Derivatives of 4-(2-*N*,*N*-Di-*n*-propylaminoethyl)-5-hydroxyindole: Synthesis and Pharmacological Effects

Joseph G. Cannon,[1,3] Ioannis Roufos,[1] Sheng Xing Ma,[2] and John Paul Long[2]

Received April 26, 1991; accepted November 27, 1991

5-Methoxy-1-methyl-4-(2-*N*,*N*-di-*n*-propylaminoethyl)indole (**12**) was synthesized from 5-hydroxyindole by a multistep synthesis. This target compound was designed as a bioisostere of "*p*-dimethoxy" catechol congeners of dopaminergic agonists derived from a variety of ring systems, in some of which *p*-dimethoxy-substituted systems are potent, active dopaminergic agonists. To complete the indole series, all possible combinations of N- and O-demethylated derivatives of **12** were prepared and were also evaluated pharmacologically. All members of this indole-derived series showed a low order of cardiovascular activity, which appeared to be independent of dopamine receptors. The lack of dopaminergic activity of **12** is cited as yet another example of the unpredictable effect of replacement of the catechol moiety of a dopaminergic agonist with a *p*-dimethoxy moiety.

KEY WORDS: dopaminergic agonism; 5-oxygenated-4-aminoethylindoles; *p*-dimethoxy bioisosteres.

INTRODUCTION

Certain derivatives of various ring systems (e.g., tetralin, **1**; aporphine, **2**; indan, **3**; octahydrobenzo[*f*]quinoline, **4**; and octahydrobenzo[*g*]quinoline, **5**) containing a dopamine moiety elicit dopaminergic agonist actions (1) (Scheme I). Replacement of the catechol moiety in these ring systems (and in dopamine itself) with a *p*-dimethoxy substitution pattern (**6–11**) produces in several of these ring systems a variety of unpredictable pharmacologic responses, including dopaminergic agonism (2–5), serotonergic agonism (6), serotonergic antagonism (7), α_1-adrenoceptor effects (2,4), and (seemingly) complete loss of pharmacologic activity of any kind (5).

The present study addresses preparation and pharmacological evaluation of an indole derivative **12** (Scheme II). Design of this molecule derived from the finding (10) that compound **13** is a dopaminergic agonist and from the resulting hypothesis (8) that the indole ring N–H in **13** is bioisosteric with a phenolic OH and that the dopamine receptor(s) cannot discriminate between N–H and OH. It was proposed (8) that the indole ring N–H of **13** interacts with a subsite on the dopamine receptor that recognizes the "meta" OH group of the dopamine molecule. We hypothesized that the N_1-methyl and 5-methoxy moieties in N_1-methyl-5-methoxy-4-(2-di-*n*-propylaminoethyl) indole, **12**, are bioisosteric with the "*p*-dimethoxy" systems.

For completeness of the structure–activity study, compounds **14–16**, representing all possible combinations of N_1 and/or O methylation, were also prepared.

MATERIALS AND METHODS

Pharmacology

Each compound was assayed using four or five male Sprague-Dawley rats (300–350 g) and the animals were maintained on a 12-hr light–dark cycle in temperature- and humidity-controlled rooms. Rats were anesthetized with urethane (1.3 g/kg, i.p.). A catheter was positioned in the femoral vein for systemic injection of drugs. The femoral arterial catheter was connected to a Statham arterial transducer and heart rate was determined by a Beckman cardiotachometer coupler triggered from the arterial pulse. Arterial pressure and heart rate were displayed on a Beckman R-611 recorder. After tracheal cannulation, the animals breathed spontaneously throughout the experiment. A heating pad was used to maintain body temperature at 37°C.

When control heart rate and arterial pressure were steady for at least 20 min after completion of surgery, compounds were administered by i.v. injection. Dose–response curves for all treatments were determined using three or four doses which were spaced by 0.48 log intervals. Sulpiride was used to inhibit dopamine receptors following i.v. doses of 2 μmol 5 min before administration of test drugs.

Results are expressed as mean ± SE. Mean arterial pressure and heart rate are presented as milligrams of Hg and beats per minute, respectively. The effects of drugs administered after pretreatments are expressed as changes from the baseline measurements (5 min). Analysis of variance and Fisher's LSD were used to detect significant differences between means. P values less than 0.05 were considered significant.

