Synthetic Studies on Condensed-Azole Derivatives. IV.[1] Synthesis and Anti-asthmatic Activities of ω-Sulfamoylalkyloxyimidazo[1,2-*b*]pyridazines

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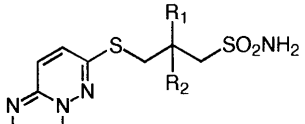
A series of novel (imidazo[1,2-*b*]pyridazin-6-yl)oxyalkylsulfonamides was synthesized and evaluated for the ability to inhibit platelet activating factor (PAF)-induced bronchoconstriction in guinea pigs. The compounds bearing a *gem*-dialkyl or a cycloalkylidene group at the 2 position of the sulfamoylpropyloxy group in the side chain were found to have potent activity. Among them, 3-(imidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (6) showed excellent anti-asthmatic activity and the longest duration of action. The compounds bearing a methyl group at the 7 or 8 position of the imidazo[1,2-*b*]pyridazine ring were found to have enhanced activity. Among them, 3-(7-methylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (25) showed the most potent inhibitory effect, and its anti-asthmatic effect in an experimental model of allergic asthma was superior to that of theophylline. The structure–activity relationships in this series of compounds are discussed.

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

In the course of our studies to improve the anti-asthmatic activity of 3-(imidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamide[2] (I, Fig. 1), we found that introduction of a substituent group into the alkyl side chain at the 6 position of the imidazo[1,2-*b*]pyridazine ring enhanced the activity.[1] Among the compounds synthesized, 3-(imidazo[1,2-*b*]pyridazin-6-yl)thio-2,2-dimethylpropanesulfonamide (II, Fig. 1) showed the most potent inhibitory effect on platelet activating factor (PAF)-induced bronchoconstriction in guinea pigs. Moreover, it prevented passively sensitized guinea pigs from developing allergic asthma upon antigen inhalation. These activities were superior to those of theophylline.

Further studies revealed that the inhibitory effect of II on PAF-induced bronchoconstriction in guinea pigs disappeared within 4 h after oral administration. This duration of action is not short; however, controlled-release formulations of theophylline for once-daily dosing are currently available for the treatment of asthma.[3] In order to increase the duration of the inhibitory effect of II, we synthesized 6-alkoxyimidazo[1,2-*b*]pyridazines based upon our assumption that the sulfur atom at the 6 position of the imidazopyridazine ring is oxidized to *S*-oxide by a metabolic reaction.[4] However, 6-alkoxy derivatives are hardly metabolized at all.

Further, in an effort to improve the anti-asthmatic activity of the 6-alkoxy derivatives, chemical modification of the alkyl side chain at the 6 position and introduction of substituents at the 2, 3, 7 and 8 positions of imidazo[1,2-*b*]pyridazine ring were carried out.



I: $R_1=R_2=H$
II: $R_1=R_2=CH_3$

Fig. 1

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

Chemistry

The synthesis of the 6-alkoxy derivatives of imidazo[1,2-*b*]pyridazines (**1**—**14**) listed in Table 1 was carried out by the route shown in Chart 1. Substituted 3-bromopropanols (**30c**,[5] **30d**,[6] **30e**,[7] **30g**—**l**,[5] **30m**,[8] **30n**[9]) were prepared following the reported procedures. Compounds **30a**—**n** were reacted with potassium thiocyanate to afford the thiocyanates (**31a**—**n**). After acetylation of **31a**—**n** with acetic anhydride, the thiocyanates (**32a**—**n**) were treated with chlorine gas under ice-cooling to obtain the sulfonyl chlorides (**33a**—**n**), followed by treatment with ammonia gas to afford the sulfonamides (**34a**—**n**). Compounds **34a**—**n** were deprotected with sodium methoxide to yield the 3-hydroxysulfonamides (**35a**—**n**). The 6-alkoxy derivatives of imidazo[1,2-*b*]pyridazines (**1**—**14**) were obtained by the reaction of the sulfonamides (**35a**—**n**) with 6-chloroimidazo[1,2-*b*]pyridazine (**36**)[10] in the presence of sodium hydride.

The synthesis of the 3-(2-, 3-, 7- and 8-substituted imidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamides (**15**—**17**, **20**—**29**) listed in Table 2 was carried out *via* the route shown in Chart 2. Substituted imidazo[1,2-*b*]pyridazines (**37**, **40**—**42**, **44**, **46**—**52**) were reacted with 3-hydroxy-2,2-dimethylpropanesulfonamide (**30f**) in the presence of sodium hydride to afford 2-, 3-, 7- and 8-substituted imidazo[1,2-*b*]pyridazines (**15**—**17**, **20**—**29**). 6-Chloro-2-methylimidazo[1,2-*b*]pyridazine (**37**)[11] and 3,6-dichloroimidazo[1,2-*b*]pyridazine (**41**)[12] were prepared following previously reported procedures. 6-Chloro-3-methylimidazo[1,2-*b*]pyridazine (**40a**) and 6-

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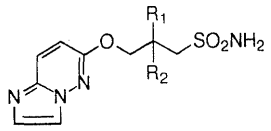
Table 1. Physical Data for Substituted Sulfamoylpropyloxyimidazo[1,2-*b*]pyridazines



Compd. No.	R_1	R_2	mp (°C)	Formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield (%)
1	H	H	201—204	$C_9H_{12}N_4O_3S$	42.18	4.72	21.86	42.16	4.77	21.62	36
2	CH_3	H	162—165	$C_{10}H_{14}N_4O_3S$	39.15	4.93	18.26	39.04	4.99	18.12	65
3	CH_2CH_3	H	143—145	$C_{11}H_{16}N_4O_3S\cdot HCl$	41.18	5.34	17.46	41.24	5.38	17.46	40
4	$CH(CH_3)_2$	H	153—156	$C_{12}H_{18}N_4O_3S\cdot HCl$	43.05	5.72	16.73	43.13	5.86	16.29	19
5	$(CH_2)_4CH_3$	H	144—145	$C_{14}H_{22}N_4O_3S$	51.51	6.79	17.16	51.41	6.77	17.10	26
6	CH_3	CH_3	206—207	$C_{11}H_{16}N_4O_3S\cdot HCl$	41.18	5.38	17.46	41.10	5.30	17.30	77
7	CH_2CH_3	CH_2CH_3	187—190	$C_{13}H_{20}N_4O_3S\cdot HCl$	44.76	6.07	16.06	44.75	6.15	15.89	61
8	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	175—176	$C_{17}H_{28}N_4O_3S$	55.41	7.66	15.20	55.13	7.60	14.91	21
9	$-(CH_2)_2-$		195—197	$C_{11}H_{14}N_4O_3S$	46.80	5.00	19.84	46.69	5.01	19.79	73
10	$-(CH_2)_3-$		238—241	$C_{12}H_{16}N_4O_3S$	48.64	5.44	18.91	48.64	5.55	18.75	58
11	$-(CH_2)_4-$		186—188	$C_{13}H_{18}N_4O_3S$	50.31	5.85	18.05	50.52	5.97	17.90	65
12	$-(CH_2)_5-$		242—244	$C_{14}H_{20}N_4O_3S\cdot HCl$	46.60	5.87	15.53	46.70	5.92	15.52	35
13	$-CH_2-O-CH_2-$		253—255	$C_{11}H_{14}N_4O_4S$	44.29	4.73	18.78	44.52	4.80	18.68	58
14	$-(CH_2)_2-O-(CH_2)_2-$		225—228	$C_{13}H_{18}N_4O_4S\cdot HCl$	43.03	5.28	15.44	43.20	5.58	15.11	59

