2-(3-Pyridyl)thiazolidine-4-carboxamide Derivatives. II.[1] Structure–Activity Relationships and Active Configuration of 2-(3-Pyridyl)thiazolidine-4-carboxamides as Platelet-Activating Factor Receptor Antagonists

Takeshi SUZUKI,* Hitoshi NAGAOKA,[2] Yutaka KONDO, Takumi TAKAHASHI, Makoto TAKEUCHI, Hiromu HARA, Munetoshi SAITO, Toshimitsu YAMADA, Kenichi TOMIOKA, Mamoru HAMADA, and Toshiyasu MASE

Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd., 21 Miyukigaoka, Tsukuba, Ibaraki 305–8585, Japan. Received March 27, 1998; accepted May 29, 1998

Conversion of the 2-(3-pyridyl)thiazolidine part of 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidine-4-carbonyl]piperazine (YM461), which is a potent platelet-activating factor (PAF) antagonist, to other rings was performed, and PAF antagonistic activities evaluated. The 2-(3-pyridyl)thiazolidine skeleton, which exists as a mixture of *cis* and *trans* diastereomers, played an important role in the potency of PAF antagonism. In this study, new effective skeletons were not uncovered, however, 2-(4-pyridyl)thiazolidine-4-carboxamides (1n and 1z) showed potent PAF antagonistic activities equal to the 3-pyridyl derivatives. From the results obtained for 1a, 1a(*S*), 1g and 1i, a *cis*-(2*R*,4*R*)-2-(3-pyridyl)thiazolidine-4-carboxamide was assumed to be the active configuration for PAF antagonism.

Key words 2-(3-pyridyl)thiazolidine-4-carboxamide; platelet-activating factor; antagonist; YM461; YM264

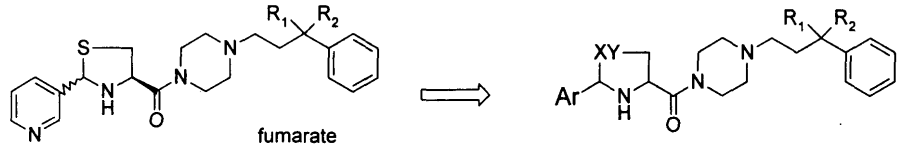
Platelet-activating factor (PAF) is an ether-linked phospholipid mediator that is released from a variety of cell types, including neutrophils, eosinophils, macrophages, platelets and endothelial cells.[3] PAF has a broad spectrum of biological actions, such as induction of platelet aggregation, increase in vascular permeability, bronchoconstriction, systemic hypotension, and cardiac and renal dysfunction.[4—8] Because of its various actions, PAF has been suggested to play an important role in the pathogenesis of asthma, shock, glomerulonephritis and other diseases,[9] and the development of PAF antagonists is thus expected to lead to methods for prevention and therapy of these diseases.

In our previous paper,[1] we reported that 2-(3-pyridyl)thiazolidine-4-carboxamides, and especially 1-(3-phenylpropyl)-4-[2-(3-pyridyl)thiazolidine-4-carbonyl]piperazine (**1a**, YM-461)[10] and 1-(3-methyl-3-phenylbutyl)-4-[2-(3-pyridyl)thiazolidine-4-carbonyl]piperazine (**1y**, YM264),[11] had potent PAF antagonistic activities.

In this work, we paid attention to the role of 2-(3-pyridyl)thiazolidine as a core skeleton, and converted it into other rings, keeping the side chain of YM461, and evaluated PAF antagonistic activities. Because 2-(3-pyridyl)thiazolidines existed as *cis* and *trans* diastereomers, the isomerization effect was examined in several solvents using YM264. In this paper, we discuss the structure–activity relationships of compounds **1**, the isomerization of YM264, and the active configuration of 2-(3-pyridyl)thiazolidine-4-carboxamides as PAF antagonists.

Synthesis 2-Arylthiazolidine-4-carboxamides (**1**) were synthesized as described in Chart 2. As a general procedure, thiazolidinecarboxylic acids (**4**), prepared from the corresponding aldehydes (**2**) and L-cysteine or homocysteine (**3**), were coupled with amine to afford compounds **1**. Other synthetic methods are shown as follows. The *cis* and *trans* isomers (**7**(*c*) and **7**(*t*)) were obtained by chromatographic separation of the isomeric mixture prepared by cyclization of bromoacetylpyridine (**5**) with L-cysteine ester and subsequent reduction. Thiazolinecarboxylic acid (**4j**) was obtained from nitrile (**8**) and L-cysteine (**9**) in refluxing EtOH. 2-Pyrrolinecarboxamide (**1k**) was obtained from 1-pyrrolinecarboxylic acid (**4k**)[12] and amine accompanied by rearrangement of the double bond, and then selectively hydrogenated to the *cis* pyrrolidine (**1g**(*c*)). The *trans* isomer (**1g**(*t*)) was isolated from the isomeric mixture prepared by reduction of **1k** with sodium cyanoborohydride. Direct isomerization of **1g**(*c*) to **1g**(*t*) using potassium *tert*-butoxide in toluene was not successful, and instead the oxidized pyrrole (**1l**), was obtained in good yield. Oxazolidine (**1f**) was obtained from aminoalcohol (**10**) and pyridine-3-aldehyde.

