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Synthesis of 1- and 3-(1-Substituted 4-Piperidinyl)-1,2,3,4-tetrahydro-2-oxoquinazolines as Potential Antihypertensive Agents

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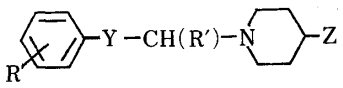
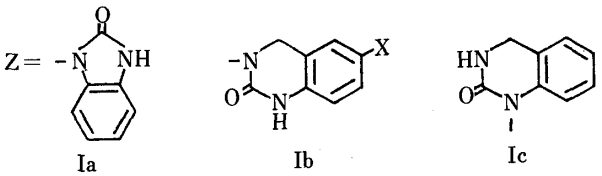
A series of 1- and 3-(1-substituted 4-piperidinyl)-1,2,3,4-tetrahydro-2-oxoquinazolines were synthesized and tested for antihypertensive activity. Among the compounds tested, 1-(2-hydroxy-2-phenethyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine derivatives were generally the most effective in lowering blood pressure in the spontaneous hypertensive rat model. Of these, 1-[2-(4-chlorophenyl)-2-hydroxyethyl]-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (**26**) (KF5908) seemed the most promising.

Keywords——antihypertensive activity; piperidine; quinazoline; alpha adrenergic blocking; reductive cleavage

Appropriately substituted piperidines often exhibit potent antihypertensive activity.[1,2] An earlier report from this laboratory described the preparation and antihypertensive activity of a series of 1-arylalkyl-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidines (Ia).[3] In an extension of that work we have found that the related 1-arylalkyl-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine derivatives also exhibit interesting antihypertensive activity. In this paper we wish to describe the synthesis and biological activity of a series of 1-arylalkylpiperidine derivatives with a quinazolinone nucleus (Ib, Ic).



Y=CO, $COCH_2$, CH(OH), $CH(OH)CH_2$



Ia Ib Ic

Chart 1

Chemistry

The 1-benzoylalkylpiperidine derivatives (**3**) listed in Tables I and II were prepared by the reaction of a piperidine intermediate, **2a**, **2b**, or **2c**, with the appropriate bromoketone by using triethylamine (TEA) as a base in dimethylformamide (DMF) or ethanol (Chart 2).

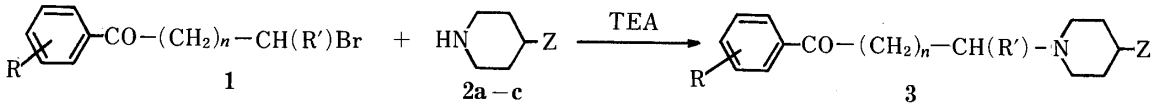
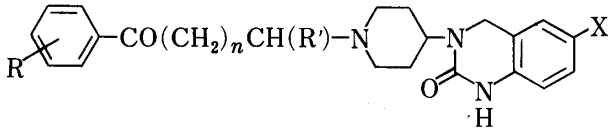


Chart 2

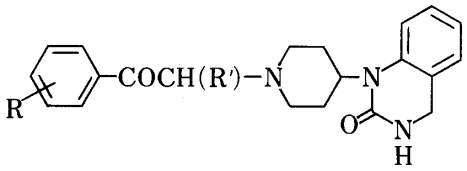
TABLE I.



Compd.	R	R′	X	*n*	Crystn. solvent	mp (°C)	% yield	Formula[a]
4	3,4-DiMeO	H	H	0	EtOH	152.0—156.0	77.4	$C_{23}H_{27}N_3O_4$
5	3,4-(OCH_2O)	H	H	0	EtOH	187.0—189.5	80.9	$C_{22}H_{23}N_3O_4$
6	3,4-DiMeO	Me	H	0	EtOH	173.0—174.5	80.4	$C_{24}H_{29}N_3O_4$
7	H	H	H	0	$CHCl_3$–EtOH	171.0—172.0	64.9	$C_{21}H_{23}N_3O_2$
8	4-MeO	H	H	0	$CHCl_3$–EtOH	199.0—201.0	66.5	$C_{22}H_{25}N_3O_3 \cdot 0.25H_2O$
9	3-Cl	H	H	0	$CHCl_3$–EtOH	172.0—174.5	50.3	$C_{21}H_{22}ClN_3O_2$
10	4-Cl	H	H	0	$CHCl_3$–EtOH	195.0—197.0	55.8	$C_{21}H_{22}ClN_3O_2$
11	3,4-DiCl	H	H	0	$CHCl_3$–EtOH	198.0—205.0	48.0	$C_{21}H_{21}Cl_2N_3O_2$
12	H	H	H	1	MeOH	160.9—163.2	70.3	$C_{22}H_{25}N_3O_2$
13	4-Cl	H	Cl	0	EtOH	Crude crystals	83.0	
14	3,4-DiMeO	H	Cl	0	EtOH	184.0—186.5	82.2	$C_{23}H_{26}ClN_3O_4$

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.

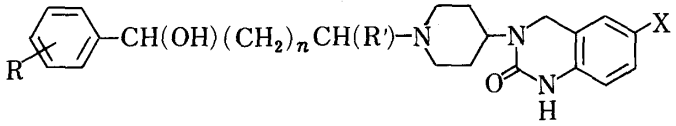


Compd.	R	R′	Crystn. solvent	mp (°C)	% yield	Fromula[a]
15	3,4-DiMeO	H	EtOH	146.0—148.0	52.7	$C_{23}H_{27}N_3O_4 \cdot 0.5C_2H_5OH$
16	3,4-(OCH_2O)	H	EtOH	171.0—173.0	65.6	$C_{22}H_{23}N_3O_4 \cdot 0.5C_2H_5OH$
17	3,4-DiMeO	Me	EtOH	154.0—156.0	58.8	$C_{24}H_{29}N_3O_4$
18	4-Cl	H	EtOH	Crude crystals	83.4	—

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.

The compounds listed in Tables III and IV were synthesized by reduction of the corresponding 1-benzoylalkylpiperidine derivatives with $NaBH_4$. Reduction of the 1-(1-benzoylethyl) derivative **6** with $NaBH_4$ in ethanol at room temperature gave diastereomixtures of the corresponding benzyl alcohol derivatives (**21** and **21′**). These diastereomixtures were separated by chromatography on silica gel with $CHCl_3$–MeOH (10 : 1, v/v) to give **21** and **21′** in 64.6 and 20.7% yields, respectively. Analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of **23** and **23′** in chloroform-*d* medium permitted assignment of the configurations. The coupling constants of the benzylic protons of **21** and **21′** were 10 and 4 Hz, respectively. These are comparable with the values of 8.3 and 4.0 Hz for pseudoephed-

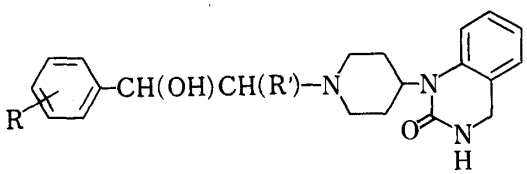
TABLE III.



