Communications to the Editor

Discovery of an Orally Active Non-Peptide Fibrinogen Receptor Antagonist

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Arterial thromboembolic events and their ischemic complications give rise to a variety of vasoocclusive disorders such as unstable angina, myocardial infarction, stroke, or peripheral arterial disease.[1−3] The acute vascular occlusion is caused by deposition and aggregation of platelets on thrombogenic surfaces such as ruptured atherosclerotic plaques leading to platelet-rich thrombus formation at the site of injury.[4] Fibrinogen binding to a platelet membrane glycoprotein, the integrin GP IIb/IIIa, is recognized as the final common pathway of platelet aggregation through cross-linking of adjacent platelets. Antagonists of GP IIb/IIIa are therefore expected to be a new promising class of antithrombotic agents offering potential advantages over present antiplatelet agents including aspirin and ticlopidine, which only interfere with one single agonistic pathway.[5]

Platelet GPIIb/IIIa antagonists reported to date include monoclonal antibodies,[6,7] polypeptides from snake venoms[8] and leeches,[9] linear and cyclic peptides containing either the arginine-glycine-aspartic acid (RGD) recognition sequence[10−14] or the carboxyl-terminal sequence from the fibrinogen γ-chain,[15] and nonpeptide antagonists.[5,16−21] Many of these compounds have been shown to inhibit platelet aggregation independent of the activating agonist, as well as to prevent thrombus formation in animal models or in humans.[5,12b,16,17a,b,19,20,22] In this communication, we report the discovery of a new potent, orally active nonpeptide GPIIb/IIIa antagonist, which mimics the RGD recognition sequence.

The Arg-Gly-Asp-Ser tetrapeptide was used as an initial lead compound. Our goal was to convert the only modestly active tetrapeptide inhibitor (IC_{50} = 100 μM for the inhibition of ADP-mediated platelet aggregation) into a potent, metabolically stable, and orally active GPIIb/IIIa antagonist (Table 1). In a first step we conformationally constrained the linear peptide by introducing a hydantoin ring. The resulting compound **1** showed an improved potency by a factor of 10. Another factor of 10 in potency was gained by replacing the serine residue by a phenylglycine in compound **2**. As has been observed by others as well,[5,12b,15] a dramatic increase in potency was obtained by replacing the flexible arginine side chain by a benzamidine. The diastereomeric mixture **3** showed an IC_{50} of 40 nM. The methyl group was introduced into the structure of **3** at the 4 position of the hydantoin ring in order to allow the isolation of individual stereoisomers since a hydrogen at the same position has proven to be acidic, thus preventing isolation of individual stereoisomers.[23]

Compound **3** provides a potent platelet aggregation inhibitor *in vitro*. Unfortunately, however, this first generation inhibitor showed only a limited bioavailability. In order to improve oral activity of respective molecules we modified the carboxyl terminus with the intention to reduce the number of polar functional groups and to lower the molecular weight of compounds. A novel series of potent platelet aggregation inhibitors was finally discovered by replacing the carboxyl-terminal Asp-Phg moiety of **3** by various β-amino acid derivatives (Table 2). Interestingly, orally active fibrinogen receptor antagonists based on quite different scaffolds where a β-amino acid derivative was incorporated at the carboxy terminus of the molecules have been reported by other research groups as well.[17d,20a] The phenyl ring of the β-amino acid appears to be important for the activity of **4**. Replacement of the phenyl ring by an alkyl side chain in **8** decreased potency *in vitro*. Exchange of the phenyl ring by the larger naphthyl ring in **7** apparently slightly decreased potency *in vitro*. Changing the electron density of the aromatic side chain in compounds **5** and **6** slightly improved the *in vitro* potency.

