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Synthesis and Pharmacological Evaluation of Piperidine Derivatives with Various Heterocyclic Rings at the 4-Position

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A series of piperidine derivatives with various heterocyclic rings at the 4-position was prepared and tested for antihypertensive activity and other biological activities. The antihypertensive effects of the present compounds in the spontaneous hypertensive rat were less potent than those of previously reported compounds. However, among the compounds tested for antiulcer activity and antiinflammatory activity, some exhibited interesting properties.

Keywords——antihypertensive activity; antiulcer activity; piperidine; antiinflammatory activity; quinazoline; 2,1,3-benzothiadiazine; 1,3-benzoxazine; 1,2,3-benzotriazine

We recently described the synthesis and pharmacological evaluation of 1-(2-hydroxy-2-phenethyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine derivatives (Ia), a new class of antihypertensive agents.[1] As a continuation of our investigations we decided to prepare various analogs (Ib—g) of these compounds as shown in Chart 1 for pharmacological evaluation, not only as antihypertensive agents, but also for other types of activity. Many 1-

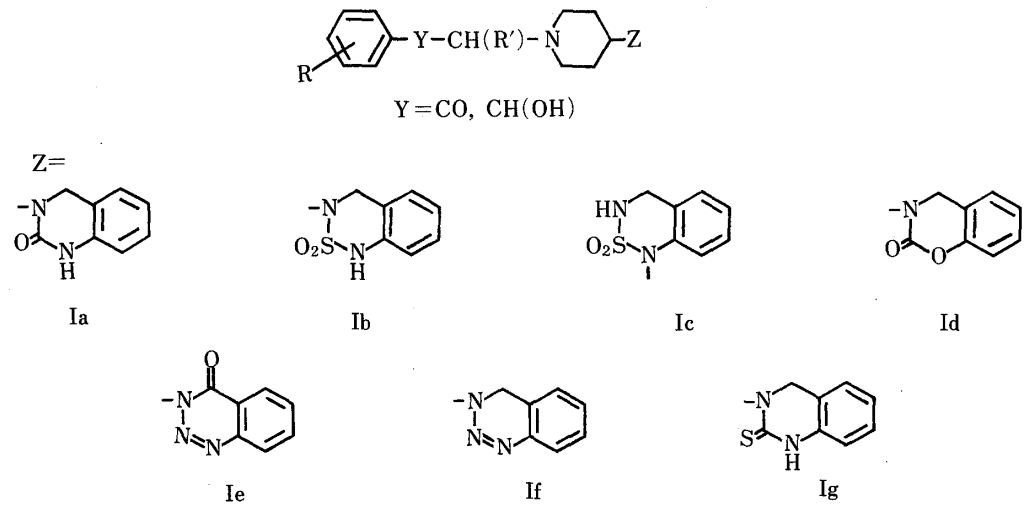


Chart 1

substituted piperidine derivatives with a benzimidazolinone ring[2] or benzoylamino group[3] at the 4-position have been synthesized in attempts to find new antihypertensive drugs. Compounds Ia have a 1,2,3,4-tetrahydro-2-oxoquinazoline ring which includes a ureido group in its structure as well as benzimidazolinone. We designed compounds of type Ib and Ic

(including a sulfamide group), of type Id (including a urethane group), and of type Ig (including a thioureido group) with the indicated groups in place of the ureido group in Ia. We also designed compounds of type Ie,[4] having a benzamide group, which is present in the structure of indoramin,[3] (an antihypertensive compound), and of type If, having a structure related to that of Ie.

Chemistry

The 1-benzoylalkylpiperidine derivatives (**4**—**17**) listed in Table I were usually prepared by the reaction of a piperidine intermediate, **2a**, **2b**, **2c**, or **2d** with the appropriate bromoketone by using triethylamine (TEA) as a base in ethanol (Chart 2). Benzyl alcohol

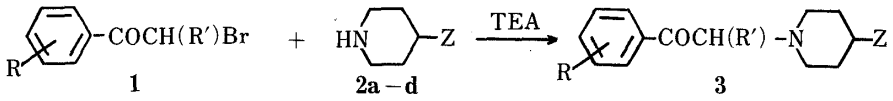
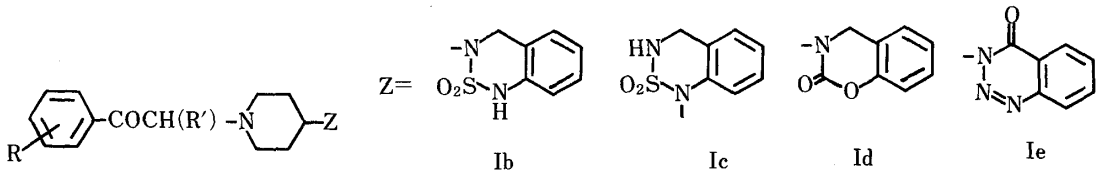


Chart 2

derivatives (**18**—**28**) listed in Table II were synthesized by reduction of the corresponding 1-benzoylalkyl derivatives with $NaBH_4$. Reduction of the 1-(1-benzoylethyl) derivative (**9**) as the free base with $NaBH_4$ in ethanol at room temperature gave diastereomixtures of the corresponding amino alcohols (**23** and **23′**). These diastereomixtures were separated by chromatography on silica gel with AcOEt to give **23** and **23′** in 18.5 and 71.7% yields, respectively. Analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the amino alcohols **23** and **23′** in chloroform-*d* medium permitted assignment of the configurations. The coupling constants of the benzylic protons of **23** and **23′** were 4 and 10 Hz, respectively. These are comparable with values of 4.0 and 8.3 Hz for ephedrine (*erythro*) and

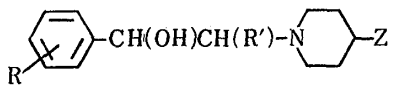
TABLE I.

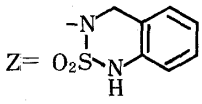


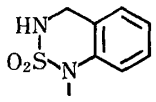
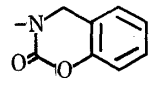
Compd.	R	R′	Z	Crystn. solvent	mp (°C)	% yield	Formula[a]
4	3,4-DiMeO	H	Ib	EtOH	173.5—175.5	35.2	$C_{22}H_{27}N_3O_5S$
5	3,4-(OCH_2O)	H	Ib	EtOH	184.0—185.5	69.5	$C_{21}H_{23}N_3O_5S$
6	3,4-DiMeO	Me	Ib		Amorphous	30.7	—
7	3,4-DiMeO	H	Ic	EtOH	102.0—104.0	83.2	$C_{22}H_{27}N_3O_5S$
8	3,4-(OCH_2O)	H	Ic	EtOH	185.0—187.0	68.3	$C_{21}H_{23}N_3O_5S$
9	3,4-DiMeO	Me	Ic	EtOH–H_2O	229.0—231.5	31.1	$C_{23}H_{29}N_3O_5S$ $HCl \cdot C_2H_5OH$
10	3,4-DiMeO	H	Id	EtOH	143.0—144.5	80.3	$C_{23}H_{26}N_2O_5$
11	3,4-(OCH_2O)	H	Id	EtOH	163.0—164.0	81.6	$C_{22}H_{22}N_2O_5$
12	3,4-DiMeO	Me	Id	EtOH	149.0—151.5	66.2	$C_{24}H_{28}N_2O_5$
13	3,4,5-TriMeO	H	Id	EtOH	152.0—153.5	41.7	$C_{24}H_{28}N_2O_6$
14	4-Cl	H	Id	EtOH	Crude crystals	75.9	—
15	3,4-DiMeO	H	Ie	$CHCl_3$–EtOH	168.0—170.5	61.4	$C_{22}H_{24}N_4O_4$
16	3,4-(OCH_2O)	H	Ie	$CHCl_3$–EtOH	204.0—206.0	77.3	$C_{21}H_{20}N_4O_4$
17	4-Cl	H	Ie	DMF–EtOH	168.5—170.2	77.0	$C_{20}H_{19}ClN_4O_2$

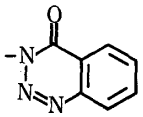
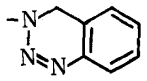
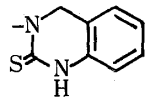
a) Compounds for which the formula is given were analyzed for C, H, and N and analytical values were within ±0.3% of the calculated values for these formulas.

