5-Isoquinolinesulfonamide Derivatives. III. Synthesis and Vasodilatory Activity of 1-(5-Isoquinolinesulfonyl)piperazine Derivatives

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On the basis of a hypothesis that cyclization and alkylation of the diamine part in formula 1 may give highly active compounds, a new series of 5-isoquinolinesulfonamide derivatives, shown as formula 2, were prepared from cyclic diamines. Their vasodilatory effects were subsequently evaluated *in vivo* according to the increase in arterial blood flow after the formulas were injected locally to the femoral and/or vertebral arteries of dogs. Cyclization of the diamine structure in formula 1 gave very potent vasodilators: 6 and 14. Acylation and sulfonylation of terminal amino nitrogen afforded much less potent compounds. In contrast to the hypothesis, alkylation on the ring carbon and the terminal nitrogen of the cyclic amine afforded less active compounds except for compound 11. The most active compounds, 6, 11 and 14, showed more potent vasodilatory effects and more selective activity to the vertebral artery than either trapidil or diltiazem.

Keywords vasodilator; structure–activity relationship; sulfonylation; sulfonamide; 5-isoquinolinesulfonamide

Introduction

It was previously reported that 5-isoquinolinesulfonamide derivatives (Chart 1, **1**) possessed vasodilatory activity.[2-5)] In amine derivatives (**1**, X=H) this activity was most potent when $n=2$, and the longer the alkyl groups, R^1 and R^2 in formula **1**, the higher the vasodilatory action.[5)] These results suggested that the vasodilatory activity was dependent on the distance between the sulfonamide and terminal amino nitrogen atoms, and also on the lipophilicity of the whole molecule. Cyclization of the sulfonamide side chain will reduce the distance between the two nitrogen atoms. Thus, the dependency of the vasodilatory action on cyclization and alkylation of the derivatives was investigated by preparing cyclic analogues of *N*-aminoalkyl-5-isoquinolinesulfonamide (Chart 1, **2**), and subsequently evaluating their vasodilatory action.

Synthesis Compounds **6**—**17** were prepared by sulfonylation of cyclic diamines in CH_2Cl_2 or $CHCl_3$ with 5-isoquinolinesulfonyl chloride (**4**)[4,6)] as shown in Chart 2 method A. To avoid the formation of a disulfonylated compound, an excess amount of diamine was used for the sulfonylation reaction. In the case of non-symmetric piperazine derivatives such as 2-methylpiperazine, the sulfonylation would afford two isomers, 1-sulfonyl and 4-sulfonyl derivatives. However, only one isomer was obtained with the reaction of **4** and an 2-alkylpiperazine. The isomer was expected to be the 4-sulfonylpiperazine derivative because of steric hindrance of the C-2 alkyl group to N-1, and this was proven by the following experiments. 2-Methylpiperazine was treated by benzyloxycarbonyl chloride prior to sulfonylation, and then sulfonylated with **4**. It was presumed that elimination of the benzyloxycarbonyl group by HBr–AcOH would yield 1-(5-isoquinolinesulfonyl)-2-methylpiperazine (**5**) as shown in Chart 2. This compound, however, had a different mp and nuclear magnetic resonance (NMR) spectrum from those of compound **8** which had been obtained by direct sulfonylation of 2-methylpiperazine with **4**. Analogues **5** and **8**

