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Synthetic Studies on Condensed-Azole Derivatives. III.[1] Synthesis and Anti-asthmatic Activities of C-Substituted Alkyl Side Chain Derivatives of ω-Sulfamoylalkylthioimidazo[1,2-*b*]pyridazines and Related Compounds

Masaaki KUWAHARA,[a] Yasuhiko KAWANO,[a] Hiroshi SHIMAZU,[a] Hiroaki YAMAMOTO,[a]
Yasuko ASHIDA,[b] and Akio MIYAKE[a,*]

Pharmaceutical Research Division, Pharmaceutical Research Laboratories III,[a] Pharmaceutical Research Laboratories II,[b] Takeda Chemical Industries, Ltd., 17–85 Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.

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A series of novel alkylthioimidazo[1,2-*b*]pyridazines was synthesized and evaluated for ability to inhibit platelet activating factor (PAF)-induced bronchoconstriction in guinea pigs. Among them, 3-(imidazo[1,2-*b*]pyridazin-6-yl)thio-2,2-dimethylpropanesulfonamide (15) showed the most potent inhibitory effect. The structure–activity relationships in this series of compounds, in particular, the effects of conversion of the imidazopyridazine ring into other heterocyclic rings, introduction of a substituent group at the 2 or 3 position of the imidazopyridazine ring and introduction of a substituent group into the alkyl side chain, are also discussed.

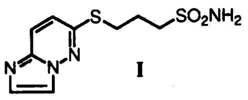
Key words anti-asthmatic effect; PAF-induced bronchoconstriction; imidazo[1,2-*b*]pyridazin; structure–activity relationship

In a previous paper[2] we reported the synthesis and anti-asthmatic activity of a series of ω-sulfamoylalkylthioimidazo[1,2-*b*]pyridazines, a new class of orally active bronchodilators. Among them, 3-(imidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamide (I, Fig. 1) showed the most potent inhibitory effect on platelet activating factor (PAF)-induced bronchoconstriction in guinea pigs, and moreover provided protection against the experimental allergic asthma induced by antigen inhalation in passively sensitized guinea pigs. These activities were superior to those of theophylline. In a study of the structure–activity relationships, it was found that a sulfamoylpropylthio group at the 6 position of the imidazo[1,2-*b*]pyridazine ring of I was most suitable for anti-asthmatic activity. In an effort to improve the anti-asthmatic activity of I, we further examined conversion of the imidazo[1,2-*b*]pyridazine ring into other heterocyclic rings, introduction of a substituent at the 2 or 3 position of the imidazo[1,2-*b*]pyridazine ring and introduction of a substituent into the alkyl side chain.

We describe here the synthesis and anti-asthmatic activities of a series of these compounds.

Chemistry

The derivatives (1—6) in which the imidazo[1,2-*b*]pyridazine ring of I has been replaced with other heterocyclic rings, listed in Table 1, were synthesized by

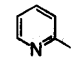
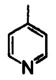
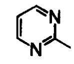
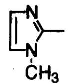
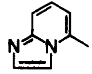
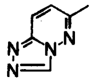


I

Fig. 1

Table 1. Physical Data for Sulfonamide Derivatives

$R{-}S{-}(CH_2)_3{-}SO_2NH_2$

Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
1		146—149	$C_8H_{12}N_2O_2S_2$	41.36	5.21	12.06	41.42	5.24	12.05	79
2		154—156	$C_8H_{12}N_2O_2S_2$	41.36	5.21	12.06	41.17	5.18	12.03	57
3		125—128	$C_7H_{12}N_3O_2S_2\cdot HCl$	31.17	4.48	15.58	30.99	4.55	15.67	45
4		129—131	$C_7H_{13}N_3O_2S_2$	35.73	5.57	17.86	35.73	5.53	17.91	45
5		188—190	$C_{10}H_{13}N_3O_2S_2\cdot HCl$	39.02	4.58	13.65	39.02	4.64	13.50	65
6		205—207	$C_8H_{11}N_5O_2S_2\cdot H_2O$	32.98	4.50	24.04	33.10	4.31	23.85	72

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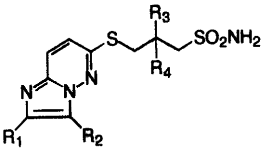
* To whom correspondence should be addressed.

Table 2. Physical Data for Substituted Sulfamoylpropylthioimidazo[1,2-*b*]pyridazines



