Synthesis and Structure–Activity Relationships of Antiallergic *N*-[4-[4-(1*H*-Indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanamides Possessing Both Antihistaminic and Anti Slow-Reacting Substance (SRS) Activities

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A series of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanamide derivatives were synthesized and tested for *in vivo* antianaphylactic activity and *in vitro* anti slow-reacting substance (SRS) activity. Among the compounds synthesized, *N*-[4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]propanamide (7) was the best balanced compound (antianaphylactic activity, $ED_{50}=0.92$ mg/kg *p.o.*; anti-SRS activity, $IC_{50}=0.89$ μg/ml). Regarding the biological activities of 7, we ascribe the antianaphylactic activity to its potent antihistaminic activity and the anti SRS activity to the inhibition of 5-lipoxygenase.

Keywords antianaphylactic activity; anti-slow-reacting substance activity; *N*-(2-thiazoyl)alkanamide; 4-(3-indolyl)piperidine; structure–activity relationship

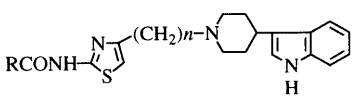
Slow-reacting substance (SRS), a mixture of leukotrienes C_4, D_4 and E_4, has been implicated in the pathology of a variety of inflammatory and allergic diseases.[1] It is well documented that SRS causes bronchoconstriction,[2] mucus production[3] and edema[4] in experimental animals and humans, and these are the principal pathophysiological characteristics of asthma. Histamine is also an important chemical mediator in the complex set of allergic responses. Some agents having potent antihistaminic activity, *e.g.*, ketotifen[5] and oxatomide,[6] are useful for the treatment of allergic diseases.

In our previous paper[7] we reported that *N*-[4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]methanesulfonamide (**1**, FK613) had potent antianaphylactic activity based mainly on its antihistaminic activity, with only negligible side effects on the central nervous system. As a continuation of our program to search for more effective antiallergic agents, we next focused on discovering an agent with dual inhibitory activities against histamine and SRS. In the hope of obtaining such a compound, compound **1** and related compounds were reevaluated for anti-SRS activity. Consequently, *N*-[4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]acetamide (**2**) was found to possess significant dual activities. We thus modified **2** to obtain a series of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanamides (**3**—**19**) as shown in Fig. 1, and tested them for pharmacological activities. Among them, *N*-[4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]propanamide (**7**) was found to have the best balance of antianaphylactic and anti-SRS activities.

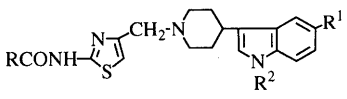
In this paper we describe the synthesis and structure–activity relationships of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanamides, as well as the pharmacological properties of **7**, which was selected for further evaluation.

Synthesis

In our previous paper,[7] compounds **2**—**5** and **17** were synthesized as key intermediates. Here, new compounds **6**—**8**, **11**—**16**, and **18** were prepared (method A in Chart 1). 4-Chloromethyl-2-thiazolamine hydrochloride (**20**)[8] was acylated with the appropriate acid chlorides or acid anhydrides to produce *N*-(4-chloromethyl-2-thiazolyl)alkanamides (**21a**—**h**), which were then condensed with indolylpiperidines (**22a**—**d**) in the presence of $NaHCO_3$ to afford the desired compounds. Compounds **9** and **10** were obtained by treating 4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolamine (**24**)[7] with the appropriate acid chlorides in the presence of triethylamine (method B). Compound **19** was prepared by reduction of **18** with iron



