Table IV. Crystal and Refinement Data for Zetidoline (4)

molecular formula	$C_{16}H_{22}ClN_3O$
molecular weight	307.82
crystal system	monoclinic
crystal dimensions (mm)	0.30 × 0.23 × 0.08
a (Å)	8.199 (1)
b (Å)	6.538 (1)
c (Å)	31.791 (1)
β (deg)	96.94 (1)
V (Å^3)	1691.85
Z	4
F(000)	656
measured density (g cm^{-3})	1.20
calculated density (g cm^{-3})	1.21
space group	$P2_1/c$
diffractometer	Enraf-Nonius CAD-4
radiation	graphite-monochromated Cu Kα (λ = 1.541 78 Å)
2θ range (deg)	4-144
unique data	3224 ($-10 \le h \le 10$, $0 \le k \le 8$, $0 \le l \le 39$)
unique data with $I \ge 2.5\sigma(I)$	1717
absorption coefficient (cm^{-1})	19.13
final R value	0.06
max and min heights in final difference Fourier map (e Å^{-3})	0.17 and −0.25

full-matrix least-squares on F with the SHELX 76 program. Many hydrogen atoms appeared in a difference Fourier map, but all were then calculated and not refined. Anisotropic temperature factors were used for all non-H atoms and isotropic ones for H atoms (corresponding to the isotropic temperature factor of the carrier atom incremented by 0.02). The final weighted least-squares cycle gave R = 0.06 with $w = 1.0[\sigma^2(F) + 0.01F^2]$. Crystal and refinement data are given in Table IV. The XRAY 76 program[20] was used for molecular geometry analysis.

Conformational Analysis and MEP Calculations. Ab initio calculations were performed with the MONSTERGAUSS program[21] and the GAUSSIAN 82 program.[22] Molecular mechanics calculations and superpositions were performed with the COMPDS package from Molecular Design Ltd. and SYBYL from Tripos Associates.

The calculations were performed on a Norsk Data ND560 and a VAX 8550 computer of the University of Lausanne and a CDC 180/855, a CRAY 1S, and a VAX 780 computer of the Federal Institute of Technology of Lausanne.

Acknowledgment. S.C. thanks the "Institut pour l'Encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture" (IRSIA, Belgium) for financial support. P.A.C., H.v.d.W. and B.T. are indebted to the Swiss National Science Foundation for Grant 3.539-0.83 and 3.508-0.86, Molecular Design Ltd. for an academic software agreement for the COMPDS and DISP packages, P. Santschi for generous computer time, and R. Calinon for computational facilities.

Registry No. 4, 51940-78-4; 5, 2033-34-3.

Supplementary Material Available: Final atomic parameters, B_{eq} values, and anisotropic thermal parameters of zetidoline (1 page). Ordering information is given on any masthead page.

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5-Isoquinolinesulfonamide Derivatives. 1. Synthesis and Vasodilatory Activity of *N*-(2-Guanidinoethyl)-5-isoquinolinesulfonamide Derivatives

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Two novel series of *N*-(2-guanidinoalkyl)-5-isoquinolinesulfonamides, **2** and **3**, were prepared. Many of the compounds possessed vasodilatory activity when injected locally into the femoral artery of dogs. The most potent compound, 1-amidino-4-(5-isoquinolylsulfonyl)-1,4-perhydrodiazepine, **33**, was comparable to diltiazem, which is used clinically as a vasodilator.

Certain sulfonamide compounds, such as thiadiazide[1] and *p*-aminobenzenesulfonamide derivatives,[2] are used clinically as drugs. Though the sulfonamide group is thought to be an important pharmacophore in these drugs, it is not as common as amide and amine groups, and it has received only limited attention as a potential structural unit in the search for new drug molecules. We have previously investigated the biological activity of aromatic sulfonamide compounds and discovered vasodilatory activity for 5-isoquinolinesulfonamide derivatives. We have also reported[3,4] that *N*-(2-guanidinoethyl)-5-isoquinolinesulfonamide, **1** (HA-1004), is an intracellular calcium antagonist.[5] While it is known that calcium antagonists have significant heterogeneity in their chemical structure,[6] **1** is the first calcium antagonist to have a sulfonamide group. It also represents a new type of calcium antagonist in that it acts intracellularly.

