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MONOGRAPH

ATOPAXAR

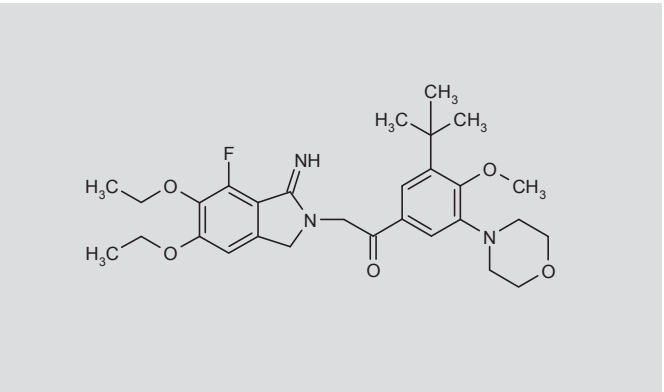
Prop INN; USAN

E-5555

Protease-Activated Receptor PAR1 Antagonist
Thrombin Inhibitor
Treatment of Acute Coronary Syndrome
Treatment of Arterial Thrombosis

1-[3-*tert*-Butyl-4-methoxy-5-(4-morpholino)phenyl]-2-(5,6-diethoxy-7-fluoro-1-imino-1,3-dihydro-1*H*-isoindol-2-yl)ethanone

InChI: 1S/C29H38FN3O5/c1-7-37-23-15-19-16-33(28(31)24(19)25(30)27(23)38-8-2)17-22(34)18-13-20(29(3,4)5)26(35-6)21(14-18)32-9-11-36-12-10-32/h13-15,31H,7-12,16-17H2,1-6H3



$C_{29}H_{38}FN_3O_5$
Mol wt: 527.6275
CAS: 751475-53-3
CAS: 474544-83-7 (hydrochloride)
EN: 415756

SUMMARY

Atherothrombotic disease, i.e., acute coronary syndromes, cerebrovascular events and peripheral arterial disease, is a major cause of morbidity and mortality worldwide. The current standard of care, the dual antiplatelet therapy consisting of aspirin combined with a thienopyridine derivative, is limited by the risk of bleeding and recurrent thrombotic events. Atopaxar (E-5555) is a novel, once-daily, orally active, potent protease-activated receptor PAR1 antagonist that has demonstrated antiplatelet and antithrombotic effects without prolonging bleeding time in relevant preclinical experimental models. In phase II clinical trials (Lessons from Antagonizing the Cellular Effects of Thrombin, LANCELOT trials), atopaxar at doses of 50, 100 and 200 mg in patients with acute coronary syndrome or high-risk coronary artery disease, inhibited thrombin receptor-activating peptide-induced platelet aggregation and did not increase clinically significant bleeding. However, at higher doses there was a significant increase in liver function abnormalities and a modest QTcF lengthening effect that future larger studies should clarify.

Key words: Atherothrombotic disease – PAR1 antagonist – Atopaxar – E-5555

SYNTHESIS*

Atopaxar is prepared as follows:

Friedel–Crafts acylation of 2-*tert*-butylphenol (I) with acetyl chloride (II) in the presence of $AlCl_3$ in cold toluene gives 1-(3-*tert*-butyl-4-hydroxyphenyl)ethanone (III) (1, 2), which by nitration with HNO_3 in cold H_2O/CH_2Cl_2 provides 1-(3-*tert*-butyl-4-hydroxy-5-nitrophenyl)ethanone (IV). *O*-Alkylation of phenol (IV) with methyl iodide by means of K_2CO_3 in DMF produces the methyl ether (V), which is reduced at the nitro group with Fe and NH_4Cl in $EtOH/H_2O$ to afford the corresponding amine (VI). Cyclocondensation of the aniline derivative (VI) with bis(2-bromoethyl) ether (VII) by means of NaI and K_2CO_3 in DMF provides the 3-morpholino-acetophenone derivative (VIII). α-Halogenation of acetophenone (VIII) with NBS by means of Et_3N and TBDMSOTf in THF yields the corresponding bromoacetophenone (IX) (1), which is finally condensed with isoindole derivative (X) in THF (1) or DMF (2). Scheme 1.

The isoindole intermediate (X) is prepared by dialkylation of 3-fluorocatechol (XI) with ethyl iodide (XII) in the presence of K_2CO_3 in DMF to give 1,2-diethoxy-3-fluorobenzene (XIII), which is brominated with Br_2 by means of NaOAc in AcOH at 70 °C to yield 1,2-dibromo-4,5-diethoxy-3-fluorobenzene (XIV). Bromide substitution in intermediate (XIV) with CuCN in DMF at 150 °C affords 4,5-diethoxy-3-fluorophthalonitrile (XV), which is finally submitted to reductive cyclization with H_2 over PtO_2 in EtOAc/EtOH/MeOH (1). Scheme 1.