Compd. No.	R_1	R_2	R_3	R_4	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	$[\alpha]_D$ (c=1.0, H_2O)	Yield (%)
7	CH_3	H	H	H	124—126	$C_{10}H_{14}N_4O_2S_2$	41.94	4.93	19.56		38
							(42.04	4.83	19.88)		
8	H	CH_3	H	H	197—201	$C_{10}H_{14}N_4O_2S_2 \cdot HCl \cdot H_2O$	35.24	5.03	16.44		63
							(35.21	4.96	16.14)		
9	H	Cl	H	H	153—155	$C_9H_{11}ClN_4O_2S_2 \cdot HCl$ $\cdot 0.2H_2O$	31.16	3.60	16.15		58
							(31.22	3.52	16.15)		
10	H	H	CH_3	H	208—210	$C_{10}H_{14}N_4O_2S_2 \cdot HCl$	37.20	4.68	17.35		22
							(37.55	4.55	17.49)		
11	H	H	CH_3(*R*)	H	157—160	$C_{10}H_{14}N_4O_2S_2 \cdot HCl \cdot H_2O$	35.24	5.03	16.44	−13.2	20
							(35.32	4.95	16.43)		
12	H	H	CH_3(*S*)	H	154—157	$C_{10}H_{14}N_4O_2S_2 \cdot HCl$ $\cdot 0.3H_2O$	36.59	4.79	17.07	+13.6	16
							(36.80	4.74	17.21)		
13	H	H	CH_2CH_3	H	120—121	$C_{11}H_{16}N_4O_2S_2$	43.98	5.37	18.65		58
							(44.11	5.38	18.50)		
14	H	H	Ph	H	80—83	$C_{15}H_{16}N_4O_2S_2 \cdot 0.5H_2O$	50.40	4.79	15.67		60
							(50.43	4.51	15.44)		
15	H	H	CH_3	CH_3	198—199	$C_{11}H_{16}N_4O_2S_2$	43.98	5.37	18.65		18
							(43.94	5.48	18.81)		
16	H	H	$-CH_2CH_2CH_2-$		189—191	$C_{12}H_{16}N_4O_2S_2 \cdot HCl$ $\cdot 0.3CH_2CH_2OH$	41.73	5.23	15.45		70
							(41.97	5.15	15.50)		

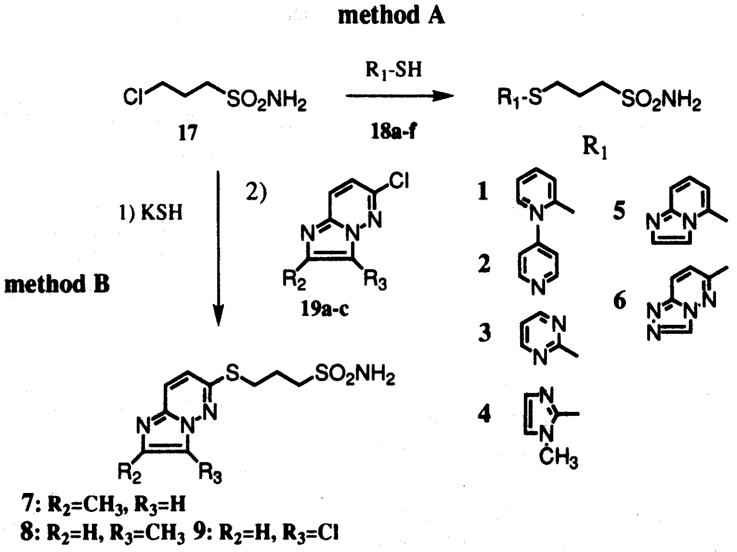


Chart 1

the route shown in Chart 1 (method A). Treatment of 3-chloropropanesulfonamide (**17**)[2] with mercapto derivatives (**18a**—**d**, **18e**,[3] **18f**[4]) in the presence of sodium methoxide gave compounds **1**—**6**. Imidazo[1,2-*b*]pyridazine derivatives (**7**—**9**) having a substituent at the 2 or 3 position were prepared *via* the route shown in Chart 1 (method B). Compound **17** was converted to the 3-mercaptopropanesulfonamide[5] by treatment with potassium hydrogen sulfide followed by reaction with imidazo[1,2-*b*]pyridazine derivatives (**19a**,[6] **19b**,[7] **19c**[6]) in the presence of sodium methoxide to afford compounds **7**—**9**. The compound (**10**) in which a methyl group has been introduced into the alkyl side chain at the 6 position of I was prepared *via* the route shown in Chart 2. (*R*,*S*)-1-Bromo-3-chloro-2-methylpropane (**20**) was converted to the thiocyanate (**21**) by reaction with potassium thiocyanate followed by treatment with chlorine gas and then ammonia gas to afford the sulfonamide (**23**).[8] Compound **23** was reacted with 6-chloroimidazo[1,2-*b*]pyridazine (**24**)[9] in the presence of sodium methoxide to afford compound **10**. We attempted to prepare the optical isomers (**11** and **12**) of **10** by the same procedure. However, the reaction of (*R*)-(−)-3-bromo-2-methylpropanol (**25a**) with potassium thiocyanate gave a racemic