In an attempt to improve the activity of **1**, we prepared analogues **2** and **3**, which possess a substituted guanidinic or sulfonamidic nitrogen or an elongated alkylene group between the sulfonamidic and guanidinic nitrogens. Their vasodilatory effects were assessed on the femoral artery

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† Bioscience Laboratory.
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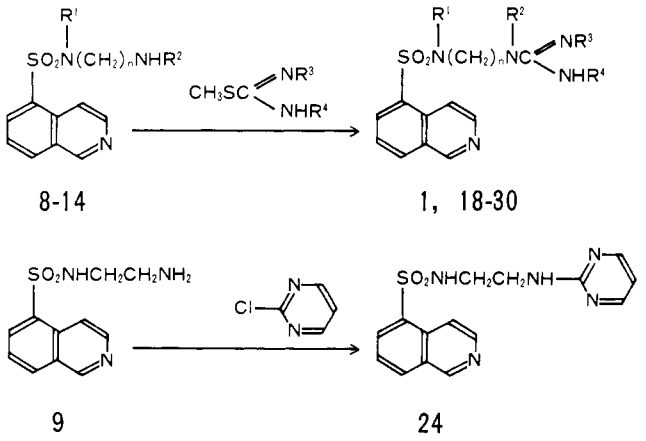
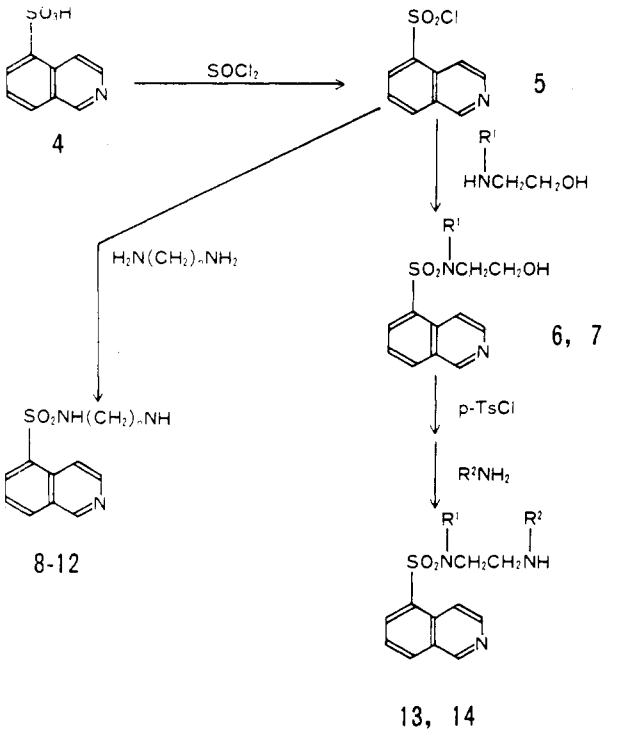
Table I. *N*-(Aminoalkyl)-5-isoquinolinesulfonamides

no.	*n*	R^1	R^2	formula (C, H, O, S)	yield, %	crystn solv	mp, °C
8	0	H	H	$C_9H_9O_2N_3S\cdot 2HCl$	45	$MeOH/H_2O$	240–241
9	2	H	H	$C_{11}H_{13}O_2N_3S\cdot 2HCl$	71	H_2O	253–254
10	3	H	H	$C_{12}H_{15}O_2N_3S\cdot 2HCl$	76	$EtOH/H_2O$	246–248
11	4	H	H	$C_{13}H_{17}O_2N_3S\cdot 2HCl$	58	$EtOH/H_2O$	220–222
12	6	H	H	$C_{15}H_{21}O_2N_3S\cdot 2HCl$	23	$EtOH/H_2O$	205–207
13	2	CH_3	H	$C_{12}H_{15}O_2N_3S\cdot 2HCl$	21	$EtOH/H_2O$	223–225
14	2	H	CH_3	$C_{12}H_{15}O_2N_3S\cdot 2HCl$	19	$MeOH/H_2O$	221–222

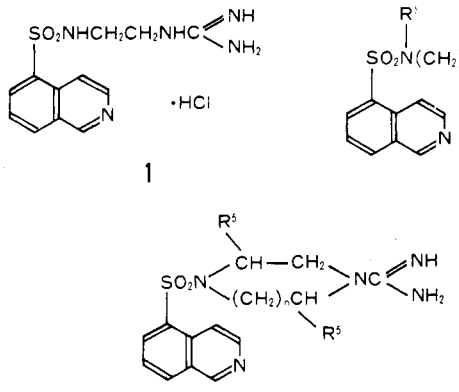
Scheme I



Scheme II



of anesthetized dogs. We report herein the synthesis and pharmacological testing of **1–3**.