An improved and industrial scaleable synthesis of 3-amino-5,6-diethoxy-4-fluoroisoindole (X) was described:

Bromination of 1,2-diethoxy-3-fluorobenzene (XIII) with NBS in acetonitrile gives 1-bromo-3,4-diethoxy-2-fluorobenzene (XVI), which undergoes bromide displacement with CuCN in DMF at 155 °C to

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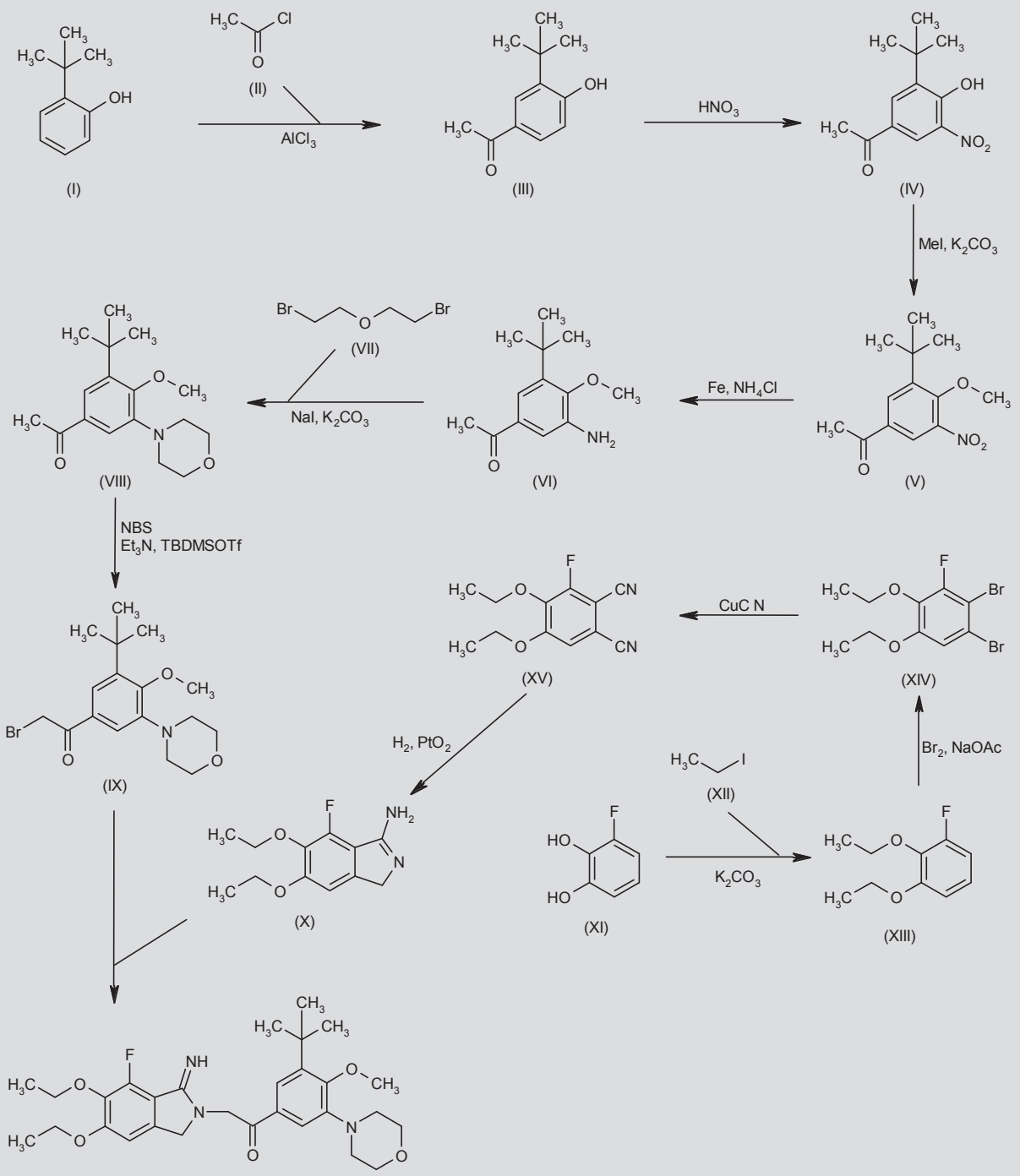
*Synthesis prepared by C. Estivill, R. Castañer, J. Bolòs. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