Pharmacological Activities and Discussion PAF antagonistic activities were measured by the inhibition of PAF-induced platelet aggregation using rabbit platelet-rich plasma



1a (YM461): $R_1 = R_2 = H$
1y (YM264): $R_1 = R_2 = CH_3$

Chart 1

* To whom correspondence should be addressed.

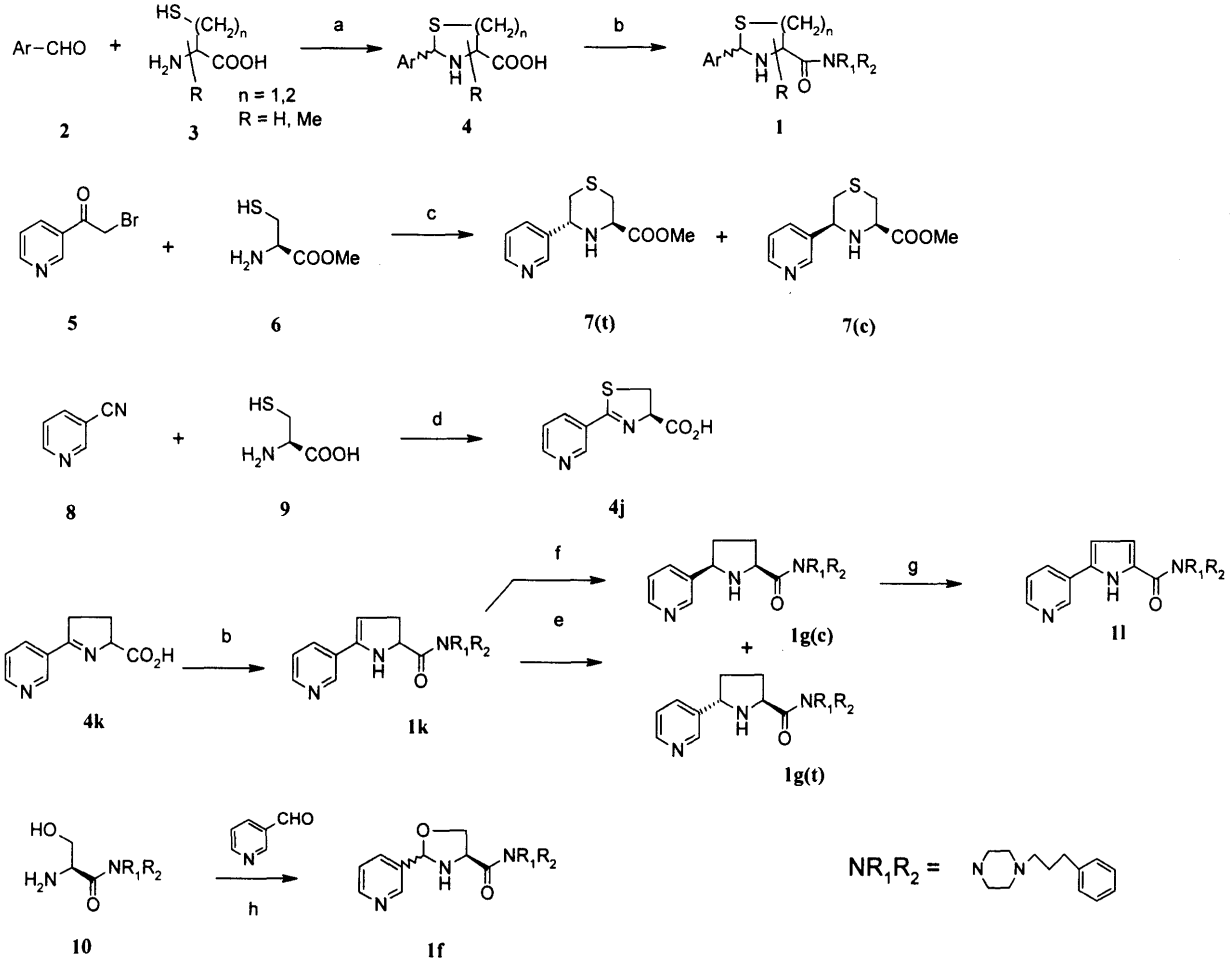


Chart 2

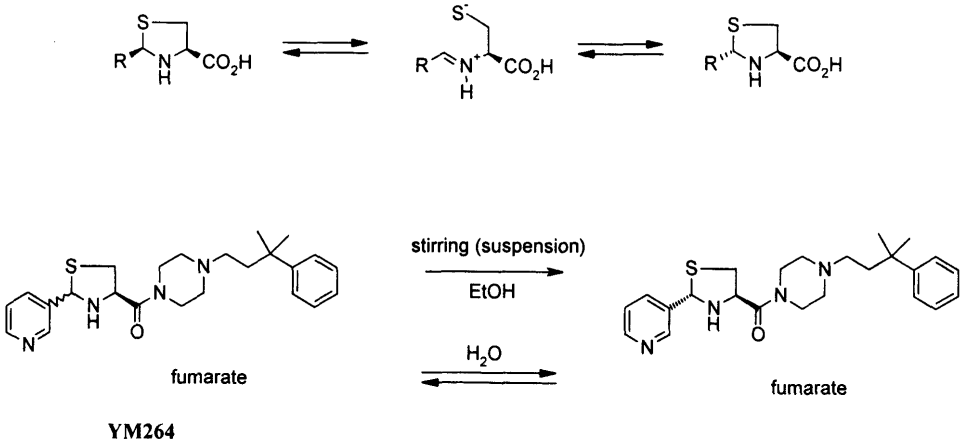
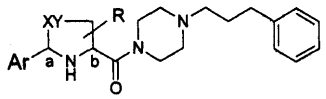


