Drugs of the Future 1998, 23(11): 1190-1198

CCC: 0377-8282/98

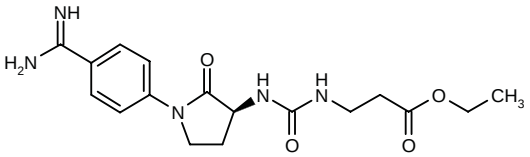
Orbofiban Acetate

Prop INNM; USAN

Platelet Antiaggregatory
Fibrinogen gpIIb/IIIa Receptor Antagonist

CS-511
SC-57099B

N-[[1-(4-Amidinophenyl)-2-oxo-3(*S*)-pyrrolidinyl]carbamoyl]-β-alanine ethyl ester monoacetate



$.CH_3CO_2H$

$C_{17}H_{23}N_5O_4.C_2H_4O_2$

CAS: 163250-91-7
CAS: 165800-05-5 [as hydrate(4:1)]
CAS: 163250-90-6 (as free base)

EN: 252850
EN: 270199 (as free base)

Synthesis

The condensation of 4-aminobenzamide (I) with *N*-(*tert*-butoxycarbonyl)-L-methionine (II) by means of 2-chloro-1-methylpyridinium iodide (CMPI) and *N*-methylmorpholine (NMM) in DMF gives the corresponding methioninamide (III), which is cyclized by means of trimethylsulfonium iodide and K_2CO_3 in hot DMSO yielding the pyrrolidinone (IV). The dehydration of (IV) with trifluoroacetic anhydride in THF affords the corresponding nitrile (V), which is deprotected with dry HCl in ethyl acetate giving the amine (VI). The condensation of (VI) with D-alanine ethyl ester (VII) and carbonyl diimidazole (CDI) in pyridine yields the substituted urea (VIII), which is treated with hydroxylamine hydrochloride and triethylamine in ethyl acetate to afford the *N*-hydroxybenzamidine (IX). Finally, this compound is hydrogenated with H_2 over Pd/C in acetic acid (1). Scheme 1.

Description

Crystals, m.p. 213-4 °C (decomp.), $[a]_D^{24}$ +13.2° (c 9.43, MeOH).

