Synthesis and Pharmacological Properties of *N*-[4-[4-(1*H*-Indol-3-yl)-piperidinoalkyl]-2-thiazolyl]alkanesulfonamides as Novel Antiallergic Agents

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A number of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanesulfonamides (8—21) were synthesized and evaluated for their preventive effects on systemic anaphylaxis in guinea pigs. Structure–activity analysis revealed that methane- and ethanesulfonamide derivatives having a one to three methylene tether between the piperidine and thiazole rings exhibited potent activity but the introduction of a substituent on the indole part reduced the activity. Administration (100 mg/kg *p.o.*) of the four compounds 8, 9, 12, 13, together with ketotifen, oxatomide, terfenadine and azelastine as reference compounds, to mice revealed that only compound 8 caused no significant increase of the sleeping time induced by hexobarbital. In addition, compound 8 (10 mg/kg i.v.) did not change the electroencephalogram in conscious rabbits. These results led to the selection of *N*-[4-[4-(1*H*-indol-3-yl)piperidinomethyl]-2-thiazolyl]methanesulfonamide (8, FK613) for further development as a novel antiallergic agent. Clinical evaluation of FK613 is now in progress.

Keywords antianaphylactic activity; *N*-(2-thiazolyl)alkanesulfonamide; 4-(3-indolyl)piperidine; ketotifen; oxatomide; structure–activity relationship

Several antiallergic agents with potent antihistaminic action, for instance ketotifen[1] and oxatomide,[2] have been demonstrated to be useful for the treatment of type I allergic diseases including asthma. It has been pointed out, however, that these agents exert non-negligible adverse effects on the central nervous system (CNS), such as drowsiness.[3] New antihistamines which lack this defect therefore represent attractive targets for drug discovery in the field of antiallergic agents. Some such desired antihistamines, terfenadine[4] and astemizole,[5] have already been discovered, but we independently focused on the search for this type of new antihistamines using oxatomide as a chemical lead.

Ueda *et al.*[6] in our research laboratories found that FR39276 (**1**, Chart 1), which has *N*-(2-thiazolyl)methanesulfonamide in place of the benzimidazole moiety in oxatomide, exhibited potent antihistaminic activity with few CNS side effects. However, compound **1** was not selected for further development, mainly because of its teratogenicity in rats. We postulated that this toxicity might be ascribed to the diphenylmethylpiperazine part of the structure, because oxatomide has also been reported to exhibit similar toxicity in rats.[7] On the other hand, Freter *et al.*[8] reported that compound **2**, in which an indolylpiperidine moiety was used instead of the diphenylmethylpiperazine in oxatomide, showed potent antihistaminic activity. We thus expected that changing the diphenylmethylpiperazine part of FR39276 into an indolylpiperidine moiety might eliminate this particular toxicity, while retaining the antihistaminic activity.

In this paper, we describe the synthesis and structure–activity relationships of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanesulfonamides (**8—21**), and the pharmacological effects on the CNS of compound **8** (FK613), which is now under clinical trial.

Chemistry The desired compounds **8—21** listed in Table I were prepared *via* the synthetic route outlined in Chart 2. The intermediates **7a—g** were produced according to the following two methods. Compounds **7a—e** were synthesized in two steps by alkylation of indolylpiperidines (**4a, b**) with *N*-[4-(chloroalkyl)-2-thiazolyl]acetamides (**3a—d**) in the presence of sodium hydrogen carbonate, followed by hydrolysis of the acetyl group in the obtained **5a—e** under acidic conditions. The other intermediates **7f, g** were prepared by direct alkylation of indolylpiperidines (**4c, d**) with 4-(chloromethyl)-2-thiazolamine hydrochloride (**6**) in the presence of triethylamine. The compounds obtained (**7a—g**) were then sulfonylated with an appropriate

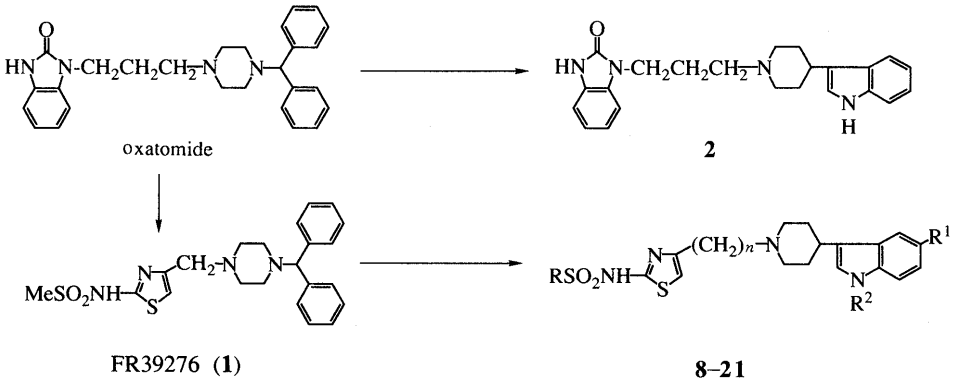
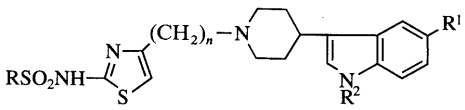


Chart 1

TABLE I. *N*-[4-[4-(1*H*-Indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanesulfonamides (**8**—**21**)