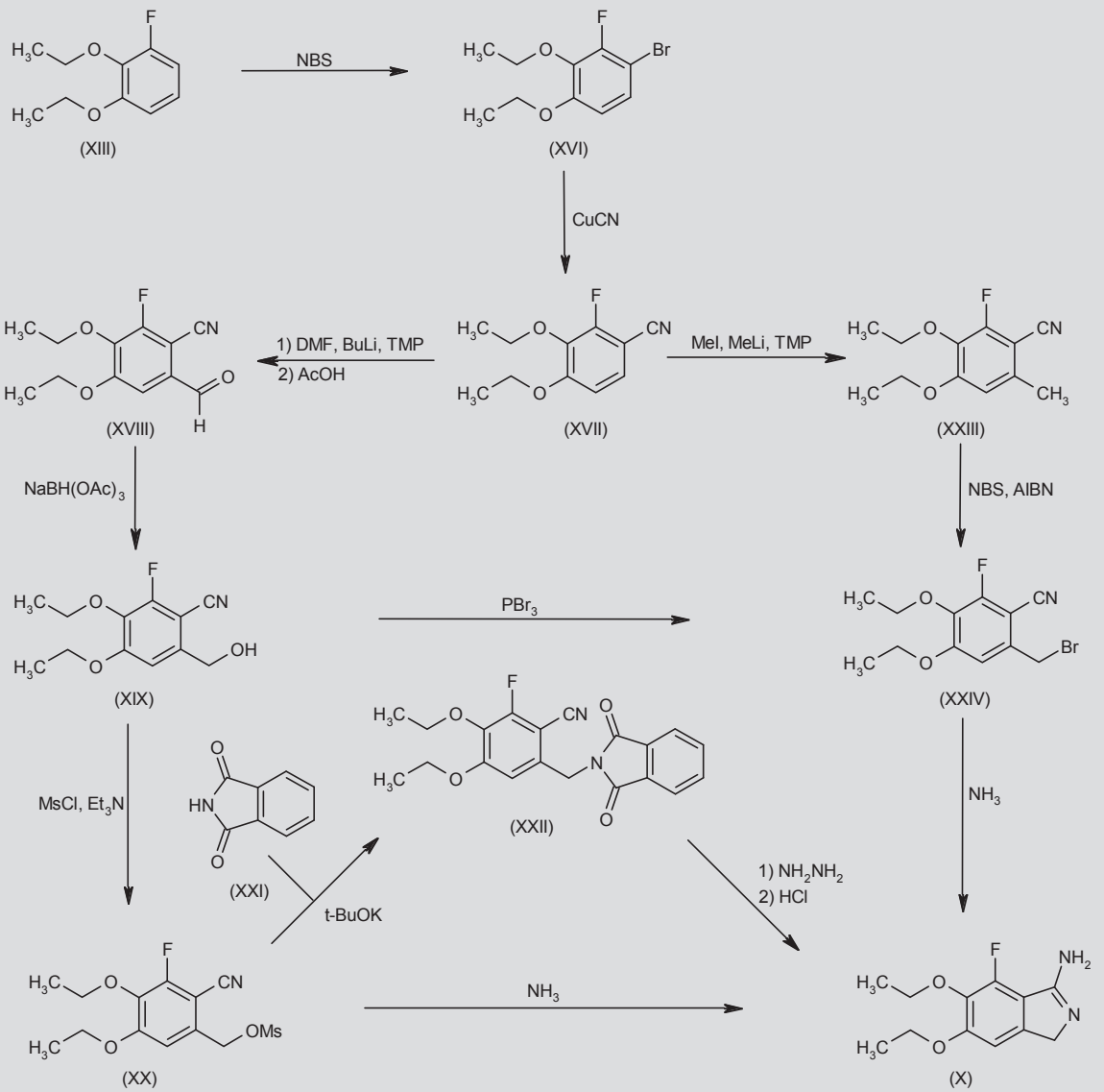
Scheme 1. Synthesis of Atopaxar



yield 3,4-diethoxy-2-fluorobenzonitrile (XVII). Metalation of compound (XVII) with BuLi in the presence of tetramethylpiperidine (TMP) in THF at –10 °C followed by reaction with DMF and quenching with AcOH leads to 3,4-diethoxy-2-fluoro-6-formylbenzonitrile (XVIII). Reduction of aldehyde (XVIII) with $NaBH(OAc)_3$ in EtOAc at 40 °C provides the benzylic alcohol (XIX), which is then activated as the mesylate (XX) by means of MsCl and Et_3N in DME. Condensation of mesylate (XX) with phthalimide (XXI) by means of *t*-BuOK in DMF furnishes the *N*-substituted phthalimide (XXII), which is finally subjected to hydrazinolysis and subsequent cyclization in the presence of HCl in THF. Also, the isoindole (X) can be obtained by direct cyclization of the cyano mesylate (XX) with NH_3 in toluene in a pressure vessel (2). Scheme 2.

Alternatively, isoindole (X) can be prepared by metalation of 3,4-diethoxy-2-fluorobenzonitrile (XVII) with MeLi in the presence of TMP in THF, followed by alkylation with MeI to afford 3,4-diethoxy-2-fluoro-6-methylbenzonitrile (XXIII), which is then brominated with

Scheme 2. Synthesis of Isoindole (X)



NBS by means of AIBN in refluxing CCl_4 to yield 6-(bromomethyl)-3,4-diethoxy-2-fluorobenzonitrile (XXIV). Benzylic bromide (XXIV) can also be prepared by treatment of primary alcohol (XIX) with PBr_3 in DME. Subsequent cyclization of the benzonitrile (XXIV) with NH_3 in toluene affords 3-amino-5,6-diethoxy-4-fluoroisoindole (X) (2). Scheme 2.

