Synthetic Studies on Condensed-Azole Derivatives. V.[1] Synthesis and Anti-asthmatic Activities of ω-Sulfamoylalkyloxy[1,2,4]triazolo[1,5-*b*]-pyridazines

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A series of novel ([1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxyalkylsulfonamides was synthesized and evaluated for the ability to inhibit platelet activating factor (PAF)-induced bronchoconstriction in guinea pigs. The compounds bearing a *gem*-dialkyl or a cycloalkylidene group at the 2 position of the sulfamoylpropyloxy group in the side chain and a methyl group at the 7 position were found to have potent activity. Among them, 2,2-diethyl-3-(7-methyl[1,2,4]-triazolo[1,5-*b*]pyridazin-6-yl)oxypropanesulfonamide (13) showed excellent anti-asthmatic activity. Compouds 13 may be of significant value in the treatment of asthma and other respiratory diseases. The structure-activity relationships in this series of compounds are discussed.

Key words anti-asthmatic effect; bronchoconstriction; [1,2,4]triazolo[1,5-*b*]pyridazine; theophylline; structure–activity relationship

In a previous paper[1] we reported the synthesis and anti-asthmatic activity of ω-sulfamoylalkyloxyimidazo-[1,2-*b*]pyridazines, a new class of orally active anti-asthmatic bronchodilators. As part of our program aimed at finding new class of anti-asthmatic bronchodilators, we further examined conversion of the imidazo[1,2-*b*]-pyridazine ring into [1,2,4]triazolo[1,5-*b*]pyridazine ring. Further, in an effort to improve the anti-asthmatic activity of the [1,2,4]triazolo[1,5-*b*]pyridazines, chemical modification of the alkyl side chain at the 6 position and introduction of substituents at the 2, 7 and 8 positions were carried out.

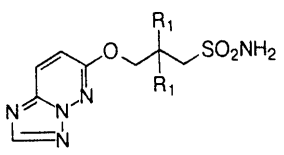
We describe here the synthesis and anti-asthmatic activities of a series of these compounds.

Chemistry

The synthesis of the 3-([1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxy-2,2-dialkylpropanesulfonamides (**1**—**7**, **13**—**16**) listed in Table 1 and 2 was carried out *via* the route shown in Chart 1. Substituted [1,2,4]triazolo[1,5-*b*]pyridazines (**25a**—**e**) were reacted with 3-hydroxypropanesulfonamides (**26a**—**e**[1]) in the presence of sodium hydride to afford **1**—**7** and **13**—**16**. [1,2,4]Triazolo[1,5-*b*]pyridazines (**25a**,[2] **25**, **b**[3] **25c**,[4] **25d**—**e**) were prepared following the reported procedures *via* the route shown in Chart 2. Aminochloropyridazines (**27a**—**d**[4,5]) were reacted with **28a** or **28b** to afford the aminomethylene derivatives (**29a**—**e**). Those were condensed with hydroxylamine hydrochloride and then treated with polyphosphoric acid to give 6-chloro[1,2,4]triazolo[1,5-*b*]pyridazines (**25a**—**e**).

The synthesis of the 3-(7-substituted[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamides (**8**—**12**) listed in Table 2 were carried out *via* the route shown in Chart 3. 6-Chloro-7-methyl[1,2,4]triazolo[1,5-*b*]pyridazine (**25b**) was oxidized with potassium dichromate to afford the carboxylic acid (**30**). After treatment of **30** with diphenylphosphoryl azide in *tert*-butyl alcohol, amino derivative (**31**) was reacted with *N*,*N*-dimethylaminomethylenesulfonamide (**32**), which was obtained by reaction of **26b** and **28a**, in the presence of sodium hydride to afford **33**. Compound **10** was obtained by deprotection

Table 1. Physical Data for Substituted Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines



Compd. No.	R_1	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
1	H	145—147	$C_8H_{11}N_5O_3S$	37.35	4.31	27.22	37.48	4.33	26.95	51
2	CH_3	181—184	$C_{10}H_{15}N_5O_3S$	42.10	5.30	24.55	41.87	5.28	24.59	83
3	CH_3CH_2	194—197	$C_{14}H_{19}N_5O_3S \cdot 0.5EtOH$	46.41	6.59	20.82	46.33	6.68	20.99	77
4	$-(CH_2)_4-$	183—185	$C_{12}H_{17}N_5O_3S$	46.29	5.50	22.49	46.20	5.47	22.42	76
5	$-(CH_2)_5-$	247—249	$C_{13}H_{19}N_5O_3S$	47.99	5.89	21.52	48.20	6.05	21.30	80

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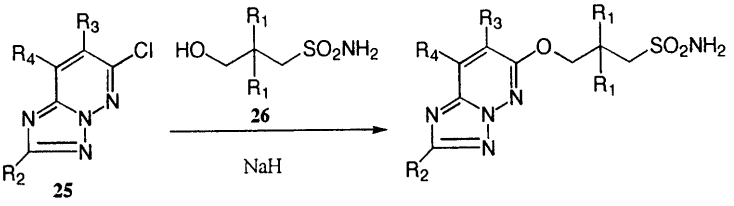
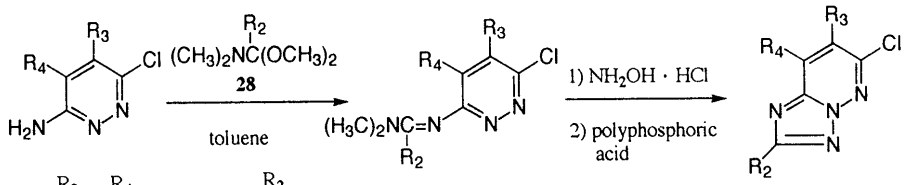


	R_2	R_3	R_4
25a	H	H	H
25b	H	CH_3	H
25c	H	CH_3	CH_3
25d	CH_3	CH_3	H
25e	CH_3	H	CH_3

	R_1
26a	H
26b	CH_3
26c	CH_2CH_3
26d	$-(CH_2)_4-$
26e	$-(CH_2)_5-$

Chart 1



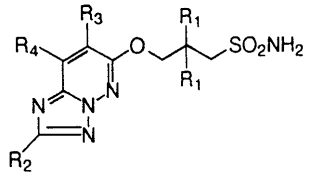
	R_3	R_4
27a	H	H
27b	CH_3	H
27c	H	CH_3
27d	CH_3	CH_3

	R_2
28a	H
28b	CH_3

	R_2	R_3	R_4
29a	H	H	H
29b	H	CH_3	H
29c	H	CH_3	CH_3
29d	CH_3	CH_3	H
29e	CH_3	H	CH_3

Chart 2

Table 2. Physical Data for 2, 7 and 8-Substituted Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines



Compd. No.	R_1	R_2	R_3	R_4	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
6	CH_3	H	CH_3	H	212—214	$C_{11}H_{17}N_5O_3S$	44.14	5.72	23.39	44.38	5.94	23.11	75
7	CH_3	H	CH_3	CH_3	175—177	$C_{12}H_{19}N_5O_3S$	45.99	6.61	22.35	46.27	6.41	22.16	25
8	CH_3	H	CN	H	192—194	$C_{11}H_{14}N_6O_3S$	42.57	4.55	27.08	42.41	4.85	27.26)	47
9	CH_3	H	OCH_3	H	233—236	$C_{11}H_{17}N_5O_4S \cdot 0.5H_2O$	40.73	5.59	21.59	40.78	5.61	21.58	53
10	CH_3	H	NH_2	H	286—289	$C_{10}H_{16}N_6O_3S$	39.99	5.37	27.98	39.79	5.35	27.67	83
11	CH_3	H	Cl	H	208—210	$C_{10}H_{14}ClN_5O_3S$	37.56	4.41	21.90	37.28	4.39	21.90	59
12	CH_3	H	Br	H	201—203	$C_{10}H_{14}BrN_5O_3S$	32.98	3.87	19.23	33.19	4.19	19.28	49
13	CH_3CH_2	H	CH_3	H	189—192	$C_{13}H_{21}N_5O_3S \cdot 0.5EtOH$	47.98	6.90	19.90	47.74	6.84	19.93	70
14	CH_3CH_2	H	CH_3	CH_3	166—168	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	49.21	6.89	20.30	50
15	CH_3CH_2	CH_3	CH_3	H	221—222	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	49.36	6.56	20.71	14
16	CH_3CH_2	CH_3	H	CH_3	159—160	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	49.04	6.65	20.36	26

of **33** using trifluoroacetic acid and hydrochloric acid. Compound **33** was treated with sodium nitrite and then cuprous derivatives to give 7-substituted[1,2,4]triazolo[1,5-*b*]pyridazines (**34a—c**). Compounds **8**, **11** and **12** were obtained by deprotection of **34a—c** using hydrochloric acid. Bromo derivative (**12**) was converted to the methoxy derivative (**9**) by treatment with sodium methoxide.

