Discovery of a Novel, Orally Active Himbacine-Based Thrombin Receptor Antagonist (SCH 530348) with Potent Antiplatelet Activity

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Abstract: The discovery of an exceptionally potent series of thrombin receptor (PAR-1) antagonists based on the natural product himbacine is described. Optimization of this series has led to the discovery of **4** (SCH 530348), a potent, oral antiplatelet agent that is currently undergoing Phase-III clinical trials for acute coronary syndrome (unstable angina/non-ST segment elevation myocardial infarction) and secondary prevention of cardiovascular events in high-risk patients.

Coronary artery disease (CAD)[a] is the leading cause of cardiovascular death in the Western world.[1–3] Acute clinical manifestations of CAD are triggered by rupture of a vulnerable atherosclerotic plaque.[4–6] The subsequent thrombotic events lead to a spectrum of clinical conditions known as acute coronary syndrome (ACS), which include Q-wave and non-Q-wave myocardial infarctions and unstable angina.[7–9] Therapeutic management of ACS includes percutaneous coronary intervention (PCI) and pharmacological therapy using antithrombotic agents.[10–12] The currently available antithrombotic agents can be classified as anticoagulants, antiplatelets, and fibrinolytic agents. Anticoagulants are addressed to the coagulation cascade, where their net effect is either to modulate the endogenous level of thrombin or inhibit the enzymatic activity of thrombin.[13,14] Antiplatelet agents inhibit platelet activation and aggregation, a key process of hemostasis and clot formation.[15,16] Fibrinolytic agents work by lysis of existing clots.[17]

Platelets are activated by a variety of agonists such as thrombin, adenosine diphosphate (ADP), thromboxane A2 (TxA2), epinephrine, collagen, etc.[18] Antiplatelet agents inhibit platelet activation via specific platelet surface receptors. Activated platelets undergo shape change, secrete granular contents, and express activated glycoprotein IIb/IIIa (GpIIb/IIIa) receptors on their surface, which bind to fibrinogen, causing platelet aggregation.[19,20] The currently available antiplatelet agents such as aspirin (TxA2 biosynthesis inhibitor by cyclooxygenase-1 inhibition) and clopidogrel (ADP receptor antagonist) have modest potency, and they are associated with an increased risk of bleeding. GpIIb/IIIa antagonists block the final common pathway of aggregation of platelets independent of the mode of activation. The currently available GpIIb/IIIa antagonists, albeit potent, are intravenous formulations and efforts to achieve safe, orally active agents based on this mechanism have failed.[21,22] Therefore, there exists an unmet clinical need for a potent, orally active antiplatelet agent with a better safety profile. The inhibition of thrombin-mediated platelet activation provides such an opportunity.

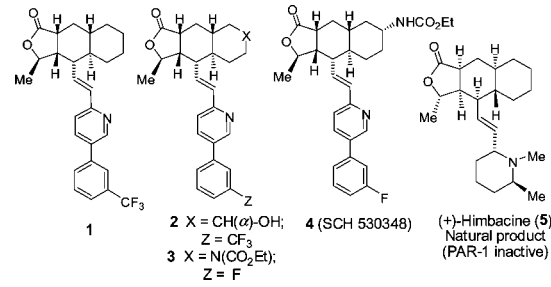

Figure 1. Himbacine-derived thrombin receptor antagonists. Compound **4** is a fourth generation thrombin receptor antagonist with exceptional oral antiplatelet effect.