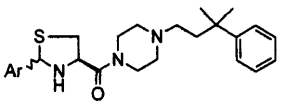
Chart 3

(PRP) and the activities are expressed as IC_{50} values (μM).

YM461 (**1a**, *R* isomer at the 4-position of the thiazolidine) was one of the most potent PAF antagonists, however, the *S* isomer (**1a**(*S*)) did not have any activity. In order to investigate the role of 2-(3-pyridyl)thiazolidine as a core skeleton, initially, the effect of the thiazolidine ring of **1a** was examined. 3-Formylthiazolidine (**1d**) was devoid of activity, and methylthiazolidine at the 2-,3-, or 5-positions (**1b**, **1c**, and **1e**) also reduced activities to about one fiftieth compared with **1a**. Oxazolidine (**1f**) had greatly reduced activity. The pyrrolidines (**1g**(*c*) and **1g**(*t*)) also had reduced activities, however the *cis* isomer **1g**(*c*) showed about eight times more potent activity than the *trans* isomer **1g**(*t*). Thiazine (**1h**) having a 6-membered ring showed only very weak activity compared with **1a**. Thiomorpholines (**1i**(*c*) and **1i**(*t*)) also had reduced activities, but the *cis* isomer **1i**(*c*) tended to be more

Table 1. PAF-Antagonist Activities of 4-(3-Phenylpropyl)piperazine-1-yl Derivatives



Compd. No.	Ar	XY	R	Configuration (a, b)	Platelet aggregation inhibition IC_{50} (μM)
1a (YM461)	3-Pyridyl	S	H	(*RS*, *R*)	0.071
1a(*S*)[a]	3-Pyridyl	S	H	(*RS*, *S*)	70% inhibn. at 100 μM
1b	3-Pyridyl	S	2-CH_3	(*RS*, *R*)	22
1c	3-Pyridyl	S	3-CH_3	(*RS*, *R*)	4.7
1d	3-Pyridyl	S	3-CHO	(*RS*, *R*)	>100
1e	3-Pyridyl	S	5,5-DiCH_3	(*RS*, *R*)	3.1
1f	3-Pyridyl	O	H	(*RS*, *S*)[b]	60
1g(*t*)	3-Pyridyl	CH_2	H	(*S*, *S*)+(*R*, *R*)	62
1g(*c*)	3-Pyridyl	CH_2	H	(*R*, *S*)+(*S*, *R*)	7.6
1h	3-Pyridyl	SCH_2	H	(*RS*, *RS*)	70
1i(*t*)	3-Pyridyl	CH_2S	H	(*R*, *R*)	46
1i(*c*)	3-Pyridyl	CH_2S	H	(*S*, *R*)	19
1j	3-Pyridyl			(—, *R*)	75
1k	3-Pyridyl			(—, *RS*)	>100
1l	3-Pyridyl			—	>100
1m	2-Pyridyl	S	H	(*RS*, *R*)	22
1n	4-Pyridyl	S	H	(*RS*, *R*)	0.18
1o	6-Me-3-pyridyl	S	H	(*RS*, *R*)	1.5
1p	2-Me-3-pyridyl	S	H	(*RS*, *R*)	0.12
1q	Phenyl	S	H	(*RS*, *R*)	>100
1r	3- Me_2N-phenyl	S	H	(*RS*, *R*)	>100
1s	3-Quinolyl	S	H	(*RS*, *R*)	8.8
1t	3-Thienyl	S	H	(*RS*, *R*)	78
1u	3-Furyl	S	H	(*RS*, *R*)	>100
1v	1-Me-3-pyrrolyl	S	H	(*RS*, *R*)	>100
1w	2-Pyrazinyl	S	H	(*RS*, *R*)	1.9
1x	3-Piperidyl	S	H	(*RS*, *R*)	90
1y (YM264)	3-Pyridyl			(*RS*, *R*)	0.030
1z	4-Pyridyl			(*RS*, *R*)	0.036

a) **1a**(*S*) means *S* isomer at (b) of **1a**. *b*) In the case of oxazolidine, the same conformation as thiazolidine was expressed as the *S* configuration.