TABLE II.



Z= 

Ib  Ic  Id

 Ie  If  Ig

Compd.	R	R′	Z	Crystn. solvent	mp (°C)	% yield	Formula[c]
18	3,4-DiMeO	H	Ib	AcOEt–hexane	171.0—172.5	35.5	$C_{22}H_{29}N_3O_5S$
19	3,4-(OCH_2O)	H	Ib	EtOH	178.0—179.0	65.6	$C_{21}H_{25}N_3O_5S$
20	3,4-DiMeO	Me	Ib	MeOH	216.0—217.0[a]	18.8	$C_{23}H_{31}N_3O_5S$
21	3,4-DiMeO	H	Ic	EtOH	144.5—146.0	82.3	$C_{22}H_{29}N_3O_5S$
22	3,4-(OCH_2O)	H	Ic	EtOH	194.5—195.0	67.3	$C_{21}H_{25}N_3O_5S$
23	3,4-DiMeO	Me	Ic	EtOH–H_2O	221.0—222.0[b]	57.8	$C_{23}H_{31}N_3O_5S \cdot HCl$
24	3,4-DiMeO	H	Id	EtOH	169.0—170.0	83.4	$C_{23}H_{28}N_2O_5$
25	3,4-(OCH_2O)	H	Id	EtOH	184.5—185.0	82.7	$C_{22}H_{24}N_2O_5$
26	3,4-DiMeO	Me	Id	EtOH	201.0—202.0[a]	60.0	$C_{24}H_{30}N_2O_5$
27	3,4,5-TriMeO	H	Id	EtOH	203.0—204.0	61.8	$C_{24}H_{30}N_2O_6$
28	4-Cl	H	Id	DMF–EtOH	200.0—201.2	76.1	$C_{21}H_{23}ClN_2O_3$
29	3,4-DiMeO	H	Ie	EtOH	159.0—159.9	29.8	$C_{22}H_{26}N_4O_4$
30	3,4-(OCH_2O)	H	Ie	DMF–EtOH	210.0—211.0	85.2	$C_{21}H_{22}N_4O_4$
31	4-Cl	H	Ie	DMF–EtOH	209.0—210.0	81.5	$C_{20}H_{21}ClN_4O_2$
32	H	H	If	AcOEt	119.2—120.6	58.8	$C_{20}H_{24}N_4O$
33	4-Cl	H	If	AcOEt	164.8—166.0	62.9	$C_{20}H_{23}ClN_4O$
34	H	H	Ig	DMF–MeOH	248.5—250.0	88.7	$C_{21}H_{25}N_3OS$
35	4-Cl	H	Ig	DMF–MeOH	199.0—200.9	58.8	$C_{21}H_{24}ClN_3OS$

a) *threo* isomer. *b*) *erythro* isomer. *c*) All compounds were analyzed for C, H, and N and analytical values were within ±0.3% of the calculated values for these formulas except for **22** (within ±0.4%).

pseudoephedrine (*threo*),[5] respectively. Similar values have been found for other epimeric amino alcohols.[6] The virtual identity of the coupling constants of these compounds supported the assignment of *erythro* configuration to **23** and *threo* to **23′**. Similar reactions of **6** and **12** also gave diastereomixtures, but only the corresponding *threo* isomers of the amino alcohols (**20** and **26**) could be isolated. It was reported by Kametani *et al.* that reduction of various salts of alpha-piperidinopropiophenone derivatives with $NaBH_4$ gave stereoselectively the corresponding *erythro* isomers.[7] In our present experiments, reduction of HCl salt of **9** with $NaBH_4$ in EtOH at room temperature gave the corresponding *erythro* isomer (**23**) as the main product with trace amounts of the *threo* isomer.

For the synthesis of 3,4-dihydro-1*H*-2,1,3-benzothiadiazine derivatives, several synthetic methods[8-11] have been reported, including the first report by Wright.[8] However, compound **2a**, which is the starting material for **7**—**9** and **21**—**23**, has not been reported. For the synthesis of **2a**, 1-benzyl-4-(2-aminomethylphenyl)aminopiperidine (**36**), which was reported previously by us,[1] was chosen as a starting material and the procedure of Houlihan *et al.* was applied.[10] However, the reaction of **36** with sulfamide at 85 °C for 24 h in pyridine afforded an uncyclized compound **38** instead of the expected cyclized compound **37**. The synthesis of **37** was accomplished in 65.6% yield by heating **36** with sulfamide under reflux for 8 h in pyridine.

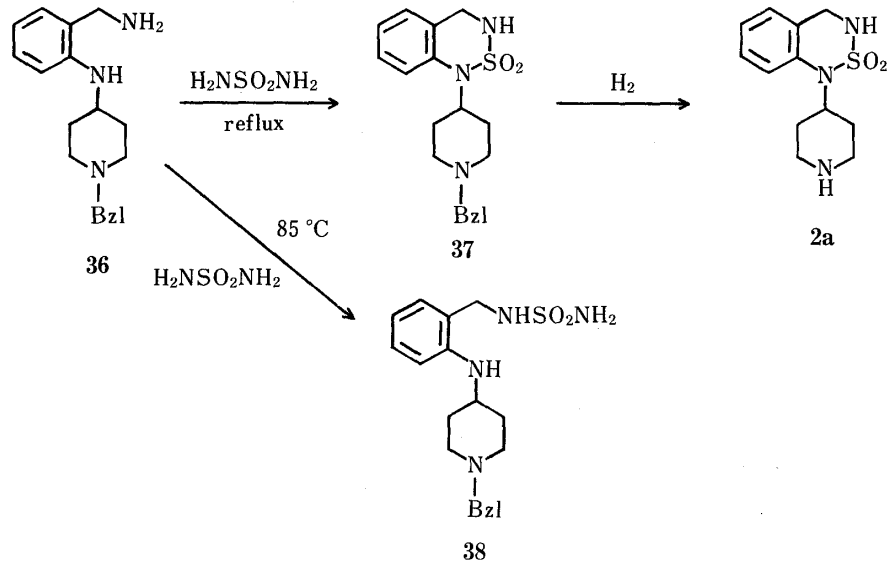


Chart 3

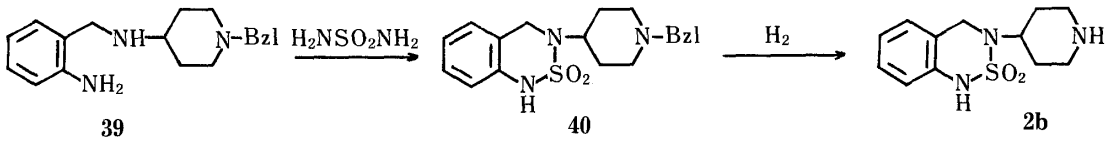


Chart 4

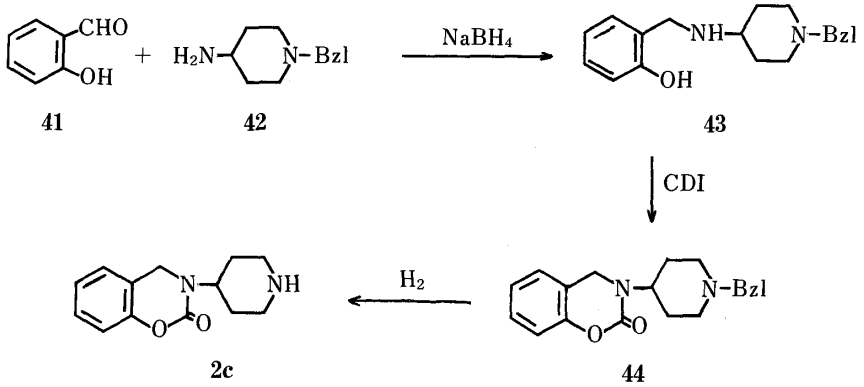


Chart 5

Subsequent debenzylation of **37** by catalytic hydrogenation over 10% Pd–C at 40 °C gave compound **2a**.

