

Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Referencia : Expediente No. **14.098.041**
Asunto : Solicitud de patente: "**TABLETA QUE CONTIENE 7-[4-(4-BENZO[B]TIOFEN-4-IL-PIPERAZIN-1-IL) BUTOXI]-1H-QUINOLIN-2-ONA O UNA DE SUS SALES**"
Solicitante : OTSUKA PHARMACEUTICAL CO., LTD.
Fecha de solicitud : 7 de Mayo de 2014

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **5262** notificado por fijación en lista el 19 de Mayo de 2015.

2. Mediante memorial del 6 de Agosto de 2015 se solicitó oportunamente plazo para responder la acción oficial No. **5262**.

3. Mediante oficio No. **5262** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a la claridad del pliego reivindicatorio, a la novedad de las reivindicaciones 1 y 2 en vista del documento **D1**: Solicitud de Patente Nacional: 13-261085-00000-0000, y al nivel inventivo de las reivindicaciones 3 a 11 en vista de los documentos **D1**: US20100179322 y **D2**: ES2318693.

4. **Respuesta a las objeciones**

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

4.1. Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 8 reivindicaciones.

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

- Se eliminaron las reivindicaciones 2, 3 y 8. Las características reveladas en las dos primeras reivindicaciones fueron incluidas en la reivindicación 1. Con respecto a la reivindicación 8, su eliminación no puede ser considerado como un desistimiento de la materia allí revelada y mi representada se reserva el derecho de volver sobre la misma durante el trámite de la presente solicitud de patente.
- Se modificó el pliego reivindicatorio con el fin de hacer claridad sobre la materia que se solicita proteger y el alcance de la misma. En particular, el nuevo pliego reivindicatorio se refiere a una tableta que contiene 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales como ingrediente activo, un excipiente (a), un aglutinante (b), un desintegrante (c) y un lubricante (d), en donde el excipiente (a) es al menos un miembro seleccionado del grupo que se compone de lactosa, almidón de maíz y celulosa microcristalina; el aglutinante (b) es hidroxipropil celulosa; el desintegrante (c) es al menos un miembro seleccionado del grupo que consiste de hidroxipropil celulosa de baja sustitución, croscarmelosa sódica, y carboximetil almidón de sodio; y el lubricante (d) es un estearato de magnesio.
- La reivindicación modificada 7 también fue modificada al limitar el excipiente, el aglutinante, el desintegrante y el lubricante. Así mismo, se especificó en la reivindicación modificada 8 que se trata de una mezcla de cobertura.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se

solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

4.2. Argumentos con respecto a la falta de Novedad

De acuerdo al artículo 16 de la Decisión 486, se determina:

***“Artículo 16:** Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica.*

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente, o en su caso, de la prioridad reconocida”.

La novedad de una invención se evalúa a través de la comparación uno a uno de sus características esenciales. De este modo, una invención puede ser objetada por novedad cuando sus características esenciales son exactamente iguales a las de un antecedente que represente el estado de la técnica conocido al momento de presentar la solicitud. Por lo tanto en caso que llegue a existir al menos una diferencia en dicha comparación, se afirma que la invención SI cumple con el requisito de novedad.

Con base en lo anterior, respetuosamente solicitamos atentamente la reconsideración de las razones por las cuales se objeta la novedad, con base en la siguiente información:

Tras las modificaciones realizadas al pliego reivindicatorio, éste se encuentra dirigido a una tableta que contiene 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales como ingrediente activo, un excipiente (a), un aglutinante (b), un desintegrante (c) y un lubricante (d), en donde el excipiente (a) es al menos un miembro seleccionado del grupo que se compone de lactosa, almidón de maíz y celulosa microcristalina; el aglutinante (b) es hidroxipropil celulosa; el desintegrante (c)

es al menos un miembro seleccionado del grupo que consiste de hidroxipropil celulosa de baja sustitución, croscarmelosa sódica, y carboximetil almidón de sodio; y el lubricante (d) es un estearato de magnesio, incluyendo las características que eran reveladas en la reivindicación original 3, que no fue objetada por falta de novedad.

Así, es claro que la materia de invención tal como se encuentra recitada en el nuevo pliego reivindicatorio se debe tener como novedosa, ya que todas las características técnicas esenciales no son anticipadas como un todo por el documento citado D1.