The synthesis of the sulfonamide derivatives (**17—24**) having a side chain of 4–6 methylene groups at the 6 position listed in Table 3 were carried out *via* the route shown in Chart 4 (method A or B).

Sulfonamides (**35a—f**) were reacted with 6-chloro-7-methyl[1,2,4]triazolo[1,5-*b*]pyridazine (**25b**) in the presence of sodium hydride to afford **17—19** and **22—24** (method A).

Compounds **20** and **21** were obtained by the reaction of *N*,*N*-dimethylaminomethylenesulfonamides (**36g, h**) and **25b** followed by deprotection using hydrochloric acid (method B).

Sulfonamides (**35a—f**) were prepared *via* the route shown in Chart 5. Ethyl esters (**37a, b**) were treated with lithium diisopropylamide, followed by treatment with 1-bromoalkylhalides to afford **38a—f**. Compounds **38a—f**

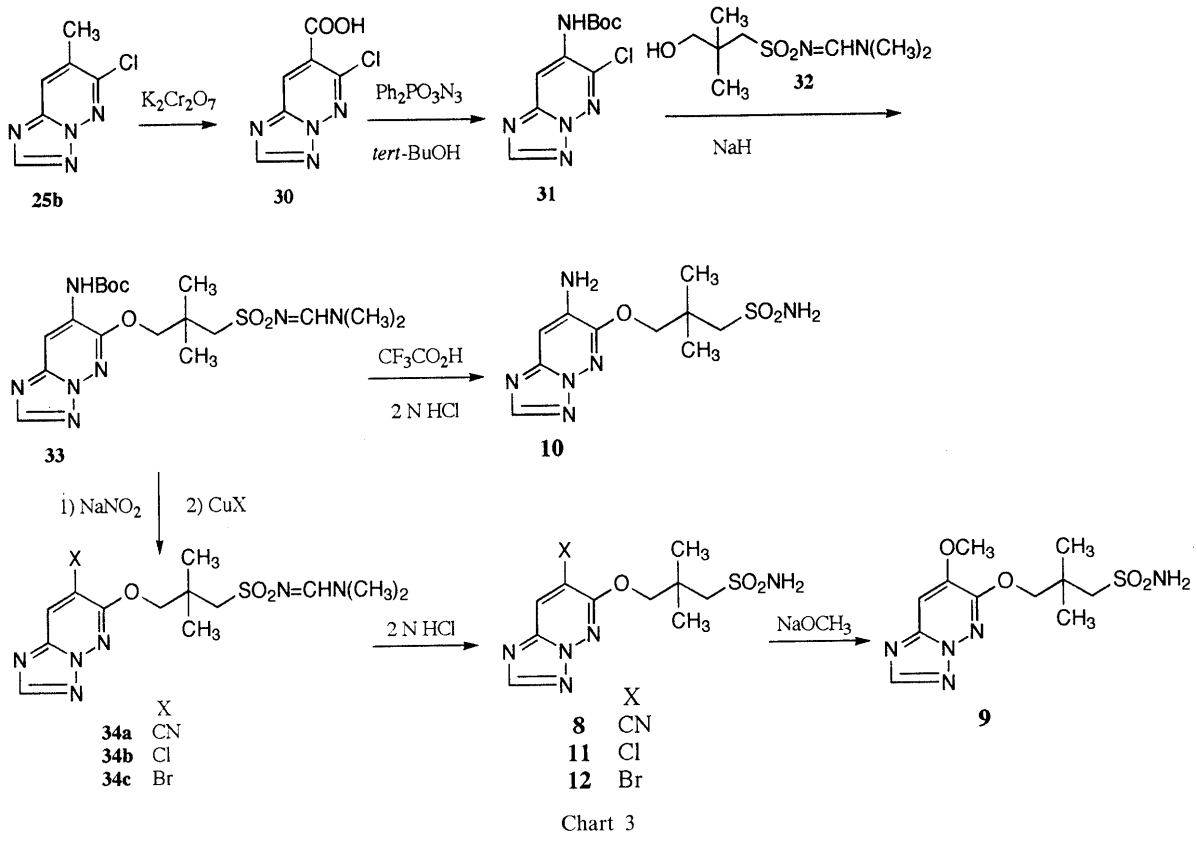
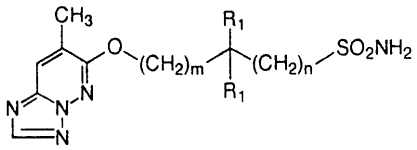


Chart 3

Table 3. Physical Data for 7-Methyl Substituted Sulfamoylalkyloxy[1,2,4]triazolo[1,5-*b*]pyridazines



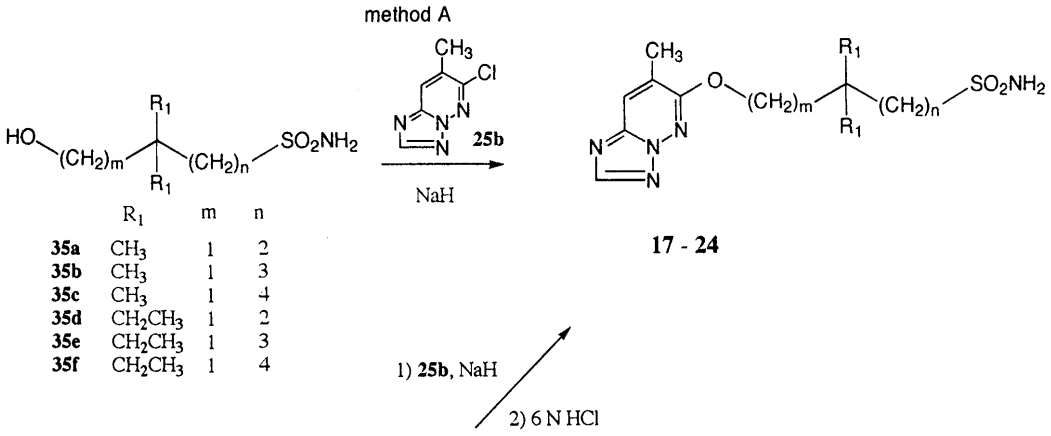
Compd. No.	R_1	*m*	*n*	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
17	CH_3	1	2	214—215	$C_{12}H_{19}N_5O_3S$	45.99	6.11	22.35	45.80	5.91	22.56	7
18	CH_3	1	3	171—172	$C_{13}H_{21}N_5O_3S$	47.69	6.46	21.39	47.45	6.39	21.18	9
19	CH_3	1	4	161—163	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	48.99	6.68	20.74	11
20	CH_3	2	2	143—144	$C_{13}H_{21}N_5O_3S$	47.69	6.46	21.39	47.69	6.46	21.39	14
21	CH_3	3	2	154—155	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	48.98	7.02	20.86	40
22	CH_3CH_2	1	2	148—149	$C_{14}H_{23}N_5O_3S$	49.25	6.79	20.51	48.99	6.98	20.24	24
23	CH_3CH_2	1	3	157—158	$C_{15}H_{25}N_5O_3S$	50.68	7.09	19.70	50.85	6.96	19.78	34
24	CH_3CH_2	1	4	132—133	$C_{16}H_{27}N_5O_3S$	52.01	7.37	18.95	51.89	7.10	19.08	5

were reacted with potassium thiocyanate to give **39a—f**. Thiocyanates (**39a—f**) were treated first with chlorine gas and then ammonia gas to afford the sulfonamides (**40a—f**). Compounds **40a—f** were reduced with lithium aluminum hydride to give sulfonamides (**35a—f**).

N,*N*-Dimethylaminomethylenesulfonamides (**36g**, **h**) were obtained *via* the route shown in Chart 6. Treatment of **36a**, which was obtained by reaction of **35a** and **28a**, with trifluoromethanesulfonic anhydride and then sodium iodide gave **41**. Cyanation reaction of **41** using potassium cyanide in the presence of 18-crown-6 afforded the cyanide (**42**). After hydrolysis of **42**, the obtained methyl ester (**43**) was reduced with lithium aluminum hydride followed by protection to give **36g**. Compound **36h** was obtained from **36g** in a manner similar to use to prepare **36g**.

Inhibition of PAF-Induced Bronchoconstriction of 6-Alkoxy[1,2,4]triazolo[1,5-*b*]pyridazines The sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines (**1—5**, Table 1) obtained in this study were evaluated for anti-asthmatic activity using PAF-induced bronchoconstriction in guinea pigs. The results are summarized in Table 4.