Platelet aggregation inhibitor **4** was found to be orally active in conscious dogs. Oral bioavailability after iv and oral administration of **4** was determined to be 5% (n = 2) by bioassay using isolated and immobilised GPIIb/IIIa.[25] The ethyl ester prodrug of **4** showed a bioavailability in conscious dogs of 55 ± 7% (n = 2). This encouraging result prompted us to synthesize all four individual stereoisomers of the diastereomeric mixture **4**. The synthesis is outlined in Scheme 1 for one particular stereoisomer. Briefly, ethyl (*S*)-2-amino-2-(4-bromophenyl)propionate (**11**) was obtained by separation of the racemate with (*R*)-mandelic acid as confirmed by X-ray analysis. The (*S*)-amino acid ester was converted to hydantoin **13** by standard methods. Coupling of **13** with (*S*)-3-amino-3-phenylpropionic acid ethyl ester, which was prepared by chain elongation starting from (*R*)-phenylglycine (Figure 8, Supporting Information), and subsequent ester cleavage provided **15** (S 1197) as the hydrochloride salt. In the same way all four stereoisomers were prepared and *in vitro* activity was assessed (Table 3). Only stereoisomer **15** proved to be a very potent platelet aggregation inhibitor.

Compound **15** inhibited dose-dependently and reversibly human and dog platelet aggregation in gel-filtered platelets (GFP), platelet rich plasma, and whole blood independent from the agonist used with IC_{50} values between 20 and 100 nM in the different systems. In addition, **15** inhibited ^{125}I-fibrinogen binding to ADP-activated human GFP[24] and isolated GPIIb/IIIa[25] in a concentration dependent manner with K_i values of 9 and

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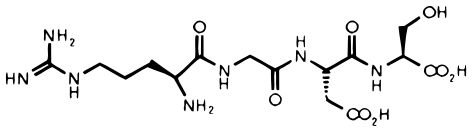
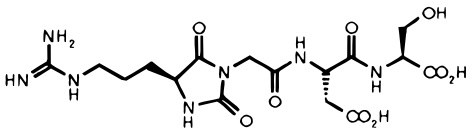
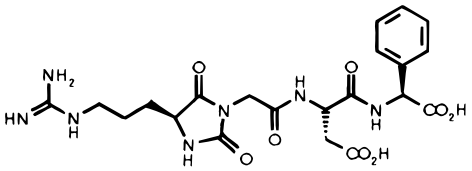
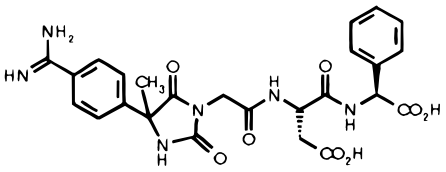
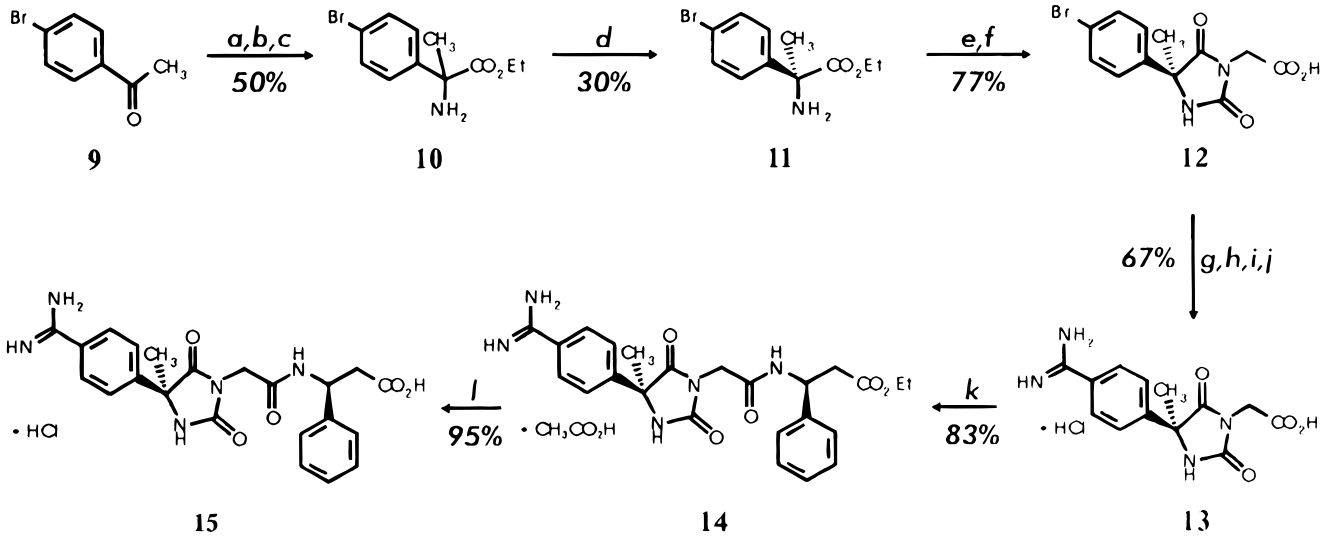
Table 1. First-Generation Platelet Aggregation Inhibitors

