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Thrombin Receptor (PAR-1) Antagonists. Solid-Phase Synthesis of Indole-Based Peptide Mimetics by Anchoring to a Secondary Amide

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Abstract—A novel, 10-step, solid-phase method, based on a secondary amide linker, was developed to construct a diverse library of indole-based SFLLR peptide mimetics as thrombin receptor (protease-activated receptor 1, PAR-1) antagonists. The key steps include stepwise reductive alkylation, urea formation, and Mannich reaction. Screening of the library led to a quick development of the SAR and the significant improvement of PAR-1 activity.

Thrombin receptors are attractive drug discovery targets because they mediate a variety of cellular actions of thrombin, such as platelet aggregation, lymphocyte mitosis, monocyte chemotaxis, and endothelial cell proliferation.[1] The first example of a thrombin receptor (protease-activated receptor 1, PAR-1) was cloned in 1991 and identified as a member of the superfamily of seven-transmembrane, G-protein-coupled receptors.[2] Thrombin activates PAR-1 by proteolytically cleaving the N-terminal extracellular domain between Arg-41 and Ser-42 to reveal a new N-terminus containing the activation motif SFLLRN, which serves as a 'tethered' peptide ligand. Three closely related protease-activated receptors, PAR-2,[3] PAR-3,[4] and PAR-4,[5] have also been cloned and each possesses a unique agonist peptide epitope. Since PAR-1 mediates many cellular actions of thrombin, a PAR-1 antagonist may have therapeutic potential for treating various disorders, such as thrombosis, restenosis, atherosclerosis, inflammation, cancer metastasis, and stroke.[1,6]

Despite the extensive structure–function data for PAR-1 agonist peptides related to SFLLRN,[7] the identification of potent and selective PAR-1 antagonists has proved to be very challenging. This situation is partially due to the unfavorable entropy for an external ligand to compete with a tethered ligand. Of the PAR-1 antagonists reported,[7b,8,9] several have notable deficiencies,[7b,8] such as weak potency, inability to inhibit thrombin-induced platelet aggregation consistently, mixed agonist-antagonist activity, and/or lack of PAR selectivity. Through a de novo design approach, we discovered a series of novel indole-based SFLLR peptide mimetics as potent and selective PAR-1 antagonists.[9] The prototype of this series, RWJ-53052 (**1**), inhibited both thrombin- and SFLLRN-NH_2-induced human platelet aggregation ($IC_{50} = 2.3$ and $0.27\,\mu M$, respectively) and bound to PAR-1 with an IC_{50} of $2.2\,\mu M$. Compound **1** was prepared via a convergent solution-phase method in nine steps (23% overall yield) from 6-nitroindole and appropriate Fmoc-protected amino acids.[9] We have developed parallel solid-phase methods for the synthesis of analogues of **1**, which proved to be much more efficient than the solution-phase method. This approach allowed us to rapidly explore the SAR and optimize the potency of the series. Herein, we report our solid-phase method that is based on a secondary amide anchor, which led to the rapid construction of a highly diverse library of analogues and the identification of RWJ-56110 (**34**) as a potent and selective PAR-1 antagonist.[9]

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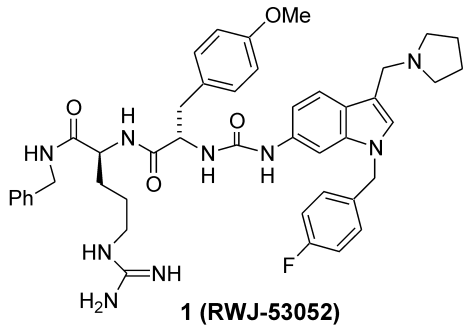