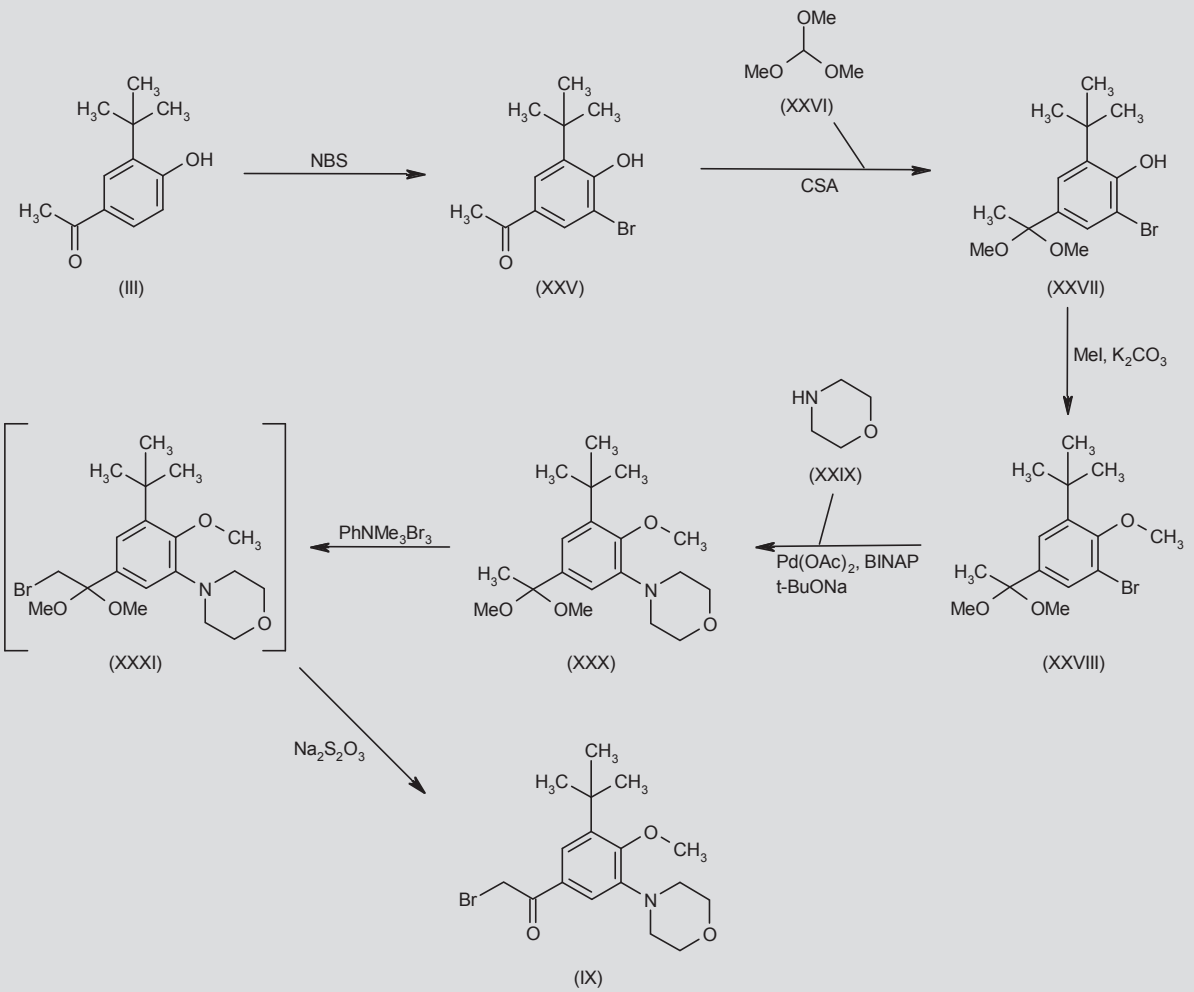
An improved and industrial scaleable synthesis of bromoacetophenone (IX) was also described:

Bromination of 1-(3-*tert*-butyl-4-hydroxyphenyl)ethanone (III) with NBS in acetonitrile yields 1-(3-bromo-5-*tert*-butyl-4-hydroxyphenyl)ethanone (XXV), which by protection with trimethyl orthoformate (XXVI) in the presence of (±)-CSA in MeOH affords the dimethyl acetal (XXVII). *O*-Methylation of phenol (XXVII) with MeI by means of K_2CO_3 in DMF provides 1-bromo-3-*tert*-butyl-5-(1,1-dimethoxyethyl)-2-methoxybenzene (XXVIII), which by Buchwald–Hartwig condensation with morpholine (XXIX) in the presence of $Pd(OAc)_2$, BINAP and *t*-BuONa in DME leads to the *N*-arylmorpholine (XXX). Bromination of compound (XXX) with $PhNMe_3Br_3$ in THF/MeOH generates the α-bromoacetal (XXXI), which, without isolation, is finally hydrolyzed by quenching in aqueous $Na_2S_2O_3$ to give bromo ketone (IX) (2). Scheme 3.

BACKGROUND

Atherothrombotic disease manifests clinically as acute coronary syndromes, cerebrovascular events and peripheral arterial disease, which are the major causes of morbidity and mortality worldwide (3). Considering acute coronary syndromes alone, an estimated 785,000 new events are diagnosed every year in the U.S. (4).

