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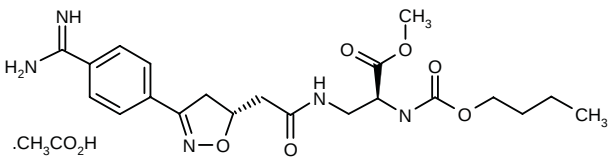
DMP 754

Antiplatelet/Antithrombotic
Glycoprotein IIb/IIIa Antagonist

Roxifiban Acetate (Prop INN)

3-[2-[3-(4-Amidinophenyl)-4,5-dihydroisoxazol-5(*R*)-yl]acetamido]-2(*S*)-(butoxycarbonylamino)propionic acid methyl ester monoacetate
3-[2-[3-[4-(Aminoiminomethyl)phenyl]-4,5-dihydro-5(*R*)-isoxazolyl]acetamido]-*N*-(butoxycarbonyl)-L-alanine methyl ester monoacetate



$C_{21}H_{29}N_5O_6.C_2H_4O_2$ Mol wt: 507.54

CAS: 176022-59-6
CAS: 170902-47-3 (as free base)

EN: 224676

Synthesis

Reaction of 4-cyanobenzaldehyde (I) with hydroxylamine sulfate in methanol gives 4-cyanobenzaldoxime (II). A 1,3-dipolar cycloaddition of (II) with isobutyl vinylacetate using *N*-chlorosuccinimide provides the racemic isoxazoline derivative (III). Treatment of (III) with lipase PS30 selectively converts the (*R*)-isomer to an optically pure acid (IV). Coupling of (IV) with methyl N^2-(*n*-butyloxycarbonyl)-L-2,3-diaminopropionate (VI), which is derived from its corresponding commerically available acid (V), gives the intermediate (VII). Treatment of (VII) with HCl in methanol and ethyl acetate followed by ammonium acetate affords DMP 754 as a crystalline product (1). Saponification of DMP 754 using LiOH provides the corresponding acid (VIII) (2). Scheme 1.

Description

Crystals, m.p. 213-4 øC.

Introduction

Platelets play an important role in hemostatic and thrombotic processes. The contribution of platelets to the hemostatic process stems from their ability to adhere to blood vessel walls at the site of injury and aggregate with each other, forming a hemostatic plug (3). Central to platelet adhesion and aggregation is glycoprotein IIb/IIIa (GPIIb/IIIa, α_{IIb}/β_3), a heterodimeric membrane protein of the integrin family present on the surface of platelets (4). GPIIb/IIIa does not expose its binding sites under normal physiological conditions. Once a vascular injury occurs, platelets are activated by a variety of agonists including adenosine diphosphate (ADP), epinephrine, thrombin and collagen, released at the interface between the vessel wall and circulating blood at the site of injury (5). In response to platelet activation, GPIIb/IIIa undergoes a substantial conformational change that exposes its binding site with high affinity for binding. GPIIb/IIIa in activated form then binds four soluble adhesive proteins: fibrinogen (6), von Willebrand factor (vWF) (7), fibronectin (8) and vitronectin (9). The plasma protein fibrinogen is a double trimer containing 6 potential binding sites for GPIIb/IIIa, 3 in each half molecule (10). The binding of a single molecule of fibrinogen to multiple GPIIb/IIIa molecules leads to cross-linking of the platelets which causes platelets to aggregate.

Under pathophysiological conditions, however, platelet activation and aggregation can lead to thrombus formation. Since platelets do not have the ability to distinguish a damaged blood vessel wall in need of repair from a thrombogenic surface such as a ruptured atherosclerotic plaque, adhesion of platelets on thrombogenic surfaces which appear in blood vessels induces formation of platelet aggregates or platelet thrombi in the lumen of vessels, and may eventually lead to vessel occlusions resulting in cardiovascular and cerebrovascular thromboembolic disorders such as unstable angina, myocardial infarction, transient ischemic attack and stroke (11-14). In these instances it is desirable to interfere with platelet aggregation therapeutically.

Inhibition of platelet aggregation by blocking one of the stimulation pathways at the activation stage has proved to be of limited efficacy since the specific inhibition of a particular agonist leaves open several alternative routes to platelet activation (15-17). An ideal antithrombotic agent must inhibit platelet aggregatiion regardless of the nature of the agonist. Since the binding of fibrino-