Compd.	R	R′	X	*n*	Crystn. solvent	mp (°C)	% yield	Formula[c]
19	3,4-DiMeO	H	H	0	EtOH	196.5—197.1	66.4	$C_{23}H_{29}N_3O_4$
20	3,4-(OCH_2O)	H	H	0	EtOH	229.5—231.5	68.2	$C_{22}H_{25}N_3O_4$
21	3,4-DiMeO	Me[a]	H	0	EtOH	220.0—223.0	64.6	$C_{24}H_{31}N_3O_4$
22	3,4,5-TriMeO	H	H	0	$CHCl_3$–EtOH	236.0—238.5	56.4[b]	$C_{24}H_{31}N_3O_5$
23	H	H	H	0	$CHCl_3$–EtOH	219.5—221.0	63.4	$C_{21}H_{25}N_3O_2$
24	4-MeO	H	H	0	$CHCl_3$–EtOH	233.0—235.0	52.0	$C_{22}H_{27}N_3O_3$
25	3-Cl	H	H	0	$CHCl_3$–EtOH	227.5—229.5	57.4	$C_{21}H_{24}ClN_3O_2$
26	4-Cl	H	H	0	$CHCl_3$–EtOH	240.0—241.0	58.5	$C_{21}H_{24}ClN_3O_2$
27	3,4-DiCl	H	H	0	$CHCl_3$–EtOH	246.5—248.0	56.6	$C_{21}H_{23}Cl_2N_3O_2$
28	H	H	H	1	EtOH	189.0—189.8	72.9	$C_{22}H_{27}N_3O_2$
29	4-Cl	H	Cl	0	EtOH	221.8—224.0	78.4	$C_{21}H_{23}Cl_2N_3O_2$
30	3,4-DiMeO	H	Cl	0	EtOH	201.2—203.0	65.0	$C_{23}H_{28}ClN_3O_4$

a) *threo* isomer. *b*) This is the yield from **2a**. The 3,4,5-trimethoxybenzoylmethyl derivative, which is the intermediate of **22**, was reduced with $NaBH_4$ without isolation. *c*) All compounds were analyzed for C, H, and N, and analytical values were within ±0.3% of the calculated values for these formulas.

TABLE IV.



Compd.	R	R′	Crystn. solvent	mp (°C)	% yield	Formula[a]
31	3,4-DiMeO	H	EtOH	173.5—175.0	55.9	$C_{23}H_{29}N_3O_4$
32	3,4-(OCH_2O)	H	EtOH	193.0—194.5	64.1	$C_{22}H_{25}N_3O_4$
33	3,4-DiMeO	Me	$CHCl_3$–EtOH	243.0—244.0	70.0	$C_{24}H_{31}N_3O_4$
34	4-Cl	H	DMF–EtOH	187.0—189.0	71.3	$C_{21}H_{24}ClN_3O_2$

a) All compounds were analyzed for C, H, and N, and analytical values were within ±0.3% of the calculated values for these formulas.

rine (*threo*) and ephedrine (*erythro*).[4] Similar values have been found for other epimeric amino alcohols.[5] The virtual identity of the coupling constants of these compounds supported the assignment of *threo* configuration to **21** and *erythro* to **21′**. Compound **33** was also obtained by similar treatment of **17**, but an attempt to isolate its stereoisomer failed. Compound **33** was converted to the acetate (**33**-Ac) to determine its configuration. The coupling constant of the benzylic proton of **33**-Ac was 9 Hz and this supported the assignment of *threo* configuration to **33** as well as **21**.

Key intermediates, **2a**, **2b**, and **2c**, have not been reported, although a general method for obtaining 1,2,3,4-tetrahydro-2-oxoquinazoline derivatives was described by Coyne *et al.*[6] These compounds were prepared as shown in Charts 3, 4 and 5. The quinazolinone **2a** was prepared in five steps from commercially available 2-nitrobenzaldehyde (**35**) and 1-benzyl-4-aminopiperidine (**36**), as shown in Chart 3.

An intermediate, 1-benzyl-4-(2-nitrophenylmethyl)aminopiperidine (**37**), was prepared