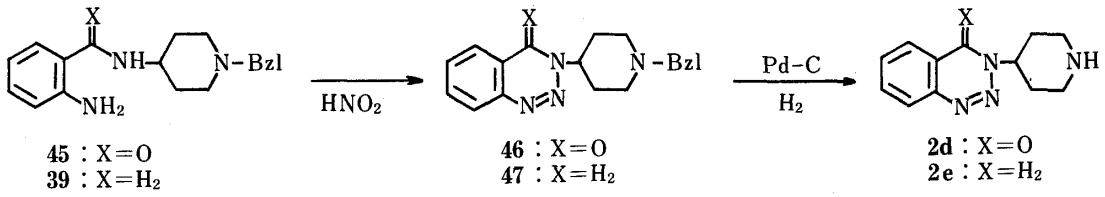
The starting material **2b** for **4**—**6** and **18**—**20** was obtained by the same procedure as described above from **39**, which was also reported previously by us,[1] as shown in Chart 4.

Compound **2c**, which is the key intermediate for **10**—**14** and **24**—**28**, was prepared from 1-hydroxybenzaldehyde and 1-benzyl-4-aminopiperidine as shown in Chart 5. An intermediate, 1-benzyl-4-(2-hydroxyphenylmethyl)aminopiperidine (**43**), was prepared by reaction of 2-hydroxybenzaldehyde (**41**) with 1-benzyl-4-aminopiperidine (**42**) in methanol, followed by reduction of the resulting Schiff base with $NaBH_4$. The preparation of 3-aminoalkyl-3,4-dihydro-1,3-benzoxazin-2-ones by cyclization of 2-hydroxybenzylamine derivatives with $COCl_2$ had been described by Richman,[12] but in our present experiments cyclization of **43** was easily performed in 77.3% yield by treatment with *N*,*N*′-carbonyldiimidazole (CDI) in tetrahydrofuran (THF). Compound **44** thus obtained was

converted into **2c** on debenzylation by catalytic hydrogenation at 40 °C.

For the preparation of **2d**, cyclization *via* diazotization of anthranilamide to the desired 1,2,3-benzotriazin-4(3*H*)-one seemed the best suited among several methods reported in the literature.[13] Accordingly, 1-benzyl-4-(2-aminobenzoyl)aminopiperidine (**45**) was chosen as the starting material. The reaction of **45** with $NaNO_2$ in dil. HCl afforded a cyclized compound **46**, which could be converted into **2d** on debenzylation by catalytic hydrogenation at 40 °C (Chart 6).

For the synthesis of **32** and **33**, **2e** was chosen as a key intermediate. The synthesis of this intermediate was attempted through the cyclization of the diamine **39** with $NaNO_2$ in dil. HCl, followed by debenzylation of the resulting cyclized compound **47** by catalytic hydrogenation at 40 °C, as in the case of the preparation of **2d**. This process was unsuccessful because the catalytic hydrogenation of the cyclized compound **47** afforded a complex mixture, possibly due to N,N-bond cleavage. Finally, the synthesis of **32** and **33** was accomplished by the cyclization ($NaNO_2$ in dil. HCl) of **54a** and **54b**, which were obtained by catalytic hydrogenation of **53a** with 10% Pd–C and of **53b** with Raney nickel. The intermediates, **53a**

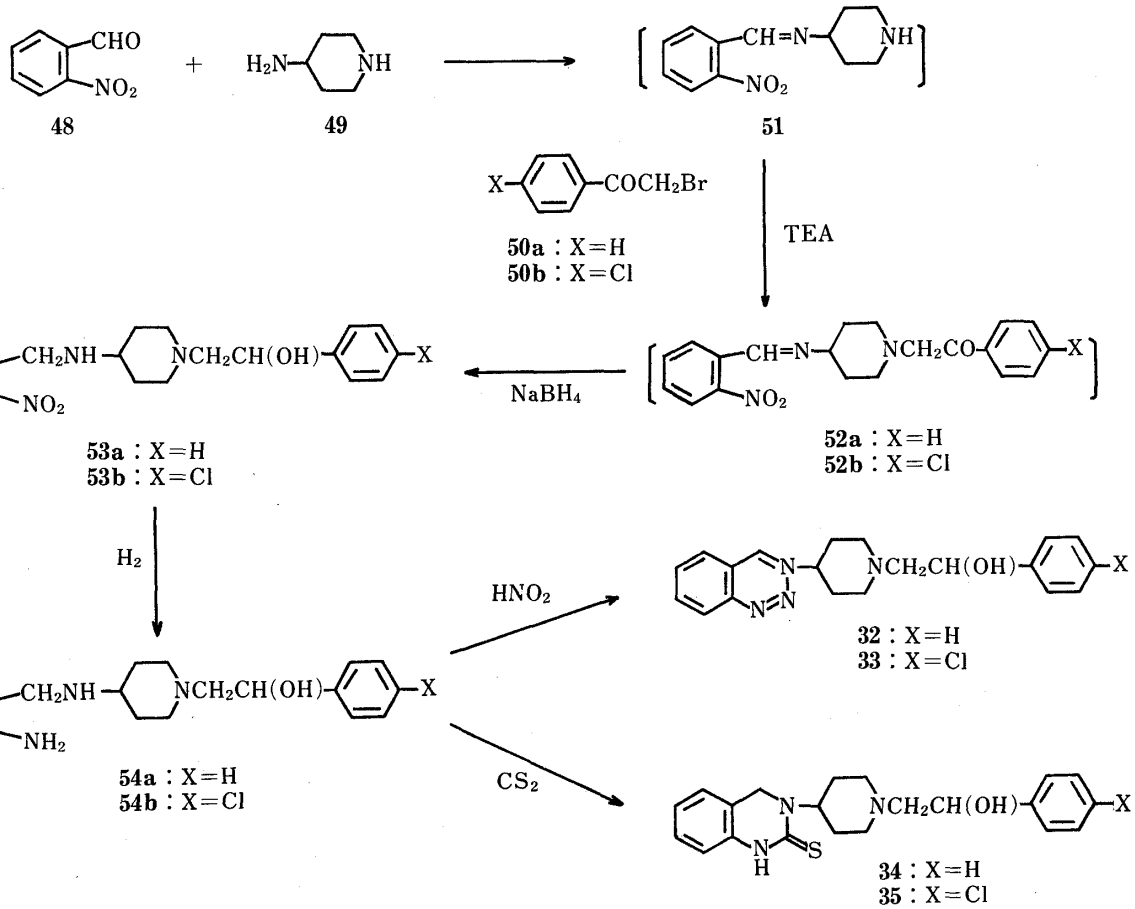


45 : X=O
39 : X=H_2

46 : X=O
47 : X=H_2

2d : X=O
2e : X=H_2

Chart 6



48 **49** **51**

50a : X=H
50b : X=Cl

53a : X=H
53b : X=Cl

52a : X=H
52b : X=Cl

32 : X=H
33 : X=Cl

54a : X=H
54b : X=Cl

34 : X=H
35 : X=Cl

Chart 7

and **53b**, were obtained by the reduction with $NaBH_4$ of the Schiff bases, **52a** and **52b**, which were prepared by the treatment of 2-nitrobenzaldehyde with 4-aminopiperidine in ethanol, followed by the reaction of the resulting Schiff base (**51**) with the corresponding bromoketones, ω-bromoacetophenone and ω-bromo-4-chloro-acetophenone, respectively. Compounds **34** and **35** were also obtained by cyclization of **54a** and **54b** with carbon disulfide in 88.7% and 58.8% yields, respectively (Chart 7).