	R^1	R^2	R	*n*	Yield (%)	mp (°C) (Recryst. solvent)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (DMSO-d_6, δ: J=Hz)
8	H	H	Me	1	22.2	207—208 (C)	$C_{18}H_{22}N_4O_2S_2$	55.36 (55.38	5.68 5.70	14.35 14.39)	1.50—3.30 (9H, m), 2.80 (3H, s), 3.50 (2H, s), 6.68 (1H, s), 6.80—7.70 (5H, m), 10.72 (1H, s)
9	H	H	Me	2	17.7	136.5—142 (B)	$C_{19}H_{24}N_4O_2S_2 \cdot H_2O$	54.01 (53.94	6.20 6.21	13.26 13.20)	1.50—3.40 (13H, m), 2.80 (3H, s), 6.41 (1H, s), 6.80—7.70 (5H, m), 10.70 (1H, br s)
10	H	H	Me	3	17.3	210—214 (B)	$C_{20}H_{26}N_4O_2S_2$	57.39 (56.99	6.26 6.21	13.39 13.23)	1.50—3.30 (15H, m), 2.72 (3H, s), 5.80 (1H, br s), 6.25 (1H, s), 6.90—7.50 (5H, m), 10.70 (1H, s)
11[b]	H	H	Me	5	81.1	219—225 (A)	$C_{22}H_{30}N_4O_2S_2 \cdot HCl$	54.70 (54.39	6.47 6.42	11.60 11.34)	1.10—2.30 (9H, m), 2.88 (3H, s), 2.71—3.8 (8H, m), 6.43 (1H, s), 6.80—7.80 (5H, m), 10.61 (1H, br s), 10.88 (1H, br s), 12.51 (1H, br s)
12	H	H	Et	1	23.7	181—186 (A)	$C_{19}H_{24}N_4O_2S_2$	56.41 (56.13	5.98 5.93	13.85 13.52)	1.22 (3H, t, J=7.6), 1.50—3.70 (11H, m), 3.47 (2H, s), 6.57 (1H, s), 6.90—7.80 (5H, m), 9.46 (1H, br s), 10.78 (1H, s)
13[b]	H	H	Et	2	9.0	222—228 (B)	$C_{20}H_{26}N_4O_2S_2 \cdot HCl$	52.79 (52.66	5.98 5.70	12.31 12.25)	1.22 (3H, t, J=7.8), 1.80—4.00 (17H, m), 6.40 (1H, s), 6.70—7.80 (5H, m), 10.75 (1H, br s)
14	H	H	Et	3	28.9	211—213 (C)	$C_{21}H_{28}N_4O_2S_2$	58.31 (58.02	6.52 6.51	12.95 12.74)	1.10 (3H, t, J=8.1), 1.60—4.10 (17H, m), 6.30 (1H, s), 6.80—7.70 (5H, m), 10.73 (1H, s)
15[b]	H	H	*n*-Pr	1	38.8	185—208 (D)	$C_{20}H_{26}N_4O_2S_2 \cdot HCl \cdot 2/3H_2O$	51.43 (51.43	6.11 5.91	11.99 11.93)	0.98 (3H, t, J=6.6), 1.72 (2H, m), 1.90—3.80 (12H, m), 4.25 (2H, s), 6.80—7.90 (6H, m), 10.90 (1H, s)
16	H	H	*n*-Pr	2	50.4	178—182 (C)	$C_{21}H_{28}N_4O_2S_2$	58.31 (57.94	6.52 6.44	12.95 12.86)	0.95 (3H, t, J=6.3), 1.30—3.40 (17H, m), 6.40 (1H, s), 6.50—7.70 (5H, m), 10.80 (1H, s)
17	H	H	*n*-Pr	3	30.4	217—220 (C)	$C_{22}H_{30}N_4O_2S_2$	59.16 (58.98	6.77 6.71	12.54 12.58)	0.92 (3H, t, J=7.8), 1.40—3.40 (19H, m), 6.32 (1H, s), 6.80—8.10 (5H, m), 10.80 (1H, s)
18[b]	H	H	iso-Pr	1	14.8	230—238 (A)	$C_{20}H_{26}N_4O_2S_2 \cdot HCl \cdot 7/10H_2O$	52.75 (52.52	6.45 6.17	11.50 11.81)	1.24 (6H, d, J=4.2), 1.80—3.70 (12H, m), 4.27 (2H, s), 6.80—7.90 (6H, m), 10.90 (1H, s)
19	OMe	H	Me	1	67.7	228—230 (C)	$C_{19}H_{24}N_4O_3S_4$	54.27 (53.91	5.75 5.35	13.32 13.41)	1.60—3.50 (9H, m), 2.93 (3H, s), 3.60 (2H, s), 3.84 (3H, s), 6.50 (1H, br s), 6.60—7.50 (5H, m), 10.63 (1H, br)
20	NO_2	H	Me	1	42.9	224—226 (C)	$C_{18}H_{21}N_5O_4S_2$	49.64 (49.26	4.86 4.59	16.08 15.96)	1.80—3.30 (9H, m), 2.92 (3H, s), 3.55 (2H, s), 5.80 (1H, br s), 6.65 (1H, br s), 7.30—8.70 (4H, m), 11.47 (1H, br s)
21[b]	H	Me	Me	1	30.0	275—279 (A)	$C_{19}H_{24}N_4O_2S_2 \cdot HCl$	51.75 (51.72	5.71 5.68	12.70 12.67)	1.90—2.20 (4H, m), 3.00 (3H, s), 3.74 (3H, s), 3.00—3.70 (5H, m), 4.21 (2H, s), 7.00—7.20 (4H, m), 7.39 (1H, d, J=7.8), 7.65 (1H, d, J=7.8)

a) A, EtOH; B, EtOH–H_2O; C, DMF–H_2O; D, MeOH. *b*) Obtained as the HCl salt.

alkanesulfonyl chloride in the presence of a base (triethylamine or *N*-methylmorpholine) to afford the objective compounds **8**—**21**. In this reaction, the bissulfonylated product was formed as a by-product, which was easily transformed to the desired monosulfonylated compound by treatment with aqueous alkaline solution.

5-Methoxy-3-(4-piperidyl)-1*H*-indole (**4b**) was prepared *via* a route similar to that used for **4a**, which was previously reported.[9] Gall *et al.*[10] reported that nitration of *N*-acetylindoline with nitric acid in sulfuric acid predominantly occurred at the 5-position in good yield. We thus utilized this procedure for the synthesis of 5-nitro-3-(4-piperidyl)-1*H*-indole (**4c**), as shown in Chart 3. Namely, the corresponding *N*-acetylindoline (**23**), which was prepared from **22**, was nitrated to produce **24**. The acetyl group at the indoline nucleus was simultaneously removed under these reaction conditions. The compound obtained (**24**) was oxidized with MnO_2 and subsequently hydrolyzed to afford **4c**. 1-Methyl-3-(4-piperidyl)-1*H*-indole (**4d**) was prepared by methylation of **22** with methyl iodide in the presence of NaH, followed by hydrolysis of the acetyl group.