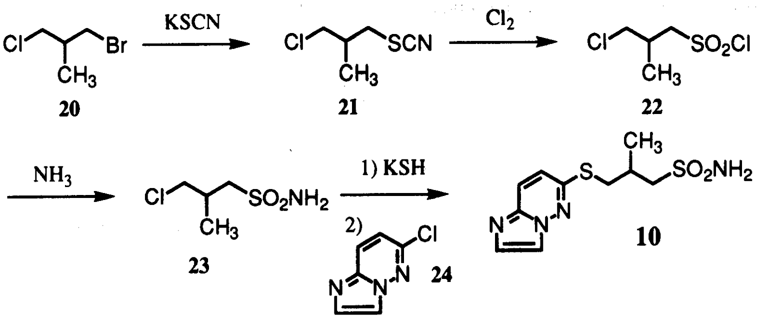


Chart 2

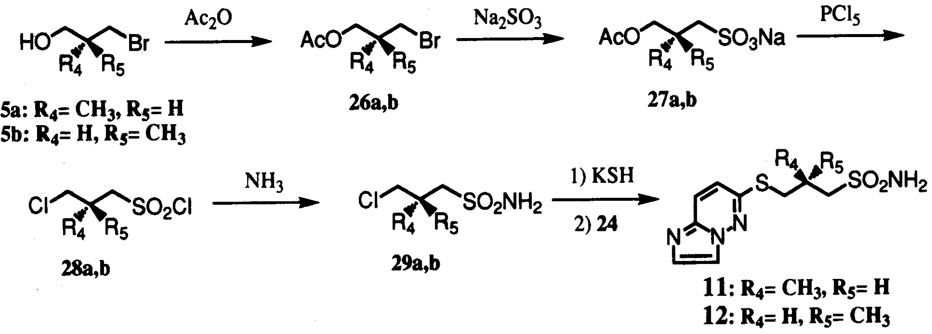


Chart 3

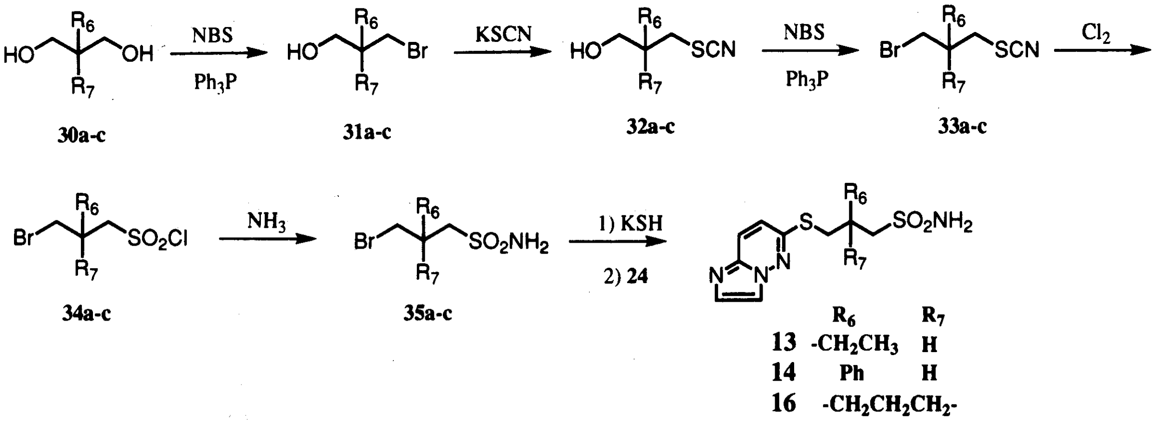


Chart 4

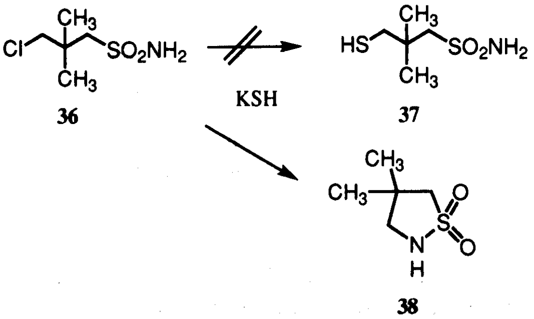


Chart 5

product. The synthesis of **11** and **12** was achieved by the procedure shown in Chart 3. After acetylation of **25a**, the resulting **26a** was reacted with sodium sulfite to afford the sulfonate (**27a**), followed by treatment with phosphorus pentachloride and then ammonia to yield the sulfonamide (**29a**). This was reacted with potassium hydrogen sulfide and then with **24** to afford compound **11**. Compound **12** was obtained from (*S*)-(+)-3-bromo-2-methylpropanol (**25b**) by the same procedures. The compounds in which an ethyl (**13**), phenyl (**14**) or cyclobutylidene (**16**) group has been introduced into the alkyl side chain at the 6 position of I were prepared *via* the route shown in Chart 4. After monobromination[10)] of the diol (**30a**—**c**[11)]), the resulting bromoalcohol (**31a**—**c**) was reacted with potassium thiocyanate followed by bromination to afford the thiocyanate (**33a**—**c**). Compounds **13**, **14** and **16** were obtained with **33a**—**c** in a manner similar to that used for preparation of **10**. To obtain the dimethyl derivative (**15**) of I, the dimethylsulfonamide (**36**) was prepared from 1-bromo-3-chloro-2,2-dimethylpropane by the procedure used to prepare **23**. Compound **36** was treated with potassium hydrogen sulfide to afford the sultam (**38**), but the thiol (**37**) could not be obtained (Chart 5). Therefore, compound **15** was obtained *via* the route outlined in Chart 6. The bromoalcohol (**39**) was reacted with potassium thiocyanate followed by acetylation to give the thiocyanate (**41**). The acetate **41** was treated with chlorine gas and then am-

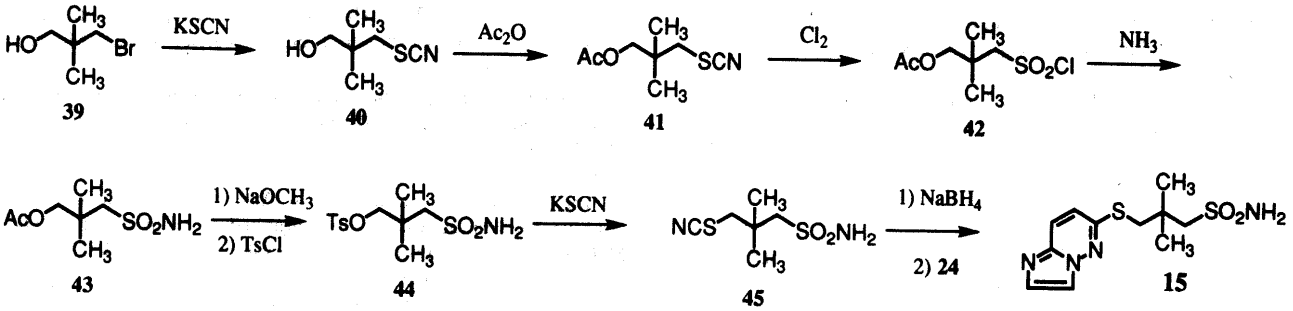


Chart 6

Table 3. Variation in Anti-asthmatic Effect among Compounds with Various Heterocyclic Rings