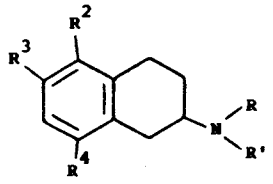
Synthesis

Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were obtained using a Bruker/IBM NR/80 FTNMR spectrometer. Chemical shifts are reported as parts per million (δ) relative to Me_4Si standard. Mass spectra were obtained with a Ribermag R10-10C spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Flash column chromatography was performed using a 150-Å-pore size, 35- to 75-μm-particle size silica (ANALTECH), and detection was done with a UV light. Radial thin-layer chromatographic separations were carried out on a Chromatotron apparatus (Harrison Research) using Kieselgel 60 PF_{254} (EM SCIENCE) as the stationary phase. Ozonolyses were done with a Welsbach T-23 ozonator.

*4-(2′-Di-*n*-propylaminoethyl)-5-methoxyindole Bifumarate (14).* Preparation of this compound was described in a separate communication (9).

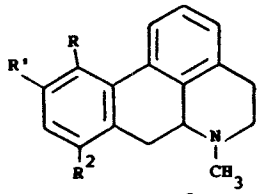
[1] Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242.
[2] Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242.
[3] To whom correspondence should be addressed.

0724-8741/92/0600-0735$06.50/0 © 1992 Plenum Publishing Corporation



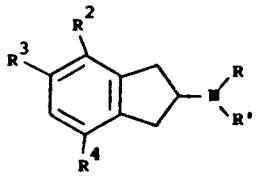
1 R = R' = alkyl
$R^2 = R^3 = OH$; $R^4 = H$

6 R = R' = alkyl
$R^2 = R^4 = OCH_3$; $R^3 = H$



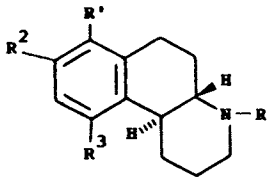
2 R = R' = OH; $R^3 = H$

7 R = $R^2 = OCH_3$; R' = H



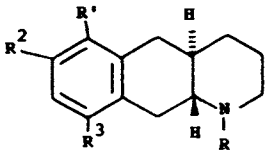
3 R = R' = alkyl
$R^2 = R^3 = OH$; $R^4 = H$

8 R = R' = alkyl
$R^2 = R^4 = OCH_3$; $R^2 = H$



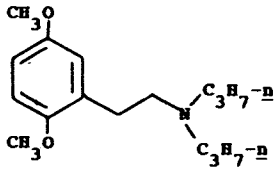
4 R = alkyl; R' = R^2 = OH
$R^3 = H$

9 R = alkyl; R' = $R^3 = OCH_3$;
$R^2 = H$



5 R = alkyl; R' = R^2 = OH;
$R^3 = H$

10 R = alkyl; R' = $R^3 = OCH_3$;
$R^2 = H$



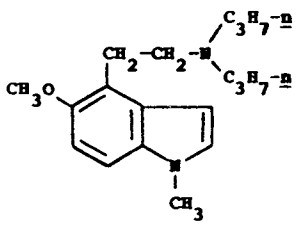
11

Scheme I

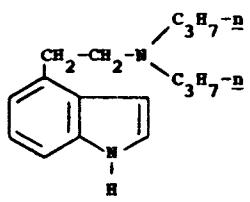
*4-(2'-Di-*n*-propylaminoethyl)-5-methoxy-*N_1*-methylindole Bifumarate (12).* A solution of 1.4 g (0.005 mol) of the free base of 14 (9) in 20 ml of Et_2O was added dropwise to $NaNH_2$ in liquid NH_3, prepared by the addition of 0.425 g (0.018 g atom) of Na to 50 ml of liquid NH_3 containing 0.1 g of $Fe(NO_3)_3 \cdot 6H_2O$. After stirring for 5 min, 0.81 g (0.0057 mol) of MeI was added dropwise; stirring was continued for 10 min, and then the NH_3 was allowed to evaporate. H_2O (50 ml) was added and the solution was extracted with two 50-ml portions of Et_2O. The pooled extracts were washed with H_2O and saturated NaCl. Removal of volatiles under reduced pressure afforded 1.10 g (75%) of a solid, MS 289 ($M^+ + 1$). A solution of this solid in 30 ml of Et_2O was mixed with a solution of 0.443 g (0.0038 mol) of fumaric acid in 900 ml of Et_2O. The solid which separated was recrystallized from EtOH–Et_2O to afford 1.0 g (67%) of a crystalline solid, mp 132–133°C. *Anal.* Calcd for $C_{22}H_{32}N_2O_5$ (Karl Fischer H_2O 1.78%): C, 64.16; H, 7.82; N, 6.72. Found: C, 64.51; H, 8.10; N, 6.84.