Scheme 3. Synthesis of Bromoacetophenone (IX)



Platelets play a pivotal role in hemostasis, preventing blood loss after injury, but also in the formation of pathological thrombi that can cause obstruction of the intravascular lumen. The platelet response to vascular injury induces platelet adhesion through the binding of platelet glycoprotein receptors to exposed extracellular proteins, mainly collagen and von Willebrand factor. Adherent, activated platelets release adenosine diphosphate (ADP) and thromboxane A2 (TXA2), while tissue factor produces thrombin locally. These agonists signal through G protein-coupled receptors on platelets and mediate paracrine and autocrine platelet activation. Activated platelets undergo shape change and express proinflammatory molecules, such as P-selectin and soluble CD40 ligand. The platelet integrin glycoprotein IIb/IIIa receptors also undergo a conformational shape change, allowing them to bind adhesive proteins, particularly fibrinogen and von Willebrand factor, leading to platelet aggregation. The interaction of the platelet aggregate with fibrin and thrombin ultimately leads to thrombus formation (3, 5, 6).

Thrombin, a serine protease, is one of the most potent platelet activators and is a key factor in blood coagulation. Platelet responses to thrombin are mediated by protease-activated receptors (PARs). Proteases activate PARs by a unique mechanism consisting of proteolytic cleavage within the extracellular *N*-terminus of the receptors, thus exposing a novel *N*-terminal sequence that, remaining tethered, binds to and activates the receptor (7, 8). There are four subtypes of PARs, three of which are activated by thrombin, namely PAR1, PAR3 and PAR4, while PAR2 is activated by trypsin. In human platelets thrombin acts through PAR1 at subnanomolar concentrations and through PAR4 at higher concentrations (7). Thrombin-dependent platelet aggregation is mediated in part by secreted ADP, and therefore, the simultaneous inhibition of PAR1 and $P2Y_{12}$ (the major platelet ADP receptor) would synergistically inhibit thrombin-induced platelet activation and aggregation (9). Endothelial cells express all PARs, and in the vessel wall PARs mediate responses involved in contractility, proliferation, inflammation and repair (10).

The current standard of care for reducing ischemic events in patients with atherothrombotic disease is the dual antiplatelet therapy consisting of aspirin combined with clopidogrel (3). Aspirin irreversibly inhibits cyclooxygenase-1 and inhibits platelet activation by blocking TXA2 production (11). Clopidogrel prevents platelet activation by irreversibly blocking the platelet ADP receptor $P2Y_{12}$ (12). Clinical trials have demonstrated the efficacy of this combination in preventing thrombotic events in patients with atherothrombotic diseases (13, 14). However, a clinical limitation of this combination is bleeding risk (15), in addition to the fact that a considerable number of patients receiving this therapy continue to experience recurrent thrombotic events (3). This lack of efficacy can be explained by the fact that platelets can be activated by multiple pathways, but the mentioned dual oral antiplatelet therapy only inhibits the pathways stimulated by TXA2 and ADP (6).

Several preclinical studies indicate that thrombin-mediated platelet activation is less important for hemostasis than thrombin-mediated cleavage of fibrinogen to fibrin (7). In addition, anticoagulants that interfere with the catalytic function of thrombin cause substantial bleeding risk in patients (16). Therefore, the inhibition of PAR1 function rather than inhibition of thrombin generation or activity appears to be a valid approach for circumventing bleeding risk in the treatment of thrombotic disease in humans (3).

Atopaxar (E-5555), the first oral PAR1 antagonist, is currently in phase II clinical trials at Eisai for the treatment of acute coronary syndrome and high-risk coronary artery disease (17, 18).

PRECLINICAL PHARMACOLOGY

The binding affinity of atopaxar for PAR1 was assessed on human platelet membranes using tritiated high-affinity thrombin receptor-activating peptide (haTRAP) as the radioligand. Atopaxar inhibited the binding of haTRAP to PAR1 with an IC_{50} of 19 nM. The comparators, TRAP and haTRAP, showed IC_{50} values of 490 and 56 nM, respectively. These results suggest that atopaxar has a binding affinity for PAR1 26 times greater than that of TRAP (19).

Atopaxar inhibited human platelet aggregation in vitro induced by thrombin or TRAP with IC_{50} values of 64 and 31 nM, respectively. Similarly, atopaxar inhibited guinea pig platelet aggregation induced by thrombin or TRAP with IC_{50} values of 130 and 97 nM, respectively. However, in both species, atopaxar did not inhibit platelet aggregation induced by ADP, PAR4-activating peptide, U-46619 (TXA2 receptor agonist) or collagen up to a concentration of 20 mM (19). Of note, the expression of PAR1 in platelets differs across species and its presence is restricted to primates and guinea pigs (20).

The antithrombotic properties of atopaxar given orally were studied in a model of photochemically induced thrombosis in guinea pigs. Atopaxar at doses of 30 and 100 mg/kg significantly prolonged the time to occlusion of the femoral artery, demonstrating an antithrombotic effect. In the same animal species, atopaxar administered orally at 10, 30 and 100 mg/kg significantly inhibited ex vivo platelet aggregation induced by thrombin and TRAP. However, atopaxar, even at 100 mg/kg, did not inhibit ex vivo platelet aggregation induced by ADP, PAR4-activating peptide, U-46619 or collagen (19).

