Brief Articles

Extremely Potent Orally Active Benzo[*g*]quinoline Analogue of the Dopaminergic Prodrug: 6-(*N*,*N*-Di-*n*-propyl)amino-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one

Danyang Liu,* Håkan V. Wikström, Durk Dijkstra, Jan B. de Vries, and Bastiaan J. Venhuis

Department of Medicinal Chemistry, University Centre for Pharmacy, University of Groningen, Antonius Deusinglaan 1, NL-9713 AV Groningen, The Netherlands

Received November 4, 2005

Enone prodrugs of dopaminergic catecholamines represent a new type of prodrug in the research area of dopamine agonists. Here, we demonstrate the first benzo[*g*]quinoline-derived enone that induces potent dopamine agonist effects similar to aminotetralin-derived enones. Significant effects of (−)-**4** were observed in microdialysis studies after administration of 1 nmol kg^{-1} sc and 3 nmol kg^{-1} po. With a potency comparable to that of the most potent apomorphines, (−)-**4** could potentially compete with L-DOPA and apomorphine in the treatment of Parkinson's disease.

Introduction

In the treatment of Parkinson's disease (PD), an important property of a dopamine (DA) agonist has been suggested to be a long duration of action, which could counteract the development of dyskinesias.[1] We previously described that (*S*)-6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one [(*S*)-PD148903, **1**] is bioactivated in vivo to its corresponding catecholamine [(*S*)-5,6-di-OH-DPAT, **2**], which acts as a potent mixed DA D_1/D_2 full agonist (Figure 1).[2] Furthermore, several analogues of **1** with different *N*-alkyl substituents induce similar or more potent dopaminergic effects.[3] Evidently, the aminotetralin-derived analogues of **1** contain a "template" for bioactivation.

It was interesting to extend this prodrug concept to the benzo[*g*]quinolines, examplified with *N*-(*n*-propyl)-6,7-di-OH-benzo[*g*]quinoline (6,7-di-OH-PBGQ, **3**). Similar to aminotetralin (**2**), the 6,7-di-OH-PBGQ (**3**) is a catecholamine and known potent, centrally acting DA receptor agonist.[4,5] It is not clear if **3** displays both D_1 and D_2 agonistic effects. However, its *N*-ethyl analogue TL333 displays such a mixed profile, as reported by Itoh et al.[6] Therefore, tricyclic enone 1-propyl-2,3,4,4a,5,7,8,9,10,10a-decahydro-1*H*-benzo[*g*]quinolin-6-one (**4**) was prepared and pharmacologically evaluated.

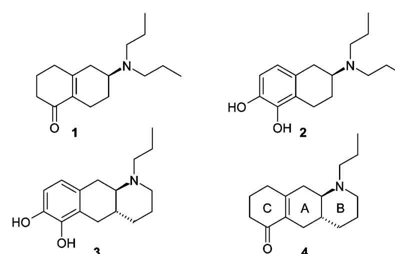
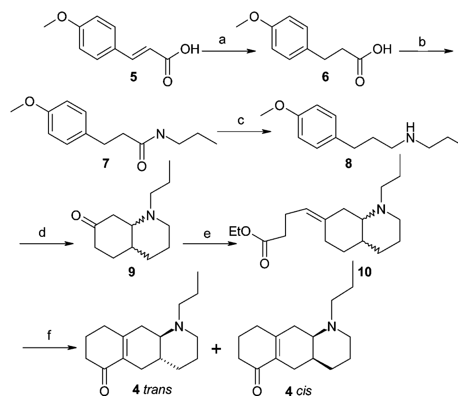


Figure 1. Molecular structures of (*S*)-PD148903 (**1**), 5,6-di-OH-DPAT (**2**), (−)-*N*-(*n*-propyl)-6,7-dihydroxybenzo[*g*]quinoline (**3**), and its analogous potential enone prodrug (**4**).

Scheme 1[a]



[a] Reagents: (a) 3 bar of H_2, 10% Pd/C; (b) (i) $SOCl_2$; (ii) *n*-$PrNH_2$, 87% over two steps; (c) $LiAlH_4$, 91%; (d) (i) Li/NH_3(l); (ii) H^+/H_2O, 70%; (e) $Br(Ph)_3P^+(CH_2)_3CO_2Et$, *t*-BuOK; (f) PPA, 100 °C, 34% over two steps.