The synthesis of *N*-[4-(3-chloropropyl)-2-thiazolyl]acetamide (**3c**) has been published in the literature.[6] However, the synthetic route involves the reaction of thiourea with 1,5-dichloro-2-pentanone, which was produced by the treatment of 4-chlorobutyryl chloride with diazomethane under HCl gas bubbling. To avoid the use of a large amount of diazomethane, we employed a different synthetic pathway

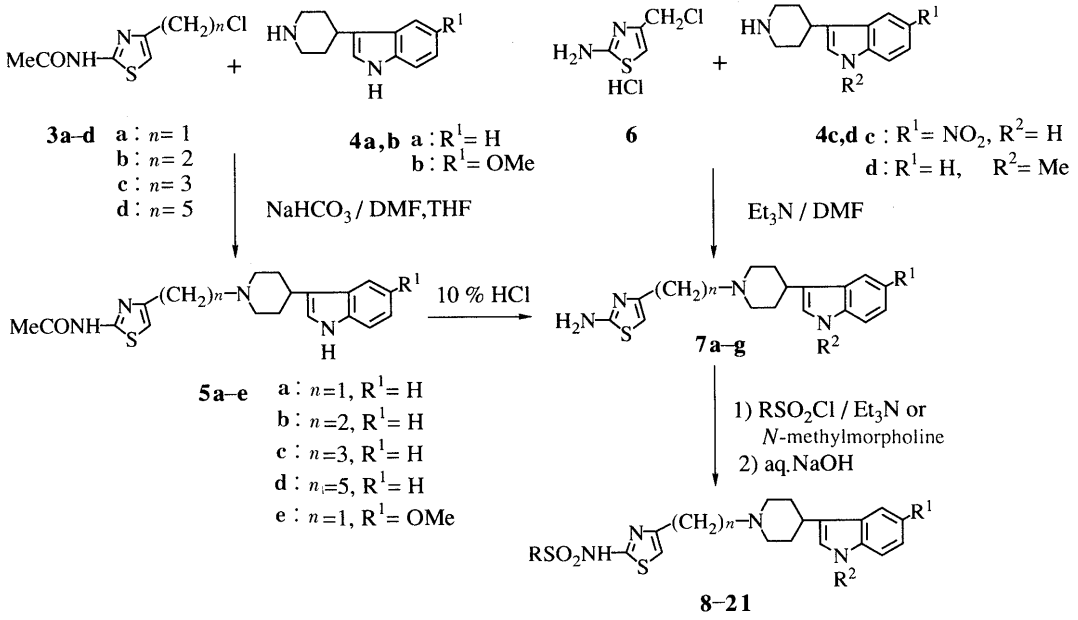


Chart 2

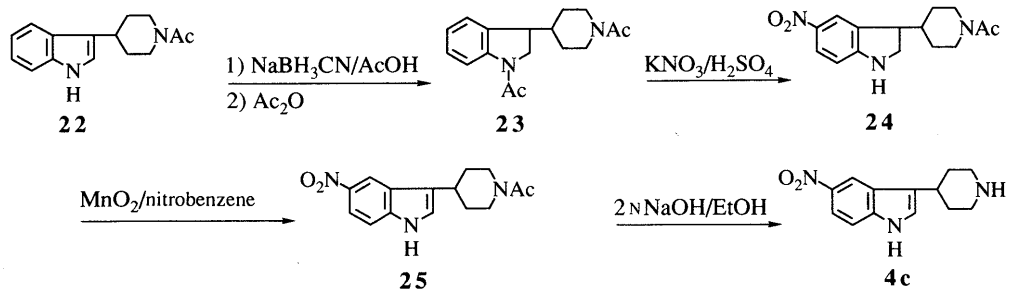


Chart 3

for **3c** (Chart 4). The treatment of **6** with refluxing water and subsequent acetylation of the resulting alcohol afforded the acetate (**26**), which was hydrolyzed to give the alcohol (**27**). The intermediate aldehyde (**28**) was then produced by oxidation of **27** with MnO_2. Wittig reaction with formylmethylidenetriphenylphosphorane was applied to the aldehyde (**28**) to give the α,β-unsaturated aldehyde (**29a**) with *E*-configuration. Compound **29a** was hydrogenated over a Pd catalyst to afford the propionaldehyde (**30a**), accompanied by a small amount of the propyl alcohol (**31a**). Then, unpurified **30a** was treated with $NaBH_4$ and the alcohol obtained (**31a**) was chlorinated with thionyl chloride to afford **3c**. From the aldehyde (**28**), *N*-[4-(5-chloropentyl)-2-thiazolyl]acetamide (**3d**) was also synthesized *via* a route similar to that of **3c**, with the only change being the use of ethyl 4-(diethylphosphono) crotonate in the first step, the Wadworth–Emmons reaction (Chart 4).

Pharmacological Results and Discussion

It has been shown that ketotifen and oxatomide are effective against egg albumin-induced systemic anaphylaxis in guinea pig.[11] We thus utilized this test for evaluation of the antiallergic activity of compounds **8**—**21** that were synthesized here. Each compound was orally administered thirty minutes before the antigen challenge. When the animals given a test compound survived for 2 h after the antigen challenge, the test compound was considered to be significantly effective against the anaphylactic asthma. The test results are summarized in Table II. The structure–activity relationship for these compounds is discussed below with regard to the influence of the alkanesulfonamide moiety (R), the tether length (*n*), and the substituents (R^1 and R^2) on the indole.

Most of the tested compounds exhibited potent activity in preventing the systemic anaphylaxis. Concerning the length of the methylene tether in methanesulfonamide derivatives (**8**—**11**), almost the same potency was seen with the compounds of $n=1$—3, although $n=2$ seems to be optimum. However, the activity of the compound of $n=5$ was drastically reduced. A similar trend was observed in the series of ethanesulfonamide derivatives (**12**—**14**) with $n=1$—3. In the series of *n*-propylsulfonamide derivatives (**15**—**17**) the compound having the $n=3$ tether exhibited more potent activity than the compounds of $n=1$ and 2.

With regard to the alkanesulfonamide moiety, the size of alkyl groups affected antianaphylactic activity to some extent. Methanesulfonamide was found to be the most suitable moiety compared to other alkanesulfonamide derivatives having the same length of methylene tether. Furthermore, increasing the number of carbon atoms in the alkanesulfonamide part tended to attenuate the potency of antianaphylactic activity.

The introduction of a methyl group at the nitrogen atom in the indole nucleus turned out significantly to reduce the