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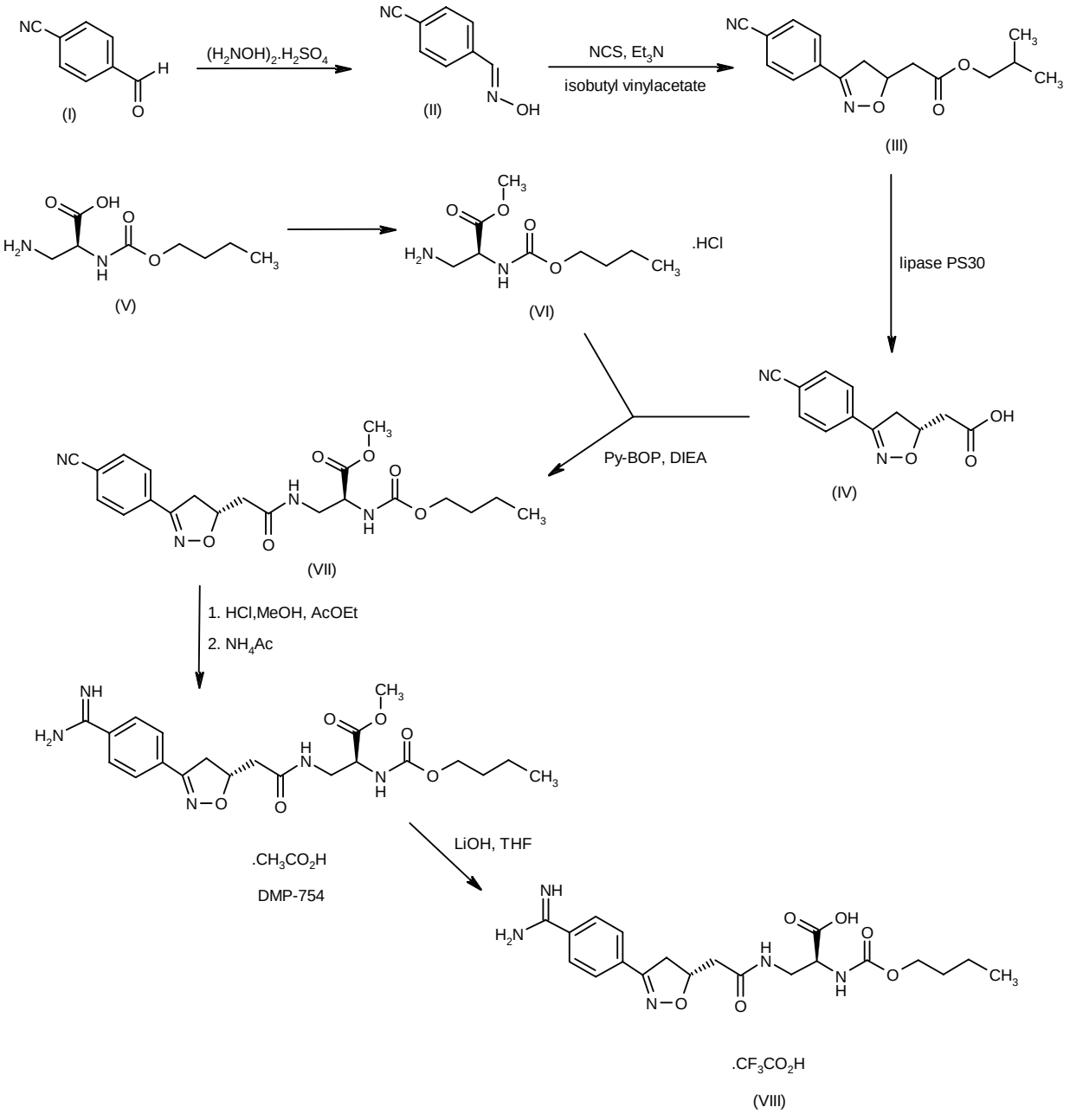
Scheme 1: Synthesis of DMP-754



gen to GPIIb/IIIa is a common endpoint of all activation pathways, inhibition of platelet aggregation by blocking the association of fibrinogen with GPIIb/IIIa represents an attractive antithrombotic strategy (15, 18, 19).

The binding of fibrinogen to GPII/IIIa is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to the adhesive proteins that bind to GPIIb/IIIa (20, 21). Several RGD-containing peptides have been shown to block fibrinogen binding and prevent the formation of platelet thrombi (22, 23). However, their therapeutic utilities are limited by the low affinity and/or the lack of oral bioavailability. Recent studies in humans with a monoclonal antibody (c7E3) for GPIIb/IIIa have suggested the antithrombotic benefit of GPIIb/IIIa antagonism (24, 25). Several selective GPIIb/IIIa antagonists, including integrelin (26), tirofiban (MK-383) (27, 28) and lamifiban (Ro-44-9883) (29, 30) are in advanced stages of clinical development, aimed primarily for intravenous use in the treatment and prevention of acute ischemic heart disease. These intravenous agents have a short duration of antiplatelet effects reflecting their fast rate of dissociation from human platelets. The orally active

GPIIb/IIIa antagonists including xemilofiban (SC-54684) (31-33), lefradafiban (BIBU-104) (34), sibrafiban (35) and orbofiban (36) have demonstrated oral antiplatelet activity in man. However, their short duration of action necessitated multiple daily dosing.