Table 2. Preparation of *trans*-Rich YM264[a]

Entry	Temperature	Time (d)	Amount of *trans* isomer (%)[b]
1	r.t.	1	86.6
2	40 °C	1	90.7
3	r.t.	14	94.3
4	40 °C	6	95.0

a) A suspension of YM264 in 20 volumes of EtOH was stirred and precipitates collected by filtration. *b*) The ratio was determined by HPLC (measuring conditions: column, nucleosil 100-5, 4.6 mm×30 cm; eluent, *n*-Hexane:CH_2Cl_2 : MeOH : Et_3N (70 : 30 : 2 : 0.2); temperature, 0 °C; flow rate, 1.0 ml/min; monitored by UV absorption (260 nm)).

Table 3. Isomerization Rate of YM264 in Various Solvents[a]

Entry	Solvent	Amount of *trans* isomer (%)[b]				
		0 min[c]	0 min	20 min	40 min	60 min
1	H_2O (pH 3.0)[d]	95	79	59	59	59
2	H_2O (pH 6.5)[d]	95	48	48	48	48
3	EtOH	95	92	80	73	60
4	AcOH	95	86	57	57	57
5	2% $Et_3N \cdot CH_2Cl_2$	95.0	94.5	93.6	93.3	92.5

a) The compound was dissolved at a 1 mg/ml concentration. *b*) Measuring conditions as described in Table 2. *c*) Ratio before dissolution. *d*) Baritton–Robinson Buffer.

potent than the *trans* isomer **1i**(*t*), as with **1g**. Compounds **1j**, **1k**, and **1l** having an sp^2 carbon at the position of the pyridine substituent almost completely lost activity.

Next, we focused on substituent effects at the pyridine moiety of **1a**. First, to investigate the substitution position, 4-pyridyl derivatives (**1n**, **1z**) retained activities, comparable to **1a** and **1y**, and **1z** was one of the most potent compounds, whereas 2-pyridyl derivative (**1m**) was weaker. Second, to study the nature of the substituents, 2-methylpyridine (**1p**) retained activity, which was ten times more potent than 6-

