Preparation and Pharmacological Characterization of *trans*-2-Amino-5(6)-fluoro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes as D_2-like Dopamine Receptor Agonists

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Received October 19, 2004

The present work reports the synthesis of *trans*-2-amino-5(6)-fluoro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (**4a**−**f**, **5a**−**f**) as a continuation of our studies to better understand the significance of the halo substituent in the *trans*-1-phenyl-2-aminoindane series and to extend knowledge of the monophenolic ligands of DA receptors. The affinity of the new compounds and related methoxylated precursors (**10**−**15** and **18**−**23**) was estimated in vitro by displacement of [^{3}H]SCH23390 (for D_1-like receptors) or [^{3}H]YM-09-151-2 (for D_2-like receptors) from homogenates of porcine striatal membranes. The results indicate that unsubstituted amines **4a**, **5a**, **10**, and **11** are poorly effective at DA receptors. The introduction of two *n*-propyl groups on the nitrogen atom (compounds **14**, **15**, **4c**, and **5c**) and *N*-allyl-*N*-methyl- or *N*-methyl-*N*-propyl- substitution (compounds **20**−**23**, **4e**, **4f**, **5e**, **5f**) increased the D_2-like affinities and selectivity. The D_2-like agonistic activity of selected compounds **15**, **20**, **21**, **4e**, **5c**, and **5e** was proved by evaluating their effects on the cyclic guanosine monophosphate (cGMP) content in rat neostriatal membranes. All tested compounds displayed a potential dopamine D_2-like agonist profile decreasing basal levels of cGMP. The selective D_2-like agonism of compounds **20** and **5e** was proved by their effects on basal striatal adenylyl cyclase activity.

Introduction

Investigations using molecular cloning technology established the existence of two families of dopamine (DA) receptors that are D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) on the basis of their ability to activate or inhibit the enzyme adenylyl cyclase.[1]

Intense research on the discovery of new dopaminergic agents has been stimulated by potential clinical usefulness of centrally acting DA receptor agonists and antagonists. In fact, several pathological conditions such as Parkinson's disease (PD), schizophrenia, and hyperprolactinemia have been linked to a dysfunction of dopaminergic transmission.[2] DA receptor agonists have been developed to alleviate the symptoms of PD, whereas DA receptor antagonists are effective in treatment of schizophrenia and other neurological and psychiatric disorders.[3] Most dopaminergic agents contain a catechol group that imparts activity but is also responsible for the low oral bioavailability of the compounds and for their sensitivity toward enzymatic degradation by catechol-*O*-methyl tranferase (COMT). For these reasons one approach to the development of centrally acting dopaminergic agents has been the preparation of noncatechol analogues of DA. The studies have been directed toward the synthesis of monohydroxylated compounds that do not suffer the drawback induced by catechol moiety. The results showed that the compounds, unlike DA, are resistant to degradation by COMT and cross the blood−brain barrier following peripheral administration.[4−7] Many fluorinated monophenolic compounds were prepared and evaluated for their dopaminergic properties on D_1-like and D_2-like receptors; the presence of the highly electronegative fluorine atom on the aromatic nucleous increases liposolubility, and the strong electronegative influence of fluorine could alter the physicochemical properties of the phenolic group and the affinity for DA receptors. Among these, 2-amino-6-fluoro-7-hydroxytetralin (**1**) was slightly selective for D_2-like receptors, while some N-substituted 2-[4(3)-fluoro-3(4)-hydroxyphenyl)]ethylamines (**2a**,**b**) showed some degree of selectivity for D_2-like receptors.[8,9] In contrast, Kozlik et al. showed that some substituted tetrahydroisoquinolines are selective for D_1-like over D_2-like receptors (with K_i of 0.18 and 450 nM, respectively, for the exemplified compound, **3**).[10]

In a previous paper we reported the synthesis and binding affinity of a series of *trans*-2-amino-5(6)-chloro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes with the aim of extending the knowledge of monophenolic ligands of DA receptors.[11] We observed that all the tested

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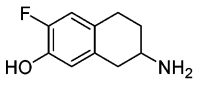
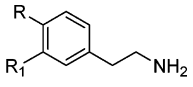
10.1021/jm040889k CCC: $30.25
Published on Web 03/09/2005

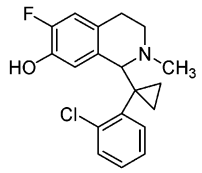
compounds were slightly effective at DA receptors, but they were altogether devoid of selectivity.



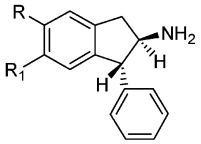
1



2a: R = OH; R_1 = F
2b: R = F; R_1 = OH



3



4a: R = OH; R_1 = F
5a: R = F; R_1 = OH

On the basis of these findings and in order to better understand the significance of the halo substituent in the aminoindane series, we report here data on the synthesis, characterization, and preliminary pharmacological evaluation of *trans*-2-amino-5(6)-fluoro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (**4a**, **5a**). The amino group was substituted with methyl, propyl, and allyl groups in view of the fact that they can modulate affinity for DA receptor subtypes.[12]

Chemistry

The *trans*-2-amino-5(6)-fluoro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes (**4a**−**f**, **5a**−**f**) were synthesized according to the procedures reported in our previous papers (Schemes 1−4).[5,11]

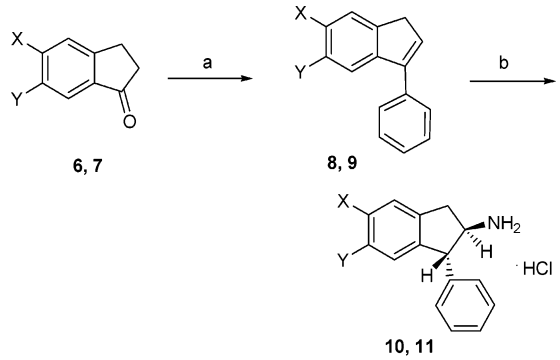
6-Fluoro-5-methoxyindan-1-one (**6**) was prepared using standard protocol.[13] 5-Fluoro-6-methoxyindan-1-one (**7**) was obtained from 3-fluoro-4-methoxybenzaldehyde as previously described.[14]

The synthesis of the new compounds **10** and **11** is shown in Scheme 1. When phenylmagnesium bromide was reacted with 6-fluoro-5-methoxy (or 5-fluoro-6-methoxy)indan-1-one (**6**, **7**), the 6-fluoro-5-methoxy (or 5-fluoro-6-methoxy)-3-phenyl-1*H*-indenes (**8**, **9**) were obtained. Treatment of **8** and **9** with $NaBH_4/BF_3$ and hydroxylamine *O*-sulfonic acid gave compounds **10** and **11**.[15] The trans configuration of **10** and **11** was established with the cis addition mechanism of the diborane and ^1H NOE (nuclear Overhauser effect) difference experiments. A strong positive NOE was found between the amino substituent and the proton at the 1-position, indicating that these groups are located on the same side of the indane nucleus. The di-*n*-propyl derivatives were obtained by alkylation of the free bases **10** and **11** with the $NaBH_4$−propionic acid complex.[16] The *N*-methyl-*N*-*n*-propyl and *N*-allyl-*N*-methyl derivatives were obtained as outlined in Scheme 4. When the amines **10**−**14**, **18**, and **19** were treated with HBr/CH_3-COOH 1:1, the phenols were obtained. Compounds **4e**,**f** and **5e**,**f** were synthesized by reaction of **20**−**23** with methionine and methanesulfonic acid.[17]

Results and Discussion

The potency and selectivity of the compounds **4a**−**f** and **5a**−**f** were evaluated according to their "in vitro"

Scheme 1[a]



6, 7 **8, 9** **10, 11**

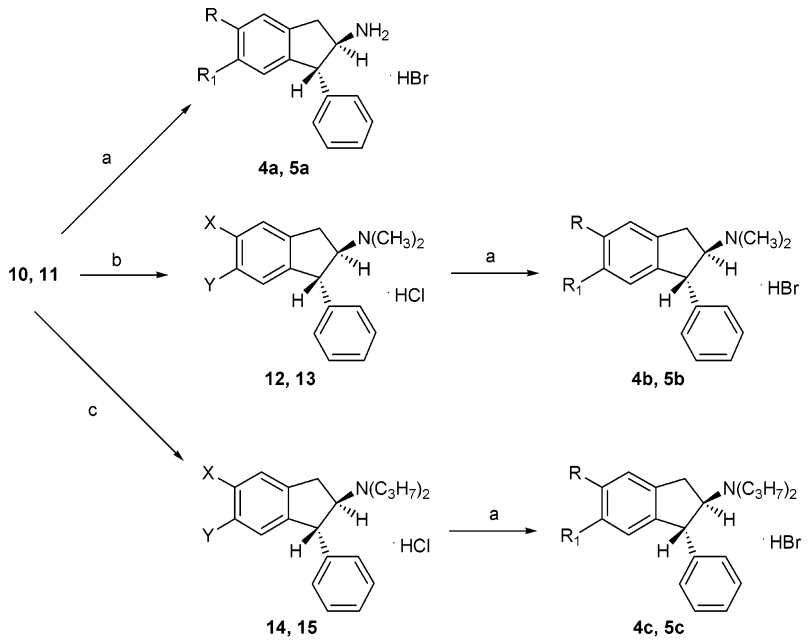
6, 8, 10: X=OCH_3; Y=F **7, 9, 11**: X=F; Y=OCH_3