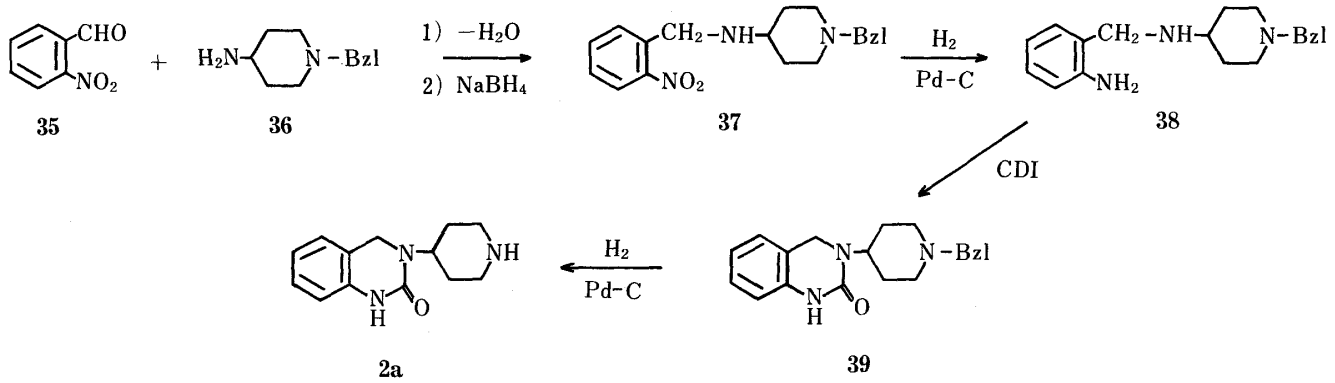


Chart 3

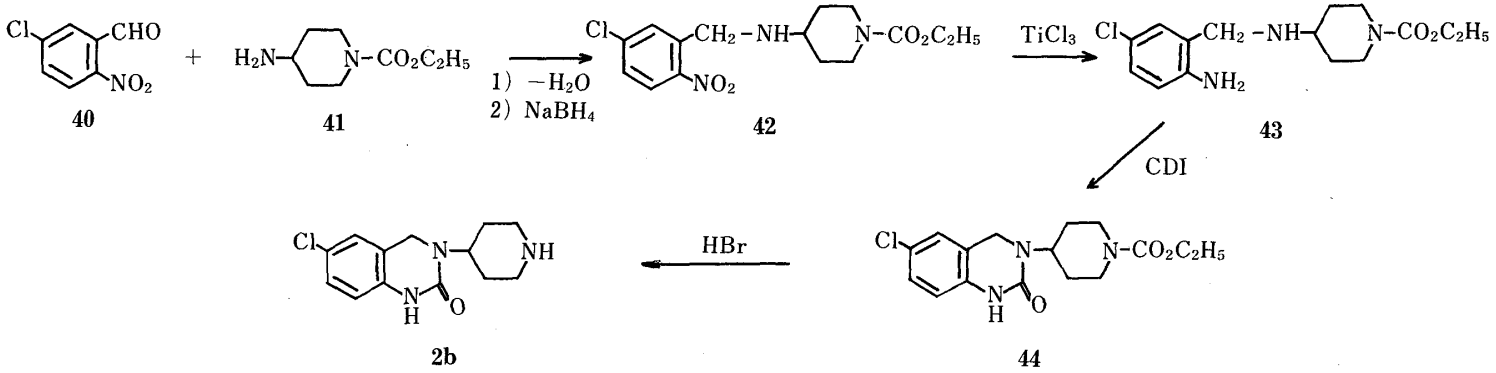
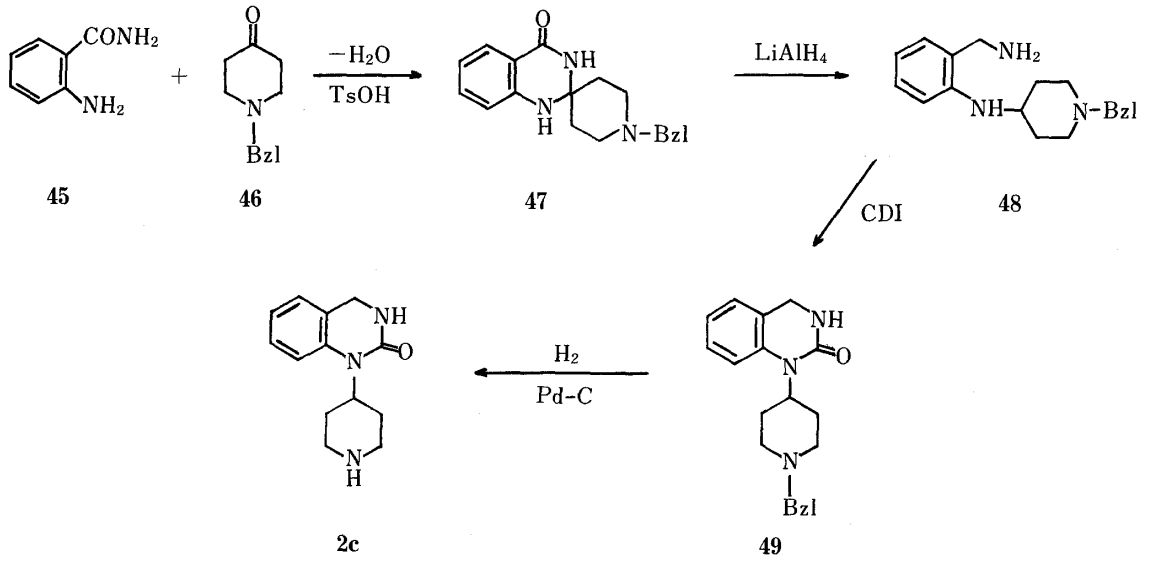


Chart 4

by reaction of 2-nitrobenzaldehyde (**35**) with 1-benzyl-4-aminopiperidine (**36**), followed by reduction with $NaBH_4$ of the resulting Schiff base. Compound **37** was converted to **38** by catalytic hydrogenation of the nitro group over 10% Pd–C at room temperature. Cyclization of the diamine **38** with *N,N'*-carbonyldiimidazole (CDI) gave 3-(1-benzyl-4-piperidinyl)quinazolinone (**39**). Debenzylation of **39** by catalytic hydrogenation over 10% Pd–C at room temperature in 50% CH_3CO_2H–CH_3OH for 4 d or at 40 °C in the presence of 1 eq of HCl in 60% aq. CH_3OH for 5 h gave 3-(4-piperidinyl)quinazolinone (**2a**).

The second quinazolinone (**2b**) was also prepared from 2-nitro-5-chlorobenzaldehyde (**40**) and 1-ethoxycarbonyl-4-aminopiperidine (**41**) as well as **2a** as shown in Chart 4. Reduction of the intermediate (**42**) to the diamine (**43**) was achieved by treatment with $TiCl_3$ and elimination of the ethoxycarbonyl group of **44** was carried out by treatment with 47% aq. HBr.

The third quinazolinone (**2c**) was synthesized in 4 steps from 2-aminobenzamide (**45**) and 1-benzyl-4-piperidone (**46**), as shown in Chart 5. In the synthetic route employed for the

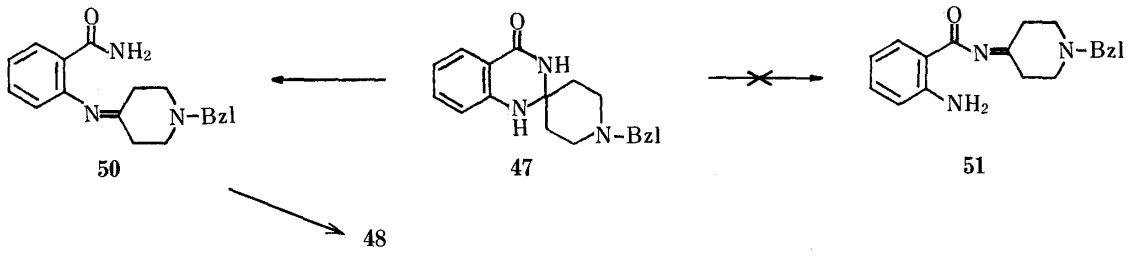


45 46 47 48 2c 49

Chart 5

preparation of **2c**, the diamine **48** was obtained by reductive cleavage of the dihydro-4-quinazolinone (**47**),[7] which was prepared by condensation of 2-aminobenzamide (**45**) with 1-benzyl-4-piperidone (**46**) in benzene using *p*-toluenesulfonic acid as a catalyst.

Mono- or disubstituted 4-quinazolinones are known to undergo reductive ring cleavage at the 1,2- or 2,3-bond *via* the intermediacy of the dihydro derivatives on treatment with metal hydrides, as shown in Chart 6.[8–10] However, metal hydride reduction of dihydro-4-

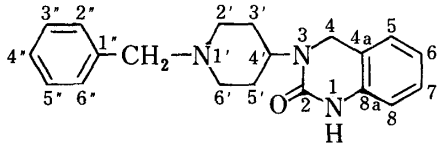


50 47 51

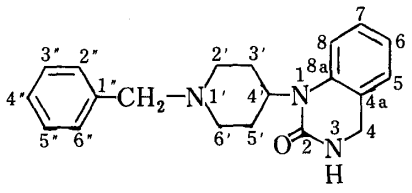
Chart 6

quinazolinones with no substituent at either of the nitrogen atoms has not been reported. We expected that the diamine (**48**) might be obtained by reductive cleavage of the 2,3-bond of **47**, since it seemed likely that the reaction would proceed *via* the intermediacy of the more stable Schiff base (**50**) by elimination of the amide rather than that of **51**, as shown in Chart 6. This was achieved selectively by treatment with $LiAlH_4$ in dioxane under reflux for 6 h in 51.6% yield. The diamine (**48**) thus obtained was converted to **2c** as well as the diamine **2a**. The structure of **48** was established by confirming the structure of **49**, obtained by the cyclization of **48** with CDI, on the basis of its spectral similarity to **39**. The physical properties of **39** and **49** are summarized in Table V. Compound **49** had the molecular formula $C_{20}H_{23}N_3O$ on the basis of its elemental analysis data and mass spectrum (MS) $m/e=321$ (M^+), and showed a strong absorption band due to the ureido group (1670 cm^{-1}) in its infrared (IR) spectrum. In its ^{1}H-NMR spectrum, a doublet peak observed at δ 4.26 (2H, $J=2.0$ Hz) assignable to the methylene protons of the quinazolinone ring was converted to a singlet peak upon deuterium oxide exchange, indicating coupling with the N–H. Furthermore, the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum showed sixteen signals which were assigned as shown in Table V. From these spectral data, the structure of **49** was assigned as 1-benzyl-4-