Compd. No.	% inhibition of PAF-induced bronchoconstriction[a]
1	41
2	41
3	9
4	14
5	53**
6	8
I	71**

[a] Compounds were given orally at a dose of 30 mg/kg 1 h before PAF treatment. Significance of differences (Dunnett's test): ** $p<0.01$ (*vs.* control).

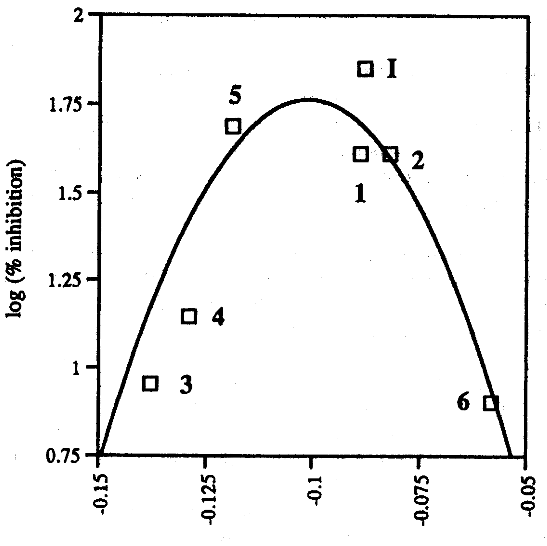


Fig. 2. Correlation between Anti-asthmatic Activity and Charge on the Nitrogen

$y=-438.92X^2-88.899X-2.738$, $r=0.810$.

Table 4. Variation in Anti-asthmatic Effect with 2 or 3 Substitution of Imidazo[1,2-*b*]pyridazines

Compd. No.	% inhibition of PAF-induced bronchoconstriction[a]
7	29
8	67**
9	54**

[a] Compounds were given orally at a dose of 30 mg/kg 1 h before PAF treatment. Significance of differences (Dunnett's test): ** $p<0.01$ (*vs.* control).

monia gas to afford the sulfonamide (**43**). Deprotection of **43** followed by tosylation produced the tosylate (**44**). After conversion of the tosyl group into thiocyanate group, the resulting **45** was reduced with sodium borohydride and then reacted with **24** in the presence of sodium methoxide to afford the dimethyl derivative (**15**).

Inhibition of PAF-Induced Bronchoconstriction The compounds obtained in this study were evaluated for anti-asthmatic activity at a dose of 30 mg/kg, *p.o.* using PAF-induced bronchoconstriction in guinea pigs. The results are summarized in Tables 3, 4 and 5.

In the series of compounds in which the imidazo[1,2-*b*]pyridazine ring has been replaced with other monocyclic rings, pyridine derivatives (**1** and **2**) showed moderate anti-asthmatic activity (Table 3). Pyrimidine (**3**) and imidazole (**4**) derivatives were less active. Of the compounds with other condensed azole rings, the imidazo[1,2-*a*]pyridine (**5**) was fairly active; however, its activity was weaker than that of imidazo[1,2-*b*]pyridazine (**I**). The activity of triazolopyridazine (**6**) was relatively low. There seemed to be a relationship between basicity of the heterocyclic ring and the anti-asthmatic activity. In order to investigate this, the common logarithm of the anti-asthmatic activity against PAF-induced bronchoconstriction was plotted against the charge on the nitrogen atom at the 1 position of the heterocyclic ring (Fig. 2). The charge on the nitrogen of the heterocyclic ring was estimated by the MNDO-PM3 method using a model compound in which the alkyl side chain was replaced with a methylthio group.[12] As can be seen in Fig. 2, the charge on the nitrogen shows a fairly good parabolic correlation ($r=0.810$) with the log of the anti-asthmatic activity. This suggests that the basicity of the heterocyclic ring is an important factor for the activity.

Introduction of a substituent group at the 2 position of the imidazo[1,2-*b*]pyridazine ring (**7**) decreased the activity (Table 4). In contrast, the activity of the 3-substituted derivatives (**8** and **9**) was comparable to that of **I**

The effects of substituents on the alkyl side chain of the imidazo[1,2-*b*]pyridazine at the 6 position were examined (Table 5). Introduction of a methyl or ethyl group (**10** and **13**) enhanced the activity. These compounds were more active than I. Introduction of a more lipophilic substituent, as in the case of **14**, however, decreased the activity. The activity of the optical isomers (**11** and **12**) of **10** was investigated. It was found that the *R*-isomer (**11**) was twice as potent as the *S*-isomer (**12**) upon intravenous administration. There was no significant difference in activity between **10** and **11**. Compound **15**

Table 5. Variation in Anti-asthmatic Effect with Substitution of the Alkyl Sidechain of Imidazo[1,2*b*]pyridazines

Compd. No.	% inhibition of PAF-induced bronchoconstriction	
	30 mg/kg, *p.o.*[a]	3 mg/kg, i.v.[b]
10	74**	77**
11	79**	56**
12	NT	30*
13	80**	NT
14	52**	NT
15	99**	74**
16	81**	NT
I	71**	45

a) Compounds were given orally 1 h before PAF treatment. *b*) Compounds were given intravenously 2 min before PAF treatment. Significance of differences (Dunnett's test): * $p<0.05$, ** $p<0.01$ (*vs.* control). NT = not tested.

