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Synthesis of Piperidine Derivatives with a Quinazoline Ring System as Potential Antihypertensive Agents

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A series of piperidine derivatives with a 2-oxo-1,2,3,4-tetrahydro-quinazoline or 2,4-dioxo-1,2,3,4-tetrahydroquinazoline ring at the 4-position were prepared and tested for antihypertensive activity. Among the compounds tested, 1-[2-hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (**20**) and 1-[2-(4-chlorophenyl)-2-hydroxyethyl]-4-(2-oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (**30**) produced relatively strong hypotension in the spontaneously hypertensive rat model.

Keywords——antihypertensive activity; piperidine; quinazoline; indole; oxidative cleavage

In the previous paper,[1] we described the preparation and antihypertensive activity of 1-substituted piperidine derivatives with a quinazolinone nucleus at the 4-position of piperidine (formula I). We were interested in the pharmacological activities and structure–activity relationships of these compounds. In an attempt to prepare compounds exhibiting stronger activity, a number of analogs having other heterocyclic rings in place of the quinazolinone ring were prepared for pharmacological evaluation,[2] but these compounds did not exhibit remarkable antihypertensive activity in experimental animals. In this report, we describe a further development of analogs having a quinazolinone ring at the 4-position of piperidine as represented by the formulas Ib, Ic, and Id (Chart 1).

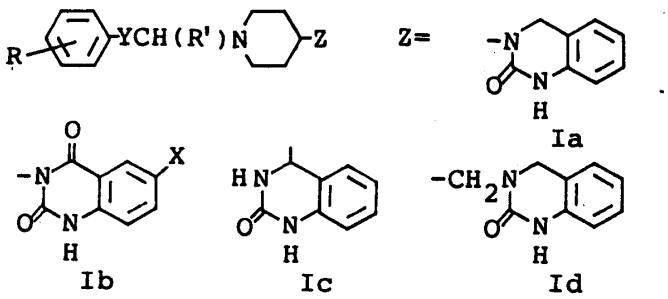


Chart 1

We designed compounds of formula Ib having a 2,4-dioxo-1,2,3,4-tetrahydroquinazoline ring (DTQ ring), which includes a ureido group and a benzamido group[3] in its structure. The fact that a DTQ ring was involved in the structure of Ketanserin[4] also prompted us to prepare these compounds. With respect to the influence of the binding position of the quinazoline ring to piperidine on the antihypertensive activity, we reported in the previous

paper that the 3-position was preferred to the 1-position.[1] In the present work, we also attempted to prepare compounds of type Ic in order to assess the influence of the quinazoline ring at the 4-position. We also designed compounds of type Id to investigate the effect of inserting a methylene group between the piperidine ring and the quinazolinone ring.

Chemistry

The 1-benzoylalkylpiperidine derivatives listed in Table I were prepared by the condensation of piperidine intermediates, **2a—e**, with the appropriate bromoketone (**1**) by using triethylamine (TEA) as a base in alcohol or *N*,*N*-dimethylformamide (DMF). 1-Benzoylalkylpiperidine derivatives thus obtained were converted into amino alcohol derivatives (Table II) by reduction with sodium borohydride ($NaBH_4$) (Chart 2).

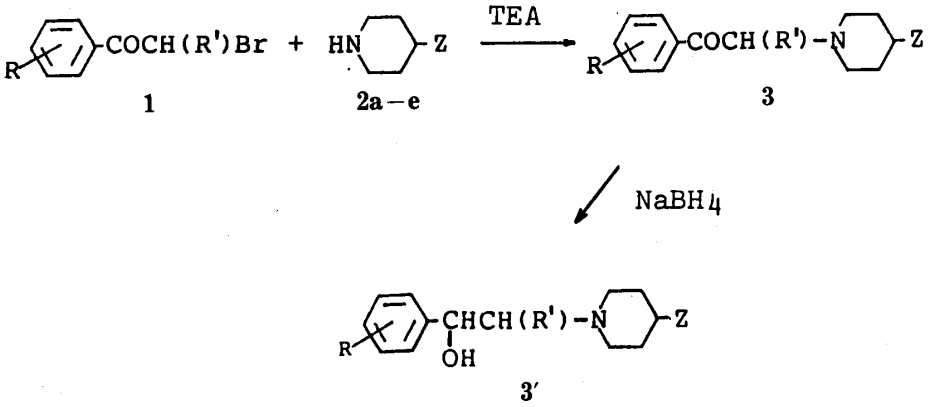


Chart 2

The intermediates, **2a** and **2b**, were prepared by reaction of **32a** and **32b**, respectively, with ethyl chloroformate, followed by cyclization with potassium hydroxide in ethanol and subsequent elimination of the ethoxycarbonyl group with 47% hydrobromic acid (HBr) as outlined in Chart 3. Compound **2c** was also obtained by nitration of **34a**, followed by elimination of the ethoxycarbonyl group.

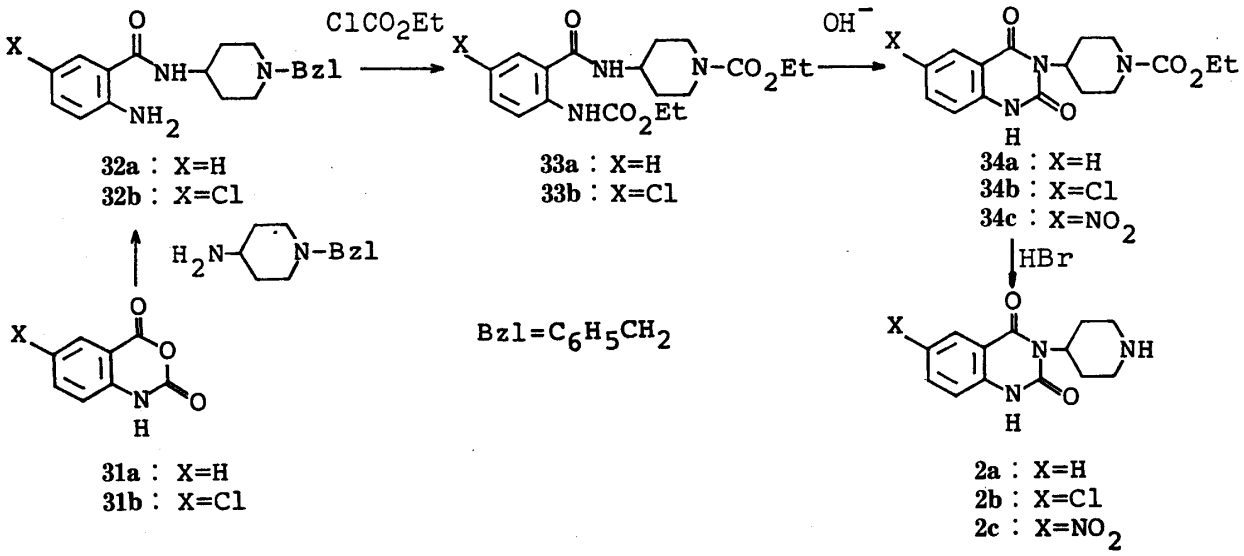
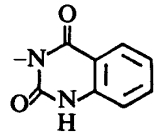
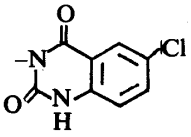
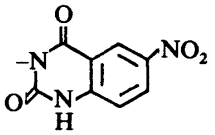
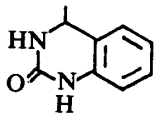
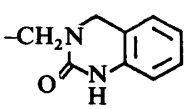


