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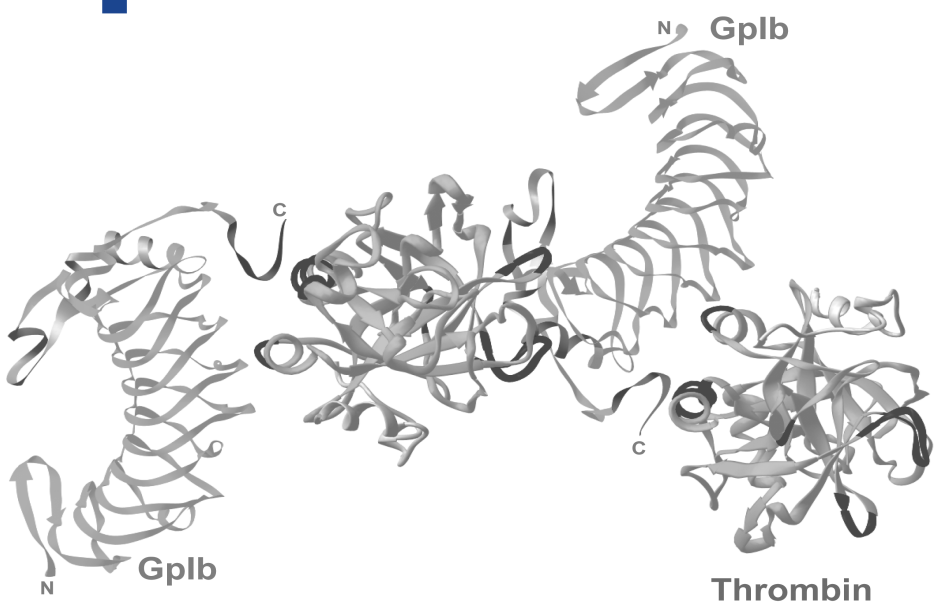
BACHEM

Product Monograph

PAR-Activating Peptides



Abstract

Proteinase-activated receptors (PARs) are a class of G-protein-coupled receptors consisting of four known members (PAR-1 to PAR-4). PARs are coupled to multiple signal transduction pathways and are involved in various physiological and pathophysiological processes including platelet activation, arterial thrombosis, inflammation and tumor progression.

Receptor signaling is initiated by enzymatic cleavage at a specific site within the extracellular N-terminal domain of PARs by a serine protease. Proteolysis results in exposure of a tethered ligand domain that interacts with the receptor resulting in activation. Short synthetic peptide sequences corresponding to the tethered ligand motif of the proteolytically generated new N-terminal region can also bind to and activate PARs.

In this monograph, Bachem offers a range of PAR-activating peptides and analogs useful for studying receptor function.

Proteinase-Activated Receptors

Proteinase-activated receptors (PARs) belong to the family of seven transmembrane G-protein-coupled receptors. Activation of PARs is initiated by proteolytic cleavage at a specific site near the N-terminus resulting in the unmasking of a particular peptide sequence, known as the tethered ligand sequence. The proteolytically generated new N-terminal domain interacts with the receptor within the extracellular loop-2 and triggers signal transduction (Fig. 1A). Proteolysis is mediated by a variety of serine proteases, among them enzymes involved in coagulation and inflammation. Short five- to six-amino acid peptides, based on the proteolytically revealed N-terminal sequence, can also activate PARs without the unmasking of the tethered ligand motif (Fig. 1B). To date, four proteinase-activated receptors have been identified, designated as PAR-1 through PAR-4. They differ in their N-terminal cleavage site, tethered ligand sequence and pharmacological characteristics.

PAR-1

Human, mouse and hamster PAR-1 (formerly known as "thrombin receptor") were cloned in the early 1990's. PAR-1 contains a thrombin cleavage site at position 41 and 42 in the N-terminal extracellular region followed by the tethered ligand sequence SFLLRN. C-terminal to this motif a cluster of negatively-charged amino acid residues is found. The sequence of this cluster shows homologies to a motif present in the leech anticoagulant protein hirudin and a number of other proteins that interact with the anion-binding exosite I of thrombin (Fig. 2).

PAR-2

PAR-2, which was cloned in 1995, lacks the cluster of negatively-charged amino acid residues within the N-terminal extracellular domain. PAR-2 can be activated by trypsin, but, in contrast to the other members of the PAR family, does not respond to thrombin.

The human and mouse homologs, which share 83% overall identity, show differences in their tethered ligand sequences. Cleavage of human PAR-2 occurs between Arg^{34} and Ser^{35} and results in the unmasking of the N-terminal tethered sequence SLIGKV, whereas the mouse receptor is cleaved between Arg^{38} and Ser^{39} revealing the tethered ligand motif SLIGRL.

Chinese hamster ovary (CHO) cells transfected with human PAR-2 respond to both human PAR- (SLIGKV) and mouse PAR (SLIGRL)-activating peptides, and to the PAR-1-derived sequence SFLLRNP.