compd	structure	IC_{50} (μM) [a]
RGDS		100 (n=2)
1		10 (n=2)
2		0.9 (n=4)
3		0.04 (n=4)

[a] Human platelets were isolated from platelet rich plasma (PRP) by gel filtration on Sepharose 2 B. The resulting suspension of gel-filtered platelets (GFP) containing 3×10^8 platelets/mL was activated with 10 μM ADP in the presence of 1 mg/mL fibrinogen and stirred at 1000 rpm at 37 °C in an aggregometer (PAP 4, Biodata, Hatboro, PA). Aggregation was measured as the maximal increase in light transmittance. Compounds were added to GFP at 37 °C 2 min before the activation with ADP. Inhibition of aggregation was expressed as IC_{50} value, i.e. the mean concentration requiring 50% inhibition in GFP samples of two to six different donors.

Scheme 1[a]



(a) KCN, $(NH_4)_2CO_3$, H_2O/ethanol, 60 °C;[28] (b) NaOH, 10 bar, 130 °C;[28] (c) HCl, ethanol, reflux; (d) (*R*)-mandelic acid, 2-propanol/MTB-ether, recrystallized; (e) (ethoxycarbonyl)methyl isocyanate, ethyl acetate; (f) HCl, reflux; (g) CuCN, DMF;[29] (h) HCl, ethanol, 0 °C;[30] (i) NH_3, 2-propanol;[30] (j) HCl, reflux; (k) (*S*)-3-amino-3-phenylpropionic acid ethyl ester, DCC, HOBt, DMF; (l) 6 N HCl.

0.17 nM, respectively, suggesting that **15** was a specific inhibitor of GPIIb/IIIa-mediated platelet aggregation. Compound **15** did not affect ristocetin-induced von Willebrand factor binding to GPIb-IX[26] or vitronectin binding to integrin $\alpha_v\beta_3$,[25] indicating specificity of **15** toward GPIIb/IIIa (data not shown).

In conscious dogs, oral bioavailability after iv and oral administration of **15** was determined to be 10% ($n = 4$) by bioassay. The ethyl ester prodrug **14** (S 5740; Scheme 1) of **15** showed an even higher bioavailability. Availability in conscious dogs was 42 ± 8% ($n = 4$) and plasma half-life was 9.9 h (Figure 1). Compound **14** (Figure 7 in Supporting Information) and the respective hydrochloride salt S 1762[27] are highly effective in preventing thrombus formation in a dog model of coronary thrombosis (Folts model).

In conclusion, **15** is a highly potent, competitive fibrinogen receptor antagonist. The respective ethyl ester prodrug **14** is an antithrombotic compound with sufficient oral availability in dogs which suggests that it may have potential for chronic treatment and prophylaxis of thrombotic diseases in humans.