Besides its central role in hemostasis and wound healing, thrombin, the main effector protease of the coagulation cascade, activates platelets and other cell types by proteolytic activation of cell surface receptors known as protease activated receptors (PARs). The proteolytic enzyme cleaves the extracellular loop of the G-protein-coupled receptor (GPCR) and the newly unmasked amino terminus acts as a "tethered ligand" that binds to the proximally located transmembrane loop of the GPCR, eliciting intracellular signaling.[23–25] Four PARs are known: PAR-1, PAR-2, PAR-3, and PAR-4. Among these, PAR-1, also known as thrombin receptor, is widely distributed in human and monkey platelets, endothelial cells, and smooth muscle cells. Among the various platelet activating ligands, thrombin is the most potent activator, and thrombin-mediated platelet aggregation plays a critical role in the pathophysiology of thrombosis.[26] Therefore, a thrombin receptor antagonist is expected to produce potent antiplatelet effects. Additionally, because thrombin-mediated fibrin generation is unaffected, such an agent is likely to have less bleeding liability than conventional antithrombotic agents.[27,28] Because thrombin is known to be mitogenic in endothelial and smooth muscle cells via the PAR-1 mechanism, a PAR-1 antagonist may have additional therapeutic utility in the treatment of vascular disorders such as atherosclerosis and restenosis that often occurs following surgical interventions.[29]

We have previously reported the discovery of PAR-1 antagonists **1**–**3** based on a lead generated from the natural product himbacine (**5**) (Figure 1).[30–33] These compounds bind to PAR-1 in a competitive manner with high affinity and are highly active in a series of functional assays that measure cellular responses to platelet activation. More importantly, these compounds showed robust inhibition of platelet aggregation in an ex vivo cynomolgus monkey model following oral administration. As reported earlier, the *ent*-himbacine absolute stereochemistry for the tricyclic region is preferred for the himbacine-derived PAR-1 antagonists.

As part of our continuing effort to optimize the potency and pharmacokinetic profile of this series, we have further explored the C-7 region of the tricyclic motif, which has been known to

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[a] Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CYP, cytochrome P450; Gp, glycoprotein; GPCR, G-protoein coupled receptor; haTRAP, high affinity thrombin receptor activating peptide; HCASMC, human coronary artery smooth muscle cells; HPBCD, hydroxypropyl-β-cyclodextrin; PCI, percutaneous coronary intervention; PAR, protease-activated receptor; PRP, platelet rich plasma ; PT, prothrombin time; APTT, activated partial thromboplastin time; TxA2, thromboxane A2.

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Scheme 1

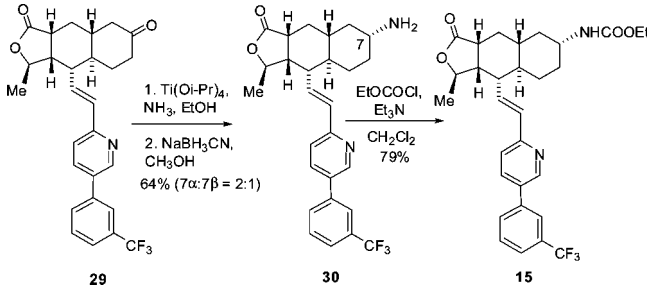
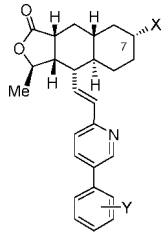


Table 1. SAR of 7-Amino Derivatives[a]



compd	X	Y	K_i[b] (nM) ± SEM
6	NH_2	*m*-F	20 ± 0.0
7	NHCOMe	*m*-CF_3	30 ± 8.5
8	NHCOEt	*m*-F	6.4 ± 1.1
9	NHCOCyPr	*m*-F	6.5 ± 0.9
10	NHCOMe	*m*-F	6.2 ± 0.6
11	NHCONHMe	*m*-F	4.4 ± 0.5
12	NHCONHEt	*m*-F	4.8 ± 0.6
13	$NHSO_2Me$	*m*-F	11 ± 2.1
14	$NHSO_2Me$	*m*-CF_3	10 ± 6.0
15	$NHCO_2Et$	*m*-CF_3	13 ± 3.2
4	**$NHCO_2Et$**	***m*-F**	**8.1 ± 1.1**
16	$NHCO_2Me$	*m*-F	6.1 ± 0.9
17	$NHCO_2Pr$	*m*-F	17 ± 4.5
18	$NHCO_2t$-Bu	*m*-CN	44 ± 8.0
19	$NMeCO_2Et$	*m*-F	4.1 ± 1.4
20	$NPrCO_2Et$	*m*-F	89 ± 20.5
21	$NMeCO_2Et$	*m*-CF_3	3.7 ± 0.05
22	$NHCO_2Et$	*m*-OMe	5.9 ± 0.3
23	$NHCO_2Et$	*o*-F	11 ± 4.9
24	$NHCO_2Et$	*m*- $CONH_2$	367 ± 98
25	$NHCO_2Et$	*m*-CN	1.8 ± 0.05
26	$NHCO_2Et$	*m*-Cl	11 ± 5.6
27	$NHCO_2Et$	3,5-F,F	5.9 ± 2.3
28	$NHCO_2Et$	2-F,3-Me	11 ± 4.0