4.3. Argumentos con respecto a la falta de Nivel Inventivo

El artículo 18 de la Decisión 486 señala lo siguiente:

***“Artículo 18.-** Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.*

Una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora

sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente solicitamos atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

El señor Examinador señala que la materia revelada en las reivindicaciones 3 a 11 no presente nivel inventivo sobre D2. En ese sentido señalamos que la reivindicación 1 de la presente invención es una tableta que comprende 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales como ingrediente activo y hidroxipropil celulosa como aglutinante. Las tabletas de los Ejemplos 1-1 a 1-3 de la presente solicitud comprenden hidroxipropil celulosa. La Tabla 2 muestra que estas tabletas tienen una excelente habilidad de desintegración. Por consiguiente, esta característica se obtiene tras la combinación de 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales con hidroxipropil celulosa.

Por su parte, D2 revela derivados de celulosa; sin embargo, D2 solamente revela la metilcelulosa como un ejemplo de aglutinante ([0119]), pero no proporciona ningún ejemplo en donde la metilcelulosa es realmente utilizada. Por el contrario, D2 revela varios compuestos representados por la fórmula (1) pero no proporciona ningún ejemplo en donde 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona es seleccionado de estos compuestos y utilizado en combinación con metilcelulosa. Adicionalmente, D2 no revela ningún ejemplo en donde la hidroxipropil celulosa es realmente utilizada en una formulación farmacéutica. Teniendo en cuenta lo anterior, no hubiese sido nada obvio para una persona versada en la materia llegar a la estructura de la presente solicitud con base a las enseñanzas de D2.

Con respecto al documento D3, revela una invención relacionada con el aripiprazol pero no revela el compuesto 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona (brexpiprazol) de la presente invención. Adicionalmente, las

propiedades físicas de este compuesto son diferentes a las propiedades del aripiprazol. Por ejemplo, sus puntos de fusión difieren de la siguiente manera:

- Brexpiprazol: 183.5-184.5°C (Recristalizado de EtOh, Ejemplo 1 de D2)
- Aripiprazol: 139-140°C (Artículo en Anexos, Compuesto 8 en la Tabla 1)

Por consiguiente, los efectos logrados por la tableta de brexpiprazol de la presente invención son confirmados por primera vez por experimentos reales. Por lo tanto, dichos efectos no hubiesen podido ser predichos por una persona versada en la materia con base a las enseñanzas de D2, donde sólo se revela el aripiprazol, que como se mencionó presente propiedades completamente diferentes a las del brexpiprazol.

Así, en los argumentos arriba presentados se pueden identificar claramente un indicio de presencia de nivel inventivo de acuerdo con el numeral 2.13.5.3.1 de la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELO DE UTILIDAD" de su despacho:

- Efecto técnico sorprendente, ya que en las tabletas obtenidas en la presente invención, es posible identificar una habilidad para una excelente desintegración.

Por lo tanto, se le debe otorgar una compensación a mi representada que demuestra nuevos hechos (efectos sorprendentes e inesperados) a las enseñanzas descritas en el estado de la técnica y contribuyen con el desarrollo de la tecnología.

Así, la presente invención es inventiva toda vez que los ejemplos y la descripción tal como fue originalmente presentada muestran claramente la mejora aportada al estado del arte por las tabletas acá reivindicadas en términos de la desintegración de dichas tabletas. Adicionalmente, es claro al señalar que el efecto (desintegración) de las tabletas acá reivindicadas no podía haber sido esperado por un técnico medio a partir de las enseñanzas de los documentos citados tal como se demostró previamente, en consonancia con los indicios de nivel inventivo que menciona tanto el

Manual Andino de Patentes como el "INSTRUCTIVO EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION Y MODELO DE UTILIDAD" de su Despacho, la invención tiene nivel inventivo.

4.4 Conclusión

Por todo lo anterior, el documento D1 no resulta anterioridad válida capaz de afectar la novedad de la invención de la presente solicitud. De la misma manera, el documento D2, el documento D3, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud.

Por lo tanto, consideramos que el Examinador está pasando por alto que una sola diferencia con respecto al estado de la técnica, permite concluir que el objeto reivindicado es nuevo. Además, está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

5. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 5262, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

6. Anexos

- Nuevo capítulo descriptivo y pliego reivindicatorio conformado por 8 reivindicaciones.
- Oshiro, et al. Novel Antipsychotic Agents with dopamine autoreceptor agonist propoerties: Synthesis and pharmacology of 7-[4-(4-phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1H)-quinolinone derivatives. J. Med. Chem. 1998.

Señor Director,


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C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-14055-0841-0038-1
CPT\CPT\ID-283376\WPC14055
No. M-2015-283376\CPT

REIVINDICACIONES MODIFICADAS

1. Una tableta que contiene 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales como ingrediente activo, un excipiente (a), un aglutinante (b), un desintegrante (c) y un lubricante (d), en donde el excipiente (a) es al menos un miembro seleccionado del grupo que se compone de lactosa, almidón de maíz y celulosa microcristalina;
el aglutinante (b) es hidroxipropil celulosa;
el desintegrante (c) es al menos un miembro seleccionado del grupo que consiste de hidroxipropil celulosa de baja sustitución, croscarmelosa sódica, y carboximetil almidón de sodio; y
el lubricante (d) es un estearato de magnesio.