Chemistry

The derivatives were synthesized by use of two routes. Guanidine derivatives **1** and **18–30** were prepared from the corresponding amines **8–14** by treatment under basic conditions with substituted *S*-methylisothioureas or 2-chloropyrimidine, as shown in Scheme I. The amines **8–14** were prepared by using the following methods.

5-Isoquinolinesulfonic acid (**4**)[7] was chlorinated with a large excess of thionyl chloride to give the hydrochloride of the corresponding sulfonyl chloride **5**, which was then used for the subsequent syntheses without further purification because of its instability. The free sulfonyl chloride, obtained by treatment of the hydrochloride with $NaHCO_3$ and extraction with CH_2Cl_2, was reacted with an excess of symmetric diamines to give sulfonamide derivatives **8–12** (Scheme II). However, in the case of asymmetric diamines, mixtures of the two possible isomers were obtained, and these proved difficult to separate. Therefore, amines **13–14** were prepared by a different route. *N*-Alkyl-*N*-(2-hydroxyethyl)-5-isoquinolinesulfonamides, obtained by sulfonylation of *N*-alkyl-2-aminoethanol with sulfonyl chloride, **5**, were tosylated and reacted with methylamine or ammonia to yield amines **13–14** (Scheme II).

The guanidination of amine derivatives with *S*-methylisothiourea could not be adapted to cyclic amine derivatives. For example, we attempted the reaction of 1-(5-isoquinolylsulfonyl)piperazine with *S*-methylisothiourea in various solvents (water, MeOH, EtOH, THF), but the desired guanidine could not be obtained. The cyclic derivatives **31–33** were synthesized by a different method utilizing the sulfonylation of cyclic aminoguanidines **15–17**. The cyclic diamines, prior to the sulfonylation, were reacted with *S*-methylisothiourea to give the corresponding monoguanidinated derivatives **15–17**. The sulfonylation of **15–17** with sulfonyl chloride **5** gave the guanidino derivatives **31–33** (Scheme III).

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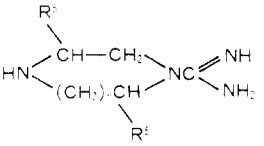
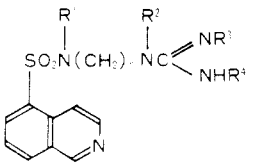
Table II. *N*-Amidinopiperazine Derivatives



no.	*n*	R^5	formula	yield, %	crystn solv	mp, °C
15	1	H	$C_5H_{12}N_4 \cdot {}^1/_2H_2SO_4$	73	EtOH	>250
16	1	CH_3	$C_7H_{16}N_4 \cdot {}^1/_2H_2SO_4$	84	EtOH	>250
17	2	H	$C_6H_{14}N_4 \cdot {}^1/_2H_2SO_4$	32	EtOH	>250

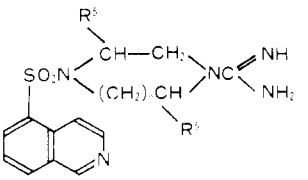
Table III. *N*-(2-Guanidinoethyl)-5-isoquinolinesulfonamide Derivatives



