isothiourea 0.5-sulfate (5 g, 35.92 mmol), and water (50 mL) was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol and water to yield **17** (4.82 g, 70%): IR (KBr) ν_{max} (cm^{-1}) 1620, 1660 (guanidine).

4-Amidino-1-(5-isoquinolylsulfonyl)-1,4-perhydrodiazepine Hydrochloride (33). To an ice-cold aqueous solution (30 mL) of 5-isoquinolinesulfonyl chloride (1.5 g, 5.68 mmol) was added slowly $NaHCO_3$ (0.48 g, 5.7 mmol) with stirring. The solution was extracted twice with CH_2Cl_2 (40 mL). The CH_2Cl_2 solution was dried with $MgSO_4$ and evaporated off. THF (40 mL) was added to the residue and this solution was added to an aqueous solution (15 mL) of **17** (2.5 g, 13 mmol) at 0 °C. The solution was stirred at 0 °C for 2 h and then acidified with HCl, and the solvent was removed under reduced pressure. The residue was dissolved in water (10 mL) and filtered. The pH of the filtrate was adjusted to 12.5 with 10 N NaOH. The precipitate was filtered and dissolved in water with a small amount of dilute HCl. The solution, following adjustment of its pH to 5.0 with NaOH, was evaporated off, and the residue was recrystallized from acetone/MeOH to give **33** (851 mg, 41%): IR (KBr) ν_{max} (cm^{-1}) 1630, 1670 (guanidine), 1330 (S=O); NMR (D_2O) δ 1.7–2.1 (2 H, m, $CH_2CH_2CH_2$), 3.4–3.8 (8 H, m, CH_2N), 7.86 (1 H, dd, isoquinoline H-7), 8.27–8.80 (4 H, m, isoquinoline H-1); mp 247–249 °C.

Biological Determination.[3] Mongrel dogs unselected as to sex (15–26 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv). The trachea was intubated, and ventilation rates (12–16 cycles/min) and tidal volumes were adjusted so as to maintain the arterial blood pH, pCO_2, and pO_2, within physiological limits. The body temperature was maintained at 37–38 °C with a heating pad. Catheters were placed in the right femoral artery and vein, and the heart rate and mean blood pressure were monitored. An electromagnetic flow probe of the extracorporeal type (Nihon Kohden, Model MFV-1200) was inserted into the left femoral artery to evaluate the increase in femoral blood flow.

The test compounds in a volume of 10 μL were injected with microinjector into a rubber tube connected to the arterial cannula over a period of 5 s. Despite the injections of drugs, neither blood pressure nor heart rate changed. At least three different amounts of each test compound were injected and the resulting changes in blood flow were assessed. After and before the administrations of three doses of each compound, 100 μg of trapidil was administered as a relative control. At least three dose–response curves per compound were obtained.

The increment in femoral blood flow by trapidil had a very big difference among individual dogs (183 ± 85% (SD), n = 12). Accordingly the vasodilatory activity was evaluated as an equipotent dose compared to trapidil, which was calculated from the dose–response curves.

Acknowledgment. We thank Masami Yanagita for his assistance in the biological testing, members of the Department of Medicinal Chemistry for their assistance in synthesis work, and Barrett B. Madrigal for his critical reading of the manuscript.

Registry No. 1, 91742-10-8; 1·HCl, 92564-34-6; 4, 27655-40-9; 5, 105627-79-0; 6, 116700-33-5; 7, 116700-34-6; 8, 116700-35-7; 9, 116700-36-8; 10, 116700-37-9; 11, 116700-38-0; 12, 116700-39-1; 13, 116700-40-4; 14, 113276-94-1; 15, 22365-47-5; 16, 92564-61-9; 17, 92586-45-3; 18, 116700-32-4; 18·HCl, 116724-50-6; 19, 116700-49-3; 19·HCl, 116700-41-5; 20, 92564-06-2; 20·HCl, 116700-42-6; 21, 92564-04-0; 21·HCl, 116700-43-7; 22, 116700-50-6; 22·HCl, 116700-44-8; 23, 92564-35-7; 23·2HCl, 116700-45-9; 24, 116700-51-7; 24·2HCl, 116700-46-0; 25, 116700-52-8; 25·2HCl, 116724-51-7; 26, 116700-53-9; 26·2HCl, 116700-47-1; 27, 116700-54-0; 27·2HCl, 116700-48-2; 28, 92564-37-9; 28·2HCl, 92564-09-5; 29, 92564-38-0; 29·2HCl, 92564-10-8; 30, 92564-40-4; 30·2HCl, 92625-77-9; 31, 92564-57-3; 31·HCl, 98646-59-4; 32, 92564-64-2; 32·HCl, 98646-62-9; 33, 92564-62-0; 33·HCl, 98672-47-0; $H_2N(CH_2)_3NH_2$, 109-76-2; $H_2N(CH_2)_4NH_2$, 110-60-1; $H_2N(CH_2)_6NH_2$, 124-09-4; $H_3CSC{=}NCN(NH_2)$, 15760-26-6; $H_3CSC{=}NNO_2(NH_2)$, 2986-25-6; $H_3CSC{=}NCH_3(NH_2)$, 44387-05-5; $H_3CSC{=}NCH_3(NHCH_3)$, 2986-23-4; $H_3CSC{=}NC_6H_5(NHC_6H_5)$, 5416-30-8; $H_3CSC{=}N(CH_2)_2NH$, 20112-79-2; $HN(CH_3)(CH_2)_2OH$, 109-83-1; $H_2N(CH_2)_2OH$, 141-43-5; $H_3CSC{=}NH(NH_2)\cdot{}^1/_2H_2SO_4$, 867-44-7; 2-chloropyrimidine, 1722-12-9; piperazine, 110-85-0; 2,5-dimethylpiperazine, 106-55-8; hexahydro-1*H*-1,4-diazepine, 505-66-8.

