Structure–Activity Relationships of Non-peptide Vasopressin V_{1a} Antagonists: 1-(1-Multi-substituted Benzoyl 4-Piperidyl)-3,4-dihydro-2(1*H*)-quinolinones

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During our systematic studies on the arginine vasopressin receptor V_{1a}-antagonistic activity of 1-(1-benzoyl substituted 4-piperidyl)-3,4-dihydro-2(1*H*)-quinolinones, we found a general substituent effect on the benzene ring. Hydrogen-bonding ability at the *ortho* position was especially important for enhancement of the affinity of multi-substituted analogs. Details of the syntheses and structure–activity relationships for this series are presented.

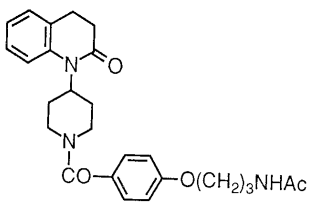
Key words vasopressin V_{1a} antagonist; non-peptide; synthesis; structure–activity relationships

Arginine vasopressin (AVP) exerts a variety of biological effects in mammals. It plays a major role in the regulation of water and solute excretion by the kidney and participates in the multifactorial regulation of a number of other physiological functions such as blood pressure control, platelet aggregation, adrenocorticotropic hormone (ACTH) secretion by the adenohypophysis, aldosterone secretion by the adrenals, factor VIII secretion, liver glycogenolysis, and uterine motility. AVP is also involved in interneuronal communication in the central nervous system.

Three AVP receptor subtypes (V_{1a}, V_{1b}, V_2) have been identified on pharmacological and functional bases. The V_2 receptors may mediate adenylate cyclase activation, playing a major role in stimulating a renal water absorption. The V_{1a} and V_{1b} receptors may mediate phospholipase C activation and intracellular calcium mobilization. The V_{1b} receptors may contribute to the stimulating effect on ACTH secretion, but all other known AVP actions are believed to be mediated by the V_{1a} receptors.

Since AVP was prepared by total synthesis,[1] numerous peptide analogs have been synthesized and evaluated in an effort to identify key structural features. Many useful agonists and antagonists have become available for defining the roles of AVP in normal and disease physiology.[2–9] We have previously described the rational and systematic design of novel non-peptide AVP V_{1a} receptor antagonists, including OPC-21268,[10] that exhibit potent binding affinity and are orally effective. Pettibone *et al.*[11] and Serradeil-Le Gal *et al.*[12] suggested that these series of quinolinone derivatives might show a large species difference in activity, based on radioligand binding studies with AVP V_{1a} receptors of rat, rhesus and human tissues. Nevertheless, Imaizumi *et al.*[13] showed that oral administration of OPC-21268 effectively and specifically antagonized the V_{1a} receptor-mediated vasoconstriction in human forearm resistance vessels. Recently Serradeil-Le Gal *et al.*[14] reported that OPC-21268 shows the same order of affinity for V_{1a} receptors in rat and cultured human aortic vascular smooth muscle cells (VSMC). These results strongly suggested the existence of human AVP V_{1a} receptor subtypes.

During our development of OPC-21268, systematic studies were undertaken in an attempt to enhance the binding affinity of OPC-21268 by introducing a multi-substituted benzoyl group on the piperidine ring. The results are presented herein.

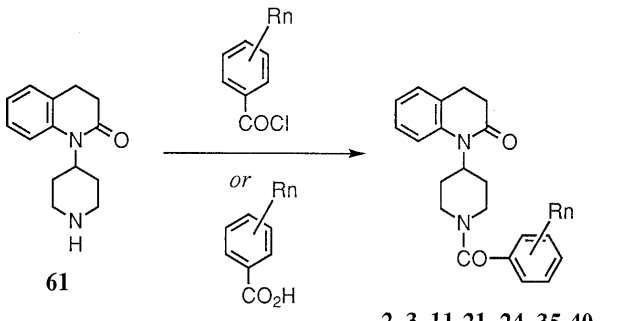


OPC-21268
IC_{50}, μM, $V_{1a}=0.44$, $V_2>100$
ID_{50}, *p.o.*, $=2.0$ mg/kg

Fig. 1

Chemistry

Simple substitution methods were employed with the reported 1-(4-piperidyl)-3,4-dihydro-2(1*H*)-quinolinone (**61**)[10] and benzoic acid derivatives obtained by usual amide-forming reactions for the synthesis of the test compounds **2**, **3**, **11**—**21**, **24**, **35**—**40**, **42**, **44**, **49**, **72**—**76**, **85** and **86** (Chart 1). The other test compounds were prepared as shown in Chart 6 to Chart 10. The melting ranges and the results of micro analyses of test compounds



61

64a-l, 68a-w

2, 3, 11-21, 24, 35-40, 42, 44, 49, 72-76, 85, 86

Rn: R^1-R^{14}

Methods A, B, C, D (see Experimental)

Chart 1

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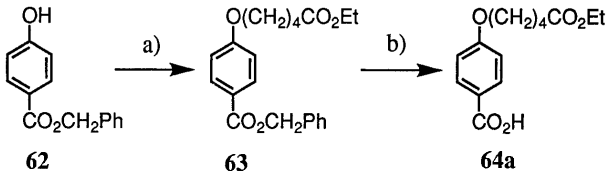
are listed in Tables 1—4.

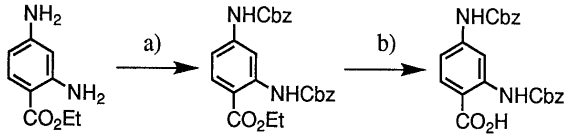
The known benzoic acid derivatives were obtained from commercial suppliers or prepared according to the literature. Others were prepared as described below (see Chart 2 to Chart 5).



62 **63** **64a**

a) Ethyl 5-bromobutylate, K_2CO_3, KI, Acetone
b) 10% Pd/C, HCO_2NH_4, DMF

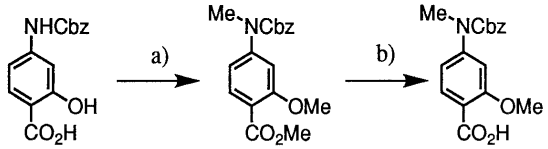
Chart 2



65 **66** **64b**

a) Cbz-Cl, $NaHCO_3$, Et_2O-H_2O b) NaOH, Dioxane-H_2O

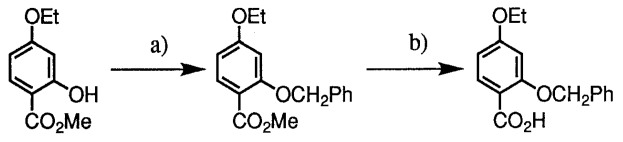
Chart 3



64l **69** **64c**

a) MeI, NaH, DMF b) NaOH, Dioxane-H_2O

Chart 4



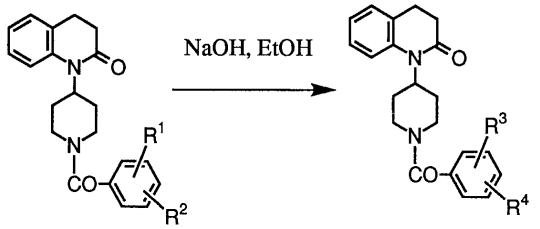
70 **71** **64d**

a) $PhCH_2Br$, NaH, DMF b) NaOH, MeOH

Chart 5

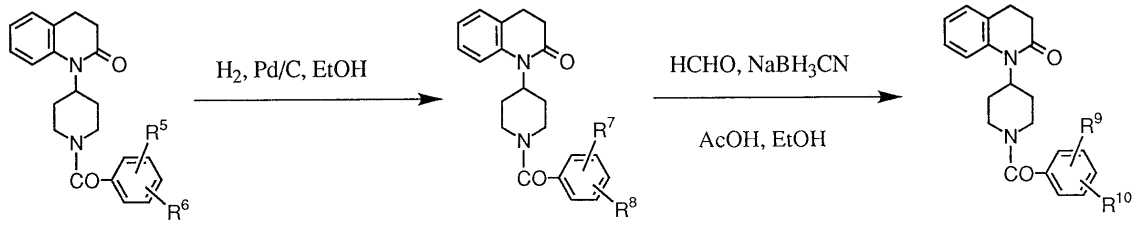
ω-Ethoxycarbonylbutoxybenzoic acid **64a** was prepared from the benzylester **62** by alkylation of the OH group followed by removal of the benzyl ester by the modified method of Ram *et al.*[15] and Lewis *et al.*[16] (Chart 2). The bis-benzyloxycarbonylamino derivative of **64b** was prepared from the bis-amino derivative of **65** by protection of the amino group with a benzyloxycarbonyl (Cbz) group followed by selective hydrolysis of the ester group of **66** (Chart 3). The *N*-methyl derivative **64c** was obtained by the simultaneous trimethylation of **64l**, and selective hydrolysis of the methyl ester furnished **69** (Chart 4). The benzyloxy derivative **64d** was obtained from **70** by benzylation of the OH group, followed by hydrolysis of the ester group of **71** (Chart 5).