2–14

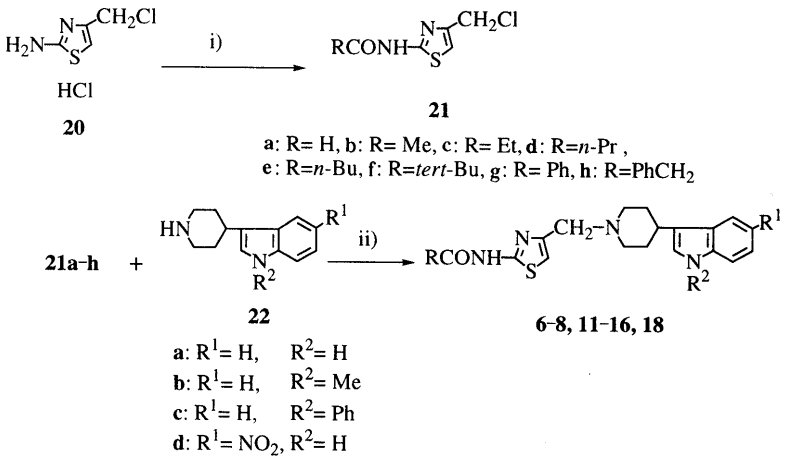


15–19

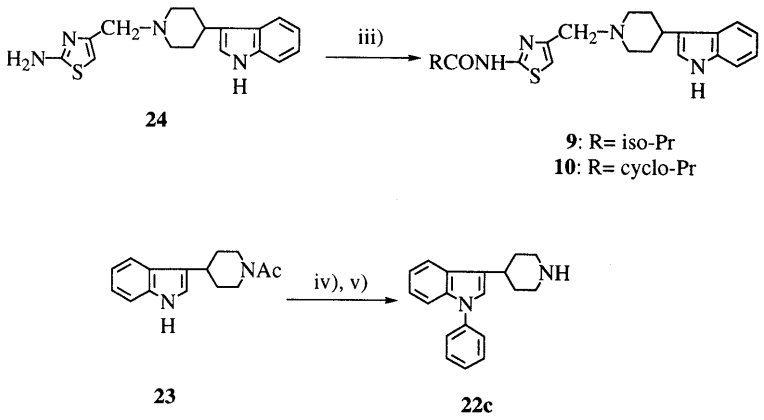
2: R= Me, *n*=1 **8**: R= *n*-Pr, *n*=1 **15**: R= Me, R^1= H, R^2= Me
3: R= Me, *n*=2 **9**: R= iso-Pr, *n*=1 **16**: R= Me, R^1= H, R^2= Ph
4: R= Me, *n*=3 **10**: R= cyclo-Pr, *n*=1 **17**: R= Me, R^1= OMe, R^2= H
5: R= Me, *n*=5 **11**: R= *n*-Bu, *n*=1 **18**: R= Et, R^1= NO_2, R^2= H
6: R= H, *n*=1 **12**: R= *tert*-Bu, *n*=1 **19**: R= Et, R^1= NH_2, R^2= H
7: R= Et, *n*=1 **13**: R= Ph, *n*=1
14: R= $PhCH_2$, *n*=1

Fig. 1

method A



method B



i) $(RCO)_2O$ or RCOCl/pyridine ii) $NaHCO_3$/DMF iii) RCOCl/ Et_3N
iv) PhBr, K_2CO_3, CuO/DMF v) aq. NaOH/EtOH

Chart 1

powder in the presence of ammonium chloride.

1-Phenyl-3-(4-piperidino)-1*H*-indole (**22c**), which was used for the preparation of compound **16**, was synthesized by the coupling reaction of 1-[4-(1*H*-indol-3-yl)-piperidino]ethanone (**23**)[9] with bromobenzene under Ullmann's conditions, followed by hydrolysis with aqueous alkaline solution.

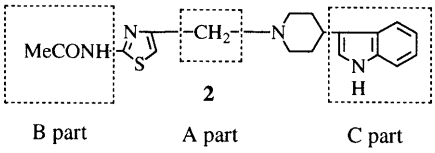


Fig. 2

Structure–Activity Relationships and Discussion

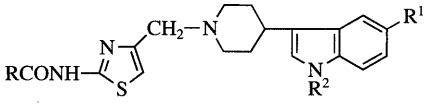
All of the compounds synthesized were evaluated for ability to inhibit systemic anaphylaxis induced by egg albumin in guinea pigs (*in vivo* assay) as well as the synthesis or release of SRS by calcium ionophore (A23187) in rat neutrophils (*in vitro* assay). In the systemic anaphylaxis assay, each compound was administered orally to guinea pigs 30 min prior to the antigen challenge, and protection from anaphylatic dyspnea was assessed in terms of the survival ratio. The pharmacological results are shown in Tables II—IV (ED_{50} or IC_{50} values).