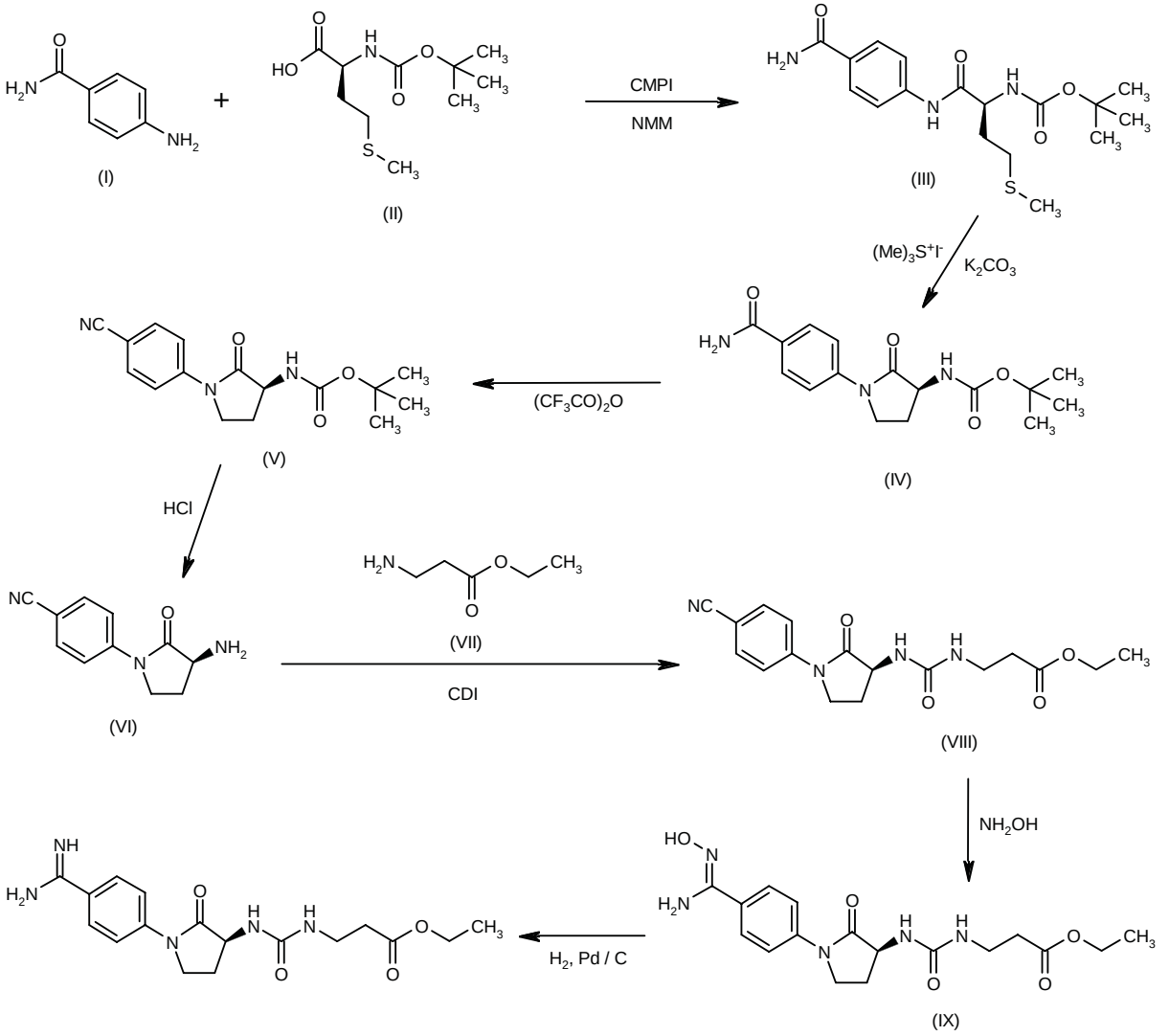
Introduction

Current therapeutic strategies to inhibit platelet function include aspirin and triflusal, which inhibit the formation of thromboxane A_2 by platelets and prevent the release of proaggregatory ADP; dipyridamole, which increases the cellular concentration of cyclic AMP; and the thienopyridines ticlopidine and the recently launched clopidogrel hydrogensulfate, which inhibit binding of ADP to its platelet receptor. More recently, the platelet fibrinogen receptor, glycoprotein (gp) IIb/IIIa, has become a target for antiplatelet therapy. In the final stages of thrombus formation, activated platelets aggregate by binding to fibrinogen via the gpIIb/IIIa receptor. The gpIIb/IIIa receptor is the principal adhesive surface receptor on the platelet surface, with up to 100,000 copies of the receptor present on each platelet. In addition to its aggregation-mediating activity, the gpIIb/IIIa receptor allows platelets to disperse and facilitates platelet adhesion to the surface of the injured vessel wall. Interruption of the platelet aggregation process through inhibition of platelet-fibrinogen binding offers an attractive approach to the effective prevention of thrombus formation. By blocking the final common pathway in the platelet aggregation cascade, gpIIb/IIIa antagonists also affect the most proximal step in thrombin generation. As such, these compounds have an extremely potent inhibitory effect on arterial thrombosis. Platelet-rich thrombus formation is a key factor in arterial vaso-occlusive disorders and acute coronary syndrome such as unstable angina, myocardial infarction and reocclusion after angioplasty – all key indications for treatment with gpIIb/IIIa antagonists (2-9).

In recent years, pharmaceutical companies have increasingly focused on the development of fibrinogen gpIIb/IIIa receptor antagonists, as shown in Table I. The pharmacological activity of fibrinogen gpIIb/IIIa receptor antagonists is discussed in the monograph on sibrafiban, which will be published in the December 1998 issue of

M. Merlos[1], P.A. Leeson[2], J. Castañer[2]. [1]Department of Pharmacology, Faculty of Pharmacy, University of Barcelona; [2]Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

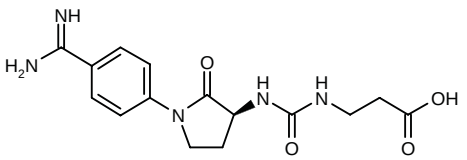
Scheme 1: Synthesis of Orbofiban



this journal. Furthermore, new therapeutic targets are being investigated for antiplatelet therapy, including platelet collagen receptors and the purinoceptor P2T (see antiplatelet therapy in Daily Essentials, 1998).

Pharmacological Actions

Orbofiban (SC-57099B) is an ester prodrug that is metabolized in the liver to the active free acid form SC-57101 [I]. This active metabolite inhibited the binding of fibrinogen to gpIIb/IIIa in ADP-activated human platelets (IC_{50} = 47 ± 8 nM) and prevented ADP (IC_{50} = 80 ± 6 nM)- or collagen (IC_{50} = 130 ± 10 nM)-induced platelet aggregation in human platelet-rich plasma (10, 11). SC-57101 also inhibited vitronectin binding to the purified human



[I]

gpIIb/IIIa receptor with an IC_{50} of 0.32 ± 0.06 nM. SC-57101 was specific for gpIIb/IIIa, showing no affinity for isolated vitronectin receptors (gp $\alpha v\beta 3$) at concentrations of up to 0.1 mM (11). There was a marked species difference in the antiplatelet effect of SC-57101, with a following potency rank order: dog ≈ human > monkey > guinea pig >> hamster >> rat (12).

Table I: Platelet gpII/IIIa receptor antagonists launched and in clinical and preclinical trials.