2. Una tableta según las reivindicaciones 1, en donde la tableta es una tableta no recubierta que contiene:
0,05 a 25% en peso de 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales;
10 a 98,5% en peso del excipiente (a);
0,1 a 20% en peso del aglutinante (b);
1 a 25% en peso del desintegrante (c); y
0,1 a 10% en peso del lubricante (d), con respecto al peso de la tableta no recubierta.

3. La tableta según cualquiera de las reivindicaciones 1 o 2, en donde por 1 parte en peso de 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales, la tableta contiene:
1 a 2000 partes en peso del excipiente (a);
0,01 a 100 partes en peso del aglutinante (b);
0,1 a 500 partes en peso del desintegrante (c); y
0,01 a 50 partes en peso del lubricante (d).

4. La tableta según cualquiera de la reivindicación 1, que además comprende una capa de revestimiento en la superficie de la misma.

5. La tableta según la reivindicación 4, la cual además contiene el colorante (e) en la capa de revestimiento, en donde el colorante (e) contiene un óxido de hierro, y la tableta contiene 0,1 a 50% en peso del colorante (e) con respecto al peso de la capa de revestimiento.
6. Una tableta según cualquiera de las reivindicaciones 1 a 5, en donde la tableta no contiene povidona ni crospovidona.
7. Un método para producir una tableta, método que contiene los pasos de:
 - (1) granular una mezcla que contiene 7-[4-(4-benzo[b]tiofen-4-il-piperazin-1-il)butoxi]-1h-quinolin-2-ona o una de sus sales, un excipiente (a), un aglutinante (b), y un desintegrante (c), y además añadiendo a dicha mezcla un lubricante (d); y
 - (2) formar la mezcla obtenida en una tableta, en la que el excipiente (a) es al menos uno de los miembros seleccionado de un grupo que contiene lactosa, almidón de maíz y celulosa microcristalina; el aglutinante (b) es hidroxipropil celulosa; el desintegrante (c) es al menos un miembro seleccionado de un grupo que contiene de hidroxipropil celulosa de baja sustitución, croscarmelosa sódica, y carboximetil almidón de sodio; y el lubricante (d) es un estearato de magnesio.
8. El método para producir la tableta según la reivindicación 7, que además comprende el paso de:
 - (3) mezclar un agente de cobertura, un colorante (e), y un medio líquido para obtener una mezcla de cobertura, y cubrir la superficie de la tableta usando la mezcla de cobertura.

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

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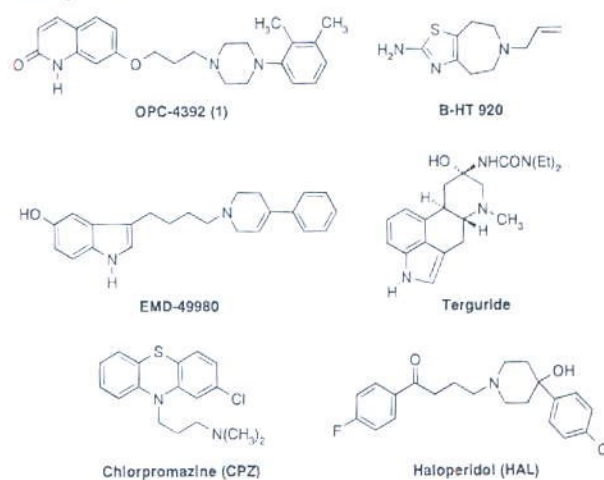
Received September 12, 1994

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-(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-(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 μ mol/kg po) and inhibited the APO induced stereotypy (ED_{50} values of 0.6 μ mol/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 μ mol/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}