Table V



39



49

	39	**49**
IR	1665 cm^{-1} (C=O)	1670 cm^{-1} (C=O)
MS	321 (M^+)	321 (M^+)
^{1}H-NMR ($CDCl_3$)	1.50—2.30 (6H, m, piperidine H), 2.84—3.08 (2H, m, piperidine H), 3.52 (2H, s, $ArCH_2N$), 4.20—4.60 [1H, m, $-CH_2CH(N)CH_2-$], 4.34 [2H, s, $ArCH_2N(C=O)-$], 6.72—7.37 (9H, m, aromatic H), 8.62 [1H, br s, $-NH(C=O)-$]	1.68—3.06 (8H, m, piperidine H), 3.58 (2H, s, $ArCH_2N$), 3.94—4.11 [1H, m, $-CH_2CH(N)CH_2-$], 4.26 [2H, d, $J=2.0$ Hz, $ArCH_2NH(C=O)$], 4.98 (1H, br s, NH), 6.95—7.39 (9H, m, aromatic H)

^{13}C-NMR ($CDCl_3$)	Carbons	Chemical shifts	Carbons	Chemical shifts
	2	154.908	2	156.687
	4	42.888	4	43.058
	4a	117.893	4a	123.010
	5	127.007	5	127.031
	6	121.573	6	122.036
	7	128.055	7	127.811
	8	113.556	8	114.871
	8a	137.168	8a	139.605
	4′	51.246	4′	55.389
	3′ 5′	28.510	3′ 5′	28.876
	2′ 6′	52.927	2′ 6′	53.707
	1″	138.387	1″	138.362
	2″ 6″	129.078	2″ 6″	129.127
	3″ 5″	128.176	3″ 5″	128.225
	4″	125.325	4″	125.740
	7″	62.943	7″	62.796

(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidine.

Biological Results

The compounds listed in Tables I to IV were examined for hypotensive activities. For this purpose, blood pressure was measured in unanesthetized spontaneously hypertensive rats (SHR) and in anesthetized normotensive rats. The SHR utilized were male Okamoto strain rats whose systolic pressure was higher than 180 mmHg at the 18th week. Systolic blood pressure was measured with a plethysmograph after preheating the tail at 37 °C for 15 min.[11] 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.

Some of the compounds were tested for hypotensive activities in anesthetized normotensive animals. Male Wistar strain rats weighing 250—320 g were anesthetized with urethane (600 mg/kg, *i.p.*) and alpha-chloralose (60 mg/kg, *i.p.*). Arterial blood pressure was measured from the left common carotid artery by means of a pressure transducer. Heart rate was also measured with a cardiotachometer triggered by pressure pulses. Test compounds were

TABLE VI. 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	206.7± 7.3		178.3± 1.7	−28.4	5
5	200	(2)	172.5	−27.5	5
6	196.7± 4.4		178.3± 4.4	−18.4	1.5
7	183.3± 6.1		160.0± 9.4	−23.3	3.5
8	222.5	(2)	185.0	−37.5	5.5
9	190.0± 4.0		173.3± 3.0	−16.7	5.5
10	200.0±10.7	(4)	183.7± 3.1	−16.3	1.5
11	180.0± 4.7		153.3± 9.9	−26.7	5.5
12	178.2± 2.0		146.2± 8.5	−32.0	3
15	185.0± 3.7	(5)	178.0± 7.2	−7.0	1.5
d)	200	(2)	142.5	−57.0	1.5
16	201.7± 7.3		185.0± 2.9	−16.7	1.5
17	198.3± 9.3		171.7± 6.0	−26.6	1.5
19	201.7± 7.3		170.0± 5.8	−31.7	5
	224.0± 6.8	(5)	183.0± 5.1	−41.0	3
20	213.3± 1.7		171.7± 1.7	−41.6	5
	210.0± 8.7		175.0± 2.9	−35.0	5
	216.0± 7.3	(5)	160.0± 5.9	−56.0	7
21	206.7± 8.8		183.3± 8.8	−23.4	1.5
22	200.0± 5.8		171.7± 1.7	−28.3	1.5
23	226.6± 9.2		171.6±10.8	−55.0	3.5
24	215	(2)	160	−55.0	3.5
25	183.3± 5.1		156.6± 9.9	−26.7	3
26	201.2± 9.2	(4)	161.2± 6.1	−40.0	3.5
27	195.0± 8.5		150.0± 6.2	−45.0	5.5
28	178.3± 5.9		136.7± 7.2	−41.6	1.5
29	210.0± 7.0		168.7± 1.0	−41.3	3
31	211.7± 6.0		201.7± 6.0	−10.0	3
32	200.0± 2.9		181.7± 1.7	−18.3	1.5
33	195.0± 5.0		180.0±15.3	−15.0	1.5
34	197.5± 4.1		162.5± 7.3	−35.0	5

a) Each compound (30 mg/kg) was administered orally, unless otherwise noted. *b)* Each number represents the mean±standard error of triplicate experiments except where otherwise noted in parentheses. *c)* The time until the maximum change was recorded after dosing. *d)* 100 mg/kg *p.o.*

dissolved or suspended at a concentration of 3 mg/ml in 0.3% (w/v) CMC saline to which a minimum quantity of Tween 80 was, if necessary, added, and intraperitoneally administered to the rats at a dose of 1 ml/100 g body weight.

All of the compounds tested produced relatively strong hypotension in unanesthetized SHR. The hypotensive potencies of the present compounds are shown in Table VI. Among these compounds, those listed in Table III (3-substituted quinazoline derivatives which are amino alcohols) showed the greatest hypotensive activities, followed by the compounds in Table I (3-substituted quinazoline derivatives which are amino ketones). Hypotensive effects produced by the compounds in Tables II and IV (1-substituted quinazoline derivatives) were relatively small.

From Table VI it can be seen that many 3-[1-(ω-aryl-ω-hydroxyalkyl)-4-piperidinyl]-1,2,3,4-tetrahydro-2-oxo-quinazolines with a wide range of aryl groups were active in lowering blood pressure in the SHR screen. As regards the substituted phenyl group of these compounds, multiple CH_3O substituents (**19**, **21**, and **22**) led to weakly active compounds. However, a single CH_3O substitution (*para* position) (**24**) provided the most potent antihypertensive activity in this series. Compound **20** with a 3,4-methylenedioxy group appeared to retain the activity. With respect to Cl substituents, *meta* substitution (**25**) led to a weakly active compound, but *para* substitution (**26**) or 3,4-disubstitution (**27**) provided about the same antihypertensive activity as that of the compound with an unsubstituted phenyl group (**23**). As regards modification in the ethyl bridge connecting the aryl group and the piperidine ring, the presence of CH_3 in the ethyl bridge (**21**) reduced the activity, as compared with the corresponding compound (**19**). However, lengthening of the chain between the rings from two to three carbons (**28**) provided about the same antihypertensive activity as that of the corresponding compound (**23**). With respect to the effect of substituents in the quinazoline portion of the molecule on hypotensive activity, Cl at the 6 position (**29**) resulted in a compound with the same activity as the corresponding compound without this substituent (**26**).

