J. Med. Chem. **1998,** *41,* 658−667

Articles

Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone Derivatives

Yasuo Oshiro,* Seiji Sato, Nobuyuki Kurahashi, Tatsuyoshi Tanaka, Tetsuro Kikuchi, Katsura Tottori, Yasufumi Uwahodo, and Takao Nishi

Third Institute of New Drug Research, Otsuka Pharmaceutical Company Ltd., 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-01, Japan

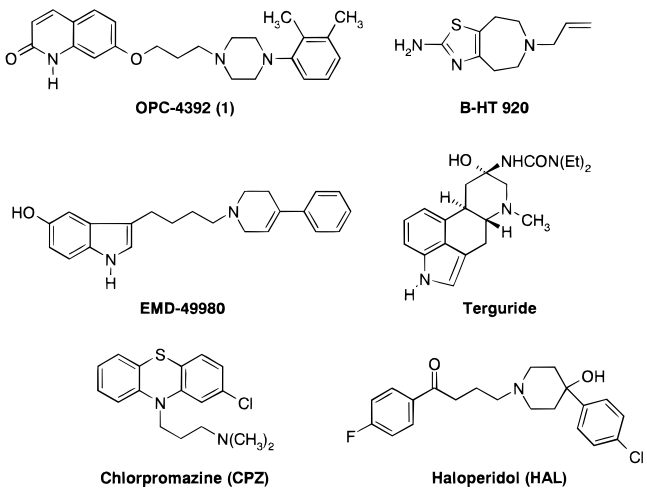
Received September 12, 1994

To develop a novel antipsychotic agent which is an agonist of dopamine (DA) autoreceptors and an antagonist of postsynaptic DA receptors, a series of 7-[4-[4-(substituted phenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinones was synthesized and their dual activities were examined. The postsynaptic DA receptor antagonistic activities of the compounds were evaluated by their ability to inhibit stereotypy induced by apomorphine in mice, and the autoreceptor agonist activities were determined by their effects on the γ-butyrolactone (GBL)-induced increase in L-dihydroxyphenylalanine (DOPA) synthesis in the mouse brain. Many compounds inhibited the stereotypic behavior, and several compounds reversed the GBL-induced increase in the DOPA synthesis. Among them, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butoxy]-3,4-dihydro-2(1*H*)-quinolinone (**28**, aripiprazole, OPC-14597) was found to have these two activities. This compound reversed the GBL-induced DOPA synthesis (ED_{50} values of 5.1 μmol/kg po) and inhibited the APO induced stereotypy (ED_{50} values of 0.6 μmol/kg po). Compound **28** induced catalepsy at 10 times higher dose than that required for the antagonism of APO-induced stereotypy (ED_{50} value of 7.8 μmol/kg po).

According to the "dopamine hypothesis of schizophrenia", a functional hyperactivity of the dopamine (DA) neuronal systems of the brain is involved as a major aspect of the disease.[1] All clinically available antipsychotic agents inhibit DA neurotransmission by blocking the postsynaptic DA receptors. Unfortunately, DA antagonism is also responsible for the most serious side effects of these agents, e.g., extrapyramidal syndrome (EPS), a parkinsonian-like syndrome caused by DA receptor blocking, tardive dyskinesia (TD), a syndrome of involuntary movements that has been linked to supersensitivity of brain DA receptors after long-term DA receptor blockage, and hyperprolactinemia, which is caused by blocking the pituitary DA receptors.[2,3] Reducing dopaminergic neurotransmission via stimulation of the DA autoreceptors has become of interest in the search for effective therapeutic agents that lack the side effects of available antipsychotic agents. The hypothesis underlying this approach stems from evidence that DA autoreceptors serve as an inhibitory feedback function of neurotransmission.[4−8]

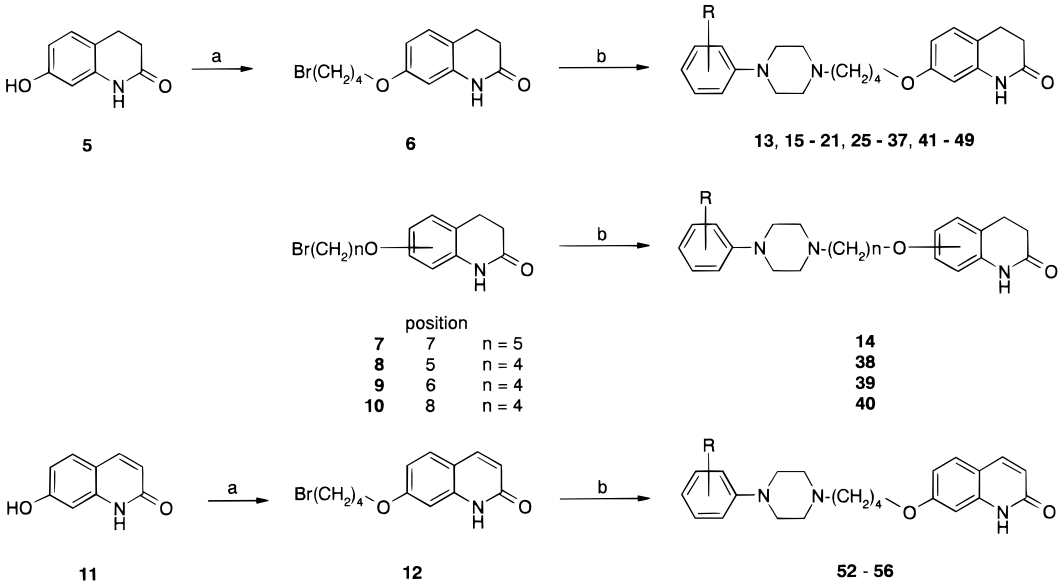
In a previous paper,[9] we reported on 7-[3-(4-phenyl-1-piperazinyl)propoxy]-2(1*H*)-quinolinone derivatives. Among them, OPC-4392 (**1** in Chart 1) was found to be an agonist of the DA autoreceptors and a weak antagonist of the postsynaptic DA D_2 receptors.[10−15] Other DA autoreceptor agonists, B-HT 920,[16] EMD-49980,[17] and Terguride,[18] have been reported to improve negative symptoms in schizophrenic patients. The clinical results with other DA autoreceptor agonists and our unpublished clinical observations with **1** strongly suggest that a DA autoreceptor agonist is effective in treating the negative symptoms and a potent DA postsynaptic receptor antagonism might be necessary for treatment of the positive symptoms in patients.[19−21] To find a more effective agent for treating both negative and positive symptoms in schizophrenia and with less side effects than the standard agents, we have searched for a compound which is an agonist of the DA autore-

Chart 1. DA Autoreceptor Agonists and D_2 Receptor Antagonists



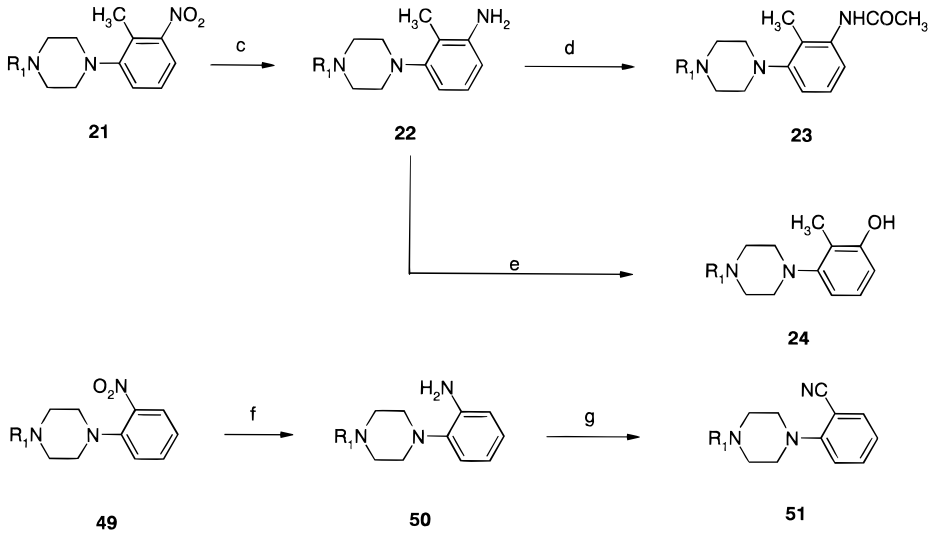
S0022-2623(94)00608-4 CCC: $15.00
Published on Web 01/31/1998

Scheme 1[a]



[a] Conditions and notation: (a) K_2CO_3, dibromoalkane in DMF; (b) NaI, TEA, phenylpiperazines in CH_3CN; $n = 4$ or 5.

Scheme 2[a]



R_1 = 4-[3,4-Dihydro-2(1*H*)-quinolinone-7-yl]oxybutyl-

[a] Conditions: (c) H_2, 3 kg/cm^3, 5% Pd−C in EtOH; (d) acetic anhydride; (e) (1) $NaNO_2$ in dilute H_2SO_4, (2) H_2SO_4; (f) $SnCl_2$ dihydrate in concentrated HCl; (g) (1) $NaNO_2$ in dilute H_2SO_4, (2) NaCN, $CuSO_4$, NH_4OH.

ceptors and a potent antagonist of the postsynaptic DA receptors. An ideal compound would be a potent and effective agent for treatment of both the positive and negative symptoms of schizophrenia with less adverse effects than clinically available agents. We have synthesized a series of new compounds with a variety of modifications of compound **1** and examined the postsynaptic DA receptor antagonist activity of all compounds synthesized by evaluation of their ability to antagonize the DA agonist apomorphine (APO) in the stereotypy test.[22] Selected compounds which showed a potent postsynaptic DA receptor antagonist activity were evaluated for their DA autoreceptor agonist activity by testing their reversing effects on the γ-butyrolactone (GBL)-induced increase in L-dihydroxyphenylalanine (DOPA) synthesis in the mouse brain.[23,24] In this paper, we describe the synthesis and the preliminary pharmacology of 3,4-dihydro-2(1*H*)-quinolinone derivatives. Structure−activity relationships (SAR) are also discussed.

