similar manner, 2- to 3-fold less ear bleeding was observed with melagatran as compared to hirudin when the agents were administered at doses resulting in 80-100% patency and complete thrombus resolution. Results indicate that melagatran is more effective against fibrin-bound thrombin (25).

Melagatran (i.v. bolus [mg/kg] + i.v. infusion [mg/kg/h], respectively: 0.15 + 0.05, 0.5 + 0.17 or 1 + 0.33) was also shown to be effective in a porcine coronary overstretch injury model of angioplasty involving the anterior descending and right coronary arteries. Treatment with the agent dose-dependently and significantly attenuated platelet deposition and reduced relative thrombus size as compared to placebo. No significant differences were observed between melagatran and heparin (200 IU/kg i.v. bolus + 20 IU/kg/h i.v. infusion) in this model (26). In contrast, melagatran (i.v. bolus [mg/kg] + i.v. infusion [mg/kg/h], respectively: 0.40 + 0.40, 0.64 + 0.60, 0.70 + 0.65 or 1.24 and 0.90) and ximelagatran (71 mg/kg p.o.) were demonstrated to be superior to heparin (50 IU/kg i.v. bolus + 50 IU/kg/h i.v. infusion) in an *ex vivo* porcine model of arterial thrombosis involving 5-min blood perfusions under low (212/s) and high (1690/s) shear through a Badimon chamber. All agents resulted in a reduction in thrombus formation (*i.e.*, platelet and fibrin deposition). However, ximelagatran treatment exhibited a threshold-dependent rather than dose-dependent effect and was effective, as was melagatran, at both low and high shear rates (27).

A study using a canine model of coronary artery thrombosis (*i.e.*, left anterior descending coronary artery [LAD]) demonstrated that melagatran (1.5 or 2.5 mg/kg via nasogastric tube 15 min prior to thrombogenic electrical stimulation [100 μA]) significantly prolonged the time to occlusive thrombus formation 4-5 times as compared to controls. Patency of the coronary artery for each melagatran dose was 68 and 75%, respectively, as compared to 14% in controls. Peak plasma concentrations following the low and high melagatran doses were 0.87 ± 0.22 and 1.38 ± 0.30 μM, respectively; APTT was prolonged by only 1.5-fold at peak plasma concentrations (28).

When compared to hirudin (i.v. bolus [mg/kg] and i.v. infusion [mg/kg/h], respectively: 0.4 + 1.2 or 1.2 + 3.6) and heparin (15 IU/kg bolus + 50 IU/kg/h i.v. infusion) in combination with recombinant tPA (rtPA; 1 mg/kg/h i.v. over 20 min) in a canine model of copper coil-induced coronary artery thrombosis, melagatran (0.10 mg/kg i.v. bolus + 0.3 mg/kg/h i.v. infusion) + rtPA starting 30 min after occlusive thrombus formation caused a significantly higher increase in LAD coronary artery blood flow; this dose of melagatran also caused a 2-fold prolongation of APTT. A lower dose of melagatran (0.033 mg/kg bolus + 0.10 mg/kg/h infusion) + rtPA resulted in effects comparable to combination therapy with the other agents (29). Another study using this same canine model of coronary artery thrombosis showed that tPA-mediated lysis of coronary arterial thrombus was associated with a significant increase in the local production of active carboxypeptidase U, an enzyme that, when activated from procarboxypeptidase U by thrombin, inhibits fibrinolysis. Melagatran (0.15 mg/kg/h i.v. infusion over 3 h) significantly inhibited the rate of carboxypeptidase U generation (5 ± 8 *vs.* 67 ± 54 U/min) and improved the thrombolytic effects of tPA. Results suggest that the efficacy of melagatran may, in part, be due to inhibition of thrombin-mediated procarboxypeptidase U activation (30).