Atopaxar administered orally at doses of 30, 300 and 1000 mg/kg did not prolong bleeding time in guinea pigs. In the same experimental model, bleeding time prolonged by tissue-type plasminogen activator (t-PA; 1 mg/kg i.v.) was not further modified when atopaxar (300 mg/kg p.o.) was administered concomitantly. Finally, fibrinogen levels or coagulation parameters such as prothrombin time or activated partial thromboplastin time were not modified by atopaxar nor t-PA (19).

An experimental model of subarachnoid hemorrhage in rabbits produced an enhancement of the contractile responses to thrombin in basilar artery ring preparations and an upregulation of PAR1 expression in this vascular tissue in comparison with control animals. In rabbits that underwent this experimental procedure, atopaxar administered parenterally almost completely reduced the enhancement of the contractile response to thrombin in the basilar artery and upregulation of PAR1 expression, therefore suggesting that atopaxar can be useful in preventing cerebral spasm in subarachnoid hemorrhage (21).

The inhibitory effects of atopaxar on rat and human smooth muscle cell proliferation stimulated by thrombin were studied in vitro. Immunoblot analysis confirmed that PAR1 is not detected in rat platelets, but PAR1 expression was detected in rat smooth muscle cells, human platelets and human smooth muscle cells. Atopaxar inhibited rat smooth muscle cell proliferation stimulated by throm-

bin and TRAP with IC_{50} values of 160 and 38 nM, respectively. Atopaxar inhibited human smooth muscle cell proliferation stimulated by 0.3 and 3 U/mL thrombin with IC_{50} values of 28 and 79 nM, respectively. In contrast, atopaxar had little or no effect in inhibiting rat and human smooth muscle cell proliferation stimulated by basic fibroblast growth factor or platelet-derived growth factor (22).

Due to the inhibitory effects of atopaxar on thrombin-induced smooth muscle cell proliferation in vitro, the compound was tested in a rat model of intimal thickening following balloon injury in vivo. Atopaxar, administered at 10 and 30 mg/kg p.o. for 16 days, decreased the cross-sectional area of the neointima and the intima/media ratio of the injured left common carotid artery, reaching statistical significance in both parameters at the higher dose. Therefore, atopaxar, by blocking PAR1, inhibits smooth muscle cell proliferation and may attenuate the vascular injury response (22).

The in vitro effects of atopaxar on platelet function beyond PAR1 blockade were assessed in healthy volunteers and in patients with coronary artery disease treated with aspirin or aspirin plus clopidogrel. Atopaxar almost completely inhibited TRAP-induced aggregation at the concentrations of 20, 50 and 100 ng/mL. Atopaxar also moderately inhibited (10-15%) ADP- and collagen-induced platelet aggregation in plasma. Therefore, it can be concluded that the antiplatelet potency of aspirin alone and combined with clopidogrel may be enhanced by atopaxar, providing a rationale for their synergistic use (23).

The effects of atopaxar on the inflammatory markers predictive of high-risk events in acute coronary syndrome patients were studied in human platelet rich-plasma from healthy volunteers in vitro. Atopaxar inhibited thrombin- and TRAP-mediated soluble form of CD40 ligand release (IC_{50} = 47 and 38 nM, respectively), without affecting ADP-induced soluble form of CD40 ligand release in human platelet-rich plasma. Atopaxar also inhibited thrombin-induced release of interleukin-6 (IC_{50} = 0.19 nM) and P-selectin expression (IC_{50} = 16 nM), respectively, in human coronary artery smooth muscle cells and human coronary artery endothelial cells. These results suggest that atopaxar may be useful in the suppression of inflammatory markers in acute coronary syndrome patients (24).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of atopaxar were studied in healthy volunteers who received 50, 100 and 200 mg of atopaxar orally for 14 days. Steady state was reached at day 11, and t_{max} and half-life (approximately 3.5 and 23 hours, respectively) were similar across dose groups. Other relevant features were that in the 100- and 200-mg dose groups C_{max} and AUC were similar; mean AUC on day 14 was about 2- to 2.8-fold higher than on day 1, and < 0.2% of the dose was excreted unchanged in urine. The active metabolite RM2 showed an AUC that corresponds to 60-86% of that of the parent compound on day 14 (25).

SAFETY

The safety of atopaxar, administered as single oral doses (20-400 mg) and repeated oral doses (50-200 mg for 14 days) was assessed in randomized, double-blind, placebo-controlled studies in healthy volunteers. Mild bleeding was observed in the group receiving 200 mg administered for 14 days, headache being the most commonly reported adverse event. There were no changes in coagulation time and bleeding time. Overall, atopaxar was well tolerated (25, 26).