Launched

1. Abciximab
   ReoPro
   Centocor (1995)
2. Eptifibatide
   Integrelin
   COR Therapeutics (1998)
3. Tirofiban HCl
   Aggrastat
   Merck & Co. (1998)

Clinical Trials

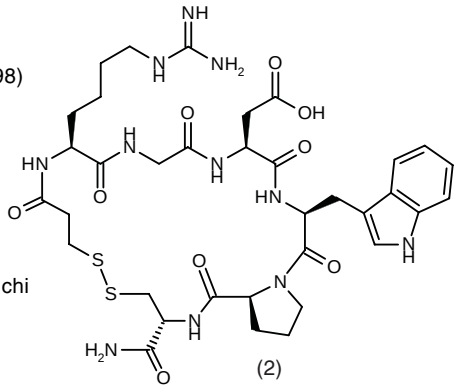
4. CT-50352*
   COR Therapeutics
5. EMD-122347/YM-028
   Merck KGaA; Yamanouchi
6. Fradafiban
   Boehringer Ingelheim
7. Lamifiban
   Roche
8. Lefradafiban
   Boehringer Ingelheim
9. Lotrafiban
   SmithKline Beecham
10. ME-3277
    Meiji Seika
11. Orbofiban acetate
    Searle; Sankyo
12. RWJ-53308
    R.W. Johnson
13. Sibrafiban
    Xubix
    Genentech; Roche
14. T-250
    Toyama
15. TAK-029
    Takeda
16. TP-9201
    Telios
17. Xemilofiban
    Searle; Sankyo
18. YM-337
    Yamanouchi

Preclinical Trials

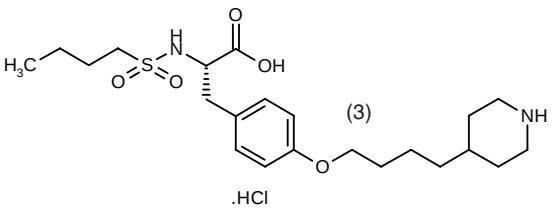
19. DMP-757
    DuPont Merck
20. G-7453
    Genentech
21. Roxifiban acetate
    DuPont Pharm.
22. RWJ-50042
    R.W. Johnson
23. SM-20302*
    Sumitomo
24. SR-121787
    Sanofi
25. TRM-147*
    Terumo
26. XV-454
    DuPont Merck

Immunoglobulin G (human-mouse monoclonal c7E3 clone p7E3VHhCγ4 Fab fragment antihuman glycoprotein IIb/IIIa receptor), disulfide with human-mouse monoclonal c7E3 clone p7E3VKhCK light chain

(1)

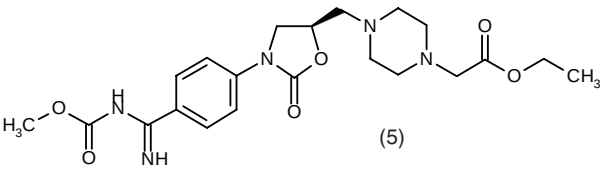


(2)

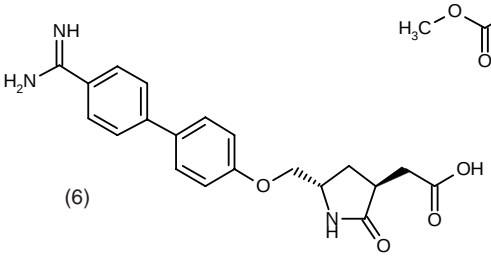


.HCl

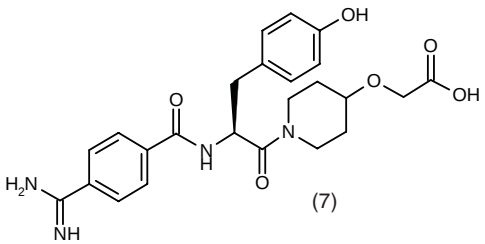
(3)



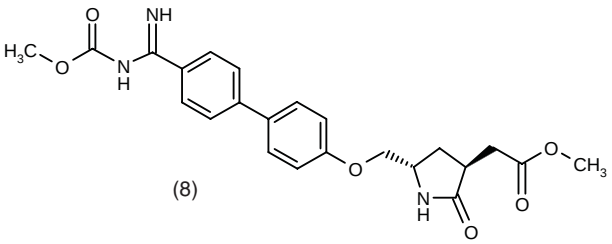
(5)



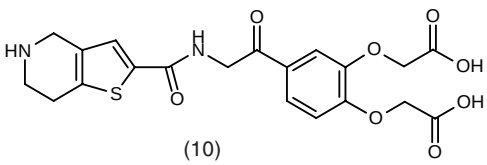
(6)



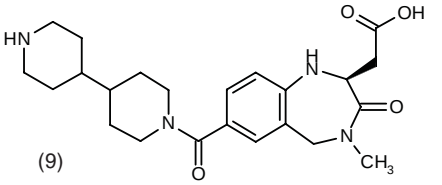
(7)



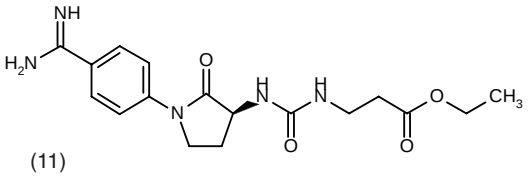
(8)



(10)