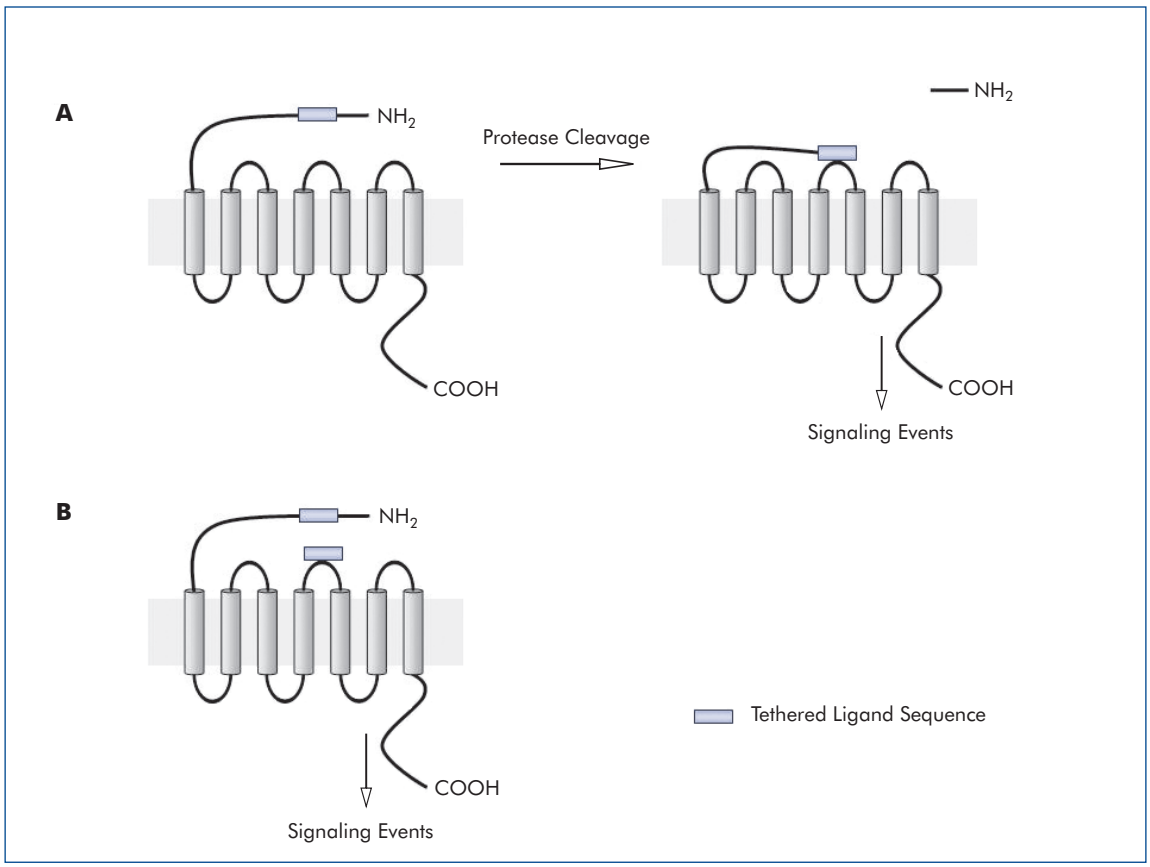


Fig. 1: PAR Activation Mechanisms

PAR-3

PAR-3 represents an additional thrombin receptor. Similar to PAR-1, a negatively-charged motif (FEEFP) is located distal to the thrombin cleavage site at Lys[38] and Thr[39]. Synthetic ligands mimicking the putative tethered ligand sequence (TFRGAP and TFRGAPPNS) or the PAR-1- and PAR-2-activating peptides, SFFLRN and SLIGRL, respectively, showed little or no activity at PAR-3. In contrast to the human receptor, the murine PAR-3 did not signal upon exposure to thrombin when overexpressed in COS-7 cells.

PAR-4

The cloning of PAR-4 was based on the identification of PAR-like sequences in expressed sequence tag (EST) databases. Human PAR-4 consists of 385 amino acids and shares 33% sequence identity with PAR-1, PAR-2, and PAR-3. It contains a potential cleavage site for thrombin and trypsin between Arg[47] and Gly[48].

The hexapeptide GYPGQV representing the tethered ligand sequence of this receptor was able to trigger signal transduction in COS-7 cells transiently transfected with human PAR-4.