no.	*n*	R^1	R^2	R^3	R^4	formula	yield, %	crystn solv	mp, °C	FBF[a]
1	2	H	H	H	H	$C_{12}H_{15}O_2N_5S \cdot HCl$	90	H_2O	235–236	1.7 ± 0.09
18	2	H	H	CN	H	$C_{13}H_{14}O_2N_6S \cdot HCl$	27	MeOH	225–226	>50
19	2	H	H	NO_2	H	$C_{12}H_{14}O_4N_6S \cdot HCl$	73	MeOH	182 dec	>10
20	2	H	H	CH_3	H	$C_{13}H_{17}O_2N_5S \cdot HCl$	9	H_2O	188–189	ND[b]
21	2	H	H	CH_3	CH_3	$C_{14}H_{19}O_2N_5S \cdot HCl$	20	$MeOH/H_2O$	180–183	>50
22	2	H	H	C_6H_5	C_6H_5	$C_{24}H_{23}O_2N_5S \cdot HCl$	24	MeOH	178–178.5	>50
23	2	H	H	$-(CH_2)_2-$		$C_{14}H_{17}O_2N_5S \cdot 2HCl$	56	$MeOH/H_2O$	190–191	24 ± 1
24	2	H	H	2-pyrimidyl		$C_{15}H_{15}O_2N_5S \cdot 2HCl$	73	MeOH/EtOH	232–247	>30
25	2	CH_3	H	H	H	$C_{13}H_{17}O_2N_5S \cdot 2HCl$	44	MeOH	240–241	1.8 ± 0.1
26	2	H	CH_3	H	H	$C_{13}H_{17}O_2N_5S \cdot 2HCl$	21	$MeOH/H_2O$	222	1.1 ± 0.08
27	0	H	H	H	H	$C_{10}H_{11}O_2N_5S \cdot 2HCl$	7	$MeOH/H_2O$	204 dec	ND[b]
28	3	H	H	H	H	$C_{13}H_{17}O_2N_5S \cdot 2HCl$	18	H_2O	244–245	4.3 ± 0.2
29	4	H	H	H	H	$C_{14}H_{19}O_2N_5S \cdot 2HCl$	49	H_2O	181–184	16 ± 1.3
30	6	H	H	H	H	$C_{16}H_{23}O_2N_5S \cdot 2HCl$	23	H_2O	169–171	3.8 ± 0.4
diltiazem										0.21 ± 0.009

[a] Increasing effect on blood flow of femoral artery. These values are expressed as equieffective dose ratios compared to trapidil (test compound dose (mg)/equieffective trapidil dose (mg)). [b] No detectable vasodilation.

Table IV. 1-Amidino-4-(5-isoquinolylsulfonyl)piperazine Derivatives



no.	*n*	R	formula	yield, %	crystn solv	mp, °C	FBF[a]
31	1	H	$C_{14}H_{17}O_2N_5S \cdot HCl$	63	acetone/MeOH	249–54	0.62 ± 0.04
32	1	CH_3	$C_{16}H_{21}O_2N_5S \cdot HCl$	16	acetone/MeOH	>260	1.60 ± 0.1
33	2	H	$C_{15}H_{19}O_2N_5S \cdot HCl$	41	aceone/MeOH	247–9	0.19 ± 0.01
diltiazem							0.21 ± 0.009

[a] See footnote *a* of Table III.

Biology

To avoid possible inconsistency between in vitro and in vivo results, we used an in vivo model for the initial screen. The vasodilatory activity was evaluated in the femoral artery of anesthetized dogs following local intraarterial administration of the compounds, and the results were expressed as equieffective dose ratios compared to trapidil (5-methyl-7-(diethylamino)[1,2,4]triazolo[1,5-*a*]pyrimidine).[8,9] These data are shown in Tables III and IV.

The activity of **1** was less than that of trapidil, and much less than that of diltiazem,[10–12] which is a well-known coronary vasodilator in humans and a calcium channel blocker.

Any substitution on the terminal guanidinic nitrogen by phenyl, alkyl, cyano, or nitro groups afforded compounds **18–24**, which were much less active than **1**.

Compound **27**, the sulfonamidic nitrogen of which is directly bonded to the guanidinic group, had no activity. This result suggested that vasodilatory activity requires an alkylene group between the sulfonamidic and guanidinic nitrogens. The data for **1** and **28–30**, which have alkylene groups of various lengths, shows that activity reaches a