[a] Absolute stereochemistry shown. 7-β-derivatives tested showed comparable K_i values; however, 7-α-derivatives were preferred due to their ease of synthesis. [b] PAR-1 binding assay ligand: [^{3}H]ha TRAP, 10 nM (K_d = 15 nM); n = 9 for compound **4**, and 2 for the rest.

undergo considerable in vivo metabolism.[30] Toward this end, various derivatives of the C-7 amine were explored. A representative synthesis of these compounds is outlined in Scheme 1. The previously reported ketone **29** was subjected to reductive amination to give the 7-α-amine-substituted tricyclic precursor as the major diastereomer.[30] Derivatization of the amine to the corresponding amide, urea, sulfonamide, and carbamate was achieved under standard conditions. In vitro binding studies were carried out on human platelet membrane-derived PAR-1 using radiolabeled high affinity thrombin receptor activating peptide ([^{3}H]haTRAP) as ligand, according to the previous reports.[34]

The in vitro binding data are provided in Table 1. The primary amine **6** inhibited PAR-1 with a K_i of 20 nM. The amides **7**−**10** showed excellent PAR-1 affinity. The urea (**11** and **12**) and sulfonamide derivatives (**13** and **14**) also showed excellent PAR-1 affinity. Similarly, the carbamates **4** and **15**−**28** were very active. There was a general trend toward reduced affinity for the bulkier alkyl carbamates (e.g., **17** and **18**) and secondary carbamates with bulkier *N*-alkyl groups (**19** vs **20**).

Table 2. Oral Ex Vivo Results in Cynomolgus Monkey Model and Corresponding Monkey Pharmacokinetics Data

compd	ex vivo platelet aggregation inhibition (duration)[a] n = 3	monkey PK[b] AUC (μM·h), C_{max} (μM)
6	<40% at 1 mg/kg (6 h)	NT
8	100% at 1 mg/kg (24 h)	11.38, 0.75
9	100% at 1 mg/kg (24 h)	5.53, 0.39
11	55% at 1 mg/kg (24 h)	2.63, 0.26
13	<40% at 1 mg/kg (6 h)	NT
15	100% at 1 mg/kg (>24 h)	5.03, 0.33
4	**100% at 0.1 mg/kg (>24 h)**	0.20, 0.018
19	inactive at 0.5 mg/kg	NT
23	80% at 0.1 mg/kg (24 h)	0.20, 0.024
25	80% at 0.1 mg/kg (24 h)	2.08, 0.20
28	100% at 1 mg/kg (24 h)	0.13, 0.020

[a] All compounds, as hydrochloride salts, were dosed in 0.4% methyl cellulose (MC) except compound **6**, which was dosed in 20% HPBCD. In general, platelet aggregation inhibition <40% is considered insignificant and >80% is considered robust. [b] AUC and C_{max} are given for Ex Vivo study animals (n = 3); $AUC_{(0-24h)}$ for all compounds.

The phenyl substitution pattern followed the previously established paradigm. In general, *ortho*- and *meta*- halogen, CF_3, or CN substitution gave the best PAR-1 binding. Certain ortho, meta-disubstitutions, as represented by **27** and **28**, were also tolerated.

