Orally Active, Nonpeptide Vasopressin V_1 Antagonists. A Novel Series of 1-(1-Substituted 4-piperidyl)-3,4-dihdyro-2(1*H*)-quinolinone

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A series of compounds has been synthesized and demonstrated to be antagonists of V_1 receptors both in vitro and in vivo. These compounds are structurally related to the 1-(4-piperidyl)-2(1*H*)-quinolinones, including OPC-21268, an orally bioavailable AVP V_1 antagonist with high V_1 specificity. It has been found that the introduction of an acetamide group on the terminal alkoxy chain of **41–44** leads to an increase in oral activity. Certain of these compounds may have efficacy in the study of AVP V_1 receptors.

Arginine vasopressin (AVP) may contribute to cardiovascular regulation by vasoconstriction and stimulation of renal water absorption through V_1 and V_2 receptors, respectively. Antagonists of the vasopressor responses to AVP can be pharmacological tools in the studies of the role(s) of AVP and may have clinical potential for the treatment of human diseases.[1,2] Therefore, a number of peptide analogs of AVP have been reported as V_1 and/or V_1/V_2 antagonists.[1-13] Reported V_1-receptor antagonists show a blocking action to vasoconstriction caused by the administration of vasopressin. However, all potent V_1-receptor antagonists so far have been peptides, which have poor oral bioavailability and some of which exhibit partial agonistic activity. We now report here the brief history of the development of our orally effective, nonpeptide AVP V_1-receptor antagonists.

Through drug design via computer has progressed remarkably, with our current knowledge, it is not yet possible to design novel nonpeptide compounds with a high affinity for a macromolecular receptor. Moreover, we could not find a shorter but still potent peptide analogue of AVP that could be transformed to a nonpeptide compound. Therefore, we turned our attention to the search for an orally bioavailable AVP antagonist around the nonpeptide OPC-18549 (**1**, Figure 1), a screening lead with 2.5 μM affinity for rat liver receptors. As compound **1** has a simple structure with V_1-selective inhibition, we then started the optimization of this molecule to enhance its activity and oral bioavailability.

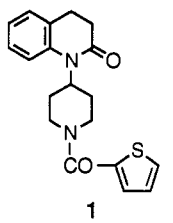

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Figure 1.

Chemistry

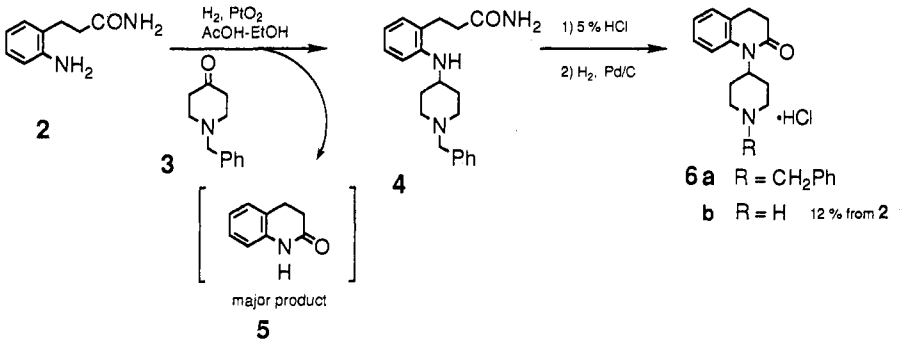
The synthesis of benzylpiperidine **6a** has been reported as in Scheme I.[14] However, piperidine **6b** was obtained only in poor yield from the dihydrocinnamamide **2**, because the major product of the reductive amination process of the 4-piperidone **3** with **2** was 2(1*H*)-quinolinone **5**. Therefore, we decided to investigate the alternative route for the synthesis of **6b** (Scheme II). The benzylpiperidine **7**[15] was condensed with β-ethoxyacryloyl chloride[16] to yield **8**. Cyclization of **8** was achieved by treatment with concentrated sulfuric acid to afford the desired product **9** in good yield. The double bond and benzyl group of **9** were removed by simultaneous hydrogenation and hydrogenolysis, and the requisite intermediate **6b** was obtained in good yield. Almost all target compounds were readily synthesized from this key intermediate **6b** with the commercially available acid chlorides or carboxylic acids as shown in Scheme III. The acetoxy group in **25–27** was hydrolyzed with potassium carbonate to provide phenol derivatives **28–30**. Reduction of the nitro group in compound **24** yielded aniline derivatives **31**. Hydrolysis of ester **32** gave carboxylic acid **33**, and treatment of **33** with oxalyl chloride followed by aqueous ammonia afforded carboxamide **34**. 4-(ω-Substituted alkoxy)benzoyl derivatives in Table III were synthesized by the routes depicted in Scheme IV. Alkylation of **30** with *N*-(bromoalkyl)-phthalimide yielded **48–53** and removal of the phthalimide protecting group with hydrazine-hydrate produced **54–59**. The formamides **60** and **61** were prepared by the standard procedure using formic acid and acetic anhydride. Acylation of **54–59** with acetic anhydride or acid chlorides furnished the desired products **62–69**. *N*-Methylation of **63** with methyl iodide afforded **70**.