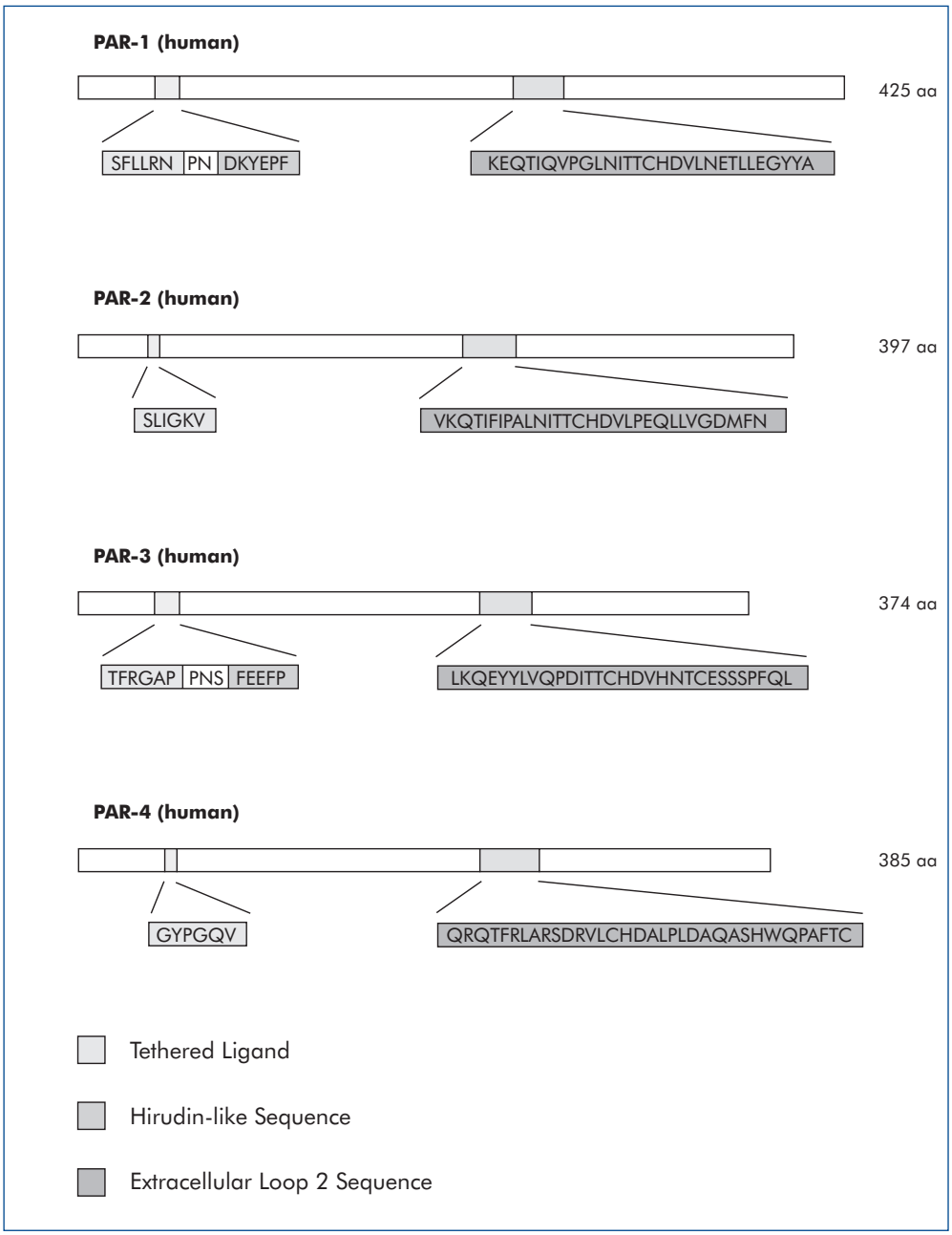


Fig. 2:
Human Proteinase-Activated Receptors

Receptor Activation

Thrombin activates PAR-1 and PAR-3 by first binding via its anion-binding exosite to the negatively charged amino acid motifs (DKYEPF for PAR-1 and FEEFP for PAR-3) C-terminally to the cleavage site. Mutations within these sequences were shown to reduce the capacity of thrombin to activate PAR-1 and PAR-3. Furthermore, γ-thrombin, which lacks the anion-binding exosite is about a 100 times less potent than α-thrombin in cleaving PAR-1 and PAR-3 at the activation site. PAR-4, which is devoid of a hirudin-like binding site for thrombin can be activated equally well by α- and γ-thrombin. As activation by thrombin is shown to be approximately 50 times less than with PAR-1, PAR-4 is considered to be a low affinity receptor.

In certain cell types, various members of the PAR family are coexpressed. Human platelets, for example, express PAR-1 and PAR-4 which exhibit different potencies and kinetics of desensitization. PAR-1 activation is transient and occurs rapidly in response to low concentrations of thrombin whereas PAR-4 responds to high concentrations of thrombin but shows a sustained action. Coexpression of this dual receptor system may have important functions in platelet aggregation.

Mouse platelets express PAR-3 and PAR-4, but not PAR-1. In this cell type, PAR-3 appears to act as a cofactor for PAR-4. Evidence for this relationship came from the observations that coexpression of PAR-3 in COS cells increased the thrombin signaling to PAR-4 6-15 times and that coexpression of the transmembrane domain of CD8 linked to the N-terminus of PAR-3 with its cluster of negatively charged amino acids facilitated thrombin signaling via PAR-4. Thrombin cleavage may be promoted by the ability of PAR-3 to concentrate thrombin at the cell surface in the vicinity of PAR-4.

Non-receptor proteins with high affinity binding sites for thrombin may equally act as cofactors for PAR activation. This has been demonstrated for glycoprotein Ib (gp1b) on human platelets. Inhibition of thrombin binding to gp1b resulted in a decrease in PAR-1 hydrolysis. The underlying mechanism might be similar to the one suggested for PAR-3 and PAR-4 on mouse platelets, in that gp1b concentrates thrombin at the cell surface and thereby facilitates PAR-1 hydrolysis.

Apart from thrombin and trypsin, additional proteases cleave and activate members of the PAR family. Among them are leukocyte proteases (such as cathepsin G and proteinase-3), the mast cell protease, tryptase, in addition to enzyme complexes functioning in the coagulation cascade like TF-FVIIa-FXa and TF-FVIIa.

Some of the proteases may act as activating or inactivating enzymes depending on the targeted receptor. For example, cathepsin G is able to activate PAR-4 but disables PAR-1, PAR-2, and PAR-3 while proteinase-3 can activate PAR-2 but inactivates PAR-1.
Interestingly, PARs can also be activated by non-mammalian enzymes. Activation by proteases from dust mites or *Porphyromonas gingivalis*, a major mediator of periodontitis, has been associated with the development of allergies and cardiovascular disorders, respectively.

Deactivation Mechanisms

PARs can couple to multiple signal transduction pathways and can therefore, regulate many cellular functions. Although cleavage results in receptors that are constitutively exposed to the tethered ligand sequences, signaling via PARs is transient. Considerable effort has been directed towards the investigation of signal termination mechanisms with a primary focus on human PAR-1 and PAR-2. Apart from the possible deactivation by cell surface proteases that cleave PARs at sites relevant for activity, signaling via PARs might also be terminated by desensitization mechanisms. These mechanisms may involve rapid phosphorylation of the receptors by G-protein receptor kinases (GRK) and/or second messenger kinases such as protein kinase C (PKC). Subsequent binding of β-arrestins to the phosphorylated PARs results in disruption of the association with heterotrimeric G-proteins and termination of the signal. In addition to receptor desensitization, responsiveness to agonists is also regulated by receptor endocytosis, which can be triggered by PAR activation. Internalization of both PAR-1 and PAR-2 proceed via a clathrin-mediated process. In contrast to PAR-1, endocytosis of PAR-2 requires β-arrestins, which act as adaptor proteins that link GRK-phosphorylated receptors to clathrin. Adaptor proteins, such as AP2, may participate in endocytosis of PAR-1.

Since activation of PARs is an irreversible mechanism, sustained signaling via these receptors requires either *de novo* synthesis or mobilization of intracellularly stored receptor molecules. Resensitization of responses to PAR-1 activators in endothelial cells and fibroblasts are for example due to the repopulation of the cell membrane with receptors derived from prominent Golgi stores. In megakaryoblasts, on the other hand, resensitization is achieved by the synthesis of new receptors. Platelets, which only need to respond once to PAR activators, lack both of these resensitization mechanisms.

Table 1: PAR Peptides (for more information, please see product list)