Several compounds from each subset were screened in a cynomolgus monkey ex vivo platelet aggregation inhibition model. The data are given in Table 2 along with drug plasma levels. The duration of platelet activity is noted in parenthesis. In general, platelet aggregation inhibition of <40% is considered insignificant at any time point and >80% inhibition of ex vivo platelet aggregation is considered robust. In this efficacy model, a more discriminating property was seen among various compounds with excellent in vitro PAR-1 affinity.

The amine precursor **6** did not show any significant inhibition of platelet aggregation. The amides **8** and **9** showed robust inhibition of platelet aggregation at 1 mg/kg with 24 h duration. However, at lower doses, these compounds had only insignificant activity (data not shown). The urea derivative **11** showed only weak activity. Likewise, the sulfonamide **13** showed only weak inhibition at the 6 h time point.

The carbamate derivatives showed a very promising profile. At 1 mg/kg, the ethyl carbamates **15** and **4** showed 100% inhibition of platelet aggregation for 24 h. Because we preferred the *m*-fluoro-substituted compound **4** to the corresponding CF_3-substituted compound **15**, due to its reduced lipophilicity, further dose-down experiments were carried out on **4**, sequentially, at 0.5, 0.3, 0.1, and 0.05 mg/kg. At all doses ≥0.1 mg/kg, we noted 100% inhibition of platelet aggregation for 24 h (Figure 2). The 0.1 mg/kg study was repeated to monitor the recovery of platelet activity. As shown in Figure 2, partial recovery of platelet function was realized in 48 h.

Compound **4** was further profiled in a series of assays. Scatchard plots of saturation binding in the presence and absence of **4** were consistent with a competitive binding profile to the PAR-1 receptor. To effectively compete against a tethered ligand, an antagonist needs to have not only high affinity but also it should have a slow dissociation from the receptor. In kinetic studies, **4** showed a long dissociation $t_{1/2}$ of about 20 h, which explains the excellent ex vivo potency and long duration of action for this compound.

The effect of **4** on aggregation responses to thrombin (10 nM), haTRAP (15 μM), ADP (20 μM), and collagen (5 μM) in

Table 3. Summary of In Vitro and Pharmacokinetic Data for Compound **4**

PAR-1 K_i	8.1 nM
inhibition of human platelet aggregation (IC_{50})	47 nM[a], 25 nM[b]
Ca^{2+} transient assay (K_i)[c]	1.1 nM
proliferation assay (K_i)[d]	13 nM
rat PK (oral)[e]: $AUC_{(0-24h)}$, C_{max}, F; IV $t_{(1/2)}$	5.3 (μM·h), 0.67 (μM), 33%; 5.1 h
monkey PK (oral)[f]: $AUC_{(0-24h)}$, C_{max}, F; IV $t_{(1/2)}$	10 (μM·h), 1.3 (μM), 86%; 13 h

[a] Induced by 10 nM thrombin. [b] Induced by 15 μM haTRAP. [c] Inhibition of thrombin-stimulated Ca^{2+} transient in HCASMC. [d] Inhibition of ^3H thymidine incorporation in HCASMC. [e] Oral and intravenous (IV) dosing of HCl salt at 10 mg/kg. [f] Oral and IV dosing of HCl salt at 1 mg/kg. Vehicle for oral dosing: 0.4% methyl cellulose; vehicle for IV dosing: 20% hydroxypropyl β-cyclodextrin.