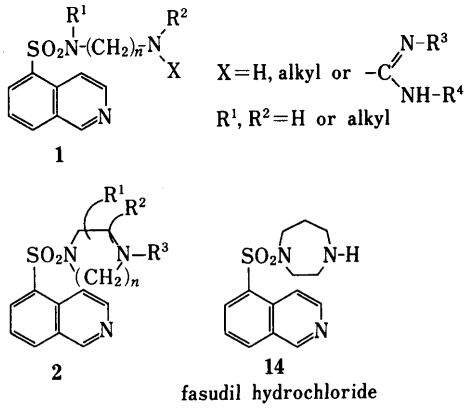


Chart 1

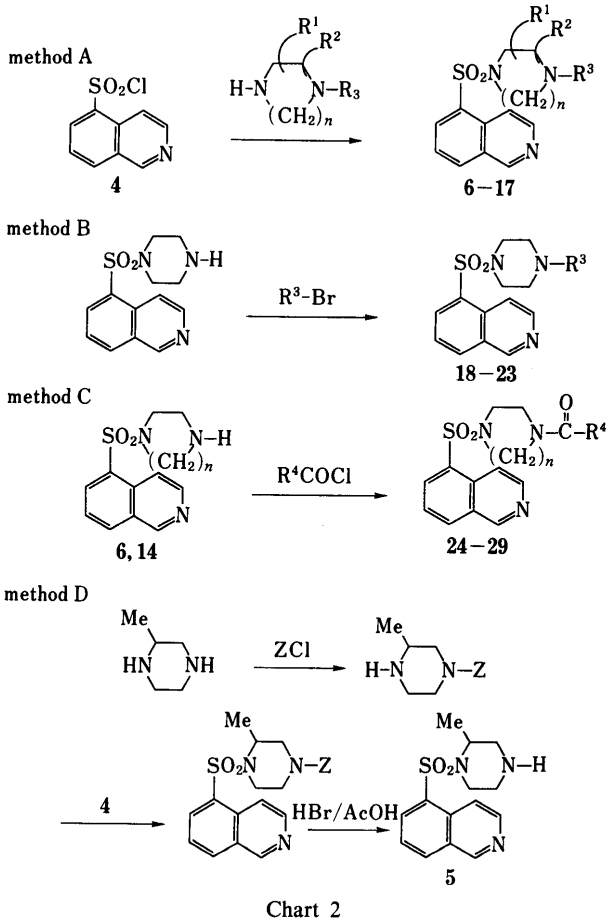


Chart 2

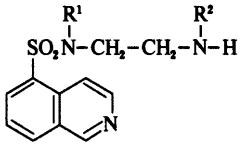
were respectively assumed to be 2-methyl and 3-methyl derivatives of 1-(5-isoquinolinesulfonyl)piperazine, which was later confirmed by comparison of their NMR spectra. The methine protons of analogues **5** and **8** had chemical shifts at 4.48 and 3.93 ppm respectively. In contrast, the chemical shift of the methine proton of 2-methylpiperazine was reported to be 3.4 ppm.[7] Thus, the large magnetic field shift from 3.4 to 4.48 ppm after sulfonylation shows the spatial closeness of the methine and the sulfonyl groups in compound **5** compared with **8**, thereby suggesting the structure to be 1-(5-isoquinolinesulfonyl)-2-methylpiperazine.

Other compounds were synthesized by alkylation or acylation of *N*-(5-isoquinolinesulfonyl)piperazine (**6**) and *N*-(5-isoquinolinesulfonyl)-1,4-perhydrodiazepin **14** as shown in Chart 2 methods B, C. Physical properties of the derivatives are listed in Table II.

Biological Activity Vasodilatory activity was determined in anesthetized dogs[2] by evaluating the incremental increase in femoral and/or vertebral artery blood flow following local injection into an artery. Subsequent incremental changes in blood flow were significantly different among individual dogs, thus vasodilatory activity was evaluated as an equipotent dose ratio, *i.e.*, comparison of the response to one using a control compound, calculated using a dose–response curve. Trapidil (100 μg), 5-methyl-7-diethylamino-*s*-triazolo[1,5-*a*]pyrimidine,[8,9] which is a well-known coronary vasodilator in humans, was used as the relative control, similarly to previous reports.[5,6] Results are listed in Tables I and II.