[a] Reagents: (a) C_6H_5MgBr, anhydrous Et_2O, anhydrous THF; (b) $NaBH_4/BF_3$, H_2NOSO_3H, diglyme, absolute EtOH, 37% HCl.

affinity for the D_1 and D_2 receptors in ligand displacement assays. The affinity is referred to as D_1-like and D_2-like for DA receptors, using porcine striatal membranes as the tissue source. [^{3}H]SCH23390 and [^{3}H]-YM09-151-2 were used as radioligands for the D_1 and D_2 receptors, respectively. The affinity of all methoxylated precursors (**10**−**15** and **18**−**23**) was also evaluated. The efficacy of compounds **15**, **20**, **21**, **4e**, **5c**, and **5e**, having the greatest affinity and selectivity for D_2-like receptors, was examined "in vitro" by evaluating their effects on cGMP content in the rat neostriatal membranes to assess their agonist or antagonist activity. Previous studies indicated that striatal cGMP content was positively controlled by D_1 agonism and negatively controlled by, or unlinked to, the D_2 receptors.[18] In our investigation, the procedure for the cGMP assay was performed using a modified HPLC method previously proposed by Spoto et al.[19] The binding studies results (see Table 1) indicate that the unsubstituted amines **10**, **11**, **4a**, and **5a** were poorly effective and, like DA, are not able to discriminate between the two subtypes of DA receptors. The secondary amines **18**, **19**, **4d**, and **5d** were slightly effective for displacing both [^{3}H]SCH23390 and [^{3}H]YM09-151-2 from D_1-like and D_2-like binding sites, respectively. The introduction of two alkyl substituents on the amino group influenced in a different way the affinity for both DA receptor families. Dimethylation of amines **10**, **11**, **4a**, and **5a** did not markedly affect D_1 and D_2 affinity, while dipropylation of unsubstituted amines (compounds **14** and **15** with **4c** and **5c**, respectively) increased only D_2 affinity (about 150-fold for compound **15**). The *N*-allyl-*N*-methyl and *N*-methyl-*N*-*n*-propyl substitution increased D_2 affinity as well, providing compounds **20**−**23**, **4e**, **4f**, **5e**, and **5f** with moderate selectivity. We previously showed that *trans*-2-amino-6-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene derivatives represent a class of selective D_1 ligands lacking a catechol group;[5] thus, in this evaluation it is noted that introduction of a fluorine atom in the 5- or 6-position of the same aminoindane series can modify DA receptor selectivity, providing compounds with affinity toward D_2-like receptors. Thus, fluoro substitution represents an important gain in D_2-like affinity and selectivity for fluoroindane derivatives over the chloroindanes or derivatives previously investigated.[5,11]

As previously mentioned, to verify whether compounds **15**, **20**, **21**, **4e**, **5c**, and **5e** behave as D_2-like

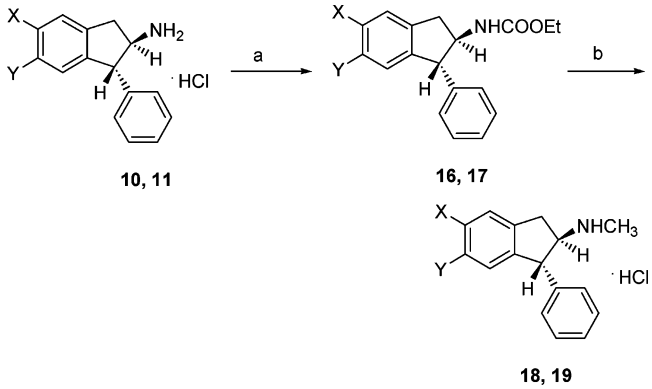
Scheme 2[a]



12, 14: X=OCH_3; Y=F **13, 15**: X=F; Y=OCH_3 **4 a-c**: R=OH; R_1=F **5 a-c**: R=F; R_1=OH

[a] Reagents: (a) CH_3COOH/HBr 48%; (b) HCOOH, HCHO 38%, absolute EtOH, 37% HCl; (c) C_2H_5COOH, $NaBH_4$, anhydrous benzene, absolute EtOH, 37% HCl.

Scheme 3[a]



16, **18**: X=OCH_3; Y=F **17**, **19**: X=F; Y=OCH_3

[a] Reagents: (a) $ClCOOC_2H_5$, Et_3N, anhydrous Et_2O; (b) $LiAlH_4$, anhydrous Et_2O, absolute EtOH, 37% HCl.

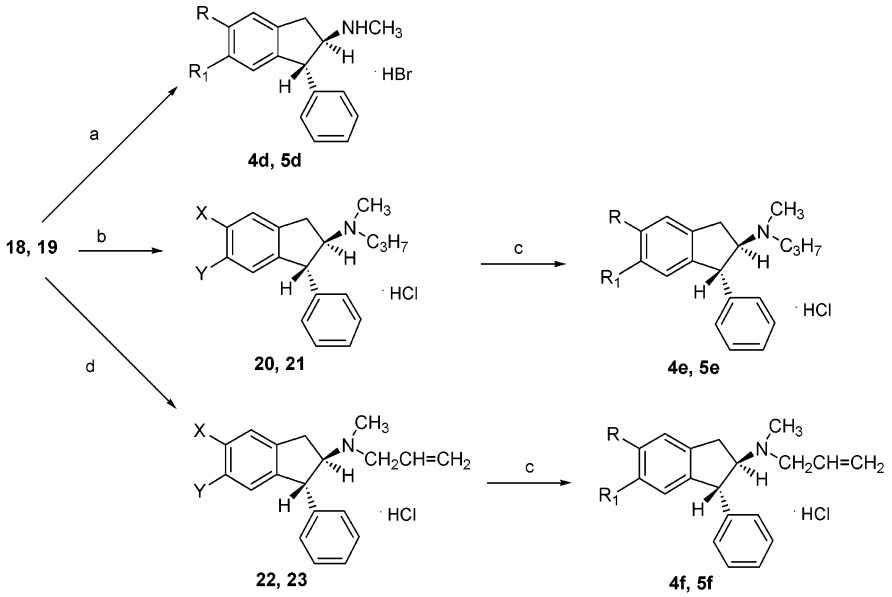
receptor agonists or antagonists, we performed functional guanylate cyclase studies in rat striatum synaptic membranes. To better characterize the guanylate cyclase assay, DA, quinpirole (D_2-like agonist), RU24213 (D_2-like agonist), sulpiride (D_2-like antagonist), SKF38393 (D_1-like agonist), and SCH23390 (D_1-like antagonist) were used as reference compounds. The obtained data are shown in Table 2 and Figure 1 (compounds **15**, **20**, **21**, **4e**, **5c**, **5e**). All of the tested compounds were able to decrease basal levels of cGMP, for which reason the mentioned derivatives had comparable potential D_2-like agonistic activity. In fact, in the same assay, although the D_2-like selective agonist quinpirole did not significantly alter cGMP levels (data not shown), RU24213 produced up to a 65% dose-related decrease in neostriatal cGMP concentration whereas D_2-like antagonism with sulpiride increased cGMP by 60%. Furthermore, in our studies, compound **5e** decreased in a concentration-dependent manner the cGMP basal level by 85% at 10 μM concentration and behaved as the most active D_2-like agonist. Among these compounds **20** and **5e** were chosen for a more detailed investigation of their dopaminergic activity at rat neostriatal membrane preparation. For these reasons the D_2-like agonistic activity was also proved using a test involving the effect of our compounds on basal striatal adenylyl cyclase activity.[20] This brain region contains D_1-like receptors associated with stimulation of membrane adenylate cyclase and cyclic adenosine monophosphate (cAMP) formation and contains D_2-like receptors linked to inhibition of enzyme activity and therefore mediating reduction of intracellular cAMP levels.[21−23] Both DA and RU24213, used as reference compounds, inhibited basal adenilate cyclase activity, with a maximal 25% inhibition at 100 μM for RU24213. In this assay, compounds **20** and **5e** displayed a D_2-like agonistic profile (Table 3). In particular compound **5e** was the most active for inhibiting in a concentration-dependent manner the basal adenylate cyclase activity, decreasing the cAMP basal concentration by 30% at 100 μM.