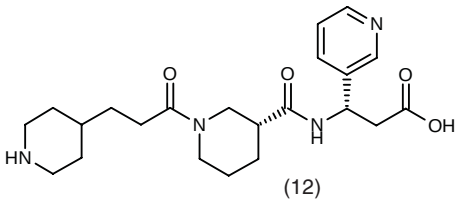


(9)

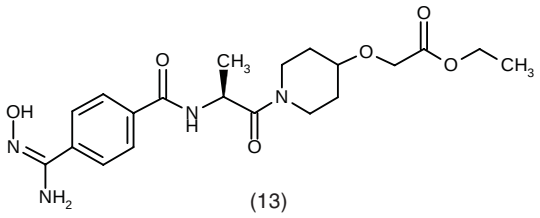


(11)

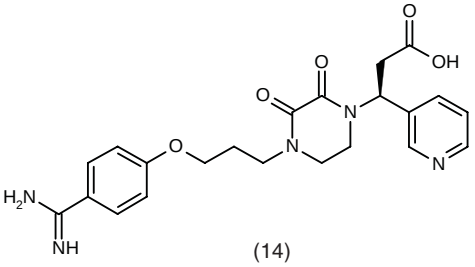
.CH_3CO_2H



(12)



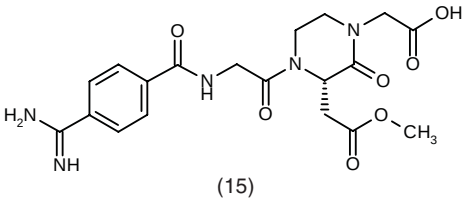
(13)



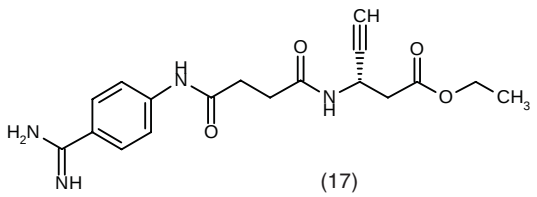
(14)

(Continued)

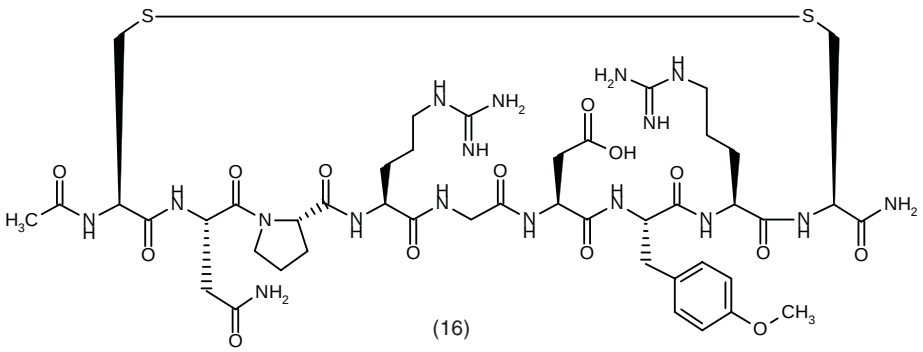
Table I: Continued.



(15)



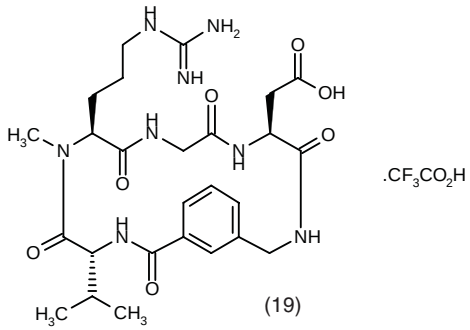
(17)



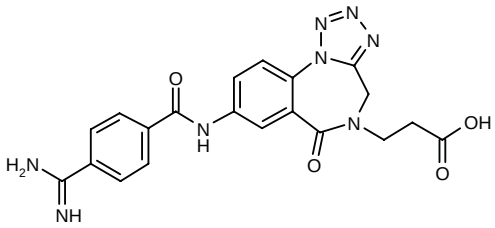
(16)

Fab fragment of the humanized anti-GPIIb/IIIa monoclonal antibody C4G1

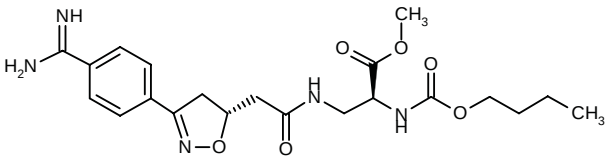
(18)



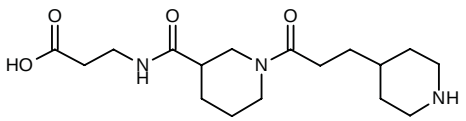
(19)



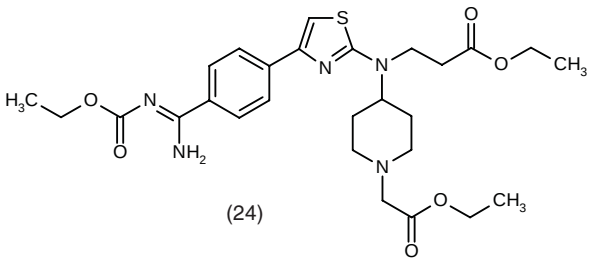
(20)



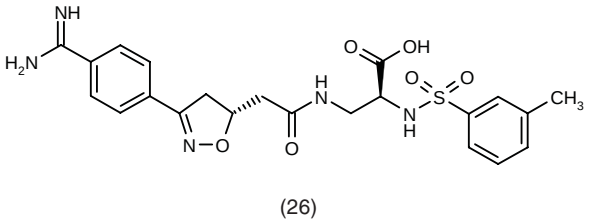
(21)



(22)



(24)



(26)

*Structure not yet detected. Source: Prous Science Ensemble database.