Some of the compounds were selected from those listed in Tables I and III, and their hypotensive activities were examined in anesthetized normotensive animals. The results are shown in Table VII. As shown, all of the compounds tested produced decreases in the blood pressure of normotensive animals. As in the case of SHR, the hypotensive potencies of the compounds in Table III tended to be higher than those of the compounds in Table I.

Table VII. Changes in Blood Pressure of Anesthetized Normotensive Rats[a]

Compd. No.	No. of animals	Initial level	Changes in blood pressure (mmHg)					
			10	30	60	120	180	240 (min)
7	3	107± 8	−21±11	−21±11	−15±10	−3± 6	−2±3	−7±11
8	3	112±11	−3± 3	−8± 4	−6± 6	−2± 4	−21±7	−19± 5
9	3	115± 3	−34± 1	−36± 1	−16± 9	−21± 3	−26±6	−15± 9
10	4	108± 8	−8± 2	−20± 6	−20± 8	−2±10	−10±7	−3±10
11	4	104± 4	−2± 4	−8± 7	0± 6	0±13	−6±9	−1± 6
14	4	101± 4	−8± 4	−10± 3	0± 6	+10± 8	−1±3	−16± 4
23	5	109± 5	−32± 3	−32± 4	−27± 5	−18± 9	−10±6	−7± 3
24	5	114± 6	−25± 6	−38± 7	−38± 8	−33± 8	−31±7	−24± 5
25	3	107± 4	−30± 5	−26± 6	−15±15	−9± 6	−25±3	−12± 7
26	6	109± 4	−28± 2	−38± 4	−29± 8	−18± 7	−20±4	−11± 5
27	8	109± 3	−10± 4	−13± 6	−6± 5	−10± 8	−9±9	−6± 5

a) Each number represents the mean ± standard error. Each compound was administered intraperitoneally at a dose of 30 mg/kg.

Table VIII. Changes in Heart Rate of Anesthetized Normotensive Rats[a]

Compd. No.	No. of animals	Initial levels	Changes in heart rate (beats/min)					
			10	30	60	120	180	240 (min)
7	3	443±32	−96±38	−97±56	−29±72	0±13	−72±21	−13±71
8	3	414±40	+2± 7	−2± 8	+13±21	+3±14	−85±40	−37±39
9	3	368±18	−80±19	−90±18	−19±50	−87±33	−90±20	−73±26
10	4	373±32	−19± 3	−63±26	−74±32	+3±41	−24±52	−42±26
11	4	379±38	−9± 3	−4± 9	−4± 9	−11±19	−47±32	−12±19
14	4	413±21	−19±29	−38±22	−34±29	−40±39	−54±27	−96± 9
23	5	373±33	−76±13	−99±18	−87±15	−56±38	−60±50	−48±36
24	5	326±10	−38±12	−78±12	−106±16	−62±16	−82± 7	−60±12
25	3	385±63	−71±22	−42±20	+27±44	−46±42	−98±45	−57±38
26	6	381±27	−46±15	−95±14	−73±27	−58±20	−69±29	−65±32
27	8	393±21	−4± 9	−16±13	−7±20	−23±32	−39±30	−14±33

a) Each number represents the mean ± standard error. Each compound was administered intraperitoneally at a dose of 30 mg/kg.

Moreover, the compounds in Table III showed relatively long-lasting hypotensive activities in anesthetized normotensive animals. Most of the compounds tested also produced a descrease in heart rate as shown in Table VIII. However, no definite correlation was observed between the decreases in blood pressure and heart rate.

The present authors have previously examined the hypotensive activities of a series of benzimidazolinone derivatives and found that their effects were mostly due to their alpha-adrenergic blocking activities.[3,12] Therefore, the alpha-adrenergic blocking activities of the present compounds were also examined. For this purpose, compounds **19** to **27** were selected, and their alpha-adrenergic blocking activities were examined with rat vas deferens preparations. However, these compounds except for **22** did not produce a substantial rightward shift of the dose–response curve for norepinephrine, the pA_2 values of these compounds being around 6.5. Exceptionally, **22** showed relatively strong alpha-blocking activity ($pA_2 = 7.47$). Compound **26** was more extensively examined and was found to show strong alpha-blocking activity when examined with isolated rat thoracic aorta; when tested at concentrations of 3×10^{-7}, 3×10^{-6}, and 3×10^{-5} M, the dose–response curve with norepinephrine, gave a pA_2 of about 7.05 ($n=6$). Therefore, the present compounds may produce hypotension through their alpha-adrenergic blocking activities on the arterial smooth muscle, though further studies are needed to confirm this.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. 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. ^{13}C-NMR spectra were obtained at 25.1 MHz on a JEOL JNM-FX-100 spectrometer, operating in a Fourier-transform mode with tetramethylsilane as an internal standard. Mass spectra were obtained on a JEOL JMS-O1SG-2 mass spectrometer.

1-[2-Oxo-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (6)——A solution of α-bromo-3,4-dimethoxypropiophenone (4.10 g, 15.0 mmol), **2a** (4.0 g, 15.0 mmol as HCl salt), and TEA (4.2 ml, 30.0 mmol) in 30 ml of DMF was stirred at room temperature for 2.5 h, then H_2O (150 ml) was added and the whole was stirred for 30 min. The resulting precipitate was collected by filtration, washed with H_2O and dried. Recrystallization of the crude crystals from ethanol (EtOH) yielded **6** (5.10 g, 80.4%). mp 173.0—174.5 °C. *Anal.* Calcd for $C_{24}H_{29}N_3O_4$: C, 68.07; H, 6.90; N, 9.92. Found: C, 67.91; H, 6.84; N, 9.90. IR (KBr): 1660—1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, $J=7$ Hz, C$\underline{H}_3$CH<), 3.95 (6H, s, 2×C$\underline{H}_3$O), 4.32 (2H, s, Ar-C$\underline{H}_2$), 8.25 (1H, br s, N$\underline{H}$).

Substituted 1-(2-Oxo-2-phenylethyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (4, 5, 7, 8, 9, and 11) and 1-(3-Oxo-3-phenylpropyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (12)——These compounds were prepared in the manner described for **10** except for the use of the appropriately substituted ω-bromoacetophenone in the place of ω-bromo-4-chloroacetophenone.

1-[2-Oxo-2-(4-chlorophenyl)ethyl]-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (10)——A mixture of **2a** (4.0 g, 15 mmol as HCl salt), ω-bromo-4-chloroacetophenone (3.5 g, 15 mmol), and TEA (4.2 ml, 30 mmol) in MeOH (60 ml) was stirred at room temperature overnight. The precipitated crystals were collected by filtration, successively washed with MeOH and H_2O, and dried to give a crude product (5.17 g, 89.9%). The crude product was recrystallized from $CHCl_3$–EtOH to give **10** (3.21 g, 55.8%) as colorless crystals, mp 193.0—195.5 °C. *Anal.* Calcd for $C_{21}H_{22}ClN_3O_2$: C, 65.71; H, 5.78; N, 10.95. Found: C, 65.44; H, 5.74; N, 10.86. IR (KBr): 1660, 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (2H, d, CH_2CO), 4.33 (2H, s, Ar-CH_2–NCO), 9.20 (1H, br s, NH).