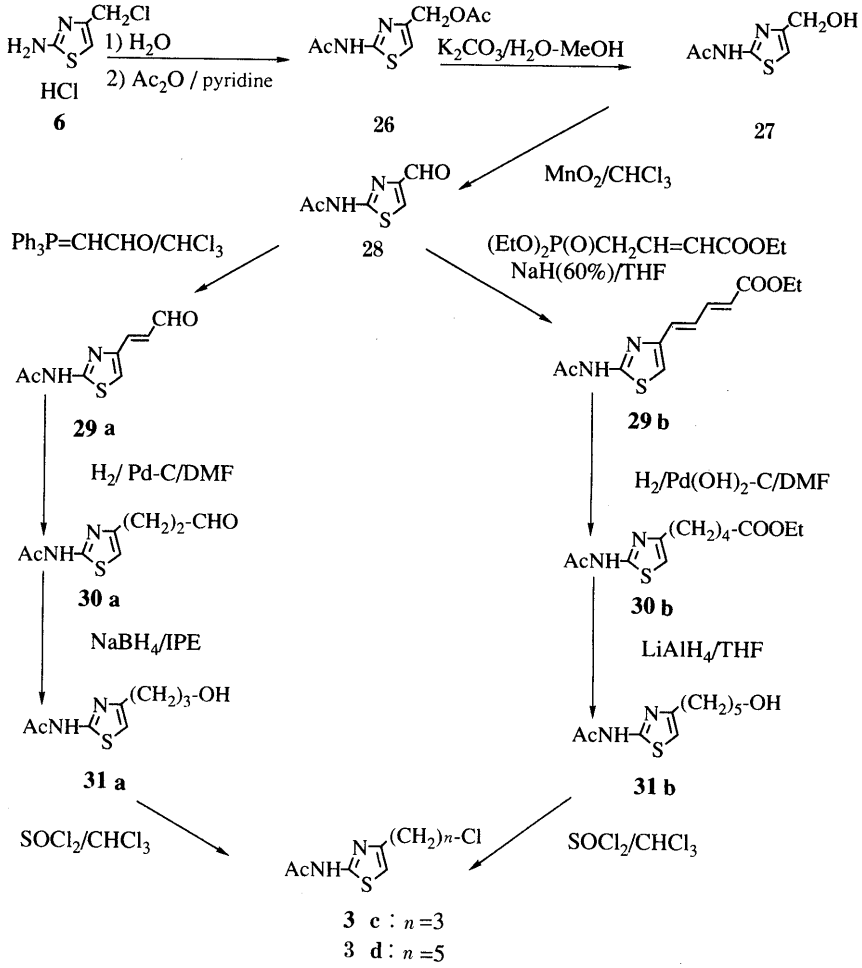
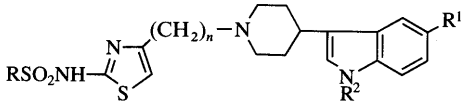


Chart 4

TABLE II. Antianaphylactic Activity of Compounds **8**—**21**



	R^1	R^2	R	n	Dose (mg/kg *p.o.*)			
					10	1.0	0.1	0.01
8	H	H	Me	1		5/5	3/5	0/5[a]
9	H	H	Me	2		5/5	5/5	1/5
10	H	H	Me	3		3/3	2/3	1/3
11	H	H	Me	5	3/3	0/3	0/3	
12	H	H	Et	1	3/3	3/3	2/3	
13	H	H	Et	2	3/3	3/3	3/3	0/3
14	H	H	Et	3	3/3	3/3	2/3	0/3
15	H	H	*n*-Pr	1	3/3	3/3	1/3	
16	H	H	*n*-Pr	2	3/3	3/3	0/3	
17	H	H	*n*-Pr	3	3/3	3/3	2/3	0/3
18	H	H	iso-Pr	1	3/3	3/3	1/3	
19	OMe	H	Me	1	1/3			
20	NO_2	H	Me	1	0/3			
21	H	Me	Me	1	3/3	1/3	0/3	

a) Effective number over total number of tested guinea pigs.

activity (**21** *vs.* **8**). In addition, the introduction of a methoxy (**19**) or a nitro (**20**) group resulted in complete loss of activity, suggesting that no substitution at the 5-position of the indole nucleus is tolerated.

Based on the potency in the above test, namely egg albumin-induced systemic anaphylaxis in guinea pig, we selected four compounds **8**, **9**, **12** and **13**. To elucidate the effect on the CNS, these compounds were tested for ability to increase the sleeping time induced by hexobarbital, when administered orally in mice. Ketotifen, oxatomide, terfenadine and azelastine were also tested as reference compounds. All the tested compounds excepting compound **8** caused a significant increase of the sleeping time at the dose of 100 mg/kg. Furthermore, compound **8**, ketotifen and oxatomide were tested for their effects on the brain waves in conscious rabbits by electroencephalography. Compound **8** exhibited no effect up to the dose of 10 mg/kg (i.v.), whereas ketotifen and oxatomide caused a significant increase of the appearance of sleeping pattern even at the dose of 1 mg/kg (i.v.). From these results, it can be concluded that compound **8** has a negligible effect on CNS, when compared with those of the reference compounds. Therefore, compound **8** (FK613) was selected as a candidate for further evaluation. The detailed pharmacological features of FK613 will be reported in due time.

In conclusion, we synthesized a new series of *N*-[4-[4-(1*H*-indol-3-yl)piperidinoalkyl]-2-thiazolyl]alkanesulfonamides and evaluated their antiallergic activity. Most of the synthesized compounds exhibited potent preventive effects against systemic anaphylaxis in guinea pigs. Among them, compound **8** (FK613) was finally selected for further evaluation. FK 613 was found to exhibit no significant CNS effect and was negative in tests of mutagenesis and

teratogenesis. It is now under clinical trial as an antiallergic agent.

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. Organic extracts were dried over anhydrous $MgSO_4$. Column chromatography was performed using Kieselgel 60 (70—230 mesh, E. Merck).

5-Methoxy-3-(4-piperidyl)-1*H*-indole (4b) A solution of 3-(1-acetyl-1,4-dihydro-4-pyridyl)-5-methoxy-1*H*-indole[9] (3.0 g, 11.2 mmol) in EtOH (150 ml) was hydrogenated on Adams catalyst (0.25 g) at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated. The residue obtained was dissolved in a mixture of 2 N NaOH (22 ml) and EtOH (30 ml), and the solution was refluxed for 18 h. After evaporation of the EtOH, the resulting precipitates were collected by filtration and recrystallized from aqueous EtOH to afford slightly brownish crystals of **4b** (1.92 g, 74.6%), mp 173—175 °C. IR (Nujol): 3310, 1215, 1030, 795 cm^{-1}. ^{1}H-NMR (dimethylsulfoxide (DMSO)-d_6) δ: 1.3—2.1 (4H, m), 2.27 (1H, s), 2.4—3.3 (5H, m), 3.72 (3H, s), 6.64 (1H, dd, J=9.0, 3.0 Hz), 6.9—7.0 (2H, m), 7.16 (1H, d, J=9.0 Hz), 10.48 (1H, s). MS m/z: 230 (M^+).

