Synthetic Studies on Condensed-Azole Derivatives. II.[1] Application of a Computer-Assisted Automated Synthesis Apparatus for the Synthesis of N-Substituted Sulfamoylpropylthioimidazo[1,2-*b*]pyridazines

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For the purpose of improving the anti-asthmatic activity of 3-(imidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamide (I), the computer-assisted automated synthesis apparatus developed at Takeda was used to modify the sulfonamide moiety of I. Several kinds of sulfonamide derivatives (1—24) were easily obtained, confirming the usefulness of the automated synthesis apparatus in the laboratory. Anti-asthmatic activity of these derivatives was examined in a platelet activating factor (PAF)-induced bronchoconstriction. Among them, the piperidino-piperidine derivative (13) was found to possess comparable activity to that of I.

Key words computer-assisted automated synthesis apparatus; PAF-induced bronchoconstriction; imidazo[1,2-*b*]-pyridazin

In a previous paper,[1] we reported the synthesis and anti-asthmatic activity of (imidazo[1,2-*b*]pyridazin-6-yl)-thioalkylsulfonamides as a new class of bronchodilator. The activity of 3-(imidazo[1,2-*b*]pyridazin-6-yl)thiopropanesulfonamide (I) was found to be greater than that of theophylline.

Recently, Sugawara *et al.* in the Takeda laboratories developed a versatile automated synthesis apparatus for preparing and isolating various kinds of compounds of pharmaceutical interest.[2] This apparatus was equipped with a chemical artificial intelligence system which could be used to prepare and isolate a series of organic compounds. All synthetic processes, introduction of reagents and solvents to the reaction unit, controlling reaction conditions, extraction, washing, drying and purification by column chromatography were automatically controlled by a personal computer. A schematic diagram of the apparatus is shown in Fig. 1. Details of the design and construction of this apparatus have been published separately.[2]

As the first application of this automated synthesis apparatus, we were interested in improving the anti-asthmatic activity of I by the chemical modification of the sulfonamide moiety. We describe here the synthesis of N-substituted sulfonamide derivatives of I by the automated synthesis apparatus and their anti-asthmatic activity using platelet activating factor (PAF)-induced bronchoconstriction.

Automated Synthesis of N-Substituted Sulfonamide Derivatives of I As described previously,[1] compound I was synthesized by the route shown in Chart 1. 3-Chloropropanesulfonyl chloride (**25**) was treated with ammonia gas under cooling to afford the sulfonamide (**26**).[3] After conversion of **26** to 3-mercaptopropanesulfonamide (**27**) by treatment with potassium hydrogen sulfide, 6-chloroimidazo[1,2-*b*]pyridazine (**28**)[4] was reacted with **27** in the presence of sodium methoxide to afford I.

When using the computer-assisted automated synthesis apparatus for the synthesis of N-substituted sulfonamides of I, the following three reaction steps were necessary (Chart 2).

Reaction 1: Preparation of sulfonamides (**30**) using sulfonyl chloride (**25**) and various kinds of amines (**29**).

Reaction 2: Thiolation of **30** by potassium hydrogen sulfide.

Reaction 3: Substitution reaction of **28** with 3-mercaptopropanesulfonamide (**31**).

A flow chart showing the reactions performed by the automated synthesis apparatus is presented in Chart 3. Namely, **25** and **29** were introduced and reacred in the reaction unit (reaction 1). The reaction mixture was