The efficacy of melagatran has also been demonstrated in studies using a rat model of cerebral infarction and a rat and porcine model of septic shock, indicating a possible therapeutic benefit of the agent in the treatment of these indications. A single oral dose of melagatran (13 mg/kg) was found to significantly decrease the volume of photochemically induced cortical infarction by 53% (31). In addition, since thrombin is known to play a role in the development of septic shock, the efficacy of melagatran was examined in a rat and porcine model of endotoxemia. In rats, treatment with melagatran (0.32, 1 and 3.2 μmol/kg/h i.v. bolus followed by continuous infusion starting 20 min before endotoxin [1 mg/kg i.v.] injection) partially or completely decreased fibrinogen consumption and partially reduced platelet consumption. Further reductions in fibrinogen consumption and a complete protection against platelet consumption were observed when

melagatran was combined with dexamethasone (1 and 10 mg/kg i.v. bolus 1 h before endotoxin injection) (32). Results obtained from studies using a porcine model of endotoxemia showed that melagatran (0.3 mg/kg i.v. bolus + 0.1 mg/kg/h continuous i.v. infusion for 3 h) significantly attenuated endotoxin-induced increases in pulmonary capillary wedge pressure and pulmonary and hepatic fibrin deposition and decreases in platelet counts; PaO_2, plasma TNF-α levels or liver function markers were unaffected by treatment (33, 34).

Although administration of melagatran is not associated with significant bleeding problems, a reversal of the anticoagulant effect of this agent may be required in certain clinical situations, such as overdose. Results from 2 studies conducted in rats and rabbits showed that administration of activated prothrombin complex concentrate (APCC; 25 U/kg or greater) following treatment with high doses of melagatran (0.7 μmol/kg i.v. bolus + 2 μmol/kg/h i.v. infusion) reversed prolonged bleeding time and blood loss. Administration of recombinant factor VIIa (10 mg/kg) resulted in only slight reversal of blood loss and bleeding time effects *in vivo*, although it effectively shortened the prolonged whole blood clotting time *ex vivo* (35, 36).

Pharmacokinetics

The intestinal permeability of ximelagatran and melagatran was compared *in vitro* in a study using monolayers of human epithelial cells from a Caco-2 cell line. The apparent permeability (Papp) values obtained were 24 ± 7 and 0.3 ± 0.1 nm/s, respectively, indicating that ximelagatran permeated 80 times faster than melagatran (37).

A study conducted in 20 healthy male volunteers reported the pharmacokinetics of single oral doses of melagatran (57-200 mg) and ximelagatran (5-98 mg). Both agents were well tolerated with no serious adverse events observed. Oral bioavailability of ximelagatran was 20% which was 2.7-5.5 times higher than that of melagatran. In addition, the variability in AUC values for ximelagatran was smaller as compared to melagatran (coefficient of variation = 20% *vs.* 38%) (37).

The pharmacokinetics of single i.v. (1.7-82 mg/kg), p.o. (0.02-3.3 mg/kg) and s.c. (0.1-5 mg) doses of melagatran and single oral dose ximelagatran (1-98 mg) were determined in a study conducted in healthy male subjects. All treatments were well tolerated. Relatively low plasma clearance (1.8 ml/min/kg), a small volume of distribution (0.22 l/kg) and a short $t_{1/2}$ value (1.7 h) were observed following i.v. melagatran. Complete bioavailability was obtained following s.c. melagatran, with peak plasma levels obtained approximately 0.5 h postdosing and a $t_{1/2}$ of 1.7 h. Plasma levels were dose-proportional and intersubject variability was low following both i.v. and s.c. dosing. The bioavailability of melagatran following oral dosing with 0.7-3.3 mg/kg was determined to be 5.8 ± 2.3%, as compared to approximately 20% observed following ximelagatran oral dosing (38).

The pharmacokinetics, metabolism and elimination of oral and i.v. ximelagatran were reported from an open-label, nonrandomized, sequential study conducted in 5 healthy males. Subjects received a single oral dose of [^{14}C]-labeled ximelagatran followed 20 days later by a single i.v. dose (10 mg). After both oral and i.v. dosing, ximelagatran was rapidly converted to melagatran; melagatran C_{max}, t_{max} and $t_{1/2}$ values obtained following oral and i.v. dosing (respectively) were: 0.355 and 0.148 μmol/l; 1.85 and 1.25 h; and 3.64 ± 0.70 and 4.29 ± 0.53 h. The major metabolite found in urine and feces was melagatran; small amounts of ximelagatran and 2 intermediary metabolites (H-338/57 and H-415/04) were also detected in plasma and urine. About 70 and 25% of the oral ximelagatran dose was excreted in feces and urine, respectively (39).