In order to elucidate the structural requirement for both activities, compound **2** was divided into three parts, A, B, and C (Fig. 2), and each part was systematically modified.

The effect of methylene chain length (A part) was initially examined. As shown in Table II, higher anti-anaphylactic activity was observed with compounds **3** ($n=2$) and **4** ($n=3$). Further lengthening of the methylene chain (compound **5**) caused a slight decrease in the activity. This trend was consistent with our previous observations in the corresponding methanesulfonamidothiazole derivatives.[7] Contrary to this trend, the anti-SRS activity was most potent with compound **2** ($n=1$), and lengthening of the methylene chain ($n=2$ and 3) resulted in a marked decrease of activity although the activity was partially restored with compound **5** ($n=5$).

Subsequently the acyl moiety on the aminothiazole (B

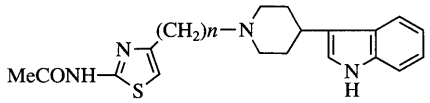
TABLE I. *N*-[4-[4-(1-*H*-Indol-3-yl)piperidinomethyl]-2-thiazolyl]alkanamide Derivatives



	R^1	R^2	R	Yield (%)	mp (°C)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (DMSO-d_6, δ; J=Hz)
6	H	H	H	21.8	217—221 (A)	$C_{18}H_{20}N_4OS$	63.51 (63.54	5.92 5.78	16.46 16.31)	1.50—3.80 (9H, m), 3.51 (2H, s), 6.80—7.70 (6H, m), 8.45 (1H, s), 10.70 (1H, br s), 12.13 (1H, br s)
7	H	H	Et	70.7	194—195 (A)	$C_{20}H_{24}N_4OS$	65.19 (65.56	6.56 6.62	15.20 15.29)	1.07 (3H, t, J=7.2 Hz), 1.20—3.80 (13H, m), 6.80—7.70 (6H, m), 10.66 (1H, br s), 12.05 (1H, br s)
8	H	H	*n*-Pr	71.0	163—165 (A)	$C_{21}H_{26}N_4OS$ ·EtOH	64.45 (64.19	7.52 7.54	13.07 13.07)	0.90 (3H, t, J=7.5 Hz), 2.45 (2H, q, J=7.5 Hz), 1.40—3.70 (9H, m), 3.53 (2H, s), 6.92 (1H, s), 6.90—7.70 (5H, m), 10.71 (1H, s), 12.05 (1H, br s)
9	H	H	iso-Pr	36.8	183—187 (A)	$C_{21}H_{26}N_4OS$ ·1/2EtOH	65.16 (65.31	7.21 7.15	13.81 13.75)	1.14 (6H, d, J=7.8 Hz), 1.20—3.70 (12H, m), 6.80—7.70 (6H, m), 10.75 (1H, br s), 12.05 (1H, br s)
10	H	H	cyclo-Pr	79.4	120—132 (B)	$C_{21}H_{24}N_4OS$ ·H_2O	63.29 (63.44	6.58 6.86	14.06 14.00)	0.60—1.30 (4H, m), 1.50—3.70 (10H, m), 3.57 (2H, s), 6.80—7.80 (6H, m), 10.90 (1H, s), 12.27 (1H, br s)
11	H	H	*n*-Bu	53.5	142—144 (A)	$C_{22}H_{28}N_4OS$ ·EtOH	65.13 (64.60	7.74 7.56	12.66 12.63)	0.80—3.70 (18H, m), 3.55 (2H, s), 6.92 (1H, s), 6.90—7.70 (5H, m), 10.73 (1H, s), 12.05 (1H, br s)