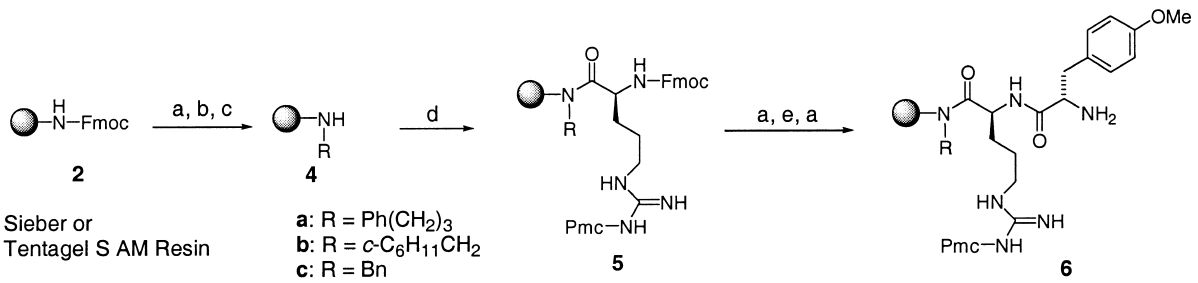
1 (RWJ-53052)

Considering the structural features of RWJ-53052, the guanidine moiety, originally believed to be important for PAR-1 activity, appears to be an appropriate point for resin attachment. However, there was no resin available at the time for anchoring the guanidine group.[10] The only other group suitable for resin attachment is the terminal amide. Thus, we attempted to attach this secondary amide NH to an amide-type resin and then construct a dipeptide segment, followed by introducing the indole scaffold. Rink amide-type resins have been widely used as an amide linker for the solid-phase synthesis of small organic molecules, for example, in the construction of indoles.[11] However, application of this resin for anchoring a secondary amide, such as in **1**, has been limited due to steric hindrance. Thus, we used the Sieber amide resin, in which the amino group is less sterically hindered than in Rink amide-type resins. The *N*-arylalkyl or *N*-alkyl group at the C-terminus was introduced via a stepwise reductive alkylation process.[12] Sieber resin **2** (0.37 mmol/g, Novabiochem) was deprotected with 20% piperidine in DMF and then treated with excess of hydrocinnamaldehyde (**3a**) in DMF/HOAc (100:1) to form an imine (Scheme 1). The excess of aldehyde was washed out before adding the reducing agent $NaBH_4$ to avoid formation of dialkylated product. The resulting resin-bound hindered secondary amine, **4a**, was successfully coupled with Fmoc-Arg(Pmc)-OH (Pmc, 2,2,5,7,8-pentamethylchroman-6-sulfonyl) by using HATU [*O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and HOAt (1-hydroxy-7-azabenzotriazole). Fmoc-echo analysis (at 290 nm)[12] of the coupled product **5** [R = $Ph(CH_2)_3$] indicated a good loading level of 0.28 mmol/g. Deprotection of the Fmoc group in **5** with piperidine was followed by coupling reaction with Fmoc-Tyr(Me)-OH in the presence of HBTU [*O*-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and HOBt, and then deprotection again with piperidine to afford **6**.

With the resin-bound dipeptide amine **6** in hand, we started to investigate the incorporation of the indole template via a urea linkage, one of the key steps in the whole synthetic process. 6-Aminoindole intermediate **8** was prepared from **7**[9] via Mannich reaction under standard solution-phase conditions followed by nitro reduction (Scheme 2). The urea formation between resin **6** [R = $Ph(CH_2)_3$] and 6-aminoindole **8** was attempted by using a reported procedure.[13] Thus, resin **6** was treated with *p*-nitrophenyl chloroformate in THF/CH_2Cl_2 in the presence of *i*-Pr_2NEt to form a carbamate intermediate and then coupled with amine **8** at 23 °C. Unfortunately, analysis of cleaved product (with TFA) from an aliquot of resin indicated that no indole was incorporated into the molecule; instead, the MS (ES^+) of the product was consistent with a dipeptide isocyanate ($NH^+ = 761$). Reasoning that an isocyanate should react with indole amine **8** at elevated temperature to form a urea bond, the reaction temperature was increased. However, after stirring at 95 °C, no change was observed by TLC and MS. Further analysis revealed that the product was peptide hydantoin **10** instead of a dipeptide isocyanate (Scheme 3).