1-[4-(1-Acetyl-2,3-dihydro-1*H*-indol-3-yl)piperidino]ethanone (23) $NaBH_3CN$ (95 g, 1.51 mol) was added portionwise to a stirred solution of **22**[9] (48.2 g, 0.2 mol) in acetic acid (1 l) at 15—20 °C over 1.5 h. The mixture was stirred at room temperature for 3 h, then additional $NaBH_3CN$ (10 g, 0.16 mol) was added and the mixture was stirred at the same temperature for 1 h. The reaction mixture was diluted with water (500 ml) and concentrated under reduced pressure. The residue obtained was dissolved in a mixture of tetrahydrofuran (THF) (200 ml) and 2 N NaOH (300 ml). The solution was stirred at room temperature for 2 h. After evaporation of THF, the residual solution was extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated. The resulting materials were chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (50 : 1) to afford 1-[4-(2,3-dihydro-1*H*-indol-3-yl)piperidino]ethanone (41.1 g, 84.6%) as a yellowish syrup. IR (neat): 3340, 3000, 1640—1605 (br) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s), 1.0—4.8 (13H, m), 6.4—7.2 (4H, m).

A mixture of the above compound (41.1 g, 0.17 mol) and acetic anhydride (300 ml) was refluxed for 3 h. After evaporation of excess acetic anhydride, the residue was dissolved in AcOEt (500 ml). The AcOEt solution was washed successively with saturated $NaHCO_3$ (100 ml), water (100 ml) and brine, and dried. After evaporation of the solvent, the crude materials were chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (40 : 1) to afford **23** (32 g, 66.4%). An analytical sample was obtained by recrystallization from EtOH–diisopropyl ether (IPE) as colorless crystals, mp 123—124 °C. IR (Nujol): 1655, 1640, 1485, 1410, 760 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.93 (3H, s), 2.15 (3H, s), 0.9—4.6 (12H, m), 6.8—7.3 (3H, m), 7.94 (1H, d, J=7.4 Hz). MS m/z: 286 (M^+).

1-[4-(2,3-Dihydro-5-nitro-1*H*-indol-3-yl)piperidino]ethanone (24) KNO_3 (0.12 g, 1.2 mmol) was added portionwise to a stirred solution of **23** (0.3 g, 1 mmol) in concentrated H_2SO_4 (5 ml) below 10 °C. The mixture was stirred at the same temperature for 1 h, then at room temperature for 7 h, and poured into ice-water. The aqueous solution was neutralized with 2 N NaOH and extracted with AcOEt. The organic layer was washed with brine and dried. After evaporation of the solvent, the crude materials were chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (50 : 1) to afford **24** (0.12 g, 39.6%). An analytical sample was obtained by recrystallization from aqueous EtOH as colorless crystals, mp 174—177 °C. IR (Nujol): 3240, 1620, 1610, 1310, 1280, 1260 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.95 (3H, s), 0.9—4.7 (12H, m), 6.37 (1H, d, J=9.0 Hz), 7.16 (1H, s), 7.73 (1H, d, J=2.0 Hz), 7.86 (1H, dd, J=9.0, 2.0 Hz). MS m/z: 289 (M^+).

1-[4-(5-Nitro-1*H*-indol-3-yl)piperidino]ethanone (25) A mixture of **24** (10 g, 34.6 mmol) and MnO_2 (17 g) in nitrobenzene (100 ml) was stirred at 150 °C in an atmosphere of nitrogen for 1 h. After cooling, the reaction mixture was filtered and the residue was washed with a mixed solvent of $CHCl_3$ and MeOH (10 : 1). The filtrate and the washed solution were combined and concentrated under reduced pressure. The resulting residue was dissolved in a mixture of $CHCl_3$ and MeOH (1 : 1, 400 ml). The solution was filtered through Celite and the filtrate was again concentrated. The resulting crude materials were recrystallized from MeOH to afford **25** (4.67 g, 47%). An analytical sample was obtained by recrystallization from MeOH as colorless crystals, mp 238—241 °C. IR (Nujol): 3250, 1625, 1615, 1515, 1330, 1110, 1000, 740 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.02 (3H, s), 1.2—4.7 (9H, m), 7.3—8.5 (4H, m), 11.49 (1H, br s). MS m/z: 287 (M^+).

5-Nitro-3-(4-piperidyl)-1*H*-indole (4c) A solution of **25** (4 g, 13.9 mmol) in a mixture of 2 N NaOH (100 ml) and EtOH (100 ml) was refluxed for 7 h. After cooling, the resulting precipitates were collected by filtration and recrystallized from aqueous EtOH to afford **4c** (2.64 g, 77.4%) as slightly brownish crystals, mp 233—239 °C. IR (Nujol): 3350, 3140, 1520, 1340, 1330, 1315, 1260, 1100 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.3—3.6 (10H, m), 7.28 (1H, s), 7.42 (1H, d, J=9.0 Hz), 7.89 (1H, dd, J=9.0, 2.0 Hz), 8.44 (1H, d, J=2.0 Hz). MS m/z: 245 (M^+).

1-Methyl-3-(4-piperidyl)-1*H*-indole (4d) NaH (60% in mineral oil, 0.45 g, 11.2 mmol) was added portionwise to an ice-cooled suspension of **22**[9] (2.72 g, 11.2 mmol) in *N*,*N*-dimethylformamide (DMF) (25 ml), and then methyl iodide (1.59 g, 11.2 mmol) was added dropwise over 30 min. The mixture was stirred at room temperature for 24 h, poured into ice-water, and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The resulting materials were triturated with IPE and filtered to afford 1-[4-(1-methyl-1*H*-indol-3-yl)piperidino]ethanone (2.5 g, 87.0%) as colorless crystals, mp 105—106 °C. IR (Nujol): 1630, 1440, 1360, 1330 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.8 (2H, m), 2.0—2.2 (2H, m), 2.13 (3H, s), 2.6—3.4 (3H, m), 3.73 (3H, s), 3.8—4.0 (1H, m), 4.7—4.9 (1H, m), 6.79 (1H, s), 7.1—7.3 (3H, m), 7.60 (1H, d, J=7.8 Hz). MS m/z: 256 (M^+).

A mixture of 1-[4-(1-methyl-1*H*-indol-3-yl)piperidino]ethanone (2.4 g, 9.38 mmol) and 2 N NaOH (50 ml) in EtOH (50 ml) was refluxed for 7 h. After evaporation of EtOH, the residual solution was extracted with a mixed solvent of $CHCl_3$ and MeOH (10 : 1). The organic layer was separated, dried, and concentrated to afford **4d** (2.1 g, 96%) as colorless crystals, mp 105—106 °C. IR (Nujol): 3200, 1610, 1320, 1230 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.5—1.7 (2H, m), 1.8—2.0 (2H, m), 2.6—3.0 (3H, m), 3.0—3.2 (2H, m), 3.71 (3H, s), 6.9—7.2 (3H, m), 7.35 (1H, d, J=7.8 Hz), 7.56 (1H, d, J=8.2 Hz). MS m/z: 214 (M^+).