1-[2-Oxo-2-(4-chlorophenyl)ethyl]-4-(6-chloro-1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (13)——Similar reaction of ω-bromo-4-chloroacetophenone (374 mg, 1.60 mmol) with **2b** (542 mg, 1.79 mmol) in the presence of TEA (0.67 ml, 4.83 mmol) in 15 ml of EtOH gave crude crystals (555 mg, 83.0%) of **13**. IR (KBr): 1658, 1692 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.3—2.5 (6H, m, piperidine H), 2.8—3.2 (2H, m, piperidine H), 3.83 (2H, s, CH_2CO), 4.15—4.45 (1H, m, N–CH<), 4.32 (2H, s, Ar-CH_2–NCO–), 9.29 (1H, s, NH).

1-[2-Oxo-2-(3,4-dimethoxyphenyl)ethyl]-4-(6-chloro-1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (14)——This compound was prepared in the manner described for **13** except for the use of ω-bromo-3,4-dimethoxyacetophenone.

1-[2-(Oxo-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidine (17)——Similar reaction of α-bromo-3,4-dimethoxypropiophenone (4.10 g, 15 mmol) with **2c** (3.46 g, 15 mmol) in the presence of TEA (2.1 ml, 15 mmol) in 30 ml of DMF and work-up as described for the preparation of **6** gave 5.14 g of crude crystals, which were recrystallized from EtOH to obtain 3.73 g (58.8%) of **17**, mp 154.0—156.0 °C. *Anal.* Calcd for $C_{24}H_{29}N_3O_4$: C, 68.07; H, 6.90; N, 9.92. Found: C, 67.96; H, 6.97; N, 9.76. IR (KBr): 1660—1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6.5 Hz, CH_3CH<), 3.97 (6H, s, 2×CH_3O), 4.27 (2H, d, J=1.0 Hz, Ar-CH_2–NCO), 5.90 (1H, br, NH).

Substituted 1-(2-Oxo-2-phenylethyl)-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidine (15, 16, and 18)——These compounds were prepared in the manner described for **17** except for the use of the appropriately substituted ω-bromoacetophenones in the place of α-bromo-3,4-dimethoxypropiophenone.

***threo*-1-[2-Hydroxy-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)-piperidine (21) and Its *erythro* Isomer (21′)**——$NaBH_4$ (1.50 g, 40 mmol) was added to a suspension of **6** (1.5 g, 3.5 mmol) in 500 ml of EtOH and the mixture was stirred for 14 h at room temperature. Then, the reaction mixture was concentrated to dryness and the residue was treated with H_2O. The precipitate was collected by filtration and dried to give a crude product (1.44 g), which was chromatographed over silica gel with $CHCl_3$–MeOH (10 : 1, v/v) to afford **21** (962 mg, 64.6%) as crystals and **21′** (308 mg, 20.7%) as an oily product. Recrystallization of **21** from EtOH gave an analytical sample, mp 221.0—223.2 °C. *Anal.* Calcd for $C_{24}H_{31}N_3O_4$: C, 67.74; H, 7.34; N, 9.87. Found: C, 67.62; H, 7.40; N, 9.73. IR (KBr): 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, d, J=6 Hz, CH_3CH<), 3.86 and 3.89 (6H, each s, 2×CH_3O), 4.20 [1H, d, J=10 Hz, –CH(OH)–], 4.38 (2H, s, Ar-CH_2), 7.32 (1H, br s, NH).

Compound **21′** could not be crystallized and its ^{1}H-NMR spectrum was measured. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6 Hz, CH_3CH<), 3.86 and 3.87 (6H, each s, 2×CH_3O), 4.35 (2H, s, Ar-CH_2–), 4.82 [1H, d, J=4 Hz, –CH(OH)–], 7.48 (1H, br s, NH).

1-(2-(4-Chlorophenyl)-2-hydroxyethyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (26)——$NaBH_4$ (2.0 g, 53 mmol) was added in portions to a suspension of **10** (2.70 g, 7 mmol) in MeOH (150 ml) at room temperature over 5 h. 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 (2.07 g, 76.7%). The crude product was recrystallized from $CHCl_3$–EtOH to give **26** (1.59 g, 58.9%), mp 240.0—241.0 °C. *Anal.* Calcd for $C_{21}H_{24}ClN_3O_2$: C, 65.36; H, 6.27; N, 10.89. Found: C, 65.09; H, 6.26; N, 10.93. IR (KBr): 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.47 [2H, d, J=6 Hz, CH(OH)CH_2], 4.32 (2H, s, Ar-CH_2–NCO), 9.20 (1H, s, NH).

Substituted 1-(2-Phenyl-2-hydroxyethyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidines (19, 20, 22—25, 27 and 30) and 1-(3-Phenyl-3-hydroxypropyl)-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (28)——These compounds were prepared from the corresponding amino ketones in the manner described for **26**.

1-[2-Hydroxy-2-(4-chlorophenyl)ethyl]-4-(6-chloro-1,2,3,4-tetrahydro-2-oxo-2-quinazolinyl)piperidine (29)——A solution of **13** (500 mg, 1.20 mmol) in 50 ml of EtOH was treated with 1.0 g (26.4 mmol) of $NaBH_4$ under reflux. Work-up as described for the preparation of **26** gave 479 mg of crude crystals, which were recrystallized from EtOH to obtain 395 mg (78.4%) of **29**, mp 221.8—224.0 °C. *Anal.* Calcd for $C_{21}H_{23}Cl_2N_3O_2$: C, 60.01; H, 5.51; N, 10.00. Found: C, 59.90; H, 5.52; N, 10.14. IR (KBr): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.33 (2H, s, Ar-CH_2–NCO).

Substituted 1-(2-Phenyl-2-hydroxyethyl)-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidines (31, 32, and 34)——These compounds were prepared from the corresponding amino ketones (**15**, **16**, and **18**) in the manner described for **26**.

***threo*-1-[2-Hydroxy-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)-**

piperidine (33)——A suspension of **17** (2.70 g, 6.4 mmol) in 150 ml of MeOH was treated with 2.0 g (53 mmol) of $NaBH_4$. Work-up as described for the preparation of **21** gave 2.07 g of crude crystals, which were recrystallized from $CHCl_3$–EtOH to obtain 1.87 g (70.0%) of **33**, mp 243.0—244.0 °C. *Anal.* Calcd for $C_{24}H_{31}N_3O_4$: C, 67.74; H, 7.34; N, 9.87. Found: C, 67.60; H, 7.39; N, 9.71. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.0 Hz, $CH_3CH<$), 3.87 and 3.90 (6H, each s, 2×CH_3O), 4.27 (2H, s, Ar-CH_2–), 5.56 (1H, s, NH). Compound **33** was converted to the acetate to determine its configuration, as described below. A solution of **33** (170 mg, 0.4 mmol) in pyridine (3 ml) was treated with acetic anhydride (2 ml), and the mixture was stirred at room temperature overnight. Then, the solution was concentrated *in vacuo* and mixed with aq. sat. $NaHCO_3$ (20 ml). White crystals that precipitated were collected by filtration, washed with H_2O (10 ml), and recrystallized from EtOH to give *threo*-1-[2-acetoxy-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidine (160 mg, 85.6%). mp 192.0—194.0 °C. *Anal.* Calcd for $C_{26}H_{33}N_3O_5$: C, 66.79; H, 7.11; N, 8.99. Found: C, 66.63; H, 7.15; N, 8.90. ^{1}H-NMR ($CDCl_3$) δ: 0.76 (3H, d, J=7 Hz, $CH_3CH<$), 2.15 (3H, s, CH_3CO_2), 3.85 and 3.90 (6H, each s, 2×CH_3O), 4.25 (2H, d, J=1.5 Hz, Ar-CH_2NH), 5.02 (1H, br d, J=1.5 Hz, NH), 5.70 [1H, d, J=9 Hz, –CH(OCOCH$_3$)–].