4-Allyl-5-benzyloxyindole (17). A mixture of 12.3 g (0.071 mol) of 4-allyl-5-hydroxyindole[9], 12.2 g (0.073 mol) of benzyl bromide, 1.5 g of tetrabutylammonium hydrogen sulfate, 60 ml of 50% NaOH, and 100 ml of benzene was stirred at room temperature for 30 min. H_2O (200 ml) was then added and the organic layer was washed with dil. HCl, H_2O, and saturated NaCl. After drying (Na_2SO_4) and evaporation of the volatiles, the crude product was chromatographed on a flash column and eluted with EtOAc–petroleum ether (1:12). Removal of the solvents under reduced pressure gave 16.5 g (88%) of pure product, mp 41–42°C. *Anal.* Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.91′; H, 6.82; N, 5.31.

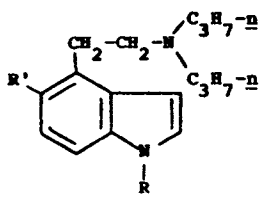
4-Allyl-5-benzyloxy-2,3-dihydroindole (18). $NaBH_3CN$ (12.5 g, 0.2 mol) was added in one portion to a solution of



12



13



14 R = H; R' = OCH_3

15 R = H; R' = OH

16 R = CH_3; R' = OH

Scheme II

17.1 g (0.065 mol) of **17** in 120 ml of glacial AcOH at 15°C, and the resulting solution was stirred at 15°C under N_2 for 20 min. H_2O (250 ml) was then added and the reaction flask was immersed in an ice–H_2O bath and made strongly basic with NaOH pellets. This mixture was extracted with three 200-ml portions of Et_2O, and the pooled extracts were washed with H_2O and saturated NaCl. The Et_2O was removed under reduced pressure and the residual yellow oil (14.8 g, 87%) was used in the next step without purification. MS *m/e* 266 ($M^+ + 1$).

4-Allyl-1-benzoyl-5-benzyloxy-2,3-dihydroindole (19). The crude product **18** (14.8 g, 0.055 mol) was suspended in 50 ml of 15% NaOH, and 10.1 g (0.072 mol) of benzoyl chloride was added. The suspension was shaken vigorously until the odor of benzoyl chloride could no longer be detected. The resulting solid was collected on a filter, dissolved in hot MeOH, and cooled. White crystals (17.6 g, 73%, from **17**) were deposited, mp 132–133°C. *Anal.* Calcd for $C_{25}H_{23}NO_2$ (Karl Fischer H_2O 0.12%): C, 81.17; H, 6.26; N, 3.78. Found: C, 81.24; H, 6.21; N, 3.74.

1-Benzoyl-5-benzyloxy-2,3-dihydroindole-4-acetaldehyde (20). Compound **19** (14 g, 0.038 mol) in 200 ml of $CHCl_3$ was ozonolyzed at −10°C. Compressed air was used as the source of O_3 and the preparation of O_3 was done under the following conditions: the voltage was set at 90 V, air pressure at 7 psig, and flow rate at 0.08 ft^3/min. The concentration of O_3 in the effluent was determined by KI oxidation and titration with $Na_2S_2O_3$ to be 0.047 g/ft^3. After absorption of the calculated amount of O_3, the ozonolysis solution was carefully concentrated at room temperature under reduced pressure, and the concentrated residue was slowly added to a round-bottom flask containing 5 g (0.076 g atom) of Zn dust in 40 ml of 75% aqueous AcOH. This mixture was stirred at 0°C until TLC analysis showed complete disappearance of the spot for the ozonolysis product. H_2O (200 ml) was added and the resulting mixture was extracted with $CHCl_3$. The extract was washed with 5% NaOH, H_2O, and saturated NaCl. The $CHCl_3$ was removed under reduced pressure and the yellow residue was dried under reduced pressure to yield 12.9 g (92%) of product which was recrystallized from EtOAc, mp 149–150°C. *Anal.* Calcd for $C_{24}H_{21}NO_3$ (Karl Fischer H_2O 0.43%): C, 77.21; H, 5.66; N, 3.75. Found: C, 77.42; H, 5.63; N, 3.36.