Chemistry

The final compound **4** was prepared with the following strategy. The starting material 3-(4-methoxyphenyl)acrylic acid (**5**) was converted to the secondary amine **8** in three steps in high yields as given in Scheme 1. The heterocyclic ring system (A) was formed by performing a Birch reduction of the aromatic ring in **8** using Li/NH_3(l).[7,8] The combination of Na/NH_3(l) was also tested;[9] however, less than 50% of the secondary amine (**8**) was reduced. The greater solubility of lithium in liquid ammonia and a higher reduction potential for lithium enhanced the reducing power of such a reaction.[10] Upon acidic hydrolysis, cyclization occurred to give **9** (ring B) as a diastereomeric mixture with a ratio of 80:20 (cis/trans) as determined by GC analysis in 70% yield. Because of a favorable steric requirement for an approach of the nitrogen atom to the conjugated system, this isomerization feature can be interpreted by assuming a predominant cis attack in preference to a trans attack in the Michael-type addition step.[11] It has been described[12] that *cis*-**9** could isomerize to the trans form in acidic media through the retro-Michael process; however, in our experiment no transformation was found. Interestingly, in the presence of 1% KOH in ethanol solution at room temperature, the cis isomer can be efficiently transformed into the trans isomer with a ratio of 11:89 (cis/trans)[13] in 78% yield.

* To whom correspondence should be addressed. Phone: +31-50-3633306. Fax: +31-50-3636908. E-mail: d.liu@rug.nl.

10.1021/jm051111h CCC: $33.50 © 2006 American Chemical Society
Published on Web 01/25/2006

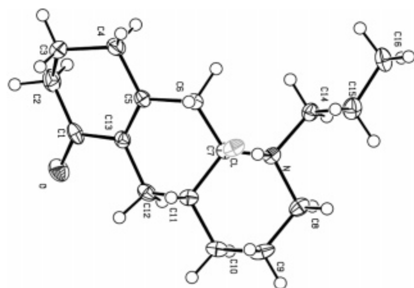
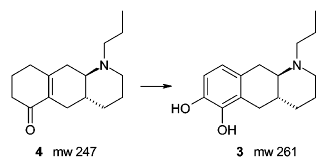


Figure 2. X-ray structure of enantiopure *trans*-(−)-**4**·HCl salt.

Scheme 2. Suggested Metabolism of **4**[a]



[a] Only the (−)-enantiomer of **4** gave detectable level of a compound believed to be 6,7-di-OH-PBGQ (**3**).

Table 1. In Vitro Affinity of (+)-**4** and (−)-**4** for Several DA Receptor Subtypes[a]

	DA D_1 (SCH23390)[b]	DA D_2 (spiperone),[b] %	DA D_3 (spiperone)[b]	DA D_4 (nemonapride)[b]
(−)-**4**	100/−1%	100/15%	50/23%	50/−4%
(+)-**4**	100/7%	100/3%	50/28%	50/−19%

[a] K_i (nM), $n = 3$. [b] Tritiated radioligand used.

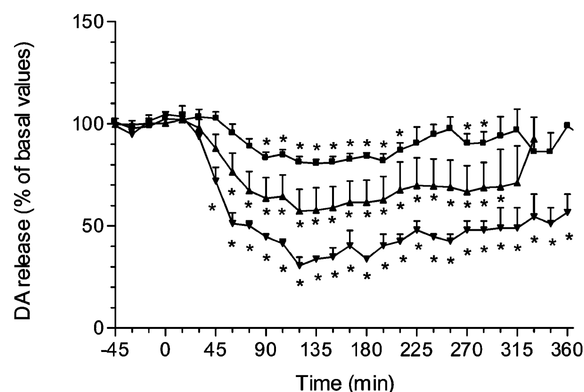


Figure 3. Effect of (−)-**4** (1, 3, and 10 nmol kg^{-1} sc; ■, ▲, and ▼, respectively) on striatal DA release in freely moving rats. The results are the mean (±SEM) of data obtained from four rats: (*) $p < 0.05$.

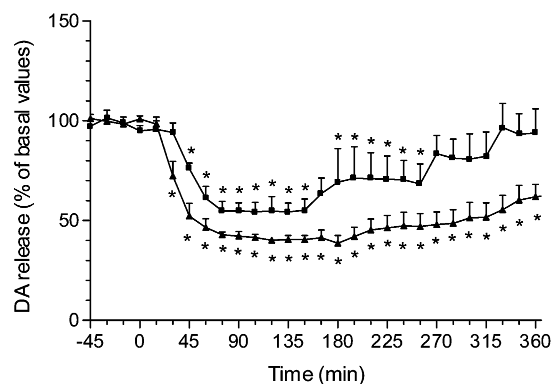


Figure 4. Effect of (−)-**4** (3 and 10 nmol kg^{-1} po; ■ and ▲, respectively) on striatal DA release in freely moving rats. The results are the mean (±SEM) of data obtained from four rats: (*) $p < 0.05$.