In dogs, orbofiban inhibited *ex vivo* collagen-induced platelet aggregation, with an ED_{50} of 0.9 mg/kg p.o. b.i.d. Bleeding time was not prolonged in dogs at intravenous doses of SC-57101 that completely inhibited ADP-induced platelet aggregation (10). Long-term oral administration of orbofiban to dogs (0.5 and 1.2 mg/kg p.o. b.i.d. for 17 days) inhibited platelet aggregation by an average of 22 ± 5% and 70 ± 10%, respectively, measured at daily trough levels. No effects on platelet count, liver and kidney tests or hematological profile were observed (13).

In a model of circumflex coronary artery injury in dogs, administration of SC-57101 as a loading dose (0.21-0.56 μg/kg/min i.v.) plus maintenance dose (0.15-0.4 μg/kg/min i.v.) had no effects on bleeding time but did produce a dose-dependent increase in the time to formation of occlusive thrombi, an increase in the percentage of platelet aggregation inhibition and a decrease in the number of dogs developing occlusive thrombi (11, 14). Similar results were obtained after carotid artery injury in dogs (14).

SC-57101 was evaluated in the Folts canine model of cyclic flow reductions (CFRs), a model considered to mimic clinical acute angina pectoris. Infusion of the drug (0.15 μg/kg/min i.v.) inhibited CFRs within 18 ± 2 min at a plasma level of 8.3 ± 1.4 ng/ml. The inhibition of CFRs was maintained for 159 ± 25 min after drug administration was discontinued. In experiments performed in the presence of epinephrine, CFRs were abolished in 5/6 dogs treated with SC-57101 (0.3 μg/kg/min i.v.) and in only 1/8 dogs given aspirin (4.3 mg/kg i.v.) (15). In the same model, orbofiban alone (2.5 mg/kg p.o.) or at a lower dose (0.625 mg/kg p.o.) combined with aspirin (81 or 162 mg p.o.) reduced or prevented cyclic flow variations, reduced the percentage of animals forming a thrombus and increased the time to thrombus formation (16).

Pharmacokinetics

Oral systemic activity in dogs was 28%, as determined by measuring the AUC following a single intravenous dose of SC-57101 compared to the AUC after a single oral dose of orbofiban. Half-life ($t_{1/2}$) of SC-57101 in dogs was 18 h, calculated from the intravenous administration curve (10). In rat studies, administration with food had less effect on gastrointestinal absorption than was the case with the structurally related compound xemilofiban. Differences between the two compounds were not likely to be due to competitive inhibition of the amino acid/peptide transporter systems (17).

Clinical Studies

Single-dose tolerability and pharmacodynamics were examined in 56 healthy volunteers randomized to receive one of seven doses of orbofiban (10-150 mg, p.o.) or placebo. Orbofiban was well tolerated and no episodes of minor or major bleeding occurred. The inhibition of ADP-induced platelet aggregation was dose-dependent, as was the increase in bleeding time (about 3.7 times the baseline at 100-150 mg orbofiban). Bleeding times > 30 min were observed in 2 subjects given 100 mg and 2 given 150 mg (18) (Box 1).

In a single-blind study, 24 healthy volunteers were randomized to four treatment groups (20, 50 and 75 mg orbofiban and placebo; n = 6/group). Orbofiban was given once daily on study days 1 and 9 and twice daily on days 2-8. Orbofiban produced a dose-dependent inhibition of platelet aggregation (from about 50% to nearly 100% inhibition measured at day 9), an increase in metabolite plasma concentration and an increase in bleeding time (2.04 ± 0.52-fold, 2.87 ± 1.2-fold and 5.54 ± 4.26-fold at 20, 50 and 75 mg, respectively). Only small differences in pharmacodynamics and pharmacokinetics were observed at steady-state (day 9) compared with those after single-dose administration (day 1). Subjects administered orbofiban experienced no severe and 2 moderate adverse events and 5 minor bleeding events. The most common adverse event was injection-site bruising (19) (Box 2).

Box 1: The safety and pharmacodynamics of single doses of orbofiban in healthy volunteers (18).