2-Acetamido-4-thiazolylmethyl Acetate (26) A solution of **6**[12] (69 g, 0.37 mol) in water (500 ml) was refluxed for 1 h, and then concentrated under reduced pressure. The residue obtained was dissolved in a solution of KOH (37 g) in MeOH (300 ml). After filtration to remove insoluble materials, the filtrate was concentrated to afford crude 4-hydroxymethyl-2-thiazolamine. Acetic anhydride (81 ml) was added dropwise to a mixture of this crude compound in pyridine (200 ml) at 7—8 °C over 40 min. The reaction mixture was stirred at room temperature overnight, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ (400 ml). The $CHCl_3$ solution was washed successively with 1 N HCl (150 ml), water (150 ml) and brine, dried, and concentrated to give **26** (72.04 g, 90.9%). An analytical sample was obtained by recrystallization from EtOH as slightly yellowish crystals, mp 143—146 °C. IR (Nujol): 3190, 3075, 1741, 1722, 1650, 1580, 1260, 736 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.24 (3H, s), 5.08 (2H, s), 6.90 (1H, s), 10.30 (1H, br s). MS m/z: 214 (M^+).

***N*-(4-Hydroxymethyl-2-thiazolyl)acetamide (27)** A mixture of **26** (72 g, 0.34 mol) and K_2CO_3 (23.2 g, 0.17 mol) in MeOH (1.1 l) and water (100 ml) was stirred at room temperature for 3.3 h. After filtration to remove insoluble materials, the filtrate was neutralized with 2 N HCl and then concentrated under reduced pressure. The residue was dissolved in a warmed mixture of $CHCl_3$ and MeOH (1 : 1, 100 ml). Insoluble materials were filtered off, and the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (10 : 1) to afford **26** (41.1 g, 71.0%). An analytical sample was obtained by recrystallization from EtOH as colorless crystals, mp 129—130 °C. IR (Nujol): 3370, 3180, 1658, 1563, 1290, 730 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.14 (3H, s), 4.48 (2H, s), 5.12 (1H, br s), 6.88 (1H, s), 12.0 (1H, br s). MS m/z: 172 (M^+).

***N*-(4-Formyl-2-thiazolyl)acetamide (28)** MnO_2 (410 g) was added to a solution of **27** (41 g, 0.24 mol) in a mixed solvent of $CHCl_3$ (287 ml) and MeOH (164 ml) and the mixture was vigorously stirred for 1.3 h. After filtration, the residue was washed with a hot mixture of $CHCl_3$ and MeOH (10 : 1, 160 ml). The combined filtrate was concentrated to afford **28** (35.04 g, 86.5%). An analytical sample was obtained by recrystallization from AcOEt as slightly yellowish crystals, mp 211—214 °C. IR (Nujol): 3180, 3100, 1690, 1670, 1275, 740 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15 (3H, s), 8.23 (1H, s), 9.77 (1H, s), 12.37 (1H, br s). MS m/z: 170 (M^+).

***N*-[4-(3-Oxopropenyl)-2-thiazolyl)acetamide (29a)** A mixture of **28** (6.05 g, 35.5 mmol) and formylmethylidenetriphenylphosphorane (10.82 g,

35.5 mmol) in $CHCl_3$ (360 ml) was stirred under reflux for 4 h. After cooling, the resulting precipitates were collected by filtration and washed with $CHCl_3$ to afford **29a** (4.52 g, 64.8%). An analytical sample was obtained by recrystallization from EtOH as slightly yellowish crystals, mp 262.5—263 °C. IR (Nujol): 3180, 3080, 1666, 1640, 1623, 1120, 756 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.20 (3H, s), 6.67 (1H, dd, J=15.0, 8.0 Hz), 7.70 (1H, d, J=15.0 Hz), 7.80 (1H, s), 9.72 (1H, d, J=8.0 Hz), 12.30 (1H, br s).

***N*-[4-(3-Oxopropyl)-2-thiazolyl]acetamide (30a)** A solution of **29a** (2.24 g, 11.4 mmol) in DMF (45 ml) was hydrogenated over 10% Pd–C (11.2 g) at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on slica gel with a mixed solvent of $CHCl_3$ and MeOH (10 : 1) to afford **30a** (2.06 g, 91.2%) as a slightly yellowish powder. IR (Nujol): 3170, 3060, 1724, 1644, 1379, 718 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.6—3.3 (4H, m), 6.57 (1H, s), 9.80 (2H, m). MS m/z: 198 (M^+).

***N*-[4-(3-Hydroxypropyl)-2-thiazolyl]acetamide (31a)** $NaBH_4$ (120 mg) was added to a solution of **30a** (2.49 g, 12.6 mmol) in IPE (170 ml) under ice-cooling. After being stirred for 1 h, the reaction mixture was concentrated and the residue obtained was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (20 : 1) to afford **31a** (1.70 g, 67.4%) as colorless crystals, mp 120—123 °C. IR (Nujol): 3400, 3200, 3080, 1660, 1560 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.6—2.2 (2H, m), 2.5—3.0 (2H, m), 2.12 (3H, s), 3.31 (1H, s), 3.2—3.7 (2H, m), 6.72 (1H, s), 11.77 (1H, s). MS m/z: 200 (M^+).

***N*-[4-(3-Chloropropyl)-2-thiazolyl]acetamide (3c)** A mixture of **31a** (1.50 g, 7.5 mmol) and $SOCl_2$ (1.1 ml) in $CHCl_3$ (2 ml) was warmed at 60 °C for 3 h. The reaction mixture was poured into ice-water and the solution was neutralized with aqueous $NaHCO_3$, then extracted with $CHCl_3$. The organic layer was dried and concentrated to afford **3c** (1.50 g, 91.7%). An analytical sample was obtained by recrystallization from toluene–*n*-hexane as colorless crystals, mp 113—115 °C. IR (Nujol): 3200, 3060, 1645, 1550 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, m), 2.23 (3H, s), 2.83 (2H, t, J=8.0 Hz), 3.54 (2H, t, J=8.0 Hz), 6.55 (1H, s), 9.7 (1H, br s). MS m/z: 218 (M^+), 176, 114.