1-Benzyl-4-(2-nitrophenylmethyl)aminopiperidine (37)——A mixture of 1-benzyl-4-aminopiperidine (**36**)·2HCl (5.24 g, 20 mmol), 2-nitrobenzaldehyde (**35**) (3.02 g, 20 mmol), and TEA (2.02 g, 20 mmol) in MeOH (30 ml) was stirred at room temperature for 1 h and then $NaBH_4$ (1.0 g, 26 mmol) was added portionwise with ice-cooling over 1 h. The mixture was further stirred at room temperature for 2 h and then poured into ice-water. The resulting mixture was extracted with ether and the extracts were washed with water and dried. After evaporation of the solvent, the residual oil was dissolved in EtOH (20 ml). The solution was mixed with 10 ml of a solution of 5.7 N HCl in ethyl acetate (AcOEt). The precipitated crystals (5.70 g, 71.6%) were collected by filtration and recrystallized from EtOH to give **37** (2.90 g, 36.4%) as the 2HCl salt, mp 260.0—263.5 °C. *Anal.* Calcd for $C_{19}H_{23}N_3O_2 \cdot 2HCl$: C, 57.29; H, 6.33; N, 10.55. Found: C, 57.19; H, 6.48; N, 10.27. ^{1}H-NMR (D_2O) δ: 1.90—4.10 (9H, m, piperidine H), 4.42 (2H, s, Ar-CH_2–N), 4.62 (2H, s, –NH–CH_2–).

1-Benzyl-4-(2-aminophenylmethyl)aminopiperidine (38)——A mixture of **37** (31.8 g, 80 mmol as the 2HCl salt) and 10% Pd–C (3.2 g) in 500 ml of H_2O was stirred at room temperature under atmospheric pressure of hydrogen. After the absorption of about 6 l of hydrogen, the catalyst was removed by filtration. The filtrate was adjusted to pH 11 with aq. NaOH and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residual oil was dissolved in 140 ml of EtOH and was mixed with 70 ml of a solution of 5.7 N HCl in AcOEt. The precipitated crystals (23.5 g, 72.6%) were collected by filtration and recrystallized from MeOH–AcOEt to give **38** (15.0 g, 46.4%) as the 3HCl salt, mp 225.0—228.0 °C. *Anal.* Calcd for $C_{19}H_{25}N_3 \cdot 3HCl$: C, 56.37; H, 6.97; N, 10.38. Found: C, 56.35; H, 7.00; N, 10.31. ^{1}H-NMR (D_2O) δ: 1.90—4.06 (9H, m, piperidine H), 4.42 (2H, s, –CH_2-Ar), 4.52 (2H, s, –NH–CH_2–), 7.46—7.80 (9H, m, aromatic H).

1-Benzyl-4-(1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (39)——A mixture of **38** (4.04 g, 10 mmol), TEA (3.04 g, 30 mmol), and CDI (2.03 g, 12.5 mmol) in acetonitrile (50 ml) was stirred at room temperature for 4 h. The solution was refluxed, after further addition of CDI (0.80 g, 5 mmol), for 20 min and allowed to stand at room temperature for 0.5—1 h. The precipitated crystals were collected by filtration, washed with H_2O and dried to give a crude product (2.50 g, 77.9%), which was recrystallized from EtOH to yield **39** (1.75 g, 54.5%) as colorless crystals, mp 204.5—205.5 °C. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 75.02; H, 7.16; N, 13.21.

4-(1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl)piperidine (2a)——Method A: A mixture of **39** (1.0 g, 3.1 mmol) and 10% Pd–C (0.10 g) in AcOH (10 ml) and MeOH (10 ml) was stirred at room temperature under atmospheric pressure of hydrogen for 4 d. The catalyst was removed by filtration and the filtrate was concentrated to leave an oil, which was dissolved in EtOH (5 ml). The solution was mixed with a solution of 5.7 N HCl in AcOEt (70 ml) and allowed to stand at room temperature overnight. The precipitated crystals were collected by filtration, washed with AcOEt and dried to give a crude product (0.74 g, 89.2%), which was recrystallized from MeOH–AcOEt to yield **2a** (0.52 g, 62.7%) as the HCl salt, mp 288.0—293.0 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O \cdot HCl$: C, 58.32; H, 6.77; N, 15.69. Found: C, 58.26; H, 6.87; N, 15.65. IR (KBr): 1665 cm^{-1}. ^{1}H-NMR (D_2O) δ: 1.70—2.59 (4H, m, piperidine H), 2.90—3.96 (4H, m, piperidine H), 4.30 [2H, s, –CH_2–N(C=O)–], 4.13—4.63 (1H, m, N–CH<), 6.70—7.46 (4H, m, aromatic H).

Method B: A mixture of **39** (64.0 g, 200 mmol), 10% Pd–C (16.0 g), and 1 N aq. HCl (200 ml) in H_2O (600 ml) and MeOH (1.2 l) was stirred at 40 °C under atmospheric pressure of hydrogen for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give a crystalline residue, which was triturated with MeOH and dried to give **2a** (44.5 g, 83.1%) as HCl salt.

1-Ethoxycarbonyl-4-(2-nitro-5-chlorophenylmethyl)aminopiperidine (42)——**42**·**HCl** (13.2 g as a crude crystals) was prepared from 1-ethoxycarbonyl-4-aminopiperidine (**41**) (8.61 g, 50 mmol) and 2-nitro-5-chlorobenzaldehyde (**40**) (9.28 g, 50 mmol) as described for **37**. Dehydrochlorination of this HCl salt gave crude crystals (7.72 g, 40.8%) which were recrystallized from AcOEt-*n*-hexane to yield **42** (5.71 g, 30.2%) as crystals, mp 73.0—76.5 °C. *Anal.* Calcd for $C_{15}H_{20}ClN_3O_4$: C, 52.71; H, 5.90; N, 12.29. Found: C, 52.77; H, 6.02; N, 12.29. ^{1}H-NMR ($CDCl_3$) δ: 0.90—2.16 (5H, m, piperidine H, NH), 1.25 (3H, t, J=7.0 Hz, –OCH_2CH_3), 2.46—3.16 (3H, m, piperidine H), 3.80—4.36 (2H, m, piperidine H), 4.07 (2H, s, –CH_2NH–), 4.13 (2H, q, J=7.0 Hz, –OCH_2CH_3), 7.26—7.96 (3H, m, aromatic H).