Table 6. Effects of Compound **15** and Theophylline on Experimental Allergic Asthma Induced by Antigen Inhalation in Guinea Pigs Passively Sensitized with Rabbit Anti-egg Albumin Serum

Compound	No. of animals	Symptom[a]				Mean score	Mortality died/total
		0	I	II	III		
Control	7	—	—	—	7	3.0±0.0	7/7
Mepyramine (3 mg/kg)	7	—	—	—	7	3.0±0.0	7/7
15 + mepyramine (3 mg/kg)	7	3	1	—	3	1.4±0.6**	0/7
Theophylline + mepyramine (3 mg/kg)	7	—	3	—	4	2.1±0.4	3/7

Compounds were given orally at a dose of 30 mg/kg 1 h before antigen challenge. *a*) 0, no symptoms; I, dyspnea; II, cyanosis; III, collapse or death. ** $p<0.01$ (*vs.* control).

having two methyl substituents was found to have the most potent inhibitory effect. The intravenous activity of compound **15** was greater than that of compound I. Introduction of a cyclobutylidene group (**16**), corresponding to a cyclo-derivative of **15**, resulted in reduced activity,but the activity was still more potent than that of I.

Compound **15** (30 mg/kg, *p.o.*) also reduced asthmatic symptoms induced by antigen inhalation in guinea pigs sensitized with anti-egg albumin serum (Table 6), whereas theophylline (30 mg/kg, *p.o.*), which has been used in the treatment of asthma for many years, had no effect on these symptoms. This result suggests that compound **15** is superior to theophylline.

In conclusion, we obtained several sulfonamide derivatives which are structurally novel anti-asthmatic compounds. The anti-asthmatic activity was influenced by the conversion of the heterocyclic ring, and the introduction of a substituent group into the imidazopyridazine ring or into the alkyl side chain. In particular, the basicity of the heterocyclic ring was an important factor for activity. Among these compounds, compound **15** possessing two methyl substituents on the alkyl side chain, showed the most potent activity in experimental models of asthma.

Experimental

The melting points were determined on a Yanagimoto hot plate micro melting point apparatus and are uncorrected. IR spectra were taken with a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian Gemini-200 (200 MHz) spectrometer using tetramethylsilane as the internal standard. Chromatography was carried out with Merck Silica gel 60 (70—230 mesh).

3-(Pyridin-2-yl)thiopropanesulfonamide (1) A mixture of 2-mercaptopyridine (**18a**, 1.67 g) and 28% methanolic NaOMe solution (3.18 g) in MeOH (30 ml) was stirred at 60 °C for 0.5 h. Compound **17** (4.11 g) in MeOH (30 ml) was then added to the reaction mixture followed by stirring at 60 °C for an additional 2 h. After the solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (30 : 1). The product was recrystallized from MeOH–Et_2O to give 2.76 g of **1** (79%) as colorless crystals.

Compounds **2**—**6** were obtained similarly. In the synthesis of **2**—**6**, **18b**—**f** were used, respectively, instead of **18a**. The chemical data for these compounds (**1**—**6**) are summarized in Tables 1 and 7.

3-(2-Methylimidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamide (7) A mixture of **17** (1.57 g) and 2 N KSH–EtOH solution (20 ml) in MeOH (20 ml) was stirred at 70 °C for 1 h. Then **19a** (1.20 g) and 28% methanolic NaOMe solution (1.48 g) were added and the reaction mixture was refluxed for 3 h with stirring. The solvent was evaporated *in vacuo*, H_2O (20 ml) was added to the residue, and the mixture was neutralized to pH 7 with 1 N HCl. The solution was extracted with EtOAc, and the extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with CH_2Cl_2–MeOH (20 : 1) and the product was recrystallized from MeOH–Et_2O to give 0.8 g of **7** (38%) as colorless crystals.

Compounds **8**—**10** were obtained similarly. In the synthesis of **8**—**10**, **19b**, **19c** and **23** were used, respectively, instead of **19a**. The chemical data for these compounds (**7**—**10**) are summarized in Tables 2 and 7.