Table 4. Physicochemical Data for 4-(3-Phenylpropyl)piperazin-1-yl Derivatives

Compd. No.	Salt	mp (°C)	MS *m/z*	^{1}H-NMR (DMSO-d_6)
1b	3HCl	129	129	1.88 and 1.96 (3H, s), 1.68—2.28 (2H, m), 2.44—2.80 (2H, m), 2.88—4.64 (13H, m), 7.12—7.48 (6H, m), 7.96—8.18 (1H, m), 8.64—9.04 (2H, m)
1c	3HCl	130	410	1.88—2.24 (2H, m), 2.36 and 2.52 (3H, s), 2.56—2.78 (2H, m), 2.78—4.60 (13H, m), 5.58 and 5.82 (1H, s), 7.08—7.44 (6H, m), 7.86—8.20 (1H, m), 8.58—9.02 (2H, m)
1d	—	Oil	424	1.65—1.98 (2H, m), 2.25—2.85 (8H, m), 3.05—3.40 (2H, m), 3.60—3.90 (4H, m), 5.05—5.70 (1H, m), 6.14 and 6.40 (1H, s), 7.00—7.50 (5H, m), 7.65—7.90 (1H, m), 8.24 (1H, s), 8.40—8.80 (3H, m)/($CDCl_3$)
1e	3HCl	136	424	1.22—1.80 (6H, m), 1.92—2.28 (1H, m), 2.44—2.80 (2H, m), 2.84—4.88 (11H, m), 6.00—6.18 (1H, m), 7.12—7.48 (5H, m), 7.92—8.12 (1H, m), 8.52—8.72 (1H, m), 8.78—9.04 (2H, m)
1f	—	Oil	380	1.60—2.05 (2H, m), 2.20—2.85 (8H, m), 3.30—4.40 (8H, m), 5.40 and 6.00 (1H, s), 7.05—7.50 (6H, m), 7.75—8.15 (1H, m), 8.50—9.00 (2H, m)/($CDCl_3$)
1g(*t*)	—	Oil	378	1.50—2.90 (15H, m), 3.40—3.80 (4H, m), 3.95—4.30 (2H, m), 7.00—7.45 (6H, m), 7.95 (1H, dt, *J*=2, 8 Hz), 8.50 (1H, dd, *J*=2, 5 Hz), 8.75 (1H, d, *J*=2 Hz)/($CDCl_3$)
1g(*c*)	3HCl	164	378	1.56—2.88 (15H, m), 3.43—3.90 (4H, m), 3.99—4.34 (2H, m), 7.04—7.44 (6H, m), 7.91 (1H, dt, *J*=2, 8 Hz), 8.53 (1H, dd, *J*=2, 5 Hz), 8.65 (1H, d, *J*=2 Hz)/(free form in $CDCl_3$)
1h	—	Oil	410	1.51—1.92 (4H, m), 2.20—2.81 (8H, m), 2.80—3.65 (6H, m), 3.95—4.20 (1H, m), 5.62 (1H, s), 6.66 (2H, s), 7.15—7.58 (6H, m), 7.58—8.05 (1H, m), 8.42—8.83 (2H, m)/($CDCl_3$)
1i(*t*)	—	Oil	410	1.60—2.00 (2H, m), 2.00—2.85 (10H, m), 2.92 (2H, d, *J*=4 Hz), 3.20—3.80 (4H, m), 3.95 (1H, dd, *J*=4, 8 Hz), 5.68 (1H, t, *J*=4 Hz), 6.90–7.44 (6H, m), 7.80 (1H, dt, *J*=2, 8 Hz), 8.47 (1H, dd, *J*=2, 5 Hz), 8.72 (1H, d, *J*=2 Hz)/($CDCl_3$)
1i(*c*)	—	Oil	410	1.60—2.00 (2H, m), 2.00—3.00 (12H, m), 3.40—3.75 (4H, m), 3.90—4.25 (2H, m), 6.95—7.40 (6H, m), 7.69 (1H, dt, *J*=2, 8 Hz), 8.49 (1H, dd, *J*=2, 5 Hz), 8.57 (1H, d, *J*=2 Hz)/($CDCl_3$)
1j	2HCl	114	394	1.90—2.30 (2H, m), 2.45—2.80 (2H, m), 2.80—4.15 (12H, m), 5.75—6.05 (1H, m), 7.10—7.25 (5H, m), 7.70—7.95 (1H, m), 8.35—8.40 (1H, m), 8.90 (1H, dd, *J*=2, 5 Hz), 9.10 (1H, d, *J*=2 Hz)
1k	3HCl	158	376	1.67—2.08 (2H, m), 2.08—2.93 (9H, m), 2.93—3.28 (2H, m), 3.30—4.32 (3H, m), 5.00—5.33 (1H, m), 7.05—7.52 (6H, m), 8.19 (1H, dt, *J*=2, 8 Hz), 8.69 (1H, dd, *J*=5, 8 Hz), 9.05 (1H, dd, *J*=2, 2 Hz)/(free form in $CDCl_3$)
1l	—	Oil	374	1.78—1.99 (2H, m), 2.19—2.99 (8H, m), 3.84 (4H, t, *J*=5 Hz), 6.59 (2H, s), 6.98—7.40 (6H, m), 7.85 (1H, dt, *J*=2, 8 Hz), 8.45 (1H, dd, *J*=2, 5 Hz), 8.85 (1H, d, *J*=2 Hz)/($CDCl_3$)
1m	Fumarate	70	396	1.55—2.00 (2H, m), 2.25—2.80 (8H, m), 2.90—3.40 (2H, m), 3.50—3.80 (4H, m), 3.85—4.15 (1H, m), 5.68 (0.7H, d, *J*=12 Hz), 5.80 (0.3H, br), 7.05—7.45 (6H, m), 7.55—7.80 (1H, m), 8.50—8.70 (1H, m)
1n	Fumarate	164	396	1.65—1.90 (2H, m), 2.20—2.70 (8H, m), 2.75—2.95 (1H, m), 3.20—3.40 (1H, m), 3.40—3.70 (4H, m), 4.15—4.30 (1H, m), 5.56 and 5.92 (1H, s), 6.65 (2H, s), 7.10—7.55 (7H, m), 8.40—8.50 (2H, m)
1o	Fumarate	88	410	1.52—1.96 (2H, m), 2.12—2.74 (11H, m), 2.83—3.77 (9H, m), 4.26 (1H, q, *J*=7 Hz), 5.52 and 5.80 (1H, s), 6.63 (2H, s), 7.00—7.40 (6H, m), 7.60—7.89 (1H, m), 8.41—8.60 (1H, m)
1p	3HCl	138	410	1.90—2.30 (2H, m), 2.85 and 2.92 (3H, s), 2.45—3.90 (14H, m), 4.10—4.70 (1H, m), 5.97 and 6.22 (1H, s), 7.15—7.50 (5H, m), 7.80—8.10 (1H, m), 8.60—8.90 (2H, m)
1q	Fumarate	69	395	1.50—2.00 (2H, m), 2.25—2.75 (8H, m), 2.90—3.80 (6H, m), 3.95—4.15 (1H, m), 5.60 (0.7H, d, *J*=12 Hz), 5.96 (0.3H, br), 7.00—7.60 (10H, m)
1r	3HCl	136	438	1.90—2.30 (2H, m), 2.10 and 2.12 (6H, s), 2.45—2.80 (4H, m), 2.80—4.05 (10H, m), 4.05—4.65 (1H, m), 5.84 and 5.97 (1H, s), 7.10—7.40 (5H, m), 7.40—7.70 (3H, m), 7.75—8.05 (1H, m)
1s	Fumarate	85	446	1.60—1.90 (2H, m), 2.30—2.55 (6H, m), 2.55—2.75 (2H, m), 2.92—3.80 (6H, m), 3.9—4.30 (1H, m), 5.80 (0.7H, d, *J*=16 Hz), 6.17 (0.3H, d, *J*=8 Hz), 7.10—7.35 (5H, m), 7.50—7.90 (3H, m), 8.00—8.40 (2H, m), 8.95—9.10 (1H, m)
1t	Fumarate	152 (dec.)	401	1.55—2.10 (2H, m), 2.25-2.80 (8H, m), 2.80—3.80 (6H, m), 3.90—4.30 (1H, m), 5.64 and 5.90 (1H, s), 7.00—7.45 (8H, m)/(free form in $CDCl_3$)
1u	Fumarate	173	385	1.65—2.05 (2H, m), 2.25—2.75 (8H, m), 2.75—3.45 (2H, m), 3.45—3.80 (4H, m), 4.05—4.20 (1H, m), 5.45 and 5.67 (1H, s), 6.45—6.76 (1H, m), 6.65 (2H, s), 7.10—7.45 (5H, m), 7.55—7.85 (2H, m)
1v	2HCl	125	398	1.90—2.30 (2H, m), 2.35—2.80 (2H, m), 2.80—4.00 (15H, m), 4.10—4.60 (1H, m), 5.65 and 5.82 (1H, s), 6.20—6.40 (1H, m), 6.70—6.85 (1H, m), 6.90—7.50 (6H, m)
1w	—	Oil	397	1.60—2.00 (2H, m), 2.25—2.80 (8H, m), 3.05—3.45 (2H, m), 3.50—4.00 (4H, m), 4.05—4.25 (1H, m), 5.67 and 5.80 (1H, s), 7.10—7.35 (5H, m), 8.60—8.85 (3H, m)/($CDCl_3$)
1x	3HCl	174	402	1.60—2.25 (6H, m), 2.40—2.80 (2H, m), 2.90—4.80 (17H, m), 7.15—7.40 (5H, m)
1z	Fumarate	138	424	1.32 (6H, s), 1.70—1.90 (2H, m), 2.10—2.20 (2H, m), 2.25—2.50 (4H, m), 2.80—3.80 (6H, m), 3.85—4.10 (1H, m), 5.56 (0.4H, d, *J*=15 Hz), 5.92 (0.6H, d, *J*=8 Hz), 7.15–7.50 (7H, m), 8.50–8.68 (2H, m)