12	H	H	*tert*-Bu	38.9	93—96 (A)	$C_{22}H_{28}N_4OS$ ·EtOH	65.13 (65.11	7.74 7.77	12.66 12.60)	1.33 (9H, s), 1.50—3.40 (9H, m), 3.56 (2H, s), 6.73 (1H, s), 6.90—7.80 (5H, m), 8.10 (1H, br s), 9.00 (1H, br s)[b]
13	H	H	Ph	37.6	104—106 (A)	$C_{24}H_{24}N_4OS$ ·EtOH	67.51 (67.70	6.45 6.42	12.11 12.13)	1.40—3.30 (9H, m), 3.37 (2H, s), 6.78 (1H, s), 6.90—8.40 (12H, m)[b]
14	H	H	$PhCH_2$	57.2	190—191 (A)	$C_{24}H_{26}N_4OS$	69.74 (69.48	6.09 5.93	13.01 13.16)	3.52 (2H, s), 3.74 (2H, s), 6.92 (1H, s), 7.31 (1H, s), 6.90—7.70 (5H, m), 10.71 (1H, s), 12.33 (1H, s)
15	H	Me	Me	14.5	176—177 (A)	$C_{20}H_{24}N_4OS$	65.19 (65.24	6.56 6.22	15.20 15.08)	1.50—3.70 (9H, m), 2.16 (3H, s), 3.55 (2H, s), 3.74 (3H, s), 6.80—7.80 (6H, m)
16	H	Ph	Me	19.4	185—187 (C)	$C_{25}H_{26}N_4OS$	69.74 (69.78	6.09 5.92	13.01 12.72)	1.60—3.30 (9H, m), 2.23 (3H, s), 3.59 (2H, s), 6.77 (1H, s), 7.09 (1H, s), 7.45 (5H, s), 7.00—7.80 (4H, m), 10.00 (1H, br s)
18	NO_2	H	Et	44.4	222—224 (A)	$C_{20}H_{23}N_5O_3S$ ·1/5EtOH	57.97 (57.78	5.73 5.49	16.57 16.38)	1.10 (3H, t, J=7.5 Hz), 1.40—3.50 (9H, m), 2.43 (2H, q, J=7.5 Hz), 3.50 (2H, s), 6.85 (1H, s), 7.30—8.50 (4H, m), 11.48 (1H, br s), 11.91 (1H, br s)
19	NH_2	H	Et	71.3	115—118 (A)	$C_{20}H_{25}N_5OS$ ·EtOH	61.51 (61.63	7.27 6.86	16.30 15.98)	1.05 (3H, t, J=7.0 Hz), 1.30—3.60 (9H, m), 2.41 (2H, q, J=7.0 Hz), 3.50 (2H, s), 4.30 (2H, br s), 6.30—7.00 (5H, m), 10.10 (1H, br s), 11.88 (1H, br s)

a) Recrystallization solvent: A, EtOH; B, MeCN; C, $(Me)_2CO$. *b*) $CDCl_3$ as a solvent.

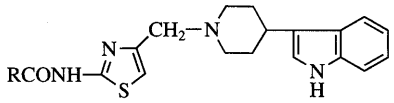
TABLE II. Modification of Methylene Chain Length (A Part)



	n	Antianaphylactic activity ED_{50}=mg/kg *p.o.*	Anti-SRS activity IC_{50}=μg/ml
2	1	0.95	8.3
3	2	0.30	21%[a]
4	3	0.26	17%[a]
5	5	0.77	14.0

a) Inhibition at 100 μg/ml.

TABLE III. Modification of Acyl Moiety on the Aminothiazole (B Part)

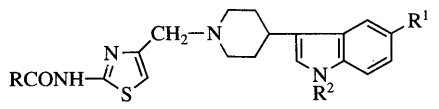


	R	Antianaphylactic activity ED_{50}=mg/kg *p.o.*	Anti-SRS activity IC_{50}=μg/ml
2	Me	0.95	8.3
6	H	2.5	25
7	Et	0.92	0.89
8	*n*-Pr	2.2	0.18
9	iso-Pr	3.4	0.75
10	cyclo-Pr	3.4	0.077
11	*n*-Bu	>10	7.9
12	*tert*-Bu	>10	8.9
13	Ph	>10	4%[b]
14	$PhCH_2$	>10	55
24	[a]	3.0	61

a) 2-Aminothiazole derivative. *b*) Inhibition at 100 μg/ml.