Ethyl (2*E*,4*E*)-5-(2-Acetamido-4-thiazolyl)penta-2,4-dienoate (29b) Ethyl 4-(diethylphosphono)crotonate (80%, 6.1 g, 19.5 mmol) was added slowly to a suspension of NaH (60% in mineral oil, 0.9 g, 22.5 mmol) in dry THF (60 ml) at 8—10 °C under an inert atmosphere. This solution was stirred for 30 min, then **28** (3.0 g, 17.6 mmol) in dry THF (100 ml) was added slowly under ice-bath cooling. The mixture was stirred at room temperature for 4 h and then saturated aqueous solution of ammonium chloride was added. After evaporation of the solvent, the residue was dissolved in a mixed solvent of $CHCl_3$ and MeOH (20 : 1). The solution was washed with brine, dried, and concentrated under reduced pressure. The residue was recrystallized from isopropyl alcohol–AcOEt to afford **29b** (1.1 g, 23.5%) as slightly yellowish crystals, mp 215—220 °C. IR (Nujol): 1700, 1645, 1625, 1585 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=8.0 Hz), 2.16 (3H, s), 4.15 (2H, q, J=8.0 Hz), 6.08 (1H, d, J=14.0 Hz), 6.97 (1H, m), 7.03 (1H, s), 7.29 (1H, m), 7.43 (1H, m), 12.20 (1H, br s). MS m/z: 266 (M^+).

Ethyl (2*E*,4*E*)-5-(2-Acetamino-4-thiazolyl)pentanoate (30b) A solution of **29b** (0.5 g, 1.88 mmol) in DMF (10 ml) was hydrogenated over 20% $Pd(OH)_2$–charcoal (0.4 g) at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated to afford **30b** (0.5 g, 97.5%) as an oil. IR (neat): 3250, 1720, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.0 Hz), 1.69 (4H, m), 2.25 (3H, s), 2.33 (2H, m), 2.66 (2H, m), 4.13 (2H, q, J=7.0 Hz), 6.52 (1H, s), 10.4 (1H, br s). MS m/z: 270 (M^+), 235, 183, 169, 127, 114.

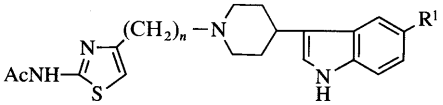
***N*-(5-Hydroxypentyl-2-thiazolyl)acetamide (31b)** $LiAlH_4$ (0.07 g) was added slowly to a stirred solution of **30b** (0.49 g, 1.81 mmol) in THF (5.5 ml) at 10—20 °C under an inert atmosphere. The whole was stirred for 4 h, then ACOEt (5 ml) and water (10 ml) were added. The resulting precipitate was filtered off and the filtrate was extracted with AcOEt. The organic layer was washed with brine, dried, and concentrated under reduced pressure. The resulting crude materials were recrystallized from AcOEt–*n*-hexane to give **31b** (0.19 g, 46.2%) as colorless crystals, mp 103—105 °C. IR (Nujol): 3360, 3180, 1660, 1565 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.1—1.8 (6H, m), 2.13 (3H, s), 2.58 (2H, m), 3.38 (2H, m), 4.28 (1H, br s), 6.79 (1H, s), 11.19 (1H, br s). MS m/z: 228 (M^+), 156, 126, 114.

***N*-(5-Chloropentyl-2-thiazolyl)acetamide (3d)** This compound was prepared in the same manner as **3c**. IR (Nujol): 3190, 3060, 1649, 1550, 1460 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.2—1.9 (6H, m), 2.10 (3H, s), 3.59 (2H, t, J=7.0 Hz), 3.60 (2H, t, J=6.0 Hz), 6.69 (1H, s), 11.19 (1H, br s).

***N*-[4-[4-(1*H*-Indol-3-yl)piperidinomethyl]-2-thiazolyl]acetamide (5a)** A mixture of **3a**[13] (0.48 g, 2.5 mmol), **4a**[9] (0.5 g, 2.5 mmol) and $NaHCO_3$ (0.31 g, 3.7 mmol) in a mixed solvent of DMF (5 ml) and THF (7 ml) was refluxed with stirring for 1.7 h. After cooling, the reaction mixture was concentrated under reduced pressure. The residue obtained was diluted with water (50 ml) and extracted with AcOEt. The organic layer was washed with brine, dried and evaporated. 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 crude materials, which were recrystallized from EtOH to afford **5a** (0.20 g, 30.2%) as slightly brownish crystals, mp 204—207 °C.

Compounds **5b—e** were also prepared by this method. The physical data of **5a—e** are listed in Table III.

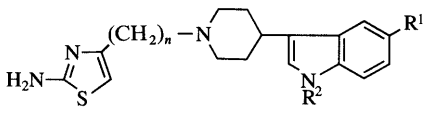
TABLE III. *N*-[4-[4-(1*H*-Indol-3-yl)piperidinoalkyl]-2-thiazolyl]acetamides (**5a—e**)



	n	R^1	Yield (%)	mp (°C) (Recryst. solvent)	IR (Nujol, cm^{-1})	Formula	Analysis (%) Calcd (Found) C	H	N	NMR (DMSO-d_6, δ: J=Hz)
5a	1	H	30.2	204—207 (EtOH)	3400, 3165, 1686, 1263	$C_{19}H_{22}N_4OS$	64.38 (64.40	6.26 6.06	15.81 15.67)	2.32 (3H, s), 1.40—3.20 (9H, m), 3.52 (2H, s), 6.80—7.70 (6H, m), 10.70 (1H, s), 12.08 (1H, s)
5b	2	H	27.8	203—204 (EtOH)	3275, 1663, 1560, 1305	$C_{20}H_{24}N_4OS$	65.19 (65.30	6.56 6.77	15.20 15.21)	2.13 (3H, s), 1.40—3.40 (13H, m), 6.80 (1H, s), 6.80—7.70 (5H, m), 10.79 (1H, s), 12.03 (1H, s)
5c	3	H	13.7	169—170 (EtOH)	3300, 3100, 1670, 1570, 1300	$C_{21}H_{26}N_4OS$	65.94 (65.76	6.85 6.36	14.65 14.46)	2.12 (3H, s), 1.40—3.30 (15H, m), 6.70 (1H, s), 6.80—7.70 (5H, m), 10.70 (1H, s), 12.00 (1H, s)
5d[a]	5	H	32.5	254—257 (EtOH)	3200, 2650, 2555, 1655, 1555	$C_{23}H_{30}N_4OS$ ·HCl·1/2EtOH	61.32 (61.13	7.29 7.13	11.92 11.12)	2.13 (3H, s), 1.10—3.70 (9H, m), 6.72 (1H, s), 6.80—7.70 (5H, m), 10.55 (1H, br s), 10.84 (1H, br s), 11.96 (1H, br s)
5e	1	OMe	60.7	123—133 (EtOH–H_2O)	3420, 1690, 1570	$C_{20}H_{24}N_4O_2S$ ·H_2O	59.68 (59.70	6.51 6.61	13.92 13.70)	2.11 (3H, s), 1.30—3.20 (9H, m), 3.52 (2H, s), 3.74 (3H, s), 6.70 (1H, dd, J=3, 9), 6.90 (1H, s), 6.98 (1H, d, J=3), 7.03 (1H, d, J=3), 7.23 (1H, d, J=9), 10.55 (1H, br s), 12.05 (1H, s)

a) Obtained as the HCl salt.