Study Design	Open, dose-finding clinical trial
Study Population	Healthy volunteers (n = 56)
Intervention Groups	Orbofiban 10, 25, 35, 50, 75, 100 or 150 mg Placebo
Adverse Events	In 2 subjects on 100 mg and 2 on 150 mg bleeding time was >30 min. Maximum tolerated dose was established at 150 mg
Results	Bleeding time prolongation: O10, 1.95; O25, 1.21; O35, 2.08; O50, 2.44; O75, 1.32; O100, 3.70; O150, 3.69 Inhibition of platelet aggregation at 8 h: O10, 8.1%; O25, 26.2%; O35, 29.8%; O50, 40.2%; O75, 75.7%; O100, 74.4%; O150, 98.6%
Conclusions	Orbofiban is safe and well tolerated at doses up to 150 mg and dose-dependently prolongs bleeding time and inhibits platelet aggregation up to 12 h after a single dose

Source: Prous Science CTLine database.

Box 2: The efficacy and safety of chronic treatment with orbofiban (19).

Study Design	Single-blind clinical trial
Study Population	Healthy volunteers (n = 24)
Intervention Groups	Orbofiban 20, 50 or 75 mg o.d. x 1 day → b.i.d. x 7 days → o.d. x 1 day Placebo
Adverse Events	No severe and 2 moderate adverse events were noted; 5 patients developed minor bleeding (injection-site bruising)
Results	Bleeding time prolongation at day 9: O25, 2.04; O50, 2.87; O75, 5.54 Platelet aggregation was dose-dependently inhibited both after single dose and at steady state
Conclusions	Orbofiban dose-dependently inhibits platelet aggregation with a minimal risk of bleeding.

Source: Prous Science CTLine database.

Box 3: The pharmacological effects of orbofiban in older cirrhotic patients (20).

Study Design	Open clinical trial
Study Population	Patients with alcoholic cirrhosis (AC) (n = 20) and healthy volunteers (HV) (n = 20)
Intervention Groups	Orbofiban 35 mg 1x
Conclusions	No differences were noted in the effects of orbofiban in both populations, which is consistent with the renal elimination of orbofiban active metabolite

Source: Prous Science CTLine database.

Liver impairment did not influence the pharmacodynamic effects of orbofiban. After single-dose administration of 35 mg orbofiban to 20 alcoholic cirrhosis patients (12 mild, 8 moderate; 11 males, 9 females) and to matched healthy volunteers, no significant differences were observed between the two groups in the time course response as measured by *ex vivo* ADP- and collagen-induced platelet aggregation. In both groups, the effect peaked at 6-8 h and returned to predose levels by 12 h. These findings are consistent with the importance of renal elimination of the active metabolite (20) (Box 3).

The safety, tolerability and efficacy of orbofiban and aspirin given in combination to 25 healthy men (16 evaluable for activity measurement) were assessed in a placebo-controlled, single-blind, sequential interaction study. The effects of oral orbofiban plus aspirin (35 mg + 150 mg/day x 5 days) on ADP- or collagen-induced platelet aggregation were additive (ADP) or synergistic (collagen) compared to each treatment alone (35 mg/day orbofiban x 5 days; 150 mg aspirin/day x 7 days). Bleeding time increased to a similar extent with orbofiban and aspirin alone, and did not vary significantly following administration of the combination. The most common adverse events were headache, dizziness, skin rash and pruritus (21) (Box 4).

In a single-blind, placebo-controlled, crossover interaction study with 17 patients, the combination of orbofiban (35 mg p.o.) plus heparin (bolus plus 24 h-infusion) did not result in a further increase in activated partial thromboplastin time (APTT) over heparin alone (heparin doses were initially titrated to achieve 1.5- to 2-fold increase in baseline APTT). No clinically significant bleeding events were observed at any point during the study (22) (Box 5).

In the randomized, placebo-controlled SOAR (Safety of Orbofiban in Acute Coronary Research) trial, 259 patients with unstable angina or recent (> 6 h but ≤ 120 h) myocardial infarction were administered orbofiban (30, 40, 50 mg b.i.d. or 50 mg once daily) or placebo for up to 3 months. All patients received concomitant aspirin (162 mg/day). In an interim pharmacodynamic study in a subgroup of 145 patients performed after 2-4 weeks of treatment, 30-50 mg b.i.d. orbofiban produced inhibition of ADP (20 μM)-induced platelet aggregation within the range of 40-60% (trough plasma levels) and 60-80% (peak plasma levels (23). With regard to safety and tolerability, another interim analysis of 130 patients completing a minimum of 1 month treatment showed dose-related increases in nonsignificant and mild bleeding events in orbofiban-treated patients as compared to placebo, but no increase in severe bleeding events. Withdrawal rates due to adverse events were 9% (placebo) and 11-16% (orbofiban-treated groups) (24) (Box 6).

The OPUS-TIMI 16 (Orbofiban in Patients with Unstable coronary Syndrome) trial, which was designed to assess the long-term safety and efficacy of orbofiban in preventing acute coronary syndromes and other major

Box 4: The safety of orbofiban in combination with aspirin (21).