Antihypertensive Activity

Methods——Spontaneously hypertensive rats (SHR) utilized were male Okamoto strain rats whose systolic pressure was higher than 180 mmHg at the 18th week after birth. Systolic blood pressure was measured with a plethysmograph after preheating the tail at 37 °C for 15 min.[14] Test compounds were suspended in 0.3% (w/v) carboxymethylcellulose (CMC) aqueous solution at a concentration of 3 mg/ml, and orally administered to the rats at a dose of 1 ml/100 g body weight.

Results——As shown in Table III, the only compounds that produced relatively strong

TABLE III. Changes in Blood Pressure of Unanesthetized SHR

Compd.[a] No.	Initial level[b] (mmHg)	Maximum level[b] (mmHg)	Maximum change (Δ mmHg)	Time[c] (h)
4	210.0± 5.8	185.0± 7.6	−25.0	5
5	221.7±13.3	205.0±12.6	−16.7	5
6	205.0± 8.3	175.0±14.8	−30.0	3
7	220.0±10.0	198.3±10.9	−21.6	1.5
8	230.0±15.3	200.0± 7.6	−30	5
9	203.7± 5.4	175.0± 2.5	−28.7	5
10	221.7± 3.3	193.3± 3.3	−28.4	5
11	233.3± 1.7	210.0± 5.8	−23.3	3
12	188.3± 8.3	180.0± 5.8	−8.3	5
13	202.5± 5.3	191.7± 6.0	−10.8	5
14	—	—	—	
15	227.5 (2)	220.0± 7.0	−7.5	1.5
16	193.3±10.9	160.0±10.2	−33.3	1.5
17	210.0± 7.9	173.7± 5.0	−36.3	1.5
18	203.3± 7.3	188.3±10.1	−15.0	1.5
19	216.7± 7.3	190.0± 5.8	−26.7	5
20	211.2± 5.7	171.2± 6.2	−40.0	5
21	223.3± 7.3	193.3±11.6	−30	1.5
22	215.0±10.0	196.7± 7.3	−18.3	1.5
23	201.7± 4.4	191.7± 6.0	−10.0	1.5
24	226.7± 4.4	205.0± 5.0	−21.7	3
25	230.0± 5.0	186.7± 6.7	−43.3	5
26	196.7± 6.0	180.0± 2.9	−16.7	1.5
27	196.7± 1.7	181.7± 6.0	−15.0	5
28	197.5± 5.4	150.0± 3.5	−47.5	5
29	197.5± 4.1	180.0± 3.5	−17.5	5
30	203.7± 5.6	162.5±16.3	−41.2	3
31	200.0± 8.7	168.7±12.7	−31.3	5
32	187.5± 5.4	138.7±11.0	−48.8	1.5
33	177.5± 4.1	155.0± 4.3	−22.5	5
34	183.7± 9.9	162.5± 4.1	−21.2	1.5
35	192.5± 8.3	163.7± 4.4	−28.8	5

a) Each compound (30 mg/kg) was administered orally. *b*) Each number represents the mean ± standard error of triplicate experiments except in the case of **15** (duplicate experiments). *c*) The time until the maximum change was recorded after dosing.

hypotension in unanesthetized SHR were **28** and **32**. The present authors have previously examined the hypotensive activities of a series of quinazolinone derivatives,[1] and the hypotensions produced by the present compounds were relatively small in comparison with those of the quinazolinone derivatives.

Antiinflammatory Activity

Methods——Female Wistar strain rats weighing 90 to 110 g were used in this experiment. The animals were divided into groups of 3. All compounds were administered orally at a dose of 100, 50, or 25 mg/kg as a suspension in 0.3% CMC solution. The animals were given the test compound, and 1 h later a phlogistic agent (1% carrageenin solution) was injected *s.c.* into one hind paw. Swelling was measured 3 h after injection by using a volume differential meter, model 7101 (Ugo Basile Co., Ltd.). The volume of the injected paw was compared with that of the other paw in each rat. The swelling rate in the rats treated with the test compound was compared with that in the control (test compound-untreated) animals. From these data, the inhibition was calculated and the antiinflammatory action was thus evaluated. The smallest dose of a compound at which the inhibition was more than 30% was defined as the minimum effective dose (MED).

Results——The antiinflammatory activities of the piperidines tested are shown in Table IV. The only compounds that showed antiinflammatory activity were **28** and **33**. The MED of **28** was 100 mg/kg and that of **33** was less than 50 mg/kg. The other compounds in Tables I and II showed no activity in this test.

Antiulcer Activity

Methods——Male Wistar strain rats weighing 100 to 130 g were starved for 24 h but allowed free access to water prior to experiments. The animals were divided into groups of 2. A test compound was administered orally at a dose of 50, 25, or 10 mg/kg as a suspension in 0.3% CMC solution. Thirty minutes later, the animal was enveloped in a piece of flexible wire gauze of fine mesh so that it was completely covered, except for the tail. In order to keep it in position and to restrict its freedom of movement, staples were fixed to the wire gauze, closely following the outline of the body, without injury to the animal. The animal was immersed in water at 22 ± 1 °C for 6 h. After this procedure, the stomach was removed and cut open along the greater curvature. The severity of the hemorrhage was compared with that of the control (test compound-untreated) animals, and classified into 5 degrees (0, absence of hemorrhage; 2, moderate hemorrhage; 3, severe hemorrhage; 4, extremely severe hemorrhage. The inhibition was calculated as follows: inhibition (%) = (total scores of the control − total scores of the test aminals)/(total scores of the control) × 100. The smallest dose of the compound which gave an inhibition of more than 60% was defined as the MED.

TABLE IV. Antiinflammatory and Antiulcer Activities in the Rats

Compd. No.	MED (mg/kg *p.o.*)	
	Antiinflammatory	Antiulcer
22	—[a]	50
25	—	50
26	—	50
27	—	50
28	100	—[b]
32	—	50
33	50	—

a) No effect at the dose of 100 mg/kg. *b*) No effect at the dose of 50 mg/kg.

Results——As shown in Table IV, **22**, **25**—**27**, and **32** each showed an MED of 50 mg/kg. The others showed no antiulcer activity at this dose.

Structure–Activity Relationships

The aim of this work was to determine the effect of various heterocyclic rings at the 4-position of piperidine on the hypotensive activity. The effect of a dioxo-benzothiadiazine ring (Ib and Ic) on the hypotensive activity was disappointing except for compound **20** which exhibited moderate activity. The effect of an oxazinone ring (Id) on the hypotensive activity was similar to that of quinazolinone (Ia), that is, with respect to the substituted phenyl group of compounds with an oxazinone ring, multiple CH_3O substituents (**24**, **26**, and **27**) led to weakly active compounds. However, *para*-Cl substitution (**28**) provided one of the most active compounds in this series. Compound **25** with a 3,4-methylenedioxy group exhibited moderate activity. These results were similar to those obtained with 3-substituted quinazolinones. With respect to the compounds with a benzotriazine ring (Ie or If), 3,4-methylenedioxy substitution (**30**) in the phenyl ring led to a moderately active compound and no substitution (**32**) provided the most active compound in this series. However, *para*-Cl substitution (**31** and **33**) led to weakly active compounds, different from the case of the quinazolinone (Ia) or oxazinone (Id) derivatives. Compounds **34** and **35** with a quinazoline-thione moiety (Ig) showed reduced activities compared with the corresponding quinazolinone derivatives described in the previous report.[1)] An interesting contrast between antiinflammatory and hypotensive properties is evident when comparing the compounds with the 4-chlorophenyl group, **28** and **33**. Compound **33** exhibited a more potent antiinflammatory activity, but a less potent hypotensive activity than **28**. On the other hand, a similar relation exists between antiulcer and hypotensive properties when comparing the compounds with a 3,4-methylenedioxyphenyl group, **22** and **25**; whereas **22** exhibited about the same antiulcer activity as **25**, it exhibited a less potent hypotensive activity than **25**.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR-27G spectrometer. ^{1}H-NMR spectra were measured on a Varian T-60 spectrometer and a JEOL JNM-PS-100 spectrometer with tetramethylsilane as an internal standard.