Chart 3

Indoles are well known to undergo ring cleavage upon treatment with oxidizing agents such as ozone (O_3), chromium trioxide (CrO_3), *etc.*[5] Therefore, this method was chosen for

TABLE I.

Compd.	R	R′	Z	Crystn. solvent	mp (°C)	Formula[a]
4	3,4-$(MeO)_2$	H		DMF–EtOH	212—214	$C_{23}H_{25}N_3O_5 \cdot 0.5H_2O$
5	3,4-$(MeO)_2$	Me		EtOH	186—187	$C_{24}H_{27}N_3O_5$
6	3,4-(OCH_2O)	H		DMF–EtOH	214—217	$C_{22}H_{21}N_3O_5$
7	3,4-$(MeO)_2$	H		DMF–EtOH	219—223	$C_{23}H_{24}ClN_3O_5 \cdot 0.5H_2O$
8	3,4-(OCH_2O)	H		DMF–MeOH	228—229	$C_{23}H_{20}ClN_3O_5$
9	H	H		MeOH	Crude crystals[b]	
10	3,4-diMeO	H		DMF–MeOH	235—238	$C_{23}H_{24}N_4O_7$
11	3,4-(OCH_2O)	H		DMF–MeOH	241—243	$C_{22}H_{20}N_4O_7$
12	3,4-$(MeO)_2$	H		DMF–EtOH	182—184	$C_{23}H_{27}N_3O_4$
13	H	H		DMF–EtOH	221—226	$C_{21}H_{23}N_3O_2 \cdot 0.25H_2O$
14	3,4-$(MeO)_2$	H		$CHCl_3$–AcOEt	171—174	$C_{24}H_{29}N_3O_4 \cdot 0.25H_2O$
15	3,4-$(MeO)_2$	Me		EtOH	169—173	$C_{25}H_{31}N_3O_4$
16	H	H		MeOH	178—179	$C_{22}H_{25}N_3O_2$
17	4-Cl	H		MeOH	142—145	$C_{22}H_{24}ClN_3O_2$

a) All compounds were analyzed for C, H, and N, and analytical values were within ±0.3% of the calculated values for these formulas. *b*) This compound was converted to **23** by reduction with $NaBH_4$ without any attempt to recrystallize it. The structure was determined by considering the structure of **23**.

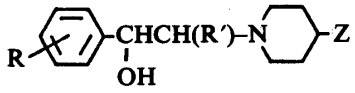
the preparation of **41**, which was a key intermediate for the synthesis of **2d** (Chart 4). First, attempts to convert **39a**, which was prepared according to Dobeneck and Goltzsche,[6] to **40a** by treatment with O_3 in acetic acid (AcOH) were made, but a complex mixture was obtained. Therefore, **39b**, which was also prepared in 25.4% yield *via* **38b** from 2-methylindole (**35b**), pyridine (**36**), and benzoyl chloride (**37**) by the same procedure as used for **39a**, was chosen as a starting material for the cleavage reaction. Treatment of **39b** with CrO_3 in AcOH at room temperature afforded **40b** in poor yield. Finally, **40b** was obtained by treatment of **39b** with O_3 in AcOH at room temperature in 79% yield. Subsequently, **40b** was converted into **41** by selective elimination of the acetyl group with 6 N hydrochloric acid–methanol (1 : 2, v/v) under reflux for 1 h in 68.4% yield. Cyclization of **41** with ethyl carbamate at 180 °C in the presence of a catalytic amount of zinc chloride ($ZnCl_2$) followed by reduction of the resulting compound (**42**) with $NaBH_4$ afforded **43**, which could be converted into the desired compound (**2d**) by further hydrolysis [4 N sulfuric acid (H_2SO_4)–methanol, 1 : 2, v/v].

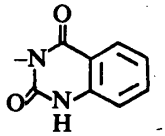
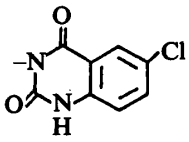
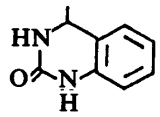
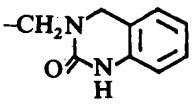
An intermediate (**2e**) was prepared as outlined in Chart 5. A Schiff base (**46**), prepared from *o*-nitrobenzaldehyde (**44**) and 4-aminomethylpiperidine (**45**), was benzylated with benzyl bromide and reduced with $NaBH_4$. The catalytic hydrogenation of the resulting nitrobenzylamine (**48**) followed by cyclization with *N*,*N*′-carbonyldiimidazole (CDI) and elimination of the benzyl group by catalytic hydrogenation afforded **2e**.

Antihypertensive Activity

Methods——Blood pressure was measured in unanesthetized spontaneously hypertensive

TABLE II.



Compd.	R	R′	Z	Crystn. solvent	mp (°C)	Formula[a]
18	3,4-$(MeO)_2$	H		EtOH	202—203	$C_{23}H_{27}N_3O_5$
19	3,4-$(MeO)_2$	Me		$CHCl_3$–EtOH[b]	251—253	$C_{24}H_{29}N_3O_5$
20	3,4-(OCH_2O)	H		DMF–EtOH	227—228	$C_{22}H_{23}N_3O_5 \cdot 0.25H_2O$
21	3,4-$(MeO)_2$	H		DMF–EtOH	228—229	$C_{23}H_{26}ClN_3O_5$
22	3,4-(OCH_2O)	H		DMF–EtOH	237—238	$C_{22}H_{22}ClN_3O_5$
23	H	H		EtOH	266—270	$C_{21}H_{22}ClN_3O_3$
24	3,4-$(MeO)_2$	H		DMF–EtOH	234—236	$C_{23}H_{29}N_3O_4$
25	H	H		DMF–MeOH	213—217	$C_{21}H_{25}N_3O_2 \cdot 0.5H_2O$
26	3,4-$(MeO)_2$	H		EtOH	172—173	$C_{24}H_{31}N_3O_4$
27	3,4-$(MeO)_2$	Me		EtOH[b]	200—202	$C_{25}H_{33}N_3O_4$
28	3,4-$(MeO)_2$	Me		EtOH[c]	173—175	$C_{25}H_{33}N_3O_4$
29	H	H		DMF–MeOH	209—211	$C_{22}H_{27}N_3O_2$
30	4-Cl	H		DMF–MeOH	210—212	$C_{22}H_{26}ClN_3O_2$