Results from 2 studies showed that the pharmacokinetics of oral ximelagatran were independent of age and ethnic origin. Results from an open-label, randomized, 3-way crossover study conducted in 6 young male and 12 elderly male and female healthy subjects administered ximelagatran p.o. (20 mg with breakfast and while fasting) and s.c. (7.5 mg) showed that the absorption and metabolism of ximelagatran to melagatran were unaffected by age. A reduction in plasma clearance was observed in elderly subjects, possibly due to decreased renal function. Although bioavailability was similar following oral dosing in the fed and fasted states, the tmax was 1 h longer when ximelagatran was given after a meal (40). An open-label, nonrandomized study conducted in 36 healthy male subjects separated equally into ethnic groups (African, Asian and Caucasian) showed that the pharmacokinetics and pharmacodynamics (*i.e.*, APTT prolongation) of a single oral ximelagatran dose (50 mg) were independent of ethnic origin. A slightly higher AUC for melagatran was observed in Asian subjects, which was possibly due to the lower creatinine clearance calculated for this group. The $t_{1/2}$ for melagatran for all groups was about 3 h. Bioavailability was approximately 20% for all groups, with a low intersubject variability observed (41).

Four separate studies conducted in healthy subjects have demonstrated that there are no significant pharmacokinetic or pharmacodynamic interactions between ximelagatran and/or melagatran and acetylsalicylic acid (ASA), diazepam, diclofenac or nifedipine.

A randomized, double-blind, placebo-controlled, 2-way crossover study in 12 subjects treated on day 1 with 450 mg ASA or placebo and 150 mg ASA on day 2 followed 80 min later by a 4-h melagatran infusion (total dose = 4.12 mg) showed that the pharmacokinetics, as well as the prolongation of bleeding time, APTT and activated coagulation time (ACT), induced by either agent alone were unaffected by cotreatment (42).

An open-label, randomized, 2-way crossover study conducted in 24 healthy males administered diazepam on day 1 or 3 (0.1 mg/kg i.v. infusion over 10 min) and ximelagatran (24 mg p.o. b.i.d.) for 8 days showed no pharmacokinetic interaction between the two agents. The

pharmacokinetics of *N*-desmethyldiazepam were also not affected by coadministration. Results suggest that ximelagatran would therefore not alter the CYP2C19-mediated metabolism of other agents and coadministration of CYP2C19 substrates would not influence the pharmacokinetics of melagatran (43, 44).

An open-label, randomized, 3-period crossover study conducted in 24 healthy males given single-dose ximelagatran alone (24 mg p.o.) or in combination with diclofenac (50 mg p.o.) reported no significant pharmacokinetic interactions between the two agents. Results suggest that ximelagatran should not alter CYP2C9-mediated metabolism of other agents and cotreatment with CYP2C9 substrates would not affect the pharmacokinetics of melagatran. The effects of ximelagatran/melagatran on APTT were unaffected by combination treatment (44, 45).

Results from an open-label, randomized, 3-period, crossover study conducted in 34 healthy males given single doses of ximelagatran (24 mg p.o.) alone and in combination with nifedipine (60 mg p.o.) demonstrated no clinically significant pharmacokinetic interaction between the agents. Results suggest that ximelagatran should not affect the CYP3A4-mediated metabolism of other agents and the pharmacokinetics of melagatran should not be altered by coadministration of CYP3A4 substrates (44, 46).

The pharmacokinetics of ximelagatran (8, 12, 18 or 24 mg p.o. b.i.d. 12-24 h before surgery) have also been examined in 600 patients undergoing total knee arthroplasty in a multicenter, randomized, blinded, parallel-group study. Data from 455 patients showed that the mean plasma melagatran levels (0.06, 0.10, 0.15 and 0.20 μmol/l on day 1 for the respective doses) and median AUC values (0.74, 1.25, 1.88 and 2.52 μmol/h/l, respectively) obtained from another study were dose-proportional. Since the pharmacokinetics of ximelagatran were predictable, it was concluded that routine monitoring is not required with this agent (47).