Table I shows the vasodilatory activity data of cyclic derivative **6** and the corresponding ring-opened compounds **30**—**32**.[4,5] The activity of these ring opened compounds was considerably lower than **6**, hence, cyclization of the diamine structure clearly enhanced the vasodilatory action. However, the ring size of the diamine part was found to

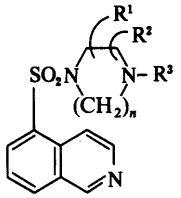
TABLE I. Vasodilatory Activities of *N*-Aminoethyl-5-isoquinolinesulfonamide Derivatives



No.	R^1	R^2	ΔFBF[a]	ΔVBF[a]
30[b]	C_2H_5	H	1.6 ±0.1	1.3 ±0.2
31[b]	CH_3	CH_3	1.5 ±0.09	1.3 ±0.1
32[b]	H	C_2H_5	1.1 ±0.05	0.78±0.4
6	$-CH_2CH_2-$		0.20±0.01	0.11±0.01
14	$-(CH_2)_3-$		0.28±0.02	0.10±0.01

a) Increasing effect on femoral or vertebral blood flow. ΔFBF and ΔVBF represent femoral and vertebral arteries, respectively. These values are expressed as equieffective dose ratios compared to trapidil. *b*) Regarding the syntheses of these compounds, see reference 4.

TABLE II. Physical Properties and Vasodilatory Activity of 5-Isoquinolinesulfonamide Compounds Derived from Cyclic Diamines



No.	R^1	R^2	R^3	*n*	Method	Yield (%)	Solvent[a]	mp (°C)	Formula	ΔFBF[b]	ΔVBF[b]
6	H	H	H	2	A	65	H_2O	251—253	$C_{13}H_{15}N_3O_2S\cdot1HCl$	0.20±0.01	0.11±0.01
7	H	H	CH_3	2	A	71	MA/H_2O	250—251	$C_{14}H_{17}N_3O_2S\cdot1HCl$	0.53±0.03	0.67±0.04
15	H	H	$C_6H_5CH_2CH=CH$	2	A	90	IPA	210—214	$C_{22}H_{23}N_3O_2S\cdot2HCl$	—	3.7±0.5
16	H	H	C_6H_5	2	A	41	IPA	222 (dec.)	$C_{19}H_{19}N_3O_2S\cdot2HCl$	1.3±0.1	4.7±0.4
17	H	H	2-$MeOC_6H_4$	2	A	67	IPA	213—216	$C_{20}H_{21}N_3O_3S\cdot1HCl$	ND	ND
18	H	H	C_2H_5	2	B	60	EA	228—229	$C_{15}H_{19}N_3O_2S\cdot2HCl$	0.85±0.09	0.43±0.02
19	H	H	*n*-C_3H_7	2	B	36	EA	221—222	$C_{16}H_{21}N_3O_2S\cdot2HCl$	0.89±0.03	0.74±0.07
20	H	H	iso-C_4H_9	2	B	15	EA	201—205	$C_{17}H_{23}N_3O_2S\cdot2HCl$	1.2±0.1	1.5±0.1
21	H	H	*n*-C_6H_{13}	2	B	42	EA/EE	189—191	$C_{19}H_{27}N_3O_2S\cdot2HCl$	2.4±0.2	—
22	H	H	$C_6H_5CH_2$	2	B	44	EA	216—218	$C_{20}H_{21}N_3O_2S\cdot2HCl$	>10	4.1±0.3
23	H	H	$C_6H_5CH_2CH_2$	2	B	19	IPA	206—210	$C_{21}H_{23}N_3O_2S\cdot2HCl$	1.3±0.2	>10
24	H	H	C_6H_5CO	2	C	80	IPA	194—195	$C_{20}H_{19}N_3O_3S\cdot1HCl$	>10	4.6±0.3
25	H	H	2-Fu–CO[c]	2	C	70	EA/EE	208—211	$C_{17}H_{16}N_3O_4S\cdot1HCl$	—	>10
26	H	H	$C_6H_5CH=CHCH_2CO$	2	C	80	IPA	194—195	$C_{22}H_{21}N_3O_3S\cdot1HCl$	—	>10
27	H	H	C_2H_5OCO	2	C	70	EA/EE	208—211	$C_{16}H_{19}N_3O_4S\cdot1HCl$	>10	3.8±0.1
14	H	H	H	3	A	65	H_2O	220.5	$C_{14}H_{17}N_3O_2S\cdot1HCl$	0.28±0.02	0.10±0.01
28	H	H	C_6H_5CO	3	C	74	EA	184—191	$C_{21}H_{21}N_3O_3S\cdot1HCl$	—	1.9±0.1
29	H	H	C_2H_5OCO	3	C	78	A	189—191	$C_{17}H_{21}N_3O_4S\cdot1HCl$	—	4.6±0.3
5	2-CH_3	H	H	2	D	15	EA/A	214—218	$C_{14}H_{17}N_3O_2S\cdot1HCl$	0.58±0.08	0.20±0.01
8	3-CH_3	H	H	2	A	54	EA/AA	249	$C_{14}H_{17}N_3O_2S\cdot1HCl$	0.48±0.06	0.19±0.02
9	3-C_6H_5	H	H	2	A	34	EA	257	$C_{19}H_{19}N_3O_2S\cdot1HCl$	1.2±0.1	0.60±0.07
10	2-CH_3	3-CH_3	H	2	A	35	EA	271—272	$C_{15}H_{19}N_3O_2S\cdot1HCl$	0.84±0.1	0.36±0.02
11	2-CH_3	5-CH_3	H	2	A	48	EA/EE	254—255	$C_{15}H_{19}N_3O_2S\cdot1HCl$	0.13±0.02	0.040±0.002
12	3-CH_3	3-CH_3	H	2	A	33	MA/IPA	257—258	$C_{15}H_{19}N_3O_2S\cdot1HCl$	1.1±0.05	0.41±0.03
13	3-CH_3	5-CH_3	H	2	A	65	EA/EE	245—246	$C_{15}H_{19}N_3O_2S\cdot1HCl$	0.55±0.1	0.23±0.02
			Diltiazem							0.21±0.009	0.15±0.008