The safety of atopaxar administered in addition to standard antithrombotic therapy was assessed in two multicenter, double-blind, placebo-controlled phase II studies performed in Japanese patients (45-80 years old), one in acute coronary syndrome patients and the other in high-risk coronary artery disease patients (Japanese-Lesson from ANtagonizing the CELlular effects Of Thrombin, J-LANCELOT Trials) (27). Atopaxar (50, 100 and 200 mg) was administered orally once daily for 12 (acute coronary syndrome patients; n = 241) or 24 weeks (coronary artery disease patients; n = 263), in addition to the standard therapy, i.e., aspirin and a thienopyridine derivative. In the acute coronary syndrome study, patients to be treated with atopaxar received a loading dose of 400 mg of the compound. The primary safety endpoint was the incidence of bleeding, reported according to CURE (28) and TIMI (29) criteria, and the secondary safety endpoint was the incidence of major cardiovascular adverse events, such as cardiovascular death, myocardial infarction, stroke or recurrent ischemia. These studies were exploratory and therefore limited in their ability to detect statistical differences between placebo and atopaxar groups.

There was a low incidence of bleeding in acute coronary syndrome and coronary artery disease patients treated with atopaxar according to CURE criteria, although there was a higher rate of TIMI bleeding with the 200-mg dose of atopaxar. Overall, atopaxar did not increase clinically significant bleeding, therefore demonstrating that additional platelet inhibition through the thrombin pathway is possible without increasing bleeding risk. The most common adverse event related to study drug was abnormal liver function. Atopaxar at 50, 100 and 200 mg increased more than three times the upper limit of normal alanine aminotransferase (ALT) levels in 0.0%, 6.2% and 14.8%, respectively, of acute coronary syndrome patients and in 1.6%, 1.5% and 11.8%, respectively, of coronary artery disease patients. In the placebo group, no patient met this criterion in both trials. On the other hand, aspartate aminotransferase (AST) increases of more than three times the upper limit of normal levels were observed in the placebo, 50, 100 and 200 mg atopaxar groups at percentages of 1.7%, 0.0%, 1.5% and 9.8%, respectively, in acute coronary syndrome patients and 0.0%, 1.6%, 0.0% and 8.8%, respectively, in coronary artery disease patients. When comparing the atopaxar-treated groups with placebo, the ALT elevation was statistically significant in acute coronary syndrome but not in coronary artery disease patients, and the AST elevation was devoid of significance in both patient groups. No patient who experienced elevation of AST or ALT more than three times the upper limit of normal levels underwent elevation of total bilirubin more than twice the upper limit of normal levels (Hy's law) (30). Atopaxar showed a trend towards dose-related lengthening of the electrocardiographic QTcF (QT corrected according to the Fridericia criteria) interval in acute coronary syndrome and coronary artery disease patients that reached statistical significance in the latter. Finally, the percentage occurrence of major cardiovascular adverse events was lower in the active combined group than in the placebo group in acute coronary syndrome and coronary artery disease patients, although the difference was not statistically significant. No cardiovascular death, myocardial infarction or stroke occurred in any group. In summary,

future studies should carefully consider the QT prolongation and liver dysfunction with high doses of atopaxar (27).

The safety and tolerability of atopaxar were also assessed in two additional larger, multicenter, double-blind, placebo-controlled phase II studies conducted in parallel in Western patients with acute coronary syndrome or coronary artery disease. In the acute coronary syndrome study (Lesson from ANtagonizing the CELlular effects Of Thrombin–Acute Coronary Syndromes Trial, LANCELOT-ACS trial) (31), patients (n = 603; 18-80 years old) were allowed to take aspirin, clopidogrel or ticlopidine. Atopaxar (400-mg loading dose followed by 50, 100 or 200 mg) was administered orally once daily for 12 weeks. The primary safety endpoint was the incidence of major bleeding, reported according to CURE (32) and TIMI definitions (33). Secondary safety endpoints were cardiovascular death, myocardial infarction, stroke or recurrent ischemia, and Holter-detected ischemia. The proportion of subjects who experimented any type of bleeding was similar between the combined atopaxar and placebo groups following CURE (atopaxar 3.1% vs. placebo 2.2%) and TIMI (atopaxar 9.2% vs. placebo 10.1%) criteria. The incidence of cardiovascular death, myocardial infarction, stroke or recurrent ischemia did not differ between the combined atopaxar and placebo groups (atopaxar 7.8% vs. placebo 8.0%). There was a statistically significant 34% reduction in Holter-detected ischemia in the combined atopaxar groups with respect to placebo during the first 48 hours after the 400-mg loading dose. Clinically significant increases in ALT (three or more times upper limit of normal) were detected more frequently with the dose of 200 mg of atopaxar (atopaxar 5.5% vs. placebo 2.5%), which resolved with continued therapy before week 12. There were no cases of Hy's law. During the treatment phase the electrocardiographic QTcF interval showed an overall decrease in the placebo and atopaxar groups. However, the mean decrease in the placebo group was greater than in the combined atopaxar groups (placebo –11.4 ms vs. atopaxar –6.4 ms; $P = 0.04$). No associated cases of syncope or malignant arrhythmias were detected. The most commonly reported adverse events were gastrointestinal disorders (6.6% in the combined atopaxar vs. 5.8% in the placebo arm). The percentage of subjects who discontinued the study was similar in the combined active atopaxar group and the placebo group (28.9% and 31.0%, respectively). To conclude, atopaxar was generally well tolerated, but larger trials are required to establish its safety profile.