part) was examined. In this study, the A part was kept as a methylene group, because the above results indicated that this length (n=1) is the best in exerting well-balanced activities in both assays. Several aliphatic acyl groups consisting of one to five carbon atoms (**6**—**12**) and aromatic acyl groups such as benzoyl (**13**) and benzylcarbonyl (**14**) were introduced into this part. As shown in Table III, acetyl (**2**) and propionyl (**7**) afforded the most potent antianaphylactic activity, whereas formyl (**6**), butyryl (**8**), isobutyryl (**9**), and cyclopropylcarbonyl (**10**) were 2- or 3-fold less potent in this assay than **2**. Introduction of a longer (**11**) or bulkier (**12**) acyl group

TABLE IV. Effect of Introduction of Substituents on the Indole Ring Nucleus



	R	R^1	R^2	Antianaphylactic activity ED_{50}=mg/kg *p.o.*	Anti-SRS activity IC_{50}=μg/ml
15	Me	H	Me	>10	3.9
16	Me	H	Ph	>10	11
17	Me	OMe	H	>10	31
18	Et	NO_2	H	>10	0.22
19	Et	NH_2	H	>10	2.8

or an aromatic acyl group (**13**, **14**) resulted in a great loss of activity. In addition, the unsubstituted aminothiazole derivative **24** was active, albeit with slightly reduced potency in comparison with **2**. With regard to the anti-SRS activity, potent activity was observed with compounds **7**—**10**. Among these compounds, **10** having a cyclopropyl carbonyl group, exhibited the most potent activity with IC_{50}=77 ng/ml. This finding is noteworthy in view of its unique structure, which is different from those of the anti-SRS agents so far reported, phenidone,[10] AA-861,[11] and TMK-777.[12] The unsubstituted compound **24**, and the formyl (**6**) or aromatic acyl (**13**, **14**) derivatives showed much lower activity. These results suggest that the acyl group has a size limitation above which it is impossible to elicit potent anti-SRS activity.

Finally, the influence of a substituent on the indole nucleus (C part) was examined. The results are shown in Table IV. All of the compounds synthesized were devoid of antianaphylactic activity, suggesting that the nitrogen atom and at least the 5-position of the indole nucleus should be unsubstituted. In contrast, the anti-SRS activity was largely unchanged, within a factor of two or three, when compared to that of the corresponding **2** or **7**.

The structure–activity relationships of compound **2** and related compounds can be summarized as follows: 1) the antianaphylactic activity was maximum with a methylene chain length of two or three, whereas the maximum anti-SRS activity was observed when the methylene chain length was one; 2) introduction of an acyl group of appropriate size on the aminothiazole moiety was critical for increasing both activities, when the methylene chain length was fixed at one; 3) introduction of a substituent on the indole part caused a marked decrease in the antianaphylactic activity, although the anti-SRS activity was retained.

Pharmacological Properties of Compound 7 Of the compounds tested in this paper, **7** proved to have the best balance of the antianaphylactic activity (ED_{50}=0.92 mg/kg *p.o.*) and anti-SRS activity (IC_{50}=0.89 μg/ml), and was thus selected for further pharmacological evaluation. In order to elucidate the origin of its antianaphylactic activity, its effect on skin reactions induced in guinea pigs by chemical mediators, histamine, leukotriene C_4, platelet-activating factor (PAF), and substance P, was evaluated. Compound **7** potently inhibited only histamine-induced skin reaction, with an ED_{50} value of 0.59 mg/kg (*p.o.*). Therefore, the antianaphylactic activity of **7** can be attributed mainly to its potent antihistaminic activity. Concerning the anti-SRS activity, **7** exhibited potent inhibitory activity (IC_{50}=0.09 μg/ml) against 5-lipoxygenase in rat neutrophils, suggesting that the anti-SRS activity of **7** stems from the inhibition of 5-lipoxygenase.