5-Isoquinolinesulfonamide Derivatives. 2. Synthesis and Vasodilatory Activity of *N*-(2-Aminoethyl)-5-isoquinolinesulfonamide Derivatives

Anri Morikawa,*,† Takanori Sone,† and Toshio Asano‡

Department of Medicinal Chemistry, Bioscience Laboratory, and Pharmaceutical Research and Development Laboratory, Asahi Chemical Industry Co., Ltd., Asahi-machi, Nobeoka-shi, Miyazaki 882, Japan. *Received April 7, 1988*

A new series of aromatic sulfonamides, the *N*-(2-aminoethyl)-5-isoquinolinesulfonamide derivatives, **3**, was synthesized from 5-isoquinolinesulfonic acid and shown to possess vasodilatory action. Vasodilatory activity was evaluated in vivo in terms of increases in arterial blood flow in dogs after local injection in the femoral and/or vertebral arteries. When the alkylene group between the two nonaromatic nitrogen atoms was ethylene, the most potent activity was obtained. Alkylations of either of the two nonaromatic nitrogens yielded more active compounds, although bulky or excessively long alkyl groups reduced the potency. Among these derivatives, **27** and **47** were equipotent to diltiazem, which is used clinically as a cardiovascular drug. These two compounds also had antihypertensive and vasodilatory activities when administered intravenously, although the activities were less than that of diltiazem when given by this route.

In the course of our studies with **1**, we found that **2**, a synthetic intermediate that possesses an amino group instead of a guanidino group, also has weak vasodilatory activity. In order to improve the vasodilatory activity of **1** and to find a new series of vasodilators, it was decided to prepare analogues of **2**. These compounds are represented by the general formula **3**.

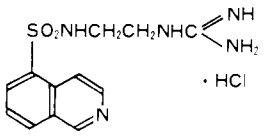
In this report, we describe the syntheses and pharmacological evaluation of **2** and its derivatives **3**.

Chemistry

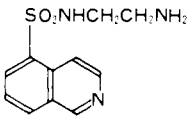
The amines **14–17** and **39–42** were prepared from the corresponding diamines by treatment with a CH_2Cl_2 solution of the sulfonyl chloride **5** (Scheme I, method A). The secondary amines **18–21** were prepared by treatment of **2** with alkyl halide in the presence of K_2CO_3 in EtOH

* Address correspondence to this author at Health Care Business Administration, Asahi Chemical Industry Co. Ltd., 1-1-1, Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.
† Bioscience Laboratory.
‡ Pharmaceutical Research and Development Laboratory.

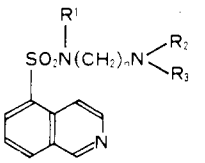
0022-2623/89/1832-0046$01.50/0



1
(HA 1004)



2



3

(Scheme I, method B). The amines **22–38** were synthesized from the corresponding alcohols (**6–13**), obtained by sulfonylation of the 2-aminoethanols with **5**. The alcohols **6–13** were tosylated with *p*-toluenesulfonyl chloride in pyridine to give the corresponding tosylates, and treatment of the tosylates with primary or secondary amines afforded **22–38** (Scheme I, method C). In method C, however, ammonia afforded only a low yield in comparison with the primary and secondary amines because of its poor reactivity with tosylates. Therefore, we adapted the Mitsunobu reaction[1] for the synthesis of primary amines **43–49**. The alcohols **6–13** were treated with triphenylphosphine, diethylazodiformate, and phthalimide in THF at room temperature to yield the corresponding phthalimide derivatives with triphenylphosphine oxide and *N*,*N*′-bis(ethoxycarbonyl)hydrazine. Elimination of the phthalimide group by hydrazine afforded the corresponding primary amines **43–49** in good yields (Scheme I, method D).

Biology

We used the in vivo increasing effect on vertebral and/or femoral artery blood flow in anesthetized dogs following local injection into an artery, as an initial means of screening the compounds. The vasodilatory activity was assessed by recording the dose that increased the blood flow as much as the standard compound, trapidil (5-methyl-7-(diethylamino)[1,2,4]triazolo[1,5-*a*]pyrimidine).[2,3] These data are expressed in Table II.

The vasodilatory effect of **2** was much less than that of the standard compound, trapidil (Table II). Both reduction and elongation of the alkylene chain between the sulfonamidic and terminal amino nitrogens yielded less active compounds, i.e. **14–17**. Consequently, the vasodilatory activities of the ethylenediamine derivatives were examined.

In order to evaluate the relationship between activity and monoalkylation of the terminal amino group, compounds **18–34** were prepared. The activities of **2** and **22–29** suggested that the longer the substituent, the more potent the activity of the derivative. Of the most active compounds, **34** showed increasing effects on the femoral and vertebral blood flows that were approximately 3 times as potent as that of trapidil. Also compound **27** had an increasing effect on femoral blood flow to the same degree as that of diltiazem.