Hydroxybenzoyl derivatives **25**—**27** and **47** were prepared from the acetoxy derivatives **21**—**23** and **72** by hydrolysis of the acetyl group (Chart 6). Aminobenzoyl and hydroxybenzoyl derivatives **77**—**79** and **48** were prepared by removal of the Cbz groups (**73**, **74**) or hydrogenolysis of the nitro group (**75**) or removal of the benzyloxy group (**76**). Reductive methylation of the amino groups of **77**—**79** with $NaBH_3CN$ gave **28**, **43** and **46**, respectively (Chart 7). Several alkylamino derivatives **51**—**54** were derived from **81**. ω-Aminocarbonyl derivatives **45** and **50** were prepared from the ω-ethoxycarbonyl



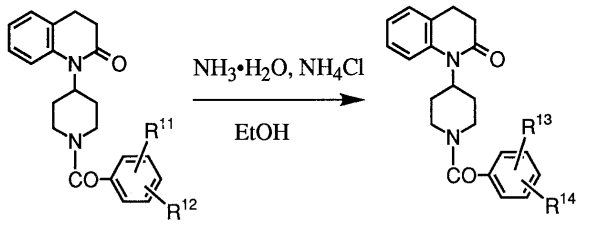
	R^1	R^2		R^3	R^4
21	2-OAc	4-OAc	**25**	2-OH	4-OH
22	2-OAc	5-OAc	**26**	2-OH	5-OH
23	3-OAc	4-OAc	**27**	3-OH	4-OH
72	2-OAc	4-OMe	**47**	2-OH	4-OMe

Chart 6



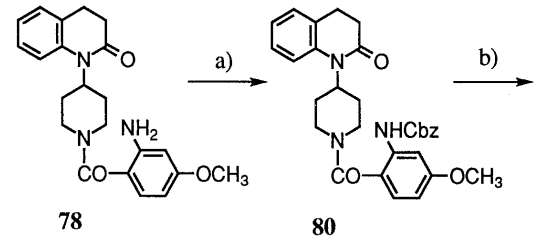
	R^5	R^6		R^7	R^8		R^9	R^{10}
73	2-NHCbz	4-NHCbz	**77**	2-NH_2	4-NH_2	**28**	2-NMe_2	4-NMe_2
74	2-OMe	4-NMeCbz	**78**	2-OMe	4-NHMe	**43**	2-OMe	4-NMe_2
75	2-NO_2	4-OMe	**79**	2-NH_2	4-OMe	**46**	2-NMe_2	4-OMe
76	2-OCH_2Ph	4-OEt	**48**	2-OH	4-OEt			

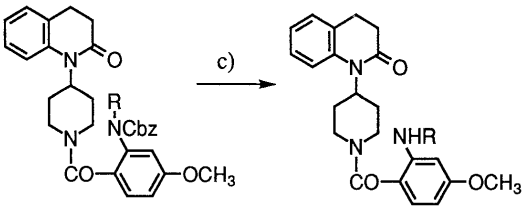
Chart 7



	R^{11}	R^{12}		R^{13}	R^{14}
85	2-OMe	4-O$(CH_2)_4CO_2Et$	**45**	2-OMe	4-O$(CH_2)_4CONH_2$
86	2-H	4-O$(CH_2)_4CO_2Et$	**50**	2-H	4-O$(CH_2)_4CONH_2$

Chart 8



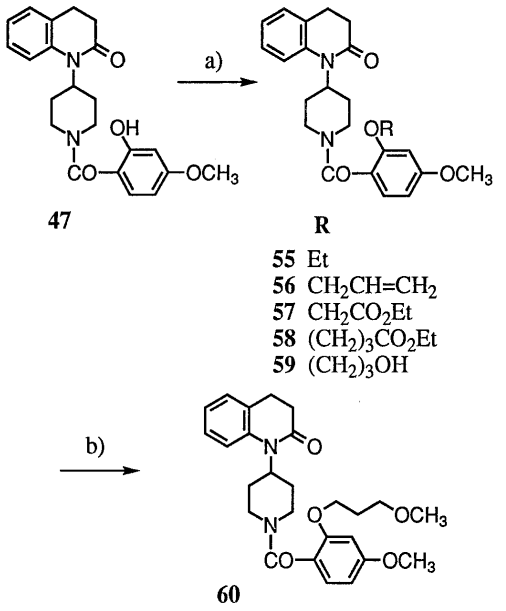


	R		R
81	Me	**51**	Me
82	Et	**52**	Et
83	n-Pr	**53**	n-Pr
84	CH_2CO_2Et	**54**	CH_2CO_2Et

a) Cbz-Cl, $NaHCO_3$, CH_2Cl_2, H_2O; b) R-I or R-Br, NaH, DMF; c) 5% Pd-C, H_2, EtOH

Chart 9

derivatives **85** and **86** by heating with $NH_3 \cdot H_2O$ and NH_4Cl in EtOH in an autoclave (Chart 8). Protection of the amino group of **78** with a Cbz group, followed by alkylation with several alkyl halides provided **81**—**84**. Removal of the Cbz group by hydrogenolysis afforded the mono-alkylamino derivatives **51**—**54** (Chart 9). 4-Methoxy-2-alkoxy derivatives **55**—**59** were obtained by alkylation of the OH group of **47**. Compound **59** was further methylated to afford **60** (Chart 10).



R
55 Et
56 $CH_2CH{=}CH_2$
57 CH_2CO_2Et
58 $(CH_2)_3CO_2Et$
59 $(CH_2)_3OH$

(a) R-Br, K_2CO_3, KI, Acetone; (b) MeI, NaH, DMF

Chart 10

Biological Results and Discussion

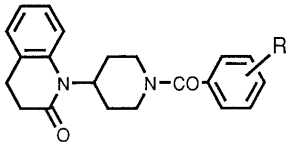
The binding studies were performed with rat liver plasma membranes (V_{1a} receptor) and kidney plasma membranes (V_2 receptor) using [^{3}H]AVP as a ligand according to reported methods[11]; the data are reported as IC_{50} values in Tables 1—4.

Table 1 shows the binding affinity of AVP V_{1a} receptor antagonists. We have classified our compounds into two series based on the hydrogen-bonding abilities of the substituent on the aromatic ring, since hydrogen bonding seemed to be a very important factor for enhancement of the receptor affinity, as described below. As we had previously reported, analogs with 4-substitution on the benzoyl group show the most potent affinity for V_{1a} receptor compared with 2- or 3- substituted analogs (Table 1, **1**—**12**). The order of potency of the substituted position on the benzene ring in this series is; 4- > 2- ≥ H > 3- (R = H, IC_{50}, μM; $V_{1a} = 1.9$, $V_2 > 50$). We then synthesized the di-substituted analogs listed in Table 1. In almost all cases, 2,4-disubstituted analogs (**14**, **25**, **28**) showed enhanced activity compared with 4- or 2-monosubstituted analogs. The 2,4-disubstituted analog **21**, however, did not show improved binding affinity compared with **4**. The 3,4- (**13**, **23**, **27**) as well as 2,3- or 2,5-disubstituted (**15**, **22**, **26**) analogs showed reduced potency. The 2,6- (**16**) or 3,5-disubstituted (**17**, **24**) analogs showed very weak affinities. Among this series of disubstituted analogs, we observed enhancement of the binding affinity by the introduction of an additional 4- or 2-substituent. These results were expected, since 4- or 2-monosubstituted analogs were more potent than the non substituted analog. The compounds substituted at the 3 position on the aromatic ring (**2**, **5**, **8**) showed very weak affinity compared with the non substituted analog. We therefore expected that the affinity would be reduced by an additional substitution at the 3 position. The results were consistent with that prediction (**13**, **15**, **17**—**19**, **22**—**24**, **26**, **27**).