Two open-label, single-dose studies revealed no differences in the pharmacokinetic and pharmacodynamic properties of ximelagatran (24 mg p.o.) between obese (BMI = 32-39 kg/m^2; n = 12) and age- and gender-matched nonobese subjects (BMI = 21-26 kg/m^2; n = 12) and between patients with mild to moderate liver impairment (n = 12) and age-, weight- and gender-matched subjects with normal liver function. These results suggest that no dose adjustments are required in obese subjects or patients with mild to moderate liver impairment (48, 49).

The pharmacokinetics of s.c. melagatran and oral ximelagatran (6, 12 or 24 mg) were examined from data obtained in 3 studies involving 216 patients treated for 8-11 days to prevent thrombosis after total knee or hip replacement surgery. Patients received either s.c. melagatran alone (1.5-4.5 mg b.i.d.) or melagatran (1, 2 or 4 mg) followed by oral ximelagatran (6, 12 or 24 mg). A one-compartment model with first-order absorption described the pharmacokinetics obtained with both s.c. melagatran and oral ximelagatran. Renal clearance was determined to be the major elimination route for unchanged melagatran. Although melagatran clearance was found to correlate with creatinine clearance and volume of distribution of melagatran correlated with body weight, it was concluded that dose adjustments based on renal function or body weight were not required in this patient group (50, 51).

However, results from an open-label, randomized, 2-period crossover, study suggest that the dose of oral ximelagatran (24 mg tablet) or s.c. melagatran (3 mg) should be reduced or the dosing interval increased in patients with severe renal dysfunction. The study included a washout period of 1-3 weeks between treatments and was conducted in 12 subjects with renal impairment (glomerular filtration rate [GFR] = 12.5 ml/min) and 12 subjects with normal renal function (GFR = 86.5 ml/min). Renally impaired subjects had higher plasma melagatran levels as compared to control subjects. The ratio of AUC in renally impaired as compared to control subjects was 5.33 and 4.03 following oral and s.c. administration of the agent, respectively. These differences were due to the lower total clearance and renal clearance of melagatran evident in renally impaired subjects. While 13.9 and 65.9% of the oral and s.c. ximelagatran dose, respectively, was excreted in urine over a 24-h period, only 8 and 37.8%, respectively, were excreted by renally impaired subjects. In addition, the relative bioavailability of melagatran after oral dosing as compared to s.c. dosing was 32% higher in renally impaired subjects and $t_{1/2}$ values were approximately 2 times longer than in control subjects. A nonlinear relationship between melagatran plasma concentrations and APTT prolongation was observed after both p.o. and s.c. dosing with no significant differences detected between renally impaired and control subjects (52).

A multicenter, randomized, open, controlled, dose-escalating, pilot study was conducted to determine the pharmacokinetics of melagatran (10-min i.v. [mg/kg/h]) + continuous i.v. infusion [mg/kg/h], respectively: 0.05 + 0.005, 0.10 + 0.01 and 0.15 + 0.015) administered to 48 patients with acute proximal deep vein thrombosis. Treatment was well tolerated with no significant bleeding events observed. Plasma levels of the agent were found to increase rapidly and were relatively constant during infusion. Plasma levels of melagatran just prior to the end of infusion were 0.17, 0.31 and 0.53 μmol/l for the respective doses; a low interpatient variability was seen for steady-state plasma levels. Prolongation of APTT correlated with plasma levels of melagatran and, after 4-6 days, a regression in thrombus size was observed in 8/12, 6/12 and 5/11 patients treated with the low, medium and high doses of the agent, respectively. Mean population clearance, volume of distribution and $t_{1/2}$ values were 6 l/h, 19 l and 2.5 h, respectively. A 67% interpatient variation in clearance was observed which was due to the linear correlation of this parameter with creatinine clearance. Thus, elderly patients with a reduced calculated creatinine clearance displayed lower melagatran

Table III: Ex vivo *results of randomized comparative studies of ximelagatran in healthy subjects (from Prous Science Integrity database).*