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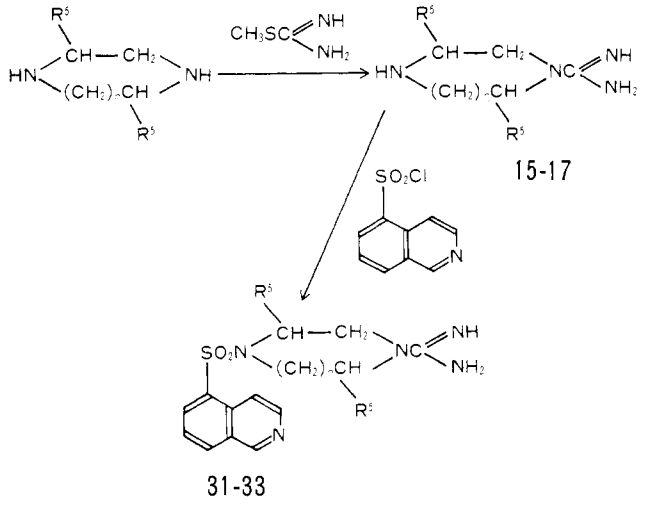
Scheme III



maximum when the carbon number of the alkylene group is 2.

The introduction of a methyl group to the sulfonamidic nitrogen (**25**) did not affect activity while introduction of a methyl group to the nonterminal guanidinic nitrogen afforded a more active compound, **26**. This increase in activity produced by the introduction of an alkyl group to the nonterminal guanidinic nitrogen contrasts markedly with substitution on the terminal guanidinic nitrogen. It is thought that the environment surrounding the guanidino group has a major influence on the activity of these sulfonamide derivatives.

Structures **31** and **33**, derived from cyclic diamines, showed higher activities than either **1** or trapidil, whereas **32** showed less activity than **1**. Compound **33**, specifically, had the most potent vasodilatory activity among the analogues of **1**, being as potent as diltiazem. It is noteworthy that there is a large difference between the vasodilatory effects of **31** and **33**, which have six- and seven-membered ring structures, respectively. This suggests that the configuration of the ring, along with the guanidinic and sulfonamidic nitrogens, contributes to vasodilatory activity.

Experimental Section

Melting points were determined in open capillary tubes on a Büchi apparatus and have not been corrected. Compounds gave satisfactory IR and NMR spectra 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, **4** (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 in CH_2Cl_2 (300 mL), filtered, and washed with two portions of CH_2Cl_2 (200 mL). The precipitate was collected and dried under reduced pressure to remove the solvent, yielding crude crystalline 5-isoquinolinesulfonyl chloride hydrochloride (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 (6).** To an ice-cold aqueous solution (100 mL) of crude **5** (50 g, 189 mmol) was added slowly $NaHCO_3$ (25.89 g, 189 mmol) with stirring. The resulting solution was extracted twice with CH_2Cl_2 (100 mL × 2). The CH_2Cl_2 solution was dried ($MgSO_4$) and added dropwise to a CH_2Cl_2 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 **6** (78.0 g, 78%): mp 144–145 °C; NMR (CD_3OD) δ 2.90 (2 H, t, CH_2N), 3.47 (2 H, t, CH_2OH), 7.77 (1 H, dd, isoquinoline H-7), 8.30–8.37 (4 H, m, isoquinoline), 9.37 (1 H, s, isoquinoline H-1). Anal. ($C_{11}H_{12}O_3NS$) C, H, N, S.

Compound **7** (mp 121–122 °C, 87%) was obtained by the same method.

***N*-[2-(Methylamino)ethyl]-5-isoquinolinesulfonamide Hydrochloride (14).** A mixture of alcohol **6** (20 g, 79.3 mmol), *p*-toluenesulfonyl chloride (27.2 g, 143.7 mmol), and dry pyridine (150 mL) was stirred at room temperature overnight. The precipitate was filtered off, and the filtrate was evaporated and dissolved in CH_2Cl_2 (150 mL). To the solution was added a 40% MeOH solution of methylamine (30 mL), and the mixture was stirred for 2 h at room temperature. The resulting solution was evaporated and chromatographed on a silica column, which was eluted by $CHCl_3$, 1% v/v MeOH/$CHCl_3$, 3% v/v MeOH/$CHCl_3$, 5% v/v MeOH/$CHCl_3$, and 10% v/v MeOH/$CHCl_3$. The 5% v/v MeOH/$CHCl_3$ fraction was evaporated and dissolved in water (30 mL), followed by adjustment of the pH to 6.0 with dilute HCl. The resulting solution was evaporated and the residue was recrystallized from MeOH/water to yield **14** (4.54 g, 19 %): mp 221–222 °C.