The third ring (C) was constructed by the introduction of a C4 moiety through a Wittig reaction.[14] The mixture of *E* and *Z* isomers was used without further purification for the final ring closure in polyphosphoric acid (PPA) at 100 °C.[15] The last cyclization step was highly regioselective at that temperature. It was observed that when the reaction was carried out at 115 °C, up to 30% of the benzo[*h*]quinoline analogue of **4** was isolated as side product. The racemic mixture was separated into its enantiomers by preparative chiral HPLC with the eluent hexane/2-propanol (99/1, containing 0.1% TEA); see Supporting Information for details.

From the X-ray analysis of enantiopure *trans*-(−)-**4** in Figure 2, it can be seen that the C7−N bond and C11−C12 bond (torsion angle 176°) and C6−C7 and C10−C11 (torsion angle 175°) are in trans configuration. The absolute configuration was proved as (*R*,*R*); see details in Supporting Information.

Both enantiomers of **4** were given in a dose of 10 μmol/kg po to male Wistar rats, and the blood and the brain samples were taken as described.[16] After the usual workup procedure with 60% CH_3CN in water for the precipitation of proteins, the samples were injected into the LC/MS/MS system. The identity of (−)-**4** and (+)-**4** was confirmed by U. Jurva[16] using high-performance liquid chromatography/tandem mass spectrometry (LC/MS/MS). Since peaks 261 and 263 were found in the samples from (−)-**4** administrated rats, compared with a standard sample of 6,7-di-OH-PBGQ (**3** as trans isomer, MW 261) synthesized in our lab, it is reasonable to assume that the catecholamine **3** is the active form of (−)-**4** in vivo (Scheme 2).

Oral administration of 10 μmol/kg of (+)-**4** did not induce any biochemical or behavioral effects. Peak 263 was found in brain and plasma samples; however, **3** was not detected in the samples collected.

Results and Discussion

In vitro, neither of the enantiomers of **4** displays any affinity for the DA D_1, D_2, D_3, and D_4 (Table 1). However, biochemical experiments in vivo strongly indicate that (−)-**4** is converted to a DA agonist. The pharmacological effects of both enantiomers were studied by measuring their effects on the DA levels in the corpus striatum, the brain area of interest in Parkinson's disease, using microdialysis in freely moving rats.[17,18] Microdialysis is a presynaptic model suitable for investigating the pharmacological effects of DA agonists. Stimulation of the autoreceptors leads to a down-regulation of dopamine synthesis and release. The results are expressed in relation to basal DA levels. For (−)-**4**, a significant decrease of 20−70% was observed after administration of 1, 3, or 10 nmol kg^{-1} sc (Figure 3). Administration of 3 or 10 nmol kg^{-1} po induced a significant decrease of 45% and 60%, respectively (Figure 4). During the microdialysis experiments the rats displayed behavior like yawning, sniffing, penile grooming, and locomotor activity.[19−21]

Comparison of these results with previously published data from our lab[17] clearly show that (−)-**4** induces strong effects after oral administration. For example, to achieve a 45% decrease in DA level after oral administration, (−)-**4** is >100-fold more potent than *N*-propylnorapomorphine and (−)-**1**. After subcutaneous administration, (−)-**4** is >10 times more potent.[2,17]

Further comparison of the effects of these compounds shows that the onset of action of (−)-**4** is more gradual and the effect is more long lasting. This may be an important characteristic because this could potentially avoid a steep plasma concentration curve that could lead to adverse effects. Compound (+)-**4** was found to be inactive at a dose of 1 μmol kg^{-1} sc as shown in Figure 5.

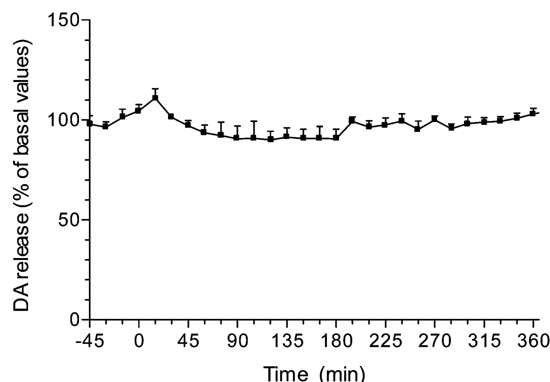


Figure 5. Effect of (+)-**4** (1 μmol kg^{-1} sc) on striatal DA release in freely moving rats. The results are the mean ($\pm$SEM) of data obtained from four rats: (*) $p < 0.05$.