Biology

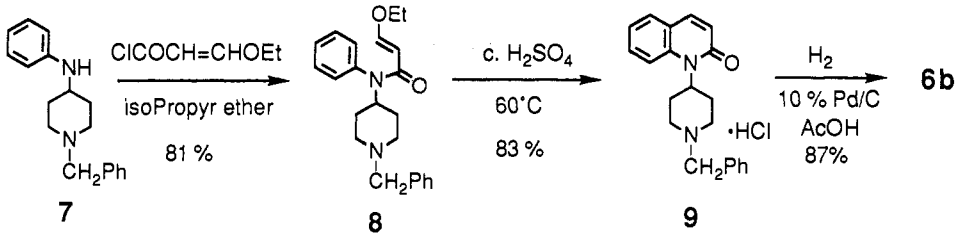
The methods for determination of AVP (rat liver = V_1 and rat kidney = V_2) receptor binding have been published elsewhere.[17-20] Antipressor studies were performed as described in a separate publication.[20] Exogenously administered AVP (30 milliunits/kg iv) induced an increase in blood pressure in conscious rats. After oral administration of the compounds, the vasoconstriction induced by exogenous AVP was inhibited in a time- and dose-dependent manner. The change of blood pressure in response to AVP-induced vasoconstriction was compared at various time points prior to and following the oral administration of the compounds at doses of 2.0–290 μM/kg. The dose of compound needed to produce a 50% inhibition of the control pressor response to AVP was used as ID_{50} values to estimate the potency of the compound.

0022-2623/93/1836-2011$04.00/0

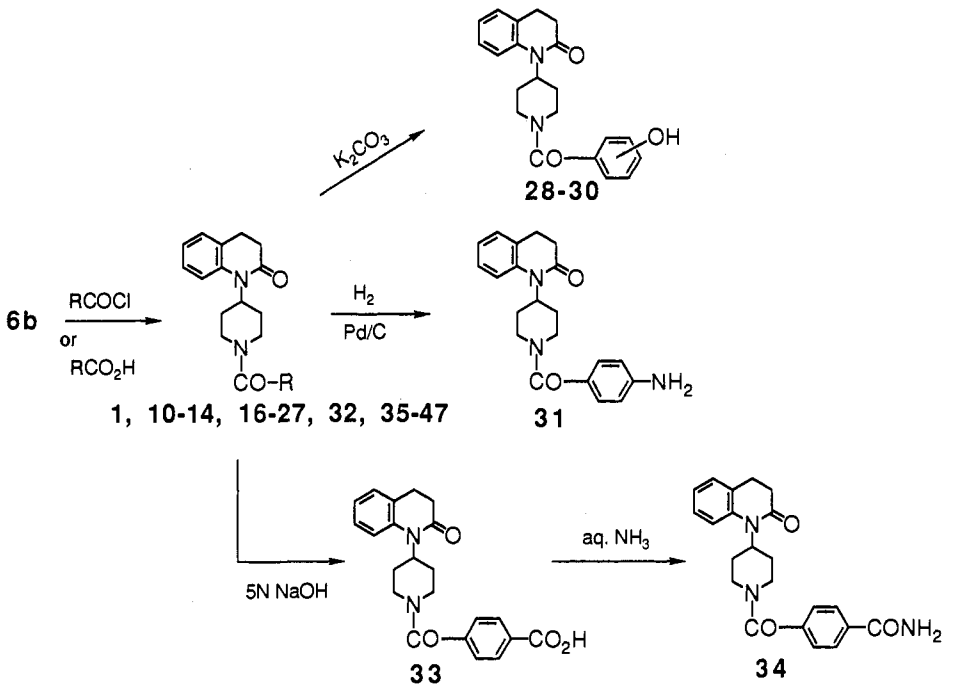
Scheme I



Scheme II



Scheme III



Results and Discussion

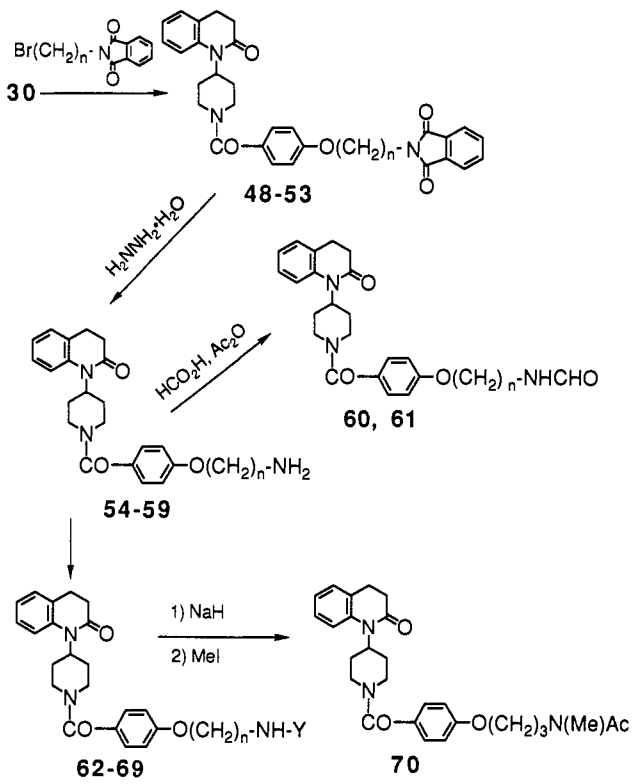
The compounds were tested primarily with respect to their affinity for the AVP receptors as measured by their ability to displace [^{3}H]AVP from its specific binding sites in rat liver (V_1 receptor) and kidney (V_2 receptor) plasma membranes, respectively; the data are reported in Tables I–III as IC_{50} values.

The initial modification studies of the screening lead **1** were focused on the terminal thiophenecarboxamide substituent. Replacement of this thiophene ring with another heteroaromatic ring did not show any activity enhancement as shown by the selected analogues **10–14** in Table I. Among these compounds, the simple phenyl derivative **14** showed modest improvement for the V_1 receptor over the lead compound **1**. The insertion of a methylene group between the carbonyl and phenyl ring as in **13** reduced the potency. Conversion of the amido bond into the aminomethylene group as in compound **6a** eliminated the binding potency;[21] methyl analogue **15** also proved essentially inactive.