Chemistry

Our new target compounds, 7-[4-(4-phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone derivatives (**13**−**51**) listed in Table 1, were prepared as shown in Schemes 1 and 2. To examine structure−activity relationships on the nucleus portion in the 3,4-dihydro-2(1*H*)-quinolinone derivatives, several analogues of 2(1*H*)-quinolinone (**52**−**56**) in Table 2 were prepared.

Intermediates, 5-, 6-, or 8-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**8**−**10**)[25,26] and 7-(5-bromopentoxy)-3,4-dihydro-2(1*H*)-quinolinone (**7**),[9] have been reported. With the application of similar procedures, 7-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**6**) and 7-(4-bromobutoxy)-2(1*H*)-quinolinone (**12**) were prepared.

Alkylation of 3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone (**5**) with 1,4-dibromobutane in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) gave 7-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**6**). Similarly, 7-hydroxy-2(1*H*)-quinolinone (**11**) was converted to 7-(4-bromobutoxy)-2(1*H*)-quinolinone (**12**). Thus prepared (*ω*-bromoalkoxy)-3,4-dihydro-2(1*H*)-quinolinones (**6**−**10**) and (4-bromobutoxy)-2(1*H*)-quinolinone (**12**) were reacted with various phenylpiperazines to afford the target compounds **13**−**21**, **25**−**49** (listed in Table 1), and **52**−**56** (listed in Table 2).

Compounds **22**−**24** and **50**−**51** were prepared as shown in Scheme 2. Catalytic reduction of compound **21** produced compound **22**. Treatment of **22** with acetic anhydride in acetic acid resulted in **23**. Reaction of **22** with sodium nitrate in a dilute sulfuric acid solution yielded diazonium salt, which was added to a 20% aqueous solution of sulfuric acid to produce **24**. Reduction of **49** with tin(II) chloride dihydrate in concentrated hydrochloric acid gave **50**. Diazotization of compound **50** in a 20% aqueous solution of sulfuric acid followed by addition of the resulting diazonium salt solution to a cuprous cyanide solution provided **51** (the Sandmeyer reaction).

Pharmacology

The postsynaptic DA receptor antagonist activity of all compounds synthesized was evaluated by the ability to inhibit APO-induced stereotypic behavior in mice (anti-APO test).[22] The clinically available standard antipsychotic agents chlorpromazine and haloperidol were also examined in the test as reference drugs, and the results are summarized in Tables 1 and 2.

The DA autoreceptor agonist activity of selected compounds was determined by their reversal effects on the GBL-induced increase in DOPA synthesis in the mouse brain.[23] The EPS liability of selected compounds was examined by measuring their ability to induce catalepsy in mice. Several compounds were tested for their α_1-adrenoceptor antagonist activity since peripheral α_1-adrenoceptor antagonism has been reported to cause autonomic side effects.[2] The results are summarized in Table 3. Furthermore, to evaluate its potential as an antipsychotic agent, the activities of the selected compound in behavioral tests with rats were compared with those of chlorpromazine, haloperidol, and compound **1**. The results are summarized in Table 4.

Results and Structure−Activity Relationships

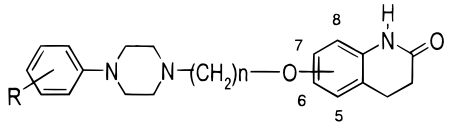
In the search for a lead compound, we initially examined the postsynaptic DA receptor antagonist activity of the compounds prepared in the previous paper (**1**−**4**).[9] As shown in Table 1, compound **1** inhibited the APO-induced stereotypy in mice with an ED_{50} of 41.3 μmol/kg po. Compound **2**, in which the nucleus portion of **1** is changed from 2(1*H*)-quinolinone to 3,4-dihydro-2(1*H*)-quinolinone, showed a higher potency than its parent compound **1**. Compound **3**, in which a methyl substituent at the 3-position on the aromatic ring in the phenylpiperazinyl moiety in **2** is replaced with a chlorine substituent, is more potent than **2**. Replacement of the side chain in **3** from propoxy to butoxy increased the potency of the resulting compound **13**, whereas with a pentoxy side chain the activity was much reduced as in compound **15**. Compound **4**, with a butoxy side chain but no substituent on the phenylpiperazinyl moiety, did not show activity. These results indicated a superiority of butoxy side chain to propoxy and pentoxy side chains in producing potent DA antagonist activity in the 3,4-dihydro-2(1*H*)-quinolinone series and also indicated that substituents in the phenylpiperazinyl moiety are required in order to display activity in this series of compounds. Thus, we selected compound **13**, having the butoxy side chain and the 4-(2-methyl-3-chlorophenyl)-1-piperazinyl moiety, as a lead compound, and a variety of modifications on it were carried out. Also, the effects of structural modifications on their DA antagonist activity were examined with respect to electronic and lipophilic factors of substituents within a series of compounds. Our purpose in this paper is to find the most potent oral administered compound. Therefore, the structure−activity relationships are discussed below with the data obtained by oral administration (Tables 1 and 2).

Postsynaptic DA Receptor Antagonist Activity. First, we examined the effects of the substituent of the aromatic ring in the phenylpiperazinyl moiety in compound **13** on the postsynaptic DA receptor antagonist activity. Replacement of the chlorine substituent at the 3-position on the phenylpiperazinyl moiety in **13** with a more bulky bromine substituent (**16**) retained the potency, but replacement with a smaller fluorine substituent (**18**) reduced the potency. Replacement of the chlorine substituent with a more electron-withdrawing nitro group (**21**) greatly enhanced the potency, whereas replacement with the nitrile group which also has a greater electron-withdrawing character but less lipophilicity than the chloro group retained the potency as in compound **20**. The compounds that possess more electron-donating substituents such as amino (**22**), acetylamino (**23**), and hydroxy (**24**) groups showed much lower potency.

Exchange of the substituents at the 2- and 3-positions in the phenylpiperazinyl moiety in **13** with each other greatly enhanced the potency (**25**). Similar enhancement of the potency was observed in the case of compound **26** (vs **16**). These results suggested that the halogen substituent at the 2-position in the phenylpiperazinyl moiety was more effective in showing the postsynaptic DA receptor antagonist activity in the series. Thus, compounds with several chlorine substituents on the phenylpiperazinyl moiety were prepared and examined. Of the compounds with two chloro substituents, compound **28**, in which the two chlorine substituents are adjacent to each other at the 2- and 3-positions in the phenylpiperazinyl moiety, showed the highest potency. Replacement of one or both chlorine substituents in compound **28** with a more bulky bromine substituent (**34** and **35**) and incorporation of another chlorine substituent at the 4-position (**36**) and 5-position (**37**) reduced the potency.

In the series of compounds with one chloro substituent on the phenylpiperazinyl moiety, the compound having a chloro substituent at the 2-position showed the highest potency (**41** > **42** > **43**), although its potency is much less than that of the compound with two chloro substituents on the phenylpiperazinyl moiety (**28**). Replacement of the chlorine substituent at the 2-position of **41**

Table 1. 7-[4-[4-(Substituted phenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone Derivatives and Their Postsynaptic DA Receptor Antagonist Activity