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

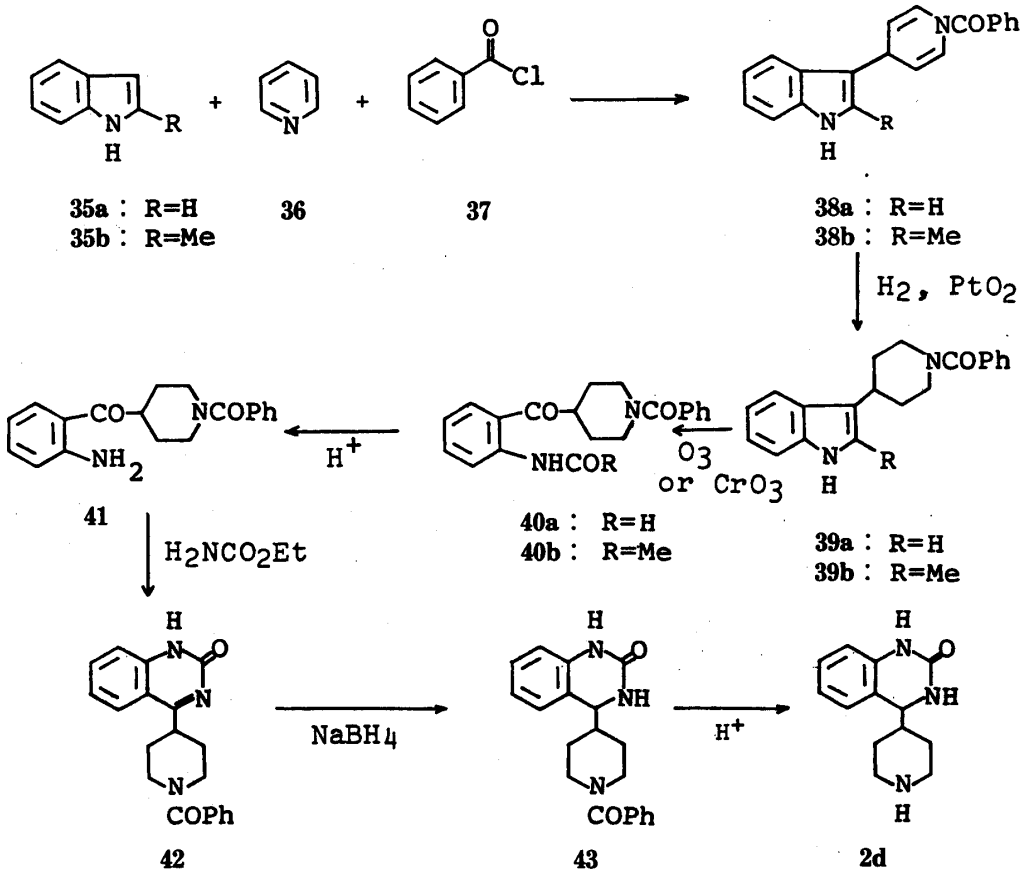


Chart 4

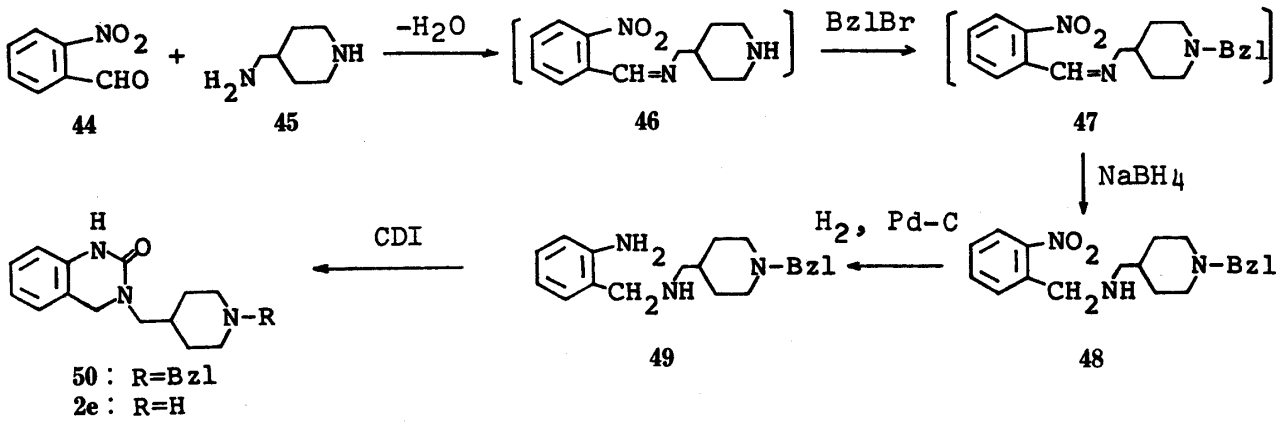


Chart 5

TABLE III. Changes in Blood Pressure of Unanesthetized SHR Treated with Test Compounds

Compd.[a] No.	Initial level[b] (mmHg)	Minimum subsequent level[b] (mmHg)	Maximum change (Δ mmHg)	Time[c] (h)
4	217.5± 6.5	202.5± 8.1	−15.0	1.5
5	206.3± 6.5 (4)	180.0± 5.0	−26.3	1.5
6	210.0± 6.1	190.0± 6.4	−20.0	1.5
7	220.0± 8.6	176.2± 9.0	−43.8	5.0
8	205.0±12.9	167.5±17.7	−37.5	3.0
10	206.0± 8.3	180.0±10.6	−26.2	3.0
11	218.7± 4.7	192.5±11.4	−26.2	5.0
16	185.0± 7.7	158.7± 5.4	−26.3	5.0
17	180.0± 4.7	165.0± 6.2	−15.0	5.0
18	198.3± 4.9	173.3± 1.4	−25.0	5.5
19	198.7± 8.5 (4)	162.5± 9.6	−36.2	3.5
20	205.0± 2.5	145.0± 5.6	−60.0	3.0
21	202.5± 9.4	173.7± 8.7	−28.8	1.5
22	210.0±16.3	173.3±11.6	−36.7	5.0
23	173.3± 9.8	165.0± 4.7	−8.3	4.0
24	202.5± 8.9	167.5± 9.7	−35.0	5.0
25	181.7± 8.1	175.0± 5.8	−6.7	1.5
26	212 ± 4.4	190 ± 7.6	−22	1.5
27	180.0± 5.0	166.7±12.0	−7	1.5
29	187.5± 6.2	158.7± 7.8	−28.8	3.0
30	208.7±10.3	145.0± 5.8	−63.7	3.0