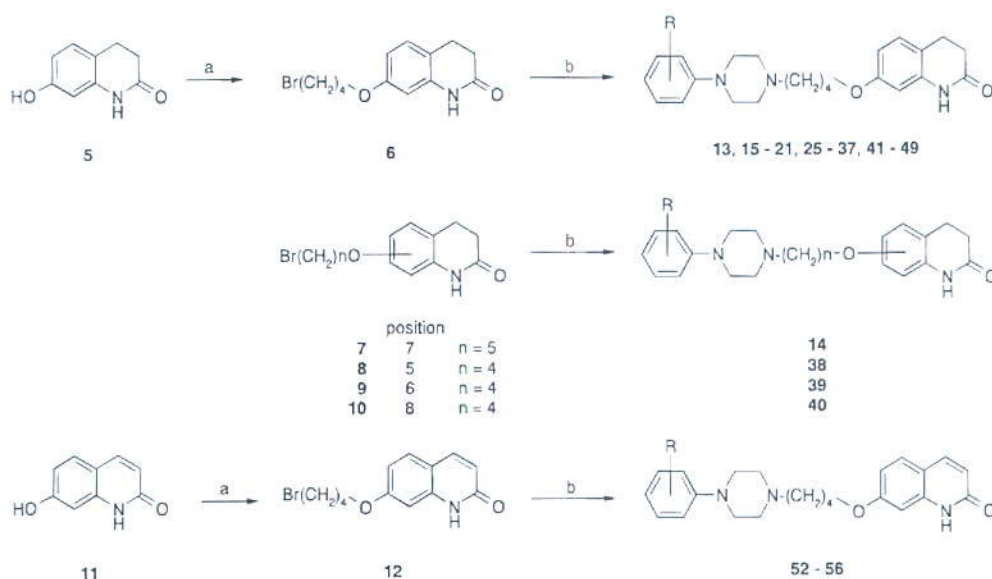
In a previous paper,⁹ we reported on 7-[3-(4-phenyl-1-piperazinyl)propoxy]-2(1*H*)-quinolinone derivatives. Among them, OPC-4392 (**1** in Chart 1) was found to be an agonist of the DA autoreceptors and a weak antagonist of the postsynaptic DA D_2 receptors.^{10–15} Other DA autoreceptor agonists, B-HT 920,¹⁶ EMD-49980,¹⁷ and Terguride,¹⁸ have been reported to improve negative symptoms in schizophrenic patients. The clinical re-

Chart 1. DA Autoreceptor Agonists and D_2 Receptor Antagonists



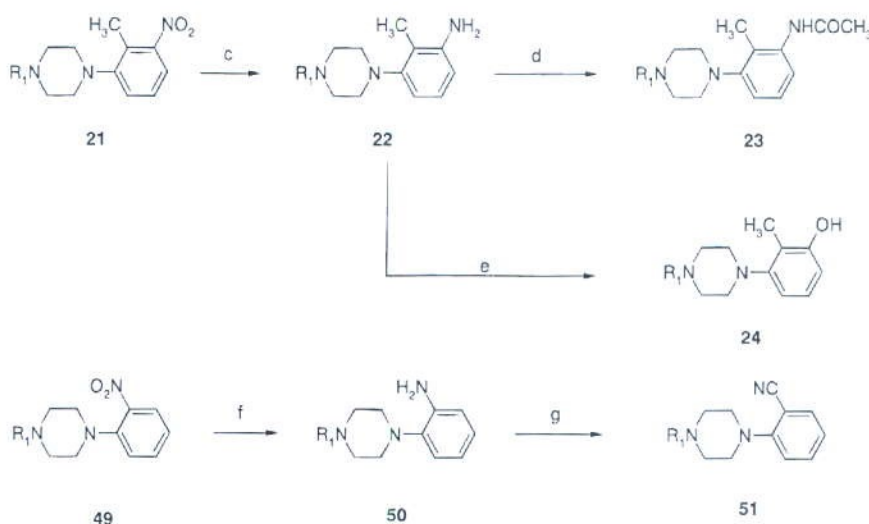
sults with other DA autoreceptor agonists and our unpublished clinical observations with **1** strongly suggest that a DA autoreceptor agonist is effective in treating the negative symptoms and a potent DA postsynaptic receptor antagonism might be necessary for treatment of the positive symptoms in patients.^{19–21} 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-

Scheme 1^a



^a Conditions and notation: (a) K₂CO₃, dibromoalkane in DMF; (b) NaI, TEA, phenylpiperazines in CH₃CN; *n* = 4 or 5.

Scheme 2^a



R₁ = 4-[3,4-Dihydro-2(1H)-quinolinone-7-yl]oxybutyl-

^a Conditions: (c) H₂, 3 kg/cm², 5% Pd-C in EtOH; (d) acetic anhydride; (e) (1) NaNO₂ in dilute H₂SO₄, (2) H₂SO₄; (f) SnCl₂ dihydrate in concentrated HCl; (g) (1) NaNO₂ in dilute H₂SO₄, (2) NaCN, CuSO₄, NH₄OH.

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 pharmacol-

ogy of 3,4-dihydro-2(1H)-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(1H)-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(1H)-quinolinone derivatives, several analogues of 2(1H)-quinolinone (**52**–**56**) in Table 2 were prepared.