Peptides	Sequence	Product	Prod. No.
PAR-1	FLLRN	TRAP-6 (2-6)	H-8325
	FSLLRN	(Phe^{1},Ser^{2})-TRAP-6	H-5996
	FSLLRYamide	(Phe^{1},Ser^{2},Tyr^{6})-PAR-1 (1-6) amide (human)	H-6286
	H-DL-Isoser-FLLRN	(DL-Isoser^{1})-TRAP-6	H-1944
	SFFLRN	PAR-1 (1-6) (mouse, rat)	H-6416
	SFLL-Cit-OH	(Cit^{5})-TRAP-5	H-1406
	SFLLR	TRAP-5	H-1408
	SFLLRamide	TRAP-5 amide	H-2938
	SFLLRN	TRAP-6	H-8365
	SFLLRNamide	TRAP-6 amide	H-2936
	SFLLRNP	TRAP-7	H-2234
	SFLLRNPNDKYEPF	TRAP-14	H-8105
	SFLLRNPNDKYEPFamide	TRAP-14 amide	H-6032
	TFLLRamide	H-Thr-Phe-Leu-Leu-Arg-NH_2	H-5848
	YFLLRNP	(Tyr^{1})-TRAP-7	H-1674
PAR-2	LSIGKVamide	H-Leu-Ser-Ile-Gly-Lys-Val-NH_2	H-6428
	SLIGKV	PAR-2 (1-6) (human)	H-5042
	SLIGKVamide	PAR-2 (1-6) amide (human)	H-4624
	SLIGRL	PAR-2 (1-6) (mouse, rat)	H-3586
	SLIGRLamide	PAR-2 (1-6) amide (mouse, rat)	H-5078
	VKGILSamide	PAR-2 (6-1) amide (human)	H-5882
PAR-3	SFNGGPamide	PAR-3 (1-6) amide (mouse)	H-6282
	TFRGAP	PAR-3 (1-6) (human)	H-4452
	TFRGAPamide	PAR-3 (1-6) amide (human)	H-6278
PAR-4	AYPGKF	(Ala^{1})-PAR-4 (1-6) (mouse)	H-6134
	AYPGKFamide	(Ala^{1})-PAR-4 (1-6) amide (mouse)	H-6046
	GYPGKF	PAR-4 (1-6) (mouse)	H-4404
	GYPGKFamide	PAR-4 (1-6) amide (mouse)	H-6054
	GYPGKR	H-Gly-Tyr-Pro-Gly-Lys-Arg-OH	H-6418
	GYPGQV	PAR-4 (1-6) (human)	H-4348
	GYPGQVamide	PAR-4 (1-6) amide (human)	H-6346

Pathophysiological Functions

Cardiovascular Disease

Thrombin and its receptors play a pivotal role in blood coagulation and thrombus formation. Inappropriate aggregation of platelets contributes to occlusive vascular disorders such as stroke, angina, and myocardial infarction. For these reasons PAR-1 antagonists have gained interest as potential anti-thrombotic agents. In a cynomolgus monkey arterial injury model, the heterocycle-based peptide-mimetic PAR-1 antagonist RWJ-58259 was shown to exhibit considerable anti-thrombotic activity despite the fact that the platelets from these animals also express PAR-4. A recent study demonstrated that PAR-1 and PAR-4 on human platelets formed heterodimers. A combination of bivalirudin (a specific, reversible and direct thrombin inhibitor) and a novel PAR-4 cell-penetrating peptide (pepducin) antagonist effectively inhibited aggregation of human platelets to high concentrations of thrombin and offered superior protection against thrombosis in guinea pigs versus single-receptor inhibition. These results suggest that targeting the PAR-1/PAR-4 complex on the outside and/or inside cell surface may represent a novel therapeutic opportunity to prevent arterial thrombosis.

Since thrombin is also involved in the recurrent narrowing of blood vessels after vascular injury, PAR antagonists may also be of interest in decreasing the risk of restenosis following cardiac/vascular surgery and angioplasty.

Inflammation

PARs play an important role in inflammation and immune responses. Following tissue injuries, thrombin mediates several inflammatory-associated effects on the vascular endothelium via activation of PAR-1, among them the synthesis and release of various cytokines and growth factors and the induction of adhesion molecule expression. PAR-2, which can be activated by trypsin and mast cell tryptase, has been implicated in pathological conditions involving inflammatory processes including arthritis, asthma, and colitis. In an animal monoarthritis model of chronic inflammation, joint swelling was substantially inhibited in PAR-2-deficient mice compared with wild-type mice. Joint inflammation induced by intra-articular carrageenan/kaolin (C/K) injection could be attenuated by antagonizing PAR-2 activation. These results pointed at PAR-2 as a novel target for the future treatment of arthritis.

In a mouse model of colitis, 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis was dose-dependently reduced by the administration of the mouse PAR-2 tethered ligand SLIGRLamide, whereas the scrambled control peptide, LSIGRLamide, was ineffective. In another study, however, a pro-inflammatory role has been attributed to activation of PAR-2 in the mouse colon. A similar controversial situation concerning the pro- or anti-inflammatory effects of PAR-2 activation has also been observed within the airways.
PAR-2 was also localized on sensory neurons where it plays a role in inflammatory hyperalgesia. Thermal hyperalgesia depended on PAR-2-induced sensitization of the transient receptor potential vanilloid receptor 1 (TRPV1) which is gated by capsaicin, protons and noxious heat. The underlying mechanism involved activation of protein kinase Cε (PKCε) and protein kinase A (PKA).

Cancer

Increasing evidence suggests that PARs may play a role in invasive and metastatic processes of various cancers. Recent studies have demonstrated that PAR-1 mRNA is expressed in human colon cancer cell lines but not in normal colonic epithelial cells. Activation of PAR-1 in the human colon cancer cell line HT-29 by thrombin or by tethered ligand sequences resulted in cell proliferation. The signaling cascade downstream of PAR-1 involved a matrix metalloproteinase-dependent release of transforming growth factor-α (TGF-α), transactivation of the epidermal growth factor (EGF) receptor and subsequent activation of extracellular signal-related protein kinase 1/2 (ERK1/2).

PAR-1 was also found to be significantly overexpressed in atypical nevi and melanomas in comparison with common melanocytic nevi.

Another study demonstrated that preincubation of human melanoma cells with thrombin resulted in enhanced chemotactic migration. The process not only required the activation of PAR-1, but was also dependent on PAR-2 since desensitization with PAR-2 agonists abolished the effect. Consistent with this finding, a combination of PAR-2 (SLIGRL) and PAR-1 (TFLLRNPNDK) agonists evoked enhanced cell motility whereas PAR-1 or PAR-2 agonists alone did not stimulate migration. Similarly, activation of PAR-1 and PAR-2 also enhanced chemokinesis in prostate cancer cells. Interestingly, in a panel of prostate cancer cell lines, increased PAR-1 expression was demonstrated in those cell lines derived from bone metastases.

PAR-1 is preferentially expressed in highly metastatic human breast carcinoma cell lines and breast carcinoma biopsy specimens. Its expression correlated with tumor progression.
Recently, it was demonstrated that MDA-MB-231, a highly invasive breast cancer cell line, expressed very high levels of functional PAR-1, PAR-2 and PAR-4 whereas minimally invasive MCF7 cells had considerably lower levels of these receptors. Although PAR-2 and PAR-4 could act as chemotactic receptors in both MDA-MB-231 and MCF7 breast cancer cells, activation of PAR-1 with thrombin or a PAR-1 agonist unexpectedly inhibited migration and invasiveness of MDA-MB-231 cells when applied as a concentration gradient in the direction of the cell movement.