a) EA, ethanol; IPA, isopropanol; EE, diethyl ether; MA, methanol; A, Acetone. *b*) See footnote of Table I. *c*) Fu, furfuryl.

have little influence on the activity.

Table II indicates that the acylated derivatives **24**—**29** had significantly less potent activity than the corresponding amine derivatives **6** and **14**. This decrease in activity by acylation on the terminal nitrogen was more than one order, being much greater than that by N- and C-alkylation. These results suggest that basicity of the terminal amine is essential for vasodilatory action.

Tertiary amine derivatives **7** and **15**—**31** also showed less potent activity than the corresponding secondary amine compounds **6** and **14**. The vasodilatory activity of the tertiary amine was dependent on the chain length of the tertiarization alkyl group. Thus the activity decrease by tertiarization with a methyl, ethyl, or propyl group (respectively **7**, **18**, and **19**) was less than one order, although tertiarization by an alkyl group longer than the propyl group decreased the vasodilatory activity by more than one order. On the other hand, benzylated and phenylated derivatives **22** and **16** were assumed to have very different amine basicities, yet showed no significant activity difference. Additionally, **17** had a sterically very bulky *ortho*-methoxyphenyl group on the terminal nitrogen and showed no detectable vasodilation. It is therefore suggested that the decrease in activity by tertiarization is due to a steric hindrance of the alkyl group to the terminal amine.

C-Alkylated diamine derivatives **5** and **8**—**13** were expected to have higher lipophilicity and activity than the non-alkylated amine **6** (Table II), however with the exception of **11**, all showed less potent activity. Among C-alkylated products, 3-phenyl and 3,3-dimethyl piperazine derivatives **9** and **13**, which have a sterically hindered terminal amine, showed the least activities. This result supports the above-mentioned dependency of the vasodilatory activity on steric environment surrounding the terminal amine. It should be noted that the 2,5-dimethyl piperazine derivative **11** demonstrated especially high vasodilatory activity, being much higher than **6**, even though it had a C-alkylated piperazine structure. The reason for this potent action is presently unknown.