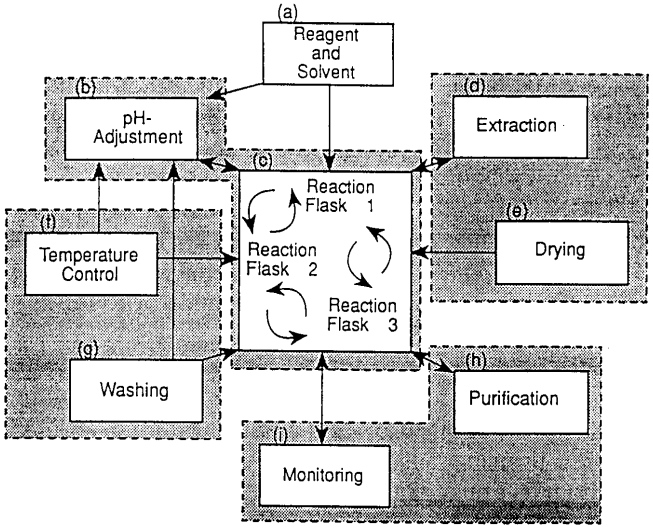

Fig. 1. Schematic Diagram of the Operating Units

(a) A reagent–solvent supply unit; reservoirs containing all the reagents, solvents and reaction solutions, and individual volumetric tubes fitted with photosensors to allow measurement of the required volumes. (b) A pH-adjustment device: a flask fitted with a pH-electrode to measure the pH of a production solution. (c) A reaction unit: two flasks with thermostatic jackets, condensers and stirrers; one flask with a condenser, stirrer and oil-bath. (d) An extraction/separation-funnel device: a glass funnel fitted with an electric sensor to allow separation of organic and aqueous phases. (e) A drying-tube device: for removing water from organic phases by passing them through a drying agent (Na_2SO_4). (f) A temperature control unit: a circulation system with hot and cold fluids for the reaction flasks and condensers. (g) A washing-exhaust/drainage unit: wash solvent reservoirs, a diaphragm pump and a drainage vessel to enable complete washing of the apparatus afer each run. (h) A purification unit: a HPLC device and a fraction collector device. (i) A reaction monitor unit: for real time sampling and HPLC analysis.

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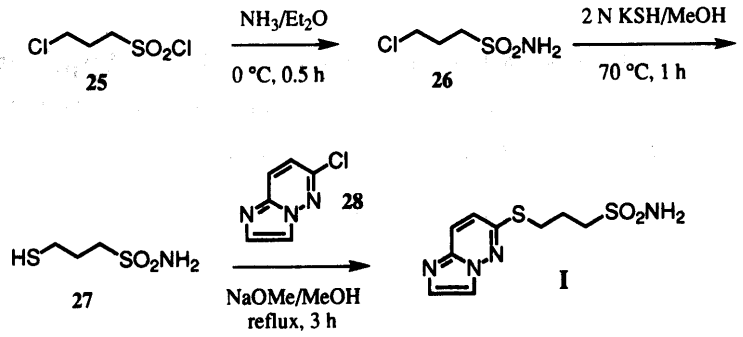


Chart 1. Synthetic Route to I

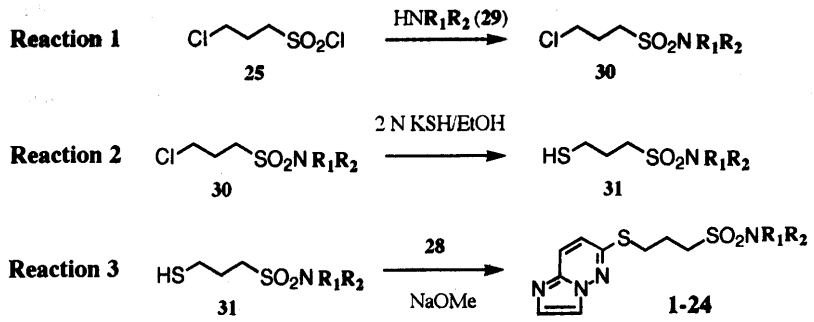


Chart 2. Synthetic Route to Sulfonamide Derivatives of I by Using the Automated Synthesis Apparatus

transfered to the extraction–drying unit and washed with water. After drying, the organic solution was transferred into the reaction unit for concentration. Methanol and ethanolic potassium hydrogen sulfide solution were added to the residue and the thiol (**31**) was prepared (reaction 2). Compound **28** and sodium methoxide were introduced into the reaction unit and allowed to react to obtain the desired compound (reaction 3). After concentration, water and ethyl acetate were added to the residue and the mixture was transferred to the extraction–drying unit. After drying, the organic layer was concentrated and the residue was transferred to the purification unit. After purification, the desired fraction was concentrated and recrystallized by hand.