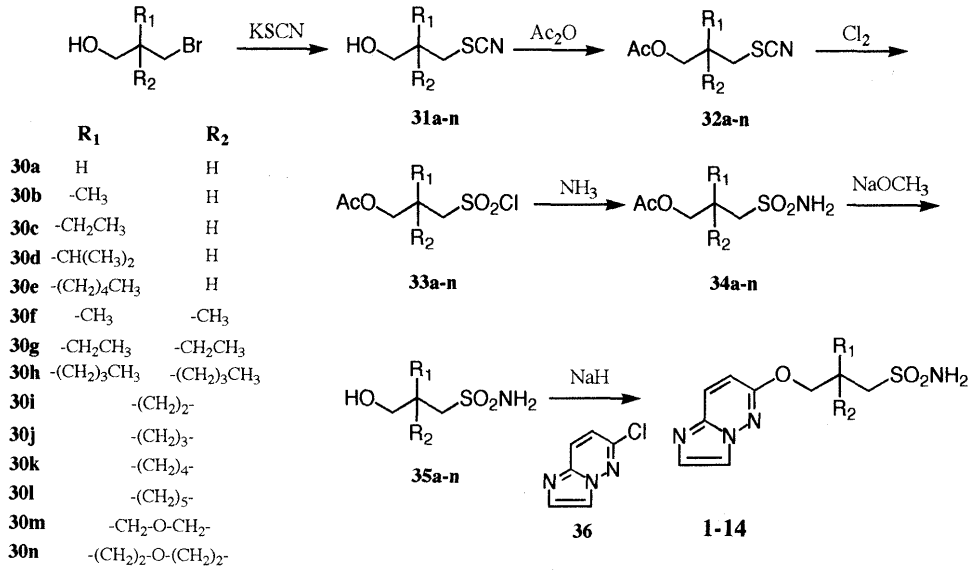


Chart 1

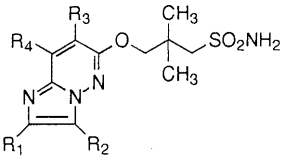
chloro-3-isopropylimidazol[1,2-*b*]pyridazine (**40b**) were synthesized *via* the route shown in Chart 3. α-Bromoaldehydes (**38a, b**)[13] were condensed with 3-amino-6-chloropyridazine (**39**)[14] to give 6-chloro-3-alkylimidazo[1,2-*b*]pyridazines (**40a, b**).

Imidazo[1,2-*b*]pyridazine derivatives (**42**, **44** and **46**) having a substituent group at the 3 position were prepared *via* the route shown in Chart 4. Nitration of 6-chloroimidazo[1,2-*b*]pyridazine (**36**) using nitric acid–sulfuric acid following Kobe's procedure[15] gave 6-chloro-3-nitroimidazo[1,2-*b*]pyridazine (**42**). The 3-amino derivative (**43**) was obtained by reduction of **42** using stannous chloride–concentrated hydrochloric acid. Acetylation of **43** using acetic anhydride afforded the acetylamino derivative (**44**). Reaction of **43** with mesyl chloride afforded the dimesylamino derivative (**45**), which was treated with potassium *tert*-butoxide to obtain the 3-mesylamino derivative (**46**). 6-Chloro-3-sulfamoylimidazo[1,2-*b*]pyridazine (**47**)[12] was prepared following the previously reported procedure.

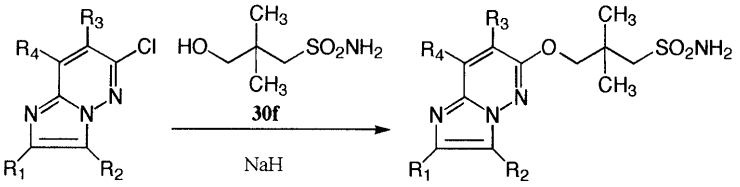
Imidazo[1,2-*b*]pyridazines (**48**—**50**,[16] **51**,[17] **52**[18]) with substituents at the 7 and 8 positions were prepared following the reported procedures.

The 3-(3-substituted imidazo[1,2-*b*]pyridazin-6-oxy-2,2-dimethylpropanesulfonamide (**18**, **19**) listed in Table 2 were prepared *via* the route shown in Chart 5. The sulfonamide group of **6** was protected by using phosphoryl chloride in *N*,*N*-dimethylformamide (DMF) to afford the *N*,*N*-dimethylaminomethylenesulfonamide (**53**). Formylation of **53** using dichloromethyl methyl ether and titanium chloride produced the 3-formyl derivative (**54**), which was treated with hydroxyamine to afford the oxime (**55**),

Table 2. Physical Data for 2-, 3-, 7- and 8-Substituted Sulfamoylpropyloxyimidazo[1,2-*b*]pyridazines



Compd. No.	R_1	R_2	R_3	R_4	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
15	CH_3	H	H	H	197—201	$C_{12}H_{18}N_4O_3S \cdot HCl \cdot 0.4H_2O$	42.14 (42.31	5.83 5.65	16.38 16.34)	86
16	H	CH_3	H	H	210—213	$C_{12}H_{18}N_4O_3S \cdot HCl$	43.05 (43.33	5.72 5.41	16.73 16.66)	64
17	H	$CH(CH_3)_2$	H	H	185—190	$C_{14}H_{22}N_4O_3S \cdot HCl$	46.34 (46.07	6.39 6.42	15.44 15.29)	62
18	H	CN	H	H	220—221	$C_{12}H_{15}N_5O_3S$	46.59 (46.74	4.89 4.86	22.64 22.67)	78
19	H	$CONH_2$	H	H	225—227	$C_{12}H_{17}N_5O_4S \cdot 0.1H_2O$	43.81 (43.61	5.27 5.22	21.28 21.16)	77
20	H	Cl	H	H	194—195	$C_{11}H_{15}ClN_4O_3S \cdot HCl \cdot 0.5H_2O$	36.27 (36.50	4.70 4.90	15.38 15.67)	82
21	H	NO_2	H	H	192—195	$C_{11}H_{15}N_5O_5S$	40.12 (40.26	4.59 4.50	21.27 21.14)	30
22	H	$NHCOCH_3$	H	H	164—168	$C_{13}H_{19}N_5O_4S \cdot HCl \cdot 1.5H_2O$	38.57 (38.42	5.73 5.88	17.30 16.99)	80
23	H	$NHSO_2CH_3$	H	H	203—205	$C_{12}H_{19}N_5O_5S_2$	38.19 (38.39	5.07 5.18	18.55 18.32)	71
24	H	SO_2NH_2	H	H	252—257	$C_{11}H_{17}N_5O_5S_2 \cdot 3.5H_2O$	30.98 (30.91	5.67 5.69	16.42 16.25)	37
25	H	H	CH_3	H	210—217	$C_{12}H_{18}N_4O_3S \cdot HCl \cdot 0.4H_2O$	42.14 (42.29	5.84 5.87	16.38 16.45)	19
26	H	H	H	CH_3	176—179	$C_{12}H_{18}N_4O_3S \cdot HCl \cdot 0.6H_2O$	41.70 (41.45	5.78 5.91	16.21 16.20)	22
27	H	H	CH_3	CH_3	210—220	$C_{13}H_{20}N_4O_3S \cdot HCl$	44.76 (44.82	6.07 5.94	16.06 15.93)	39
28	H	H	$-(CH_2)_4-$		215—225	$C_{15}H_{22}N_4O_3S \cdot HCl$	48.06 (48.00	6.18 6.22	14.94 14.65)	30
29	H	H	$-CH=CH-CH=CH-$		201—211	$C_{15}H_{18}N_4O_3S \cdot HCl$	48.58 (48.26	5.16 5.38	15.11 14.82)	66



	R_1	R_2	R_3	R_4
37	CH_3	H	H	H
40a	H	CH_3	H	H
40b	H	$CH(CH_3)_2$	H	H
41	H	Cl	H	H
42	H	NO_2	H	H
44	H	$NHCOCH_3$	H	H
46	H	$NHSO_2CH_3$	H	H
47	H	SO_2NH_2	H	H
48	H	H	CH_3	H
49	H	H	H	CH_3
50	H	H	CH_3	CH_3
51	H	H	$-(CH_2)_4-$	
52	H	H	$-CH=CH-CH=CH-$	

Chart 2

followed by dehydration with acetic anhydride to afford the cyano derivative (**56**). Compound **18** was obtained by deprotection of **56** using hydrochloric acid. Hydrolysis of the cyano group of **56** gave the carbamoyl derivative (**57**), which was deprotected to give **19**.

Inhibition of PAF-Induced Bronchoconstriction of 6-

Alkoxyimidazo[1,2-*b*]pyridazines The 6-alkoxy derivatives of imidazo[1,2-*b*]pyridazines (**1**—**14**, Table 1) 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 Table 3.

Compound **1** showed potent anti-asthmatic activity (66%) comparable to that of I, which suggested that conversion of the 6-alkylthioimidazo[1,2-*b*]pyridazine to the 6-alkoxy derivative did not affect the activity.

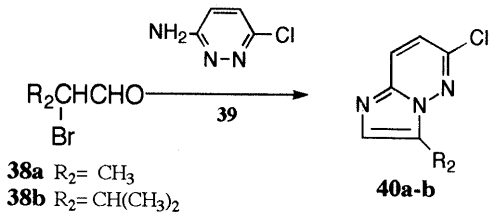


Chart 3

Consequently, the effect of introduction of monoalkyl substituents at the 2 position of the sulfamoylpropyloxy group in the side chain at the 6 position of the imidazo[1,2-*b*]pyridazine were examine. Introduction of a methyl group (**2**) did not decrease the inhibitory potency, but the ethyl derivative (**3**) tended to be less active. Introduction of an isopropyl group (**4**) enhanced the activity. When a more lipophilic substituent was introduced as in the case of **5**, however, the activity was relatively low.