To avoid undesired hydantoin **10**, dipeptide **6** must be removed from exposure to *p*-nitrophenyl chloroformate. Therefore, we attempted to generate the *p*-nitrophenyl carbamate intermediate with indole amine **8**. Disappointingly, treatment of **8** with *p*-nitrophenyl chloroformate caused the decomposition of Mannich base of **8**. To overcome this problem, indole amine **9**, prepared from **7** via nitro reduction, was used and an effort was made to introduce the Mannich base on the solid phase after urea formation. Thus, the urea was produced by treating **9** with 0.83 equiv of *p*-nitrophenyl chloroformate in the presence of *i*-Pr_2NEt at −20 °C for 5 min and then coupled with resin-bound dipeptide amine **6** (0.24 equiv). The reaction mixture was allowed to warm to 23 °C and then stirred for 3 h. TLC and MS analysis on the cleaved material indicated that the desired urea **11** was the major product along with a small amount of peptide hydantoin **10** (less than 10%).

Our initial test of the Mannich reaction on resin **11** turned out to be problematic. Under the common Mannich conditions used in solution phase (pyrrolidine/



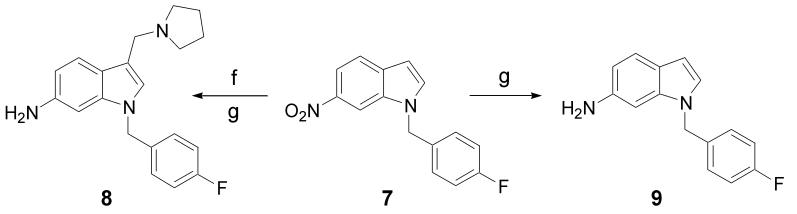
2 Sieber or Tentagel S AM Resin

4 **a**: R = $Ph(CH_2)_3$ **b**: R = *c*-$C_6H_{11}CH_2$ **c**: R = Bn

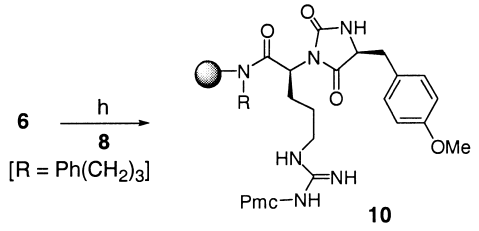
5

6

Scheme 1. (a) Piperidine, DMF; (b) aldehyde (**3**), DMF/HOAc (100:1, for Sieber resin), or $CH(OMe)_3$ (for Tentagel S AM resin); (c) $NaBH_4$, DMF/MeOH (10:3, for Sieber resin), or $NaB(OAc)_3H$, $ClCH_2CH_2Cl$/HOAc (100:1, for Tentagel S AM resin); (d) Fmoc-Arg(Pmc)-OH, HATU, HOAt, *i*-Pr_2NEt, DMF; (e) Fmoc-Tyr(Me)-OH, HBTU, HOBt, *i*-Pr_2NEt, DMF.



Scheme 2. (f) Pyrrolidine, HCHO, HOAc; (g) Me_2NNH_2, $FeCl_3 \cdot 6H_2O$, charcoal, MeOH, reflux.



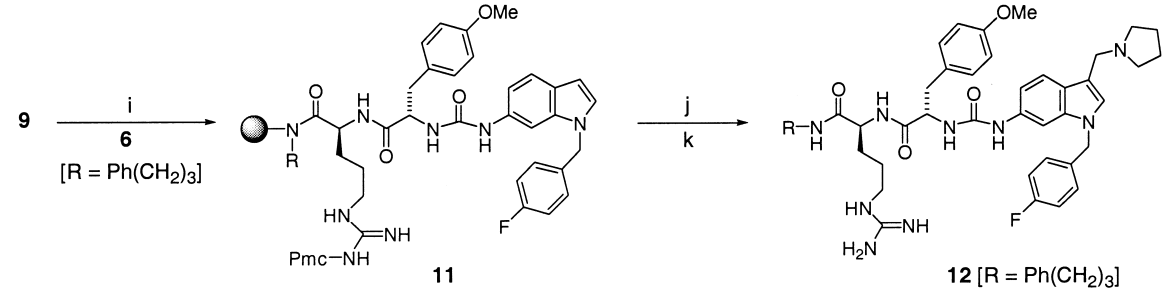
Scheme 3. (h) *p*-$NO_2C_6H_4OCOCl$, *i*-Pr_2NEt, THF/CH_2Cl_2.