Substitution on the terminal nitrogen with bulky alkyl groups gave less potent compounds, **20**, **30**, and **38**, than with nonbulky alkyl groups. The vasodilatory activities

Table I. *N*-(Hydroxyethyl)-5-isoquinolinesulfonamide Derivatives

no.	R^1	yield, %	mp, °C	recrysn solv[a]	formula
6	H	78	144–145	E	$C_{11}H_{12}O_3N_2S$
7	CH_3	87	121–122	E	$C_{12}H_{14}O_3N_2S$
8	C_2H_5	84	88–89	E	$C_{13}H_{16}O_3N_2S$
9	*i*-C_3H_7	90	76–79	E	$C_{14}H_{18}O_3N_2S$
10	*n*-C_4H_9	79	62–64	A	$C_{15}H_{20}O_3N_2S$
11	*n*-C_6H_{13}	85	95–97	A	$C_{17}H_{24}O_3N_2S$
12	*n*-C_8H_{17}	54	oil		$C_{19}H_{28}O_3N_2S$
13	$C_6H_5CH_2$	63	108–110	A/M	$C_{18}H_{18}O_3N_2S$

[a] E, ethanol; A, acetone; M, methanol.

of **18–21** and **31–34**, which are substituted benzylamine derivatives, suggested that the introduction of electron-donating groups to the aromatic ring produces compounds of greater potency. However, structure **33**, which has the strongest electron donor in the molecule, had only little activity.

Dialkylation of the terminal amino group did not afford potent compounds **35–39**.

Analogues **40–49**, in which the sulfonamidic nitrogen is substituted, generally produced strong increases in arterial blood flow. Similar to the case of alkylation on the terminal amino nitrogen, it is thought that the longer the alkyl group bonded to the sulfonamidic nitrogen, the more potent its vasodilatory effect. However, in the case of substitution on the sulfonamidic nitrogen, excessive elongation of the alkyl group diminished the vasodilatory effects, as shown by **48**. The low activities of **45** and **49** may have been caused by the substitution of bulky alkyl groups on the sulfonamidic nitrogens. This decrease in activity by bulky groups is analogous to the case of substitution on the terminal amino group. The most active compound, **47**, possessed a vasodilatory effect on the vertebral artery that was as potent as that of diltiazem.[4–6]

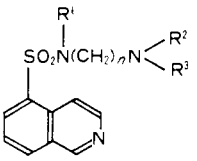
These results suggest that both the lipophilicity and the steric environment of the sulfonamidic side chain in the 5-isoquinolinesulfonamide derivatives influence the vasodilatory activity.

The above consideration of the vasodilatory activities of 5-isoquinolinesulfonamide compounds is based on the biological effect of the local injection into the artery. Intraarterial injection had no influence on cardiovascular parameters such as blood pressure and heart rate. We evaluated the effects of the most active compounds of this series, **47** and **27**, on heart rate, blood pressure, vertebral artery blood flow, and coronary blood flow when administered intravenously. As shown in Table III, **47** and **27** also had an antihypertensive activity when intravenously administered, but their activities were less potent than that of diltiazem. Although diltiazem reduced heart rate, the former two compounds accelerated it. This fact suggests that there is a difference between the effects of diltiazem and 5-isoquinolinesulfonamide derivatives on the heart.

It has already been reported that **1** has an inhibitory effect on protein kinase C and that it may be an intra-

(1) Mitsunobu, O. *Synthesis* **1981**, 1.
(2) Libuda, H. *Z. Arztl. Fortbild.* **1972**, *66*(23), 1208.
(3) Fuller, H. *Pharmazie* **1971**, *26*(9), 554.
(4) Nagao, T.; Ikeo, T.; Sato, M. *Jpn. J. Pharmacol.* **1977**, *27*, 330.
(5) Sato, M.; Nagao, T.; Yamaguchi, I.; Nakajima, H.; Kitomoto, A. *Arzneim.-Forsch.* **1971**, *21*, 1338.
(6) Henry, P. D. *Am. H. Cardiol.* **1980**, *46*, 1047.