Study drug	Dose	n	Results		Conclusions	Ref.
			Thrombin generation reduction:			
Ximelagatran	60 mg po	54	–61%		Reduction in thrombin generation in active treatment groups	54, 55
Dalteparin	120 IU/kg sc		–77%			
Control						
			Thrombin generation reduction at 2h:			
Ximelagatran	15 mg po	120	–14%		Dose-dependent reduction in thrombin generation	56-58
Ximelagatran	30 mg po		–29%*			
Ximelagatran	60 mg po		–48%*			
Enoxaparin	100 U/kg sc		–68%*			
r-Hirudin	0.4 mg/kg iv bolus → 0.15 mg/kg/h iv x 2h →					
Control	0.075 mg/kg/h iv x 2h		–4			
			Thrombus area at 2 h:			
			Low shear rate	*High shear rate*		
Ximelagatran	20 mg po	60			Dose dependent reduction in total thrombus area formation	59
Ximelagatran	40 mg po		–29%*	–24%*		
Ximelagatran	80 mg po		–41%*	–15%		
r-Hirudin	0.4 mg/kg iv bolus → 0.15 mg/kg/h iv x 2h → 0.075 mg/kg/h iv x 3h		–73%*	–40%*		
			–43%*	–24%*		

*$p < 0.05$ *vs.* baseline

clearance rates. A 37% interpatient variation was observed for volume of distribution which was found to be due to a correlation of this measurement with body weight. However, the pharmacokinetic parameters obtained were independent of age and gender (53).

Clinical Studies

Ex vivo *pharmacodynamic studies in healthy volunteers*

A randomized, open-label study conducted in 54 healthy male volunteers demonstrated the efficacy of ximelagatran (60 mg p.o.) as compared to dalteparin (120 IU/kg s.c.) in reducing thrombin generation *ex vivo*. Plasma levels of melagatran and dalteparin were 0.48 mM and 0.79 U/ml, respectively, postdosing. Analysis of venous blood samples showed a significant prolongation in the lag phase (41 and 95% for ximelagatran and dalteparin, respectively) of thrombin generation and a reduction in thrombin production (61 and 77% for ximelagatran and dalteparin, respectively). In addition, 2 markers of thrombin generation (*i.e.*, prothrombin fragment 1+2 and thrombin-antithrombin complex [TAT]) levels in shed blood from subject forearm incisions from both treatment groups were significantly reduced at 2 and 4 h postdosing as compared to baseline and untreated control subjects, further indicating inhibition of thrombin (54, 55).

Similar efficacy was observed for single-dose ximelagatran (15, 30 or 60 mg p.o.) in a randomized, open-label, parallel-group study conducted in 120 healthy male subjects. The trial compared ximelagatran to treatment with r-hirudin (0.4 mg/kg i.v. bolus + 0.15 mg/kg/h infusion for 2 h and a subsequent infusion of 0.075 mg/kg/h for 2 h), enoxaparin (100 U/kg s.c.) and placebo *ex vivo* using the ETP method. While a significant decrease in thrombin generation as compared to baseline was seen at 2 and 4 h postdosing treatment with r-hirudin (–45% at 2 h and –47% at 4 h) and enoxaparin (–68% at 2 h and –68% at 4 h), ximelagatran dose-dependently reduced ETP by –14, –29 and –48% at 2 h and –10, –20 and –28% at 4 h with doses of 15, 30 and 60 mg, respectively (56-58).

Results from a randomized, open-label study involving 60 healthy male volunteers and using an *ex vivo* model of arterial thrombosis (*i.e.*, perfusion of subject blood under low [212/s] and high [1690/s] rates through a Badimon chamber containing highly thrombogenic surfaces) demonstrated that ximelagatran (20, 40 or 80 mg p.o.) significantly and dose-dependently reduced total thrombus area as compared to baseline. The reducing effects of the agent were observed under both low (–29, –41 and –73% at 2 h and –43, –28 and –59% at 5 h postdosing for the 20, 40 and 80 mg doses, respectively) and high (–24, –15 and –40% at 2 h and –13, –24 and –31% at 5 h for the respective doses) shear conditions and were comparable to effects observed from blood samples from subjects treated with r-hirudin (0.4 mg/kg i.v. + 0.15 mg/kg/h infusion for 2 h and a subsequent infusion of 0.075 mg/kg/h for 3 h). Results suggest that ximelagatran may have potential long-term efficacy for the treatment of arterial thrombosis (59).

The results of these *ex vivo* studies are summarized in Table III.