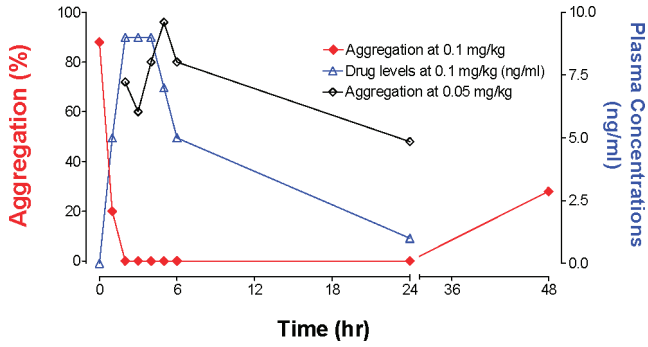


Figure 2. Inhibition of ex vivo haTRAP-induced platelet aggregation by **4** in cynomolgus monkeys ($n = 3$) after oral administration. Complete inhibition of platelet aggregation is achieved for 24 h post dosing with partial recovery occurring at 48 h at 0.1 mg/kg. The pharmacokinetic data suggests that only low plasma concentration is required for robust platelet aggregation inhibition. Ex vivo platelet aggregation to haTRAP was performed in whole blood using impedance aggregometry.

human platelet-rich plasma (PRP) was evaluated in a comparative experiment. The compound showed potent inhibition of thrombin-induced platelet aggregation with an IC_{50} of 47 nM and haTRAP-induced platelet aggregation with an IC_{50} of 25 nM, whereas it showed no inhibition of platelet aggregation induced by other agonists such as ADP, collagen, a standard thromboxane mimetic 9,11-dideoxy-11α,9α-epoxymethanoprostaglandin F2α (U46619),[35] and a PAR-4 agonist peptide.

In additional functional assays, compound **4** inhibited thrombin-induced calcium transient in human coronary artery smooth muscle cells (HCASMC) with a K_i of 1.1 nM (Table 3). It also inhibited thrombin-stimulated thymidine incorporation in HCASMC with a K_i of 13 nM. Pharmacokinetic profiling of **4** was done in rat and monkey models. Following oral administration, compound **4** was well absorbed in rat (68%; 10 mg/kg) and in monkey (82%; 1 mg/kg) models. T_{max} was observed at about 3 h in rats and 1 h in monkeys. The elimination half-life was 5.1 h in rats and 13 h in monkeys. The oral bioavailability was 33% in rats and 86% in monkeys.

Compound **4** did not affect clotting parameters (PT, prothrombin time; APTT, activated partial thromboplastin time), confirming that its mechanism of action is not by active site inhibition of thrombin or other coagulation proteinases. The compound was selective over a number of GPCRs, ion channels, and receptors that it was tested against at the CEREP laboratories and was inactive in the PAR-2, PAR-3 binding, and PAR-4 functional assays. Compound **4** showed no cytochrome P450 (CYP450) enzyme inhibition potential, including metabolism and mechanism-based inhibition against various isozymes (CYP 1A2, 2C9, 2C19, 2D16, and 3A4) in human liver microsomes even at a relatively high concentration (90 μM). In an 8-day enzyme induction study in rats, the compound showed a clean profile. Mass balance studies conducted in rat and monkey models using tritiated **4** gave full recovery of radioactivity within the targeted period of 7 days. Because of its excellent safety margin and superior potency, carbamate **4** was advanced to full development.

In summary, our efforts in the thrombin receptor antagonist area have culminated in the discovery of a highly potent thrombin receptor antagonist **4**. Compound **4** represents a fourth generation thrombin receptor antagonist with a K_i of 8.1 nM. The unique properties of **4** are underscored by its excellent oral bioavailability in multiple species, its high potency in a series of in vitro functional assays, and its potent oral activity in an ex vivo cynomolgus monkey model of platelet aggregation. Compound **4** was 30 times more potent than the initial development candidate in the series, showing complete obliteration of agonist induced platelet activation at 0.1 mg/kg with >24 h duration of activity (versus comparable efficacy at 3 mg/kg for the initial candidate).[31] After successfully completing phase-I and phase-II clinical studies, compound **4** has entered phase-III clinical studies for acute coronary syndrome (unstable angina/non-ST segment elevation myocardial infarction) and secondary prevention of cardiovascular events in high-risk patients.[36]

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Supporting Information Available: Experimental procedures for platelet aggregation studies, PAR-1 binding assay, and synthesis and characterization of intermediates and selected final products. This material is available free of charge via Internet at http://pubs.acs.org.

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