Table II. *N*-(2-Aminoethyl)-5-isoquinolinesulfonamides



no.	*n*	R^1	R^2	R^3	formula (C, H, O, N, S)	method (×)	yield, %	recrystn solv[a]	mp, °C	FBF[b]	VBF[b]
2	2	H	H	H	$C_{11}H_{13}O_2N_3S$·HCl	A	71	H_2O	253–254	2.0 ± 0.3	1.8 ± 0.3
14	0	H	H	H	$C_9H_9O_2N_3S$·2HCl	A	45	H_2O	240–241	ND	>100
15	3	H	lH	H	$C_{12}H_{15}O_2N_3S$·HCl	A	76	H_2O	246–248	3.6 ± 0.1	5.1 ± 0.3
16	4	H	H	H	$C_{13}H_{17}O_2N_3S$·HCl	A	58	H_2O	220–222	2.7 ± 0.2	4.2 ± 0.08
17	6	H	H	H	$C_{15}H_{21}O_2N_3S$·HCl	A	23	H_2O	205–207	2.4 ± 0.1	1.4 ± 0.4
22	2	H	CH_3	H	$C_{12}H_{15}O_2N_3S$·HCl	C	46	A/MA	221–222	1.7 ± 0.2	3.7 ± 0.2
23	2	H	C_2H_5	H	$C_{13}H_{17}O_2N_3S$·HCl	C	43	A	151–152	2.7 ± 0.3	4.2 ± 0.3
24	2	H	*n*-C_3H_7	H	$C_{14}H_{19}O_2N_3S$·HCl	C	56	A	155–156	1.6 ± 0.2	2.7 ± 0.3
25	2	H	*n*-C_4H_9	H	$C_{15}H_{21}O_2N_3S$·HCl	C	59	A	177–178	1.3 ± 0.1	4.6 ± 0.5
26	2	H	*n*-C_5H_9	H	$C_{16}H_{23}O_2N_3S$·HCl	C	26	A	159–161	1.0 ± 0.10	2.4 ± 0.2
27	2	H	*n*-C_6H_{13}	H	$C_{17}H_{25}O_2N_3S$·HCl	C	68	A	118–120	0.23 ± 0.02	0.17 ± 0.06
28	2	H	*n*-C_8H_{17}	H	$C_{19}H_{29}O_2N_3S$·2HCl	C	17	A	132–133		0.53 ± 0.08
29	2	H	*n*-$C_{10}H_{21}$	H	$C_{21}H_{33}O_2N_3S$·2HCl	C	66	A	138–142		0.49 ± 0.10
30	2	H	c-C_6H_{11}	H	$C_{17}H_{23}O_2N_3S$·HCl	C	65	A	199–200		1.4 ± 0.2
31	2	H	$C_6H_5CH_2$	H	$C_{18}H_{19}O_2N_3S$·2HCl	C	60	A	217–220		0.57 ± 0.1
32	2	H	4-$MeOC_6H_4CH_2$	H	$C_{19}H_{21}O_3N_3S$·2HCl	C	67	EA	146–149	0.43 ± 0.08	0.38 ± 0.07
33	2	H	3,4-$(MeO)_2C_6H_3CH_2$	H	$C_{20}H_{23}O_4N_3S$·2HCl	C	38	EA	188–191	3.7 ± 0.4	4.3 ± 0.5
34	2	H	$C_6H_5CH_2CH_2$	H	$C_{19}H_{21}O_2N_3S$·2HCl	C	41	A	138–142	0.32 ± 0.07	0.31 ± 0.04
18	2	H	4-$ClC_6H_4CH_2$	H	$C_{18}H_{18}O_2N_3SCl$·2HCl	B (Br)	20	EA/EE	246–247	1.0 ± 0.11	0.25 ± 0.02
19	2	H	3-$ClC_6H_4CH_2$	H	$C_{18}H_{18}O_2N_3SCl$·2HCl	B (Cl)	34	EA/EE	218–220	0.83 ± 0.03	0.26 ± 0.01
20	2	H	2-$ClC_6H_4CH_2$	H	$C_{18}H_{18}O_2N_3SCl$·2HCl	B (Cl)	18	EA/EE	223–227	2.6 ± 0.2	1.5 ± 0.1
21	2	H	4-$NO_2C_6H_4CH_2$	H	$C_{18}H_{18}O_4N_4S$·2HCl	B (Br)	72	H_2O	207–208	2.5 ± 0.3	1.5 ± 0.3
35	2	H	CH_3	c-C_6H_{11}	$C_{18}H_{25}O_2N_3S$·2HCl	C	58	EA/EE	145–148	0.83 ± 0.08	1.7 ± 0.3
36	2	H	*n*-C_3H_7	*n*-C_6H_{13}	$C_{20}H_{31}O_2N_3S$·HCl	C	56	A	135–137	1.9 ± 0.10	1.7 ± 0.2
37	2	H	*n*-C_3H_{13}	*n*-C_6H_{13}	$C_{23}H_{37}O_2N_3S$·HCl	C	53	A	120–125	1.2 ± 0.12	0.48 ± 0.09
38	2	H	*i*-C_3H_7	*i*-C_3H_7	$C_{17}H_{25}O_2N_3S$·HCl	C	27	H_2O	232–233		2.7 ± 0.2
39	2	H	CH_3	CH_3	$C_{13}H_{17}O_2N_3S$·HCl	A	79	EA/H_2O	227–228		1.4 ± 0.2
40	2	CH_3	CH_3	H	$C_{13}H_{17}O_2N_3S$·HCl	A	32	EA/H_2O	209–212	1.5 ± 0.09	1.3 ± 0.1
41	2	C_2H_5	C_2H_5	H	$C_{15}H_{21}O_2N_3S$·HCl	A	36	EA/H_2O	221–222	1.1 ± 0.05	0.78 ± 0.04
42	2	$C_6H_5CH_2$	$C_6H_5CH_2$	H	$C_{25}H_{25}O_2N_3S$·HCl	A	47	MA/H_2O	108–109		1.8 ± 0.2
43	2	CH_3	H	H	$C_{12}H_{15}O_2N_3S$·HCl	D	67	EA/H_2O	223–225		1.6 ± 0.3
44	2	C_2H_5	H	H	$C_{13}H_{17}O_2N_3S$·HCl	D	56	EA/H_2O	238–240		1.3 ± 0.2
45	2	*i*-C_3H_7	H	H	$C_{14}H_{19}O_2N_3S$·HCl	D	51	EA/H_2O	258		3.3 ± 0.5
46	2	*n*-C_4H_9	H	H	$C_{15}H_{21}O_2N_3S$·HCl	D	54	EA/H_2O	245–246		0.27 ± 0.01
47	2	*n*-C_6H_{13}	H	H	$C_{17}H_{25}O_2N_3S$·HCl	D	47	EA/A	189–191		0.12 ± 0.007
48	2	*n*-C_8H_{17}	H	H	$C_{19}H_{29}O_2N_3S$·HCl	D	43	EA/A	171–175		0.92 ± 0.1
49	2	$C_6H_5CH_2$	H	H	$C_{18}H_{19}O_2N_3S$·HCl	D	58	EA/H_2O	142–145		1.92 ± 0.3
diltiazem										0.21 ± 0.009	0.15 ± 0.008

[a] EA, ethanol; MA, methanol; EE, diethyl ether. [b] Increasing effect on femoral or vertebral blood flow. FBF and VBF: mean femoral and vertebral arteries, respectively. These values are expressed as equipotent dose ratios compared to trapidil.