HCHO/HOAc), the reaction of **11** was very sluggish, even at elevated temperature (80 °C). Reaction condition studies led to identification of 1,4-dioxane/HOAc (4:1) as co-solvent which allowed the Mannich reaction of resin **11** to proceed smoothly at 25–50 °C (Scheme 4). One-pot Pmc deprotection and resin cleavage was conducted by using TFA/*i*-Pr_3SiH/1,2-ethanedithiol/H_2O (90:1:4.5:4.5) at 23 °C. The resulting crude cleaved product was triturated with Et_2O to afford the desired product **12** [R = $Ph(CH_2)_3$] in 37% overall yield (based on the loading level of resin **4a**) and about 80% purity by reverse-phase HPLC.

We then tested the reaction (**2**→**4**, Scheme 1) by using other aldehydes. Stepwise reductive alkylation of the Sieber resin with cyclohexanecarboxaldehyde (**3b**) was as effective as with **3a** to give resin **4b**. However, the chemistry was less successful when benzaldehyde (**3c**) was used, where reductive alkylation of the Sieber resin was incomplete under various reaction conditions. Tentagel S AM resin was then identified to be a better anchor for introducing a benzyl group. Thus, Tentagel S AM resin (0.23 mmol/g, Rapp Polymere) was treated with benzaldehyde in trimethylorthoformate[14] overnight and then the excess of aldehyde was removed by washing. The resulting imine was treated immediately with $NaB(OAc)_3H$ in $ClCH_2CH_2Cl$/HOAc to afford resin **4c**. Coupling of **4c** with Fmoc-Arg(Pmc)-OH in the presence of HATU and HOAt proceeded smoothly as seen with **4a** and **4b** to give resin **5** (R = Bn) with a good loading level of 0.20 mmol/g, as determined by Fmoc-echo at 290 nm.[12]

By using resins **4a**–**c** and subsequent parallel solid-phase chemistry, as described above,[15] we constructed a library of indole-based peptide mimetics bearing diverse substituents around the indole scaffold (R, R^1, R^2, R^3, A^1 and A^2, Table 1). Over 200 individual analogues have been prepared. Typically, the products displayed 75–85% purity as determined by reverse-phase HPLC and this purity was sufficient for biological evaluation and SAR interpretation. Representative compounds were purified and retested and their activities were consistent with those of the crude products.

Compounds prepared via the solid-phase methods were tested for inhibition of platelet aggregation induced by thrombin, SFLLRN-NH_2, collagen, and U46619 (thromboxane mimetic). We also examined their competitive binding versus [^{3}H]-*S*-(*p*-F-Phe)-homoarginine-L-homoarginine-KY-NH_2 to PAR-1 on the membranes of CHRF-288-11 cells.[9] The representative compounds with their in vitro biological data are presented in Table 1. Replacement of benzyl of R in **1** with 3-phenylpropyl (**12**) or cyclohexylmethyl (**18**) resulted in a 2- to 4-fold decrease of potency against thrombin-induced gel-filtered platelet aggregation, though similar binding affinities to PAR-1 were observed for all three compounds.[16] Substitution of 4-F of R^1 with 2-Cl (**13**), 2-Me (**15** and **28**) or 2,6-diCl (**26**) led to more potent analogues. However, a larger group, such as CO_2Me (**22**) or OCF_3 (**23** and **24**), could not be tolerated at the 4-position. Pyrrolidine (R^2R^3N) was generally preferred over piperidine (**17** and **19**), diethylamine (**16** and **20**) or azetidine (**25**). A further improvement of potency was achieved by substituting Tyr(Me) of A^1 in **26** with 3,4-diF-Phe (**31**). We also replaced the guanidine moiety in **31** with a primary amine (**32**). This guanidine group was