TABLE IV. 4-[4-(1*H*-Indol-3-yl)piperidinoalkyl]-2-thiazolamines (**7a—g**)



	n	R^1	R^2	Yield (%)	mp (°C) (Recryst. solvent)	IR (Nujol, cm^{-1})	MS (*m/z*)	^{1}H-NMR (DMSO-d_6, δ: *J*=Hz)
7a	1	H	H	38.7	195—198 (EtOH)	3300, 1380, 1330	312 (M^+)	1.40—3.40 (11H, m), 6.30 (1H, s), 6.77 (2H, s), 6.80—7.70 (5H, m), 10.70 (1H, s)
7b	2	H	H	88.6	173.5—176 (EtOH)	3425, 3250, 1615, 1505	326 (M^+)	1.30—3.30 (13H, m), 6.15 (1H, s), 6.74 (2H, s), 6.80—7.70 (5H, m), 10.70 (1H, br s)
7c	3	H	H	65.9	108—109 ($EtOH-H_2O$)	3450, 3100, 1635, 1530	340 (M^+)	1.50—3.00 (15H, m), 6.03 (1H, s), 6.68 (2H, s), 6.90—7.50 (5H, m), 10.70 (1H, s)
7d	5	H	H	100	Oil	3450, 3100, 1377	368 (M^+)	1.00—3.10 (19H, m), 6.07 (2H, s), 6.70 (2H, s), 6.80—7.60 (6H, m), 10.66 (1H, s)
7e	1	OMe	H	82.6	192—194[a]	3420, 3290, 1630, 1208	342 (M^+)	1.50—3.30 (11H, m), 3.40 (2H, s), 3.82 (3H, s), 6.37 (1H, s), 6.60—7.50 (4H, m), 10.61 (1H, br s)
7f	1	NO_2	H	71.4	225—227[a]	3500, 3410, 3210, 1605, 1517, 1327, 1247, 1087	357 (M^+)	1.60—3.30 (11H, m), 3.40 (2H, s), 6.38 (1H, s), 6.70—6.90 (2H, m), 7.40 (1H, s), 7.51 (1H, d, *J*=7), 8.01 (1H, dd, *J*=2, 7), 8.33 (1H, d, *J*=2), 10.61 (1H, s)
7g	1	H	Me	66.0	194—196[a]	3350, 3100, 1630, 1530, 1505	326 (M^+)	1.50—3.30 (11H, m), 3.40 (2H, s), 3.85 (3H, s), 6.40 (1H, s), 6.60—7.70 (4H, m)

a) Used for the next reaction without purification.

4-[4-(1*H*-Indol-3-yl)piperidinomethyl]-2-thiazolylamine (7a) A mixture of **5a** (1.2 g, 3.4 mmol) and aqueous 10% HCl (9 ml) in EtOH (3 ml) was stirred at 80 °C for 2.5 h. After evaporation of the EtOH, 10% NaOH was added slowly to the residue under ice-water cooling. The resulting precipitates were collected by filtration, washed with water and recrystallized from EtOH to afford **7a** (0.41 g, 38.7%) as slightly brownish crystals, mp 195—198 °C.

Compounds **7b—e** were also prepared by this method. The physical data of **7a—e** are listed in Table IV.

4-[4-(5-Nitro-1*H*-indol-3-yl)piperidinomethyl]-2-thiazolylamine (7f) A mixture of **4c** (0.43 g, 1.8 mmol), **6**[12] (0.42 g, 2.3 mmol) and Et_3N (1.1 ml, 7.9 mmol) in DMF (4.3 ml) was stirred at 35 °C for 4 h. The reaction mixture was diluted with water (22 ml). The resulting gum was separated by decantation and triturated with 60% EtOH (5 ml). The objective materials were collected by filtration to afford **7f** (0.45 g, 71.4%) as a slightly brownish powder, mp 225—227 °C.

Compound **7g** was also prepared by this method. The physical data of **7f, g** are listed in Table IV.

***N*-[4-[4-(1*H*-Indol-3-yl)piperidinomethyl]-2-thiazolyl]methanesulfonamide (8)** A solution of methanesulfonyl chloride (1.2 ml, 15.6 mmol) in CH_2Cl_2 (1.5 ml) was added slowly to a mixture of **7a** (1.73 g, 5.54 mmol) and Et_3N (3.1 ml, 33.3 mmol) in DMF (15 ml) at 5—7 °C. After being stirred at the same temperature for 3.5 h, the reaction mixture was diluted with water (50 ml) and extracted with a mixed solvent of $CHCl_3$ and MeOH (10:1). The organic layer was washed with brine, dried, and evaporated. The resulting residue was dissolved in THF (40 ml). Then 10% NaOH (20 ml) was added slowly to the solution and the mixture was stirred overnight. The reaction mixture was neutralized with diluted HCl and the mixture was extracted with a mixed solvent of $CHCl_3$ and MeOH (10:1). The organic layer was washed with brine, dried, and evaporated. The resulting residue was chromatographed on silica gel with a mixed solvent of $CHCl_3$ and MeOH (10:1). The desired fractions were collected and evaporated to give crude materials, which were recrystallized from aqueous DMF to afford **8** (0.48 g, 22.2%) as slightly brownish crystals, mp 207—208 °C.

Compounds **9—21** were prepared by this method, although *N*-methylmorpholine instead of Et_3N was used as a base in the cases of **11, 19, 20** and **21**. The physical data of **8—21** are listed in Table I.

Biological Activities Systemic Anaphylaxis in Guinea Pigs: Male Hartley strain guinea pigs were used. Systemic anaphylaxis was induced by the method described previously.[14] Briefly, the animals were sensitized passively with rabbit antiserum raised against egg albumin (EA) by intravenous administration and challenged with an aerosolized EA solution at 24 h after sensitization. When test-drug-administered animals survived for 2 h after the antigen challenge, they were considered to have been protected from anaphylactic asthma. The test compounds were given orally 30 min before the challenge.

Effect on Sleeping Time Induced by Hexobarbital in Mice: Ten ICR strain mice weighing about 25 g were used in each group. Hexobarbital (82.5 mg/kg) was injected intraperitoneally, and the latency and duration of the induced sleep were recorded. Sleep was taken to correspond to loss of the righting reflex. The test drugs were given orally 60 min before the injection of hexobarbital.

Effect on the Electroencephalogram of Conscious Rabbits: White strain rabbits weighing 2—3.6 kg were used. The procedure followed the method described previously for ketotifen.[15]

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