methylpyridine (**1o**). Amongst the other ring derivatives, designed to have heteroatoms at the β position from the thiazolidine substituent, pyrazine (**1w**) and quinoline (**1s**) had moderate activity, but other ring derivatives (**1q**, **1r**, **1t**, **1u**, **1v**, and **1x**) lost all activity.

Modifications of the 2-(3-pyridyl)thiazolidine part did not show any improvements, and it was concluded that the steric environment formed by 2-(3-pyridyl)thiazolidine was very

important for PAF antagonism, and that this part was sensitively affected by substituents or ring systems. Also it was suggested that there were some interaction sites on the PAF receptor at the *meta* or *para* direction of the pyridine substituent.

It is well-known that diastereomers at the 2-position of thiazolidines equilibrate by the mechanism shown in Chart 3.[13] In order to consider the active configuration of 2-(3-pyridyl)thiazolidine-4-carboxamides, the isomeric effect was examined by using YM264.

In a stirring suspension of EtOH, YM264 (fumarate) partially dissolved in and then crystallized into the more stable *trans* isomer, and 95% *trans*-rich YM264 was obtained after 6 d at 40 °C. Next, the isomerization rate of this *trans*-rich YM264 was examined. In protic solvents like H_2O and AcOH, isomerizaiton was very rapid and reached an equilibrium state instantly. In EtOH, it was also completed within 1 h. Whereas it was slow in aprotic solvents like CH_2Cl_2 and the ratio decreased only 3% in 1 h. These results indicated that isomerization of YM264 was accelerated by protonation and it was thus difficult to know the active configuration of 2-(3-pyridyl)thiazolidine-4-carboxamide directly from the results of pharmacological activities, even if a pure *cis* or *trans* isomer was obtained. Therefore, considering the results of **1g** and **1i**, the less stable *cis* isomer was assumed to be the active configuration in 2-(3-pyridyl)thiazolidine-4-carboxamides.

In conclusion, modifications of the 2-(3-pyridyl)thiazolidine part of YM461 and an isomerization study were performed. The 2-(3-pyridyl)thiazolidine skeleton, which existed as a mixture of diastereomers, was very important for potency of PAF antagonism, and *cis*-(2*R*,4*R*)-2-(3-pyridyl)-thiazolidine-4-carboxamide was assumed to be the active configuration for these PAF antagonists.

Experimental

Melting points were recorded on a Yanaco MP-3 melting point apparatus and are uncorrected. ^{1}H-NMR were measured with a JEOL FX-90Q, FX-100 or GSX-400 spectrometer with tetramethylsilane as an internal standard. Mass spectra were determined on an MS-5970 or JEOL JMS-DX300 mass spectrometer. Column chromatography was carried out on silica gel (Wakogel C-200).

Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. In general, organic extract was dried over Na_2SO_4 or $MgSO_4$ and the solvent was evaporated under reduced pressure. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry Ar.

General Procedure for (4*R*)-2-Arylthiazolidine-4-carboxylic Acids (4) A solution of arylaldehyde (5 mmol) in EtOH (12 ml) was added portionwise to a solution of L-cysteine (5 mmol) in H_2O (7 ml) and the reaction mixture was stirred overnight. The precipitates were collected by filtration to afford **4** (70—90%).