Compound **1** showed moderate anti-asthmatic activity (43%), which suggested that conversion of the imidazopyridazine ring to triazolopyridazine ring did not affect the activity. Introduction of dimethyl (**2**), diethyl (**3**), and cyclopentylidene (**4**) groups at the 2 position of the sulfamoylpropyloxy group increased the inhibitory activity but the cyclohexylidene derivative (**5**) tended to be less

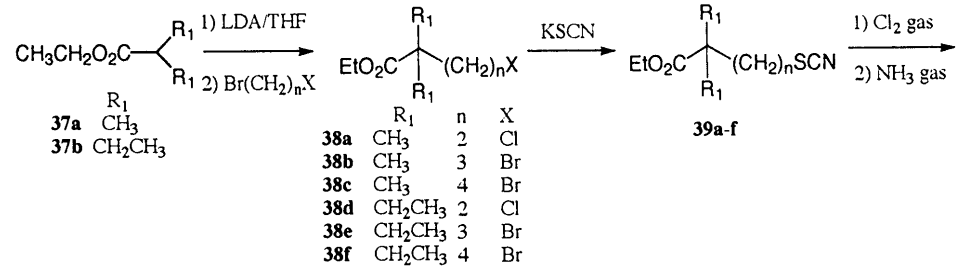


	R_1	m	n
35a	CH_3	1	2
35b	CH_3	1	3
35c	CH_3	1	4
35d	CH_2CH_3	1	2
35e	CH_2CH_3	1	3
35f	CH_2CH_3	1	4

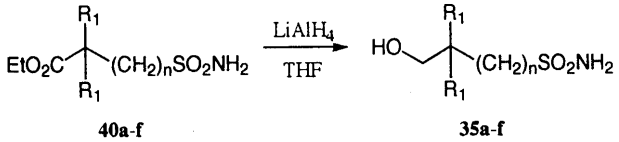
36g-h

	R_1	m	n
36g	CH_3	2	2
36h	CH_3	3	2

Chart 4

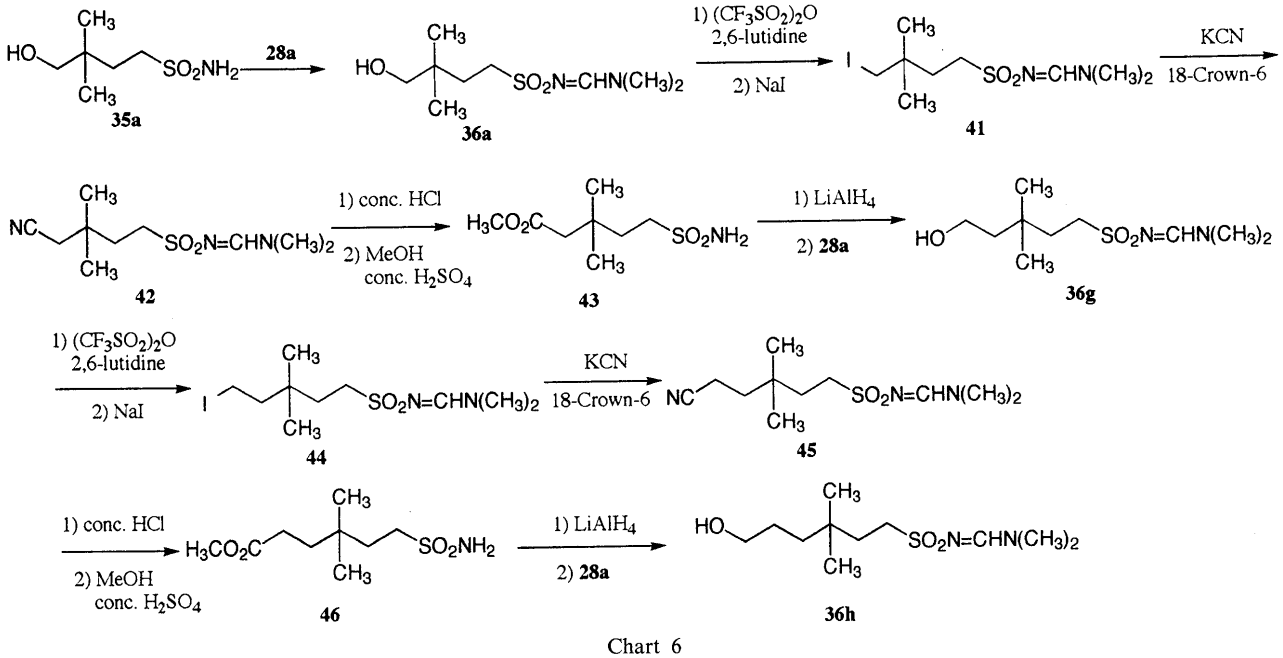


	R_1	n	X
38a	CH_3	2	Cl
38b	CH_3	3	Br
38c	CH_3	4	Br
38d	CH_2CH_3	2	Cl
38e	CH_2CH_3	3	Br
38f	CH_2CH_3	4	Br



40a-f **35a-f**

Chart 5



35a **36a** **41** **42** **43** **36g** **44** **45** **46** **36h**

Chart 6

Table 4. Variation in Anti-asthmatic Effect with Substitution of the Alkyl Side Chain of [1,2,4]Triazolo[1,5-*b*]pyridazines

Compd. No.	% Inhibition of PAF-induced bronchoconstriction	
	10 mg/kg, i.v.[a]	30 mg/kg, *p.o.*[b]
1	43	NT
2	60**	59**
3	69**	57**
4	NT	73**
5	NT	43

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

Table 5. Variation in Anti-asthmatic Effect with Substitution of the Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines

Compd. No.	mg/kg, *p.o.*[a]	% Inhibition of PAF-induced bronchoconstriction
6	10	43**
7	30	26
8	10	69**
9	3	61**
10	30	4
11	10	70**
12	10	40
13	3	62**
14	30	26
15	10	30
16	10	6

a) Compounds were given orally 1 h before PAF treatment. Significance of differences (Dunnett's): ** $p<0.01$ (*vs.* control).

Table 6. Variation in Anti-asthmatic Effect with Side Chain Length of the 7-Methyl Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines

Compd. No.	% Inhibition of PAF-induced bronchoconstriction[a]
17	44
18	NT
19	39*
20	55*
21	30
22	61**
23	77**
24	76**

a) Compounds were given orally at a dose of 10 mg/kg 1 h before PAF treatment. Significance of differences (Dunnett's): ** $p<0.01$, * $p<0.05$ (*vs.* control).

active.

The effect of introduction of substituents at the 2, 7 and 8 positions of the [1,2,4]triazolo[1,5-*b*]pyridazines (**6**—**16**, Table 2) were examined by oral administration using PAF-induced bronchoconstriction (Table 5). Introduction of a methyl group at the 7 position of the [1,2,4]triazolo[1,5-*b*]pyridazine ring (**6**, **13**) increased the anti-asthmatic activity. The inhibitory activity of compound **13** having diethyl side chain was 3 times potent than that of **6**. On the other hand, the compounds with dimethyl substituents at the triazolopyridazine ring (**7**, **14**—**16**) showed lower activity. These data are in accord with the results for 3-(7- or 8-methylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamides reported in our previous work.[1)]

Table 7. Effects of Compound **13** and Theophylline on the Contraction of Guinea Pig Trachea Strips Induced by Various Spasmogens

Agonist	IC_{50} (mM)	
	Compound **13**	Theophylline
Histamine	0.07	0.06
U-46619	0.14	0.07
LTD_4	0.21	0.11
Carbachol	0.15	0.44
KCl	0.15	0.29

Table 8. Effects of Compound **13** on Antigen-Mediated Immediate and Late Airway Responses in Actively Sensitized Guinea Pigs

	Dose (mg/kg)	No. of animals	IAR % change in sRaw (1 min)	LAR *AUC* (4 to 8 h)
Control		9	1026 ± 60	479 ± 138
Compound **13**	1	9	545 ± 172 (47)*	256 ± 45 (47)*
	3	9	564 ± 104 (45)**	231 ± 107 (52)**
	10	9	450 ± 104 (56)**	18 ± 42 (96)**

Compounds were given orally 1 h before and 3 h after antigen challenge. IAR: Immediate airway response. sRaw: Specific airway resistance. LAR: Late airway response. Each value represents the mean ± S.E. of 8—9 animals. ( ): % Inhibition. Significance of differences (Dunnett's test): * $p<0.05$, ** $p<0.01$ (*vs.* control).

Introduction of a cyano (**8**), methoxy (**9**) or chloro (**11**) group, at the 7 position of the triazolopyridazine ring increased the activity. But the amino (**10**), or bromo (**12**) derivatives showed lower activity. No correlation was observed between the anti-asthmatic activity and the electron-withdrawing intensity of the substituents.

We next examined the effect of side-chain length of the [1,2,4]triazolo[1,5-*b*]pyridazin-6-yl-oxyalkylsulfonamides (**17**—**24**, Table 3) by oral administration. As shown in Table 6, these compounds showed moderate actvity, but the length of the side chain did not appreciably influence the potency.