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

rats (SHR). The 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 of the tail at 37 °C for 15 min.[7] Test compounds were suspended in 0.3% (w/v) carboxymethyl-cellulose 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 and Discussion

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

in unanesthetized SHR were **20** and **30**. The effect of the DTQ ring (**Ib**) on the hypotensive activity was disappointing except for compound **20** with the 3,4-methylenedioxy group in the phenyl ring, which exhibited more potent hypotensive activity than the corresponding 3-quinazolinone derivative described in the previous report.[1] As regards the effect of insertion of the methylene bridge between the quinazolinone ring and the piperidine ring (**26**, **27**, **29** and **30**), the activities were reduced except for **30**, as compared with the corresponding quinazolinone derivatives described in the previous report.[1] As regards the influence of the binding position of the quinazolinone ring to piperidine on the antihypertensive activity, it is difficult to draw conclusions from only a limited number of experiments. However, it appears that the 4-position is not preferred to the 3-position.

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 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian T-60 spectrometer using tetramethylsilane as an internal standard.

1-(3,4-Dimethoxybenzoylmethyl)-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (4)——A mixture of α-bromo-3,4-dimethoxyacetophenone[8] (2.59 g, 10 mmol), **2a**·HBr (3.26 g, 10 mmol), and TEA (2.8 ml, 20 mmol) in MeOH (100 ml) was stirred overnight at room temperature. White crystals that precipitated were collected by filtration, washed successively with MeOH and H_2O, and dried to give crude crystals (3.77 g, 80.6%). This product (1.6 g) was recrystallized twice from DMF–EtOH to afford an analytical sample (749 mg), mp 212—214 °C. *Anal.* Calcd for $C_{23}H_{25}N_3O_5 \cdot 0.5H_2O$: C, 63.88; H, 6.06; N, 9.72. Found: C, 63.95; H, 5.95; N, 9.92. IR (KBr): 1645, 1670, 1703 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.2—3.4 (8H, m, piperidine H), 3.61 (2H, s, $-CH_2COAr$), 3.70 (6H, s, $2\times-OCH_3$), 4.2—4.8 (1H, m, >CHN), 6.6—7.7 (7H, m, aromatic H).

Substituted 1-Benzoylmethyl-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidines (5—11)——These compounds were prepared from **1a**, **1b**, or **1c** in the same manner as described for **4**, except for the use of the appropriately substituted α-bromoacetophenones.

1-(3,4-Dimethoxybenzoylmethyl)-4-(2-oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (12)——A mixture of α-bromo-3,4-dimethoxyacetophenone (258.9 mg, 1 mmol), **2d** (231 mg, 1 mmol), and TEA (0.14 ml, 1 mmol) in MeOH (5 ml) was stirred at room temperature overnight. Crystals that precipitated were collected by filtration, washed successively with MeOH (10 ml) and H_2O (50 ml), and dried to give a crude product (360 mg, 88.0%), which was recrystallized from $CHCl_3$ to yield a pure sample (272 mg, 66.5%) of **12** as crystals, mp 182—184 °C. *Anal.* Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.26; H, 6.83; N, 10.00. IR (KBr): 1690, 1675 cm^{-1} (shoulder). ^{1}H-NMR ($CDCl_3$) δ: 1.4—3.1 (9H, m, piperidine H), 3.71 (2H, s, $-CH_2COAr$), 3.90 and 3.93 (6H, each s, $2\times-OCH_3$), 4.29 (1H, m, >CHNHCO–), 5.66 (1H, br s, NH), 6.70—7.73 (7H, m, aromatic H), 7.87 (1H, br s, NH).

1-Benzoylmethyl-4-(2-oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (13)——This compound was prepared in the same manner as described for **12** except for the use of α-bromoacetophenone. Yield, 70.7% as crystals, mp 221—226 °C. *Anal.* Calcd for $C_{21}H_{23}N_3O_2 \cdot 0.25H_2O$: C, 71.26; H, 6.69; N, 11.87. Found: C, 71.24; H, 6.84; N, 11.78. IR (KBr): 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 1.2—3.2 (9H, m, piperidine H), 3.80 (2H, s, $-CH_2COAr$), 4.27 (1H, m, >CHNHCO–), 6.76—8.01 (9H, m, aromatic H).

1-[1-(3,4-Dimethoxybenzoyl)ethyl]-4-(2-oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (15)——Similar reaction of α-bromo-3,4-dimethoxypropiophenone[9] (2.73 g, 10 mmol) and **2e**·HCl (2.82 g, 10 mmol) gave crude crystals (3.3 g, 75.5%). Recrystallization of this material (1 g) from $CHCl_3$–MeOH afforded pure crystals (860 mg) of **15**. mp 169—173 °C. *Anal.* Calcd for $C_{25}H_{31}N_3O_4$: C, 68.63; H, 7.14; N, 9.61. Found: C, 68.61; H, 7.21; N, 9.44. IR (KBr): 1675, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6.5 Hz, >CHCH$_3$), 3.30 (2H, d, J=6 Hz, CH_2N), 3.90 and 3.93 (6H, each s, $2\times-OCH_3$), 4.40 (2H, s, $-CONCH_2Ar$), 8.03 (1H, br s, NH).

Substituted 1-Benzoylmethyl-4-(2-oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (14, 16 and 17)——These compounds were prepared in the same manner as described for **15**, except for the use of the appropriately substituted α-bromoacetophenones.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (18)——A suspension of **4** (2.00 g, 4.28 mmol) in isopropanol (150 mmol) was, after addition of $NaBH_4$ (1.0 g, 26.4 mmol), refluxed for 2 h and then concentrated to give the residue. This was taken up in H_2O (50 ml), and the mixture was allowed to stand at room temperature for 1 h to give crude crystals (1.66 g, 82.7%). Recrystalization from EtOH yielded pure crystals (1.42 g, 70.8%) of **18**, mp 202—203 °C. *Anal.* Calcd for $C_{23}H_{27}N_3O_5$: C, 64.92; H, 6.40; N, 9.88. Found: C, 64.67; H, 6.30; N, 9.81. IR (KBr): 1655, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.2—3.3 [10H, m, $NCH_2CH(OH)$, piperidine H], 3.60 and 3.63 (6H, each s, $2\times-OCH_3$), 4.2—4.9 [3H, m, $-CH(OH)-$, >CHN–], 6.45—7.7 (7H, m, aromatic H), 10.73 (1H, br s, NH).