Table III. Hemodynamic Effects Given Intravenously to Anesthetized Dogs

entry	% of changes from control[a]			
	HR[b]	MBP[c]	VBF[d]	CBF[e]
27	3.9 ± 0.9	−16.8 ± 2.6	93.7 ± 40.0	45.7 ± 21.4
47	2.8 ± 1.7	−11.4 ± 1.9	91.4 ± 28.3	53.6 ± 16.6
diltiazem	−8.0 ± 4.4	−28.9 ± 4.9	180 ± 43	91.3 ± 21.1

[a] The data used to calculate the percentage of changes were the maximum observed changes. Each results is the mean ± SE. [b] Heart rate (n = 12). [c] Mean blood pressure (n = 12). [d] Vertebral blood flow (n = 6). [e] Coronary blood flow (n = 6).

cellular calcium antagonist.[7] The new vasodilators described above have quite similar chemical structures to that of **1**, but it is unclear whether they have the same effect as **1**, and further research will therefore be necessary in order to define the mechanism of action of these compounds.

Experimental Sections

Melting points were determined in open capillary tubes on a Büchi apparatus and have not been corrected. Compounds gave satisfactory IR and NMR spectral data and were obtained respectively on a Hitachi 260-10 IR spectrophotometer and a JEOL JNM-PMX-60 NMR spectrophotometer. Elemental analyses were performed by the analytical department at the Nobeoka plant, Asahi Chemical Industry Co., Ltd., and were within ±0.4% of the calculated values.

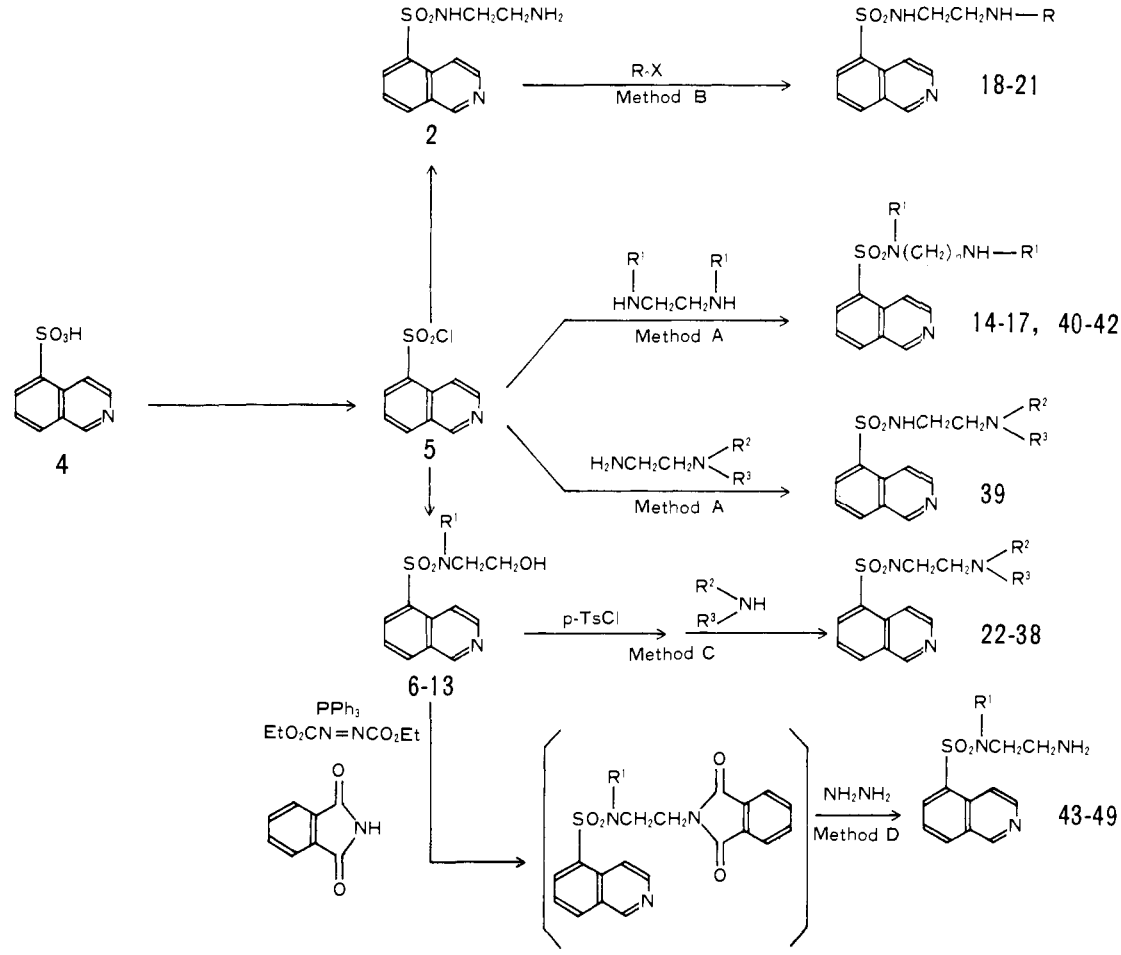
5-Isoquinolinesulfonyl Chloride Hydrochloride (5). A mixture of 5-isoquinolinesulfonic acid (100 g), $SOCl_2$ (750 g), and DMF (2 mL) was refluxed for 2 h, and the resulting solution was evaporated to remove the $SOCl_2$. The residue was suspended with $CHCl_3$ (300 mL), filtered, and washed with two portions of $CHCl_3$ (200 mL). The precipitate was collected and dried under reduced pressure to remove the solvent, yielding crude crystalline 5-isoquinolinesulfonyl chloride hydrochloride (**6**) (123.13 g, 91%). As this compound is not stable, it was used for the subsequent syntheses without further purification.