Anti-asthmatic Activities of Compound 13 The bronchodilating activity of compound **13** on the contraction of guinea pig trachea strips induced by several spasmogens was examined. The results were compared with those obtained with theophylline, and are summarized in Table 7. Compound **13** at concentrations of 10^{-4} to 10^{-3} M inhibited the spasmogen-induced contractile response of guinea pig trachea strips in a concentration-dependent manner, and the IC_{50} values were 0.07 (histamine), 0.14 (U-46619), 0.21 (LTD_4), 0.15 (carbachol) and 0.15 (KCl) mM. The bronchodilating activity of compound **13** was comparable to that of theophylline.

Compound **13** (1, 3 and 10 mg/kg, *p.o.*) inhibited antigen-mediated immediate (1 min) and late (4—8 h) airway responses in actively sensitized guinea pigs (Table 8).

Compound **13** (1, 3 and 10 mg/kg, *p.o.*) also dose-dependently reduced increase of total cells, eosiophil and other fraction in broncho-alveolar lavage fluid of the guinea pigs at 24 h after antigen inhalation (Fig. 1).

In conclusion, we synthesized a series of 3-([1,2,4]tri-

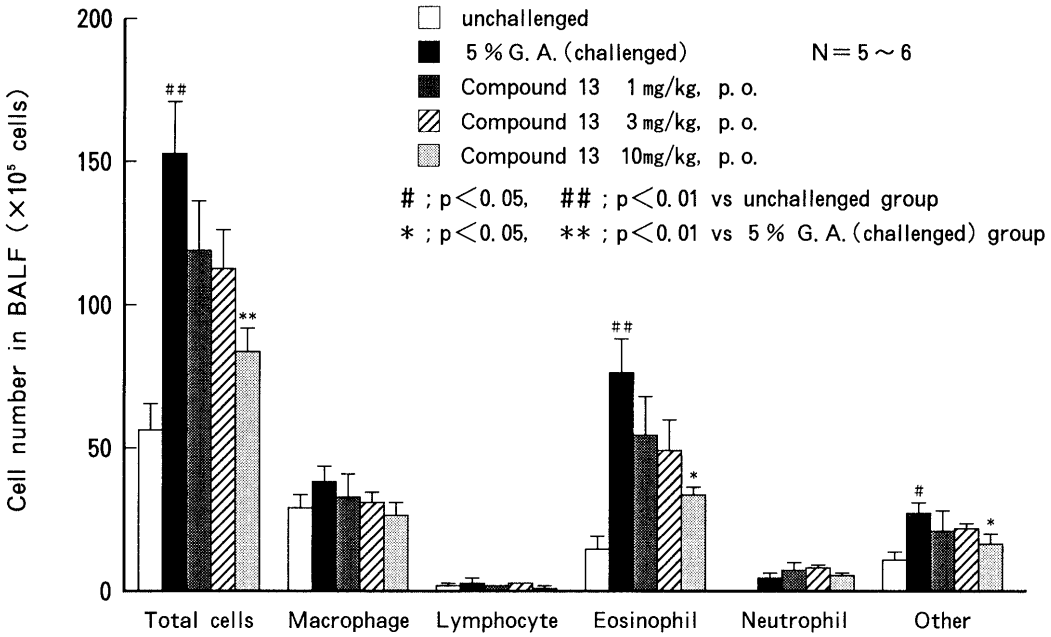


Fig. 1. Effects of Compound **13** on Eosinophil Leukocytic Infiltration in Broncho-alveolar Lavage Fluid 24 h after Antigen Inhalation in Actively Sensitized Guinea Pigs

azolo[1,5-*b*]pyridazin-6-yl)oxyalkylsulfonamides, which have novel structures, representing a new class of orally active anti-asthmatic compounds. Among them, 2,2-diethyl-3-(7-methyl[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)-oxypropanesulfonamide (**13**) showed excellent anti-asthmatic activity in experimental models of asthma, and may be of significant value in the treatment of asthma and other respiratory diseases.

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-([1,2,4]Triazolo[1,5-*b*]pyridazin-6-yl)oxypropanesulfonamide (1) To a solution of **26a**[1] (835 mg) in DMF (12 ml) was added NaH (60% dispersion in mineral oil, 480 mg) by portions followed by stirring for 1 h at room temperature. 6-Chloro[1,2,4]triazolo[1,5-*b*]pyridazine (**25a**,[2] 829 mg) was added to the reaction mixture and stirring was continued for 18 h at room temperature. Ice-water was then added, and the pH of the solution was adjusted to 4 with 5 N HCl. The mixture was extracted with THF, and the extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was recrystallized from MeOH to give 811 mg of **1** (colorless crystals, 51%). mp 145—147 °C. IR (KBr): 1550, 1490, 1335, 1280, 1149 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.1—2.4, 3.1—3.3 (each 2H, m), 4.48 (2H, t, J=6 Hz), 6.91 (2H, s), 7.33, 8.32 (each 1H, d, J=10 Hz), 8.48 (1H, s). *Anal.* Calcd for $C_8H_{11}N_5O_3S$: C, 37.35; H, 4.31; N, 27.22. Found: C, 37.48; H, 4.33; N, 26.95.

Compounds **2**—**7** and **13**—**16** were obtained similarly. In the synthesis of **2**—**7** and **13**—**16**, **25a**—**e** and **26b**—**e** were used, respectively, instead of **25a** and **26a**. The physical data for these compounds (**1**—**7** and **13**—**16**) are summarized in Table 1, 2, 9 and 10.

Compounds **17**—**19** and **22**—**24** were also obtained similarly. In the synthesis of **17**—**19** and **22**—**24**, **25b** and **35a**—**f** were used, respectively, instead of **25a** and **26a**. The physical data for these compounds (**17**—**19** and **22**—**24**) are summarized in Table 3 and 11.

7-*tert*-Butoxycarbonylamino-6-chloro[1,2,4]triazolo[1,5-*b*]pyridazine (31) An ice-cold solution of **25b**[3] (8.39 g) in conc. H_2SO_4 (42 ml) was added $K_2Cr_2O_7$ (16.2 g) by portions followed by stirring for 0.5 h at room temperature and for 1 h at 90 °C. The mixture was cooled and poured into ice-water (400 ml), the resulting crystal was collected by filtration and washed with H_2O and EtOAc to give 8.68 g of **30**. A mixture of **30** (2.98 g), diphenylphosphoryl azide (4.84 ml) and Et_3N (2.51 ml) in *tert*-BuOH (50 ml) was refluxed for 7 h. After the solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel with CH_2Cl_2–MeOH (97:3) to give 2.22 g of **31** (colorless crystals, 48%). mp 138—141 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.52 (9H, s), 8.54, 8.61 (each 1H, s), 9.54 (1H, br s). *Anal.* Calcd for $C_{10}H_{12}ClN_5O_2$: C, 44.54; H, 4.48; N, 25.97. Found: C, 44.44; H, 4.61; N, 26.23.

3-(7-*tert*-Butoxycarbonylamino[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)-oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (33) Compound **33** was prepared from **31** (3.6 g) and **32** (4.56 g) in the same manner as described for **1**. Compound **32** was prepared from **26b** (3.34 g) and **28a** (2.26 ml) in the same manner as described for **36a**. **33** (colorless crystals, 5.18 g, 88%). mp 120—122 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (6H, s), 1.53 (9H, s), 2.77, 3.05 (each 3H, s), 3.39, 4.28 (each 2H, s), 8.03, 8.35, 8.39 (each 1H, s), 9.30 (1H, br s). *Anal.* Calcd for $C_{18}H_{29}N_7O_5S$: C, 43.19; H, 6.85; N, 19.59. Found: C, 43.35; H, 6.60; N, 19.55.

3-(7-Amino[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (10) An ice-cold mixture of **33** (5.10 g) and anisole (24 ml) was treated with CF_3CO_2H (86 ml), and the mixture was stirred for 1.5 h at room temperature. After the solvent was evaporated *in vacuo*, and ice-water was added to the residue. The mixture was neutralized with $NaHCO_3$ followed by extraction with EtOAc–THF (2:1). The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was taken up in 2 N HCl (5 ml) followed by stirring for 45 min at 100 °C. The pH of the solution was then adjusted to 7 with $NaHCO_3$. The resulting crystals were collected by filtration and washed with ice-water to give 2.47 g of **10** (colorless crystals, 83%). mp 286—289 °C. IR (KBr): 3300, 1635, 1520, 1330, 1235 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.25 (6H, s), 3.30, 4.25, 6.30 (each 2H, s), 6.58 (1H, s), 6.85 (2H, s), 8.06 (1H, s). *Anal.* Calcd for $C_{10}H_{16}N_6O_3S$: C, 39.99; H, 5.37; N, 27.98. Found: C, 39.79; H, 5.35; N, 27.67.