***threo*-1-[1-(3,4-Dimethoxyphenyl)-1-hydroxy-2-propyl]-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (19)**——A solution of **5** (3.00 g, 6.86 mmol) in MeOH (150 ml) was, after addition of $NaBH_4$ (2 g, 52.8 mmol), stirred at room temperature overnight. White crystals that precipitated were filtered off, washed successively with MeOH and H_2O, and dried to give white crystals (2.02 g, 67.1%), which were recrystallized from $CHCl_3$–EtOH to yield pure crystals (1.15 g, 38.2%) of **19**, mp 251—253 °C. *Anal.* Calcd for $C_{24}H_{29}N_3O_5$: C, 65.58; H, 6.65; N, 9.56. Found: C, 65.46; H, 6.66; N, 9.51. IR (KBr): 1710, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.68 (3H, d, J=6 Hz, >CHC$\underline{H}_3$), 1.3—3.3 (9H, m, piperidine H, >C$\underline{H}$CH$_3$), 3.62 and 3.65 (6H, each s, 2×–OC$\underline{H}_3$), 4.05 [1H, d, J=8 Hz, –C$\underline{H}$(OH)–], 4.3—4.9 (2H, m, >C$\underline{H}$N, O$\underline{H}$), 6.4—7.7 (7H, m, aromatic H), 10.7 (1H, br s, N$\underline{H}$).

Substituted 1-(2-Hydroxy-2-phenylethyl)-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (20—23)——These compounds were prepared in the same manner as described for **18** from the corresponding aminoketones.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-4-(2-oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (24)——A suspension of **12** (600 mg, 1.47 mmol) in EtOH (40 ml) was, after addition of $NaBH_4$ (300 mg, 7.93 mmol), stirred at room temperature for 2 d. White crystals that precipitated were filtered off, washed successively with MeOH and H_2O, and dried to give a crude product (546 mg, 90.4%), which was recrystallized from DMF–EtOH to yield pure crystals (477 mg, 79.0%) of **24**, mp 234—236 °C. *Anal.* Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 66.94; H, 7.11; N, 10.13. IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD) δ: 1.06—3.29 [11H, m, piperidine H, CH(OH)C$\underline{H}_2$], 3.86 and 3.88 (6H, each s, 2×–OC$\underline{H}_3$), 4.30 (1H, m, >C$\underline{H}$NHCO–), 4.55—4.77 (1H, m, –C$\underline{H}$(OH)CH$_2$–), 6.76—7.29 (7H, m, aromatic H).

1-(2-Hydroxy-2-phenylethyl)-4-(2-oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (25)——This compound was prepared from **13** in the same manner as described for **24**. Yield, 93.5% as crystals, mp 213—217 °C. *Anal.* Calcd for $C_{21}H_{25}N_3O_2 \cdot 0.5H_2O$; C, 69.98; H, 7.27; N, 11.66. Found: C, 70.17; H, 7.04; N, 11.66. IR (KBr): 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.2—3.3 [12H, m, piperidine H, CH(O$\underline{H}$)C$\underline{H}_2$], 4.31 (1H, m, >C$\underline{H}$NHCO–), 4.57—4.79 [1H, m, C$\underline{H}$(OH)], 6.03 (1H, br s, N$\underline{H}$), 6.68—7.42 (9H, m, aromatic H), 8.36 (1H, br s, N$\underline{H}$).

***threo*-1-[1-(3,4-Dimethoxyphenyl)-1-hydroxy-2-propyl]-4-(2-oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (27) and *erythro*-Isomer (28)**——$NaBH_4$ (1.7 g, 45 mmol) was added to a suspension of **15** (1.97 g, 4.5 mmol) in EtOH (50 ml). The mixture was stirred at room temperature for 3 d. Crystals that precipitated were collected by filtration and recrystallized from EtOH to give **27** (1.12 g). The filtrate of the reaction mixture was concentrated *in vacuo*, then mixed with H_2O to give a precipitate (363 mg), which was combined with the crystalline residue (100 mg) obtained by concentration of the mother liquor of recrystallization. This product was chromatographed on silica gel. Elution with $CHCl_3$–MeOH (20:1) gave **27** (177 mg) and subsequently **28** (179 mg, 9.0%). Recrystallization of **28** from EtOH gave an analytical sample.

Compound **27**: mp 200—202 °C. *Anal.* Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.12; H, 7.68; N, 9.51. IR (KBr): 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 3.36 (2H, d, J=6 Hz, CHC$\underline{H}_2$–), 3.85 and 3.88 (6H, each s, 2×–OC$\underline{H}_3$), 4.19 [1H, d, J=10 Hz, –C$\underline{H}$(OH)–], 4.46 (2H, s, ArC$\underline{H}_2$N), 6.63—7.33 (7H, m, aromatic H), 8.31 (1H, br s, N$\underline{H}$).

Compound **28**: mp 173—175 °C. *Anal.* Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.15; H, 7.60; N, 9.53. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, d, J=7 Hz, >CHC$\underline{H}_3$), 3.31 (2H, d, J=6 Hz, >CHC$\underline{H}_2$–), 3.83 (6H, s, 2×–OC$\underline{H}_3$), 4.40 (2H, s, ArC$\underline{H}_2$N<), 4.73 [1H, d, J=4 Hz, –C$\underline{H}$(OH)–], 6.56—7.3 (7H, m, aromatic H), 8.1 (1H, br s, N$\underline{H}$).

1-Benzyl-4-(2-aminobenzoylamino)piperidine (32a)——A mixture of isatoic anhydride[10] (48.9 g, 0.30 mol), 1-benzyl-4-aminopiperidine·2HCl[11] (78.6 g, 0.30 mol), and TEA (84 ml, 0.60 mol) in dioxane (600 ml) was refluxed with stirring for 2 h. The crystalline residue obtained by evaporation of the solvent was triturated with H_2O, filtered, and dried to give crude crystals (68.8 g, 74.4%) of **32a**. Recrystallization from MeOH gave an analytical sample, mp 167—168 °C. *Anal.* Calcd for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N, 13.58. Found: C, 73.43; H, 7.58; N, 13.43. IR (KBr): 1622 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—3.1 (8H, m, piperidine H), 3.48 (2H, s, ArC$\underline{H}_2$N), 3.63—4.21 (1H, m, >C$\underline{H}$N), 5.43 (2H, br s, N$\underline{H}_2$), 5.98 (1H, d, J=7.2 Hz, –CON$\underline{H}$–), 6.41—6.80 (2H, m, aromatic H), 7.26 (5H, s, $C_6\underline{H}_5CH_2$), 7.00—7.46 (2H, m, aromatic H).