*1-Benzoyl-5-benzyloxy-4-(2'-di-*n*-propylaminoethyl)-2,3-dihydroindole (21).* A solution of 8.2 g (0.022 mol) of **20** and 9.8 g (0.07 mol) of di-*n*-propylamine HCl in 100 ml of MeOH was stirred for 4 hr at room temperature with 25 g of 3-Å molecular sieves. $NaBH_3CN$ (2.1 g, 0.033 mol) was then added and stirring was continued overnight. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give an off-white solid which was taken up in 100 ml of 5% NaOH. This solution was extracted with Et_2O. The ethereal extract was washed with saturated NaCl and volatiles were removed under reduced pressure. The residue was taken up in Et_2O, cooled in an ice bath, and treated with excess dil. HCl. The aqueous solution was separated and was made alkaline with NaOH pellets, and the resulting mixture was repeatedly extracted with Et_2O. Evaporation of the pooled extracts under reduced pressure afforded 7 g (70%) of a white solid which was used in the next step without further purification. The product was characterized as its oxalate salt. A portion of the crude product was dissolved in a minimum amount of Me_2CO and this solution was mixed with an excess volume of a 5% solution of oxalic acid in Me_2CO. The solid which separated was taken up in $CHCl_3$ and this solution was washed several times with 5% NaOH. The organic layer was evaporated under reduced pressure and the residual white powder was dried under reduced pressure. This material was dissolved in a minimum amount of Me_2CO and this solution was treated with a slight excess of a 5% solution of oxalic acid in Me_2CO. The white solid which separated was recrystallized from EtOH–Et_2O, mp 166–167°C. *Anal.* Calcd for $C_{32}H_{36}N_2O_6$ (Karl Fischer H_2O 0.12%): C, 70.21; H, 6.99; N, 5.11. Found: C, 70.29; H, 6.98; N, 5.15.

*5-Benzyloxy-4-(2'-di-*n*-propylaminoethyl)indole (22).* A solution of 7.5 g (0.016 mol) of **21**, 12.5 g (0.111 mol) of K-O-*t*-Bu, and 0.594 g (0.033 mol) of H_2O in 50 ml of Et_2O was stirred overnight at ambient temperature, during which time a slow stream of air was passed through the mixture. When no more starting material, **21**, could be detected by TLC analysis, the reaction flask was cooled in an H_2O-ice bath and 200 ml of H_2O was added. The ethereal layer was washed with H_2O and saturated NaCl. Evaporation of volatiles afforded a greenish white solid which was chromatographed on a flash column and eluted with EtOAc/petroleum ether (3:5) to yield 3.21 g (56%) of an off-white solid which was characterized as its oxalate salt, prepared as described above for **21**. Mp 147–148°C (EtOH–Et_2O). *Anal.* Calcd for $C_{25}H_{32}N_2O_5$ (Karl Fischer H_2O 0.61%): C, 67.74; H, 7.28; N, 6.32. Found: C, 67.71; H, 7.38; N, 6.28.

*4-(2'-Di-*n*-propylaminoethyl)-5-hydroxyindole Fumarate (15).* Compound **22** (0.35 g, 1 mmol) in 20 ml of Et_2O was treated with excess ethereal HCl. The resulting gummy salt was repeatedly washed with anhydrous Et_2O until it solidified, then it was dissolved in 100 ml of EtOAc. To this solution was added 0.2 g of 5% Pd/C (wet with a few drops of H_2O) and the mixture was hydrogenolyzed in a Parr apparatus at room temperature at an initial pressure of 54 psig. The reduction mixture was filtered through Celite; the filtrate was evaporated to dryness under reduced pressure, the residue was taken up in $CHCl_3$, and this solution was washed with 5% $NaHCO_3$. Evaporation of the $CHCl_3$ afforded a greenish liquid which was purified using the Chromatotron apparatus (EtOAc–petroleum ether, 3:5). The eluate was taken up in a small volume of Et_2O and this solution was treated with 0.116 g of fumaric acid in 300 ml of Et_2O. The white solid fumarate salt which separated was dried under reduced pressure. Yield, 0.210 g (54%). Mp 236–237°C. *Anal.* Calcd for $C_{36}H_{52}N_4O_6$ (Karl Fischer H_2O 0.51%): C, 67.56; H, 8.18; N, 8.75. Found: C, 67.65; H, 8.25; N, 8.55.