The substituent effects on the phenyl ring are shown in Table II. Compounds **16–30** were made to evaluate the effect of the substituents' ring position on binding affinity. The substitution in the para position almost always shows a greater binding affinity for the V_1 receptors compared to the ortho or meta positions. More importantly, para substitution with methyl or acetoxy (**21**, **27**) provided a substantial affinity enhancement for the V_1 receptor compared to **14**.

Introduction of para substituents on the benzoyl ring, however, produced wide variations in V_1 receptor affinity depending on the substituent as shown in Table II. The

Scheme IV



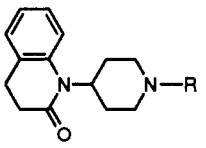
carboxy group (**33**), for example, exhibited significant reductions in V_1 receptor affinity which may be attributable to the charge. On the other hand, the substitution of methyl, acetoxy, dimethylamino, bromo, and methoxy (**21**, **27**, **37**, **39**, and **40**) provided the increment of binding affinity over the nonsubstituted congener **14**. Introduction of amine, ester, acetamide, and cyano (**31**, **32**, **35**, and **36**) groups gave virtually no improvement in receptor binding affinity or were slightly detrimental to V_1 binding. These results suggested that the more lipophilic groups exhibited a more potent binding affinity. On the basis of this observation, two types of compounds were prepared: alkoxy series **40–44** and alkyl series **45–47**. The results of this study showed that the most potent compounds in these series were ethoxy **41** and propyl **46**, respectively, both chain lengths being three atoms.[22]

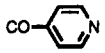
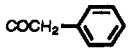
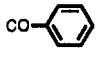
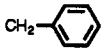
The effect of anti vasopressor activity was then examined by oral administration to conscious rat, as illustrated by the selected analogues in Table II. These compounds were found to be orally effective V_1 antagonists, though the antagonist potency was not satisfactory. Encouraged by these results, we continued the modification of this new lead compound (**41**). In order to improve oral activity, we hypothesized that this compound had sufficient lipophilicity but poor water solubility, thus suggesting the introduction of a hydrophilic group.

The results of the hydrophilic substituent series are shown in Table III. The effects of such hydrophilic substituents differ entirely from the unsubstituted series **40–44** in Table II. In the simple amino series **54–59**, it seems that the longer chain shows the most potent V_1 binding affinity, and compound **59** shows the highest binding affinity (IC_{50} 0.068 μM). However, both in the formyl amino series **60–61** and acetyl amino series **62–67**, the potency of binding affinity was not as greatly changed as in the simple amino series. We found that the optimal length of the alkoxy chain for binding affinity is six carbons when the hydrophilic substituent is acetamide.

The comparison of binding affinities between a series of compounds **55–58** and **63–66**, whose chain length, n is 3–6 atoms, indicates that the basicity of the terminal amino group is not critical. *N*-Methylation of the amide nitrogen (**70**) had virtually no affect in V_1 binding compared to **63** or **68** which suggests that the terminal amide bond could

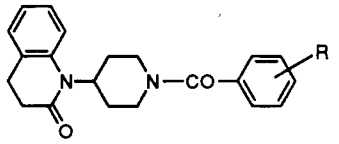
Table I. Binding Affinity of AVP V_1 Receptor Antagonists



no.	R	method[a]	mp (°C)	formula[b]	receptor affinity[c] IC_{50} (μM) V_1	V_2
1		A	129–132	$C_{19}H_{20}N_2O_2S$	2.5	>100
10		B	*d*	$C_{19}H_{20}N_4O_2 \cdot {}^1/_4H_2O$	26	>100
11		A	105–108	$C_{20}H_{21}N_3O_2$	37	>100
12		a	108–111	$C_{19}H_{20}N_2O_3$	11	>100
13		A	*d*	$C_{22}H_{24}N_2O_2 \cdot {}^1/_4H_2O$	12	>100
14			108–111	$C_{21}H_{22}N_2O_2$	1.9	>50
15	Me	*e*	111–113	$C_{15}H_{20}N_2O \cdot {}^1/_4H_2O$	>100	>50
6a		*e*	225–230	$C_{21}H_{24}N_2O \cdot HCl \cdot {}^1/_4H_2O$	>100	>100

[a] See the Experimental Section for specific details. [b] Carbon, hydrogen, and nitrogen analyses were within ±0.4% of the theoretical. [c] Compounds were tested for their ability to displace [^{3}H]AVP from its specific binding sites in rat liver (V_1 receptor) and kidney (V_2 receptor) plasma membrane preparations (see refs 19 and 20). [d] Amorphous solid. [e] See ref 14.