Conclusion

The lack of affinity of (−)-**4** observed in vitro and the highly potent dopaminergic effects in vivo indicate a bioactivation mechanism similar to that of (−)-**1** and its close analogues. The "template for bioactivation" of enones thus may very well extend from bicyclic systems to a tricyclic system.

In microdialysis, (−)-**4** is active at extremely low doses sc and po. The effects observed in this model are stronger than those induced by *N*-propylnorapomorphine and (−)-**1**. Furthermore, the effects at the lower doses tested last considerably longer.

These properties taken together make (−)-**4** an extremely interesting candidate for development into a drug to improve the drug therapy of PD.

Experimental Section

3-(4-Methoxyphenyl)propionic Acid *N*-Propylamide (7). 3-(4-Methoxyphenyl)acrylic acid (10 g, 55.7 mmol) was dissolved in ethanol (200 mL), and a catalytic amount of 10% Pd/C (120 mg) was added. After shaking for 3 h under an H_2 atmosphere (3 bar) at room temperature, the mixture was filtered over Celite and evaporated. The residue (10.2 g, white solid) obtained was refluxed in DCM (220 mL) with thionyl chloride (10 mL, 137 mmol) for 1.5 h. The volatiles were evaporated, and the resulting oil was dissolved in DCM (100 mL). This solution was added to a vigorously stirred mixture of 5% aqueous NaOH (230 mL), DCM (120 mL), and *n*-propylamine (7 mL, 85 mmol). After the mixture was stirred for 1 h, the aqueous layer was extracted with DCM (3 $\times$ 100 mL). The general workup procedure yielded the amide **7** as a white solid (10.7 g, 48.4 mmol, 87%), mp 90−91 °C. IR (neat) cm^{-1} 3303, 2960, 1641, 1542; ^{13}C NMR (CDCl$_3$) δ 170.7, 156.5, 131.4, 127.8, 112.4, 53.7, 39.7, 37.3, 29.4, 21.3, 9.8 ppm; ^{1}H NMR (CDCl$_3$) δ 7.11 (d, 2H, J = 4.4 Hz), 6.81 (d, 2H, J = 4.4, 2.2 Hz), 5.52 (br s, 1H), 3.77 (s, 3H), 3.14 (m, 2H), 2.91 (m, 2H), 2.43 (m, 2H), 1.45 (m, 2H), 0.85 (t, 3H, J = 7.3 Hz) ppm; MS (EI) m/z 221 (M$^+$).

***N*-(3-(4-Methoxyphenyl)propyl)-*N*-propylamine (8).** To a stirred mixture of LiAlH$_4$ (3.6 g, 94.6 mmol) in THF (80 mL) was added dropwise a solution of amide **7** (10.4 g, 47.1 mmol) in THF (80 mL). After refluxing for 3.5 h, the mixture was cooled to 50 °C and excess hydride was destroyed by usual workup procedure. The amine **8** was obtained as an oil (8.9 g, 43 mmol, 91%). IR (neat) cm^{-1} 2931, 2832, 1612, 1513; ^{13}C NMR (CDCl$_3$) δ 156.2, 132.6, 127.7, 112.2, 53.7, 50.3, 47.9, 31.2, 30.3, 21.5, 10.3 ppm; ^{1}H NMR (CDCl$_3$) δ 7.11 (d, 2H, J = 8.8 Hz), 6.81 (d, 2H, J = 8.6 Hz), 3.77 (br, s, 3H), 2.51−2.66 (m, 6H), 1.98 (br, s, 1H), 1.42−1.83 (m, 4H), 0.90 (t, 3H, J = 7.6 Hz) ppm; MS (EI) m/z 207 (M$^+$).