Experimental

Melting points were measured on a Mitamura capillary melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a Varian EM-390 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a Hitachi M80 mass spectrometer (electron ionization). Organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was performed using Kieselgel 60 (70—230 mesh, E. Merck).

***N*-(4-Chloromethyl-2-thiazolyl)methanamide (21a)** Acetic formic anhydride (1.7 g, 19 mmol) was added slowly to a solution of 2-amino-4-chloromethylthiazole hydrochloride (**20**)[8] (2.0 g, 10.8 mmol) and pyridine (3.2 ml) in *N*,*N*-dimethyl formamide (DMF) (10 ml) at 0—5 °C with stirring. Stirring was continued at this temperature for 1 h, then the reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed successively with 1 N HCl and brine, and dried. The solvent was evaporated to give **21a** as a slightly brownish powder (0.94 g, 49.2%), mp 173—175 °C (dec.).

Compound **21b** was prepared according to the method described in the literature.[13]

***N*-(4-Chloromethyl-2-thiazolyl)propanamide (21c)** Propionyl chloride (30.0 g, 0.32 mol) was added slowly to a solution of **20** (50.0 g, 0.27 mol) and pyridine (50 ml) in DMF (250 ml) at 0—3 °C. Stirring was continued for 20 min, then the reaction mixture was poured into ice-water (1500 ml) and the resulting precipitates were collected by filtration to afford **21c** as a slightly brownish powder (28.2 g, 50.9%). An analytical sample was obtained by recrystallization from toluene as colorless crystals, mp 238—241 °C.

Compounds **21d,e,h** were prepared in the same manner as **21c**.

***N*-(4-Chloromethyl-2-thiazolyl)-2,2-dimethylpropanamide (21f)** A mixture of **20** (1.0 g, 5.4 mmol) and pivalic anhydride (5 ml, 24.6 mmol) was heated at 115 °C with stirring for 2 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was diluted with ethyl ether and the whole was concentrated under reduced pressure. The residual solid was triturated with ethyl ether and collected by filtration to give **21f** (0.47 g, 37.3%) as a slightly brownish powder, mp 138—139 °C.

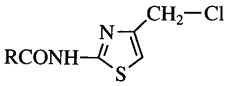
Compound **21g** was prepared similarly.

The physical data of **21a** and **21c**—**h** are listed in Table V.

1-Phenyl-3-(4-piperidyl)-1*H*-indole (22c) A mixture of 1-[4-(1*H*-indol-3-yl)piperidino]ethanone (**23**)[9] (10.0 g, 41.3 mmol), bromobenzene (6.48 g, 41.3 mmol), K_2CO_3 (5.70 g, 41.3 mmol) and copper(II) oxide (0.26 g, 3.3 mmol) in dry DMF (10 ml) was refluxed for 30 h. After cooling, the mixture was diluted with $CHCl_3$ and filtered. The filtrate was concentrated under reduced pressure and the resulting materials were chromatographed on alumina gel (400 g) with a mixture of toluene and AcOEt (20 : 1). The desired fractions were collected and evaporated to give 1-[4-(1-phenyl-1*H*-indol-3-yl)piperidino]ethanone (10.2 g, 77.5%) as a yellowish syrup. IR (neat): 1640, 1600, 1500, 1220, 745, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40—3.50 (7H, m), 2.11 (3H, s), 3.93 (1H, d, *J*=13.5 Hz), 4.77 (1H, d, *J*=13.5 Hz), 7.08 (1H, s), 7.45 (5H, s), 7.00—7.80 (4H, m). MS *m/z*: 318 (M^+).