Table II. AVP V_1 Receptor Antagonists



no.	R	method[a]	mp (°C)	receptor affinity[c] IC_{50} (μM) formula[b]	V_1	V_2	antipressor activity % inhibition[d]
16	2-Cl	A	175–178	$C_{21}H_{21}ClN_2O_2$	9.9	>100	
17	3-Cl	A	123–126	$C_{21}H_{21}ClN_2O_2 \cdot {}^1/_4H_2O$	4.4	>100	
18	4-Cl	A	111–112	$C_{21}H_{21}ClN_2O_2$	1.2	78	
19	2-Me	A	169–172	$C_{22}H_{24}N_2O_2$	8.4	>100	
20	3-Me	A	144–146	$C_{22}H_{24}N_2O_2$	1.3	>100	
21	4-Me	A	112–113.5	$C_{22}H_{24}N_2O_2$	0.50	>100	23 ± 8.9 (290)[e]
22	2-NO_2	A	207–209	$C_{21}H_{21}N_3O_4$	8.4	>100	
23	3-NO_2	A	*f*	$C_{21}H_{21}N_3O_4$	3.1	>100	
24	4-NO_2	A	142–145	$C_{21}H_{21}N_3O_4$	2.0	>100	
25	2-OAc	A	159–161	$C_{23}H_{24}N_2O_4$	1.4	>100	
26	3-OAc	B	*f*	$C_{23}H_{24}N_2O_4$	3.7	>100	
27	4-OAc	C	170–171	$C_{24}H_{24}N_2O_4$	0.49	>100	
28	2-OH	*g*	156–158	$C_{21}H_{22}N_2O_3$	1.5	>100	
29	3-OH	*g*	188–189	$C_{21}H_{22}N_2O_3$	6.3	>100	
30	4-OH	*g*	182–183	$C_{21}H_{22}N_2O_3$	1.3	>100	
31	4-NH_2	*g*	198–199	$C_{21}H_{23}N_3O_2$	3.7	>100	
32	4-CO_2Me	A	160–162	$C_{23}H_{24}N_2O_4$	3.5	>100	
33	4-CO_2H	*g*	233–235	$C_{22}H_{22}N_2O_4$	>100	>100	
34	4-$CONH_2$	*g*	101–104	$C_{22}H_{23}N_3O_3$	11	>100	
35	4-NHAc	B	85–90	$C_{23}H_{25}N_3O_3 \cdot {}^3/_4H_2O$	2.8	>100	
36	4-CN	A	169–172	$C_{21}H_{21}N_3O_2$	3.1	>100	
37	4-NMe_2	B	153–155	$C_{23}H_{27}N_3O_2$	0.47	>100	
38	4-F	A	105–107	$C_{21}H_{21}FN_2O_2$	1.4	>100	
39	4-Br	A	124–126	$C_{21}H_{21}BrN_2O_2$	0.50	73	NE (240)[e,h]
40	4-OMe	A	93–96	$C_{22}H_{24}N_2O_3$	0.62	>100	
41	4-OEt	C	97–99	$C_{23}H_{26}H_2O_3$	0.21	>100	75 ± 3.4 (79)[e,i]
42	4-OPr	B	110–111	$C_{24}H_{28}N_2O_3 \cdot {}^1/_4H_2O$	0.32	>100	65 ± 6.1 (76)[e]
43	4-OBu	B	*f*	$C_{25}H_{30}N_2O_3 \cdot {}^1/_4H_2O$	0.42	>100	
44	4-OHex	B	*f*	$C_{27}H_{34}N_2O_3 \cdot {}^1/_3H_2O$	1.5	54	
45	4-Et	A	133–134	$C_{23}H_{28}N_2O_2$	0.50	80	
46	4-Pr	A	113–117	$C_{24}H_{28}N_2O_2$	0.33	>100	86 ± 6.0 (270)[e]
47	4-Bu	A	103–104	$C_{25}H_{30}N_2O_2$	0.35	83	

[a] See the Experimental Section for specific details. [b,c] See Table I for an explanation of tabulated data. [d] The inhibition was expressed as percent change in diastolic blood pressure increased by AVP (30 milliunits/kg, iv) before and after test compounds po administration. Except where indicated, a number of determinations was four. [e] Dosage in parentheses (μM/kg). [f] Amorphous solid. [g] See the Experimental Section. [h] NE = no effect. [i] $n = 7$.

not act as hydrogen bond donor with the receptor. Furthermore, none of the compounds in this paper exhibited apparent V_2 binding affinity.

The data in Table III show further, however, that the relative orders of potency of the various analogues in the in vitro assay do not always translate well into in vivo antagonistic activity. For example, the potent in vitro compounds (**56**, **57**, **59**) do not show potent activity in vivo. The enhancement of anti vasopressor activity by oral administration was achieved by adding an acetyl group to the amine of the terminal alkoxy chain such as **62–66**. Noteworthy, the compound **63** (OPC-21268), which did not show the highest binding affinity, shows the most potent oral activity. Replacement of the amide linkage of **63** with a urethane, such as **69**, was slightly detrimental to the in vivo activity. Conversion of the acetyl group of **63** into formyl or propionyl such as **60** and **68** lowered the oral activity.

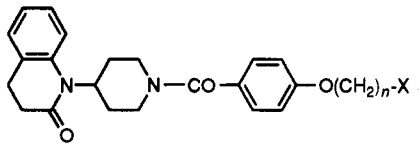
In conclusion, we have described the development of the 1-(4-piperidyl)-2(1*H*)-quinolinone, OPC-21268 (**63**). This compound is an orally effective, nonpeptide antagonist for the AVP receptor and turned out to be a pure V_1 antagonist. By using simple subtitution chemistry, we quickly achieved modest enhancement in binding affinity compared with the initial lead as V_1 blockers and also discovered that the introduction of an acetamide group at the terminus of the alkoxy chain leads to an increase in oral activity. We hope that the compounds disclosed in this paper will become important pharmacological tools in the future study of the V_1 receptor.

Experimental Section

Melting points were determined by a Yanagimoto Micro Point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded on either a Bruker AC-200 (200 MHz) spectrometer or a Bruker AC-250 (250 MHz) spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_5 (TSP) as an internal standard. Elemental analyses were determined with on a Yanaco MT-5 CHN CORDER, and were within ±0.4% of theory unless noted otherwise. All compounds were routinely checked by TLC with Merck silica gel 60 F254 precoated plates.