The compounds (**6**—**8**) bearing two alkyl substituents in the alkyl side chain of the imidazopyridazine ring were more active than the monoalkyl derivatives (**2**—**5**). Dimethyl (**6**) and diethyl derivatives (**7**) showed excellent inhibitory effects (80% and 91% respectively). The dibutyl derivatives (**8**) was less active, but its activity was comparable to that of I.

In the series of the compounds (**9**—**12**) having a cycloalkylidene substituent on the side chain, the

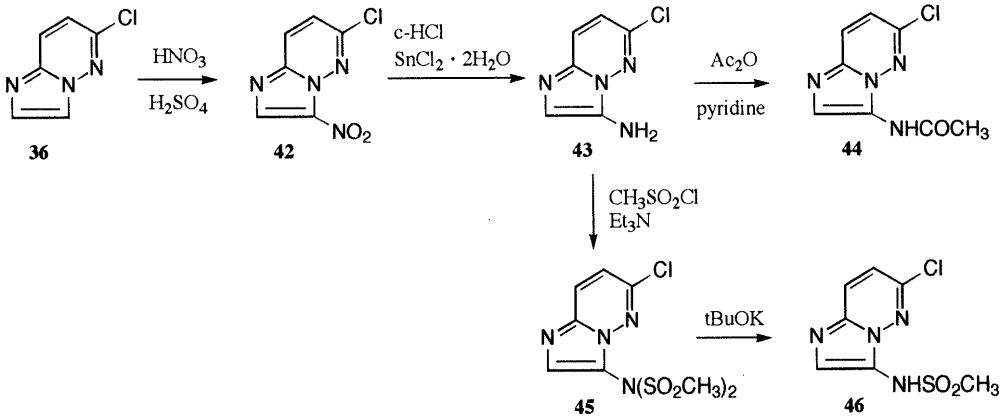


Chart 4

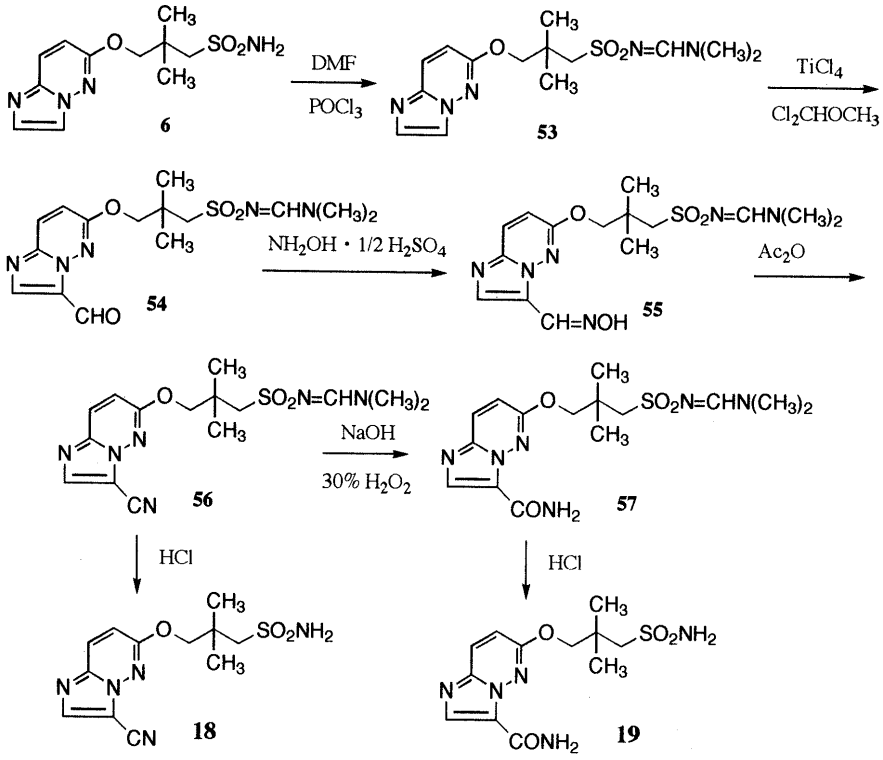


Chart 5

Table 3. 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]	ID_{50} (mg/kg, i.v.)[b]
1	66**	
2	68**	
3	55**	
4	85**	
5	49**	
6	80**	0.6
7	91**	0.7
8	67**	
9	46*	
10	84**	
11	90**	
12	92**	0.7
13	63**	
14	65**	
I	71**	
II		0.9

a) Compounds were given orally 1 h before PAF treatment. *b*) Compounds were given intravenously 2 min before PAF treatment. Significans of differences (Dunnett's): ** $p<0.01$, * $p<0.05$ (*vs.* control).

Table 4. Inhibitory Effects of Imidazo[1,2-*b*]pyridazines on PAF-induced Bronchoconstriction in Guinea Pigs

Compd. No.	% inhibition of PAF-induced bronchoconstriction[a]			
	1	2	4	8 h[b]
6	72**	66**	74**	48**
7	91**		79**	35
12	87**		75**	16

a) Compounds were given orally at a dose of 30 mg/kg. *b*) Time after administration. Significans of differences (Dunnett's): $p<0.01$ (*vs.* control).

cyclopropyl derivative (**9**) showed moderate activity. Introduction of cyclobutylidene (**10**), cyclopentylidene (**11**) and cyclohexylidene groups (**12**) increased the inhibitory activity, and extending the cycloalkyl ring on the alkyl side chain produced an increase in the anti-asthmatic activity.

Compounds with an oxygen atom in the cycloalkylidene substituents (**13** and **14**) showed potent activity; however, their activities were weaker than those of the corresponding cycloalkyl derivatives (**10** and **12**).

Dose–response relationships of several compounds (**6**, **7** and **12**) which showed excellent oral potency were examined by intravenous administration using PAF-induced bronchoconstriction. The results were compared with those obtained for II and are summarized in Table 3. The ID_{50} values were 0.6 (**6**), 0.7 (**7**) and 0.7 (**12**) mg/kg. The anti-asthmatic activiries of **6**, **7** and **12** were superior to that of II (0.9 mg/kg).

Duration of Anti-asthmatic Activity of 6-Alkoxyimidazo-[1,2-*b*]pyridazines The duration of the anti-asthmatic activity of compounds **6**, **7** and **12** was examined by oral administration using PAF-induced bronchoconstriction. As shown in Table 4, the inhibitory effect of compounds **7** and **12** disappeared within 8 h after administration. On the other hand, compound **6** having two methyl substituents on the alkyl side chain retained its inhibitory effect 8 h after oral administration.

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

Compd. No.	mg/kg, i.v.[a]	% inhibition of PAF-induced bronchoconstriction	ID_{50} (mg/kg, i.v.)
15	10	29	
16	3	70**	
17	10	18	
18	3	32	
19	3	23	
20	3	61**	
21	3	5	
22	10	25	
23	10	12	
24	10	8	
25	1	76**	0.1
26	1	64**	0.8
27	3	67**	
28	3	75**	
29	3	40	
6	3	80**	0.6

a) Compounds were given intravenously 2 min before PAF treatment. Significans of differences (Dunnett's): $p<0.01$ (*vs.* control).

Inhibition of PAF-Induced Bronchoconstriction of 2-, 3-, 7- and 8-Substituted Imidazo[1,2-*b*]pyridazines We next examined the effect of introduction of substituents at the 2, 3, 7 and 8 positions of the imidazo[1,2-*b*]pyridazine ring (Table 2) by intravenous administration using PAF-induced bronchoconstriction in guinea pigs. The results are summarized in Table 5.

Introduction of a methyl group at the 2 position of the imidazo[1,2-*b*]pyridazine ring (**15**) decreased the anti-asthmatic activity. On the other hand, the compound with a methyl group at the 3 position of the imidazopyridazine ring (**16**) showed potent activity, comparable to that of **6**. These data are in accord with the results for the 3-(imidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamides reported in our previous work.[1] Compound **17**, having an isopropyl group at the 3 position of the imidazopyridazine ring, showed lower activity. Introduction of an electron-withdrawing group, such as a cyano (**18**), carbamoyl (**19**), nitro (**21**), acetylamino (**22**), mesyl (**23**) or sulfamoyl (**24**) group, at the 3 position decreased the inhibitory activity, but the compound with a chlorine atom (**20**) at position 3 had activity comparable to that of **6**. No correlation was observed between the anti-asthmatic activity and the electron-withdrawing intensity of the substituent. These results suggest that the anti-asthmatic activity is decreased by steric hindrance at positions 2 and 3.