Study Design	Single-blind, placebo-controlled, crossover clinical trial
Study Population	Healthy male volunteers (n = 25)
Intervention Groups	Orbofiban, 35 mg o.d. x 5 days Aspirin, 150 mg o.d. x 7 days Orbofiban, 35 mg o.d. + Aspirin, 150 mg o.d. x 5 days
Adverse Events	Headache, dizziness, skin rash and pruritus were the most common in all groups
Results	Inhibition of collagen/ADP-induced platelet aggregation at 12 h: O, 10.9/17.2%; A, 27.4/3.4%; O+A, 63.0/27.8% Bleeding time prolongation: O, 2.11; A, 2.03; O+A, 2.97
Conclusions	Orbofiban combined with aspirin has an additive effect while being safe and well tolerated

Source: Prous Science CTLine database.

Box 5: The safety and pharmacodynamics of orbofiban alone or in combination with heparin (22).

Study Design	Single-blind, crossover, placebo-controlled clinical trial
Study Population	Unidentified patients (n = 17)
Intervention Groups	Heparin (to an aPTT of 1.5-2.0 times baseline) Orbofiban, 35 mg p.o. o.d. + Heparin x 3 days Orbofiban, 35 mg p.o. o.d. + Placebo x 3 days
Results	aPTT (change) at 12 h: O, –1.5 sec; H, 17.6 sec; O+H, 25.4 sec PAI (change) at 12 h: O, 14.3%; H, –1.2%; O+H, 13.7%
Conclusions	Orbofiban combined with heparin is safe and well tolerated and does not prolong aPTT

Source: Prous Science CTLine database.

Box 6: The tolerability of orbofiban in patients with unstable angina/myocardial infarction (24).

Study Design	Randomized, placebo-controlled clinical trial
Study Population	Patients hospitalized with unstable angina or myocardial infraction (n = 259)
Intervention Groups	Orbofiban, 30 mg b.i.d.* Orbofiban, 40 mg b.i.d.* Orbofiban, 50 mg b.i.d.* Orbofiban, 50 mg q.d.* Placebo*
Withdrawals [causes]	O30, 1% [bleeding], 16% [adverse events] O40, 4% [bleeding], 11% [adverse events] O50 b.i.d., 0% [bleeding], 16% [adverse events] O50 q.d., 4% [bleeding], 12% [adverse events] P, 0% [bleeding], 9% [adverse events]
Adverse Events	Bleeding events (insignificant/mild/severe): O30, 7/2/1 patients; O40, 7/6/0 patients; O50b.i.d., 10/4/0 patients; O50q.d., 4/7/0 patients; P, 4/1/0 patients
Conclusions	Orbofiban dose-dependently increases mild bleeding but is well tolerated during chronic treatment

*At the time of this interim analysis, 130 patients had completed at least 1 month of treatment. All patients received 162 mg/day of aspirin. Source: Prous Science CTLine database.

cardiovascular events in patients with unstable angina or myocardial infarction, has been dicontinued, although treatment of patients who have already received at least 30 days of therapy will be completed. Preliminary data from the trial showed an unexpected excess of early (30-day) mortality in one of the two active treatment arms. The two groups of patients were treated identically with orbofiban during the first 30 days, and researchers were unable to discern the reason for the discrepancy. Based on an analysis by the independent data safety monitoring board (DSMB) and with full support from Searle, the TIMI group has ended further patient enrollment as a precautionary measure. Additionally, the DSMB has unanimously endorsed a plan to continue double-blind treatment of all the more than 8000 patients who are beyond the 30-day time point in order to further study the safety and efficacy of orbofiban.

Orbofiban acetate is in phase III clinical testing at Searle (26) and the licensee Sankyo is evaluating the product in phase II trials in Japan (27).

Manufacturer

G.D. Searle & Co. (US), licensed to Sankyo Co., Ltd. (JP).

References

1. Abood, N.A., Flynn, D.L., Laneman, S.A., Nosal, R., Schretzman, L.A. (G.D. Searle & Co.). *Process for the preparation of amidino phenyl pyrrolidine β-alanine analogs.* US 5484946.

2. Lefkovits, J., Plow, E.F., Topol, E. *Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine.* New Engl J Med 1995, 332: 1553.

3. Prous, J.R. *Antiplatelet therapy.* In: The Year's Drug News - Therapeutic Targets, 1995 Edition, Prous Science, S.A., Barcelona, 1995, 267-78.

4. Coller, B.S. *Platelet GPIIb/IIIa antagonists: The first anti-integrin receptor therapeutics.* J Clin Invest 1997, 100(Suppl.): 57.

5. Tscheng, J.E. *Glycoprotein IIb/IIIa receptor inhibitors: Putting the EPIC, IMPACT II, RESTORE, and EPILOG trials into perspective.* Am J Cardiol 1996, 78: 35.

6. Coller, B.S. *GPIIb/IIIa antagonists: Pathophysiology and therapeutic insights from studies of c7E3 Fab.* Thromb Haemost 1997, 78: 730.

7. Timmis, G.C., Khurana, S. *Advances in platelet therapy in coronary artery disease: Importance of the platelet gpIIb/IIIa receptor.* J Interv Cardiol 1997, 10: 327.

8. Braunwald, E. et al. *Rationale and clinical evidence for the use of gpIIb/IIIa inhibitors in acute coronary syndromes.* Am Heart J 1998, 135: S56.