compd	position	*n*	R	yield[a] (%)	recryst solvent[b]	mp (°C)	formula	anal.[c]	DA receptor antagonistic activity, ED_{50} (CL)[d]
13	7	4	2-Me, 3-Cl	35	A	146−148	$C_{24}H_{30}N_3O_2Cl$	C,H,N	2.8 (1.2−8.9)
14	7	5	2-Me, 3-Cl	32	A	151−153	$C_{25}H_{32}N_3O_2Cl$	C,H,N	>23[e]
15	7	4	2-Me, 5-Cl	84	A	110−111	$C_{24}H_{30}N_3O_2Cl$	C,H,N	>23[e]
16	7	4	2-Me, 3-Br	84	B	151−152	$C_{24}H_{30}N_3O_2Br$	C,H,N	2.1 (1.1−3.6)
17	7	4	2-Me, 4-Br	82	A	152−153	$C_{24}H_{30}N_3O_2Br$	C,H,N	21[f]
18	7	4	2-Me, 3-F	71	B	141−143	$C_{24}H_{30}N_3O_2F\cdot 0.25H_2O$	C,H,N	7.2[g]
19	7	4	4-Me, 3-Cl	70	A	117−118	$C_{24}H_{30}N_3O_2Cl$	C,H,N	>7.0[e]
20	7	4	2-Me, 3-CN	32	B	181−182	$C_{25}H_{30}N_4O_2$	C,H,N	4.1 (3.2−5.1)
21	7	4	2-Me, 3-NO_2	61	B	165−166	$C_{24}H_{30}N_4O_4$	C,H,N	0.7 (0.2−1.4)
22	7	4	2-Me, 3-NH_2	55	B	171−173	$C_{24}H_{32}N_4O_2$	C,H,N	>25[e]
23	7	4	2-Me, 3-$NHCOCH_3$	70	B	186−188	$C_{26}H_{34}N_4O_3$	C,H,N	>25[e]
24	7	4	2-Me, 3-OH	24	B	208−210	$C_{24}H_{31}N_3O_3\cdot 1.5H_2O$	C,H,N	>8.0[h]
25	7	4	2-Cl, 3-Me	72	A	133−134	$C_{24}H_{30}N_3O_2Cl$	C,H,N	0.9 (0.5−1.2)
26	7	4	2-Br, 3-Me	44	A	125−126	$C_{24}H_{30}N_3O_2Br$	C,H,N	0.9 (0.5−1.2)
27	7	4	2,3-$(Me)_2$	94	B	136−137	$C_{25}H_{33}N_3O_2$	C,H,N	3.4 (2.5−4.4)
28	7	4	2,3-$(Cl)_2$	87	A	139−140	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	0.6 (0.5−0.8)
29	7	4	2,4-$(Cl)_2$	67	A	153−155	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	>7.0[e]
30	7	4	2,5-$(Cl)_2$	67	A	134−135	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	2.7 (1.1−5.2)
31	7	4	2,6-$(Cl)_2$	75	B	133−134	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	>7.0[h]
32	7	4	3,4-$(Cl)_2$	73	A	134−136	$C_{23}H_{27}N3O_2Cl_2$	C,H,N	>7.0[h]
33	7	4	3,5-$(Cl)_2$	77	A	134−135	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	1.1 (0.2−2.7)
34	7	4	2-Br, 3-Cl	29	B	154−156	$C_{23}H_{27}N_3O_2BrCl$	C,H,N	2.4 (1.0−4.7)
35	7	4	2,3-$(Br)_2$	80	B	150−151	$C_{23}H_{27}N_3O_2Br_2$	C,H,N	1.1 (0.2−2.9)
36	7	4	2,3,4-$(Cl)_3$	73	B	164−166	$C_{23}H_{26}N_3O_2Cl_3$	C,H,N	6.4 (5.5−7.7)
37	7	4	2,3,5-$(Cl)_3$	34	B	174−176	$C_{23}H_{26}N_3O_2Cl_3$	C,H,N	0.8 (0.4−1.2)
38	5	4	2,3-$(Cl)_2$	72	C	190−192	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	>22[h]
39	6	4	2,3-$(Cl)_2$	81	C	194−197	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	>22[e]
40	8	4	2,3-$(Cl)_2$	79	A	122−123	$C_{23}H_{27}N_3O_2Cl_2$	C,H,N	>22[h]
41	7	4	2-Cl	27	A	103−104	$C_{23}H_{28}N_3O_2Cl\cdot 0.2H_2O$	C,H,N	2.9 (1.2−5.6)
42	7	4	3-Cl	64	A	102−103	$C_{23}H_{28}N_3O_2Cl$	C,H,N	7.5 (6.4−9.0)
43	7	4	4-Cl	49	A	138−139	$C_{23}H_{28}N_3O_2Cl\cdot 0.2H_2O$	C,H,N	>8.0[e]
44	7	4	2-Br	61	B	105−106	$C_{23}H_{28}N_3O_2Br$	C,H,N	3.9 (3.3−4.7)
45	7	4	2-F	41	A	122−123	$C_{23}H_{28}N_3O_2F$	C,H,N	>8.0[e]
46	7	4	2-Me	42	A	135−136	$C_{24}H_{31}N_3O_2$	C,H,N	2.5 (2.1−2.8)
47	7	4	2-OMe	44	B	125−126	$C_{24}H_{31}N_3O_3$	C,H,N	0.6 (0.3−1.0)
48	7	4	2-OEt	33	A	189−191	$C_{25}H_{33}N_3O_3\cdot HCl$	C,H,N	0.2 (0.1−0.4)
49	7	4	2-NO_2	50	B	112−113	$C_{23}H_{28}N_4O_4$	C,H,N	>7.0[e]
50	7	4	2-NH_2	34	D	130−132	$C_{23}H_{30}N_4O_2$	C,H,N	>25[h]
51	7	4	2-CN	18	E	150−151	$C_{24}H_{28}N_4O_2\cdot 1.5H_2O$	C,H,N[i]	>23[h]
1	7[j]	3	2,3-$(Me)_2$						41.3
2	7	3	2,3-$(Me)_2$						26.0
3	7	3	2-Me, 3-Cl						16.6 (14.6−19.1)
4	7	4	H						>28[e]
chlorpromazine									12.1 (9.0−17.7)
haloperidol									0.24 (0.08−0.98)

[a] Yields were not optimized in most cases. [b] A = EtOH, B = MeOH, C = EtOH−$CHCl_3$, D = EtOH−iPr_2O, E = CH_3CN. [c] C,H,N analyses were within ±0.4% of the calculated value. [d] Inhibition of the apomorphine-induced stereotyped behavior in mice. Test compound was administered orally to 10 mice 1 h before subcutaneous injection of apomorphine (1.5 mg/kg sc). The ED_{50} values and 95% confidence limits were calculated by the linear regression analysis and are presented in μmol/kg po. CL represents 95% confidence limits. [e] Inactive at below given dose. [f] No confidence limit; 51% inhibition at a single given dose. [g] No confidence limit; 49% inhibition at a single given dose. [h] Inactive at a single given dose. [i] N: calcd, 13.85; found, 13.03. [j] 7-[3-[4-(2,3-Dimethylphenyl)-1-piperazinyl]propoxy]-2-(1*H*)-quinolinone (OPC-4392).

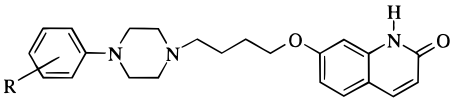
with more electron-donating groups such as methyl (**46**), methoxy (**47**), and ethoxy groups (**48**) enhanced the potency, whereas electron-withdrawing groups such as nitro and nitrile groups diminished the activity (**49** and **51**).

Next, the effects of the positional change of the side chain attached to the 3,4-dihydro-2(1*H*)-quinolinone nucleus in compound **28** was examined. Change in the 4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy side chain from the 7-position in **28** to the 5-, 6-, and 8-positions in the 3,4-dihydro-2(1*H*)-quinolinone nucleus produced the inactive compounds **38**−**40**.

The effects of modifying the nucleus portion of the compounds were then examined. As shown in Table 2, the 2(1*H*)-quinolinone derivatives (**52**−**56**) were equipotent to their corresponding 3,4-dihydro-2(1*H*)-quinolinone analogues (**13**, **16**, **27**, **28** and **48**).

In the structure−activity relationships, the structural requirements for the postsynaptic DA receptor antagonist activity found in this series are as follows: (1) In

Table 2. 2(1*H*)-Quinolinone Analogues and Their Postsynaptic DA Receptor Antagonist Activity



compd	R	yield[a] (%)	recryst solvent[b]	mp (°C)	formula	anal.[c]	DA receptor antagonistic activity, ED_{50} (CL)[d]
52	2-Me, 3-Cl	84	F	174−176	$C_{24}H_{28}N_3O_2Cl \cdot 0.1H_2O$	C,H,N	2.8 (1.9−5.1)
53	2-Me, 3-Br	50	A	168−169	$C_{24}H_{28}N_3O_2Br$	C,H,N	2.1 (1.9−2.3)
54	2,3-$(Cl)_2$	51	A	144−146	$C_{23}H_{25}N_3O_2Cl_2$	C,H,N	0.9 (0.5−1.2)
55	2,3-$(Me)_2$	69	F	161−161.5	$C_{25}H_{31}N_3O_2 \cdot 0.2H_2O$	C,H,N	3.4 (2.4−4.4)
56	2-OEt	33	A	151 dec[e]	$C_{25}H_{31}N_3O_3 \cdot 2HCl \cdot 0.5H_2O$	C,H,N	0.24 (0.14−0.34)

[a] Yields were not optimized in most cases. [b] A = EtOH, F = MeOH−$CHCl_3$. [c] C,H,N analyses were within ±0.4% of the calculated value. [d] Inhibition of the apomorphine-induced stereotypy of behavior in mice. ED_{50} values and confidence limits (CL) were calculated using the linear regression analysis and are presented in μmol/kg po. [e] Decomposed.

Table 3. Pharmacology of the Selected Compounds

	ED_{50} (CL)				
compd	DA receptor antagonist activity[a] (A)	DA autoreceptor agonist activity[b]	catalepsy[c] (B)	α_1-adrenoceptor antagonist activity[d]	ED_{50} ratio, B/A
13	2.8	3.5 (1.4−7.2)	5.6 (3.3−8.9)	>299	2.0
16	2.1	1.3 (0.1−4.0)	NT	NT	
21	0.7	>23	5.9 (3.2−8.9)	>146	8.7
25	0.9	>23	1.4 (0.2−3.7)	>150	1.5
26	0.9	>2.1	NT	NT	
27	3.4	9.1 (3.7−84.7)	13.5 (10.8−18.4)	>314	3.9
28	0.6	5.1 (1.3−29.2)	7.8 (7.1−8.7)	>286	13
33	1.1	>22	NT	>256	
37	0.8	>21	NT	>265	
48	0.2	0.65 (0.20−11.5)	4.4 (3.9−5.2)	7.0 (6.1−7.8)	20
52	2.8	20.1 (11.2−94.4)	12.6 (7.7−24.1)	>299	4.5
54	0.9	>22	NT	>287	
55	3.4	3.9 (0.7−18.6)	10.5 (7.3−19.6)	>156	3.1
56	0.24	>20	NT	>127	
1	41.3	3.5 (1.6−5.6)	73.2 (66.8−80.2)	151 (96.1−236.0)	1.8
CPZ	12.1	IA	24.5 (21.4−27.9)	19.7 (19.1−22.0)	2.0
HAL	0.24	IA	0.9 (0.88−0.98)	>341	3.7

[a] See Tables 1 and 2. ED_{50} values are presented in μmol/kg po. [b] Inhibition of the GBL-induced increase in DOPA accumulation in mice. The ED_{50} values and 95% confidence limits (CL) were calculated using the linear regression analysis and are presented in μmol/kg po. The compounds with ED_{50} values indicated with a greater than sign (>) were inactive at below the given dose. [c] Induction of catalepsy in mice. The ED_{50} values and 95% confidence limits (CL) were calculated using the probit method and are presented in μmol/kg po. [d] Inhibition of the lethal effects of noradrenaline in mice. The ED_{50} values and 95% confidence limits (CL) were calculated using the probit method and are presented in mmol/kg po The compounds with ED_{50} values indicated with a greater than sign (>) were inactive at below the given dose. IA, inactive up to 10 mg/kg po; NT, not tested.