In a different study PAR-1 was shown to be a matrix metalloprotease-1 (MMP-1) receptor that promotes invasion and tumorigenesis of breast cancer cells.

Conclusions

PARs with their unique activation mechanism play a key role in hemostasis but are also involved in pathophysiological processes such as arterial thrombosis, inflammation, and tumor progression. The underlying mechanisms involving a variety of proteases and signaling components are only partly understood.

PAR agonists have proven valuable tools for specifically addressing the role of the individual receptors and have significantly improved our understanding of this receptor family.
Future work, in particular the use of receptor knock-out animals, will be needed to gain a deeper insight into the complex network of PAR signaling.

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PAR-Activating Peptides, Analogs and Fragments offered by Bachem

Product	Prod. No.		References
H-Gly-Tyr-Pro-Gly-Lys-Arg-OH (Proteinase Activated Receptor 4 (1-5)-Arg (mouse); Thrombin Receptor-Like 3 (1-5)-Arg (mouse); Coagulation Factor II Receptor-Like 3 (1-5)-Arg (mouse); GYPGKR) **Trifluoroacetate salt**	**H-6418**	Solubility: at least 1 mg/ml in water $C_{30}H_{48}N_{10}O_8$ M_r: 676.77	
H-Leu-Ser-Ile-Gly-Lys-Val-NH_2 (LSIGKVamide) **Trifluoroacetate salt**	**H-6428**	A partially reversed human PAR-2 activating peptide serving as an inactive control for PAR-2 agonist (H-4624). Solubility: in water $C_{28}H_{54}N_8O_7$ M_r: 614.79	[1]
H-Met-Ser-Arg-Pro-Ala-Cys-Pro-Asn-Asp-Lys-Tyr-Glu-OH (T1)	**H-2514**	This peptide is based on the sequence of the thrombin receptor domain that functions as a tethered ligand for the receptor itself. It has been selected from a phage peptide library as an inhibitor of thrombin triggered platelet aggregation, serotonin release and tyrosine phosphorylation. Its anti-aggregatory activity was about ten-fold higher than that of the previously reported peptide antagonists of the thrombin receptor. Solubility: at least 1 mg/ml in 0.1 % trifluoroacetic acid $C_{58}H_{91}N_{17}O_{20}S_2$ M_r: 1410.60 [207553-92-2]	[2,3,4]
PAR-1 (1-6) (mouse, rat) (Proteinase Activated Receptor 1 (1-6) (mouse, rat); Thrombin Receptor (1-6) (mouse, rat); SFFLRN) H-Ser-Phe-Phe-Leu-Arg-Asn-OH **Trifluoroacetate salt**	**H-6416**	PAR-1 agonist. Solubility: at least 1 mg/ml in water $C_{37}H_{54}N_{10}O_9$ M_r: 782.90 [140436-67-5] net	[5]
(Phe[1],Ser[2],Tyr[6])-PAR-1 (1-6) amide (human) (FSLLRYamide) H-Phe-Ser-Leu-Leu-Arg-Tyr-NH_2 **Trifluoroacetate salt**	**H-6286**	PAR-2 antagonist. This peptide FSLLRY-NH_2 inhibited activation of PAR-2 by trypsin in PAR-2 receptor expressing KNRK cells. Half-maximal inhibition of calcium signaling was observed at about 50 µM. In contrast, the activation of PAR-2 by SLIGRL-NH_2 (PAR-2 (1-6) amide (mouse, rat) (H-5078)) was not inhibited by FSLLRY-NH_2. Solubility: 1 mg/ml in water $C_{39}H_{60}N_{10}O_8$ M_r: 796.97 [245329-02-6] net	[6,7]
PAR-2 (1-6) (human) (Proteinase Activated Receptor 2 (1-6) (human); Thrombin Receptor-Like 1 (1-6) (human); Coagulation Factor II Receptor-Like 1 (1-6) (human); SLIGKV) H-Ser-Leu-Ile-Gly-Lys-Val-OH **Trifluoroacetate salt**	**H-5042**	PAR-2 agonist that can be used for the investigation of receptor functions. Solubility: 10 mg/ml in water $C_{28}H_{53}N_7O_8$ M_r: 615.77 [202933-49-1] net	[8,9,10]
PAR-2 (1-6) (mouse, rat) (Proteinase Activated Receptor 2 (1-6) (mouse, rat); Thrombin Receptor-Like 1 (1-6) (mouse, rat); Coagulation Factor II Receptor-Like 1 (1-6) (mouse, rat); SLIGRL) H-Ser-Leu-Ile-Gly-Arg-Leu-OH **Trifluoroacetate salt**	**H-3586**	Tethered ligand sequence of mouse PAR-2, which like the thrombin receptor is a protease-activated receptor present in keratinocytes. It was found to be equipotent with SFLLRN (H-8365) in activating keratinocyte inositolphospholipid hydrolysis and calcium mobilization. Solubility: 10 mg/ml in water $C_{29}H_{55}N_9O_8$ M_r: 657.81 [164081-25-8] net	[11]
PAR-2 (1-6) amide (human) (SLIGKVamide; Proteinase Activated Receptor 2 (1-6) amide (human); Thrombin Receptor-Like 1 (1-6) amide (human); Coagulation Factor II Receptor-Like 1 (1-6) amide (human)) H-Ser-Leu-Ile-Gly-Lys-Val-NH_2 **Trifluoroacetate salt**	**H-4624**	This peptide corresponding to the tethered ligand sequence of human PAR-2 (protease activated receptor 2) can be used to investigate receptor functions. Solubility: 5 mg/ml in water $C_{28}H_{54}N_8O_7$ M_r: 614.79 [190383-13-2] net	[12,13, 14]

PAR-Activating Peptides, Analogs and Fragments offered by Bachem (continued)