*5-Benzyloxy-4-(2'-di-*n*-propylaminoethyl)-*N*$_1$-methylindole Oxalate (23).* A solution of 1.05 g (3 mmol) of **22** in 20 ml of Et_2O was added dropwise to a solution of $NaNH_2$ in liquid NH_3, prepared by addition of 0.25 g (0.011 g atom) of Na to 40 ml of liquid NH_3 containing 0.03 g of $Fe(NO_3)_3$. After stirring for 5 min, 0.5 g (3.5 mmol) of MeI was added dropwise and stirring was continued for 10 min. The NH_3 was allowed to evaporate and the residue was taken up in 50 ml of H_2O. This solution was extracted with two 50-ml portions of Et_2O. Removal of volatiles from the

pooled extracts under reduced pressure afforded 0.71 g (65%) of a solid which was homogeneous on TLC analysis (SiO_2, EtOAc–hexanes, 3:5). This material was dissolved in 15 ml of Me_2CO and was added to a solution of 0.18 g (2 mmol) of oxalic acid in 20 ml of Me_2CO. The solid which separated was recrystallized from EtOH–Et_2O, mp 165–166°C. *Anal.* Calcd for $C_{26}H_{34}N_2O_5$ (Karl Fischer H_2O 0.10%): C, 68.83; H, 7.53; N, 6.10. Found: C, 68.68; H, 7.47; N, 6.10.

*5-Hydroxy-4-(2'-di-*n*-propylaminoethyl)-N_1-methylindole Bifumarate (16).* A suspension of 0.4 g (1 mmol) of **23** in 190 ml of EtOAc was hydrogenolyzed over 0.4 g of 10% Pd/C in a Parr apparatus, at an initial pressure of 22 psig. The mixture was filtered through Celite; the filtrate was evaporated under reduced pressure and the residue was taken up in 50 ml of 5% $NaHCO_3$. This solution was extracted with Et_2O. The solvent was removed from the extract under reduced pressure to give a yellow liquid which was taken up in a fresh portion of Et_2O. The resulting solution was treated with a small excess of a saturated solution of fumaric acid in Et_2O; a white solid separated. Yield, 0.055 g (15%); mp, 181–182°C (from EtOH–Et_2O). *Anal.* Calcd for $C_{21}H_{30}N_2O_5$ (Karl Fischer H_2O 0.43%): C, 64.31; H, 7.76; N, 7.15. Found: C, 64.28; H, 7.77; N, 7.15.

RESULTS

Chemistry

Preparation of 4-(2'-di-*n*-propylaminoethyl)-5-methoxyindole (**14**) by a reaction sequence which exploits Claisen rearrangement of 5-allyloxyindole, subsequent oxidation of the allyl double bond of the 2,3-dihydro derivative of the rearrangement product (4-allyl-5-hydroxyindole), and a novel oxidative method for aromatization of 2,3-dihydroindole derivatives has been described in detail in a separate communication (9). This chemistry forms the basis for synthesis of the other target compounds (**12**, **15**, **16**). For preparation of water-soluble salts for pharmacological studies, the free bases of the target compounds were treated with fumaric acid. Compounds **12**, **14**, and **16** separated as the bifumarate salt, but **15** was isolated as the fumarate salt. Spectral data (NMR, MS) for all intermediates and final compounds were consistent with the proposed structures.

Pharmacology

All compounds (**12**, **14–16**) were much less potent/active than we predicted on the basis of our prior studies (10), which demonstrated that **13** is a potent and long-acting DA_2 receptor agonist. The compounds in the present study were no more than one-tenth as active as **13** (Table I). Hypotension and bradycardia induced by **13** were completely inhibited by pretreatment with sulpiride, but in the present study of **12** and **14–16**, sulpiride (2 μmol/kg, i.v.) was devoid of antagonist properties. The duration of hypotension and bradycardia produced by **12** and **14–16** was no longer than 5–10 min. The mechanism of the modest cardiovascular effects of **12** and **14–16** was not determined. An oxygen substituent on position 5 of the indole ring, adjacent to the aminoethyl side chain, is detrimental to dopaminergic agonist effects. It is noteworthy that a hydroxyl group positional isomer of **15**, 6-hydroxy-4-[2-(di-*n*-propylamino)ethyl]indole, is a potent/active dopaminergic agonist (11). The low order of pharmacological effect of **12** provides yet another example of the unpredictability of the effect of the "*p*-dimethoxy" moiety on dopaminergic agonism.