***N*-(2-Aminoethyl)-5-isoquinolinesulfonamide Hydrochloride (9).** To a mixture of crude **5** (10 g, 37.9 mmol) and water (150 mL) was added slowly $NaHCO_3$ (3.19 g, 37.9 mmol) with stirring and cooling on ice. The resulting solution was extracted twice with CH_2Cl_2 (100 mL × 2). The organic layer was dried ($MgSO_4$) and added dropwise to a solution of ethylenediamine (11.39 g, 189 mmol) and CH_2Cl_2 (100 mL) with stirring and ice-cooling. The solution was stirred for 1 h at room temperature, washed with water, and evaporated to remove the solvent. The residue was chromatographed on a column of silica gel, which was eluted with 10% v/v MeOH/$CHCl_3$. The fractions were treated with HCl to give **9** (7.70 g, 71%): NMR (D_2O) δ 2.63–3.23 (4 H, m, CH_2CH_2), 7.83 (1 H, dd, isoquinoline H-7), 8.30–8.77 (4 H, m, aromatic hydrogens), 9.30 (1 H, s, isoquinoline H-1).

10–12 were obtained by the same method.

5-Isoquinolinesulfonohydrazide Dihydrochloride (8). To a cold mixture of **5** (5.0 g, 18.9 mmol) and water (50 mL) was added slowly $NaHCO_3$ (1.59 g, 18.9 mmol) with cooling on ice, and the solution was extracted with two portions of CH_2Cl_2 (150 mL × 2). The organic layer was dried ($MgSO_4$), evaporated, and dissolved in THF (50 mL). To the solution was added 2.25 mL of hydrazine hydrate slowly with ice-cooling, followed by stirring at 0 °C for 1 h. The precipitate was filtered, washed with THF (50 mL), and dissolved in MeOH/water with diluted HCl to adjust the pH to 2.0. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH/water to yield **8** (2.52 g, 45%): mp 240–241 °C.

***N*-(2-Guanidinoethyl)-5-isoquinolinesulfonamide Hydrochloride (1).** A mixture of **9** (10 g, 34.7 mmol), *S*-methylisothiourea 0.5-sulfate (14.5 g, 104 mmol), 2 N NaOH (52 mL), and water (200 mL) was stirred at 80 °C for 3 h. On cooling, the crystalline product was filtered off, washed with water, and dissolved in water with a small amount of HCl. After the pH of the solution had been adjusted to 6.0 with NaOH, the solvent was removed under reduced pressure. The residue was recrystallized from water to give **1** (10.31 g, 90%): IR (KBr) ν_{max} (cm^{-1}) 1650, 1680 (guanidine), 1320 (S=O).

18–23 and **25–30** were obtained by the same method.

***N*-[2-(2-Pyrimidylamino)ethyl]-5-isoquinolinesulfonamide Dihydrochloride (24).** A mixture of **9** (8.63 g, 30 mmol), 2-chloropyrimidine (1.14 g, 10 mmol), KOH (3.36 g, 60 mmol), and ethanol (40 mL) was refluxed for 4 h. The solution was then evaporated under reduced pressure. The residue was extracted with CH_2Cl_2 (50 mL), washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The resulting residue was chromatographed on silica gel and eluted with 20% v/v MeOH/$CHCl_3$. The solvent was removed under reduced pressure. The residue was then dissolved in dilute HCl, evaporated off, and recrystallized from MeOH to give **24** (2.94 g, 73%): IR (KBr) ν_{max} (cm^{-1}) 1330 (S=O); NMR (D_2O) δ 2.95–3.35 (4 H, m, NCH_2CH_2N), 6.55 (1 H, t, pyrimidine H-4), 7.83 (1 H, dd, isoquinoline H-7), 8.23 (2 H, d, pyrimidine H-2,4), 8.50–8.81 (5 H, m, isoquinoline), 9.5 (1 H, s, isoquinoline H-1).

4-Amidino-1,4-perhydrodiazepine 0.5-Sulfate (17). A mixture of 1,4-perhydrodiazepine (7.2 g, 71.0 mmol), *S*-methyl-

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.

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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

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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

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