β-Ethoxy-*N*-phenyl-*N*-(1-benzyl-4-piperidyl)acrylamide (8). To a solution of 1-benzyl-4-anilinopiperidine **7** (0.90 g, 3.4 mmol) and triethylamine (0.50 g, 4.9 mmol) in isopropyl ether (30 mL) at 70 °C was added dropwise β-ethoxyacryloyl chloride (0.7 g, 5.2 mmol), and the mixture was refluxed for 1 h. The reaction mixture was poured into ice–water followed by extraction with ethyl acetate. The organic layers were dried ($MgSO_4$) and evaporated. The resulting residue was triturated with *n*-hexane to afford **8** (1.1 g, 89%) as a white solid: mp 107–111 °C; NMR ($CDCl_3$) δ 1.19 (3H, t, J = 5.7 Hz), 1.42 (2H, dq, J = 3.0, 9.8 Hz), 1.77 (2H, d, J = 9.6 Hz), 2.12 (2H, dt, J = 1.6, 9.5 Hz), 2.88 (2H, d, J = 9.3 Hz), 3.43 (2H, s), 3.68 (2H, q, J = 5.6 Hz), 4.65–4.76 (1H, m), 4.82 (1H, d, J = 9.6 Hz), 7.05–7.07 (2H,

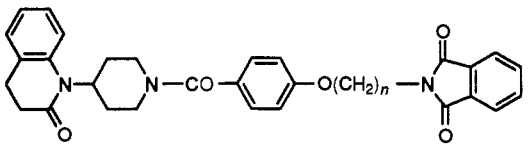
Table III. AVP V_1 Receptor Antagonists



no.	n	X	mp (°C)	formula[a]	receptor affinity[b] IC_{50} (μM) V_1	V_2	antipressor activity % inhibition[c]	ID_{50} (μM/kg)[d]
54	2	NH_2	*e*	$C_{23}H_{27}N_3O_3O_3 \cdot {}^3/_2H_2O$[f]	2.0	>100		
55	3	NH_2	*e*	$C_{24}H_{29}N_3O_3 \cdot {}^3/_4H_2O$	0.75	>100		
56	4	NH_2	*e*	$C_{25}H_{31}N_3O_3 \cdot {}^1/_4H_2O$	0.33	>100	31 ± 14 (23)[g]	
57	5	NH_2	*e*	$C_{26}H_{33}N_3O_3 \cdot {}^5/_4H_2O$[h]	0.28	>100	NE (22)[g,i,j]	
58	6	NH_2	*e*	$C_{27}H_{35}N_3O_3 \cdot {}^5/_4H_2O$[k]	0.10	>100		
59	8	NH_2	*e*	$C_{29}H_{39}N_3O_3 \cdot H_2O$	0.068	44	NE (20)[g,i,j]	
60	3	NHCHO	*e*	$C_{25}H_{29}N_3O_4$	0.24	>100	50 ± 13 (23)[g,j]	
61	4	NHCHO	*e*	$C_{26}H_{31}N_3O_4 \cdot H_2O$	0.25	>100		
62	2	NHAc	*e*	$C_{25}H_{29}N_3O_4 \cdot {}^1/_4H_2O$	0.42	>100	80 ± 4.7 (23)[g,j]	7.7
63	3	NHAc	147.5–149	$C_{26}H_{31}N_3O_4 \cdot {}^1/_4H_2O$	0.44	>100	93 ± 4.0 (22)[g]	4.4
64	4	NHAc	*e*	$C_{27}H_{33}N_3O_4 \cdot {}^1/_4H_2O$	0.21	>100	78 ± 9.3 (21)[g,l]	5.3
65	5	NHAc	*e*	$C_{28}H_{35}N_3O_4 \cdot {}^1/_2H_2O$	0.16	>100	81 ± 6.3 (21)[g]	4.7
66	6	NHAc	*e*	$C_{29}H_{37}N_3O_4 \cdot {}^1/_4H_2O$	0.12	>100	72 ± 12 (20)[g,l]	10
67	8	NHAc	*e*	$C_{31}H_{41}N_3O_4 \cdot {}^1/_4H_2O$	0.30	>100	NE (19)[g,i]	
68	3	NHCOEt	*e*	$C_{27}H_{33}N_3O_4 \cdot {}^5/_4H_2O$[m]	0.78	>100		
69	3	$NHCO_2Me$	*e*	$C_{26}H_{31}N_3O_5$	0.36	>100	73 ± 9.2 (21)[g]	8.6
70	3	N(Me)Ac	*e*	$C_{27}H_{33}N_3O_4 \cdot {}^1/_4H_2O$	0.54	>100		

[a] Except where indicated, satisfactory analyses (±0.4%) were obtained for C, H, N. [b] See footnote *c*, Table I. [c] See footnote *d*, Table II. [d] ID_{50} represents the 50% inhibition dose for AVP (30 milliunits/kg, iv) induced vasoconstriction when test compounds are orally administrated. [e] Amorphous solid. [f] H: calcd, 7.19; found 6.61. [g] Dosage in parentheses (μM/kg). [h] H: calcd, 7.81; found 7.30. [i] NE = no effect. [j] n = 3. [k] H: calcd, 8.01; found, 7.42. [l] n = 5. [m] N: calcd, 8.64; found, 8.22.