In Table 2, the substituent effects of groups having poor hydrogen-bonding ability are summarized. In this series the order of the affinity in relation to the substituted position on the phenyl ring is 4- > H ≥ 3- > 2- (**29**—**34**). Analogs disubstituted at positions 3,4 showed similar potency to the monosubstituted analogs, whereas 2,4-disubstituted analogs showed reduced activity (**36**, **40**).

The results presented in Tables 1 and 2 suggest that we may predict the effects of additional substituents on the aromatic ring by using the order of potency for similarly

Table 1. Analytical Data and Binding Affinity of AVP V_{1a} Receptor Antagonists



No.	R	Method[a]	Yield (%)	mp (°C) (Recrystal. solvt.)	Formula[a]	Analysis (%) Calcd (Found)			Receptor affinity[c] IC_{50}, μM	
						C	H	N	V_{1a}	V_2
1	4-OCH_3[d]								0.49	>100
2	3-OCH_3	A	[e]	90—92 (CH_2Cl_2–*n*-hexane)	$C_{22}H_{24}N_2O_3$	72.51 (72.45)	6.64 6.70	7.69 7.57)	2.6	>100
3	2-OCH_3	A	76	151.5—152.5 (CH_2Cl_2–*n*-hexane)	$C_{22}H_{24}N_2O_3$	72.51 (72.53)	6.64 6.65	7.69 7.51)	0.65	36
4	4-OAc[d]								0.49	>100
5	3-OAc[d]								3.7	>100
6	2-OAc[d]								1.4	>100
7	4-OH[d]								1.3	>100
8	3-OH[d]								6.3	>100
9	2-OH[d]								1.5	>100
10	4-NMe_2[d]								0.47	>100
11	3-NMe_2	B	[e]	168—169 (CH_2Cl_2–*n*-hexane)	$C_{23}H_{27}N_3O_2$	73.18 (73.19)	7.21 7.15	11.13 11.15)	0.99	>100
12	2-NMe_2	C	65	209—211 (AcOEt–EtOH)	$C_{23}H_{27}N_3O_2$	73.18 (73.33)	7.21 7.36	11.13 11.10)	0.61	46
13	3,4-OCH_3	A	29	121—124 (*n*-hexane–EtOH)	$C_{23}H_{26}N_2O_4$	70.03 (70.16)	6.64 6.62	7.10 7.11)	7.1	>100
14	2,4-OCH_3	A	33	141—143 (*n*-hexane–EtOH)	$C_{23}H_{26}N_2O_4$	70.03 (69.85)	6.64 6.56	7.10 7.05)	0.44	65
15	2,3-OCH_3	B	79	194—195 (*n*-hexane–EtOH)	$C_{23}H_{26}N_2O_4$	70.03 (69.90)	6.64 6.60	7.10 7.01)	5.0	>100
16	2,6-OCH_3	B	75	202—204 (*n*-hexane–EtOH)	$C_{23}H_{26}N_2O_4 \cdot 1/5H_2O$	69.40 (69.32)	6.68 6.41	7.04 6.82)	32	>100
17	3,5-OCH_3	A	98	154—154.5 (CH_2Cl_2–*n*-hexane)	$C_{23}H_{26}N_2O_4$	70.03 (69.91)	6.64 6.71	7.10 6.91)	8.3	>100
18	2,4,5-OCH_3	B	58	123—126 (*n*-hexane–EtOH)	$C_{24}H_{28}N_2O_5$	67.91 (67.93)	6.65 6.64	6.60 6.53)	6.7	>100
19	3,4,5-OCH_3	A	71	139—139.5 (CH_2Cl_2–*n*-hexane)	$C_{24}H_{28}N_2O_5$	67.91 (67.50)	6.65 6.50	6.60 6.12)	38	>100
20	2,4,6-OCH_3	B	75	193—196 (*n*-hexane–EtOH)	$C_{24}H_{28}N_2O_5$	67.91 (67.56)	6.65 6.51	6.60 6.37)	8.9	>100
21	2,4-OAc	A	17	81.5—84 (CH_2Cl_2–*n*-hexane)	$C_{25}H_{26}N_2O_6 \cdot 1/2H_2O$	65.35 (67.91)	5.92 6.65	6.10 6.60)	0.86	>100
22	2,5-OAc	D	[e]	134—137 (AcOEt–Et_2O)	$C_{25}H_{26}N_2O_6$	66.65 (66.54)	5.82 5.90	6.22 6.06)	77	>100
23	3,4-OAc	D	73	117—119 (CH_2Cl_2–*n*-hexane)	$C_{25}H_{26}N_2O_6 \cdot 1/4H_2O$	65.99 (65.92)	5.87 5.75	6.16 6.17)	6.1	>100
24	3,5-OAc	A	30	171.5—172.5 (CH_2Cl_2–*n*-hexane)	$C_{25}H_{26}N_2O_6$	66.65 (66.32)	5.82 5.58	6.22 6.37)	21	>100
25	2,4-OH	[e]	18	[f]	$C_{21}H_{22}N_2O_4 \cdot 1/4H_2O$	68.00 (67.94)	6.11 6.06	7.55 7.25)	0.82	>100
26	2,5-OH	[e]	56	245—249 (EtOH–MeOH)	$C_{21}H_{22}N_2O_4$	68.83 (68.62)	6.05 6.03	7.65 7.56)	67	>100
27	3,4-OH	[e]	43	234—236 (EtOH–Et_2O)	$C_{21}H_{22}N_2O_4$	68.83 (68.46)	6.05 6.06	7.65 7.54)	6.5	>100
28	2,4-NMe_2	[e]	56	162—164 (*n*-hexane–EtOH)	$C_{25}H_{32}N_4O_2$	71.40 (71.17)	7.67 7.68	13.32 13.26)	0.39	50

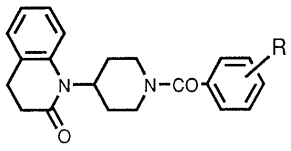
a) See Experimental for details. *b*) Carbon, hydrogen, and nitrogen analyses were within ±0.4% of theoretical. *c*) Compounds were tested for the ability to displace [^{3}H]AVP from its specific binding sites in rat liver (V_{1a} receptor) and kidney (V_2 receptor) plasma membrane preparations (see ref. 10*b*). *d*) Reported in ref. 10. *e*) See Experimental. *f*) Amorphous solid.

monosubstituted analogs.

We next investigated 2,4-disubstituted aromatic rings where the substituents are different. Table 3 illustrates the substituent effects on biological activity. A 2-substituent possessing hydrogen-bonding capability shows remarkable enhancement of the binding affinity (**41**—**48**) compared with the mono 4-substituted compound. In addition, good binding was still observed with a longer chain at the 4-position (**45**, **50**). This finding might be useful help for further improvement of drug activity profiles.

Table 4 illustrates the structure–activity relationships of 4-methoxy-2-substituted analogs. As shown in Table 1,

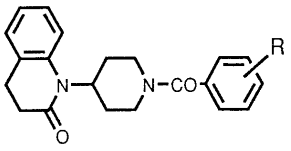
Table 2. Analytical Data and Binding Affinity of AVP V_{1a} Receptor Antagonists



No.	R	Method[a]	Yield (%)	mp (°C) (Recrystal. solvt.)	Formula[b]	Analysis (%) Calcd (Found)			Receptor affinity[c] IC_{50}, μM	
						C	H	N	V_{1a}	V_2
29	4-CH_3[d]								0.50	>100
30	3-CH_3[d]								1.3	>100
31	2-CH_3[d]								8.4	>100
32	4-Cl[d]								0.88	>100
33	3-Cl[d]								4.4	>100
34	2-Cl[d]								9.9	>100
35	3,4-CH_3	A	89	131.5—132.5 (EtOH–*n*-hexane)	$C_{23}H_{26}N_2O_2$	76.21 (76.09	7.23 7.19	7.73 7.44)	0.43	79
36	2,4-CH_3	A	98	159—160 (CH_2Cl_2–*n*-hexane)	$C_{23}H_{26}N_2O_2$	76.21 (76.17	7.23 7.23	7.73 7.59)	2.9	>100
37	3,5-CH_3	C	[d]	177—180 (Et_2O–*n*-hexane)	$C_{23}H_{26}N_2O_2$	76.21 (75.95	7.23 7.32	7.73 7.59)	3.6	>100
38	2,5-CH_3	A	75	172—172.5 (CH_2Cl_2–*n*-hexane)	$C_{23}H_{26}N_2O_2$	76.21 (76.39	7.23 7.23	7.73 7.68)	16	>100
39	3,4-Cl	A	73	[e]	$C_{21}H_{22}Cl_2N_2O_2$	62.54 (62.42	5.00 5.01	6.95 6.77)	1.1	>100
40	2,4-Cl	A	64	[e]	$C_{21}H_{22}Cl_2N_2O_2$	62.54 (62.34	5.00 4.99	6.95 6.97)	4.3	>100

a) See Experimental for details. *b, c*) See footnotes to Table 1. *d*) Reported in ref. 10. *e*) Amorphous solid.