General Procedure for Preparation of 1-(2-Arylthiazolidin-4-ylcarbonyl)-4-(3-phenylpropyl)piperazines (1) A mixture of carboxylic acid (**4**) (1 mmol), DCC (1 mmol), HOBT (1 mmol), and 1-(3-phenylpropyl)-piperazine (1 mmol) in THF (10 ml) was stirred overnight at room temperature. The reaction mixture was diluted with AcOEt, and insoluble materials removed by filtration. The filtrate was washed with aqueous $NaHCO_3$ and brine, dried and concentrated. The residue was purified by column chromatography on SiO_2 eluting with $CHCl_3$–MeOH to afford **1**.

(3*R*,5*R*)- and (3*S*, 5*R*)-5-(3-Pyridyl)thiomorpholine-3-carboxylic Acid Methyl Ester (7(*t*) and 7(*c*)) A solution of 3-bromoacetylpyridine hydrobromide (28.1 g, 100 mmol) and L-cysteine methyl ester hydrochloride (17.2 g, 100 mmol) in H_2O (100 ml) was stirred at room temperature. After 4 h, pyridine (25 ml) and sodium borohydride (3.80 g) were added to the mixture, followed by stirring overnight. The mixture was diluted with H_2O (500 ml) and extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated. The residue was chromatographed on SiO_2 eluting with *n*-hexane–AcOEt (2 : 1) to afford *trans* isomer **7**(*t*) as a white solid (4.90 g, 21%, less polar compound) and *cis* isomer **7**(*c*) as a white solid (4.70 g, 20%). **7**(*t*): mp 98—101 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (1H, dd, J= 3, 13 Hz), 2.78 (1H, dd, J=11, 13 Hz), 3.00—3.20 (2H, m), 3.83 (3H, s), 4.04 (2H, t, J=4 Hz), 4.34 (1H, dd, J=3, 11 Hz), 7.27 (1H, dd, J=5, 8 Hz), 7.75 (1H, dt, J=2, 8 Hz), 8.53 (1H, dd, J=2, 5 Hz), 8.65 (1H, d, J=2 Hz). **7**(*c*): mp 135—138 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (1H, dd, J=3, 13 Hz), 2.77 (1H, dd, J=10, 13 Hz), 2.80—2.95 (2H, m), 3.76 (3H, s), 3.70—3.92 (2H, m), 4.70 (1H, dd, J=3, 10 Hz), 7.28 (1H, dd, J=5, 8 Hz), 7.77 (1H, dt, J=2, 8 Hz), 8.58 (1H, dd, J=2, 5 Hz), 8.61 (1H, d, J=2 Hz).

2-(3-Pyridyl)-3,4-dihydrothiazole-4-carboxylic Acid (4j) A mixture of **8** (4.16 g, 40 mmol) and L-cysteine (4.84 g, 40 mmol) in EtOH (50 ml) was refluxed for 6 h. The mixture was concentrated, and the residue diluted with aqueous NaOH and washed with AcOEt. The water layer was adjusted to pH 2 with 1N HCl and the precipitates collected by filtration to afford **4j** as a white solid (7.54 g, 91%). ^{1}H-NMR (DMSO-d_6) δ: 2.80—2.90 (2H, m), 5.37 (1H, t, J=9 Hz), 7.56 (2H, dt, J=5, 8 Hz), 8.18 (1H, dt, J=2, 8 Hz), 8.76 (1H, dd, J=2, 5 Hz), 8.95 (1H, d, J=2 Hz). FAB-MS (Pos.) *m/z*: 209 (M^++1).

***cis*-1-(3-Phenylpropyl)-4-[2-(3-pyridyl)pyrrolidine-5-carbonyl]piperazine (1g(*c*))** A solution of **1k** (320 mg, 1.7 mmol) in EtOH (10 ml) was hydrogenated over platinum oxide (100 mg) at room temperature for 7 h. After removing catalyst, the mixture was concentrated and the residue chromatographed on SiO_2 eluting with $CHCl_3$–MeOH–aq. NH_3 (10 : 1 : 0.1) to afford **1g**(*c*) as an oil (150 mg, 47%).

***trans*-1-(3-Phenylpropyl)-4-[2-(3-pyridyl)pyrrolidin-4-ylcarbonyl]-piperazine (1g(*t*))** Sodium cyanoborohydride (50 mg) was added to a solution of **1k** (114 mg, 0.6 mmol) in 3 ml of THF–MeOH–1 N HCl (10 : 10 : 1) at room temperature, and the mixture was stirred for 1 h. The mixture was quenched with 1 N HCl and made alkaline with K_2CO_3. The mixture was then extracted with $CHCl_3$. The organic extract was washed with brine, dried and concentrated. The residue was chromatographed on SiO_2 eluting with $CHCl_3$–MeOH–aq. NH_3 (10 : 1 : 0.1) to afford **1g**(*t*) as an oil (45 mg, 39%, less polar compound) and **1g**(*c*) as an oil (50 mg, 44%).

1-(3-Phenylpropyl)-4-[2-(3-pyridyl)oxazolidine-4-carbonyl]piperazine (1f) A solution of **10** (800 mg, 2.6 mmol), pyridine-3-aldehyde (340 mg, 3.2 mmol), and *p*-toluenesulfonic acid (10 mg) in benzene (35 ml) was refluxed for 8 h azeotropically. After cooling, the mixture was diluted with AcOEt. The extract was washed with saturated $NaHCO_3$, H_2O, and brine successively, dried and concentrated. The residue was chromatographed on SiO_2 eluting with $CHCl_3$–MeOH (10 : 1) to afford **1f** as an oil (500 mg, 50%).