3-(7-Chloro[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (11) An ice-cold solution of **33** (335 mg) in $CHCl_3$ (2 ml) was treated with $NaNO_2$ in H_2O (2 ml) followed by stirring for 15 min. CuCl (135 mg) was added and the reaction mixture was further stirred for 15 min at the same temperature. The mixture was neutralized with 1 N NaOH solution followed by extraction with EtOAc–THF (2:1). The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with CH_2Cl_2–MeOH (94:6) to give 220 mg of **34b** (colorless crystals, 59%). A solution of **34b** in 2 N HCl (5 ml) was stirred for 45 min at 100 °C. The pH of the solution was then adjusted to 7 with $NaHCO_3$. The resulting crystals were recrystallized from MeOH to give 152 mg of **11** (colorless crystals, 59%). mp 208—210 °C. IR (KBr): 3360, 1530, 1495,

Table 9. IR and ^{1}H-NMR Data for Substituted Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6, δ: ppm)
1	1550, 1490, 1335, 1280, 1149	2.1—2.4, 3.1—3.3 (each 2H, m), 4.48 (2H, t, J=6 Hz), 6.91 (2H, s), 7.33, 8.32 (each 1H, d, J=10 Hz), 8.48 (1H, s)
2	3300, 1550, 1490, 1330, 1275, 1140	1.24 (6H, s), 3.21, 4.26, 6.94 (each 2H, s), 7.33, 8.31 (each 1H, d, J=10 Hz), 8.47 (1H, s)
3	3280, 1550, 1490, 1330, 1310, 1155	0.87 (6H, t, J=7 Hz), 1.5—1.8 (4H, m), 3.19, 4.34, 6.95 (each 2H, s), 7.31, 8.30 (each 1H, d, J=10 Hz), 8.48 (1H, s)
4	3305, 1495, 1345, 1145, 840	1.5—2.0 (8H, m), 3.30, 4.36, 6.92 (each 2H, s), 7.32, 8.31 (each 1H, d, J=10 Hz), 8.47 (1H, s)
5	3310, 1550, 1490, 1330, 1280, 1150	1.3—1.9 (10H, m), 3.30, 4.44, 6.93 (each 2H, s), 7.32, 8.31 (each 1H, d, J=10 Hz), 8.48 (1H, s)

Table 10. IR and ^{1}H-NMR Data for 2, 7 and 8-Substituted Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6, δ: ppm)
6	3310, 1500, 1335, 1315, 1250, 1145	1.25 (6H, s), 2.34 (3H, s), 3.23, 4.26, 6.94 (each 2H, s), 8.16, 8.38 (each 1H, s)
7	3250, 1495, 1335, 1320, 1120	1.25 (6H, s), 2.28, 2.54 (each 3H, s), 3.23, 4.24, 6.92 (each 2H, s), 8.35 (1H, s)
8	3357, 2112, 1528, 1493, 1336, 1147	1.27 (6H, s), 3.23, 4.34, 6.97 (each 2H, s), 8.52, 8.75 (each 1H, s)
9	3330, 1515, 1345, 1330, 1230, 1145	1.24 (6H, s), 3.20 (2H, s), 3.99 (3H, s), 4.26, 6.97 (each 2H, s), 7.71, 8.29 (each 1H, s)
10	3300, 1635, 1520, 1330, 1235	1.25 (6H, s), 3.30, 4.25, 6.30 (each 2H, s), 6.58 (1H, s), 6.85 (2H, s), 8.06 (1H, s)
11	3360, 1530, 1495, 1340, 1310, 1150	1.26 (6H, s), 3.23, 4.33, 6.97 (each 2H, s), 8.51, 8.75 (each 1H, s)
12	3140, 1535, 1500, 1340, 1150	1.28 (6H, s), 3.23, 4.34, 6.97 (each 2H, s), 8.52, 8.75 (each 1H, s)
13	3310, 1500, 1330, 1250, 1185, 1145	0.88 (6H, t, J=7 Hz), 1.5—1.8 (4H, m), 2.33 (3H, s), 3.21, 4.34, 6.94 (each 2H, s), 8.16, 8.39 (each 1H, s)
14	3300, 1495, 1330, 1190, 1160	0.88 (6H, t, J=7 Hz), 1.5—1.8 (4H, m), 2.26, 2.54 (each 3H, s), 3.21, 4.32, 6.94 (each 2H, s), 8.35 (1H, s)
15	3305, 3170, 1540, 1500[a]	0.88 (6H, t, J=7.2 Hz), 1.62 (4H, q, J=7.2 Hz), 2.31, 2.49 (each 3H, s), 3.21, 4.31, 6.93 (each 2H, s), 8.02 (1H, s)
16	3300, 1615, 1575[a]	0.85 (6H, t, J=7 Hz), 1.58 (4H, q, J=7 Hz), 2.45, 2.52 (each 3H, s), 3.17, 4.28, 6.96 (each 2H, s), 7.11 (1H, d, J=1.2 Hz)

a) Bujol.

Table 11. IR and ^{1}H-NMR Data for 7-Methyl Substituted Sulfamoylpropyloxy[1,2,4]triazolo[1,5-*b*]pyridazines

Compd. No.	IR (Nujol) cm^{-1}	^{1}H-NMR (DMSO-d_6, δ: ppm)
17	3290, 3180, 1580, 1540	1.06 (6H, s), 1.80—1.95 (2H, m), 2.33 (3H, s), 2.97—3.09 (2H, m), 4.09, 6.75 (each 2H, s), 8.16, 8.38 (each 1H, s)
18	3230, 1540	1.05 (6H, s), 1.45—1.59 (2H, m), 1.66—1.86 (2H, m), 2.33 (3H, s), 2.96 (2H, t, J=7.8 Hz), 4.08 (2H, s), 6.72 (2H, br s), 8.15, 8.37 (each 1H, s)[a]
19	3280, 3165, 1540	1.05 (6H, s), 1.38—1.60, 1.67—1.98 (each 4H, m), 2.37 (3H, s), 3.15 (2H, t, J=7.8 Hz), 4.14 (2H, s), 4.77 (2H, br s), 7.78, 8.25 (each 1H, s)
20	3330, 3170, 1575, 1540, 1500	1.00 (6H, s), 1.66—1.89 (4H, m), 2.30 (3H, s), 2.94—3.10 (2H, m), 4.43 (2H, t, J=6.8 Hz), 6.77 (2H, br s), 8.16, 8.39 (each 1H, s)
21	3305, 3190, 1545	0.91 (6H, s), 1.29—1.46 (2H, m), 1.57—1.88 (4H, m), 2.30 (3H, s), 2.85—3.04 (2H, m), 4.35 (2H, t, J=6.3 Hz), 6.75 (2H, br s), 8.15, 8.37 (each 1H, s)
22	3320, 3165, 1540, 1495	0.84 (6H, t, J=7.0 Hz), 1.42 (4H, q, J=7.0 Hz), 1.76—1.91 (2H, m), 2.31 (3H, s), 2.89—3.03 (2H, m), 4.11 (2H, s), 6.77 (2H, br s), 8.15, 8.39 (each 1H, s)
23	3305, 3245, 1540	0.86 (6H, t, J=7.4 Hz), 1.46 (4H, q, J=7.4 Hz), 1.48 (2H, t, J=7.6 Hz), 1.79—1.98 (2H, m), 2.36 (3H, s), 3.07 (2H, t, J=7.6 Hz), 4.21 (2H, s), 5.54 (2H, br s), 7.76, 8.24 (each 1H, s)[a]
24	3300, 3150, 1540	0.85 (6H, t, J=7.4 Hz), 1.35—1.55 (8H, m), 1.78—1.98 (2H, m), 3.13 (2H, t, J=8.0 Hz), 4.18 (2H, s), 4.76 (2H, br s), 7.77, 8.25 (each 1H, s)[a]

a) ^{1}H-NMR ($CDCl_3$, δ: ppm).

1340, 1310, 1150 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (6H, s), 3.23, 4.33, 6.97 (each 2H, s), 8.51, 8.75 (each 1H, s). *Anal.* Calcd for $C_{10}H_{14}ClN_5O_3S$: C, 37.56; H, 4.41; N, 21.90. Found: C, 37.28; H, 4.39; N, 21.90.

Compounds **8** and **12** were obtained similarly. In the synthesis of **8** and **12**, CuCN and CuBr were used, respectively, instead of CuCl. The physical data for these compounds (**8** and **12**) are summarized in Tables 2 and 10.