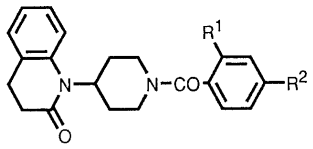
Table 3. Analytical Data and Binding Affinity of AVP V_{1a} Receptor Antagonists



No.	R	Method[a]	Yield (%)	mp (°C) (Recrystal. solvt.)	Formula[b]	Analysis (%) Calcd (Found)			Receptor affinity[c] IC_{50}, μM	
						C	H	N	V_{1a}	V_2
41	2-OMe,4-OEt	[d]	29	174—175 (*n*-hexane–EtOH)	$C_{24}H_{28}N_2O_4$	70.57 (70.42	6.91 6.91	6.86 6.76)	0.062	>100
42	2-OMe,4-SMe	B	74	[e]	$C_{23}H_{26}N_2O_3S \cdot 1/4H_2O$	66.56 (66.56	6.44 6.34	6.75 6.64)	0.082	36
43	2-OMe,4-NMe_2	[d]	47	93—96 (*n*-hexane–EtOH)	$C_{24}H_{29}N_3O_3 \cdot 2/3H_2O$	68.71 (68.81	7.29 7.25	10.02 10.06)	0.19	>100
44	2-OMe,4-Cl	B	55	84—87 (*n*-hexane–EtOH)	$C_{22}H_{23}ClN_2O_3 \cdot 1/4H_2O$	65.51 (65.24	5.87 5.53	6.94 6.95)	0.27	31
45	2-OMe,4-O$(CH_2)_4CONH_2$	[d]	55	[e]	$C_{27}H_{33}N_3O_5 \cdot 4/5H_2O$	65.65 (65.72	7.06 6.79	8.51 8.22)	0.17	>100
46	6-NMe_2,4-OMe	[d]	43	138—140 (EtOH)	$C_{24}H_{29}N_3O_3$	70.73 (70.84	7.17 7.22	10.31 10.29)	0.19	>100
47	2-OH,4-OMe	[d]	81	140.5—142 (EtOH)	$C_{22}H_{24}N_2O_4$	69.46 (69.17	6.36 6.24	7.36 7.25)	0.18	>100
48	2-OH,4-OEt	[d]	94	138—140 (EtOH)	$C_{23}H_{26}N_2O_4 \cdot 3/4H_2O$	67.71 (67.79	6.79 6.78	6.87 6.68)	0.12	>100
49	4-SMe	B	64	[e]	$C_{22}H_{24}N_2O_2S \cdot 1/10H_2O$	69.12 (69.11	6.38 6.04	7.33 7.05)	0.21	74
50	4-O$(CH_2)_4CONH_2$	[d]	40	[e]	$C_{26}H_{31}N_3O_4 \cdot 1/2H_2O$	68.10 (68.16	7.03 6.96	9.16 9.00)	0.33	>100

a) See Experimental for details. *b, c*) See footnotes to Table 1. *d*) See Experimental. *e*) Amorphous solid.

Table 4. Analytical Data and Binding Affinity of AVP V_{1a} Receptor Antagonists



No.	R^1	R^2	Method	Yield (%)	mp (°C)	Formula[b]	Analysis (%) Calcd (Found)			Receptor affinity[c] IC_{50}, μM	
							C	H	N	V_{1a}	V_2
51	NHMe	OMe	a)	89	d)	$C_{23}H_{27}N_3O_3 \cdot 1/3H_2O$	69.15 (69.14)	6.90 6.82	10.52 10.55)	0.56	>100
52	NHEt	OMe	a)	82	d)	$C_{24}H_{29}N_3O_3$	70.73 (70.45)	7.17 7.16	10.31 10.25)	0.33	>100
53	NH-*n*Pr	OMe	a)	96	d)	$C_{25}H_{31}N_3O_3 \cdot 1/4H_2O$	70.45 (70.26)	7.45 7.33	9.86 9.83)	0.27	>100
54	$NHCH_2CO_2Et$	OMe	a)	89	d)	$C_{26}H_{31}N_3O_5 \cdot 1/2H_2O$	65.80 (66.02)	6.80 6.61	8.86 8.87)	1.6	>100
55	OEt	OMe	a)	56	d)	$C_{24}H_{28}N_2O_4$	70.57 (70.32)	6.91 6.60	6.86 6.74)	0.2	>100
56	O-Allyl	OMe	a)	55	d)	$C_{25}H_{28}N_2O_4 \cdot 1/3H_2O$	70.40 (70.29)	6.77 6.65	6.57 6.48)	0.15	>100
57	OCH_2CO_2Et	OMe	a)	73	d)	$C_{26}H_{30}N_2O_6 \cdot 1/8H_2O$	66.62 (66.54)	6.50 6.20	5.98 6.10)	0.65	>100
58	$O(CH_2)_3CO_2Et$	OMe	a)	87	d)	$C_{28}H_{34}N_2O_6 \cdot 1/4H_2O$	67.38 (67.11)	6.97 6.78	5.61 5.55)	1.5	>100
59	$O(CH_2)_3OH$	OMe	a)	84	d)	$C_{25}H_{30}N_2O_5 \cdot 1/4H_2O$	67.78 (67.77)	6.94 6.76	6.32 6.46)	0.27	>100
60	$O(CH_2)_3OMe$	OMe	a)	91	d)	$C_{26}H_{32}N_2O_5 \cdot 1/2H_2O$	67.66 (67.77)	7.21 7.23	6.07 6.01)	0.41	74

a) See Experimental. *b, c*) See footnotes to Table 1. *d*) Amorphous solid.

the 4-methoxy substituted analog showed potent binding affinity for the V_{1a} receptor. The analogs listed in Table 4 illustrates the effect of 2-substituents on the biological activity. As shown in Table 4, the inclusion of a CO_2Et group (**54**, **57**, **58**) as a 2-substituent reduced the binding affinity for the V_{1a} receptor. It appears that increasing the chain length up to 3 carbons in the 2-substituent has little effect on binding affinity.

Based on the results described above, we considered that the enhanced binding affinities of our test compounds to the AVP V_{1a} receptor can be interpreted in terms of multiple interactions: (a) hydrogen bonding between the receptor and the 2-substituent (hydrogen-bonding acceptor) on the benzene group; (b) additional 3- or 5- and even 6-substituents may interfere with hydrogen bonding of the 2-substituent with the receptor, reducing the affinity, so that 2,4-disubstitution is optimum for enhancement of the affinity; (c) The substituent like CO_2Et at the 2-position on the benzene ring reduces the affinity.