***N*-*n*-Propyl-7-keto-1,2,3,4,4a,5,8,8a-octahydro[6*H*]quinoline (9).** Amine **8** (12.3 g, 59.4 mmol) was dissolved in dry THF (120 mL) and *t*-BuOH (11.9 mL, 130 mmol). The mixture was cooled to −60 °C, and liquid NH$_3$ (120 mL) was introduced. Li metal (1.6 g) was gradually added in small portions, and the blue mixture was stirred at −60 °C for 4 h. The color was discharged by addition of a MeOH/aqueous NH$_4$Cl (saturated) solution (1/1, 40 mL). After NH$_3$ was evaporated, the pH of the slurry was adjusted to 1 by the addition of concentrated HCl and the mixture was stirred overnight at room temperature. The mixture was basified with 4 N NaOH. After general workup, a dark-red oil was obtained that was purified by column chromatography (silica, treated with NH$_3$, DCM/methanol, gradient) to yield **9** as a mixture of trans and cis isomers (1:4), a light yellow oil (8.1 g, 41.5 mmol, 70%). R_f: trans 0.72, cis 0.78 (DCM/MeOH = 5:1). *trans*-**9**: ^{13}C NMR (CDCl$_3$) δ 207.9, 61.6, 58.9, 52.5, 50.1, 43.5, 38.5, 38.0, 28.7, 22.8, 14.8, 9.3 ppm; ^{1}H NMR (CDCl$_3$) δ 2.95 (dt, 1H, J = 6.4, 13.9 Hz), 1.11−2.60 (m, 17H), 0.72 (t, 3H, J = 7.3 Hz) ppm; MS (EI) m/z 195 (M$^+$). *cis*-**9**: ^{13}C NMR (CDCl$_3$) δ 209.0, 62.6, 60.0, 53.5, 51.1, 44.5, 39.5, 39.0, 29.7, 23.8, 15.8, 10.3 ppm; ^{1}H NMR (CDCl$_3$) δ 3.54 (t, 1H, J = 4.4 Hz), 1.14−2.90 (m, 17H), 0.76 (t, 3H, J = 7.3 Hz) ppm; MS (EI) m/z 195 (M$^+$). Anal. ($C_{12}H_{21}NO$) C, H, N.

***trans*-*N*-*n*-Propyl-7-keto-1,2,3,4,4a,5,8,8a-octahydro[6*H*]-quinoline (9).** *cis*-**9** (4.4 g, 22.6 mmol) was dissolved in 1% KOH ethanol solution (440 mL) and stirred at room temperature under N$_2$ for 3 days. The solvent was evaporated and worked up. After evaporation of the solvent, the residue was purified by column chromatography (silica, treated with NH$_3$, DCM/MeOH, gradient) to yield 3.4 g of mainly *trans*-**9** (17.4 mmol, 78%; according to GC, 10% cis left; the mixture was used for further reaction).

***N*-*n*-Propyl-2,3,4,4a,5,6,7,8,9,10,10a-decahydrobenzo[*g*]quinoline-6-one (4).** To a suspension of *t*-BuOK (3.8 g, 34 mmol) in dry DMF (6 mL) under N$_2$ at 0 °C was added dropwise a solution of (3-ethoxycarbonylpropyl)triphenylphosphonium bromide (14.1 g, 37.4 mmol) in dry DMF (50 mL). After the addition, the mixture was stirred at 0 °C for 30 min. A solution of **9** (3.3 g, 17.0 mmol) in dry DMF (6 mL) was added at 0 °C under N$_2$. After the mixture was stirred at 0 °C for 4 h, the temperature was allowed to rise to room temperature and the stirring was continued overnight. After general workup, a brown oil **10** was obtained and was dissolved in DCM (25 mL). The solution was added to PPA (45 g) at 100 °C while stirring for 4 h. After cooling, ice (100 g) was slowly introduced and extracted with DCM to remove the byproduct from the last step. Ammonia (25% water solution) was added until pH > 8 was attained. After general workup, the residue was purified by column chromatography (silica, treated with NH$_3$, DCM/methanol, gradient) to result in *trans*-**4** (1.4 g, 5.67 mmol, 33% over two steps) as a light-yellow oil. ^{13}C NMR (CDCl$_3$) δ 197.2, 153.2, 129.9, 59.3, 54, 51.3, 36.2, 36.0, 35.5,30.0, 29.5, 28.2, 23.8, 20.8, 16.3,16.6 ppm; ^{1}H NMR (CDCl$_3$) δ 3.51 (d, 1H, J = 11.0 Hz), 2.65 (m, 2H), 2.21−2.47 (m, 8H), 1.87−2.18 (m, 4H), 1.60−1.79 (m, 3H), 1.37−1.59 (m, 2H), 1.01−1.31 (m, 2H), 0.86 (t, 3H, J = 7.3 Hz) ppm. MS (EI) m/z 247 (M$^+$). Anal. ($C_{16}H_{25}NO$) C, H, N. *cis*-**4** (0.13 g, 0.53 mmol, 3% over two steps) was obtained as a light-yellow oil. ^{13}C NMR (CDCl$_3$) δ 197.6, 152.5, 128.8, 55.2, 53.3, 45.2, 36.4, 31.9, 29.9, 26.4, 24.0, 23.5, 21.0, 18.8, 10.5 ppm; ^{1}H NMR (CDCl$_3$) δ 3.03 (t, 1H, J = 6.1 Hz), 2.52−2.61 (m, 1H), 2.34−2.49 (m, 6H), 2.21−2.30 (m, 4H), 2.02 (m, 3H), 1.18−1.68 (m, 7H), 0.87 (t, 3H, J = 7.3 Hz) ppm; MS (EI) m/z 247 (M$^+$). The products were subsequently converted to the hydrochloric salt and recrystallized from ethanol/diethyl ether: *cis*-**4**·HCl, mp 186 °C; *trans*-**4**·HCl, mp 237 °C.