Table IV. Phthalimide Derivatives



no.	n	mp (°C)	formula[a]
48	2	*b*	$C_{31}H_{29}N_3O_5$[c]
49	3	*b*	$C_{32}H_{29}N_3O_5$
50	4	171–173	$C_{33}H_{29}N_3O_5$
51	5	*b*	$C_{34}H_{29}N_3O_5$[c]
52	6	*b*	$C_{35}H_{29}N_3O_5 \cdot {}^1/_2H_2O$
53	8	*b*	$C_{37}H_{29}N_3O_5 \cdot {}^1/_4H_2O$

[a] See footnote *b*, Table I. [b] Amorphous solid. [c] This compound was isolated but not purified or analyzed before use in the next step.

m), 7.08–7.41 (8H, m), 7.47 (1H, d, J = 9.6 Hz). Anal. ($C_{23}H_{28}N_2O_2$) C, H, N.

1-(1-Benzyl-4-piperidyl)-2(1*H*)-quinolinone Hydrochloride (9). The amide **8** (157 g, 0.431 mol) was added portionwise to concentrated sulfuric acid (800 mL) at 60 °C, and the mixture was stirred for 0.5 h at 60 °C. The reaction mixture was poured into ice–water, and aqueous sodium hydroxide was added until the pH of the solution remained in the range 8–9. The solution was extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was then dissolved in ethyl alcohol. The solution was adjusted to pH 3 with hydrochloric acid, and the resulting preciptate was recovered by filtration to provide **9** (132 g, 86%) as colorless scales: mp 257–262 °C; NMR (DMSO-d_6) δ 1.69–2.01 (2H, m), 3.04–3.72 (6H, m), 4.36 (2H, s), 5.22 (1H, br s), 6.58 (1H, d, J = 9.5 Hz), 7.28 (1H, dd, J = 7.4, 7.4 Hz), 7.41–8.38 (8H, m), 7.90 (1H, d, J = 9.5 Hz), 11.65 (1H, br s). Anal. ($C_{21}H_{22}N_2O \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

3,4-Dihydro-1-(4-piperidyl)-2(1*H*)-quinolinone Hydrochloride (6b). A mixture of **9** (83.7 g, 0.236 mol) and 10% palladium/carbon (8 g) in 0.6 L of acetic acid at 80 °C was stirred under 5 atm of hydrogen in a glass autoclave for 5 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under vacuum. The residue was dissolved in water, and the solution was adjusted to pH 11 with 5 N aqueous sodium hydroxide and then extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was dissolved in ethyl alcohol. The solution was adjusted to pH 3 with hydrochloric acid, and the resulting precipitate was recovered by filtration to provide **6b** (60.6 g, 96%) as colorless scales: mp 274–278 °C; NMR (DMSO-d_6) δ 1.70–2.02 (2H, m), 2.36–2.64 (2H, m), 2.64–3.53 (8H, m), 4.25–4.55 (1H, m), 6.96–7.14 (1H, m), 7.14–7.38 (2H, m), 7.41 (1H, d, J = 8.1 Hz), 9.17 (2H, br s). Anal. ($C_{14}H_{18}N_2O \cdot HCl \cdot {}^1/_4H_2O$) C, H, N.

Method A. Preparation of Methyl 4-[[4-[3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl]-1-piperidyl]carbonyl]benzoate (32). To a solution of **6b** (5.8 g, 22 mmol) in methylene chloride (100 mL) was added methyl terephthaloyl chloride (5.6 g, 28 mmol) at 0–5 °C, followed by the addition of trimethylamine (12 mL) at 0–5 °C. The reaction mixture was stirred overnight at room temperature. The mixture was poured into water and extracted with methylene chloride. The organic layers were dried over sodium carbonate and concentrated. Column chromatography (elution: 5–10% methanol/methylene chloride), and crystallization with *n*-hexane–ethanol gave **32** (6.33 g, 74%) as white powder: mp 160–162 °C; NMR ($CDCl_3$) δ 1.64–2.03 (2H, m), 2.52–3.26 (8H, m), 3.69–3.94 (1H, m), 3.94 (3H, s), 4.24–4.49 (1H, m), 4.38–5.07 (1H, m), 6.97–7.33 (4H, m), 7.52 (2H, d, J = 8.5 Hz), 8.09 (2H, d, J = 8.5 Hz). Anal. ($C_{23}H_{24}N_2O_4$) C, H, N.

Method B. Preparation of 3,4-Dihydro-1-[1-[4-(dimethylamino)benzoyl]-4-piperidyl]-2(1*H*)-quinolinone (37). To a solution of **6b** (0.56 g, 2.1 mmol), 4-(dimethylamino)benzoic acid (0.51 g, 3.1 mmol), and bis(2-oxo-3-oxazolyldinyl)phosphinic chloride (0.85 g, 3.3 mmol) in methylene chloride (10 mL) was added dropwise triethylamine (1.2 mL, 8.4 mmol) at 0–5 °C, and the solution was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted with methylene chloride. The extract was dried (Na_2CO_3) and concentrated. Column chromatography in 3:1 hexane–ethyl acetate over silica gel followed by recrystallization from hexane–ethanol yielded **37** (0.43 g, 55%) as a white solid: mp 153–155 °C; NMR ($CDCl_3$) δ 1.72–1.88 (2H, m), 2.52–3.08 (8H, m), 3.00 (6H, s), 4.24–4.76 (3H, m), 6.68 (2H, d, J = 8.9 Hz), 6.96–7.33 (4H, m), 7.41 (2H, d, J = 8.9 Hz). Anal. ($C_{23}H_{27}N_3O_2$) C, H, N.