In conclusion, we have established the general substituent effects on the terminal benzene ring of 1-(1-multisubstituted benzoyl 4-piperidyl)-3,4-dihydro-2(1*H*) quinolinones. As a result, we were able to obtain enhanced affinity with disubstituted analogs such as **41** and **42**, which are about 5- to 7- fold more potent than OPC-21268. These potent AVP V_{1a} antagonists may be useful tools for studies of the pharmacology of the V_{1a} receptors. Studies are continuing to achieve still greater activity by further structual modification.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus without correction. ^{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 a Yanaco MT-5 CHN Corder, and were within ±0.4% of theoretical unless otherwise noted. All compounds were routinely checked by TLC with Merck Silica gel 60 F_{254} precoated plates. The following known benzoic acid derivatives were prepared according to the literature: 2,4-diacetoxybenzoic acid (**64e**),[17] 2,5-diacetoxybenzoic acid (**64f**),[18] 3,4-diacetoxybenzoic acid (**64g**),[19] 3,5-diacetoxybenzoic acid (**64h**),[18] 4-ethoxy-2-methoxybenzoic acid (**64i**),[20] 2-acetoxy-4-methoxybenzoic acid (**64j**),[21] 4-methoxy-2-nitrobenzoic acid (**64k**),[22] ethyl 2,4-diaminobenzoate (**65**),[23] 4-benzyloxycarbonylamino-2-hydroxybenzoic acid (**64l**),[24] and methyl 4-ethoxy-2-hydroxybenzoate (**71**).[25] The following benzoic acid derivatives were purchased from commercial suppliers: benzyl 4-hydroxybenzoate (**62**), 3-methoxybenzoyl chloride (**68a**), 2-methoxybenzoyl chloride (**68b**), 3-dimethylaminobenzoic acid (**68c**), 2-dimethylaminobenzoic acid (**68d**), 3,4-dimethoxybenzoyl chloride (**68e**), 2,4-dimethoxybenzoyl chloride (**68f**), 2,3-dimethoxybenzoic acid (**68g**), 2,6-dimethoxybenzoic acid (**68h**), 3,5-dimethoxybenzoyl chloride (**68j**), 2,4,5-trimethoxybenzoic acid (**68k**), 3,4,5-trimethoxybenzoyl chloride (**68l**), 2,4,6-trimethoxybenzoic acid (**68m**), 3,4-dimethylbenzoyl chloride (**68n**), 2,4-dimethylbenzoyl chloride (**68o**), 3,5-dimethylbenzoic acid (**68p**), 2,5-dimethylbenzoyl chloride (**68q**), 3,4-dichlorobenzoyl chloride (**68r**), 2,4-dichlorobenzoyl chloride (**68s**), 2-methoxy-4-methylthiobenzoic acid (**68t**), 4-chloro-2-methoxybenzoic acid (**68u**), 4-methylthiobenzoic acid (**68v**) and 4-(4-ethoxycarbonylbutoxy)-2-methoxybenzoic acid (**68w**).[26]

Method A for Preparation of 1-[1-(3-Methoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (2) A solution of 3-methoxybenzoyl chloride **68a** (1.59 g, 9.3 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a solution of **61** (1.53 g, 6.6 mmol) and Et_3N (4 ml, 28.7 mmol) in CH_2Cl_2 (40 ml) under ice cooling. The reaction mixture was stirred for 1 h in an ice bath, then poured into ice-water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was

chromatographed on a silica gel column, followed by crystallization of the product from *n*-hexane to provide **2** (1.78 g, 73%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.62—2.03 (m, 2H), 2.52—3.38 (m, 8H), 3.68—4.03 (m, 1H), 3.83 (s, 3H), 4.28—4.52 (m, 1H), 4.72—5.07 (m, 1H), 6.87—7.48 (m, 8H).

Method B for Preparation of 1-[1-(3-Dimethylaminobenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (11) Triethylamine (0.54 ml, 3.9 mmol) was added dropwise to a mixture of **61** (0.3 g, 1.3 mmol), 3-dimethylaminobenzoic acid **68c** (0.32 g, 1.9 mmol), and bis(2-oxo-3-oxazolydinyl)phosphinic chloride (BOP-Cl, 0.55 g, 2.2 mmol) in CH_2Cl_2 (10 ml) at 0—5 °C. The solution was stirred for 1 h at room temperature, poured into ice-water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography, and the product was crystallized from CH_2Cl_2–*n*-hexane to give **11** (0.42 g, 84%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.03 (m, 2H), 2.52—3.23 (m, 8H), 2.97 (s, 6H), 3.82—4.15 (m, 1H), 4.26—4.52 (m, 1H), 4.74—5.07 (m, 1H), 6.67—6.84 (m, 3H), 6.97—7.34 (m, 5H).

Method C for Preparation of 1-[1-(3,5-Dimethylbenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (37) Diethyl phosphoro cyanidate (DEPC, 0.55 ml, 3.6 mmol) was added to a solution of 3,5-dimethylbenzoic acid **68p** (0.39 g, 2.6 mmol) in dimethylformamide (DMF) (5 ml), followed by the addition of a solution of **61** (0.5 g, 2.2 mmol) in DMF (2 ml) at 0 °C. The mixture was stirred for 3 h. The solvent was removed under reduced pressure, and the residue was partitioned between water and AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography, and the product was crystallized from Et_2O–*n*-hexane to give **37** (0.43 g, 55%) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 1.61—1.98 (m, 2H), 2.33 (s, 6H), 2.48—3.19 (m, 8H), 3.78—4.08 (m, 1H), 4.24—4.47 (m, 1H), 4.72—5.05 (m, 1H), 6.96—7.32 (m, 7H).

Method D for Preparation of 1-[1-(2,5-Diacetoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (22) A mixture of 2,5-diacetoxybenzoic acid **64f** (1.3 g, 5.2 mmol) and $SOCl_2$ (10 ml) was heated at reflux for 2 h. The mixture was concentrated under reduced pressure and the residue was dissolved in toluene. The solvent was evaporated *in vacuo* to remove the thionyl chloride. A solution of the resultant acid chloride in DMF (2 ml) was added dropwise to a mixture of **62** (1 g, 4.3 mmol) and Et_3N (0.9 ml, 6.5 mmol) in DMF (10 ml) at 0—5 °C. After 2 h at 0—5 °C, the mixture was poured into H_2O, and extracted with AcOEt. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography followed by recrystallization from AcOEt–Et_2O to afforded **22** (1.4 g, 72%) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 1.52—1.96 (m, 2H), 2.18—3.16 (m, 8H), 2.30 (s, 6H), 3.70—3.87 (m, 1H), 4.18—4.36 (m, 1H), 4.77—5.02 (m, 1H), 6.94—7.33 (m, 7H).

1-[1-(2-Acetoxy-4-methoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (72) By method D, 2-acetoxy-4-methoxybenzoic acid **64j** (1.1 g, 5.2 mmol) was condensed with **61** (0.6 g, 2.6 mmol) to give **72** (0.3 g, 33%) as colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.97 (m, 2H), 2.31 (s, 3H), 2.48—3.17 (m, 8H), 3.82 (s, 3H), 4.13—4.63 (m, 2H), 4.70—5.02 (m, 1H), 6.67—6.88 (m, 2H), 6.97—7.49 (m, 5H).

1-[1-[2,4-Bis(benzyloxycarbonylamino)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (73) By method B, 2,4-bisbenzyloxycarbonylaminobenzoic acid **64b** (2.27 g, 5.4 mmol) was condensed with **61** (1.24 g, 5.4 mmol) to give **73** (1.37 g, 48%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.73—1.91 (m, 2H), 2.51—3.08 (m, 8H), 3.51—5.06 (m, 3H), 5.19 (s, 2H), 6.95—7.48 (m, 17H), 8.09 (d, 1H, J=2.0 Hz), 8.67 (s, 1H).

1-[1-[4-(*N*-Benzyloxycarbonyl-*N*-methylamino)-2-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (74) By method B, 4-(*N*-benzyloxycarbonyl-*N*-methylamino)-2-methoxybenzoic acid **64c** (2 g, 6.3 mmol) was condensed with **61** (1.12 g, 4.9 mmol) to give **74** (1.9 g, 74%) as a colorless amorphous solid. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.61—1.95 (m, 2H), 2.44—3.22 (m, 8H), 3.33 (s, 3H), 3.59—3.74 (m, 1H), 3.75—3.92 (m, 3H), 4.29—4.72 (m, 1H), 4.89—5.08 (m, 1H), 5.18 (s, 2H), 6.80—7.42 (m, 12H).

1-[1-(4-Methoxy-2-nitrobenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (75) By method D, 4-methoxy-2-nitrobenzoic acid **64k** (5.6 g, 28.4 mmol) was condensed with **61** (5.48 g, 23.8 mmol). The crude product was purified by silica gel column chromatography to give **75** (7.27 g, 75%) as colorless prisms, mp 151—154 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.54—2.03 (m, 2H), 2.33—3.32 (m, 8H), 3.38—4.38 (m, 2H), 3.91 (s, 3H), 4.78—5.14 (m, 1H), 6.93—7.48 (m, 6H), 7.67 (d, 1H, J=2.5 Hz). *Anal.* Calcd for $C_{22}H_{23}N_3O_5$: C, 64.53; H, 5.66; N, 10.26. Found: C, 64.42; H, 5.70; N, 10.26.