A mixture of 1-[4-(1-phenyl-1*H*-indol-3-yl)piperidino]ethanone (5.0 g, 16.0 mmol) and 2 N NaOH (60 ml) in EtOH (30 ml) was refluxed for 13 h. After evaporation of EtOH, the aqueous solution obtained was extracted with a mixed solvent of $CHCl_3$ and MeOH (30 : 1). The organic layer was separated, dried, and evaporated. The resulting residue was chromatographed on alumina gel with a mixture of $CHCl_3$ and MeOH (100 : 1). The desired fractions were collected and evaporated to give **22c** (2.1 g, 96%) as a yellowish syrup. IR (neat): 2800—2300, 1600, 1500, 1460, 1380, 1320, 1300, 1230, 1140, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.82 (2H, m), 2.06—2.14 (3H, m), 2.70—3.25 (5H, m), 7.11 (1H, s), 7.14—7.72 (9H, m). MS *m/z*: 276 (M^+). **22c** was treated with 18%

TABLE V. Physical Data for *N*-[4-(Chloromethyl)-2-thiazolyl]alkanamides



	R	Yield (%)	mp (°C)	MS (*m/z*)	IR (Nujol, cm^{-1})	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
21a	H	49.2	173—174[a]	176 (M^+) 178 (M^++2)	3165, 3120, 1690, 1565, 1288	4.74 (2H, s), 7.30 (1H, s), 8.48 (1H, s), 12.30 (1H, br s)
21c	Et	50.9	126—127[b]	204 (M^+) 206 (M^++2)	3300, 1698, 1553, 1270	1.23 (3H, t, J=7.2 Hz), 2.53 (2H, q, J=7.2 Hz), 4.55 (2H, s), 6.94 (1H, s), 10.19 (1H, br s)
21d	*n*-Pr	94.6	115—117[a]	218 (M^+) 220 (M^++2)	3260, 1690, 1550, 1265	0.90 (3H, t, J=7.0 Hz), 1.63 (2H, sext, J=7.0 Hz), 2.40 (2H, t, J=7.0 Hz), 4.68 (2H, s), 7.16 (1H, s), 12.20 (1H, br s)
21e	*n*-Bu	97.0	111—116[a]	232 (M^+) 234 (M^++2)	3260, 1694, 1550, 1165	0.80—2.70 (9H, m), 4.70 (2H, s), 7.16 (1H, s), 12.23 (1H, br s)
21f	*tert*-Bu	37.3	138—139[a]	232 (M^+) 234 (M^++2)	3270, 1658, 1535, 1152	1.33 (9H, s), 4.57 (2H, s), 6.90 (1H, s), 9.00 (1H, br s)[c]
21g	Ph	46.9	129—131[a]	254 (M^+) 256 (M^++2)	3370, 1673, 1293	4.45 (2H, s), 6.95 (1H, s), 7.30—8.30 (6H, m)[c]
21h	$PhCH_2$	97.1	100—103[a]	266 (M^+) 268 (M^++2)	3180, 3060, 1655, 1335, 1310, 1140	3.79 (2H, s), 4.73 (2H, s), 7.26 (1H, s), 7.36 (5H, s), 12.50 (1H, br s)

a) Used in the next reaction without further purification. *b*) Recrystallized from toluene. *c*) $CDCl_3$ as a solvent.

methanolic hydrogen chloride to afford the hydrochloride as colorless crystals, mp 279—282 °C. *Anal.* Calcd for $C_{19}H_{20}N_2 \cdot HCl$: C, 72.95; H, 6.77; N, 8.95. Found: C, 73.43; H, 6,55; N, 9.14.

***N*-[4-(4-(1*H*-Indol-3-yl)piperidinomethyl]-2-thiazolyl]methanamide (6)** A mixture of **21a** (0.88 g, 4.99 mmol), **22a**[9] (1.00 g, 4.99 mmol), $NaHCO_3$ (0.46 g, 5.49 mmol), and NaI (88 mg) in DMF (10 ml) was heated at 50 °C for 2 h. After cooling, the inorganic salts were filtered off, and washed with a mixture of $CHCl_3$ and MeOH (10 : 1). The combined filtrate and the washing were concentrated under reduced pressure. The resulting residue was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (50 : 1). The desired fractions were collected and evaporated to give a crude product, which was recrystallized from EtOH to afford **6** (0.37 g, 21.8%) as slightly brownish crystals, mp 217—221 °C.