***N*-(2-Hydroxyethyl)-5-isoquinolinesulfonamide (7).** To an ice-cold aqueous solution (100 mL) of crude **6** (50 g, 189 mmol) was added slowly $NaHCO_3$ (25.89 g, 189 mmol) with stirring. The resulting solution was extracted twice with $CHCl_3$ (100 mL × 2). The $CHCl_3$ solution was dried ($MgSO_4$) and added dropwise to a $CHCl_3$ solution (100 mL) of 2-aminoethanol (34.63 g, 567 mmol) at 0 °C. The solution was stirred for 1 h at room temperature, washed with water, and evaporated off. The residue was recrystallized from ethanol to give **7** (37.2 g, 78%): mp 144–145 °C.

Method A. *N*-Ethyl-*N*-[2-(ethylamino)ethyl]-5-isoquinolinesulfonamide Hydrochloride (41). To a mixture of

(7) Hidaka, H.; Inagaki, M.; Kawamoto, S.; Sasaki, Y. *Biochemistry* **1984**, *23*, 5036.

Scheme I



crude **5** (5.28 g, 20 mmol) and water (100 mL) was added slowly $NaHCO_3$ (1.68 g, 20 mmol) with ice-cooling and stirring. The resulting solution was extracted twice with CH_2Cl_2 (50 mL × 2). The organic layer was dried ($MgSO_4$) and added dropwise to an ice-cold solution of *N,N'*-diethylethylenediamine (3.48 g, 30 mmol) and CH_2Cl_2 (60 mL). The solution was stirred for 1 h at room temperature, washed with water, and extracted with 6 N HCl. Neutralization of the aqueous layer with $NaHCO_3$ precipitated crude crystalline of **41**. Recrystallization with ethanol/water afforded **41** (2.48 g, 36%): mp 221–222 °C.

Method B. *N*-[2-[(*p*-Nitrobenzyl)amino]ethyl]-5-isoquinolinesulfonamide Dihydrochloride (21). A mixture of **2** (12.9 g, 45 mmol), *p*-nitrobenzyl bromide (3.24 g, 15 mmol), K_2CO_3 (9.9 g, 100 mmol), and THF (150 mL) was stirred overnight, and the solvent was removed. The residue was extracted with CH_2Cl_2 (100 mL) and washed with by water. The amine was extracted from the organic layer with 2 N HCl (80 mL). The aqueous layer was condensed to 40 mL under reduced pressure to give a precipitate. This precipitate was recrystallized from water to yield **21** (4.95 g, 72%): mp 207–208 °C.

Method C. *N*-[2-(Hexylamino)ethyl]-5-isoquinolinesulfonamide Hydrochloride (27). A mixture of the alcohol **6** (5.05 g, 20 mmol), *p*-toluenesulfonyl chloride (4.19 g, 22 mmol), and dry pyridine (20 mL) was heated at 50 °C for 1 h. After cooling, the precipitate was filtered off, and the filtrate was evaporated off under reduced pressure. To the residue was added a THF (40 mL) solution of *n*-hexylamine (8.10 g, 80 mmol), and the mixture was heated in an autoclave at 80 °C for 6 h and evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (40 mL) and washed with water. The amine was extracted from the organic layer with 1 N HCl and extracted again with CH_2Cl_2 (20 mL × 2) from the basic aqueous layer. The organic layer was dried (Na_2SO_4) and chromatographed on a silica gel column, eluted with $CHCl_3$ and 1% v/v MeOH/$CHCl_3$. The 1% v/v MeOH/$CHCl_3$ fraction was evaporated under reduced pressure and treated in the same way as for method A. The hydrochloride of **27** was obtained by recrystallization from acetone (5.06 g, 68%): mp 159–161 °C.

Method D. *N*-(2-Aminoethyl)-*N*-hexyl-5-isoquinolinesulfonamide Hydrochloride (47). To the mixture of **11** (3.36 g, 11 mmol), phthalimide (2.62 g, 11 mmol), and dry THF (20 mL) was added dropwise a THF solution (5 mL) of diethyl azodiformate (1.915 g, 11 mmol) at room temperature. The solution was stirred overnight and evaporated under reduced pressure, and diethyl ether (30 mL) was added. The precipitate (*N,N'*-bis(ethoxycarbonyl)hydrazine) was filtered off and washed with a small amount of ether (20 mL × 2). The filtrate was evaporated off and dissolved in EtOH (20 mL). To the ethanol solution was added hydrazine hydrate (1.50 g, 30 mmol), and the solution was refluxed for 2 h. After cooling, the precipitate (phthalhydrazide) was filtered off and washed with two portions of $CHCl_3$ (20 mL × 2). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column, which was eluted with $CHCl_3$ and 5% v/v MeOH/$CHCl_3$. The 5% v/v MeOH/$CHCl_3$ fraction was evaporated and dissolved in water (5 mL) with a small amount of dilute HCl. The pH of the aqueous solution was 6.0. The resulting solution was evaporated and the residue was recrystallized from EtOH/acetone to yield **47** (1.75 g, 47.1%): mp 189–191 °C.