Table 2. Modification of **3** at the Carboxy Terminus

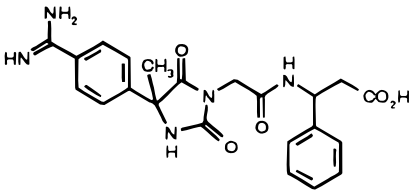
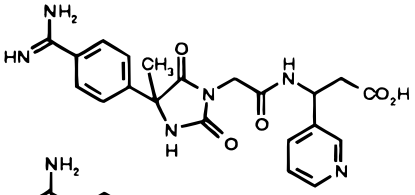
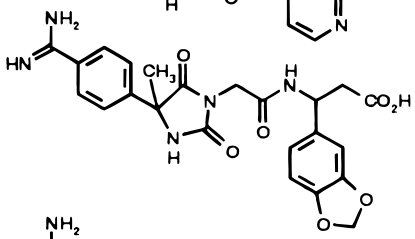
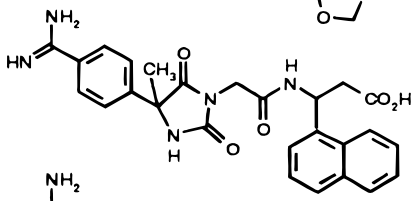
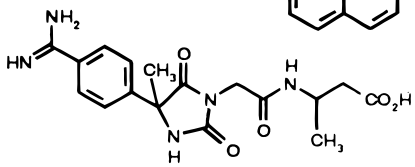
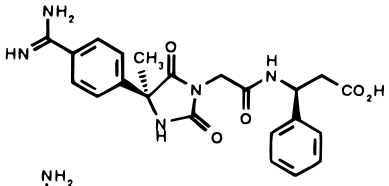
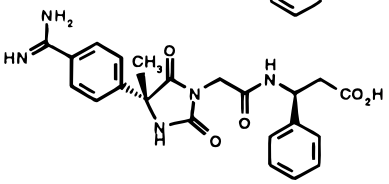
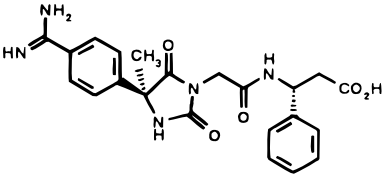
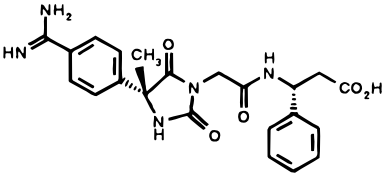
compd	structure	IC_{50} (μM) [a]
4		0.2 (n=4)
5		0.1 (n=4)
6		0.08 (n=4)
7		0.3 (n=4)
8		2.0 (n=4)

Table 3. Stereoisomers of **4**

compd	structure	IC_{50} (μM) [a]
15		0.02 (n=6)
16		6 (n=4)
17		50 (n=4)
18		5 (n=4)

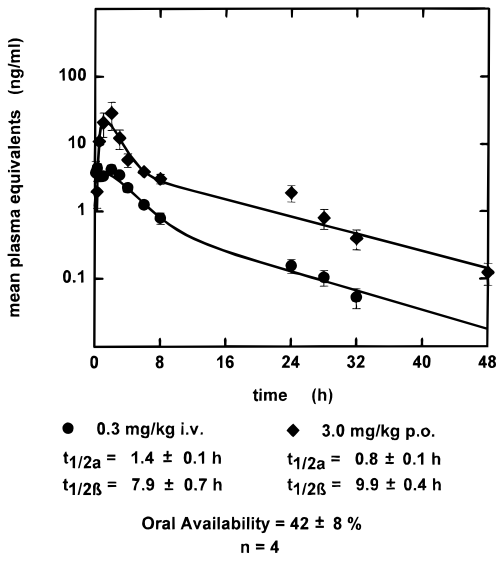


Figure 1. Kinetics of active plasma equivalents in dogs. Identical dogs were treated with **14** intravenously and orally, respectively, and blood was taken for plasma analysis at time points as indicated. Active plasma equivalents were determined in a bioassay using the inhibition of ^{125}I-fibrinogen binding to isolated and immobilized glycoprotein IIb-IIIa. Each data point represents the mean of plasma concentrations obtained from four treated dogs.

Supporting Information Available: Crystal structure of [(*R*)-1-(4-bromophenyl)-1-(ethoxycarbonyl)ethyl]ammonium (S)-mandelate, a scheme illustrating the synthesis of (*S*)- or (*R*)-3-amino-3-phenylpropionic acid ethyl ester, and a figure demonstrating activity of **14** in a dog model (Folts) of coronary thrombosis (21 pages). Ordering information is given on any current masthead page.

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(23) Incorporation of a methyl group into the structure of **2** at the 4 position of the hydantoin ring increased the potency by not more than a factor of 2, suggesting that the methyl group by itself is not the major cause for the strong increase in potency of **3** compared to **2**.

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