The N-substituted sulfonamides (**1**—**24**) of I synthesized by the automated synthesis apparatus are listed in Tables 1—3. The automated synthesis apparatus was run for 10 h to synthesize a N-substituted sulfonamide of I (150 mg—1 g) starting from **25** (15 mmol).

Anti-asthmatic Activities of Sulfonamide Derivatives The anti-asthmatic activity of the N-substituted sulfonamides was examined by oral administration using PAF-induced bronchoconstriction and the activities of typical compounds are summarized in Table 4.

Introduction of propyl, isopropyl and allyl groups (**1**, **2**, **3**) decreased the activity. The compounds having a functional group at the end of the alkyl chain, pyridinyl ethyl (**8**) and methylpyrrolylethyl (**9**) derivatives showed moderate activity. In the series of N-substituted piperazinyl derivatives (**16**—**18**), **16** and **18** showed relatively low activities. The piperonyl derivative (**17**) retained activity, though its activity was weaker than that of I. The piperidino-piperidine derivative (**13**) was more active than I.

In conclusion, we obtained novel N-substituted sulfamoylpropylthiomidazo[1,2-*b*]pyridazines by the first

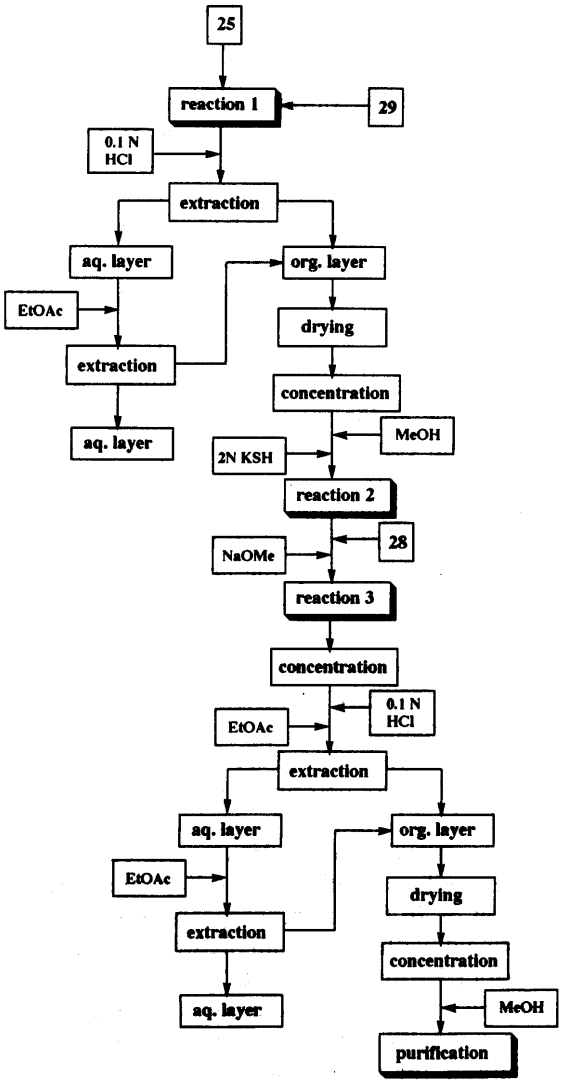
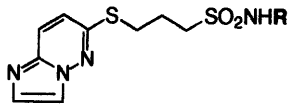