1-[1-(2-Benzyloxy-4-ethoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (76) By method D, 2-benzyloxy-4-ethoxybenzoic acid **64d** (4.66 g, 16.9 mmol) was condensed with **61** (3 g, 13 mmol) to give **76** (4.2 g, 67%) as a white powder. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.32—1.48 (m, 3H), 1.56—1.92 (m, 2H), 2.48—3.18 (m, 8H), 3.59—4.78 (m, 4H), 4.87—5.25 (m, 3H), 6.40—6.59 (m, 2H), 6.71—7.53 (m, 9H).

Ethyl 4-[4-[4-(3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl)-1-piperidylcarbonyl]-2-methoxyphenoxy]valerate (85) By method D, 4-(4-ethoxycarbonylbutoxy)-2-methoxybenzoic acid **68w** (5.73 g, 19.3 mmol) was reacted with **61** (5.16 g, 19.3 mmol) to give **85** (6.96 g, 71%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7.1 Hz), 1.57—1.94 (m, 6H), 2.32—3.26 (m, 10H), 3.58—5.05 (m, 10H), 6.42—6.56 (m, 2H), 6.97—7.33 (m, 5H).

Ethyl 5-[4-[4-(3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl)-1-piperidylcarbonyl]phenoxy]valerate (86) By method C, 4-(4-ethoxycarbonylbutoxy)-benzoic acid **64a** (1.6 g, 6 mmol) was condensed with **61** (1.1 g, 4.8 mmol) to provide **86** (2.1 g, 92%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7.1 Hz), 1.63—2.00 (m, 6H), 2.32—2.44 (m, 2H), 2.48—3.12 (m, 8H), 3.75—5.03 (m, 5H), 4.14 (q, 2H, J=7.1 Hz), 6.90 (d, 2H, J=8.7 Hz), 6.98—7.27 (m, 4H), 7.43 (d, 2H, J=8.7 Hz).

Benzyl 4-(4-Ethoxycarbonyl)butoxybenzoate (63) Ethyl 5-bromobutylate (5.0 ml, 31.6 mmol) was added to a mixture of benzyl 4-hydroxybenzoate **62** (4.8 g, 210 mmol), K_2CO_3 (4.3 g, 31.5 mmol), and KI (5.24 g, 31.6 mmol) in acetone (200 ml). The mixture was heated at reflux for 1 d, and concentrated *in vacuo*. The residue was taken up in H_2O and CH_2Cl_2, and the solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure to give crude **63**, which was used immediately in the next step. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 3H, J=7.1 Hz), 1.73—1.89 (m, 4H), 2.35 (t, 2H, J=6.7 Hz), 4.01 (t, 2H, J=5.6 Hz), 4.13 (q, 2H, J=7.1 Hz), 5.33 (s, 2H), 6.89 (d, 2H, J=8.9 Hz), 7.26—7.46 (m, 5H), 8.02 (d, 2H, J=8.9 Hz).

4-(4-Ethoxycarbonyl)butoxybenzoic Acid (64a) A mixture of **63** and HCO_2NH_4 (10 g, 159 mmol) in DMF (200 ml) containing 10% Pd–C (1.5 g) was heated at reflux for 2 h. The catalyst was removed by filtration. The filtrate was poured into H_2O, and the resultant crystals were collected by filtration to afford **64a** (5.1 g, 91%) as a white powder, mp 95.5—96.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7.1 Hz), 1.72—1.97 (m, 4H), 2.40 (t, 2H, J=6.5 Hz), 4.05 (t, 2H, J=5.6 Hz), 4.14 (q, 2H, J=7.1 Hz), 6.92 (d, 2H, J=8.9 Hz), 8.05 (d, 2H, J=8.9 Hz).

Ethyl 2,4-Bis(benzyloxycarbonylamino)benzoate (66) Benzyloxycarbonyl chloride (Cbz-Cl, 5.4 ml, 37.8 mmol) was added dropwise to a mixture of ethyl 2,4-diaminobenzoate **65** (5.21 g, 31.3 mmol), $NaHCO_3$ (8.9 g, 11.0 mmol), H_2O (100 ml), and Et_2O (10 ml) at 0—5 °C. The mixture was stirred for 5 h at room temperature. Then $NaHCO_3$ (3.8 g, 46.9 mmol) was added, followed by the dropwise addition of Cbz-Cl (5.4 ml, 37.8 mmol) at 0—5 °C. The whole was stirred for 5 h at room temperature, then extracted with AcOEt. The organic solution was dried over Na_2CO_3, and concentrated. The resultant residue was purified by silica gel column chromatography to provide **66** (11 g, 81%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (s, 3H), 5.19 (s, 2H), 5.20 (s, 2H), 7.07 (br s, 1H), 7.28—7.47 (m, 11H), 7.95 (d, 1H, J=8.8 Hz), 8.32 (d, 1H, J=2.2 Hz), 10.68 (br s, 1H).

2,4-Bis(carbobenzyloxyamino)benzoic Acid (64b) A mixture of **66** (4.14 g, 9.5 mmol), NaOH (1.15 g, 28.8 mmol), H_2O (5 ml), and dioxane (60 ml) was stirred overnight at room temperature. The solution was diluted with H_2O, and 1 N HCl was added to adjust the pH to 2—4. The mixture was extracted with AcOEt, dried over $MgSO_4$, and concentrated. The cake thus obtained was triturated in *n*-hexane followed by filtration to give **64b** (2.24 g, 54%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (s, 3H), 5.22 (s, 4H), 7.07 (br s, 1H), 7.32—7.48 (m, 11H), 8.04 (d, 1H, J=8.8 Hz), 8.37 (d, 1H, J=2.2 Hz), 10.45 (br s, 1H), 12.52 (br s, 1H).

Methyl 4-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-2-methoxybenzoate (69) A solution of 4-benzyloxycarbonylamino-2-hydroxybenzoic acid **64l** (5 g, 17.4 mmol) in DMF (50 ml) was treated with 60% NaH (2.8 g, 70 mmol) and the mixture was stirred for 1 h at room temperature. Then MeI (4.33 ml, 69.6 mmol) was added at 0—5 °C. The whole was stirred overnight at room temperature, poured into H_2O, and extracted with AcOEt–toluene. The organic layer was dried over Na_2CO_3 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **69** (4 g, 73%) as a white powder. ^{1}H-NMR

($CDCl_3$) δ: 3.36 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 5.19 (s, 2H), 6.85 (dd, 1H, J=8.4, 2.0 Hz), 6.96 (d, 1H, J=2.0 Hz), 7.23—7.45 (m, 5H), 7.80 (d, 1H, J=8.4 Hz).

4-(*N*-Carbobenzyloxy-*N*-methylamino)-2-methoxybenzoic Acid (64c) A mixture of **69** (1 g, 3.2 mmol), NaOH (0.19 g, 4.8 mmol), H_2O (2 ml), and dioxane (15 ml) was stirred overnight. It was poured into H_2O, diluted HCl was added to adjust the pH to 1—2, and the solution was extracted with AcOEt. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* to give **64c** (0.89 g, 88%) as a white powder. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 3.39 (s, 3H), 3.96 (s, 3H), 5.22 (s, 2H), 6.98 (dd, 1H, J=8.6, 2.0 Hz), 7.16 (d, 1H, J=2.0 Hz), 7.30—7.41 (m, 5H), 8.13 (d, 1H, J=8.6 Hz), 10.52 (br s, 1H).

Methyl 2-Benzyloxy-4-ethoxybenzoate (71) A solution of methyl 4-ethoxy-2-hydroxybenzoate **70** (22.68 g, 116 mmol) in DMF (400 ml) was treated with 60% NaH (5.55 g, 139 mmol) at room temperature. The mixture was stirred for 1 h, then benzyl bromide (15.1 ml, 127 mmol) was added at room temperature. The reaction mixture was stirred overnight, poured into H_2O, and extracted with AcOEt–toluene. The organic layer was dried over Na_2CO_3, and concentrated to give **71** (33.0 g, 100%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (t, 3H, J=7.0 Hz), 3.87 (s, 3H), 4.04 (q, 2H, J=7.0 Hz), 5.16 (s, 2H), 6.43—6.55 (m, 2H), 7.15—7.67 (m, 5H), 7.81—7.95 (m, 1H).