In conclusion, this report describes a series of *trans*-2-amino-5(6)-fluoro-6(5)-hydroxy-1-phenyl-2,3-dihydro-1*H*-indenes that in binding assays demonstrated affinity for both D_1-like and D_2-like DA receptors. On the other hand, the *N*-allyl-*N*-methyl and di-*n*-propyl derivatives showed affinity and selectivity for D_2-like receptors. In a guanylate cyclase assay the compounds showed high potential D_2-like agonistic activity. In the adenilate cyclase assay, selected compounds **20** and **5e** displayed an inhibitory profile and behaved as D_2-like agonists. From this series of evaluations, compound **5e** emerged as the derivative with the best overall D_2-like agonistic profile.

Experimental Section

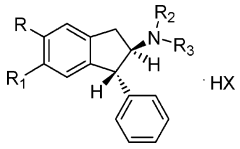
Melting points (mp) were determined on a Buchi B-540 apparatus and are uncorrected. Microanalyses were performed

Scheme 4[a]



[a] Reagents: (a) CH_3COOH/HBr 48%; (b) *n*-C_3H_7I, K_2CO_3, acetone; (c) CH_3SO_3H, methionine, HCl; (d) $CH_2{=}CH{-}CH_2Br$, K_2CO_3, absolute EtOH.

Table 1. Inhibition of [^{3}H]SCH23390 (D_1-like) and [^{3}H]YM-09-151-2 (D_2-like) Binding to Porcine Striatal Membranes of *trans*-2-Amino-6-fluoro-5-hydroxy-(or 5-fluoro-6-hydroxy)-1-phenyl-2,3-dihydro-1*H*-indenes **4a**−**f** and **5a**−**f** and Their Methoxy Derivatives **10**−**15** and **18**−**23**



						K_i (μM)[a]	
compd	R	R_1	R_2	R_3	X	D_1-like	D_2-like
10	OCH_3	F	H	H	Cl	16 ± 2.1	12 ± 2.2
12	OCH_3	F	CH_3	CH_3	Cl	7.6 ± 0.6	4.3 ± 0.57
14	OCH_3	F	*n*-C_3H_7	*n*-C_3H_7	Cl	83 ± 4.6	0.55 ± 0.07
18	OCH_3	F	H	CH_3	Cl	71 ± 3.9	3.1 ± 0.3
20	OCH_3	F	*n*-C_3H_7	CH_3	Cl	16 ± 3.2	0.27 ± 0.02
22	OCH_3	F	$CH_2CH{=}CH_2$	CH_3	Cl	15 ± 1.4	0.31 ± 0.02
11	F	OCH_3	H	H	Cl	19 ± 1.8	17 ± 0.89
13	F	OCH_3	CH_3	CH_3	Cl	16 ± 1.5	1.9 ± 0.12
15	F	OCH_3	*n*-C_3H_7	*n*-C_3H_7	Cl	32 ± 2.8	0.17 ± 0.03
19	F	OCH_3	H	CH_3	Cl	19 ± 1.3	2.6 ±0.10
21	F	OCH_3	*n*-C_3H_7	CH_3	Cl	20 ± 1.9	0.48 ±.04
23	F	OCH_3	$CH_2CH{=}CH_2$	CH_3	Cl	19 ± 1.3	0.64 ± 0.05
4a	OH	F	H	H	Br	8.3 ± 0.4	15 ± 0.8
4b	OH	F	CH_3	CH_3	Br	5.9 ± 0.5	NA[b]
4c	OH	F	*n*-C_3H_7	*n*-C_3H_7	Br	54 ± 2.9	12 ± 0.6
4d	OH	F	H	CH_3	Br	7.2 ± 0.6	4.3 ± 0.4
4e	OH	F	*n*-C_3H_7	CH_3	Cl	12 ± 0.8	0.24 ± 0.01
4f	OH	F	$CH_2CH{=}CH_2$	CH_3	Cl	9.0 ± 0.3	0.64 ± 0.04
5a	F	OH	H	H	Br	9.6 ± 0.7	19 ± 0.8
5b	F	OH	CH_3	CH_3	Br	7.7 ± 0.4	4.5 ± 0.2
5c	F	OH	*n*-C_3H_7	*n*-C_3H_7	Br	26 ± 1.2	0.92 ± 0.05
5d	F	OH	H	CH_3	Br	9.6 ± 0.8	5.1 ± 0.3
5e	F	OH	*n*-C_3H_7	CH_3	Cl	16 ± 0.8	0.65 ± 0.04
5f	F	OH	$CH_2CH{=}CH_2$	CH_3	Cl	13 ± 0.9	0.96 ± 0.07
dopamine						2.44 ± 0.14	3.31 ± 0.43
SCH23390						$8.1 \times 10^{-3} \pm 0.5 \times 10^{-3}$	NT[c]
quinpirole						NT[c]	1.26 ± 0.11

[a] The K_i values are mean values ± SEM of at least three experiments. [b] NA = not active until 1×10^{-5} M. [c] NT = not tested.

on a 1106 Carlo Erba CHN analyzer, and the results were within 0.4% of the calculated values. ^{1}H NMR spectra were recorded on a Varian VXR 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si). The IR spectra were obtained on a Perkin-Elmer FTIR 1600 spectrometer as Nujol mulls or liquid films. The identity of all new compounds was confirmed by elemental analysis and NMR data. Homo-

Table 2. Striatal cGMP Content (Basal Level 11.82 ± 0.59 pmol/mg Protein) in Rat Neostriatal Membranes after the Incubation of DA, SKF38393, RU24213, SCH23390, Sulpiride, Methoxylated Compounds **15**, **20**, and **21** and Hydroxylated Compounds **4e**, **5c**, and **5e**, Each at 0.1, 1, and 10 μM[a]

	striatal cGMP content (pmol/mg protein)		
compd	0.1 μM	1.0 μM	10 μM
DA	11.70 ± 0.59	6.15 ± 0.25*	4.02 ± 0.12**
SKF38393	12.41 ± 0.62	17.41 ± 0.52*	18.20 ± 0.55**
SCH23390	11.47 ± 0.69	6.62 ± 0.26*	6.15 ± 0.25*
RU24213	10.40 ± 0.62	7.45 ± 0.45*	3.78 ± 0.17**
SULPIRIDE	12.53 ± 0.63	17.26 ± 0.69*	17.73 ± 0.53*
15	10.64 ± 0.53	6.97 ± 0.28*	5.79 ± 0.12*
21	10.40 ± 0.42	6.86 ± 0.27*	3.90 ± 0.12**
20	11.23 ± 0.45	4.96 ± 0.20**	3.78 ± 0.15**
5e	10.87 ± 0.54	5.79 ± 0.23*	1.78 ± 0.09**
5c	11.58 ± 0.58	7.32 ± 0.29*	4.37 ± 0.13**
4e	11.47 ± 0.57	7.45 ± 0.30*	5.56 ± 0.17**

[a] Data represent the mean ± SEM of triplicate determinations: (*) $p < 0.05$ vs control; (**) $p < 0.01$ vs control.

geneity was confirmed by TLC on silica gel Merck 60 F_{254}. Solutions were routinely dried over anhydrous sodium sulfate prior to evaporation. Chromatographic purifications were performed using Merck 60 70−230 mesh ASTM silica gel column.

6-Fluoro-5-methoxy-1-phenyl-1*H*-indene (8). To the magnetically stirred suspension of 0.97 g (40 mmol) of magnesium, a crystal of iodine, and 20 mL of anhydrous Et_2O was added 5 mL of a solution of bromobenzene, obtained from 6.34 g (40 mmol) of bromobenzene in 100 mL of anhydrous Et_2O. The solution became muddy by heating, then at room temperature the remaining solution of bromobenzene was added dropwise. The reaction mixture was refluxed for 3 h. After the mixture cooled, a solution of 6-fluoro-5-methoxyindan-1-one (**6**) (5.4 g, 30 mmol) in 45 mL of anhydrous THF was added. The reaction mixture was refluxed overnight. After the mixture cooled, 64 g of ice and 1.6 g of NH_4Cl were added and the mixture was stirred for 5 min. The resulting aqueous solution was acidified with 30 mL of 2 N HCl and extracted with Et_2O. The organic solution was dried and filtered. Removal of the solvent afforded a product that was purified by column chromatography with cyclohexane/AcOEt 9.5:0.5 as eluent (R_f = 0.44): yield 84%. ^{1}H NMR ($CDCl_3$): δ 7.63−7.18 (m, 7H, ArH), 6.53 (t, 1H, J = 2.05 Hz, =CH−), 3.94 (s, 3H, OCH_3), 3.47 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 153.73 and 150.53 (d, 1C, J(C−F) = 963 Hz, C−F), 145.94 and 145.75 (d, 1C, J(C−F) = 46 Hz, C−OCH_3), 140.74 and 140.70 (d, 1C, J(C−F) = 12 Hz, =C−Ar), 137.21 and 137.11 (d, 1C, J(C−F) = 30 Hz, C−C=), 136.00 (s, 1C, C−CH_2), 130.42 (s, 1C, Ar), 129.01 (s, 2C, Ar), 128.93 (s, 1C, =CH), 128.00 (s, 2C, Ar), 127.67 (s, 1C, Ar), 110.16 and 110.13 (d, lC, J(C−F) = 9 Hz, CH−C−OCH_3), 108.53 and 108.26 (d, 1C, J(C−F) = 81 Hz, CH−C−F), 56.92 (s, 1C, OCH_3), 38.39 (s, 1C, CH_2). Anal. (C_{16} H_{13}FO) C, H.