Introduction of a methyl group at the 7 position of the imidazopyridazine ring (**25**) increased the potency to 3 times that of **6**. Shifting the position of the methyl group from position 7 to 8 did not affect the activity, and compound **26** also showed excellent activity. Compounds with a methyl substituent at both the 7 and 8 positions of the imidazopyridazine ring (**27**) or with a cyclohexylene group (**28**) showed activity comparable to that of **6** but weaker than those of **25** and **26**. Introduction of a phenylene group (**29**) at the 7 and 8 positions decreased

the activity.

Dose–response relationships of compounds **25** and **26** were examined by intravenous administration using PAF-induced bronchoconstriction. The results were compared with those for **6** (Table 5). The ID_{50} values were 0.1 (**25**) and 0.8 (**26**) mg/kg, respectively. The anti-asthmatic activity of compound **25** was superior to that of **6** (ID_{50}, 0.6 mg/kg).

Compound **25** (1, 3 and 10 mg/kg, *p.o.*) also dose-dependently reduced asthmatic sympotoms induced by antigen inhalation in guinea pigs passively sensitized with rabbit anti-egg albumin serum. The results were compared for those obtained with theophylline, and are summarized in Table 6. In addition to alleviating the asthmatic signs, compound **25** decreased the incidence of mortality. Theophylline (30 mg/kg, *p.o.*) had no significant effect on these symptoms. This suggests that compound **25** is superior to theophylline.

We obtained several 3-(imidazo[1,2-*b*]pyridazin-6-yl)-oxyalkylsulfonamides: a new class of orally active anti-asthmatic compounds. It was found that 3-(imidazo-[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (**6**) showed excellent anti-asthmatic activity and the longest duration of action. Moreover, the anti-asthmatic activity was influenced by the introduction of substituent groups into the imidazopyridazine ring. Among the compounds synthesized, 3-(7- or 8-methylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (**25** and **26**) showed excellent anti-asthmatic activity, and the anti-asthmatic effects of compound **25** in an experimental model of allergic asthma were superior to those of theophylline.

Table 6. Effects of Compound **25** and Theophylline on Experimental Allergic Asthma Induced by Antigen Inhalation in Guinea Pigs Passively Sensitized with Rabbit Anti-egg Albumin Serum

Compd.	No. of animals	Symptom[a] 0	I	II	III	Mean score	Mortality died/total
Control	14	—	—	—	14	3.0±0.0	14/14
Mepyramine (3 mg/kg)	14	—	—	—	14	3.0±0.0	9/14
25 (1 mg/kg) + mepyramine (3 mg/kg)	13	0	6	2	5	1.9±0.3*	4/13
25 (3 mg/kg) + mepyramine (3 mg/kg)	13	1	5	4	3	1.7±0.3**	3/13
25 (10 mg/kg) + mepyramine (3 mg/kg)	13	3	7	1	2	1.2±0.3**	1/13
Theophylline (30 mg/kg) + mepyramine (3 mg/kg)	14	1	5	0	8	2.1±0.3	6/14

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

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-Hydroxypropyl Thiocyanate (31a) A mixture of 3-bromo-1-propanol (**30a**, 50 g) and KSCN (33.3 g) in MeOH (200 ml) was refluxed for 5 h. After the precipitate was filtered off, the filtrate was evaporated *in vacuo*. H_2O was added to the residue followed by extraction with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give 36.7 g of **31a** (colorless oil, 73%). IR (neat): 2150, 1740, 1365, 1240, 1040 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.02—2.18 (2H, m), 3.12 and 3.83 (each 2H, t, J=7 Hz).

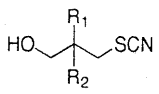
Compounds **31b—n** were obtained similarly. In the synthesis of **31b—n**, **30b—n** were used, respectively, instead of **30a**. The chemical data for these compounds (**31a—l**) are summarized in Table 7.

3-Acetoxypropyl Thiocyanate (32a) A mixture of **31a** (36.7 g) and Ac_2O (950 g) in pyridine (100 ml) was stirred at room temperature for 2 d. After the solvent was evaporated *in vacuo*, 0.2 N HCl (500 ml) was added to the residue followed by extraction with CH_2Cl_2 (500 ml). The extract was dried over $MgSO_4$ and evaporated *in vacuo* to give 41.3 g of **32a** (colorless oil, 83%). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.15—2.23 (2H, m), 3.05 and 4.23 (each 2H, t, J=6.5 Hz).

Compounds **32b—n** were obtained similarly. In the synthesis of **32b—n**, **31b—n** were used, respectively, instead of **31a**. The chemical data for these compounds (**32a—n**) are summarized in Table 8.

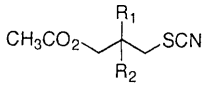
3-Acetoxypropanesulfonamide (34a) A solution of **32a** (41.3 g) in H_2O (200 ml) was bubbled with Cl_2 gas for 1 h under ice-cooling with stirring followed by extraction with Et_2O (200 ml × 2). After the extract was dried over $MgSO_4$, the solvent was evaporated *in vacuo* to give 30.5 g of **33a** (colorless oil, 59%). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.10—2.46 (2H, m), 3.78 and 4.25 (each 2H, t, J=6 Hz). Compound **33a** was dissolved in CH_2Cl_2 (500 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,

Table 7. Physical Data for Hydroxythiocyanate



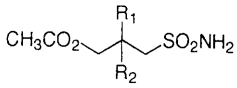
Compd. No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
31a	H	H	73	2.02—2.18 (2H, m), 3.12, 3.83 (each 2H, t, J=7 Hz)
31b	CH_3	H	94	1.10 (3H, d, J=7 Hz), 2.12 (1H, m), 2.88—2.98, 3.15—3.24, 3.53—3.62 and 3.68—3.77 (each, 1H, m)
31c	CH_2CH_3	H	89	0.98 (3H, t, J=7 Hz), 1.50 (2H, q, J=7 Hz), 1.66 (1H, br s), 1.70—2.00 (1H, m), 3.00—3.30 and 3.50—3.90 (each 2H, m)
31d	$CH(CH_3)_2$	H	90	0.97 and 1.00 (each 3H, d, J=6.5 Hz), 1.72—1.80 and 1.82—1.95 (each 1H, m), 3.13—3.20 (2H, m), 3.67—3.76 and 3.84—3.92 (each 1H, m)
31e	$(CH_2)_4CH_3$	H	95	0.87—0.93 (3H, m), 1.30—1.41 (8H, m), 1.93—1.98 (1H, m), 3.10—3.14 (2H, m), 3.60—3.69 and 3.77—3.85 (each 1H, m)
31f	CH_3	CH_3	78	1.05 (6H, s), 3.07 and 3.48 (each 2H, s)
31g	CH_2CH_3	CH_2CH_3	97	0.85 (3H, t, J=7 Hz), 1.34 (2H, q, J=7 Hz), 3.09 and 3.49 (each 2H, br s)
31i	$-(CH_2)_2-$		93	0.60—0.90 (4H, m), 1.77 (1H, t, J=4.5 Hz), 3.18 (2H, s), 3.62 (2H, d, J=4.5 Hz)
31k	$-(CH_2)_4-$		95	1.70 (1H, br s), 1.95 (6H, s), 3.28 and 3.77 (each 2H, s)
31l	$-(CH_2)_5-$		60	1.47 (10H, br s), 1.65 (1H, t, J=4 Hz), 3.18 (2H, s), 3.58 (2H, d, J=4 Hz)