Therapeutical intervention studies

The efficacy of treatment with melagatran followed by ximelagatran as a prophylaxis of venous thromboembolism has been demonstrated in a number of trials including the METHRO I, II and III studies. The preliminary safety and efficacy of melagatran and ximelagatran were shown in a randomized, parallel-group trial involving patients scheduled for elective total hip or knee replacement (METHRO I). Patients (n = 138) were administered either 3 s.c. doses (1, 2, and 4 mg b.i.d.) of melagatran (for 2 days before surgery) followed by ximelagatran (6, 12 and 24 mg b.i.d. p.o. starting the morning after surgery for 6-9 days) or dalteparin (5000 IU once daily s.c.). Melagatran/ximelagatran was well tolerated. Thromboembolic events were seen in only 20.5 and 18.6% of the patients receiving melagatran/ximelagatran and dalteparin, respectively, following surgery; no pulmonary embolism or severe bleeding events were seen. It was concluded that melagatran/ximelagatran has good potential as a treatment for the prevention of venous thromboembolism following orthopedic surgery (60, 61).

Similarly, the efficacy of melagatran/ximelagatran (1, 1.5, 2.25 or 3 mg melagatran s.c. b.i.d. before surgery followed by 8, 12, 18 or 24 mg ximelagatran p.o. b.i.d. starting the morning after surgery and continued for 7-10 days) was shown and compared to dalteparin (5000 IU once daily s.c. starting the evening before surgery) or placebo in the multicenter, randomized, double-blind, parallel-group METHRO II study conducted in 1916 patients undergoing total hip or knee replacement surgery. Analysis of the phlebograms obtained from 1473 patients showed a significant dose-dependent reduction in venous thromboembolism for patients treated with melagatran/ximelagatran; the highest dose of melagatran/ximelagatran was significantly superior to dalteparin. Results from 1477 patients indicated a significant dose-dependent decrease in proximal deep vein thrombosis and pulmonary embolism with melagatran/ximelagatran treatment. Total bleeding time, wound rupture reoperation and nonsurgical bleedings were similar for all treatment groups (62, 63).

These results were complemented with those of the METHRO III trial in which the efficacy and safety of melagatran/ximelagatran (3 mg melagatran s.c. starting 4-12 h postsurgery followed by 24 mg ximelagatran p.o. b.i.d. for 8-11 days) were shown to be comparable to treatment with enoxaparin (40 mg once daily s.c. starting the evening before surgery) as a thromboprophylaxis after total hip or knee replacement surgery. The trial was a randomized, double-blind, double-dummy, parallel-group trial conducted in 2788 patients. From the venograms of 2268 patients, the rates of proximal deep vein thrombosis and pulmonary embolism for the melagatran/ximelagatran and enoxaparin groups were 5.7 and 6.2%, respectively, and the rates for total venous thromboembolism were 31.0 and 27.3%, respectively. Total bleeding (1115 ± 596 and 1101 ± 599 ml, respectively) and the percentage of patients requiring blood transfusions (61.8 and 66.1%, respectively) were similar in both melagatran/ximelagatran and enoxaparin groups (64).

The efficacy and safety of ximelagatran alone (8, 12, 18 or 24 mg p.o. started 12-24 h postsurgery and continued for 6-12 days) as compared to open-label enoxaparin (30 mg s.c. b.i.d.) as a prophylaxis against venous thromboembolism after total knee replacement surgery have also been examined in a multicenter, randomized, blinded, dose-finding phase II study conducted in 594 adults undergoing elective surgery. Both agents were well tolerated and of the 443 evaluable patients, the incidence of venous thromboembolism (27, 19.8, 28.7 and 15.8% for the respective ximelagatran doses and 22.7% for enoxaparin) and proximal deep vein thrombosis/pulmonary embolism (6.6, 2.0, 5.8, and 3.2%, respectively for ximelagatran and 3.1% for enoxaparin) was similar in both treatment groups. Incidence of major bleeding was low, occurring only in the 18 mg ximelagatran group (2.4%) and the enoxaparin group (0.8%). The 24 mg p.o. b.i.d. ximelagatran dose was recommended for phase III studies (65).