***trans*-2-Amino-6-fluoro-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (10).** A dry flask equipped with a dropping funnel, condenser, and magnetic stirrer was flushed with nitrogen. A solution of 0.4 g (10.3 mmol) of $NaBH_4$ in 15 mL of diglyme was introduced, followed by 6.0 g (25 mmol) of **8**. The flask was immersed in an ice−water bath, and the BF_3·Et_2O (1.95 g, 13.75 mmol) was added dropwise. The solution was then stirred at room temperature for 3 h. After this time NH_2OSO_3H (3.2 g, 27.5 mmol) in 15 mL of diglyme was added and the solution was heated to 80 °C for 3 h. The solution was cooled, treated with 10 mL of concentrated HCl, and then poured into 100 mL of water. The acidic aqueous phase was extracted with Et_2O to remove diglyme and residual boronic acid. The solution was then made strongly alkaline with 2 N NaOH, and the amine was extracted with Et_2O. The residue was purified by column chromatography with $CHCl_3$/CH_3OH 6:1 as eluent (R_f = 0.5). Then it was dissolved in EtOH (11 mL) and 37% HCl (0.5 mL) was added: mp 231−233 °C; yield 35%. IR ν_{max} (KBr): 3422 (NH_3^+), 2943 (OCH_3) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.66 (bs, 3H, NH_3^+), 7.37−7.17 (m, 6H, ArH), 6.72 (m, 1H, ArH), 4.52 (d, 1H, J = 4.69 Hz, CH−Ar), 3.89 (m, 1H, CH−N^+), 3.83 (s, 3H, OCH_3), 3.39 (dd, 1H, J_1 = 16.12 Hz, J_2 = 7.62 Hz, CH_2), 3.03 (dd, 1H, J_1 = 16.12 Hz, J_2 = 5.27 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ 153.60 and 150.38 (d, 1C, J(C−F) = 966 Hz, C−F), 147.80 and 147.65 (d, 1C, J(C−F) = 45 Hz, C−OCH_3), 147.76 (s, 1C, Ar), 136.31 and 136.07 (d, 1C, J(C−F) = 72 Hz, C−CH−Ar), 135.64 and 135.55 (d, 1C, J(C−F) = 27 Hz, C−CH_2), 129.42 (s, 2C, Ar), 128.71 (s, 2C, Ar), 127.91 (s, 1C, Ar), 112.91 and 112.66 (d, 1C, J(C−F) = 75 Hz, CH−C−F), 110.74 and 110.49 (d, 1C, J(C−F) = 75 Hz, CH−C−OCH_3), 59.35 (s, 1C, CH−N^+), 56.83 (s, 1C, OCH_3), 55.32 (s, 1C, CH−Ar), 36.97 (s, l C, CH_2). Anal. ($C_{16}H_{17}$ClFNO) C, H, N.

***trans*-2-Amino-6-fluoro-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrobromide (4a).** A stirred solution of the methoxylated amine **10** (1.5 g, 5 mmol), acetic acid (10 mL), and freshly distilled 48% HBr (10 mL) was refluxed for 4 h. The solution was evaporated "in vacuo"; the residue was dissolved in absolute EtOH and evaporated. The product was recrystallized from AcOEt/Et_2O: mp 213-215 °C; yield 97%. IR ν_{max} (KBr): 3385 (OH), 3068 (NH_3^+) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.82 (s, 1H, OH), 8.25 (bs, 3H, NH_3^+), 7.38−7.15 (m, 5H, ArH), 6.93 (m, 1H, ArH), 6.63 (m, 1H, ArH), 4.34 (d, 1H, J = 5.27 Hz, CH−Ar), 3.91 (m, 1H, CH−N^+), 3.34 (dd, 1H, J_1 = 16.85 Hz, J_2 = 7.62 Hz, CH_2), 2.88 (dd, 1H, J_1 = 16.85 Hz, J_2 = 4.10 Hz, CH_2). ^{13}C NMR (DMSO-d_6): δ 153.17 and 149.99 (d, 1C, J(C−F) = 954 Hz, C−F), 145.52 and 145.35 (d, 1C, J(C−F) = 51 Hz, C−OH), 141.84 (s, 1C, Ar), 139.96 and 139.81 (d, 1C, J(C−F) = 46 Hz, C−CH−Ar), 134.31 and 134.20 (d, 1C, J(C−F) = 33 Hz, C−CH_2), 129.44 (s, 2C, Ar), 128.69 (s, 2C, Ar), 127.93 (s, 1C, Ar), 114.21 and 114.12 (d, 1C, J(C−F) = 27 Hz, CH−C−OH), 113.04 and 112.78 (d, 1C, J(C−F) = 78 Hz, CH−C−F), 59.29 (s, 1C, CH−N^+), 55.40 (s, 1C, CH−Ar), 36.73 (s, 1C, CH_2). Anal. ($C_{15}H_{15}$BrFNO) C, H, N.

***trans*-*N*,*N*-Dimethyl-2-amino-6-fluoro-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (12).** A suspension of methoxylated amine **10** (0.9 g, 3 mmol) in 12 mL of 95% formic acid and 8 mL of 38% formaldehyde was stirred at reflux for 4 h, during which time a solution formed. The volatiles were evaporated "in vacuo", and the residue was dissolved in CH_2Cl_2 and partitioned with saturated aqueous $NaHCO_3$. The organic phase was dried and evaporated to afford a crude product that was purified by column chromatography with $CHCl_3$/CH_3OH 6:1 as eluent (R_f = 0.70). Then it was dissolved in EtOH (11 mL) and 37% HCl (0.5 mL) was added: mp 181−182 °C; yield 80%. IR ν_{max} (KBr): 3446 (NH^+), 2939 (OCH_3) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.35 (bs, 1H, NH^+), 7.38−7.24 (m, 5H, ArH), 7.14 (m, 1H, ArH), 6.54 (m, 1H, ArH), 4.81 (d, 1H, J = 5.49 Hz, CH−Ar), 4.28 (m, 1H, CH−N^+), 3.82 (s, 3H, OCH_3), 3.46 (dd, 1H, J_1 = 16.80 Hz, J_2 = 7.80 Hz, CH_2), 3.36 (dd, 1H, J_1 = 16.80 Hz, J_2 = 7.62 Hz, CH_2), 2.71 and 2.62 (two s, 6H, CH_3). ^{13}C NMR (DMSO-d_6): δ 153.61 and 150.38 (d, 1C, J(C−F) = 969 Hz, C−F), 147.87 and 147.72 (d, 1C, J(C−F) = 45 Hz, C−OCH_3), 142.83 (s, 1C, Ar), 136.32 and 136.23 (d, 1C, J(C−F) = 27 Hz, C−CH−Ar), 135.64 and 135.60 (d, 1C, J(C−F) = 12 Hz, C−CH_2), 129.63 (s, 2C, Ar), 128.67 (s, 2C, Ar), 127.95 (s, 1C, Ar), 112.54 and 112.29 (d, 1C, J(C−F) = 75 Hz, CH−C−F), 110.32 and 110.16 (d, 1C, J(C−F) = 65 Hz, CH−C−OCH_3), 72.91 (s, 1C, CH−N^+), 56.81 (s, 1C, OCH_3), 52.43 (s, 1C, CH−Ar), 40.48 and 40.20 (two s, 2C, CH_3), 34.08 (s, 1C, CH_2). Anal. ($C_{18}H_{21}$ClFNO) C, H, N.