It was hypothesized using the structure activity relationship data[5] of acyclic amine derivatives (Chart 1, **1**), that both cyclic and lipophilic structure would produce high vasodilatory activity. However, this was in contrast to the above results which show that cyclization afforded potent derivatives, whereas high lipophilicity caused by both N- and C-alkylation reduced vasodilatory activity except in **11**. The most active derivatives we obtained were **6**, **11**, and **14**, and it is surprising that their activities were equal to or greater than that of diltiazem,[10-12] a well-known calcium antagonist which is also clinically used as a cardiovascular agent. Although not being listed in Table I, the ratios of the vasodilatory effect on the femoral artery to that on the vertebral artery (ΔFBF/ΔVBF) in **6**, **11**, and **14**, indicating selectivity of the vasodilatory action, were 1.8, 3.3, and 2.8 respectively, and were larger than those of either diltiazem or trapidil, 1.4 and 1.0 respectively. These parameters show that derivatives **11** and **14** especially possessed a high selectivity to the vertebral artery.

Recently, it was reported that fasudil hydrochloride **14** may be an intracellular calcium antagonist, and also produce an antispasm effect on dogs subjected to delayed cerebral vasospasm induced by experimental subarachnoid hemorrhage (SAH).[13] This compound is now under phase III clinical trial in Japan for treatment of SAH.

Experimental

General Procedures Melting points were determined in open capillary tubes on a "Buchi" apparatus and have not been corrected. All compounds prepared gave satisfactory infrared (IR) and NMR spectra data on Hitachi 26-010 IR and JEOL JNM-PMX-60 or JNM-GX-400 ^{1}H-nuclear magnetic resonance spectrophotometers. All compounds were obtained as colorless crystals by recrystallization. Elemental analyses were performed by the Analytical Department, Nobeoka Plant, Asahi Chemical Industry Co., Ltd., and were within 0.4% of the calculated values.

Method A. *d,l*-1-(5-Isoquinolinesulfonyl)-3-methylpiperazine (8) To a mixture of **4**[4,5] (13.20 g, 50 mmol) and water (100 ml) was added slowly $NaHCO_3$ (4.20 g, 50 mmol) with ice cooling and stirring. The resulting solution was extracted twice with CH_2Cl_2 (100 ml × 2). The organic layer was dried with $MgSO_4$ and added dropwise to an ice-cold solution of *d,l*-2-methylpiperazine (20.03 g, 200 mmol) and CH_2Cl_2 (100 ml). The solution was stirred for 1 h at room temperature, washed twice with water, and extracted with 6 N HCl (50 ml). Neutralization of the HCl layer with $NaHCO_3$ precipitated a crude crystalline compound. Recrystallization with MeOH–H_2O afforded **6** (11.63 g, 71%), mp 249 °C. NMR (D_2O) (ppm): 1.35 (t, 3, CH3), 2.93 (dd, 1, C2Ha), 3.16 (dt, 1, C5Ha), 3.24 (m, 1, C6Ha), 3.49 (m, 1, C5Heq), 3.53 (m, 1, C3Ha), 3.90 (m, 1, C5Heq), 3.93 (m, 1, C2Heq), 7.85 (t, 1, isoquinoline-C7H), 8.30 (d, 1, isoquinoline-C4H), 8.35 (d, 1, isoquinoline-C8H), 8.40 (d, 1, isoquinoline-C6H), 8.60 (d, 1, isoquinoline-C3H), and 9.25 (s, 1, isoquinoline-C1H).

Method B. 1-(5-Isoquinolinesulfonyl)-4-butylpiperazine Hydrochloride (20) A mixture of 1-(5-isoquinolinesulfonyl)piperazine hydrochloride (**5**) (5.00 g, 15.93 mmol), 2-methylpropyl bromide (2.18 g, 15.93 mmol), K_2CO_3 (5.00 g, 36.2 mmol), and EtOH (80 ml) was refluxed for 6 h. The resulting mixture was filtered, evaporated, extracted with $CHCl_3$, and washed twice with water. The organic layer was extracted with 6 N HCl and the aqueous layer was evaporated under reduced pressure to yield crude **20**. The precipitate was recrystallized from EtOH to afford colorless needles (0.971 g, 15%), mp 201—205 °C.