Method C. Preparation of 1-[1-(4-Ethoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (41). *p*-Ethoxybenzoic acid (7.5 g, 45.1 mmol), thionyl chloride (16 mL, 219 mmol), and chloroform (100 mL) was mixed and refluxed for 2 h. The solvent was removed in vacuo, and the residue was dissolved in toluene. The solvent was removed on a rotary evaporator and the evaporation with toluene repeated to remove all of the thionyl chloride. This acid chloride, dissolved in

methylene chloride (30 mL), was added dropwise to a solution of **6b** (5.79 g, 21.7 mmol) and triethylamine (30 mL) in methylene chloride (70 mL) at 0–5 °C, and the reaction mixture was stirred for 2 h at room temperature. The mixture was poured into water and extracted with methylene chloride. The organic layers were dried over sodium carbonate and concentrated. Column chromatography in 5:1 hexane–ethyl acetate over silica gel followed by recrystallization from hexane–ethanol yielded **41** (6.54 g, 80%) as colorless needles: mp 97–99 °C; NMR ($CDCl_3$) δ 1.43 (3H, 2, J = 6.9 Hz), 1.66–2.03 (2H, m), 2.51–3.20 (8H, m), 3.70–5.30 (2H, br s), 4.16 (2H, q, J = 6.9 Hz), 4.40 (1H, m), 6.90 (2H, d, J = 8.7 Hz), 6.98–7.32 (4H, m), 7.43 (2H, d, J = 8.7 Hz). Anal. ($C_{23}H_{26}N_2O_3$) C, H, N.

3,4-Dihydro-1-[1-(4-hydroxybenzoyl)-4-piperidyl]-2(1*H*)-quinolinone (30). A mixture of **27** (12.4 g, 29.5 mmol) and potassium carbonate (13 g, 94.1 mmol) in methanol (100 mL) was stirred overnight at room temperature. The reaction mixture was poured into aqueous ammonium chloride and extracted with chloroform. The organic layers were dried ($MgSO_4$) and concentrated. The residue was crystallized with *n*-hexane–ethanol to **30** (11.2 g, 97%) as a white powder: mp 182–183 °C; NMR ($CDCl_3$) δ 1.69–2.02 (2H, m), 2.51–3.26 (8H, m), 3.90–5.04 (3H, m), 6.80 (2H, d, J = 8.5 Hz), 6.98–7.37 (4H, m), 7.31 (2H, d, J = 8.5 Hz), 8.46 (1H, s). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

3,4-Dihydro-1-[1-(4-aminobenozyl)-4-piperidyl]-2(1*H*)-quinolinone (31). A mixture of **24** (4.21 g, 11.1 mmol) and 5% palladium/carbon (1 g) in ethanol (100 mL) was stirred under hydrogen atomosphere (1 atm) at room temperature. After absorption of 750 mL of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated. The crude mixture was chromatographed over silica gel in 50:1–10:1 methylene chloride–methanol and crystallized with *n*-hexane–ethanol to yield **31** (3.6 g, 93%) as a white powder: mp 198–199 °C; NMR ($CDCl_3$) δ 1.69–1.96 (2H, m), 2.49–3.12 (8H, m), 3.39–4.83 (5H, m), 6.65 (2H, d, J = 8.5 Hz), 6.96–7.42 (4H, m), 7.33 (2H, d, J = 8.5 Hz). Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

4-[[4-[3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl]-1-piperidyl]-carbonyl]benzoic Acid (33). To a solution of sodium hydroxide (1.94 g, 48.5 mmol) in methanol (100 mL) was added **32** (6.33 g, 16.1 mmol), and the solution was stirred at room temperature overnight. The reaction mixture was poured into water, adjusted to pH 2 with hydrochloric acid, and extracted with chloroform. The combined organic phases were dried ($MgSO_4$) and concentrated. The residue was crystallized with *n*-hexane–ethanol to give **33** (4.5 g, 74%) as a white powder: mp 232–235 °C; NMR ($CDCl_3$) δ 1.65–2.04 (2H, m), 2.51–3.27 (8H, m), 3.67–3.94 (1H, m), 4.24–4.48 (1H, m), 4.82–5.06 (1H, m), 6.97–7.32 (4H, m), 7.48 (1H, br s), 7.56 (2H, d, J = 8.3 Hz), 8.15 (2H, d, J = 8.3 Hz). Anal. ($C_{22}H_{22}N_2O_4$) C, H, N.

3,4-Dihydro-1-[1-(4-carbamoylbenzoyl)-4-piperidyl]-2-(1*H*)-quinolinone (34). To a solution of **33** (0.50 g, 1.3 mmol) in methylene chloride (10 mL) was added dropwise oxalyl chloride (0.14 mL, 1.6 mmol) at 0–5 °C, and the solution was refluxed for 1 h. After concentration, the residue was dissolved in methylene chloride (10 mL). To a solution was added 25% aqueous ammonia (1 mL), and the solution was stirred overnight at room temperature. The resulting crystals were collected by filtration and recrystallized from ether–*n*-hexane to give **34** (200 mg, 40%) as a white powder: mp 101–104 °C; NMR ($CDCl_3$) δ 1.53–2.03 (2H, m), 2.52–3.24 (8H, m), 3.56–3.97 (1H, m), 4.21–4.47 (1H, m), 4.76–5.07 (1H, m), 5.70 (1H, br s), 6.19 (1H, br s), 6.99–7.32 (4H, m), 7.53 (2H, d, J = 8.4 Hz), 7.86 (2H, d, J = 8.4 Hz). Anal. ($C_{22}H_{23}N_3O_3$) C, H, N.