Chart 3. Flow Chart for Synthesis of Sulfonamide Derivatives of I

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



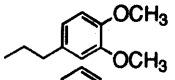
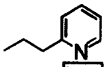
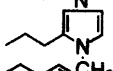
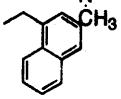
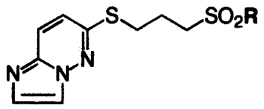
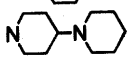
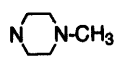
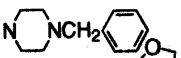
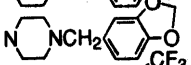
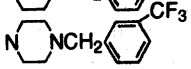
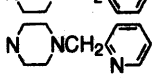
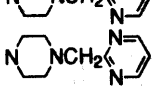
Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N	Yield (%)
1	$CH_2CH_2CH_3$	107—108	$C_{12}H_{18}N_4O_2S_2$	45.84	5.77	17.82	45.86	5.79	17.65	10
2	$CH(CH_3)_2$	112—113	$C_{12}H_{18}N_4O_2S_2$	45.84	5.77	17.82	46.10	5.77	17.89	13
3	$CH_2CH=CH_2$	89—90	$C_{12}H_{16}N_4O_2S_2$	46.13	5.16	17.93	46.29	5.10	17.85	31
4	OCH_3	139—141	$C_{10}H_{14}N_4O_3S_2$	39.72	4.67	18.53	39.68	4.67	18.45	8
5	CH_2CH_2OH	119—120	$C_{11}H_{16}N_4O_3S_2$	41.76	5.10	17.71	41.83	5.08	17.97	20
6	$CH_2CH_2N(CH_2CH_3)_2$	151—153	$C_{15}H_{25}N_5O_2S_2\cdot(COOH)_2$	40.31	6.37	13.82	40.48	6.13	13.82	12
7		104—105	$C_{19}H_{24}N_4O_4S_2\cdot0.5H_2O\cdot$fumarate	49.19	5.20	9.98	49.39	5.06	10.02	10
8		84—86	$C_{16}H_{19}N_5O_2S_2$	50.91	5.07	18.55	50.95	5.10	18.29	16
9		49—50	$C_{16}H_{21}N_5O_2S_2\cdot H_2O$	48.34	5.83	17.62	48.48	5.87	17.63	16
10		113—115	$C_{20}H_{20}N_4O_2S_2$	58.23	4.89	13.58	58.34	5.10	13.42	24

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



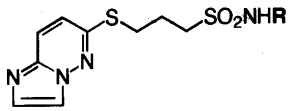
Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N	Yield (%)
11	$N(CH_2CH_3)_2$	151—153	$C_{13}H_{20}N_4O_2S_2\cdot HCl$	42.79	5.80	15.35	42.84	5.73	15.43	11
12		79—80	$C_{14}H_{20}N_4O_2S_2$	49.39	5.92	16.46	49.57	5.92	16.52	6
13		116—118	$C_{19}H_{29}N_5O_2S_2\cdot0.2H_2O$	53.19	6.95	16.32	53.36	6.81	16.42	5
14		80—81	$C_{13}H_{18}N_4O_3S_2$	45.60	5.30	16.36	45.59	5.30	16.27	5
15		154—156	$C_{14}H_{21}N_5O_2S_2\cdot HCl\cdot3H_2O$	37.70	6.33	15.70	37.53	6.77	15.61	6
16		225—227	$C_{20}H_{25}N_5O_2S_2\cdot2HCl$	47.62	5.39	13.88	47.40	5.50	13.73	31
17		203—206	$C_{21}H_{25}N_5O_4S_2\cdot2HCl$	45.98	4.96	12.77	45.93	4.94	12.53	9
18		173—176	$C_{21}H_{24}F_3N_5O_2S_2\cdot2HCl$	42.78	3.95	12.47	42.99	4.17	12.70	17
19		121—123	$C_{19}H_{24}N_6O_2S_2$	51.65	5.30	20.08	51.43	5.25	20.06	24
20		153—155	$C_{18}H_{23}N_7O_2S_2$	48.67	5.05	23.37	48.70	5.00	23.49	15

application of our automated synthesis apparatus. The anti-asthmatic activity of the piperidino-piperidine derivative (**13**) was found to be comparable with that of I. We believe that this system will make it possible to achieve greater efficiency in the laboratory for medicinal chemists, by reducing the manpower required for organic synthesis of a series of compounds with modified substitutent groups.