Method C. 1-Benzoyl-4-(5-isoquinolinesulfonyl)piperazine Hydrochloride (24) An aqueous solution of **4** (10.00 g, 31.9 mmol) was alkalized by 1 N NaOH and extracted with CH_2Cl_2 (100 ml). The organic layer was dried with $MgSO_4$. To the solution, Et_3N (4.83 g, 47.8 mmol) and then CH_2Cl_2 solution (50 ml) of benzoyl chloride (4.93 g, 35.05 mmol) were added dropwise with ice cooling. The resulting solution was stirred at room temperature for 2 h, washed with 0.01 N HCl until the aqueous layer became acidic, washed with water, and dried fully under reduced pressure. The residue was dissolved in water using a small amount of diluted HCl, evaporated to remove water, and recrystallized from 1-methylethanol to yield **24** (8.92 g, 67%), mp 219 °C.

Method D. *d,l*-1-(5-Isoquinolinesulfonyl)-2-methylpiperazine Hydrochloride (7) To an ice-cold mixture of 2-methylpiperazine (24.00 g, 240 mmol), Et_3N (24.24 g, 0.24 mmol), and $CHCl_3$ (400 ml) was added benzyloxycarbonyl chloride (34.10 g, 200 mmol). The solution was stirred at room temperature for 4 h and washed with water. After extraction with HCl, the extract was alkalized by NaOH and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ solution afforded crude 1-benzyloxycarbonyl-3-methylpiperazine (32.93 g, 70.5%). To an ice-cold mixture of **4**[4,5] (26.41 g, 100 mmol), water (200 ml) and CH_2Cl_2 (200 ml) was added slowly $NaHCO_3$ (8.4 g, 100 mmol) with stirring. The organic layer was dried over $MgSO_4$ and added dropwise to an ice-cold CH_2Cl_2 solution (100 ml) of the crude 1-benzyloxycarbonyl-3-methylpiperazine (23.4 g, 100 mmol) and Et_3N (27.8 ml, 200 mmol). After being stirred overnight at room temperature, the solution was washed with water and then HCl until the pH of the aqueous layer was less than 3.0. The organic layer was dried and evaporated under reduced pressure. Separation of the residue with silica gel column chromatography afforded an oily 1-benzyloxycarbonyl-4-(5-isoquinolinesulfonyl)-3-methylpiperazine (22.1 g, 52.1%). To the liquid was added a 25% acetic acid solution (67.1 ml) of HBr, and the solution was stirred overnight. The precipitate was filtered, washed with ether, and dissolved in $CHCl_3$ with an aqueous solution of NaOH and $CHCl_3$. After evaporation of the organic layer, the residue was purified by silica gel column chromatography. The evaporated fraction was dissolved with water (20 ml), and the pH of the solution was adjusted to 5.0 with HCl. The solution was evaporated under reduced pressure, and recrystallization of the residue from EtOH–acetone yielded **7** (12.0 g, 15% from 2-methylpiperazine). NMR (D_2O) (ppm): 1.30 (t, 3, CH3), 3.00

(dt, 1, C5Ha), 3.23 (dd, 1, C3Ha), 3.38 (d, 1, C3Heq), 3.46 (d, 1, C5Heq), 3.60 (dt, 1, C6Ha), 3.91 (br d, 1, C6Heq), 4.48 (m, 1, C2Heq), 7.75 (t, 1, isoquinoline-C7H), 8.10 (d, 1, isoquinoline-C4H), 8.25 (d, 1, isoquinoline-C8H), 8.40 (d, 1, isoquinoline-C6H), 8.60 (d, 1, isoquinoline-C3H), 9.25 (s, 1, isoquinoline-C1H).

Biological Determination The femoral and vertebral blood flow in dogs was measured according to the previously reported procedure.[4,5]

Acknowledgment The authors thank M. Yanagita for his assistance in the biological testing.

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