Product	Prod. No.		References
PAR-2 (6-1) amide (human) (retro-PAR-2 (1-6) amide (human); Proteinase Activated Receptor 2 (6-1) amide (human), Thrombin Receptor-Like 1 (6-1) amide (human); Coagulation Factor II Receptor-Like 1 (6-1) amide (human); VKGILSamide) H-Val-Lys-Gly-Ile-Leu-Ser-NH_2 **Trifluoroacetate salt**	**H-5882**	Retro-sequence of the proteinase-activated receptor-2 (PAR-2). Commonly used as an inactive control. Solubility: 5 mg/ml in water $C_{28}H_{54}N_8O_7$ M_r: 614.79	[8,15]
PAR-2 (1-6) amide (mouse, rat) (SLIGRLamide; Proteinase Activated Receptor 2 (1-6) amide (mouse, rat); Thrombin Receptor-Like 1 (1-6) amide (mouse, rat); Coagulation Factor II Receptor-Like 1 (1-6) amide (mouse, rat)) H-Ser-Leu-Ile-Gly-Arg-Leu-NH_2 **Trifluoroacetate salt**	**H-5078**	Protease-activated receptor-2 (PAR-2) selective agonist. Solubility: 1 mg/ml in water $C_{29}H_{56}N_{10}O_7$ M_r: 656.83 [171436-38-7] net	[13,16, 17,18, 19,20]
2-(2-Furoyl)-PAR-2 (2-6)-Orn amide (mouse, rat) (2-(2-Furoyl)-LIGRLOamide) 2-(2-Furoyl)-Leu-Ile-Gly-Arg-Leu-Orn-NH_2 **Trifluoroacetate salt**	**H-6246**	2-(2-Furoyl)-PAR-2 (2-6)-Orn amide (mouse, rat) is a potent and selective PAR-2 agonist. In cultured human PAR-2-expressing cells H-6246 was equally effective as SLIGRLamide (H-5078), in rat PAR-2-expressing cells it was 10 to 25 times more potent than SLIGRLamide in increasing intracellular calcium levels. In bioassays of tissue PAR-2 activity, measured as arterial vasodilation and hyperpolarization this agonist was 10 to 300 times more potent than H-5078. Solubility: 1mg/ml in water $C_{36}H_{63}N_{11}O_8$ M_r: 777.97 [729589-58-6] net	[21,22]
PAR-3 (1-6) (human) (TFRGAP; Proteinase Activated Receptor 3 (1-6) (human); Thrombin Receptor-Like 2 (1-6) (human); Coagulation Factor II Receptor-Like 2 (1-6) (human)) H-Thr-Phe-Arg-Gly-Ala-Pro-OH **Trifluoroacetate salt**	**H-4452**	Mimicks the putative tethered ligand of human PAR-3 (protease activated receptor 3). Solubility: 10mg/ml in water $C_{29}H_{45}N_9O_8$ M_r: 647.73 [320347-28-2] net	[23]
PAR-3 (1-6) amide (mouse) (SFNGGPamide; Proteinase Activated Receptor 3 (1-6) amide (mouse); Thrombin Receptor-Like 2 (1-6) amide (mouse); Coagulation Factor II Receptor-Like 2 (1-6) amide (mouse)) H-Ser-Phe-Asn-Gly-Gly-Pro-NH_2 **Trifluoroacetate salt**	**H-6282**	Murine PAR-3-derived tethered ligand sequence which does not activate PAR-3, but rather activates PAR-1 and PAR-2, either in Jurkat T-cells or in other PAR-expressing cells. Solubility: 1mg/ml in water $C_{25}H_{36}N_8O_8$ M_r: 576.61 [261521-21-5] net	[24]
PAR-3 (1-6) amide (human) (TFRGAPamide; Proteinase Activated Receptor 3 (1-6) amide (human); Thrombin Receptor-Like 2 (1-6) amide (human); Coagulation Factor II Receptor-Like 2 (1-6) amide (human)) H-Thr-Phe-Arg-Gly-Ala-Pro-NH_2 **Trifluoroacetate salt**	**H-6278**	Human PAR-3-derived tethered ligand sequence which does not activate PAR-3, but rather activates PAR-1 and PAR-2, either in Jurkat or in other PAR-expressing cells. Solubility: 1mg/ml in acetic acid $C_{29}H_{46}N_{10}O_7$ M_r: 646.75	[24]
PAR-4 (1-6) (human) (Thrombin Receptor-Like 3 (1-6) (human); Coagulation Factor II Receptor-Like 3 (1-6) (human); GYPGQV; Proteinase Activated Receptor 4 (1-6) (human)) H-Gly-Tyr-Pro-Gly-Gln-Val-OH **Trifluoroacetate salt**	**H-4348**	This hexapeptide corresponding to the amino terminus of the fourth protease-activated receptor (PAR-4) after the cleavage at Arg^{47}/Gly^{48} was tested for its ability to stimulate COS cells expressing PAR-4. This peptide readily activated both wild-type and mutant PAR-4 (R47A) at 500 µM, whereas thrombin and trypsin only activate the wild-type PAR-4. Solubility: 1 mg/ml in water $C_{28}H_{41}N_7O_9$ M_r: 619.68 [225779-44-2] net	[25,26, 27]