(*S*)-(−)-3-Chloro-2-methylpropane-1-sulfonamide (29a) A mixture of (*R*)-(−)-3-bromo-2-methyl-1-propanol (**25a**, 30 g) and Ac_2O (150 ml) in pyridine (100 ml) was stirred at 70 °C for 3 h. After the solvent was evaporated *in vacuo*, H_2O (200 ml) was added to the residue followed by extraction with Et_2O. The extract was separated, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford **26a** (colorless oil, 24.4 g, 64%). IR (neat): 2965, 1742, 1232, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, $J=7$ Hz), 2.08 (3H, s), 2.15—2.19 (1H, m), 3.43 (2H, d, $J=5.5$ Hz), 4.01—4.08 (2H, m). A mixture of **26a** (24 g) and Na_2SO_3 (15 g) in H_2O (60 ml) was refluxed for 20 h; concentrated HCl (17.9 ml) was added to the reaction mixture followed by refluxing for an additional 1 h. After cooling, the mixture was neutralized to pH 7 with 20% NaOH and concentrated to 30 ml. The resulting precipitate was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was treated with PCl_5 (57 g) in portions under ice-cooling, and the mixure was allowed to stand for 1 h at room temperature, then poured into ice-water (500 ml) followed by extraction with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting hexane–CH_2Cl_2 (1 : 1) to give **28a** (colorless oil, 3 g, 13%). IR (neat): 2970, 1735, 1372, 1167 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, $J=7$ Hz), 2.77—2.81 (1H, m), 3.57—3.62 (2H, m), 3.77—3.83 and 4.00—4.05 (each 1H, m). A solution of **28a** (3 g) in CH_2Cl_2 (50 ml) was bubbled with NH_3 gas for 1 h under ice-cooling with stirring. After the precipitate was filtered off, the filtrate was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give 1.35 g of **29a** (50%) after recrystallization from hexane. mp 52—53 °C. $[\alpha]_D$ −4.9° ($c=1.0$, MeOH). IR (KBr): 3355, 1559, 1323, 1132 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, $J=7$ Hz), 2.50—2.62 and 3.00—3.10 (each 1H, m), 3.39—3.81 (3H, m), 4.72 (2H, br s). *Anal.* Calcd for $C_4H_{10}ClNO_2S$: C, 27.99; H, 5.87; N, 8.16. Found: C, 28.02; H, 6.01; N, 7.99.

Compound **11** was prepared from **29a** and **24** by the same procedures as used to prepare **7**. The chemical data for **11** are summarized in Tables 2 and 7.

(*R*)-(+)-3-Chloro-2-methylpropane-1-sulfonamide (29b) Compound **29b** was prepared from **25b** in the same manner as described for **29a**. mp 55—57 °C. $[\alpha]_D$ +6.0° ($c=1.0$, MeOH). IR (KBr): 3360, 1560, 1335, 1138 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, $J=7$ Hz), 2.50—2.68 and 3.00—3.10 (each 1H, m), 3.40—3.71 (3H, m), 4.75 (2H, br s). *Anal.* Calcd for $C_4H_{10}ClNO_2S$: C, 27.99; H, 5.87; N, 8.16. Found: C, 27.92; H, 5.91; N, 8.00.

Compound **12** was prepared from **29b** and **24** by the same procedures as used to prepare **7**. The chemical data for **12** are summarized in Tables 2 and 7.

3-Bromo-2-ethylpronane-1-sulfonamide (35a) *N*-Bromosuccinimide (7.2 g) was added in portions to an ice-cold mixture of **30a** (4.2 g) and triphenylphosphine (5.96 g) in CH_2Cl_2 (40 ml), and the mixture was stirred for 0.5 h under ice-cooling, then at room temperature for 1 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel with n-C_6H_{12}–EtOAc (1 : 1) to give 5.19 g of **31a** (colorless oil, 77%). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz), 1.33—1.49 (2H, m), 1.58—1.90 (1H, m), 1.60 (1H, br s), 3.41—3.78 (4H, m). A mixture of **31a** and KSCN (6.02 g) in *N*,*N*-dimethylformamide (DMF) (30 ml) was stirred for 70 min at 100 °C. After cooling, the reaction mixture was poured into brine and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with n-C_6H_{12}–EtOAc (2 : 1) to give **33a** (colorless oil, 3.3 g, 73%). IR (neat): 3430, 2975, 2940, 2890, 2150, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7 Hz), 1.42—1.53 (2H, m), 1.66 (1H, br s), 1.72—2.00 (1H, m), 3.05—3.31 (2H, m), 3.58—3.90 (1H, m). *N*-Bromosuccinimide (4.04 g) was added in portions to a solution of **32a** (3.3 g) and triphenylphosphine (5.96 g) in CH_2Cl_2 (40 ml) under ice-cooling. The mixture was stirred for 1 h at room temperature, then the solvent was evaporated *in vacuo*. The residue was chromatographed on silica gel with n-C_6H_{12}–EtOAc (10 : 1) to give 4.70 g of **33a** (colorless oil, 98%). IR (neat): 2975, 2940, 2150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.5 Hz), 1.42—1.68 (2H, m), 1.98—2.07 (1H, m), 2.92—3.21 (2H, m), 3.37—3.82 (2H, m). A solution of **33a** (2.09 g) in 50% AcOH (30 ml) was bubbled with Cl_2 gas for 1 h under ice-cooling with stirring. The solvent was evaporated *in vacuo*, and the residue was dissolved in CH_2Cl_2 (25 ml) and bubbled with NH_3 gas for 0.5 h under ice-cooling. After the precipitate was filtered off, the filtrate was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel with n-C_6H_{12}–EtOAc (3 : 2) and the product was recrystallized from Et_2O to give 1.58 g of **35a** (68%). mp 63—65 °C. IR (KBr): 3330, 1540, 1304, 1119 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7.5 Hz), 1.45—1.82 (4H, m), 2.16—2.41 (1H, m), 3.54—3.90 (2H, m), 4.80 (2H, s). *Anal.* Calcd for $C_5H_{12}BrNO_2S$: C, 26.10; H, 5.26; N, 6.09. Found: C, 26.14; H, 5.11; N, 6.26.

Compounds **35b** and **35c** were prepared by the same procedures as used to prepare **35a**. In the synthesis of **35b** and **35c**, **30b** and **30c**[11)] were used, respectively, instead of **30a**.