Intermediates, 5-, 6-, or 8-(4-bromobutoxy)-3,4-dihydro-2(1H)-quinolinone (**8**–**10**)^{25,26} and 7-(5-bromopentoxymethyl)-3,4-dihydro-2(1H)-quinolinone (**7**).⁹ have been reported. With the application of similar procedures, 7-(4-bromobutoxy)-3,4-dihydro-2(1H)-quinolinone (**6**) and 7-(4-bromobutoxy)-2(1H)-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 ED₅₀ of 41.3 μ mol/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).

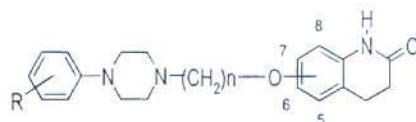
Postsynaptic DA Receptor Antagonist Activity.

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), acetamino (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-(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 ₃ O ₂ Cl	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 ₃ O ₂ Cl	C,H,N	>23 ^e
15	7	4	2-Me, 5-Cl	84	A	110–111	C ₂₄ H ₃₀ N ₃ O ₂ Cl	C,H,N	>23 ^e
16	7	4	2-Me, 3-Br	84	B	151–152	C ₂₄ H ₃₀ N ₃ O ₂ Br	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 ₃ O ₂ Br	C,H,N	21 ^f
18	7	4	2-Me, 3-F	71	B	141–143	C ₂₄ H ₃₀ N ₃ O ₂ F·0.25H ₂ O	C,H,N	7.2 ^g
19	7	4	4-Me, 3-Cl	70	A	117–118	C ₂₄ H ₃₀ N ₃ O ₂ Cl	C,H,N	>7.0 ^e
20	7	4	2-Me, 3-CN	32	B	181–182	C ₂₅ H ₃₀ N ₄ O 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 ₄ O ₂	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 ₄ O ₂	C,H,N	>25 ^e
23	7	4	2-Me, 3-NHCOCH ₃	70	B	186–188	C ₂₆ H ₃₄ N ₄ O ₃	C,H,N	>25 ^e
24	7	4	2-Me, 3-OH	24	B	208–210	C ₂₄ H ₃₁ N ₃ O ₃ ·1.5H ₂ O	C,H,N	>8.0 ^h
25	7	4	2-Cl, 3-Me	72	A	133–134	C ₂₄ H ₃₀ N ₃ O ₂ Cl	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 ₃ O ₂ Br	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 ₃ O 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 ₃ O ₂ Cl 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 ₃ O ₂ Cl ₂	C,H,N	>7.0 ^e
30	7	4	2,5-(Cl) ₂	67	A	134–135	C ₂₃ H ₂₇ N ₃ O ₂ Cl 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 ₃ O ₂ Cl ₂	C,H,N	>7.0 ^h
32	7	4	3,4-(Cl) ₂	73	A	134–136	C ₂₃ H ₂₇ N ₃ O ₂ Cl ₂	C,H,N	>7.0 ^h
33	7	4	3,5-(Cl) ₂	77	A	134–135	C ₂₃ H ₂₇ N ₃ O ₂ Cl 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 ₃ O ₂ BrCl	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 ₃ O ₂ Br 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 ₃ O ₂ Cl 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 ₃ O ₂ Cl 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 ₃ O ₂ Cl ₂	C,H,N	>22 ^h
39	6	4	2,3-(Cl) ₂	81	C	194–197	C ₂₃ H ₂₇ N ₃ O ₂ Cl ₂	C,H,N	>22 ^e
40	8	4	2,3-(Cl) ₂	79	A	122–123	C ₂₃ H ₂₇ N ₃ O ₂ Cl ₂	C,H,N	>22 ^h
41	7	4	2-Cl	27	A	103–104	C ₂₃ H ₂₈ N ₃ O ₂ Cl·0.2H ₂ O	C,H,N	2.9 (1.2–5.6)
42	7	4	3-Cl	64	A	102–103	C ₂₃ H ₂₈ N ₃ O ₂ Cl	C,H,N	7.5 (6.4–9.0)
43	7	4	4-Cl	49	A	138–139	C ₂₃ H ₂₈ N ₃ O ₂ Cl·0.2H ₂ O	C,H,N	>8.0 ^e
44	7	4	2-Br	61	B	105–106	C ₂₃ H ₂₈ N ₃ O ₂ Br	C,H,N	3.9 (3.3–4.7)
45	7	4	2-F	41	A	122–123	C ₂₃ H ₂₈ N ₃ O ₂ F	C,H,N	>8.0 ^e
46	7	4	2-Me	42	A	135–136	C ₂₄ H ₃₁ N ₃ O ₂	C,H,N	2.5 (2.1–2.8)
47	7	4	2-OMe	44	B	125–126	C ₂₄ H ₃₁ N ₃ O ₃	C,H,N	0.6 (0.3–1.0)
48	7	4	2-OEt	33	A	189–191	C ₂₅ H ₃₃ N ₃ O ₃ ·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 ₄ O ₄	C,H,N	>7.0 ^e
50	7	4	2-NH ₂	34	D	130–132	C ₂₃ H ₃₀ N ₄ O ₂	C,H,N	>25 ^h
51	7	4	2-CN	18	E	150–151	C ₂₄ H ₂₈ N ₄ O ₂ ·1.5H ₂ O	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–CHCl₃, D = EtOH–iPr₂O, E = CH₃CN. ^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 ED₅₀ 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).