***trans*-*N*,*N*-Dimethyl-2-amino-6-fluoro-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrobromide (4b).** The methoxylated dimethylamine **12** was converted into **4b** according to the procedure described for the synthesis of **4a**: mp 213-215 °C; yield 70%. IR ν_{max} (KBr): 3297 (OH), 2950 (NH^+) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H, OH), 9.87 (bs, 1H, NH^+), 7.36−7.23 (m, 5H, ArH), 6.91 (m, 1H, ArH), 6.48 (m, 1H, ArH), 4.69 (d, 1H, J = 4.39 Hz, CH−Ar), 4.27 (m, 1H, CH−N^+), 3.40 (dd, 1H, J_1 = 17.31 Hz, J_2 = 7.69 Hz, CH_2), 3.25 (dd, 1H, J_1 = 17.31 Hz, J_2= 4.13 Hz, CH_2), 2.76 and 2.66 (two s, 6H, CH_3). ^{13}C NMR (DMSO-d_6): δ 153.17 and 149.98 (d, 1C, J(C−F) = 957 Hz, C−F), 145.62 and 145.44 (d, 1C, J(C−F) = 54 Hz, C−OH), 142.90 (s, 1C, Ar), 135.51 and 135.42 (d, 1C,

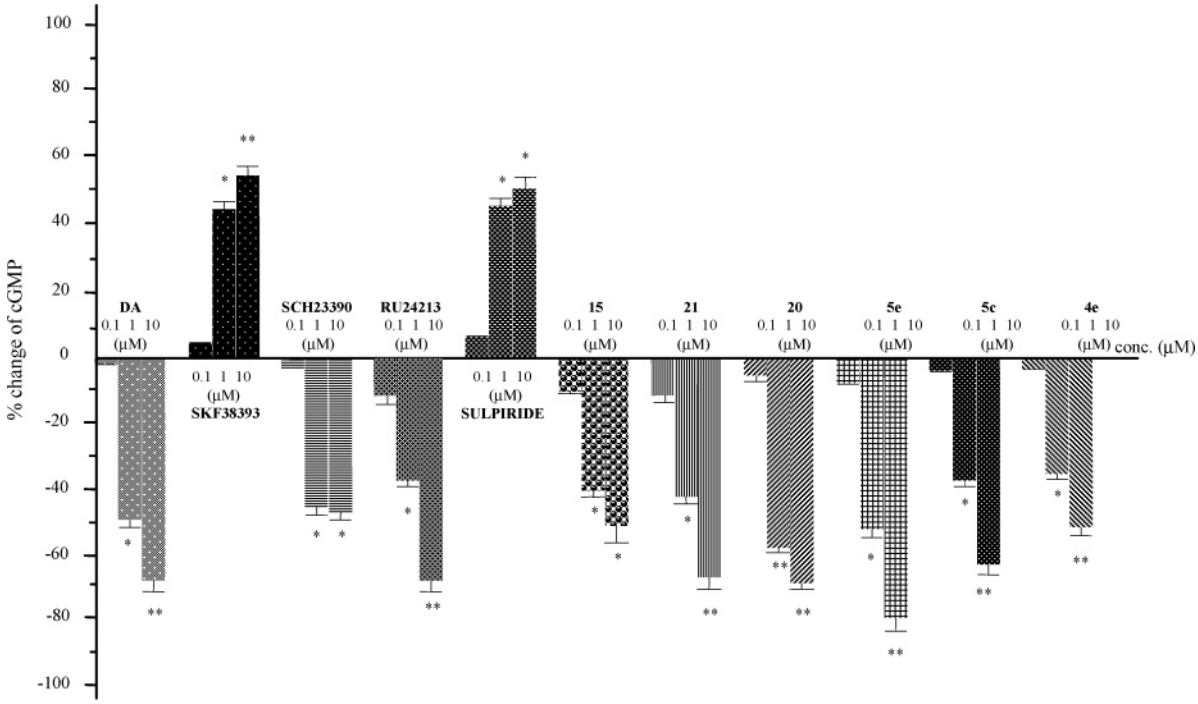


Figure 1. Percent variation in the concentration of cGMP in rat neostriatal membranes of the incubation of DA, SKF38393, SCH23390, RU24213, sulpiride, methoxylated compounds **15**, **21**, **20**, and hydroxylated compounds **4e**, **5a**, and **5e**, each at 0.1, 1, and 10 μM. Data represent the mean ± SEM of triplicate determinations: (*) $p < 0.05$ vs control; (**) $p < 0.01$ vs control.

Table 3. Striatal cAMP Content (Basal Level 105.70 ± 8.5 pmol/mg Protein) in Rat Neostriatal Membranes after the Incubation of RU24213, Methoxylated Compound **20**, and Hydroxylated Compound **5e**, Each at 1, 10, and 100 μM[a]

	striatal cAMP content (pmol/mg protein)		
compd	1 μM	10 μM	100 μM
DA	95.13 ± 3.4	89.85 ± 3.9*	85.62 ± 4.2*
RU24213	103.59 ± 5.2	93.13 ± 4.3*	79.27 ± 3.9*
20	104.64 ± 4.0	102.53 ± 4.3	84.56 ± 2.7*
5e	102.53 ± 5.2	93.02 ± 4.2*	74.42 ± 2.8**

[a] Data are the mean values ± SEM of triplicate determinations: (*) $p < 0.05$ vs control; (**) $p < 0.01$ vs control.

J(C−F) = 27 Hz, C−CH−Ar), 134.94 and 134.85 (d, 1C, J(C−F) = 27 Hz, C−CH_2), 129.61 (s, 2C, Ar), 128.63 (s, 2C, Ar), 127.93 (s, 1C, Ar), 113.66 and 113.59 (d, 1C, J(C−F) = 22 Hz, CH−C−OH), 112.72 and 112.46 (d, 1C, J(C−F) = 78 Hz, CH−C−F), 73.04 (s, 1C, CH−N^+), 52.33 (s, 1C, CH−Ar), 40.48 and 40.21 (two s, 2C, CH_3), 33.62 (s, 1C, CH_2). Anal. ($C_{17}H_{19}BrFNO$) C, H, N.

***trans*-*N*,*N*-Di-*n*-propyl-2-amino-6-fluoro-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrocloride (14).** To the magnetically stirred solution of amine **10** (2.5 g, 8.4 mmol) in anhydrous benzene (40 mL) was added $NaBH_4$ (3.15 g, 84 mmol) and then propionic acid (10.4 g, 140 mmol). The mixture was refluxed for 3 h and after cooling was basified with 2 N NaOH. The organic phase was evaporated, and the oily residue was purified by column chromatography with $CHCl_3$/CH_3OH 6:1 as eluent. Then it was dissolved in EtOH (11 mL) and 37% HCl (0.5 mL) was added: mp 75−77 °C; yield 60%. IR ν_{max} (KBr): 3426 (NH^+), 2928 (OCH_3) cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.67 (bs, 1H, NH^+), 7.40−7.11 (m, 6H, ArH), 6.39 (m, 1H, ArH), 4.89 (d, 1H, J = 7.03 Hz, CH−Ar), 4.50 (m, 1H, CH−N^+), 3.82 (s, 3H, OCH_3), 3.51 (dd, 1H, J_1 = 14.07 Hz, J_2 = 7.04 Hz, CH_2), 3.37 (dd, 1H, J_1 = 14.07 Hz, J_2 = 7.03 Hz, CH_2), 2.87 and 2.83 (two m, 4H, CH_2−N^+), 1.60 and 1.29 (two m, 4H, CH_2−C−N^+), 0.82 and 0.49 (two t, 6H, CH_3). ^{13}C NMR (DMSO-d_6): δ 156.82 and 153.60 (d, 1C, J(C−F) = 965 Hz, C−F), 147.64 and 147.48 (d, 1C, J(C−F) = 48 Hz, C−OCH_3), 143.00 (s, l C, Ar), 136.72 and 136.58 (d, l C, J(C−F) = 42 Hz, C−CH−Ar), 135.30 and 135.18 (d, 1C, J(C−F) = 36 Hz, C−CH_2), 129.68 (s, 2C, Ar), 128.86 (s, 2C, Ar), 128.04 (s, 1 C, Ar), 112.51 and 112.27 (d, 1C, J(C−F) = 73 Hz, CH−C−F), 110.12 and 110.01 (d, 1C, J(C−F) = 33 Hz, CH−C−OCH_3), 75.80 (s, 1C, CH−N^+), 70.14 and 69.81 (two s, 2C, CH_2−N^+), 56.84 (s, l C, OCH_3), 52.57 (s, 1C, CH−Ar), 34.94 (s, 1C, CH_2), 17.38 and 16.39 (two s, 2C, CH_2−C−N^+), 11.68 and 11.00 (two s, 2C, CH_3). Anal. ($C_{22}H_{29}ClFNO$) C, H, N.