Product	Prod. No.		References
PAR-4 (1-6) (mouse) (GYPGKF; Proteinase Activated Receptor 4 (1-6) (mouse); Thrombin Receptor-Like 3 (1-6) (mouse); Coagulation Factor II Receptor-Like 3 (1-6) (mouse)) H-Gly-Tyr-Pro-Gly-Lys-Phe-OH **Trifluoroacetate salt**	**H-4404**	This PAR-4 activating peptide caused secretion and aggregation of PAR-3 deficient mouse platelets. Solubility: 50 mg/ml in water $C_{33}H_{45}N_7O_8$ M_r: 667.76 [213018-42-9] net	[28]
(Ala[1])-PAR-4 (1-6) (mouse) ((Ala[1])-Proteinase Activated Receptor 4 (1-6) (mouse); (Ala[1])-Thrombin Receptor-Like 3 (1-6) (mouse); (Ala[1])-Coagulation Factor II Receptor-Like 3 (1-6) (mouse); AYPGKF) H-Ala-Tyr-Pro-Gly-Lys-Phe-OH **Trifluoroacetate salt**	**H-6134**	Solubility: 1 mg/ml in water $C_{34}H_{47}N_7O_8$ M_r: 681.79 [380900-00-5] net	[29,30]
PAR-4 (1-6) amide (human) (Proteinase Activated Receptor 4 (1-6) amide (human); Coagulation Factor II Receptor-Like 3 (1-6) amide (human); Thrombin Receptor-Like 3 (1-6) amide (human); GYPGQVamide) H-Gly-Tyr-Pro-Gly-Gln-Val-NH_2 **Trifluoroacetate salt**	**H-6346**	Tethered ligand sequence of human PAR-4. Solubility: in water $C_{28}H_{42}N_8O_8$ M_r: 618.69 [245443-51-0] net	[31,32,33]
PAR-4 (1-6) amide (mouse) (Proteinase Activated Receptor 4 (1-6) amide (mouse); Coagulation Factor II Receptor-Like 3 (1-6) amide (mouse); GYPGKFamide; Thrombin Receptor-Like 3 (1-6) amide (mouse)) H-Gly-Tyr-Pro-Gly-Lys-Phe-NH_2 **Trifluoroacetate salt**	**H-6054**	Protease-activated receptor-4 activating peptide derived from murine PAR-4. H-Gly-Tyr-Pro-Gly-Lys-Phe-NH_2 was able to cause rat platelet aggregation with an EC_{50} value of 40 µM. Its effect on leukocyte rolling and adherence points at a role of PAR-4 in mediating proinflammatory processes. Solubility: at least 1mg/ml in 0.1 % trifluoroacetic acid $C_{33}H_{46}N_8O_7$ M_r: 666.78 [245443-52-1] net	[20,34]
(Ala[1])-PAR-4 (1-6) amide (mouse) ((Ala[1])-Proteinase Activated Receptor 4 (1-6) amide (mouse); (Ala[1])-Thrombin Receptor-Like 3 (1-6) amide (mouse); (Ala[1])-Coagulation Factor II Receptor-Like 3 (1-6) amide (mouse); AYPGKFamide) H-Ala-Tyr-Pro-Gly-Lys-Phe-NH_2 **Trifluoroacetate salt**	**H-6046**	This peptide based on the proteolytically-revealed tethered ligand sequence of the murine proteinase-activated receptor-4 (PAR-4) was shown to cause platelet aggregation with an EC_{50} value of about 15 µM. Solubility: 1 mg/ml in water $C_{34}H_{48}N_8O_7$ M_r: 680.80 [352017-71-1] net	[34]
H-Phe-Pro-Arg-OH	**H-3916**	FPR is a tripeptide analog of the thrombin-receptor-derived peptide SFLLR (H-1408). In the chick chorioallantoic membrane system it inhibited angiogenesis and caused a complete reversal of the angiogenesis-promoting effect of the thrombin-receptor-activating tetradecapeptide (TRAP (1-14), H-8105). FPR has potential applications in the nonthrombotic actions of thrombin, e.g. cancer and inflammation, where angiogenesis is thought to play a pivotal role. Solubility: 50 mg/ml in 50 % methanol $C_{20}H_{30}N_6O_4$ M_r: 418.50 [37553-80-3]	[35]
H-Thr-Phe-Leu-Leu-Arg-NH_2 ((Thr[1])-TRAP-5 amide; TFLLRamide) **Trifluoroacetate salt**	**H-5848**	Selective agonist of PAR-1. Solubility: 1 mg/ml in water $C_{31}H_{53}N_9O_6$ M_r: 647.82 [197794-83-5] net	[36]

PAR-Activating Peptides, Analogs and Fragments offered by Bachem (continued)

Product	Prod. No.		References
TRAP-5 (Thrombin Receptor Activator Peptide 5; PAR-1 (1-5) (human); Proteinase Activated Receptor 1 (1-5) (human); Thrombin Receptor (1-5) (human); Coagulation Factor II Receptor (1-5) (human)) H-Ser-Phe-Leu-Leu-Arg-OH **Trifluoroacetate salt**	**H-1408**	This pentapeptide is the minimal peptide length which retains full activity in releasing serotonin from human platelets. Solubility: at least 1 mg/ml in DMSO $C_{30}H_{50}N_8O_7$ M_r: 634.78 [141685-53-2] net	[37]
(Cit^5)-TRAP-5 ((Cit^5)-Thrombin Receptor Activator Peptide 5; (Cit^5)-PAR-1 (1-5) (human); (Cit^5)-Proteinase Activated Receptor 1 (1-5) (human); (Cit^5)-Thrombin Receptor (1-5) (human); (Cit^5)-Coagulation Factor II Receptor (1-5) (human)) H-Ser-Phe-Leu-Leu-Cit-OH **Trifluoroacetate salt**	**H-1406**	The substitution of Arg^5 with citrulline resulted in a peptide with improved biological activity. Solubility: in water and most aqueous buffers $C_{30}H_{49}N_7O_8$ M_r: 635.76 [287184-84-3] net	[37]
TRAP-5 amide (Thrombin Receptor Activator Peptide 5 amide; PAR-1 (1-5) amide (human); Proteinase Activated Receptor 1 (1-5) amide (human); Thrombin Receptor (1-5) amide (human); Coagulation Factor II Receptor (1-5) amide (human)) H-Ser-Phe-Leu-Leu-Arg-NH_2 **Trifluoroacetate salt**	**H-2938**	Thrombin receptor agonist peptide. Solubility: in water $C_{30}H_{51}N_9O_6$ M_r: 633.79 [141923-41-3] net	[38]
TRAP-6 (SFLLRN; Proteinase Activated Receptor 1 (1-6) (human); Thrombin Receptor (1-6) (human); Coagulation Factor II Receptor (1-6) (human); Thrombin Receptor Activator Peptide 6) H-Ser-Phe-Leu-Leu-Arg-Asn-OH **Trifluoroacetate salt**	**H-8365**	This hexapeptide corresponding to residues 42-47 of the thrombin receptor has been shown to be a thrombin receptor activator. It caused half-maximal platelet aggregation at approx. 0.8 µM and was 5 times more potent than the parent peptide H-8105. In addition, SFLLRN is effective in causing tyrosine phosphorylation, inhibition of cAMP formation, and an increase in cytosolic Ca^{2+}. Solubility: at least 1 mg/ml in water with agitation $C_{34}H_{56}N_{10}O_9$ M_r: 748.88 [141136-83-6] net	[4,26, 39,40, 41,42]
(DL-Isoser^1)-TRAP-6 ((DL-Isoser^1)-Thrombin Receptor Activator Peptide 6; (DL-Isoser^1)-PAR-1 (1-6) (human); (DL-Isoser^1)-Proteinase Activated Receptor 1 (1-6) (human); (DL-Isoser^1)-Thrombin Receptor 1 (1-6) (human); (DL-Isoser^1)-Coagulation Factor II Receptor (1-6) (human)) H-DL-Isoser-Phe-Leu-Leu-Arg-Asn-OH **Trifluoroacetate salt**	**H-1944**	This racemic isoserine analog of SFLLRN (H-8365) has only 15-20% of the platelet aggregating activity of SFLLRN. In compensation this peptide significantly resists degradation by aminopeptidase M and is much more stable in plasma and serum. Solubility: in water. $C_{34}H_{56}N_{10}O_9$ M_r: 748.88 [150242-29-8] net	[43]
(Phe^1,Ser^2)-TRAP-6 ((Phe^1,Ser^2)-PAR-1 (1-6) (human); (Phe^1,Ser^2)-Proteinase Activated Receptor 1 (1-6) (human); (Phe^1,Ser^2)-Thrombin Receptor 1 (1-6) (human); (Phe^1,Ser^2)-Coagulation Factor II Receptor (1-6) (human); FSLLRN) H-Phe-Ser-Leu-Leu-Arg-Asn-OH **Trifluoroacetate salt**	**H-5996**	(Phe^1,Ser^2)-TRAP-6 represents a peptide in which the two amino-terminal amino acids of TRAP-6 (H-8365) were reversed. Solubility: at least 1 mg/ml in water with agitation $C_{34}H_{56}N_{10}O_9$ M_r: 748.88 [374898-11-0] net	