2-Benzyloxy-4-ethoxybenzoic Acid (64d) A mixture of **71** (33.2 g, 116 mmol), NaOH (24 g, 600 mmol) in MeOH (600 ml) was heated at reflux for 1 d. The solvent was removed under reduced pressure, and the residue was dissolved in H_2O. The diluted solution was washed with Et_2O, and the pH was adjusted to 1—2 by the addition of 1 N HCl. The resultant crystals were collected by filtration to give **64d** (30 g, 95%) as a white powder. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.43 (t, 3H, J=7.0 Hz), 4.09 (q, 2H, J=7.0 Hz), 5.25 (s, 2H), 6.59—6.67 (m, 2H), 7.36—7.55 (m, 5H), 8.14 (d, 1H, J=8.7 Hz), 10.61 (br s, 1H).

1-[1-(2,5-Dihydroxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (26) A mixture of **22** (1.1 g, 2.4 mmol) and 5 N NaOH (1.5 ml, 7.5 mmol) in EtOH (10 ml) was stirred for 30 min at room temperature, then concentrated under reduced pressure. The residue was taken up in diluted HCl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography, followed by recrystallization from EtOH–MeOH to give **26** (0.5 g, 56%) as colorless prisms, mp 245—249 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.82 (m, 2H), 2.47—3.22 (m, 9H), 4.17—4.78 (m, 2H), 6.53 (d, 1H, J=2.6 Hz), 6.58—6.75 (m, 2H), 6.96—7.08 (m, 1H), 7.18—7.33 (m, 3H), 8.94 (s, 1H), 9.08 (s, 1H).

In a similar manner to that described above, compounds **25**, **27** and **47** were prepared from **21**, **23** and **72**, respectively. Analytical data are listed in Table 1 and Table 3.

1-[1-(2,4-Diaminobenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (77) A mixture of **73** (1.37 g, 2.6 mmol), 5% Pd–C (200 mg) and EtOH (20 ml) was stirred under an H_2 atmosphere at room temperature. After 115 ml (5.2 mmol) of H_2 had been absorbed, the catalyst was removed by filtration, and the solution was concentrated. The residue was purified by silica gel column chromatography to give **77** (0.16 g, 17%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.72—1.91 (m, 2H), 2.48—3.04 (m, 8H), 3.95 (br s, 4H), 4.28—4.58 (m, 3H), 5.94—6.10 (m, 2H), 6.93—7.32 (m, 5H).

1-[1-[2-Methoxy-4-(methylamino)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (78) A mixture of **74** (1.8 g, 3.4 mmol) and 5% Pd–C (0.3 g) in EtOH (30 ml) was stirred under H_2 atmosphere at 1 atm. After 76 ml of H_2 had been absorbed, the catalyst was removed by filtration, and concentrated to give **78** (1.18 g, 95%) as colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.56—1.95 (m, 2H), 2.45—3.28 (m, 8H), 2.85 (s, 3H), 3.62—4.03 (m, 5H), 4.32—5.12 (m, 2H), 6.10 (d, 1H, J=2.0 Hz), 6.20 (dd, 1H, J=8.2, 2.0 Hz), 6.95—7.31 (m, 4H).

1-[1-(2-Amino-4-methoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (79) A solution of **75** (6.5 g, 15.9 mmol) in EtOH (70 ml) containing 5% Pd–C (0.8 g) was stirred under H_2. After 1067 ml of H_2 had been absorbed, the catalyst was removed by filtration. The solvent was removed by evaporation, and the residue was purified by silica gel column chromatography, triturated with EtOH–Et_2O–*n*-hexane afforded **79** (4.73 g, 79%) as colorless needles, mp 169—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.73—1.93 (m, 2H), 2.52—3.08 (m, 8H), 3.78 (s, 3H), 4.22—4.77 (m, 5H), 6.22—6.38 (m, 2H), 6.98—7.33 (m, 5H). *Anal.* Calcd for $C_{22}H_{25}N_3O_3$: C, 69.63; H, 6.64; N, 11.07. Found: C, 69.50; H, 6.56; N, 11.06.

1-[1-(4-Ethoxy-2-hydroxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (48) A mixture of **76** (4.2 g, 8.7 mmol) and 10% Pd–C (0.4 g) in EtOH (80 ml) was stirred under an H_2 atmosphere at 1 atm. After 194 ml (8.7 mmol) of H_2 had been absorbed, the catalyst was removed by filtration and washed with $CHCl_3$. The filtrate was concentrated, and the resultant crystals were recrystallized from EtOH to give **48** (3.2 g, 94%) as a white powder, mp 138—140 °C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.42 (t, 3H, J=7.0 Hz), 1.78—1.95 (m, 2H), 2.52—2.98 (m, 6H), 2.93—3.12 (m, 2H), 4.04 (q, 2H, J=7.0 Hz), 4.36—4.52 (m, 3H), 6.40 (dd, 1H, J=8.8, 2.5 Hz), 6.51 (d, 1H, J=2.5 Hz), 6.98—7.32 (m, 5H), 10.46 (s, 1H).

1-[1-(2,4-Bis(*N*,*N*-dimethylamino)benzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (28) A mixture of **77** (511 mg, 1.4 mmol) and HCHO (1.8 ml, 19.4 mmol) in MeOH (10 ml) was treated with $NaBH_3CN$ (352 mg, 5.6 mmol) at 0—5 °C. The solution was stirred for 2 h at 0—5 °C and overnight at room temperature, then concentrated under reduced pressure. The residue was diluted with AcOEt, washed with H_2O, and then extracted with AcOEt. The organic layer was dried over Na_2CO_3, and concentrated. The residue was purified by silica gel column chromatography, and recrystallized from *n*-hexane–EtOH to give **28** (0.2 g, 34%) as pale gray powder. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.53—1.96 (m, 2H), 2.26—3.24 (m, 8H), 2.89 (s, 6H), 2.97 (s, 6H), 3.61—3.83 (m, 1H), 4.20—4.58 (m, 1H), 4.85—5.07 (m, 1H), 6.12—6.23 (m, 1H), 6.30 (dd, 1H, J=8.5, 2.3 Hz), 6.97—7.32 (m, 5H).

1-[1-(4-Dimethylamino-2-methoxybenzoyl)-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (43) A mixture of **78** (0.5 g, 1.4 mmol) and HCHO (35%, 0.54 ml, 5.8 mmol) in MeOH (10 ml) was treated with $NaBH_3CN$ (86.4 mg, 1.4 mmol) at 0—5 °C. The mixture was stirred for 2 h at 0—5 °C and for 1 h at room temperature, then poured into H_2O, and extracted with AcOEt. The organic layer was dried over Na_2CO_3 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **43** (0.26 g, 47%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 1.53—1.93 (m, 2H), 2.35—3.24 (m, 11H), 2.98 (s, 3H), 3.62—3.98 (m, 4H), 4.33—5.08 (m, 2H), 6.18 (d, 1H, J=2.2 Hz), 6.32 (dd, 1H, J=8.5, 2.2 Hz), 6.97—7.33 (m, 5H).

1-[1-[2-(*N*,*N*-Dimethylamino)-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (46) A solution of **79** (0.5 g, 1.3 mmol) in MeCN (10 ml) was treated with 37% HCHO (1.1 ml, 13.5 mmol), followed by the addition of AcOH (0.5 ml) at 0—5 °C. Then $NaBH_3CN$ (0.36 g, 5.7 mmol) was added at 0—5 °C. After having been stirred for 2 h at room temperature, the mixture was poured into H_2O, and extracted with AcOEt. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography, and recrystallized from EtOH to afford **46** (0.23 g, 43%) as colorless flakes. ^{1}H-NMR ($CDCl_3$) δ: 1.54—1.96 (m, 2H), 2.38—3.35 (m, 8H), 2.90 (s, 6H), 3.48—3.76 (m, 1H), 3.81 (s, 3H), 4.20—4.54 (m, 1H), 4.86—5.07 (m, 1H), 6.38—6.53 (m, 2H), 6.95—7.33 (m, 5H).