Table 8. Physical Data for Acetoxythiocyanates



Compd. No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
32a	H	H	83	2.08 (3H, s), 2.15—2.23 (2H, m), 3.05 and 4.23 (each 2H, t, J=6.5 Hz)
32b	CH_3	H	91	1.25 (3H, d, J=7 Hz), 2.11 (3H, s), 2.62—2.79 (1H, m), 3.54—3.65 (1H, m), 3.88—4.05 (2H, m), 4.16—4.24 (1H, m)
32c	CH_2CH_3	H	89	0.99 (3H, t, J=7.5 Hz), 1.55 (2H, q, J=7.5 Hz), 1.90—2.20 (1H, m), 2.08 (3H, s), 3.06 (2H, d, J=6.5 Hz), 4.00—4.30 (2H, m)
32d	$CH(CH_3)_2$	H	49	0.99 (6H, t, J=6.5 Hz), 1.89—2.08 (2H, m), 2.08 (3H, s), 2.97—3.22 and 4.04—4.33 (each 2H, m)
32e	$(CH_2)_4CH_3$	H	97	0.86—0.92 (3H, m), 1.26—1.42 (8H, m), 2.05—2.11 (1H, m), 2.08 (3H, s), 3.06 (2H, d, J=6.5 Hz), 4.01—4.10 and 4.19—4.26 (each 1H, m)
32f	CH_3	CH_3	94	1.10 (6H, s), 2.10 (3H, s), 3.04 and 3.93 (each 2H, s)
32g	CH_2CH_3	CH_2CH_3	77	0.86 (6H, t, J=7 Hz), 1.43 (4H, q, J=7 Hz), 2.09 (3H, s), 3.09 and 3.96 (each 2H, s)
32h	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	75	0.89 (6H, t, J=6.5 Hz), 1.18—1.37 (12H, m), 2.08 (3H, s), 3.09 and 3.94 (each 2H, s)
32i	$-(CH_2)_2-$		66	0.79 (4H, s), 2.10 (3H, s), 3.12 and 4.08 (each 2H, s)
32j	$-(CH_2)_3-$		76	1.80—2.10 (6H, m), 2.09 (3H, s), 3.24 and 4.22 (each 2H, s)
32k	$-(CH_2)_4-$		68	1.50—1.80 (8H, m), 2.09 (3H, s), 3.17 and 4.00 (each 2H, s)
32l	$-(CH_2)_5-$		95	1.49 (10H, s), 2.09 (3H, s), 3.14 and 4.05 (each 2H, s)
32m	$-CH_2-O-CH_2-$		85	2.11 (3H, s), 3.45 and 4.48 (each 2H, s), 4.53 and 4.57 (each 2H, d, J=7 Hz)
32n	$-(CH_2)_2-O-(CH_2)_2-$		57	1.50—1.70 (4H, m), 2.10 (3H, s), 3.18 (2H, s), 3.50—3.90 (4H, m), 4.17 (2H, s)

Table 9. Physical Data for Acetoxythiocyanates



Compd. No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
34a	H	H	98	2.08 (3H, s), 2.16—2.24 (2H, m), 3.23 and 4.21 (each 2H, t, J=6 Hz), 5.31 (2H, br s)
34b	CH_3	H	88	1.19 (3H, d, J=7 Hz), 2.09 (3H, s), 2.46—2.55 (1H, m), 2.97—3.08 and 3.26—3.36 (each 1H, m), 4.06—4.11 (2H, m), 5.16 (2H, br s)
34c	CH_2CH_3	H	67	0.98 (3H, t, J=7.5 Hz), 1.55 (2H, q, J=7.5 Hz), 2.10—2.50 (1H, m), 2.08 (3H, s), 3.00—3.40 and 4.10—4.30 (each 2H, m), 5.03 (2H, br s)
34d	$CH(CH_3)_2$	H	54	0.94—0.98 (each 3H, d, J=6.5 Hz), 1.92—2.10 (1H, m), 2.08 (3H, s), 2.19—2.30 (1H, m), 3.13—3.17 and 4.23—4.26 (each 2H, m), 5.07 (2H, br s)
34e	$(CH_2)_4CH_3$	H	20	0.89 (3H, t, J=7 Hz), 1.24—1.36 (6H, m), 1.48—1.59 (2H, m), 2.08 (3H, m), 2.31—2.34 (1H, m), 3.12—3.31 and 4.16—4.21 (each 2H, m), 4.98 (2H, br s)
34f	CH_3	CH_3	52	1.22 (6H, s), 2.10 (3H, s), 3.24 and 4.10 (each 2H, s), 4.08 (2H, br s)
34g	CH_2CH_3	CH_2CH_3	52	0.88 (6H, t, J=7 Hz), 1.55 (4H, q, J=7 Hz), 2.09 (3H, s), 3.24 and 4.14 (each 2H, s), 4.87 (2H, br s)
34h	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	12	0.91 (6H, t, J=7 Hz), 1.10—1.90 (12H, m), 2.09 (3H, s), 3.25 and 4.12 (each 2H, s), 4.93 (2H, br s)
34i	$-(CH_2)_2-$		37	0.60—1.00 (4H, m), 2.10 (3H, s), 3.23 and 4.14 (each 2H, s), 5.10 (2H, br s)
34j	$-(CH_2)_3-$		70	1.80—2.40 (6H, m), 2.10 (3H, s), 3.43 and 4.38 (each 2H, s), 4.79 (2H, br s)
34k	$-(CH_2)_4-$		69	1.50—1.90 (8H, m), 2.10 (3H, s), 3.35 and 4.14 (each 2H, s), 4.83 (2H, br s)
34l	$-(CH_2)_5-$		67	1.30—1.80 (10H, m), 2.09 (3H, s), 3.33 and 4.25 (each 2H, s), 4.98 (2H, br s)
34m	$-CH_2-O-CH_2-$		73	2.12 (2H, s), 3.67 and 4.60 (each 2H, s), 4.52 and 4.74 (each 2H, d, J=7 Hz), 5.10 (2H, br s)
34n	$-(CH_2)_2-O-(CH_2)_2-$		74	1.60—1.90 (4H, m), 2.10 (3H, s), 3.40 and 4.34 (each 2H, s), 3.73 (4H, t, J=5.5 Hz), 5.14 (2H, s)

dried over $MgSO_4$ and evaporated *in vacuo* to give 28.6 g of **34a** (colorless oil, 98%). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s), 2.16—2.24 (2H, m), 3.23 and 4.21 (each 2H, t, J=6 Hz), 5.31 (2H, br s).

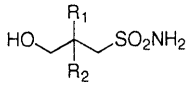
Compounds **34b—n** were obtained similarly. In the synthesis of **34b—n**, **32b—n** were used, respectively, instead of **32a**. The chemical data for these compounds (**34a—n**) are summarized in Table 9.

3-Hydroxypropanesulfonamide (35a) A mixture of **34a** (28.6 g) and 28% methanolic NaOMe solution (30.45 g) in MeOH (100 ml) was stirred for 0.5 h at room temperature. After the solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel eluting with CH_2Cl_2–MeOH (20 : 1), and the eluate was evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give 10.2 g of **35a** as colorless crystals (49%), mp 35—38 °C. IR (KBr): 3340, 1565, 1322, 1141 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.02—2.10, 3.18—3.26 and 3.67—3.75 (each 2H, m), 3.99 (1H, t, J=5 Hz), 6.04 (2H, br s). *Anal.* Calcd for $C_3H_9NO_3S$: C, 25.89; H, 6.52; N, 10.06. Found: C, 25.71; H, 6.85; N, 9.95.

Compounds **35b—n** were obtained similarly. In the synthesis of **35b—n**, **34b—n** were used, respectively, instead of **35a**. The chemical data for these compounds (**35a—n**) are summarized in Table 10.

3-(Imidazo[1,2-*b*]pyridazin-6-yl)oxypropanesulfonamide (1) To a solution of **35a** (1.39 g) in DMF (50 ml) was added NaH (60% dispersion in mineral oil, 480 mg) by portions followed by stirring for 1 h at 70 °C. 6-Chloroimidazo[1,2-*b*]pyridazine (**36**, 1.69 g) was added to the reaction mixture followed by stirring for 4 h at 70 °C. After the solvent was