1-Ethoxycarbonyl-4-(2-amino-5-chlorophenylmethyl)aminopiperidine (43)——A mixture of **42** (4.10 g, 12 mmol)

and 16% aq. $TiCl_3$ (69.4 g, 72 mmol as $TiCl_3$), in 12 N HCl (8 ml), and H_2O (140 ml) was stirred at room temperature for 12 h. Then, the mixture was adjusted to pH 11 with aq. NaOH and extracted with AcOEt. The extracts were washed with brine, dried and evaporated. The crystalline residue was triturated with *n*-hexane to afford crude crystals (2.54 g, 67.9%), which were recrystallized from AcOEt to yield **43** (1.17 g, 31.3%), mp 120.0—122.8 °C. *Anal.* Calcd for $C_{15}H_{22}ClN_3O_2$: C, 57.78; H, 7.11; N, 13.48. Found: C, 57.52; H, 7.29; N, 13.25. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.0 Hz, $-OCH_2C\underline{H}_3$), 3.78 (2H, s, $ArC\underline{H}_2NH-$), 4.13 (2H, q, J=7.0 Hz, $-OC\underline{H}_2CH_3$), 6.48—7.13 (3H, m, aromatic $\underline{H}$).

1-Ethoxycarbonyl-4-(6-chloro-1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl)piperidine (44)——This compound was prepared from **43** (2.8 g, 9.0 mmol) as described for **39**. Yield: 1.55 g (51.0%) (recrystallized from EtOH). mp 207.5—209.4 °C. *Anal.* Calcd for $C_{16}H_{20}ClN_3O_3$: C, 56.89; H, 5.97; N, 12.44. Found: C, 56.80; H, 5.93; N, 12.67. IR (KBr): 1655, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.0 Hz, $-OCH_2C\underline{H}_3$), 6.62—7.25 (3H, m, aromatic $\underline{H}$), 8.63 (1H, br s, $N\underline{H}$).

4-(6-Chloro-2-oxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (2b)——A solution of **44** (1.3 g, 3.9 mmol) in 47% aq. HBr (20 ml) was stirred under reflux for 1.5 h, made basic with aq. NaOH, and extracted with $CHCl_3$. The extracts were washed with brine, dried, and concentrated. The crystalline residue was dissolved in MeOH (5 ml), and the solution was mixed with 5 ml of a solution of 5.7 N HCl in AcOEt to give crude crystals (882 mg, 75.9%), which were recrystallized from EtOH to yield **2b** (608 mg, 52.3%) as the HCl salt, mp 297.0—299.0 °C. *Anal.* Calcd for $C_{13}H_{16}ClN_3O$: C, 51.67; H, 5.67; N, 13.90. Found: C, 51.64; H, 5.67; N, 13.63. IR (KBr): 1668 cm^{-1}. ^{1}H-NMR (CD_3OD+D_2O) δ: 4.46 (2H, s, Ar-$C\underline{H}_2$-N<), 6.73—7.33 (3H, m, aromatic $\underline{H}$).

1-Benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydro-quinazolin)]-4′-one (47)——A mixture of 2-aminobenzamide (**45**) (13.6 g, 0.1 mol), 1-benzyl-4-piperidone (**46**) (18.9 g, 0.1 mol), and *p*-toluenesulfonic acid monohydrate (1.0 g, 5.26 mmol) in benzene (200 ml) was stirred under reflux for 6 h. The H_2O formed during the reaction was separated by means of a Dean–Stark apparatus. The resulting suspension was concentrated, and saturated aq. $NaHCO_3$ (200 ml) was added to the residue. This mixture was extracted with AcOEt and precipitated crystals in the water layer were collected by filtration, successively washed with H_2O and MeOH, and dried to afford an almost pure product (27.0 g, 87.8%), which was recrystallized from MeOH to give **47** (17.5 g, 56.9%) as colorless crystals, mp 262.0—262.5 °C (lit.[7] mp 258 °C from THF).

1-Benzyl-4-(2-aminomethylphenyl)aminopiperidine (48)——1-Benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**47**) (614.8 mg, 2 mmol) was added to a suspension of $LiAlH_4$ (246 mg, 6.5 mmol) in dry dioxane (7 ml) without cooling. The reaction mixture was stirred for 1 h without heating and then refluxed with stirring for an additional 6 h. After cooling, the reaction mixture was poured into ice-water. The resulting suspension was poured into a funnel previously coated with a filter aid, and subjected to suction filtration. The cake on the funnel was treated with $CHCl_3$ and filtered. The organic layer was washed with H_2O, dried, and concentrated to give a crude product (373 mg, 63.2%), which was recrystallized from EtOH to give **48** (304.7 mg, 51.6%) as pale yellow crystals, mp 117.0—118.0 °C. *Anal.* Calcd for $C_{19}H_{25}N_3$: C, 77.25; H, 8.53; N, 14.22. Found: C, 77.45; H, 8.66; N, 13.98. ^{1}H-NMR ($CDCl_3$) δ: 0.83—3.63 (12H, m, piperidine $\underline{H}$, $-N\underline{H}_2$, $-N\underline{H}-$), 3.50 (2H, s, $C_6H_5-C\underline{H}_2-N<$), 3.83 (2H, s, $-C\underline{H}_2-NH_2$), 6.40—7.40 (9H, m, aromatic $\underline{H}$).

1-Benzyl-4-(1,2,3,4-tetrahydro-2-oxo-1-quinazolinyl)piperidine (49)——CDI (17.4 g, 107 mmol) was added to a solution of 1-benzyl-4-(2-aminomethylphenyl)aminopiperidine (**48**) (23.0 g, 78 mmol) in acetonitrile (200 ml) over 3 h with stirring at 40 to 60 °C. The mixture was then cooled to room temperature and stirred for an additional 2 h. The precipitated crystals were collected by filtration, successively washed with H_2O and MeOH, and dried to afford a crude product (16.8 g, 67.1%), which was recrystallized from MeOH to give **49** (12.2 g, 48.6%) as colorless crystals, mp 119.5—120.5 °C. *Anal.* Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.76; H, 7.31; N, 13.16.

4-(1,2,3,4-Tetrahydro-2-oxo-1-quinazolinyl)piperidine (2c)——A mixture of **49** (16.0 g, 50 mmol), 10% Pd–C (4.0 g), and 1 N aq. HCl (50 ml) in H_2O (150 ml) and MeOH (300 ml) was stirred at 40 °C under atmospheric pressure of hydrogen for 5 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to leave a white crystalline residue, which was dissolved in H_2O (50 ml). The solution was adjusted to pH 10 with aq. 5 N NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, and dried. After removal of the solvent, the crystalline residue was triturated with 50 ml of a mixture of AcOEt and *n*-hexane (1 : 1, v/v) and collected by filtration to give a crude product (9.9 g, 85.7%), which was recrystallized from H_2O–EtOH to yield **9** (5.1 g, 44.2%) as colorless crystals, mp 153.0—155.0 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.54; H, 7.56; N, 18.12.

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