PAF-Induced Platelet Aggregation Rabbit PRP were obtained by centrifugation at 270×***g*** for 10 min. The platelet concentrations were adjusted with platelet-poor plasma to 5×10^8 cells/ml for rabbit. Platelet aggregation was measured by the method of Born[14] using a Hema Tracer VI (Niko Bioscience, Tokyo, Japan). Various concentrations of the test compounds were added to the PRP 2 min prior to the addition of PAF (10 nM for rabbit). All experiments were carried out within 4 h following blood collection to avoid a decrease in the sensitivity of the platelets to the aggregation agent.

Acknowledgements We are indebted to Drs. K. Murase, M. Takeda, H. Ino, and G. Kon for helpful discussions, and the staff of the Measurement Division Laboratories for the measurement of NMR and mass spectra, and for elemental analyses. We also thank T. Hanazato and M. Akiho for the biological results.

References and Notes

1) Nagaoka H., Hara H., Suzuki T., Takahashi T., Takauchi M., Matsuhisa A., Saito M., Yamada T., Tomioka K., Mase T., *Chem. Pharm. Bull.*, **45**, 1659—1664 (1997).
2) Deceased, July 22, 1996.
3) *a*) Page C. P., "Asthma: Basic Mechanisms and Clinical Management," ed. by Barns P. J., Rodger I. W., Thomson N. C., Academic Press, London, 1988, pp. 283—304; *b*) Pinckard R. N., Lundwig J. C., McManus L. M., "Inflammation: Basic Principles and Clinical Correlates," ed. by Gallin J. I., Goldstein I. M., Snyderman R., Raven Press, New York, 1988, pp. 139—167; *c*) Cooper K., Parry M., "Annual Reports in Medicinal Chemistry," Vol. 24, ed. by Allen R. C., Academic Press, New York, 1989, pp. 81—90, and references therein; *d*) Hosford D., Braquet P., "Progress in Medicinal Chemistry," Vol. 27, ed. by Ellis G. P., West G. B., Elsevier Amsterdam, 1990, pp. 325—380.
4) Benveniste J., Le Couedic J. P., Kamoun P., *Lancet*, i, 344—345

(1975).
5) O'Flaherty J. T., Wykle R. L., Miller C. H., Lewis J. C., Waite M., Bass D. A., McCall C. E., DeChatelet L. O., *Am. J. Pathol.*, **103**, 70—79 (1981).
6) Vargaftig B. B., Lefort J., Chignard M., Benveniste J., *Eur. J. Pharmacol.*, **65**, 185—192 (1980).
7) Blank M. L., Snyder F., Beyers W., Brooks B., Muirhead D. E., *Biochem. Biophys. Res. Commun.*, **90**, 1194—1200 (1979).
8) Vemulapalli S., Chin P. J. S., Barnett A., *Hypertension*, **6**, 489—493 (1984).
9) Vargaftig B. B., Benveniste J., *Trends Pharmacol. Sci.*, **4**, 341—343 (1983).
10) *a*) Tomioka K., Garrido R., Ahmed A., Stevenson S. S., Abraham W. M., *Eur. J. Pharmacol.*, **170**, 209—215 (1989); *b*) Yamada T., Saito M., Mase T., Hara H., Nagaoka H., Murase K., Tomioka K., *Lipids*, **26**, 1179—1183 (1991).
11) *a*) Yamada T., Tomioka K., Horie M., Mase T., Hara H., Nagaoka H., *Arch. Int. Pharmacodyn. Therapie*, **308**, 123—136 (1990); *b*) Yamada T., Tomioka K., Horie M., Sakurai Y., Nagaoka H., Mase T., *Biochem. Biophys. Res. Commun.*, **176**, 781—785 (1991).
12) *a*) Hellmann H., Dieterich D., *Justus Liebigs Ann. Chem.*, **656**, 53—63 (1962); *idem*, *ibid.*, **672**, 97—102 (1964); *b*) *Idem*, *Angew. Chem.*, **74**, 78 (1962).
13) *a*) Fife T. H., Natarajan R., Shen C. C., Bembi R., *J. Am. Chem. Soc.*, **113**, 3071—3079 (1991); *b*) Györgydeák Z., Kajtár-Peredy M., Kajtár J., Kajtár M., *Justus Liebigs Ann. Chem.*, **1987**, 927—934; *c*) Sheppard G. S., Pireh D., Carrera G. M., Bures M. G., Heyman H. R., Steinman D. H., Davidsen S. K., Phillips J. G., Guinn D. E., May P. D., Conway R. G., Rhein D. A., Calhoun W. C., Albert D. H., Magoc T. J., Carter G. W., Summer J. B., *J. Med. Chem.*, **37**, 2011—2032 (1994); *d*) Györgydeák Z., Szilágyi L., Kajtár J., Argay G., Kálmán A., *Monatsch. Chem.*, **125**, 189—208 (1994).
14) Born G. V. R., *J. Physiol.* (London), **162**, 67—68 (1962).