***trans*-*N*,*N*-Di-*n*-propyl-2-amino-6-fluoro-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrobromide (4c).** The methoxylated dipropylamine **14** was converted into hydroxylated **4c** according to the procedure described for the synthesis of **4a**: mp 145−147 °C; yield 67%. IR ν_{max} (KBr): 3382 (OH), 3162 (NH^+) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.88 (s, 1H, OH), 9.75 (bs, 1H, NH^+), 7.38−7.32 (m, 5H, ArH), 6.89 (m, 1H, ArH), 6.34 (m, 1H, ArH), 4.66 (d, 1H, J = 7.04 Hz, CH−Ar), 4.44 (m, 1H, CH−N^+), 3.54 (dd, 1H, J_1 = 16.41 Hz, J_2 = 7.04 Hz, CH_2), 3.35 (dd, 1H, J_1 = 16.41 Hz, J_2 = 6.44 Hz, CH_2), 3.03 and 2.49 (two m, 4H, CH_2−N^+), 1.54 and 1.25 (two m, 4H, CH_2−C−N^+), 0.83 and 0.57 (two t, 6H, CH_3). ^{13}C NMR (DMSO-d_6): δ 154.49 and 151.29 (d, 1C, J(C−F) = 960 Hz, C−F), 145.34 and 145.18 (d, 1C, J(C−F) = 48 Hz, C−OH), 143.02 (s, 1C, Ar), 134.97 and 134.82 (d, 1C, J(C−F) = 45 Hz, C−CH−Ar), 131.70 and 131.62 (d, 1C, J(C−F) = 24 Hz, C−CH_2), 129.67 (s, 2C, Ar), 128.78 (s, 2C, Ar), 128.06 (s, 1C, Ar), 113.59 and 113.27 (d, 1C, J(C−F) = 95 Hz, CH−C−F), 112.45 and 112.34 (d, 1C, J(C−F) = 32 Hz, CH−C−OH), 70.06 (s, 1C, CH−N^+), 53.01 (s, 1C, CH−Ar), 52.50 and 52.19 (two s, 2C, CH_2−N^+), 34.58 (s, 1C, CH_2), 17.87 and 17.00 (two s, 2C, CH_2−C−N^+), 11.52 and 11.04 (two s, 2C, CH_3). Anal. ($C_{21}H_{27}BrFNO$) C, H, N.

***trans*-6-Fluoro-5-methoxy-1-phenyl-2-[(ethoxycarbonyl)amino]-2,3-dihydro-1*H*-indene (16).** A solution of ethyl chloroformate (1.18 g, 11 mmol) in anhydrous Et_2O (15 mL) was added dropwise to a solution of amine **10** (3.2 g, 11 mmol) in anhydrous Et_2O (70 mL) and triethylamine (3.1 mL, 22 mmol) and was cooled at 0 °C. The reaction mixture was allowed to reach room temperature and then was stirred for 1 h. Water was then added, and the aqueous solution was extracted with $CHCl_3$. The combined organic phases were dried and evaporated. The solid residue was recrystallized from AcOEt: mp 123−125 °C; yield 75%. IR ν_{max} (KBr): 3310 (NH), l675 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.34 (bs, 1H, NH), 7.30−

7.05 (m, 5H, ArH), 6.87 (m, 1H, ArH), 6.67 (m, 1H, ArH), 5.01 (m, 1H, CH−N), 4.34 (d, 1H, J = 6.45 Hz, CH−Ar), 4.09 (m, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 3.36 (dd, 1H, J_1 = 15.24 Hz, J_2 = 7.61 Hz, CH_2), 2.77 (dd, 1H, J_1 = 15.24 Hz, J_2 = 7.03 Hz, CH_2), 1.25 (t, 3H, J = 7.05 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 158.03 (s, 1C, C=O), 153.93 and 150.68 (d, 1C, J(C−F) = 975 Hz, C−F), 147.61 and 147.46 (d, 1C, J(C−F) = 45 Hz, C−OCH_3), 141.38 (s, 1C, Ar), 136.05 and 135.91 (d, 1C, J(C−F) = 42 Hz, C−CH−Ar), 135.83 and 135.68 (d, 1C, J(C−F) = 45 Hz, C−CH_2), 128.93 (s, 2C, Ar), 128.39 (s, 2C, Ar), 127.40 (s, 1C, Ar), 113.19 and 112.93 (d, 1C, J(C−F) = 78 Hz, CH−C−F), 109.81 and 109.66 (d, 1C, J(C−F) = 72 Hz, CH−C−OCH_3), 61.81 (s, 1C, CH−N), 57.80 (s, 1C, CH−Ar), 56.68 (s, 1C, OCH_3), 38.72 (s, 1C, OCH_2), 29.93 (s, 1C, CH_2), 14.74 (s, 1C, CH_3). Anal. ($C_{19}H_{21}FNO_3$) C, H, N.

***trans*-6-Fluoro-5-methoxy-2-(methylamino)-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (18).** A solution of **16** (3.2 g, 9.6 mmol) in anhydrous THF (40 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (0.7 g, 18.4 mmol) in anhydrous Et_2O (70 mL) under a nitrogen atmosphere. The mixture was heated to 40 °C for 24 h. The reaction was then terminated by the addition of water (0.7 mL), 15% NaOH (0.7 mL), and finally water (2.1 mL). The solid was filtered and washed with Et_2O. The filtrates were dried and evaporated. The oily residue was purified by column chromatography with $CHCl_3$/CH_3OH 6:1 as eluent. Then it was dissolved in EtOH (11 mL) and 37% HCl (0.5 mL) was added: mp 173−175 °C; yield 97%. IR ν_{max} (KBr): 2958 (NH_2^+), 2956 (OCH_3) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.47 (bs, 2H, NH_2^+), 7.35−7.15 (m, 6H, ArH), 6.63 (m, 1H, ArH), 4.61 (d, 1H, J = 5.27 Hz, CH−Ar), 3.97 (m, 1H, CH−N^+), 3.82 (s, 3H, OCH_3), 3.34 (dd, 1H, J_1 = 16.99 Hz, J_2 = 6.62 Hz, CH_2), 3.13 (dd, 1H, J_1 = 16.99 Hz, J_2 = 4.69 Hz, CH_2), 2.48 (t, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 153.58 and 150.36 (d, 1C, J(C−F) = 966 Hz, C−F), 147.79 and 147.64 (d, 1C, J(C−F) = 45 Hz, C−OCH_3), 142.13 (s, 1C, Ar), 135.99 and 135.94 (d, 1C, J(C−F) = 15 Hz, C−CH−Ar), 135.90 and 135.85 (d, 1C, J(C−F) = 15 Hz, C−CH_2), 129.51 (s, 2C, Ar), 128.79 (s, 2C, Ar), 127.97 (s, 1C, Ar), 112.65 and 112.39 (d, 1C, J(C−F) = 78 Hz, CH−C−F), 110.55 and 110.45 (d, 1C, J(C−F) = 30 Hz, CH−C−OCH_3), 66.80 (s, 1C, CH−N^+), 56.81 (s, 1C, OCH_3), 53.89 (s, 1C, CH−Ar), 35.27 and 35.10 (d, 1C, J(C−F) = 51 Hz, CH_2), 31.77 (s, 1C, CH_3). Anal. ($C_{19}H_{21}FNO_3$) C, H, N.

***trans*-6-Fluoro-5-hydroxy-2-(methylamino)-1-phenyl-2,3-dihydro-1*H*-indene Hydrobromide (4d).** Compound **4d** was prepared from **18** (1.5 g, 5 mmol) according to the procedure described for the synthesis of **4a**: mp 132−134 °C; yield 94%. IR ν_{max} (KBr): 3237 (OH), 3023 (NH_2^+) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.88 (s, 1H, OH), 8.59 (bs, 2H, NH_2^+), 7.38−7.14 (m, 5H, ArH), 6.92 (m, 1H, ArH), 6.36 (m, 1H, ArH), 4.44 (d, 1H, J = 6.03 Hz, CH−Ar), 3.96 (m, 1H, CH−N^+), 3.36 (dd, 1H, J_1 = 16.71 Hz, J_2 = 7.10 Hz, CH_2), 2.94 (dd, 1H, J_1 = 16.71 Hz, J_2 = 6.82 Hz, CH_2), 2.52 (t, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 148.75 and 145.34 (d, 1C, J(C−F) = 1023 Hz, C−F), 142.43 and 141.95 (d, 1C, J(C−F) = 144 Hz, C−OH), 138.74 (s, 1C, Ar), 137.66 and 137.48 (d, 1C, J(C−F) = 54 Hz, C−CH−Ar), 132.33 and 132.26 (d, 1C, J(C−F) = 21 Hz, C−CH_2), 128.26 (s, 2C, Ar), 127.97 (s, 2C, Ar), 127.04 (s, 1C, Ar), 118.00 and 117.82 (d, 1C, J(C−F) = 54 Hz, CH−C−F), 112.86 and 112.56 (d, 1C, J(C−F) = 90 Hz, CH−C−OH), 66.45 (s, 1C, CH−N^+), 54.20 (s, 1C, CH−Ar), 34.81 and 34.65 (d, 1C, J(C−F) = 48 Hz, CH_2), 29.39 (s, 1C, CH_3). Anal. ($C_{16}H_{17}$BrFNO) C, H, N.