Product	Prod. No.		References
TRAP-6 amide (Thrombin Receptor Activator Peptide 6 amide; PAR-1 (1-6) amide (human); Proteinase Activated Receptor 1 (1-6) amide (human); Thrombin Receptor (1-6) amide (human); Coagulation Factor II Receptor (1-6) amide (human)) H-Ser-Phe-Leu-Leu-Arg-Asn-NH_2 **Trifluoroacetate salt**	**H-2936**	Thrombin receptor agonist peptide. Solubility: in water $C_{34}H_{57}N_{11}O_8$ M_r: 747.90 [141923-40-2] net	[38]
TRAP-6 (2-6) (Proteinase Activated Receptor 1 (2-6) (human); Thrombin Receptor (2-6) (human); Coagulation Factor II Receptor (2-6) (human); FLLRN; Thrombin Receptor Activator Peptide 6 (2-6)) H-Phe-Leu-Leu-Arg-Asn-OH **Trifluoroacetate salt**	**H-8325**	Inhibits platelet aggregation induced by SFLLRN or thrombin. Solubility: at least 1 mg/ml in 0.1 % trifluoroacetic acid with agitation $C_{31}H_{51}N_9O_7$ M_r: 661.80 [141136-84-7] net	[44]
TRAP-7 (SFLLRNP; PAR-1 (1-7) (human); Proteinase Activated Receptor 1 (1-7) (human); Thrombin Receptor (1-7) (human); Coagulation Factor II Receptor (1-7) (human)) H-Ser-Phe-Leu-Leu-Arg-Asn-Pro-OH **Trifluoroacetate salt**	**H-2234**	This thrombin receptor agonist corresponds to residues 42-48 of the thrombin receptor. It is as effective as thrombin in inducing Ca^{2+} mobilization and protein kinase C activation in some T cell lines. Solubility: in water $C_{39}H_{63}N_{11}O_{10}$ M_r: 846.01 [145229-76-1] net	[45]
(Tyr^1)-TRAP-7 ((Tyr^1)-PAR-1 (1-7) (human); (Tyr^1)-Proteinase Activated Receptor 1 (1-7) (human); (Tyr^1)-Thrombin Receptor (1-7) (human); (Tyr^1)-Coagulation Factor II Receptor (1-7) (human); YFLLRNP) H-Tyr-Phe-Leu-Leu-Arg-Asn-Pro-OH **Trifluoroacetate salt**	**H-1674**	This peptide is an antagonist to α-thrombin and to the thrombin receptor agonist peptide SFLLRNP in human platelets. It might be a useful tool for the differentiation between several possible activation states of the human platelet thrombin receptor. Solubility: in 50 % acetic acid $C_{45}H_{67}N_{11}O_{10}$ M_r: 922.10 [149440-16-4] net	[46]
TRAP-14 (PAR-1 (1-14) (human); Proteinase Activated Receptor 1 (1-14) (human); Thrombin Receptor (1-14) (human); Coagulation Factor II Receptor (1-14) (human); SFLLRNPND-KYEPF) H-Ser-Phe-Leu-Leu-Arg-Asn-Pro-Asn-Asp-Lys-Tyr-Glu-Pro-Phe-OH **Trifluoroacetate salt**	**H-8105**	Cloning and expression of a functional human thrombin receptor have revealed a protein with seven transmembrane domains and a large extracellular amino-terminal extension. Thrombin cleaves within this extension, thereby creating a new receptor amino-terminus that functions as a tethered ligand and activates the receptor. A 14-amino acid peptide mimicking this new amino-terminus has been found to be a potent thrombin receptor activator as well as an effective agonist for platelet activation. Solubility: at least 1 mg/ml in water with agitation $C_{81}H_{118}N_{20}O_{23}$ M_r: 1739.95 [137339-65-2] net	[39,47, 48]
TRAP-14 amide (Proteinase Activated Receptor 1 (1-14) amide (human); PAR-1 (1-14) amide (human); Thrombin Receptor (1-14) amide (human); Coagulation Factor II Receptor (1-14) amide (human); SFLLRNPNDKYEPFamide) H-Ser-Phe-Leu-Leu-Arg-Asn-Pro-Asn-Asp-Lys-Tyr-Glu-Pro-Phe-NH_2 **Trifluoroacetate salt**	**H-6032**	TRAP-14 amide has been shown to inhibit monocyte spreading on fibronectin-coated slides. The rapidly induced withdrawal of pseudopodial processes and rounding of the cells is accompanied by nitric oxide and endothelin-1 release. Spreading might be inhibited by autocrine endothelin-1 release and subsequent endothelin B receptor-dependent nitric oxide production. Solubility: at least 1 mg/ml in water with agitation $C_{81}H_{119}N_{21}O_{22}$ M_r: 1738.96 [141923-36-6] net	[49]

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The cover shows a ribbon diagram of the GpIba-Thrombin Complex.

John J. Dumas, Ravindra Kumar, Jasbir Seehra, William S. Somers and Lidia Mosyak;
Crystal Structure of the GpIba-Thrombin Complex Essential for Platelet Aggregation. Science **301**, 222 (2003).

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Published by
Bachem AG
Hauptstrasse 144
4416 Bubendorf
Switzerland

Date November 2006

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