Table 4. Comparison of Biological Activities in Rats of Compound **28** and Reference Agents[a]

	ED_{50} (μmol/kg po)			
comp	inhibition of GBL-induced increase in DOPA synthesis	inhibition of APO-induced streotyped behavior (A)	catalepsy (B)	ratio of ED_{50}, B/A
1	15.1 (10.2−22.0)	1860 (1250−3730)	>2600	>1.4
28	6.9 (4.5−10.7)	11.8 (8.5−15.4)	149 (137−161)	12.6
haloperidol	inactive	1.1 (0.5-1.3)	1.9 (1.6−2.1)	1.7
chlorpromazine	inactive	28.4 (24.5−33.2)	0.8 (0.8−0.9)	0.03

[a] Numbers in parentheses represent 95% confidence limits.

the (phenylpiperazinyl)alkoxy side chain, the butoxy side chain is preferred to the propoxy and pentoxy side chains. (2) One or two substituents on the aromatic ring in the phenylpiperazinyl moiety are necessary; the 2-ethoxy analogue **48** is best in the compounds with one substituent on the aromatic ring, and the 2,3-dichloro analogue **28** is best in the compounds with two or more substituents on the aromatic ring. (3) The substituted (phenylpiperazinyl)butoxy side chain at the 7-position in the 3,4-dihydro-2(1*H*)-quinolinone nucleus is essential for activity. (4) The 3,4-dihydro-2(1*H*)-quinolinone and 2(1*H*)-quinolinone derivatives with the same (phenylpiperazinyl)butoxy moiety are equipotent to each other.

The compounds which showed higher potency in the anti-APO test than chlorpromazine were selected for further examination.

DA Autoreceptor Agonist Activity. The selected compounds were tested for their ability to reverse GBL-induced increase in DOPA synthesis in the mouse brain. This effect reflects DA autoreceptor agonistic activity. The DA autoreceptor agonist **1** and selected compound **28** dose-dependently reversed the GBL-induced increase

in DOPA synthesis (0.3, 1, 3, 10 mg/kg po), but these two compounds did not completely antagonize GBL even at the highest dose in this model (70% inhibition at 10 mg/kg po). As shown in Table 3, compound **28** and the DA autoreceptor agonist **1** reversed the GBL-induced increase in DOPA synthesis. Compounds with the 3-chloro-2-methyl (**13**) and 2,3-dimethyl (**27**) phenylpiperazinyl moieties showed activity almost equipotent to that of compound **1**, whereas compounds with the 2-methyl-3-nitro (**21**), 2-chloro-3-methyl (**25**), 2-bromo-3-methyl (**26**), 3,5-dichloro (**33**), and 2,3,5-trichloro (**37**) phenylpiperazinyl moieties were inactive up to 10 mg/kg po. The effects of change in the nucleus portion of the 3,4-dihydro-2(1*H*)-quinolinone derivatives were also observed. The 2(1*H*)-quinolinone **55** showed higher activity than the 3,4-dihydro-2(1*H*)-quinolinone **27** with the same (2,3-dimethylphenyl)piperazinyl moiety as **1**. In contrast, the 2(1*H*)-quinolinone derivatives with the 3-chloro-2-methyl-, 2,3-dichloro-, and 2-ethoxyphenylpiperazinyl moieties (**52**, **54**, and **56**) were much less active than the 3,4-dihydro-2(1*H*)-quinolinone derivatives with the corresponding side chain (**13**, **28**, and **48**).

Compounds **28** and **48**, which were the two most potent compounds in the anti-APO test, also displayed activity in the test for reversal of GBL-induced increase in DOPA synthesis comparable to that of DA autoreceptor agonist **1**.

Adverse Effects. The EPS liability and α_1-adrenoceptor antagonist activity of selected compounds were examined. Typical antipsychotic agents induce catalepsy. Selected compounds were also examined for their ability to induce catalepsy in mice. As shown in Table 3, compound **25** was the most potent compound. The compound did not show the DA autoreceptor agonist activity. Compounds **28** and **48** also induced catalepsy but with 10 and 20 times higher ED_{50} values than that of the anti-APO test in mice (ED_{50} of 7.8 and 4.4 μmol/kg po, respectively), suggesting their lower propensity to induce EPS than the typical antipsychotic agent examined. The cataleptogenic effects of typical antipsychotic agents have been shown to be correlated to their potency of postsynaptic DA receptor antagonistic activities.[27] An atypical antipsychotic agent, clozapine, has been reported not to induce catalepsy in mice, and its lack of cataleptogenic effects has been explained to be attributable to its potent antimuscarinic effects.[28,29] However, these antimuscarinic effects are unlikely in compound **28** since **28** did not inhibit the lethal effects of physostigmine in rats up to 300 mg/kg po.[30] Furthermore, compound **25**, which does not show DA autoreceptor agonistic activity, is the most potent cataleptogenic compound in the series of compounds examined. Thus, the weak cataleptogenic effects of **28** and **48** may contribute to its DA autoreceptor agonistic activity at present, although further investigations to determine the mechanism of their pharmacological effects are necessary.

Selected compounds were also tested for their α_1-adrenoceptor antagonist activity since peripheral α_1-adrenoceptor antagonism has been known to cause autonomic side effects.[2] As seen in Table 3, chlorpromazine and **1** showed α_1-adrenoceptor antagonist activity with ED_{50} values of 19.7 and 150.7 μmol/kg po, respectively. Among the compounds examined, the monosubstituted phenylpiperazinyl analogue **48** showed the highest potency in this activity, whereas the disubstituted phenylpiperazinyl analogues and **28** were inactive up to 286 μmol/kg po. An abnormality of noradrenaline neurotransmission in schizophrenia patients has been reported.[31] Although a beneficial effect of this activity in treatments of these patients has been suggested,[32] compound **48** requires further studies with respect to its potent α_1-adrenoceptor antagonist activity.

Data presented in Table 3 show that compounds **13**, **27**, **28**, **52**, and **55** are D_2 receptor antagonists and DA autoreceptor agonists and are very weak α_1-adrenoceptor antagonists. The profile of these compounds is quite similar to that of **1** when tested in mice. Therefore, we compared their effects on the APO-induced stereotypy in rats with that of compound **1** at 1, 2, 4, and 6 h after oral administration of 30 mg/kg po. Compounds **1**, **27**, and **55**, which have the (2,3-dimethylphenyl)piperazinyl moiety, did not inhibit the APO-induced stereotypy at 1−6 h after oral administration of 30 mg/kg. In contrast to this, compounds **13** and **52**, which possess the (3-chloro-2-methylphenyl)piperazinyl moiety, inhibited the APO-induced stereotypy at 1, 2, 4, and 6 h after administration, and maximum inhibition was found at 2 and 4 h after administration, ED_{50} values estimated as 49.5 (27.8−169.4) and 50.5 (38.5−71.1) μmol/kg po, respectively. Compound **28**, which possesses the (2,3-dichlorophenyl)piperazinyl moiety, was the most potent of the compounds tested in rats. Complete inhibition was observed at 2 h after oral administration, and the ED_{50} value was estimated as 11.8 (8.5−15.4) μmol/kg po. These results suggested that the methyl substituent in the phenylpiperazinyl moiety is more vulnerable to a first-pass metabolism in rats than the chloro substituent in the phenylpiperazinyl moiety in those compounds. Thus, compound **28** was selected for further examination of its clinical potential as an antipsychotic agent in comparisons with standard agents such as chlorpromazine and haloperidol in rats.

As shown in Table 4, the DA autoreceptor agonist and postsynaptic DA receptor antagonist activities of **28** were also confirmed in two tests in rats. Compound **28**, chlorpromazine, and haloperidol inhibited the APO-induced stereotypic behavior in rats with ED_{50} values of 11.8, 28.4, and 1.1 μmol/kg po, respectively. Compounds **28** and **1** antagonized the GBL-induced increase in DA synthesis in the rat brain with ED_{50} values of 6.9 and 15.7 μmol/kg po, respectively. Compounds **1** and **28** showed lower activities in rats than in mice after oral administration. These differences in potencies between mice and rats may be attributable to the difference in first-pass metabolism between the two species. Compound **28** induced catalepsy in rats with an ED_{50} value of 149.2 μmol/kg po, which is about 10 times higher than that for APO-induced stereotypic behavior test as seen in mice. Thus, **28** was confirmed in mice and rats to have these dual activities and a low potential to induce the EPS.

Because of its attractive profile and its minimal adverse effect after toxicological studies, compound **28** was selected as a candidate for clinical evaluations in schizophrenic patients.

Conclusion

To develop a novel antipsychotic agent which acts as an agonist at DA autoreceptors and as an antagonist at postsynaptic DA receptors, a series of 7-[4-(4-phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1*H*)-quinolinone derivatives were synthesized and their dual activities were examined. In the course of these studies, compound **28** was found to possess the desired dual activities. Our results indicated that **28** is an agonist of the DA autoreceptors, and it also acts as an antagonist of the postsynaptic DA receptors almost equipotently to standard antipsychotic agents. This compound showed lower potential to induce catalepsy than the standard agent and did not show α_1-adrenoceptor antagonist activity. Thus, **28** may be a potent and effective agent for treatment of both the negative and positive symptoms in schizophrenia with less adverse effects than clinically available agents.