***trans*-*N*-Methyl-*N*-*n*-propyl-2-amino-6-fluoro-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (20).** A mixture of amine **18** (1.6 g, 5.2 mmol) in acetone (80 mL), anhydrous K_2CO_3 (2.15 g, 15.5 mmol), and iodopropane (1.77 g, 10.4 mmol) was stirred to reflux for 3 h. At the end of this period another portion of iodopropane (0.9 g, 10 mmol) was added and the suspension was refluxed for 2 h. After removal of the solvent "in vacuo", water was added and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried, filtered, and evaporated. The oily residue was purified by column chromatography with AcOEt as eluent (R_f = 0.30). Then it was dissolved in EtOH (11 mL) and 37% HCl (0.5 mL) was added: mp 183−185 °C; yield 55%. IR ν_{max} (KBr): 2967 (NH_2^+), 2966 (OCH_3) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.21 (bs, 1H, NH^+), 7.38−7.11 (m, 6H, ArH), 6.54 (m, 1H, ArH), 4.81 (d, 1H, J_1 = 6.39 Hz, CH−Ar), 4.31 (m, 1H, CH−N^+), 3.82 (s, 3H, OCH_3), 3.50 (dd, 1H, J_1 = 15.92 Hz, J_2 = 6.24 Hz, CH_2), 3.00 (dd, 1H, J_1 = 15.92 Hz, J_2 = 6.11 Hz, CH_2), 2.98 and 2.87 (two d, 2H CH_2−N^+), 2.65 and 2.57 (two d, 3H, CH_3−N^+), 1.62 and 1.39 (two m, 2H, CH_2−C−N^+), 0.82 and 0.62 (two t, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 153.6l and 150.38 (d, 1C, J(C−F) = 690 Hz, C−F), 147.86 and 147.71 (d, 1C, J(C−F) = 45 Hz, C−OCH_3), 143.14 (s, 1C, Ar), 136.36 and 136.27 (d, 1C, J(C−F) = 27 Hz, C−CH−Ar), 135.69 and 135.57 (d, 1C, J(C−F) = 36 Hz, C−CH_2), 129.66 (s, 2C, Ar), 128.62 (s, 2C, Ar), 127.98 (s, 1C, Ar), 112.47 and 112.33 (d, 1C, J(C−F) = 42 Hz, CH−C−F), 110.07 and l09.97 (d, l C, J(C−F) = 30 Hz, CH−C−OCH_3), 71.45 (s, 1C, CH−N^+), 56.81 (s, 1C, OCH_3), 55.51 and 55.24 (two s, 1C, CH_2−N^+), 52.77 (s, 1C, CH−Ar), 37.66 and 37.55 (two s, 1C, CH_3−N^+), 34.15 and 33.90 (d, 1C, J(C−F) = 75 Hz, CH_2), 17.57 and 16.84 (two s, 1C, CH_2−C−N^+), 11.58 and 11.23 (two s, 1C, CH_3). Anal. ($C_{20}H_{25}$ClFNO) C, H, N.

***trans*-*N*-Methyl-*N*-*n*-propyl-2-amino-6-fluoro-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (4e).** To the product **20** (1.64 g, 4.7 mmol) were added water (3.6 mL), methanesulfonic acid (57 mL), and methionine (7.9 g, 53.2 mmol). The mixture was stirred at 25 °C for 4 days, then poured into ice−water (65 mL) and made basic (pH 8) with 15% NH_4OH. The mixture was extracted with AcOEt. The organic extracts, washed with aqueous $NaHSO_3$ and water, were dried and evaporated. The residue was dissolved in EtOH (11 mL), and 37% HCl (0.5 mL) was added: mp 160−162 °C; yield 70%. IR ν_{max} (KBr): 3233 (OH), 3014 (NH_2^+) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.50 (s, 1H, OH), 11.25 (bs, 1H, NH^+), 7.43−7.10 (m, 6H, ArH), 6.53 (m, 1H, ArH), 4.66 (d, 1H, J = 5.83 Hz, CH−Ar), 4.30 (m, 1H, CH−N^+), 3.50 (dd, 1H, J_1 = 15.06 Hz, J_2 = 6.03 Hz, CH_2), 3.35 (dd, 1H, J_1 = 15.06 Hz, J_2 = 5.58 Hz, CH_2), 2.96 and 2.84 (two m, 2H, CH_2−N^+), 2.63 and 2.54 (two s, 3H, CH_3−N^+), 1.63 and 1.37 (two m, 2H, CH_2−C−N^+), 0.81 and 0.59 (two t, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 153.17 and 150.13 (d, 1C, J(C−F) = 912 Hz, C−F), 142.10 and 141.72 (d, 1C, J(C−F) = 120 Hz, C−OH), 138.64 (s, 1C, Ar), 137.73 and 137.56 (d, 1C, J(C−F) = 51 Hz, C−CH−Ar), 132.25 and 132.19 (d, 1C, J(C−F) = 18 Hz, C−CH_2), 128.55 (s, 2C, Ar), 127.23 (s, 2C, Ar), 125.75 (s, l C, Ar), 117.48 and 117.30 (d, 1C, J(C−F) = 54 Hz, CH−C−F), 112.34 and 112.04 (d, 1C, J(C−F) = 86 Hz, CH−C−OH), 78.21 (s, 1C, CH−N^+), 56.93 and 55.70 (two s, 1C, CH_2−N^+), 50.22 (s, 1C, CH−Ar), 39.96 and 39.31 (two s, 1C, CH_3−N^+), 32.03 and 31.68 (d, 1C, J(C−F) = 105 Hz, CH_2), 18.52 and 17.75 (two s, 1C, CH_2−C−N^+), 11.84 and 11.39 (two s, 1C, CH_3). Anal. ($C_{19}H_{23}$ClFNO) C, H, N.

***trans*-*N*-Allyl-*N*-methyl-2-amino-6-fluoro-5-methoxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (22).** A mixture of amine **18** (1.6 g, 5.2 mmol) in absolute EtOH (35 mL), anhydrous K_2CO_3 (0.77 g, 5.6 mmol), and allyl bromide (1.22 g, 10 mmol) was stirred at 60 °C for 3 h. After removal of the solvent "in vacuo", water was added and the mixture was extracted with Et_2O. The combined organic extracts were dried, filtered, and evaporated. The oily residue was purified by column chromatography with AcOEt as eluent. The desired fraction was collected and evaporated. The residue was dissolved in EtOH (11 mL), and 37% HCl (0.5 mL) was added: mp 200−202 °C; yield 54%. IR ν_{max} (KBr): 2983 (NH_2^+), 3006 (OCH_3) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.42 (bs, 1H, NH^+), 7.53−7.25 (m, 5H, ArH), 6.98 (m, 1H, ArH), 6.83 (m, 1H, ArH), 6.11−5.97 (m, 1H, CH=), 5.60−5.52 (m, 2H, CH_2=), 4.70 (d, 1H, J = 5.95 Hz, CH−Ar), 4.21 (m, 1H, CH−N^+), 3.98 (s, 3H, OCH_3), 3.83 (dd, 1H, J_1 = 15.20 Hz, J_2 = 6,34 Hz, CH_2), 3.72 (dd, 1H, J_1 = 15.20 Hz, J_2 = 5.36 Hz, CH_2), 3.52 (m, 2H, CH_2−N^+), 2.39 (s, 3H, CH_3−N^+). ^{13}C NMR (DMSO-d_6): δ 155.23 and 152.14 (d, 1C, J(C−F) = 927 Hz, C−F), 144.85 and 144.54 (d, 1C, J(C−F) = 93 Hz, C−OCH_3), 139.02 (s, 1C, Ar), 136.86 and 136.68 (d, 1C, J(C−F) = 54 Hz, C−CH−Ar), 128.87 and 128.63

(d, 1C, J(C−F) = 72 Hz, C−CH_2), 128.55 (s, 2C, Ar), 127.23 (s, 2C, Ar), 126.54 (s, 1C, Ar), 126.46 (s, 1C, CH═), 125.10 (s, 1C, CH_2═), 114.40 and 114.23 (d, 1C, J(C−F) = 60 Hz, C−C−OCH_3), 113.23 and 112.93 (d, 1C, J(C−F) = 90 Hz, CH−C−F), 78.22 (s, 1C, CH−N^+), 60.91 and 60.73 (two s, 1C, CH_2−N^+), 56.13 (s, 1C, OCH_3), 53.50 (s, 1C, CH−Ar), 40.69 and 40.47 (two s, 1C, CH_3−N^+), 34.06 and 33.82 (d, 1C, J(C−F) = 72 Hz, CH_2). Anal. ($C_{20}H_{23}ClFNO$) C, H, N.