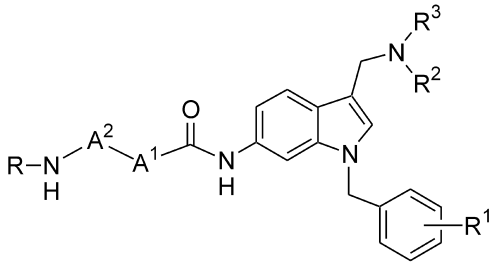


Scheme 4. (i) *p*-$NO_2C_6H_4OCOCl$, *i*-Pr_2NEt, CH_2Cl_2; (j) pyrrolidine, HCHO, 1,4-dioxane/HOAc (4:1); (k) TFA/*i*-Pr_3SiH/$HSCH_2CH_2SH$/H_2O (90:1:4.5:4.5).

originally believed to be important for PAR-1 activity[17] but caused undesirable cardiovascular effects in an anesthetized guinea pig hemodynamic model. The Orn analogue **32** was equally potent as **31** in thrombin- and SFLLRN-NH_2-induced gel-filtered platelet aggregation, as well as PAR-1 binding assays, and showed an improved cardiovascular hemodynamic profile over **31**. However, **32** showed a decreased selectivity over collagen. Systematic changes of the aminoalkyl side chain length in **32** led to **34** (RWJ-56110), a potent and selective PAR-1 antagonist.[9] Given the successful replacement of the guanidine with a primary amine, a trityl resin-based solid-phase method was then developed for the further synthesis of RWJ-56110 analogues.[9] Modification of the indole template of RWJ-56110 to an indazole resulted in RWJ-58259,[18] a second-generation, indazole-based PAR-1 antagonist, which serves as a suitable agent for in vivo assessment of the therapeutic potential of PAR-1 antagonists.

We have developed a novel, efficient secondary amide-linked resin-based solid-phase method for construction of a diverse library of indole-based peptide mimetics as PAR-1 antagonists. Screening of the library led to a quick development of the SAR of this peptide mimetic series, a significant improvement in potency over the prototype RWJ-53052, and the identification of RWJ-56110 as a potent and selective PAR-1 antagonist.

Table 1. Platelet aggregation and PAR-1 binding IC_{50} values (μM)[a]