1-(3,4-Dimethoxybenzoylmethyl)-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-3-yl)piperidine (4)——A solution of ω-bromo-3,4-dimethoxyacetophenone (3.88 g, 15 mmol), **2b** (4.56 g, 15 mmol) and TEA (3.04 g, 30 mmol) in $CHCl_3$ (100 ml) was stirred at room temperature for 2 d. The reaction mixture was washed with H_2O, dried and concentrated *in vacuo*. The oily residue was crystallized from MeOH to give crude crystals (2.57 g), which were recrystallized from EtOH to yield **4** (2.35 g, 35.2%) as crystals, mp 173.5—175.5 °C. *Anal.* Calcd for $C_{22}H_{27}N_3O_5S$: C, 59.31; H, 6.11; N, 9.43. Found: C, 59.45; H, 6.14; N, 9.17. IR (KBr): 1670, 1345, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.75 (2H, s, $-C\underline{H}_2CO-$), 3.90 and 3.93 (6H, each s, $2\times-OC\underline{H}_3$), 4.67 (2H, s, $-C\underline{H}_2Ar$), 5.83 (1H, br s, N$\underline{H}$).

Substituted 1-Benzoylmethyl-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-3-yl)piperidines (5 and 6)——These compounds were prepared in the manner described for **4**, except for the use of the appropriately substituted ω-bromoacetophenones.

1-(3,4-Methylenedioxybenzoylmethyl)-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine (8)——Similar reaction of ω-bromo-3,4-methylenedioxyacetophenone (3.64 g, 15 mmol) with **2a** (4.55 g, 15 mmol) in the presence of TEA (4.2 ml, 30 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) gave crude crystals (5.73 g), which were recrystallized from EtOH to yield **8** (4.39 g, 68.3%) as crystals, mp 185.0—187.0 °C. *Anal.* Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.59; H, 5.62; N, 9.76. Found: C, 58.81; H, 5.39; N, 9.58. IR (KBr): 1685, 1335, 1165 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (2H, s, $-C\underline{H}_2CO-$), 4.36 (2H, d, $-C\underline{H}_2Ar$, J=2 Hz), 6.12 (2H, s, $-OC\underline{H}_2O-$).

Substituted 1-Benzoylmethyl-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidines (7 and 9)——These compounds were prepared in the manner described for **8** except for the use of the appropriately substituted ω-bromoacetophenones.

1-(3,4,5-Trimethoxybenzoylmethyl)-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidine (13)——Similar reaction of ω-bromo-3,4,5-trimethoxyacetophenone (4.33 g, 15 mmol) with **2c** (4.03 g, 15 mmol) in the presence of TEA (4.2 ml, 30 mmol) in MeOH (100 ml) gave crude crystals (5.8 g, 88.0%), which were recrystallized twice from EtOH to yield **13** (2.75 g, 41.7%) as crystals, mp 152.0—153.5 °C. *Anal.* Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36.

Found: C, 65.62; H, 6.51; N, 6.23. IR (KBr): 1690, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (2H, s, $-C\underline{H}_2CO-$), 3.93 (9H, s, $3\times-OC\underline{H}_3$), 4.41 (2H, s, $-C\underline{H}_2Ar$).

Substituted 1-Benzoylmethyl-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidines (10—12 and 14)——These compounds were prepared in the manner described for **13** except for the use of the appropriately substituted ω-bromoacetophenones.

Substituted 1-Benzoylmethyl-4-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidines (15 and 16)——These compounds were prepared in the manner described for **17** except for the use of the appropriately substituted ω-bromoacetophenones.

1-(4-Chlorobenzoylmethyl)-4-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidine (17)——A solution of ω-bromo-4-chloroacetophenone (2.33 g, 10 mmol), **2d** (2.29 g, 10 mmol) and TEA (1.4 ml, 10 mmol) in MeOH (400 ml) was stirred at room temperature overnight. The resulting precipitate was collected by filtration, successively washed with MeOH, and H_2O, and then dried to give a crude product (3.42 g, 89.5%). The crude product was recrystallized from DMF–EtOH to yield **17** (2.94 g, 77.0%) as crystals, mp 168.5—170.2 °C. *Anal.* Calcd for $C_{20}H_{19}ClN_4O_2$: C, 62.75; H, 5.00; N, 14.63. Found: C, 62.60; H, 5.04; N, 14.63. IR (KBr): 1685 cm^{-1} ^{1}H-NMR ($CDCl_3$) δ: 1.75—3.4 (8H, m, piperidine $\underline{H}$), 3.83 (2H, s, $-C\underline{H}_2CO-$), 4.8—5.4 (1H, m, $>C\underline{H}N$), 7.33—8.5 (8H, m, aromatic $\underline{H}$).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazine-3-yl)piperidine (18)——$NaBH_4$ (1.5 g, 40.0 mmol) was added portionwise with ice-cooling over 1.5 h to a solution of **4** (2.66 g, 5.98 mmol) in MeOH (150 ml). After additional stirring under ice-cooling for 3 h, the reaction mixture was stirred overnight at room temperature and concentrated *in vacuo*. The residue was taken up with H_2O, and the solution was adjusted to pH 10 with 1 N aq. HCl, then extracted with ethyl acetate (AcOEt) to give an oily product, which was crystallized from AcOEt–hexane to give **18** (0.95 g, 35.5%) as crystals, mp 171.0—172.5 °C. *Anal.* Calcd for $C_{22}H_{29}N_3O_5S$: C, 59.04; H, 5.53; N, 9.39. Found: C, 59.31; H, 6.63; N, 9.09. IR (KBr): 1350, 1340, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.43 [2H, d, $-CH(OH)C\underline{H}_2-$], 3.86 (6H, s, $2\times OC\underline{H}_3$), 4.70 (2H, s, $NC\underline{H}_2Ar$).

***threo*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-3-yl)piperidine (20)**——$NaBH_4$ (2.0 g, 52.9 mmol) was added in portions to a solution of **6** (2.0 g, 4.4 mmol) in MeOH (100 ml) over 1 h at 0—10 °C. The resulting mixture was stirred overnight at room temperature and concentrated. The residue was mixed with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and concentrated to give an oily residue, which was chromatographed over silica gel with $CHCl_3$–MeOH (20 : 1, v/v). The product was crystallized from MeOH to afford **20** (0.38 g, 18.8%), mp 216.0—217.0 °C. *Anal.* Calcd for $C_{23}H_{31}N_3O_5S$: C, 59.85; H, 6.77; N, 9.10. Found: C, 59.70; H, 6.77; N, 8.86. ^{1}H-NMR ($CDCl_3$) δ: 0.72 (3H, d, $J=7$ Hz, $C\underline{H}_3CH<$), 4.12 [1H, d, $J=10$ Hz, $-C\underline{H}(OH)-$], 4.70 (2H, s, $ArC\underline{H}_2-$).

1-[2-(3,4-Methylenedioxyphenyl)-2-hydroxyethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-3-yl)piperidine (19) and 1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl]piperidine (21)——These compounds were prepared in the manner described for **18** from the corresponding amino ketones.

1-[2-(3,4-Methylenedioxyphenyl)-2-hydroxyethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine (22)——Similar reaction of **8** (3.0 g, 6.99 mmol) with $NaBH_4$ (1.5 g, 40.0 mmol) in MeOH (150 ml) gave a crude product (2.43 g, 80.6%), which was recrystallized from EtOH to yield **22** (2.03 g, 67.3%) as crystals, mp 194.5—195.0 °C. *Anal.* Calcd for $C_{21}H_{25}N_3O_5S$: C, 58.32; H, 6.06; N, 9.72. Found: C, 58.08; H, 5.86; N, 9.33. IR (KBr): 1345. 1175 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.40 (2H, s, $-C\underline{H}_2Ar$), 5.96 (2H, s, $-OC\underline{H}_2O-$), 7.6 (1H, br s, $N\underline{H}$).