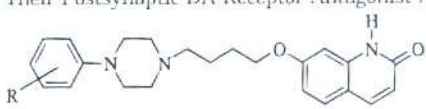
Next, the effects of the positional change of the side chain attached to the 3,4-dihydro-2(1*H*)-quinolinone nucleus in compound 28 was examined. Change in the 4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy side chain from the 7-position in 28 to the 5-, 6-, and 8-positions

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 ₃ O ₂ Cl·0.1H ₂ O	C,H,N	2.8 (1.9–5.1)
53	2-Me, 3-Br	50	A	168–169	C ₂₄ H ₂₈ N ₃ O ₂ Br	C,H,N	2.1 (1.9–2.3)
54	2,3-(Cl) ₂	51	A	144–146	C ₂₃ H ₂₅ N ₃ O ₂ Cl 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 ₃ O ₂ ·0.2H ₂ O	C,H,N	3.4 (2.4–4.4)
56	2-OEt	33	A	151 dec ^e	C ₂₅ H ₃₁ N ₃ O ₃ ·2HCl·0.5H ₂ O	C,H,N	0.24 (0.14–0.34)

^a Yields were not optimized in most cases. ^b A = EtOH, F = MeOH–CHCl₃. ^c C,H,N analyses were within ±0.4% of the calculated value. ^d Inhibition of the apomorphine-induced stereotypy of behavior in mice. ED₅₀ 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

compd	ED ₅₀ (CL)				ED ₅₀ ratio, B/A
	DA receptor antagonist activity ^a (A)	DA autoreceptor agonist activity ^b	catalepsy ^c (B)	α ₁ -adrenoceptor antagonist activity ^d	
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	1A	24.5 (21.4–27.9)	19.7 (19.1–22.0)	2.0
HAL	0.24	1A	0.9 (0.88–0.98)	>341	3.7

^a See Tables 1 and 2. ED₅₀ values are presented in μmol/kg po. ^b Inhibition of the GBL-induced increase in DOPA accumulation in mice. The ED₅₀ values and 95% confidence limits (CL) were calculated using the linear regression analysis and are presented in μmol/kg po. The compounds with ED₅₀ values indicated with a greater than sign (>) were inactive at below the given dose. ^c Induction of catalepsy in mice. The ED₅₀ 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 ED₅₀ values and 95% confidence limits (CL) were calculated using the probit method and are presented in mmol/kg po. The compounds with ED₅₀ values indicated with a greater than sign (>) were inactive at below the given dose. 1A, 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