The dual activities of **28** have been confirmed by biochemical and pharmacological studies.[30] In addition to its reversal effects on the GBL in the DOPA synthesis described in this paper, **28** reversed reserpine-induced increase in tyrosine hydroxylase activity in mouse and rat brain.[30] Furthermore, the reversal effects of **28** in the test with GBL was blocked by pretreatment of the DA receptor antagonist haloperidol.[30] The postsynaptic DA receptor antagonist activity of **28** was also supported by the following results. In contrast to a DA receptor agonist (apomorphine), **28** did not evoke postsynaptic DA receptor-stimulating behavioral signs such as hyperlocomotion in the reserpinized mice and contralateral rotation in rats with unilateral striatal 6-hydroxydopamine lesions.[30] Compound **28** also binds to the [^{3}H]-spiperone-labeled D_2 receptors in the rat frontal cortex (K_i = 1.2 nM), limbic forebrain (K_i = 0.4 nM), and striatum (K_i = 0.8 nM).[30] Further biochemical and behavioral investigations on compound **28** with respect to its dual activities have been reported.[34−41] Clinical trials with **28** (aripiprazole, OPC-14597) are currently in progressed in Japan and the United States.

Experimental Section

Melting points were determined by a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC-250 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Elementary analyses for carbon, hydrogen, and nitrogen were carried out on a Yanaco MT-5 CHN recorder. Where analyses are indicated only as symbols of elements, analytical results obtained are within 0.4% of the theoretical value. All compounds were routinely checked by TLC with Merck silica gel 60 F254 precoated plates.

7-(4-Bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (6). A mixture of 7-hydroxy-3,4-dihydro-2(1*H*)-quinolinone (**5**) (16.7 g, 0.1 mol), K_2CO_3 (13.8 g, 0.1 mol), and 1,4-dibromobutane (64.8 g, 0.3 mol) in DMF (500 mL) was stirred for 4 h at 60 °C and then diluted with water (500 mL). An organic layer was extracted with ethyl acetate (AcOEt), and the extract was washed, dried, and evaporated to dryness in vacuo. Recrystallization from EtOH gave **6** (78%) as colorless needles: mp 110.5−111 °C; ^{1}H NMR (DMSO-d_6) δ 1.81 (2H, m, -CH_2-), 1.95 (2H, m, -CH_2-), 2.41 (2H, t, J = 7 Hz, -CH_2CO-), 2.78 (2H, t, J = 7 Hz, -CH_2-C-CO-), 3.60 (2H, t, J = 6 Hz, -CH_2Br), 3.93 (2H, t, J = 6 Hz, O-CH_2-), 6.43 (1H, d, J = 2.5 Hz), 6.49 (1H, dd, J = 2.5, 8 Hz), 7.04 (1H, d, J = 8 Hz), 9.98 (1H, s, NHCO). Anal. ($C_{13}H_{16}NO_2Br$) C, H, N.

7-(4-Bromobutoxy)-2(1*H*)-quinolinone (12). In a manner similar to compound **6**, 7-hydroxy-2(1*H*)-quinolinone (**11**) (16.3 g, 0.1 mol), 1,4-dibromobutane (64.8 g, 0.3 mol), and K_2CO_3 (13.8 g, 0.1 mol) in DMF (500 mL) were stirred for 4 h to give **12** (29%) as a white powder. An analytical sample was obtained by recrystallization from AcOEt as colorless granules: mp 126−128 °C; ^{1}H NMR (DMSO-d_6) δ 1.92 (4H, m, −C−CH_2CH_2−C-), 3.62 (2H, t, J = 6 Hz, -CH_2Br), 4.05 (2H, t, J = 6 Hz, O-CH_2-), 6.30 (1H, d, J = 9 Hz, -C═CH-CO-), 6.79 (2H, m, H8, H6), 7.56 (1H, d, J = 8 Hz, H5), 7.89 (1H, d, J = 9 Hz, -CH═C-CO-), 11.59 (1H, s, NHCO). Anal. ($C_{13}H_{14}NO_2Br$) C, H, N.

General Procedure for Preparation of 3,4-Dihydro-2(1*H*)-quinolinone Derivatives (Table 1). 7-[4-[4-(3-Chloro-2-methylphenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (13). A mixture of **6** (2.0 g, 6.7 mmol) and NaI (2.0 g, 13.3 mmol) in CH_3CN (50 mL) was refluxed for 30 min and then cooled to room temperature. 1-(3-Chloro-2-methylphenyl)piperazine (2.0 g, 9.49 mmol) and triethylamine (TEA; 2 mL, 14.5 mmol) were added to the mixture, and the resulting mixture was refluxed for 4 h. Precipitated crystals were filtered off, and the filtrate was evaporated under reduced pressure. The residue was extracted with AcOEt, and the extract was washed, dried, and concentrated to dryness in vacuo. Recrystallization from EtOH gave **13** (35%) as colorless needles: mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (4H, m, −CH_2CH_2-), 2.34 (3H, s, CH_3), 2.47 (2H, t, J = 7 Hz, −CH_2CO-), 2.61 (6H, m, −CH_2N(CH_2-)CH_2-), 2.90 (6H, m, −CH_2PhCH_2-, −CH_2−C−CO), 3.96 (2H, t, J = 6 Hz, O−CH_2-), 6.32 (1H, d, J = 2.5 Hz, H8), 6.52 (1H, dd, J = 2.5, 8 Hz, H6), 6.94 (1H, m, aromatic H), 7.08 (3H, m, aromatic H), 8.05 (1H, s, NHCO). Anal. ($C_{24}H_{30}N_3O_2Cl$) C, H, N.

Compounds **15**−**21**, **25**−**37**, and **41**−**49** were prepared in a manner similar to that for **13** by reacting **6** (6.7 mmol) with 2 equiv of the corresponding phenylpiperazine derivatives (13 mmol). 1-(2-Chlorophenyl)piperazine, 1-(3-chlorophenyl)piperazine, 1-(4-chlorophenyl)piperazine, 1-(2-fluorophenyl)piperazine, 1-(2-ethoxyphenyl)piperazine, 1-(2-methoxyphenyl)-piperazine, and 1-(*o*-tolyl)piperazine were purchased from Aldrich Chemical Co. Inc. 1-(2,3-Dichlorophenyl)piperazine was prepared by application of the reported method.[42] 1-(3-Chloro-2-methylphenyl)piperazine, 1-(2,3-dimethylphenyl)piperazine, and 1-(2,5-dichlorophenyl)piperazine were prepared according to the reported procedure.[43] 1-(2,4-Dichlorophenyl)-piperazine, 1-(2,6-dichlorophenyl)piperazine, 1-(3,5-dichlorophenyl)piperazine, 1-(2-methyl-3-fluorophenyl)piperazine, 1-(2-methyl-3-bromophenyl)piperazine, 1-(2-methyl-3-cyanophenyl)piperazine, 1-(2-methyl-3-nitorophenyl)piperazine, 1-(2-chloro-3-methylphenyl)piperazine, 1-(2,3,5-trichlorophenyl)-piperazine, and 1-(2,3,4-trichlorophenyl)piperazine were prepared from the corresponding aniline (0.127 mol) and bis(2-bromoethyl)amine hydrobromide (0.15 mol) by application of the reported method.[44] 1-(2-Nitrophenyl)piperazine, 1-(2-bromophenyl)piperazine, 1-(2,3-dibromophenyl)piperazine, and 1-(2-bromo-3-chlorophenyl)piperazine were prepared from the corresponding ethyl 4-phenyl-1-piperazinecarboxylate derivatives, which were obtained from ethyl 1-piperazinecarboxylate and 2-halogenonitrobenzene derivatives by application of the reported method[45] with modification. The modification made was that 2-halogenonitrobenzene derivatives were used instead of 2-chloropyrimidine derivatives.

7-[5-[4-(3-Chloro-2-methylphenyl)-1-piperazinyl]pentoxy]-3,4-dihydro-2(1*H*)-quinolinone (14). In a manner similar to that for **13**, 7-(5-bromopentoxy)-3,4-dihydro-2(1*H*)-quinolinone (**7**)[9] (2.0 g, 6.4 mmol) was reacted with 1-(3-chloro-2-methylphenyl)piperazine (2.0 g, 9.49 mol) and TEA (2 mL, 14.5 mmol) in the presence of NaI (2.0 g, 13.3 mmol) in CH_3-CN (50 mL) to afford **14** (32%): mp 146−148 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (4H, m, -CH_2CH_2-), 1.82 (2H, m, −CH_2-), 2.34 (3H, s, CH_3), 2.45 (2H, t, J = 7 Hz, -CH_2CO-), 2.60 (6H, m, -CH_2N(CH_2-)CH_2-), 2.92 (6H, m, -CH_2PhCH_2-, -CH_2-C-CO), 3.95 (2H, t, J = 6 Hz, O-CH_2-), 6.34 (1H, d, J = 2.5 Hz, H8), 6.52 (1H, dd, J = 2.5, 8 Hz, H6), 6.95 (1H, m, aromatic H), 7.05 (3H, m, aromatic H), 8.20 (1H, s, NHCO). Anal. ($C_{25}H_{32}N_3O_2Cl$) C, H, N.

7-[4-[4-(3-Amino-2-methylphenyl)-1-piperazinyl]butoxy]-

3,4-dihydro-2(1*H*)-quinolinone (22). A mixture of 7-[4-[4-(2-methyl-3-nitrophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (**21**) (5.1 g, 10 mmol) and 5% palladium on carbon (500 mg) in EtOH (100 mL) was hydrogenated in a Parr apparatus under 4 kg/cm^3 hydrogen pressure. After the catalyst was filtered off, the filtrate was concentrated in vacuo. Recrystallization from MeOH gave **22** (55%) as colorless needles: mp 171−173 °C; ^{1}H NMR ($CDCl_3$) δ 1.79 (4H, m, -CH_2CH_2-), 2.12 (3H, s, CH_3), 2.47 (2H, t, J = 7 Hz, -CH_2CO-), 2.61 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.90 (6H, m, -CH_2-C-CO-, CH_2-$NPhCH_2$-), 3.60 (2H, br, NH_2), 3.96 (2H, t, J = 6 Hz, O-CH_2-), 6.32 (1H, d, J = 2.5 Hz, H8), 6.46 (3H, m, aromatic H), 6.99 (1H, d, J = 8 Hz, aromatic H), 7.03 (1H, d, J = 8 Hz, aromatic H), 8.05 (1H, s, -NHCO-). Anal. ($C_{24}H_{32}N_4O_2$) C, H, N.