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. Design and construction of the auto-

Table 3. Physical Data for N-Arylsubstituted Sulfamoylpropylthioimidazo[1,2-*b*]pyridazines



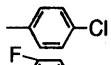
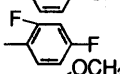
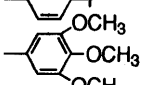
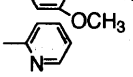
Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd C	H	N	Found C	H	N	Yield (%)
21		135—137	$C_{15}H_{15}N_4O_2S_2 \cdot HCl$	47.05	3.95	14.63	46.96	3.96	14.73	2
22		125—126	$C_{15}H_{14}F_2N_4O_2S_2$	46.87	3.67	14.57	46.92	3.66	14.53	4
23		179—180	$C_{18}H_{22}N_4O_5S_2$	49.30	5.06	12.78	49.08	5.07	12.54	3
24		170—172	$C_{14}H_{15}N_5O_2S_2$	48.12	4.33	20.04	47.84	4.21	20.07	7

Table 4. Variation in Anti-asthmatic Effect with N-Substituted Sulfonamides of Imidazo[1,2-*b*]pyridazine

Compd. No.	% inhibition of PAF-induced bronchoconstriction[a]	Compd. No.	% inhibition of PAF-induced bronchoconstriction[a]
1	14	**13**	80**
2	15	**16**	10
3	23	**17**	57**
8	41*	**18**	13
9	41*	**I**	71**

a) Compounds were given orally at a dose of 30 mg/kg 1 h before PAF treatment. Significance of differences (Dunnett's test): * $p<0.05$, ** $p<0.01$ (*vs.* control).

Table 5. IR and ^{1}H-NMR Data for N-Substituted Sulfamoylpropylthioimidazo[1,2-*b*]pyridazines