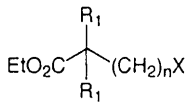
3-(7-Methoxy[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (9) A mixture of **12** (500 mg) and 28% methanolic NaOMe solution (0.65 ml) in MeOH (10 ml) was refluxed for 5 h. After cooling, the pH of the solution was adjusted to 4 with conc. HCl, the resulting crystals were collected by filtration and recrystallized from MeOH to give 195 mg of **9** (colorless crystals, 53%). mp 233—236 °C. IR (KBr): 3330, 1515, 1345, 1330, 1230, 1145 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (6H, s), 3.20 (2H, s), 3.99 (3H, s), 4.26, 6.97 (each 2H, s), 7.71, 8.29 (each 1H, s). *Anal.* Calcd for $C_{11}H_{17}N_5O_4S \cdot 0.5H_2O$: C, 40.73; H, 5.59; N, 21.59. Found: C, 40.78; H, 5.61; N, 21.58.

Ethyl 4-Chloro-2,2-dimethylbutyrate (38a) A 1.6 M solution of *n*-butyllithium in hexane (93.6 ml) was added to a stirred solution of diisopropylamine (22.2 ml) in THF (150 ml) at −5—0 °C. After being stirred at −5—0 °C for 30 min, the reaction mixture was cooled to −78 °C and ethyl isobutyrate (**37a**, 19.0 ml) was added. Stirring was continued at −78 °C for 45 min. A solution of 1-bromo-2-chloroethane (11.9 ml) in THF (10 ml) was then added dropwise to the mixture. The whole was further stirred at −78 °C for 1 h and at room temperature for 2 h, then poured into an excess of aqueous NH_4Cl solution and extracted with EtOAc, The extract was washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a residue, which was distilled to give 24.4 g of **38a** (colorless oil, 97%). bp 54—56 °C/0.25 mmHg. IR (neat): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, s), 1.26 (3H, t, J=7 Hz), 2.06, 3.51 (each 2H, t, J=8.1 Hz), 4.14 (2H, q, J=7 Hz).

Compounds **38b—f** were obtained similarly. The physical data for these compounds (**38a—f**) are summarized in Table 12.

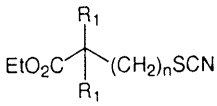
Ethyl 2,2-Dimethyl-4-thiocyanatobutyrate (39a) A mixture of **38a** (22.1 g) and KSCN (14.5 g) in DMF (100 ml) was stirred at 100 °C for 7 h, then diluted with water, followed by extraction with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was distilled to give 16.43 g of **39a** (colorless oil, 66%). bp 109—110 °C/0.30 mmHg. IR (neat): 2150, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, s), 1.27 (3H, t, J=7.2 Hz), 2.00—2.12, 2.86—2.97 (2H, m), 4.15 (2H, q, J=7.2 Hz).

Table 12. Physical Data for **38a—f**



Compd. No.	R_1	n	X	Formula	Yield (%)	bp (°C/mmHg)	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$, δ: ppm)
38a	CH_3	2	Cl	$C_8H_{15}ClO_2$	97	54— 56/0.25	1725	1.22 (6H, s), 1.26 (3H, t, J=7.0 Hz), 2.06, 3.51 (each 2H, t, J=8.1 Hz), 4.14 (2H, q, J=7.0 Hz)
38b	CH_3	3	Br	$C_9H_{17}BrO_2$	85	71— 73/0.25	1725	1.18 (6H, s), 1.25 (3H, t, J=7.0 Hz), 1.58—1.91 (4H, m), 3.38 (2H, t, J=6.4 Hz), 4.12 (2H, q, J=7.0 Hz)
38c	CH_3	4	Br	$C_{10}H_{19}BrO_2$	98	62— 64/0.40	1725	1.17 (6H, s), 1.25 (3H, t, J=7.2 Hz), 1.33—1.63, 3.33—3.50 (each 4H, m), 4.12 (2H, q, J=7.2 Hz)
38d	CH_3CH_2	2	Cl	$C_{10}H_{19}ClO_2$	76	69— 72/0.30	1725	0.81 (6H, t, J=7.0 Hz), 1.26, 1.61 (each 4H, q, J=7.2 Hz), 2.07, 3.45 (each 2H, t, J=8.6 Hz), 4.15 (2H, q, J=7.0 Hz)
38e	CH_3CH_2	3	Br	$C_{11}H_{21}BrO_2$	75	98—102/0.30	1725	0.79 (6H, t, J=7.4 Hz), 1.25 (3H, t, J=7.0 Hz), 1.51—1.86 (8H, m), 3.39 (2H, t, J=6.2 Hz), 4.14 (2H, q, J=7.0 Hz)
38f	CH_3CH_2	4	Br	$C_{12}H_{23}BrO_2$	73	103—110/0.30	1725	0.77 (6H, t, J=7.6 Hz), 1.25 (3H, t, J=7.0 Hz), 1.50—1.68 (8H, m), 1.85 (2H, t, J=7.0 Hz), 3.41 (2H, t, J=6.7 Hz), 4.13 (2H, q, J=7.0 Hz)

Table 13. Physical Data for **39a—f**

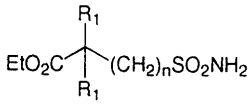


Compd. No.	R_1	n	Formula	Yield (%)	bp (°C/mmHg)	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$, δ: ppm)
39a	CH_3	2	$C_8H_{15}NO_2S$	66	109—111/0.30	2150, 1725	1.24 (6H, s), 1.27 (3H, t, J=7.2 Hz), 2.00—2.12, 2.86—2.97 (each 2H, m), 4.15 (2H, q, J=7.2 Hz)
39b	CH_3	3	$C_9H_{17}NO_2S$	96	107—110/0.18	2150, 1720	1.20 (6H, s), 1.27 (3H, t, J=7.0 Hz), 1.60—1.89 (4H, m), 2.94 (2H, t, J=6.8 Hz), 4.14 (2H, q, J=7.0 Hz)
39c	CH_3	4	$C_{10}H_{19}NO_2S$	74	123—125/0.40	2150, 1730	1.17 (6H, s), 1.25 (3H, t, J=7.2 Hz), 1.33—1.65 (4H, m), 1.73—2.08 (2H, m), 2.94 (2H, t, J=7.2 Hz), 4.12 (2H, q, J=7.2 Hz)
39d	CH_3CH_2	2	$C_{10}H_{19}NO_2S$	78	105—108/0.30	2155, 1725	0.81 (6H, t, J=7.4 Hz), 0.83 (3H, t, J=7.4 Hz), 1.27 (3H, t, J=7.0 Hz), 1.54—1.72 (4H, m), 2.00—2.13, 2.80—2.92 (2H, m), 4.17 (2H, q, J=7.0 Hz)
39e	CH_3CH_2	3	$C_{11}H_{21}NO_2S$	90	125—130/0.30	2145, 1720	0.80 (6H, t, J=7.6 Hz), 1.27 (3H, t, J=7.0 Hz), 1.49—1.78 (4H, m), 1.61 (4H, q, J=7.6 Hz), 2.90—3.02 (2H, m), 4.15 (2H, q, J=7.0 Hz)
39f	CH_3CH_2	4	$C_{12}H_{23}NO_2S$	97	145—148/0.30	2150, 1720	0.78 (6H, t, J=7.6 Hz), 1.25 (3H, t, J=7.0 Hz), 1.21—1.68 (8H, m), 1.82 (2H, m), 2.95 (2H, t, J=7.4 Hz), 4.14 (2H, q, J=7.0 Hz)

Compounds **39b—f** were obtained similarly. The physical data for these compounds (**39a—f**) are summarized in Table 13.

Ethyl 2,2-Dimethyl-4-sulfamoylbutyrate (40a) A solution of **39a** (42.5 g) in AcOH–H_2O (1 : 1, 400 ml) was bubbled with Cl_2 gas for 3 h under ice-cooling with stirring followed by extraction with CH_2Cl_2. The extract was dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residual oil was dissolved in CH_2Cl_2 (250 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 chromatographed on silica gel with *n*-C_6H_{14}–EtOAc (3 : 1 to 1 : 1) to yield 40.7 g of **40a** (colorless oil, 86%). IR (neat): 3360, 3250, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, s), 1.26 (3H, t, J=7.2 Hz), 2.00—2.13, 3.06—3.19 (each 2H, m), 4.14 (2H, q, J=7.2 Hz), 4.86 (2H, br s).