4-[4-[4-(3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl)-1-piperidylcarbonyl]-2-methoxyphenoxy]valeramide (45) A mixture of **85** (0.9 g, 1.8 mmol), 25% $NH_3 \cdot H_2O$ (10 ml), and NH_4Cl (0.1 g) in EtOH (10 ml) was heated at 100—110 °C in an autoclave for 20 h, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **45** (0.47 g, 55%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.49—2.42 (m, 8H), 2.47—3.27 (m, 8H), 3.58—4.08 (m, 6H), 4.25—4.73 (m, 1H), 4.86—5.03 (m, 1H), 5.62 (br s, 1H), 5.80 (br s, 1H), 6.44—6.56 (m, 2H), 6.98—7.34 (m, 5H).

4-[4-[4-(3,4-Dihydro-2-oxo-1*H*-quinolin-1-yl)-1-piperidylcarbonyl]-phenoxy]butylcarboxamide (50) A mixture of **86** (1.0 g, 2.1 mmol), 25% $NH_3 \cdot H_2O$ (17 ml) and NH_4Cl (0.2 g) in MeOH (8 ml) was heated at 100 °C in an autoclave for 2 h. After cooling, the mixture was concentrated under reduced pressure. The residue was taken up in H_2O, and the solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and subjected to silica gel column chromatography. The product was recrystallized from CH_2Cl_2–*n*-hexane to give **50** (0.38 g, 41%) as colorless prisms. ^{1}H-NMR ($CDCl_3$) δ: 1.67—2.07 (m, 6H), 2.20—2.43 (m, 2H), 2.51—3.18 (m, 8H), 3.92—5.05 (m, 5H), 5.28—5.80 (m, 2H), 6.89 (d, 2H, J=8.6 Hz), 6.96—7.34 (m, 4H), 7.42 (d, 2H, J=8.6 Hz).

1-[1-[2-(Benzyloxycarbonylamino)-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (80) Cbz-Cl (0.87 ml, 5.9 mmol) was added dropwise to a mixture of **78** (2.03 g, 5.35 mmol), $NaHCO_3$ (1.34 g, 16 mmol) in CH_2Cl_2 (40 ml) and H_2O (40 ml) at 0—5 °C. The mixture was stirred for 30 min, then further Cbz-Cl (0.87 ml, 5.9 mmol) was added at 0—5 °C. After additional stirring for 30 min, the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give

80 (2.56 g, 93%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.73—1.93 (m, 2H), 2.51—3.08 (m, 8H), 3.84 (s, 3H), 4.23—4.66 (m, 3H), 5.21 (s, 2H), 6.57 (dd, 1H, J=8.5, 2.5 Hz), 6.95—7.52 (m, 10H), 7.87 (d, 1H, J=2.5 Hz), 8.81 (br s, 1H).

1-[1-[2-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (81) A solution of **80** (1.8 g, 3.5 mmol) in DMF (30 ml) was treated with 60% NaH (0.17 g, 4.25 mmol), then the mixture was stirred for 30 min at 45—50 °C. It was cooled to 0—5 °C, then MeI (0.33 ml, 5.3 mmol) was added. The whole was stirred for 1 h at room temperature, poured into H_2O, and extracted with AcOEt. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **81** (1.8 g, 97%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.53—1.92 (m, 2H), 2.25—2.94 (m, 8H), 3.18—4.22 (m, 5H), 3.80 (s, 3H), 4.95—5.42 (m, 3H), 6.67—7.52 (m, 12H).

1-[1-[2-(*N*-Benzyloxycarbonyl-*N*-ethyl)amino-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (82) By the same procedure as used for the preparation of **81**, **80** (1.3 g, 2.5 mmol) was reacted with EtI (0.24 ml, 3.0 mmol) to give **82** (1.33 g, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (t, 3H, J=7.4 Hz), 1.48—1.90 (m, 2H), 2.15—2.98 (m, 8H), 3.21—5.45 (m, 7H), 3.81 (s, 3H), 6.65—7.51 (m, 12H).

1-[1-[2-(*N*-Benzyloxycarbonyl-*N*-propyl)amino-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (83) By the same procedure as used for the preparation of **81**, **80** (0.77 g, 1.5 mmol) was reacted with *n*-PrBr (0.16 ml, 1.8 mmol) to give **83** (0.57 g, 68%) as colorless needles. mp 146—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, 3H, J=7.5 Hz), 1.46—1.91 (m, 4H), 2.21—3.00 (m, 8H), 3.16—4.28 (m, 4H), 3.80 (s, 3H), 4.56—5.53 (m, 3H), 6.58—7.55 (m, 12H). *Anal.* Calcd for $C_{33}H_{37}N_3O_5$: C, 71.33; H, 6.71; N, 7.56. Found: C, 71.34; H, 6.72; N, 7.53.

1-[1-[2-(*N*-Benzyloxycarbonyl-*N*-ethoxycarbonylmethyl)amino-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (84) By the same procedure as used for the preparation of **81**, **80** (4.0 g, 7.79 mmol) was reacted with ethyl bromoacetate (1.04 ml, 9.4 mmol) to give **84** (4.16 g, 89%) as colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (t, 3H, J=7.2 Hz), 1.52—1.92 (m, 2H), 2.13—2.96 (m, 8H), 3.28—5.43 (m, 5H), 3.78 (s, 2H), 3.82 (s, 3H), 4.19 (q, 2H, J=7.2 Hz), 6.78—7.45 (m, 12H).

1-[1-[4-Methoxy-(2-methylamino)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (51) A solution of **81** (1.9 g, 3.6 mmol) in EtOH (50 ml) containing 5% Pd–C (0.2 g) was stirred under an H_2 atmosphere at room temperature. After 80.7 ml of H_2 had been absorbed, the catalyst was removed by filtration. The filtrate was concentrated and the residue was purified by silica gel column chromatography to give **51** (1.26 g, 89%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.68—1.92 (m, 2H), 2.52—3.07 (m, 8H), 2.83 (s, 3H), 3.82 (s, 3H), 4.28—4.57 (m, 3H), 5.55 (br s, 1H), 6.14—6.28 (m, 2H), 6.97—7.31 (m, 5H).

In a similar manner to that described above, compounds **52**, **53** and **54** were prepared from **82**, **83** and **84**, respectively. Analytical data are listed in Table 4.

1-[1-[2-(3-Hydroxypropoxy)-4-methoxybenzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (59) A mixture of **47** (0.3 g, 0.79 mmol), 3-bromo-1-propanol (0.16 g, 1.15 mmol), K_2CO_3 (0.22 g, 1.6 mmol), and KI (0.26 g, 1.6 mmol) in acetone (30 ml) was heated at reflux for 6 h, then concentrated under reduced pressure. The residue was taken up in H_2O, and the solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated, then the residue was purified by silica gel column chromatography to provide **59** (0.29 g, 84%) as a colorless amorphous solid. ^{1}H-NMR ($CDCl_3$) δ: 1.58—2.31 (m, 4H), 2.44—3.30 (m, 8H), 3.60—4.50 (m, 6H), 3.81 (s, 3H), 4.70—5.15 (m, 1H), 6.43—6.60 (m, 2H), 6.99—7.33 (m, 5H).

In a similar manner to that described above, compounds **55**—**58** were prepared from **47**. Analytical data are listed in Table 4.

1-[1-[4-Methoxy-2-(3-methoxypropoxy)benzoyl]-4-piperidyl]-3,4-dihydro-2(1*H*)-quinolinone (60) A solution of **59** (0.34 g, 0.78 mmol) in DMF (20 ml) was treated with 60% NaH (0.1 g, 2.5 mmol) followed by the addition of MeI (0.12 ml, 1.9 mmol) at 0—5 °C. After having been stirred for 3 h at room temperature, the mixture was poured into H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, then the residue was purified by silica gel column chromatography to afford **60** (0.32 g, 91%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.77 (m, 1H), 1.77—1.94 (m, 1H), 1.94—2.33 (m, 2H), 2.33—3.24 (m, 8H), 3.35 (s, 3H), 3.42—3.77 (m, 3H), 3.81 (s, 3H), 3.95—4.27 (m, 2H), 4.40 (m, 1H), 4.87—5.07 (m, 1H), 6.42—6.62 (m, 2H), 6.98—7.32 (m, 5H).

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