Table I. Influence of Indole Derivatives on Arterial Pressure and Heart Rate in Rats Anesthetized with Urethane

Compound No.	Dose	Mean Arterial Pressure Decrease[a]	Heart Rate Change[a]
	μg/kg, *i.v.*	$X \pm$ SEM	$X \pm$ SEM
12	100	13.5 ± 2.4	−10.7 ± 5
	300	21.5 ± 2.6	−22.5 ± 3.9
14	100	5.5 ± 1.6	−6.2[b]
	300	21.0 ± 2.1	−17.0 ± 3.7
15	100	9 ± 2.1	+5[b]
	300	17.0 ± 3.4	+17.0 ± 6.7
16	100	12.0 ± 2.0	−7[b]
	300	28.5 ± 1.7	−18.0 ± 1.7

[a] Sulpiride pretreatment, 500 μg/kg i.v., did not alter cardiovascular responses to the compounds.
[b] Responses were small and variable.

REFERENCES

1. J. G. Cannon. Dopamine agonists: Structure-activity relationships. *Prog. Drug Res.* 29:303–414 (1985).
2. S. P. Arneric, J. P. Long, D. B. Goodale, J. Mott, J. M. Laboski, and G. E. Gebhardt. RDS-127 (2-di-*n*-propylamino-4,7-dimethoxyindane): Central effects of a new dopamine receptor agonist. *J. Pharmacol. Exp. Ther.* 224:161–170 (1983).
3. R. D. Sindelar, J. Mott, C. F. Barfknecht, S. P. Arneric, J. R. Flynn, J. P. Long, and R. K. Bhatnagar. 2-Amino-4,7-dimethoxyindan derivatives: Synthesis and assessment of dopaminergic and cardiovascular actions. *J. Med. Chem.* 25:858–864 (1982).
4. R. M. De Marinis, D. H. Shah, R. F. Hall, J. P. Hieble, and R. G. Pendleton. α-Adrenergic agents. 2. Synthesis and α_1-agonist activity of 2-aminotetralins. *J. Med. Chem.* 25:136–141 (1982).
5. J. G. Cannon, V. E. D. Amoo, J. P. Long, R. K. Bhatnagar, and J. R. Flynn. *p*-Dimethoxy-substituted *trans*-octahydrobenzo[*f*]- and [*g*]quinolines: Synthesis and assessment of dopaminergic agonist effects. *J. Med. Chem.* 29:2529–2534 (1986).
6. S. P. Arneric, A. Roetker, J. P. Long, J. Mott, and C. F. Barfknecht. Effects of semirigid methoxamine analogs on vascular smooth muscle: Studies of methoxy-2-aminotetralin and 2-aminoindan derivatives. *Arch. Int. Pharmacodyn Ther.* 257:263–273 (1982).
7. J. G. Cannon, H. Jackson, J. P. Long, P. Leonard, and R. K. Bhatnagar. 5-HT_{1A}-receptor antagonism: N-Alkyl derivatives of (*R*)-(−)-8,11-dimethoxynoraporphine. *J. Med. Chem.* 32:1959–1962 (1989).
8. J. G. Cannon. The design of potential anti-parkinsonian drugs: What is the dopaminergic pharmacophore in ergot alkaloids? *Proc. Iowa Acad. Sci.* 93:169–174 (1986).
9. J. G. Cannon and I. Roufos. Synthetic route to 4-(2-aminoethyl)-5-hydroxyindole derivatives. *J. Heterocyc. Chem.* 27:2093–2095 (1990).
10. J. G. Cannon, B. J. Demopoulos, J. P. Long, J. R. Flynn, and F. M. Sharabi. Proposed dopaminergic pharmacophore of lergotrile, pergolide, and related ergot alkaloid derivatives. *J. Med. Chem.* 24:238–240 (1981).
11. J. G. Cannon, T. Lee, M. Ilhan, J. Koons, and J. P. Long. 6-Hydroxy-4-[2-(di-n-propylamino)ethyl]indole: Synthesis and dopaminergic actions. *J. Med. Chem.* 27:386–389 (1984).