***erythro*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine (23)**——$NaBH_4$ (2 g, 52.9 mmol) was added in portions to a suspension of **9** (1.7 g, 3.4 mmol as the HCl salt) in MeOH over 30 min at 0—5 °C. The resulting mixture was stirred for 5 h and concentrated. The residue was mixed with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and concentrated to give an oily product, which was crystallized as the HCl salt of **23** (1.41 g, 82.5%) containing trace amounts of the *threo* isomer (**23′**), which could not be detected by ^{1}H-NMR. The crude crystals were recrystallized from EtOH to give **23** (987 mg, 57.8%) as the HCl salt, mp 221.0—222.0 °C. *Anal.* Calcd for $C_{23}H_{31}N_3O_5S\cdot HCl$: C, 55.47; H, 6.48; N, 8.44. Found: C, 55.50; H, 6.70; N, 8.18.

The ^{1}H-NMR spectrum of this compound was measured after it had been freed from HCl. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, $J=7$ Hz, $C\underline{H}_3CH<$), 4.46 (2H, s, $ArC\underline{H}_2-$), 4.83 [1H, d, $J=4$ Hz, $-C\underline{H}(OH)-$].

***erythro*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine (23) and Its *threo* Isomer (23′)**——$NaBH_4$ (220 mg, 5.8 mmol) was added to a solution of **9** (179 mg, 0.39 mmol as the free base) in EtOH (10 ml) and the mixture was stirred for 1 h at room temperature. Then, the reaction mixture was concentrated to dryness, mixed with H_2O, and extracted with $CHCl_3$. The extracts were washed with H_2O, dried, and concentrated to give a crude oil, which was chromatographed over silica gel with AcOEt to afford **23** (33 mg, 18.5%) and **23′** (128.7 mg, 71.7%) as oily products. Compound **23′** could not be crystallized and its ^{1}H-NMR spectrum was measured. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, $J=7$ Hz, $C\underline{H}_3CH<$), 4.15 [1H, d, $J=10$ Hz, $-C\underline{H}(OH)-$], 4.44 (2H, s, $ArC\underline{H}_2-$).

Substituted 1-(2-Phenyl-2-hydroxyethyl)-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidines (24, 25, and 28)——These compounds were prepared in the manner described for **27** from the corresponding amino ketones.

***threo*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidine (26)**——$NaBH_4$ (2.0 g, 52.9 mmol) was added in portions to a suspension of **12** (2.8 g, 6.6 mmol) in MeOH (150 ml) over 1 h at 0—10 °C. Then, the resulting mixture was stirred overnight at room temperature. The precipitated crystals were collected by filtration, successively washed with MeOH and H_2O, and dried to give a crude product (1.90 g, 68.2%). The crude product was recrystallized from EtOH to give **26** (1.67 g, 60.0%), mp 201.0—202.0 °C. *Anal.* Calcd for $C_{24}H_{30}N_2O_5$: C, 67.59; H, 7.09; N, 6.57. Found: C, 67.67; H, 7.27; N, 6.52. IR (KBr): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=7 Hz, $CH_{\beta}CH<$), 3.86 and 3.90 (6H, each s, 2×$-OCH_3$), 4.20 [1H, d, J=10 Hz, $-CH(OH)-$], 4.41 (2H, s, $ArCH_2-$).

1-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxyethyl]-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidine (27)——Similar reaction of **13** (2.8 g, 6.4 mmol) with $NaBH_4$ (2.5 g, 66.1 mmol) in MeOH (150 ml) gave a crude product (1.96 g, 68.8%), which was recrystallized from EtOH to yield **27** (1.76 g, 61.8%) as crystals, mp 203.0—204.0 °C. *Anal.* Calcd for $C_{24}H_{30}N_2O_6$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.30; H, 7.00; N, 6.26. IR (KBr): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s, $-OCH_3$), 3.86 (6H, s, 2×$-OCH_3$), 4.40 (2H, s, $-CH_2Ar$).

Substituted 1-(2-Phenyl-2-hydroxyethyl)-4-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidines (29 and 30)——These compounds were prepared in the manner described for **31** from the corresponding amino ketones.

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-4-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidine (31)——$NaBH_4$ (4.0 g, 105.7 mmol) was added to a solution of **17** (1.60 g, 4.19 mmol) in EtOH (400 ml), and the mixture was stirred for 17 h at room temperature. The reaction mixture was concentrated to dryness and the residue was treated with H_2O. The precipitate was collected by filtration, successively washed with H_2O, MeOH, and ether and dried to give a crude product (1.49 g), which was recrystallized from DMF–EtOH to yield **31** (1.31 g, 81.5%) as crystals, mp 209.0—210.0 °C. *Anal.* Calcd for $C_{20}H_{21}ClN_4O_2$: C, 62.42; H, 5.50; N, 14.56. Found: C, 62.51; H, 5.51; N, 14.49. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75—3.6 (8H, m, piperidine H), 4.6—5.4 (2H, m, $-NCH<$, $-CH(OH)-$), 7.33 (4H, s, aromatic H), 7.6—8.46 (4H, m, aromatic H).

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-4-(3,4-dihydro-1,2,3-benzotriazin-3-yl)piperidine (33)——A solution of $NaNO_2$ (276 mg, 4.0 mmol) in H_2O (2 ml) was added in portions to a solution of **54b** (1.43 g, 4.0 mmol) in 12 N HCl (3 ml) and H_2O (40 ml) at 0 °C. The mixture was stirred for 5 h at 0 °C, then basified with conc. aq. NaOH, and extracted with $CHCl_3$. The extract was concentrated to give crude crystals (1.17 g), which were recrystallized from AcOEt to yield **33** (927 mg, 62.9%) as crystals, mp 164.8—166.0 °C. *Anal.* Calcd for $C_{20}H_{23}ClN_4O$: C, 64.77; H, 6.25; N, 15.11. Found: C, 64.75; H, 6.42; N, 14.83. IR (KBr): 1585, 1490, 1455, 1428 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.35 (2H, s, $-CH_2Ar$), 4.55—4.88 (1H, m, $-CHOH-$), 6.8—7.6 (8H, m, aromatic H).

1-(2-Phenyl-2-hydroxyethyl)-4-(3,4-dihydro-1,2,3-benzotriazin-3-yl)piperidine (32)——Compound **32** (979 mg, 58.8%) was prepared from **54a** (1.98 g, 5 mmol) as described for **33**. mp 119.2—120.6 °C. *Anal.* Calcd for $C_{20}H_{24}N_4O$: C, 71.19; H, 7.47; N, 16.60. Found: C, 71.28; H, 7.21; N, 16.52. IR (KBr): 1460, 1445, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.34 (2H, s, $-CH_2Ar$), 4.75 (1H, t, J=7 Hz, $-CHOH-$).

1-Benzyl-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine·HCl (37)——A solution of 1-benzyl-4-(2-aminomethylphenyl)aminopiperidine (33.0 g, 112.4 mmol), sulfamide (21.6 g, 224.8 mmol) in pyridine (250 ml) was refluxed with heating for 8 h. The reaction solution was cooled to room temperature, concentrated, and mixed with H_2O. The resulting mixture was, after being adjusted to pH 9 with conc. aq. NaOH, extracted with $CHCl_3$ and the extracts were washed with H_2O, dried and concentrated to obtain an oily residue, which was dissolved in EtOH (150 ml). This solution was mixed with 50 ml of 5.7 N HCl in AcOEt. The resulting solution was concentrated to give a crystalline residue, which was mixed with EtOH (50 ml) and collected by filtration to give crude crystals (29.0 g, 65.6%) of **37**, 200 mg of which was recrystallized from MeOH–ether to yield 86.6 mg of pure crystals, mp 235.0—239.5 °C. IR (KBr): 1330, 1165 cm^{-1}. *Anal.* Calcd for $C_{19}H_{24}ClN_3O_2S$: C, 57.93; H, 6.14; N, 10.67. Found: C, 57.67; H, 6.15; N, 10.56.