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
1	3055, 2870, 1535, 1455, 1325, 1285, 1130	0.91 (3H, t, J=8 Hz), 1.58—1.62 and 2.29—2.40 (each 2H, m), 2.95—3.41 (6H, m), 4.75—4.79 (1H, m), 6.80 and 7.75 (each 1H, d, J=10 Hz), 7.63 and 7.84 (each 1H, s)
2	3060, 2860, 1530, 1320, 1285, 1125, 1065	1.22 (6H, d, J=6.5 Hz), 2.31—2.35 (2H, m), 3.22 and 3.36 (each 2H, t, J=7 Hz), 3.77 (1H, m), 4.14 (1H, br s), 6.84 and 7.76 (each 1H, d, J=9.5 Hz), 7.65 and 7.98 (each 1H, s)
3	3030, 2825, 1553, 1527, 1322, 1302, 1147, 1130	2.11—2.15 (2H, m), 3.17 and 3.31 (each 2H, t, J=8 Hz), 3.58 (2H, br s), 5.03—5.25 (2H, m), 5.74—5.80 (1H, m), 7.14 and 7.98 (each 1H, d, J=9.5 Hz), 7.35 (1H, br s), 7.69 and 8.18 (each 1H, s)
4	2980, 2740, 1535, 1455, 1325, 1294, 1155	2.20—2.50 (2H, m), 3.30—3.49 (4H, m), 3.79 (3H, s), 6.92 and 7.76 (each 1H, d, J=10 Hz), 7.61 and 7.91 (each 1H, d, J=1 Hz)
5	3290, 1535, 1455, 1325, 1292, 1125	2.08—2.15 and 2.96—3.16 (each 2H, m), 3.20—3.44 (4H, m), 4.76 and 7.13 (each 1H, br s), 7.13 and 7.97 (each 1H, d, J=9 Hz), 7.68 and 8.18 (each 1H, s)
6	3405, 1720, 1625, 1515, 1470, 1400, 1320, 1145	1.18 (6H, t, J=7 Hz), 2.10—2.14 (2H, m), 2.48—2.59 and 3.10—3.18 (each 4H, m), 3.31 (4H, q, J=7 Hz), 7.15 and 7.99 (each 1H, d, J=9.5 Hz), 7.54—7.58 (1H, m), 7.69 and 8.19 (each 1H, d, J=1 Hz)
7	3110, 1690, 1515, 1455, 1330, 1140	1.99—2.08 and 2.64—2.70 (each 2H, m), 3.11—3.30 (6H, m), 3.71 and 3.74 (each 3H, s), 6.63 (2H, s), 6.70 (1H, dd, J=2, 8 Hz), 6.83 (1H, d, J=2 Hz), 6.85 (1H, d, J=8 Hz), 7.12 and 7.97 (each 1H, d, J=9 Hz), 7.21 (1H, t, J=6 Hz), 7.68 and 8.15 (each 1H, s)
8	3090, 2880, 1594, 1527, 1315, 1282, 1137, 1115	2.03—2.09 (2H, m), 2.91 and 3.15 (each 2H, t, J=7 Hz), 3.28—3.35 (4H, m), 7.13 and 7.93 (each 1H, d, J=8 Hz), 7.22—7.27 (2H, m), 7.67 and 8.14 (each 1H, s), 7.72 (1H, dd, J=2, 6.5 Hz), 8.48 (1H, d, J=5 Hz)
9	3100, 1530, 1450, 1320, 1160	2.24—2.31, 2.81—2.88 and 3.10—3.18 (each 2H, m), 3.33—3.42 (4H, m), 3.51—3.57 (3H, m), 4.54 (1H, br s), 5.92, 6.03 and 6.56 (each 1H, br s), 6.83 and 7.75 (each 1H, d, J=9.5 Hz), 7.66 and 7.84 (each 1H, d, J=1 Hz)
10	3060, 1538, 1469, 1325, 1142	2.05—2.18 (2H, m), 3.14—3.27 (4H, m), 4.60 (2H, br s), 7.12 and 7.98 (each 1H, d, J=9.5 Hz), 7.44—7.54 (4H, m), 7.68 and 8.17 (each 1H, s), 7.84—8.00 (3H, m)
11	3050, 1465, 1360, 1320, 1135	1.22 (6H, t, J=7 Hz), 2.33—2.40 and 3.05—3.12 (each 2H, m), 3.32 (4H, q, J=7 Hz), 3.43—3.50 (2H, m), 7.40 and 8.52 (each 1H, d, J=9.5 Hz), 7.88 and 8.02 (each 1H, s)
12	2915, 2850, 1605, 1525, 1460, 1330, 1155	1.57—1.68 (6H, m), 2.30—2.38 and 3.04—3.12 (each 2H, m), 3.22—3.27 (4H, m), 3.33—3.40 (2H, m), 6.85 and 7.76 (each 1H, d, J=9.5 Hz), 7.67 and 7.86 (each 1H, s)
13	2920, 1530, 1450, 1325, 1285, 1140	1.42—1.85 (11H, m), 2.30—2.37 (2H, m), 2.45—2.48 (4H, m), 2.70—2.82 (2H, m), 3.05—3.13, 3.33—3.40 and 3.83—3.91 (each 2H, m), 6.84 and 7.76 (each 1H, d, J=9.5 Hz), 7.67 and 7.87 (each 1H, d, J=1.5 Hz)

Table 5. (continued)