The efficacy and safety of fixed-dose oral ximelagatran (24 mg b.i.d. for 7-12 days starting the morning after surgery) as compared to enoxaparin (30 mg s.c. b.i.d.) to prevent venous thromboembolism after total hip arthroplasty were shown in a multicenter, randomized, double-blind phase III study conducted in a total of 1838 patients. The overall rate of evaluable venography was 85.4%. Although the frequency of venous thromboembolism was low in both treatment groups, enoxaparin-treated patients had significantly fewer incidences as compared to ximelagatran-treated patients (9.3 *vs.* 12.4%, on-site interpretation; 4.6 *vs.* 7.9, ICAC [independent central adjudication committee] review). Similar low bleeding rates were seen in both groups (66).

A multicenter, randomized, double-blind phase III trial involving 680 patients undergoing total knee arthroplasty showed the efficacy and safety of ximelagatran (24 mg p.o. b.i.d.) as compared to warfarin (p.o. once daily to achieve a target INR of 2.5) or placebo for 7-12 days as a prophylaxis against venous thromboembolism. An ICAC central review determined that the rates of overall venous thromboembolism (19.2 *vs.* 25.7%) and proximal deep vein thrombosis/pulmonary embolism (3.3 *vs.* 5.0%) were better for the group treated with ximelagatran as compared to warfarin, although statistical significance was not reached. However, on-site assessment revealed statistical significance in favor of ximelagatran over warfarin. The incidence of major and minor bleeding events was low for both groups (67).

The efficacy and tolerability of ximelagatran as a treatment for acute deep vein thrombosis were examined in a multicenter, randomized trial conducted in 350 patients with deep vein thrombosis of the lower extremities. Patients were administered either blinded ximelagatran (24, 36, 48 or 60 mg p.o. b.i.d.) or open-label dalteparin followed by warfarin. Results from venograms from 295 patients indicated that 69% of the patients treated with ximelagatran and 69% of those treated with dalteparin/

Table IV: Randomized, double-blind comparative studies of ximelagatran in the prophylaxis and treatment of venous thromboembolism (from Prous Science Integrity database).

	Dose	n		Conclusions	Ref.
Prophylaxis in arthroplasty			Total venous thromboembolism		
Melagatran + Ximelagatran Melagatran + Ximelagatran Melagatran + Ximelagatran Dalteparin	1 mg sc bid x 2d + 6 mg po bid x 6-9d 2 mg sc bid x 2d + 12 mg po bid x 6-9d 4 mg sc bid x 2d + 24 mg po bid x 6-9d 5000 IU sc od x 8-12d	105	20.5% 18.6%	No pulmonary embolism No severe bleeding Melagatran + Ximelagatran as safe and effective as dalteparin	60, 61
Melagatran + Ximelagatran Melagatran + Ximelagatran Melagatran + Ximelagatran Melagatran + Ximelagatran Dalteparin	1 mg sc bid/8 mg po bid x 7-10d 1.5 mg sc bid/12 mg po bid x 7-10d 2.25 mg sc bid/18 mg po bid x 7-10d 3 mg sc bid/24 mg po bid x 7-10d 5000 IU sc od	1473	 ↓↓+	Dose-dependent decrease of venous thromboembolism Melagatran 3/Ximelagatran 24 better than dalteparin	62, 63
Melagatran + Ximelagatran Enoxaparin	3 mg sc + 24 mg po bid x 8-10d 40 mg sc od x 8-11d	2268	31.0% 27.3%	Similar total bleeding Melagatran + Ximelagatran as safe and effective as enoxaparin	64
Ximelagatran Ximelagatran Ximelagatran Ximelagatran Enoxaparin	8 mg po bid x 6-12d 12 mg po bid x 6-12d 18 mg po bid x 6-12d 24 mg po bid x 6-12d 30 mg sc bid x 6-12d	443	27.0% 19.8% 28.7% 15.8% 22.7%	Similar bleeding Ximelagatran as safe and effective as enoxaparin	65
Ximelagatran Enoxaparin	24 mg po bid x 7-12d 30 mg sc bid x 7-12d	1816	12.4%* 9.3%	Ximelagatran was effective and well tolerated, without excess bleeding	66
Ximelagatran Warfarin	24 mg po bid x 7-12d Dose adjusted per INR x 7-12d	537	25.7% 19.2%*	Similar total bleeding Ximelagatran as safe and effective as warfarin	67
Treatment of deep venous thrombosis in legs			Thrombus regression	Thrombus progression	
Ximelagatran Ximelagatran Ximelagatran Ximelagatran Dalteparin → Warfarin	24 mg po bid x 14d 36 mg po bid x 14d 48 mg po bid x 14d 60 mg po bid x 14d x 14d	295	 69% 69%	 8% 3%	Similar severe bleeding Ximelagatran as safe and effective as dalteparin/warfarin to limit progression of acute deep venous thrombosis of the lower extremities	68, 69