3-Bromo-2-phenylpropane-1-sulfonamide (**35b**) Colorless oil (74%). IR (neat): 3375, 3280, 1330, 1250, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.43—3.91 (5H, m), 4.29 (2H, br s), 7.15—7.52 (5H, m).

3-Bromo-2,2-cyclobutylidenepropane-1-sulfonamide (**35c**) Colorless needles (61%). mp 118—120 °C. IR (neat): 3325, 1551, 1310, 1161 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.83—2.41 (6H, m), 3.54, 3.91 and 4.80 (each 2H, s).

Compounds **13**, **14** and **16** were prepared from **35a**—**c**, respectively, by the procedures as used to prepare **7**. The chemical data for these compounds are summarized in Tables 2 and 7.

3-Acetoxy-2,2-dimethylpropane-1-sulfonamide (**43**) A mixture of **39** (83.5 g) and KSCN (73 g) in DMF (300 ml) was stirred at 130 °C for 4 h. After cooling, the reaction mixture was poured into H_2O and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give 64.7 g of **40** (colorless oil, 89%). IR (neat): 3450, 2970, 2155, 1470, 1050 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, s), 1.65—1.80 (2H, m), 3.04 (1H, br s), 3.43—3.51 (2H, m). A mixture of **40** (64 g) and Ac_2O (450 ml) in pyridine (450 ml) was stirred for 15 h at room temperature. The solvent was evaporated *in vacuo*, and H_2O was added to the residue, followed by extraction with Et_2O. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$ and evaporated *in vacuo* to afford 71.3 g of **41** (colorless oil, 86%). IR (neat): 2970, 2150, 1740, 1380, 1235, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (6H, s), 2.08 (3H, s), 3.02 and 3.91 (each 2H, s). A solution of **41** (71 g) in 50% AcOH (200 ml) was bubbled with Cl_2 gas for 1 h under ice-cooling with stirring. After the solvent was evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 (200 ml) and bubbled with NH_3 gas for 1 h under ice-cooling. The precipitate was filtered off, and the filtrate was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from Et_2O to give 53.7 g of **43** as colorless crystals (70%). mp 106—109 °C. IR (neat): 3330, 1715, 1330, 1270, 1255, 1155 cm^{-1}.

Table 7. IR and ^{1}H-NMR Data for Sulfonamide Derivatives

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
1	3300, 1585, 1550, 1450, 1410, 1330, 1145	2.03—2.10, 3.06—3.14 and 3.23—3.32 (each 2H, m), 6.82 (2H, br s), 7.09—7.15, 7.28—7.33, 7.60—7.68 and 8.43—8.46 (each 1H, m)
2	3300, 1580, 1330, 1145	1.98—2.12 (2H, m), 3.10—3.25 (4H, m), 6.86 (2H, br s), 7.30 and 8.38 (each 2H, d, J=3 Hz)
3	3170, 1591, 1333, 1141	2.13—2.15, 3.07—3.15 and 3.21—3.28 (each 2H, m), 6.83 (2H, br s), 7.23 (1H, t, J=5 Hz), 8.64 (2H, d, J=5 Hz)
4	3135, 1569, 1462, 1280, 1133	1.91—2.09 (2H, m), 3.04—3.11 (4H, m), 3.59 (3H, s), 6.84 (2H, br s), 6.94 and 7.25 (each 1H, d, J=1.5 Hz)
5	2950, 1634, 1503, 1324, 1131	2.04—2.11 (2H, m), 3.17 and 3.44 (each 2H, t, J=7 Hz), 6.89 (2H, br s), 7.61—7.65 (1H, m), 7.89—7.91 (2H, m), 8.32 and 8.38 (each 1H, d, J=2 Hz)
6	3345, 1605, 1535, 1470, 1335, 1155	2.13—2.20, 3.11—3.19 and 3.31—3.38 (each 2H, m), 6.86 (2H, br s), 7.28 and 8.21 (each 1H, d, J=10 Hz), 9.51 (1H, s)
7	3325, 1535, 1325, 1295, 1135, 1190	2.25—2.40 (2H, m), 2.45 (3H, s), 3.20—3.40 (4H, m), 6.54 (2H, br s), 6.85 and 7.64 (each 1H, d, J=9.5 Hz), 7.69 (1H, s)
8	3225, 1552, 1467, 1319, 1151	2.20—2.27 (2H, m), 2.58 (3H, s), 3.17 and 3.43 (each 2H, t, J=8 Hz), 6.82 (2H, br s), 7.69 and 8.27 (each 1H, d, J=9.5 Hz), 8.04 (1H, s)
9	3430, 1530, 1320, 1130	2.25—2.32, 3.20—3.27 and 3.43—3.53 (each 2H, m), 6.87 (2H, br s), 7.23 and 8.01 (each 1H, d, J=9.5 Hz), 7.79 (1H, s)
10	3065, 1479, 1322, 1152, 1127	1.21 (3H, d, J=7 Hz), 2.40—2.59 and 2.96—3.07 (each 1H, m), 3.17—3.29 (2H, m), 3.40—3.51 (1H, m), 6.92 (2H, br s), 7.69 and 8.27 (each 1H, d, J=9.5 Hz), 8.20 and 8.52 (each 1H, d, J=2 Hz)
11	3390, 1472, 1319, 1145, 1123	1.21 (3H, d, J=7 Hz), 2.47 (1H, m), 3.02 (1H, dd, J=6, 14 Hz), 3.21 (1H, d, J=6 Hz), 3.29 (1H, t, J=6 Hz), 3.44 (1H, dd, J=6, 14 Hz), 6.92 (2H, br s), 7.67 and 8.26 (each 1H, d, J=9.5 Hz), 8.18 and 8.51 (each 1H, d, J=2 Hz)
12	3200, 1465, 1340, 1250, 1135	1.21 (3H, d, J=7 Hz), 2.46 (1H, m), 3.02 (1H, dd, J=7.5, 14.5 Hz), 3.20 (1H, d, J=7 Hz), 3.29 (1H, t, J=7 Hz), 3.43 (1H, dd, J=5, 14.5 Hz), 6.91 (2H, br s), 7.66 and 8.24 (each 1h, d, J=10 Hz), 8.24 and 8.49 (each 1H, d, J=2 Hz)
13	3315, 2970, 1530, 1450, 1315, 1280, 1140, 1120	0.95 (3H, t, J=7.5 Hz), 1.40—1.80 (2H, m), 2.20—2.40 (1H, m), 3.00—3.50 (4H, m), 6.91 (2H, br s), 7.13 and 7.96 (each 1H, d, J=9.5 Hz), 7.67 and 8.15 (each 1H, s)
14	1530, 1445, 1320, 1280, 1140, 1120, 1100	3.30—3.90 (5H, m), 6.89 (2H, br s), 7.10—7.50 (5H, m), 7.03 and 7.90 (each 1H, d, J=9.5 Hz), 7.67 and 8.13 (each 1H, s)
15	3050, 1470, 1325, 1140	1.22 (6H, s), 3.17 and 3.44 (each 2H, s), 6.95 (2H, br s), 7.15 and 7.93 (each 1H, d, J=9.5 Hz), 7.67 and 8.18 (each 1H, s)
16	1470, 1335, 1330, 1270, 1140, 1115	1.70—2.30 (6H, m), 3.35—3.83 (2H, s), 7.02 (2H, s), 7.71 and 8.26 (each 1H, d, J=9.5 Hz), 7.68 and 8.21 (each 1H, s)