In the coronary artery disease study (Lessons from ANtagonizing the CELlular effect Of Thrombin-Coronary Artery Disease trial, LANCELOT-CAD trial) (34), patients (N = 720; 45-80 years of age) were allowed to take aspirin, clopidogrel or ticlopidine. Atopaxar (50, 100 or 200 mg) was administered orally once daily for 24 weeks. The primary safety endpoint was the incidence of bleeding, according to CURE and TIMI definitions. The key secondary endpoints were cardiovascular death, myocardial infarction, stroke or refractory ischemia. There was a higher rate of bleeding in the atopaxar group in comparison with placebo, either according to CURE (atopaxar 3.9% vs. placebo 0.6%) or TIMI (atopaxar 10.3% vs. placebo 6.8%) criteria. Nevertheless, there was no difference between atopaxar and placebo when considering major bleeding (CURE and TIMI criteria). The incidence of cardiovascular death, myocardial infarction, stroke or recurrent ischemia did not differ between the combined atopaxar and placebo groups (atopaxar 2.6% vs. placebo 4.6%). Clinically significant increases in ALT and AST (three or more times the upper limit of normal) were detected more frequently with the dose of 200 mg of atopaxar (atopaxar 5.9% and 3.8%, respectively, vs. placebo 0.0%). These elevations tended to be transient. There were no cases of Hy's law. Modest increases in the QTcF were detected in the higher-dose atopaxar arms compared with placebo. Overall, more subjects discontinued the study in the atopaxar group than in the placebo group (20.8% vs. 13.6%). In conclusion, larger trials are required to establish the safety of atopaxar for the treatment of patients with atherosclerotic vascular disease.

CLINICAL STUDIES

In a randomized, double-blind, placebo-controlled, multiple-dose study in 36 healthy volunteers, atopaxar administered at 50, 100 and 200 mg for 14 days inhibited platelet aggregation induced by thrombin by 58-65%, 90-91% and 90-95%, respectively (25). In a similar phase I study, atopaxar administered at single doses of 20, 50, 100, 200 or 400 mg inhibited thrombin-induced platelet aggregation in a dose-dependent manner, achieving maximum effects at 6 hours. A single dose of 50 mg or greater inhibited platelet aggregation by more than 80%. Atopaxar did not inhibit ADP-induced platelet aggregation (26).

The inhibitory effects of atopaxar on TRAP-induced platelet aggregation were measured in acute coronary syndrome and coronary artery disease patients enrolled in the phase II J-LANCELOT trial (27). Atopaxar at 50 mg inhibited platelet aggregation by 20-50% in acute coronary syndrome patients and by 50-60% in coronary artery disease patients. In both studies, the inhibition of platelet aggregation by atopaxar at 100 and 200 mg was over 90% at trough. The antiaggregatory effects disappeared at 2 weeks upon the cessation of atopaxar administration.

Similar results were obtained in the LANCELOT-ACS (31) and LANCELOT-CAD trials (34). Indeed, in 63 acute coronary syndrome patients enrolled in the LANCELOT-ACS trial, the mean inhibition of TRAP-induced platelet aggregation at week 12 with respect to predose was 66.5%, 71.5% and 88.9%, respectively, in the 50-, 100- and 200-mg atopaxar groups. After the loading dose of 400 mg, in all active atopaxar groups the mean inhibition of platelet aggregation was 74% at 1-3 hours, reaching 92% inhibition at 3-6 hours (31). In 80 coronary artery disease patients participating in the LANCELOT-CAD trial, high levels of inhibition of TRAP-induced platelet aggregation were achieved with atopaxar, with a dose-dependent rapid onset and offset. At 4-6 hours after the first dose of 100 and 200 mg of atopaxar, a rapid and nearly complete inhibition of platelet aggregation was reached that lasted for 24 hours. In contrast, the first dose of 50 mg produced a 38% inhibition that diminished over time and disappeared at 24 hours. However, after 2 weeks of daily dosing, all treatment groups showed near complete inhibition of platelet aggregation. Markers of inflammation, measured in the entire study population, showed no overall consistent trends for an antiinflammatory effect of atopaxar by measuring high-sensitivity C-reactive protein, placental growth factor, myeloperoxidase and interleukin-6, interleukin-18 and interleukin-1 beta. Only the platelet-inflammatory biomarker CD40 ligand tended to be lower in the atopaxar groups (34).

CONCLUSIONS

The current standard of care for atherothrombotic disease, the dual antiplatelet therapy consisting of aspirin combined with a thienopyridine derivative, is limited by bleeding risk and recurrent thrombotic events. Atopaxar is the first oral PAR1 antagonist, and in preclinical studies demonstrated antiplatelet and antithrombotic effects without prolonging bleeding time. In phase II clinical trials in patients with acute coronary disease or high-risk coronary artery disease (LANCELOT trials), atopaxar at the doses of 50, 100 and 200 mg once daily inhibited TRAP-induced platelet aggregation and did not increase clinically significant bleeding. However, at the higher doses there was a significant increase in liver function abnormalities and a modest QTcF lengthening effect that future larger studies should clarify.

SOURCE

Eisai Co., Ltd. (JP).

DISCLOSURES

The author states no conflicts of interest.

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