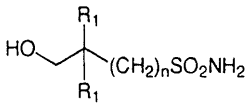
Table 14. Physical Data for **40a—f**



Compd. No.	R_1	n	Formula	Yield (%)	mp (°C)	IR (neat) cm^{-1}	^{1}H-NMR ($CDCl_3$, δ: ppm)
40a	CH_3	2	$C_8H_{17}NO_4S$	86	Oil	3360, 3250, 1725	1.23 (6H, s), 1.26 (3H, t, J=7.2 Hz), 2.00—2.13, 3.06—3.19 (each 2H, m), 4.14 (2H, q, J=7.2 Hz), 4.86 (2H, br s)
40b	CH_3	3	$C_9H_{19}NO_4S$	78	Oil	3350, 3260, 1720	1.20 (6H, s), 1.26 (3H, t, J=7.4 Hz), 1.61—1.93 (4H, m), 3.11 (2H, t, J=7.0 Hz), 4.14 (2H, q, J=7.4 Hz), 4.88 (2H, br s)
40c	CH_3	4	$C_{10}H_{21}NO_4S$	67	Oil	3350, 3260, 1725	1.17 (6H, s), 1.25 (3H, t, J=7.2 Hz), 1.32—1.64 (4H, m), 1.85, 3.12 (each 2H, t, J=7.6 Hz), 4.12 (2H, q, J=7.2 Hz), 4.84 (2H, br s)
40d	CH_3CH_2	2	$C_{10}H_{21}NO_4S$	57	93—94	3350, 3250, 1720[a]	0.83 (6H, t, J=7.4 Hz), 1.27 (3H, t, J=7.0 Hz), 1.61 (4H, q, J=7.4 Hz), 2.03—2.16, 2.99—3.13 (each 2H, m), 4.17 (2H, q, J=7.0 Hz), 4.84 (2H, br s)
40e	CH_3CH_2	3	$C_{11}H_{23}NO_4S$	72	66—67	3290, 3225, 1710[a]	0.79 (6H, t, J=7.4 Hz), 1.26 (3H, t, J=7.2 Hz), 1.61 (4H, q, J=7.4 Hz), 1.66—1.85 (4H, m), 3.11 (2H, t, J=6.6 Hz), 4.15 (2H, q, J=7.2 Hz), 4.84 (2H,br s)
40f	CH_3CH_2	4	$C_{12}H_{25}NO_4S$	59	Oil	3360, 3260, 1720	0.77 (6H, t, J=7.4 Hz), 1.25 (3H, t, J=7.2 Hz), 1.19—1.40 (2H, m), 1.58 (4H, q, J=7.4 Hz), 1.49—1.69, 1.85, 3.12 (2H, m), 4.13 (2H, t, J=7.2 Hz), 4.71 (2H, br s)

a) Nujol.

Table 15. Physical Data for **35a—f**



Compd. No.	R_1	n	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
35a	CH_3	2	75—76	$C_6H_{15}NO_3S$	39.76	8.34	7.73	39.80	8.10	7.92	77
35b	CH_3	3	Oil	$C_7H_{17}NO_3S$	Not analysed						84
35c	CH_3	4	Oil	$C_8H_{19}NO_3S$	Not analysed						83
35d	CH_3CH_2	2	79—80	$C_8H_{19}NO_3S$	45.91	9.15	6.69	46.00	9.20	6.69	96
35e	CH_3CH_2	3	Oil	$C_9H_{21}NO_3S$	Not analysed						96
35f	CH_3CH_2	4	64—65	$C_{10}H_{23}NO_3S$	50.60	9.77	5.90	50.90	9.58	6.15	97

Table 16. IR and ^{1}H-NMR Data for Hydroxysulfonamides (**35a—f**)

Compd. No.	IR: cm^{-1} (a: Nujol, b: neat)	^{1}H-NMR (DMSO-d_6, δ: ppm)
35a	3480, 3420, 3300 (a)	0.81 (6H, s), 1.54—1.68, 2.85—2.98 (each 2H, m), 3.09 (2H, d, J=5.2 Hz), 4.58 (1H, t, J=5.2 Hz), 6.68 (2H, br s)
35b	3500, 3350, 3240, 1630 (b)	0.90 (6H, s), 1.35—1.50, 1.75—1.97 (each 2H, m), 3.12 (2H, t, J=7.8 Hz), 3.35 (2H, s), 5.04 (2H, br s)
35c	3500, 3330, 3260 (b)	0.87 (6H, s), 1.21—1.54 (4H, m), 1.76—1.94 (2H, m), 2.05 (1H, s), 3.16 (2H, t, J=8.0 Hz), 3.31 (2H, s), 5.13 (2H, br s)
35d	3470, 3350, 3250, 1560 (a)	0.74 (6H, t, J=7.4 Hz), 1.58 (4H, q, J=7.4 Hz), 1.50—1.66, 2.83—2.97 (each 2H, m), 3.11 (2H, s), 6.71 (2H, br s)
35e	3480, 3310, 1560 (b)	0.79 (6H, t, J=7.6 Hz), 1.14—1.45 (6H, m), 1.70—1.89 (2H, m), 2.05 (1H, s), 3.12 (2H, t, J=7.6 Hz), 3.39 (2H, s), 5.18 (2H, br s)
35f	3430, 3170, 1570 (a)	0.78 (6H, t, J=7.2 Hz), 1.15—1.49 (4H, m), 1.23 (4H, q, J=7.2 Hz), 1.67 (1H, s), 1.85 (2H, m), 3.15 (2H, t, J=4.6 Hz), 3.35 (2H, s), 4.90 (2H, br s)

Compounds **40b—f** were obtained similarly. The physical data for these compounds (**40a—f**) are summarized in Table 14.

4-Hydroxy-3,3-dimethylbutanesulfonamide (35a) A solution of **40a** (1.56 g) in THF (8 ml) was added dropwise to an ice-cold suspension of $LiAlH_4$ (0.35 g) in THF (30 ml), followed by stirring at the same temperature for 0.5 h and then at room temperature for 0.5 h. The reaction was quenched carefully with water, then the mixture was acidified with 2 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with n-C_6H_{14}–EtOAc (1 : 3). The eluate was concentrated *in vacuo* and the residue was recrystallized from iso-Pr_2O to yield 0.94 g of **35a** (colorless crystals, 77%). mp 75—76 °C. IR (KBr): 3480, 3420, 3300 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.81 (6H, s), 1.54—1.68, 2.85—2.98 (each 2H, m), 3.09 (2H, d, J=5.2 Hz), 4.58 (1H, t, J=5.2 Hz), 6.68 (2H, br s). *Anal.* Calcd for $C_6H_{15}NO_3S$: C, 39.76; H, 8.34; N, 7.73. Found: C, 39.80; H, 8.10; N, 7.92.

Compounds **35b—f** were obtained similarly. The physical data for these compounds (**35a—f**) are summarized in Tables 15 and 16.

4-Hydroxy-3,3-dimethylbutane-*N*,*N*-dimethylaminomethylenesulfonamide (36a) A mixture of **35a** (2.30 g) and *N*,*N*-dimethylformamide dimethyl acetal (**28a**, 1.59 g) in toluene (40 ml) was stirred at 70 °C for 0.5 h. The solvent was evaporated *in vacuo*, and the residue was recrystallized from Et_2O to give 2.86 g of **36a** (colorless prisms, 95%). mp 69—70 °C. IR (Nujol): 3430, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (6H, s), 1.69—1.84 (2H, m), 1.94 (1H, t, J=4.8 Hz), 2.98—3.11 (2H, m), 3.05, 3.14 (each 3H, s), 3.34 (2H, d, J=4.8 Hz), 8.05 (1H, s). *Anal.* Calcd for $C_9H_{20}N_2O_3S$: C, 45.74; H, 8.53; N, 11.85. Found: C, 45.83; H, 8.49; N, 12.09.

4-Iodo-3,3-dimethylbutane-*N*,*N*-dimethylaminomethylenesulfonamide (41) Trifluoromethanesulfonic anhydride (6.6 ml) was added dropwise to a solution of **36a** (5.50 g) in CH_2Cl_2 (50 ml) at 0 °C. The mixture was stirred for 20 min, then 2,6-lutidine (4.7 ml) was added dropwise at 0 °C followed by stirring for 20 min at 0 °C. The mixture was diluted with H_2O and extracted with EtOAc. The extract was washed with aq. $KHSO_4$ and then H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the residue and NaI (13.5 g) in acetone (100 ml) was refluxed for 2 h, then diluted with H_2O and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with n-C_6H_{14}–EtOAc (1 : 3). The eluate was concentrated *in vacuo* and the residue was recrystallized from iso-Pr_2O to give 8.44 g of **41** (colorless crystals, 80.4%). mp 81—82 °C. IR (Nujol): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (6H, s), 1.78—1.91, 2.92—3.04 (2H, m), 3.06 (3H, s), 3.12 (2H, s), 3.16 (3H, s), 8.05 (1H, s). *Anal.* Calcd for $C_9H_{19}IN_2O_2S$: C, 31.22; H, 5.53; N, 8.09. Found: C, 31.67; H, 5.68; N, 8.18.