1-Benzyl-4-(2-amino-5-chlorobenzoylamino)piperidine (32b)——Similar reaction of 5-chloroisatoic anhydride[10] (19.75 g, 0.10 mol) and 1-benzyl-4-aminopiperidine·2HCl (26.21 g, 0.10 mol) gave crude crystals (16.3 g, 47.5%) of **32b**. Recrystallization from MeOH gave an analytical sample, mp 182—185 °C. *Anal.* Calcd for $C_{19}H_{22}ClN_3O$: C, 66.37; H, 6.45; N, 12.22. Found: C, 66.24; H, 6.50; N, 12.11. IR (KBr): 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.1—3.1 (8H, m, piperidine H), 3.49 (2H, s, ArC$\underline{H}_2$N), 3.62—4.28 (1H, m, >C$\underline{H}$N), 5.43 (2H, br s, N$\underline{H}_2$), 5.98 (1H, d, J=7.0 Hz, –CON$\underline{H}$–), 6.53 (1H, d, J=8.2 Hz, aromatic H), 7.28 (5H, s, $C_6\underline{H}_5CH_2$), 6.98—7.52 (2H, m, aromatic H).

1-Ethoxycarbonyl-4-(2-ethoxycarbonylaminobenzoylamino)piperidine (33a)——A mixture of **32a** (20 g, 64.9 mmol) and ethyl chloroformate (200 ml) was refluxed at 93 °C with stirring for 3 h, then concentrated, and mixed with *n*-hexane. The precipitate crystals were collected by filtration, washed with *n*-hexane and dried to give a crude product (22.9 g, 97.1%) of **33a**. Recrystallization from MeOH afforded an analytical sample, mp 161—162 °C. *Anal.* Calcd for $C_{18}H_{25}N_3O_5$: C, 59.49; H, 6.93; N, 11.56. Found: C, 59.25; H, 7.01; N, 11.29.

1-Ethoxycarbonyl-4-(2-ethoxycarbonylamino-5-chlorobenzoylamino)piperidine (33b)——Reaction of **32b** (16 g, 46.6 mmol) and ethyl chloroformate (50 ml) as described for **33a** gave crude crystals (17.2 g, 88.7%) of **33b**.

1-Ethoxycarbonyl-4-(2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (34a)——A solution of **33a** (20.7 g, 57.0 mmol) and KOH (9.3 g, 16.6 mmol) in EtOH (140 ml) was refluxed for 3 h and allowed to stand at room temperature overnight. The precipitated white crystals were filtered off, washed successively with EtOH and H_2O, and dried to give a crude product (10.0 g, 55.3%), which was recrystallized from EtOH to afford crystals (8.3 g, 45.9%) of **34a**. mp 243—244 °C. *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.37; H, 6.04; N, 13.19. IR (KBr): 1720, 1692, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.4—3.2 (6H, m, piperidine H), 3.8—4.4 (4H, m, $-OCH_2CH_3$, piperidine H), 4.63—5.30 (1H, m, >CHN), 6.93—8.03 (4H, m, aromatic H), 11.40 (1H, br s, NH).

1-Ethoxycarbonyl-4-(6-chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (34b)——A solution of **33b** (15.4 g, 38.7 mmol) in EtOH (120 ml) was treated with KOH (7.6 g, 135 mmol) as described for **34a** to give crude crystals (11.2 g, 82.3%), which were recrystallized from EtOH to afford pure crystals (10.4 g, 76.4%) of **34b**. mp 246—248 °C. *Anal.* Calcd for $C_{16}H_{18}ClN_3O_4$: C, 54.63; H, 5.16; N, 11.94. Found: C, 54.69; H, 5.31; N, 11.74. IR (KBr): 1725, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.4—3.2 (6H, m, piperidine H), 3.8—4.4 (4H, m, $-OCH_2CH_3$, piperidine H), 4.63—5.30 (1H, m, >CHN), 11.46 (1H, br s, NH).

4-(2,4-Dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (2a)——A suspension of **34a** (6.5 g, 20.5 mmol) in 47% aq. HBr (170 ml) was refluxed with stirring for 8 h, then concentrated to 25 ml and allowed to stand at room temperature for 1 h. The precipitated white crystals were filtered off, washed successively with H_2O, MeOH and ether, and dried to give crude crystals (5.8 g, 86.4%) as the HBr salt, which was recrystallized from H_2O–EtOH to give crystals (4.6 g, 68.9%) of **2a**, mp >300 °C. *Anal.* Calcd for $C_{13}H_{15}N_3O_2 \cdot HBr$: C, 47.87; H, 4.94; N, 12.88. Found: C, 47.66; H, 5.04; N, 12.64. IR (KBr): 1700, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.6—3.7 (8H, m, piperidine H), 4.8—5.4 (1H, m, >CHN), 7.0—8.1 (4H, m, aromatic H), 9.0 (2H, br s, NH·HBr), 11.6 (1H, br s, CONH).

4-(6-Chloro-2,4-dioxo-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (2b)——Reaction of **34b** (10 g, 28.4 mmol) in EtOH (50 ml) and 47% aq. HBr (150 ml) as described for **2a** gave crude crystals (9.3 g, 90.9%) of **2b**·HBr. This product was recrystallized from H_2O–EtOH to give pure crystals (7.2 g, 70.4%), mp >300 °C. *Anal.* Calcd for $C_{13}H_{14}ClN_3O_2 \cdot HBr$: C, 43.30; H, 4.19; N, 11.65. Found: C, 43.10; H, 4.07; N, 11.63. IR (KBr): 1700, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.6—3.7 (8H, m, piperidine H), 4.8—5.4 (1H, m, >CHN), 7.4—8.0 (3H, m, aromatic H), 9.0 (2H, br s, NH·HBr), 11.7 (1H, br s, CONH).

1-Ethoxycarbonyl-4-(2,4-dioxo-6-nitro-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (34c)——A solution of **34a** (28.5 g, 90 mmol) in conc. H_2SO_4 (180 ml) was stirred, after addition of fuming nitric acid (d=1.50) (3.45 ml), at room temperature for 5.5 h, then poured into ice water (1.2 l). The pale yellow crystals that precipitated were collected by filtration to give crude crystals (30.6 g, 93.9%) of **34c**. This product was recrystallized from EtOH to obtain pure crystals (20.2 g, 62.0%), mp 162—165 °C. *Anal.* Calcd for $C_{16}H_{18}N_4O_6$: C, 53.04; H, 5.01; N, 15.46. Found: C, 53.02; H, 4.99; N, 15.29. IR (KBr): 1725, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (3H, t, J=7 Hz, $-OCH_2CH_3$), 1.4—3.2 (6H, m, piperidine H), 3.8—4.4 (4H, m, $-OCH_2CH_3$, piperidine H), 4.60—5.30 (1H, m, >CHN), 7.26 (1H, d, J=9 Hz, aromatic H), 8.36 (1H, dd, J=9, 3 Hz, aromatic H), 8.53 (1H, d, J=3 Hz, aromatic H), 11.94 (1H, br s, NH).