Pharmacology. All enones were tested as their hydrochloride salts unless noted otherwise. The drugs were dissolved in physiological (0.9%) saline immediately before use. All in vivo experiments were performed at the laboratory animal unit of the Rijksuniversiteit Groningen, The Netherlands. Microdialysis procedure was performed following the literature procedure.[17]

Receptor Binding. The in vitro binding affinity experiments were performed at Lundbeck AC/S, Copenhagen, Denmark.

The compounds *trans*-(−)-**4** and (+)-**4** were tested for in vitro binding at the D$_1$, D$_2$, D$_3$, and D$_4$ receptors. The displacement of the radioligand was measured at a fixed concentration of the test compound (50 or 100 nM). The estimate was based on this

concentration of the test compound above or the concentration below the IC_{50} of the radioligand. When the displacement of the radioligand is below the IC_{50} at the tested concentration, the test compound is considered to be inactive at the receptor.

D_1 Binding. The method was described by Hyttel and Larsen.[22,23] By this method, the inhibition by drugs of the binding of [^{3}H]SCH 23390 (0.20 nM, K_d = 0.45 nM) to dopamine D_1 receptors in membranes from rat corpus striatum was determined in vitro.

D_2 Binding. The method was described by Hyttel and Larsen.[24,25] By this method, the inhibition by drugs of the binding of [^{3}H]spiperone (0.50 nM, K_d = 0.20 nM) to dopamine receptors in membranes from rat corpus striatum is determined in vitro.

D_3 Binding. A modified method from R. G. Mackenzie et al.[26] was used. By this method, the inhibition by drugs of the binding of [^{3}H]spiperone (0.3 nM, K_d = 0.45 nM) to membranes of human cloned dopamine D_3 receptors expressed in Chinese hamster ovary (CHO) cells is determined in vitro. CHO cells expressing the human cloned D_3 dopamine receptor are harvested, and the cell suspension was centrifuged at 1000 rpm for 7 min at 4 °C. The supernatant is frozen. On the day of the experiment, the cell pellet is thawed at room temperature and diluted in assay buffer (25 mM Tris-HCl (pH 7.4) + 6.0 mM $MgCl_2$ + 1.0 mM EDTA) to the desired concentration. An amount of 50 μL of displacer (10 μM haloperidol, text compound or assay buffer) and an amount of 230 L of buffer are added to a 96-well deep plate. Then 50 μL of 0.3 nM [^{3}H]-spiperone is added. The reaction is initiated by addition of 670 μL of membrane suspension (test concentration of 26 μg of protein/ 670 μL). Packard GF/C unifilter (96 well) is pretreated with 0.1% PEI solution 10−15 min before filtration. After 60 min of incubation at 25 °C the reaction is terminated by filtration at the Tomtec unifilter. The filters are washed twice with ice-cold assay buffer. The filters are dried for 1.5 h at 50 °C, 35 μL of scintillation liquid is added, and bound radioactivity is counted in Wallac Tri-Lux scintillation counters.

D_4 Binding. The method was described by Meier et al.[27] By this method, the inhibition by drugs of the binding of [^{3}H]-nemonapride (0.50 nM, K_d = 0.20 nM) to cloned human dopamine D_4 receptors is determined in vitro.