9. Peter, K., Schwarz, M., Ylänne, J., Kohler, B., Moser, M., Nordt, T., Salbach, P., Kübler, W., Bode, C. *Induction of fibrinogen binding and platelet aggregation as a potential intrinsic property of various glycoprotein IIb/IIIa (αIIbβ3) inhibitors.* Blood 1998, 92: 3240-9.

10. Nicholson, N., Taite, B., Panzer-Knodle, S. et al. *Biological activity of orbofiban, an orally active inhibitor of glycoprotein IIb/IIIa and platelet aggregation.* Thromb Haemost 1997, Suppl.: Abst PS-2719.

11. Nicholson, N.S., Haas, N.F., Panzer-Knodle, S.K., Salyers, A.K., Szalony, J.A., Taite, B.B., Engleman, V.W. *Preclinical studies of orbofiban, a potent, specific platelet receptor antagonist.* J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 1995.

12. Ogawa, T., Sugidachi, A., Shimoji, T., Suzuki, N., Nagasawa, T., Kawamura, Y., Komokata, Y., Naganuma, H., Asai, F. *Inhibitory effects of orbofiban, a novel GPIIb/IIIa antagonist, on platelet aggregation.* Jpn J Pharmacol 1998, 76(Suppl. 1): Abst P-184.

13. Nicholson, N.S., Taite, B.B., Szalony, J.A., Salyers, A.K., Haas, N.F., Panzer-Knodle, S.K., Engelman, V.W., Feigen, L.P., Page, J.D. *Orbofiban is a new orally active antiplatelet agent acting by antagonism of fibrinogen binding.* FASEB J 1998, 12(5): Abst 4174.

14. Szalony, J.A., Taite, B.B., Frederick, L.G., Suleymanov, O.D., King, L.W., Salyers, A.K., Nicholson, N.S. *Prevention of vascular thrombosis in dogs by the active metabolite of orbofiban.* FASEB J 1998, 12(5): Abst 4175.

15. Frederick, L.G., Suleymanov, O.D., Nicholson, N.S. *Efficacy of active moiety of orbofiban in canine model of cyclic flow reductions.* J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 1996.

16. Frederick, L.G., Suleymanov, O.D., Szalony, J.A., Taite, B.B., Salyers, A.K., King, L.W., Nicholson, N.S. *Interaction of orally administered orbofiban with aspirin or heparin: Effects on thrombus formation.* Eur Heart J 1998, 19(Suppl.): Abst P492.

17. Qiu, H., Cook, C.S., Lee, K.-H., Milton, M., Schoenhard, G. *Effects of nutrients and vehicle pH on the in situ and in vivo absorption of antithrombotic agents xemilofiban and orbofiban in rats.* Pharm Res 1997, 14(11, Suppl.): Abst 4113.

18. Oliver, S., Karim, A., Burns, D.M., Anders, R.J. *Pharmacodynamics and tolerability of orbofiban, a new antiplatelet agent.* J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 1994.

19. Oliver, S., Karim, A., Burns, D.M., Anders, R.J. *Multiple-dose orbofiban is a potent oral antiplatelet agent that demonstrates a dose-dependent response.* Eur Heart J 1998, 19(Suppl.): Abst P495.

20. Noveck, R.J., McMahon, F.G., Di Angelo, A., Karim, A. *Single dose pharmacodynamic effects (PD) of orbofiban (ORB), an orally active IIb/IIIa platelet antagonist in alcoholic cirrhosis (AC) and healthy subjects (NL).* Clin Pharmacol Ther 1998, 63(2): Abst PIII-101.

21. Oliver, S., Karim, A., Burns, D.M., Anders, R.J. *Effect of aspirin on orbofiban tolerability and pharmacodynamics.* J Am Coll Cardiol 1998, 31(5, Suppl. C): Abst 1993.

22. Oliver, S., Karim, A., Burns, D.M., Anders, R.J. *Orbofiban is a safe, potent antiplatelet agent without significant pharmacodynamic interaction with heparin.* Eur Heart J 1998, 19(Suppl.): Abst P494.

23. Ferguson, J.J., Deedwania, P.C., Kereiakes, D.J., Fitzgerald, D., Anders, R.J., Burns, D.M., Bryzinski, B.S. *Sustained platelet GPIIb/IIIa blockade with oral orbofiban: Interim pharmacodynamic results of the SOAR study.* J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 837-3.

24. Deedwania, P.C., Ferguson, J.J., Kereiakes, D.J., Fitzgerald, D., Anders, R.J., Burns, D.M., Bryzinski, B.S. *Sustained platelet GPIIb/IIIa blockade with oral orbofiban: Interim safety and tolerability results of the SOAR study.* J Am Coll Cardiol 1998, 31(2, Suppl. A): Abst 1028-111.

25. *Searle revises OPUS-TIMI 16 trial evaluating orbofiban acetate.* Daily Essentials Nov 25, 1998.

26. *Orbofiban development status.* Searle Company Communication Oct 13, 1998.

27. *Focus on Sankyo's R&D activities at home and abroad.* Daily Essentials Oct 9, 1998.