Table 10. Physical Data for Hydroxysulfonamides



Compd. No.	R_1	R_2	Yield (%)	^{1}H-NMR ($CDCl_3$) δ
35a	H	H	49	2.02—2.10, 3.18—3.26 and 3.67—3.75 (each 2H, m), 3.99 (1H, t, J=5 Hz), 6.04 (2H, br s)
35b	CH_3	H	74	1.06 (3H, d, J=7 Hz), 2.00—2.15, 2.67—2.78 and 3.12—3.21 (each 1H, m), 3.27—3.40 (2H, m), 4.70 (1H, t, J=6 Hz), 6.77 (2H, br s)
35c	CH_2CH_3	H	88	0.86 (3H, t, J=7.5 Hz), 1.47 (2H, q, J=7.5 Hz), 1.80—2.00 (1H, m), 2.70—3.20 and 3.30—3.60 (each 2H, m), 4.59 (1H, t, J=6 Hz), 6.77 (2H, br s)
35d	$CH(CH_3)_2$	H	93	0.91 and 0.95 (each 3H, d, J=6.5 Hz), 1.95—2.05, 3.15—3.20 and 3.60—3.83 (each 2H, m), 6.50 (2H, br s)
35e	$(CH_2)_4CH_3$	H	95	0.89 (3H, t, J=7 Hz), 1.26—1.48 (10H, m), 2.12—2.26 (1H, m), 3.19—3.39 and 3.55—3.89 (each 2H, m), 5.28 (2H, br s)
35f	CH_3	CH_3	82	1.14 (6H, s), 3.23 and 3.57 (each 2H, s), 6.76 (2H, br s)
35g	CH_2CH_3	CH_2CH_3	67	0.86 (6H, t, J=7.0 Hz), 1.50 (4H, q, J=7.0 Hz), 2.00 (1H, d, J=5.0 Hz), 3.22 (2H, s), 3.66 (2H, d, J=5.0 Hz), 5.00 (2H, br s)
35h	$(CH_2)_3CH_3$	$(CH_2)_3CH_3$	47	0.92 (6H, t, J=7 Hz), 1.10—1.80 (12H, m), 3.23 (2H, s), 3.65 (2H, d, J=6 Hz), 5.00 (2H, br s)
35i	$-(CH_2)_2-$		89	0.60—0.90 (4H, m), 3.20 (1H, t, J=4.5 Hz), 3.26 (2H, s), 3.62 (2H, d, J=4.5 Hz), 5.58 (2H, br s)
35j	$-(CH_2)_3-$		90	1.80—2.20 (6H, m), 1.90 (1H, d, J=4.5 Hz), 3.45 (2H, s), 3.90 (2H, d, J=4.5 Hz), 5.00 (2H, br s)
35k	$-(CH_2)_4-$		75	1.64 (8H, br s), 2.48 (1H, d, J=4.5 Hz), 3.30 (2H, s), 3.59 (1H, d, J=4.5 Hz), 6.00 (2H, br s)
35l	$-(CH_2)_5-$		61	1.30—1.70 (10H, m), 2.00 (1H, d, J=4.5 Hz), 3.33 (2H, s), 3.72 (2H, d, J=4.5 Hz), 5.38 (2H, br s)
35m	$-CH_2-O-CH_2-$		90	3.64 (2H, s), 4.10 (2H, d, J=5.5 Hz), 4.27 (1H, t, J=5.5 Hz), 4.47 and 4.66 (each 2H, d, J=6.5 Hz), 6.38 (2H, br s)
35n	$-(CH_2)_2-O-(CH_2)_2-$		73	1.50—1.90 (4H, m), 3.55 (1H, t, J=5.0 Hz), 3.38 (2H, s), 3.60—3.80 (4H, m), 3.85 (2H, d, J=5.0 Hz), 4.83 (2H, br s)

evaporated *in vacuo*, the residue was chromatographed on silica gel eluting with CH_2Cl_2–EtOAc (10 : 1) and recrystallized from MeOH to give 0.93 g of **1** (36%) as colorless needles, mp 201—204 °C. IR (KBr): 3285, 1625, 1550, 1490, 1320, 1290, 1205, 1135 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.15—2.28 (2H, m), 3.17 and 4.41 (each 2H, t, J=6.5 Hz), 6.87 and 8.00 (each 1H, d, J=10 Hz), 6.90 (2H, br s), 7.60 and 8.05 (each 1H, d, J=1 Hz). *Anal.* Calcd for $C_9H_{12}N_4O_3S$: C, 42.18; H, 4.72; N, 21.86. Found: C, 42.16; H, 4.77; N, 21.62.

Compounds **2**—**14** were obtained similarly. In the synthesis of **2**—**14**, **35b**—**n** were used, respectively, instead of **35a**. The chemical data for these compounds (**2**—**14**) are summarized in Tables 1 and 11.

6-Chloro-3-methylimidazo[1,2-*b*]pyridazine (40a) A mixture of 3-amino-6-chloropyridazine (**39**, 5.0 g) and 2-bromopropanal (**38a**, 6.3 g) in EtOH (55 ml) was refluxed for 2 h. After the solvent was evaporated *in vacuo*, H_2O was added to the residue. The mixture was adjusted to pH 7 with Na_2CO_3 followed by extraction with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from H_2O to give 5.39 g of **40a** (colorless needles, 83%), mp 76—77 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.57 (3H, s), 7.00 and 7.87 (each 2H, t, J=9.5 Hz), 7.59 (1H, s). *Anal.* Calcd for $C_7H_6ClN_3$: C, 50.17; H, 3.61; N, 25.07. Found: C, 50.32; H, 3.57; N, 24.91.

6-Chloro-3-isopropylimidazo[1,2-*b*]pyridazine (40b) Compound **40b** was obtained from **38b** by the same procedures as described for **40a**, yield 79%, mp 49—50 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36 (6H, d, J=7 Hz), 3.20—3.55 (1H, m), 7.29 (1H, d, J=9 Hz), 7.66 (1H, s), 8.17 (1H, d, J=9 Hz). *Anal.* Calcd for $C_9H_{10}ClN_3$: C, 55.25; H, 5.15; N, 21.48. Found: C, 55.35; H, 4.86; N, 21.46.

6-Chloro-3-acetylaminoimidazo[1,2-*b*]pyridazine (44) To an ice-cooled solution of $SnCl_2$ (13.56 g) and conc. HCl (20 ml) was added 6-chloro-3-nitroimidazo[1,2-*b*]pyridazine (**42**, 2 g) with stirring. The mixture was stirred at room temperature for 10 min and then heated at 100 °C for an additional 15 min. H_2O was added to the mixture, and the pH was adjusted to 5 with 2 N NaOH. After the precipitate was filtered off, the solution was extracted with EtOAc–tetrahydrofuran (THF) (2 : 1). The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to give 1.16 g of 6-chloro-3-aminoimidazo[1,2-*b*]pyridazine (**43**, 71%) as brown crystals, mp 160—164 °C. ^{1}H-NMR (DMSO-d_6) δ: 4.00 (2H, br s), 6.83 and 7.78 (each 1H, d, J=9 Hz), 7.26 (1H, s). To a solution of **43** (1 g) and CH_2Cl_2 (15 ml) was added Ac_2O (2.26 ml) and pyridine (1.94 ml) followed by stirring at room temperature for 6 h. The resulting crystals were collected by filtration and washed with Et_2O to give 0.97 g of **44** (74%) as light brown crystals, mp 238—239 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.19 (3H, s), 7.28 and 8.17 (each 1H, d, J=10 Hz), 7.90 and 10.60 (each 1H, s). *Anal.* Calcd for $C_8H_7ClN_4O$: C, 45.62; H, 3.35; N, 26.60. Found: C, 45.42; H, 3.49; N, 26.61.

6-Chloro-3-*N*,*N*-dimethylsulfonylaminoimidazo[1,2-*b*]pyridazine (45) To an ice-cooled solution of **43** (2.53 g) and CH_2Cl_2 (50 ml) was added Et_3N (5.25 ml) and methanesulfonylchloride (2.91 ml) with stirring. After the mixture was stirred for 0.5 h at room temperature, the solvent was evaporated *in vacuo*. The residue was dissolved in EtOAc–THF (2 : 1), and the solution was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the resulting crystals were collected by filtration and washed with EtOAc to give 4.23 g of **45** (87%) as colorless crystals, mp 222—225 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.21 and 3.32 (each 3H, s), 7.53 and 8.22 (each 1H, d, J=9 Hz), 10.35 (1H, s), *Anal.* Calcd for $C_8H_9ClN_4O_4S_2$: C, 29.59; H, 2.79; N, 17.25. Found: C, 29.61; H, 2.51; N, 17.29.

6-Chloro-3-methylsulfonylaminoimidazo[1,2-*b*]pyridazine (46) To an ice-cooled solution of **45** (520 mg) in THF (20 ml) was added *tert*-BuOK (377 mg) with stirring. After the mixture was stirred for 0.5 h at room temperature, H_2O (30 ml) and 1 N HCl (1.76 ml) were added followed by saturation with NaCl. 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 chromatographed on silica gel eluting with CH_2Cl_2–MeOH (20 : 1). The eluate was evaporated *in vacuo* and the residue was recrystallized from CH_2Cl_2–Et_2O to give 250 mg of **46** as colorless crystals (63%), mp 194—196 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.15 (3H, s), 7.39 and 8.21 (each 1H, d, J=9 Hz), 7.80 (1H, s), 10.25 (1H, br s). *Anal.* Calcd for $C_7H_7ClN_4O_2S$: C, 34.08; H, 2.86; N, 22.71. Found: C, 34.15; H, 2.95; N, 22.42.

3-(2-Methylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide Hydrochloride (15) To a solution of **30f** (1.34 g) in DMF (20 ml) was added NaH (60% dispersion in mineral oil, 680 mg) by portions followed by stirring for 0.5 h at room temperature.