The ^{1}H-NMR spectrum of this compound was measured after it had been freed from HCl. ^{1}H-NMR ($CDCl_3$) δ: 1.66—2.33 (6H, m, piperidine H), 2.6—3.2 (2H, m, piperidine H), 3.48 (2H, s, $-CH_2Ar$), 4.0 (1H, m, piperidine H), 4.43 (2H, s, $-CH_2Ar$), 4.80 (1H, br s, NH), 7.0—7.4 (9H, m, aromatic H).

4-(3,4-Dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-1-yl)piperidine·HCl (2a)——A mixture of **37** (4.0 g, 10.2 mmol) and 10% Pd–C (1.0 g) in H_2O (40 ml) and MeOH (60 ml) was stirred at 40 °C under atmospheric pressure of hydrogen for 20 h. The catalyst was removed by filtration and the filtrate was concentrated to give a crystalline residue, which was mixed with MeOH (4 ml) and collected by filtration to obtain crude crystals (1.9 g). The crude crystals were recrystallized from MeOH–ether to yield **2a** (1.52 g, 49.1%) as crystals, mp 238.5—240.0 °C. *Anal.* Calcd for $C_{12}H_{18}ClN_3O_2S$: C, 47.44; H, 5.97; N, 13.83. Found: C, 47.32; H, 6.19; N, 13.70. IR (KBr): 1340, 1160 cm^{-1}.

The ^{1}H-NMR spectrum of this compound was measured after it had been freed from HCl. ^{1}H-NMR ($CDCl_3$) δ: 1.60—3.26 (8H, m, piperidine H), 4.40 (2H, s, $-CH_2Ar$), 6.86—7.46 (4H, m, aromatic H).

1-Benzyl-4-(3,4-dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazin-3-yl)piperidine·HCl (40)——A solution of 1-benzyl-4-(2-aminophenylmethyl)aminopiperidine (590 mg, 2.0 mmol) and sulfamide (600 mg, 6.2 mmol) in pyridine (12 ml) was refluxed with heating for 2 h. The reaction solution was cooled to room temperature and poured into 50 ml of ice water. The white crystals deposited were collected by filtration, washed with H_2O (10 ml) and dried to obtain crude crystals (520 mg, 72.8%). The crude product was dissolved in MeOH (5 ml). This solution was mixed with 5 ml of

5.7 N HCl in AcOEt, and the mixture was evaporated to give a crystalline residue, which was recrystallized from MeOH–ether to yield **40** (461 mg, 58.5%) as crystals, mp 249.0—252.0 °C. *Anal.* Calcd for $C_{19}H_{24}ClN_3O_2S$: C, 57.93; H, 6.14; N, 10.67. Found: C, 58.02; H, 6.26; N, 10.46.

The ^{1}H-NMR spectrum of this compound was measured after it had been freed from HCl. ^{1}H-NMR ($CDCl_3$) δ: 1.37—2.27 (6H, m, piperidine H), 2.66—3.10 (2H, m, piperidine H), 3.42 (2H, s, $-CH_2Ar$), 3.83 (1H, m, NCH<), 4.62 (2H, s, $-CH_2Ar$), 5.76 (1H, s, NH), 6.33—7.46 (9H, m, aromatic H).

4-(3,4-Dihydro-2,2-dioxo-1*H*-2,1,3-benzothiadiazine-3-yl)piperidine·HCl (2b)——A mixture of **40** (7.14 g, 20 mmol) and 10% Pd–C (2 g) in 1 N HCl (20 ml), H_2O (60 ml) and MeOH (120 ml) was stirred at 40 °C under atmospheric pressure of hydrogen for 20 h. The catalyst was removed by filtration and the filtrate was concentrated to obtain a crude product (5.0 g, 82.3%), which was recrystallized from MeOH to yield **2b** (3.83 g, 63.1%) as crystals, mp 259.0—262.0 °C. *Anal.* Calcd for $C_{12}H_{18}ClN_3O_2S$: C, 47.44; H, 5.97; N, 13.83. Found: C, 47.27; H, 6.02; N, 13.58. IR (KBr): 1330, 1155 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.47—2.20 (4H, m, piperidine H), 2.60—4.35 (5H, m, piperidine H), 4.63 (2H, s, $-CH_2Ar$), 6.60—7.40 (4H, m, aromatic H), 9.10 (2H, br s, NH·HCl), 10.46 (1H, s, SO_2NH).

1-Benzyl-4-(2-hydroxyphenylmethyl)aminopiperidine (43)——A solution of salicylaldehyde (9.76 g, 80 mmol) and 1-benzyl-4-aminopiperidine (15.1 g, 80 mmol) in MeOH (100 ml) was stirred at room temperature for 1 h and then $NaBH_4$ (3.2 g, 85 mmol) was added portionwise with ice-cooling over 1.5 h. The mixture was further stirred at room temperature for 2 h and then poured into ice-water. The light yellow crystals deposited were separated by filtration and then dissolved in AcOEt (200 ml). The solution was washed with brine, dried and subsequently concentrated to obtain crude crystals (19.0 g, 80.4%), which were recrystallized from EtOH to yield **43** (12.0 g, 50.8%) as crystals, mp 92.5—93.0 °C. *Anal.* Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 76.97; H, 8.10; N, 9.37. ^{1}H-NMR ($CDCl_3$) δ: 3.45 (2H, s, $-CH_2C_6H_5$), 3.96 (2H, s, $-CH_2Ar$).

1-Benzyl-4-(2-oxo-3,4-dihydro-2*H*-1,3-benzoxazine-3-yl)piperidine (44)——A mixture of **43** (17.7 g, 60 mmol) and 1,1′-carbonyldiimidazole (19.4 g, 120 mmol) in THF (150 ml) was stirred for 2 h, refluxed for 30 min, then concentrated under reduced pressure. The resulting crystalline residue was mixed with H_2O and separated by filtration to obtain crude crystals (18.0 g, 93.4%). The crude crystals were recrystallized from AcOEt–hexane to yield **44** (14.9 g, 77.3%), mp 106.0—107.0 °C. *Anal.* Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.80; H, 6.98; N, 8.74. IR (KBr): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.50 (2H, s, $-CH_2C_6H_5$), 4.36 (2H, s, $-CH_2Ar$).

4-(2-Oxo-3,4-dihydro-2*H*-1,3-benzoxazin-3-yl)piperidine·HCl (2c)——A mixture of **44** (16.0 g, 50 mmol) and 10% Pd–C (4.0 g) in H_2O (150 ml), 1 N HCl (50 ml) and MeOH (300 ml) was stirred at 40 °C under atmospheric pressure of hydrogen overnight. The catalyst was removed by filtration and the filtrate was concentrated to give a crystalline residue, which was mixed with MeOH and collected by filtration to obtain **2c** (11.4 g, 84.9%) as crystals, mp 288.0—290.0 °C. *Anal.* Calcd for $C_{13}H_{17}ClN_2O_2$: C, 58.10; H, 6.38; N, 10.42. Found: C, 57.92; H, 6.40; N, 10.26. IR (KBr): 1695 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.53 (2H, s, $-CH_2Ar$).