Biological Determination.[8,9] Intraarterial Injection. Mongrel dogs unselected as to sex (15–26 kg) were anesthetized with pentobarbital sodium (35 mg/kg iv). The trachea was intubated, and ventilation rates (12–16 cycles/min) and tidal volumes (22–27 mL/kg) were adjusted so as to maintain the arterial blood pH, pCO_2, and pO_2, within physiological limits. Catheters were placed in the right femoral artery to measure the pulsatile arterial blood flow. Heart rate was monitored with a

(8) Asano, T.; Hidaka, H. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 454.
(9) Asano, T.; Ikegami, I.; Satoh, S.; Shibuya, M.; Takayasu, M. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 1033.

cardiotachometer (Sanei, 2336A) triggered by a lead II electrocardiogram. Mean blood pressure was measured with a pressure transducer (Sanei, 45266). The body temperature was maintained at 37-38 °C with a heating pad.

When the vertebral arterial blood flow was measured, arterial blood taken from the left femoral artery was led to the right vertebral artery. An electromagnetic flow probe (Nihon Kohden, Model MFV-1200) of the extracorporeal type was inserted into this circuit.

In the case of femoral blood flow, an electromagnetic flow probe of extracorporeal type (Nihon Kohden, Model MFV-1200) was inserted into the left femoral artery.

Compounds in a volume of 10 μL were injected with a microinjector into a rubber tube connected to the arterial cannula over a period of 5 s. Despite drug injections, neither blood pressure nor heart rate changed. At least three different amounts of each test compound were injected and the changes in blood flow were assessed. After and before the administration of three doses of each compound, 100 μg of trapidil was administered as a relative control. At least three dose–response curves per compound were obtained. From these dose–response curves, the dose that gave the same increasing effect on the femoral arterial blood flow as 100 μg of trapidil was calculated.

The increments in femoral and vertebral blood flow by trapidil were 165 ± 73% (SD) (n = 30) and 130 ± 78% (SD) (n = 30), respectively.

Intravenous Injection. In order to monitor the vertebral or coronary arterial blood flow, arterial blood of an anesthetized mongrel dog taken from the left femoral artery was led to the right vertebral or coronary artery. An electromagnetic flow probe was inserted into the circuit. Heart rate and mean blood pressure were monitored with a cardiotachometer and pressure transducer in a manner similar to that for intraarterial injection. Compounds in a volume of 100 μL were injected (0.3 mg/kg). Changes in cardiovascular parameters, heart rate, mean blood pressure, and femoral or vertebral blood flow were monitored and evaluated as a percentage.

Acknowledgment. We thank Masami Yanagita for his assistance in the biological testing, members of the Department of Medicinal Chemistry for their assistance in synthesis work, and Barrett B. Madrigal for his critical reading of the manuscript.