Table 11. IR and ^{1}H-NMR Data for Substituted Sulfamoylpropyloxyimidazo[1,2-*b*]pyridazines

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
1	3285, 1625, 1550, 1490, 1320, 1290, 1205, 1135	2.15—2.28 (2H, m), 3.17 and 4.41 (each 2H, t, J=6.5 Hz), 6.87 and 8.00 (each 1H, d, J=10 Hz), 6.90 (2H, br s), 7.60 and 8.05 (each 1H, d, J=1 Hz)
2	3282, 1620, 1552, 1323, 1141	1.19 (3H, d, J=7 Hz), 2.51—2.53, 2.93—3.06 and 3.21—3.31 (each 1H, m), 4.26 (2H, d, J=6 Hz), 6.88 and 8.02 (each 1H, d, J=10 Hz), 6.92 (2H, br s), 7.61 and 8.06 (each 1H, s)
3	3100, 1595, 1510, 1445, 1335, 1145	0.95 (3H, t, J=7.5 Hz), 1.63 (2H, q, J=7.5 Hz), 2.20—2.50 (1H, m), 3.00—3.30 (2H, m), 4.46 (2H, d, J=5.5 Hz), 6.96 (2H, br s), 7.44 and 8.34 (each 1H, d, J=10 Hz), 8.19 and 8.48 (1H, d, J=2 Hz)
4	3318, 1617, 1549, 1483, 1309, 1290, 1138	0.93 and 0.96 (each 2H, d, J=6.5 Hz), 2.03—2.12 and 2.27—2.35 (each 1H, m), 3.08 and 4.40 (each 2H, d, J=6 Hz), 6.87 and 8.00 (each 1H, d, J=10 Hz), 6.93 (2H, br s), 7.61 and 8.06 (each 1H, s)
5	3315, 1620, 1551, 1489, 1315, 1145	0.87 (3H, t, J=7 Hz), 1.29—1.40 (6H, m), 1.51—1.62 (2H, m), 2.32—2.54 (1H, m), 3.01—3.21 and 4.43—4.47 (each 2H, m), 6.95 (2H, br s), 7.45 and 8.35 (each 1H, d, J=10 Hz), 8.20 and 8.48 (each 1H, d, J=1.5 Hz)
6	3310, 1622, 1555, 1493, 1328, 1155	1.24 (6H, s), 3.22 and 4.28 (each 2H, s), 6.96 (2H, br s), 7.46 and 8.35 (each 1H, d, J=10 Hz), 8.19 and 8.48 (each 1H, d, J=2 Hz)
7	3130, 1590, 1505, 1435, 1325, 1150	0.87 (6H, t, J=7.5 Hz), 1.54—1.67 (4H, m), 3.22 and 4.37 (each 2H, s), 6.98 (2H, br s), 7.48 and 8.38 (each 1H, d, J=10 Hz), 8.23 and 8.52 (each 1H, d, J=2 Hz)
8	3310, 1608, 1545, 1489, 1324, 1285, 1140	0.87 (6H, t, J=7 Hz), 1.10—1.70 (12H, m), 3.19 and 4.26 (each 2H, s), 6.93 (2H, br s), 6.86 and 7.99 (each 1H, d, J=10 Hz), 7.60 and 8.07 (each 1H, s)
9	3305, 1618, 1547, 1496, 1330, 1319, 1122	0.70—1.00 (4H, m), 3.20 and 4.39 (each 2H, s), 6.93 (2H, br s), 7.51 and 8.36 (each 1H, d J=10 Hz), 8.21 and 8.47 (each 1H, d, J=2 Hz)
10	3305, 1550, 1490, 1330, 1290, 1160, 1145	1.80—2.40 (6H, m), 3.39 and 4.52 (each 2H, s), 6.88 and 8.00 (each 1H, d, J=10 Hz), 6.93 (2H, br s), 7.61 and 8.07 (each 1H, s)
11	3360, 1550, 1490, 1330, 1290, 1150	1.50—1.90 (8H, m), 3.29 and 4.29 (each 2H, s), 6.86 and 7.99 (each 1H, d, J=10 Hz), 6.93 (2H, br s), 7.60 and 8.06 (each 1H, s)
12	3175, 1595, 1505, 1445, 1340, 1150	1.35—1.70 (8H, m), 1.75—1.90 (2H, m), 3.32 and 4.45 (each 2H, s), 6.97 (2H, br s), 7.47 and 8.37 (each 1H, d, J=10 Hz), 8.21 and 8.52 (each 1H, d, J=2 Hz)
13	3290, 1550, 1500, 1360, 1330, 1290, 1150	3.66 and 4.73 (each 2H, s), 4.51 and 4.70 (each 2H, d, J=6.5 Hz), 6.90 and 8.02 (each 1H, d, J=9.5 Hz), 7.09 (2H, br s), 7.63 and 8.10 (each 1H, s)
14	3140, 1505, 1435, 1335, 1330, 1150	1.50—2.00 (4H, m), 3.50—3.90 (4H, m), 3.46 and 4.52 (2H, s), 7.05 (2H, s), 7.47 and 8.37 (each 1H, d, J=10 Hz), 8.21 and 8.52 (each 1H, d, J=2 Hz)

6-Chloro-2-methylimidazo[1,2-*b*]pyridazine (**37**, 1.34 g) was then added and the reaction mixture was further stirred for 0.5 h at room temperature. After the mixture was stirred for 40 min at 70 °C, the solvent was evaporated *in vacuo*. Ice-wateer (30 ml) was added to the residue, and the pH was adjusted to 6 with 1 N HCl. The resulting crystals were collected by filtration and dissolved in a small amount of MeOH. Saturated methanolic HCl (1 ml) was added to the solution, and the crystalline precipitate was collected by filtration to give 2.32 g of **15** (86%) as colorless needles, mp 197—201 °C. IR (KBr): 3065, 1600, 1500, 1320, 1305, 1130 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (6H, s), 2.49 (3H, s), 3.01 and 4.27 (each 2H, s), 6.96 (2H, br s), 7.44 and 8.31 (each 1H, d, J=10 Hz), 8.26 (1H, s). *Anal.* Calcd for $C_{12}H_{19}ClN_4O_3S \cdot 0.4H_2O$: C, 42.14; H, 5.83; N, 16.38. Found: C, 42.31; H, 5.65; N, 16.34.

Compounds **16**, **17** and **20**—**29** were obtained similarly. In the synthesis of **16**, **17** and **20**—**29**, **40**—**42**, **44** and **46**—**52** were used, respectively, instead of **37**. The chemical data for these compounds (**16**, **17** and **20**—**29**) are summarized in Tables 2 and 12.

3-(Imidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (53) A mixture of DMF (7 ml) and $POCl_3$ (4.55 g) was stirred at room temperature for 20 min. **6** (2.84 g) was added to the reaction mixture followed by stirring for 15 h at room temperature. The reaction mixture was poured into a saturated $NaHCO_3$ solution, and the pH was adjusted to 8 with $NaHCO_3$. The solution was extracted with EtOAc (50 ml × 3), and the extract was washed with brine and dried over $MgSO_4$. After the solvent was evaporated *in vacuo*, the residue was recrystallized from Et_2O to give 2.79 g of **53** (82%) as colorless prisms, mp 137—138 °C. IR (KBr): 3410, 1620 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (6H, s), 2.93 and 3.06 (each 3H, s), 3.22 and 4.25 (each 2H, s), 6.67 and 7.79 (each 1H, d, J=9.5 Hz), 7.60 and 7.72 (each 1H, s), 8.02 (1H, s). *Anal.* Calcd for $C_{14}H_{21}N_5O_3S$: C, 49.54; H, 6.24; N, 20.63. Found: C, 49.54; H, 6.15; N, 20.59.

3-(3-Formylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (54) To an ice-cold solution of **53** (1.35 g) and CH_2Cl_2 (12 ml) was added titanium chloride (2.64 ml) and dichloromethyl methyl ether (0.8 ml) followed by stirring for 1 h at room temperature. The reaction mixture was poured into ice-water (120 ml), and the pH of the solution was adjusted to 8 with $NaHCO_3$. After the solution was extracted with CH_2Cl_2, the extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with EtOAc–MeOH (4 : 1), and the eluate was evaporated *in vacuo*. The residue was recrystallized from CH_2Cl_2–Et_2O to give 318 mg of **54** as colorless crystals (22%), mp 127—128 °C. IR (KBr): 3430, 1675, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 2.99 and 3.12 (each 3H, s), 3.23 and 4.38 (each 2H, s), 6.99 and 7.92 (each 1H, d, J=9.5 Hz), 8.04, 8.25 and 10.29 (each 1H, s). *Anal.* Calcd for $C_{15}H_{21}N_5O_4S \cdot 0.1H_2O$: C, 48.79; H, 5.79; N, 18.97. Found: C, 48.67; H, 5.80; N, 18.79.