3,4-Dihydro-1-[1-[4-(3-phthalimidopropoxy)benzoyl]-4-piperidyl]-2(1*H*)-quinolinone (49). A mixture of **30** (8.0 g, 22.8 mmol), *N*-(3-bromopropyl)phthalimide (6.7 g, 25 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (3.8 g, 25 mmol) in 2-propanol (100 mL) was refluxed for 8 h and concentrated. The residue was poured into water and extracted with ethyl acetate. The organic layers were washed with 0.5 N hydrochloric acid and water, dried ($MgSO_4$), and concentrated. Column chromatography (elution: 0–5% methanol/dichloromethane) afforded **49** (9.1 g, 74%) as a viscous oil: NMR ($CDCl_3$) δ 1.62–1.95 (2H, m), 2.07–2.33 (2H, m), 2.43–3.16 (8H, m), 3.92 (2H, t, J = 6.8 Hz), 4.06 (2H, t, J = 6.1 Hz), 3.95–5.05 (3H, m), 6.80 (2H, d, J = 8.7 Hz), 6.95–7.39 (4H, m), 7.38 (2H, d, J = 8.7 Hz), 7.65–8.00 (4H, m). Anal. ($C_{32}H_{29}N_3O_5$) C, H, N.

1-[1-[4-(3-Aminopropoxy)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (55). A solution of **49** (9.5 g, 17.7 mmol) and hydrazine hydrate (1.12 g, 22 mmol) in ethanol (100 mL) was refluxed for 2.5 h. After cooling, the reaction mixture was adjusted to pH 2–3 with hydrochloric acid. The resulting suspension was filtered, and the filtrate was concentrated. The residue was poured into water, and aqueous sodium hydroxide was added until the pH of the solution remained in the range 8–9. The solution was extracted with ethyl acetate. The combined organic phases were dried ($MgSO_4$) and evaporated. Column chromatography (elution: 0–5% methanol/dichloromethane) afforded **55** (5.18 g, 72%) as a viscous oil: NMR ($CDCl_3$) δ 1.57–2.10 (6H, m), 2.47–3.18 (8H, m), 2.92 (2H, t, J = 6.8 Hz), 4.08 (2H, t, J = 6.1 Hz), 4.10–5.15 (3H, m), 6.82–7.58 (8H, m). Anal. ($C_{24}H_{29}N_3O_3 \cdot {}^3/_4H_2O$) C, H, N.

3,4-Dihydro-1-[1-[4-[3-(formylamino)propoxy]benzoyl]-4-piperidyl]-2(1*H*)-quinolinone (60). A mixture of formic acid (0.23 mL) and acetic anhydride (0.49 mL) was stirred at 50–60 °C for 1.5 h. After cooling, **55** (0.7 g, 1.7 mmol) was added to the mixture, and the mixture was stirred for 22 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. Column chromatography (elution: 4% methanol/dichloromethane) afforded **60** (0.27 g, 36%) as an amorphous solid: NMR ($CDCl_3$) δ 1.67–1.94 (2H, m), 2.04 (2H, quint, J = 6.2 Hz), 2.53–3.20 (8H, m), 3.51 (2H, q, J = 6.2 Hz), 3.65–5.15 (2H, br), 4.06 (2H, t, J = 6.2 Hz), 4.37 (1H, m), 6.29 (1H, br s), 6.91 (2H, d, J = 8.7 Hz), 6.98–7.29 (4H, m), 7.43 (2H, d, J = 8.7 Hz), 8.14 (1H, s). Anal. ($C_{25}H_{28}N_3O_4$) C, H, N.

1-[1-[4-[3-(Acetylamino)propoxy]benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (63). To a solution of **55** (0.40 g, 0.98 mmol) in acetic anhydride (5 mL) was added concentrated sulfuric acid (1 drop) at room temperature, and the solution was stirred for 3 h. The reaction mixture was poured into ice–water and extracted with ethyl acetate. The organic layers were washed with 0.5 N NaOH and brine, dried ($MgSO_4$), and concentrated. Column chromatography (elution: 1–2% methanol/dichloromethane) afforded **63** (0.32 g, 72%) as colorless needles: mp 147.5–149 °C; NMR ($CDCl_3$) δ 1.63–2.15 (4H, m), 1.99 (3H, s), 2.49–3.20 (8H, m), 3.35–3.60 (2H, m), 3.90–5.10 (3H, m), 4.06 (2H, t, J = 5.9 Hz), 5.89 (1H, br s), 6.89 (2H, d, J = 8.7 Hz), 6.95–7.37 (4H, m), 7.43 (2H, d, J = 8.7 Hz). Anal. ($C_{26}H_{31}N_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

3,4-Dihydro-1-[1-[4-[3-[*N*-methyl-*N*-acetylamino]propoxy]benzoyl]-4-piperidyl]-2(1*H*)-quinolinone (70). A solution of **63** (0.2 g, 0.44 mmol) in dimethylformamide (5 mL) was treated with sodium hydride (60% dispersion in oil, 21 mg) at room temperature, and the mixture was stirred for 1 h. To this mixture was added dropwise a solution of methyl iodide (81 mg, 0.57 mmol) in dimethylformamide (1 mL), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and concentrated. Column chromatography in 1% methanol/dichloromethane over silica gel afforded **70** (0.13 g, 63%) as a colorless amorphous solid: NMR ($CDCl_3$) δ 1.60–2.23 (7H, m), 2.45–3.23 (11H, m), 3.42–3.69 (2H, m), 3.85–5.14 (3H, m), 4.01 (2H, t, J = 6.1 Hz), 6.90 (2H, d, J = 8.5 Hz), 6.97–7.36 (4H, m), 7.36–7.57 (2H, m). Anal. ($C_{27}H_{33}N_3O_4 \cdot {}^1/_4H_2O$) C, H, N.

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