+$p < 0.0001$ *vs.* Dalteparin; *$p < 0.05$

warfarin showed regression of thrombus size; progression was observed in 8 and 3% of the patients, respectively. One patient each in the 24 mg and 36 mg ximelagatran groups and 2 patients from the dalteparin/warfarin group developed severe hemorrhage during treatment. Decreases in pain, edema and circumference of affected leg were comparable in both treatment groups (68, 69).

The results of these therapeutic intervention studies are summarized in Table IV.

Ximelagatran may also be effective as a treatment of pulmonary embolism according to results of an open-label, pilot study in which 12 hemodynamically stable patients with scintigraphy-verified symptomatic pulmonary embolism and deep vein thrombosis were treated with the agent (48 mg b.i.d.) for 6-9 days followed by conventional heparin and warfarin therapy. Treatment with ximelagatran was well tolerated and after the 6-9 days of treatment, an improvement in pulmonary embolism and deep vein thrombosis symptoms was observed. Moreover, 11 patients had regressed or unchanged scintigraphies of which 5 showed no perfusion defects. The rate of leg edema was also decreased from 61% at baseline to 46% with no moderate or severe pain reported. No severe bleeding or deaths occurred (70).

The efficacy of long-term ximelagatran treatment has also been evaluated and compared to warfarin as a preventive therapy for stroke in patients with atrial fibrillation. In the randomized, double-blind, 12-week SPORTIF II (Stroke Prevention by ORal Thrombin Inhibitor in atrial Fibrillation) study, 257 patients with chronic nonvalvular atrial fibrillation (NVAF) and a moderate to high risk for stroke were given either ximelagatran (20, 40 or 60 mg

p.o. b.i.d.) or warfarin (doses to achieve an INR of 2-3). Incidence of minor bleeding was similar and low in both groups. While no patients experienced major bleeding events in the ximelagatran group, 1 warfarin-treated patient suffered a major bleeding event. One nonfatal ischemic stroke and 1 transient ischemic attack (TIA) were observed in the ximelagatran group and 2 TIAs were seen in the warfarin group. It was concluded that ximelagatran at doses up to 60 mg was safe and effective for 12 weeks as a preventive treatment for stroke in patients with atrial fibrillation (71, 72).

The efficacy and tolerability of ximelagatran were further demonstrated from preliminary results of the ongoing SPORTIF IV, an open-label continuation of the SPORTIF II study in which 254 patients with NVAF and at least 1 additional stroke risk factor received fixed doses of ximelagatran (36 mg b.i.d.) or warfarin for 21-24 months. The number of events (stroke/TIA and major bleeds) per 100 treatment years for the ximelagatran-treated group (1.8 and 0.9, respectively) was lower than that observed in the warfarin group (6.8 and 4.1, respectively). The 3 strokes seen in the ximelagatran group were ischemic and nonfatal while the 2 strokes seen in the warfarin group were either ischemic or hemorrhagic and both were fatal. Although asymptomatic elevations in S-ALAT were seen in a few patients treated with ximelagatran, levels were reduced spontaneously with continued therapy or discontinuation. No intracranial or fatal bleeds were observed and coagulation monitoring was not necessary with ximelagatran (73).

Melagatran is in phase III clinical studies for the subcutaneous prevention and treatment of venous thrombosis. Its prodrug ximelagatran is also in phase III clinical evaluation for the oral prevention and treatment of venous thrombosis, as well as the prevention of stroke in patients with atrial fibrillation (74, 75).

Manufacturer

AstraZeneca plc (GB).

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