Compounds **7**—**8**, **11**—**16**, and **18** were similarly prepared by this method.

***N*-[4-[4-(1*H*-Indol-3-yl)piperidinomethyl]-2-thiazolyl]-2-methylpropanamide (9)** A solution of isobutyryl chloride (1.4 ml, 13.4 mmol) in CH_2Cl_2 (2.5 ml) was added slowly to a mixture of **24**[7] (1.0 g, 3.2 mmol) and Et_3N (2.8 ml, 20.0 mmol) in DMF (10 ml) at 0—5 °C. The mixture was stirred at this temperature for 3.5 h, then filtered, and the filtrate was concentrated under reduce pressure. The resulting syrup was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (20 : 1). The desired fractions were collected and evaporated to give a crude material, which was recrystallized from aqueous EtOH to afford **9** (0.45 g, 36.8%) as slightly brownish crystals, mp 183—187 °C.

Compound **10** was similarly prepared by this method.

***N*-[4-[4-(5-Amino-1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]propanamide (19)** Compound **18** (1.39 g, 3.4 mmol), EtOH (60 ml) and Fe powder (1.13 g) was added successively to a solution of NH_4Cl (1.08 g, 20 mmol) in H_2O (20 ml). The resulting mixture was heated at 80 °C with stirring. After 2 h, the reaction mixture was filtered and the residue on the filter was washed with hot EtOH. The combined filtrate and the washing were concentrated under reduced pressure. The resulting residue was made basic to litmus with 2 N NaOH, and then extracted with AcOEt. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (50 : 1). The desired fractions were collected and evaporated to give a crude material, which was recrystallized from EtOH to afford **19** (0.92 g, 71.3%) as slightly brownish crystals, mp 115—118 °C.

The physical data of **6**—**16** and **18**—**19** are listed in Table I.

Biological Activities Antianaphylactic activity in guinea pigs was assayed as described previously.[7]

Anti SRS Activity: Male Sprague-Dawley rats aged 8 weeks were used. Eighteen hours after an i.p. injection of 0.1% glycogen, neutrophils were collected from the peritoneal washings of rats. The synthesis and release of SRS from rat neutrophils were induced and measured by the method described previously.[14] Briefly, the cells suspended in Tyrode's solution were incubated with indomethacin and arachidonic acid and then challenged with calcium ionophore (A23187). After 10 min, the reaction was terminated by centrifugation and the supernatant was bioassayed in a superfused guinea pig ileum in the presence of mepyramine, atropine and methysergide.

Skin Reaction: Male Hartley strain guinea pigs were used. The guinea pigs were sensitized intradermally on their backs with 0.1 ml of diluted homologous anti-egg albumin (EA) serum containing immunoglobullin E (IgE) (1 : 64) and 0.1 ml of diluted homologous EA serum containing immunoglobulin G (IgG) (1 : 4000) at 7 and 1 d before challenging, respectively. The sensitized guinea pigs were injected intradermally with chemical meditator solution [histamine (1 μg/0.1 ml), PAF (10 ng/0.1 ml), LTD_4 (10 ng/0.1 ml) or substance P (0.1 ng/0.1 ml)] and immediately given intravenously 1 ml of saline containing EA (5 mg) and Evans blue (5 mg). After 1 h, the animals were decapitated, and the skin reaction was evaluated by expressing the size of the stained area as the mean of the longest and shortest diameter. The test compound was administered orally 30 min before challenge.

5-Lipoxygenase Inhibitory Activity: The inhibitory effect on 5-lipoxygenase was assayed according to the method described in the literature.[15] In brief, the neutrophils of rats were sonicated by an ultrasonic disruptor and then centrifuged at 3000 rpm for 10 min. The supernatant was used as the enzyme source of 5-lipoxygenase. The reaction mixture was incubated for 7 min at 37 °C after addition of [1-^{14}C]arachidonic acid (10 μCi/ml). 5-Lipoxygenase activity was expressed as the conversion rate of arachidonic acid to 5-hydroxy-6,8,11,14-eicosatetraenoic acid and leukotriene B_4.

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