Efforts at DuPont Merck to identify nonpeptide GPIIb/IIIa antagonists were aimed at developing potent, orally active agents with appropriate duration for once-daily dosing. These efforts culminated in the discovery of DMP 754 (roxifiban acetate) (37, 38), the methyl ester and acetate form of (VIII) (2).

Pharmacological Actions

In vitro *effects*

Compound (VIII), the free acid of DMP 754, inhibited fibrinogen binding to purified platelet GPIIb/IIIa receptor with an IC_{50} value of 0.25 ± 0.05 nM. It also inhibited [^{125}I]-fibrinogen binding to ADP-activated human platelet (gel purified) with an IC_{50} value of 10.5 ± 3 nM.

Compound (VIII) was a potent, agonist-independent inhibitor of platelet aggregation (37). Using the human platelet-rich plasma light-transmittance aggregometry assay (40), it inhibited human platelet aggregation induced by either ADP (10 μmol/l), epinephrine (1 mmol/l), collagen (20 μg/ml), PAF (10 μmol/l) or thrombin (0.5 IU/ml) with IC_{50} values of 19 ± 3.8, 15 ± 4.5, 24 ± 6.7, 16 ± 2.6 and 35 ± 4.3 nM, respectively. DMP 754 itself was essentially inactive in inhibiting human platelet aggregation induced with a variety of agonists, with an IC_{50} > 1000 nM. Upon its conversion with esterases to its free acid, DMP 754 demonstrated a potency similar to (VIII). The IC_{50} values for inhibition were 32 ± 4.3 nM for ADP (10 μmol/l), 19 ± 2.4 nM for epinephrine (1 mmol/l), 33 ± 7.8 nM for collagen (20 μg/ml), 24 ± 3.3 nM for PAF (10 μmol/l) and 41 ± 4.4 nM for thrombin (0.5 IU/ml).

The inhibition of (VIII) to platelet aggregation was also determined using platelet-rich plasma obtained from various animal species (39). While a similar potency to the inhibition of human platelet aggregation was observed using platelets from mongrel dog, rhesus monkey, baboon, sheep, guinea pig and mouse with IC_{50}s of 0.027, 0.043, 0.040, 0.020, 0.024 and 0.060 μmol, respectively, (VIII) displayed a moderate to weak inhibitory activity for pig, rabbit and rat, with respective IC_{50}s of 0.16, 1.6 and 5.8 μmol.

Compound (VIII) demonstrated a high degree of specificity for GPIIb/IIIa over other closely related integrins (39, 41). It was > 10,000-fold less effective in inhibiting $\alpha_v\beta_3$-mediated adhesion of fibrinogen to human umbilical vein endothelial cells (HUVEC), $\alpha_v\beta_5$-mediated adhesion of fibronectin to SK-breast cancer cell line and $\alpha_5\beta_1$- and $\alpha_4\beta_1$-mediated adhesion of fibronectin to Jurkat cells than in inhibiting human platelet aggregation.

The affinities of (VIII) to activated platelets *versus* unactivated platelets were determined. It was found that it bound with high affinity to both activated and unactivated human platelets, with K_ds of 0.8 nM and 2.5 nM, respectively. This result appeared to be similar to that of the antibody c7E3, which bound equally to the activated and unactivated human platelets (K_ds = 9.1 nM and 9.2 nM, respectively) (41).

Compound (VIII) exhibited a tight association with human, baboon and, to a lesser extent, canine platelets. The $t_{1/2}$ of dissociation was 7 ± 0 min for human, 8 ± 1 min for baboon and 1.4 ± 0.1 min for canine platelets. The tighter association of (VIII) with baboon platelets than with canine platelets probably accounted for the longer duration of antiaggregatory effect in baboon than in dog, as will be discussed later.

In vivo *effects*

The *in vivo* antiplatelet efficacy of (VIII) and its prodrug DMP 754 was evaluated using different animal species (2). The administration of an i.v. bolus dose of 0.025 mg/kg of (VIII) to conscious or anesthetized dogs resulted in an immediate 90-100% inhibition of *ex vivo* platelet aggregation which declined to approximately 40% over 5 h. DMP 754 demonstrated a dose-dependent inhibition of *ex vivo* ADP (100 μM)-induced platelet aggregation after oral administration to conscious dogs at 0.1-0.4 mg/kg. A greater than 90% inhibition of platelet aggregation was achieved within 2 h and 60% inhibition of platelet aggregation was maintained for 12 h after oral doses of 0.3-0.4 mg/kg of DMP 754.

A profile similar to that in dogs was observed when DMP 754 was administered at an oral dose of 0.3 mg/kg to conscious rhesus monkeys. A greater than 80-90% inhibition of *ex vivo* platelet aggregation was achieved within 2 h, which declined to approximately 60% over 12 h.