X-ray Crystallographic Data of Compound (−)-4. The HCl salt of (−)-**4** was recrystallized from absolute EtOH and ether as a colorless cubic crystal. The crystallographic data for (−)-**4** in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-273828. A copy of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or form the Cambridge Crystallographic Data Centre (CCDC) at 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44-1223/336-033, e-mail deposit@ccdc.cam.ac.uk).

Acknowledgment. We gratefully acknowledge Dr. Auke Meetsma (Crystal Structure Center, University of Groningen) for X-ray analysis and Lundbeck A/S (Denmark) for the in vitro binding study and financial support.

Supporting Information Available: General experimental procedures including results from chiral HPLC separation of *trans*-**4**, elemental analysis data, and selected X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Maratos, E. C.; Jackson, M. J.; Pearce, R. K.; Jenner, P. Antiparkinsonian activity and dyskinesia risk of ropinirole and L-DOPA combination therapy in drug naive MPTP-lesioned common marmosets (*Callithrix jacchus*). *Mov. Disord.* **2001**, *16* (4), 631−641.

(2) Venhuis, B. J.; Wikström, H. V.; Rodenhuis, N.; Sundell, S.; Wustrow, D.; Meltzer, L. T.; Wise, L. D.; Johnson, S. J.; Dijkstra, D. A new type of prodrug of catecholamines. An opportunity to improve the treatment of Parkinson's disease. *J. Med. Chem.* **2002**, *45*, 2349−2351.

(3) Venhuis, B. J.; Dijkstra, D.; Wustrow, D. J.; Meltzer, L. T.; Wise, L. D.; Johnson, S. J.; Heffner, T. G.; Wikström, H. V. Orally active analogs of the dopaminergic prodrug 6-(*N*,*N*-di-*n*-propylamino)-3,4,5,6,7,8-hexahydro-2*H*-naphthalen-1-one. Synthesis and pharmacological activity. *J. Med. Chem*. **2003**, *46*, 584−590.

(4) Costall, B.; Lim, S. K.; Naylor, R. J.; Cannon, J. G. On the preferred rotameric conformation for dopamine agonist action: an illusory quest? *J. Pharm. Pharmacol.* **1982**, *34*, 246−254.

(5) Cannon, J. G.; Lee, T.; Beres, J. A.; Goldman, H. D. *N*-Alkyl derivatives of *trans*-6,7-dihydroxy-1,2,3,4,4a,5,10,10b-octahydrobenzo[*g*]quinoline, a congener of apomorphine lacking the non-oxygenated aromatic ring. *J. Heterocycl. Chem.* **1980**, *17*, 1633−1636.

(6) Itoh, Y.; Goldman, M. E.; Kebabian, J. W. TL 333, a benzhydro[*g*]-quinoline, stimulates both D_1 and D_2 dopamine receptors: Implications for the selectivity of LY 141865 towards the D_2 receptor. *Eur. J. Pharmacol.* **1985**, *108*, 99−101.

(7) Bonjoch, J.; Catena, J.; Valls, N. Total synthesis of (±)-deethylibophyllidine: studies of a Fischer indolization route and a successful approach via a Pummerer rearrangement/thionium ion-mediated indole cyclization. *J. Org. Chem*. **1996**, *61*, 7106−7115.

(8) Parker, K. A.; Fokas, D. Convergent synthesis of (±)-dihydroisocodeine in 11 steps by the tandem radical cyclization strategy. A formal total synthesis of (±)-morphine. *J. Am. Chem. Soc*. **1992**, *114*, 9688−9689.

(9) Dryden, H. L.; Webber, G. M.; Burtner, R. R.; Cella, J. A. The use of sodium metal in the Birch reduction of aromatic compounds. *J. Org. Chem*. **1961**, *26*, 3237−3245.

(10) Wilds, A. L.; Nelson, N. A. A superior method for reducing phenol ethers to dihydro derivatives and unsaturated ketones. *J. Am. Chem. Soc*. **1953**, *75*, 5360−5365.

(11) Momose, T.; Uchida, S.; Yamaashi, N.; Imanishi, T. *N*-Benzoyloctahydro-7(1*H*)-quinolone: exclusive isomerization of the ring junction to cis rather than trans fusion. *Heterocycles* **1975**, *3* (9), 713−718.

(12) Grob, C. A.; Wilkens, H. J. Decahydrochinoline. 3. teil [1]. synthese und konfiguration der epimeren 7-hydroxy-*trans*-decahydrochinoline (Decahydroquinoline. 3. Part 1. Synthesis and configuration of the epimer 7-hydroxy-*trans*-decahydroquinoline). *Helv. Chim. Acta*. **1965**, *48*, 808−816.