7-[4-[4-[3-(Acetylamino)-2-methylphenyl]-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (23). Acetic anhydride (0.2 mL, 2.05 mmol) was added to a solution of **22** (0.7 g, 1.7 mmol) in acetic acid (10 mL) at ice-cooled temperature. The mixture was stirred for 3 h at room temperature and evaporated in vacuo. Recrystallization from MeOH gave **23** (70%) as a pale-yellow powder: mp 186−188 °C; ^{1}H NMR ($CDCl_3$) δ 1.71 (4H, m, -CH_2CH_2-), 2.21 (6H, s, CH_3, CH_3CO-), 2.48 (2H, t, J = 7 Hz, -CH_2CO-), 2.60 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.90 (6H, m, -CH_2-C-CO-CH_2NPhCH_2-), 3.96 (2H, t, J = 6 Hz, O-CH_2-), 6.29 (1H, d, J = 2.5 Hz, H8), 6.52 (1H, dd, J = 2.5, 8.5 Hz, H6), 6.91 (1H, d, J = 8 Hz, aromatic H), 6.92 (1H, br, -NHAc), 7.05 (1H, d, J = 8 Hz, aromatic H), 7.17 (1H, t, J = 8 Hz, H7), 7.46 (1H, d, J = 8 Hz, aromatic H), 7.68 (1H, s, -NHCO-). Anal. ($C_{26}H_{34}N_4O_3$) C, H, N.

3,4-Dihydro-7-[4-[4-(3-hydroxy-2-methylphenyl)-1-piperazinyl]butoxy]-2(1*H*)-quinolinone (24). A solution of $NaNO_2$ (0.19 g, 26.0 mmol) in water (1 mL) was added dropwise to a solution of **22** (1.0 g, 24.4 mmol) in a 30% solution of sulfuric acid (50 mL) below −5 °C. After stirring for 30 min, the resulting mixture was added cautiously to a 20% solution of sulfuric acid at 40 °C with vigorous stirring. The mixture was neutralized with a 10% KOH solution and extracted with CH_2Cl_2 (200 mL). The extract was washed, dried, and evaporated to dryness in vacuo. Recrystallization from MeOH gave **24** (24%) as orange needles: mp 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 1.58 (2H, m, -CH_2-), 1.73 (2H, m, -CH_2-), 2.03 (3H, s, CH_3), 2.37 (4H, m, -CH_2CO-, -CH_2-), 2.66 (4H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.77 (6H, m, -CH_2-C-CO-, -CH_2NPhCH_2-), 3.92 (2H, t, J = 6 Hz, O-CH_2-), 6.47 (4H, m, aromatic H), 6.91 (1H, t, J = 8 Hz, aromatic H), 7.04 (1H, d, J = 8 Hz, aromatic H), 9.13 (1H, s, OH), 9.98 (1H, s, -NHCO-). Anal. ($C_{24}H_{31}N_3O_3\cdot 1.5H_2O$) C, H, N.

5-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (38). A mixture of 5-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**8**)[25] (2.0 g, 6.7 mmol) and NaI (1.5 g, 10.1 mmol) in CH_3CN (30 mL) was refluxed for 30 min and then cooled to room temperature. 1-(2,3-Dichlorophenyl)piperazine (1.7 g, 7.37 mmol) and TEA (1.4 mL, 7.37 mmol) were added to the mixture and stirred for 4 h at 80 °C. The precipitated crystals were filtered, washed, and dried. Recrystallization from EtOH−$CHCl_3$ gave **38** (72%) as colorless flakes: mp 190−192 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (4H, m, -CH_2CH_2-), 2.50 (2H, t, J = 7 Hz, -CH_2CO-), 2.61 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.97 (2H, t, J = 7 Hz, -CH_2-C-CO-), 3.08 (4H, m, -CH_2NPhCH_2-), 4.02 (2H, t, J = 6 Hz, O-CH_2-), 6.39 (1H, d, J = 8 Hz, aromatic H), 6.57 (1H, d, J = 8 Hz, aromatic H), 6.95 (1H, m, aromatic H), 7.15 (3H, m, aromatic H), 7.99 (1H, s, -NHCO-). Anal. ($C_{23}H_{27}N_3O_2Cl_2$) C, H, N.

6-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (39). This compound was prepared from 6-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**9**)[26] (2.0 g, 6.7 mmol), and 1-(2,3-dichlorophenyl)piperazine (1.7 g, 7.37 mmol) and TEA (1.4 mL, 7.37 mmol) in the presence of NaI (2.0 g, 13.3 mmol) in CH_3CN (50 mL) with 81% yield as colorless flakes (EtOH−$CHCl_3$): mp 194−197 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (4H, m, -CH_2CH_2-), 2.49 (2H, t, J = 7 Hz, -CH_2CO-), 2.62 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.93 (2H, t, J = 7 Hz, -CH_2-C-CO), 3.07 (4H, m, -CH_2NPhCH_2-), 3.96 (2H, t, J = 6 Hz, O-CH_2-), 6.71 (3H, m, aromatic H), 6.96 (1H, m, aromatic H), 7.14 (2H, m, aromatic H), 8.32 (1H, s, -NHCO-). Anal. ($C_{23}H_{27}N_3O_2Cl_2$) C, H, N.

8-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (40). This compound was prepared from 8-(4-bromobutoxy)-3,4-dihydro-2(1*H*)-quinolinone (**10**)[25] (2.0 g, 6.7 mmol), 1-(2,3-dichlorophenyl)piperazine (1.7 g, 7.37 mmol), and TEA (1.4 mL, 7.37 mmol) in the presence of NaI (2.0 g, 13.3 mmol) in CH_3CN (50 mL), with 79% yield as colorless prisms (EtOH): mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (4H, m, -CH_2CH_2-), 2.49 (2H, t, J = 7 Hz, -CH_2CO-), 2.63 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.97 (2H, t, J = 7 Hz, -CH_2-C-CO), 3.08 (4H, m, -CH_2NPhCH_2-), 4.05 (2H, t, J = 6 Hz, O-CH_2-), 6.76 (2H, d, J = 8 Hz, aromatic H), 6.91 (1H, d, J = 8 Hz, aromatic H), 6.96 (1H, m, aromatic H), 7.14 (2H, m, aromatic H), 7.78 (1H, s, -NHCO-). Anal. ($C_{23}H_{27}N_3O_2Cl_2$) C, H, N.

3,4-Dihydro-7-[4-[4-(2-nitrophenyl)-1-piperazinyl]-butoxy]-2(1*H*)-quinolinone (49). This compound was prepared from **6** (2.7 g, 9.21 mmol), 1-(2-nitrophenyl)piperazine (2.3 g, 11.1 mmol), and TEA (1.49 mL, 13.7 mmol) in the presence of NaI (2.07 g, 13.8 mmol) in CH_3CN (30 mL). Recrystallization from MeOH provided **49** in 50% yield as yellow granules: mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (4H, m, -CH_2CH_2-), 2.50 (2H, t, J = 7 Hz, -CH_2CO-), 2.65 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.93 (2H, t, J = 7 Hz, -CH_2-C-CO-), 3.11 (4H, m, -CH_2NPhCH_2-), 3.99 (2H, t, J = 6 Hz, O-CH_2-), 6.37 (1H, d, J = 2.5 Hz, H8), 6.55 (1H, dd, J = 2.5, 8 Hz, H6), 7.06 (2H, m, aromatic H), 7.16 (1H, dd, J = 2.5, 8 Hz, aromatic H), 7.50 (1H, m, aromatic H), 7.78 (1H, dd, J = 2.5, 8 Hz, aromatic H), 8.30 (1H, s, -NHCO-). Anal. ($C_{23}H_{28}N_4O_4$) C, H, N.

7-[4-[4-(2-Aminophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (50). $SnCl_2$ dihydrate (6.5 g, 28.8 mmol) was added in portions to a solution of **49** (3.5 g, 8.25 mmol) in EtOH and 12 N HCl (30 mL), and the resulting mixture was stirred for 1 h at 60 °C. Then the mixture was poured into ice−water (100 mL), made basic by addition of a KOH pellet, and extracted with CH_2Cl_2 (200 mL). The extract was washed, dried, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, 3% MeOH in $CHCl_3$). Recrystallization from EtOH−*iso*propyl ether afforded **50** as pale-brown granules in 34% yield: mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (4H, m, -CH_2CH_2-), 2.47 (2H, t, J = 7 Hz, -CH_2CO-), 2.61 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.89 (6H, m, -CH_2-C-CO-, -CH_2NPhCH_2-), 3.96 (4H, m, O-CH_2-, -NH_2), 6.34 (1H, d, J = 2.5 Hz, H8), 6.52 (1H, dd, J = 2.5, 8 Hz, H6), 6.75 (2H, m, aromatic H), 6.99 (3H, m, aromatic H), 8.32 (1H, s, -NHCO-). Anal. ($C_{23}H_{30}N_4O_2$) C,H,N.