Registry No. **2**, 84468-17-7; **2**·HCl, 116970-50-4; **6**, 116700-33-5; **7**, 116700-34-6; **8**, 111541-58-3; **9**, 116970-51-5; **10**, 116970-52-6; **11**, 111541-55-0; **12**, 116970-53-7; **13**, 116970-54-8; **14**, 92564-42-6; **14**·2HCl, 116700-35-7; **15**, 84468-18-8; **15**·HCl, 116970-55-9; **16**, 84468-16-6; **16**·HCl, 116970-56-0; **17**, 84477-66-7; **17**·HCl, 116970-57-1; **18**, 116971-01-8; **18**·2HCl, 116970-58-2; **19**, 117254-10-1; **19**·2HCl, 116970-59-3; **20**, 116971-02-9; **20**·2HCl, 116970-60-6; **21**, 116971-03-0; **21**·2HCl, 116970-61-7; **22**, 84478-11-5; **22**·HCl, 116970-62-8; **23**, 116970-89-9; **23**·HCl, 116970-63-9; **24**, 116970-90-2; **24**·HCl, 116970-64-0; **25**, 116970-91-3; **25**·HCl, 116970-65-1; **26**, 116970-92-4; **26**·HCl, 116970-66-2; **27**, 116970-93-5; **27**·HCl, 116970-67-3; **28**, 116970-94-6; **28**·2HCl, 116970-68-4; **29**, 116970-95-7; **29**·2HCl, 116970-69-5; **30**, 116970-96-8; **30**·HCl, 116970-70-8; **31**, 116970-97-9; **31**·2HCl, 116970-71-9; **32**, 116970-98-0; **32**·2HCl, 116970-72-0; **33**, 116970-99-1; **33**·2HCl, 116970-73-1; **34**, 116971-00-7; **34**·2HCl, 116970-74-2; **35**, 116971-04-1; **35**·2HCl, 116970-75-3; **36**, 116971-05-2; **36**·HCl, 116970-76-4; **37**, 116971-06-3; **37**·HCl, 116970-77-5; **38**, 116971-07-4; **38**·HCl, 116970-78-6; **39**, 116971-08-5; **39**·HCl, 116970-79-7; **40**, 111541-20-9; **40**·HCl, 116970-80-0; **41**, 111541-21-0; **41**·HCl, 116970-81-1; **42**, 111541-25-4; **42**·HCl, 116970-82-2; **43**, 111540-96-6; **43**·HCl, 116970-83-3; **44**, 116971-09-6; **44**·HCl, 116970-84-4; **45**, 111540-97-7; **45**·HCl, 116970-85-5; **46**, 111540-98-8; **46**·HCl, 116970-86-6; **47**, 111540-99-9; **47**·HCl, 111541-46-9; **48**, 111541-00-5; **48**·HCl, 116970-87-7; **49**, 111541-01-6; **49**·HCl, 116970-88-8; $NH_2(CH_2)_2OH$, 141-43-5; $CH_3NH(CH_2)_2OH$, 109-83-1; $CH_3CH_2NH(CH_2)_2OH$, 110-73-6; $(CH_3)_2CHNH(CH_2)_2OH$, 109-56-8; $CH_3(CH_2)_3NH(CH_2)_2OH$, 111-75-1; $CH_3(CH_2)_5NH(CH_2)_2OH$, 54596-69-9; $CH_3(CH_2)_7NH(CH_2)_2OH$, 32582-63-1; $C_6H_5CH_2NH(CH_2)_2OH$, 104-63-2; $CH_3CH_2NH(CH_2)_2NHCH_2CH_3$, 111-74-0; $NH_2(CH_2)_3NH_2$, 109-76-2; $NH_2(CH_2)_4NH_2$, 110-60-1; $NH_2(CH_2)_6NH_2$, 124-09-4; $NH_2(CH_2)_2NHCH_3$, 108-00-9; $CH_3NH(CH_2)_2NHCH_3$, 110-70-3; $C_6H_5CH_2NH(CH_2)_2NHCH_2C_6H_5$, 140-28-3; o-$ClC_6H_4CH_2Cl$, 611-19-8; m-$ClC_6H_4CH_2Cl$, 620-20-2; p-$ClC_6H_4CH_2Cl$, 622-95-7; $CH_3(CH_2)_5NH_2$, 111-26-2; $CH_3(CH_2)_4NH_2$, 110-58-7; $CH_3(CH_2)_7NH_2$, 111-86-4; $CH_3(CH_2)_9NH_2$, 2016-57-1; c-$C_6H_{11}NH_2$, 108-91-8; $C_6H_5CH_2NH_2$, 100-46-9; p-$CH_3OC_6H_4CH_2NH_2$, 2393-23-9; 3,4-$(CH_3O)_2C_6H_3CH_2NH_2$, 5763-61-1; $C_6H_5(CH_2)_2NH_2$, 64-04-0; c-$C_6H_{11}NHCH_3$, 100-60-7; $CH_3(CH_2)_5NH(CH_2)_2CH_3$, 20193-73-1; $[CH_3(CH_2)_5]_2NH$, 143-16-8; p-$NO_2C_6H_4CH_2Br$, 100-11-8; isoquinolinesulfonic acid, 27655-40-9; 5-isoquinolinesulfonyl chloride hydrochloride, 105627-79-0.

Structure–Activity Relationships in Prazosin-Related Compounds. Effect of Replacing a Piperazine Ring with an Alkanediamine Moiety on α_1-Adrenoreceptor Blocking Activity

Dario Giardinà,* Livio Brasili, Maurizio Gregori, Maurizio Massi,† Maria T. Picchio, Wilma Quaglia, and Carlo Melchiorre*

Department of Chemical Sciences and Institute of Pharmacology and Pharmacognosy, University of Camerino, 62032 Camerino (MC), Italy. *Received April 18, 1988*

Several prazosin-related compounds were synthesized in which the piperazine ring of prazosin (1) was replaced by an alkanediamine chain and were evaluated for their blocking activity on α_1- and α_2-adrenoreceptors in isolated rat vas deferens. All the compounds investigated proved highly selective toward the α_1-adrenoreceptor owing to a very low affinity for α_2-adrenoreceptors. Furthermore, compounds **2**, **9**, and **13** were also investigated in vivo to determine their hypotensive effect on anesthetized rats, which were compared with that of prazosin (1). It was confirmed that the piperazine moiety of 1 is not essential for potency. However, optimum activity depends on two parameters: carbon-chain length of the alkanediamine moiety and N-methylation of both the amide and the 2-amino functions. In the desmethyl series, optimum activity was associated with the lower homologues (**2**–**4**) bearing a chain of two to four methylenes whereas in the *N*,*N*′-dimethyl series peak potency was observed with a six-carbon chain as in **13**. Compound **13** proved the most active of the series and was more potent than prazosin (1) in both in vivo and in vitro assays. It is hypothesized that the α_1-adrenoreceptor incorporates a lipophilic area that is located between the binding sites for the quinazoline and the furoyl moieties and is able to accommodate a polymethylene chain.

Prazosin (1) is a potent and highly selective α_1-adrenoreceptor antagonist.[1] At clinically relevant concentrations, it acts as a peripheral vasodilator by competitively antagonizing the vascular postsynaptic α_1-adrenoreceptor and is used to treat patients with hypertension and congestive

† Institute of Pharmacology and Pharmacognosy.

(1) Cambridge, D.; Davey, M. J.; Massingham, R. *Br. J. Pharmacol.* **1977**, *59*, 514P.

0022-2623/89/1832-0050$01.50/0