4-Cyano-3,3-dimethylbutane-*N*,*N*-dimethylaminomethylenesulfonamide (42) A mixture of **41** (1.85 g), KCN (0.49 g) and 18-crown-6 in DMSO (30 ml) was stirred for 14 h at 100 °C, then mixture was diluted with H_2O and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with n-C_6H_{14}–EtOAc (1 : 9). The eluate was concentrated *in vacuo* and the residue was recrystallized from Et_2O to give 1.11 g of **42** (colorless crystals, 87.2%). mp 53—54 °C. IR (Nujol): 3580, 3525, 2240, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (6H, s), 1.82—1.94 (2H, m), 2.27 (2H, s), 2.96—3.07 (2H, m), 3.05, 3.15 (each 3H, s), 8.04 (1H, s). *Anal.* Calcd for $C_{10}H_{19}N_3O_2S$: C, 48.96; H, 7.81; N, 17.13. Found: C, 48.88; H, 7.82; N, 16.77.

Methyl 5-Aminosulfonyl-3,3-dimethylvalerate (43) A mixture of **42** (490 mg) and conc. HCl (10 ml) was refluxed (125—130 °C) for 16 h and then concentrated to dryness. The residue was dissolved in MeOH (12 ml) and conc. H_2SO_4 (4 drops) was added followed by refluxing for 14 h. The solvent was evaporated *in vacuo*, then the residue was diluted with H_2O and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with n-C_6H_{14}–EtOAc (1 : 4) to give 350 mg of **43** (oil, 78.5%). IR (neat): 3350, 3260, 1720, 1560 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (6H, s), 1.84—1.98 (2H, m), 2.25 (2H, s), 3.10—3.23 (2H, m), 3.68 (3H, s), 5.01 (2H, br s).

5-Hydroxy-3,3-dimethylpentane-*N*,*N*-dimethylaminomethylenesulfonamide (36g) A solution of **43** (352 mg) in THF (10 ml) was added dropwise to an ice-cold suspension of $LiAlH_4$ (101 mg) in THF (20 ml), followed by stirring for 40 min at 0 °C. The reaction was quenched carefully with H_2O and the mixture was made acid with 2 N HCl, then extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the residue and *N*,*N*-dimethylformamide dimethyl acetal (**28a**, 0.24 g) in toluene (8 ml) was stirred at 80 °C for 45 min. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (20 : 1) to give 286 mg of **36g** (oil, 73%). IR (neat): 3500, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, s), 1.52 (2H, t, J=7.2 Hz), 1.67—1.81 (3H, m), 2.94—3.06 (2H, m), 3.04, 3.14 (each 3H, s), 3.70 (2H, t, J=7.2 Hz), 8.03 (1H, s). *Anal.* Calcd for $C_{10}H_{22}N_2O_3S$: C, 47.97; H, 8.86; N, 11.19. Found: C, 47.71; H, 8.62; N, 11.44.

Compounds **44—46** and **36h** were prepared from **36g** by the same procedures as used to prepare **36g**.

5-Iodo-3,3-dimethylpentane-*N*,*N*-dimethylaminomethylenesulfonamide (44) Colorless crystals (74%). mp 105—106 °C. IR (Nujol): 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (6H, s), 1.65—1.78, 1.84—1.98, 2.91—3.03 (each 2H, m), 3.05, 3.14 (each 3H, s), 3.06—3.19 (2H, m), 8.05 (1H, s). *Anal.* Calcd for $C_{10}H_{21}IN_2O_2S$: C, 33.34; H, 5.88; N, 7.78. Found: C, 33.57; H, 5.97; N, 8.09.

5-Cyano-3,3-dimethylpentane-*N*,*N*-dimethylaminomethylenesulfonamide (45) Oil (82%). IR (neat): 3580, 3525, 2240, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (6H, s), 1.57—1.80 (4H, m), 2.32 (2H, t, J=7.6 Hz), 2.91—3.04 (2H, m), 3.05, 3.15 (each 3H, s), 8.05 (1H, s).

Methyl 5-Aminosulfonyl-3,3-dimethylhexanoate (46) Oil (90%). IR (neat): 3350, 3260, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (6H, s), 1.54—1.85 (4H, m), 2.30, 3.10 (each 2H, t, J=8.0 Hz), 3.68 (3H, s), 4.89 (2H, br s).

6-Hydroxy-3,3-dimethylhexane-*N*,*N*-dimethylaminomethylenesulfonamide (36h) Oil (86%). IR (neat): 3480, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (6H, s), 1.20—1.33 (2H, m), 1.46—1.78 (4H, m), 1.61 (1H, s), 2.98 (2H, t, J=6.4 Hz), 3.05, 3.14 (each 3H, s), 3.62 (2H, t, J=6.4 Hz), 8.04 (1H, s).

3,3-Dimethyl-5-(7-methyl[1,2,4]triazolo[1,5-*b*]pyridazin-6-yl)oxypentanesulfonamide (20) A solution of **36g** (820 mg) in THF (25 ml) was treated with NaH (60% dispersion in mineral oil, 150 mg) by portions followed by stirring for 1 h at room temperature. Then **25b** (540 mg) was added and the mixture was stirring for 20 h at room temperature. Ice-water was added, and the pH of the solution was adjusted to 4 with 2 N HCl. The mixture was extracted with EtOAc, and the extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and 6 N HCl (8 ml) was added to the residue followed by stirring for 30 min at 110 °C. Ice-water was added and the whole was extracted with EtOAc–THF (2 : 1). The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with $CHCl_3$–MeOH (30 : 1). The eluate was evaporated *in vacuo* and the residue was recrystallized from EtOAc–Et_2O to give 150 mg of **20** (colorless crystals, 14%). mp 143—144 °C. IR (Nujol): 3330, 3170, 1575, 1540, 1500 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.00 (6H, s), 1.66—1.89 (4H, m), 2.30 (3H, s), 2.94—3.10 (2H, m), 4.43 (2H, t, J=6.8 Hz), 6.77 (2H, br s), 8.16, 8.39 (each 1H, s). *Anal.* Calcd for $C_{13}H_{21}N_5O_3S$: C, 47.69; H, 6.46; N, 21.39. Found: C, 47.69; H, 6.46; N, 21.39.

Compound **21** was obtained similarly. In the synthesis of **21**, **36h** and **25b** were used, instead of **36g** and **25b**. The physical data for these compounds (**20** and **21**) are summarized in Tables 3 and 11.

PAF-Induced Bronchoconstriction in Guinea Pigs Groups of 6 Hartley guinea pigs (male, body weight about 450 g) were used in each group. The bronchoconstriction induced by PAF was measured according to the method of Konzett–Rösler.[6] The increase in respiratory overflow volume of animals treated by PAF (1 μg/kg, i.v.) was expressed as % of the maximal overflow volume (100%) obtained by obstruction of the airway. Details are given in our previous paper.[7]

Spasmogen-Induced Contraction of Trachea Strips Male Hartley guinea pigs (about 400 g) were killed by a sharp blow to the neck and exsanguinated. Tracheae were removed and tracheal strips were prepared using the method of Takagi *et al.*[8] Details are given in our previous paper.[7]

Antigen-Mediated Immediate and Late Airway Responses in Actively Sensitized Guinea Pigs[9] Hartley guinea pigs were sensitized by exposure to aerosolized ovalbumin (1% in saline) for 10 min on 2 occasions separated by 7 d. After an additional week, the guinea pigs were challenged by exposure to antigen aerosol (2% in saline) for 5 min. Mepyramine malate (5 mg/kg) was administered intraperitoneally 30 min before challenge. Specific airway resistance (sRaw) was measured in a whole-body plethysmograph (Buxco model P). Mesurements of sRaw were made 1 min, 10 min, 2 h, 3 h, 4 h, 5 h, 6 h, 7 h and 8 h after challenge.

A test compound suspended in 5% gum arabic solution was administered orally 1 h before antigen challenge.

Eosinophil Infiltration in Broncho-Alveolar Lavage (BAL) Fluid after Antigen Inhalation in Actively Sensitized Guinea Pigs[10] BAL was performed to 24 h after antigen challenge. Animals were anesthetized i.p. and killed with an overdose of pentobarbital sodium (Nembutal, 100 mg/kg; Abbott Laboratories). The trachea was exposed and cannulated with a polyethylene tubing connected to a syringe. The lungs were lavaged by flushing with three 5-ml aliquots of saline at 37 °C instilled through the tracheal cannula. The recovered fluid was combined and centrifuged ($400 \times g$ for 5 min at 4 °C) to remove the supernatant. The cell pellet was resuspended in 1 ml of Hanks' balanced salt solution. Total cell counts were done with a hemocytometer with Turk's stain. Differential cell counts were undertaken on cytocentrifuged preparations (Cytospin II; Shandon Southern Instruments, Pittsburgh, PA) stained with May-Giemsa stain. A minimum of 400 cells were counted and classified as macrophages, eosinophils, neutrophils, lymphocytes and other cells based on normal morphological criteria.

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