7-[4-[4-(2-Cyanophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (51). A solution of $NaNO_2$ (210 mg, 3.04 mmol) in water (3 mL) was added dropwise to a solution of compound **50** (1.0 g, 2.54 mmol) in a 20% H_2SO_4 solution (25 mL) at 0 °C. After stirring for 30 min, the diazonium salt solution was poured into a mixture of KCN (1.6 g, 24.6 mmol), $CuSO_4$ pentahydrate (1.5 g, 6 mmol), and 37% NH_4OH (1.5 mL) in water (20 mL) at room temperature, and the mixture was stirred for another 1 h. The precipitates were filtered and dissolved in CH_2Cl_2. The solution was washed, dried, and concentrated in vacuo to give a crude oily product which was purified by column chromatography (SiO_2, 2% MeOH in $CHCl_3$). Recrystallization from CH_3CN provided **51** as a pale-brown powder in 18% yield: mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 1.76 (4H, m, -CH_2CH_2-), 2.46 (2H, t, J = 7 Hz, -CH_2CO-), 2.65 (6H, m, -$CH_2N(CH_2$-$)CH_2$-), 2.89 (2H, t, J = 7 Hz, -CH_2-C-CO-), 3.22 (4H, m, -CH_2NPhCH_2-), 3.96 (2H, t, J = 6 Hz, O-CH_2-), 6.31 (1H, d, J = 2.5 Hz, H8), 6.51 (1H, dd, J = 2.5, 8 Hz, H6), 6.98 (3H, m, aromatic H), 7.54 (2H, m, aromatic H), 8.05 (1H, s, -NHCO-). Anal. ($C_{24}H_{28}N_4O_2\cdot 1.5H_2O$) C,H,N.

General Procedure for Preparation of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-2(1*H*)-quinolinones 52−56 (Table 2). 7-[4-[4-(3-Chloro-2-methylphenyl)-1-piperazinyl]-butoxy]-2(1*H*)-quinolinone (52). A mixture of **12** (2.5 g, 8.3 mmol), NaI (2.0 g, 13 mmol), TEA (2 mL, 14.3 mmol) and 1-(3-chloro-2-methylphenyl)piperazine (2.5 g, 11.9 mmol), in

acetonitrile (50 mL) was refluxed for 4 h with stirring. The reaction mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed, dried, and evaporated in vacuo. Recrystallization from MeOH−$CHCl_3$ gave **52** (84%) as colorless needles: mp 174−176 °C; ^{1}H NMR ($CDCl_3$) δ 1.74 (2H, m, -CH_2-), 1.87 (2H, m, -CH_2-), 2.34 (3H, s, CH_3), 2.51 (2H, t, J = 6 Hz, -CH_2-), 2.64 (4H, m, -$CH_2N(CH_2$-)-C-), 2.92 (4H, m, -CH_2NPhCH_2-), 4.11 (2H, t, J = 6 Hz, O-CH_2-), 6.52 (1H, d, J = 9 Hz, -C=CHCO-), 6.80 (2H, m, H6, H8), 6.93 (1H, d, J = 8 Hz, aromatic H), 7.07 (2H, d, J = 8 Hz, aromatic H), 7.45 (1H, d, J = 8 Hz, aromatic H), 7.72 (1H, d, J = 9 Hz, -CH=C-CO-), 12.63 (1H, s, -NHCO-). Anal. ($C_{24}H_{28}N_3O_2Cl$·0.1H_2O) C, H, N.

Pharmacology. Male ICR mice weighing 20−30 g (Clea Japan) and male Wistar rats weighing 148−250 g (Japan SLC Inc.) were used. The test compounds were suspended in 0.5% gum arabic−0.9% saline; haloperidol (Serenace, Dai-Nippon), GBL (Sigma), chlorpromazine (Contomin, Yoshitomi), and 3-hydroxybenzylhydrazine 2HCl (NSD-1015, Nakarai) were diluted with 0.9% saline; APO HCl (Sigma) was dissolved in 0.9% saline.

Inhibition of APO-Induced Stereotypy of Behavior (Anti-APO Test). Mice and rats were fasted overnight (16−20 h). Test compounds were orally administered to groups of 10 mice or 6 rats 1 h before APO (1.5 mg/kg sc) injection. Stereotypy of behavior was observed for 1 min at 10-min intervals for 40 min starting 20 min after APO injection and scored according to the method reported.[22] The ED_{50} values and 95% confidence limits were calculated using the linear regression analysis method, and the values are presented as μmol/kg po in Tables 1−4.

Inhibition of GBL-Induced Increase in DOPA Synthesis. Mice and rats were fasted overnight (16−20 h), and test compounds were orally administered 1 h before sacrifice. GBL (750 mg/kg ip) and NSD-1015 (100 mg/kg ip) were given to animals 35 and 30 min before sacrifice, respectively, according to the method reported.[23] DOPA was determined according to the literature method.[11,46] A Chemocosorb 5-ODS (20- × 4.6-mm i.d.) separation column was used. The mobile phase contained 50 mM KH_2PO_4, 8 mM H_3PO_4, and 2.5 mM EDTA·2Na in 0.7% acetonitrile (pH 3). The ED_{50} values and 95% confidence limits were calculated using the linear regression analysis method, and the values are presented as μmol/kg po in Tables 3 and 4.

Catalepsy Test. The test compounds and reference drugs were orally administered to groups of 10 mice or 6 rats, and catalepsy was observed at 0, 1, 2, 4, 6, and 8 h after administration. The animals were put in an unnatural posture with their forelimbs on a vertical plate. When this posture was maintained for over 30 s, the animal was judged to have catalepsy. The ED_{50} values and 95% confidence limits were calculated by the probit method, and the values are presented as μmol/kg po in Tables 3 and 4.

Anti-Epinephrine Test. This test was performed by the method reported.[9] The test compounds and reference drugs were orally administered to groups of 10 mice and 6 rats. Epinephrine was injected at 40 mg/kg ip 60 min after administration of the compounds or reference drugs. The 24-h survival rate was observed; the ED_{50} values and 95% confidence limits were estimated using the probit method, and the values are presented as μmol/kg po in Tables 3 and 4.

Acknowledgment. We express our appreciation to Mr. K. Tamura for his assistance and useful suggestions in the preparation of intermediates of compounds and to Mr. T. Miwa for his assistance in measurements of biological activities of the compounds.

Supporting Information Available: Additional NMR data on final compounds (9 pages). Ordering information is given on any current masthead page.

References

(1) Jannsen, P. A.; Niemergars, C, J. E.; Schellenkens, K. H. K. Is It Possible to Predict the Clinical Effects of Neuroleptic Drugs (Majortranquilizers) from Animal Data? *Arzneim-Forsch. (Drug Res.)* **1965**, *15*, 104.

(2) Simpson, G. M.; Pi, E. H.; Sramek, J. J. Adverse Effects of Antipsychotic Agents. *Drugs* **1981**, *21*, 138−151.

(3) Simpson, G. M.; Pi, E. H.; Sramek, J. J. Management of Tardive Dyskinesia: Current Update. *Drugs* **1982**, *23*, 381−393.

(4) Carlsson, A. Receptor-Mediated Control of Dopamine Metabolism. In *Pre- and Postsynaptic Receptor*; Usdin, E., Bunny, W. E., Eds.; Marcel Dekker: New York, 1975; pp 49−65.

(5) Seyfried, C. A.; Boettcher, H. Central D_2-Autoreceptor Agonists with Special Reference to Indolylbutylamines. *Drugs Future* **1990**, *15*, 819−832.

(6) Caprathe, B. W.; Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Dugsley, T. A.; Meltzen, L. T.; Parvez, M. Dopamine Autoreceptor Agonist as Potential Antipsychotics. 3. 6-Propyl-4,5,5a,6,7,8-hexahydrothiazolo[4,5-*f*]quinolin-2-amine. *J. Med. Chem.* **1991**, *34*, 2736−2746.

(7) Hacksell, U.; Arvidsson, L.; Svensson, U.; Nilsson, J. L. G.; Sanchez, D.; Wickström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. 3-Phenylpiperidines. Central Dopamine-Autoreceptor Stimulating Activity. *J. Med. Chem.* **1981**, *24*, 1475−1482.

(8) Jaen, J. C.; Wise, L. D.; Heffner, T. G.; Dugsley, T. A.; Meltzen, L. T. Dopamine Autoreceptor Agonist as Potential Antipsychotics. 1. (Aminoalkoxy)anilines. *J. Med. Chem.* **1988**, *31*, 1621−1625.

(9) Banno, K.; Fujioka, T.; Kikuchi, T.; Oshiro, Y.; Hiyama, T.; Nakagawa, K. Studies on 2(1*H*)-Quinolinone Derivatives as Neuroleptic Agents I. Synthesis and Biological Activities of (4-Phenyl-1-piperazinyl)propoxy-2(1*H*)-quinolinone Derivatives. *Chem. Pharm. Bull.* **1988**, *36*, 4377−4388.

(10) Kikuchi, K.; Hirata, Y.; Minami, M.; Nagatsu, T. Effects of 7-[3-[4-(2,3-Dimethylphenyl)-piperazinyl]propoxy]-2(1*H*)-quinolinone (OPC-4392), A Newly Synthesized Agonist for Presynaptic D_2-Receptor, on Tyrosine Hydroxylation in Rat Striatal Slice. *Life Sci.* **1988**, *42*, 343−349.

(11) Yasuda, Y.; Kikuchi, T.; Suzuki, S.; Tsushi, M.; Yamada, K.; Hiyama, T. 7-[3-[4-(2,3-Dimethylphenyl)-piperazinyl]propoxy]-2(1*H*)-quinolinone (OPC-4392), A Presynaptic Dopamine Autoreceptor Agonist and Postsynaptic D_2-Receptor Antagonist. *Life Sci.* **1988**, *42*, 1941−1954.

(12) Sasa, M.; Ohno, Y.; Takaori, S. Presynaptic Inhibition of Excitatory Input from the Substantia Nigra to Caudate Nucleous Neurons by a Substituted Quinoline Derivative, 7-[3-[4-(2,3-Dimethylphenyl)-piperazinyl]propoxy]-2(1*H*)-quinolinone (OPC-4392). *Life Sci.* **1988**, *43*, 263−269.