***trans*-*N*-Allyl-*N*-methyl-2-amino-6-fluoro-5-hydroxy-1-phenyl-2,3-dihydro-1*H*-indene Hydrochloride (4f).** Compound **4f** was prepared from **22** (1.63 g, 4.7 mmol) according to the procedure described for the synthesis of **4e**: mp 194−196 °C; yield 62%. IR ν_{max} (KBr): 3315 (OH), 3126 (NH_2^+) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.36 (s, 1H, OH), 11.25 (bs, 1H, NH^+), 7.55 7.21 (m, 5H, ArH), 6.96 (m, 1H, ArH), 6.81 (m, 1H, ArH), 6.10−5.96 (m, 1H, CH═), 5.58−5.52 (m, 2H, CH_2═), 4.68 (d, 1H, J = 4.92 Hz, CH−Ar), 4.37 (m, 1H, CH−N^+), 3.92 (m, 2H, CH_2−N^+), 3.59 (dd, 1H, J_1 = 14.26 Hz, J_2 = 6.44 Hz, CH_2), 3.34 (dd, 1H, J_1 = 14.26 Hz, J_2 = 4.82 Hz, CH_2), 2.39 (s, 3H, CH_3−N^+). ^{13}C NMR (DMSO-d_6): δ 153.25 and l50.57 (d, 1C, J(C−F) = 804 Hz, C−F), 142.19 and 141.48 (d, 1C, J(C−F) = 213 Hz, C−OH), 139.14 (s, 1C, Ar), 137.65 and 137.47 (d, 1C, J(C−F) = 54 Hz, C−CH−Ar), 132.32 and 132.25 (d, 1C, J(C−F) = 21 Hz, C−CH_2), 128.58 (s, 1C, Ar), 127.40 (s, 2C, Ar), 126.84 (s, 2C, Ar), 126.46 (s, 1C, CH═), 125.10 (s, 1C, CH_2═), 117.67 and 117.50 (d, 1C, J(C−F) = 51 Hz, CH−C−F), 112.54 and 112.23 (d, 1C, J(C−F) = 93 Hz, CH−C−OH), 78.81 (s, 1C, CH−N^+), 60.91 and 60.57 (two s, 1C, CH_2−N^+), 50.22 (s, 1C, CH−Ar), 40.15 and 40.02 (two s, 1C, CH_3−N^+), 31.93 and 31.50 (d, 1C, J(C−F) = 129 Hz, CH_2). Anal. ($C_{19}H_{21}ClFNO$) C, H, N.

Pharmacological Methods. Receptor Radioligand Binding Assays. [^{3}H]YM-09-151-2 (a D_2-like receptor antagonist, 85.5 Ci/mmol) and [^{3}H]SCH23390 (a D_1-like receptor antagonist, 86 Ci/mmol) were purchased from NEN Life Science and from Amersham International, respectively. Dopamine-HCl and all other reagents were obtained from commercial suppliers.

Striatal tissue was isolated from porcine brains. The porcine striatal membranes were prepared as previously described.[24] In brief, tissue was homogenized in 20 volumes of ice-cold 50 mM Tris-HCl buffer at pH 7.4 (buffer T) containing protease inhibitors (20 μg/mL soybean trypsin inhibitor, 200 μg/mL, and 160 μg/mL benzamidine), using an Ultra-Turrax TP-1810 (3 × 20 s). The homogenate was centrifuged for 10 min at 50000g at 4 °C. The resulting pellet was then washed once by resuspension in fresh buffer T and centrifugated as before. The final pellet was frozen at −20 °C until the time of assay.

For D_1-like and D_2-like receptor binding assays, the porcine striatal pellet was suspended in buffer T and homogenized by Ultra-Turrax. [^{3}H]SCH23390 binding to D_1-like receptors was assayed in a final incubation volume of 0.5 mL, which contained crude membranes (∼0.2 mg of protein), radioligand (∼0.5 nM), and the tested compound in the range 10^{-8}−10^{-4} M concentrations at 30 °C for 60 min.

[^{3}H]YM-09151-2 binding to D_2-like receptors was assayed in a final incubation volume of 2 mL. Striatal membranes (∼0.2 mg of protein) were incubated with radioligand (∼0.3 nM) and various concentrations (10^{-8}−10^{-4} M) of the tested compound at 30 °C for 60 min. All assays were performed in duplicate.

Incubation was terminated by dilution to 5 mL with ice-cold buffer T, followed immediately by rapid filtration through glass fiber Whatman GF/C filters. The filters were then washed (3 × 5 mL) with buffer T, and the amount of radioactivity retained on them was determined by a Packard 1600 TR liquid scintillation counter at 66% efficiency. Nonspecific binding was defined in the presence of 2.5 mM dopamine.

The compounds were dissolved in ethanol. The level of ethanol did not exceed 1% and was maintained constant in all tubes. At least six different concentrations of each compound were used. The IC_{50} values, computer-generated using a nonlinear regression formula on a computer program (version 3.0 of GraphPad Prism, San Diego, CA), were converted to K_i values according to the equation of Cheng and Prusoff.[25] Protein concentration was assayed by the method of Lowry et al.[26]

Neostrital cGMP and cAMP Activity Studies. Quinpirole (a D_2-like receptor agonist), sulpiride (a D_2-like receptor antagonist), SCH38393 (a D_1-like receptor agonist), SCH23390 (a D_1-like receptor antagonist), and dopamine-HCl were purchased from Sigma-Aldrich Chemie GmbH, Steinheim, Germany. The *N*-*n*-propyl-*N*-(2-phenylethyl)-2-(3-hydroxyphenyl)-ethylamine hydrobromide (RU24213) was synthesized in our laboratory. Striatal tissue was isolated from rat brain. The striatal membranes were prepared as previously described.[24]

G-Case Activity Analysis. The enzymatic analysis was carried out using the method of Spoto et al.[19] with minor modifications: 0.1 M phosphate buffer, pH 7.0, 33.2 M $MgCl_2$ with addition of 2.25 mM IBMX (MixA) to 37 °C. The reaction was started by the addition of 54 μM of GTP, in a final volume of 500 μL. The mixture was incubated for 60 min at 37 °C, after the reaction had been stopped with 10 μL of 2 M HCl, and boiled for 5 min in bath water. Later the sample was centrifuged for 10 min at 16000g and then filtered through a nylon-66 filter (0.2 μm; Rainin Corporation). The obtained limpid filtered product was used directly for the analysis in HPLC, or was kept to −80 °C. The HPLC system was from Beckman and consisted of two 110A pumps, a variable-wavelength spectrophotometer SPD-10AV vp (Shimadzu) measuring at 254 nm, and an autosampler Promis (SparK, Holland). The column used was a 5 μm Li-Chrospher 100 CH 18/2 Merck (250 mm × 4 mm). The mobile phase employed for the separation of nucleotides consisted of 200 mM ammonium acetate (pH 6.0) with 2% acetonitrile (v/v). The flow rate was 1 mL/min; the detection was performed at 254 nm. Peak identities were confirmed by coelution with standards. Quantitative measurements were carried out by comparison using standard solutions of known concentrations. Analysis was confirmed with the cGMP enzyme-linked immunoabsorption assay (cGMP EIA kit; Biomol) following the manufacturer's recommendation, using nonacetylated cyclic nucleotides as a standard and acetylcholine esterase-linked cGMP as a competitor.

Data are presented as mean values ± SEM and were analyzed using analysis of variance (ANOVA). Student's t-test was used to assess the statistical significance of the difference between two means.

A-Case Activity Analysis. The enzymatic analysis was carried out using the method of Spoto et al.[20] with minor modifications: 0.1 M Tris-HCl buffer (pH 8.3), 10 mM $MgCl_2$, 0.1 M KCl at 37 °C. Control experiments were performed using a commercial preparation (Sigma), where the enzyme concentration was 0.4 μM. The time-course of reaction was 60 min. The reaction was terminated by adding HCl to give the final 0.01 M and transferring the tubes with reaction mixture into a boiling water bath for 5 min. The sample was then centrifuged for 10 min at 12 000 rpm, and the supernatant was filtered through a nylon-66 filter (0.2 μm; Rainin Corporation). The clear filtrate obtained was used directly for HPLC assay or stored at −80 °C.

The HPLC system was from Shimadzu and consisted of an LC-9 A pump, a variable-wavelength spectrophotometer SPD-10AV vp measuring at 254 nm, an autoinjector SIL-10 A xl, and a system controller SCL-10A. The column used was a 5 μm Li-Chrospher 100 CH 18/2 Merck (250 mm × 4 mm). The mobile phase employed for the separation of nucleotides consisted of 200 mM ammonium acetate (pH 6.0) with 1.5% acetonitrile (v/v). The flow rate was 1 mL/min; the detection was performed at 254 nm. Peak identities were confirmed by coelution with standards. Quantitative measurements were carried out by comparison using standard solutions of known concentrations. Analysis was confirmed with the cAMP enzyme-linked immunoabsorption assay (cAMP EIA kit; Biomol) following the manufacturer's recommendation, using nonacetylated cyclic nucleotides as a standard and acetylcholine esterase-linked cAMP as a competitor.

Data are presented as mean values ± SEM and were analyzed using analysis of variance (ANOVA). Student's *t*-test was used to assess the statistical significance of the difference between two means.

Acknowledgment. Financial support from Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) is gratefully acknowledged. We thank Prof. Francesco Claudi for many helpful discussions and Mr. Domenico Rapposelli for his skillful technical assistance.

Supporting Information Available: Spectral data of compounds **9**, **11**, **5a**, **13**, **5b**, **15**, **5c**, **17**, **19**, **5d**, **21**, **5e**, **23**, **5f** and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM040889K