DMP 754 also produced a dose-dependent inhibition of ADP (100 μM)-induced *ex vivo* platelet aggregation following oral administration to ketamine/xylazine sedated baboons. Maximal inhibition of platelet aggregation was achieved at an oral dose of 0.3 mg/kg. Longer duration in baboon (~24 h) than in dog or rhesus monkey (about 12 h) was observed at a dose of 0.3 mg/kg. The longer duration in antiplatelet effect of DMP 754 in baboon than in dog might be due to the tighter association (*i.e.*, slow dissociation rate or K_{off}) of (VIII) with baboon platelets than with canine platelets or perhaps due to the slow and relatively more sustained gastrointestinal absorption of DMP 754 in sedated baboon. However, an extended duration of antiplatelet efficacy was demonstrated in baboons after i.v. administration of DMP 754 as compared to dogs, favoring the differences in K_{off} to be the main reason for the differences in the duration of antiplatelet efficacy between the two species. Since the association of (VIII) with human platelets was found to be similar to that with baboon platelets, the profile of DMP 754 in man was expected to be similar to that in baboon, suggesting a once-daily dosing of DMP 754 in man.

DMP 754 prevented the incidence of platelet-dependent cyclic flow reductions (CFRs) with an ED_{90-100} of < 0.1 mg/kg i.v. or p.o. Administration of DMP 754 (0.1 mg/kg i.v. or 0.3-0.5 mg/kg p.o.) in canines exhibited maximal antithrombotic efficacy in preventing electrically induced carotid and coronary artery thrombosis. DMP 754 also demonstrated significant i.v. and oral antithrombotic efficacy ($p < 0.001$) at relatively low doses in different settings of arterial thrombosis in canines. Maximal platelet aggregation inhibition was achieved at 50 to ≥ 80% receptor occupancy dependent upon the agonist used in either citrate or heparin. The antithrombotic efficacy of DMP 754 was not affected by rechallenge with epinephrine or by the shear stress level. In contrast, aspirin (10 mg/kg p.o. x 2 days) and ticlopidine (300 mg/kg p.o. x 3 days) prior to the initiation of arterial thrombosis were only effective in reducing the incidence of CRFs, but were ineffective in reducing the incidence of electrolytic injury-induced occlusive arterial thrombosis. Additionally, in the same models, hirudin but not heparin demonstrated antithrombotic efficacy which was reversed upon rechallenge with epinephrine.

Pharmacokinetics

The pharmacokinetics of (VIII) (42) were evaluated in male beagle dogs (n = 4/dose) following administration of single i.v. bolus doses of 0.04, 0.4 and 1.0 mg/kg. Plasma concentrations of (VIII) declined polyexponentially with comparable terminal elimination phase half-lives ($t_{1/2}$) for all three doses. The mean values (± SD) of $t_{1/2}$ were 10.4 ± 1.9, 11.8 ± 2.0 and 12.2 ± 1.6 h, respectively. The systemic plasma clearance (CL) and volume of distribution at steady-state (V_{ss}) of (VIII), however, increased with dose. The mean CL values were 1.0 ± 0.2, 4.1 ± 0.8 and 6.3 ± 0.4 ml/min/kg, whereas the mean V_{ss} values were 0.8 ± 0.1, 3.4 ± 0.6 and 4.4 ± 0.7 l/kg at 0.04, 0.4 and 1.0 mg/kg doses, respectively. These results demonstrated that (VIII) exhibited nonlinear pharmacokinetics in beagle dogs. The *in vitro* plasma protein binding values of (VIII) in fresh dog platelet-rich plasma at 5, 25 and 100 ng/ml, determined using the method described previously (43), were 85, 85 and 59%, respectively. The nonlinear clearance and distribution characteristics of (VIII) appeared to be related to its saturable binding to platelets.

In vitro, DMP 754 was converted rapidly to its free acid form (VIII) in human and canine liver homogenates with $t_{1/2}$ values of 2.4 min and 23 min, respectively. The conversion rates of DMP 754 to (VIII) were much slower in human and canine plasma with $t_{1/2}$s of 7.6 h and 5.5 h, respectively. *In vivo*, rapid and full conversion of DMP 754 to (VIII) was observed. No DMP 754 was detected and (VIII) was the only compound detected over time after p.o. or i.v. administration of DMP 754 in dogs.

The rate of gastrointestinal absorption of DMP 754 in dogs was rapid with peak plasma concentrations of (VIII) obtained within 1.5 h following oral administration of 0.4 mg/kg of DMP 754. Plasma C_{max} values averaged 93.9 ± 7.2 ng/ml (mean ± SE, n = 4). The apparent bioavailability, defined as percent of (VIII) found in plasma following oral administration of DMP 754, was estimated to be 20.8%.

Manufacturer

DuPont Merck (US).

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