(13) Momose, T.; Uchida, S.; Kinoshita, M.; Imanishi, T. Octahydro-7(1*H*)-quinolones. III. Cis−trans isomerization of octahydro-7(1*H*)-quinolone analogues. *Chem. Pharm. Bull*. **1978**, *26* (2), 620−626.

(14) Seltzer, S. Models for bacteriorhodopsin-catalyzed dark cis−trans isomerization of bound retinal. *J. Am. Chem. Soc*. **1990**, *112*, 4477−4483.

(15) Rae, I. D.; Umbrasas, B. N. 3,4,5,6,7,8-Hexahydronaphthalen-1(2*H*)-ones. Synthesis and photoaddition to (*Z*)-1,2-dichloroethylene. *Aust. J. Chem*. **1975**, *28*, 2669−2680.

(16) Jurva, U. Electrochemistry on-line with mass spectrometry; instrumental methods for in vitro generation and detection of drug metabolites. Ph.D. Thesis, Rijksuniversiteit Groningen, The Netherlands, 2004, pp 135−141.

(17) Rodenhuis, N.; Dijkstra, D.; DeBoer, P.; Vermeulen, E. S.; Timmerman, W.; Wikström, H. V. Dopamine D_2 activity of *R*-(−)-apomorphine and selected analogs: a microdialysis study. *Eur. J. Pharmacol*. **2000**, *387* (1), 39−45.

(18) Rodenhuis, N. Neuropharmacological evaluation of a new dopaminergic prodrug with anti-Parkinsonian potential. New centrally acting dopaminergic agents with an improved oral availability: synthesis and pharmacological evaluation. Ph.D. Thesis, Rijksuniversiteit Groningen, The Netherlands, 2000, pp 98−106.

(19) Waddington, J. L. Behavioural correlates of the action of selective D_1 dopamine receptor antagonists. Impact of SCH 23390 and SKF 83566, and functionally interactive D_1:D_2 receptor systems. *Biochem. Pharmacol*. **1986**, *35*, 3661−3667.

(20) Waddington, J. L.; O'Boyle, K. M. Drugs acting on brain dopamine receptors: a conceptual re-evaluation five years after the first selective D_1 antagonist. *Pharmacol. Ther*. **1989**, *43*, 1−52.

(21) Clark, D.; White, F. J. D_1 Dopamine receptor: the search for a function: a critical evaluation of the D_1/D_2 dopamine receptor classification and its functional implications. *Synapse* **1987**, *1*, 347−388.

(22) Hettel, J. Preferential Labeling of Adenylate Cyclase Coupled Dopamine Receptors with Thioxanthene Neuroleptics. In *Advances in Dopamine Research: Advances in the Biosciences*; Kohasaka, M., Shohmori, T., Woodruff, G. N., Eds.; Pergamon Press Ltd.: Oxford, U.K., 1982; pp 147−152.

(23) Hyttel, J.; Arnt, J. Characterization of binding of [^{3}H]-SCH 23390 to dopamine D_1 receptors. Correlation to other D_1 and D_2 measures and effect of selective lesions. *J. Neural Transm.* **1987**, *68*, 171−189.

(24) Hyttel, J. Effect of prolonged treatment with neuroleptics on dopamine D_1 and D_2 receptor density in corpus striatum in mice. *Acta Pharamacol. Toxicol*. **1986**, *59*, 387−391.

(25) Hyttel, J. Age related decrease in the density of dopamine D_1 and D_2 receptors in corpus striatum of rats. *Pharmacol. Toxicol*. **1987**, *61*, 126−129.
(26) MacKenzie, R. G.; Vanleeuwen, D.; Pugsley, T. A.; Shih, Y. H.; Demattos, S. B.; Tang, L.; Todd, R. D.; O'Malley, K. L. Characterization of the human dopamine D_3 receptor expressed in transfected cell lines. *Eur. J. Pharmacol*. **1994**, *266*, 79−85.
(27) Liao, Y.; Venhuis, B. J.; Rodenhuis, N.; Timmerman, W.; Wikstrom, H. V.; Meier, E.; Sundell, S. New (sulfonyloxy)piperazinyldibenzazepines as potential typical antipsychotics: chemistry and pharmacological evaluation. *J. Med. Chem*. **1999**, *42*, 2235−2244.

JM051111H