Compd	R^1	R^2R^3N	A^1	A^2	R	Gel-filtered platelet aggregation[b]				Binding[c]
						Thrombin	SFLLRN-NH_2	Collagen	U46619	
1	4-F	$(CH_2)_4N$	Tyr(Me)	Arg	Bn	2.32 + 0.11	0.27 ± 0.01	IA	IA	2.2 ± 0.5
12	4-F	$(CH_2)_4N$	Tyr(Me)	Arg	Php[d]	8.5 ± 1.3	0.6 ± 0.2	16.1 ± 2.5	21.4 ± 5.6	1.3
13	2-Cl	$(CH_2)_4N$	Tyr(Me)	Arg	Php	2.6	0.14	12.0	44.4	0.38
14	3-Me	Et_2N	Tyr(Me)	Arg	Php	1.3	0.21	10.2	IA	2.6
15	2-Me	$(CH_2)_4N$	Tyr(Me)	Arg	Php	1.0	0.20	11.9	44.2	1.0
16	2-Me	Et_2N	Tyr(Me)	Arg	Php	3.0	0.23	17.0	IA	2.5
17	2-Me	$(CH_2)_5N$	Tyr(Me)	Arg	Php	4.8	0.31	13.0	IA	0.73
18	4-F	$(CH_2)_4N$	Tyr(Me)	Arg	Chm[e]	4.4	0.64	37.6 ± 22.6	12.5	2.6
19	4-F	$(CH_2)_5N$	Tyr(Me)	Arg	Chm	23.8 ± 6.8	1.0 ± 0.1	26.1 ± 10.9	26.2 ± 15.7	2.3
20	4-F	Et_2N	Tyr(Me)	Arg	Chm	11.1 ± 4.7	0.9 ± 0.4	25.8 ± 7.6	39.5 ± 13.6	3.1
21	3-Me	$(CH_2)_5N$	Tyr(Me)	Arg	Chm	11.7 ± 5.0	0.9 ± 0.4	27.5 ± 7.8	36.3 ± 11.2	3.2
22	4-CO_2Me	$(CH_2)_4N$	Tyr(Me)	Arg	Chm	38.7	IA	IA	IA	3.5
23	4-OCF_3	$(CH_2)_4N$	Tyr(Me)	Arg	Chm	40.3 ± 10.3	4.8 ± 0.5	40.4 ± 19.1	33.0 ± 7.7	2.5
24	4-OCF_3	$(CH_2)_5N$	Tyr(Me)	Arg	Chm	36.5 ± 10.6	6.4 ± 0.5	33.1 ± 13.9	43.5 ± 23.7	5.6
25	4-F	$(CH_2)_3N$	Tyr(Me)	Arg	Bn	9.7	0.4 ± 0.2	IA	IA	3.3
26	2,6-diCl	$(CH_2)_4N$	Tyr(Me)	Arg	Bn	0.90 ± 0.34	0.30 ± 0.09	46.3 ± 28.6	IA	1.3 ± 0.00
27	4-F	$(CH_2)_4N$	4-NO_2-Phe	Arg	Bn	6.1	0.13	16.5	IA	1.1
28	2-Me	$(CH_2)_4N$	4-NO_2-Phe	Arg	Bn	1.3	0.15	20.6	IA	0.8
29	2-Me	$(CH_2)_4N$	4-CN-Phe	Arg	Bn	0.62	0.6 ± 0.5	25.9	IA	6.4
30	2,6-diCl	$(CH_2)_4N$	4-CN-Phe	Arg	Bn	0.48	0.07	IA	IA	5.3
31	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Arg	Bn	0.57 ± 0.21	0.18 ± 0.21	IA	IA	0.82 ± 0.34
32	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Orn[f]	Bn	0.6 ± 0.2	0.1 ± 0.05	15.7 ± 9.9	IA	0.5 ± 0.3
33	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Lys	Bn	0.7 ± 0.3	0.1 ± 0.02	21.3	41.9	0.3 ± 0.00
34	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Dbu[g]	Bn	0.34 ± 0.04	0.16 ± 0.05	IA	IA	0.44 ± 0.21
35	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Dpr[h]	Bn	0.9 ± 0.2	0.5 ± 0.3	36.9	IA	0.92
36	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	His	Bn	0.46	0.2 ± 0.01	34.0	IA	1.3
37	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Cit[i]	Bn	1.9	0.3 ± 0.1	IA	IA	0.24
38	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Gln	Bn	7.9 ± 7.4	2.0 ± 1.8	IA	IA	1.8
39	2,6-diCl	$(CH_2)_4N$	3,4-DiF-Phe	Met	Bn	10.7 ± 10.1	0.4 ± 0.1	IA	IA	11.2

[a]Results are expressed as mean ± SEM ($n \geq 2$; $n = 1$ for values without error limits). IA denotes inactivity @ 50 μM of test compound.
[b]Concentrations of agonists for aggregation studies: α-thrombin, 0.15 nM; SFLLRN-NH_2, 2 μM; collagen, 3 μg/mL; U46619, 0.3 μM.
[c]Thrombin receptor (PAR-1) binding assay; ligand: [^{3}H]-*S*-(*p*-F-Phe)-homoarginine-L-homoarginine-KY-NH_2, 10 nM (K_d = 15 nM).
[d]Php, 3-phenylpropyl.
[e]Chm, cyclohexylmethyl.
[f]Orn, ornithine.
[g]Dbu, 2,4-diaminobutyric acid.
[h]Dpr, 2,3-diaminopropionic acid.
[i]Cit, citrulline.

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15. Other 6-aminoindole intermediates with different R^1 groups were prepared in the same way as was **9**, from 6-nitroindole.
16. For some compounds in Table 1, inconsistencies were observed between receptor binding and functional activity in platelet aggregation. The reason for this is not yet understood. However, other laboratories have observed similar inconsistencies with their PAR-1 antagonists.[8b,f]
17. Representative guanidine-containing PAR-1 antagonists from our series, including **1**, **14**, and **31** in this paper, were tested in a chromogenic assay for thrombin inhibition and showed no activity at 100 μM, thereby excluding a direct enzyme-based mechanism of inhibition.
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