4-(2,4-Dioxo-6-nitro-1,2,3,4-tetrahydro-3-quinazolinyl)piperidine (2c)——Reaction of **34c** (6 g, 16.6 mmol) in 47% aq. HBr (180 ml) as described for **2a** gave crude crystals (5.44 g, 88.6%) of **2c** as the HBr salt, which was recrystallized from H_2O–EtOH to afford pure crystals (4.8 g, 78.2%). mp >300 °C. *Anal.* Calcd for $C_{13}H_{14}N_4O_4 \cdot HBr$: C, 42.07; H, 4.07; N, 15.09. Found: C, 42.06; H, 3.98; N, 14.99. IR (KBr): 1720, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + CD_3OD) δ: 1.6—3.5 (8H, m, piperidine H), 4.8—5.4 (1H, m, >CHN), 7.33 (1H, d, J=9 Hz, aromatic H), 8.43 (1H, dd, J=9, 3 Hz, aromatic H), 8.60 (1H, d, J=3 Hz, aromatic H).

1-Benzoyl-4-(2-methylindol-3-yl)-1,4-dihydropyridine (38b)——Benzoyl chloride (56.2 g, 400 mmol) was added to 2-methylindole (52.4 g, 400 mmol) in pyridine (800 ml) and the mixture was stirred at room temperature for 7 d. The solution was adjusted to pH 5 with conc. HCl after addition of ice and extracted with AcOEt. The residue, after removal of the solvent *in vacuo*, was crystallized from ether to afford **38b** (34.1 g, 27.2%). ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s, $-CH_3$), 4.36—4.60 (1H, m, >CH–), 4.80—5.20 [2H, m, $(=CH)_2CH$–], 6.70—7.73 (11H, m, aromatic H), 7.95 (1H, br s, NH).

1-Benzoyl-4-(2-methylindol-3-yl)piperidine (39b)——A mixture of **38b** (32 g, 102 mmol) and PtO_2 (2 g) in EtOH (2 l) was stirred at room temperature under a hydrogen atmosphere for 42 h. The catalyst was filtered off and washed with $CHCl_3$ (1 l). The solvent was removed *in vacuo* and the residue was crystallized from EtOH to give **39b** (30.3 g, 93.5%). Recrystallization from DMF–EtOH afforded an analytical sample: mp 263—265 °C. *Anal.* Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.09; H, 6.98; N, 8.79. IR (KBr): 1608 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, $-CH_3$), 6.93—7.66 (9H, m, aromatic H), 7.93 (1H, br s, NH).

1-Benzoyl-4-(2-acetylaminobenzoyl)piperidine (40b)——Method A: Ozone was passed through a stirred solution of **39b** (10 g, 31.5 mmol) in AcOH (100 ml) for 2 h at room temperature and then the solution was poured into ice-water (1 l). The pale yellow crystals that precipitated were collected by filtration, washed with H_2O, and dried to afford a crude product (8.68 g, 79.0%). Recrystallization from AcOEt–petroleum ether gave an analytical sample, mp 143—145 °C. *Anal.* Calcd for $C_{21}H_{22}N_2O_3$: C, 71.78; H, 6.33; N, 7.99. Found: C, 71.77; H, 6.37; N, 7.93. IR (KBr): 1618, 1638, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.13 (4H, m, piperidine H), 2.22 (3H, s, $COCH_3$), 2.66—4.97 (5H, m, piperidine H), 6.93—8.00 (8H, m, aromatic H), 8.73 (1H, dd, J=8, 2 Hz, aromatic H), 11.56 (1H, br s, NH).

Method B: A solution of CrO_3 (200 mg, 2.0 mmol) in H_2O (0.4 ml) was added dropwise to a solution of **39b** (367.7 mg, 1.16 mmol) in AcOH (4 ml) at room temperature over 30 minutes. The mixture was stirred for an additional 1 h, then poured into H_2O and extracted with AcOEt. The extract was washed successively with sat. aq. $NaHCO_3$ and H_2O, dried, and concentrated *in vacuo* to give an oily residue, which was chromatographed on silica gel. Elution with AcOEt–hexane (7:3, v/v) afforded **40b** (58 mg, 14.3%).

1-Benzoyl-4-(2-aminobenzoyl)piperidine (41)——A solution of **40b** (20 g, 57.3 mmol) in MeOH (200 ml) and 6 N HCl (100 ml) was refluxed for 1 h. The MeOH was evaporated off, and the residual solution was adjusted to pH 7 with $NaHCO_3$, then extracted with AcOEt. The extract was washed with brine, and concentrated. The crystalline residue was mixed with MeOH and collected by filtration to give a crude product (12.0 g, 68.4%), which was recrystallized from EtOH to yield **41** (9.79 g, 55.7%), mp 148—149 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.98; H, 6.65; N, 9.01. IR (KBr): 1640, 1624 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.06 (4H, m, piperidine H), 2.76—3.76 (3H, m, piperidine H), 3.90—4.80 (2H, m, piperidine H), 6.10—6.80 (4H, m, aromatic H, NH_2), 7.06—7.86 (7H, m, aromatic H).

1-Benzoyl-4-[2-(1*H*)-quinazolinon-4-yl]piperidine (42)——A mixture of **41** (7 g, 22.7 mmol), ethyl carbamate (31.5 g, 35.4 mmol), and $ZnCl_2$ (0.6 g, 4.4 mmol) was stirred at 180 °C for 1 h under a nitrogen atmosphere, then allowed to cool to room temperature, and treated with H_2O. Crude crystals thus obtained were collected by filtration, washed with H_2O, and dissolved in $CHCl_3$. The solution was filtered. Evaporation of the solvent gave a crystalline residue (6.78 g, 89.7%), which was recrystallized from EtOH to afford **42** (4.37 g, 57.8%). mp >300 °C. *Anal.* Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.00; H, 5.63; N, 12.52. IR (KBr): 1660, 1630, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76—2.20 (4H, m, piperidine H), 2.73—3.86 (3H, m, piperidine H), 4.03—4.93 (2H, m, piperidine H), 7.13—8.06 (9H, m, aromatic H), 13.50 (1H, br s, NH).