comp	ED ₅₀ (μmol/kg po)			
	inhibition of GBL-induced increase in DOPA synthesis	inhibition of APO-induced stereotyped 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 ED₅₀ values than that of the anti-APO test in mice (ED₅₀ of 7.8 and 4.4 μ mol/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 ED₅₀ values of 19.7 and 150.7 μ mol/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 μ mol/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 D₂ 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, ED₅₀ values estimated as 49.5 (27.8–169.4) and 50.5 (38.5–71.1) μ mol/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 ED₅₀ value was estimated as 11.8 (8.5–15.4) μ mol/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 ED₅₀ values of 11.8, 28.4, and 1.1 μ mol/kg po, respectively. Compounds **28** and **1** antagonized the GBL-induced increase in DA synthesis in the rat brain with ED₅₀ values of 6.9 and 15.7 μ mol/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 ED₅₀ value of 149.2 μ mol/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 [³H]-spiperone-labeled D₂ 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 micro-melting point apparatus and are uncorrected. ¹H 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), K₂CO₃ (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; ¹H NMR (DMSO-*d*₆) δ 1.81 (2H, m, -CH₂-), 1.95 (2H, m, -CH₂-), 2.41 (2H, t, $J = 7$ Hz, -CH₂CO-), 2.78 (2H, t, $J = 7$ Hz, -CH₂-C-CO-), 3.60 (2H, t, $J = 6$ Hz, -CH₂Br), 3.93 (2H, t, $J = 6$ Hz, O-CH₂-), 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. (C₁₃H₁₆NO₂Br) 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 K₂CO₃ (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; ¹H NMR (DMSO-*d*₆) δ 1.92 (4H, m, -CH₂CH₂-C-), 3.62 (2H, t, $J = 6$ Hz, -CH₂Br), 4.05 (2H, t, $J = 6$ Hz, O-CH₂-), 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. (C₁₃H₁₄NO₂Br) 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 CH₃CN (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; ¹H NMR (CDCl₃) δ 1.77 (4H, m, -CH₂CH₂-), 2.34 (3H, s, CH₃), 2.47 (2H, t, $J = 7$ Hz, -CH₂CO-), 2.61 (6H, m, -CH₂N(CH₂)CH₂-), 2.90 (6H, m, -CH₂PhCH₂-), -CH₂-C-CO-), 3.96 (2H, t, $J = 6$ Hz, O-CH₂-), 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. (C₂₄H₃₀N₃O₂Cl) 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-nitrophenyl)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 method⁴⁵ 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 CH₃CN (50 mL) to afford **14** (32%): mp 146–148 °C; ¹H NMR (CDCl₃) δ 1.56 (4H, m, -CH₂CH₂-), 1.82 (2H, m, -CH₂-), 2.34 (3H, s, CH₃), 2.45 (2H, t, $J = 7$ Hz, -CH₂CO-), 2.60 (6H, m, -CH₂N(CH₂)CH₂-), 2.92 (6H, m, -CH₂PhCH₂-), -CH₂-C-CO-), 3.95 (2H, t, $J = 6$ Hz, O-CH₂-), 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. (C₂₅H₃₂N₃O₂Cl) 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/cm² 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; ¹H NMR (CDCl₃) δ 1.79 (4H, m, -CH₂CH₂-), 2.12 (3H, s, CH₃), 2.47 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.61 (6H, m, -CH₂N(CH₂)CH₂-), 2.90 (6H, m, -CH₂-C-CO-, CH₂-NPhCH₂-), 3.60 (2H, br, NH₂), 3.96 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₄H₃₂N₂O₂) C, H, N.

7-[4-[4-(3-Acetylaminophenyl)-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; ¹H NMR (CDCl₃) δ 1.71 (4H, m, -CH₂CH₂-), 2.21 (6H, s, CH₃, CH₃CO-), 2.48 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.60 (6H, m, -CH₂N(CH₂)CH₂-), 2.90 (6H, m, -CH₂-C-CO-CH₂NPhCH₂-), 3.96 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₈H₃₄N₄O₄) C, H, N.

3,4-Dihydro-7-[4-[4-(3-hydroxy-2-methylphenyl)-1-piperazinyl]butoxy]-2(1*H*)-quinolinone (24). A solution of NaNO₂ (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 CH₂Cl₂ (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; ¹H NMR (DMSO-*d*₆) δ 1.58 (2H, m, -CH₂-), 1.73 (2H, m, -CH₂-), 2.03 (3H, s, CH₃), 2.37 (4H, m, -CH₂CO-, -CH₂-), 2.66 (4H, m, -CH₂N(CH₂)CH₂-), 2.77 (6H, m, -CH₂-C-CO-, -CH₂NPhCH₂-), 3.92 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₄H₃₁N₃O₃·1.5H₂O) 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 CH₃CN (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-CHCl₃ gave **38** (72%) as colorless flakes: mp 190–192 °C; ¹H NMR (CDCl₃) δ 1.81 (4H, m, -CH₂CH₂-), 2.50 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.61 (6H, m, -CH₂N(CH₂)CH₂-), 2.97 (2H, t, *J* = 7 Hz, -CH₂-C-CO-), 3.08 (4H, m, -CH₂NPhCH₂-), 4.02 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₃H₂₇N₃O₂Cl₂) 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 CH₃CN (50 mL) with 81% yield as colorless flakes (EtOH-CHCl₃): mp 194–197 °C; ¹H NMR (CDCl₃) δ 1.24 (4H, m, -CH₂CH₂-), 2.49 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.62 (6H, m, -CH₂N(CH₂)CH₂-), 2.93 (2H, t, *J* = 7 Hz, -CH₂-C-CO-), 3.07 (4H, m, -CH₂NPhCH₂-), 3.96 (2H, t, *J* = 6 Hz, O-CH₂-), 6.71 (3H, m, aromatic H), 6.96 (1H, m,