(13) Akaike, A.; Ohno, Y.; Sasa, M.; Takaori, S. Excitatory and Inhibitory Effects of Dopamine on Neuronal Activity of the Caudate Nucleous Neurons in vitro. *Brain Res.* **1987**, *418*, 262−272.

(14) Momiyama, T.; Sasa, M.; Takaori, S. D_2-Receptor-Mediated Inhibition by a Substituted Quinolinone Derivative, 7-[3-[4-(2,3-Dimethylphenyl)piperazinyl]propoxy]-2(1*H*)-quinolinone (OPC-4392), of Dopaminergic Neurons in the Ventral Tegmental Area. *Life Sci.* **1990**, *47*, 761−769.

(15) Zang, X.; Nakata, Y.; Kikuchi, T.; Segawa, T. Interactions of 7-[3-[4-(2,3-Dimethylphenyl)-piperazinyl]propoxy]-2(1*H*)-quinolinone (OPC-4392) with ^{3}H-Spiperone and ^{3}H-SCH 23390 Binding in Rat Striatum: Effects of Lesions. *Pharm. Res.* **1990**, *7*, 280−282.

(16) Lipka, G.; Woedemann, K.; Benkert, O.; Holsboer, F. Presynaptic Dopamine Receptor Agonist (B−HT-920): Treatment of Schizophrenia. *Psychopharmacology (Suppl.)* **1988**, *96*, 333.

(17) Klimke, A.; Klieser, E. Antipsychotic Efficacy of the Dopaminergic Autoreceptor Agonist EMD 49980 (Roxindol). *Pharmacopsychiat.* **1991**, *24*, 107−112.

(18) Olbrich, R.; Schanz, H. The Effects of the Partial Dopamine Agonist Terguride on Negative Symptoms in Schizophrenics. *Pharmacopsychiat.* **1988**, *21*, 389−390.

(19) Seeman, P.; Lee, T.; Chau-Wong, M.; Wong, K. Antipsychotic Drug Does and Neuroleptic/Dopamine Receptors. *Nature (London)* **1976**, *261*, 717−719.

(20) Seeman, P. Brain Dopamine Receptors. *Pharmacol. Rev.* **1980**, *32*, 229−313.

(21) Creese, I.; Burt, D. R.; Snyder, S. H. Dopamine Receptors and Average Clinical Doses. *Science* **1976**, *192*, 481−483.

(22) Puech, A. J.; Riox, P.; Poncelet, M.; Brochet, D.; Chermat, R.; Simon, P. Pharmacological Properties of New Antipsychotic Agents: Use of Animal Models. *Neuropharmacology* **1981**, 1279−1284.

(23) Walters, J. R.; Roth, R. H. Dopaminergic Neurons: Drug-Induced Antagonism of the Increase in Tyrosine Hydroxylase Activity Produced by Cessation of Impulse Flow. *J. Pharmacol. Exp. Ther.* **1974**, *191*, 82−91.

(24) Walters, J. R.; Roth, R. H. Dopaminergic Neurons: An in vivo System for Measuring Drug Interactions with Presynaptic Receptors. *Naunyn-Schmiederberg's Arch. Pharmacol.* **1976**, *296*, 5−14.
(25) Nakagawa, K.; Uchida, M.; Oka, K. (Haloalkyloxy)carbostyrils. Japan Kokai JP 75-58125; *Chem. Abstr.* **1977**, *87*, 84841g.
(26) Nishi, T.; Yamamoto, K.; Shimizu, T.; Kanbe, T.; Kimura, Y.; Nakagawa, K. Studies on 2-Oxoquinoline Derivatives as Blood Platelet Aggregation Inhibitors. I. Alkyl 4-(2-oxo-1,2,3,4-tetrahydro-6-quinolyloxy)butylates and Related Compounds. *Chem. Pharm. Bull.* **1983**, *31*, 798−810.
(27) Creese, I.; Burt, D. R.; Snyder, S. H. Dopamine Receptors and Average Clinical Doses. *Science* **1976**, *192*, 481−483.
(28) Richelson, E. Neuroleptic Affinities for Human Brain Receptors and Their Use in Predicting Adverse Effects. *J. Clin. Psychiat.* **1984**, *45*, 331−336.
(29) Andrew, F.; Rennie, C. H. Clozapine: A Review of Its Pharmacological Properties and Therapeutic Use in Schizophrenia. 1. *Drugs* **1990**, *40* (5), 722−747.
(30) Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Hirose, T.; Miwa, T.; Oshiro, Y.; Morita, S. 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]-butoxy]-3,4-dihydro-2(1*H*)-quinolinone (OPC-14597), a New Putative Antipsychotic Drug with Both Presynaptic Dopamine Autoreceptor Agonistic Activity and Postsynaptic D_2 Receptor Antagonistic Activity. *J. Pharmacol. Exp. Ther.* **1995**, *274* (1), 329−336.
(31) Hornykiewicz, O. Brain Catecholeamines in Schizophrenia: A Good Case for Noradrenaline. *Nature* **1982**, *299*, 484.
(32) Masson, S. T. Designing a Non-Neuroleptic Antischizophrenic Drug: The Noradrenergic Strategy. *Trends Pharmacol. Sci.* **1983**, *4*, 353.
(33) An Kammen, D. P.; Antelman, S. Minireview: Impaired Noradrenergic Transmission in Schizophrenia? *Life Sci.* **1984**, *34*, 1403.
(34) Amano, T.; Matsubayashi, H.; Momiyama, T.; Ishihara, K.; Todo, N.; Sasa, M. Antagonizing Effect of Novel Antipsychotic Quinolinone Derivative (OPC-14597) on Dopaminergic Inhibition of Neuronal Activities in the Nucleus Accumbens. *Prog. Neuropsychopharm. Biol. Psychiat.* **1995**, *19* (1), 105−116.
(35) Murasaki, M. Recent Progress in Development of Psychotropic Drugs (2): Antipsychotics. *Nihon Shinkei Seishin Yakurigaku Zasshi* **1995**, *15* (3), 191−210.
(36) Semba, J.; Watanabe, A.; Kito, S.; Toreu, M. Behavioral and Neurochemical Effects of OPC-14597, a Novel Antipsychotic Drug, on Dopaminergic Mechanism in Rat Brain. *Neuropharmacology* **1995**, *34* (7), 785−791.
(37) Inoue, T.; Domae, M.; Yamada, K.; Furukawa, T. Effects of the Novel Antipsychotic Agent 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (OPC-14597) on Prolactin Release from the Rat Anterio Pitutary Gland. *J. Pharmacol. Exp. Ther.* **1996**, *277* (1), 137−143.
(38) Fujikawa, M.; Nagashima, M.; Inoue, T.; Yamada, K.; Furukawa, T. Partial Agonistic Effects of OPC-14597, a Potential Antipsychotic Agent, on Yawning Behavior in Rats. *Pharmacol. Biochem. Behav.* **1996**, *53* (4), 903−909.
(39) Momiyama, T.; Amano, T.; Todo, N.; Sasa, M. Inhibition by a Putative Antipsychotic Quinolinone Derivative (OPC-14597) of Dopaminergic Neurons in the Ventaral Tergmental Area. *Eur. J. Pharmacol.* **1996**, *310* (1), 1−8.
(40) Semba, J.; Sakai, M.; Miyoshi, R.; Mataga, N.; Fukamachi, F.; Kito, S. Differential Expression of c-fos mRNA in Rat Prefrontal Cortex, Striatum, N. Accumbens and Lateral Septum after Typical and Atypical Antipsychotics: an in situ Hybridization Study. *Neurochem. Int.* **1996**, *29* (4), 435−442.
(41) Yamada, S.; Harano, M.; Yokoo, H.; Tanaka, M. Antagonistic Effects of OPC-14597, a Novel Antipsychotic Drug, on Quinpirol- and (−)-Sulpiride-induced Changes in Evoked Dopamine Release in Rat Striatal Slices. *J. Pharm. Pharmacol.* **1997**, *49* (2), 206−208.
(42) Pollard, C. B.; Wicker, H. T., Jr. Derivatives of Piperazine. XXIV. Synthesis of 1-Arylpiperazines and Amino Alcohol Derivatives. *J. Am. Chem. Soc.* **1954**, *76*, 1853−1855.
(43) Otsubo, J.; Furubayashi, K.; Nakagawa, K.; Higuchi, S. Preparation of Phenylpiperazine Derivatives. Jpn. Kokai Tokkyo Koho JP 82-42,679 *Chem. Abstr.* **1982**, *97*, 92317n.
(44) Matsuyama, T.; Watanabe, N. Preparation Method of Phenylpiperazine Derivatives. *Jpn. Kokai Tokkyo Kouhou* JP 85-41670, Koei Chemical Co. Ltd.; *Chem. Abstr.* **1985**, *103*, 87905r.
(45) Yevich, P. J.; New, S. J.; Lobeck, G. W.; Dextraze, P.; Bernstein, E.; Taylor, P. D.; Yocca, D. F.; Eison, S. M.; Temple, L. D., Jr. Synthesis and Biological Characterization of α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol and Analogues as Potential Atypical Antipsychotic Agents. *J. Med. Chem.* **1992**, *35*, 4516−4525.
(46) Westerich, B. H. C.; Mulder, T. B. A. Determination of Picomole Amounts of Dopamine, Noradrenaline, 3,4-Dihydroxyphenylalanine, 3,4-Dihydroxyphenylacetic Acid, Homovanillic Acid and 5-Hydroxy-indoleacetic Acid in Nervous Tissue after One-step Purification on Sephadex G-10, Using High-Performance Liquid Chromatography with a Novel Type of Electrochemical Detection. *Neurochem*istry **1981**, *36*, 1449−146.

JM940608G