Compd. No.	IR (KBr) cm^{-1}	^{1}H-NMR (DMSO-d_6)
14	3030,1470, 1320, 1155	2.17—2.26 (2H, m), 3.27—3.43 (12H, m), 7.75 and 8.30 (each 1H, d, J=9.5 Hz), 8.24 and 8.56 (each 1H, d, J=2 Hz)
15	3360, 2680, 1470, 1350, 1145	2.05—2.10 (2H, m), 2.77 (3H, s), 3.34—3.42 (4H, m), 3.72—3.95 (8H, m), 7.65 and 8.25 (each 1H, d, J=10 Hz), 8.16 and 8.54 (each 1H, d, J=1 Hz)
16	3030, 1470, 1320, 1155	2.13—2.20 and 3.05—3.12 (each 2H, m), 3.29—3.42 (6H, m), 3.68—3.72 and 4.10—4.25 (each 2H, m), 4.36 (2H, s), 7.42—7.49 (3H, m), 7.62—7.66 (2H, m), 7.64 and 8.23 (each 1H, d, J=10 Hz), 8.15 and 8.53 (each 1H, dd, J=1.5 Hz)
17	3440, 2910, 1500, 1470, 1445, 1365, 1325, 1260, 1155	2.10—2.17 (2H, m), 3.29—3.47 (8H, m), 3.59—3.78 (4H, m), 4.26 and 6.08 (each 2H, s), 6.98—7.03 (2H, m), 7.28 (1H, s), 7.61 and 8.23 (each 1H, d, J=9.5 Hz), 8.12 and 8.51 (each 1H, d, J=2 Hz)
18	3450, 1515, 1475, 1325, 1150	2.17—2.26 (2H, m), 3.27—3.43 (14H, m), 7.13 and 7.25 (each 1H, d, J=7.5 Hz), 7.23 (1H, s), 7.46 (1H, t, J=7.5 Hz), 7.75 and 8.30 (each 1H, d, J=9.5 Hz), 8.24 and 8.56 (each 1H, d, J=2 Hz)
19	2850, 1605, 1595, 1325, 1145	2.33—2.40 and 3.09—3.16 (each 2H, m), 3.34—3.42 (6H, m), 3.62—3.67 (4H, m), 6.63—6.72 (2H, m), 6.83 and 7.73 (each 1H, d, J=9 Hz), 7.48—7.55 (1H, m), 7.64 and 7.84 (each 1H, s), 8.19—8.22 (1H, m)
20	3420, 1585, 1545, 1505, 1355, 1320, 1145	2.33—2.40 and 3.08—3.16 (each 2H, m), 3.33—3.41 (6H, m), 3.92—3.97 (4H, m), 6.57 (1H, t, J=5 Hz), 6.83 and 7.74 (each 1H, d, J=9.5 Hz), 7.64 and 7.84 (each 1H, d, J=1 Hz), 8.33 (2H, d, J=5 Hz)
21	3040, 2705, 1595, 1540, 1490, 1455, 1325, 1150	2.08—2.20 (2H, m), 3.23—3.33 (4H, m), 7.07 and 7.96 (each 1H, d, J=9.5 Hz), 7.15 and 7.27 (each 2H, d, J=9 Hz), 7.70 and 8.11 (each 1H, d, J=1 Hz), 9.98 (1H, br s)
22	3130, 2720, 1605, 1505, 1325, 1150	2.29—2.42 (2H, m), 3.23—3.35 (4H, m), 6.80 and 7.76 (each 1H, d, J=9 Hz), 6.75—6.83 (2H, m), 7.56—7.58 (1H, m), 7.66 and 7.80 (each 1H, d, J=1 Hz)
23	3430, 2940, 1605, 1530, 1510, 1450, 1330, 1145, 1125	2.10—2.21 (2H, m), 3.23—3.35 (4H, m), 3.61 (3H, s), 3.67 (6H, s), 6.49 (2H, s), 7.07 and 7.95 (each 1H, d, J=9.5 Hz), 7.68 and 8.10 (each 1H, s)
24	3430, 1635, 1530, 1395, 1280, 1130, 1115	2.30—2.42 (2H, m), 3.31—3.41 (4H, m), 6.78 and 7.77 (each 1H, d, J=10 Hz), 6.79—6.82 (1H, m), 7.40 (1H, d, J=9 Hz), 7.70 and 7.66 (each 1H, d, J=1 Hz), 7.68—7.72 and 8.13—8.15 (each 1H, m)

mated synthesis apparatus have been reported elsewhere.[2]