aromatic H), 7.14 (2H, m, aromatic H), 8.32 (1H, s, -NHCO-). Anal. (C₂₃H₂₇N₃O₂Cl₂) 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 CH₃CN (50 mL), with 79% yield as colorless prisms (EtOH): mp 122–123 °C; ¹H NMR (CDCl₃) δ 1.75 (4H, m, -CH₂CH₂-), 2.49 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.63 (6H, m, -CH₂N(CH₂)CH₂-), 2.97 (2H, t, *J* = 7 Hz, -CH₂-C-CO-), 3.08 (4H, m, -CH₂NPhCH₂-), 4.05 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₃H₂₇N₃O₂Cl₂) 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 CH₃CN (30 mL). Recrystallization from MeOH provided **49** in 50% yield as yellow granules: mp 112–113 °C; ¹H NMR (CDCl₃) δ 1.77 (4H, m, -CH₂CH₂-), 2.50 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.65 (6H, m, -CH₂N(CH₂)CH₂-), 2.93 (2H, t, *J* = 7 Hz, -CH₂-C-CO-), 3.11 (4H, m, -CH₂NPhCH₂-), 3.99 (2H, t, *J* = 6 Hz, O-CH₂-), 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, d, *J* = 2.5, 8 Hz, aromatic H), 8.30 (1H, s, -NHCO-). Anal. (C₂₃H₂₈N₄O₄) C, H, N.

7-[4-[4-(2-Aminophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (50). SnCl₂ 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 CH₂Cl₂ (200 mL). The extract was washed, dried, and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, 3% MeOH in CHCl₃). Recrystallization from EtOH-isopropyl ether afforded **50** as pale-brown granules in 34% yield: mp 130–132 °C; ¹H NMR (CDCl₃) δ 1.75 (4H, m, -CH₂CH₂-), 2.47 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.61 (6H, m, -CH₂N(CH₂)CH₂-), 2.89 (6H, m, -CH₂-C-CO-, -CH₂NPhCH₂-), 3.96 (4H, m, O-CH₂-, -NH₂), 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. (C₂₃H₃₀N₄O₂) C, H, N.

7-[4-[4-(2-Cyanophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1*H*)-quinolinone (51). A solution of NaNO₂ (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% H₂SO₄ 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), CuSO₄ pentahydrate (1.5 g, 6 mmol), and 37% NH₄OH (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 CH₂Cl₂. The solution was washed, dried, and concentrated in vacuo to give a crude oily product which was purified by column chromatography (SiO₂, 2% MeOH in CHCl₃). Recrystallization from CH₃CN provided **51** as a pale-brown powder in 18% yield: mp 150–151 °C; ¹H NMR (CDCl₃) δ 1.76 (4H, m, -CH₂CH₂-), 2.46 (2H, t, *J* = 7 Hz, -CH₂CO-), 2.65 (6H, m, -CH₂N(CH₂)CH₂-), 2.89 (2H, t, *J* = 7 Hz, -CH₂-C-CO-), 3.22 (4H, m, -CH₂NPhCH₂-), 3.96 (2H, t, *J* = 6 Hz, O-CH₂-), 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. (C₂₄H₂₈N₄O₂·1.5 H₂O) 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 $\text{MeOH}-\text{CHCl}_3$ gave **52** (84%) as colorless needles; mp 174–176 °C; ^1H NMR (CDCl_3) δ 1.74 (2H, m, $-\text{CH}_2-$), 1.87 (2H, m, $-\text{CH}_2-$), 2.34 (3H, s, CH_3), 2.51 (2H, t, $J = 6$ Hz, $-\text{CH}_2-$), 2.64 (4H, m, $-\text{CH}_2\text{N}(\text{CH}_2-)\text{C}-$), 2.92 (4H, m, $-\text{CH}_2\text{NPhCH}_2-$), 4.11 (2H, t, $J = 6$ Hz, $\text{O}-\text{CH}_2-$), 6.52 (1H, d, $J = 9$ Hz, $-\text{C}=\text{CHCO}-$), 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, $-\text{CH}=\text{C}-\text{CO}-$), 12.63 (1H, s, $-\text{NHCO}-$). Anal. ($\text{C}_{24}\text{H}_{28}\text{N}_3\text{O}_2\text{Cl}\cdot 0.1\text{H}_2\text{O}$) 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 (Contonin, 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 $\mu\text{mol/kg po}$ 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 Chemocorb 5-ODS (20 $\times$ 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 $\text{EDTA}\cdot 2\text{Na}$ 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 $\mu\text{mol/kg po}$ 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 $\mu\text{mol/kg po}$ 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 $\mu\text{mol/kg po}$ in Tables 3 and 4.

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

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