1-Benzyl-4-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidine (46)——A solution of $NaNO_2$ (10.0 g, 144 mmol) in H_2O (60 ml) was added in portions to a solution of 1-benzyl-4-(2-aminobenzoyl)aminopiperidine (44.4 g, 144 mmol) in 12 N HCl (48 ml) and H_2O (600 ml) at 0 °C over 30 min. After additional stirring for 2.5 h, the solution was adjusted to pH 9 with conc. aq. NaOH and extracted with $CHCl_3$. The extracts were washed with brine, dried, and concentrated *in vacuo* to give a crystalline residue, which was mixed with ether (50 ml) and collected by filtration to yield crude crystals (36.2 g). The crude crystals were recrystallized from EtOH to yield **46** (33.5 g, 72.9%) as crystals, mp 138.2—139.0 °C cm^{-1}. Calcd for $C_{19}H_{20}N_4O$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.46; H, 6.28; N, 17.40. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (2H, s, $-CH_2C_6H_5$), 4.70—5.36 (1H, m, >CHN).

4-(3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)piperidine (2d)——A mixture of **46** (12.8 g, 40 mmol), acetic acid (2.4 g, 40 mmol) and 10% Pd–C (4.0 g) in H_2O (160 ml) and MeOH (240 ml) was stirred at 40 °C under atmospheric pressure of hydrogen for 3 h. The catalyst was filtered off. The filtrate was concentrated to 100 ml and basified with conc. aq. NaOH. Precipitated crystals were collected by filtration and washed with H_2O to give **2d** (5.0 g, 54.1%). This product (100 mg) was recrystallized from EtOH to give pure crystals (64 mg) for analysis. mp 235.0—236.9 °C. *Anal.* Calcd for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.68; H, 6.20; N, 24.16. IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (1H, br s, NH), 1.85—2.45 (4H, m, piperidine H), 2.70—3.50 (4H, m, piperidine H), 4.95—5.35 [1H, m, $-CH_2CH(N<)CH_2-$], 7.66—8.43 (4H, m, aromatic H).

1-Benzyl-4-(3,4-dihydro-1,2,3-benzotriazin-3-yl)piperidine (47)——Crude crystals (6.1 g) of **47** were prepared from **39** (10.6 g, 26.2 mmol) as described for **46**. This crude product was mixed with *n*-hexane (180 ml), refluxed with heating and filtered. The filtrate was evaporated to give a crystalline residue (5.0 g), which was recrystallized from *n*-hexane to yield **47** (3.0 g, 37.4%) as crystals, mp 81.8—82.5 °C. *Anal.* Calcd for $C_{19}H_{22}N_4$: C, 74.49; H, 7.24; N, 18.28. Found: C, 74.28; H, 7.30; N, 18.30. ^{1}H-NMR ($CDCl_3$) δ: 3.53 (2H, s, $-CH_2C_6H_5$), 4.33 (2H, s, >NCH_2Ar).

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-4-(2-nitrophenylmethyl)aminopiperidine·2HCl (53b)——4-Choloro-ω-bromoacetophenone (23.3 g, 100 mmol) was added to a mixture of 4-aminopiperidine·2HCl (16.33 g, 100 mmol), 2-nitrobenzaldehyde (15.11 g, 100 mmol) and TEA (42 ml, 300 mmol) in MeOH (100 ml), which had been stirred at room temperature for 1 h. The reaction mixture was stirred at room temperature for 3.5 h and then $NaBH_4$ (15 g, 397 mmol) was added portionwise with ice-cooling over 1.5 h. After further stirring for 17 h, the mixture was worked up as usual to give an oily product, which was crystallized from MeOH–AcOEt as the 2HCl salt, **53b** (30.9 g, 67.1%).

This product (200 mg) was recrystallized from EtOH–H_2O–AcOEt to give pure crystals (111 mg) for analysis. mp 247.5—248.8 °C. *Anal.* Calcd for $C_{20}H_{26}Cl_3N_3O_3$: C, 51.90; H, 5.66; N, 9.08. Found: C, 51.72; H, 5.63; N, 9.16. ^{1}H-NMR (CD_3OD+D_2O) δ: 4.43 (2H, s, $-CH_2Ar$), 5.03 (1H, t, J=6 Hz, $-CHOH-$).

1-(2-Phenyl-2-hydroxyethyl)-4-(2-nitrophenylmethyl)aminopiperidine·2HCl (53a)——Crude crystals (24.8 g, 58.3%) of **53a** were prepared from 4-aminopiperidine·2HCl (16.3 g, 100 mmol), 2-nitrobenzaldehyde (15.1 g, 100 mmol) and ω-bromoacetophenone (19.9 g, 100 mmol) as described for **53b** and used for the preparation of **54a** without further purification.

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-4-(2-aminophenylmethyl)aminopiperidine·2HCl (54b)——A mixture of **53b** (9.20 g, 20 mmol) and Raney nickel (3.3 g) in H_2O (45 ml) and MeOH (150 ml) was stirred at room temperature under atmospheric pressure of hydrogen. After absorption of 1.4 l of hydrogen, the catalyst was removed by filtration and the filtrate was concentrated to dryness and treated with MeOH to give **54b** (2.86 g, 33.2%) as crystals. This product (200 mg) was recrystallized from EtOH–H_2O–AcOEt to afford pure crystals (25 mg) for analysis. mp 214.0—215.5 °C. *Anal.* Calcd for $C_{20}H_{28}Cl_3N_3O$: C, 55.50; H, 6.52; N, 9.71. Found: C, 55.21; H, 6.53; N, 9.74.

1-(2-Phenyl-2-hydroxyethyl)-4-(2-aminophenylmethyl)aminopiperidine·2HCl (54a)——A mixture of **53a** (18.0 g, 42.4 mmol) and 10% Pd–C (1.7 g) in MeOH (500 ml) was stirred under atmospheric pressure of hydrogen. After absorption of sufficient hydrogen (3.2 l), the catalyst was removed by filtration and the filtrate was concentrated to give **54a** (9.29 g, 55.4%) as crystals. This product (1 g) was recrystallized from MeOH to afford pure crystals (648 mg) for analysis. mp 200.5—202.0 °C. *Anal.* Calcd for $C_{20}H_{29}Cl_2N_3O$: C, 60.30; H, 7.34; N, 10.55. Found: C, 60.23; H, 7.50; N, 10.48.

1-(2-Phenyl-2-hydroxyethyl)-4-(1,2,3,4-tetrahydro-2-thio-quinazolin-3-yl)piperidine (34)——A solution of **53a** (as the free base) (1.80 g, 5.59 mmol) and carbon disulfide (CS_2) (15.8 ml, 263 mmol) in EtOH (50 ml) was refluxed with stirring for 5 h and allowed to stand at room temperature overnight. Precipitated crystals were collected by filtration and recrystallized from DMF–MeOH to yield **34** (1.81 g, 88.7%) as crystals, mp 248.5—250.0 °C. *Anal.* Calcd for $C_{21}H_{25}N_3OS$: C, 68.63; H, 6.86; N, 11.43. Found: C, 68.43; H, 7.00; N, 11.17. ^{1}H-NMR (DMSO-d_6) δ: 4.43 (2H, s, $-CH_2Ar$), 4.56—4.86 (1H, m, $-CHOH-$), 6.80—7.50 (9H, m, aromatic H).

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-4-(1,2,3,4-tetrahydro-2-thioxo-quinazolin-3-yl)piperidine (35)——Similar reaction of **54b** (as the free base) (1.50 g, 4.21 mmol) with CS_2 (20 ml, 332 mmol) in EtOH (50 ml) gave crude crystals (1.39 g), which were recrystallized to yield **35** (986 mg, 58.8%) as crystals, mp 199.0—200.9 °C. *Anal.* Calcd for $C_{21}H_{24}ClN_3OS$: C, 62.75; H, 6.02; N, 10.45. Found: C, 62.51; H, 6.01; N, 10.56. ^{1}H-NMR ($CDCl_3$) δ: 4.42 (2H, s, $-CH_2Ar$), 4.60—4.90 (1H, m, $-CHOH-$), 6.66—7.43 (8H, m, aromatic H), 8.85 (1H, br s, NH).

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