1-Benzoyl-4-(2-oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (43)——A solution of **42** (1 g, 3.0 mmol) in isopropanol (15 ml), after addition of $NaBH_4$ (0.5 g, 13.2 mmol), was refluxed for 3 h, then concentrated. The residue was mixed with H_2O. Crude crystals that precipitated were collected by filtration, washed with H_2O, and dissolved in $CHCl_3$. The residue obtained by evaporation of the solvent was crystallized from MeOH to give a crude product (813 mg, 81.0%), which was recrystallized from EtOH to afford **43** (534 mg, 53.1%), mp 233—234 °C. *Anal.* Calcd for $C_{20}H_{21}N_3O_2$: C, 71.62; H, 6.31; N, 12.53. Found: C, 71.47; H, 6.38; N, 12.46. IR (KBr): 1690, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.0 (5H, m, piperidine H), 2.4—3.1 (2H, m, piperidine H), 3.5—4.0 (1H, m, piperidine H), 4.32 (1H, m, >CHNH–), 4.4—5.0 (1H, m, piperidine H), 6.40 (1H, br s, NH), 6.7—7.4 (9H, m, aromatic H), 8.82 (1H, br s, NH).

4-(2-Oxo-1,2,3,4-tetrahydro-4-quinazolinyl)piperidine (2d)——A solution of **43** (5 g, 14.9 mmol) in MeOH (50 ml) and 4 N H_2SO_4 (100 ml) was refluxed for 3 d, and then, after evaporation of the MeOH, extracted with $CHCl_3$. The water layer was basified with aq. NaOH and extracted with $CHCl_3$. The extract was concentrated *in vacuo* and crystallized from MeOH to give a crude product (1.6 g, 46.2%), which was recrystallized from EtOH to yield **2d** (0.7 g, 20.3%), mp 224—226 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.47; H, 7.40; N, 17.88. IR (KBr): 1690 cm^{-1}. ^{1}H-NMR (DMSO-d_6 + CD_3OD) δ: 0.88—1.68 (5H, m, piperidine H), 2.02—3.12 (4H, m, piperidine H), 4.1 (1H, m, >CHNH), 6.66—7.16 (4H, m, aromatic H).

1-Benzyl-4-(2-nitrophenylmethylaminomethyl)piperidine·2HCl (48)——A solution of 4-aminomethylpiperidine[10] (57 g, 0.50 mol) and 2-nitrobenzaldehyde (75.5 g, 0.50 mol) in 1 l of MeOH was stirred at room temperature for 3 h. This solution was further stirred, after addition of TEA (70 ml, 0.50 mol) and benzylbromide (59 ml, 0.50 mol), at room temperature overnight. $NaBH_4$ (60 g, 1.60 mol) was added portionwise over 3 h under ice-cooling. The resulting mixture was stirred overnight at room temperature and concentrated *in vacuo*. The residue was mixed with H_2O and extracted with AcOEt to give crystals (130.4 g, 63.3%) of **48** as the 2HCl salt from HCl–MeOH. Recrystallization from EtOH afforded an analytical sample, mp 234—238 °C. *Anal.* Calcd for $C_{20}H_{25}N_3O_2 \cdot 2HCl$: C, 58.26; H, 6.60; N, 10.19. Found: C, 58.12; H, 6.42; N, 10.16. IR (KBr): 1574, 1527, 1345 cm^{-1}. ^{1}H-NMR ($CDCl_3$, as free base) δ: 0.9—3.1 (12H, m, piperidine H, $-NHCH_2CH<$), 3.45 (2H, s, $-CH_2Ar$), 3.98 (2H, s, $-CH_2Ar'$), 7.0—8.1 (9H, m, aromatic H).

1-Benzyl-4-(2-aminophenylmethylaminomethyl)piperidine·2HCl (49)——A mixture of **48**·2HCl (24.8 g, 60 mmol) and 10% Pd–C (2.5 g) in MeOH (400 ml) was stirred under atmospheric pressure of hydrogen at room temperature. After absorption of 180 mmol of hydrogen, the catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a crystalline residue, which was triturated with MeOH and collected by filtration to afford crystals (11.7 g, 63.1%) of **49** as the 2HCl salt. Recrystallization from MeOH gave an analytical sample, mp 226—228 °C. *Anal.* Calcd for $C_{20}H_{27}N_3 \cdot 2HCl$: C, 62.82; H, 7.64; N, 10.99. Found: C, 62.61; H, 7.71; N, 10.89. ^{1}H-NMR (DMSO-d_6) δ: 4.05 (2H, s, $-CH_2Ar$), 4.30 (2H, s, $-CH_2Ar'$), 6.4—7.9 (9H, m, aromatic H).

1-Benzyl-4-(2-oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (50)——A mixture of **49** (9.55 g, 25 mmol, as the 2HCl salt), TEA (7 ml, 50 mmol), and CDI (10 g, 62 mmol) in 100 ml of acetonitrile was refluxed for 3 h and allowed to cool to room temperature. The precipitated crystals were collected by filtration, washed successively with acetonitrile and H_2O, and dried to give crystals (5.2 g, 62.1%) of **50**. Recrystallization from MeOH afforded an analytical sample, mp 177—179 °C. *Anal.* Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.13; H, 7.67; N, 12.28. IR (KBr): 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13—2.2 (7H, m, piperidine H), 2.56—3.1 (2H, m, piperidine H), 3.33 (2H, d, J=6 Hz, $>CHCH_2N$), 3.48 (2H, s, $-CH_2Ar$), 4.42 (2H, s, $-CH_2Ar'$), 6.56—7.43 (9H, m,

aromatic H), 8.82 (1H, br s, NH).

4-(2-Oxo-1,2,3,4-tetrahydro-3-quinazolinylmethyl)piperidine (2e)——A mixture of **50** (5.0 g, 15 mmol), 10% Pd–C (1.0 g), and 1 N HCl (15 ml) in MeOH (90 ml) and H_2O (45 ml) was stirred at 40 °C under a hydrogen atmosphere for 14.5 h and concentrated after removal of the catalyst by filtration. The crystalline residue thus obtained was triturated with AcOEt, collected by filtration, and dried to give crystals (3.77 g, 89.2%) of **2e**·HCl. Recrystallization from MeOH afforded an analytical sample, mp 214—216 °C. *Anal.* Calcd for $C_{14}H_{19}N_3O \cdot HCl$: C, 59.67; H, 7.15; N, 14.91. Found: C, 59.50; H, 7.24; N, 14.80. IR (KBr): 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.0—2.3 (5H, m, piperidine H), 1.6—3.5 (6H, m, >CHCH_2N, piperidine H), 4.44 (2H, s, –CH_2Ar), 6.6—7.35 (4H, m, aromatic H), 9.25 (3H, br s, CONH, NH_2Cl).

References and Notes

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