3-(3-Hydroxyiminomethylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (55) To a solution of **54** (4.33 g) and 50% aq. THF (120 ml) was added hydroxyamine sulfate (3.28 g). $NaHCO_3$ (3.36 g) was then added to the reaction mixture by portions. After stirring for 0.5 h at room temperature, the solvent was evaporated *in vacuo*. The residue was recrystallized from H_2O to give 4.41 g of **55** as colorless crystals (98%), mp 101—102 °C. IR (KBr): 3440, 3190, 1635 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (6H, s), 2.95 and 3.08 (each 3H, s), 3.24 and 4.34 (each 2H, s), 6.79 and 7.89 (each 1H, d, J=9.5 Hz), 8.00, 8.09 and 8.56 (each 1H, s). *Anal.* Calcd for $C_{15}H_{22}N_6O_4S \cdot 1.2H_2O$: C, 44.59; H, 6.09; N, 20.80. Found: C, 44.56; H, 6.09; N, 20.59.

3-(3-Cyanoimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (56) A solution of **55** (1.1 g) and Ac_2O (25 ml) was stirred at 140 °C for 5 h. After the solvent was evaporated *in vacuo*, the residue was chromatographed on silica gel eluting with EtOAc, and the eluate was evaporated *in vacuo*. The residue was recrystallized from EtOAc–*n*-C_6H_4 to give 887 mg of **57** as colorless crystals (85%), mp 131—132 °C. IR (KBr): 3430, 2230, 1632 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, s), 3.01 and 3.12 (each 3H, s), 3.22 and 4.36 (each 2H, s), 6.95 and 7.90 (each 1H, d, J=9.5 Hz), 8.04 and 8.07 (each 1H, s). *Anal.* Calcd for $C_{15}H_{20}N_6O_3S$: C, 49.44; H, 5.53; N, 23.06. Found: C, 49.49; H, 5.33; N, 23.03.

3-(3-Carbamoylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropane-*N*,*N*-dimethylaminomethylenesulfonamide (57) To an ice-cold solution of **56** (1 g) and dimethyl sulfoxide (DMSO) (1 ml) was added ice-cold 1 N NaOH–30% H_2O_2 solution (1 : 1, 1 ml) followed by stirring for 0.5 h. Ice-water (5 ml) was added to the reaction mixture followed by extraction with CH_2Cl_2 (20 ml). The extract was washed with brine, dried over

Table 12. IR and ^{1}H-NMR Data for 2-, 3-, 7- and 8-Substituted Imidazo[1,2-*b*]pyridazines

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
15	3065, 1600, 1500, 1320, 1305, 1130	1.23 (6H, s), 2.49 (3H, s), 3.01 and 4.27 (each 2H, s), 6.96 (2H, br s), 7.44 and 8.31 (each 1H, d, J=10 Hz), 8.26 (1H, s)
16	3230, 1597, 1553, 1494, 1334, 1149	1.25 (6H, s), 2.53 (3H, s), 3.23 and 4.35 (each 2H, s), 6.95 (2H, br s), 7.47 and 8.37 (each 1H, d, J=10 Hz), 8.04 (1H, s)
17	3210, 1590, 1490, 1340, 1150	1.25 (6H, s), 1.39 (6H, d, J=7 Hz), 3.2—3.6 (1H, m), 3.23, 4.34 and 6.96 (each 2H, s), 7.48 and 8.36 (each 1H, d, J=10 Hz), 8.05 (1H, s)
18	3290, 3040, 2235, 1335, 1155	1.24 (6H, s), 3.21 and 4.26 (each 2H, s), 6.93 (2H, br s), 7.22 and 8.24 (each 1H, d, J=10 Hz), 8.40 (1H, s)
19	3420, 3260, 1652, 1342, 1150	1.24 (6H, s), 3.21 and 4.29 (each 2H, s), 6.93 (2H, br s), 7.10 and 8.18 (each 1H, d J=9.5 Hz), 7.79 and 7.92 (each 1H, br s), 8.11 (1H, s)
20	3410, 1590, 1535, 1500, 1340, 1155	1.24 (6H, s), 3.22 and 4.28 (each 2H, s), 6.95 (2H, br s), 7.18 and 8.19 (each 1H, d, J=10 Hz), 7.99 (1H, s)
21	3265, 1550, 1520, 1460, 1360, 1325, 1300, 1280	1.25 (6H, s), 3.22, 4.31 and 6.94 (2H, s), 7.35 and 8.31 (each 1H, d, J=10 Hz), 8.65 (1H, s)
22	3415, 1690, 1570, 1325, 1160	1.25 (6H, s), 2.27 (3H, s), 3.23, 4.38 and 6.96 (each 2H, s), 7.35 and 8.27 (each 1H, d, J=10 Hz), 8.11 (1H, s), 10.74 (1H, s)
23	3260, 1565, 1485, 1340, 1325, 1155	1.23 (6H, s), 3.14 (3H, s), 3.20, 4.25 and 6.92 (each 2H, s), 6.92 and 7.99 (each 1H, d, J=10 Hz), 7.54 (1H, s), 9.98 (1H, s)
24	3350, 1550, 1460, 1350, 1155	1.13 (6H, s), 3.22 and 4.17 (each 2H, s), 6.91 and 7.98 (each 1H, d, J=9.5 Hz), 7.55 (1H, s), 6.93 and 8.50 (each 2H, br s)
25	3250, 1500, 1340, 1325, 1160	1.25 (6H, s), 2.41 (3H, s), 3.23, 4.29 and 6.95 (each 2H, s), 8.15 and 8.44 (each 1H, d, J=2 Hz), 8.24 (1H, s)
26	3400, 1610, 1500, 1340, 1320, 1200, 1150	1.23 (6H, s), 2.63 (3H, s), 3.26, 4.27 and 6.96 (each 2H, s), 7.37 (1H, s), 8.21 and 8.43 (each 1H, d, J=2 Hz)
27	3230, 1505, 1340, 1320, 1300, 1160	1.25 (6H, s), 2.33 and 2.61 (each 3H, s), 3.24, 4.28 and 6.94 (each 2H, s), 8.20 and 8.43 (each 1H, d, J=2 Hz)
28	3260, 1350, 1330, 1315, 1245, 1150	1.24 (6H, s), 1.8—2.0 (4H, m), 2.6—2.8 and 2.8—3.1 (each 2H, m), 3.23, 4.28 and 6.94 (each 2H, s), 8.19 and 8.44 (each 1H, d, J=2 Hz)
29	3260, 1535, 1330, 1270, 1150	1.33 (6H, s), 3.33, 4.46 and 6.97 (each 2H, s), 8.0—8.9 (4H, m), 8.16 and 8.44 (each 1H, d, J=2 Hz)

$MgSO_4$ and evaporated *in vacuo*. The residue was recrystallized from EtOAc–*n*-C_6H_4 to give 850 mg of **57** as colorless crystals (81%), mp 204.5—205.5 °C. IR (KBr): 3400, 3125, 1663, 1632 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.34 (6H, s), 2.98 and 3.11 (each 3H, s), 3.21 and 4.42 (each 2H, s), 6.01 and 8.15 (each 1H, br s), 6.89 and 7.95 (each 1H, d, J=9.5 Hz), 8.03 and 8.35 (each 1H, s).

3-(3-Carbamoylimidazo[1,2-*b*]pyridazin-6-yl)oxy-2,2-dimethylpropanesulfonamide (19) A solution of **57** (1.06 g) in 2 N HCl (4 ml) was refluxed for 0.5 h. The pH of the solution was then adjusted to 8 with $NaHCO_3$. The resulting crystals were collected by filtration and washed with H_2O to give 700 mg of **19** (77%) as colorless crystals, mp 225—227 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.24 (6H, s), 3.21 and 4.29 (each 2H, s), 6.93 (2H, br s), 7.10 and 8.18 (each 1H, d, J=9.5 Hz), 7.79 and 7.92 (each 1H, br s), 8.11 (1H, s). *Anal.* Calcd for $C_{12}H_{17}N_5O_4S \cdot 0.1H_2O$: C, 43.81; H, 5.27; N, 21.28. Found: C, 43.61; H, 5.22; N, 21.16.

Compound **18** was synthesized from **56** in a similar manner. The chemical data for **18** are summarized in Tables 2 and 12.

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 (1 μg/kg, i.v.) was measured according to the method of Konzett–Rössler.[19] Details are given in our previous paper.[2]

Experimental Allergic Asthma Induced by Inhalation of Antigen in Conscious Passively Sensitized Guinea Pigs Inhalation of antigen was used to provoke experimental allergic asthma 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.*[20] Details are given in our previous paper.[2]

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