^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, s), 2.08 (3H, s), 3.85 and 3.97 (each 2H, s). *Anal.* Calcd for $C_7H_{15}NO_4S$: C, 40.18; H, 7.23; N, 6.69.Found: C, 39.90; H, 7.38; N, 6.67.

2,2-Dimethyl-3-tosyloxypropane-1-sulfonamide (44) A mixture of **43** (53 g) and 28% methanolic NaOMe solution (36.5 g) in MeOH (300 ml) was stirred for 1.5 h at room temperature, then evaporated *in vacuo*. The residue was chromatographed on silica gel with CH_2Cl_2–MeOH (9 : 1), and the eluate was evaporated *in vacuo*. The residue was dissolved in pyridine (65 ml), and tosyl chloride (21.6 g) was added to the solution in portions under ice-cooling with stirring. The mixture was stirred for 2 h under ice-cooling, CH_2Cl_2 (500 ml) was added, and the whole was washed with 2 N HCl and H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from Et_2O to give 32.4 g of **44** as colorless crystals (40%). mp 59—60 °C. IR (KBr): 3320,1360, 1335, 1190, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (6H, s), 2.44 (3H, s), 3.20 and 3.92 (each 2H, s), 4.90 (2H, br s), 7.35 and 7.80 (each 2H, d, $J=9$ Hz). *Anal.* Calcd for $C_{12}H_{19}NO_5S_2$: C, 44.84; H, 5.96; N, 4.36. Found: C, 44.84; H, 6.01; N, 4.27.

3-(Imidazo[1,2-*b*]pyridazin-6-yl)thio-2,2-dimethylpropanesulfonamide (15) A mixture of **44** (24.2 g) and KSCN (14.6 g) in DMF (150 ml) was heated at 130 °C for 4 h with stirring. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel with CH_2Cl_2–EtOAc (1 : 1) to give 5.71 g of **45** (colorless oil, 37%). IR (neat): 3350, 3260, 2970, 2150, 1330, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (6H, s), 3.26 and 3.29 (each 2H, s), 5.22 (2H, br s). A solution of **45** (1.47 g) in EtOH (50 ml) was treated with $NaBH_4$ (0.41 g) in portions. The mixture was stirred at 80 °C for 1 h, then **24** (670 mg) and 28% methanolic NaOMe solution (0.81 ml) were added and the whole was refluxed for 1 h with stirring. After the solvent was evaporated *in vacuo*, H_2O was added to the residue, followed by extraction with EtOAc–THF (1 : 1). The extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting CH_2Cl_2–MeOH (10 : 1) and recrystallized from EtOH to give 438 mg of **15** (18%). The chemical data for **15** are summarized in Tables 2 and 7.

PAF-Induced Bronchoconstriction in Guinea Pigs Groups of 6 hartley guinea pigs (male, body weight about 450 g) were used. The bronchoconstriction induced by PAF (1 μg/kg, i.v.) was measured according to the method of Konzett–Rössler.13) Details are given in our previous paper.2)

Experimental Allergic Asthma Induced by Inhalation of Antigen in Conscious Passively Sensitized Guinea Pigs Experimental allergic asthma was provoked by inhalation of antigen in guinea pigs passively sensitized by intravenous injection of 0.5 ml of rabbit anti-egg albumin (EA) serum; animals were challenged by inhalation of antigen 1 d after sensitization. The asthmatic symptoms were evaluated according to the method of Yamamura *et al.*14) Details are given in our previous paper.2)

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