General Procedure for the Preparation of Sulfonamide Derivatives of I Using the Automated Synthesis Apparatus A solution of 3-chloropropanesulfonyl chloride (**25**, 1 M) in EtOAc was stored in the reservoir 1 and introduced into reaction flask 1, after measurement of its volume (15 ml, 15 mmol) using the volumetric tubes. The solution was then stirred at 0 °C for 3 min. In a similar manner, a solution of an amine (**29**, 2 M) in EtOAc was stored in reservoir 2 and added dropwise (10 s × 100 times) into reaction flask 1, after volume (15 ml, 30 mmol) had been measured using the volumetric tubes. The resulting reaction mixture was stirred at 0 °C for 30 min, and 0.1 N HCl was then added to the mixture from reservoir 3 after measurement of its volume (30 ml) using the volumetric tubes. The resulting two-phase mixture was stirred for 3 min, then transferred to the extraction–separation funnel using a diaphragm pump. After standing for 3 min to allow separation of the two layers, the upper organic layer was introduced into reaction flask 2 through a drying tube (Na_2SO_4, 65 g). From reservoir 4, EtOAc was introduced into reaction flask 1 after its volume (30 ml) had been measured using the volumetric tubes, and then trransferred into the extraction–separation funnel using a diaphragm pump. Air was bubbled for 1 min through the funnel to help re-extraction and the organic layer was passed through a drying tube before being collected in reaction flask 2. The organic solution was concentrated under reduced pressure at 50 °C for 20 min, and MeOH from reservoir 5 was introduced into reaction flask 2 after its volume (10 ml) had been measured using the volumetric tubes, to dissolve the residue. A solution of KSH (2 mM/ml) in EtOH stored in reservoir 6 was introduced into reaction flask 2 after its volume (15 ml) had been measured using the volumetric tubes. The reaction mixture was heated with stirring at 70 °C for 1 h and then 28% methanolic NaOMe solution stored in reservoir 7 was introduced into reaction flask 2 after its volume (3 ml) had been measured using the volumetric tubes. A MeOH solution of 6-chloroimidazo[1,2-*b*]pyridazine (**28**, 1.5 mM/ml) stored in reservoir 8 was introduced into the reaction flask 2 after its volume (10 ml) had been measured using the volumetric tubes. The reaction mixture was refluxed at 100 °C for 1.5 h and concentrated under reduced pressure at 50 °C for 25 min. Then 0.1 N HCl (30 ml) was added to the residue from reservoir 3 and EtOAc (30 ml) stored in reservoir 4 was introduced into reaction flask 2 after their volumes had been measured using the volumetric tubes. After air was bubbled for 1 min in order to stir the solution, the mixture was transferred to the extraction–separation funnel using a diaphragm pump. After standing for 3 min to allow separation of the two layers, the upper organic layer was introduced into reaction flask 3 through a new drying tube. The aqueous layer was extracted with EtOAc (30 ml) in a similar manner to that described above. The EtOAc solution collected in flask 3 was concentrated at 50 °C for 20 min under reduced pressure. From reservoir 5, MeOH was introduced into reaction flask 3 after its volume (15 ml) had been measured using the volumetric tubes. The mixture was then bubbled with air and stirred to dissolve the residue. The resulting MeOH solution was transferred to reservoir 9, then charged onto a column of silica gel (Merck, 35—70 mesh, 3 × 45 cm) and eluted with CH_2Cl_2 followed by CH_2Cl_2–MeOH (40 : 1). The desired fraction was concentrated and the resulting residue was recrystallized from MeOH–Et_2O to give the corresponding N-substituted sulfonamide derivatives (**1**—**20**). For the preparation of the N-arylsubstituted sulfonamides (**21**—**24**), the reaction mixture of **25** and **29** (reaction 1) in EtOAc was refluxed for 1 h, followed by the same procedure as above. The chemical data for these compounds are summarized in Tables 1—3 and 5.

PAF-Induced Bronchoconstriction in Guinea Pigs Groups of 6 hartley guinea pigs (male, body weight about 450 g) were used. The bronchoconstriction induced by PAF (1 μg/kg, i.v.) was measured according to the method of Konzett–Rössler.[5] Details are given in our previous paper.[1]

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